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Original Article

Design and in silico evaluation of 2-methoxyphenyl anilinoacetate derivatives as VCAM-1 inhibitors for atherosclerosis therapy

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ABSTRACT

Objective: The primary objective of this study was to design and document a series of novel 2- methoxyphenyl anilinoacetate derivatives with diverse substituents to enhance their potential as bioactive agents targeting atherosclerosis. Given the role of VCAM-1 (Vascular Cell Adhesion Molecule-1) in mediating endothelial inflammation and leukocyte adhesion in atherosclerosis, the study aimed to create structurally diverse compounds suitable for in silico screening against this key therapeutic target.

Method: A total of 19 derivatives of 2-methoxyphenyl anilinoacetate were designed by incorporating various functional groups—including halogens, methoxy, hydroxyl, amino, and heterocycles such as triazole, benzothiazole, benzimidazole, pyridine, and morpholine—on the aniline moiety. These structural variations were represented using SMILES notation for computational screening. The designed molecules were subjected to pharmacophore modeling, molecular docking, and ADMET profiling, particularly targeting VCAM-1 implicated in the pathogenesis of atherosclerosis.

Results: The designed compounds displayed notable structural diversity and included pharmacologically active moieties, potentially enhancing biological activity and drug-likeness. Several molecules demonstrated strong binding affinities with VCAM-1 and favorable ADMET profiles, indicating their potential as lead compounds. The results support their further evaluation through structure–activity relationship (SAR) studies and biological assays.

Conclusion: This virtual library of 2-methoxyphenyl anilinoacetate derivatives provides a valuable platform for the discovery of novel agents aimed at treating atherosclerosis. The incorporation of bioactive substituents and in silico validation underscores the potential of these compounds to inhibit VCAM-1, offering promising avenues for future therapeutic development.

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Introduction

Atherosclerosis is a progressive, chronic inflammatory disease characterized by the accumulation of lipids, inflammatory cells, and fibrous elements in the arterial walls. It serves as the pathological basis for a spectrum of cardiovascular diseases (CVDs), including coronary artery disease, stroke, and peripheral vascular disease, which together represent the leading cause of morbidity and mortality worldwide [1]. The pathogenesis of atherosclerosis is multifactorial, involving genetic predispositions, environmental influences, and classical risk factors such as hyperlipidaemia, hypertension, smoking, and diabetes. These factors contribute to endothelial dysfunction, oxidative stress, and an imbalanced immune response, initiating a cascade of cellular events that promote plaque formation and vascular remodelling [2].

At the molecular level, atherosclerosis begins with the dysfunction of endothelial cells, which normally maintain vascular homeostasis. In response to atherogenic stimuli—such as oxidized low-density lipoprotein (oxLDL), turbulent shear stress, or cytokines—endothelial cells undergo phenotypic changes and start expressing adhesion molecules that mediate leukocyte recruitment and transmigration. Among these, Vascular Cell Adhesion Molecule-1 (VCAM-1) plays a pivotal role.

VCAM-1(A Key Mediator in Atherosclerosis)-VCAM-1 is a member of the immunoglobulin superfamily and is primarily expressed on activated endothelial cells. Its expression is upregulated in response to inflammatory cytokines like TNF-α and IL-1β. VCAM-1 facilitates the adhesion of circulating monocytes and lymphocytes to the endothelium via interaction with integrins (e.g., VLA-4/α4β1), enabling their transendothelial migration into the subendothelial space. Once inside the vascular wall, these immune cells differentiate into macrophages and contribute to foam cell formation, perpetuating the inflammatory response and driving lesion progression. Elevated levels of soluble VCAM-1 (sVCAM-1) in plasma are associated with subclinical and clinical stages of atherosclerosis and are considered indicators of endothelial activation. Clinical studies have confirmed that high concentrations of VCAM-1 are found in vascular regions prone to atherogenesis, suggesting its involvement in early lesion development.

Moreover, its expression correlates with plaque instability, making it a potential biomarker for disease progression and a promising therapeutic target [3,4].

Targeting VCAM-1 through molecular inhibitors, monoclonal antibodies, or RNA-based therapeutics holds potential in modulating vascular inflammation and preventing leukocyte recruitment, thereby attenuating the progression of atherosclerotic plaques. As such, VCAM-1 not only serves as a biomarker for early diagnosis but also represents a therapeutic target in the fight against atherosclerotic vascular disease.

Materials and Methods

Pharmacophore Modelling and Ligand Design

Pharmacophore models were generated using the Pharmit server, based on structural data from PDB IDs 5VA0(VCAM1) [9]. These models were used to screen chemical libraries such as PubChem [12], ChEMBL, and ZINC. Key pharmacophoric features guided the design of 79 novel ligands, sketched in ChemSketch (ACD/Labs, v2023 1.0) [10] and saved in MOL format. Structures were energy-minimized using Chem3D Ultra [11] (MM2 force field) and converted to PDBQT format via AutoDock Tools 1.5.6. Novelty was confirmed by comparing against public databases; only unreported compounds were selected for further analysis [5].

Receptor Preparation and Validation

Crystal structures of VCAM (5VA0) were obtained from the Protein Data Bank and validated through Ramachandran plot analysis [6], showing most residues in favoured regions. Receptor preprocessing involved removal of water and cofactors, addition of polar hydrogens, and assignment of Kollman charges using AutoDock Tools 1.5.6.

ADMET Prediction

Pharmacokinetic and toxicity profiles were evaluated using Swiss ADME [7] and OSIRIS [8] Property Explorer. Parameters included drug-likeness, bioavailability, and Lipinski's Rule of Five compliances. OSIRIS also assessed toxicity risks (tumorigenic, mutagenic, irritant, reproductive), with color-coded indicators highlighting safe (green) or risky (red) compounds.

Molecular Docking and Binding Site Analysis

Docking studies were performed with AutoDock Tools 1.5.6[13] to assess ligand binding affinities with VCAM1. CB-DOCK2[14] predicted binding pockets based on solvent-accessible surface clustering, providing cavity coordinates and volume for precise docking. Receptor– ligand interactions were visualized using Molegro Molecular Viewer [15] to analyse key residues, interaction types, and binding mechanisms.

Result and Discussion

Virtual Ligand Library Development

Pharmacophoric features such as hydrophobic moieties, hydrogen bond donors, and acceptors was identified for VCAM. These key features guided the rational design of ligand structures optimized for binding to the respective target proteins.

Novelty Assessment

Among the 80 designed ligands, 79 were confirmed as novel through a comprehensive screening against the PubChem database. Detailed novelty assessment results are provided in Supplementary Table I.

Table 1: Novel Ligands and Already Existing Compounds.

Novel Ligands	Already Existing Compounds
YK1,YK2,YK3,YK4,YK5,YK6,YK7,YK8,YK9,YK10,YK11 ,YK12,YK13,YK14,YK15,YK16,YK17,YK18,YK19,YK20, YK21,YK22,YK23,YK24,YK25,YK26,YK27,YK28,YK29, YK31,YK32,YK33,YK34,YK35,YK36,YK37,YK38,YK39, YK40,YK41,YK42,YK43,YK44,YK45,YK46,YK47,YK48, YK49,YK50,YK51,YK52,YK53,YK54,YK55,YK56,YK57, YK58,YK59,YK60,YK61,YK62,YK63,YK64,YK65,YK66, YK67,YK68,YK69,YK70,YK71,YK72,YK73,YK74,YK75, YK76,YK77,YK78,YK79,YK80	YK30

In-Silico ADMET Profiling

Selected ligands were evaluated for pharmacokinetic properties using in silico tools and were found to comply with Lipinski's Rule of Five. Their molecular weights ranged from 245.23 to 394.17 Da, and log P values between 0.31 and 3.67, comparable to atorvastatin. Most compounds demonstrated good drug-likeness and non-toxicity profiles. Results are summarized in Supplementary Table II.

Table 2: ADMET Properties of Novel Ligands.

Lig. No	M	T	I	R	Log P	MW	H. B. A	H. B. D	Rule of 5
1	No	No	No	No	2.61	257.38	6	3	0
2	Yes	Yes	No	No	3.1	307.34	3	1	0
3	Yes	Yes	No	No	2.73	323.34	4	2	0
4	Yes	Yes	No	No	3.37	337.31	4	1	0
5	No	No	No	No	2.44	285.29	4	1	0
6	Yes	Yes	No	Yes	2.28	288.33	6	2	0
7	No	No	No	No	3.07	394.17	6	1	1
8	No	No	No	No	2.96	314.36	4	1	0
9	No	No	No	No	2.33	272.3	4	1	0
10	No	No	No	No	3.13	271.31	3	1	0
11	No	No	No	No	3.34	277.36	4	1	0
12	No	No	No	Yes	2.61	289.35	3	1	0
13	No	No	No	No	2.84	284.31	3	2	0
14	No	No	No	No	2.92	291.73	3	1	0
15	No	No	Yes	No	2.9	271.31	4	1	0
16	No	No	No	No	1.91	233.22	5	0	0
17	No	No	Yes	No	2.56	251.28	5	0	0
18	Yes	Yes	No	No	3.55	354.44	3	1	0

19	No	No	No	No	2.26	232.24	4	0	0
20	Yes	Yes	No	No	3	323.35	4	1	0
21	Yes	Yes	No	No	3.3	355.43	4	1	0
22	No	No	No	No	2.84	325.32	5	1	0
23	No	No	No	No	3.07	355.34	6	1	0
24	No	No	No	No	2.08	325.31	6	2	0
25	No	No	No	No	3.06	339.34	5	1	0
26	No	No	No	No	2.67	355.34	6	2	0
27	No	No	No	No	2.31	304.25	8	1	0
28	No	No	No	No	2.17	275.26	6	2	0
29	No	No	No	Yes	2.83	289.29	6	1	0
31	No	No	No	No	2.68	271.31	3	1	0
32	No	No	No	No	2.59	325.28	6	1	0
33	No	No	No	Yes	0	265.29	7	4	0
34	No	No	No	Yes	0	281.29	8	4	0
35	No	No	No	No	-3.58	265.29	7	3	0
36	No	No	No	No	2.41	224.21	5	0	0
37	No	No	Yes	Yes	2.68	235.28	4	0	0
38	No	No	Yes	No	2.62	249.31	4	0	0
39	No	No	No	No	3.04	279.33	5	0	0
40	No	No	No	No	2.63	278.35	5	1	0
41	No	No	No	No	2.58	245.27	3	0	0
42	No	No	No	No	2.59	266.29	6	2	0
43	No	No	No	No	2.73	280.32	6	1	0
44	No	No	No	No	2.45	264.32	5	2	0
45	No	No	No	No	2.38	285.29	5	1	0
46	No	No	No	No	3.2	337.29	7	0	0
47	No	No	No	No	3.22	311.37	4	0	0
48	No	No	No	No	2.11	308.29	7	0	0
49	No	No	No	No	2.88	303.74	4	0	0
50	No	No	No	No	3.08	299.32	5	0	0
51	No	No	No	No	2.07	292.24	6	1	0
52	No	No	Yes	No	2.59	301.29	5	1	0
53	No	No	Yes	No	2.87	264.32	5	1	0
54	No	No	No	No	3.19	278.35	5	0	0
55	No	No	No	No	3.47	294.35	6	0	0
56	No	No	Yes	Yes	3.58	374.65	3	1	1
57	No	No	No	No	3.34	319.78	4	1	0
58	No	No	No	No	2.67	311.34	4	1	0
59	No	No	No	No	2.14	302.28	5	1	0
60	No	No	No	No	2.11	259.26	5	1	0
61	No	No	No	Yes	2.24	285.29	5	1	0
62	Yes	Yes	No	No	3.12	326.39	3	1	0
63	No	No	Yes	No	2.06	285.29	4	1	0

64	Yes	Yes	Yes	Yes	2.65	327.55	5	0	0
65	No	No	No	No	2.9	316.37	3	1	0
66	No	No	No	No	2.77	314.38	4	1	0
67	Yes	Yes	Yes	Yes	2.53	286.33	3	2	0
68	No	No	No	No	2.37	296.32	4	1	0
69	No	No	No	Yes	3.17	338.71	6	0	0
70	No	No	No	No	3.31	330.33	6	0	0
71	No	No	No	No	2.79	345.3	7	0	0
72	No	No	No	No	3.45	314.33	5	0	0
73	No	No	No	No	2.64	287.27	6	0	0
74	No	No	No	No	3.34	369.37	7	0	0
75	No	No	No	No	2.44	307.3	7	0	0
76	No	No	No	No	3.68	351.39	7	1	0
77	No	No	Yes	No	3.14	295.33	6	0	0
78	No	No	No	No	3.06	364.78	7	1	0
79	No	No	Yes	No	3.45	350.41	6	0	0
80	No	No	No	No	1.91	245.23	5	1	0

Molecular Docking Studies

The structural quality of VCAM 1 was validated via Ramachandran plot analysis (Fig. I), with over 82% of residues, respectively, in the most favoured regions. Active sites were predicted and are summarized in Table III and their structure summarized in Table IV. Ligands with favourable ADMET profiles were docked against both targets, with atorvastatin serving as the reference compound. Binding energies ranged from –5.66 to –8.02 kcal/mol for VCAM1 indicating strong target affinity.

Table 3: Binding Score of Ligands.

S. No	Ligand	Docking Score
1	YK8	-7.66
2	YK16	-6.35
3	YK23	-6.91
4	YK24	-6.98
5	YK26	-7.85
6	YK27	-6.71
7	YK28	-7.17
8	YK35	-7.01
9	YK40	-6.47
10	YK42	-5.66
11	YK43	-7.39
12	YK48	-8.02
13	YK51	-6.71
14	YK55	-6.98
15	YK59	-6.48
16	YK60	-7.01
17	YK66	-7.11
18	YK71	-7.8

19	YK74	-7.02
20	YK75	-6.74
21	YK76	-6.62
22	YK78	-6.87
23	atorvastatin	-4.83

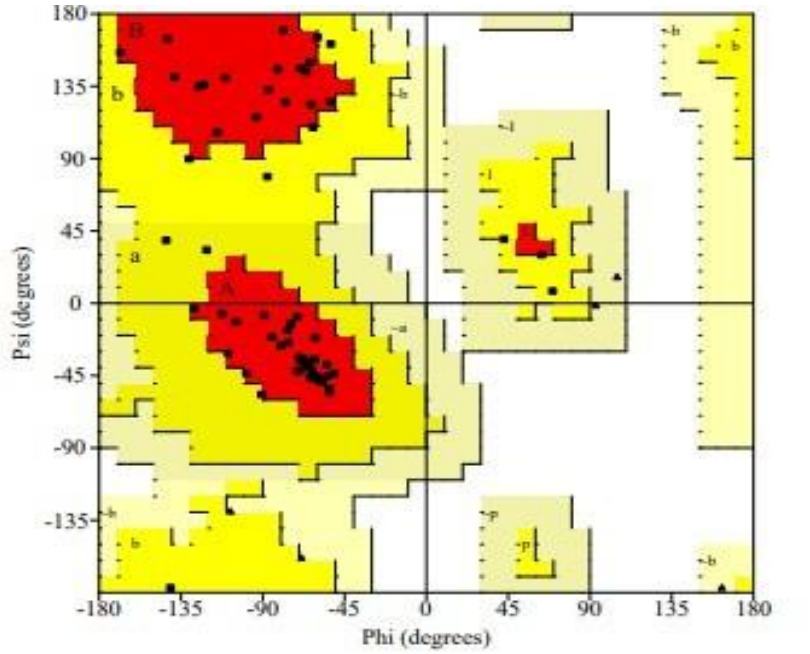

Figure 1: Ramachandran Plot For VCAM-1.

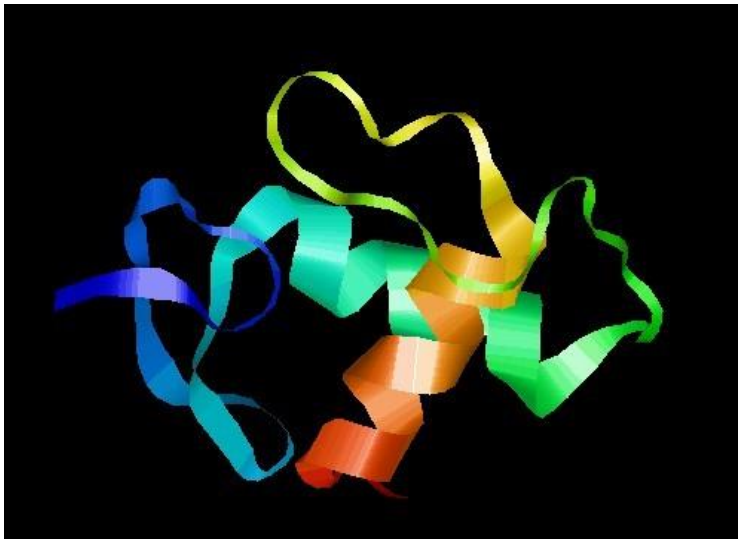

Figure 2: 3D Structure of Protein by Rasmol Tool.

Best predicted binding cavity for Molecular docking:

VCAM-1: 18,-23,0 (x,y,z)

Interaction Visualization

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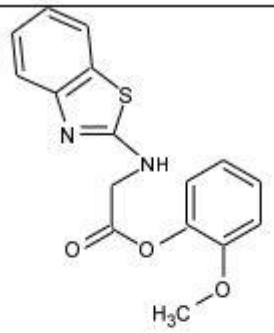
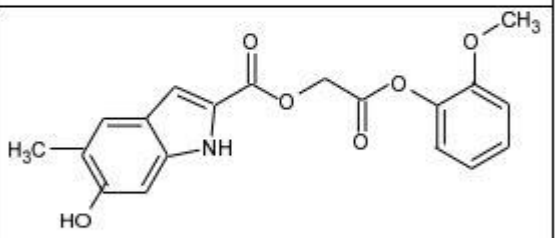
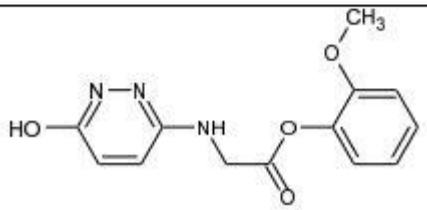
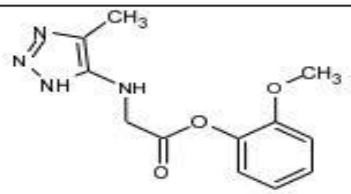
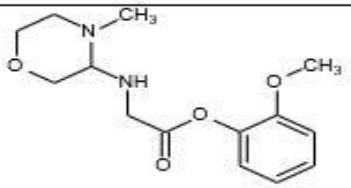
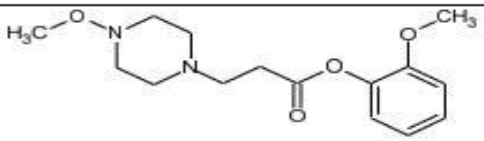
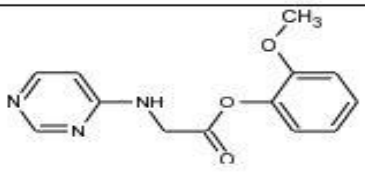
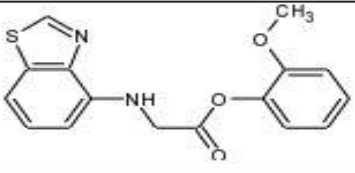
Ligand–receptor complexes were visualized to examine binding modes. Key interacting residues, interaction types, and spatial configurations were analysed to better understand binding mechanisms. The results are compiled in Table V

Table 4: Chemical Structure of Top-Performing Ligands Based on Docking Scores.

Ligand No.	Structure
YK8	
YK26	
YK28	
YK35	
YK43	
YK55	
YK60	
YK66	

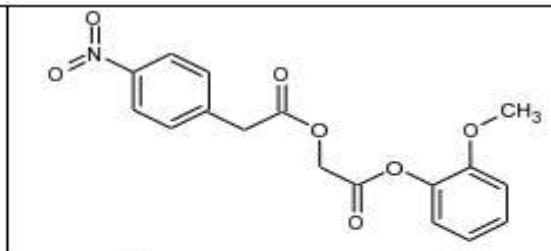
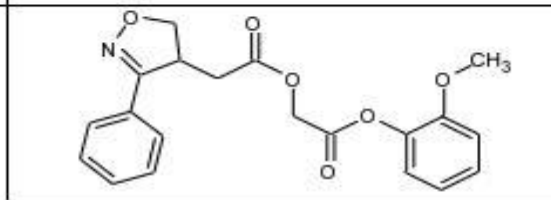
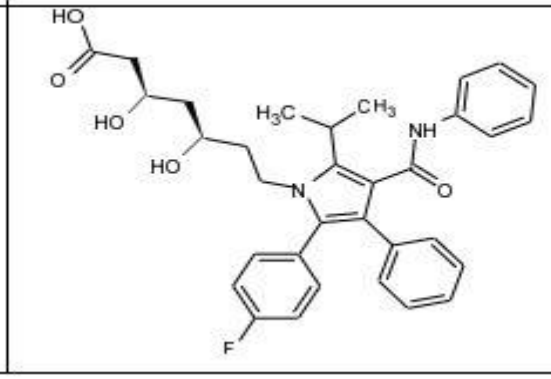
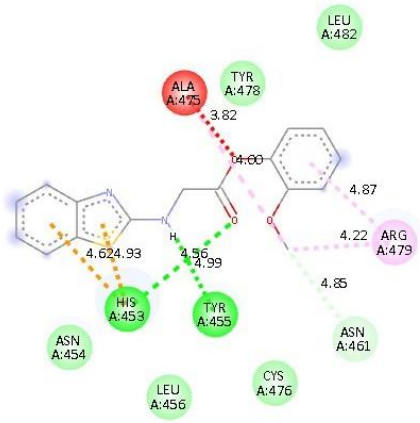
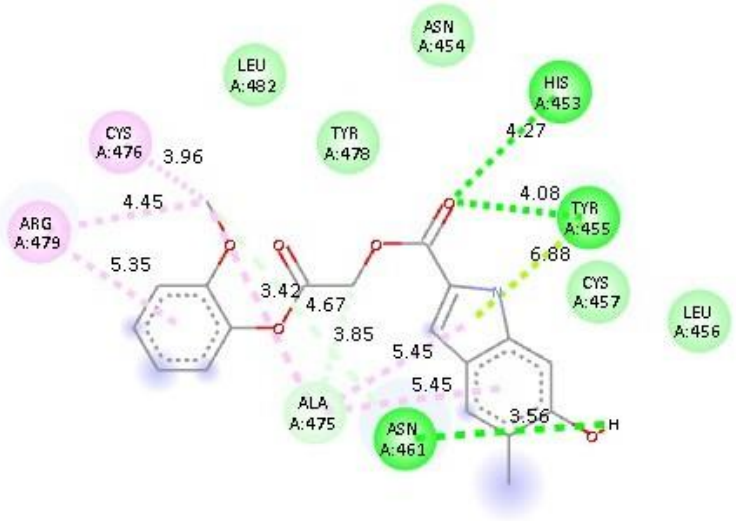
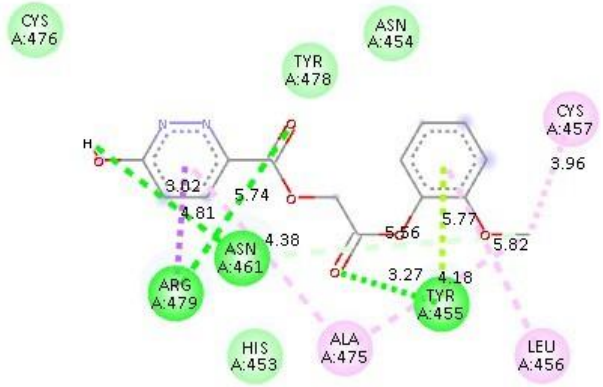
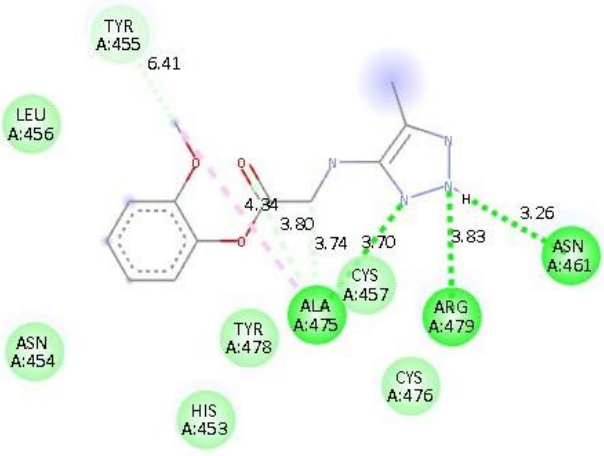
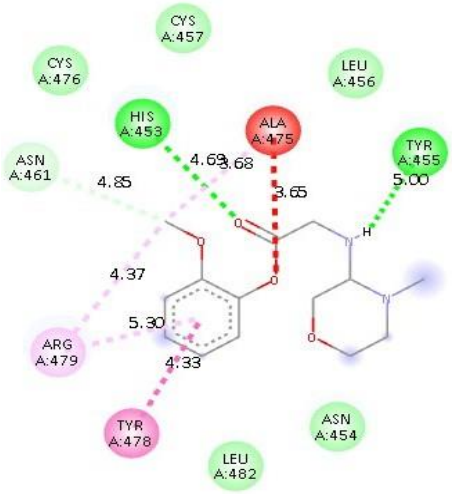
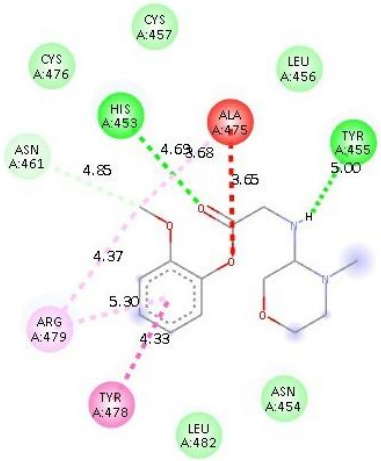
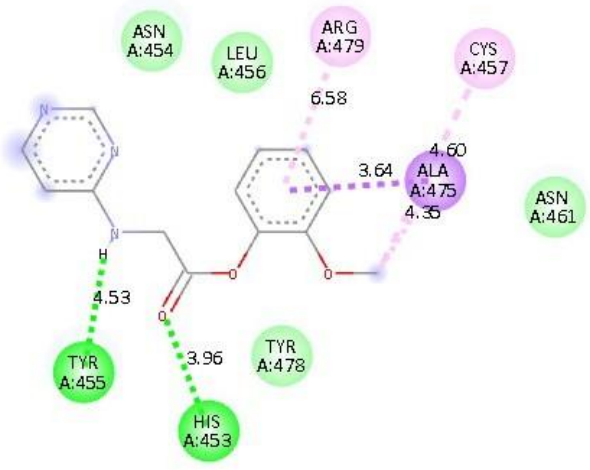
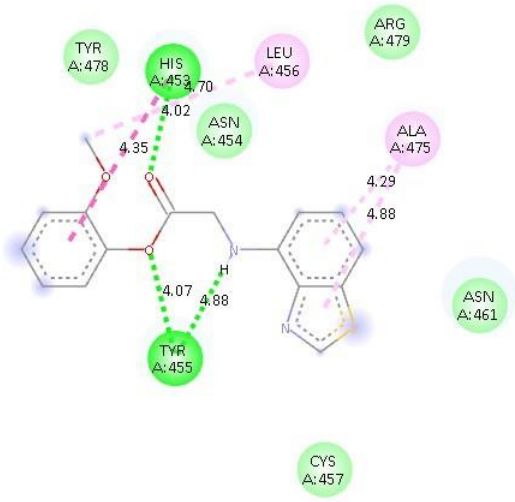
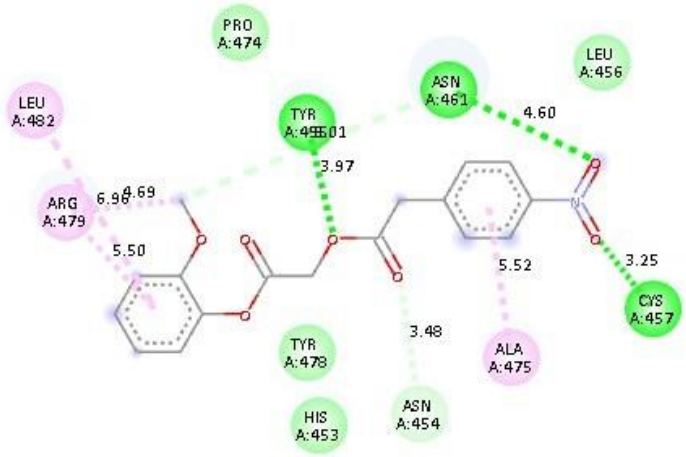
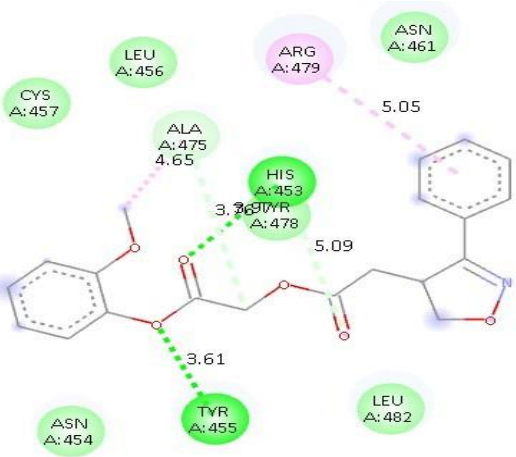
YK71	
YK74	
Atorvastatin	

Table 5: Visualization Of Ligand Receptor Interactions

Ligand No.	VCAM(5AV0)
YK8	

YK26	
YK28	
YK35	

YK43	
YK55	
YK60	

YK66	
YK71	
YK74	

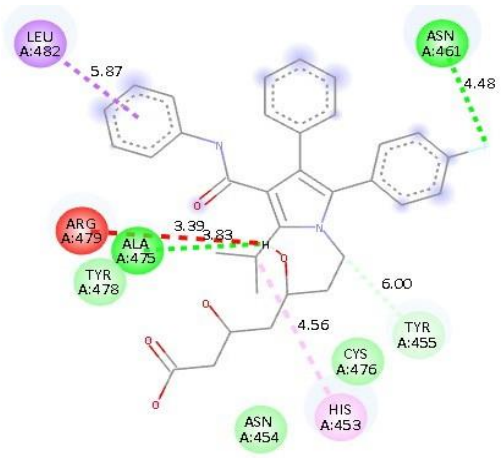
Atorvastatin	

Table 6: Ligand-Receptor Binding.

Ligand Code	VCAM1
YK8	Tyr455
YK26	Tyr455,Asn461
YK28	Tyr455,Asn461
YK35	Asn461,Arg479
YK43	Tyr455
YK55	Ala475,Cys457
YK60	Tyr455,His453
YK66	Tyr455, His453
YK71	Tyr455, His453, Cys457, Ala475, Asn461
YK74	Tyr455, His453
Atorvastatin	Ala475

Conclusion

This study successfully designed a structurally diverse library of 2-methoxyphenyl anilinoacetate derivatives, strategically modified to enhance pharmacological potential against vascular cell adhesion molecule-1 (VCAM-1), a key player in the progression of atherosclerosis. Through the integration of electron-donating and electron-withdrawing substituents, as well as various heterocyclic moieties, the synthesized compounds demonstrated favourable drug-likeness, non- toxic ADMET profiles, and strong binding affinities in molecular docking studies. Notably, several compounds outperformed the reference drug atorvastatin in docking scores against VCAM-1, indicating potential as lead candidates for therapeutic intervention in vascular inflammation and plaque development. These findings highlight the promise of these novel derivatives as scaffolds for further

optimization and biological evaluation in the search for targeted anti-atherosclerotic agents.

Author Contributions

All authors contributed equally to this research. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

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Ethical Approvals

This study does not involve experiments on animals or human subjects.

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