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Microwave Assisted Synthesis and Antidiabetic Activity of Novel 5-[4-(Substituted) Benzylidine]Thiazolidine-2,4-Dione

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Abstract

A series of novel 5-[4-(substituted) benzylidine]thiazolidine-2,4-dione have been synthesized and evaluated for antidiabetic activity on male Wistar rats by Oral Glucose Tolerance Test (OGTT) method using pioglitazone as standard. The newly synthesized compounds have been characterized by IR, Mass and ^{1}H NMR spectroscopic studies and report of them supports the structures of compounds. Comparison of data was performed by one way ANOVA followed by post-test, Dunnett's multiple comparison tests. Some of the compounds have shown promising antidiabetic activity.

Keywords: Thiazolidine-2,4-dione; Antidiabetic; OGTT; ANOVA

Introduction

Diabetes mellitus is one of life threatening disorder found in most of the countries in the world which is due to impaired carbohydrate, fat and protein metabolism [1]. Type 2 diabetes (non-insulin dependent diabetes mellitus; NIDDM) is characterized by high level of blood glucose and impaired insulin action [2]. Currently available therapies for type 2 diabetes include the sub-cutaneous administration of insulin and the use of various oral agents: sulfonylureas, biguanides (metformin), α-glucosidase inhibitors, benzoic acid derivatives, thiazolidinediones (pioglitazone, rosiglitazone) [3]. Thiazolidinediones such as pioglitazone, rosiglitazone and troglitazone have made a great contribution to therapy for type 2 diabetes. In recent years, the treatment of type 2 diabetes has been revolutionized with the advent of thiazolidinedione (TZD) class of molecules that ameliorate insulin resistance and thereby normalize elevated blood glucose, lipid, and insulin levels in rodent models of Type 2 diabetes and obesity [4-7], and recent clinical data support their efficacy in obese diabetic patients [8].

A survey of TZDs class of PPARγ agonists, three -dimensional quantitative structure-activity-relationships (3D-QSAR) studies and crystal structure information reveal that the pharmacophoric feature of these agents essentially consists of three parts: (1) an acidic head group, (2) central aromatic region and (3) a lipophilic side chain [9]. The acidic head group containing TZD ring makes several specific hydrogen-bonding interactions, Hydrogen Bond Donor (HBD) and hydrogen bond acceptor (HBA) with His449, Tyr473, His323, Ser289 and Gln286 protein residue of PPARγ receptor (Figure 1) [10]. A lipophilic side chain is an effector region of the PPARγ receptor, which modifies the pharmacokinetic and toxicity profiles. This is an important region of the molecule where wide choice of lipophilic substituents can be made to design better antidiabetic agents. And there is linker region, which containing central aromatic ring is essential for activity. Because this region has a limited space and hence large substituted fragments in the central aromatic region leads to reduced activity [11].

Thus, based upon SAR and QSAR study of various antidiabetic thiazolidinediones, the present investigation was aimed at the modification of effector site and linker region without modification of 2,4-thiazolidinedione ring toward development of better and safer antidiabetic agents than the available ones (Figure 2). We have designed a new series of antidiabetic agents, which mainly consist of 2,4-thiazolidinedione ring system, attached to sterically hindered aromatic group, with suitable linker (Figure 2). Total 10 new antidiabetic agents will be prepared either by varying linker region or electron withdrawing/donating groups on sterically hindered aromatic ring (effector region) system.

Synthesis of the compounds was confirmed by physical and spectral characterization. Compounds thus formed were subjected to further evaluation for their *in-vivo* anti-diabetic activity by using standards protocols.

Experimental

Chemistry

All reactions were conducted under microwave condition and performed using oven dried glassware. Melting points of all compounds were determined in open capillaries and are uncorrected. TLC was performed on microscopic slides (2 × 7.5 cms) coated with Silica-Gel-G and spots were visualized by exposure to iodine vapor. IR spectra of all compounds were recorded in KBr (Merck) on FT-IR 8400S Shimadzu spectrophotometer. Mass spectra were recorded on SHIMADZU LCMS 2010 EV Mass Spectrometer. ^{1}H NMR spectra were obtained on BRUKER Advance-II 400 MHz instrument in DMSO as solvent and chemical shift were measured as parts per million downfield from tetramethylsilane (TMS) as internal standard.

Procedure for synthesis of 2,4-thiazolidinedione (3): Solution containing Chloroacetic acid **(1)** (0.6 mol) in 60 mL of water and thiourea **(2)** (0.6 mol) dissolved in 60 mL of water were placed in 250 mL round-bottomed flask. The mixture was stirred for 15 min., followed by cooling to obtain white precipitates. To the content of the flask 60 mL of conc. HCl was added slowly from dropping funnel. The mixture was refluxed for 6 min. at 250 watts in microwave. On cooling the content of the flask solidified into a cluster of white needles. The

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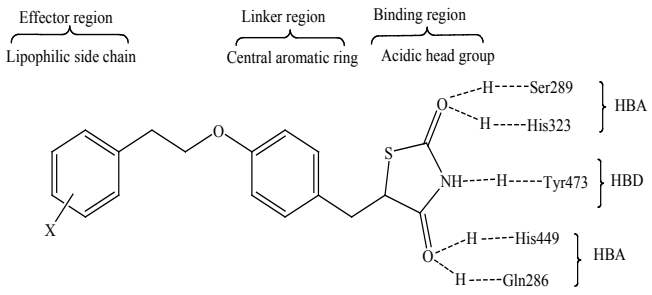


Figure 1: General Functional Group Requirement for PPARγ agonist, based upon SAR and QSAR Study of various antidiabetic thiazolidinedione's.

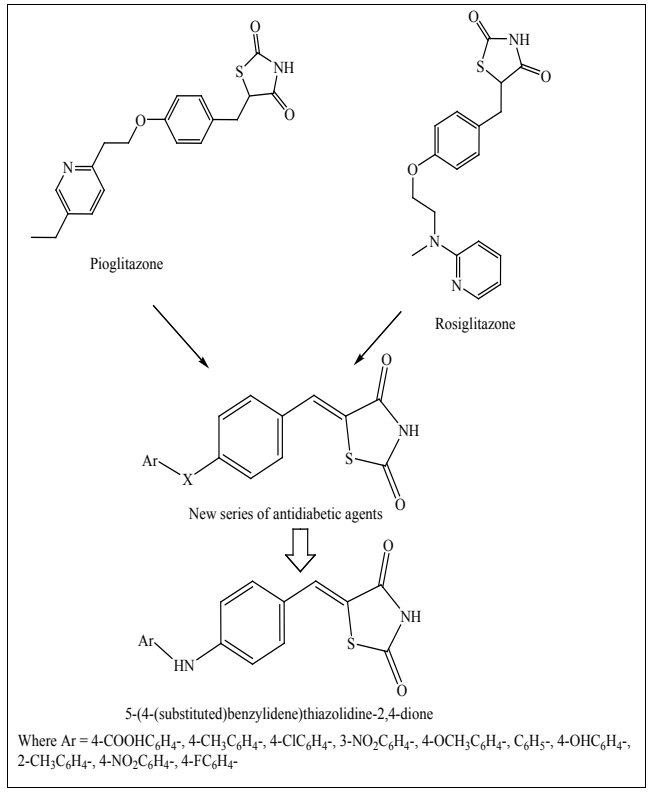


Figure 2: Design Strategy and General Structure of thiazole derivatives, designed based upon pioglitazone and rosiglitazone structure.

product was filtered and washed with water to remove the trace of HCl and dried. The product was recrystallized from ethyl alcohol. Yield 90%; Melting point 123-125°C; Mass m/z 118.1 $[M+H]^+$; IR (cm^{-1}) 3145 (NH), 1755 (C=O), 1608 and 1550 and 1455 (C=C Ar).

Procedure for synthesis of 5-(4-chlorobenzylidine)-2,4-thiazolidinedione (5): To a solution of 4-chlorobenzaldehyde **(4)** (0.25 mol) and 2,4-thiazoidinedione **(3)** (0.25 mol) in hot glacial acetic acid (50 mL), fused sodium acetate (1.8 g) was added and then it was refluxed for 5 min. in microwave at 200 watts. Upon completion of the reaction, 300 mL of water was added and the precipitate obtained was filtered, washed with water and recrystallized from glacial acetic acid. Yield 85%; Melting point 183-185°C; Mass m/z 240.3 $[M+H]^+$; IR (cm^{-1}) 3150 (NH), 1745 (C=O), 1608 (C=C Ar), 835 (Ar C-Cl).

Procedure for synthesis of 5-[4-(substituted) benzylidene] thiazolidine-2,4-diones (7a-7j): 5-(4-chlorobenzylidene)-2,4-thiazolidinedione **(5)** (0.01 mol), appropriate primary amine **(6)** (0.01 mol), potassium carbonate (0.012 mol) and acetonitrile (7 mL) were refluxed in microwave at 200 watt for 2-4 min. After completion of the reaction, the reaction mass was diluted with 30 mL of ice cold water. The product was filtered and recrystallized from ethanol.

Spectra of 5-[4-(substituted) benzylidene] thiazolidine-2,4-diones

5-[4-(4-amino benzoic acid) benzylidene] thiazolidine-2,4-dione (7a): Yield 71%; Melting point 218-220°C; Mass m/z 341.3 $[M+H]^+$; IR (cm^{-1}) 3470 (OH), 3145 (NH), 1755 (C=O), 1455 (Ar C-C), 720 (C-S); 1H NMR (ppm) δ 2.1993(s, 1H, Ar-C**H**-); δ 4.1987(s, 1H, Ar-N**H**-Ar); δ 7.0595(s, 1H, -C=O-N**H**-C=O); δ 7.0948-8.0522(m, 8H, Ar-**H**); δ 12.3752(s, 1H, -COO**H**).

5-[4-(4-amino toluene) benzylidene] thiaolidine-2,4-dione (7b): Yield 65%; Melting point 215-217°C; Mass m/z 311.3 $[M+H]^+$; IR (cm^{-1}) 3040 (NH), 1750 (C=O), 1485 (Ar C-C), 725 (C-S); 1H NMR (ppm) δ 2.1158(s,1H, Ar-C**H**-); δ 2.5856(s, 3H, Ar-C**H3**); δ 4.1443(s, 1H, Ar-N**H**-Ar); δ 7.2077(s, 1H, -C=O-N**H**-C=O); δ 7.4426-7.6933(m, 8H, Ar-**H**).

5-[4-(4-amino chloro benzene) benzylidine] thiaolidine-2,4-dione (7c): Yield 90%; Melting point 204-207°C; Mass m/z 331.7 $[M+H]^+$; IR (cm^{-1}) 3140 (NH), 1730 (C=O), 1475 (Ar C-C), 838 (C-Cl), 715 (C-S)**;** 1H NMR (ppm) δ 2.1511(s, 1H, Ar-C**H**-); δ 4.1541(s, 1H, Ar-N**H**-Ar); δ 7.4518(s, 1H, -C=O-N**H**-C=O); δ 7.4670-7.9783(m, 8H, Ar-**H**).

5-[4-(3-amino nitro benzene) benzylidene] thiaolidine-2,4-dione (7d): Yield 82%; Melting point 201-204°C; Mass m/z 341 $[M]^+$; IR (cm^{-1}) 3120 (NH), 1715 (C=O), 1537 (NO_2), 1420 (Ar C-C), 710 (C-S); ^{1}H NMR (ppm) δ 2.1511(s, ^{1}H, Ar-C**H**-); δ 4.2359(s, 1H, Ar-N**H**-Ar); δ 7.3520(s, 1H, -C=O-N**H**-C=O); δ 7.4518-7.9832(m, 8H, Ar-**H**).

5-[4-(4-amino anisole) benzylidene] thiaolidine-2,4-dione (7e): Yield 73%; Melting point 210-213°C; Mass m/z 326.9 $[M]^+$; IR (cm^{-1}) 3130 (NH), 1725 (C=O), 1480 (Ar C-C), 712 (C-S)**;** 1H NMR (ppm) δ 2.1087(s, 1H, Ar-C**H**-); δ 3.7253(s, 3H, -O-C**H3**); δ 4.2357(s, 1H, Ar-N**H**-Ar); δ 6.8113(s, 1H, -C=O-N**H**-C=O); δ 7.4346-7.7231(m, 8H, Ar-**H**).

5-[4-(4-amino benzene) benzylidine] thiaolidine-2,4-dione (7f): Yield 81%; Melting point 205-207°C; Mass m/z 297.4 $[M+H]^+$; IR (cm^{-1}) 3090 (NH), 1760 (C=O), 1450 (Ar C-C), 715 (C-S)**;** 1H NMR (ppm) δ 2.1018(s, 1H, Ar-C**H**-); δ 4.2067(s, 1H, Ar-N**H**-Ar); δ 6.9975(s, 1H, -C=O-N**H**-C=O); δ 7.2345-7.8427(m, 9H, Ar-**H**).

5-[4-(4-amino hydroxy phenyl) benzylidine] thiaolidine-2,4-dione (7g): Yield 78%; Melting point 205-211°C; Mass m/z 313.5 $[M+H]^+$; IR (cm^{-1}) 3360 (OH), 3115 (NH), 1765 (C=O), 1465 (Ar C-C), 711 (C-S); 1H NMR (ppm) δ 2.1080(s, 1H, Ar-C**H**-); δ 3.8413(s, 1H, Ar-N**H**-Ar); δ 5.1743(s, 1H, Ar-O**H**); δ 6.8231(s, 1H, -C=O-N**H**-C=O); δ 7.4346-7.7231(m, 8H, Ar-**H**).

5-[4-(2-amino toluene) benzylidene] thiaolidine-2,4-dione (7h): Yield 90%; Melting point 204-207°C; Mass m/z 311.5 $[M+H]^+$; IR (cm^{-1}) 3130 (NH), 1750 (C=O), 1485 (Ar C-C), 720 (C-S); 1H NMR (ppm) δ 2.1038(s,1H, Ar-C**H**-); δ 2.5756(s, 3H, Ar-C**H3**); δ 4.1378(s, 1H, Ar-N**H**-Ar); δ 7.2077(s, 1H, -C=O-N**H**-C=O); δ 7.4426-7.7731(m, 8H, Ar-**H**).

5-[4-(4-nitro phenyl amino) benzylidene] thiaolidine-2,4-dione (7i): Yield 80%; Melting point 201-203°C; Mass m/z 342.8 $[M+H]^+$; IR (cm^{-1}) 3120 (NH), 1715 (C=O), 1535 (NO2), 1475 (Ar C-C), 710 (C-S)**;**

1H NMR (ppm) δ 2.1432(s, 1H, Ar-C**H**-); δ 4.2169(s, 1H, Ar-N**H**-Ar); δ 7.2567(s, 1H, -C=O-N**H**-C=O); δ 7.3518-7.9932(m, 8H, Ar-**H**).

5-[4-(4-fluoro phenyl amino) benzylidene] thiaolidine-2,4-dione (7j): Yield 82%; Melting point 199-201°C; Mass m/z 315.5 $[M+H]^+$; IR (cm^{-1}) 3140 (NH), 1730 (C=O), 1460 (Ar C-C), 705 (C-S); 1H NMR (ppm) δ 2.1321(s, 1H, Ar-C**H**-); δ 4.1743(s, 1H, Ar-N**H**-Ar); δ 7.3167(s, 1H, -C=O-N**H**-C=O); δ 7.4594-7.9872(m, 8H, Ar-**H**).

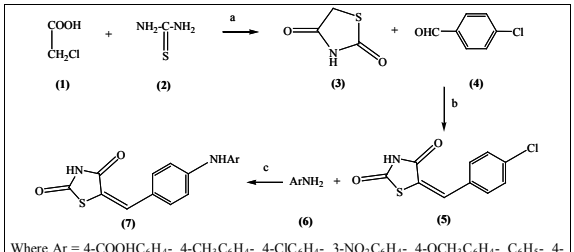
Chemistry

The synthetic route of the compounds is outlined in Figure 3. A series of several novel 5-[4-(Substituted) Benzylidene]Thiazolidine-2,4-Dione were prepared in three steps. Initially 2, 4-thiazolidinedione **(3)** was synthesized by 1, 3 dipolar cycloaddition [12] of thiourea **(2)** and chloroacetic acid **(1)** in presence of water. Knoevenagel's condensation [13] of 4-chloro benzaldehyde **(4)** with 2,4-thiazolidinedione **(3)** in the presence of sodium acetate gave 5-(4-chlorobenzylidene) 2, 4-thiazolidinedione **(5)**. This intermediate was common to all molecules being synthesized. The desired compounds 5-[4-(Substituted) Benzylidene]Thiazolidine-2,4-Diones **(7)** were prepared by reaction of 5-(4-chlorobenzylidene) 2, 4-thiazolidinedione **(5)** with some commercially available substituted primary aromatic amines **(6)** in presence of K_2CO_3 and acetonitrile using microwave irradiation of 200 watt for 2-4 minutes. The compounds **(7)** shown characteristic N-H stretching peaks near 3040-3200 cm^{-1}, C=O stretching peaks near 1760-1610 cm^{-1}, aromatic C-C stretching peaks near 1400-1500 cm^{-1}, C-Cl stretching peaks near 802-843 cm^{-1} and C-S stretching peaks near 650-750 cm^{-1}. In the ^1H NMR spectra of compounds **(7)**, the proton of N-H of secondary amine exhibited a singlet in the region of δ 3.9 to 4.33. The proton of N-H of amide exhibited a singlet in the region of δ 6.9 to 7.2 and aromatic protons were resonating as multiplet in the region of δ 7.2 to 7.9.

In-vivo Antidiabetic Activity

Oral glucose tolerance test

***In-vivo* study of synthesized compounds by OGTT:** The oral glucose tolerance test (OGTT) measures the body's ability to use a type of sugar, called glucose that is the body's main source of energy. OGTT, a test of immense value and sentiment, in favour of using fasting plasma glucose concentration alone was seen as a practical attempt to simplify and facilitate the diagnosis of diabetes. Hyperglycemia is an important factor in the development and progression of the complications of diabetes mellitus.



Where Ar = 4-$COOHC_6H_4$-, 4-$CH_3C_6H_4$-, 4-ClC_6H_4-, 3-$NO_2C_6H_4$-, 4-$OCH_3C_6H_4$-, C_6H_5-, 4-OHC_6H_4-, 2-$CH_3C_6H_4$-, 4-$NO_2C_6H_4$-, 4-FC_6H_4-

Reagents and Conditions: (a) H_2O, Conc. HCl, Reflux, Microwave irradiation (250 watt), 6 min.; (b) Glacial acetic acid, Sodium acetate, Reflux, Microwave irradiation (200 watt), 5 min.; (c) K_2CO_3, Acetonitrile, Reflux, Microwave irradiation (200 watt) 2-4 min.

Figure 3: Reaction scheme for synthesis of designed compounds.

Anti-diabetic activity

Method: Oral glucose tolerance test.

Animals used: Albino Wistar rat.

No. of animals used: 6 (in each group).

Dose of std. drug: 30 mg/kg (pioglitazone).

Route of administration: Oral.

Group I: normal control group.

Group II: pioglitazone control group (30 mg/kg).

Group-III-XII: were treated with synthesized compounds. The synthesized compounds were dissolved in suspension of 1% CMC.

Requirements: Instruments: Glucometer. **Chemicals:** 1% CMC.

Standard drug: Pioglitazone (30 mg/kg) aq. solution was prepared using 1% CMC.

Test compounds: Solution of compounds was prepared and administered orally similar to that of standard drug.

Apparatus: feeding needles (for oral dosing), syringes (1 ml, 2 ml).

Experimental design and procedure

Albino Wistar rats weighing about 200-250 gm were taken for study. Group I served as a normal control group while Group II for pioglitazone control group. Group III-XII was treated with synthesized compounds. Special diets are fed for 30 to 90 days prior to the OGTT. We carry out the OGTT by fasting animals for 18 hours, taking a blood sample from the tail under local anesthesia and then gavaging with glucose solution (3 gm/kg) of body weight. Blood samples are taken 30, 60, 90 and 120 minutes after the glucose meal and analyzed for blood glucose with a clinical glucometer. The reference drug and the synthesized compounds were administered orally with oral feeding tube to the rats. OGTT for non-diabetic rats were performed according to the standard method.

Group I stands for normal control group. Group II is treated with pioglitazone (30 mg/kg body weight). The synthesized compounds were dissolved 1% CMC in according to 30 mg/kg of body weight. Then the solution was administered orally to the glucose fed rats and blood was collected from the rat by cutting the tail. Blood sample was taken in a strip and then measured the glucose concentration level by glucometer and plasma glucose level in mg/dl was being monitored at 0, 30, 60 90, 120 minutes. Data were expressed as Mean ± Standard Error of Mean (SEM). Statistical comparisons were performed by one-way ANOVA followed by Dunnett's Multiple Comparison Test and the values were considered statistically significant when $P<0.05$ [14].

Results and Discussion

Based upon SAR and QSAR study of various antidiabetic thiazolidinediones, the present investigation was aimed at the modification of effector site and linker region without modification of 2, 4-thiazolidinedione ring toward development of better and safer antidiabetic agents than the available ones. In this regard, we have designed a new series of antidiabetic agents (thiazole derivatives), which mainly consist of 2, 4-thiazolidinedione ring system, attached to sterically hindered aromatic group, with suitable linker.

The series of 5-(4-(substituted) benzylidene) thiazolidine-2,4-diones **(7)** contains 2,4-thiazolidinedione ring which is necessary for

binding to receptor site, central six membered benzene aromatic ring as a linker region and substituted primary aromatic amines as an effector region responsible for lipophilicity of molecule. In this series (Table 1; Figures 4 and 5), the compound **7e** having electron releasing 4-methoxy substitution on aromatic ring had shown potent antidiabetic activity, while compounds **7g** and **7h** having electron releasing 4-hydroxy and 2-methyl substitution respectively, on aromatic ring have shown moderate antidiabetic activity as compared to standard pioglitazone. It was observed that the most of the active compounds possessed electron releasing group on aromatic ring of lipophilic site. It was also noted that substitution on aromatic ring at the 2nd and/or 4th position with electron releasing group of lipophilic site shows good antidiabetic activity than any other position. Compounds **7b** containing 4-methyl substitution on aromatic ring and **7f** containing no aromatic substitution have also shown antidiabetic activity. The remaining compounds **7a**, **7c**, **7d**, **7i** and **7j** substituted with 4-carboxyl, 4-chloro, 3-nitro, 4-nitro and 4-fluoro respectively, on aromatic ring have shown less antidiabetic activity as compared to pioglitazone.

Conclusion

Study concludes that compounds containing thiazolidinedione ring have better antidiabetic activity. 2, 4-thiazolidinedione compounds containing more lipophilic group increases antidiabetic activity. The presence of 2, 4-thiazolidinedione ring is involved in strong interactions with the receptor binding sites and due to more effective binding these compounds have shown more potential to be an active antidiabetic agents. If compounds possessing electron releasing substitution at 2nd and/or 4th position on aromatic ring of lipophilic region synthesized in future it may exhibit promising antidiabetic activity.

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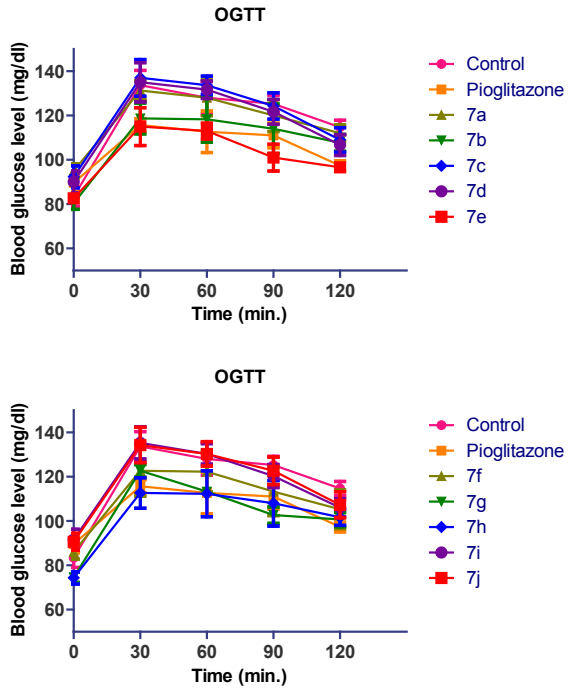

Figure 4: Effect of Compounds 7a-7j (at 30 mg/kg, Oral) on Glucose Excursion in OGTT of Albino Wistar Rats. Each Bar Represents Mean ± SEM (n=6).

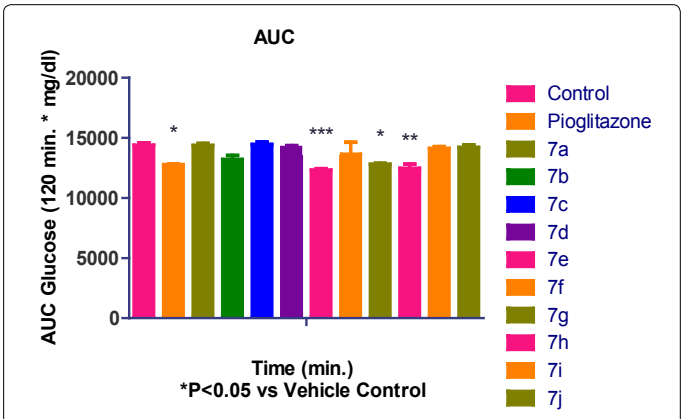

Figure 5: Effect of Compounds 7a-7j (at 30 mg/kg, Oral) on AUC Glucose (120 min*mg/dL) in OGTT of Albino Wistar Rats. Each Bar Represents Mean ± SEM (n=6).

Groups	AUC (0-120 min) glucose	Statistically Significance
Vehicle Control	14380 ± 485.0773	
Pioglitazone	12755 ± 132.5707	P<0.05 (*)
Compound 7a	14365 ± 388.6837	Not significant
Compound 7b	13185 ± 836.3761	Not significant
Compound 7c	14450 ± 454.1751	Not significant
Compound 7d	14175 ± 420.357	Not significant
Compound 7e	12315 ± 277.5338	P<0.05 (**)
Compound 7f	13620 ± 2462.255	Not significant
Compound 7g	12790 ± 209.3442	P<0.05 (*)
Compound 7h	12465 ± 836.3761	P<0.05 (**)
Compound 7i	14105 ± 385.584	Not significant
Compound 7j	14185 ± 534.439	Not significant

Each data set represents mean ± SEM (n=6) and data were analysed by One Way ANOVA followed by Dunnet's multiple comparison t test where P<0.05 vs. vehicle control group.

Table 1: Effect of Compounds 7a-7j (at 30 mg/kg, Oral) on AUC Glucose (120 min. mg/dL) in OGTT of Albino Wistar Rats.

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