Title
New process for the synthesis of agomelatine

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Applicant(s)
Les Laboratoires Servier

Inventor(s)
Hardouin, Christophe; Lecouve, Jean-Pierre

Agent / Attorney
Allens Patent & Trade Mark Attorneys, Deutsche Bank Place Corner Hunter and Phillip Streets, SYDNEY, NSW, 2000

Related Art
EP 1564202 B1
NEW PROCESS FOR THE SYNTHESIS OF AGOMELATINE

Abstract

A process for the industrial synthesis of the compound of formula (I) is described.

![Chemical Structure](image)

(I)
Invention Title: New process for the synthesis of agomelatine

The following statement is a full description of this invention, including the best method of performing it known to us:
The present invention relates to a new process for the industrial synthesis of agomelatine, or \( N-[2-(7\text{-methoxy-1-naphthyl})\text{ethyl}]\text{acetamide} \), of formula (I):

\[
\text{MeO} \quad \text{NHCOMe}
\]

Agomelatine, or \( N-[2-(7\text{-methoxy-1-naphthyl})\text{ethyl}]\text{acetamide} \), has valuable pharmacological properties.

It has, in fact, the double characteristic of being, on the one hand, an agonist of receptors of the melatonergic system and, on the other hand, an antagonist of the \( 5\text{-HT}_{2c} \) receptor. These properties provide it with activity in the central nervous system and, more especially, in the treatment of major depression, seasonal affective disorder, sleep disorders, cardiovascular pathologies, pathologies of the digestive system, insomnia and fatigue due to jet-lag, appetite disorders and obesity.

Agomelatine, its preparation and its use in therapeutics have been described in European patent specifications EP 0 447 285 and EP 1 564 202.

In view of the pharmaceutical value of this compound, it has been important to be able to produce it using an effective industrial synthesis process which is readily transferable to the industrial scale and which provides agomelatine in a good yield and with excellent purity.

Patent specification EP 0 447 285 describes production of agomelatine in eight steps starting from 7-methoxy-1-tetralone, in an average yield of less than 30 %. In patent specification EP 1 564 202, the Applicant developed a new, much more effective and industrialisable synthesis route in only four steps starting from 7-methoxy-1-tetralone that
makes it possible to obtain agomelatine in highly reproducible manner in a well-defined crystalline form. However, the search for new synthesis routes, especially starting from starting materials that are less costly than 7-methoxy-1-tetralone, is currently still relevant.

The Applicant has continued his investigations and has developed a new process for the synthesis of agomelatine starting from 3-methoxyacenaphthoquinone: this new starting material has the advantage of being simple, readily obtainable in large quantities at less cost. 3-Methoxyacenaphthoquinone moreover also has the advantage of having a naphthalene ring system in its structure, which avoids inclusion of an aromatisation step into the synthesis, a step that is always problematic from an industrial point of view.

This new process moreover makes it possible to obtain agomelatine in reproducible manner and without requiring laborious purification, with a purity that is compatible with its use as a pharmaceutical active ingredient.

More specifically, the present invention relates to a process for the industrial synthesis of the compound of formula (I):

\[
\text{MeO} \quad \text{NHCOMe} \quad \text{MeO}
\]

(I),

which process is characterised in that 3-methoxyacenaphthoquinone of formula (II):

\[
\text{MeO} \quad \text{O} \quad \text{O}
\]

(II)

is reacted in the presence of a strong base to yield the compound of formula (III):
which is subjected to amination to yield the compound of formula (IV):

which is subjected to the action of a reducing system to yield the compound of formula (V):

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

The compound of formula (II) is accessible to the person skilled in the art by means of conventional chemical reactions and/or chemical reactions described in the literature.

Advantageously, the conversion of the compound of formula (II) into the compound of formula (III) according to the invention is carried out using NaNH₂, ((CH₃)₃-Si)₂NLi (LiHMDS) or ((CH₃)₃-Si)₂NNa (NaHMDS).
The amination reaction is preferably carried out using NH₄Cl and propylphosphonic anhydride.

As the reducing system in the conversion of the compound of formula (IV) into the compound of formula (V) according to the invention preference is given to LiAlH₄ or to the couple BH₃·THF/AlCl₃.

This process is 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 simple, low-cost starting material;

- it makes it possible to avoid an aromatisation reaction because the naphthalene ring system is present in the starting substrate;

- finally, the compound of formula (I) obtained has, in reproducible manner, the characteristics of the crystalline form described in patent specification EP1564202.

The compound of formula (IV) obtained according to the process of the invention is new and useful as an intermediate in the synthesis of agomelatine, wherein it is subjected to a reduction reaction, then to a coupling reaction with acetic anhydride.

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as 'comprises' or 'comprising', will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to
the present invention as it existed in Australia before the priority date of each claim of this specification.

The Examples hereinbelow illustrate the invention without limiting it in any way.

Example 1: \( N-[2-(7\text{-Methoxy-1-naphthyl})\text{ethyl}]\text{acetamide} \)

**Step A: (7-Methoxy-1-naphthyl)(oxo)acetic acid**

In a reactor, 4 mg of 18-crown-6 ether and then 230 mg of \( \text{NaNH}_2 \) are successively introduced into a suspension of 100 mg of 3-methoxyacenaphthoquinone in 1 ml of DMSO. The mixture is stirred for 30 minutes at ambient temperature. Water (2 ml) is then added, followed by 2N HCl solution (3 ml). After two extractions with ethyl acetate, the solvents are dried over \( \text{Na}_2\text{SO}_4 \) and then evaporated off to yield the title product in the form of a yellow solid in a yield of 88 % and with a chemical purity of more than 94 %.

*Melting point:* 99°C

**Step B: 2-(7-Methoxy-1-naphthyl)-2-oxoacetamide**

In a reactor, 1 g of the compound obtained in Step A is introduced into 30 ml of acetonitrile, and there are then added 4.39 g of propylphosphonic anhydride and 438 mg of \( \text{NH}_4\text{CI} \) and, at the end of the addition, 3.8 ml of diisopropylamine at ambient temperature. The solution is stirred for 4 hours under nitrogen, the solvents are then evaporated off, the residue is taken up in saturated aqueous NaCl solution, and extraction with ethyl acetate is carried out. The solvents are then dried over \( \text{Na}_2\text{SO}_4 \) and then evaporated off to yield the title product in the form of an orange solid in a yield of 80 % and with a chemical purity of 90 %.

*Melting point:* 112°C

**Step C: 2-(7-Methoxy-1-naphthyl)ethanamine**

480 mg of the compound obtained in Step B dissolved in THF (20 ml) are introduced into a reactor, followed by 2 eq. of \( \text{AlCl}_3 \) and finally, slowly, 6 eq. of \( \text{BH}_3\text{THF} \) solution, and the reaction mixture is stirred for 2.5 hours. Water (12 ml) is then added, followed by 25 ml of 1N sodium hydroxide solution together with 800 mg of solid sodium hydroxide, and three extractions with methyl tert-butyl ether (20 ml) are carried out. The solvents are then dried...
over Na$_2$SO$_4$ and then evaporated off to yield the title product in the form of a yellow oil in a yield of 80 % and with a chemical purity of 95%.

**Step D: N-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide**

In a reactor, 5 g of the compound obtained in Step C and 2 g of sodium acetate are introduced into ethanol. The mixture is stirred, 2.3 g of acetic anhydride are then added, the reaction mixture is heated to reflux and 20 ml of water are added. The reaction mixture is allowed to return to ambient temperature and the precipitate obtained is filtered off, washed with an ethanol/water 35/65 mixture to yield the title product in a yield of 80 % with a chemical purity of 99 %.

**Melting point:** 108°C

**Example 2:** Determination of the crystalline form of the compound N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide obtained in Example 1

Data recording was carried out using the D8 high-resolution diffractometer from Bruker AXS with the following parameters: an angular range of 3°-90° in terms of 2θ a step of 0.01° and 30 s per step. The N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide powder obtained in Example 1 was deposited on a transmission mounting support. The X-ray source is a copper tube (\(\lambda\)CuK$_{a1}$ = 1.54056 Å). The mounting includes a front monochromator (Ge(111) crystal) and an energy-resolved solid-state detector (MXP-D1, Moxtec-SEPH).

The compound is well crystallised: the line width at half-height is of the order of 0.07° in terms of 2θ.

The following parameters were accordingly determined:

- crystal structure of unit cell: monoclinic
- unit cell parameters: \(a = 20.0903\) Å, \(b = 9.3194\) Å, \(c = 15.4796\) Å, \(\beta = 108.667°\)
- space group: P2$_1$/n
- number of molecules in the unit cell: 8
- volume of the unit cell: \(V_{\text{unit cell}} = 2746.742\) Å$^3$
- density: \(d = 1.13\) g/cm$^3$. 
Example 3: Determination, by means of the X-ray powder diffraction diagram, of the crystalline form of the N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide compound obtained in Example 1

The crystalline form of the compound obtained in Example 1 is characterised by the following X-ray powder diffraction diagram, measured using a Siemens D5005 diffractometer (copper anticathode) and expressed in terms of interplanar distance d, Bragg's angle 2 theta, and relative intensity (expressed as a percentage in relation to the most intense line):

<table>
<thead>
<tr>
<th>Angle 2 theta (°)</th>
<th>Interplanar distance d (Å)</th>
<th>Intensity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.26</td>
<td>9.544</td>
<td>23</td>
</tr>
<tr>
<td>10.50</td>
<td>8.419</td>
<td>13</td>
</tr>
<tr>
<td>15.34</td>
<td>5.771</td>
<td>24</td>
</tr>
<tr>
<td>17.15</td>
<td>5.165</td>
<td>100</td>
</tr>
</tbody>
</table>
The claims defining the invention are as follows:

1. A process for the industrial synthesis of the compound of formula (I)

   \[
   \text{MeO} \quad \text{NHCOMe} \\
   \text{(I)}.
   \]

   wherein 3-methoxyacenaphthoquinone of formula (II):

   \[
   \text{MeO} \\
   \text{O} \\
   \text{O} \\
   \text{MeO} \\
   \text{(II)}
   \]

   is reacted in the presence of a strong base to yield the compound of formula (III):

   \[
   \text{MeO} \\
   \text{HO} \\
   \text{C} \\
   \text{O} \\
   \text{MeO} \\
   \text{(III)}.
   \]

   which is subjected to amination to yield the compound of formula (IV):

   \[
   \text{MeO} \\
   \text{H}_2\text{N} \\
   \text{C} \\
   \text{O} \\
   \text{MeO} \\
   \text{(IV)}.
   \]

   which is subjected to the action of a reducing system to yield the compound of formula (V):
which is successively subjected to the action of sodium acetate and then acetic anhydride to yield the compound of formula (I), which is isolated in the form of a solid.

2. The process for the synthesis of the compound of formula (I) according to claim 1, wherein the conversion of the compound of formula (II) into the compound of formula (III) is carried out using NaNH₂.

3. The process for the synthesis of the compound of formula (I) according to claim 1, wherein the conversion of the compound of formula (IV) into the compound of formula (V) is carried out using the couple BH₃·THF/AlCl₃.

4. The compound of formula (IV)

for use as an intermediate in the synthesis of agomelatine.

5. Use of the compound of formula (IV) according to claim 4 in the synthesis of agomelatine.
6. Use of compound of formula (II)

![Chemical Structure](image)

(II)

in the synthesis of agomelatine.

7. Use of compound of formula (III)

![Chemical Structure](image)

(III),

in the synthesis of agomelatine.

8. The process for the synthesis of agomelatine according to claim 1 starting from a compound of formula (III), wherein the compound of formula (III) is obtained by the synthesis process according to claim 1 or claim 2.

9. The process for the synthesis of agomelatine according to claim 1 starting from a compound of formula (IV), wherein the compound of formula (IV) is obtained by the synthesis process according to claim 1 or claim 2.

10. Process for the synthesis of agomelatine according to claim 1 starting from a compound of formula (V), wherein the compound of formula (V) is obtained by the synthesis process according to any one of claims 1 to 3.
11. A process for the industrial synthesis of the compound of formula (I) substantially as hereinbefore described with reference to any one of the Examples.