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HALOGEN-SUBSTITUTED THIAZOLE-LINKED SCHIFF BASE DERIVATIVES AS POTENT ANTIOXIDANT AGENTS: GREEN SYNTHESIS, DPPH RADICAL SCAVENGING AND MOLECULAR DOCKING AGAINST ASCORBATE PEROXIDASE (PDB ID: 6XV4)

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ABSTRACT

A novel series of structurally diverse Thiazole-Linked Schiff base derivatives (LM-1 to LM-10) was synthesised via a three-step protocol involving nucleophilic substitution, Boc deprotection and Schiff base formation under mild conditions. Lemon juice was used as an efficient green catalyst and ethanol as the solvent, yielding the target compounds in 85–95% isolated yields. The structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry. The derivatives exhibited significant antioxidant activity, and compound LM-7 showed the highest radical scavenging potential. Molecular docking against PDB ID: 6XV4 revealed strong binding affinities for LM-7, LM-5 and LM-8, indicating potential multifunctional activity. *In-silico* ADME analysis suggested favourable oral bioavailability and drug-likeness for the series. This research contributes significantly to the field of medicinal chemistry by providing a rational, green, and computationally validated approach for the development of novel antioxidant scaffolds. The findings align with SDG-3 (Good Health and Well-being) by addressing oxidative stress-related diseases and laying a foundation for future in vitro and in vivo studies, ultimately guiding the rational design of more effective and bioavailable antioxidant therapeutics.

Keywords: Thiazole, Schiff Base, Antioxidant Activity, Molecular Docking, Green Synthesis, ADME Prediction, Halogen Substitution.

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INTRODUCTION

Oxidative stress, arising from the excessive generation of reactive oxygen species (ROS), plays a critical role in the onset and progression of numerous pathological conditions, including cancer, cardiovascular disorders, neurodegenerative diseases and viral infections[1-3]. In healthy tissues, ROS levels are kept in balance by intrinsic antioxidant defence mechanisms; however, when this balance is disrupted, uncontrolled ROS accumulation triggers oxidative injury to cellular macromolecules such as lipids, proteins, and DNA, thereby impairing normal cellular function.[4] Antioxidant compounds counteract this damage through multiple mechanisms, including neutralisation of free radicals, sequestration of redox-active metal ions, and disruption of chain oxidation reactions.[5] Nevertheless, many currently available antioxidants—both of natural and synthetic origin-are hampered by inadequate stability, restricted bioavailability, and safety concerns, highlighting the pressing demand for structurally novel antioxidant agents with superior therapeutic profiles.[6,7] Schiff bases, characterised by the presence of an azomethine (–C=N–) linkage, have emerged as an important class of compounds in medicinal chemistry due to their straightforward synthesis, structural flexibility, and wide range of biological activities, including antioxidant, antimicrobial, anti-inflammatory, and antiviral effects.[8-10] Their radical-scavenging capacity is generally ascribed to proton- or electron-transfer mechanisms mediated by the azomethine (C=N) bond, along with stabilisation of the resulting radical species via extended conjugation through the imine-containing framework.[11,12] When heterocyclic moieties are incorporated into Schiff base scaffolds, the resulting hybrids frequently display improved pharmacological profiles, likely due to extended pi-electron systems, enhanced membrane permeability, and a stronger tendency to engage with macromolecular targets.[13]

Thiazole derivatives are important heterocyclic scaffolds found in many biologically active compounds and approved drugs.[14,15] The five-membered thiazole ring, bearing both nitrogen and sulfur heteroatoms, is capable of mediating a diverse array of non-covalent contacts with protein residues—including hydrogen bonds, aromatic stacking, cation-pi forces, and hydrophobic interactions—all of which collectively enhance receptor-binding capacity.[16] Reported literature indicates that thiazole-incorporated Schiff base hybrids surpass their non-heterocyclic counterparts in antioxidant potency, enzyme inhibition, and broader pharmacological relevance, underscoring the pivotal contribution of the thiazole unit to overall bioactivity.[17,18] However, detailed structure-activity relationship studies are still limited. Few studies combine experimental antioxidant evaluation with molecular docking analysis for thiazole-linked Schiff bases. Molecular docking has become a powerful computational tool for understanding ligand-protein interactions at the molecular level and for rationalising experimentally observed biological activities. Molecular docking was performed using Ascorbate peroxidase (PDB ID: 6XV4) as the target protein. This enzyme plays an essential role in antioxidant defence by catalysing the reduction of hydrogen peroxide using Ascorbic acid as an electron donor. The well-defined active site and the presence of a heme prosthetic group make this protein a suitable model for evaluating the binding interactions and potential antioxidant activity of small molecules through molecular docking analysis. Consequently, compounds possessing antioxidant properties may exert indirect protective effects by modulating oxidative stress-mediated cellular responses and interacting with redox-sensitive biological targets.[19] Taken together, the unique pharmacological potential of thiazole-Schiff base hybrids combined with the suitability of Ascorbate peroxidase as a redox-relevant computational target provides a compelling basis for the present investigation into the design, green synthesis, and antioxidant evaluation of these novel derivatives. Despite extensive research on thiazole-based Schiff bases as potential antioxidant agents, several important gaps remain. Most reported studies primarily focus on either chemical synthesis or preliminary antioxidant screening, with limited efforts devoted to integrating experimental antioxidant assays with detailed computational investigations. In many cases, molecular docking studies are performed using general protein targets without selecting enzymes directly involved in oxidative stress regulation. Furthermore, the interaction of thiazole-linked Schiff bases with antioxidant defence enzymes such as Ascorbate peroxidase (PDB ID: 6XV4) has not been sufficiently explored, particularly in relation to their binding behaviour within the heme-containing active site and the resulting structure-activity relationships. The lack of comprehensive studies combining synthesis, antioxidant evaluation and docking analysis limits a deeper understanding of the molecular features responsible for enhanced antioxidant activity. These limitations highlight the need for systematic investigations that integrate experimental antioxidant assays with molecular docking studies using biologically relevant antioxidant enzymes. Such an approach could provide valuable insights into ligand protein interactions, structure-activity relationships and the rational design of more effective antioxidant compounds. The present study is aligned with Sustainable Development Goal 3 (SDG-3): Good Health and Well-being, as it targets the development of novel antioxidant compounds aimed at combating oxidative stress-related diseases such as cancer, cardiovascular disorders, and neurodegenerative conditions. By employing an environmentally friendly green synthesis strategy and integrating experimental antioxidant evaluation with computational molecular docking, this research aims to bridge critical gaps in the literature and contribute meaningfully to the discovery of safe, effective, and drug-like antioxidant candidates.

EXPERIMENTAL

Material and Methods

All chemicals and reagents were obtained from commercial suppliers (TCI Chemicals and Avra Laboratories). The progress of reactions was monitored by thin-layer chromatography (TLC) using pre-coated silica gel 60 F_{254} aluminium plates (Merck). TLC spots were visualised under ultraviolet (UV) light. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C, using $CDCl_3$ as the solvent. Tetramethylsilane (TMS) was employed as the internal standard. Chemical shifts (δ) are reported in parts per million (ppm) relative to TMS, and coupling constants (J) are given in Hertz (Hz). The following abbreviations were used to denote multiplicities: s = singlet, d = doublet, t = triplet, brs = broad singlet, dd = double doublet, m = multiplet. ES-MS were acquired using a Waters Q-TOF micro mass spectrometer equipped with an electrospray ionisation (ESI) source.

Procedure for Synthesis of (S)-2-amino-3-(4-(benzyloxy)phenyl)-N-(thiazol-2-yl) propanamide (4)

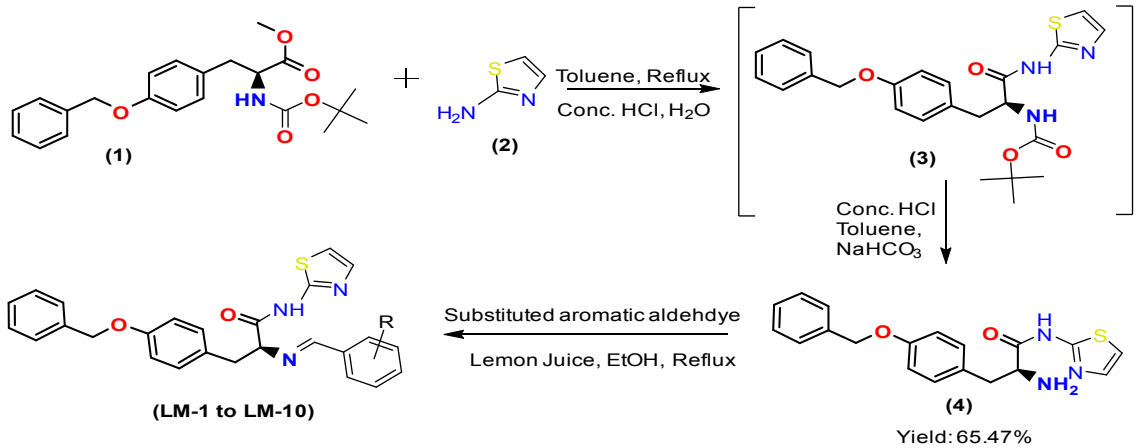
A solution of compound 1 (5 g, 0.013 mol) and thiazol-2-amine (1.3 g, 0.013 mol) in toluene (25 mL) was refluxed for 4 h. The reaction was monitored by TLC (DCM: MeOH: 9:1). After completion of the reaction, the reaction mixture was cooled to 10–15°C and 1% aq. HCl solution (15 mL) was added. After layer separation, the organic layer was dried over sodium sulphate and filtered. The toluene mother liquor contained compound **3**. To this solution, conc. HCl (3 mL) was added, and the reaction mixture was warmed to 45–50°C. The reaction was monitored by TLC (DCM: MeOH: 9:1). After completion, the slurry mass was filtered and washed with toluene (5 mL). The wet solid was dissolved in DCM (20 mL) and aq. 5% sodium bicarbonate solution (20 mL) was added, and stirred for 15 min. The layer was separated, and the organic layer was evaporated at atmospheric pressure to give a light brown solid of **4** (yield: 3 gm, 65.47%).

The General Approach for the Preparation of LM-1 to LM-10 Derivatives

Equimolar quantities of compound 4 and aromatic aldehyde (1 mmol) were dissolved in absolute ethanol. Subsequently, 2 mL of freshly extracted lemon juice was introduced as a natural acid catalyst. The reaction mixture was heated under reflux conditions for 4-5 h. The progress of the reaction was monitored by thin-layer chromatography (DCM: MeOH: 9:1) until complete consumption of compound 4 was observed. After completion, the reaction mixture was poured into crushed ice with chilled water, resulting in the precipitation of the product. The solid was filtered, washed thoroughly with absolute ethanol, and dried at room temperature to afford LM-1 to LM-10 derivatives.

RESULTS AND DISCUSSION

A novel and structurally diverse series of Thiazole-Linked Schiff base derivatives designated as LM-1 to LM-10 was synthesised via an efficient three-step synthetic protocol, as illustrated in Scheme-1. The structures of the resulting compounds are presented in Fig.-1. In the first step, methyl (S)-3-(4-(benzyloxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate (1) was refluxed with 2-aminothiazole (2) in toluene solvent at 110°C to 112°C, yielding tert-butyl (S)-(3-(4-(benzyloxy)phenyl)-1-oxo-1-(thiazol-2-ylamino)propan-2-yl)carbamate (3). This synthesis proceeds via a nucleophilic substitution mechanism, wherein the amino group of 2-aminothiazole (2) attacks the activated carbonyl centre, forming a N-(thiazol-2-yl)amide linkage with compound 1. Upon completion of the reaction, in situ Boc deprotection of compound (3) was carried out using aqueous HCl solution, followed by neutralisation with sodium bicarbonate, to afford (S)-2-amino-3-(4-(benzyloxy)phenyl)-N-(thiazol-2-yl)propanamide (4). In the final step, Schiff base condensation of compound (4) with various substituted aromatic aldehydes using lemon juice as a catalyst to obtain the desired target derivatives (LM-1 to LM-10) in good to excellent yields.



Scheme-1: Synthesis of Thiazole-Linked Schiff Base Derivatives (LM-1 to LM-10)

Different catalysts were examined to determine the most suitable conditions for the synthesis of the LM-1 compound under reflux in ethanol. The results show that both the type of catalyst and reaction time significantly affect the yield of the desired Schiff base product. Among the catalysts tested, lemon juice produced the highest yield (88.2%) within 4 h of reflux.

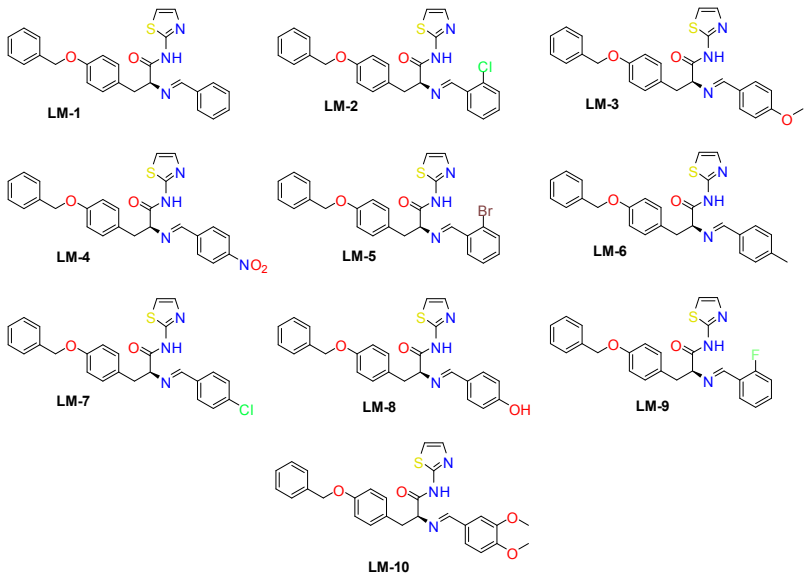


Fig.-1: Structural Representation of Thiazole-Linked Schiff Base Derivatives (LM-1 to LM-10)

This improved efficiency may be attributed to the presence of natural organic acids, mainly citric acid, which can effectively activate the carbonyl group of the aldehyde and facilitate nucleophilic attack by the amine, promoting the formation of the imine (C=N) bond. In addition, lemon juice provides a simple and environmentally friendly catalytic system, making it a suitable green alternative for this reaction. Acetic acid also demonstrated good catalytic activity, affording a yield of 85.1% after 4 h of reflux. A similar yield (84.3%) was obtained when concentrated HCl was used as the catalyst under reflux for 5 h. The use of p-toluenesulfonic acid resulted in a moderate yield of 80.2% after 5 h of reflux. The Lewis acid zinc chloride also catalysed the reaction, producing a yield of 78.3% after 6 h. Heterogeneous catalysts such as montmorillonite K-10 clay and Amberlyst-15 resin gave comparatively lower yields of 75.6% and 72.2%, respectively, even after longer reaction times of 8 h.

Table-1: Screening of Catalysts for the Synthesis of LM-1 Compound

Catalyst	Reaction Conditions	Yield (%)
Acetic acid (CH_3 COOH)	Reflux, 4 h, Ethanol	85.1
p-Toluenesulfonic acid (p-TsOH)	Reflux, 5 h, Ethanol	80.2
Zinc chloride ($ZnCl_2$)	Reflux, 6 h, Ethanol	78.3
Montmorillonite K-10 clay	Reflux, 8 h, Ethanol	75.6
Amberlyst-15 resin	Reflux, 8 h, Ethanol	72.2
Conc. HCl	Reflux, 5 h, Ethanol	84.3
Lemon juice	Reflux, 4 h, Ethanol	88.2

Further, solvent screening was carried out to identify the most suitable solvent for the synthesis of the LM-1 compound under reflux conditions. Among the solvents examined, ethanol provided the best results, giving a higher yield of the LM-1 compound within a shorter reaction time. This may be attributed to its moderate polarity, which allows good solubility of both the aldehyde and amine reactants while also facilitating effective interaction with the catalyst. Taken together, ethanol proved to be the most suitable solvent for the synthesis of the LM-1 compound, providing improved reaction efficiency and higher yield compared with the other solvents tested.

The synthesised compounds LM-1 to LM-10 were characterised using IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry. In the IR spectra, a broad absorption band observed in the region 3350–3670 cm^{-1} was attributed to N-H stretching of the secondary amide. A strong absorption in the 1600–1667 cm^{-1} region confirmed the C=N stretching of the azomethine bond. Phenyl ring C=C stretching resonances were detected at 1415–1479 cm^{-1}, while C-N stretching appeared in the 1200–1285 cm^{-1} range. C-O stretching of the benzyloxy ether was recorded between 1000–1160 cm^{-1}, and the characteristic C-S band of the

thiazole ring was identified in the 636–671 cm^{-1} region. The ^{1}H NMR spectra further supported the structures of the synthesized compounds. A singlet appearing in the range δ 8.63–8.78 ppm corresponds to the amide NH proton. Another singlet around δ 8.01–8.09 ppm was assigned to the azomethine proton (–CH=N–), confirming the formation of the Schiff base linkage.

Table-2: Solvent Screening for Synthesis of LM-1 Compound

Solvent	Reaction Conditions	Yield (%)
Ethanol	Reflux, 4 h	88.2
Methanol	Reflux, 4 h	82.5
Acetonitrile	Reflux, 5 h	76.8
Toluene	Reflux, 6 h	71.4
Dichloromethane	Reflux, 5 h	69.2
Water	Reflux, 6 h	64.7

The aromatic protons appeared as multiplets and doublets between δ 6.86 and 7.63 ppm. A singlet at δ 5.00–5.05 ppm corresponds to the benzylic methylene protons (O-CH_2). The N-CH signal resonated as a triplet at δ 4.61–4.66 ppm, while the methylene protons (CH_2) flanking the benzyloxy unit gave signals near δ 2.81–2.87 ppm. The ^{13}C NMR spectra also confirmed the proposed structures. A characteristic signal around δ 169 ppm corresponds to the amide carbonyl carbon (C=O). Signals observed in the region δ 160–163 ppm were assigned to the azomethine carbon and heteroaromatic carbons of the thiazole ring. The aromatic carbons appeared between δ 114 and 137 ppm. The benzylic methylene carbon (O-CH_2) signal fell at δ 73–74 ppm; the N-CH carbon resonated near δ 69–70 ppm; and the propanamide methine carbon was observed at δ 38–39 ppm. Finally, the mass spectra of the synthesised compounds showed prominent $(M+1)^+$ peaks corresponding to their molecular weights. The observed molecular ion peaks were consistent with the calculated molecular masses of the respective compounds, confirming the successful synthesis of the target thiazole-based Schiff base derivatives.

Antioxidant Activity

The LM-1 to LM-10 were tested for their antioxidant property using the free stable radical 2,2-diphenyl-1-picrylhydrazyl (DPPH). All the synthesized compounds exhibited significant antioxidant activity. The antioxidant activity was evaluated using their percentage inhibition at three different concentrations (50, 100 and 150 µg/mL) and compared with ascorbic acid as the standard. The results are presented in Table-3. At 50 µg/mL, all compounds showed moderate antioxidant activity, with % inhibition values ranging from 23.24% (LM-3) to 40.20% (LM-7). When the concentration was increased to 100 µg/mL, a significant rise in % inhibition was observed for all derivatives. LM-7 (60.21%) again showed the most promising activity, followed by LM-5 (57.21%) and LM-2 (56.48%). At the highest concentration (150 µg/mL), the maximum activity was recorded for LM-7 (75.20%), comparable to the standard ascorbic acid (80.30%). Statistical analysis of DPPH scavenging activity was calculated as per the reported literature[19] and shown in Table-4.

Molecular Docking

Molecular docking was performed to evaluate the antioxidant activity of target compounds by using Schrödinger software.[20] Molecular docking studies were carried out for the synthesised compounds (LM-1 to LM-10) as ligands using the target protein with PDB ID: 6XV4. Among all, LM-7 showed the best binding interaction with a G-score of –6.300 and a binding energy of –46.098 kcal/mol, which was slightly better than the standard compound, ascorbic acid (G-score –6.059, binding energy –32.236 kcal/mol).

Table-3: Antioxidant Activity of LM-1 to LM-10

Compound	% Inhibition at 50 µg/mL	% Inhibition at 100 µg/mL	% Inhibition at 150 µg/mL
Control	0	0	0
LM-1	28.20	52.58	59.60
LM-2	32.2	56.48	70.23
LM-3	23.24	47.16	54.91
LM-4	29.35	54.55	62.31
LM-5	33.2	57.21	70.43

LM-6	26.00	49.55	55.30
LM-7	40.20	60.21	75.2
LM-8	26.46	51.80	58.11
LM-9	24.22	48.25	55.20
LM-10	30.2	55.23	65.23
Ascorbic acid	48.70	67.20	80.30

Table-4: Statistical Analysis of DPPH Scavenging Activity of LM-1 to LM-10 Compounds

Sample	R^2	F value	DFn, DFd	P value	Deviation from horizontal
LM-1	0.964	26.8	1,1	0.121	Not significant
LM-2	0.983	57.8	1,1	0.083	Not significant
LM-3	0.951	19.4	1,1	0.142	Not significant
LM-4	0.972	34.7	1,1	0.107	Not significant
LM-5	0.984	61.5	1,1	0.081	Not significant
LM-6	0.946	17.6	1,1	0.150	Not significant
LM-7	0.989	91.0	1,1	0.066	Not significant
LM-8	0.962	25.4	1,1	0.125	Not significant
LM-9	0.948	18.3	1,1	0.147	Not significant
LM-10	0.974	37.5	1,1	0.103	Not significant
Ascorbic acid	0.992	123.0	1,1	0.057	Not significant

Compounds LM-5 and LM-8 also showed strong affinities with binding energies of –50.164 and –45.313 kcal/mol, respectively. LM-9 showed the weakest binding (G-score –4.931) with only hydrophobic interaction and no hydrogen bonding. In summary, most of the ligands demonstrated good binding potential toward the target protein, with LM-7, LM-5 and LM-8 standing out as the most promising candidates. Their combination of hydrogen bonding, π-cation interactions and multiple hydrophobic contacts likely contributes to their high binding affinity and stability within the active site. These results suggest that these compounds could serve as good leads for further *in vitro* and *in vivo* evaluation.

Table-5: Molecular Docking Results of Thiazole-Linked Schiff Base Derivatives (LM-1 to LM-10) (PDB ID: 6XV4)

Comp Code	G-Score	Binding Energy (kcal/mol)	Hydrogen Bond	π-cation Stacking	Hydrophobic Interactions
LM-1	-5.456	-42.761	--	--	ILE76, CYS32, PRO34, LEU35, PRO178, PRO183, LEU184, ALA167
LM-2	-5.727	-41.497	ARG172	--	ALA167, PRO178, LEU80, PRO183, LEU184
LM-3	-4.688	-37.129	--	ARG172, HIP169	CYS32, PRO34, LEU35, ILE76, LEU80, ALA167
LM-4	-5.506	-42.098	ARG172	--	CYS32, PRO34, LEU35, ILE76, LEU80, ALA167
LM-5	-5.976	-50.164	HIP169, ARG31	--	CYS32, PRO34, LEU35, ILE76, PRO178, ALA167

LM-6	-5.405	-41.667	ARG172	ARG172	CYS32, PRO34, LEU35, ILE76, LEU80, ALA167
LM-7	-6.300	-46.098	ARG172, HIP169	ARG172	CYS32, PRO34, LEU35, ILE76, LEU80, ALA167, PRO183, LEU184
LM-8	-5.329	-45.313	ARG172	ARG31, HIP169	PRO34, LEU35, ILE76, PRO178, PRO183, LEU184, ALA167
LM-9	-4.931	-45.117	--	--	PRO178, PRO183, LEU184, ALA167, ALA168
LM-10	-5.704	-47.157	--	HIP169	CYS32, PRO34, LEU35, ALA167, ALA168, PRO183, LEU184
Ascorbic acid	-6.059	-32.236	LEU35, HIP169, ARG172	--	CYS32, PRO34, ALA167

Fig.-2: Docking Pose and 2D Interactions of Compound LM-7 in Cavity of 6XV4

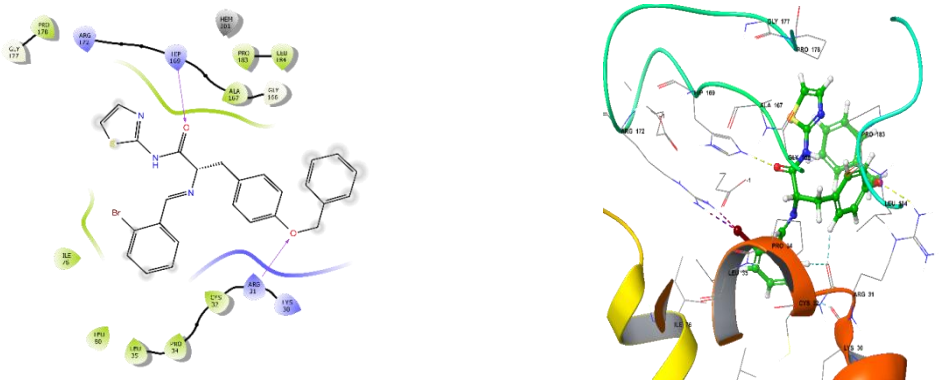


Fig.-3: Docking Pose and 2D Interactions of Compound LM-5 in Cavity of 6XV4

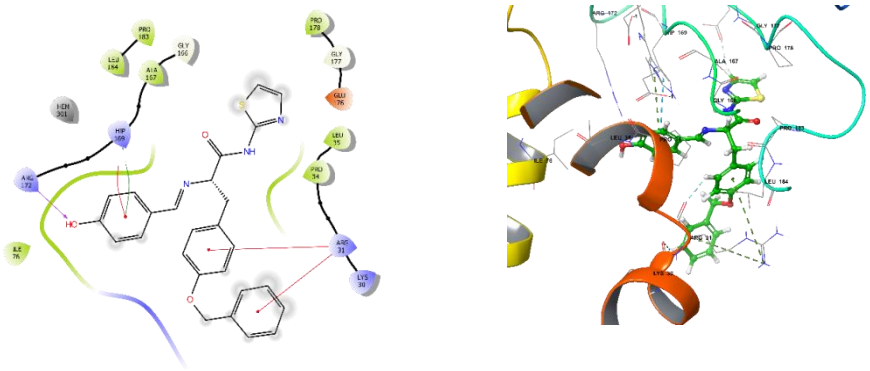


Fig.-4: Docking Pose and 2D Interactions of Compound LM-8 in Cavity of 6XV4

In-silico ADME Prediction

The pharmacokinetic properties of the synthesized compounds (LM-1 to LM-10) were evaluated using *in-silico* ADME prediction tools to determine their drug-likeness and potential oral bioavailability.[21] Key physicochemical descriptors—including MW, miLogP, TPSA, number of rotatable bonds, hydrogen bond donors and acceptors, and %ABS—were computed and assessed against Lipinski's Rule of Five criteria.[22] Molecular weights across the series spanned 443.54–522.44 g/mol, and miLogP values ranged from 3.87 to 4.82, consistent with adequate lipophilicity. TPSA values (87.3–103.2 Å^2) remained well within the accepted 140 Å^2 ceiling associated with satisfactory intestinal permeability.[24] The predicted %ABS values ranged from 73.4% to 78.9%, suggesting favourable oral absorption. The number of hydrogen bond donors and acceptors for all compounds remained within the permissible limits defined by Lipinski's criteria. In conclusion, the majority of the synthesised compounds complied with Lipinski's rule with no significant violations, except LM-5, where an elevated molecular mass introduced a single rule violation. Overall, the series presents a satisfactory oral pharmacokinetic profile suitable for further drug development.

Table-6: Predicted Pharmacokinetic Parameters of Synthesized Compounds (LM-1 to LM-10)

Entry	%ABS	TPSA (Å^2)	n-rotB	MV	MW (g/mol)	miLogP	n-ON	n-OHNH	Lipinski Violation	Drug-likeness Score
LM-1	78.9	87.3	7	415.6	443.54	4.21	5	2	0	0.52
LM-2	77.8	90.4	7	430.2	477.99	4.56	5	2	0	0.49
LM-3	77.1	92.5	8	428.7	473.57	4.08	6	2	0	0.47
LM-4	73.7	102.3	7	432.8	488.54	3.92	7	2	0	0.44
LM-5	78.9	87.3	7	439.8	522.44	4.82	5	2	1	0.46
LM-6	78.9	87.3	7	421.5	457.56	4.34	5	2	0	0.50
LM-7	78.9	87.3	7	432.4	477.99	4.55	5	2	0	0.51
LM-8	73.4	103.2	7	418.9	459.54	3.87	6	3	0	0.48
LM-9	78.9	87.3	7	426.1	461.53	4.28	5	2	0	0.50
LM-10	74.8	99.1	8	441.3	489.60	3.95	7	2	0	0.46

Structure Activity Relationship (SAR)

The antioxidant activity of the synthesized derivatives (LM-1 to LM-10) was evaluated using the DPPH radical scavenging assay, and the results showed that the activity depends on the substituents present on the aromatic ring. Among the compounds, LM-7 exhibited the highest antioxidant activity due to the presence of a chloro (–Cl) group, which helps stabilize the radical intermediate. LM-5, containing a bromo (–Br) substituent, and LM-2 also showed significant activity, indicating the positive effect of halogen substitution. Compounds with electron-donating groups such as hydroxyl (–OH) and methoxy (–OCH_3) displayed moderate activity, while LM-3 and LM-9 showed lower antioxidant effects. The findings of this study directly contribute to Sustainable Development Goal 3 (SDG-3): Good Health and Well-being. Oxidative stress is a key mediator of chronic non-communicable diseases, including cancer, cardiovascular diseases, and neurodegenerative disorders, all of which are priority health concerns under SDG-3. By identifying potent antioxidant candidates such as LM-7, LM-5, and LM-8 through both

experimental DPPH assay and computational molecular docking, the present work provides a scientifically sound and practically relevant contribution towards the discovery of novel therapeutic agents targeting oxidative stress-associated pathological conditions.

Spectral Characterization Data

(S,E)-2-(benzylideneamino)-3-(4-(benzyloxy)phenyl)-N-(thiazol-2-yl)propanamide (LM-1)
Off white solid; Yield: 88.2%; mp: 125–127 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (s, 1H, NH), 8.06 (s, 1H, C=N), 7.42–7.32 (m, 10H, Ar-H), 7.13–7.11 (d, 2H), 6.88–6.86 (d, 2H), 6.55–6.53 (d, 1H), 5.05 (s, 2H, CH_2-Ar), 4.64–4.62 (t, 1H), 3.20–3.16 (m, 1H), 2.86–2.84 (m, 1H); ^{13}C NMR (125 MHz): δ 169.4, 162.6, 160.5, 157.2, 137.2, 130.9, 130.1, 128.6, 127.9, 127.6, 127.2, 115.7, 114.7, 108.9, 73.9, 69.6, 38.8; IR (KBr): 3352 (N-H), 2954, 1641 (C=N), 1418 (C=C), 1284 (C-N), 1135 (C-O), 656 cm^{-1}(C-S). ESMS (M+1): 442.2.

(S,E)-2-(2-chlorobenzylideneamino)-3-(4-(benzyloxy)phenyl)-N-(thiazol-2-yl)propanamide (LM-2)
Light yellow solid; Yield: 86.3%; mp: 158–160 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (s, 1H, NH), 8.02 (s, 1H, C=N), 7.63–7.60 (d, 2H), 7.38–7.32 (m, 6H), 7.10–7.08 (d, 2H), 6.87–6.85 (d, 2H), 6.57–6.55 (d, 1H), 5.04 (s, 2H), 4.66–4.63 (t, 1H), 3.14–3.11 (m, 1H), 2.84–2.81 (m, 1H); ^{13}C NMR: δ 169.5, 162.1, 160.6, 157.5, 137.2, 136.9, 134.1, 130.8, 129.2, 128.9, 128.6, 127.9, 127.4, 114.8, 109.5, 73.9, 69.9, 38.8; IR (KBr): 3599 (N-H), 1654 (C=N), 1280 (C-N), 1146 (C-O), 781 (C-Cl), 656 cm^{-1}(C-S). ESMS (M+1): 476.2.

(S,E)-2-(4-methoxybenzylideneamino)-3-(4-(benzyloxy)phenyl)-N-(thiazol-2-yl)propanamide (LM-3)
Off white solid; Yield: 92.1%; mp: 135–138 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.75 (s, 1H, NH), 8.03 (s, 1H, C=N), 7.54–7.52 (d, 2H), 7.38–7.30 (m, 6H), 7.13–7.11 (d, 2H), 6.88–6.86 (d, 4H), 6.55–6.53 (d, 1H), 5.05 (s, 2H), 4.64–4.61 (t, 1H), 3.75 (s, 3H, OCH_3), 3.20–3.16 (m, 1H), 2.86–2.84 (m, 1H); ^{13}C NMR: δ 169.5, 162.6, 160.5, 157.4, 137.0, 130.8, 130.0, 128.6, 127.9, 127.5, 124.1, 114.7, 114.0, 108.9, 73.8, 69.6, 55.4, 38.9; IR: 3437 (N-H), 1606 (C=N), 1249 (C-N), 1159 (C-O), 646 cm^{-1}(C-S). ESMS (M+1): 471.2.

(S,E)-2-(4-nitrobenzylideneamino)-3-(4-(benzyloxy)phenyl)-N-(thiazol-2-yl)propanamide (LM-4)
Light yellow solid; Yield: 93.2%; mp: 98–99 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.75 (s, 1H, NH), 8.29–8.28 (d, 2H), 8.03 (s, 1H, C=N), 7.95–7.93 (d, 2H), 7.41–7.30 (m, 6H), 7.13–7.11 (d, 2H), 6.88–6.86 (d, 4H), 6.55–6.53 (d, 1H), 5.05 (s, 2H), 4.64–4.61 (t, 1H), 3.20–3.16 (m, 1H), 2.86–2.84 (m, 1H); ^{13}C NMR: δ 169.4, 162.05, 160.6, 157.2, 149.3, 140.9, 137.3, 130.8, 129.1, 128.6, 127.4, 123.9, 114.9, 109.3, 73.9, 69.9, 38.7; IR: 3387 (N-H), 1649 (C=N), 1494 & 1415 (NO_2), 1153 (C-O), 657 cm^{-1}(C-S). ESMS (M+1): 487.3.

(S,E)-2-(2-bromobenzylideneamino)-3-(4-(benzyloxy)phenyl)-N-(thiazol-2-yl)propanamide (LM-5)
Light brown solid; Yield: 85.6%; mp: 120–122 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (s, 1H, NH), 8.04 (s, 1H, C=N), 7.82–7.81 (d, 1H), 7.44–7.30 (m, 6H), 7.22–7.17 (m, 1H), 7.10–7.08 (d, 2H), 6.88–6.86 (d, 4H), 6.56–6.54 (d, 1H), 5.00 (s, 2H), 4.63–4.61 (t, 1H), 3.31–3.13 (m, 1H), 2.87–2.84 (m, 1H); ^{13}C NMR: δ 169.6, 162.02, 160.5, 157.3, 141.6, 137.3, 135.0, 132.1, 130.8, 129.1, 128.6, 127.4, 121.3, 114.9, 109.5, 73.9, 69.9, 38.7; IR: 3661 (N-H), 1667 (C=N), 1071 (C-O), 738 (C-Br), 654 cm^{-1}(C-S). ESMS (M+1): 520.2.

(S,E)-3-(4-(benzyloxy)phenyl)-2-((4-chlorobenzylidene)amino)-N-(thiazol-2-yl)propanamide (LM-6)
White solid; Yield: 85.6%; mp: 142–144 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (s, 1H, NH), 8.02 (s, 1H, C=N), 7.63–7.61 (d, 1H), 7.40–7.32 (m, 6H), 7.10–7.08 (d, 2H), 6.87–6.85 (d, 4H), 6.57–6.55 (d, 1H), 5.04 (s, 2H), 4.66–4.63 (t, 1H), 3.14–3.11 (m, 1H), 2.84–2.81 (m, 1H), 2.35 (s, 3H, CH_3); ^{13}C NMR: δ 169.4, 162.7, 157.4, 150.0, 137.0, 130.9, 129.9, 128.6, 127.4, 124.1, 123.0, 117.0, 114.7, 109.5, 73.9, 69.9, 38.9, 23.5; IR: 3673 (N-H), 1660 (C=N), 1093 (C-O), 659 cm^{-1}(C-S). ESMS (M+1): 456.2.

(S,E)-2-(4-chlorobenzylideneamino)-3-(4-(benzyloxy)phenyl)-N-(thiazol-2-yl)propanamide (LM-7)
Yellowish solid; Yield: 91.2%; mp: 162–164 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.67 (s, 1H, NH), 8.09 (s, 1H, C=N), 7.54–7.52 (d, 4H), 7.41–7.32 (m, 4H), 7.18–7.11 (m, 4H), 6.88–6.86 (d, 2H), 6.55–6.53 (d, 1H), 5.05 (s, 2H), 4.64–4.61 (t, 1H), 3.20–3.16 (m, 1H), 2.86–2.84 (m, 1H); ^{13}C NMR: δ 169.5, 163.7,

157.6, 136.9, 133.1, 130.6, 128.6, 127.9, 127.4, 116.9, 114.9, 109.8, 74.0, 69.9, 38.7; IR: 1623 (C=N), 1000 (C-O), 740 (C-Cl), 636 cm^{-1}(C-S). ESMS (M+1): 476.2.

(S,E)-2-(4-hydroxybenzylideneamino)-3-(4-(benzyloxy)phenyl)-N-(thiazol-2-yl)propanamide (LM-8)
White solid; Yield: 94.2%; mp: 128–130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.95 (s, 1H, OH), 8.75 (s, 1H, NH), 8.02 (s, 1H, C=N), 7.51–7.31 (m, 8H), 7.10–7.08 (d, 2H), 6.89–6.87 (d, 2H), 6.80–6.78 (d, 2H), 6.59–6.57 (d, 1H), 5.03 (s, 2H), 4.65–4.63 (t, 1H), 3.14–3.11 (m, 1H), 2.84–2.81 (m, 1H); ^{13}C NMR: δ 169.4, 162.6, 160.5, 157.2, 137.2, 130.9, 130.1, 128.6, 127.9, 127.6, 127.2, 115.7, 114.7, 109.2, 73.9, 69.6, 38.8; IR: 1602 (C=N), 1026 (C-O), 661 cm^{-1}(C-S). ESMS (M+1): 458.2.

(S,E)-2-(2-fluorobenzylideneamino)-3-(4-(benzyloxy)phenyl)-N-(thiazol-2-yl)propanamide (LM-9)
Brown solid; Yield: 92.1%; mp: 97–99 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.78 (s, 1H, NH), 8.01 (s, 1H, C=N), 7.82–7.81 (d, 1H), 7.44–7.32 (m, 6H), 7.22–7.17 (d, 2H), 7.10–7.05 (m, 3H), 6.88–6.86 (d, 3H), 6.58–6.56 (d, 1H), 5.00 (s, 2H), 4.63–4.61 (t, 1H), 3.16–3.13 (m, 1H), 2.87–2.84 (m, 1H); ^{13}C NMR: δ 169.4, 162.02, 160.4, 157.2, 137.2, 131.3, 130.8, 128.6, 127.9, 127.6, 127.2, 124.0, 120.3, 116.2, 107.9, 73.9, 69.8, 38.8; IR: 1646 (C=N), 1036 (C-O), 668 cm^{-1}(C-S). ESMS (M+1): 460.5.

(S,E)-2-(3,4-dimethoxybenzylideneamino)-3-(4-(benzyloxy)phenyl)-N-(thiazol-2-yl)propanamide (LM-10)
Pale pink colour; Yield: 90.3%; mp: 113–115 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (s, 1H, NH), 8.06 (s, 1H, C=N), 7.42–7.31 (m, 6H), 7.12–7.10 (d, 3H), 6.99–6.97 (d, 1H), 6.89–6.87 (d, 1H), 6.68–6.66 (d, 2H), 5.03 (s, 2H), 4.64–4.62 (t, 1H), 3.78 (s, 6H, CH_3), 3.16–3.12 (m, 1H), 2.86–2.84 (m, 1H); ^{13}C NMR: δ 169.4, 162.7, 157.4, 150.0, 137.2, 130.9, 129.9, 128.6, 127.5, 124.1, 123.0, 117.0, 114.7, 109.0, 73.9, 69.6, 55.4, 38.9; IR: 1648 (C=N), 1026 (C-O), 671 cm^{-1}(C-S). ESMS (M+1): 502.2.

CONCLUSION

A novel series of Thiazole-Linked Schiff base derivatives (LM-1 to LM-10) was efficiently synthesised using a three-step protocol under mild and environmentally friendly conditions, with lemon juice as a green catalyst and ethanol as the optimal solvent. Structural characterisation by IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry confirmed the successful formation of the target compounds. All derivatives exhibited significant antioxidant activity in a concentration-dependent manner, with halogen-substituted compounds, particularly LM-7, showing the highest radical scavenging potential. Molecular docking studies against PDB ID: 6XV4 revealed strong binding interactions for LM-7, LM-5 and LM-8, suggesting potential multifunctional activity. In-silico ADME predictions indicated favourable oral absorption, drug-likeness, and pharmacokinetic properties for the series. In summary, these results highlight the synthesised derivatives as promising candidates for further biological evaluation. This study supports the objectives of Sustainable Development Goal 3 (SDG-3): Good Health and Well-being, by contributing to the rational discovery of novel antioxidant drug candidates that may help prevent and manage oxidative stress-associated chronic diseases. Future studies should focus on in vitro and in vivo biological evaluation of the most active compounds, particularly LM-7, to further validate their therapeutic potential.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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