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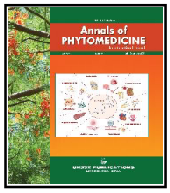

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Molecular docking and pharmacophore modelling of Schiff base derived thiazolidinones as peroxiredoxin and tyrosinase inhibitors for oxidative stress

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Abstract

An imbalance in the redox state causes cellular oxidative stress. The two enzymes involved in these conditions are peroxiredoxin and tyrosinase. This study evaluates the inhibitory potential of twenty-two Schiff base-derived thiazolidinones using *in silico* tools against these targets. The techniques employed were molecular docking, MMGBSA, pharmacophore modelling, physicochemical, and PASS. Compound 2b had the highest docking score against human peroxiredoxin (-5.675 kcal/mol) and tyrosinase (-7.252 kcal/mol). The PASS tool indicated that all of the compounds would have antioxidant potential. With the highest survival value, the pharmacophore hypothesis shows the optimal alignment of the active ligands. These compounds show promising binding affinity against multitarget for oxidative stress inhibitors. Future research efforts might focus on synthesising and refining compound 2b through additional pharmacological research to verify its effectiveness.

1. Introduction

In recent times, research has shown that oxidative stress (Lobo *et al*., 2010) and related mitochondrial dysfunction are significant contributors to the pathophysiologic mechanisms (Forman and Zhang, 2021) underlying diseases like Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis, depression, and memory loss (Perkins *et al.,* 2014). An essential antioxidant enzyme called peroxiredoxin (Perkins *et al.,* 2015) has a variety of uses in controlling oxidative stress. They are essential in accelerating the reduction of H_2O_2 and different peroxides (Declercq *et al*., 2001) and can successfully remove these reactive oxygen species (Hofmann *et al.,* 2002). Peroxiredoxin enzymes are variable in their oligomeric forms and can be controlled by various post-translational modifications and processes, such as hyperoxidative inactivation (James *et al*., 2024).

Tyrosinase enzyme is involved in numerous pathways connected to many human diseases (Eskandani *et al.,* 2010). The oxidative stress hypothesis suggests that melanocyte impairment could be related to increased oxidative stress with consequent induction of H_2O_2 accumulation (Ji *et al.,* 2021). Tyrosinase encourages the hydroxylation of L-tyrosine to produce L-dopa, which is then transformed into dopaquinone.

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Several Schiff base derivatives were scientifically designed and synthesised as multipurpose medications to treat multitargeted diseases (Raju *et al.*, 2017). Schiff bases with an azomethine group (–C=N–), usually arise by condensing active primary amines and carbonyl groups. Numerous studies have demonstrated the superiority of Schiff base derivatives as oxidation inhibitors throughout the history of antioxidant development (Avram *et al.,* 2021). The important roles that thiosemicarbazide (Karatepe *et al*., 2006) and thiazolidinones play in pharmaceutical chemistry make them bioactive moieties of great interest due to the presence of sulphur and nitrogen heteroatoms (Szychowski *et al.,* 2021). This significant class of substances has observable pharmacological and biological characteristics, including antioxidant, antiviral, antibacterial, antifungal, and anticancer effects (Kaminsky *et al.,* 2017).

This study focused on the design and *in silico* analysis of the thiosemicarbazide thiazolidinones generated from Schiff bases. They were evaluated for their inhibitory efficacy against tyrosinase and peroxiredoxin by molecular docking, binding free energy, pharmacophore modelling, physicochemical, and PASS in the current study (Dheeraj *et al*., 2023). Future research may entail synthesis, *in vitro*, and *in vivo* investigation to examine its possible uses.

2. Materials and Methods

2.1 *In silico* platform

Using molecular docking to target proteins with ligands has shown to be a very successful method. For this study, for all computational analyses, the Schrodinger Maestro version was utilised. It included multiple modules, such as glide XP docking, LigPrep, pharmacophore hypothesis, and MMGBSA for binding free energy estimates (Schrodinger Release 2020-4).

2.2 Molecular docking studies and MMGBSA binding free energy

For this study, twenty-two Schiff base-derived thiazolidinones were designed from a two-step reaction scheme. Substitution (R) groups were aromatic aldehydes (bromo, chloro, nitro, hydroxy, methoxy, trifluoro) and hetero aldehydes such as (furan, thiophene, pyrrole, piperidine, pyridine, benzothiophene). Schiff bases were designed by using thiosemicarbazide and different aldehydes and further converted to thiazolidinones (2a-v) (Figure 1). They were proceeded to molecular docking (Saif *et al*., 2024; Flama *et al*., 2024). The ligprep module in Schrodinger was utilised to generate low-energy conformations, and the OPLS3 force field was applied to reduce energy. The two proteins are peroxiredoxin (PDB ID:1HD2) and tyrosinase (PDB ID:5I38). The protein preparation wizard processed the proteins, which used the OPLS3 force to minimise energy. Using receptor grid generation, a grid box encircled the co-crystal active site. By using flexible docking in ligand sampling, the XP approach enables a more thorough investigation of the ligand-binding space. The ligand that is most likely to form the most stable complex with the target protein can be identified using the glide score, a measurement of binding affinity (James *et al*., 2023). The Schrodinger prime module was utilised to ascertain the binding energy of the receptor-ligand complex. The Prime module is used in this calculation to get the total free energy in dGbind (kcal/mol) (Sahin *et al*., 2021).

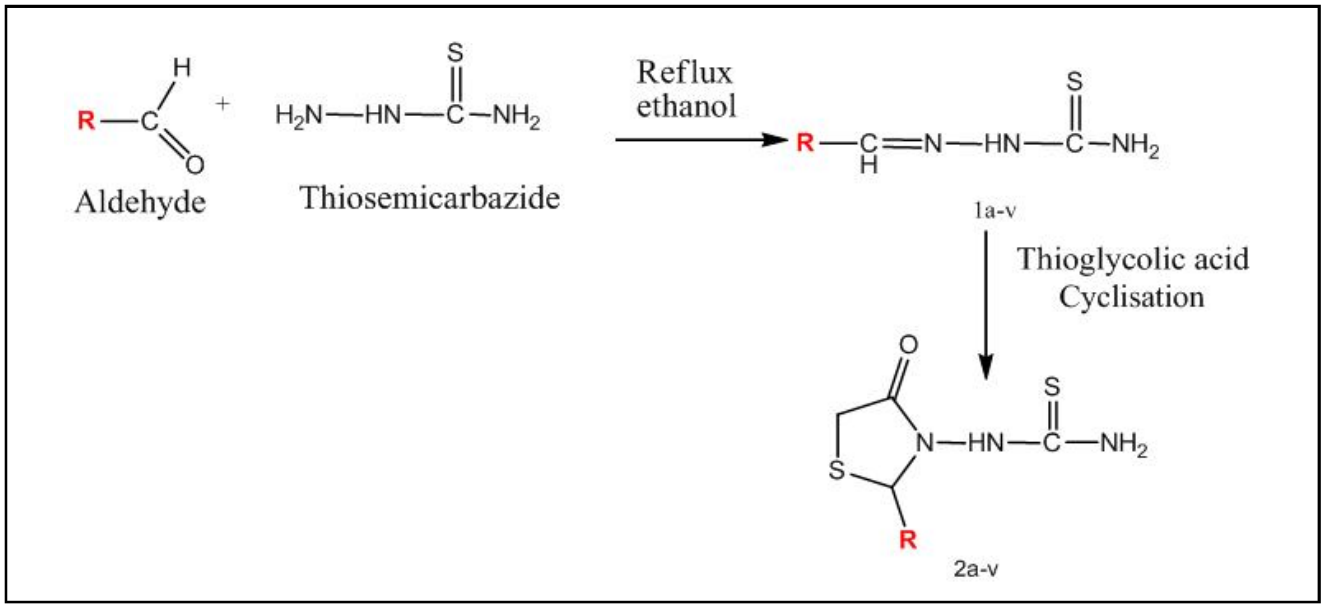

Figure 1: Scheme for designing novel thiazolidinones from Schiff base.

2.3 Pharmacophore modelling

The Schrodinger software phase application generated pharmacophore models using a receptor-based pharmacophore method. The pharmacophore model generated by this method defines the spatial arrangements of functional groups critical for the biological activity of the ligands under investigation (Fathima *et al*., 2024).

2.4 Physicochemical characteristics

The Schrodinger software QikProp function is useful for determining ligand molecules' physicochemical characteristics. Understanding bioavailability and drug-likeness properties is made easier using this tool. The ligands were selected and added to the QikProp program for analysis after they had been created (James *et al*., 2023). Physicochemical data such as donor and acceptor hydrogen bonds, molecular weight, and log P (partition coefficient) were analysed. The compounds were also assessed using the Lipinski Rule of Five, guidelines for determining drug-likeness based on particular physicochemical characteristics (Repasky *et al*., 2012). The pharmacokinetic properties are useful in deciding whether or not to explore them as potential treatment options (James *et al*., 2024).

2.5 Prediction of the biological activity of substances (PASS)

Medicinal chemists and researchers can make well-informed decisions on molecular structure modification to maximise intended pharmacological results and avoid unwanted side effects by knowing the atom-level contributions to activity spectra. The rational creation of molecules with enhanced therapeutic characteristics is aided by this procedure (Lagunin *et al*., 2000).

3. Results

3.1 Molecular docking

Twenty-two Schiff base-derived thiazolidinone inhibitors were chosen for docking studies with two targets for their antioxidant properties (1HD2) and tyrosinase inhibitory efficacy (5I38).

3.1.1 Binding with 1HD2

Compound 2b shows the highest docking score of -5.675 kcal/mol and hydrophobic interaction with Ile119, Phe120, Pro40, Leu149, Pro45 and Cys47 and also forms hydrogen bonds with Glu195 and Asn205. It also shows polar interaction with Thr147 and Thr44 (Table 1 and Figure 2).

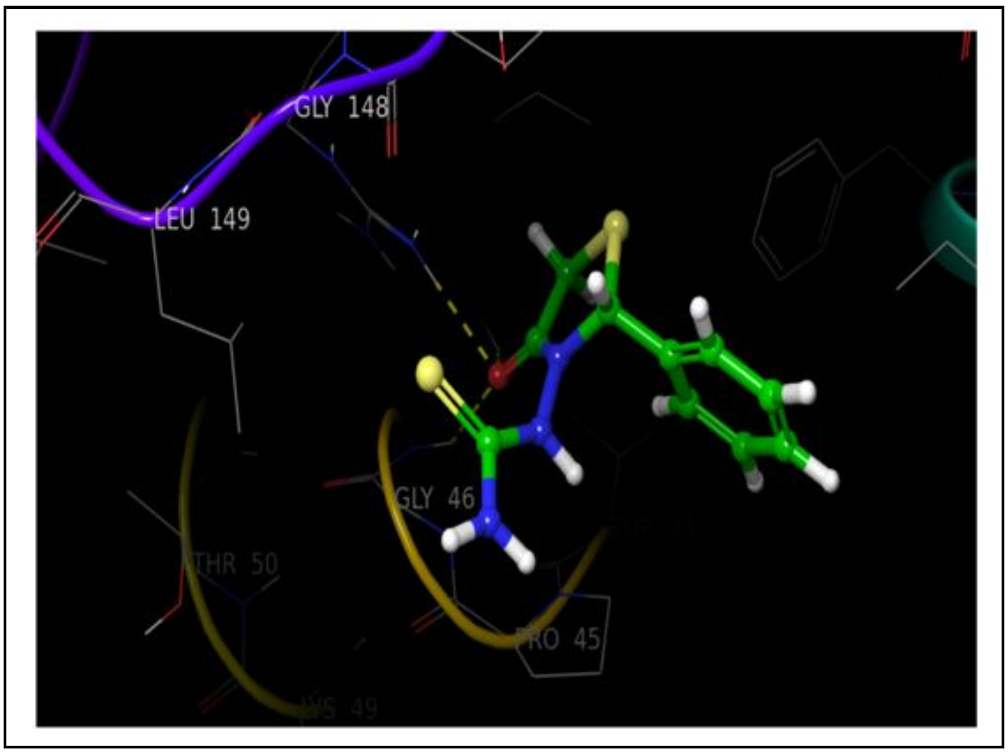

Figure 2: 3D interaction of compound 2b with peroxiredoxin enzyme (1HD2).

3.1.2 Binding with 5138

Compound 2b form hydrogen bonds with Asn205 and Glu195, polar interaction with Hie42, His208, His231, His60, Asn205 and His204, and hydrophobic interaction with Met215, Val217, Val218, Ala221, Phe227, Met61, Phe197, and Phe65. Compound 2b shows the highest docking score of -7.252 kcal/mol (Table 1 and Figure 3).

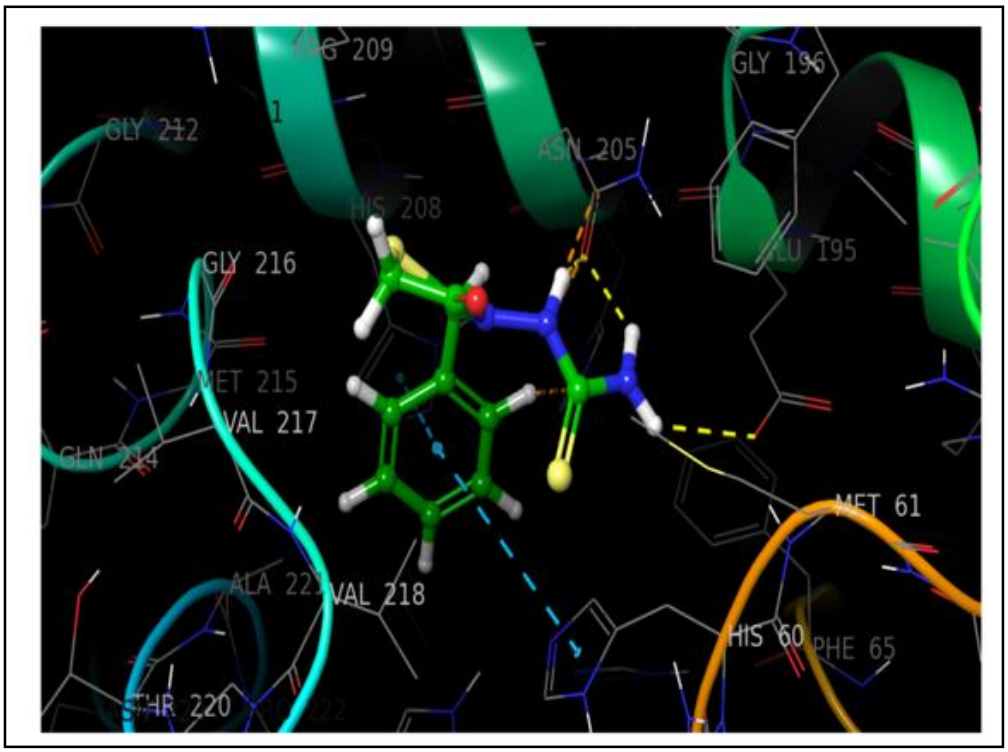

Figure 3: 3D interaction of compound 2b with tyrosinase enzyme (5I38).

3.2 Binding free energy calculation

Tyrosinase (5I38) and human peroxiredoxin (1HD2) enzymes have G bind values between -25.72 and -60.70 kcal/mol and -37.91 to 53.92, respectively. The best-interacted chemical compound 2b has shown -39.70 for 1HD2 and -36.16 for 5I38 (Table 1).

Table 1: Docking score and molecular interactions with target proteins 1HD2 and 5I38

S.No.	Compound code	PDB ID	Docking score	MMGBSA dG Bind	Hydrogen bonds
1	2a	1HD2	-5.644	-43.16	Arg127, Cys47
		5I38	-7.244	-51.07	Asn205, Glu195
2	2b	1HD2	-5.675	-39.70	Arg127, Cys47
		5I38	-7.252	-36.16	Asn205,Glu195
3	2c	1HD2	-5.652	-44.98	Arg127, Cys47
		5I38	-7.242	-46.60	Glu195, Asn205
4	2d	1HD2	-5.640	-50.36	Cys47, Arg127
		5I38	-7.147	-52.62	His204
5	2e	1HD2	-4.561	-41.08	Arg127, Cys47
		5I38	-6.155	-42.49	Asn205, Glu195
6	2f	1HD2	-4.651	-49.50	Arg127, Cys47
		5I38	-6.251	-27.41	-
7	2g	1HD2	-4.386	-38.93	Arg127, Cys47
		5I38	-6.165	-39.06	-
8	2h	1HD2	-4.334	-47.19	Arg127, Cys47
		5I38	-6.167	-42.68	Gly216
9	2i	1HD2	-4.296	-40.79	Arg127, Cys47
		5I38	6.168	-36.80	-
10	2j	1HD2	-5.656	-50.49	Arg127, Cys47
		5I38	-7.250	-48.67	His204
11	2k	1HD2	-4.212	-37.98	Arg127,Cys47
		5I38	-6.163	-35.64	His204, Asn205
12	2l	1HD2	-4.640	-47.20	Arg127,Cys47
		5I38	-6.238	-40.99	His204, Glu195
13	2m	1HD2	-5.659	-42.89	Arg127,Cys47
		5I38	-7.249	-27.92	-
14	2n	1HD2	-4.156	-40.83	Arg127, Cys47
		5I38	-6.159	-32.01	Glu195,Asn205
15	2o	1HD2	-4.643	-42.59	Arg127,Cys47
		5I38	-6.240	-29.29	His60
16	2p	1HD2	-4.116	-37.91	Arg127, Cys47
		5I38	-6.154	-34.83	Asn205,Glu195
17	2q	1HD2	-5.648	-43.01	Arg127, Cys47
		5I38	-7.248	-25.72	His204, Asn205

18	2r	1HD2	-5.647	-41.89	Arg127,Cys47
		5I38	-7.246	-49.25	His204
19	2s	1HD2	-5.645	-39.58	Arg127,Cys47
		5I38	-7.243	-37.67	Glu195,Asn205
20	2t	1HD2	-4.641	-53.92	Cys47, Arg127
		5I38	-6.245	-60.70	Asn204, Glu195, His204
21	2u	1HD2	-5.642	-43.49	Arg127, Cys47
		5I38	-7.243	-46.78	His204
22	2v	1HD2	-4.839	-47.20	Arg127,Cys47
		5I38	-6.150	-46.78	His204,Gleu195
23	Benzoic acid	1HD2	-5.506	-27.37	His60
24	Kojic acid	5I38	-7.156	-40.17	Gly216,His60

3.3 Pharmacophore hypothesis of compound 2b

2b is expected to create hydrogen bonds with residues Arg127 and Cys47 when docked with the human peroxiredoxin enzyme (1HD2). This hydrogen bond formation is expected to be assisted by the acceptor group (A1) between the carbonyl group in the thiazolidinone ring. Further, it forms hydrogen bonds with residues Asn205 and Glu195 when docked with tyrosinase enzyme (5I38), with the help of donor groups (D3, D4, and D5) between amino groups found in thiourea. Moreover, it engaged in pi-pi stacking interactions (R7) with the aromatic (AR) residues His60 and His208. These residues are critical in ligand-protein interactions because they are essential in forming hydrogen bonds (Figure 4).

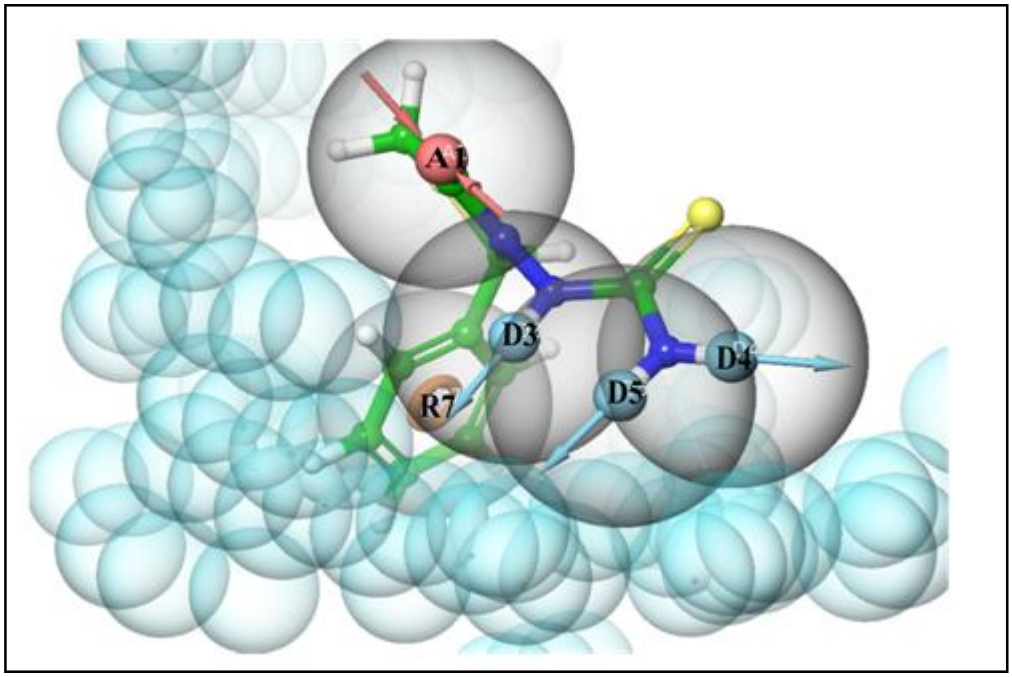

Figure 4: Pharmacophore hypothesis of compound 2b.

3.4 Physicochemical properties

Using QikProp, we were able to ascertain the physicochemical parameters. It determines the compound's druglikeness property, and all compounds follow the Lipinski rule of five. The molecular weight was between the suggested range (242.31-332.23). Lipophilicity QPlogPo/w ranged from -0.183 to 2.731, falling within -2.0 to 6.5, the acceptable limit. The predicted number of donors and acceptors for hydrogen bonds (0.0-6.0 donors and 2.0-20 acceptors) was within the allowed range (Table 2).

Table 2: Physicochemical properties of thiazolidinone derivatives

S.No.	Compound code	Molecular weight	Log P	Donor HB	Acceptor HB	Rule of five
1.	2a	332.23	2.34	2.25	4.75	0
2.	2b	253.33	1.65	2.25	4.75	0
3.	2c	298.33	1.13	2.25	5.75	0
4.	2d	289.36	0.69	3.25	7.20	0
5.	2e	254.32	1.22	2.25	5.75	0
6.	2f	283.36	1.84	2.25	5.50	0
7.	2g	243.29	1.28	2.25	5.25	0
8.	2h	309.41	2.63	2.25	4.75	0
9.	2i	259.35	1.79	2.25	4.75	0
10.	2j	287.78	2.24	2.25	4.75	0
11.	2k	242.31	1.04	3.25	4.75	0
12.	2l	260.37	0.17	3.25	6.25	0
13.	2m	298.33	1.25	2.25	5.75	0
14.	2n	262.34	-0.18	2.25	7.95	0
15.	2o	269.33	1.09	3.25	5.50	0
16.	2p	254.32	0.88	2.25	6.25	0
17.	2q	287.78	2.38	2.25	4.75	0
18.	2r	321.33	2.73	2.25	4.75	0
19.	2s	271.32	1.86	2.25	4.75	0
20.	2t	292.37	1.48	2.25	6.25	0
21.	2u	287.78	2.11	2.25	4.75	0
22.	2v	254.32	0.85	2.25	6.25	0
23.	Benzoic acid	122.12	1.86	1.00	2.00	0
24.	Kojic acid	142.11	-0.63	2.00	4.95	0

3.5 Prediction of the biological activity of substances (PASS)

For peroxidase inhibitors, the thiazolidinone derivatives have a range of Pa values of $0.192 < Pa < 0.457$ and $0.032 < Pa < 0.529$ for catechol oxidase inhibitors. Nucleoside oxidase (H_2O_2-forming) inhibitor (0.147) and NADPH peroxidase inhibitor (0.302) have possible activity values in 2b. The context provided by the comparison with a typical medication helps to comprehend the compound's potential efficacy (Table 3).

Table 3: Predicted biological activity of compounds using PASS

S. No.	Compound code	Activity	Pa	Pi
1.	2a	Peroxidase inhibitor	0.327	0.159
		Catechol oxidase inhibitor	0.114	0.096
2.	2b	Nucleoside oxidase (H_2O_2-forming) inhibitor	0.147	0.144
		NADPH peroxidase inhibitor	0.302	0.159
3.	2c	Catechol oxidase inhibitor	0.116	0.094
4.	2d	NADPH peroxidase inhibitor	0.245	0.211
		Catechol oxidase inhibitor	0.154	0.071
5.	2e	Nucleoside oxidase (H_2O_2-forming) inhibitor	0.249	0.072
		Catechol oxidase inhibitor	0.529	0.010
6.	2f	Peroxidase inhibitor	0.252	0.091

7.	2g	Catechol oxidase inhibitor	0.032	0.306
8.	2h	NADPH peroxidase inhibitor	0.269	0.188
		Catechol oxidase inhibitor	0.208	0.053
9.	2i	NADPH peroxidase inhibitor	0.261	0.195
		Catechol oxidase inhibitor	0.208	0.053
10.	2j	NADPH peroxidase inhibitor	0.245	0.211
11.	2k	Catechol oxidase inhibitor	0.331	0.032
12.	2l	Peroxidase inhibitor	0.388	0.110
13.	2m	Peroxidase inhibitor	0.192	0.141
14.	2n	NADPH peroxidase inhibitor	0.348	0.280
		Catechol oxidase inhibitor	0.245	0.046
15.	2o	Peroxidase inhibitor	0.293	0.067
		NADPH peroxidase inhibitor	0.332	0.138
16.	2p	Catechol oxidase inhibitor	0.327	0.033
		Peroxidase inhibitor	0.382	0.114
17.	2q	Peroxidase inhibitor	0.457	0.071
18.	2r	Peroxidase inhibitor	0.301	0.186
		Catechol oxidase inhibitor	0.113	0.097
19.	2s	Catechol oxidase inhibitor	0.114	0.096
20.	2t	Peroxidase inhibitor	0.336	0.151
		Catechol oxidase inhibitor	0.143	0.076
21.	2u	Peroxidase inhibitor	0.426	0.086
		NADPH peroxidase inhibitor	0.274	0.183
		Catechol oxidase inhibitor	0.117	0.093
22.	2v	Peroxidase inhibitor	0.443	0.078
		Catechol oxidase inhibitor	0.292	0.038
23.	Benzoic acid	NADPH peroxidase inhibitor	0.869	0.005
		Catechol oxidase inhibitor	0.866	0.002
		Oxidoreductase inhibitor	0.751	0.010
		Oxidising agent	0.568	0.004
24.	Kojic acid	Melanin inhibitor	0.433	0.004
		Peroxidase inhibitor	0.449	0.045
		Antioxidant	0.333	0.018
		NADPH oxidoreductase inhibitor	0.042	0.042

4. Discussion

Using *in silico* techniques, we have identified the molecular interactions of thiazolidinone derivatives. Compound 2b interacted well with the enzymes tyrosinase (5I38) and human peroxiredoxin (1HD2). Hydrogen bonding is critical in molecular interactions, especially concerning vital amino acids. These bonds enhance the stability and specificity of interactions between molecules, such as in enzyme-substrate complexes, receptor-ligand binding, and protein-protein interactions. They can impact the overall binding affinity and significantly influence the orientation of interacting partners, often determining the geometry and strength of the interaction. All the chosen compounds have potent tyrosinase inhibitory and antioxidant properties compared to their co-crystals, benzoic acid (IHD2) and kojic acid (5I38). Hydrophobic, polar and hydrogen bond interactions were present with human peroxiredoxin and tyrosinase enzymes (James *et al*., 2023).

The extra-precision docking results are further validated using the Molecular Mechanics-Generalized Born Surface Area (MM-GBSA) methodology to estimate the binding free energy of ligand-protein complexes more accurately. MM-GBSA calculates the free energy of binding by combining molecular mechanics energies, solvation effects, and surface area considerations, providing a comprehensive evaluation of the interaction. This calculated binding energy reflects the binding affinity of the compound to the protein, offering valuable insights into the stability and strength of the complex. By analysing these values, researchers can assess which compounds may serve as potent inhibitors or modulators of the target protein, aiding drug discovery and design efforts (James *et al*., 2024).

The pharmacophore model is a helpful tool for understanding and predicting the essential components needed for ligand binding and biological activity. It has revealed the significant biological features responsible for biological action, such as hydrogen bonding and aromatic rings. From the physicochemical properties analysis, it has been discovered that all derivatives adhere to Lipinski's RO5 without exceptions. Overall, it is implied that all compounds qualify as drug-like molecules.

This encouraged us to use *in silico* approaches to work on the molecular interaction and uncover their pharmacophoric and chemical groups, demonstrating the originality of the current study. To confirm the interaction mechanism found by computerised screening, enzyme inhibitory experiments conducted both *in vitro* and *in vivo* are necessary.

5. Conclusion

In silico investigations were conducted to ascertain the binding interaction and affinity of novel thiazolidinone derivatives of Schiff bases against human peroxiredoxin (1HD2) and tyrosinase (5I38) enzymes. Compounds outperformed typical medications in terms of docking scores. For peroxiredoxin and tyrosinase, compound 2b has the highest docking scores. The designed substances can be categorised as druglike molecules based on their physicochemical features. The chemicals demonstrate encouraging inhibitory activity against the chosen target proteins, indicating that they could be helpful for oxidative stress. The potential of these drugs is supported by extensive molecular docking, binding free energy, pharmacophore hypothesis, physicochemical parameters and biological activity predictions using PASS. The results point to a direction for further study and development, suggesting that these derivatives of thiazolidinone may have multiple uses as multitargeted medications for disorders associated with oxidative stress and hyperpigmentation. Future research should focus on their refinement and optimisation to improve these compounds' therapeutic efficacy and safety profiles.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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