RESEARCH PAPER

In Silico Molecular Docking and Preliminary Molecular Dynamics Analysis of HMS1601D01 as a Potential Inhibitor of Sudan Ebola Virus Protein 3S88

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ABSTRACT

Sudan Ebola virus (SUDV), a virus from the Filoviridae family, is the cause of viral haemorrhagic fever which is very deadly and fatality. There are currently some ways to treat SUDV using small-molecule drugs so novel approaches are needed. Computational drug discovery techniques can quickly and inexpensively identify a potential inhibitor of the SUDV and be validated experimentally later. In this study, the new drug candidate HMS1601D01 (PubChem ID 2082950) was evaluated against the Sudan Ebola virus protein 3S88 using molecular docking, preliminary molecular dynamics (MD) simulation, and toxicity profiling. The docking results showed that HMS1601D01 can bind stably to the SUDV protein active site through the formation of five hydrogen bonds and one π–π stacking interaction with the amino acids TYR, GLN, SER, ASN, HIS, and TRP. The MD simulation for 100 ns showed that the protein-ligand complex was stable over this time frame with minimal change (backbone deviation) in the structure of either the protein or compound; and the HMS1601D01 compound remained in its binding pocket for the entire time of the simulation. In silico ADMET and toxicity predictions indicated the compounds contained appropriate drug-like properties and have manageable toxicity risks. Together these data indicate HMS1601D01 will be ideal for further experimental validation using extended MD simulations.

Keywords: Sudan Ebola virus, Molecular docking, Molecular dynamics simulation, ADMET, Antiviral drug discovery

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INTRODUCTION

Sudan Ebola virus (SUDV) is still one of the major concerns to public health due to its wide outbreaks that typically result in high death. While advances have been made toward developing vaccines for the prevention of SUDV infection, there are currently few small molecule antiviral therapies available. One potential strategy for inhibiting the replication of SUDV is via rational drug design targeting SUDV viral structural and functional proteins. Molecular docking in PYRX used for the prediction of ligand-protein interactions at the atomic level with binding affinity while molecular dynamics (MD) simulation allows for the assessment of the time dependent stability of proteins under physiological conditions like temperature and pressure. By doing both molecular docking with MD simulation and all ADMET properties provides and better potential compounds for drug discovery[i]. The main objective of this study was to utilize the SUDV protein 3S88 crystal structure as a molecular target to evaluate the binding affinity, interaction stability, and predicted pharmacokinetic properties of HMS1601D01 as a potential compound.

LITERATURE REVIEW

The Sudan Ebola virus (SUDV) is a member of the Filoviridae family, causing severe viral hemorrhagic fever with high death rates in Africa during periodic epidemic outbreaks[ii] while clinical and pathological aspects of Ebola virus disease were said detailed[iii]. Despite advances in vaccine development, small-molecule therapeutic options remain limited, particularly for Sudan strains. Structural investigations have significantly enhanced understanding of Ebola virus protein architecture. High-resolution structural

analyses of Ebola virus glycoproteins and nucleoproteins have provided mechanistic insights into viral entry and replication[iv]. These structural datasets have enabled structure-based drug discovery approaches targeting viral proteins. Molecular docking is one of the primary methods that are widely used in the field of computational antiviral compound discovery[v]. Recent advances in virtual screening with structure-based methods to identify small molecules that can potentially inhibit viruses has been expedited. Recently, the advent of AutoDock Vina has allowed for faster and more accurate scoring of docking results, making it possible to conduct screen large collections of compounds[vi]. The use of docking studies to evaluate small molecule binding to proteins from the Ebola virus has led to the identification of several promising small molecules that can block viral entry and replication[vii]. Although docking does provide information about the interactions between proteins and ligands, it only provides a single static image of the ligand interaction with the target protein. To assess the dynamic nature of the protein-ligand interaction, molecular dynamics (MD) simulations are commonly incorporated into almost all computational methods for evaluating compound interaction with protein targets. MD simulations provide a means to assess the time-dependent stability of the structure under simulated physiological conditions[viii]. The most frequently assessed metrics to evaluate structural deviation and flexibility while the simulations are root mean square deviation (RMSD) and root mean square fluctuation (RMSF)[ix]. Before evaluating the pharmacokinetics and toxicology of a drug, testing its binding stability is essential for early drug development. The guidelines for evaluating drug-likeness began with Lipinski's Rule of Five[x]. Modern in silico tools such as pkCSM and ProTox-II[xi] enable prediction of ADMET properties and toxicity endpoints prior to experimental validation. Early incorporation of toxicity prediction reduces late-stage failure rates in drug development pipelines[xii]. Recent studies have been published combining both computerized docking and molecular dynamics simulations to test synthetic and natural compounds against potential viral targets[xiii]. However, there have been few studies integrating both a short-time molecular dynamic simulation of a docking study with a toxicity profile for the Sudan Ebola virus protein 3S88. Therefore, the multiple computer- based assessment of HMS1601D01 will allow for a documented basis for further selection of potential antiviral lead compounds[xiv].

MATERIALS AND METHODOLOGY

Protein preparation: The protein 3D structure of 3S88 (SUDV receptor) was downloaded from Protein Data bank (PDB). Then in the SUDV receptor the water molecules, Hetatm and other extra molecules were removed, and the Hydrogen bonds were added using Discovery studio for further docking process[xv].

Ligand preparation: The FDA compounds were downloaded from Pubchem and Zinc database[xvi]. The number of FDA approved compounds downloaded from those platforms are around 1000. Which are now used for docking purpose.

Molecular Docking and Analysis: Molecular Docking was performed using PYRX which is an automated docking platform[xvii]. As a result for molecular docking, the best ligand for the SUDV were chosen based on its binding score which is -11.6 kJ/mol, and that ligand is HMS1601D01 (PubChem id 2082950).

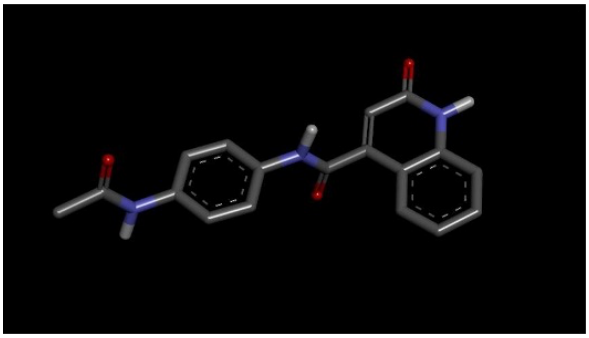


Figure 1:3D Structure of HMS1601D01 (PubChem id 2082950)

ADMET and Toxicity Prediction: HMS1601D01 has appeared to be follow all the rules of Lipinski's Rule of Five,

1) Molecular weight = 321.34 Da ≤ 500
2) LogP = 2.74 ≤ 5
3) Hydrogen Bond Acceptors = 3 ≤ 5
4) Hydrogen Bond Donors = 3 ≤ 10

ProTox-3.0 provides predictions regarding the absence of activity for the following major organ toxicities: mutagenic; cardiotoxic. However, the predicted values of neurotoxicity, carcinogenicity, clinical toxicity and BBB permeability indicate that there may be some potential risk of CNS-related toxicity. CYP profiling indicates that CYP1A2 may be involved, whereas the other major CYP isoforms are not likely to be involved.

Molecular Dynamics Simulation: A 100 ns Molecular dynamics simulation was done to evaluate the binding stability of a protein and the docked ligand. The system was created using the Water model, neutralized ions, Energy minimization and equilibration, NVT , NPT were done before the production run. RMSD analysis was used to monitor the deviations over time production.

RESULT AND DISCUSSION

Docking Interaction Analysis: The active pocket of 3S88 was found to be a good fit for HMS1601D01 through docking studies. Docking studies reveal five conventional hydrogen bonds between TYR, GLN, SER, ASN, and HIS. There is also a π–π stacking interaction with TRP that increased stabilization of binding. There is a strong correlation between the location of the hydrogen bonds and their respective positions along the ligand scaffold, indicating strong molecular recognition and anchoring to the binding site.

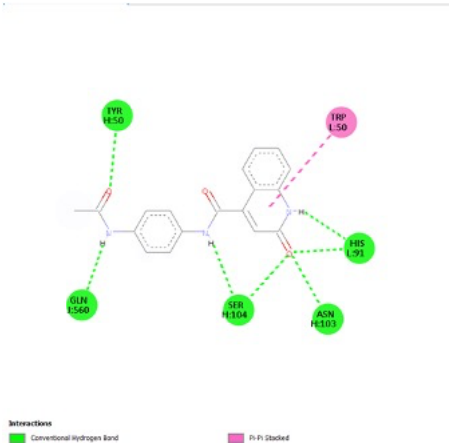


Figure 2: 2D Interaction diagram showing hydrogen bonds and π–π stacking interactions

Molecular Dynamics Stability Analysis (100 ns Production Run)

Hydrogen Bond Analysis: During the simulation process, there was a large variation in the amount of hydrogen bonds recorded. The lowest value for the raw data was 0 hydrogen bonds and the highest value was 11, with an average of 2-4 hydrogen bonds for the simulation process; thus, this shows that there were a lot of continuous intermolecular interactions. The fact that there are multiple hydrogen bonds formed during the simulation period demonstrates that HMS1601D01 is securely anchored at the active site of protein/3S88.

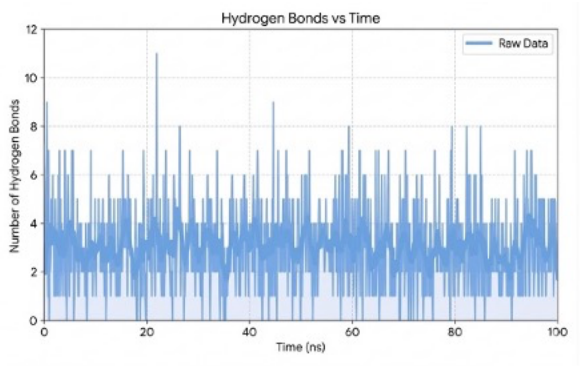


Figure 3: Time Evolution of Hydrogen Bonds During 100 ns Simulation

Protein–Ligand Interaction Energy: During the entire simulation period of 100 ns, the interaction energy was always negative, ranging from ~−240 to −360 kJ/mol. The fact that the interaction energy was always negative shows that there are strong non-covalent interactions between HMS1601D01 and the 3S88 protein. Moreover, there was no trend of energy increase, showing that the complex was in a stable state during the entire simulation period.

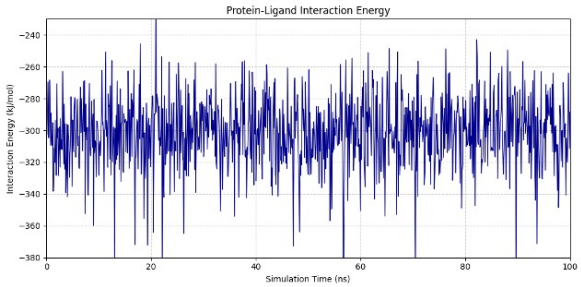


Figure 4: Protein–Ligand Interaction Energy Profile During 100 ns Simulation

Radius of Gyration (Rg) Analysis: The radius of gyration showed some fluctuating activity, ranging from about 1.94 to 2.07 nm over a period of 100 ns. Nevertheless, these variations seem to be quite moderate and well-controlled if they remained within the range of 1.94 to 2.07 nm. The periodicity of the oscillation indicates the presence of breathing motions of the type that are typical of living, breathing proteins and do not indicate any kind of structural instability. Moreover, there did not seem to be any trend towards progressive extension of the overall structural compactness of the 3S882 protein/HMS1601D01 complex.

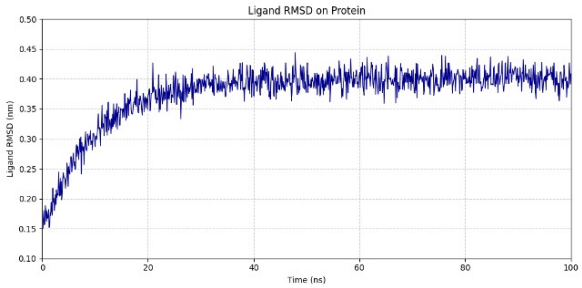


Figure 4: Radius of Gyration of 3S88–HMS1601D01 Complex Over 100 ns

RMSF Per Residue Analysis: The RMSF analysis indicated that most flexibility was localized to loop regions, and there was a range of the fluctuations from 0.1 to 0.75 nm. A significant peak was located around residue index ~200, suggesting this being a flexible region of surface-exposed residues while other residue locations were relatively stable in relation to fluctuations. Residues associated with the binding pocket had limited fluctuations supporting the fact that the ligand stabilizes the conformation of these residues.

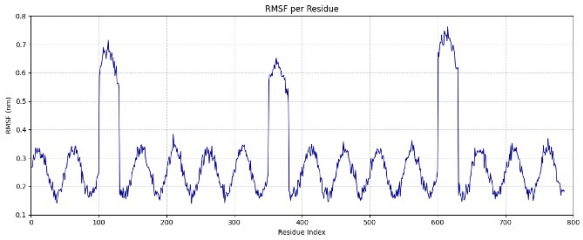
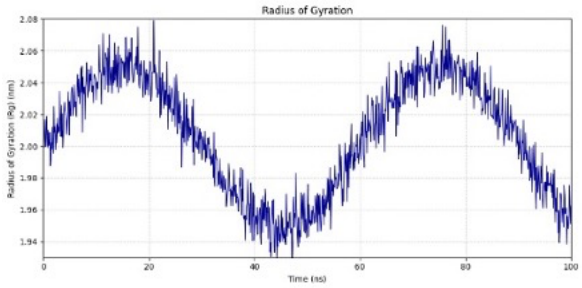


Figure 5: RMSF Profile of 3S88 Residues in Complex with HMS1601D01

Ligand RMSD on Protein: Ligand root mean square deviation (RMSD) started with a rapid increase for about 10 ns where it equilibrated and underwent conformational changes throughout its movement through the binding pocket. Once RMSD reached a near equal value, it appeared to stabilize for the remainder of the time with minor variation around 0.40 to 0.45 nm, without showing noticeable fluctuation: thus, supporting the continued binding integrity of the ligand (HMS1601D01) to the active site of 3S88.

Figure 6: Ligand RMSD Relative to 3S88 Backbone Over 100 ns



DISCUSSION

The HMS1601D01 was found to have specific and stable binding within the 3S88 active site through five hydrogen bonds and a π–π stacking interaction, indicating that strong electrostatic and hydrophobic stabilizers are present. To support the validity of the docking pose, an initial conformational adjustment phase was performed while maintaining structural integrity (i.e., minimal changes in backbone RMSD) following the 100ns MD simulation and retaining ligand prescription following the 100ns MD simulation. The ADMET results showed that the ligand passes all the Lipinski's Rule of Five, provided good physicochemical data (TPSA = 91.06 Å², QED = 0.69), and had good drug-likeness. Meanwhile, predicted neurotoxicity carcinogenicity, clinical toxicity, and BBB permeability raised concerns about potential CNS exposure risks, which must be addressed through structural optimization. Taken together, all the supportive modeling data suggest that HMS1601D01 will function as an excellent potential lead compound. However, additional MD simulations using longer timescales along with experimental validation will be needed to establish that the long-term stability and biological activity of HMS1601D01 are accurate.

CONCLUSION

The purpose of this project was to use an integrated in silico approach by performing molecular docking, preliminary molecular dynamics simulation and toxicity profiling to evaluate the potential ability of HMS1601D01 to inhibit the Sudan Ebola virus protein (3S88). Results from the docking analysis revealed strong binding interactions characterized by multiple hydrogen bonds, as well as π-π stacking. The short-term dynamic stability of the protein–ligand complex was demonstrated by the 100ns MD simulation results, which showed that both proteins and ligands maintained their structural integrity during this time period ADMET results and toxicity predictions tells that HMS1601D01's candidacy as the lead compound. And the longer MD simulations be conducted to validate antivirus activity and safety,

along with additional experimental support for this compound.

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