

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 03-018885

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

PCT FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **537**

DE FECHA **27 DE FEBRERO DE 2004** EL TERMINO HABIL SEÑALADO POR

LA LEY EXPIRA EL **27 DE MAYO DEL 2004**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO ___ **X** _____

Bogotá D.C, SEPTIEMBRE DE 2007

29
78

SUBSTITUTED THIAZOLIDINEDIONE DERIVATIVES

This invention relates to certain novel compounds, to a process for preparing such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

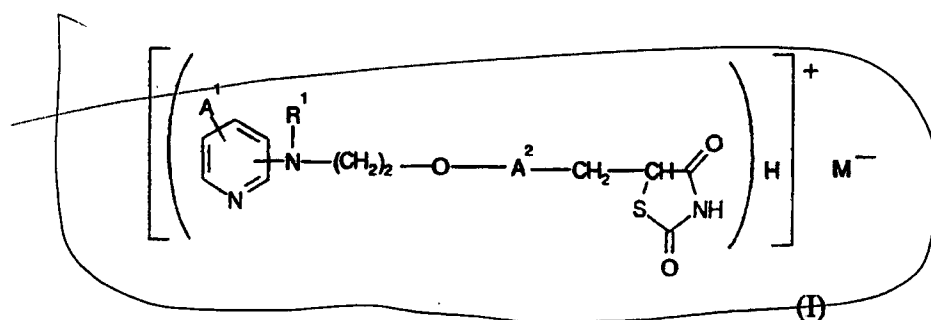
European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having hypoglycaemic and hypolipidaemic activity.

It is now surprisingly indicated that a specific group of compounds from within formula (I) of EP-A-0,306,228 have improved selectivity of action and are therefore of particular use in the treatment of Type II diabetes. These compounds are also indicated to be of particular use for the treatment and/or prophylaxis of other diseases including hyperlipidaemia, hypertension and cardiovascular disease, especially atherosclerosis. In addition these compounds are considered to be useful for treating certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating, such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia.

These compounds show good aqueous stability and good stability in the solid form, certain of these compounds are indicated to be particularly stable. In addition these compounds are significantly more soluble in water than the corresponding free base.

The surprising and advantageous stability and aqueous solubility of these compounds provides for significant formulation and bulk handling advantages.

Accordingly, the present invention provides a compound of formula (I):



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

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

- 2 -

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

Suitable counter-ions M^- include ions provided by pharmaceutically acceptable acids.

A suitable source of counter-ions M^- is provided by those pharmaceutically acceptable acids having a pK_a in the range of from 0.1 to 4.5 and especially in the range of from 1.75 to 2.5.

Favoured pharmaceutically acceptable acids include mineral acids, such as hydrobromic, hydrochloric and sulphuric acids, and organic acids, such as methanesulphonic, tartaric and maleic acids, especially tartaric and maleic acid.

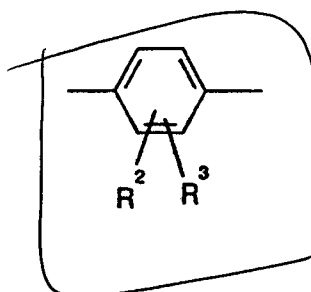
A preferred counter-ion is the maleate ion $HOOC.CH=CH.COO^-$.

Preferably, A^1 is hydrogen.

Suitable optional substituents for the moiety A^2 include up to three substituents selected from halogen, substituted or unsubstituted alkyl or alkoxy.

Favourably, A^2 represents a moiety of formula (e):

20



(e)

wherein R^2 and R^3 each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

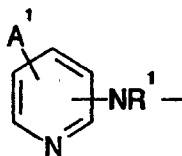
Suitably, R^2 and R^3 each independently represent hydrogen, halogen, alkyl or alkoxy.

Preferably, R^2 and R^3 each represent hydrogen.

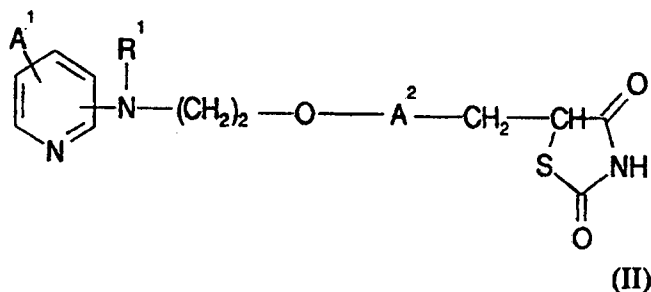
Suitably, R^1 represents hydrogen, alkyl, acyl, especially acetyl, or benzyl.

30 Preferably, R^1 represents an alkyl group, for example a methyl group.

Preferably the moiety :



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 above defined counter-ion M⁻; and thereafter if required preparing a pharmaceutically acceptable solvate thereof.

10 A suitable source of a counter-ion M⁻ is a pharmaceutically acceptable acid.

A suitable source of counter-ions includes pharmaceutically acceptable acids having a pK_a in the range of from 1.5 to 4.5, especially in the range of from 1.75 to 2.5.

15 Favoured pharmaceutically acceptable acids include mineral acids, such as hydrobromic, hydrochloric and sulphuric acids, and organic acids, such as methanesulphonic, tartaric and maleic acids.

A preferred source of a counter-ion is maleic acid.

20 The reaction between the compound of formula (I) and the source of counter-ion M⁻ is generally carried out under conventional salt forming conditions, for example by admixing the compound of formula (I) and the source of counter-ion M⁻, suitably in approximately equimolar amounts but preferably using a slight excess of the source of counter-ion M⁻, in a solvent, generally a C₁₋₄ alkanolic solvent such as ethanol, at any temperature which provides a suitable rate of formation of the required product, generally at an elevated temperature for example at the reflux temperature of the solvent and thereafter crystallising the required product.

25 Pharmaceutically acceptable solvates of the compound of formula (I) may be prepared using conventional chemical procedures.

The compound of formula (II) may be prepared according to methods disclosed in EP-A-0306228.

30 Suitable sources of counter-ion are known commercially available sources, such as maleic acid, or the required source may be prepared according to known procedures.

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

NOVEL COMPOUNDS

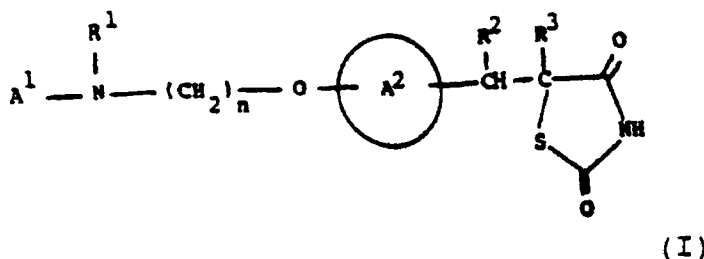
This invention relates to certain substituted thiazolidinedione derivatives, to a process for preparing such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

European Patent Applications, Publication Numbers 0008203, 0139421, 0155845, 0177353, 0193256, 0207581 and 0208420 relate to thiazolidinedione derivatives which are disclosed as having hypoglycaemic and hypolipidaemic activity. Chem. Pharm. Bull 30 (10) 3580-3600 also relates to certain thiazolidinedione derivatives having hypoglycaemic and hypolipidaemic activities.

It has now surprisingly been discovered that certain novel substituted-thiazolidinedione derivatives show improved blood-glucose lowering activity and are therefore of potential use in the treatment and/or prophylaxis of hyperglycaemia and are of particular use in the treatment of Type II diabetes.

These compounds are also indicated to be of potential use for the treatment and/or prophylaxis of other diseases including hyperlipidaemia, hypertension, cardiovascular disease and certain eating disorders.

Accordingly, the present invention provides 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.

Suitable aromatic heterocyclyl groups include substituted or unsubstituted, single or fused ring aromatic heterocyclyl groups comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur or nitrogen.

Favoured aromatic heterocyclyl groups include substituted or unsubstituted single ring aromatic heterocyclyl groups having 4 to 7 ring atoms, preferably 5 or 6 ring atoms.

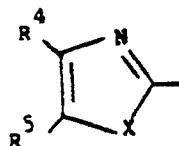
In particular, the aromatic heterocyclyl group comprises 1, 2 or 3 heteroatoms, especially 1 or 2, selected from oxygen, sulphur or nitrogen.

Suitable values for A¹ when it represents a 5- membered aromatic heterocyclyl group include thiazolyl and oxazolyl, especially oxazolyl.

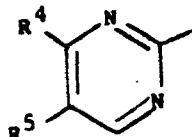
Suitable values for A¹ when it represents a 6- membered aromatic heterocyclyl group include pyridyl or pyrimidinyl.

Suitably R² and R³ each represent hydrogen.

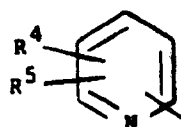
Preferably, A¹ represents a moiety of formula (a), (b) or (c):



(a)



(b)

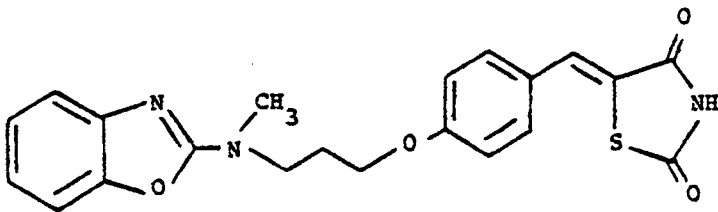


(c)

5-(4-[3-(N-Methyl-N-(2-benzoxazolyl)amino)propoxy]benzylidene)-2,4-thiazolidinedione

5

10



15

The title compound (m.p. 202-204° C) was prepared from 4-[3-(N-methyl-N-(2-benzoxazolyl)amino)propoxy]benzaldehyde (5.3g) and 2,4-thiazolidinedione (2.2g) by a similar procedure to that described in Example 4.

20

¹H NMR δ (DMSO - d₆)

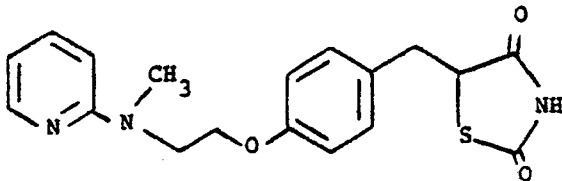
2.0-2.35 (2H, complex); 3.15 (3H, s); 3.7 (2H, t); 4.2 (2H, t); 7.0-7.7 (8H, complex); 7.8 (1H, s); 12.0 (1H, broad s, exchanges with D₂O).

EXAMPLE 30

25

5-(4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione

30



35

The title compound (m.p. 153-5° C; MeOH) was obtained from 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione by a similar procedure to that described in Example 1.

40

¹H NMR δ (DMSO - d₆)

2.9-3.4 (2H, complex); 3.1 (3H, s); 3.9 (2H, t); 4.15 (2H, t); 4.8 (1H, complex); 6.5-6.85 (2H, complex); 6.8 (2H, d); 7.2 (2H, d); 7.5 (1H, complex); 8.1 (1H, d); 12.05 (1H, broad s, exchanges with D₂O).

45

EXAMPLE 31

50

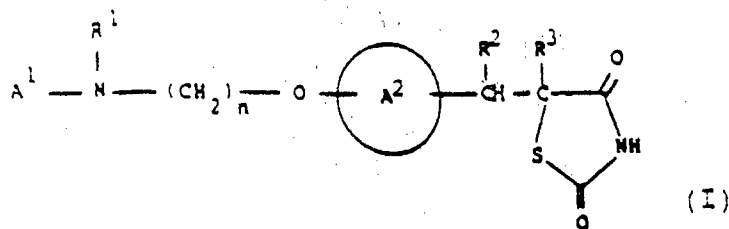
55

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;

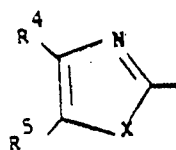
R² and R³ each represent hydrogen, or R² and R³ together represent a bond;

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

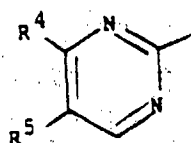
n represents an integer in the range of from 2 to 6.

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.

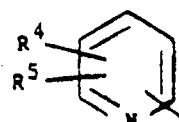
3. A compound according to claim 1 or claim 2, wherein A¹ represents a moiety of formula (a), (b) or (c):



(a)



(b)



(c)

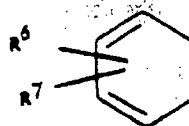
wherein:

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)