# Massive Virtual screening and evaluation of small molecule inhibitors of the Papain-like protease of SARS-CoV-2

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## Abstract

In the face of the rapid emergence and spread of new variants of the type 2 coronavirus causing acute respiratory syndrome, it is necessary to seek new pharmacological treatments for the disease, especially for patients infected by the new and more aggressive variants of the virus. In the present work, we selected ˜18,000 compounds with similar structure to GRL0617 (Tanimoto index greater than 80 %) from the PubChem database with ˜109 million compounds. Molecular docking was used to assess the affinity of the selected compounds, in which GRL0617 was included as an internal control. Then, based on the ligand efficacy index obtained as molecular docking, 500 compounds with higher affinity than GRL0617 for papain-like protease were considered. Finally, based on ADME parameters within the acceptable range for a drug, the seven best compounds were selected. Next, 200 ns molecular dynamics simulation studies, [?]G calculations using generalized Born and surface continuous solvation molecular dynamics, and quantum mechanical calculations were performed with the selected candidates. Using this In Silico protocol, seven papain-like protease inhibitors are proposed: three compounds with binding free energy like GRL0617 (D28, D04 and D59), three compounds with higher binding free energy than GRL0617 (D60, D99 and D06) and one compound (D24) that binds to a region of the enzyme that could block inhibition by the host immune system. The compounds proposed in this study could be used for invitro testing or smart drug design, accelerating the development of an effective treatment for this disease.

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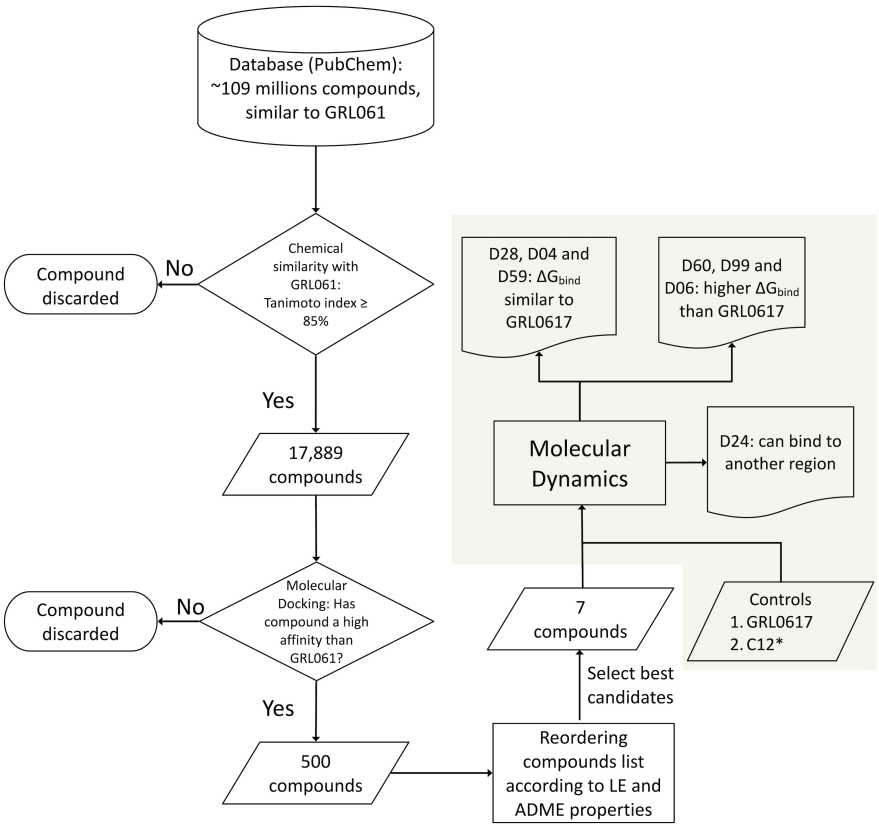

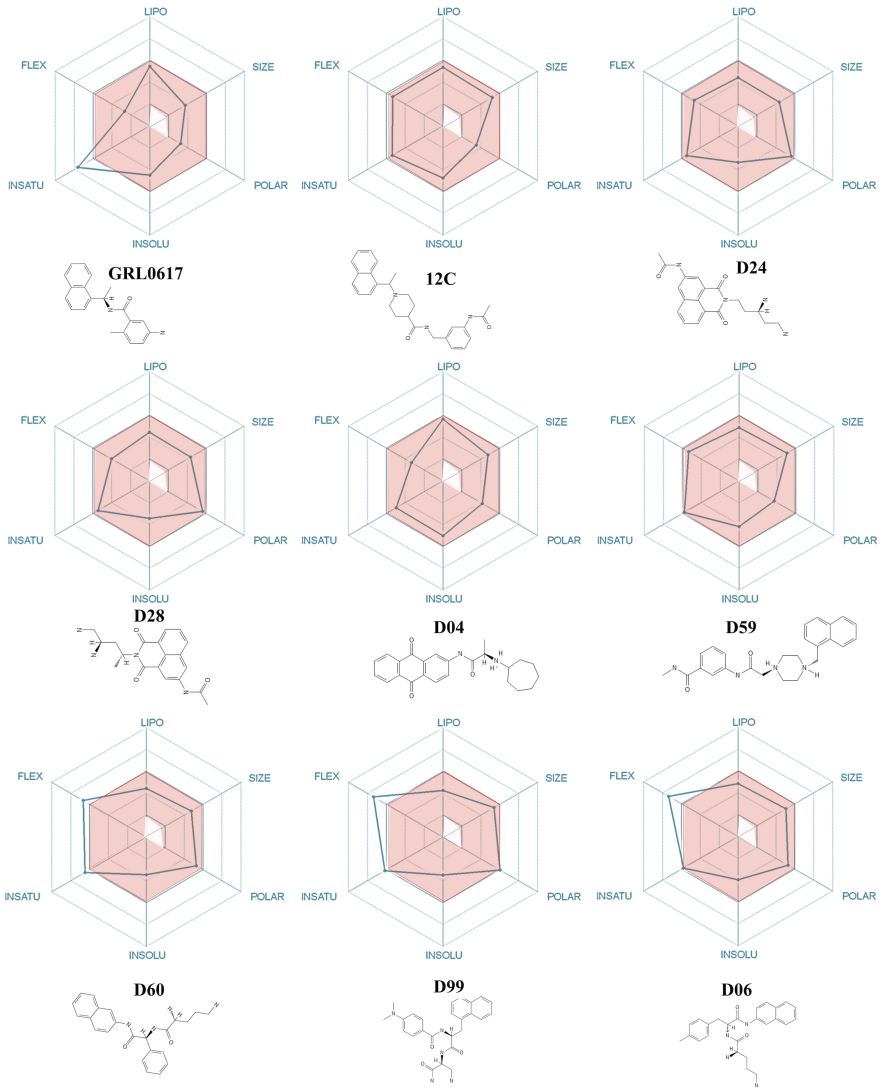

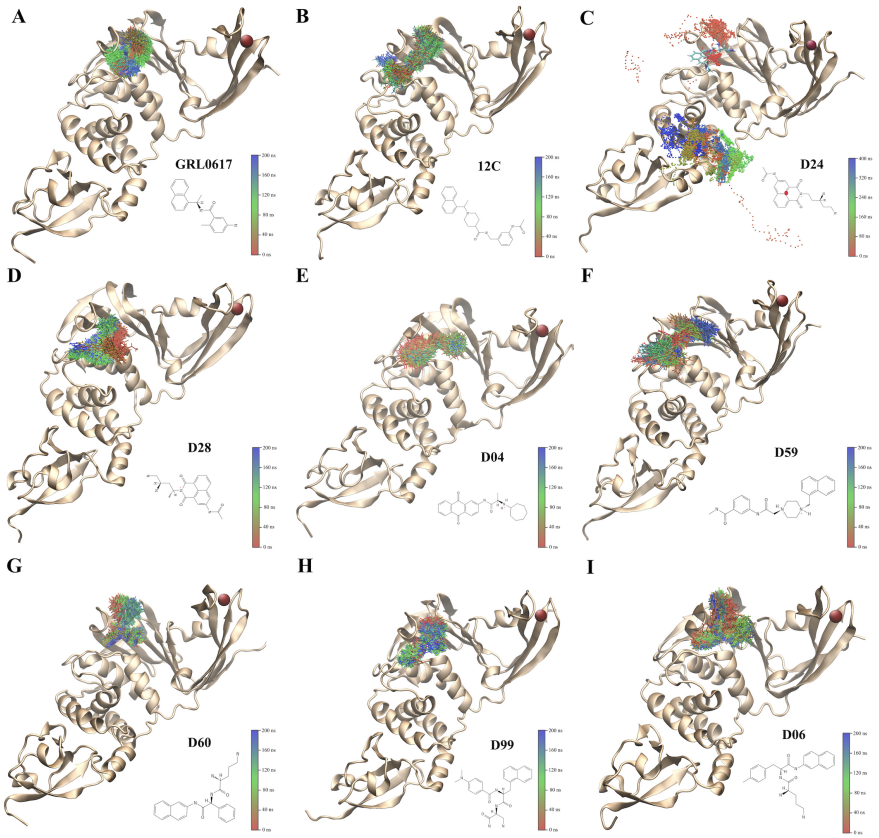


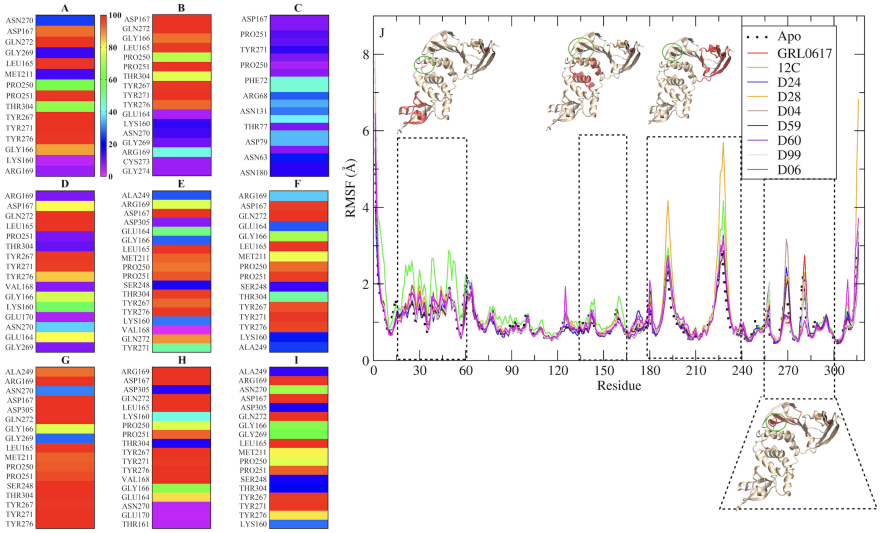

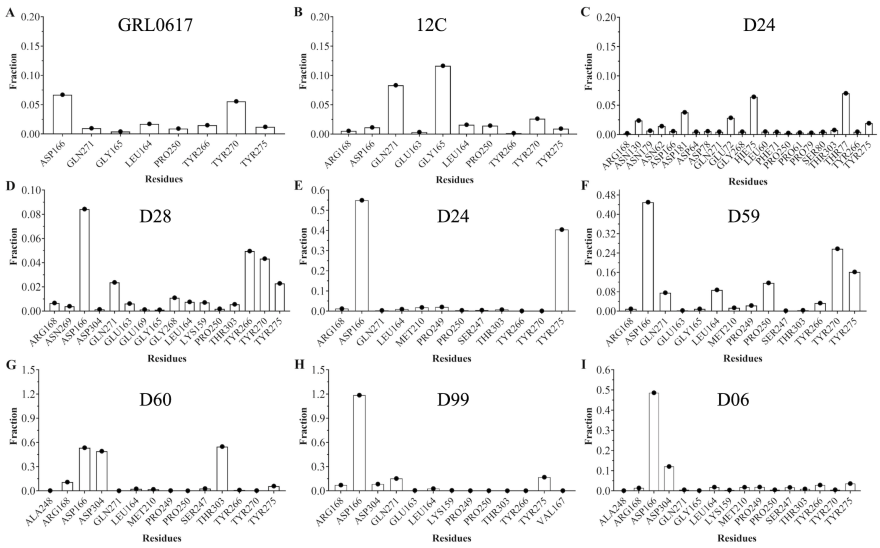

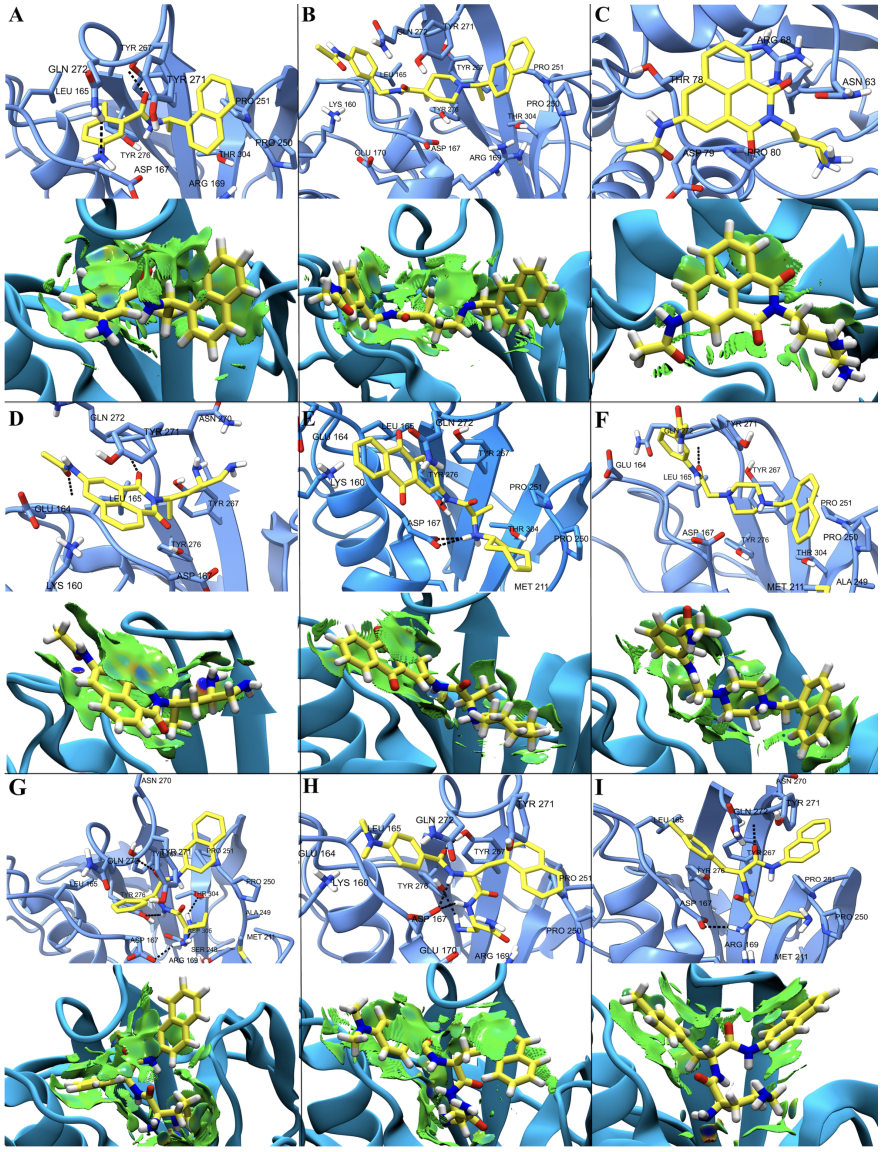

| *IC50 (μM) | | |
|---|---|---|
| | Ub | 2.67 +/- 0.35 |
| | Prot | 6.97 +/- 1.34 |

| | |
|---|---|
| Ub | 2.00 +/- 0.29 |
| Prot | 6.69 +/- 1.34 |