

Targeting PPAR γ Receptor Using New Phosphazene Derivative Containing Thiazolidinedione: Design, Synthesis, and Glucose Uptake

Shaikha S. Al Neyadi¹, Abdu Adem², Naheed Amir², Ibrahim M. Abdou^{1*}

¹Department of Chemistry, College of Science, UAE University, Al-Ain, UAE

²Department of Pharmacology, College of Health and Science, UAE University, Al-Ain, UAE

Email: *shaikha.alneyadi@uaeu.ac.ae

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Abstract

The peroxisome proliferator activator receptor- γ (PPAR- γ) remained the most effective target for management of diabetes mellitus. The present work endeavors rational designing new PPAR- γ agonist bearing cyclotriphosphazene and thiazolidine-2,4-dione scaffolds. Thiazolidinedione (TZD) derivatives are the novel class of oral antidiabetic drugs which are selective agonist for the nuclear PPAR γ that enhances the transcription of several insulin responsive genes but TZDs are known to cause weight gain, hepatotoxicity and fluid retention. So, cyclotriphosphazene containing thiazolidine-2,4-dione was designed, synthesized as PPAR γ agonist. The *in-vitro* antidiabetic activity showed that compound **8** has similar activity and exhibited higher glucose uptake in comparison to pioglitazone as reference drugs. This research opened new avenues for smart designing of molecules with high efficiency towards the management of hyperglycemia.

Keywords

Type 2 Diabetes, PPARs, TZD Compound, Cyclotriphosphazene

1. Introduction

Diabetes mellitus is a heterogenous group of disorder, characterized by a state of chronic hyperglycemia, resulting from a variety of etiologies either environmental and genetics, acting jointly [1]. Typically, diabetes is a long term metabolic disorder with a number of complications including cardiovascular, renal, neurological, ocular and other such inter-related problems. Diabetes mellitus (DM)

is one of the major health problems in the world today. The incidence of the disease currently is estimated to reach 300 million by the year 2025. Most cases will be of Type 2 diabetes mellitus, which strongly linked with a sedentary life style and obesity. Recently, chemistry of 2,4-thiazolidinediones (TZDs) has attracted attention as they have been found to exhibit several biological activities, such as antihyperglycemic, anti-inflammatory, antimalarial, antioxidant, anti-tumor, cytotoxic, antimicrobial, and antiproliferative. Thiazolidinediones (TZDs), which are known to sensitize tissues to insulin, have been developed and clinically used as antidiabetic agents. They have been shown to reduce plasma glucose, lipid, and insulin levels, and used for the treatment of type 2 diabetes [2]. As agonists of nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR- γ), thiazolidinediones (TZD) reduce insulin resistance in the liver and peripheral tissues; increase the intake of insulin-dependent glucose and decrease withdrawal of glucose from the liver [3]. Many drugs have been approved from this class for the treatment of diabetes like Rosiglitazone, Pioglitazone, Ciglitazone and many more. Though the marketed drugs show additive effect with other antihyperglycemic agents, they are also prone to show toxicity. For example, Rosiglitazone shows hepatotoxicity [4].

Phosphazenes are class compounds with interesting properties. They showed a number of characteristics such as biomedical properties and applications due to their strong antitumor activity [5]. Their antimicrobial and biological activities on bacterial and yeast cells have been studied [6]. A variety of substitution reactions of the reactive P-Cl bonds provide a wide range of cyclophosphazene derivatives, which have diverse applications [7]. These derivatives are usually synthesized by nucleophilic substitution reactions using alcohol, phenol, amines, Grignard reagents and thiols [8]. Their physical and chemical properties can be tailored by appropriate substituents on the phosphorus atoms.

Hence, there is a need for the development of newer and safer drugs from this class. There is still an urgent need for novel anti-diabetic agents that should have a similar degree of efficacy with a potential to reduce long-term complications. In our efforts to develop the biological profile of these analogues, we have reported an efficient synthesis and screening of new thiazolidinedione derivative as potential antidiabetic drugs. Inspired by the diverse biological properties of thiazolidinedione moiety and cyclotriphosphazene, in the present study, an attempt has been made to synthesize title compound by employing hybridization approach with the hope that the resulting new molecules will have anti-diabetic activity. The structures of the synthesized compounds were assigned based on elemental analysis, IR, ^1H , ^{13}C and ^{31}P NMR spectroscopy. The compound was also screened for their *in-vitro* antidiabetic activity.

2. Material and Methods

2.1. Chemistry

All reagents and chemicals were purchased from Sigma-Aldrich and used with-

out further purification. Thin-layer chromatography (TLC) was performed on silica gel glass plates (Silica gel, 60 F₂₅₄, Fluka) and the spots were visualized under a UV lamp. Column chromatography was performed on a Kieselgel S (silica gel S, 0.063 - 0.1 mm). The melting points were recorded on a Gallenkamp apparatus and were uncorrected. Infrared spectra were measured using KBr pellets on a Thermo Nicolet model 470 FT-IR spectrophotometer. ¹H-NMR spectra were recorded on 400 MHz Varian instruments using DMSO-*d*₆ and CDCl₃ solutions and tetramethylsilane (TMS) as an internal reference. The elemental analysis was performed on Elemental Analysis performed on *Leco* Model CHN-600 *elemental* analyzer. Microwave synthetic protocol done using CEM Microwave system.

2.1.1. Synthesis of 2,2-Dichloro-4,4,6,6-Bis [Spiro (2',2''-Dioxy-1',1''-Biphenyl)]Cyclotriphosphazene (3)

N₃P₃Cl₆ (2 g, 5.75 mmol), bip-henyl-2,2'-diol (2.14 g, 11.51 mmol) and K₂CO₃ (3.98 g, 28.77 mmol) were mixed in 20 ml acetone at 0°C. The reaction mixture was stirred at room temperature for 24 hours and when the reaction was complete the solvent was removed *in vacuo*. The product was extracted by washing with 20 ml of DCM three times. The solvent was then removed under vacuum to produce a white powder. Yield 88%; mp = 274°C; ¹H NMR (CDCl₃, 400 MHz): δ ppm 7.53 (4H, d, *J* = 7.5, H₃), 7.63 (4H, t, *J* = 7.6, H₃), 7.33 (8H, m, H₂, H₄); ¹³C NMR (CDCl₃, 100 MHz): δ ppm 147.8 (d, *J*_{POC} 8.9 Hz, C₁), 130.0 (C₅), 129.8 (C₃), 128.8 (C₆), 126.6 (C₄), 122.0 (C₂).

2.1.2. 2,2-Bis(4-Formylphenoxy)-4,4,6,6-Bis[Spiro(2',2''-Dioxy-1',1''-Biphenyl)]Cyclotriphosphazene (5)

To a mixture of **3** (1 mmol) and 4-hydroxybenzaldehyde (2 mmol) in dry acetonitrile, kept at 0°C, K₂CO₃ (5 mmol) was added. The reaction was stirred on the ice-bath for 5 minutes then the vessel was closed immediately and was subjected to microwave irradiation at 140°C for about 30 min. After cooling to r.t, 20 mL of ethyl acetate was added and solution was neutralized with drop wise addition of ~6 M HCl (pH = 7 - 7.5), washed with a saturated NaHCO₃ and NaCl solution (1:3, 1 × 50 mL). Aqueous layer was rewashed with ethyl acetate (2 × 25 mL) and the combined organic layer was dried. The product was purified by silica gel column chromatography with hexanes/dichloromethane/ethylacetate as an eluent to give **5**. This compound was white powder, yield 89%; mp: 224°C; ¹H NMR (DMSO, 400 MHz): δ ppm 7.14 (4H, d, *J* = 7.80 Hz), 7.38 - 7.65 (12H, m), 7.68 (4H, t), 8.13 (4H, d, 8.2 Hz), 10.10 (2H, s, CHO); ¹³C NMR (DMSO, 100 MHz): δ ppm 192.3 (CHO), 154.6 (C₁₀), 147.6 (C₁), 134.5 (C₈), 132.4 (C₅), 130.8 (C₇), 130.5 (C₃), 128.3 (C₆), 127.3 (C₄), 122.1 (C₂), 122.1 (C₉).

2.1.3. Synthesis of Phosphazene-Thiazolidinedione (8)

A mixture of *N*-methylthiourea **6** (3.0 mmol, 0.27 g), chloroacetic acid **7** (3.6 mmol, 0.2 ml) and aldehyde **5** (3.0 mmol, 0.74 g) was heated under microwave irradiation at 90°C - 110°C for 10 - 20 min. After cooling to room temperature,

the reaction mixture was extracted with CH_2Cl_2 . The organic layer washed with aqueous NaHCO_3 , water and dried over anhydrous Na_2SO_4 . The solvent was removed under vacuum and the residue was recrystallized from EtOH/water to give **7** as pale yellow powder; yield 90%; mp 213°C ; IR (KBr, cm^{-1}): 3423(NH), 3064 (C-H, aromatic), 1688 (C=O), 1503 (C=N); $^1\text{H-NMR}$ [$\text{DMSO-}d_6$, 400 MHz]: (δ , ppm) 3.07 (s, 6H, CH_3), 5.73 (brs, 2H, NH, exchanges with D_2O), 7.14 - 7.16 (4H, d, $J = 7.80$ Hz), 7.39 - 7.53 (m, 12H, aromatic H), 7.64 (m, 4H, aromatic H), 7.79 - 7.81 (4H, d, $J = 8.2$ Hz), 7.95 (s, 2H, methylene); $^{13}\text{C-NMR}$ [$\text{DMSO-}d_6$, 100 MHz]: (δ , ppm) 28.3 (CH_3), 122.1, 122.3, 127.2, 128.2, 130.4, 130.8, 131.2, 131.8, 132.6, (aromatic C), 147.48 (methylene C), 151.42 (C-O), 151.48 (C-O), 166.23 (C=N), 167.75 (C=O); $^{31}\text{P NMR}$: 9.44 (t), 25.33 (d); Anal. Calcd for $\text{C}_{46}\text{H}_{34}\text{N}_7\text{O}_8\text{P}_3\text{S}_2$: C, 56.97; H, 3.53; N, 10.11; S, 6.61; Found: C, 57.42; H, 3.61; N, 10.40; S, 6.89.

2.2. Anti-Diabetic Activity

2.2.1. In-Vitro Testing

1) Cell culture

βTC6 cells, a mouse immortalized insulin-secreting pancreatic beta cell line (T-SV40), were grown in DMEM culture medium containing 25.0 mM glucose, 1.0 mM sodium pyruvate, 4.0 mM L-glutamine, 44.0 mM sodium bicarbonate, 15.0% (v/v) FBS, and 50.0 $\mu\text{g/ml}$ gentamicin in a 5.0% CO_2 incubator at 37°C . The medium was changed every 48 hrs with fresh culture medium and cells sub-cultured as necessary to prevent over-confluence. Cells were passaged by treatment with 0.25% trypsin and 0.91 mM EDTA at passages 6 - 8.

2) Insulin secretion assay

βTC6 cells (0.1×10^6 cells/ml) was cultured in a 24-well plate for 48 hr in 5% CO_2 incubator at 37°C . The cells were then preincubated for 30 minutes in modified Krebs/Ringer buffer (KRB) (118.5 mM NaCl, 25 mM NaHCO_3 , 4.74 mM KCl, 1.19 mM MgSO_4 , 2.54 mM CaCl_2 , 10 mM HEPES, 1.19 mM KH_2PO_4 , 0.1% BSA, pH 7.4) in the CO_2 incubator. Resultant cells were washed and incubated for another 30 min with fresh buffer. Solutions of compound **8** (10^{-6} - 10^{-12} M) were prepared by diluting the stock standard solutions by KRB. Solutions having 0.000004% DMSO were obtained. 250 μl of the different concentrations were added to the cells and incubated in a 5% CO_2 incubator at 37°C for 120 min in the absence and presence of 2.80 mM glucose solution. Total reaction volume was 1 ml for each experiment. To maintain total volume of 1 ml, either 750 μl or 500 μl KRB was added first followed by 250 μl of 4 time's concentrated dose of compound and glucose (Basal experiment: 750 μl KRB + 4X 250 μl test drug. Glucose stimulated experiment: 500 μl KRB + 4X 250 μl glucose 2.8 mM + 4X 250 μl test drug). After incubation, the supernatant layers were collected and subjected to sandwich ELISA using a high range insulin assay kit according to the manufacturer's instruction. As per instructions from the manufacturer of the kit, 10 μl samples were incubated with enzyme conjugate solutions on shaker plates for 2.0 hrs at room temperature. The plates were washed, TMB was added

for 15 min and the reaction was stopped. The color intensity of solutions was read at 450 nm with a Tecan microplate reader. The sensitivity of insulin ELISA was 216 p mol/L. The average intra and inter assay coefficients of variation were 3.37% and 2.29%, respectively. The levels of insulin were expressed as p mol/L.

2.2.2. Glucose Uptake Cell-Based Assay

Cayman's Glucose Uptake Cell-based Assay Kit was used as a tool for studying modulators of cellular glucose uptake. The kit employs 2-[*N*-(7-nitrobenz-2-oxa-1,3-dioxol-4-yl)amino]-2-deoxyglucose (2-NBDG), a fluorescently-labeled deoxyglucose analog, as a probe for the detection of glucose taken up by cultured cells. β T6 Cells at 5×10^4 cells/mL was seeded onto a 96-well clear flat bottom black plate and allowed to adhere overnight at 37°C, 5% CO₂ in tissue culture media (DMEM containing 25 mM glucose, 1 mM Sodium Pyruvate, 4 mM L-Glutamine, 44.05 mM Sodium Bicarbonate (NaHCO₃), 15% (v/v) FBS, and 50 µg/ml Gentamicin). The complete medium was then removed and the cells were washed with Krebs/Ringer buffer (KRB) (118.5 mM NaCl, 25 mM NaHCO₃, 4.74 mM KCl, 1.19 mM MgSO₄, 2.54 mM CaCl₂, 10 mM HEPES, 1.19 mM KH₂PO₄, 0.1% BSA, pH 7.4). Conditioning of the cells proceeded at 37°C, 5% CO₂ for 30 mins, two times. The conditioning buffer was then removed and replaced with 450 µM 2-NBDG along with 10 µM either test compound or 10 µM reference drug in KRB. The cells were then incubated further at 37°C, 5% CO₂ for 10 mins to allow them to endocytose the glucose analog. At the end of the treatment, plate was centrifuged for 5 min at 400× g at room temperature. The 2-NBDG in basal medium was then removed and the cells were washed with 200 µl Cell-Based Assay Buffer. Plate was centrifuge for 5 min at 400× g at room temperature. 100 µl of Cell-Based Assay Buffer was added to each well after the aspiration of the supernatant. The amount of 2-NBDG taken up by cells was measured immediately at excitation and emission wavelengths of 485 nm and 535 nm respectively in TECAN infinite M200 micro plate reader.

2.2.3. Statistical Analysis

Experimental results were expressed as mean ± SEM and statistically assessed by SPSS-20. The difference between test animals and control was evaluated using the Student t-test.

3. Results and Discussion

3.1. Chemistry

The synthesis to produce the dioxybiphenyl derivative **3** *via* the reaction depicted in **Figure 1**. Starting from hexachlorocyclotriphosphazene **1**, two equivalents of bip-henyl-2,2'-diol **2** were added to four equivalents of potassium carbonate. In this case, only two equivalents of the reagent are needed as one bip-henyl-2,2'-diol is capable of bonding to one phosphorus atom through the two deprotonated oxygen molecules. Two phosphorus atoms are then substituted with this bulky group. This reaction was performed in acetone as the reaction has been proven

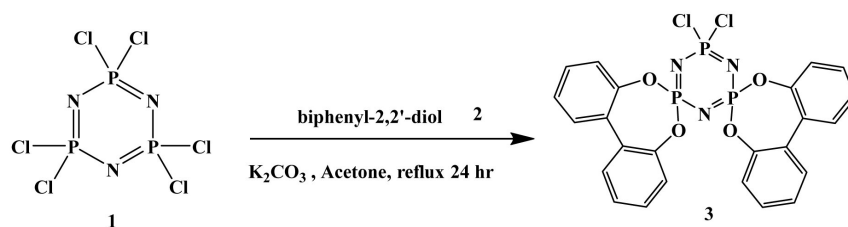


Figure 1. Synthesis of compound 3.

to occur faster in acetone than in THF [9]. It was also not necessary to reflux the first step in this reaction as this bifunctional nucleophile promotes the replacement of the chlorine atoms. In fact, the trimer and biphenol were added to acetone that was cooled in an ice bath. This is presumably done to prevent the reaction from taking place too fast and forming trimer that is triply substituted with biphenyl-2,2'-diol [9]. When the first nucleophilic oxygen reacts with the phosphorus atom, it activates the phosphorus atom for further substitution (geminal substitution) [10]. The neighbouring oxygen is the next-closest nucleophile and substitution of the second chlorine atom occurs. Crosslinking of trimer molecules does not occur because the closest reactive site is on the same molecule [9]. The reaction mixture was stirred at room temperature for 24 hours under an atmosphere of dry nitrogen because biphenyl-2,2'-diol is air sensitive. The solvent was then removed under vacuum and the product extracted with DCM. More than one product can possibly form during the reaction, but the main product is isolated *via* extraction and recrystallisation as the solubility of the doubly and triply substituted derivatives differs in different solvents.

The reaction depicted in **Figure 2** was carried out by microwave in which 2 equiv. of 4-hydroxybenzaldehyde reacted with **3** in the presence of K_2CO_3 in acetonitrile for 30 min at $140^\circ C$ gave 2,2-bis(4-formylphenoxy)-4,4,6,6-bis [spiro(2',2''dioxyl',1''-biphenyl)]cyclophosphazene **5**. It is necessary to increase temperature in this step as the groups on the cyclophosphazene ring are quite bulky, causing steric hindrance which would mean that the reaction will need more energy to take place. It was not necessary to do this reaction under inert conditions. The work-up for the second step is similar to the first step. The solvent was removed under vacuum and the product extracted with dichloromethane (DCM). The DCM was then removed *in vacuo*.

The new phosphazene derivative containing a thiazolidine-2,4-dione **8** was synthesized from the reaction of **5** with *N*-methyl thiourea and monochloroacetic acid under microwave-irradiation for 15 min succeeded to afford the desired product **8** in 90% yield. Compound **8** was characterized by elemental analysis, FT-IR, 1H , ^{13}C , ^{31}P NMR techniques (**Figure 3**).

The structure of the obtained compound was established based on their elemental analysis together with their compatible spectra data. The IR spectra of compound showed characteristic absorption bands at 3423 cm^{-1} and 1688 cm^{-1} corresponding to the -NH and C=O groups in the obtained structure. Another band at 1503 cm^{-1} attributed to C=N group. In addition, the 1H -NMR spectrum

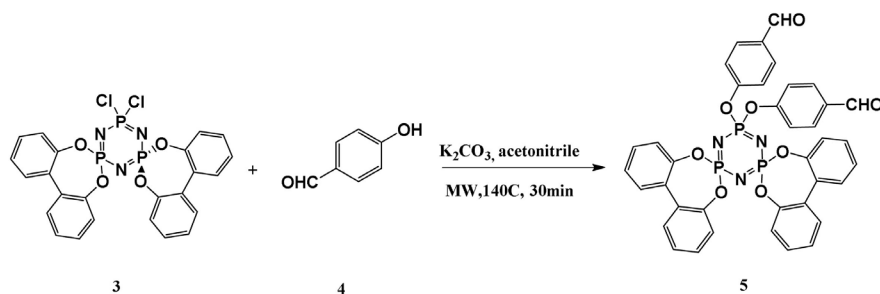


Figure 2. Synthesis of compound 5.

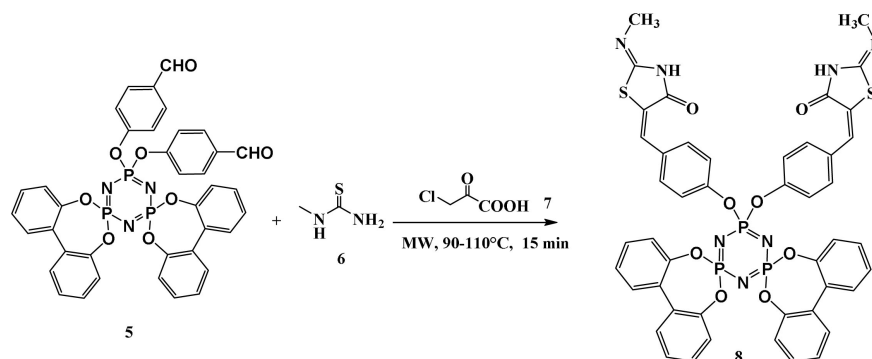


Figure 3. Synthesis of compound 8.

showed the absence of aldehyde protons at $\delta = 10.01$ ppm confirmed the formation of the product. $^1\text{H-NMR}$ spectrum indicated the presence of amino group in the region of $\delta = 5.73$ ppm accounting to two protons indicates the formation of target compound which discharged with D_2O . Besides, the appearance of singlet signal at $\delta = 7.95$ ppm for the methine-group hydrogen indication formation of *Z*-isomer which is more downfield compared to *E*-isomer. The $^{13}\text{C-NMR}$ spectrum showed signal at $\delta = 147.5$ assigned for the methane carbon. The (C=O) carbon of thiazolidione resonate at $\delta = 167.8$ ppm. The elemental analysis (C, N and H) found for all the condensed products was in close agreement with the calculated values (**Figure 4**). The ^{31}P NMR spectrum of **8** two signals were observed as one doublet and one triplet, which indicates that the two phosphorus atoms attached to the dioxybiphenyl ring are not magnetically equal. This non-equivalence of the two phosphorus atoms maybe due to the difference in the angle of twist of the two phenyl groups of the biphenyl moieties and their twists in a different direction. The reason for this reversal twist/distortion could be due to the advantageous thermodynamically stable seven-membered dioxybiphenyl ring conformation by imparting reduced 6,6' hydrogen-hydrogen contacts without broadening the O-P-O angle.

3.2. Anti-Diabetic Activity

Peroxisome proliferator-activated receptors (PPARs) are known transcription factors that directly control the expression of genes involved in lipid and glucose metabolism [11]. The mechanism of PPARs has been described [12]. Among the

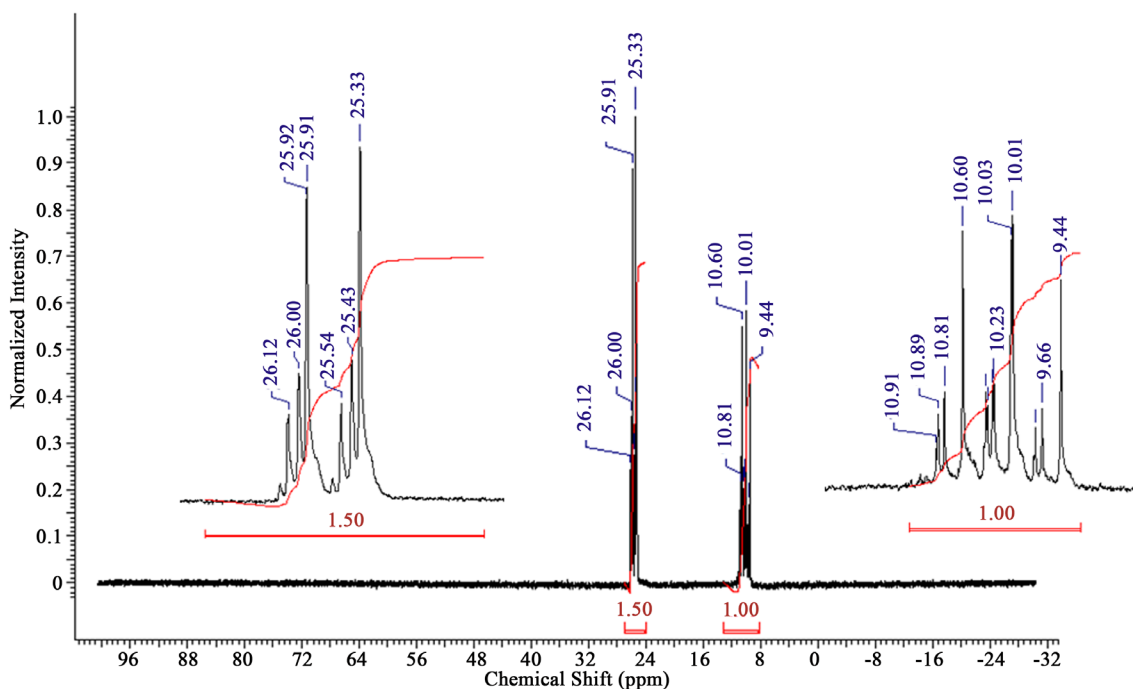


Figure 4. The ^{31}P NMR spectrum of compound **8**.

three isotypes of PPARs (PPAR α , PPAR β and PPAR γ), PPAR γ is the most studied for drug discovery. PPAR γ was not only identified as a key regulator of adipogenesis, but it also plays an important role in type 2 diabetes, cellular differentiation, insulin sensitization, atherosclerosis and cancer [13]. A class of high-affinity PPAR γ synthetic ligands includes the anti-diabetic thiazolidinedione (TZD) drugs, such as troglitazone, rosiglitazone, pioglitazone and ciglitazone [14]. Rosiglitazone and pioglitazone are currently marketed PPAR γ activators used for the treatment of type 2 diabetes to reduce hyperglycemia by promoting insulin action without additional insulin secretion [15]. TZD-type improves insulin resistance with side effects like weight gain, fluid retention and edema. In the present study, a novel and effective thiazolidinedione-2,4-dione derivative have been synthesized as potential antidiabetic drugs that may bind and activate PPAR γ and enhances insulin sensitivity. An *in-vitro* study showed that the new thiazolidinedione-2,4-dione derivative provides a new insight concerning their effect on PPAR γ .

3.2.1. Effect of Compound **8** on Insulin Secretion from βTC6 Cell Line

Secretion of insulin by βTC6 cells was measured using the high range insulin Sandwich ELISA kit. **Figure 5(a)** shows the effect of pioglitazone on insulin secretion in the presence and absence of 2.88 mM glucose. As can be seen from **Figure 5(a)**, pioglitazone does not show any effect on basal or glucose stimulated insulin secretion. The effects of compound **8** at 10^{-12} , 10^{-9} , 10^{-6} M concentrations were investigated on insulin secretion in absence and presence of 2.8 mM glucose from βTC6 cells. Compound **8** did not show any effect on the secretion of insulin in the absence or presence of glucose (**Figure 5(b)**).

3.2.2. Glucose Uptake Assay

The results of the *in vitro* glucose uptake study indicate that the compound **8** was found to exhibit remarkable potential to flush glucose into the mentioned cells as compared to standard reference Pioglitazone. Compound **8** happens to be a potent compound by enhancing the glucose uptake significantly ($P < 0.05$) (Figure 6).

4. Conclusion

In this study, we report the synthesis of novel phosphazene derivatives containing Thiazolidinediones group using the reaction of 2,2-bis(4-formylphenoxy)-4,4,6,6-bis[spiro(2',2'')-dioxo-1',1''-biphenyl]cyclotriphosphazene with *N*-methyl thiourea and monochloroacetic acid under microwave-irradiation. All products were generally obtained in high yields (88% - 90%). The *in-vitro* antidiabetic activity showed that compound exhibited higher glucose uptake in comparison to pioglitazone as reference drugs. Thus, analogs of phosphazene derivatives of thiazolidinediones may be potential insulin sensitizers and may be developed further in the future in the management of diabetes. The study also provides directions in designing more potent, safe, selective and cost-effective molecule.

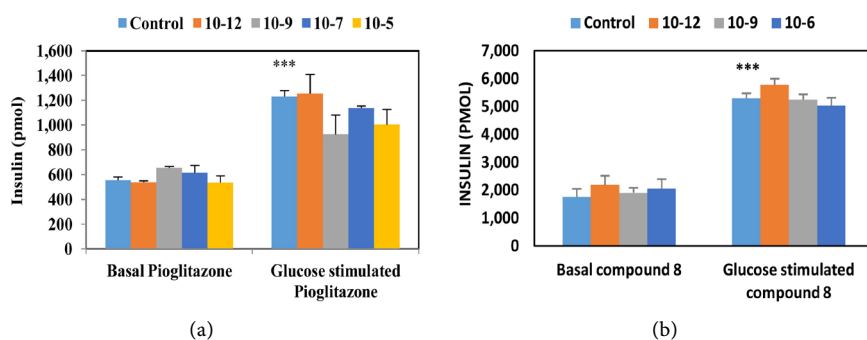


Figure 5. The effects of the Pioglitazone (a) and compound **8** (10^{-12} - 10^{-6} M) (b) on insulin secretion in β TC6 cells in the absence (basal) and in the presence of 2.8 mM glucose concentration. Results are means of triplicates \pm SEM; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ from relative basal control and #* $P < 0.05$, ## $P < 0.01$, ### $P < 0.001$ from glucose 2.8 mM.

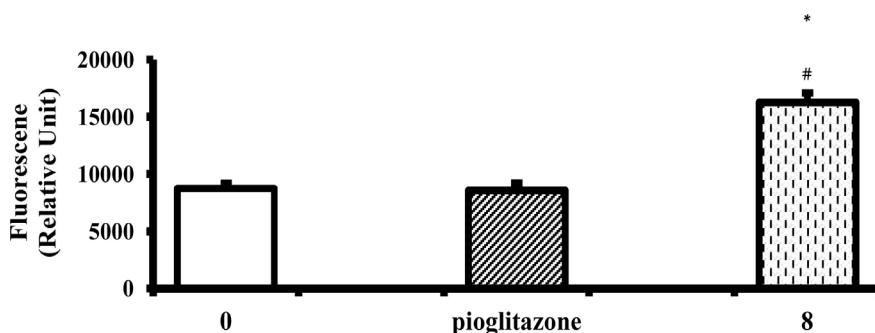


Figure 6. The effects of compound **8** (10 μ M) on glucose uptake from β TC6 cells. Results are means of triplicates \pm SEM; * $P < 0.05$ vs. control (zero concentration); #* $P < 0.05$ vs. reference drug (pioglitazone).

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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