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Synthesis and Anti-Diabetic Evaluation of Some Biuret Derivatives in Streptozotocin-Induced Diabetic Mice

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ABSTRACT:

The Present study was conducted to examine the anti-diabetic effect of eighteen biuret derivatives in Streptozotocin-induced diabetic mellitus mice. Due to the similarity in chemical structure between biuret derivatives and anti-diabetic drugs such as glibenclamide and metformin, these compounds may exhibit an anti-diabetic effect. In this study, eighteen biuret derivatives were synthesized, and their anti-diabetic effects on streptozotocin-induced diabetic mellitus in male mice were evaluated. Their anti-diabetic effect was compared with glibenclamide, used as a reference agent, and their vehicle after 1, 2, and 4 hours of administration. The results of the present study indicated that these synthesized biuret derivatives need at least two hours to reduce blood glucose. The anti-diabetic effect of these compounds increased with time. There are some relationships between their effects and structures. Among these compounds, which have short (phenyl alkylamine) and (aminoquinaldine) moieties, showed the best activity. In contrast, derivatives with long-chain (phenyl propylamine), (mercaptobenzothiazole), and (phenyl tetrazole) substituents, which lead to more lipophilicity, had no significant hypoglycemic effect. These biuret derivatives can be considered as potential anti-diabetic agents in mice, showing comparable anti-diabetic activity to glibenclamide. Some of them exhibited both dose- and time-dependent effects in mice, similar to glibenclamide.

Keywords: Biuret; Anti-diabetic effect; Streptozotocin; Glibenclamide; Mice.

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1. Introduction

Diabetic mellitus is expected to rise from 171 million cases in 2000 to 366 million cases in 2030 and 642 million cases by 2040 [1]. This disease is conventionally divided into four subtypes: type I and latent autoimmune diabetes of the adult (LADA), type II, type III (specific types due to other causes such as monogenic diabetic syndromes, diseases of the exocrine pancreas, and drug- or chemical-induced diabetes), and type IV gestational diabetes [2]. Either type I or LADA often results from autoimmune beta-cell destruction, mediated by pancreatic autoantibodies in the blood [3]. Plasma or serum identification of such antibodies is a strong indication that the patient will ultimately require insulin treatment to maintain glucose homeostasis [4]. Correct diagnosis requires sequencing of known diabetic genes, which are valuable for accurate choice of treatment [5]. Around 10–15% of the diabetic patients are considered to have type I and 75–80% type II after exclusion of other types (III and IV) [2].

Harold Himsworth defined the presence of insulin-sensitive and insulin-insensitive diabetes in 1936 [6, 7]. In 1950, RD Lawrence suggested a new clinical classification of diabetic patients into those who are not insulin-deficient and those who are insulin inefficient. Types I and II were created in 1955 and have since been used for patient groups with different definitions related to the main clinical characteristics of severity, age at onset, insulin sensitivity, and insulin deficiency [8]. The discovery of autoantibodies to pancreatic islet cells led to the concept of autoimmunity, which is used to define type I of the disease [9]. In some patients, signs of both beta-

cell autoimmune destruction and profound insulin resistance have been shown [10]. Causes of type II of the disease are multifactorial, resulting from the combined effects of either genetic or unhealthy lifestyles such as physical inactivity and poor diet. Unfortunately, 30 to 80% of type II diabetic patients are estimated to be undiagnosed. Despite advances in drug therapy and the availability of clinical practice guides, only 30 percent of patients achieve the target values of normo-glycaemia [11, 12]; therefore, the development of newer compounds can result in a more effective management of this condition.

Biuret derivatives have been associated with a wide variety of different pharmacological activities. McColl and colleagues have reported the synthesis of some biuret, as well as their effect on the secretion of gastric acid and prevention of peptic ulcers [13]. Synthesis of N, N`-diphenyl, N-phenyl-N`-alkylphenyl, and N, N`-bis alkylphenyl biurets and analogous compounds by replacing one phenyl group with 2-methyl quinoline-4-yl, benzo[d]thiazol-2-ylthio, and (1-phenyl-1H-tetrazol-5-yl) thio moieties, and their cytotoxic effect against the T47D breast cancer cell line has been shown [14]. In addition, Adibpour and her coworkers have reported the antinociceptive effect of certain biuret derivatives [15]. Kajitani et al. also investigated the analgesic and antiinflammatory properties of arylbiurets [16]. Also, it has been demonstrated that biuret derivatives are capable of inhibiting the pteridine reductase one activity of various Leishmania strains, suggesting that these compounds have the potential to act as antileishmaniasis drugs. In comparison to glucantime, the activity of certain N, N'-diphenyl, N-phenyl-N'-alkylphenyl, and N, N'-bis alkylphenyl biurets was found to be significantly higher against Leishmania major and Leishmania infantum promastigotes [17].

Kriesel et al. demonstrated the hypoglycemic activity of p-toluenesulfonyl-biurets and alkyl p-toluenesulfonylthiocarbamates in non-diabetic mice [18]. Due to the similarity in chemical structure between biuret derivatives and anti-diabetic drugs such as sulfonylureas and biguanides, these compounds may have an anti-diabetic effect. The present study was conducted to examine the anti-diabetic effect of some biuret derivatives using streptozotocin-induced diabetic mellitus in mice.

2. Materials & Methods

2.1. Chemicals

Phenyl propyl amines, aniline, bromopropyl ammonium bromide, streptozotocin (STZ), glibenclamide, phosphate buffer, and dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich, USA. Benzyl amines, 2-phenylethylamine, 4-aminoquinaldin, 2-mercaptobenzothiazol, phenyl chloroformate, potassium isocyanate, pyridine, sodium chloride, sodium sulfate, and concentrated sulfuric acid were purchased from Merck, Germany.

2.2. Synthesis of phenyl-substituted biuret derivatives

Synthesis and purification of the biuret derivatives (4e-4v in Figure 1) were performed as previously reported [14]. Briefly, biurets were prepared through the reaction of several phenyl allophanates synthesized from phenyl chloroformate and urea derivatives with variously substituted amines.

2.3. Study animals

Male mice weighing 20.2 to 25.6 g were used. The animals were kept in Plexiglass cages with a 12 h light/12 h dark cycle and temperature control (22±2°C). They were provided with an unlimited supply of food and water. Each animal was used only once per experiment, and all procedures were conducted in accordance with the Guide for the Care and Use of Laboratory Animals of the Institutional Animal Ethical Committee (IP.ZUMS.REC.1397.247).

2.4. Diabetic induction

The diabetes was induced by intraperitoneal injection of streptozotocin (50 mg/kg) for 5 days continuously. Fasting blood sugar (FBS) was measured after three days. The animals were considered diabetic if blood glucose levels were more than 200 mg/dL [19].

2.5. Assessment of the anti-diabetic effect of the biuret compounds

In order to evaluate the anti-diabetic effect of biuret derivatives (compounds 4e-4v in Figure 1), diabetic mice (n=5) were administered 10, 30, and 90 mg/Kg of the tested compounds. Similar doses of glibenclamide were administered to three different groups of diabetic mice, too. Another group of diabetic animals received a mixture of DMSO (≤3%) and water (used as the vehicle for the compounds or glibenclamide). The plasma glucose concentration was measured with a glucometer either prior to or at (1, 2, and 4 hours) after the drug administration. Blood samples (10 µL) were collected from the animals' tail veins, and the collection of specimens was conducted in accordance with all applicable laws, guidelines, and regulations. As a measure of anti-diabetic activity, the comparison of fasting blood sugar (FBS) levels to those of the control groups (DMSO 3% and glibenclamide, used as negative and positive controls, respectively) was utilized for statistical analysis. Animals had access to food and water after compound administration.

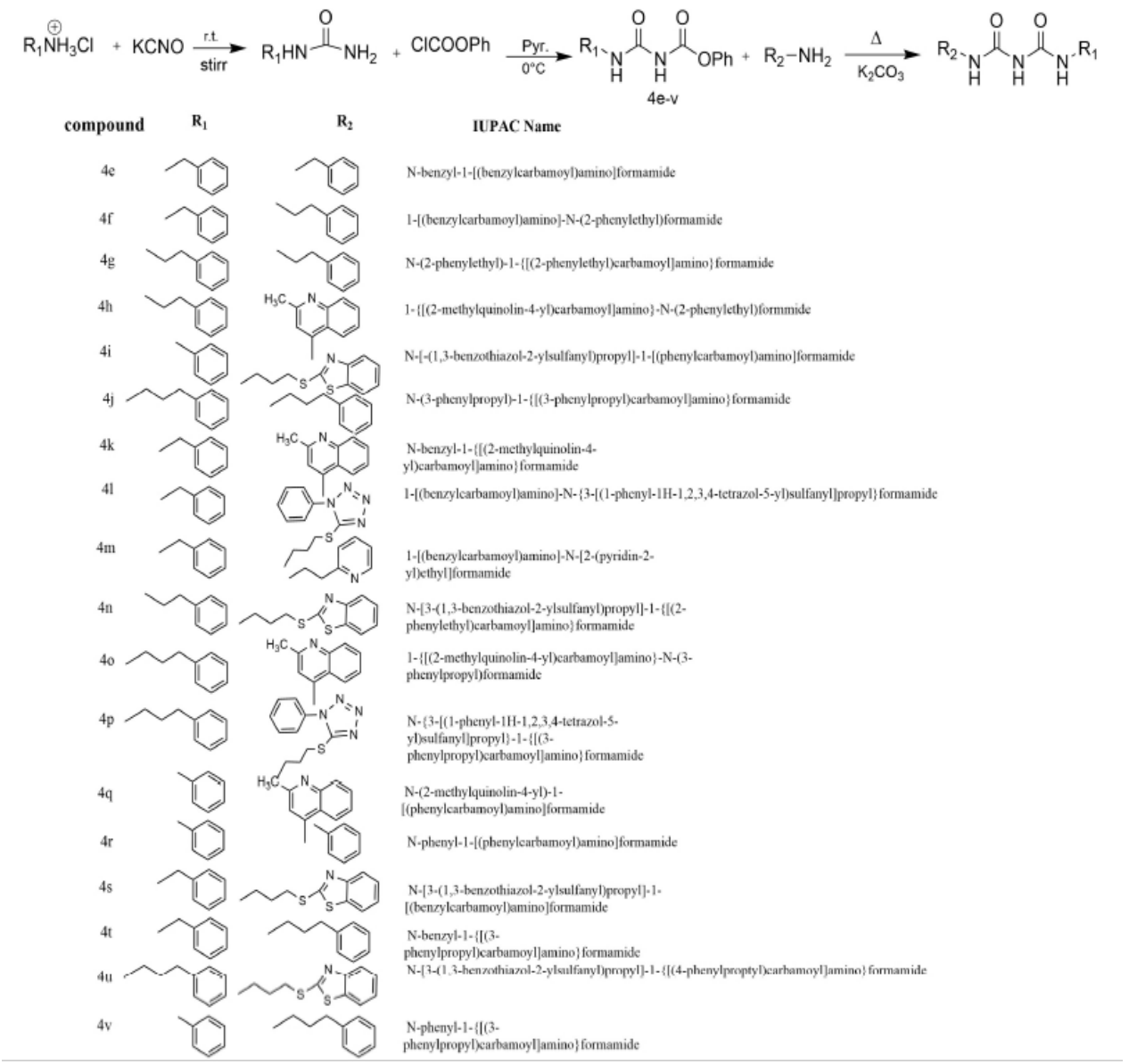

Figure 1. The chemical structures and their IUPAC names of 4e to v compounds.

2.6. Lethal dose 50 (LD50) evaluations

A 4-Level Up and Down Procedure is indicated for the lethal dose 50 (LD_{50}) estimation of these biuret derivatives in mice [20].

2.7. Statistical analyses

Following the analysis of variance (ANOVA), Tukey's test was used to compare the changes in blood glucose concentration between the different biuret derivatives and the control groups (DMSO 3% and glibenclamide). Repeated-measures analysis of covariance was performed to assess the time-dependent effect of the tested biuret compound. P-values less than 0.05 were considered statistically significant.

3. Results & Discussion

3.1. Dose-dependent effects of biuret compound treatments in diabetic mice

The hypoglycemic effect of glibenclamide was dose dependent [$F(3, 12)=31.412$, 39.629 and 71.497, $P<0.001$ for all] for 1, 2 and 4 hours respectively, also the effect of 4e was dose dependent after 2 and 4 hours of the biuret

administration [F(3, 12)= 0.77, 6.826 and 20.981, P=0.97, 0.004 and <0.001 for 1, 2 and 4 hours respectively], moreover this effect of 4f was dose dependent after 2 and 4 hours of the biuret administration [F(3, 12)=0.08, 8.689 and 17.915, P=0.97, 0.001 and <0.001 for 1, 2 and 4 hours respectively], furthermore the effect of 4g was dose dependent after 2 and 4 hours of the biuret administration [F(3, 12)=0.08, 3.864 and 10.381, P=0.97, 0.03 and <0.001 for 1, 2 and 4 hours respectively], additionally the effect of 4h was dose dependent after 2 and 4 hours of the biuret administration [F(3, 12)=0.296, 28.049 and 44.6, P=0.82, <0.001 and <0.001 for 1, 2 and 4 hours respectively].

The hypoglycemic effect of 4i was not dose dependent [F(3, 12)=0.561, 2.974 and 2.538, P=0.64, 0.06 and 0.09 for 1, 2 and 4 hours respectively], but this outcome of 4j was dose dependent after 2 and 4 hours of the biuret administration [F(3, 12)=0.67, 3.712 and 3.33, P=0.58, 0.03 and 0.04 for 1, 2 and 4 hours respectively], also the effect of 4k was dose dependent after 4 hours of the biuret administration [F(3, 12)=0.392, 0.341 and 11.522, P=0.76, 0.79 and <0.001 for 1, 2 and 4 hours respectively], likewise the influence of 4l was dose dependent after 4 hours of the biuret administration [F(3, 12)=0.311, 0.344 and 11.347, P=0.81, 0.79 and <0.001 for 1, 2 and 4 hours respectively], similarly the consequence of 4m was dose dependent after 4 hours of the biuret administration [F(3, 12)= 0.311, 2.312 and 40.988, P=0.7, 0.11 and <0.001 for 1, 2 and 4 hours respectively], nonetheless the effect of 4n was not dose dependent [F(3, 12)=2.66, 1.3 and 0.478, P=0.08, 0.3 and 0.7 for 1, 2 and 4 hours respectively], moreover the hypoglycemic result of 4o was not dose dependent [F(3, 12)=0.957, 0.82 and 1.609, P=0.43, 0.5 and 0.22 for 1, 2 and 4 hours respectively], besides the outcome of 4p was not dose dependent [F(3, 12)=0.725, 0.381 and 0.263, P = 0.55, 0.76 and 0.85 for 1, 2 and 4 hours respectively], on the other hand the hypoglycemic influence of 4q was dose dependent after 2 and 4 hours of the biuret administration [F(3, 12)= 0.253, 10.969 and 38.713, P=0.85, <0.001 and <0.001 for 1, 2 and 4 hours respectively], similarly the effect of 4r was dose dependent after 2 and 4 hours of the biuret administration [F(3, 12)= 0.581, 6.542 and 13.42, P=0.63, 0.004 and <0.001 for 1, 2 and 4 hours respectively], But, this effect of 4s was not dose dependent [F(3, 12)=0.241, 0.56 and 0.732, P=0.86, 0.64 and 0.58 for 1, 2 and 4 hours respectively], however the hypoglycemic outcome of 4t was dose dependent after 2 and 4 hours of the biuret administration [F(3, 12)=0.998, 7.365 and 10.561, P=0.41, 0.03 and <0.001 for 1, 2 and 4 hours respectively], but then again, the effect of 4u was not dose dependent [F(3, 12)=2.411, 1.025 and 2.308, P=0.1, 0.4 and 0.11 for 1, 2 and 4 hours respectively], then this outcome of 4u was dose dependent after 4 hours of the biuret administration [F(3, 12)=0.597, 1.027 and 15.896, P=0.62, 0.4 and <0.001 for 1, 2 and 4 hours respectively].

Biuret derivatives have been shown several pharmacological activities, e.g., lessening secretion of gastric acid and the prevention of peptic ulcers [13], cytotoxic effect against T47D breast cancer cell line was shown [14], antinociceptive effect [15], analgesic and antiinflammatory properties [16], and inhibiting the pteridine reductase one activity of various leishmania strains [17]. Due to the similarity in chemical structure between these biuret derivatives and (sulfonylureas and biguanides), the present study was conducted.

From the viewpoint of dose-dependent effects of glibenclamide or biuret compound treatments in diabetic mice, they can be divided into four kinds of effects.

First: dose-dependent effects at all times (1, 2, and 4 hours after treatment), which have been shown just by glibenclamide. Second: dose-dependent effect after both 2 and 4 hours of treatment, which have been represented by 4e, 4f, 4g, 4h, 4j, 4q, 4r, 4t and 4v. Third dose dependent effects only after 4 hours of treatment which have been indicated by 4k, 4l, and 4m. Fourth: dose independent effect which has been showed by 4i, 4n, 4o, 4p, 4s and 4u.

Dose-dependent data (Figures 2-4) indicated that in diabetic mice, the highest reduction in glucose level was seen by 4e, 4f, 4g, 4h, 4j, 4q, 4r, 4t, and 4v biuret compounds. Moreover, all the biuret derivatives, except 4i, 4n, 4o, 4p, and 4u, showed a relatively statistically significant anti-diabetic effect in streptozotocin-induced diabetic mice in comparison to the control (DMSO) group. Among the eighteen biuret derivatives which have been tested for the anti-diabetic effect, compounds 4e to h were found to have a comparable effect to glibenclamide.

3.2. Time-dependent effects of biuret compound treatments in diabetic mice

The hypoglycemic effect of 10, 30 and 90 mg/Kg glibenclamide was time dependent [F(2, 8)=116.037, 77.178 and 23.421, P<0.001, <0.001 and <0.001 for 10, 30 and 90 mg/Kg respectively, also this effect of 30 and 90 mg/Kg 4e was time dependent [F(2, 8)=3.388, 8.761 and 23.664, P=0.08, 0.01 and <0.001 for 10, 30 and 90 mg/Kg respectively], moreover, the result of 10 and 30 and 90 mg/Kg 4f was time dependent [F(2, 8)=10.1, 60.05 and 112.195, P<0.001, <0.001 and <0.001 for 10, 30 and 90 mg/Kg respectively], furthermore the effect of 10, 30 and 90 mg/Kg 4g was time dependent [F(2, 8)=5.168, 38.05 and 82.458, P=0.01, <0.001 and <0.001 for 10, 30 and 90 mg/Kg respectively].

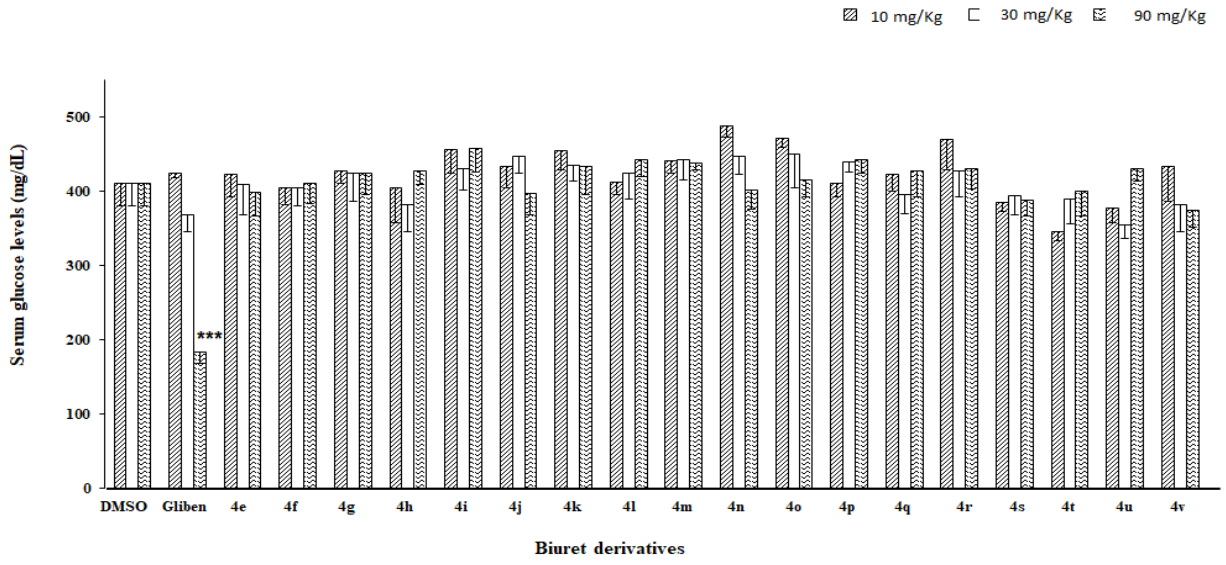

Figure 2. Fasting blood sugar (FBS) in diabetic animals which received Gliben (glibenclamide) or biuret compounds (10, 30 and 90mg/Kg) after 1hour of the biuret compound administration: 4e to v compounds: *** represent P< 0.001 respectively in coprarisson to DMSO control group.

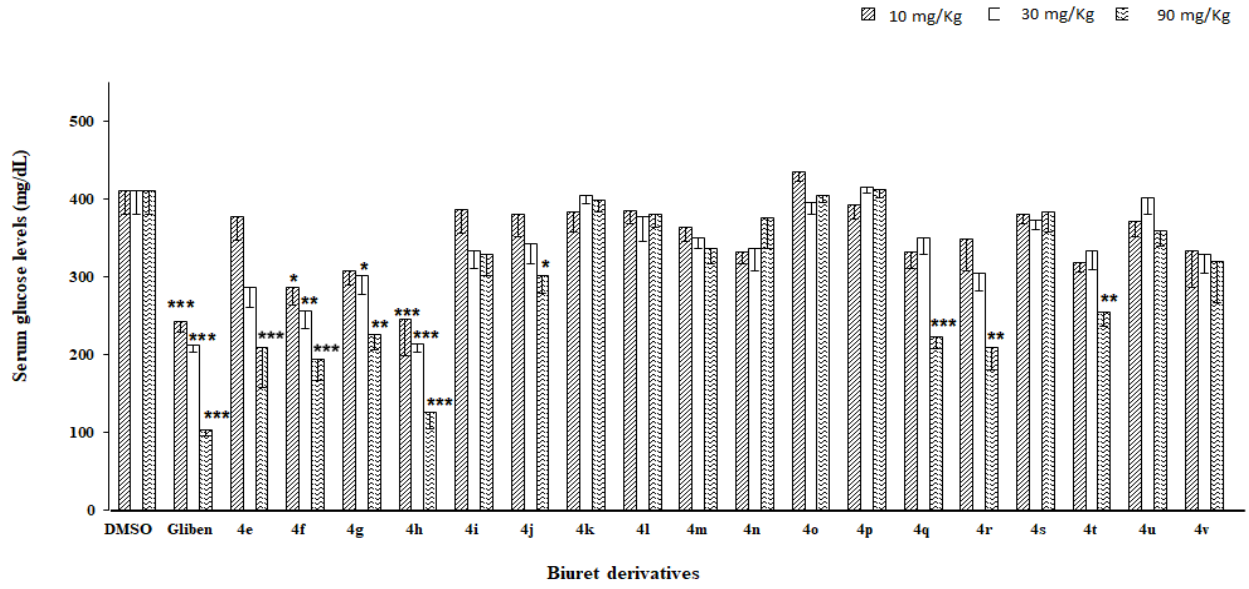

Figure 3. Fasting blood sugar (FBS) in diabetic animals which received Gliben (glibenclamide) or biuret compounds (10, 30 and 90mg/Kg) after 2 hours of the biuret compound administration: 4e to v compounds: *, ** and *** represent P<0.05, 0.01 and 0.001 respectively in comparison to DMSO control group.

The consequence of 10, 30 and 90 mg/Kg 4h was time dependent too [F(2, 8)=18.167, 20.481 and 167.002, P=0.001, 0.001 and <0.001 for 10, 30 and 90 mg/Kg respectively], also the influence of 90 mg/Kg 4i was time dependent [F(2, 8)=3.864, 4.203 and 11.563, P=0.06, 0.057and 0.004 for 10, 30 and 90 mg/Kg respectively] moreover, the consequence of 30 and 90 mg/Kg 4j was time dependent [F(2, 8)=2.907, 5.526 and 6.931, P=0.11, 0.03 and 0.01 for 10, 30 and 90 mg/Kg respectively], also the effect of 10, 30 and 90 mg/Kg 4k was time dependent [F(2, 8)=8.561, 15.701 and 30.115, P=0.01, 0.002 and <0.001 for 10, 30 and 90 mg/Kg respectively], the hypoglycemic outcome of 30 and 90 mg/Kg 4l was time dependent too [F(2, 8)=4.382, 13.138 and 59.407, P=0.05, 0.003 and <0.001 for 10, 30 and 90 mg/Kg respectively], the hypoglycemic influence of 10, 30 and 90 mg/Kg 4m was time dependent [F(2, 8)= 12.869, 21.24 and 79.772, P=0.003, 0.001 and <0.001 for 10, 30 and 90 mg/Kg respectively].

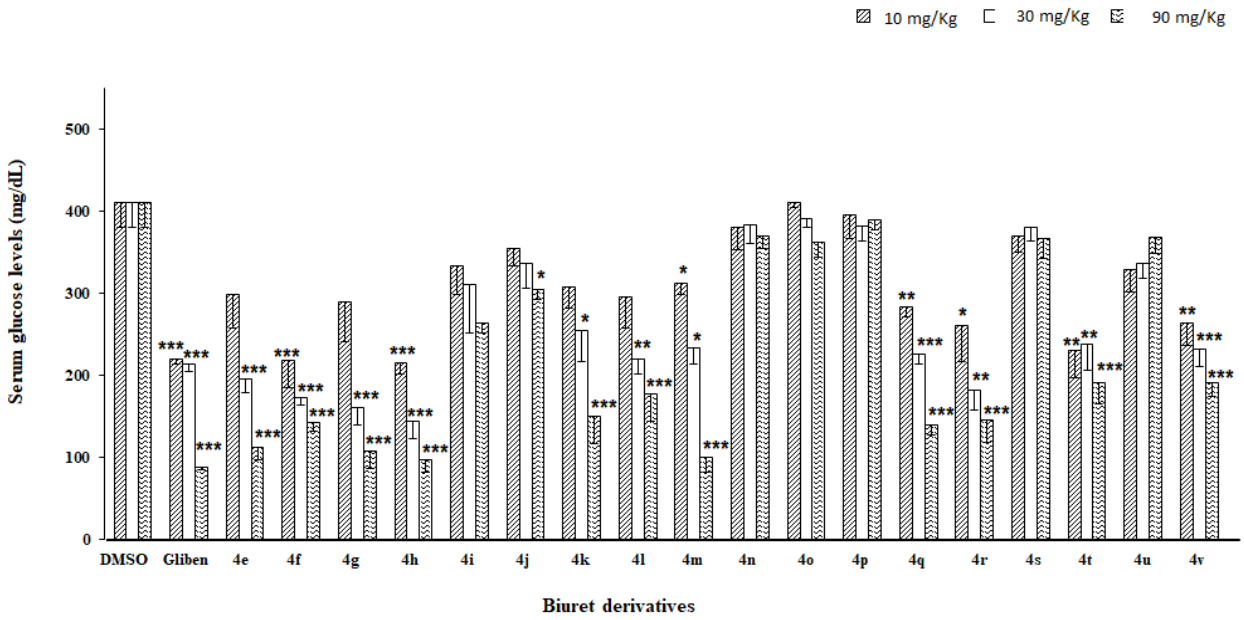

Figure 4. Fasting blood sugar (FBS) in diabetic animals which received Gliben (glibenclamide) or biuret compounds (10, 30 and 90mg/Kg) after 4 hours of the biuret compound administration: 4e to v compounds: *,** and *** represent P< 0.05, 0.01 and 0.001 respectively in coprarisson to DMSO control group.

Moreover the effect of 10 and 30 mg/Kg 4n was time dependent [F(2, 8)=8.464, 4.808 and 0.305, P=0.01, 0.04 and 0.745 for 10, 30 and 90 mg/Kg respectively], additionally the result of 10 mg/Kg 4o was time dependent [F(2, 8)=6.99, 1.599 and 2.174, P=0.01, 0.26 and 0.17 for 10, 30 and 90 mg/Kg respectively], moreover **t**he consequence of 30 mg/Kg 4p was time dependent [F(2, 8)=0.33, 5.61 and 3.049, P = 0.728, 0.03 and 0.104 for 10, 30 and 90 mg/Kg respectively], furthermore hypoglycemic effect of 10, 30 and 90 mg/Kg 4q was time dependent [F(2, 8)=16.682, 18.359 and 110.292, P=0.001, 0.001 and <0.001 for 10, 30 and 90 mg/Kg respectively, the effect of 10, 30 and 90 mg/Kg 4r was time dependent too [F(2, 8)=28.204, 17.184 and 50.472, P<0.001, =0.001 and <0.001 for 10, 30 and 90 mg/Kg respectively], but the effect of 4s was not time dependent [F(2, 8)=0.271, 0.487 and 0.243, P=0.76, 0.63 and 0.79 for 10, 30 and 90 mg/Kg respectively], on the other hand the outcome of 10, 30 and 90 mg/Kg 4t was time dependent [F(2, 8)=5.19, 12.66 and 25.607, P=0.03, 0.003 and <0.001 for 10, 30 and 90 mg/Kg respectively], moreover, the effect of 4u was not time dependent [F(2, 8)=1.075, 2.449 and 3.943, P=0.38, 014 and 0.06] for 10, 30 and 90 mg/Kg respectively], but the result of 10, 30 and 90 mg/Kg 4v was time dependent [F(2, 8)=4.714, 13.39 and 8.343, P=0.04, 0.003 and 0.01 for 10, 30 and 90 mg/Kg respectively].

From the standpoint of time-dependent effects, the treatments with glibenclamide or biuret compounds in diabetic mice exhibited six distinct effects.

First: time-dependent effect by all doses (10, 30, and 90 mg/kg), which have been shown by glibenclamide, 4f, 4g, 4h, 4k, 4m, 4q, 4r, 4t, and 4v. Second, a time-dependent effect was observed at just 10 mg/kg, as presented by 40. Third: time-dependent effect by both 10 and 30 mg/Kg, which has been revealed by 4n. Fourth: time-dependent effects at 30 and 90 mg/kg, as represented by 4e, 4j, and 4l. Fifth: A time-dependent effect is observed at just 90 mg/kg, as represented by 4i. Sixth: a time-independent effect, which 4s and 4u have represented.

Repeated measures analysis of covariance (time dependency) results have shown that glibenclamide, 4f, 4g, 4h, 4j, 4m, 4q,4r,4t, 4v resulted in a time-dependent effect by all doses. However, both 4u and 4s showed an independent hypoglycemic effect in this setting (Figures 5-7).

Dissimilar to glibenclamide, the effect of these biuret compounds on plasma glucose level occurs after two hours of drug administration. These observations could be related to the moderate to high lipophilicity of most of the derivatives, which leads to slower distribution of them from the site of administration. The lowest anti-diabetic effects were seen by derivatives contain (mercaptobenzothiazole), (phenyl tetrazole) and (phenyl propylamine) moieties (4i, 4n, 4u, 4p and 4o), which have less water solubility, moderate to high log P as well as larger molecular size in comparison to the other more potent biuret derivatives (4f, 4g, 4h, 4j, 4m, 4q,4r,4t, 4v) which could lead to lowest activity perhaps due to fewer distribution and unfavored interaction with their receptors.

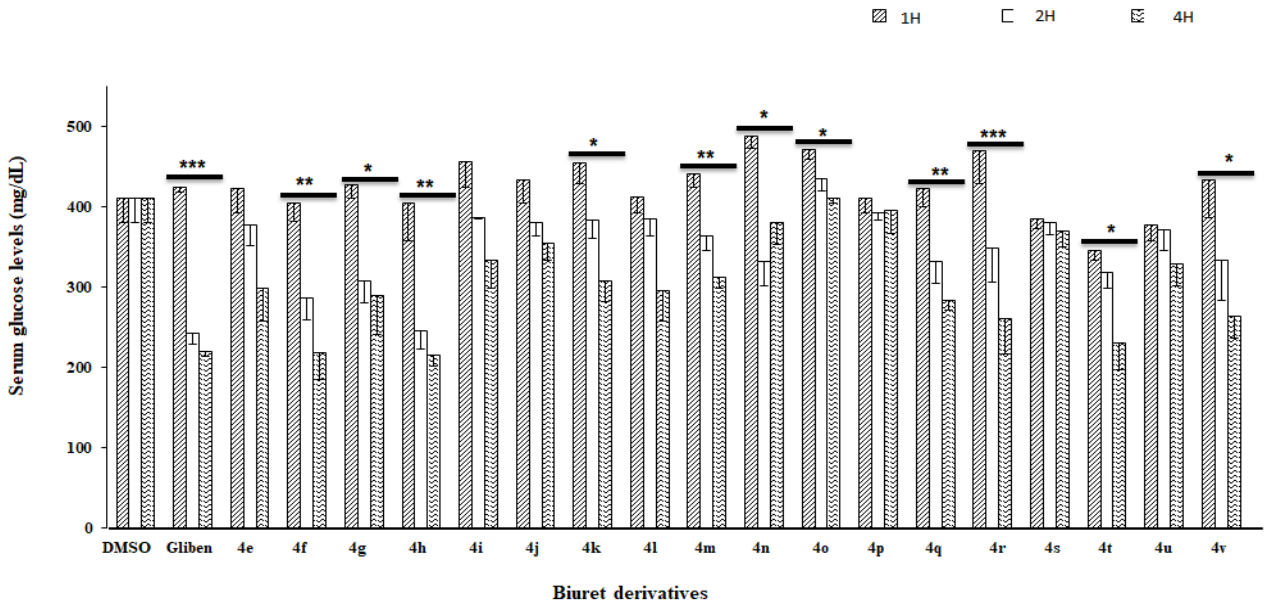

Figure 5. Fasting blood sugar (FBS) in diabetic animals which received Gliben (glibenclamide) or biuret compounds (10 mg/Kg), after 1, 2 and 4 hours of biuret compounds adminidtration): 4e to v compounds: *, ** and *** represent P< 0.05, 0.01 and 0.001 respectively.

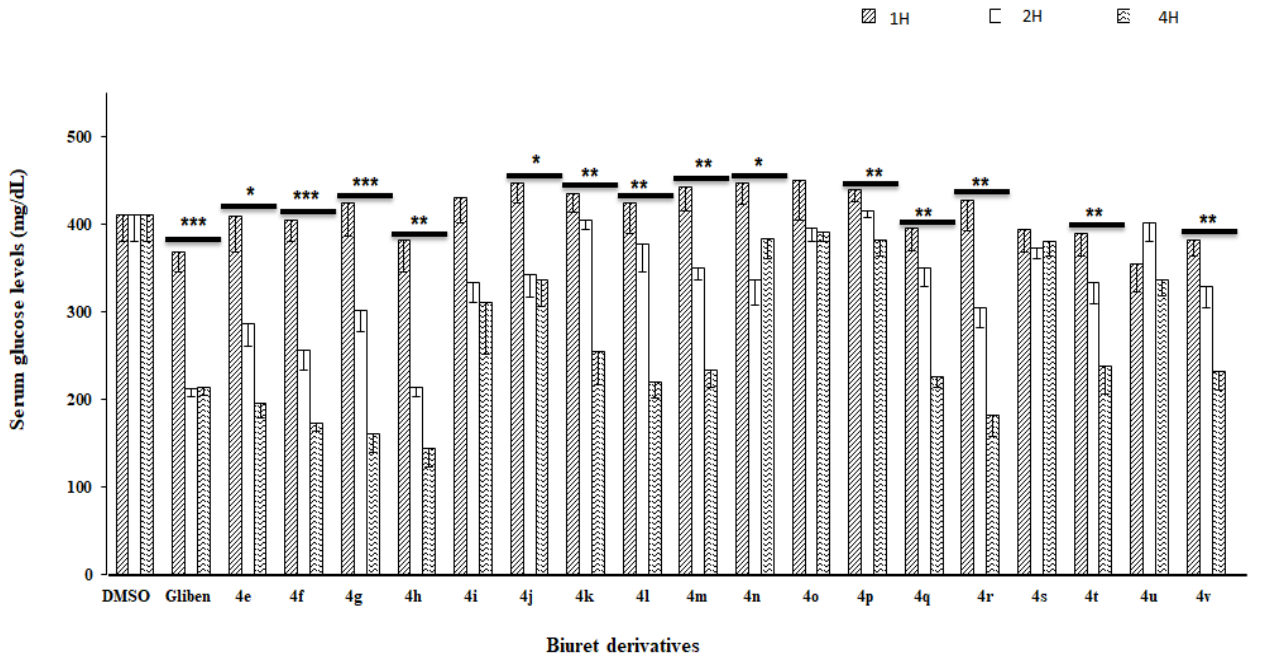

Figure 6. Fasting blood sugar (FBS) in diabetic animals which received Gliben (glibenclamide) or biuret compounds (30 mg/Kg), after 1, 2 and 4 hours of biuret compounds adminidtration): *, ** and *** represent P< 0.05, 0.01 and 0.001 respectively.

However, to accurately determine the hypoglycemic mechanism of action of these biurets, further studies on the identification of their receptor and the interaction between them and their receptor, as well as the determination of their QSAR, should be considered in the future. The result of LD50 assessments showed that the LD50 of all these compounds was greater than 100 mg/Kg.

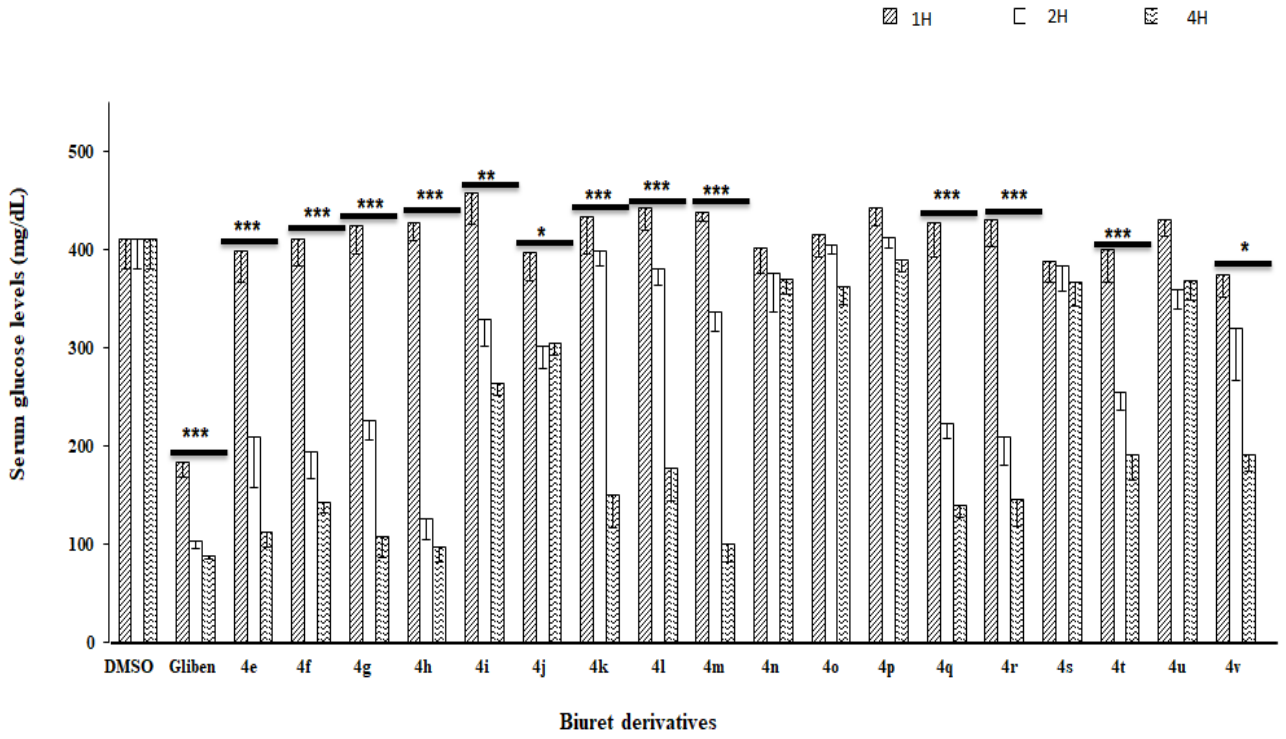

Figure 7. Fasting blood sugar (FBS) in diabetic animals which received Gliben (glibenclamide) or biuret compounds (90 mg/Kg), after 1, 2 and 4 hours of biuret compounds adminidtration): 4e to v compounds: *, ** and *** represent P< 0.05, 0.01 and 0.001 respectively.

4. Conclusion

These biuret derivatives can be considered as potential anti-diabetic agents in mice, and some of them showed comparable anti-diabetic activity to glibenclamide. Additionally, compounds 4e, 4f, and 4h exhibited both dose-dependent and time-dependent effects in mice, but their onset of action was longer than that of glibenclamide.

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Conflict of interest

There is no conflict of interest.

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