Title: THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES

Abstract: The compounds invented constitute a new series of thiazolidine derivatives, 5-benzylidene-3-(4-methyl-benzyl)-thiazolidine-2,4-diones (ATDZs) substituted in benzylidene ring and 5-(1H-indol-3-yl-methylene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione (ITDZ); all have pharmacological uses and anti-diabetic effects. These, therefore, represent a new series of anti-diabetic agents which act on the nuclear receptor hormone PPARg, exhibiting hypoglycemic properties and potential for therapeutic use as anti-diabetes drugs.
THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES

OBJECT OF THE INVENTION

This invention concerns arylidenethiazolidinedione (ATDZs) and indolidenethiazolidinedione (ITDZ) compounds that have been identified as having hypoglycemic properties and therefore show potential for use as anti-diabetes drugs.

TECHNICAL STAGE

*Diabetes mellitus* (DM) is a syndrome with multiple origins, resulting from insulin deficiency and/or the incapacity of the insulin to produce its effects. It is characterized by chronic hyperglycemia with disruption to the metabolism of carbohydrates, lipids and proteins. In the long term, the consequences of DM can lead to damage, dysfunction and failure in a variety of organs, specially the kidneys, eyes, nerves and blood vessels.

According to the classification recommended by the *WHO - World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus* (1999), the following types of DM have been identified: DM Type 1 which results primarily in the destruction of beta cells in the pancreas and has a tendency to lead to cetoacidosis 2) DM Type 2 which results, in general, in various degrees of resistance to insulin and deficiency in insulin secretion.

The category "other types of DM" includes various forms of DM caused by: a) functional genetic defects in beta cells; b) genetic defects in the action of insulin c) diseases of the exocrine pancreas; d) pathologies of the endocrine system; e) factors induced by drugs or chemical agents; f) infections; g) atypical forms of immuno-mediated diabetes; h) other genetic syndromes generally associated with diabetes; and i) diabetes in pregnancy.

The thiazolidinediones (TDzs), also called glitazones or gitazones, are known to be insulin sensitizers and have been developed and used clinically as anti-diabetes agents (Iwata *et al.*, *Journal of Molecular Graphics and Modeling*, 2001, v. 19, p. 536-542).
These compounds were observed to act on the metabolism of glucose, the lipids, the levels of insulin and have been used in the treatment of diabetes mellitus DM Type 2 (Spiegelman, *Diabetes* 1998, v. 47, p. 507-514).

As this is a new class of drugs that sensitize peripheral insulin in DM Type 2, valuable work has been carried out on finding out how they function.

It is now known that the molecular target of the thiazolidinediones is associated with a nuclear receptor called PPARg (peroxisome proliferator-activated receptor), Reginato and Lazar, *TEM* 1999, v. 10, n. 1, p. 9-13.

The thiazolidinediones reduce resistance to insulin by allowing insulin to act on receptors in tissue. However, they are ineffective when there are low levels of serum glucose in the absence of insulin (Henry, *Endocrinol. Metab. Clin. North Am.* 1997, v. 26, p. 553-573). In models using animals with DM Type 2, the thiazolidinediones reduce, not only the levels of glucose, but also the insulin, the triglycerides and fatty acids to near normal levels (Fujita *et al.*, *Diabetes* 1983, v. 32, n. 9, p. 804-10; Spencer and Markham, *Drugs*, 1997, v. 54, p. 89-101).

**DESCRIPTION OF THE INVENTION**

The substances obtained using this invention constitute a new series of thiazolidine derivatives, 5-arylidene-3-(4-methyl-benzyl)-thiazolidine-2,4-diones substituted in the 5 position of the thiazolidine ring by benzylidene or indolydene groups; all have pharmacological uses and anti-diabetic effects.

These compounds therefore represent a new series of anti-diabetic agents acting on the PPARg nuclear receptor hormone.

The synthetic route used to obtain the compounds invented begins with the alkylation of the thiazolidine ring in position 3 using 4-methyl-benzyl chloride in the presence of sodium hydroxide as an alkaline agent.

The 4-methyl-benzyl-thiazolidine-2,4-dione is condensed with the substituted esters (2-cyano-3-phenyl)-ethyl acrylate or 2-cyano-3-(2,3-dihydro-1H-indol-3-yl)-acrylic acid ethyl ester in the presence of piperidine leading to the aryldene or indolydene thiazolidinedione derivatives (TDZs).

**EVALUATION OF HYPOGLYCEMIC ACTIVITY**

The thiazolidinediones (TDZs) were evaluated in male or female albino Swiss
mice, weighing between 20 and 30g, and suffering from diabetes experimentally induced using pirimidine-2,4,5,6-tetraone (aloxane). The animals were initially deprived of food for 12 to 14 hours. Subsequently, the ATDZ and ITDZ derivatives were put in a suspension of CMC (carboxy methyl cellulose) 0.25% at the concentration to be tested. The control animals received only the vehicle solution. After 1 (one) hour of oral administration of the drugs, the animals were anaesthetised with diethyl ether to collect blood by puncture of the retro-orbital plexus, in the presence of potassium fluoride. The plasma is obtained using a centrifuge set at, a 4500 rpm, twice for 15 minutes each at 4°C. The concentration of plasmatic glucose is determined by the classic enzymatic method of glucose oxidasis (Werner, Rey and Wielinger, Z. Anal. Chem. 1970, v.252, p.224-228). The effect on the level of plasmatic glucose of each compound tested was calculated as a percentage of the value for the control group. A reduction in normal values for plasmatic glucose was observed after seven days at doses varying from 1 to 10 mg/Kg for the compounds tested.

SYNTHESIS OF COMPOUNDS

Procedure for preparing 3-(4-methyl-benzyl)-thiazolidine-2,4-dione.

Potassium hydroxide dissolved in ethanol was added to a mixture of thiazolidine-2,4-dione and ethanol. The resulting mixture was left to react at room temperature for 30 minutes. The mixture was put through a filter and washed using ethanol, thereby obtaining potassium thiazolidine salt. DMF (dimethylformamide) and 4-methyl-benzyl chloride dissolved in DMF were added to the salt produced. After 45 minutes of reaction, the mixture was put through a filter and the residue treated with diethyl ether. The 3-(4-methyl-benzyl)-thiazolidine-2,4-dione formed was purified by successive crystallizations in an appropriate solvent. C_{11}H_{11}NO_{2}S, Yield 21 %, F 70-72°C.

Procedure for the preparation of the (2-cyano-3-aryl)-ethyl acrylates and 2-cyano-3-[(2,3-dihydro-1H-indol-3-yl)-acrilic acid ethyl ester derivatives.

The substituted aldehyde and the ethyl-cyanacetate were introduced in a balloon in the presence of piperidine and anhydrous benzene as a solvent. It
was heated by reflux to a temperature of 110°C, for 8 hours. The (2-cyano-3-aryl)-ethyl acrylates and 2-cyano-3-(2,3-dihydro-1H-indol-3-yl)-acrilic acid ethyl ester were purified by successive crystallizations or by flash chromatography in silica gel 60.

Procedure for the preparation of 5-arylidene-3-(4-methyl-benzyl)-thiazolidine-2,4-dione and 5-(1H-indol-3-yl-methylene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione derivatives.

By heating 3-(4-methyl-benzyl)-thiazolidine-2,4-dione, dissolved in anhydrous ethanol, with the (2-cyano-3-aryl)-ethyl acrylates and 2-cyano-3-(2,3-dihydro-1H-indol-3-yl)-acrilic acid ethyl ester to a temperature of 80°C for 4 hours, the final products were precipitated, filtered, and purified by washing, successive crystallizations or "flash" chromatography in silica gel 60.

Proof of Structure:
The proof of the structures of the synthesized compounds was carried out using the infra-red spectra recorded on an IFS 66 Bruker apparatus, in KBr pastilha, magnetic resonance spectra of the nuclear proton on a Bruker AC 300 P spectrophotometric apparatus, using DMSOδ6 as a solvent, and by mass spectra, on electronic impact at 70eV registered on an HP 5987 apparatus. The spectroscopic characteristics in infra-red and magnetic ressonance of nuclear proteins of the thiazolidinediones (TDZs) prepared are in conformity with the structures. Using mass spectrometry, fragmentations were observed and the intensity of the isotope peaks on electron impact proved to be in conformity with the proposed structures.

Compounds Synthesized:

5-(4-chloro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ2).

5-(4-hydroxibenzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ3).

5-(2-chloro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ4).

5-(4-methoxy-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ5).
5-(2,4-dimethoxy-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ6).
5-(3-chloro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ7).
3-(4-methyl-benzyl)-5-(4-methyl-benzylidene)-thiazolidine-2,4-dione, (GQ8).
5-(2-bromo-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ9).
5-(4-dimethylamino-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ10).
5-(1H-indol-3-yl-methylene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ11).
5-(4-benzylxoy-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ12).
5-(3-fluoro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ14).
5-(4-fluoro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ15).
5-(2-methoxy-5-bromo-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ16).
5-(2,4-dichloro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ17).
5-(3,4-dichloro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ18).
3-(4-methyl-benzyl)-5-(4-nitro-benzylidene)-thiazolidine-2,4-dione, (GQ19).
5-(3-bromo-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ21).
5-(3-bromo-4-methoxy-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ22).
3-(4-methyl-benzyl)-5-(4-phenyl-benzylidene)-thiazolidine-2,4-dione, (GQ23).
The present invention can be understood even better through the description which follows and the figures in the appendix, where Fig. 1 represents the general formula of the benzylidene-thiazolidinedione (ATDZs) compounds. The R radical corresponds to the substituents: para-chloro (GQ2), para-hydroxi (GQ3), ortho-chloro (GQ4), para-methoxi (GQ5), ortho, para-dimethoxi (GQ6), meta-chloro (GQ7), para-methyl (GQ-8), ortho-bromo (GQ9), para-dimethyl- amino (GQ10), para-benzylxii (GQ12), meta-fluoro (GQ14), para-fluoro (Q15), ortho-methoxi, meta-bromo (GQ16), ortho, para-dichloro (GQ17), meta, para-dichloro (Q18), para-nitro (Q19), meta-bromo (GQ21), meta-bromo, para-methoxi (GQ22), para-phenyl (GQ-23). Fig. 2 represents the formula of the compound 5-(1H-indol-3-yl-methylene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione (GQ11). These compounds (ATDZs and ITDZ) were isolated in the Z configuration.

The IUPAC nomenclature, the compound code, its brute formula and the fusion points are given below:

5-(4-chloro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ2), C_{18}H_{14}CINO_2S, F182-184°C.
5-(4-hydroxi-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ3), C_{18}H_{15}NO_3S, F194-196°C.

- (2-chloro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ4), C_{18}H_{14}CINO_2S, F114-116°C.
5-(4-methoxi-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ5), C_{19}H_{17}NO_3S, F133-135°C.
5-(2,4-dimethoxi-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ6), C_{20}H_{19}NO_4S, F160-161°C.
5-(3-chloro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ7), C_{19}H_{14}CINO_2S, F143-145°C.
3-(4-methyl-benzyl)-5-(4-methyl-benzylidene)-thiazolidine-2,4-dione, (GQ8), C_{19}H_{17}NO_2S, F139-141°C.
5-(2-bromo-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ9), C_{18}H_{14}BrNO_2S, F109-111°C.
5-(4-dimethylamino-benzylidene)-3-(4-methyl-benzyl)-
thiazolidine-2,4-dione, (GQ10), C_{20}H_{20}N_2O_2S, F178-180°C.

5-(4-benzyloxi-benzyldene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ12), C_{25}H_{21}NO_3S, F155-157°C.

5-(3-fluoro-benzyldiene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ14), C_{19}H_{14}FNO_2S, F159-161°C.

5-(4-fluoro-benzyldiene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ15), C_{18}H_{14}FNO_2S, F122-124°C.

5-(2-methoxy-5-bromobenzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ16), C_{19}H_{13}BrNO_3S, F145-147°C.

55-(2,4-dichloro-benzyldiene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ17), C_{18}H_{13}Cl_2NO_2S, F139-141°C.

5-(3,4-dichloro-benzyldiene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ18), C_{18}H_{13}Cl_2NO_2S, F153-154°C.

3-(4-methyl-benzyl)-5-(4-nitro-benzyldiene)-thiazolidine-2,4-dione, (GQ19), C_{18}H_{14}N_2O_4S, F189-191°C.

5-(3-bromo-benzyldiene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ21), C_{19}H_{14}BrNO_2S, F126-127°C.

5-(3-bromo-4-methoxy-benzyldiene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ22), C_{19}H_{16}BrNO_3S, F180-181°C.

3-(4-methyl-benzyl)-5-(4-phenyl-benzyldiene)-thiazolidine-2,4-dione, (GQ23), C_{24}H_{19}NO_2S, F185-186°C.

5-(1H-indol-3-yl-methylene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ11), C_{20}H_{16}N_2O_2S, F229-231°C.

The thiazolidinedione (ATDZs and ITDZ) derivatives presented in Figures 1 and 2, referred to here, were synthesized in accordance with the experimental procedures described above.
CLAIMS

1.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, act on the nuclear receptor hormone PPARg, and represent a new series of thiazolidine derivatives, 5-arylidene-3-(4-methyl-benzyl)-thiazolidine-2,4-dione (ATDZs) substituted in benzylidene ring and 5-(1H-indol-3-yl-methylene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione (ITDZ), all with pharmacological uses and anti-diabetic effects.

2.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, in accordance with specification 1, above, characterized by compounds with the formula 5-(4-chloro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ2).

3.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, in accordance with specification 1, above, characterized by compounds with the formula 5-(4-hydroxy-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ3).

4.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, in accordance with specification 1, above, characterized by compounds with the formula 5-(2-chloro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ4).

5.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, in accordance with specification 1, above, characterized by the compound with the formula 5-(4-methoxy-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ5).

6.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, in accordance with specification 1, above, characterized by the compound with the formula 5-(2,4-dimethoxy-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ6).

7.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, in accordance with specification 1, above, characterized by the compound with the formula 5-(3-chloro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ7).

8.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC
PROPERTIES, in accordance with specification 1, above, characterized by the compound with the formula 3-(4-methyl-benzyl)-5-(4-methyl-benzylidene)-thiazolidine-2,4-dione, (GQ8).

9.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, in accordance with specification 1, above, characterized by the compound with the formula 5-(2-bromo-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ9).

10.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, in accordance with specification 1, above, characterized by the compound with the formula 5-(4-dimethylamino-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ10).

11.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, in accordance with specification 1, above, characterized by the compound with the formula 5-(1H-indol-3-yl-methylene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ11).

12.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, in accordance with specification 1, above, characterized by the compound with the formula 5-(4-benzylmethoxy-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ12).

13.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, in accordance with specification 1, above, characterized by the compound with the formula 5-(3-fluoro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ14).

14.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, in accordance with specification 1, above, characterized by the compound with the formula 5-(4-fluoro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ15).

15.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, in accordance with specification 1, above, characterized by the compound with the formula 5-(2-methoxy-5-bromo-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ16).

16.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC
PROPERTIES, in accordance with specification 1, above, characterized by the compound with the formula 5-(2,4-dichloro-benzylidene)-3-(4-methylbenzyl)-thiazolidine-2,4-dione, (GQ17).

17.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, in accordance with specification 1, above, characterized by the compound with the formula 5-(3,4-dichloro-benzylidene)-3-(4-methylbenzyl)-thiazolidine-2,4-dione, (GQ18).

18.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, in accordance with specification 1, above, characterized by the compound with the formula 3-(4-methyl-benzyl)-5-(4-nitro-benzylidene)-thiazolidine-2,4-dione, (GQ19).

19.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, in accordance with specification 1, above, characterized by the compound with the formula 5-(3-bromo-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ21).

20.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, in accordance with specification 1, above, characterized by the compound with the formula 5-(3-bromo-4-methoxy-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione, (GQ22).

21.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, in accordance with specification 1, above, characterized by the compound with the formula 3-(4-methyl-benzyl)-5-(4-phenyl-benzylidene)-thiazolidine-2,4-dione, (GQ23).

22.- THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, in accordance with specification 1, above, and a preparation procedure characterized by alkilation of the thiazolidine ring in position 3, using 4-methyl-benzyl chloride in the presence of sodium hydroxide as an alkaline agent and 4-methyl-benzyl-thiazolidine-2,4-dione to be condensed with the substituted esters (2-cyano-3-phenyl)-ethyl acrylate or 2-cyano-3-(2,3-dihydro-1H-indol-3-yl)-acrylic acid ethyl ester in the presence of piperidine, leading to the aryldiene-thiazolidinedione (ATDZs) and indolidene-thiazolidinedione (ITDZ) derivatives.
23. THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, and preparation procedures in conformity with specification 22, above, characterized by potassium hydroxide dissolved in ethanol being added to a mixture of thiazolidine-2,4-dione and ethanol and left to react at ambient temperature for 30 minutes. The mixture prepared in this way is filtered and washed in ethanol, thereby obtaining potassium thiazolidine salt. Subsequently, it is added to the DMF (dimethylformamide) salt formed and the 4-methyl-benzyl chloride dissolved in DMF. After 45 (forty-five) minutes of reaction, the mixture is filtered and the residue is treated with diethyl ether. The 3-(4-methyl-benzyl)-thiazolidine-2,4-dione formed is purified by successive crystallizations in an appropriate solvent. C_{11}H_{11}NO_{2}S, Yield 21 %, F 70-72°C.

24. THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, and preparation procedures in conformity with specification 23, above, characterized by following the preparation of the esters (2-cyano-3-phenyl)-ethyl acrylate or 2-cyano-3-(2,3-dihydro-1H-indol-3-yl)-acrylic acid ethyl ester derivatives, introducing the substituted aldehyde and ethyl cyanacetate in a balloon in the presence of piperidine and anhydrous benzene as a solvent, and subsequently heating it to a temperature of 110°C, for 8 (eight) hours; the esters (2-cyano-3-phenyl)-ethyl acrylate or 2-cyano-3-(2,3-dihydro-1H-indol-3-yl)-acrylic acid ethyl ester are purified by successive crystallizations or by flash chromatography in silica gel 60.

25. THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES, and procedures for its preparation, in conformity with specification 24, above, characterized by following the preparation of 5-arylidene-3-(4-methyl-benzyl)-thiazolidine-2,4-dione and 5-(1H-indol-3-ylmethylene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione derivatives by heating 3-(4-methyl-benzyl)-thiazolidine-2,4-dione, dissolved in anhydrous ethanol, with the esters (2-cyano-3-phenyl)-ethyl acrylate or 2-cyano-3-(2,3-dihydro-1H-indol-3-yl)-acrylic acid ethyl ester at a temperature of 80°C for 4 hours, leading to the precipitation of the final products, which shortly after are filtered and purified by washing, successive crystallizations or “flash” chromatography
in silica gel 60.

26.- **THIAZOLIDINEDIONE COMPOUNDS WITH HYPOGLYCEMIC PROPERTIES**, as described in the foregoing specifications, exhibiting hypoglycemic properties and the potential for use in anti-diabetic therapy by way of oral administration.
Figure 2