Antihyperglycemic and Antihyperlipidemic Effects of Newly Synthesized Glibenclamide Analogues on Streptozotocin-diabetic Rats

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Key words
- ⟳ glibenclamide
- ⟳ sulfonylurea
- ⟳ antihyperglycemic
- ⟳ antihyperlipidemic activities

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Abstract
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In this study, new glibenclamide analogues (**5a–d**) with substituted pharmacological triethoxysilyl propan, allyl and ethoxyphenyl groups for cyclohexyl moiety have been synthesized by condensing sulfonamide (**4**) with related isocyanate or isothiocyanate's compounds. The newly synthesized drugs were evaluated for their antihyperglycemic and antihyperlipidemic activities with streptozotocin (STZ)-induced diabetic rats. All showed hypoglycemic and hypolipidemic activities compared to the control animals but **5c** and **5d** exhibited more and significant lowering blood activities similar to glibenclamide. This was concerned with identical affinities to bind with SUR1 receptor. Moreover, the new drugs displayed high efficiency for reducing serum LDL level which resulted in a high HDL/LDL ratio as a good lipid profile compared to other groups.

Introduction
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Type 1 diabetes mellitus (Insulin Dependent Diabetes Mellitus, IDDM) and Type 2 diabetes mellitus (Non Insulin Dependent Diabetes Mellitus, NIDDM) are now recognized as the serious global health problems growing rapidly worldwide. In patients with type 2 diabetes whose insulin-secreting capacity is intact, their ability to produce adequate insulin in the presence of elevated glucose is lost [1].

In this metabolic disorder, a defect in the pancreatic β cells leads to a drop in insulin levels and the inability to metabolize the excess levels of blood glucose (hyperglycemia). The inability to sufficiently stimulate the cellular uptake of glucose (insulin resistance) leading to a compensatory increase in the production of insulin (hyperinsulinemia) is the other feature of this defect which can result in many illnesses such as dubbed syndrome X, obesity, dyslipidemia (hypertriglyceridemia and low HDL cholesterol) and hypertension, which cause cardiovascular risks [2].

Blood glucose level is usually well controlled by diet therapy and exercise in the early stages of type 2 diabetes. However, as a result of poor control, various antidiabetic drugs are used depending on the pathophysiology of individual patients, such as α-glucosidase inhibitors for postprandial hyperglycemia, biguanides (it enhances insulin action at the post receptor level in peripheral tissues such as muscles), thiazolidinediones (it enhances the insulin action and promotes glucose utilization in peripheral tissues) for insulin resistance therapy (a deficit in protein tyrosine phosphorylation in the insulin signal transduction cascade [3]) and sulfonylureas (SU, most commonly used as antidiabetic agents) for deficiency in insulin secretion by pancreatic β cells. When insulin secretion is severely impaired and ineffective, insulin therapy is required to control blood glucose levels even in type 2 diabetes [4].

The major action of the sulfonylureas is to stimulate the release of insulin from β cells even when glucose levels are low. They act by affecting the ATP-sensitive potassium channels. These channels are hetero-octameric complex which have also been identified in many neurons, cardiac myocytes, skeletal muscle, vascular and non-vascular smooth muscles. They are composed of 2 subunits: sulfonylurea receptors (SUR1, SUR2A and SUR2B) and inwardly rectifying potassium channels (KIR6.1 or KIR6.2) [5].

SUs bind appropriately not only to SUR1 in β cells but also to SUR2A (as found in cardiac smooth muscle) and SUR2B (as found in brain and smooth muscle) with lower affinities. On binding to SUR1, potassium efflux is blocked, leading to depolarization of the membrane. This depolarization opens voltage-dependent calcium channels, resulting in an influx of calcium. At higher intracellular calcium concentrations, calcium

sensitive proteins act to promote the release of stored insulin from the cells [1].

Improvement in lipoprotein abnormalities is also associated with improved glucose control [6]. Several studies on hypolipidemic activity of anti-diabetic drugs are available in literature [7,8]. Sulfonylurea therapy also indicates significant changes in plasma lipids, in total and very-low density lipoprotein triglyceride. The cholesterol level was reduced to near-normal levels by some [9]. Low specificity of the biological action, delayed time of onset, the long duration of the effects and various side effects represented the major limitations of the first generation sulfonylureas which were introduced 40 years ago for controlling diabetes. The major side effects induced by this class of agents included excessive lowering of plasma glucose levels and binding to cardiac receptors which resulted in the failure of coronary vasodilatation upon demand and subsequent deleterious cardiac effects. The new sulfonylureas (also termed second generation sulfonylureas) were introduced in the late 1970s and exhibited a safer profile with increased potency and a decreased risk of side effects [10]. Glibenclamide or "Glyburide" (5-chloro-*N*-(4-[*N*-(cyclohexylcarbamoyl) sulfamoyl] phenethyl)-2-methoxybenzamide, **5a**) is an oral and potent well-known second-generation of the sulfonylureas group used in the curing NIDDM clinically and is more potent than first-generation in this group [11]. In this paper, new analogues (**5b–d**) of glibenclamide (**5a**) (⊙ Fig. 1) by changing of cyclohexyl with allyl, ethoxyphenyl and triethoxysilyl propane substituted were all synthesized. Many amine derivatives of these compounds have shown pharmacological properties especially for lowering blood glucose level in the

treatment of NIDDM [12–17]. Glucose and lipid-lowering activities of new synthesized compounds were evaluated and compared to glibenclamide and control groups by known procedure [18].

Material and Methods
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General

5-chloro-2-methoxy benzoic acid, chlorosulfonic acid, thionyl chloride, allyl isothiocyanate, 4-ethoxyphenyl isocyanate, 3-(triethoxysilyl) propane isocyanate, cyclohexyl isocyanate, 2-phenylethyl amine, dimethyl formamide (DMF), acetone and all other chemicals were purchased from Merck (Darmstadt, Germany) and Sigma-Aldrich chemical Co. (United States of America). Glibenclamide (**5a**) was synthesized according to the procedures available in the literature [19].

Melting points (uncorrected) were determined with a digital Electrothermal melting point apparatus (model 9100, Electrothermal Engineering Ltd., Essex, UK). ^{1}H and ^{13}C NMR spectra were recorded with a Bruker 300 MHz (model AMX, Karlsruhe, Germany) spectrometer (internal reference: TMS). IR spectra were recorded with a Thermo Nicolet FT-IR (model Nexus-870, Nicolet Instrument Corp, Madison, Wisconsin, USA) spectrometer. Mass spectra were recorded with an Agilent Technologies 5973, Mass Selective Detector (MSD) spectrometer (Wilmington, USA). Elemental analyses were carried out using a Perkin-Elmer, CHN elemental analyzer model 2400. Column chromatographic separations were performed over Acros silica gel (No.7631-86-9 particle size 35-70 micrometer, Geel, Belgium).
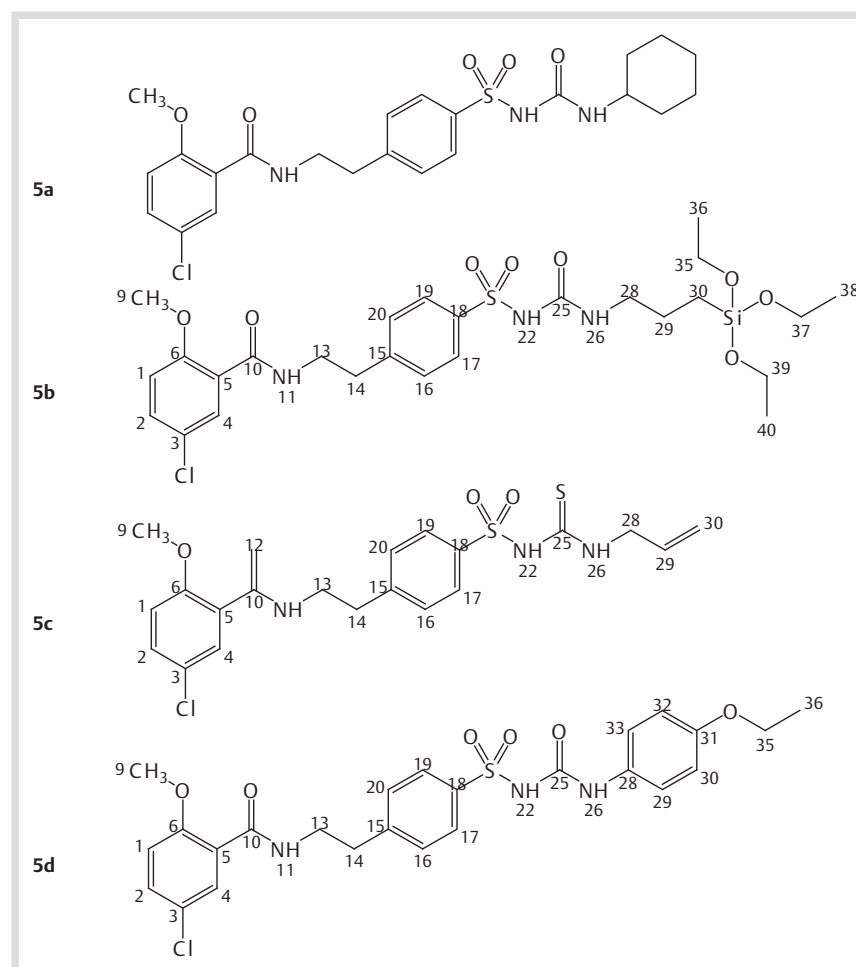

Fig. 1 Structural formula for Glybenclamide **5a** and newly synthesized compounds **5b–d**.

Synthesis of compounds (1–4)

These intermediates were prepared according to the literature [19] with some modifications.

General procedure for the preparation of the compounds (5a–5d)

A dried acetone solution (20 ml) of sulfonamide intermediate (**4**, 2.6 mmol) and potassium carbonate (1.1 g) were refluxed for 1 h. Related isocyanate or isothiocyanate compounds (4.18 mmol) were added to the reaction mixtures and refluxed for additional 16 h. Then it was poured into water, filtered, extracted with 10% HCl and the final desired compounds (**5a–d**) were collected (○ **Fig. 2**).

5-chloro-N-(4-[N-(3-(triethoxysilyl) propanecarbamoyl) sulfamoyl]phenethyl)-2-methoxybenzamide (5b)

White solid, m.p: 142.7 °C; IR (KBr, cm^{-1}): 3382, 2939, 2850, 1687, 1639, 1543, 1480, 1339, 1271, 1160, 586; ^{1}H-NMR (δ/ ppm): 8.48 (b, 1H, sec. amide, H^{11}); 7.83 (d, j=2.6 Hz, 2H, benzene-SO$_2$, H^{17,19}); 7.75 (d, j=0.7 Hz, 1H, benzene-amide, H^4); 7.64 (d, j=1.5 Hz, 1H, benzene-Cl, H^2); 7.41 (d, j=2.6 Hz, 2H, C-C-benzene, H^{16,20}); 7.15 (d, j=7.5 Hz, 1H, benzene-methoxy, H^1); 6.1 (b, 2H, urea, H^{22,26}); 3.81 (s, 3H, O-CH$_3$, H^9); 3.75 (q, 6H, Si-O-CH$_2$, H^{33,35,37}); 3.60 (t, 2H, amide-CH$_2$-CH$_2$, H^{13}); 3.35 (t, 2H, urea-CH$_2$, H^{28}); 2.85 (t, 2H, amide-CH$_2$-CH$_2$, H^{14}); 1.69 (m, 2H, urea-CH$_2$-CH$_2$-CH$_2$-Si(OEt)$_3$, H^{29}); 1.20 (t, 9H, Si-O-CH$_2$-CH$_3$, H^{36,38,40}); 0.61 (t, 2H, urea-CH$_2$-CH$_2$-CH$_2$-Si(OEt)$_3$, H^{30}); ^{13}C-NMR (δ/ppm): 18.78 (Si-O-CH$_2$-CH$_3$, C^{36,38,40}); 23.41(CH$_2$-CH$_2$-Si, C^{30}), 34.71 (CH$_2$-CH$_2$-Si, C^{29}), 38.67(amide-CH$_2$-CH$_2$, C^{14}), 40.05 (amide-CH$_2$, C^{13}), 40.37 (-NH-CH$_2$, C^{28}), 52.19 (Si-O-CH$_2$-CH$_3$, C^{35,3,39}), 56.76 (O-CH$_3$, C^9), 114.10 (phenyl, C^1), 124.34 (phenyl, C^{3,5,17,19}), 127.32 (phenyl, C^{4,16,20}), 131.55 (phenyl, C^2), 138.21(SO$_2$-phenyl, C^{18}), 145.22(C-C-phenyl, C^{15}), 151.28 (phenyl-methoxy, C^6), 155.68 (urea, C^{25}), 163.67 (sec. amide, C^{10}); Anal. Calcd. for C$_{26}$H$_{38}$ClN$_3$O$_8$SSi: C, 50.68%; H, 6.22%; N, 6.82%.
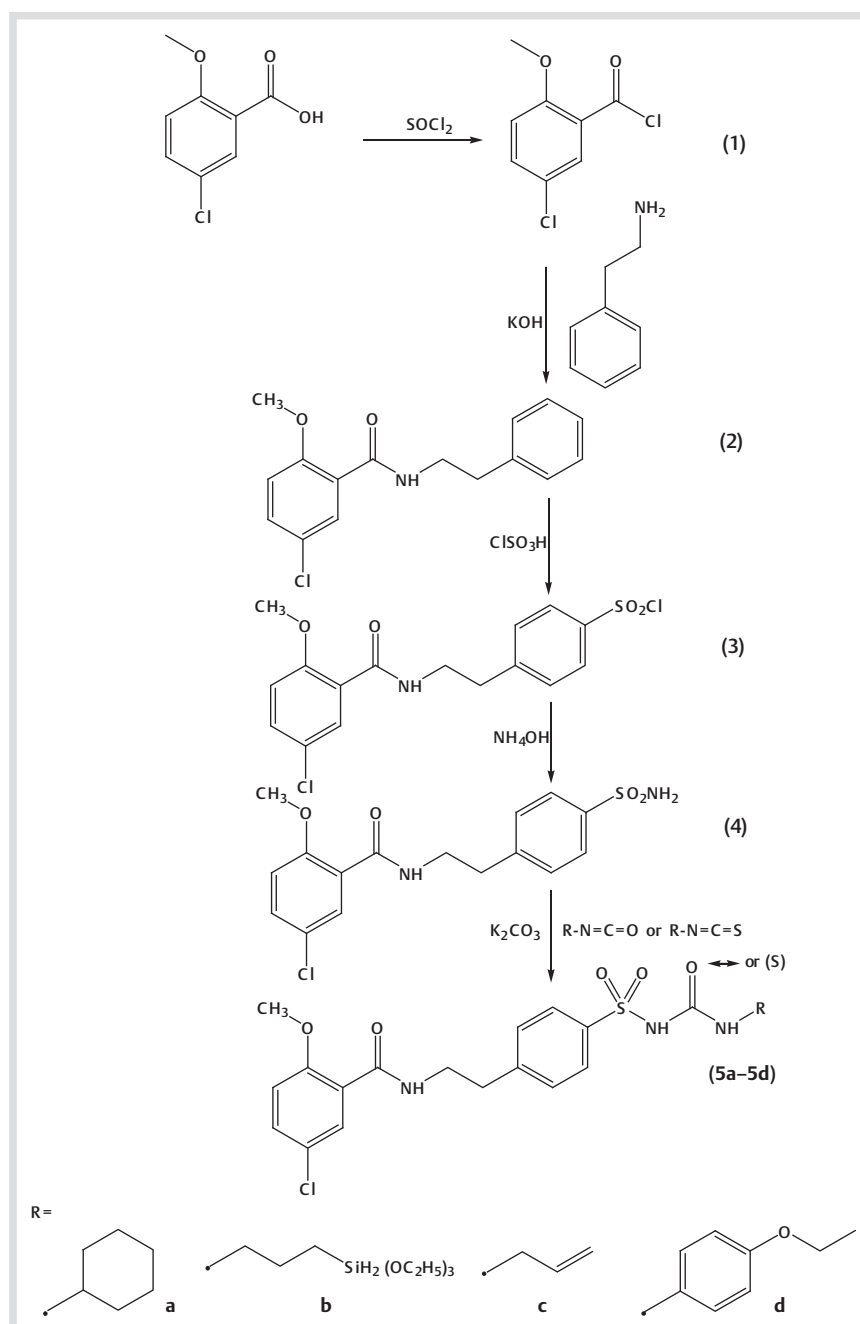

Fig. 2 Schematic synthesis of intermediates and final compounds.

Found: C, 50.72%; H, 6.25%; N, 6.79%; *MS: m/z (regulatory intensity):* 616 (12), 600 (59), 558 (100), 502 (41), 481 (68), 453 (93).

5-chloro-N-(4-[N-(allylcarbamoyl) sulfamoyl] phenethyl)-2-methoxybenzamide (5c)

White Solid, m.p: 137.3°C; IR (KBr, cm^{-1}): 3407, 3231, 2938, 2850, 1718, 1648, 1595, 1480, 1385, 1123, 812, 574; ^{1}H-NMR (δ/ppm): 8.49 (b, 1H, sec. amide, H^{11}); 7.79 (d, j=2.9 Hz, 2H, benzene-SO$_2$, H^{17,19}); 7.73 (d, j=0.5 Hz, 1H, benzene-amide, H^4); 7.70 (d, j=1.5 Hz, 1H, benzene-Cl, H^2); 7.41 (d, j=2.6 Hz, 2H, C-C-benzene, H^{16,20}); 7.23 (d, j=7.5 Hz, 1H, benzene-methoxy, H^1); 6.1 (b, 2H, thiourea, H^{22,26}); 5.89 (m, 1H, ethylene CH, H^{29}); 5.21 (m, 1H, ethylene CH$_2$, H^{30}); 5.18 (m, j=9.8 Hz, 1H, ethylene CH$_2$, H$^{30'}$); 4.21 (d, j=7.1 Hz, 2H, thiourea-CH$_2$, H^{28}); 3.80 (s, 3H, O-CH$_3$, H^9); 3.65 (t, 2H, amide-**CH$_2$**-CH$_2$, H^{13}); 2.87 (t, 2H, amide-CH$_2$-**CH$_2$**, H^{14}); ^{13}C-NMR (δ/ppm): 34.73 (amide-CH$_2$-**CH$_2$**, C^{14}), 40.36 (amide-**CH$_2$**-CH$_2$, C^{13}), 46.59 (-NH-CH$_2$, C^{28}), 56.29 (O-CH$_3$, C^9), 114.11 (ethylene CH$_2$, C^{30}), 116.27 (phenyl, C^{1,5}), 127.48 (phenyl, C^{2,3,4,16,17,19,20}), 133.13 (ethylene CH, C^{29}), 137.25 (SO$_2$-phenyl, C^{18}), 145.88 (C-C-phenyl, C^{15}), 156.04 (phenyl-methoxy, C^6), 165.06 (sec. amide, C^{10}), 178.34 (thiourea, C^{25}). Anal. Calcd. for C$_{20}$H$_{22}$ClN$_3$O$_4$S$_2$: C, 51.33%; H, 4.74%; N, 8.98%. Found: C, 51.36%; H, 4.77%; N, 8.96%; *MS: m/z (regulatory intensity):* 468 (12), 411 (16), 367 (22), 341 (25), 290 (36), 279 (83), 256 (100).

5-chloro-N-(4-[N-(4-ethoxyphenylcarbamoyl) sulfamoyl] phenethyl)-2-methoxybenzamide (5d)

White solid, m.p: 194.4°C; IR (KBr, cm^{-1}): 3310, 2978, 1717, 1627, 1554, 1462, 1343, 1248, 1152, 812, 540; ^{1}H-NMR (δ/ppm): 8.91 (b, 1H, NH-phenyl, H^{26}), 8.55 (b, 1H, sec. amide, H^{11}); 7.85 (d, j=2.8 Hz, 2H, benzene-SO$_2$, H^{17,19}); 7.70 (d, j=0.4 Hz, 1H, benzene-amide, H^4); 7.64 (d, j=1.2 Hz, benzene-Cl, H^2); 7.45–7.59 (m, 4H, H^{16,20}, H^{29,33}); 7.24 (d, j=6.9 Hz, 1H, benzene-methoxy, H^1); 6.91 (d, j=7.1 Hz, 2H, phenyl-OEt, H^{30,32}); 6.2 (b, 1H, SO$_2$-NH, H^{22}); 4.12 (q, 2H, O-C**H$_2$**-CH$_3$, H^{35}); 3.79 (s, 3H, O-CH$_3$, H^9); 3.65 (t, 2H, amide-C**H$_2$**-CH$_2$, H^{13}); 2.89 (t, 2H, amide-CH$_2$-**CH$_2$**, H^{14}); 1.42 (t, 3H, O-CH$_2$-**CH$_3$**, H^{36}); ^{13}C-NMR (δ/ppm): 14.69 (O-CH$_2$-**CH$_3$**, C^{36}), 34.73 (amide-CH$_2$-**CH$_2$**, C^{14}), 40.34 (amide-**CH$_2$**-CH$_2$, C^{13}), 56.20 (O-CH$_3$, C^9), 63.11 (O-**CH$_2$**-CH$_3$, C^{35}), 114.49 (phenyl, C^{1,30,32}), 120.87 (phenyl, C^{5,29,33}), 124.37 (phenyl, C^{3,17,19}), 127.60 (phenyl, C^{3,4,16,20}), 131.55 (phenyl, C^2), 138.01 (SO$_2$-phenyl, C^{18}), 145.44 (C-C-phenyl, C^{15}), 154.04 (phenyl-methoxy, C^6), 156.63 (phenyl-OEt, C^{31}), 155.70 (urea, C^{25}), 163.70 (sec. amide, C^{10}). Anal. Calcd. for C$_{25}$H$_{26}$ClN$_3$O$_6$S: C, 56.44%; H, 4.93%; N, 7.90%. Found: C, 56.48%; H, 4.96%; N, 7.87%; *MS: m/z (regulatory intensity):* 531 (21), 519 (26), 453 (42), 455 (21), 413 (26), 367 (42), 394 (100).

Pharmacological methods
Animals

At the beginning of the experiment, 60 adult male NMRI rats weighing 190–220 g (Razi Institute, Iran), with blood glucose under 150 mg/dl as non-diabetic animals were randomly selected and housed 3–4 per cage in a temperature-controlled colony room under 12 h light/dark cycle. Animals were given free access to water and standard laboratory rat chow (Pars Company, Tehran, Iran). All of the experiments were conducted between 11 a.m. and 4 p.m. under normal room light and 25°C. This study was carried out in accordance with the policies provided in the Guide for the Care and Use of Laboratory Animals (NIH) and those of the Research Council of Shahed University of Medical Sciences (Tehran, Iran).

Serum parameters analysis

For the induction of diabetes, a single dose of stereptozotocin (STZ) (Sigma, U.K.) in 60 mg/kg was injected intraperitonealy to all selected animals (with serum glucose under 150 mg/dl). They were randomly divided into 5 groups: Control, Glybenclamide (**5a**), triethoxysilyl propane (**5b**), allyl (**5c**) and ethoxyphenyl (**5d**) groups. These drugs (each one at 0.25 mg/kg, i.p) were injected to the animals' everyday from day 3 to 6 after STZ injection. Glucose in the serum as the main parameter for efficiency of origin or new antidiabetic drugs were measured on days 4 and 16. Other serum parameters i.e., triglyceride, total cholesterol, LDL, HDL and VLDL were all calculated on day 16 after STZ application [18]. For measuring the above mentioned serum parameters, blood samples were collected. Serum glucose concentrations, triglyceride, total cholesterol and HDL cholesterol levels were spectrophotometrically measured using appropriate kits (Zistshimi, Tehran). Only those animals with serum glucose content of higher than 250 mg dl^{-1} were selected as diabetics for the following measurements. However, LDL and very low density lipoprotein (VLDL) cholesterol levels were calculated using the following formula:

$$VLDL = Triglyceride/5$$

$$LDL = Total\ cholesterol - HDL\ cholesterol - VLD$$

Statistical analysis

Data from the measurements were expressed as the means±S.E.M. Comparisons were carried out using one way analysis of variance (ANOVA) followed by post-hoc Tukey test and p-value <0.05 as the level of significance.

Results
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Chemistry

Sulfonylurea compounds (such as glibenclamide) are chemically urea derivatives with an arylsulphonyl group to one nitrogen and another group which usually determines the lipophilic properties of the molecule attached to terminal nitrogen of urea such as alkyl, alicyclic, heterocyclic and etc. [20].

The desired titled products (**5a–d**) were synthesized from readily available materials. Moreover, a convenient synthetic route has been developed and depicted in ◘ **Fig. 1**. Initially, 5-chloro-2-methoxy benzoyl chloride (**1**) was synthesized from 5-chloro-2-methoxy benzoic acid and thionyl chloride in the presence of DMF as a catalyst. Then, it was reacted with 2-phenylethylamine in the presence of potassium hydroxide to obtain 5-chloro-2-methoxy-N-phenethylbenzamide (**2**). Reaction of **2** with chlorosulphonic acid in chloroform and ammonium hydroxide solution yields sulfonyl chloride (**3**) and sulfonamide (**4**) compounds [19]. The sulfonamide compound (**4**) was reacted with corresponding isothiocyanate or isocyanates in acetone to obtain the final drugs (**5a–d**). Spectroscopic data (IR, ^{1}H and ^{13}C NMR, Mass, CHN) confirmed the structure of new compounds. The purity of the compounds was determined by TLC using ethyl acetate-hexane as the eluent.

Pharmacology
General Consideration

Mortality (number of death), morbidity (defined as any abnormal condition or behavior due to a disorder), irritability (a con-

dition of aggressiveness or increased response on handling) and other related abnormal states were observed in experimental animals. However, the motor coordination index (measured by Rota-rod apparatus, Harvard, UK) did not indicate any significant differences between treated rats.

The effect of 5a–d compounds on serum glucose level: There was no blood serum level difference for glucose between the control and experimental groups 4 days after STZ injection (○ **Fig. 3**). However, 16 days after STZ application, a significant reduction in glucose level was found in **5a** (265.00 ± 44.76), **5c** (284.28 ± 77.04) and **5d** (265.00 ± 51.99) compared to the control groups (558.00 ± 53.69) ($p < 0.01$).

The effect of 5a–d compounds on serum lipid profiles: The mean values of blood serum parameters including cholesterol, triglyceride, LDL, HDL and HDL/LDL ratios are shown in ○ **Table 1**. As indicated, LDL levels in **5c** and **5d** reached 15.48 ± 5.98 and 24.10 ± 4.20 respectively, which were significant compared to the control groups (43.96 ± 4.89) ($p < 0.05$). Moreover, HDL level in **5d** (49.63 ± 3.27) experimental groups was reduced significantly (60.57 ± 8.29) ($p < 0.05$). However, a large HDL/LDL ratio was found as a good sign for lipid profile in **5c** (4.4) and **5d** (2.05) groups.

Discussion
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Type II diabetes patients are frequently forced to follow multi-pharmacological therapeutic regimens composed of several drugs, targeted to glycaemic control on the one hand, and to reduction of cardiovascular complications on the other [21]. Inhibitors of KATP channel activity fall into 2 groups: the first group interacts with Kir6.2 and the second with SUR. Sulfonylureas closed KATP channels by binding with high affinity to SUR

Fig. 3 The effect of Glybenclamide and its new derivates on serum glucose level at 4 and 16 days after STZ injection. Bars show the mean ± SEM serum glucose. n = 12 in each group. ** p < 0.01 show the difference with control group.

and also with low affinity to Kir6.2. All drugs that block KATP channels stimulate insulin secretion, but only those that interact with the SUR subunit are used therapeutically to treat NIDDM [22]. In addition to β cells, the cardiovascular system also shares KATP-channels. Some sulphonylurea derivatives have been reported to block the opening of KATP-channels in myocardial and vascular smooth muscle cells and may have adverse cardiovascular effects [23]. There are 3 sulphonylurea receptor isoforms: SUR1, and 2 splice products of a single gene differing only in their carboxyterminal 42 ± 45 amino acids, SUR2A and SUR2B. While SUR1 acts as the regulatory subunit of the KATP-channels in β-cells and many neurons, SUR2A is suggested to represent the sulphonylurea receptor in the heart and skeletal muscles and SUR2B in smooth muscle [24]. So far, many analogues of glibenclamide have been synthesized by changing liphophilic and hydrophilic regions of the molecule by different chemical groups; for example, exchanging cyclohexyl ring of **5a** by a methyl group markedly reduces the selectivity for SUR1 [24–26]. Glibenclamide has been reported to bind with high affinity to SUR1, but with more than 100 fold lower affinity to SUR2A and SUR2B. Also the affinities for its binding to SUR1 or SUR2A and SUR2B are very similar to the affinities for its binding to membranes from β-cells or heart and vascular smooth muscle, respectively [26]. Therefore, the search for novel glibenclamide derivatives originates from the idea that to ameliorate the insulin resistance without stimulating insulin release from β-cells and to improve the behavior by adding new chemical moieties to its structure while preserving its more binding affinity to SUR1 and less to SUR2 receptors [27] for targeted to glycaemic control and to reduce the side effects known to be a risk factor for ischemic heart disease, on the other hand. Ethoxyphenyl amine (ethoxyaniline) derivatives showed Na$^+$/ Ca^{2+} exchanger (NCX) inhibition activities that resulted in glucose-dependent increases in Ca^{2+} and insulin secretion and also excellent activity for glucokinase as the targets for developing novel glucose-sensitive insulinotropic and lowering blood glucose level drugs for treatment of NIDDM [12–14].

Ethoxysilyl derivatives also indicated antidiabetic properties [17]. Arylamine analogues have shown antagonistic properties at the melanin-concentrating hormone receptor 1 (commonly abbreviated as MCH R1, MCH1, and MCH-1R), which are important mediators of body weight, treatment of obesity and other associated or related diseases and conditions such as NIDDM [15, 16]. Therefore, these key antidiabetic ligands are selected for substitution instead of cyclohexyl moiety in glibenclamide.

All of the newly synthesized drugs showed more antidiabetic effects compared to the control groups. Newly triethoxysilyl propane compound (**5b**) showed less anti-hyperglycemic effects compared to other treatment drugs which may be caused by higher steric hindrance of triethoxy groups on Si atom as a factor in the lack of binding to the SUR1 receptor. Allyl and ethoxyphe-
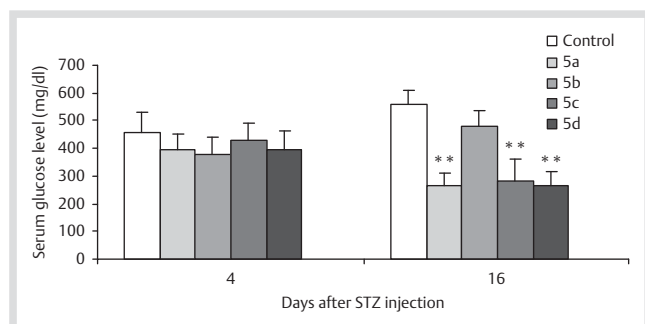
Table 1 Blood serum lipid parameters in control and experimental animals.

Group tests	Serum parameter (mg/dl)				
	Cholesterol	TG	LDL	HDL	HDL/LDL ratio
Control	148.28 ± 19.14	118.57 ± 12.29	43.96 ± 4.89	60.57 ± 8.29	1.37
5a	168.83 ± 23.43	125.32 ± 14.06	38.86 ± 5.75	55.57 ± 7.41	1.43
5b	137.63 ± 15.57	150.60 ± 07.69	39.60 ± 5.81	58.02 ± 4.24	1.46
5c	142.65 ± 17.70	171.05 ± 12.50	15.48 ± 5.98 *	68.74 ± 3.67	4.4
5d	152.16 ± 16.89	139.32 ± 08.71	24.10 ± 4.20 *	49.63 ± 3.27 *	2.05

Numbers show mean ± SEM, *p < 0.01 comparison with control animals. n = 12

nyl analogues (**5c, d**) exhibited more significant lowering blood activities similar to glibenclamide (**5a**), high efficiency for reduction of serum LDL level which results in a high HDL/LDL ratio (as a good lipid profile) leading to more production and significant hypolipidemic activities compared to other groups. No significant difference in triglycride and cholesterol levels in newly synthesized drugs and glibenclamide was observed.

These results indicated that similar affinities that bind with SUR1 receptor and stimulate β cells of pancreas would lead to the same antidiabetic effects in these new drugs which are identical to glibenclamide and extra pancreatic activities in the liver, kidney, brain, skeleton, heart, smooth muscles [1,28] or other mechanisms including insulin-mediated lipolytic activity by inhibition of hormone-sensitive lipase or lipogenic enzymes [29], and/or activation of lipoprotein lipase [30], may be proposed for these higher hyporlipidemic activities.

Conclusion
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It can be concluded that changing cyclohexyl moiety with aryl and ethoxyphentl groups can produce more significant hypoglycemic potency and more marked reduction in serum LDL level which results in a high HDL/LDL ratio (as a good lipid profile). This may be considered as a useful result for hypolipidemic interpretation activities of sulfonylurea drugs in future.

Acknowledgements
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Conflict of Interest
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The authors have declared no conflict of interest.

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