

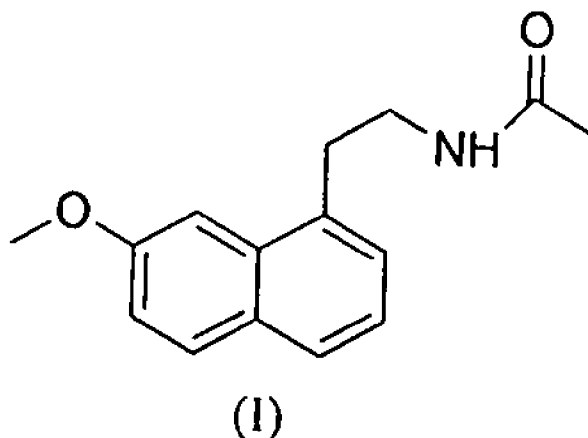


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- (71) **Applicant:** CADILA HEALTHCARE LIMITED [IN/IN]; Zydus Tower, Satellite Cross Roads, Ahmedabad 380015, Gujarat (IN).
- (72) **Inventors:** DWIVEDI, Shri Prakash Dhar; Cadila Healthcare Limited, Zydus Tower, Satellite Cross Roads, Ahmedabad - 380015, Gujarat (IN). PRASAD, Ashok; Cadila Healthcare Limited, Zydus Tower, Satellite Cross Roads, Ahmedabad - 380015, Gujarat (IN). SHAH, Niraj Shyamal; Cadila Healthcare Limited, Zydus Tower, Satellite Cross Roads, Ahmedabad - 380015, Gujarat (IN). PATEL, Mayur Ramnikbhai; Cadila Healthcare Limited, Zydus Tower, Satellite Cross Roads, Ahmedabad - 380015, Gujarat (IN).
- (74) **Agents:** SUBRAMANIAM, Hariharan et al.; Subramaniam & Associates, Central Square, Suite-328, Plaza III, 20 Manoharlal Khurana Marg, Bara Hindu Rao (off, Rani Jhansi Road), Delhi - 110006 (IN).
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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

[Continued on next page]

(54) **Title:** AN IMPROVED PROCESS FOR PREPARATION OF AGOMELATINE

(57) **Abstract:** The present invention provides an improved process for preparing agomelatine of formula (I). The process comprises reacting 7-methoxy tetralone with cyanoacetic acid in an organic solvent to obtain (7-methoxy-3,4-dihydro-1-naphthalenyl)acetone nitrile of Formula (B); treating compound of Formula (B) with a catalyst to obtain (7-methoxy-1-naphthyl)acetonitrile of Formula (C); reducing compound of formula (C) with hydrogen in presence of Raney nickel in ammoniacal methanol medium and subsequently converting to a salt using hydrochloric acid to obtain 2-(7-methoxy-1-naphthyl)ethanamine hydrochloride of formula (D); iv) reacting compound of formula (D) with acetic anhydride or acetic chloride in an organic solvent in presence of a base and a catalyst to obtain agomelatine of Formula (I); and optionally purifying agomelatine of Formula (I). The present invention also provides a process for preparing polymorphic Form-I of agomelatine of formula (I) comprising treating agomelatine of formula (I) in a suitable organic solvent; and isolating polymorphic Form-I of agomelatine of formula (I).



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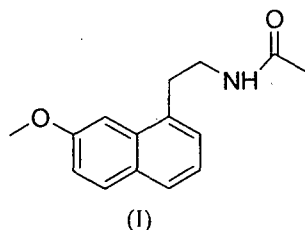
AN IMPROVED PROCESS FOR PREPARATION OF AGOMELATINE

FIELD OF THE INVENTION

The present invention relates to an improved process for preparation of agomelatine. The present invention also relates to process for preparing (7-Methoxy-1-naphthyl) acetonitrile, a key intermediate in the preparation of agomelatine.

BACKGROUND OF THE INVENTION

Agomelatine is an agonist of melatoninergic system receptors and an antagonist of the 5-HT_{2C} receptor. Those properties confer activity in the central nervous system and, more especially, in the treatment of severe depression, seasonal affective disorders, sleep disorders, cardiovascular pathologies, and pathologies of the digestive system, insomnia and fatigue resulting from jetlag, appetite disorders and obesity. Agomelatine is under regulatory review in US and is being approved in EU. It is available in the EU market under the brand name Valdoxan. Agomelatine is chemically described as N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide and represented by the structural formula (I)



U.S. Patent No. 5,225,442 A describes agomelatine, a pharmaceutical composition, a method of treatment, and a process for the preparation thereof.

U.S. Patent No. 7,544,839 B2 describes the preparation of agomelatine.

U.S. application No. 2010/0036162 A1 describes the preparation of agomelatine as illustrated by below scheme:

J. Med. Chem., 1992, 35, 1486-1489 discloses the synthesis of agomelatine wherein final recrystallization is from cyclohexane-toluene.

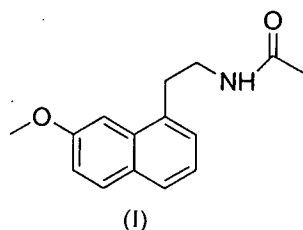
Synthetic communication, 2001, 31 (4), 621 -629 discloses the synthesis of agomelatine from 7-methoxy-1-tetralone by using LiCH_2CN at -78°C followed by dehydrogenation with DDQ.

The process for the preparation of agomelatine is also reported in JMC 1994, vol 37, 3231-3239.

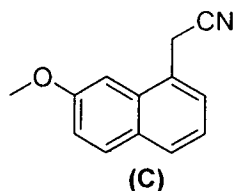
The crystalline forms II, III, IV, V and VI are reported in U.S. Patent No. 7,250,531 B2, 7,635,721 B2, US 7,645,905 B2, US 7,358,395 B2 and 8,067,639 B2 respectively.

SUMMARY OF THE INVENTION

In one general aspect, there is provided an improved process for preparing agomelatine of formula (I)

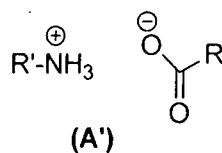


In another general aspect, there is provided a process for preparing (7-Methoxy-1-naphthyl) acetonitrile of Formula (C);



the process comprising:

i) reacting 7-Methoxy tetralone of Formula (A) with cyanoacetic acid in a suitable organic solvent; wherein the water formed during the reaction is removed, in the presence of a catalytic amount of a compound of formula (A')



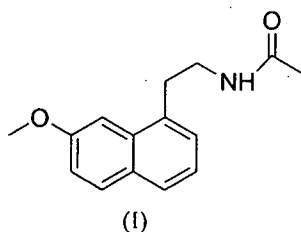
wherein R represents hydrogen or $\text{C}_1\text{-C}_2$ alkyl;

R' represents hydrogen, linear or branched (C₃-C₁₀)alkyl, unsubstituted or substituted aryl, or unsubstituted or substituted linear or branched aryl (C₁-C₆)alkyl,

to obtain (7-Methoxy-3,4-dihydro-1-naphthalenyl)acetonitrile of Formula (B)

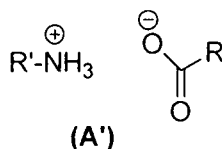
ii) treating (7-Methoxy-3,4-dihydro-1-naphthalenyl)acetonitrile of Formula (B) with an aromatization catalyst to obtain (7-Methoxy-1-naphthyl)acetonitrile of Formula (C).

In another general aspect, there is provided an improved process for preparing agomelatine of formula (I)



the process comprising:

i) reacting 7-methoxy tetralone of Formula (A) with cyanoacetic acid in a suitable organic solvent; wherein the water formed during the reaction is removed, in the presence of a catalytic amount of a compound of formula (A')



wherein R represents hydrogen or C₁-C₂ alkyl;

R' represents hydrogen, linear or branched (C₃-C₁₀)alkyl, unsubstituted or substituted aryl, or unsubstituted or substituted linear or branched aryl (C₁-C₆)alkyl,

to obtain (7-methoxy-3,4-dihydro-1-naphthalenyl)acetonitrile of Formula (B);

ii) treating (7-methoxy-3,4-dihydro-1-naphthalenyl)acetonitrile of Formula (B) with an aromatization catalyst to obtain (7-methoxy-1-naphthyl)acetonitrile of Formula (C);

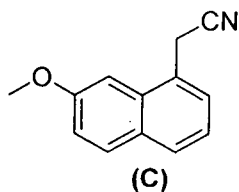
iii) reducing (7-methoxy-1-naphthyl)acetonitrile of Formula (C) with hydrogen in presence of Raney nickel in ammoniacal methanol medium and subsequently converted to a salt using hydrochloric acid to obtain 2-(7-methoxy-1-naphthyl)ethanamine

hydrochloride of formula (D);

- iv) reacting 2-(7-methoxy-1-naphthyl)ethanamine hydrochloride of formula (D) with acetic anhydride or acetic chloride in a suitable organic solvent in presence of a base and a catalyst to obtain agomelatine of Formula (I); and
- v) optionally purifying agomelatine of Formula (I).

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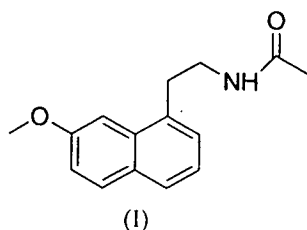
In another general aspect, there is provided use of (7-Methoxy-1-naphthyl) acetonitrile of Formula (C);



in the preparation of agomelatine of formula (I).

10

In another general aspect, there is provided a process for preparing polymorphic Form-I of agomelatine of formula (I)



the process comprising:

- 15 i) treating agomelatine of formula (I) in a suitable organic solvent;
- ii) isolating polymorphic Form-I of agomelatine of formula (I)

In another general aspect, there is provided agomelatine of formula (I) having purity of greater than about 99%, specifically greater than about 99.5%, more specifically greater than about 99.9%, and most specifically greater than about 99.98% and having all other

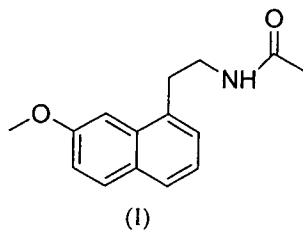
20 impurities less than 0.1% as measured by HPLC.

In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of agomelatine and one or more pharmaceutically

25 acceptable carriers, excipients or diluents.

DETAILED DESCRIPTION OF THE INVENTION

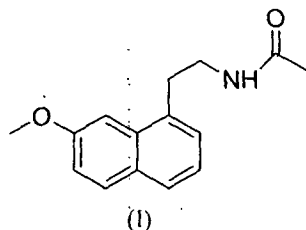
The present invention relates to an improved process for the preparation of N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide compound of formula (I)



- 5 As used herein the present invention, the term "suitable solvents" wherever necessary, is selected from "ester solvents" like ethyl acetate, methyl acetate, isopropyl acetate; "ether solvents" like tetrahydrofuran, diethylether, methyl tert-butyl ether; "hydrocarbon solvents" like toluene, hexane, heptane, pet.ether and cyclohexane; "polar aprotic solvents" like dimethylformamide, dimethyl acetamide, dimethyl sulfoxide, acetonitrile;
- 10 "ketone solvents" like acetone, methylethyl ketone, methyl isobutyl ketone; "alcohol solvents" like methanol, ethanol, n-propanol, isopropanol, n-butanol, diglycol and isobutanol; "chloro solvents" like dichloromethane, chloroform, and dichloroethane; and "polar solvents" like water; and also mixtures thereof.

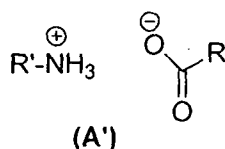
- The term "base" herein the present invention is selected from inorganic bases like alkali
- 15 metal, and alkaline earth metal alkoxides, hydroxides, carbonates and bicarbonates such as lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium tert-butoxide, potassium tert-butoxide, sodium carbonate, potassium carbonate, sodium bicarbonate and potassium bicarbonate; and organic bases like ammonia, triethylamine, tributyl amine, dimethyl aniline, N-methyl piperidine and N-methyl pyrrolidine, N-methyl morpholine,
- 20 diisopropyl methylamine, diisopropyl amine, diisopropyl ethylamine, cyclohexyldimethyl amine, piperidine, dimethyl amino pyridine, pyridine, lithium hexamethyldisilazidem (LiHMDS), sodium hexamethyldisilazide (NaHMDS) and tetraalkyl ammonium hydroxide such as tetrabutyl ammonium hydroxide.

- An aspect of the present invention is to provide an improved process for the preparation of
- 25 agomelatine of formula (I)



the process comprising:

- i) reacting 7-Methoxy tetralone of Formula (A) with cyanoacetic acid in a suitable organic solvent; wherein the water formed during the reaction is removed, in the presence
5 of a catalytic amount of a compound of formula (A')

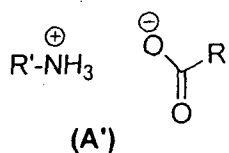


wherein R represents hydrogen or C₁-C₂ alkyl;

- 10 R' represents hydrogen, linear or branched (C₃-C₁₀) alkyl, unsubstituted or substituted aryl, or unsubstituted or substituted linear or branched aryl (C₁-C₆)alkyl, to obtain (7-Methoxy-3,4-dihydro-1-naphthalenyl)acetonitrile of Formula (B);
- ii) treating (7-Methoxy-3,4-dihydro-1-naphthalenyl)acetonitrile of Formula (B) with an aromatization catalyst in a suitable organic solvent to obtain (7-Methoxy-1-naphthyl)acetonitrile of Formula (C);
- 15 iii) reducing (7-methoxy-1-naphthyl)acetonitrile of Formula (C) with hydrogen in presence of Raney nickel in ammoniacal methanol medium and subsequently converted to a salt using hydrochloric acid to obtain 2-(7-methoxy-1-naphthyl)ethanamine hydrochloride of formula (D);
- 20 iv) reacting 2-(7-Methoxy-1-naphthyl)ethanamine hydrochloride of formula (D) with acetic anhydride in a suitable organic solvent in presence of a base and a catalyst to obtain agomelatine of Formula (I); and
- v) optionally purifying agomelatine of Formula (I).

The suitable organic solvent for step (a) is selected from one or more of hydrocarbons, halogenated solvents, nitriles, amides, alcohol, ketones, ester and the like. In particular, the suitable solvent comprises toluene, xylene, ethylbenzene dimethyl formamide, dimethyl acetamide, methylene dichloride, acetonitrile, C₁-C₄ straight chain or branched
 5 alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate and the likes. Particularly, the solvent may be toluene.

In the reaction for the conversion of the compound of Formula (A) to a compound of Formula (B) in step (i) a catalyst of formula (A') as represented below is involved:



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wherein R represents hydrogen or C₁-C₂ alkyl;

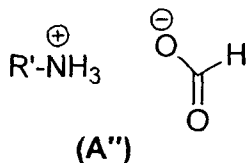
R' represents hydrogen, linear or branched (C₃-C₁₀) alkyl, unsubstituted or substituted aryl, or unsubstituted or substituted linear or branched aryl (C₁-C₆)alkyl,

Advantageously, R' represents hydrogen, an unsubstituted or substituted phenyl group,
 15 more especially an unsubstituted phenyl group.

The preferred group for R' is the hexyl group.

The preferred group for R is the hydrogen.

The preferred catalyst used in the conversion of the compound of Formula (A) to the compound of Formula (B) according to the process of the invention is benzylammonium
 20 formate of formula (A''):



The compound of Formula (B) obtained in step (i) may be proceeded for step (ii) without isolation.

The compound of formula (B) may be formed in-situ and proceeded for step (ii) without isolation.

5 The suitable aromatizing agent for step (ii) is selected from sulphur, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or a proton acceptor selected from nitro alkanes or nitro arenes such as nitromethane, nitro ethane, nitro benzene and the like, optionally in the presence of a base selected from alkali metal or alkaline earth metal or tetraalkyl ammonium hydroxides, alkoxides, carbonates and bicarbonates; or a phase transfer catalyst such as alkyl ammonium and alkyl phosphonium salts, especially bromide or
10 other halides; wherein, the alkyl group is straight chain or branched containing 1-20 carbon atoms, most commonly 1-12 carbon atoms such as tetramethyl, tetraethyl, tetrabutyl, tetrapentyl, methyl-trialkyl, butyltripropyl, heptyltriethyl, octyltriethyl and the like. Particularly the aromatizing agent may be 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

15

The suitable organic solvent for step (ii) is selected from aromatic hydrocarbons, C₁-C₄ straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate and the likes. Particularly, the solvent may be toluene.

20

The suitable temperature for step (ii) is in the range of 15°C to 30°C, preferably the temperature may be 10°C to 20°C.

25 The suitable organic solvent for step (iii) is selected from one or more of hydrocarbons, halogenated solvents, alcohols, ketones, esters and the like. Particularly the solvent may be methanol.

30 The suitable hydrogenation catalyst for reduction step (iii) is selected from Raney-Ni, lithium aluminum hydride, Palladium/C, Al₂O₃. Particularly the reducing agent may be Raney-Ni.

The suitable organic solvent for salt formation in step (iii) is selected from one or more of hydrocarbons, halogenated solvents, alcohols, ketones, esters and the like. Particularly the solvent may be ethyl acetate.

5 The suitable organic solvent for step (iv) is selected from selected from aromatic hydrocarbons, C₁-C₄ straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate, halogenated solvent, pyridine, dimethyl formamide, cyclohexane and the likes. Particularly, the solvent may be methylene dichloride.

10

The suitable base for step (iv) is selected either from organic bases or inorganic bases like alkali metal, and alkaline earth metal alkoxides, hydroxides, carbonates and bicarbonates such as lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium tert- butoxide, potassium tert-butoxide, sodium carbonate, potassium carbonate, sodium bicarbonate and
15 potassium bicarbonate.

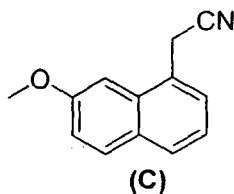
Organic base is selected from ammonia, triethylamine, tributyl amine, dimethyl aniline, N-methyl piperidine and N-methyl pyrrolidine, N- methyl morpholine, diisopropyl methylamine, diisopropyl amine, diisopropyl ethylamine.

Particularly, the base for step (iv) may be triethylamine.

20 The suitable catalyst for step (iv) is N, N-dimethylpyridin-4-amine.

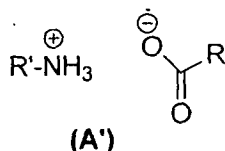
The suitable solvent for purification of agomelatine in step (v) is selected from one or more of hydrocarbons, halogenated solvents, nitriles, amides, alcohol, ketones, ester and the like. In particular, the suitable solvent comprises toluene, xylene, ethylbenzene dimethyl formamide, dimethyl acetamide, methylene dichloride, acetonitrile, C₁-C₄
25 straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate and the likes. Particularly, the solvent may ethyl acetate.

In another aspect, there is provided a process for preparing (7-Methoxy-1-naphthyl)
30 acetonitrile of Formula (C);



the process comprising:

- i) reacting 7-Methoxy tetralone of Formula (A) with cyanoacetic acid in a suitable organic solvent; wherein the water formed during the reaction is removed, in the presence of a catalytic amount of a compound of formula (A')

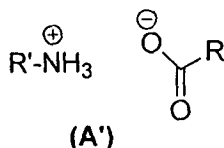


wherein R represents hydrogen or C₁-C₂ alkyl;

- R' represents hydrogen, linear or branched (C₃-C₁₀)alkyl, unsubstituted or substituted aryl, or unsubstituted or substituted linear or branched aryl (C₁-C₆)alkyl, to obtain (7-Methoxy-3,4-dihydro-1-naphthalenyl)acetonitrile of Formula (B)
- ii) treating (7-Methoxy-3,4-dihydro-1-naphthalenyl)acetonitrile of Formula (B) with an aromatization catalyst to obtain (7-Methoxy-1-naphthyl)acetonitrile of Formula (C).

- The suitable organic solvent for step (i) is selected from one or more of hydrocarbons, halogenated solvents, nitriles, amides, alcohol, ketones, ester and the like. In particular, the suitable solvent comprises toluene, xylene, ethylbenzene dimethyl formamide, dimethyl acetamide, methylene dichloride, acetonitrile, C₁-C₄ straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate and the likes. Particularly, the solvent may be toluene.

In the reaction for the conversion of the compound of Formula (A) to a compound of Formula (B) in step (i) a catalyst of formula (A') as represented below is involved:



wherein R represents hydrogen or C₁-C₂ alkyl;

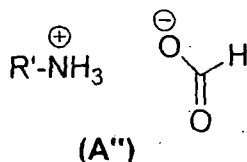
R' represents hydrogen, linear or branched (C₃-C₁₀) alkyl, unsubstituted or substituted aryl, or unsubstituted or substituted linear or branched aryl (C₁-C₆)alkyl,

Advantageously, R' represents hydrogen, an unsubstituted or substituted phenyl group,
5 more especially an unsubstituted phenyl group.

The preferred group for R' is the hexyl group.

The preferred group for R is the hydrogen.

The preferred catalyst used in the conversion of the compound of Formula (A) to the compound of Formula (B) according to the process of the invention is benzylammonium formate of formula (A'')



The compound of Formula (B) obtained in step (i) may be proceeded for step (ii) without isolation.

The compound of formula (B) may be formed in-situ and proceeded for step (ii) without isolation.

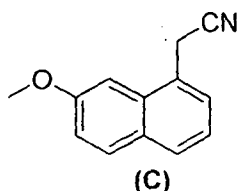
The suitable aromatizing agent for step (ii) is selected from sulphur, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or a proton acceptor selected from nitro alkanes or nitro arenes such as nitromethane, nitro ethane, nitro benzene and the like, optionally in the presence of a base selected from alkali metal or alkaline earth metal or tetraalkyl ammonium hydroxides, alkoxides, carbonates and bicarbonates; or a phase transfer catalyst such as alkyl ammonium and alkyl phosphonium salts, especially bromide or other halides. Wherein, the alkyl group is straight chain or branched containing 1-20 carbon atoms, most commonly 1-12 carbon atoms such as tetramethyl, tetraethyl, tetrabutyl, tetrapentyl, methyl-trialkyl, butyltripropyl, heptyltriethyl, octyltriethyl and the like. Particularly the aromatizing agent may be 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

The suitable organic solvent for step (ii) is selected from aromatic hydrocarbons, C₁-C₄ straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate and the likes. Particularly, the solvent may be toluene.

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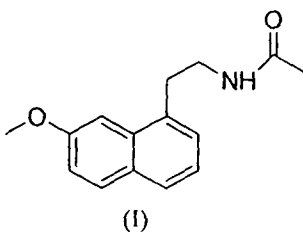
The suitable temperature for step (ii) is in the range of 15°C to 30°C, preferably the temperature may be 10°C to 20°C.

In another general aspect, there is provided use of (7-Methoxy-1-naphthyl) acetonitrile of
10 Formula (C);



in the preparation of agomelatine of formula (I).

15 In another general aspect, there is provided a process for preparing polymorphic Form-I of agomelatine of formula (I).



the process comprising:

- i) treating agomelatine of formula (I) in a suitable organic solvent;
- 20 ii) isolating polymorphic Form-I of agomelatine of formula (I)

The suitable solvent for step (i) is selected from one or more of hydrocarbons, halogenated solvents, nitriles, amides, alcohol, ketones, ester and the like. In particular, the suitable solvent comprises toluene, xylene, ethylbenzene dimethyl formamide, dimethyl acetamide, methylene dichloride, acetonitrile, C₁-C₄ straight chain or branched alcohols,

acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate and the likes. Particularly, the solvent may be ethyl acetate.

In another general aspect, there is provided agomelatine of formula (I) having purity of greater than about 99%, specifically greater than about 99.5%, more specifically greater than about 99.9%, and most specifically greater than about 99.98% and having all other
5 impurities less than 0.1% as measured by HPLC.

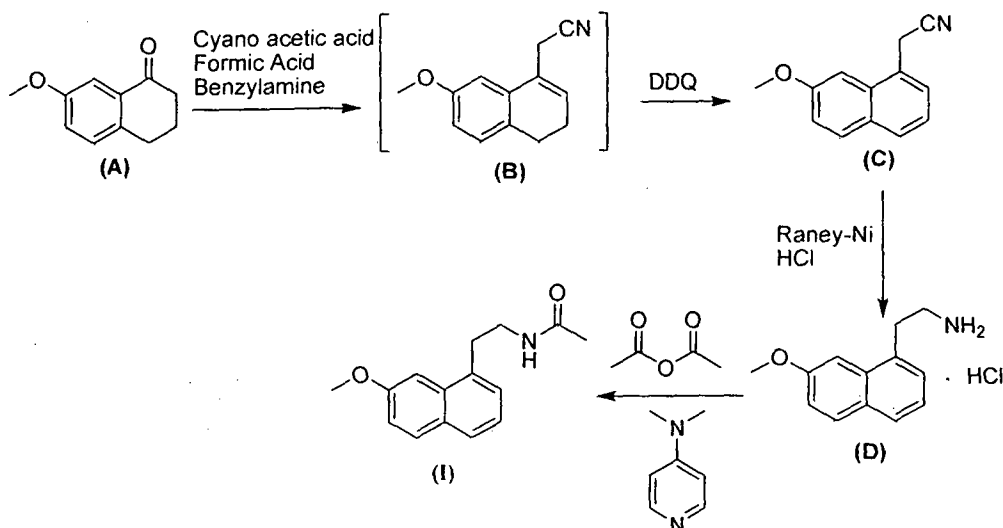
In another aspect the present invention provides a pharmaceutical composition comprising as its active ingredient crystalline form of agomelatine of formula (I). With the active ingredient, the pharmaceutical composition includes one or more pharmaceutically
10 acceptable excipients/diluents. The pharmaceutical composition of the present invention may be in the form of a solid or liquid dosage forms for oral, parenteral or topical use and may have immediate or sustained release characteristics. The dosage forms possible include tablets, capsules, powders, granules, creams, lotions, ointments, injectable, ophthalmic or optic solutions, suspensions, elixirs and the like.

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The present invention is further illustrated by the following example which is 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.

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The process for preparing agomelatine as per present invention may be represented as shown in Scheme-1:



Scheme-1

Working Examples:**5 Example 1: Preparation of (7-methoxy-1-naphthyl)acetonitrile of Formula (C)**

7-methoxy-1-tetralone of Formula (A) (200 g), toluene (1000 ml), cyanoacetic acid (140 g), benzyl amine (30 g) and formic acid (13 g) were added at 25°C to 35°C and stirred for 20 minutes. The reaction mass was heated to 110°C to 120°C and maintained for 30 to 36 hours. The reaction mass was treated with Sodium hydroxide solution (500 ml) and organic layer (7-Methoxy-3,4-dihydro-1-naphthalenyl)acetonitrile of Formula (B) was taken for the next step. Toluene (1000 ml) and 2,3-Dichloro-5,6-dicyano 1,4-benzoquinone (240 g) was added at 25°C to 35°C. The reaction mass was cooled to 10°C to 20°C and separated organic layer of compound of Formula (B) was added and maintained for 1 hour. The reaction mass was washed with Toluene (200.0 mL) and treated with Sodium bicarbonate solution (500 ml). The organic layer was treated with charcoal (10 g) and finally treated with ethanol (300 ml) at 25-30°C. The reaction mass was heated at 50°C to 55°C followed by addition of water (200 ml) and cooled to 25°C to 30°C. The reaction mass was filtered and washed with chilled ethanol (2x50ml) afforded (7-methoxy-1-naphthyl)acetonitrile of Formula (C).

Yield – 76%

Example 2: Preparation of 2-(7-methoxy-1-naphthyl)ethanamine hydrochloride of Formula (D)

Methanol (500 ml) was added to an autoclave with 1 Kg/cm² pressure of Ammonia gas at 10°C to 15°C and stirred for 1 hour followed by addition of (7-methoxy-1-naphthyl)acetonitrile of Formula (C) (70 g). Raney Nickel (14 g) was added and 5.0 Kg/cm² pressure of Hydrogen gas was applied at 15°C to 25°C. The reaction was heated to 50°C to 55°C. The reaction mass was filtered and treated with ethyl acetate (500 ml) at 25°C to 35°C and cooled to 0°C to 5°C followed by addition of Con. HCl acid and maintained for 1 hour. The reaction mass was filtered and washed with chilled ethyl acetate (2 X 50 ml) afforded 2-(7-methoxy-1-naphthyl)ethanamine hydrochloride of formula (D)
Yield – 83%

Example 3: Preparation of agomelatine of formula (I)

2-(7-methoxy-1-naphthyl)ethanamine hydrochloride of formula (D) (25 g) and methylene dichloride (120 ml) was added at 25°C to 35°C and stirred for 15 minutes followed by addition of triethyl amine (25 g). The reaction mass was stirred for 30 minutes and cooled to 10°C to 20°C. Acetic anhydride (12 g) was added and stirred for 1 hour. The reaction mass was treated with water (200 ml) followed by treatment of sodium bicarbonate solution (125 ml) and hydrochloric acid solution (125 ml). Organic layer was treated with ethyl acetate (50 ml) and heated at 45°C to 50°C followed by treatment of charcoal (2 g). The reaction mass was filtered and washed with chilled ethyl acetate (10 ml) afforded agomelatine of formula (I).
Yield - 90%

Example 4: Preparation of agomelatine of formula (I)

2-(7-methoxy-1-naphthyl)ethanamine hydrochloride of formula (D) (25 g) and methylene dichloride (120 ml) was added at 25°C to 35°C and stirred for 15 minutes followed by addition of triethyl amine (25 g). The reaction mass was stirred for 30 minutes and cooled to 10°C to 20°C. Acetyl chloride (9 g) was added and stirred for 1 hour. The reaction mass was treated with water (200 ml) followed by treatment of sodium bicarbonate solution (125 ml) and hydrochloric acid solution (125 ml). Organic layer was treated with ethyl acetate (50 ml) and heated at 45°C to 50°C followed by treatment of charcoal (2 g). The

reaction mass was filtered and washed with chilled ethyl acetate (10 ml) afforded agomelatine of formula (I).

Yield - 90%

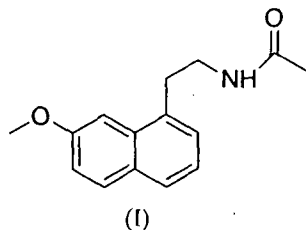
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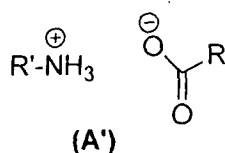
We Claim:

1. An improved process for preparing agomelatine of formula (I).



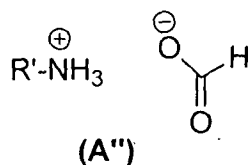
the process comprising:

- 5 i) reacting 7-methoxy tetralone of Formula (A) with cyanoacetic acid in a suitable organic solvent; wherein the water formed during the reaction is removed, in the presence of a catalytic amount of a compound of formula (A')



- 10 wherein R represents hydrogen or C₁-C₂ alkyl;
 R' represents hydrogen, linear or branched (C₃-C₁₀)alkyl, unsubstituted or substituted aryl, or unsubstituted or substituted linear or branched aryl (C₁-C₆)alkyl,
 to obtain (7-methoxy-3,4-dihydro-1-naphthalenyl)acetonitrile of Formula (B);
- 15 ii) treating (7-methoxy-3,4-dihydro-1-naphthalenyl)acetonitrile of Formula (B) with an aromatization catalyst to obtain (7-methoxy-1-naphthyl)acetonitrile of Formula (C);
- iii) reducing (7-methoxy-1-naphthyl)acetonitrile of Formula (C) with hydrogen in presence of Raney nickel in ammoniacal methanol medium and subsequently
- 20 converted to a salt using hydrochloric acid to obtain 2-(7-methoxy-1-naphthyl)ethanamine hydrochloride of formula (D);
- iv) reacting 2-(7-methoxy-1-naphthyl)ethanamine hydrochloride of formula (D) with acetic anhydride or acetic chloride in a suitable organic solvent in presence of a base and a catalyst to obtain agomelatine of Formula (I); and
- 25 v) optionally purifying agomelatine of Formula (I).

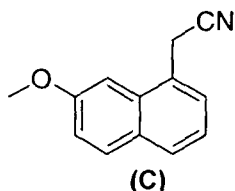
2. The process as claimed in claim 1(i), wherein suitable organic solvent may be selected from one or more of hydrocarbons, halogenated solvents, nitriles, amides, alcohol, ketones, ester and the like. In particular, the suitable solvent comprises toluene, xylene, ethylbenzene dimethyl formamide, dimethyl acetamide, methylene dichloride, acetonitrile, C₁-C₄ straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate and butyl acetate.
3. The process as claimed in claim 1(i), wherein suitable organic solvent may be toluene.
4. The process as claimed in claim 1(i), wherein R represents a formate group.
5. The process as claimed in claim 1(i), wherein R' represents a benzyl group.
6. The process as claimed in claim 1(i), wherein the catalyst used is benzylammonium formate of formula (A'')



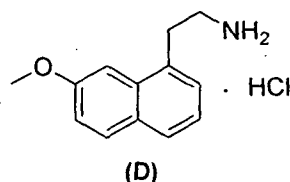
7. The process as claimed in claim 1(ii), wherein aromatization catalyst may be selected from sulphur, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or a proton acceptor selected from nitro alkanes or nitro arenes such as nitromethane, nitro ethane and nitro benzene.
8. The process as claimed in claim 1(ii), wherein aromatization catalyst may be DDQ.
9. The process as claimed in claim 1(ii), wherein the preferred temperature range for aromatization reaction may be 10°C to 20°C.

10. The process as claimed in claim 1(iv), wherein suitable organic solvent may be selected from aromatic hydrocarbons, C₁-C₄ straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate, halogenated solvent, pyridine, dimethyl formamide and cyclohexane.
11. The process as claimed in claim 1(iv), wherein suitable organic solvent may be methylene dichloride.
12. The process as claimed in claim 1(iv), wherein suitable base may be selected from organic bases or inorganic bases like ammonia, triethylamine, tributyl amine, dimethyl aniline, N-methyl piperidine and N-methyl pyrrolidine, N-methyl morpholine, diisopropyl methylamine, diisopropyl amine, diisopropyl ethylamine, alkali metal, and alkaline earth metal alkoxides, hydroxides, carbonates and bicarbonates such as lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium tert-butoxide, potassium tert-butoxide, sodium carbonate, potassium carbonate, sodium bicarbonate and potassium bicarbonate.
13. The process as claimed in claim 1(iv), wherein suitable base may be triethylamine.
14. The process as claimed in claim 1(iv), wherein suitable catalyst may be N, N-dimethylpyridin-4-amine.
15. The process as claimed in claim 1(v), wherein solvent for purification of agomelatine may be selected from one or more of hydrocarbons, halogenated solvents, nitriles, amides, alcohol, ketones, ester and the like. In particular, the suitable solvent comprises toluene, xylene, ethylbenzene dimethyl formamide, dimethyl acetamide, methylene dichloride, acetonitrile, C₁-C₄ straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate and butyl acetate.
16. The process as claimed in claim 1(v), wherein solvent for purification of agomelatine may be ethyl acetate.

17. An improved process for preparing agomelatine of Formula (I) starting from the (7-Methoxy-1-naphthyl) acetonitrile compound of Formula (C);

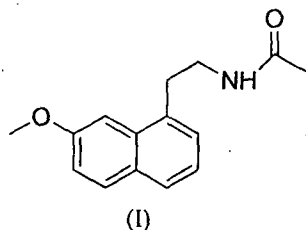


wherein compound of Formula (C) is obtained by the process according to any one of claims 1 to 9, and is subsequently subjected to reduction with hydrogen in the presence of Raney nickel in ammoniacal methanol and then converted to a salt using hydrochloric acid to yield 2-(7-Methoxy-1-naphthyl)ethanamine hydrochloride of formula (D).



which is subjected successively to the action of triethylamine and then acetic anhydride to yield the compound of formula (I), which is isolated in the form of a solid.

18. A process for preparing polymorphic Form-I of agomelatine of formula (I)



the process comprising:

- i) treating agomelatine of formula (I) in a suitable organic solvent;
- ii) isolating polymorphic Form-I of agomelatine of formula (I).

19. The process as claimed in claim 18, wherein suitable solvent may be selected from one or more of hydrocarbons, halogenated solvents, nitriles, amides, alcohol, ketones, ester and the like. In particular, the suitable solvent comprises toluene, xylene, ethylbenzene dimethyl formamide, dimethyl acetamide, methylene dichloride, acetonitrile, C₁-C₄ straight chain or branched alcohols, acetone, methyl

isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate; particularly, the solvent may be ethyl acetate.

- 5 20. Agomelatine of Formula (I) prepared by process as claimed in claim 1 is having purity of greater than about 99%, specifically greater than about 99.5%, more specifically greater than about 99.9%, and most specifically greater than about 99.98% and having all other impurities less than 0.1% as measured by HPLC.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2013/000682

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C213/02 C07C231/02 C07C253/30
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)
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 practicable, search terms used)

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	----- WO 2011/128413 A1 (RATIOPHARM GMBH [DE]; FISCHER DIRK [DE]; MATZDORF THORSTEN [DE]; NESS) 20 October 2011 (2011-10-20) claims; examples	18-20
X	----- WO 2011/054917 A1 (RATIOPHARM GMBH [DE]; FISCHER DIRK [DE]) 12 May 2011 (2011-05-12) claims; examples ----- -/-	18-20



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

20 March 2014

Date of mailing of the international search report

28/03/2014

Name and mailing address of the ISA/

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

Authorized officer

Zervas, Brigitte

INTERNATIONAL SEARCH REPORT

International application No

PCT/IN2013/000682

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

International application No

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