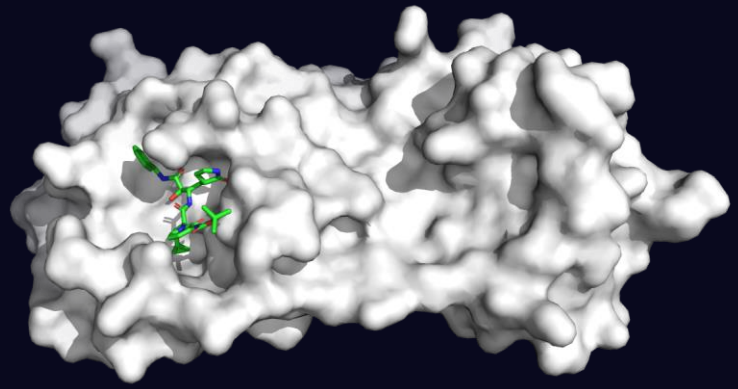
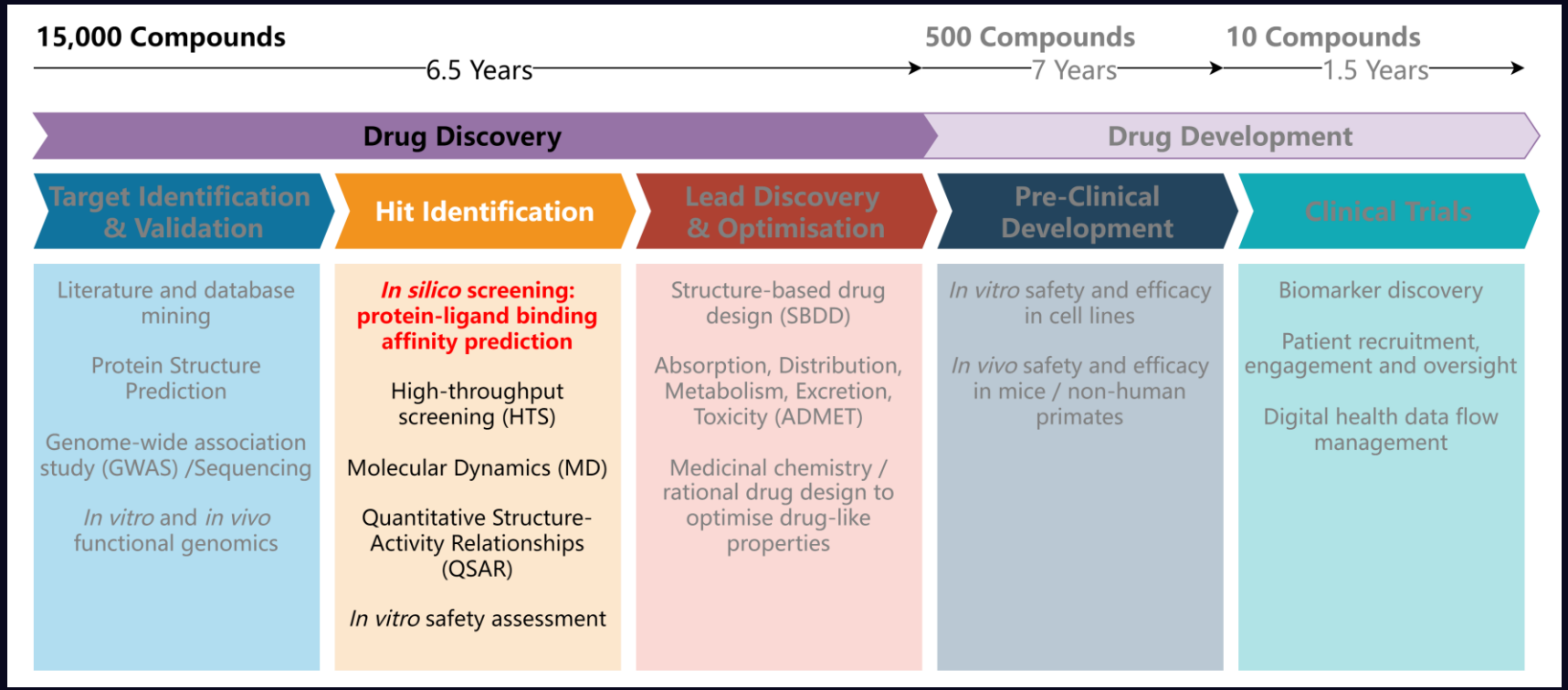
COMPARATIVE ASSESSMENT OF DOCKING SOFTWARE FOR VIRTUAL SCREENING OF COVID-19 DRUG CANDIDATES



SARS-CoV-2 Main Protease & Inhibitor

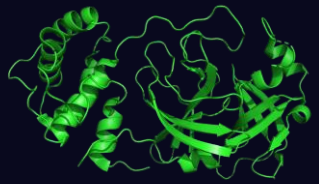
Xi Yang (Ian)

Background: Early Drug Discovery

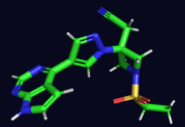


SARS-CoV-2 Main Protease: Focusing on 1 active site

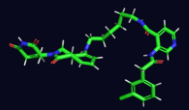
- **Drug target:** SARS-CoV-2 main protease (Mpro)
- **Compound library:** Natural products, known inhibitors, clinically-approved drugs for other diseases (23 in total, very different scaffold)



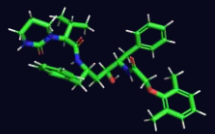
SARS-CoV-2 Main Protease



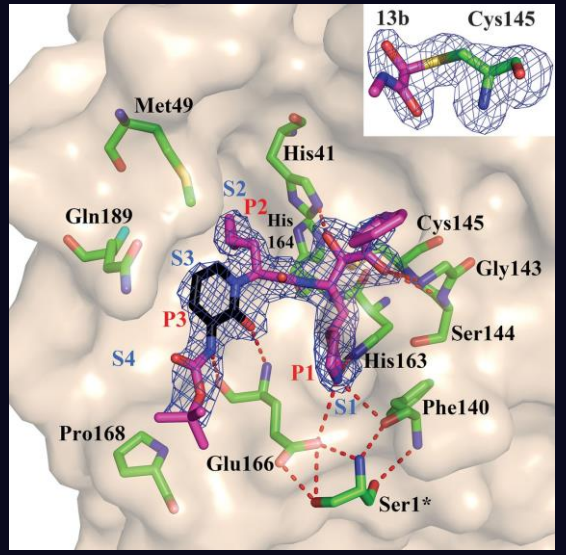
Baricitinib (Natural Product)



DAR-DIA-9e4459de-1 (Known inhibitor – COVID Moonshot)



Lopinavir (Approved drug for HIV)

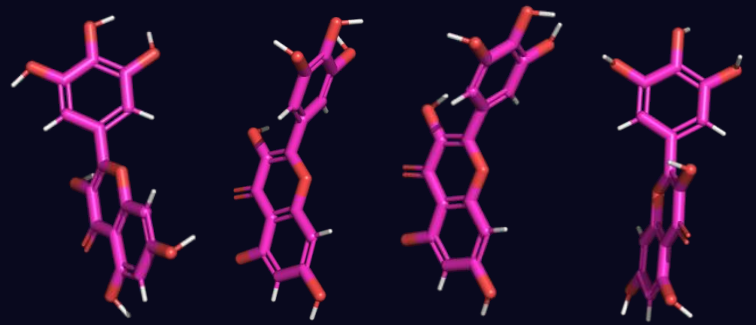


Active site: **Sn** indicate the binding pockets for moieties **Pn** on the ligand (only showing 1 active site, 4 were investigated in this study)

1. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors | Science, https://www.science.org/doi/10.1126/science.abb3405, (accessed 1 May 2024)

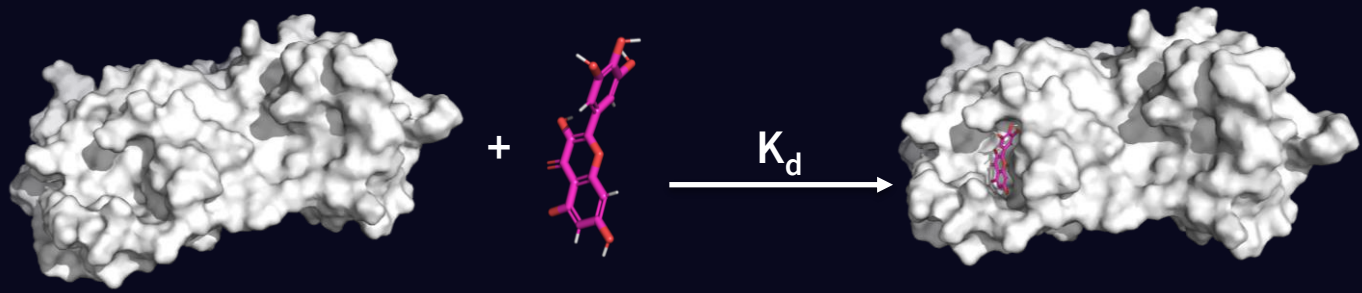
My Project: Binding Affinity Prediction

- **Binding Affinity K_d:** how strong is the protein-ligand interaction?
- **Quick scoring:** molecular docking
  - Protein is assumed **static** in docking
- **Slow scoring:** physics-based computations
- Comparison between 3 docking software:
  - Docking algorithm: suggests ligand poses
  - Scoring function: predicts binding affinity



Different poses of one ligand

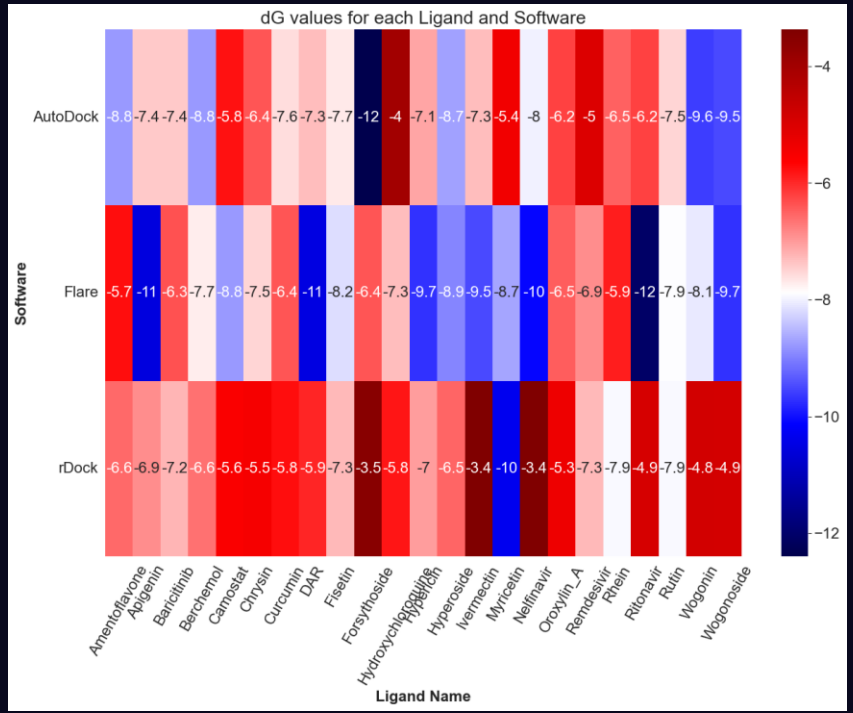
Software	
Autodock Vina	
rDock	
Flare	

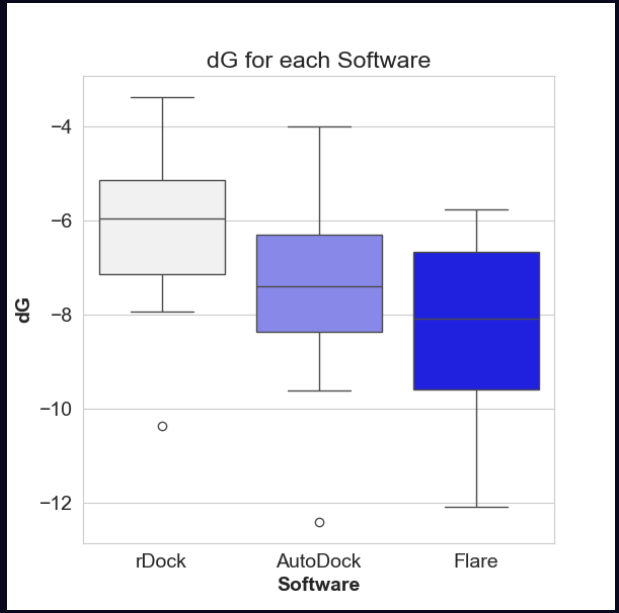


Binding affinity predicted by a scoring function

How do dG results differ from software to software?

- Free Energy of Binding (dG): Lower dG = higher binding affinity K_d
- rDock scores ligands more harshly
- Flare scores ligands more favourably



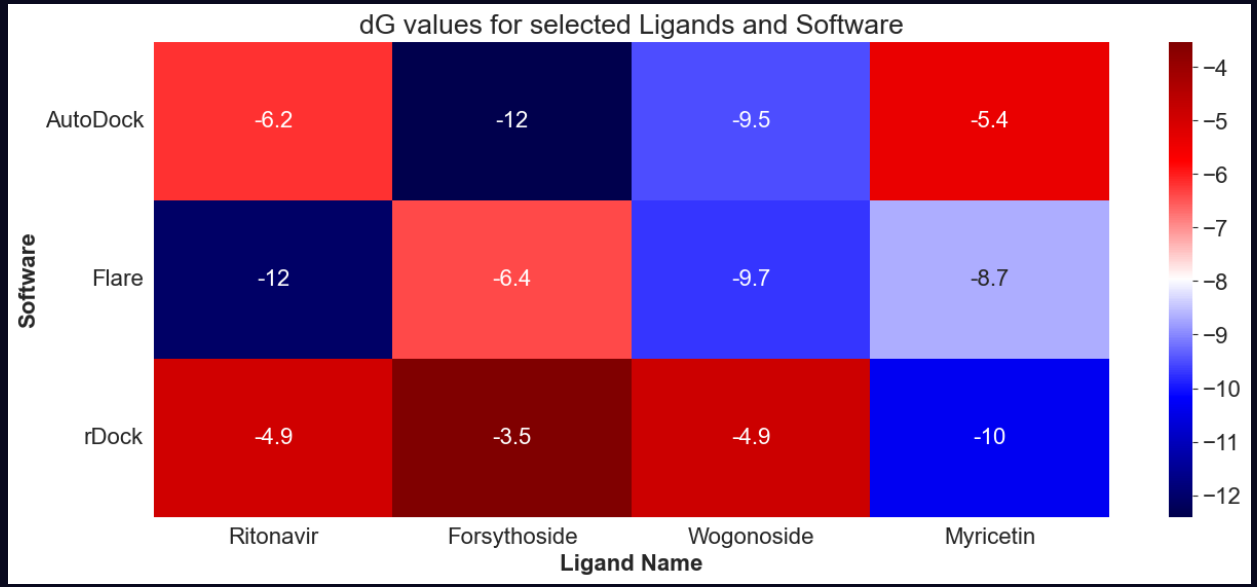


Pair	Independent t-test p-value
AutoDock-Flare	0.12
AutoDock-rDock	***0.012***
Flare-rDock	***0.000091***

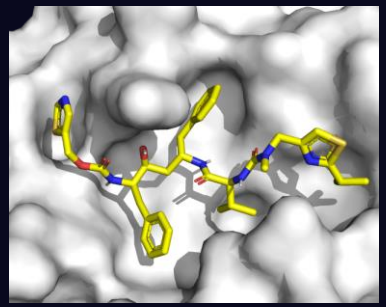
Significantly different predictions

4 ligands (out of 23)

- Free Energy of Binding (dG): Lower dG = higher binding affinity K_d

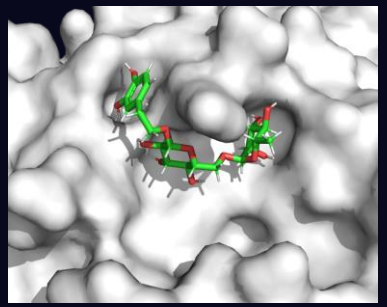


Ligands with lowest predicted dG



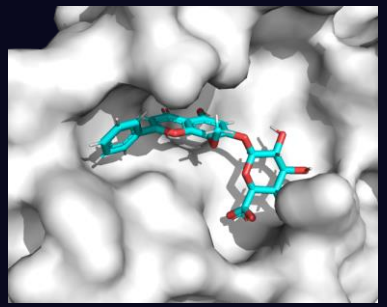
Ritonavir (HIV drug)

dG = - 12 kcal/mol in Flare



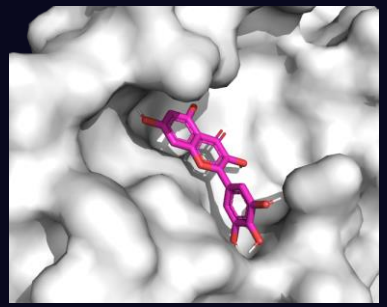
Forsythoside (Natural product)

dG = -12 kcal/mol in AutoDock



Wogonoside(Natural product)

dG ~ -9.7 kcal/mol in Flare



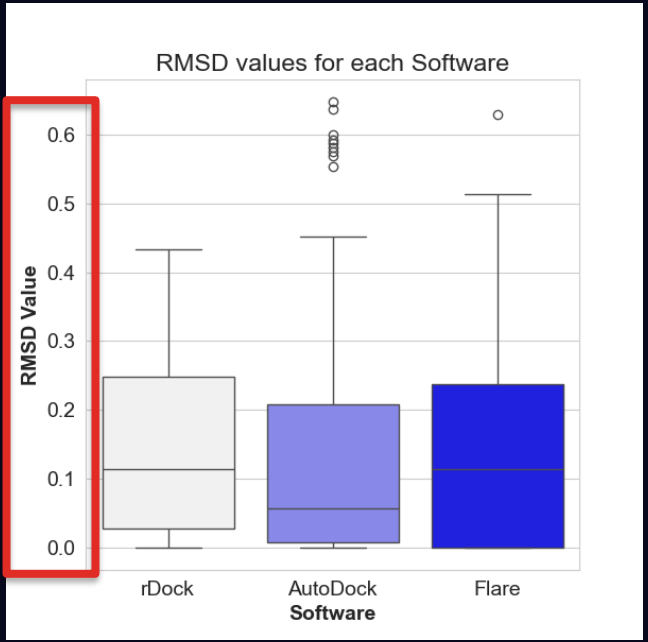
Myricetin (Natural product)

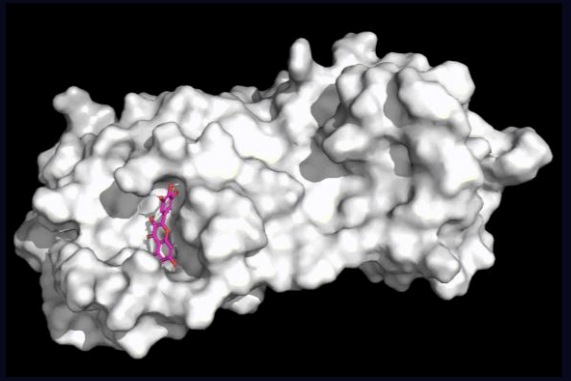
dG ~ -10 in rDock

Increasing dG (worse binding affinity)

Performance of Software

- Each docking algorithm suggests several ligand poses
- **RMSD:** Measures differences in coordinates with the best ligand pose (lowest dG)





Ligand poses of myricetin suggested by Flare

Pair	Mann-Whitney U test p-value
AutoDock-Flare	0.44
AutoDock-rDock	0.10
Flare-rDock	0.47

No significant difference between software performances

Conclusion & Future Work

- Cannot determine which is better (based on RMSD results).

Future work

- Screening against a much **larger compound library** e.g., a few thousand molecules
- **Benchmarking** against existing experimental values
- **Physics-based computations:** Molecular Dynamics (MD) **simulation**
- **Consensus scoring:** consider multiple scoring functions