https://doi.org/10.48047/AFJBS.6.13.2024.1267-1276

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

# Synthesis And Evaluation of antidiabetic activity of 3,5-Disubstituted-2,4Thiazolidinedione Derivatives

**P. Laxmi Madhuri[1], G. Rajitha[2*]**

[1]Malla Reddy Institute of Pharmaceutical Sciences, Maissammaguda, Dhulapally (Post via Hakimpet), Secunderabad Telangana- 500100, India.
Email: madhurirupakula@gmail.com
[2*]Institute of Pharmaceutical Technology, Sri Padmavati Mahila Visvavidyalayam, Tirupati,
Andhra Pradesh -517502, India
Corresponding Email: [2*]rajitha.galla@gmail.com

Volume 6, Issue 13, July 2024

Received: 02 June 2024

Accepted: 30 June 2024
Published: 24 July 2024
*doi: 10.48047/AFJBS.6.13.2024.1267-1276*

**ABSTRACT:**

Hyperglycemia, characterized by elevated glucose levels in blood, is a major metabolic disorder which on longterm contributes to several complications like hyperlipidemia and subsequent cardiovascular events, kidney damage and microvascular complications. Novel 3,5-disubstituted thiazolidinediones were synthesized by the reaction of thiazolidinediones with biphenylcarbox aldehyde by Knoevenagel condensation reactions and the obtained products upon treatment with alkyl /aryl halides gave the synthesized products. The synthesized compounds were characterized by IR, NMR, and Mass spectra. The synthesized compounds were evaluated for antidiabetic activity in alloxan-induced hyperglycemic rats and the compound IId exhibited good control over hyperglycemia when compared with pioglitazone.

**Keywords:** hyperglycemia, thiazolidinedione, molecular docking, biphenylcarboxaldehyde.

## 1. Introduction

Diabetes mellitus, characterized by chronic hyperglycemia due to insulin deficiency or resistance, is a leading cause of morbidity and mortality worldwide. It often coexists with hyperlipidemia, a condition marked by elevated levels of lipids in the blood, including cholesterol and triglycerides. This comorbidity exacerbates cardiovascular risk and complicates disease management. pathways, further increasing blood glucose and lipid levels. Managing diabetes the key strategies to achieve this include: diet and lifestyle modifications. Medications to achieve normal levels, regular monitoring of blood glucose and lipid levels are essential for optimal management.

Thiazolidinediones (TZDs), also known as glitazones, are a class of heterocyclic compounds widely recognized for their potent antidiabetic properties, primarily through their role as agonists of the peroxisome proliferator-activated receptor gamma (PPARγ). [Grygiel-Górniak,
B. *et al.,*2014]. By activating PPARγ, TZDs improve insulin sensitivity, regulate glucose metabolism, and exert anti-inflammatory effects. [Willson, T. M., et al ., 2000] Beyond their well-documented antidiabetic activity, recent research has highlighted the potential of TZDs in addressing hyperlipidemia, a critical risk factor for cardiovascular diseases often associated with diabetes.[Virendra S.A.*et al.,*2022] TZDs have shown promise in normalizing lipid profiles through their multifaceted mechanisms, including modulation of lipid metabolism, enhancement of lipid uptake and storage in adipocytes, and reduction of lipogenesis in hepatocytes.[ Lehmann, J. M., et al.1995]

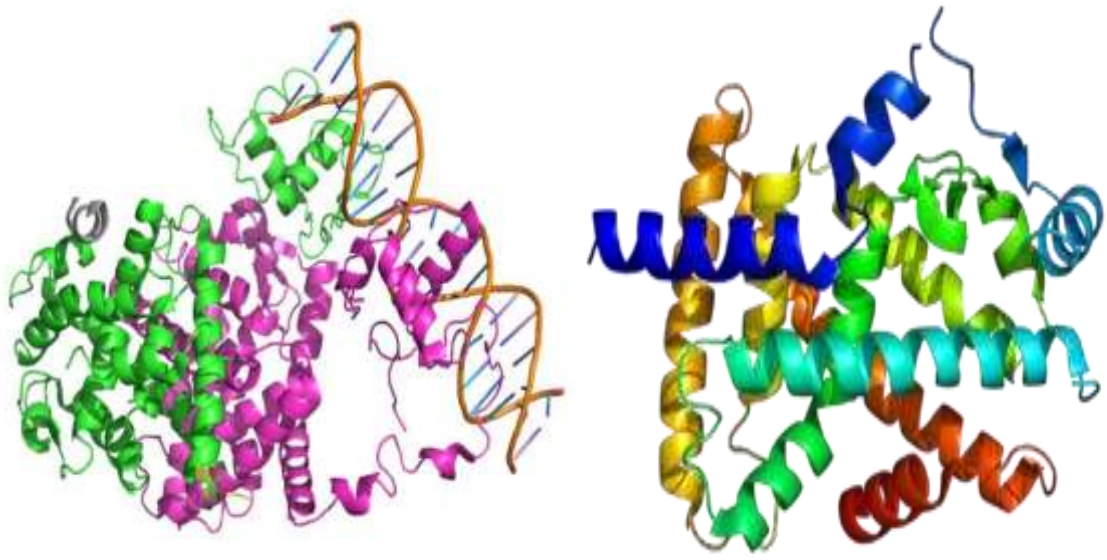


Fig 1: 3D Structure of PPARγ and PPARα

PPARα is a nuclear receptor principally expressed in tissues with high fatty acid oxidation, such as the liver, heart, kidney, and muscle. [Berger, J., & Moller, D. E. (2002)] Upon activation by ligands such as TZDs, PPARα constitutes a heteromolecular dimer with the retinoid X receptor (RXR). This composite dimer then binds to specific PPAR response elements (PPREs) in the promoter regions of target genes, modulating transcription. [Chawla, A. *et al.,* 2001] The dual activation of PPARγ and PPARα by TZDs enhances their effectiveness in addressing metabolic syndrome, which encompasses insulin resistance,

elevated blood glucose levels, dyslipidemia, and hypertension. [Lehrke, M. *et al.,* (2005)] PPARγ activation primarily improves insulin sensitivity and glucose homeostasis, while PPARα activation complements these benefits by improving lipid metabolism and reducing inflammation, providing comprehensive metabolic advantages. Hence in this article, we have synthesized novel 3,5- disubstituted-1,3-thiazolidinediones and evaluated them for invivo antihyperglycemic activity and molecular docking studies at the PPARα receptor further supported the dual PPARα/γ agonist activity of these compounds.

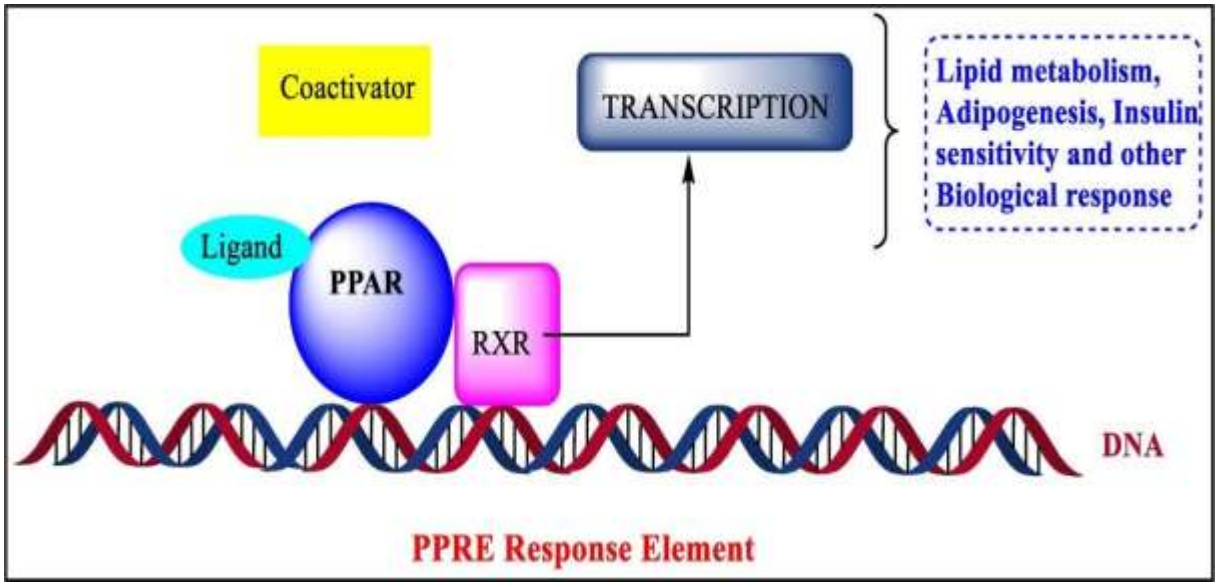



Fig 1: Mechanism of action of PPARα receptor

**Materials and methods**

The Chemicals and solvents used in the present study were used in pure grade without purification and are purchased from Merck, Sd Fine Chemicals Limited, Sigma Aldrich USA. Digital melting point was used to determine the melting points of the synthesized compounds. Using Silica gel 60 F254 plates from Merck company, Germany, TLC was done using ethyl acetate and ether in 4:6 ratio. UV chamber and iodine chamber were used to observe the spots. For absorbance measurements, Schimadzu UV Visible double spectrophotometer with UV probe 2.71 software was used. Using the Perkin Elmer FT-IR spectrophotometer by pellets of potassium bromide technique the IR was analysed. $CDCl_3$ and DMSO as the solvent the

$^1$HNMR &$^{13}$C NMR spectra were recorded on Bruker 500 MHz NMR spectrophotometer. Shimadzu mass spectrophotometer was used for the determination of the mass spectra.

**Synthesis of 5-([1,1'-biphenyl]-4-ylmethylene)-2,4- thiazolidinedione [I]**

3.2 mmol of both thiazolidinedione and 4-biphenylcarboxaldehyde were added to a reaction vessel and a catalytic amount (0.5ml) of pyridine, and 20 ml of ethanol were added and refluxed for 18 hours. After the reaction completion which was confirmed by the TLC the reaction mixture was cooled. The precipitated crude 5-([1,1'-biphenyl]-4-yl methylene)-2,4- thiazolidinedione was filtered and washed with cold $H_2O$ [G. Bruno, *et al*., 2002]. The crude product was refined by recrystallization using ethanol as a solvent.

**Synthesis of 3-substituted -5- ([1,1'- biphenyl] -4- ylmethylene)- 2,4- thiazolidinediones (Ia-h)**

In a reaction vessel,5-([1,1'-biphenyl]-4-ylmethylene)-2,4-thiazolidinedione I (0.02 mmol) and substituted alkyl/aryl chlorides (0.02 mmol) were taken, and sodium hydroxide (0.02 mmol) in 20ml ethanol: water (1:1) solution was added. The reaction mixture was refluxed for 18-20 hrs. [Shubhanjali Shukla, *et al*., 2012]. The products crystallized upon cooling and were purified by recrystallization using ethanol.

**Fig.2 Schematic representation for the synthesis of 3-substituted-5-([1,1'-biphenyl]-4-yl methylene)-2,4-thiazolidinedione Step I**

5-([1,1'-biphenyl]-4-yl methylene)-1,3-thiazolidine -2,4-dione (I)

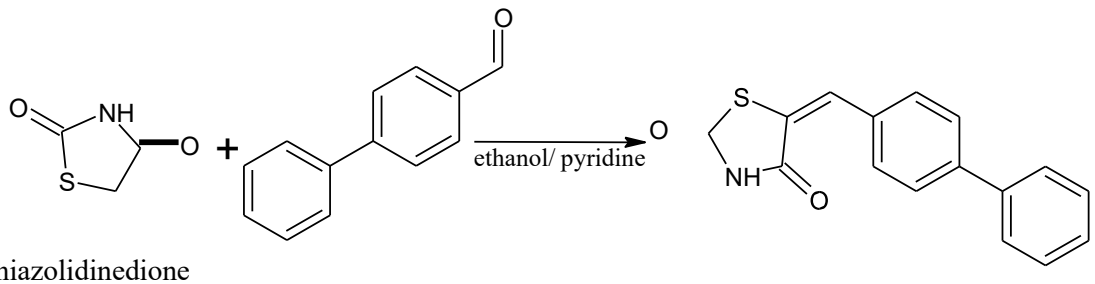
halides

R

IIa -$CH_3$

IIe- pentyl

3-substituted-5-([1,1'-biphenyl]-4-yl methylene ) -1,3-thiazolidine-2,4-dione (II a-g)

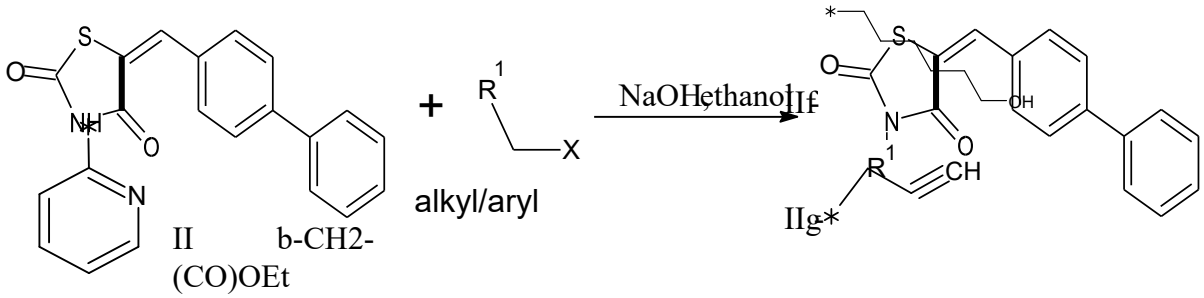



1,3-thiazolidinedione

[1,1'-biphenyl]-4-carbaldehyde

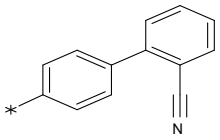
5-([1,1'-biphenyl]-4-yl methylene ) -1,3- thiazolidine-2,4-dione (I)

**Step II**




II c-

IId -




**Pharmacological evaluation Animals and Treatment**

Healthy male Wistar albino rats, weighing between 170 and 230 grams, were sourced from Prasad Vyas Lab in Uppal, Hyderabad. They were kept in polypropylene cages under controlled laboratory conditions, with a temperature maintained at 25°C ± 5°C and a 12-hour light/dark cycle. The rats had unrestricted access to both food and water. All protocols for assessing antidiabetic activity were approved by the Institutional Animal Ethics Committee (IAEC) under the Committee for Control and Supervision of Experiments on Animals, New Delhi (approval number: 01/MRIPS/CPCSEA-IAEC/Hyd/2023).

**Antihyperglycemic Activity**

The antihyperglycemic activity was conducted on 5 compounds in alloxan-induced diabetic rats. Diabetes was induced by administering freshly prepared 100 mg alloxan by blending in 1 ml of normal saline solution, after an overnight fast. To prevent drug-induced hypoglycemia, the rats were given a 5% glucose solution overnight [Pratik Prakash Maske, *et al*., 2023]. Two days later, glucose levels were measured, and rats with blood glucose levels exceeding 200 mg/dL were selected for further study [Alomari, *et al*.,2015]. Based on dose selection experiments, the effective dose for reducing plasma glucose levels was determined to be 25mg/kg per day. All compounds were administered intraperitoneally (i.p.) dissolved in DMSO. The rats were divided into the groups which served as control, diabetic control, diabetic rats treated with standard pioglitazone and diabetic rats treated with synthesized compounds. Blood samples were collected from the retro-orbital plexus under light anesthesia (using ethyl ether) 1 hour after compound administration on the $0^{th}$, $7^{th}$,$14^{th}$ and $21^{st}$ days. Blood glucose levels were measured utilizing the ACCU Check glucose monitoring device.

**Molecular Docking**

The structure of the ternary complex of PPARα (PDB ID: 1K7L) was retrieved from the Protein Data Bank (PDB) and was devised using the Schrödinger Suite 2021-4 Protein Preparation W izard module, minimized with the optimized potentials for simulations-3 (OPLS-3) molecular force field, and the RMSD of the crystallographic atom set at 0.3 Å[Lucia fernanda *et.al.,* 2012].

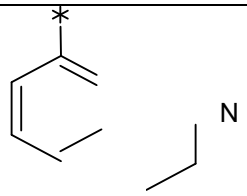
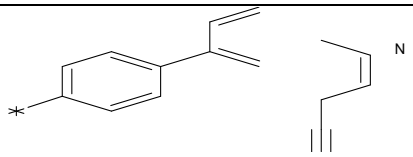
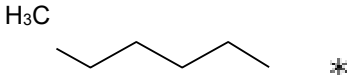
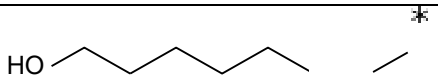
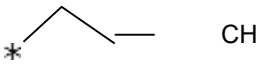
A grid box was created to exemplify the active site.[Sasikala, *et.al.,* 2019]
3D structures of the compounds were produced and optimized using the LigPrep module of the Schrödinger Suite 2021-4. The 2D structures were converted to 3D, energy minimized, optimized for geometry, desalted, and chirality corrected. Ligands were minimized using the OPLS-3 force field until an RMSD of 2.0 Å was achieved. Docking was performed using the G-module of the Schrödinger Suite 2021-4 in extra precision (XP) mode with default parameters[Rajitha G, *et.al.,* 2014]. The binding modes with the best Glide scores were selected and analyzed using the XP visualizer of the Glide module. The Glide scores of the compounds were compared with that of standard pioglitazone. The ligand-receptor complexes' binding free energy and post-docking energy minimization were carried out using the Prime Molecular Mechanics – Generalized Born Surface Area (MM-GB/SA) method in Schrödinger 2021.

## 2. Results and discussions

The compounds were synthesized in good yields ranging from 65-85%. (Table 1). The purity of the compounds was confirmed by melting point and thin layer chromatography kept with ethyl acetate and ether (4:6). Characterisation of 5-[([1,1'-biphenyl]-4-yl)methylidene] thiazolidine-2,4-dione by using IR, NMR, and mass spectroscopy, the details of which were published in our earlier article[ G.Rajitha *et.al*]. The IR spectra of the synthesized compounds exhibited characteristic peaks of the aromatic C-H stretch at 3000-3034 $cm^{-1}$, C=O group stretch at 1670 $cm^{-1}$ and 1730 $cm^{-1}$, C-N peak at 1310-130 $cm^{-1}$, C-S peak at 750 $cm^{-1}$, the mass of the synthesized compounds ranged from 282 – 472 gms, from the $^{1}H$ NMR (400 MHz, $CDCl_3$) the δ of the aromatic protons ranged from 8.10 – 7.27, aliphatic protons ranged from 1.26-1.31, from the $^{13}$ C NMR ( 500 MHz, $CDCl_3$) δ of the C=O carbons was observed between
167.96 and 166.53, the δ of the aromatic carbons ranged between 148.0 to 123.0, the δ of the
C-S carbon was observed at 121.9, the δ of the aliphatic carbons ranged at 27.96-14.11. Thus, the above data helped to establish the synthesized compounds' structure.

**Table 1: Physicochemical properties of the 5-([1,1'-biphenyl]-4-yl methylene)-3substituted thiazolidine-2,4-diones**

| S.No. | Compound | $R^1$ | Molecular formula | MWt. gms | % yield | MP° C |
|---|---|---|---|---|---|---|
| 1 | I | H | $C_{16}H_{11}NO_2S$ | 282 | 78 | 224 |
| 2 | IIa | $CH_3$ | $C_{17}H_{13}NO_2S$ | 295 | 71.2 | 234 |
| 3 | IIb | -CH2-(CO)OEt | $C_{20}H_{17}NO_4S$ | 367 | 83.3 | 250 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 4 | IIc |  | $C_{22}H_{16}N_2O_2S$ | 372 | 73 | 247 |
| 5 | IId |  | $C_{30}H_{20}N_2O_2S$ | 472 | 76 | 260 |
| 6 | IIe |  | $C_{21}H_{21}NO_2S$ | 351 | 85.3 | 245 |
| 7 | IIf |  | $C_{22}H_{23}NO_3S$ | 381 | 88 | 263 |
| 8 | IIg |  | $C_{19}H_{13}NO_2S$ | 319 | 75 | 280 |

**Pharmacological evaluation**

As per our research we reported earlier [G. Rajitha et.al.,2024] on invitro antioxidant activity and docking studies at PPARγ [G. Rajitha et.al.,2024]and PPARα active site, five compounds IIb, IIc, IId, IIe & IIf were selected for the *in-vivo* antihyperglycemic activity in alloxan-induced diabetic rats.

Most of the compounds exhibited prominent antidiabetic activity compared to the standard pioglitazone. Compound IId with the 2-cyano biphenyl methylene substitution showed a prominent reduction in the blood glucose level while compound IIf with hydroxy hexyl group was also observed to decrease the blood glucose levels. These studies revealed that the presence of hydrophobic groups like aromatic and higher alkyl groups at the N3 position enhanced the antihyperglycemic activity than the unsubstituted thiazolidinediones as reported earlier.

**Table2: Serum Blood Glucose Leves**

| **Groups** | **0 DAY** | **7 DAY** | **14 DAY** | **21 DAY** |
|---|---|---|---|---|
| **Normal control** | 94.63±2.54 | 96.27±2.66 | 97.29±2.08 | 95.23±2.14 |
| **Diabetic control** | 308.24±3.97 | 310.43±4.83 | 301.17±2.26 | 299.67±2.87 |
| **Standard control** | 311.87±1.73 | 209.36±3.97 | 137.68±2.76 | 83.33±1.94 |

| | | | | |
|---|---|---|---|---|
| **IIb** | 308.82±3.44 | 193.24±3.15 | 153.65±3.26 | 123.35±2.26 |
| **IIc** | 299.73±2.78 | 272.28±2.87 | 215.58±2.17 | 153.87±3.28 |
| **IId** | 302.78±3.07 | 184.32±4.07 | 144.27±3.06 | 94.65±2.65 |
| **IIe** | 297.68±2.72 | 271.23±1.06 | 225.73±2.95 | 155.98±2.14 |
| **IIf** | 302.57±2.44 | 193.65±2.872 | 154.36±3.53 | 106.96±3.26 |

Antidiabetic effect at a dose of 25 mg/Kg of rat at $0^{th}$ day (pre-drug values), $7^{th}$ day,14 $^{th}$ day and $21^{st}$ day (post-drug values) for each group of compounds (IIb, IIc, IId, IIe, IIf) compared to diabetic- control "DC". Data analyzed by one way ANOVA using graph prism pad method and expressed as mean ± SEM from 6 observations and is considered significant if $p<0.05$* and $p<0.005$**

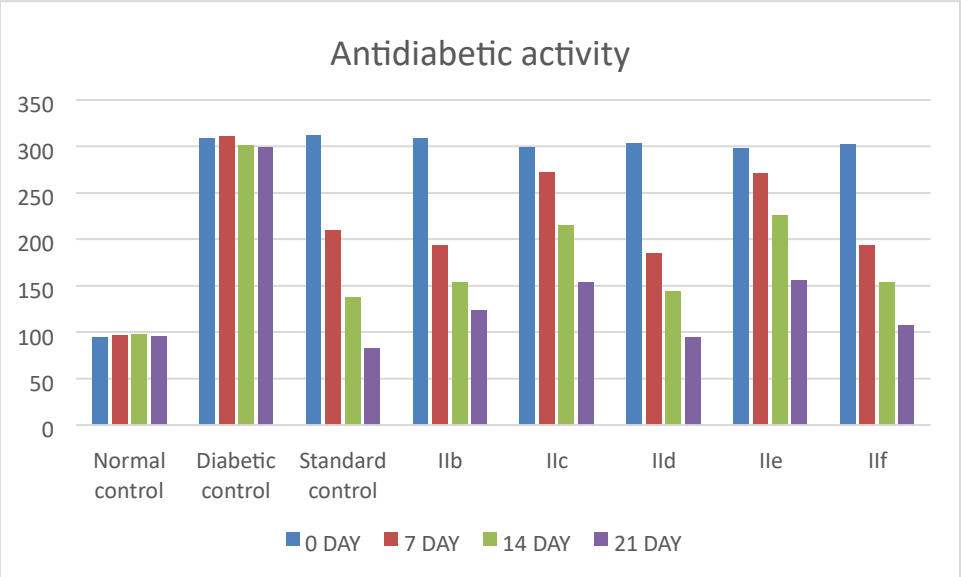



**FIG 3: The blood glucose level of hyperglycemic loaded rats on $0^{th}$, $7^{th}$ ,$14^{th}$, and $21^{st}$ day for each group of compounds.**

In the homologous series, as the number of alkyl groups increased the antidiabetic activity increased. Presence of a hydroxyl group or cyano groups on the alkyl and aromatic substitution further increased the hypoglycemic activity. The interaction substitution on the $3^{rd}$ position of thiazolidinedione enhanced the antihyperglycemic activity than the methyl group. The studies inferred that polar groups substituted on the alkyl or benzyl group at the $3^{rd}$ position of thiazolidinedione might be responsible for the additional binding interactions

at the receptor which accounted for their potent activity as per the literature [Manal.Y.Sameeh, *et.al.,*2022].

**Molecular docking**

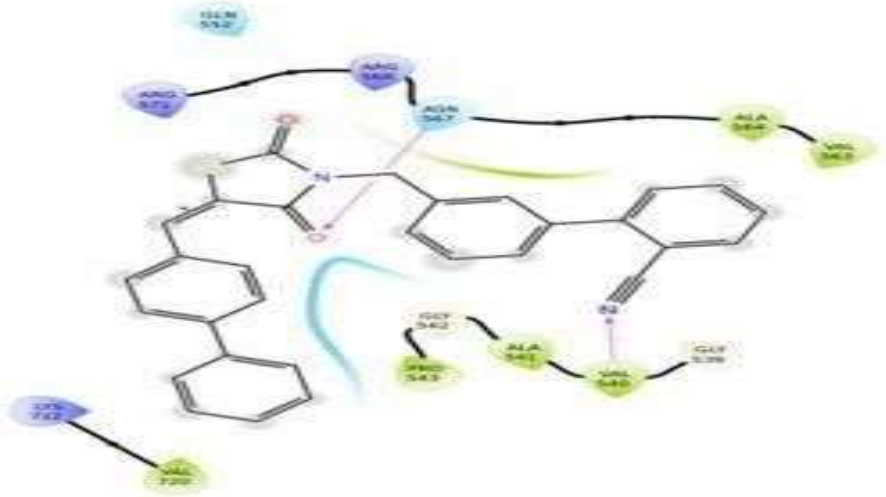
The glide scores and binding free energies of the molecules were reported in Table 4. The designed molecules were found to interact with the PPARα receptor by Hydrophobic bonding, pi-pi stacking, hydrogen bonding, and polar interactions (FIG: 4) were observed mainly with the binding site residues: glu 269, Ser 280, Thr 279, Gln 277, Phe 273, Cys 276, Tyr 314. Phe 318, Ile 317, leu 321, Leu 344, Leu 347.

TABLE 4: glide score, binding free energies & binding free energies

| S.No | Compound | G Score (kcal/mol) | Binding energy (kcal/mol) |
|---|---|---|---|
| 1 | I | -9.2 | -36.3 |
| 2 | IIa | -8.422 | -40.45 |
| 3 | IIb | -7.724 | -55.79 |
| 4 | IIc | -8.554 | -58.51 |
| 5 | IId | -7.654 | -50.77 |
| 6 | IIe | -9.2 | -35.34 |
| 7 | IIf | -6.417 | -42.57 |
| 8 | IIg | -8.538 | -63.81 |
| 9 | IIh | -6.565 | -42.64 |
| 10 | Pioglitazone | -7.5 | -55.2 |

All the compounds showed *in silico* activity at the PPAR α receptor with the G score ranging from -6.417 to –9.20 kcal/mol. The compounds I, IIa, IIb,IIc, IId, IIe and II g showed G scores more potent than the standard pioglitazone (-7.5 kcal/mol). The post-docking minimization revealed binding free energies (ΔG bind values) from -36.3 kcal/mol to -63.81 kcal/mol. The highest binding energy at the PPAR α receptor shown by compound IIg (-63.81 kcal/mol) indicates better binding affinity, highly stable interactions, and the most thermodynamically favorable binding. Further, it can be understood that the presence of a polar group on the alkyl group and benzyl group at the 3$^{rd}$ position of thiazolidinedione might be responsible for the increased binding interactions at the PPAR alpha receptor. The studies also revealed that the presence of only alkyl or aryl groups on the N3 position did not contribute to the formation of stable complexes with the receptor, resulting in their poor binding interactions at the active site of PPAR α.

Fig:4 – binding interactions of IId at the PPARα receptor by hydrogen bonding, polar interactions, and hydrophobic interactions can be observed.



## 3. Conclusion

The synthesized compounds were assessed for antihyperglycemic activity in alloxan-induced diabetic rats. From these studies, it was revealed that compounds IId and IIf exhibited potent antidiabetic activity. Molecular docking at the PPAR α receptor further established compounds IId and IIf as potent compounds with antihyperlipidemic activity. From the in vivo and molecular docking studies, it was disseminated that the presence of hydrophobic groups on the alkyl or benzyl group at the 3rd position of thiazolidinedione might be responsible for the additional binding interactions at the receptor which accounted for their potent activity as reported in earlier studies.

**Acknowledgements**
We, G. Rajitha and P. Laxmi Madhuri thank all the people who helped us in the completion of this work.

**Conflicts Of Interest**
There are no conflicts of interest to declare

## 4. References


1. Berger J, Moller DE. The mechanisms of action of PPARs. Annu Rev Med. 2002; 53: 409-35. doi: 10.1146/annurev.med.53.082901.104018. PMID: 11818483.
2. Chawla A, Repa JJ, Evans RM, Mangelsdorf DJ. Nuclear receptors and lipid physiology: opening the X-files. Science. 2001 Nov 30; 294(5548):1866-70. doi: 10.1126/scien ce.294.5548.1866. PMID: 11729302.
3. Lehrke M, Lazar MA. The many faces of PPARgamma. Cell. 2005 Dec 16; 123(6):993-9. doi: 10.1016/j.cell.2005.11.026. PMID: 16360030.
4. Grygiel-Górniak, B. Peroxisome proliferator-activated receptors and their ligands: nutritional and clinical implications - a review. Nutr J 13, 17 (2014). https://doi.org/10.11 86/1475-2891-13
5. Virendra, S.A.; Kumar, A.; Chawla, P.A.; Mamidi, N. Development of Heterocyclic PPAR Ligands for Potential Therapeutic Applications. Pharmaceutics 2022, 14, 2139. https://doi.org/10.3390/pharmaceutics14102139.
6. Willson, T. M., et al. "The PPARs: from orphan receptors to drug discovery." Journal of Medicinal Chemistry 43.4 (2000): 527-550.

*to 10*

7. Jiirgen M. Lehmanns, Linda B. Moore:j:, Tracey A. Smith-Oliver:j:, William O. Wilkison§, Timothy M. Willsonll, and Steven A. KliewerLehmann, J. M., et al. An antidiabetic thiazolidinedione is a high-affinity ligand for peroxisome proliferator-activated receptor gamma (PPARγ).Journal of Biological Chemistry 270.22 (1995): 12953-12956.
8. Ginsberg HN, Elam MB, Lovato LC, Crouse JR, 3rd, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff DC, Jr, Cushman WC, Simons-Morton DG, Byington RP. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010; 362: 1563–1574.
9. Goldberg IJ. Clinical review 124: Diabetic dyslipidemia: causes and consequences. J Clin Endocrinol Metab. 2001 Mar; 86(3):965-71. doi: 10.1210/jcem.86.3.7304. PMID: 11238470.
10. Krauss RM. Atherogenic lipoprotein phenotype and diet-gene interactions. J Nutr. 2001 Feb; 131(2):340S-3S. doi: 10.1093/jn/131.2.340S. PMID: 11160558.
11. G. Bruno, L. Costantino, C. Curinga, R. Maccari, F. Monforte, F. Nicolo, R. Ottana and M.G. Vigorita. Synthesis and Aldose Reductase Inhibitory Activity of 5-Arylidene-2, 4-thiazolidinediones, Bioorganic & Medicinal Chemistry. 10, 1077–1084, 2002.
12. Shubhanjali Shukla, Pankaj Kumar, Nirupam Das, N.S. Hari Narayana Moorthy, Sushant Kumar Shrivastava, Piyush Trivedi, Radhey Shyam Srivastava. Synthesis, Characterization, Biological Evaluation and Docking of Coumarin Coupled Thiazolidinedione Derivatives and its Bioisosteres as PPAR γ agonists. Med. Chem. 2012; 8: 834-845.
13. Pratik Prakash Maske, Popat Sonappa Kumbhar, Ashok Gurulingappa Wali, John Intru Disouza, Maya Sharma1 Antioxidant, Antidiabetic and Lipid Profiling of Spermadicyton Suaveolens in Streptozotocin (STZ) Induced Diabetic Rats Braz. J. Pharm. Sci. 2023;59: e21820 http://dx.doi.org/10.1590/s2175-97902023e21820.
14. Manal Y. Sameeh1 , Manal M. Khowdiary 1,2, Hisham S. Nassar 3,4, Mahmoud M.

Abdelall, 4 , Hamada H. Amer 5 Abdelaaty Hamed 4 and Ahmed A. Elhenawy 3,4le Thiazolidinedione Derivatives: In Silico, In Vitro, In Vivo, Antioxidant and Anti-Diabetic Evaluation, Molecules 2022, 27, 830.

15. Alomari, Abdulaziz & Elhenawy, Ahmed & Salama, Abeer & All, M. & Nassar, Haifa. (2015). Synthesis, characterization and discovery novel anti-diabetic and anti-hyperlipidemic thiazolidinedione derivatives. International Journal of Pharmaceutical Sciences Review and Research. 31. 23-30.
16. Sasikala M, Rajitha G. (2019). Cytotoxic oxindole derivatives: in vitro EGFR inhibition, pharmacophore modeling, 3D-QSAR and molecular dynamics studies. Journal of Receptors and Signal Transduction, 2019; 39(5-6), 1–10.
17. Rajitha G, Prasad KVSRG, Umamaheswari A, Prardhan D, Bharathi K. Synthesis, biological evaluation, and molecular docking studies of N- (α- acetamido cinnamoyl) aryl hydrazine derivatives as antiinflammatory and analgesic agents. Medicinal Chemistry Research. 2014;23: 5204-5214.
18. Lucia Fernanda C. da Costa Leite, Rosa Helena Veras Mourao, Maria do Carmo Alves de Lima, Suely Lins Galdino, Marcelo Zaldini Hernandes et al., Synthesis, biological evaluation and molecular modeling studies of arylidene-thiazolidinediones with potential hypoglycemic and hypolipidemic activities; Eur. J. Med. Chem. 2007; 42: 1263e1271 doi:10.1016/j.ejmech.2007.02.015.