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Method for producing (4S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro pyrimidine-5-carbonitrile

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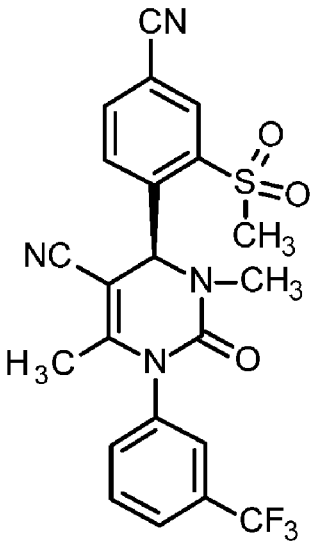
[Fortsetzung auf der nächsten Seite]

(54) **Title**: METHOD FOR PRODUCING (4S)-4-[4-CYANO-2-(METHYLSULFONYL)PHENYL]-3,6-DIMETHYL-2-OXO-1-[3-(TRIFLUOROMETHYL)PHENYL]-1,2,3,4-TETRAHYDRO PYRIMIDINE-5-CARBONITRILE

(54) **Bezeichnung** : VERFAHREN ZUR HERSTELLUNG VON (4S)-4-[4-CYANO-2-(METHYLSULFONYL)PHENYL]-3,6-DIMETHYL-2-OXO-1-[3-(TRIFLUORMETHYL)PHENYL]-1,2,3,4-TETRAHYDRO PYRIMIDIN-5-CARBONITRIL



(I),

(57) **Abstract**: The invention relates to a novel and improved method for producing (4S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro pyrimidine-5-carbonitrile of formula (I), and to the production and use of the crystal form (A) of (4S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro pyrimidine-5-carbonitrile of formula (I).

(57) **Zusammenfassung**: Die vorliegende Erfindung betrifft ein neues und verbessertes Verfahren zur Herstellung von (4S)-4-[4- Cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2,3,4-tetrahydro pyrimidin-5-carbonitril der Formel (I), sowie die Herstellung und Verwendung der Kristallform (A) von (4S)-4-[4-Cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2,3,4-tetrahydro pyrimidin- -carbonitril der Formel (I).

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Erklärungen gemäß Regel 4.17:

— *hinsichtlich der Berechtigung des Anmelders, ein Patent zu beantragen und zu erhalten (Regel 4.17 Ziffer ii)*

Veröffentlicht:

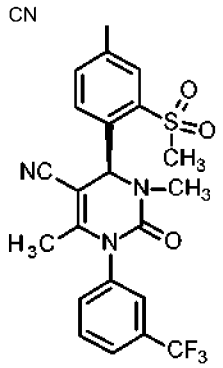
— *mit internationalem Recherchenbericht (Artikel 21 Absatz 3)*

— *vor Ablauf der für Änderungen der Ansprüche geltenden Frist; Veröffentlichung wird wiederholt, falls Änderungen eingehen (Regel 48 Absatz 2 Buchstabe h)*

Method for preparation of (4S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo-1-[3-(trifluormethyl)phenyl] -1,2,3,4-tetrahydro pyrimidine-5-carbonitrile

The present invention concerns improved methods for the preparation of (4S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2 ,3,4-tetrahydro pyrimidine-5-carbonitrile and its crystal form (A), which is used in the preparation of medications.

The compound (4S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2



,3,4-tetrahydro pyrimidine-5-carbonitrile is known from WO 2009/080199 Al and corresponds to the formula (I)

The compound of formula (I) is an inhibitor of human leukocyte elastase (HLE, EC 3.4.21.37), also known as human neutrophil elastase (HNE, hNE). Human leukocyte elastase belongs to the family of the serine proteases. The proteolytic enzyme is found in the azurophilic granules of polymorphonuclear leukocytes (PMN leukocytes). The intracellular elastase plays an important role in defense against pathogens by breaking down foreign particles which are taken up through phagocytosis. Activated neutrophil cells release HNE from the granules into the extracellular space (extracellular HNE), a portion of the liberated HNE remaining on the outside of the neutrophil cell membrane (membrane-bound HNE). The highly active enzyme is able to break down a multitude of connective tissue proteins, such protein elastin, collagen and fibronectin. Elastin occurs in high concentrations in all tissue types exhibiting high elasticity, such as in the lungs and in arteries. In a number of pathological processes (such as tissue damage), HNE plays a role in tissue breakdown and remodeling. Furthermore, HNE is an important modulator in inflammatory processes. For example, HNE induces a heightened gene expression of interleukin-8 (IL-8).

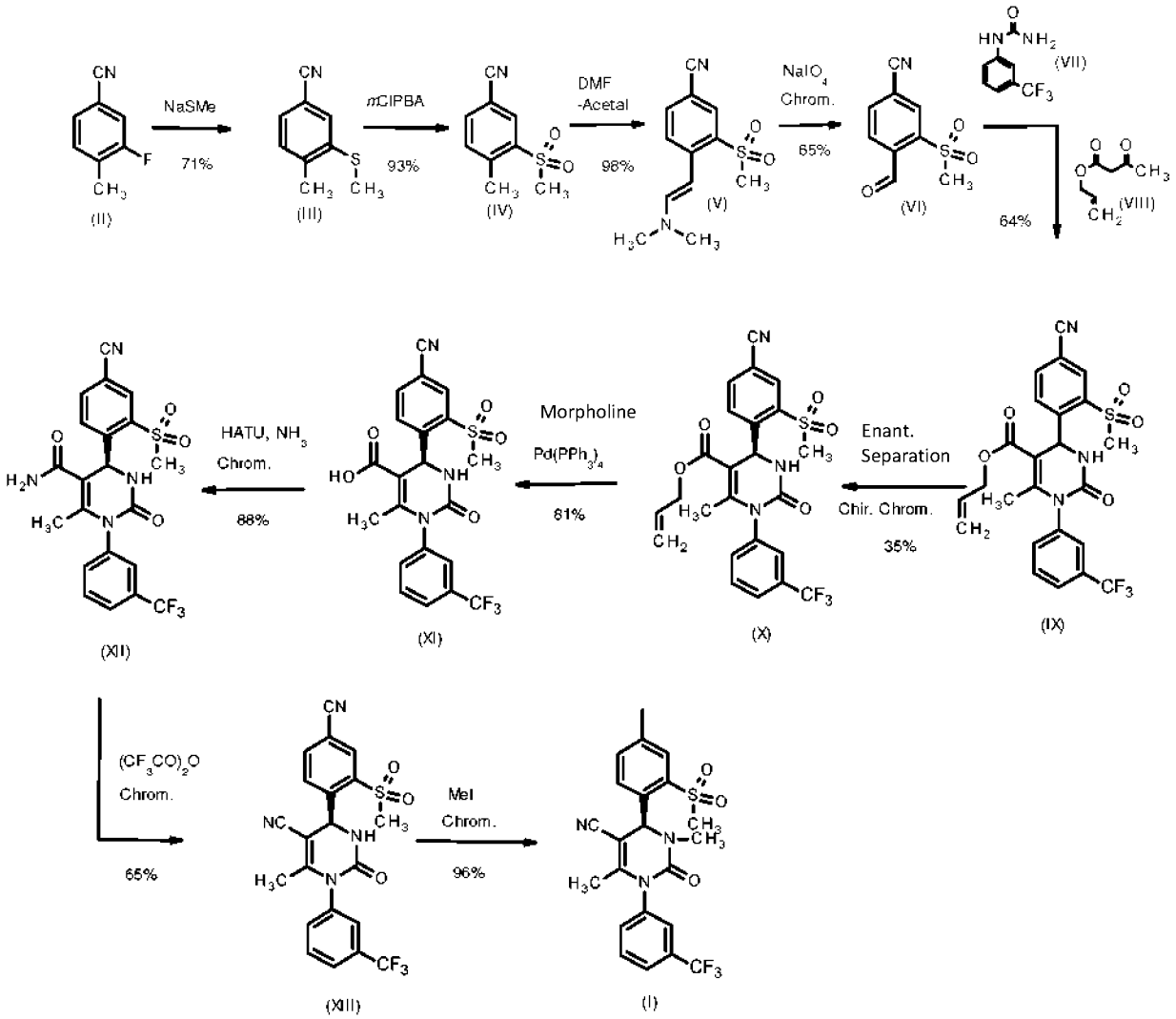
It is therefore presumed that HNE plays an important role in many illnesses, injuries and pathological alterations whose origin and/or progression are related to an inflammatory

occurrence and/or a proliferative and hypertrophic tissue and vessel remodeling. These may be in particular diseases and/or damage to the lungs or the cardiovascular system, or it may involve a sepsis, cancer illnesses, or other inflammatory diseases. HNE inhibitors are used especially in the treatment and/or prevention of diseases of the lungs and the cardiovascular system.

In WO 2009/080199 A1 a method is also described for the preparation of the compound of formula (I), being regarded as the closest prior art. In this case, starting from 3-fluor-4-methylbenzonitrile, the target compound (I) is prepared in 10 steps with a total yield of 4.45% of theory. The compound is obtained by concentration of chromatography fractions as an amorphous solid; a defined crystallization method of the end stage to established a defined crystal form has not yet been described.

The following diagram shows in detail the intermediate steps carried out in WO 2009/080199 A1.

Scheme 1



The above sketched reaction scheme is described in WO 2009/080199 A1 as follows: the reaction sequence from a compound of formula (II) through the compounds of formulas (III), (IV) and (V) to a compound of formula (VI) in scheme 6 and examples 1A, 2A method B, 3A method B and 4A

method B; the reaction sequence from a compound of formula (VI) through a compound of formula (IX) to a compound of formula (X) in scheme 1 and examples 3 and 4; und the reaction sequence from a compound of formula (X) through the compounds of formulas (XI) and (XII) to a compound of formula (XIII) in scheme 2 and examples 5A, 5 and 6. The synthesis of the compound of formula (I) is described in example 33 method B.

One uses 4 chromatographic purifications, as well as one chiral chromatography step for the separating of the enantiomers (IX).

This method known from WO 2009/080199 Al has various drawbacks in the management of the reaction, which have especially unfavorable effects during the preparation of the compound of formula (I) on a technical scale.

The overall yield at around 4.45% of theory is very low. Many steps occur in very high dilution and with very large reagent surplus. Thus, in particular, the sequence for the preparation of the nitrile-aldehyde intermediate of 4-formyl-3-(methylsulfonyl)benzonitrile (VI), which has a central role in this synthesis, is not acceptable from an atomic-economic standpoint.

In the synthesis per WO 2009/080199 Al, the racemic allyl ester of formula (IX) was separated by means of chiral chromatography into the enantiomers and the S-enantiomer (X) was isolated in a 35% yield. Such a chromatographic separation of the racemates is very cost and time intensive and thus disadvantageous to a synthesis on a large technical scale.

Furthermore, this method as described in WO 2009/080199 cannot be transferred to a technical scale, since on the one hand very costly reagents are used, such as trifluoracetic acid anhydride and O-(7-azabenzotriazol-1-yl)-N,N,N,N'-tetramethyluronium hexafluorophosphate (HATU). Trifluoracetic acid anhydride is used to convert the compound of formula (XII) into the compound of formula (XIII), HATU is used to convert the compound of formula (XI) into the compound of formula (XII). Nor does a process on technical scale allow the use of any toxic reagents. This is a disadvantage *per se*, and furthermore these toxic substances must be removed from the end product (I) to below the maximum allowable limit in the product based on regulatory reasons, which means an additional expense. This is especially so for the alkylation with methyl iodide in fivefold excess as the last step in the synthesis sequence, since it must be assured that the alkylation reagent methyl iodide, recognized as being carcinogenic, is entirely purified out. The use of benzotriazoles such as HATU is also forbidden on a large technical scale for reasons of toxicity. Moreover, many intermediate chromatographic purifications are performed according to the method described in WO 2009/080199, which are generally very cost intensive. Therefore, there was a need for a practicable large technical scale synthesis which provides the compound of formula (I) in reproducible manner in high overall yield, with low costs of production and high purity, and meeting all regulatory requirements needing to be obeyed so that the substance can be

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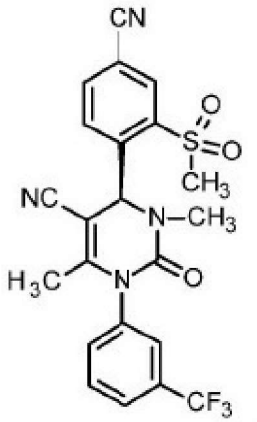
used in clinical trials and for later official dispensing filing. It would also be advantageous to isomerize the unwanted enantiomer and return the resulting racemate to the process once again. Surprisingly, a very efficient method has now been found for the preparation of the compound of formula (I), which meets the aforementioned requirements. The new method according to the invention (method variant (A) furnishes the target compound (I) in 8 steps (see schemes 7, 2 and 3, below) in more than 17% of theory overall yield without a chromatographic purification of intermediates. An alternative method variant (B) (see schemes 7, 4, 5 and 6, below) of the method according to the invention furnishes the target compound (I) in 9 steps, likewise without a chromatographic purification of intermediates, while the overall yield depends on the reaction management, as described below.

According to a first aspect, the present invention provides a compound of formula (I)



(I),

in the crystal form (A), wherein the X-ray diffraction pattern of the compound shows peak maxima of the 2 theta angle at 7.5, 12.4, 15.1, 18.5, 18.7, 22.9, 24.7 and 26.5.

According to a second aspect, the present invention provides a method for producing the compound of formula (I) in the crystal form (A) according to the first aspect, wherein a compound of formula (I), present in one or more crystal forms or as a solvate, is crystallized out in an alcohol, after which the resulting crystal paste is heated to about 50-80°C and stirred for another 2-5 h at this temperature.

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An embodiment of the present invention provides a method for the treatment of an illness, the method comprising administering to a subject in need thereof a compound according to the first aspect.

According to a third aspect, the present invention provides a method for the treatment and/or prevention of a disease of the lungs and/or the cardiovascular system, or for promoting wound healing, the method comprising administering to a subject in need thereof a compound according to the first aspect, wherein the disease of the lungs and/or the cardiovascular system or wound is associated with or modulated by HNE activity.

An embodiment of the present invention provides a method for the treatment and/or prevention of pulmonary arterial hypertonia (PAH) and other forms of pulmonary hypertonia (PH), of chronic obstructive lung diseases (COPD), of acute lung injury (ALI), of acute respiratory disease syndrome (ARDS), of pulmonary emphysema, of alpha 1-antitrypsin deficiency (AATD), of cystic fibrosis (CF), of bronchiectasis, or to promote wound healing, the method comprising administering to a subject in need thereof a compound according to the first aspect.

According to a fourth aspect, the present invention provides a pharmaceutical containing the compound of formula (I) in the crystal form (A) as claimed in the first aspect in more than 90 wt. percent in relation to the total amount of the contained compound of formula (I).

An embodiment of the present invention provides use of a compound of formula (I) in the crystal form (A) according to the first aspect in the manufacture of a medicament for the treatment of an illness

According to a fifth aspect, the present invention provides use of a compound of formula (I) in the crystal form (A) according to the first aspect for producing a pharmaceutical for the treatment of pulmonary arterial hypertonia (PAH) and other forms of pulmonary hypertonia (PH), of chronic obstructive lung diseases (COPD), of acute lung injury (ALI), of acute respiratory disease syndrome (ARDS), of pulmonary emphysema, of alpha 1-

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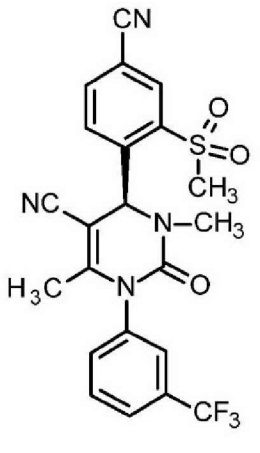
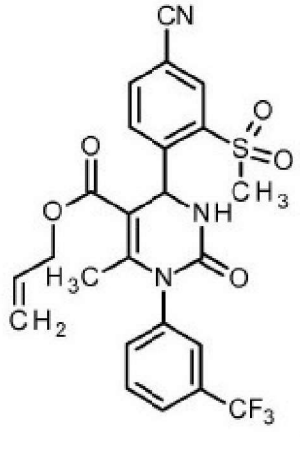
antitrypsin deficiency (AATD), of cystic fibrosis (CF), of bronchiectasis, or to promote wound healing, wherein the disease of the lungs and/or the cardiovascular system or wound is associated with or modulated by HNE activity.

According to a sixth aspect, the present invention provides a method for producing a compound of formula (I) in the crystal form (A) according to the first aspect,



(I),

wherein one reacts a compound of formula (IX):



(IX)

a-1) in the presence of a methylation agent and a base to form a compound of formula (XVI)

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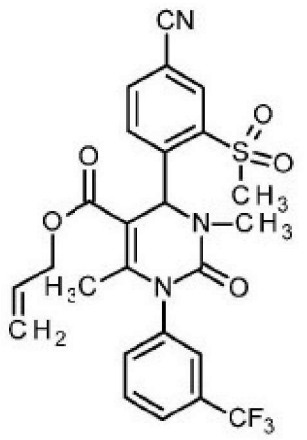
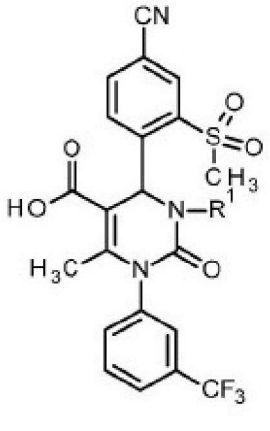


(XVI)

;

then

a-2) reacts a compound of formula (XVI) in the presence of a palladium catalyst and a secondary amine base to form a compound of formula (XXVI)



(XXVI),

in which R^1 stands for methyl,

or

b-1) reacts a compound of formula (IX) in the presence of a palladium catalyst and a secondary amine base to form a compound of formula (XXVI), in which R^1 stands for hydrogen;

then

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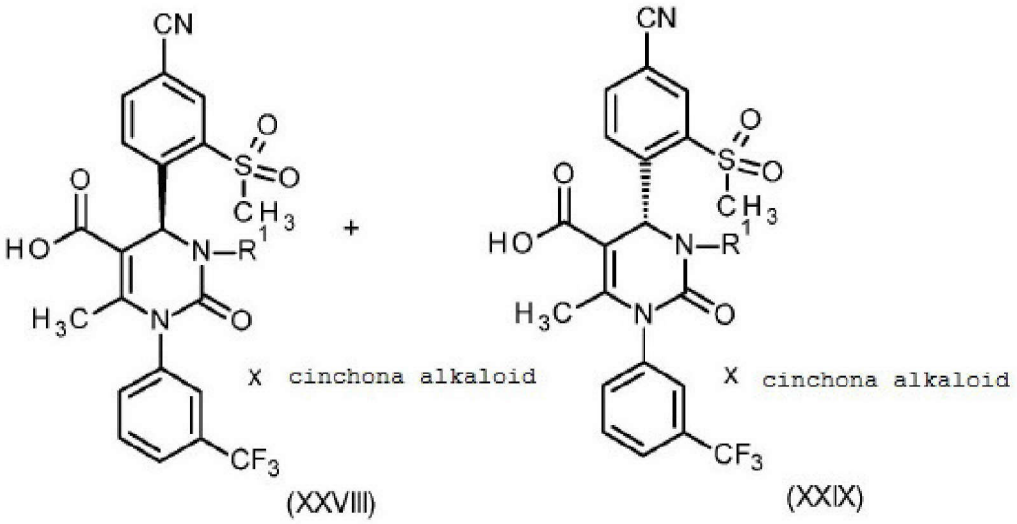
c) reacts a compound of formula (XXVI), in which R^1 stands for hydrogen or methyl, in the presence of a cinchona alkaloid and a solvent to form a compounds of formula (XXVIII) and/or (XXIX)

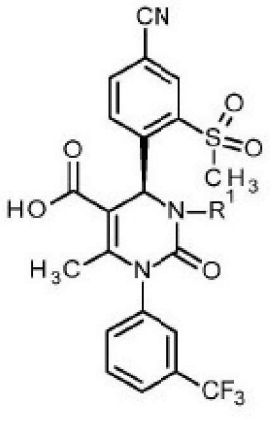


(XXVIII) (XXIX)

in which R^1 in formula (XXVIII) and in formula (XXIX) stands for hydrogen or in which R^1 in formula (XXVIII) and in formula (XXIX) stands for methyl; then

d) isolates a compound of formula (XXVIII); then

e) reacts a compound of formula (XXVIII) in the presence of a strong acid to form a compound of formula (XXVII)



(XXVII)

in which R^1 stands for hydrogen or methyl; then

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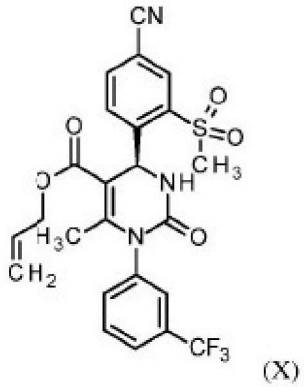
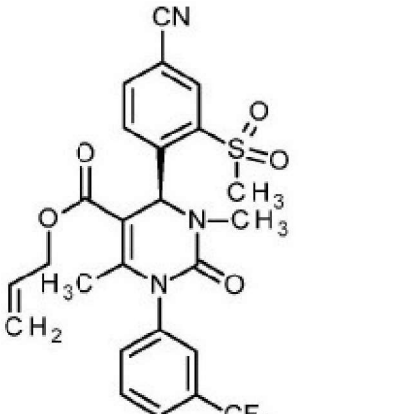
b-2) if R^1 in the compound of formula (XXVII) stands for hydrogen, one reacts a compound of formula (XXVII) in the presence of an allyl halide or sulfonate and a base to form a compound of formula (X)



(X)

then

b-3) reacts a compound of formula (X) in the presence of a methylation agent and a base to form a compound of formula (XXIII)



(XXIII)

then

b-4) reacts a compound of formula (XXIII) in the presence of a palladium catalyst and a secondary amine base to form a compound of formula (XXVII)

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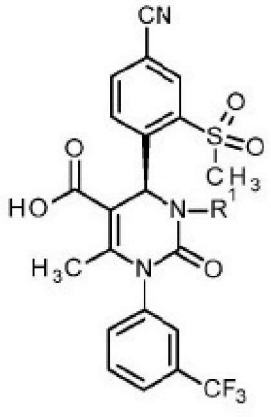

(XXVII)

in which R^1 stands for methyl; then

f) reacts a compound of formula (XXVII), in which R^1 stands for methyl, in the presence of an activation reagent, to form a compound of formula (XIX)

(XIX)

then

g) reacts a compound of formula (XIX) in the presence of a dehydrating agent to form a compound of formula (I)

According to a seventh aspect, the present invention provides a compound of formula (I)

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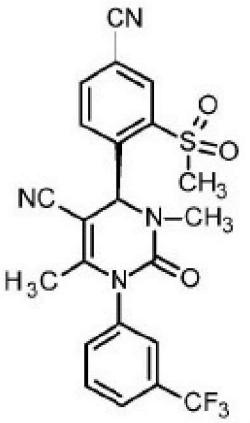
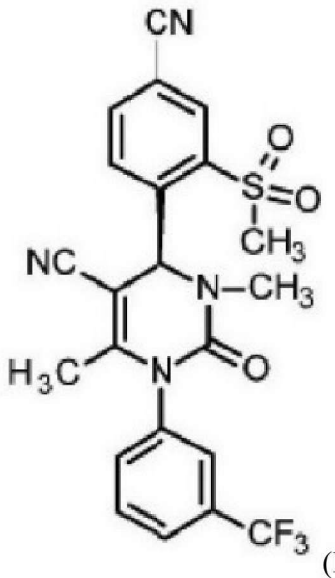


(I),

in the crystal form (A) produced by a method according to the second or sixth aspects .

The subject matter of the present invention is a method for preparation of compounds of formula (I)



(I),

characterized in that one reacts a compound of formula (IX)

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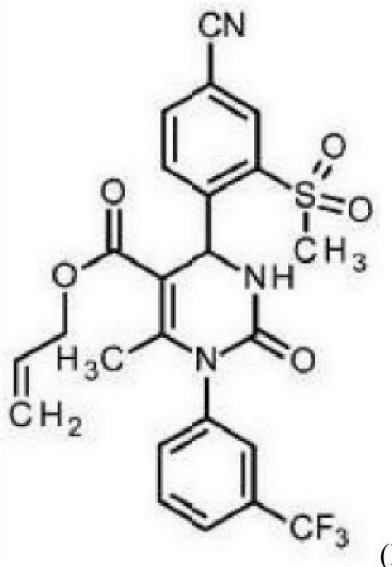
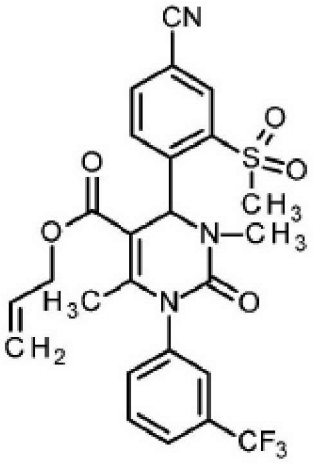


(IX)

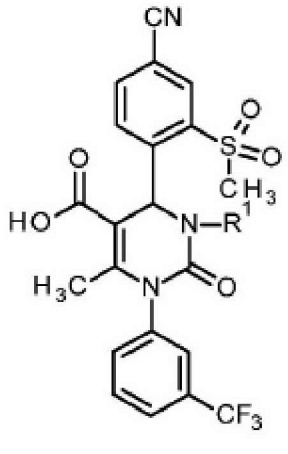
a-1) in the presence of a methylation agent and a base to form a compound of formula (XVI);



(XVI)

then

a-2) reacts a compound of formula (XVI) in the presence of a palladium catalyst and a secondary amine base to form a compound of formula (XXVI)



(XXVI),

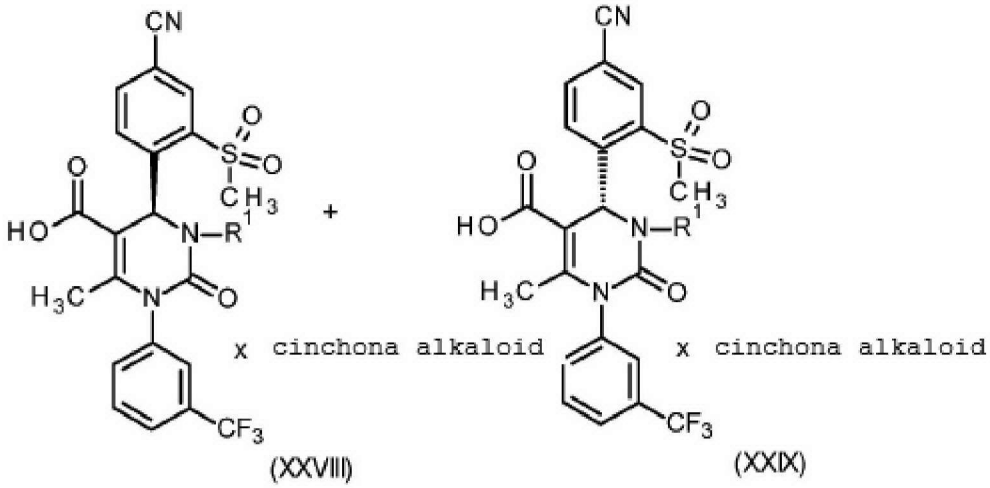
in welcher R^1 stands for methyl,

or

b-1) reacts it in the presence of a palladium catalyst and a secondary amine base to form a compound of formula (XXVI), in which R^1 stands for hydrogen;

then

c) reacts a compound of formula (XXVI), in which R^1 stands for hydrogen or methyl, in the presence of a cinchona alkaloid and a solvent to form compounds of formulas (XXVIII) and (XXIX)

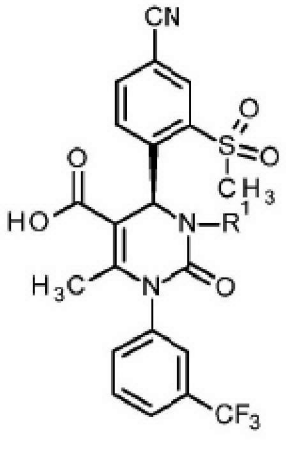


(XXVIII) (XXIX)

in which R^1 in formula (XXVIII) and in formula (XXIX) stands for hydrogen or in which R^1 in formula (XXVIII) and in formula (XXIX) stands methyl; then

d) isolates a compound of formula (XXVIII); then

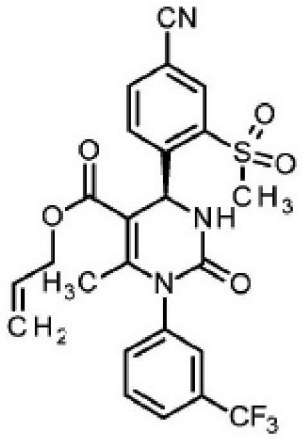
e) reacts a compound of formula (XXVIII) in presence of a strong acid to form a compound of formula (XXVII)



(XXVII)

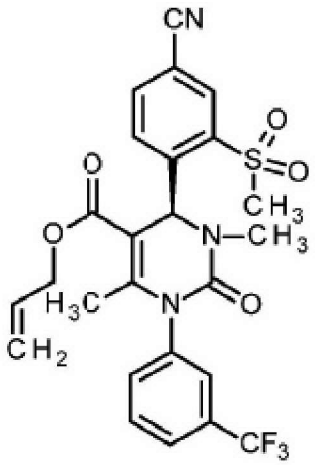
in which R^1 stands for hydrogen or methyl; then

b-2) in the event that R^1 in the compound of formula (XXVII) stands for hydrogen, one reacts a compound of formula (XXVII) in the presence of an allyl halide or sulfonate and a base to form a compound of formula (X)



(X)

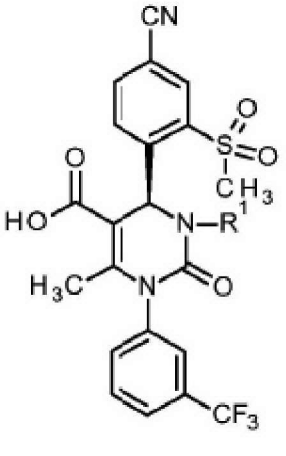
b-3) reacts a compound of formula (X) in the presence of a methylation agent and a base to form a compound of formula (XXIII)



(XXIII)

then

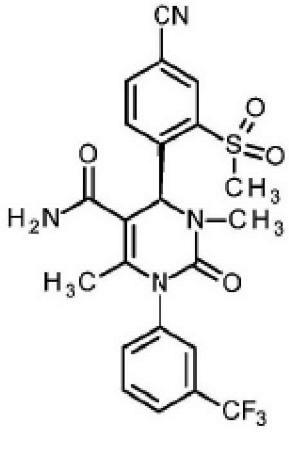
b-4) reacts a compound of formula (XXIII) in the presence of a palladium catalyst and a base to form a compound of formula (XXVII)



(XXVII)

in which R^1 stands for methyl; then

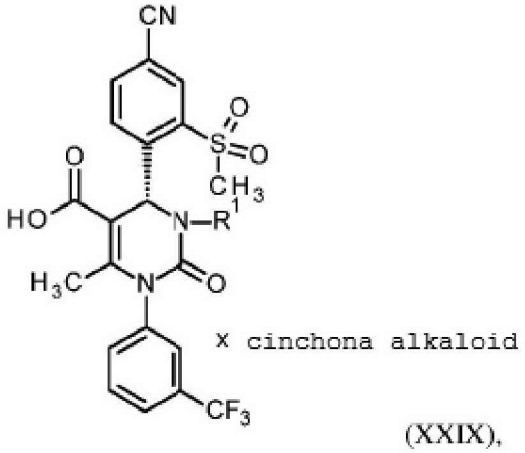
f) reacts a compound of formula (XXVII), in which R^1 stands for methyl, in the presence of an activation reagent, to form a compound of formula (XIX)



(XIX)

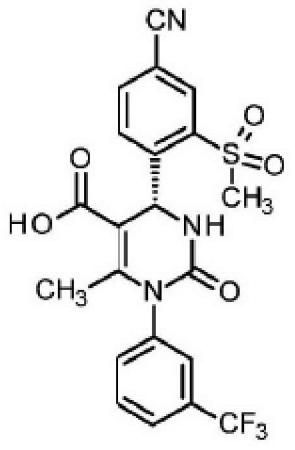
reacts a compound of formula (XIX) in the presence of a dehydrating agent, to form a compounn of formula (I);

and optionally after reaction step c) isolates a compound of formula (XXIX)



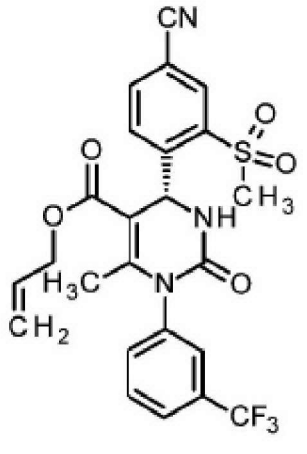
(XXIX),

in which R^1 stands for hydrogen, reacts this according to step e) in the presence of a strong acid to form a compound of formula (XXX)



(XXX)

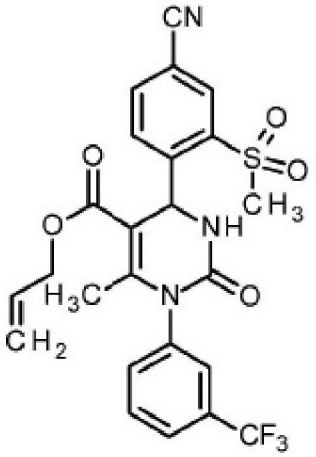
then reacts a compound of formula (XXX) according to reaction step b-2) in the presence of an allyl halide or sulfonate and a base to form a compound of formula (XXXI)



(XXXI)

then

h) reacts a compound of formula (XXXI) in the presence of a strong, non-nucleophilic base in a solvent and under simultaneous heating to form the racemate of formula (IX)



(IX)

then reacts a compound of formula (IX) according to the above-described reaction steps b-1), c), d), e), b-2), b-3), b-4), f) and g) to form a compound of formula (I);

and optionally the reaction steps of isolation of a compound of formula (XXIX), its reaction by reaction step e) in the presence of a strong acid to form a compound of formula (XXX), the subsequent reaction of a compound of formula (XXX) per reaction step b-2) in the presence of an allyl halide or sulfonate and a base to form a compound of formula (XXXI), and then the repeated performance of the reaction steps h), b-1), c), d), e), b-2), b-3), b-4), f) and g) one or more times.

The method according to the invention is described in two method variants. Method variant (A) comprises the above-described steps a-1), a-2), c), d), e), f) and g). The racemate splitting, a key step of the synthesis, takes place in method variant (A) at the step of the compound of formula (XXVI), in which R^1 stands for methyl. Method variant (B) comprises the above-described steps b-1), c), d), e), b-2), b-3), b-4), f) and g). The racemate splitting, a key step of the synthesis, takes place in method variant (B) at the step of the compound of formula (XXVI), in which R^1 stands for hydrogen.

According to one embodiment of the present invention, R^1 in formulas (XXVI), (XXVII), (XXVIII) and (XXIX) stands for methyl and the method comprises the above-described reaction steps a-1), a-2), c), d), e), f) and g).

According to one embodiment of the present invention, R^1 in formulas (XXVI), (XXVII), (XXVIII) and (XXIX) stands for hydrogen and the method comprises the above-described reaction steps b-1), c), d), e), b-2), b-3), b-4), f) and g).

According to one embodiment of the present invention, R^1 in formulas (XXVI), (XXVII), (XXVIII) and (XXIX) stands for hydrogen and the method comprises the above-described reaction steps b-1), c), d), e), b-2), b-3), b-4), f) and g) and after reaction step c) a compound of formula (XXIX) is isolated, this is reacted per reaction step e) in the presence of a strong acid to form a compound of formula (XXX); then a compound of formula (XXX) is reacted per reaction

step b-2) in the presence of an allyl halide or sulfonate and a base to form a compound of formula (XXXI); then

h) a compound of formula (XXXI) is reacted in the presence of a strong, non-nucleophilic base in a solvent and under simultaneous heating to form the racemate of formula (IX); then

a compound of formula (IX) is reacted per the above described reaction steps b-1), c), d), e), b-2), b-3), b-4), f) and g) to form a compound of formula (I);

and optionally the steps of isolation of a compound of formula (XXIX), its reaction by reaction step e) in the presence of a strong acid to form a compound of formula (XXX), the subsequent reaction of a compound of formula (XXX) per reaction step b-2) in the presence of an allyl halide or sulfonate and a base to form a compound of formula (XXXI), and then the repeated performance of the reaction steps h), b-1), c), d), e), b-2), b-3), b-4), f) and g) one or more times

Methylation agents which can be used for the reaction steps a-1) and b-3) are, for example, methyl iodide, dimethyl sulfate, dimethyl carbonate, toluene sulfonic acid methyl ester or methane sulfonic acid methyl ester, preferably methyl iodide and dimethyl sulfate. Bases which can be used for the reaction steps a-1) and b-3) are, for example, sodium hydride, sodium hexamethyl disilazane or lithium hexamethyl disilazane, preferably sodium hexamethyl disilazane and lithium hexamethyl disilazane. As the solvent for reaction step a-1), tetrahydrofuran (THF) is used in 4-6 fold excess in terms of the weight of the compound of formula (IX). The reaction temperature is -70 to 40° C, preferably 0 to 30° C.

According to one embodiment of the present invention, the reaction steps a-1) and b-3) use 2 eq. of dimethyl sulfate (Me_2SO_4) as the methylation agent and sodium bis(trimethylsilyl)amide (NaHMDS) as the base.

WO 2009/080199 Al also describes a synthesis pathway making it possible to introduce the methyl group as early as the allyl ester step (X). Using LiHMDS, deprotonation was done at a temperature of -78° C and then the methyl group was introduced by adding 5 eq. of methyl iodide. The methylated S-allyl ester after processing and chromatographic purification was obtained in a yield of 59% (example 122). The saponification to the corresponding acid (XVIII) is likewise described (example 35A). However, no further reaction to form the end product of formula (I) via the amide (XIX) is described here.

With the goal of avoiding an alkylation with methyl iodide at the end step, according to one embodiment of the method of the invention the racemic allyl ester of formula (IX) is methylated by analogy with the synthesis described in WO 2009/080199 Al (example 122). Unlike the synthesis described in WO 2009/080199 Al, the methylation of the allyl ester in the method of the invention occurs at the stage of the racemate. The reaction according to the invention has significant improvements as compared to the prior art. Thanks to the use of NaHMDS as the base,

the reaction can be carried out at a temperature of 20° C in a 4 to 6 fold excess of THF, referred to the weight of the compound of formula (IX). This is significant for a synthesis on a large technical scale, since now no cost-intensive low-temperature reactor is required. Furthermore, the rather costly methylation agent methyl iodide can be replaced by the economical alkylation reagent dimethyl sulfate. One uses 2 eq. of dimethyl sulfate. The excess methylation agent after the end of the reaction is removed by adding aqueous ammonia solution. The product (XVI) can be isolated directly from the reaction mixture by water precipitation. After isolation, drying is done in a vacuum. The yields of this reaction are generally > 80 % of theory.

Palladium catalysts which can be used for the saponification of the allyl esters of formula (XVI), (IX) or (XXIII) per reaction steps a-2), b-1) and b-4) are, for example, palladium-(O)-phosphane complexes such as tetrakis (triphenylphosphine) palladium(0) ($Pd(PPh_3)_4$) or palladium-acetate/triphenylphosphine ($PdOAc_2/PPh_3$), preferably Pd-acetate/tripenylphosphine. Secondary amine bases which can be used for the reaction step a-2) are, for example, morpholine, piperidine, diisopropyl amine or N-methyl-piperazine, preferably morpholine and N-methyl-piperazine. As the solvent for the reaction steps a-2), b-1) and b-4), tetrahydrofuran (THF) is used for example in 3-5 fold excess, referred to the weight of the compound of formula (XVI), (IX) or (XXIII).

According to one embodiment of the present invention, in reaction steps a-2), b-1) and b-4) palladium acetate ($PdOAc_2$) with triphenylphosphine (PPh_3) is used as the palladium catalyst and morpholine is used as the base.

The saponification of the racemic allyl ester (XVI) to the free acid (XVII) is done in reliance on the protocol as published in WO 2009/080199 Al (example 5A, here at the stage of the S-enantiomer). The reaction according to the invention has significant improvements over the prior art.

Thus, the relatively costly as well as air-sensitive catalyst palladium tetrakistriphenylphosphine is replaced by the stable palladium acetate with addition of triphenylphosphine as ligand. Furthermore, the catalyst quantity can also be reduced from 0.05 eq. to 0.003 eq. The palladium-catalyzed allyl ester cleavage is carried out in a 3 to 5 fold excess of THF, referring to the weight of the compound of formula (XVI), at temperatures of 40 to 60° C in 1 to 3 h with adding of morpholine as the base. The product (XVII), which occurs as a THF-solvate, can be isolated directly from the reaction mixture by water precipitation. After the isolation, it is dried in a vacuum. The yields of this reaction are generally > 95 % of theory.

The splitting of the racemate mixture of the acids of formula (XXVI), where R^1 is hydrogen or methyl, according to reaction step c) of the present invention is a key step in the method of the invention for the preparation of the compound of formula (I). Cinchona alkaloids which can be used for reaction step c) (racemate splitting) are chosen from the group consisting of quinine,

quinidine, cincholin and cincholidine. Preferable are quinine and quinidine. Solvents which can be used for reaction step c) are for example aqueous alcohol systems, preferably isopropanol/water, especially preferably isopropanol/water in a ratio of 9:1. Furthermore, esters of acetic acid may be used as the solvent for reaction step c), preferably the C_2 to C_5 alkyl acetates, especially preferably n-butyl acetate.

According to one embodiment of the present invention, the cinchona alkaloid for reaction step c) is chosen from the group consisting of quinine and quinidine.

According to one embodiment of the present invention, the solvent for reaction step c) is chosen from C_2-C_5 alkyl esters of acetic acid, C_1-C_6 alcohols and mixtures of C_1-C_6 alcohols and water.

According to one embodiment of the present invention, for reaction step c) in the case of the reactio nof a compound of formula (XXVI), in which R^1 stands for methyl, a combination of quinidine as the cinchona alkaloid and n-butyl acetate as the solvent is used. The diastereomer quinidine salts of the compound of formula (XXVI), in which R^1 stands for methyl, may be separated from each other according to the method of the invention in solvents such as the esters of acetic acid, preferably the C_2 to C_5 substituted esters, especially preferably n-butyl acetate. Thus, the racemic compound of formula (XXVI), in which R^1 stands for methyl, is reacted in a 4 to 6 fold excess of butyl acetate, referred to the weight of the compound of formula (XXVI with R^1=methyl), while adding 1.0 to 1.1 eq. of quinidine at 40° C to 60° C. In this cases, the diastereomer quinidine salt of the S-acid (compound of formula (XX)) crystallizes out predominantly, while the R-form (compound of formula (XXI)) remains in solution.

For the isolation of the compound of formula (XXVIII), in which R^1 stands for hydrogen or methyl, in reaction step d), the solid is filtered off, washed with the solvent used in reaction step c), and dried in vacuum.

Strong acids which can be used for reaction step e) are, for example, aqueous hydrochloric acid, aqueous hydrobromic acid, or aqueous sulfuric acid.

According to one embodiment of the present invention, acidification down to pH 1 is done in reaction step e) with aqueous hydrochloric acid.

According to one embodiment of the present invention, in reaction step e) the diastereomer-pure quinidine salt (compound of formula (XX)) is suspended in water to release the acid. After acidification with aqueous hydrochloric acid (down to pH = 1), the quinidine auxiliary base remains in solution as a hydrochloride, while the enantiomer-pure acid (compound of formula (XXVII), in which R^1 stands for methyl) precipitates out. After isolation, drying is done in vacuum. The yields of this racemate splitting and liberation of the S-acid (compound of formula (XXVII), in which R^1 stands for methyl) are generally > 40% of theory, with an enantiomer excess of >98%.

The other isomer can likewise be obtained from the mother liquor of the racemate splitting by concentrating and subsequent aqueous acidic processing.

According to another embodiment of the present invention, for reaction step c) in the event of the reaction of a compound of formula (XXVI), in which R^1 stands for hydrogen, a combination of quinine as the cinchona alkaloid and a mixture of isopropanol and water as the solvent is used. The diastereomer quinine salts of the acid of formula (XXVI), in which R^1 stands for hydrogen, are separated from each other in aqueous alcoholic systems, preferably isopropanol/water, especially preferably isopropanol/water in a ratio of 9:1. According to this embodiment, the racemic acid of formula (XXVI), in which R^1 stands for hydrogen, is reacted in 6 to 10 fold excess of isopropanol/water, referred to the weight of the compound of formula (XXVI), while adding 1.0 to 1.1 eq. of quinine at 40° C to 60° C. Primarily the diastereomer quinine salt of the S-acid (compound of formula (XXIV)) crystallizes in this process, while the R-form (compound of formula (XXV)) remains in solution.

For the isolating of the compound of formula (XXIV) per reaction step d), the solid is filtered off, washed with isopropanol/water, and dried in vacuum.

According to step e), in order to liberate the acid of formula (XXVII), in which R^1 stands for hydrogen, the diastereomer-pure quinidine salt (XXIV) is suspended in water. After acidification with aqueous hydrochloric acid (down to pH = 1), the quinine auxiliary base remains in solution as a hydrochloride, while the enantiomer-pure acid precipitates out. After isolation, drying is done in vacuum. The yields of this racemate splitting and liberation of the S-acid of formula (XXVII), in which R^1 stands for hydrogen, are generally > 45% of theory, with an enantiomer excess of >98%. The total yield of this reaction sequence is 18%.

The other isomer can likewise be obtained from the mother liquor of the racemate splitting by concentrating and subsequent aqueous acidic processing.

The success of such a racemate splitting is highly dependent on the substance and cannot be predicted. The method according to the invention for racemate splitting as described in reaction step c) is therefore surprising.

The methylation of the compound of formula (XXVII), in which R^1 stands for hydrogen, cannot be done directly with the free carboxylic acid of formula (XXVII, R^1=hydrogen). Therefore, the carboxylic acid of formula (XXVII, R^1=hydrogen) must first be converted to a corresponding ester, preferably back to an allyl ester of formula (X). This is done by the methods basically known to the skilled person per reaction step b-2) of the present invention by alkylation with an allyl halide or sulfonate, such as an allyl bromide, allyl chloride, allyl iodide, allyl methane sulfonate or allyl toluene sulfonate in the presence of bases such as potassium carbonate, sodium hydroxide, potassium hydroxide, sodium carbonate or sodium hydride in solvents such as acetone. In this

way, the carboxylic acid (XI) can be converted in a yield of 95% into the corresponding allyl ester (X). The following steps to the target compound (I) are carried out similar to the method described in variant (A).

According to one embodiment, allyl bromide in the presence of potassium carbonate is used for the reaction step b-2).

The formation of the amide from the acid was done in the synthesis according to WO 2009/080199 Al with the assistance of the quite costly amide coupling reagent O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU). The amide could only be obtained after chromatographic purification. It is obvious that such a method cannot be realized on a large technical scale and thus there was a need for an alternative procedure.

It has been found, surprisingly, that during a reaction of the carboxylic acid of formula (XXVII, R^1=methyl) in THF, the amide of formula (XIX) crystallizes out directly after water precipitation from the reaction solution and can be obtained in high yield and purity. For this, in reaction step f) according to the present invention, the carboxylic acid of formula (XXVII, R^1=methyl) is at first reacted with an activation reagent to form the imidazolide. The activation reagent may be, for example, l,1'-carbonyl diimidazole together with ammonia or 1,1'-carbonyl diimidazole together with hexamethyl disilazane.

According to one embodiment of the present invention, the carboxylic acid of formula (XXVII, R^1=mcthyl) is reacted with 1.2 to 1.7 eq., preferably 1.4 to 1.5 eq. of 1,1'-carbonyl diimidazole in THF at temperatures between 20 - 50° C at first to form the imidazolide. As the preferred technique, it has been found to first stir for 1 to 2 hours at 20° C and then to stir additionally for 2 to 3 hours at 50° C. After the end of the activation, one adds 5-20 eq., preferably 10 eq. of aqueous ammonia solution and stirs for 16-24 hours, preferably 16 hours, at room temperature. By a brief heating, the excess ammonia can be gassed out from the reaction mixture. For the processing, the reaction solution is slowly added to water. In this process, the product precipitates and can be isolated by filtration or centrifugation. One washes with water and dries in a vacuum at elevated temperature (30 to 100° C, preferably 40° C to 70° C). The yields are very high and generally amount to > 90% of theory.

The formation of the nitrile from the amide was done in the synthesis per WO 2009/080199 Al by dehydrating with 2 eq. of trifluoracetic anhydride in THF. The nitrile could only be obtained after chromatographic purification. It is obvious that such a method cannot be realized on a large technical scale and thus there was a great need for an alternative procedure.

Suitable dehydrating agents for the dehydrating of amides to form nitriles according to reaction step g) of the method of the invention are, for example, 1-propane phosphonic acid anhydride (T3P) or trifluoracetic acid anhydride. In particular, 1-propane phosphonic acid anhydride (T3P)

has proven to work well for this reaction step. This reagent can be preferred as a 50% solution in ethyl acetate. It is significantly easier to handle than the extremely hydrolysis-sensitive trifluoracetic acid anhydride. For this, the amide of formula (XIX) is first reacted with diisopropylethylamine (Hünig base) and then with 1-propane phosphonic acid anhydride (T3P). To complete the reaction, it is briefly reflux heated. After the end of the reaction, the mixture is reacted with water and extracted. After this, the organic phase is washed with saturated sodium hydrogen carbonate solution and the organic phase containing the compound of formula (I) is separated.

Since the compound of formula (I) is being developed in the form of a tablet, there is a great demand for the isolated compound of formula (I) to be isolated in reproducible manner in a definite crystalline form, so that one can assure a reproducible bio-availability.

One embodiment of the invention is also the compound of formula (I) in crystal form (A), characterized in that the X-ray diffraction pattern of the compound shows peak maxima of the 2 theta angle at 7.5, 12.4, 15.1, 18.5, 18.7, 22.9, 24.7 and 26.5.

According to one embodiment of the invention, the method according to the invention provides the compound of formula (I) in crystal form (A), characterized in that the X-ray diffraction pattern of the compound of formula (I) shows peak maxima of the 2 theta angle at 7.5, 12.4, 15.1, 18.5, 18.7, 22.9, 24.7 and 26.5.

One embodiment of the invention is also the compound of formula (I) in the crystal form (A), characterized in that the Raman spectrum of the compound shows band maxima at 3075, 2928, 2918, 2236, 2216, 1646, 1605, 1195 and 1004 cm^{-1}.

According to one embodiment of the invention, the method according to the invention provides the compound of formula (I) in the crystal form (A), characterized in that the Raman spectrum of the compound shows band maxima at 3075, 2928, 2918, 2236, 2216, 1646, 1605, 1195 and 1004 cm^{-1}.

One embodiment of the invention is a method for preparation of the compound of formula (I) in the crystal form (A), characterized in that a compound of formula (I), present in one or more crystal forms or as a solvate, is crystallized out in an alcohol, preferably ethanol, after which the resulting crystal paste is heated to 50-80° C and further stirred for 2-5 h at this temperature.

One embodiment of the invention is the compound of formula (I) in crystal form (A) for treatment of illnesses.

One embodiment of the invention is the compound of formula (I) in crystal form (A) for use in a method for treatment and/or prevention of diseases of the lungs and the cardiovascular system and for promoting wound healing, especially for chronic wounds.

One embodiment of the invention is the compound of formula (I) in crystal form (A) for use in a method for treatment and/or prevention of pulmonary arterial hypertonia (PAH) and other forms

of pulmonary hypertonia (PH), of chronic obstructive lung diseases (COPD), of acute lung injury (ALI), of acute respiratory disease syndrome (ARDS), of pulmonary emphysema, of alpha-l-antitrypsin deficiency (AATD), of cystic fibrosis (CF), of bronchiectasis and to promote wound healing, especially chronic wounds.

One embodiment of the invention is a pharmaceutical containing the compound of formula (I) in crystal form (A) in more than 90 wt. percent referred to the total quantity of the contained compound of formula (I).

One embodiment of the invention is the use of the compound of formula (I) in crystal form (A) for the preparation of a pharmaceutical for treatment of diseases of the lungs and the cardiovascular system and for promoting wound healing, especially for chronic wounds.

One embodiment of the invention is a method for the treatment of diseases of the lungs and the cardiovascular system and for the promoting of wound healing, especially for chronic wounds, by administering an effective quantity of the compound of formula (I) crystal form (A).

Another embodiment of the invention is a method for the preparation of a compound of formula (I) in crystal form (A), characterized in that one prepares a compound of formula (I) according to the method of the invention, crystallizes the compound of formula (I) from the organic phase from reaction step g) of the method of the invention in an alcohol, preferably ethanol, and then heats the resulting crystal paste to 50-80° C and further stirs for 2-5 h at this temperature.

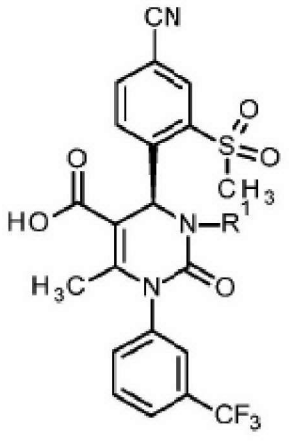
For the final crystallization method, because of GMP-technical reasons the product solution in ethyl ester is at first subjected to a particle filtration and then reacted at reflux temperature (60° C - 80° C) with ethanol, preferably using ethanol denatured with toluene. Under continued adding of ethanol (toluene-denatured), the ethyl ester is distilled off. The compound of formula (I) crystallizes out. In order to ensure a better filtering ability, the crystal paste is heated to 60° C - 80° C and further stirred for 4 h at this temperature. One cools down to 20° C, and then the crystals are isolated and dried in a vacuum at 40 - 50° C. The yields are generally > 80% of theory. The achieved chemical purity of > 99.2% and the content of around 100% correspond to the criteria for commercial products according to the ICH Guideline. The quantity of residual solvent, in this case ethanol, is < 0.1%. The optical purity is >> 99 % e.e.

The crystallization method is very robust and furnishes the desired crystal form (A) in reproducible manner (melting point 232° C). The compound of formula (I) is generally micronized and formulated into tablets at the pharmacy. It is found that the crystal form (A) possesses very good stability properties, even at high humidity, and can be stored for more than 3 years with no loss of stability.

As described above, the NH-allyl ester of formula (XXXI) can be prepared by isolation of a compound of formula (XXIX), its reaction per reaction step e) in the presence of a strong acid to

form a compound of formula (XXX) and then the reaction of a compound of formula (XXX) per reaction step b-2) in the presence of an allyl halide or sulfonate and a base. It has been discovered surprisingly that this NH-allyl ester of formula (XXXI) can be racemized. It is thus possible to transform the unwanted enantiomer, which accrues in large quantities, back to the racemic form and thus return it to the process. For this, the carboxylic acid obtained from the mother liquors of the racemate splitting, containing primarily R, is at first converted into an allyl ester under the above-described conditions similar to step b-2) according to the invention. By treatment with strong, non-nucleophilic bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in solvents, such as THF, the primarily R-containing mixture can be racemized almost completely by reflux heating for several hours. After adding the reaction mixture to water, the racemic allyl ester of formula (IX) precipitates out, is isolated and dried. The allyl ester of formula (IX) is then saponified once more under the above-described conditions per reaction step b-1) to form the acid of formula (XXVI, R^1 = hydrogen). With this method, it was possible to recover 40% of the quantity of acid of formula (XXVI, R^1 = hydrogen) that was used for the racemate splitting. With a recovery cycle, it was possible to boost the total yield of the reaction sequence from an original 18% to 25%.

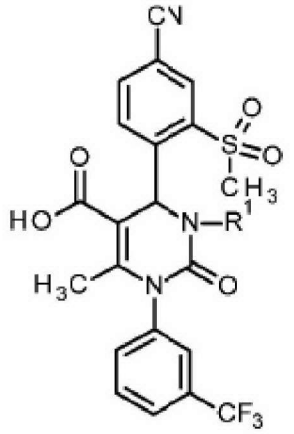
Another embodiment of the present invention is a method for preparation of a compound of formula (XXVII)



(XXVII),

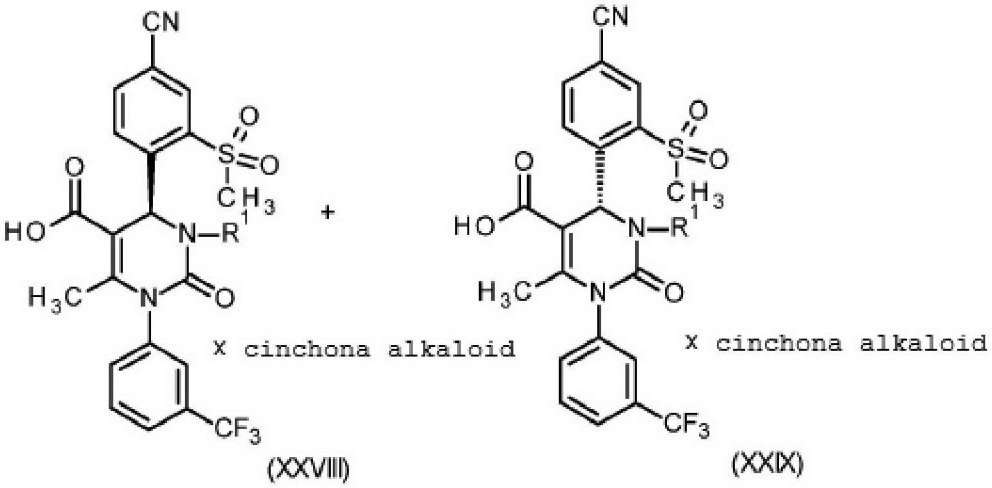
characterized in that one

c) reacts a compound of formula (XXVI)



(XXVI)

in the presence of a cinchona alkaloid and a solvent to form compounds of formulas (XXVIII) and (XXIX)



(XXVIII) (XXIX)

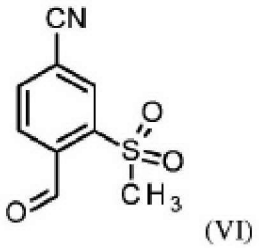
d) then isolates a compound of formula (XXVIII); then

e) reacts a compound of formula (XXVIII) in the presence of a strong acid to form a compound of formula (XXVII),

where R^1 in the compounds of formulas (XXVI), (XXVII), (XXVIII) and (XXIX) stands for hydrogen or methyl.

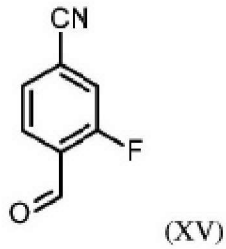
The reaction conditions for this reaction sequence are as described above.

Another embodiment of the present invention is a method for the preparation of a compound of formula (VI)



(VI)

characterized in that one reacts a compound of formula (XV)



(XV)

in the presence of $NaSO_2Me$ and DMSO of sulfolan at 40-60° C to form a compound of formula (VI).

According to one embodiment of the present invention, the reaction of the compound of formula (XV) to form the compound of formula (VI) is done in a 3-5 fold excess of DMSO or sulfolan, referred to the weight of the compound of formula (XV).

One advantage of this high concentration of the compound of formula (XV) in the reaction batch is an increased economy of the method.

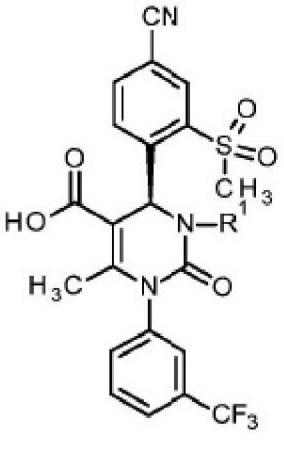
As starting material for 4-formyl-3-(methylsulfonyl)benzonitrile of formula (VI) one uses 4-bromo-2- fluorbenzaldehyde of formula (XIV), which is at first converted into 3-fluoro-4-formylbenzonitrile of formula (XV) in known manner by methods familiar to the skilled person (Synth. Commun. 1994, 887-890, Angew. Chemie 2003, 1700-1703, Tetrahedron Lett. 2007, 2555-2557, Tetrahedron Lett. 2004, 1441-1444, JACS 2003, 125, 2890-2891, 15 Journal of Organometallic Chemistry 689 (2004), 4576-4583). It has proven to be especially advantageous to perform a palladium-catalyzed reaction with potassium hexacyanoferrate * 3 H_2O

as the cyanide source (Tetrahedron Lett. 48 (2007), 1087-1090). For this, 4-bromo-2-fluorbenzaldehyde (XIV) is placed in DMF (4- 6 fold excess referred to the weight of the compound of formula (XIV)), 0.22 eq. of potassium hexacyanoferrate * 3 H2O and 1 eq. of sodium hydrogen carbonate are provided and then 0.005 eq. of palladium acetate are added. Heating is done for 3 hours at 120° C. The solution is cooled down to 20° C, then water and MtBE are added. The organic phase is separated, the aqueous phase is again washed with MtBE and then the combined MtBE phases are concentrated while adding water. The product precipitates out. After isolation, drying is done in a vacuum. The yields of this reaction are generally > 75% of theory. Meanwhile, 3-fluoro-4-formylbenzonitrile (XV) has also become commercially available. The introduction of a methylsulfonyl group into a 2-fluoro-substituted benzaldehyde has been described for example in WO 2004/52858 (ELI LILLY). The reaction of 2-fluorobenzaldehyde with sodium methane sulfinate in DMSO at 100° C in 16 h furnished the desired product, but only in 50% yield. Surprisingly, it has been discovered that 3-fluoro-4-formylbenzonitrile (XV) is converted entirely to the desired 4-formyl-3-(methylsulfonyl)benzonitrile (VI) already under relatively mild reaction conditions (40-60° C, preferably 50° C, 4 h) in a 3 to 5-fold excess of DMSO, referred to the weight of the compound of formula (XV), by reaction with sodium methane sulfinate. It was possible to isolate the product directly from the reaction mixture by water precipitation. After the isolation, drying is done in a vacuum. The yields of this reaction are generally > 90% of theory.

Thus, a very efficient approach has been found for the intermediate stage of 4-formyl-3-(methylsulfonyl)benzonitrile (VI).

It was possible to prepare the condensation product of the Biginelli reaction, (rac)-allyl 4-(4-cyano-2-(methylsulfonyl)phenyl)-
6-methyl-2-oxo-l-[3-(trifluormethyl)phenyl]-l,2,3,4-tetrahydropyrimidine-5-carboxylate (IX) from 4-formyl-3-(methylsulfonyl)benzonitrile (VI), l-[3-(trifluormethyl)phenyl]urea (VII) and allyl-3-oxobutanoate (VIII) in reliance on the synthesis protocol as published in WO 2009/080199 Al. Here as well, it was possible to significantly boost the yield from 64% to 87%.

Subject matter of the present invention is also compounds of formula (XXVII)

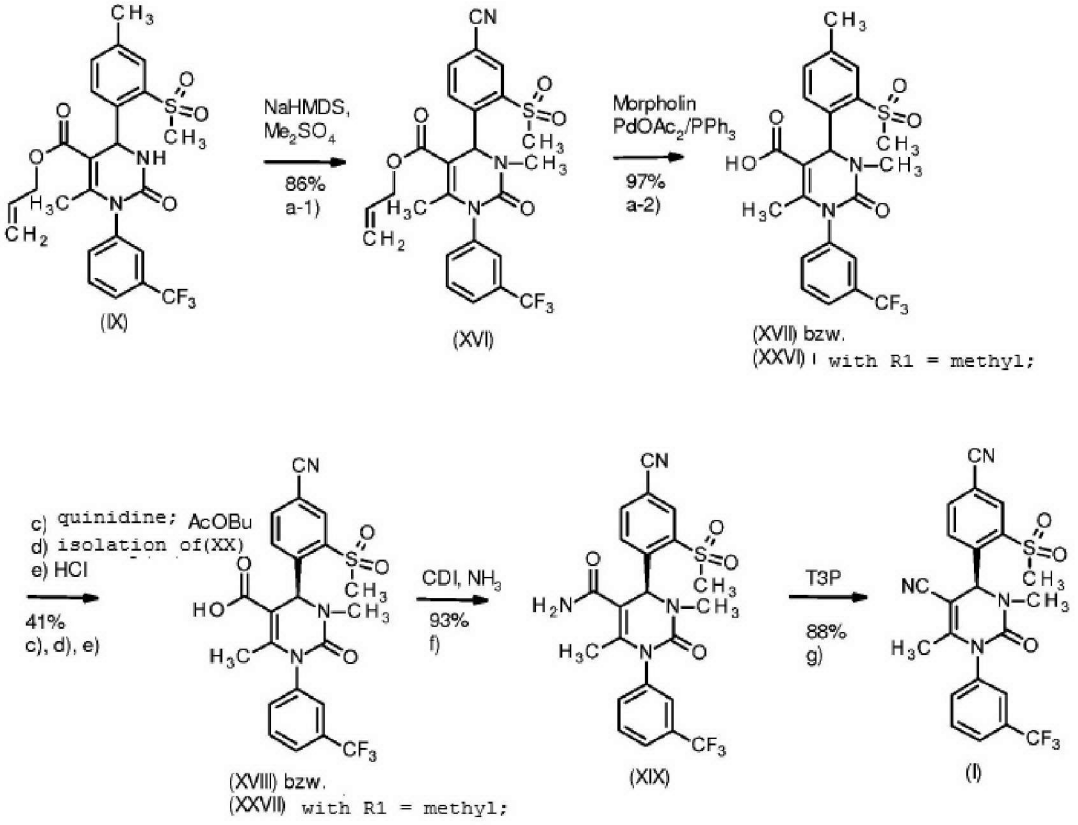


(XXVII),

in which R^1 stands for hydrogen or methyl, as well as its salts and solvates.

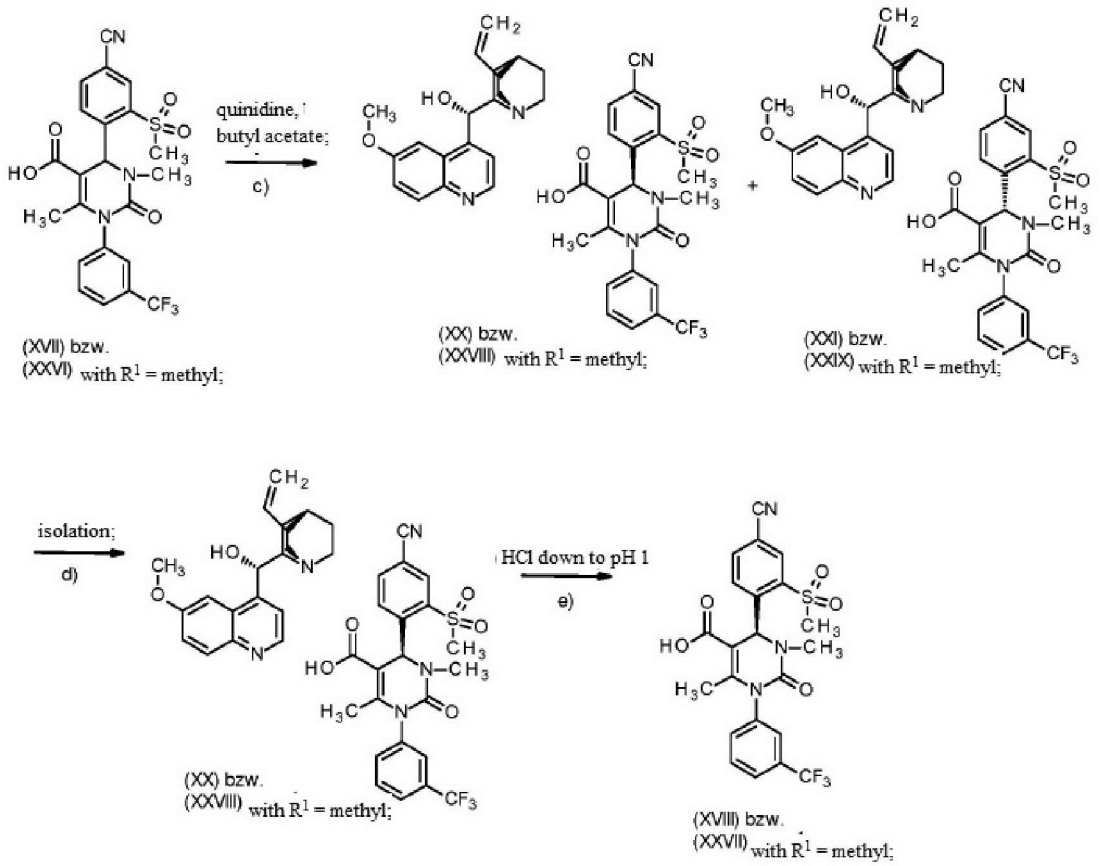
The following scheme 2 shows in detail the intermediate stages of method variant (A).

Scheme 2



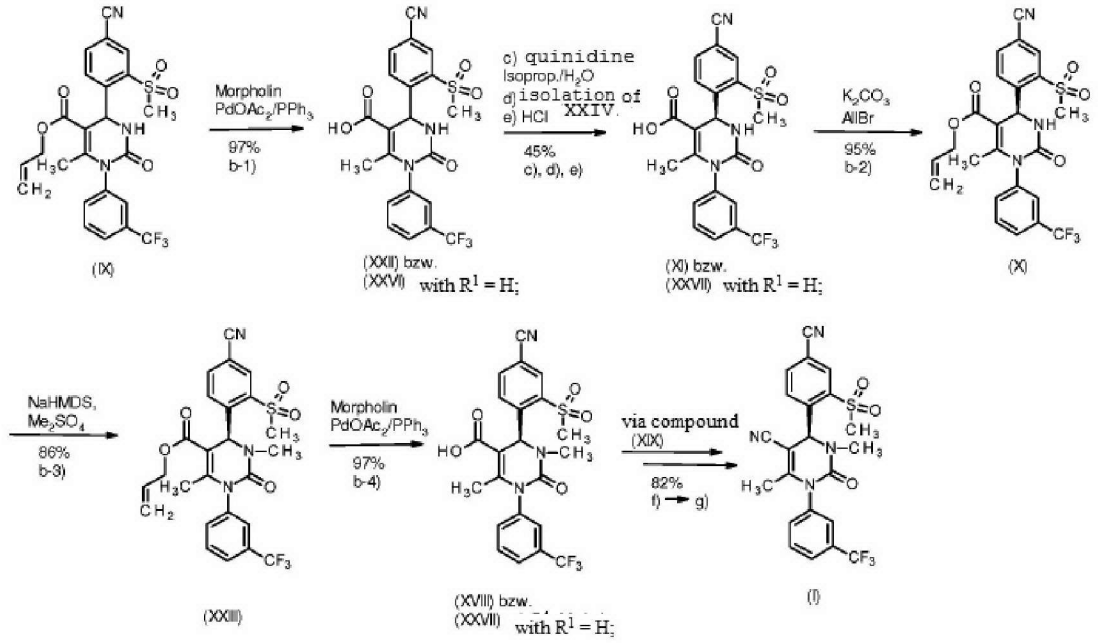
According to one embodiment of the present invention, the steps shown in the following scheme 3 are performed during the racemate splitting in the context of method variant (A).

Scheme 3



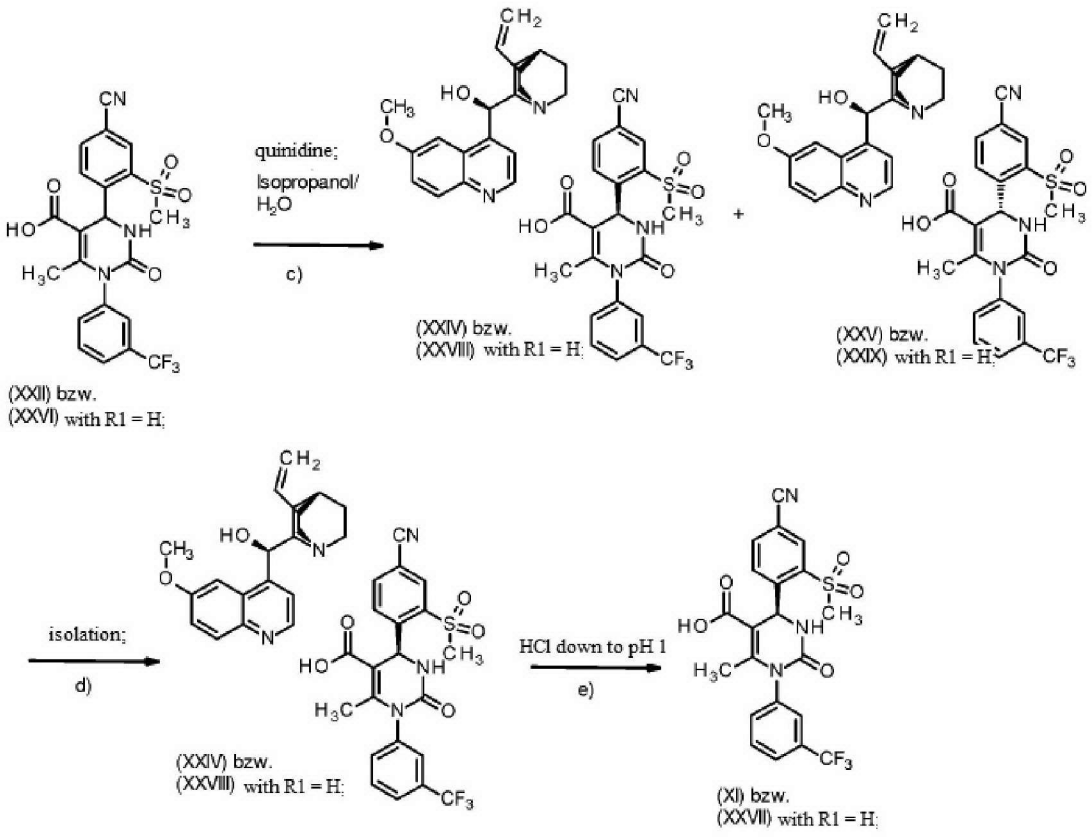
The following scheme 4 shows in detail the intermediate steps of method variant (B)

Scheme 4



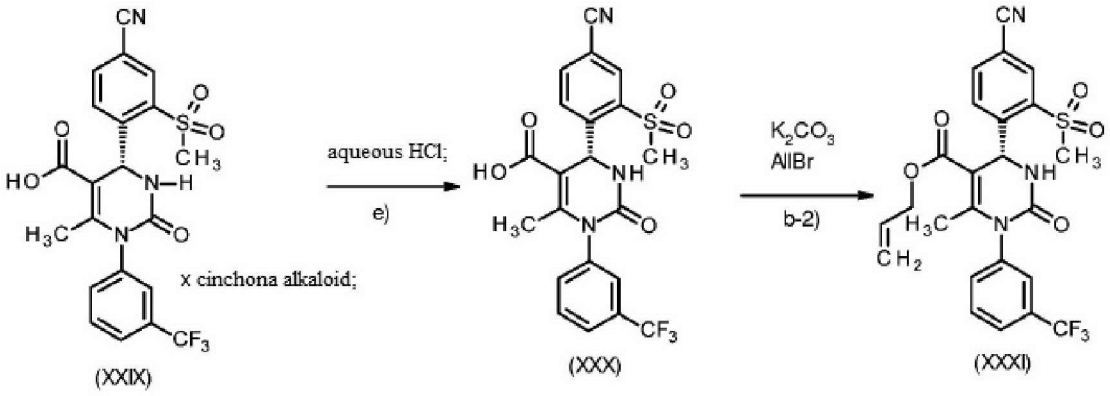
According to one embodiment of the present invention, the steps shown in the following scheme 5 are performed during the racemate splitting in the context of method variant (B).

Scheme 5



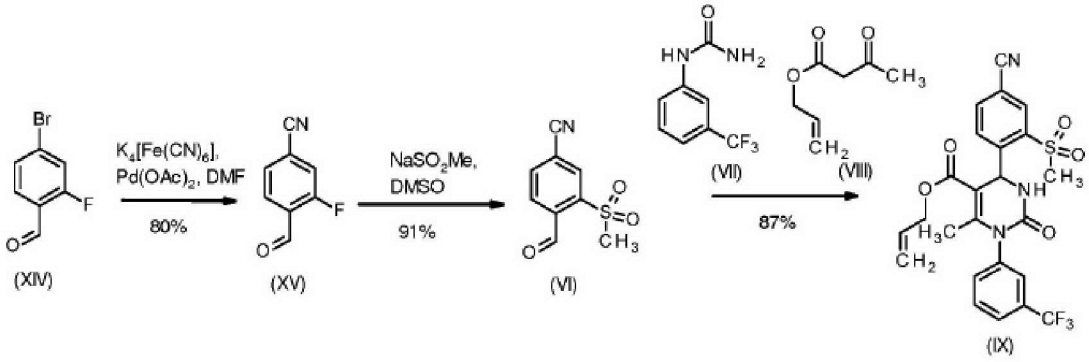
According to one embodiment of the present invention, the steps shown in the following scheme 6 are performed during the racemate splitting in the context of method variant (B), wherein the unwanted R-isomer is racemized and again put back into the process. This reaction sequence may be carried out once or several times, as desired.

Scheme 6



The reaction sequence for the synthesis of 4-bromo-2-fluorobenzaldehyde of formula (XIV) to form the compound of formula (IX) is represented in the following scheme 7:

Scheme 7



With the new synthesis according to the invention it is possible to prepare the target compound (I) in efficient manner. The method affords substantial advantages over the prior art, in terms of scalability and technical procedure. The overall yield is significantly higher than published data, and moreover a very high purity of the active substance is achieved. The new method enables the reproducible, economical preparation of the drystal form (A), not previously described in the prior art. With the method of the invention presented here, several kg of material have already been prepared successfully for clinical trials.

Abbreviations:

AllBr	allyl bromide
aq.	aqueous, aqueous solution
c	concentration
cat.	catalytically
CDI	N,N'-carbonyl diimidazole
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCI	direct chemical ionization (during MS)
dest.	distilled
DIEA	N,N-diisopropyl ethyl amine
DMAP	4-N,N-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
d. Th.	of theory (for yield)
ee	enantiomer excess
ent	enantiomer-pure, enantiomer
eq.	equivalent(s)
ESI	electrospray ionization (during MS)
Et	ethyl
GC-MS	gas chromatography-coupled mass spectrometry
h	hour(s)
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HPLC	high-pressure, high-performance liquid chromatography
konz.	concentrated
LC-MS	liquid chromatography-coupled mass spectrometry
Me	methyl
min	minute(s)
MS	mass spectrometry
MTBE	methyl-tert.-butyl ether
NaHMDS	sodium-bis(trimethylsilyl)amide
NMR	nuclear resonance spectrometry
Ph	phenyl
quant.	quantitative (for yield)
rac	racemic, racemate
RT	room temperature
Rt	retention time (in HPLC)
Schmp.	melting point
TFAA	trifluoracetic acid anhydride
THF	tetrahydrofuran
T3P	1-propane phosphonic acid anhydride
UV	ultraviolet spectrometry
v/v	volume to volume ratio (of a solution)

Sample embodiments:

Example 1

4-formyl-3-fluorobenzonitrile (XV)

400 g (1.97 mol) of 4-bromo-2-fluorobenzaldehyde (XIV) as a solution in 2.0 l of DMF were combined with 183 g (0.433 mol) of potassium hexacyanoferrate ($K_4[Fe(CN)_6]$) and 165.5 g (1.97 mol) of sodium hydrogen carbonate and 2.2 g (9.85 mmol) of palladium acetate was added. Stirring was done for 2.5 hours at 120° C. This was allowed to cool to 20° C and then 2.0 l of water was added to the batch. Extraction was done with 4.0 l of MtBE and the aqueous phase was again washed with 1.5 l of MtBE. The organic phases were combined and reacted with 2 l of water. The MtBE was for the most part distilled off at 30° C in slight vacuum. The product crystallized out. It was cooled down to 3° C and stirred for one hour at this temperature. The product was filtered off and again washed with water (twice 0.8 1). Drying was done at 40° C in vacuum. Yield: 241 g (80% of theory) of a beige-colored solid.

MS (EIpos): m/z = 150 [M+H]+

1H-NMR (400 MHz, DMSO-d6): δ = 7.87 (d, 1H), 7.01 (s, 1H), 8.10 (d, 1H), 10.25 (s, 1H).

Example 2

4-formyl-3-methylsulfonylbenzonitrile (VI)

200 g (1.34 mol) of 4-formyl-2-fluorobenzonitrile (XV) were provided as a solution in 0.8 l of DMSO and 192 g (1.88 mol) of the sodium salt of methane sulfinic acid was added. Stirring was done for 4 hours at 50° C. This was allowed to cool to 20° C. The reaction mixture was added to 8.0 l of water. The product crystallized out. Stirring was done for one hour at room temperature. The product was filtered off and washed with water (2 times, 0.1 l). Drying was done at 40° C in vacuum. Yield: 256 g (91% of theory) of a beige-colored solid.

MS (ESIpos): *m/z (%)* = 191.1 (15) $[M-18]^+$, 161.0 (100).

1H-NMR (400 MHz, DMSO-d6): δ = 3.57 (s, 3H), 8.10 (d, 1H), 8.38 (d, 1H), 8.45 (s, 1H), 10.62 (s, 1H).

Example 3

(rac)-4-[4-cyano-2-(methylsulfonyl)phenyl]-6-methyl-2-oxo-1-[3-trifluoromethyl)phcnyl]-1,2,3,4-tetra- hydropyrimidine-5-carboxylic acid, allyl ester (IX)

To phosphoric acid triethyl ester (124.3 g, 683 mmol) there was added diphosphorus pentoxide (64.6 g, 455 mmol) in 3 portions at 20° C and stirring was done for 3 h at 40° C. Dilution was then done with THF (115 ml), stirring for 30 min at 20° C, and there was added 4-formyl-3-(methylsulfonyl)benzonitrile (VI) (119 g, 569 mmol) and l-[3-(trifluoromethyl)phenyl]urea (VII) (116 g, 569 mmol). After this, allyl acetoacetate (VIII) (121 g, 852 mmol) was apportioned for 20 min, whereupon the temperature increased to around 60° C. The mixture was stirred for 4 h at 80° C. For the processing, water (115 ml) was added at 40° C and stirring was done for 30 min at 25° C. The product was filtered off and washed with water (280 ml). The residue was stirred with MtBE (280 ml) for 20 min, again filtered off and washed with MtBE (220 ml). Drying was done at 40° C in vacuum. Yield: 259 g (87% of theory) of a beige-colored solid.

MS (ESIpos): *m/z (%)* = 520.2 (100) $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.15 (s, 3H), 3.45 (s, 3H), 4.45 (m, 2H), 4.95 (d, 1H), 5.05 (d, 1H), 5.65 (m, 1H), 6.40 (d, 1H), 7.20 (d, 1H), 7.70 (m, 2H), 7.80 (m, 1H), 7.85 (br. s, 1H), 8.10 (br. d, 1H), 8.25 (d, 1H), 8.35 (s, 1H).

Example 4

(rac)-4-[4-cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1, 2,3,4- tetrahydropyrimidine-5-carboxylic acid, allyl ester (XVI)

(rac)-4-[4-cyano-2-(methylsulfonyl)phenyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2,3, 4-tetra- hydropyrimidine-5-carboxylic acid allyl ester (IX) (500 g, 0.962 mol) was prepared at 20° C in THF (2.51) and combined with a 1 M solution of sodium hexamethyldisilazide (NaHMDS) in THF (203 g; 1.107 mol). After 10 min of stirring, dimethylsulfate (243 g; 1.925 mol) was added and the mixture was stirred for 2 h at RT. The reaction mixture was added to a solution of 26% aqueous ammonia solution (315 g; 4.812 mol) in 3 l of water and rinsed with 250 ml of THF. Stirring was done overnight, then cooled to 5° C. The product was filtered off and washed with water (1 l). Drying was done at 40° C in vacuum.

Yield: 443 g (86% of theory) of a beige-colored solid.

MS (ESIpos): *m/z (%)* = 534.1 (100) $[M+H]^+$; MS (ESIneg): *m/z* (%) = 532.1 (100) $[M-H]^-$.

^{1}H -NMR (400 MHz, DMSO-d_6): δ = 2.05 (s, 3H), 2.79 (s, 3H), 3.51 (s, 3H), 4.55 (m, 2H), 5,03 (d, 1H), 5.12 (d, 1H), 5.72 (m, 1H), 6.80 (s, 1H), 7.70 (m, 2H), 7.80 (m, 1H), 7.95 (br. s, 1H), 8.15 (br. d, 1H), 8.25 (d, 1H), 8.52 (s, 1H).

Example 5

(rac)-4-[4-cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo1l-[3-(trifluoromethyl)phenyl]-1, 2,3,4- tetrahydropyrimidine-5-carboxylic acid THF-solvate (XXVI)

(rac)-4-[4-cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1, 2,3,4- tetrahydropyrimidine-5-carboxylic acid, allyl ester (XVI) (485.6 g, 0.910 mol) was prepared at 20° C in THF (2.275 1) and combined with morpholine (118.9 g; 1.365 mol). Nitrogen was conducted into the reaction mixture for 1 h. Then heating was done to 50° C, the mixture was combined with palladium-(II)-acetate (511 mg; 2.275 mmol) and triphenylphosphine (2388 mg; 9.102 mmol) and stirred for 2 h at 50° C. After cooling, the reaction mixture was placed in 4.5 l of water. 2 N hydrochloric acid was used to adjust to pH = 2 and the resulting crystallizate was stirred overnight. The product was filtered off and washed with water (1.8 1). Drying was done at 40° C in vacuum. Yield: 504 g (98% of theory, referred to the mono-THF solvate) of a beige-colored solid.

MS (ESIpos): *m/z (%)* = 494.0 (100) $[M+H]^+$.

^{1}H -NMR (400 MHz, DMSO-d_6): δ = 1.76 (m, 4 H; THF), 2.08 (s, 3H), 2.77 (s, 3H), 3.48 (s, 3H), 3.60 (m, 4H, THF), 6.72 (s, 1H), 7.75 (m, 2H), 7.82 (m, 1H), 7.92 (br. s, 1H), 8.11 (br. d, 1H), 8.27 (d, 1H), 8.46 (s, 1H), 12.75 (br. s, 1H).

Example 6

(S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2 ,3,4- tetrahydropyrimidine-5-carboxylic acid, quinidine salt (XXVIII)

(rac)-4-[4-cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1, 2,3,4- tetrahydropyrimidine-5-carboxylic acid THF-solvate (XXVI) (555 g, 0.910 mol) was prepared at 20° C in butyl acetate (2.22 1) and combined with (+)-quinidine (334.3 g; 1.03 mol). Heating was then done to 50° C and stirring for 1 h at 50° C. After cooling to 5° C, filtering was done and the filter cake was stirred with butyl acetate (1.2 1), filtered again, and washed with butyl acetate (0.7 1). Drying was done at 40° C in vacuum. Yield: 361 g (45% of theory) of a cream-colored solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.58 (m, 2H), 1.79 (m, 1H), 2.04 (m, 1H), 2.07 (s, 3H), 2.33 (m, 1H), 2.77 (s, 3H), 2.79 (m, 1H), 2.90 (m, 2H), 3.21 (m, 1H), 3,33 (m, 2H), 3.51 (s, 3H), 3.90 (s, 3H), 5.11 (d, 1H), 5.14 (d, 1H), 5.53 (br. s, 1H), 6.09 (ddd, 1H), 6.72 (s, 1H), 7.75 (m, 2H), 7.82 (m, 1H), 7.92 (br. s, 1H), 8.11 (br. d, 1H), 8.27 (d, 1H), 8.46 (s, 1H), 12.75 (br. s, 1H).

Example 7

(S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2,3,4- tetrahydropyrimidine-5-carboxylic acid (XXVII)

The quinidine salt of (S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (XXVIII) (360 g, 0.405 mol) was suspended at 60° C in a mixture of water (3.9 l) and isopropanol (0.4 l) and adjusted with 2 N of hydrochloric acid to pH = 1 and stirred for 1 h at 60° C. After cooling to 20° C, filtering was done, washing with water (0.6 l) and the filter cake was stirred with water (1.2 l), filtered again, and washed with water (1.2 l). Drying was done at 40° C in vacuum. Yield: 196 g (92% of theory) of a cream-colored solid.

MS (ESIpos): ***m/z (%)*** = 494.0 (100) $[M+H]^+$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.08 (s, 3H), 2.77 (s, 3H), 3.48 (s, 3H), 6.72 (s, 1H), 7.75 (m, 2H), 7.82 (m, 1H), 7.92 (br. s, 1H), 8.11 (br. d, 1H), 8.27 (d, 1H), 8.46 (s, 1H), 12.75 (br. s, 1H).

Example 8

(S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2,3,4- tetrahydropyrimidine-5-carbamide (XIX)

(S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo-l-[3-(trifluormethyl)phenyl]-1,2,3,4- tetrahydropyrimidine-5-carboxylic acid (XXVII) (390.5 g, 0.791 mol) was dissolved in THF (3.9 l). To remove residual traces of water, 2 l of THF was distilled off at 80° C bath temperature. This was combined with 1,1-carbonyldiimidazole (192.5 g, 1.187 mol) at 0° C and stirred for 1 h at 20° C and for 2 h at 50° C. After this, a 26% ammonia solution (518 g, 7.91 mol) was apportioned at 25° C and stirring was done for 16 h. The reaction mixture was heated to 50° C for 2 h, and excess ammonia was gassed out. After cooling, the reaction mixture was slowly added to 7.8 l of water and the resulting crystallizate was stirred overnight. The product was filtered off and washed with water (2.4 l). Drying was done at 40° C in vacuum. Yield: 361 g (92% of theory) of a cream-colored solid.

MS (ESIpos): *m/z (%)* = 493.0 (100) $[M+H]^+$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.73 (s, 3H), 2.73 (s, 3H), 3.45 (s, 3H), 6.55 (s, 1H), 7.34 (br. s, 1H), 7.48 (br. s, 1H), 7.73 (m, 2H), 7.80 (m, 2H), 8.11 (d, 1H), 8.43 (d, 1H), 8.47 (s, 1H).

Example 9

(S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2,3,4- tetrahydropyrimidine-5-carbonitrile (I)

(S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2,3,4- tetrahydropyrimidine-5-carbamide (XIX) (400 g, 0.812 mol) was dissolved in ethyl acetate (1.6 l). This was combined with N-ethyldiisopropylamine (262.4 g, 2.031 mol) at 20° C and stirred for 15 min at 20° C. After this, a 50% solution of 1-propane phosphonic acid anhydride in ethyl acetate (1.137 kg, 1.79 mol) was apportioned at 2° C, 26%, reflux heated, and stirred for 2 h. This was allowed to cool to 20° C and 3.4 l of water was added to the batch. After phase separation, the organic phase was washed with saturated sodium hydrogen carbonate solution (1.2 l). The organic phase was heated to 60° C and distilled off in a slight vacuum while at the same time adding ethanol (toluene denatured). The product crystallizes out. After the crystallization was finished, reflux heating was done and stirring for 4 h. Cooling was done to 20° C and stirring at this temperature for one hour. The product was filtered off and washed once with water (1.2 1) and once with ethanol (toluene denatured) (0.4 1). Drying was done at 50° C in vacuum. Yield: 344 g (89% of theory) white crystals of the stable crystal form (A) with a melting point of 232° C, purity: 99.4 %, content: 99.3%

MS (ESIpos): *m/z* (%) = 475.1 (100) $[M+H]^+$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1,81 (s, 3H), 2.70 (s, 3H), 3.52 (s, 3H), 6.48 (s, 1H), 7.65 - 8.40 (m, 6H), 8.46 (s, 1H).

Example 10

(rac)-4-[4-cyano-2-(methylsulfonyl)phenyl]-6-methyl-2-oxo-1-[3-trifluoromethyl)phcnyl]-1,2,3,4-tetra- hydropyrimidine-5-carboxylic acid (XXII)

(rac)-4-[4-cyano-2-(methylsulfonyl)phenyl]-6-methyl-2-oxo-1-[3-trifluoromethyl)phcnyl]-1,2,3,4-tetra- hydropyrimidine-5-carboxylic acid, allyl ester (IX) (420 g, 0.808 mol) was prepared at 20° C in THF (2.1 l) and combined with morpholine (105.6 g; 1.213 mol). Nitrogen was conducted into the reaction mixture for 1 h. After this, it was combined with bis(triphenylphophine) palladium-(II)-chloride (284 mg; 0.404 mmol) and triphenylphosphine (424 mg; 1.617 mmol) and the mixture was stirred for 2 h at RT. It was then combined once again with bis(triphenylphophine) palladium-(II)-chloride (284 mg; 0.404 mmol) and triphenylphosphine (424 mg; 1.617 mmol) and the mixture was stirred for 2 h at RT. The reaction mixture was added to 4 l of water. It was adjusted to pH=2 with 2 N hydrochloric acid and the resulting crystallizate was stirred overnight. The product was filtered off and washed with water (1.71). Drying was done at 40° C in vacuum.

Yield: 575 g (97% of theory) of a beige-colored solid.

MS (ESIpos): ***m/z (%)*** = 480.0 (100) $[M+H]^+$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.12 (s, 3H), 3.48 (s, 3H), 6.32 (s, 1H), 7.12 (s, 1H), 7.72 (m, 2H), 7.80 (m, 1H), 7.88 (br. s, 1H), 8.13 (br. d, 1H), 8.27 (d, 1H), 8.37 (s, 1H), 12.62 (br. s, 1H).

Example 11

(S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-6-methyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2,3,4-tetra- hydropyrimidine-5-carboxylic acid, quinine salt (XXIV)

(rac)-4-[4-cyano-2-(methylsulfonyl)phenyl]-6-methyl-2-oxo-1-[3-trifluoromethyl)phcnyl]-1,2,3,4-tetra- hydropyrimidine-5-carboxylic acid (XXII) (563.7 g, 1.176 mol) was prepared at 20° C in a mixture of isopropanol/water (9:1; 4.2 l) and combined with (-)-quinine (381.4 g; 1.176 mol). After this, it was heated to 50° C and stirred for 1 h at 50° C. After cooling to 5° C it was filtered off and the filter cake was washed with a mixture of isopropanol/water (9 : 1; 1.2 l). Drying was done at 40° C in vacuum.

Yield: 432 g (46% of theory) of a cream-colored solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.58 (m, 2H), 1.79 (m, 1H), 2.04 (m, 1H), 2.10 (s, 3H), 2.33 (m, 1H), 2.79 (m, 1H), 2.90 (m, 2H), 3.21 (m, 1H), 3.33 (m, 2H), 3.46 (s, 3H), 3.90 (s, 3H), 5.11 (d, 1H), 5.14 (d, 1H), 5.53 (br. s, 1H), 6.09 (m, 1H), 6.33 (s, 1H), 7.10 (s, 1H), 7.73 (m, 2H), 7.82 (m, 1H), 7.90 (br. s, 1H), 8.11 (br. d, 1H), 8.27 (d, 1H), 8.44 (s, 1H), 12.70 (br. s, 1H).

Example 12

(S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-6-methyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2,3,4-tetra- hydropyrimidine-5-carboxylic acid (XI)

(S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-6-methyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2,3,4-tetra- hydropyrimidine-5-carboxylic acid, quinine salt (XXIV) (430 g, 0.535 mol) was suspended at 60° C in a mixture of water (4.2 l) and isopropanol (0.4 l) and adjusted to pH=1 with 2 N hydrochloric acid and stirred for 1 h at 60° C. After cooling to 20° C, filtering was done and the filter cake washed three times with water (0.6 l). Drying was done at 40° C in vacuum.

Yield: 251 g (98% of theory) of a cream-colored solid.

MS (ESIpos): *m/z (%)* = 480.0 (100) $[M+H]^+$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.12 (s, 3H), 3.48 (s, 3H), 6.32 (s, 1H), 7,12 (s, 1H), 7.72 (m, 2H), 7.80 (m, 1H), 7.88 (br. s, 1H), 8.13 (br. d, 1H), 8.27 (d, 1H), 8.37 (s, 1H), 12.62 (br. s, 1H).

Example 13

(S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-6-methyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2,3,4-t

etra- hydropyrimidine-5-carboxylic acid, allyl ester (X)

(S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-6-methyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2,3,4-tetra- hydropyrimidine-5-carboxylic acid (XI) (250 g, 0.521 mol) was prepared at 20° C in acetone (1.5 l) and combined with potassium carbonate (72 g; 0.521 mol). After 10 min of stirring, allyl bromide was added (79 g; 652 mol) and the mixture was stirred under reflux for 6 h. After cooling, 1.4 l of water was added to the reaction mixture and stirring was done for 60 min. The product was filtered off, washed twice with water (0.6 l) and twice with MtBE (0.6 l). Drying was done at 40° C in vacuum.

Yield: 258 g (95% of theory) of a cream-colored solid.

MS (ESIpos): ***m/z (%)*** = 534.1 (100) $[M+H]^+$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.05 (s, 3H), 2.79 (s, 3H), 3.51 (s, 3H), 4.55 (m, 2H), 5.03 (d, 1H), 5.12 (d, 1H), 5.72 (m, 1H), 6.80 (s, 1H), 7.70 (m, 2H), 7.80 (m, 1H), 7.95 (br. s, 1H), 8.15 (br. d, 1H), 8.25 (d, 1H), 8.52 (s, 1H).

Example 14

(S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-3,6-dimethyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2,3,4- tetrahydropyrimidine-5-carboxylic acid, allyl ester (XXIII)

(S)-4-[4-cyano-2-(methylsulfonyl)phenyl]-6-methyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2,3,4-tetra- hydropyrimidine-5-carboxylic acid, allyl ester (X) (250 g, 0.481 mol) was prepared at 20° C in THF (1.25 l) and combined with a 1 M solution of sodium hexamethyldisilazide (NaHMDS) in THF (102 g; 0.554 mol). After 10 min of stirring, dimethylsulfate was added (122 g; 0.964 mol) and the mixture was stirred for 2 h at RT. The reaction mixture was added to a solution of 26% aqueous ammonia solution (178 g; 2.4 mol) in 1.5 l of water and rinsed with 200 ml of THF. Stirring was done overnight and cooling to 5° C. The product was filtered off and washed with water (0.6 l). Drying was done at 40° C in vacuum.

Yield: 230 g (89% of theory) of a beige-colored solid.

MS (ESIpos): *m/z (%)* = 534.1 (100) $[M+H]^+$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.05 (s, 3H), 2.79 (s, 3H), 3.51 (s, 3H), 4.55 (m, 2H), 5.03 (d, 1H), 5.12 (d, 1H), 5.72 (m, 1H), 6.80 (s, 1H), 7.70 (m, 2H), 7.80 (m, 1H), 7.95 (br. s, 1H), 8.15 (br. d, 1H), 8.25 (d, 1H), 8.52 (s, 1H).

Example 15

(R)-4-[4-cyano-2-(methylsulfonyl)phenyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetra- hydropyrimidine-5-carboxylic acid (XXX)

The combined mother liquors and washing liquors from example 11, containing the quinine salt of (R)-4-[4-cyano-2-(methylsulfonyl)phenyl]-6-methyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (XXV) were concentrated down to a crystal paste. This was taken up in water (5.0 l), adjusted with 2 N hydrochloric acid to pH = 1 and stirred for 1 h at 60° C. After cooling to 20° C, filtering was done and the filter cake was washed three times with water (1.0 l). Drying was done at 40° C in vacuum.

Yield: 293 g (52% of theory, referred to the input of XXII) of a cream-colored solid. Ratio of R-enantiomer to S-enantiomer: 88 : 12.

MS (ESIpos): *m/z (%)* = 480.0 (100) $[M+H]^+$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.12 (s, 3H), 3.48 (s, 3H), 6.32 (s, 1H), 7.12 (s, 1H), 7.72 (m, 2H), 7.80 (m, 1H), 7.88 (br. s, 1H), 8.13 (br. d, 1H), 8.27 (d, 1H), 8.37 (s, 1H), 12.62 (br. s, 1H).

Example 16

(R)-4-[4-cyano-2-(methylsulfonyl)phenyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetra- hydropyrimidine-5-carboxylic acid, allyl ester (XXXI)

(R)-4-[4-cyano-2-(methylsulfonyl)phenyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetra- hydropyrimidine-5-carboxylic acid (XXX) (292 g, 0.609 mol) was prepared at 20° C in acetone (1.6 l) and combined with potassium carbonate (84 g; 0.609 mol). After 10 min of stirring, allyl bromide was added (92 g; 761 mol) and the mixture was stirred under reflux for 6 h. After cooling, 1.5 l of water was added to the reaction mixture and stirring was done for 60 min. The product is filtered off, washed twice with water (0.6 l) and twice with MtBE (0.6 l). Drying is done at 40° C in vacuum.

Yield: 301 g (95% of theory) of a cream-colored solid.

MS (ESIpos): *m/z (%)* = 534.1 (100) $[M+H]^+$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.05 (s, 3H), 2.79 (s, 3H), 3.51 (s, 3H), 4.55 (m, 2H), 5.03 (d, 1H), 5.12 (d, 1H), 5.72 (m, 1H), 6.80 (s, 1H), 7.70 (m, 2H), 7.80 (m, 1H), 7.95 (br. s, 1H), 8.15 (br. d, 1H), 8.25 (d, 1H), 8.52 (s, 1H).

Example 17

Isomerization of (R)-4-[4-cyano-2-(methylsulfonyl)phenyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4

-tetra- hydropyrimidine-5-carboxylic acid, allyl ester (XXXI) into (rac)-4-[4-cyano-2-(methylsulfonyl)phenyl]-6-methyl-2-oxo-1-[3-trifluoromethyl)phcnyl]-1,2,3,4-tetra- hydropyrimidine-5-carboxylic acid, allyl ester (IX)

(R)-4-[4-cyano-2-(methylsulfonyl)phenyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetra- hydropyrimidine-5-carboxylic acid, allyl ester (XXXI) (292 g, 0.609 mol) was prepared at 20° C in acetone (1.6 l) and combined with potassium carbonate (84 g; 0.609 mol). After 10 min of stirring, allyl bromide was added (92 g; 761 mol) and the mixture was stirred for 6 h under reflux. After cooling, 1.5 l of water was added to the reaction mixture and stirring was done for 60 min. The product was filtered off, washed twice with water (0.6 l) and twice iwth MtBE (0.6 l). Drying was done at 40° C in vacuum.

Yield: 301 g (95% of theory) of a cream-colored solid.

MS (ESIpos): *m/z (%)* = 534.1 (100) $[M+H]^+$.

*H-NMR (400 MHz, DMSO-d_6): δ = 2.05 (s, 3H), 2.79 (s, 3H), 3.51 (s, 3H), 4.55 (m, 2H), 5.03 (d, 1H), 5.12 (d, 1H), 5.72 (m, 1H), 6.80 (s, 1H), 7.70 (m, 2H), 7.80 (m, 1H), 7.95 (br. s, 1H), 8.15 (br. d, 1H), 8.25 (d, 1H), 8.52 (s, 1H).

Example 18

Physicochemical characterization of compound of formula (I) in crystal form (A)

Parameters of the X-ray diffraction measurement for the compound of formula (I) in crystal form (A):

Device: Transmission diffractometer PANalytical X'Pert PRO with PIXcel counter (multichannel)

Scan axis	2Theta-Omega
Start position [°2Th.]	2.0000
End position [°2Th.]	37.9900
Type of divergence diaphragm	fixed
Size of divergence diaphragm [°]	1.0000
Temperature of measurement [°C]	25
Anode material	Cu
K-Alpha 1 [Ä]	1.54060
Generator setting	40 mA, 40 kV
Diffractometer type	Transmission diffractometer
Goniometer radius [mm]	240.00
Focus-Div. diaphragm distance [mm]	91.00
Primary beam monochromator	focusing X-ray mirror
Sample rotation	yes

Table 1: Peak maxima [2 Theta] of the X-ray diffraction pattern of the compound (I) in crystal form (A)

Peak maximum [2 Theta] Compound (I), crystal form (A)		
7.5	20.0	28.0
10.0	20.8	28.1
11.5	20.9	28.3
11.9	21.8	28.7
12.2	22.5	29.2
12.4	22.9	29.6
13.2	23.1	30.3
14.7	23.4	30.5
15.1	23.5	30.8
15.8	24.0	31.7
16.0	24.7	32.2
16.5	25.1	32.4
17.8	25.3	33.4
18.5	25.6	33.8
18.7	26.5	34.2
19.4	27.1	34.5
19.8	27.4	

Measurement conditions for the Raman spectroscopy for measurement of the compound of formula (I) in crystal form (A):

Device	Bruker Raman RFS 100/S
Number of Scans	64
Resolution	2 – 4 cm^{-1}
Laser Power	50 mW
Laser Wavelength	1064 mm

Table 2: Band maxima of the Raman spectrum of compound (I) in crystal form (A)

Band maximum [cm-1] Modification I		
3087	1312	589
3075	1299	580
3067	1238	535
3044	1195	490
3019	1169	471
2993	1154	457
2969	1142	443
2928	1091	435
2918	1077	403
2236	1066	365
2216	1056	346
2184	1015	329
1646	1004	298
1605	994	280
1443	910	255
1435	873	240
1418	795	217
1411	767	190
1395	761	171
1387	746	149
1361	683	128
1354	674	111
1331	645	

Description of figures:

Figure 1: X-ray diffraction pattern of compound of formula **(I)** in crystal form (A)

Figure 2: Raman spectrum of compound of formula **(I)** in crystal form (A)

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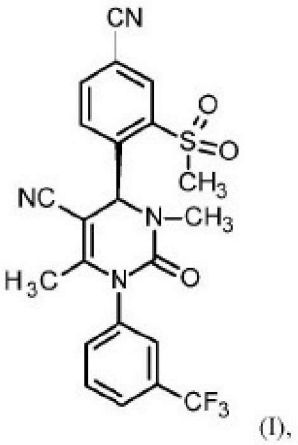
Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

The claims defining the invention are as follows:

1. A compound of formula (I)



(I),

in the crystal form (A), wherein the X-ray diffraction pattern of the compound shows peak maxima of the 2 theta angle at 7.5, 12.4, 15.1, 18.5, 18.7, 22.9, 24.7 and 26.5.

2. The compound of formula (I) in the crystal form (A) according to claim 1, wherein the Raman spectrum of the compound shows band maxima at 3075, 2928, 2918, 2236, 2216, 1646, 1605, 1195 and 1004 cm^{-1}.

3. A method for producing the compound of formula (I) in the crystal form (A) according to claim 1 or 2, wherein a compound of formula (I), present in one or more crystal forms or as a solvate, is crystallized out in an alcohol, after which the resulting crystal paste is heated to about 50-80°C and stirred for another 2-5 h at this temperature.

4. A method according to claim 3, wherein the alcohol is ethanol.

5. A method for the treatment and/or prevention of a disease of the lungs and/or the cardiovascular system, or for promoting wound healing, the method comprising administering to a subject in need thereof a compound as claimed in claim 1 or 2, wherein the disease of the lungs and/or the cardiovascular system or the wound is associated with or modulated by HNE activity.

6. The method according to claim 5, wherein the wound is a chronic wound.

7. A method according to claim 6, wherein the disease of the lungs and/or the cardiovascular system is selected from the group consisting of pulmonary arterial hypertonia (PAH) and other forms of pulmonary hypertonia (PH), chronic obstructive lung diseases (COPD), acute lung injury (ALI), acute respiratory disease syndrome (ARDS), pulmonary emphysema, alpha l-antitrypsin deficiency (AATD), cystic fibrosis (CF) and bronchiectasis.

8. A pharmaceutical containing the compound of formula (I) in the crystal form (A) as claimed in any claim 1 or 2 in more than 90 wt. percent in relation to the total amount of the contained compound of formula (I).

9. Use of a compound of formula (I) in the crystal form (A) as claimed in claim 1 or 2 in the manufacture of a medicament for the treatment of a disease of the lungs and/or the cardiovascular system, or for promoting wound healing, wherein the disease of the lungs and/or the cardiovascular system or the wound is associated with or modulated by HNE activity.

10. Use according to claim 9, wherein the wound is a chronic wound.

11. Use according to claim 9, wherein the disease of the lungs and/or the cardiovascular system is selected from the group consisting of pulmonary arterial hypertonia (PAH) and other forms of pulmonary hypertonia (PH), chronic obstructive lung diseases (COPD), acute lung injury (ALI), acute respiratory disease syndrome (ARDS), pulmonary emphysema, alpha l-antitrypsin deficiency (AATD), cystic fibrosis (CF)and bronchiectasis.

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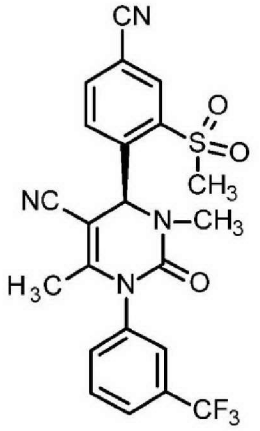
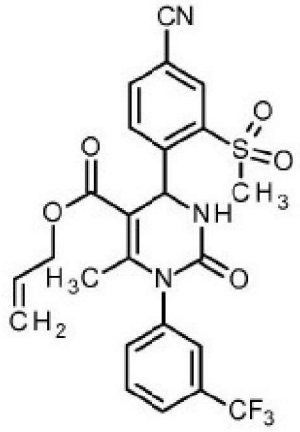
12. A method for producing a compound of formula (I) in the crystal form (A) according to



(I),

claim 1 or 2,

wherein one reacts a compound of formula (IX):



(IX)

a-1) in the presence of a methylation agent and a base to form a compound of formula (XVI)

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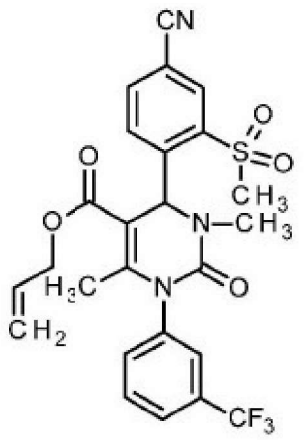
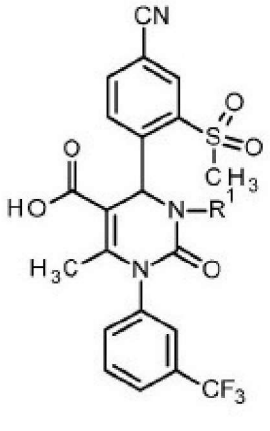


(XVI)

;

then

a-2) reacts a compound of formula (XVI) in the presence of a palladium catalyst and a secondary amine base to form a compound of formula (XXVI)



(XXVI),

in which R^1 stands for methyl,

or

b-1) reacts a compound of formula (IX) in the presence of a palladium catalyst and a secondary amine base to form a compound of formula (XXVI), in which R^1 stands for hydrogen;

then

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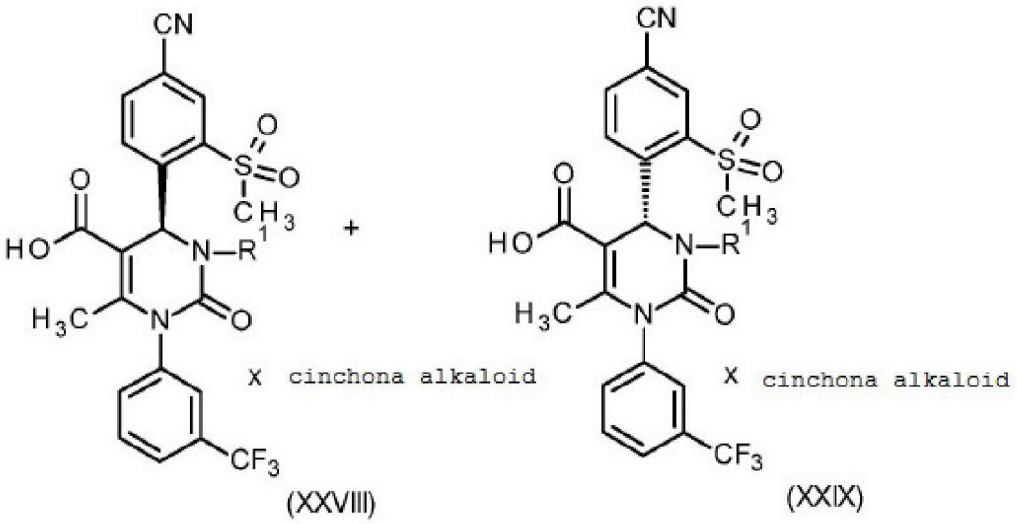
c) reacts a compound of formula (XXVI), in which R^1 stands for hydrogen or methyl, in the presence of a cinchona alkaloid and a solvent to form a compounds of formula (XXVIII) and/or (XXIX)

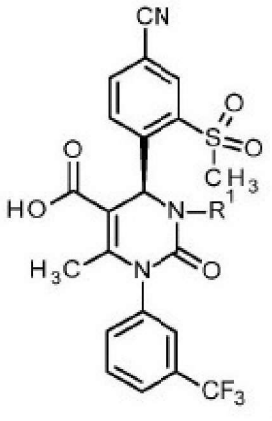


(XXVIII) (XXIX)

in which R^1 in formula (XXVIII) and in formula (XXIX) stands for hydrogen or in which R^1 in formula (XXVIII) and in formula (XXIX) stands for methyl; then

d) isolates a compound of formula (XXVIII); then

e) reacts a compound of formula (XXVIII) in the presence of a strong acid to form a compound of formula (XXVII)



(XXVII)

in which R^1 stands for hydrogen or methyl; then

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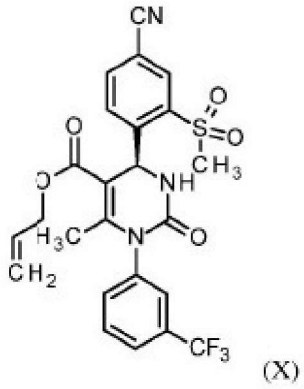
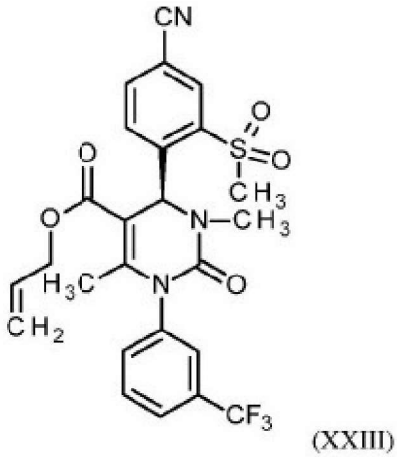
b-2) if R^1 in the compound of formula (XXVII) stands for hydrogen, one reacts a compound of formula (XXVII) in the presence of an allyl halide or sulfonate and a base to form a compound of formula (X)



(X)

then

b-3) reacts a compound of formula (X) in the presence of a methylation agent and a base to form a compound of formula (XXIII)



(XXIII)

then

b-4) reacts a compound of formula (XXIII) in the presence of a palladium catalyst and a secondary amine base to form a compound of formula (XXVII)

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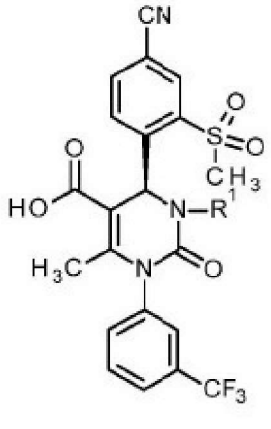
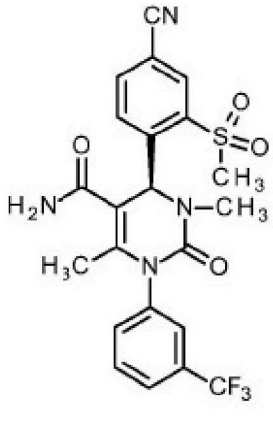


(XXVII)

in which R^1 stands for methyl; then

f) reacts a compound of formula (XXVII), in which R^1 stands for methyl, in the presence of an activation reagent, to form a compound of formula (XIX)

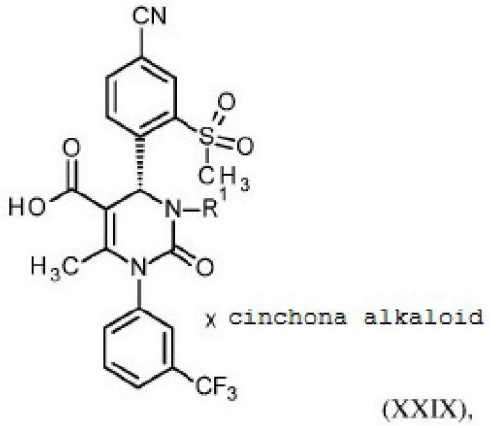


(XIX)

then

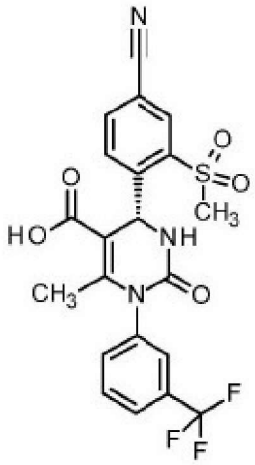
g) reacts a compound of formula (XIX) in the presence of a dehydrating agent to form a compound of formula (I).

13. A method according to claim 12, wherein after reaction step c), one isolates a compound of formula (XXIX)



(XXIX),

in which R^1 stands for hydrogen, reacts this according to step e) in the presence of a strong acid to form a compound of formula (XXX)



(XXX)

then reacts a compound of formula (XXX) according to reaction step b-2) in the presence of an allyl halide or sulfonate and a base to form a compound of formula (XXXI)

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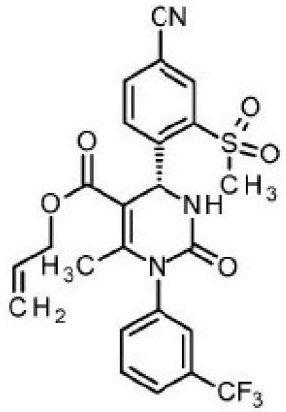
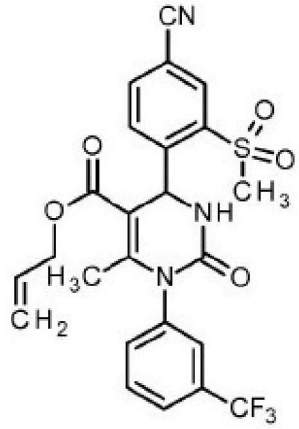


(XXXI)

then

h) reacts a compound of formula (XXXI) in the presence of a strong, non-nucleophilic base in a solvent and under simultaneous heating to form the racemate of formula (IX)



(IX)

then reacts a compound of formula (IX) according to the above-described reaction steps b-1), c), d), e), b-2), b-3), b-4), f) and g) to form a compound of formula (I).

14. A method according to claim 12 or 13, wherein the reaction steps of isolation of a compound of formula (XXIX), its reaction according to reaction step e) in the presence of a strong acid to form a compound of formula (XXX), the subsequent reaction of a compound of formula (XXX) according to reaction step b-2) in the presence of an allyl halide or sulfonate and a base to form a compound of formula (XXXI), and then the performance of reaction steps h), b-1), c), d), e), b-2), b-3), b-4), f) and g) are repeated one or more times.

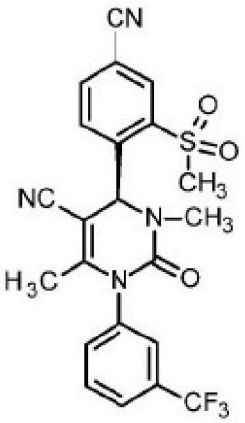
15. A method according to any one of claims 12 to 14, wherein:
R^1 in formulas (XXVI), (XXVII), (XXVIII) and (XXIX) stands for methyl and the method comprises the reaction steps a-1), a-2), c), d), e), f) and g); or

R^1 in formulas (XXVI), (XXVII), (XXVIII) and (XXIX) stands for hydrogen and the method comprises the reaction steps b-1), c), d), e), b-2), b-3), b-4), f) and g).

16. A method according to any one of claims 12 to 15, wherein one crystallizes out the compound of formula (I) from the organic phase from reaction step g) in an alcohol, and then heats the resulting crystal paste to about 50-80°C and stirs this for another 2-5 h at this temperature.

17. A method according to claim 16, wherein the alcohol is ethanol.

18. A compound of formula (I):



(I),

in the crystal form (A) produced by a method according to any one of claims 3, 4 or 12 to 17.

Fig. 1: X-ray diffraction pattern of the compound of formula (I) in crystal form (A)

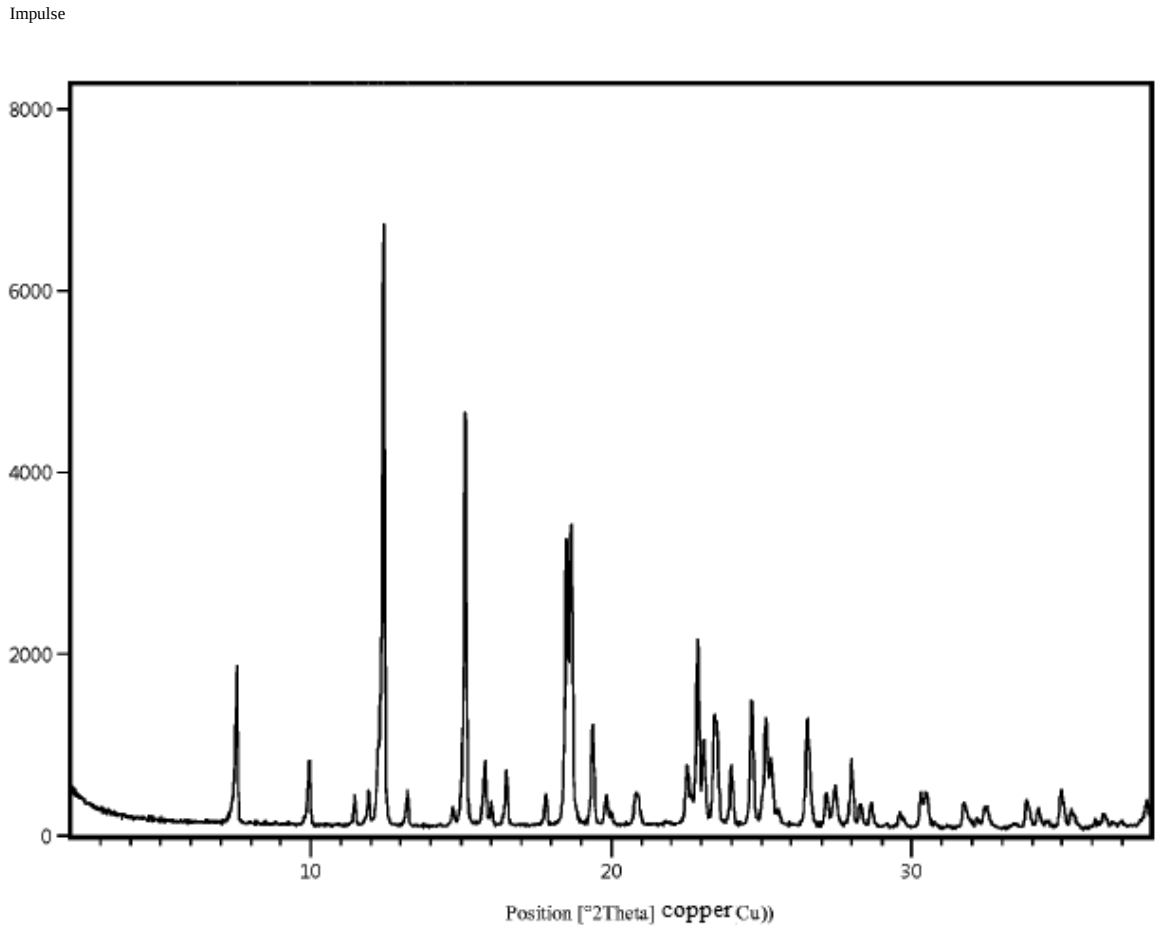


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Fig. 2: Raman spectrum of the compound of formula (I) in crystal form (A)