

Bogotá D.C., 10 de noviembre de 2015

Doctor:

JOSÉ LUIS SALAZAR LÓPEZ

Director de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Industria y Turismo

Ciudad

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 13-156552- -00017-0000

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Act. 329 CTOINFORMACION Folios: 20

A

Referencia: Respuesta Oficio 12959 del 3 de noviembre de 2015

Radicado No.: 13-156552

Patente de invención: "PROCEDIMIENTO DE SÍNTESIS DE LA AGOMELATINA A PARTIR DE BUT-3-ENONITRILO Y METOXIFENILETANONA SUSTITUÍDA"

CLAUDETTE VERNOT HERNÁNDEZ, mayor de edad con domicilio en la ciudad de Bogotá, identificada con la cédula de ciudadanía No. 51.722.517 de Bogotá, abogada en ejercicio portadora de la tarjeta profesional No. 57.111 del Consejo Superior de la Judicatura, en mi calidad de apoderada de la sociedad **LES LABORATOIRES SERVIER**, conforme al poder que obra en el expediente, por medio del presente escrito y encontrándome dentro del término concedido, me dirijo a Usted para dar respuesta al oficio de la referencia.

I. DESCORRE TRASLADO

En atención a lo dispuesto mediante Oficio No. 12959, notificado por fijación en lista de fecha 3 de noviembre de 2015, me permito dar respuesta al Recurso de Reposición interpuesto por la sociedad **LAFRANCOL S.A.S.**, contra la Resolución 38739 del 30 de julio de 2015, por medio de la cual se otorga patente de invención a la creación titulada "PROCEDIMIENTO DE SÍNTESIS DE LA AGOMELATINA A PARTIR DE BUT-3-ENONITRILO Y METOXIFENILETANONA SUSTITUÍDA", con los siguientes argumentos:

La presente invención está dirigida a una ruta de síntesis específica para obtener agomelatina a partir de un compuesto xantato de fórmula (III), en donde los compuestos de fórmula (IV), (V), (VI) y (VII) son compuestos intermediarios.

La Oposición cita los siguientes dos documentos del arte previo:

- EP0447285
- US5225442

De hecho, US5225442 es una solicitud divisional de US5194614 la cual es la solicitud correspondiente de EP0447285 presentada en los Estados Unidos de América.

En resumen, la información divulgada en EP0447285 y US522442 es básicamente la misma dado que los dos documentos divulgan la misma invención.
Como recordatorio:

- (i) EP0447285 ya había sido citado por Lanfrancol en la Oposición presentada en 2014;
- (ii) Este documento también es citado en la especificación de la presente solicitud.

Este documento describe un proceso de 8 pasos para la preparación de agomelatina a partir de 7-metoxi-1-tetralona. Más precisamente, este proceso involucra la acción del bromoacetato de etilo, seguido de aromatización y saponificación para obtener el ácido correspondiente, el cual es luego convertido en acetamida y, posteriormente, es deshidratado para obtener (7-metoxi-1-naftil)acetonitrilo, a lo cual le sigue reducción, y luego condensación del cloruro de acetilo.

La ruta de síntesis divulgada en EP0447285 es dramáticamente diferente del proceso de la invención, ya que esta se basa en reacciones químicas clásicas (no en reacciones de radicales) y los intermediarios clave son también marcadamente diferentes.

Una vez más, nos gustaría destacar las siguientes características del proceso de la invención:

- El cianuro de alilo y un compuesto xantato son utilizados como materiales de partida en el proceso de la invención. Estos nuevos materiales de partida tienen la ventaja de ser simples y fácilmente obtenibles en grandes cantidades a un costo menor, mientras que la preparación de 7-metoxi-1-tetralona utilizado en EP0447285 es cara.

- Esta ruta de síntesis está basada en llevar a cabo reacciones de radicales libres que no son muy comúnmente utilizadas, pero que son sin embargo muy eficaces. La conversión de estas reacciones a una escala industrial utilizando reactores de flujo continuo es prometedora, puesto que se vuelve más simple el controlar la propagación de la reacción en cadena.

- Por último, este nuevo proceso además hace posible la obtención de agomelatina de manera reproducible y sin necesidad de purificación laboriosa, con una pureza que es compatible con su uso como un ingrediente farmacéutico activo. De hecho, la agomelatina se puede, en consecuencia, sintetizar en 6 pasos en el curso de los cuales sólo uno de los intermediarios es aislado.

Como consecuencia, el proceso de la invención no puede ser anticipado basado en el conocimiento técnico divulgado en EP0447285. Es un proceso alternativo que es compatible con requisitos industriales.

Por todas estas razones, la presente invención es novedosa y cumple con el requisito de nivel inventivo con base en EP0447285.

Observamos que el Oponente no presenta ningún argumento preciso y serio que desafíe la patentabilidad de nuestra invención. Sólo se mencionan declaraciones generales.

Además, el Oponente afirma que el Informe de Búsqueda Internacional de la solicitud PCT correspondiente indica que la presente invención carece de novedad y nivel inventivo, lo cual no es cierto. Por favor ver adjunto la Opinión Escrita Internacional de W02012/113999 en donde la novedad y el nivel inventivo del presente caso han sido reconocidos y tenga en cuenta también que los casos correspondientes han sido otorgados en los Estados Unidos de América.

Consideramos que los argumentos expuestos a lo largo de este escrito permitirán superar las objeciones presentadas por la recurrente.

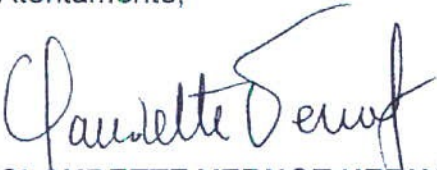
II. ANEXOS

1. **Anexo 1:** Reporte de Búsqueda Internacional PCT/FR2012/000005
2. **Anexo 2:** Opinión Escrita Internacional de W02012/113999
3. **Anexo 3:** Patente US 8,853,449 B2

III. NOTIFICACIONES

Recibiré notificaciones en la secretaria de su Despacho, en la Carrera 13A # 89 – 38 Oficina 539 de esta ciudad y/o en el correo electrónico estrategia@estrategiajuridica.net.

Atentamente,



CLAUDETTE VERNOT HERNÁNDEZ

C.C. No. 51.722.517 de Bogotá

T.P. No. 57.111 del C.S. de la J

ANEXO No. 1

REPORTE DE BÚSQUEDA INTERNACIONAL PCT/FR2012/000005

PROCEDIMIENTO DE SÍNTESIS DE LA AGOMELATINA A PARTIR DE BUT-3-ENONITRILO Y
METOXIFENILETANONA SUSTITUÍDA

LES LABORATOIRES SERVIER

INTERNATIONAL SEARCH REPORT

International application No
PCT/FR2012/000005

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	C07C231/02	C07C233/18
	C07C253/30	C07C255/37
		C07C255/40
ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
C07C		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
EPO-Internal, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 564 202 A1 (SERVIER LAB [FR]) 17 August 2005 (2005-08-17) cited in the application claims; examples 1,2	1-20
A	EP 0 447 285 A1 (ADIR [FR]) 18 September 1991 (1991-09-18) cited in the application page 5, line 32 - page 6, line 35; example 1	1-20
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* 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 document 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		Date of mailing of the international search report
8 March 2012		26/03/2012
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Ginoux, Claude

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/FR2012/000005

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1564202	A1	17-08-2005	AP 1839 A 10-04-2008
		AR 047741 A1 15-02-2006	
		AT 407921 T 15-09-2008	
		AU 2005200616 A1 01-09-2005	
		AU 2010207746 A1 26-08-2010	
		BR PI0500393 A 27-09-2005	
		CA 2495967 A1 13-08-2005	
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		CU 23515 A3 19-05-2010	
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		ES 2314588 T3 16-03-2009	
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		HK 1078563 A1 21-09-2007	
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		KR 20060042943 A 15-05-2006	
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		PT 1564202 E 22-10-2008	
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		SI 1564202 T1 31-12-2008	
		UA 78825 C2 25-04-2007	
		US 2005182276 A1 18-08-2005	
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		WO 2005077887 A1 25-08-2005	
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EP 0447285	A1	18-09-1991	AT 89263 T 15-05-1993
			AU 634350 B2 18-02-1993
			CA 2036876 A1 28-08-1991
			DE 69100079 D1 17-06-1993
			DE 69100079 T2 09-12-1993
			DE 122009000040 I1 05-11-2009
			DK 0447285 T3 16-08-1993
			EP 0447285 A1 18-09-1991
			ES 2059069 T3 01-11-1994
			FR 2658818 A1 30-08-1991
			HK 57197 A 09-05-1997
			IE 910640 A1 28-08-1991
			JP 2624901 B2 25-06-1997
			JP 7048331 A 21-02-1995
			LU 91587 A9 22-09-2009
			NL 300396 I1 01-10-2009
			OA 9482 A 15-11-1992
			PT 96890 A 31-10-1991
			US 5194614 A 16-03-1993
			US 5225442 A 06-07-1993

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/FR2012/000005

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 5318994 A	07-06-1994
		ZA 9101403 A	27-11-1991

ANEXO No. 2

OPINIÓN ESCRITA INTERNACIONAL DE W02012/113999

PROCEDIMIENTO DE SÍNTESIS DE LA AGOMELATINA A PARTIR DE BUT-3-ENONITRILO Y
METOXIFENILETANONA SUSTITUÍDA

LES LABORATOIRES SERVIER

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

TRANSLATION
PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference 20098-P10		Date of mailing (day/month/year) see form PCT/ISA/210
FOR FURTHER ACTION See paragraph 2 below		
International application No. PCT/FR2012/000005	International filing date (day/month/year) 04.01.2012	Priority date (day/month/year) 05.01.2011
International Patent Classification (IPC) or both national classification and IPC C07C231/02, C07C233/18, C07C253/30, C07C255/37, C07C255/40		
Applicant LES LABORATOIRES SERVIER		

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/EP	Date of completion of this opinion	Authorized officer
Facsimile No.		Telephone No.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/FR2012/000005

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
- a. type of material
- ☐ a sequence listing
- ☐ table(s) related to the sequence listing
- b. format of material
- ☐ on paper
- ☐ in electronic form
- c. time of filing/furnishing
- ☐ contained in the international application as filed
- ☐ filed together with the international application in electronic form
- ☐ furnished subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/FR2012/000005

Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement		
1. Statement			
Novelty (N)	Claims	1-20	YES
	Claims		NO
Inventive step (IS)	Claims	1-20	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-20	YES
	Claims		NO
2. Citations and explanations:			
Reference is made to the following document: EP 1 564 202 A1 (SERVIER LAB [FR]) 17 August 2005 (2005-08-17) Document D1, which is considered to be the prior art closest to the subject matter of claim 1, describes a method for preparing N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide (agomelatine) from 7-methoxy-1-tetralone (see relevant passages cited in the search report). D1 discloses the reaction of tetralone with cyanoacetic acid, which produces the intermediate compound (7-methoxy-3,4-dihydro-1-naphthalenyl)acetonitrile. Consequently, the subject matter of claim 1 differs from said known method in that the reaction uses allyl cyanide and a dithiocarbonate with formula (III) as starting materials; it is therefore novel (PCT Article 33(2)). The problem addressed by the present invention can be			

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/FR2012/000005

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement

considered to be that of developing an alternative method for preparing agomelatine.

The solution to this problem as proposed in claim 1 of the present application is considered to involve an inventive step (PCT Article 33(3)), for the following reasons:

a person skilled in the art would not have found any indication in the prior art that would suggest replacing 7-methoxy-1-tetralone with a compound such as the compound of formula (III) as starting material for synthesizing agomelatine.

Claims 2 to 14 as well as claims 19 and 20 (for the latter however, see Box VIII) are dependent on claim 1 and as such likewise meet the requirements in respect of novelty and inventive step.

The compounds of formula (V) and (VI) claimed in claims 15 and 17, respectively, are not known in the prior art and are intermediates in the synthesis of agomelatine. The subject matter of said claims is therefore also considered to be novel and to involve an inventive step. The same applies to the use of said compounds in the synthesis of agomelatine, claimed in claims 16 and 18.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/FR2012/000005

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The subject matter of dependent claims 19 and 20 is not clear since it appears to be redundant in relation to the subject matter of claim 1 (PCT Article 6).

ANEXO No. 3

PATENTE US 8,853,449 B2

PROCEDIMIENTO DE SÍNTESIS DE LA AGOMELATINA A PARTIR DE BUT-3-ENONITRILO Y
METOXIFENILETANONA SUSTITUÍDA

LES LABORATOIRES SERVIER



US008853449B2

(12) **United States Patent**
Zard et al.

(10) **Patent No.:** **US 8,853,449 B2**
(45) **Date of Patent:** **Oct. 7, 2014**

(54) **PROCESS FOR THE SYNTHESIS OF AGOMELATINE**

(75) Inventors: **Samir Zard**, Gif-sur-Yvette (FR);
Béatrice Sire, Palaiseau (FR); **Mehdi Boumediene**, Choisy le Roi (FR)

(73) Assignee: **Les Laboratoires Servier**, Suresnes Cedex (FR)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/977,799**

(22) PCT Filed: **Jan. 4, 2012**

(86) PCT No.: **PCT/FR2012/000005**
§ 371 (c)(1),
(2), (4) Date: **Jul. 1, 2013**

(87) PCT Pub. No.: **WO2012/113999**
PCT Pub. Date: **Aug. 30, 2012**

(65) **Prior Publication Data**
US 2013/0289307 A1 Oct. 31, 2013

(30) **Foreign Application Priority Data**
Jan. 5, 2011 (FR) 11 00024

(51) Int. Cl.
C07C 231/06 (2006.01)
C07C 255/33 (2006.01)
C07C 231/02 (2006.01)
C07C 255/40 (2006.01)
C07C 255/37 (2006.01)
C07C 253/30 (2006.01)
C07C 233/18 (2006.01)

(52) U.S. Cl.
CPC **C07C 231/06** (2013.01); **C07C 231/02** (2013.01); **C07C 255/40** (2013.01); **C07C**

2102/10 (2013.01); **C07C 255/37** (2013.01);
C07C 253/30 (2013.01); **C07C 233/18** (2013.01)

USPC **564/124**; 564/130; 558/426; 558/428; 558/430

(58) **Field of Classification Search**
CPC **C07C 231/06**; **C07C 255/33**
USPC **564/124**, 130; 558/426, 428, 430
See application file for complete search history.

(56) **References Cited**
U.S. PATENT DOCUMENTS

5,318,994 A 6/1994 Andrieux et al.
7,544,839 B2 6/2009 Souvie et al.

FOREIGN PATENT DOCUMENTS

EP 0447285 9/1991
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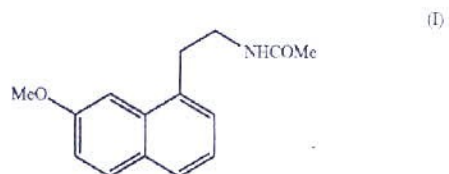
OTHER PUBLICATIONS

International Search Report for PCT/FR2012/000005 of Mar. 8, 2012.
International Preliminary Report on Patentability Written Opinion for PCT/FR2012/000005, 2012.

Primary Examiner — Shailendra Kumar
(74) *Attorney, Agent, or Firm* — Hueschen and Sage

(57) **ABSTRACT**

Process for the industrial synthesis of the compound of formula (I)



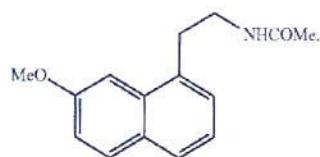
17 Claims, No Drawings

1

PROCESS FOR THE SYNTHESIS OF AGOMELATINE

This application is a 371 of PCT/FR12/00005, filed Jan. 4, 2012.

The present invention relates to a new process for the industrial synthesis of agomelatine, or N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide, of formula (I):



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

It has, in fact, the double characteristic of being, on the one hand, an agonist of receptors of the melatoninergic system and, on the other hand, an antagonist of the 5-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 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.

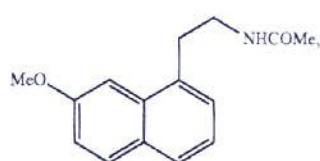
The Applicant has continued his investigations and has developed a new process for the synthesis of agomelatine starting from allyl cyanide and a xanthate compound; these new starting materials have the advantage of being simple and readily obtainable in large quantities at less cost.

This synthesis route is based on carrying out free radical reactions that are not very commonly used but are nevertheless very effective. Converting these reactions to the industrial scale using continuous-flow reactors is promising as it becomes simpler to control propagation of the chain reaction.

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. Indeed, agomelatine can accordingly be synthesised in 6 steps in the course of which only two of the intermediates are isolated.

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

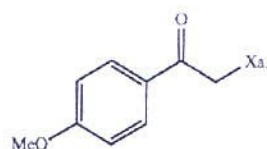
2



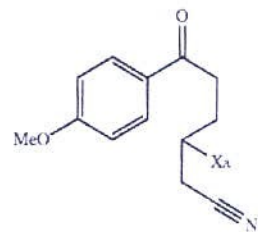
which process is characterised in that allyl cyanide of formula (II):



is reacted, in the presence of a free radical initiator, with a compound of formula (III):

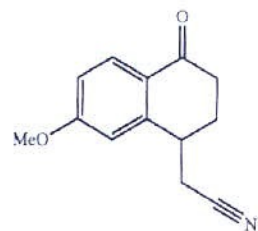


wherein Xa represents a group —S—C(S)—OR in which R represents a linear or branched (C₁-C₆)alkyl group, to yield the compound of formula (IV):



wherein Xa is as defined hereinbefore,

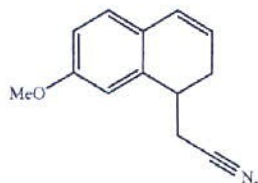
it being possible for this latter compound optionally to be isolated, before being subjected to a cyclisation reaction in the presence of a free radical initiator in order to form the compound of formula (V):



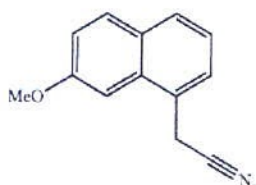
which compound of formula (V) also optionally may be isolated,

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which is subjected to a reduction-dehydration reaction to yield the compound of formula (VI):

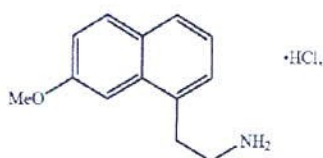


which is then subjected to an aromatisation reaction to yield the compound of formula (VII):



which is subjected to reduction using hydrogen in the presence of Raney nickel in a polar protic medium and to reaction with acetic anhydride to yield the compound of formula (I), which is isolated in the form of a solid.

In a preferred embodiment of the invention, the compound of formula (VII) is then subjected to reduction using hydrogen in the presence of Raney nickel in an ammoniacal ethanol medium and then converted into a salt using hydrochloric acid to yield the compound of formula (VIII):



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.

Alternatively, the compound of formula (VII) can be subjected to reduction by hydrogen in the presence of Raney nickel in a medium comprising acetic anhydride in a polar protic medium to yield the compound of formula (I), which is isolated in the form of a solid.

In a preferred compound of formula (III), Xa represents a group $-S-C(S)-OC_2H_5$.

In the processes according to the invention, initiation of the free radical reactions is carried out by thermal means. Preferably, the reaction mixture is heated to a temperature of from 50° C. to 140° C. Even more preferably, cyclisation is carried out at a temperature of from 130 to 135° C.

Peroxides are free radical initiators that are especially suitable for carrying out the step of addition of the compound of formula (II) to the compound of formula (III), or for performing cyclisation of the compound of formula (IV) to form the compound of formula (V). By way of example, there may be mentioned, especially, diisobutyl peroxide, cumyl peroxy-

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neodecanoate, tert-amyl peroxyneodecanoate, di(2-ethyl-hexyl)peroxydicarbonate, tert-butyl peroxyneodecanoate, dibutyl peroxydicarbonate, dicetyl peroxydicarbonate, dimyristyl peroxydicarbonate, tert-butyl peroxyneohexanoate, tert-amyl peroxy-pivalate, didecanoate peroxide, tert-amyl peroxy-2-ethylhexanoate, tert-butyl peroxyisobutyrate, 1,4-di(tert-butylperoxycarbonyl)cyclohexane, tert-butyl peroxyacetate, tert-butyl peroxybenzoate, di-tert-amyl peroxide, tert-butyl cumyl peroxide, bis(tert-butyl)peroxide, dicumyl peroxide, dilauroyl peroxide (DLP) or di(4-tert-butylcyclohexyl)peroxydicarbonate.

Preferably, the reaction is initiated in the presence of dilauroyl peroxide.

The amount of dilauroyl peroxide used in the cyclisation is preferably from 1 to 2.5 equivalents.

In a preferred embodiment of the invention, dilauroyl peroxide is added to the medium in stages.

The addition and/or cyclisation reactions are carried out in a solvent customarily used in free radical chemistry such as 1,2-dichloroethane, dichloromethane, benzene, toluene, trifluoromethylbenzene, chlorobenzene, hexane, cyclohexane, heptane, octane, ethyl acetate, tert-butyl alcohol, and mixtures thereof.

Preference is given to using ethyl acetate in the step of addition of the compound of formula (II) to the compound of formula (III), whilst cyclisation of the compound of formula (IV) to form the compound of formula (V) is advantageously carried out in chlorobenzene, ethyl acetate or ethyl butyrate. In this latter reaction, chlorobenzene is more especially preferred.

Conversion of the compound of formula (V) into the compound of formula (VI) is advantageously carried out in the presence of a Lewis acid such as aluminium isopropoxide or samarium isopropoxide. This conversion is moreover preferably carried out in an alcohol (primary or secondary), and even more preferably in isopropanol.

Preferably, a catalytic amount of p-toluenesulphonic acid is added to the mixture once all the tetralone (V) has been consumed at the end of conversion of the compound of formula (V) into the compound of formula (VI).

Aromatisation of compound (VI) is carried out in the presence of a quinone, preferably in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or tetrachlorobenzoquinone (TCQ). Even more preferably, aromatisation is carried out in the presence of TCQ at the reflux of toluene.

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.

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 good yields, starting from a simple, low-cost starting material;

only the intermediates of formulae (VI) and (VII) require a purification and isolation step.

The compounds of formulae (V) and (VI) obtained according to the process of the invention are new and useful as intermediates in the synthesis of agomelatine.

The Examples hereinbelow illustrate the invention without limiting it in any way. For the purpose of validating the reaction route, the synthesis intermediates were systematically isolated and characterised. However, it is possible to considerably optimise the procedures by limiting the number of intermediates isolated. Accordingly, Example 2 given hereinbelow corresponds to the same reaction route as that used in Example 1 but with the difference that only (7-meth-

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oxy-1,2-dihydro-1-naphthyl]acetonitrile and (7-methoxy-1-naphthyl]acetonitrile were isolated.

EXAMPLE 1

N-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide

Step A: S-[1-(cyanomethyl)-4-(4-methoxyphenyl)-4-oxobutyl]-O-ethyl dithiocarbonate

A solution of allyl cyanide (4.8 mL, 60.0 mmol) and S-[2-(4-methoxyphenyl)-2-oxoethyl]-O-ethyl dithiocarbonate¹ (8.1 g, 30.0 mmol) in ethyl acetate (30 mL) is heated at reflux for 15 minutes under a nitrogen atmosphere. There is added, firstly, an amount of dilauroyl peroxide (10 mol %) to the solution under reflux. After 1 hour 30 minutes, another amount of dilauroyl peroxide (5 mol %) is also introduced. When the reagents have been completely consumed, the mixture is cooled to ambient temperature and concentrated under reduced pressure. The crude mixture is then purified by flash column chromatography (petroleum ether-ethyl acetate: 95-5 to 80-20) to yield the title compound in the form of an oil in a yield of 98%.

¹S-[2-(4-methoxyphenyl)-2-oxoethyl]-O-ethyl dithiocarbonate is obtained according to the protocol described in Batanero, B. et al., *J. Org. Chem.* 2001, 66, 320.

¹H NMR (δ , ppm) 7.93 (m, 2H, CH-4), 6.93 (m, 2H, CH-3), 4.67-4.57 (m, 2H, CH₂-13), (CDCl₃, 400 MHz) 3.99 (m, 1H, CH-9), 3.87 (s, 3H, CH₃-1), 3.15 (t, 2H, J=7.3 Hz, CH₂-7), 2.95 (dd, 2H, J=17.0, 6.0 Hz, CH₂-10), 2.41-2.31 (m, 1H, CH₂-8), 2.19-2.08 (m, 1H, CH₂-8), 1.41 (t, 3H, J=7.1 Hz, CH₃-14).

Step B: (7-Methoxy-4-oxo-1,2,3,4-tetrahydro-1-naphthyl]acetonitrile

The compound of Step A, used directly without having been purified, is redissolved in chlorobenzene (900 mL) and the solution is refluxed for 15 minutes under a nitrogen atmosphere. Dilauroyl peroxide is then gradually added to the solution under reflux (10 mol % every 10 minutes). When the reaction is complete, the mixture is cooled to ambient temperature and concentrated under reduced pressure. Acetonitrile is then introduced in order to cause a large part of the dilauroyl peroxide compounds to precipitate out. The mixture is then filtered, concentrated under reduced pressure and purified by flash column chromatography (petroleum ether-ethyl acetate: 60-40) to yield the title compound in solid form in a yield of 40%.

HRMS (EI, m/z) Calc. for C₁₃H₁₃NO₂: 215.0946; found: 215.0946.

Step C: (7-Methoxy-1,2-dihydro-1-naphthyl]acetonitrile

Aluminium isopropoxide (2.05 g, 10.0 mmol) is added to a solution of the compound obtained in Step B (680 mg, 3.15 mmol) in isopropanol (15 mL) at ambient temperature. The reaction mixture is refluxed. When the reagents have been completely consumed, a few crystals of p-toluenesulphonic acid monohydrate are added and a Dean-Stark apparatus is mounted on top of the flask. The mixture is again refluxed for 1 hour, during which the isopropanol is gradually replaced with toluene by means of the Dean-Stark apparatus. A 1N HCl solution is then added and the resulting phases are separated. The aqueous phase is extracted with ethyl acetate, the organic phases being washed with saturated NaHCO₃ solution and with saturated NaCl solution, then dried over MgSO₄, filtered and concentrated under reduced pressure. The residue is purified by column chromatography (petro-

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leum ether-ethyl acetate: 80-20) to yield the title product in the form of an oil in a yield of 85%.

HRMS (EI, m/z) Calc. for C₁₃H₁₃NO: 199.0997. found: 199.1001.

Step D: (7-Methoxy-1-naphthyl]acetonitrile

Method A:

To a solution of the compound obtained in Step C (1.0 g, 5.0 mmol) in dichloromethane (50 mL) at ambient temperature there is added DDQ (1.4 g, 6.0 mmol). The reaction mixture is stirred for 2 days and is then washed with saturated NaHCO₃ solution. The aqueous phase is extracted with ethyl acetate, the organic phase being washed with saturated NaCl solution, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue is purified by column chromatography (petroleum ether-ethyl acetate: 80-20) to yield the title product in solid form in a yield of 55%.

Method B:

To a solution of TCQ (615 mg, 2.5 mmol) in toluene (1.5 mL) heated to 80° C. there is added the compound obtained in Step C (462 mg, 2.3 mmol) dissolved in toluene (3.5 mL). The mixture is then refluxed for 2.5 hours and is then diluted with water and extracted with petroleum ether. The organic phase is washed with NaOH solution (30% by weight) and with water and is then dried over MgSO₄, filtered and concentrated under reduced pressure. The residue is purified by column chromatography (petroleum ether-ethyl acetate: 80-20) to yield the title product in solid form in a yield of 61%.

HRMS (EI, m/z) Calc. for C₁₃H₁₁NO: 197.0841. found: 197.0838.

Step E:

N-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide

The reaction was carried out on a larger batch in order to optimise the yield obtained: 136 g of Raney nickel, 2.06 L of ethanol and 0.23 L of water are introduced into an 8 L reactor. Whilst stirring at 70° C. and under 30 bars of hydrogen, the compound obtained in Step D (0.8 kg) dissolved in acetic anhydride (2.4 L) is slowly added. At the end of the addition, the reaction mixture is stirred for 1 hour under hydrogen at 30 bar, the reactor is then decompressed and the liquors are filtered. After concentration of the mixture, the residue is crystallised from a mixture of ethanol/water 35/65 to yield the title product in a yield of 89% and with a chemical purity greater than 99%.

Melting point: 108° C.

EXAMPLE 2

N-[2-(7-ethoxy-1-naphthyl)ethyl]acetamide

Step A:

(7-Methoxy-1,2-dihydro-1-naphthyl]acetonitrile

A solution of allyl cyanide (6.75 mL, 84.0 mmol) and S-[2-(4-methoxyphenyl)-2-oxoethyl]-O-ethyl dithiocarbonate¹ (11.3 g, 42.0 mmol) in ethyl acetate (45 mL) is heated at reflux for 15 minutes under a nitrogen atmosphere. There is added, firstly, an amount of dilauroyl peroxide (10 mol %) to the solution under reflux. After 1 hour 30 minutes, another amount of dilauroyl peroxide (5 mol %) is also introduced. When the reagents have been completely consumed, the mixture is cooled to ambient temperature and concentrated under reduced pressure. The crude mixture is redissolved in chlorobenzene (640 mL) and the solution is refluxed for 15 min-

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utes under a nitrogen atmosphere. Dilauroyl peroxide is then gradually added to the solution under reflux (10 mol % every 10 minutes). When the reaction is complete, the mixture is cooled to ambient temperature and concentrated under reduced pressure. Acetonitrile is then introduced in order to cause a large part of the dilauroyl peroxide compounds to precipitate out. The mixture is then filtered and concentrated under reduced pressure. Half the crude oil thereby obtained is redissolved in isopropanol (100 mL) at ambient temperature in the presence of aluminium isopropoxide (13.6 g, 66.6 mmol). The reaction mixture is refluxed. When the reagents have been completely consumed, a few crystals of p-toluenesulphonic acid monohydrate are added and a Dean-Stark apparatus is mounted on top of the flask. The mixture is again refluxed for 2 hours, during which the isopropanol is gradually replaced with toluene by means of the Dean-Stark apparatus. A 1N HCl solution is then added and the resulting phases are separated. The aqueous phase is extracted with ethyl acetate, the organic phases being washed with saturated NaHCO₃ solution and with saturated NaCl solution, then dried over MgSO₄, filtered and concentrated under reduced pressure. The residue is purified by column chromatography (petroleum ether-ethyl acetate: 80-20) to yield the title product in the form of an oil in a yield of 24%.

HRMS (EI, m/z) Calc. for C₁₃H₁₃NO: 199.0997, found: 199.1001.

Step B: (7-Methoxy-1-naphthyl)acetonitrile

The procedure is analogous to Step D of Example 1.

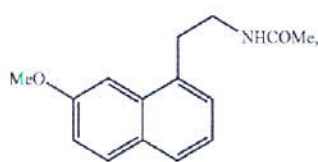
Step C:

N-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide

The procedure is analogous to Step E of Example 1.

The invention claimed is:

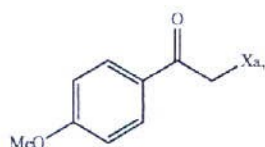
1. A process for the synthesis of a compound of formula (I):



wherein allyl cyanide of formula (II):

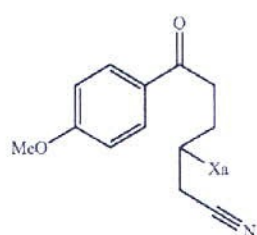


is reacted, in the presence of a free radical initiator, with a compound of formula (III):

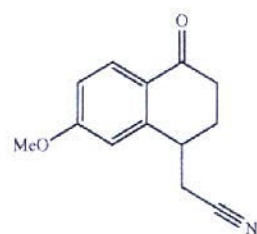


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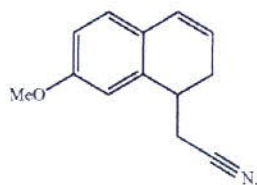
wherein Xa represents a group —S—C(S)—OR in which R represents a linear or branched (C₁-C₆)alkyl group, to yield the compound of formula (IV):



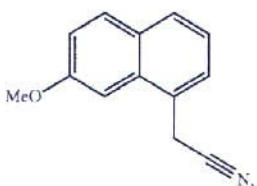
wherein Xa is as defined hereinbefore, wherein this latter compound may be optionally isolated, before being subjected to a cyclisation reaction in the presence of a free radical initiator in order to form the compound of formula (V):



which compound of formula (V) may also be optionally isolated, which compound of formula (V) is subjected to a reduction-dehydration reaction to yield the compound of formula (VI):



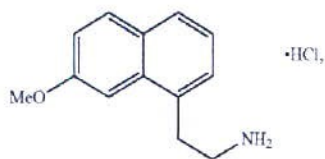
which is then subjected to an aromatisation reaction to yield the compound of formula (VII):



which is subjected to reduction using hydrogen in the presence of Raney nickel in a polar protic medium and to reaction with acetic anhydride to yield the compound of formula (I), which is isolated in the form of a solid.

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2. The process according to claim 1, wherein the compound of formula (VII) is subjected to reduction using hydrogen in the presence of Raney nickel in an ammoniacal ethanol medium and then converted into a salt using hydrochloric acid to yield the compound of formula (VIII):



(VIII)

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.

3. The process according to claim 1, wherein the compound of formula (VII) is subjected to reduction by hydrogen in the presence of Raney nickel in a medium comprising acetic anhydride in a polar protic medium to yield the compound of formula (I), which is isolated in the form of a solid.

4. The process according to claim 1, wherein the group Xa represents $-S-C(S)-OC_2H_5$.

5. The process according to claim 1, wherein the free radical reactions are initiated by thermal means at a temperature of from 50 to 140° C.

6. The process according to claim 1, wherein cyclisation of the compound of formula (IV) is carried out at a temperature of from 130 to 135° C.

7. The process according to claim 1, wherein the step of addition of the compound of formula (III) to the compound of formula (III) and that of cyclisation of the compound of formula (IV) are initiated in the presence of dilauroyl peroxide.

8. The process according to claim 1, wherein the step of addition of the compound of formula (II) to the compound of formula (III) is carried out in chlorobenzene.

9. The process according to claim 1, wherein the step of cyclisation of the adduct of formula (IV) to form the compound of formula (V) is carried out in ethyl acetate.

10. The process according to claim 1, wherein the conversion of the compound of formula (V) into the compound of formula (VI) is carried out in the presence of aluminium isopropoxide.

11. The process according to claim 1, wherein the conversion of the compound of formula (V) into the compound of formula (VI) is carried out in isopropanol.

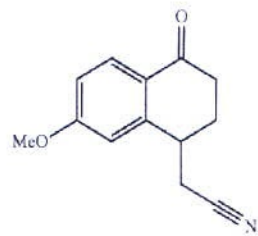
12. The process according to claim 1, wherein a catalytic amount of p-toluenesulphonic acid is added to the mixture at the end of conversion of the compound of formula (V) into the compound of formula (VI).

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13. The process according to claim 1, wherein the aromatisation of the compound of formula (VI) is carried out in the presence of a quinone.

14. The process according to claim 1, wherein the aromatisation of the compound of formula (VI) is carried out in the presence of TCQ at the reflux of toluene.

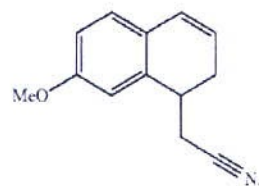
15. A process for the synthesis of agomelatine starting from the compound of formula (V):



(V)

wherein the compound of formula (V) is obtained according to the process according to claim 1.

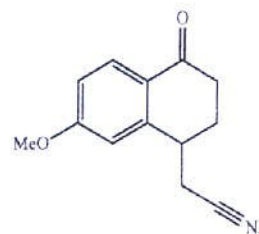
16. A process for the synthesis of agomelatine starting from the compound of formula (VI):



(VI)

wherein the compound of formula (VI) is obtained according to the process according to claim 1.

17. A compound of formula (V):



(V)

* * * * *