Computational Drug Design: Molecular Docking of Lopinavir with HIV-1 Protease

Rui Zhang

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Abstract

This report rewrites a high-school research project on molecular docking into a concise English portfolio artifact. The original project used Schrödinger Maestro to study the interaction between lopinavir, an HIV protease inhibitor, and HIV-1 protease (PDB structure 1MIU). The work prepared ligand and protein structures, generated docking grids of 15, 18, and 20 Å, compared Glide GScore values, and interpreted hydrogen-bond, hydrophobic, and electrostatic interactions. The strongest docking score reported in the project was obtained for the 18 Ågrid, conformation LOP_18_1, with Glide GScore −11.898.

1 Context

The project was completed at Shanghai Foreign Language School Affiliated to SISU, Minhang Foreign Language School, during Grade 11. It was supervised with guidance from teachers and mentors and later listed in my CV as "Computational Drug Design: Molecular Docking of HIV Protease Inhibitors". The final project received First Prize in the 2021 Shanghai Youth Science and Innovation Workstation Competition.

The public version here is not a new biomedical claim. It is a cleaned portfolio version showing early experience with computational modelling, molecular docking software, scientific reporting, and interpretation of simulation output.

2 Research Question

How can molecular docking be used to model the binding of lopinavir to HIV-1 protease, and how do grid settings affect the predicted docking conformation and interaction analysis?

3 Background

HIV protease is an aspartyl protease involved in processing viral precursor proteins into mature viral components. Inhibiting this enzyme can prevent the formation of mature infectious viral particles. Lopinavir is a peptidomimetic HIV protease inhibitor commonly discussed in combination with ritonavir in clinical contexts. In this project, lopinavir was treated as the ligand and HIV-1 protease as the receptor.

The original report framed molecular docking as a computer-aided drug-design method. Docking does not replace experimental pharmacology, but it can help generate hypotheses about binding poses, active-site interactions, and relative stability under different computational settings.

4 Methods

The workflow followed the structure below.

1. Build and prepare the two-dimensional and three-dimensional molecular structure of lopinavir.
2. Prepare and optimize the HIV-1 protease receptor structure from PDB 1MIU.
3. Set protonation and structure-preparation parameters close to physiological conditions.
4. Generate docking grids with side lengths of 15, 18, and 20 Å.
5. Dock lopinavir into HIV-1 protease under each grid setting.
6. Compare the top docking conformations using Glide GScore and qualitative interaction analysis.

The original project used OPLS force-field settings during preparation and docking. Protein preparation included adding missing atoms or side-chain information, removing irrelevant water or hetero groups where appropriate, setting protonation state, and performing local energy minimization.

5 Docking Results

The best reported poses from the three grid settings are summarized in Table 1. More negative Glide GScore values indicate stronger predicted docking scores in this context.

Grid size	Best conformation	Glide GScore
15 Å	LOP_15_1	-10.758
18 Å	LOP_18_1	-11.898
20 Å	LOP_20_1	-10.192

Table 1: Best reported conformation from each grid condition.

The full ranked set reported in the original project is shown in Table 2. The 18 Ågrid produced the strongest score overall.

6 Interaction Analysis

For the 15 Ågrid, the top conformation was interpreted through hydrogen-bond interactions involving protonated Asp25/Ash25 and Ile50, with possible electrostatic contributions near Asp29 and Asp30 and hydrophobic interactions near residues such as Ala28, Leu23, and Pro81.

For the 18 Ågrid, the best pose LOP_18_1 was interpreted as the most stable overall. The original analysis reported seven hydrogen bonds, including interactions involving Ile50 on both chains and protonated Asp25/Ash25 residues, together with hydrophobic contacts involving Leu23, Ala28, and Val32 and electrostatic interactions near acidic residues.

For the 20 Ågrid, the best pose was interpreted as relying more heavily on electrostatic interactions near Asp29, Asp30, and protonated Asp residues, despite the absence of hydrogen bonds in the top conformation.

Rank	Grid	Conformation	Glide GScore
1	18 Å	LOP_18_1	-11.898
2	15 Å	LOP_15_1	-10.758
3	20 Å	LOP_20_1	-10.192
4	15 Å	LOP_15_2	-10.116
5	15 Å	LOP_15_3	-9.629
6	18 Å	LOP_18_2	-9.490
7	20 Å	LOP_20_2	-9.348
8	15 Å	LOP_15_4	-9.266
9	18 Å	LOP_18_3	-9.192
10	18 Å	LOP_18_4	-9.032
11	20 Å	LOP_20_3	-8.536
12	20 Å	LOP_20_4	-8.461

Table 2: Ranked docking conformations reported in the original project.

7 Limitations

This was a high-school computational project rather than a validated drug-discovery study. Docking scores are sensitive to receptor preparation, grid definition, protonation choices, force-field settings, and software assumptions. The work did not include molecular dynamics, free-energy calculations, experimental validation, or comparison with a broader ligand library. Therefore, the result should be read as early computational modelling practice and not as a clinical or pharmacological conclusion.

8 What I Learned

The project introduced me to scientific literature review, receptor and ligand preparation, professional molecular-modelling software, docking-score interpretation, and the importance of explaining computational results through both numbers and molecular interactions. It also made visible the difference between running software and validating a scientific claim.

9 Future Work

Natural extensions would include comparing lopinavir with other HIV protease inhibitors, repeating the workflow with consistent receptor-preparation protocols, adding molecular-dynamics simulation, comparing known crystal structures, and documenting the exact input files and software parameters in a reproducible repository.