

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
20 May 2010 (20.05.2010)

(10) International Publication Number  
**WO 2010/055481 A1**

PCT

(51) International Patent Classification:  
**C07D 307/93** (2006.01) **C07C 69/618** (2006.01)

(21) International Application Number:  
PCT/IB2009/055038

(22) International Filing Date:  
12 November 2009 (12.11.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
2403/MUM/2008 14 November 2008 (14.11.2008) IN

(71) Applicant (for all designated States except US): **WATSON PHARMA PRIVATE LIMITED** [IN/IN]; 201/301, Corporate Enclave, HDO-Corporate Bldg., B Wing, B.D. Sawant, Marg, Chakala, Off Western Express Highway, Andheri (East) Maharashtra, Mumbai 400099 (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BHANU, Manjunath Narayan** [IN/IN]; A-101, Montvert Altesse Pashan sus Road, Pashan Maharashtra, Pune 211021 (IN). **SINHA, Chandrasekhar** [IN/IN]; C-6/4, 1:2, Sector 5 CBD Belapur Maharashtra, Navi Mumbai 400614 (IN). **AHER, Bhupesh** [IN/IN]; 74/530, Tapovan Society M.H.B. Colony, Sarvodaya Nagar Jogeshwari (E) Maharashtra, Mumbai 400060 (IN). **BANDAL, Amol** [IN/IN]; Hariom - Om Shanti (Ext.) 2nd Floor, R., No. 301 Damkhadi, Roha Maharashtra, Raigad 402109 (IN). **PARAB, Atul** [IN/IN]; Bldg. No. 15/303 Opp. Sundar Vihar Hotel, Pratiksha Nagar Sion (E) Maharashtra, Mumbai 400022 (IN).

(74) Agent: **NAIR, Gopakumar G.**; Gopakumar Nair Associates, "Shivmangal, 3rd Floor, Near Big Bazaar, Akurli Road, Kandivli (East), 400 101-Mumbai (IN).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

**Published:**

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: PROCESS FOR THE PREPARATION OF RAMELTEON

(57) Abstract: Disclosed herein is a process for resolving N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)] ethylamine into its isomers using an optically active acid and a process for preparing ramelteon from the resolved isomer.



WO 2010/055481 A1

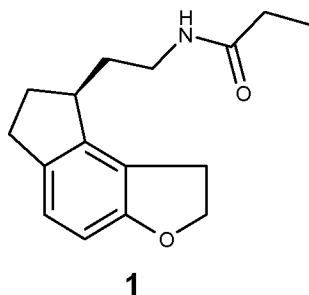
## PROCESS FOR THE PREPARATION OF RAMELTEON

### FIELD OF THE INVENTION:

The present invention relates to a process for the preparation of (S)-N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)ethyl]propionamide, commonly known as ramelteon, in its pure isomeric form substantially free from its enantiomeric isomer.

### BACK GROUND OF INVENTION:

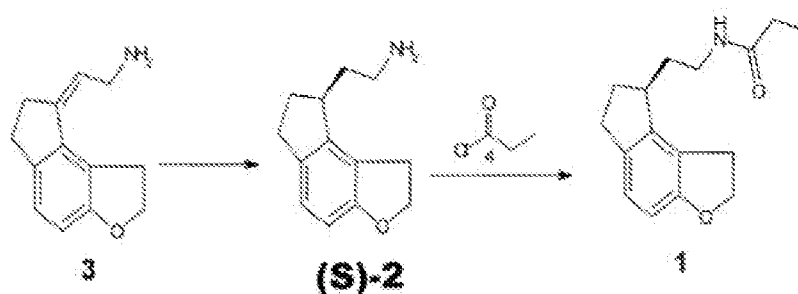
Ramelteon (**1**) is a melatonin receptor agonist with both high affinity for melatonin MT<sub>1</sub> and MT<sub>2</sub> receptors and selectivity over the MT<sub>3</sub> receptor.



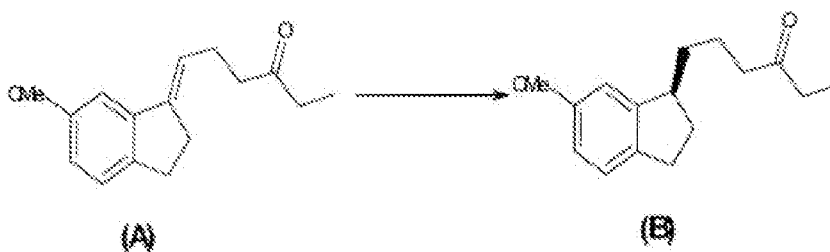
Ramelteon demonstrates full agonist activity *in vitro* in cells expressing human MT<sub>1</sub> or MT<sub>2</sub> receptors, and high selectivity for human MT<sub>1</sub> and MT<sub>2</sub> receptors compared to the MT<sub>3</sub> receptor.

Ramelteon has demonstrated efficacy in the treatment of insomnia characterized by difficulty with sleep onset. Approximately one in three American adults complains of some type of insomnia, and 20 million Americans suffer from chronic insomnia, which is characterized by difficulty falling asleep, difficulty staying asleep, or poor quality sleep, often leading to impairment of next-day functioning. Insomnia has been linked to a variety of health problems, including obesity, diabetes, hypertension, heart disease, and depression. Ramelteon has also been prescribed for long-term use in adults, provides a unique therapeutic mechanism of action for therapy of insomnia and represents a new treatment option.

United States Patent No. 6,034,239 discloses the formation of chiral intermediates (S)-(-)-N-[2-(1,6,7,8,-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethylamine (sometimes referred to as compound S-2 or intermediate compound S-2) by the catalytic asymmetric hydrogenation of 2-(1,2,6,7,-tetrahydro-8H-indeno[5,4-b]furan-8-ylidene)ethylamine (compound 3 in the reaction scheme shown below) in the presence of a catalytic amount of BINAP–ruthenium complex in approximately 89% e.e. (enantiomeric excess). Following the catalytic reaction, the product is purified by preparing acid salts and acylated with propionyl chloride (compound 4 in the reaction scheme shown below) to obtain ramelteon (compound 1 in the reaction scheme shown below) in its pure (S) isomer form.

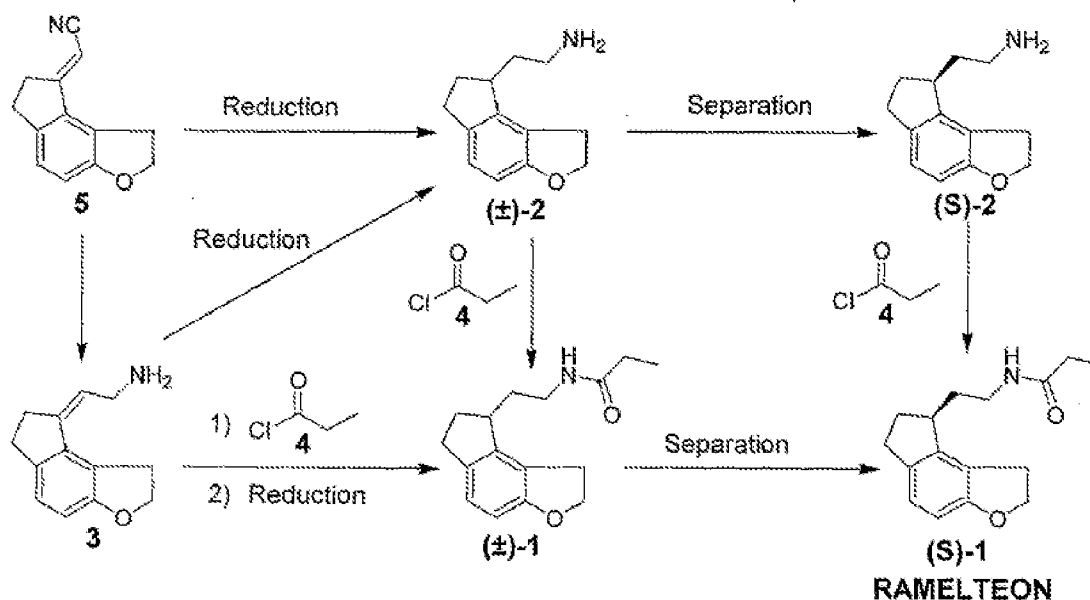


An alternate process for preparing ramelteon is disclosed in the Journal of Medicinal Chemistry, Vol. 45, pp. 4222-4239 (2002), wherein the exo double bond of intermediates (A) shown below was asymmetrically reduced using (S)-2, 2'-bis-(diphenylphosphino)-1, 1'-binaphthyl (binap)-Ru complex as the catalyst to obtain the enantiomerically pure compound (B). Compound (B) is subsequently converted to ramelteon (1) through the intermediate steps of Claisen condensation, ozonolysis and cyclization.



Both of the above processes uses expensive catalyst and give poor enantioselectivity. Additionally, these processes are expensive due to the need to perform multiple purifications steps in order to achieve an enantioselectivity of at least about 99% or greater of the desired isomer.

PCT Patent Publication No. WO 2008/062468 A2 discloses the following process for the preparation of ramelteon:

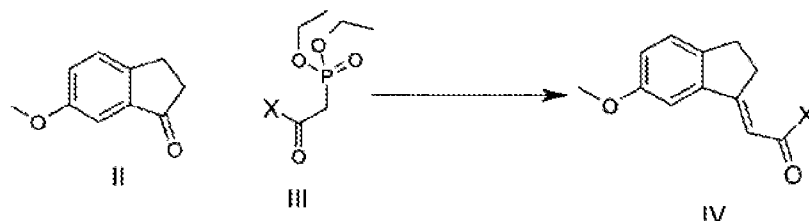


WO 2008/062468 teaches that separation of the enantiomers of intermediate (2) may be accomplished by: i) optical resolution of the racemic amine intermediate (2) by preparing acid salts with chirally pure acids; or ii) chromatographic techniques using chiral and/or achiral stationary phases for batch process, super critical or sub critical chromatography and/or continuous process chromatography. Although WO 2008/062468 mentions the possible use of optical resolution with chirally pure acids, there is no further teaching, discussion or disclosure of this method. WO 2008/062468 does, however, provide detailed descriptions of chromatographic methods for separating the isomers of intermediate compound (2). The disclosed chromatographic process suffers the following disadvantages:

- Preparative chromatography is time consuming & expensive;
- Highly sophisticated instrumentation required;

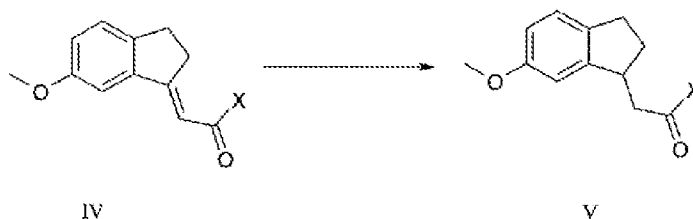
- Not commercially feasible.

PCT Patent Publication No. WO 2008/106179 discloses a process for the preparation of ramelteon that involves the following reaction steps:



wherein X= O-alkyl or NH<sub>2</sub>

and chiral reduction of the compound of formula IV in the presence of Ru-BINAP complex under hydrogen atmosphere in an organic solvent.



The process disclosed in WO 2008/106179 is similar to the process disclosed in United States Patent No. 6,034,239 and the Journal of Medicinal Chemistry, Vol. 45 in that a Ru-BINAP complex is employed.

Resolution of racemic mixtures via reaction with optically active acids and the subsequent crystallization of the resulting salts is preferably employed when the chiral carbon of the racemic compound is an alpha carbon (*i.e.*, one carbon removed) to the functional group forming the acid addition salt. As the distance between the chiral carbon of the racemic compound to the functional group of the racemic compound increases to beta (*i.e.*, two carbon removed) & gamma (*i.e.*, three carbon removed), the resolution of the diastereomeric salt becomes more difficult and not very useful.

Ramelteon has a chiral center at the gamma carbon, which makes the separation of the isomer with an optically active acid quite a daunting task. Similarly, N-[2-(1, 6, 7, 8,-tetrahydro-2H-indeno [5, 4-b]furan-8-yl)]ethylamine (compound 2), an intermediate useful in the

production of ramelteon has a chiral center at the gamma carbon which would lead a skilled artisan to believe that optical resolution with an optically active acid could prove difficult.

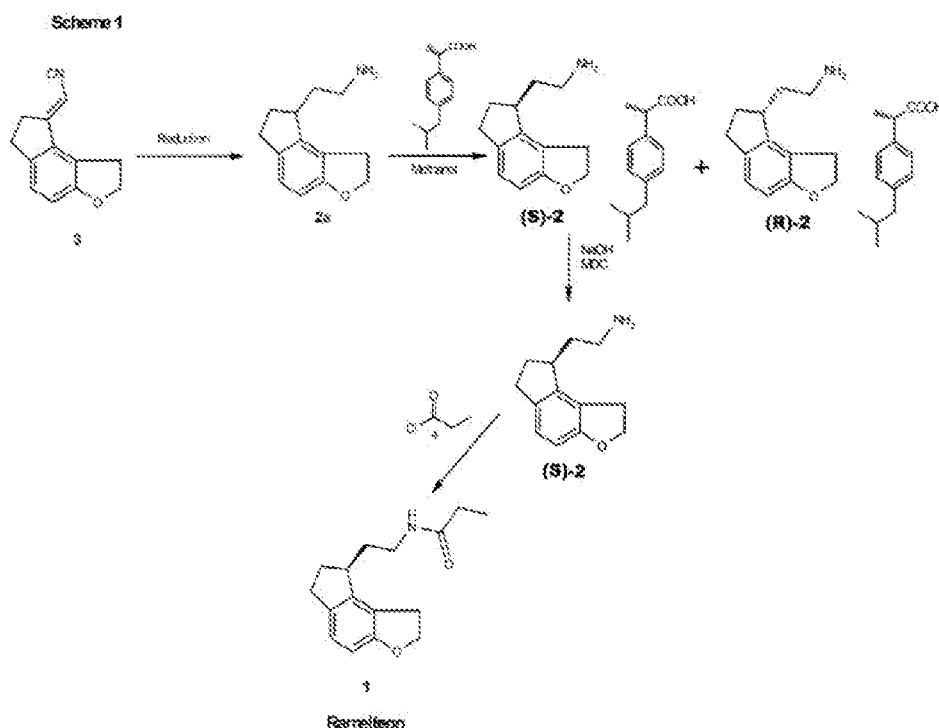
Although a number of methods for preparing ramelteon are disclosed in the art, a need still exists to develop a process for preparing ramelteon in enantiomerically pure form which is cost effective, uses easily available reagents, is scalable with ease and overall commercially viable. This need and others is met by the present invention.

#### **SUMMARY OF THE PRESENT INVENTION:**

The present invention is a process for resolving N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound 2) into its isomers using an optically active acid to achieve high enantioselectivity of the desired isomer. The optically active acid is preferably a straight, branched or cyclic organic acid or a phenyl substituted organic acid.

The present invention further includes a process for the synthesis of ramelteon that comprises the step of separating N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound 2) into its isomers using an optically active acid to achieve high enantioselectivity of the desired isomer. This embodiment may further include the step of acylating the substantially pure enantiomer, (S)-N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound (S)-2) using a suitable acylating agent, such as propionyl chloride) to provide (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide (ramelteon or compound 1) substantially free of the (R)-isomer.

One embodiment of the present invention for the preparation of ramelteon is shown below in Scheme 1.



A further embodiment of the present invention includes a process for preparing ramelteon and (S)-N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound (S)-2) which does not employ any ruthenium complex or compounds.

A still further embodiment of the present invention includes a process for preparing ramelteon and (S)-N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound (S)-2) which does not employ any chromatographic purifications steps or procedures.

#### DETAILED DESCRIPTION OF THE INVENTION:

The present invention is a process for resolving N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound 2) into its isomers using an optically active acid to achieve high enantioselectivity of the desired isomer, preferably (S)-N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine. The process comprises the step of:

- i) reacting N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound 2) with an optically active acid to produce a diastereomeric salt of (S)-N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound (S)-2) and the optically

active acid or a diastereomeric salt of (R)-N-2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl) ethylamine (compound (R)-2) and the optically active acid;

- ii) isolating (S)-N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound (S)-2) from the reaction mixture of step (i).

The N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound 2) employed in the present invention can be prepared by any means known in the industry such as those described in United States Patent No. 6,034,239, WO 2008/062468 and WO 2008/106179. The N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound 2) can be reacted with the optically active acid by suspending or dissolving the N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound 2) and optically active acid in a solvent, preferably an organic solvent such as a C<sub>1</sub>-C<sub>6</sub> alcohol and most preferably an organic solvent such as methanol, ethanol or isopropanol or mixtures thereof.

Examples of the optically active acid useful in the present invention include D-lactic acid, D-tartaric acid, D-malic acid, 1S-10-camphorsulfonic acid, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenyl acetic acid, D-mandelic acid, di-P-anisoyl-D-tartaric acid, m-parachloro anilide, dibenzoyl-D-tartaric acid, S-(+)-1.1'-binaphthalene-2,2'-dihydrogen phosphate, S-2-(4-isobutylphenyl)propionic acid & mixtures thereof. The preferred optically active acids are straight, branched or cyclic organic acids such as D-lactic acid, D-tartaric acid, D-malic acid, 1S-10-camphorsulfonic acid or a phenyl substituted organic acid such as (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenyl acetic acid, D-mandelic acid, m-parachloro anilide, dibenzoyl-D-tartaric acid and S-2-(4-isobutylphenyl)propionic acid. The most preferred optically active acids are the aforementioned phenyl substituted organic acids or mixtures thereof.

The molar ratio of N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound 2) to optically active acid can range from about 1:0.5 to about 1:5, preferably about 1:0.75 to about 1:3 and most preferably about 1:0.9 to about 1:1.3.



The isolation of (S)-N-2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)ethylamine (compound (S)-2) from the reaction mixture N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound 2) and the optically active acid can be accomplished by any means commonly used in the chemical arts such as solvent extraction or crystallization.

One embodiment of the present invention comprises reacting N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound 2) with an optically active acid, preferably a phenyl substituted organic acid such as S-2-(4-isobutylphenyl)propionic acid, to produce a diastereomeric salt of (S)-N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound (S)-2) and the optically active acid. The salt of compound (S)-2 is isolated from the reaction mixture, preferably by precipitation, and then purified by conventional techniques such as recrystallization to obtain a salt of compound (S)-2 having a chiral purity of greater than 98% enantioselectivity, preferably greater than 98.5% enantioselectivity and most preferably greater than 99.0% enantioselectivity.

The purified salt is then converted to the free base form of (S)-N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound (S)-2) by conventional techniques. One embodiment of this aspect of the invention obtains the free base by suspending the purified salt of (S)-N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound (S)-2) and the optically active acid in an appropriate solvent such as water and adjusting the pH of the aqueous suspension to about 8-13, preferably 9-12 and most preferably about 10-12. The pH may be adjusted by adding an appropriate base such as aqueous sodium hydroxide to the aqueous suspension. After the pH has been adjusted, the free base form of (S)-N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound (S)-2) is isolated from the reaction mass. The free base form of compound (S)-2 can be isolated by any conventional means known in the chemical arts.

One embodiment of the present invention isolates the free base form of (S)-N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound (S)-2) from the basic aqueous suspension by an extraction with an appropriate organic solvent, preferably an aprotic solvent and most preferably a halogenated organic solvent such as dichloromethane.

Once the free base form of (S)-N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound (S)-2) is isolated from the basic aqueous suspension, it may be washed, dried and/or further purified to produce (S)-N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound (S)-2) with a chiral purity of greater than 98% enantioselectivity, preferably greater than 98.5% enantioselectivity and most preferably greater than 99.0% enantioselectivity.

A further embodiment of the present invention comprises the additional step of converting the (S)-N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound (S)-2) with a chiral purity of greater than 98% enantioselectivity, preferably greater than 98.5% enantioselectivity and most preferably greater than 99.0% enantioselectivity, into ramelteon.

The (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)]ethylamine (compound (S)-2) can be converted to ramelteon by acylating the (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)]ethylamine (compound (S)-2) using a suitable acylating agent, such as propionyl chloride, to produce ramelteon. A number of processes for acylating (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)]ethylamine (compound (S)-2) to produce ramelteon are described in United States Patent No. 6,034,239, Japanese Patent Publication No. 11080106, WO 2008/062468 and WO 2008/106179.

One aspect of the present invention for the preparing ramelteon comprises the steps of:

- i) dissolving the (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)]ethylamine (compound (S)-2) prepared by the above described resolution process with an optically active organic acid in a suitable organic solvent, preferably a polar aprotic solvent such as dimethylsulfoxide, dimethylformamide and tetrahydrofuran and more preferably a halogenated organic solvent such as dichloromethane;
- ii) adding an acylating agent, preferably propionyl chloride, to solution of step (i); and
- iii) isolating the ramelteon from the reaction mixture of step (ii).

The molar amount of acylating agent, *i.e.*, propionyl chloride, employed in the above process should be equivalent or slightly in excess of the molar amount of (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)]ethylamine (compound (S)-2). Preferably the molar

ratio of acylating agent to compound (S)-2 should be about 1:1 to about 2:1, preferably about 1:1 to about 1.5:1. The acylation reaction may occur under ambient conditions, *i.e.*, room temperature and normal atmospheric pressure.

It is also desirable to include a base in the solution of step (i) and/or the reaction mixture of step (ii) to react with the acid formed during the acylation reaction. Examples of some of the bases that can be added during the process are tertiary amines such as triethyl amine and diisopropyl ethylamine. The amount of the base added to the above process should be molar equivalent to the amount of acylating agent added during step (ii).

Once the acylation reaction is completed, the ramelteon may be isolated from the reaction mixture by any conventional methods known in the chemical arts. One embodiment of the present invention employs a solvent extraction wherein water is added to the reaction mixture and the organic solvent of step (i), which contains the ramelteon, is separated from the aqueous layer. The organic solvent is then removed to obtain the ramelteon. The resulting ramelteon may be purified to obtain a final product with a chiral purity of greater than 98% enantioselectivity, preferably greater than 98.5% enantioselectivity and most preferably greater than 99.0% enantioselectivity.

## **EXAMPLES**

### **Example 1**

#### **Preparation of (S)-N-2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl) ethylamine (Compound (S)-2)**

A solution of N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)ethylamine (45 g; 0.22 mol) in methanol (225 ml) is added to a solution of S-(+)-2-(4-isobutylphenyl)propionic acid (41 g; 0.20 mol) in methanol (205 ml) at 25-30°C. The reaction mixture is concentrated to dryness under reduced pressure. The crude salt precipitated is recrystallized in methanol to give a diastereomeric salt of (S)-N-2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl) ethylamine with (S)-(+)-2-(4-isobutylphenyl) propionic acid having a chiral purity of greater than 90% enantioselectivity.

The product obtained is recrystallized from methanol to give the pure salt having chiral purity of 99% or greater enantioselectivity.

The purified salt is suspended in water and the pH of the suspension is adjusted to 11-12 using aqueous sodium hydroxide. The reaction mixture is extracted with dichloromethane, washed with water and evaporated to give the pure (S)-N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine (compound (S)-2), substantially free from its (R) isomer.

## **Example 2**

### **Preparation of (S)-N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethyl propionamide (ramelteon)**

Triethyl amine (15.15 g, 0.15 mol) and propionyl chloride (13.66 g, 0.15 mol) were added to a solution of S-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5,4-b]furan-8-yl)]ethylamine (25 g, 0.12 mol) (compound (S)-2) (prepared in Example 1) in dichloromethane and stirred at room temperature for 2 hours. 75 mL water was added to the reaction mixture, and the layers were separated. The dichloromethane layer was concentrated under reduced pressure and purified from a mixture of acetone and hexane to give (S)-N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl) ethyl] propionamide (compound 1) having a chiral purity of 99% or greater enantioselectivity.

The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein, any of the terms “comprising,” “consisting essentially of” and “consisting of” may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

We claim:

1. A process for resolving N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)] ethylamine comprising the step of:

- i) reacting N-[2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl)]ethylamine with an optically active acid to produce a salt of (S)-N-2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl) ethylamine and the optically active acid or a salt of (R)-N-2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl) ethylamine and the optically active acid;
- ii) isolating (S)-N-2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl) ethylamine from the reaction mixture of step (i) wherein the process does not employ any ruthenium complex or compounds.

2. The process as described in claim 1 wherein the optically active acid is a straight, branched or cyclic organic acid.

3. The process as described in claim 2 wherein the optically active acid is selected from the group consisting of D-lactic acid, D-tartaric acid, D-malic acid, 1S-10-camphorsulfonic acid and combinations thereof.

4. The process as described in claim 1 wherein the optically active acid is a phenyl substituted organic acid.

5. The process as describe in claim 4 wherein the optically active acid is selected from the group consisting of (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenyl acetic acid, D-mandelic acid, m-parachloro anilide, dibenzoyl-D-tartaric acid, S-2-(4-isobutylphenyl)propionic acid and combinations thereof.

6. The process as described in claim 5 wherein the optically active acid is S-2-(4-isobutylphenyl)propionic acid.

7. The process of claim 1 further comprising the step of converting the (S)-N-2-(1, 6, 7, 8-tetrahydro-2H-indeno [5, 4-b] furan-8-yl) ethylamine from step (ii) into ramelteon.
8. The process of claim 7 wherein the converting step comprises:
- a) dissolving the (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)]ethylamine in an organic solvent;
  - b) adding an acylating agent to the solution of step (a); and
  - c) isolating the ramelteon from the reaction mixture of step (b).
9. The process of claim 8 wherein the organic solvent of step (a) is a polar aprotic solvent.
10. The process of claim 8 wherein the organic solvent is selected from the group consisting of dimethylsulfoxide, dimethylformamide, tetrahydrofuran and mixtures thereof.
11. The process of claim 8 wherein the organic solvent of step (a) is a halogenated organic solvent.
12. The process of claim 8 wherein the organic solvent is dichloromethane.
13. Ramelteon produced according to the process of claim 7.
14. Ramelteon produced according to the process of claim 8.
15. The process according to claim 1 which does not employ any chromatographic purifications steps or procedures.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 09/55038

A. CLASSIFICATION OF SUBJECT MATTER  
IPC(8) - C07D 307/93; C07C 69/618 (2010.01)  
USPC - 549/458; 560/56; 564/180

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)

IPC(8): C07D 307/93; C07C 69/618 (2010.01)

USPC: 549/458; 560/56; 564/180

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

USPC: 549/458; 560/56; 564/180; 514/468 (Keywords limited - See list for keywords)

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

PubWEST(USPT,PGPB,EPAB,JPAB); DialogPRO(Chemistry); Google Scholar

Search Terms: ramelteon, "optically active", lactic, tartaric, camphorsulfonic, isomer\$2, metal, ethylamine, isobutylphenyl

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---	WO 2008/062468 A2 (Ramdharane et al.) 29 May 2008 (29.05.2008), especially pg 2, ln 11-13; pg 3, ln 18-21; pg 3, scheme 1; pg 5, ln 1-9; pg 5, ln 26-27	1, 7, 13 -----
Y		2-6, 8-12, 14, 15
Y	US 2008/0214559 A1 (Lange et al.) 04 September 2008 (04.09.2008), especially, para [0024], [0026], [0027], [0053]	2-6
Y	US 6,348,485 B1 (Ohkawa et al.) 19 February 2002 (19.02.2002), especially, col 8, ln 50-59	8-12, 14, 15
Y	US 5,321,154 A (Nohira) 14 June 1994 (14.06.1994), especially, col 2, ln 25-32	5, 6
Y	US 2008/0242877 A1 (Kansal et al.) 02 October 2008 (02.10.2008), especially, para [0002], [0054]	11, 12
A	US 6,218,429 B1 (Ohkawa et al.) 17 April 2001 (17.04.2001), entire document	1-15

☐ 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 application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

"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

02 February 2010 (02.02.2010)

Date of mailing of the international search report

19 MAR 2010

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents  
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774