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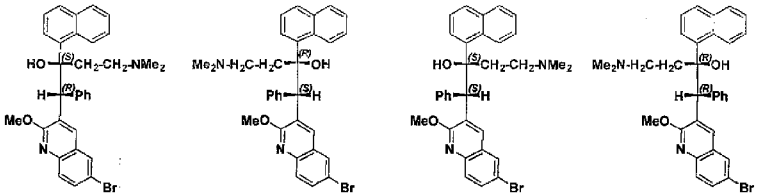
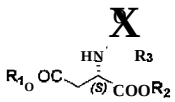
(54) Title: NEW POSSIBILITIES OF CHIRAL RESOLUTION OF BEDAQUILINE



Ia **lb** **Ila** **lib**

I-rac = **Ia:Ib** **Il-rac** = **na:IIb**



(Ilia)

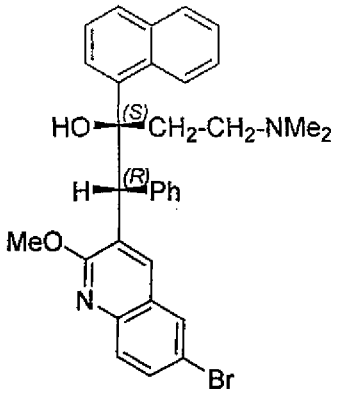
(57) Abstract: A method of performing isolation and purification of bedaquiline (la) from a mixture of stereoisomers of 6-bromo-2-methoxy-quinolin-3 -yl)-4-dimethylamino-2-(1 -naphthyl)- 1 - phenyl-butan-2-ol identified as I-rac, being a mixture of the stereoi - somers of formulae la, lb, and Il-rac, being a mixture of the stereoisomers of formulae Ila, lib, with any ratio of individual constitu - ents of the mixture, wherein said mixture is dissolved together with derivatives of N-benzoyl-L-aspartic acid Ilia, wherein R_i and R_2 independently stand for hydrogen, a primary, secondary or tertiary C_1-C_4 alkyl, a primary or secondary amide, wherein always at least one of the R_i or R_2 symbols stands for hydrogen; and R_3 is a C_{5}-C_{12} aryl, C_{5}-C_{12} heteroaryl with one or more heteroatoms, which may be further substituted by a halogen, amino group, carbonyl, or carboxyl, or its functional derivative, preferably phenyl, naphthyl, tolyl, or mesytyl, and the resulting salt is recrystallized from a suitable solvent or mixture, which can be ketones, esters, ethers, amides, nitriles or organic acids, alcohols, aliphatic and aromatic hydrocarbons, chlorinated hydrocarbons, water and/or their mixtures.

WO 2016/116076 A1

New possibilities of chiral resolution of bcdaquiline

Technical Field

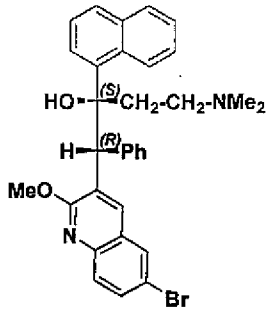
The invention relates to an isolation method of the solid form of (li?,2*S*)-l-(6-bromo-2-methoxyquinolin-3-yl)-4-dimethylamino-2-(l -naphthyl)-! -phenyl-butan-2-ol of formula **(la)**



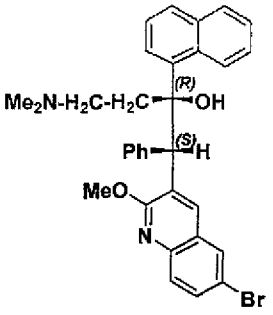
BEDAQUILIN

(Ia)

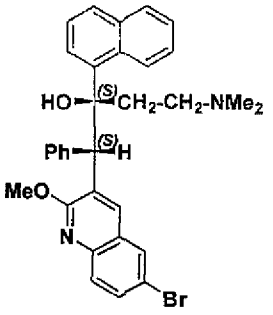
known as bedaquiline. Bedaquiline is isolated from a mixture of the corresponding stereoisomers **(la** - (li?,25)-(6-bromo-2-methoxy-qiunolin-3-yl)-4-dimethylamino-2-(l-naphthyl)-l-phenyl-butan-2-ol, **Ib** - (15',2ii)-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(l-naphthyl)-l-phenyl-butan-2-ol, **IIa** - (lS,2S)-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(l-naphthyl)-l-phenyl-butan-2-ol, **IIb** - (l*R*,2i?)-(6-bromo-2-memoxy-quinolm-3-yl)-4-dimemylamino-2-(l-naphthyl)-l-phenyl-butan-2-ol), or the corresponding racemate **I-rac (I-rac** = mixture of the **la : lb** isomers in the 1:1 ratio) by means of crystallization with *N*-benzoyl-I-aspartic acid (formula **III),** or its derivatives as a chiral crystallization agent.



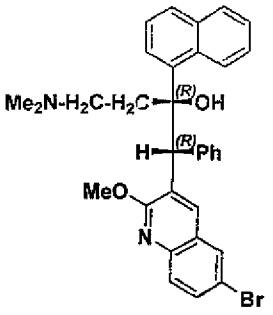
Ia



Ib



Ila

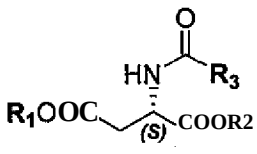


lib

I-rac = Ia:Ib in 1:1 ratio

II-rac = IIa:IIb in 1:1 ratio

Bedaquiline is isolated from a mixture of the corresponding stereoisomers by means of crystallization with derivatives of iV-benzoyl-I-aspartic acid as a chiral crystallization agent:



In the formula, R_1 and R_2 independently stand for hydrogen, a primary, secondary or tertiary **C1-C4** alkyl, a primary or secondary amide, wherein always at least one of the R_1 or R_2 symbols stands for hydrogen; and

R_3 is a **C5-C12** aryl, or C_5-C_{12} heteroaryl with one or more heteroatoms, which may be further substituted by a halogen, amino group, carbonyl, or carboxyl; or its functional derivative, preferably phenyl, naphthyl, tolyl, or mesytyl.

Background Art

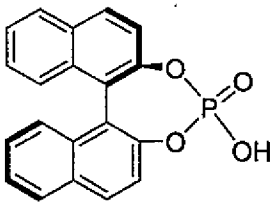
(\R,2S)- 1-(6-Bromo-2-memoxy-quinolin-3-yl)-4-dimethylamino-2-(1-naphthyl)- 1-phenyl-butan-2-ol, which is known as bedaquiline **Ia** (CAS no. 843663-66-1), belongs to the group of quinoline derivatives that can be used as microbial inhibitors.

The (6-bromo-2-memoxyquinolin-3-yl)-4-dimethyla^ ino-2-(1-naphthyl)-1-phenyl-butan-2-ol molecule has two chiral centres, thus its 4 stereoisomers **Ia-b** and **Ila-b** are known. However, the *{\R,2S)* isomer **(la)** can only be used as a microbial inhibitor.

Preparation of this molecule and its use for the treatment of microbial diseases is described in a patent (WO 2004/011436). The said patent describes preparation of the target compound

from a mixture with the other three isomers, wherein bedaquiline was isolated by means of fraction crystallization followed by column chromatography on a chiral stationary phase.

Isolation of bedaquiline from a racemic mixture by means of crystallization with the chiral agent ((/-)-(-)- 1,1 '-bmaphthyl-2,2'-diyl hydrogen phosphate **(IV)** or its derivatives is described in a patent (WO 2006/ 125769).



(R)-{-)-l,l'-binaphthyl-2,2'-diyl hydrogen phosphate

(IV)

Specialized literature also describes an asymmetrical synthesis of bedaquiline. However, the said procedure represents a 12-stage synthesis with the total yield of 5%, which makes this synthesis unusable in the industrial scale (Y. Saga, R. Motoki, S. Makino, Y. Shimizu, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2010,** 132, 7905). A similar synthesis was also described in a patent (JPN TK 201 1/1096837 (201 1, CAN 155:379672))

The biological activity together with the role of bedaquiline in the treatment of infections related to resistant mycobacteria strains is described in an article in *Future Medicinal* **(2011,** 3(1 1), 1345-1360)

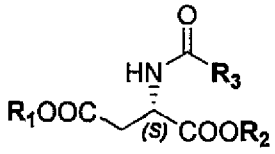
The above mentioned facts indicate that resolution by means of diastereomeric salts with chiral acids appears to be the most viable method of industrial preparation of enantiomerically pure bedaquiline **Ia.**

The chiral purity of the product and reaction yield are influenced by the reaction conditions and selection of the chiral agent used for the crystallization. It is clear that for the preparation of bedaquiline with a high reaction yield, chemical and chiral purity, suitable chiral substances and optimal reaction (crystallization) conditions must be used.

Disclosure of Invention

The invention provides isolation of bedaquiline from the **I-rac** mixture of stereoisomers, or **I-rac** with admixed Π**-rac,** wherein **I-rac** and **II-rac** are in any ratio, with the use of *N*-benzoyl-i-aspartic acid or its chiral derivatives **Ilia,** and methods of its isolation. The isolation is

achieved through crystallization of bedaquiline with *N*-benzoyl-Z-aspartic acid **III,** or a selected chiral derivative of *N*-benzoyl-Z-aspartic acid **Ilia**



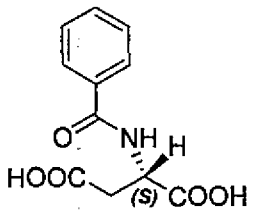
Ilia

wherein R_1 and R_2 independently stand for hydrogen, a primary, secondary or tertiary Ci-C_4 alkyl, a primary or secondary amide, wherein always at least one of the R_1 or R_2 symbols stands for hydrogen; and

R_3 is a C_5-C_{12} aryl, or C_5-C_{12} heteroaryl with one or more heteroatoms, which may be further substituted by a halogen, amino group, carbonyl, or carboxyl; or its functional derivative, preferably phenyl, naphthyl, tolyl, mesytyl,

in a suitable solvent or mixtures of solvents.

In an especially preferred embodiment R_1=R_2 stand for hydrogen and **R3** is phenyl:



W-benzoyl-I-aspartic acid

("I)

It has been unexpectedly found out that the derivatives of iV-benzoyl-Z-aspartic acid used make it possible to isolate bedaquiline **la** in a high yield, with a high chemical and diastereomeric purity. The described isolation procedures can be easily transferred into the industrial scale to obtain a sufficient quantity of bedaquiline for commercial use.

A clear advantage of derivatives of JV-benzoyl-i-aspartic acid is the possibility to only use 0.5 molar equivalents of the chiral acid with respect to the input raw material **I-rac.** Which is a significant innovative element from the point of view of industrial production, its economy and the environmental aspect.

Another advantage of using derivatives of *N*-benzoyl-Z-aspartic acid is the possibility to isolate the diastereoisomeric salt of bedaquiline directly by crystallization from a mixture of all the four isomers **(I-rac** or **I-rac** with admixed **Il-rac** wherein **I-rac** and **Il-rac** are in any

ratio). In addition, if the resolution starts from the **I-rac** mixture with admixed **II-rac,** only 0.25 molar equivalents of derivatives of *N*-benzoyl-X-aspartic acid with respect to the **I-rac** content is sufficient. Which clearly represents a considerable advantage from the point of view of industrial production and its economy.

N-benzoyl-Z-aspartic acid **III** represents a "green reagent" from the point of view of the environmental impact.

Detailed description of the invention

The invention provides isolation of the solid form of bedaquiline **Ia** from a mixture of the corresponding stereoisomers by means of crystallization with *N*-benzoyl-Z-aspartic acid and its chiral derivatives **IIIa** as a crystallization agent and methods of performing the same.

Crystallization of bedaquiline with *N*-benzoyl-Z-aspartic acid and its chiral derivatives **IIIa** can be used to isolate bedaquiline **Ia** in a solid form in a high yield, with a high chemical and enantiomeric purity.

The isolated solid form of bedaquiline **Ia** may have various internal arrangements (polymorphism) with different physical-chemical properties depending on the conditions of its isolation. For this reason, the invention relates to isolation of bedaquiline with the use of derivatives of *N*-benzoyl-i-aspartic acid under various conditions with the use of a number of common solvents or their mixtures.

The described isolation procedures are suitable for isolation of bedaquiline **Ia** in a solid form with high chemical and optical purity; they can be easily transferred into the industrial scale to provide a sufficient quantity of bedaquiline for commercial use.

Isolation of bedaquiline **Ia** is carried out with the use of crystallization with *N*-benzoyl-I-aspartic acid or its chiral derivatives **IIIa** as a crystallization agent, in a suitable solvent, which can be ketones, esters, ethers, amides, nitriles, or organic acids, alcohols, aliphatic and aromatic hydrocarbons, chlorinated hydrocarbons, water and/or their mixtures. Aliphatic C_1-C_4 alcohols, C_5-C_7 alkanes, esters of C_1-C_4 acids with primary C_1-C_4 alcohols, secondary C_3-C_6 alcohols, cyclic ethers or their mixtures are preferred. The most commonly used solvents are ethanol, isopropanol, acetonitrile, tetrahydrofuran, 1,4-dioxane, hexane, heptane or their mixtures.

The final product is typically precipitated or crystallized at temperatures in the range of -30°C to the boiling point of the solvent.

Preparation of a mixture of the **Ia-b IIa-b** stereoisomers of 6-bromo-2-methoxy-3-quinolyl-4-dimethylamino-2-(l-naphthyl)-l-phenyl-butan-2-ol and isolation of the **I-rac** racemic mixture is described in a patent (WO 2004/01 1436).

Bedaquiline **la** can be isolated from the racemic mixture in a solid form by means of chiral HPLC (WO 2004/01 1436) and/or with the use of (*R*)-(-)-1,1'-binaphthyl-2.2'-diyl hydrogen phosphate (WO 2006/125769). It has been found out that chiral derivatives of *N*-benzoyl-I-aspartic acid can be advantageously used for isolation of bedaquiline as the chiral crystallization agent in a suitable solvent or a mixture of solvents.

A clear advantage of *N*-benzoyl-Z-aspartic acid or its chiral derivatives is the possibility to only use 0.5 molar equivalents of the chiral acid with respect to the input raw material **I-rac.** Which is a significant innovative element from the point of view of industrial production, its economy and the environmental aspect.

Another advantage of using derivatives of JV-benzoyl-I-aspartic acid or its chiral derivatives is the possibility to isolate the diastereoisomeric salt of bedaquilme directly by crystallization from a mixture of all the four isomers **(I-rac** or **I-rac** with admixed **II-rac,** wherein **I-rac** and **II-rac** are in any ratio). In addition, if the resolution starts from a **I-rac** mixture with admixed **II-rac,** only 0.25 molar equivalents of derivatives of JV-benzoyl-Z-aspartic acid with respect to the **I-rac** content is sufficient. Which clearly represents a considerable advantage from the point of view of industrial production and its economy.

The free base of bedaquiline **Ia** can be released from the given salt with the use of a suitable base, e.g. carbonate or phosphate base. **K2CO3, KHCO3,** Na_2C0_3, $NaHC0_3$, Na_3P0_4, or Na_2HP0_4 can be preferably used. As an example, extraction of the free base with the use of toluene and an aqueous solution of K_2C0_3 can be mentioned; wherein the base is, after releasing, in the organic layer, which can be separated, and after its evaporation bedaquiline **la** can be isolated as a solid substance.

A crystalline form of the free base of bedaquiline **la** with the melting point of 118°C is described in a patent (WO 2004/01 1436).

The invention is clarified in a more detailed way using the working examples below. These examples, which illustrate the improvement of the procedure in accordance with the invention, only have an illustrative character and do not restrict the scope of the invention in any respect.

Experimental part

High-performance liquid chromatography (HPLC)

Separation of the enantiomers of bedaquiline and verification of the optical purity of the products were carried out in an OJ-3R column, 150x4.6 mm ID, 3 μm, with the use of the triemylamine buffer pH 8 - acetonitrile (40+60) mobile phase at the flow rate of 1 ml/min and separation temperature of 35°C. The injection volume of the analyzed sample, which was dissolved in methanol to the concentration of 0.5 mg/ml, was 5 μl. Bedaquiline was detected by UV detection at 227 nm.

Examples

Example 1

Preparation of the mixture of the **Ia-b IIa-b** stereoisomers was performed by modification of the procedure described in the patent WO 2004/01 1436.

Example 2

Preparation of the racemic mixture **I-rac** was performed by modification of the procedure described in the patent WO 2004/01 1436.

Example 3

Isolation of bedaquiline **la** with the use of 0.5 equivalents of *N*-benzoyl-L-aspartic acid III in 1,4-dioxane

300.5 mg (0.5414 mmol) of **I-rac** was dissolved in 0.9 ml of 1,4-dioxane at 60°C. Subsequently, 64.2 mg (0.2707 mmol) of *N*-benzoyl-Z-aspartic acid **HI** was added and the mixture was stirred at 60°C for 15 minutes. The clear solution was cooled down to 24°C during 60 minutes and further stirred for 2 hours. Inoculation of the solution with prepared crystallization inocula can also be used. The resulting white crystals were filtered off, washed with a dioxane/hexane mixture (1:1 *V:V, 2* x 0.3 ml) and dried in a vacuum drier at 40°C (for 12 h), which provided 165 mg (77%) of the diastereoisomeric salt of bedaquiline **la** with *N*-benzoyl-Z-aspartic acid **III** with the chiral purity of 95%.

Example 4

Recrystallization of the diastereoisomeric salt of bedaquiline **la** with *N*-benzoyl-Z-aspartic acid **HI** prepared in Example 3.

165 mg of the diastereoisomeric salt of bedaquiline with *N*-benzoyl-Z-aspartic acid with the optical purity of 95 % was dissolved in a hot state in 1.1 ml of 1.4-dioxane. After cooling of the solution to 24°C, solid matter separated during continuous stirring in the course of 2 h, which was filtered, washed with a dioxane/hexane mixture (1:1 *V:V,* l x 0.3 ml, 2 x 0.2 ml) and dried in a vacuum drier at 40°C for 16 hours. Crystallization yield 119 mg (72%). The solid fraction obtained by filtration contained the salt of bedaquiline **la** with *N*-benzoyl-X-aspartic acid **III** with the chiral purity of 99% *ee.*

Example 5

Isolation of bedaquiline **la** by means of 1 equivalent of *N*-benzoyl-i-aspartic acid **III** in 1,4-dioxane

1.0 g (1.8 mmol) of **I-rac** was dissolved at 60 °C in 0.9 ml of 1,4-dioxane, containing 0.5% of water. Subsequently, 427 mg (1.8 mmol) of *N*-benzoyl-Z-aspartic acid **III** was added and the mixture was stirred at 60°C for 15 minutes. The clear solution was inoculated with the diastereomeric salt **Ia** with **III** and left to slowly cool down. When 40°C was achieved, hexane (1 ml) was added, the mixture was slowly cooled down to 24°C and further stirred for 2 hours. The resulting white crystals were filtered off, washed with a dioxane/hexane mixture (1:1 *V:V,* 3 x 0.5 ml) and dried in a vacuum drier at 40°C (for 12 h), which provided 662 mg (89%) of diastereoisomeric salt of bedaquiline **Ia** with *N*-benzoykL-aspartic acid **III** with the chiral purity of 98% ee.

Example 6

Recrystallization of the diastereoisomeric salt of bedaquiline **la** with *N*-benzoyl-I-aspartic acid **III** prepared in Example 5.

660 mg of the diastereoisomeric salt of bedaquiline **la** with JV-benzoyl-i-aspartic acid **III** with the optical purity of 98% *ee* was dissolved in a hot state in 3.3 ml of **1.4-dioxane.** After cooling of the solution to 24°C, solid matter separated during continuous stirring in the course of 2 h, which was filtered, washed with a dioxane/hexane mixture (1:1 *V:V,* 1 x 0.5 ml, 2 x 0.4

ml) and dried in a vacuum drier at 40°C for 16 hours. The crystallization yield was 527 mg (80 %) of the salt of bedaquiline **Ia** with *N*-benzoyl-Z-aspartic acid **III** with the chiral purity of 99.9% *ee.*

Example 7

Isolation of the base of bedaquiline **Ia** from its diastereoisomeric salt with *N*-benzoyl-Z-aspartic acid

135.6 mg (0.171 mmol) of the diastereoisomeric salt of bedaquiline **Ia** with *N*-benzoyl-Z-aspartic acid **III** with the optical purity of 99.9% was suspended in 2 ml of toluene. After addition of 2 ml of an aqueous solution of potassium carbonate (70 mg, 0.500 mmol) and subsequent intensive stirring for 15 minutes, the organic layer was separated, dried over Na_2S0_4 and concentrated *in vacuo.* The obtained solid fraction contained the bedaquiline base (93 mg, 98%) with the chiral purity of > 99.9 *ee %*.

Example 8

Isolation of bedaquiline **Ia** from the **I-rac : II-rac** stereoisomer mixture by means of *N*-benzoyl-Z-aspartic acid **III**

100 mg (0.180 mmol) of the equimolar mixture of the **I-rac, II-rac** stereoisomers was dissolved in 0.6 ml of 1,4-dioxane at 60°C. 10.6 mg (0.25 equiv., 0.045 mmol) of *N*-benzoyl-I-aspartic acid was added to the solution and stirred at 60°C for 15 minutes. After cooling of the solution to 24°C, solid matter separated during continuous stirring in the course of 30 minutes, which was filtered and dried in a vacuum drier at 40°C for 16 hours. (Inoculation of the solution with prepared crystallization inocula can also be used). Crystallization yield 32 mg (23%; 91% calculated to the salt of bedaquiline with **III** only). The solid fraction obtained by filtration contained the salt of bedaquiline **Ia** with *N*-benzoyl-Z-aspartic acid **III** with the chiral purity of 86%.

Example 9

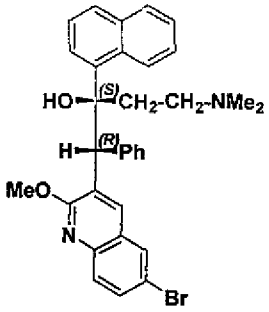
Isolation of bedaquiline **Ia** from the **I-rac : II-rac** stereoisomer mixture by means of *N*-benzoyl-Z,-aspartic acid **(III)**

300 mg (0.54 mmol) of the equimolar mixture of the **I-rac, II-rac** stereoisomers was dissolved in 1.2 ml of 1,4-dioxane, containing 0.5% of water, at 60°C. 128 mg (0.54 mmol) of *N*-

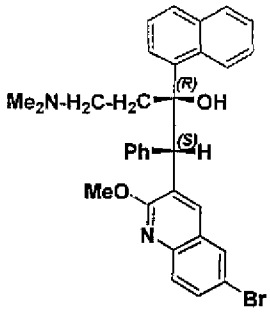
benzoyl-Z-aspartic acid **III** was added to the solution and stirred at 60°C for 15 minutes. The clear solution was inoculated with the diastereomeric salt **la** with **III** and left to slowly cool down. When 40°C was achieved, hexane (0.3 ml) was added, the mixture was slowly cooled down to 24°C and further stirred for 2 hours. The resulting white crystals were filtered off, washed with a dioxane/hexane mixture (1:1 *V:V*, 3 x *0.1* ml) and dried in a vacuum drier at 40°C (for 12 h), which provided 57 mg (49% calculated to the salt of bedaquiline with **III** only) of the diastereoisomeric salt of bedaquiline **la** with *N*-benzoyl-X-aspartic acid **III** with the chiral purity of 99% *ee.*

Claims

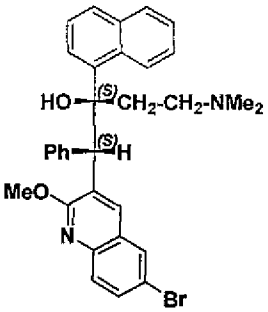
1. A method of performing isolation and purification of bedaquiline (la) from a mixture of stereoisomers of (6-bromo-2-memoxy-quinolin-3-yl)-4-dimethylamino-2-(1-naphthyl)-1-phenyl-butan-2-ol identified as I-rac, being a mixture of the stereoisomers of formulae la, Ib, and II-rac, being a mixture of the stereoisomers of formulae IIa, IIb,



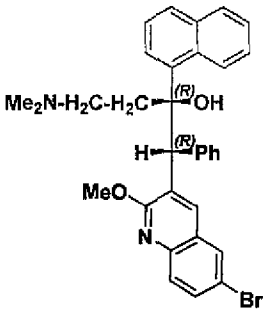
Ia



Ib



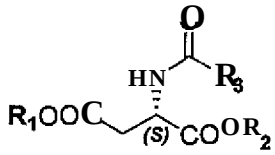
IIa



IIb

I-rac = Ia:Ib **II-rac = IIa:IIb**

with any ratio of individual constituents of the mixture, characterized in that said mixture is dissolved together with derivatives of N-benzoyl-L-aspartic acid of formula **IIIa**



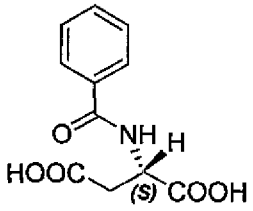
(IIIa)

wherein R_1 and R_2 independently stand for hydrogen, a primary, secondary or tertiary C_1-C_4 alkyl, a primary or secondary amide, wherein always at least one of the R_1 or R_2 symbols stands for hydrogen; and

R_3 is a C_5-C_{12} aryl, C_5-C_{12} heteroaryl with one or more heteroatoms, which may be further substituted by a halogen, amino group, carbonyl, or carboxyl, or its functional derivative, preferably phenyl, naphthyl, tolyl, or mesytyl,

and the resulting salt is recrystallized from a suitable solvent or mixture, which can be ketones, esters, ethers, amides, nitriles or organic acids, alcohols, aliphatic and aromatic hydrocarbons, chlorinated hydrocarbons, water and/or their mixtures.

2. The method according to claim 1, characterized in that the isolation from the mixture of (1R,2S)- (1S.2R)- (1S,2S)- (1R,2R) (la, lb, Ila, lib; I-rac with admixed II-rac) is accomplished through crystallization of a salt with N-benzoyl-L-aspartic acid of formula III



N-benzoyl-*L*-aspartic acid

(III)

3. The method according to claim 1 or 2, characterized in that the isolation is accomplished from a mixture of (la, lb) (1R,2S)- and (lS,2R)-(2-bromo-6-methoxy-quinolin-2-yl)-3-dimethylamino-4-(2-naphthyl)- 1-phenyl-butan- 1-ol.

4. The method according to claim 3, characterized in that the isolation is accomplished with 0.5 equivalents of N-benzoyl-L-aspartic acid.

5. The method according to claim 3, characterized in that the isolation is accomplished with 1 equivalent of N-benzoyl-L-aspartic acid.

6. The method according to any of the previous claims, characterized in that the isolation is accomplished from dioxane as the solvent.

7. The method according to any of the previous claims, characterized in that the isolation is accomplished from dioxane as the solvent with addition of a co-solvent.

8. The method according to claim 7, characterized in that the co-solvent is a **C5-C7** alkane or substituted benzene.

9. The method according to claim 8, characterized in that the co-solvent is hexane, heptane, toluene or xylene, or their mixture.

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2016/000006

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D215/227
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/011436 A1 (JANSSEN PHARMACEUTICA NV [BE] ; VAN GESTEL JOZEF FRANS ELISABE [BE] ; GU) 5 February 2004 (2004-02-05) cited in the application example B7	1-9
A	WO 2006/125769 A1 (JANSSEN PHARMACEUTICA NV [BE] ; PORSTMANN FRANK RALF [CH] ; HORNS STEFAN) 30 November 2006 (2006-11-30) cited in the application page 21, line 27 - page 23, line 18; claim 1	1-9

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

☒ See patent family annex.

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 March 2016	05/04/2016

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

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