Research Article

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Synthesis and *in vitro* Antidiabetic Evaluation of Some New Thiazolidinone Derivatives bearing Sulfonamide moiety

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Abstract: Nowadays, diabetes mellitus (DM) has shown as a significant global health concern with a remarkable increase in its prevalence. In this study, we have focused our efforts to synthesize a new series of thiazolidin-4-ones bearing sulfonamide moiety (**5a-h** and **6a-h**) *via* a multistep reaction strategy in high to excellent yields. Reaction of *p*-toluene sulfonyl chloride with ethyl glycinate or β-alanie afforded compounds **1a,b** which then allowed to react with hydrazine to give the corresponding hydrazide deivatives **2a,b**. The reaction of hydrazides **2a,b** with different aromatic aldehydes resulted in the formation of hydrazone derivatives **3a-h** and **4a-h**. Finally compounds **3a-h** and **4a-h** were reacted with ethyl thioglycalate to give the expected thiazolidinone derivatives **5a-h** and **6a-h** respectively. The obtained products were characterized according to their elemental and spectral analyses. To find the antidiabetic potentials of the synthesized compounds (**5a-h** and **6a-h**), *in vitro* α-amylase inhibitory activity compared to Glitazone as reference was performed. The results of the antidiabetic assay were very encouraging because compounds **5c**, **5f**, **5g** and **5h** showed excellent inhibitions activity against α-amylase enzyme.
Keywords: Sulfonamide, thiazolidinone, antidiabetic, in vitro, synthesis, inhibition.

1. Introduction

Diabetes mellitus (DM) is a common chronic health problem and around the world 416 million people are suffering from it. This number is expected to reach 618 million cases by 2040 [1–4]. Diabetes mellitus (DM) was classified into two main classes: type-1 (DMI) and type-2 (DMII) [5,6]. More than 90% of cases were diagnosed as DMII (non-insulin dependent diabetes mellitus; NIDDM). DMII is recognized by tissue resistance to the action of insulin combined with a reduction in insulin secretion because of resistance or deficiency against a beta cell that requires insulin to control the disease [6].

Diabetes mellitus has caused significant morbidity and mortality due to microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (heart attack, stroke and peripheral vascular disease) complications [7].

Thiazolidinediones (TZDs) are efficient DMII drug type [8]. Several TZDs' derivatives have been marketed for the treatment of DMII such as pioglitazone, rosiglitazone, ragaglitazar, balaglitazone [9] (Figure 1). Clinical studies showed that mixed therapy between α-glucosidase inhibitors and PPAR-γ-agonists (peroxisome proliferator-activated receptor [10–11] was a helpful strategy for treatment of DMII, as acarbose combined with pioglitazone, the first prevents NIDDM and reduces the cardiovascular problem [12] and the second acting on cardiovascular action and antiatherosclerosis [13-16].

Pioglitazone is a diabetes drug (thiazolidinedione-type, also called "glitazones") used along with a proper diet and exercise program to control high blood sugar in patients with type 2 diabetes. It works by helping to restore your body's proper response to insulin, thereby lowering your blood sugar.

In this work, considering these knowledge; in our continuation of our screening program to search for antidiabetic compounds [17], new thiazolidinone derivatives were synthesized, looking forward that would help to find new antidiabetic compounds bearing thiazolidine moiety.

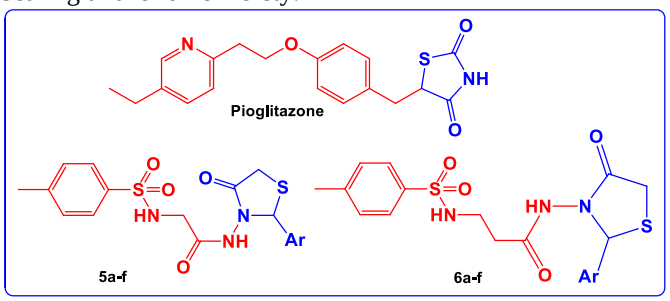


Figure 1: Designed molecules compliance of Pioglitazone pharmacophore.

2. Materials and methods

2.1. Chemistry

All melting points were determined on a Koffler melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C NMR spectra were recorded on a Bruker avance 400 MHz spectrometer using TMS as internal reference (chemical shifts in δ, ppm), and IR spectra were obtained on a Nicolet 710 FT-IR spectrometer (KBr, ν_{max} in cm^{-1}). Mass spectra were recorded on a GC-MSQP 1000EX Schimadzu at the Microanalytical laboratory, Cairo University, Cairo, Egypt.

Elemental analyses were recorded on Vario El Fab-Nr elemental analyzer (Cairo University).

2.1.1. Synthesis of ethyl 2-(4-methylphenyl-sulfonamido) acetate 1a:

Method A:

A round-bottomed flask fitted with a reflux condenser was charged with *p*-Toluenesulfonyl chloride (4.77 g, 25 mmol), potassium carbonate (4.14 g, 30 mmol) and dimethylsulfoxide (20 mL). The resulting suspension was heated to 50 °C and stirred for 2 hours then the resulting solution was cooled to room temperature and then treated with ethyl glycinate (2.58 mL, 25 mmol) in dimethylsulfoxide (5 mL) added dropwise. The mixture was heated to 50 °C and stirred until TLC showed full consumption of starting material. The mixture was cooled to room temperature, ice cold water (100 mL) added, the organic layer separated, and the aqueous layer extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with a 15 % aqueous solution of potassium hydroxide (100 mL), water (100 mL) and a saturated aqueous solution of sodium chloride (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo.

Method B: *p*-Toluenesulfonyl chloride (1.9 g, 10 mmol) was added to glycine (1.5 g, 20 mmol) dissolved in an aqueous solution of potassium carbonate (60 mmol, 50 mL). The reaction mixture was stirred at 100 ºC for 6 h, then left overnight at room temperature, filtered and then treated with dilute hydrochloric acid. The solid *N*-(4-methylbenzenesulfonyl)glycine obtained was crystallized from aqueous ethanol.

Sulfuric acid (0.5 mL) was added to *N*-(4-methylbenzene-sulfonyl)glycine (4.58 g, 20 mmol) dissolved in ethanol (30 mL) and the mixture was heated under reflux for 2-3 hrs. The reaction was monitored by TLC at regular intervals. After completion of the reaction, the reaction mixture was concentrated to remove excess ethanol. The product, *N*-(4-ethylbenzenesulfonyl) glycine methyl ester **1a** was poured into water, neutralized with sodium bicarbonate and recrystallized from acetone.

Synthesis of ethyl 3-(4-methylphenylsulfonamido)-propanoate 1b:

p-Toluenesulfonyl chloride (1.9 g, 10 mmol) was added to β-alanine (1.78 g, 20 mol) dissolved in an aqueous solution of potassium carbonate (0.06 mol, 50 ml). The reaction mixture was stirred at 100 ºC for 6 h, then left overnight at room temperature, filtered and then treated with dilute hydrochloric acid. The solid *N*-(4-methylbenzenesulfonyl)glycine obtained was crystallized from aqueous ethanol.

2.1.2. Synthesis of *N*-(2-hydrazinyl-2-oxoethyl)-4-methylbenzenesulfonamide 2a,b:

Compound **1a,b** (10 mmol) was added in small portions to a stirred solution of 85% hydrazine hydrate (3 mL) in 5 mL ethanol. The mixture was heated under reflux for 6 h. While cooling to room temperature, the resulting precipitate was filtered in vacuo, washed with cold water, and dried to give the corresponding hydrazide 2 as a white solid.

2a: Yield: 84%; m.p. 155–156 ºC.

2b: Yield: 65%; m.p. 170–172 ºC.

2.1.3. Synthesis ofv (*E*)-*N*-(2-(2-(arylmethylene)hydrazinyl)-2-oxoethyl)-4-methylbenzenesulfonamide 3a-h and (*E*)-*N*-(3-(2-(arylmethylene)hydrazinyl)-3-oxopropyl)-4-methyl-benzenesulfonamide 4a-h:

To a magnetically stirred suspension of compound **2a,b** (0.5 mmol) in anhydrous methanol (3 mL) was added the appropriate aldehyde (0.5 mmol). Shortly, the solution became homogeneous and within minutes the resulting hydrazone began to precipitate. After the mixture was stirred for 1–2 h more at room temperature, the precipitate was collected by filtration, washed with a small quantity of cold methanol and dried. Recrystallization of the reaction product from methanol gave the corresponding hydrazone.

2.1.4. Synthesis of 2-(4-methylphenylsulfonamido)-*N*-(4-oxo-2-aryylthiazolidin-3-yl)acetamide 5a-h and *N*-(2-aryl-4-oxothiazolidin-3-yl)-3-(4-methylphenylsulfonamido) prop-anamide 6a-h:

An equimolar amount (10 mmol) of the appropriate compound **3a-h** or **4a-h**, ethyl thioglycalate (1.1 mL, 10 mmol) in ethanol (20 mL) in the presence of pipredine (0.005 mol, 0.5 mL). The mixture was heated under reflux for 5 hours (monitored using a TLC), then poured into ice. The formed solid was collected by filtration and recrystallized from Ethanol.

2-(4-Methylphenylsulfonamido)-*N*-(4-oxo-2-phenylthiazolidin-3-yl)acetamide 5a:

Yield (2.8 g, 70%), pale gray crystals, m.p. 238 ºC, Anal. data: ($C_{18}H_{19}N_3O_4S_2$, 405.08): C, 53.32; H, 4.72; N, 10.36; S, 15.82. Found: C, 53.30; H, 5.09; N, 10.62; S, 15.57%. IR (υ_{max}, cm^{-1}): 3278, 3163 (2NH), 3024 ($CH_{aromatic}$), 2983 ($CH_{aliphatic}$), 1742 ($C{=}O_{thiazolidinone}$), 1678 (C=O), 1366, 1106 (S=O). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.32 (s, 3H, $CH_{3\ tosyl}$), 3.84 (s, 2H, $CH_{2glycine}$), 4.24 (s, 2H, $CH_{2Thiazolidinone}$), 5.30 (s, 1H, CH-Ar), 7.24 to 7.75 (m, 9H, ArH), 8.16 (s, 1H, NH, exchangeable by D_2O), 9.87 (s, 1H, NH, exchangeable by D_2O). ^{13}C NMR (DMSO-d_6), δ ppm: 22.1, 36.2, 46.8, 64.7, 126.3, 127.1, 128.3, 128.8, 129.5, 136.5, 136.9, 139.1, 168.4, 170.3.

2-(4-Methylphenylsulfonamido)-*N*-(4-oxo-2-*p*-tolyl-thiazolidin-3-yl)acetamide 5b:

Yield (3.2 g, 78%), pale yellow crystals, m.p. 245 ºC, Anal. data: ($C_{19}H_{21}N_3O_4S_2$, 419.1): C, 54.40; H, 5.05; N, 10.02; S, 15.29. Found: C, 53.96; H, 4.81; N, 9.68; S, 15.02%. IR (υ_{max}, cm^{-1}): 3270, 3168 (2NH), 3020 ($CH_{aromatic}$), 2980 ($CH_{aliphatic}$), 1740 ($C{=}O_{thiazolidinone}$), 1675 (C=O), 1365, 1108 (S=O). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.30 (s, 3H, CH_{3tolyl}), 2.34 (s, 3H, $CH_{3\ tosyl}$), 3.82 (s, 2H, $CH_{2glycine}$), 4.20 (s, 2H, $CH_{2Thiazolidinone}$), 5.34 (s, 1H, CH-Ar), 7.22 to 7.72 (m, 8H, ArH), 8.12 (s, 1H, NH, exchangeable by D_2O), 9.85 (s, 1H, NH, exchangeable by D_2O). ^{13}C NMR (DMSO-d_6), δ ppm: 21.8, 22.1, 36.3, 46.5, 64.6, 126.2, 127.3, 128.2, 128.7, 129.4, 136.6, 136.8, 139.2, 168.6, 170.1.

***N*-(2-(4-Chlorophenyl)-4-oxothiazolidin-3-yl)-2-(4-methyl-phenylsulfonamido)acetamide 5c:**

Yield (3.77 g, 86%), yellow needles, m.p. 228 ºC, Anal. data: ($C_{18}H_{18}ClN_3O_4S_2$, 439.94): C, 49.14; H, Cl, 8.06; 4.12; N, 9.55; S, 15.29. Found: C, 48.86; H, 3.85; Cl, 7.76; N, 9.68; S, 14.58%. IR (υ_{max}, cm^{-1}): 3276, 3162 (2NH), 3025 ($CH_{aromatic}$), 2982 ($CH_{aliphatic}$), 1744 ($C{=}O_{thiazolidinone}$), 1676 (C=O), 1366, 1112 (S=O). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.32 (s, 3H, CH_{3tosyl}), 3.86 (s, 2H, $CH_{2glycine}$), 4.24 (s, 2H, $CH_{2Thiazolidinone}$), 5.36 (s, 1H, CH-Ar), 7.28 to 7.77 (m, 8H, ArH), 8.15 (s, 1H,

NH, exchangeable by D_2O), 9.88 (s, 1H, NH, exchangeable by D_2O). ^{13}C NMR (DMSO-d_6), δ ppm: 22.1, 36.5, 46.3, 64.2, 126.1, 127.5, 128.1, 128.5, 129.5, 136.7, 136.5, 139.5, 168.7, 170.5.

***N*-(2-(4-(Dimethylamino)phenyl)-4-oxothiazolidin-3-yl)-2-(4-methylphenylsulfonamido)acetamide 5d:**

Yield (3.6 g, 80%), bright yellow needles, m.p. 212 ºC, Anal. data: ($C_{20}H_{24}N_4O_4S_2$, 448.56): C, 53.55; H, 5.39; N, 12.49; S, 14.30. Found: C, 53.05; H, 9.01; N, 12.20; S, 14.18%. IR (υ_{max}, cm^{-1}): 3266, 3172 (2NH), 3034 ($CH_{aromatic}$), 2976 ($CH_{aliphatic}$), 1752 ($C{=}O_{thiazolidinone}$), 1670 (C=O), 1369, 1111 (S=O). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.34 (s, 3H, CH_{3tolyl}), 3.04 (s, 6H, $2CH_3$), 3.82 (s, 2H, $CH_{2glycine}$), 4.21 (s, 2H, $CH_{2Thiazolidinone}$), 5.37 (s, 1H, CH-Ar), 6.98 to 7.74 (m, 8H, ArH), 8.14 (s, 1H, NH, exchangeable by D_2O), 9.80 (s, 1H, NH, exchangeable by D_2O). ^{13}C NMR (DMSO-d_6), δ ppm: 21.2, 35.8, 41.2, 46.8, 64.4, 126.2, 127.4, 128.3, 128.4, 129.4, 136.8, 136.0, 139.1, 168.5, 170.3. MS: m/z: 448.12 (100.0).

2-(4-Methylphenylsulfonamido)-*N*-(2-(naphthalen-1-yl)-4-oxothiazolidin-3-yl)acetamide 5e:

Yield (3.2g, 70%), gray crystals, m.p. 256 ºC, Anal. data: ($C_{22}H_{21}N_3O_4S_2$, 455.55): C, 58.00; H, 4.65; N, 9.22; S, 14.08. Found: C, 57.76; H, 4.24; N, 8.90; S, 13.78%. IR (υ_{max}, cm^{-1}): 3270, 3165 (2NH), 3028 ($CH_{aromatic}$), 2981 ($CH_{aliphatic}$), 1745 ($C{=}O_{thiazolidinone}$), 1672 (C=O), 1362, 1102 (S=O). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.34 (s, 3H, $CH_{3\ tosyl}$), 3.84 (s, 2H, $CH_{2glycine}$), 4.22 (s, 2H, $CH_{2Thiazolidinone}$), 5.35 (s, 1H, CH-Ar), 7.18-7.78 (m, 11H, ArH), 8.15 (s, 1H, NH, exchangeable by D_2O), 9.87 (s, 1H, NH, exchangeable by D_2O). ^{13}C NMR (DMSO-d_6), δ ppm: 21.3, 35.3, 46.8, 62.7, 126.3, 126.8, 127.1, 127.6, 128.3, 128.8, 129.2, 129.8, 136.2, 136.5, 136.9, 138.8, 139.1, 139.8, 168.0, 170.1. MS: m/z: 455.10 (100.0%).

***N*-(2-(3-Hydroxyphenyl)-4-oxothiazolidin-3-yl)-2-(4-methylphenylsulfonamido)acetamide 5f:**

Yield (3.2 g, 76%), yellow needles, m.p. 232 ºC, Anal. data: ($C_{18}H_{19}N_3O_5S_2$, 421.49): C, 51.29; H, 4.54; N, 9.97; S, 15.22. Found: C, 51.01; H, 4.23; N, 9.61; S, 14.98%. IR (υ_{max}, cm^{-1}): 3442 (OH), 3278, 3172 (2NH), 3018 ($CH_{aromatic}$), 2985 ($CH_{aliphatic}$), 1748 ($C{=}O_{thiazolidinone}$), 1678 (C=O), 1364, 1114 (S=O). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.32 (s, 3H, CH_{3tosyl}), 3.88 (s, 2H, $CH_{2glycine}$), 4.22 (s, 2H, $CH_{2Thiazolidinone}$), 5.34 (s, 1H, CH-Ar), 7.28-7.70 (m, 8H, ArH), 8.12 (s, 1H, NH, exchangeable by D_2O), 9.88 (s, 1H, NH, exchangeable by D_2O), 11.86 (br, 1H, 0H, exchangeable by D_2O). ^{13}C NMR (DMSO-d_6), δ ppm: 22.3, 36.6, 46.6, 64.5, 126.1, 127.5, 128.1, 128.5, 129.5, 136.0, 136.5, 139.5, 168.6, 170.6.

2-(4-Methylphenylsulfonamido)-*N*-(2-(3-nitrophenyl)-4-oxothiazolidin-3-yl)acetamide 5g:

Yield (3.15g, 70%), yellow crystals, m.p. 268 ºC, Anal. data: ($C_{18}H_{18}N_4O_6S_2$, 450.49): C, 47.99; H, 4.03; N, 12.44; S, 14.24. Found: C, 47.69; H, 3.82; N, 12.08; S, 14.00%. IR (υ_{max}, cm^{-1}): 3286, 3180 (2NH), 3027 ($CH_{aromatic}$), 2975 ($CH_{aliphatic}$), 1745 ($C{=}O_{thiazolidinone}$), 1674 (C=O), 1366, 1118 (S=O). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.34 (s, 3H, CH_{3tosyl}), 3.87 (s, 2H, $CH_{2glycine}$), 4.24 (s, 2H, $CH_{2Thiazolidinone}$), 5.36 (s, 1H, CH-Ar), 7.28-7.78 (m, 8H, ArH), 8.10 (s, 1H, NH, exchangeable by D_2O), 9.88 (s, 1H, NH, exchangeable by D_2O. ^{13}C NMR (DMSO-d_6), δ ppm: 22.2, 36.5, 46.3, 64.7, 126.2, 127.1, 128.1, 128.8, 129.5, 136.1, 136.8, 139.5, 168.6, 170.6. MS: m/z: 450.07 (100.0%).

(E)-2-(4-Methylphenylsulfonamido)-*N*-(4-oxo-2-styrylthiazolidin-3-yl)acetamide 5h:

Yield (3.2 g, 75%), pale yellow crystals, m.p. 266 ºC, Anal. data: ($C_{20}H_{21}N_3O_4S_2$, 431.53): C, 55.67; H, 4.91; N, 9.74; S, 14.86. Found: C, 55.40; H, 4.76; N, 9.48; S, 14.60%. IR (υ_{max}, cm^{-1}): 3270, 3168 (2NH), 3028, 3012 ($CH_{aromatic}$), 2982 ($CH_{aliphatic}$), 1745 ($C{=}O_{thiazolidinone}$), 1678 (C=O), 1366, 1112 (S=O). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.34 (s, 3H, CH_{3tosyl}), 3.86 (s, 2H, $CH_{2glycine}$), 4.24 (s, 2H, $CH_{2Thiazolidinone}$), 5.37 (s, 1H, CH-Ar), 6.19 (m, 1H, $CH_{olefinic}$), 6.26 (d, 1H, $CH_{2Thiazolidinone}$), 7.18 to 7.75 (m, 9H, ArH), 8.10 (s, 1H, NH, exchangeable by D_2O), 9.88 (s, 1H, NH, exchangeable by D_2O). ^{13}C NMR (DMSO-d_6), δ ppm: 21.8, 22.1, 36.3, 46.5, 64.6, 121.2, 123.5, 126.1, 127.4, 128.2, 128.6, 129.4, 136.1, 136.6, 139.4, 168.5, 170.4. MS: m/z: 431.10 (100.0%).

3-(4-Methylphenylsulfonamido)-*N*-(4-oxo-2-phenylthiazolidin-3-yl)propanamide 6a:

Yield (3.14 g, 75%), yellow needles, m.p. 246 ºC, Anal. data: ($C_{19}H_{21}N_3O_4S_2$, 419.52): C, 54.40; H, 5.05; N, 10.02; S, 15.29. Found: C, 54.16; H, 4.83; N, 9.91; S, 14.98%. IR (υ_{max}, cm^{-1}): 3271, 3175 (2NH), 3012 ($CH_{aromatic}$), 2980 ($CH_{aliphatic}$), 1743 ($C{=}O_{thiazolidinone}$), 1670 (C=O), 1365, 1114 (S=O). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.32 (s, 3H, CH_{3tosyl}), 2.42 (t, 2H, $CH_{2alanine}$), 3.88 (s, 2H, $CH_{2alanine}$), 4.24 (s, 2H, $CH_{2Thiazolidinone}$), 5.35 (s, 1H, CH-Ar), 7.25-7.77 (m, 9H, ArH), 8.15 (s, 1H, NH, exchangeable by D_2O), 9.85 (s, 1H, NH, exchangeable by D_2O). ^{13}C NMR (DMSO-d_6), δ ppm: 22.3, 36.2, 37.3, 46.5, 64.5, 126.1, 127.5, 128.1, 128.5, 129.5, 136.0, 136.5, 139.5, 168.6, 170.6. MS: m/z: M^{+1} 420 (11.0%).

3-(4-Methylphenylsulfonamido)-*N*-(4-oxo-2-*p*-tolylthiazolidin-3-yl)propanamide 6b:

Yield (3.33 g, 77%), pale yellow needles, m.p. 255 ºC, Anal. data: ($C_{20}H_{23}N_3O_4S_2$, 433.54): C, 55.41; H, 5.35; N, 9.69; S, 14.79. Found: C, 55.16; H, 5.03; N, 9.38; S, 14.44%. IR (υ_{max}, cm^{-1}): 3278, 3177 (2NH), 3018 ($CH_{aromatic}$), 2985 ($CH_{aliphatic}$), 1748 ($C{=}O_{thiazolidinone}$), 1676 (C=O), 1368, 1116 (S=O). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.30 (s, 3H, CH_{3tosyl}), 2.34 (s, 3H, CH_{3tolyl}), 2.40 (t, 2H, $CH_{2alanine}$), 3.86 (s, 2H, $CH_{2alanine}$), 4.20 (s, 2H, $CH_{2Thiazolidinone}$), 5.33 (s, 1H, CH-Ar), 7.22-7.70 (m, 8H, ArH), 8.12 (s, 1H, NH, exchangeable by D_2O), 9.83 (s, 1H, NH, exchangeable by D_2O). ^{13}C NMR (DMSO-d_6), δ ppm: 22.3, 36.1, 36.8, 37.7, 46.1, 64.8, 126.1, 127.3, 128.2, 128.6, 129.8, 136.1, 136.6, 139.7, 168.2, 170.4. MS: m/z: M^{+1}435 (4.0%).

***N*-(2-(4-Chlorophenyl)-4-oxothiazolidin-3-yl)-3-(4-methylphenylsulfonamido)propanamide 6c:**

Yield (3.7 g, 82%), yellow needles, m.p. 248 ºC, Anal. data: ($C_{19}H_{20}ClN_3O_4S_2$, 453.96): C, 50.27; H, 4.44; Cl, 7.81, N, 9.26; S, 14.13. Found: C, 50.05; H, 4.13; Cl, 7.55, N, 9.02; S, 13.87%. IR (υ_{max}, cm^{-1}): 3277, 3170 (2NH), 3025 ($CH_{aromatic}$), 2981 ($CH_{aliphatic}$), 1745 ($C{=}O_{thiazolidinone}$), 1677 (C=O), 1365, 1111 (S=O). ^{1}H-NMR (DMSO-d_6), δ ppm: 2.32 (s, 3H, CH_{3tosyl}), 2.41 (t, 2H, $CH_{2alanine}$), 3.88 (s, 2H, $CH_{2alanine}$), 4.24 (s, 2H, $CH_{2Thiazolidinone}$), 5.35 (s, 1H, CH-Ar), 7.28-7.75 (m, 8H, ArH), 8.16 (s, 1H, NH, exchangeable by D_2O), 9.85 (s, 1H, NH, exchangeable by D_2O). ^{13}C NMR (DMSO-d_6), δ ppm: 22.3, 36.1, 36.8, 37.7, 46.1, 64.8, 126.1, 127.3, 128.2, 128.6,

129.8, 136.1, 136.6, 139.7, 168.2, 170.4. MS: m/z: M^{+2}455 (12.0%).

***N*-(2-(4-(Dimethylamino)phenyl)-4-oxothiazolidin-3-yl)-3-(4-methylphenylsulfonamido)propanamide 6d:**

Yield (3.8 g, 82%), yellow needles, m.p. 248 ºC, Anal. data: ($C_{21}H_{26}N_4O_4S_2$, 462.59): C, 54.52; H, 5.67; N, 12.11; S, 13.86. Found: C, 54.22; H, 5.33; N, 11.85; S, 13.57%. IR (υ_{max}, cm^{-1}): 3278, 3172 (2NH), 3022 ($CH_{aromatic}$), 2984 ($CH_{aliphatic}$), 1748 ($C{=}O_{thiazolidinone}$), 1675 (C=O), 1362, 1113 (S=O). ^{1}H-NMR (DMSO-d$_6$), δ ppm: 2.32 (s, 3H, CH_{3tosyl}), 2.41 (t, 2H, $CH_{2alanine}$), 3.06 (s, 6H, $2CH_3$), 3.86 (s, 2H, $CH_{2alanine}$), 4.22 (s, 2H, $CH_{2Thiazolidinone}$), 5.36 (s, 1H, CH-Ar), 7.25-7.77 (m, 8H, ArH), 8.15 (s, 1H, NH, exchangeable by D_2O), 9.84 (s, 1H, NH, exchangeable by D_2O). ^{13}C NMR (DMSO-d$_6$), δ ppm: 22.3, 36.1, 36.8, 37.7, 46.1, 64.8, 126.1, 127.3, 128.2, 128.6, 129.8, 136.1, 136.6, 139.7, 168.2, 170.4. MS: m/z: M^{+1}462 (5.8%).

3-(4-Methylphenylsulfonamido)-*N*-(2-(naphthalen-1-yl)-4-oxothiazolidin-3-yl)propanamide 6e:

Yield (3.5 g, 75%), yellow needles, m.p. 218 ºC, Anal. data: ($C_{23}H_{23}N_3O_4S_2$, 469.58): C, 58.83; H, 4.94; N, 8.95; S, 13.66. Found: C, 58.46; H, 4.66; N, 8.60; S, 13.35%. IR (υ_{max}, cm^{-1}): 3275, 3162 (2NH), 3025 ($CH_{aromatic}$), 2982 ($CH_{aliphatic}$), 1748 ($C{=}O_{thiazolidinone}$), 1678 (C=O), 1366, 1118 (S=O). ^{1}H-NMR (DMSO-d$_6$), δ ppm: 2.34 (s, 3H, CH_{3tosyl}), 2.40 (t, 2H, $CH_{2alanine}$), 3.86 (s, 2H, $CH_{2alanine}$), 4.22 (s, 2H, $CH_{2Thiazolidinone}$), 5.36 (s, 1H, CH-Ar), 7.18-7.78 (m, 11H, ArH), 8.10 (s, 1H, NH, exchangeable by D_2O), 9.88 (s, 1H, NH, exchangeable by D_2O). ^{13}C NMR (DMSO-d$_6$), δ ppm: 22.3, 36.2, 37.3, 46.5, 64.5, 125.6, 126.1, 126.8, 127.5, 128.1, 128.5, 129.3, 129.8, 136.0, 136.5, 137.2, 137.8, 139.1, 139.5, 168.0, 170.3. MS: m/z: M^{+1} 470 (7.0%).

***N*-(2-(3-Hydroxyphenyl)-4-oxothiazolidin-3-yl)-3-(4-methylphenylsulfonamido)propanamide 6f:**

Yield (3.4 g, 78%), yellow needles, m.p. 232 ºC, Anal. data: ($C_{19}H_{21}N_3O_5S_2$, 435.52): C, 52.40; H, 4.86; N, 9.65; S, 14.73. Found: C, 52.15; H, 4.53; N, 9.41; S, 14.48%. IR (υ_{max}, cm^{-1}): 3445 (OH), 3273, 3166 (2NH), 3020 ($CH_{aromatic}$), 2981 ($CH_{aliphatic}$), 1746 ($C{=}O_{thiazolidinone}$), 1675 (C=O), 1366, 1115 (S=O). ^{1}H-NMR (DMSO-d$_6$), δ ppm: 2.34 (s, 3H, CH_{3tosyl}), 3.88 (s, 2H, $CH_{2alanine}$), 3.86 (s, 2H, $CH_{2alanine}$), m4.24 (s, 2H, $CH_{2Thiazolidinone}$), 5.35 (s, 1H, CH-Ar), 7.28-7.72 (m, 8H, ArH), 8.15 (s, 1H, NH, exchangeable by D_2O), 9.86 (s, 1H, NH, exchangeable by D_2O), 11.88 (br, 1H, 0H, exchangeable by D_2O). ^{13}C NMR (DMSO-d$_6$), δ ppm: 22.1, 36.5, 37.3, 46.5, 64.5, 126.1, 127.4, 128.2, 128.5, 129.4, 1361, 136.3, 139.4, 168.5, 170.4.

3-(4-Methylphenylsulfonamido)-*N*-(2-(3-nitrophenyl)-4-oxothiazolidin-3-yl)propanamide 6g:

Yield (3.2g, 70%), yellow crystals, m.p. 272 ºC, Anal. data: ($C_{19}H_{20}N_4O_6S_2$, 464.52): C, 49.13; H, 4.34; N, 12.06; S, 13.81. Found: C, 48.89; H, 3.22; N, 11.88; S, 13.55%. IR (υ_{max}, cm^{-1}): 3288, 3185 (2NH), 3027 ($CH_{aromatic}$), 2977 ($CH_{aliphatic}$), 1748 ($C{=}O_{thiazolidinone}$), 1678 (C=O), 1366, 1115 (S=O). ^{1}H-NMR (DMSO-d$_6$), δ ppm: 2.34 (s, 3H, CH_{3tosyl}), 3.87 (s, 2H, $CH_{2alanine}$), 3.86 (s, 2H, $CH_{2alanine}$), 4.24 (s, 2H, $CH_{2Thiazolidinone}$), 5.35 (s, 1H, CH-Ar), 7.28-7.78 (m, 8H, ArH), 8.10 (s, 1H, NH, exchangeable by D_2O), 9.88 (s, 1H, NH, exchangeable by D_2O. ^{13}C NMR (DMSO-d$_6$), δ ppm: 22.2, 36.5, 37.3, 46.3, 64.7, 126.2, 127.1, 128.1, 128.8, 129.5, 136.1, 136.8, 139.5, 168.6, 170.6. MS: m/z: M^{+1}465.07 (100.0%).

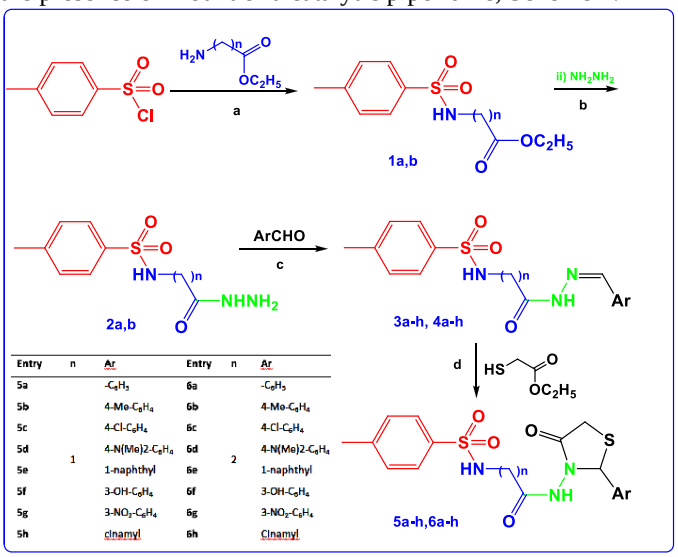
(E)-3-(4-Methylphenylsulfonamido)-*N*-(4-oxo-2-styrylthiazolidin-3-yl)propanamide 6h:

Yield (3.1 g, 70%), pale yellow crystals, m.p. 262 ºC, Anal. data: ($C_{21}H_{23}N_3O_4S_2$, 445.56): C, 56.61; H, 5.20; N, 9.43; S, 14.39. Found: C, 56.40; H, 4.96; N, 9.25; S, 14.00%. IR (υ_{max}, cm^{-1}): 3274, 3166 (2NH), 3025, 3022 ($CH_{aromatic}$), 2980 ($CH_{aliphatic}$), 1748 ($C{=}O_{thiazolidinone}$), 1675 (C=O), 1368, 1116 (S=O). ^{1}H-NMR (DMSO-d$_6$), δ ppm: 2.34 (s, 3H, CH_{3tosyl}), 3.86 (s, 2H, $CH_{2alanine}$), 3.86 (s, 2H, $CH_{2alanine}$), 4.24 (s, 2H, $CH_{2Thiazolidinone}$), 5.37 (s, 1H, CH-Ar), 6.19 (m, 1H, $CH_{olefinic}$), 6.26 (d, 1H, $CH_{2Thiazolidinone}$), 7.18 to 7.75 (m, 9H, ArH), 8.10 (s, 1H, NH, exchangeable by D_2O), 9.88 (s, 1H, NH, exchangeable by D_2O). ^{13}C NMR (DMSO- d$_6$), δ ppm: 21.8, 22.1, 36.3, 37.2, 46.5, 64.6, 121.2, 123.5, 126.1, 127.4, 128.2, 128.6, 129.4, 136.1, 136.6, 139.4, 168.5, 170.4. MS: m/z: M^{+1}465.10 (8.0%).

3. Results and Discussion:

3.1. Chemistry

The synthetic strategy for the title compounds **5a–h** and **6a-h** are described in Scheme 1. The *p*-toluenesulfonyl chloride was first reacted with ethyl glycinate hydrochloride or β-alanine under two different experimental conditions (see experimental section), to give the key intermediate methyl N-(4-toluenesulfonyl)-glycinate **1a** and/or ethyl 3-(4-methylphenylsulfonamido)propanoate **1b** in good yields. This intermediate compunds **1a,b** were then converted to their corresponding hydrazides **2a,b** by refluxing with hydrazine hydrate in ethanol. The condensation of the hydrazide **2a,b** with various aromatic aldehydes and ketones in methanol afforded the title compounds **3a–h** and **4a-h**, respectively. The precursors arylsulfonylaminoacetic acid hydrazide **2a,b** and their corresponding hydrazones **3a-h** and **4a-h** were prepared according to the literature methods [18-21]. Thiazolidinone derivatives **5a-h** and **6a-h** were obtained from the reaction of Schiff bases **3a–h** and **4a-h** with ethyl glycolate in ethanol in the presence of mount of a catalytic piperidine, Scheme 1.

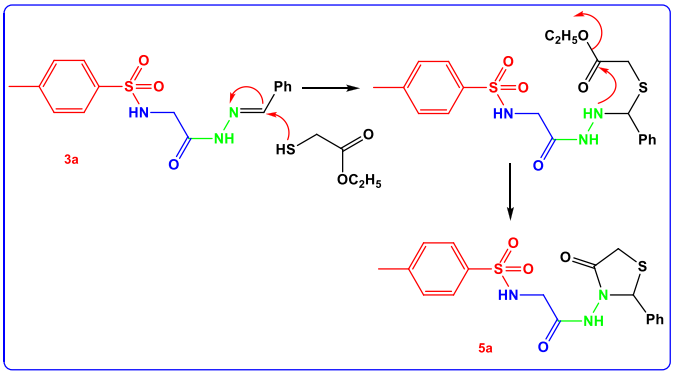


Entry	n	Ar	Entry	n	Ar
5a	1	-C_6H_5	6a	2	-C_6H_5
5b		4-Me-C_6H_4	6b		4-Me-C_6H_4
5c		4-Cl-C_6H_4	6c		4-Cl-C_6H_4
5d		4-N(Me)2-C_6H_4	6d		4-N(Me)2-C_6H_4
5e		1-naphthyl	6e		1-naphthyl
5f		3-OH-C_6H_4	6f		3-OH-C_6H_4
5g		3-NO_2-C_6H_4	6g		3-NO_2-C_6H_4
5h		cinamyl	6h		Cinamyl

Scheme 1: Synthesis of Thiazolidinone derivatives.

The reaction mechanism of the formation of Thiazolidinone derivatives was assumed to proceed via a preliminary nucleophilic attack of ethyl mercaptoacetate thiol group onto the imine function group in the Schiff base **3a** followed by another intramolecular nucleophilic attack of of NH group to the ester carbonyl group and subsequent elimination os ethanol molecules and formation of thiazolidinone ring **5a**, Scheme 2.

The structures of the newly synthesized thizolidinone derivatives were elucidated based on their IR, ^{1}H-NMR, ^{13}C-MRand elemental analyses. The IR spectra of the obtained compounds exhibited the presence of two NH groups at 3311 to 3150 cm^{-1}. Also a new peak was revealed a strong peak at 1725 to 1710 for C=O of thiazolidinone ring, other peak at 1685 to 1665 for amidic C=O group. Another peak at 11363 to 1106 cm^{-1} corresponding to S=O groups. In addition, the ^{1}H-NMR spectra revealed the appearance of new singlet for CH_{3tosyl} group in the range 2.32 to 2.36 ppm. A new singlet signal was found in the range 3.60 to 3.82 ppm due to the $CH_{2glycine}$ group, another singlet signal at 4.12-4.25 ppm for $CH_{2thiazolidinone}$. D_2O exchangeable peaks at 8.12 and 9.75 for NH groups. ^{13}C-NMR spectra of the obtained compounds showed the appearance of new signals at range δ 21.61 to 21.32 ppm due to CH_{3tosyl} group, which confirmed the expected structure of sulfonamides.



Scheme 2. The suggested reaction mechanism of the formation of thiazolidinone deivatives.

3.2. Biological screening

In vitro antidiabetic study (Inhibition of α-amylase enzyme)

Starch solution (0.1%) was prepared by dissolving 0.1 g of starch in 100 mL of sodium acetate buffer (pH = 4.8, 16 mM). An enzyme solution was prepared by dissolving 27.5 mg of α-amylase in 100 mL of deionized H_2O. A colorimetric reagent was prepared by dissolving 1 g of 3,5-dinitro salicylic acid in deionized H_2O (20 mL) and 0.16 g sodium hydroxide (in 10 mL deionized H_2O) and 4 g of sodium potassium tartrate was added gradually to the mixture. The mixture was mixed well and the volume was made up to 100 mL using deionized H_2O. Both control (100 µL) and the TZD derivatives (100 µL) were separately mixed with the starch solution (100 µL) and left for 30 minutes to react with the α-amylase solution (under alkaline conditions at 25 ºC). The action was recorded after 5 minutes. The liberated maltose was measured quantitatively by the reduction of 3,5-dinitro salicylic acid to 3-amino-5-nitrosalicylic acid. This reaction was measured at 540 nm. [22–24].

All the synthesized compound(s) were tested for their *in vitro* antidiabetc potential at different concentrations from 6.25 to 100 mg/dL by using enzymes α-amylase in order to check their percent inhibition. All compound(s) shows dose dependent increase in percentage inhibition. The synthesized thiazolisdinone derivatives showed significant activity (98.0%, 97.56%, and 75.90%) against α-amylase enzyme at different concentrations. The results of the experiment are summarized in Table 1 and Figure 2.

Table 1: Effect of Some Thiazolidinone Derivatives (TZDs) on Glucose Diffusion.

Compound	Absorbance				
	6.25 mg/dL	12.5 mg/dL	25 mg/dL	50 mg/dL	100 mg/dL
Glitazone	0.258	0.315	0.376	0.420	0.488
5a	0.200	0.288	0.360	0.390	0.421
5b	0.229	0.260	0.345	0.426	0.468
5c	0.203	0.255	0.320	0.387	0.478
5d	0.170	0.205	0.243	0.295	0.366
5e	0.210	0.252	0.334	0.415	0.455
5f	0.225	0.275	0.355	0.432	0.480
5g	0.205	0.260	0.348	0.422	0.467
5h	0.225	0.263	0.341	0.429	0.470
6b	0.134	0.189	0.239	0.288	0.345
6c	0.108	0.156	0.202	0.239	0.267
6d	0.129	0.188	0.225	0.271	0.340
6e	0.125	0.175	0.202	0.255	0.303

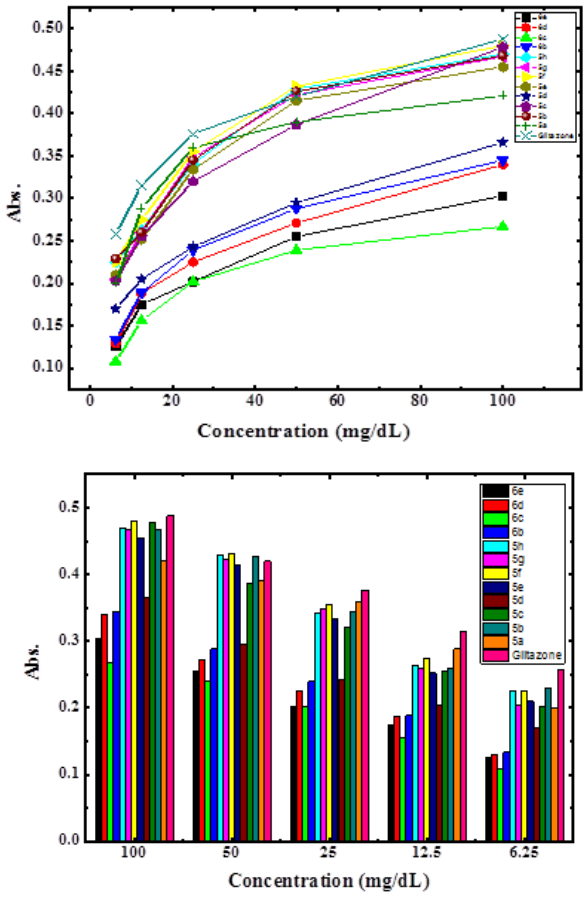


Fig. 2: Inhibition efficiency of α-amylase enzyme of the synthesized compounds compared to glitazone

4. Conclusion

A series of novel TZD **5a-h** and **6b-e** derivatives were synthesized from N-(2-(2-benzylidenehydrazinyl)-2-oxoethyl)-4-methylbenzenesulfonamide or N-(3-(2-benzylidene-hydrazinyl)-3-oxopropyl)-4-methylbenzenesulfonamide triazole derivatives 1a-h under green chemistry conditions. The aforementioned compounds exhibited significant *in vitro* antidiabetic activity. Structures of the newly obtained compounds were characterized based on their spectral and elemental data.

CRediT authorship contribution statement:

Conceptualization, Mounir A. A. Mohamed and Ahmed M. M. El-Saghier; methodology Mounir A. A. Mohamed and Moshira Helmy Fouad; software, Mounir A. A. Mohamed and Moshira Helmy Fouad; validation, Mounir A. A. Mohamed, Moshira Helmy Fouad and Ahmed M. M. El-Saghier; formal analysis, Mounir A. A. Mohamed, Moshira Helmy Fouad and Ahmed M. M. El-Saghier; investigation Mounir A. A. Mohamed, Moshira Helmy Fouad and Ahmed M. M. El-Saghier; resources, Mounir A. A. Mohamed, Moshira Helmy Fouad and Ahmed M. M. El-Saghier; data curation Mounir A. A. Mohamed and Moshira Helmy Fouad; writing—review and editing, Mounir A. A. Mohamed; supervision, Mounir A. A. Mohamed, and Ahmed M. M. El-Saghier; project administration, Mounir A. A. Mohamed; Antimicrobial Activity, Mounir A. A. Mohamed. All authors have read and agreed to the published version of the manuscript.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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