AUSTRALIA 662658

P/00/001 28/5/91
Section 29

Patents Act 1990

PATENT REQUEST: STANDARD PATENT/PATENT OF ADDITION

We, being the person identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying standard complete specification.

Full application details follow.

[71] Applicant: ADIR ET COMPAGNIE

Address: 1 RUE CARLE HEBERT, F 92415 COURBEVOIE CEDEX, FRANCE

[70] Nominated Person: ADIR ET COMPAGNIE

Address: 1 RUE CARLE HEBERT, F 92415 COURBEVOIE CEDEX, FRANCE

[54] Invention Title: NEW THIAZOLIDINEDIONE COMPOUNDS, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

[72] Name(s) of actual inventor(s): GILBERT REGNIER, YVES CHARTON, JACQUES DUHAULT AND JOSEPH ESPINAL

[74] Address for service in Australia: c/o WATERMARK PATENT & TRADEMARK ATTORNEYS, of The Atrium, 290 Burwood Road, Hawthorn, Victoria 3122, Australia Attorney Code: WM

BASIC CONVENTION APPLICATION(S) DETAILS

[31] Application Number	[33] Country	Country Code	[32] Date of Application
92 12123	FRANCE	FR	12TH OCTOBER 1992

Basic Applicant(s): ADIR ET COMPAGNIE

Drawing number recommended to accompany the abstract .....

By our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS

.....

Louis C. Gebhardt
Registered Patent Attorney

DATED this 8th day of October 1993.

C 006041 111093

P/00/008b 12/11/91
Section 29 (1)
Regulation 3.1 (2)

AUSTRALIA

Patents Act 1990

NOTICE OF ENTITLEMENT

(To be filed before acceptance)

We, **ADIR ET COMPAGNIE**, 1 rue Carle Hébert, F92415 Courbevoie Cedex, France, being the applicant in respect of Application No. 48905/93 state the following:-

The Person nominated for the grant of the patent has entitlement from the actual inventors by assignment.

The person nominated for the grant of the patent is the applicant of the basic application listed on the patent request form.

The basic application listed on the request form is the first application made in a Convention country in respect of the invention.

By our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS

.....

~~Carolyn J. Harris~~ KAREN J. SINCLAIR
Registered Patent Attorney

DATED 29 June 1995

AU9348905

(12) PATENT ABRIDGMENT (11) Document No. AU-B-48905/93
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 662658

(54) Title
NEW THIAZOLIDINEDIONE COMPOUNDS, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

International Patent Classification(s)
(51)[5] **C07D 277/34** **C07D 417/10** **C07D 417/12** **A61K 031/425**

(21) Application No. : **48905/93** (22) Application Date : **11.10.93**

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(71) Applicant(s)
ADIR ET COMPAGNIE

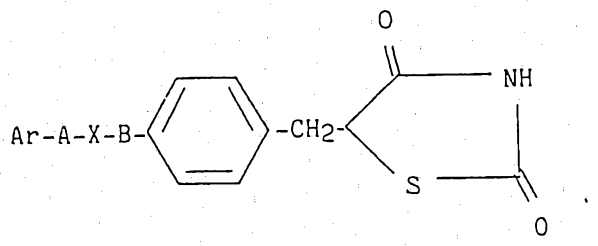
(72) Inventor(s)
GILBERT REGNIER; YVES CHARTON; JACQUES DUHAULT; JOSEPH ESPINAL

(74) Attorney or Agent
WATERMARK PATENT & TRADEMARK ATTORNEYS , Locked Bag 5, HAWTHORN VIC 3122

(56) Prior Art Documents
AU 593754 31078/89 C07D 417/10
AU 61285/90 C07D 277/34
AU 70906/91 C07D 277/34

(57) Claim

1) Thiazolidinedione compounds of formula I :



(I)

wherein :

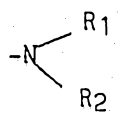
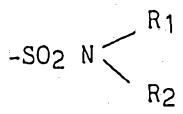
Ar represents :

a) a polymethylene ring containing from 5 to 7 carbon atoms which is optionally substituted by one or more alkyl radicals having from 1 to 5 carbon atoms,

b) a mono-, bi- or tri-cyclic unsaturated hydrocarbon radical which is optionally mono- or poly-substituted by a halogen atom, a trifluoromethyl radical, a straight-chain or branched alkyl, alkoxy or alkylthio radical

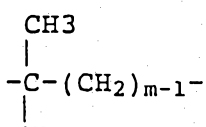
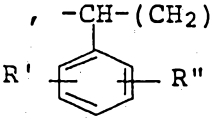
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each having from 1 to 5 carbon atoms, an acyloxy radical, a hydroxy radical or a radical of the formula

 or  in each of which

R_1 and R_2, which are the same or different, each represents a hydrogen atom, or a straight-chain or branched alkyl radical having from 1 to 5 carbon atoms, or R_1 and R_2, together with the nitrogen atom to which they are bonded, represent a heterocycle having from 4 to 7 ring members optionally including (in addition to the nitrogen atom) an oxygen or sulphur atom, or

c) a mono-, bi- or tri-cyclic heterocyclic radical containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulphur atoms, which is optionally substituted by an oxo radical and/or by one or more halogen atoms or alkyl radicals (having from 1 to 5 carbon atoms) or phenyl radicals, each phenyl radical itself optionally being substituted by one or more halogen atoms or trifluoromethyl radicals or alkyl or alkoxy radicals each having from 1 to 5 carbon atoms ;

A represents : a single bond, a hydrocarbon chain having 2 or 3 carbon atoms and including a double bond, or a chain of the formula $-(CH_2)_m-$,  ,  ,

$-O-(CH_2)_m-$ or $-S-(CH_2)_m-$ wherein :

- m is an integer from 1 to 3 and R' and R", which are the same or different, each represents a hydrogen atom or a straight-chain or branched alkyl radical having from 1 to 5 carbon atoms;

X represents an oxygen atom, -CONR- or $-SO_2NR-$ wherein R represents a hydrogen atom or a straight-chain or branched

.../3

alkyl radical having from 1 to 5 carbon atoms and optionally including a double bond,

or, when A represents a single bond and Ar represents a phenyl radical, R may also represent a carbonyl radical bonded to Ar by its free bond such that Ar-A-X together form a phthalimido radical;

B represents a saturated hydrocarbon chain having from 1 to 6 carbon atoms which is optionally branched and/or substituted by a hydroxy radical or an oxo radical;

and their enantiomers and diastereoisomers, as well as their addition salts with a pharmaceutically acceptable acid.

7) A method of treating conditions of insulin resistance and/or non-insulin-dependent diabetes which may or may not be associated with hypertension comprising administering to a patient requiring such treatment a pharmaceutically effective amount of a compound as claimed in any one of claims 1 to 4 in adjunct with suitable excipients.

P/00/011 28/5/91
Regulation 3.2(2)

AUSTRALIA

662658

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ORIGINAL
COMPLETE SPECIFICATION
STANDARD PATENT

Application Number:

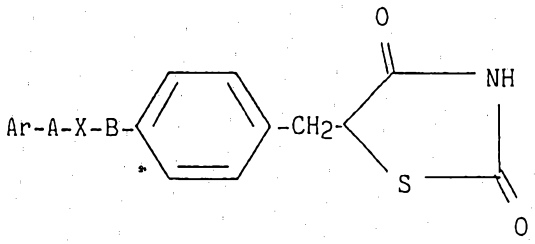
Lodged:

Invention Title: NEW THIAZOLIDINEDIONE COMPOUNDS, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The following statement is a full description of this invention, including the best method of performing it known to us :-

The present invention relates to new thiazolidinedione compounds, a process for their preparation and pharmaceutical compositions containing them.

It relates more especially to :
- thiazolidinedione compounds of formula I :



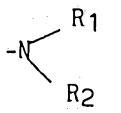
(I)

wherein :

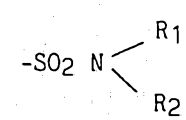
Ar represents :

a) a polymethylene ring containing from 5 to 7 carbon atoms which is optionally substituted by one or more alkyl radicals having from 1 to 5 carbon atoms,

b) a mono-, bi- or tri-cyclic hydrocarbon radical such as, for example, a phenyl, naphthyl, fluorenyl, dibenzocycloheptenyl or biphenylyl radical, each of which is optionally mono- or poly-substituted by a halogen atom, such as, for example, a fluorine, chlorine or bromine atom, a trifluoromethyl radical, a straight-chain or branched alkyl, alkoxy or alkylthio radical each having from 1 to 5 carbon atoms, an acyloxy radical, a hydroxy radical or a radical of the formula



or

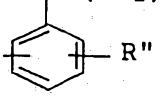


in each of which

R_1 and R_2, which are the same or different, each

represents a hydrogen atom, or a straight-chain or branched alkyl radical having from 1 to 5 carbon atoms, or R_1 and R_2, together with the nitrogen atom to which they are bonded, represent a heterocycle having from 4 to 7 ring members optionally including (in addition to the nitrogen atom) an oxygen or sulphur atom, or

c) a mono-, bi- or tri-cyclic heterocyclic radical containing 1 or 2 hetero atoms selected from nitrogen, oxygen and sulphur atoms, such as, for example, a furyl, thienyl, pyrrolinyl, pyridyl, pyrazinyl, oxazolyl, thiazolyl, indolyl, imidazolyl, chromanyl or xanthenyl radical, each of which is optionally substituted by an oxo radical and/or by one or more halogen atoms or alkyl radicals (having from 1 to 5 carbon atoms) or phenyl radicals, each phenyl radical itself optionally being substituted by one or more halogen atoms or trifluoromethyl radicals or alkyl or alkoxy radicals each having from 1 to 5 carbon atoms ;

A represents : a single bond, a hydrocarbon chain having 2 or 3 carbon atoms and including a double bond, or a chain of the formula $-(CH_2)_m-$, $-C(CH_3)_2-(CH_2)_{m-1}-$, $-CH(R')-(CH_2)_{m-1}-$,  , $-O-(CH_2)_m-$ or $-S-(CH_2)_m-$ wherein :

- m is an integer from 1 to 3 and R' and R", which are the same or different, each represents a hydrogen atom or a straight-chain or branched alkyl radical having from 1 to 5 carbon atoms;

X represents an oxygen atom, -CONR- or -SO_2NR- wherein R represents a hydrogen atom or a straight-chain or branched alkyl radical having from 1 to 5 carbon atoms and optionally including a double bond,

or, when A represents a single bond and Ar represents a phenyl radical, R may also represent a carbonyl radical bonded to Ar by its free bond such that Ar-A-X together form a phthalimido radical;

B represents a saturated hydrocarbon chain having from 1 to 6 carbon atoms which is optionally branched and/or substituted by a hydroxy radical or an oxo radical;

and also the enantiomers and, when B is branched, the corresponding diastereoisomers.

The prior art is illustrated especially by the patent applications EP 008203, WO 8607056, EP 207581, WO 8504171 and WO 9207850 which relate to thiazolidine-2,4-dione compounds which can be used as antidiabetic agents.

Apart from the fact that the compounds of the present invention are new, they differ from the previously known thiazolidine-2,4-dione compounds in the intensity of their pharmacological properties.

Insulin resistance and the lack of secretion of insulin are responsible for the glucose intolerance observed in patients having non-insulin-dependent diabetes.

The therapeutic agents currently available essentially allow correction of the lack of insulin secretion without necessarily improving the sensitivity to insulin of peripheral tissues (muscles, adipose tissue).

Thiazolidine-2,4-dione compounds are capable of causing a

reduction in glycaemia and of improving glucose tolerance in non-insulin-dependent diabetic models without causing an increase in the secretion of insulin.

The compounds of the present invention have the advantage of being especially powerful (more especially compared with ciglitazone, a reference compound belonging to the same chemical class) whilst at the same time not exhibiting harmful haematological effects, as will be demonstrated by the pharmacological study described hereinafter.

The compounds of the present invention may thus be used in the treatment of conditions of insulin resistance and/or of non-insulin-dependent diabetic conditions, making it possible to obtain a better control of glycaemia but with a reduced level of circulating insulin. The prevention of that relative hyperinsulinaemia, associated with a reduction in circulating triglycerides resulting from the action of those compounds, may assist in reducing the risks of macroangiopathy.

The same compounds may furthermore be used in the treatment of hypertension in older patients exhibiting insulin resistance which may or may not be associated with other metabolic anomalies.

The present invention relates also to pharmaceutical compositions comprising as active ingredient a compound of formula I or a physiologically tolerable salt thereof, mixed with or in association with one or more appropriate pharmaceutical excipients.

The pharmaceutical compositions so obtained are generally in dosage form containing from 100 to 200 mg of active

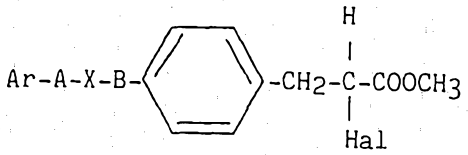
ingredient. They may, for example, be in the form of tablets, dragées, gelatin capsules, suppositories or injection or drinkable solutions, and may be administered by the oral, rectal or parenteral route.

The dosage may vary, especially in accordance with the age and weight of the patient, the administration route, the nature of the disorder, and associated treatments, and ranges from 100 to 200 mg of active ingredient from 2 to 3 times per day.

The present invention relates also to a process for the preparation of compounds of formula I characterised in that :

- either,

A) a compound of formula II :



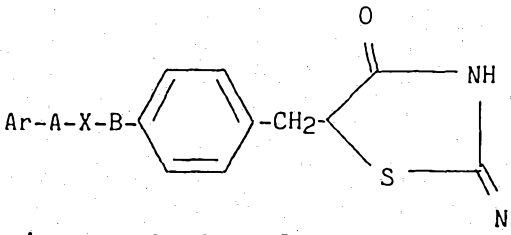
(II)

wherein :

- Ar, A, X and B are as defined hereinbefore and
- Hal represents a chlorine or bromine atom,

is reacted with thiourea $(H_2N-\overset{\overset{S}{\|}}{C}-NH_2)$,

and the imine so obtained of formula III :



(III)

wherein Ar, A, X and B are as defined hereinbefore, is hydrolysed;

- or,

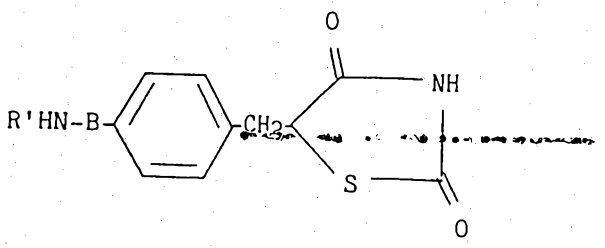
B) a compound of formula IV :

Ar-A-X′ (IV)

wherein :

- Ar and A are as defined hereinbefore and
- X′ represents COCl, SO_2Cl, an activated ester or $-(CO)_2O$,

is reacted with a compound of formula V :



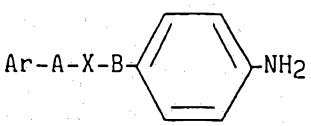
(V)

wherein :

- B is as defined hereinbefore and
- R′ represents a hydrogen atom or a straight-chain or branched alkyl radical having from 1 to 5 carbon atoms.

Method A, described by T. Sohda et al, Chem. Pharm. Bull., 30 (10) 3580-3600 (1982), is especially suitable for the preparation of compounds I if carried out in an appropriate solvent such as, for example, methanol, ethanol, sulfolane^R or dimethylformamide, heating the mixture of compound II and thiourea at 100-120°C for from 6 to 10 hours and then hydrolysing compound III by means of a strong acid, such as HCl or H_2SO_4.

The starting materials of formula II were prepared from amines of formula :



which were themselves obtained by hydrogenating corresponding nitrated compounds under a pressure of $3x10^5$ Pa in the presence of Raney nickel.

Method B is advantageously carried out by reacting the compounds IV and V at a temperature of 20-25°C for from 8 to 15 hours in a suitable solvent, such as, for example, tetrahydrofuran, dimethylformamide or acetonitrile, alone or in the form of a mixture, in the presence of an acceptor for the acid formed during the course of the reaction.

That acceptor may be, for example, triethylamine or an excess of the compound V used for the synthesis. Furthermore, compounds of formula I wherein the group Ar is substituted, inter alia, by a hydroxy radical, may also be prepared by hydrolysing corresponding acyloxy compounds in the presence of sodium hydroxide solution.

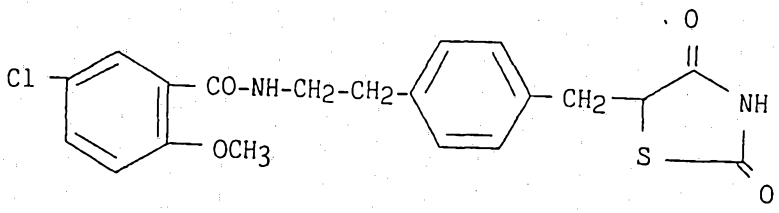
Compounds I prepared in accordance with method A or B may be purified by crystallisation from appropriate customary organic solvents or by flash chromatography on an Amicon silica support (35-70μ) using as eluant appropriate solvents such as : CH_2Cl_2, CH_2Cl_2/acetone (95:5), toluene/ethanol (95:5), under a pressure of 0.5 to 1 atmosphere of nitrogen.

The compounds of formula I may be converted into addition salts with acids, which salts, as such, form part of the invention. There may be mentioned as acids that can be used for the formation of those salts, for example, in the mineral series, hydrochloric, hydrobromic, nitric, sulphuric and phosphoric acid and, in the organic series, acetic, propionic, maleic, fumaric, tartaric, oxalic, benzoic, methanesulphonic and isethionic acid.

The following Examples illustrate the present invention. Unless specified otherwise, the melting points are determined using a Kofler hot plate.

Example 1

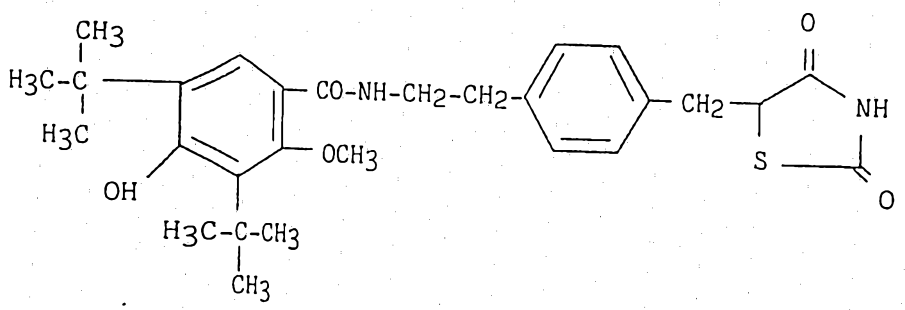
5-{4-[2-(2-methoxy-5-chlorobenzamido)ethyl]benzyl}thiazolidine-2,4-dione.



A mixture of 4.1 g of methyl 3-{4-[2-(2-methoxy-5-chlorobenzamido)ethyl]phenyl}-2-chloropropionate (oil) and 1.52 g of thiourea are heated for 10 hours at 120°C in 40 ml of sulfolane^{R}. The imine formed is hydrolysed by adding 14 ml of 2N HCl to the mixture and heating the whole at 100°C for 8 hours. When the reaction is complete, the whole is diluted with 600 ml of water and the aqueous portion is decanted off. The gummy product is extracted with CH_2Cl_2 and the organic solution is washed with water. After evaporation of the solvent, the residue is purified on 90 g of silica by flash chromatography using a mixture of CH_2Cl_2 and methanol (95:5) as eluant. The evaporated eluates yield 2.6 g of the desired compound in crystallised form, m.p. : 182°C.

Example 2

(R,S)-5-{4-[2-(4-hydroxy-3,5-di-tert-butylbenzamido)-ethyl]benzyl}thiazolidine-2,4-dione

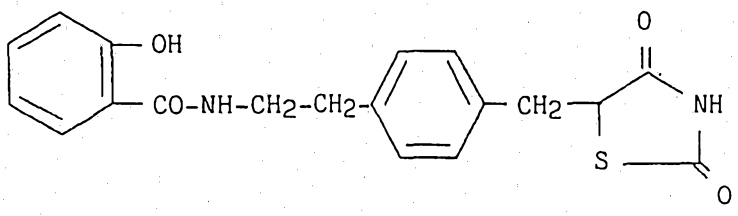


1.9 g of 1,1-carbonyldiimidazole is added to a solution of 3 g of 4-hydroxy-3,5-di-tert-butylbenzoic acid in 150 ml of anhydrous tetrahydrofuran and the solution is stirred at room temperature for 8 hours. 3 g of 5-[4-(2-aminoethyl)benzyl]thiazolidine-2,4-dione (melting at 200°C) are then added and the mixture is stirred at room temperature for 15 hours. The solvent is then evaporated off and the residue is taken up in a mixture of 10 % Na_2CO_3 in CH_2Cl_2. The precipitate is filtered and then purified by flash chromatography on 180 g of silica using a mixture of CH_2Cl_2 and methanol (97:3) as eluant.

After evaporation of the eluates, 3 g of the desired compound in amorphous form are collected. The 5-[4-(2-aminoethyl)benzyl]thiazolidine-2,4-dione starting material was prepared by the method according to SOHDA et al from methyl 3-[4-(2-acetamidoethyl)phenyl]-2-chloro-propionate (oil).

Example 3

(R,S)-5-{4-[2-(salicyloylamino)ethyl]benzyl}thiazolidine-2,4-dione.



2.3 g of acetylsalicyloyl chloride are added to a solution of 3 g of 5-[4-(2-aminoethyl)benzyl]thiazolidine-2,4-dione and 1.16 g of triethylamine in 50 ml of anhydrous dimethylformamide and the mixture is stirred at room temperature for 15 hours.
The dimethylformamide is then evaporated off and the residue is taken up in CH_2Cl_2 and water.
The organic phase is separated off and then evaporated under reduced pressure. 5.3 g of an oily residue are obtained which are chromatographed on 170 g of silica using a mixture of CH_2Cl_2 and acetone (90:10) as eluant. Evaporation of the eluates leaves 3 g of amorphous product which is dissolved in 50 ml of ethanol and then hydrolysed in the presence of 8.5 ml of N NaOH at room temperature for 5 hours. The solvent is then evaporated off, the product is taken up in N HCl and the resulting white crystals are suction-filtered.
1.9 g of the desired compound are obtained. M.p. : 184°C.

Examples 4 to 50

The following compounds were prepared by operating analogously to the methods described above :

4) 5-{4-[2-(phthalimido)ethyl]benzyl}thiazolidine-2,4-dione, m.p. : 180°C.

5) 5-{4-[2-(diphenylacetylamino)ethyl]benzyl}thiazolidine-2,4-dione, amorphous product.

6) (R,S)-5-{4-[2-(3,3-diphenylpropionamido)ethyl]benzyl}thiazolidine-2,4-dione, m.p. 148°C.

7) (R,S)-5-{4-[2-(2,5-dimethoxybenzamido)ethyl]benzyl}thiazolidine-2,4-dione, m.p. : 182°C.

8) (R,S)-5-{4-[2-(4-methoxyphenylsulphamoyl)ethyl]benzyl}thiazolidine-2,4-dione, m.p. : 143°C.

9) (R,S)-5-{4-[2-(3-trifluoromethylbenzamido)ethyl]benzyl}thiazolidine-2,4-dione, m.p. : 130°C.

10) (R,S)-5-{4-[2-(3,4-dichlorobenzamido)ethyl]benzyl}thiazolidine-2,4-dione, m.p. : 170°C.

11) (R,S)-5-{4-[2-(phenylacetylamino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. : 128°C.

12) (R,S)-5-{4-[2-(phenoxyacetylamino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. : 138°C.

13) (R,S)-5-{4-[2-(cyclopentylcarbonylamino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. : 154°C.

14) (R,S)-5-{4-[2-(fur-2-ylcarbonylamino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. : 150°C.

15) (R,S)-5-{4-[2-(5-methyl-1,2-oxazol-3-ylcarbonylamino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. : 148°C.

16) (R,S)-5-{4-[2-(2-hydroxy-5-chlorobenzamido)ethyl]benzyl}thiazolidine-2,4-dione, m.p. : 242-244°C.

17) (R,S)-5-{4-[2-(2-amino-5-chlorobenzamido)ethyl]benzyl} thiazolidine-2,4-dione, m.p. (cap): 196-200°C.

18) (R,S)-5-{4-[2-(2-dimethylamino-5-chlorobenzamido)ethyl] benzyl}thiazolidine-2,4-dione, m.p. (cap): 162-164°C.

19) (R,S)-5-{4-[2-(5-methoxyindol-2-ylcarbonylamino)-ethyl] benzyl}thiazolidine-2,4-dione, m.p. : 232-236°C.

20) (R,S)-5-{4-[2-(pyrid-3-ylcarbonylamino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. (cap): 238-240°C.

21) (R,S)-5-{4-[2-(pyrid-4-ylcarbonylamino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. (cap): 278-280°C.

22) (R,S)-5-{4-[2-(cinnamylcarbonylamino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. (cap): 76-78°C.

23) (R,S)-5-{4-[2-(3-phenylthiopropionamido)ethyl]benzyl} thiazolidine-2,4-dione, m.p. (cap): 76-78°C.

24) (R,S)-5-{4-[(R,S)-2-(2,5,7,8-tetramethyl-6-hydroxy chroman-2-ylcarbonylamino)ethyl]benzyl}thiazolidine-2,4-dione, amorphous product.

25) (R,S)-5-{4-[2-(pyrazin-2-ylcarbonylamino)ethyl]benzyl} thiazolidine-2,4-dione, m.p. : 198-200°C.

26) (R,S)-5-{4-[2-(pyrid-2-ylcarbonylamino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. : 160°C.

27) (R,S)-5-{4-[2-(indol-2-ylcarbonylamino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. : 256°C.

28) (R,S)-5-{4-[2-(2-dimethylaminobenzamido)ethyl]benzyl} thiazolidine-2,4-dione, m.p. : 180°C.

29) (R,S)-5-{4-[2-(2-piperidino-5-chlorobenzamido)ethyl] benzyl}thiazolidine-2,4-dione, m.p. : 164-166°C.

30) (R,S)-5-{4-[2-(fur-3-ylcarbonylamino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. : 176-178°C.

31) (R,S)-5-{4-[2-(5-methyl-2-phenyloxazol-4-ylcarbonylamino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. (cap) : 178-180°C.

32) (R,S)-5-{4-[2-(5-methyl-2-phenyloxazol-4-ylacetylamino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. (cap) : 146-150°C.

33) (R,S)-5-{4-[3-(2-methoxy-5-chlorobenzamido)propyl]benzyl} thiazolidine-2,4-dione, m.p. (cap) : 142°C.

34) (R,S)-5-{4-[2-(2-methoxy-5-trifluoromethylbenzamido)ethyl] benzyl}thiazolidine-2,4-dione, m.p. (cap) with decomposition >160°C.

35) (R,S)-5-{4-[2-(thien-2-ylcarbonylamino)ethyl]benzyl} thiazolidine-2,4-dione, m.p. (cap) : 150-152°C.

36) (R,S)-5-{4-[(5-chloro-2-methoxybenzamido)methyl]benzyl} thiazolidine-2,4-dione, m.p. (cap) : 150-152°C.

37) (R,S)-5-{4-[2-(5-chloro-2-methoxyphenylacetamido)ethyl] benzyl}thiazolidine-2,4-dione, m.p. (cap) : 116-118°C.

38) (R,S)-5-{4-[2-(4-amino-5-chloro-2-methoxybenzamido)ethyl] benzyl}thiazolidine-2,4-dione, m.p. (cap) of the

corresponding hydrochloride : 125-130°C.

39) (R,S)-5-{4-[1-oxo-2-(5-chloro-2-methoxybenzamido)-ethyl] benzyl}thiazolidine-2,4-dione, m.p. (cap) : 190-192°C.

40) (R,S)-5-{4-[1-hydroxy-2-(5-chloro-2-methoxybenzamido) ethyl]benzyl}thiazolidine-2,4-dione, m.p. (cap) : 175-178°C.

41) (R,S)-5-{4-[2-(3,5-di-tert-butyl-4-hydroxyphenoxy)-ethyl] benzyl}thiazolidine-2,4-dione, m.p. (cap) : 118-120°C.

42) (R,S)-5-{4-[2-(3-ethyl-4-methyl-2-oxo-3-pyrrolin-1-ylcarbonylamino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. (cap) : 178-180°C.

43) (R,S)-5-{4-[2-(3-(3,4-dimethoxyphenyl)prop-2-enoyl-amino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. (cap) : 178-180°C.

44) (R,S)-5-{4-[2-(3-(3,4-methylenedioxyphenyl)prop-2-enoyl-amino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. (cap) : 155-157°C.

45) (R,S)-5-{4-[2-(xanthen-9-ylcarbonylamino)ethyl]benzyl} thiazolidine-2,4-dione, m.p. (cap) : 138-140°C.

46) (R,S)-5-{4-[2-(2,2-(2,6-dimethylphenyl)acetylamino)ethyl] benzyl}thiazolidine-2,4-dione, m.p. : 182°C.

47) (R,S)-5-{4-[2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylcarbonylamino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. (cap) : 180-182 C.

48) (R,S)-5-{4-[2-(3-(4-hydroxy-3-methoxyphenyl)prop-2-enoylamino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. (cap) : 172-176°C.

49) (R,S)-5-{4-[2-(fluoren-9-ylcarbonylamino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. (cap) : 180-184°C.

50) (R,S)-5-{4-[2-(3-(4-acetoxy-3-methoxyphenyl)prop-2-enoylamino)ethyl]benzyl}thiazolidine-2,4-dione, m.p. (cap): 135-140°C.

Example 51

PHARMACOLOGICAL STUDY

A/ Study of the activity of the compounds of the invention on a non insulin-dependent diabetic model (NIDDM)

The animals (ob/ob mice) are treated each day, for 4 days, by the oral administration of the compounds of the invention suspended in a 20 % Senegal gum solution.
Before and after treatment, that is to say on d0 and on d5, blood is taken by piercing the orbital sinus and the glycaemia is determined.
Table 1 shows the doses of the different compounds that need to be administered to obtain the same hypoglycaemic effect (base 100).

Table 1 : Doses causing the same hypoglycaemic effect in ob/ob mice

Compounds	Dose mg/kg/day for 4 days	Hypoglycaemic activity
ciglitazone	50-100	100
Example 1	$\leqq$10	100
Example 3	25	100
Example 4	10	100
Example 6	10	100
Example 7	25	100
Example 14	10	100
Example 15	25	100
Example 25	10	100
Example 28	10	100
Example 33	25	100
Example 35	20	100
Example 36	20	100
Example 40	50	100
Example 41	50	100
Example 43	25	100
Example 44	10	100
Example 45	15	100
Example 46	40	100

B/ Study of the activity of the compounds of the invention on a model having reduced glucose tolerance associated with hyperinsulinaemia and hyperlipaemia.

The animals (Zucker Fa/Fa male rats) are treated each day, for 10 days, by the oral administration of the compounds of the invention at a dose of 5 mg/kg/day suspended in a 20 % Senegal gum solution. On the 11th day the animals are sacrificed and blood is collected in order to determine glycaemia, plasma triglycerides and immuno-reactive insulin. The animals are also weighed before and after treatment.

Under those conditions the compounds of the invention do not have any influence on the level of circulating glucose but decrease the level of triglycerides (TG) and free fatty acids (FFA) in the plasma and also the level of immuno-reactive insulin. The activity is the same as, or superior to, that of other reference thiazolidinedione compounds.

Table 2 : Pharmacological study of Zucker Fa/Fa male rats

	Dose (mg/kg/day) for 10 days	Weight ΔP % $d_{11}-d_1$	Glycaemia (%)	Plasma insulin (%)	TG (%)	FFA (%)
Control	0	+100	100	100	100	100
pioglitazone	5	+320	115	49	35	57
Example 1	5	+112	113	71	94	83
Example 4	5	+132	108	72	78	108
Example 28	5	+103	99	75	89	110

Administered per os to male SDCD rats weighing 175 g, contrary to pioglitazone the compounds are without effect

on the specified elements of the blood and the plasma volume:

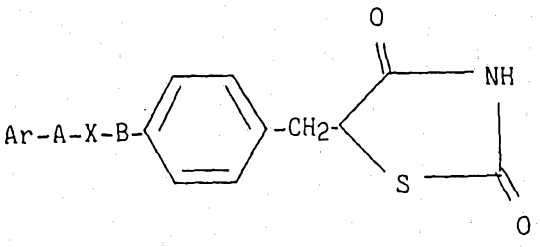
Table 3 (control values = 100)

Duration of treatment : 8 days	White corpuscles	Red corpuscles	Haemato-crit	Haemo-globin
pioglitazone: 100 mg/kg/d	- 46 %	- 37 %	- 26 %	- 29 %
Example 1:				
100 mg/kg/d	- 6 %	- 2 %	+ 11 %	+ 11 %
250 mg/kg/d	- 4 %	- 11 %	+ 4 %	+ 4 %

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

CLAIMS

1) Thiazolidinedione compounds of formula I :



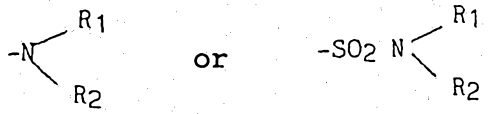
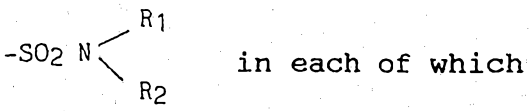
(I)

wherein :

Ar represents :

a) a polymethylene ring containing from 5 to 7 carbon atoms which is optionally substituted by one or more alkyl radicals having from 1 to 5 carbon atoms,

b) a mono-, bi- or tri-cyclic unsaturated hydrocarbon radical which is optionally mono- or poly-substituted by a halogen atom, a trifluoromethyl radical, a straight-chain or branched alkyl, alkoxy or alkylthio radical each having from 1 to 5 carbon atoms, an acyloxy radical, a hydroxy radical or a radical of the formula

 or  in each of which

R_1 and R_2, which are the same or different, each represents a hydrogen atom, or a straight-chain or branched alkyl radical having from 1 to 5 carbon atoms, or R_1 and R_2, together with the nitrogen atom to which they are bonded, represent a heterocycle having from 4 to 7 ring members optionally including (in addition to the nitrogen atom) an oxygen or

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sulphur atom, or

c) a mono-, bi- or tri-cyclic heterocyclic radical containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulphur atoms, which is optionally substituted by an oxo radical and/or by one or more halogen atoms or alkyl radicals (having from 1 to 5 carbon atoms) or phenyl radicals, each phenyl radical itself optionally being substituted by one or more halogen atoms or trifluoromethyl radicals or alkyl or alkoxy radicals each having from 1 to 5 carbon atoms ;

A represents : a single bond, a hydrocarbon chain having 2 or 3 carbon atoms and including a double bond, or a chain of the formula $-(CH_2)_m-$, $-\overset{CH_3}{\underset{CH_3}{C}}-(CH_2)_{m-1}-$, $-CH(R')-(C_6H_4)-R''$,

$-O-(CH_2)_m-$ or $-S-(CH_2)_m-$ wherein :

- m is an integer from 1 to 3 and R' and R", which are the same or different, each represents a hydrogen atom or a straight-chain or branched alkyl radical having from 1 to 5 carbon atoms;

X represents an oxygen atom, -CONR- or $-SO_2NR-$ wherein R represents a hydrogen atom or a straight-chain or branched alkyl radical having from 1 to 5 carbon atoms and optionally including a double bond,

or, when A represents a single bond and Ar represents a phenyl radical, R may also represent a carbonyl radical bonded to Ar by its free bond such that Ar-A-X together form a phthalimido radical;

B represents a saturated hydrocarbon chain having from 1 to 6 carbon atoms which is optionally branched and/or substituted by a hydroxy radical or an oxo radical;

and their enantiomers and diastereoisomers, as well as their addition salts with a pharmaceutically acceptable acid.

2) 5-{4-[2-(2-methoxy-5-chlorobenzamido)ethyl]-benzyl}thiazolidine-2,4-dione.

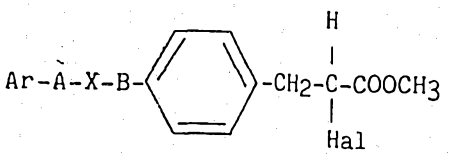
3) 5-{4-[2-(phthalimido)ethyl]benzyl}thiazolidine-2,4-dione.

4) (R,S)-5-{4-[2-(2-dimethylaminobenzamido)ethyl]-benzyl}thiazolidine-2,4-dione.

5) Process for the preparation of the compounds of claim 1, characterised in that :

- either,

A) a compound of formula II :



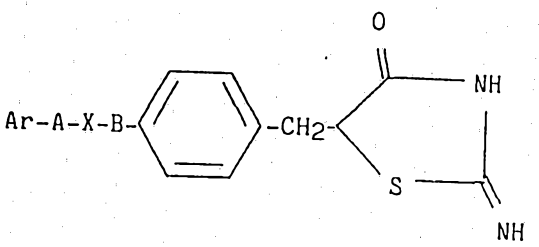
(II)

wherein :

- Ar, A, X and B are as defined in claim 1 and
- Hal represents a chlorine or bromine atom,

is reacted with thiourea ($H_2N-C(=S)-NH_2$),

and the imine so obtained of formula III :



(III)

wherein Ar, A, X and B are as defined hereinbefore, is hydrolysed;

- or,

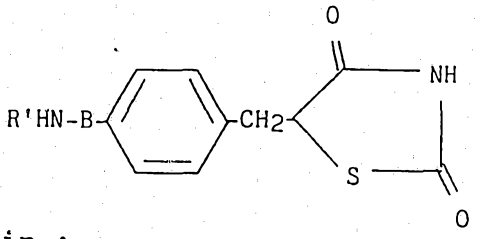
B) a compound of formula IV :

Ar-A-X' (IV)

wherein :

- Ar and A are as defined in claim 1 and
- X' represents COCl, SO_2Cl, an activated ester or Ar-A-X comprising a phthalic anhydride radical

is reacted with a compound of formula V :



(V)

wherein :

- B is as defined in claim 1 and
- R' represents a hydrogen atom or a straight-chain or branched alkyl radical having from 1 to 5 carbon atoms;

and, if desired, the isomers of the compounds so obtained are separated by conventional methods of separation and/or the said compounds are converted into their addition salts with a pharmaceutically acceptable acid.

6) Pharmaceutical compositions containing as active ingredient at least one compound according to any one of claims 1 to 4, alone or in combination with one or more

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appropriate pharmaceutical excipients.

7) A method of treating conditions of insulin resistance and/or non-insulin-dependent diabetes which may or may not be associated with hypertension comprising administering to a patient requiring such treatment a pharmaceutically effective amount of a compound as claimed in any one of claims 1 to 4 in adjunct with suitable excipients.

DATED this 29th day of June, 1995

ADIR ET COMPAGNIE

WATERMARK PATENT & TRADEMARK ATTORNEYS
290 BURWOOD ROAD
HAWTHORN VICTORIA 3122
AUSTRALIA

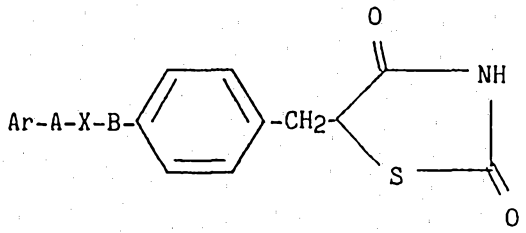
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ABSTRACT

NEW THIAZOLIDINEDIONE COMPOUNDS,
A PROCESS FOR THEIR PREPARATION
AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

ADIR ET COMPAGNIE
1 rue Carle Hébert
F 92415 COURBEVOIE CEDEX

New thiazolidinedione compounds of formula :



wherein Ar, A, X and B are as defined in the description, their enantiomers, diastereoisomers and pharmaceutically acceptable acid addition salts.

They may be used therapeutically especially in the treatment of conditions of insulin resistance and/or non-insulin-dependent diabetes which may or may not be associated with hypertension.