Docking of the pyrimidin-5-amine to SARS–CoV–2 Main protease

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Introduction

Molecular docking is a computational technique used to predict the preferred orientation (pose) and binding affinity of a small molecule (ligand) within the binding site of a target macromolecule, typically a protein. By combining search algorithms that explore ligand conformational space with scoring functions that estimate the free energy of binding (ΔG), docking enables the rapid *in silico* screening of a lot of compounds for drug discovery.

In this study, we employ SwissDock[1], a web-based docking service powered by the EADock DSS engine and implementing the "Attracting Cavities" method. SwissDock automates the entire calculation from ligand and protein preparation, to job submission on cloud resources and results in formats compatible with PyMOL, Chimera, and other molecular viewers.

In this work, the target is the main protease (M^{pro}) of SARS–CoV–2, a cysteine protease essential for the proteolytic processing of viral polyproteins and therefore an antiviral drug target. As ligand I selected the non-covalent inhibitor pyrimidin-5-amine (Z1741970824), represented by the SMILES string `NC1=NC=NC=C1`. The structure of SARS–CoV–2 M^{pro} with Z1741970824 is deposited in the Protein Data Bank under PDB ID 5RF3[2].

Results

Table 1 and Figure 1 summarize the AC and SwissParam scores for the ten clusters generated by SwissDock. Cluster 0 exhibits the most favorable mean binding energies, guiding our focus towards its internal poses.

Table 1: Summary of scores for each cluster.

Cluster number	AC Score	SwissParam Score
0	-58.80	-5.93
1	-57.96	-5.89
2	-57.50	-5.83
3	-57.28	-5.70
4	-55.61	-5.70
5	-55.39	-5.55
6	-55.15	-5.65
7	-55.14	-5.47
8	-55.09	-5.51
9	-55.04	-5.45

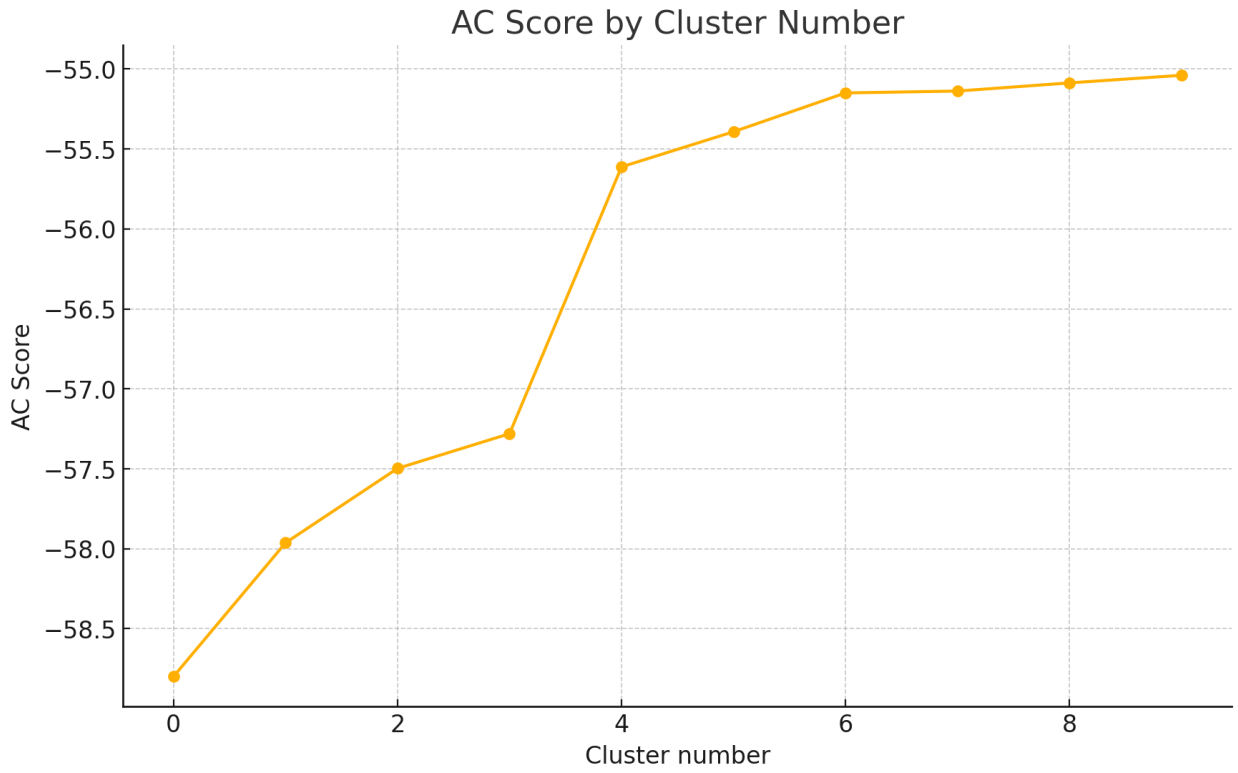

Figure 1: AC scores across all clusters.

Table 2 and Figure 2 detail the score distribution within cluster 0, highlighting its internal variability and identifying the top-scoring member.

Table 2: Scores for members of cluster 0.

Member	AC Score	SwissParam Score
1	-58.80	-5.93
2	-58.79	-5.94
3	-56.94	-5.83
4	-56.21	-5.77
5	-55.31	-5.73
6	-54.49	-5.66
7	-54.47	-5.66
8	-53.69	-5.57

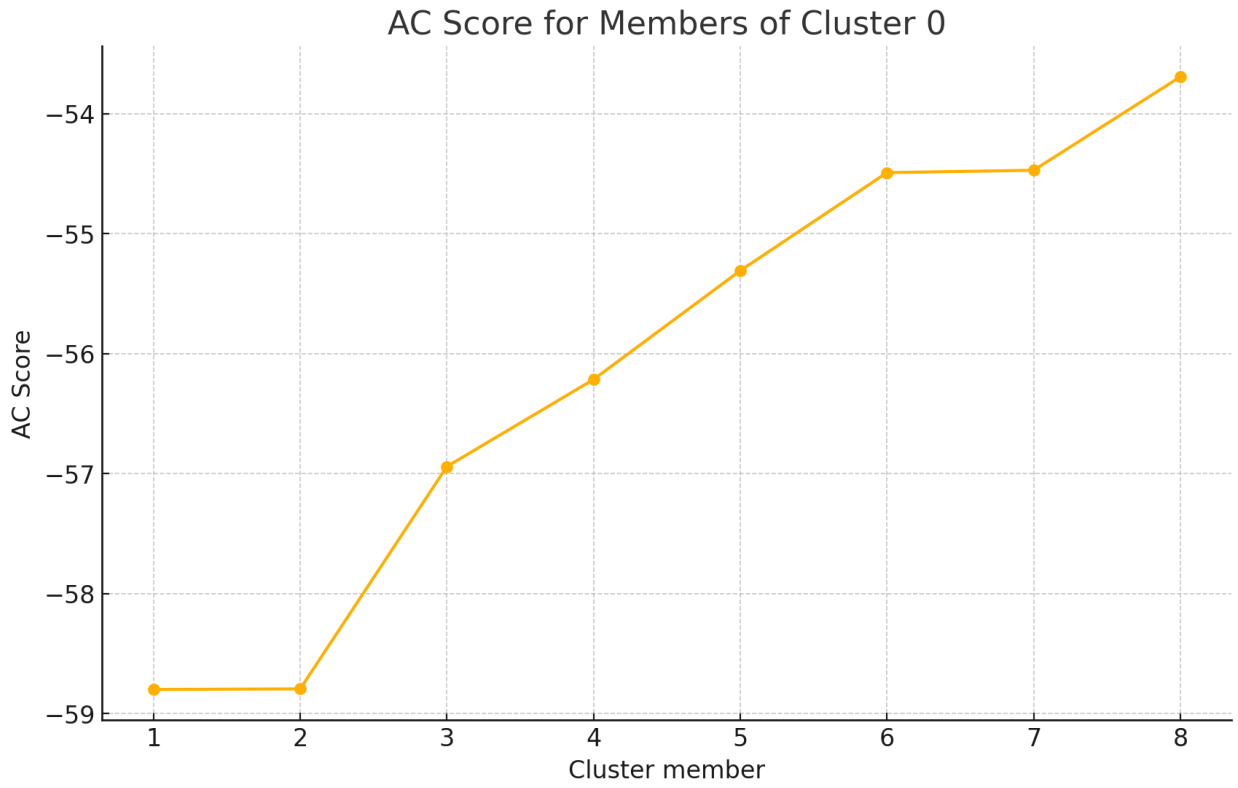

Figure 2: AC scores for each member of cluster 0.

The *AC Score* (Attracting Cavities Score) is the internal scoring function used by SwissDock program. It combines geometric fit and empirical energy terms to approximate the binding free energy of each pose: more negative values indicate more favorable protein–ligand interactions. Based on the AC Score ranking, the optimal docking pose corresponds to **member 1 of cluster 0**, as it exhibits the lowest AC Score among all sampled conformations.

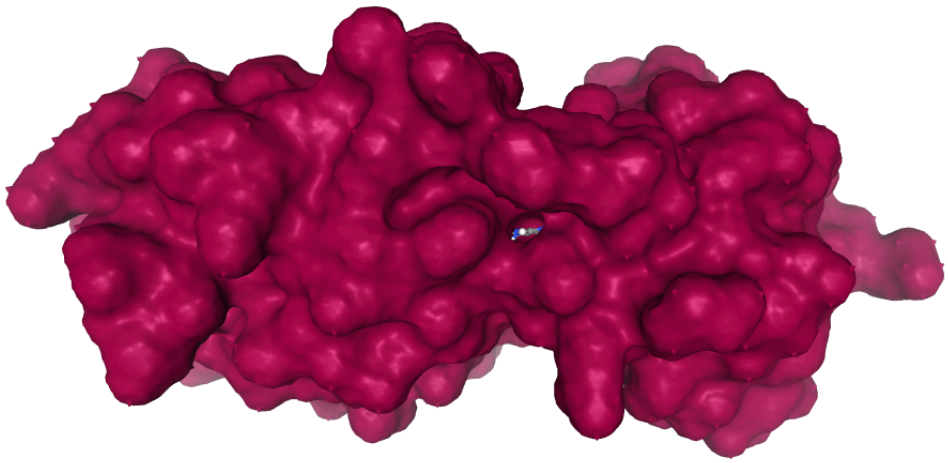

Figure 3: Best docking pose (member 1 of cluster 0) of Z1741970824 shown within the molecular surface of SARS–CoV–2 M^{pro} binding cavity.

The Figure 3 shows the best docking pose of the ligand (member 1 of cluster 0) inside the M^{pro} binding cavity.

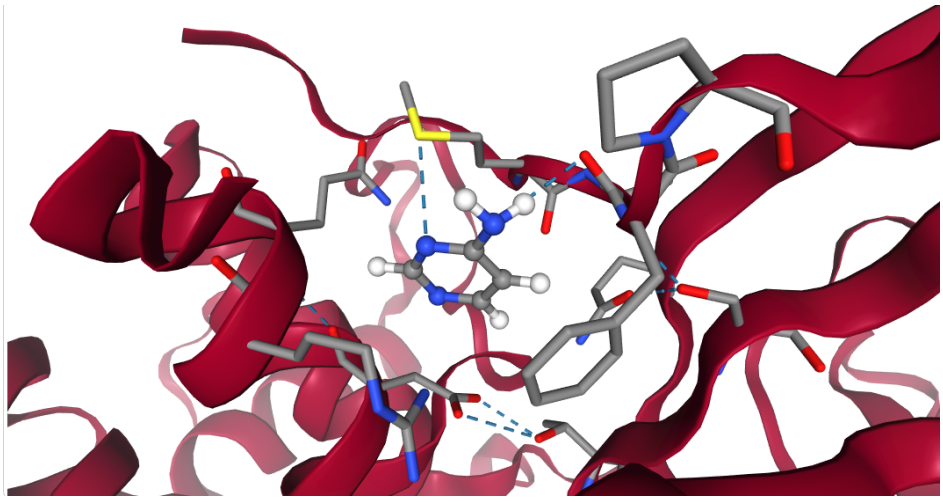

Figure 4: Hydrogen-bond interactions (blue dashed lines) between Z1741970824 and SARS–CoV–2 M^{pro}, showing H-bonds to the sulfur atom of Met6 and the backbone carbonyl oxygen of Ala7.

As shown in Figure 4, the pyrimidin-5-amine establishes two key hydrogen bonds within the M^{pro} active site: one between the ligand and the sulfur atom of Met6, and a second between the ligand and the backbone carbonyl oxygen of Ala7, contributing to the stabilization of the binding pose.

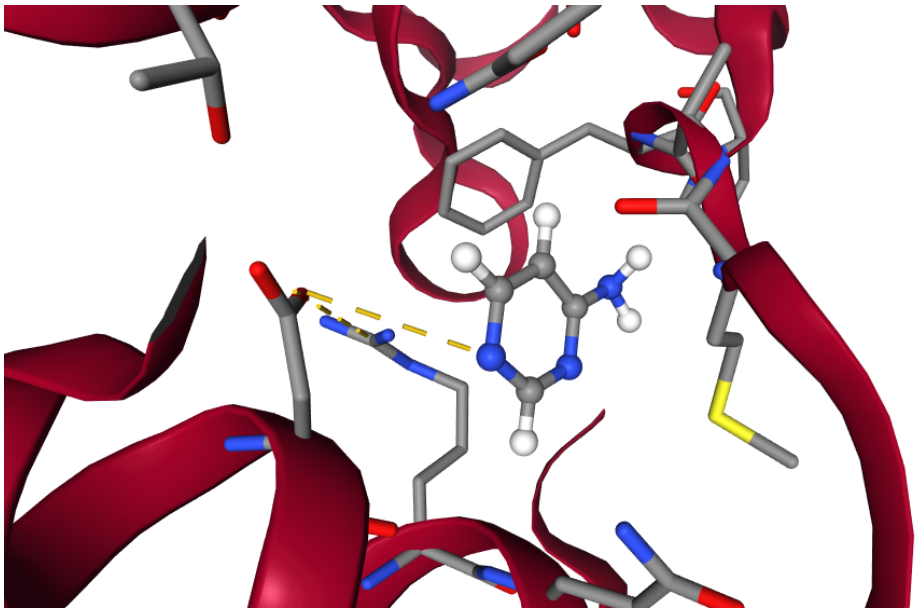

Figure 5: Ionic interaction (yellow dashed line) between the protonated amine and the carboxylate side chain of Asp295 in SARS–CoV–2 M^{pro}.

As shown in Figure 5, he pyrimidin-5-amine establishes an ionic interaction with the side chain of Asp295, further stabilizing the binding pose.

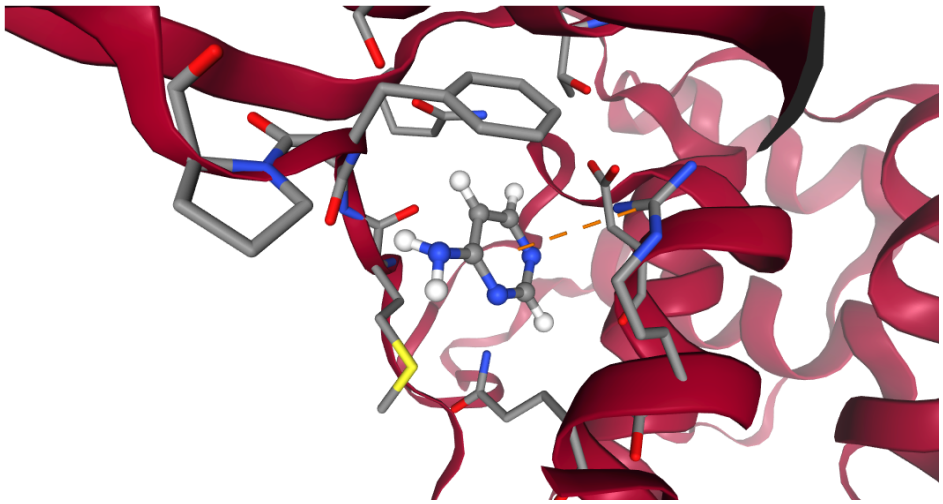

Figure 6: Cation–π interaction (orange dashed line) between the aromatic pyrimidine ring of the ligand and the Arg298 in SARS–CoV–2 M^{pro}.

As illustrated in Figure 6, the ligand forms a cation–π interaction with its aromatic ring and the positively charged group of Arg298.

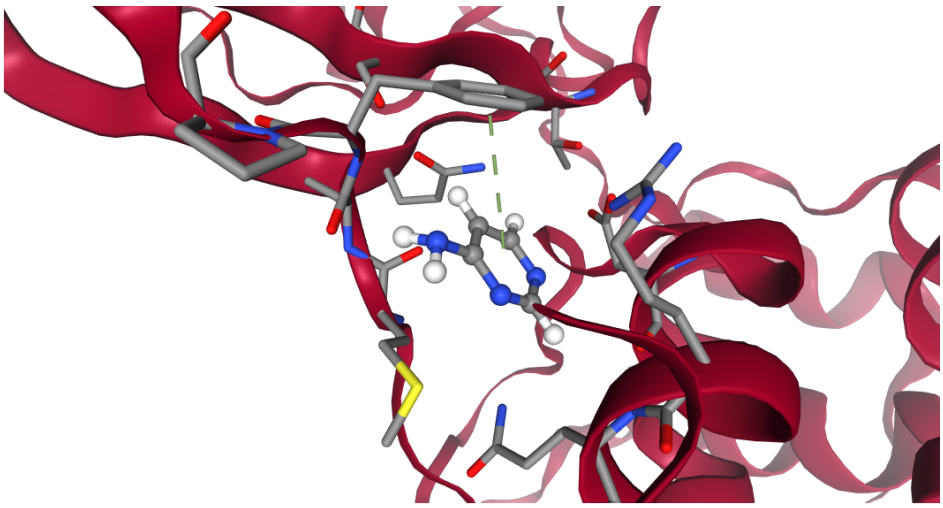

Figure 7: π–π stacking interaction (light green dashed line) between the aromatic pyrimidine ring of the ligand and the phenyl side chain of Phe8 in SARS–CoV–2 M^{pro}.

As illustrated in Figure 7, the pyrimidin-5-amine has a π–π stacking interaction with the phenyl ring of Phe8.

No hydrophobic contacts were observed between the ligand and the SARS–CoV–2 M^{pro} binding pocket under the defined docking conditions.

Conclusions

In this work, we used SwissDock to predict the binding mode of the inhibitor Z1741970824 in the SARS–CoV–2 main protease. Through cluster analysis, we identified the optimal pose (member 1 of cluster 0) based on the lowest AC Score, indicating a favorable energetic fit in the active site.

The selected pose forms two hydrogen bonds with Met6 and Ala7, an ionic interaction with Asp295, and both cation–π and π–π contacts with Arg298 and Phe8, respectively. No hydrophobic contacts were observed.

References

[1] Grosdidier A., Zoete V., Michielin O. SwissDock, a protein–ligand docking web service based on EADock DSS. *Nucleic Acids Research* **39**, W270–W277 (2011).

[2] Berman H. M., Westbrook J., Feng Z., et al. The Protein Data Bank. *Nucleic Acids Research* **28**, 235–242 (2000).