INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

Title: PROCESS FOR PREPARING (S)-PREGABALIN BY OPTICAL RESOLUTION OF RACEMIC PREGABALIN

Abstract: The present invention relates to a novel process for preparing (S)-Pregabalin by optical resolution of racemic Pregabalin. This invention also relates to (S)-Pregabalin(-)-O,O'-dibenzoyl-L-tartrate or a hydrate, a solvate, a polymorph thereof of Formula (Vila) and to two crystalline forms of (S)-Pregabalin(-)-O,O'-dibenzoyl-L-tartrate.
Process for preparing (S)-Pregabalin by optical resolution of racemic Pregabalin

Field of the invention

The present invention relates to a novel process for preparing (S)-Pregabalin by optical resolution of racemic Pregabalin. This invention also relates to two crystalline forms of (S)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate (Vila).

Background of the invention

γ-Aminobutyric acid (GABA) is one of the most widely distributed inhibitory neurotransmitters involved in the regulation of brain neuronal activity. The concentration of GABA is regulated by two pyridoxal 5'-phosphate dependent enzymes: L-glutamic acid decarboxylase (GAD), which catalyzes conversion of L-glutamic acid to GABA, and GABA aminotransferase, which degrades GABA to succinic semialdehyde. When the concentration of GABA diminishes below a threshold level in the brain, convulsions may result and, conversely, raising the GABA level appears to terminate seizures. The term "seizure" means excessive unsynchronized neuronal activity that disrupts normal brain function.

(±)-3-aminomethyl-5-methyl-l-hexanoic acid (Pregabalin), which is also called β-isobutyl-γ-aminobutyric acid or isobutyl-GABA, increases the concentration of GABA by activating GAD and is a potent anticonvulsant: it has the ability to suppress seizure while avoiding the undesirable side effect of ataxia. Pregabalin is useful as a therapeutic agent for the treatment of pain, epilepsy, convulsions, psychiatric disorders, attention deficit, hypersensitivity disorder, anxiety and mood disorders.

It has been discovered that the anticonvulsant effect of racemic Pregabalin is stereoselective. The anticonvulsant effect of racemic Pregabalin is primarily attributable to the (S)-Pregabalin. (S)-Pregabalin shows better anticonvulsant activity than the R-stereoisomer (see, for example, Yuen et al., Bioorganic & Medicinal Chemistry Letters, 1994, 4, 823).

(S)-Pregabalin is a compound of Formula (I)
[(S)-(+)-3-aminomethyl-5-methyl-l-hexanoic acid], which is disclosed in EP 641 330 B 1 and marketed under the trade name Lyrica®.

The commercial utility of Pregabalin requires an efficient, cost effective and safe method for preparing the S-enantiomer substantially free of the R-enantiomer in a large scale.

The resolution of racemates constitutes the main method for industrial preparation of pure enantiomers.

Several methods have been used to prepare (S)-Pregabalin. Typically, the racemic mixture is synthesized and then subsequently resolved into its R- and S-enantiomers.

In a typical resolution process, the racemic mixture is converted to a mixture of diastereomeric salts by reaction with a suitable chiral resolving agent, which is typically a chiral acid or base, often selected from naturally occurring compounds, in a suitable solvent or solvent mixture. Unlike the enantiomers from which they are formed, the diastereomers frequently have very different physical properties, including crystal formation and solubility. In general, one diastereomeric salt crystallizes and the other one stays in solution. A further recrystallization from the same solvent or solvent mixture affords the diastereomeric salt with the desired enantiopurity. The chiral resolving agent is then removed and recovered, giving the free desired enantiomer. The unwanted enantiomer is typically released, racemised and recycled through the process. In order for resolution by diastereomeric crystallization to be economically viable, a 40% or better recovery of material with an enantiomeric purity above 95% must be achieved.

In a typical resolution process for (S)-Pregabalin, the racemic mixture is combined with the chiral resolving agent in a suitable solvent or solvent mixture, and the suspension is heated until complete dissolution is achieved. Then the system is cooled in order for the enriched diastereomeric salt to crystallize.
U.S. Patent No. 5,637,767 discloses a process for the resolution of racemic Pregabalin, which involves selective crystallization of a diastereoisomeric salt of the racemic Pregabalin with the chiral resolving agent (S)-(+-)mandelic acid, as depicted in Scheme 1.

Scheme 1:

A diastereomeric salt of Pregabalin with (S)-(+-)mandelic acid of Formula (II) was obtained by heating to 50-65°C a solution of racemic Pregabalin (1 mol) and an excess of (S)-(+-)mandelic acid (1.5 mol) in isopropanol and water. Batch heating and temperature are kept to the minimum necessary to dissolve solids in order to minimize acid catalyzed decomposition of racemic Pregabalin to the corresponding lactam. Removal of (S)-mandelic acid from the diastereoisomeric salt of Formula (II) to give the enriched (S)-Pregabalin was done using tetrahydrofuran and water at 0-5°C for several hours. Tetrahydrofuran is an extremely flammable liquid and may form explosives peroxides.

U.S. Patent No. 5,616,793 and the patent application WO 2006/122259 disclose a process which involves the resolution of the racemic key intermediate (±)-3-(carbamoylmethyl)-5-methylhexanoic acid of Formula (III), instead of racemic
Pregabalin itself, to obtain the compound of Formula (V), that can be converted to (S)-Pregabalin via a Hofmann reaction.

U.S. Patent No. 5,616,793 discloses a process for the preparation of (S)-Pregabalin, which involves resolution of the racemic key intermediate of Formula (III), with the chiral resolving agent (R)-(+-)-α-phenylethylamine, in a solvent mixture of chloroform and ethanol to obtain the diastereomeric salt (IV) and then the desired R-enantiomer of Formula (V), according to Scheme 2.

Scheme 2:

However, according to Chemical Development of CI-1008, An Enantiomerically Pure Anticonvulsant Organic Process Research & Development, 1997, 1, 26-38, this synthetic method was avoided because it requires the use of chloroform.
The patent application WO 2006/122259 overcomes this problem by resolution of the racemic key intermediate of Formula (III), with the chiral resolving agent lR,2S-(-)-ephedrine or lR,2S-(-)-ephedrine.HCl in acetone.

Both methods include the heating of the racemic compound with the chiral resolving agent in an organic solvent to obtain the diastereomeric salt. Such a production is then economically and ecologically disadvantageous. Besides, the racemic key intermediate of Formula (III) is only an intermediate of one synthetic route to prepare (S)-Pregabalin, whereas racemic Pregabalin is the final key intermediate of many synthetic methods, such as the processes described in U.S. Patent No. 5,637,767; U.S. Patent No. 6,924,377 or U.S. Patent Application No. 20050043565.

Thus, there is a need for an optical resolution process of racemic Pregabalin that overcomes the limitations of the above resolution procedures.

For the economic viability of a large scale resolution process for (S)-Pregabalin, an optimization of the following parameters is therefore desirable: cheap and readily available resolving agent; inexpensive and eco-compatible solvent or solvent mixture; energetic costs for the dissolution of diastereomeric mixture; crystallization time of the enriched diastereomeric salt.

An object of the present invention is to provide a novel, efficient, economic and commercially useful process for the optical resolution of racemic Pregabalin to obtain (S)-Pregabalin, that avoids the above-identified problems. This invention also relates to two crystalline forms of the compound of (S)-Pregabalin-(-)-O,O’-dibenzoyl-L-tartrate (VII).

**Summary of the invention**

Processes are provided for preparing (S)-Pregabalin by optical resolution of racemic Pregabalin.

In one embodiment, the invention provides a process for preparing (S)-Pregabalin, or a hydrate, a solvate, a polymorph thereof, by optical resolution of racemic Pregabalin comprising:

a) dissolving racemic Pregabalin with a chiral acid resolving agent of Formula (VI)
wherein $R_i$ and $R_2$ are the same and each is hydrogen or methyl, and an acid, in at least a suitable solvent;

b) pouring the solution in water in order to precipitate the enriched diastereomeric salt;

c) recovering the enriched diastereomeric salt;

d) enriching the collected diastereomeric salt by recrystallizing it in at least a suitable solvent to obtain an optically pure diastereomeric salt;

e) isolating free (S)-Pregabalin.

In another embodiment, the invention provides a process for preparing (S)-Pregabalin, or a hydrate, a solvate, a polymorph thereof, by optical resolution of racemic Pregabalin comprising:

a) dissolving racemic Pregabalin with a suitable acid in water;

b) adding a chiral acid resolving agent of Formula (VI)

wherein $R_i$ and $R_2$ are the same and each is hydrogen or methyl;

c) mixing the suspension at a suitable temperature in order to form the enriched diastereomeric salt;
d) recovering the enriched diastereomeric salt;
e) enriching the collected diastereomeric salt by recrystallizing it in at least a suitable solvent to obtain an optically pure diastereomeric salt;
f) isolating free (S)-Pregabalin.

In another embodiment, the invention provides a process for preparing (S)-Pregabalin, or a hydrate, a solvate, a polymorph thereof, by optical resolution of racemic Pregabalin, comprising:

a) suspending racemic Pregabalin with a chiral acid resolving agent of Formula (VI)

\[
\begin{align*}
\text{HOOC} & \quad \text{O} \\
& \quad \text{O} \\
& \quad \text{COOH} \\
\text{R}_1 - \text{O} & \quad \text{O} \\
& \quad \text{R}_2
\end{align*}
\]

(VI)

wherein \( R_1 \) and \( R_2 \) are the same and each is hydrogen or methyl; and an acid, in at least a suitable solvent;
b) heating the suspension;
c) cooling the suspension obtained in step b);
d) recovering an optically pure diastereomeric salt;
e) isolating free (S)-Pregabalin.

In another embodiment, the invention provides a process for isolating (S)-Pregabalin, or a hydrate, a solvate, a polymorph thereof from the optically pure diastereomeric salt of formula (VII)
wherein $R_i$ and $R_2$ are the same and each is hydrogen or methyl, comprising:

a) dissolving the optically pure diastereomeric salt in at least a suitable solvent;

b) adding a base in order to precipitate free (S)-Pregabalin;

c) recovering free (S)-Pregabalin.

In another embodiment, the invention provides a pharmaceutical composition comprising (S)-Pregabalin made by optical resolution of racemic Pregabalin of the present invention optionally together with at least one pharmaceutically acceptable excipient.

In another embodiment, the invention provides the use of (S)-Pregabalin made by optical resolution of racemic Pregabalin of the present invention for the preparation of a medicament.

In another embodiment, the invention provides (S)-Pregabalin made by optical resolution of racemic Pregabalin of the present invention for use as a medicament.

In another embodiment, the invention provides (S)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate or a hydrate, a solvate, a polymorph thereof of Formula (Vila).
In another embodiment, the invention provides a crystalline Form α of (S)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate (Vila), characterized by an X-ray powder diffraction pattern comprising peaks at about 9.7, 14.1, 16.3, 17.4, 19.4, 19.8, 21.6, 24.1° ± 0.2° 2θ and a differential scanning calorimetry endothermic maximum peak at about 164°C.

In another embodiment, the invention provides a crystalline Form β of (S)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate (Vila), characterized by an X-ray powder diffraction pattern comprising peaks at about 7.1, 11.6, 13.4, 16.3, 17.3, 18.3, 22.8, 23.7° ± 0.2° 2θ and a differential scanning calorimetry endothermic maximum peak at about 160°C.

**Brief Description of the Drawings**

Figure 1 provides an XRPD pattern of crystalline Form α of (S)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate (Vila).

Figure 2 provides a DSC thermogram of crystalline Form α of (S)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate (Vila). It shows a peak at 163.73 0°C with an onset at 160.99 0°C.

Figure 3 provides an XRPD pattern of crystalline Form β of (S)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate (Vila).

Figure 4 provides a DSC thermogram of crystalline Form β of (S)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate (Vila). It shows a peak at 159.81 0°C with an onset at 157.37 0°C.

**Detailed description of the invention**

AU terms as used herein in this application, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. Other more specific definitions for certain terms as used in the present application are as set forth below and are intended to apply uniformly through-out the specification and claims unless an otherwise expressly set out definition provides a broader definition.
The term "racemic" refers to a chiral sample which contains both the (+) and (-) isomers in equal amounts.

The term "chiral acid resolving agent" refers to an acidic compound that can lead to the precipitation of the diastereomer containing the desired enantiomer in high chemical and optical yields.

The term "enriched diastereomeric" refers to a compound that has more of one diastereomer than another.

The term "optically pure" refers to a sample containing greater than about 95% of the desired diastereoisomer or enantiomer by weight, preferably greater than about 98% of the desired diastereoisomer or enantiomer by weight, and more preferably greater than about 99.5% of the desired diastereoisomer or enantiomer by weight, based upon the total weight of the active ingredient. For example, the optically pure diastereomeric salt (S)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate (Vila) is substantially free of (R)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate. The term "substantially free" means that a diastereoisomer contains less than about 5% weight percent, preferably less than 2% weight percent, and more preferably less than about 0.5% weight percent of the other diastereoisomer or enantiomer.

The term "lower alcohol" refers to straight chain or branched alkyl residues containing 1 to 4 carbon atoms with one hydroxy group, such as methanol, ethanol, n-propanol, isopropanol, n-butanol, tert-butanol and the like.

The term "lower ketone" refers to straight chain or branched alkyl residues containing 3 to 6 carbon atoms with one keto group, such as acetone, methylethylketone, diethylketone, isobutylmethylketone and the like.

The term "about" encompasses the range of experimental error that may typically occur in a measurement.

The term "hydrate" refers to a solvate comprising a disclosed or claimed compound and a stoichiometric or non-stoichiometric amount of water.

The term "solvate" refers to a molecular complex comprising a disclosed or claimed compound and a stoichiometric or non-stoichiometric amount of one or more solvent molecules (e.g., EtOH).
The term "polymorph" refers to the property of some molecules and molecular complexes to assume more than one crystalline or amorphous form in the solid state.

The term "excipient" herein means any substance, not itself a therapeutic agent, used as a carrier or vehicle for delivery of a therapeutic agent to a subject or added to a pharmaceutical composition to improve its handling or storage properties or to permit or facilitate formation of a dose unit of the composition into a discrete article such as a tablet, capsule, pill, powder, granule, pellet, lozenge, pastille, elixir, syrup, solution, suspension, emulsion, drop, lotion, spray, tincture, cream, ointment, gel, unguent, suppository and transdermal devices for oral, enteral, parenteral or topical administrations.

The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The present invention provides a novel, efficient and economic method for the resolution of (S)-Pregabalin from racemic Pregabalin, particularly suited for large scale preparation. Optically pure (S)-Pregabalin was obtained by optical resolution of racemic Pregabalin.

The process of this invention is carried out with a chiral acid resolving agent and an acid, in accordance with the "Pope-Peachey" method known in the art (see, for example, Pope, W. J., Peachey, S. J., J. Chem. Soc., 75, 1066 (1899), and Sheldon, P. A., Chirotechnology, Marcel Dekker Inc., 1993).

The chiral acid resolving agent is a compound of Formula (VI)
wherein \( R_i \) and \( R_2 \) are the same and each is hydrogen or methyl; preferably \( R_i \) and \( R_2 \) are hydrogen.

The acid is selected from inorganic or organic acids, such as hydrochloric acid, sulphuric acid, phosphoric acid, formic acid, acetic acid, oxalic acid, citric acid, maleic acid, fumaric acid, lactic acid, malic acid, benzoic acid, L-tartaric acid, D-tartaric acid, S-camphor-10-sulfonic acid, methanesulfonic acid, p-toluensulfonic acid. Preferred acids are hydrochloric acid, formic acid, L-tartaric acid.

Preferably the molar ratio of racemic Pregabalin/chiral acid resolving agent/acid is 1:0.5:0.5 mole/mole or 1:0.5:1 mole/mole. This molar ratio of racemic Pregabalin/chiral acid resolving agent gave a diastereomeric salt of (S)-Pregabalin with an optical purity much higher than the obtained with other tried molar ratios.

The processs of this invention for the resolution of (S)-Pregabalin from racemic Pregabalin is exemplified in Scheme 3.

Scheme 3:
According to the process of the present invention:
- An optically pure diastereomeric salt of an optically pure diastereomeric salt of (S)-Pregabalin may be obtained straight by suspending racemic Pregabalin with a chiral acid resolving agent and an acid, in at least a suitable solvent (Method C); or
- when an enriched diastereomeric salt of (S)-Pregabalin (obtained from racemic
Pregabalin, a chiral acid resolving agent and an acid in a suitable solvent or straight in
water) is first precipitated in water, afterwards it may be further enriched by
recrystallizing it in at least a suitable solvent to obtain an optically pure diastereomeric
salt of (S)-Pregabalin (Methods A and B).

In this last case, (Methods A and B), the dissolution and/or the suspension of
racemic Pregabalin, a chiral acid resolving agent and an acid as well as the
precipitation of the diastereomeric salt in a suitable solvent and/or in water may
preferably and advantageously be carried out at the same temperature, for any
convenient period of time. A suitable temperature is from about 0°C to about 25°C;
preferably the temperature is from about 10°C to about 20°C; more preferably the
temperature is about 15°C.

The enriched diastereomeric salt was further enriched by mixing it with at least a
suitable solvent to obtain an optically pure diastereomeric salt at any convenient
temperature that provides the suspension of the diastereomeric salt for any convenient
period of time. Preferably a suitable temperature is comprised from about 40°C to
about reflux temperature of the solvent used; more preferably the temperature is the
reflux temperature of the solvent used.

Suitable solvents include, but are not limited to, an alcohol, an ester, a ketone, a
nitrile, water, or mixtures thereof. Preferred solvents include an alcohol, preferably a
lower alcohol, more preferably methanol or ethanol and still more preferably
methanol; a ketone, preferably lower ketone, more preferably acetone; or water.

One skilled in the art will appreciate that by adjusting concentration, temperature
and time or by seeding with (S)-Pregabalin(−)-O,O′-dibenzoyl-L-tartrate (Vila) or by
another inducement, the yield first of the diastereomeric salt of (S)-Pregabalin, than of
(S)-Pregabalin may be optimized.

Following or during the optical resolution of the racemic Pregabalin, the isolated
solids, diastereomeric salt or the pure enantiomer, can be recovered with methods well
known to those skilled in the art for the separation of the solid from the mother liquor,
for example by filtration, with or without the assistance of pressure and/or vacuum, or
by centrifugation, or by decantation. The collected solids are washed with at least a
suitable solvent and dried by conventional methods well known to those skilled in the
art. The isolated solids may be dried at each stage in the resolution or carried on the next step as solvent-wet solids with comparable results.

In one embodiment, the invention provides a process for preparing (S)-Pregabalin, or a hydrate, a solvate, a polymorph thereof, by optical resolution of racemic Pregabalin comprising:

a) dissolving racemic Pregabalin with a chiral acid resolving agent of Formula (VI)

\[
\begin{align*}
\text{HOOC} & \quad \text{COOH} \\
\text{R}_1 & \quad \text{R}_2 \\
\end{align*}
\]

wherein \( R_1 \) and \( R_2 \) are the same and each is hydrogen or methyl, and an acid, in at least a suitable solvent;

b) pouring the solution in water in order to precipitate the enriched diastereomeric salt;

c) recovering the enriched diastereomeric salt;

d) enriching the collected diastereomeric salt by recrystallizing it in at least a suitable solvent to obtain an optically pure diastereomeric salt;

e) isolating free (S)-Pregabalin.

The acid is selected from inorganic or organic acids, as defined above. Preferably the acid is an organic acid, more preferably L-tartaric acid.

Preferably, \( R_1 \) and \( R_2 \) are hydrogen.

Preferably the molar ratio of racemic Pregabalin/chiral acid resolving agent/acid is 1:0.5:0.5 mol/mol.

Any solvent capable of dissolving the mixture of racemic Pregabalin, chiral acid resolving agent and acid (step a)) is a suitable solvent of the invention. Suitable solvents include but are not limited to alcohols, preferably lower alcohols; preferably methanol or ethanol and still more preferably methanol. Preferably racemic Pregabalin
is in a ratio of about 1:5 to about 1:10 weight/volume to the solvent used (step a)). Preferably the solvent used is in a ratio of about 1:5 to about 1:20 volume/volume to the water used (step b)).

A suitable temperature for dissolving the mixture of racemic Pregabalin, chiral acid resolving agent and acid (step a)) is preferably from about 0°C to about 25°C; more preferably the temperature is from about 10°C to about 20°C; yet more preferably the temperature is about 15°C.

A suitable temperature for precipitating the enriched diastereomeric salt from water (step b) is preferably from about 0°C to about 25°C; preferably the temperature is from about 10°C to about 20°C; more preferably the temperature is about 15°C.

The enriched diastereomeric salt (step c)) can be recovered with methods well known to those skilled in the art for the separation of the solid from the mother liquor, as described above. The collected solid is washed with water and optionally dried by conventional methods well known to those skilled in the art.

Any solvent capable of suspending the diastereomeric salt and from which the enriched diastereomeric salt may be isolated (step d)) is a suitable solvent of the invention. Suitable solvents include but are not limited to ketones, preferably lower ketones, more preferably acetone. The diastereomeric salt is preferably in a ratio of about 1:5 to about 1:10 weight/volume to the solvent used. Any convenient temperature that provides the suspension of the diastereomeric salt may be employed for any convenient period of time. Preferably a suitable temperature for suspending the diastereomeric salt is from about 40°C to about reflux temperature of the solvent used; more preferably the temperature is the reflux temperature of the solvent used. Preferably a suitable temperature for recovering the enriched diastereomeric salt is from about 0°C to about 25°C; preferably from about 10°C to about 20°C; more preferably the temperature is about 15°C.

The optically pure diastereomeric salt was then recovered with methods well known to those skilled in the art for the separation of the solid from the mother liquor, as described above. The collected solid is washed with the solvent used in step d), and optionally dried by conventional methods well known to those skilled in the art. An optically pure diastereomeric salt was obtained. Preferably an optically pure
diastereomeric salt product with an enantiopurity of at least 99.5:0.5 (S/R) was obtained.

In another embodiment, the invention provides a process for preparing (S)-Pregabalin, or a hydrate, a solvate, a polymorph thereof, by optical resolution of racemic Pregabalin comprising:

a) dissolving racemic Pregabalin with a suitable acid in water;

b) adding a chiral acid resolving agent of Formula (VI)

\[
\begin{align*}
\text{HOOC} & \quad \text{COOH} \\
\text{R}_1 & \quad \text{O} \\
\text{R}_1 & \quad \text{O} \\
\text{R}_2 & \\
\end{align*}
\]

wherein \(R_1\) and \(R_2\) are the same and each is hydrogen or methyl;

c) mixing the suspension at a suitable temperature in order to form the enriched diastereomeric salt;

d) recovering the enriched diastereomeric salt;

e) enriching the collected diastereomeric salt by recrystallizing it in at least a suitable solvent to obtain an optically pure diastereomeric salt;

f) isolating free (S)-Pregabalin.

Preferably, \(R_1\) and \(R_2\) are hydrogen.

The acid is selected from inorganic or organic acids, as defined above. Preferably the acid is an organic acid, more preferably L-tartaric acid.

Preferably the molar ratio of racemic Pregabalin/acid/chiral acid resolving agent is 1:1:0.5 mol/mol.

Preferably racemic Pregabalin is in a ratio of about 1:20 to about 1:50 weight/volume to the water used.

A suitable temperature in order to dissolve or mix the reagents (steps a) and c)) is preferably from about 0°C to about 25°C; more preferably the temperature is from about 10°C to about 20°C; yet more preferably the temperature is about 15°C. Mixing
can be performed over any convenient period of time, preferably over a period between six hours to several hours; more preferably for about twelve hours.

The enriched diastereomeric salt (step d)) can be recovered with methods well known to those skilled in the art for the separation of the solid from the mother liquor, as described above. The collected solid is washed with water and optionally dried by conventional methods well known to those skilled in the art.

As described above, any solvent capable of suspending the diastereomeric salt and from which the enriched diastereomeric salt may be isolated is a suitable solvent for step e). Suitable solvents include but are not limited to ketones, preferably lower ketones, more preferably acetone. The diastereomeric salt is preferably in a ratio of about 1:5 to about 1:10 weight/volume to the solvent used. Any convenient temperature that provides the suspension of the diastereomeric salt may be employed for any convenient period of time. Preferably a suitable temperature for suspending the diastereomeric salt is from about 40°C to about reflux temperature of the solvent used; more preferably the temperature is the reflux temperature of the solvent used. Preferably a suitable temperature for recovering the enriched diastereomeric salt is from about 0°C to about 25°C; more preferably from about 10°C to about 20°C; yet more preferably the temperature is about 15°C.

The optically pure diastereomeric salt was then recovered with methods well known to those skilled in the art for the separation of the solid from the mother liquor, as described above. The collected solid is washed with the solvent used in step e), and optionally dried by conventional methods well known to those skilled in the art. An optically pure diastereomeric salt was obtained. Preferably an optically pure diastereomeric salt product with an enantiopurity of at least 99.5:0.5 (S/R) was obtained.

In another embodiment, the invention provides a process for preparing (S)-Pregabalin, or a hydrate, a solvate, a polymorph thereof, by optical resolution of racemic Pregabalin, comprising:

a. suspending racemic Pregabalin with a chiral acid resolving agent of Formula (VI)
wherein \( R_i \) and \( R_2 \) are the same and each is hydrogen or methyl; and an acid, in at least a suitable solvent;

b. heating the suspension;
c. cooling the suspension obtained in step b);
d. recovering an optically pure diastereomeric salt;
e. isolating free (S)-Pregabalin.

The chiral acid resolving agent is a compound of Formula (VI) as defined above. Preferably, \( R_i \) and \( R_2 \) are hydrogen.

The acid is selected from inorganic or organic acids, as defined above. In a preferred embodiment of the present invention, the acid is an inorganic acid; more preferably hydrochloric acid (37%). In another preferred embodiment of the present invention, the acid is an organic acid, more preferably formic acid. Preferably the molar ratio of racemic Pregabalin/chiral acid resolving agent/acid is 1:0.5:0.5 mole/mole.

Any solvent capable of suspending the mixture of racemic Pregabalin, chiral acid resolving agent and acid (step a)) and capable of recovering the diastereomeric salt (step d)) is a suitable solvent of the invention. Suitable solvents include but are not limited to ketones, preferably lower ketones, more preferably acetone. Preferably racemic Pregabalin is in a ratio of about 1:5 to about 1:20 weight/volume to the solvent used.

The suspension obtained in step a) is heated in step b) to a suitable temperature. Any convenient temperature that provides the suspension (step b)) of the diastereomeric salt may be employed for any convenient period of time. Preferably, the temperature is comprised from about 40°C to about reflux temperature of the solvent used; more preferably the temperature is the reflux temperature of the solvent.
used. Heating (step b)) may be performed over any convenient period of time, preferably over a period between one hour to three hours; more preferably for about one hour.

In step d) the suspension is cooled to recover the diastereomeric salt. A suitable temperature is preferably from about 0°C to about 25°C; more preferably from about 10°C to about 20°C; yet more preferably the temperature is about 15°C. The optically pure diastereomeric salt may be recovered with methods well known to those skilled in the art for the separation of the solid from the mother liquor, as described above. The collected solid may be washed with the solvent used in step a), and optionally dried by conventional methods well known to those skilled in the art. An optically pure diastereomeric salt was obtained. Preferably an optically pure diastereomeric salt product with an enantiopurity of at least 99:1 (S/R) was obtained.

In another step of the process of this invention, free (S)-Pregabalin is obtained from the diastereomeric salt of formula (VII), preferably from (S)-Pregabalin-(−)-O,O'-dibenzoyl-L-tartrate (Vila), with methods well known to those skilled in the art. The conditions under which an enantiomer is recovered from its diastereomeric salt with a chiral resolving agent are well known to those skilled in the art, and any such condition known in the art may be used to obtain free (S)-Pregabalin from the diastereomeric salt of formula (VII), more preferably from (S)-Pregabalin-(−)-O,O'-dibenzoyl-L-tartrate (Vila). (S)-Pregabalin, or a hydrate, a solvate, a polymorph thereof, can be performed, for example, by neutralising the diastereomeric salt formed with a base to separate (S)-Pregabalin and the salt of the chiral acid resolving agent used, which can be recovered to use in other reaction cycles.

In another embodiment, the invention provides a process for isolating (S)-Pregabalin, or a hydrate, a solvate, a polymorph thereof from the optically pure diastereomeric salt of formula (VII)
wherein R\textsubscript{i} and R\textsubscript{2} are the same and each is hydrogen or methyl, comprising:

a) dissolving the optically pure diastereomeric salt in at least a suitable solvent;

b) adding a base in order to precipitate free (S)-Pregabalin;

c) recovering free (S)-Pregabalin.

Preferably, R\textsubscript{i} and R\textsubscript{2} are hydrogen.

Any solvent capable of dissolving the optically pure diastereomeric salt (step a)) is a suitable solvent for step a). Suitable solvents include but are not limited to alcohols, preferably lower alcohols, preferably methanol or ethanol and still more preferably methanol. Preferably diastereomeric salt of (S) Pregabalin is in a ratio of about 1:1 to about 1:5 weight/volume to the solvent used. Preferably, the solution of step a) is cooled to a temperature from about -5°C to about 5°C, preferably the temperature is about 0°C. A suitable temperature to recover the diastereomeric salt is from about -5°C to about 5°C; preferably the temperature is about 0°C.

Examples of bases include, but are not limited to, aqueous ammonia (33%), sodium hydroxide, sodium bicarbonate, sodium carbonate, potassium hydroxide, potassium bicarbonate, potassium carbonate; preferably aqueous ammonia (33%). Preferably the optically pure diastereomeric salt is in a ratio of 1:1 mole/mole to the base used.

(S)-Pregabalin was then recovered with methods well known to those skilled in the art for the separation of the solid from the mother liquor, as described above. The collected solid is washed with the solvent used in the process and dried by conventional methods well known to those skilled in the art. An optically pure (S)-Pregabalin was obtained. Preferably an optically pure (S)-Pregabalin with an enantiopurity of at least 99.95:0.05 (S/R) was obtained.
Moreover, the chiral acid resolving agent can be recovered from the mother liquors by means of neutralization with a suitable acid, in order to precipitate the chiral acid resolving agent. Any acid is a suitable acid of the invention. The acid is selected from inorganic or organic acids. Examples of acids include, but are not limited to, aqueous hydrochloric acid, sulphuric acid, formic acid, acetic acid.

The solid is collected by means of methods well known to those skilled in the art, for the separation of the solid from the mother liquor, as described above; washed with the solvent used in the process, optionally dried by conventional methods well known to those skilled in the art and recycled to the resolution process.

The diastereomeric salt of (S)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate of Formula (VII) is novel.

In another embodiment, the invention provides (S)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate, or a hydrate, a solvate, a polymorph thereof of Formula (Vila):

The compounds of this invention may exist in different polymorphic forms, i.e., different crystalline forms.

Various polymorphs formed by the compound of formula (Vila), forming part of this invention, may be prepared by crystallization of compound of formula (Vila) under different conditions. For example, using different solvents commonly used or their mixtures for crystallization; using different temperatures for crystallizations; various modes of cooling, ranging from very fast to very slow cooling during
crystallizations. Polymorphs may also be obtained by heating the compound followed by gradual or fast cooling.

The presence of polymorphs may be determined by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC).

In another embodiment, the invention provides a crystalline Form α of (S)-Pregabalin-(-)-O,O’-dibenzoyl-L-tartrate (Vila), characterized by an X-ray powder diffraction pattern as depicted in Figure 1, which comprises characteristic diffraction peaks at about 9.7, 14.1, 16.3, 17.4, 19.4, 19.8, 21.6, 24.1° +/- 0.2° 2Θ.

A crystalline Form α of (S)-Pregabalin-(-)-O,O’-dibenzoyl-L-tartrate (Vila) has the characteristic DSC thermogram as depicted in Figure 2. The DSC thermogram shows a characteristic endothermic maximum peak at about 164°C.

In another embodiment, the invention provides a crystalline Form β of (S)-Pregabalin-(-)-O,O’-dibenzoyl-L-tartrate (Vila), characterized by an X-ray powder diffraction pattern as depicted in Figure 3, which comprises characteristic diffraction peaks at about 7.1, 11.6, 13.4, 16.3, 17.3, 18.3, 22.8, 23.7° +/- 0.2° 2Θ.

A crystalline Form β of (S)-Pregabalin-(-)-O,O’-dibenzoyl-L-tartrate (Vila) has the characteristic DSC thermogram as depicted in Figure 4. The DSC thermogram shows a characteristic endothermic maximum peak at about 160°C.

A crystalline form β of (S)-Pregabalin-(-)-O,O’-dibenzoyl-L-tartrate (Vila) can be also obtained by dissolving crude (S)-Pregabalin and (-)-O,O’-dibenzoyl-L-tartraric acid in at least a suitable polar solvent and distilling off the solvent. Any solvent capable of dissolving (S)-Pregabalin and (-)-O,O’-dibenzoyl-L-tartraric acid is a suitable solvent. Suitable solvents include but are not limited to alcohols, preferably lower alcohols, more preferably methanol.

Beneficial aspects of the process of the present invention have been identified and can be summarised as follows:

a) The chiral acid resolving agent is cheap and commercially available.

b) Typically, 0.5 molar equivalents of the chiral acid resolving agent are used relative to the racemic Pregabalin. Unlike the classical resolution approaches, which require stoichiometric amounts of the chiral resolving agent, this process utilizes sub-stoichiometric quantities of the chiral resolving agent.

c) Inexpensive and eco-compatible solvent or solvent mixture are used.
d) The enriched diastereomeric salt of (S)-Pregabalin can be obtained in an aqueous medium giving a great advantage.

e) The enriched diastereomeric salt of (S)-Pregabalin can be obtained without heating.

f) The present resolution method allow to obtain an optically pure (S)-Pregabalin in high yield and with an enantiomeric purity over 99.5%, with favourable energetic costs for the dissolution of diastereomeric mixture and favourable crystallization time of the enriched diastereomeric salt.

g) The chiral acid resolving agent can be easily recovered in a state of high purity, such that it can be re-used in one or more subsequent resolution processes.

Thus, for the above reasons, the process of the present invention has both economic and environmental advantages.

As mentioned above the compound of the invention has useful therapeutic properties. (S)-Pregabalin may be administered per se or, preferably as a pharmaceutical composition.

In another embodiment, the invention provides a pharmaceutical composition comprising (S)-Pregabalin made by optical resolution of racemic Pregabalin of the present invention optionally together with at least one pharmaceutically acceptable excipient.

Excipients include, by way of illustration and not limitation, diluents, fillers, agglutinants, disintegrants, disintegration inhibitors, absorption accelerators, binders, carriers, suspending/dispersing agents, film formers/coatings, adhesives, antiadherents, wetting agents, lubricants, glidants, preservatives, sorbents, surface active agents, substances added to mask or counteract a disagreeable taste or odor, flavorings, colorants, fragrances, aromatising agents, sweeteners and substances added to improve appearance of the composition.

A person skilled in the art is aware of a whole variety of such excipient compounds suitable to formulate a pharmaceutical composition. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.
(S)-Pregabalin, together with a conventionally employed excipient, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets, capsules, pills, powders, granules, pellets, lozenges, pastilles, or liquids, such as solutions, suspensions, emulsions, drops, lotions, sprays, tinctures, syrups, elixirs, or capsules filled with the same, all for oral use, or in the form of sterile injectable solutions for parenteral (including subcutaneous, intramuscular, and intravenous) use, or in the form of suppositories for rectal use, or in the form of creams, ointments, gels, unguents for topical use and other forms suitable for the inhalatory or transdermal administrations. Such pharmaceutical compositions and unit dosage forms thereof may comprise ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

Pharmaceutical compositions containing (S)-Pregabalin can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Generally, the compounds of this invention are administered in a pharmaceutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

The pharmaceutical compositions of the present invention can be administered by a variety of routes including oral, rectal, parenteral (including subcutaneous, intravenous, intramuscular), topical, transdermal, ophthalic and intranasal. The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. Typical unit dosage forms include prefilled, premeasured ampoules or syringes of the liquid compositions or pills, tablets, capsules, powders, granules, pellets, lozenges, pastilles, suppositories or the like in the case of solid compositions. In such compositions, (S)-Pregabalin is usually a minor component (from about 0.1 to about 50% by weight or preferably
from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder, such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfme cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose salts and other substituted and unsubstituted celluloses, gum tragacanth or gelatine; an excipient, such as starch or lactose, a disintegrating agent, such as alginic acid, primogel, or corn starch; a lubricant, such as magnesium stearate, hydrogenated castor oil, polyethylene glycol; a glidant, such as colloidal silicon dioxide; a sweetening agent, such as sorbitol, sucrose, aspartame or saccharin; or a flavoring agent, such as maltol, vanillin, menthol, citric acid, pepper-mint, methyl salicylate, or orange flavoring.

Liquid forms suitable for oral administration may include a suitable aqueous or non-aqueous vehicle with buffers, suspending and dispersing agents, colorants, flavors and the like.

Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As above mentioned, (S)-Pregabalin in such compositions is typically a minor component, with the remainder being the injectable carrier and the like.

The above described components for orally administered or injectable compositions are merely representative. Further materials as well as processing techniques and the like are set out in Part 5 of Remington ‘s Pharmaceutical Sciences, 20th Edition, 2000, Merck Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference. (S)-Pregabalin of this invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can also be found in the incorporated materials in Remington ‘s Pharmaceutical Sciences.

In another embodiment, the invention provides the use of (S)-Pregabalin made by optical resolution of racemic Pregabalin of the present invention for the preparation of a medicament. (S)-Pregabalin can be used, but not limited to, for the prophylaxis and/or treatment of condition or disorder related to diminished concentration of
GABA; for the preparation of an anti-convulsant medicament, an anti-psychotic medicament, an anti-anxiety medicament, an anti-pain medicament. Compositions of the present invention are useful for, but not limited to, the treatment of pain, epilepsy, convulsions, psychiatric disorders, attention deficit hypersensitivity disorder, anxiety and mood disorders. The compound of the present invention for their therapeutic or preventive use in the above mentioned pathologies will be preferably used in a pharmaceutical composition suitable for the oral, rectal, parenteral (including subcutaneous, intravenous, intramuscular), topical, transdermal, ophtalmic and intranasal administration.

Although the most suitable administration in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral.

In another embodiment, the invention provides (S)-Pregabalin made by optical resolution of racemic Pregabalin of the present invention for use as a medicament.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.

In the following, the present invention shall be illustrated by means of some examples, which are not construed to be viewed as limiting the scope of the invention.

Racemic Pregabalin can be prepared in accordance with well-known procedures. Suitable processes, without restriction, are illustratively disclosed in U.S. Patent No. 5,637,767; U.S. Patent No. 6,924,377 or U.S. Patent Application No. 20050043565.

**Examples**

The NMR, HPLC, DSC and XRPD data provided in the examples described below are obtained as follow:

1H NMR spectra were performed on a Jeol Eclipse 300, using CD3OD as solvent. The chemical shifts are reported in δ ppm relative to TMS.

Chiral HPLC analysis was performed on an Agilent 1100 with simple linear gradient of 0.05 M triethylamine (adjusted to pH 3 with phosphoric acid)/acetonitrile on a Spheri-5 RP-18 cartridge column and a wavelength of 340 nm.
DSC thermal analysis was performed on a Mettler Toledo Star 822e differential scanning calorimeter. Approximately 2-5 mg samples were placed in aluminium pans and heated from 30 to 250°C in a dry nitrogen atmosphere at a heating rate of 10°C/minute.

XRPD analysis was performed on a APD 2000 Ital Structures diffractometer at room temperature, using a CuKa tube (40 kV, 30 mA, λ = 1.5418 Å) as the X-ray source. Data collection was made in 2Θ step scan mode, at a scan speed of 0.02°/s in the range of 3° to 40° in 2Θ. Approximately 100 mg samples were accurately ground and placed on an aluminium sampler.

Enantiomeric purity of the diastereomeric salts were determined by means of derivatization with FDAA (l-fluoro-2,4-dinitrophenyl-5-L-alanine amide, Marfey’s reagent) in acetone and 1.0 M sodium bicarbonate at 40°C.

**Example 1**

Resolution of racemic Pregabalin (Method A)

**Step 1**

Racemic Pregabalin (16 g, 100.6 mmol), (-)-O,O'-dibenzoyl-L-tartaric acid (VI) (17.9 g, 50 mmol) and L-tartaric acid (7.5 g, 50 mmol) were dissolved in methanol (50 ml) at 15°C. The resulting solution was poured in a 1000 ml flask, containing water (500 ml) at 15°C. While stirring, a white solid precipitated. The solid was collected by filtration, washed with water and dried under vacuum at 50°C to give an enriched diastereomeric salt (-)-O,O'-dibenzoyl-L-tartrate (VII) (21.5 g).

Chiral Purity (HPLC): (S)/(R) = 87/13.

**Step 2**

The enriched diastereomeric salt (-)-O,O'-dibenzoyl-L-tartrate (VII) (21.5 g) was suspended in acetone (110 ml), and the mixture was refluxed for ten minutes. After cooling to 15°C, the solid was collected by filtration, washed with acetone and dried under vacuum at 50°C to afford the diastereomeric salt (S)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate (VII) (17.2 g) as a white to off-white solid.

Overall yield: 66%.

Chiral Purity (HPLC): (S) > 99.5 %.
1H NMR (CD$_3$OD, 300 MHz): δ 0.87-0.92 (t, J=6.75 Hz, 6H), 1.17-1.22 (t, J=7.05 Hz, 2H), 1.55-1.76 (m, IH), 2.11-2.22 (m, IH), 2.36-2.38 (dd, J$_1$=5.22 Hz, J$_2$=1.68 Hz, 2H), 2.88-2.90 (m, 2H), 5.90 (s, IH), 7.46-7.51 (m, 4H), 7.59-7.62 (m, 2H), 8.11-8.14 (m, 4H).

XRPD pattern as substantially depicted in Figure 1, with characteristic diffraction peaks at 9.7, 14.1, 16.3, 17.4, 19.4, 19.8, 21.6, 24.1° ± 0.2° 2Θ.

DSC thermogram as substantially depicted in Figure 2, with an endothermic maximum peak at about 164°C.

**Example 2**

Resolution of racemic Pregabalin (Method B)

**Step 1**

To a solution of racemic Pregabalin (16 g, 100.6 mmol) and L-tartaric acid (15 g, 100 mmol) in water (500 ml) at 15°C, (-)-O,O’-dibenzoyl-L-tartaric acid (VI) (17.9 g, 50 mmol) was added. The resulting suspension was stirred at 15°C for twelve hours. The solid was collected by filtration, washed with water and dried under vacuum at 50°C to give an enriched diastereomeric salt (-)-O,O’-dibenzoyl-L-tartrate (VII) (23 g).

Chiral Purity (HPLC): (S)/(R) = 84/16.

**Step 2**

The enriched diastereomeric salt (-)-O,O’-dibenzoyl-L-tartrate (VII) (23 g) was suspended in acetone (120 ml), and the mixture was refluxed for ten minutes. After cooling to 15°C, the solid was collected by filtration, washed with acetone and dried under vacuum at 50°C to afford the diastereomeric salt (S)-Pregabalin(-)-O,O’-dibenzoyl-L-tartrate (VII) (18.4 g) as a white to off-white solid.

Overall yield: 71%.

Chiral Purity (HPLC): (S) > 99.5%.
$^1$HNMR (CD$_3$OD, 300 MHz): $\delta$ 0.87-0.92 (t, J=6.75 Hz, 6H), 1.17-1.22 (t, J=7.05 Hz, 2H), 1.55-1.76 (m, IH), 2.11-2.22 (m, IH), 2.36-2.38 (dd, Ji=5.22 Hz, $J_2$=1.68 Hz, 2H), 2.88-2.90 (m, 2H), 5.90 (s, IH), 7.46-7.51 (m, 4H), 7.59-7.62 (m, 2H), 8.11-8.14 (m, 4H).

XRPD pattern as substantially depicted in Figure 1, with characteristic diffraction peaks at 9.7, 14.1, 16.3, 17.4, 19.4, 19.8, 21.6, 24.1° ± 0.2° 2Θ.

DSC thermogram as substantially depicted in Figure 2, with an endothermic maximum peak at about 164°C.

Example 3

Resolution of racemic Pregabalin (Method C)

Step 1

Racemic Pregabalin (16 g, 100.6 mmol), (-)-O,O'-dibenzoyl-L-tartaric acid (VI) (17.9 g, 50 mmol) and formic acid (2.3 g, 50 mmol) were suspended under stirring in acetone (150 ml). The resulting mixture was refluxed for one hour. After cooling to 15°C, the solid was collected by filtration, washed with acetone and dried under vacuum at 50°C to afford the diastereomeric salt (S)-Pregabalin(-)-O,O'-dibenzoyl-L-tartrate (VII) (12 g).

Yield: 46%

Chiral Purity (HPLC): (S) > 98.5%.

$^1$H NMR (CD$_3$OD, 300 MHz): $\delta$ 0.87-0.92 (t, J=6.75 Hz, 6H), 1.17-1.22 (t, J=7.05 Hz, 2H), 1.55-1.76 (m, IH), 2.11-2.22 (m, IH), 2.36-2.38 (dd, Ji=5.22 Hz, $J_2$=1.68 Hz, 2H), 2.88-2.90 (m, 2H), 5.90 (s, IH), 7.46-7.51 (m, 4H), 7.59-7.62 (m, 2H), 8.11-8.14 (m, 4H).

XRPD pattern as substantially depicted in Figure 1, with characteristic diffraction peaks at 9.7, 14.1, 16.3, 17.4, 19.4, 19.8, 21.6, 24.1° ± 0.2° 2Θ.
DSC thermogram as substantially depicted in Figure 2, with an endothermic maximum peak at about 164°C.

Example 4

Resolution of racemic Pregabalin (Method C)

Step 1

Racemic Pregabalin (16 g, 100.6 mol), (-)-O,O'-dibenzoyl-L-tartaric acid (VI) (17.9 g, 50 mmol) and hydrochloric acid (37%) (4.96 g, 50 mmol of anhydrous HCl) were suspended under stirring in acetone (150 ml). The resulting mixture was refluxed for one hour. After cooling to 15°C, the solid was collected by filtration, washed with acetone and dried under vacuum at 50°C to afford the diastereomeric salt (S)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate (VII) (18.2 g) as a white to off-white solid.

Overall yield: 70%.

Chiral Purity (HPLC): (S) > 99.5%.

1H NMR (CD3OD, 300 MHz): \( \delta 0.87-0.92 \) (t, \( J=6.75 \) Hz, 6H), 1.17-1.22 (t, \( J=7.05 \) Hz, 2H), 1.55-1.76 (m, IH), 2.11-2.22 (m, IH), 2.36-2.38 (dd, \( J_1=5.22 \) Hz, \( J_2=1.68 \) Hz, 2H), 2.88-2.90 (m, 2H), 5.90 (s, IH), 7.46-7.51 (m, 4H), 7.59-7.62 (m, 2H), 8.11-8.14 (m, 4H).

XRPD pattern as substantially depicted in Figure 1, with characteristic diffraction peaks at 9.7, 14.1, 16.3, 17.4, 19.4, 19.8, 21.6, 24.1 ° ± 0.2° 2Θ

DSC thermogram as substantially depicted in Figure 2, with an endothermic maximum peak at about 164°C.

Example 5

Isolation of free (S)-Pregabalin

(S)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate (VII) with an enantiopurity of 99.5:0.5 (S)/(R) (15 g, 29 mmol) was dissolved under stirring in methanol (30 ml), and the resulting solution was cooled to 0°C. Aqueous ammonia (33%) (1.50 g, 29 mmol of anhydrous NH3) was added. The solid precipitated was collected by
filtration, washed with cold methanol and dried under vacuum at 50°C to afford (S)-Pregabalin (4.3 g).

Yield: 93%.

Chiral Purity (HPLC): (S)/(R) = 99.95:0.05

\( ^1H \) NMR (CD\(_3\)OD, 300 MHz): \( \delta \) 0.90-0.94 (dd, \( J_1=6.57 \) Hz, \( J_2=4.89 \) Hz, 6H), 1.16-1.22 (t, \( J=7.05 \) Hz, 2H), 1.62-1.74 (m, IH), 1.98-2.10 (m, IH), 2.15-2.47 (m, 2H), 2.79-2.98 (m, 2H).

Example 6
Preparation of form β of (S)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate (VII)

(S)-Pregabalin (10 g, 62.9 mmol) and (-)-O,O'-dibenzoyl-L-tartaric acid (VI) (22.5 g, 62.9 mmol) were dissolved in methanol (50 ml) at room temperature. The solvent was distilled off under vacuum to afford the crystalline form β of (S)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate (VII) (32.5 g) as a white to off-white solid.

\( ^1H \) NMR (CD\(_3\)OD, 300 MHz): \( \delta \) 0.87-0.92 (t, \( J=6.75 \) Hz, 6H), 1.17-1.22 (t, \( J=7.05 \) Hz, 2H), 1.55-1.76 (m, IH), 2.11-2.22 (m, IH), 2.36-2.38 (dd, \( J_1=5.22 \) Hz, \( J_2=1.68 \) Hz, 2H), 2.88-2.90 (m, 2H), 5.90 (s, IH), 7.46-7.51 (m, 4H), 7.59-7.62 (m, 2H), 8.11-8.14 (m, 4H).

XRPD pattern as substantially depicted in Figure 3, with characteristic diffraction peaks at ± 7.1, 11.6, 13.4, 16.3, 17.3, 18.3, 22.8, 23.7° ± 0.2° 2Θ.

DSC thermogram as substantially depicted in Figure 4, with an endothermic maximum peak at about 160°C.
Claims

1. A process for preparing (S)-Pregabalin, or a hydrate, a solvate, a polymorph thereof, by optical resolution of racemic Pregabalin comprising:
   a) dissolving racemic Pregabalin with a chiral acid resolving agent of Formula (VI)

\[
\text{HOOC} \quad \text{O} \quad \text{COOH}
\]

(VI)

wherein \( R_1 \) and \( R_2 \) are the same and each is hydrogen or methyl, and an acid, in at least a suitable solvent,;
   b) pouring the solution in water in order to precipitate the enriched diastereomeric salt;
   c) recovering the enriched diastereomeric salt;
   d) enriching the collected diastereomeric salt by recrystallizing it in at least a suitable solvent to obtain an optically pure diastereomeric salt;
   e) isolating free (S)-Pregabalin.

2. The process according to claim 1, wherein \( R_1 \) and \( R_2 \) are hydrogen.

3. The process according to claim 1, wherein the acid is selected from inorganic or organic acids, such as hydrochloric acid, sulphuric acid, phosphoric acid, formic acid, acetic acid, oxalic acid, citric acid, maleic acid, fumaric acid, lactic acid, malic acid, benzoic acid, L-tartaric acid, D-tartaric acid, S-camphor-10-sulfonic acid, methanesulfonic acid, p-toluensulfonic acid.

4. The process according to claim 3, wherein the acid is an organic acid, preferably L-tartaric acid.

5. The process according to claim 1, wherein the racemic Pregabalin/chiral acid resolving agent/acid molar ratio is 1:0.5:0.5 mole/mole.
6. The process according to claim 1, wherein the solvent used in step a) is an alcohol, preferably a lower alcohol, more preferably methanol or ethanol.
7. The process according to claim 6, wherein the solvent is methanol.
8. The process according to claim 1, wherein racemic Pregabalin in step a) is in a ratio of about 1:5 to about 1:10 weight/volume to the solvent used.
9. The process according to claim 1, wherein steps a) and b) are carried out at a temperature from about 0°C to about 25°C; preferably from about 10°C to about 20°C; more preferably the temperature is about 15°C.
10. The process according to claim 1, wherein the solvent used in step b) is in a ratio of about 1:5 to about 1:20 volume/volume to the water used.
11. The process according to claim 1, wherein said solvent used in step d) is a ketone; preferably a lower ketone; more preferably acetone.
12. The process according to claim 1, wherein the diastereomeric salt in step d) is in a ratio of about 1:5 to about 1:10 weight/volume to the solvent used.
13. The process according to claim 1, wherein in step d):
   a) the diastereomeric salt is suspended at a temperature from about 40°C to about reflux temperature of the solvent used; preferably the temperature is the reflux temperature of the solvent used;
   b) the enriched diastereomeric salt is recovered at a temperature comprised from about 0°C to about 25°C; preferably from about 10°C to about 20°C; more preferably the temperature is about 15°C.
14. A process for preparing (S)-Pregabalin, or a hydrate, a solvate, a polymorph thereof, by optical resolution of racemic Pregabalin comprising:
   a) dissolving racemic Pregabalin with a suitable acid in water;
   b) adding a chiral acid resolving agent of Formula (VI)
wherein $R_1$ and $R_2$ are the same and each is hydrogen or methyl;
c) mixing the suspension at a suitable temperature in order to form the
enriched diastereomeric salt;
d) recovering the enriched diastereomeric salt;
e) enriching the collected diastereomeric salt by recrystallizing it in at least
a suitable solvent to obtain an optically pure diastereomeric salt;
f) isolating free (S)-Pregabalin.

15. The process according to claim 14, wherein the acid is an acid as defined in
claim 3.

16. The process according to claim 15, wherein the acid is an organic acid,
preferably L-tartaric acid.

17. The process according to claim 14, wherein $R_1$ and $R_2$ are hydrogen.

18. The process according to claim 14, wherein the racemic Pregabalin/acid/chiral
acid resolving agent molar ratio is 1:1:0.5 mole/mole.

19. The process according to claim 14, wherein racemic Pregabalin is in a ratio of
about 1:20 to about 1:50 weight/volume to the water used.

20. The process according to claim 14, wherein the temperature in steps a) and c) in
order to dissolve or mix the reagents is from about 0°C to about 25°C; preferably
from about 10°C to about 20°C; more preferably the temperature is about 15°C.

21. The process according to claim 14, wherein the solvent used in step e) is a
ketone; preferably a lower ketone; more preferably acetone.

22. The process according to claim 14, wherein the diastereomeric salt in step e) is
in a ratio of about 1:5 to about 1:10 weight/volume to the solvent used.

23. The process according to claim 22, wherein:

a) the diastereomeric salt is suspended at a temperature from about 40°C to
about reflux temperature of the solvent used; preferably the temperature is
the reflux temperature of the solvent used;
b) the enriched diastereomeric salt is recovered at a temperature from about
0°C to about 25°C; preferably from about 10°C to about 20°C; more
preferably the temperature is about 15°C.

24. A process for preparing (S)-Pregabalin, or a hydrate, a solvate, a polymorph
thereof, by optical resolution of racemic Pregabalin, comprising:
a) suspending racemic Pregabalin with a chiral acid resolving agent of
Formula (VI)

\[
\text{HOOC} \quad \text{O} \quad \text{COOH}
\]

(VI)

wherein \( R_1 \) and \( R_2 \) are the same and each is hydrogen or methyl;
and an acid, in at least a suitable solvent;
b) heating the suspension;
c) cooling the suspension obtained in step b);
d) recovering an optically pure diastereomeric salt;
e) isolating free (S)-Pregabalin.

25. The process according to claim 24, wherein \( R_1 \) and \( R_2 \) are hydrogen.
26. The process according to claim 24, wherein the acid is an acid as defined in
claim 3.
27. The process according to claim 26, wherein the acid is an inorganic acid; more
preferably hydrochloric acid (37%).
28. The process according to claim 26, wherein the acid is an organic acid, more
preferably formic acid.
29. The process according to claim 24, wherein the racemic Pregabalin/chiral acid
resolving agent/acid molar ratio is 1:0.5:0.5 mole/mole.
30. The process according to claim 24, wherein said solvent used in step a) is a
ketone; preferably a lower ketone; more preferably acetone.
31. The process according to claim 24, wherein in step a) the racemic Pregabalin is
in a ratio of about 1.5 to about 1:20 weight/volume to the solvent used.
32. The process according to claim 24, wherein in step b) the suspension is heated at
a temperature from about 40°C to about reflux temperature of the solvent used;
preferably the temperature is the reflux temperature of the solvent used.
33. The process according to claim 24, wherein in step c) the mixture is cooled to a
temperature from about 0°C to about 25°C; preferably from about 10°C to about
20°C; more preferably the temperature is about 15°C.

34. A process for isolating (S)-Pregabalin, or a hydrate, a solvate, a polymorph
thereof from the optically pure diastereomeric salt of formula (VII)

(CH₃)₂
COOH

(VII)

wherein R₁ and R₂ are the same and each is hydrogen or methyl
comprising:

a) dissolving the optically pure diastereomeric salt in at least a suitable solvent;
b) adding a base in order to precipitate free (S)-Pregabalin;
c) recovering free (S)-Pregabalin.

35. The process according to claim 34, wherein R₁ and R₂ are hydrogen.

36. The process according to claim 34, wherein the solvent used in step a) is an
alcohol; preferably a lower alcohol, more preferably methanol or ethanol and
still more preferably methanol.

37. The process according to claim 34, wherein the diastereomeric salt is in a ratio
of about 1:1 to about 1:5 weight/volume to the solvents used.

38. The process according to claim 34, wherein the solution of step a) is cooled to a
temperature from about -5°C to about 5°C, preferably the temperature is about
0°C.

39. The process according to claim 36, wherein the base is selected from aqueous
ammonia (33%), sodium hydroxide, sodium bicarbonate, sodium carbonate,
potassium hydroxide, potassium bicarbonate, potassium carbonate.

40. The process according to claim 39, wherein the base is aqueous ammonia (33%).
41. A pharmaceutical composition comprising (S)-Pregabalin made by the process of any of claims 1, 14, 24 or 34 optionally together with at least one pharmaceutically acceptable excipient.

42. Use of (S)-Pregabalin made by the process of any of claims 1, 14, 24 or 34, for the preparation of a medicament.

43. (S)-Pregabalin made by the process of any of claims 1, 14, 24 or 34, for use as a medicament.

44. (S)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate or a hydrate, a solvate, a polymorph thereof of Formula (Vila)

45. A crystalline Form α of (S)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate (Vila), characterized by:
   a) an X-ray powder diffraction pattern comprising peaks at about 9.7, 14.1, 16.3, 17.4, 19.4, 19.8, 21.6, 24.1° +/- 0.2° 2Θ,
   b) a differential scanning calorimetry endothermic maximum peak at about 164°C.

46. A crystalline Form according to claim 45, characterized by an X-ray powder diffraction pattern in accordance with Figure 1.

47. A crystalline Form according to claim 45, characterized by a differential scanning calorimetry in accordance with Figure 2.

48. A crystalline Form β of (S)-Pregabalin-(-)-O,O'-dibenzoyl-L-tartrate (Vila), characterized by
   a) an X-ray powder diffraction pattern comprising peaks at about 7.1, 11.6, 13.4, 16.3, 17.3, 18.3, 22.8, 23.7° +/- 0.2° 2Θ.
b) a differential scanning calorimetry endothermic maximum peak at about 160°C.

49. A crystalline Form according to claim 48, characterized by an X-ray powder diffraction pattern in accordance with Figure 3.

50. A crystalline Form according to claim 48, characterized by a differential scanning calorimetry in accordance with Figure 4.
Fig. 2
A. **CLASSIFICATION OF SUBJECT MATTER**

INV. C07C69/78  C07C227/34  C07C229/08  A61K31/197  A61P25/08

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

B. **RELDs SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D  A61K  A61P  C07C

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 practical search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. **DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Category</th>
<th>Citation of document with indication where appropriate of the relevant passages</th>
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<td>US 5 637 767 A (GROTE TODD M [US] ET AL) 10 June 1997 (1997-06-10) cited in the application See lines 40-52, column 1; line 20, column 14 to line 32, column 15.</td>
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D. Further documents are listed in the continuation of Box C.

- 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 document published on or after the international filing date
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- 'X' document of particular relevance the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search: 27 August 2008

Date of mailing of the international search report: 02/09/2008

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Menchaca, Roberto
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