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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

SUPERINDUSTRIA Y COMERCIO

Radicacion : 03018885 00000003 Folios: 2
Fecha (AMD): 2004-07-15 09:54:05
Tramite : 011 PCT-PATENT 379 FASE NACI 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Ref: Expediente No. 03.018.885

Solicitud de patente de invención titulada:

"LA SAL DE CLORHIDRATO DE 5-[4-[2-(N-METIL-N-(2-PIRIDIL)AMINO)ETOXI]BENCIL]TIAZOLIDIN-2,4-DIONA."

Solicitante: SMITHKLINE BEECHAM P.L.C.

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN EL ARTICULO 44 DE LA DECISION 486, GACETA No. 537

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado del solicitante, respetuosamente me permito solicitar, que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma. Dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina de Naciones. Adjunto recibo por el monto de \$177.000 pesos para cubrir la tasa correspondiente, según la Resolución 37323 del año 2003.

Atentamente,



CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por \$177.000 pesos

FTT/P2003/000031 040624

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CLARITERAISBECK

Patentes, marcas y diseños

DEPARTAMENTO DE INDUSTRIA Y COMERCIO
DIVISION DE NIEVAS CREACIONES

_____ 2 _____

Ref: Expediente No. 03.018.982

Señal de patente de invención (símbolo):

ALA PAT. DE CLORHIDRATO DE 5-14-12 (METIL-1,2-PERDIO) (4,4-NOI FORN)

REPRESENTACIONES DE LA PATENTE

SOLICITANTE: SINTETIKI EFTHAI P.L.C.

SOLICITUD DE EXAMEN DE PATENTABILIDAD
EL ARTICULO 10 DE LA LEY DE PATENTES

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá D.C., identificado en como aparece al pie de mi firma, en mi condición de apoderado del solicitante, se persono ante la Señal de patente de invención (símbolo) de la invención sobre los recubrimientos de patentes en la invención de la invención y lo esbozado en el artículo 14 de la Ley de la Comisión de la Comisión de la invención. Adjunto recibo por el monto de \$1.77.000 pesos para cubrir la tasa correspondiente según la Resolución 17323 del año 2003.

Atentamente,
CARLOS R. OLARTE
C.C. 20.782.17 de Bogotá
I.D. 24.392
Adjunto recibo por \$1.77.000 pesos

27
2
76

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 55,080
FECHA : JULIO 12 DE 2004

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03018885 00000003 Folios: 2
Fecha (AMD): 2004-07-15 09:54:05
Tramite : 011 PCT-PATENT 379 FASE NACI 530 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
FREDERICK TORRES	CONSIGNACION	BANCO POPULAR	050-00110-6	23286882	12/07/2004	9,344,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILID	177,000.00
	TOTAL :	\$ 177,000.00

SON: CIENTO SETENTA Y SIETE MIL PESOS

RESPONSABLE :



RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

MIT : 80015083-3

RECIBO DE CASH : 04 - 25.000
FECHA : JULIO 15 DE 2004

***** COMISIONACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PAGO	V. PAGO
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FREDERICK TORRES	COMISIONACION	BANCO POPULAR	050-00110-A	3330883	13/07/2004	2.334,000.00
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***** C E P T O *****

CANT. RECIBIDO	CONCEPTO	TOTAL CONCEPTO
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1 20002-01-01	114 PTC CAP-11 EXAMEN DE PATENTABILIDAD	277,000.00
TOTAL :		277,000.00

SOM : CIENTO SETENTA Y SIETE MIL PESOS



RECIBO DE CASH AL CASH AL EXPEDIENTE Nº.

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 ☒ _____

Bogotá D.C, SEPTIEMBRE DE 2007

DIVISION DE NUEVAS CREACIONES

RADICACION EXPEDIENTE Nº 03-018885

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

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 486/00.

SE PRESENTARON OPPOSICIONES POR PARTE DE TERCEROS

SI ☐ NO ☒

BOGOTÁ D.C. SEPTIEMBRE DE 2007

SUBSTITUTED THIAZOLIDINEDIONE DERIVATIVES

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

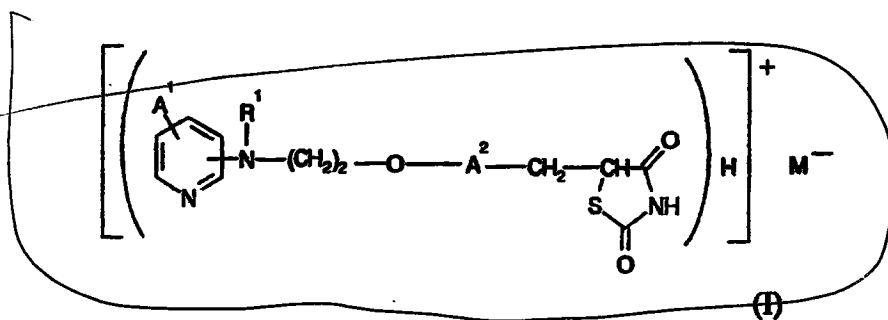
European Patent Application, Publication Number 0,306,228 relates to certain
 thiazolidinedione derivatives disclosed as having hypoglycaemic and hypolipidaemic
 activity.

10 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,
 15 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.

20 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
 25 compounds provides for significant formulation and bulk handling advantages.

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



30

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

SUBSTITUTED TRIAZOLIDINONE DERIVATIVES

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

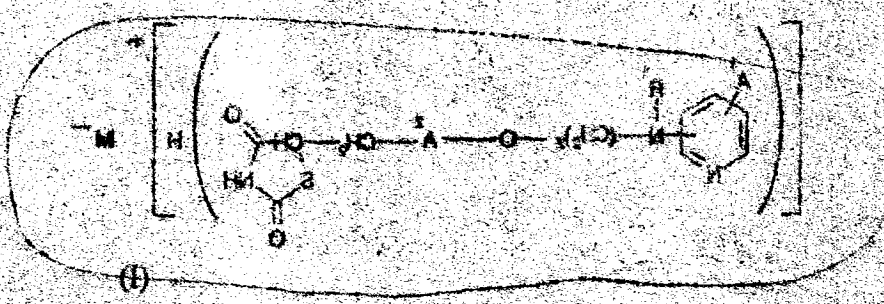
European Patent Application Publication Number 0 306 128 relates to certain triazolidinone derivatives disclosed as having hypoglycaemic and hepatoprotective activity.

It is now surprisingly indicated that a specific group of compounds from within formula (I) of EP-A-0 306 128 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 psychopathia, hypertension and cardiovascular disease.

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 bulimia.

The 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 packaging advantages. Accordingly, the present invention provides a compound of formula (I):



wherein A is a triazole ring substituted with an R group, B is a methylene group, C is a carbonyl group, D is an ester group, and E is a side chain.

R1 represents a hydrogen atom, an alkyl group, an aryl group, or a substituted or unsubstituted heterocyclic group, wherein the methyl moiety may be substituted or unsubstituted.

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- 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.

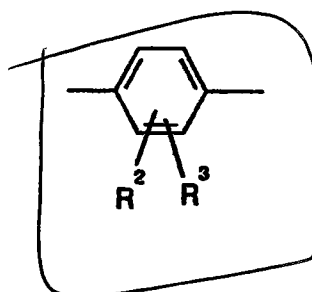
A preferred counter-ion is the maleate ion $HOOC.CH=CH.COO^-$.

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.

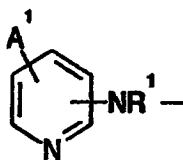
Suitably, R^2 and R^3 each independently represent hydrogen, halogen, alkyl or alkoxy.

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

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

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

Preferably the moiety :



substituted with group A¹ represents hydrogen or 1 to 4 optional substituents selected from the group consisting of alkyl, alkoxy, aryl and halogen or A¹.
 A² represents a substituent on adjacent carbon atoms which substituents together with the carbon atoms to which they are attached form a substituted or unsubstituted group. A² represents a substituent having 1 to 3 optional substituents, and A² represents a substituent.

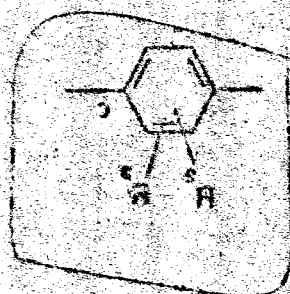
2. A suitable counter-ion M⁺ includes ions provided by pharmaceutically acceptable salts.

A suitable source of counter-ions M⁺ is provided by those pharmaceutically acceptable salts having a pK_a in the range of from 0.1 to 4.5 and especially in the range of from 1.5 to 3.5.

Favoured pharmaceutically acceptable acids include mineral acids such as hydrochloric, hydrobromic and sulphuric acids, and organic acids, such as acetic, propionic, tartaric and malic acids, especially tartaric and malic acids. A preferred counter-ion is the malate ion HOOC-CH₂-CH₂-COO⁻.

Especially, A¹ is hydrogen.

3. The optional substituents for the moiety A² include up to three substituents selected from halogen, substituted or unsubstituted alkyl or alkoxy. Preferably, A² represents a moiety of formula (c):

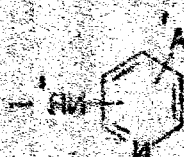


wherein R₂ and R₃ each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.
 Similarly, R₄ and R₅ each independently represent hydrogen, substituted or unsubstituted alkyl or alkoxy.

Preferably, R₂ and R₃ each represent hydrogen.

Similarly, R₄ represents hydrogen, alkyl, aryl, especially aryl or halogen.

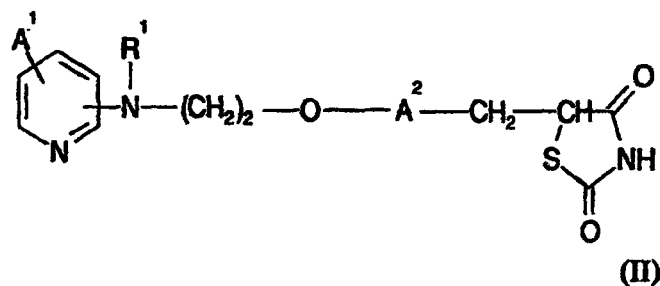
Preferably, R₄ represents an aryl group, for example a methyl group. Preferably, the moiety:



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- 4 -

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



5

wherein R^1 , A^1 and A^2 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.

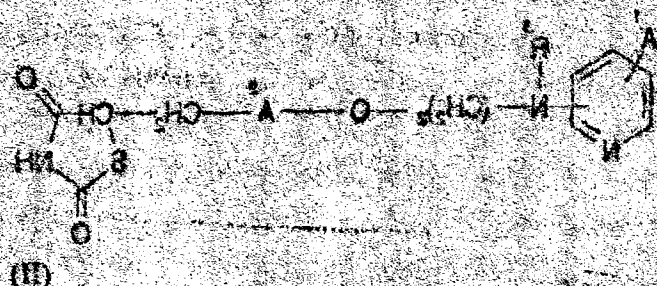
20 The reaction between the compound of formula (I) and the source of counter-ion M^- is generally carried out under conventional salt forming conditions, for example by admixing the compound of formula (I) and the source of counter-ion M^- , suitably in approximately equimolar amounts but preferably using a slight excess of the source of counter-ion M^- , in a solvent, generally a C_{1-4} 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.

pharmaceutically acceptable solvent thereof, which process comprises reacting a compound of formula (I):



wherein R¹, A¹ and A² are as defined in relation to formula (I), with a source of a defined counter-ion M⁺; and wherein it is required preparing a pharmaceutically acceptable solvent thereof.

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 1.2 to 4.2, especially in the range of from 1.7 to 3.2.

Known pharmaceutically acceptable acids include mineral acids, such as hydrochloric, hydrobromic and sulphuric acids, and organic acids, such as methanesulphonic, tartaric and malic acids.

A protected source of a counter-ion is a weak acid. 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 adding the compound of formula (I) and the source of counter-ion M⁺ to a solvent in which the compound of formula (I) is slightly soluble, but which is miscible with the source of counter-ion M⁺, in a solvent, generally a C₁-C₄ alkane, such as

ethyl acetate, which provides a suitable rate of formation of the desired product. Generally, the reaction is carried out at a temperature of from 0°C to 25°C, and the reaction is carried out for a period of from 1 hour to 24 hours.

The compound of formula (II) may be prepared according to methods known in the art, such as by reacting the compound of formula (I) with a suitable source of counter-ion M⁺ in a solvent, generally a C₁-C₄ alkane, such as ethyl acetate, which provides a suitable rate of formation of the desired product.

The compound of formula (II) may be prepared according to methods known in the art, such as by reacting the compound of formula (I) with a suitable source of counter-ion M⁺ in a solvent, generally a C₁-C₄ alkane, such as ethyl acetate, which provides a suitable rate of formation of the desired product.

The compound of formula (II) may be prepared according to methods known in the art, such as by reacting the compound of formula (I) with a suitable source of counter-ion M⁺ in a solvent, generally a C₁-C₄ alkane, such as ethyl acetate, which provides a suitable rate of formation of the desired product.

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
10 wherein the test compounds are stored under controlled conditions of temperature and 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

action has involved at least one person who is a member of the

no similar case where the fact was not known to be dangerous at the time.

...and the ...

100-443887-100

1. The first step in the process is to identify the problem or issue that needs to be addressed. This involves gathering information and understanding the context of the problem.

CONFIDENTIAL

1. The first step in the process is to identify the problem or issue that needs to be addressed. This involves gathering information and understanding the context of the problem.

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32

100-443887-100

100-443887-1000

Maritime transport in Europe (The shipping sector in Europe 2006), 2006, 10-11

ALL INFORMATION CONTAINED HEREIN IS UNCLASSIFIED EXCEPT WHERE SHOWN OTHERWISE

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[illegible]

As mentioned above the complexity of the investigation and the need to develop an effective management system

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...and the ...

Stock 12

Thus the present invention provides a computer system and

the same time, the fact that the same person is not always the same person is also a fact.

times, it is to assist in the maintenance of

in a further investigation and cooperation

... ..

... ..

[illegible]

(continued)

(continued)

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1. *Journal of the American Medical Association*, 1997; 277: 1033-1038.

1. The first step in the process is to identify the problem or issue that needs to be addressed. This involves gathering information and understanding the context of the problem.

[illegible]

100

10. The following table shows the number of people who have been convicted of a crime in the United States since 1970, by race and sex. The data are from the U.S. Department of Justice, Bureau of the Census, and the U.S. Department of Education, Office of Education Statistics.

100

100

NOVEL COMPOUNDS

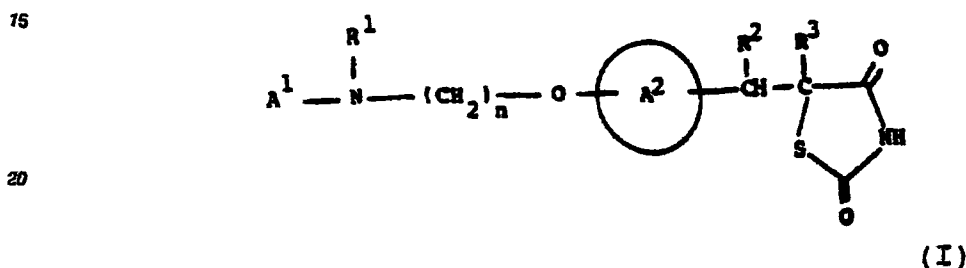
This invention relates to certain substituted thiazolidinedione derivatives, to a process for preparing such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

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):



25 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;

30 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.

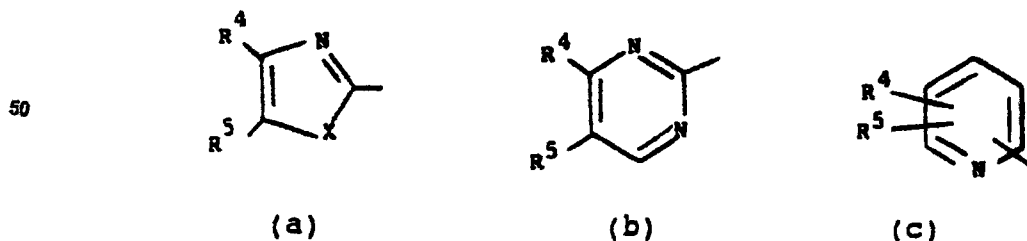
In particular, the aromatic heterocyclyl group comprises 1, 2 or 3 heteroatoms, especially 1 or 2, selected from oxygen, sulphur or nitrogen.

40 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.

45 Suitably R² and R³ each represent hydrogen.

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



NOVEL COMPOUNDS

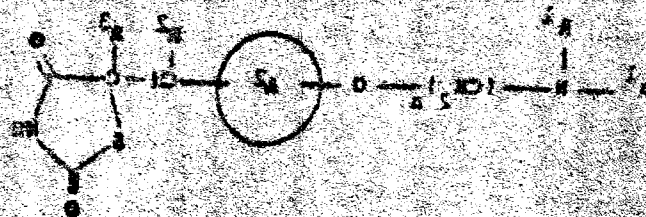
This invention relates to certain substituted heterocyclic derivatives to a process for preparing and compounds to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

European Patent Application, Publication Number 0055203, 0139421, 0185642, 0177323, 0193226, 0207191 and 0133420 relate to substituted heterocyclic derivatives which are disclosed as having hypoglycaemic and hypolipidaemic activity. Chem. Pharm. Bull. 30 (10) 3589-3600 also relates to certain heterocyclic derivatives having hypoglycaemic and hypolipidaemic activities.

It was now surprisingly been discovered that certain novel substituted heterocyclic derivatives show improved blood glucose lowering activity and are therefore of potential use in the treatment and/or prophylaxis of hypoglycaemia 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 hypertension, hypercholesterolaemia, obesity and certain eating disorders.

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



(I)

or a derivative from thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutical composition thereof, wherein:

A represents a substituted or unsubstituted aromatic heterocyclic group;

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

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

A₁ represents a heteroatom having in total up to five valence electrons and is selected from nitrogen in the range of from 2 to 6;

Substituents on the heterocyclic groups include substituted or unsubstituted, single or fused ring, aromatic or heterocyclic groups comprising up to 4 hetero atoms in each ring selected from oxygen, sulfur or nitrogen;

Preferred aromatic heterocyclic groups include substituted or unsubstituted single ring aromatic heterocyclic groups having 4 to 7 ring atoms, preferably 5 or 6 ring atoms;

In particular, the aromatic heterocyclic groups comprise 1, 2 or 3 heteroatoms, preferably 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen;

Substituents on A₁ when it represents a 5-membered aromatic heterocyclic group include hydrogen and oxygen, especially oxygen;

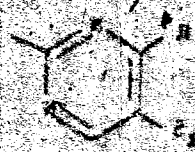
Substituents on A₁ when it represents a 6-membered aromatic heterocyclic group include hydrogen or hydrogen, especially hydrogen;

S₁ and S₂ each represent hydrogen;

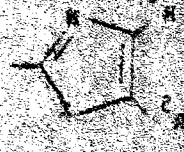
Formula (I) represents a moiety of formula (a), (b) or (c):



(a)



(b)



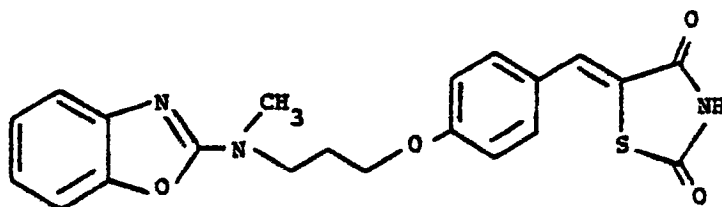
(c)

83 84

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).

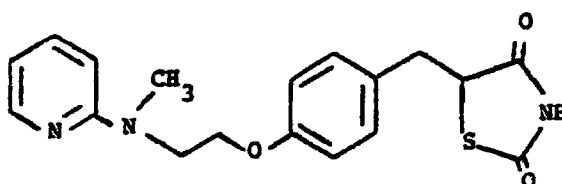
EXAMPLE 30

25

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

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35



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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.

¹H NMR δ (DMSO - d₆)

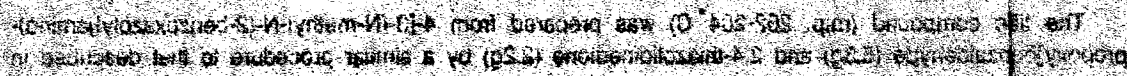
2.9-3.4 (2H, complex); 3.1 (3H, s); 3.9 (2H, t); 4.15 (2H, t); 4.8 (1H, complex); 6.5-6.85 (2H, complex); 6.8 (2H, d); 7.2 (2H, d); 7.5 (1H, complex); 8.1 (1H, d); 12.05 (1H, broad s, exchanges with D₂O).

45

EXAMPLE 31

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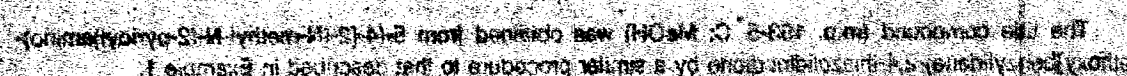


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H1) DSI #8 H1) BT 1000000 H2) TT-CT #1 H3) SA #1 H3) TB #2 H3) BT 7000000 H3) ST 50000
H3) C 10000000 H3) ST 1000000

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0.2 (m, 2H, CH₂), 0.1 (s, 3H, CH₃).

100

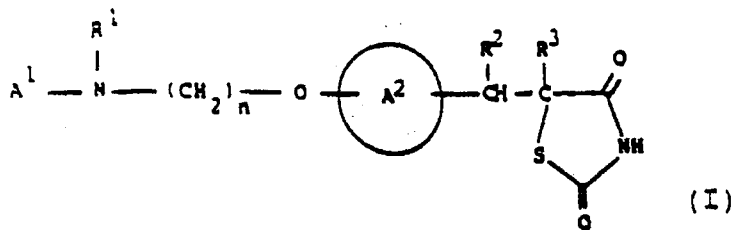
EP 0 306 228 A1

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;

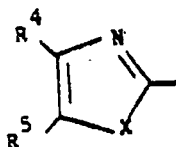
R² and R³ each represent hydrogen, or R² and R³ together represent a bond;

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

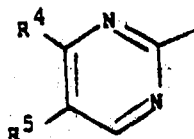
n represents an integer in the range of from 2 to 6.

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.

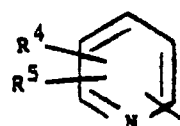
3. A compound according to claim 1 or claim 2, wherein A¹ represents a moiety of formula (a), (b) or (c):



(a)



(b)



(c)

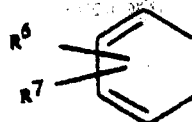
wherein:

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)

