

In Silico Analysis of Repurposed Antiviral Drugs for Marburg Virus Management

P. Suriyakala¹, K. Vijayalakshmi², S. Asmitha³, A. Christy Menusha⁴, V. Varshini⁵, N. Sharmila⁶,
M. Masco⁷, M. Bhuvanesh⁸

^{1,2,3,4,5,6,7,8} *Thanthai Roever College of Pharmacy, Perambalur*

Abstract—Marburg virus disease (MVD) is a highly lethal hemorrhagic fever caused by the Marburgvirus (MARV), a zoonotic pathogen belonging to the Filoviridae family. Since its identification in 1967, MVD has posed significant public health threats due to rapid disease progression, high case fatality rates, and limited therapeutic options. This study addresses the molecular characteristics, transmission pathways, symptomatology, and current challenges in managing MVD, with emphasis on its zoonotic origins primarily from *Rousettus aegyptiacus* bats. To address the urgent need for effective treatments, in silico molecular docking was employed to evaluate the binding affinities of existing antiviral drugs—indinavir, zalcitabine, zidovudine, delavirdine, and acyclovir—against the Marburg VP24 matrix protein (PDB ID: 4OR8). Indinavir demonstrated the strongest binding affinity (−9.0 kcal/mol), with key interactions at ILE 204, GLY 185, GLN 186, LYS 103, LYS 182, LEU 183, and THR 184 via van der Waals forces, hydrogen bonding, and alkyl interactions. Comprehensive virtual analyses including physicochemical profiling, ADME pharmacokinetics, drug-likeness assessment (Lipinski, Ghose, Veber, Egan, Muegge), PASS biological activity prediction, and ProTox-II toxicity prediction support the feasibility of these candidates. These findings underscore the potential of drug repurposing as a viable strategy against MVD and provide a robust foundation for subsequent preclinical and clinical investigations.

Index Terms—Marburg virus disease; Filoviridae; antiviral drug repurposing; in silico molecular docking; VP24; ADME; pharmacokinetics; zoonotic pathogen

I. INTRODUCTION

Marburg virus disease (MVD) is an uncommon but extremely deadly viral hemorrhagic fever caused by the Marburgvirus (MARV), which belongs to the Filoviridae family

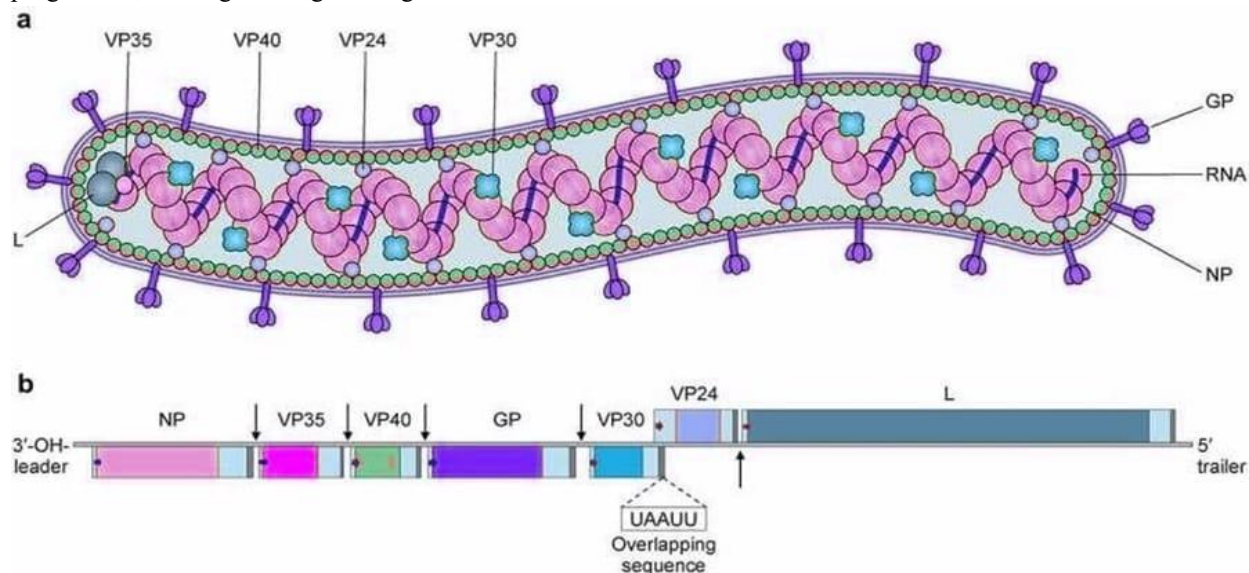
and the Mononegavirales order. The virus was first discovered at the same time in 1967 in Marburg and Frankfurt in Germany, as well as in Belgrade, which was part of Yugoslavia at the time. Since then, the disease has led to several outbreaks, mainly in sub-Saharan Africa, with mortality rates varying from 23% to 100% [1,2]. MVD manifests through a rapid decline in health, marked by fever, bleeding, and multiple organ failures, including liver, spleen, and kidney involvement, frequently resulting in death within 8 to 9 days after symptoms start [3,4].

MARV is grouped under the Marburgvirus genus, which includes a single species known as Marburg marburgvirus; phylogenetic studies differentiate between two viral types: MARV and Ravn virus (RAVV) [5,6]. The Egyptian fruit bat (*Rousettus aegyptiacus*) has been recognized as the main zoonotic reservoir, with most human infections originating in caves or mines inhabited by bats [7–13]. The composition of MARV consists of seven proteins: nucleoprotein (NP), RNA-dependent RNA polymerase (L), polymerase cofactor VP35, transcriptional activator VP30, major matrix protein VP40, minor matrix protein VP24, and surface glycoprotein (GP)[17]. At present, there is no officially approved antiviral treatment for MVD. The usual care involves supportive measures, such as fluid replenishment and managing symptoms, which remain the primary treatment approach. The lack of specific therapies, along with the high rate of transmission and deadly nature of the virus, highlights the urgent need for innovative drug development strategies. Drug repurposing, which involves finding new medical uses for existing approved drugs, is a practical and economical approach that utilize already available safety information to fast-track therapeutic

advancements [22].

Computational techniques, especially molecular docking, have turned into essential instruments for the preliminary identification of possible drug candidates. The VP24 matrix protein of MARV serves as a structurally stable target involved in the processes of viral assembly, budding, and disease progression, making it a logical target for treatment

possibilities [17]. This research utilized PyRx-based molecular docking with VP24 (PDB ID: 4OR8) to assess five known antiviral agents: indinavir, zalcitabine, zidovudine, delavirdine, and acyclovir, and in addition, it evaluated their pharmacokinetic, drug-likeness, biological efficacy, and toxicity profiles using validated in silico systems.



II. EPIDEMIOLOGY AND GLOBAL OUTBREAKS

Since its initial identification in 1967, Marburg virus has been responsible for geographically dispersed outbreaks predominantly concentrated in African nations, with sporadic incursions into European and

Central Asian settings via infected materials or laboratory incidents. Table 1 summarises the major documented outbreaks in chronological order, highlighting case fatality rates, suspected origins, and epidemiological contexts [18].

Table 1. Major documented outbreaks of Marburg virus disease in chronological order.

Year	Location	Origin	CFR	Notable Details	Strain(s)
1967	Germany/Serbia	Uganda	23%	Simultaneous outbreaks in lab workers handling African Green Monkeys	MARVCi67 et al.
1975	South Africa	Zimbabwe	33%	Traveller from Zimbabwe; transmission to companion and nurse	MARV Cn/Hogan/Ozo
1980/1987	Kenya	Kitum Cave	50/100%	Travel to Kitum Cave, Mt. Elgon National	MARVMu; RAVVRavn

				Park	
1990	Russia	Laboratory	100%	Laboratory contamination incident	_____
1998-2000	DRC	Durba, DRC	83%	Youngmale gold-mine workers; Durba Declared epicentre	Multiple strains
2004-2005	Angola	Uige Province	90%	Largest outbreak on record; children disproportionately affected	MARV Angola
2007, 2012, 2014 and 2017	Uganda	Various districts	25-100%	Mine-associated outbreaks; Kitaka cave bats implicated	MARV-01Uga et al.
2021	Guinea	Gueckedou	100%	Single fatal case; post-mortem confirmation	_____
2022	Ghana	Ashanti	~75%	Two confirmed fatal cases; ongoing research	_____
Feb-Jun 2023	Tanzania/Equatorial Guinea	_____	67%	WHO confirmed outbreak; cross-border alert	_____
Dec 2024	Rwanda	Kigali	~23%	66 confirmed cases; majority healthcare workers	_____

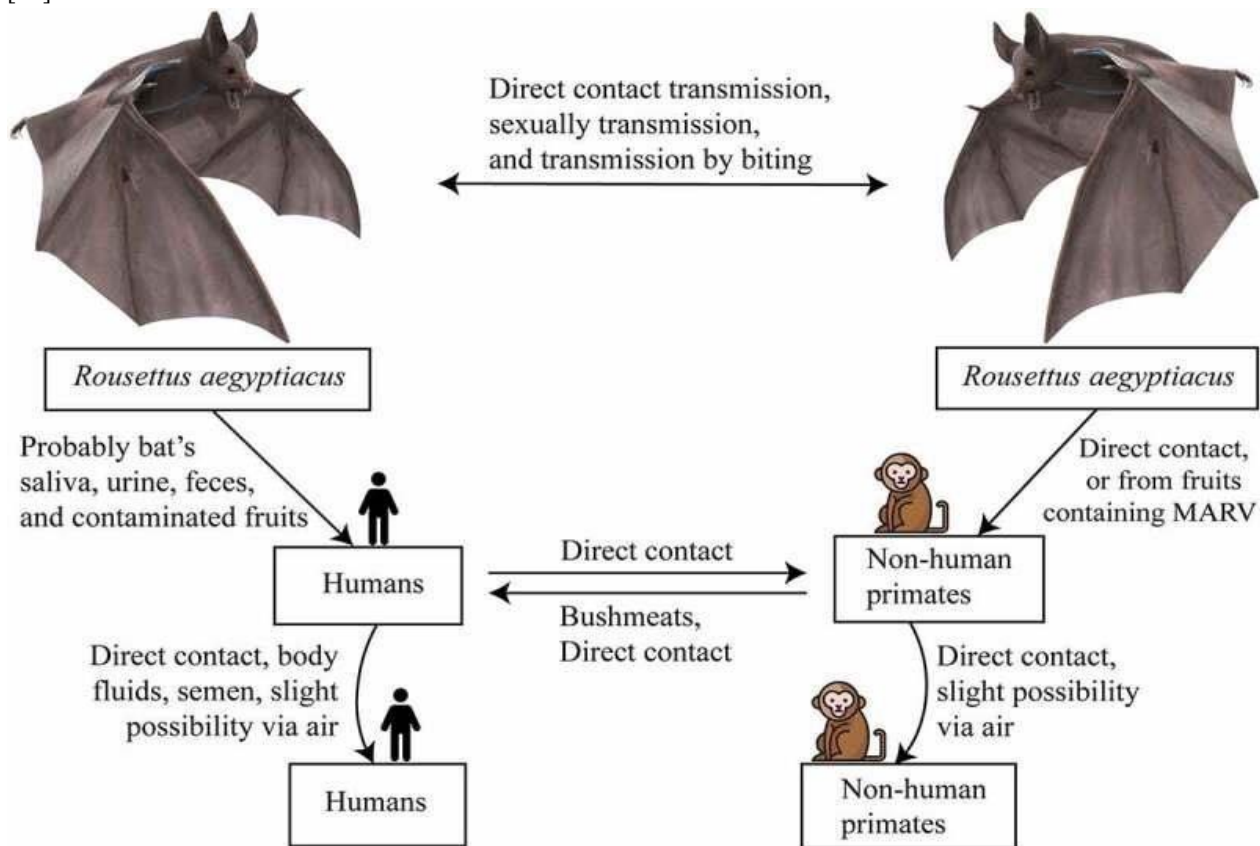
The 2004–2005 Angola outbreak, with a case fatality rate of 90% and 252 confirmed cases, remains the largest MVD outbreak on record. The most recent outbreak in Rwanda (December 2024) was notable for its disproportionate impact on healthcare workers in Kigali, signalling continued nosocomial transmission risk [18].

III. TRANSMISSION ROUTES AND CLINICAL PRESENTATION

3.1 Transmission

Zoonotic transmission occurs through prolonged or direct contact with infected reservoir bats (*R. aegyptiacus*) via bites or exposure to bodily fluids, faeces, or blood. Human-to-human transmission is mediated by direct contact with infected body fluids including blood, urine, saliva, faeces, vomit, breast milk, amniotic fluid, sweat, and semen [19,20]. Healthcare settings present heightened risk for nosocomial transmission, as evidenced by the 2024 Rwanda outbreak. Environmental contamination of surfaces with infectious fluids, and laboratory exposure, constitute additional transmission pathways

[20].



3.1. Clinical Manifestation and Disease Progression

Following an incubation period of 2–21 days (reported ranges: 2–26 days) [23–25], MVD presents in sequential stages. Initial symptoms include high fever, rigors, severe headache, malaise, and myalgia. By day 3–5, gastrointestinal manifestations—watery diarrhoea, abdominal cramping, nausea, and vomiting—emerge alongside a characteristic non-pruritic maculopapular rash on the trunk. In severe cases, jaundice, progressive weight loss, disorientation, haemorrhage from multiple sites, and hepatic failure supervene. Late-stage disease may include testicular inflammation and severe renal impairment. Fatal outcomes, predominantly from hypovolaemic shock and massive blood loss, typically occur within 8–9 days of symptom onset [14,20].

IV. AIMS AND OBJECTIVES

The overarching aim of this study was to identify potential antiviral drugs suitable for repurposing against Marburg virus via integrated in silico

methodologies. The specific objectives were:

- Molecular Docking: Assess binding affinity and interaction profiles of selected antiviral compounds with Marburg VP24 protein (PDB: 4OR8) using AutoDock Vina via PyRx.
- ADME Analysis: Evaluate pharmacokinetic properties and oral drug-likeness using SwissADME.
- Toxicity Prediction: Predict acute oral toxicity, organ toxicity, and toxicological endpoints using ProTox-II.
- Biological Activity Prediction: Estimate probable pharmacological activities using PASS online.
- Drug Comparison: Compare candidate compounds against established antivirals based on computational outputs.
- Candidate Selection: Identify the most promising drug candidate for further in vitro and in vivo validation.

V. MATERIALS AND METHODOLOGY

5.1. Target Protein Preparation

The crystal structure of Marburg virus VP24 matrix

protein (PDB ID: 4OR8) was retrieved from the RCSB Protein Data Bank (www.rcsb.org) in PDB format. The three-dimensional structure was imported into BIOVIA Discovery Studio Visualizer for pre-processing. Heteroatoms, crystallographic water molecules, and co-crystallised ligands were systematically removed to eliminate non-specific interactions during docking simulations. Polar hydrogen atoms were added to ensure accurate representation of the electrostatic environment, enabling appropriate hydrogen bond formation. Structural integrity was visually inspected prior to docking.

5.2. Ligand Preparation

Five clinically approved antiviral compounds—indinavir (HIV protease inhibitor), zalcitabine (reverse transcriptase inhibitor, NRTI), zidovudine (reverse transcriptase inhibitor, NRTI), delavirdine (non-nucleoside reverse transcriptase inhibitor, NNRTI), and acyclovir (DNA polymerase inhibitor)—were selected based on their established antiviral mechanisms. Canonical SMILES strings were retrieved from PubChem (pubchem.ncbi.nlm.nih.gov). Two-dimensional structures were generated in ACD/ChemSketch via the SMILES conversion function and saved as .mol files. Ligand files were subsequently imported into BIOVIA Discovery Studio, where explicit hydrogen atoms were added. All ligands were exported in .pdb format compatible with molecular docking platforms.

5.3. Molecular Docking

Molecular docking simulations were conducted using PyRx (Python Prescription 0.8), capitalising on its integrated AutoDock Vina algorithm for virtual screening. Both the pre-processed protein and energy-minimised ligands were imported in PDBQT format. The active binding site on VP24 was defined based on available literature and PyRx binding site prediction capabilities. Grid box parameters (centre coordinates and dimensions) were optimised to fully encompass the identified binding cavity. Each ligand underwent multiple docking runs, yielding binding energy values (ΔG , kcal/mol) as quantitative measures of predicted binding affinity. The top-ranked docked complexes were exported and visualised in BIOVIA Discovery Studio to characterise protein-ligand interaction types and key

amino acid residues involved.

5.4. ADME and Drug-Likeness Prediction

Pharmacokinetic and drug-likeness profiles were determined using the SwissADME web platform (www.swissadme.ch). Canonical SMILES for each compound were submitted to compute physicochemical descriptors, lipophilicity (via five independent models: iLOGP, XLOGP3, WLOGP, MLOGP, and SILICOS-IT), water solubility, ADME parameters, blood-brain barrier permeability, P-glycoprotein substrate prediction, CYP enzyme inhibition/substrate profiles, and skin permeability. Drug-likeness was evaluated against Lipinski, Ghose, Veber, Egan, and Muegge filters; oral bioavailability was scored using the Abbott bioavailability score. The BOILED-Egg model was applied to predict passive gastrointestinal absorption and blood-brain barrier penetration.

5.5. PASS Prediction

Pharmacological activity spectra were predicted using PASS Online (Prediction of Activity Spectra for Substances), a Bayesian algorithm-based tool trained on over 260,000 biologically active compounds. Each ligand SMILES was submitted for activity prediction across a library of >4,000 biological activity terms. Results were reported as probability of activity (P_a) and probability of inactivity (P_i); compounds with $P_a > P_i$ were considered active for a given pharmacological endpoint. Average predictive accuracy of PASS approaches 95% based on leave-one-out cross-validation [PASS documentation].

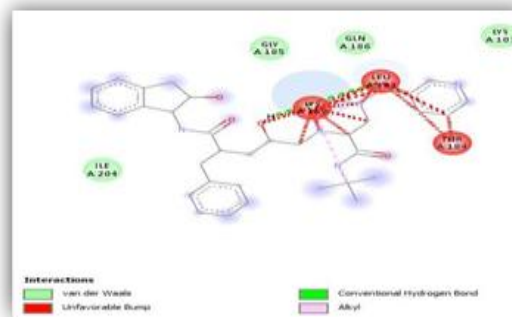
5.6. Toxicity Prediction

In silico toxicity profiling was performed using the ProTox-II webserver (tox-new.charite.de/protox_II). The platform employs machine learning algorithms for multilevel toxicity prediction including: (i) acute oral toxicity with LD50 values and GHS toxicity classification; (ii) organ toxicity—specifically hepatotoxicity; and (iii) toxicological endpoints including mutagenicity, carcinogenicity, immunotoxicity, and cytotoxicity. Results were expressed as predicted toxicity class and percentage confidence scores.

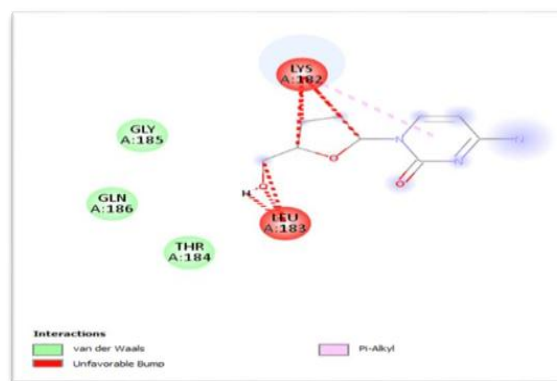
VI. RESULTS AND DISCUSSION

6.1. Molecular Docking: Binding Affinity and Interaction Analysis

All five antiviral compounds successfully docked within the active binding pocket of Marburg VP24 (PDB: 4OR8). Binding energies ranged from -7.2 to -9.0 kcal/mol (Table 2). Indinavir demonstrated the highest binding affinity (-9.0 kcal/mol), forming a conventional hydrogen bond with LEU 183 and alkyl interactions with LYS 182, supplemented by extensive van der Waals contacts with GLY 185, GLN 186, LYS 103, ILE 204, and THR 184. Zalcitabine and zidovudine (both -7.5 kcal/mol) showed comparable affinities predominantly via van der Waals interactions and pi-alkyl contacts at overlapping residues. Delavirdine (-7.4 kcal/mol) exhibited a broader interaction profile including hydrogen bonding with ALA 2, pi-anion interactions at LEU 183, and pi-alkyl contacts mediated by its benzene moiety. Acyclovir (-7.2 kcal/mol) formed hydrogen bonds with GLN 186 and pi-alkyl interactions at LYS 182, with notable unfavourable bumps at LYS 182 and LEU 183 indicating minor steric conflicts.



2D Structure of indinavir with VP24



2D Structure of zalcitabine with VP24

Table 2. Molecular docking scores and protein-ligand interaction profiles of antiviral compounds against Marburg VP24 (PDB: 4OR8).

Ligand	ΔG (kcal/mol)	Interacting Amino Acids	Bond Types
Indinavir	-9.0	ILE 204, GLY 185, GLN 186, LYS 103, LYS 182, LEU 183, THR184	Van der Waals, H-bond, Alkyl
Zalcitabine	-7.5	GLY 185, GLN 186, THR 184, LYS 182, LEU 183	Van der Waals, Pi-Alkyl
Zidovudine	-7.5	GLY 185, GLN 186, THR 184, LYS 182, LEU 183	Van der Waals
Delavirdine	-7.4	GLY 185, GLN 186, THR 184, LYS 182, LEU 183, GLN 105, ALA 2, GLU 3	Van der Waals, H-bond, Pi-Alkyl, Pi-Anion
Acyclovir	-7.2	GLY 185, GLN 186, THR 184, LYS 182, LEU 183	H-bond, Pi-Alkyl

Key Finding: Indinavir exhibited the strongest binding affinity (-9.0 kcal/mol) among all tested compounds, forming stable hydrogen bonds and hydrophobic interactions with key VP24 residues, positioning it as the most promising

repurposing candidate.

6.1. Physicochemical Properties

Physicochemical descriptors computed via SwissADME are summarised in Table 3. Indinavir

(MW: 613.79 g/mol) exceeds Lipinski's 500 g/mol threshold, a characteristic shared by several clinically effective antivirals. Its Csp3 fraction (0.47) reflects appropriate structural diversity, balancing sp² aromatic and sp³ aliphatic character to confer metabolic stability. Fourteen rotatable bonds, while exceeding the ideal ≤ 10 , impart conformational flexibility critical for accommodating the irregular VP24 binding pocket. Hydrogen bond acceptors (7)

and donors (4) fall within Lipinski limits, supporting aqueous solubility and adequate bioavailability. A TPSA of 118.03 Å² satisfies the ≤ 140 Å² threshold for acceptable membrane permeability. Lighter analogues such as zalcitabine (MW: 211.22 g/mol) and acyclovir (MW: 225.20 g/mol) are fully Lipinski-compliant; however, their moderate docking scores suggest lower target complementarity for VP24.

Table 3. *Physicochemical descriptors of selected antiviral candidates computed by SwissADME.*

Drug	MW (g/mol)	Heavy Atoms	Arom. Atoms	Frac Csp3	Rot. Bonds	HBA	HBD	TPSA (Å ²)
Indinavir	613.79	45	18	0.47	14	7	4	118.03
Zalcitabine	211.22	15	6	0.56	2	4	2	90.37
Zidovudine	267.24	19	6	0.60	3	7	2	134.07
Delavirdine	456.56	32	15	0.36	7	4	3	118.81
Acyclovir	225.20	16	9	0.38	4	5	3	119.05

6.2. Lipophilicity Analysis

Lipophilicity profiles were evaluated using five independent computational models (Table 4). Indinavir's consensus log P (2.78) indicates balanced lipophilicity, ensuring adequate intestinal membrane permeability without excessive tissue accumulation. The divergence between iLOGP (4.05) and MLOGP (1.33) reflects

the heterogeneous molecular regions of the compound. Acyclovir (consensus log P: -0.99) and zalcitabine (-0.45) are highly hydrophilic, which may favour renal clearance but limit passive permeability. Delavirdine (1.94) and zidovudine (-0.15) occupy intermediate positions consistent with their established clinical pharmacokinetics.

Table 4. *Lipophilicity profiles of antiviral candidates assessed by five independent computational models.*

Drug	iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS -IT	ConsensusLogP	Interpretation
Indinavir	4.05	2.92	1.63	1.33	3.97	2.78	Balanced lipophilicity
Zalcitabine	1.05	-1.30	-0.82	-0.70	-0.47	-0.45	Hydrophilic
Zidovudine	1.76	0.05	-0.52	-1.25	-0.78	-0.15	Hydrophilic
Delavirdine	2.55	2.45	2.65	0.75	1.31	1.94	Moderate lipophilicity
Acyclovir	0.48	-1.56	-1.48	-1.83	-0.57	-0.99	Highly hydrophilic

6.3. Pharmacokinetic (ADME) Profile

All five compounds demonstrated high predicted gastrointestinal absorption (Table 5). None exhibited blood-brain barrier permeability, a desirable characteristic minimising central nervous system adverse effects. Indinavir and delavirdine are P-glycoprotein substrates, which has implications for efflux-mediated bioavailability and potential drug-drug interactions. Delavirdine uniquely inhibits

CYP2C9, CYP2D6, and CYP3A4, indicating a broad cytochrome P450 interaction profile that warrants clinical pharmacokinetic caution. The remaining compounds showed minimal CYP450 interactions, suggesting a lower risk of metabolic drug interactions. All compounds demonstrated low predicted skin permeability (log Kp: -7.35 to -8.78 cm/s), consistent with negligible transdermal absorption following systemic administration.

Table 5. *Pharmacokinetic (ADME) properties and CYP450 interaction profiles.*

Drug	GI Abs	BBB	P-gp	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4	Log Kp (cm/s)
Indinavir	High	No	Yes	No	No	No	No	No	-7.97
Zalcitabine	High	No	No	No	No	No	No	No	-8.51
Zidovudine	High	No	No	No	No	No	No	No	-7.89
Delavirdine	High	No	Yes	No	No	Yes	Yes	Yes	-7.35
Acyclovir	High	No	No	No	No	No	No	No	-8.78

6.4. Drug-Likeness Assessment

Drug-likeness evaluation using multiple validated pharmaceutical filters is summarised in Table 6. All five compounds satisfy Lipinski's Rule of Five, supporting their candidacy as orally administered drugs. None pass the Ghose filter, attributable primarily to molecular weight constraints; however, this filter was developed for CNS drugs and is less

discriminating for antiviral applications. Zalcitabine, delavirdine, and acyclovir satisfy the Veber and Egan filters, indicating favourable passive permeability and oral absorption predictions. All compounds share an Abbott bioavailability score of 0.55, indicating moderate but clinically relevant oral bioavailability—consistent with their established clinical use.

Table 6. *Drug-likeness assessment of antiviral candidates against validated pharmaceutical filters.*

Drug	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score
Indinavir	Yes	No	No	Yes	No	0.55
Zalcitabine	Yes	No	Yes	Yes	Yes	0.55
Drug	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score
Zidovudine	Yes	No	Yes	No	Yes	0.55
Delavirdine	Yes	No	Yes	Yes	Yes	0.55
Acyclovir	Yes	No	Yes	Yes	Yes	0.55

6.5. PASS Biological Activity Prediction

PASS prediction results are detailed below. Indinavir demonstrated high predicted probability for antiviral (HIV) activity (Pa: 0.758) and HIV-1 protease inhibition (Pa: 0.670), consistent with its established mechanism of action (Table 7a). Zalcitabine showed high predicted activity as an RNA-directed DNA polymerase inhibitor (Pa: 0.906) and DNA synthesis inhibitor (Pa: 0.887) (Table 7b). Zidovudine

demonstrated the highest predicted antiviral activity (Pa: 0.939) and reverse transcriptase inhibition (Pa: 0.932) (Table 7c). Delavirdine exhibited more modest predicted antiviral activities (Pa: 0.289 for broad antiviral) reflective of its NNRTI mechanism (Table 7d). Acyclovir showed strong predicted activity against herpesviruses (Pa: 0.794) and poxviruses (Pa: 0.880) (Table 7e).

Table 7a. PASS Prediction—Indinavir

Pa	Pi	Predicted Activity
0.758	0.003	Antiviral (HIV)
0.753	0.004	Antiviral (Broad)
0.691	0.005	Cytochrome P450 inhibitor
0.670	0.002	HIV-1 protease inhibitor
0.633	0.003	CYP2D6inhibitor
0.602	0.039	CYP3Asubstrate
0.518	0.005	CYP3A4inhibitor
0.396	0.039	Cardiotonic

Table 7b. PASS Prediction—Zalcitabine

Pa	Pi	Predicted Activity
0.961	0.003	CDP-Glycerol glycerophosphotransferase inhibitor
0.906	0.002	RNA-directed DNA polymerase inhibitor
0.899	0.005	TP53 expression enhancer
0.887	0.003	DNA synthesis inhibitor
0.869	0.005	Cytostatic
0.848	0.003	Antiviral (poxvirus)
0.826	0.004	Antiviral (Broad)
0.718	0.003	Antiviral (Herpesvirus)

Table 7c. PASS Prediction—Zidovudine

Pa	Pi	Predicted Activity
0.939	0.003	Antiviral (Broad)
0.932	0.002	RNA-directed DNA polymerase inhibitor
0.913	0.002	DNA synthesis inhibitor
0.883	0.002	DNA-directed RNA polymerase inhibitor
0.840	0.003	Antineoplastic antimetabolite
0.726	0.001	Thymidine kinase inhibitor
0.733	0.008	Antiviral (poxvirus)

Table 7d. PASS Prediction—Delavirdine

Pa	Pi	Predicted Activity
0.533	0.173	Gluconate 2-dehydrogenase inhibitor
0.463	0.011	CYP2C9 inhibitor
0.408	0.019	Antialcoholic
0.395	0.018	RNA-directed DNA polymerase inhibitor
0.395	0.039	Anti-obesity
0.289	0.041	Antiviral (Broad)
0.242	0.017	Antiviral (HIV)

Table 7e. PASS Prediction—Acyclovir

Pa	Pi	Predicted Activity
0.945	0.002	ADP-thymidine kinase inhibitor
0.906	0.002	Aldehyde oxidase substrate
0.880	0.002	Antiviral (poxvirus)
0.835	0.004	Antiviral (Broad)
0.817	0.003	DNA-directed DNA polymerase inhibitor
0.794	0.002	Antiviral (Herpesvirus)
0.724	0.001	Antiviral (CMV)

6.6. Toxicity Prediction (ProTox-II)

In silico toxicological profiling via ProTox-II is summarised in Table 8. Indinavir, zalcitabine, and acyclovir are classified as GHS Toxicity Class 5 (LD50: 5000 mg/kg), corresponding to low acute oral toxicity. Zidovudine exhibits the highest LD50 (8000 mg/kg; Class 6, practically non-toxic). Delavirdine, with an LD50 of 1395 mg/kg (Class 4), demonstrates moderate acute toxicity. Regarding specific endpoints, indinavir shows predicted hepatotoxic

potential (72% confidence) and high predicted immunotoxicity (97%), warranting further clinical monitoring. Zalcitabine shows predicted mutagenicity (70%). Zidovudine is predicted carcinogenic (83%) and mutagenic (86%), consistent with known clinical genotoxicity observations. Delavirdine demonstrates predicted cytotoxicity (52%). Acyclovir shows the most favourable overall safety profile with predicted hepatoprotection (96% inactive) and low cytotoxicity (81% inactive).

Table 8. *In silico* toxicological profile of antiviral candidates predicted by ProTox-II.

Drug	LD50 (mg/kg)	Tox. Class	Hepatotox.	Carcinog.	Immunotox.	Mutagenic.	Cytotox.
Indinavir	5000	5	Active 72%	Inactive 63%	Active 97%	Inactive 75%	Inactive 69%
Zalcitabine	5000	5	Active 56%	Inactive 50%	Inactive 99%	Active 70%	Inactive 96%
Zidovudine	8000	6	Active 52%	Active 83%	Inactive 99%	Active 86%	Inactive 85%
Delavirdine	1395	4	Inactive 60%	Inactive 60%	Active 98%	Inactive 66%	Active 52%
Acyclovir	5000	5	Inactive 96%	Active 53%	Inactive 99%	Inactive 53%	Inactive 81%

VII. DRUG PROFILES

The five selected antiviral compounds represent distinct mechanistic classes. Indinavir is a HIV-1 protease inhibitor originally approved for

antiretroviral therapy; its optimised structure for enzymatic binding pockets explains its superior docking performance against VP24. Zalcitabine and zidovudine are nucleoside reverse transcriptase inhibitors (NRTIs) that function as chain terminators

following triphosphorylation by cellular kinases; their compact nucleoside scaffolds facilitate efficient entry into VP24's binding pocket. Delavirdine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with a bulkier molecular framework accommodating diverse binding interactions. Acyclovir is a guanosine analogue active against herpesviruses, functioning as a selective inhibitor of viral DNA polymerase following thymidine kinase-mediated phosphorylation; its high hydrophilicity and favourable safety profile are notable.

VIII. CONCLUSION

This study employed a systematic *in silico* workflow to evaluate the repurposing potential of five approved antiviral drugs against Marburg virus VP24 matrix protein, integrating molecular docking, physicochemical analysis, ADME pharmacokinetics, drug-likeness assessment, PASS biological activity prediction, and ProTox-II toxicity profiling. Among the compounds evaluated, indinavir emerged as the most promising candidate, demonstrating superior binding affinity (−9.0 kcal/mol) with extensive hydrogen bonding and hydrophobic interactions at key VP24 residues (ILE 204, GLY 185, GLN 186, LYS 103, LYS 182, LEU 183, THR 184). Indinavir also satisfies Lipinski drug-likeness criteria and demonstrates high predicted oral bioavailability, balanced lipophilicity, and minimal CYP450 interactions.

Collectively, the computational evidence presented herein supports indinavir as a high-priority candidate warranting progression to *in vitro* cytopathic effect assays and *in vivo* preclinical evaluation in established MVD animal models. Given its current availability only as an oral capsule, novel pharmaceutical formulations—including injectables, modified-release tablets, or topical systems—warrant investigation to optimise systemic exposure in acute MVD settings. Future studies integrating molecular dynamics simulations, quantum mechanical calculations, and experimental binding assays will be essential to validate and extend these computational findings, ultimately contributing to the accelerated development of safe and effective therapeutics against Marburg virus.

Clinical Implication: Indinavir, an approved HIV protease inhibitor with an established clinical

safety record, represents a viable candidate for Marburg virus drug repurposing. Novel formulation strategies could maximise therapeutic in acute haemorrhagic fever settings.

DECLARATIONS

Conflicts of Interest

The authors declare no conflicts of interest.

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This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethical Approval

Not applicable. This study involved exclusively computational analyses with no human participants, animal subjects, or patient-identifiable data.

Data Availability

Protein structure data used in this study are publicly available from the RCSB Protein Data Bank (PDB ID: 4OR8). Chemical compound data are available from PubChem (pubchem.ncbi.nlm.nih.gov). All computational analysis parameters are reported in the Methods section.

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