



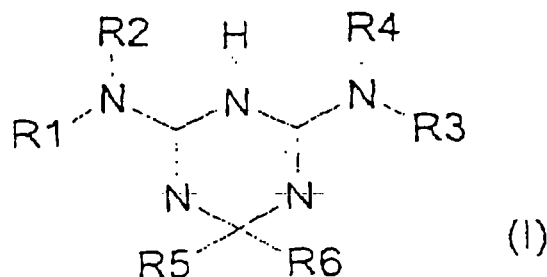
Amine-containing derivatives of dihydro-1,3,5-triazine
and their therapeutic applications

The present invention relates to amine-containing derivatives of dihydro-1,3,5-triazine which are useful in the treatment of pathological conditions associated with the insulin-resistance syndrome.

Amine-containing derivatives of dihydro-1,3,5-triazine having hypoglycaemic properties have been described in JP-A-73 64 088 and JP-A-79 14 986.

The aim of the present invention is to provide novel compounds having improved properties.

The subject of the present invention is thus a compound of general formula (I):



in which:

R1, R2, R3 and R4 are chosen independently from the groups:

- H,
- (C1-C20)alkyl optionally substituted with halogen, (C1-C5)alkyl, (C1-C5)alkoxy, (C3-C8)cycloalkyl,
- (C2-C20)alkenyle optionally substituted with halogen, (C1-C5)alkyl, (C1-C5)alkoxy,
- (C2-C20)alkyne optionally substituted with halogen, (C1-C5)alkyl, (C1-C5)alkoxy,
- (C3-C8)cycloalkyl optionally substituted with (C1-C5)alkyl, (C1-C5)alkoxy,
- (C3-C8)heterocycloalkyl carrying one or more heteroatoms chosen from N, O, S and optionally substituted with (C1-C5)alkyl, (C1-C5)alkoxy,
- (C6-C14)aryl (C1-C20)alkyl optionally



substituted with amino, hydroxyl, thio, halogen,
(C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio,
(C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl-
(C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl,
5 carboxymethyl or carboxyethyl,

- (C6-C14)aryl optionally substituted with
amino, hydroxyl, thio, halogen, (C1-C5)alkyl,
(C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino,
(C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano,
10 trifluoromethyl, carboxyl, carboxymethyl or carboxy-
ethyl,

- (C1-C13)heteroaryl carrying one or more
heteroatoms chosen from N, O, S and optionally
substituted with amino, hydroxyl, thio, halogen,
15 (C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio,
(C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl-
(C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl,
carboxymethyl or carboxyethyl,

~~it being possible for R1 and R2, on the one~~
20 hand, and R3 and R4, on the other hand, to form with
the nitrogen atom an n-membered ring (n between 3 and
8) comprising or otherwise one or more heteroatoms
chosen from N, O, S and being capable of being
substituted with one or more of the following groups:
25 amino, hydroxyl, thio, halogen, (C1-C5)alkyl,
(C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino,
(C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano,
trifluoromethyl, carboxyl, carboxymethyl or
carboxyethyl,

30 R5 and R6 are chosen independently from the groups:

- H,
- (C1-C20)alkyl optionally substituted with
amino, hydroxyl, thio, halogen, (C1-C5)alkyl,
(C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino,
35 (C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano,
trifluoromethyl, carboxyl, carboxymethyl or carboxy-
ethyl,

- (C2-C20)alkenyle optionally substituted
with amino, hydroxyl, thio, halogen, (C1-C5)alkyl,

(C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino,
(C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano,
trifluoromethyl, carboxyl, carboxymethyl or carboxy-
ethyl,

5 - (C2-C20)alkyne optionally substituted with
amino, hydroxyl, thio, halogen, (C1-C5)alkyl,
(C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino,
(C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano,
trifluoromethyl, carboxyl, carboxymethyl or carboxy-
10 ethyl,

 - (C3-C8)cycloalkyl optionally substituted
with amino, hydroxyl, thio, halogen, (C1-C5)alkyl,
(C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino,
(C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano,
15 trifluoromethyl, carboxyl, carboxymethyl or carboxy-
ethyl,

 - (C3-C8)heterocycloalkyl carrying one or more
heteroatoms chosen from N, O, S and optionally
~~substituted with amino, hydroxyl, thio, halogen,~~
20 (C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio,
(C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl-
(C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl,
carboxymethyl or carboxyethyl,

 - (C6-C14)aryl optionally substituted with
25 amino, hydroxyl, thio, halogen, (C1-C5)alkyl,
(C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino,
(C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano,
trifluoromethyl, carboxyl, carboxymethyl or carboxy-
ethyl,

30 - (C1-C13)heteroaryl carrying one or more
heteroatoms chosen from N, O, S and optionally
substituted with amino, hydroxyl, thio, halogen,
(C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio,
(C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl-
35 (C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl,
carboxymethyl or carboxyethyl,

 - (C6-C14)aryl(C1-C5)alkyl optionally
substituted with amino, hydroxyl, thio, halogen,
(C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio,

(C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl-
(C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl,
carboxymethyl or carboxyethyl,

it being possible for R5 and R6 to form with
5 the carbon atom to which they are attached an
m-membered ring (m between 3 and 8) comprising or
otherwise one or more heteroatoms chosen from N, O, S
and being capable of being substituted with amino,
hydroxyl, thio, halogen, (C1-C5)alkyl, (C1-C5)alkoxy,
10 (C1-C5)alkylthio, (C1-C5)alkylamino, (C6-C14)aryloxy,
(C6-C14)aryl(C1-C5)alkoxy, cyano, trifluoromethyl,
carboxyl, carboxymethyl or carboxyethyl,
or being capable of forming with the carbon atom a
C10-C30 polycyclic residue optionally substituted
15 with amino, hydroxyl, thio, halogen, (C1-C5)alkyl,
(C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino,
(C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano,
trifluoromethyl, carboxyl, carboxymethyl or
carboxyethyl;
20 it being possible for the nitrogen atom of a hetero-
cycloalkyl or heteroaryl group to be substituted with a
(C1-C5)alkyl, (C3-C8)cycloalkyl, (C6-C14)aryl,
(C6-C14)aryl(C1-C5)alkyl or (C1-C6)acyl group,
with the exclusion of the compounds of formula I in
25 which:

a - R1 = H, R2 = H, R3 = H, R5 = CH3, R6 = CH3
and R4 = phenethyl, phenoxyethyl, 2-phenylthioisopropyl
or benzyl;

b - R1 = H, R2 = H, R3 = H or CH3, R4 = H,
30 methyl, butyl or phenethyl, R5 = H or ethyl and R6 is
3-methyl-5-isoxazolyl, 5-methyl-3-isoxazolyl, 3-methyl-
5-pyrazolyl or (5-methyl-3-isoxazolyl)methyl,

c - R1, R2, R3 and R4 represent a hydrogen
atom,

35 as well as the tautomeric, enantiomeric, diastereo-
isomeric and epimeric forms and the pharmaceutically
acceptable salts.

The expression m-membered ring formed by R5 and
R6 is understood to mean in particular a saturated ring

such as a cyclohexyl, piperidinyl or tetrahydropyranyl group.

The expression polycyclic group formed by R5 and R6 is understood to mean an optionally substituted
5 carbon-containing polycyclic group and in particular a steroid residue.

A particular group of compounds of formula (I) is that in which R5 is hydrogen.

Another particular group of compounds of
10 formula (I) is that in which R5 and R6 form with the carbon atom to which they are attached an m-membered ring (m between 3 and 8) comprising or otherwise one or more heteroatoms chosen from N, O, S and being capable of being substituted with one or more of the following
15 groups: (C1-C5)alkyl, amino, hydroxyl, (C1-C5)alkyl-amino, (C1-C5)alkoxy, (C1-C5)alkylthio, (C6-C14)aryl, (C6-C14)aryl(C1-C5)alkoxy,

or form with the carbon atom a C10-C30 poly-
cyclic residue optionally substituted with amino,
20 hydroxyl, thio, halogen, (C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl.

Another particular group of compounds of
25 formula (I) is that in which R5 and R6 are chosen independently from the groups:

- (C1-C20)alkyl optionally substituted with
amino, hydroxyl, thio, halogen, (C1-C5)alkyl,
(C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino,
30 (C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl.

A more particular group of compounds of
formula (I) is that in which R1 and R2 are chosen
35 independently from the groups specified above with the exception of the hydrogen atom and R3 and R4 represent a hydrogen. More particularly, a preferred group of compounds of formula (I) is that in which R1 and R2 are an alkyl, advantageously methyl, group and R3 and R4

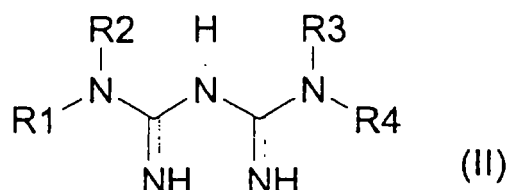
represent a hydrogen.

The invention also relates to the tautomeric, enantiomeric, diastereoisomeric and epimeric forms of the compounds of general formula (I).

5 The compounds of general formula (I) possess basic nitrogen atoms which may be monosalified or disalified with organic or inorganic acids.

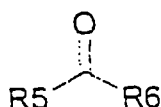
The compounds of general formula (I) may be prepared by reacting a compound of general formula (II)

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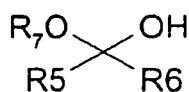


in which R1, R2, R3 and R4 are as defined above, with a compound of general formula (III), (IV) or (V)

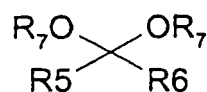
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(III)



(IV)



(V)

in which R5 and R6 are as defined above and R7 is a methyl or ethyl group, in a polar solvent (for example ethanol or dimethylformamide) in the presence of an organic acid (for example camphorsulphonic acid) or of an inorganic acid (for example hydrochloric acid).

20 The compounds of general formula (II) are biguanides whose synthesis is routine to every person skilled in the art. We will cite for example some publications describing the synthesis of such compounds (FR 1537604, FR 2132396; K.H. Slotta and R. Tschesche, Ber., 1929 (62b), 1398; S.L. Shapiro, V.A. Parrino, E. Rogow and L. Freedman, J. Org. Chem., 1959 (81), 3725; S.L. Shapiro, V.A. Parrino and L. Freedman, J. Org. Chem., 1959 (81), 3728; S.L. Shapiro, V.A. Parrino and L. Freedman, J. Org. Chem., 1959 (81), 4636).

The compounds according to the present invention are useful in the treatment of pathological conditions associated with the insulin-resistance syndrome (X syndrome).

5 Insulin-resistance is characterized by a reduction in the action of insulin (cf. Presse Médicale, 1997, 26 (No. 14), 671-677) and is involved in a large number of pathological states, such as diabetes and more particularly non-insulin-dependent diabetes (type II
10 diabetes or NIDDM), dyslipidaemia, obesity, high blood pressure, as well as certain microvascular and macrovascular complications such as atherosclerosis, retinopathies and neuropathies.

In this regard, reference may be made for
15 example to Diabète, vol. 37, 1988, 1595-1607; Journal of Diabetes and its complications, 1998, 12, 110-119 or Horm. Res., 1992, 38, 28-32.

In particular, the compounds of the invention have a high hypoglycaemic activity.

20 The compounds according to the present invention can also be used to treat chronic complications which are in particular due to the formation of "advanced glycosylation end-products" noted AGEs which are derived from the glycoxidation reaction between
25 glucose, its oxidation derivatives and the amino functional groups of proteins, including the so-called Maillard reactions for glycation of glyoxal for example.

Indeed, recently published data clearly show
30 the impact of AGEs on renal complications (Nephrol. Dial. Transplant., 2000, 15 (suppl 2), 7-11), on atherosclerosis, Alzheimer's disease and other neurodegenerative diseases (Glycoconj. J., 1998, 15 (10), 1039-42; Brain Res., 2001, 888(2), 256). The
35 formation of AGE may also play an important part in the pathogenesis of angiopathy, in particular in diabetics, and also in senility (J. Neuropathol. Exp. Neurol., 2000, 59 (12), 1094).

The subject of the present invention is there-

fore also pharmaceutical compositions comprising, as active ingredient, a compound according to the invention.

5 These pharmaceutical compositions are particularly intended for treating diabetes, pathological conditions due to the formation of AGEs, such as, in particular, renal complications, atherosclerosis, angiopathy, Alzheimer's disease, neurodegenerative diseases and senility.

10 The pharmaceutical compounds according to the invention may be provided in forms intended for administration by the parenteral, oral, rectal, per-mucosal or percutaneous route.

15 They will therefore be provided in the form of injectable solutions or suspensions or multidose vials, in the form of uncoated or coated tablets, sugar-coated tablets, capsules, gelatin capsules, pills, cachets, powders, suppositories or rectal capsules, solutions or suspensions, for percutaneous use in a polar solvent, 20 for permucosal use.

25 The excipients which are suitable for such administrations are the derivatives of cellulose or of microcrystalline cellulose, the alkaline-earth carbonates, magnesium phosphate, starches, modified starches, lactose for the solid forms.

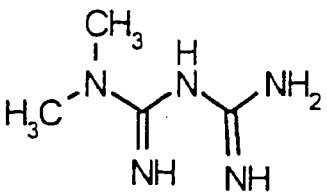
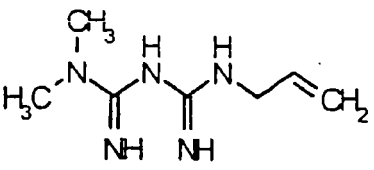
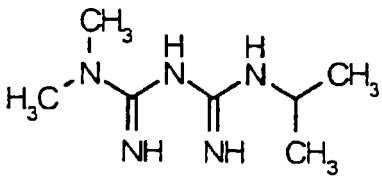
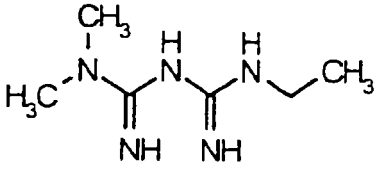
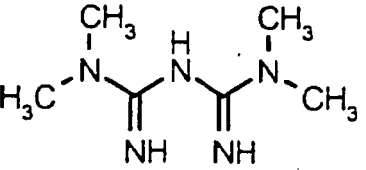
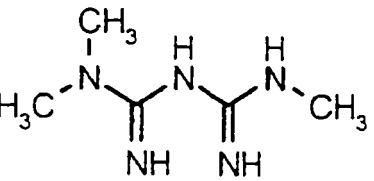
30 For rectal use, cocoa butter or the stearates of polyethylene glycol are the preferred excipients.

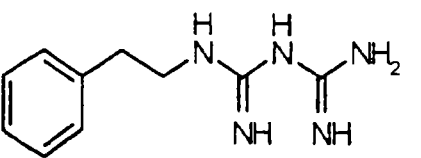
 For parenteral use, water, aqueous solutions, physiological saline, isotonic solutions are the 30 vehicles most conveniently used.

 The dosage may vary within wide limits (0.5 mg to 1 000 mg) according to the therapeutic indication and the route of administration, as well as the age and weight of the subject.

35 By way of example, here are a few biguanides of formula II used in the synthesis of derivatives of formula I.

TABLE I

	Formula	Salt	m.p. in °C (Köfler)
A		HCl	223-225
B		HCl	176-178
C		HCl	230-232
D		HCl	210-212
E		HCl	254-256
F		HCl	158-160

G		HCl	100-102
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The following examples illustrate the preparation of the compounds of formula I.

5

EXAMPLE 1

Synthesis of 2-amino-3,6-dihydro-4-dimethylamino-6-ethyl-1,3,5-triazine hydrochloride

23 ml of propionaldehyde and 3.6 g of camphor-sulphonic acid are added to a solution of compound A (25.7 g; 0.155 mol) in 200 ml of DMF. After refluxing for 2 hours, the solvent is removed under vacuum and 100 ml of acetonitrile are added. The solid formed is drained and dried (21.9 g; 69%).

m.p. = 218-220°C

¹H NMR (DMSO-d₆, 200 MHz): 1.10 (t, 3H); 1.80 (m, 2H); 3.20 (s, 6H); 4.83 (m, 1H); 7.57 (m, 2H); 8.65 (s, 1H); 8.90 (s, 1H)

¹³C NMR (DMSO-d₆, 50 MHz): 6.41 (CH₃); 27.59 (CH₂); 35.64 (CH₃); 60.75 (CH); 155.01 (C=N); 156.67 (C=N)

20

EXAMPLE 2

Synthesis of 2,4-bisdimethylamino-3,6-dihydro-6-methyl-1,3,5-triazine hydrochloride

61 ml of acetal and 5 g of camphorsulphonic acid are added to a solution of compound E (41.10 g; 0.212 mol) in 200 ml of absolute ethanol. The whole is heated under reflux for 72 hours and then concentrated. The crude material is triturated with acetonitrile and the solid formed is drained and then recrystallized from acetonitrile. 24 g (51.5%) of a solid are obtained.

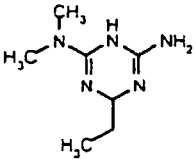
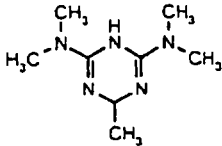
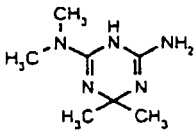
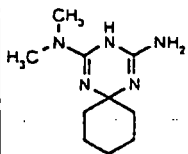
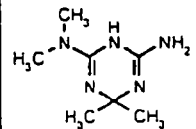
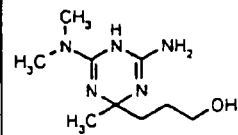
m.p. = 200-202°C

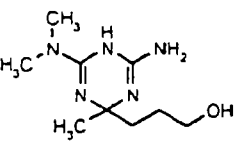
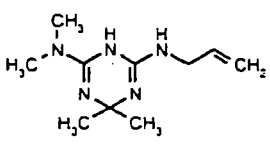
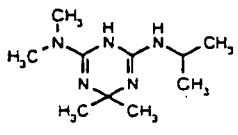
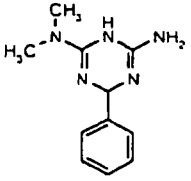
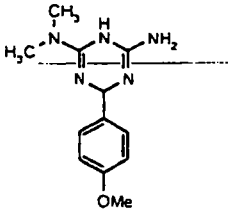
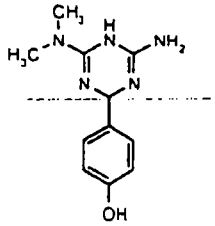
¹H NMR (DMSO-d₆, 200 MHz): 1.34 (d, 3H); 3.02 (s, 6H); 4.72 (m, 1H); 4.83 (m, 1H); 8.80 (s, 2H)

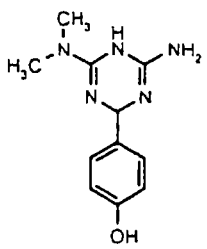
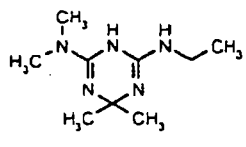
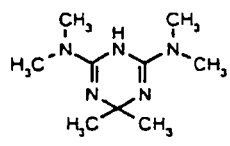
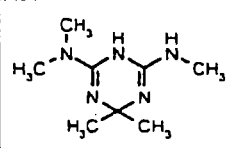
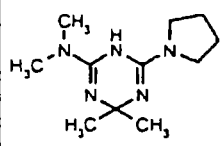
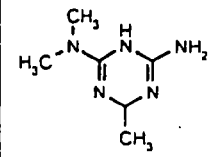
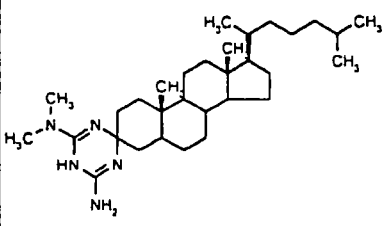
^{13}C NMR (DMSO- d_6 , 50 MHz): 22.59 (CH₃); 37.76 (CH₃); 59.02 (CH); 156.35 (C=N)

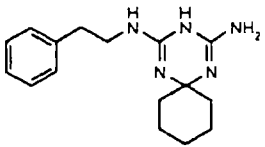
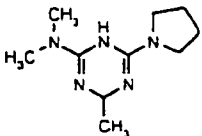
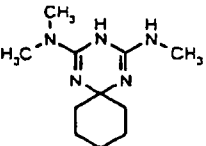
The characteristics of these compounds and of other compounds of formula I are given in Table II below:

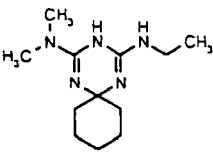
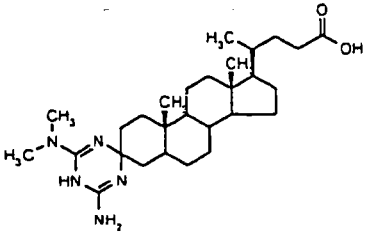
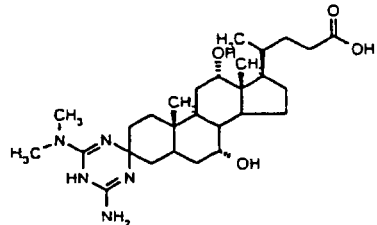
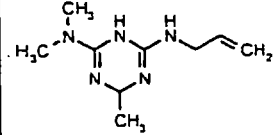
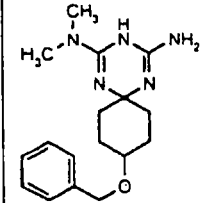
TABLE II

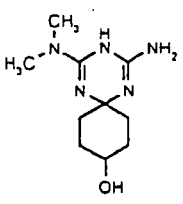
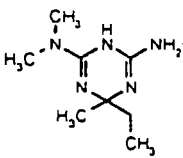
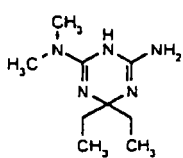
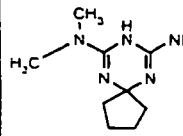
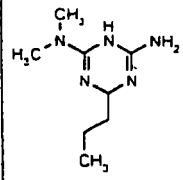
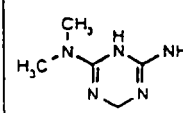
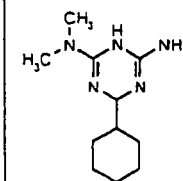
	Formula	Salt	m.p. in °C (Köfler)	^{13}C NMR 50.32 MHz
1		HCl	218-220	DMSO- d_6 6.41, CH ₃ 27.59, CH ₂ 35.64, 2 CH ₃ 60.75, CH 155.01, 156.67, 2 quaternary C
2		HCl	200-202	DMSO- d_6 22.58, 37.75, 5 CH ₃ 59.01, CH 156.34, 2 quaternary C
3			193-195	DMSO- d_6 32.06, 37.40, 2 CH ₃ 67.85, 158.16, 3 quaternary C
4		HCl	243-245	DMSO- d_6 21.66, 25.19, 37.72, 3 CH ₂ 37.89, 2 CH ₃ 67.51, 156.83, 158.24, 3 quaternary C
5		Methane- sulphonate	174-176	DMSO- d_6 34.31, 41.36, 44.79, 5 CH ₃ 69.75, 160.30, 161.44, 3 quaternary C
6			138-140	DMSO- d_6 28.04, CH ₂ 30.84, 37.40, 3 CH ₃ 42.06, 62.24, 2 CH ₂ 70.00, 158.24, 158.69, 3 quaternary C

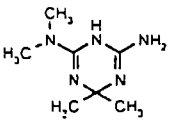
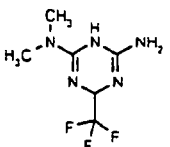
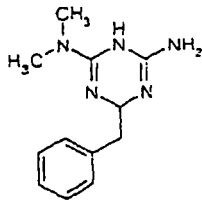
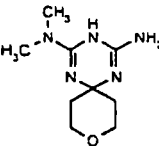
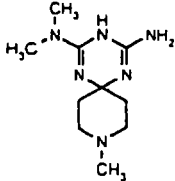
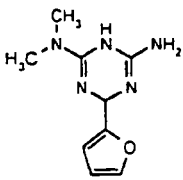
7		HCl	150-152	DMSO-d6 27.39, CH2 28.78, 39.14, 3 CH3 40.21, 61.30, 2 CH2 68.46, 156.48, 157.84 3 quaternary C
8		HCl	124-126	DMSO 28.95, 38.65, 2 CH3 42.77, CH2 69.75, quaternary C 115.93, CH2 149.12, CH 155.70, 156.16, 2 quaternary C
9		HCl	149-151	DMSO-d6 26.20, 32.39, 40.73, 6 CH3 46.16, CH 60.09, 158.83, 159.14, 3 quaternary C
10		HCl	239-241	DMSO-d6 37.78, 2 CH3 62.39, CH 126.66, 129.47, 5 CH 141.87, 156.52, 158.38, 3 quaternary C
11		HCl	221-223	DMSO-d6 37.23, 55.60, 3 CH3 61.88, CH 114.32, 127.66, 4 CH 133.17, 156.11, 157.86, 159.93, 4 quaternary C
12		HCl	251-253	DMSO-d6 37.75, 2 CH3 62.67, 116.16, 128.16, 5 CH 131.72, 156.64, 158.31, 158.88, 4 quaternary C

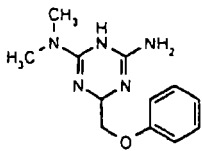
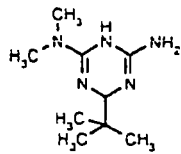
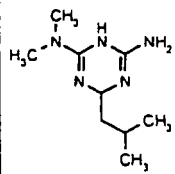
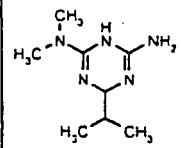
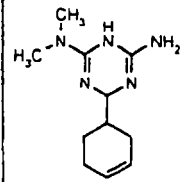
13			> 260	DMSO-d6 39.55, 39.71, 2 CH3 65.92, 117.71, 130.17, 5 CH 131.72, 156.64, 158.31, 158.88, 4 quaternary C
14		Fumarate	172-174	15.48, 29.33, 3 CH3 35.68, CH2 37.43, 2 CH3 65.71, quaternary C 135.47, 2 CH 156.21, 156.63, 168.35, 4 quaternary C
15		HCl	250-252	DMSO-d6 28.74, 37.38, 6 CH3 66.53, 155.28, 3 quaternary C
16		HCl	183-185	DMSO-d6 32.62, 40.96, 5 CH3 69.37, 159.30, 160.19, 3 quaternary C
17		HCl	> 260	DMSO-d6 22.78, 2 CH3 28.96, 2 CH2 40.13, 2 CH3 42.73, 2 CH2 65.63, 155.42, 155.71, 3 quaternary C
18		HCl	229-231	DMSO-d6 22.97, 37.76, 3 CH3 58.59, CH 157.85, 159.39, 2 quaternary C
19		HCl	> 260	Concise spectrum DMSO-d6 69.06, 159.78, 161.17, 3 quaternary C

20		carbonate	170-180	CF ₃ CO ₂ D 22.43, 25.71, 36.86, 38.71, 43.12, 7 CH ₂ 67.88, quaternary C 127.47, 129.55, 129.93, 5 CH 140.22, 158.72, 159.65, 3 quaternary C
21		Carbonate	> 140	DMSO-d ₆ 20.51, CH ₃ 24.73, 25.39, 2 CH ₂ 39.98, 2 CH ₃ 46.44, 47.91, 2 CH ₂ 58.49, CH 154.58, 156.63, 160.61, 3 quaternary C
22		HCl	> 260	DMSO-d ₆ 21.18, 24.68, 3 CH ₂ 27.26, CH ₃ 37.00, 2 CH ₂ 37.37, 2 CH ₃ 67.12, 155.89, 156.86, 3 quaternary C

23		HCl	248-250	DMSO-d6 15.11, CH3 21.17, 24.70, 35.39, 37.04, 6 CH2 37.36, 2 CH3 67.09, 155.90, 156.21, 3 quaternary C
24		HCl	> 260	Concise spectrum DMSO-d6 67.46, 68.80, 156.76, 157.47, 157.99, 159.14, 3 quaternary C 175.90, 176.11, COOH
25		HCl	> 260	Concise spectrum DMSO-d6 64.87, 69.85, 2 CHOH 66.55, 154.91, 156.19, 3 quaternary C 173.75, COOH
26		HCl	91-93	DMSO-d6 25.76, 37.28, 3 CH3 43.28, CH2 64.27, CH 115.21, CH2 137.55, CH 159.79, 160.77, 2 quaternary C
27		HCl	> 260	DMSO-d6 25.69, 27.25, 4 CH2 39.13, 2 CH3 67.25, quaternary C 70.01, CH2 72.50, CH 128.17, 128.34, 129.07, 5 CH 139.79, 156.81, 158.30, 3 quaternary C

28		HCl	> 250	DMSO-d6 29.83, 34.4, 4 CH2 38.83, 2 CH3 66.17, CH 67.06, 156.25, 157.28, 3 quaternary C
29		Carbonate	133-135	DMSO-d6 7.25, 26.81, 2 CH3 34.32, CH2 37.17, 2 CH3 68.59, 156.46, 157.71, 160.78, 4 quaternary C
30		Carbonate	140-144	DMSO-d6 8.68, 2 CH3 34.54, 2 CH2 37.91, 2 CH3 74.98, 157.84, 159.14, 160.82, 4 quaternary C
31		HCl	207-209	DMSO-d6 22.50, 2 CH2 38.00, 2 CH3 39.78, 2 CH2 75.51, 157.18, 158.37, 3 quaternary C
32		Carbonate	decomposes	DMSO-d6 14.55, CH3 17.20, CH2 37.45, 2 CH3 39.00, CH2 62.43, CH 157.52, 159.04, 160.65, 3 quaternary C
33		HCl	> 260	D2O 37.90, 2 CH3 48.69, CH2 154.82, 156.33, 2 quaternary C
34		Para-toluene-sulphonate	201-203	DMSO-d6 21.65, CH3 25.95, 26.07, 26.58, 26.89, 27.50, 5 CH2 37.56, 2 CH3 44.74, 66.56, 126.32, 129.08, 6 CH 138.99, 145.86, 158.18, 156.86, 4 quaternary C

35		HCl	157-159	DMSO-d6 29.10, 37.86, 4 CH3 65.90, 154.82, 156.33, 3 quaternary C
36		Para-toluene-sulphonate	251-253	DMSO-d6 21.14, 37.26, 3 CH3 114.80, 120.70, 126.41, 132.12, CF3 125.82, 128.54, 4 CH 138.37, 145.49, 155.78, 157.18, 4 quaternary C
37		Para-toluene-sulphonate	159-161	DMSO-d6 21.17, 36.95, 3 CH3 42.60, CH2 62.10, 126.86, 127.21, 128.55, 128.63, 130.32, 10 CH 135.14, 138.30, 145.67, 156.18, 157.44, 5 quaternary C
38		HCl	> 260	DMSO-d6 37.41, 2 CH3 37.47, 62.73, 4 CH2 64.76, 156.35, 157.77, 3 quaternary C
39		HCl	> 260	DMSO-d6 34.12, 2 CH2 38.63, 42.60, 3 CH3 48.72, 2 CH2 64.01, 156.11, 157.78, 3 quaternary C
40		HCl	225-227	DMSO-d6 37.19, 2 CH3 56.58, 107.94, 110.93, 144.00, 4 CH 152.78, 155.85, 157.47, 3 quaternary C

41		Para-toluene-sulphonate	194-196	DMSO-d6 21.17, 37.03, 3 CH3 60.37, CH 70.05, CH2 115.08, 121.60, 125.84, 128.54, 129.95, 10 CH 138.28, 145.64, 156.40, 157.70, 158.45, 5 quaternary C
42		HCl	> 260	DMSO-d6 24.12, 37.15, 5 CH3 39.90, quaternary C 68.39, CH 156.57, 158.10, 2 quaternary C
43		HCl	decomposes	DMSO-d6 22.95, 23.05, 2 CH3 25.87, CH 36.94, 2 CH3 45.71, CH2 62.38, CH 157.15, 157.42, 158.34, 3 quaternary C
44		HCl	213-215	DMSO-d6 15.99, 17.12, 2 CH3 34.57, CH 37.17, 2 CH3 65.68, CH 156.45, 158.12, 2 quaternary C
45		Para-toluene-sulphonate	217-219	DMSO-d6 21.17, CH3 22.53, 24.48, 25.30, 3 CH2 37.20, 2 CH3 40.07, 64.37, 2 CH 125.68, 125.83, 127.19, 128.61, 6 CH 138.53, 145.24, 156.06, 157.36, 4 quaternary C

Results of pharmacological studies will be given below.

STUDY OF THE ANTIDIABETIC ACTIVITY IN THE NOSTZ RAT

The antidiabetic activity of the compounds of formula (I) administered orally was determined on an experimental model of non-insulin-dependent diabetes induced in rats by Streptozotocin.

The non-insulin-dependent diabetes model is obtained in rats by neonatal injection (on the day of birth) of streptozotocin.

The diabetic rats used were 8 weeks old. The animals were kept, from the day of their birth to the day of the experiment, in an animal house at a controlled temperature of 21 to 22°C and subjected to a fixed cycle of light (from 7 am to 7 pm) and darkness (from 7 pm to 7 am). Their diet consisted of a maintenance diet, water and food were provided "ad libitum", with the exception of the 2 hours of fasting preceding the tests when the food is withdrawn (postabsorptive state).

The rats were treated by the oral route for one (D1) or four (D4) days with the product to be tested. Two hours after the last administration of the product and 30 minutes after anaesthetizing the animals with sodium pentobarbital (Nembutal®), 300 µl of blood sample are collected from the end of the tail.

By way of example, results obtained are assembled in Table III. These results show the efficacy of the compounds of formula (I) in reducing glycaemia in the diabetic animals. These results are expressed as a percentage variation of glycaemia at D1 and D4 (number of days of treatment) relative to D0 (before the treatment).

TABLE III

Compounds	20 mg/kg/D		200 mg/kg/D	
	D1	D4	D1	D4
1	-7	-2	-13	-15
2	-11	-10	-12	-12
3	-10	-8	-18	-22
4	0	-1	-20	-10
7	-8	-11	-10	-16
15	-8	-9	-4	-5
17	-12	-8	-8	-14
18	-6	-4	-29	-28
19	-10	-6	-4	-14
21	-7	-2	-21	-24
22	-23	-16	-13	0
25	-4	-11	-7	-6
26	-6	-11	-14	-9
27	-14	-9	-12	-13
28	-4	-1	-4	-13
31	-5	-11	-3	-15
32	2	0	-22	-18
33	-7	-6	-9	-14
34	-5	-15	-6	-21
37	-7	-8	-10	-15
39	-6	-6	-4	-7
40	-8	-12	-18	-18
42	-5	-4	-26	-17
43	-4	-16	-12	-17
44	-7	-6	-22	-25

STUDY OF THE ANTIGLYCATION ACTIVITY

The compounds (1) are also capable of inhibiting the so-called Maillard reactions by "capturing effect" on the α -dicarbonyl-containing derivatives such as glyoxal - this is the antiglycation effect. This Maillard reaction inhibiting effect of the compounds according to the invention was studied *in vitro* by assaying ketamines ("fructosamines") produced during the incubation of albumin with methylglyoxal in the

presence or otherwise of a compound of formula (I) according to the invention.

5 A solution of bovine albumin at 6.6 mg/ml in 0.2 M phosphate buffer, pH 7.4, is incubated with 1 mM methylglyoxal in the presence or otherwise of a compound according to the invention at a concentration of 10 mM. The incubation is carried out under sterile conditions at 37°C for 6 days. At the end of the incubation period, the quantity of ketamines is
10 measured with a commercially available fructosamine assay kit ("FRA" kit, product reference: 0757055, Roche S.A. products) according to the manufacturer's instructions.

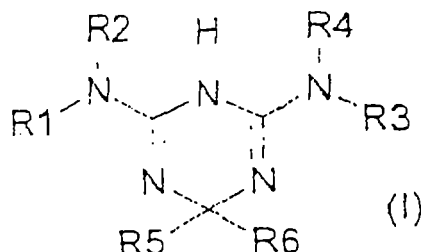
15 By way of example, results obtained under these experimental conditions are assembled in Table IV: level of fructosamine after incubation of the albumin with the methylglyoxal in the presence of compounds (I) according to the invention in relation to the level of
20 fructosamine when albumin is incubated with methylglyoxal in the absence of the compounds (I) according to the invention.

TABLE IV

Compounds (I)	Reduction in the level of fructosamines (%)
1	62
10	80
11	89
12	90
13	95
18	69
33	79
34	64
36	66
37	65
40	66
43	68
45	67

CLAIMS

1. Compounds of general formula (I):



5

in which:

10 R1, R2, R3 and R4 are chosen independently from the groups:

- H,
- (C1-C20)alkyl optionally substituted with halogen, (C1-C5)alkyl, (C1-C5)alkoxy, (C3-C8)cycloalkyl,
- 15 - (C2-C20) alkenyle optionally substituted with halogen, (C1-C5)alkyl, (C1-C5)alkoxy,
- (C2-C20)alkyne optionally substituted with halogen, (C1-C5)alkyl, (C1-C5)alkoxy,
- (C3-C8)cycloalkyl optionally substituted
- 20 with (C1-C5)alkyl, (C1-C5)alkoxy,
- (C3-C8)heterocycloalkyl carrying one or more heteroatoms chosen from N, O, S and optionally substituted with (C1-C5)alkyl, (C1-C5)alkoxy,
- (C6-C14)aryl(C1-C20)alkyl optionally
- 25 substituted with amino, hydroxyl, thio, halogen, (C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl- (C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl,
- 30 - (C6-C14)aryl optionally substituted with amino, hydroxyl, thio, halogen, (C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano,

trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl,

- (C1-C13)heteroaryl carrying one or more heteroatoms chosen from N, O, S and optionally substituted with amino, hydroxyl, thio, halogen, (C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl-(C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl,

it being possible for R1 and R2, on the one hand, and R3 and R4, on the other hand, to form with the nitrogen atom an n-membered ring (n between 3 and 8) comprising or otherwise one or more heteroatoms chosen from N, O, S and being capable of being substituted with one or more of the following groups: amino, hydroxyl, thio, halogen, (C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl,

R5 and R6 are chosen independently from the groups:

- H,

- (C1-C20)alkyl optionally substituted with amino, hydroxyl, thio, halogen, (C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl,

- (C2-C20) alkenyle optionally substituted with amino, hydroxyl, thio, halogen, (C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl,

- (C2-C20)alkyne optionally substituted with amino, hydroxyl, thio, halogen, (C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxy-

ethyl,

- (C3-C8)cycloalkyl optionally substituted
with amino, hydroxyl, thio, halogen, (C1-C5)alkyl,
(C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino,
5 (C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano,
trifluoromethyl, carboxyl, carboxymethyl or carboxy-
ethyl,

- (C3-C8)heterocycloalkyl carrying one or more
heteroatoms chosen from N, O, S and optionally
10 substituted with amino, hydroxyl, thio, halogen,
(C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio,
(C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl-
(C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl,
carboxymethyl or carboxyethyl,

15 - (C6-C14)aryl optionally substituted with
amino, hydroxyl, thio, halogen, (C1-C5)alkyl,
(C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino,
(C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano,
trifluoromethyl, carboxyl, carboxymethyl or carboxy-
20 ethyl,

- (C1-C13)heteroaryl carrying one or more
heteroatoms chosen from N, O, S and optionally
substituted with amino, hydroxyl, thio, halogen,
(C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio,
25 (C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl-
(C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl,
carboxymethyl or carboxyethyl,

- (C6-C14)aryl(C1-C5)alkyl optionally
substituted with amino, hydroxyl, thio, halogen,
30 (C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio,
(C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl-
(C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl,
carboxymethyl or carboxyethyl,

35 it being possible for R5 and R6 to form with
the carbon atom to which they are attached an
m-membered ring (m between 3 and 8) comprising or
otherwise one or more heteroatoms chosen from N, O, S
and being capable of being substituted with amino,
hydroxyl, thio, halogen, (C1-C5)alkyl, (C1-C5)alkoxy,

(C1-C5)alkylthio, (C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl
(C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or
carboxyethyl,

or being capable of forming with the carbon atom a C10-C30 polycycl
5 residue **optionally substituted** with amino, hydroxyl, thio, halogen,
(C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino, (C6-C14)
aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano, trifluoromethyl, carboxy
carboxymethyl or carboxyethyl,

it being possible for the nitrogen atom of a heterocycloalkyl or heteroar
10 group to be substituted with a (C1-C5)alkyl, (C3-C8)cycloalkyl, (C6-C14)aryl
(C6-C14)aryl(C1-C5)alkyl or (C1-C6)acyl group, wherein, when R1 and R2
represent a hydrogen atom or R3 and R4 represent a hydrogen, then R3
and R4 or R1 and R2 are defined as above with the exception of H,
with the exclusion of the compounds of formula I in which:

15 $R1 = R2 = H,$
and $R3 = R4 = Me,$ or $R1 = R2 = Me$ and $R3 = R4 = H,$ and
 $R5 = H$ and R6 is 3-methyl-5-isoxazolyl,

as well as the tautomeric, enantiomeric, diastereoisomeric and epime
forms and the pharmaceutically acceptable salts.

2. Compounds of formula (I) according to Claim 1, in which R5
25 hydrogen.

3. Compounds of formula (I) according to Claim 1, in which R5 a
R6 form with the carbon atom to which they are attached an m-member
ring (m between 3 and 8) comprising or otherwise one or more heteroatom
chosen from N, O, S and which can be substituted with amino, hydroxyl, th
30 halogen, (C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino,
(C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano, trifluoromethyl,
carboxyl, carboxymethyl or carboxyethyl,

or form with the carbon atom a C10-C30 polycyclic residue optionally substituted with amino, hydroxyl, thio, halogen, (C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl.

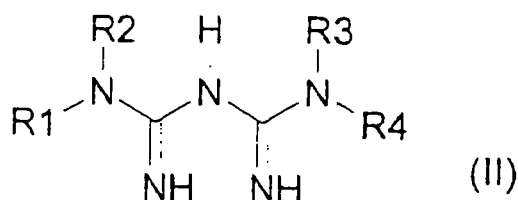
4. Compounds of formula (I) according to Claim 1, in which R5 is a (C2-C20)alkyl group substituted with amino, hydroxyl, thio, halogen, (C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl.

5. Compounds of formula (I) according to Claim 1, in which R5 and R6 are chosen from (C1-C20)alkyl groups optionally substituted with amino, hydroxyl, thio, halogen, (C1-C5)alkyl, (C1-C5)alkoxy, (C1-C5)alkylthio, (C1-C5)alkylamino, (C6-C14)aryloxy, (C6-C14)aryl(C1-C5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl.

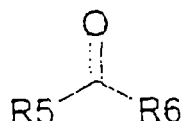
6. Compounds of formula (I) according to any one of Claims 1 to 5 in which R1 and R2 are chosen independently from the groups specified in Claim 1 with the exception of the hydrogen atom and R3 and R4 represent a hydrogen.

7. Compounds of formula (I) according to Claim 6, in which R1 and R2 are a methyl group and R3 and R4 represent a hydrogen.

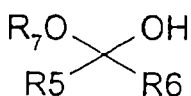
8. Method for preparing a compound according to Claim 1 comprising reacting a compound of general formula (II)



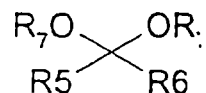
in which R1, R2, R3 and R4 are as defined above, with a compound of general formula (III), (IV) or (V)



(III)



(IV)



(V)

in which R5 and R6 are as defined above and R7 is a methyl or ethyl group, in a polar solvent in the presence of an organic or inorganic acid.

- 5 9. Pharmaceutical composition comprising, as active ingredient, a compound according to any one of Claims 1 to 7.
- 10 10. Use of a compound according to any one of Claims 1 to 7, for the manufacture of a medicament intended for the treatment of pathological conditions associated with the insulin-resistance syndrome.
11. Use of a compound according to any one of Claims 1 to 7, for the manufacture of a medicament intended for the treatment of diabetes.
- 15 12. Use of a compound according to any one of Claims 1 to 7, for the manufacture of a medicament intended for the treatment of pathological conditions due to the formation of AGEs.
- 20 13. Use of a compound according to any one of Claims 1 to 7, for the manufacture of a medicament intended for the treatment of pathological conditions selected from renal complications, atherosclerosis, angiopathy, Alzheimer's disease, neurodegenerative diseases and senility.