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Repurposing FDA-approved drugs against the Crimean-Congo haemorrhagic fever virus: an *in silico* study

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ABSTRACT

The Crimean-Congo haemorrhagic fever (CCHF) is a severe viral illness with a case fatality rate of up to 30%, typically transmitted to humans through bites from infected soft ticks. In the absence of US Food and Drug Administration (FDA)-approved antiviral therapies, novel therapeutic strategies are urgently required. This study has employed an *in silico* drug repurposing approach targeting the ovarian tumor domain (OTU) protease of the Crimean-Congo haemorrhagic fever virus (CCHFV), by utilizing FDA-approved pharmacological agents. A total of 1,379 compounds were virtually screened *via* molecular docking and molecular dynamics (MD) simulations in order to assess their binding affinities and structural stabilities. Paromomycin exhibited the strongest binding profile, with an extra precision Glide score (XP GScore) of -11.156 kcal/mol and a root mean square deviation (RMSD) consistently below 5 Å over the 50-nsec MD trajectory. Mapping against the enzymatic region of the CCHFV OTU protease has revealed multiple interactions with key catalytic residues, thereby suggesting that paromomycin may act as a reversible inhibitor of this viral protease. These findings support the hypothesis that computational techniques can identify promising candidates for CCHF treatment and underscore the need for further experimental validation of these predictions.

1. Introduction

The Crimean-Congo haemorrhagic fever (CCHF) is a viral illness caused by the Crimean-Congo haemorrhagic fever virus (CCHFV). First docu-

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mented in the Crimean region in 1944, CCHF remains a pressing global health concern due to its high case fatality rate, ranging from 10% to 30%. The disease affects an estimated 10,000–15,000 individuals annually, resulting in approximately 500 deaths worldwide[1]. Currently, no antiviral therapy for CCHF is approved by the US Food and Drug Administration (FDA). Although the World Health Organization (WHO) has proposed ribavirin as a potential treatment, its efficacy remains unverified and may depend on prompt administration[2]. The virus's high transmissibility and lethality – compounded by limited management strategies and the absence of preventive tools – underscore the need for innovative therapeutic interventions[3].

Advancements in computational biology have introduced *in silico* approaches that accelerate the identification of antiviral drug candidates[4]. This study harnesses molecular docking and molecular dynamics (MD) simulations in order to repurpose FDA-approved drugs targeting the CCHFV ovarian tumor domain-like protease (OTU protease); an enzyme implicated in the virus's evasion of host immune responses.

2. Methodology

The three-dimensional structure of the CCHFV OTU protease was retrieved from the Protein Data Bank (PDB; ID: 5V5H). Protein preparation was performed using by the Glide suite. Structural refinement included bond correction and hydrogen atom addition *via* the Protein Preparation Wizard. Energy minimization was executed at physiological pH (7.0) using the Optimized Potentials for Liquid Simulations force field, version 4 (OPLS4), with a root mean square deviation (RMSD) cut-off of 0.30 Å.

A random set of 1,379 FDA-approved compounds was selected for virtual screening. Ligand structures were obtained from the ZINC20 database (https://zinc20.docking.org/substances/subsets/fda/). Each ligand was optimized using OPLS4 with atom-specific partial charges and conformer generation at pH 7.0. Molecules containing more than 1,000 atoms were excluded.

Molecular docking was conducted *via* Glide, focusing on interactions at the OTU protease active site. The catalytic triad – cysteine (Cys40), aspartate (Asp37), and histidine (His151) – was prioritized based on prior enzymatic studies. Ligand affinity rankings were determined by extra precision Glide score (XP GScore).

Subsequent MD simulations of the top five ligands were executed by using the Desmond module in Schrödinger for a duration of 50 nsec. Trajectory analysis included RMSD evaluation to assess ligand–protein complex stability. Further docking validation was performed with the Discovery Studio version 20.1 software, where the ligand–residue interactions were visualized and quantified.

3. Results and Discussion

The undertaken virtual screening of 1,379 FDA-approved drugs has identified five lead candidates exhibiting XP GScore values between -11.156 and -7.21 kcal/mol (Figure 1). Of these, paromomycin demonstrated the strongest binding (Figure 1A), supported by superior MD stability.

Paromomycin, an aminoglycoside antibiotic, achieved the most negative binding affinity (XP GScore: -11.156 kcal/mol), confirming its status as the top-ranked ligand for the OTU protease. MD analysis revealed consistent RMSD values below 5 Å, thereby indicating robust binding over the simulation period. These data suggest that paromomycin can effectively associate with the protease active site, potentially inhibiting CCHFV's capacity to evade immune detection. Interaction mapping has highlighted several key residue engagements that likely contribute to paromomycin's specificity and stability (Figure 1A).

Previous literature supports the involvement of Cys40, His151, and Asp37 as catalytic residues within the OTU protease[5]. In addition, paromomycin has shown a binding affinity for an adjacent pocket spanning Y89–W99[6], suggesting a dual inhibitory mechanism and targeting both catalytic and modulatory sites. Beyond CCHF, paromomycin has demonstrated efficacy against parasitic infections and antiviral activity against SARS-CoV-2[7], thereby reinforcing its repurposing potential. This cross-utility advocates for the adoption of broader *in silico* screening frameworks in order to address emergent viral threats.

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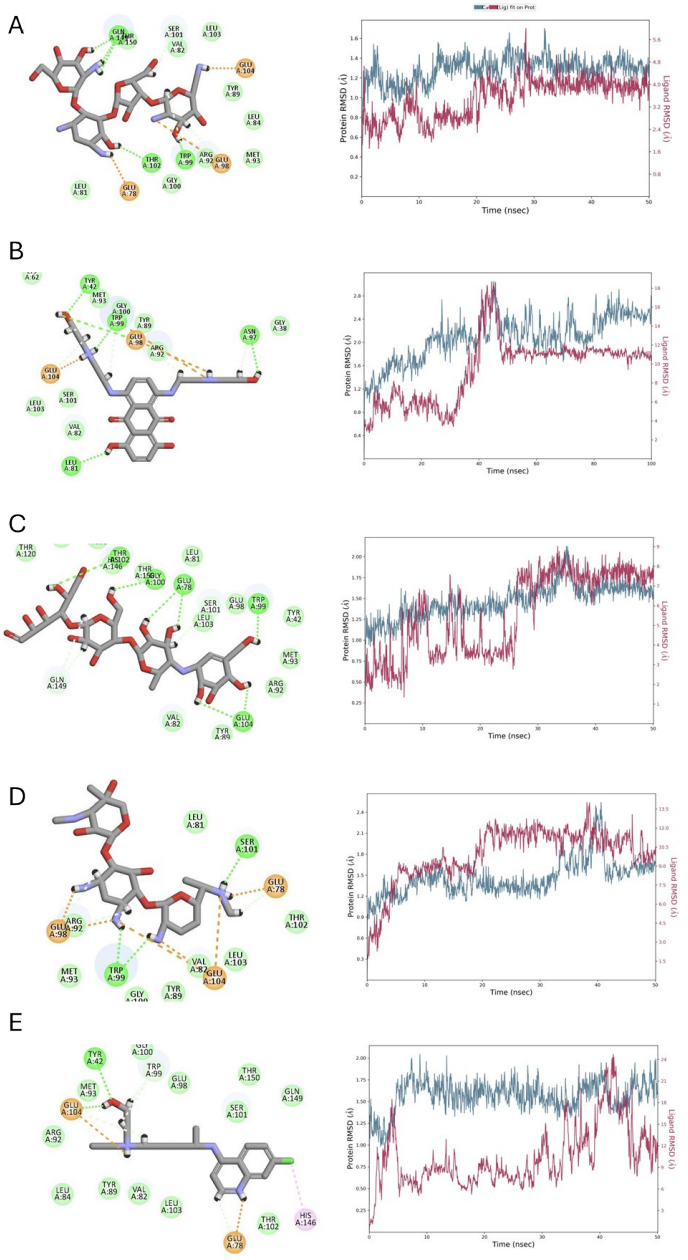

Figure 1. *Molecular docking and dynamics analysis of US Food and Drug Administration (FDA)-approved drugs targeting the Crimean-Congo haemorrhagic fever virus (CCHFV) ovarian tumor domain (OTU) protease. Panels (A–E) present the molecular docking and molecular dynamics (MD) simulation results of five drugs approved by the FDA targeting the CCHFV OTU protease: paromomycin (A), mitoxantrone (B), acarbose (C), gentamicin (D), and hydroxychloroquine (E). The left sub-panels depict two-dimensional (2D) ligand–residue interaction maps, focusing on catalytically and structurally relevant residues: cysteine (Cys40), histidine (His151), aspartate (Asp37), and the pocket region Y89–W99. The right sub-panels show root mean square deviation (RMSD) plots across 50-nsec MD trajectories, highlighting paromomycin's superior conformational stability (RMSD <5 Å). The obtained XP GScore values were as follows: A, -11.156 kcal/mol; B, -8.931 kcal/mol; C, -8.941 kcal/mol; D, -7.577 kcal/mol; E, -7.210 kcal/mol.*

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Our findings validate computational drug repurposing as a powerful approach for identifying viable inhibitors of CCHFV OTU protease, warranting further *in vitro* and *in vivo* evaluation[4,8]. Finally, this workflow may be applicable to other high-mortality pathogens lacking approved treatments.

4. Conclusion

Our study reinforces the utility of *in silico* screening of FDA-approved compounds as a viable strategy for antiviral drug discovery. The obtained binding affinities and residue-level interactions underscore the method's potential to accelerate therapeutic development for emerging viral diseases.

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None.

Conflicts of interest

None exist.

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