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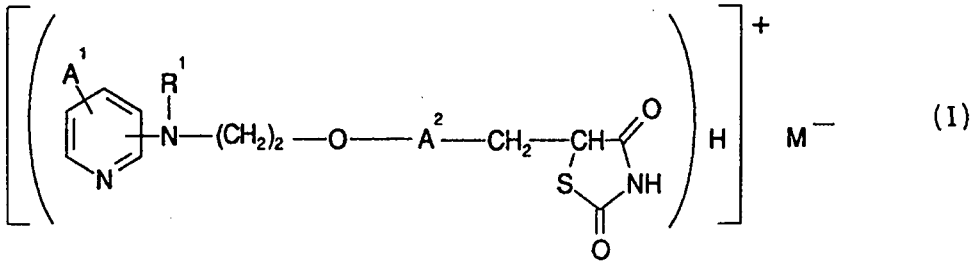


(I)

(57) Abstract

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 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; a process for preparing such a compound, a pharmaceutical composition comprising such a compound and the use of such a compound and composition in medicine.

SUBSTITUTED THIAZOLIDINEDIONLE 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.

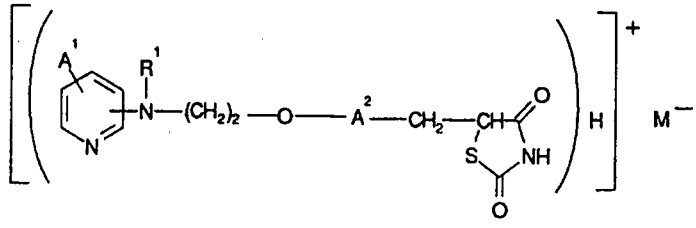
European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having hypoglycaemic and hypolipidaemic activity.

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 aqeous solubility of these compounds provides for significant formulation and bulk handling advantages.

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



(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

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.

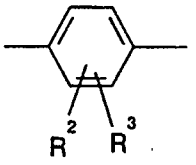
Favoured pharmaceutically acceptable acids include mineral acids, such as hydrobromic, hydrochloric and sulphuric acids, and organic acids, such as methanesulphonic, tartaric and maleic acids, especially tartaric and maleic acid.

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):



(e)

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

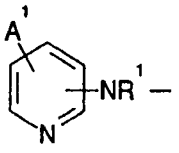
Suitably, R^2 and R^3 each independently represent hydrogen, halogen, alkyl or alkoxy.

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

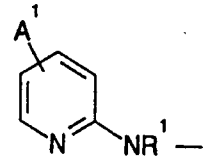
Suitably, R^1 represents hydrogen, alkyl, acyl, especially acetyl, or benzyl.

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

Preferably the moiety :



in formula (I) is a moiety of formula :



wherein A^1 and R^1 are as defined above

A preferred compound of formula (I) is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione maleic acid salt.

The compounds of formula (I) are salts. The present invention extends to all forms of such salts including those provided by association of the salting hydrogen with all possible salt forming parts of the molecule and especially that provided by association with the pyridine nitrogen.

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.

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, nitro, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

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

Suitable alkyl groups, including alkyl groups *per se* and alkyl groups that form part of other groups such as alkoxy groups, are C_{1-12} alkyl groups having straight or branched carbon chains, especially C_{1-6} alkyl groups e.g. methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl or tert-butyl groups.

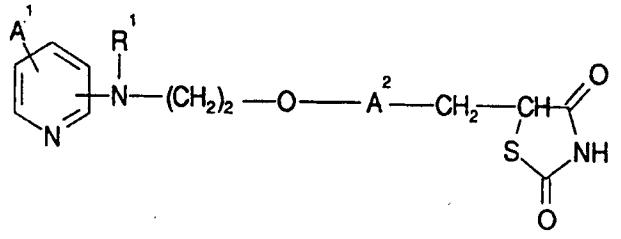
Suitable substituents for any alkyl group include those indicated above in relation to the term "aryl".

Suitable acyl groups include alkylcarbonyl groups.

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



(II)

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.

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.

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.

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.

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.

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.

thereof for use in the treatment of hypertension, cardiovascular disease and certain eating disorders.

Cardiovascular disease includes in particular atherosclerosis.

Certain eating disorders include 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.

A compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable solvate thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention also provides 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.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

Usually the pharmaceutical compositions of the present invention will be adapted for oral administration, although compositions for administration by other routes, such as by injection and percutaneous absorption are also envisaged.

Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

In accordance with conventional pharmaceutical practice the carrier may comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant, flavourant or other conventional adjuvant.

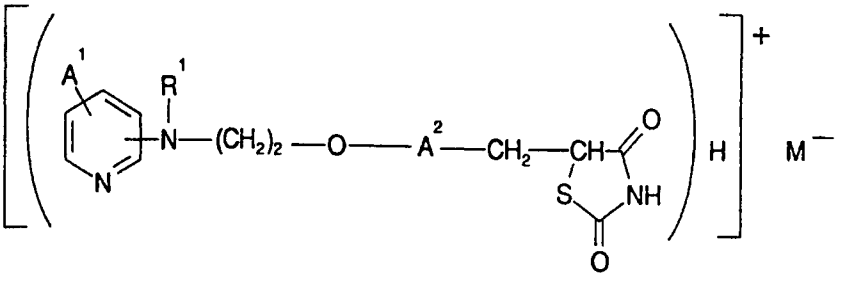
Typical carriers include, for example, microcrystalline cellulose, starch, sodium starch glycollate, polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium stearate or sodium lauryl sulphate.

Most suitably the composition will be formulated in unit dose form. Such unit dose will normally contain an amount of the active ingredient in the range of from 0.1 to 1000 mg, more usually 0.1 to 500 mg, and more especially 0.1 to 250 mg.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycaemia in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of formula (I), or a

Claims

1. A compound of formula (I):



(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 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.

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.

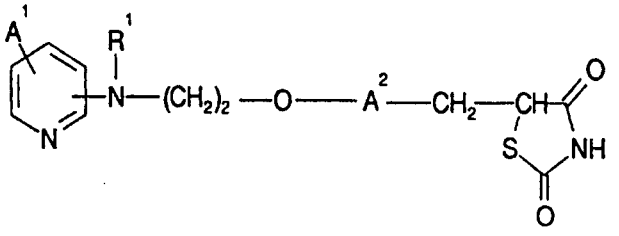
3. A compound according to claim 1 or claim 2, wherein M^- is provided by a pharmaceutically acceptable acid having a pK_a in the range of from 1.75 to 2.5.

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

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), or a tautomeric

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



(II)

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

!0. 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