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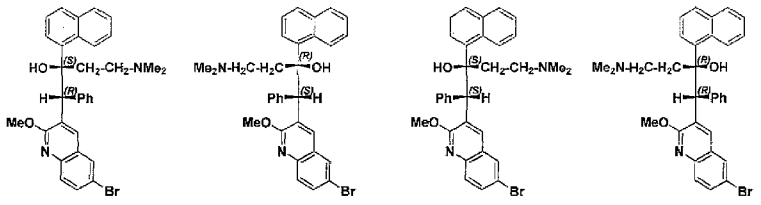
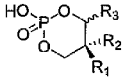
(54) **Title**: CHIRAL RESOLUTION OF BEDAQUILINE BY USING CYCLCIC PHOSPHORIC ACIDS



Ia **Ib** **IIa** **IIb**

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



(IV)

(57) **Abstract**: A method of performing isolation and purification of bedaquiline (Ia) from a mixture of stereoisomers of 6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(l-naphthyl)-l- phenyl-butan-2-ol identified as I-rac, being a mixture of the stereoisomers of formulae Ia, Ib, and II-rac, being a mixture of the stereoisomers of formulae IIa, IIb, with any ratio of individual constituents of the mixture, wherein said mixture is dissolved together with derivatives of 1,3 -propanediol hydrogen phosphate of formula IV, wherein R_1, R_2, and R_3 independently stand for hydrogen, a halogen, C_1-C_6 alkyl, aryl, naphthyl, phenyl and preferably a halogenated phenyl or phenyl substituted in any way, and the resulting salt is crystallized.

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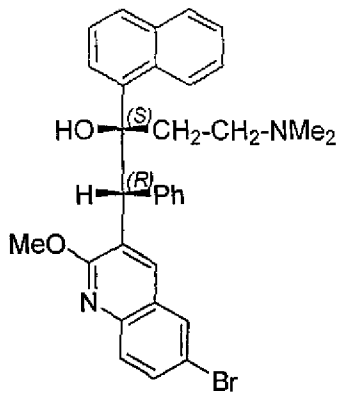
CHIRAL RESOLUTION OF BEDAQUILINE BY USING CYCLCIC PHOSPHORIC ACIDS

Technical Field

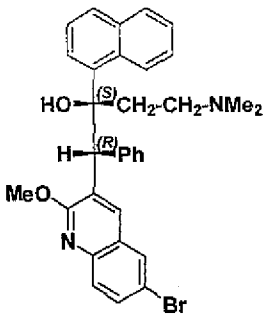
The invention relates to isolation of a solid form of (1*R*,2*S*)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-dimethylamino-2-(1-naphthyl)-1-phenyl-butan-2-ol of formula **Ia**,



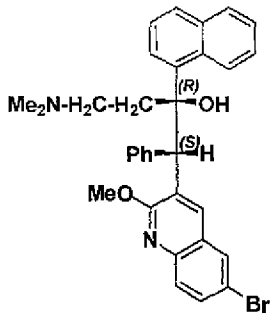
BEDAQUILIN

(Ia)

known as bedaquiline. Bedaquiline is isolated from a mixture of the corresponding stereoisomers (**Ia** - (1*R*,2*S*)-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(1-naphthyl)-1-phenyl-butan-2-ol, **Ib** - (1*S*,2*R*)-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(1-naphthyl)-1-phenyl-butan-2-ol, **IIa** - (1*S*,2*S*)-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(1-naphthyl)-1-phenyl-butan-2-ol, **IIb** - (1*R*,2*R*)-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(1-naphthyl)-1-phenyl-butan-2-ol), or the corresponding racemate **I-rac** (**I-rac** = mixture of the **Ia** : **Ib** isomers in the 1:1 ratio) by means of crystallization with (*S*)-(+)-1-phenyl-1,3-propanediol-2,2-dimethyl hydrogen phosphate (formula **IIIs**; CAS RN: 98674-81-8), or its derivatives, as a chiral crystallization agent.

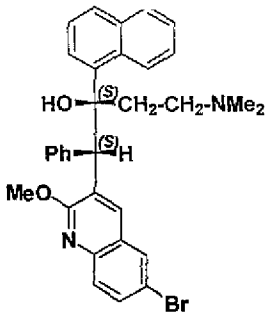


Ia

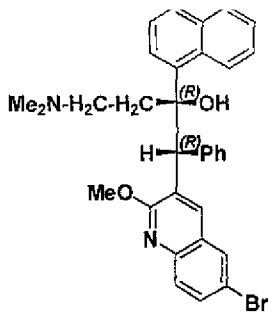


Ib

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

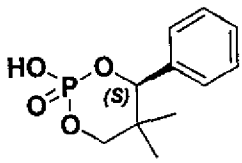


IIa

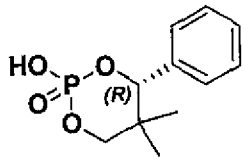


IIb

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



III*s*



III*r*

Ia: (1*R*,2*S*)-(6-Bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(1-naphthyl)-1-phenyl-butan-2-ol
Ib: (1*S*,2*R*)-(6-Bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(1-naphthyl)-1-phenyl-butan-2-ol
IIa: (1*S*,2*S*)-(6-Bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(1-naphthyl)-1-phenyl-butan-2-ol
IIb: (1*R*,2*R*)-(6-Bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(1-naphthyl)-1-phenyl-butan-2-ol

I-rac = mixture of the **Ia** and **Ib** isomers in the 1:1 ratio
II-rac = mixture of the **IIa** and **IIb** isomers in the 1:1 ratio

Background Art

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

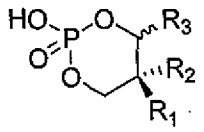
Preparation of this molecule and its use for the treatment of microbial diseases is described in a patent (WO 2004/011436). Bedaquiline was isolated from a diastereoisomeric mixture by means of chiral liquid chromatography. Isolation of bedaquiline from a mixture of the corresponding stereoisomers by means of crystallization with the chiral agent (*R*)-(-)-1,1′-

binaphthyl-2.2′-diyl hydrogen phosphate or its derivatives is described in a patent (WO 2006/125769).

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 obvious 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 a mixture of stereoisomers containing the **I-rac** isomers, possibly with admixed **II-rac**, I-rac and II-rac being in any ratio, with the use of chiral derivatives of 1,3-propanediol hydrogen phosphate (general **formula IV**) and methods of its isolation. The isolation is carried out by crystallization of a salt of bedaquiline **Ia** with the selected chiral derivative of 1,3-propanediol-hydrogen phosphate **IV** in a suitable solvent or mixtures of solvents.



(IV)

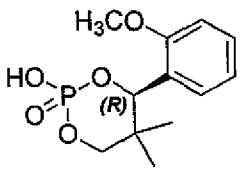
R_1, R_2, and R_3 independently stand for hydrogen, a halogen, C_1-C_6 alkyl, aryl, naphthyl, phenyl, and preferably a halogenated phenyl or phenyl substituted in any way.

It has been unexpectedly found out that the derivatives of 1,3-propanediol-hydrogen phosphate **IV** used make it possible to isolate bedaquiline in a high yield, with a high chemical and enantiomeric purity. The described isolation procedures can be easily transferred into the industrial scale to obtain a sufficient amount of bedaquiline for commercial use.

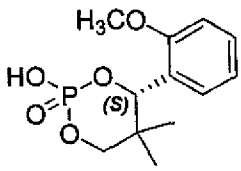
Detailed description of the invention

The invention provides isolation of bedaquiline from a mixture of stereoisomers containing the **I-rac** isomers, possibly with admixed **II-rac**, I-rac and II-rac being in any ratio. In a preferred case the content of I-rac in the mixture with II-rac is 60 to 100%. The method brings very good results e.g. with the content of I-rac of 80% and more. The isolation is carried out with

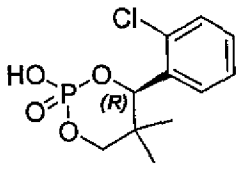
the use of crystallization with 1,3-propanediol hydrogen phosphate **IV** and its chiral derivatives as the crystallization agent; and methods of performing the same. As an example of a suitable chiral agent one can mention the use of (*R*)-(+)-1-(2-methoxyphenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate (CAS RN: 98674-82-9; formula **V**), or (*R*)-(+)-1-(2-chlorophenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate (CAS RN: 98674-87-4; formula **VI**).



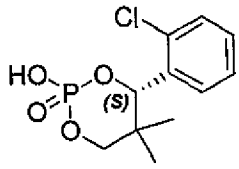
Vr



Vs



VIr



VIs

Crystallization of mixtures of diastereoisomeric salts of the bedaquiline isomers **Ia-b, IIa-b** with 1,3-propanediol hydrogen phosphate and its derivatives makes it possible to isolate bedaquiline in a solid form in a high yield, with high chemical and enantiomeric purity.

The isolated solid form of bedaquiline 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 1,3-propanediol hydrogen phosphate 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 amount of bedaquiline for commercial use.

Isolation of bedaquiline **Ia** is carried out by means of crystallization of the bedaquiline isomers **Ia-b, IIa-b** with derivatives of 1,3-propanediol hydrogen phosphate 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, esters or their mixtures are preferred. The most commonly used solvents are ethanol, isopropanol, acetonitrile, tetrahydrofuran or their mixtures.

The resulting diastereoisomeric salt of bedaquiline **Ia** is precipitated or crystallized, typically at temperatures in the range of -30°C to the boiling point of the solvent.

Preparation of a mixture of the stereoisomers of 6-bromo-2-methoxy-3-quinolyl-4-dimethylamino-2-(1-naphthyl)-1-phenyl-butan-2-ol **Ia-b, IIa-b**, isolation of the racemic mixture **I-rac** of (1*S*,2*R*)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-dimethylamino-2-(1-

naphthyl)-1-phenyl-butan-2-ol and bedaquiline **Ia** ((1*R*,2*S*)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-dimethylamino-2-(1-naphthyl)-1-phenyl-butan-2-ol) is described in a patent (WO 2004/011436).

Bedaquiline **Ia** can be isolated from the racemic mixture **I-rac** in a solid form by means of chiral HPLC (WO 2004/011436) or with the use of (*R*)-(-)-1,1′-binaphthyl-2.2′-diyl hydrogen phosphate (WO 2006/125769). In this invention it has been found out that it is possible to advantageously use chiral derivatives of 1,3-propanediol hydrogen phosphate for isolation of bedaquiline as the chiral crystallization agent in a suitable solvent or a mixture of solvents.

To compare the effect of the method in accordance with this invention and that of WO 2006/125769, the result of Example 8 (below in this description) can be compared to the result of Example 1 in the cited document. Both the methods were carried out with comparable ratios, i.e. I-rac : II-rac is about 11 : 2. According to Example 1 of WO 2006/125769, 63% of all bedaquiline contained in the mixture was crystallized in this way. Our method, as demonstrated in our Example 8, provided 95% of all bedaquiline. Thus, the separation in accordance with this invention is more efficient than the methods described so far.

The free base of bedaquiline **Ia** can be released from the given diastereoisomeric salt with the use of a suitable base, e.g. a carbonate or phosphate base. K_2CO_3, $KHCO_3$, Na_2CO_3, $NaHCO_3$, Na_3PO_4, or Na_2HPO_4 can be preferably used. As an example, extraction of the free base with the use of toluene or Me-THF and an aqueous solution of K_2CO_3 can be mentioned, wherein bedaquiline **Ia** can be isolated as a solid substance after releasing of the base in the organic layer, which can be separated, and after its evaporation.

A crystalline form of the free base of bedaquiline with the melting point of 118°C is described in a patent (WO 2004/011436).

The invention is clarified in a more detailed way using the working examples below. These examples, which illustrate new possibilities of isolation of bedaquiline in a solid form 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

triethylamine 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 a mixture of the stereoisomers of 6-bromo-2-methoxyquinolin-3-yl-4-dimethylamino-2-(1-naphthyl)-1-phenyl-butan-2-ol **I-rac, II-rac** was carried out in accordance with the procedure described in the patent WO 2006/125769 ("Step C").

Example 2

Preparation of the **I-rac** mixture was carried out in accordance with the procedure described in the patent WO 2004/011436 (Example B7).

Example 3

Isolation of the salt of bedaquiline **Ia** with (*R*)-(-)-1-(2-phenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **IIIr** from ethanol

100 mg ($1.80 \cdot 10^{-4}$ mol) of the **I-rac** racemic mixture was dissolved in 13 ml of anhydrous ethanol under reflux. 44.5 mg ($1.80 \cdot 10^{-4}$ mol) of (*R*)-(-)-1-(2-phenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate (98%) (CAS RN: 98674-80-7) was dissolved in 2.2 ml of ethanol and this solution was added to the solution of the diastereoisomeric mixture and left to be stirred under reflux for 10 minutes. After cooling of the solution to the room temperature with continuous stirring, solid matter separated, 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 75.6 mg (52.3 %). The solid fraction obtained by filtration contained the salt of (1*S*,2*R*)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-dimethylamino-2-(1-naphthyl)-1-phenyl-butan-2-ol **Ib** with (*R*)-(-)-1-(2-phenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate with the chiral purity of 99.9%.

After the filtration, the mother liquor was evaporated with the use of a vacuum evaporator and the obtained solid matter was re-dried in a vacuum drier at 40°C for 16 hours. The evaporation of the mother liquor provided 68.9 mg (47.7%) of solid matter representing the

diastereoisomeric salt **Ia** with (*R*)-(-)-1-(2-phenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **IIIr** with the chiral purity of 95%.

Example 4

Isolation of the salt of bedaquiline **Ia** with (*R*)-(-)-1-(2-phenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **IIIr** from the **I-rac** racemic mixture in isopropyl alcohol.

100 mg ($1.80 \cdot 10^{-4}$ mol) of the **I-rac** racemic mixture was dissolved in 13 ml of isopropyl alcohol under reflux. 44.5 mg ($1.80 \cdot 10^{-4}$ mol) of (*R*)-(-)-1-(2-phenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **IIIr** (98%) (CAS RN: 98674-80-7) was dissolved in 2.2 ml of isopropyl alcohol and this solution was added to the solution of the racemic mixture and left to be stirred under reflux for 10 minutes. After cooling of the solution to the room temperature with continuous stirring, solid matter separated, 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 73.6 mg (50.9%). The solid fraction obtained by filtration contained the salt of (1*S*,2*R*)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-dimethylamino-2-(1-naphthyl)-1-phenyl-butan-2-ol **Ib** and (*R*)-(-)-1-(2-phenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **IIIr** with the chiral purity of 99.7%.

After the filtration the mother liquor was evaporated with the use of a vacuum evaporator and the obtained solid matter was re-dried in a vacuum drier at 40°C for 16 hours. The evaporation of the mother liquor provided 70.9 mg (49.1%) of solid matter representing the diastereoisomeric salt **Ia** with (*R*)-(-)-1-(2-phenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **IIIr** with the chiral purity of 96.6%.

Example 5

Isolation of the salt of bedaquiline **Ia** with (*S*)-(+)-1-(2-phenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate (**IIIs**) from the **I-rac** racemic mixture in isopropyl alcohol

100 mg ($1.80 \cdot 10^{-4}$ mol) of the **I-rac** racemic mixture was dissolved in 13 ml of anhydrous isopropyl alcohol under reflux. 44.5 mg ($1.80 \cdot 10^{-4}$ mol) of (*S*)-(+)-1-(2-phenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **IIIs** (98 %) (CAS RN: 98674-81-8) was dissolved in 2.2 ml of isopropyl alcohol and this solution was added to the **I-rac** solution and left to be stirred under reflux for 10 minutes. After cooling of the solution to the room temperature with continuous stirring, solid matter separated, 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 72.1 mg (49.5%). The solid fraction obtained by filtration contained the salt of bedaquiline **Ia** with (*S*)-(+)-1-(2-phenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **IIIs** (with the chiral purity of 99.6% (HPLC purity 98%)).

Example 6

Isolation of the salt of bedaquiline **Ia** with (*R*)-(+)-1-(2-chlorophenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate (**VIr**) from isopropyl alcohol

100 mg

($1.80 \cdot 10^{-4}$ mol) of the **I-rac** racemic mixture was dissolved in 13 ml of isopropyl alcohol under reflux. 48.3 mg ($1.80 \cdot 10^{-4}$ mol) of (*R*)-(+)-1-(2-chlorophenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate (CAS RN: 98674-87-4) **VIr** (97%) was dissolved in 2.2 ml of isopropyl alcohol and this solution was added to the **I-rac** solution and left to be stirred under reflux conditions for 10 minutes. After cooling of the solution to the room temperature with continuous stirring, solid matter separated, 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 63.8 mg (43%). The solid fraction obtained by filtration contained the salt of bedaquiline **Ia** with (*R*)-(+)-1-(2-chlorophenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **VIr** with the chiral purity of 99.2%.

Example 7

Isolation of the salt of bedaquiline **Ia** with (*R*)-(+)-1-(2-methoxyphenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **Vr** from the **I-rac** racemic mixture in isopropyl alcohol

100 mg ($1.80 \cdot 10^{-4}$ mol) of the **I-rac** racemic mixture was dissolved in 13 ml of isopropyl alcohol under reflux. 47.5 mg ($1.80 \cdot 10^{-4}$ mol) of (*R*)-(+)-1-(2-methoxyphenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate (CAS RN: 98674-82-9) **Vr** (97%) was dissolved in 2.2 ml of isopropyl alcohol and this solution was added to the **I-rac** solution and left to be stirred under reflux for 10 minutes. After cooling of the solution to the room temperature with continuous stirring, solid matter separated, 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 72 mg (49%). The solid fraction obtained by filtration contained the salt of bedaquiline **Ia** with (*R*)-(+)-2-hydroxy-4-(2-methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaphosphane 2-oxide **Vr** with the chiral purity of 99.8%.

Example 8

Isolation of the salt of bedaquiline **Ia** with (*R*)-(+)-1-(2-methoxyphenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **Vr** from the **I-rac** and **II-rac** mixture of isomers **(11:2)** in isopropyl alcohol

100 mg ($1.80 \cdot 10^{-4}$ mol) of the mixture of the **I-rac and II-rac (11:2)** mixture of isomers was dissolved in 13 ml of isopropyl alcohol under reflux. 47.5 mg ($1.80 \cdot 10^{-4}$ mol) of (*R*)-(+)-1-(2-methoxyphenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **Vr** (97 %) was dissolved in 2.2 ml of isopropyl alcohol and this solution was added to the solution of the mixture of the stereoisomers and was left to be stirred under reflux for 10 minutes. After cooling of the solution to the room temperature with continuous stirring, solid matter separated, 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 59.3 mg (40.2%; 95% calculated to bedaquiline only). The solid fraction obtained by filtration contained the salt of bedaquiline **Ia** with (*R*)-(+)-2-hydroxy-4-(2-methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaphosphane 2-oxide **Vr** with the chiral purity of 99.7%.

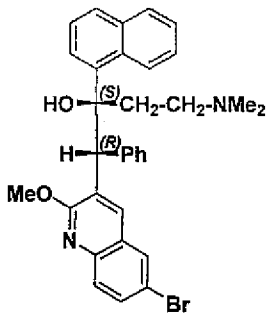
Example 9

Isolation of the free base of bedaquiline **Ia**.

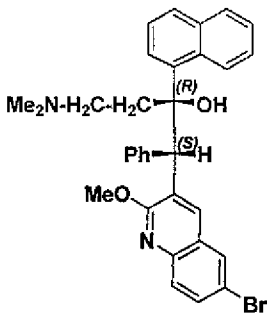
Isolation of the free base of bedaquiline from the respective salt was carried out in accordance with the procedure described in a patent (WO 2006/125769).

Claims

1. A method of performing isolation and purification of bedaquiline (Ia) 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 stereoisomers of formulae Ia, Ib, and II-rac, being a mixture of the stereoisomers of formulae IIa, IIb, with any ratio of individual constituents of the mixture, characterized in that said mixture is dissolved together with at least one derivative of 1,3-propanediol hydrogen phosphate of formula IV

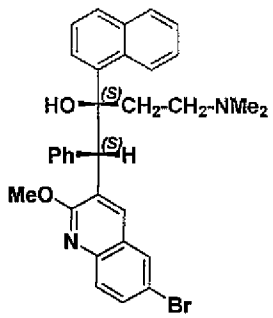


Ia

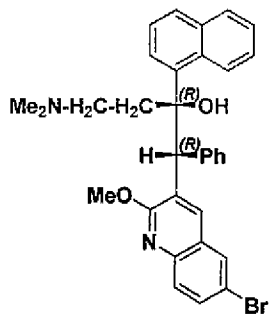


Ib

I-rac = Ia:Ib

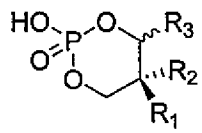


IIa



IIb

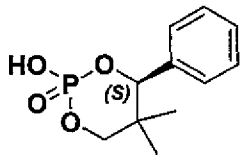
II-rac = IIa:IIb



(IV)

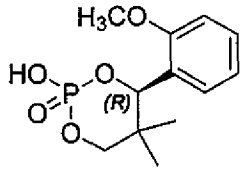
wherein R_1, R_2, and R_3 independently stand for hydrogen, a halogen, C_1-C_6 alkyl, aryl, naphthyl, phenyl, and preferably a halogenated phenyl or phenyl substituted in any way, and the resulting salt is crystallized.

2. The method according to claim 1, characterized in that the isolation from the mixture of (1R,2S)- (1S,2R)- (1S,2S)- (1R,2R) of formulae **Ia, Ib, IIa, IIb; I-rac with admixed II-rac** is accomplished through crystallization of a salt of (*S*)-(+)-1-(2-phenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **IIIs.**



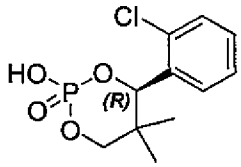
III*s*

3. The method according to claim 1, characterized in that the isolation from the mixture of (1R,2S)- (1S,2R)- (1S,2S)- (1R,2R) (**Ia, Ib, IIa, IIb; I-rac with admixed II-rac**) is accomplished through crystallization of a salt of (*R*)-(+)-1-(2-methoxyphenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **Vr.**



Vr

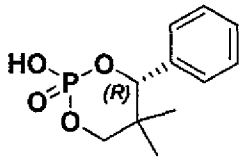
4. The method according to claim 1, characterized in that the isolation from the mixture of (1R,2S)- (1S,2R)- (1S,2S)- (1R,2R) (**Ia, Ib, IIa, IIb**) is accomplished through crystallization of a salt of (*R*)-(+)-1-(2-chlorophenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **VIr**



VI*r*

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

6. The method according to claim 5, characterized in that a salt with (R)-(-)-1-(2-phenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **IIIr** is crystallized from the mixture **(Ia, Ib)** of (1R,2S)- and (1S,2R)-.

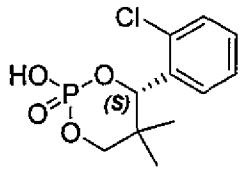


III*r*

7. The method according to claim 5, characterized in that a salt with (S)-(+)-1-(2-phenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **IIIs** is crystallized from the mixture **(Ia, Ib)** of (1R,2S)- and (1S,2R)-.

8. The method according to claim 2, characterized in that a salt with (R)-(+)-1-(2-chlorophenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **VIr** is crystallized from the mixture **(Ia, Ib)** of (1R,2S)- and (1S,2R)-.

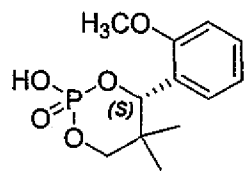
9. The method according to claim 2, characterized in that a salt with (S)-(-)-1-(2-chlorophenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **VIs** is crystallized from the mixture **(Ia, Ib)** of (1R,2S)- and (1S,2R)-.



VIs

10. The method according to claim 2, characterized in that a salt with (*R*)-(+)-1-(2-methoxyphenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **Vr** is crystallized from the mixture **(Ia, Ib)** of (1R,2S)- and (1S,2R)-.

11. The method according to claim 2, characterized in that a salt with (*S*)-(-)-1-(2-methoxyphenyl)-1,3-propanediol-2,2-dimethyl hydrogen phosphate **Vs** is crystallized from the mixture **(Ia, Ib)** of (1R,2S)- and (1S,2R)-.



Vs

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2016/000003

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D215/22 C07F9/09 C07B57/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07F C07B

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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/125769 A1 (JANSSEN PHARMACEUTICA NV [BE]; PORSTMANN FRANK RALF [CH]; HORNS STEFAN) 30 November 2006 (2006-11-30) the whole document -----	1-11
Y	EP 1 227 085 A1 (TAKEDA CHEMICAL INDUSTRIES LTD [JP]) 31 July 2002 (2002-07-31) claims; examples 3,4 -----	1-11

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

☒ See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
15 March 2016	21/03/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gavriliu, Daniela

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CZ2016/000003

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