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Synthesis and Hypoglycemic Activity of Novel Pyrimidine Derivatives Containing Oxadiazole And Imidazolidine Ring

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Abstract

Peroxisome proliferator activator receptor-γ (PPAR-γ) remains the most successful target for management of diabetes mellitus. In the present study, we aimed to rationally design novel PPAR-γ agonists with pyrimidine moiety. These novel pyrimidine derivatives were synthesized by incorporating pharmacologically-significant heterocycles, namely substituted imidazolidine and oxadiazole moieties via multistep synthesis protocols. The structures of all the newly synthesized intermediates and target molecules were established by elemental analysis, infrared (IR) and 1D-NMR spectral data. The newly synthesized compounds were screened for their in vitro hypoglycemic activities. Pyrimidine-containing imidazolidine showed better results than oxadiazole compounds.

Diabetes mellitus (DM) is a heterogenous group of disorders characterized by a state of chronic hyperglycemia, resulting from a diversity of etiologies, environmental and genetics, acting jointly. [1] Characteristically, diabetes is a long-term metabolic disorder with many complications, including cardiovascular, renal, neurological, ocular, and other inter-related problems. DM is one of the major health problems in the world today. The incidence of DM is estimated to reach 300 million by the year 2025. Type 2 DM, which is strongly associated with a sedentary life style and obesity, accounts for most cases of DM. Recently, the chemistry of pyrimidines has attracted attention, because pyrimidines have been found to exhibit several biological activities, such as diuretic, antitumor, anti-HIV, cardiovascular properties and activity against polioherpes viruses.[2] In addition, pyrimidine or its analogs possess antibacterial, [3] antifungal, [4] antileishmanial, [5] anti-inflammatory,[6]antihypertensive, [7] antipyretic, [8] antidiabetic, [9] antiallergic, [10] anticonvulsant, [11] antioxidant, [12]and antihistaminic activities. [13, 14] They also act as calcium channel blockers. [15] During the last two decades, several pyrimidine derivatives have been developed and found to have wide clinical and pharmacological applications. [16] Many drugs have been approved from this class for the treatment of diabetes, such as rosiglitazone, pioglitazone, and ciglitazone. Although the marketed drugs showed additive effects with other antihyperglycemic agents, they are prone to exhibit toxicity. For example, rosiglitazone shows hepatotoxicity. [17] Therefore, there is an urgent need to develop newer and safer anti-diabetic agents from this class of compounds having a similar degree of efficacy with a potential to reduce long-term complications. In our efforts to improve the biological profile of these analogs, we have reported an efficient microwave-assisted synthesis and screening of new glitazone derivatives as potential anti-diabetic drugs. Hybridization is an approach to design new drug molecules. Owing to the diverse biological properties of imidazolidine and oxadiazole moieties as well as pyrimidines, in the present study, we attempted to synthesize compounds with potential anti-diabetic activity by employing hybridization approach. The structures of the synthesized compounds were assigned based on elemental analysis, and infrared (IR) and 1D-NMR spectral data. The compounds were also screened for in vitro anti-diabetic activity.

All reagents and chemicals were purchased from Sigma-Aldrich and used without 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 melting point apparatus and were uncorrected. IR spectra were measured using KBr pellets on a Thermo Nicolet 470 FT-IR spectrophotometer. 1H-NMR spectra were recorded on a 400 MHz Varian spectrometer using DMSO-d6 and CDCl3 solutions, and tetramethylsilane (TMS) as an internal reference. Elemental analysis was performed on a Leco

CHN-600 elemental analyzer. The microwave synthetic protocol was performed using the CEM microwave system. A mixture of pyrimidine aldehyde 1 (0.03 mol) and semicarbazide HCl 2 (0.05 mol) in ethanol (20 ml) was refluxed for 3 h at 100□C. The solvent was distilled, and the solid mass obtained was used without further purification.

The solid mass (0.01 mol) and sodium carbonate (0.01 mol) were dissolved in water (25 mL). To this mixture, iodine (0.01 mol) and potassium iodide (0.01 mol) were added, and the reaction mixture was refluxed for 2 h at 100oC. The reaction mixture was then allowed to cool. The resultant solid was filtered, washed with water, and recrystallized from methanol to give 4a-c.

5-{2□-[p-Chlorophenyl)amino]pyrimidin-5□-yl}-1,3,4-oxadiazol-2-amine (4a): yellow crystals; yield 80%; mp 282□C; IR (KBr, cm-1): 3309, 3113 (NH2), 1666 (C=N), 1589 (C=C); 1H-NMR [DMSO-d6, 400 MHz]: (δ, ppm) 7.55 (brs, 2H, NH2, exchangeable with D2O), 7.64 (d, 2H, aromatic, J = 8.0 Hz), 8.43 (d, 2H, aromatic, J = 8.0 Hz), 9.24 (s, 2H, H4,6-pyrimidine), 12.88 (brs, 1H, NH exchangeable with D2O); 13C-NMR [DMSO-d6, 100 MHz]: (δ, ppm) 117.9 (C5-pyrimidine), 129.5–136.9 (aromatic), 153.9 (C4,6-pyrimidine), 154.3 (C2-pyrimidine), 163.1 (C2-oxadiazole), 164.9 (C4-oxadizole); Anal. Calcd for C12H9ClN6O: C, 49.92; H, 3.14; N, 29.11; Found: C, 50.37; H, 4.93; N, 34.13; Anal. Calcd for C12H9ClN6O·2C4H6O6: C, 40.79; H, 3.59; N, 14.27; Found: C, 40.98; H, 3.40; N, 14.28.

5-(2□-Morpholinopyrimidin-5□-yl)-1,3,4-oxadiazol-2-amine (4b): off-white crystals; yield 82%; mp 263□C; IR (KBr, cm-1): 3457, 3274 (br, NH2), 2954 (C-H aliphatic), 1662 (C=N), 1600 (C=C); 1H-NMR [DMSO-d6, 400 MHz]: (δ, ppm) 3.66–3.79 (m, 8H, morpholine), 6.49 (brs, 2H, NH2, exchangeable with D2O), 8.73 (s, 2H, H4,6-pyrimidine); 13C-NMR [DMSO-d6, 100 MHz]: (δ, ppm) 44.4 (morpholine), 66.4 (morpholine), 118.4 (C5-pyrimidine), 135.3 (C4,6-pyrimidine), 156.6 (C2-pyrimidine), 157.2 (C2-oxadiazole), 161.2 (C4-oxadizole); Anal. Calcd for C10H12N6O2: C, 48.38; H, 4.87; N, 33.85; Found: C, 48.83; H, 4.94; N, 34.10; Anal. Calcd for C10H12N6O2. C4H6O6: C, 42.21; H, 4.55; N, 21.10; Found: C, 42.40; H, 4.37; N, 21.11.

5-[2□-(n-Propylamino)pyrimidin-5□-yl]-1,3,4-oxadiazol-2-amine (4c): white crystals; yield 76%; mp 211□C; IR (KBr, cm-1): 3464,3442 (NH2), 3256 (NH), 2957 (C-H aliphatic), 1673 (C=N) , 1528 (C=C); 1H-NMR [DMSO-d6, 400 MHz]: (δ, ppm) 0.86–0.9 (m, 3H, CH3), 1.49–1.58 (m, 2H, CH2), 3.22–3.25 (m, 2H, CH2), 6.46 (brs, 2H, NH2 ,exchangeable with D2O), 7.89 (s, 1H, NH ,exchangeable with D2O), 8.63 (s, 2H, H4,6 -pyrimidine); 13C-NMR [DMSO-d6, 100 MHz]: (δ, ppm) 11.9 (CH3, propyl), 22.6 (CH2, propyl),42.9 (CH2, propyl),117.8 (C5-pyrimidine), 135.8 (C4,6-pyrimidine), 157.3 (C2-pyrimidine), 162.4 (C2-oxadiazole), 163.7 (C4-oxadizole); Anal. Calcd for C9H12N6O: C, 49.08; H, 5.49; N, 38.16; Found: C, 49.53; H, 5.56; N, 38.44; Anal. Calcd for C9H12N6O.2C4H6O6: C, 39.24; H, 4.65; N, 16.15; Found: C, 39.43; H, 4.46; N, 16.18.

(E)-2-(p-Fluorobenzylidene) hydrazinecarboxamide (6): A mixture of p-fluoro benzaldehyde 5 (0.01 mol, g) and semicarbazide HCl 2 (0.02 mol) in ethanol (20 mL) was refluxed for 3 h at 100□C. The solvent was removed under reduced pressure; the solid was recrystallized and collected by filtration to produce 6 as a white powder; yield 93%; mp 232□C; 1H-NMR [DMSO-d6, 400 MHz]: (δ, ppm) 6.49 (brs, 2H, NH2, exchangeable with D2O), 7.18 (m, 2H, aromatic), 7.74 (m, 2H, aromatic), 7.80 (s, 1H, olefinic H), 10.22 (brs, 1H, NH exchangeable with D2O); 13C-NMR [DMSO-d6, 100 MHz]: (δ, ppm) 116.1-131.8 (aromatic C), 138.7 (olefinic C), 157.3 (C=O), 164.2 (C-F).

(E)-3-[(p-Fluorobenzylidene) amino] imidazolidine-2,4-dione (8): A mixture of 6 (0.01 mol, 2.2 g), ethyl chloroacetate 7 (0.01 mol, 1.1 mL), and fused sodium acetate (0.1 mol, 0.8 g) in ethanol was heated under reflux for 2 h. The reaction mixture was allowed to cool to room temperature (25oC) and the mixture was poured into ice water. The solid collected by filtration was recrystallized to afford 8 as a white powder in 87% yield, mp 224□C; 1H-NMR [DMSO-d6, 400 MHz]: (δ, ppm) 4.34 (CH2), 7.20–7.25 (2H, m, phenyl), 7.78–7.80 (2H, m, phenyl), 7.84 (s, 1H, olefinic H), 10.27 (1H, brs, NH exchangeable with D2O); 13C-NMR [DMSO-d6, 100 MHz]: (δ, ppm) 42.9 (CH2), 129.0–135.8 (aromatic C), 156.6 (olefinic C), 157.3 (C=O), 162.4 (C-F), 163.7(C=O).

(Z)-5-{2□-[p-Chlorophenylamino) pyrimidin-5□-yl] methylene}-3-(E)-(p-fluorobenzylidene amino) imidazolidine-2,4-dione (10): A mixture of 8 (0.1 mmol, 0.02 g) and pyrimidine aldehyde 1a (0.1 mmol, 0.02 g) in ethanol was heated under microwave irradiation. The reaction mixture was allowed to cool to room temperature. The solid obtained was filtered and recrystallized from ethanol to give 10 as a yellow powder; yield 85%; mp 226□C; IR (KBr, cm-1): 3411 (NH), 1687 (C=O),1600 (C=N); 1H-NMR [DMSO-d6, 400 MHz]: (δ, ppm) 7.18 (m, 2H, p-fluorophenyl), 7.41 (s, 1H, olefinic H), 7.57 (d, 2H, p-chlorophenyl, J = 8.0 Hz), 7.69 (brs, 1H, NH, exchangeable with D2O), 7.77 (m, 2H, p-fluorophenyl), 7.82 (s, 1H, olefinic H), 8.35(d, 2H, p-chlorophenyl, J = 8.0 Hz), 8.93 (s, 2H, H4,6- pyrimidine), 10.25 (brs, 1H, NH, exchangeable with D2O); 13C-NMR [DMSO-d6, 100 MHz]: (δ, ppm) 126.9–139.7 (aromatic C), 153.9 (C=O), 155.3 (C4,6-pyrimidine), 157.1 (olefinic C), 158.6 (C=O), 160.7 (C-F), 162.1 (C2-pyrimidine); Anal. Calcd for C21H14ClFN6O2: C, 57.74; H, 3.23; N, 19.24; Found: C, 58.0; H, 3.31; N, 19.33.

βTC6 cells, a mouse immortalized insulin-secreting pancreatic beta cell line (T-SV40), were grown in Dulbecco's modified Eagle's 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) fetal bovine serum, and 50.0 μg/mL gentamicin in a 5% CO2 incubator at 37°C. The medium was replaced every 48 h with fresh culture medium, and the cells were sub-cultured as necessary to prevent over-confluence. The cells were passaged by treatment with 0.25% trypsin and 0.91 mM EDTA at passages 6-8.

βTC6 cells (0.1 x 106 cells/mL) were cultured in a 24-well plate for 48 h in 5% CO2 incubator at 37°C. The cells were then preincubated for 30 min in modified 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) in the CO2 incubator. The resultant cells were washed and incubated for another 30

min with fresh buffer. Solutions of the synthesized compounds (10-6–10-12 M) were prepared by diluting the stock standard solutions with KRB. Solutions having 0.000004% DMSO were obtained. Different concentrations of the solutions of synthesized compounds (250 ?L) were added to the cells and incubated in 5% CO2 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 a total volume of 1 mL, either 750 µL or 500 µL KRB was added, followed by 250 µL of four times (4X) 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 high range insulin assay kit, according to the manufacturer's instruction. In total, 10 µL of samples were incubated with enzyme conjugate solutions on shaker plates for 2 h at room temperature (25. The plates were washed and TMB was added for 15 min; the reaction was then stopped. The color intensity of solutions was read at 450 nm with a Tecan microplate reader. The sensitivity of insulin ELISA was 216 pmol/L. The average intra and inter assay coefficients of variation were 3.37 and 2.29%, respectively. The levels of insulin were expressed as pmol/L. The experimental results were expressed as mean±SEM, and statistically assessed by SPSS-20.

The glitazone normally possess a polar thiazolidinedione ring system as the head followed by a hydrophobic benzyloxy moiety or aniline moiety as trunk linked by a two-carbon atom linker and a hydrophobic ring as a tail for better anti-hyperglycemic activity [18] (Fig. 1). Keeping these structural features in mind, we have designed newer glitazone analogus by retaining similar template pharmacophore structure, however, a new modification on linker region, effector region and hydrophobic region of glitazone have been introduced.

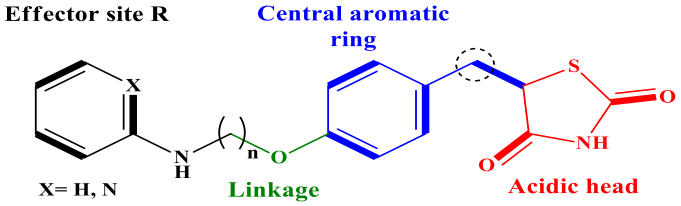


Figure 1: Basic Pharmacophore Features Of A Glitazone Ppar-Γ Agonist.

Considering the above structural features of glitazones, we designed structures of some novel glitazones incorporated with pyrimidine moiety. In this class of compounds, 2,4-thiazolidinedione moiety which served as the hydrophilic head will be replacing by oxadiazole moiety (Figure 2) or Imidazolidine-2,4-dione (Figure 3) and the central phenyl ring present in the current synthetic peroxisome proliferator-activated receptors PPAR agonists drug was replaced with a novel pyrimidine scaffold.

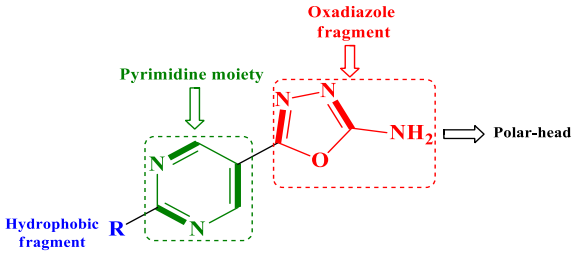
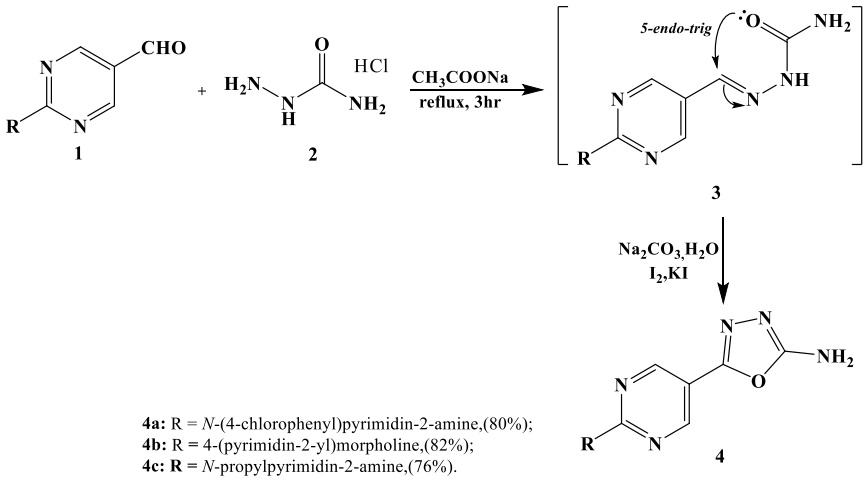


Figure 2: Design Template For The Synthesis Of Compounds 4a-C.

The synthesis of the target compounds **4a-c** was initiated by a simple condensation reaction between 5-formylpyrimidine **1** and semicarbazide **2.** This was followed by *in situ* intermolecular *5-endo-trig* cyclization to form dihydro-oxadiazole, which is oxidized in the presence of iodine/potassium iodide to produce the final products **4a-c** in good yield (76–82%) (Scheme 1).



Scheme 1: Synthesis Of 1,3,4-Oxadiazole Derivatives 4a-C.

The structures of the obtained compounds were established based on their elemental analysis together with compatible spectral data. The IR spectrum of **4a** showed characteristic absorption bands at 1589 cm^{-1} and 1666 cm^{-1} corresponding to the C=N and C=C groups. Another two broad bands appeared at 3309 cm^{-1} and 3113 cm^{-1}, which were attributed to the NH_2 group. In addition, the IR spectrum showed the absence of the carbonyl group of pyrimidine aldehyde. The ^{1}H-NMR spectrum indicated the presence of the amino group in the region of δ = 7.55 ppm; this is attributed to two protons, indicating the formation of target compounds that were discharged with D_2O. Moreover, a singlet signal at δ = 9.24 ppm was attributed to H-4 and H-6 of pyrimidine, equivalent to two protons. The ^{13}C-NMR spectrum showed a signal at δ = 163.1 ppm, which was attributed to C-2 oxadiazole. The oxadiazole C-4 resonated at δ = 164.9 ppm. The elemental analysis results of all the condensed products were in agreement with the calculated values.

Imidazolidine-2,4-dione and its heterocyclic derivatives represent an interesting class of compounds that possess a wide range of biological activities, such as anti-inflammatory [19], antimicrobial [20], and anticonvulsant [21] properties. In the present study, we tried to modify imidazolidine-2,4-dione ring by introducing pyrimidine ring as a new substituent at the 5-position and investigated its anti-diabetic activity (Figure 2).

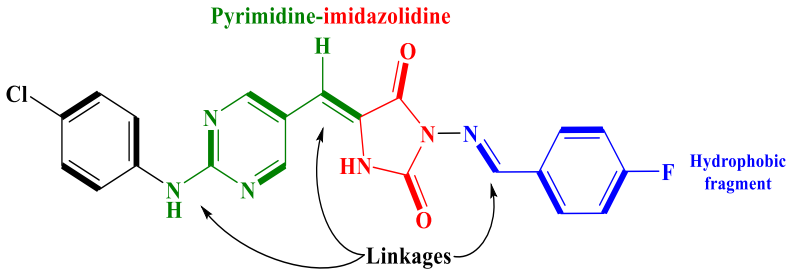
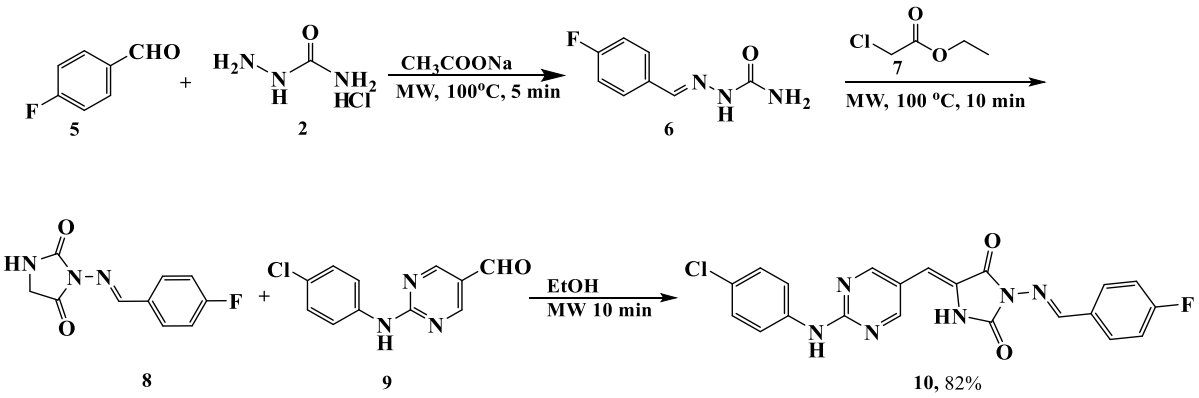


Figure 3: Designed Template Of Compound 10.

Compound **10** was synthesized in three steps by microwave irradiation. In the first step, the condensation of aromatic aldehyde **5** with semicarbazide **2** afforded **6** in 93% yield. In the second step, the intermediate of imidazolidine-2,4-dione **8** was synthesized by reacting **6** with ethyl chloroacetate **7** in fused sodium acetate. Finally, **8** was reacted with 5-formylpyrimidine derivative **9** to produce **10** in 82% yield (Scheme 2).



Scheme 2: Synthesis Of Imidazolidine-2,4-Dione 10.

The suggested structure of **10** was confirmed based on its elemental analysis and spectroscopic data. The IR spectrum of **10** showed characteristic absorption bands at 1687 cm^{-1} and 3411 cm^{-1}, which corresponded to C=O and -NH functional groups, respectively. The ^{1}H-NMR spectrum of **10** showed two singlet signals at δ = 7.41 and 7.82 ppm, corresponding to the two olefinic protons. A broad band observed at δ = 7.69 ppm was attributed to the NH proton exchanged with D_2O. Imidazole–NH resonated at δ = 10.25 ppm exchanged with D_2O. $H_{4,6}$-pyrimidine resonated as a singlet signal at δ = 8.93 ppm. The ^{13}C-NMR spectrum of **10** showed two signals corresponding to two carbonyl groups at δ = 153.7 and 158.6 ppm.

Secretion of insulin by βTC6 cells was measured using the high-range insulin Sandwich ELISA kit. Figure 4 shows the effect of glucose on insulin secretion of βTC6 cells in the absence of drugs. Glucose at a concentration of 2.8 mM induced mild insulin secretion of approximately 3000 pmol/L, which was used in subsequent testing of the novel pyrimidine analogs and the positive control pioglitazone. Figure 5a shows the effect of pioglitazone on insulin secretion in the presence and absence of 2.88 mM glucose. Pioglitazone did not show any effect on basal or glucose-stimulated insulin secretion. The effects of oxadiazole pyrimidine derivatives **4a-c** and imidazolidine pyrimidine derivative **10** at concentrations of 10^{-12},10^{-9}, and 10^{-6} M were investigated on insulin secretion in the absence and presence of 2.8 mM glucose from βTC6 cells (Figure 5 b, c, d). Among pyrimidine-containing oxadiazoles (**4a-c), 4b** did not show any effect on insulin secretion in the absence of glucose, but decreased glucose-stimulated insulin release from βTC6 cells (Figure. 5c). Hence **4b** could not be a viable antidiabetic compound since it will cause hyperglycemia by inhibiting insulin release in the presence of glucose. Compounds **4a** and **4c** showed increase in basal insulin secretion but did not show any effect on glucose-stimulated insulin release from βTC6 cells (Figure 5 b and d). The significant basal insulin secretion could cause hypoglycemia. However, they can be used postprandial since they release insulin in the presence of glucose. The pyrimidine-containing imidazolidine **10** had no effect on basal insulin release, but increased glucose-stimulated insulin release (Figure 5e). Compound **10** is of particular interest because it does not influence basal insulin secretion, and in the presence of glucose it increased insulin secretion, thereby preventing hyperglycemia. It could be concluded from our results that pyrimidine-containing imidazolidine is better anti glycemic compound than oxadiazole compounds.

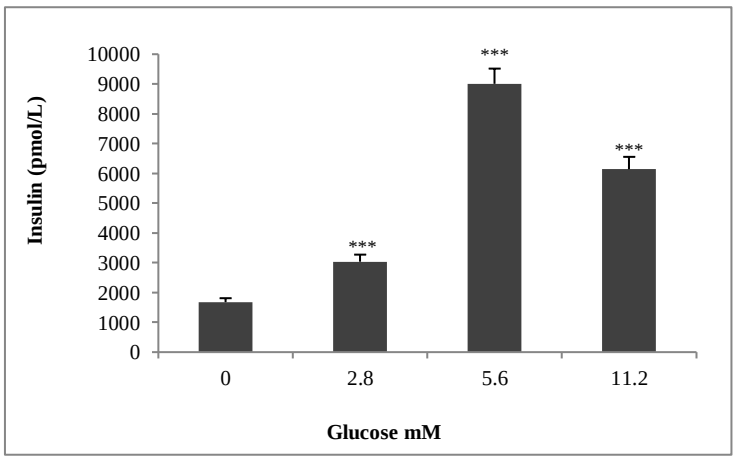


Fig. 4. Glucose response of βTC6 cells in the absence of drugs. Plotted values are means of triplicates ± SEM; * P < 0.05, ** P < 0.01, *** P < 0.001 versus 0 mM glucose.

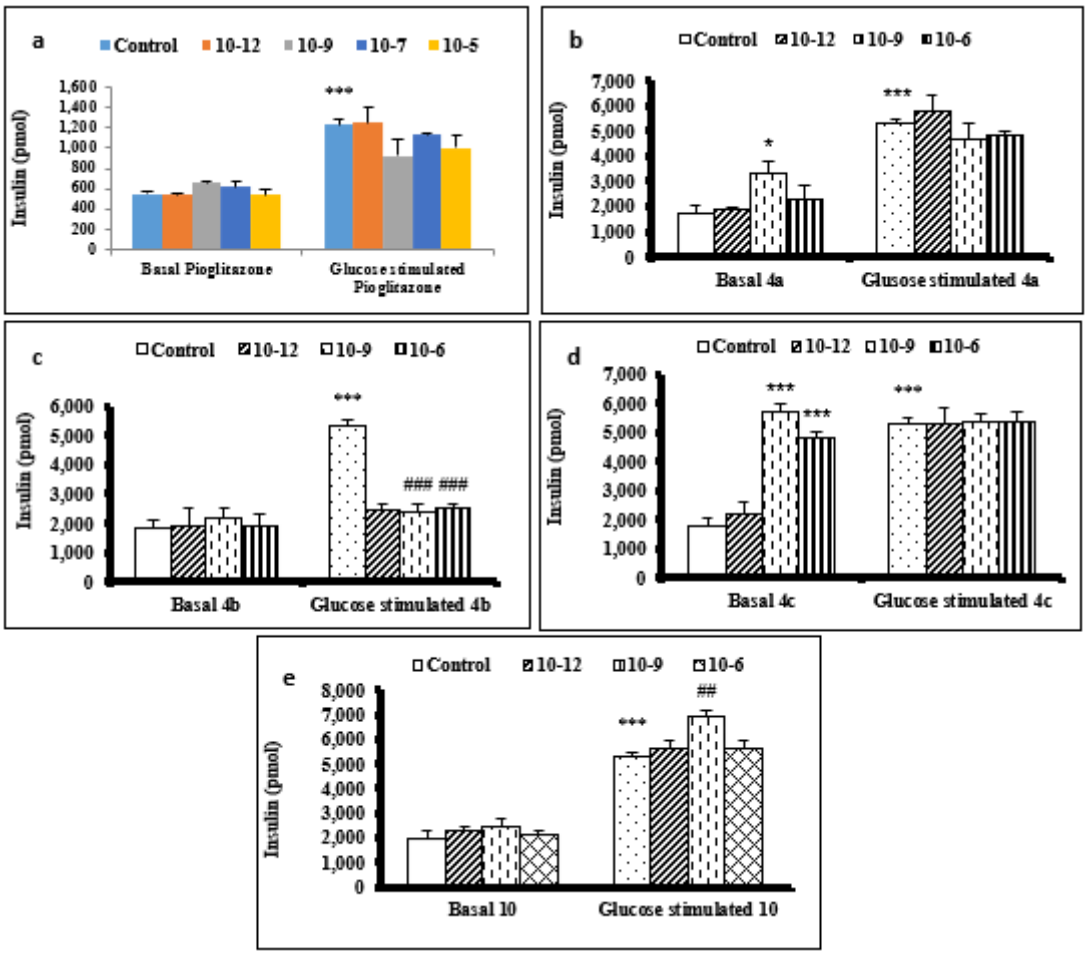


Figure 5: Effects Of Pioglitazone And The Pyrimidines 4a, 4b, 4c, 10 (10-12–10-6m) On Insulin Secretion In Btc6 Cells In The Absence (Basal) And Presence Of 2.8 Mm Glucose. The Results Are Means Of Triplicates ± Sem; *P < 0.05, ** P < 0.01, *** P < 0.001 From Relative Basal Control And #P < 0.05, ## P < 0.01, ### P < 0.001 From Control Glucose (2.8 Mm).

In conclusion, we designed and synthesized a new glitazone adducts, and the structures of the compounds were confirmed. Our results showed that the pyrimidine-containing imidazolidine compound **10** demonstrated better results than oxadiazole compounds **4(a-c)**. Thus, analogs of imidazolidine-pyrimidine derivatives may be potential insulin sensitizers, and these findings can open new therapeutic strategies in the management of diabetes in the future. Our study also provides new directions in designing more potent, safe, selective, and cost-effective molecules.

Declarations of interest

No conflict of interest

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