Marine metabolites for HIV control: A multi-target *in-silico* approach

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ABSTRACT

This study evaluates the potential of marine sponge-derived metabolites as multi-target inhibitors of Human Immunodeficiency Virus (HIV), aiming to overcome the limitations of current antiretroviral therapies. An in silico molecular docking study was conducted on 15 compounds, including FDA-approved drugs (Efavirenz, Darunavir, Lenacapavir) and marine-derived phytoconstituents from Dysidea, Axinella, and Hippospongia species. The compounds were docked against key HIV targets: reverse transcriptase (RT), capsid protein (CP), and protease (PR). ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiling was performed to assess pharmacokinetic and safety parameters, including blood-brain barrier penetration (logBB) and toxicity indices (LD_{50}, mutagenicity, CYP enzyme inhibition). Hippospongide A showed strong dual-target inhibition against RT (-7.1 kcal/mol) and PR (-9.4 kcal/mol), comparable to Darunavir. Avarone exhibited broad-spectrum efficacy (RT: -7.0, CP: -7.4, PR: -8.7 kcal/mol) and notable CNS penetrability (logBB: 0.26). Hippospongide A was non-mutagenic with low toxicity (LD_{50}: -0.5), although it showed moderate inhibition of CYP2C19/2C9 enzymes. Avarone, despite its mutagenicity, had strong multi-target and CNS potential. Marine sponge metabolites, particularly Hippospongide A and Avarone, show promise as next-generation HIV therapeutics. From this in-silico study, we confirmed that Hippospongide A is ideal for systemic viral suppression, while Avarone offers potential for targeting CNS reservoirs.

Keywords: ADMET profiling, HIV inhibitors, marine sponges, molecular docking

INTRODUCTION

Human Immunodeficiency Virus (HIV) continues to pose a severe worldwide health burden, with approximately 38 million people relying on lifelong antiretroviral regimens to control viral progression and prevent the onset of AIDS (Forsythe *et al*., 2019). While existing FDA-approved medications, including reverse transcriptase blockers such as Efavirenz and protease-targeting drugs like Darunavir, have markedly extended patient survival, persistent therapeutic limitations remain (Rathbun *et al.*, 2006). Long-term treatment frequently encounters obstacles, including adverse reactions, evolving drug-resistant viral variants, and restricted availability in underserved communities (Inzaule *et al*., 2017). These challenges collectively underscore the pressing necessity for innovative antiviral candidates featuring novel mechanisms, enhanced safety profiles, and cost-effective production.

Our investigation employs a strategic multi-target approach against HIV by simultaneously disrupting three essential viral proteins. Reverse transcriptase performs the critical function of converting viral RNA

into DNA capable of integrating into host chromosomes (Hu and Hughes, 2012). HIV protease enables viral maturation by cleaving precursor polyproteins into functional components. The capsid protein visualized through structural modelling (PDB 1E6J) constructs the conical core that safeguards viral genetic material while coordinating early infection processes, including uncoating and nuclear import (Handa *et al.*, 2025). Attacking these distinct targets creates complementary therapeutic effects: RT inhibition blocks the establishment of permanent viral genetic material in host cells, protease suppression halts production of infectious particles, and capsid interference impedes post-entry replication events. This coordinated strategy aims to achieve superior antiviral synergy while minimizing the emergence of resistance, a common weakness of single-target therapies. Figure 1 illustrates this multi-stage intervention approach across the viral lifecycle.

To identify potential candidates, we conducted molecular docking analyses on a curated library of marine sponge metabolites. These included brominated alkaloids, terpenoid derivatives, and lactone-based compounds are selected from *Dysidea, Axinella, and Hippospongia* species (Ariyasoma *et al.,* 2023 and Abdelaleem *et al*., 2020). Marine sponge metabolites were chosen for this study because marine organisms, particularly sponges, are increasingly recognized as prolific and unique sources of bioactive natural products with distinct chemical scaffolds not commonly found in terrestrial plants. (Varijakzhan *et al*., 2021). Their ecological exposure to microbial stressors has driven the evolution of potent chemical defence mechanisms, many of which interact with viral enzymes and structural proteins (Rathore *et al.,* 2023). This unique biochemical reservoir provides a strong rationale for exploring sponge-derived compounds as novel anti-HIV candidates, particularly those capable of multi-target inhibition. Binding affinities and interaction patterns against HIV reverse transcriptase, protease, and capsid targets were systematically compared to clinically approved reference inhibitors. This screening methodology aims to uncover structurally novel scaffolds suitable for developing next-generation therapeutics with improved resistance profiles and reduced toxicity.

MATERIALS AND METHODS

Computational tools

The study employed an integrated computational workflow utilizing specialized software for structure-based drug discovery. PubChem and the RCSB Protein Data Bank served as primary repositories for retrieving ligand structures and target protein coordinates, respectively (Kim, 2021). Molecular format conversions and energy minimization were performed using Open Babel to ensure structural compatibility (O'Boyle *et al.*, 2011). Docking simulations leveraged AutoDockTools for parameterization and grid generation, while binding interactions were visualized and analyzed in Biovia Discovery Studio (Baroroh S.Si. M.Biotek. *et al.,* 2023). Pharmacokinetic and toxicity profiles were predicted using SwissADME and pkCSM to evaluate drug-likeness and safety parameters (Pires *et al.,* 2015).

Selection and preparation of ligands

A diverse panel of reference inhibitors and sponge-derived compounds was curated for screening. Clinically approved drugs included Efavirenz (reverse transcriptase inhibitor), lenacapavir (capsid inhibitor), and Darunavir (protease inhibitor). 6 compounds were selected from the *Axinella* species including 3-Bromohymenialdisine, 12-Chloro-11-hydroxydibromoisophakellin, Debromohymenialdisine, N-Methylmanzacidin C, Stevensine, and Debromohymenialdisine (Yalçın *et al.,* 2007). One compound, namely Hippospongides A selected from the

Hippospongia species (Chang *et al.*, 2012). Remaining 6 compounds are selected from the *Dysidea* species including Avarol, Avarone, Dysideanin A, Dysideanin B, Furodysinin lactone, Spongia-13(16),14-dien-19-oic acid (Fathallah *et al*., 2023). These compounds are selected based on the literature search. All ligands were downloaded from PubChem in SDF format, protonated at physiological pH, converted to PDBQT using Open Babel, and energy-minimized with the MMFF94 force field to optimize 3D conformations (Bakale *et al.*, 2025).

Target protein selection and preparation

Three critical HIV-1 proteins were selected: reverse transcriptase (PDB: 3LP3) , protease (PDB: 1HVR), and capsid (PDB: 1E6J). Crystal structures were obtained from the RCSB PDB, prioritizing resolutions ≤2.5 Å and ligand-bound states. Proteins were prepared by removing water molecules, heteroatoms, and non-essential ions. Polar hydrogens and Kollman charges were added in AutoDockTools, followed by energy refinement using the CHARMM force field in Discovery Studio to correct steric clashes and optimize side-chain orientations.

Active site prediction

Binding sites were defined using crystallographic evidence of native co-crystallized ligands (e.g., Efavirenz for RT, Darunavir for protease) and literature-guided residues. For capsid (1E6J), which lacks a canonical small-molecule binding site, the (NTD) inter-protomer interface implicated in capsid dimerization was targeted (Wilbourne and Zhang, 2021). Discovery Studio's "Binding Site" module supplemented these predictions by identifying pockets with high propensity for ligand engagement based on surface geometry and hydrophobicity.

Molecular Docking Protocol

Docking simulations employed Auto Dock Vina integrated within Auto Dock Tools. A grid box encompassing the active site residues was parameterized with dimensions 25×25×25 Å (x/y/z) and 0.375 Å spacing. Exhaustiveness was set to 20 to ensure robust conformational sampling. Ligands were subjected to flexible docking with rotational bonds enabled, while protein residues remained rigid (Cavasotto and Abagyan, 2004). Each compound underwent 10 independent runs, with the lowest-energy pose retained for further analysis.

The grid box was centered at coordinates (x = 22.5, y = 45.7, z = 37.9) for the protease active site, with dimensions 25 × 25 × 25 Å and a grid spacing of 0.375 Å. For reverse transcriptase and capsid, grid centers were set at (x = 30.4, y = 58.2, z = 62.5) and (x = 41.7, y = 33.8, z = 52.1), respectively. Exhaustiveness was fixed at 20 to ensure thorough conformational sampling.

To validate the docking protocol, co-crystallized ligands (Efavirenz for RT, Darunavir for PR, and Lenacapavir for CP) were re-docked into their native binding sites. The resulting RMSD values were ≤ 2.0 Å, confirming the accuracy and reproducibility of the docking setup.

Docking analysis

Binding poses were evaluated using empirical scoring metrics (ΔG in kcal/mol) and interaction patterns. Discovery Studio analysed hydrogen bonds, hydrophobic contacts, π-stacking, and ionic interactions between ligands and key residues (RT: Asp443, Glu478, Asp498, and His539, PR: Asp25 and Asp29, and CP: Pro1, Met5, Leu7, Gln8, Gly9, Val10 & Leu13). Compounds were benchmarked against reference inhibitors (Efavirenz/Darunavir/Lenacapavir) to identify scaffolds with superior or comparable binding affinities. Stability assessments included root-mean-square deviation (RMSD) calculations for docked poses relative to crystallographic ligands.

ADMET prediction

Drug-likeness and toxicity risks were profiled using SwissADME and pkCSM. Key parameters included Lipinski's Rule of Five compliance, bioavailability scores, cytochrome P450 inhibition, and permeability (Caco-2/BBB). Toxicity endpoints covered AMES mutagenicity, hepatotoxicity, hERG inhibition, and LD_{50} (oral rat acute toxicity). Compounds exhibiting favourable binding energy but poor ADMET profiles were deprioritized to focus on viable therapeutic candidates.

RESULTS AND DISCUSSION

Docking

In this docking study, a total of 15 compounds were evaluated for their potential to inhibit three crucial proteins of the Human Immunodeficiency Virus (HIV): reverse transcriptase (RT), capsid protein (CP), and protease (PR). These proteins play essential roles in the HIV lifecycle, making them important targets for drug design. The test group included three FDA-approved antiretroviral drugs, Efavirenz, Darunavir, and Lenacapavir, as well as twelve bioactive compounds derived from marine sources, often referred to as marine phytoconstituents. Each compound's effectiveness was measured by its binding energy (in kcal/mol), with more negative values indicating stronger binding and, potentially, better inhibitory effects, which is shown in Table 1 (Compounds showing higher negative values demonstrate better binding potential). The binding energy values showed consistency across replicate docking runs, with variations within ±0.3 kcal/mol, indicating stable and reproducible interaction trends. Nevertheless, due to the semi-empirical nature of docking scoring functions, these energies should be interpreted qualitatively, emphasizing relative ranking rather than absolute values.

Among the standard drugs, Lenacapavir showed the strongest interaction with the reverse transcriptase enzyme (-7.7 kcal/mol), highlighting its specialized activity against this target. Darunavir displayed the highest affinity for the HIV protease (-9.8 kcal/mol), confirming its role as a highly effective protease inhibitor. Efavirenz, although widely used, showed moderate binding across all targets (RT: -7.2, CP: -5.4, PR: -7.5), suggesting a broader but less potent interaction profile.

Interestingly, several marine compounds demonstrated competitive or even superior binding compared to the standard drugs. Avarone emerged as a promising multi-target inhibitor, binding strongly to all three proteins (RT: -7.0, CP: -7.4, PR: -8.7), indicating its potential to interfere with multiple stages of the viral lifecycle. Avarol, structurally related to Avarone, also showed high affinity, particularly for CP (-6.9) and PR (-8.5). Hippospongide A stood out with an exceptionally strong binding to protease (-9.4 kcal/mol), nearly matching Darunavir's potency, along with good binding to RT (-7.1). Another notable candidate, 12-Chloro-11-hydroxydibromoisophakellin, exhibited strong binding to PR (-9.2). On the other end of the spectrum, Dysideanin A consistently displayed weak interactions with all three targets (RT and CP: -3.6, PR: -5.1), suggesting minimal therapeutic potential as an HIV inhibitor.

Pharmacokinetic profile

The drug-likeness and pharmacokinetic properties of the selected compounds were analyzed using in silico ADMET predictions, shown in Table 2. According to Lipinski's Rule of Five, 12 compounds showed no violations, indicating good potential for oral bioavailability. Only two compounds, Darunavir and Avarol, had one violation, and Lenacapavir had three violations, suggesting limited drug-like behavior. In terms of predicted oral bioavailability, 14 compounds scored high (≥0.55), with Spongia acid having the highest score (0.85), while Lenacapavir had the lowest (0.17). Regarding absorption, nine compounds showed high Caco-2 permeability (log Papp > 0.9),

suggesting efficient intestinal absorption. Compounds such as Avarone and Dysideanin B had particularly high permeability, whereas a few compounds like Stevensine and 12-Chloro-11-hydroxydibromoisophakellin showed low permeability. Blood-brain barrier (BBB) penetration was limited in most compounds, with only Avarone, Dysideanin B, and N-Methylmanzacidin C showing positive logBB values, indicating the potential to cross the BBB.

Metabolic predictions showed varied inhibition of cytochrome P450 (CYP) enzymes. Efavirenz, Lenacapavir, and Hippospongide A were found to inhibit multiple CYP enzymes, which could influence drug–drug interactions. Single CYP inhibition was observed in Avarol, Avarone, and Dysideanin B. Notably, seven compounds, including Darunavir and Spongia acid, showed no CYP inhibition, indicating a lower likelihood of metabolic interference. While specific elimination data, such as clearance rate, were not directly available, compounds with lower permeability and poor CYP interaction profiles may exhibit slower elimination.

In terms of toxicity, only two compounds, Avarone and Dysideanin B, were predicted to be AMES mutagenic. Hepatotoxicity was present in nine compounds, including Efavirenz and Darunavir, suggesting a risk for liver-related adverse effects. Most compounds were non-hepatotoxic. Only one compound, Debromohymenialdisine, showed potential hERG II inhibition, indicating low overall cardiotoxicity risk. Based on predicted acute toxicity (LD_{50}), Avarol and Avarone were identified as the most toxic, while Spongia acid was the least toxic compound among the set.

The docking results reveal significant insights into the inhibitory potential of marine phytoconstituents against key HIV targets, with detailed implications for antiretroviral drug development. Binding affinity, measured in kilocalories per mole (kcal/mol), quantifies how strongly a compound interacts with its target. Critically, more negative values indicate stronger binding, meaning the compound can more effectively disrupt the virus's lifecycle. For example, Darunavir's exceptional protease binding (-9.8 kcal/mol) makes it a clinical gold standard, as it tightly inhibits this essential HIV enzyme.

Reverse Transcriptase (RT) inhibition

Marine-derived compounds demonstrated significant potential in inhibiting HIV Reverse Transcriptase (RT), a critical enzyme responsible for converting viral RNA into DNA, a key step in viral replication (Sarafianos *et al*., 2009). The docking was targeted specifically at the RNase H domain of RT, which plays an essential catalytic role and requires coordination with divalent metal ions such as Mn^{2+} or Mg^{2+} (Neamati, 2011). Depending on the crystallization environment, water molecules or calcium ions may also be observed. The core catalytic residues involved in this domain include Asp443, Glu478, Asp498, and His539, which facilitate substrate binding and cleavage activity, as shown in Figure 2 (a,b,c).

Among the standard drugs, Lenacapavir exhibited the most favourable binding affinity (-7.7 kcal/mol), validating its potency. Notably, the marine-derived compounds Avarone (-7.0 kcal/mol) and Hippospongide A (-7.1 kcal/mol) outperformed Efavirenz (-7.2 kcal/mol), a widely used RT inhibitor in current antiretroviral therapy, as shown in Table 1. This suggests these natural products may possess comparable or superior binding potential, warranting further investigation. Avarone, in particular, demonstrated consistent multi-target affinity across RT, CP, and PR, indicating a structurally versatile molecule capable of fitting into diverse viral protein binding sites. This adaptability might stem from its planar quinonoid structure, which allows effective interactions within the RT active site, potentially coordinating with key catalytic residues and metal ions.

Capsid Protein (CP) inhibition

The HIV capsid protein (CP) plays a pivotal role in protecting the viral RNA genome and facilitating key stages of viral replication, including nuclear import and integration *(*Ding *et al.*, 2016). Inhibiting the capsid protein can disrupt viral assembly and maturation, making it an attractive therapeutic target. Specifically, the N-terminal domain (NTD) of the capsid protein is critical for oligomerization and structural stability, and thus a prime site for small-molecule inhibition.

In the present study, marine-derived compounds demonstrated superior binding affinity to the CP when compared to FDA-approved standards. Avarone exhibited the highest binding affinity among all tested compounds (-7.4 kcal/mol), followed by Avarol (-6.9 kcal/mol), both outperforming Lenacapavir (-6.8 kcal/mol), which is currently one of the most effective capsid-targeting, as shown in Table 1. The enhanced performance of Avarone and Avarol is likely attributable to their structural characteristics, particularly their hydrophobic quinone framework, which promotes stable interactions with the hydrophobic residues within the capsid's NTD domain. The 3D and 2D docked image of the hit molecules with the capsid protein is shown in Figure 3 (a,b,c). Notably, Avarone's strong and consistent binding to CP positions it as a leading candidate for capsid-targeted antiretroviral therapy. Its potential to interfere with capsid assembly or stability suggests a mechanism that could complement or enhance existing treatment regimens, particularly in the face of emerging drug resistance.

Protease (PR) inhibition

HIV protease (PR) is an essential viral enzyme responsible for cleaving the Gag and Gag-Pol polyproteins into functional structural proteins and enzymes (Fun *et al.*, 2012). This maturation step is crucial for producing infectious viral particles; thus, protease inhibition effectively halts the HIV lifecycle. The enzyme's active site typically includes conserved Asp25 and Asp29 residues from each monomer, forming a catalytic dyad that mediates substrate hydrolysis through acid-base catalysis.

In this docking analysis, marine-derived compounds demonstrated remarkable potential as protease inhibitors, with binding affinities that closely approached or even rivalled that of the FDA-approved benchmark, Darunavir (-9.8 kcal/mol). Among these, Hippospongide A showed a particularly high affinity (-9.4 kcal/mol), followed closely by 12-Chloro-11-hydroxydibromoisophakellin (-9.2 kcal/mol). The strong binding of Hippospongide A is especially noteworthy, as its interaction profile suggests potential engagement with PR's catalytic aspartates via hydrogen bonding or metal coordination, mirroring the interaction mechanisms of Darunavir.

Furthermore, Hippospongide A exhibited potent dual-target binding, with high affinity for both RT (-7.1 kcal/mol) and PR (-9.4 kcal/mol). This indicates a broader spectrum of inhibitory activity, offering the potential to disrupt multiple stages of the viral replication cycle, an important trait for reducing viral escape and resistance. The 2D and 3D binding pose depicted in Figure 4 (a,b,c). These findings underscore the promise of Hippospongide A and related marine scaffolds as templates for next-generation protease inhibitors, with possible multi-target capabilities that could be further explored through molecular dynamics and structural optimization.

ADMET profile

The in silico ADMET evaluation revealed that most of the selected marine and synthetic compounds exhibit promising oral drug-like characteristics. Fourteen out of fifteen compounds complied with Lipinski's Rule of Five, with minimal violations, which strongly correlated with high predicted oral bioavailability (≥0.55). Spongia acid stood

out as the most bioavailable compound (0.85), likely due to its optimal physicochemical properties, including balanced lipophilicity and molecular weight. In contrast, Lenacapavir showed poor bioavailability (0.17), which aligns with its three Lipinski violations and suggests limited oral efficacy. Compounds like Avarone and Dysideanin B exhibited high Caco-2 permeability, indicating favourable absorption profiles. However, a few compounds with low permeability, such as Stevensine, may require prodrug strategies or nano-formulation to enhance their oral bioavailability. Regarding distribution, only a few compounds, including Avarone and Dysideanin B, demonstrated significant blood-brain barrier (BBB) penetration, making them potential candidates for central nervous system (CNS) indications, albeit with a possible risk of neurotoxicity. Meanwhile, compounds like Lenacapavir and Darunavir were non-penetrant, making them more suited for peripheral therapeutic targets.

Metabolic profiling showed a wide range of CYP inhibition potential among the compounds. Multi-CYP inhibitors like Efavirenz and Lenacapavir pose a higher risk of drug–drug interactions, potentially requiring careful dose adjustments in clinical settings, especially when co-administered with drugs metabolized by CYP1A2, 2C9, or 3A4 enzymes. On the other hand, compounds such as Darunavir and Spongia acid did not inhibit any major CYP isoforms, indicating safer profiles in polypharmacy. Toxicity assessments raised concerns for several candidates. Hepatotoxicity was observed in nine compounds, consistent with clinical data for Efavirenz and Darunavir. Mutagenicity was predicted in Avarone and Dysideanin B, which could be addressed through structural modification to improve safety. Although most compounds showed minimal cardiotoxicity, Debromohymenialdisine's predicted hERG inhibition warrants further cardiac evaluation. Acute toxicity data highlighted Avarol and Avarone as potentially hazardous due to low LD_{50} values, while Spongia acid was again confirmed as a relatively safe compound with high LD_{50} and favourable ADMET properties.

Based on the cumulative ADMET profile, Spongia acid emerges as a high-priority candidate for further development, showing strong bioavailability, metabolic stability, and low toxicity, making it ideal for non-CNS applications. Avarol also presents a balanced profile with moderate permeability and minimal toxicity concerns. In contrast, compounds like Lenacapavir, despite their clinical relevance, demonstrated several ADMET liabilities, including poor absorption and high hepatotoxicity. Likewise, Avarone and Dysideanin B, though suitable for CNS delivery, may require optimization to reduce their mutagenic and toxic risks. Future research should focus on derivatizing high-risk but pharmacologically interesting compounds, such as Avarone and Dysideanin B, to retain therapeutic potential while minimizing safety concerns. In vivo validation of Spongia acid's pharmacokinetic and toxicity profiles, as well as mechanistic studies on hepatotoxicity in Efavirenz and Darunavir analogues, will be crucial steps in advancing these candidates toward clinical consideration.

Structural and therapeutic implications

Marine-derived compounds show strong promise as next-generation HIV inhibitors, particularly due to their ability to engage multiple viral targets with high affinity. While FDA-approved drugs tend to be more target-specific Lenacapavir, for instance, shows strong binding to RT (-7.7 kcal/mol) and CP (-6.8), but weaker interaction with PR (-7.9), and Darunavir binds well to PR (-9.8) but only moderately to RT and CP (around -6.3 and -5.5 respectively) marine candidates present a broader inhibition profile. Avarone stands out with consistently high binding scores across RT (-7.0), CP (-7.4), and PR (-8.7), thanks to its flexible quinonoid structure. Likewise, Hippospongide A combines strong PR (-9.4) and RT (-7.1) affinity through its

macrocyclic lactone framework, and Avarol shows comparable inhibition of CP (-6.9) and PR (-8.5), surpassing drugs like Efavirenz, which binds modestly to all three sites.

In addition to their binding efficiency, many marine compounds also show more favourable ADMET profiles. Spongia acid, for example, has the highest oral bioavailability (0.85), no signs of toxicity or CYP enzyme inhibition, and an excellent safety margin (LD_{50}: 2.46). Avarone and Dysideanin B exhibit good blood-brain barrier penetration (logBB: 0.26 and 0.43, respectively), offering potential to reach HIV reservoirs in the CNS, something current drugs fail to achieve. However, some compounds still need optimization. Avarone's mutagenic potential and Hippospongide A's mild CYP inhibition highlight areas for structural refinement. Also, low permeability observed in 12-Chloro-11-hydroxydibromoisophakellin suggests the need for advanced formulation strategies like nano-delivery. Overall, these findings suggest that marine-derived scaffolds not only expand the scope of HIV inhibition but also offer safer and more pharmacologically versatile candidates for future drug development.

CONCLUSION

Based on the *in-silico* study, Hippospongide A and Avarone emerged as the most promising leads against multi-drug-resistant HIV by combining high potency, complementary mechanisms, and distinct pharmacokinetic advantages. Hippospongide A provides dual inhibition of HIV reverse transcriptase and protease, surpassing standard drugs like Efavirenz in RT inhibition and rivaling Darunavir in protease targeting, with a favorable safety profile and low predicted toxicity. Avarone, meanwhile, demonstrates strong efficacy across all three major viral targets and uniquely penetrates the blood-brain barrier, positioning it to address HIV reservoirs in the CNS, an area where current treatments like Lenacapavir fall short. However, Avarone's mutagenic and hepatotoxic potential necessitates structural refinement. Together, these compounds present solutions to resistance and viral persistence challenges. As these findings are based on computational models, further experimental validation is required to confirm efficacy and safety in biological systems.

Abbreviation

2D= Two-Dimensional; 3D= Three-Dimensional; Å= Ångström (unit of molecular distance); ADMET= Absorption, Distribution, Metabolism, Excretion, and Toxicity; AIDS= Acquired Immunodeficiency Syndrome; AMES= Ames Mutagenicity Test; BBB= Blood-Brain Barrier; CAI= Capsid Inhibitor; Caco-2= Human Colorectal Adenocarcinoma Cell Line (used for permeability assay); CNS= Central Nervous System; CP= Capsid Protein; CYP= Cytochrome P450 Enzymes (general); CYP1A2= Cytochrome P450 Family 1 Subfamily A Member 2; CYP2C9= Cytochrome P450 Family 2 Subfamily C Member 9; CYP2C19= Cytochrome P450 Family 2 Subfamily C Member 19; CYP2D6= Cytochrome P450 Family 2 Subfamily D Member 6; CYP3A4= Cytochrome P450 Family 3 Subfamily A Member 4; ΔG= Gibbs Free Energy Change; DNA= Deoxyribonucleic Acid; FDA= Food and Drug Administration; Gag= Group-specific Antigen Polyprotein; HIV= Human Immunodeficiency Virus; hERG= Human Ether-à-go-go-Related Gene (cardiotoxicity marker); kcal/mol= Kilocalories per Mole (unit of binding energy); LD_{50} = Lethal Dose for 50% of the Test Population (acute toxicity index); logBB= Logarithm of Brain-to-Blood Concentration Ratio; logP= Logarithm of Partition Coefficient (lipophilicity); logPapp= Logarithm of Apparent Permeability Coefficient (Caco-2 assay); Mg^{2+} = Magnesium Ion; Mn^{2+} = Manganese Ion; MMFF94= Merck Molecular Force Field 94; NTD= N-terminal Domain (of capsid protein); PDB= Protein Data Bank; PDBQT= Protein Data Bank format with Partial Charge and Atom Type; PI= Protease Inhibitor; pkCSM=

Pharmacokinetics and Chemistry-based Signature Method; PR= Protease; PubChem= Public Chemical Database (NIH); RCSB= Research Collaboratory for Structural Bioinformatics; RNA= Ribonucleic Acid; RMSD= Root Mean Square Deviation; RT= Reverse Transcriptase; RTI= Reverse Transcriptase Inhibitor; SDF= Structure Data File; SwissADME= Swiss Absorption, Distribution, Metabolism, and Excretion Predictor; ΔG= Change in Gibbs Free Energy (Docking score)

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1: Binding affinities (kcal/mol) of FDA-approved drugs and marine-derived compounds with HIV targets: reverse transcriptase (RT), capsid protein (CP), and protease (PR).

S.no	Compound name	Binding affinity		
		Reverse transcriptase	**Capsid protein**	**Protease**
	Standard			
1	Efavirenz	-7.2	-5.4	-7.5
2	Darunavir	-6.3	-5.5	-9.8
3	Lenacapavir	-7.7	-6.8	-7.9
	Marine phytoconstituent			
4	3-Bromohymenialdisine	-5.5	-5.7	-8.3
5	12-Chloro-11-hydroxydibromoisophakellin	-5.8	-5.6	-9.2
6	Avarol	-6.8	-6.9	-8.5
7	Avarone	-7	-7.4	-8.7
8	Debromohymenialdisine	-5.8	-5.7	-7.8
9	Dysideanin A	-3.6	-3.6	-5.1
10	Dysideanin B	-6.1	-4.6	-6.8
11	Furodysinin lactone	-5.9	-4.9	-7.9
12	Hippospongide A	-7.1	-6.6	-9.4
13	N-Methylmanzacidin C	-5.1	-4.8	-6.9
14	Spongia-13(16),14-dien-19-oic acid	-5.8	-5.2	-8.6
15	Stevensine	-5.4	-5.4	-7.7

Table 2: In silico ADMET profile of marine sponge-derived compounds and reference antiretroviral drugs.

Compound	Lipinski	Bioavailability	CYP Inhibition	Caco-2 (log Papp)	BBB (logBB)	AMES	Hepatotoxicity	hERG II Inhibition	LD50 (log mg/kg)
Efavirenz	0	0.55	CYP1A2,2C19,2C9	1.13	0.33	No	Yes	No	-0.26
Darunavir	1	0.55	-	0.76	-1.34	No	Yes	No	0.08
Lenacapavir	3	0.17	CYP2C19,2C9,3A4	0.81	-2.5	No	Yes	No	0.34
3-Bromohymenialdisine	0	0.55	-	0.04	-0.92	No	Yes	No	0.27
12-Chloro-11-hydroxydibromoisophakellin	0	0.55	-	-0.11	-2.47	No	No	No	0.15
Avarol	1	0.55	CYP1A2	1.3	-0.02	No	No	No	-0.58
Avarone	0	0.55	CYP2C19	1.56	0.26	Yes	Yes	No	-0.41
Debromohymenialdisine	0	0.55	-	-0.2	-0.52	No	Yes	Yes	0.72
Dysideanin A	0	0.55	-	0.87	-0.81	No	Yes	No	-0.19
Dysideanin B	0	0.55	CYP2D6	1.52	0.43	Yes	No	No	-0.54
Furodysinin lactone	0	0.55	-	1.28	0.33	No	No	No	0.01
Hippospongide A	0	0.55	CYP2C19,2C9	1.33	-0.05	No	No	No	-0.5
N-Methylmanzacidin C	0	0.55	-	-0.02	0.79	No	No	No	0.73
Spongia-13(16),14-dien-19-oic acid	0	0.85	-	1.44	0	No	No	No	2.46
Stevensine	0	0.55	-	-0.1	-1.31	No	Yes	No	0.66

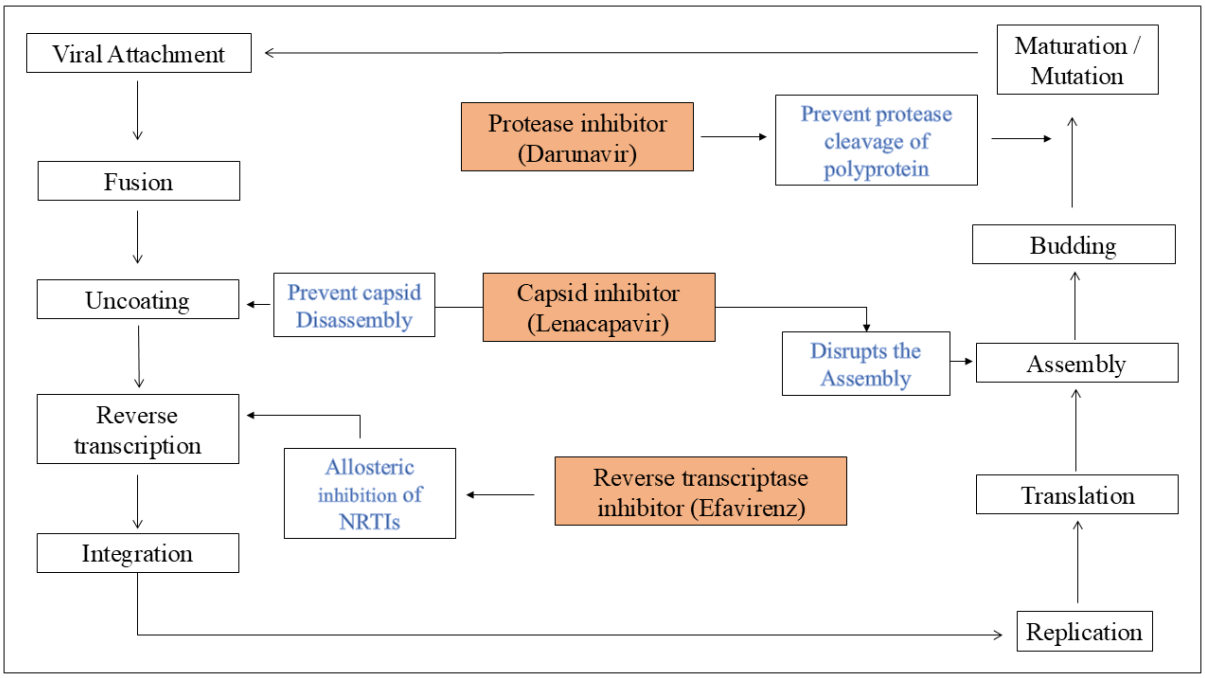

Figure 1: Classification of antiretroviral inhibitors targeting distinct stages of the HIV life cycle.

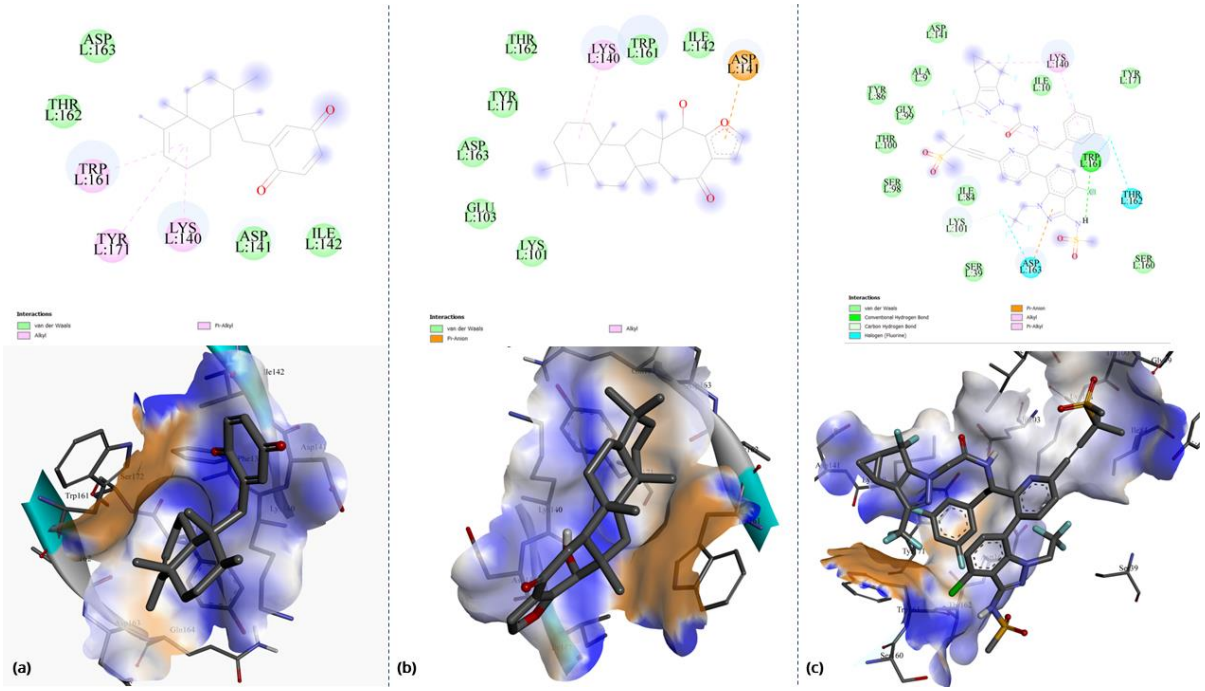

Figure 2: The best binding poses of (a) Avarone, (b) Hippospongide A, and (c) Efavirenz with the reverse transcriptase (3LP3)

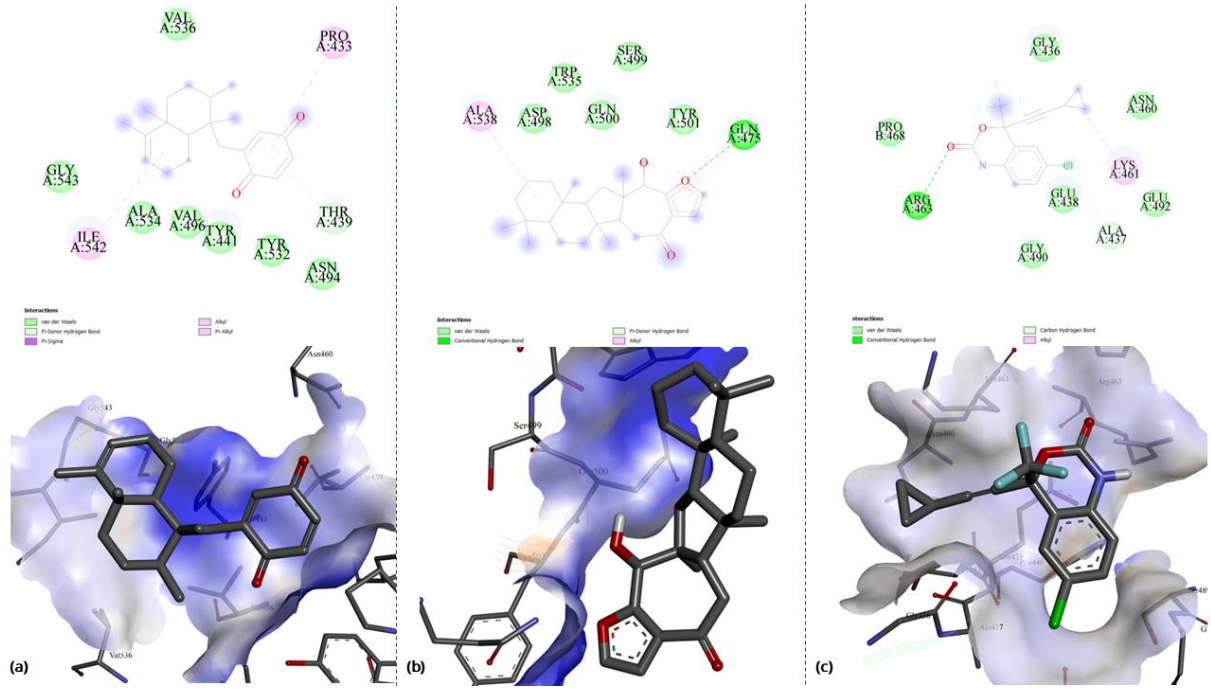

Figure 3: The best binding poses of (a) Avarone, (b) Hippospongide A, and (c) Lenacapavir with the Capsid Protein (1E6J)

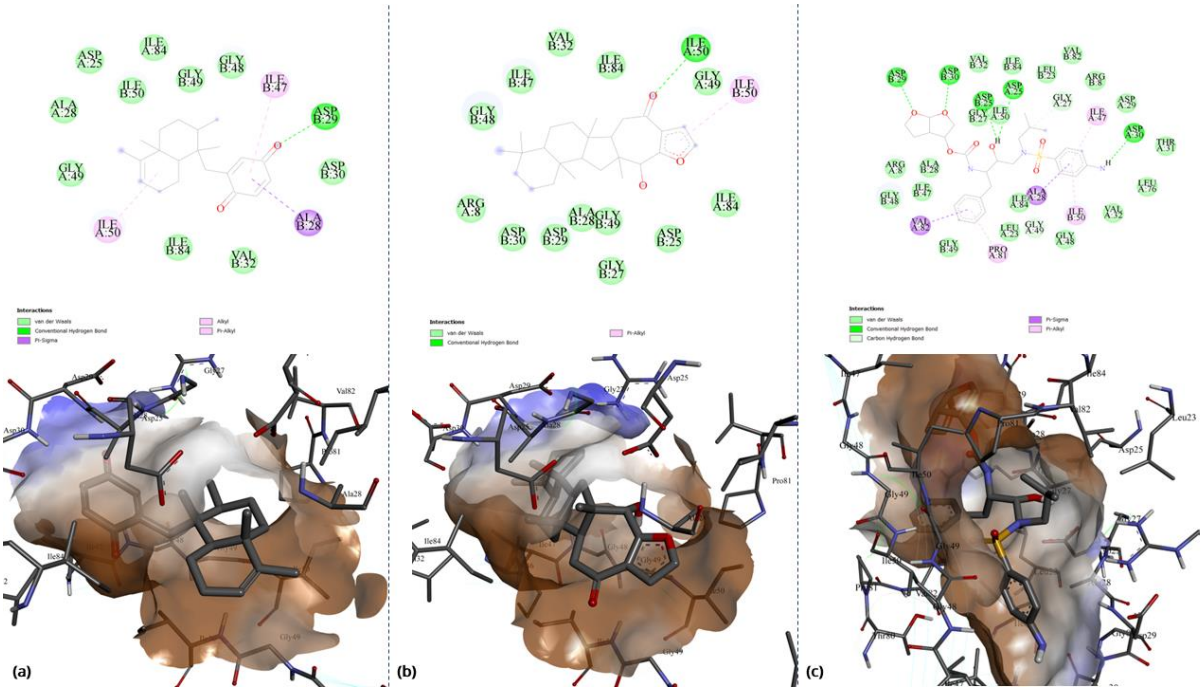

Figure 4: The best binding poses of (a) Avarone, (b) Hippospongide A, and (c) Darunavir with the enzyme Protease (1HVR)