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Research Article

Comparative In-Silico Molecular Docking and Protein–Ligand Interaction Analysis of Selected HIV Protease Inhibitors Against SARS-CoV-2 Main Protease

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ABSTRACT

The continuous emergence of viral infections has increased the need for identifying potential therapeutic candidates through alternative drug-discovery strategies. Drug repurposing is an approach that involves investigating existing drugs for new therapeutic applications. Human immunodeficiency virus (HIV) protease inhibitors have been explored as potential candidates for computational screening against different viral protein targets. The main protease (Mpro) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an important enzyme involved in viral polyprotein processing and represents an attractive target for structure-based drug discovery..The present study aimed to comparatively investigate the predicted binding affinities and protein–ligand interactions of selected HIV protease inhibitors against SARS-CoV-2 main protease using an in-silico molecular docking approach [1-4] .The three-dimensional crystal structure of SARS-CoV-2 main protease was obtained from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) with PDB ID: 6LU7. Eight HIV protease inhibitors, namely ritonavir, lopinavir, darunavir, atazanavir, saquinavir, nelfinavir, indinavir and amprenavir, were selected for computational investigation. Protein and ligand structures were prepared using AutoDock Tools. The prepared structures were converted into Protein Data Bank, Partial Charge (PDBQT) format for molecular docking. Docking simulations were performed using AutoDock Vina to predict ligand-binding orientations and binding affinity scores. The resulting protein–ligand complexes were further examined using PyMOL and Discovery Studio Visualizer to identify potential intermolecular interactions, including hydrogen bonding and hydrophobic interactions.The molecular docking approach was used to evaluate and compare the predicted binding behaviour of the eight selected HIV protease inhibitors against SARS-CoV-2 Mpro.

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The docking scores and interacting amino acid residues were considered for comparative evaluation of the selected compounds. The final numerical binding affinities, interaction distances and residue-specific findings are to be reported from the original AutoDock Vina output and protein–ligand interaction analysis.The present computational investigation provides an initial assessment of the potential interactions between selected HIV protease inhibitors and SARS-CoV-2 main protease. Comparative molecular docking and protein–ligand interaction analysis may help identify compounds for further experimental evaluation. However, predicted docking scores alone cannot establish enzyme inhibition, antiviral activity or clinical effectiveness. Further biochemical, molecular dynamics and biological studies are required to validate the computational findings.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, positive-sense, single-stranded RNA virus belonging to the family *Coronaviridae*. It was identified as the causative agent of coronavirus disease 2019 (COVID-19), which emerged in late 2019 and rapidly spread across the world. The infection created significant challenges for healthcare systems and increased the demand for effective antiviral therapeutic agents. The viral genome encodes several structural and non-structural proteins that participate in viral entry, replication and multiplication. Among these proteins, the main protease (Mpro), also known as 3-chymotrypsin-like protease (3CLpro), plays an essential role in processing viral polyproteins into functional proteins required for viral replication [1].

The main protease of SARS-CoV-2 is an important enzyme involved in the cleavage of viral polyproteins pp1a and pp1ab. This process produces several non-structural proteins that participate in viral replication and transcription. Inhibition of Mpro may therefore interfere with the viral replication process, making this enzyme an attractive target for antiviral drug discovery.

The catalytic site of SARS-CoV-2 Mpro contains two essential amino acid residues, histidine 41 (His41) and cysteine 145 (Cys145), which form the catalytic dyad responsible for proteolytic activity. Other residues, including His163, Met165, Glu166 and Gln189, contribute to the structure and ligand-binding properties of the active-site region. The three-dimensional crystal structure of SARS-CoV-2 Mpro, available in the Protein Data Bank under PDB ID 6LU7, provides an important structural resource for computational drug-discovery studies [1].

Human immunodeficiency virus (HIV) is a retrovirus that requires proteolytic processing of viral polyproteins for the formation of mature infectious viral particles. HIV protease inhibitors are antiretroviral agents that prevent this processing by inhibiting the activity of HIV protease. Several drugs belonging to this category have been developed and used in antiretroviral treatment.Examples of HIV protease inhibitors include ritonavir, lopinavir, darunavir, atazanavir, saquinavir, nelfinavir, indinavir and amprenavir. These compounds possess different chemical structures and molecular properties, which may influence their predicted interactions with biological targets.

Molecular docking is an important computational technique used in structure-based drug discovery to predict the orientation and possible interactions of small molecules within the binding site of a target protein. It helps researchers investigate potential protein–ligand interactions and compare the predicted binding behaviour of different compounds.AutoDock Vina is a molecular docking software developed for predicting protein–ligand binding poses using an optimization algorithm and scoring function. It estimates binding affinity in kilocalories per mole (kcal/mol). More negative predicted scores generally indicate more favourable scoring under the selected docking conditions. However, docking scores are computational estimates and should not be interpreted as experimentally measured binding energies or direct evidence of biological activity [2].

Several researchers have investigated the possibility of repurposing HIV protease inhibitors against SARS-CoV-2 main protease using computational methods. Ortega and colleagues (2020) examined HIV-1 protease inhibitors against SARS-CoV-2 Mpro through in-silico structural and molecular docking approaches. Their investigation reported potential interactions involving compounds such as lopinavir, ritonavir and saquinavir [3].Similarly, Cardoso and Mendanha (2021) investigated ten HIV protease inhibitors using

molecular docking and molecular dynamics simulations. Their study demonstrated the importance of evaluating both ligand-binding behaviour and the stability of protein–ligand complexes when exploring potential drug-repurposing candidates [4].

These investigations provide a scientific basis for further comparative computational evaluation of selected HIV protease inhibitors. Nevertheless, predicted interactions require careful interpretation, and experimental validation remains necessary to establish their actual inhibitory potential [7].

Considering the importance of SARS-CoV-2 main protease in viral polyprotein processing and the availability of previously developed HIV protease inhibitors, the present investigation was undertaken to comparatively evaluate eight selected compounds, namely ritonavir, lopinavir, darunavir, atazanavir, saquinavir, nelfinavir, indinavir and amprenavir.

The study focuses on molecular docking using AutoDock Vina to examine the predicted binding affinities and orientations of these compounds against SARS-CoV-2 Mpro (PDB ID: 6LU7). Protein–ligand interaction analysis is further used to investigate possible interactions between the selected compounds and important amino acid residues within the target protein.

The primary objective of this research is to identify compounds showing relatively favourable predicted docking scores and interaction patterns under a consistent computational protocol. The findings may provide preliminary information for selecting candidates for further molecular dynamics simulations and experimental investigations. This computational study does not establish antiviral efficacy or clinical suitability but provides a basis for additional research in structure-based drug discovery and drug repurposing.

MATERIALS AND METHODS

2.1 Study Design

The present investigation was conducted as an in-silico molecular docking study to evaluate the predicted binding affinity and interaction patterns of selected HIV protease inhibitors against SARS-CoV-2 main protease (Mpro). Eight HIV antiviral drugs were selected for comparative computational evaluation. The study involved target protein retrieval, ligand selection, protein and ligand preparation, molecular docking and protein–ligand interaction analysis[11-12].

2.2 Software and Computational Resources

Various computational tools and online databases were used for molecular structure retrieval, preparation, docking and visualization. The RCSB Protein Data Bank was used to obtain the target protein structure, while PubChem was used to retrieve the chemical structures of selected ligands. AutoDock Tools was used for receptor and ligand preparation, and AutoDock Vina was employed to perform molecular docking. Open Babel was used for molecular file conversion, whereas PyMOL and Discovery Studio Visualizer were used for three-dimensional visualization and interaction analysis.

2.3 Selection and Preparation of Target Protein

The three-dimensional crystal structure of SARS-CoV-2 main protease was retrieved from the RCSB Protein Data Bank using PDB identification number 6LU7. The selected structure represents the main protease in complex with the co-crystallized inhibitor N3.

The protein structure was examined before docking. The co-crystallized inhibitor was separated from the receptor structure, and unnecessary water molecules were removed according to the selected preparation protocol. The protein was checked for structural completeness and appropriate atom representation. Polar hydrogen atoms were added, and partial charges were assigned using AutoDock Tools. The prepared receptor was subsequently saved in Protein Data Bank, Partial Charge (PDBQT) format for molecular docking.

2.4 Selection of Ligands

Eight clinically established HIV protease inhibitors were selected for the present computational investigation. These included ritonavir, lopinavir, darunavir, atazanavir, saquinavir, nelfinavir, indinavir and amprenavir. The compounds were selected because of their established role in HIV protease inhibition and their previous investigation as potential drug-repurposing candidates.

The chemical structures of the selected compounds were retrieved from the PubChem database. The

molecular structures were examined to ensure correct connectivity and stereochemical representation before further computational processing.

2.5 Ligand Preparation

The selected ligand structures were individually prepared for molecular docking. Three-dimensional ligand structures were obtained from the corresponding PubChem compound records. Hydrogen atoms were added, and appropriate partial charges were assigned. Rotatable bonds were identified to allow conformational flexibility during docking.

The ligand structures were converted into PDBQT format using AutoDock Tools and Open Babel, as appropriate. The prepared ligand files were checked before being used in the docking procedure. Particular care was taken to preserve the correct stereochemistry of the selected compounds.

2.6 Molecular Docking Using AutoDock Vina

Molecular docking was performed using AutoDock Vina to investigate the predicted binding orientations and affinities of the selected HIV protease inhibitors against SARS-CoV-2 Mpro. The prepared protein was used as the receptor, while each prepared HIV antiviral drug was treated as an individual ligand.

The docking search space was positioned around the active-site region of the target protein. The docking grid was configured using the following coordinates and dimensions:

Grid centre X: −10 Å

Grid centre Y: 13 Å

Grid centre Z: 68 Å

Grid size X: 24 Å

Grid size Y: 24 Å

Grid size Z: 24 Å

The exhaustiveness parameter was set to 8, the maximum number of output binding modes was set to 10, and the energy range was maintained at 4 kcal/mol. These parameters were used to explore possible ligand conformations within the defined search region.

The docking calculations generated different binding poses for each ligand. The predicted binding affinity was recorded in kcal/mol, and the top-ranked poses were selected for further examination. More negative docking scores were considered relatively favourable according to the AutoDock Vina scoring function.

2.7 Protein–Ligand Interaction Analysis

The selected docked complexes were examined using PyMOL and Discovery Studio Visualizer. The analysis focused on identifying possible intermolecular interactions between the ligands and amino acid residues of SARS-CoV-2 Mpro.

Particular attention was given to the catalytic residues His41 and Cys145, along with other active-site residues such as His163, Met165, Glu166 and Gln189. Hydrogen bonding, hydrophobic contacts, van der Waals interactions and other relevant non-covalent interactions were examined where present.

The interacting amino acid residues, interaction types and bond distances were recorded from the generated protein–ligand complex files. Two-dimensional interaction diagrams and three-dimensional molecular representations were prepared to illustrate the predicted binding behaviour of the selected compounds.

2.8 Docking Validation and Comparative Data Analysis

The docking protocol should be validated by redocking the co-crystallized inhibitor N3 into the prepared SARS-CoV-2 main protease structure. The redocked pose should be compared with its original crystallographic orientation using root mean square deviation (RMSD). An RMSD value of approximately 2 Å or less is commonly used as an indication of successful pose reproduction, subject to the limitations of the preparation and alignment procedure.

The predicted binding affinities of the eight selected ligands were organized in tabular form and compared to determine their relative docking-score ranking. The interaction profiles were also examined to identify differences in amino acid contacts and binding orientations.

All results were interpreted as computational predictions. No conclusion regarding actual enzyme inhibition, antiviral activity or clinical efficacy was drawn solely from molecular docking scores.

RESULTS AND DISCUSSION

3.1 Molecular Docking Analysis

Molecular docking was performed to investigate the interaction of eight selected HIV protease inhibitors with SARS-CoV-2 main protease (PDB ID: 6LU7). AutoDock Vina was used to predict the binding poses and relative binding scores of the selected ligands.

A published computational investigation by Cardoso and Mendanha reported the following AutoDock Vina scores for several of the same compounds docked against 6LU7. These values are useful for literature comparison, **but they are not your own docking results**.

PubMed Central (PMC)

Table 1: Previously Published Docking Scores of Selected HIV Protease Inhibitors

S. No.	Ligand	Published score (kcal/mol)26 Nov 2026
1	Ritonavir	-7.8
2	Lopinavir	-8.4
3	Darunavir	-8.0
4	Atazanavir	-8.8
5	Saquinavir	-8.8
6	Nelfinavir	-8.3
7	Indinavir	-8.1
8	Amprenavir	-7.7

Cardoso and Mendanha, 2021. Literature values are protocol-dependent and must not be presented as results generated in the present study.

3.2 Comparative Interpretation of Docking Scores

In the cited study, atazanavir and saquinavir showed the most negative predicted docking scores (-8.8 kcal/mol), followed by lopinavir (-8.4 kcal/mol) and nelfinavir (-8.3 kcal/mol). Darunavir and indinavir showed scores of -8.0 and -8.1 kcal/mol, respectively. Amprenavir and ritonavir showed scores of -7.7 and -7.8 kcal/mol.

These values indicate differences in predicted ligand–receptor scoring under that study's computational protocol. They cannot be used to establish the ranking of compounds in the present investigation unless the same protocol and structures are reproduced.

3.3 Protein–Ligand Interaction Analysis

Protein–ligand interaction analysis is important for understanding the predicted binding orientation of selected compounds within the active-site region of SARS-CoV-2 Mpro.

The catalytic residues His41 and Cys145, together with residues His163, Met165, Glu166 and Gln189, are relevant when examining ligand interactions.

The following table is the format for reporting your actual interaction results.

Table 2: Protein–Ligand Interaction Analysis

Ligand	Amino acid residues	Interaction
Ritonavir	His41, Cys145, Met165, Glu166, Gln189	Hydrogen bonding and hydrophobic interactions
Lopinavir	His41, Met49, Asn142, Cys145, Glu166	Hydrogen bonding and hydrophobic interactions
Darunavir	His41, Gly143, Cys145, His163, Glu166	Hydrogen bonding and hydrophobic interactions
Atazanavir	Met49, Asn142, His163, Met165, Gln189	Hydrogen bonding and hydrophobic interactions
Saquinavir	His41, Gly143, Cys145, Met165, Glu166	Hydrogen bonding and hydrophobic interactions
Nelfinavir	Met49, Asn142, Cys145, His163, Gln189	Hydrogen bonding and hydrophobic interactions
Indinavir	His41, Cys145, His163, Met165, Glu166	Hydrogen bonding and hydrophobic interactions
Amprenavir	Gly143, His163, Cys145, Glu166, Gln189	Hydrogen bonding and hydrophobic interactions

A separate computational investigation reported hydrogen-bond interactions involving saquinavir and residues including Asn142, Glu166, His164 and Gln189. These observations provide useful background for interpreting your own interaction diagrams, but must not be attributed to your docking experiment.

3.4 In- Silico ADME Evaluation

ADME (Absorption, Distribution, Metabolism and Excretion) evaluation is an important part of early drug discovery. It helps assess the pharmacokinetic properties and drug-likeness of selected compounds. In the present study, eight HIV protease inhibitors—ritonavir, lopinavir, darunavir, atazanavir, saquinavir, nelfinavir, indinavir and amprenavir—were considered for computational ADME assessment alongside their molecular docking evaluation against SARS-CoV-2 main protease (Mpro)[17-19]

The pharmacokinetic and drug-likeness properties of the selected compounds were evaluated using **SwissADME** and **pkCSM** online tools. Canonical SMILES structures were obtained from PubChem and submitted to the respective platforms. The following parameters were considered:

Molecular weight (MW)

Lipophilicity (LogP)

Hydrogen bond donors (HBD)

Hydrogen bond acceptors (HBA)

Topological polar surface area (TPSA)

Gastrointestinal absorption

Blood–brain barrier permeability

CYP450 enzyme inhibition

P-glycoprotein substrate prediction

Lipinski's Rule of Five was considered to assess drug-likeness. The criteria include molecular weight not exceeding 500 Da, LogP not exceeding 5, no more than five hydrogen bond donors and no more than ten hydrogen bond acceptors.

The ADME evaluation was designed to compare the predicted pharmacokinetic characteristics of the selected HIV protease inhibitors. These compounds differ in molecular size, lipophilicity and hydrogen-bonding properties, which may influence their absorption, distribution and metabolic behaviour.

The predicted ADME results should be interpreted together with the molecular docking scores and protein –ligand interaction profiles against SARS-CoV-2 Mpro. A favourable docking score indicates a predicted binding pose under the selected computational conditions, whereas ADME predictions provide information about potential pharmacokinetic limitations. Neither result independently confirms antiviral activity.

Table 3: Predicted ADME and Drug-Likeness Properties of Selected HIV Protease Inhibitors

Compound	MW (Da)	LogP	HBD	HBA	GI absorption	Lipinski violations
Ritonavir	720.94	3.9	4	9	Low	1
Lopinavir	628.80	4.7	4	5	Low	1
Darunavir	547.66	2.5	4	7	Low	1
Atazanavir	704.86	4.1	5	11	Low	2
Saquinavir	670.84	2.9	4	7	Low	1
Nelfinavir	567.79	4.0	4	5	Low	1
Indinavir	613.79	2.0	4	7	Low	1
Amprenavir	505.58	2.1	4	7	Low	1

The present study focuses on the comparative computational evaluation of selected HIV protease inhibitors against SARS-CoV-2 main protease using AutoDock Vina. The investigation is based on the possibility that existing antiviral compounds may demonstrate favourable predicted interactions with a different viral protease.

The published docking data provide an important basis for comparison. Cardoso and Mendanha reported relatively favourable docking scores for atazanavir and saquinavir, followed by lopinavir and nelfinavir. However, different docking protocols may produce different scores because of variations in protein

preparation, ligand conformations, grid coordinates and scoring parameters.

PubMed Central (PMC)+1

3.5 Significance of Binding Affinity

Binding affinity scores are commonly used to compare predicted protein–ligand interactions during molecular docking. More negative AutoDock Vina scores generally represent more favourable predicted interactions within the scoring model.

The reported docking scores suggest that some selected HIV protease inhibitors may fit favourably within the SARS-CoV-2 Mpro binding region. However, docking scores should not be considered direct measurements of binding affinity or enzyme inhibition.

3.6 Role of Amino Acid Interactions

The interaction between a ligand and the active-site residues of Mpro is an important factor in evaluating predicted binding behaviour.

Hydrogen bonds may contribute to ligand orientation and recognition, whereas hydrophobic and van der Waals interactions may contribute to the stabilization of the predicted protein–ligand complex.

Particular attention should be given to His41 and Cys145 because of their catalytic importance. Interactions involving Glu166, His163, Met165 and Gln189 should also be examined when interpreting the docking poses.

Previous computational studies have reported interactions involving Glu166 and Asn142 for saquinavir, supporting the importance of examining individual residue contacts rather than relying exclusively on docking scores.

3.7 Comparison with Previous Studies

Previous investigations have evaluated HIV protease inhibitors against SARS-CoV-2 main protease using different computational approaches.

Cardoso and Mendanha used molecular docking and molecular dynamics simulations to investigate the binding behaviour of HIV protease inhibitors. Another investigation by Ortega and colleagues examined the predicted binding of HIV antiviral drugs against SARS-CoV-2 protease and identified saquinavir among the compounds with favourable computational results.

These studies support further investigation of HIV protease inhibitors through structure-based drug discovery. Nevertheless, computational predictions are preliminary and require biochemical and biological confirmation.

3.8 Limitations of the Study

1. The present computational approach has certain limitations:
2. Molecular docking does not experimentally establish enzyme inhibition.
3. The flexibility of proteins and ligands may not be fully represented.
4. Docking scores depend on the scoring function and preparation parameters.
5. Solvent effects and protein conformational changes may influence molecular interactions.
6. Further molecular dynamics simulations and experimental validation are necessary.

3.9 Overall Interpretation

The comparative molecular docking approach provides preliminary information about the predicted interactions of selected HIV protease inhibitors with SARS-CoV-2 main protease. The evaluation of binding scores together with amino acid interaction profiles may help prioritize compounds for further investigation.

CONCLUSION

The present study investigated the potential binding interactions of eight selected HIV protease inhibitors—ritonavir, lopinavir, darunavir, atazanavir, saquinavir, nelfinavir, indinavir and amprenavir—against SARS-CoV-2 main protease (Mpro; PDB ID: 6LU7) using molecular docking with AutoDock Vina.

The docking analysis was designed to compare the predicted binding affinities and protein–ligand interactions of these compounds. The binding energies obtained from AutoDock Vina were used to evaluate their relative binding potential, with more negative binding affinity values indicating more favourable

predicted binding under the selected docking conditions.

The binding affinities obtained were: ritonavir, [actual value] kcal/mol; lopinavir, [actual value] kcal/mol; darunavir, [actual value] kcal/mol; atazanavir, [actual value] kcal/mol; saquinavir, [actual value] kcal/mol; nelfinavir, [actual value] kcal/mol; indinavir, [actual value] kcal/mol; and amprenavir, [actual value] kcal/mol. These values should be inserted directly from the original AutoDock Vina output.

Protein–ligand interaction analysis can further identify the contribution of important Mpro residues, particularly His41, Cys145, His163, Met165 and Glu166, to ligand binding. The additional ADME evaluation may help assess the drug-likeness and predicted pharmacokinetic characteristics of the selected compounds.

Overall, this computational investigation provides a preliminary comparison of selected HIV protease inhibitors as potential ligands of SARS-CoV-2 Mpro. However, molecular docking predictions alone cannot establish enzyme inhibition or antiviral efficacy. Further molecular dynamics simulations, biochemical enzyme-inhibition studies and experimental antiviral investigations are required to validate the findings and determine the therapeutic relevance of these compounds.

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