ORIGINAL ARTICLE

Computational Study of Novel Aldose Reductase Inhibitors as Antidiabetic Potential: A Dual Inhibitor

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Abstract

Background: Diabetes mellitus is a chronic metabolic disorder marked by hyperglycemia due to insufficient insulin production or action. One major contributor to diabetes-related complications is aldose reductase (AR), which increases sorbitol and fructose accumulation under hyperglycemic conditions. Inhibiting AR is a promising strategy to mitigate such complications. **Objectives:** The objective is to identify and evaluate potential AR inhibitors (ARIs) through computational molecular docking methods for improved glycemic control. **Materials and Methods:** A total of 82 compounds were computationally screened against AR (PDB ID: 1ADS) using molecular docking techniques. The workflow included ligand and protein preparation, grid generation, and docking analysis. Standard drugs (pioglitazone and epalrestat) were used for comparison. **Results:** Docking scores of the compounds ranged from −12.012 to −4.28. Standard drugs pioglitazone and epalrestat scored −12.012 and −10.705, respectively. Based on docking scores and interaction profiles, 22 compounds (RS1–RS22) were selected for further analysis. These compounds formed stable hydrogen bonds with AR, indicating strong binding affinity and potential inhibitory activity. **Conclusion:** The study highlights several novel compounds as promising ARIs with potential antidiabetic effects. These findings warrant further investigation through *in vitro* and *in vivo* studies to validate their efficacy and safety for diabetes treatment.

Key words: Aldose reductase, aldose reductase inhibitors, diabetes mellitus, hyperglycemia, molecular docking study

INTRODUCTION

Diabetes mellitus is a metabolic disease characterized by chronic hyperglycemia caused by inadequate insulin secretion, insulin action, or both.[1] It poses a major challenge to global health due to its increasing prevalence and associated complications such as cardiovascular disease, neuropathy, retinopathy, and kidney disease.[2] There are many ways to effectively manage diabetes, including lifestyle changes, blood sugar monitoring, and medications.[3] These drugs can be divided into several groups according to their mechanism of action, including insulin, α-glucosidase inhibitors, and others.[4] However, although many antidiabetic drugs are available, there is a need to design a new treatment that can provide better glycemic control and reduce the risk of diabetes complications. In hyperglycemic states, aldose reductase (AR) causes the reduction of glucose to sorbitol and subsequent conversion of sorbitol to fructose.[5] Accumulation of sorbitol and fructose can cause osmotic stress and oxidative damage, leading to diabetes complications.[6] Therefore, AR inhibitors (ARIs) have attracted attention as potential drugs to prevent or reduce these complications. By targeting the polyol pathway, ARIs may provide two ways to control diabetes: Improving glycemic control and preventing long-term complications.[7]

AR is a key enzyme in the polyol pathway of glucose metabolism, catalyzing the reduction of glucose to sorbitol. Under normal physiological conditions, this pathway plays a minor role in glucose metabolism.[8] However, in hyperglycemic states such as diabetes, the activity of AR increases, resulting in the accumulation of sorbitol and fructose.[8] This combination leads to osmotic stress, oxidative damage, and the subsequent development of various diabetic conditions such as neuropathy, retinopathy, nephropathy, and cataracts.[10] This enzyme may

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promote the development of diabetic complications. ARIs, are compounds designed to prevent the reduction of glucose to sorbitol and thereby reduce the effects of excessive sorbitol.[11] By targeting the polyol pathway, ARIs aim to reduce the incidence and severity of diabetes complications and improve overall patient outcomes.[12] To go forward. Early ARIs such as tristate and Epalrestat show some promise but are generally limited by issues with efficacy, bioavailability, and adverse side effects.[13]

Despite these challenges, ongoing research continues to focus on discovering and optimizing new ARIs with improved treatments. By examining the biochemical mechanisms, efficacy, and safety of these inhibitors, we aim to identify compounds that may reduce the severity of diabetes complications.[14] In addition, this study aims to understand the overall effects of AR inhibition in diabetes treatment; this could pave the way for further information and targeted treatment.[15] Make a program that not only improves blood sugar control but also prevents diabetes-related complications. The ultimate goal is to improve the quality of life of people with diabetes by providing better and safer treatment.[16]

Molecular docking is a computational technique used to predict the desired orientation of one molecule when it is attached to another to form a fixed surface.[17] This approach plays an important role in drug discovery and development because it allows scientists to model the interactions between small particles (such as potential drugs) and target proteins at the atomic level.[18] The main goal of molecular docking is to predict the coordination and interaction patterns between ligands (potential drugs) and protein targets to gain insight into the molecular basis of effective and specific drugs.[19] First, it allows for the virtual screening of large libraries against protein targets, reducing the time and cost associated with screening experiments. Second, docking studies can help identify important interactions and binding sites, leading to more efficient design and selection of drug candidates.[20] In addition, molecular docking provides important information about the binding and orientation of the ligand, which is important for understanding the mechanism of action of the ligand.[21]

AR is an important enzyme involved in the polyol pathway of glucose metabolism, and its inhibition is thought to be a good strategy to prevent diabetes.[22] Using molecular docking systems, we can evaluate potential ARIs, predict their relationships, and demonstrate their interactions with AR.[23] By analysing docking studies, we aim to identify potential inhibitors that show good affinity with AR. Information obtained from these docking studies is important in guiding the next experiment and activity correlation. Its role in drug discovery.[24] By combining molecular tools with other computational and experimental methods, we seek to discover new ARIs that could improve the treatment of diabetes and its related complications.[25]

MATERIALS AND METHODS

Computational studies

Based on the data analysis, the reaction was developed, and as per the reaction, the 2-Thioxo 4-thiazolidinedione derivatives were designed and drown in 2D and 3D models for further studies by chem Drow application.[26] By Molecular docking compounds were docked with the selected protein, and on basis of result compound were selected.

Molecular docking study using Schrodinger LLC

Structural docking studies were performed using poses predicted by docking using the Glide module v11.1 program (Schrodinger LLC., New York, USA; http://www.schrodinger.com). All thiazolidine ring structures were assembled with human AR holoenzyme (PDB ID: 1ADS). Schrödinger software is generally used for all of the following steps. The steps involved are as follows:

- Ligand preparation
- Protein preparation
- Grid generation
- Docking studies.

Ligand preparation

All compound structures were built with ChemDraw Ultra v8.0 (Cambridge Soft Corporation, Cambridge, MA, USA; http://www.cambridgesoft.com), and their 3D structures were further minimized with the LigPrep wizard of the Schrödinger maestro software (version 11.1) program (Schrodinger LLC., New York, USA; http://www.schrodinger.com),[27] During this step, the tautomer's and ionization state of the ligands were pH of 7.0 ± 2.0.[28] The force field utilized in this study was configured to OPLS2005, to generate a single low-energy 3D structure for each input structure, and the rest of the parameter values by default. During this step, chirality was maintained, compounds of the library were prepared, and compounds were docked.[29]

Protein selection and preparation

The 3D structure of the target protein, human AR holoenzyme (PDB ID: 1ADS), was selected and downloaded from RCSB Protein Data Bank https://doi.org/10.2210/pdb1ADS/pdb) This protein [Figure 1] is reported to bind with the drug Epalrestat and pioglitazone. The protein was imported, optimized, and minimized.[30] All the other chains and water molecules were deleted and the co-crystallized ligand was removed. Finally, a low-energy minimized protein structure was obtained and used for further docking studies.[31]

Grid generation

Minimized protein was used for grid generation, which involved a selected ligand as the reference, as it signifies the binding sites of the drug with respect to the target. The generated grid was used for further docking of new molecules.[32]

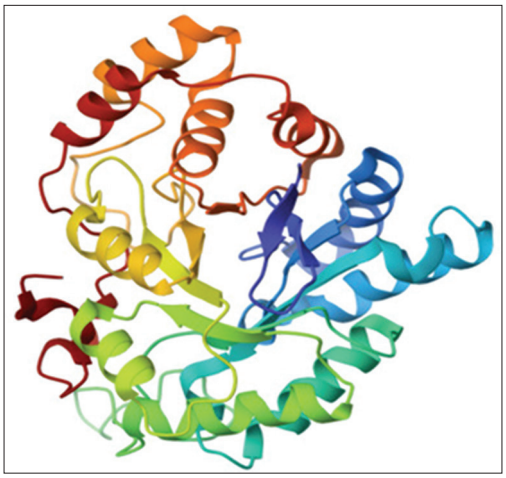


Figure 1: Image of protein 1ADS

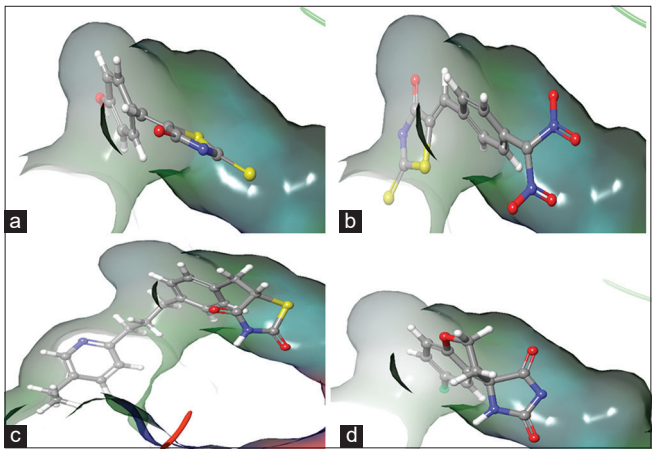


Figure 2: Extra precision glide docking with 1ADS of compound (a) RS1 (b) RS2 (c) Pioglitazone and (d) Epalrestat

Docking studies

For the molecular docking study, the receptor grid was constructed around the structural coordinates of the co-crystallized ligand nicotinamide adenine dinucleotide phosphate (NADPH).[33] The dimensions of the grid are as follows: X-21.81, Y-26.92, and Z-72.64. The docking study was conducted utilizing the SP mode of the Glide module in Schrodinger software (version 11.1).[34] The validation of the docking protocol was conducted by comparing the docked pose of the co-crystalized ligand with the pose created through molecular docking. After the completion of the docking process, the poses were evaluated and ranked according to their respective docking scores.[35] On the basis of Dock Score, the best 22 compounds were selected for further study, named as RS1 to RS22.

RESULTS

Overview of docking results

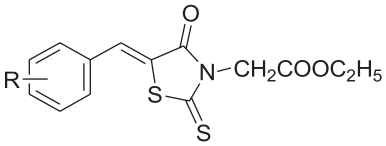
The docking study using the Glide module of Schrodinger software involved the synthesis of 2-thio-4-thiazolidinedione derivatives immobilized by human AR holoenzyme (PDB ID: 1ADS) probe assay. Docking scores and interaction patterns were evaluated to identify compounds with high affinity and potential as ARIs. A total of 82 compounds were docked with docking scores ranging from −12.012 to −4.28. The docking scores, Glide gscore, and Glide emodel energy of the designed substituted derivatives are summarized in Table 1. As a basis for comparison, the docking scores of the standard drugs pioglitazone and Epalrestat were −12.012 and −10.705, respectively.

Docking scores and interaction analysis

The top-performing compounds demonstrated significant binding affinity, as indicated by their negative docking scores. For instance, RS1 (P-Formaldehyde) exhibited a docking score of −11.912, closely approaching the performance of the standard pioglitazone.

Selected compounds for further study

Based on docking scores and interaction profiles, 22 compounds were selected for further experimental studies. These compounds demonstrated promising docking scores and stable binding interactions with AR, suggesting potential as effective inhibitors Table 2. Lists the selected compounds along with their molecular formula and weight. The IUPAC name is mentioned in Table 3 of the selected compounds. As shown in Figure 2, extra precision glide docking with 1ADS of compound (a) RS1, (b) RS2, (c) Pioglitazone, and (d) Epalrestat has been shown.



Basic structure

Structural analysis

Pioglitazone stands out as the ligand with the strongest binding affinity, reflected in its highest docking score and extensive network of hydrogen bonds, salt bridges, and pi bonds. RS1 also shows promising binding characteristics, similar to the standard ligands. Key residues such as Lys21, Trp20, and Tyr209 are crucial for binding interactions across the ligands, indicating they are essential targets for optimizing ligand design. This analysis provides a foundation for further computational and experimental studies to validate these interactions and explore the therapeutic potential of these ligands.

In order to validate the docking process, the co-crystalized ligand (NADPH) with the target was subjected to re-docking, and the resulting RMSD value was compared. The generated

Table 1: Docking score, glide gscore, glide emodel energy of the designed substituted derivatives

S. No.	Substitution (R)	Docking score	Glide gscore	Glide emodel
1.	P-Formaldehyde	−11.912	−11.973	−170.091
2.	4-Chlorbenzaldehyde	−10.762	−10.856	−85.786
3.	Vanillin	−10.336	−10.69	−77.633
4.	Cinnamaldehyde	−10.189	−10.291	−74.331
5.	3-Nitro benzaldehyde	−9.708	−9.875	−80.26
6.	2 Chlorobenzaldehyde	−9.936	−10.35	−85.941
7.	2 Nitro benzaldehyde	−9.84	−10.268	−78.035
8.	4- Fluro benzaldehyde	−9.727	−10.191	−99.798
9.	4- Nitro benzaldehyde	−9.619	−10.158	−69.816
10.	Benzaldehyde	−9.589	−9.924	−71.076
11.	Formaldehyde	−9.525	−9.66	−74.886
12.	Acetaldehyde	−9.517	−9.974	−86.405
13.	Ethyl Vanillin	−9.476	−9.643	−80.752
14.	1,3,5 Trioxane	−9.3	−9.849	−78.587
15.	Salicaldehyde	−9.244	−9.426	−81.005
16.	Anisaldehyde	−9.171	−9.55	−70.615
17.	P-Chlorobenzaldehyde	−9.117	−9.585	−69.592
18.	2-Methoxybenzaldehyde	−9.087	−9.239	−70.099
19.	Furfuraldehyde	−9.078	−9.658	−65.014
20.	P-Dimethyl amino benzaldehyde	−9.034	−9.61	−68.163
21.	3-Methoxybenzaldehyde	−8.989	−9.568	−71.412
22.	4 Hydroxy benzaldehyde	−8.985	−9.414	−87.832
23.	Syringaldehyde	−8.984	−9.564	−68.429
24.	3-Cl	−8.989	−9.568	−71.412
25.	4-dimethylamino	−8.985	−9.414	−87.832
26.	2,3-DiOCH3	−8.984	−9.564	−68.429
27.	Thiophene-2-carboxaldehyde	−8.887	−9.436	−79.744
28.	Nicotinaldehyde	−8.79	−9.134	−72.449
29.	Isonicotinaldehyde	−8.747	−9.235	−90.871
30.	3,4-diOH	−8.732	−8.899	−70.315
31.	4-CN	−8.716	−9.144	−61.758
32.	4-Br	−8.709	−9.288	−66.223
33.	4-difluoromethane	−8.697	−9.276	−75.206
34.	4-dichloromethane	−8.639	−8.839	−79.062
35	4-dinitromethane	−8.633	−9.061	−58.972
36.	4-dimethylmethane	−8.614	−8.906	−82.688
37.	4-diCF3methane	−8.507	−8.641	−66.343
38.	2-diNO2methane	−8.455	−9.034	−68.287
39.	3-diNO2methane	−8.445	−8.564	−71.911
40.	3-diClmethane	−8.434	−8.862	−64.048
41.	4-diCNmethane	−8.407	−8.408	−54.284
42.	4-diBrmethane	−8.29	−8.718	−63.284
43.	2-bromo benzaldehyde	−8.247	−8.827	−72.425
44.	2- fluro benzaldehyde	−8.215	−8.794	−66.429

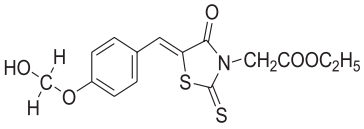
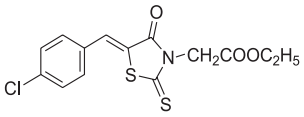
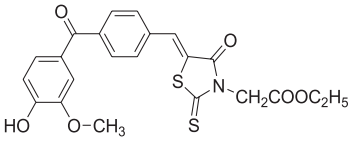
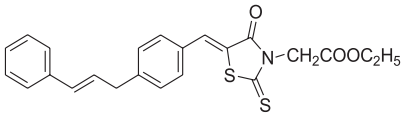
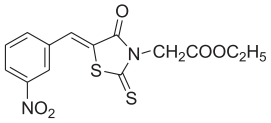
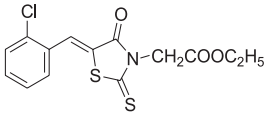
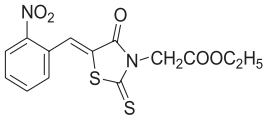
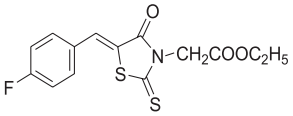
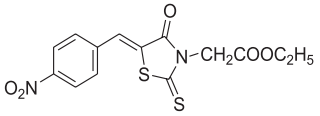
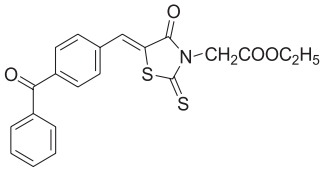
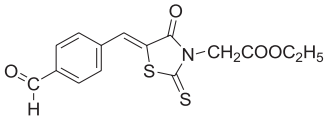
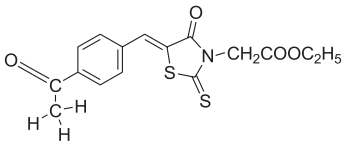
(Contd...)

Table 1: *(Continued)*

S. No.	Substitution (R)	Docking score	Glide gscore	Glide emodel
45.	2-OH benzaldehyde	−8.161	−8.771	−60.051
46.	2,4 dihydroxy benzaldehyde	−8.12	−8.699	−69.37
47.	2,4 dimethoxy benzaldehyde	−8.082	−8.308	−69.111
48.	Tri-fluro methoxy benzaldehyde	−8.049	−8.174	−51.568
49.	3-Methoxy benzaldehyde	−8.002	−8.381	−64.305
50.	4- furfuraldehyde	−7.964	−8.188	−56.41
51.	3,4 dinitro benzaldehyde	−7.953	−8.177	−56.22
52.	2,3,4 trinitro benzaldehyde	−7.951	−8.175	−71.228
53.	3,4-dimethoxybenzaldehyde	−7.921	−8.2	−66.817
54.	2,3-dichlorobenzaldehyde	−7.911	−8.096	−50.688
55.	2-dimethylamino benzaldehyde	−7.854	−8.248	−93.194
56.	2,3-dicyanobenzaldehyde	−7.851	−8.064	−62.134
57.	3-bromo-2-methoxybenzaldehyde	−7.824	−8.26	−55.499
58.	2,3,4-trihydroxybenzyaldehyde	−7.816	−8.079	−70.088
59.	5-bromo-2-methoxybenzaldehyde	−7.755	−8.183	−61.073
60.	2,4-difluorobenzaldehyde	−7.736	−8.165	−60.943
61.	Difluoro methyl benzaldehyde	−7.709	−8.138	−59.855
62.	4-ethylbenzaldehyde	−7.708	−8.136	-54.213
63.	Cyanomethyl benzaldehyde	−7.654	−7.867	-63.635
64.	3-dibromomethyl benzaldehyde	−7.607	−7.868	−53.485
65.	2,5-bis-dinitromethyl benzaldehyde	−7.607	−7.868	−53.485
66.	3,4,5-trihydroxybenzaldehdye	−7.57	−8.181	−53.446
67.	2,5-dihydroxybenzaldehyde	−7.56	−7.606	−61.358
68.	4-oxo-5-(pyrazin-2-ylmethylene	−7.544	−7.805	−48.497
69.	4-oxo-5-(pyrimidin-4-ylmethylene	−7.49	−8.067	−59.767
70.	3,4-dimethylamino) benzaldehyde	−7.323	−7.504	−55.518
71.	4-bromo-3-chlorobenzaldehyde	−7.323	−7.504	−55.518
72.	2,3,4-trichlorobenaldehyde	−7.218	−8.062	−61.483
73.	4- Methyl thio benzaldehyde	−7.173	−7.752	−45.728
74.	3,4-methylthio benzaldehyde	−7.04	−7.379	−78.955
75.	3-methoxy-4-methylamino benzaldehyde	−6.319	−6.328	−44.658
76.	3-hydroxy-4-nitrobenzaldehyde	−6.301	−6.515	−51.314
77.	2-chloro-6-hydroxbenzaldehyde	−6.021	−7.71	−49.1
78.	3,5-dimethoxybenzaldehyde	−5.441	−5.835	−54.882
79.	2,5-dibromobenzaldehyde	−5.35	−5.931	−36.153
80.	2,5-dibromobenzaldehyde	−4.84	−5.268	−40.651
81.	3,4-trifluoromethyl benzaldehyde	−4.784	−5.177	−33.533
82.	3,4,5-trifluoro methyl benzaldehyde	−4.28	−4.859	−49.116
83.	Pioglitazone (standard)	−12.012	−12.073	−169.093
84.	Epalrestat (standard)	−10.705	−10.826	−88.741

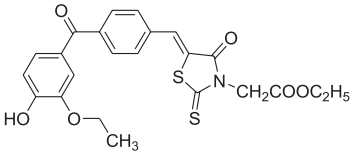
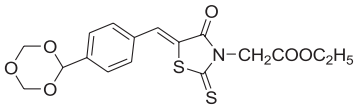
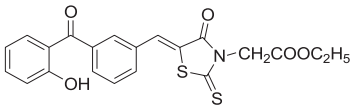
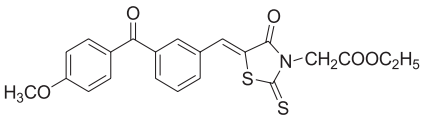
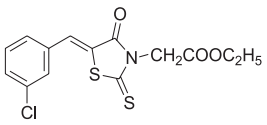
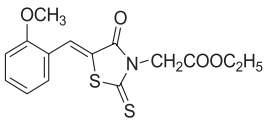
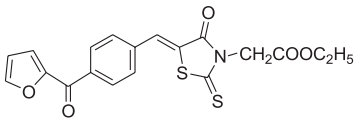
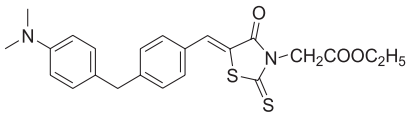
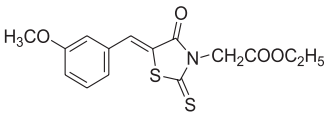
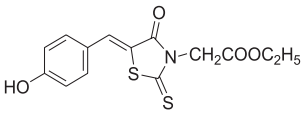
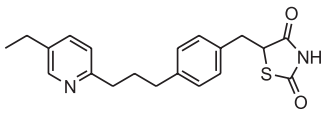
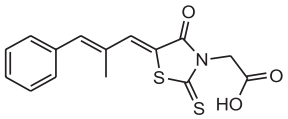
docked pose exhibited similarity to the crystallized pose, with a measured value of 1.5 Å., This result increased our confidence in the docking method. Among all, the Pioglitazone exhibited the highest docking score (−12.012 kcaL/moL). Another known AR (Epalrestat) (−10.705 kcaL/moL) included in this study. The most prominent top 6 compounds exhibited in −10.336–−9.7036 kcaL/moL. The above Tables 4 and figure display the docking scores and their significant interactions with the target protein. The most prominent interacting residues involved in inhibitors are Trp20, Lys21, Tyr209.

Table 2: Selected designed compounds with their structure, Mol formula, and Mol weight

S. No	Sample ID	Derivative	Structure	Mol formula	Mol Wt.
1.	RS-1	P-Formaldehyde		$C_{15}H_{13}NO_4S_2$	335.05
2.	RS-2	4-Chlorbenzaldehyde		$C_{14}H_{12}ClNO_3S_2$	340.99
3.	RS-3	Vanillin		$C_{22}H_{19}NO_6S_2$	457.07
4.	RS-4	Cinnamaldehyde		$C_{23}H_{21}NO_3S_2$	423.1
5.	RS-5	3-Nitro Benzaldehyde		$C_{14}H_{12}N_2O_5S_2$	352.02
6.	RS-6	2 Chlorobenzaldehyde		$C_{14}H_{12}ClNO_3S_2$	340.99
7.	RS-7	2 Nitro Benzaldehyde		$C_{14}H_{12}N_2O_5S_2$	352.02
8.	RS-8	4- Fluro Benzaldehyde		$C_{14}H_{12}FNO_3S_2$	325.02
9.	RS-9	4- Nitro Benzaldehyde		$C_{14}H_{12}N_2O_5S_2$	352.02
10.	RS-10	Benzaldehyde		$C_{21}H_{17}NO_4S_2$	411.06
11.	RS-11	Formaldehyde		$C_{15}H_{13}NO_4S_2$	335.05
12.	RS-12	Acetaldehyde		$C_{17}H_{15}NO_4S_2$	361.04

(Contd...)

Table 2: *(Continued)*

S. No	Sample ID	Derivative	Structure	Mol formula	Mol Wt.
13.	RS-13	Ethyl Vanillin		$C_{23}H_{21}NO_6S_2$	471.08
14.	RS-14	1,3,5 Trioxane		$C_{17}H_{17}NO_6S_2$	395.05
15.	RS-15	Salicaldehyde		$C_{21}H_{15}NO_5S_2$	427.05
16.	RS-16	Anisaldehyde		$C_{22}H_{19}NO_5S_2$	441.07
17.	RS-17	P-Chlorobenzaldehyde		$C_{14}H_{12}ClNO_3S_2$	340.99
18.	RS-18	2-Methoxybenzaldehyde		$C_{15}H_{15}NO_4S_2$	337.04
19.	RS-19	Furfuraldehyde		$C_{19}H_{15}NO_5S_2$	401.04
20.	RS-20	P-Dimethyl amino benzaldehyde		$C_{23}H_{24}N_2O_3S_2$	440.12
21.	RS-21	3-Methoxybenzaldehyde		$C_{15}H_{15}NO_4S_2$	337.04
22.	RS-22	4 Hydroxy benzaldehyde		$C_{14}H_{13}NO_4S_2$	323.03
23.	Standard	Pioglitazone		$C_{20}N_{22}N_2O_2S$	354.14
24.	Standard	Epalrestat		$C_{15}H_{13}NO_3S_2$	319.03

Comparative analysis with standard drugs

The comparative analysis of the selected compounds with the standard drugs pioglitazone and Epalrestat indicated that several designed derivatives had docking scores and interaction patterns comparable to or better than the standards. This suggests that these derivatives may offer effective inhibition of AR, potentially translating to

Table 3: IUPAC name of the selected compound

S. No.	Comp.Code	R	IUPAC name
1.	RS1	P-formaldehyde	(Z)-ethyl2-(5-(4-(hydroxymethoxy) benzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate (p formaldehyde)
2.	RS2	4-Chlorbenzaldehyde	(Z)-ethyl 2-(5-(4-chlorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate
3.	RS3	Vanillin	(Z)-ethyl 2-(5-(4-(3-ethoxy-4-hydroxybenzoyl) benzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate
4.	RS4	Cinnamaldehyde	Ethyl 2-((Z)-5-((E)-4-cinnamylbenzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate
5.	RS5	3-Nitro benzaldehyde	(Z)-ethyl 2-(5-(3-nitrobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate
6.	RS6	2 chlorobenzaldehyde	(Z)-ethyl 2-(5-(2-chlorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate
7.	RS7	2-nitrobenzaldehyde	(Z)-ethyl 2-(5-(2-nitrobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate
8.	RS8	4- Fluorobenzaldehyde	(Z)-ethyl 2-(5-(4-fluorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate
9.	RS9	4- Nitrobenzaldehyde	(Z)-ethyl 2-(5-(4-fluorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate
10.	RS10	Benzaldehyde	(Z)-ethyl 2-(5-(4-benzoylbenzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate
11.	RS11	Formaldehyde	(Z)-ethyl 2-(5-(4-formylbenzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate
12.	RS12	Acetaldehyde	(Z)-ethyl 2-(5-(4-(1-oxoprop-1-en-2-yl) benzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate (acetaldehyde)
13.	RS13	Ethyl vanillin	(Z)-ethyl 2-(5-(4-(3-ethoxy-4-hydroxybenzoyl) benzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate
14.	RS14	1,3,5 Trioxane	(Z)-ethyl 2-(5-(4-(1,3,5-trioxan-2-yl) benzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate
15.	RS15	Salicaldehyde	(Z)-ethyl 2-(5-(4-(3-ethoxy-4-hydroxybenzoyl) benzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate
16.	RS16	Anisaldehyde	(Z)-ethyl 2-(5-(3-(4-methoxybenzoyl) benzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate
17.	RS17	P-Chlorobenzaldehyde	(Z)-ethyl 2-(5-(3-chlorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate
18.	RS18	2-Methoxybenzaldehyde	(Z)-ethyl 2-(5-(3-chlorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate
19.	RS19	Furfuraldehyde	(Z)-ethyl 2-(5-(4-(4-(dimethylamino) benzyl) benzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate
20.	RS20	P-dimethyl amino benzaldehyde	(Z)-ethyl 2-(5-(4-(4-(dimethylamino) benzyl) benzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate
21.	RS21	3-Methoxybenzaldehyde	(Z)-ethyl 2-(5-(3-chlorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate
22.	RS22	4-hydroxybenzaldehyde	(Z)-ethyl 2-(5-(4-hydroxybenzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetate

Table 4: Molecular docking score and important interactions of ligands with the target

S.No.	Ligand	Docking score	Hydrogen bond	Salt bridge	Pi bond
1.	RS1	−11.912	Lys21, Ser210	Lys21	Tyr209
2.	RS2	−10.762	Trp20, Asn160, Gln183	Lys21	Tyr209
3.	RS3	−10.336	Trp20, Asn160, Gln183	Lys21	Tyr209
4.	RS4	−10.189	Trp20	Lys21	Lys77
5.	RS5	−9.708	Asn160, Ser210, Lys262	Lys21	Trp20
6.	RS6	−9.936	Trp20, Asn160	Lys21	His110, Tyr209
7.	pioglitazone (Standard)	−12.012	Asp216	Lys21, Asp43, Arg268	Lys77, His110, Tyr209, Arg268
8.	Epalrestat (Standard)	−10.705	Trp20, Lys21, Tyr111	Lys21	Tyr209

improved glycemic control and reduced diabetes-related complications.

Insights and future directions

Molecular docking studies have provided a good insight into the interaction mode and coordination of the formed 2-Thioxo 4-thiazolidinedione derivatives with AR. These compounds exhibit high docking scores and good interactions and are strong candidates for further *in vitro* and *in vivo* studies to confirm their efficacy and safety as ARIs. Future studies will focus on the synthesis and biochemical evaluation of these compounds, as well as research on their pharmacokinetics and side effects. The main goal is to develop new treatments that can provide better glycemic control and reduce diabetes complications, thus improving the quality of life of people with diabetes. Moreover, the combination has good potential for subsequent validation and optimization phases.

CONCLUSION

This study investigated the potential of 2-Thioxo 4-thiazolidinedione derivatives as ARIs to improve glycemic control and reduce diabetes complications. Through molecular docking studies using the Schrödinger software package, 82 compounds were identified from the human AR holoenzyme (PDB ID: 1ADS). Docking results identified 22 compounds (RS1-RS22) with good connections and interactions with important regions of the residue. Enzyme activity. In particular, RS1 (p-formaldehyde), RS2 (4-chlorobenzaldehyde), and RS3 (vanillin) exhibited the highest scores, indicating good binding ability. These compounds interact with important residues such as LEU 370, ILE 268, and CYS 269, demonstrating their ability to inhibit the enzyme.

Comparative analysis with drug models such as pioglitazone and Epalrestat showed that many designs had comparable or better docking scores; This indicates good potential. In addition, positive RMSD values of these compounds indicate stability and reliability, thus increasing their properties as drugs. The importance of the problems. The successful identification of high-affinity agents by molecular docking laid the foundation for further *in vitro* and *in vivo* studies to confirm their efficacy and safety. Finally, this study demonstrates the potential of novel 2-Thoxo 4-thiazolidinedione derivatives to contribute to the development of diabetes treatment to improve the lives of affected individuals by providing better glycemic control and reducing long-term complications.

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