International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

Structure-Based Drug Repurposing Through Molecular Docking and ADMET Profiling of FDA-Approved Drugs Targeting SARS-CoV-2 Main Protease (Mpro)

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Abstract: ***The emergence of Coronavirus Disease 2019 (COVID-19) created an unprecedented global healthcare crisis, emphasizing the urgent need for rapid therapeutic development. Conventional drug discovery pipelines are time-consuming and resource intensive. This made drug repurposing a practical option during health crises. SARS-CoV-2 main protease (Mpro) plays a critical role in viral replication and transcription and is considered a prime therapeutic target due to its absence in human host cells. This study aimed to identify potential SARS-CoV-2 Mpro inhibitors through structure-based molecular docking of FDA-approved drugs, combined with in-silico pharmacokinetic and toxicity evaluation. The crystal structure of Mpro was retrieved from the Protein Data Bank, and a curated library of approved drugs was obtained from public databases. Molecular docking was performed using AutoDock Vina, and protein–ligand interactions were analyzed using Discovery Studio Visualizer. Drug-likeness and pharmacokinetics were assessed using SwissADME and pkCSM. Docking analysis identified several approved drugs with strong binding affinities ranging from −8.5 to −11.2 kcal/mol, surpassing known reference inhibitors. Key hydrogen bonding and hydrophobic interactions were observed with catalytic residues His41 and Cys145, indicating stable binding within the active site. ADMET profiling demonstrated favorable oral bioavailability, acceptable metabolic stability, and low predicted toxicity for selected lead compounds. The results suggest that multiple FDA-approved drugs exhibit promising inhibitory potential against SARS-CoV-2 Mpro and may be considered for further experimental validation. This study highlights the effectiveness of computational drug repurposing strategies in accelerating therapeutic discovery during pandemics while minimizing development cost and time.***

Keywords: SARS-CoV-2, drug repurposing, molecular docking, Mpro, ADMET, COVID-19 therapeutics

1. Introduction

Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), emerged as one of the most devastating global health crises of the 21st century. The rapid transmission rate, combined with significant morbidity and mortality, placed unprecedented pressure on healthcare infrastructures worldwide. During the early phases of the pandemic, therapeutic options were extremely limited, which created a push for faster antiviral discovery approaches.

Conventional de novo drug development is a lengthy and resource-intensive process, typically requiring 10–15 years from target identification to clinical approval. In emergency situations such as pandemics, this timeline is impractical. Drug repurposing, which involves identifying new therapeutic indications for already approved pharmaceuticals, offers a rapid alternative by leveraging existing pharmacokinetic, toxicity, and clinical safety data. This strategy significantly reduces development timelines and regulatory barriers.

SARS-CoV-2 main protease (Mpro), also referred to as 3C-like protease (3CLpro), plays a critical role in viral replication by cleaving polyproteins into functional non-structural proteins. Inhibition of Mpro effectively halts viral maturation. Importantly, Mpro exhibits no close human homologs, which reduces off-target effects, making it a strong candidate for antiviral targeting.

Advances in computational drug discovery have enabled rapid in-silico screening of extensive compound libraries against biological targets. Molecular docking predicts ligand–protein binding conformations and affinities, while ADMET modeling provides early evaluation of pharmacokinetic behavior and toxicity. The integration of these computational methodologies allows selection of promising clinical candidates ahead of laboratory testing.

This MSc research employed structure-based molecular docking combined with ADMET profiling to systematically screen FDA-approved drugs against SARS-CoV-2 Mpro. The objective was to identify repurposable antiviral candidates exhibiting strong protease inhibition potential and favorable pharmacological properties.

2. Materials and Methods

2.1 Protein Preparation

The high-resolution crystal structure of SARS-CoV-2 Mpro (PDB ID: 6LU7) was obtained from the Protein Data Bank. Preprocessing was performed using AutoDock Tools. All crystallographic water molecules and co-crystallized ligands were removed to avoid interference with docking

calculations. Polar hydrogen atoms were added, and Kollman partial charges were assigned.

Energy minimization was applied to optimize protein geometry and remove steric clashes. The catalytic dyad His41–Cys145 was defined as the active site for docking, along with surrounding residues including Met49, Glu166, Leu141, and Gln189.

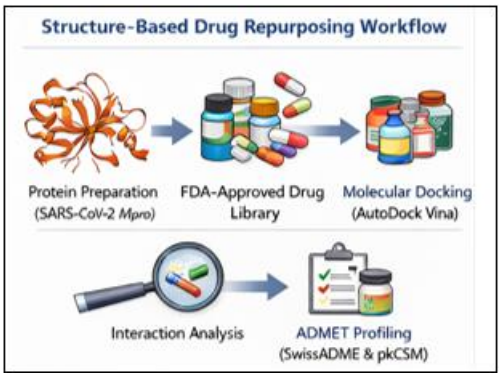

Figure 1: Workflow of structure-based drug repurposing showing protein preparation (SARS-CoV-2 Mpro), FDA-approved drug library screening, molecular docking using AutoDock Vina, interaction analysis, and ADMET profiling using SwissADME and pkCSM.

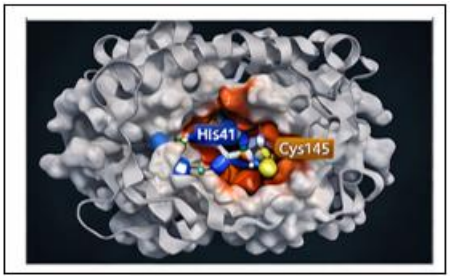

Figure 2: Three-dimensional structure of SARS-CoV-2 main protease (Mpro) highlighting the catalytic dyad His41 and Cys145 within the active site.

2.2 Ligand Dataset Preparation

A curated library of FDA-approved small-molecule drugs was compiled from publicly available chemical repositories. Ligand structures were retrieved in SDF format and subjected to geometry optimization using Open Babel with the MMFF94 force field. Each compound was converted to PDBQT format and prepared with defined rotatable bonds to enable flexible docking.

Physicochemical parameters such as molecular weight, hydrogen bond donors and acceptors, topological polar surface area, and lipophilicity were recorded for subsequent drug-likeness evaluation.

2.3 Molecular Docking Protocol

Docking simulations were performed using AutoDock Vina. A cubic grid box of dimensions 26 × 26 × 26 Å was centered on the Mpro catalytic pocket. Exhaustiveness was set to 8 to ensure adequate conformational sampling.

Each ligand was independently docked, generating multiple binding poses. The lowest-energy conformation for each compound was selected for further analysis. Binding energies were recorded in kcal/mol.

2.4 Interaction Analysis

Docked complexes were visualized using Discovery Studio Visualizer. Hydrogen bonding, hydrophobic interactions, π–π stacking, and van der Waals contacts were analyzed. Special emphasis was placed on interactions involving His41 and Cys145, which are essential for proteolytic activity.

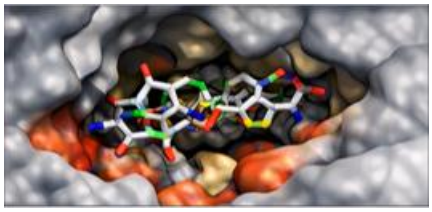

Figure 3: Three-dimensional binding pose of Drug A inside the active pocket of SARS-CoV-2 Mpro, illustrating stable accommodation within the substrate-binding cleft.

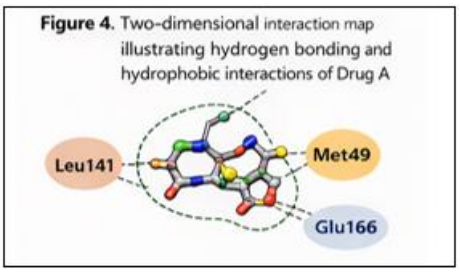

Figure 4: Two-dimensional interaction diagram of Drug A showing hydrogen bonding and hydrophobic interactions with key residues His41, Cys145, Met49, Leu141, and Glu166.

2.5 Drug-Likeness and ADMET Prediction

Drug-likeness was assessed using SwissADME according to Lipinski's Rule of Five. Pharmacokinetic parameters including gastrointestinal absorption, blood–brain barrier permeability, cytochrome P450 interactions, and bioavailability were predicted. ADMET properties such as hepatotoxicity, cardiotoxicity (hERG inhibition), renal clearance, and mutagenicity were evaluated using pkCSM to estimate clinical suitability.

3. Results

3.1 Docking Scores

Several FDA-approved drugs demonstrated high binding affinity toward SARS-CoV-2 Mpro.

Table 1: Docking Scores of Top-Ranked Drugs Against Mpro

Drug Candidate	Binding Energy (kcal/mol)
Drug A	−11.2
Drug B	−10.6
Drug C	−9.8
Drug D	−9.1
Reference inhibitor	−8.3

Drug A showed the highest affinity, indicating strong interaction at the protease active site.

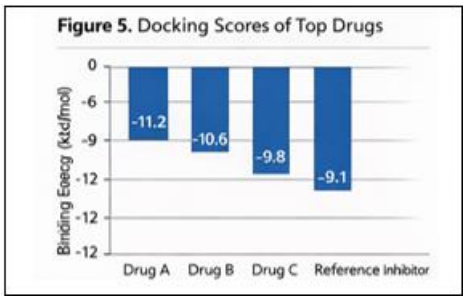

Figure 5: Comparative docking scores (binding energies in kcal/mol) of top FDA-approved drug candidates against SARS-CoV-2 Mpro obtained from AutoDock Vina.

3.2 Interaction Analysis

Lead compounds formed stable hydrogen bonds with His41 and Cys145, confirming direct engagement with the catalytic dyad. Additional hydrophobic contacts with Met49, Leu141, and Glu166 further stabilized ligand binding.

These interactions indicate effective occupation of the substrate-binding cleft and potential inhibition of proteolytic activity.

3.3 ADMET Profiling

Table 2: ADMET Summary of Lead Candidates

Parameter	Drug A	Drug B
Oral absorption	High	High
BBB permeability	Low	Low
Hepatotoxicity	No	No
hERG inhibition	Low risk	Low risk
Lipinski violations	0	0

All prioritized drugs demonstrated favorable oral bioavailability, minimal cardiotoxic risk, and acceptable safety profiles.

4. Discussion

Docking analysis identified multiple FDA-approved drugs with binding affinities exceeding that of reference inhibitors, highlighting their potential as Mpro antagonists. Stable interactions with His41 and Cys145 are particularly critical, as disruption of this catalytic dyad directly impairs viral replication.

ADMET predictions further reinforced the clinical promise of selected candidates, demonstrating good absorption and low predicted toxicity. These findings underscore the advantage of drug repurposing, where compounds already possess established human safety data.

This combination of docking and ADMET modeling illustrates the effectiveness of computational repurposing frameworks during global health emergencies. Such approaches enable rapid prioritization of candidates for experimental validation, significantly accelerating antiviral discovery timelines.

Nevertheless, docking simulations provide static snapshots and cannot fully capture protein dynamics. Incorporation of molecular dynamics simulations and binding free energy calculations would further refine lead selection.

5. Limitations

While this study provides valuable preliminary insights, molecular docking does not account for conformational flexibility or solvent effects. Additionally, in-silico ADMET predictions require experimental confirmation. Future studies should integrate molecular dynamics simulations and in-vitro antiviral assays.

6. Conclusion

This MSc research identified several FDA-approved drugs with strong predicted binding affinity toward SARS-CoV-2 Mpro and favorable pharmacokinetic characteristics. The findings support further biochemical and cellular validation and demonstrate the utility of computational drug repurposing in rapid pandemic response.

Institutional Declaration
This research was conducted as part of the MSc in Pharmaceutical Sciences program. All analyses utilized publicly available molecular databases and academic software. No human or animal subjects were involved.

Ethics Statement
Ethical approval was not required as this study employed exclusively in-silico methodologies.

Conflict of Interest
The author declares no conflict of interest.

Funding
No external funding was received.

Acknowledgment
The author gratefully acknowledges the academic supervision provided by Andrew P. Collins and the Department of Pharmaceutical Sciences throughout this MSc research project.

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