Indian Journal of Biochemistry & Biophysics
Vol. 63, April 2026, pp. 408-419
DOI: 10.56042/ijbb.v63i4.20602

Molecular simulations and docking studies for evaluating the pharmacokinetic properties of microalgal compounds targeting HIV-2 GP120

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Received 01 July 2025; *revised 23 October 2025*

Molecular docking and molecular dynamics (MD) simulations were performed to investigate the interactions between HIV-2 GP120 and marine algal-derived compounds. Using the CHARMM force field and AutoDock software, seven microalgal ligands were screened, among which Quinazolin-4(3H)-one exhibited the strongest binding affinity of −9.5 kcal/mol against the HIV-2 GP120 receptor (PDB ID: 5CAY). The MD simulations confirmed the structural stability of the Quinazolin-4(3H)-one–GP120 complex with an average RMSD of 1.5–2.0 Å over 103 frames, indicating minimal conformational fluctuations during the simulation period. Furthermore, ADMET analysis revealed 99% predicted human intestinal absorption, no Lipinski's rule violations, and favourable bioavailability (0.55), suggesting strong drug-like behavior. These quantitative results support the selection of Quinazolin-4(3H)-one as the most promising compound among the tested ligands. Overall, this study provides simulation-based insights into ligand stability, pharmacokinetic performance, and receptor interactions, offering a potential framework for designing novel inhibitors targeting the HIV-2 GP120 viral entry mechanism.

Keywords: Antiviral drug design, HIV-2, Microalgal bioactive, Molecular docking, Quinazolin-4(3H)-one

HIV, or human immunodeficiency virus, is a member of the lentivirus family of retroviruses and can cause AIDS in both HIV-1 and HIV-2 forms[1,2]. HIV-1 was first to be identified and now more is common everywhere. West African HIV-2 is less harmful than HIV-1[3]. Many aspects of them are similar, such as the intracellular replication mechanisms, the routes of transmission (such as sexual contact, sharing of needles and transfusion) and the clinical results. The notable distinctions between HIV-1 and HIV-2 reveal details about the virus's pathogenesis, tropism and evolutionary history. RNA genome of HIV is small (10 kb)[4], it is always dependent on the machinery of the host cell. Nine genes found in the virus's genome translate into 19 different proteins and polyproteins. HIV destroys a particular kind of CD_4^+ and CD_8^- cells from blood cell that is important in the body's ability to fight against infection, which affects your CMI system[5,6]. HIV-1 and HIV-2/SIV are genetically related and share a wide range of characteristics, such as the ability to infect CD_4^+ CCR_5^+ T-lymphocytes, monocytes/macrophages and microglia. HIV-1 and HIV-2 have 40% of the same amino acids in their envelopes (Env) and 30% of the same sequence overall[7]. HIV viruses contain glycoproteins that are targeted by vaccines and broadly neutralizing antibodies (bNAbs).

The recent pharmaceutical approach focuses on a combination of medications (HAART (highly active antiretroviral therapy)[8] that target multiple stages of viral replication, including entry, fusion, integration, reverse transcription and protein maturation. To find suitable treatment combinations, new chemicals were linked to the structures of HIV proteins using molecular docking techniques[9,10]. The antiviral properties of Ethyl iso- allocholate with a target main

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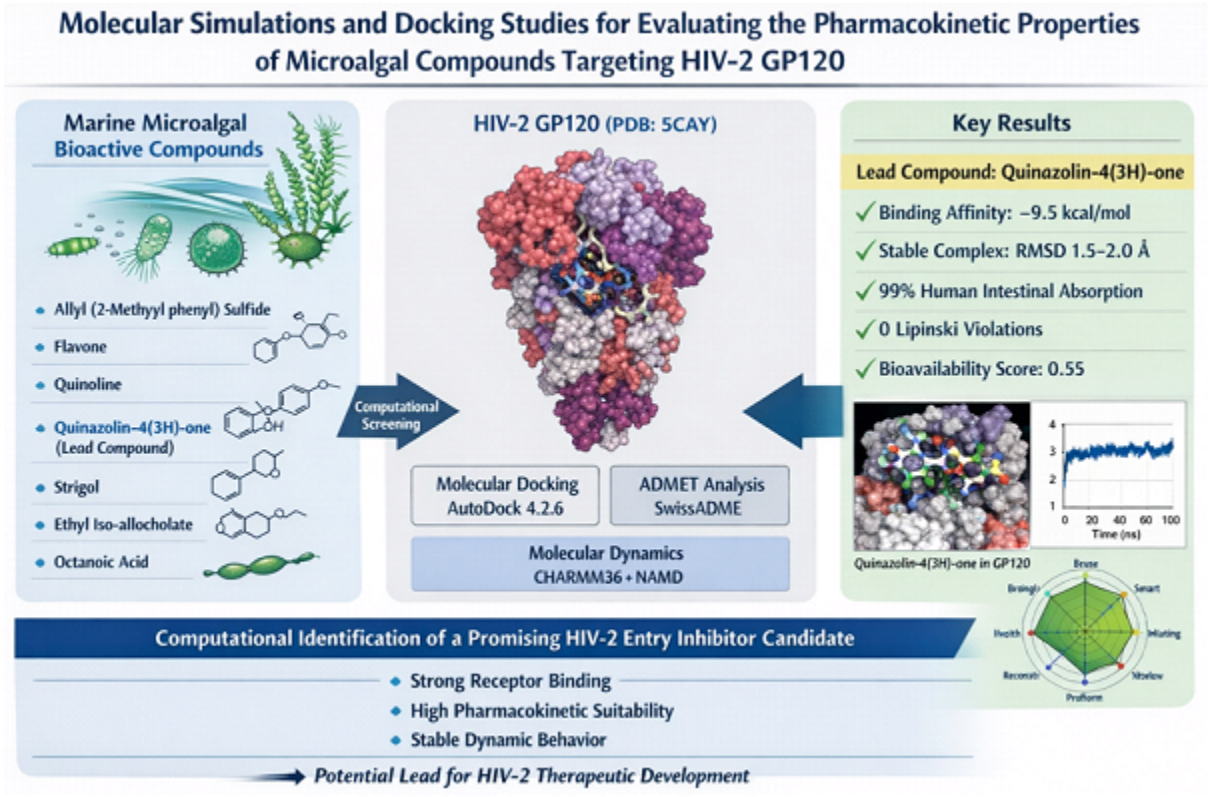

Graphical abstract

protease (Mpro) active binding site reside at locations Cys-145 and His-41 and are able to effectively control of SARS-CoV-2 virus[11]. Ethyl iso-allocholate is another component of *Lpomoea obscura* L., which has been shown to have antiviral activity against SARS-CoV by preventing the viral genome from adhering to target proteins like ACE2 and primary protease (MPro)[12]. Octanoic acid is bound to the amide moieties of the C-28 side chain, the HIV-1 virus is effectively inhibited. The recent pharmaceutical approach focuses on a combination of medications (Highly active antiretroviral therapy) that target multiple stages of viral replication, including entry, fusion, integration, reverse transcription and protein maturation. Micro algal compounds are anti-viral compounds (Fig. 1 and Table 1). Some drug has antiviral qualities that help prevent HIV infections.

Materials and Methods

Building up receptors and ligands

The HIV-2 GP120 (PDB ID: 5CAY) was obtained from the PDB (protein data bank). The natural microalgal compounds obtained from GC-MS

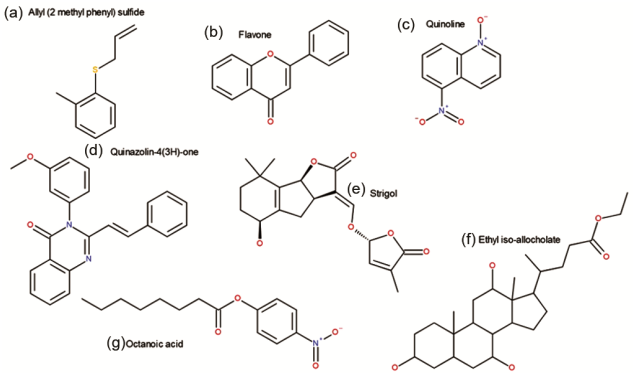

Fig. 1 — Chemical Structure of Marine algal compounds: (a) Allyl (2-methylphenyl) sulphide; (b) Flavone; (c) Quinoline; (d) Quinazolin-4(3H)-one; (e) Strigol; (f) Ethyl iso-allocholate; and (g) Octonic acid

studies[23], 2D structure of Allyl (2methylphenyl) sulphide, Flavone, quinolone, Quinazolin-4(3H)-one, Strigol, Ethyl iso- allocholate and Octonicacid (Fig. 2a-g) was created in Biovia Draw, then saved in PDBQT (Protein Data Bank, Partial Charge (Q), & Atom Type (T) format. and Mol2 file formats using the MGL Tools. The water molecules were not present in the three-dimensional coordinate dataset. We assessed the effectiveness of geometry

Table 1 — Anti-viral studies from Micro algae compounds

Marine Algal Compound	Compound	Effect	References
Flavonoid gallate ester	Phenolic compounds	Anti-HIV-1 integrase activity	Kim *et al*., 1999[13]
Quinazolin-4(3H)-one	Alkaloid	Anti-HIV activity	Sulthana *et.al.,* 2020[14]
Quinazolin-4(3H)-one	Alkaloid	SARS coronavirus	Selvam *et.al.,* 2007[15]
Quinoline	Alkaloid	Non-nucleoside reverse transcriptase inhibitors	Singh *et.al.,* 2022[16]
Quinoline	Alkaloid	Anti-HIV-1	Hajimahdi *et.al.,* 2016[17]
Strigol	Steroid	Anti-HCMV	Matteo *et.al.,* 2020[18]
Allyl (2-methylphenyl) sulphide	Organo sulphur compound	Anti-cancer	Sujithra *et al.,* 2018[19]
Ethyl iso- allocholate	Steroid	SARS-CoV-2 inhibitor	Illah Sailah *et.al.*, 2021[20]
Ethyl iso- allocholate	Steroid	Anti-HIV activity	Zubair *et.al.*, 2021[21]
Octonic acid	Fatty acid	Anti SARSCoV-2 activity	Srivastava *et.al.*, 2020[22]
Betulinylamino-octanoic acid amides	Fatty acid	Anti-HIV activity	Srivastava *et.al.*, 2020[22]
Octonic acid	Fatty acid	Antioxidant and anti-HIV activities	Srivastava *et.al.*, 2020[22]

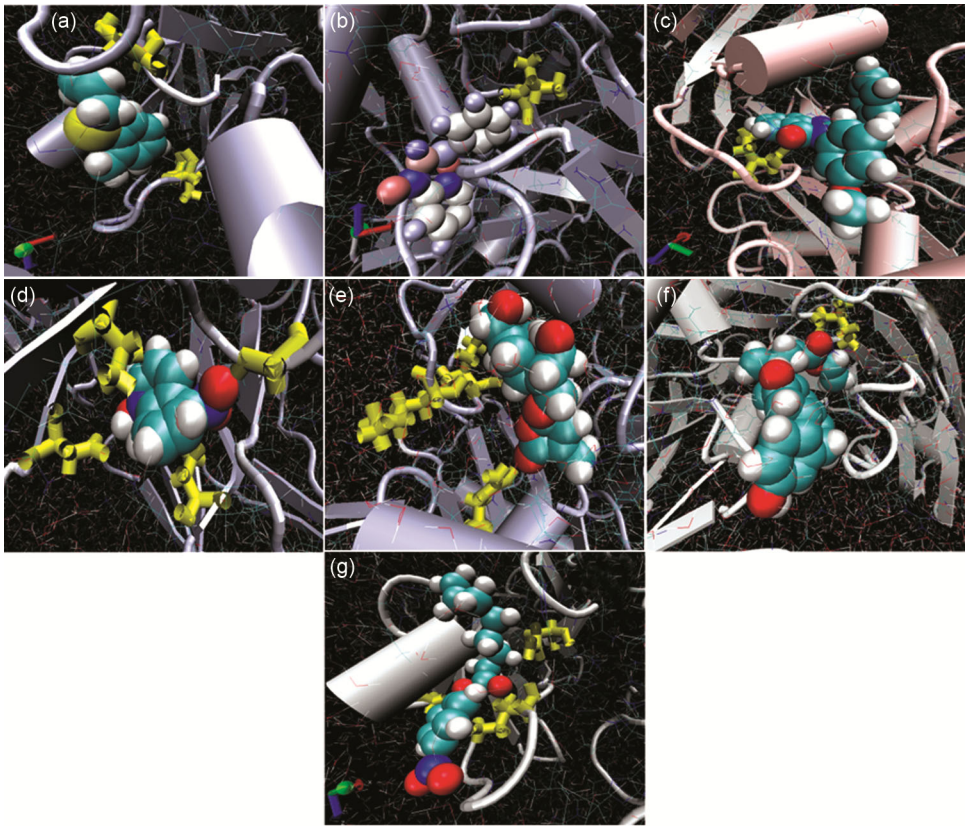

Fig. 2 — Docking results of Microalgal compounds against HIV-2 GP120 (5CAY): Receptor interaction with compounds (a) Allyl (2-methylphenyl) sulfide; (b) Flavone; (c) Quinazolin-4(3H)-one; (d) Quinoline; (e) Strigol; (f) Ethyl iso-allocholate; and (g) Octonic acid as space fill model representation, (a-g are VMD software representation)

optimization for a number of frequently used functionals. For the UCSF Chimera program, Gasteiger atomic partial charges were introduced and energy minimization was performed ten thousand times.

The forecast for an active site

The ligand molecules can bind to receptor proteins in a very small area on a catalytic active site to initiate the desired activity. Identifying this active site residue in the target protein is highly beneficial for de novo

drug design (DNDD) and molecular pairing. Because the target proteins shape is constantly changing, it is challenging to identify this catalytic binding site with precision. An energetically favourable binding site for protein 5CAY was determined using a Q-Site Finder, which uses a simple van der Waals probe and the interaction energy.

Properties of Lead and Drug potential

Drug development propensity was determined by Pfizer's rule of five (RO5)[23,24] and other methods. We computed the physicochemical, absorption, distribution, metabolism and excretion (ADME) and drug likeness parameters using the SwissADME online tool (http://www.swissadme.ch/).

Research on molecular docking

We utilized Autodock 4.2.6 (http://autodock. scripps.edu) to investigate flexible docking. Microalgal compounds and HIV-2 GP120 (5CAY) were submitted in PDB format with the default settings. A docking algorithm assigns hydrogens, charges, flexible torsions and other properties to both the protein and the ligands. A polar hydrogen atom ionized the target protein. Protein and ligands were supplemented with Kollman unified charge and Gasteiger charge, respectively. The ligand was also ascribed rigid roots. It was necessary to convert the 3D structure of HIV 2 GP120 (5CAY) and its ligands to PDBQT format so that AutoDock calculation could be performed. The ligand molecules were constructed, refined and converted into a Mol2 file with the use of Biovia Draw. PDBQT files were created by assigning nonpolar hydrogen atoms to the atom. The web server Cresset Flare 4.0.1 was utilized to determine the binding location of the ligands on HIV-2 GP120. Grid-based model was developed in order to unravel the binding energies of the protein in simulation. Run time was decreased using the grid-based method. Upon adjustment of the protein grid box, calculations were performed for the x, y and z center coordinates, along with the total grid dimensions, resulting in the values of (-28.4611, -52.4553, 18.9195) and (59.3991101098, 86.5997601318, 80.424099865) respectively. The docking simulation employed the Lamarckian genetic algorithm. PyMol was used to investigate how protein ligand complexes interacted with the positions and bond lengths of respective amino acids. A variety of parameters, including drug similarity, total surface area, relative PSA, polar surface area, acceptors, donors, flexibility, RB, cLogP, clogS, H-acceptors and others were computed using Osiris Data Warrior 5.5.0.

Prediction of physiochemical characteristics

The physiochemical and pharmacological features of the microalgal compounds were predicted using the molecular property prediction server from mol-inspiration. The combined influence was determined using the mol-soft online server by combining the pharmacokinetics, pharmacodynamics and the drug similarity model scores.

Simulation of protein-ligand complexes

The Visual Molecular Dynamics (VMD) v 1.9. 4 software tool was used to simulate ligand protein complexes. We chose the ligand protein complex with Molecular Dynamics simulations lowest binding energy. The target protein was investigated using the CHARMM 36 force field with NAMD software and 103 frame MDS. In effect, 103 frames were generated on a supercomputer using CHARMM GUI web server, followed by a multiple file for psf and pdb (5CAY) and ligands were created using the VMD's TCL script. TIP3P coordinate framework has 3.0 of water in each direction and this water was used to address an issue. A total of ten steps per cycle with electrostatic evaluations were conducted, with an integrator setting of 2 fs/step for all stiff bonds and nonbonded frequencies at 2.5 Å. TCL scripts assisted in adjusting periodic boundary conditions and PME. The water constraints were eliminated by diminishing the baseline protein energy over 1000 Powel algorithmic steps at 310K. 103 frames of simulations were run using Langevin dynamics simulation were performed in order to modify the system's kinetic energy, temperature and/or pressure without a binding pocket. Protein structure was not altered by applied parameters during the process of unbinding ligand. In this study, we analysed the MD simulation data for 5CAY -ligand complexes, and used VMD to determine atoms stability using the Root Mean Square Deviation (RMSD) method. In the forcefield description of the interatomic forces, both bonded and the non-bonded terms are included. It is further divided into covalent bonding and hybridization, as well as improper angles and improper-dihedrals. NAMD plots illustrate bonding terms, angles, dihedrals and improper-dihedrals.

Results and Discussion

Molecular Docking

Molecular docking studies were performed to elucidate the binding interactions between HIV-2

GP120 (PDB ID: 5CAY) and selected microalgal-derived compounds. The primary objective was to predict the optimal binding conformation, interaction residues, and affinity of each ligand toward the GP120 receptor. The receptor and ligand structures were prepared in AutoDock 4.2.6, with all non-essential water molecules removed and hydrogen atoms added to the receptor using MGLTools. Partial charges were assigned using Gasteiger–Marsili parameters, and the receptor was defined as rigid while the ligands were treated as flexible to allow torsional freedom. A grid-based docking approach was employed to identify energetically favorable binding sites. The grid box was centered on the active pocket coordinates (x = −28.46, y = −52.45, z = 18.91) with dimensions of 59.4 × 86.6 × 80.4 Å, encompassing the receptor's catalytic region. The Lamarckian Genetic Algorithm (LGA) was used for conformational sampling with a population size of 150, a maximum of 2.5×10^6 energy evaluations, and 100 independent runs per ligand. The resulting docked poses were ranked based on the lowest binding free energy (ΔG, kcal/mol) and clustering RMSD values.

The docking analysis revealed that Quinazolin-4(3H)-one exhibited the highest binding affinity of −9.5 kcal/mol, surpassing other microalgal compounds such as Flavone (−8.3 kcal/mol), Strigol (−9.0 kcal/mol), and Octanoic acid (−6.8 kcal/mol). The best-ranked pose of Quinazolin-4(3H)-one formed stable hydrogen-bond interactions with key residues Lys35, Gly382, Asp471, and Thr481, indicating strong complementarity with the GP120 binding site[25]. The interaction visualization using PyMOL and Cresset Flare 4.0.1 confirmed the ligand's snug fit within the hydrophobic pocket, supported by van der Waals and electrostatic stabilization[26]. Physicochemical and drug-likeness parameters were further analysed using SwissADME and Data Warrior 5.5.0. Quinazolin-4(3H)-one exhibited a molecular weight of 354.4 g/mol, LogP of 4.24, and TPSA of 41.9 $Å^2$, complying with Lipinski's rule of five. The docking and molecular property results collectively indicate that Quinazolin-4(3H)-one possesses strong receptor affinity, favourable pharmacokinetic features, and potential as a lead compound for HIV-2 GP120 inhibition[27].

Binding site and ligand conformation

The 3D structure of HIV-2 GP120 (5CAY) is investigated and chimera-based optimization was used to reduce the potential energy of microalgal compounds. The amino acid residues at the catalytic site for HIV-2 GP120 are determined using Q site Finder. The Figures 2 & 3 shows the interaction of the target protein 5CAY with the ligand (Micro algal compounds A, B, C, D, E, F and G) with a binding affinity of -5.4 (A), -8.3 (B), -9.5 (C), -6.9 (D) and -9 (E), -9 (4: A) and -6.8 (4: B) Kilocalories per mole. The catalytic active binding site is located at the following locations ILE 24, SER 42 (A), ILE 24 and ARG 59 (B), ILE 24 (C), LYS 35, GLY 382, ASP 471, THR 481 (D), LYS 22, SER 23, ARG 491(E), ILE 24, ARG 59 (4: A) and ILE 24, GLY 65, ASN 39 (4: B). This program checks the binding mode and stability of microalgal compounds with 5CAY by removing more amino acid residues and selecting only those that interact with HIV-2 GP120. Our docking analysis allowed as to identify ligand docking configuration of microalgal compounds is dependent upon binding energy (Table 2). Calculation was conducted for each compound to determine which conformation had the lowest binding energy. The binding energy value of Quinazolin-4(3H)-one was found to be lower than that of the other microalgal compounds, suggesting a better affinity for binding to protein ligands. In our study, Quinazolin-4(3H)-one

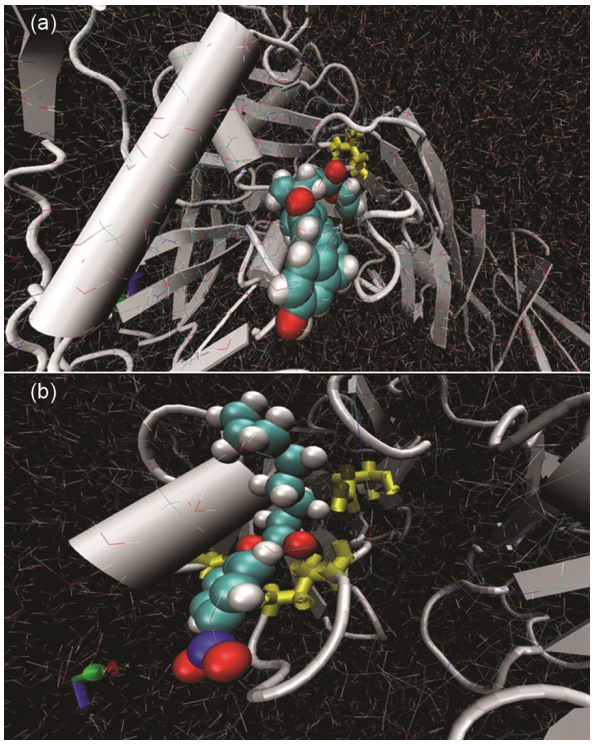

Fig. 3 — Molecular docking visualization of additional microalgal compounds with HIV-2 GP120 receptor (PDB ID: 5CAY). Docked interactions for (a) Ethyl iso-allocholate; and (b) Octanoic acid are illustrated using PyRx/AutoDock tools

Table 2 — Chemical characteristics of Marine compounds

Compound Properties	Compounds						
	A	B	C	D	E	F	G
Ligand	Allyl (2methyl phenyl) sulfide	Flavone	Quinazolin-4(3H)-one	Quinoline	Strigol	Ethyl_iso-allocholate	Octanicacid
Binding Affinity (Kcal/mol)	-5.4	-8.3	-9.5	-6.9	-9	-9	-6.8
Molecular Weight	164.3	222.2	354.4	190.2	346.4	436.6	265.3
SlogP	3.1	3.2	5	2.1	2.4	5.1	3.8
TPSA	25.30	26.3	41.9	77.3	82.1	87	72.1
Flexibility	3	0	1.4	0.3	3.4	10.9	6.8
Rotatable Bonds (RB)	3	1	4	1	3	8	8
cLogP	3.2466	3.3728	4.2401	0.5785	1.2004	4.0136	3.4511
cLogS	-3.249	-3.744	-5.076	-5.166	-2.926	-4.908	-3.996
H-Acceptors	0	2	4	5	6	5	5
H-Donors	0	0	0	0	1	3	0
Total Surface Area	141.31	171.98	279.06	133.58	242.16	326.26	219.5
Relative PSA	0.12377	0.13397	0.13653	0.33448	0.28568	0.19107	0.24355
Polar Surface Area (PSA)	25.3	26.3	41.9	71.28	82.06	86.99	72.12
Druglikeness	-3.8454	0.24192	1.7837	-7.74	-0.21801	-12.439	-31.69

bound around −9.5 kcal/mol. Its mechanism of binding was analysed by examining the binding of Quinazolin-4(3H)-one into the catalytic site of 5CAY. Physicochemical, lipophilicity, water solubility, pharmacokinetic, medicinal chemistry and drug similarity parameters are shown in (Table 2). The drug-likeness of allyl (2 methyl phenyl) sulfide, flavone, Quinazolin-4(3H)-one, quinoline, strigol, ethyl iso- allocholate and octonic acid found to be -3.8454, 0.24192, 1.7837, -7.74, -0.21801, -12.439 and -31.69. Molecules with or without drug-like qualities can be distinguished using the Pfizer's rule of five. The mutagenic property of flavone was found to be on the higher side and other compounds are lower side but marine algae compounds had no tumorigenic potential.

MD Simulation

The primary objective of the molecular dynamics (MD) simulations were to elucidate the structural stability and dynamic behaviour of HIV-2 GP120 (PDB ID: 5CAY) in complex with selected microalgal compounds. The simulations were conducted using the CHARMM36 force field integrated with NAMD software to explore the temporal evolution of protein–ligand interactions. MD simulations, in conjunction with molecular docking, provided insights into conformational flexibility and atomic motion within the protein–ligand complexes under physiological conditions. Each simulation system was solvated in a TIP3P water box extending 3.0 Å from the protein surface, and charge neutralization was achieved by adding counterions. The system underwent energy minimization for 5, 000 steps, followed by gradual equilibration to 310 K using the Langevin thermostat. Integration was performed with a 2 fs timestep over 103 simulation frames, applying periodic boundary conditions and Particle Mesh Ewald (PME) for long-range electrostatics. Structural trajectories were analysed using Visual Molecular Dynamics (VMD) software, with the RMSD (Root Mean Square Deviation) metric employed to evaluate overall complex stability. RMSD trajectory plots (Figures 4-9) illustrate the temporal stability of HIV-2 GP120 complexes with each ligand. The Quinazolin-4(3H)-one complex exhibited minimal backbone deviations (average RMSD: 1.5–2.0 Å), confirming strong structural stability throughout the simulation[28]. Visualization modes included (A) trace selection of α-carbon atoms, (B) backbone atoms, and (C) combined heavy-atom selections (C, CA, N, O), allowing detailed assessment of atomic fluctuations[29]. In addition to dynamic stability, the pharmacokinetic characteristics of the ligands were evaluated using SwissADME and admeSAR platforms. The results

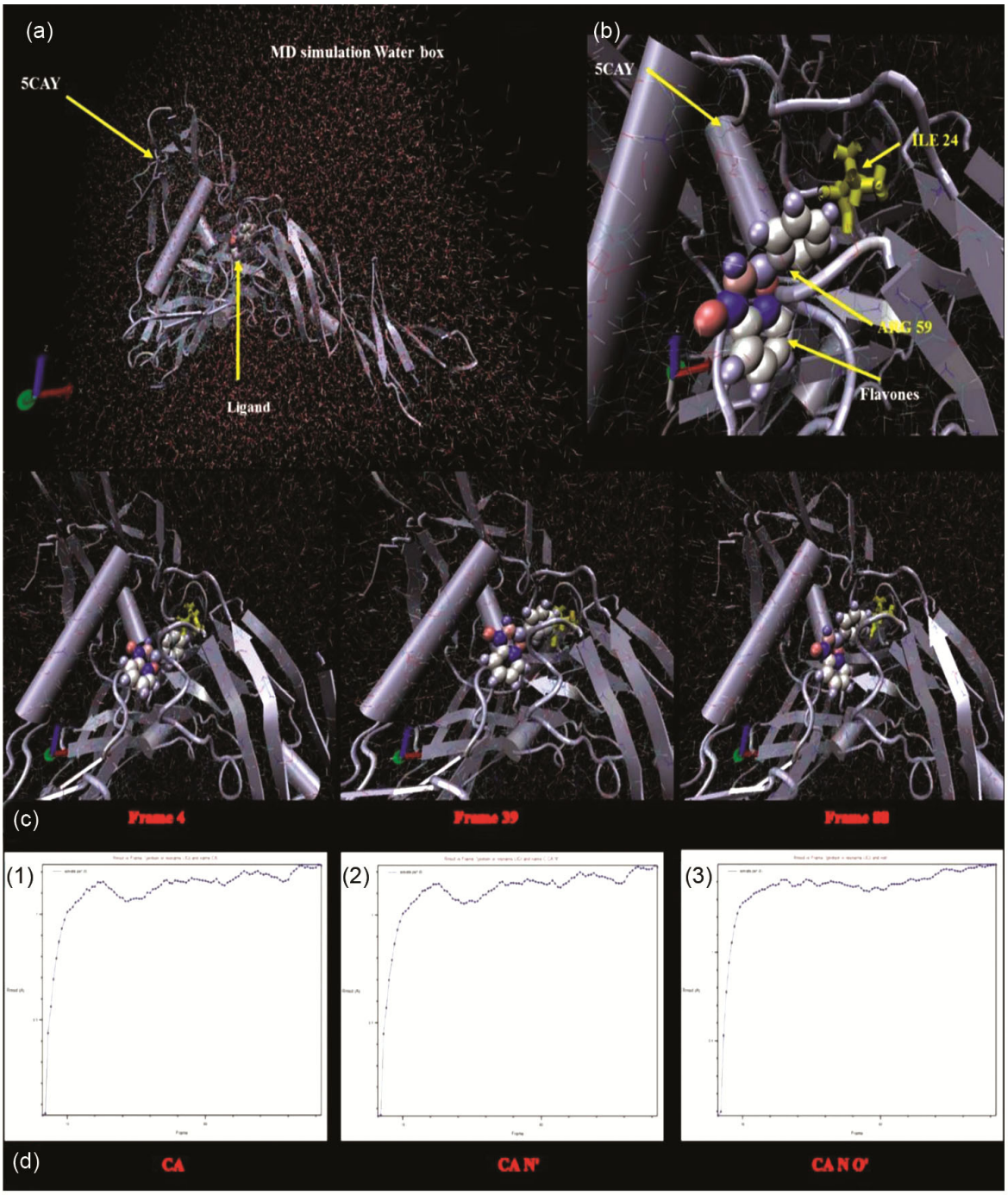

Fig. 4 — Molecular dynamics (MD) simulation of the HIV-2 GP120–Flavone complex. (a) TIP3P water box representation of the solvated complex; (b) 5CAY receptor interaction with Flavone; (c) Simulation trajectory frames generated using NAMD/VMD software; and (d) RMSD trajectory plot showing backbone and C-alpha atom stability over 103 simulation frames

confirmed that all selected marine-derived compounds satisfied Lipinski's Rule of Five, with Quinazolin-4(3H)-one showing optimal absorption, permeability, and bioavailability parameters. Notably, the compound demonstrated high gastrointestinal absorption and no rule violations, indicating strong potential for oral bioavailability[30]. Furthermore, based on ADMET analysis (Table 3), Quinazolin-4(3H)-one fulfilled the lead-likeness criteria, signifying its suitability for further optimization as a potential HIV-2 GP120 inhibitor.

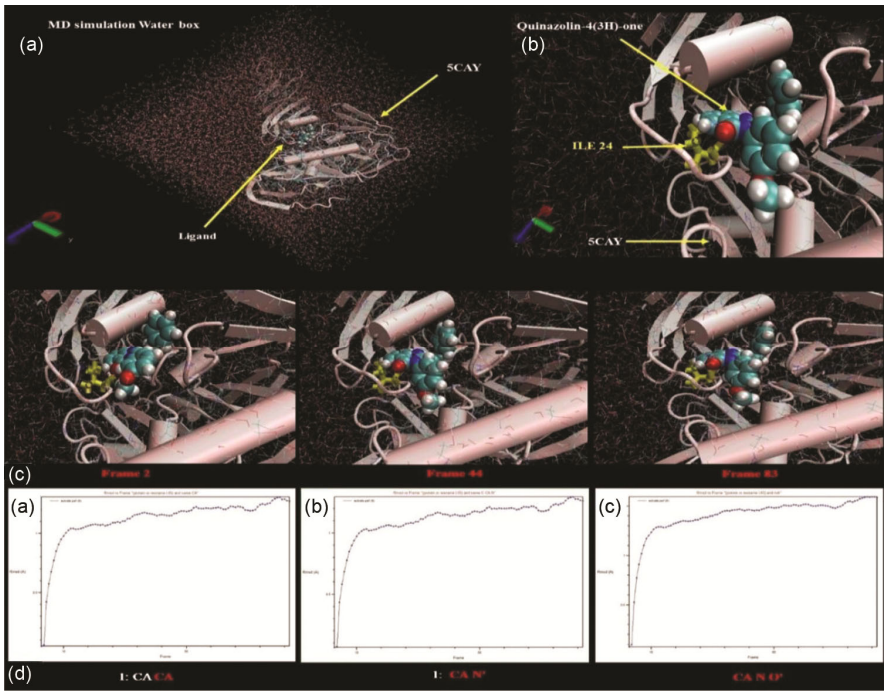

Fig. 5 — Molecular dynamics (MD) simulation of the HIV-2 GP120–Quinazolin-4(3H)-one complex. (a) TIP3P water box representation of the solvated system; (b) Receptor–ligand interaction view of Quinazolin-4(3H)-one within the 5CAY binding pocket; (c) Simulation trajectory snapshots generated using VMD/NAMD tools; and (d) RMSD trajectory analysis illustrating stable complex conformation with minimal atomic deviation (~1.5–2.0 Å) throughout 103 frames

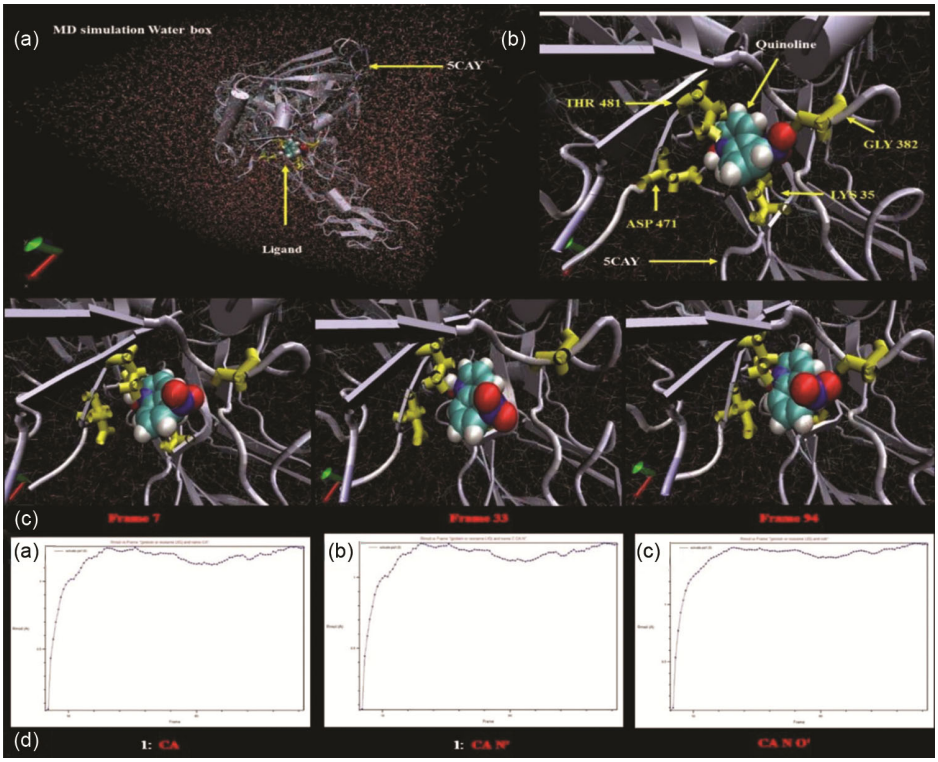

Fig. 6 — Molecular dynamics (MD) simulation of the HIV-2 GP120–Quinoline complex. (a) TIP3P water box structure; (b) Protein–ligand interaction visualization of 5CAY and Quinoline; (c) Time-frame snapshots from MD simulation; and (d) RMSD plot of carbon backbone atoms, indicating moderate stability with minor conformational variations during simulation

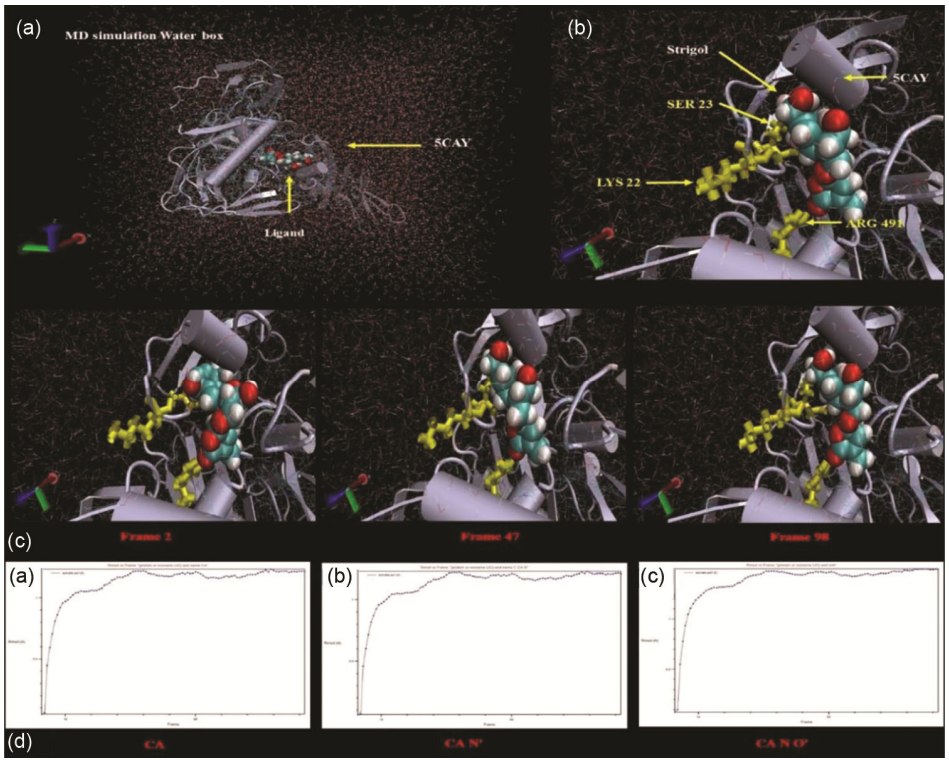

Fig. 7 — Molecular dynamics (MD) simulation of the HIV-2 GP120–Strigol complex. (a) TIP3P water box configuration; (b) Binding interaction of Strigol with HIV-2 GP120; (c) Simulation time-frame representation from VMD/NAMD output; and (d) RMSD trajectory showing structural deviation trends, confirming intermediate complex stability

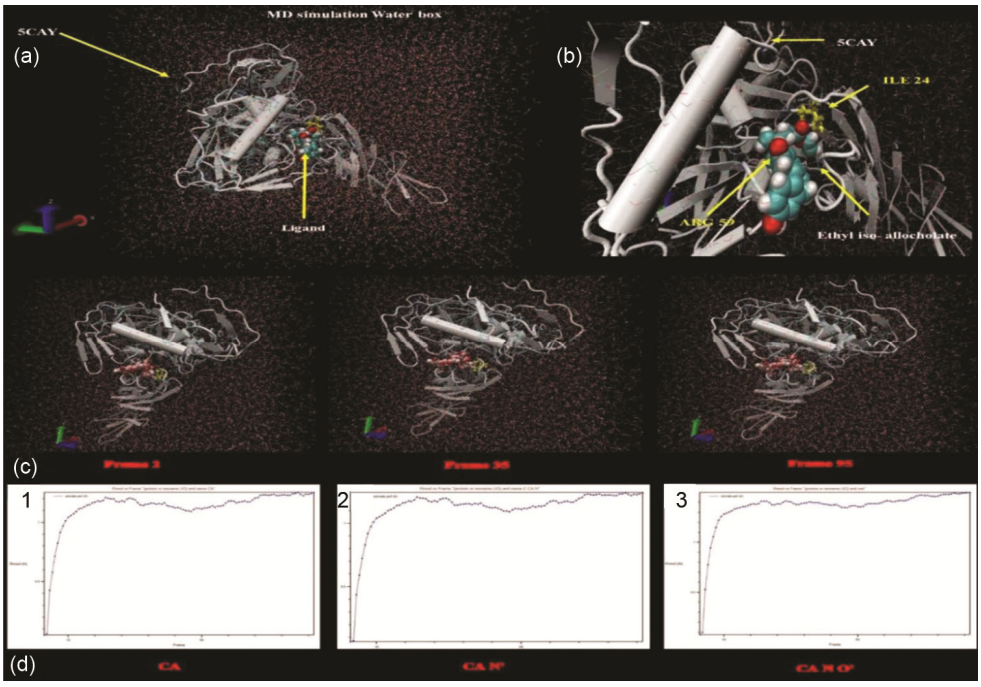

Fig. 8 — Molecular dynamics (MD) simulation of the HIV-2 GP120–Ethyl iso-allocholate complex. (a) Solvated TIP3P water box model; (b) Protein–ligand interaction visualization of Ethyl iso-allocholate bound to GP120; (c) Simulation trajectory over 103 frames; and (d) RMSD analysis plot showing the structural deviation and stability of the complex across simulation time

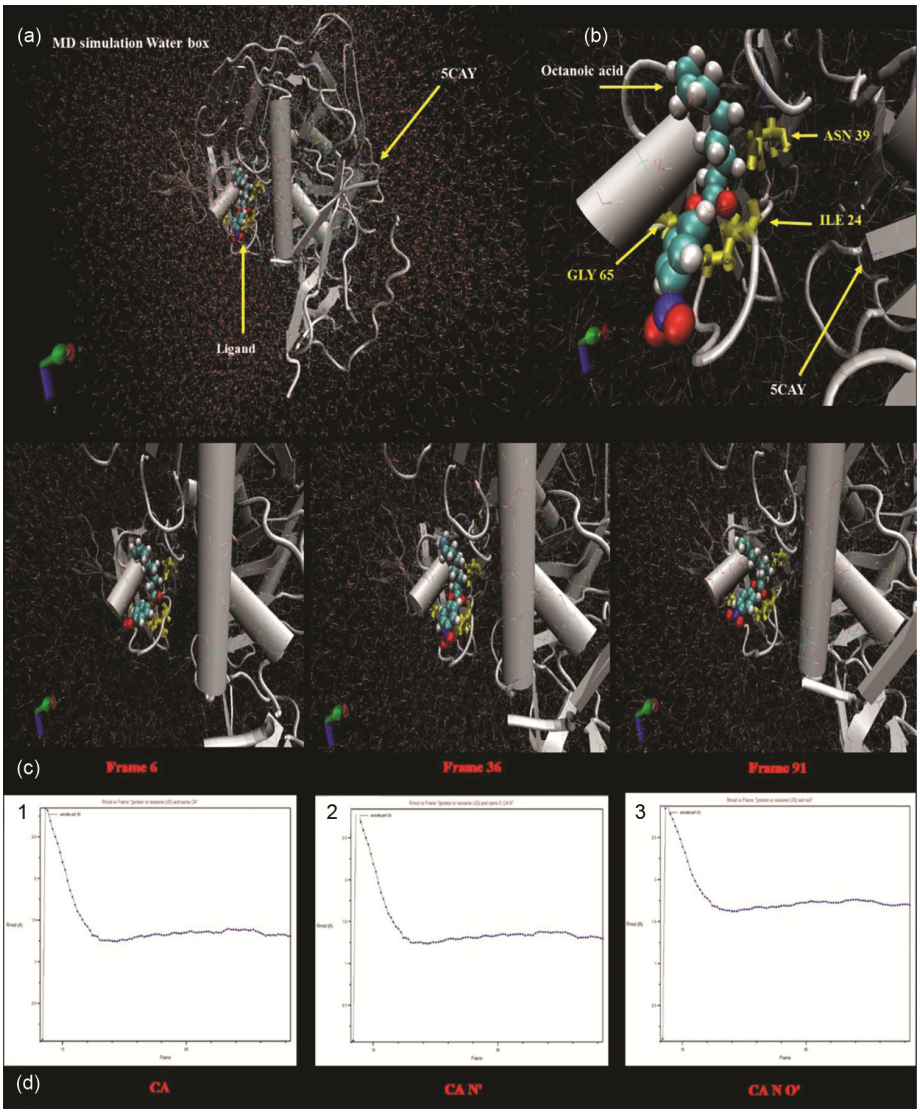

Fig. 9 — Molecular dynamics (MD) simulation of the HIV-2 GP120–Octanoic acid complex. (a) TIP3P water box system used in MD simulation; (b) Binding interaction of Octanoic acid with GP120 receptor; (c) Simulation trajectory snapshots; and (d) RMSD trajectory plot indicating structural stability and dynamic behaviour of the protein–ligand complex throughout the simulation

Table 3 — ADMET properties: Quinazolin-4(3H)-one

Quinazolin-4(3H)-one	Value	Probability	Quinazolin-4(3H)-one	Value	Probability
LogP	2.67		Acute Oral Toxicity (c)	III	0.6904
AlogP	3.45	-	Water solubility logS	-2.943	
Human Intestinal Absorption	+	.9929	Plasma protein binding	0.941	100%
Caco-2	+	0.8396	Acute Oral Toxicity log(1/(mol/kg))	2.438	
Blood Brain Barrier	+	1.0000	Lipinski	Yes; 0 violation	
Human oral bioavailability	+	0.8000	Ghose	Yes	
Subcellular localization	Mitochondria	0.7741	Veber	Yes	
CYP1A2 inhibition	+	0.5119	Bioavailability Score	Yes	0.55
Carcinogenicity (binary)	-	0.9316	Lead-likeness	Yes	
Hepatotoxicity	+	0.7500			

Conclusion

In this study, seven marine algal-derived ligands were computationally screened for their interaction with the HIV-2 GP120 receptor using molecular docking, ADMET, and molecular dynamics (MD) simulations. Among the analyzed compounds, Quinazolin-4(3H)-one demonstrated the most favorable binding affinity (−9.5 kcal/mol) and high structural stability, with an average RMSD of 1.5–2.0 Å during simulation, indicating a stable protein–ligand complex. The compound also exhibited strong pharmacokinetic properties, including 99% human intestinal absorption, compliance with Lipinski's rule of five, and favourable bioavailability. However, a balanced interpretation of the results reveals that Quinazolin-4(3H)-one may pose potential hepatotoxicity and CYP1A2 inhibition risks, as predicted by in-silico ADMET screening. These findings highlight the need for structural optimization to mitigate such limitations before further development. Moreover, as the present study is entirely computational, experimental validation through *in vitro* and *in vivo* assays is essential to confirm biological efficacy and safety. For translational progression, future work will focus on conducting *in vitro* binding and inhibition assays to validate the docking and MD results, followed by *in vivo* pharmacokinetic and toxicity evaluations to assess absorption, distribution, metabolism, and excretion (ADME) profiles. Furthermore, structure–activity relationship (SAR) and lead optimization studies will be undertaken to enhance potency while minimizing toxicity. Collectively, these efforts will help advance Quinazolin-4(3H)-one from computational discovery toward a potential preclinical candidate for HIV-2 therapeutic development.

Acknowledgement

The authors gratefully acknowledge to the Quantee Data Tech Pvt. Ltd for providing all the necessary facilities to carry out the research work.

Conflict of interest

All authors declare no conflict of interest.

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