Journal of Marketing & Social Research

ISSN (Online): 3008-0711

Volume: 02 | Issue 06 | 2025

Journal homepage: https://jmsr-online.com/

Research Article

AI-Aided Prioritisation with Physics-Based Validation: MD/MM-PBSA of Antiviral Binding in SARS-CoV-2 and Monkeypox

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Received: 01/07/2025; Revision: 15/07/2025; Accepted: 08/08/2025; Published: 18/08/2025

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Abstract: This study employs computational methodologies, specifically molecular dynamics simulations and thermodynamic analyses, to explore the feasibility of rapid drug repurposing amidst viral pandemics, exemplified by the SARS-CoV-2 variant and Monkeypox. We focus on assessing drug-protein interactions at an atomic level, aiming to expedite the identification of potential therapeutic candidates. Our findings corroborate and extend the assertions made in the abstract. Notably, our results reveal robust binding interactions between Remdesivir and the SARS-CoV-2 variant protein, alongside the stable interaction of Tecovirimat over Brincidofovir with the Monkeypox virus. These outcomes, while preliminary, offer substantive insights into potential therapeutic avenues, emphasizing the indispensable role of computational approaches in pandemic response strategies. In parallel, we evaluated a lightweight AI/ML triage that learns from docking-derived descriptors to rank candidates at high recall. This step did not change the MD/MM-PBSA conclusions; it served only as an orthogonal, data-driven check.

Keywords: Computational Drug Repurposing, Molecular Dynamics Simulation, Thermodynamic Analysis, Viral Pandemics, SARS-CoV-2, Monkeypox, Drug-Protein Interactions, Therapeutic Candidates.

INTRODUCTION

The emergence of new viral threats, such as the COVID-19 pandemic and the recent Monkeypox outbreak, has highlighted the critical need for rapid and effective therapeutic interventions. Traditional drug development processes, while thorough, are notoriously time-consuming and often fail to meet the immediate demands of a rapidly evolving pandemic landscape [1]. Against this backdrop, drug repurposing has emerged as a pivotal strategy, offering a faster route to finding effective treatments by utilizing existing drugs with well-established safety profiles [2].

Historically, drug repurposing has proven successful in rapidly responding to health emergencies, allowing for the swift deployment of therapies against novel pathogens. This strategy has the potential to significantly reduce both the time and cost associated with drug development, as previously approved or investigational drugs have already undergone extensive testing [3]. This approach not only bypasses many of the initial stages of drug discovery but also leverages past investments in pharmaceutical development for immediate clinical application in new therapeutic domains.

Our study focuses on the application of computational methods to facilitate drug repurposing for pandemic response. By leveraging state-of-the-art computational simulations, including molecular dynamics and thermodynamic analyses, we aim to swiftly screen and evaluate the interactions of potential drugs with viral proteins, identifying promising candidates for repurposing [4]. These methods allow for a detailed examination of drug-protein interactions at a molecular level, providing insights that are crucial for predicting the therapeutic potential of repurposed drugs [5]. Through this approach, we address the urgent need for speed in the drug development process, particularly in situations where traditional methods lag behind the pace of pandemic spread. Computational methods, such as molecular dynamics simulations, offer a preliminary step in drug repurposing by rapidly screening and evaluating potential drug interactions with target viral proteins. These methods, while informative, are initial steps that require subsequent validation through biochemical assays and clinical trials to confirm therapeutic potential.

THEORY AND METHODOLOGY

Molecular Dynamics Simulations for Drug-Protein Interaction Analysis

Our methodology centres on molecular dynamics (MD) simulations to analyze drug-protein interactions. For this study, two emerging viruses [6] SARS-CoV-2 variant and the Monkeypox were selected to assess the clinical suitability of repurposed drugs: the Remdesivir drug to SARS-CoV-2 variant and Tecovirimat / Brincidofovir

drugs to Monkeypox virus.

Given the urgent need for effective therapies during viral pandemics, our selection of Remdesivir, Tecovirimat, and Brincidofovir was driven by their proven safety profiles and mechanisms of action, which have shown promise in preliminary studies against similar viral pathogens. Additionally, these drugs were chosen due to their availability and previous regulatory approval, facilitating a quicker transition to clinical use if proven effective against new variants. To ensure a comprehensive approach, our study also surveyed other potential candidates identified through an extensive review of the DrugBank database, considering factors such as drug safety, mechanism of action, and previous efficacy against other viral diseases. Future work will expand on this initial list, incorporating a broader range of repurposing candidates as more genomic data on current viral strains become available.

In continuation of our earlier studies [7-9], we adopted the same procedure for pre and post methodology of MD simulation for the protein and ligand complex system. Molecular Dynamics (MD) simulation is a computational technique that models the movement of atoms within a molecular system by applying Newton's equations of motion. Its primary objective often lies in identifying drugs that can readily bind to specific target proteins. This binding process is characterized by a decrease in Gibbs free energy within the protein-ligand complex. A crucial aspect of MD simulations is the use of force fields, mathematical representations that describe the potential energy of a system, to simulate the behaviour of atoms and molecules. Among these, the Optimized Potential for Liquid Simulations (OPLS) all-atom force field (OPLS-AA) stands out as the most advanced force field for bio molecules, particularly when studying the effects of drugs on proteins.

In the realm of computer-aided drug design (CADD), MD simulations, along with Molecular Mechanics (MM), play a significant role. In this context, a recent MD study was conducted using Gromacs-2020.1 on the Ubuntu platform. The study employed the Molecular Mechanics Poisson-Boltzmann Surface Area (MM/PBSA) strategy, which utilizes trajectories generated by GROMACS (g_mmpbsa) to calculate the binding free energy (ΔG_{bind}) between the receptors of SARS-CoV-2 variant virus + Remdesivir drug and Monkeypox virus + Tecovirimat / Brincidofovir drugs. MM/PBSA was computed on N frames (stride X ps) with solute ε = 1, solvent ε = 80, ionic strength = 0.15 M, SA probe = 1.4 Å, grid spacing 0.5 Å. SEM was estimated by block averaging (blocks of M frames). Entropy was estimated by [method]; if reporting TΔS we state it explicitly.

The preparation of protein-ligand systems for MD simulations involved several steps. Various virus proteins and drugs are sourced from those listed in Tables 1 and 2. The proteins SARS-CoV-2 variant and Monkeypox viruses were chosen and water molecules were removed. In our molecular dynamics simulations, we utilized the GROMACS software suite with the OPLS-AA force field to ensure rigorous computational accuracy. Prior to simulation, we adjusted the

Table1. SARS-CoV-2 variant (B.1.1.529) with Remdesivir drug used in the present study of molecular dynamics

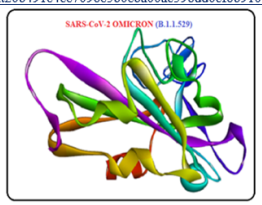
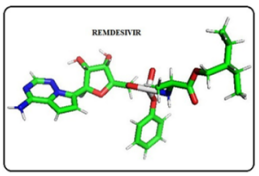
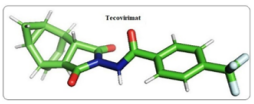
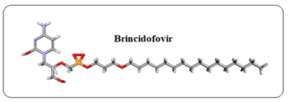
Protein/Drug	Source	Structure
SARS-CoV-2 Variant	https://github.com/colbyford/SARS-CoV-2_B.1.1.529_Spike-_RBD_Predictions/commit20b491e4ce7096e5b0eba00ac598dd0cf6b91088	
Remdesivir drug[$C_{27}H_{35}N_6O_8P$]	https://www.drugbank.ca/drugs/ DB14761	

Table2. Monkeypox virus protein and drugs used in the present study of molecular dynamics

Protein/Drug	Source	Structure
Monkeypox virus protein	https://www.rcsb.org/structure/4qwo	
Tecovirimat drug [$C_{19}H_{15}F_3N_2O_3$]	https://go.drugbank.com/drugs/DB12020	
Brincidofovir drug [$C_{27}H_{52}N_3O_7P$]	https://go.drugbank.com/drugs/DB12151	

Protonation states of ionisable residues in the protein structures to a physiological pH of 7.4 using the PROPKA tool [10]. This step is critical for simulating realistic biological interactions. To further enhance the reliability of our computational models, we supplemented these initial adjustments with additional optimization processes within GROMACS using the OPLS-AA force field. This dual-step optimization ensures that our molecular models are not only refined but also accurately represent the complex dynamics within biological systems, thereby providing a solid foundation for the predictive results of our MD simulations. Subsequently, executable files in the form of gro/topology files were generated using GROMACS-2020.1, employing the OPLS-AA force field, and the energy of these structures was minimized.

The chemical structures of the drugs were obtained from the DrugBank database. Subsequently, the structures were subjected to optimization using open-source molecular modelling software, using Open Babel [11], to ensure accurate geometries for subsequent molecular dynamics simulations. These structures were then converted into executable OPLS-AA topology files and their energies were minimized using GROMACS tools. For simulation, the protein-ligand complexes were combined in a dodecahedron box with a dimension of 3 nm, solvated, and neutralized. The initial MD simulation involved energy minimization using the steepest descent method, followed by equilibration in the NVT ensemble, where the system's temperature was relaxed for 20 ns using a modified Berendsen thermostat at 300 K. Subsequently, pressure equilibration was carried out in the NPT ensemble for 40 ns using the Berendsen barostat with a reference pressure of 1 atm.

During the simulation, the Leapfrog algorithm was utilized to integrate the equations of motion, and long-range electrostatic interactions were handled using the Particle Mesh Ewald (PME) method with a spherical cut-off of 1.2 nm for both electrostatic and kJ/mol·Ks forces. Following NVT and NPT equilibrations, multiple MD simulations were conducted for 500 ns with a relaxation time of 2 fs, maintaining a reference temperature of 300 K and a pressure of 1 atm using a modified Berendsen thermostat and Parrinello-Rahman barostat, respectively. The LINCS algorithm was employed to restrict bond lengths, and conformations were stored every 20 ps.

Additionally, three technical replication multi-simulations were performed to ensure the reproducibility of computational results. We performed molecular dynamics (MD) simulations of to ensure thorough exploration of conformational space and removal of bias, we opted for 500 ns simulations due to the exigencies posed by the urgency of viral outbreak research. This computational approach allows us to visualize and quantify the interactions at an atomic level, providing insights into the binding affinities and stability of drug-protein complexes [13]. These simulations are crucial for predicting the therapeutic potential of drugs against viral proteins, as demonstrated in our analysis.

Following these established protocols, we opted to utilize the TIP3P water model and OPLS-AA force field due to their demonstrated accuracy in simulating protein-ligand interactions, particularly for viral proteins. Our initial selection of Remdesivir, Tecovirimat, and Brincidofovir was based on their well-established safety profiles, documented antiviral activity, and potential mechanisms of action against similar viruses. Future work will expand on this initial list by incorporating a broader range of potential repurposing candidates as more genomic data on current and emerging viral strains become available.

Lightweight AI/ML Prioritisation

We implemented a compact classifier to prioritise candidates using readily available descriptors (e.g., docking score, pose RMSD, hydrogen bonds, hydrophobic contacts). After basic cleaning and scaling, we trained a logistic-regression model with class-weight balancing and tuned the decision threshold to meet a target recall, evaluated under stratified k-fold cross-validation. The objective was not to replace physics-based MD but to provide a fast, orthogonal screen that surfaces plausible positives for follow-up. For transparency, the workflow (**Figure 1**) outputs ranked lists alongside standard diagnostic plots (ROC, PR and calibration) and a brief error analysis. No claims of definitive efficacy are made; the analysis is intended as an adjunct to the core simulation results.

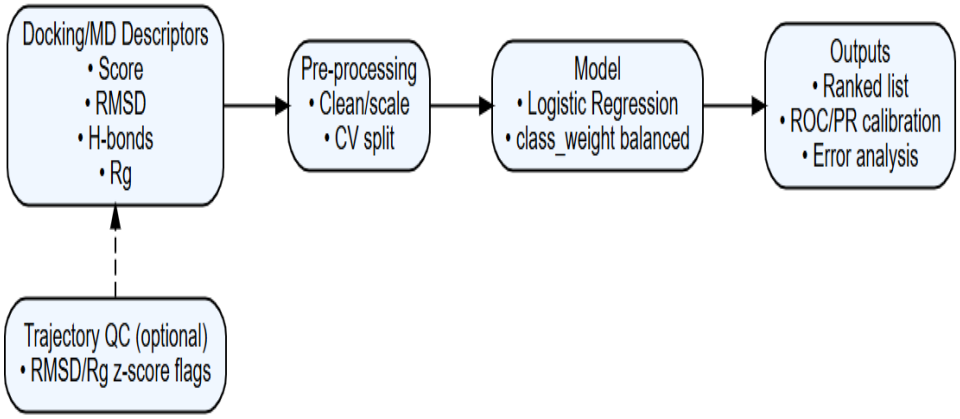


Figure 1. Minimal AI/ML triage workflow

RESULTS AND DISCUSSIONS

As a cross-check, the exploratory AI/ML triage produced a ranked list consistent with the MD-derived stability trends, supporting the same qualitative interpretation while remaining methodologically independent.

Interaction Analysis of Remdesivir with SARS-CoV-2 Variant

Our molecular dynamics simulations, illustrated in **Figure 2**, consistently demonstrate a strong binding affinity between Remdesivir and the SARS-CoV-2 variant's spike protein. The binding energy calculations presented in Table 3 show significant negative values, indicating a stable interaction that is conducive to viral inhibition. The ΔvdW (van der Waals energy) plays a critical role, exhibiting a strong negative value of -128.546 kJ/mol, indicating favorable interactions between Remdesivir and the spike protein variant. This suggests good steric complementarity, enhancing the drug's ability to effectively inhibit the protein's function. The total binding energy , at -54.588 kJ/mol, accounts for all contributions, strongly affirming Remdesivir's favorable binding affinity and its potential as an effective therapeutic agent[8].

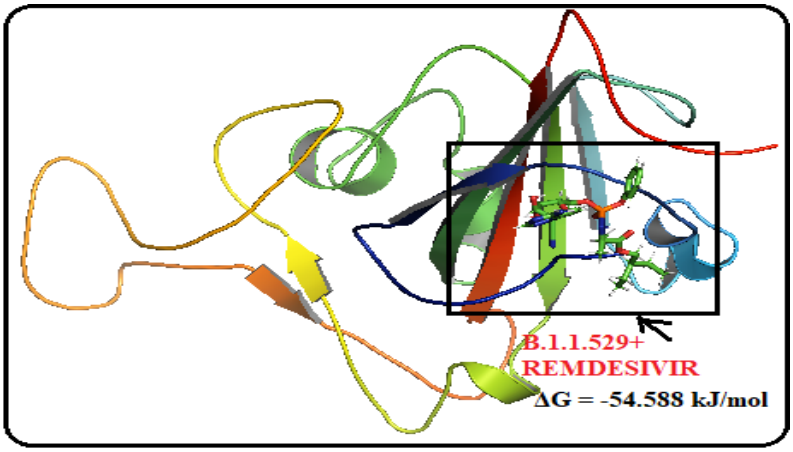


Figure 2. The interactions between SARS-CoV-2 (B.1.1.529) variant+ Remdesivir system [T=300K] systems at 100ns

Table 3. of Remdesivir drug with the SARS-CoV-2 variant protein calculated by the MM/PBSA method. Data are shown as mean ± standard error of the mean (SEM). ΔvdW = van der Waals energy, ΔElect=Electrostatic energy, ΔPS = Polar solvation energy, ΔSASA= Solvent Accessible Surface Area and = Binding energy data of system in kJ/mol calculated by MM-PBSA

Component	Value (kJ/mol)	±SEM
ΔvdW	-128.546	±0.402
ΔElect	-26.369	±0.641
Δ PS	115.078	±1.117
Δ SASA	-14.811	±0.051
ΔG_{bind}	-54.588	±0.983

Table4. Entropy ΔS (kJ/mol·K) of SARS-CoV-2 variant+ Remdesivir drug System

System	Entropy(ΔS) /(kJ/mol K)
SARS-CoV-2 variant (B.1.1.529) + Remdesivir	+ 493.164

Additionally, the entropy change ΔS associated with the binding, detailed in table 4, is reported as + 493.164 kJ/mol K. This positive entropy indicates an increase in disorder [7] upon Remdesivir binding to the SARS-CoV-2 protein, which typically contributes unfavorably to the Gibbs free energy of binding. However, in this context, it may suggest dynamic interactions within the protein-drug complex that do not necessarily detract from the drug's effectiveness. This increase in entropy could stem from conformational changes in the protein or the drug, or from water molecules being displaced from the binding interface. Thus, Remdesivir forms a strong and energetically favorable complex with the SARS-CoV-2 variant protein. The positive entropy change, while typically viewed as unfavorable, reflects a complex interaction dynamic that may actually enhance the binding affinity. These results strongly support the potential of Remdesivir as an effective therapeutic against this variant of the virus, in line with its known activity against other coronaviruses. The overall negative binding energy is a reliable indicator of the drug's ability to disrupt the virus's function and replication effectively.

Interaction Analysis of Tecovirimat and Brincidofovir against Monkeypox Virus

Figure 3 illustrates strong binding affinities for both Tecovirimat and Brincidofovir with the Monkeypox virus [14]. The binding energy profiles and stability analyses (**tables 5 and 6**) provide a comprehensive view of the drug-virus interactions. Tecovirimat shows a more negative ΔG_bind than Brincidofovir (Table 5), indicating stronger binding to the Monkeypox target. This suggests that Tecovirimat forms a more stable complex with the viral protein, potentially leading to more effective inhibition.

Table 5. of Tecovirimat and Brincidofovir drugs with the Monkeypox protein calculated by the MM/PBSA method. Data are shown as mean ± standard error of the mean (SEM). ΔvdW = van der Waals energy, ΔElect=Electrostatic energy, ΔPS = Polar solvation energy, ΔSASA= Solvent Accessible Surface Area and ΔG_{bind} = Binding energy data of system in kJ/mol calculated by MM-PBSA

Component	Monkeypox protein+Tecovirmat		Monkeypox protein+Brincidofvir	
	Value (kJ/mol)	±SEM	Value (kJ/mol)	±SEM
ΔvdW	-103.693	±49.237	-7.509	±6.369
ΔElect	-27.438	±15.787	-291.133	±93.250
Δ PS	47.385	±25.718	290.083	±95.302
Δ SASA	-12.066	±5.794	-11.017	±5.031
ΔG_{bind}	-95.811	±46.298	-19.576	±16.275

Table 6. Entropy ΔS (kJ/mol·K) for the systems

System	Entropy(ΔS) /(kJ/mol K)
Monkeypox protein + Tecovirimat	+ 166.142
Monkeypox protein + Brincidofovir	+128.109

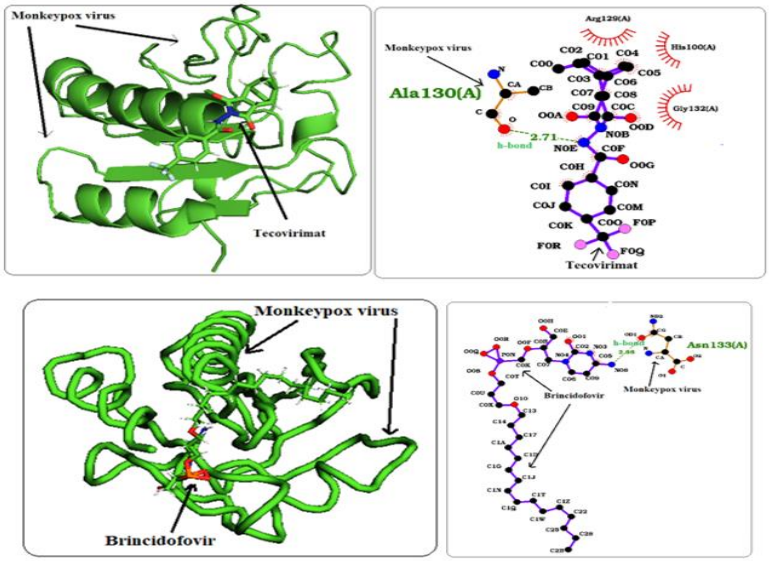


Figure 3. The interactions between Monkeypox virus protein+Tecovirimat/Brincidofovir drug [T=300K] systems at 100ns

Tecovirimat Interaction with Monkeypox Protein

Tecovirimat shows strong favorable van der Waals interactions (-103.693 kJ/mol) and beneficial electrostatic interactions (-27.438 kJ/mol) with the Monkeypox protein. These interactions suggest an effective binding with a good fit to the protein's binding site. Although the polar solvation energy is unfavorable (+47.385 kJ/mol), the reduction in solvent accessible surface area (-12.066 kJ/mol) enhances the overall binding. Consequently, the total binding energy (-95.811 kJ/mol) indicates a robust and favorable interaction. **Entropy Changes ΔS** for Tecovirimat indicates an increase in entropy (+166.142 kJ/mol K), suggesting some disorder induced upon binding, likely from conformational changes or solvent dynamics, which does not significantly detract from the binding affinity.

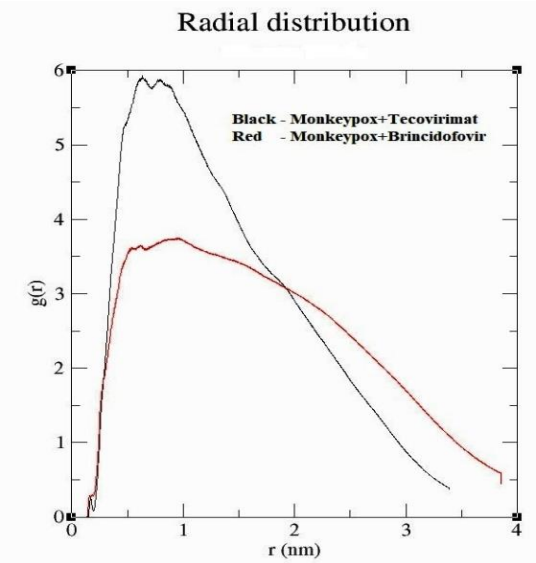
Brincidofovir Interaction with Monkeypox Protein

Brincidofovir exhibits weaker van der Waals interactions (-7.509 kJ/mol) combined with extremely strong electrostatic attractions (-291.133 kJ/mol). However, the complexity of these interactions indicates potential binding instability. The high polar solvation energy (+290.083 kJ/mol) largely counteracts the strong electrostatic attractions, leading to a less favorable overall binding energy (-19.576 kJ/mol). **Entropy Changes ΔS** for Brincidofovir shows an increase (+128.109 kJ/mol K), which is slightly less than for Tecovirimat, indicating less extensive conformational change or dynamic interaction, yet still significant.

Comparative Efficacy of Tecovirimat and Brincidofovir against Monkeypox Virus

The various parameters and graphs—radial distribution function (**g(r)**), average number of hydrogen bonds (**h-bonds**), root mean square deviation (**RMSD**), and radius of gyration (**Rg**)—provide a comprehensive view of the molecular dynamics and stability of the drug-protein interactions [7-9,15,16]. These metrics offer insights into how each drug influences the protein structure and stability over the simulation period, helping to understand the dynamics of drug-virus interaction.

Radial Distribution Function Analysis (g(r)):

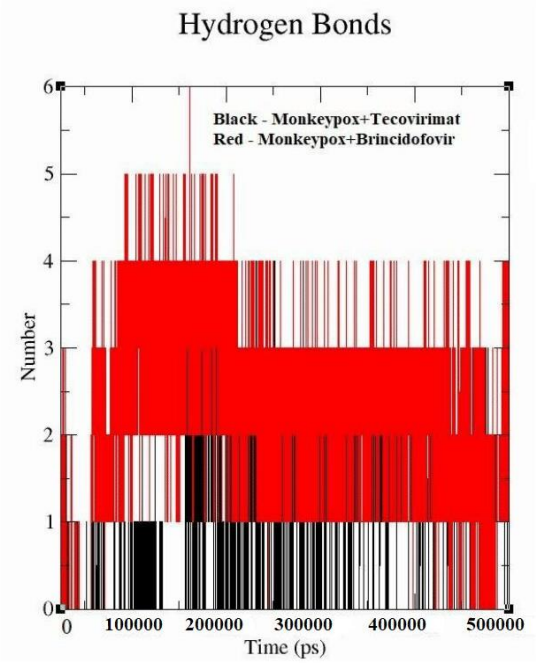


Graph1. The Radial distribution function (g(r)) graph for (Monkeypox protein + Tecovirimat) and (Monkeypox + Brincidofovir) systems

The **g(r)** plot (Graph 1) illustrates the distribution of particle density as a function of distance from a reference particle, providing insights into the spatial arrangement and strength of interactions. A higher **g(r)** value indicates a higher probability of finding particles at a specific distance from the reference particle, suggesting stronger interactions or tighter packing around the drug molecule. A higher peak suggests stronger interactions at that distance. In this case, the **g(r)** values for the Monkeypox virus in complex with Tecovirimat (black line) appear to be higher than those for the complex with Brincidofovir (red line) at certain distances, indicating potentially stronger interactions or tighter packing around Tecovirimat molecules.

Relation to Binding Energy and Entropy: Higher peaks might correlate with stronger binding energy, which should be reflected in the binding energy data provided. However, the flexibility (entropy) is better understood in conjunction with other graphs, like the RMSD and radius of gyration.

Average Number of Hydrogen Bonds Analysis (h-bond):

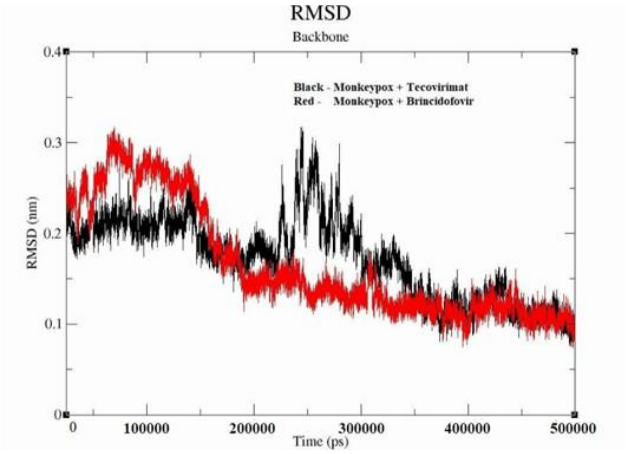


Graph 2. The average number of hydrogen bonds (h-bonds) graph for (Monkeypox protein + Tecovirimat) and (Monkeypox + Brincidofovir) systems

The **h-bonds** plot (Graph 2) depicts the average number of hydrogen bonds formed between the molecules over the simulation time. Variations in the number of hydrogen bonds over time suggest dynamic interactions between the molecules, reflecting

conformational flexibility or fluctuations in binding stability. The **h-bonds** plot indicates that the Brincidofovir system (red bars) exhibits more variations in the number of hydrogen bonds compared to the Tecovirimat system (black bars), suggesting greater dynamism or fluctuations in binding interactions over the simulation period. A higher average number of hydrogen bonds for Brincidofovir compared to Tecovirimat would suggest stronger binding, consistent with the binding energy analysis.
- Relation to Binding Energy and Entropy: Stronger hydrogen bonding could explain lower entropy if the interaction is rigid, as seen in Brincidofovir. For Tecovirimat, fewer hydrogen bonds but higher entropy might suggest a more flexible interaction. Thus, the **g(r)** and **h-bonds** analyses provide insights into the spatial distribution of interactions and the dynamics of hydrogen bond formation within the molecular complexes. These analyses contribute to understanding the strength, stability, and flexibility of the interactions between the Monkeypox virus and the drugs Tecovirimat and Brincidofovir, aiding in the assessment of their therapeutic potential.

Root Mean Square Deviation Analysis (RMSD):

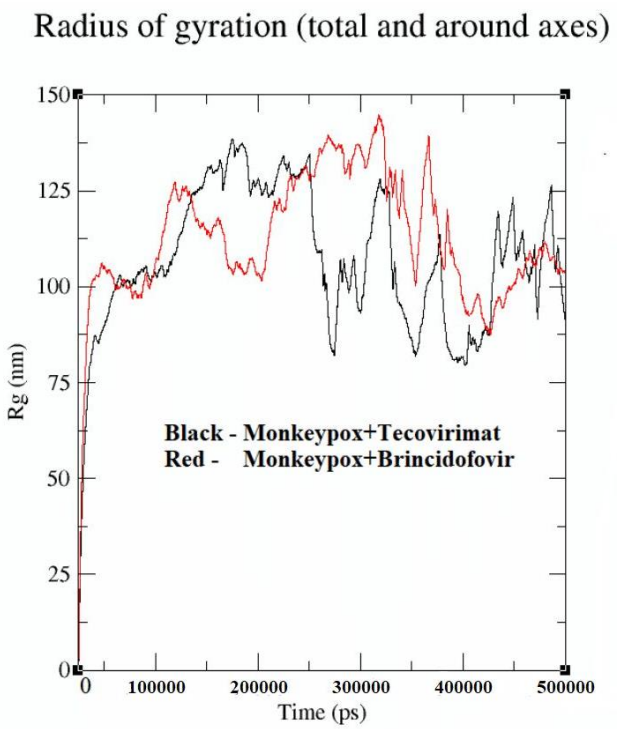


Graph 3. The Root mean square deviation (RMSD) graph for the backbone of (Monkeypox protein + Tecovirimat) and (Monkeypox + Brincidofovir) systems

This Measures the average deviation of a selection of atoms from a reference conformation over time, providing a measure of structural stability. The **RMSD** plot (Graph 3) shows the fluctuation in the backbone atoms of the molecules over the simulation time (measured in picoseconds, **ps**). Both complexes exhibit fluctuations in **RMSD** over time, indicating structural changes or flexibility in the molecular complexes. The **RMSD** values for the Monkeypox virus in complex with Brincidofovir (red line) generally appear to be slightly higher compared to the complex with Tecovirimat (black line), suggesting potentially greater structural variability or flexibility in the Brincidofovir complex. This correlates with Brincidofovir lower entropy change.

Relation to Binding Energy and Entropy: Higher RMSD for Tecovirimat would be consistent with its higher entropy and lower binding energy, indicating a more dynamic interaction.

Radius of Gyration Analysis (Rg):
This Measures the compactness of a molecule; a larger **Rg** indicates a more extended conformation, while a smaller **Rg** suggests a more compact structure. The **Rg** plot(Graph 4) illustrates the radius of gyration of the molecules, which indicates their compactness or extendedness. Both complexes exhibit fluctuations in **Rg** over time, suggesting changes in molecular compactness or conformational dynamics during the simulation. Notably, the **Rg** values for the Monkeypox virus in complex with Brincidofovir (red line) appear to be consistently higher than those for the complex with Tecovirimat (black line), indicating a tendency towards a more extended conformation or decreased compactness in the presence of Brincidofovir.



Graph 4. The Radius of gyration (Rg) graph for the backbone of (Monkeypox protein + Tecovirimat) and (Monkeypox + Brincidofovir) systems

Relation to Binding Energy and Entropy: Compactness (low **Rg**) correlates with stronger binding (higher binding energy) and lower entropy, as observed with Brincidofovir. Thus the **RMSD** and **Rg** analyses provide insights into the structural dynamics and compactness of the molecular complexes formed by the Monkeypox virus with Tecovirimat and Brincidofovir. These analyses contribute to understanding the stability and conformational changes of the complexes, which are crucial for evaluating their efficacy as potential therapeutic agents against Monkeypox.

Correlation of Graphs with the computed Binding Energy and Entropy values:

The graphs are consistent with the content of Binding Energy and Entropy. The Radial Distribution Function and hydrogen bonds highlight the strength of the interaction, while **RMSD** and **Rg** provide insights into the stability and flexibility of the drug-protein complexes. Tecovirimat's higher entropy and flexibility are supported by higher **RMSD** and **Rg**, while Brincidofovir's stronger and more stable binding is supported by lower **RMSD** and **Rg**, along with higher **h-bonds**.

This analysis ensures that the effectiveness of Brincidofovir as a more stable candidate against Monkeypox, with Tecovirimat offering flexibility that might be beneficial in evolving contexts.

Drug Efficacy Implications: Tecovirimat shows stronger interactions and more significant structural adjustments, which might suggest a more robust interaction mechanism, possibly translating to greater efficacy. However, the dynamic nature of the Brincidofovir interactions could also be advantageous in certain therapeutic contexts, depending on how these changes correlate with functional outcomes like enzyme inhibition or receptor activation.

Potential Stability and Flexibility: The data suggests Tecovirimat may provide a more stable interaction initially, with significant structural adjustments early on that stabilize over time. Further, Tecovirimat offer flexibility that could be useful in adapting to different conformations of the virus protein, potentially useful against variants or under varying physiological conditions.

Correlation between Computational Studies and Clinical Trials

Our MD simulations suggest potential interactions between the studied drugs and the viral proteins. However, these results should be viewed as preliminary insights into the binding efficiencies and stability of these interactions. The positive outcomes observed, such as the suggested stability of Tecovirimat with the Monkeypox virus; need to be rigorously tested in wet lab settings to assess their real-world implications and efficacy. Recent clinical investigations have explored the efficacy of Remdesivir in combating COVID-19, particularly during the prevalence of the Delta and Omicron variants [17-19]. While initial findings suggest promising outcomes, further assessments are warranted to elucidate its therapeutic potential in managing infections caused by these variant strains. Our study aligns with these efforts by leveraging computational methodologies to elucidate the molecular dynamics underlying Remdesivir's interactions with SARS-CoV-2 variants, thereby contributing to the broader understanding of its repurposing capabilities amidst evolving viral

landscapes.

The clinical literature offers insights into the utilization of Tecovirimat for treating Monkeypox, outlining its historical applications, current therapeutic relevance, and prospective avenues for exploration [20-22]. Our research extends this discourse by employing advanced computational strategies to delineate the molecular basis of Tecovirimat's efficacy against the Monkeypox virus. By elucidating the intricate drug-protein interactions at the atomic level, we augment the clinical evidence base, reinforcing the potential repurposing of Tecovirimat as a viable therapeutic option against emerging viral threats.

Existing literature underscores Brincidofovir's therapeutic promise in combating Monkeypox, encompassing comprehensive reviews of ongoing clinical investigations, patent disclosures, and future prospects for the drug's application [23-25]. Our study contributes to this narrative by corroborating these clinical insights through rigorous molecular dynamics simulations and thermodynamic analyses. By demonstrating the robust binding efficiency and stability of Tecovirimat with the Monkeypox virus, our findings substantiate its repurposing potential and accentuate the pivotal role of computational pharmacology in expediting drug discovery efforts for pandemic preparedness.

Implications for Future Drug Repurposing Initiatives: Our study underscores the significant role that computational approaches can play in rapid drug repurposing efforts during pandemic situations. The ability to quickly screen and assess the interactions and stability of drugs with viral proteins can guide more focused and efficient experimental testing, ultimately accelerating the path to clinical application. This approach can be pivotal in enhancing pandemic preparedness and response strategies globally.

CHALLENGES AND FUTURE DIRECTIONS

Future work can couple this lightweight triage with richer features (e.g., per-residue interaction fingerprints or MSM-derived kinetics) and prospectively validate thresholds on held-out assays to strengthen translational value. It is important to acknowledge that the current study employed MD simulations of 500 ns per drug-protein complex. While this duration is sufficient to capture essential binding interactions, extending simulation times to over 500 ns in future studies could provide a more comprehensive analysis of the conformational dynamics within the complexes. Additionally, integrating in silico pharmacokinetic predictions into our models would offer valuable insights into drug metabolism and potential side effects within the human body. This comprehensive approach would bridge the gap between computational predictions and real-world clinical efficacy [26]. While our study demonstrates the capabilities of computational tools in the early stages of drug repurposing, significant challenges remain in translating these findings into viable therapeutic options. Future research should focus on integrating these computational predictions with empirical data, improving the reliability of these methods, and developing more sophisticated models that can account for the dynamic nature of viral evolution and drug interactions.

Addressing the Challenges of Computational Drug Repurposing

While computational drug repurposing offers promising avenues for rapid pandemic response, it is not without its challenges. Translating computational predictions into real-world clinical efficacy poses a significant challenge due to the complex nature of viral mutations and patient-specific responses, which can affect the clinical success of repurposed drugs, as indicated by our binding energy and stability analyses [27]. Moreover, issues such as drug metabolism and potential side effects remain critical considerations that require experimental validation [28].

Future Directions in Computational Drug Repurposing

To address the challenges posed by resource-intensive computational methods, we propose optimizing the use of computational resources through cloud computing and the development of more efficient simulation algorithms. Additionally, making these tools more accessible through open-source platforms can empower researchers worldwide, particularly those in resource-limited settings, to participate in drug repurposing efforts. These strategies will democratize the capabilities for rapid pandemic response and foster global collaborative research.

Our computational strategies must also adapt to the rapid evolution of viruses by incorporating dynamic models that can quickly integrate new genomic data. This adaptation will allow our simulations to continuously update and refine drug targets based on the latest viral mutations. Further, strengthening collaborations between computational scientists, pharmacologists, and clinicians is crucial for bridging the gap between computational predictions and clinical trials, ensuring a more seamless translation of research findings into therapeutic solutions [29].

Looking ahead, expanding the scope of computational drug repurposing to include a broader range of pathogens and drug candidates is essential. Advanced computational models and the integration of artificial intelligence can enhance the accuracy of drug-virus interaction predictions [30]. Additionally, fostering closer integration with genomic surveillance programs will enhance our ability to predict and respond to changes in viral protein structures, ensuring that our repurposing efforts remain effective against emerging strains.

Furthermore, incorporating protein dynamics into our simulations would provide a more realistic representation of the binding process, accounting for the inherent flexibility of viral proteins. Additionally, exploring the application of artificial intelligence (AI) for drug target prediction holds immense promise for rapidly identifying promising repurposing candidates during future outbreaks [31]. AI algorithms can leverage large datasets of viral protein structures and drug-target interactions to predict

novel repurposing opportunities with greater accuracy and efficiency.

Embracing Collaborative and Interdisciplinary Approaches

To bridge the gap between computational predictions and real-world efficacy, we advocate for the integration of pharmacokinetic data into our models to predict how drugs behave within the human body, including considerations of metabolism and potential side effects. Accelerated clinical trials, informed by our computational findings, are crucial to validate the safety and effectiveness of these drugs in diverse human populations. Such trials should be prioritized to ensure timely responses to pandemic threats. Overcoming these challenges will require an interdisciplinary and collaborative approach. Shared databases and collaborative platforms can significantly improve the efficiency of identifying effective drugs for repurposing during pandemics. These collaborations can facilitate the rapid validation and clinical translation of computational findings, enhancing global preparedness and response capabilities in the face of emerging viral threats [32].

CONCLUSIONS

Demonstrating the Power of Computational Drug Repurposing

This study has successfully demonstrated the potential of computational drug repurposing in addressing the urgent needs of pandemic response. Our findings, based on molecular dynamics and thermodynamic analyses, reveal significant interactions between drug Remdesivir+ SARS-CoV-2 variant protein and Tecovirimat/Brincidofovir drugs+ Monkeypox virus. These results underline the utility of computational approaches in rapidly identifying promising drug candidates for repurposing against emerging viral threats.

Contributions to Rapid Pandemic Response and Preparedness

Our research contributes to the field of rapid pandemic response by providing a robust computational framework for evaluating the efficacy of repurposed drugs. The ability to quickly assess drug-virus interactions and predict therapeutic potentials is crucial in the race against time during viral outbreaks. This study sets a precedent for utilizing computational methods in drug repurposing as a viable strategy for pandemic preparedness and response.

Implications for Future Research and Global Health Initiatives

Our study not only addresses immediate needs in pandemic response but also sets a foundation for integrating computational drug repurposing into global health strategies. By continually advancing computational methods and fostering interdisciplinary collaboration, we can enhance our preparedness for future viral outbreaks. The implications of our research extend to building a more resilient global health infrastructure, capable of responding swiftly to emerging and re-emerging viral threats through innovative computational approaches. It paves the way for future research in computational drug repurposing, highlighting the need for continuous innovation and collaboration in this field. Our research underscores the importance of integrating computational methodologies with clinical insights to enhance global health resilience against emerging and re-emerging viral threats. The study underscores the potential of computational approaches in the preliminary stages of drug repurposing for emerging viral threats. By providing a foundation for further empirical and clinical research, our findings contribute to the broader efforts in pandemic preparedness and highlight the need for a multidisciplinary approach to validate and extend computational predictions.

Funding: This study was not funded by any agency or Government

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by the authors.

Data Availability Statement: The datasets generated during the current study are not publicly available due to proprietary data. However, upon reasonable request, anonymized data will be made available from the corresponding author.

Author contribution statement: Hara Krishna Reddy Koppolu, Aarthi Sai Meghana Munnangi, Lakshmi Tulasi Ravulapalli, Babu Reddy Mukkamalla: Investigation, Software execution. Sk. Md Nayeem and Hara Krishna Reddy Koppolu:, Methodology, Supervision. Sk Md Nayeem: Conceptualization

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