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(54) Title: PROCESSES FOR THE PREPARATION OF SOLIFENACIN OR A SALT THEREOF

(57) Abstract: The present invention describes recovery and racemization of (1R)-Phenyl- 1,2,3,4-tetrahydroisoquinoline of compound of formula (III) to obtain racemic 1- phenyl-1, 2,3,4-tetrahydroisoquinoline of compound of formula (I) and its further resolution to get (1S)-1-phenyl-1, 2, 3, 4-tetrahydroisoquinoline (intermediate B) in high chemical and chiral purity, which is the key intermediate for the preparation of (3R)-azabicyclo[2.2.2]oct-3-yl (1S)-1-phenyl-3,4-dihydroisoquinoline-2-(1H)- carboxylate.



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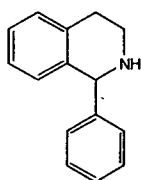
PROCESSES FOR THE PREPARATION OF SOLIFENACIN OR A SALT THEREOF.

FIELD OF THE INVENTION

5 The invention relates to processes for the preparation of solifenacin or a salt thereof. In particular, it relates to a process for the recovery and racemization of (1R)-Phenyl-1,2,3,4-tetrahydroisoquinoline to obtain (1S)-1-phenyl-1, 2, 3, 4-tetrahydroisoquinoline in high chemical and chiral purity, which is particularly useful for the preparation of solifenacin or a salt thereof.

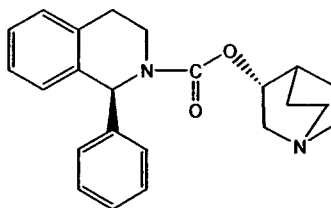
10 BACKGROUND OF THE INVENTION

1-phenyl-1,2,3,4-tetrahydroisoquinoline of the following Formula (I),



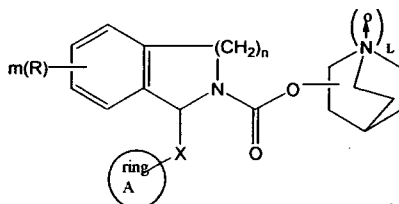
Formula (I)

is a key intermediate for the preparation of (3R)-azabicyclo[2.2.2]oct-3-yl (1S)-1-phenyl-3,4-dihydroisoquinoline-2-(1H)-carboxylate, also known as solifenacin or YM-905 (in its free base form) and YM-67905 (in its succinate form). Solifenacin succinate is available in the market in the tablet form under the trade name, Vesicare®. It is a urinary antispasmodic of the anticholinergic class. It is used in the treatment of overactive bladder with urge incontinence and acts as a selective antagonist to the M (3) receptor. [Chilman-Blair, Kim et.al, *Drugs Of Today*, **40**(4):343-353, 2004].

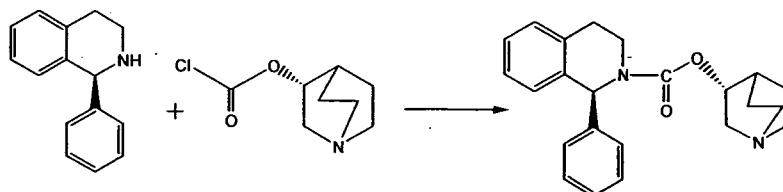


YM-905

The compound (3R)-azabicyclo[2.2.2]oct-3-yl (1S)-1-phenyl-3,4-dihydroisoquinoline-2-(1H)-carboxylate was first disclosed in U.S. Patent No. 6,017,927 ("the '927 patent") by Yamanouchi Pharmaceuticals. The '927 patent also discloses compounds of the following general Formula:

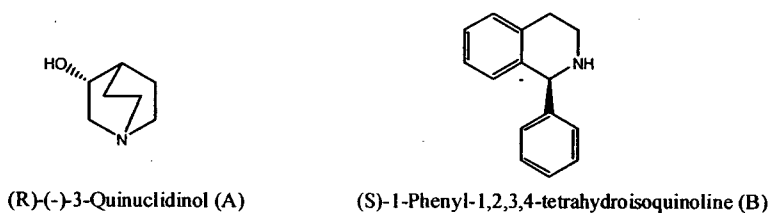


A specific method for the preparation of (3R)-azabicyclo[2.2.2]oct-3-yl (1S)-1-phenyl-3,4-dihydroisoquinoline-2-(1H)-carboxylate or a salt thereof disclosed in the '927 patent, is depicted in the following scheme (Scheme-1).



Scheme 1

In general, two processes for synthesizing Solifenacin are known in the art, which use the following key intermediates or their derivatives as starting materials.



The '927 patent describes a process using these two intermediates (A) and (B) shown in the above scheme 1.

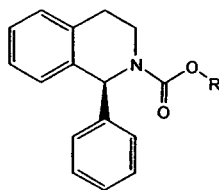
Another process for the synthesis of solifenacin is disclosed by Mealy, N., et al. in *Drugs of Future*, **24**(8): 871-874(1999).

The optical resolution of 1-phenyl-1, 2, 3, 4-tetrahydroisoquinoline is disclosed in *Monatshefte fur chemie*, vol. **53-54**:956-962(1929) to obtain (1S)-phenyl-1,2,3,4-tetrahydroisoquinoline i.e. intermediate B . The procedure involves addition of a solution of (D)-tartaric acid in water to free base. A similar method with slight modification is disclosed in J. Chem. Soc. Perkin. Trans I, (4), 869-73 (1988) and also in Naito et al. in J. Med. Chem. **48**(21): 6597-6606 (2005) with modified method using ethanol for addition of tartaric acid and recrystallization from water to obtain (1S)-phenyl-1,2,3,4-tetrahydroisoquinoline is disclosed. The process involves multiple steps of crystallization.

International Publication (PCT) WO 2008019055 discloses a process for optical resolution of 1-phenyl-1,2,3,4-tetrahydroisoquinoline (I).

U.S. Publication No. 20080114029 discloses a new crystalline form I of (S)-(+)-1-phenyl-1,2,3,4-tetrahydroisoquinoline and process for its preparation. The process
5 discloses combining (S)-(+)-1-phenyl-1,2,3,4-tetrahydroisoquinoline tartarate in water and an inorganic base in THF or toluene as a solvent.

International Publication (PCT) WO 2008011462 discloses processes for the preparation of (3R)-azabicyclo[2.2.2]oct-3-yl (1S)-1-phenyl-3,4-dihydroisoquinoline-2-(1H)-carboxylate by reacting a compound of Formula (D), wherein R= (C₁-C₄) alkyl, aryl, or aralkyl group. Further, it discloses the recovery of 1-phenyl-1,2,3,4-
10 tetrahydroisoquinoline from the mother liquor generated during the resolution stage in the preparation of (1S)-phenyl-1,2,3,4-tetrahydroisoquinoline. The drawback of this process is that it requires high temperature and longer reaction time for completion of the reaction and also suffers from the problems like, low yield and tedious work-up.



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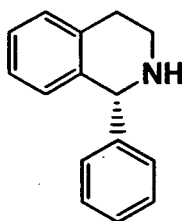
Formula (D)

However, there exists a need in the art for the recovery of racemic 1-phenyl-1,2,3,4-tetrahydroisoquinoline, which gives high yield and also suitable for large scale preparation. The process disclosed herein for the recovery of the racemic 1-phenyl-1,
20 2,3,4-tetrahydroisoquinoline improves the overall yield and makes this process cost effective.

SUMMARY OF THE INVENTION

In one aspect there is provided a racemization process for the preparation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline racemate. The process includes:

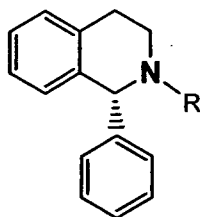
25 (a) providing a material comprising (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline of a compound of Formula (III);



Formula (III)

(b) reacting the material of step-a with one or more suitable acid chlorides, acid anhydrides, alkyl or aryl chloroformates in the presence of a suitable base in one or more suitable solvents to obtain a compound of Formula (II),

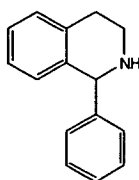
5



Formula (II)

wherein R is COOR₁ and COR₂, wherein R₁ is vinyl, allyl, 2,2,2-trichloroethyl, -CH₂Ph, or substituted -CH₂Ph, and R₂ is alkyl, substituted alkyl, or substituted halo alkyl group;

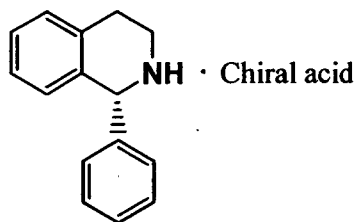
10 (c) hydrolyzing the compound of Formula (II) in the presence of one or more bases or acids in one or more suitable solvents to obtain the 1-phenyl-1,2,3,4-tetrahydroisoquinoline racemate of the compound of Formula (I).



Formula (I)

15

In another aspect there is provided a racemization process for the preparation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline racemate from a diastereomeric salt of (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline of a compound of Formula (IV):



Formula (IV)

20

The process includes: (a) providing a material comprising a suitable diastereomeric salt of (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (IV); (b) reacting the material with one or more bases, optionally in the presence of one or more suitable solvents to form (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline of a compound of

- Formula (III); (c) reacting the (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline of the compound of Formula (III) with one or more suitable carboxylated or acetylating reagents in the presence of one or more suitable bases in one or more suitable solvents to obtain a compound of Formula (II), wherein R, R₁ and R₂ are as defined above; and
- 5 (d) hydrolyzing the compound of Formula (II) in the presence of one or more bases or acids in one or more suitable solvents to obtain the 1-phenyl-1,2,3,4-tetrahydroisoquinoline racemate of the compound of Formula (I).

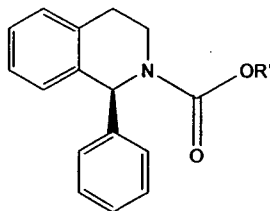
In another aspect there is provided a process for the preparation of (1S)-1-phenyl-1, 2, 3, 4-tetrahydroisoquinoline in high chemical and chiral purity or a pharmaceutically acceptable salt thereof. The process includes the steps of :

10 (a) providing a material comprising a suitable diastereomeric salt of (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (IV); (b) reacting the material with one or more bases, optionally in the presence of one or more suitable solvents to form (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline of a compound of Formula (III); (c) reacting the (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline of the compound of Formula (III) with suitable acid chlorides or suitable acid anhydrides or suitable alkyl or aryl chloroformates in the presence of one or more suitable bases in one or more suitable solvents to obtain a compound of Formula (II), wherein R, R₁ and R₂ are as defined above; and (d)

15 hydrolyzing the compound of Formula (II) in the presence of one or more bases or acids in one or more suitable solvents to obtain the 1-phenyl-1,2,3,4-tetrahydroisoquinoline racemate, which can be further resolved by using suitable resolving agents in a suitable solvent to get (1S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline.

25 In another aspect provided a process for the preparation of solifenacin or salt thereof. The process includes the steps: (a) The (1S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline react with aryl carbonate or its chloroformate, substituted aryl carbonate or chloroformate, heteroaryl carbonate or chloroformate, substituted heteroaryl carbonate or its chloroformate in suitable solvents and suitable base to obtain

30 the compound of Formula (V), wherein R' is alkyl, aryl, substituted aryl, substituted alkyl, or substituted halo alkyl group. (b) The compound of Formula (V) is further react with (R)-3-quinuclidinol in presence of a suitable base in suitable solvent to obtain (+)-(1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydro-isoquinoline-2-carboxylate.



Formula (V)

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "THF" refers to tetrahydrofuran, the term "DCM" refers to dichloro methane, the term "DMF" refers to dimethylformamide, the term "DIPE" refers to di-isopropyl ether, the term "MTBE" refers to methyl t-butyl ether, the term "DMSO" refers to dimethyl sulfoxide, the term "DMA" refers to dimethylacetamide, the term "IPA" refers to isopropyl alcohol.

As used herein, the term "racemization" of a mixture of enantiomerically enriched unwanted isomer (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline of a compound of Formula (III) and (1S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline means a process of converting the mixture to 1-phenyl-1,2,3,4-tetrahydroisoquinoline racemate, wherein the starting mixture is a material comprising (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline of a compound of Formula (III) wherein the R:S ratio of the starting mixture is about above 65:35, for example, about above 70:30. In particular, the R:S ratio may be about above 80:20.

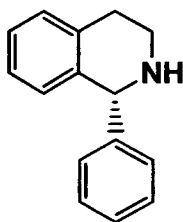
In general, the starting mixture of (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline of the compound of Formula (III) and (1S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline comprises more of (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline of the compound of Formula (III) than (1S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline. The "racemization" reduces the relative amount of R-enantiomer and increases the relative amount of S-enantiomer to form the 1-phenyl-1,2,3,4-tetrahydroisoquinoline racemate.

As used herein, the 1-phenyl-1,2,3,4-tetrahydroisoquinoline racemate of the compound of Formula (I) is a material wherein the R:S ratio is about 60:40, for example, about above 55:45. In particular, the R:S may be about 50:50.

The inventors have developed a process for recycling the (R) enriched enantiomer of 1-phenyl-1,2,3,4-tetrahydroisoquinoline, which is obtained from resolution of 1-phenyl-1,2,3,4-tetrahydroisoquinoline using suitable resolving agents, to produce more of the (S) enantiomers. The 1-phenyl-1,2,3,4-tetrahydroisoquinoline is commercially available. In particular, it may be prepared by a method disclosed in JMC 1989, 32, 1242-1248 and JMC 2005, 48, 6597-6606.

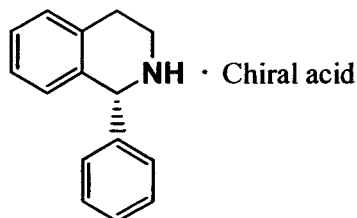
Chirally enriched (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline of Formula (III) may be isolated after treating the diastereomeric salt of (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline of Formula (IV) using suitable base in the presence of one or more suitable solvents. The diastereomeric salt of (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline of Formula (IV) is formed with suitable resolving agents, which in turn is obtained from the mother liquor (filtrate) after resolution of 1-phenyl-1,2,3,4-tetrahydroisoquinoline (I). It can be racemized to obtain the racemic 1-phenyl-1,2,3,4-tetrahydroisoquinoline of Formula (I), which can be further resolved by using suitable resolving agents in a suitable solvent to get (1S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline in high chemical and chiral purity. This compound is a key intermediate for the synthesis of the drug solifenacin, (3R)-azabicyclo[2.2.2]oct-3-yl (1S)-1-phenyl-3,4-dihydroisoquinoline-2-(1H)-carboxylate.

The inventors have developed a process for the racemization of (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline of Formula (II). The process includes isolating a chirally enriched (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline of a compound of Formula (III),



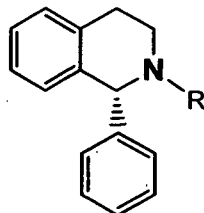
Formula (III)

from an aqueous solution of a diastereomeric salt of (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (IV), alternatively from the solution of diastereomeric salt of (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (IV) using a suitable base optionally in the presence of one or more suitable solvents;



Formula (IV)

reacting the (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (III) with one or more suitable carboxylated or acylating reagents in the presence of a suitable base in one or more suitable solvents to obtain a compound of Formula (II), wherein, R is COOR₁ and COR₂, wherein R₁ is vinyl, allyl, 2,2,2-trichloroethyl, -CH₂Ph, substituted -CH₂Ph, etc, and R₂ is alkyl, substituted alkyl, substituted halo alkyl, etc; and



Formula (II)

hydrolyzing the N-substituted 1-phenyl-1,2,3,4-tetrahydroisoquinoline of the compound of Formula (II) in the presence of one or more suitable bases or acids in one or more suitable solvents at a suitable temperature to obtain racemic 1-phenyl-1,2,3,4-tetrahydroisoquinoline (I).

In general, the isolation of chirally enriched (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (III) from the aqueous solution can be done by adding a suitable inorganic base or an organic base. The precipitated (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (III) may be isolated by steps including one or more of filtration, washing and drying. It may be further purified to achieve desired chemical and chiral purity by making various salts, for example hydrochloride, sulphate, and the like.

Alternatively, the isolation of the (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (III) from the solution of diastereomeric salt of (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (IV) may be carried out by distilling out the solvents and extracting the product into one or more suitable solvents using a suitable base and water, collecting the organic layer containing the product, washing the organic layer with a wash solution, and isolating the product after distillation of the solvent(s).

Suitable solvents which can be used for isolation may include one or more of alcohols, for example, methanol, ethanol, isopropanol, butanol, 1,2-dimethoxy ethanol,

2-methoxy ethanol, 2-ethoxy ethanol, isoamyl alcohol and ethylene glycol; esters, for example, ethyl acetate and isopropyl acetate; chlorinated solvents, for example, chloroform and dichloromethane; nitriles, for example, acetonitrile; hydrocarbons, for example, toluene, xylene and chlorobenzene; ketones, for example, acetone, methyl ethyl ketone; ethers, for example, diethyl ether, 1,4-dioxane, DIPE, MTBE, THF; aprotic polar solvents such as DMF, DMSO, DMA; water or their suitable mixtures.

Suitable bases, which can be used for the isolation, may include one or more of NaHCO_3 , Na_2CO_3 , K_2CO_3 , LiOH , NaOH , KOH and the like. Suitable organic base is selected from ammonia, C (1-5) alkyl amines, C (1-5) substituted alkyl amines such as triethylamine, diisopropylamines, diisopropylethyl amines, heterocyclic saturated or unsaturated base such as pyridine, piperidine, morpholine and the like or mixtures thereof.

In general, the (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline of Formula (III) may be reacted with a suitable carboxylated or acylating reagent selected from acid chlorides or suitable acid anhydrides to obtain amides or substituted amides and with suitable alkyl or aryl chloroformates to obtain n-alkyl carbamates, substituted n-alkyl carbamates in the presence of a suitable base in a suitable solvent(s) by standard techniques reported in Text book-Title: Protective Groups in Organic Synthesis, 3rd Edition, John Wiley & Sons, Chapter 7, page no. 494-653, By-T.W. Greene and Peter G. M. Wuts and references therein to provide the compound of Formula (II).

The acid chlorides, which may be used, include one or more of acetyl chloride, chloroacetyl chloride, dichloroacetyl chloride, trifluoroacetyl chloride, and the like. A wide variety of reagents can be used to prepare alkyl chloroformates such as chloroformates of vinyl, allyl, 2,2,2-trichloroethyl, and the like. A wide variety of reagents can be used to prepare aryl chloroformates such as phenyl, 4-nitrophenyl and the like.

Suitable solvents which can be used include one or more of alcohols like methanol, ethanol, isopropanol, butanol, 1,2-dimethoxy ethanol, 2-methoxy ethanol, 2-ethoxy ethanol, isoamyl alcohol and ethylene glycol; esters like ethyl acetate and isopropyl acetate; chlorinated solvents like chloroform and dichloromethane; nitriles like acetonitrile; hydrocarbons like toluene, xylene and chlorobenzene; ketones like acetone, methyl ethyl ketone; ethers like diethyl ether, 1,4-dioxane, DIPE, MTBE, THF; aprotic polar solvents such as DMF, DMSO, DMA or their suitable mixtures.

Suitable bases which can be used include one or more of NaHCO_3 , Na_2CO_3 , K_2CO_3 , LiOH , NaOH , KOH and the like. Suitable organic base is selected from ammonia, $\text{C}_{(1-5)}$ alkyl amines, $\text{C}_{(1-5)}$ substituted alkyl amines such as triethylamine, diisopropylamines, diisopropylethyl amines, heterocyclic saturated or unsaturated base
5 such as pyridine, piperidine, morpholine and the like or mixtures thereof.

The hydrolysis of N-substituted 1-phenyl-1,2,3,4-tetrahydroisoquinoline of the compound of Formula (II) may be carried out in the presence of one or more suitable bases or suitable acids in one or more suitable solvents at a suitable temperature to obtain racemic 1-phenyl-1,2,3,4-tetrahydroisoquinoline of the compound of Formula
10 (I). The isolation of the 1-phenyl-1,2,3,4-tetrahydroisoquinoline of the compound of Formula (I) from the aqueous solution can be done by adding a suitable inorganic base/acid or an organic base/acid. The process may further include filtration, washing and drying of the precipitated 1-phenyl-1,2,3,4-tetrahydroisoquinoline of the compound of Formula (I).

15 In general, the isolation of the 1-phenyl-1,2,3,4-tetrahydroisoquinoline of compound of Formula (I) from the solution of 1-phenyl-1,2,3,4-tetrahydroisoquinoline (I) may be carried out after removing the solvent(s), adding water and one or both of a suitable base and acid. Removing the solvents may include one or more of distillation, distillation under vacuum, evaporation, or decantation. The process may further include
20 filtration, washing and drying of the precipitated 1-phenyl-1,2,3,4-tetrahydroisoquinoline of the compound of Formula (I).

Alternatively, the isolation of the 1-phenyl-1,2,3,4-tetrahydroisoquinoline of the compound of Formula (I) from the solution of 1-phenyl-1,2,3,4-tetrahydroisoquinoline may be carried out by adding water and one or both of a suitable base and acid into the
25 solution, collecting the organic layer, washing the organic layer with a wash solution, and isolating the product after removing the solvent(s). Removing the solvents may include one or more of distillation, distillation under vacuum, evaporation, or decantation.

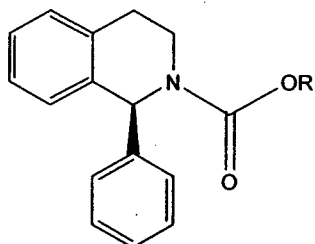
The hydrolysis may be carried out using reagents which assist in the cleavage of
30 the N-substituted group to obtain 1-phenyl-1,2,3,4-tetrahydroisoquinoline of the compound of Formula (II) by standard techniques reported in the literature, to provide the compound of Formula (I) (For example, Protection and Deprotection of amines in Text book -Title: Protective Groups in Organic Synthesis, 3rd Edition, John Wiley & Sons, Chapter 7, page no. 494-653, By-T.W. Greene and Peter G. M. Wuts).

Suitable acid which can be used for the hydrolysis may include one or more of inorganic acids such as HCl, H₂SO₄, HBr, HNO₃, and the like; organic acids selected from lower alkyl acid such as HCOOH, CH₃COOH, CH₃CH₂COOH; lower haloalkyl acid such as CF₃COOH, dichloroacetic acid; phosphoric acid, lower alkyl phosphonic acid such as methylphosphonic acid, phenylphosphonic acid, BF₃.OEt₂, and the like or mixtures thereof.

Suitable bases, which can be used for the hydrolysis, may include one or more of inorganic bases such as alkali and alkaline earth metal carbonates and hydroxide or suitable mixtures thereof.

Suitable solvents which can be used for the hydrolysis may include one or more of alcohols, such as methanol, ethanol and like; ethers such as THF, 1,4-dioxane and like; aprotic solvents like DMF, dimethylacetamide; water or suitable mixtures thereof.

The (1S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline react with aryl carbonate or its chloroformate, substituted aryl carbonate or chloroformate, heteroaryl carbonate or chloroformate, substituted heteroaryl carbonate or its chloroformate such as ethyl chloroformate, 4-nitrophenyl chloroformate, 2-dipyridyl carbonate to obtain the compound of Formula (V), wherein R' is alkyl, aryl, substituted aryl, substituted alkyl, or substituted halo alkyl group.



Formula (V)

The compound of Formula (V) react with (R)-3-quinuclidinol in presence of a base in suitable solvent to obtain (+)-(1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydro-isoquinoline-2-carboxylate.

Suitable solvents which can be used for may include one or more of alcohols, for example, methanol, ethanol, isopropanol, butanol, 1,2-dimethoxy ethanol, 2-methoxy ethanol, 2-ethoxy ethanol, isoamyl alcohol and ethylene glycol; esters, for example, ethyl acetate and isopropyl acetate; chlorinated solvents, for example, chloroform and dichloromethane; nitriles, for example, acetonitrile; hydrocarbons, for example, toluene, xylene and chlorobenzene; ketones, for example, acetone, methyl

ethyl ketone; ethers, for example, diethyl ether, 1,4-dioxane, DIPE, MTBE, THF; aprotic polar solvents such as DMF, DMSO, DMA; water or their suitable mixtures.

Suitable bases, which can be used for may include one or more of NaHCO_3 , Na_2CO_3 , K_2CO_3 , LiOH , NaOH , KOH and the like. Suitable organic base is selected
5 from ammonia, C (1-5) alkyl amines, C (1-5) substituted alkyl amines such as triethylamine, diisopropylamines, diisopropylethyl amines, heterocyclic saturated or unsaturated base such as pyridine, piperidine, morpholine and the like or mixtures thereof.

The present invention is further illustrated by the following examples which are
10 provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example 1: Isolation of (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline from the aqueous filtrate

15 Resolution of (R:S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (100 g) was carried out using (D)-(-)-tartaric acid in water as per the literature method known in the art (Ref 1.- J. Chem. Soc. Perkin. Trans I, (4), 869-73 (1988), Ref. 2.- Monatshefte Fur. Chemie, vol. 53-54:956-962(1929)) and diastereomeric (D)-(-)-tartaric acid salt of (1S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline was filtered out as a solid. The filtrate
20 containing enantiomerically enriched (D)-(-)-tartaric acid salt of (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline was collected and a clear aqueous solution 40 % aq. sodium hydroxide (NaOH , 85 mL) was added at room temperature when solid was precipitated. The precipitated solid was filtered and washed with water and dried. The weight of enantiomerically enriched (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline was 61.0 g. (%
25 Purity by HPLC-97.0 %; % Chiral purity of R-isomer -79.0 %).

Example 2: Preparation of N-chloroacetyl-(1R)-phenyl-1,2,3,4-tetrahydroisoquinoline

To a dry 250 mL three neck flask, enantiomerically enriched (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (10 g), dichloromethane (100 mL) and triethylamine (5.22 g) were charged at room temperature. The reaction mixture was cooled to -10 to
30 -5 °C. Then chloroacetyl chloride (6.0 g) was added drop by drop over a period of 1 h at -5 to 5 °C. The reaction mixture was warmed to room temperature and stirred for 4-5 h at room temperature. To the reaction mixture, water and dichloromethane were added. It was transferred into a separating funnel. The organic layer was separated and washed with a brine solution. The organic layer was dried over anhydrous sodium

sulfate. The solvent was then distilled out completely under a reduced pressure on Buchi rotavapor to obtain enantiomerically enriched N-chloroacetyl-(1R)-phenyl-1,2,3,4-tetrahydroisoquinoline as a liquid (Wt.-13.5 g; % Purity by HPLC-97.4 %).

Example 3: Preparation of N-chloroacetyl-(1R)-phenyl-1,2,3,4-tetrahydroisoquinoline

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To a dry 50 mL three neck flask, enantiomerically enriched (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (2.0 g), acetone (15 mL) and anhyd. potassium carbonate (1.57 g) was charged at room temperature. The reaction mixture was cooled to -5 to 0 °C after 30min. Then chloroacetyl chloride (1.18 g) was added slowly at -5 to 5 °C. The reaction mixture was warmed to room temperature and stirred for 5-6 h at room temperature. TLC was checked for the completion of the reaction. The product was isolated by usual work-up.

Example 4: Preparation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline

To a dry 250 mL three neck flask, enantiomerically enriched N-chloroacetyl-(1R)-phenyl-1,2,3,4-tetrahydroisoquinoline (13.5g), 35 % conc. HCl (65 mL) and 85 % aq. phosphoric acid (13 mL) were charged at 25-50 °C. The reaction mixture was heated to 95 to 100 °C and stirred for 8-10 h and subsequently cooled to room temperature. The reaction mixture was transferred into a separating funnel and subsequently washed with toluene and ethyl acetate. The aqueous layer was collected and was basified with 40 % aq. NaOH solution up to 9-10 pH at room temperature. The solid was precipitated and was extracted in ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was then distilled out completely under a reduced pressure on Buchi rotavapor to obtain 1-phenyl-1,2,3,4-tetrahydroisoquinoline (Wt.-8.5 g; % Purity by HPLC-95.9 %; % Chiral purity by HPLC: % of S-isomer-49.95 % and % of R-isomer-50.05 % i.e. racemic compound).

Example 5: Preparation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline

To a 250 mL three neck flask, enantiomerically enriched N-chloroacetyl-(1R)-phenyl-1,2,3,4-tetrahydroisoquinoline (13.6 g), 35 % conc. HCl (50 mL) and conc. sulfuric acid (13 mL) were charged at 25-30 °C. The reaction mixture was heated to 95 to 100 °C and was stirred for 8-10 h and subsequently was cooled to room temperature. It was basified with 40 % aq. NaOH solution up to 9-10 pH at room temperature. The solid was precipitated. It was filtered and was washed with water and dried in a hot-air oven at 40-50 °C till constant weight was obtained (Wt.-9.4 g; % Purity by HPLC-97.2 %; % Chiral purity by HPLC: % of S-isomer-48.86 % and % of R-isomer-51.14 %).

Example 6: Preparation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline

To a 25 mL three neck flask, enantiomerically enriched N-chloroacetyl-(1R)-phenyl-1,2,3,4-tetrahydroisoquinoline (2.0 g), 35 % conc. HCl (2.0 mL) and water (2.0 mL) were charged at 25-30 °C. The reaction mixture was heated to 95 to 100 °C and was stirred for 18-20 hrs and subsequently was cooled to room temperature. It was basified with 40 % aq. NaOH solution up to 9-10 pH at room temperature. The solid was precipitated. It was filtered and was washed with water and dried in a hot-air oven at 40-50 °C till constant weight was obtained (Wt.-1.3 g; % Purity by HPLC-96.1 %; % Chiral purity by HPLC: % of S-isomer-42.0 % and % of R-isomer-58.0 %).

10 Example 7: Preparation of enantiomerically enriched N-acetyl-(1R)-phenyl-1,2,3,4-tetrahydroisoquinoline

To a dry 100 mL three neck flask, enantiomerically enriched (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (5 g), dichloromethane (25 mL) and triethylamine (2.5 g) were charged at room temperature. The reaction mixture was cooled to -10 to -5 °C. Then acetyl chloride (2.0 g) was added drop by drop over a period of 15 min. at -5 to 5 °C. The reaction mixture was warmed to room temperature and was stirred for 3-4 h at room temperature. Then again triethylamine (1.75 g) was added and the reaction mixture was cooled to -10 to -5 °C. Then acetyl chloride (1.4 g) was added drop by drop over a period of 10 min. at -5 to 5 °C. The reaction mixture was warmed to room temperature and stirred for 6-7 h at room temperature. To the reaction mixture water was added and was transferred into a separating funnel. The organic layer was separated and washed with water and brine solution. The organic layer was dried over anhydrous sodium sulfate. The solvent was then distilled out completely under a reduced pressure on Buchi rotavapour to obtain enantiomerically enriched N-acetyl-(1R)-phenyl-1,2,3,4-tetrahydroisoquinoline (Wt.-5.8 g; % Purity by HPLC-96.1 %).

25 Example 8: Preparation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline

To 50 mL three neck flask, enantiomerically enriched N-acetyl-(1R)-phenyl-1,2,3,4-tetrahydroisoquinoline (3.0 g), 35 % conc. HCl (18 mL) and 85 % aq. phosphoric acid (4 mL) were charged at 25-30 °C. The reaction mixture was heated to 95 to 100 °C and stirred for 16 h. To the reaction mixture 35 % conc. HCl (5 mL) was added and was stirred for another 8 h at 95 to 100 °C. TLC was checked, starting compound was unreacted. Again to the reaction mixture 35 % conc. HCl (5 mL) was added and stirred for another 8 h at 95 to 100 °C. It was cooled to room temperature and was transferred into a separating funnel. The reaction mixture was washed with

ethyl acetate. The aqueous layer was collected and was basified with 40 % aq. NaOH solution up to 9-10 pH at room temperature. The reaction mixture was extracted in ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was then distilled out completely under a reduced pressure on
5 Buchi rotavapour to obtain 1-phenyl-1,2,3,4-tetrahydroisoquinoline (Wt.-1.1 g; % Purity by HPLC-98.4 %; % Chiral purity by HPLC: % of S-isomer-49.35 % and % of R-isomer-50.65 %).

Example 9: Preparation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline

To a dry 100mL three neck flask, enantiomerically enriched (1R)-phenyl-
10 1,2,3,4-tetrahydroisoquinoline (2.0g) was dissolved in 20mL dichloromethane, 1.45g anhydrous potassium carbonate were charged at 20-25 ° C. The reaction mixture was cooled to 0 to 5 °C, 1.93g 4-nitrophenyl chloroformate was charged portion wise at 0 to 5 °C, was stirred at 20-25 °C for 2 hr and subsequently cold water was added in to reaction mixture. The reaction mixture was transferred into a separating funnel and
15 organic layer was separated, washed with water and brine solution, dried over anhydrous sodium sulfate. The solvent was then distilled out completely under a reduced pressure on Buchi rotavapour to obtain N-protected 1-phenyl-1,2,3,4-tetrahydroisoquinoline (Wt.-3.8 g).

A solution of sodium hydroxide (2.0g) in absolute alcohol was added & refluxed at 75-
20 80 °C for 4 to 5 hrs. Subsequently, solvent was distilled out completely under a reduced pressure on Buchi rotavapor and cold water was added. The solid was filtered, wash with water & dried. Wt. of 1-phenyl-1,2,3,4-tetrahydroisoquinoline was 1.0 g. (% Purity by HPLC-96.23 %, % Chiral purity of R-isomer 60.26 % & S-isomer 39.74 %).

Example 10: Resolution of (R/S)-1-phenyl-1,2,3,4-tetrahydro-isoquinoline

To a 250 mL three neck flask water (70 mL) and (R/S)-1-phenyl-1,2,3,4-
25 tetrahydroisoquinoline (20 g) were charged. Reaction mixture was heated to 65-70 °C. D-(-)-tartaric acid dissolved in water (20 mL) was added to the reaction mixture at 65-70 °C and stirred for 30 minutes. The reaction mixture was further heated to 90-95 °C and stirred for 1 h. The reaction mixture was cooled to 55 °C. To the clear solution
30 0.250 g seeding of (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline was added. Reaction mixture was further cooled to 32-35 °C and stirred for 30 minutes. Solid product was filtered and washed with cold water. It was dried in a fan dryer at 70-80 °C till constant weight obtained. The (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline was obtained. (Yield-40.0 %, % Chemical purity-98.0 %, % Chiral purity of S-isomer-97.2 %).

Example 11: Preparation of (S)- Ethyl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate

To a dry, 25 mL round bottom flask was charged (S)-1-phenyl-1,2,3,4-tetrahydro-isoquinoline (1 g) and acetone (6 mL) at room temperature (RT). It was cooled to 5 to 10 °C and ethyl chloroformate (0.52 g) was added slowly into the reaction mixture. It was heated to reflux temperature and stirred till completion of the reaction. Distilled out the solvent at reduced pressure. To the residue dil. Aq. HCl and dichloromethane were added. It was transferred into a separating funnel. Organic layer was collected. It was washed with saturated. Sodium bicarbonate solution. Organic layer was collected and dried over anhydrous. Sodium sulfate. It was concentrated under reduced pressure to obtain Ethyl (S)-1-phenyl-1,2,3,4-tetrahydro-isoquinoline-2-carboxylate. (1.2 g, % Yield-89.0 %), % Purity by HPLC- 97.7 % and % Chiral purity-99.1 %.

Example 12. Preparation of (+)-(1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydro-isoquinoline-2-carboxylate (Solifenacin)

To a cooled solution of freshly prepared sodium methoxide (4.2 g), (R)-3-quinuclidinol (10 g) was added under N₂ atmosphere. It was stirred at 5-30 °C for 30 min. Distilled out the solvent at reduced pressure. To the semi-solid mass dry toluene was added and reaction mixture was heated to reflux temperature and stirred for 1 to 2 h. The reaction mixture was cooled to 60-70 °C. (S)-Ethyl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (20 g) dissolved in dry toluene (160 mL) and dry DMF (25 mL) were added. It was again heated to reflux temperature and stirred for 10 to 12 h while distilling off toluene to remove ethanol after every 15 min. intervals with addition of fresh quantity of dry toluene. It was cooled to room temperature. The (+)-(1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydro-isoquinoline-2-carboxylate (Solifenacin) (18.2 g, 72 % yield) was obtained.

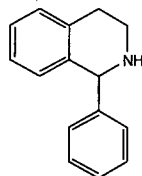
% Chemical purity 97.37 %, % Chiral purity by HPLC – 99 %.

SOR (1 % in EtOH at 25 °C): 123.2 °

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 intended to be included within the scope of the present invention.

We Claim:

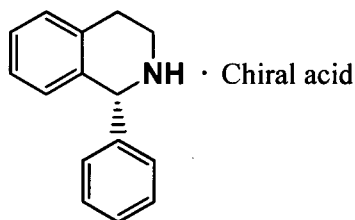
1. A racemization process for the preparation of 1-phenyl-1, 2,3,4-tetrahydroisoquinoline of a compound of Formula (I),



Formula (I)

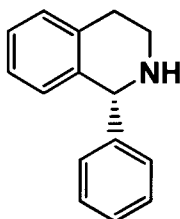
the process comprising:

- (a) providing a material comprising a suitable diastereomeric salt of (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (IV);



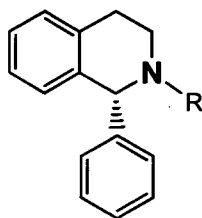
Formula (IV)

- (b) reacting the material with one or more bases, optionally in the presence of one or more suitable solvents to form (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline of a compound of Formula (III);



Formula (III)

- (c) reacting the (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline of the compound of Formula (III) with one or more suitable carboxylated or acetylating reagents in the presence of one or more suitable bases in one or more suitable solvents to obtain a compound of Formula (II),



Formula (II)

wherein R is COOR₁ and COR₂, wherein R₁ is vinyl, allyl, 2,2,2-trichloroethyl, -CH₂Ph, or substituted -CH₂Ph, and R₂ is alkyl, substituted alkyl, or substituted halo alkyl group;

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(d) hydrolyzing the compound of Formula (II) in the presence of one or more bases or acids in one or more suitable solvents to obtain the 1-phenyl-1,2,3,4-tetrahydroisoquinoline racemate of the compound of Formula (I).

2. The process as claimed in claim 1, step (a), wherein the material further comprises (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline of the compound of Formula (III) such that R:S ratio of the starting mixture is about above 65:35.
3. The process as claimed in claim 2, wherein the R:S ratio of the starting mixture is about above 70:30.
4. The process as claimed in claim 2, wherein the R:S ratio of the starting mixture is about above 80:20.
5. The process as claimed in claim 1, step (b), wherein the suitable base comprises one or more of (carbonate, bicarbonate, alkali hydroxide base), sodium carbonate, potassium carbonate, sodium bicarbonate, lithium hydroxide, sodium hydroxide, potassium hydroxide, ammonia, triethyl amine, pyridine, diisopropylethyl amine, piperidine, morpholine or mixtures thereof.
6. The process as claimed in claim 1, step (b), wherein the suitable solvent comprises one or more of alcohols, esters, chlorinated solvents, nitriles, hydrocarbons, ketones, aprotic polar, water, or their suitable mixtures.
7. The process as claimed in claim 1, step (c), wherein the suitable reagent comprises one or more of acid chlorides, acid anhydrides, alkyl or aryl chloroformates or derivatives thereof.
8. The process as claimed in claim 1, step (c), wherein the suitable base comprises one or more of (carbonate, bicarbonate, alkali hydroxide base), sodium carbonate, potassium carbonate, sodium bicarbonate, lithium hydroxide, sodium hydroxide,

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potassium hydroxide, ammonia, triethylamine, diisopropylethylamine, N-ethyl-diisopropylamine, pyridine, piperidine, or mixtures thereof.

9. The process as claimed in claim 1, step (c), wherein the suitable solvent comprises one or more of alcohols, esters, chlorinated solvents, nitriles, hydrocarbons, ketones, aprotic polar or their suitable mixtures.
10. The process as claimed in claim 1, step (d), wherein the base comprises one or more of alkali and alkaline earth metal carbonates and hydroxide or suitable mixtures thereof.
10. The process as claimed in claim 1, step (d), wherein the acid comprises one or more of inorganic acids such as HCl, H₂SO₄, HBr, HNO₃; organic acids selected from lower alkyl acid such as HCOOH, CH₃COOH, CH₃CH₂COOH; lower haloalkyl acid such as CF₃COOH, dichloroacetic acid; phosphoric acid, lower alkyl phosphonic acid such as methylphosphonic acid, phenylphosphonic acid, BF₃.OEt₂ or mixture thereof.
11. The process as claimed in claim 1, step (d), wherein the suitable solvent comprises one or more of alcohols, ethers, aprotic solvents, water or mixtures thereof.
12. A recycling process for the (R) enriched enantiomer of 1-phenyl-1,2,3,4-tetrahydroisoquinoline comprises treatment of diastereomeric salt of (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline with one or more suitable organic or inorganic base.
13. The process as claimed in claim 12, wherein suitable base comprises one or more of (carbonate, bicarbonate, alkali hydroxide base), sodium carbonate, potassium carbonate, sodium bicarbonate, lithium hydroxide, sodium hydroxide, potassium hydroxide, ammonia, triethylamine, diisopropylethylamine, N-ethyl-diisopropylamine, pyridine, piperidine, or mixtures thereof.
14. A process for the preparation of solifenacin or a salt thereof, the process comprising converting the 1-phenyl-1, 2,3,4-tetrahydroisoquinoline of the compound of Formula (I) prepared according to any as claimed in claims 1-13 to solifenacin or a salt thereof.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IN2010/000645

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D217/02 C07D453/02
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2009/139002 A2 (MSN LAB LTD [IN]; SATYANARAYANA REDDY MANNE [IN]; ESWARAIHA SAJJA [IN]) 19 November 2009 (2009-11-19) page 8; examples	14
X	WO 2008/011462 A2 (REDDYS LAB LTD DR [IN]; REDDYS LAB INC DR [US]; MATHAD VIJAYAVITTHAL T) 24 January 2008 (2008-01-24) page 3 - page 4; claims; figure 1	1-14
X	EP 1 757 604 A1 (ASTELLAS PHARMA INC [JP]) 28 February 2007 (2007-02-28) claims; examples	14
A	EP 0 801 067 A1 (YAMANOUCHI PHARMA CO LTD [JP]) 15 October 1997 (1997-10-15) the whole document	1-14
	-/-	



Further documents are listed in the continuation of Box C.



See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" 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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

31 March 2011

Date of mailing of the international search report

11/04/2011

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INTERNATIONAL SEARCH REPORT

International application No

PCT/IN2010/000645

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NAITO RYO ET AL: "Synthesis and antimuscarinic properties of quinuclidin-3-yl 1,2,3,4-tetrahydroisoquinoline-2-carboxylate derivatives as novel muscarinic receptor antagonists", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 48, no. 21, 20 October 2005 (2005-10-20), pages 6597-6606, XP002523332, ISSN: 0022-2623, DOI: DOI:10.1021/JM050099Q [retrieved on 2005-09-28] page 6599	1-14
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IN2010/000645

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WO 2009139002	A2	19-11-2009	NONE
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