Bioorganic Chemistry 92 (2019) 103290

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

Synthesis, structural characterization and *in vivo* anti-diabetic evaluation of some new sulfonylurea derivatives in normal and silicate coated nanoparticle forms as anti-hyperglycemic agents

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ARTICLE INFO

Keywords:
Diabetes mellitus
Sulfonylurea
Gliclazide
Diamicron
Anti-diabetic drug

ABSTRACT

Series of new sulfonylurea derivatives (gliclazide analogues) was synthesized and characterized. Thus, *p*-tolylsulfonylisocyanate was left to react with different amino derivatives under mild conditions to afford the desired sulfonylurea derivatives **1–5**. The molecular structure of the compound *N*-(2,6-Dichlorophenylcarbamoyl)-4-methylbenzenesulfonamide, **1c** has been elucidated by single crystal X-ray diffraction. Anti-diabetic properties of the synthesized compounds relative to anti-diabetic drug (gliclazidem MR60) were carried out, where most of the tested compounds showed significant activity for reducing the blood glucose level. The results revealed that compounds **1c** and **5** showed better anti-diabetic activities compared with gliclazide. Activity of the most potent derivatives of sulfonylurea compounds namely **1c** and **5** were increased using coated nanostructure tetraethyl orthosilicate (TEOS) as a modified release (MR) agent. The effect of the prepared sulfonylurea compounds against the diabetic condition was investigated using specific selected biomarkers as of liver enzyme activities as transaminases (AST, ALT) and alkaline phosphatase (ALP), lipids profiles; total cholesterol (TC), triacylglycerols (TG) and total lipid (TL). The antioxidants, oxidative stress biomarkers and histological examination were also examined and discussed.

1. Introduction

Diabetes mellitus is metabolic disease where human have high blood sugar. This increase in blood sugar level is either due to presence of insufficient insulin, or because the cells do not respond to the produced insulin [1]. The high blood sugar produces symptoms such as frequent urination, increased thirst and increased hunger. Diabetic human without treated suffer from many acute and chronic complications. Some of acute complications are diabetic ketoacidosis and nonketotic hyperosmolar coma. Some of chronic complications are chronic renal failure, cardiovascular disease, and diabetic retinal damage. So, treatment of diabetes is very important.

Many useful drugs have been developed and they are sometime appropriate to avoid troubles caused by sensitivity to insulin. Sulfonylurea drugs are one of the first widely used oral anti-diabetic drugs and in the medical community sulfonylurea drugs were used as complementary to metformin. They prevent the long-term complications of diabetes, which caused by changes in the blood vessels. Sulfonylurea drug (such as gliclazide) help to stimulate the pancreas to secrete insulin. Gliclazide is an oral hypoglycemic drug and classified as a first and second-generation sulfonylurea [2,3]. Gliclazide protect human pancreatic β-cells from hyperglycemia-induced apoptosis [4] and prevents accumulation of fat in arteries in type 2 diabetes [5].

Accordingly, and in a connection with our previous works on organic and organometallic compounds in conjunction to our interest in preparation of bioactive molecule [6–13], the present study is directed to prepare derivatives of some new sulfonylurea compounds as gliclazide analogues that may be useful for treatment of diabetes.

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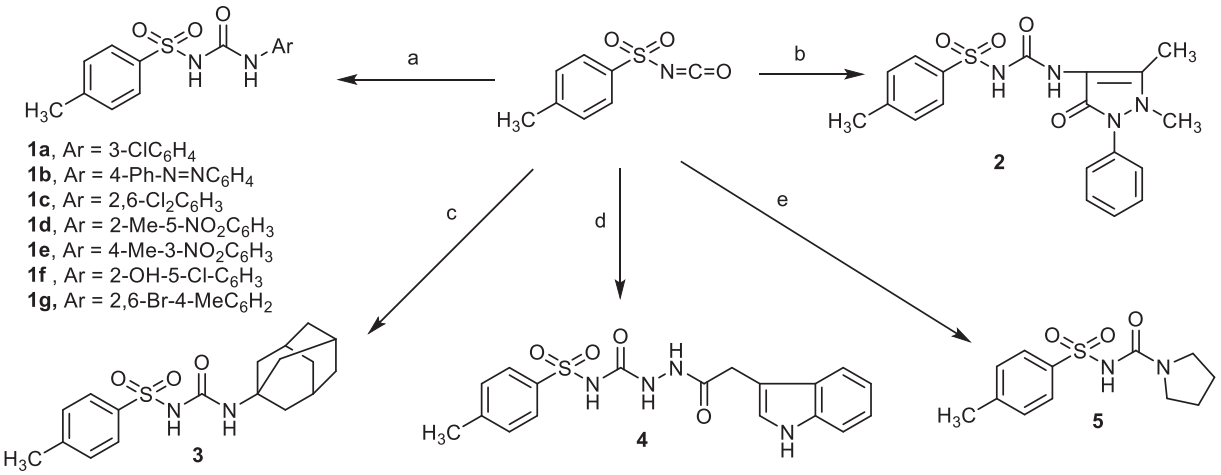
https://doi.org/10.1016/j.bioorg.2019.103290
Received 10 February 2019; Received in revised form 30 July 2019; Accepted 16 September 2019
Available online 18 September 2019
0045-2068/



Scheme 1. Synthesis of sulfonylurea derivatives. Reagents: (a) aniline derivatives, (b) 4-aminoantipyrine, (c) 1-adamantylamine, (d) 2-(1*H*-indol-3-yl) acetohydrazide, (e) pyrrolidine.

2. Results and discussion

2.1. Chemistry

p-Tolylsulfonylisocyanate was used as a precursor for the synthesis of different types of sulfonylurea derivatives *via* nucleophilic addition reaction under mild conditions. Different substituents on phenyl moiety were applied for discussing their effect on the anti-diabetic activity. Thus, when *p*-tolylsulfonylisocyanate was left to react with mono-, di-, and tri-substitued anilines, the corresponding sulfonylurea derivatives **1a-g** were afforded in good yields (Scheme 1). Also, upon reacting *p*-tolylsulfonylisocyanate with 4-amino-antipyrine, the sulfonylurea derivative bearing a pyrazole moiety **2** was obtained. To obtain another sulfonylurea derivative, *p*-tolylsulfonylisocyanate was left to react with 1-adamantylamine to afford sulfonylurea derivative **3**. Also, upon reacting *p*-tolylsulfonylisocyanate with 2-(1*H*-indol-3-yl)acetohydrazide gave and pyrrolidine, the corresponding sulfonylurea derivative **4** and **5** were obtained, respectively.

Structures of the synthesized sulfonylurea derivatives were confirmed by careful studying of their infrared IR, NMR as well as elemental analyses. IR spectrum of products **1a-g** revealed the NH peaks in the regions 3433–3269 and 3283–3198 cm^{-1}, carbonyl peaks at 1698–1671 cm^{-1} region and SO_2 at 1353–1344 and 1197–1149 cm^{-1} regions. ^1H NMR spectra of all the obtained products supported these assignments and added a strong evidence for these interpretations. ^1H NMR spectrum of compound **5**, as representative example, was characterized by the presence of two signals at: $\delta = 1.77$ and 3.25 ppm corresponding for pyrrolidine protons. A single signal at 2.39 ppm was observed for the methyl protons. Beside the latter three aliphatic signals, the ^1H NMR spectrum of compound **5** exhibited two douplet signals for AB aromatic protons at: 7.38 and 7.82 ppm with two proton integral value which are assigned to protons at C-2,6 and C-3,5 carbons of *p*-tolyl moiety. The broad exchangeable single at 10.41 ppm is assigned for the imine proton. The ^{13}C NMR spectra of all the obtained products supported these assignments and added a strong evidence for these interpretations. ^{13}C NMR spectrum of compound **5**, as representative example, showed three signals in the aliphatic region. The signals at 21.4, 25.2 and 46.3 ppm are due to pyrrolidine and methyl carbons. The signals resonated at: 128.0 and 129.5 ppm are assigned to 4CH carbons, while the signals resonated at 138.6 and 143.6 ppm are assigned to 2C carbons. The signals resonated in the deshielded region at 150.9 ppm is assigned to C═O carbon.

The sufonylurea derivative **1c** crystallizes from ethylacetate in the monoclinic space group P 1 21/n 1 with four molecules in the unit cell. The bond lengths of S1−O2 and S1−O3 are 1.430 (2) Å and 1.423 (3) Å, respectively, and the distances of S1−N1 and S1−C5 are 1.650 (2) Å and 1.754 (2) Å, respectively. The N1−C6, C6−N2 and C6−O1 bond lengths are 1.393 (3) Å, 1.340 (3) Å and 1.227 (3) Å, respectively. The bon angles of the S1−N1−C6, N1−C6−N2, N1−S1−C5 and C6−N2−C7 are 129.72(17)°, 117.7(2)°, 105.64(11)° and 121.5(2)°, respectively. On the other hand, the bond angles of O3−S1−C5 and O2−S1−C5 have the same value 108.31(12)° and 108.80(12)°, respectively. In the same manner, the bond angles of N1−S1−O3 and N1−S1−C5 have the same value 105.34(11)° and 105.64(11)°, respectively. The torsion angles of the plans S1N1C6N2 and C5S1N1C6 are 11.54° and 85.70°, respectively. Therefore the geometry sphere around the sulfer ion could illustrate as *pseudo*-tetrahedral. These values are well comparable to those found in sulfamethoxazole [14] as depicted in Fig. 1.

2.2. Preparation of silicate coated particles of 1c and 5 by TEOS

Although, some of these compounds are appeared very useful in their actual prepared form, we need to determine their effects in nanoscale in a trail to reduce the effective dose, prevent side effects, augments their effects without any hazards for the dose and allow the compounds to penetrate arteries and interact with beta cells receptors through their nanoforms. Compound **1c** exhibited particle size around 1204 nm, while after coating with tetraethyl orthosilicate (TEOS) *via* sol-gel technique, it was 427 nm. On the other hand, compound **5** exhibited particles size around 256 nm, after coating with tetraethyl orthosilicate (TEOS) it becomes about 115 nm (Table 1). Therefore, we can conclude that the prepared silicate coated particles showed stable particles with particle size in nanoscale. The compounds of silicate coated *via* the technique of sol-gel led to enhancement of their effect, through their easily penetrate to pancreas with the completely dose to

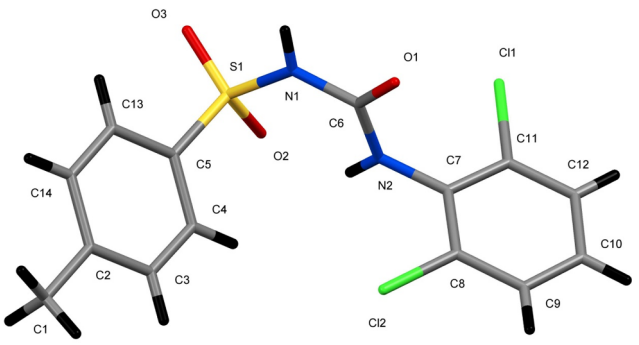


Fig. 1. X-ray crystal structure of *N*-(2,6-Dichlorophenylcarbamoyl)-4-methylbenzene-sulfonamide, **1c**.

Table 1
Particle size distribution analysis using DLS technique.

Sample code	Particle size (d·nm)	PDI
1c	1204.00 ± 70.00*	0.575
1c coated with TEOS	427.00 ± 30.40	1.00
5	256.00 ± 6.60*	0.329
5 coated with TEOS	115.00 ± 10.60	1.00

Statistical analysis is carried out using paired T-test computer program, where * is highly significant at P ≤ 0.0001.

stimulate insulin secretion. Also, these formulated nanoparticles may be interact with the receptors of the remaining β-cells of pancreas and protect them from oxidative -induced apoptosis [4]. Furthermore, the nano-compounds can be transfuse and succeed in forcing a way into fine arteries, prevent accumulation of fat diabetes type 2 [5]. The obtained data was confirmed by SEM-micrographs for the compounds **1c** and **5** in comparison with the coated ones. SEM images of compound **1c** showed needle-like shape particles, while after coating; it was observed stable spherical-like shape structure. On the other hand, compound **5** showed rough surface with rigid particles, while after coating with TEOS, it was observed soft brittle particles. The aforementioned results proved that silicate coated compounds *via* sol-gel technique could be successful prepared with different morphologies that led to enhancement of their different applications.

2.3. Evaluation of the biological activity

2.3.1. Streptozotocin-induced hyperglycemia

Streptozotocin with certain dose cause partially pancreatic β-cells damage. In addition, breakdown of glycogen from liver is responsible for the enhancement in gluconeogensis. Anti-diabetic properties of the synthesized sulfonyl urea derivatives were carried out. From the obtained results it was noticed that, compounds **1c** and **5** recorded significant reduction in blood glucose level compared to diabetic rats with highest reduction in blood glucose level in comparison with that of standard drug (gliclazide, MR60), which is classified as a third generation sufonylurea derivatives [15]. Additionally, an insignificant difference in blood glucose level was observed for the other tested compounds (Table 2). Percentages of improvement in blood glucose level of our synthesized anti-diabetic compounds and gliclazide as reference drug (Fig. 2).

$$\text{Percentage Change} = \frac{Mean\ of\ treated - Mean\ of\ control}{Mean\ of\ control} \text{X100}$$

Table 2
Effects of different synthesized compounds on blood glucose level in STZ induced diabetic rats.

Groups	Parameters		
	Blood glucose level (mg/dL)	% Change	% Improvement
Control	90.60 ± 5.90f	–	–
Diabetic	389.80 ± 9.77 g	330.24	–
1b	365.20 ± 7.25 g	303.09	27.15
1c	213.60 ± 9.90 h	135.76	194.48
1f	345.80 ± 8.70 g	281.68	48.56
1 g	348.80 ± 12.50 g	284.99	45.25
2	328.24 ± 6.70 g	262.29	67.95
3	329.00 ± 10.20 g	263.13	67.11
5	200.6 ± 11.27 h	121.41	208.83
Gliclazide	269.60 ± 10.17e	197.57	132.67

Data are given in mean ± SD from 10rats in each group. Values in parentheses represent % of improvements from control. Statistical analysis are carried out using one way analysis of variance (ANOVA) using Co-Stat Computer program, where unshared letters are significant at $p \leq 0.05$.

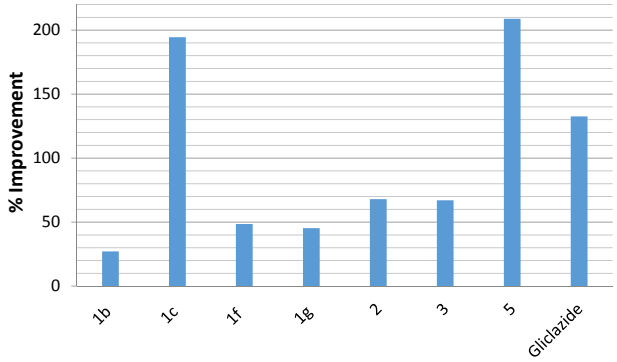


Fig. 2. Percentages of improvement in blood glucose level of our synthesized anti-diabetic compounds and gliclazide as reference drug.

$$\text{Percentage of Improvement} = \frac{Mean\ of\ disease - Mean\ of\ treated}{Mean\ of\ control} \text{X100}$$

Significant increase in blood glucose level was noticed in diabetic rats compared to normal control with percentage increase 330%. Silicate coated particles ofcompounds**1c** and **5**declared highest improvement percentages in blood glucose levels reach to 302.65 and 309.71%, respectively (Table 3).

2.3.2. Liver function enzyme activities

Aminotransferases (ALT and AST) and ALP activity were markedly elevated in STZ-treated animals. High blood glucose level resulted in hepatolysis which reflected by high aminotransferases activity as a leading cause of diabetic complication. Hepatic enzymes exhibited significant elevation in serum of diabetic rats recorded percentages 64.07, 89.38 and 169.55%, respectively, for AST, ALT and ALP. Compounds **1c** and**5**showed marked amelioration in blood glucose level. Upon treated diabetic rats with compounds **1c** and **5** more or less similar results were observed for hepatic enzyme activities in comparison with gliclazide (Table 4). Silicate coated particles of compounds**1c** and **5** coated by TEOS exhibited higher improvement in the hepatic enzymes effect compared to their relative silicate coated particles of gliclazide. The comparison between the AST, ALT, ALP enzyme activities of our synthesized compounds and gliclazide as a reference anti-diabetic agent is illustrated graphically in Fig. 3.

2.3.3. Profile of lipid

The current study showed dramatic increment in TG, TC and TL levels in diabetic rats. This elevation may be due to activation of lipoprotein lipase by insulin which decomposes triglycerides. Deficiency

Table 3
Comparative effects between normal and silicate coated particles among compounds **1c**, **5** and gliclazide on blood glucose level in STZ-induced diabetic rats.

Groups		Parameters		
		Blood glucose level (mg/dL)	% Change	% Improvement
Control		90.60 ± 5.90	–	–
Diabetic		389.80 ± 9.77	330.24	–
1c	Normal form	213.60 ± 9.90	135.76	194.49
	Silicate coated particles	109.2 ± 6.22	20.53	309.71
5	Normal form	200.6 ± 11.27	121.41	208.83
	Silicate coated particles	115.6 ± 9.00	27.59	302.65
Gliclazide	Normal form	269.60 ± 10.1	197.57	132.67
	Silicate coated particles	169.0 ± 7.22	86.53	243.70

Table 4
Comparative effects among compounds **1c**, **5** as well as gliclazide and their silicate coated particles on AST, ALT and ALP enzyme activities in STZ-induced diabetic rats.

Groups		Parameters								
		AST			ALT			ALP		
		U/L	% Change	% Improvement	U/L	% Change	% Improvement	U/L	% Change	% Improvement
Control		79.60 ± 3.97^{f}	–	–	45.20 ± 4.14^{e}	–	–	430.40 ± 12.3^{g}	–	–
Diabetic		130.60 ± 6.72^{c}	64.07	–	85.60 ± 4.12$^{b, c}$	89.38	–	1160.16 ± 20.46$^{b, c}$	169.55	–
1c	Normal form	63.30 ± 2.80^{f}	15.83	48.24	63.30 ± 2.80^{a}	40.04	49.34	630.00 ± 13.53^{a}	46.38	123.18
	Nano form	68.60 ± 5.10^{f}	−13.82	77.89	53.80 ± 2.80^{f}	19.03	70.35	477.00 ± 15.8^{e}	10.83	158.73
5	Normal form	90.80 ± 3.90^{a}	14.07	50	64.20 ± 5.40^{a}	42.04	47.35	653.51 ± 19.53^{a}	51.84	117.72
	Nano form	70.00 ± 8.50^{f}	−12.06	76.13	47.20 ± 4.21^{g}	4.42	84.96	400.00 ± 10.1^{e}	−7.06	176.62
Gliclazide	Normal form	89.00 ± 7.10^{f}	11.81	52.26	62.00 ± 6.20^{a}	37.17	52.21	710.67 ± 18.03^{f}	65.12	104.44
	Nano form	63.4 ± 8.40^{f}	−20.35	84.42	49.00 ± 3.55^{f}	8.40	80.97	600.20 ± 23.8^{a}	39.45	130.10

Data are given in mean ± SD from 10 rats in each group. Values in parentheses represent % of improvements from control. Statistical analysis are carried out using one way analysis of variance (ANOVA) using Co-Stat Computer program, where unshared letters are significant at $p \leq 0.05$.

Fig. 3. Comparison of the AST, ALT, ALP activities among **1c**, **5** compounds and gliclazide as standard anti-diabetic reference drug.

of insulin leads to fail in the activation of lipase enzyme, hence, causing hypertriglyceridemia. Marked elevation in lipid profile; TC, TG and TL levels (relative to control) in diabetic rats with percentages 214.74, 239.01 and 136.65%, respectively was observed (Table 5). Obvious improvement in lipid profile levels was noticed upon treatment of the diabetic rats with compounds **1c** and **5** in comparison with gliclazide-reached to 171.98, 87.35 and 61.68%, respectively for **1c** and182.74, 119.12 and 86.65%, respectively for compound **5**. Silicate coated particles of compound **1c** exhibited higher improvement recorded 209.57, 204.46 and 122.49%, respectively in comparison with that of gliclazide (200.73, 183.17 and 109.16%, respectively). While, an interesting silicate coated particles of compound **5**exhibited higher improvement percentages for TC, TG and TL at 212.36, 217.37, and 131.83%. The comparison between the TG, TC and TL profiles of compounds **1c**, **5** and gliclazidewas showed graphically in Fig. 4.

2.3.4. Antioxidants study

The antioxidant defense systems are represented in two ways either enzymatic or non-enzymatic. In diabetes mellitus, the oxidative stress can be resulted from the increased production of free radicals with/or a marked reduction of antioxidant defenses including enzymatic and non-enzymatic antioxidant. Noticeable improvement in the antioxidant enzyme levels, GSH content as well as MDA level upon treatment of diabetic rats with compounds **1c** and **5**compared to their corresponding standard drug (Tables 6 and 7). However, compound **5** showed more effect than **1c** compared to standard drug. Silicate coated particles of compounds **1c** and**5** showed more potent effect than their corresponding normal form in ameliorating oxidative stress marker, MDA and antioxidant enzymes as well as hepatic GSH. In general, compound **5** showed higher effect than **1c**, while silicate coated particles of compound **5** showed the highest effect compared to its relative silicate coated particles standard drug as shown in Fig. 5.

2.3.5. Histopathological studies

2.3.5.1. Histopathological examination of liver. As shown in Table 8 and Fig. 6. Liver of control rats **(G1)** rats demonstrated the normal structure of hepatic lobule. Hepatic architecture of diabetic rats **(G2)** declared congestion of hepatic sinusoids, cytoplasmic vacuolation of hepatocytes and fibroplasia in the portal triad. Diabetic rats treated with **1c (G3)** exhibited central vein congestion and hepatic sinusoids, slight congestion of hepatic sinusoids and congestion of hepato portal blood vessel. Liver of diabetic rats treated with silicate coated nanoparticles of compound **1c (G4)** showed no histopathological changes, while Kupffer cells activation were noticed. Liver of diabetic rats treated with compound **5 (G5)** showed cytoplasmic vacuolation of hepatocytes, congestion of central vein and hepatic sinusoids. Liver of diabetic rats treated with silicate coated nanoparticles of compound **5 (G6)** showed slight hydropic degeneration of hepatocytes. Liver of diabetic rats treated with gliclazide **(G7)** showed Kupffer cells activation. Liver of diabetic rats treated with silicate coated nanoparticles of gliclazide (**G8**)

Table 5
Comparative effects among compounds **1c**, **5** and gliclazide (normal and silicate coated particles-forms) on TC, TG and TL levels.

Groups		Parameters								
		TC			TG			TL		
		mg/dL	% Change	% Improvement	mg/dL	% Change	% Improvement	mg/dL	% Change	% Improvement
Control		88.10 ± 5.01^{b}	–	–	31.38 ± 6.79^{b}	–	–	600.10 ± 18.00^{b}	–	–
Diabetic		277.29 ± 14.76^{a}	214.74	–	106.38 ± 6.36^{a}	239.01	–	1420.14 ± 22.0^{a}	136.65	–
1c	Normal form	125.78 ± 11.90^{c}	42.77	171.98	78.97 ± 7.33^{f}	151.66	87.35	1050.00 ± 23.00^{e}	74.97	61.68
	Nano form	92.66 ± 9.76^{b}	5.18	209.57	42.22 ± 3.60^{e}	34.54	204.46	685.10 ± 13.00^{b}	14.16	122.49
5	Normal form	116.30 ± 12.80^{c}	32.01	182.74	69.00 ± 7.60^{c}	119.89	119.12	900.13 ± 21.00^{c}	50.00	86.65
	Nano form	90.20 ± 11.80^{b}	2.380	212.36	38.17 ± 8.69^{h}	21.64	217.37	629.00 ± 33.00^{b}	4.82	131.83
Gliclazide	Normal form	138.29 ± 12.90^{e}	56.97	157.76	75.97 ± 2.69^{f}	142.10	96.91	1102.20 ± 29.00^{e}	83.67	52.98
	Nano form	100.45 ± 7.80^{b}	14.02	200.73	48.90 ± 3.60^{g}	55.83	183.17	765.10 ± 18.00^{h}	27.50	109.16

Results are given in mean ± SD from 15 rats in each group. Values in parentheses represent % of improvements from control.Statistical analysis are carried out using one way analysis of variance (ANOVA) using Co-Stat Computer program, where unshared letters are significant at $p \leq 0.05$.

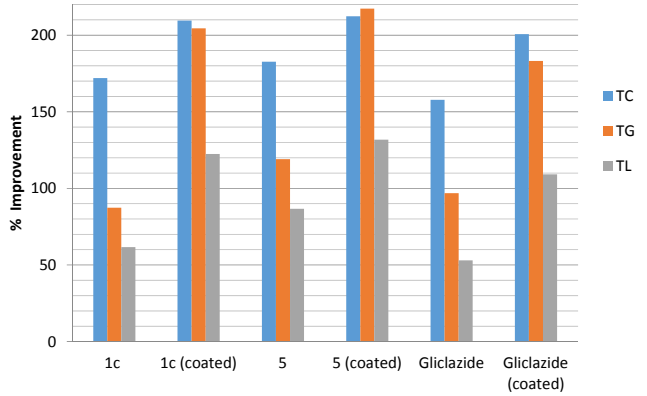


Fig. 4. Comparison of the lipid profile TC, TG and TL levels among compounds **1c**, **5** and gliclazide.

showed no histopathological changes.

2.3.5.2. Histopathological examination of kidneys. As shown in Table 9 and Fig. 7. Kidney of control rats showed normal structure of renal parenchyma (**G1**). Diabetic rat demonstrated vacuolation of epithelial lining renal tubules and cystic dilatation of renal tubules (**G2**). Kidney of diabetic rats treated with**1c (G3)** showed in some slides congestion of renal blood vessels while the remained slides declared no structural changes. Kidney of diabetic rats treated with silicate coated nanoparticles of compound **1c (G4)** showed no histopathological change. Kidney of diabetic rats treated withcompound**5 (G5)** showed no histopathological changes. Kidney of diabetic rats treated with silicate coated particles of compound **5 (G6)** showed in some slides vacuolation of epithelial lining renal tubules and congestion of glomerular tuft while the remained slides exhibited no structural changes. Kidney of diabetic rats treated with gliclazide **(G7)** showed no changes. In some slides showed congestion of renal blood vessel. Kidney of diabetic rats treated with silicate coated nanoparticles of gliclazide (**G8**) showed no histopathological changes.

2.3.5.3. Histopathological examination of Pancreas. As shown in Table 10 and Fig. 7. Pancreas of rat **(G1)** revealed no changes. Pancreas of diabetic rats **(G2)** exhibited vacuolation of islets of Langerhan's cells of and focal hemorrhage. Pancreas of diabetic rat treated with compound **1c (G3)** demonstrated vacuolation of some cells of islets of Langerhan's. Pancreas of diabetic rat treated with silicate coated particles of compound **1c (G4)** showed no structural changes. Pancreas of diabetic rat treated with compound **5 (G5)** declared no changes. In some slides vacuolation of few cells of islets of Langerhan's were appeared. Pancreas of diabetic rat treated with silicate coated particles of compound **5 (G6)** showed no histopathological changes in some slides necrosis of sporadic cells of islets of Langerhan's were appeared. Pancreas of diabetic rats treated with gliclazide (**G7**) showed no histopathological changes. In some slides slight congestion of pancreatic blood vessel were appeared. Pancreas of diabetic rats treated with silicate coated nanoparticles of gliclazide (**G8**) showed no histopathological changes as shown in Fig. 8.

2.4. Single crystal X-ray diffraction

A single Crystals suitable for X-ray diffraction analysis were obtained from a saturated ethylacetate solution at room temperature. The X-ray crystal structures were determined by using a Rigaku R-AXISRAPID diffractometer and Bruker X8 Prospector. The collection of single crystal data was made at room temperature by using Cu-Kα radiation. The structures were solved by using direct methods and

Table 6
Comparative effects among compounds **1c, 5** and gliclazide on enzymatic antioxidants.

Groups		Parameters								
		CAT			SOD			GST		
		µMol/min/mg protein	% Change	% Improvement	µMol/min/mg protein	% Change	% Improvement	mmol/min/mg protein	% Change	% Improvement
Control		9.40 ± 0.15^{a}	–	–	52.35 ± 6.80^{a}	–	–	790.34 ± 31.56^{a}	–	–
Diabetic		3.04 ± 0.10^{b}	−67.66	–	15.73 ± 1.22^{b}	−69.95	–	230.39 ± 27.34^{b}	169.55	–
1c	Normal form	5.90 ± 0.40^{c}	−37.23	30.43	27.70 ± 4.50^{c}	−47.08	22.87	497.80 ± 21.90^{e}	10.83	33.83
	Nano form	6.90 ± 0.12^{d}	−26.60	41.06	44.94 ± 5.50^{d}	−14.14	55.81	623.30 ± 28.59^{d}	46.38	49.71
5	Normal form	5.80 ± 0.20^{c}	−38.30	29.36	27.34 ± 3.29^{c}	−47.76	22.18	560.70 ± 23.44^{c}	−7.06	41.79
	Nano form	7.05 ± 0.06^{d}	−25.00	42.66	44.39 ± 4.26^{d}	−15.19	54.76	636.60 ± 25.42^{d}	51.84	51.39
Gliclazide	Normal form	3.90 ± 0.19^{b}	−58.51	9.15	20.80 ± 2.12^{b}	−60.26	9.69	490.20 ± 18.35^{e}	39.45	32.87
	Nano form	5.16 ± 0.04^{c}	−45.11	22.55	31.45 ± 3.01^{c}	−39.91	30.03	580.03 ± 20.33^{c}	65.12	44.23

Table 7
Comparative effects among compounds **1c, 5** and gliclazide on antioxidant and oxidative stress biomarkers.

Groups		Parameters								
		GPx			GSH			MDA		
		mmol/min/mg protein	% Change	% Improvement	mmol/mg	% Change	% Improvement	mmol/mg tissue	% Change	% Improvement
Control		920.25 ± 21.31^{a}	–	–	1401.13 ± 30.15^{a}	–	–	11.95 ± 1.32^{a}	–	–
Diabetic		300.00 ± 32.90^{b}	−67.40	–	600.80 ± 19.89^{b}	−57.12	–	35.88 ± 4.31^{b}	200.25	–
1c	Normal form	680.80 ± 25.11^{c}	−26.02	41.38	775.30 ± 19.73^{e}	−57.12	12.45	24.15 ± 2.68^{e}	102.09	98.16
	Nano form	739.35 ± 23.9^{d}	−19.66	47.72	983.90 ± 21.41^{h}	−29.78	27.34	21.57 ± 4.12^{c}	80.50	119.75
5	Normal form	670.90 ± 32.28^{c}	−27.10	40.30	1098.31 ± 26.31^{c}	−21.61	35.51	21.44 ± 2.50^{c}	79.41	120.87
	Nano form	794.99 ± 23.90^{d}	−13.61	53.7	1270.30 ± 28.43^{d}	−9.34	47.78	19.13 ± 2.50^{d}	60.08	140.17
Gliclazide	Normal form	500.90 ± 35.34^{e}	−45.57	−21.83	597.34 ± 13.76^{b}	−57.37	0.24	28.35 ± 2.70^{h}	137.24	63.10
	Nano form	590.69 ± 15.35^{h}	−35.81	−31. 59	711.92 ± 16.35^{e}	−49.19	7.93	21.79 ± 4.09^{c}	82.34	117.91

Results are given in mean ± SD from 15 rats in each group. Values in parentheses represent % of improvements from control.Statistical analysis are carried out using one way analysis of variance (ANOVA) using Co-Stat Computer program, where unshared letters are significant at $p \leq 0.05$.

Fig. 5. Percentages of improvement of antioxidant and oxidative stress biomarkers using compounds **1c**, **5** and gliclazide.

expanded using Fourier techniques. Thenon-hydrogen atoms were refined anisotropically [28].

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21/n 1, with Z = 4 for the formula unit, $C_{14}H_{12}Cl_2N_2O_3S$. The final anisotropic full-matrix least-squares refinement on F^2 with 200 variables converged at R1 = 5.37%, for the observed data and wR2 = 14.54% for all data. The goodness-of-fit was 1.110. The largest peak in the final difference electron density synthesis was 0.507 $e^-/Å^3$ and the largest hole was −0.770 $e^-/Å^3$ with an RMS deviation of 0.120 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.477 g/cm^3 and F(000), 736 e^-.The CCDC number is 1883953.

3. Conclusions

In summary, the treatment of sulfonyl isocyanate with selected amino derivatives afforded newer sulfonylurea derivatives **1–5** that showed a significant anti-diabetic properties. The results indicated that the synthesized derivatives revealed decrease in the mean blood glucose for rats previously induced with diabetes mellitus type 2. It was noticed also, the silicate coated nanoparticles of the active compounds **1c** and **5** enhanced the biological properties and it is considered as potential lead compounds in diabetes treatment as comparison to gliclazideas a reference drug.

4. Experimental

4.1. Chemistry

All melting points are recorded on digital Gallen Kamp MFB-595 instrument and may be uncorrected. The IR spectra (KBr) (cm^{-1}) were measured on a JASCO spectrophotometer. ^{1}H NMR spectra were recorded on Bruker spectrometers (400 MHz) and are reported relative to deuterated solvent signals in deuterateddimethylsulfoxide (DMSO-d_6). ^{13}C NMR spectra were recorded on Bruker Spectrometers (100 MHz) in deuterateddimethylsulfoxide (DMSO-d_6).

4.1.1. N-(arylcarbamoyl)-4-methylbenzenesulfonamide

To a solution of requisite amines (0.01 mol) in acetonitrile (in case of compound **3**, dichloromethane was used) (20 mL), *p*-methylbenzenesulfonylisocyanate (0.01 mol) was added while stirring at room temperature. The reaction mixture was stirred to the desired time, by following with TLC. The obtained precipitate was filtered off, washed with cold acetonitrile (two times) dried well, and recrystallized from ethanol to give:

4.1.1.1. N-(3-Chlorophenylcarbamoyl)-4-methylbenzenesulfonamide [16] ***(1a)***. Yield 95%; m.p. 188–190 °C. IR (KBr, cm^{-1}): 3314, 3283 (NH), 1683 (C═O), 1347, 1167 (SO_2). ^{1}H NMR (DMSO-d_6, δ): 2.41 (s, 3H,

Table 8
Tesion score of liver for diabetic and treated diabetic rats with tested compounds.

Groups		Parameters				
		Histopathological lesion				
		Kupffer cells activation	Congestion of central vein & sinusoids	Vacuolation of hepatocytes	Hydropic degeneration of hepatocytes	Portal fibroplasia
Normal control		–	–	–	–	–
Diabetic		+ +	+ + +	+ +	–	+ +
1c	Normal form	+	+ +	–	–	–
	Silicate coated particles	+	–	–	–	–
5	Normal form	+	+ +	+ +	–	–
	Silicate coated particles	–	–	–	+ + /+	–
Gliclazide	Normal form	+	+	–	–	–
	Silicate coated particles	–	–	–	–	–

(–) normal histological structure, (+) mild change, (+ +) moderate change, (+ + +) severe change.

CH_3),7.07 (d, 1H, J = 8 Hz, Ar-H),7.13–7.32 (m, 2H, Ar-H), 7.43(d, 2H, J = 8 Hz, Ar-H), 7.52 (s, 1H, Ar-H), 7.87 (d, 2H, J = 8 Hz, Ar-H), 8.90 (br, 1H, NH), 9.60 (br, 1H, NH). Anal. For $C_{14}H_{13}ClN_2O_3S$: Calcd. C, 51.77; H, 4.03; N, 8.63. Found: C, 51.85; H, 3.98; N, 8.54.

*4.1.1.2. 4-Methyl-N-(4-(phenyldiazenyl)phenylcarbamoyl) benzenesulfonamide (**1b**).* Yield 87%; m.p. 208–210 °C. IR (KBr, cm^{-1}): 3317, 3275 (NH), 1698 (C═O), 1346, 1197 (SO_2). ^{1}H NMR (DMSO-d_6, δ): 2.41 (s, 3H, CH_3), 7.45 (d, 2H, J = 8 Hz, Ar-H), 7.48–7.62 (m, 5H, Ar-H), 7.85 (m, 4H, Ar-H), 7.89 (d, 2H, J = 8 Hz, Ar-H), 9.13 (br, 1H, NH), 10.75 (br, 1H, NH).^{13}C NMR (DMSO-d_6, δ): 21.5, 113.9, 119.6, 122.2, 122.8, 124.4, 125.6, 126.1, 128.0, 129.8, 131.5, 137.6, 141.7, 144.4, 148.1, 149.8, 152.6, 153.2. Anal. For $C_{20}H_{18}N_4O_3S$: Calcd. C, 60.90; H, 4.60; N, 14.20. Found: C, 60.85; H, 4.58; N, 14.14.

*4.1.1.3. N-(2,6-Dichlorophenylcarbamoyl)-4-methylbenzenesulfonamide (**1c**).* Yield 95%; m.p. 180–182 °C. IR (KBr, cm^{-1}): 3272, 3231 (NH), 1666 (C═O), 1347, 1164 (SO_2). ^{1}H NMR (DMSO-d_6, δ): 2.38 (s,3H, CH_3), 7.21–7.50 (m, 5H, Ar-H), 7.72 (d, 1H, J = 8.0 Hz, Ar-H), 7.84 (d, 1H, J = 8.0 Hz, Ar-H), 8.45 (br, 1H, NH), 11.17 (br, 1H, NH). ^{13}C NMR (DMSO-d_6, δ): 21.5, 117.5, 118.8, 126.1, 127.7, 128.9, 129.8, 132.4, 134.5, 137.7, 141.5, 142.3, 144.2, 149.8. Anal. For $C_{14}H_{12}Cl_2N_2O_3S$: Calcd. C, 46.81; H, 3.37; N, 7.80. Found: C, 46.64; H, 3.41; N, 7.69.

*4.1.1.4. 4-Methyl-N-(2-methyl-5-nitrophenylcarbamoyl) benzenesulfonamide (**1d**).* Yield 66%; m.p. 220–223 °C. IR (KBr, cm^{-1}): 3329 (NH), 1692 (C═O), 1344, 1149 (SO_2). ^{1}H NMR (DMSO-d_6, δ): 2.28 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 7.45 (m, 3H, Ar-H), 7.88 (m, 3H, Ar-H), 8.34(s, 1H, Ar-H), 8.61 (br, 1H, NH), 11.06 (br, 1H, NH). ^{13}C NMR (DMSO-d_6, δ): 18.1, 21.5, 107.6, 110.7, 115.1, 118.7, 126.1, 127.9, 130.0, 131.7, 136.4, 137.3, 144.6, 146.5, 149.9. Anal. For $C_{15}H_{15}N_3O_5S$: Calcd. C, 51.57; H, 4.33; N, 12.03. Found: C, 51.63; H, 4.28; N, 12.09.

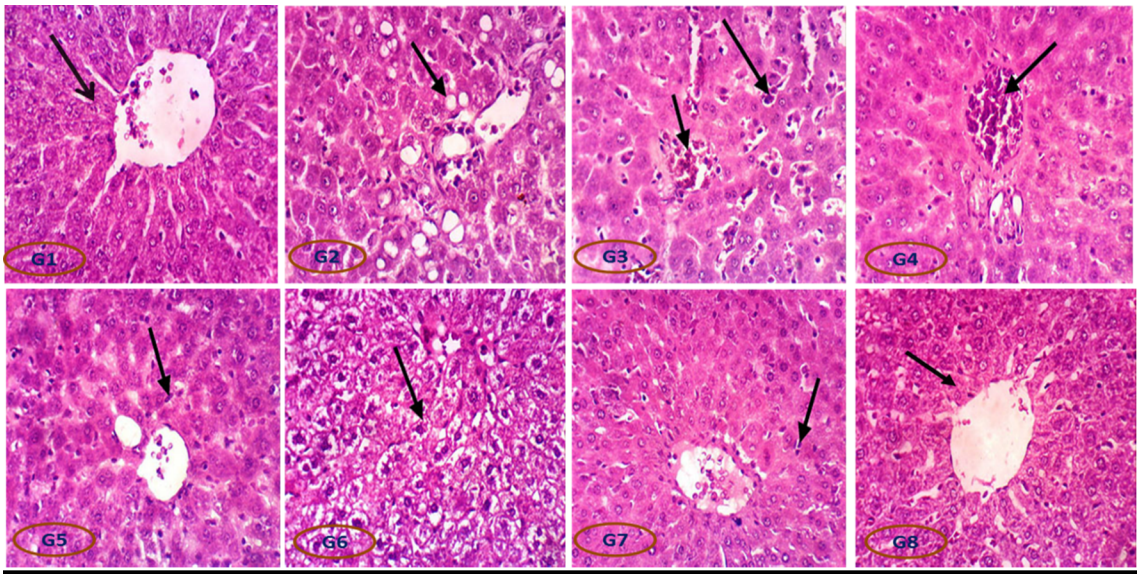


Fig. 6. Liver sections of control rats **(G1)** showing the normal structure of hepatic lobule. Liver of diabetic rats **(G2)** revealing congestion of hepatic sinusoids cytoplasmic, fibroplasia in the portal triad and vacuolation of hepatocytes. Liver of diabetic rats treated with **1c (G3)** showing some cytoplasmic vacuolation of hepatocytes also few congestion of central vein and enhanced most hepatic cells. Liver of diabetic rats treated with silicate coated nanoparticles of compound **1c (G4)** showing hepatic cells nearly control while few congestion of central vein. Liver of diabetic rats treated with compound **5 (G5)** showing no histopathological changes with Kupffer cells activation. Liver of diabetic rats treated with silicate coated nanoparticles of compound **5 (G6)** showing slight hydropic degeneration of hepatic cells. Liver of diabetic rats treated with gliclazide **(G7)** showing no histopathological changes with some Kupffer cells activation. Liver of diabetic rats treated with silicate coated nanoparticles of gliclazide (**G8**) showing no histopathological changes with normal hepatic cells (H & E × 200).

Table 9
Lesion score of kidney of diabetic and diabetic-treated rats with the tested compounds.

Groups		Parameters			
		Histopathological lesion			
		Congestion of renal blood vessels	Vacuolation of renal tubules	Congestion of glomerular tuft	Cystic dilatation of renal tubules
Normal control		–	–	–	–
Diabetic		+ +	+ +	+ +	+ +
1c	Normal form	+ +	–	–	–
	silicate coated particles	–	–	–	–
5	Normal form	–	–	–	–
	silicate coated particles	–	+	+	–
Gliclazide	Normal form	+	–	–	–
	silicate coated particles	–	–	–	–

(–) normal histological structure, (+) mild change, (+ +) moderate change, (+ + +) severe change

*4.1.1.5. 4-Methyl-N-(4-methyl-3-nitrophenylcarbamoyl) benzenesulfonamide (**1e**).* Yield 58%; m.p. 204–205 °C. IR (KBr, cm^{-1}): 3288, 3195 (NH), 1694 (C═O), 1350, 1165 (SO_2). ^{1}H NMR (DMSO-d_6, δ): 2.41 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 7.39 (d, 1H, *J* = 8 Hz, Ar-H), 7.44 (d, 2H,*J* = 8 Hz, Ar-H), 7.51 (d, 1H, *J* = 8 Hz, Ar-H), 7.87 (d, 2H, *J* = 8 Hz, Ar-H), 8.10(s, 1H, Ar-H), 9.12 (br, 1H, NH), 10.75 (br, 1H, NH). ^{13}C NMR (DMSO-d_6, δ): 19.3, 21.5, 108.7, 114.7, 119.5, 124.2, 126.1, 128.0, 130.0, 133.5, 137.6, 144.4, 149.2, 150.0. Anal. For $C_{15}H_{15}N_3O_5S$: Calcd. C, 51.57; H, 4.33; N, 12.03. Found: C, 51.65; H, 4.29; N, 11.94.

*4.1.1.6. N-(5-Chloro-2-hydroxyphenylcarbamoyl)-4-methylbenzenesulfonamide (**1f**).* Precipitate was obtained after treatment with cold water, yield 73%; m.p. 198–200 °C. IR (KBr, cm^{-1}): 3483, 3373, 3329, 3209 (NH & OH), 1706, 1680 (C═O), 1345, 1155 (SO_2). ^{1}H NMR (DMSO-d_6, δ): 2.41 (s, 3H, CH_3), 6.85 (m, 2H, Ar-H), 7.44 (d, 2H, *J* = 8 Hz, Ar-H), 7.85 (m, 3H, Ar-H), 8.46 (br, 1H, NH), 10.28 (br, 1H, NH), 10.90 (br, 1H, OH). Anal. For $C_{14}H_{13}ClN_2O_4S$: Calcd. C, 49.34; H, 3.85; N, 8.22. Found: C, 49.25; H, 3.81; N, 8.13.

*4.1.1.7. N-(2,6-Dibromo-4-methylphenylcarbamoyl)-4-methylbenzenesulfonamide (**1 g**).* Yield 52%; m.p. 238–240 °C. IR (KBr, cm^{-1}): 3269 (NH), 1671(C═O), 1353, 1170 (SO_2). ^{1}H NMR (DMSO-d_6, δ): 2.28 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.42 (d, 2H, *J* = 8 Hz, Ar-H), 7.50 (s, 2H, Ar-H), 7.84 (d, 2H, *J* = 8 Hz, Ar-H), 8.24(br, 1H, NH), 10.92 (br, 1H, NH). ^{13}C NMR (DMSO-d_6, δ): 20.2, 21.5, 108.2, 124.5, 126.1, 127.8, 129.7, 132.6, 137.8, 141.1, 142.3, 144.2, 149.8. Anal. For $C_{15}H_{14}Br_2N_2O_3S$: Calcd. C, 38.98; H, 3.05; N, 6.06. Found: C, 39.05; H, 3.07; N, 5.89.

*4.1.1.8. N-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylcarbamoyl)-4-methyl Benzenesulfonamide (**2**).* Yield 62%; m.p. 150–152 °C. IR (KBr, cm^{-1}): 3433, 3120 (NH), 1629 (C═O). ^{1}H NMR (DMSO-d_6, δ): 2.08 (s,3H, CH_3),2.41(s,3H, CH_3),3.04 (s,3H, CH_3),7.34 (m, 3H, Ar-H), 7.42 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.50 (t, 2H, *J* = 7.9 Hz, Ar-H), 7.64 (br, 1H, NH), 7.85 (d, 2H, *J* = 8.0 Hz, Ar-H), 10.67 (br, 1H, NH). ^{13}C NMR (DMSO-d_6, δ): 9.2, 19.4, 34.2, 104.8, 116.3, 120.4, 122.2, 124.8, 125.8, 127.5, 127.8, 133.3, 135.7, 142.2, 148.9, 150.2, 160.0. Anal. For $C_{19}H_{20}N_4O_4S$: Calcd. C, 56.99; H, 5.03; N, 13.99. Found: C, 57.11; H, 5.00; N, 13.86.

*4.1.1.9. 4-Methyl-N-(ricycle[3.3.1.13,7]dec-1-ylcarbamoyl) benzenesulfonamide(**3**).* Yield 61%; m.p. 150–152 °C. IR (KBr, cm^{-1}): 3425, 3343 (NH), 2911 (CH-aliph.), 1700 (C═O), 1371, 1132 (SO_2). ^{1}H NMR (DMSO-d_6, δ): 1.51–2.13(m, 15H, adamantyl), 2.38 (s,3H, CH_3), 6.03 (br., 1H, NH), 7.27 (br., 1H, NH), 7.36 (d, 2H, *J* = 8 Hz,Ar-H), 7.72 (d, 2H, *J* = 8 Hz, Ar-H). ^{13}C NMR (DMSO-d_6, δ): 21.4, 28.8, 29.3,

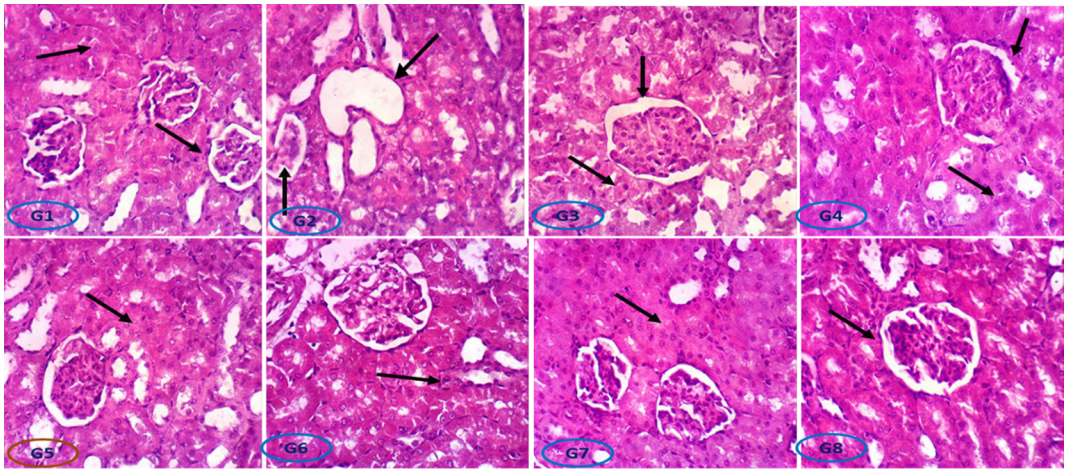


Fig. 7. Kidney of control rats showed the normal histological structure of renal parenchyma (**G1**). Kidney of diabetic rat showed vacuolation of epithelial lining renal tubules and cystic dilatation of renal tubules (**G2**). Kidney of diabetic rats treated with **1c (G3)** showed in some slides congestion of renal blood vessels while the remained slides showed no histopathological changes. Kidney of diabetic rats treated with silicate coated nanoparticles of compound **1c (G4)** showed no histopathological change. Kidney of diabetic rats treated with compound **5 (G5)** showed no histopathological changes. Kidney of diabetic rats treated with silicate coated particles of compound **5 (G6)** showed in some slides vacuolation of epithelial lining renal tubules and congestion of glomerular tuft while the remained slides showed no histopathological changes. Kidney of diabeticrats treated with gliclazide **(G7)** showed no histopathological changes. In some slides showed congestion of renal blood vessel. Kidney of diabetic rats treated with silicate coated nanoparticles of gliclazide (**G8**) showed no histopathological changes.

Table 10
Lesion score of pancreas of diabetic and diabetic-treated rats with tested the compounds.

Groups		Parameters			
		Histopathological lesion			
		Congestion of pancreatic blood vessels	Necrosis of cells of islets of Langerhan's	Vacuolation of cells of islets of Langerhan's	Focal haemorrhage
Normal control		–	–	–	–
Diabetic		+	+	++	++
1c	Normal form	–	–	++	–
	Silicate coated particles	–	–	–	–
5	Normal form	–	–	+	–
	Silicate coated particles	–	+	–	–
Gliclazide	Normal form	+	–	–	–
	Silicate coated particles	–	–	–	–

(–) normal histological structure, (+) mild change, (++) moderate change, (+++) severe change.

35.5, 36.4, 41.7, 50.6, 126.1, 127.4, 129.8, 141.9, 142.3. Anal. For $C_{18}H_{24}N_2O_3S$: Calcd. C, 62.04; H, 6.94; N, 8.04. Found: C, 62.11; H, 6.91; N, 7.92.

4.1.1.10. 2-(2-(1H-Indol-3-yl)acetyl)-N-tosylhydrazinecarboxamide ***(4)***. Yield 62%; m.p. 150–152 °C. IR (KBr, cm^{-1}): 3401 (NH), 1732 (C═O), 1380, 1114 (SO_2). ^{1}H NMR (DMSO-d_6, δ): 2.40 (s, 3H, CH_3), 3.53 (s, 2H, CH_2), 6.97 (m, 1H, Ar-H), 7.07 (t, 1H, J = 8.0 Hz, Ar-H), 7.20 (s, 2H, Ar-H), 7.30–7.45 (m, 3H, Ar-H & NH), 7.55 (m, 1H, Ar-H), 7.73 (d, 1H, J = 8 Hz, Ar-H), 7.82 (d, 2H, J = 8.0 Hz, Ar-H), 8.35 (br, 1H, NH), 9.78 (br, 1H, NH), 10.80 (br, 1H, NH). ^{13}C NMR (DMSO-d_6, δ): 21.5, 30.9, 108.4, 111.7, 118.8, 119.1, 121.4, 124.3, 126.1, 127.8, 129.7, 129.8, 136.6, 137.8, 142.3, 144.2, 152.1, 170.6. Anal. For $C_{18}H_{18}N_4O_4S$: Calcd. C, 55.95; H, 4.70; N, 14.50. Found: C, 56.04; H, 4.72; N, 14.54.

4.1.1.11. N-[(4-Methylphenyl)sulfonyl]pyrrolidine-1-carboxamide ***(5)***. Yield 93%; m.p. 228–230 °C. IR (KBr, cm^{-1}): 3267 (NH), 2976, 2935, 2879 (CH-aliph.), 1695 (C═O), 1367, 1090 (SO_2). ^{1}H NMR (DMSO-d_6, δ): 1.77 (m, 4H, $2CH_2$), 2.39 (s, 3H, CH_3), 3.25 (m, 4H, $2CH_2$), 7.38 (d, 2H, J = 8.0 Hz, Ar-H), 7.82 (d, 2H, J = 8.0 Hz, Ar-H), 10.41 (br, 1H, NH). ^{13}C NMR (DMSO-d_6, δ): 21.4, 25.2, 46.3, 128.0, 129.5, 138.6, 143.6, 150.9. Anal. For $C_{12}H_{16}N_2O_3S$: Calcd. C, 53.71; H, 6.01; N, 10.44. Found: C, 53.64; H, 5.98; N, 10.51.

4.2. Biochemical studies of the synthesized products

The diabetic rats was orally administrated 150 mg/kg body weight of synthetic organic compounds in both normal and nanoforms for 30 days [3]. Likewise, the diabetic rats was orally administrated anti-diabetic gliclazide reference drug 150 mg/kg body weight daily for 30 days [4].Blood glucose level was measured in blood serum according to the method of Trinder [17]. Liver function enzyme activities, alanine and aspartate amino tranferases (AST and ALT) as well as alkaline phosphatase (ALP) were determined in mice serum according to the Reitman [18] and Belfield [19] methods. Serum total lipids concentration was determined according to the method of Zollner [20], serum triglyceride (TG) concentration was determined according to the

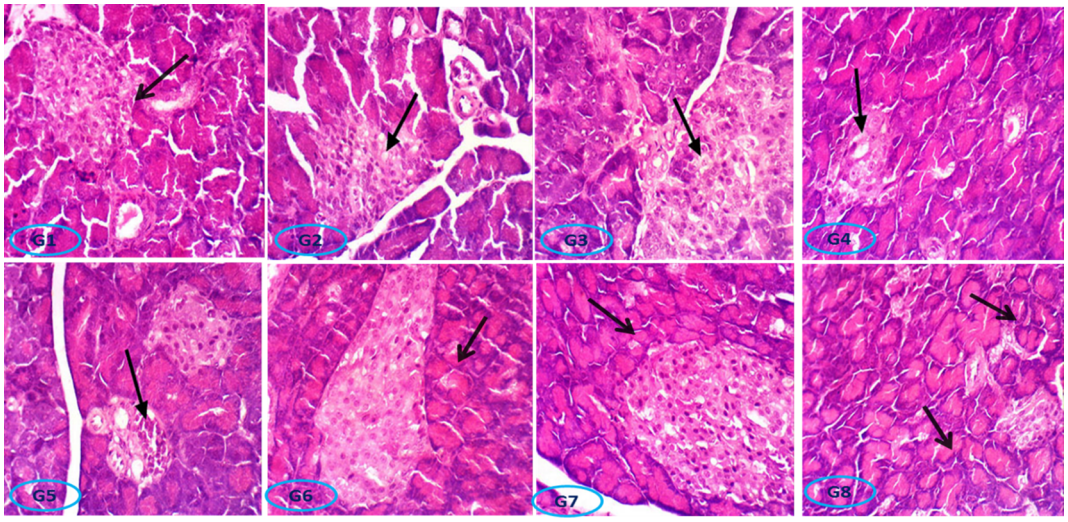


Fig. 8. Pancreas of rat **(G1)** showed no histopathological changes. Pancreas of diabetic rats **(G2)** showed vacuolation of cells of islets of Langerhan's and focal haemorrhage. Pancreas of diabetic rat treated with compound **1c (G3)** showed vacuolation of some cells of islets of Langerhan's. Pancreas of diabetic rat treated with silicate coated particles of compound **1c (G4)** showed no histopathological changes. Pancreas of diabetic rat treated with compound **5 (G5)** showed no histopathological changes. In some slides vacuolation of few cells of islets of Langerhan's were appeared. Pancreas of diabetic rat treated with silicate coated particles of compound **5 (G6)** showed no histopathological changes in some slides necrosis of sporadic cells of islets of Langerhan's were appeared. Pancreas of diabetic rats treated with gliclazide (**G7**) showed no histopathological changes. In some slides slight congestion of pancreatic blood vessel were appeared. Pancreas of diabetic rats treated with silicate coated nanoparticles of gliclazide (**G8**) showed no histopathological changes.

method of Fassati and Prencipe [21] and serum total cholesterol concentration was estimated according to the method of Allain [22]. Liver nitrite (NO) level was estimated [23]. GSH level was assayed in liver homogenate according to Beutler method [24] Liver MDA level was estimated according to the method of Satoh [25]. GR was determined according to the method of Goldberg and Spooner [26] and SOD according to the Nishikimi et al. [27].

Acknowledgments

This work was supported by the National Research Centre (NRC) under project number 11010338. We are grateful to Dr. Wael M. Tohamy for the help in the X-ray diffraction.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.103290.

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