Original Article

Design, Synthesis, Hypoglycemic Activity and Molecular Docking Studies of 3-substituted-5-[(furan-2-yl)-methylene]-thiazolidine-2,4-dione Derivatives

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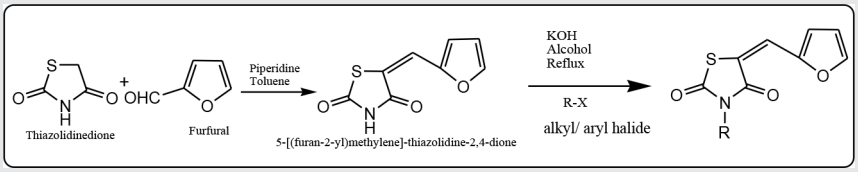
ABSTRACT

Background: From the wide range of previous literature studies indicated that thiazolidinedione's reacts with substituted benzaldehydes undergoes knoevenagel condensation gives respective arylidene derivatives. In our attempt all the titled compounds were designed and developed by replacement of substituted benzaldehydes with furan- 2-aldehyde, so that furan moiety was introduced in the molecule. **Materials and Methods:** 5-[(furan-2-yl)-methylene]-thiazolidine-2,4-dione was prepared via knoevenagel condensation by the reaction of thiazolidine-2,4-dione and furfural. Further it was coupled with various alkyl/ aryl halides in alcoholic potassium hydroxide to produce various derivatives 2a-2j. The titled compounds furthermore prepared by microwave assisted synthesis technique. Synthesized compounds were analysed by physical and spectral characterization methods. Developed furan bearing thiazolidine-2,4-diones were evaluated for *in-vivo* hypoglycemic property. Molecular docking analysis was carried out to observe the binding interaction of designed ligands at PPARγ target receptor protein. **Results and Conclusion:** Microwave irradiation technique produced high yield at less reaction time in comparison with traditional conventional method. *In-vivo* hypoglycemic activity evaluation revealed that, electron releasing groups (-OH and –OCH3) containing compounds 2d and 2g found to possess significant activity in acute study as well as in chronic study. Even the molecular docking studies at PPARγ receptor protein (PDB ID-2PRG), electron releasing groups containing compounds 2d and 2g exhibit significant binding affinity having high binding energy of -9.02 kcal/mol and -8.61 kcal/mol when compared with standard ligand rosiglitazone.



Key words: Thiazolidinedione derivatives, Synthesis, Hypoglycemic Activity, Molecular Docking, PDB ID-2PRG.

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INTRODUCTION

Diabetes mellitus (DM) is universally widespread chronic metabolic disorder during which elevated blood sugar levels take place over a prolonged period of time and symptoms comprises recurrent urination, increased hunger and thirsty. DM is allied with rigorous degenerative complications for instance nephropathy, cataract, neuropathy, accelerated atherosclerosis, retinopathy and stroke and increased the risk of myocardial infarction. Onset of these pathologies is a remarkable event throughout both

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type 1 and type 2 diabetes. Still severe challenging therapeutically problems for prevention and control for diabetic patients as they stand for the leading causes of morbidity and mortality.[1] Long ago type 2 diabetes seen only in adults, but presently the incident often even in children. In general, up to 80% of insulin stimulated glucose disposal takes place in the skeletal muscles, which is considered the foremost site of insulin resistance in type 2 diabetes.[2] Worldwide the incidence of diabetes in all age groups was expected to be 4.4% by the year 2030. By the year 2030, it may rise up to 366 million. The rate of diabetes frequency is high in men than in women. By the year 2030, urban diabetes population is expected to double in the developing countries than in 2000. Across the worldwide the majority demographic transform to diabetes frequency appears to exist an increase in the diabetic people proportion greater than 65 years of age. Thus, there is a demand in developing novel drug candidates in this region.[3]

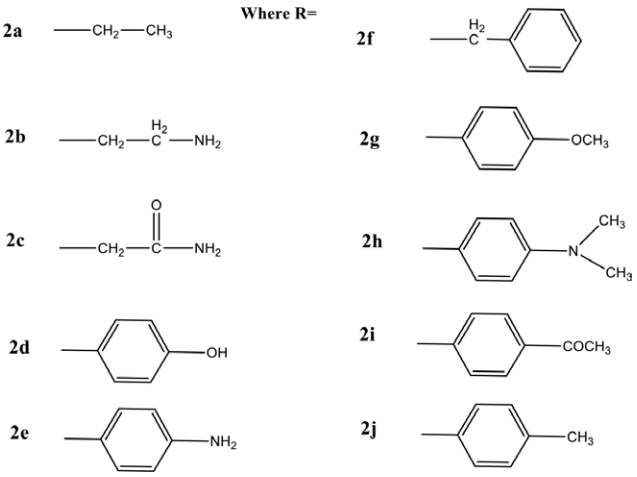
Thiazolidine-2,4-dione (TZD) is the most important heterocyclic moiety with much attention particularly in the treatment of type 2 diabetes. It is a 5-membered unsaturated heterocyclic compound consists of S and N heteroatoms at the 1st and 3rd position of the ring respectively and has two ketone functional groups at 2nd and 4th positions respectively. Troglitazone, ciglitazone, pioglitazone, rosiglitazone are the TZD class of drugs possessing insulin sensitizing property. In the year 2000, troglitazone was withdrawn from the market owing to hepatotoxicity. TZDs produce hypoglycemic activity significantly by lowering the blood glucose levels through the activation of peroxisomal proliferator activated receptors gamma type (PPARγ).[4] TZDs improve the insulin action and promotes utilization of glucose in peripheral tissues. The accurate mechanism of TZDs still not been elucidated, but expected to show agonistic properties by binding with PPARγ nuclear receptors.[5] Thiazolidinedione's also known as glitazones, act by binding to PPARγ receptors, type of nuclear receptors regulates glucose and fat metabolism. Those molecules correct hyperglycemia and hyperinsulinemia in several animal models of NIDDM. Glucose clamp studies have clearly shown an improvement of insulin-induced glucose utilization (in skeletal muscle). TZDs exert their antidiabetic effects through activation of gamma isoform of the peroxisomal proliferator-activated receptor (PPARγ) leads to alter the transcription of several genes involved in glucose and lipid metabolism and energy balance. TZDs reduce insulin resistance in adipose tissue, muscle and in the liver. However, PPARγ is predominantly expressed in adipose tissue. It is possible that the effect of TZDs on insulin resistance in muscle and liver is promoted *via* endocrine signaling from adipocytes. Although there are still many unknown factors about the mechanism of action of TZDs in type 2 diabetes, it is clear that these agents have the potential to benefit the "insulin resistance syndrome" associated with the disease. Hence, TZDs may have potential benefits on the secondary complications of type 2 diabetes.[6,7]

Recent developments in the area of TZDs found to possess an extensive array of biological actions for the instance antidiabetic,[8,9] protein tyrosine phosphatise 1B inhibitory,[10,11] 15-hydroxyprostaglandin dehydrogenase inhibitory,[12] hypolipidemic,[13,14] aldose reductase inhibitory,[15,16] anti-inflammatory,[17,18] antimicrobial,[19,20] antitubercular,[21,22] antioxidant,[23,24] and antitumor activities.[25] From the wide range of previous literature studies indicated that thiazolidinedione's reacts with substituted benzaldehydes undergoes knoevenagel condensation gives respective arylidene derivatives. In our attempt all the titled compounds were designed and developed by replacement of substituted benzaldehydes with furan-2-aldehyde, so that furan moiety was introduced in the molecule.

MATERIALS AND METHODS

Commercial Merck grade reagents and solvents were procured and further used without purification. E. Merck grade silica gel 60GF-254 precoated thin layer chromatography (TLC) plates procured and used to monitor the reaction progress and completion. TLC spots were observed using ultraviolet light of UV-cabinet and in iodine chamber. Fourier Transform Infrared Spectrometer (FT-IR) spectra were recorded with a Bruker FT-IR analyzer spectrophotometer by compression of compound with anhydrous KBr under vacuum using the KBr pressed pellet technique. Chemical shifts in δ, ppm of proton nuclear magnetic resonance (^{1}H-NMR) and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on a Bruker AMX-400 MHz spectrometer using tetramethylsilane as reference standard and deuterated dimethyl sulfoxide (DMSO) as solvent. Mass spectra were recorded in Agilent LC-MSD-1200 mass spectrometer. Round bottom flask connected with reflux condenser setup was used for conventional synthesis on REMI magnetic stirrer with thermostat. Raga's scientific microwave system (RGSSIRR model) having different power levels (140W to 700W) was used for microwave assisted synthesis. Electrical melting point apparatus was used to determine melting point and were uncorrected. In the *in-vivo* hypoglycemic study wistar albino rats were used

by dividing them into different groups and each group contained 6 rats (n=6).



Experimental

Synthesis of 5-[(furan-2-yl)-methylene]-thiazolidine-2,4-dione (1)

Conventional synthesis

Mixture of equal molar concentrations (0.01 mol) of thiazolidine-2,4-dione and furfural was taken in 8 ml of toluene. To the reaction mixture, 0.4 ml of piperidine was added, refluxed at 110-120°C for about 8 hr. Chromatographic TLC method was used to observe the reaction progress and completion. At room temperature the reaction mixture was cooled, add 1M HCl solution and ice-water. Resulted solid precipitate content was filtered, washed from cold water followed by dry toluene. Crude product was recrystallized from ethanol.[26]

Microwave synthesis

0.4 ml of piperidine was added to 0.01 mol equimolar concentrations of thiazolidine-2,4-dione and furfural in 8 ml of toluene. Reaction mixture was irradiated using RGSSIRR model Raga's microwave at 350W power level and 120°C temperature for about 8 min. After the reaction completion, diluted with 1M HCl and ice-water; obtained precipitate was filtered off, washed from cold water followed by dry toluene. Finally it was recrystallized from ethanol.[27]

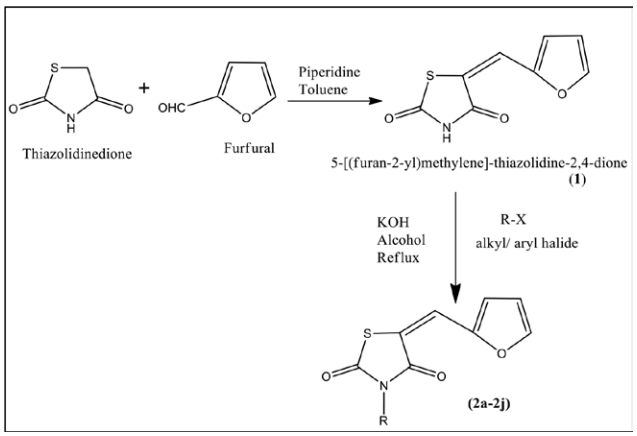


Figure 1: Scheme of synthesis of 3-substituted-5-[(furan-2-yl)-methylene]-thiazolidine-2,4-dione derivatives.

5-[(furan-2-yl)-methylene]-thiazolidine-2,4-dione (1) was obtained as yellow powder analyzed for the yield 68.58% (conventional synthesis), 82.51% (Microwave synthesis), mp 230-232°C, R_f value is 0.52 (benzene and ethyl acetate 8:2 ratio). FTIR spectrum showed the characteristic intense bands in cm^{-1} at 3364.42 (-NH-), 1668.26 (C=O), 1234.05 (C-N), 2964.28 (-CH), 3029.61 (=C-H), 620.42 (C-S) and 1628.52 (C=C). The ^{1}H-NMR spectrum showed the characteristic signals at 400 MHz in DMSO-d_6 with δ 11.09 (1H, s, TZD-NH-), δ 8.18 (1H, s, =CH- methylene), 6.42-6.56 (1H, t, furan-4'-H), 7.05-7.38 (1H, d, furan-3'-H), 7.65-7.81 (1H, d, furan-5'-H). The ^{13}C-NMR spectrum showed the characteristic signals at 400 MHz in DMSO-d_6 with δ 168.4, δ 166.5, δ 153.2, δ 146.5, δ 143.2, δ 123.4, δ 114.0, δ 111.5. The mass spectrum of the compound (2) was further confirms with ESI-MS: m/z(M^+) 195.

Synthesis of 3-substituted-5-[(furan-2-yl)-methylene]-thiazolidine-2,4-diones (2a-2j)

Conventional synthesis

0.01 mol ethanolic potassium hydroxide solution was added in drop wise to ethanolic suspension of 0.01 mol 5-[(furan-2-yl)-methylene]-thiazolidine-2,4-dione (1), stirred at for 15 to 20 min at room temperature. 0.01 mol aryl/ alkyl halide was added, refluxed for about 6-7.5 hr with stirring. Chromatographic TLC method was used to observe the reaction progress and completion (toluene-ethylacetate; 7:3). Cool the reaction mixture, diluted with ice water. Further, obtained solid precipitate was filtered off, washed from cold water and diethyl ether. Crude product was recrystallized from ethanol.[28]

Microwave synthesis

A mixture of 2 mmol anhydrous potassium carbonate in 5 ml of acetone and 5 ml of DMF and 0.01 mol 5-[(furan-2-yl)-methylene]-thiazolidine-2,4-dione (**1**) in acetone contents were stirred for about 20 min at room temperature. Add 0.01 mol Aryl/ alkyl halide and placed in RGSSIRR model Raga's microwave, irradiated at 300W power level, 120°C temperature for about 10-12 min. After the reaction completion, it was cooled, diluted with ice water, obtained solid precipitate was filtered off, washed from cold water and diethyl ether. Further it was purified by recrystallization from ethanol.[29]

Spectral data of synthesized compounds (2a-2j)

3-ethyl-5-[(furan-2-yl)-methylene]-thiazolidine-2,4-dione (2a):- FTIR [cm^{-1}]: 3008.57 (=C-H), 2936.45 (C-H), 1750.15 (C=O), 1708.54 (C=O), 1228.50 (C-N), 1658.24 (C=C), 1124.17 (C-O-C), 615.22 (C-S). ^{1}H-NMR [δ, 400 MHz]: 8.36 (1H, s, =CH- methylene), 6.72-6.98 (1H, t, furan-4'-H), 7.15-7.28 (1H, d, furan-3'-H), 7.90-8.01 (1H, d, furan-5'-H), 1.36-1.44 (3H, t, -CH_2- CH_3), 2.45-2.68 (2H, m, -CH_2- CH_3). ^{13}C-NMR [δ, 100 MHz]: 175.1, 168.6, 153.3, 144.2, 141.1, 123.4, 114.1, 111.4, 36.5, 22.4. ESI-MS: m/z[M^+] 223.

3-(2-aminoethyl)-5-[(furan-2-yl)-methylene]-thiazolidine-2,4-dione (2b):- FTIR [cm^{-1}]: 3388.45 (-NH-), 1768.24 (C=O), 1721.25 (C=O), 1205.47 (C-N), 2975.17 (C-H), 3024.48 (=C-H), 621.21 (C-S), 1640.47 (C=C), 1145.28 (C-O-C). ^{1}H-NMR [δ, 400 MHz]: 8.41 (1H, s, =C<u>H</u>- methylene), 6.66-6.85 (1H, t, furan-4'-H), 7.03-7.41 (1H, d, furan-3'-H), 7.78-8.10 (1H, d, furan-5'-H), 3.54-3.81 (2H, t, -C<u>H</u>$_2$- CH_2-NH_2), 2.83-2.3.08 (2H, m, -CH_2- C<u>H</u>$_2$-NH_2), 2.43-2.61(2H, t, -CH_2- CH_2-N<u>H</u>$_2$) . ^{13}C-NMR [δ, 100 MHz]: 170.5, 164.3, 151.5, 145.7, 141.8, 121.8, 115.5, 111.7, 54.6, 35.2. ESI-MS: m/z[M^+] 238.

3-(2-aminoacetyl)-5-[(furan-2-yl)-methylene]-thiazolidine-2,4-dione (2c):- FTIR [cm^{-1}]: 3315.57 (-NH-), 1725.14 (C=O), 1695.32 (C=O), 1216.17 (C-N), 2958.22 (C-H), 3052.54 (=C-H), 619.52 (C-S), 1651.21 (C=C), 1128.62 (C-O-C). ^{1}H-NMR [δ, 400 MHz]: 8.53 (1H, s, =C<u>H</u>- methylene), 6.52-6.75 (1H, t, furan-4'-H), 7.14-7.22 (1H, d, furan-3'-H), 7.53-7.63 (1H, d, furan-5'-H), 4.14 (2H, s, -C<u>H</u>$_2$-CO-NH_2), 5.27 (2H, s, - CH_2-CO-N<u>H</u>$_2$). ^{13}C-NMR [δ, 100 MHz]: 175.5, 168.1, 165.6, 153.2, 146.8, 142.7, 123.9, 114.9, 110.3, 48.6. ESI-MS: m/z[M^+] 252.

3-(4-hydroxyphenyl)-5-[(furan-2-yl)-methylene]-thiazolidine-2,4-dione (2d):- FTIR [cm^{-1}]: 3555.14 (-OH), 1716.05 (C=O), 1684.42 (C=O), 1228.61 (C-N), 2968.17 (C-H), 3034.11 (=C-H), 622.42 (C-S), 1669.75 (C=C), 1137.82 (C-O-C). ^{1}H-NMR [δ, 400 MHz]: 8.46 (1H, s, =C<u>H</u>- methylene), 6.35-6.61 (1H, t, furan-4'-H), 7.24-7.59 (1H, d, furan-3'-H), 7.71-7.92 (1H, d, furan-5'-H), 5.74 (1H, s, -OH), 6.54-6.79 (2H, d, phenyl 3'-H and 5'-H), 7.41-7.62 (2H, d, phenyl 2'-H and 6'-H). ^{13}C-NMR [δ, 100 MHz]: 178.4, 167.1, 156.8, 153.6, 148.2, 144.5, 128.4, 125.7, 123.8, 118.2, 114.1, 112.4. ESI-MS: m/z[M^+] 287.

3-(4-aminophenyl)-5-[(furan-2-yl)-methylene]-thiazolidine-2,4-dione(2e):- FTIR [cm^{-1}]: 3321.02 (-NH-), 1730.17 (C=O), 1699.21 (C=O), 1247.57 (C-N), 2974.33 (C-H), 3082.11 (=C-H), 620.08 (C-S), 1648.69 (C=C), 1108.17 (C-O-C). ^{1}H-NMR [δ, 400 MHz]: 8.49 (1H, s, =C<u>H</u>- methylene), 6.09-6.25 (1H, t, furan-4'-H), 7.53-7.63 (1H, d, furan-3'-H), 8.05-8.18 (1H, d, furan-5'-H), 4.68 (2H, s, -NH_2), 6.41-6.53 (2H, d, phenyl 3'-H and 5'-H), 7.32-7.45 (2H, d, phenyl 2'-H and 6'-H). ^{13}C-NMR [δ, 100 MHz]: 178.8, 167.4, 155.8, 147.8, 144.4, 140.8, 126.2, 123.2, 120.4, 118.4, 115.7, 110.2. ESI-MS: m/z[M^+] 286.

3-(benzyl)-5-[(furan-2-yl)-methylene]-thiazolidine-2,4-dione (2f):- FTIR [cm^{-1}]: 1729.64 (C=O), 1695.09 (C=O), 1232.51 (C-N), 2951.17 (C-H), 3044.27 (=C-H), 618.10 (C-S), 1648.07 (C=C), 1122.59 (C-O-C). ^{1}H-NMR [δ, 400 MHz]: 8.13 (1H, s, =C<u>H</u>- methylene), 6.30-6.56 (1H, t, furan-4'-H), 7.64-7.79 (1H, d, furan-3'-H), 7.85-7.99 (1H, d, furan-5'-H), 4.49 (2H, s, -C<u>H</u>$_2$-Phenyl), 7.10-7.48 (5H, m, phenyl). ^{13}C-NMR [δ, 100 MHz]: 175.8, 167.6, 153.1, 149.2, 147.9, 144.6, 129.7, 126.4, 123.2, 121.6, 117.2, 113.2, 45.3. ESI-MS: m/z[M^+] 285.

3-(4-methoxyphenyl)-5-[(furan-2-yl)-methylene]-thiazolidine-2,4-dione (2g):- FTIR [cm^{-1}]: 3064.67 (=C-H), 1739.32 (C=O), 1697.35 (C=O), 1234.17 (C-N), 2978.42 (C-H), 619.64 (C-S), 1658.23 (C=C), 1151.97 (C-O-C). ^{1}H-NMR [δ, 400 MHz]: 8.56 (1H, s, =C<u>H</u>- methylene), 6.11-6.40 (1H, t, furan-4'-H), 7.37-7.48 (1H, d, furan-3'-H), 8.15-8.27 (1H, d, furan-5'-H), 3.72 (3H, s, -OCH_3), 6.53-6.67 (2H, d, phenyl 3'-H and 5'-H), 7.58-7.69 (2H, d, phenyl 2'-H and 6'-H). ^{13}C-NMR [δ, 100 MHz]: 174.4, 166.2, 156.7, 151.5, 145.3, 141.5, 127.0, 124.4, 121.4, 117.7, 114.1, 112.4, 57.7. ESI-MS: m/z[M^+] 301.

3-[4-(dimethylamino)phenyl]-5-[(furan-2-yl)-methylene]-thiazolidine-2,4-dione (2h):- FTIR [cm^{-1}]: 1731.74 (C=O), 1685.24 (C=O), 1259.34 (C-N), 2938.29 (C-H), 3085.37 (=C-H), 628.36 (C-S), 1673.41 (C=C), 1138.46 (C-O-C). ^{1}H-NMR [δ, 400 MHz]: 8.19 (1H, s, =C<u>H</u>- methylene), 6.84-6.93 (1H, t, furan-4'-H), 7.08-7.29 (1H, d, furan-3'-H), 7.79-7.88 (1H, d, furan-5'-H), 2.96 (6H, s, -dimethylamino), 6.52-6.65 (2H, d, phenyl 3'-H and 5'-H), 7.48-7.56 (2H, d, phenyl 2'-H and 6'-H). ^{13}C-NMR [δ, 100 MHz]: 177.8, 165.4, 158.3, 153.5, 148.4, 142.6, 128.6, 125.3, 122.7, 118.3, 115.8, 111.5, 42.5. ESI-MS: m/z[M^+] 314.

3-(4-acetylphenyl)-5-[(furan-2-yl)-methylene]-thiazolidine-2,4-dione (2i):- FTIR [cm^{-1}]: 1715.62 (C=O), 1659.08 (C=O), 1238.19 (C-N), 2959.17 (C-H), 3066.26 (=C-H), 620.11 (C-S), 1685.22 (C=C), 1129.65 (C-O-C). ^{1}H-NMR [δ, 400 MHz]: 8.34 (1H, s, =C<u>H</u>- methylene), 6.68-6.79 (1H, t, furan-4'-H), 7.11-7.32 (1H, d, furan-3'-H), 7.51-7.68 (1H, d, furan-5'-H), 2.58 (3H, s, -COC<u>H</u>$_3$), 7.84-7.96 (2H, d, phenyl 3'-H and 5'-H), 7.55-7.68 (2H, d, phenyl 2'-H and 6'-H). ^{13}C-NMR [δ, 100 MHz]: 195.5, 175.2, 164.6, 153.8, 146.8, 142.3, 137.5, 132.1, 129.8, 125.5, 122.4, 114.6, 111.8, 30.8. ESI-MS: m/z[M^+] 313.

***3-(p-tolyl)-5-[(furan-2-yl)-methylene]-thiazolidine-2,4-dione (2j)*:-** FTIR [cm^{-1}]: 3025.40 (=C-H), 1737.19 (C=O), 1703.55 (C=O), 1256.46 (C-N), 2989.20 (C-H), 627.41 (C-S), 1674.57 (C=C), 1149.22 (C-O-C). ^{1}H-NMR [δ, 400 MHz]: 8.48 (1H, s, =CH- methylene), 6.12-6.39 (1H, t, furan-4'-H), 6.61-6.75 (1H, d, furan-3'-H), 8.17-8.26 (1H, d, furan-5'-H), 2.52 (3H, s, $-CH_3$), 7.30-7.45 (2H, d, phenyl 3'-H and 5'-H), 7.51-7.63 (2H, d, phenyl 2'-H and 6'-H). ^{13}C-NMR [δ, 100 MHz]: 177.2, 168.7, 152.4, 146.3, 143.6, 135.1, 130.6, 128.2, 124.1, 122.8, 112.5, 110.2, 26.6. ESI-MS: m/z[M^+] 285.

In-vivo Hypoglycemic Activity Evaluation

In-vivo hypoglycemic study was conducted on alloxan induced Wistar-Albino rats of either sex using tail tipping technique.[30,31] Rats (170-200 g weight) were procured from Sainadh Animal Supplier Agencies, Hyderabad. Initially before commencement of experiments, rats were acclimatized in the animal house laboratory for 1 week, feed with pellet and water *ad libitum*. Rats were placed in cages for about 12 hr dark cycle and 12 hrs light cycle at room temperature. For about 24 hr, acclimatized animals were reserved for fasting with water *ad libitum*, intraperitoneally alloxan monohydrate (120 mg/kg) in normal saline solution was administered. After one hr of alloxan monohydrate administration animals were given *ad libitum*. For a day, in feeding bottle 5% dextrose solution was given to control the premature hypoglycemic segment. Blood drop was collected from the tail vein portion, the blood glucose levels were measured with the help of digital Accu-Chek glucose monitor.

After 72 hr of alloxination, the rats possess blood glucose levels beyond 150 mg/dl were grouped for the acute and chronic studies (each group consists of 6 rats, *n*=6). In the acute study, test sample equivalent to 200 mg/kg as average human intake was considered 36 mg/kg single dose. Test samples were given by oral route with 0.25% carboxy methyl cellulose solution. Standard rosiglitazone of 30 mg/kg body weight dose was given to the rats. A dose of 35 mg/kg body weight was given to the rats as test sample during acute study. At 0, 1, 2, 4, 6 and 8 hr the blood samples were collected and measured the glucose levels of blood. By considering the acute study results, the test samples were particularly selected in the chronic study and doses of 35 mg/kg and 70 mg/kg body weight was given to the rats. Blood glucose levels measured after 30 min of dose administration and considered 0^{th} day. Further the glucose levels of blood were measured on 7^{th} day and 15^{th} day.

During hypoglycaemic activity screening, study protocol approvals were taken from Institutional Animal Ethics Committee (IAEC)) and Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) with registration no.1847/PO/Re/S/16/CPCSEA. Glucose levels of blood and body weights were mentioned as mean ± standard error of mean (SEM). Values were analyzed from one-way analysis of variance (ANOVA) followed by Dunnet's'*t*' test.

Molecular Docking Studies

Numerous factors involved in selection of protein for docking studies for example structure must be determined through X-ray diffraction, 2.0 to 2.5 Å resolution, consists of co-crystallized ligand, 3D structure of selected protein does not contain any protein breaks.[32] Target receptor co-crystal structure was taken from protein data bank PDB ID-2PRG (2.3 Å resolution). Commonly used docking validation method was done by pose selection whereby docking programs used to re-dock into the target active site with a known conformation and orientation, typically from the co-crystal structure. Programs that were able to return poses below a preselected Root Mean Square Deviation (RMSD) value from the known conformation usually below 1.5 or 2 Å depending on ligand size are considered to have performed successfully. Target protein was arranged by removing heteroatom portions, water molecules, non-receptor atoms, other ions, etc. Thiazolidine-2,4-dione moiety containing anti-diabetic drugs possess activity through PPARγ receptor protein active site.[33] Designed compounds molecular docking studies was performed on selected target 2PRG for their potential PPARγ agonist property.[34] Different ligands were modelled with the software ChemDraw Ultra 12.0 and transformed as appropriate 3D model structure, subjected to intend for energy minimization, which is necessary in the PDB files development and molecular docking. Docking was carried out on the designed ligands at the active site region of 2PRG using Auto-Dock 4.2.6. Binding interactions between diverse thiazolidine-2,4-dione ligands and 2PRG active site region was observed by considering active site as a rigid molecule and ligands being flexible. To predict the binding energy, docking was performed on prepared ligands at 2PRG active site region for best fit locations using rosiglitazone as standard reference ligand.

RESULTS AND DISCUSSION

Chemistry

Knoevenagel condensation of thiazolidine-2,4-dione and furfural gives 5-[(furan-2-yl)-methylene]-thiazolidine-2,4-dione (1). Further it was coupled with various alkyl/ aryl halides in alcoholic KOH to produce

Table 1: Physical characterization data of synthesized compounds 2a-2j.

Compound	m.p. (ºC)	Molecular formula	Molecular weight	Conventional synthesis		Microwave synthesis	
				% yield	reaction time	% yield	reaction time
2a	160-162	$C_{10}H_9NO_3S$	223.25	68.48	6 hr	73.85	10 min
2b	192-194	$C_{10}H_{10}N_2O_3S$	238.26	66.63	6.5 hr	74.42	12 min
2c	188-190	$C_{10}H_8N_2O_4S$	252.25	65.59	7 hr	72.56	10 min
2d	204-206	$C_{14}H_9NO_4S$	287.29	72.45	7.5 hr	80.15	11 min
2e	176-178	$C_{14}H_{10}N_2O_3S$	286.31	65.30	6.5 hr	73.25	12 min
2f	186-188	$C_{15}H_{11}NO_3S$	285.32	67.28	7 hr	71.63	10 min
2g	210-212	$C_{15}H_{11}NO_4S$	301.32	71.61	7.5 hr	80.55	10 min
2h	224-226	$C_{16}H_{14}N_2O_5S$	314.36	70.74	7 hr	78.42	12 min
2i	200.-202	$C_{16}H_{11}NO_4S$	313.33	68.48	6.5 hr	77.28	11 min
2j	194-196	$C_{15}H_{11}NO_3S$	285.32	71.26	7 hr	78.45	12 min

Table 2: Effect of synthesized compounds 2a-2j on blood glucose levels of alloxan induced diabetic rats (Acute Study).

Compound	Mean ± SEM of Blood glucose level mg/dl					
	0 hr	1 hr	2 hr	4 hr	6 hr	8 hr
Normal	123.22±2.18	121.58±3.04	121.47±2.45	122.23±3.21	121.52±4.07	122.54±2.63
Standard	396.55±4.12*	250.44±4.11**	193.33±3.52	155.84±3.42**	110.36±3.18	103.32±3.51*
2a	330.5±3.28*	294.11±4.56*	238.61±5.16*	212.31±4.35	238.12±5.42	265.34±3.56*
2b	329.18±5.11*	301.3±4.45	288.15±3.12	270.41±2.62	260.61±3.32**	285.14±2.65
2c	335.6±3.48*	310.51±2.21	295.4±2.68*	276.42±4.64**	258.4±2.08	275.5±5.35*
2d	320.55±4.22	283.2±5.48**	210.61±5.32*	159.51±6.35	118.54±4.31**	106.61±2.46
2e	349.46±3.64	315.3±2.67	265.28±4.65**	241.65±2.84	256.94±2.61*	279.15±2.69**
2f	338.66±3.54**	304.64±5.09*	279.35±4.62**	260.19±2.64	275.27±4.35*	290.53±3.47*
2g	325.24±4.27*	273.64±3.51*	199.46±3.62	150.33±4.49*	120.46±4.38**	105.63±3.38
2h	332.18±3.68*	292.3±2.34 **	279.64±3.09	255.46±4.81*	263.31±5.34	282.06±4.35
2i	320.0±3.91**	301.26±3.38*	295.42±5.06	268.38±3.18*	275.25±2.67**	300.57±4.11*
2j	328.16±2.34	297.42±4.67*	278.3±2.62	255.38±3.38**	264.39±3.65	285.26±2.15

Standard Drug: Rosiglitazone; Statistical analysis was done by One-way ANOVA followed by Dunnet's 't' test.
** P<0.01 (considered as significant), * P<0.001.

various derivatives 2a-2j (Figure 1). The titled compounds were developed by conventional and microwave assisted synthesis. Comparative study and physical characterization results of conventional and microwave synthesis were given in Table 1.

In-vivo hypoglycaemic efficacy

According to the above mentioned animal study protocols, acute study results were mentioned in Table 2 with respect to standard rosiglitazone stated that significant activity was shown by compounds 2d and 2g. Results of chronic study were mentioned in Table 3 stated that significant activity was shown at a dose of 70 mg/kg body weight by the compounds 2d and 2g.

Molecular docking results

Docking was done to rationalize the experimental biological activity. Docking was performed by means of recently updated version Auto-Dock dock engine 4.2.6 software. Co-crystallized ligand rosiglitazone was used for docking validation. It was extracted from 2PRG and redocked the co-crystallized ligand into the pose of active site receptor protein. Validation was performed by computing the root mean square deviation (RMSD) value by overlying the structures of co-crystallized ligand and redocked ligand. The RMSD value was found to be 1.28 Å, suggested that method was valid enough to be used for docking studies of other compounds. Binding interactions were observed in Pymol 1.7.4.5. Binding energy (in kcal/mol), hydrogen bonds, hydrogen bond lengths, number of hydrogen bonds and interacted amino acid residues were recognized at the target protein active site, the values were given in Table 4. Standard ligand rosiglitazone showed -8.32 kcal/mol binding energy; forms five hydrogen bonds with bond lengths 3.19, 3.28, 2.54, 2.38, 4.11 and identified the interacted

Table 3: Effect of compounds 2d and 2g on fasting blood glucose level and body weight of alloxan induced diabetic rats (Chronic Study 15 days).

Compound	Blood glucose in mg/dl			Body Weight in g		
	Day 0	Day 7	Day 15	Day 0	Day 7	Day 15
Standard	**358.42±4.13**	**215.25±3.62****	**164.34±2.11***	**196.5±3.67**	**194.68±2.08***	**195.16±3.68***
2d (35 mg/kg bw)	368.09±2.64*	230.27 ± 3.31*	182.14±3.65*	195.94±2.68*	196.68± 4.61**	195.35±2.95*
2d (70 mg/kg bw)	354.32±4.68	210.52±2.09*	167.34±3.18	196.38±2.31*	195.38±2.41*	196.68±4.68
2g (35 mg/kg bw)	350.44±3.36*	230.49 ± 3.27	188.62±4.68*	197.61±2.07	195.35 ± 3.89**	195.46±2.95*
2g (70 mg/kg bw)	349.38±3.21*	225.49± 2.64*	165.24±2.85*	196.42±2.63*	196.38± 3.69*	194.2±1.65*

Standard Drug: Rosiglitazone; Statistical analysis is done by One-way ANOVA followed by Dunnet's '*t*' test.
** *P*<0.01 (considered as significant), * *P*<0.001.

Table 4: Binding energy and amino acid residues interacted by the compounds 2a-2j with the target PPARγ protein PDB ID - 2PRG.

Compound	Binding energy (kcal/mol)	No. of H bonds	H-bond length	Amino acid residues interacted
Rosiglitazone	−8.32	5	3.19, 3.28, 2.54, 2.38, 4.11	Gln286, Tyr473, His323, Arg288, His449, Met364, Cys285, Ser289
2a	−7.05	3	1.86, 5.88, 3.90	Leu270, Glu283, Ile341, Gly284
2b	−7.89	4	3.29, 4.49, 3.64, 4.01	Cys285, Ile341, Met364, Val339, Ile 326, Arg288, Ala292, Leu330
2c	−6.27	3	2.86, 4.22, 3.41	Arg288, Cys285, His449, Phe363, Phe282
2d	−9.02	9	3.32, 2.39, 2.80, 3.45, 3.30, 3.61, 2.87, 2.87, 3.87	Tyr473, Ser289, His323, Tyr327, His449, Leu330, Cys285
2e	−7.15	4	1.95, 3.27, 2.48, 3.12	Gln283, Arg288,Leu333, Gly284, His449,Ile341
2f	−7.35	3	4.36, 3.72, 3.99	Cys285, Met348, Ile341, Ala292, Ile326, Arg288, Leu330
2g	−8.61	4	2.88, 1.74, 3.18, 4.26	His449, Arg288, Val339, Phe282
2h	−8.10	3	1.96, 2.18, 2.85	Met364, Cys285, Leu270, His449, Arg288
2i	−7.17	5	3.64, 2.45, 3.94, 1.61	Ala292, His449, Tyr327, Leu330
2j	−7.65	3	3.46, 2.81, 3.72	Cys288, Leu270, Ser289, His449, Phe363

amino acids Gln286, Tyr473, His323, Arg288, His449, Met364, Cys285, Ser289. Target PDB ID- 2PRG protein 3D-structure was given in Figure 2.

The interaction complex of standard ligand rosiglitazone at with 2PRG active site was mentioned in Figure 3. Compound 2d produced binding energy -9.02 kcal/mol; forms nine hydrogen bonds with bond lengths 3.32, 2.39, 2.80, 3.45, 3.30, 3.61, 2.87, 2.87, 3.87 and identified the interacted amino acids Tyr473, Ser289, His323, Tyr327, His449, Leu330, Cys285 were represented in Figure 4. Compound 2g produced binding energy -8.61 kcal/mol; forms four hydrogen bonds with bond lengths 2.88, 1.74, 3.18, 4.26 and identified the interacted amino acids His449, Arg288, Val339, Phe282 were represented in Figure 5. Designed ligands 2d and 2g

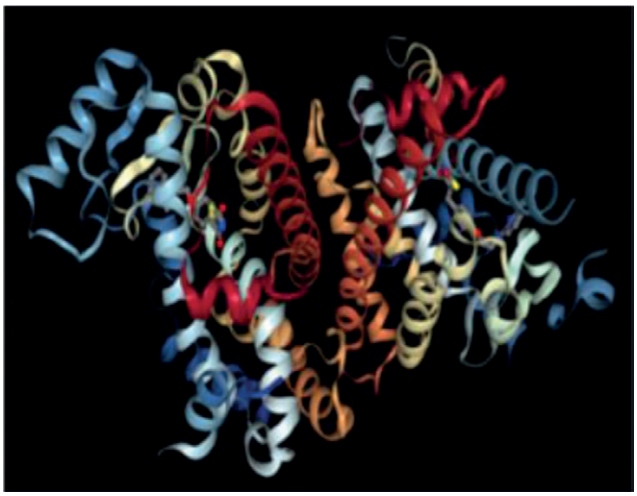


Figure 2: PPARγ protein 3D-structure from PDB ID- 2PRG.

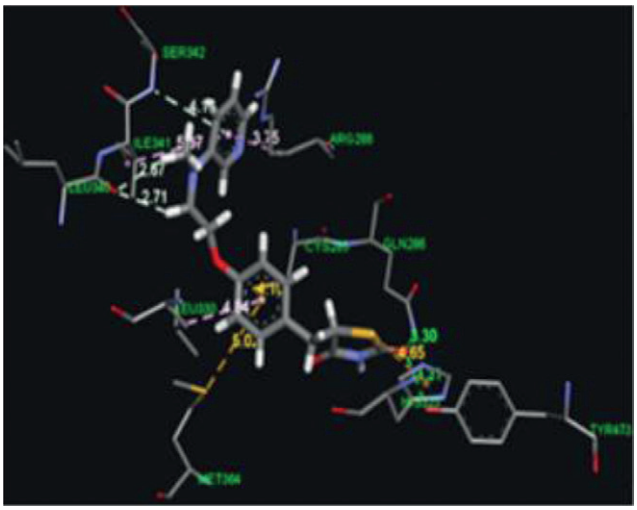


Figure 3: Binding mode of Rosiglitazone at PPAR$_y$ protein PDB ID-2PRG active site.

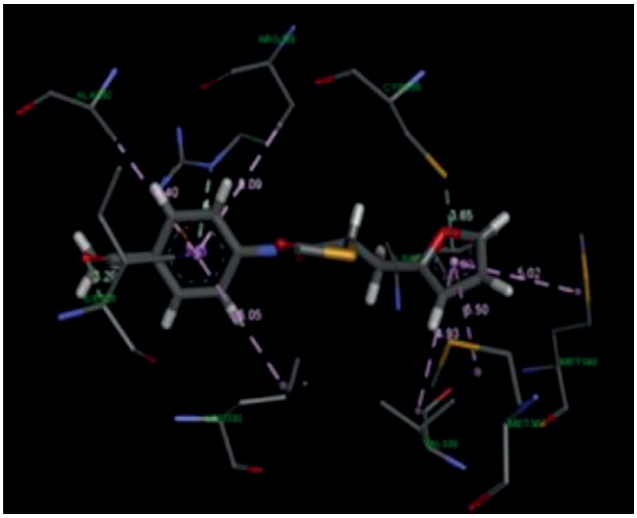


Figure 4: Binding mode of compound 2d at PPAR$_y$ protein PDB ID- 2PRG active site.

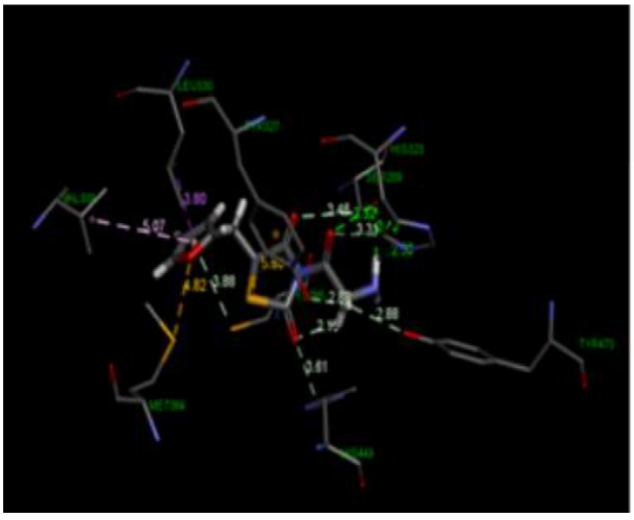


Figure 5: Binding mode of compound 2g at PPAR$_y$ id-2PRG active site.

shown promising binding affinity with binding energy -9.02 and -8.61 kcal/mol respectively in comparison to the standard rosiglitazone.

CONCLUSION

In this investigation an efficient versatile approach have been described to obtain various analogues of 3-substituted-5-[(furan-2-yl)-methylene]-thiazolidine-2,4-diones possessing alkyl/ aryl substitution at 3rd position and furyl methylene substitution at 5th position was developed. Titled compounds 2a-2j were designed, synthesized with electron releasing and electron withdrawing groups by conventional and microwave synthesis methods. Microwave irradiation synthesis produced high yields at less reaction time intervals than in conventional synthesis. Spectrally and physically the compounds were characterized. The rationale of experimental *in-vivo* hypoglycemic activity revealed that electron releasing groups (–OH and –OCH_3) containing compounds 2d and 2g found to possess significant *in-vivo* hypoglycemic activity in both acute study, chronic study. Even the molecular docking studies revealed that, electron releasing groups containing compounds 2d and 2g displayed significant binding affinity at the 2PRG PPARγ receptor protein active site. In 2d and 2g compounds, at 3rd position presence of –OH and –OCH_3 electron donating groups on the phenyl moiety may possibly considered as beneficial potential compounds.

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CONFLICT OF INTEREST

Authors declared no conflicts of interest.

ABBREVIATIONS

PPARγ: Peroxisomal proliferator activated receptors gamma type; **PDB:** Protein data bank; **DM:** Diabetes mellitus, **TZD:** Thiazolidine-2,4-dione; **TLC:** Thin layer chromatography; **^{1}H-NMR:** Proton Nuclear magnetic resonance; **^{13}C-NMR:** C-13 Nuclear magnetic resonance; **DMF:** Dimethyl formamide; **DMSO:** Dimethyl sulfoxide; **IR:** Infra-red; **m.p.:** Melting point; **IAEC:** Institutional Animal Ethics Committee; **CPCSEA:** Committee for

the Purpose of Control and Supervision of Experiments on Animals; **ANOVA:** Analysis of variance; **RMSD:** Root Mean Square Deviation; **SEM:** Mean±standard error of mean.

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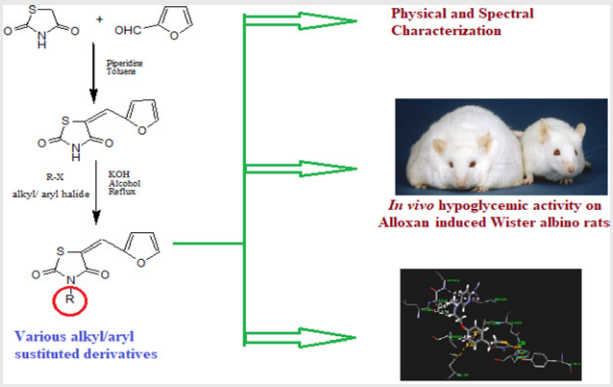
PICTORIAL ABSTRACT



SUMMARY

Thiazolidine-2,4-dione scaffold is a promising pharmacophore as PPARγ receptor agonist.

In view of this, designed and synthesized various thiazolidine-2,4-diones possessing alkyl/ aryl substitution at 3rd position and furyl methylene substitution at 5th position.

Microwave irradiation synthesis produced high yield at less reaction time in comparison to conventional synthesis.

In-vivo hypoglycemic activity screening, molecular docking studies revealed only two compounds shown promising hypoglycemic activity and good binding affinity at PPARγ receptor protein PDB ID- 2PRG.

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