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(54) Title: PROCESSES FOR THE PREPARATION OF N-[2-(7-METHOXY-1-NAPHTHYL)ETHYL]ACETAMIDE

(57) Abstract: The present invention relates to processes for the synthesis of N-[2-(7-methoxy-1-naphthethyl)] acetamide, amorphous form of N-[2-(7-methoxy-1-naphthethyl)] acetamide and pharmaceutical compositions thereof.



**PROCESSES FOR THE PREPARATION OF N-[2-(7-METHOXY-1-NAPHTHYL)
ETHYL] ACETAMIDE**

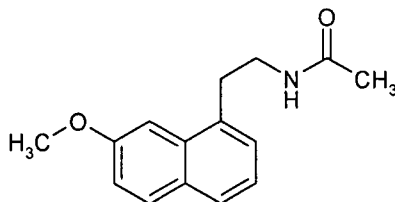
BACKGROUND OF THE INVENTION

1. Technical field:

The present invention relates to processes for the preparation of N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide. More specifically, the present invention relates to processes for the industrial synthesis of the compound of formula (I).

2. Brief description of the related art:

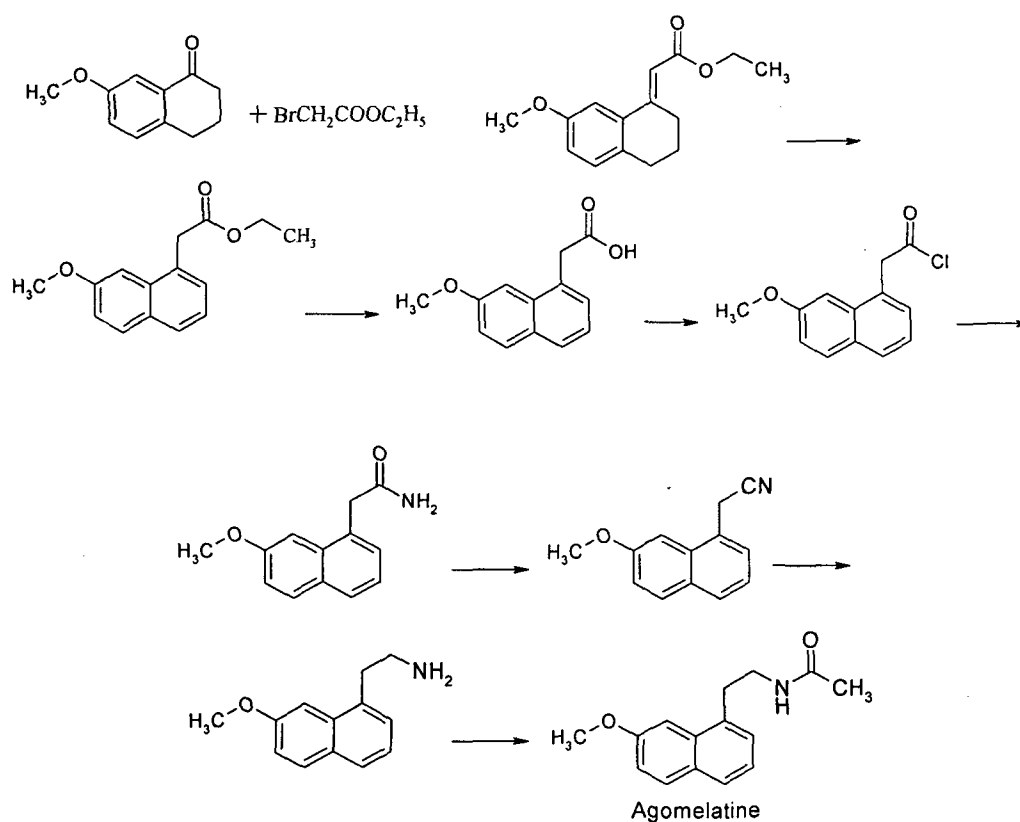
Agomelatine is on one hand, an agonist of melatoninergetic system receptors and, on the other hand, an antagonist of the 5-HT_{2C} receptor. Those properties confer activity in the central nervous system and, more especially, in the treatment of severe depression, seasonal affective disorders, sleep 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 in the form of tablets in dosage strength 25 mg. Agomelatine is chemically described as N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide (herein after referred by generic name agomelatine) and is represented by the structural formula I



I

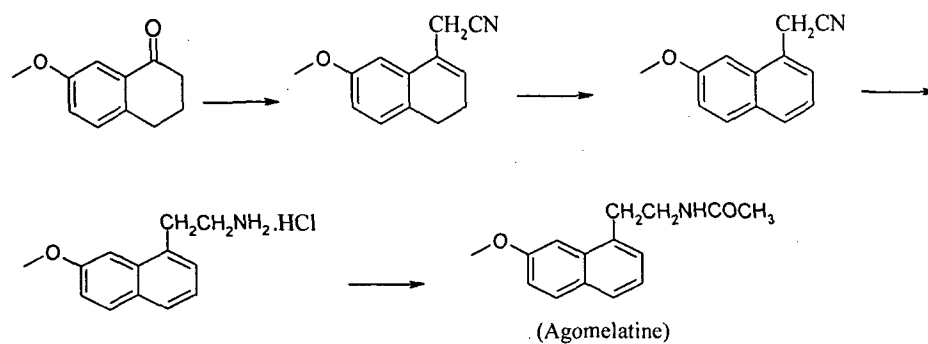
U.S. Patent No. 5,225,442 describes agomelatine, a pharmaceutical composition, a method of treatment, and a process for the preparation thereof.

US '442 discloses a process for the preparation of agomelatine which is illustrated by the below scheme:

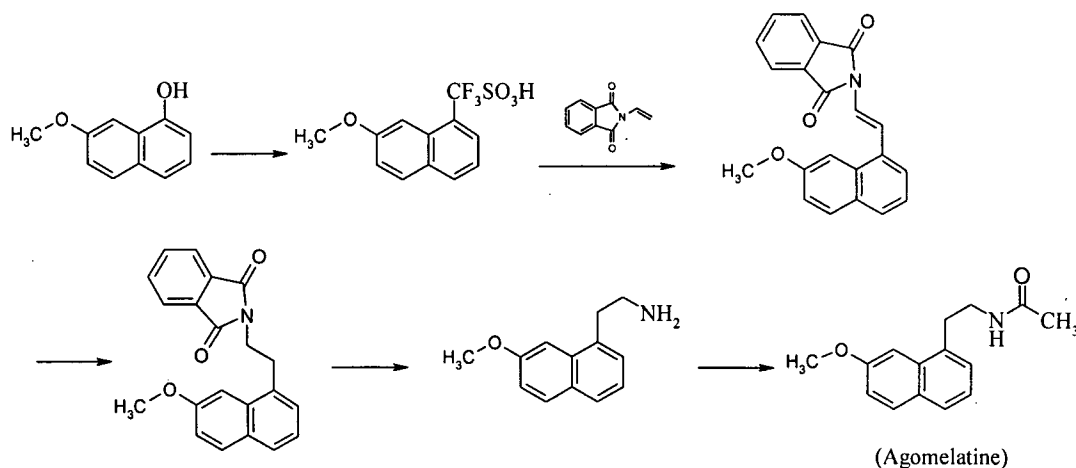


U.S. Patent No. US 7544839 describes the preparation of agomelatine as illustrated by below

5 scheme :



US application US 2010/0036162 A1 describes the preparation of agomelatine as illustrated by below scheme:



Aforementioned processes uses expensive reagents and involve prolong reaction time periods thus rendering the processes expensive and not viable on commercial scale thus posing a need for an improved process for the preparation of agomelatine and its intermediates, which avoids the use of hazardous and expensive chemicals thus reducing the formation of process related impurities.

Normally in high temperature reactions like at about 200°C the compounds will decompose but advantageously here in the aromatization reaction for the conversion of compound of formula IIIa to compound of formula IIIb decomposition will not take place as the starting compound of formula IIIa is being used in the salt form .

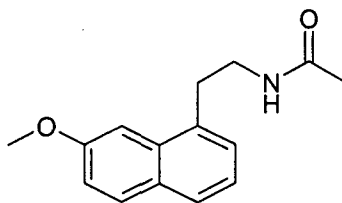
In view of the pharmaceutical value of this compound, it is important to be able to obtain by cost effective and simple processes that are readily transposable to an industrial scale and that results in agomelatine in a good yield and with excellent purity.

The processes of present invention are simple, eco-friendly, inexpensive, reproducible, and robust and feasible on an industrial scale.

SUMMARY OF THE INVENTION

The present invention relates to processes for the preparation of N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide (I).

In one aspect, the present invention provides a process for the preparation of N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide of formula I



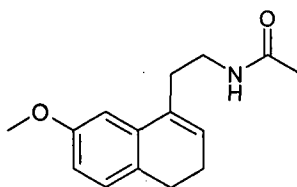
I

I

comprising:

aromatization of N-[2-(7-methoxy-3,4-dihydro-1-naphthyl)ethyl]acetamide compound of

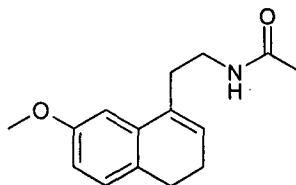
5 formula II



II

using suitable reagent to afford compound of formula I.

In another aspect, the present invention provides a process for the preparation of N-[2-(7-methoxy-3,4-dihydro-1-naphthyl)ethyl]acetamide compound of formula II

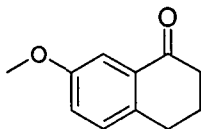


II

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comprising:

a) reacting the compound 7-methoxy-1-tetralone of formula V

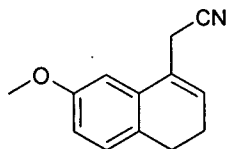


V

with CNCH_2COOR where R is Na, K, Ca, NH_4^+ , H, $\text{C}_1\text{-C}_8$ alkyl straight chain or

15 branched or aryl alkyl in the presence of ammonium salt and an organic solvent to give the

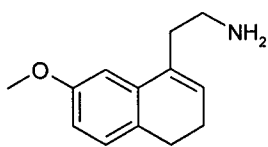
compound (7-methoxy-3,4-dihydro-1-naphthalenyl) acetonitrile of formula IV



IV

b) subjecting the intermediate compound of formula IV to reduction using a suitable reducing agent to provide the compound (7-methoxy-3,4-dihydro-1-naphthyl) ethyl amine of formula

5 III or a salt thereof

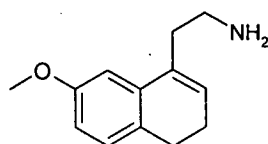


III

c) reacting the resultant intermediate compound of formula III or a salt thereof with acetylating agent to afford compound of formula II.

In yet another aspect, the present invention provides novel compound of formula III or

10 a salt thereof

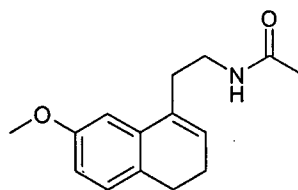


III

and its use as an intermediate in the synthesis of active naphthalene derivatives like agomelatine (I) wherein the compound of formula III in the form of HCl salt is characterized by XRPD and DSC which are substantially in accordance with the fig. 5 and 6.

15

In yet further aspect, the present invention provides compound of formula II

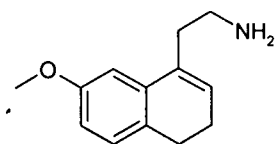


II

and its use as an intermediate in the synthesis of active naphthalene derivatives like agomelatine (I) wherein the compound of formula II is characterized by XRPD and DSC which are substantially in accordance with the fig. 3 and 4.

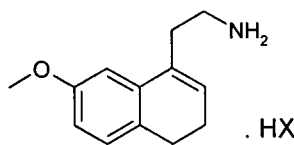
In another aspect, the present invention provides an alternate process for the preparation of N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide of formula I comprising:

- a) conversion of compound (7-methoxy-3,4-dihydro-1-naphthyl) ethyl amine of formula III



III

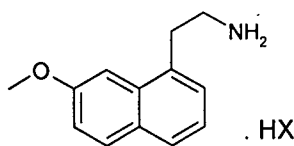
into the compound (7-methoxy-3,4-dihydro-1-naphthyl) ethyl amine salt of formula IIIa



IIIa

Wherein HX is an organic or inorganic acids such as HCl, HBr, maleic acid, oxalic acid, tartaric acid, and the like,

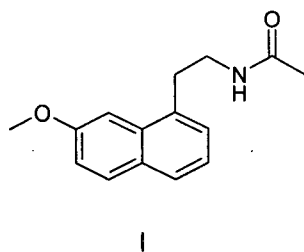
- b) aromatisation of compound of formula IIIa or III using a suitable reagent to give the compound (7-methoxy-1-naphthyl) ethyl amine or a salt thereof of formula IIIb



IIIb

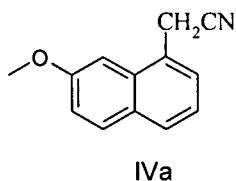
Where HX is same as defined above.

- c) acetylation of compound (7-methoxy-1-naphthyl) ethyl amine or a salt thereof of formula IIIb to give the compound N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide of formula I



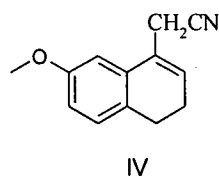
by using suitable acetylating agent.

In yet further aspect, the present invention provides a process for the synthesis of (7-methoxy-1-naphthyl) acetonitrile of formula (IVa)



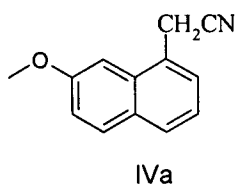
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by aromatization of the compound (7-methoxy-3,4-dihydro-1-naphthalenyl)acetonitrile of formula IV



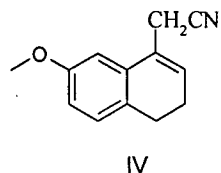
10 using sulphur.

In yet further aspect, the present invention provides a process for the synthesis of (7-methoxy-1-naphthyl) acetonitrile of formula (IVa)



by aromatization of the compound (7-methoxy-3,4-dihydro-1-naphthalenyl)acetonitrile of formula IV

15



using hydrogenation catalyst in the absence of allyl compound.

In yet still further aspect, the present invention provides a process for purifying agomelatine comprising: a) providing a solution or suspension of agomelatine in a solvent or a mixture of solvents or their aqueous mixtures and b) precipitating the solid from the solution, and c) recovering the agomelatine in pure form.

5 In yet another aspect, the present invention provides an amorphous form of agomelatine alone or in combination with a pharmaceutically acceptable carrier characterized by X- ray powder diffraction pattern, which is substantially in accordance with Figure 2.

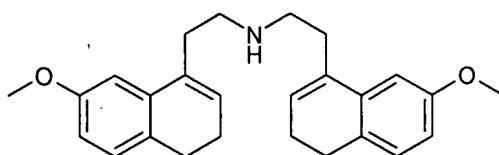
In another aspect, the present invention provides a process for the preparation of amorphous agomelatine comprising:

- 10 a) providing a solution of agomelatine alone or in combination with a pharmaceutically acceptable carrier in a solvent or mixture of solvents or aqueous mixtures thereof; and
b) evaporation of the solvent(s) or by adding an antisolvent or by sudden cooling to obtain the amorphous agomelatine.

15 In yet another aspect, the present invention provides agomelatine having purity greater than about 98.0 area % to about 99.0 area% as measured by HPLC, preferably greater than about 99.0area% to about 99.5area%, more preferably greater about 99.5area% to about 99.9area%.

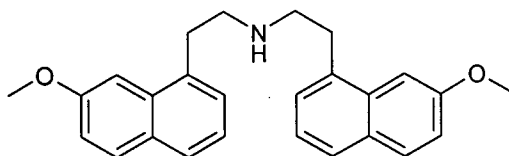
In yet further aspect, the present invention provides agomelatine having individual impurities lower than about 0.15 area %, and total impurities lower than about 0.5 area % by
20 HPLC.

In another aspect, the present invention provides Agomelatine (I) having the compound bis-(7-methoxy-3,4-dihydro-1-naphthyl)ethylamine of structure



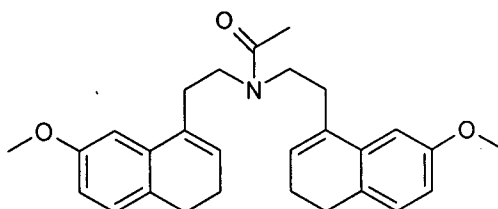
in an amount less than or equal to 0.10 area percent, as measured by HPLC.

25 In yet another aspect, the present invention provides Agomelatine (I) having the compound bis-(7-methoxy-1-naphthyl)ethylamine of structure



in an amount less than or equal to 0.10 area percent, as measured by HPLC.

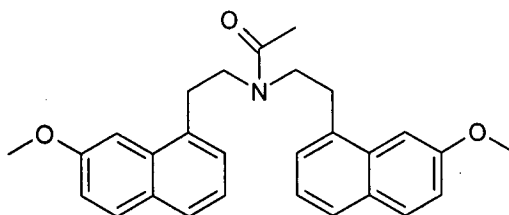
In another aspect, the present invention provides Agomelatine (I) having the compound bis-[(7-methoxy-3,4-dihydro-1-naphthyl)ethyl] acetamide of structure



5

in an amount less than or equal to 0.10 area percent, as measured by HPLC.

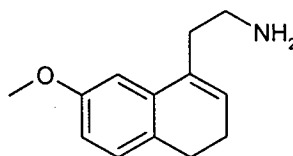
In yet another aspect, the present invention provides Agomelatine (I) having the compound bis-[(7-methoxy-1-naphthyl)ethyl]acetamide of structure



10

in an amount less than or equal to 0.10 area percent, as measured by HPLC.

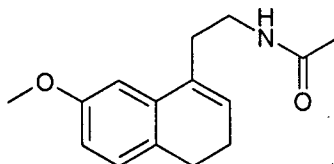
In yet another aspect, the present invention provides Agomelatine (I) having the compound represented by the structure



in an amount less than or equal to 0.10 area percent, as measured by HPLC.

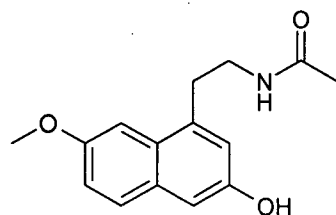
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In yet another aspect, the present invention provides Agomelatine (I) having the compound represented by the structure

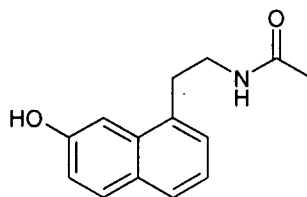


in an amount less than or equal to 0.10 area percent, as measured by HPLC.

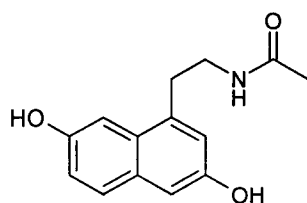
In yet another aspect, the present invention provides Agomelatine (I) having the following compounds represented by the structures



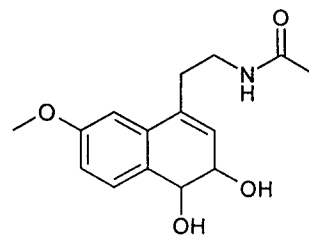
3-Hydroxy agomelatine



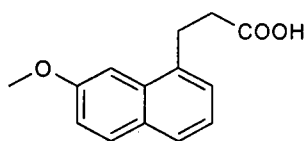
7-desmethyl agomelatine



3-Hydroxy-7-desmethyl agomelatine



3,4-dihydrodiol agomelatine



desacetamide-agomelatine-
carboxylic acid

each in an amount less than or equal to 0.10 area percent, as measured by HPLC.

In another aspect of the present invention agomelatine (I) obtained by the processes described herein has 50 volume-percent of the particles (D_{50}) having a size of less than or equal to about 400 microns, specifically less than or equal to about 300 microns, more specifically less than or equal to about 100 microns, still more specifically less than or equal to about 60 microns, and most specifically less than or equal to about 15 microns.

In a yet further aspect, the present invention relates to a pharmaceutical composition comprising agomelatine of formula I and atleast a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWING

Fig. 1: is a schematic representation of the processes of the present invention.

Fig. 2: is an X-ray powder diffraction pattern of amorphous agomelatine.

Fig. 3: is an X-ray powder diffraction pattern of intermediate compound of formula II.

Fig. 4: is a Differential Scanning Calometry endotherm curve of intermediate

compound of formula II.

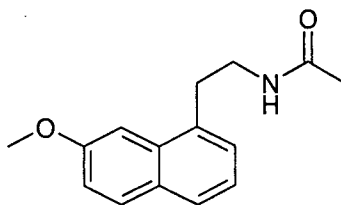
Fig. 5: is an X-ray powder diffraction pattern of intermediate compound of formula IIIa.

Fig. 6: is a Differential Scanning Calometry endotherm curve of intermediate compound of formula IIIa.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to processes for the preparation of N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide of formula I.

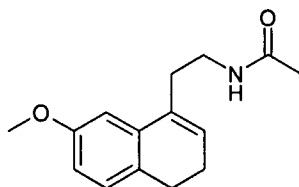
In one embodiment of the present invention, there is provided a process for the preparation of N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide or a pharmaceutically acceptable salts thereof of formula I,



I

comprising:

aromatization of the compound N-[2-(7-methoxy-3,4-dihydro-1-naphthyl)ethyl]acetamide of formula II



II

using suitable reagent.

The suitable reagent includes but not limited to sulphur, hydrogenation catalysts such as palladium on carbon in various percentages, platinum oxide, Raney Nickel, palladium oxide and the like; Preferably sulphur in any form is being used.

The molar ratio of sulphur to the compound of formula (II) can be from about 5:1 to about 1:1, preferably 1:1.

The optionally used solvents include but are not limited to water, halogenated solvents such as dichloromethane, ethylene dichloride, chloroform, chlorobenzene and the like; esters
5 such as ethyl acetate, isopropyl acetate, tertiary butyl acetate and the like; hydrocarbon solvents such as n-heptane, cyclohexane, n-hexane, toluene, xylene and the like; ethers such as tetrahydrofuran, 1,4-dioxane and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N,N-dimethylacetamide (DMA), N-methyl pyrrolidine (NMP) and the like; or mixtures thereof in various proportions without
10 limitation. Preferably the reaction is being carried in the absence of solvent or neat.

The reaction time and the temperature should be suitable to bring the reaction to completion at a minimum time, without the production of unwanted side products. In general, it is convenient to carry out the reaction at a temperature of from about 35°C to about 200°C, preferably at a temperature of from about 175°C to about 190 °C. The time required for the
15 reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagent and solvent employed. However, provided that the reaction is effected under the preferred conditions discussed above, a period of from about 1 hour to about 10 hours, preferably from about 1 hour to 5 hours.

The reported processes in the literature for the preparation of agomelatine or its
20 intermediates results in the formation of various impurities and bye products leading to keep several purification steps intermitanantly at various stages thus resulting in very poor yields and purities of the intermediates and final product.

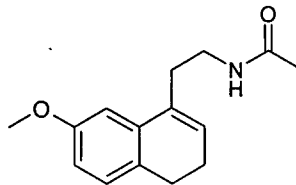
Advantageously, the process of present invention provides the compound of formula I from intermediate compound of formula II by using sulphur resulting in higher yields and
25 purities which would results in higher yields and purities of final product. And moreover the present process is very cost effective, reproducible and more viable on commercial scale.

The compound of formula I may be obtained in crystalline or amorphous form.

The compound of formula I is optionally converted into a pharmaceutically acceptable salt for purification purposes based on the requirement.

30 The compound of formula I is optionally purified by recrystallisation, using a solvent or mixture of solvents; such as aqueous methanol, ethanol, isopropyl alcohol, n-hexane, aqueous N,N-dimethyl formamide, cyclohexane, acetone, acetonitrile and mixtures thereof.

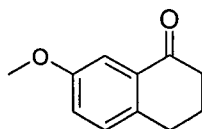
In another embodiment of the present invention, there is provided a process for the preparation of N-[2-(7-methoxy-3,4-dihydro-1-naphthyl)ethyl] acetamide compound of formula II



II

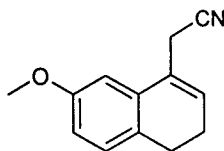
5 comprising:

a) reacting 7-methoxy -1-tetralone compound of formula V



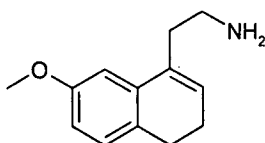
V

with CNCH_2COOR where R is Na, K, Ca, NH_4^+ , H, $\text{C}_1\text{-C}_8$ alkyl straight chain or branched or aryl alkyl in the presence of ammonium salt and an organic solvent to give the compound (7-methoxy-3,4-dihydro-1-naphthalenyl) acetonitrile of formula IV



IV

b) reduction of the intermediate compound of formula IV using suitable reducing agent in to give the compound (7-methoxy-3,4-dihydro-1-naphthyl) ethyl amine or a salt thereof formula III



III

c) reacting the resultant intermediate compound of formula III or a salt thereof with acetylating agent to afford compound of formula II.

The cyano reagents used in step a) can be CNCH_2COOR where R is Na, K, Ca, NH_4^+ , H, C_1 - C_8 alkyl straight chain or branched or aryl alkyl. For example cyano acetic acid, methyl cyano acetate, ethyl cyano acetate and the like; or mixtures thereof. Preferably cyano acetic acid is being used.

- 5 The molar ratio of cyano acetic acid to the compound of formula V can be from about 5:1 to about 1:1, preferably 1:1.

The suitable ammonium derivatives in step a) that can be used include but are not limited to ammonium acetate, ammonium hydroxide, ammonia gas, ammonium carbonate and the like or mixtures thereof. Preferably ammonium acetate.

- 10 The organic solvents that can be used in step a) include but are not limited to halogenated solvents such as dichloromethane, ethylene dichloride, chloroform, chlorobenzene and the like; esters such as ethyl acetate, isopropyl acetate, tertiary butyl acetate and the like; hydrocarbon solvents such as n-heptane, cyclohexane, toluene, xylene and the like; or mixtures thereof in various proportions without limitation. Preferably toluene is being used.

- 15 The reaction time and the temperature should be suitable to bring the reaction to completion at a minimum time, without the production of unwanted side products. In general, it is convenient to carry out the reaction at a temperature of from about 35°C to about 200°C, preferably at a temperature of from about 95°C to about 120 °C. More preferably at boiling temperatures of the solvents used. The time required for the reaction may also vary widely,
20 depending on many factors, notably the reaction temperature and the nature of the reagent and solvent employed. However, provided that the reaction is effected under the preferred conditions discussed above, a period of from about 1 hour to about 40 hours, preferably from about 30 hour to 40 hours.

- 25 The suitable reducing agents that can be used in step b) can include but are not limited to hydrogenation catalysts such as palladium carbon in various percentages, platinum oxide, Raney Nickel, palladium oxide and the like; other reducing agent such as sodium borohydride, lithium aluminum hydride, n-butyl lithium, Vitride and the like. Preferably the hydrogenation catalyst Raney Nickel is being used.

- 30 The solvents that can be used in step b) include but are not limited to water, alcohols such as methanol, ethanol and the like; halogenated solvents such as dichloromethane, ethylene dichloride, chloroform, chlorobenzene and the like; esters such as ethyl acetate, isopropyl acetate, tertiary butyl acetate and the like; hydrocarbon solvents such as n-heptane,

cyclohexane, n-hexane, toluene, xylene and the like; or mixtures thereof in various proportions without limitation. Preferably ethanol is being used.

The reaction time and the temperature should be suitable to bring the reaction to completion at a minimum time, without the production of unwanted side products. In general, it is convenient to carry out the reaction at a temperature of from about 30°C to about 100°C, preferably at a temperature of from about 35°C to about 40 °C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagent and solvent employed. However, provided that the reaction is effected under the preferred conditions discussed above, a period of from about 1 hour to about 15 hours, preferably from about 2 to 5 hours.

The conversion of intermediate compound of formula IV to the compound of formula III can also be performed using sodium borohydride and nickel chloride.

The suitable acetylating agents that can be used in step c) can include but are not limited to acetic anhydride, acetyl halide like acetyl chloride, acetyl bromide, acetyl iodide and the like. Preferably acetic anhydride is being used.

The organic solvents that can be used in step c) include but are not limited to alcohols such as methanol, ethanol, isopropyl alcohol and the like; halogenated solvents such as dichloromethane, ethylene dichloride, chloroform, chlorobenzene and the like; esters such as ethyl acetate, isopropyl acetate, tertiary butyl acetate and the like; hydrocarbon solvents such as n-heptane, cyclohexane, n-hexane, toluene, xylene and the like; or mixtures thereof in various proportions without limitation. Preferably dichloromethane or ethanol or toluene or ethyl acetate is being used.

The reaction time and the temperature should be suitable to bring the reaction to completion at a minimum time, without the production of unwanted side products. In general, it is convenient to carry out the reaction at a temperature of from about -10°C to about 20°C, preferably at a temperature of from about 0°C to about 5 °C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagent and solvent employed. However, provided that the reaction is effected under the preferred conditions discussed above, a period of from about 15 minutes to about 5 hours, preferably from about 30 minutes to about 1 hour.

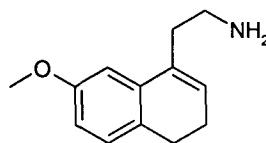
Optionally the reaction step c) is being carried out by employing a base.

The bases that can be used is selected from the group consisting of organic bases such as triethylamine, tributylamine, N-methylmorpholine, pyridine, 4-dimethylaminopyridine, lutidine, collidine and the like; inorganic bases such as sodium methoxide, sodium ethoxide or potassium t-butoxide; alkali metal carbonates, such as sodium carbonate or potassium carbonate; and alkali metal hydroxides, such as sodium hydroxide or potassium hydroxide. Preferably, triethylamine. The amount of base employed is an equimolar amount to 5 times the equimolar amount of the starting material of formula III. When an excess of an organic amine is employed as the base, this may optionally serve as the solvent.

In another embodiment of the present invention, there is provided an alternate process for the preparation of N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide or a pharmaceutically acceptable salt thereof

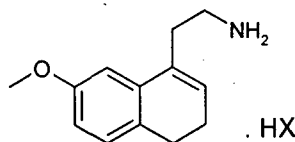
comprising:

- a) conversion of compound (7-methoxy-3,4-dihydro-1-naphthyl) ethyl amine of formula III



III

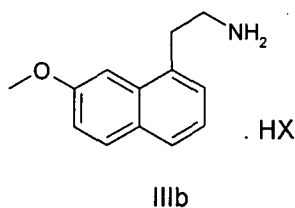
into the compound (7-methoxy-3,4-dihydro-1-naphthyl) ethyl amine salt of formula IIIa



IIIa

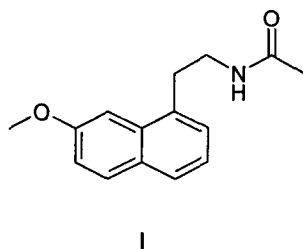
Wherein HX is an organic or inorganic acids such as HCl, HBr, maleic acid, oxalic acid, tartaric acid, and the like.

- b) aromatisation of compound of formula IIIa or III to give the compound (7-methoxy-1-naphthyl) ethyl amine or a salt thereof of formula IIIb



Where HX is same as defined above.

c) acetylation of compound (7-methoxy-1-naphthyl) ethyl amine or a salt thereof of formula IIIb to give the compound-[2-(7-methoxy-1-naphthyl) ethyl] acetamide of formula I



5

by using suitable acetylating agent.

In step a) the compound of formula III is converted into acid addition salt such as hydrobromic acid salt, iodic acid salt, hydrogen sulfate salt, besylate salt, paratoluene sulfonate salt, mesylate salt, tartarate salt and the like. Preferably hydrochloric acid salt is being prepared.

10

The conversion takes place by reaction of the compound of formula III with a suitable acid like hydrochloric acid by any means can be gaseous form or dissolved in a solvent form or aqueous form in any percentage (%v/v). Preferably in solvent saturated with hydrochloric acid gas. More preferably isopropyl alcohol saturated with a hydrochloric acid gas.

15

The organic solvents that can be used in step a) include but are not limited to water, alcohols such as methanol, ethanol, isopropyl alcohol and the like; halogenated solvents such as dichloromethane, ethylene dichloride, chloroform, chlorobenzene and the like; hydrocarbon solvent such as toluene, xylene, cyclohexane and the like; esters such as ethyl acetate, isopropyl acetate, tertiary butyl acetate and the like; ketones such as acetone, methyl isobutyl ketone, methyl ethyl ketone, 2-butanone and the like; nitriles such as acetonitrile, propionitrile and the like; or mixtures thereof in various proportions without limitation. Preferably toluene or isopropyl alcohol is being used.

20

The reaction time and the temperature in step a) In general; it is convenient to carry out the reaction at a temperature of from about -10°C to about 100°C, preferably at a temperature

of from about 0°C to about 5°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagent and solvent employed. However, provided that the reaction is effected under the preferred conditions discussed above, a period of from about 15 minutes to about 5 hours, preferably from about 30 minutes to 1 hour is sufficient.

In the reaction step b) the suitable reagent include sulphur or its derivatives, hydrogenation catalysts such as palladium carbon in various percentages, platinum oxide, Raney Nickel, palladium oxide and the like can be used; Preferably sulphur in any form is being used.

The molar ratio of sulphur to the compound of formula (IIIa) can be from about 5:1 to about 1:1, preferably 1:1.

The optionally used solvents that can include but are not limited to water, halogenated solvents such as dichloromethane, ethylene dichloride, chloroform, chlorobenzene and the like; esters such as ethyl acetate, isopropyl acetate, tertiary butyl acetate and the like; hydrocarbon solvents such as n-heptane, cyclohexane, n-hexane, toluene, xylene and the like; ethers such as tetrahydrofuran, 1,4-dioxane and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N,N-dimethylacetamide (DMA), N-methyl pyrrolidine (NMP) and the like; or mixtures thereof in various proportions without limitation. Preferably the reaction is being carried in the absence of solvent or neat.

The conversion of compounds of formulae III and IIIa to the compound of formula IIIb are usually carried out in the absence of solvents.

The reaction time and the temperature should be suitable to bring the reaction to completion at a minimum time, without the production of unwanted side products. In general, it is convenient to carry out the reaction at a temperature of from about 35°C to about 200°C, preferably at a temperature of from about 170°C to about 190 °C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagent and solvent employed. However, provided that the reaction is effected under the preferred conditions discussed above, a period of from about 1 hour to about 10 hours, preferably from about 1 hour to 5 hours.

The suitable acetylating agents that can be used in step c) can include but are not limited to acetic anhydride, acetyl halide like acetyl chloride, acetyl bromide, acetyl iodide and the like. Preferably acetic anhydride is being used.

The solvents that can be used in step c) include but are not limited to water, alcohols such as methanol, ethanol and the like; halogenated solvents such as dichloromethane, ethylene dichloride, chloroform, chlorobenzene and the like; esters such as ethyl acetate, isopropyl acetate, tertiary butyl acetate and the like; hydrocarbon solvents such as n-heptane, cyclohexane, n-hexane, toluene, xylene and the like; or mixtures thereof in various proportions without limitation. Preferably ethanol is being used.

The reaction time and the temperature should be suitable to bring the reaction to completion at a minimum time, without the production of unwanted side products. In general, it is convenient to carry out the reaction at a temperature of from about -10°C to about 20°C, preferably at a temperature of from about 0°C to about 5 °C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagent and solvent employed. However, provided that the reaction is effected under the preferred conditions discussed above, a period of from about 15 minutes to about 5 hours, preferably from about 30 minutes to 1 hour.

Optionally the reaction step c) is being carried out by employing a base.

The bases that can be used is selected from the group consisting of organic bases such as triethylamine, tributylamine, N-methylmorpholine, pyridine, 4-dimethylaminopyridine, lutidine, collidine and the like; inorganic bases alkali metal carbonates, such as sodium carbonate or potassium carbonate and the like; other base such as sodium acetate, ammonium acetate, potassium acetate and the like; Preferably, triethylamine is being used. The amount of base employed is an equimolar amount to 5 times the equimolar amount of the starting material of formula IIIb. When an excess of an organic amine is employed as the base, this may optionally serve as the solvent.

Optionally the intermediates compounds of formulae III and II are converted to an acid addition salt by reacting with a suitable acid preferably mineral acid to make it into stable form.

Optionally the intermediate compounds of formulae III and II are being isolated in solid form by recrystallization using polar aprotic solvents such as acetone, acetonitrile and the like.

After completion of the reaction, the desired compounds can be obtained from the reaction mixture by conventional means known in the art. For example, the working-up of reaction mixtures, especially in order to isolate desired compounds, follows customary procedures, known to the organic chemists skilled in the norms of the art and steps, e.g.

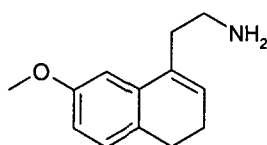
selected from the group comprising but not limited to extraction, neutralization, crystallization, chromatography, evaporation, drying, filtration, centrifugation and the like.

Optionally the processes for the preparation of agomelatine of present invention can also be carried out by one pot synthesis.

5 Advantageously, the processes of present invention described herein produces the intermediates and the final product in high yields and purities than the processes reported in the literature that too using simple and cost effective industrially applicable processes.

These processes are especially valuable for the following reasons: it makes it possible to obtain the compound of formula (I) on an industrial scale in excellent yields, starting from a
10 simple, low-cost starting material; finally, the compound of formula (I) obtained has, in reproducible manner.

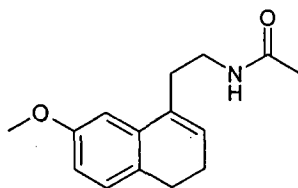
In another embodiment of the present invention, there is provided compound of formula III or a salt thereof



III

15 and its use as an intermediate in the synthesis of active naphthalene derivatives like agomelatine (I) wherein the compound of formula III in the form of HCl salt is characterized by XRPD and DSC which are substantially in accordance with the fig. 5 and 6.

In yet another embodiment of the present invention, there is provided compound of formula II



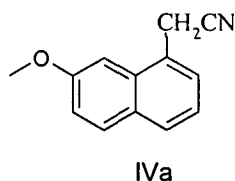
II

20 and its use as an intermediate in the synthesis of active naphthalene derivatives like agomelatine (I) wherein the compound of formula II is characterized by XRPD and DSC which are substantially in accordance with the fig. 3 and 4.

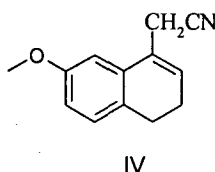
The compounds of formula (III) and (II) obtained according to the processes of the invention are novel and useful as intermediates in the synthesis of active naphthalene derivatives like agomelatine (I), which were identified, characterized and confirmed by the characterization data like C^{13} NMR, 1H NMR, MASS, IR.

5 The compounds of formula (III) and (II) obtained can be crystalline or amorphous.

In yet further embodiment, the present invention provides a process for the synthesis of (7-methoxy-1-naphthyl) acetonitrile of formula (IVa)



10 by aromatization of the compound (7-methoxy-3,4-dihydro-1-naphthalenyl) acetonitrile of formula IV



using suitable reagent.

15 The suitable reagent used include but not limited to sulphur and the like; Preferably sulphur in any form is being used.

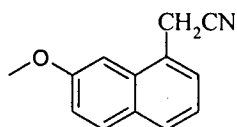
The molar ratio of sulphur to the compound of formula (II) can be from about 5:1 to about 1:1, preferably 1:1.

20 The optionally used solvents that can include but are not limited to water, halogenated solvents such as dichloromethane, ethylene dichloride, chloroform, chlorobenzene and the like; esters such as ethyl acetate, isopropyl acetate, tertiary butyl acetate and the like; hydrocarbon solvents such as n-heptane, cyclohexane, n-hexane, toluene, xylene and the like; ethers such as tetrahydrofuran, 1,4-dioxane and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N,N-dimethylacetamide (DMA), N-methyl pyrrolidine (NMP) and the like; or mixtures thereof in various proportions without
25 limitation. Preferably the reaction is being carried in the absence of solvent or neat.

The conversion of compound of formula IV to the compound of formula IVa is usually carried out in the absence of solvents.

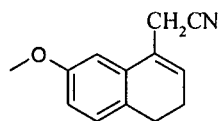
The reaction time and the temperature should be suitable to bring the reaction to completion at a minimum time, without the production of unwanted side products. In general, it is convenient to carry out the reaction at a temperature of from about 35°C to about 200°C, preferably at a temperature of from about 185°C to about 190 °C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagent and solvent employed. However, provided that the reaction is effected under the preferred conditions discussed above, a period of from about 1 hour to about 10 hours, preferably from about 1 hour to 5 hours is sufficient.

In yet further embodiment, the present invention provides a process for the synthesis of (7-methoxy-1-naphthyl) acetonitrile of formula (IVa)



IVa

by aromatization of the compound (7-methoxy-3,4-dihydro-1-naphthalenyl)acetonitrile of formula IV



IV

using hydrogenation catalyst in the absence of allyl compound.

The hydrogenation catalysts used include but not limited to palladium carbon in various percentages, platinum oxide, Raney Nickel, palladium oxide and the like; Preferably palladium -carbon is being used.

The organic solvents that can be used include but are not limited to water, alcohols such as methanol, ethanol and the like; halogenated solvents such as dichloromethane, ethylene dichloride, chloroform, chlorobenzene and the like; esters such as ethyl acetate, isopropyl acetate, tertiary butyl acetate and the like; hydrocarbon solvents such as n-heptane,

cyclohexane, n-hexane, toluene, xylene and the like; or mixtures thereof in various proportions without limitation. Preferably o-xylene is being used.

The reaction time and the temperature should be suitable to bring the reaction to completion at a minimum time, without the production of unwanted side products. In general,
5 it is convenient to carry out the reaction at a temperature of from about 30°C to about 200°C or reflux temperature of the solvent(s) used. Preferably at temperature from about 75°C to about

200°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagent and solvent employed. However, provided that the reaction is effected under the preferred conditions discussed above,
10 a period of from about 1 hour to about 15 hours, preferably from about 5 to 8 hours.

The conversion of compound of formula IV to the compound of formula IVa reported was by hydrogenation process using palladium on carbon in the presence of ally compound like ally methacrylate which is expensive and not feasible on commercial scale.

The process of conversion of compound of formula IV to the compound of formula IVa
15 of the present invention is most cost effective and well suited on industrial scale.

Like any synthetic compound, agomelatine (I) can contain extraneous compounds or impurities that can come from many sources. These extraneous materials can be unreacted starting materials, by-products of the reaction, products of side reactions, or degradation products. Impurities in agomelatine or any active pharmaceutical ingredient (API) are
20 undesirable and, in extreme cases, might even be harmful to a patient being treated with a dosage form containing the API. It is also known in the art that impurities in an API may arise from degradation of the API itself, which is related to the stability of the pure API during storage, and the manufacturing process, including the chemical synthesis. Process impurities include unreacted starting materials, chemical derivatives of impurities contained in starting
25 materials, synthetic by-products, and degradation products. In addition to stability, which is a factor in the shelf life of the API, the purity of the API produced in the commercial manufacturing process is clearly a necessary condition for commercialization. Impurities introduced during commercial manufacturing processes must be limited to very small amounts, and are preferably substantially absent. For example, the International Conference on
30 Harmonization of Technical Requirements for Registration for Human Use (ICH) Q7A guidance for API manufacturers requires that process impurities be maintained below set limits by specifying the quality of raw materials, controlling process parameters, such as temperature,

pressure, time, and stoichiometric ratios, and including purification steps, such as crystallization, distillation, and liquid-liquid extraction, in the manufacturing process. At certain stages during processing of the API, agomelatine, it must be analyzed for purity, typically, by HPLC, TLC or GC analysis, to determine if it is suitable for continued processing and, ultimately, for use in a pharmaceutical product. The API need not be absolutely pure, as absolute purity is a theoretical ideal that is typically unattainable. Rather, purity standards are set with the intention of ensuring that an API is as free of impurities as possible, and, thus, are as safe as possible for clinical use. As discussed above, in the United States, the Food and Drug Administration guidelines recommend that the amounts of some impurities be limited to less than 0.1 percent.

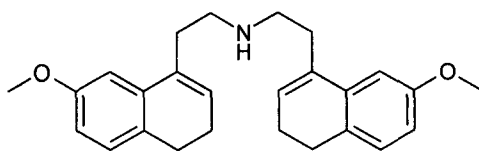
In another embodiment, the present invention provides a process for purifying agomelatine (I) comprising: a) providing a solution or suspension of agomelatine (I) in a solvent or a mixture of solvents or their aqueous mixtures and b) precipitating the solid from the solution, and c) recovering the agomelatine (I) in pure form.

The solvents include but are limited to water, alcohols such as methanol, ethanol, isopropanol and the like; ketones such as acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl methyl ketone and the like; nitriles such as acetonitrile, propionitrile and the like; hydrocarbons such as toluene, n-hexane, n-heptane, cyclohexane and the like; aprotic polar solvents such as N,N-dimethyl formamide (DMF), dimethyl sulfoxide (DMSO) and the like; ethers such as dimethyl ether, diethyl ether, isopropyl ether, methyl tertiary butyl ether (MTBE), tetrahydrofuran, 1,4-dioxane and the like; esters such as ethyl acetate, isopropyl acetate, isobutyl acetate, t-butyl acetate and the like; or mixtures thereof in various proportions without limitation. Preferably ethyl acetate.

In yet another embodiment, the present invention provides agomelatine (I) having purity greater than about 98.0 area% to about 99.0 area % as measured by HPLC, preferably greater than about 99.0 area % to about 99.5 area %, more preferably greater about 99.5 area % to about 99.9 area %.

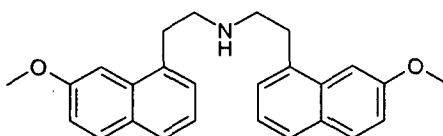
In a still further embodiment, the present invention provides agomelatine (I) having individual impurities lower than about 0.15 area %, preferably lower than about 0.1 area % and total impurities lower than about 0.5 area% by HPLC.

In another embodiment, the present invention provides Agomelatine (I) having an impurity bis-(7-methoxy-3,4-dihydro-1-naphthyl)ethylamine of structure



in an amount less than about 0.10 area percent, as measured by HPLC.

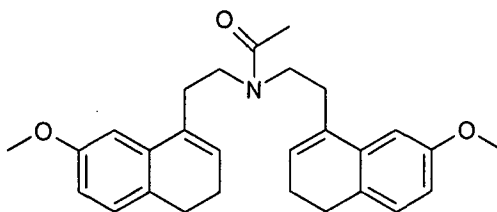
In yet another embodiment, the present invention provides Agomelatine (I) having an impurity bis-(7-methoxy-1-naphthyl)ethanamine represented by the structure



5

in an amount less than about 0.10 area percent, as measured by HPLC.

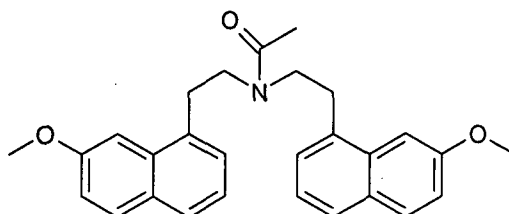
In another embodiment, the present invention provides Agomelatine (I) having the compound bis-[(7-methoxy-3,4-dihydro-1-naphthyl)ethyl] acetamide of structure



10

in an amount less than or equal to 0.10 area percent, as measured by HPLC.

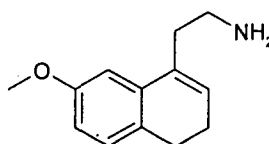
In yet another embodiment, the present invention provides Agomelatine (I) having the compound bis-[(7-methoxy-1-naphthyl)ethyl]acetamide of structure



in an amount less than or equal to 0.10 area percent, as measured by HPLC.

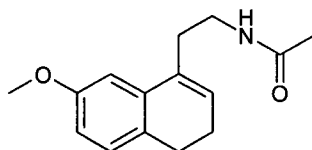
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In yet still further embodiment, the present invention provides Agomelatine (I) having an impurity represented by the structure



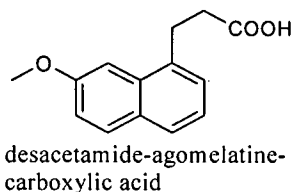
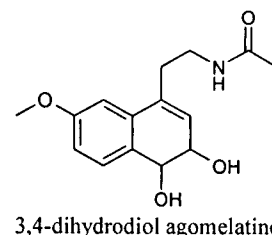
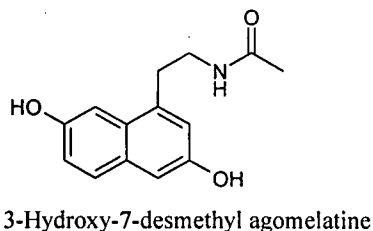
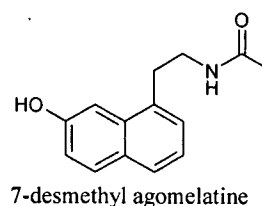
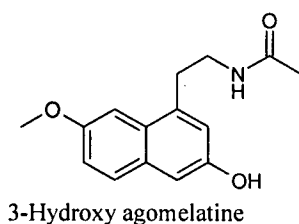
in an amount less than about 0.10 area percent, as measured by HPLC.

In a still further embodiment, the present invention provides Agomelatine (I) having an impurity represented by the structure



in an amount less than about 0.10 area percent, as measured by HPLC.

- 5 In another embodiment, the present invention provides Agomelatine (I) having impurities represented by the structures



- 10 each in an amount less than about 0.10 area percent, as measured by HPLC.

High Performance Liquid Chromatography (HPLC):

The content of impurities in the final product agomelatine (I) and the purity of the final product Agomelatine or a pharmaceutically acceptable salt thereof was measured by high performance liquid chromatography by using chromatographic system under the following conditions:

- 15 Column : Merck, HiBar, Purospherstar RP-18e, 250x4.6mm; 5 µm or equivalent.
 Detector wavelength: 231nm; Oven temperature: 30°C; Flow rate : 1.0 ml / min
 Injection volume : 10µL ; Run time : 60mins. ; Concentration: 0.3 mg/ml.
 Diluent: Methanol

Buffer preparation: Prepare 0.01 M of monobasic sodium phosphate anhydrous and adjust the pH to 2.5 with dilute phosphoric acid (50%v/v).

Mobile phase preparation: Prepare a mixture of Buffer, acetonitrile and methanol in the ratio of 450: 350: 200 and mix and pass through membrane filter (0.45µm) and degas.

5 In one embodiment, agomelatine (I) obtained by the processes described here in above has a D₅₀ particle size of less than or equal to about 400 microns, specifically less than or equal to about 300 microns, more specifically less than or equal to about 100 microns, still more specifically less than or equal to about 60 microns, and most specifically less than or equal to about 15 microns.

10 The particle sizes of the agomelatine (I) obtained by the processes of present invention may be reduced by a mechanical process of reducing the size of particles which includes any one or more of cutting, chipping, crushing, milling, grinding, micronizing, trituration or other particle size reduction methods known in the art, to bring the solid state form to the desired particle size range.

15 The discovery of new amorphous forms of active pharmaceutical ingredients (API's) provides opportunities to improve the performance characteristics of a pharmaceutical product. Such discoveries enlarge the repertoire of materials that a formulation scientist has available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic.

20 Generally, amorphous solids offer opportunities for solubility and bioavailability enhancement since these materials are more soluble than the crystalline form of the same compound. The rate of dissolution is also a consideration in formulating syrups, elixirs and other liquid medicaments.

25 In yet another aspect, the present invention provides an amorphous form of agomelatine alone or in combination with a pharmaceutically acceptable carrier characterized by X- ray powder diffraction pattern, which is substantially in accordance with Figure 2.

In another aspect, the present invention provides a process for the preparation of amorphous agomelatine comprising:

- 30 a) providing a solution of agomelatine alone or in combination with a pharmaceutically acceptable carrier in a solvent or mixture of solvents or aqueous mixtures thereof; and
b) evaporation of the solvents or by adding an anti solvent to obtain the amorphous agomelatine.

As used herein, a solvent is any liquid substance capable of dissolving agomelatine.

As used herein, the term "antisolvent" means a liquid in which a compound is poorly soluble.

The addition of an antisolvent to a solvent reduces the solubility of a compound.

As used herein a mixture of solvents refers to a composition comprising more than one
5 solvent.

In (a) above, the process provides a solution of agomelatine in a solvent or mixture of solvents or aqueous mixtures thereof; and

The solution of agomelatine can be obtained by dissolving agomelatine in a solvent or mixture of solvents or their aqueous mixtures thereof.

10 The solvents that can be used include, but are not limited to water, alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, and tertiary butyl alcohol and the like; ketonic solvents such as acetone, methyl ethyl ketone, methyl isobutyl ketone, 2-butanone and the like; halogenated solvents such as dichloromethane, ethylene dichloride, chloroform and the like; nitrile solvents such as acetonitrile, propionitrile and the like; esters
15 such as ethyl acetate, isopropyl acetate and the like; or mixtures thereof in various proportions without limitation. Preferably, dichloromethane or methanol or acetone.

The temperature for obtaining a clear and homogenous solution can range from about 25°C to about 75°C or the boiling point of the solvent/s used, preferably from about 25°C to about 40°C.

20 The solution obtained is optionally filtered through celite or diatomaceous earth to separate the extraneous matter present or formed in the solution by using conventional filtration techniques known in the art.

The pharmaceutically acceptable carriers that can be used for the preparation of amorphous agomelatine include, but are not limited to, pharmaceutical hydrophilic carriers
25 such as polyvinylpyrrolidone (homopolymers, also called "povidone," or copolymers of N-vinylpyrrolidone), gums, cellulose derivatives (including hydroxypropyl methylcellulose, hydroxypropyl cellulose and others), cyclodextrins, gelatins, hypromellose phthalate, sugars, polyhydric alcohols. The use of mixtures of more than one of the pharmaceutical carriers to provide desired release profiles or for the enhancement of stability is within the scope of this
30 invention. Also, all viscosity grades, molecular weights, commercially available products, their copolymers, mixtures are all within the scope of this invention without limitation.

These lists of solvents and pharmaceutically acceptable carriers are merely

representative of those that can be used, and the lists are not intended to be exhaustive or limiting. Generally, the more volatile solvents are preferred to reduce the energy requirements for subsequent solvent removal.

5 The antisolvents include, but are not limited to water, hydrocarbon solvents such as n-hexane, n-heptane, cyclohexane, petroleum ether, toluene and the like or mixtures thereof in various proportions without limitation. Preferably n-hexane.

Evaporation or removal of solvent(s) is accomplished by, for example, substantially complete evaporation of the solvent, concentrating the solution, cooling to obtain amorphous form and filtering the solid under inert atmosphere. Alternatively, the solvent may also be removed by evaporation. Evaporation can be achieved at sub-zero temperatures by the lyophilisation or freeze-drying technique. The solution may also be completely evaporated in, for example, a pilot plant rota vapor, a vacuum paddle dryer or in a conventional reactor under vacuum above about 720 mm Hg by flash evaporation techniques by using an agitated thin film dryer (ATFD), or evaporated by spray drying to obtain a dry amorphous powder. Preferably, 10 the methods for drying are spray drying or vertical agitated thin-film drying (or evaporation).

In the preferred spray drying technique, a solution of agomelatine in (b) is sprayed into the spray drier at the flow rate ranging from about 10 ml/hr to about 300 ml/hr, preferably at flow rate of about 40 ml/hr to about 200ml/hr. The air inlet temperature to the spray drier used may range from about 25°C to about 150°C, preferably from about 60°C to about 110°C and 20 the outlet air temperature used may range from about 30°C to about 90°C preferably from about 35°C to about 50°C.

Agitated thin film evaporation technology, on the other hand, involves separating the volatile component using indirect heat transfer coupled with mechanical agitation of the flowing film under controlled condition. In vertical agitated thin-film drying (or evaporation) 25 (ATFD-V), the starting solution is fed from the top into a cylindrical space between a centered rotary agitator and an outside heating jacket. The rotor rotation agitates the downside-flowing solution while the heating jacket heats it.

The amorphous agomelatine can also be precipitated by sudden cooling of the solution comprising agomelatine to below about -5°C.

30 Recovery of agomelatine (I) can be achieved by any conventional methods known in the art, for example filtration.

The agomelatine (I) substantially in an amorphous form obtained by the above process may be further dried in, for example, vacuum tray dryer, rotocon vacuum dryer, vacuum paddle dryer or pilot plant rotavapor, to further lower residual solvents. When implemented, the preferred instrument is a vacuum tray dryer.

5 The characterization of amorphous agomelatine and the crystalline forms of intermediate compounds of formula II and IIIa were done using Bruker axs D8 advance X-ray powder diffractometer having Copper-K α radiation. Approximately 1 g of sample was gently flattened on a sample holder and scanned from 2 to 50° two theta, at 0.03° two theta per step and a step time of 1 second (or 0.5 seconds). The sample was simply placed on the sample
10 holder. The sample was rotated at 30rpm at a voltage 40 KV and current 35 mA.

Optionally seeding of the corresponding polymorph is used to obtain the desired polymorph by adding to the solution of agomelatine to afford the desired polymorph of agomelatine.

In yet another embodiment, agomelatine (I) obtained by the processes of present
15 invention has residual organic solvents or organic volatile impurities comprises less than the amount recommended for pharmaceutical products, as set forth for example in ICH guidelines and U.S. pharmacopoeia; less than about 500ppm of dichloromethane, less than 1000ppm of methanol, ethanol, ethyl acetate, isopropyl alcohol, acetone, less than about 100 ppm of acetonitrile and 50 ppm of toluene.

20 The different physicochemical properties of the active ingredient and those of its excipients are to be considered, as these properties affect the process and formulation properties of the compound. Various important physicochemical properties include but are not limited to particle sizes, density (bulk density and tapped density), compressibility index, Hausner's ratio, angle of repose, etc. Particle sizes of active pharmaceutical ingredient can
25 affect the solid dosage form in numerous ways. For example, content uniformity (CU) of pharmaceutical dosage units can be affected by particle size and size distribution. This will be even more critical for low-dose drugs and satisfactory dosage units of low doses cannot be manufactured from a drug that does not meet certain particle size and size distribution specifications. Also particle sizes play an important role in dissolution of active ingredient
30 form the final dosage form for certain drugs like agomelatine because of their poor solubility.

Hence, these physicochemical properties not only affect the processes of the preparing the pharmaceutical formulations but also affect the performance of the pharmaceutical product both in vitro and in vivo.

5 The D10, D50, and D90 values are useful ways for indicating a particle size distribution. D90 is a size value where at least 90 percent of the particles have a size smaller than the stated value. Likewise D10 refers to 10 percent of the particles having a size smaller than the stated value. D50 refers to at least 50 percent of the particles having a size smaller than the stated value and D [4,3] value refers to a mean particle size. Methods for determining D10, D50, D90 and D [4,3] include those using laser light diffraction with equipment sold by
10 Malvern Instruments Ltd.

In the field of pharmaceutical formulation, it is notable that particle size plays a pivotal role in the solubility properties of an API, like agomelatine. Particle size reduction techniques are employed to increase a compound's solubility. Particle size reduction increases the surface area of the solid phase that is in contact with the liquid medium. However, particle size
15 reduction cannot alter the solubility of the compound in a solvent, which is a thermodynamic quantity. At instances where the rate of dissolution of a poorly soluble drug is the rate limiting factor in its rate of absorption by the body, it is recognized that the bioavailability of such drugs may be enhanced when administration occurs in a finely divided state. Further, particle size can also affect how free crystals or a powdered form of a drug will flow past each other,
20 which in turn, has consequences in the production process of pharmaceutical products containing the drug.

The solubility and bioavailability of an active pharmaceutical ingredient may be affected by various factors. It is recognized that there is an inverse relationship between solubility and bioavailability and particle size; whereupon, the available surface area for drug
25 dissolution correlates to the rate of dissolution and solubility. A smaller particle size enhances both the solubility and the rate of dissolution of a drug, which in turn, may improve its bioavailability and potentially its toxicity profiles.

The lack of solubility of a drug poses a challenge. Solubility may affect the bioavailability of a poorly water soluble active ingredient like for eg. Agomelatine. Hence,
30 there is a need in the art to prepare active pharmaceutical ingredients, such as agomelatine, with lesser particle size distribution and high surface area to obtain formulations with greater bioavailability.

Agomelatine of defined particle size may be produced by precipitation from appropriate solvents. Particle size may be adjusted by customary methods such as cooling, pH adjustment, pouring a concentrated solution into an anti-solvent and/or by co-precipitation so as to obtain a precipitate with the appropriate particle size distribution.

5 Further, agomelatine of defined particle size may be produced by known methods of particle size reduction starting with crystals, powder aggregates and coarse powder of either crystalline or amorphous agomelatine. The principal operations of conventional size reduction are milling of a feedstock material and sorting of the milled material by size. A fluid energy mill, or micronizer, is an especially preferred type of mill for its ability to produce particles of
10 small size in a narrow size distribution.

The present invention provides crystal particles of agomelatine (I) obtained by the processes herein described, has 50 volume-percent of the particles (D_{50}) having a size of less than or equal to about 400 microns, specifically less than or equal to about 300 microns, more specifically less than or equal to about 100 microns, still more specifically less than or equal to
15 about 60 microns, and most specifically less than or equal to about 15 microns.

As used herein, the term " μm " refers to "micrometer" which is 1×10^{-6} meter.

As used herein, "crystalline particles" means any combination of single crystals, aggregates and agglomerates.

As used herein "Particle Size Distribution (P.S.D.)" means the cumulative volume size
20 distribution of equivalent spherical diameters as determined by laser diffraction at 1 bar dispersive pressure in a Sympatec Helos equipment.

"Mean particle size distribution, i.e., $d(0.5)$ " correspondingly, means the median of said particle size distribution.

The term "micronization" used herein means a process or method by which the size of a
25 population of particles is reduced. As used herein, the term "micron" or " μm " both refer to "micrometer" which is 1×10^{-6} meter.

As used herein, "Particle Size Distribution (P.S.D.)" means the cumulative volume size distribution of equivalent spherical diameters as determined by laser diffraction in Malvern Master Sizer 2000 equipment or its equivalent.

30 Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the

foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

In yet another embodiment there is provided pharmaceutical compositions comprising at least a therapeutically effective amount of highly pure agomelatine (I) and at least a pharmaceutically acceptable excipient. Such pharmaceutical compositions may be administered to a mammalian patient for the treatment or prevention of major depressive episodes in adults in a dosage form, e.g., solid, liquid, powder, elixir, aerosol, syrups, injectable solution, etc. Dosage forms may be adapted for administration to the patient by oral, buccal, parenteral, ophthalmic, rectal and transdermal routes or any other acceptable route of administration. Oral dosage forms include, but are not limited to, tablets, pills, capsules, syrup, troches, sachets, suspensions, powders, lozenges, elixirs and the like. The highly pure agomelatine or a pharmaceutically acceptable salt thereof substantially free of hydrazine impurity may also be administered as suppositories, ophthalmic ointments and suspensions, and parenteral suspensions, which are administered by other routes.

The dosage forms may contain highly pure agomelatine substantially free of process related impurities as part of a composition. The pharmaceutical compositions may further contain one or more pharmaceutically acceptable excipients. Suitable excipients and the amounts to use may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field, e.g., the buffering agents, sweetening agents, binders, diluents, fillers, lubricants, wetting agents and disintegrants described hereinabove.

Tablets and powders may also be coated with an enteric coating. The enteric-coated powder forms may have coatings containing at least phthalic acid cellulose acetate, hydroxypropylmethyl cellulose phthalate, polyvinyl alcohol phthalate, carboxy methyl ethyl cellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, the coating agents may be employed with suitable plasticizers and/or extending agents. A coated capsule or tablet may have a coating on

the surface thereof or may be a capsule or tablet comprising a powder or granules with an enteric-coating.

Tableting compositions may have few or many components depending upon the tableting method used, the release rate desired and other factors. For example, the compositions described herein may contain diluents such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose salts and other substituted and unsubstituted celluloses; starch; pregelatinized starch; inorganic diluents such calcium carbonate and calcium diphosphate and other diluents known to one of ordinary skill in the art. Yet other suitable diluents include waxes, sugars (e.g. lactose) and sugar alcohols such as mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin.

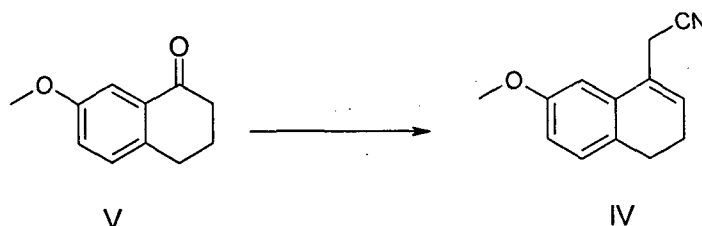
Other excipients include binders, such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes; disintegrants such as sodium starch glycolate, crospovidone, low-substituted hydroxypropyl cellulose and others; lubricants like magnesium and calcium stearate and sodium stearyl fumarate; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

The processes for the preparation of agomelatine of the present invention are simple, eco-friendly, robust, reproducible, cost effective and amenable on commercial scale.

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.

EXAMPLES

Example-1: Preparation of (7-methoxy-3,4-dihydro-1-naphthalenyl)acetonitrile (IV)

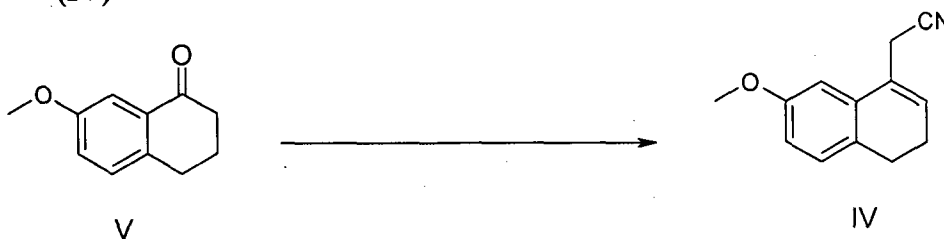


40gms of cyanoacetic acid and 500ml. of toluene were charged in a clean dry 1 liter 4 neck RBF equipped with a dean stalk apparatus. 50gms of 7-methoxy-1-tetralone (V) and

23gms of ammonium acetate were charged and the resultant reaction mixture was heated to azeotropic reflux until completion of the reaction. After completion of the reaction, the reaction mass was cooled to about 25-30°C and filtered followed by washing the toluene layer (filtrate) with 3x50 ml. of demineralised water. The solvent was distilled completely under vacuum to give 56 gms of the title compound as a crude residue.

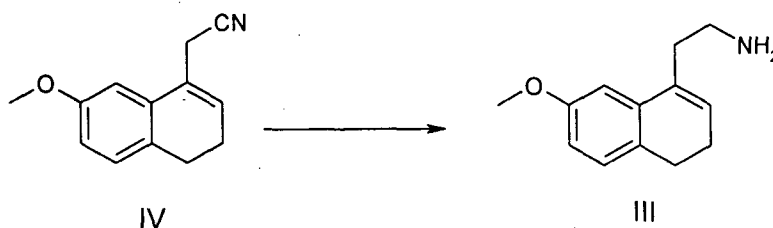
Purity by GC: 95%.

Example 2: Alternate preparation of (7-methoxy-3,4-dihydro-1-naphthyl)acetonitrile (IV)



Taken 50gr. of 7-methoxy-1-tetralone (V), 40gr. of cyanoacetic acid, 9gr. of heptanoic acid and 7.5gr. of benzyl amine in 250ml. of toluene. The resultant solution was heated to reflux temperature. Reflux was continued until the complete conversion of the reactant. Cooled the reaction mass to 0-5°C. Filtered and washed with 50ml. of toluene. Then toluene layer was washed with (3x50ml.) of 2N. NaOH solution and (3x50ml.) of demineralised water. Separated the toluene layer and distilled under vacuum to afford 56.0gr of the title compound as crude residue.

Example-3: Preparation of (7-methoxy-3,4-dihydro-1-naphthyl)ethylamine (III)

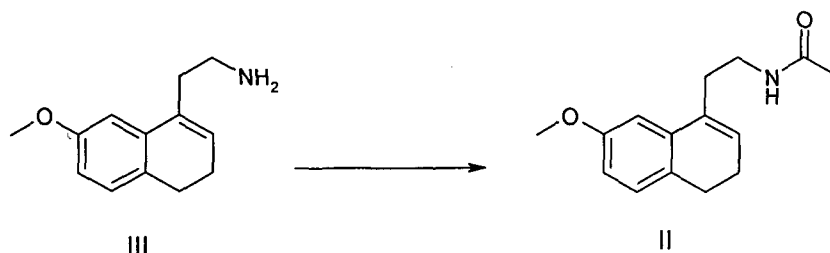


50gms of (7-methoxy-3,4-dihydro-1-naphthalenyl)acetonitrile (IV), 300ml. of ethanol and the reaction solution was given carbon treatment using 2.5gms of charcoal carbon. Then filtrate, 25ml of Raney Ni and 115ml. of aqueous ammonia solution were charged in a clean and dry 1 liter autoclave vessel. To the resultant reaction suspension 6kg/m² of H₂ pressure was passed at about 40°C for about 3hrs under agitation. After completion of the reaction, the reaction mass was cooled to about 25-30°C and the reaction mass was filtered on celite to separate the Raney Ni.

The filtrate was distilled completely at about 40°C under vacuum to obtain 50 gms of the title compound as a residue.

Purity by HPLC: 94%.

Example-4: Preparation of N-[2-(7-methoxy-3,4-dihydro-1-naphthyl)ethyl]acetamide (II)



5

50gms of (7-methoxy-3,4-dihydro-1-naphthyl)ethylamine (III) and 250ml. of ethanol were charged into a clean and dry 1 liter 4 neck RB flask followed by cooling to about 0-5°C. Then 25ml. of acetic anhydride was added drop-wise at about 0-5°C over about 30 mins. The resultant reaction mixture was stirred at about 0-5°C for about 30min. The reaction mixture was distilled completely under vacuum to afford 55gms of the title compound as a residue. Purity by HPLC: 94%.

10

¹H-NMR data: (in CDCl₃) (AV 300MHZ)

δ1.962(3H,singlet,CH₃-CO-), δ2.242-2.281(2H,triplet,Ar-CH₂-), δ2.619-2.646(2H,multiplet,-CH₂-CH₂),

δ2.676-2.703(2H,multiplet,-CH₂-), δ3.404-3.469(2H,multiplet,-CH₂-NH), δ3.818 (3H,singlet,-OCH₃-), δ5.542(1H,singlet,-NH-), δ5.929 (1H,multiplet,-CH-), δ6.694-6.721(1H,multiplet,ArH), δ6.882(1H,multiplet,ArH), δ7.052-7.079(1H,multiplet,ArH).

15

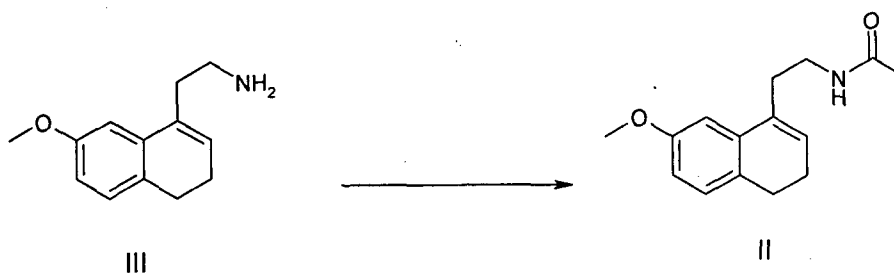
Mass: (M+1)=246,m/z=268(M+Na),m/z=187

IR: 3243 Cm⁻¹,3075 Cm⁻¹,2926 Cm⁻¹,2826 Cm⁻¹,1652 Cm⁻¹,1602 Cm⁻¹,1494 Cm⁻¹,1364 Cm⁻¹

1,1303 Cm⁻¹,1206 Cm⁻¹,1175 Cm⁻¹,1037 Cm⁻¹,901 Cm⁻¹,874 Cm⁻¹,816 Cm⁻¹,745 Cm⁻¹

20

Example 5: Preparation of N-[2-(7-methoxy-3,4-dihydro-1-naphthyl)ethyl]acetamide(II) using a base



Taken 20gr. of 7-methoxy-3,4-dihydro-1-naphthyl ethylamine (III) and 10gr. of triethylamine in 100ml. of dichloromethane and cooled to 0-5°C. Added 11gr. of acetic anhydride drop-wise at below 10°C and stirred for 30min. at 0-5°C. Then organic layer was washed with (3x50ml.) of demineralised water. Separated the organic layer and distilled off the solvent completely to afford 22.5gr. of the title compound.

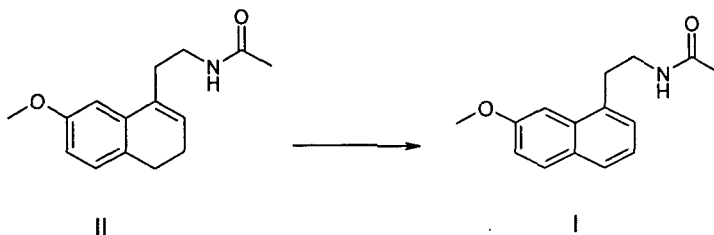
Alternate processes for the conversion of compound of formula III to II

Example -6: 20gr. of (7-methoxy-3,4-dihydro-1-naphthyl)ethylamine was dissolved in 100ml. of dichloromethane. The resulting solution was cooled to 0-5°C. Then added acetic anhydride solution drop-wise below 10°C. Stirred for 30 min. at 0-5°C. Separated the layers, washed the dichloromethane layer with 3x50 ml. of demineralised water. The dichloromethane layer was distilled under vacuum to furnish 23gr. of the title compound. Purity by HPLC: 94%.

Example -7: 20gr. of (7-methoxy-3,4-dihydro-1-naphthyl)ethylamine was dissolved in 100ml. of toluene. The resulting solution was cooled to 0-5°C. Then added acetic anhydride solution drop-wise below 10°C. Stirred for 30min. at 0-5°C. Separated the layers, washed the toluene layer with 3x50ml. of demineralised water. The toluene layer was distilled under vacuum to give 23gr. of the title compound.

Example -8: 20gr. of (7-methoxy-3,4-dihydro-1-naphthyl)ethylamine was dissolved in 100ml. of ethyl acetate. The resulting solution was cooled to 0-5°C. Then added acetic anhydride solution drop-wise below 10°C. Stirred for 30min. at 0-5°C. Separated the layers, washed the ethyl acetate layer with 3x50ml. of demineralised water. The ethyl acetate layer was distilled under vacuum to give 23gr. of the title compound.

Example-9: Preparation of N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide (I)



20gms of N-[2-(7-methoxy-3,4-dihydro-1-naphthyl)ethyl]acetamide (II) and 6.5gms of sulphur were charged into a clean and dry 500ml RB Flask followed by heating to about 180°C and for about 30min. The resultant reaction mass was cooled to about 60-65°C then 100ml of ethanol was charged and stirred for about 30min. The reaction solution was given

carbon treatment with 2 gms of carbon. Then the reaction solution was distilled completely under vacuum followed by recrystallisation of the residue using from toluene and n-hexane mixture to afford 18gms of the title compound.

Yield: 5gms.

5 **Alternate process for the preparation of Agomelatine (I)**

Example 1: Preparation of (7-methoxy-3,4-dihydro-1-naphthyl) ethyl amine HCl (IIIa)

15gms of (7-methoxy-3,4-dihydro-1-naphthyl) ethyl amine (III) was dissolved in 45 ml of ethyl acetate. The resultant solution was cooled to about 0-5°C and 10ml of conc. Hydrochloric acid was added followed by stirring for about 30 minutes. The separated solid
10 was filtered and the solid was washed with 20 ml of ethyl acetate or acetone. The solid obtained was dried to afford 15gms of the title compound. Purity by HPLC: 99%.

¹H-NMR data: (in CDCl₃) (AV 300MHZ)

δ2.247-2.289(2H,quartet,-CH₂-CH₂-), δ2.662-2.715(2H,triplet,Ar-CH₂-), δ2.785-
2.835(2H,triplet,-CH₂-CH₂), δ3.063-3.114(2H,triplet,-CH₂-NH₂.HCl), δ3.789(3H,singlet,-
15 OCH₃), δ6.033-6.063(1H,triplet,-CH-), δ6.729-6.764(1H,multiplet,ArH), δ6.829-
6.837(1H,multiplet,ArH), δ7.073-7.101(1H,multiplet,ArH).

Mass: (M+1)=204(without HCl)

IR: 3019Cm⁻¹,3002 Cm⁻¹,2989 Cm⁻¹,2931 Cm⁻¹,2883 Cm⁻¹,2830 Cm⁻¹,1601 Cm⁻¹,1571 Cm⁻¹,
1,1496 Cm⁻¹, 1464 Cm⁻¹,1421 Cm⁻¹,1277 Cm⁻¹,1255 Cm⁻¹,1175 Cm⁻¹,1039 Cm⁻¹,948 Cm⁻¹,856
20 Cm⁻¹,797 Cm⁻¹

Example 2: Preparation of (7-methoxy-3,4-dihydro-1-naphthyl) ethyl amine HCl (IIIa)
using Toluene + IPA.HCl

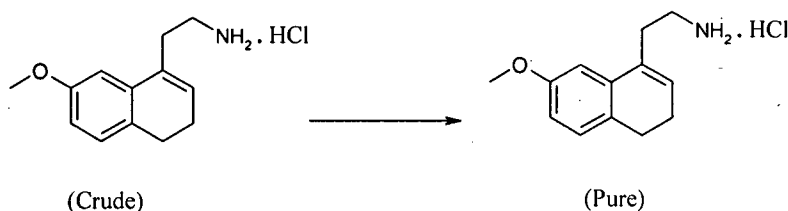
50gr. of crude (7-methoxy-3,4-dihydro-1-naphthyl)ethylamine was dissolved in 250ml. of toluene at room temperature. To this solution added isopropanol-hydrochloric acid (IPA-HCl) drop-wise at the temperature below 35°C until P^H≤2. After consumption of half-volume
25 of IPA-HCl, solid formation was observed. After acidification the reaction mass was stirred for 30min. at room temperature. Then cooled to 0-5°C and stirred for 30min. at the same temperature. The obtained solid was filtered and washed with 50ml. of chilled toluene and dried to furnish 50.5gr. of the title compound.

30 Purity by HPLC: 99%.

Example 3: Preparation of (7-methoxy-3,4-dihydro-1-naphthyl) ethyl amine HCl (IIIa) using IPA + IPA.HCl

50gr. of crude (7-methoxy-3,4-dihydro-1-naphthyl)ethylamine was dissolved in 150ml. of isopropyl alcohol at room temperature. To this solution added IPA-HCl drop-wise at the temperature. During the addition, the temperature should not exceed 35°C. When $\text{pH} \leq 2$, the addition of IPA-HCl was stopped. The reaction mass was stirred for 30min. at room temperature. Then cooled to 0-5°C and stirred for 30min. at the same temperature. The obtained solid was filtered and washed with 50ml. of chilled isopropyl alcohol and dried to afford 45.0gr. of the title compound. Purity by HPLC: 99%.

Purification of (7-methoxy-3,4-dihydro-1-naphthyl) ethyl amine HCl (IIIa)



Taken 20gr. of crude compound, added 60ml. of ethanol. The resulted mixture was heated to reflux temperature. Dissolution was observed under reflux. 2gr. of carbon treatment was given to the obtained solution. Filtered, cooled the filtrate to 0-5°C and stirred at this temperature for 30min. Filtered and dried to provide 16gr. of the pure compound.

Purity by HPLC=99.9%

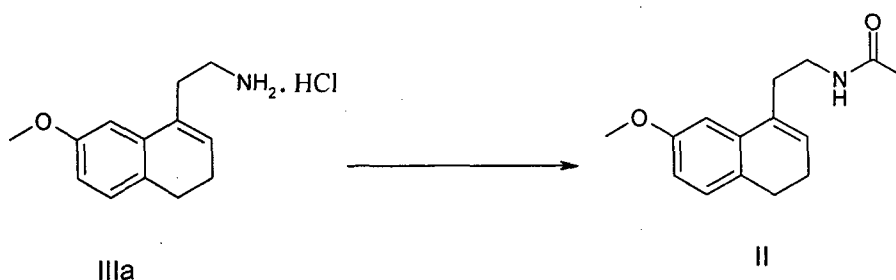
Example 4: Preparation of (7-methoxy-1-naphthyl) ethyl amine HCl (IIIb)

50 gms of (7-methoxy-3,4-dihydro-1-naphthyl) ethyl amine HCl (IIIa) and 15 gms of sulphur were charged in a clean and dry RB flask followed by heating to about 180-185°C. The resultant suspension was stirred at same temperature for about 30 mins. Then cooled to about 60-65°C followed by charging of 100ml of ethanol. The resultant reaction solution was stirred for about 30 mins. then carbon treatment was given using 2.5 gms of charcoal carbon. The solution was filtered on celite and the filtrate was distilled completely under vacuum to afford 45 gms of the title compound.

The following compounds were prepared analogous to the example 4. (IIIa to IIIb)

	HCl salt	HBr salt	HSO ₄ Salt	Besylate salt	PTSA salt	Mesylate salt	Tartrate salt
Compound IIIa Used (in gms)	50	50	50	50	50	50	50
Compound IIIb yield (in gms)	47	45	41	35	37	42	40

Example 12: Alternate preparation of N-[2-(7-methoxy-3,4-dihydro-1-naphthyl)ethyl]acetamide (II)

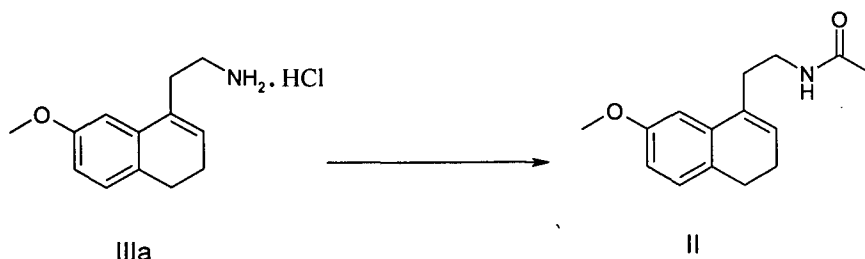


- 5 Taken 20gr. of 7-methoxy-3,4-dihydro-1-naphthyl ethylamine hydrochloride (IIIa), 7gr. of sodium acetate and 10gr. of acetic anhydride in 100ml. of ethanol. The mixture was heated to reflux temperature and maintained for 30min. Then the reaction mass was cooled to room temperature. Decomposed the reaction mass into 250ml. of water, extracted with (3x100ml.) of dichloromethane. Distilled-off the solvent completely to give 20gr. of crude residue, which was
- 10 crystallized from diisopropylether and was dried to give 10gr. of the title compound.
- M.P: 68-72°C

The following compounds were prepared analogous to the example 12. (IIIa to II)

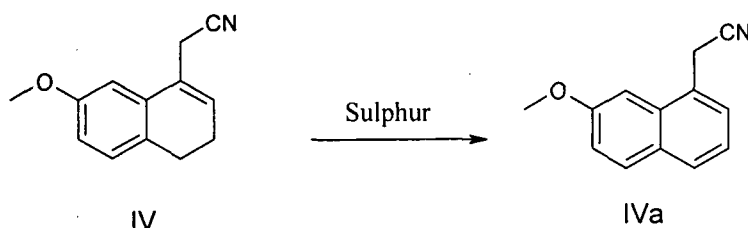
	HCl salt	HBr salt	HSO ₄ Salt	Besylate salt	PTSA salt	Mesylate salt	Tartrate salt
Compound IIIa Used (in gms)	20	20	20	20	20	20	20
Compound II yield (in gms)	20	15	12	13	11	12.5	10

Example 20: Alternate preparation of N-[2-(7-methoxy-3,4-dihydro-1-naphthyl)ethyl]acetamide (I)



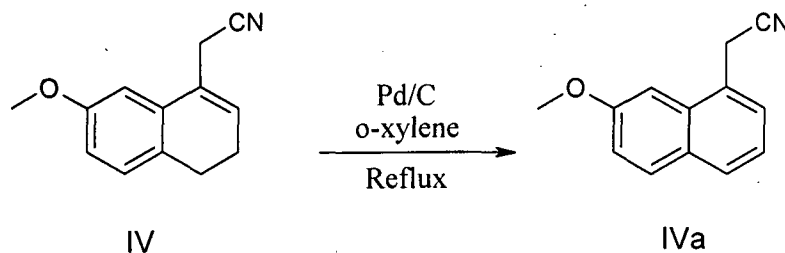
Taken 50gr. of 7-methoxy-3,4-dihydro-1-naphthylethylamine hydrochloride (IIIa), 17.5gr. of sodium acetate and 24gr. of acetic anhydride in 250ml. of ethanol. The mixture was heated to reflux and maintained for 30min. Then the reaction mass was cooled to room temperature. Added 500ml. of demineralised water, cooled to 5-10°C and stirred for 30min. at the same temperature. Filtered the solid and washed with 50ml. of demineralised water and dried to obtain 50gr. of the title compound.

Example 21: Preparation of (7-methoxy-1-naphthyl)acetonitrile (IVa)



(i) Taken 60gr. of (7-methoxy-3,4-dihydro-1-naphthyl)acetonitrile (IV) in a 1lit. RBF. Added 24gr. of sulphur. Then heated to about 175°C and stirred for 10min. at the same temperature. Then cooled to 50-60°C. Added 430ml. of 20% aq. ethanol solution and heated to 70-75°C. 6gr. of carbon treatment was given to the solution. Taken the filtrate, cooled to 5-10°C and maintained for 30min. at the same temperature. Filtered the solid and washed with 30ml. of chilled 20% aq. ethanol and dried to furnish 20gr. of the title compound.

Example 22: Preparation of (7-methoxy-1-naphthyl)acetonitrile (IVa) using palladium-carbon without using ally compound



5 Taken 30gr. of 7-methoxy-3,4-dihydro-1-naphthyl acetonitrile (IV) and 4gr. of 5% palladium on carbon in 150ml. of o-xylene. The resultant solution was heated to reflux temperature and maintained for 7hrs. The solvent was distilled under vacuum to give the crude residue and recrystallised from 120ml. of 20% aq. ethanol solution to give 10gr. of the title compound.

Purification methods of Agomelatine

Example 1: Purification of Agomelatine using Ethyl acetate

10 To 16gr. of crude agomelatine, added 40ml. of ethyl acetate. The resultant mixture was heated to about 60-65°C to dissolve. The resultant solution was treated with 2gms of carbon and filtered hot and washed with 8-10ml. of ethyl acetate. The filtrate was cooled to about 0-5°C and stirred for about 30min. The separated solid was filtered to afford 12.8 gr. of the pure agomelatine.

15 Purity by HPLC: 99.87 area %; total impurities: 0.13 area %; single max imp. : 0.05 area %.

Example 2: Purification of Agomelatine using Acetone

20 To 16gr. of crude agomelatine, added 40ml. of acetone. The resultant mixture was heated to about 60-65°C to dissolve. The solution was treated with 2gr. of carbon and filtered hot and washed with 8-10ml. of acetone. The filtrate was cooled to about 0-5°C and stirred for about 30min. The separated solid was filtered to afford 11gr. of the pure agomelatine.

Example 3: Purification of Agomelatine using acetonitrile

25 To 16gr. of crude agomelatine, added 40ml. of acetonitrile. The resultant mixture was heated to 60-65°C to dissolve. The solution was treated with 2gr. of carbon and filtered hot washed with 8-10ml. of acetonitrile. The filtrate was cooled to about 0-5°C and stirred for 30min. The separated solid was filtered to afford 12 gr. of the pure agomelatine.

Example 4: Purification of Agomelatine using a mixture of Ethyl acetate and n-hexane

30 (a) To 20gr. of crude agomelatine, added 200ml. of ethyl acetate: n-hexane (1:1) mixture. The mixture was heated to 55-60°C. Dissolution was observed at 55°C. The resultant solution was cooled to 0-5°C and stirred for 30min. at the same temperature. The separated solid was filtered and washed with 20ml. of chilled ethyl acetate and n-hexane (1:1) mixture to give 15 gr. of the pure agomelatine.

35

(b) 10gr. of crude agomelatine was dissolved in 100ml. of ethyl acetate at room temperature. Then added 500ml. of n-hexane drop-wise at room temperature. Formation of solid was observed. Stirred for 15min. at room temperature. The reaction mass was filtered and washed with 30ml. of n-hexane and dried to yield 7 gr. of pure agomelatine.

5 **Example 5: Purification of Agomelatine using 50% aqueous methanol**

To 2gr. of crude agomelatine, added 20ml. of 50% aqueous methanol solution. The mixture was heated to reflux temperature (70-75°C). Dissolution was observed at reflux. The solution was then cooled to 0-5°C and stirred for 30min. at the same temperature. The
10 separated solid was filtered and washed with 10ml. of 50% v/v aqueous methanol solution to give 1.5gr. of pure agomelatine.

Example 6: Purification of Agomelatine using toluene

To 1gr. of crude agomelatine, added 10ml. of toluene and heated to 70°C. Dissolution
15 was clear at 70°C. The resulting solution was then cooled to 0-5°C and stirred for 30min. at the same temperature. The separated solid was filtered and dried to obtain 0.5gr. of pure agomelatine.

Example 7: Purification of Agomelatine using toluene-hexane (2:1)

To 2gr. of crude agomelatine, added 30ml. of toluene-hexane (2:1) mixture. The
20 mixture was heated to 55-60°C. Dissolution was clear at 60°C. Then cooled to 0-5°C and stirred for 30 min. at the same temperature. The separated solid was filtered and washed with 15ml. of chilled toluene-hexane (2:1) mixture to give 1.5gr. pure agomelatine.

Example 8: Purification of Agomelatine using chloroform: n-hexane (2:1)

To 2gr. of crude agomelatine, added 20ml. of chloroform:n-hexane(2:1) mixture. The
25 mixture was heated to 50-55°C. Dissolution was clear at 50°C. Then cooled to 0-5°C and stirred for 30min. at the same temperature. The separated solid was filtered and washed with 10ml. of chilled chloroform: n-hexane (2:1) mixture to give 1.5gr. pure agomelatine.

Example 9: Purification of Agomelatine using water and ethanol (6.5: 3.5)

To 10gr. of crude agomelatine, added 100ml. of water/ethanol (6.5: 3.5) mixture. The
30 mixture was heated to 60-65°C. Dissolution was clear at 65°C. Then cooled to 0-5°C and stirred for 30min. at the same temperature. The separated solid was filtered and washed with 20ml. of aqueous ethanol mixture to give 8.0 gr. pure agomelatine.

Example 10: Purification of Agomelatine using ethanol

To 5gr. of crude agomelatine, added 10ml. of ethanol. The mixture was heated to 50-55°C. Dissolution was clear at 50°C. Then cooled to 0-5°C and stirred for 30min. at the same temperature. The separated solid was filtered and dried to give 3.0gr. pure agomelatine.

Example 11: Purification of Agomelatine from diisopropylether

To 3gr. of crude agomelatine, added 180ml. of diisopropylether. The mixture was heated to reflux temperature (65-68°C). Dissolution was clear under reflux. Then cooled to 0-5°C and stirred for 30min. at the same temperature. The separated solid was filtered and dried to give 2.0gr. pure agomelatine.

Preparation of Amorphous Agomelatine**Example 1: Preparation of amorphous agomelatine (I)**

A solution of agomelatine (I) (5g) in dichloromethane (100 ml) was subjected to spray drying at 65° and obtained solid was dried at about 40°C for 1 hr. under reduced pressure to give 4.5 g of the title compound as white powder.

Example 2: Preparation of amorphous agomelatine (I)

A solution of agomelatine (I) (5g) in dichloromethane (100 ml) was subjected to freeze drying at -25° and the solid obtained was dried at about 40°C for 1 hr. under reduced pressure to give 4.5 g of the title compound as white powder.

Example 3: Preparation of amorphous agomelatine (I)

A solution of agomelatine (5g) in acetone (100 mL) in a clean and dry round bottom flask, was heated to 40.° C. and then the cooled to about 5 °C for about 30 minutes. The separated solid was filtered and washed with 10 ml of acetone. The obtained solid is dried for 4 hours at about 40°C to afford 4 gms of the title compound.

Example 4: Preparation of amorphous Agomelatine (I)

5 gms of Agomelatine was dissolved in a mixture of acetonitrile (100 ml) and water (10 ml) at about 50°C. The solution was cooled to about 5°C for about 1 hour. The separated solid was filtered and the solid was washed with acetonitrile (10ml). The solid obtained was dried at about 40°C for about 1 hour to afford 4 g of the title compound.

Example 5: Preparation of amorphous Agomelatine (I)

5 gms of Agomelatine was dissolved in a mixture of ethanol (100 ml) and water (10 ml) at about 50°C. The solution was cooled to about 5°C for about 1 hour. The separated solid

was filtered and the solid was washed with ethanol and water (10ml). The solid obtained was dried at about 40°C for about 1 hour to afford 4 g of the title compound.

Example 6: Preparation of amorphous agomelatine using Povidone

2 gms of agomelatine, 2 gms of povidone (PVP K30) were dissolved in 200 ml of
5 dichloromethane with the aid of heating to a temperature of 40° C. The solution was filtered in the hot condition and the dichloromethane was removed using distillation in a Buchi Rotavapor apparatus under a vacuum of 0-20 torr. 3.8 grams of amorphous agomelatine was obtained.

Example 7: Preparation of amorphous agomelatine (I) by solvent-antisolvent technique.

To 200 ml of n-hexane a solution of agomelatine (I) (5g) in dichloromethane (100 ml)
10 was added to precipitate solid. The solid separated was filtered and obtained solid was dried at about 40°C for 1 hr. under reduced pressure to give 4.5 g of the title compound as white powder.

Example 7: Preparation of amorphous agomelatine (I) by sudden cooling.

5 gms of Agomelatine was dissolved in acetone (100 ml) at about 50°C. The solution
15 was suddenly cooled to about -10°C for about 1 hour. The separated solid was filtered and the solid was washed with acetone (10ml). The solid obtained was dried at about 40°C for about 1 hour to afford 4 g of the title compound.

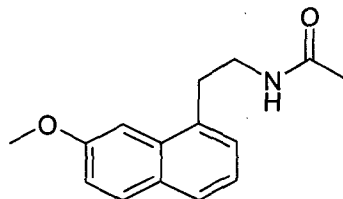
20

25

30

Claims:

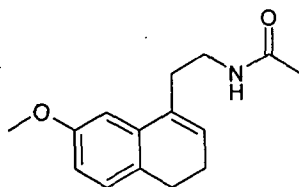
1) A process for the preparation of N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide of formula I,



I

5 comprising:

aromatization of compound N-[2-(7-methoxy-3,4-dihydro-1-naphthyl) ethyl] acetamide of formula II

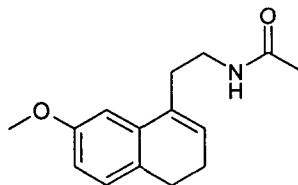


II

using suitable reagent.

- 10 2) The process of claim 1, wherein the suitable reagent is selected from the group consisting of sulphur or a derivative, hydrogenation catalysts such as palladium carbon in various percentages, platinum oxide, Raney Nickel, palladium oxide or mixture thereof.
- 3) The process of claim 2, wherein the reagent used is sulphur.
- 4) The process of claim 1, wherein the organic solvent is selected from the group consisting of
 - 15 alcohols like methanol, ethanol, halogenated solvents like dichloromethane, ethylene dichloride, chloroform, chlorobenzene, esters like ethyl acetate, isopropyl acetate, tertiary butyl acetate, hydrocarbons like n- heptane, cyclohexane, n- hexane, toluene, xylene or mixtures thereof.
- 5) The process of claim 1, wherein the process is optionally carried out in the absence of
 - 20 solvents.
- 6) The process of claim 1, wherein the reaction is carried out at a temperature of from about 35°C to about 190°C.
- 7) A process for the preparation of N-[2-(7-methoxy-3,4-dihydro-1-naphthyl) ethyl]

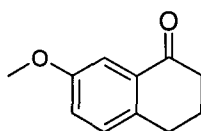
acetamide compound of formula II



II

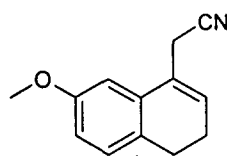
comprising:

a) reacting the compound 7-methoxy -1-tetralone of formula V



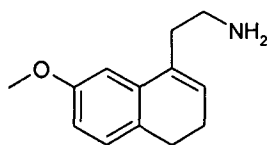
V

with CNCH_2COOR where R is Na, K, Ca, NH_4^+ , H, $\text{C}_1\text{-C}_8$ alkyl straight chain or branched or aryl alkyl in the presence of ammonium salt and an organic solvent to give the compound (7-methoxy-3,4-dihydro-1-naphthalenyl) acetonitrile of formula IV



IV

b) subjecting the intermediate compound of formula IV to reduction using suitable reducing agent to give the compound (7-methoxy-3,4-dihydro-1-naphthyl) ethyl amine or a salt thereof formula III



III

c) reacting the resultant intermediate compound of formula III or a salt thereof with a suitable acetylating agent to give the compound of formula II.

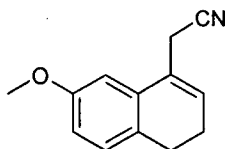
8) The process of claim 7, wherein the cyano compound used in step a) is selected from cyano acetic acid, methyl cyano acetate, ethyl cyano acetate or mixtures thereof, preferably cyano acetic acid.

- 9) The process of claim 7, wherein the ammonium salt in step a) is selected from ammonium acetate, ammonium carbonate or mixtures thereof, preferably ammonium acetate.
- 10) The process of claim 7, wherein the organic solvent used in step a) is selected from
5 halogenated solvents like dichloromethane, ethylene dichloride, chloroform, chlorobenzene, esters like ethyl acetate, isopropyl acetate, tertiary butyl acetate, hydrocarbons like toluene, xylene, or mixtures thereof in various proportions without limitation. Preferably toluene.
- 11) The process of claim 7, wherein the reaction step a) the temperature is from about 35°C to
10 about 200°C, preferably at a temperature of from about 95°C to about 120 °C and the reaction time is from about 1 hour to about 40 hours.
hours.
- 12) The process of claim 7, wherein the reducing agent used in step b) is selected from hydrogenation catalysts like palladium carbon in various percentages, platinum oxide,
15 Raney Nickel, palladium oxide, the other reducing agent such as sodium borohydride, lithium aluminium hydride, Vitride, n-butyl lithium . Preferably Raney Nickel.
- 13) The process of claim 7, wherein the organic solvent used in step b) is selected from alcohols like methanol, ethanol, halogenated solvents like dichloromethane, ethylene
20 dichloride, chloroform, chlorobenzene, esters like ethyl acetate, isopropyl acetate, tertiary butyl acetate, hydrocarbons cyclohexane, toluene, xylene, or mixtures thereof in various proportions without limitation. Preferably ethanol.
- 14) The process of claim 7, wherein the reaction step b) the temperature is from about 30°C to about 100°C, preferably at a temperature of from about 35°C to about 40 °C and the time period of from about 1 hour to about 15 hours, preferably from about 2 to 5 hours.
- 25 15) The process of claim 7, wherein the acetylating agent used in step c) is selected from the acetic anhydride, acetyl halide halide like acetyl chloride, acetyl bromide, acetyl iodide, and the like. Preferably acetic anhydride.
- 16) The process of claim 7, wherein the organic solvent used in step c) is selected from alcohols like methanol, ethanol, isopropyl alcohol, halogenated solvents like
30 dichloromethane, ethylene dichloride, chloroform, chlorobenzene, esters like ethyl acetate, isopropyl acetate, tertiary butyl acetate, hydrocarbons like cyclohexane, n-hexane, toluene, xylene or mixtures thereof in various proportions without limitation. Preferably

dichloromethane or ethanol or toluene or ethyl acetate.

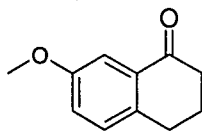
17) The process of claim 7, wherein the reaction temperature in step c) from about -10°C to about 20°C, preferably from about 0°C to about 5 °C and the time from about 15 minutes to about 5 hours, preferably from about 30 minutes to about 1 hour.

5 18) A process for the preparation of (7-methoxy-3,4-dihydro-1-naphthalenyl) acetamide of formula IV



IV

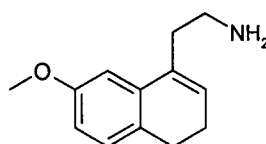
reacting the compound 7-methoxy -1-tetralone of formula V



V

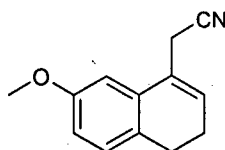
10 with CNCH_2COOR where R is Na, K, Ca, NH_4^+ , H, $\text{C}_1\text{-C}_8$ alkyl straight chain or branched or aryl alkyl in the presence of ammonium salt and an organic solvent.

19) A process for the preparation of the compound (7-methoxy-3,4- dihydro- 1-naphthyl) ethyl amine or a salt thereof formula III



III

15 subjecting the compound (7-methoxy-3,4-dihydro-1-naphthalenyl) acetonitrile of formula IV

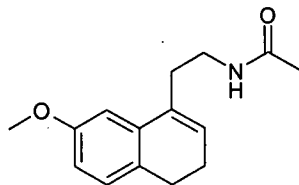


IV

to reduction using suitable reducing agent.

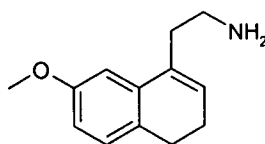
20) A process for the preparation of N-[2-(7-methoxy-3,4-dihydro-1-naphthyl) ethyl]

acetamide compound of formula II



II

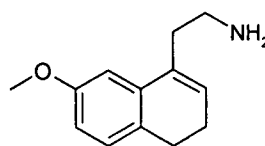
by acetylation of the compound (7-methoxy-3,4-dihydro-1-naphthyl) ethyl amine or a salt thereof formula III



III

using a suitable acetylating agent

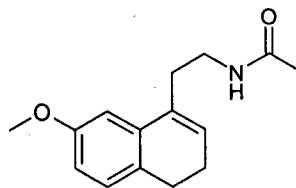
21) A compound of formula III or a salt thereof



III

and its use as an intermediate in the synthesis of active naphthalene derivatives like agomelatine (I) wherein the compound of formula III in the form of HCl salt is characterized by XRPD and DSC which are substantially in accordance with the fig. 5 and 6.

22) A compound of formula II



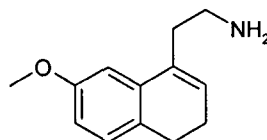
II

and its use as an intermediate in the synthesis of active naphthalene derivatives

like agomelatine (I), wherein the compound of formula II is characterized by XRPD and DSC which are substantially in accordance with the fig. 3 and 4.

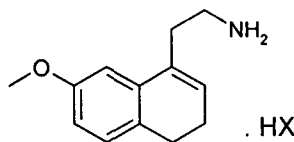
23) A process for the preparation of N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide of formula (I) comprising:

- 5 a) conversion of compound (7-methoxy-3,4-dihydro-1-naphthyl) ethyl amine of formula III



III

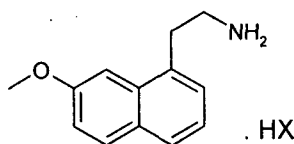
into the compound (7-methoxy-3,4-dihydro-1-naphthyl) ethyl amine salt of formula IIIa



IIIa

- 10 Wherein X is Cl⁻, Br⁻, F⁻, I⁻, HSO₄ etc.

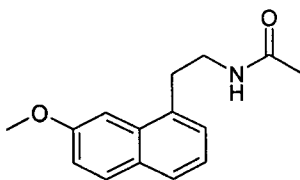
b) aromatisation of compound of formula IIIa or III to give the compound (7-methoxy-1-naphthyl) ethyl amine or a salt thereof formula IIIb



IIIb

- 15 Wherein HX is an organic or inorganic acids such as HCl, HBr, maleic acid, oxalic acid, tartaric acid, and the like using suitable reagent.

c) acetylation of compound (7-methoxy-1-naphthyl) ethyl amine or a salt thereof of formula IIIb to give the compound N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide of formula I



I

by using suitable acetylating agent.

- 24) The process of claim 23, wherein the step a) the compound of formula III is optionally converted to acid addition salt like hydrochloric acid salt, hydrobromic acid salt,
 5 iodic acid salt, hydrogen sulfate salt, besylate salt, paratoluene sulfonate salt, mesylate salt, tartarate salt and the like. Preferably hydrochloric acid salt
- 25) The process of claim 23, wherein the conversion takes place by reaction of the compound of formula III with a suitable acid in the form of gas or gas dissolved in a solvent form or aqueous form in any percentage (%v/v).
- 10 26) The process of claim 23, wherein the solvent used in step a) is selected from water, alcohols like methanol, ethanol, isopropyl alcohol, halogenated solvents like dichloromethane, ethylenedichloride, chloroform, chlorobenzene, hydrocarbons like toluene, xylene, cyclohexane, esters like ethyl acetate, isopropyl acetate, tertiary butyl acetate, ketones like acetone, methyl isobutyl ketone, methyl ethyl ketone, 2-butanone ,
 15 nitriles like acetonitrile, propionitrile or mixtures thereof in various proportions without limitation. Preferably toluene or isopropyl alcohol.
- 27) The process of claim 23, wherein the reaction temperature in step a) is from about -10°C to about 20°C, preferably at a temperature of from about 0°C to about 5°C and the time period is from about 15 minutes to about 5 hours, preferably from about 30
 20 minutes to 1 hour.
- 28) The process of claim 23, wherein the reagent used in step b) is selected from sulphur in any form, hydrogenation catalysts such as palladium carbon in various percentages, platinum oxide, Raney Nickel, palladium oxide or mixtures thereof.
- 29) The process of claim 23, wherein the conversion of compound of formula IIIa to the
 25 compound of formula IIIb is optionally performed in the presence of solvents.
- 30) The process of claim 23, wherein the reaction temperature in step b) is from about 35°C to about 200°C, preferably at a temperature of about 190 °C and the time period is

from about 1 hour to about 10 hours, preferably from about 1 hour to 5 hours.

31) The process of claim 23, wherein the suitable acetylating agent used in step c) is selected from acetic anhydride, acetic acid, and the like. Preferably acetic anhydride.

32) The process of claim 23, wherein the organic solvent used in step c) is selected from
5 alcohols like methanol, ethanol, halogenated solvents like dichloromethane, ethylene dichloride, chloroform, chlorobenzene, esters like ethyl acetate, isopropyl acetate, tertiary butyl acetate, hydrocarbons like cyclohexane, toluene, xylene or mixtures thereof in various proportions without limitation. Preferably ethanol.

33) The process of claim 23, wherein the reaction temperature in step c) is from about -10°C
10 to about 20°C, preferably from about 0°C to about 5 °C and the time period is from about 15 minutes to about 5 hours, preferably from about 30 minutes to about 1 hour.

34) The process of claim 23, wherein the acetylation process is optionally carried out using a base.

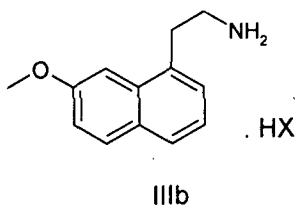
35) The process of claim 34, wherein the base is selected from the group consisting of organic
15 bases like triethylamine, tributylamine, N-methylmorpholine, pyridine, 4-dimethylaminopyridine, lutidine, collidine, inorganic bases like sodium carbonate, potassium carbonate, sodium hydroxide or potassium hydroxide. Preferably, triethylamine.

36) A process for purifying agomelatine

comprising: a) providing a solution or suspension of agomelatine or a salt thereof in
20 a solvent or a mixture of solvents or their aqueous mixtures and b) precipitating the solid from the solution, and c) recovering the agomelatine in pure form.

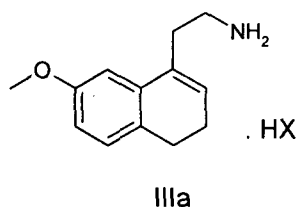
37) The process of claim 36, wherein the solvent(s) is selected from the group comprising of
25 water, alcohols like methanol, ethanol, isopropanol and ketones like acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl methyl ketone and nitriles like acetonitrile, propionitrile and hydrocarbons like n-hexane, n-heptane, cyclohexane, esters like ethyl acetate, isopropyl acetate, isobutyl acetate, t-butyl acetate and the like; or mixtures thereof in various proportions without limitation. Preferably ethyl acetate.

38) A process for the preparation of compound (7-methoxy-1-naphthyl) ethyl amine or a salt thereof formula IIIb



Wherein HX is an organic or inorganic acids such as HCl, HBr, maleic acid, oxalic acid, tartaric acid, and the like.

by aromatization of compound (7-methoxy-3,4-dihydro-1-naphthyl) ethyl amine salt of formula IIIa

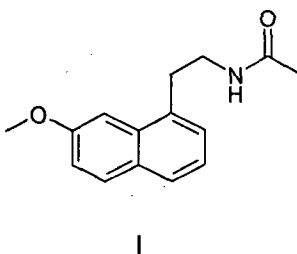


Wherein Wherein HX is an organic or inorganic acids such as HCl, HBr, maleic acid, oxalic acid, tartaric acid, and the like

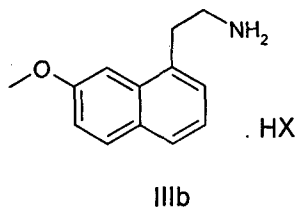
using suitable agent like sulphur, hydrogenation catalysts such as palladium carbon in

various percentages, platinum oxide, Raney Nickel, palladium oxide or mixtures thereof.

39) A process for the preparation of compound N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide of formula I



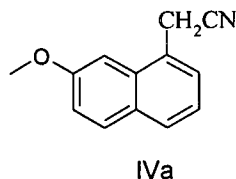
by acetylation of compound (7-methoxy-1-naphthyl) ethyl amine or a salt thereof of formula IIIb



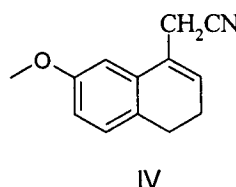
Where X is same as defined above.

using suitable acetylating agent.

40) A process for the synthesis of (7-methoxy-1-naphthyl) acetonitrile of formula (IVa)



5 by aromatization of the compound (7-methoxy-3,4-dihydro-1-naphthalenyl) acetonitrile of formula IV

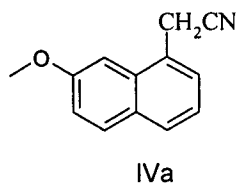


using sulphur.

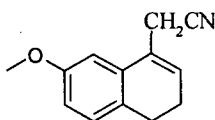
41) The process of claim 40, wherein the organic solvent is selected from the group consisting
10 of halogenated solvents like dichloromethane, ethylene dichloride, chloroform, chlorobenzene, esters like ethyl acetate, isopropyl acetate, tertiary butyl acetate, hydrocarbon solvents like n-heptane, cyclohexane, n-hexane, toluene, xylene or mixtures thereof. Preferably the reaction is being carried in the absence of solvent or neat.

42) The process of claim 40, wherein the reaction is carried out at a temperature of from about
15 50°C to about 190°C and the reaction time is from about 1 hour to about 10 hours.

43) An alternate process for the synthesis of (7-methoxy-1-naphthyl) acetonitrile of formula (IVa)



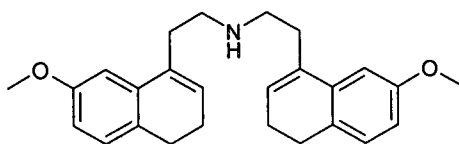
20 by aromatization of the compound (7-methoxy-3,4-dihydro-1-naphthalenyl)acetonitrile of formula IV



IV

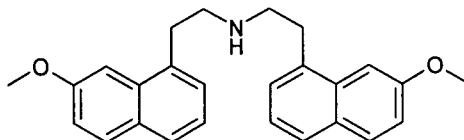
using hydrogenation catalyst in the absence of allyl compound.

- 44) The process of claim 43, wherein the hydrogenation catalyst is selected from the group consisting of palladium on carbon, platinum oxide, Raney Nickel, palladium oxide .
- 5 45) The process of claim 44, wherein the hydrogenation catalyst is palladium –carbon.
- 46) The process of claim 43, wherein the solvent is selected from the group consisting of water, alcohols like methanol, ethanol, esters like ethyl acetate, isopropyl acetate, tertiary butyl acetate, hydrocarbon solvents like toluene, xylene or mixtures thereof.
- 47) The process of claim 46, wherein the solvent used is xylene.
- 10 48) The process of claim 43, wherein the reaction is carried out from about 75°C to about reflux temperature of the solvent(s) used and the time period is from about 5 to 8 hours.
- 49) A process for purifying agomelatine (I) comprising:
 - a) providing a solution or suspension of agomelatine (I) in a solvent or a mixture of solvents or their aqueous mixtures and b) precipitating the solid from the solution, and
 - 15 c) recovering the agomelatine (I) in pure form.
- 50) The process of claim 46, wherein the solvent is selected from the group water, alcohols like methanol, ethanol, isopropanol, ketones like acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl methyl ketone, nitriles like acetonitrile, propionitrile, hydrocarbons like toluene, n-hexane, n-heptane, cyclohexane, ethers like dimethyl ether, diethyl ether,
- 20 isopropyl ether, methyl tertiary butyl ether (MTBE), tetrahydrofuran, 1,4-dioxane, esters like ethyl acetate, isopropyl acetate, isobutyl acetate, t-butyl acetate or mixtures thereof in various proportions without limitation. Preferably ethyl acetate.
- 51) Agomelatine obtained by the processes described above, has purity greater than about 98.0 area % to about 99.9area% as measured by HPLC
- 25 52) Agomelatine having individual impurities lower than about 0.15 area %, and total impurities lower than about 0.5 area% by HPLC.
- 53) Agomelatine having the compound bis-(7- methoxy- 3,4- dihydro-1-naphthyl) ethylamine represented by the structure



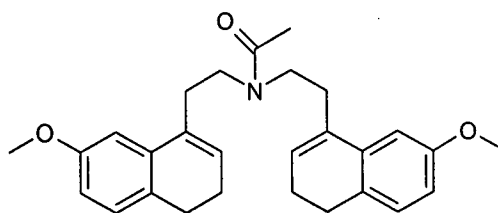
in an amount less than or equal to 0.10 area percent, as measured by HPLC.

- 54) Agomelatine having the compound bis-(7-methoxy-1-naphthyl)ethanamine represented by the structure



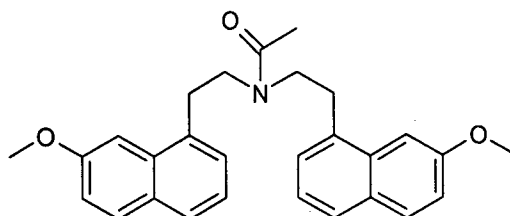
in an amount less than or equal to 0.10 area percent, as measured by HPLC.

- 55) Agomelatine having the compound bis-[(7-methoxy-3,4-dihydro-1-naphthyl)ethyl]acetamide of structure



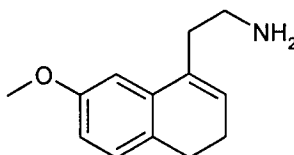
in an amount less than or equal to 0.10 area percent, as measured by HPLC.

- 56) Agomelatine having the compound bis-[(7-methoxy-1-naphthyl)ethyl]acetamide of structure



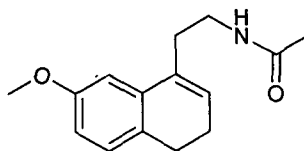
in an amount less than or equal to 0.10 area percent, as measured by HPLC.

- 57) Agomelatine having the compound represented by the structure



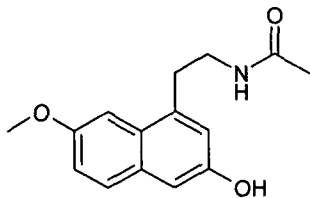
in an amount less than or equal to 0.10 area percent, as measured by HPLC.

58) Agomelatine having the compound represented by the structure

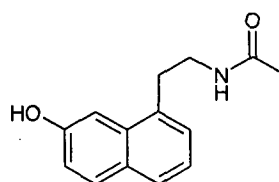


in an amount less than or equal to 0.10 area percent, as measured by HPLC.

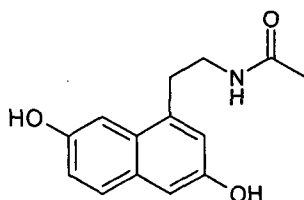
59) Agomelatine comprising the following compounds represented by the Structures



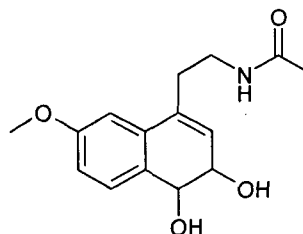
3-Hydroxy agomelatine



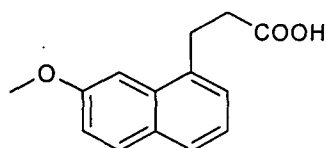
7-desmethyl agomelatine



3-Hydroxy-7-desmethyl agomelatine



3,4-dihydrodiol agomelatine



desacetamide-agomelatine-
carboxylic acid

each in an amount less than or equal to 0.10 area percent, as measured by HPLC.

60) Crystal particles of Agomelatine of preceding claims having 50 volume-percent of the particles (D_{50}) a size of less than or equal to about 400 microns, specifically less than or equal to about 300 microns, more specifically less than or equal to about 100 microns, still more specifically less than or equal to about 60 microns, and most specifically less than or equal to about 15 microns.

61) Amorphous form of agomelatine.

62) A process for the preparation of amorphous agomelatine comprising:

a) providing a solution of agomelatine alone or along with a pharmaceutically acceptable

carrier in a solvent or mixture of solvents or aqueous mixtures thereof; and

b) evaporation of the solvents or by adding anti solvent to obtain the amorphous agomelatine.

63) The process of claim 62, wherein the solvent(s) is selected from the group consisting of
5 water, alcohols like as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, and tertiary butyl alcohol, ketonic solvents like acetone, methyl ethyl ketone, methyl isobutyl ketone, 2-butanone, halogenated solvents like dichloromethane, ethylene dichloride, chloroform, nitrile solvents like acetonitrile, propionitrile, esters like ethyl acetate, isopropyl acetate, or mixtures thereof in various proportions without
10 limitation.

64) The process of claim 62, wherein the solvents used are dichloromethane, or acetone or ethyl acetate or acetonitrile or mixture thereof.

65) The process of claim 62, wherein the temperature for obtaining a clear and homogenous solution is from about 25°C to about 75°C or the boiling point of the solvent/s used,
15 preferably from about 25°C to about 40°C.

66) The process of claim 62, wherein the solution obtained is optionally filtered through celite or diatomaceous earth to separate the extraneous matter present or formed in the solution by using conventional filtration techniques known in the art.

67) The process of claim 62, wherein the removal of solvent(s) is by dry distillation under
20 vacuum or concentrating the solution, cooling to obtain amorphous form or by the lyophilisation or freeze-drying technique or by spray drying or by adding antisolvent or by sudden cooling to obtain a dry amorphous powder.

68) A pharmaceutical composition comprising agomelatine of formula I obtained by the processes described above and at least one pharmaceutically acceptable carrier.

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Fig.1. of 6

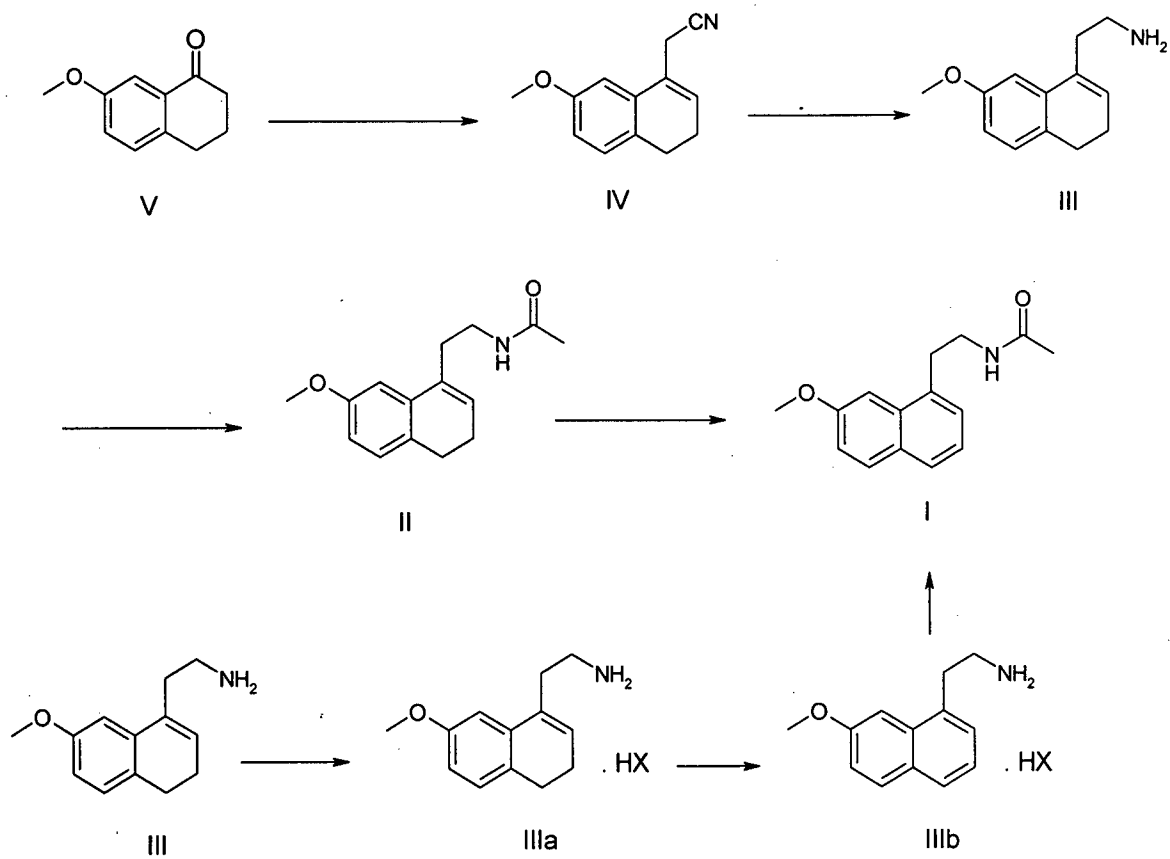


Fig. 1

Fig.2. of 6

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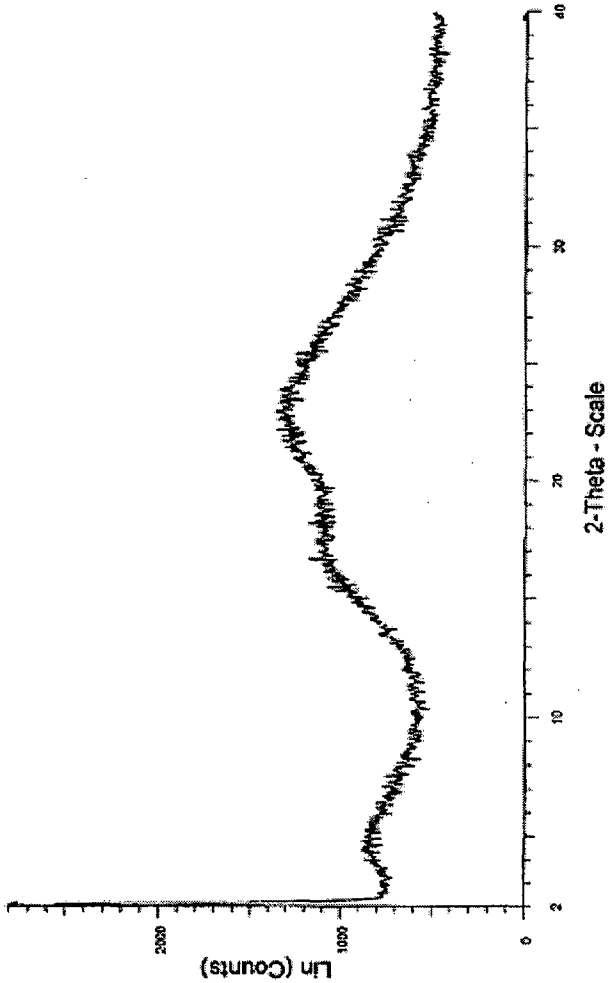


Fig 2

Fig 3 of 6

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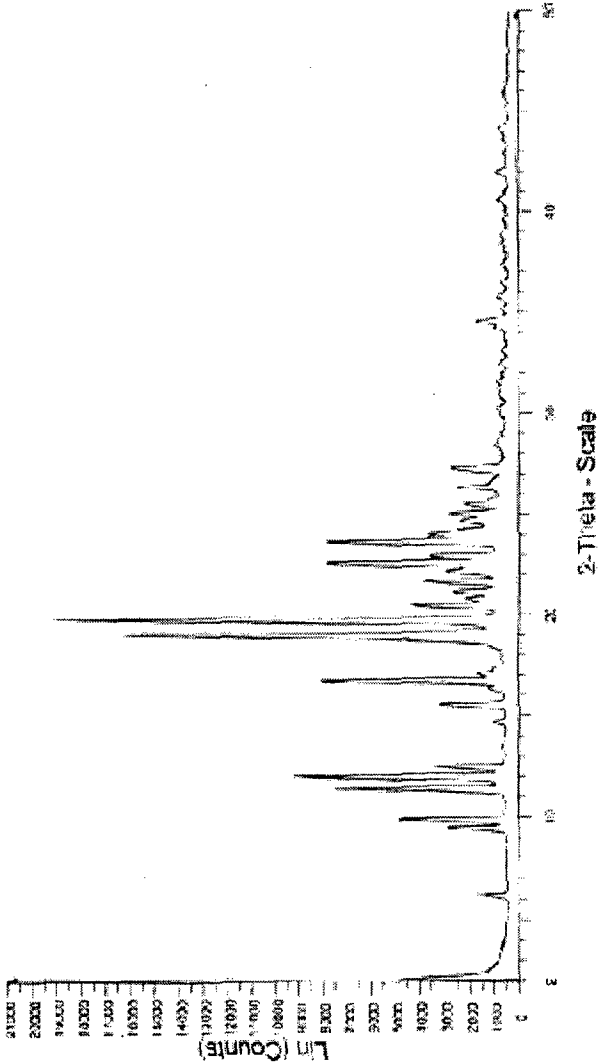


Fig 3

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Fig 4 of 6

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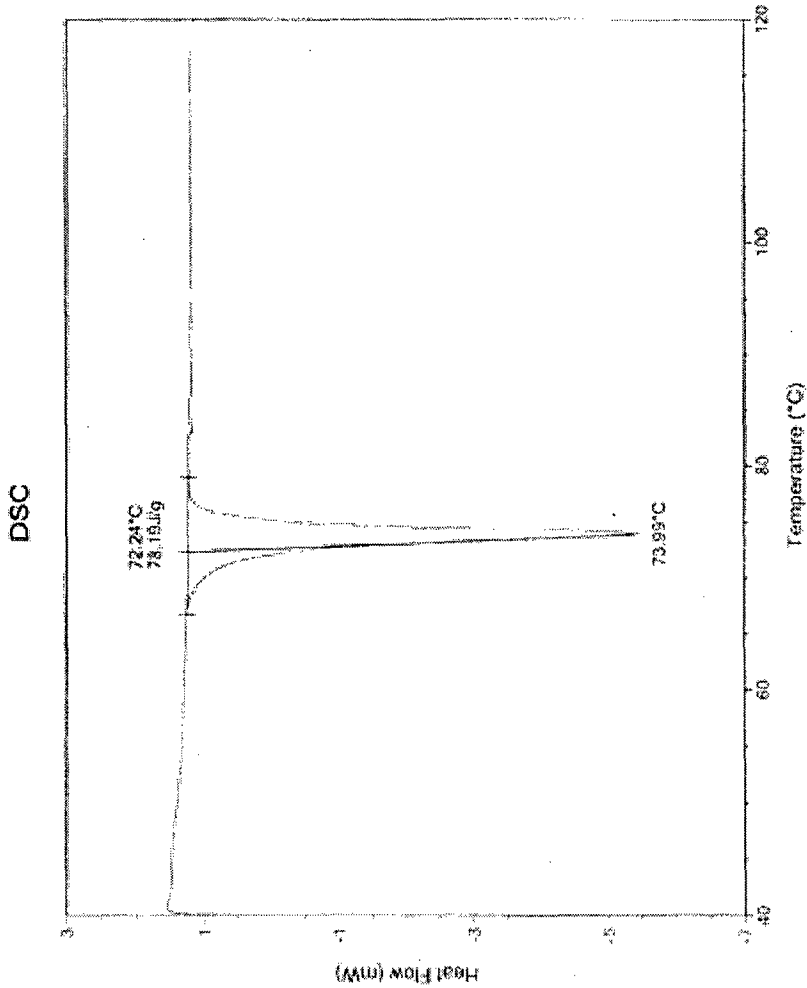


Fig 4

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Fig 5 of 6

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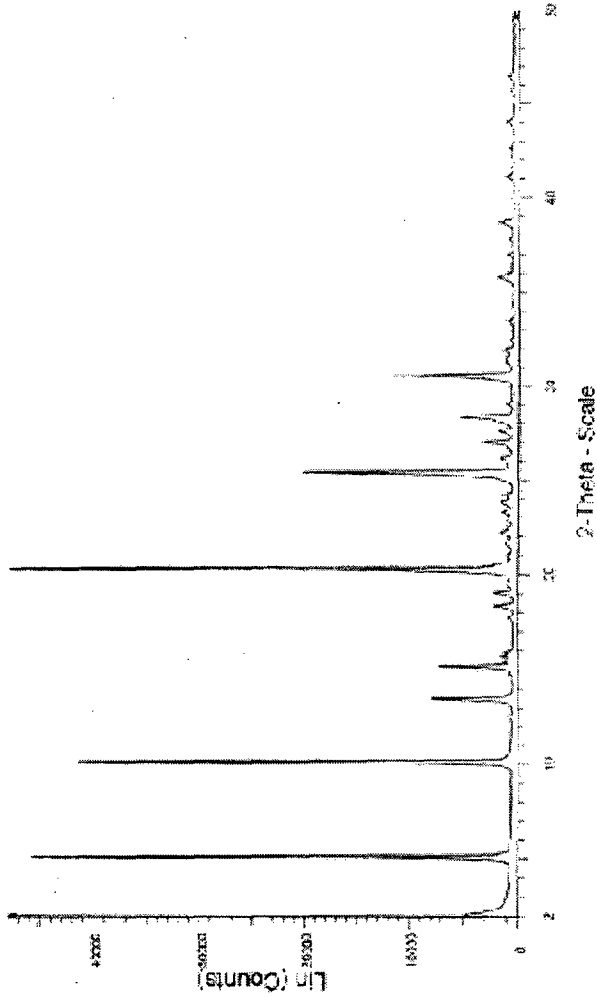


Fig 5

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Fig 6 of 6

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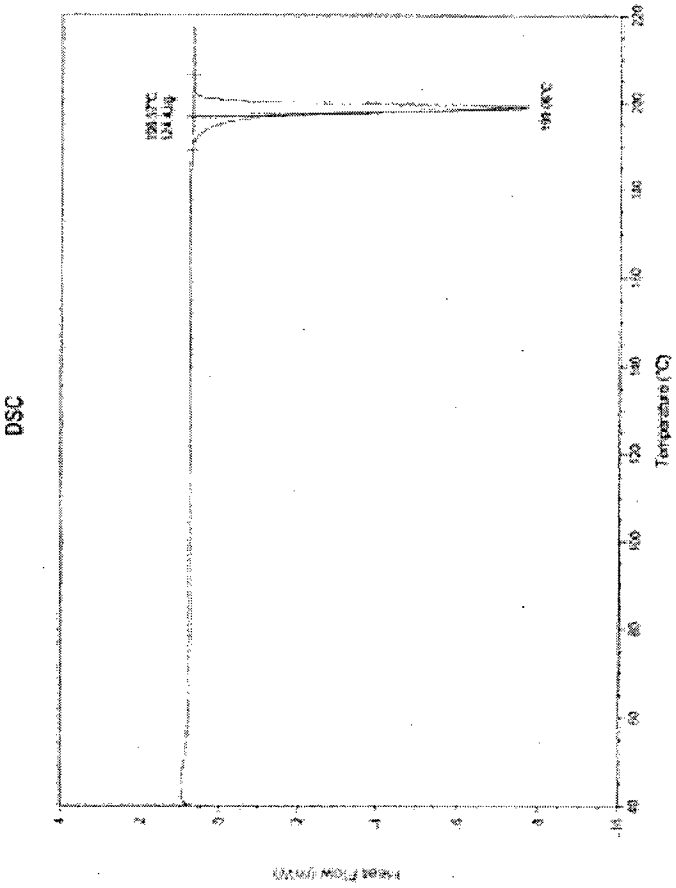


Fig 6

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN 11/00003

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07C 231/00 (2011.01)

USPC - 564/130

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)
USPC: 564/130Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 564/124; 564/133; 564/139; 564/169; 564/219 (see search terms below)

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

WEST: PGPB, USPT, USOC, EPAB, JPAB

GOOGLE: Scholar/patents: 2-(7-methoxy-1-naphthyl)ethyl acetamide crystal preparation agomelatine reduction raney nickel
cyanoacetic acid naphthyl tetrahydro\$ aromatization sulfur toluene bis\$ impurity hplc acetic anhydride acetylation amorphouse crystalline

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2005/01882276 A1 (SOUVIE et al.) 18 August 2005 (18.08.2005) para [0001], [0019]-[0020], [0023]-[0025];[0071];[0077];[0079];[0079]-[0086];[0094]	1-2, 4, 6-39, 49-60 ----- 3, 5, 40-48, 62-67
X --- Y	US 2010/0036165 A1 (MARTINS et al.) 11 February 2010 (11.02.2010) para [0008]	61 ----- 62-67
Y	TANG et al. Improved Synthesis of 3-Methylcholanthrene. Journal of Organic Chemistry, 1981, Vol 46, pp 3429-3432; pg 3429, abstract; col 2, para 2; pg 3430, Scheme 1, Compounds 8a,b to 2a,b; pg 3432, col 2, para 2 "compound 2A"	3, 5, 40-48

☐ 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

15 September 2011 (15.09.2011)

Date of mailing of the international search report

28 SEP 2011

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

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN 11/00003

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 68
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.