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Research Paper

In Silico Design and Identification of Novel Thiazolidinedione Derivatives as PPAR-Gamma Receptor Agonists for the Treatment of Type 2 Diabetes Mellitus

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ABSTRACT

Type 2 diabetes mellitus is a chronic metabolic disorder with insulin resistance and impaired glucose homeostasis. PPAR-Gamma is a key regulator of glucose and lipid metabolism and a well-established therapeutic target. The present study is to synthesize and identify new thiazolidinedione derivatives as a potential PPAR-Gamma agonist by In Silico methods. A number of compounds were designed and molecular docking studies were conducted using CB-DOCK2 to assess their binding affinity and interaction with target receptor. Also pharmacokinetic and toxicity properties of compounds were determined using QSAR analysis and ADMET profiling by ChemMaster software. Docking results showed that some derivatives exhibited strong binding affinities and favourable interactions with major active site residues of the receptor. QSAR analysis confirmed structural elements involved in biological activity. ADMET predictions suggested acceptable pharmacokinetic properties with low toxicity profiles for top ranked compounds. The results suggest that the identified thiazolidinedione derivatives can be promising candidates for further development as PPAR-Gamma agonists in the treatment of Type 2 Diabetes Mellitus. Nevertheless, further experimental confirmation through in vitro and in vivo studies is essential to verify the therapeutic potential of these compounds.

INTRODUCTION

Diabetes Mellitus (DM) is one of the oldest known metabolic disorders, with descriptions dating back to ancient Egyptian manuscripts about 3000 years ago [1]. The classification of diabetes into type 1 and type 2 was clearly defined in the early 20th Century, improving understanding of disease mechanisms and management [2]. Type 2

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Diabetes Mellitus (non-insulin dependent diabetes) is the most common form of Diabetes Mellitus and is characterised by hyperglycemia, insulin resistance and relative insulin deficiency [3]. Type 2 Diabetes Mellitus results from a combination of factors and the interactions between genetic predisposition, environmental influences and lifestyle related behavioural factors are complex [4]. Individuals with Type 2 Diabetes Mellitus are at risk of short-term and long-term complications, including cardiovascular diseases, neuropathy, nephropathy and retinopathy, which contribute substantially to morbidity and mortality globally. The disease can be left undiagnosed for years, especially in growing countries where access to healthcare is restricted [4].

EXISTING TREATMENTS OF TYPE 2 DIABETES MELLITUS:

The management of type 2 diabetes mellitus is mainly aimed at maintaining optimal glycemic control and preventing long-term complications. Lifestyle modification involving dietary changes, weight reduction and increased physical activity are essential in improving insulin sensitivity and are usually the initial treatment [5].

Pharmacological therapy is initiated when lifestyle interventions alone are not sufficient. The currently available pharmacological treatments for type 2 Diabetes Mellitus are summarized below:

Table 1: Existing therapeutic agents used in the management of type 2 Diabetes Mellitus [5]

DRUG CLASS	EXAMPLE DRUG(S)	MECHANISM OF ACTION
BIGUANIDES	Metformin	↓ Hepatic glucose production ↑ Insulin sensitivity
SULFONYLUREAS	Glipizide Glibenclamide	Stimulate pancreatic insulin secretion
THIAZOLIDINEDIONES (TZD)	Pioglitazone, Rosiglitazone	Activate PPAR-Gamma ↑ Insulin sensitivity in adipose tissue and muscles
DPP-4 INHIBITORS	Sitagliptin Linagliptin	↑ Incretin Hormones ↑ Insulin Release
SGLT2 INHIBITORS	Dapagliflozin Canagliflozin	↑ Glucose excretion via urine
GLP-1 RECEPTOR AGONISTS	Liraglutide Exenatide	↑ Insulin , ↓ Glucagon, Slow gastric emptying
INSULIN THERAPY	Human Insulin, analogues	Direct glucose lowering

Despite the availability of multiple therapeutic options, limitations such as side effects, drug resistance and incomplete glycemic control necessitate the development of novel therapeutic agents.

RATIONALE FOR NOVEL THERAPEUTIC APPROACHES:

Type 2 Diabetes Mellitus has many therapeutic options, but effective long-term management has become a challenge due to limitations such as adverse effects, high cost and less patient compliance. Metformin is one of the frequently used drugs that are usually well tolerated but may cause gastrointestinal disturbances [6]. In addition, Sulfonylureas are connected with the hazards of hypoglycemia and gaining of physical weight which can negatively impact patient outcomes [7]. Furthermore, newer agents such as SGLT2 inhibitors and GLP1 receptor agonists are useful but expensive and can cause side-effects such as

urinary tract infection or gastrointestinal upset [5]. These limitations underline the requirement for safer, more effective and affordable therapeutic alternatives. The Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma) is a nuclear receptor. It plays a key role in the regulation cum direction of glucose metabolism, lipid homeostasis and insulin sensitivity. It is a hopeful beneficial target in the administration of Type 2 Diabetes Mellitus. PPAR-Gamma activation improves insulin sensitivity in peripheral tissue and as such is an attractive drug target [8].

Computational approaches such as molecular docking have emerged as powerful tools in modern drug discovery, enabling the identification and optimization of potential drug candidates by predicting their binding affinity and interaction with target proteins. Therefore, the present study aims to evaluate potential ligands targeting PPAR-Gamma using *In Silico* docking techniques to identify novel compounds with improved efficacy and reduced side effects.

MATERIALS AND METHODOLOGY [9-13]:

A) SOFTWARE AND WEB SERVERS:

- Protein Data Bank
- Pub Chem
- CB-DOCK2
- Auto Dock Tools
- ChemMaster

B) METHODS:

i. Selection of Receptor and Ligand preparation:

The Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma) was selected as target for the study. The crystal structure of the ligand-binding domain (LDB) was retrieved from the RCSB Protein Data Bank (PDB) using the PDB accession code 1KNU [14]. This structure was selected because it represents the receptor in an active conformation complexed with a high affinity agonist.

Standard reference ligands, such as Pioglitazone, were retrieved from the PubChem database [15]. A series of Thizolidinedione (TZD) derivatives were designed and prepared for docking using standard energy-minimization protocols to reach their local minima [16].

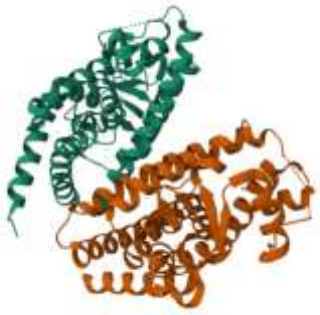


Figure 1: Human Peroxisome Proliferator Activated Receptor Gamma ligand-binding domain

(1KNU)

Table 2: Standard Compound

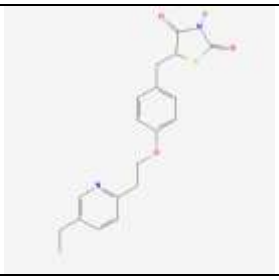
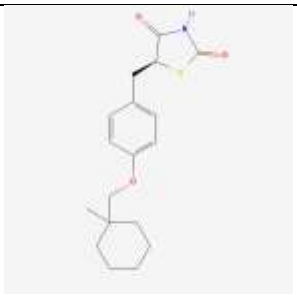
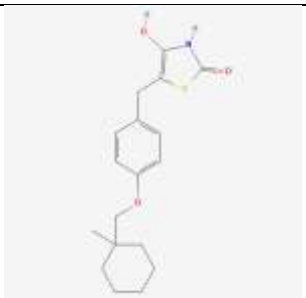
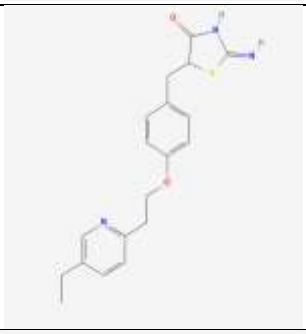
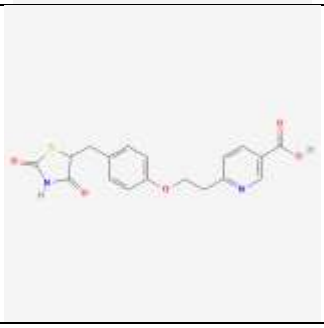
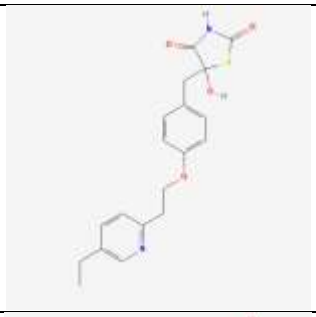
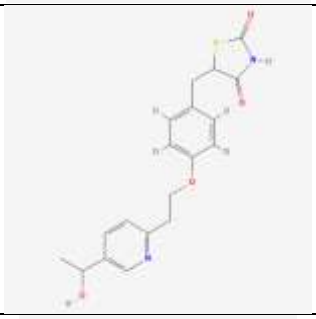
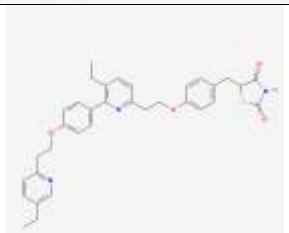
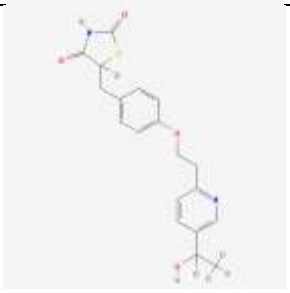
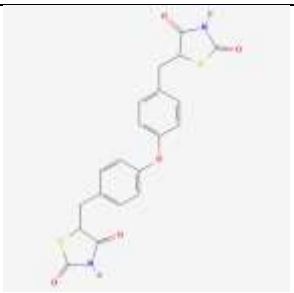
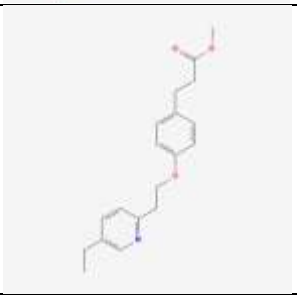
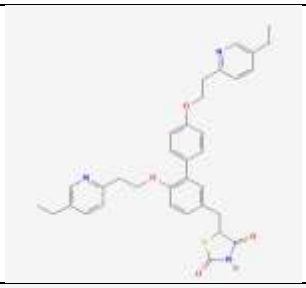
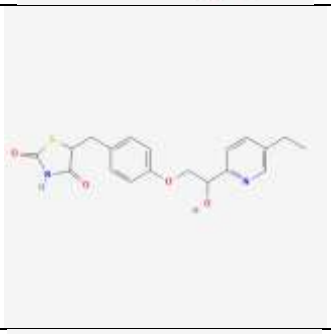
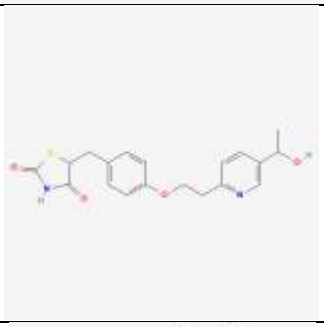
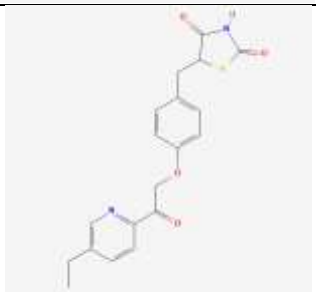
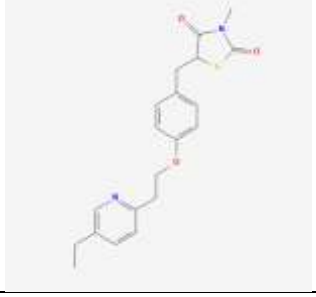
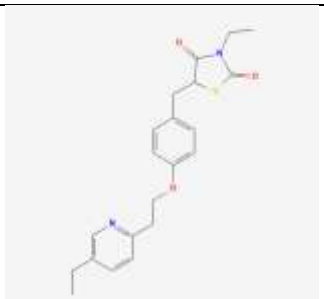
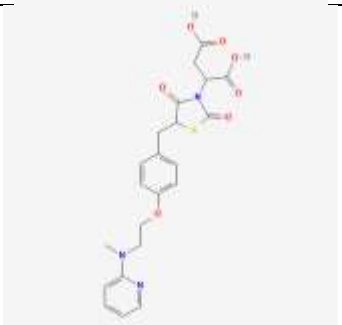
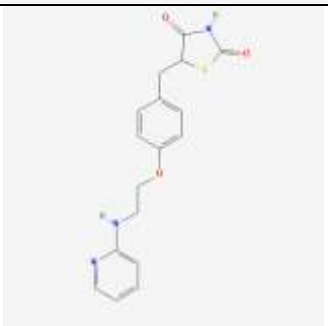
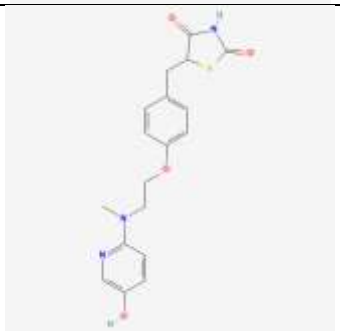
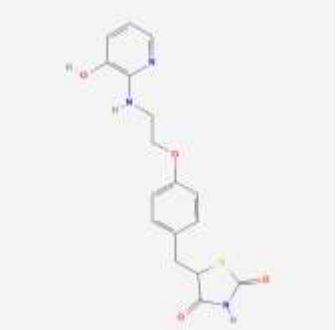
Sl. No.	Standard Compound	Structure
1	Pioglitazone	

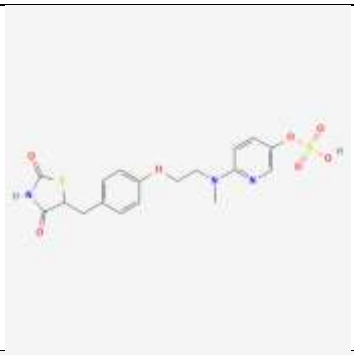
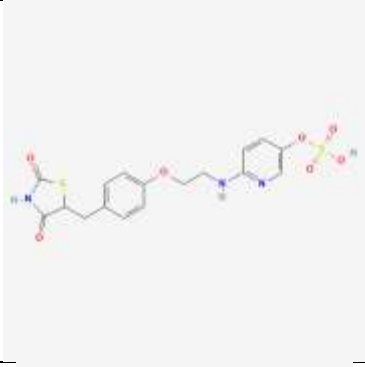
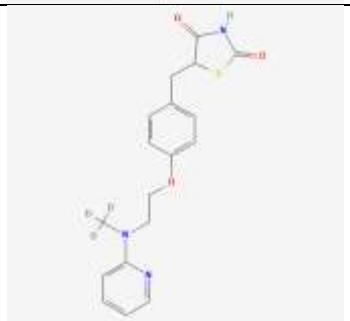
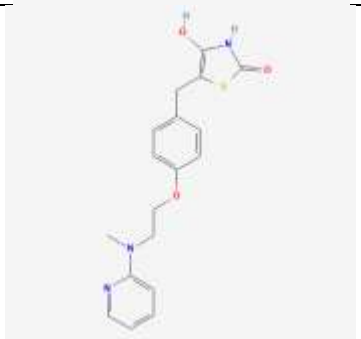
Table 3: List of Test Samples

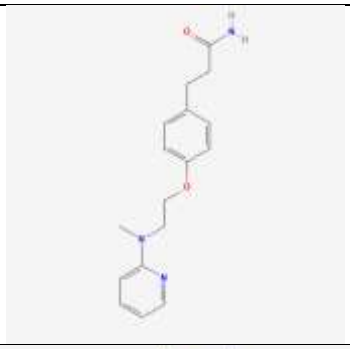
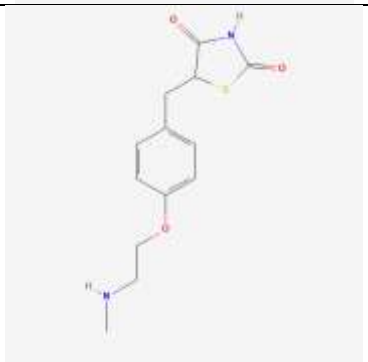
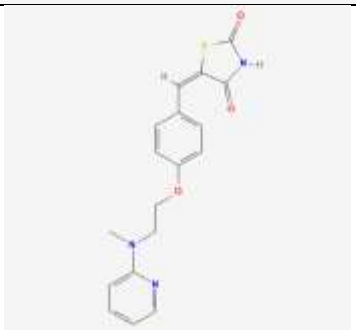
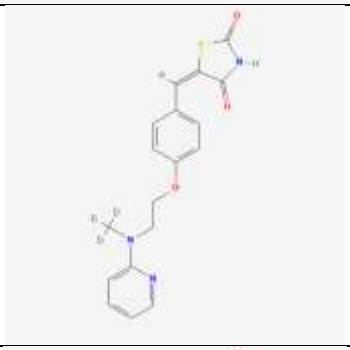
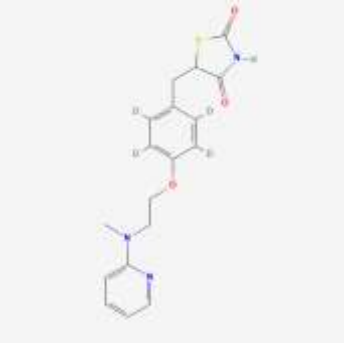
Sl. No.	Test Samples	Structure
1	TEST SAMPLE 1	
2	TEST SAMPLE 2	
3	TEST SAMPLE 3	
4	TEST SAMPLE 4	

5	**TEST SAMPLE 5**	
6	**TEST SAMPLE 6**	
7	**TEST SAMPLE 7**	
8	**TEST SAMPLE 8**	
9	**TEST SAMPLE 9**	
10	**TEST SAMPLE 10**	

11	**TEST SAMPLE 11**	
12	**TEST SAMPLE 12**	
13	**TEST SAMPLE 13**	
14	**TEST SAMPLE 14**	
15	**TEST SAMPLE 15**	

16	**TEST SAMPLE 16**		
17	**TEST SAMPLE 17**		
18	**TEST SAMPLE 18**		
19	**TEST SAMPLE 19**		
20	**TEST SAMPLE 20**		

21	**TEST SAMPLE 21**	
22	**TEST SAMPLE 22**	
23	**TEST SAMPLE 23**	
24	**TEST SAMPLE 24**	
25	**TEST SAMPLE 25**	

26	**TEST SAMPLE 26**	
27	**TEST SAMPLE 27**	
28	**TEST SAMPLE 28**	
29	**TEST SAMPLE 29**	
30	**TEST SAMPLE 30**	

ii. Molecular Docking and Virtual Screening:

Molecular docking was performed using CB-DOCK2 server to evaluate the binding affinity of the 30 designed derivatives [17]. The CB-DOCK2 algorithm was used for blind docking, which involves automatic cavity detection followed by docking with the AutoDock Vina engine. The compounds were selected based on their binding energy (Vina score) and their ability to mimic the orientation of the co-crystallized agonist found in the 1KNU structure.

Table 4: Receptor Activated Site (Coordinates)

Receptor	X	Y	Z
Human Peroxisome Proliferator Activated Receptor Gamma ligand - binding domain (1KNU)	**15**	**66**	**12**

Table 5: Molecular Docking analysis of Pioglitazone with the PPAR-Gamma Receptor (1KNU)

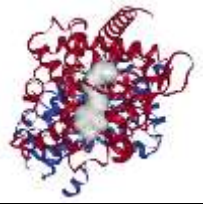
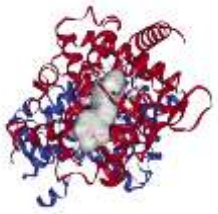
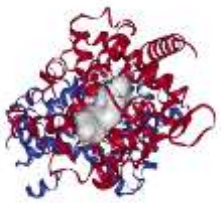
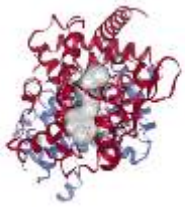
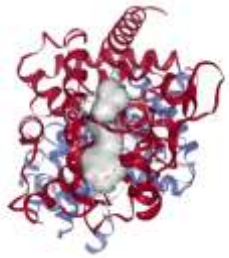
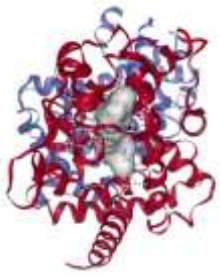
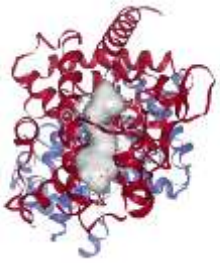
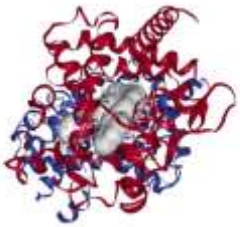
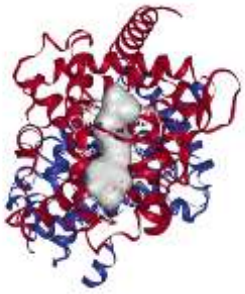
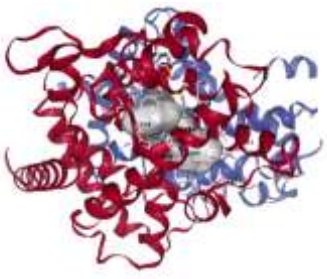
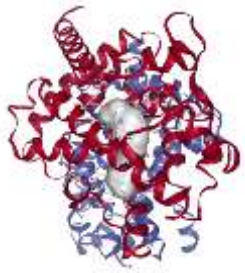
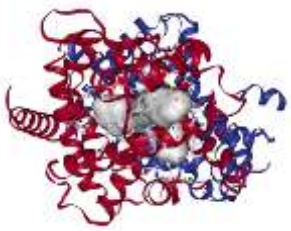
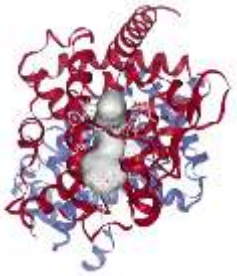
Sl. No.	Name of the Standard Compound	Docking Result [Binding Energy (kcal/mol)]	Molecular Docking
1	Pioglitazone	–9.4	

Table 6: Molecular docking results of the sample compounds against the PPAR-Gamma Receptor (1KNU)

Sl. No.	Name of the Test Sample	Docking Result [Binding Energy (kcal/mol)]	Molecular Docking
1	Test Sample 1	–9.5	
2	Test Sample 2	–8.9	
3	Test Sample 3	–9.5	

4	Test Sample 4	–9.5	
5	Test Sample 5	–8.6	
6	Test Sample 6	–9.6	
7	Test Sample 7	–11.1	
8	Test Sample 8	−9.5	
9	Test Sample 9	−10.8	

10	Test Sample 10	−8.1	
11	Test Sample 11	−11.5	
12	Test Sample 12	−9.5	
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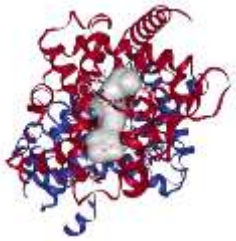
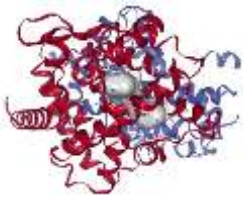
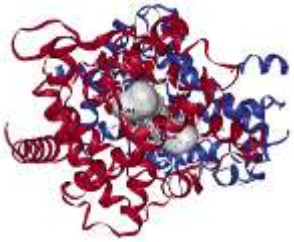
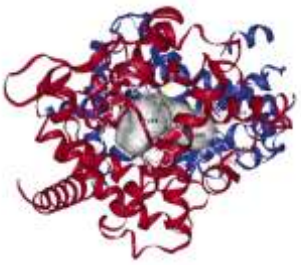
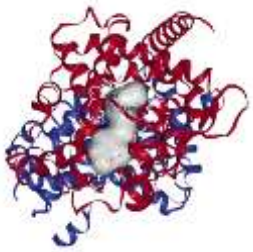
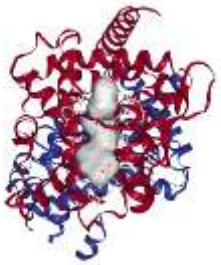
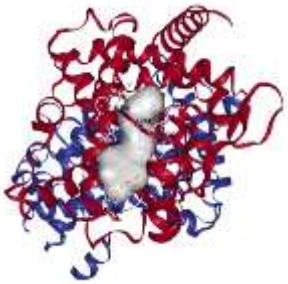
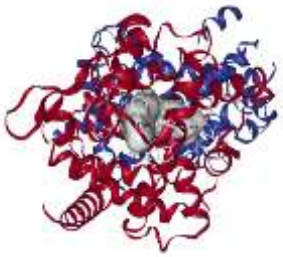
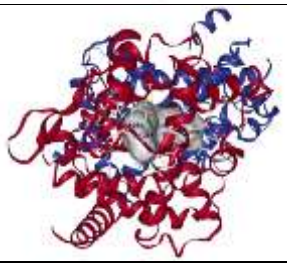
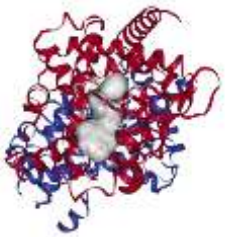
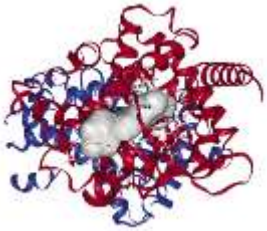
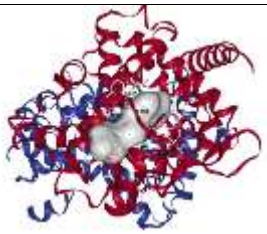
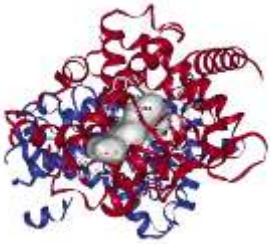
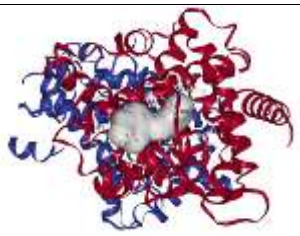
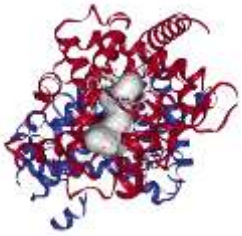
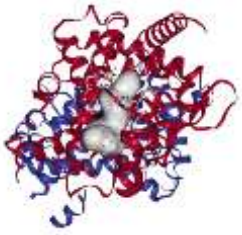
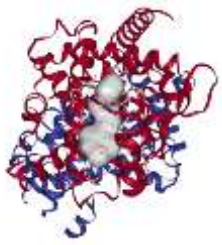
14	Test Sample 14	−9.4	
15	Test Sample 15	−9.4	
16	Test Sample 16	−9.3	

17	Test Sample 17	−9.1	
18	Test Sample 18	−9.3	
19	Test Sample 19	−9.5	
20	Test Sample 20	−9.0	
21	Test Sample 21	−9.5	
22	Test Sample 22	−9.2	

23	Test Sample 23	−9.1	
24	Test Sample 24	−9.4	
25	Test Sample 25	−9.0	
26	Test Sample 26	−8.1	
27	Test Sample 27	−7.7	
28	Test Sample 28	−9.1	
29	Test Sample 29	−8.8	

30	Test Sample 30	−9.3	

iii. **QSAR MODEL DEVELOPMENT:**

The selected 30 derivatives were subjected to Quantitative Structure Activity Relationship (QSAR) analysis using ChemMaster software [19].

Physicochemical descriptors including Molecular Weight, LogP, Hydrogen Bond Donor, Hydrogen Bond Acceptor, Molar Refractivity (MR), Rotatable Bonds were calculated for each compound.

The dataset was classified into training and test sets. Multiple Linear Regression (MLR) was used to generate the predictive model. The model's reliability was assessed through the coefficient of determination (R^2) and error metrices (RMSE, MAE) [20].

RESULTS AND DISCUSSION:

i. Physiochemical Screening and Drug-Likeness:

The 30 designed thiazolidinedione (TZD) derivatives were initially screened for their pharmacokinetic potential using Lipinski's Rule of Five (RoF). High oral bioavailability is a prerequisite for effective Type 2 Diabetes Mellitus (T2 DM) treatments [21].

Table 7: Drug-likeness evaluation of the designed TZD derivatives

Sl. No.	Molecular Formula	Molecular Weight	Log P < 5	H-Bond Donor <5	H-Bond Acceptor	Molar Refractivity	Rotatable Bonds	Lipinski's Rule Compliance
1	$C_{18}H_{23}NO_3S$	333.453	3.9299	1	4	91.7507	6	YES
2	$C_{18}H_{23}NO_3S$	333.453	4.082	2	4	92.5395	7	YES
3	$C_{19}H_{21}N_3O_2S$	355.463	2.9744	2	5	100.2084	8	YES
4	$C_{18}H_{16}N_2O_5S$	372.402	2.2954	2	7	95.459	7	YES
5	$C_{19}H_{20}N_2O_4S$	372.446	2.4796	2	6	99.0395	9	YES
6	$C_{19}H_{20}N_2O_4S$	376.4704	2.6505	2	6	99.1335	9	YES
7	$C_{34}H_{35}N_3O_4S$	581.738	6.4055	1	7	166.1277	15	NO MW>500 LogP>5
8	$C_{19}H_{20}N_2O_4S$	377.4765	2.6505	2	7	99.1335	9	YES
9	$C_{20}H_{16}N_2O_5S_2$	428.491	3.2671	2	7	110.2014	6	YES
10	$C_{19}H_{23}NO_3$	313.397	3.3711	0	4	89.593	10	YES
11	$C_{34}H_{35}N_3O_4S$	581.738	6.4055	1	7	166.1277	15	NO MW>500 LogP>5
12	$C_{19}H_{20}N_2O_4S$	372.446	2.6505	2	6	99.1335	9	YES
13	$C_{19}H_{20}N_2O_4S$	372.446	2.6505	2	6	99.1335	9	YES
14	$C_{19}H_{18}N_2O_4S$	370.43	2.7998	1	6	98.5042	8	YES
15	$C_{20}H_{22}N_2O_3S$	370.474	3.5018	0	5	102.505	9	YES
16	$C_{21}H_{24}N_2O_3S$	384.501	3.8919	0	5	107.122	10	YES

17	$C_{22}H_{23}N_3O_7S$	473.507	2.1312	2	10	120.4456	12	YES
18	$C_{17}H_{17}N_3O_3S$	343.408	2.4666	2	6	93.2854	7	YES
19	$C_{18}H_{19}N_3O_4S$	373.434	2.1965	2	7	99.7305	9	YES
20	$C_{17}H_{17}N_3O_4S$	359.407	2.1722	3	7	94.9502	8	YES
21	$C_{18}H_{19}N_3O_7S_2$	453.498	1.6725	2	10	110.2423	11	YES
22	$C_{17}H_{17}N_3O_7S_2$	439.471	1.6482	3	10	105.462	10	YES
23	$C_{18}H_{19}N_3O_3S$	361.4594	2.4909	1	6	98.0657	8	YES
24	$C_{18}H_{19}N_3O_3S$	360.4533	2.4909	1	6	98.0657	8	YES
25	$C_{18}H_{19}N_3O_3S$	357.435	2.643	2	6	98.8545	9	YES
26	**$C_{17}H_{21}N_3O_2$**	**299.374**	**2.0147**	**1**	**4**	**86.9594**	**9**	**YES**
27	$C_{13}H_{16}N_2O_3S$	280.349	1.1789	2	5	74.4854	7	YES
28	$C_{18}H_{17}N_3O_3S$	355.419	2.9207	1	6	98.5507	7	YES
29	$C_{18}H_{17}N_3O_3S$	358.4373	2.9207	1	6	98.5507	7	YES
30	$C_{18}H_{19}N_3O_3S$	361.4594	2.4909	1	6	98.0657	8	YES

- **Compliance:** 93.3% (n=28) of the library demonstrated strict adherence to Ro5 parameters.
- **Lipophilicity and Molecular Weight:** Most compounds maintained a molecular weight under 500Da and LogP under 5.0. However , compounds 7 and 11 (MW: 581.7; LogP: 6.4) were flagged as outliners, suggesting potential challenges with passive membrane permeability [22]
- **Molar Refractivity (MR):** The calculated MR values (74.4 to 166.1) indicated a broad range of molecular volumes, providing a diverse dataset for subsequent QSAR modeling.

ii. Quantitative Structure Activity Relationship (QSAR) Analysis :

A 2D-QSAR study was executed via ChemMaster (Version 1.3) using Multiple Linear Regression (MLR) to determine the structural drivers of activity.

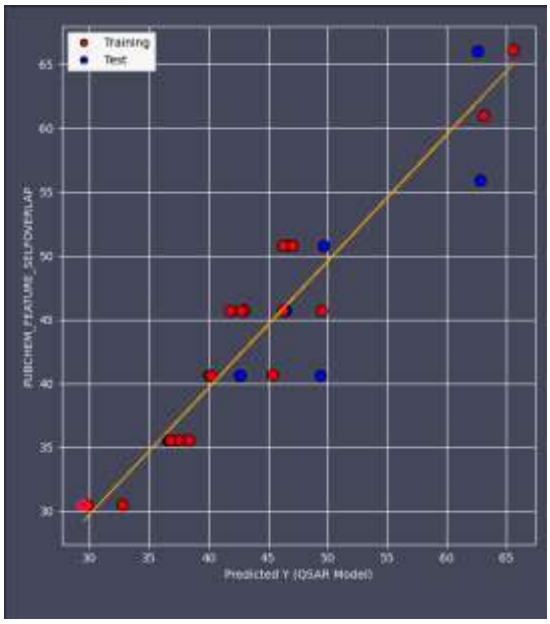


Figure 2: QSAR MODEL

- **Statistical Validation:** The generated model demonstrated high internal and external predictive power

- **Training Set (R^2):** 0.911
- **Test Set (R^2):** 0.836
- **Training Set RMSE:** 2.655
- **Test Set RMSE:** 4.419
- **Training Set MAE:** 2.253
- **Test Set MAE:** 3.448

An R^2 value exceeding 0.6 is considered the threshold for a reliable QSAR model; thus, our model's 0.911 correlation indicates excellent fit [20]. The proximity of the test set R^2 (0.836) to the training set suggests the model is robust and avoids overfitting.

- **Discussion of Molecular Descriptors:**

The predictive equation is as follows:

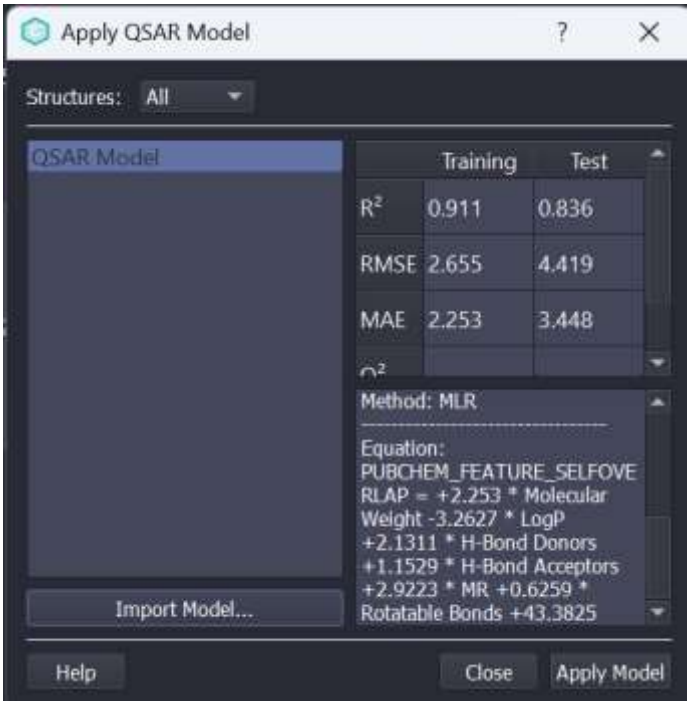


Figure 3: Regression Equation and Validation Parameters

- **Negative LogP Correlation:** The negative coefficient (-3.26) suggests that as lipophilicity increases, the predicted feature value decreases. This indicates that while the PPAR-Gamma pocket is hydrophobic, excessive 'greasiness' may hinder the molecule's interaction or solubility.
- **Positive MR and H-Bonding**: The positive coefficients for MR and Hydrogen Bond Donors (+2.13) suggest that molecular bulk and polar interactions are primary drivers for stabilization within the receptor site.

iii. Molecular Docking and Binding Affinity (PDB: 1KNU):

Using CB-DOCK2, the 30 derivatives were docked into the lignd-binding domain (LBD) of the PPAR-Gamma receptor. The best performing compounds occupied the hydrophobic 'Y-Shaped' cavity, establishing critical hydrogen bonds with His323 and Tyr473. Stabilizing the Tyr473 residue is essential for the activation of the AF-2 surface, which facilitates the recruitment of co-activators necessary for the anti-diabetic response [22,23].

iv. ADMET and Safety Profiling (Toxicity Analysis):

To address the historical safety concerns associated with glitazones (e.g., hepatotoxicity,

cardiotoxicity, etc.) an in-depth ADMET profile was established for the series.

Table 8: *In Silico* ADMET and Safety profiling of the selected TZD derivatives

Sl. No. (Compounds)	Clinical Toxicity	Carcinogenicity	Mutagenicity	Drug Induced Liver Injury (DILI)	Acute Toxicity (LD_{50})	hERG Blocking	Skin Reaction	PPAR-Gamma
1	0.3602	0.3483	0.3102	0.7783	2.2038	0.2481	0.6459	0.3669
2	0.2303	0.0415	0.2324	0.4114	2.7917	0.3286	0.3641	0.1182
3	0.2191	0.2759	0.0983	0.804	2.6666	0.4128	0.5003	0.1926
4	0.4804	0.2666	0.1951	0.9755	1.8492	0.017	0.3826	0.1666
5	0.3761	0.2201	0.1422	0.9201	2.5432	0.1907	0.3224	0.2189
6	0.3364	0.1706	0.1148	0.9259	2.2668	0.1221	0.2035	0.1278
7	0.2732	0.2509	0.2764	0.9637	2.5813	0.618	0.2604	0.3226
8	0.382	0.283	0.133	0.6539	2.8561	0.2004	0.304	0.0175
9	0.3718	0.4553	0.4237	0.9779	2.4361	0.2528	0.6017	0.4661
10	0.1066	0.1515	0.0618	0.4011	2.1961	0.4703	0.3803	0.0095
11	0.3227	0.2293	0.2783	0.9674	2.6744	0.6014	0.2216	0.3013
12	0.299	0.3205	0.1925	0.9319	2.1428	0.1511	0.2965	0.1759
13	0.3339	0.1275	0.1249	0.9175	2.2398	0.0928	0.2287	0.0898
14	0.3141	0.3854	0.2309	0.9777	2.1374	0.0816	0.3641	0.3811
15	0.2788	0.2509	0.1172	0.9009	2.2652	0.3723	0.4464	0.1416
16	0.2666	0.2631	0.1297	0.879	2.2352	0.4659	0.4333	0.161
17	0.6434	0.1437	0.1581	0.9644	2.2432	0.0503	0.2002	0.1968
18	0.4957	0.5151	0.1779	0.9468	1.8498	0.3547	0.6579	0.239
19	0.3997	0.4046	0.1306	0.9588	2.0091	0.2391	0.5005	0.26
20	0.3685	0.3163	0.0786	0.9416	1.899	0.3416	0.6208	0.3194
21	0.6518	0.3184	0.4049	0.9768	1.7452	0.1622	0.3797	0.1615
22	0.6435	0.3174	0.3559	0.9684	1.5125	0.2307	0.4744	0.1439
23	0.2217	0.2995	0.1452	0.806	2.352	0.2001	0.5274	0.0186
24	0.4408	0.5075	0.2015	0.8979	2.1776	0.2124	0.3913	0.0403
25	0.3046	0.2222	0.188	0.8373	2.3273	0.5481	0.2503	0.0815
26	0.3587	0.6066	0.2478	0.3537	2.3771	0.3812	0.1904	0.0066
27	0.5043	0.6925	0.2849	0.79	1.8785	0.1386	0.8405	0.0788
28	0.3851	0.6236	0.2786	0.9868	2.362	0.2786	0.6355	0.2454
29	0.4168	0.5913	0.2589	0.959	2.5032	0.2299	0.4898	0.0676
30	0.4979	0.5378	0.2027	0.9618	2.2775	0.2474	0.4668	0.1879

- **Hepatotoxicity (DILI):** DILI scores were monitored as a primary safety end point. Scores ranged significantly from 0.18 to 0.98.
- **Acute Toxicity (LD_{50}):** The series displayed moderate acute toxicity levels, with LD_{50} values typically between 1.8 and 2.8.
- **Cardiotoxicity (hERG):** Cardiotoxic risks (hERG blocking) remained mostly under 0.50, signifying low hazards of medication-induced arrhythmia [24].

v. Lead Identification

Based on the convergence of docking scores, QSAR reliability and safety parameters, five lead compounds were identified as candidates for further synthesis:

Table 9: Top 5 Least Toxic Compounds

Compound Serial Number	Justification
26	Lowest (favourable) DILI Good LD_{50}
23	Balanced profile Moderate toxicity in all parameters
3	Very Low Carcinogenicity Good LD_{50} but high DILI
5	High Liver Toxicity Overall good
18	Stable profile, Acceptable toxicity but not best

SELECTION AND JUSTIFICATION OF LEAD CANDIDATE:

Among the 30 derivatives, Compound 26 was prioritized as the primary lead candidate. This section is justified by its balanced performance across all computational filters:

- **Binding Efficacy:** It demonstrated high affinity for the 1KNU receptor and successfully stabilized the Tyr473 residue.
- **Predictive Potency:** The QSAR model placed Compound 26 in the High-Activity Quadrant.
- **Superior Safety Profile:** Most significantly, Compound 26 exhibited the most favourable toxicity parameters, recording the favourable DILI score (0.3537) and a favourable LD_{50} (2.3771).

CONCLUSION

The study successfully integrated molecular docking, 2D-QSAR modelling and ADMET profiling to evaluate 30 TZD derivatives against the PPAR-Gamma (1KNU). The developed QSAR model proved highly reliable (R^2=0.911), identifying molecular bulk and hydrogen bonding as key contributors to activity. Compound 26 emerged as the most promising lead candidate due to its excellent binding affinity and significantly reduced hepatotoxicity profile compared to traditional agents.

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CONFLICT OF INTEREST: None

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