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DRUG SYNTESIS

DESIGN, SYNTHESIS, AND CHARACTERIZATION OF SOME NOVEL THIAZOLIDINE-2,4-DIONE DERIVATIVES AS ANTIDIABETIC AGENTS

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Abstract: The number of thiazolidine-2,4-dione compounds is quite well established to reduce blood glucose levels. The current study focuses on designing and synthesizing novel thiazolidine-2,4-dione derivatives as antidiabetic agents. Initially, thiourea was reacted with chloroacetic acid to yield the intermediate compound 2-iminothiazolidine-4-one, which was then converted into compound thiazolidine-2,4-dione in an acidic medium with reflux. The second step is to prepare 5-aryl idene-2,4-thiazolidinedione via the Knoevenagel condensation of vanillin with thiazolidine-2,4-dione, which is catalyzed by piperidine. Finally, a series of novel azo derivatives were synthesized by an azo coupling reaction of 5-arylidene-2,4-thiazolidinedione with aromatic amines. Physical methods (gauge melting point), thin-layer chromatography (TLC), and spectroscopic methods (IR, ^{1}H-NMR, and Mass) were used to investigate compounds. The antidiabetic activity of the prepared derivatives was investigated using a sucrose-loaded model. The experiment revealed an excellent result in terms of blood glucose reduction.

Keywords: thiazolidine-2,4-diones, vanillin, Knoevenagel condensation, azo derivatives, Pioglitazone

Diabetes is defined as a pathological condition in which the pancreas does not produce the required insulin, or the body cells fail to bind to the hormone insulin despite its normal secretion. It is accompanied by many clinical signs such as the desire to eat, drink more water, general lethargy. The disease is treated with a healthy diet, insulin injections, and oral medications. The two main types are type 1 and type 2 diabetes mellitus (1). Type 1 diabetes (T1D) is entitled juvenile diabetes or insulin-dependent diabetes, and it accounts for 5-10% of persons with diabetes caused by beta-cell damage in the pancreas. As a result, insulin insufficiency is unavoidable. T1D may be due to weak autoimmune or unknown causes. Type 2 diabetes (T2D), adult-onset or non-insulin-dependent diabetes, is induced by tissue resistance to insulin action. The majority of diabetic patients have T2D. Most cases are of the second type and represent approximately 90% of patients (2, 3).

Several antidiabetic drugs can be used alone or in combination to treat diabetes. Meglitinides, biguanides, sulphonylurea, and α-glucosidase inhibitors are among them. Thiazolidinediones (TZDs) or glitazones are antihyperglycemic agents that decrease insulin resistance and improve insulin action, thereby improving glycemic control to normal values (3).

Thiazolidinone is a five-membered ring, as shown in Figure 1, having several heteroatoms such as a sulfur atom that takes position 1 in the pentagonal ring, a nitrogen atom at position 3, and a carbonyl group at positions 2, 4, or 5 (4). The thiazolidinedione nucleus is widely involved in active biological agents such as antidiabetic (5), antifungal (6), anti-HIV (7), anti-inflammatory (8), analgesic (9), antibacterial (10), antidepressant (11), and anti-tumor activity (12).

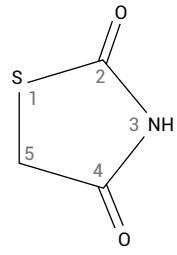

Figure 1. Thiazolidine-2,4-dione moiety.

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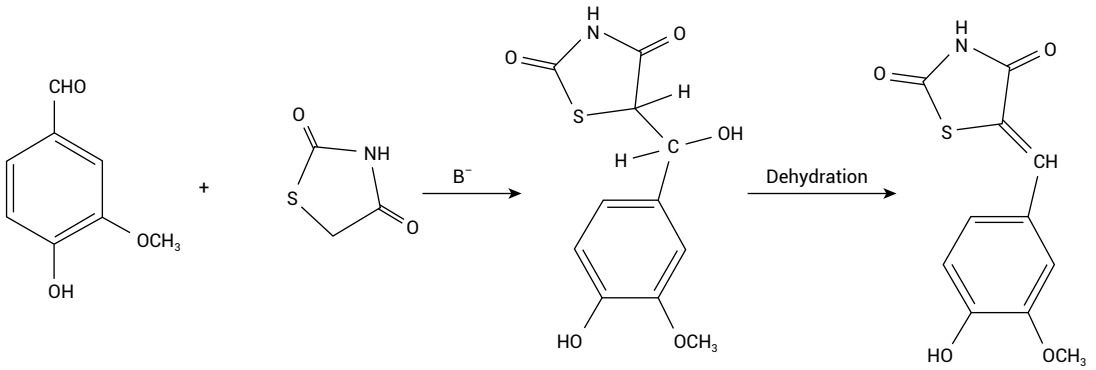


Scheme 1. Knoevenagel condensation.

The cyclization reaction between chloroacetic acid and thiourea in an acidic medium is the most well-known method for synthesizing thiazolidine-2,4-dione molecules reported in the literature (13-16). The Knoevenagel condensation reaction between aromatic aldehydes and the active methylene of thiazolidine-2,4-dione results in the production of benzyldithiazolidine-2,4-dione compounds, Scheme 1 (17, 18). Benzylidenethiazolidine-2,4-diones are pharmacologically active heterocyclic substances possessing five-membered rings with bioactive heteroatoms (N, S, and O) heterocyclic atoms with a wide range of biological activities, including antimicrobial (19), antidiabetic (20), anti-obesity (21), anti-inflammatory (22), anti-proliferative and anti-tumor (23).

The purpose of this study was to synthesize novel derivatives of the thiazolidine-2,4-dione, followed by the characterization of chemical structures for these derivatives by using a variety of physical and spectroscopic techniques. The next step was to evaluate the antidiabetic efficacy for the newly synthesized derivatives by applying the sucrose-loaded model in rats.

EXPERIMENTAL

Materials

Chemical materials utilized in this work were purchased from Merck Company (Germany). The melting point of all the resulting compounds was measured using the electrical melting point apparatus (Stuart SMP 30, Japan). The reactions were followed up using thin-layer chromatography (TLC), the spots were photographed with a UV apparatus (Tran's illuminators /Germany). The infrared (IR) spectra were measured in cm^{-1} units using KBr granules in (SHIMADZU/ Japan) device at the University of Basrah., College of Science, Department of Chemistry. The ^{1}H-NMR spectra (ppm) were recorded and measured on the BRUKER 500 Hz apparatus using a phosphorus parameter as an internal standard of the instrument. Mass spectra were recorded and measured using MSD (JAPAN) apparatus, electron impact (70 EV) in Faculty of Chemistry, University of Tehran, Islamic Republic of Iran.

Methods

Synthesis of 2-iminothiazolidin-4-one (A) & thiazolidine-2,4-dione (B)

The methodology for synthesis was adopted from Pattan et al. (20). A solution contains 5.6 g (0.06 M) of chloroacetic acid in 6 mL distilled water (D.W) with 4.6 g (0.06 M) of thiourea in 6 mL (D.W) mix with 50 mL ethanol in a round flask (150 mL) and stirs it about 15 min until a white precipitate is formed from the intermediate 2-iminothiazolidin-4-one (A). The concentrated hydrochloric acid (6 mL) was added drop by drop into the solution reaction until the precipitation vanished. Reflux was continued for about 12 h; then, the solution was refrigerated in an ice bath to form thiazolidine-2,4-dione (B).

Compound (A): chemical formula $C_3H_4N_2OS$, M.W. (g. mol^{-1}) 116.14, Mp. = 250-251ºC, yield 77.6%, R_f. 0.75 eluent MeOH: chloroform 2: 8, color: glassy white. IR ν_{max} cm^{-1}: 3286.81 (NH-), 1589.4 (C=O), 1685.84 (imine C=NH), 671.69 (C-S).

Compound (B): chemical formula $C_3H_3NO_2S$, M.W. (g. mol^{-1}) 116.99, m. p. 125-127ºC, yield 82%, R_f. 0.6 hexane: ethyl acetate 3: 7, color: glassy white. IR ν_{max} cm^{-1}: 3136.36 (NH-), 1743.71 (C=O), 617 C-S). ^{1}H-NMR (ppm) δ in DMSO-*d6*: HN- (1H 12.1), CH_2- (2H 3.8).

Synthesis of (z)-5(4-hydroxy-3-methoxybenzylidine)-2,4- thiazolidinedione (compound V)

The synthesis procedure is based on Pattan et al. (20). In 250 mL round bottom flask, a solution of 2.3 g (0.02 M) of 2,4-thiazolidinedione (B) with 3.1 g (0.02 M) of vanillin in 150 mL ethanol, 1.2 g (0.15 M) piperidine, was refluxed for ten h. The solution was cooled, and concentrated hydrochloric acid (HCl) was added dropwise until a yellow precipitate was produced. The resulting solid (V) was filtered, dried, and recrystallized with ethanol.

Compound V: chemical formula $C_{11}H_9NO_4S$, M.W. (g. mol^{-1}) 251.26, m.p 225-227ºC, yield 40.8%, R_f. 0.85 eluent hexane: acetone 9: 2, color: light yellow, IR ν_{max} cm^{-1}: 3525.99 (OH-stretching), 1288.49 (OH-bending), 1014.59 (OCH_3 stretching), 617 (C-S), 1678.13 (C=O), 3194.23 (NH-). ^{1}H NMR (ppm) δ in DMSO-*d6* solvent: OH- (1H 9.9), NH- (1H 12.13), Ha- (1H 6.94), H_b (1H 7.07), H_c (1H 7.18), CH_3 (3H 3.8), H-ethylene (1H 7.9). GC-MS spectra at (m/z = 180.1, 137.1, 169, 65.1) represented the molecular ion [M^+].

Synthesis of series derivatives (V_1-V_7)

Solution (a): in beaker (250 mL) 1.2 g (0.005 M) of (V) with 0.005 M (NaOH) in 100 mL ethanol were stirred for 15 min.

Solution (b): a solution (0.005 M) from (V_1-V_7) amines: (aniline), (*p*-chloroaniline), (*p*-methoxyaniline), (*p*-nitroaniline), (*p*-hydroxyaniline), (*p*-methylsulfonyl amine) and (3,4,5-trimethoxyaniline) was dissolved in 5 mL concentrated HCl with (10 mL) distilled water.

Then, the solution (b) was added dropwise to the solution (a) for 30 min at 0-5ºC, stirred about 30 min, and the crushed ice water was added to form a solid precipitate, acidified, filtered, washed residue with distilled water three times, dried then recrystallized from ethanol (25, 26).

Compound V1*:* IUPAC name 5-((E)-4-hydroxy-3-methoxy-5-((Z)-phenyldiazenyl) benzylidene) thiazolidine-2,4-dione, molecular formula $C_{17}H_{13}N_3O_4S$, M.W. (g. mol^{-1}) 355.37, Mp. = 196-198°C, yield 56%, R_f. 0.56 eluent acetone: hexane 9: 2, color: very dark green. IR ν_{max} cm^{-1}: 3525.99 (str. -OH), 1280.78 (bending-OH), 3205.8 (str. NH-), 1207.48 (CH_3O-), 1678.13 (str. C=O), 613.38 (str. C-S). ^{1}H NMR (ppm) δ in DMSO-*d6* solvent: OH- (1H 10.1), NH- (1H 12.55), CH_3- (3H 3.9), H-ethylene- (1H 9.2), H_b- (1H 7.09), H_c- (1H 7.24), H_d- (1H 7.39), H_e- (1H 7.5), H_f- (1H 7.18). Mass spectra at (m/z = 251.1, 137.1, 180.1, 109) represented the molecular ion [M^+].

Compound V2*:* IUPAC name 5-((Z)-4-chlorophenyl) diazenyl)-4-hydroxy-5-methoxybenzylidene) thiazolidine-2,4-dione, molecular formula $C_{17}H_{12}N_3O_4Cl$, M.W. (g. mol^{-1}) 389.81, Mp. = 204-206°C, yield 71%, R_f. 0.43 eluent acetone: hexane 9: 2, color: yellow green. IR ν_{max} cm^{-1}: 3525.99 (stretching-OH), 1288.48 (bending-OH), 3198.08 (NH-), 1014.59 (CH_3O-), 1678.13 (C=O), 802.4 (C-Cl), 613.38 (C-S). ^{1}H NMR (ppm) δ in DMSO-*d6* solvent: HO- (1H 9.98), NH- (1H 12.49), CH_3O- (3H 3.91), H-ethylene (1H 7.73), H_b- (1H 6.94), H_c- (1H 7.07), H_e- δ (1H 7.18), H_f- (1H 7.12). Mass spectra at (m/z = 251.1, 137.1, 180.1, 76.5) represented the molecular ion [M^+].

Compound V3*:* IUPAC- name 5-((Z)-4-hydroxy-3-methoxy-5-((E)-4-methoxy phenyl) diazenyl) benzylidene) thiazolidine-2,4-dione molecular formula $C_{18}H_{12}N_3O_5S$, M.W. (g. mol^{-1}) 385.39, Mp. = 230-232ºC, yield 61%, R_f. 0.28 eluent acetone: hexane 9: 2, color: light green. IR ν_{max} cm^{-1}: 3464.27 (stretching-OH), 1288.49 (bending-OH), 3194.23 (NH-), 1014.59 (CH_3O-)$_a$, 925.86 (CH_3O-)$_b$. 617.24 (C-S), 1681.98 (C=O). ^{1}H NMR (ppm) δ in DMSO-*d6* solvent: HO- (1H 9.97), HN- (1H 12.49), H-ethylene (1H 7.72), CH_3O- (3H 3.83), H_b- (1H 6.94), H_c- (1H 7.09), H_e - (1H 7.9), H_f- (1H 7.18). Mass spectra at (m/z = 251.1, 137.1, 180.1, 107.3, 76.2) represented the molecular ion [M^+].

Compound V4: IUPAC-name 5-((Z)-4-hydroxy-3-methoxy-5-((z)-(4-nitrophenyl) diazenyl) benzylidene) thiazolidine-2,4-dione molecular formula $C_{17}H_{12}N_4O_6S$, M.W. (g. mol^{-1}) 400.37, Mp. = 278-280ºC, yield 54%, R_f. 0.33 eluent hexane: acetone 9: 2, color yellow green. IR ν_{max} cm^{-1}: 3525.99 (str.-OH), 1284.63 (bending-OH), 3198.08 (str. NH-), 1678.0 (str. C=O) 1516.1 (symmetric -NO_2), 1334.78 (symmetric -NO_2), 1018.45 (CH_3O-), 613.38 (str. C-S). ^{1}H NMR (ppm) δ in DMSO-*d6* solvent: HO- (1H 9.98), HN- (1H 12.48), CH_3O- (3H 3.9), H-ethylene (1H 7.77), H_b- (1H 6.94), H_c- (1H 7.09), H_c- (1H 7.9), H_f - (1H 7.18). Mass spectra at (m/z = 251.1, 137.1, 180.1, 122.1) represented the molecular ion [M^+].

Compound V5*:* IUPAC name 5-((Z)-4-hydroxy-3-((z)-(4-hydroxyphenyl) diazenyl-5-methoxybenzylidene) thiazolidine-2,4-dione molecular formula $C_{17}H_{13}N_3O_5S$, M.W. (g. mol^{-1}), Mp. = 217-219ºC, yield 61%, R_f. 0.7 eluent hexane: acetone 9: 2, color: light yellow. IR ν_{max} cm^{-1}: 3525.99 (str.-OH), 1280.78 (bending-OH), 1014.59 (str. CH_3O-), 3198.08 (str. HN-), 1678.13 (str. C=O), 613.38 (str. C-S). ^{1}H NMR (ppm) δ in DMSO-*d6*: HO- δ (1H 9.97), HN- (1H 12.49), CH_3O- (3H 3.91), H-ethylene (1H 3.91), H_b (1H 7.07), H_c (1H 7.09), H_e (1H 6.93), H_f (1H 7.19).

Mass spectra at (m/z = 251.1, 137.1, 180.1, 93) represented the molecular ion [M^+].

Compound V6*:* IUPAC name 5-((E)-4-hydroxy-3-methoxy-5-((Z)-(4(methylsulfonyl)phenyl) diazenyl) benzylidene) thiazolidine- molecular formula $C_{18}H_{15}N_3O_6S_2$, M.W. (g. mol^{-1}) 433.45, Mp. = 263-265°C, yield 55%, R_f. 0.79 eluent hexane: acetone 9: 2, color: brown green. IR ν_{max} cm^{-1}: 3525.99 (str.-OH), 1280.78 (bending-OH), 1678.13 (str. C=O), 1014.59 (str.CH_3O-), 1334.78 (str. S=O), 613.38 (str. C-S), 3198.08 (str. HN-). ^{1}H NMR (ppm) δ in DMSO-*d6* solvent: HO- (1H 9.49), HN- (1H 12.01), CH_3O- (3H 3.36), SO_2- CH_3 (3H 3.37), H-ethylene (1H 7.25), H_b (1H 6.46), H_c (1H 6.48), H_e (1H 6.62), H_f (1H 6.76). Mass spectra at (m/z = 251.1, 137.1, 180.1, 159.1) represented the molecular ion [M^+].

Compound V7*:* IUPAC name 5-((Z)-4-hydroxy-3-methoxy-5-((E)-(3,4,5-trimethoxyphenyl) diazenyl) benzylidene) thiazolidine-2,4-dione molecular formula $C_{20}H_{19}N_3O_7S$, M.W. (g. mol^{-1}) 445.45, Mp. = 249-251°C, yield 60%, R_f. 0.2 eluent hexane: acetone 9: 2, color: brown green. IR ν_{max} cm^{-1}: 3464.27 (str.-OH), 1288.49 (bending-OH), 3194.23 (str.HN-), 1014.59 (str. CH_3O-), 617.24 (str. C-S), 1618.98 (str. C=O). ^{1}H NMR (ppm) δ in DMSO-*d6* solvent: HO- (1H 9.97), HN- (1H 12.48), CH3O- (3H 3.8), H-ethylene (1H 7.73), H_b (1H 7.09), H_c (1H 7.18), H_f (1H 6.94). Mass spectra at (m/z = 251.1, 137.1, 180.1, 167) represented the molecular ion [M^+].

Pharmacology

Animals

The Animal House Unit at the University of Basrah's College of Pharmacy donated twenty-four mature male Swiss rats weighing 180-200 g for this study. The rats were divided into six groups (n = 6), and the animals were housed in isolated plastic cages and kept in the animal's room under a controlled temperature of 22 ± 4°C and 30 ± 15% humidity, 12-h dark/12-h light cycle for a week before being used for acclimatization. The animals were fed standard chow and tap water. The Animal Ethics Committee at the University of Basrah in Iraq (No. 2013/32) approved all of the procedures involving animals mentioned in this work.

Antidiabetic activity

The study of the antidiabetic effect of the derivatives synthesized was achieved by using the sucrose-loaded model in the rats according to (Datar and Aher) with some modifications (27). Study rats were fasted overnight and allowed free access to water, and blood glucose levels were measured when fasting (0 h) before injecting the prepared compounds and the standard drug. Sucrose 5% solution was administered to rats via feeding bottle after measuring blood glucose levels at 0 h to avoid early hypoglycemia. Blood samples were withdrawn from all animals at 0, 1, 2, and 4 h. Experimental animals (rats) were spliced haphazardly into ten groups (n = 6). Animals of group 1 were injected intraperitoneally (i.p.) with 100 µL of DMSO only and served as a control group. The standard antidiabetic drug (Pioglitazone) at a dose of 0.5 mg/kg in 100 µL of DMSO was injected intraperitoneally (i.p.) to rats of group 2. Rats of groups 3-10 were injected intraperitoneally (i.p.) of the synthesized compounds **V**, **V1-V7** at a dose of 0.5 mg/kg in 100 µL of DMSO.

Blood collection and blood glucose measurement

Blood samples were collected by a tail tapping method, and a digital glucometer estimated blood glucose levels. The animal's tail is sterilized with 70% ethanol every time blood is drawn.

Statistical analysis

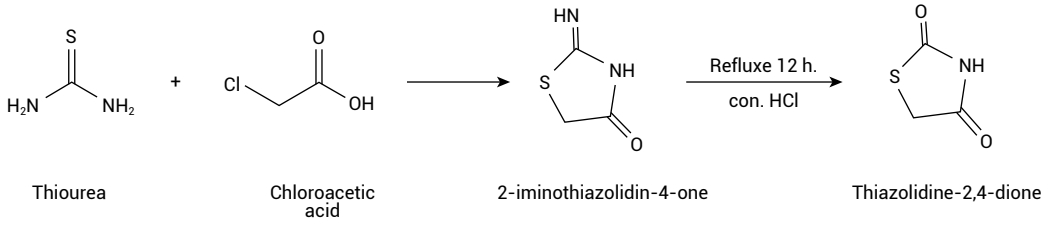
The data of all trials in this study are presented as the mean ± standard deviation. ANOVA was used for statistical analysis, followed by Dunnett's t-test. The probability (*P*) values less than 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Chemistry

The thiazolidine-2,4-dione (B) was prepared by using thiourea and chloroacetic acid in medium acidic condensation, as shown in Scheme 2, depending on the adapted method of Pattan et al. (20). To obtain better results, the experiment was repeated at different times to inspect the effect of the first experiment applied in a period of 10 h; the yield was 33%, as mentioned in the literature. Also, it was conducted in 32 h, the yield was 28%, and it was repeated within 14 h, the yield was 82%. Therefore, it was concluded that the perfect time for the maximum outcome was 14 h; these tests coincided with less water. TLC monitored the reactions with several eluents, and the best alienated was accessed in a mixture of hexane: ethyl acetate with a ratio of (3 : 7) as eluent. The product was then purified using absolute ethanol.

Thiazolidine-2,4-dione (**B**) reacting with vanillin in a basic medium (using piperidine) in ethanol produced compound **V** (29) (Scheme 3). When compound **V** reacts with several different aldehydes in a basic ethanol medium, derivatives (**V1-V7**) would be produced, as shown in Scheme 4. These



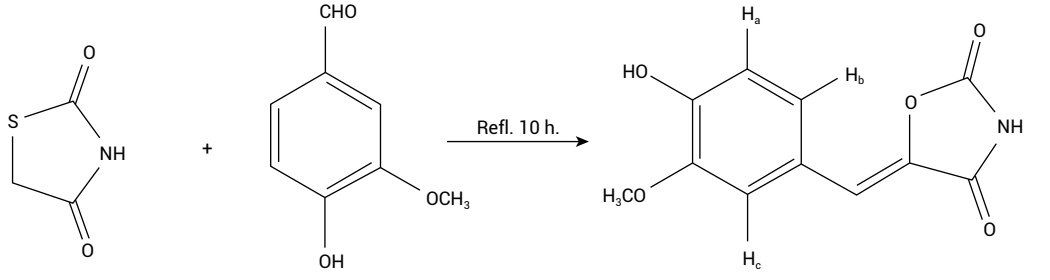
Scheme 2. Synthesis of thiazolidine-2,4-dione.

derivatives were prepared through a nucleophilic substitution reaction on the ring at 5-position.

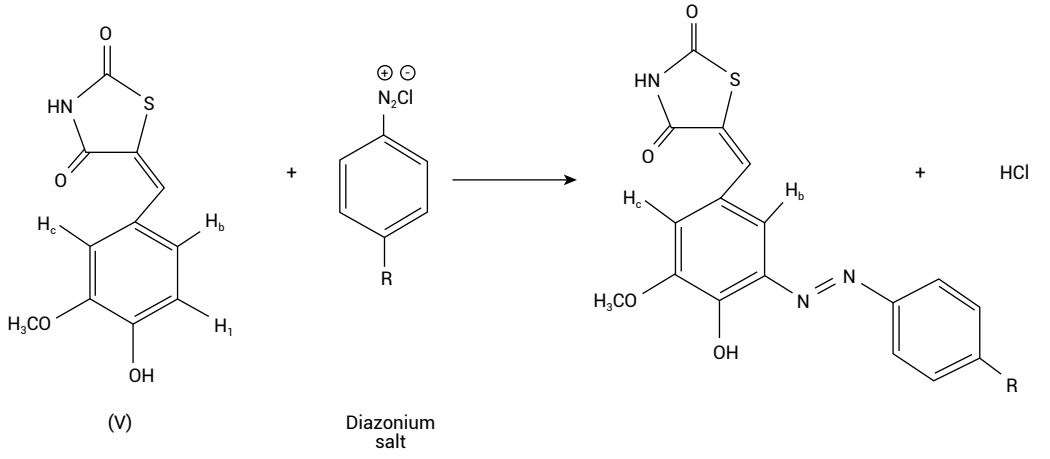
All compounds **B**, **V**, **V1-V7,** were diagnosed by spectroscopic methods and gave prominent bands some shared between compounds **B**, **V**, **V1-V7**. In the FT-IR spectrum: the medium band at 3136.36 cm^{-1} is due to NH stretching. Also, strong absorption bands at 1342.5 cm^{-1} are due to C-N stretching. Moreover, the spectra showed a strong absorption band due to C=O stretching, which appeared at 1743.71 cm^{-1}, medium broadband at 617.24 cm^{-1} due to C-S stretching (17-19). In ^{1}H-NMR spectra in DMSO-d6, all compounds gave a signal at δ 2.5 ppm, which was due to DMSO solvent (25, 26). They also gave a singlet signal at δ 12.1–12.5 ppm, H due to NH (28), and a single signal at δ 7.18–7.72 ppm, H due to H-ethylene (30). Mass spectra at (m/z = 180.1, 137.1, 169, 65.1, 251.1) represented the molecular ion [M^{+}].

Derivatives were diagnosed based on spectroscopic measurements. They differed in specific signals for everyone, as will be explained: -

In FT-IR spectra compound, **V** showed a weak signal at 3525.99 cm^{-1} due to (OH-stretching), a strong signal at 1288.49 cm^{-1} due to (OH-bending), a medium signal at 1014.59 cm^{-1} due to (OCH_3 stretching). Compound **V1** showed a strong band due to aromatic (C=C) at 1512.24 cm^{-1} (24), compound **V2** showed a weak band at 802.41 cm^{-1} due to (C-Cl) bond, the weak band appeared in 1014.59 cm^{-1} due to (OCH_3) bond in compound **V3**, strong stretching band at 1516.1 cm^{-1} due to (NO_2) in compound **V4**, compound **V5** showed a weak band at



Scheme 3. Synthesis of compound **V**.



Scheme 4. Synthesis of derivatives V_1-V_7.
Where R = H (V_{1}), Cl (V_{2}), OCH_3 (V_{3}), NO_2 (V_4), OH (V_5), SO_2CH_3 (V_6), [3,4,5-(OCH_{3})$_3$ (V_7)]

Table 1. Blood glucose levels of (V, **V1-V7**) compounds in experimental animals (mg/dL).

Compound	0 h	1 h	2 h	4 h
Control (DMSO)	96.3 ± 2.54	140.5 ± 4.9	136.8 ± 5.21	128.5 ± 3.98
Standard (Pioglitazone)	98.5 ± 4.35	119 ± 3.57***	95.5 ± 5.12***	107.5 ± 3.62***
V	94.5 ± 3.18	105.6 ± 5.04***	96.8 ± 1.82***	102.8 ± 2.97***
V1	95.4 ± 3.55	125.5 ± 4.21***	103.2 ± 3.91***	110.3 ± 4.42***
V2	103.5 ± 3.65	105.2 ± 4.22***	99.5 ± 3.63***	90.5 ± 2.35***
V3	100 ± 3.58	115 ± 4.31***	110.4 ± 5.27***	86.4 ± 3.54***
V4	92.8 ± 3.32	111.5 ± 5.3***	105.6 ± 4.08 ***	84.5 ± 3.55***
V5	98.2 ± 2.29	108.4 ± 4.97***	97.2 ± 3.69***	85.3 ± 3.9***
V6	96.5 ± 3.86	98.5 ± 5.01***	82.5 ± 2.87***	86.2 ± 4.25***
V7	91.6 ± 2.17	91.5 ± 3.58***	86.2 ± 4.21***	80.6 ± 3.25***

Each value is the mean ± S.D. for six rats, *p < 0.05, **p < 0.01, ***p < 0.001 compared with normal control. Data analyzed by using one-way ANOVA followed by T-test.

3483.56 cm^{-1} due to (OH) in the aromatic ring, compound **V6** showed a weak band at 1334.78 cm^{-1} due to (SO_2CH_3 cm-1), compound **V7** showed strong stretching at 1014.59 cm^{-1} due to three bonds of (OCH_3) (29).

In ^{1}H-NMR in DMSO-*d6* solvent compound **B** showed singlet signal at δ 3.8 ppm, 2H due to CH_2. Compound **V** gave doublet of doublets signal at δ 7.75 ppm due to (C-H_a)**,** doublet signal at δ 6.94 ppm due to (C-H_b), singlet signal at δ 7.18 (ppm), 1H due to (C-H_c), compound **V1** showed doublet of doublet signal at δ 6.8 (ppm), 1H due to H_e – aromatic, doublet signal at δ 7.3 (ppm), 1H due to H_f –aromatic, doublet signal at δ 7.43 (ppm), 1H for H_d- aromatic. Moreover, singlet signal at δ 7.72 (ppm), 1H due to H-ethylene, singlet signal at δ 9.97 (ppm), 1H due to (OH) and strong singlet signal at δ 3.83 (ppm), 3H due to OCH_3. For compounds **V2, V4, V5, V6, V7**, the disappearance of the signal (H_d at δ 7.43 ppm) was their evidence because of the addition of the aromatic azo group in position 9 of compound **V** (30).

From the Mass spectra (m/z), the signals at 251.1, 385.2, 389.0, 387.0, 4000.2, 502.3, and 551.6 denote the [M^+] molecular ions of **V-V7** excluding **V5** compounds, respectively. Therefore, the indications that the thiazolidinedione-derived structures synthesized in our study are correct. All derivatives had similar fragmentation mechanisms.

Biological evaluation

After preparing the derivatives and verifying their structures, A study was performed to investigate the biological activity of these substances (antidiabetic effect), and the experiment was conducted by applying a sucrose-loaded model in rats and an application with some modifications (27). The study gave results indicating that the standard antidiabetic drug (Pioglitazone) showed an increase in the blood glucose level at 1 h, followed by a decrease at 2 h, but rises again at 4 h. The compounds **V V1** also showed the same pattern of results, but the rest of the compound's series (**V2-V7**) showed a decrease at 1 h, and they continued to show a reduction in the level of blood glucose as shown in Table 1 and Figure 2. Based on earlier experimental results, it is possible to deduce that the substances (**V2-V7**) are better at lowering the blood

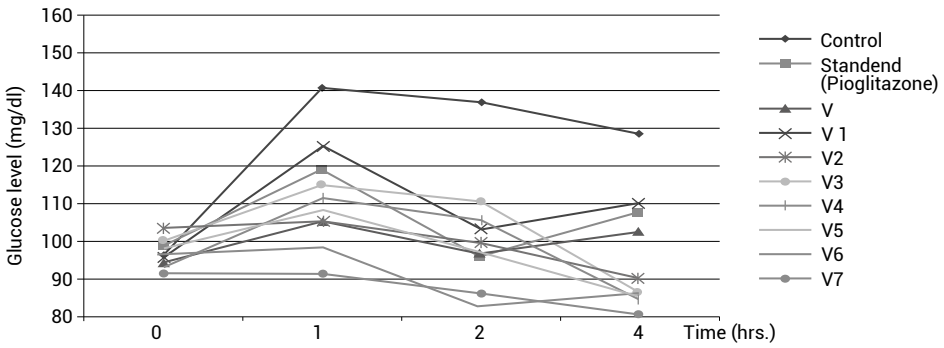


Figure 2. Blood glucose levels of V-series compounds in experimental animals (mg/dL).

sugar level than the commercially marketed pioglitazone product.

CONCLUSIONS

The study proved that following the method (Knoevenagel condensation) in the preparation of thiazolidinedione derivatives is a suitable method because it is easy and low-cost. Depending on diagnostic procedures TLC, IR, ^{1}H-NMR, and mass spectroscopy, the correct formulations of the prepared derivatives were confirmed. These compounds have shown excellent results and a very effective effect in lowering blood glucose levels when injecting to a group of study animals (rats) with specific concentrations compared to the commercial drug (Pioglitazone), especially the two compounds **V6** and **V7**.

Conflict of interest

The authors declare no conflict of interest.

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