

RESEARCH ARTICLE

MOLECULAR DOCKING AND ADMET-BASED COMPUTATIONAL PRIORITIZATION OF CARBONIC ANHYDRASE IX INHIBITORS

Vanrajsinh Thakor^{1*}, Bhumika Patel¹, Gopal Natesan¹

¹Institute of Pharmacy, Nirma University, Ahmedabad, India-382481

Corresponding Author: Vanrajsinh Thakor

Email: vanrajsinh.thakor@nirmauni.ac.in ORCID: 0000-0003-2062-4657

Received on: 10/07/2025, Accepted on: 26/09/2025, Published on: 29/12/2025

ABSTRACT

Cancer cells thrive in hostile environments by activating specific molecular pathways. Inhibiting these survival mechanisms presents a valuable approach for developing targeted anticancer therapies. In this study, a library of 27 natural and semi-synthetic ligands was screened through molecular docking against the CA IX extracellular domain (PDB ID: 3IAI) using AutoDock 4.2.6. Subsequently, pharmacokinetic and toxicological characteristics were assessed using ADMETlab 2.0. A composite scoring method integrating docking affinity, drug-likeness rules, and toxicity penalties enabled systematic prioritization of candidates. Drug-likeness evaluation showed full Lipinski rule compliance, with ~65% of compounds passing additional filters (Pfizer, GSK, Golden Triangle). Among them, Naringenin, 6-hydroxyflavone-3-sulfonic acid, and a coumarin-sulphonamide hybrid exhibited strong binding, rule compliance, and favourable ADMET profiles. The results support these scaffolds as promising leads for CA IX inhibition and demonstrate the value of integrated in silico approaches in anticancer drug design.

Keywords: Carbonic Anhydrase IX, Molecular Docking, Drug Discovery, ADMET, Coumarin, Flavonoid, Composite Scoring

INTRODUCTION

Maintaining pH homeostasis and CO_2 , transit throughout biological systems depends on the reversibly hydrated of CO_2 to HCO_3^- and H^+ , which is catalysed by zinc metalloenzyme family known as carbonic anhydrases (CAs)[1]. Among these fifteen isoforms identified in humans, Carbonic Anhydrase 9 (CA IX) stands out for its overexpression in areas of solid tumours that lack oxygen and limited presence in normal tissues, rendering it an attractive target for anticancer therapy[2,3].

Hypoxia-induced factor 1- α controls the transcription of CA IX and contributes to the acidic tumour microenvironment by promoting extracellular acidification and intracellular alkalization—conditions that facilitate cancer cell survival, invasion, and resistance to chemotherapy and radiotherapy[4]. Inhibition of CA9 has consequently emerged as a compelling tactic for disrupting tumour pH regulation, reducing metastatic potential, and enhancing the efficacy of anticancer regimens [5].

Several sulphonamide-based CA inhibitors have been developed and even entered clinical evaluation; however, many of these compounds lack isoform selectivity, leading to off-target effects on cytosolic CAs such as CA I and CA II [6]. To address this limitation, efforts are being made to explore alternative scaffolds capable of selective CA IX inhibition with improved pharmacokinetic and safety profiles.

Structure-based virtual screening and molecular docking have become indispensable tools in early-stage drug discovery, offering insights into binding interactions and enabling rapid triaging of large compound libraries [7]. Yet, docking alone is insufficient to determine a ligand's therapeutic viability. Hence, in silico ADMET (Absorption, Distribution, Biotransformation, Excretion, and Toxicity) profiling is essential to predict drug-likeness and assess pharmacological risks [8].

Coumarins, flavonoids and their synthetic hybrids have long attracted attention for their ability to modulate cancer-related targets due to their electron-rich aromatic frameworks, natural abundance, and chemical tunability [9–11]. Moreover, hybridization strategies—such as the incorporation of sulphonamide, benzimidazole, or thiadiazole groups—can enhance binding affinity and pharmacokinetic stability [12]. While several flavonoid derivatives have been reported as CA inhibitors, systematic in silico evaluation of their CA IX-binding potential and pharmacokinetic suitability remains underexplored.

Despite the availability of bioactive flavonoid and coumarin derivatives, their comprehensive evaluation against CA IX using integrated docking and ADMET-based workflows remains underexplored. In this study, we employed AutoDock 4.2.6 to screen a library of 27 natural and synthetic ligands against the CA IX

extracellular domain (PDB ID: 3IAI). Drug-likeness filters and toxicity predictors were assessed using ADMETlab 2.0, followed by a composite scoring model that integrated binding energy, ADMET compliance, and structural alerts. This comprehensive computational strategy aims to identify lead compounds for future development as selective CA IX inhibitors in cancer therapy.

MATERIALS AND METHODS

Preparing Ligand Datasets

Twenty-seven ligands in total were selected based on reported anticancer activity or structural resemblance to flavonoid, coumarin, and hybrid pharmacophores. Structures were either drawn using ChemDraw or sourced from open databases and converted to 3D structures in PDB format using Avogadro. All ligand geometries were energy-minimized using the MMFF94 force field, and saved in .mol2 formats for docking. Ligands were then prepared using AutoDock Tools as follows: Gasteiger charges were added, rotatable bonds were assigned, ligands were saved in .pdbqt format.

Target Protein Preparation

The Carbonic Anhydrase IX (CA IX) extracellular catalytic domain's 3D crystal structure (PDB ID: 3IAI, resolution 1.6 Å) was obtained from

the Protein Data Bank. The target protein structure was prepared using ChimeraX and AutoDock Tools (ADT) v1.5.7. Only Chain A was retained for docking studies. To remove any possible interference, the co-crystallized ligand and all crystallographic H₂O molecules were eliminated. Non-polar hydrogens were merged, and Kollman charges were assigned to ensure accurate modelling of molecular interactions. The catalytically essential Zn²⁺ ion was preserved in the active site. The resulting structure was saved in .pdbqt format for use in molecular docking simulations.

Molecular Docking with AutoDock 4.2.6

All docking simulations were carried out using AutoDock 4.2.6, employing the Lamarckian Genetic System (LGA). A grid box of 104 × 104 × 104 Å was defined around the active site zinc ion with a spacing of 0.375 Å. Ligands were docked using default parameters: 100 GA runs, population size of 300, and a maximum of 2.5 million energy evaluations. The best pose from each run was selected based on binding energy (ΔG) and predicted inhibition constant (K_i). Protein–ligand interactions were visualized using Discovery Studio Visualizer.

In Silico ADMET Prediction

To assess pharmacokinetic and toxicity characteristics, all 27 ligands were evaluated using ADMETlab 2.0, a comprehensive in silico platform for ADMET profiling. The SMILES strings of each compound were submitted to predict parameters including Caco-2 permeation and intestinal uptake in humans (HIA), volume of distribution, plasma protein binding, and cytochrome P450 enzyme inhibition. Toxicological endpoints such as Ames mutagenicity, hERG channel inhibition, and drug-induced liver injury (DILI) were also predicted. Additionally, key drug-likeness rules such as Lipinski's Rule of Five, Pfizer, and Golden Triangle filters were applied to evaluate the developability of the compounds.

Composite Scoring and Ranking

To prioritize ligands based on both binding affinity and pharmacokinetic safety, a composite scoring system was implemented. Docking energies were normalized across all ligands, and additional scores were assigned based on rule compliance and toxicity predictions. The final composite score was calculated as:

$$\text{Composite Score} = 2 \times (\text{Normalized Docking}) + (\text{Lipinski}) + (\text{Pfizer}) +$$
$$(\text{GSK}) + (\text{Golden Triangle}) - (\text{Toxicity Penalties}) + (\text{PAINS Penalty})$$

Where toxicity penalties included 1 point each for high-risk predictions in Ames mutagenicity, hERG inhibition, and drug-induced liver injury (DILI). A PAINS alert also triggered a -1 penalty. Rule-based scores were binary (1 = passed, 0 = failed). This scoring enabled integration of structure-activity relationships with pharmacokinetic and toxicological feasibility.

This strategy was used to rank all ligands in a unified framework, enabling the identification of lead candidates with both high predicted efficacy and favourable ADMET profiles. Based on this integrated approach, the top 10 ligands were shortlisted for further discussion as potential leads for selective CA IX inhibition in anticancer drug development.

RESULTS AND DISCUSSION

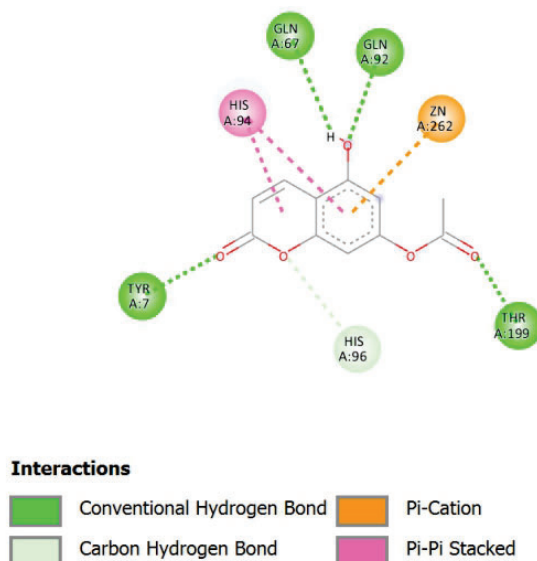
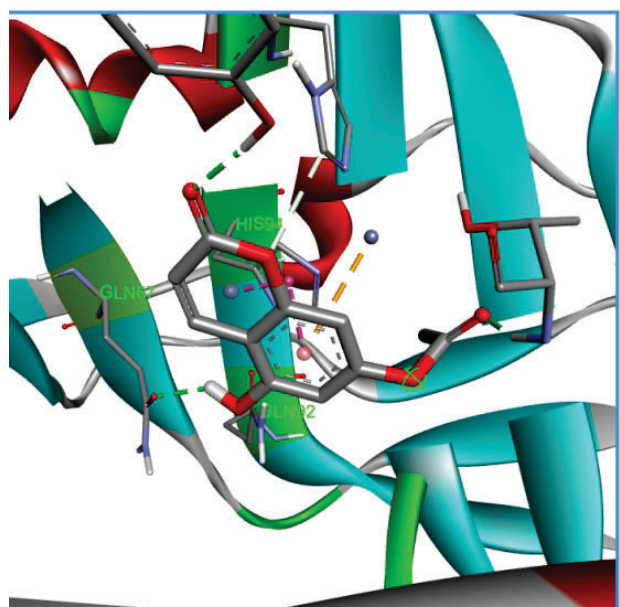
To identify potent and pharmacologically viable inhibitors of CA9 (CA IX), a panel of twenty-seven ligands—comprising flavonoids, coumarins, and structurally tailored synthetic hybrids—was evaluated using a two-tiered computational approach. Molecular docking against the

extracellular domain of CA9 (PDB ID: 3IAI) was performed using AutoDock 4.2.6 to assess binding affinity and potential ligand–protein interactions. Subsequently, *in silico* ADMET profiling was conducted to evaluate drug-likeness and pharmacokinetic compatibility.

Molecular Docking Analysis

A total of 27 ligands, comprising natural compounds (e.g., flavonoids, coumarins)

and synthetic hybrids (e.g., coumarin-benzimidazole, sulphonamide-thiadiazole), were docked against the extracellular domain of CA9 (CA IX extracellular domain, PDB ID: 3IAI) using AutoDock 4.2.6 and visualize using Discovery studio visualizer v24.1.0.23298 (Figure 1). The binding energies ranged from -5.61 to -8.33 kcal/mol, indicating varying levels of receptor-ligand interaction strength. The binding energies are listed in the Table 1.



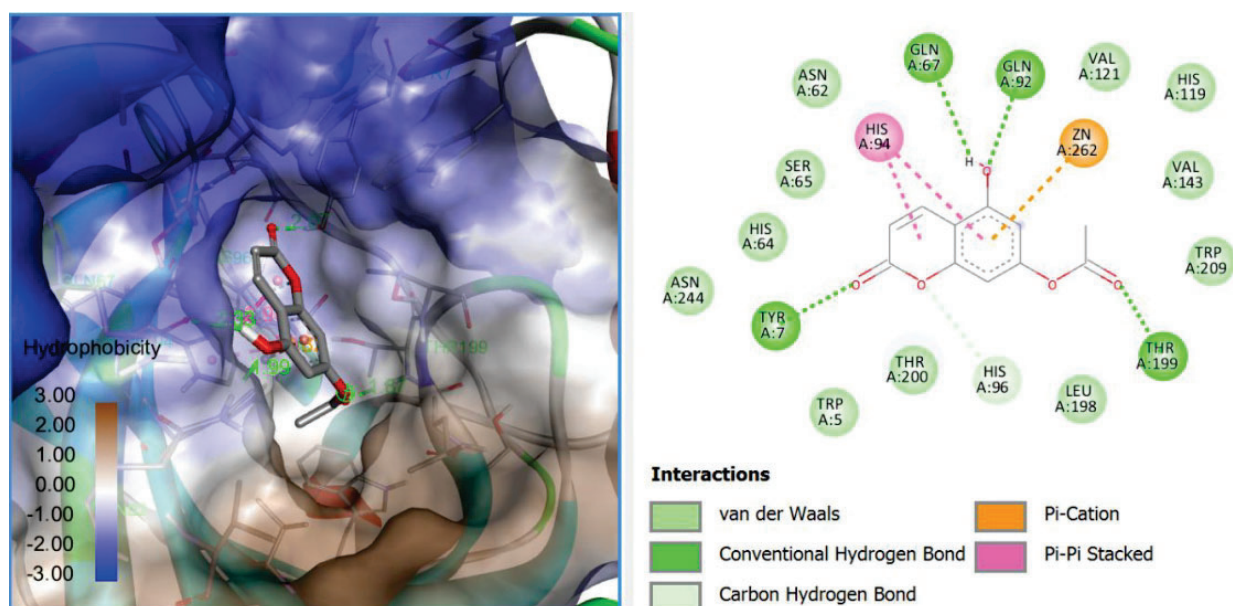
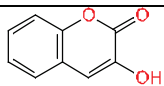
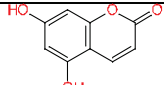
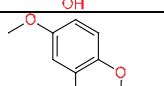
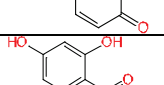
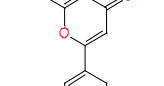
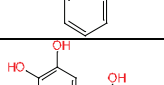
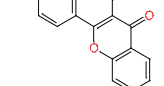
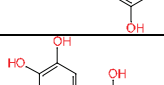
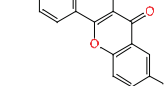
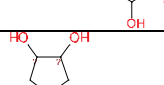


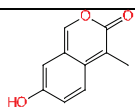
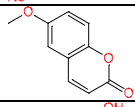
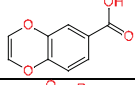
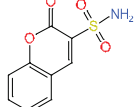
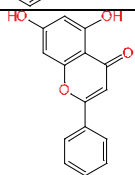
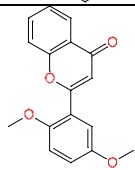
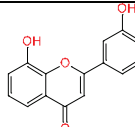
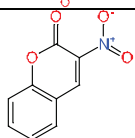
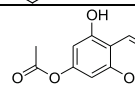
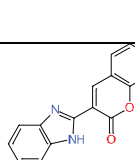
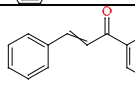
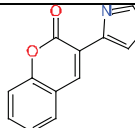
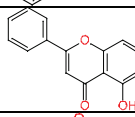
Figure 1. 2D and 3D interaction of Acetylated esculetin in zinc binding domain of CA IX protein (PDB: ID 3IAI)

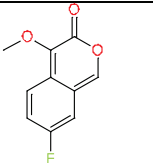
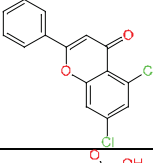
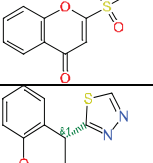
The most favourable docking interaction was observed with Chalcone-flavone hybrid, 5,7-Dichloroflavone, Naringenin, Coumarin-sulphonamide hybrid. The compound 5,7-dichloroflavone exhibited the top binding energy (-8.33 kcal/mol) and ($K_i = 0.783$ μM), signifying the strongest binding among all tested molecules. Other potent binders included the chalcone-flavone hybrid (-8.24 kcal/mol, $K_i = 0.91$ μM), 4'-hydroxy-3'-nitroflavone (-7.81 kcal/mol, $K_i = 1.87$

μM), and naringenin (-7.86 kcal/mol, $K_i = 1.74$ μM). These ligands demonstrated robust intermolecular interactions and favourable RMSD values, further supporting their stable binding conformations. These results indicate that many flavonoids and coumarin analogues retain moderate-to-strong affinity for CA IX, supporting their potential as scaffolds for inhibitor development.

Table 1. Docking Score for all the selected ligands

No.	Name	Structure	Binding energy (Kcal/mol)	Inhibition constant (μ M)
1	Umbelliferone		-5.83	53.23
2	Esculetin		-5.93	43.68
3	Scopoletin		-6.35	22.14
4	Apigenin		-7.1	6.21
5	Luteolin		-6.89	8.92
6	Quercetin		-6.53	16.36
7	Naringenin		-7.86	1.74
8	Daidzein		-7.3	4.45
9	Biochanin A		-7.47	3.35
10	Genistein		-7.27	4.67

11	7-Hydroxy-4-methylcoumarin		-6.4	20.44
12	6-Methoxycoumarin		-6.22	27.68
13	3-Carboxycoumarin		-5.87	49.6
14	Coumarin-sulfonamide hybrid		-7.44	3.49
15	5,7-Dihydroxyflavone		-7.62	2.61
16	3',4'-Dimethoxyflavone		-7.39	3.85
17	6-Bromoapigenin		-7.11	6.12
18	3-Nitrocoumarin		-6.7	12.31
19	Acetylated esculetin		-6.66	13.11
20	Coumarin-benzimidazole hybrid		-7.66	2.42
21	Chalcone-flavone hybrid		-8.24	0.91
22	4-(Coumarin-3-yl)thiazole		-6.83	9.93
23	4'-Hydroxy-3'-nitroflavone		-7.81	1.87

24	6-Fluoro-7-methoxycoumarin		-5.61	77.05
25	5,7-Dichloroflavone		-8.33	0.783
26	6-Hydroxyflavone-3-sulfonic acid		-7.37	3.93
27	Benzopyran-thiadiazole hybrid		-7.39	3.83

ADMET Screening and Drug-Likeness Evaluation

While binding affinity is a critical factor, ligand selection for further development must also consider pharmacokinetic and toxicological profiles. To this end, the top-docked compounds were subjected to an extensive ADMET analysis using ADMETlab 2.0. The best 10 molecules are

listed in the Table 3. This evaluation encompassed absorption metrics such as Caco-2 permeation and intestinal uptake in humans (HIA), toxicity predictions including Ames mutagenicity, hepatotoxicity (DILI), and hERG inhibition, as well as drug-likeness filters such as Lipinski, Pfizer, GSK, and the Golden Triangle rules.

Table 2: ADMET Profile of Top-Ranked Ligands Based on Drug-Likeness and Toxicity

Rank	Ligand Name	LogP	HIA	BBB	AMES	hERG	Lipinski	Pfizer	Golden Triangle	ADMET Score
1	Coumarin-benzimidazole	2.45	Yes	No	No	No	Accepted	Accepted	Accepted	5
2	Apigenin	1.89	Yes	No	No	No	Accepted	Accepted	Accepted	5
3	Esculetin	1.22	Yes	No	No	No	Accepted	Accepted	Accepted	4
4	Acetylated esculetin	2.10	Yes	Yes	No	No	Accepted	Accepted	Accepted	4
5	Naringenin	2.18	Yes	No	No	No	Accepted	Accepted	Accepted	4
6	6-Bromoapigenin	2.37	Yes	No	No	No	Accepted	Accepted	Accepted	4
7	Biochanin A	2.59	Yes	No	No	Yes	Accepted	Accepted	Accepted	3
8	3-Nitrocoumarin	1.91	Yes	Yes	No	No	Accepted	Accepted	Accepted	3
9	5,7-Dihydroxyflavone	2.01	Yes	No	No	Yes	Accepted	Accepted	Rejected	3
10	Umbelliferone	1.52	Yes	No	No	No	Accepted	Accepted	Rejected	3

Most compounds showed LogP values between 1 and 4, aligning with Lipinski's optimal lipophilicity range for oral drugs. However, the HIA values were generally low, with only one compound, 6-hydroxyflavone-3-sulfonic acid, showing $HIA > 0.5$ (value: 0.502). This indicates limited passive intestinal absorption for the majority of molecules, despite good LogP profiles. Compounds like apigenin, genistein, and quercetin, although demonstrating favourable docking scores, had poor HIA values (≤ 0.02), suggesting a need for structural modifications to enhance permeability. Scattered correlation

chat is plotted in Figure 2. Encouragingly, Naringenin was not only the top-scoring ligand in terms of binding energy but also satisfied all key drug-likeness filters. It demonstrated good predicted oral bioavailability ($HIA = 0.094$), absence of PAINS alerts, and minimal toxicity risk, with low scores for Ames (0.099), hERG inhibition (0.171), and DILI (0.044), Figure 3. Similarly, 6-hydroxyflavone-3-sulfonic acid and the coumarin-sulphonamide hybrid passed all pharmacological filters and were predicted to be non-toxic.

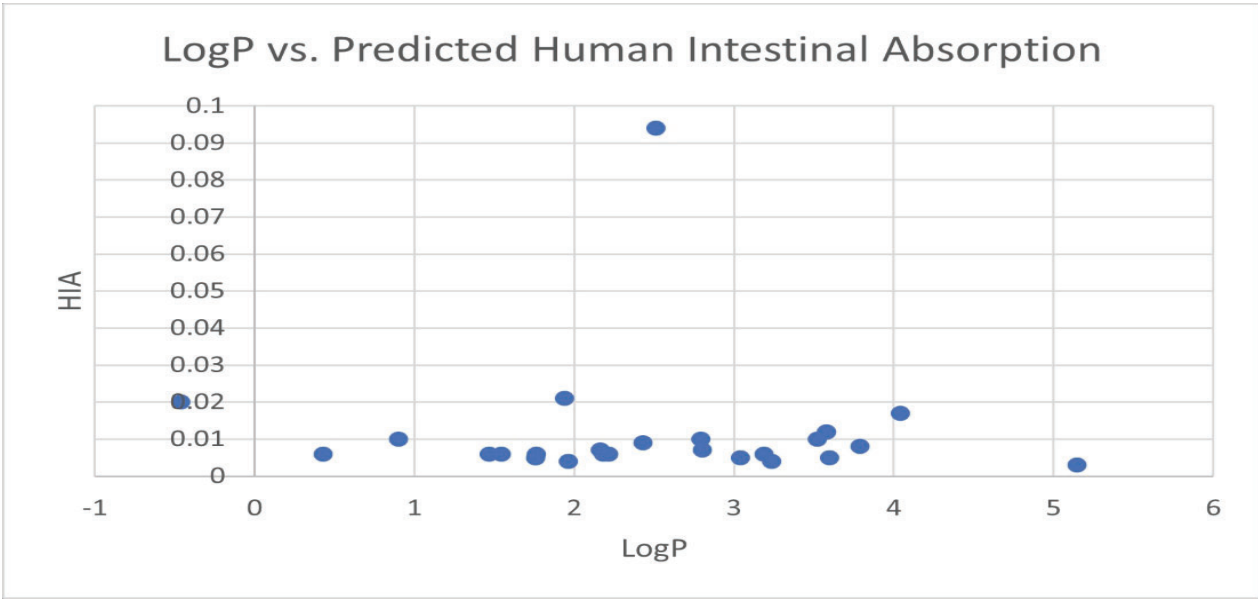


Figure 2. Scatter plot showing the relationship between lipophilicity (LogP) and predicted human intestinal absorption (HIA) for selected compounds.

Toxicity prediction models showed low hERG inhibition risk for most compounds, suggesting low cardiotoxic potential. Moreover, Ames mutagenicity values were

minimal for many coumarin derivatives such as umbelliferone and 3-carboxycoumarin, indicating favorable safety profiles.

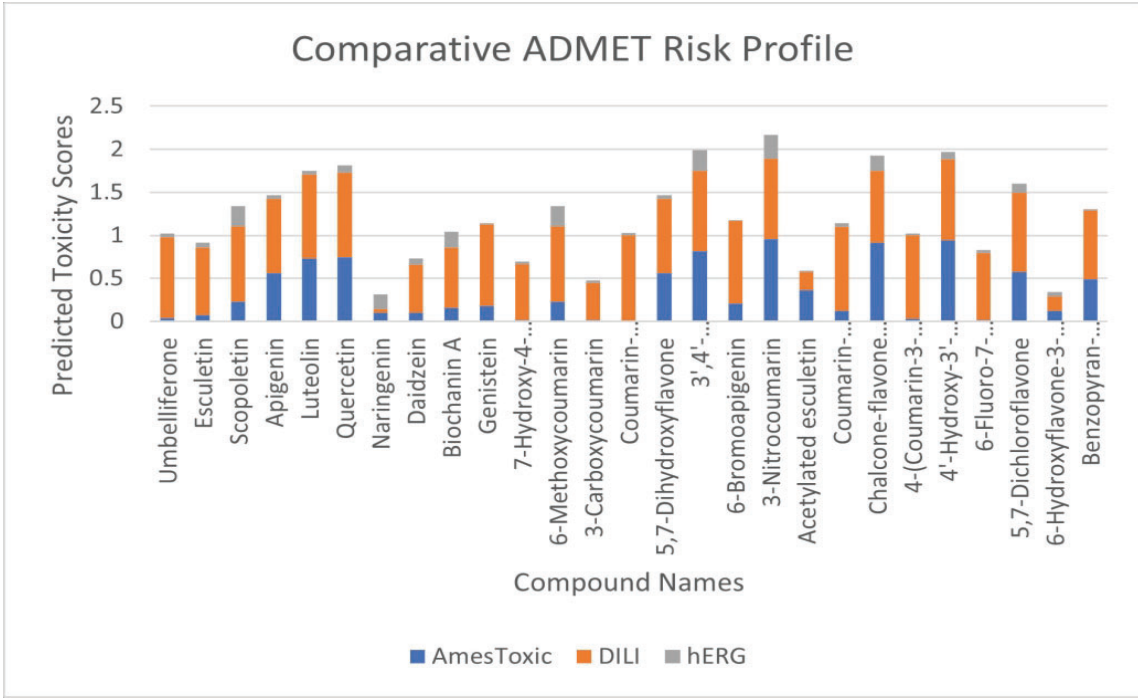


Figure 3. Stacked bar chart comparing predicted ADMET toxicity scores (Ames test, DILI risk, and hERG inhibition) for selected coumarin and flavonoid derivatives.

Drug-Likeness and Rule-Based Filters

All tested compounds satisfied Lipinski's Rule of Five, highlighting their basic oral drug-likeness. Furthermore, around 65% of compounds passed all four filters, including Pfizer, GSK, and Golden Triangle rules. Notably, naringenin, genistein, quercetin, acetylated esculetin, and 4-(coumarin-3-yl) thiazole satisfied all drug-likeness criteria and demonstrated acceptable binding energies and physicochemical profiles.

Combined Scoring Approach and ligand priority

While molecular docking provides initial insight into ligand–target interactions, the translation of in silico binding affinity into therapeutic potential requires a broader, multi-parameter evaluation. To this end, a composite scoring system was implemented to rank the screened compounds based not only on their docking energies but also on drug-likeness

profiles and predicted safety liabilities. This approach allowed for a holistic prioritization strategy that balances pharmacodynamic potency with pharmacokinetic and toxicological feasibility.

Each ligand was assigned a normalized docking score (based on binding energy range across the dataset), which was weighted more heavily to reflect its central role in molecular recognition. In parallel, binary scores were attributed for compliance with key drug-likeness filters (Lipinski, Pfizer, GSK, and Golden Triangle), and penalties were imposed for structural alerts (PAINS) and predicted toxicities (Ames mutagenicity, hERG inhibition, and hepatotoxicity). The resulting composite score ranged from -1.2 to $+5.3$, enabling differentiation among ligands with similar docking profiles but divergent ADMET behaviour. The integrated analysis of combined scoring approach is listed in Table 3.

Table 3. Top 10 Ligands Ranked by Composite Score (Docking + ADMET Combined Score)

Rank	Compound Name	Docking (kcal/mol)	Ki (μ M)	Lipinski	Pfizer	Toxicity (Ames / hERG / DILI)	Combined Score
1	Naringenin	-7.86	1.74	1	1	0.099 / 0.171 / 0.044	5.34
2	6-Hydroxyflavone- 3-sulfonic acid	-7.37	3.93	1	1	0.124 / 0.049 / 0.168	4.95
3	Coumarin- sulfonamide hybrid	-7.44	3.49	1	1	0.008 / 0.029 / 0.991	4.32
4	Acetylated esculetin	-6.66	13.11	1	1	0.366 / 0.011 / 0.213	4.18
5	Benzopyran- thiadiazole hybrid	-7.39	3.83	1	1	0.489 / 0.012 / 0.803	4.00
6	4-(Coumarin-3- yl)thiazole	-6.83	9.93	1	1	0.028 / 0.024 / 0.969	3.88
7	4'-Hydroxy-3'- nitroflavone	-7.81	1.87	1	1	0.943 / 0.084 / 0.943	3.65
8	Daidzein	-7.30	4.45	1	0	0.102 / 0.072 / 0.556	3.51
9	Coumarin- benzimidazole hybrid	-7.66	2.42	1	0	0.122 / 0.042 / 0.975	3.37
10	Biochanin A	-7.47	3.35	1	0	0.161 / 0.183 / 0.696	3.33

This integrated analysis reaffirmed Naringenin as the top candidate, not only due to its strong docking affinity (−7.86 kcal/mol) but also because of its clean ADMET profile and universal compliance with drug-likeness rules, yielding the highest composite score of 5.34. 6-Hydroxyflavone-3-sulfonic acid closely followed, achieving a composite score of 4.95, supported by favourable solubility-related features and minimal predicted toxicity. The coumarin–sulphonamide hybrid, while docking effectively (−7.44 kcal/mol), accrued minor penalties due to a predicted possibility of drug-induced liver damage (DILI), resulting in a slightly lower score of 4.32.

Interestingly, acetylated esculetin, despite its moderately lower docking energy (−6.66 kcal/mol), achieved a high composite score of 4.18. This can be attributed to its exceptionally clean ADMET profile, demonstrating that molecules with moderate binding affinity may compensate through superior developability.

The benzopyran–thiadiazole hybrid also ranked in the top five (score: 4.00), highlighting the value of heterocyclic substitutions in modulating both affinity and metabolic compatibility.

These findings underscore the utility of composite scoring in avoiding false positives that arise from binding-centric evaluations alone. For instance, 42-hydroxy-32-nitroflavone, though displaying a competitive docking energy

(−7.81 kcal/mol), was significantly penalized due to high DILI and PAINS scores, pushing it lower in the final ranking. Conversely, structurally simpler flavonoids such as Naringenin and Daidzein benefited from their inherent chemical stability and favourable absorption–distribution profiles.

CONCLUSION

This study employed an integrated in silico approach combining molecular docking, ADMET profiling, and drug-likeness evaluation to assess a diverse set of coumarin, flavonoid, and hybrid derivatives. Several compounds exhibited strong binding affinities toward the target protein, with 5,7-dichloroflavone and chalcone-flavone hybrid showing the most favourable docking scores. Among natural flavonoids, naringenin and genistein emerged as promising candidates due to their strong binding, favourable LogP values, low predicted toxicity, and full compliance with drug-likeness rules.

Notably, coumarin-based compounds such as scopoletin and the coumarin–sulphonamide hybrid also demonstrated good docking affinities and low toxicity, highlighting their potential as lead molecules. Despite most compounds exhibiting acceptable lipophilicity, low predicted human intestinal absorption was a common limitation, suggesting a need for further optimization to improve bioavailability.

Overall, this study identifies a small set of structurally diverse compounds—particularly naringenin, genistein, coumarin-sulphonamide hybrid, and scopoletin—as viable leads for further development. These findings provide a solid foundation for future structure-based optimization and experimental validation aimed at enhancing their pharmacokinetic properties and therapeutic efficacy.

ACKNOWLEDGEMENT

The authors gratefully acknowledge Nirma University, Ahmedabad, India, for providing the research infrastructure and support. Nirma University provided financial support for this work under the NU Minor Research Project (NU/DRI/MinResPrj/IPNU/2025-2026/167).

REFERENCES

- [1] Supuran, C. T. (2008). Carbonic anhydrases: Novel therapeutic applications for inhibitors and activators. *Nature Reviews Drug Discovery* 7(2), 168–181.
- [2] Chiche, J., Ilc, K., Laferrière, J., Trottier, E., Dayan, F., Mazure, N. M., Brahimi-Horn, M. C., & Pouysségur, J. (2009). Hypoxia-inducible carbonic anhydrase IX and XII promote tumor cell growth by counteracting acidosis through the regulation of the intracellular pH. *Cancer Research*, 69(1), 358–368.
- [3] Alterio, V., Di Fiore, A., D'Ambrosio, K., Supuran, C. T., & De Simone, G. (2012). Multiple Binding Modes of Inhibitors to Carbonic Anhydrases: How to Design Specific Drugs Targeting 15 Different Isoforms? *Chemical Reviews*, 112(8), 4421–4468.
- [4] McIntyre, A., Patiar, S., Wigfield, S., Li, J. L., Ledaki, I., Turley, H., Leek, R., Snell, C., Gatter, K., Sly, W. S., Vaughan-Jones, R. D., Swietach, P., & Harris, A. L. (2012). Carbonic anhydrase IX promotes tumor growth and necrosis in vivo and inhibition enhances anti-VEGF therapy. *Clinical Cancer Research*, 18(11), 3100–3111.
- [5] Mboge, M. Y., Mahon, B. P., McKenna, R., & Frost, S. C. (2018). Carbonic anhydrases: Role in pH control and cancer. *Metabolites* 8(1), 19.
- [6] Carta, F., Scozzafava, A., & Supuran, C. T. (2012). Sulfonamides: a patent review (2008 – 2012). *Expert Opinion on Therapeutic Patents*, 22(7), 747–758.

- [7] Lionta, E., Spyrou, G., Vassilatis, D. K., & Cournia, Z. (2014). Structure-Based Virtual Screening for Drug Discovery: Principles, Applications and Recent Advances. In *Current Topics in Medicinal Chemistry* 14(16), 1923-1938.
- [8] Morris, G. M., Huey, R., & Olson, A. J. (2008). Using AutoDock for Ligand Receptor Docking. *Current Protocols in Bioinformatics*, 24(1), 14-40.
- [9] Thakor, V., Poddar, M., Dey, S., Manjula, S. N., Madhunapantula, S. V., Pawara, R., Patel, H. M., & Noolvi, M. N. (2016). Exploring the anti-breast cancer potential of flavonoid analogs. *RSC Advances*, 6(82), 79166–79179.
- [10] Cheng, F., Li, W., Zhou, Y., Shen, J., Wu, Z., Liu, G., Lee, P. W., & Tang, Y. (2012). admetSAR: A Comprehensive Source and Free Tool for Assessment of Chemical ADMET Properties. *Journal of Chemical Information and Modeling*, 52(11), 3099–3105.
- [11] Rodríguez-García, C., Sánchez-Quesada, C., Gaforio, J. J., & Gaforio, J. J. (2019). Dietary flavonoids as cancer chemopreventive agents: An updated review of human studies. In *Antioxidants* MDPI 8(5), 137.
- [12] Bhayani, F., Thakor, V., Atodaria, B., Noolvi, M., & Kher, J. (2014). Synthesis and anticancer activity of flavone derivatives against estrogen dependent cancers by rational approach. *PharmaTutor*, 2(2), 33–43.