PROCESS FOR OBTAINING (S)-2-BENZYL-4-((3AR,7AS)-HEXAHYDRO-1H-ISOINDOL-2(3H)-YL)-4-OXO-OBTANOIC ACID AND SALTS THEREOF

Comprising reacting compound (IV) with compound (V) in a solvent to give (S)-mitiglinide (II) and compound (III) as a by-product; removing the solvent and adding ethyl acetate to precipitate compound (III); collecting the solid and applying at least one cycle process comprising: - refluxing the solution of compound (III) with an organic solvent to give (S)-mitiglinide (II) and further compound (III) as a by-product, - removing the organic solvent and adding ethyl acetate to precipitate compound (III); and - separating the mother liquors from the solid, and mixing all the mother liquors; removing the ethyl acetate from the mother liquors to obtain (S)-mitiglinide.
PROCESS FOR OBTAINING (S)-2-BENZYL-4-((3aR,7aS)-HEXAHYDRO-1H-ISOINDOL-2(3H)-YL)-4-OXOBUTANOIC ACID AND SALTS THEREOF.

FIELD OF THE INVENTION

The present invention relates to a new and efficient process for obtaining (S)-mitiglinide, (S)-2-benzyl-4-((3aR,7aS)-hexahydro-1/-/-isoindol-2(3/-/)-yl)-4-oxobutanoic acid, a compound represented by the formula (II):

![Chemical Structure](image)

(II)

and pharmaceutically acceptable salts or hydrate thereof with a high yield and purity.

BACKGROUND OF THE INVENTION

Mitiglinide dihydrate calcium salt (I) is a hypoglycemic agent for the treatment of type 2 diabetes widely described. It is marketed as a calcium dihydrate under the tradename of Glufast®.

![Chemical Structure](image)

(I)

Mitiglinide was first disclosed by the European patent EP0507534 to Kissei as well as its therapeutic applications. EP0507534 describes methods for preparing succinic acid compounds which are useful as therapeutic agents for the treatment of diabetes. These methods present some disadvantages, in particular, long reaction times, the use of halogenated solvents which are toxic and environmentally harmful as well as the use of unfeasible industrial purification methods such as column chromatography. Therefore, there are not yet industrial methods for obtaining mitiglinide or its pharmaceutically acceptable salts, using safe, easily accessible and inexpensive reactants and solvents whereby
mitiglinide is obtained in a high yield and purity.

The paper "Synthesis of KAD-1229 through amidation of bis-activated esters and discussion of regioselectivity of the reactions", Acta Chimica Sinica, Vol 67, 2009, No. 22, 2635-2640, discloses the preparation of mitiglinide by the reaction of different regioselectivities amidation. As disclosed in this paper the reaction of different active esters with octahydroisoindole yields different proportion of the desired product, (S)-2-benzyl-4-((3aR,7aS)-hexahydro-1H-isoindol-2(3H)-yl)-4-oxobutanoic acid, and the undesired regioisomer, (3S)-3-benzyl-4-(hexahydro-1/-/-isoindol-2(3/-/)-yl)-4-oxobutanoic acid as can be shown in the following scheme.

According to this paper, (S)-3-benzylidihydrofuran-2,5-dione is reacted with (3aR,7aS)-octahydro-1 H-isoindole yielding a molar ratio of (S)-2-benzyl-4-((3aR,7aS)-hexahydro-1/-/-isoindol-2(3/-/)-yl)-4-oxobutanoic acid, and the undesired regioisomer, (3S)-3-benzyl-4-(hexahydro-1/-/-isoindol-2(3/-/)-yl)-4-oxobutanoic acid, of 55.4 and 46.6, respectively.
In addition, ES21 84304 discloses the synthesis of a substituted perhydroisoindol of formula (I), also named (la), and pharmaceutically acceptable salts thereof.

\[
\text{(I)}
\]

Said patent discloses that in methanol or methylene chloride, acid of formula (la) tends to generate a mixture of regioisomers of formula (l/a) and formula (l/b). A kinetic study showed that the percentage of acid of formula (lb), (3S)-3-benzyl-4-(hexahydro-1 H-isoindol-2(3H)-yl)-4-oxobutanoic acid, increases over time and temperature and only in the presence of an amine. Thus the kinetic formation of the undesired regioisomer (lb) is significantly slowed down.

\[
\begin{align*}
\text{(l/a)} & \quad \Rightarrow \\
\text{(l/b)} & 
\end{align*}
\]

**BRIEF DESCRIPTION OF THE INVENTION**

The present invention provides a new and efficient process for obtaining (S)-mitiglinide. According to the process of the present invention (S)-mitiglinide is obtained with a high purity and good yield.

The present inventors have found a new and efficient process for obtaining (S)-mitiglinide, represented as compound of formula (II), from the by-product (3S)-3-benzyl-4-(hexahydro-1/-/-isoindol-2(3/-/-)-yl)-4-oxobutanoic acid, the undesired regioisomer represented in the present invention by formula (III).

Advantageously, the process for obtaining (S)-mitiglinide increases the global yield of the process to obtain commercial mitiglinide and other pharmaceutically acceptable salts and allows obtaining (S)-mitiglinide at industrial scale in high purity.

The present invention provides a process for obtaining (S)-mitiglinide, its pharmaceutically
acceptable salts or hydrates thereof in high purity and good yield, comprising:

i) reacting (S)-3-benzyldihydrofuran-2,5-dione of formula (IV) with (3aR,7aS)-octahydro-1/-/-isoindole hydrochloride of formula (V) in a organic solvent to yield (S)-mitiglinide of formula (II):

\[
\begin{align*}
\text{(IV)} & \quad + \quad \text{(V)} \\
\text{(II)}
\end{align*}
\]

wherein (S)-mitiglinide of formula (II) is obtained in a mixture with (3S)-3-benzyl-4-(hexahydro-1H-isoindol-2(3/-/)-yl)-4-oxobutanoic acid of formula (III) as a by-product (not represented in the above scheme),

ii) removing the organic solvent from the mixture of compounds of formula (II) and (in);

iii) adding ethyl acetate so that the compound of formula (III) is isolated as a solid and reserving the obtained mother liquors containing (S)-mitiglinide;

iv) collecting the solid of the previous step iii) and applying at least one cycle process comprising:

a. mixing the obtained solid of formula (III) in an organic solvent and refluxing the obtained mixture to give (S)-mitiglinide of formula (II) and further compound of formula (III) as a by-product,

\[
\begin{align*}
\text{(III)} & \quad \rightleftharpoons \quad \text{(II)} \\
\text{(I)} & \quad + \quad \text{(II)} \\
\text{(III)}
\end{align*}
\]

b. removing the organic solvent and adding ethyl acetate, so that the compound of formula (III) is isolated as a solid, and
c. separating the mother liquors from the solid obtained in step b), and optionally repeating steps a) to c) as many times as desired, and

v) collecting all the mother liquors obtained in the previous steps,

vi) removing the remaining ethyl acetate from the mother liquors to obtain (S)-mitiglinide and, if desired

vii) and optionally, treating (S)-mitiglinide obtained in step vi) to obtain a salt or a hydrate thereof,

viii) and optionally, purifying the obtained solid.

The authors of the present invention have found that the separation step of both regioisomers is a critical step. In order to separate both regioisomers, the solvent should be removed from the mixture, for example by evaporation, and adding ethyl acetate so that regioisomer of formula (III) is precipitated as a white solid, thus the mother liquors are obtained. Afterwards, said white solid is mixed in an organic solvent to give a mixture of compound of formula (III). Said mixture, consisting of the regioisomer of formula (III) and the solvent, will be used as reactive compound for obtaining (S)-mitiglinide in a cyclic process that will be described in the second aspect of the present invention. This cycle process may be repeated as many times as desired.

As used herein, the term "organic solvent" of step i) refers to "a component of a mixture which is present in excess, or whose physical state is in the same as that of the mixture". Normally the term "organic solvent" includes any substance containing carbon, hydrogen and optionally, oxygen and is normally a liquid at 25 °C or is easily converted to a liquid by elevating the temperature up to 100 °C. In addition, the term organic solvent further refers to a combination of two or more of these substances mixed together. Any solvent having the above described properties can be employed in the present invention. Examples of solvent classes useful herein are, but are not limited to, linear or branched alcohols, alkoxylated alcohols, aryloxylated alcohols, polyols, glyceryl esters, polymeric ethers, ketones, hydrocarbons and mixtures thereof. Suitable solvents are benzyl alcohol, benzyl benzoate, 2-benzylxyethanol, benzyl glycol, 1,2-butanediol, 1,3-butanediol, 1,4-butanediol, 2,3-butanediol, butoxyethyl acetate (regular), butyl acetate, t-butyl acetate, n-butanol, t-butanol, butylene glycol, butylene glycol propionate, butyloctanol, butyloctyl benzoate, C7-8
Isoparaffin, C8-9 Isoparaffin, C9-11 Isoparaffin, C9-13 isoparaffin, cyclohexanedimethanol, cyclohexanone, decane, 1,10-decanediol, diethoxydiglycol, dimethyl glutarate, dimethyl maleate, 1,4-dioxane, dioxolane, dipropylene glycol, dipropylene glycol dimethyl ether, dipropyl oxalate, ethoxydiglycol, ethoxydiglycol acetate, ethyl acetate, ethylene glycol, ethylene glycol mono-n-butyl ether, ether hexanediol, ethylhexyl acetate, ethylhexyl benzoate, ethyl lactate, glycerine, hexane, hexandiol, 1,2-hexanediol, 1,2,6-hexanetriol, hexylene glycol, isobutoxypropanol, isododecane, isopentylidol, isopropyl acetate, isopropyl alcohol, 3-methoxybutanol, methoxybutanol, methoxyethanol, methoxyisopropanol, methoxymethylbutanol, methyl acetate, methyl hexyl ether, pentyleneglycol, 2-phenoxyethanol, 1-phenoxy-2-propanol, 2-phenylethanol, propanediol, propyl acetate, propyl alcohol, propylene glycol, trimethyl-1,3-pentanediol, acetone, methyl ethyl ketone, methyltertbutyl ether, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, diisopropyl ether, acetonitrile, toluene, dichloromethane, methyl cyclohexane and xylene. Preferably, the solvent is acetonitrile, ethyl acetate and dichloromethane. Most preferably, the solvent is dichloromethane.

The organic solvent used for refluxing the compound of formula (III) in step a) in the cycle process for obtaining (S)-mitiglinide may be selected from, but not limited to, a linear or branched alcohol containing from 1 to 4 carbon atoms or a non polar solvent, such as toluene, 1,4-dioxane, xylene or mixtures thereof. Preferably, the solvent is toluene and xylene. Most preferably, the solvent is toluene.

In the step viii), the term "purification" means to carry out a purification process to give a purified product. Said purification process may be any know purification process by a skilled person in the art such as solvent extraction, filtration, slurring, washing, phase separation, evaporation, centrifugation or crystallization.

There is still another aspect of the present invention. The second aspect of the present invention is to provide a process for obtaining (S)-mitiglinide wherein compound of formula (III) is used as a reactive compound. The process is characterized in that at least once cycle comprising the following steps is carried out:

a) mixing the solid of formula (III) in an organic solvent and refluxing the obtained mixture to give (S)-mitiglinide of formula (II) and further compound of formula (III) as a by-product,
b) removing the organic solvent and adding ethyl acetate, so that the compound of formula (III) is isolated as a solid, and

c) separating the mother liquors from the solid obtained in step b), and optionally repeating steps a) to c) as many times as desired, and

wherein the mother liquors contains (S)-mitiglinide of formula (II), and the solid contains the regioisomer of formula (III) which may be mixed with an organic solvent (step a) when a new cycle is carried out.

The organic solvent used for refluxing the compound of formula (III) in step a) in the cycle process for obtaining (S)-mitiglinide may be selected from, but not limited to, a linear or branched alcohol containing from 1 to 4 carbon atoms or a non-polar solvent, such as toluene, 1,4-dioxane, xylene or mixtures thereof. Preferably, the solvent is toluene and xylene. Most preferably, the solvent is toluene.

The solid corresponds to (3S)-3-benzyl-4-(hexahydro-1/-/-isoindol-2(3/-/)-yl)-4-oxobutanoic acid, the undesired regioisomer represented by the formula (III), and the mother liquors contain to the desired product represented by the formula (II). (S)-mitiglinide may be isolated by known industrial process such as evaporation, distillation, concentration, filtration, centrifugation or phase separation.

This cycle process may be repeated as many times as desired so that in each cycle new (S)-mitiglinide and further by-product are obtained.

Advantageously, the invention provides a process with a greater atomic efficiency, due to the fact that the ratio of atoms from the respective initial reagents that are incorporated into the final product is as higher as possible. The increase in the atomic efficiency also leads to a reduction in the amount of residues generated in the reaction process, which will have to be treated.
Thus, compound of formula (II) obtained according to the process of the present invention which may be used for obtaining mitiglinide calcium salt (I), a pharmaceutically acceptable salt, or a hydrate thereof is also encompassed in the scope of the present invention.

**DETAILED DESCRIPTION**

In order to provide an efficient process for obtaining (S)-mitiglinide, the inventors have reproduced the reaction between (S)-3-benzyldihydrofuran-2,5-dione of formula (IV) and (3aR,7aS)-octahydro-1/-/-isoindole of formula (V) described in the paper "Synthesis of KAD-1229 through amidation of bis-activated esters and discussion of regioselectivity of the reactions", Acta Chimica Sinica, Vol 67, 2009, No. 22, 2635-2640, to know if other by-products different from (3S)-3-benzyl-4-(hexahydro-1/-/-isoindol-2(3/-/)-yl)-4-oxobutanoic acid of formula (III) are generated.

Advantageously, it has found that although the energy efficiency in the above-mentioned reproduced reaction is very poor, about 50 per cent, no additional by-products are generated different from compound of formula (III).

In view of the prior art, the problem to be solved by the present invention may be seen as to provide a process for obtaining (S)-mitiglinide with a greater atomic efficiency and a lower amount of residues to be treated, which further is industrially acceptable, environmentally safe and whereby (S)-mitiglinide is obtained in high purity.

The solution is based on a process that recycles the by-product generated in the reaction between (S)-3-benzyldihydrofuran-2,5-dione of formula (IV) and (3aR,7aS)-octahydro-1/-/-isoindole hydrochloride of formula (V) in the presence of a solvent, for example methylene chloride, to obtain (S)-mitiglinide of formula (II):

\[
\text{(IV) + (V) \rightarrow (II)}
\]

In the above reaction, (S)-mitiglinide of formula (II) is obtained together with the undesired regioisomer, (3S)-3-benzyl-4-(hexahydro-1/-/-isoindol-2(3/-/)-yl)-4-oxobutanoic acid, represented by formula (III) as a by-product, in a percentage of about fifty per cent.
Thus, a mixture of (S)-mitiglinide and said by-product of formula (III) is obtained. The solvent is removed from the mixture of compounds of formula (II) and (III) for example, by evaporation, and ethyl acetate is added. With this treatment, the undesired regioisomer of formula (III) is isolated as a white solid and the mother liquors containing (S)-mitiglinide are separated from the solid.

The solid collected from the previous step is used for obtaining (S)-mitiglinide by applying at least one cycle of the following process comprising:

a) mixing the solid of formula (III) in an organic solvent and refluxing the obtained mixture to give (S)-mitiglinide of formula (II) and further compound of formula (III) as a by-product,

b) removing the organic solvent and adding ethyl acetate, so that the compound of formula (III) is isolated as a solid, and

c) separating the mother liquors from the solid obtained in step b), and optionally repeating steps a) to c) as many times as desired.

Then, all the mother liquors obtained in the previous steps are collected and (S)-mitiglinide is isolated by removing the ethyl acetate from the mother liquors.

Optionally, the obtained (S)-mitiglinide represented by formula (II) is treated to obtain a salt or a hydrate thereof. For example, if (S)-mitiglinide is treated with a source of calcium ions, mitiglinide calcium salt dihydrate of formula (I) is obtained:
The source of calcium ions is a salt, which can provide a calcium cation. Suitable sources of calcium ions, organic or inorganic, may be, for example, calcium halides, such as calcium chloride, calcium nitride, calcium acetate or mixtures thereof.

Finally, the product obtained is purified by a known industrial method if necessary. Advantageously, the inventors have found a process for obtaining (S)-mitiglinide which uses \((3S)-3\text{-benzy}-4-(\text{hexahydro-1/-/-isoindol-2(3/-/-)-yl})-4\text{-oxobutanoic acid, the undesired regioisomer of formula (III), as a reactive compound in each cycle.}

With the present invention it is provided an industrially advantageous process for the preparation of (S)-mitiglinide that allows to increase the global yield of the process and that allows to obtain (S)-mitiglinide at industrial scale in high purity.

According to the process of the present invention, \((S)-2\text{-benzy}-4-((3aR,7aS)-\text{hexahydro-1/-/-isoindol-2(3/-/-)-yl})-4\text{-oxobutanoic acid of formula (II) is obtained without needing an amine or other compounds disclosed in the prior art.}

According to the invention, the process leads to favor the equilibrium to (S)-mitiglinide of formula (II) to the detriment of compound of formula (III).

In each cycle, regioisomers of formula (II) and (III) are obtained, one the desired product represented by formula (II) and the other, the undesired product represented by formula (III):

To separate both regioisomers, firstly it is necessary to remove the solvent from the mixture, for example by evaporation which give a paste containing both regioisomers. Ethyl acetate is
added to the paste which allows the compound of formula (III) to be isolated as a white solid. Thus, the undesired regioisomer of formula (III), (3S)-3-benzyl-4-(hexahydro-1/-/-isoindol-2(3/-/-yl)-4-oxobutanoic acid, is filtered off and the mother liquors are separated. The mother liquors contain the desired product (S)-mitiglinide of formula (II), (S)-2-benzyl-4-((3aR,7aS)-hexahydro-1/-/-isoindol-2(3/-/-yl)-4-oxobutanoic acid, as an oil.

The inventors of the present invention have found that the separating step is a critical step. No other solvents different from ethyl acetate are acceptable for separating both regioisomers.

The organic solvent used in the above reaction step for refluxing the compound of formula (III) of the process for obtaining (S)-mitiglinide may be selected from, but not limited to, a linear or branched alcohol containing from 1 to 4 carbon atoms or a non polar solvent, such as toluene, 1,4-dioxane, xylene or mixtures thereof. Preferably, the solvent is toluene and xylene. Most preferably, the solvent is toluene.

The ratio of organic solvent to compound of formula (III) may be from 100:1 (v/w) to 5:1 (v/w), 100 volumes of solvent per gram of solid to 5 volumes of solvent per gram of solid. Preferably, the ratio is about 10:1.

In a preferred embodiment, the organic solvent used for refluxing the compound of formula (III) of the process for obtaining (S)-mitiglinide is toluene and it is used in a ratio of 10:1, 10 volumes of solvent per gram of solid.

The reaction temperature may be the reflux temperature of the solvent or the reflux temperature of the mixtures of solvents used in the process. For example, if the solvent is toluene, the reflux temperature would be about 110°C.

The cycle process according to the second aspect of the present invention may be repeated as many times as desired in order to obtain additional (S)-mitiglinide in each cycle. Therefore, according to the present invention it is also provided a process for obtaining (S)-mitiglinide and a process that allows reducing the by-products of formula (III) generated during the reaction of compound (IV) with compound (V).

Advantageously, the present invention provides a process with a greater atomic efficiency wherein the proportion of atoms from the respective initial reagents that are incorporated into
the final product is optimum and this translates itself into a reduction of the amounts of residues to be treated.

EXAMPLES

Example 1

Synthesis of (S)-2-benzyl-4-((3aR,7aS)-hexahydro-1 H-isooindol-2(3H)-yl)-4-oxobutanoic acid (II) and (3S)-3-benzyl-4-(hexahydro-1H-isooindol-2(3H)-yl)-4-oxobutanoic acid (III)

85 g of (3aR,7aS)-octahydro-1 H-isooindole hydrochloride (V) and 100 g of (S)-3-benzyldihydrofuran-2,5-dione (IV) were mixed in 700 mL of methylene chloride. The mixture was treated with 384 mL of a solution of 3 N sodium hydroxide and then, stirred at 23 °C for 1 hour. 40 mL of 3 N hydrochloric acid were added to the mixture.

The organic layer was washed with 400 mL of water and the pH was adjusted to pH=2-3 with a solution of 3 N hydrochloric acid and brine (400 mL). The organic phase was concentrated under reduced pressure and 500 mL of ethyl acetate were added to the residue obtaining a filtered residue of 68.8 g of compound (III) from the first cycle as white solid. The mother liquors containing the compound (II) from the first cycle were separated.

690 mL of toluene were added to the 68.8 g obtained in the precedent step and were heated to reflux, maintaining conditions for 30 min. Then, the solvent was distilled under vacuum. 700 mL of ethyl acetate were added to the residue obtaining a filtered residue of 46.8 g of compound (III) from the second cycle as white solid. The mother liquors containing the compound (II) from the second cycle were separated.

470 mL of toluene were added to the 46.8 g obtained in the precedent step and were heated to reflux, maintaining conditions for 30 min. Then, the solvent was distilled under vacuum. 500 mL of ethyl acetate were added to the residue obtaining a filtered residue of 27.7 g (16.7 %) of compound (III) from the third cycle as white solid. The mother liquors containing the compound (II) from the third cycle were separated.

${}^1$H-NMR (200 MHz, CDCl$_3$)(regioisomer of formula (III)) $\delta$: 1.10-1.37 (m, 8H); 1.94-2.20 (m, 2H); 2.53-2.93 (m, 5H); 3.16-3.37 (m, 4H); 4.27 (s, OH); 7.15-7.27 (m, 5H).
Synthesis of bis [(2S)-2-benzyl-3-(c/s-hexahydroisoindolin-2-ylcarbonyl)propionate] dihydrate (mitiglinide calcium salt (I))

The mother liquors containing the compound (II) from the first cycle, compound (II) from the second cycle and compound (II) from the third cycle were mixed and the solvent was distilled under vacuum. The residue was dissolved in 1.9 L of ethanol and then 77.9 mL of a solution of 6 N sodium hydroxide were added. 166 g of CaCl₂·2H₂O in 2 L water previously mixed and vigorously stirred were added to the mixture to obtain the crystals that were separated by filtration. The product was purified twice from a mixture of ethanol and water (95:5 and 1:1, respectively) giving bis [(2S)-2-benzyl-3-(c/s-hexahydroisoindolin-2-ylcarbonyl)propionate] dihydrate calcium salt (mitiglinide calcium salt (I)) as a white solid.

Yield: 55 % from (S)-3-benzyldihydrofuran-2,5-dione (IV)
HPLC purity: 99.9 %.
mp: 198-214 °C.

¹H-NMR (200 MHz, CDCl₃) δ: 1.11-1.27 (m, 16H); 1.97-2.26 (m, 12H); 2.75-3.29 (m, 10H); 7.18-7.26 (m, 10H).

Example 2

Synthesis of (S)-2-benzyl-4-((3a/?,7aS)-hexahydro-1H-isooindol-2(3H)-yl)-4-oxobutanoic acid (II) and (3S)-3-benzyl-4-(hexahydro-1H-isooindol-2(3H)-yl)-4-oxobutanoic acid (III)

40 mL of xylene were added to 3.7 g of (3S)-3-benzyl-4-(hexahydro-1H-isooindol-2(3/-/)-yl)-4-oxobutanoic acid (III) from the first cycle and the mixture was heated to 100°C, maintaining conditions for 2 hours. The solvent was distilled under vacuum. 50 mL of ethyl acetate were added to the residue and the product was filtered off giving 1.3 g (35 % yield) of the regioisomer of formula (III) from the second cycle as white solid.

The mother liquors containing the compound (II) were separated and the solvent was distilled under vacuum obtaining 2.4 g of (S)-2-benzyl-4-((3aR,7aS)-hexahydro-1H-isooindol-2(3H)-yl)-4-oxobutanoic acid (II) as a colorless oil.

Yield: 65 % from (3S)-3-benzyl-4-(hexahydro-1H-isooindol-2(3H)-yl)-4-oxobutanoic acid (III)
HPLC purity: 78 %

¹H-NMR (200 MHz, CDCl₃) (regioisomer of formula (III)) δ: 1.10-1.37 (m,8H); 1.94-2.20
(m,2H); 2.53-2.93 (m,5H); 3.16-3.37 (m,4H); 4.27 (s,OH); 7.15-7.27 (m,5H).

$^1$H-NMR (200 MHz, CDCl$_3$) (8303) $\delta$: 1.11-1.27 (m,16H); 1.97-2.26 (m,12H); 2.75-3.29 (m, 10H); 7.18-7.26 (m, 10H).
1. A process for obtaining (S)-mitiglinide, a pharmaceutically acceptable salt or hydrate thereof, comprising the following steps:

i) reacting (S)-3-benzyldihydrofuran-2,5-dione represented by formula (IV),

\[
\text{(IV)}
\]

with (3aR,7aS)-octahydro-1/-/-isoindole hydrochloride represented by formula (V) in an organic solvent,

\[
\text{(V)}
\]

to give the compound of formula (II)

\[
\text{(II)}
\]

and (3S)-3-benzyl-4-(hexahydro-1/-/-isoindol-2(3/-/)-yl)-4-oxobutanoic acid as a by-product of formula (III)

\[
\text{(III)}
\]

and characterized in that further comprises:

ii) removing the organic solvent from the mixture of compounds of formula
and (III);

iii) adding ethyl acetate so that the compound of formula (III) is isolated as a solid and reserving the obtained mother liquors containing (S)-mitiglinide;

iv) collecting the solid of the previous step iii) and carrying out at least one cycle process comprising:

   a) mixing the obtained solid of formula (III) in an organic solvent and refluxing the obtained mixture to give (S)-mitiglinide of formula (II) and further compound of formula (III), as a by-product,

   b) removing the organic solvent and adding ethyl acetate, so that the compound of formula (III) is isolated as a solid, and

   c) separating the mother liquors from the solid obtained in step b), and optionally repeating steps a) to c) as many times as desired, and

v) collecting all the mother liquors obtained in the previous steps,

vi) removing the remaining ethyl acetate from the mother liquors to obtain (S)-mitiglinide and, if desired

vii) and optionally, treating (S)-mitiglinide obtained in step vi) to obtain a salt or a hydrate thereof,

viii) and optionally, purifying the obtained solid.

2. A process for obtaining (S)-mitiglinide, a pharmaceutically acceptable salt or hydrate thereof, characterized in that it is carried out at least one cycle process comprising:

   a) mixing the solid of formula (III) in an organic solvent and refluxing the obtained mixture to give (S)-mitiglinide of formula (II) and further
b) removing the organic solvent and adding ethyl acetate, so that the compound of formula (III) is isolated as a solid, and

c) separating the mother liquors from the solid obtained in step b), and optionally repeating steps a) to c) as many times as desired.

wherein the mother liquors contain (S)-mitiglinide of formula (II), and the solid contains the compound of formula (III) which may be reused in a new cycle as a reactive compound.

and optionally, treating (S)-mitiglinide obtained in step c) to obtain a salt or a hydrate thereof, and optionally, purifying the obtained solid.

3. Process according to claim 1 or 2, wherein the organic solvent used in step a) of the cycle process is selected from the group consisting of an alcohol containing from 1 to 4 carbon atoms, or a non polar solvent, such as toluene, 1,4-dioxane, xylene or mixtures thereof.

4. Process according to claim 1 or 2, wherein the organic solvent used in step a) of the cycle process are toluene or xylene or mixtures thereof.

5. Process according to claim 1 or 2, wherein the organic solvent used in step a) of the cycle process is toluene.

6. Process according to any preceding claim, wherein the ratio of organic solvent in step a) of the cycle process to solid is from 100:1 to 5:1 (v/w).

7. Process according to claim 6, wherein the ratio of organic solvent in step a) of the cycle process to solid is about 10:1 (v/w).
8. Process according to claims 1 to 5, wherein the solvent used in step a) of the cycle process is toluene and the ratio of toluene to solid is about 10:1 (v/w).

9. A process according to claim 1 to 8, wherein the salt obtained is a calcium salt.

10. Use of a compound of formula (III), (3S)-3-benzyl-4-(hexahydro-1H-isoindol-2(3/-/)-yl)-4-oxobutanoic acid as a reactive compound, for obtaining (S)-mitiglinide of formula (II), salts or hydrates thereof.

11. Use of a compound of formula (III), (3S)-3-benzyl-4-(hexahydro-1H-isoindol-2(3/-/)-yl)-4-oxobutanoic acid as a reactive compound, for obtaining (S)-mitiglinide dihydrate calcium salt of formula (I).
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D209/44

ADD.

According to International Patent Classification (IPC) or into 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 , CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
  "L" document wherein may throw doubts on priority claim(s) one of which is cited to establish the publication date of another citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed

"X" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"Y" 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

"Z" 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

Date of the actual completion of the international search

17 September 2013

Date of mailing of the international search report

26/09/2013

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Megido, Benigno
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>US 6133454 A</td>
<td>17-10-2000</td>
<td>AT 224368 T</td>
<td>15-10-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 734398 B2</td>
<td>14-06-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 8445098 A</td>
<td>25-01-1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 9810657 A</td>
<td>03-10-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2295992 A1</td>
<td>14-01-1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1261879 A</td>
<td>02-08-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69808092 D1</td>
<td>24-10-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69808092 T2</td>
<td>30-04-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 994854 T3</td>
<td>30-12-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2184304 T3</td>
<td>01-04-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 2765578 A1</td>
<td>08-01-1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HK 1028610 A1</td>
<td>24-10-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HU 0002778 A2</td>
<td>29-01-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 4056093 B2</td>
<td>05-03-2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2002507222 A</td>
<td>05-03-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO 996577 A</td>
<td>02-03-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ 501835 A</td>
<td>24-11-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PL 337728 A1</td>
<td>28-08-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT 994854 E</td>
<td>31-12-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 6133454 A</td>
<td>17-10-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 9901430 A1</td>
<td>14-01-1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZA 9805882 A</td>
<td>26-01-1999</td>
</tr>
</tbody>
</table>