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(54) **Title**: METHOD OF ISOLATION OF A MIXTURE OF ENANTIOMERS OF 1-(6-BROMO-2-METHOXYQUINOLIN-3-YL)-4-(DIMETHYLAMINO)-2-(NAPHTHALEN-1-YL)-1-PHENYLBUTAN-2-OL

(57) **Abstract**: A method of isolation of the E1 and E2 optical isomers, forming an enantiomeric mixture, from a mixture of four optical isomers E1, E2, E3, E4, wherein the enantiomeric mixture of E3 and E4 is first separated from the solution and subsequently the mixture of E1 and E2 is isolated in the form of a base in the mother liquors, wherein E1 is (1R,2S)-1-(6-bromo-2-memoxyqumolm-3-yl)-4-(dimethylamino)-2- (naphthalen-1-yl)-1-phenylbutan-2-ol, E2 is the (1S,2R)-enantiomer of the same compound, and E3 and E4 are the (1R,2R) and (1S,2S) enantiomers, respectively.

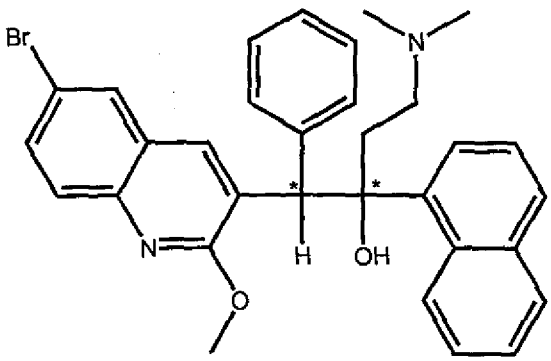
METHOD OF ISOLATION OF A MIXTURE OF ENANTIOMERS OF 1-(6-BROMO-2-METHOXYQUINOLIN-3-YL)-4-(DIMETHYLAMINO)-2-(NAPHTHALEN-1-YL)-1-PHENYLBUTAN-2-OL

Technical Field

A method of isolation of the E1 and E2 optical isomers forming an enantiomeric mixture, from a mixture of four optical isomers E1, E2, E3, E4, wherein an enantiomeric mixture of E3 and E4 is first separated from said mixture and subsequently a mixture of E1 and E2 is isolated in the form of a base in mother liquors.

Background Art

1-(6-Bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol of formula I



I

is a substance with two optical centres, having four optical isomers. Thus, the (1S,2S); (1R,2R); (1S,2R) and (1R,2S) isomers of 1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol can be distinguished.

From another point of view this mixture can be referred to as a mixture of two racemates having different physical properties. Thus, one can define an E I racemic mixture of the (1R,2S) and (1S,2R) enantiomers, which can be referred to as E1 and E2, as well as an E II racemic mixture of the (1R,2R) and (1S,2S) enantiomers E3 and E4. These identifications will be used hereinafter throughout the description of the invention.

The basic patent WO 2004/011436 has mentioned the enantiomer, (αS,βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinoline ethanol (E1), as a substance used for the treatment of mycobacterial disorders, especially for the treatment of disorders caused by the pathogenic mycobacteria *Mycobacterium (M.) tuberculosis, M. bovis, M. avium* and *M. marinum*.

In the basic patent WO 2004/011436, the isolation of the E1 enantiomer from the diastereoisomeric mixture EI is carried out by means of chiral chromatography.

In the first section of the description of the invention in the process patent EP 1888604 B1, the isolation of the optical isomers is carried out by crystallization, which is a more advantageous method for the preparation of (αS,βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2- methoxy-α-1-naphthalenyl-β-phenyl-3-quinoline ethanol (E1) in a larger production scale as compared to the chiral chromatography method.
The mixture of four optical isomers is prepared using the same method as mentioned in the basic patent. The obtained reaction mixture consists of two racemic mixtures.

Isolation of E1 from the mixture of optical mixture is carried out, in the patent EP 1888604 B1, by separation with the chiral compound of 4-hydroxydinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4-oxide or its derivatives.
The process of this separation comprises a reaction of a mixture containing the stereoisomers of (6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol with the above mentioned chiral separating agent in a suitable solvent. This is followed by separation of the precipitated salt and its re-crystallization, or stirring in a suitable solvent. Finally, the base of (6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol is released from this salt.
Out of the many derivatives of the chiral compound of 4-hydroxydinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4-oxide, (11bR)-4-hydroxydinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4-oxide is mentioned as the most advantageous one.
As the most suitable solvent for separation of (αS,βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinoline ethanol from the mixture of optical isomers, a mixture of acetone and dimethyl sulfoxide is mentioned.

One molar equivalent of the derivative of 4-hydroxydinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4-oxide is mentioned in the patent as the most suitable quamountantity for separation of the stereoisomer (αS,βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2- methoxy-α-1-naphthalenyl-β-phenyl-3-quinoline ethanol.

For good separation of the salt, the patent mentions inoculation of the reaction mixture with a mixture with the salt of (αS,βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinoline ethanol*(11bR)-4-hydroxydinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4-oxide.

The inoculation with this salt can be done both before and after addition of the chiral compound of 4-hydroxydinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4-oxide.

The chiral compound of 4-hydroxydinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4-oxide is added to the mixture of stereoisomers of (6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol in the form of a solution in a dipolar aprotic solvent, best in dimethyl sulfoxide.

An improvement of the optical and chemical quality by means of the salt of (αS,βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinoline ethanol*4-hydroxydinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4-oxide is achieved through its re-crystallization or stirring as a suspension, namely in acetone, N,N-dimethyl formamide, or a mixture of N,N-dimethyl formamide with water or an alcohol, dimethyl sulfoxide, or its mixture with water or an alcohol. Acetone is the most suitable one of the above mentioned solvents or their mixtures.

The release of the base of (6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol from the salt with 4-hydroxydinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4-oxide is achieved, according to the process patent, by means of reaction of the salt with a suitable base in a suitable organic solvent. Toluene or tetrahydrofuran can be used as the organic solvent, toluene being more suitable. Suitable bases are carbonates (sodium or potassium), hydrogen carbonates (sodium or potassium), sodium phosphate and hydrogen phosphate. Potassium carbonate is mentioned as more suitable.

Increasing of the purity of the base of (αS,βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinoline ethanol can be achieved by crystallizing the same from a suitable solvent, e.g. from toluene or ethanol.

The second section of the invention description mentions an alternative isolation of E1 by separation after the reaction with (11bS)-4-hydroxydinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4-oxide. E1 is obtained from the mother liquor after separation of the resulting precipitate of the E2 stereoisomer. The alternative isolation process is analogous to the process mentioned in the first section of the description of the invention.

The document also deals with a process of isolation of (αS,βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinoline ethanol (E1), wherein the starting mixture of the four stereoisomers of 6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinoline ethanol is prepared by reaction of 3-benzyl-6-bromo-2-methoxyquinoline and (3-dimethylamino)-1′-propionaphthone in the presence of lithium diisopropylamide at a temperature of from -70°C to -80°C in tetrahydrofuran.
A suitable acid is added to the reaction mixture, e.g. acetic acid, at a reduced temperature (less than 0 °C). The (αR,βS) stereoisomer is isolated from the mixture of the stereoisomers with the use of the chiral compound 4-hydroxydinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4-oxide or its derivatives (procedure, see the first section of the document).

In the said process, an enrichment of the mixture was also used, which means increasing of the content of the racemic mixture of (αS,βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinoline ethanol and (αR,βS)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinoline ethanol by removing the racemic mixture of (αR,βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinoline ethanol and (αS,βS)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinoline ethanol.
The reaction mixture, to which a suitable acid (e.g. acetic acid) has been added, is used as the starting mixture of this enrichment step.

Disclosure of Invention

The invention provides a method of isolation of the mixture E I of enantiomers of (1R,2S)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (E1) and (1S,2R)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-

1-yl)-1-phenylbutan-2-ol (E2) from a mixture of E I and E II, i.e. of the four optical isomers (E1, E2, E3 and E4), consisting of first separating the E3 and E4 enantiomers from said mixture, followed by further processing of the mother liquors so that the E1 and E2 enantiomers can be isolated therefrom.

In a preferred embodiment, the racemate of E1 and E2 obtained this way is converted to salts with an organic or inorganic acid. The following acids can be used for such conversion: hydrochloric, hydrobromic, sulphuric, phosphoric, L-tartaric, DL-tartaric, D-tartaric, citric or oxalic acids. After purification, these salts are converted back to the E1 and E2 bases by treatment with an inorganic base.

Detailed description of the invention

A mixture containing the four optical isomers is prepared, the synthesis being carried out in the same way as described in the basic patent WO 2004/011436, or EP 1888604 B1, by reaction of 3-benzyl-6-bromo-2-methoxyquinoline and (3-dimethylamino)-1′-propionaphthone in the presence of lithium diisopropylamide at a temperature of -60°C to -80°C in a solvent selected from cyclic ethers, best in tetrahydrofuran.

The isolation of the enantiomeric mixture of compounds E1 and E2 (E I) in the basic form from the mixture of the four optical isomers is carried out by removing of the enantiomeric pair of the E3 and E4 compounds (E II) by crystallization in a suitable solvent. The resulting precipitate of E II is separated by filtration, while a mixture of the E1 and E2 enantiomers remains in the mother liquor, their contents being significantly higher than the contents of the E3 and E4 enantiomers.

Further enrichment of the contents of the E1 and E2 enantiomers in relation to the contents of the E3 and E4 enantiomers is carried out after concentration of the mother liquor by crystallization in a suitable content. In this manner, it is possible to obtain a product in the basic form, which contains a mixture of the E3 and E4 enantiomers, the contents of these enantiomers being lower than 3%. The chemical and optical purity of the product obtained this way can be increased by its re-crystallization from a suitable solvent. In this description of the invention the term suitable solvent refers to such a solvent that enables separation of at least one crystal of the desired solid phase; i.e. of the mixture of E3 and E4 in the first step, of E1

and E2 after concentration of the mother liquors in the second step and, finally, E1 and E2 of a higher purity in the third step.

The mixture of the four optical isomers E1, E2, E3 and E4 is prepared by a reaction of 3-benzyl-6-bromo-2-methoxyquinoline and (3-dimethylamino)-1′-propionaphthone in the presence of lithium diisopropylamide at a temperature of -60°C to -80°C in a solvent selected from cyclic ethers, best in tetrahydrofuran. After addition of water to the reaction mixture, an organic layer separates, which contains four optical isomers, (1R,2S)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (E1), (1S,2R)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (E2), (1R,2R)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (E3) and (1S,2S)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (E4).

This organic layer is partly concentrated and crystallized at the room temperature to provide a precipitate containing the enantiomeric mixture E II in a high content relative to the content of the enantiomeric mixture E I. The content of the enantiomeric mixture E I varies in the range of 5-20%. The content of the enantiomeric mixture E I is determined using the liquid chromatography method.

The resulting mixture E II is separated by filtration and the mother liquor is further concentrated. Crystallization at a temperature of 5 to 10°C provides a second fraction of the enantiomeric mixture E II. This is removed by filtration and the mother liquor contains the enantiomeric mixture E I in a high content relative to the content of the enantiomeric mixture E II. The content of the enantiomeric mixture E II varies in the range of 5-25%. The content of the enantiomeric mixture E II is determined using the liquid chromatography method.

The mother liquor, enriched in the enantiomeric mixture E I, is concentrated and a suitable solvent is added.

The solvent can be a C_1 to C_4 alcohol, an ester, a dipolar aprotic one, or a cyclic ether.

The most suitable ones are methan-1-ol, isopropyl acetate, acetonitrile, or 2-methyltetrahydrofuran.

By addition of the solvent, a precipitate results, which is removed by filtration. A product with a low content of the enantiomeric mixture E II is obtained and, at the same time, the chemical quality of said product is increased as this process removes some side products of the reaction and substantially reduces the contents of some of them. The chemical purity can be further

increased by re-crystallization of the crude isolate. For the recrystallization, alcohols, esters and cyclic ethers and their mixtures can be selected. Suitable solvents are propan-1-ol, propan-2-ol, ethyl acetate, isopropyl acetate, 2-methyltetrahydrofuran.

The mother liquor obtained by removal of the precipitated enantiomeric mixture E II by filtration can also be processed in the following way.

This invention also relates to a method of isolation of the enantiomeric mixture E I (E1, E2) in a high chemical and optical purity by means of formation of salts of the individual optical isomers.

A mixture of all the four optical isomers E1, E2, E3 and E4 is again prepared by a reaction of 3-benzyl-6-bromo-2-methoxyquinoline and (3-dimethylamino)-1´-propionaphthone in the presence of lithium diisopropylamide at a temperature of -60°C to -80°C in a solvent selected from cyclic ethers, best in tetrahydrofuran. After addition of water to the reaction mixture, an organic layer separates, which contains the four above mentioned optical isomers.

This organic layer is concentrated and crystallized at the room temperature to result in precipitation of the enantiomeric mixture E II, which is separated by filtration.

The mother liquor contains a solution of the enantiomers E I in a solvent used as the reaction environment, selected from cyclic ethers, best in 2-methyltetrahydrofuran or tetrahydrofuran.

The content of the enantiomeric mixture E II in the obtained mother liquor usually varies in the range of 5 to 25%. The contents of compounds are determined using the liquid chromatography method.

An inorganic or organic acid dissolved in water or in a suitable organic solvent is added to this solution of enantiomers E I. A suitable organic solvent is ethanol, acetonitrile, tetrahydrofuran, or 2-methyltetrahydrofuran.

To produce salts of the E1 and E2 enantiomers, hydrochloric acid, sulphuric acid, phosphoric acid, L-tartaric acid, DL-tartaric acid, D-tartaric acid, citric acid and oxalic acid can be used.

A salt prepared this way contains a very low amount of the salts of enantiomers E II, usually less than 1%.

Re-crystallization of the salt of enantiomers E I in a suitable solvent provides a product with a content of the enantiomeric mixture E II lower than 0.15%.

Examples of a suitable solvent are a C_1 to C_4 alcohol, isopropyl acetate, ethyl methyl ketone, tetrahydrofuran, or 2-methyltetrahydrofuran.

The content of enantiomers E II in the crystallized compound is determined using the liquid chromatography method.

The base is released from the salt of the E1 and E2 enantiomers by extraction with a suitable organic solvent and an aqueous solution of an inorganic base.

For the extraction, e.g., 2-methyltetrahydrofuran or toluene and an aqueous solution of inorganic carbonates or hydrogen carbonates can be used.

2-Methyltetrahydrofuran and sodium carbonate appear to be the most suitable.

The base of the enantiomeric mixture E I purified this way can be used for the preparation of (1R,2S) bedaquiline in a quality complying with pharmaceutical purposes. The optical isomer (1R,2S) of bedaquiline separates as a solid substance after crystallization of the enantiomer E I with a suitable chiral acid in a suitable solvent. Re-crystallization in a suitable solvent provides the product in an acceptable chemical and optical purity. For the re-crystallization, alcohols, cyclic ethers and dipolar aprotic solvents and their mixtures can be selected.

Experimental part

(A)

Preparation of a mixture of the enantiomers of (6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol

A solution of lithium diisopropylamide (0.05 mol), as a 2-molar solution in a tetrahydrofuran, heptane, ethylbenzene mixture, is added to tetrahydrofuran (20 ml), cooled down to -50 to -60°C, in an apparatus under an inert atmosphere. The mixture is cooled down to -65 to -75°C and a solution of 3-benzyl-6-bromo-2-methoxyqunoline (0.0314 mol) in tetrahydrofuran (17 ml) is added during 10 to 20 minutes. This mixture is stirred at a temperature of -65 to -70°C for 30 to 60 minutes. Then, a solution of (3-dimethylamino)-1´-propionaphthone (0.0352 mol) in tetrahydrofuran (17 ml) is added during 15 to 30 minutes. The reaction mixture is stirred at a temperature of -65 to -70°C for 30 to 150 minutes. After this time period, water (100 ml) is slowly added to the reaction mixture dropwise. 2-Methyltetrahydrofuran (35 ml) is added to the mixture and the mixture is stirred for 30 minutes. The formed organic layer is separated. More 2-methyltetrahydrofuran (45 ml) is added; the organic layer is shaken with a sodium chloride solution and separated.

(B)

Isolation of the enantiomeric mixture of (1R,2S) -1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (E1) and (1S,2R)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (E2)

(1)

The organic layer obtained by the process in accordance with (A) is partly concentrated and the mixture is left to crystallize at the room temperature for 17 hours and the precipitate is aspirated and washed with 2-methyltetrahydrofuran.

A solid substance is obtained containing 80% of the E3+E4 enantiomers and 0.5% of the E1+E2 enantiomers.

The mother liquor is further concentrated and left to crystallize at 5 to 10°C. A precipitate results, which is removed by aspiration.

A solid substance is obtained with the composition of 76% of the E3+E4 enantiomers and 5% of the E1+E2 enantiomers

The mother liquor is concentrated and isopropyl acetate is added. The resulting precipitate is aspirated and washed with a solvent.

A product is obtained with the composition of 7% of the E3+E4 enantiomers and 85% of the E1+E2 enantiomers.

Yield: 6.5 g (37.3 %).

(2)

The organic layer obtained by the process in accordance with (A) is concentrated, acetonitrile (100 ml) is added and the mixture is brought to boil. A solid substance suspension is formed, which is aspirated in the hot state.

The solid substance removed by filtration is washed with acetonitrile and dried. Its composition: 85% of the E3+E4 enantiomers, 1.2% of the E1+E2 enantiomers.

After cooling to the room temperature, a precipitate separates from the mother liquor, which is aspirated and washed with the solvent.

A product is obtained with the composition of 6% of the E3+E4 enantiomers and 82% of the E1+E2 enantiomers.

Yield: 2.1 g (12%).

The other mother liquor is concentrated, an ethanol – heptane mixture 1:1 (20 ml) is added and the mixture is stirred at the room temperature. The resulting precipitate is aspirated and washed with the solvent.
A product is obtained with the composition of 17% of the E3+E4 enantiomers and 71% of the E1+E2 enantiomers.
Yield: 0.9 g (5%).

Preparation of salts of the enantiomers (1R,2S)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (E1) and (1S,2R)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (E2)

The organic layer obtained by the process in accordance with (A) is used for the preparation of the salts of the enantiomers.
This is processed by the procedure of B1 or B2.
The product enriched in the E1 and E2 enantiomers is used for the preparation of the salts.

General procedure of preparation of salts of the E1 and E2 enantiomers

The enriched product is dissolved in tetrahydrofuran at a temperature of 40-50°C. After cooling to 30°C a solution of an acid is added. The resulting precipitate is stirred at the room temperature for 2-3 hours. The precipitate is aspirated, washed and dried.
If no precipitate separates at the room temperature, the mixture is cooled to a temperature lower than 0°C.

Preparation of the hydrochloride of the E1 + E2 enantiomers

6.4 g of the starting base (content of the E3 + E4 enantiomers: 24%) is dissolved in tetrahydrofuran (45 ml) under boiling. 1 equivalent of 1.25 M hydrogen chloride in ethanol is added to the solution cooled down to 30°C. The mixture is stirred at the room temperature for 2 hours and the separated precipitate is aspirated. After washing with tetrahydrofuran the precipitate is dried.
Yield: 5.0 g (73.3%).
HPLC: 97% content of the E1 + E2 enantiomers, 1.9% content of the E3 + E4 enantiomers

Preparation of the oxalate of the E1 + E2 enantiomers

220 mg of the starting base (content of the E3 + E4 enantiomers: 17%) is dissolved in tetrahydrofuran (1.5 ml) under boiling. A solution of oxalic acid dihydrate (1 equivalent) in methanol is added to the mixture. The solution is cooled down to -10°C and the separated precipitate is aspirated. After washing with tetrahydrofuran the precipitate is dried.

Yield: 160 g (59%).

HPLC: 95% content of the E1 + E2 enantiomers, 0.8% content of the E3 + E4 enantiomers.

Claims

1. A method of isolation of the E1 and E2 optical isomers, forming an enantiomeric mixture, from a mixture of four optical isomers E1, E2, E3, E4, characterized in that the enantiomeric mixture of E3 and E4 is first separated from the solution and subsequently a mixture of E1 and E2 is isolated in the form of a base in the mother liquors,
wherein E1 is (1R,2S)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol, E2 is the (1S,2R)-enantiomer of the same compound, and E3 and E4 are the (1R,2R) and (1S,2S) enantiomers, respectively.

2. The method according to claim 1, characterized in that the mixture of E1 and E2 in the form of a base is further converted to salts, purified in this form and subsequently converted back to the base.

3. The method according to claim 1 or 2, characterized in that the E3 and E4 isomers are separated from the solution of the four optical isomers in a cyclic ether.

4. The method according to claim 3, characterized in that the cyclic ethers are selected from tetrahydrofuran or 2-methyltetrahydrofuran or a mixture of both the above mentioned cyclic ethers.

5. The method according to claim 4, characterized in that, after addition of a further solvent, solid bases of the E1 and E2 isomers in a mixture thereof are separated from the mother liquor obtained by separation of the E3 and E4 isomers.

6. The method according to claim 5, characterized in that the further solvent is selected from esters selected from isopropyl acetate, ethyl acetate or from alcohols such as methanol, C_6-C_8 hydrocarbons, acetonitrile or their mixtures.

7. The method according to claim 6, characterized in that the separation is carried out at a temperature of -15 to +20°C.

8. A method of preparing a salt of the E1 and E2 isomers according to claim 2, characterized in that the mixture of the E1 and E2 base is converted to salts in tetrahydrofuran or 2-methyltetrahydrofuran or in their mixture by addition of an inorganic or organic acid in water or in an organic solvent.

9. The method according to claim 8, characterized in that the inorganic or organic acid are selected from hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, L-tartaric acid, DL-tartaric acid, D-tartaric acid, citric acid and oxalic acid.

10. The method according to claim 9, characterized in that the preparation of the salts of the E1 and E2 isomers is carried out at a temperature of -15 to +20°C.

11. The method according to any one of claims 8 to 10, characterized in that the base is released from the mixture of the salts of the E1 and E2 optical isomers with the use of an organic solvent selected from 2-MeTHF, toluene, ethyl methyl ketone, isobutyl methyl ketone, butan-1-ol and a base selected from inorganic carbonates, hydrogen carbonates, hydroxides, phosphates, hydrogen phosphates and dihydrogen phosphates.

12. A salt of formula B*HA, wherein B is a mixture of the E1 and E2 optical isomers, wherein E1 is (1R,2S)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol and E2 is the (1S,2R)-enantiomer of the same compound and HA is an acid selected from HCl, HBr, H_2SO_4, H_3PO_4, L-tartaric, DL-tartaric, D-tartaric, and citric acid.

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2016/000005

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D215/227 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 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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 888 604 B1 (JANSSEN PHARMACEUTICA NV [BE]) 14 March 2012 (2012-03-14) cited in the application paragraph [0065] - paragraph [0070] ----- -/--	1-12

[X] Further documents are listed in the continuation of Box C.

[X] 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
8 March 2016	15/03/2016

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

International application No
PCT/CZ2016/000005

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LEE S ET AL: "Handbook of Pharmaceutical Salts: Properties, Selection , and Use, Chapter 8 (Large-Scale Aspects of Salt Formation: Processing of Intermediates and Final Products, Chapter 12 (Monographs on Acids and Bases)", 1 January 2002 (2002-01-01), HANDBOOK OF PHARMACEUTICAL SALTS : PROPERTIES, SELECTION, AND USE, ZÜRICH : VERL. HELVETICA CHIMICA ACTA ; WEINHEIM [U.A.] : WILEY-VCH, DE, PAGE(S) 191 - 192,211, XP002548973, ISBN: 978-3-906390-26-0 paragraph [8.1.1] - paragraph [8.1.3] paragraph [8.1.6] paragraph [8.1.9] -----	1-12

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International application No
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