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Señor Jefe
DIVISION DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Bogotá, D.C.

SUPERINDUSTRIA Y COMERCIO
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Re: Expediente No. 00 28.927
Solicitud de Patente a nombre de
SMITHKLINE BEECHAM p.l.c.
Código 02 - 01 - 538

En relación con la solicitud contenida en el Expediente de la referencia y, en particular, con la publicación del extracto de la misma en la Gaceta de la Propiedad Industrial No. 517 del 27 de Junio de 2002, por medio del presente escrito muy respetuosamente me permito solicitarle se sirva proceder a efectuar el **EXAMEN DE PATENTABILIDAD** de la solicitud aquí contenida.

Como consecuencia de esta solicitud, acompaño el comprobante de pago por concepto de la tasa establecida para la misma, Recibo No. 02- 50.287 -

De Usted atentamente,

GERMAN CASTILLO GRAU
I.P. No. 2978 del C.S.J.



Industria y Comercio

SUPERINTENDENCIA

93

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 02 - 50,287
FECHA : JULIO 31 DE 2002

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CASTILLO GRAU Y ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	3234561	30/07/2002	1,829,920.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	05-01-01	SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN
		TOTAL :	\$ 318,000.00

SON: TRESCIENTOS DIEZ Y OCHO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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12 **EUROPEAN PATENT APPLICATION**

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The title of the invention has been amended
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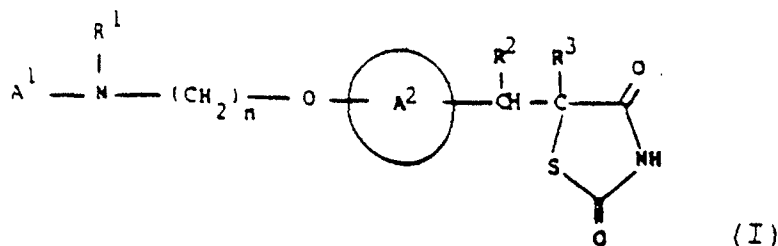
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54 **Substituted thiazolidinedione derivatives.**

57 Compounds of formula (I):



EP 0 306 228 A1

or a tautomeric form thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, wherein:

A¹ represents a substituted or unsubstituted aromatic heterocyclyl group;

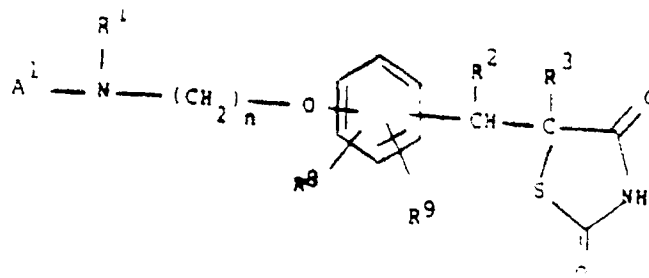
R¹ represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

R² and R³ each represent hydrogen, or R² and R³ together represent a bond;

A² represents a benzene ring having in total up to five substituents; and

n represents an integer in the range of from 2 to 6;

pharmaceutical compositions containing such compounds and the use of such compounds and compo-



(II)

or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, wherein A¹, R¹, R², R³, and n are as defined in relation to formula (I) and R⁸ and R⁹ are as defined in relation to formula (e).

Suitably, n represents an integer 2, 3 or 4, notably 2 or 3 and especially 2.

Suitably, R¹ represents hydrogen, alkyl, acyl, especially acetyl, or benzyl.

Preferably, R¹ represents a methyl group.

As indicated above a compound of formula (I) may exist in one of several tautomeric forms, all of which are encompassed by the present invention. It will be appreciated that the present invention encompasses all of the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof, including any stereoisomeric forms thereof, whether as individual isomers or as mixtures of isomers.

Suitable substituents for any heterocyclyl group include up to 4 substituents selected from the group consisting of: alkyl, alkoxy, aryl and halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a benzene ring, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be substituted or unsubstituted.

When used herein the term 'aryl' includes phenyl and naphthyl optionally substituted with up to five, preferably up to three, groups selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxy, amino, nitro, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

When used herein the term 'halogen' refers to fluorine, chlorine, bromine and iodine; preferably chlorine.

When used herein the terms 'alkyl' and 'alkoxy' relate to groups having straight or branched carbon chains, containing up to 12 carbon atoms.

Suitable alkyl groups are C₁₋₁₂ alkyl groups, especially C₁₋₆ alkyl groups e.g. methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl or tert-butyl groups.

Suitable substituents for any alkyl group include those indicated above in relation to the term "aryl".

Suitable pharmaceutically acceptable salts include salts of the thiazolidinedione moiety, and, where appropriate, salts of carboxy groups.

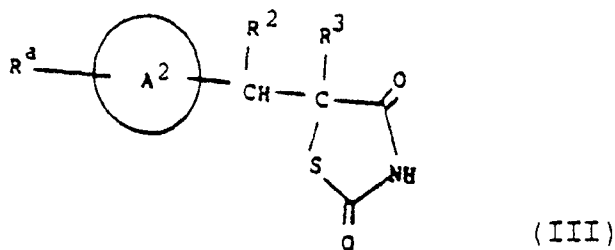
Suitable pharmaceutically acceptable salts of the thiazolidinedione moiety include metal salts especially alkali metal salts such as the lithium, sodium and potassium salts.

Suitable pharmaceutically acceptable salts of carboxy groups include metal salts, such as for example aluminium, alkali metal salts such as sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine or quinoline.

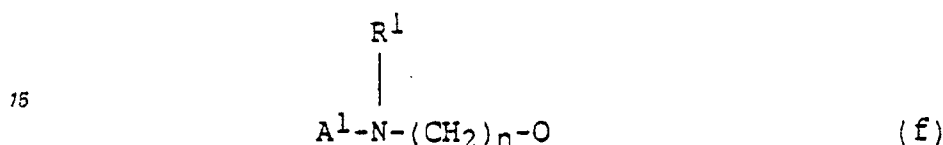
Suitable pharmaceutically acceptable solvates include hydrates.

In a further aspect the present invention also provides a process for the preparation of a compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable hydrate thereof, which process comprises reacting a compound of formula (III):

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10 wherein R^2 , R^3 and A^2 are as defined in relation to formula (I), and R^4 is a moiety convertible to a moiety of formula (f):



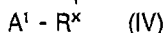
20 wherein R^1 , A^1 , and n are as defined in relation to formula (I), with an appropriate reagent capable of converting R^4 to the said moiety (f) and thereafter, if required, carrying out one or more of the following optional steps:

- (i) converting a compound of formula (I) to a further compound of formula (I);
- (ii) preparing a pharmaceutically acceptable salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

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Suitably, R^4 represents $R^1HN-(CH_2)_n-O-$ wherein R^1 and n are as defined in relation to formula (I).

Suitably, when R^4 is $R^1HN-(CH_2)_n-O-$, an appropriate reagent capable of converting R^4 to a moiety (f) is a compound of formula (IV):



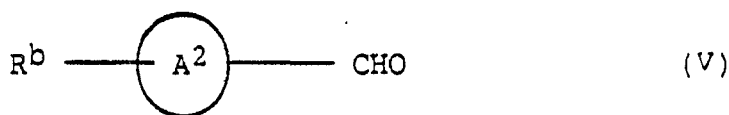
30 wherein A^1 is as defined in relation to formula (I) and R^x represents a leaving group.

A suitable leaving group R^x includes a halogen atom, preferably a chlorine or bromine atom, or a thioalkyl group for example a thiomethyl group.

35 The reaction between the compound of formula (III) and the appropriate reagent may be carried out under conditions suitable to the particular compound of formula (III) and the reagent chosen; thus for example the abovementioned reaction between a compound of formula (III) wherein R^4 represents $R^1HN-(CH_2)_n-O-$ and the compound of formula (IV), may be carried out in any suitable solvent, for example tetrahydrofuran, at a temperature in the range of between 0 and 60°C.

A compound of formula (III) may be prepared from a compound of formula (V):

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45 wherein A^2 is as defined in relation to the compound of formula (I) and R^b is a moiety R^a , or a moiety convertible to a moiety R^a ; by reaction of the compound of formula (V) with 2,4-thiazolidinedione; and thereafter if required carrying out one or more of the following optional steps:

- (i) reducing a compound of formula (III) wherein R^2 and R^3 together represent a bond, into a compound of formula (III) wherein R^2 and R^3 each represent hydrogen;
- 50 (ii) converting a moiety R^b to a moiety R^a .

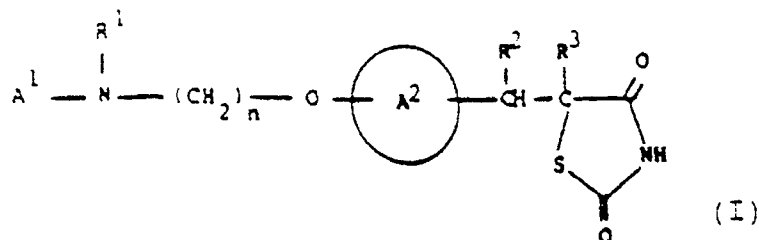
55 The reaction between the compound of formula (V) and 2,4-thiazolidinedione will of course be carried out under conditions suitable to the nature of the compound of formula (V), in general the reaction being carried out in a solvent such as toluene, suitably at an elevated temperature such as the reflux temperature of the solvent and preferably in the presence of a suitable catalyst such as piperidinium acetate or benzoate. Favourably, in the reaction between the compound of formula (V) and 2,4-thiazolidinedione, the water produced in the reaction is removed from the reaction mixture, for example by means of a Dean and Stark apparatus.

Toxicology

No toxicological effects were indicated for any of the compounds of the invention in any of the abovementioned tests.

Claims

1. A compound of formula (I):



or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, characterised in that:

A¹ represents a substituted or unsubstituted aromatic heterocyclyl group;

R¹ represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

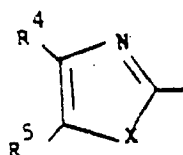
R² and R³ each represent hydrogen, or R² and R³ together represent a bond;

A² represents a benzene ring having in total up to five substituents; and

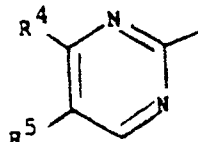
n represents an integer in the range of from 2 to 6.

2. A compound according to claim 1, wherein A¹ represents a substituted or unsubstituted, single or fused ring aromatic heterocyclyl group comprising up to 4 hetero atoms in the ring selected from oxygen, sulphur or nitrogen.

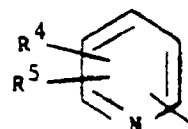
3. A compound according to claim 1 or claim 2, wherein A¹ represents a moiety of formula (a), (b) or (c):



(a)



(b)



(c)

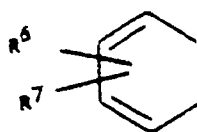
wherein:

R⁴ and R⁵ each independently represents a hydrogen atom, an alkyl group or a substituted or unsubstituted aryl group or when R⁴ and R⁵ are each attached to a carbon atom, then R⁴ and R⁵ together with the carbon atoms to which they are attached form a benzene ring wherein each carbon atom represented by R⁴ and R⁵ together may be substituted or unsubstituted; and in the moiety of formula (a)

X represents oxygen or sulphur.

4. A compound according to claim 3, wherein R⁴ and R⁵ each independently represent hydrogen, alkyl or a substituted or unsubstituted phenyl group.

5. A compound according to claim 3, wherein R⁴ and R⁵ together represent a moiety of formula (d):



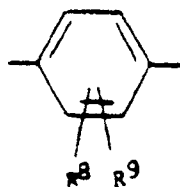
(d)

wherein R^6 and R^7 each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

6. A compound according to claim 5, wherein R^6 and R^7 both represent hydrogen.

7. A compound according to any one of claims 1 to 6, wherein A^2 represents a moiety of formula (e):

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(e)

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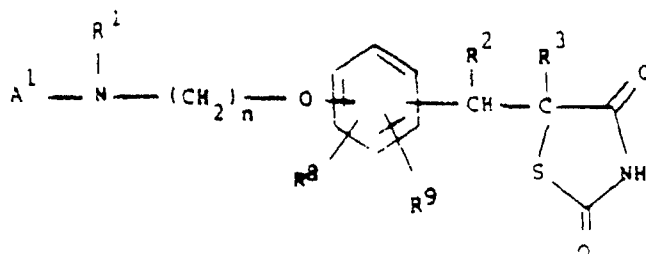
wherein R^8 and R^9 each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

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8. A compound according to claim 7, wherein R^8 and R^9 each represent hydrogen.

9. A compound according to claim 1, of formula (II):

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(II)

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, wherein A^1 , R^1 , R^2 , R^3 and n are as defined in relation to formula (I) in claim 1 and R^8 and R^9 are as defined in relation to formula (e) in claim 7.

10. A compound according to any one of claims 1 to 9, wherein n represents an integer 2 or 3.

11. A compound according to any one of claims 1 to 10, wherein R^1 represents a methyl group.

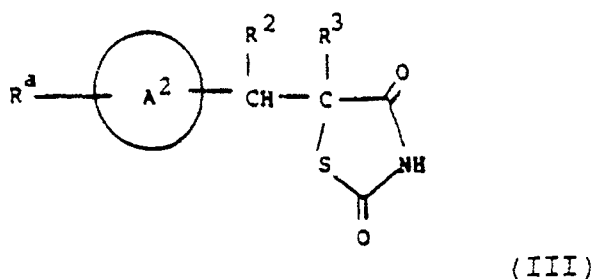
12. A compound according to claim 1, selected from the list consisting of:

- 5-(4-[2-(N-methyl-N-(2-benzothiazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-(2-benzothiazolyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-(2-benzoxazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-(2-benzoxazolyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-(2-pyrimidinyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-(2-pyrimidinyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-[2-(4,5-dimethylthiazolyl)]amino)ethoxy]benzyl)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-[2-(4,5-dimethylthiazolyl)]amino)ethoxy]benzylidene)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-(2-thiazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-(2-thiazolyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-(2-(4-phenylthiazolyl))amino)ethoxy]benzyl)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-(2-(4-phenylthiazolyl))amino)ethoxy]benzylidene)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-[2-(4-phenyl-5-methylthiazolyl)]amino)ethoxy]benzyl)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-[2-(4-phenyl-5-methylthiazolyl)]amino)ethoxy]benzylidene)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)]amino)ethoxy]benzyl)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)]amino)ethoxy]benzylidene)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-[2-(4-methylthiazolyl)]amino)ethoxy]benzyl)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-[2-(4-methylthiazolyl)]amino)ethoxy]benzylidene)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-[2-(5-phenyloxazolyl)]amino)ethoxy]benzyl)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-[2-(5-phenyloxazolyl)]amino)ethoxy]benzylidene)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-[2-(4,5-dimethyloxazolyl)]amino)ethoxy]benzyl)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-[2-(4,5-dimethyloxazolyl)]amino)ethoxy]benzylidene)-2,4-thiazolidinedione;
- 5-(4-[2-(N-methyl-N-(2-imidazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione;

- 5-[4-(2-(2-pyrimidinylamino)ethoxy)benzylidene]-2,4-thiazolidinedione;
 5-(4-[2-(N-acetyl-N-(2-pyrimidinyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione;
 5-(4-(2-(N-(2-benzothiazolyl)-N-benzylamino)ethoxy)benzylidene)-2,4-thiazolidinedione;
 5-(4-(2-(N-(2-benzothiazolyl)-N-benzylamino)ethoxy)benzyl)-2,4-thiazolidinedione;
 5 5-(4-[3-(N-methyl-N-(2-benzoxazolyl)amino)propoxy]benzyl)-2,4-thiazolidinedione;
 5-(4-[3-(N-methyl-N-(2-benzoxazolyl)amino)propoxy]benzylidene)-2,4-thiazolidinedione;
 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione; and
 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof
 and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.
 10 13. A process for the preparation of a compound of formula (I), or a tautomeric form thereof and/or a
 pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, characterised
 in that the process comprises either:
 (a) reacting a compound of formula (III):

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wherein R^2 , R^3 and A^2 are as defined in relation to formula (I), and R^a is a moiety convertible to a moiety of
 formula (f):

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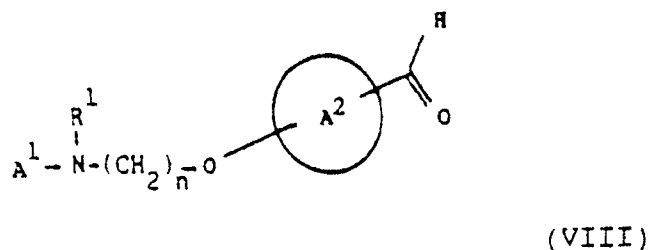
35

wherein R^1 , A^1 , and n are as defined in relation to formula (I), with an appropriate reagent capable of
 converting R^a to the said moiety (f); or

(b) reacting a compound of formula (VIII):

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wherein R^1 , A^1 , A^2 , and n are as defined in relation to formula (I) with 2,4-thiazolidinedione; and thereafter, if
 required, carrying out one or more of the following optional steps:

- (i) converting a compound of formula (I) to a further compound of formula (I);
- (ii) preparing a pharmaceutically acceptable salt of the compound of formula (I) and/or a pharmaceutically
 acceptable solvate thereof.

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14. A pharmaceutical composition comprising a compound of formula (I) according to claim 1, or a
 tautomeric form thereof or a pharmaceutically acceptable salt thereof or pharmaceutically acceptable
 solvate thereof, and a pharmaceutically acceptable carrier therefor.

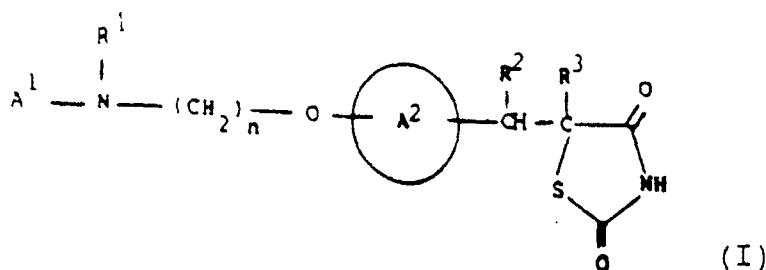
15. A compound of formula (I) according to claim 1, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

16. A compound of formula (I) according to claim 1, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of hyperglycaemia and/or hyperlipidaemia.

17. The use of a compound of formula (I) according to claim 1, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperglycaemia and/or hyperlipidaemia.

Claims for the following Contracting State: ES

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



or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, wherein:

A¹ represents a substituted or unsubstituted aromatic heterocyclyl group;

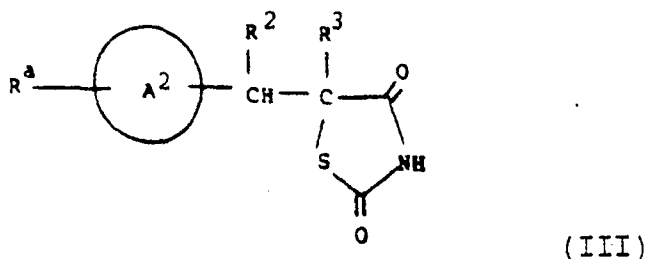
R¹ represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

R² and R³ each represent hydrogen, or R² and R³ together represent a bond;

A² represents a benzene ring having in total up to five substituents; and

n represents an integer in the range of from 2 to 6; characterised in that the process comprises either:

(a) reacting a compound of formula (III):



wherein R², R³ and A² are as defined in relation to formula (I), and Rᵃ is a moiety convertible to a moiety of formula (f):



wherein R¹, A¹, and n are as defined in relation to formula (I), with an appropriate reagent capable of converting Rᵃ to the said moiety (f); or

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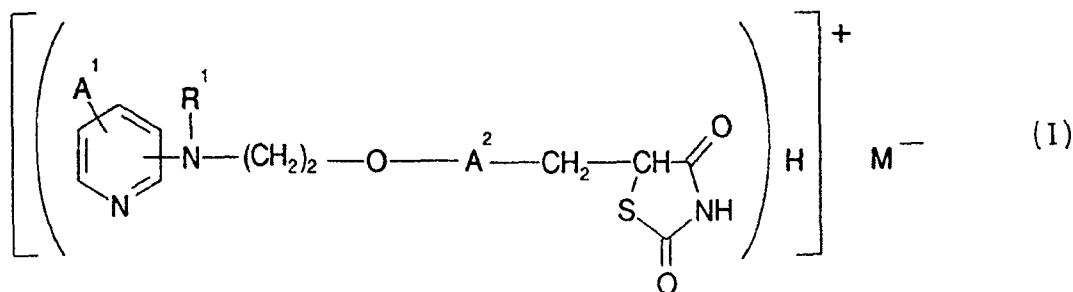


101

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 417/12, A61K 31/425 A61K 31/44	A1	(11) International Publication Number: WO 94/05659 (43) International Publication Date: 17 March 1994 (17.03.94)
(21) International Application Number: PCT/GB93/01853 (22) International Filing Date: 1 September 1993 (01.09.93) (30) Priority data: 9218830.9 5 September 1992 (05.09.92) GB (71) Applicant (for all designated States except US): SMITH-KLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): POOL, Colin, Ripley [GB/GB]; ROMAN, Robin, Sherwood [US/GB]; Smith-Kline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB). BRIGHWELL, Malcolm, David [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). TREMPER, Alan, William [US/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB).		(74) Agent: RUTTER, Keith; SmithKline Beecham, Corporate Intellectual Property, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB). (81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.

(54) Title: SUBSTITUTED THIAZOLIDINEDIONE DERIVATIVES



(57) Abstract

A compound of formula (I) or a tautomeric form thereof and/or a pharmaceutically acceptable solvate thereof, wherein: R¹ represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group; A¹ represents hydrogen or 1 to 4 optional substituents selected from the group consisting of: alkyl, alkoxy, aryl and halogen or A¹ represents two substituents on adjacent carbon atoms

Where appropriate the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof may be prepared as individual isomers using conventional chemical procedures.

The stability of the compounds of the invention may be determined using
5 conventional quantitative analytical methods: For example the stability of the compounds in the solid form may be determined by using accelerated stability tests such as differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and isothermal testing at elevated temperatures including conventional storage tests wherein the test compounds are stored under controlled conditions of temperature and
10 humidity over known periods of time. Quantitative analysis of the test compounds, against appropriate reference standards before, during and after the storage period allows the stability of the test compound to be determined.

As stated the compounds of the invention are significantly more soluble in water than the corresponding free base. Thus a convenient method for determining
15 the stability of the compounds of the invention in aqueous solution involves determining the degree of precipitation of the parent free base from an aqueous solution of the test compound at known conditions of temperature and over known periods of time. We have found that the compounds of formula (I) show good aqueous stability. In particular the compounds of formula (I) wherein M^- represents
20 maleate or tartrate are particularly stable in aqueous solution. Most surprisingly, the compounds of formula (I) wherein M^- represents a maleate ion, HOOC.CH=CH.COO^- , were found to be particularly stable in aqueous solution.

The quantitative analysis of the test compounds in the above mentioned tests may be carried out using conventional methods, generally chromatographic methods
25 such as high pressure liquid chromatography.

As mentioned above the compounds of the invention are indicated as having useful therapeutic properties:

The present invention accordingly provides a compound of formula (I), and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic
30 substance.

Thus the present invention provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of hyperglycaemia.

In a further aspect the present invention also provides a compound of formula
35 (I), or a tautomeric form thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment and/or prophylaxis of hyperlipidaemia.

As indicated hereinbefore the present invention also provides a compound of formula (I) or a tautomeric form thereof and/or a pharmaceutically acceptable solvate

Example 1**5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione,
maleic acid salt**

5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (470g) and maleic acid (137g) were dissolved in ethanol (41.) at boiling. The hot solution was filtered via diatomaceous earth and was then allowed to cool slowly with gentle agitation. After leaving in a refrigerator at 0-5°C for several hours, the maleate salt was filtered off, washed with ethanol and dried in vacuo at 50° to give 446g (73%) of product, m.p. 120-121°C. P-f

¹H NMR δ (d₆-DMSO): 3.0-3.35 (2H, complex); 3.10 (3H, s); 3.95 (2H, t); 4.15 (2H, t); 4.85 (1H, complex); 6.20 (2H, s); 6.65 (1H, t); 6.85 (3H, complex); 7.15 (2H, d) 7.65 (1H, t); 8.05 (1H, complex); 11.85-12.1 (1H, broad, exchanges with D₂O).

A very broad signal was observed in the range 2-5ppm which is thought to be due to residual water from the solvent and the exchangeable carboxylic acid protons.

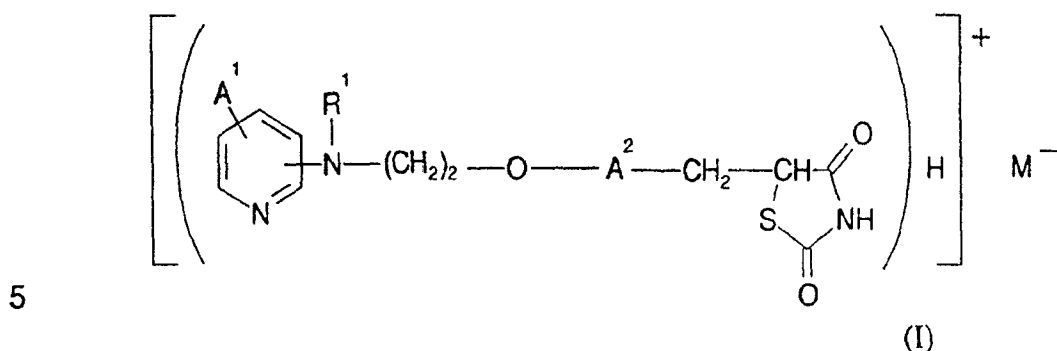
Example 2**5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione,
maleic acid salt**

5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt (294.6g, 0.825M) and maleic acid (95.8g 0.825m) were stirred in refluxing ethanol (2.7l) until all the solid had dissolved. Decolourising charcoal was added and the hot solution filtered through celite, allowed to cool to room temperature with stirring. After cooling in a refrigerator at 0-5°C for several hours, the title compound was filtered, collected and dried at 50°C under vacuum overnight to give 364.1g (87%) of product, m.p. 119 - 119.5°C. P-f

The ¹H NMR spectra was as for Example 1.

Claims

1. A compound of formula (I):



or a tautomeric form thereof and/or a pharmaceutically acceptable solvate thereof, wherein:

10

R^1 represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

A^1 represents hydrogen or 1 to 4 optional substituents selected from the group consisting of: alkyl, alkoxy, aryl and halogen or A^1 represents two substituents on adjacent carbon atoms, which substituents together with the carbon atoms to which they are attached form a substituted or unsubstituted aryl group;

15

A^2 represents a benzene ring having 1 to 3 optional substituents; and M^- represents a counter-ion.

20

2. A compound according to claim 1, wherein M^- is provided by a pharmaceutically acceptable acid having a pK_a in the range of from 0.1 to 4.5.

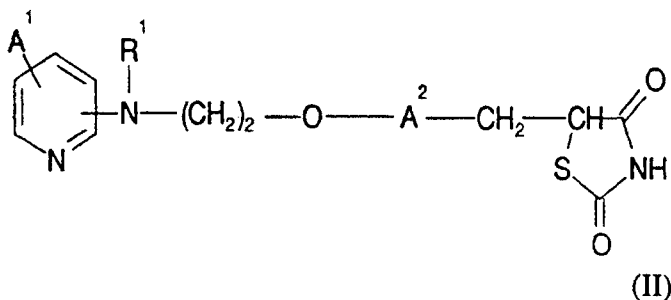
- 25 3. A compound according to claim 1 or claim 2, wherein M^- is provided by a pharmaceutically acceptable acid having a pK_a in the range of from 1.75 to 2.5.

4. A compound according to any one of claims 1 to 3, wherein M^- is the maleate ion $HOOC.CH=CH.COO^-$.

- 30 5. A compound according to claim 1, being 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt

6. A process for the preparation of a compound of formula (I)

form thereof, and/or a pharmaceutically acceptable solvate thereof, which process comprises reacting a compound of formula (II):



wherein R¹, A¹ and A² are as defined in relation to formula (I), with a source of counter-ion M⁻; and thereafter if required preparing a pharmaceutically acceptable solvate thereof.

7. A process according to claim 6, wherein the source of counter-ion M⁻ includes pharmaceutically acceptable acids having a pK_a in the range of from 1.5 to 4.5 or from 1.75 to 2.5.

8. A process according to claim 6, wherein the source of a counter-ion M⁻ is maleic acid.

9. A pharmaceutical composition comprising a compound of formula (I), or a tautomeric form thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

10. A compound of formula (I), or a tautomeric form thereof, or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

11. A compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of hyperglycaemia, hyperlipidaemia, hypertension, cardiovascular disease and certain eating disorders.

12. A method for the treatment and/or prophylaxis of hyperglycaemia, hyperlipidaemia, hypertension, cardiovascular disease and certain eating disorders in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of formula (I), or a tautomeric form thereof and/or

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a pharmaceutically acceptable solvate thereof to a human or non-human mammal in need thereof.

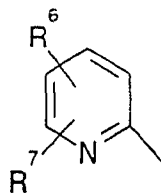
13. The use of a compound of formula (I), or a tautomeric form thereof and/or a
5 pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperglycaemia, hyperlipidaemia, hypertension, cardiovascular disease and certain eating disorders.

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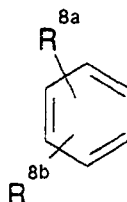
(51) International Patent Classification ⁶ : A61K 31/00, 31/425, 31/44	A1	(11) International Publication Number: WO 95/21608 (43) International Publication Date: 17 August 1995 (17.08.95)
(21) International Application Number: PCT/EP95/00441 (22) International Filing Date: 7 February 1995 (07.02.95) (30) Priority Data: 9402624.2 10 February 1994 (10.02.94) GB 9410214.2 21 May 1994 (21.05.94) GB 9426019.7 22 December 1994 (22.12.94) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): BUCKINGHAM, Robin, Edwin [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). (74) Agent: RUTTER, Keith; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: USE OF INSULIN SENSITISERS FOR TREATING RENAL DISEASES		
(57) Abstract A method for the treatment and/or prophylaxis of renal diseases including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease, and microalbuminuria which method comprises the administration of an effective, non-toxic amount of an insulin sensitiser to a human or non-human mammal in need thereof.		



(c')

wherein R^6 and R^7 are as defined in relation to formula (c).

- 5 In one favoured aspect R^6 and R^7 together represent a moiety of formula (d):



(d)

10

wherein R^{8a} and R^{8b} each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

- Suitably, R^{8a} and R^{8b} each independently represent hydrogen, halogen, alkyl or alkoxy. Favourably, R^{8a} represents hydrogen. Favourably, R^{8b} represents hydrogen. Preferably, R^{8a} and R^{8b} both represent hydrogen.

- 15 In a further favoured aspect R^6 and R^7 each independently represent hydrogen, alkyl or a substituted or unsubstituted phenyl group and more favourably, R^6 and R^7 each independently represent hydrogen, alkyl or phenyl.

- Preferably, for the moiety of formula (a), R^6 and R^7 together represent the moiety of formula (d).

- 20 Preferably, for the moieties of formula (b), (c) or (c'), R^6 and R^7 both represent hydrogen.

- It will be appreciated that the five substituents of A^2 include three optional substituents. Suitable optional substituents for the moiety A^2 include halogen, substituted or unsubstituted alkyl or alkoxy.

- 25 Further suitable, favoured and preferred values for variables A^2 , R^1 , R^2 , R^3 and n are as defined in EP 0306228 and WO94/05659.

A preferred compound of formula (I) is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione or a tautomeric form thereof

and/or a pharmaceutically acceptable salt thereof, especially a maleic acid salt thereof, and/or a pharmaceutically acceptable solvate thereof.

As indicated above, a compound of formula (I) may exist in one of several tautomeric forms, all of which are encompassed in the method of the present invention. It will be appreciated that the present invention encompasses the administration of all of the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof, including any stereoisomeric forms thereof, whether as individual isomers or as mixtures of isomers.

Suitable substituents for any heterocyclyl group of the compounds of formula (I) include up to 4 substituents selected from the group consisting of: alkyl, alkoxy, aryl and halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a benzene ring, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be substituted or unsubstituted.

The suitable, favoured and preferred thiazolidinedione insulin sensitisers disclosed in European Patent Applications, Publication Numbers: 0306228, 0008203, 0139421, 0032128, 0428312, 0489663, 0155845, 0257781, 0208420, 0177353, 0319189, 0332331, 0332332, 0528734, 0508740; International Patent Application, Publication Numbers 92/18501, 93/02079, 93/22445 and United States Patent Number 5104888 are those compounds defined as suitable, favoured and preferred in the respective patent publications.

The suitable, favoured and preferred acyclic insulin sensitisers disclosed in International Patent Applications, Publication Numbers WO91/19702, WO92/03425, WO93/21166 and WO94/01420 and United States Patent Number 5232945 are those compounds defined as suitable, favoured and preferred in the respective patent publications.

Other suitable, favoured and preferred insulin sensitisers are the suitable, favoured and preferred compounds disclosed in European Patent Application, Publication Number 0533933, International Patent Application, Publication Number WO 93/02079, Japanese Patent Application Publication Number 05271204 and United States Patent Number 5264451.

Also specifically included in the method of the invention are the specific examples disclosed in the above mentioned patent applications.

When used herein the term 'insulin sensitiser' relates to compounds which

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Bogotá, D.C., Abril 15 de 2005

Doctor

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ASUNTO	Radicación No.	00 028 927
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	10727
	Folios	0

Como resultado del examen de patentabilidad de la solicitud de patente de invención, realizado según lo establece el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico:

1. Documentos estudiados

Para el presente estudio se tuvieron en cuenta el nuevo capítulo descriptivo comprendido en los folios 67 - 78 y el nuevo capítulo reivindicatorio de los folios 79 - 80 de la solicitud en estudio.

2. Objeto de la Invención

El objeto de la presente solicitud de patente de invención consiste en:

Las reivindicaciones 1 - 8, 11, 12, 14, se refieren a un polimorfo de la sal del ácido maléico de la 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona.

La reivindicación 9 menciona un proceso para preparar un polimorfo que se caracteriza porque una disolución del compuesto en etanol a elevada temperatura se enfría de manera que se produce la cristalización del polimorfo, después de lo cual se recupera.

La reivindicación 10 se refiere a una composición que contiene un polimorfo de la reivindicación 1 y un vehículo.

La reivindicación 13 se refiere al uso del polimorfo.

El problema planteado en esta solicitud es la necesidad de proporcionar un nuevo producto farmacéutico para tratamiento y/o profilaxis de diabetes mellitus.

Para resolver este problema técnico la solicitud en estudio proporciona un

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polimorfo de la sal del ácido maléico de la 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A 23 K 31/12 // 31/425 // 31/44; C 07 D 417/12.

También se reivindica prioridad de las Solicitudes de Patente de Gran Bretaña 9909471.6 de abril 23 de 1999 y 9912195.6 de mayo 25 de 1999, con respecto a las cuales la fecha de presentación de la actual solicitud cumple el plazo máximo permitido.

3. Reivindicaciones de Uso

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*.

El artículo 21 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"Los productos o procedimientos ya patentados, comprendidos en el estado de la técnica, de conformidad con el Artículo 16 de la presente Decisión, no serán objeto de nueva patente, por el simple hecho de atribuirse un uso distinto al originalmente comprendido por la patente inicial"*.

La reivindicación 13 se refiere al uso del polimorfo.

Se observa que el uso del polimorfo, de la reivindicación 13, que no es una invención de producto ni de procedimiento, no es patentable de acuerdo con las normas citadas, que especifican que los usos no son patentables.

De manera que la reivindicación 13, de acuerdo con los artículos 14 y 21 no es patentable.

4. Determinación del Estado de la Técnica

El artículo 16 de la decisión 486 de la comisión de la Comunidad Andina que establece que *"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida"*.

Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40".

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es abril 23 de 1999, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

No.	Documento	Título	Fecha de Publicación
D1	EP 0 306 228	Derivados de Tiazolidindiona sustituidos	Mar 8, 1989
D2	WO 94 05659	Derivados de Tiazolidindiona sustituidos	Mar 17, 1994
D3	WO 95 210608	Uso de sensibilizadores de insulina para tratar enfermedades renales	Ag. 17, 1995

5. Evaluación de los requisitos de Patentabilidad

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*.

En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar el cumplimiento de los requisitos de novedad, nivel inventivo y aplicación industrial, con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la Novedad

El Art. 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente, o, en su caso, de la prioridad reconocida.*

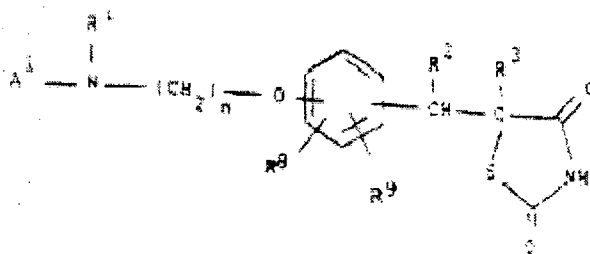
Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el Art 40”.

Las reivindicaciones 1 - 8, 11, 12, 14, se refieren a un polimorfo de la sal del ácido maléico de la 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona.

La reivindicación 9 menciona un proceso para preparar un polimorfo que se caracteriza porque una disolución del compuesto en etanol a elevada temperatura se enfría de manera que se produce la cristalización del polimorfo, después de lo cual se recupera.

La reivindicación 10 se refiere a una composición que contiene un polimorfo de la reivindicación 1 y un vehículo.

D1 enseña compuestos de estructura:



Enseña además que dentro de los solvatos farmacéuticamente aceptables se incluyen los hidratos (página 4). Y menciona las sales farmacéuticamente aceptables y los solvatos farmacéuticamente aceptables de estos compuestos (Ver reivindicación 1). La reivindicación 14 enseñaba una composición que contiene este compuesto y un vehículo.

D2 enseña la sal del ácido maléico de la 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona. Ver págs 5, 8 y 9. La pág 10 enseña una composición que contiene este compuesto y un vehículo. En la página 8, ejemplo 2, se enseña un proceso para preparar un polimorfo que se caracteriza porque el compuesto se disuelve en etanol a elevada temperatura y luego se enfría de manera que se produce la cristalización del polimorfo, después de lo cual se recuperan los cristales. (ver página 8, ejemplo 2).

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D3 enseña la 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona, sus formas tautómeras y las sales farmacéuticamente aceptables, en especial la sal del ácido maléico, y los solvatos farmacéuticamente aceptables de este compuesto.

Se observa que el compuesto de la sal del ácido maléico de la 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona de las reivindicaciones 1 - 8, 11, 12, 14 de esta solicitud ya se había obtenido en D1, D2 y D3. Se aclara además que el ser un polimorfo es una característica inherente al compuesto y el hecho de definirla ahora en esta solicitud no lo hace nuevo. Solo si el espectro del compuesto fuese nuevo, entonces el compuesto también sería diferente y nuevo. De manera que el compuesto reivindicado no es nuevo.

Con referencia a la reivindicación 10 que se refiere a una composición que contiene un polimorfo de la reivindicación 1 y un vehículo, se observa que puesto que el compuesto que caracteriza a la composición no es nuevo, tampoco lo es la composición. Además esta composición ya se había enseñado en D1 y D2, de manera que no es nueva.

Con respecto al proceso de la reivindicación 9 para preparar un polimorfo que se caracteriza porque una disolución del compuesto en etanol a elevada temperatura se enfría de manera que se produce la cristalización del polimorfo, después de lo cual se recupera, se observa que D2 ya enseñaba un proceso para preparar un polimorfo que se caracteriza porque el compuesto se disuelve en etanol a elevada temperatura y luego se enfría de manera que se produce la cristalización del polimorfo, después de lo cual se recuperan los cristales. (ver página 8, ejemplo 2). De manera que el proceso reivindicado no es nuevo.

Evaluación del Nivel Inventivo

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *Se considerará que una invención tiene nivel inventivo, si para*

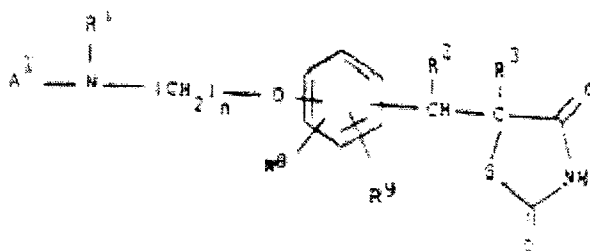
una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.

Las reivindicaciones 1 - 8, 11, 12, 14, se refieren a un polimorfo de la sal del ácido maléico de la 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona.

La reivindicación 9 menciona un proceso para preparar un polimorfo que se caracteriza porque una disolución del compuesto en etanol a elevada temperatura se enfría de manera que se produce la cristalización del polimorfo, después de lo cual se recupera.

La reivindicación 10 se refiere a una composición que contiene un polimorfo de la reivindicación 1 y un vehículo.

D1 enseña compuestos de estructura:



Enseña además que dentro de los solvatos farmacéuticamente aceptables se incluyen los hidratos (página 4). Y menciona las sales farmacéuticamente aceptables y los solvatos farmacéuticamente aceptables de estos compuestos (Ver reivindicación 1). La reivindicación 14 enseñaba una composición que contiene este compuesto y un vehículo.

D2 enseña la sal del ácido maléico de la 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona. Ver págs 5, 8 y 9. La pág 10 enseña una composición que contiene este compuesto y un vehículo. En la página 8, ejemplo 2, se enseña un proceso para preparar un polimorfo que se caracteriza porque el compuesto se disuelve en etanol a elevada temperatura y luego se enfría de manera que se produce la cristalización del polimorfo, después de lo cual se recuperan los cristales. (ver página 8, ejemplo 2).

D3 enseña la 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona, sus formas tautómeras y las sales farmacéuticamente aceptables, en especial la sal del ácido maléico, y los solvatos farmacéuticamente aceptables de este compuesto.

Se observa que la combinación de las enseñanzas de estas anterioridades: D2 que enseña la sal del ácido maléico de la 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona (ver págs 5, 8 y 9); una composición que contiene este compuesto y un vehículo (ver pág 10); un proceso para preparar un polimorfo que se caracteriza porque el compuesto se disuelve en etanol a elevada temperatura y luego se enfría de manera que se produce la cristalización del polimorfo, después de lo cual se recuperan los cristales. (ver página 8, ejemplo 2) y D3 que enseña la 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona, sus formas tautómeras y las sales

farmacéuticamente aceptables, en especial la sal del ácido maléico, y los solvatos farmacéuticamente aceptables de este compuesto; sugiere un polimorfo de la sal del ácido maléico de la 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona, las composiciones que lo contienen y el proceso para prepararlo que se caracteriza porque se disuelve el compuesto en etanol, se eleva la temperatura, se enfría de manera que se produce la cristalización del polimorfo y se recuperan los cristales, objeto de esta solicitud. Las reivindicaciones no mencionan una característica que conceda un efecto diferente o especial al compuesto ni a las composiciones, así que son obvias y evidentes para una persona versada en la materia. Entonces debido a que: (a) el compuesto, la conformación de las composiciones y el proceso de esta solicitud, a partir de las anterioridades, son evidentes para una persona conocedora de la materia; porque siendo bien conocidos el compuesto 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona, las composiciones que lo contienen y el proceso para prepararlo que se caracteriza porque se disuelve el compuesto en etanol, se eleva la temperatura, se enfría de manera que se produce la cristalización del polimorfo y se recuperan los cristales, para una persona conocedora de la materia era evidente el realizarlos de manera similar, teniendo en cuenta estos compuestos; (b) las reivindicaciones de esta solicitud no mencionan una característica que conceda un efecto diferente o especial al compuesto, las composiciones ó el proceso, que pueda considerarse como un aporte a la técnica, porque las anterioridades ya enseñaban el compuesto, los vehículos y las etapas del proceso de cristalización requeridas, así que estas son obvias para una persona versada en la materia y (c) el problema planteado en esta solicitud era la necesidad de proporcionar un nuevo producto farmacéutico para tratamiento y/o profilaxis de diabetes mellitus y puesto que para resolver este problema técnico la solicitud proporciona un polimorfo de la sal del ácido maléico de la 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona, es decir de manera similar a como se resolvía en las anterioridades D1, D2 y D3; entonces esta solicitud no tiene **nivel inventivo**.

El hidrato no tiene nivel inventivo porque es de conocimiento general que las sales pueden aparecer en forma anhidra y en forma hidratada.

El método mencionado es una forma convencional para obtener una sal cristalizada, de modo que también carece de nivel inventivo.

Lo reivindicado tendría nivel inventivo si el hidrato fuera nuevo y si además presentara propiedades sorprendentes y resolviera un problema que no se había resuelto en la técnica, en comparación con el compuesto del estado del arte.

6. Conclusión

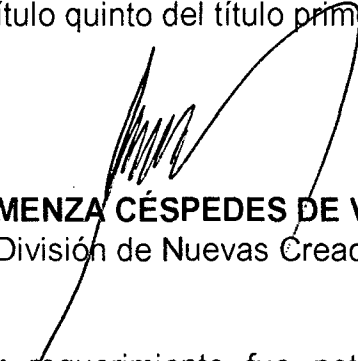
En conclusión, los requisitos de patentabilidad de la presente solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	EP 0 306 228	1 a 12 y 14	Novedad y nivel inventivo
D2	WO 94 05659	1 a 12 y 14	Novedad y nivel inventivo
D3	WO 95 210608	1 a 12 y 14	Novedad y nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente

comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No. 10 de 2001.


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

El anterior requerimiento fue notificado por fijación en lista, de fecha
05 MAYO 2005

CONCEPTO TÉCNICO No. 510	EXAMINADOR TÉCNICO Código 202007
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