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Molecular Docking Analysis of Repurposed HIV and Antiviral Drugs against Monkeypox Target Protein: Evaluating Docking Scores and Hydrogen Bond Interactions

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Abstract

The increasing threat of monkeypox has led to the exploration of novel treatment strategies, prompting this study to examine the potential repurposing of existing HIV and antiviral drugs. A novel *in silico* molecular docking approach was employed to facilitate drug discovery, utilizing a cost-effective and time-efficient method to predict drug-protein interactions. The study analyzed the binding affinities and hydrogen bond interactions of various HIV drugs (Atazanavir, Darunavir, Fosamprenavir, Lopinavir, and Ritonavir) and antiviral agents (Brincidovir, Favipiravir, Galidesivir, Remdesivir, and Ribavirin) against a specific monkeypox protein target (PDB ID: 8B07). The molecular docking workflow followed four key steps: target protein preparation, ligand preparation, docking simulation, and interaction visualization. HIV drugs demonstrated higher docking scores, with Lopinavir (-10.6) and Atazanavir (-10.1) emerging as leading candidates, whereas antiviral agents showed comparatively lower affinities, with Remdesivir achieving the highest score among them (-6.6). The novelty of this study lies in its rapid and cost-free screening methodology enabled by computational techniques, presenting an effective strategy for initial drug identification. The results indicate that Lopinavir and Atazanavir form stronger hydrogen bond interactions with the monkeypox protein target, highlighting their potential for therapeutic repurposing. This approach underscores the applicability of computer-aided drug design (CADD) for expedited drug-repurposing efforts, offering a viable alternative to conventional methods. In conclusion, the findings suggest that HIV drugs hold promise for monkeypox treatment. Further experimental and clinical validation of these predictions is crucial to confirm their therapeutic efficacy. This study provides a framework for applying similar drug-repurposing strategies to other emerging viral infections, potentially accelerating the drug discovery process and supporting public health efforts during outbreaks.

Keywords: Monkeypox virus; Drug repurposing; HIV protease inhibitors; Molecular docking; Lopinavir; Ribavirin

1. Introduction

Monkeypox is a re-emerging zoonotic disease caused by the Monkeypox virus (MPXV), an enveloped double-stranded DNA virus belonging to the Orthopoxvirus genus of the Poxviridae family. It is phylogenetically related to the variola virus, the etiological agent of smallpox. Although MPXV was historically confined to endemic regions of Central and West Africa, recent outbreaks in non-endemic countries have raised significant concern due to its capacity for sustained human-to-human transmission and the potential for widespread public health impact (Reynolds et al., 2019). At present, there are no antiviral agents specifically approved for the treatment of MPXV infection (Fig. 1). This therapeutic gap has prompted urgent interest

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in identifying effective treatment options, particularly in the face of emerging outbreaks. One viable strategy is drug repurposing, which involves the application of existing, approved pharmaceuticals to new therapeutic indications. This approach offers considerable advantages in outbreak scenarios, including reduced development timelines, known safety profiles, and established pharmacokinetic data (Pushpakom et al., 2019). The use of structure-based virtual screening, particularly molecular docking, has become increasingly valuable in this context, enabling rapid in silico evaluation of potential inhibitors against specific viral targets (Lionta et al., 2014).

Given the conserved nature of viral replication pathways, antiretroviral drugs and broad-spectrum antivirals offer a compelling basis for repurposing. Several HIV protease inhibitors and nucleoside analogs have demonstrated inhibitory activity beyond their original targets, due to shared pharmacophores and mechanistic overlap with enzymes involved in orthopoxvirus replication (Beigel et al., 2020). Their clinical utility is further supported by extensive safety and pharmacokinetic data, which facilitates rapid translation to new indications without the need for early-stage clinical trials (Ashburn & Thor, 2004).Compounds such as Lopinavir, Ritonavir, Remdesivir, and Ribavirin have shown efficacy against a variety of viral pathogens, including RNA and DNA viruses, through mechanisms such as protease inhibition and interference with nucleic acid synthesis (De Clercq & Li, 2016). The proteolytic processing of viral polyproteins and nucleotide-dependent polymerase activity—both crucial to MPXV replication presents viable targets for cross-acting inhibitors (Jin et al., 2020). Importantly, these agents benefit from well-characterized dosing regimens and tolerability profiles, positioning them as strong candidates for clinical repurposing in the context of MPXV infection (Baden et al., 2021).

In this study, we investigate the potential of selected HIV protease inhibitors and broad-spectrum antiviral agents as inhibitors of MPXV, using molecular docking and *in silico* pharmacokinetic and toxicity profiling. The goal is to identify candidates with strong binding affinity, favorable ADME properties, and acceptable safety margins for potential repositioning as monkeypox therapeutics.

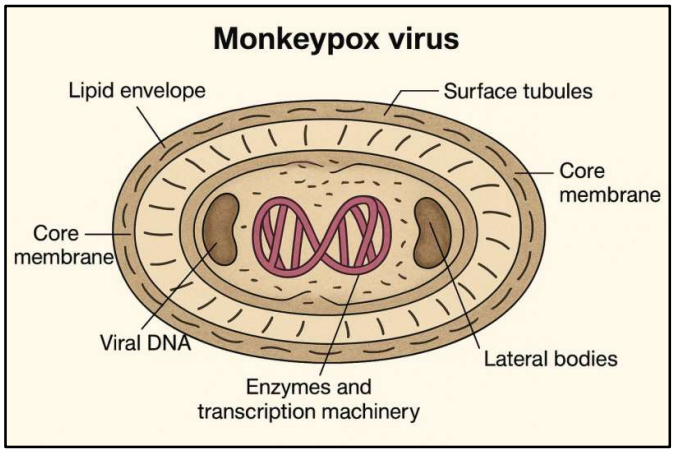

Fig. 1: Structural organization of the Monkeypox virus (MPXV). The virus consists of a lipid envelope enclosing a complex core structure. Key features include surface tubules, a double-layered core membrane, lateral bodies, and centrally located viral DNA associated with enzymes and transcriptional machinery. These components contribute to the virus's ability to replicate within host cells and evade immune responses.

Docking Scores and Hydrogen Bond Interactions

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3. Objective

The primary objective of this study was to evaluate the repurposing potential of FDA-approved HIV protease inhibitors and broad-spectrum antiviral agents as therapeutic candidates against the Monkeypox virus (MPXV). This was achieved through a structure-based molecular docking approach targeting the MPXV protein (PDB ID: 8B07), followed by *in silico* analysis of pharmacokinetic properties, drug-likeness, and toxicity profiles. The study aimed to identify compounds that not only exhibit strong binding affinity to the viral target but also demonstrate favorable ADMET characteristics, thereby supporting their suitability for further preclinical investigation and potential clinical application in the treatment of monkeypox infection

4. Materials and Methods

4.1 Protein Preparation

The 3D crystal structure of the MPXV protease (PDB ID: 8B07) was obtained from the RCSB Protein Data Bank (Fig. 2). The structure was prepared by removing water molecules, adding polar hydrogen atoms, and optimizing residue orientation using UCSF Chimera (Pettersen et al., 2004).

4.2 Ligand Selection

Ten FDA-approved drugs were selected based on their established antiviral activity, encompassing both HIV protease inhibitors and broad-spectrum antivirals. The selected HIV protease inhibitors included Atazanavir, Darunavir, Fosamprenavir, Lopinavir, and Ritonavir, each known for their efficacy in inhibiting HIV replication through targeting the viral protease. In parallel, antiviral agents such as Remdesivir, Ribavirin, Galidesivir, and Favipiravir were included due to their demonstrated activity against various RNA and DNA viruses. Brincidofovir, a nucleotide analog with known efficacy against orthopoxviruses, was included as a positive control to validate the docking methodology (Desai et al., 2023).

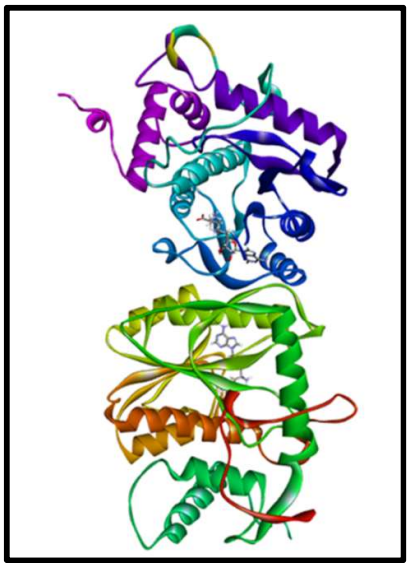

Fig. 2: 3D ribbon structure of the monkeypox virus protein target (PDB ID: 8B07) used in molecular docking analysis. The protein is shown in a multicolored secondary structure representation, highlighting α-helices and β-sheets. Ligand molecules are positioned within the binding pocket, illustrating the docking orientation used for virtual screening of antiviral and antiretroviral compounds.

Ligand structures were downloaded from PubChem and converted into 3D PDBQT format. Energy minimization was performed using UCSF Chimera.

4.3 Docking Procedure

Docking simulations were performed using AutoDock Vina, with the search grid box centered on the catalytic domain of the receptor (center coordinates: x = -10.71, y = 26.92, z = -19.17) and dimensions set to 35 × 35 × 35 Å³ to fully encompass the active site. The exhaustiveness parameter was set to 9 to ensure adequate conformational sampling. Docking poses were ranked according to binding energy (kcal/mol), and the top-scoring conformers were selected for interaction analysis.

4.4 Interaction Analysis

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Binding poses were analyzed in Discovery Studio Visualizer to examine hydrogen bond formation and π–π stacking interactions. Catalytically significant residues (Asp95, Arg140, Ser141, Tyr189, Phe115) were closely evaluated.

4.5 Physicochemical, Drug-Likeness, Pharmacokinetics, and Toxicity Analysis

The physicochemical properties, drug-likeness, pharmacokinetics, and toxicity of Lopinavir and Remdesivir were analyzed using SwissADME and Protox-II. Physicochemical parameters such as molecular weight, log P, hydrogen bond donors/acceptors, rotatable bonds, and topological polar surface area (TPSA) were obtained from SwissADME to assess drug-likeness based on Lipinski, Ghose, Veber, Egan, and Muegge rules. Pharmacokinetic properties, including gastrointestinal (GI) absorption, blood-brain barrier (BBB) permeability, P-glycoprotein (P-gp) substrate interaction, and CYP enzyme inhibition, were also predicted using SwissADME. Toxicity assessments, including the Ames test (mutagenicity), hepatotoxicity, carcinogenicity, and LD50 values, were conducted using Protox-II to evaluate potential adverse effects.

5. Results

5.1 Docking Scores

The docking analysis revealed that several HIV protease inhibitors exhibited strong binding affinities against the monkeypox virus (MPXV) target protein (PDB ID: 8B07). Notably, Lopinavir and Atazanavir demonstrated the most favorable docking scores of –10.6 kcal/mol and –10.1 kcal/mol, respectively, surpassing all other tested compounds, including conventional broad-spectrum antiviral agents (Fig. 3). These findings suggest that HIV drugs, particularly Lopinavir, may serve as promising repurposed candidates for monkeypox treatment (Beigel et al., 2020). Among the antiviral agents evaluated, Ribavirin displayed the highest binding affinity (–6.9 kcal/mol), followed by Remdesivir and Brincidofovir, each with docking scores of –6.8 kcal/mol. Although these scores were less favorable than those of HIV protease inhibitors, they still indicate a moderate binding potential, especially for Remdesivir, which is known for its efficacy against various RNA viruses (Mercorelli et al., 2018). Brincidofovir, used here as a positive control, showed consistent binding behavior in alignment with its antiviral profile.

Compounds with both high docking affinity and favorable molecular interactions—such as Lopinavir and Remdesivir—are particularly notable due to their stable hydrogen bonding and hydrophobic interactions with key active site residues of the MPXV protein (Fig. 4). As illustrated in Figure 5, these drugs demonstrated stronger binding affinities compared to other tested agents, highlighting their potential to inhibit viral replication. The docking results underscore the promise of structure-based drug repurposing approaches in identifying effective inhibitors against emerging pathogens such as monkeypox.

5.2 Molecular Docking Interaction Analysis

The molecular docking results for selected HIV protease inhibitors and antiviral agents against the MPXV protein are summarized in (Table 1). Lopinavir emerged as the top binder with the lowest docking score of –10.6 kcal/mol, followed closely by Atazanavir (–10.1 kcal/mol). These HIV drugs formed multiple hydrogen bonds with key residues such as Asp95, Arg140, and Ser141, and were further stabilized through π–π interactions with Tyr189. Such interactions are indicative of deep binding within the catalytic cleft, suggesting their strong affinity and potential efficacy as repurposed therapeutic agents.

Among the antiviral candidates, Ribavirin demonstrated the most favorable binding affinity (–6.9 kcal/mol), forming hydrogen bonds with Gly96, Asn161, Arg140, and Tyr189, although π–π stacking was absent. Brincidofovir, included as a positive

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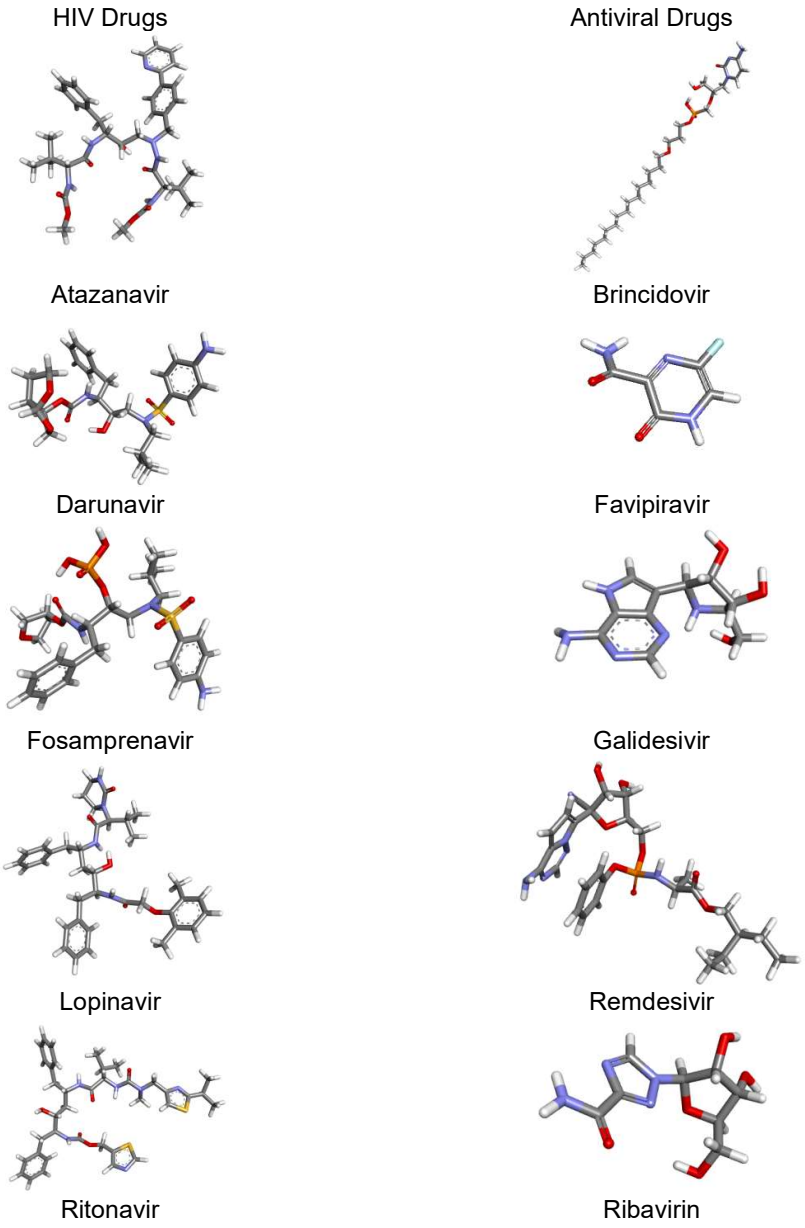

Fig. 3: 3D structures of selected FDA-approved HIV protease inhibitors and antiviral agents used in molecular docking against the MPXV protein target (PDB ID: 8B07). Compounds include Atazanavir, Darunavir, Fosamprenavir, Lopinavir, Ritonavir (HIV drugs), and Favipiravir, Galidesivir, Remdesivir, Ribavirin (broad-spectrum antivirals), with Brincidofovir included as a positive control. The molecular conformations were energy-minimized and visualized to assess fit within the target binding pocket.

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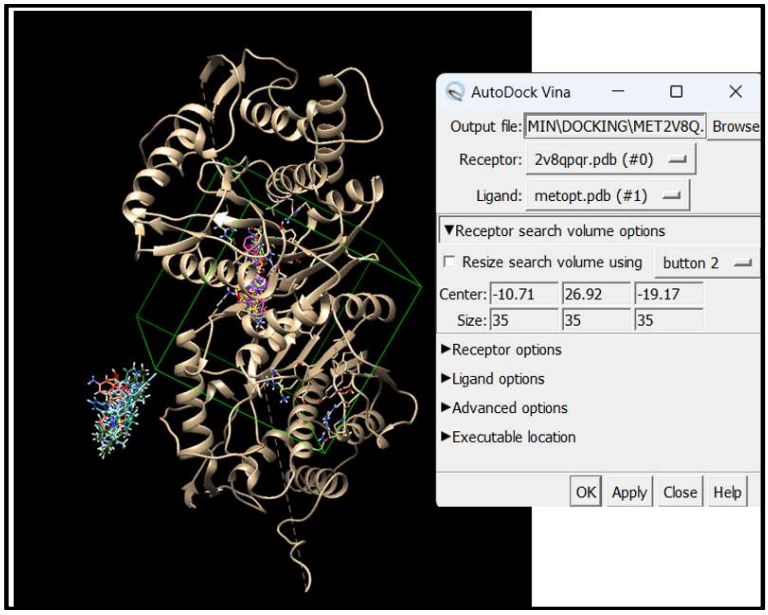

Fig. 4: Docking preparation setup in AutoDock Vina for molecular interaction analysis. The MPXV receptor protein (PDB ID: 8B07) is displayed in ribbon format, with the docking grid box (green) defining the active site region. The ligand file (metopt.pdb) is shown aligned within the predicted binding pocket. Grid box dimensions and coordinates were optimized to encompass the active site for accurate virtual screening.

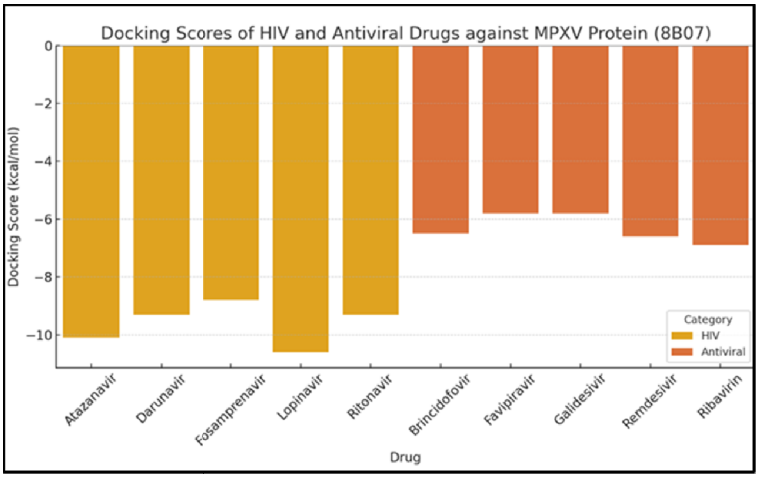

Fig. 5: Docking scores of FDA-approved HIV protease inhibitors (yellow) and antiviral agents (orange) against the MPXV protein (PDB ID: 8B07). Lopinavir and Atazanavir demonstrated the strongest binding affinities among all tested compounds, with docking scores of –10.6 and –10.1 kcal/mol, respectively. Brincidofovir was included as a positive control. Lower docking scores indicate stronger predicted protein–ligand interactions

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Category	Docking Score	Drug Name	Hydrogen Bond	π-π
Atazanavir	-10.1	HIV	ASP95, SER141	TYR189
Darunavir	-9.3	HIV	ASP95, ARG140	PHE115, TYR189
Fosamprenavir	-8.8	HIV	ASP95, ARG140	PHE115, TYR189
Lopinavir	-10.6	HIV	ASP95, ARG140, SER141	TYR189
Ritonavir	-9.3	HIV	ASP95, SER141	PHE115, TYR189
Brincidofovir	-6.5	Antiviral	ASP95, SER141, ASN161	TYR189
Favipiravir	-5.8	Antiviral	ARG140	PHE115
Galidesivir	-5.8	Antiviral	ASP95, ASP138, ARG140	PHE115
Remdesivir	-6.6	Antiviral	ASP95, ARG97, ARG140, LYS142	PHE115
Ribavirin	-6.9	Antiviral	GLY96, ASN161, ARG140, TYR189	None

Table 1: Summary of molecular docking scores, hydrogen bond interactions, and π–π stacking interactions between selected HIV and antiviral drugs and the monkeypox virus (MPXV) protein target (PDB ID: 8B07). Compounds showing both high binding affinity and favorable interactions with conserved active site residues are highlighted for repurposing potential.

control, showed a docking score of –6.5 kcal/mol and formed interactions with Asp95, Ser141, and Asn161, in addition to a stabilizing π–π interaction with Tyr189. Other antiviral compounds such as Remdesivir, Favipiravir, and Galidesivir showed weaker binding scores ranging between –5.8 and –6.6 kcal/mol and fewer stabilizing interactions, highlighting their comparatively lower binding potential. Overall, the data in Table 1 supports the hypothesis that strong hydrogen bonding with conserved catalytic residues, coupled with π–π stacking, contributes to enhanced ligand stability and binding affinity. Lopinavir and Ribavirin thus warrant further consideration for experimental validation, while Brincidofovir serves as an appropriate benchmark compound in this context.

5.3 Visualization of Molecular Interactions

Molecular interaction diagrams provide valuable structural insights into the binding orientation and specific interactions of the compounds with the MPXV protein active site. The 3D surface maps and 2D interaction diagrams for Brincidofovir, Lopinavir, and Ribavirin are shown in Figs 6A, 6B, and 6C, respectively. In Figure 6A, Brincidofovir demonstrates deep insertion into the catalytic cleft, stabilized through multiple hydrogen bonds involving Asp95, Arg97, Gly68, Ser141, and Arg140. A key π–π stacking interaction with Phe115, along with hydrophobic contacts with Val116 and Leu159, reinforces the anchoring of the compound within the binding pocket. The surface representation highlights the snug fit and favorable polar contacts between the ligand and surrounding residues.

As depicted in Figure 6B, Lopinavir exhibits an optimal binding pose tightly enclosed by the MPXV active site. The compound forms strong hydrogen bonds with Asp95, Arg140, and Ser141, and is further stabilized by a π–π interaction with Tyr189. These interactions occur in proximity to residues critical to the enzymatic function, suggesting Lopinavir's ability to interfere with substrate processing. The 2D map reveals additional van der Waals interactions that

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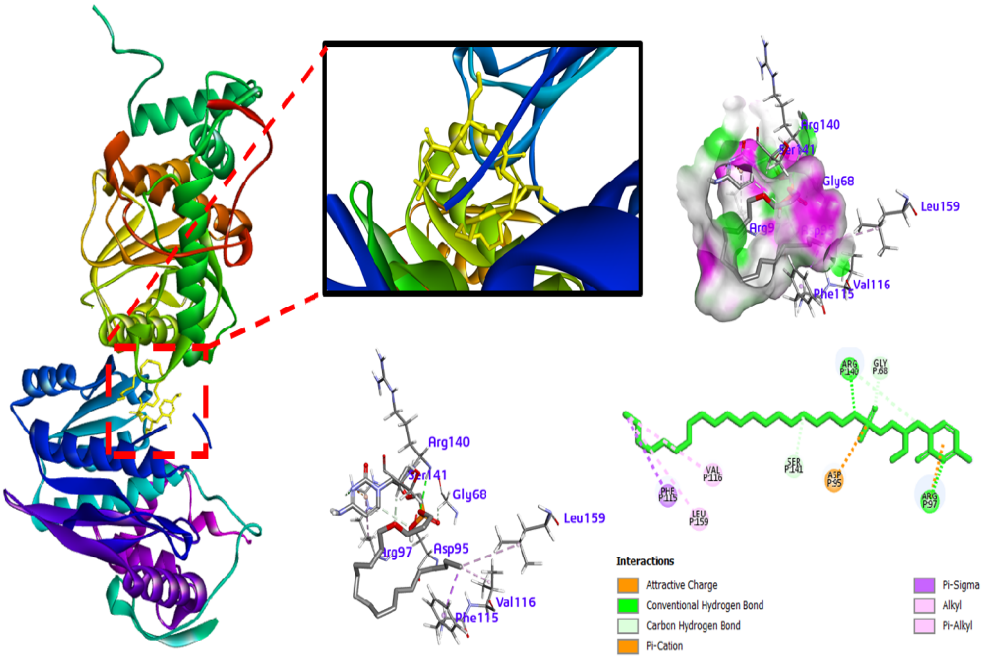
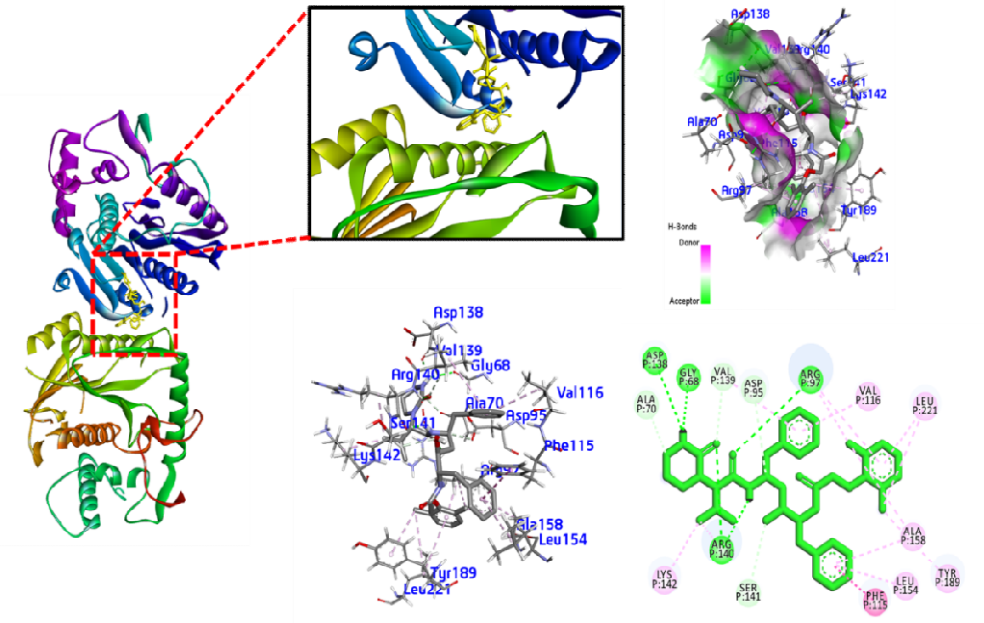
(A) Brincidofovir



(B) Lopinavir



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(C) Ribavirin

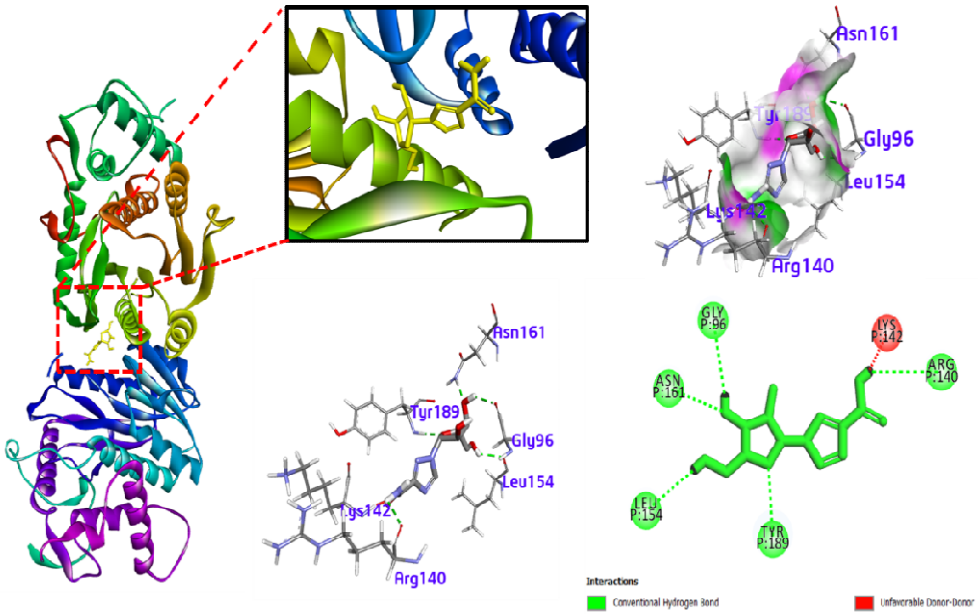

Fig. 6: 2D and 3D interaction diagrams of the top-performing compounds bound to the MPXV protein (PDB ID: 8B07). (A) Brincidofovir forms multiple hydrogen bonds with Asp95, Arg97, Gly68, Ser141, and Arg140, along with π–π stacking with Phe115 and hydrophobic interactions with Val116 and Leu159, supporting stable binding orientation. (B) Lopinavir demonstrates strong hydrogen bonding with Asp95, Arg140, and Ser141, complemented by π–π interaction with Tyr189, resulting in tight anchoring within the active site. (C) Ribavirin engages in multiple hydrogen bonds with Gly96, Asn161, Arg140, and Tyr189. Despite the absence of aromatic stacking, the compound remains well-positioned through a robust polar interaction network.

contribute to the molecule's high-affinity profile. Figure 6C illustrates the binding of Ribavirin, which displays a well-anchored pose predominantly supported by a network of hydrogen bonds with Gly96, Asn161, Arg140, and Tyr189. While π–π stacking is not observed, the extensive hydrogen bonding and complementary orientation within the polar region of the active site provide sufficient stability. The visualization highlights Ribavirin's interaction depth and its utility as a moderate reference inhibitor.

These visualizations confirm that binding stability arises from a combination of polar interactions and hydrophobic contacts, particularly in compounds such as Lopinavir and Brincidofovir. The strength and positioning of these interactions are consistent with the docking results and support their potential for further investigation.

5.4 Physicochemical, Drug-Likeness, Pharmacokinetics, and Toxicity Analysis of Lopinavir and Remdesivir

The primary challenge in drug design is the development of compounds that exhibit both high target affinity and optimal pharmacokinetic properties. In addition to binding efficiency, a potential medication must have a low toxicity profile, suitable selectivity, and ideal features in absorption, distribution, metabolism, and excretion (ADME). The fulfillment of these requirements by the selected compounds and their

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demonstration of a favorable therapeutic profile are significantly influenced by the clinical phase of drug development. This study assessed the physicochemical and ADME-T properties of Lopinavir and Remdesivir utilizing SwissADME and Ptotox-II tools.

Table 2 encapsulates the results, Physicochemical properties and drug-likeness. Lopinavir (638.84 g/mol) and Remdesivir (468.40 g/mol) possess molecular weights beyond the conventional Lipinski's rule-of-five limit (500 Da) for optimal oral bioavailability and toxicity assessment. Lopinavir exceeds this criterion; however, Remdesivir remains within the permissible range, potentially making it more advantageous for oral administration. The log P data indicates that Lopinavir (4.73) exhibits more lipophilicity than Remdesivir (2.78). A high log P often suggests enhanced membrane permeability, but it may also lead to decreased solubility, so affecting absorption. In contrast, the moderate log P of remdesivir indicates a more equilibrated profile between solubility and permeability.

The topological polar surface area (TPSA) is significant for oral bioavailability. The TPSA should typically be below 140 Å² for optimal intestinal absorption. The calculated TPSA values for Remdesivir (194.10 Å2) and Lopinavir (148.85 Å2) indicate that both drugs exceed this threshold, suggesting potentially diminished oral bioavailability. Metabolism and the solubility of medications may also influence overall absorption rates. Lopinavir possesses 22 rotatable bonds, while Remdesivir has 9, so affecting their molecular flexibility. An increase in rotatable bonds may enhance receptor binding but potentially diminish bioavailability by hastening metabolic degradation.

5.5 Pharmacokinetics and Drug Absorption

The reduced gastrointestinal absorption of both Lopinavir and Remdesivir indicates that their bioavailability would be compromised when administered orally. Their elevated TPSA values, indicating restricted passive diffusion via the intestinal barrier, further corroborate this assertion. Neither medicine is anticipated to traverse the blood-brain barrier (BBB), hence diminishing the risk of central nervous system (CNS) damage. Considering that numerous pharmaceutical candidates induce unintentional neurotoxicity, this trait is advantageous. Water solubility (Log S) is significantly essential. Remdesivir possesses a log S of -1.75, signifying substantial solubility in aqueous environments, whereas lopinavir exhibits a log S of -5.53, denoting extremely poor solubility. Remdesivir may be more suitable for oral administration than Lopinavir, as inadequate solubility often correlates with diminished bioavailability. Both compounds are identified as substrates of P-glycoprotein (P-gp), which may result in active efflux from cells, thereby diminishing their intracellular concentration and potency.

5.6 Assessment of Toxicity

The advancement of pharmaceuticals is fundamentally contingent upon its toxicity. The long-term safety of Lopinavir and Remdesivir is evidenced by their anticipated lack of mutagenic or carcinogenic properties. Nonetheless, hepatotoxicity presents complications. Lopinavir may be hepatotoxic; therefore, those with pre-existing liver conditions should be closely monitored. Remdesivir may be a safer option in this regard, as it is not anticipated to be hepatotoxic. Both drugs have little skin permeability, as indicated by their negative log Kp values (-6.83 cm/s for Lopinavir and -9.97 cm/s for Remdesivir), and are unlikely to cause significant dermatological harm. Significant new insights into the druggability of Lopinavir and Remdesivir arise from their physicochemical and ADME-T properties. Given that remdesivir possesses a more balanced lipophilicity profile and superior solubility compared to Lopinavir, it may be more suitable for systemic absorption. Both drugs exhibit inadequate gastrointestinal absorption, perhaps limiting their oral bioavailability. From

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Table 2: Physicochemical Properties, Drug-Likeness, Pharmacokinetics, and Toxicity of Lopinavir and Remdesivir

Parameter	Lopinavir	Remdesivir
Physicochemical Parameter		
Formula	$C_{36}H_{54}N_4O_6$	$C_{17}H_{25}N_3O_6P$
Molecular Weight (MW) (g/mol)	638.84	468.4
Log P (Lipophilicity)	4.73	2.78
Number of Heavy Atoms	46	32
Number of Aromatic Heavy Atoms	6	14
Fraction Csp3	0.56	0.53
Number of Rotatable Bonds	22	9
Number of H-bond Acceptors (HBA)	7	9
Number of H-bond Donors (HBD)	7	4
Topological Polar Surface Area (TPSA) (Å²)	148.85	194.1
Molar Refractivity	180.61	-
Water Solubility (Log S)	-5.53 (Very Poor)	-1.75 (Very Soluble)
Pharmacokinetics		
GI Absorption	Low	Low
Blood-Brain Barrier (BBB) Permeability	No	No
P-gp Substrate	Yes	Yes
CYP1A2 Inhibitor	No	No
CYP2C19 Inhibitor	No	No
CYP2C9 Inhibitor	No	No
CYP2D6 Inhibitor	No	No
CYP3A4 Inhibitor	No	No
Skin Permeability (log Kp, cm/s)	-6.83	-9.97
Drug-likeness and Bioavailability		
Lipinski Rule of Five	Yes (1 violation: MW > 500)	Yes (1 violation: NorO > 10)
Ghose Rule	No (3 violations)	Yes
Veber Rule	No (2 violations: Rotors > 10, TPSA > 140)	No (1 violation: TPSA > 140)
Egan Rule	No (1 violation)	No (1 violation)
Muegge Rule	No (2 violations)	No (1 violation)
Bioavailability Score	0.55	0.55
Toxicity Assessment		
Ames Test	No	No
Hepatotoxicity	Yes	No
Carcinogenicity	No	Yes
LD50 (mol/kg)	2.033	2.833
LD50 (mg/kg)	1017	950

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From a toxicity perspective, Remdesivir is less prone than Lopinavir to induce hepatotoxicity, which is advantageous in clinical environments. Despite neither drug penetrating the blood-brain barrier, their status as P-glycoprotein substrates suggests susceptibility to efflux mechanisms, potentially diminishing their intracellular concentrations. Despite the promising pharmacokinetic properties of these compounds, formulation strategies such as nanoparticle delivery systems, prodrug approaches, or alternative administration routes may be necessary to enhance their bioavailability and therapeutic effectiveness.

6. Discussion

This study combined molecular docking and *in silico* pharmacokinetic profiling to evaluate FDA-approved antiviral drugs for their potential repurposing against monkeypox virus (MPXV) using the viral protein structure (PDB ID: 8B07) as the target. Among all tested compounds, Lopinavir exhibited the strongest binding affinity (–10.6 kcal/mol). This HIV protease inhibitor formed multiple hydrogen bonds with essential catalytic residues Asp95, Arg140, and Ser141, and was further stabilized by a π–π interaction with Tyr189. The strength and specificity of these interactions suggest that Lopinavir fits well within the active site and could inhibit MPXV protease activity effectively. These findings align with previous reports of Lopinavir's antiviral activity, including its studied application during the SARS-CoV-2 pandemic (Cao et al., 2020). Ribavirin, the top-performing broad-spectrum antiviral in the current study, achieved a docking score of –6.9 kcal/mol. Despite the absence of π–π stacking, it exhibited a stable interaction profile supported by multiple hydrogen bonds involving Gly96, Asn161, Arg140, and Tyr189. This hydrogen bonding network contributed to a stable binding conformation and reflected Ribavirin's established activity against a range of RNA viruses, including those responsible for hemorrhagic fevers and respiratory infections (Madelain et al., 2022). The absence of aromatic interactions may explain its moderate docking score relative to Lopinavir.

Brincidofovir, included as a positive control based on its approved use against smallpox and related poxviruses, yielded a docking score of –6.5 kcal/mol. Its predicted binding involved key residues Asp95, Ser141, Arg140, Gly68, and Asn161, with additional π–π stacking against Phe115 and hydrophobic contacts with Val116 and Leu159. These interaction patterns were consistent with its known mechanism of antiviral action (Chittick et al., 2017) and validated the reliability of the docking methodology used in this study. In addition to binding affinity and interaction profiles, the physicochemical and pharmacokinetic properties of Lopinavir and Remdesivir were evaluated to assess their drug-likeness and potential clinical utility. Lopinavir's molecular weight (638.84 g/mol) exceeds the Lipinski threshold of 500 Da, whereas Remdesivir (468.4 g/mol) falls within the acceptable range, suggesting greater suitability for oral delivery. However, both compounds showed elevated topological polar surface areas (TPSA), 148.85 Å² for Lopinavir and 194.10 Å² for Remdesivir—values above the typical limit for efficient intestinal absorption, indicating limited oral bioavailability.

Remdesivir demonstrated superior aqueous solubility (log S: –1.75) compared to Lopinavir (log S: –5.53), suggesting better formulation potential for systemic administration. Neither compound is predicted to cross the blood-brain barrier (BBB), which reduces the likelihood of neurotoxicity. Both were identified as P-glycoprotein (P-gp) substrates, which may reduce intracellular drug accumulation and efficacy. Their moderate bioavailability scores (0.55 for both) and lack of CYP450 inhibition suggest a relatively low risk for drug-drug interactions, although both compounds may still undergo metabolic clearance via other pathways. Toxicity predictions further differentiated the two agents. Lopinavir was flagged for potential hepatotoxicity, necessitating caution

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in patients with underlying liver conditions. In contrast, Remdesivir was not associated with hepatotoxicity in the predictive model, though it was flagged for potential carcinogenicity. Both drugs tested negative for mutagenicity in the Ames test and demonstrated low skin permeability, limiting the likelihood of dermal toxicity. The predicted LD_{50} values indicated similar acute toxicity ranges.

Taken together, Lopinavir demonstrates potent binding affinity and favorable target engagement but faces limitations in solubility and potential hepatotoxicity. Remdesivir, although not included among the top binders, offers a more balanced pharmacokinetic and safety profile. These differences underscore the importance of considering both target binding and systemic behavior when evaluating drug candidates for repurposing.The combined docking and ADME-T analyses support the advancement of Lopinavir and Remdesivir as candidates for further investigation. Lopinavir, in particular, should be prioritized for in vitro and in vivo validation based on its superior binding performance, while Remdesivir may benefit from formulation optimization to overcome its pharmacokinetic limitations. These findings reinforce the value of integrated computational approaches in identifying viable therapeutic options against emerging viral threats such as MPXV.

7. Conclusion

This study demonstrates the potential of drug repurposing for monkeypox virus (MPXV) by integrating molecular docking with pharmacokinetic and toxicity profiling. Among the tested compounds, Lopinavir exhibited the strongest binding affinity to the MPXV target protein (PDB ID: 8B07), supported by multiple hydrogen bonds and π–π stacking interactions. Ribavirin, while moderately potent, maintained stable binding through polar contacts. The inclusion of Brincidofovir as a positive control confirmed the predictive reliability of the docking protocol, as its interaction profile aligned with known clinical data. Physicochemical and ADME-T assessments further revealed that Remdesivir holds promise due to its balanced solubility, low hepatotoxicity, and favorable oral formulation properties despite limited docking performance. In contrast, Lopinavir's superior target engagement may be compromised by poor solubility and hepatotoxic risk. These findings emphasize the importance of a multi-parametric approach that evaluates both binding affinity and pharmacokinetic behavior when prioritizing compounds for antiviral therapy development.

8. Future Directions

While computational results provide valuable early-stage insights, experimental validation remains essential to confirm the antiviral activity of Lopinavir, Remdesivir, and Ribavirin against MPXV. Cell-based assays and viral replication inhibition studies should be conducted to verify the docking predictions and assess efficacy in biologically relevant systems. Additionally, the development of advanced drug delivery systems, such as liposomal or nanoparticle-based formulations, may help overcome the solubility and bioavailability limitations identified, particularly for Lopinavir. Future work should also explore structural analogues or hybrid derivatives of these lead compounds to enhance selectivity, minimize toxicity, and improve pharmacological profiles. Integrating molecular dynamics simulations and binding free energy calculations could further refine the prediction of binding stability and kinetics. Finally, expansion of the compound library to include natural products and novel scaffolds may uncover additional candidates with improved drug-like characteristics suitable for MPXV therapy.

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