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NOVEL INDOLE CONTAINING THIAZOLIDINEDIONE DERIVATIVES AS POTENT EUGLYCEMIC AND HYPOLIPIDAEMIC AGENTS

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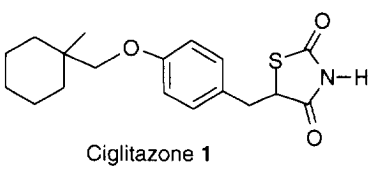
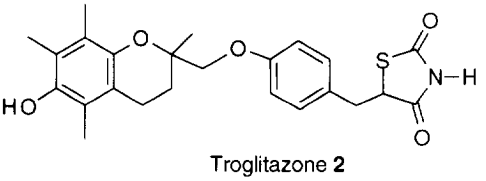
Abstract: Several thiazolidinediones having indol as heterocyclic moiety have been synthesized and evaluated for euglycemic properties. A few of them have been found to be superior to troglitazone.

During the last decade the search for a new class of compounds having euglycemic activity for the treatment of Non-Insulin-Dependent-Diabetes Mellitus (NIDDM), typically characterized by peripheral insulin resistance, hyperglycemia, hyperinsulinemia, has gained considerable importance.[1] It has been reported that sulfonylureas, the most commonly used oral hypoglycemics, potentiate insulin action in peripheral tissue [2] but mainly stimulate insulin secretion from β-cells which might bring about undesired side effects such as hypoglycemia. Consequently, there is need for new therapeutic options which do not involve increasing circulating insulin concentration.[3]



Ciglitazone **1**



Troglitazone **2**

In preclinical rodent models of obesity, insulin resistance and hyperglycemia, thiazolidinediones ameliorate insulin resistance and normalize plasma glucose and plasma insulin without causing hypoglycemia even at very high doses.[4] The discovery of ciglitazone **1**,[5] has spurred uninterrupted interest in this class of compounds with greatly improved *in vivo* potency.[6] Hulin *et.al* have recently published an excellent review compiling the recent status of insulin sensitizers in NIDDM model.[7] However, due to unsatisfactory efficacy and safety profile of these agents in preclinical testing,[8] none of the thiazolidinedione class of compounds has reached the market so far. Only recently the first candidate troglitazone **2** has been registered for launching in Japan.[9] Presently, various non-thiazolidinediones analogs are also being tested for their insulin sensitizer activities.[10] Some of the tryptophan derivatives have been reported to lower the blood glucose following a single dose in KKAy mice (dose : 50 mg / kg).[11,12] Tryptophan being a commonly occuring amino acid in human beings might show an improved toxicity profile.[13] Thus, we synthesized several thiazolidinediones having tryptophan and indole moieties and tested for their euglycemic activities.

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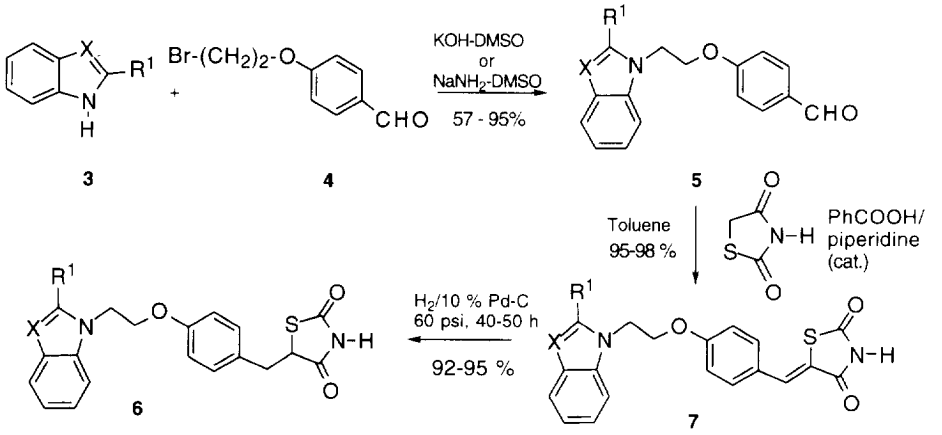
In the present communication we describe the preparation of several thiazolidinediones having tryptophan or indole moieties and their euglycemic activities in *db/db* and *ob/ob* mice. The compounds reported in the Table-1 were synthesized by alkylation of the appropriate heterocycle **3** with 4-(2-bromoethoxy)benzaldehyde **4** as shown in scheme 1 to give 57-95 % of aldehyde **5.** The aldehyde **5** was treated with thiazolidinedione in the presence of piperidinium benzoate in refluxing toluene with azeotropic removal of water to give excellent yield (95-98%) of **7**. Finally, thiazolidinedione **7** was reduced to **6** by hydrogenation in the presence of Pd-C (10 %) at 60 psi of hydrogen at *ca* 25 °C in dioxane during 40 - 50 h. Usually, 1.2 to 1.5 equivalent of Pd-C (10 %) is required for the hydrogenation of **7** to **6,** which might be attributed to the poisoning of Pd-catalyst due to thiazolidine moiety. The reduction of **7** to **6** can also be affected using magnesium (17.0 eq) in methanol for 6 h at *ca* 30 °C. [14]



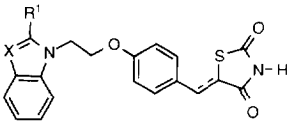
Scheme 1

Biological evaluations The antidiabetic activities of compound **6** and **7** were tested in 8 - 12 weeks old C57BL/KJ *db/db* mice and 10 week old C57BL/6J *ob/ob* mice obtained from Jackson Laboratories, U.S.A. The compounds were fed *via* oral gavage at a dose of 100 - 200 mg / kg. Blood samples were collected on 0, 3rd, 6th and 9th days and were analysed for blood sugar. The results are shown in the Table - 1. In the biological test, a group of 4 - 5 animals (male or female) were used with a vehicle control and troglitazone (200 mg/kg p.o.) as standard for comparison. At the end of the 9th day, the % reduction in triglyceride level was calculated and in few cases, mice were subjected to oral glucose tolerance test. From table 1 it is clear that several compounds showed similar or better blood glucose and triglyceride lowering activities than troglitazone. We have selected compound **6c** for a detailed evaluation in *db/db* and *ob/ob* mice at various doses. In *db/db* mice, compound **6c** produced 60 - 70 % reduction in blood glucose level after 3 days treatment even at 50 mg / kg dose. Similarly, in *ob/ob* mice, a dose of 20 mg / kg was sufficient for normalizing the blood glucose level. These results indicate that compound **6c** is far superior euglycemic and hypolipidaemic agent than troglitazone. Compound **6c** also showed considerable reduction of cholesterol level in blood.

Coclusion: Thus, we have been able to prepare a thiazolidinedione with greater potency/efficacy compared

to troglitazone. Further studies of these compounds for toxicity, bioavailability, stability *etc.* are under progress and will be reported later.

Table - 1 : Thiazolidinedione 6 and 7 and their Biological Activities



Compound No.	R^1	X	Dose mg/kg	Redn. in % RBS[a] 3, 6,9 days	% Redn. in AUC[b]	% Redn. in TG [c]
6c	H	CH	200	64,68,74	55	77
6e	4,5-Benzo-		100	0,0,0	ND	21
7a	H	$CCH_2CHCOOH$ (NH$_2$)	100	0, 29,0		64
7b	COOH	CH	200	50,39,12	ND	0
7c	H	CH	200	27,40,33	15	37
7d	H	N	200	22,31,33	ND	76
7e	4,5-Benzo-		100	0,0,0	ND	44
Troglitazone	-	-	200	14, 16,24	20	50

(a) % Redn. in RBS = Random Blood Sugar was measured on 0, 3rd, 6th and 9th days, % reduction was calculated. (b) % Redn. in AUC = Glucose tolerance test (GTT) was performed 24 h after withdrawal of drugs. GTT was performed on 18 h fasted animals after feeding 3 g / kg of Glucose. (c) TG = Triglyceride were measured on 0 and 9th day. ND = Not determined.

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14. All the compounds were fully charaterized. Structural data for **6c** is presented here: mp 103 °C; ^{1}H NMR ($CDCl_3$) δ 8.18 (bs, 1 H), 7.65 (d, *J* = 7.4 Hz, 1 H), 7.39 (d, *J* = 8.30 Hz, 1 H), 7.30 - 7.15 (m, 2 H), 7.08 (d, *J* = 8.72 Hz, 2 H), 6.76 (d, *J* = 8.72 Hz, 2 H), 6.50 (d, *J* = 2.92 Hz, 2 H), 4.50 (t, *J* = 5.52 Hz, 2 H), 4.43 (dd, *J* = 9.45, 3.75 Hz, 1 H), 4.23 (t, *J* = 5.52 Hz, 2 H), 3.39 (dd, *J* = 14.11, 3.74 Hz, 1 H), 3.04 (dd, *J* = 14.11 and 9.45 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 174.64, 170.95, 157.64, 135.99, 130.28, 128.57, 128.32, 128.17, 121.58, 121.00, 119.48, 114.72, 109.16, 101.59, 66.77, 53.56, 45.52, 37.50; Mass *m/e*: M^+ = 366.

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