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REVIEW ARTICLE

Synthesis and Evaluation of the Hypoglycemic and Hypolipidemic Activity of Sulfonamide-benzothiazole Derivatives of Benzylidene-2,4-thiazolidnedione

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Abstract: Thiazolidinediones (TZDs) and sulfonamides are important and highly consumption class of antidiabetic drugs having insulin sensitizing and stimulating properties in patients with type 2 diabetes, respectively. In this paper, some novel benzothiazole derivatives of TZD-sulfonamides were synthesized (**I-IV**) and evaluated for anti-hyperglycemic and anti-hyperlipidemic activities in the STZ-induced diabetic rat model. Results indicated that all new conjugated compounds showed significant hypoglycemic activities compared to control animals that were better for **I** and **IV** than others. Moreover, these new compounds displayed high efficiency for lowering lipid profiles as compared to control and standard (Pioglitazone) groups that was significant and higher for **I** than others. It is concluded that these new conjugated TZD-sulfonamide-benzothiazoles (**I-IV**) can indicate useful results for hypoglycemic and hypolipidemic activities compared to control and standard groups, respectively with different mechanism that is closer to TZDs' analogs.

Keywords: Hypoglycemic and hypolipidemic activities, STZ-induced diabetic rat model, Sulfonamide-benzothiazole Derivatives, Thiazolidinediones (TZDs).

1. INTRODUCTION

Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin or the body's cells cannot effectively use it. This disease is characterized by high blood glucose level and exists as two forms (Type 1 and 2). Type 1diabetes known as insulin-dependent (IDDM) or childhood-onset is characterized by a lack of insulin production while non-insulin dependent type of diabetes mellitus (NIDDM, Type 2 diabetes) due to impaired insulin action [1]. For treatment of NIDDM, various pharmacological agents have been developed which include biguanidines, sulfonylureas, 2,4-thiazolidinediones (TZD's), *etc*. Biguanidines enhance insulin action at the post receptor level in peripheral tissues such as muscles which lactic acidosis is the main problem with them. Sulfonylureas activate pancreatic beta cells and inhibition of the ATP sensitive K^+ channel, to produce insulin secretion which sudden dropping of blood sugar is a serious fatal problem with them. 2,4-Thiazolidinediones (TZDs) have long been considered as anti-hyperglycemic compounds by ameliorating insulin resistance and significantly reduce glucose but the liver toxicity is the major problem of using them [2, 3]. The disadvantages associated with using these compounds are severe hypoglycemia, weight gain and the hyperinsulinemia, known to be a risk factor for ischemic heart disease. Therefore, compounds that ameliorate the insulin resistance and/or stimulating insulin release from beta cells without the mentioned side effects have been developed for the treatment of Type 2 DM [4]. In order to synthesize the novel TZDs with better safety and efficacy, the lipophilic moiety of glitazone in this family was replaced by hydrophilic sulfonamide group and aminobenzothiazoles (**6-9**, with significant and effective hypoglycemic activity [5,6] to obtain the new conjugated TZD-sulfonamide-benzothiazoles (**I-IV**) which have two main pharmacophores (Thiazolidinediones and sulfonamide group, Scheme **1**). Then glucose and lipid-lowering activities of these new compounds were evaluated and compared with control and Pioglitazone (a standard drug of TZDs family) groups by known procedures [7].

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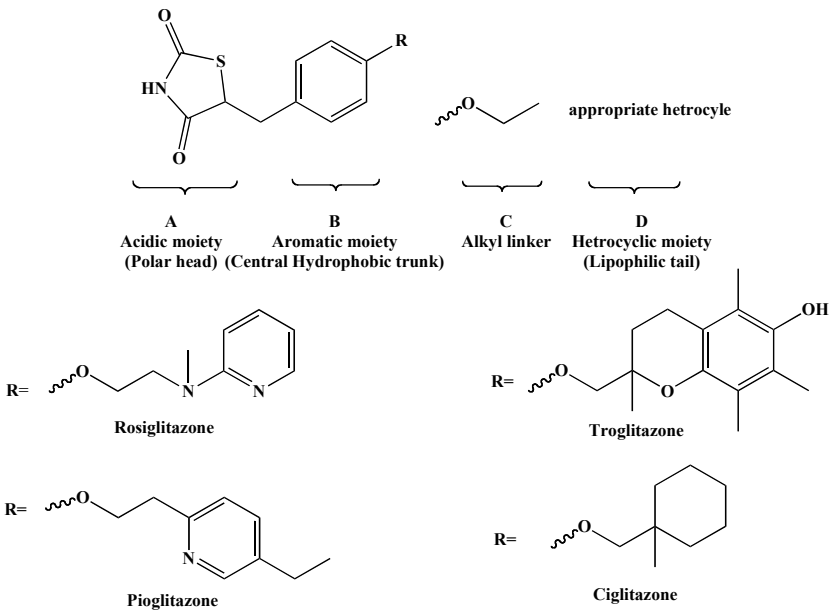


Scheme (1). Simplified and typical pharmacophore structure of glitazones.

2. MATERIAL AND METHODS

2.1. General

Chloroacetic acid, Benzaldehyde, Chlorosulfonic acid, Thiourea, Pioglitazone and all other chemicals were purchased from Merck (Darmstadt, Germany) and Sigma-Aldrich (UK) companies. Melting points (uncorrected) were determined by a digital Electrothermal melting point apparatus (model 9100, Electrothermal Engineering Ltd., Essex, UK). ^{1}H and ^{13}C NMR spectra were recorded by a Bruker 300 MHz (model AMX, Karlsruhe, Germany) spectrometer (internal reference: TMS). IR spectra were recorded by a Thermo Nicolet FT-IR (model Nexus-870, Nicolet Instrument Corp, Madison, Wisconsin, U.S.A.) spectrometer. Mass spectra were recorded by the Agilent Technology-5973, Mass Selective Detector (MSD) spectrometer (Wilmigton, USA). Elemental analyses were performed by using a Heraeus CHN elemental analyzer. Column chromatographic separations were performed over across silica gel (No.7631-86-9 particle size 35-70 micrometer, Geel, Belgium).

2.2. Preparations (Schemes 2 and 3)

2,4-thiazolidinedione (TZD, 3)

It was synthesized by refluxing of chloroacetic acid (**1**) and thiourea (**2**) using water as solvent for 12 h and cooled to obtain white crystals of 2,4-thiazolidinedione (m.p. 123-125°C) according to the literature [8].

5-benzylidine 2,4-thiazolidinedione (4)

It was synthesized by refluxing of 2,4-thiazolidinedione (**3**) and benzaldehyde in dry toluene as solvent and cooled to obtain white crystals of 5-benzylidine 2,4-thiazolidinedione (m.p. 240-242°C) according to the literature [8].

4-cholorosulphonyl-benzylidine 2,4- thiazolidinedione (5)

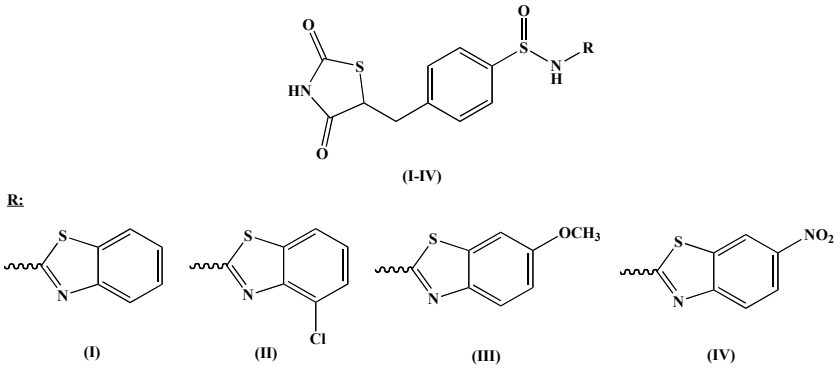
It was synthesized by adding of chlorosulfonic acid to 5-benzylidine 2,4-thiazolidinedione **(4)** and refluxed for 1h, cooled and poured into crushed ice to yield the product (m.p. 180-181°C) according to the literature [8].

General Method for Synthesizing of New Derivatives (I-IV)

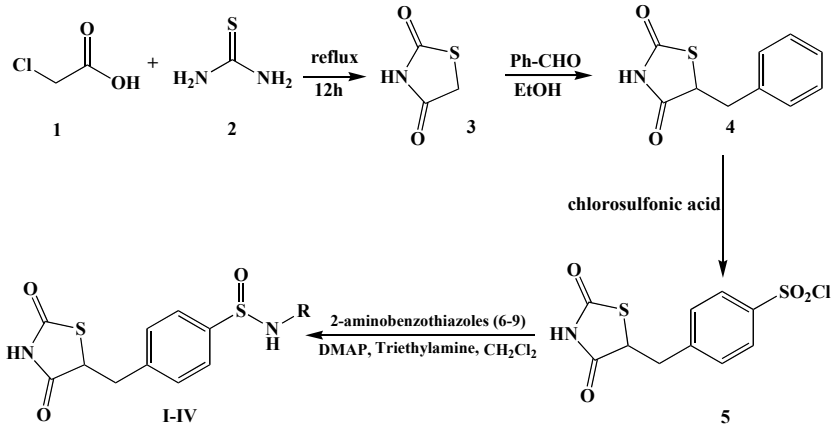
Triethylamine and a catalytic amount of 4-dimethylaminopyridine (DMAP) were added to a solution of 4-cholorosulphonyl-benzylidine 2,4- thiazolidinedione (**5**, 0.006 mol). The reaction mixture was stirred at room temperature for 15 min. Then, a solution of 2-amino benzothiazole derivatives (**6-9**, 0.003 mol) was added droopingly. The reaction mixture was stirred at 40°C for 6–10 h. Next, complete conversion as indicated by TLC, the solvent was removed in vacuo, the residue was neutralized with saturated $NaHCO_3$ solution and the aqueous layer was extracted with ethyl acetate, washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo and the precipitated solids were recrystallized from an appropriate solvent or purified by column chromatography as follow:

N-(benzothiazol-2-yl)-4-((2,4-dioxothiazolidin-5-ylidene)methyl)benzenesulfonamide (I)

Yield: 53%, Brown solid, m.p.: 145-148°C, IR (KBr) cm^{-1}: 3304, 2928, 2737, 1694, 1634, 1537, 1450, 1313, 1168, 1013, 752. ^{1}H-NMR: 4.12-4.14 (1 H, m), 7.01-7.9 (9H), 8-8.07 (1 H, m). ^{13}C-NMR: 46.7, 118.4, 121.8, 121.9, 122.9, 126.4, 127.3, 129.1, 130.2, 130.6, 131.3, 131.7, 132.9, 167.5, 172.5. MS: m/z (regulatory intensity): 416 (4), 341 (33), 325 (14), 297 (7), 242 (35), 214 (18), 178 (31), 150 (100), 123 (78), 96 (76), 69 (50), 45 (28). Anal. Calcd. for $C_{17}H_{11}N_3O_4S_3$: C, 48.91%; H, 2.66%; N, 10.07%. Found: C, 48.98%; H, 2.71%; N, 10.04%.



Scheme (2). Chemical formula of novel synthesized analogs (**I-IV**).



Scheme (3). Synthesis steps of intermediates (**1-5**) and final compounds (**I-IV**).

N-(4-Chlorobenzothiazol-2-yl)-4-((2,4-dioxothiazolidin-5-ylidene)methyl)benzenesulfonamide(II)

Yield: 50%, Yellow solid, m.p.: 153-155°C, IR (KBr) cm^{-1}: 3452, 3058, 2722, 1695, 1636, 1535, 1410, 1311, 1170, 1112, 1033, 726. ^{1}H-NMR: 3.07-3.4 (1 H, m), 6.94-7.95 (8H), 8.06-8.08 (1 H, m). ^{13}C-NMR: 46.6, 120.6, 122.1, 122.3, 126.4, 127.3, 130.5, 132, 132.9, 150.1, 168.2, 171.4. MS: m/z (regulatory intensity): 452 (12), 351 (36), 325 (9), 297 (8), 284 (23), 267 (12), 237 (11), 226 (10), 213 (46), 201 (15), 184 (100), 173 (16), 166 (24) 57 (72). Anal. Calcd. for $C_{17}H_{10}ClN_3O_4S_3$: C, 45.18; H, 2.23; N, 9.30; Found: C, 45.25; H, 2.27; N, 9.27.

4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-(6-methoxybenzo[d]thiazol-2-yl)benzenesulfonamide (III)

Yield: 57%, Brown solid, m.p.: 142-144°C, IR (KBr) cm^{-1}: 3366, 3194, 2953, 2547, 1670, 1540, 1472, 1221, 1167, 1031, 816, 702. ^{1}H-NMR: 1.37-1.43 (3 H), 3.14-3.18 (1 H, m), 6.94-7.94 (8H), 8.06-8.08 (1 H, m). ^{13}C-NMR: 56.5, 107.7, 115.4, 116.1, 125, 126.8, 127.2, 130.1, 131, 131.8, 134.3, 135.1, 156.8, 168, 168.7, 172.3. MS: m/z (regulatory intensity): 447 (4), 439 (7), 429 (4), 354 (5), 325 (5), 286 (14), 271 (15), 253 (5), 233 (16), 215 (7), 205 (10), 192 (29), 180 (94), 165 (100), 134 (64), 121 (17), 110 (15), 89 (14), 69 (16), 44 (14). Anal. Calcd. for $C_{18}H_{13}N_3O_5S_3$: C, 48.31%; H, 2.93%; N, 9.39%; Found: C, 48.39%; H, 2.98%; N, 9.36%.

4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-(6-nitrobenzothiazol-2-yl)benzenesulfonamide (IV)

Yield: 64%, Yellow solid, m.p.: 215-225°C. IR (KBr) cm^{-1}: 3408, 3067, 2762, 1693, 1640, 1525, 1449, 1294, 1240, 1185, 1123, 1038, 623. ^{1}H-NMR: 3.07-3.16 (1 H, m), 7.4-8.23 (8H), 8.63-8.67 (1 H, m). ^{13}C-NMR: 46.6, 46.7, 117.7, 118.4, 122.8, 124.9, 127.2, 130.5, 132, 134, 141.5, 150.1, 159.4, 167.5, 172.6. MS: m/z (regulatory intensity): 462 (10), 216 (15), 195 (100), 165 (85), 149 (30), 137 (15), 122 (98), 105 (20), 95 (20), 63 (45). Anal. Calcd. for $C_{17}H_{10}N_4O_6S_3$: C, 44.15%; H, 2.18%; N, 12.11%; Found: C, 44.22%; H, 2.22%; N, 12.09%.

2.3. Pharmacological Methods

Animals

At the beginning of the experiment, 54 adult male NMRI rats weighing 190-220 g (Razi Institute, Iran), with blood glucose under 150 mg/dl as non-diabetic animals were randomly selected and housed three to four per cage in a temperature-controlled colony room under 12 h light/dark cycle. Animals were given free access to water and standard laboratory rat chow (Pars Company, Tehran, Iran). All of the experiments were conducted between 11 a.m. and 4 p.m. under normal room light at 25°C. This study was carried out in accordance with the policies provided in the Guide for the Care and Use of Laboratory Animals (NIH) and those of the

Research Council of Shahed University of Medical Sciences (Tehran, Iran).

Serum Parameters Analysis

Diabetes was induced in rats by intraperitoneal (i.p.) injection of streptozotocin (Sigma, US) at a dose of 70 mg/kg [7], dissolved in 0.1 M cold citrate buffer (pH=4.5) [9]. Then the selected animals (with serum glucose under 150 mg/dl) were randomly divided into six groups; Control, Pioglitazone and its newly analogues (**I-IV**) were injected to the animal groups every day from the 3rd till day 16 after STZ injection. Glucose of the serum as the main parameter for efficiency of origin or new anti-diabetic compounds were measured due to the STZ injection on days 4, 9 and 16. We used glucose test strips (Easy Gluco) and a drop of blood which was attained from dorsal vein of the tail for measurement of the serum glucose level. Lipid profiles i.e., triglyceride, total cholesterol, LDL and HDL were evaluated on day 16. The necessary blood (close to 5 ml) for lipid profiles quantifying was acquired from retro-orbital plexus. However, due to removing of the serum, its lipids parameters including triglyceride, total cholesterol and HDL cholesterol levels were measured by using spectrophotometer and appropriate kits (Zistshimi, Tehran) for each parameter. LDL and very low-density lipoprotein (VLDL) cholesterols were calculated by applying the following formula:

VLDL = Triglyceride/5

LDL = Total cholesterol − HDL cholesterol – VLD

2.4. Statistical Analysis

Data from the measurements was expressed as means ± S.E.M. Comparisons were carried out using one way analysis of variance (ANOVA) followed by post-hoc Tukey test and p values less than 0.05 were considered as significant differences.

3. RESULTS

3.1. Chemistry

The new compounds (**I-IV**) and intermediates (**1-5**) were designed using a matrix of 4-cholorosulfonyl-benzylidine 2,4- thiazolidinedione **(5)** and four aminobenzothiazoles (**6-9**, Scheme **2** and **3**). First, 5-benzylidine 2,4-thiazolidinedione **(4)** was prepared by refluxing a solution of 2,4-thiazolidinedione (**3**) and benzaldehyde in dry toluene. Then 4-cholorosulphonyl-benzylidine 2,4- thiazolidinedione **(5)** was synthesized by the sulfonation of **4** with chlorosulfonic acid according to the published method [8].

Finally, desired new analogues were obtained by the reaction of **5** with 2-aminobenzothiazole and its electron-donating and electron-withdrawing substituted (**6-9**) in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) and triethylamine. The structures of all new synthesized compounds were determined by CHN elemental analysis and spectral data (FT-IR, ^{1}H and ^{13}C- NMR and Mass).

3.1. Pharmacology

3.1.1. The Effect of Pioglitazone and Its New Analogues on Serum Glucose Level

There was no blood serum level glucose difference between control and treatment groups 4 days after STZ injection. However, on days 9 and 16 following STZ application, a significant reduction in glucose level was found in pioglitazone and other new compounds with respect to the control animals ($p < 0.05$). In the midst of the components, pioglitazone could exert a major anti-hyperglycemic activity in comparison with other compounds 16 days after STZ application ($p < 0.05$) (Fig. **1**).

3.1.2. The Effect of Pioglitazone and Its New Analogues on

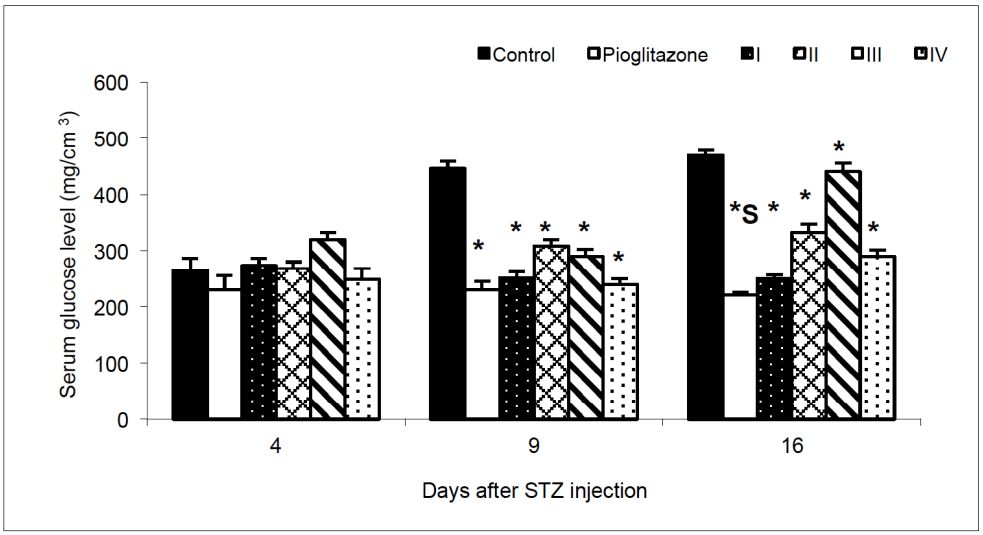


Fig. (1). The effect of pioglitazone and its new synthesized analogues on serum glucose level on days 4, 9 and 16 after STZ injection. Bars show the mean ± SEM serum glucose. n = 9 in each group. * and $ $p < 0.05$ shows the difference with control and other treatment groups, respectively.

Serum Triglyceride (TG), Total Cholesterol, LDL and HDL Levels

The mean values of blood serum parameters including cholesterol, triglyceride, LDL, HDL and HDL/LDL ratio are shown in Table 1. Nevertheless, Statistical analysis showed a marked reduction in LDL (45.96 ± 8.17) and enhancement in HDL (75.84 ± 8.17) in **I** which was significant with same control groups 72.02 ± 4.53 and 30.56 ± 4.53, respectively ($p < 0.05$). Regarding the mentioned data for LDL and HDL in **I**, a good high HDL/LDL ratio (1.6) compared to control (0.42) is apparent (Table **1**).

4. DISCUSSION

TZDs belong to 5-arylidene-2,4-thiazolidinediones family which have many pharmacological effects such as aldose reductase (ALR2) inhibitory and agonistic activity of peroxisome proliferator-activated receptor gamma (PPAR-γ) for glucose-lowering action [10,11]. So, these agents show the dual effects: antihyperglycemic activity by agonistic activity on PPARγ and also aldose reductase inhibitory action by binding with ALR2 active site [12, 13].

These classes of compounds have essentially an acidic head group (polar TZD ring system, **A**), a central phenyl ring (**B**) and a hydrophobic tail group (**D**) joined by alkyl linker (**C**). Several modifications have been attempted in the tail and head groups toward developing more potent and safer drugs that proved that these modifications could modulate their biological activities (Scheme **1**) [14].

Moreover, sulfonamides are important class of drugs which have many pharmacological activities such as antidiabetic, antimicrobial, etc [15-17] and act as hypoglycemic agents in the same manner as sulfonylurea derivatives via stimulating of pancreatic beta cells and also inhibition of the ATP sensitive K^+ channel [18].

In this paper, because of wide spectrum of biological activities of compounds containing thiazolidine-2,4-dione (TZD) [19] and sulfonamide [15-17], nucleus which belongs to the class of insulin sensitizers and insulin stimulating antidiabetic agents, respectively. Therefore, new conjugated compounds with these main pharmacophores were synthesized. Also, for increasing the pharmacological activities, aminobenzothiazoles (**6-9**) with considerable antidiabetic activity [5,6], were added to these compounds in order to obtain new dual hypoglycemic drugs which control blood glucose level through two mechanisms [16].

The results indicated that all new analogues (**I-IV**) showed significant hypoglycemic activity compared to control animals that were higher for **I** and **IV** than others (Fig. **1**).

In this test, derivatives with substituted aminobenzothiazoles by chlorine and methoxy groups (**II** and **III**) displayed lower activity than others that this may be due to higher steric hindrance of these mentioned chemical groups compared to other ones.

Although, not all these new conjugated analogs could reveal better antidiabetic activities compared to standard TZD drug (Pioglitazone) which may be due to lower affinity of mentioned compounds to PPAR-γ and/or ALR2 active site that are the main mechanisms of hypoglycemic activities of TZDs.

Also, these results revealed that the mentioned analogs could not act as stimulated of beta cells which is the main hypoglycemic mechanism of sulfonamide drugs because of lower antidiabetic property of these new compounds than pioglitazone (as a TZD standard drug).

The investigation on lipid lowering activities also showed that, these new compounds could diminish TG and LDL levels and increase HDL level and HDL/LDL ratio (which were significant for **I**) as positive factors in lowering blood serum lipid indexes compared to control and standard group (pioglitazone) but no reduction of cholesterol level was seen in all groups (Table **1**).

In this test, unsubstituted benzothiazole derivative (**I**) showed the best and significant hypolipidemic activities compared to other analogs and TZD standard one (pioglitazone). In addition, all of the new conjugated synthesized compounds showed better anti-lipidemic effects compared to pioglitazone as the TZD candidate that may be due to additional sulfonamide-benzothiazols in these new compounds with hypolipidemic activities [20-21].

CONCLUSION

It is concluded that new conjugated TZD-sulfonamide-benzothiazoles show useful results for hypoglycemic and

Table 1. Blood serum triglyceride, total cholesterol, LDL, HDL and HDL/LDL ratio in control and treatment animals.

Group Tests	Serum Parameter (mg/dl)				
	Cholesterol	TG	LDL	HDL	HDL/LDL Ratio
Control	108.62 ± 7.42	94.09 ± 11.17	72.02 ± 4.53	30.56 ± 4.53	0.42
Pioglitazone	132.1 ± 6.70	108.11 ± 23.04	83.8 ± 3.96	40.25 ± 3.96	0.48
I	131.96 ± 8.59	91.83 ± 16.29*	45.96 ± 8.17 *	75.84 ± 8.17 *	1.60 *
II	113.60 ± 8.5	81.62 ± 20.01	61.18 ± 9.50	43.68 ± 9.5	0.71
III	128.45 ± 6.86	105.62 ± 16.22	73.26 ± 9.11	54.32 ± 9.11	0.74
IV	129.18 ± 6.9	83.12 ± 15.23	84.63 ± 4.52	37.12 ± 4.52	0.43

hypolipidemic activities compared to control and standard TZD (pioglitazone) groups, respectively. These results were significant and better for derivatives with unsubstituted and nitro-benzothiazoles than other analogs in antidiabetic activity but not to Pioglitazone. In addition, these new compounds could improve lipid profiles compared to control and pioglitazone groups. It seems that the hypoglycemic mechanism of these new conjugated analogs may be more similar to TZDs' one but with lower affinity to related receptors and/or ALR2 active site. Conversely, stimulated of beta cells or other sulfonamide's mechanisms may be responsible for hypolipidemic activities of mentioned drugs. However, the exact hypoglycemic and hypolipidemic mechanisms of this class of antidiabetic drugs are important subjects that need further investigation in future studies.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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