



No. 05-058754- -00004-0000

Fecha: 2007-06-27 16:59:31 Dep. 2020 NUECREACION
Tra. 2 PATENTES Eve: 1 REGDEPOSITO
Act. 329 CTOINFORMACION Folios: 13

SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: EXPEDIENTE 05-058-754

TÍTULO SOLICITADO: "FORMA CRISTALINA ALFA DEL RANELATO DE ESTRONCIO, PROCEDIMIENTO PARA SU PREPARACIÓN Y COMPOSICIONES FARMACÉUTICAS QUE LA CONTIENEN".

PUBLICACIÓN: GACETA 571 DE 29 de Diciembre 2006, NÚMERO DE PUBLICACIÓN 195

PRIORIDAD: FR 0410335 de 30/09/2004

SOLICITANTE: LES LABORATOIRES SERVIER

APODERADO: GUSTAVO ADOLFO PALACIO CORREA

TRÁMITE: SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 28 de Marzo de 2007, en los siguientes términos:

I. RATIFICACIÓN

Comedidamente me permito insistir en los argumentos planteados en la oposición, los cuales demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14, 16 y 18 de la Decisión 486 de 2000 y que por ello no merece recibir el beneficio patentario.

Me permito ratificar los argumentos expuestos, con el fin de justificar la razón por la cual debe negarse la solicitud que nos ocupa:

- En primer término, la patente europea EP 0 415 850, publicada el 06 de Marzo de 1991 y titulada "NOUVEAUX SELS DE MÉTAUX BIVALENTS DE L'ACIDE N,N-DI(CARBOXYMÉTHYL) AMINO-2 CYANO-3 CARBOXYMÉTHYL-4 CARBOXY-5 THIOPHÈNE, LEUR PROCÉDÉ DE PRÉPARATION ET LES COMPOSITIONS PHARMACEUTIQUES LES RENFERMANT", revela compuestos dentro de los cuales se encuentra el ahora reivindicado en la solicitud colombiana en trámite, y hace referencia al empleo de los mismos en el tratamiento de enfermedades óseas, en la misma forma pretendida en la solicitud colombiana en trámite.
- Por su parte, la patente europea EP 0 813 869 publicada el 29 de Diciembre de 1997 y titulada "UTILISATION DE SELS DE STRONTIUM POUR LE TRAITEMENT DE L' ARTHROSE", revela la utilización de ranelato de estroncio y composiciones farmacéuticas que lo contienen en el tratamiento de artrosis, al igual que ocurre en la solicitud colombiana en trámite.
- De igual manera la publicación internacional WO 2004/029036 del 08 de abril de 2004 y titulada "THE NOVEL METHOD FOR THE INDUSTRIAL SYNTHESIS OF STRONTIUM RANELATE AND THE HYDRATES THEREOF", revela un método para la síntesis industrial de ranelato de estroncio e hidratos del mismo, también menciona el uso del ranelato de estroncio en el tratamiento de osteoporosis y otras enfermedades óseas, al igual que ocurre en la solicitud colombiana en trámite.
- Diversas las publicaciones científicas demuestran con anterioridad a la fecha de prioridad de la solicitud en curso el conocimiento del uso de esta sustancia en el tratamiento de enfermedades óseas, en especial osteoporosis y/o artrosis tal y como se pretende reivindicar en la solicitud colombiana en trámite.^{1,2,3, 4 y 5.}

¹ Strontium ranelate increases cartilage matrix formation. (eng; includes abstract) By Henrotin Y, Journal Of Bone And Mineral Research: The Official Journal Of The American Society For Bone And Mineral Research [J Bone Miner Res], 2001 Feb; Vol. 16 (2), pp. 299-308; PMID: 11204430

2
127

- El hecho de obtenerse una nueva forma cristalina de ranelato de estroncio no otorga a la solicitud el indispensable Nivel Inventivo, pues es bien sabido que la formación de una forma cristalina no implica en sí misma un esfuerzo o aporte al arte previo, en tanto dichas formas son diferentes posibilidades en las que intrínsecamente pueden presentarse las sustancias en el estado sólido⁶, siendo el hábito cristalino la descripción del aspecto externo de los cristales, mientras que la estructura interna es la disposición de los elementos dentro del sólido, razón por la cual una sustancia con una misma estructura cristalina interna puede presentar diversos hábitos cristalinos, en función de las condiciones bajo las cuales ha cristalizado.
- Frente a idénticas solicitudes (relacionadas a formas cristalinas "novedosas"), es necesario tener en cuenta que este Despacho ha resuelto la negación de dichas solicitudes relacionadas con formas cristalinas de algunos compuestos por incumplir el requisito de nivel inventivo⁷; y si bien es cierto que la forma cristalina descrita en la solicitud en trámite no pertenece a las mismas sustancias que se revelaban en las solicitudes que fueron negadas, lo importante es el hecho de que se trata del mismo tema, referido a manifestaciones cristalinas específicas de una molécula ya conocida.

II. COMPLEMENTO DE INFORMACIÓN

- La patente estadounidense US 2004/0059135 publicada el 25 de Marzo de 2004 y titulada "PROCESS FOR THE INDUSTRIAL SYNTHESIS OF THE METHYL DIESTER OF 5-AMINO-3-CARBOXYMETHYL-4-CYANO-2-

² Strontium ranelate: dose-dependent effects in established postmenopausal vertebral osteoporosis--a 2-year randomized placebo controlled trial. (eng; includes abstract) By Meunier PJ, The Journal Of Clinical Endocrinology And Metabolism [J Clin Endocrinol Metab], 2002 May; Vol. 87 (5), pp. 2060-6; PMID: 11994341

³ Strontium Ranelate in Osteoporosis Current Pharmaceutical Design, September 2002, Vol. 8 Issue: Number 21 p1907-1916, 10p; (AN 4237876)

⁴ Osteoporosis: A Pharmacotherapy Update Journal of Pharmacy Practice, January 01, 2003, Vol. 16 Issue: Number 3 p164-169, 6p; (AN 4875227)

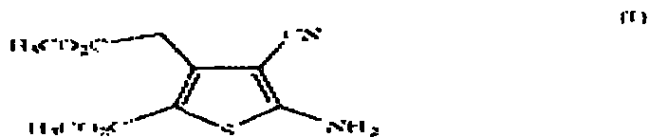
⁵ Design and methodology of the phase 3 trials for the clinical development of strontium ranelate in the treatment of women with postmenopausal osteoporosis. (eng; includes abstract) By Meunier PJ, Osteoporosis International: A Journal Established As Result Of Cooperation Between The European Foundation For Osteoporosis And The National Osteoporosis Foundation Of The USA [Osteoporos Int], 2003; Vol. 14 Suppl 3, pp. S66-76; PMID: 12730769

⁶ Vila Jato José Luis. Tecnología Farmacéutica, Vol. I, Parte I, Cáp. I "Preformulación" Veiga D., Alegre E., Torrado J., Editorial Síntesis S.A. Madrid 2001. Pág. 44 y 45.

⁷ Solicitud Colombiana 96-037-513 y Solicitud Colombiana 96-037-514.

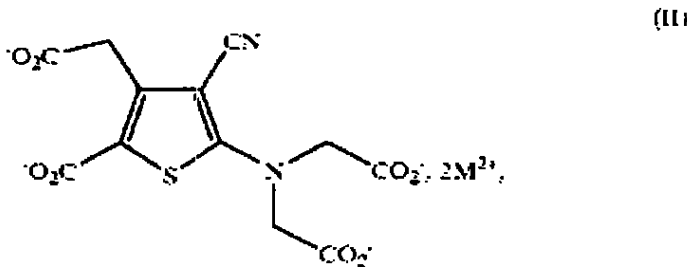
THIOPHENECARBOXYLIC ACID, AND APPLICATION TO THE SYNTHESIS OF BIVALENT SALTS OF RANELIC ACID AND THEIR HYDRATES", revela:

(57) **ABSTRACT**
 Process for the industrial synthesis of the compound of formula (I):



Application to the synthesis of bivalent salts of ranelic acid and more especially strontium ranelate and its hydrates.

[0003] The compound of formula (I) obtained according to the process of the invention is useful in the synthesis of ranelic acid, its strontium, calcium or magnesium salts of formula (II):

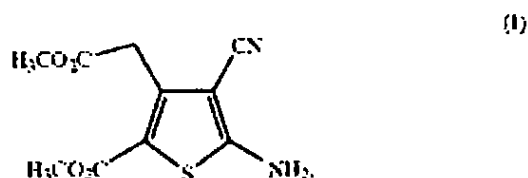


[0004] wherein M represents strontium, calcium or magnesium, and hydrates of the said salts.

[0013] The compound of formula (I) thereby obtained is especially useful in the synthesis of ranelic acid, its strontium, calcium or magnesium salts and hydrates of the said salts, more especially strontium ranelate and its hydrates, wherein it is reacted with an ester of bromoacetic acid to yield the corresponding tetraester, which is then converted into ranelic acid or into a strontium, calcium or magnesium salt thereof.

[]

8. Process for the synthesis of strontium ranelate and its hydrates, starting from a compound of formula (I):

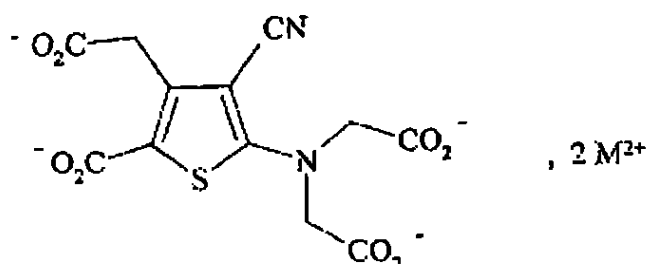


which is reacted with an ester of bromoacetic acid to yield the corresponding tetraester, which is converted into strontium ranelate,

wherein the compound of formula (I) is obtained by a synthesis process according to claim 1.

Este documento permite observar la obtención del ácido ranélico así como varias de sus sales, especialmente la obtención de ranelato de estroncio.

➤ La publicación internacional WO 2004/029034 del 08 de abril de 2004 y titulada "SYNTHESE D'ESTERS D' ACIDE THIOPHENECARBOXYLIQUES POUR LA FABRICATION DE SELS L'ACIDE RANELIQUE" revela compuestos de la fórmula:



Donde M representa estroncio, calcio o magnesio, y en donde dichos compuestos son útiles en el tratamiento de trastornos osteoporóticos y relacionados, lo anterior permite demostrar nuevamente la obtención de esta sal del ácido ranélico, así como su utilidad en el tratamiento de enfermedades de este tipo.

En conclusión, como se ha demostrado a través de todos estos argumentos, la obtención de una, en gracia de discusión, nueva forma cristalina de ranelato de estroncio no entraña nivel inventivo como para acceder a la concesión del privilegio de patente solicitado.

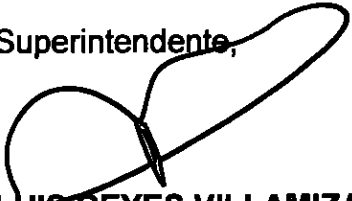
Cabe anotar, por último, que en tanto los documentos mencionados en este escrito y en la oposición inicial revelan procesos de obtención de ácido Ranélico o sus sales, entre las que se encuentra Ranelato de Estroncio en forma sólida, resulta razonable concluir que por no hacerse referencia en los mismos a que el producto obtenido sea amorfo, en los mismo se anticiparían las formas cristalinas ahora reivindicadas.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales, y que en consecuencia el Despacho decrete, además de la negación de la solicitud en comento, el archivo del expediente que lo contiene.

III. ANEXOS

- La patente americana US 2004/0059135 publicada el 25 de Marzo de 2004 y titulada "PROCESS FOR THE INDUSTRIAL SYNTHESIS OF THE METHYL DIESTER OF 5-AMINO-3-CARBOXYMETHYL-4-CYANO-2-THIOPHENE CARBOXYLIC ACID, AND APPLICATION TO THE SYNTHESIS OF BIVALENT SALTS OF RANELIC ACID AND THEIR HYDRATES." Paginas 1 a 3.
- La publicación internacional WO 2004/029034 del 08 de abril de 2004 y titulada "SYNTHESE D'ESTERS D' ACIDE THIOPHENECARBOXYLIQUES POUR LA FABRICATION DE SELS L'ACIDE RANELIQUE" paginas 1 y 2.

Señor Superintendente,



JOSE LUIS REYES VILLAMIZAR
C.C. 79.152.473 de Usaquén
T.P. 44655 del C. S de la J.



US 20040059135A1

*
131(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0059135 A1****Vaysse-Ludot et al.**(43) **Pub. Date:****Mar. 25, 2004**

(54) **PROCESS FOR THE INDUSTRIAL SYNTHESIS OF THE METHYL DIESTER OF 5-AMINO-3-CARBOXYMETHYL-4-CYANO-2-THIOPHENECARBOXYLIC ACID, AND APPLICATION TO THE SYNTHESIS OF BIVALENT SALTS OF RANELIC ACID AND THEIR HYDRATES**

(76) **Inventors:** Lucile Vaysse-Ludot, Rancon (FR);
Jean-Pierre Lecouve, Le Havre (FR);
Pascal Langlois, La Neuville (FR)

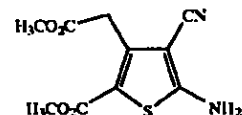
Correspondence Address:
The Firm of Hueschen and Sage
500 Columbia Plaza
350 East Michan Avenue
Kalamazoo, MI 49007 (US)

(21) **Appl. No.:** 10/669,738(22) **Filed:** Sep. 24, 2003(30) **Foreign Application Priority Data**

Sep. 24, 2002 (FR)..... 02.11764

Publication Classification(51) **Int. Cl.⁷** C07D 333/38(52) **U.S. Cl.** 549/61(57) **ABSTRACT**

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



(I)

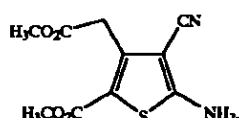
Application to the synthesis of bivalent salts of ranelic acid and more especially strontium ranelate and its hydrates.

8
132

**PROCESS FOR THE INDUSTRIAL SYNTHESIS OF
THE METHYL DIESTER OF
5-AMINO-3-CARBOXYMETHYL-4-CYANO-2-
THIOPHENECARBOXYLIC ACID), AND
APPLICATION TO THE SYNTHESIS OF
BIVALENT SALTS OF RANELIC ACID AND THEIR
HYDRATES**

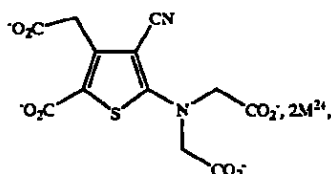
[0001] The present invention relates to a process for the industrial synthesis of the methyl diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and to the application thereof in the industrial production of bivalent salts of ranelic acid and their hydrates.

[0002] More specifically, the present invention relates to a new process for the industrial synthesis of the compound of formula (I):



(I)

[0003] The compound of formula (I) obtained according to the process of the invention is useful in the synthesis of ranelic acid, its strontium, calcium or magnesium salts of formula (II):



(II)

[0004] wherein M represents strontium, calcium or magnesium, and hydrates of the said salts.

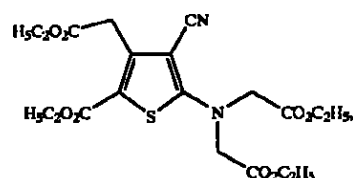
BACKGROUND OF THE INVENTION

[0005] The bivalent salts of ranelic acid have very valuable pharmacological and therapeutic properties, especially pronounced anti-osteoporotic properties, making these compounds useful in the treatment of bone diseases.

DESCRIPTION OF THE PRIOR ART

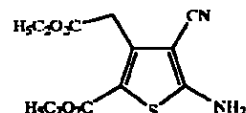
[0006] The bivalent salts of ranelic acid, and more especially strontium ranelate, the preparation thereof and the therapeutic use thereof have been described in the European Patent Specification EP 0 415 850.

[0007] That Patent Specification describes the synthesis of strontium ranelate starting from the ethyl tetraester of formula (III):



(III)

[0008] which is itself obtainable starting from the ethyl diester of formula (IV):



(IV)

[0009] Synthesis of the intermediate of formula (IV) has been described in the publication Bull. Soc. Chim. France 1975, pp. 1786-1792 and in the publication J. Chem. Tech. Biotechnol. 1990, 47, pp. 39-46, by reaction between diethyl 3-oxoglutarate, malononitrile and sulphur in ethanol, in the presence of morpholine or diethylamine.

[0010] That process has the advantage of using readily accessible starting materials and of being simple to put into practice; however, when transferred to the scale of several hundred kilograms, it does not allow the compound of formula (IV) to be obtained in a yield greater than 70%.

[0011] In view of the pharmaceutical interest of strontium ranelate and the tonnages produced, it has been important to be able to synthesise a diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid of excellent purity, in a yield of at least 77%, which is reproducible on an industrial scale.

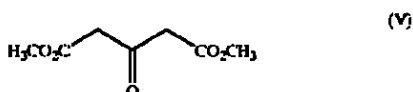
**DETAILED DESCRIPTION OF THE
INVENTION**

[0012] The Applicant has now developed an effective industrial synthesis process allowing the methyl diester of formula (I) to be obtained in a yield of at least 77% and with a purity greater than 97%.

[0013] The compound of formula (I) thereby obtained is especially useful in the synthesis of ranelic acid, its strontium, calcium or magnesium salts and hydrates of the said salts, more especially strontium ranelate and its hydrates, wherein it is reacted with an ester of bromoacetic acid to yield the corresponding tetraester, which is then converted into ranelic acid or into a strontium, calcium or magnesium salt thereof.

[0014] More specifically, the present invention relates to a process for the industrial synthesis of the compound of formula (I).

[0015] which process is characterised in that dimethyl 3-oxoglutarate of formula (V):



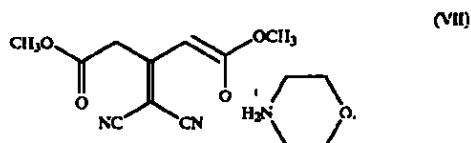
[0016] is reacted with malonitrile of formula (VI):



[0017] in methanol,

[0018] in the presence of morpholine in an amount greater than 0.95 mol per mol of compound of formula (V),

[0019] to yield the compound of formula (VII):



[0020] which is then reacted with sulphur in an amount greater than 0.95 mol per mol of compound of formula (V);

[0021] the reaction mixture is then heated at reflux;

[0022] and the compound of formula (I) thereby obtained is isolated by precipitation in the presence of water, followed by filtration.

[0023] The process, accordingly improved by the use of these very specific conditions, and especially by the intermediate formation of the compound of formula (VII), which can, if desired, be isolated, allows the compound of formula (I) to be obtained with excellent purity and in a yield of at least 77% which is reproducible on the scale of several hundred kilograms, which represents a major gain in yield in view of the large tonnages of strontium ranelate produced.

[0024] The amount of methanol is preferably from 1 to 3 ml per gram of compound of formula (V).

[0025] The temperature of reaction between the compounds of formulae (V) and (VI) is preferably less than 50° C.

[0026] The reaction time at reflux after addition of the sulphur is preferably from 1 hour 30 minutes to 3 hours.

[0027] Methyl 5-amino-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate of formula (I) and the intermediate of formula (VII) are new compounds which are useful as synthesis intermediates in the chemical or pharmaceutical industry, especially in the synthesis of strontium ranelate, and accordingly form an integral part of the present invention.

[0028] The Examples hereinbelow illustrate the invention but do not limit it in any way.

EXAMPLE 1

[0029] Methyl 5-amino-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate

[0030] Introduce into a reactor 400 kg of dimethyl 3-oxoglutarate, 158 kg of malonitrile and 560 litres of methanol and then, whilst maintaining the temperature of the reaction mixture below 40° C., 199.6 kg of morpholine.

[0031] Then introduce 73.6 kg of sulphur and subsequently bring the mixture to reflux.

[0032] After reacting for 2 hours, stop refluxing and add water until precipitation occurs. Filter off the precipitate obtained, wash it and dry it.

[0033] Methyl 5-amino-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate is thereby obtained in a yield of 77% and with a chemical purity of 98%.

EXAMPLE 2

[0034] Methyl 5-amino-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate

[0035] Introduce into a reactor 400 kg of dimethyl 3-oxoglutarate, 158 kg of malonitrile and 560 litres of methanol and then, whilst maintaining the temperature of the reaction mixture below 40° C., 199.6 kg of morpholine.

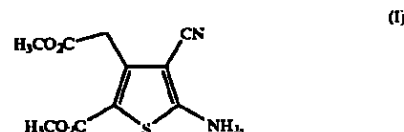
[0036] The compound of formula (VII) thereby obtained, or the addition salt of methyl 3-(dicyanomethylene)-5-hydroxy-5-methoxy-4-pentenoate with morpholine, is isolated by filtration after cooling of the mixture and is then reacted with 73.6 kg of sulphur in methanol.

[0037] The mixture is then brought to reflux.

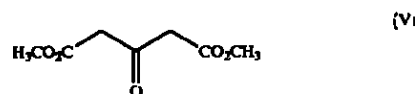
[0038] After reacting for 2 hours, stop refluxing and add water until precipitation occurs. Filter off the precipitate obtained, wash it and dry it.

We claim:

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



wherein dimethyl 3-oxoglutarate of formula (V):



is reacted with malononitrile of formula (VI):

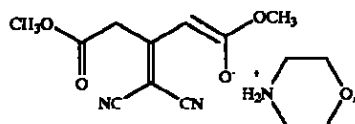


(VI)

in methanol,

in the presence of morpholine in an amount greater than 0.95 mol per mol of compound of formula (V),

to yield the compound of formula (VII)



(VII)

which is then reacted with sulphur in an amount greater than 0.95 mol per mol of compound of formula (V);

the reaction mixture is then heated at reflux;

and the compound of formula (I) thereby obtained is isolated by precipitation in the presence of water, followed by filtration.

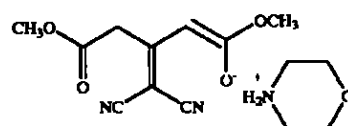
2. Synthesis process according to claim 1, wherein the amount of methanol is from 1 to 3 ml per gram of compound of formula (V).

3. Synthesis process according to claim 1, wherein the temperature of reaction between the compounds of formulae (V) and (VI) is less than 50° C.

4. Synthesis process according to claim 1, wherein the reaction time at reflux after addition of the sulphur is from 1 hour 30 minutes to 3 hours.

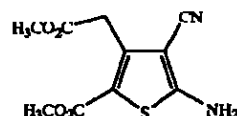
5. Methyl 5-amino-4-cyano-3-(2-methoxy-2-oxoethoxy)-2-thiophenecarboxylate.

6. The compound of formula (VII):



(VII)

7. Process for the synthesis of ranelic acid, its strontium, calcium or magnesium salts and hydrates of the said salts, starting from a compound of formula (I):

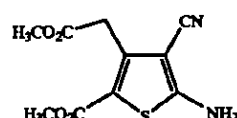


(I)

which is reacted with an ester of bromoacetic acid to yield the corresponding tetraester, which is converted into ranelic acid or a strontium, calcium or magnesium salt thereof,

wherein the compound of formula (I) is obtained by a synthesis process according to claim 1.

8. Process for the synthesis of strontium ranelate and its hydrates, starting from a compound of formula (I):



(I)

which is reacted with an ester of bromoacetic acid to yield the corresponding tetraester, which is converted into strontium ranelate,

wherein the compound of formula (I) is obtained by a synthesis process according to claim 1.

* * * * *

(12) DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRAITÉ DE COOPÉRATION
EN MATIÈRE DE BREVETS (PCT)

(19) Organisation Mondiale de la Propriété
Intellectuelle
Bureau international



(43) Date de la publication internationale
8 avril 2004 (08.04.2004)

PCT

(10) Numéro de publication internationale
WO 2004/029034 A1

(51) Classification internationale des brevets⁷ :
C07D 333/38

(21) Numéro de la demande internationale :
PCT/FR2003/002775

(22) Date de dépôt international :
22 septembre 2003 (22.09.2003)

(25) Langue de dépôt : français

(26) Langue de publication : français

(30) Données relatives à la priorité :
02/11765 24 septembre 2002 (24.09.2002) FR

(71) Déposant (pour tous les États désignés sauf US) : LES
LABORATOIRES SERVIER [FR/FR]; 12, place de la
Défense, F-92415 Courbevoie Cedex (FR).

(72) Inventeurs; et

(75) Inventeurs/Déposants (pour US seulement) :
VAYSSE-LUDOT, Lucile [FR/FR]; 150, route de Rançon,
F-76490 Saint-Wandrille-Rançon (FR). LECOUBE,
Jean-Pierre [FR/FR]; 93, rue du Docteur Vigné, F-76600
Le Havre (FR). LANGLOIS, Pascal [FR/FR]; 3, allée du
Bassin, F-76210 Saint-Jean de la Neuville (FR).

(74) Mandataire : LES LABORATOIRES SERVIER; 12,
place de la Défense, F-92415 Courbevoie Cedex (FR).

(81) États désignés (national) : AE, AG, AL, AM, AT, AU, AZ,
BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ,
DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH,
GM, GR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MY, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC,
SD, SI, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,
UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) États désignés (régional) : brevet ARIPO (GH, GM, KE,
LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), brevet
eurasien (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), brevet
européen (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK,
TR), brevet OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

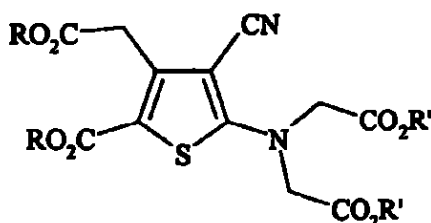
Publiée :

- avec rapport de recherche internationale
- avant l'expiration du délai prévu pour la modification des
revendications, sera republiée si des modifications sont re-
çues

En ce qui concerne les codes à deux lettres et autres abrévia-
tions, se référer aux "Notes explicatives relatives aux codes et
abréviations" figurant au début de chaque numéro ordinaire de
la Gazette du PCT.

(54) Title: SYNTHESIS OF THIOPHENECARBOXYLIC ACID ESTERS FOR THE PRODUCTION OF RANELIC ACID SALTS

(54) Titre : SYNTHÈSE D'ESTERS D'ACIDE THIOPHENECARBOXYLIQUES POUR LA FABRICATION DE SELS DE
L'ACIDE RANELIQUE



(57) Abstract: The invention relates to method for the industrial
synthesis of compounds having formula (I), wherein R and R',
which may be identical or different, each represent a linear or
branched alkyl group (C₁-C₆). The invention is intended for the
synthesis of the divalent salts of ranelic acid and, more specifi-
cally, of strontium ranelate and the hydrates thereof.

(I)

(57) Abrégé : Procédé de synthèse industriel des composés de
formule (I), dans laquelle R et R', identiques ou différents, repré-
sentent chacun un groupement alkyle (C₁-C₆) linéaire ou ramifié.

Application à la synthèse des sels bivalents de l'acide ranelique, et plus particulièrement du ranelate de strontium et de ses hydrates.

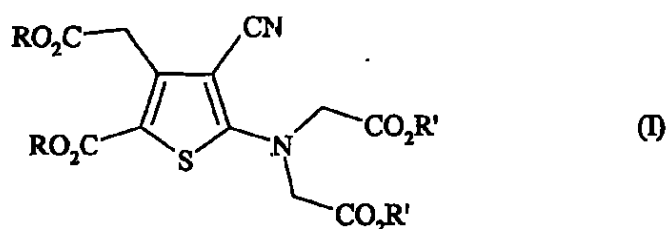
WO 2004/029034 A1

12
136

SYNTHESE D'ESTERS D'ACIDE THIOPHENECARBOXYLIQUE POUR LA FABRICATION DE SELS DE L'ACIDE RANELIQUE

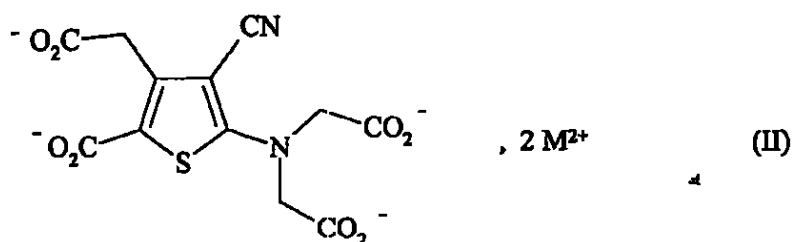
La présente invention concerne un procédé de synthèse industriel des tétraesters de l'acide 5-[bis(carboxyméthyl)amino]-3-carboxyméthyl-4-cyano-2-thiophénecarboxylique, et leur application à la production industrielle des sels bivalents de l'acide ranélique et de leurs hydrates.

- 5 Plus spécifiquement, la présente invention concerne un nouveau procédé de synthèse industriel des dérivés de formule (I) :



dans laquelle R et R', identiques ou différents, représentent chacun un groupement alkyle (C₁-C₆) linéaire ou ramifié.

- 10 Les composés de formule (I) obtenus selon le procédé de l'invention sont utiles dans la synthèse de l'acide ranélique, de ses sels de strontium, de calcium ou de magnésium de formule (II) :



137

dans laquelle M représente le strontium, le calcium ou le magnésium,

et des hydrates desdits sels.

Les sels bivalents de l'acide ranélique possèdent des propriétés pharmacologiques et thérapeutiques très intéressantes, notamment des propriétés anti-ostéoporotiques remarquables, qui rendent ces composés utiles dans le traitement des maladies osseuses.

Les sels bivalents de l'acide ranélique, et plus particulièrement le ranélate de strontium, sa préparation et son utilisation en thérapeutique ont été décrits dans le brevet européen EP 0415 850.

Compte tenu de l'intérêt pharmaceutique de ce composé, il était important de pouvoir accéder à l'intermédiaire de formule (I) avec un procédé de synthèse industriel performant, permettant l'obtention du composé de formule (I) avec un bon rendement et une excellente pureté, mais également facilement transposable à l'échelle industrielle.

Le journal Bull. Soc. Chim. France 1975, pp. 1786-1792, décrit l'obtention d'un dérivé de formule (I) (R = R' = éthyle) par réaction de l'acide 5-amino-3-(carboxyméthyl)-4-cyano-2-thiophénecarboxylique avec le bromoacétate d'éthyle, en présence de carbonate de potassium, suivie d'un isolement en milieu hydro-organique très dilué.

Cependant, le faible rendement de cette réaction (65 %), la grande quantité de rejets aqueux salins générée par cette réaction, et surtout le temps de réaction très important (5 jours), étaient totalement dissuasifs quant à l'utilisation de cette réaction à l'échelle industrielle.

La Demanderesse a présentement mis au point un procédé de synthèse industriel simple, permettant d'obtenir le composé de formule (I) avec un très bon rendement, un temps de réaction considérablement plus court et une pureté excellente, et dans lequel les rejets aqueux salins sont complètement supprimés.

2020
Bogotá, D.C.,

Doctor:
Gustavo Adolfo Palacio Correa
Apoderado

Oficio N°: 9841

ASUNTO:	Radicación N°	05-58754
	Trámite	002
	Evento	001
	Actuación	440
	Folios	033

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Tecnoquímicas S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior oficio fue notificado por fijación en lista de fecha, 16 AGO. 2007.

202021

BOGOTÁ, 17 DE AGOSTO DE 2007.

RETIRO OPPOSICIÓN.

Huissu CR.