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European Journal of Medicinal Chemistry 40 (2005) 1129–1133
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
www.elsevier.com/locate/ejmech

Original article

Synthesis and Biological Activity of Novel Acridinylidene and Benzylidene thiazolidinediones

R.H. Mourão [a], T.G. Silva [a], A.L.M. Soares [a], E.S. Vieira [a], J.N. Santos [a], M.C.A. Lima [a], V.L.M. Lima [a], S.L. Galdino [a], J. Barbe [b], I.R. Pitta [a,*]

[a] *Departamento de antibioticos, universidade federal de Pernambuco, centro de ciências biológicas, 50670-901 Recife, Brasil*
[b] *GERCTOP – UMR CNRS 6178, université de la Méditerranée, faculté de pharmacie, 13385 marseille cedex 5, France*

Received 2 December 2004; received in revised form 30 May 2005; accepted 6 June 2005

Available online 29 August 2005

Abstract

A novel set of acridinylidene thiazolidinediones and benzylidene thiazolidinediones was synthesized by nucleophilic addition of cyanoacrylates. Some of these compounds were evaluated for their glucose lowering capability and their effects on the triglyceride level in alloxan diabetic mice.

Keywords: Thiazolidinediones; hypoglycaemic agents

1. Introduction

The thiazolidinediones (TZDs) or glitazones are oral hypoglycaemic agents, which act mainly by increasing tissue sensitivity especially adipose tissue, to insulin [1–4]. Various studies report the effects of TZDs on the metabolism of lipids, on cell differentiation and on some cardiovascular risk factors [5,6]. The first compound described was ciglitazone, which produced a dramatic decrease in the glycaemia level in animal models but showed poor clinical effect. In 1997 troglitazone was launched onto the market, but had to be withdrawn in the USA in March 2000 because of idiosyncratic liver failure. Since 1999, rosiglitazone and pioglitazone have been available in Europe as second line drugs restricted to combination therapy while in the United States, their use has been allowed as first line agents in monotherapy or in combination with other drugs [4]. It was demonstrated that the molecular target of the TZDs is part of the nuclear receptor called Peroxisome Proliferator-Activated Receptor-gamma (PPAR-γ) which controls the differentiation of adipocytes [3], the metabolism of fatty acids and alters the expression of genes that are also regulated by insulin [7]. This paper describes the synthesis and gives the structural characteristics of several derivatives of the 5-benzylidene-3-(4-methyl-benzyl)-thiazolidine-2,4-dione substituted on the benzylidene moiety and those of the 3-benzyl-5-acridinylidene-thiazolidine-2,4-dione substituted on the benzyl ring branched on the thiazolidine moiety. Some of these compounds were evaluated in after oral administration at doses of 10 mg/kg or 30 mg/kg in alloxan diabetic mice. Plasma glucose (PG) and triglyceride (TG) levels were measured and compared with rosiglitazone (10 mg/kg p.o.) as the reference drug.

2. Chemistry

The 5-benzylidene-3-(4-methyl-benzyl)-thiazolidine-2,4-diones, **3**, were prepared by a nucleophilic addition of the 3-(4-methyl-benzyl)-thiazolidine-2,4-dione, **2**, on selected aryl-substituted ethyl-(2-cyano-3-phenyl)-acrylates [8] according to Daboun et al. [9]. Synthetic pathways are portrayed in Fig. 1. Thiazolidine-2,4-dione, **1**, was *N*-(3)-alkylated in the presence of potassium hydroxide which leads to the thiazolidine potassium salt which reacts with benzyl or phenacyl halides in hot alcoholic medium [10]. The 3-benzyl (or phenacyl)-thiazolidine-2,4-diones, **2** or **7**, were obtained in this way. The acridinylidene thiazolidinedione derivatives, **8a-8d**, were synthesized by a nucleophilic addition of substi-

* Corresponding author.
E-mail address: IRPITTA@aol.com (I.R. Pitta).

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doi:10.1016/j.ejmech.2005.06.002

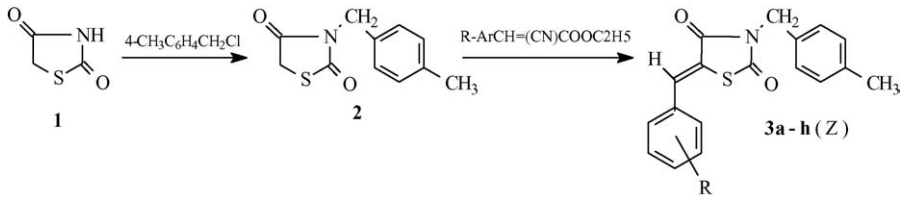

Fig. 1. Synthetic pathways of benzylidene-thiazolidinediones.

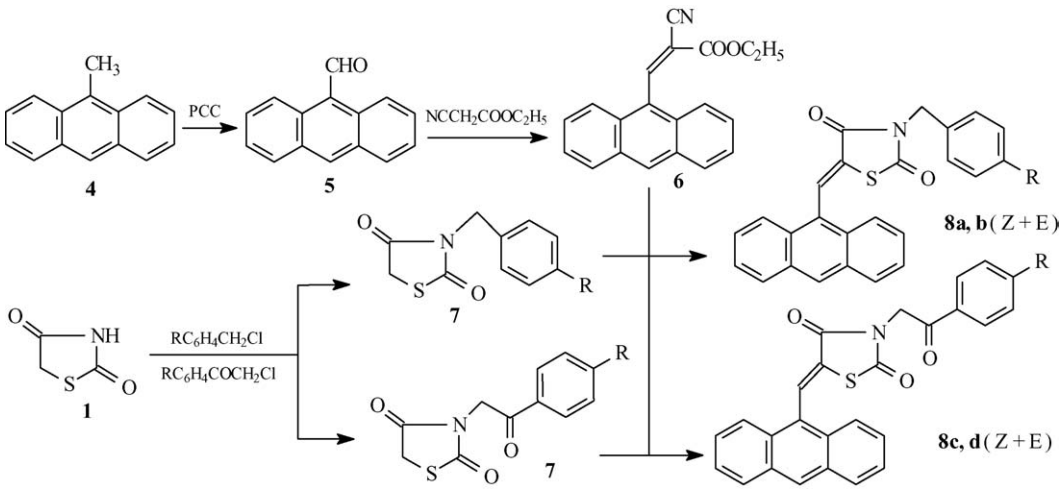

Fig. 2. Synthetic pathways of acridinylidene-thiazolidinediones.

tuted thiazolidinediones, **7**, on 9-[ethyl-(2′-cyano)-acrylate]-acridine, **6**. Direct condensation of 9-acridinaldehyde, **5**, with the substituted thiazolidinediones, **7**, did not led to the expected 3-benzyl-5-acridinylidene-thiazolidine-2,4-diones, **8a-8d**. 9-Methyl-acridine, **4**, was prepared from diphenylamine treated with zinc dichloride in acetic acid medium according to Tsuge et al. [11]. Subsequent oxidation of **4** with pyridinium chlorochromate according to Mosher et al. [12], gave 9-acridinaldehyde, **5**. Condensation of **5** with ethyl cyanoacetate in the presence of piperidine in hot anhydrous benzene led to the 9-[ethyl-(2′-cyano)-acrylate]-acridine, **6**. Synthetic pathways are portrayed in Fig. 2. Benzylidene-thiazolidinediones were isolated in a single isomeric form. X-ray crystallographic studies and ^{13}C NMR have demonstrated the preferred Z configuration for 5-arylidene-thiazolidinones [13]. In contrast, acridinylidene-thiazolidinedione derivatives, **8a-8d**, were isolated as isomeric mixtures. The isomers were readily identified by ^{1}H NMR, the ethylene proton being more deshielded in the isomer Z than it is in the isomer E, owing to the cis-position of the exocyclic carbonyl function. Chemical shifts listed in the experimental part are those of the Z isomer, which is the prevalent isomer. MS data fully agree with the structure proposed.

3. Results and Discussion

The glucose and triglyceride lowering effects after oral administration of new thiazolidine analogues, **3a-3f**, in alloxan diabetic mice are summarized in Table 1. All the compounds tested show a dose-dependent hypoglycaemic activity during the 15 days treatment. The decrease in the level of plasma glucose observed with these compounds was progressive throughout the treatment, especially at a 30 mg/kg/day dose. After 15 days of treatment with this dose, compound **3c** showed a better biological activity than other compounds do in both parameters analysed, i.e. around 50% decrease in PG and 59% decrease in TG. However, this compound was recognized to be very toxic, with a 50% mortality rate during

Table 1
Effect of oral administration of benzylidene-thiazolidinedione derivatives on the glucose (PG) and triglyceride (TG) levels in mice with alloxan-induced hyperglycaemia with reference to rosiglitazone

Compound	Dose (mg/kg/day p.o.)	% of decrease[a] in PG[b] at day				TG[b] at day
		1	3	10	15	15
3a	10	4	12	17	19	22
	30	1.5	7	18.5	23	48
3b	10	0.5	10	10	19	15
	30	9	12.5	24.5	43	26
3c	10	4	1	24	21	38
	30	16.5	21	29	51	59
3d	10	NE	NE	17	22	40
	30	9	17	30	35	46.5
3e	10	3	NE	23	15	8
	30	10	12	23	41	44
3f	10	NE	7	11	9	22
	30	8	NE	14	20	33
Rosiglitazone	10	23	24.5	22.5	37	43

[a] standard deviation is less than 0.05 in all cases.
[b] in mg/dL.

Table 2
Effect of oral administration of benzylidene-thiazolidinedione derivatives and rosiglitazone (10 mg/kg/day), on the change in body weight and mortality of mice with alloxan-induced hyperglycaemia

Tested Group	Dose (mg/kg p.o.)	Body weight (g) ± SD			
		Initial	Final (day 15)	% of corporal loss	% of mortality
Normoglycaemic	-	27.0 ± 1.0	28.5 ± 1.7	-	0
Diabetic + CMC	10[a]	25.2 ± 0.8	22.4 ± 2.6	11	20
" + 3a	10	25.3 ± 0.6	23.3 ± 1.4	8	0
	30	28.0 ± 0.8	24.9 ± 1.1	11	17
" + 3b	10	26.4 ± 0.4	26.2 ± 0.8	0.75	20
	30	25.0 ± 0.9	21.1 ± 0.6	16	14
" + 3c	10	21.3 ± 0.7	21.7±1.6	-	50
	30	26.4 ± 1.2	22.7 ± 2.0	14	50
" + 3d	10	27.9 ± 2	23.3 ± 2.7	16	17
	30	24.0 ± 0.8	21.3 ± 1.5	11	0
" + 3e	10	22.7 ± 1.5	20.2 ± 0.9	11	17
	30	24.4 ± 0.7	21.9 ± 0.7	10	0
" + 3f	10	29.1 ± 3.4	27.2 ± 3.0	6.5	0
	30	25.3 ± 0.4	24.0 ± 0.9	5	0
" + Rosiglitazone	10	26.5 ± 0.4	27.4 ± 1.3	-	17

[a] this value is given in mL/kg p.o.

the treatment at the two doses tested. In contrast, the other compounds, although they produced less reduction in PG and TG rates, had a very low if not zero mortality rate (Tables 1,2). The percentage for mortality observed in the case of a 10 mg/kg/day dose of **3a,3b,3d-3f** was also very low. The mortality observed with the 10 mg/kg/day dose could not be due to the compounds under evaluation but to the hyperglycaemia caused by alloxan, as the mortality rate for diabetic animals treated with this vehicle (CMC 0.5%) is in the same range. The presence of the two methoxy groups in position 2 and 4 of the benzylidene ring in **3d** led to a reduction in hypoglycaemia (35%) and hypolipidemia (46%) activity, although this compound did not show toxicity and there were no deaths at the 30 mg/kg/day dose as observed with **3c** which is only substituted by one methoxy group. The change in the position of the chlorine atom on the phenyl ring led to a significant hypoglycaemic activity ($P < 0.05$). This is clearly demonstrated by comparing the 4-chloro derivative **3a** (PG =23%; TG = 48%) with the 2-chloro substituted one **3b** (PG = 43%; TG = 26%). However, the opposite is seen for the hypolipidemic activity which is greater with **3a** than it is with **3b**.

4. Conclusion

The new 5-arylidene-3-(4-methyl-benzyl)-thiazolidine-2,4-diones investigated have shown promising glucose lowering activity. Their activity on the triglyceride level is close to that of the rosiglitazone when used at the same concentration but activity is much better at higher concentration (30 mg/kg) which can be used safely because of the low toxicity of compounds evaluated. These results indicate the need for additional investigations, chiefly about the agonistic effect of these drugs on PPAR-γ and PPAR-α.

5. Experimental protocols

5.1. Chemistry

Melting points were measured in a capillary tube on a Buchi (or Quimis) apparatus. Thin Layer Chromatography was performed on silicagel plates Merck $60F_{254}$. Infrared spectra of 1% KBr pellets were recorded on a Bruker IFS66 spectrometer (or Perkin Elmer 1310 spectrometer for compounds **3a-3d**). ^{1}H NMR spectra were recorded on a Bruker AC 300 P spectrophotometer in DMSO-d_6 as solvent, with tetramethylsilane as internal standard. Mass spectra were recorded on Delsi-Nermag R 1010 C spectrometer (or HP 5897 for compounds **8a-8d**). The published chemical data on **2,4,5,6** [14], are not reported here.

Analyses of all the compounds prepared were within ± 0.4% of the theoretical values.

***5-Benzylidene-3-(4-methyl-benzyl)-thiazolidine-2,4-diones*, 3a-3h**: general procedure.

A mixture of 3-(4-methyl-benzyl)-thiazolidine-2,4-dione, **2**, (0.59 g, 2.5 mmol) and ethyl-(2-cyano-3-phenyl)-acrylate (2.7 mmol) is refluxed for 2-6 h in absolute ethanol (20 mL) with piperidine (0.25 mL) added. After cooling, precipitates are purified by column chromatography or crystallized in suitable solvents.

***5-(4-Chloro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione*, 3a.**

$C_{18}H_{14}ClNO_2S$, yield: 0.427 g (89%). Mp: 184 °C. TLC benzene: ethyl acetate (95:5) R_f: 0.8. IR cm^{-1} (KBr): υ 1730, 1670, 1600, 1374, 1335, 1138, 820. ^{1}H NMR (δ ppm, DMSO-d_6): 2.27 (s, CH_3), 4.79 (s, NCH_2), 7.97 (s, CH), 7.17 (m, 4H benzyl), 7.63 (m, 4H benzylidene). Ms, m/z (%) : 343(M^+ 100), 344(22.2), 345(24.6),105(96.9), 103(6).

***5-(2-Chloro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione*, 3b.**

$C_{18}H_{14}ClNO_2S$, yield: 0.087 g (30%). Mp: 116 °C. TLC benzene: ethyl acetate (95:5) R_f: 0.74. IR cm^{-1} (KBr): υ 1738,

1682, 1598, 1370, 1310, 755. ^{1}H NMR (δ ppm, DMSO-d_6): 2.28 (s, CH_3), 4.8 (s, NCH_2), 8.06 (s, CH), 7.16 (d, 2H benzyl, J = 8.1 Hz), 7.23 (d, 2H benzyl, J = 8.1 Hz), 7.51-7.54 (m, 2H benzylidene), 7.59-7.62 (m, 1H benzylidene), 7.64-7.67 (m, 1H benzylidene). Ms, m/z (%): 343(M^+ 45.1), 344(5.7), 345(8), 308(52.8), 280(5.2), 105(100), 94(7.8).

***5-(4-Methoxy-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione*, 3c.**

$C_{19}H_{17}NO_3S$, yield: 0.354 g (77%). Mp: 135 °C. TLC benzene: ethyl acetate (95:5) R_f: 0.83. IR cm^{-1} (KBr): υ 1738, 1672, 1588, 1503, 1365, 1260, 820. ^{1}H NMR (δ ppm, DMSO-d_6): 2.28 (s, CH_3), 3.84 (s, OCH_3), 4.79 (s, NCH_2), 7.93 (s, CH), 7.16 (d, 2H benzyl, J = 8.4 Hz), 7.21 (d, 2H benzyl, J = 8.1 Hz), 7.12 (d, 2H benzylidene, J = 9 Hz), 7.61 (d, 2H benzylidene, J = 9 Hz). Ms, m/z (%): 339(M^+ 58.3), 340(15), 341(4),105(100).

***5-(2,4-Dimethoxy-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione*, 3d.**

$C_{20}H_{19}NO_4S$, yield: 0.197 g (77%). Mp: 161 °C. TLC benzene: ethyl acetate (95:5) R_f: 0.76. IR cm^{-1} (KBr): υ 1720, 1675, 1575, 1367, 1267, 1147, 830. ^{1}H NMR (δ ppm, DMSO-d_6): 2.27 (s, CH_3), 3.85 (s, OCH_3), 3.9 (s, OCH_3), 4.77 (s, NCH_2), 8.06 (s, CH), 6.7 (s, 1H benzylidene), 6.71 (d, 1H benzylidene, J = 8.4 Hz), 7.39 (d, 1H benzylidene, J = 8.4 Hz), 7.15 (d, 2H benzyl, J = 8.1 Hz), 7.19 (d, 2H benzyl, J = 8.1 Hz). Ms, m/z (%): 369(M^+ 100), 370(12.7), 371(14.1), 264(29.2), 105(14.5).

***5-(4-Dimethylamino-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione*, 3e.**

$C_{20}H_{20}N_2O_2S$, yield: 0.215 g (47%). Mp: 180 °C. TLC benzene: ethyl acetate (95:5) R_f: 0.75. IR cm^{-1} (KBr): υ 1726, 1673, 1593, 1380, 811. ^{1}H NMR (δ ppm, DMSO-d_6): 2.27 (s, CH_3), 3.02 (s, $N(CH_3)_2$), 4.77 (s, NCH_2), 8.06 (s, CH), 6.82 (d, 2H benzylidene, J = 9 Hz), 7.46 (d, 2H benzylidene, J = 9 Hz), 7.14 (d, 2H benzyl, J = 8.1 Hz), 7.19 (d, 2H benzyl, J = 8.4 Hz). Ms, m/z (%): 352(M^+ 41.7), 353(2.1), 177(46.6), 176(34.6), 161(12), 105(100), 89(23.3), 77(37.2).

***5-(4-Benzyloxy-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione*, 3f.**

$C_{25}H_{21}NO_3S$, yield: 0.323 g (58%). Mp: 157 °C. TLC benzene: ethyl acetate (95:5) R_f: 0.86. IR cm^{-1} (KBr): υ 1736, 1677, 1593, 1263, 826. ^{1}H NMR (δ ppm, DMSO-d_6): 2.28 (s, CH_3), 4.79 (s, NCH_2), 5.21 (s, OCH_2), 7.93 (s, CH), 7.15-7.21 (m, 4H benzyl, 2H benzylidene), 7.35-7.46 (m, 5H benzyloxy), 7.61 (d, 2H benzylidene, J = 9 Hz). Ms, m/z (%): 415(M^+ 17.3), 416(2.5), 91(100), 77(6.9).

***5-(4-Fluoro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione*, 3g.**

$C_{18}H_{14}FNO_2S$, yield: 0.387 g (87%). Mp: 124 °C. TLC benzene: ethyl acetate (95:5) R_f: 0.81. IR cm^{-1} (KBr): υ 1736, 1685, 1613, 1376, 1291, 680. ^{1}H NMR (δ ppm, DMSO-d_6): 2.27 (s, CH_3), 4.8 (s, NCH_2), 7.96 (s, CH), 7.15 (d, 2H benzyl, J = 8.1 Hz), 7.21 (d, 2H benzyl, J = 8.4 Hz), 7.33-7.38 (m, 1H benzylidene), 7.45-7.5 (m, 2H benzylidene), 7.56-7.64 (m, 1H benzylidene). Ms, m/z (%): 327(M^+ 100), 328(16.4), 329(6.6), 105(91.8), 91(4.2).

***5-(5-Bromo-2-methoxy-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione*, 3h.**

$C_{19}H_{16}BrNO_3S$, yield: 0.352 g (62%). Mp: 147 °C. TLC *n*-hexane: ethyl acetate (70:30) R_f: 0.78. IR cm^{-1} (KBr): υ 1733, 1684, 1604, 1339, 1283, 808. ^{1}H NMR (δ ppm, DMSO-d_6): 2.27 (s, CH_3), 3.89 (s, OCH_3), 4.78 (s, NCH_2), 7.96 (s, CH), 7.15 (d, 2H benzyl, J = 8.1 Hz), 7.2 (d, 2H benzyl, J = 8.4 Hz), 7.14 (d, 1H benzylidene, J = 9.3 Hz), 7.53 (d, 1H benzylidene, J = 2.4 Hz), 7.65 (dd 1H benzylidene, J = 9,3 Hz). Ms, m/z (%): 417(M^+ 60), 386(7.1), 227(13), 199(11), 105(100), 91(31), 77(23.5).

***3-Benzyl (or phenacyl)-5-acridinylidene-thiazolidine-2,4-diones,* 8a-8d** : general procedure.

Benzyl (or phenacyl) thiazolidine, **7** (0.9 mmol) and 9-[ethyl-(2′-cyano)-acrylate]-acridine, **6**, (0.9 mmol) are dissolved in absolute ethanol (8 mL). The solution is refluxed for 4 h in the presence of a small amount of piperidine as catalyst. The precipitate obtained is filtered and washed with water. Compounds isolated are of acceptable purity and were analysed without further recrystallization.

***5-Acridin-9-yl-methylene-3-benzyl-thiazolidine-2,4-dione*, 8a.**

$C_{24}H_{16}N_2O_2S$, yield: 0.124 g (88%). Mp: 150-152 °C. TLC *n*-hexane: ethyl acetate (7:3) R_f: 0.41. IR cm^{-1} (KBr): υ 1750, 1694, 1623, 1381, 1339, 1149, 761. ^{1}H NMR (δ ppm, DMSO-d_6): 4.89 (s, NCH_2), 7.41-7.4 (m, 4H benzyl), 7.39-7.34 (m, 1H benzyl), 7.72-7.66 (m, 2H acridine), 7.94-7.89 (2H acridine), 8.14 (d, 2H acridine, J = 8.4 Hz), 8.24 (d, 2H acridine, J = 8.4 Hz), 8.79 (s, 1H, CH). Ms, m/z (%): 396(M^+ 4.2), 397(1.9), 305(8), 235(100), 232(26.6), 231(20.4), 91(10.1).

***5-Acridin-9-yl-methylene-3-(4-fluoro-benzyl)-thiazolidine-2,4-dione*, 8b.**

$C_{24}H_{15}FN_2O_2S$, yield: 0.095 (56%). Mp: 200-202 °C. TLC *n*-hexane: ethyl acetate (7:3) R_f: 0.58. IR cm^{-1} (KBr): υ 1749, 1693, 1604, 1382, 1337, 1152, 763. ^{1}H NMR (δ ppm, DMSO-d_6): 4.88 (s, NCH_2), 7.23 (t, 2H benzyl, J = 9 Hz), 7.45-7.5 (m, 2H benzyl), 7.71-7.66 (m, 2H acridine), 7.94-7.89 (m, 2H acridine), 8.14 (d, 2H acridine, J = 8.7 Hz), 8.24 (d, 2H acridine, J = 8.7 Hz), 8.78 (s, 1H, CH). Ms, m/z (%): 414(M^+ 12.9), 415(4), 305(34.3), 261(19.9), 235(100), 234(44.1), 231(68.8), 191(16.9), 109(32.6).

***5-Acridin-9-yl-methylene-3[2-(4-nitro-phenyl)-2-oxo-ethyl]-thiazolidine-2,4-dione*, 8c.**

$C_{25}H_{15}N_3O_5S$ yield: 0.136 g (70%). Mp: 229-230 °C. TLC *n*-hexane: ethyl acetate (7:3) R_f: 0.3. IR cm^{-1} (KBr): υ 1747, 1699, 1629, 1603, 1530, 1346, 1222, 855, 761. ^{1}H NMR (δ ppm, DMSO-d_6): 5.49 (s, NCH_2), 7.77-7.71 (m, 2H acridine), 7.97-7.92 (m, 2H acridine), 8.13 (d, 2H acridine, J = 8.7 Hz), 8.26 (d, 2H acridine, J = 9 Hz), 8.88 (s, 1H, CH). Ms, m/z (%): 469(M^+ 50), 470(16.2), 235(93.1), 234(30.8), 230(79.2), 150(100), 120(35.5), 104(40).

***5-Acridin-9-yl-methylene-3[2-(4-fluoro-phenyl)-2-oxo-ethyl]-thiazolidine-2,4-dione*, 8d.**

$C_{25}H_{15}FN_2O_3S$, yield: 0.084 g (48%). Mp: 213-214 °C. TLC *n*-hexane: ethyl acetate (7:3) R_f: 0.41. IR cm^{-1} (KBr): υ 1754, 1701, 1596, 1411, 1381, 1229, 1154, 759. ^{1}H NMR (δ

ppm, DMSO-d_6): 5.39 (s, NCH_2), 7.46 (t, 2H benzyl, J = 8.7 Hz), 7.76-7.71 (m, 2H acridine), 7.97-7.91 (m, 2H acridine), 8.12 (d, 2H acridine, J = 8.7 Hz), 8.26 (d, 2H acridine, J = 8.4 Hz), 8.26-8.21 (m, 2H benzyl), 8.87 (s, 1H, CH). Ms, m/z (%): 442(M^+ 20.2), 443(5.8), 235(31.5), 234(14.1), 230(40.5), 191(9.5), 123(100), 113(12.2).

5.2. Animals and treatment

The experiment used 8 to 9 week-old Swiss albino mice of both sexes, with weight between 22 and 30 g. Animals were provided by the Bioterium of the Antibiotics Department of the Federal University of Pernambuco (UFPE) ; they were kept in a small colony in the animal house at a temperature of 25 ± 3 °C, with 12 hour cycles of light and darkness, receiving standard feed (Purina®) and water as required. The experimental procedure was approved by the Local Committee for Animal Ethics. (CCB – UFPE). Drugs **3a-3f**, were suspended at a concentration of 10 and 30 mg/kg/day, in a solution of 0.5% carboxymethylcelulose (CMC) and they were administered orally for 15 days to groups of hyperglycaemic Swiss mice (N = 6, three males and three females). Hyperglycaemia was induced by alloxan monohydrate at a 80 mg/kg p.o. dose. After a 10 days treatment, mice with a 200-350 mg/dL PG level and a 100-250 mg/dL TG level were selected for further experiments. By comparison, the standard level was then around 100-130 mg/dL. Blood samples were regularly collected from the animals after they had been fed between 8 h and 10 h in the morning, the blood being taken from the retro-orbital plexus under a light anaesthetic (ethyl ether) one hour after the administration of the compounds on different days throughout the treatment (1, 3, 10 and 15 days). Levels of plasma glucose and triglycerides were analysed using commercially available kits (LABTEST-Brazil), based on enzymatic methods [15]. Control groups of diabetic and normoglycaemic animals were treated with the vehicle solution (CMC 0.5% 10mL/kg). Rosiglitazone 10 mg/kg/day was used as standard drug. Effects on the glucose and triglyceride levels of the compounds, vehicle and rosiglitazone were calculated as a percentage of reduction, using the formula 1-[(TT/OT)/(TC/OC)] x 100, where TT = treated test on the day; OT = treated test at day zero; TC = control test on the day; OC = control at day zero, according to Gurram et al. [16]. The diabetic animals treated with 0.5% CMC were used as controls in the above formula.

Acknowledgments

The CAPES/COFECUB (Coordenação de Aperfeiçoamento de Pessoal do Ensino Superior/Comité Français d'Evaluation et de Coopération Universitaire avec le Brésil) and CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) are gratefully acknowledged for their support to the join research programme.

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