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((Aminoiminomethyl) amino) alkanecarboxamides and their applications in therapy

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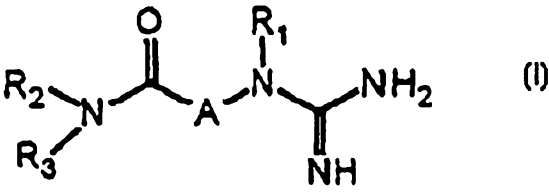
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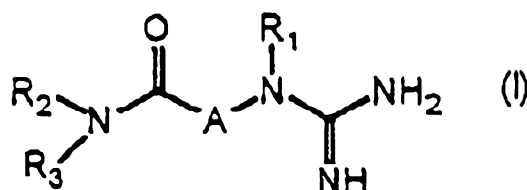
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(21) International Application Number: PCT/EP99/10468 (22) International Filing Date: 30 December 1999 (30.12.99) (30) Priority Data: 99/00194 11 January 1999 (11.01.99) FR (71) Applicant (for all designated States except US): MERCK PATENT GMBH [DE/DE]; Frankfurter Strasse 250, D-64293 Darmstadt (DE). (72) Inventors; and (75) Inventors/Applicants (for US only): MOINET, Gérard [FR/FR]; 15, rue Lamartine, F-91400 Orsay (FR). CRAVO, Daniel [FR/FR]; 123, avenue Jules Ferry, F-78500 Sartrouville (FR). MESANGEAU, Didier [FR/FR]; 5, rue Auguste Renoir, F-77380 Combs la Ville (FR). DOARE, Liliane [FR/FR]; 33, avenue Marmont, F-91170 Viry Chatillon (FR). KERGOAT, Micheline [FR/FR]; 5, Villa des Bois, F-91440 Bures sur Yvette (FR).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.
(54) Title: ((AMINOIMINOMETHYL) AMINO) ALKANECARBOXAMIDES AND THEIR APPLICATIONS IN THERAPY  (I) (57) Abstract The invention relates to a pharmaceutical composition comprising as active principle a compound of general formula (I), in which R₁, R₂, R₃ and A are as defined in Claim 1. These compositions can be used in the treatment of pathologies associated with insulin resistance syndrome.		

((Aminoiminomethyl)amino)alkanecarboxamides and their applications in therapy

The present invention relates to the use of derivatives of the ((aminoiminomethyl)amino)alkane-carboxamide type in the treatment of pathologies associated with insulin resistance syndrome.

The present invention therefore provides pharmaceutical compositions comprising as active principle a compound of general formula (I)



in which:

R_1 is selected from one of the following groups:

- H;
- (C_1-C_{20}) alkyl substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, (C_1-C_5) alkyl, (C_1-C_5) alkoxy, (C_1-C_5) alkylthio, (C_1-C_5) alkylamino, trifluoromethyl;

R_2 and R_3 are selected independently from

- H;
- (C_3-C_8) cycloalkyl substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, (C_1-C_5) alkyl, (C_1-C_5) alkoxy, (C_1-C_5) alkylthio, (C_1-C_5) alkylamino, trifluoromethyl;

- (C_3-C_8) heterocycloalkyl containing one or more heteroatoms selected from N, O and S and substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, (C_1-C_5) alkyl, (C_1-C_5) alkoxy, (C_1-C_5) alkylthio, (C_1-C_5) alkylamino, trifluoromethyl;

a nitrogen atom can additionally be substituted by a (C_6-C_{14}) aryl, (C_6-C_{14}) acyl or (C_1-C_5) alkyl group;

- (C_6-C_{14}) aryl substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, halogen, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl, cyano;

- 5 - (C₁-C₁₃)heteroaryl containing one or more heteroatoms selected from N, O and S and substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, halogen, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl, cyano;

- 10 a nitrogen atom can additionally be substituted by a (C₆-C₁₄)aryl, (C₆-C₁₄)acyl or (C₁-C₅) alkyl group;

- (C₆-C₁₄)aryl-(C₁-C₅)alkyl substituted or unsubstituted by one or more of the following groups:

- 15 amino, hydroxyl, halogen, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl, cyano;

and A is selected from the groups:

-CH₂-,

-CH₂-CH₂-,

- 20 -CHR₄-,

R₄ being selected from:

- H;

- (C₁-C₂₀)alkyl substituted or unsubstituted by one or more of the following groups:

- 25 amino, hydroxyl, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl;

- (C₃-C₈)cycloalkyl substituted or unsubstituted by one or more of the following groups:

- 30 amino, hydroxyl, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl;

- (C₃-C₈)heterocycloalkyl containing one or more heteroatoms selected from N, O and S and substituted or unsubstituted by one or more of the following groups:

- 35 amino, hydroxyl, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl;
a nitrogen atom can additionally be substituted by a (C₆-C₁₄)aryl, (C₆-C₁₄)acyl or (C₁-C₅) alkyl group;

and their solvates and pharmaceutically acceptable salts.

The heteroaryl groups are selected in particular from pyridyl, pyrimidinyl, furyl, pyrrolyl, thienyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, benzothienyl, indolyl, benzofuryl and imidazolyl.

The heterocycloalkyl groups are selected in particular from piperidinyl, morpholinyl, piperazinyl, tetrahydrofuryl, tetrahydrothienyl, pyrrolidinyl and tetrahydropyranyl.

A preferred group of compounds of formula I is constituted in which R_1 is H or (C_1-C_6) alkyl.

A preferred group of compounds of formula I is constituted in which:

R_2 is selected from

- (C_3-C_8) cycloalkyl substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, (C_1-C_5) alkyl, (C_1-C_5) alkoxy, (C_1-C_5) alkylthio, (C_1-C_5) alkylamino, trifluoromethyl;

- (C_6-C_{14}) aryl substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, halogen, (C_1-C_5) alkyl, (C_1-C_5) alkoxy, (C_1-C_5) alkylthio, (C_1-C_5) alkylamino, trifluoromethyl, cyano;

- (C_1-C_{13}) heteroaryl containing one or more heteroatoms selected from N, O and S and substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, halogen, (C_1-C_5) alkyl, (C_1-C_5) alkoxy, (C_1-C_5) alkylthio, (C_1-C_5) alkylamino, trifluoromethyl, cyano;

a nitrogen atom can additionally be substituted by a (C_6-C_{14}) aryl, (C_6-C_{14}) acyl or (C_1-C_5) alkyl group.

A particularly preferred group of compounds of formula I is constituted in which R_2 is selected from a (C_6-C_{14}) aryl group possibly substituted as defined above.

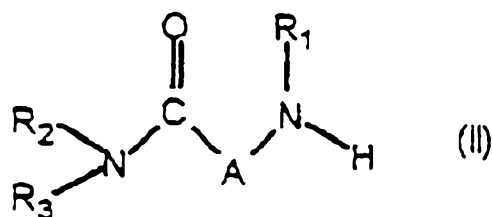
To the knowledge of the Applicant, the compounds of formula (I) are novel with the exception

of α -guanidinoacetanilide, which is described by Mazundar (Indian Drugs 1989, 27, 5, 292), i.e. the compound of formula I in which $R_1 = H$, $R_2 = \text{phenyl}$ and $R_3 = H$.

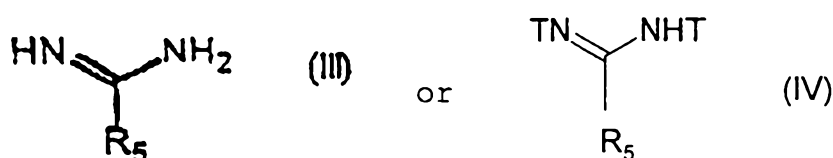
5 The invention also relates to the tautomeric forms, to the enantiomers, diastereoisomers and epimers of the compounds of general formula (I).

The compounds of general formula (I) have basic nitrogen atoms and can be monosalified or disalified by
10 mineral or organic acids.

The compounds of formula (I) can be prepared by reacting a compound of formula:



15 with a compound of formula:



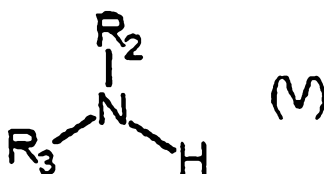
in which:

R_5 is selected from $-\text{SCH}_3$, pyrazolyl or $-\text{SO}_3\text{H}$,
and

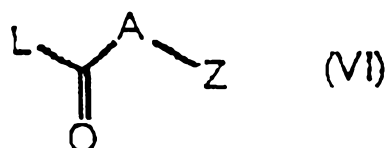
20 T is a tert-butyloxycarbonyl or benzyloxycarbonyl protective group.

The compounds of formula (II) can be prepared in accordance with a process in which:

a) a compound of formula:



25 in which R_2 and R_3 are as defined above is reacted with an acyl halide of general formula (VI):



in which:

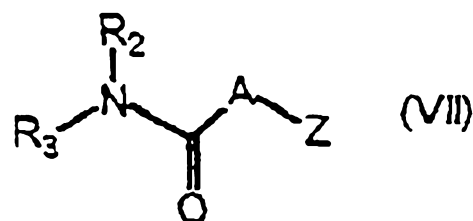
A is as defined above,

5 L represents a chlorine or bromine atom or an activated ester form,

Z represents a chlorine or bromine atom or a protected amino group,

to form a compound of general formula (VII):

10



in which R₂, R₃, A and Z are as defined above;

b) the compound of general formula (VII) is reacted with potassium phthalimide and then with
15 hydrazine monohydrate or else with a nitride followed by a reduction to form a compound of general formula (II) in which R₁ = H.

In the case where Z is a protected amino group, it is appropriate to deprotect it at this stage to form
20 a compound of general formula (II).

The compounds of general formula (II) in which R₁ is other than H can be obtained by reacting a compound of formula (VII) with an amine of general formula (VIII):

25



The compositions according to the present invention are useful in the treatment of pathologies
30 associated with insulin resistance syndrome (syndrome X).

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 diabetes or NIDDM), dyslipidaemia, obesity, arterial hypertension, and certain microvascular and macrovascular complications such as atherosclerosis, retinopathies and neuropathies.

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

15 In particular, the compositions of the invention exhibit a strong hypoglycaemic activity.

The compositions according to the present invention can also be used for treating the chronic complications due to the formation of "advanced glycosylation end products", written AGEs, which result from the glycoxidation reaction between glucose, its oxidation derivatives and the amino functions of proteins, including the so-called Maillard reactions of glycation of glyoxal for example.

25 The pharmaceutical compositions according to the invention can be provided in forms which are intended for parenteral, oral, rectal, permucous or percutaneous administration.

They will therefore be provided in the form of solutions or suspensions for injection or multi-dose bottles, in the form of plain or coated tablets, film-coated tablets, wafer capsules, gelatin capsules, pills, cachets, powders, suppositories or rectal capsules, or solutions or suspensions for percutaneous use in a polar solvent or for permucous use.

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

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

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

The dosage can vary within wide limits (from 0.5 mg to 1000 mg) depending on the therapeutic indication and the administration route, and also on the age and weight of the individual.

The following examples illustrate the preparation of the compounds of formula (I) and of various intermediates.

A - Preparation Example of compounds of formula (VII).

Preparation of N-(2,6-dimethylphenyl)-3-chloropropanamide

A 2 l three-necked flask is charged with 121.8 g of 2,6-dimethylaniline, 300 ml of isopropyl ether and 150 ml of water. 126.5 g of 3-chloropropanoyl chloride are added at a rate such that the internal temperature is between 5 and 10°C. At the end of the addition, the reaction medium is stirred for 3 h. The precipitate formed is filtered off with suction, washed with isopropyl ether and then with water and finally dried. 126 g of white crystals are obtained.

m.p. = 134-136°C

¹H NMR (DMSO-d₆, 200 MHz):

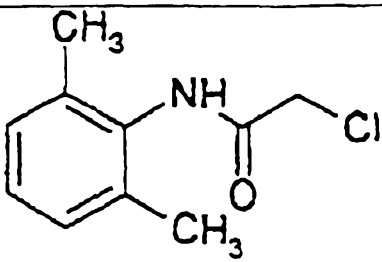
2.18 (s, 6H); 2.81 (t, 2H); 3.88 (t, 2H); 7.03 (d, 3H); 9.40 (s, 1H)

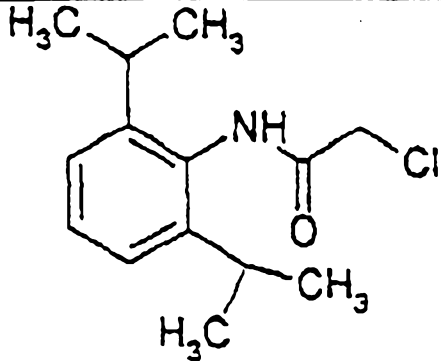
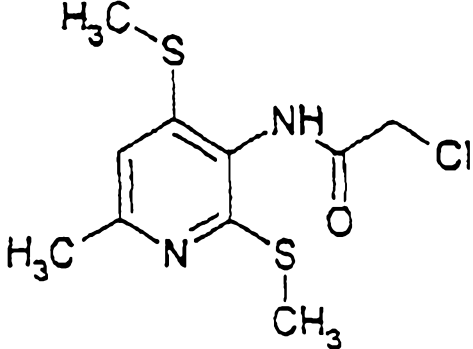
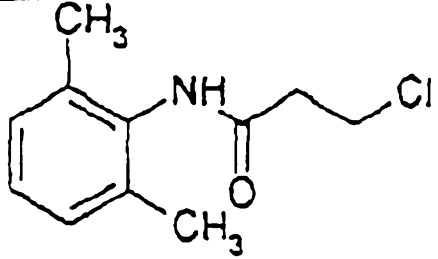
The formulae and characteristics of compounds of formula (VII) have been collated in Table 1.

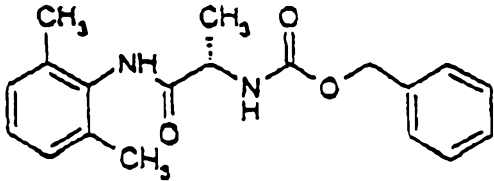
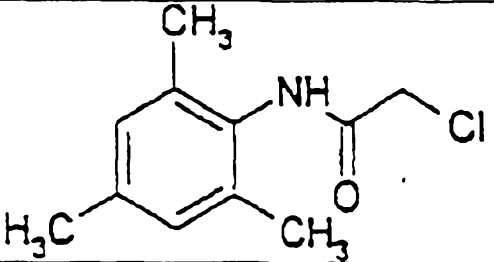
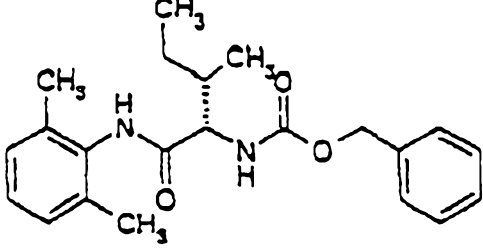
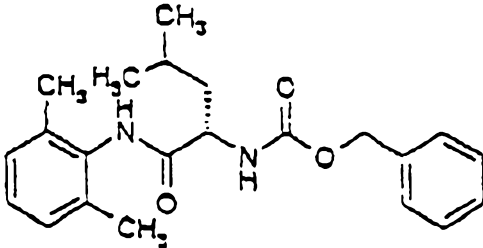
Table 1

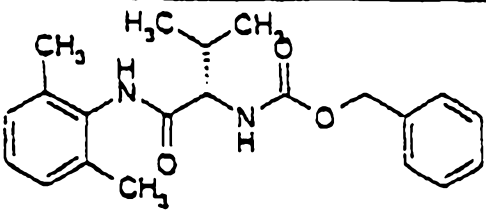
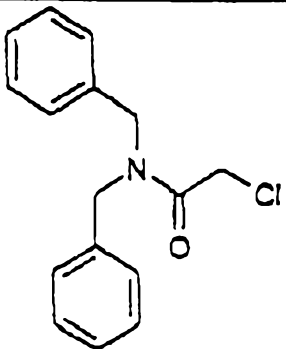
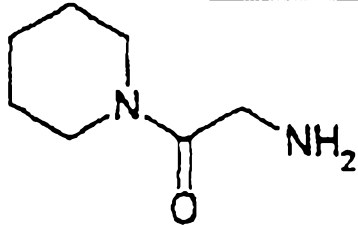
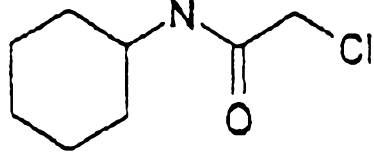
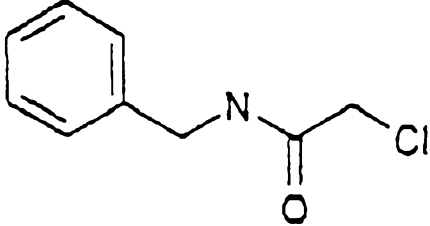
35

Compound	Structure	m.p. in °C (Köfler)	¹ H NMR 200 MHz d ppm
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Compound	Structure	m.p. in °C (Köfler)	¹ H NMR 200 MHz d ppm
1		146-148 lit.: 146-148	DMSO-d6 2.25 (s, 6H) 4.35 (s, 2H) 9.10 (s, 3H) 9.62 (s, 1H)

2	 <chem>CC(C)C1=CC=C2C(=C1)C(=NC2=CC=C2)C(=O)NCCCl</chem>	148-150 lit.: 151.4- 151.9	CDC13 1.20 (d, 12H) 3.00 (m, 2H) 4.20 (s, 2H) 7.20 (m, 3H) 7.82 (s, 1H)
3	 <chem>CC1=CC=C(NC(=O)NCCCl)S1C</chem>	197-199 lit.: 190-192	DMSO-d6 2.65 (2s, 9H) 4.50 (s, 2H) 7.13 (s, 1H) 10.06 (s, 1H)
4	 <chem>CC1=CC=C2C(=C1)C(=CNC2=CC=C2)C(=O)NCCCl</chem>	134-136 lit.: 134-136	DMSO-d6 2.18 (s, 6H) 2.81 (t, 2H) 3.88 (t, 2H) 7.03 (d, 3H) 9.40 (s, 1H)

Compound	Structure	m.p. in °C (Köfler)	¹ H NMR 200 MHz δ ppm
5		176-178	DMSO-d6 1.23 (d, 3H) 2 (s, 6H) 4.15 (m, 1H) 4.90 (s, 2H) 6.90 (s, 3H) 7.23 (s, 5H) 7.45 (d, 1H) 9.20 (s, 1H)
6		184-186	DMSO-d6 2.20 (s, 6H) 2.40 (s, 3H) 4.35 (s, 2H) 7.00 (s, 2H) 9.62 (s, 1H)
7		195-197	DMSO-d6 1.0 (t, 3H) 1.18 (d, 3H) 1.25-2.00 (m, 3H) 2.30 (s, 6H) 4.20 (t, 1H) 5.30 (q, 2H) 7.20 (s, 3H) 7.50 (s, 5H) 7.70 (d, 2H) 9.55 (s, 1H)
8		oil	DMSO-d6 1.0 (t, 6H) 1.69 (m, 3H) 2.18 (s, 6H) 4.30 (q, 1H) 5.09 (q, 2H) 7.09 (s, 3H) 7.40 (s, 5H) 7.63 (d, 1H) 9.40 (s, 1H)

9		210-212	DMSO-d6 1.0 (t, 6H) 1.70 (m, 1H) 2.13 (s, 6H) 4.10 (t, 1H) 5.11 (q, 2H) 7.05 (s, 3H) 7.36 (s, 5H) 7.50 (d, 1H) 9.40 (s, 1H)
10		oil	DMSO-d6 4.30 (s, 4H) 4.40 (s, 2H) 7.02 (m, 10H)
11		172-174	DMSO-d6 4.33 (s, 2H) 7.42 (m, 3H) 8.21 (s, 1H)
12		114-116	DMSO-d6 1.39 (m, 5H) 1.80 (m, 4H) 3.66 (s, 2H) 4.16 (s, 2H) 8.25 (d, 1H)
13		133-135	DMSO-d6 3.99 (s, 2H) 4.16 (d, 2H) 7.16 (m, 5H) 8.62 (s, 1H)

B - Preparation Example of compounds of formula (II)

Preparation of N-(2,6-dimethylphenyl)-3-aminopropanamide

A three-necked flask is charged with 400 ml of DMF, 100 g of N-(2,6-dimethylphenyl)-3-chloropropanamide and 95.7 g of potassium phthalimide. After 3 h of stirring at reflux, the reaction medium is cooled to room temperature and 600 ml of water are added. Stirring is continued for 1.5 h. The precipitate formed is filtered off with suction and washed with water. 140 g of white crystals (m.p. >260°C) are obtained.

The crystals are charged to a three-necked flask with 800 ml of 95° ethanol and 23.7 g of hydrazine monohydrate. After 3 h of stirring at reflux, 39 ml of concentrated hydrochloric acid are added and stirring is continued for 1 h. The precipitate formed is filtered off, and washed with ethanol and the ethanolic phases are concentrated. The crude product obtained is taken up in water; the insoluble material remaining is filtered off and the aqueous phase is concentrated to give 108 g of a cream-white solid.

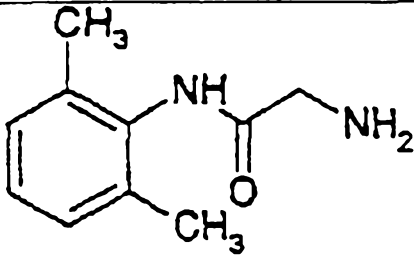
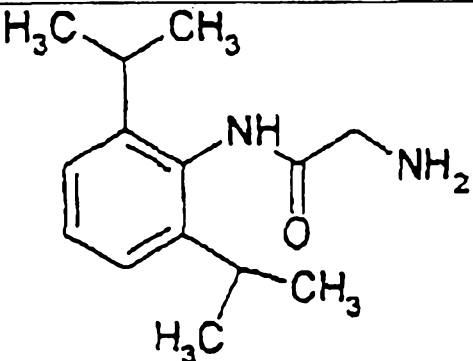
m.p. = 239-241°C

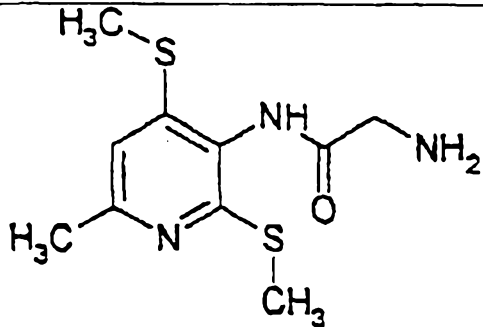
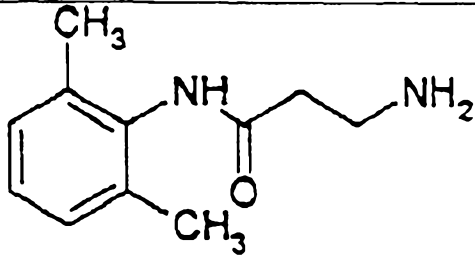
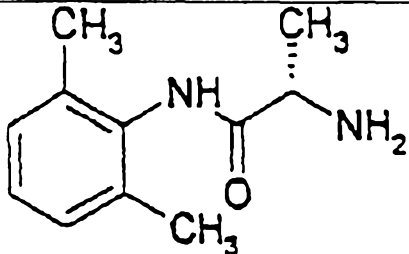
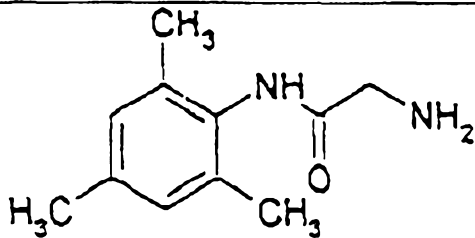
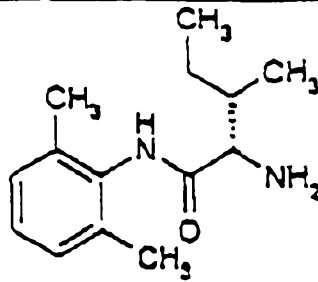
¹H NMR (DMSO-d₆, 200 MHz):

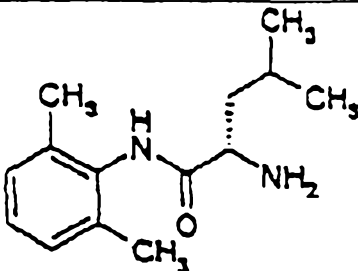
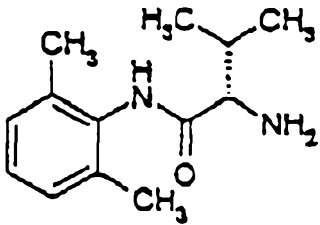
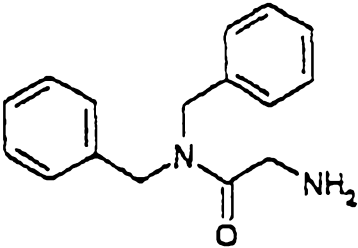
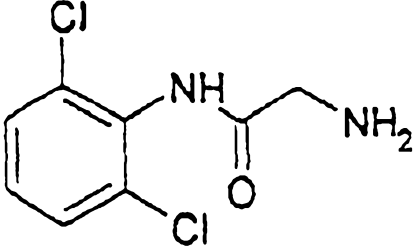
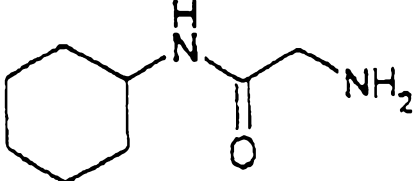
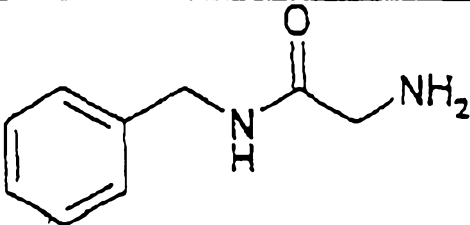
2.22 (s, 6H); 2.44 (t, 2H); 2.88 (t, 2H); 7.07 (s, 3H); 9.50 (s, 1H).

The formulae and characteristics of compounds of formula (II) have been collated in Table 2.

- 13 -
Table 2

Compound	Structure	m.p. in °C (Köfler)	¹ H NMR 200 MHz d ppm
1		>260 (HCl) lit.: 296	DMSO-d6 2.15 (d, 6H) 3.90 (d, 2H) 7.12 (s, 3H) 8.40 (s, 3H) 10.15 (s, 1H)
2		118-120	DMSO-d6 0.88 (s, 12H) 2.77 (m, 2H) 3.11 (s, 2H) 6.92 (m, 3H) 9.07 (s, 1H)

3		132-134	DMSO-d6 2.40 (s, 6H) 2.48 (s, 3H) 3.34 (s, 3H) 4.26 (s, 3H) 6.90 (s, 1H)
4		239-241 (HCl) lit.: 239-240	DMSO-d6 2.22 (s, 6H) 2.44 (t, 2H) 2.88 (t, 2H) 7.07 (s, 3H) 9.50 (s, 1H)
Compound	Structure	m.p. in °C (Köfler)	¹ H NMR 200 MHz δ ppm
5		73-75	DMSO-d6 1.25 (d, 3H) 2.13 (s, 6H) 3.50 (m, 3H) 7.00 (s, 3H)
6		119-121	DMSO-d6 2.09 (s, 6H) 2.18 (s, 3H) 3.28 (s, 2H) 6.87 (s, 2H)
7		74-76	DMSO-d6 1.04 (t, 3H) 1.20 (d, 3H) 1.30 (m, 1H) 1.78 (m, 3H) 2.25 (s, 6H) 3.35 (d, 1H) 7.13 (s, 3H) 9.40 (s, 1H)

8		oil	DMSO-d6 1.0 (t, 6H) 1.63 (m, 3H) 2.21 (s, 6H) 3.45 (m, 1H) 7.12 (s, 3H)
9		71-73	DMSO-d6 0.90 (d, 3H) 1.05 (d, 3H) 2.04 (m, 1H) 2.25 (s, 6H) 3.27 (d, 1H) 7.03 (s, 3H)
10		oil	DMSO-d6 3.00 (s, 2H) 3.54 (s, 2H) 4.54 (d, 4H) 7.33 (m, 10H)
11		108-110	DMSO-d6 3.57 (s, 2H) 4.69 (s, 3H) 7.51 (t, 1H) 7.75 (d, 2H)
12		89-91	DMSO-d6 1.47 (t, 5H) 1.91 (m, 5H) 3.24 (s, 2H) 3.77 (m, 1H) 7.83 (d, 1H)
13		oil	DMSO-d6 2.69 (s, 2H) 3.34 (s, 2H) 4.50 (d, 2H) 7.49 (m, 5H) 8.52 (s, 1H)

C - Preparation Example of compounds of formula (II)

Preparation of N-(2,6-dimethylphenyl)-2-methylamino-acetamide

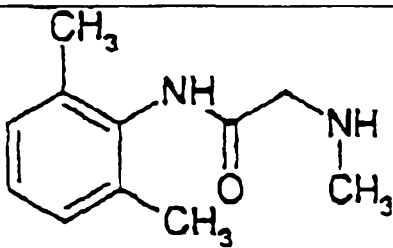
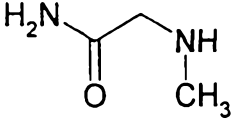
A closed stainless-steel reactor is charged with 80 g of N-(2,6-dimethylphenyl)-2-chloro-acetamide and 600 ml of a 40% aqueous methylamine solution. The mixture is heated with stirring at 80°C for 4 h and then concentrated under vacuum. The crude product is taken up in water and washed with dichloromethane. The aqueous solution is basified using sodium hydroxide solution and extracted with dichloromethane. The organic phase is dried over sodium sulphate and concentrated to give 60 g of a colourless oil.

¹H NMR (DMSO-d₆, 200 MHz):

2.15 (s, 6H); 2.44 (s, 3H); 3.50 (s, 2H); 6.50 (s, 1H); 7.70 (s, 3H); 9.58 (s, 1H)

The formulae and characteristics of compounds have been collated in Table 3.

Table 3

Compound	Structure	m.p. in °C (Köfler)	¹ H NMR 200 MHz δ ppm
1		oil	DMSO-d ₆ 2.15 (s, 6H) 2.44 (s, 3H) 3.50 (s, 2H) 6.50 (s, 1H) 7.07 (s, 3H) 9.58 (s, 1H)
2		oil	¹³ C NMR 50 MHz δ ppm DMSO-d ₆ 34.80 CH ₃ -N 54.28 CH ₂ 180.09 C=O

D - Preparation Example of compounds of formula (I)

Preparation of 2-aminoiminomethylamino-N-(cyclohexyl)-acetamide

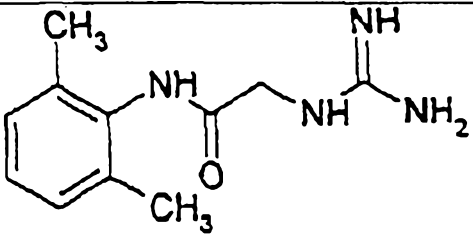
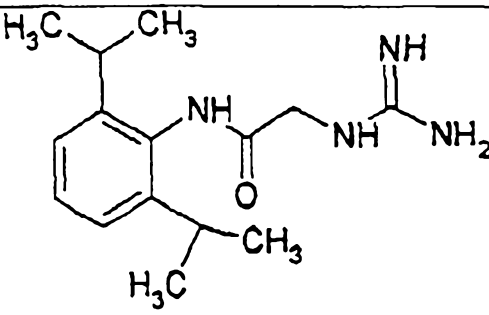
5 A round-bottomed flask is charged with 15 g of
2-amino-N-(cyclohexyl)-acetamide, 14,6 g 1-
aminoiminomethylpyrazole hydrochloride and 100 ml of
dioxane. After 18 h stirring at reflux, the reaction
medium is cooled to room temperature and precipitate
10 which has formed is filtered off with suction. 16 g of
a white solid are obtained.

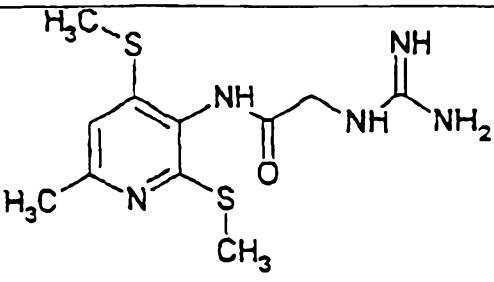
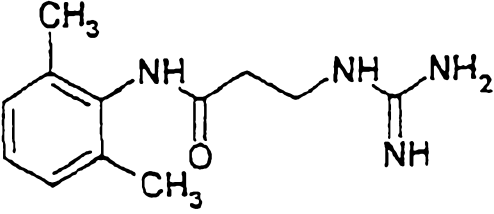
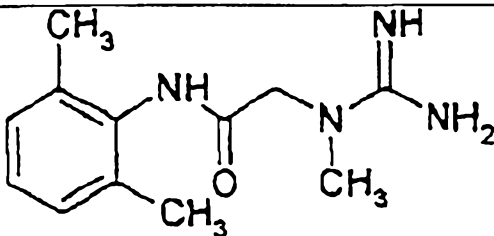
m.p. = 232-234°C

¹H NMR (DMSO-d₆, 200 MHz): 1.19 (m, 5H); 1.62
(m, 5H); 3.46 (m, 1H); 3.78 (d, 2H); 7.21 (s, 4H); 7.68

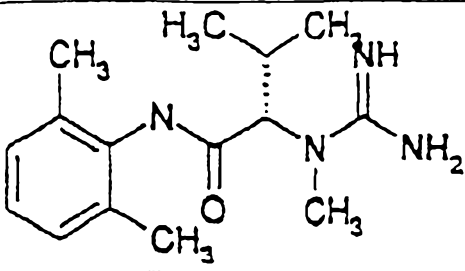
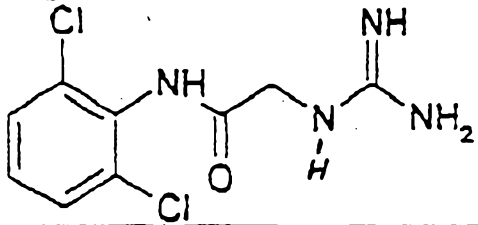
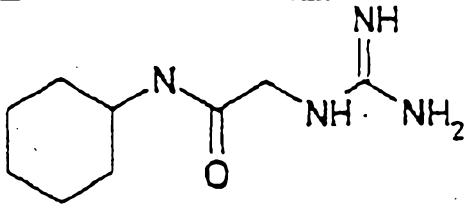
15 The formulae and characteristics of compounds
of formula (I) have been collated in Table 4.

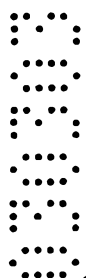
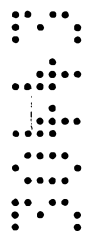
Table 4

Example	Structure	m.p. in °C (Köfler)	¹ H NMR 200 MHz d ppm
1		255-257 (0.5 H ₂ SO ₄)	DMSO-d ₆ 2.25 (s, 6H) 4.25 (s, 2H) 7.15 (s, 3H) 7.95 (s, 3H) 8.35 (s, 1H) 10.10 (s, 1H)
2		260-262 (HCl)	DMSO-d ₆ 1.31 (d, 12H) 3.22 (m, 2H) 4.35 (s, 2H) 7.37 (m, 3H) 7.64 (s, 2H) 7.91 (s, 2H) 9.91 (s, 1H)

3		249-251 (HCl)	DMSO-d6 2.40 (3s, 9H) 4.15 (s, 2H) 6.92 (s, 1H) 7.44 (s, 3H) 7.74 (s, 1H) 9.88 (s, 1H)
4		223-225	DMSO-d6 2.16 (s, 6H) 2.65 (t, 2H) 3.50 (t, 2H) 7.08 (s, 3H) 7.31 (m, 3H) 7.85 (s, 2H) 9.69 (s, 1H)
5		227-229 (HCl)	DMSO-d6 2.05 (s, 6H) 2.88 (s, 3H) 4.25 (s, 2H) 6.95 (s, 4H) 9.68 (s, 1H)

Compound	Structure	m.p. in °C (Köfler)	¹ H NMR 200 MHz δ ppm
6		159-161 (HCl)	DMSO-d6 1.53 (d, 3H) 2.27 (s, 6H) 4.85 (m, 1H) 7.20 (s, 3H) 7.55 (s, 2H) 8.10 (d, 1H) 10.00 (s, 1H)
7		>260 (HCl)	DMSO-d6 2.15 (s, 6H) 2.24 (s, 3H) 4.18 (d, 2H) 6.90 (s, 2H) 7.50 (s, 2H) 7.87 (s, 1H) 9.70 (s, 1H)
8		amorphous (HCl)	DMSO-d6 1.0 (m, 6H) 1.30 (m, 1H) 1.50 (m, 1H) 1.93 (m, 1H) 2.25 (s, 6H) 4.60 (d, 1H) 7.17 (s, 3H) 7.95 (s, 2H) 9.55 (s, 1H)
9		amorphous (HCl)	DMSO-d6 1.05 (d, 6H) 1.69 (m, 3H) 2.18 (s, 6H) 4.87 (s, 1H) 7.15 (s, 3H) 8.02 (s, 2H) 10.18 (s, 1H)

10		amorphous (HCl)	DMSO-d6 1.0 (m, 6H) 2.25 (m, 7H) 4.57 (t, 1H) 7.12 (s, 3H) 8.08 (s, 2H) 10.20 (s, 1H)
12		181-183 (HCl)	DMSO-d6 4.30 (d, 2H) 7.52 (m, 3H) 7.91 (s, 1H) 10.45 (s, 1H)
14		232-234 (HCl)	DMSO-d6 1.19 (m, 5H) 1.62 (m, 5H) 3.46 (m, 1H) 3.78 (d, 2H) 7.21 (s, 4H) 7.68 (t, 1H) 8.16 (d, 1H)



The results of pharmacological studies will be given below.

STUDY OF THE ANTIDIABETIC ACTIVITY IN THE NOSTZ RAT

5 The antidiabetic activity of the compounds of formula (I) was determined orally on an experimental model of non-insulin-dependent diabetes induced in the rat using streptozotocin.

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

15 The diabetic rats used are 8 weeks old. The animals are kept from the day of their birth to the day of the experiment in an animal house at a regulated temperature of from 21 to 22°C and are subjected to a fixed cycle of light (from 7.00 am to 7.00 pm) and darkness (from 7.00 pm to 7.00 am). Their diet consisted of a maintenance diet; water and food were provided ad libitum, except for the 2 hours' fasting prior to the tests in which food is withdrawn (post-absorptive state).

20 The rats are treated orally for one (d1) or four (d4) days with the test product. Two hours after the final administration of the product and 30 minutes after anaesthesia of the animals with sodium pentobarbital (Nembutal®), 300 ml of blood is sampled from the end of the tail.

25 Results obtained are collated, by way of example, in Table 5. These results demonstrate the efficacy of the compounds of formula (I) in reducing glycaemia in diabetic animals. These results are expressed as a percentage change in glycaemia on d1 and d4 (number of days of treatment) relative to d0 (before treatment).

Table 5

Example	20 mg/kg/d		200 mg/kg/d	
	d1	d4	d1	d4
1	-3	-7	-20	-24
3	+7	-7	-5	-4
4	-1	-11	-13	-15
5	-2	-7	-16	-25

5

Compounds	20 mg/kg/d		200 mg/kg/d	
	d1	d4	d1	d4
6	+8	-3	-4	-18
7	-9	-9	-3	-10
8	-11	-14	-8	-10
9	-4	-15	+7	-4
10	-13	-15	-3	-16
11	-14	-9	-3	-16
12	-9	-13	-14	-27

STUDY OF THE ANTIGLYCOXIDATION ACTIVITY

5 The compounds (I) are also capable of
inhibiting the so-called Maillard reactions by means of
a "scavenging" effect on α -dicarbonyl derivatives such
as glyoxal - this is the antiglycation effect. This
inhibitory effect on the Maillard reaction by the
compounds of formula (I) was studied *in vitro* by
10 assaying the ketamines ("fructoamines") produced during
the incubation of albumin with methylglyoxal in the
presence or absence of a compound of formula (I).

A 6.6 mg/ml solution of bovine albumin in 0.2 M
phosphate buffer pH 7.4 is incubated with 1 mM
15 methylglyoxal in the presence or absence of a compound
according to the invention at a concentration of 1 mM.
The incubation is carried out under sterile conditions
at 37°C for 6 days. At the end of the incubation
period, the amount of ketamines is measured with a
20 commercially available fructoamine assay kit (kit
"FRA", product reference: 0757055, Roche S.A. products)
in accordance with the manufacturer's instructions.
Under these experimental conditions, the level of
fructoamine following incubation of albumin with
25 methylglyoxal in the presence of a compound of formula
(I) is from 30 to 50% lower than that observed when
albumin is incubated with methylglyoxal in the absence
of the compound of formula (I).

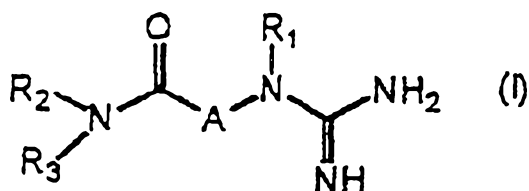
Throughout this specification and the claims
which follow, unless the context requires otherwise, the
word "comprise", or variations such as "comprises" or
"comprising", will be understood to imply the inclusion
of a stated integer or step or group of integers or steps
but not the exclusion of any other integer or step or
group of integers or steps.

The reference to any prior art in this
specification is not, and should not be taken as, an
acknowledgment or any form of suggestion that the prior art
forms part of the common general knowledge in Australia.



THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Pharmaceutical composition comprising as active principle a compound of general formula (I)



in which:

R₁ is selected from one of the following groups:

- H;
- (C₁-C₂₀)alkyl substituted or unsubstituted by one or more of the following groups:
 - amino, hydroxyl, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl;

R₂ is selected from

- (C₃-C₈)cycloalkyl substituted or unsubstituted by one or more of the following groups:
 - amino, hydroxyl, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅) alkylthio, (C₁-C₅)alkylamino, trifluoromethyl;
 - (C₆-C₁₄)aryl substituted or unsubstituted by one or more of the following groups:
 - amino, hydroxyl, halogen, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl, cyano;
 - (C₁-C₁₃)heteroaryl containing one or more heteroatoms selected from N, O and S and substituted or unsubstituted by one or more of the following groups:
 - amino, hydroxyl, halogen, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl, cyano;
- a nitrogen atom can additionally be substituted by a (C₆-C₁₄)aryl, (C₆-C₁₄)acyl or (C₁-C₅)alkyl group;

R₃ is selected from



- H;

-(C₃-C₈)cycloalkyl substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl;

-(C₃-C₈)heterocycloalkyl containing one or more heteroatoms selected from N, O and S and substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl;

a nitrogen atom can additionally be substituted by a (C₆-C₁₄)aryl, (C₆-C₁₄) acyl or (C₁-C₅)alkyl group;

-(C₆-C₁₄)aryl substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, halogen, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl, cyano;

-(C₁-C₁₃)heteroaryl containing one or more heteroatoms selected from N, O and S and substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, halogen, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl, cyano;

a nitrogen atom can additionally be substituted by a (C₆-C₁₄)aryl, (C₆-C₁₄) acyl or (C₁-C₅)alkyl group;

-(C₆-C₁₄)aryl-(C₁-C₅)alkyl substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, halogen, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl, cyano;

and A is selected from the groups:

-CH₂-

-CH₂-CH₂-



-CHR₄-,

R₄ being selected from:

- H;

- (C₁-C₂₀)alkyl substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl;

- (C₃-C₈)cycloalkyl substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl;

- (C₃-C₈)heterocycloalkyl containing one or more heteroatoms selected from N, O and S and substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl;

a nitrogen atom can additionally be substituted by a (C₆-C₁₄)aryl, (C₆-C₁₄) acyl or (C₁-C₅)alkyl group;

and solvates and pharmaceutically acceptable salts thereof.

2. Composition according to Claim 1, comprising as active principle a compound of general formula I in which R₁ is selected from H and a (C₁-C₆)alkyl group.

3. Composition according to Claim 1, comprising as active principle a compound of general formula I in which R₂ is selected from a (C₆-C₁₄) aryl group possibly substituted as defined in Claim 1.

4. Compounds of general formula (I)

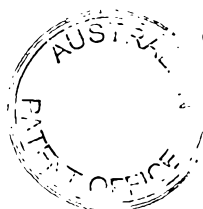


R_1 is selected from one of the following groups:

- H;
- (C₁-C₂₀)alkyl substituted or unsubstituted by one or more of the following groups:
 - amino, hydroxyl, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl;

R_2 is selected from

- (C₃-C₈)cycloalkyl substituted or unsubstituted by one or more of the following groups:
amino, hydroxyl, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅) alkylthio
(C₁-C₅)alkylamino, trifluoromethyl;
- (C₆-C₁₄)aryl substituted or unsubstituted by one or more of the following groups:
amino, hydroxyl, halogen, (C₁-C₅)alkyl, (C₁-C₅)alkoxy,
(C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl, cyano;
- (C₁-C₁₃)heteroaryl containing one or more heteroatoms selected from N, O and S and substituted or unsubstituted by one or more of the following groups:
amino, hydroxyl, halogen, (C₁-C₅)alkyl, (C₁-C₅)alkoxy,
(C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl, cyano;
- a nitrogen atom can additionally be substituted by a (C₆-C₁₄)aryl, (C₆-C₁₄)acyl or (C₁-C₅)alkyl group;



R₃ is selected from

- H;
- (C₃-C₈)cycloalkyl substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl;

- (C₃-C₈)heterocycloalkyl containing one or more heteroatoms selected from N, O and S and substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl;

a nitrogen atom can additionally be substituted by a (C₆-C₁₄)aryl, (C₆-C₁₄) acyl or (C₁-C₅)alkyl group;

- (C₆-C₁₄)aryl substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, halogen, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl, cyano;

- (C₁-C₁₃)heteroaryl containing one or more heteroatoms selected from N, O and S and substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl, cyano;

a nitrogen atom can additionally be substituted by a (C₆-C₁₄)aryl, (C₆-C₁₄) acyl or (C₁-C₅)alkyl group;

- (C₆-C₁₄)aryl-(C₁-C₅)alkyl substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl, cyano;

and A is selected from the groups:

-CH₂-



-CH₂-CH₂-,

-CHR₄-,

R₄ being selected from:

- H;

- (C₁-C₂₀)alkyl substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl;

- (C₃-C₈)cycloalkyl substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl;

- (C₃-C₈)heterocycloalkyl containing one or more heteroatoms selected from N, O and S and substituted or unsubstituted by one or more of the following groups:

amino, hydroxyl, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, trifluoromethyl;

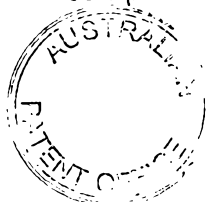
a nitrogen atom can additionally be substituted by a (C₆-C₁₄)aryl, (C₆-C₁₄) acyl or (C₁-C₅)alkyl group;

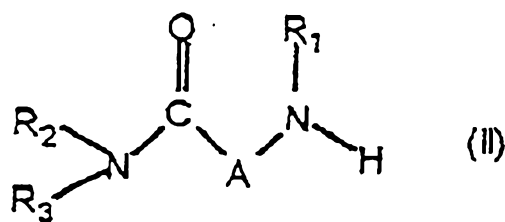
and solvates and pharmaceutically acceptable salts thereof, with the exception of the compound of formula (I) in which R₁ = H, R₂ = phenyl and R₃ = H.

5. Compounds of formula I according to Claim 4 in which R₁ is selected from H and a (C₁-C₆)alkyl group.

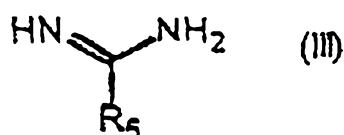
6. Compounds according to Claim 4 in which R₂ is selected from a (C₆-C₁₄)aryl group possibly substituted as defined in Claim 1.

7. Process for preparing a compound according to Claim 4 by reacting a compound of formula:

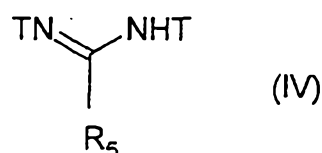




with a compound of formula:



or



in which:

R₅ is selected from -SCH₃, pyrazolyl or -SO₃H,

and

T is a tert-butyloxycarbonyl or benzyloxycarbonyl protective group.

8. Use of a compound as defined in Claim 4 for the manufacture of a medicament for the treatment of pathologies associated with insulin resistance syndrome.

9. Use of a compound as defined in Claim 4 for the manufacture of a medicament with hypoglycaemic activity.

10. Use of a compound as defined in Claim 4 for the manufacture of a antiglycoxidational medicament.

11. A method for treating a patient suffering from a pathology associated with insulin resistance syndrome, comprising administering to a patient in need of such treatment an effective amount of a composition of Claim 1.



12. Compounds of the general formula (I), processes for preparing same and uses thereof substantially as hereinbefore described with reference to the examples.

5 DATED THIS 27th day of February, 2003.

MERCK PATENT GMBH

By Its Patent Attorneys

DAVIES COLLISON CAVE

