

Drug Repurposing for COVID-19

Introduction

What is the PyRx and what its importance:

PyRx is a Virtual Screening software for Computational Drug Discovery that can be used to screen libraries of compounds against potential drug targets. PyRx enables Medicinal Chemists to run Virtual Screening from any platform and helps users in every step of this process from data preparation to job submission and analysis of the results. PyRx is written in Python programming language and it can run on nearly any modern computer, from PC (personal computer) to supercomputer.

It's importance:

- 1- Identifying lead compounds: PyRx enables the screening of small-molecule libraries against macromolecular targets to find compounds with desired biological functions.
- 2- Ease of use: PyRx has an intuitive user interface that runs on all major operating systems (Linux, Windows, and Mac OS), making it accessible and user-friendly for researchers.
- 3- Integrating docking wizards: PyRx integrates AutoDock 4 and AutoDock Vina as docking wizards, providing a powerful platform for molecular docking investigations.
- 4- Visualizing docking results: PyRx can be used in combination with tools like Biovia Discovery Studio Visualizer to visualise and analyse the results of molecular docking simulations.

Steps to Use PyRx:

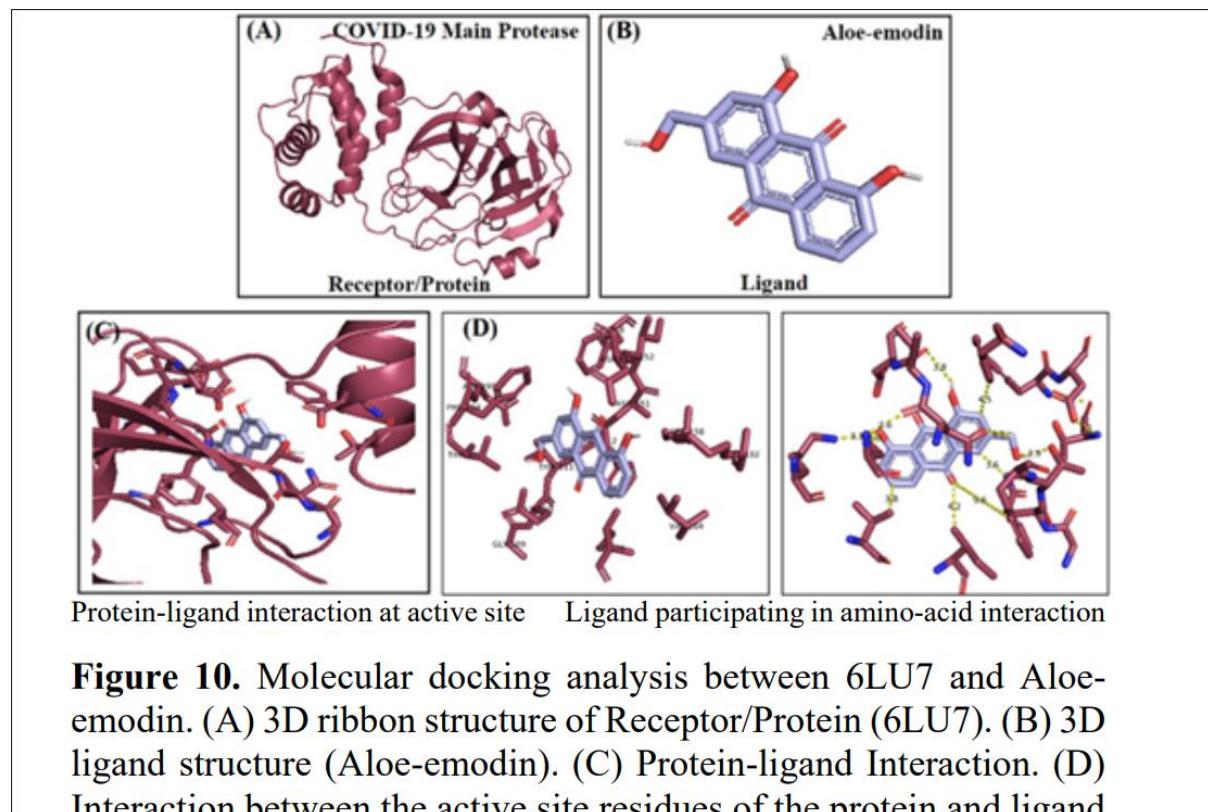
- 1- Load Receptor and Ligands: Open PyRx, load the receptor protein, and the ligand molecules you want to dock.
- 2- Prepare for Docking: Convert the molecular files to the appropriate format if necessary. Define the docking parameters and the grid box around the active site of the receptor.
- 3- Run Docking: Execute the docking simulation. PyRx will use AutoDock Vina to calculate the binding poses and affinities.
- 4- Analyse Results: Review the docking results, visualise the binding conformations, and analyse the interactions to identify potential drug candidates.

In silico identification of potent FDA approved drugs against Coronavirus COVID-19 main protease: 6LU7 Experiment:

- Active Site: The structure includes a detailed view of the active site where the inhibitor N3 is bound. This active site is characterised by a catalytic dyad consisting of a cysteine (Cys145) and histidine (His41) residue.
- Binding Interaction*: The inhibitor N3 forms multiple interactions with the protease, including hydrogen bonds and hydrophobic interactions, stabilising its binding within the active site.
- Understanding the structure of SARS-CoV-2 Mpro and its interaction with inhibitors like N3 is vital for the development of antiviral drugs targeting COVID-19. The high-resolution crystal structure provides detailed insights into the enzyme's active site, guiding the design of more effective inhibitors.

The paper work

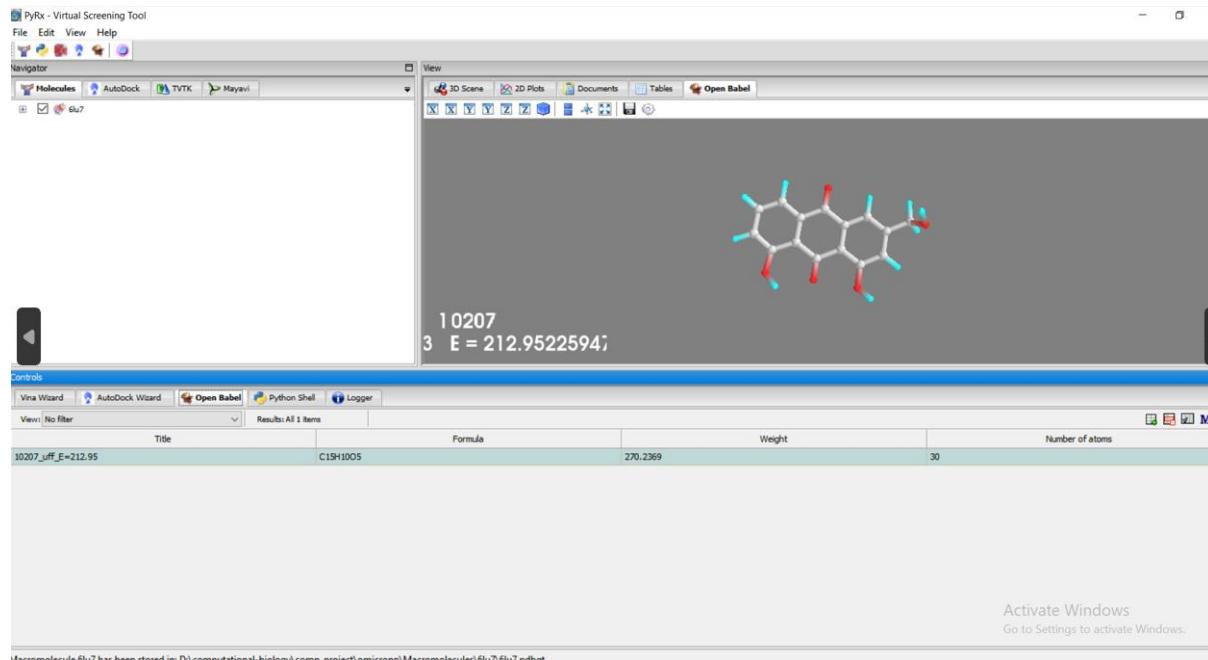
Aloe-emodin Ligand



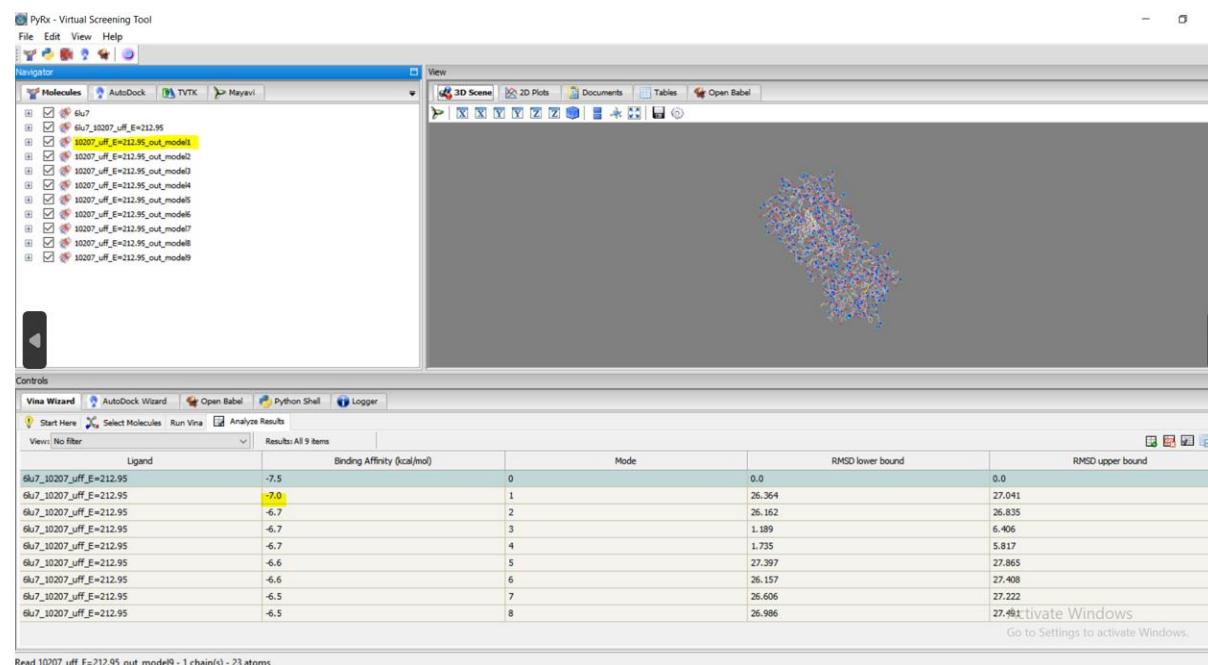
Our work

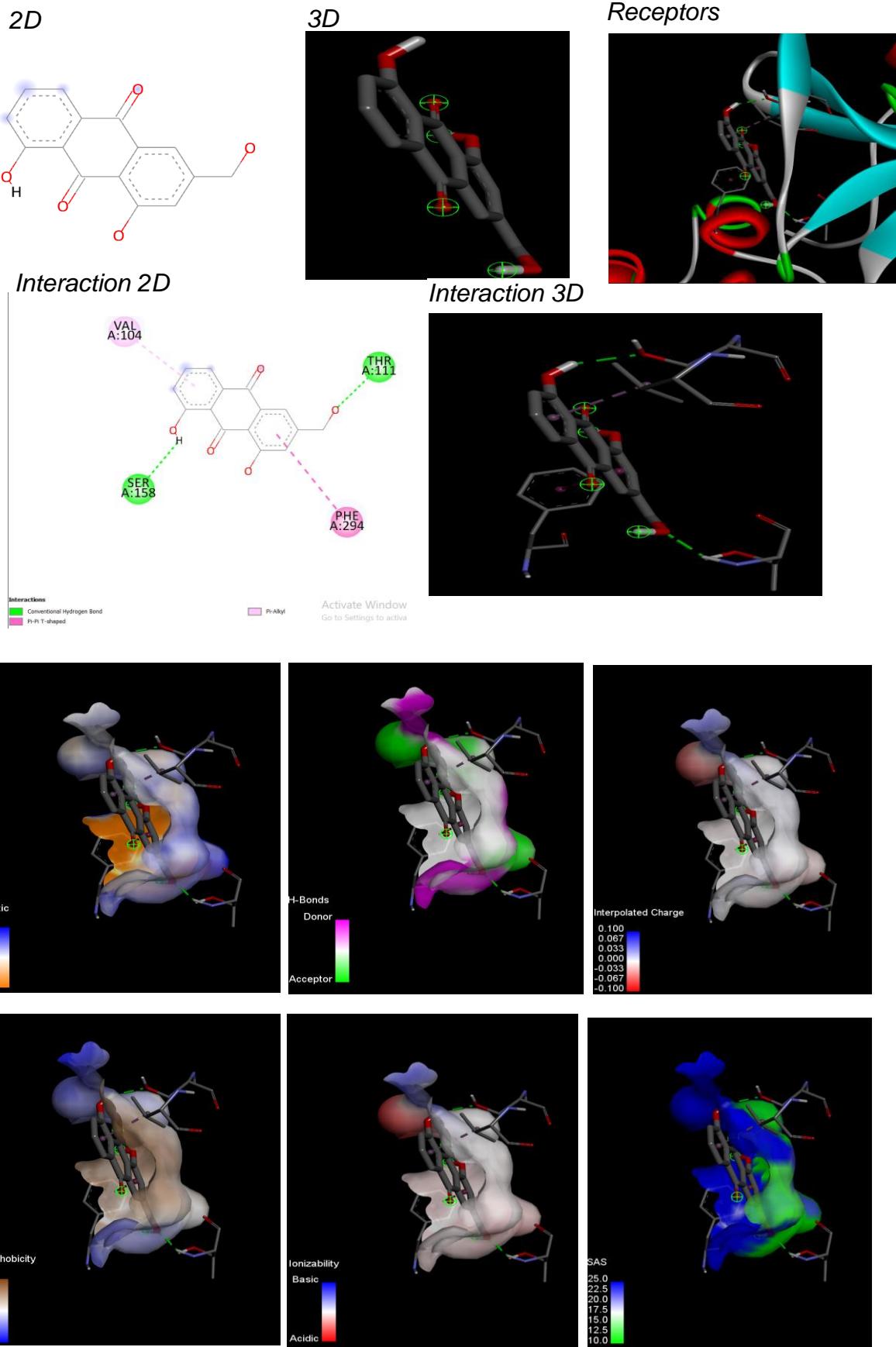
Aloe-emodin Ligand

- Minimise Energy



- Choose Model





Enoxacin ligan Paper Work

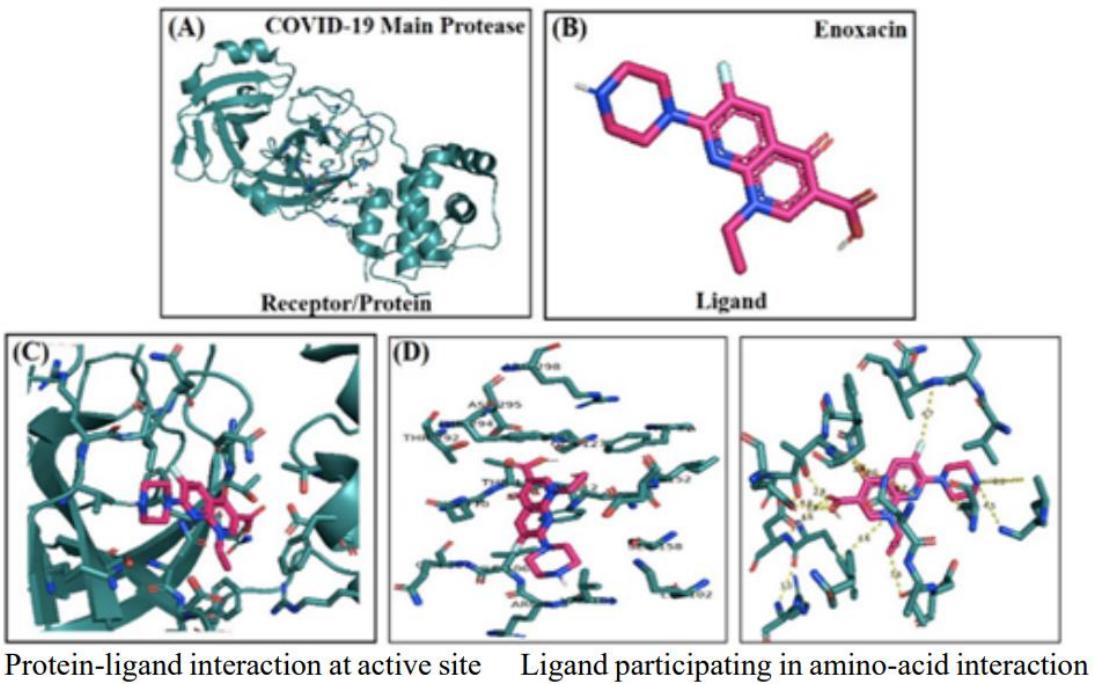
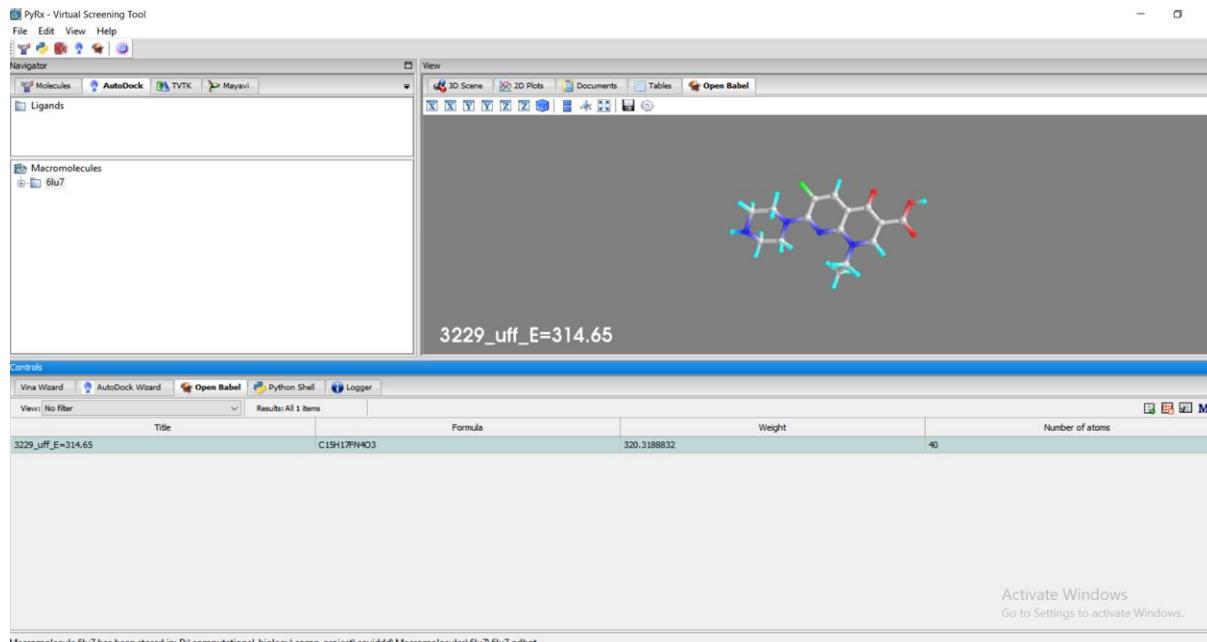


Figure 9: Molecular docking analysis between 6LU7 and Enoxacin. (A) 3D ribbon structure of Receptor/Protein (6LU7). (B) 3D ligand structure (Enoxacin). (C) Protein-ligand Interaction. (D) Interaction between the active site residues of the protein and ligand. [Activate Windows](#)

Our Work

Minimize Energy



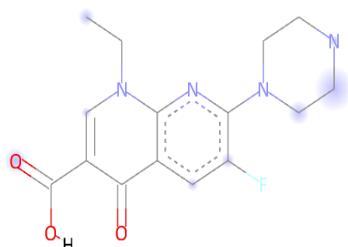
Choose Model

The screenshot shows the PyRx software interface. In the top left, the 'Navigator' panel lists several molecular models, with '3229_uff_E=314.65_out_model9' selected. The main window displays a 3D molecular structure in a grid-based binding site. Below the 3D view is a table of results:

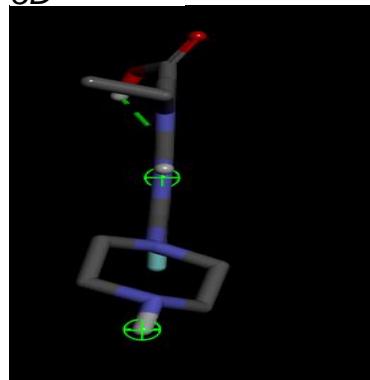
Ligand	Binding Affinity (kcal/mol)	Mode	RMSD lower bound	RMSD upper bound
Gu7_3229_uff_E=314.65	-7.1	0	0.0	0.0
Gu7_3229_uff_E=314.65	-6.9	1	1.881	3.194
Gu7_3229_uff_E=314.65	-6.9	2	3.954	5.686
Gu7_3229_uff_E=314.65	-6.7	3	3.596	7.065
Gu7_3229_uff_E=314.65	-6.5	4	3.787	6.86
Gu7_3229_uff_E=314.65	-6.5	5	3.855	6.888
Gu7_3229_uff_E=314.65	-6.4	6	3.645	5.78
Gu7_3229_uff_E=314.65	-6.4	7	4.14	7.579
Gu7_3229_uff_E=314.65	-6.3	8	3.953	7.346

At the bottom right, a message says 'Activate Windows'.

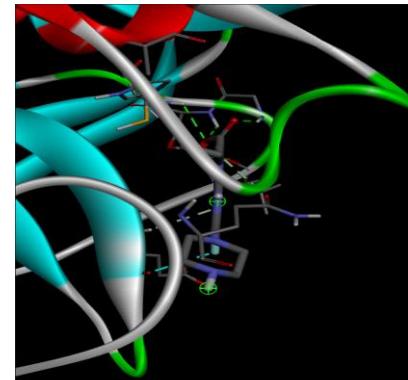
2D



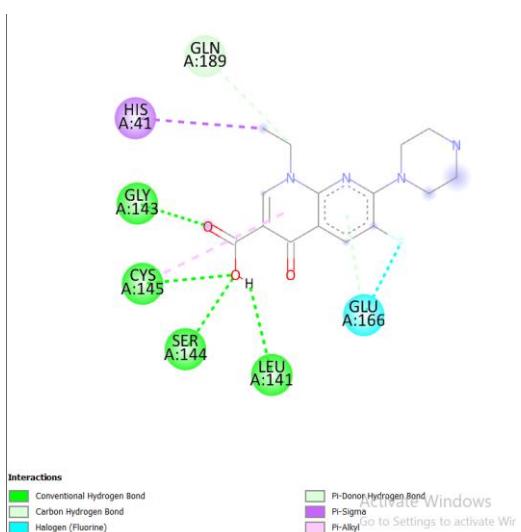
3D



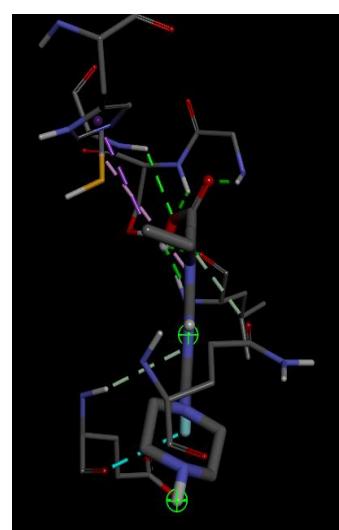
Receptors

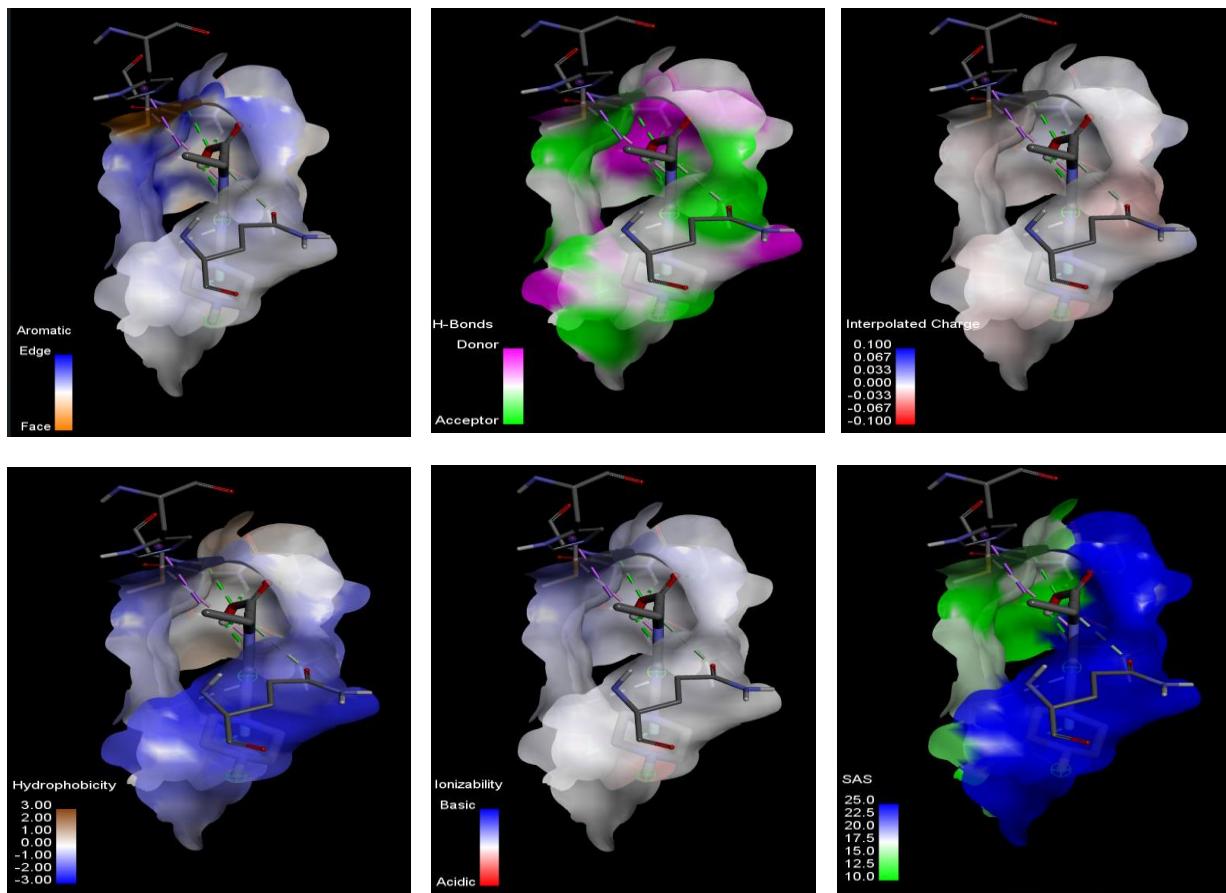


Interaction 2D

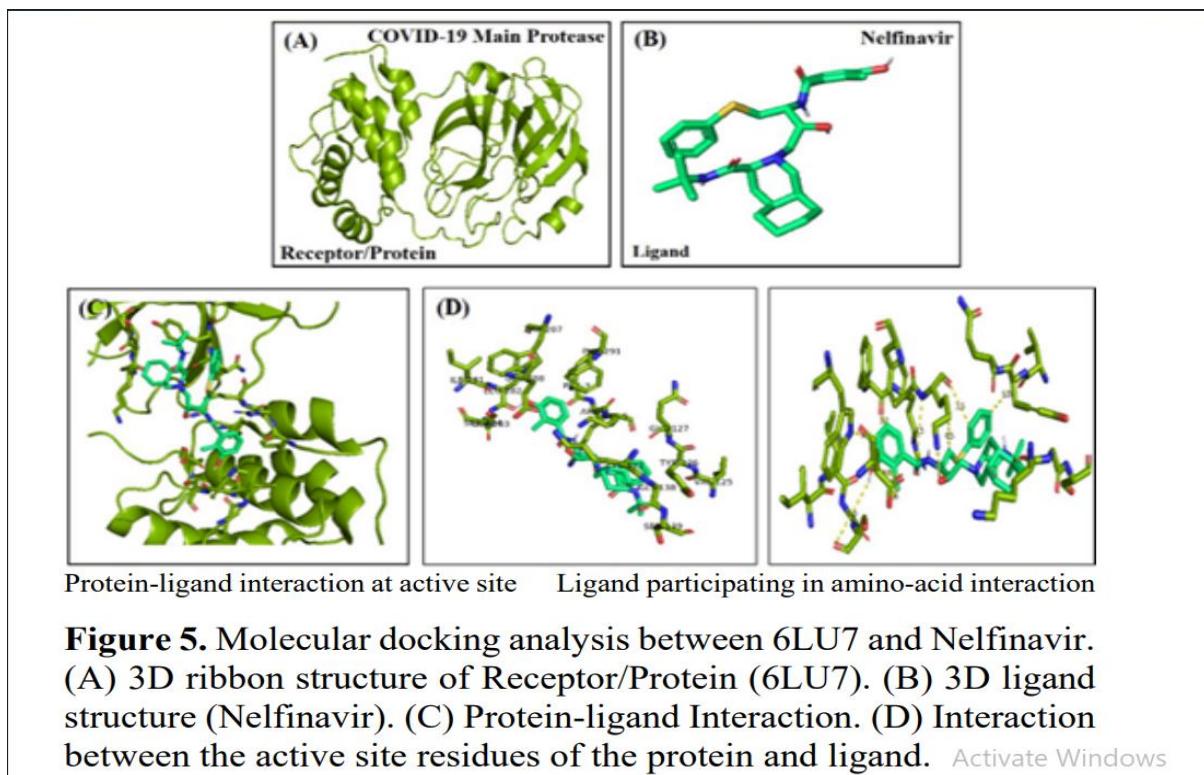


Interaction 3D



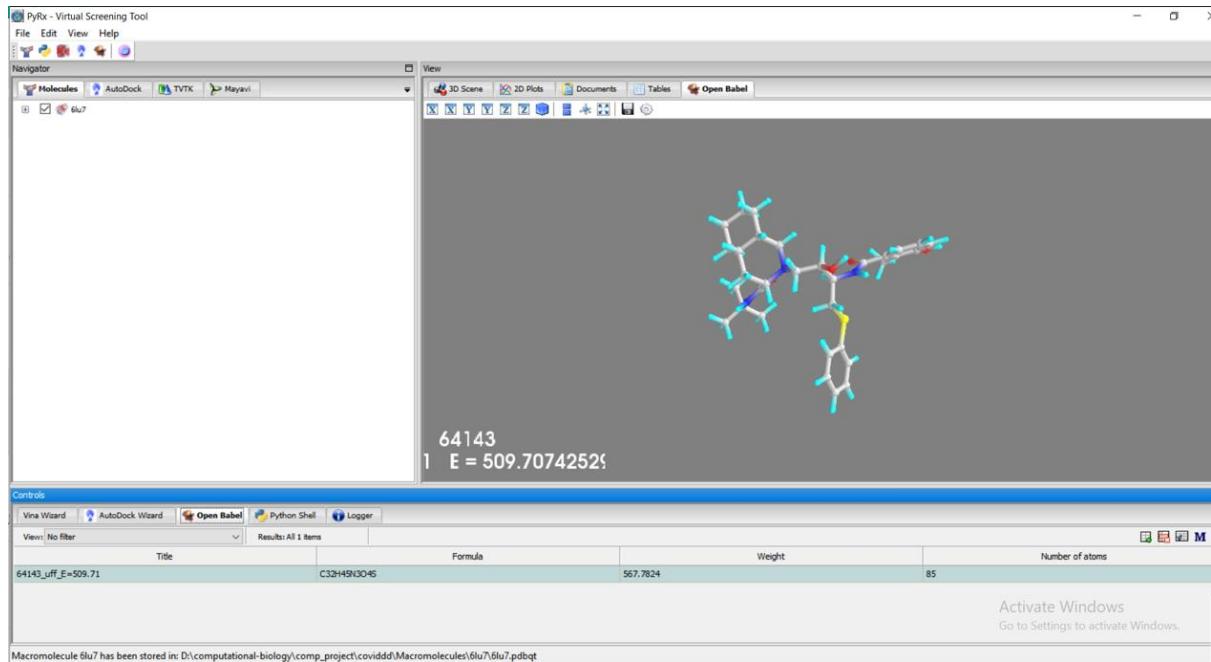


Nelfinavir ligand Paper Work

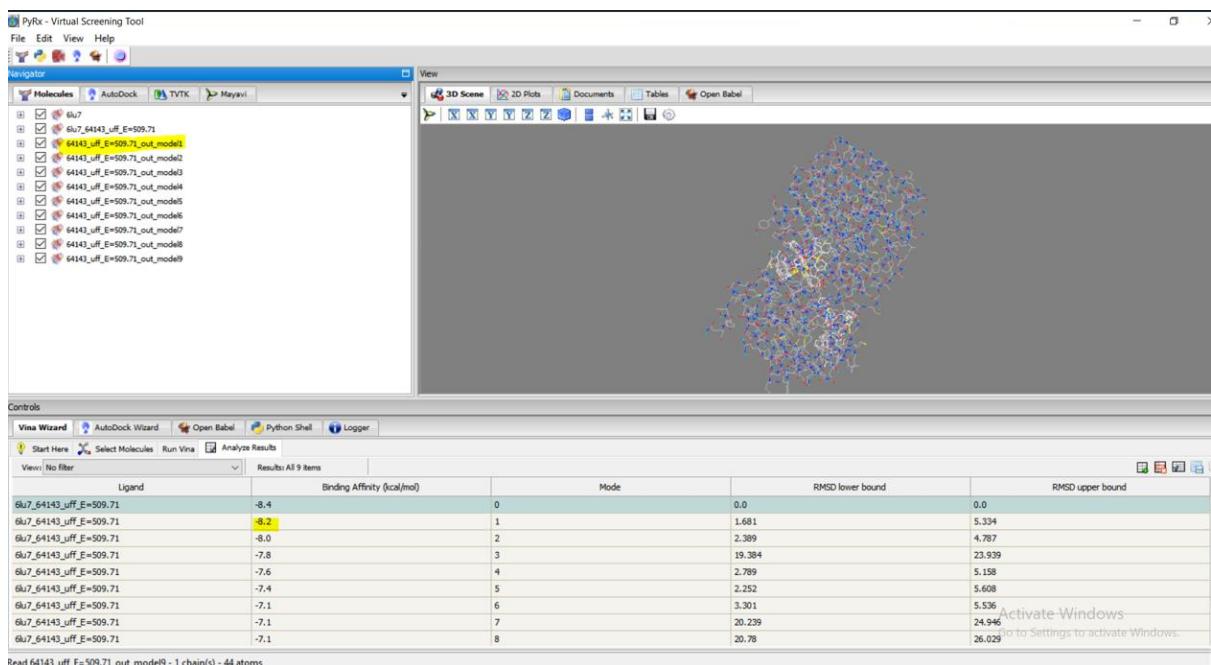


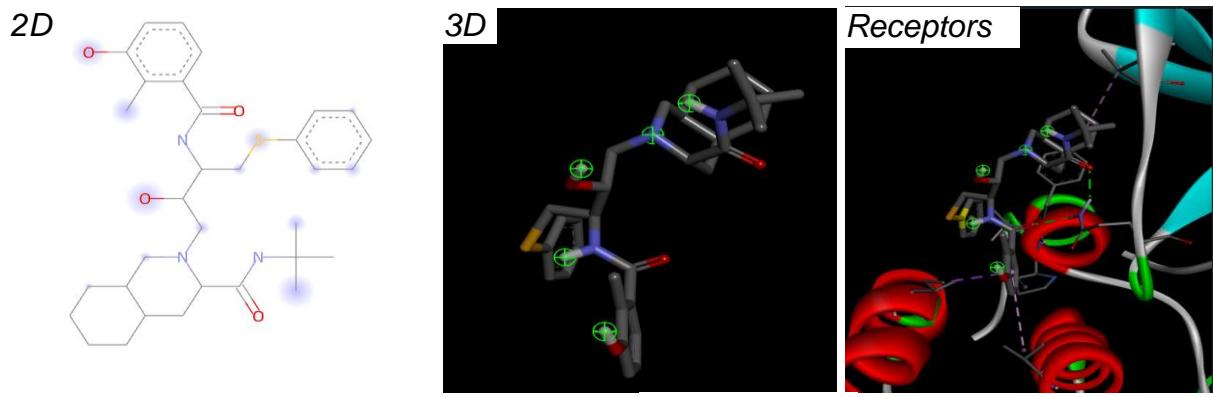
Our Work

Minimize Energy

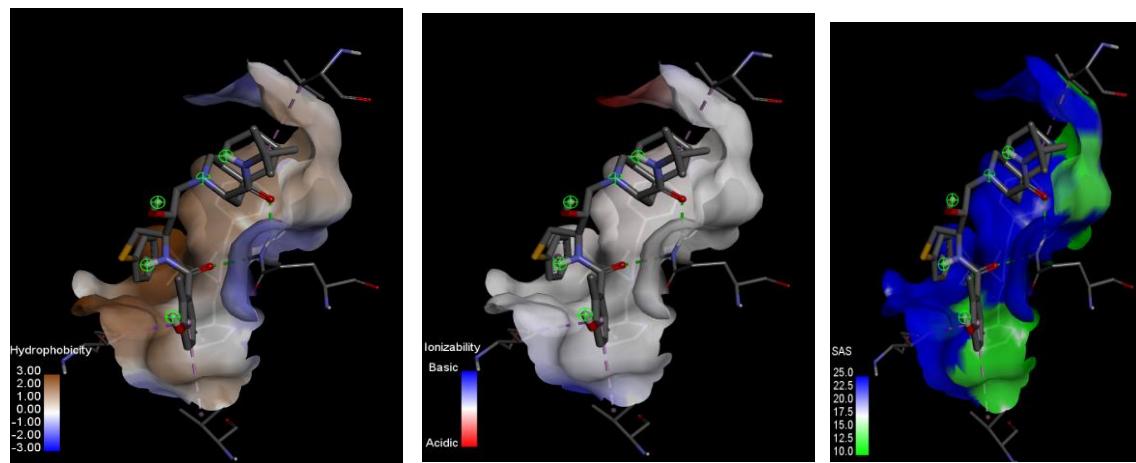
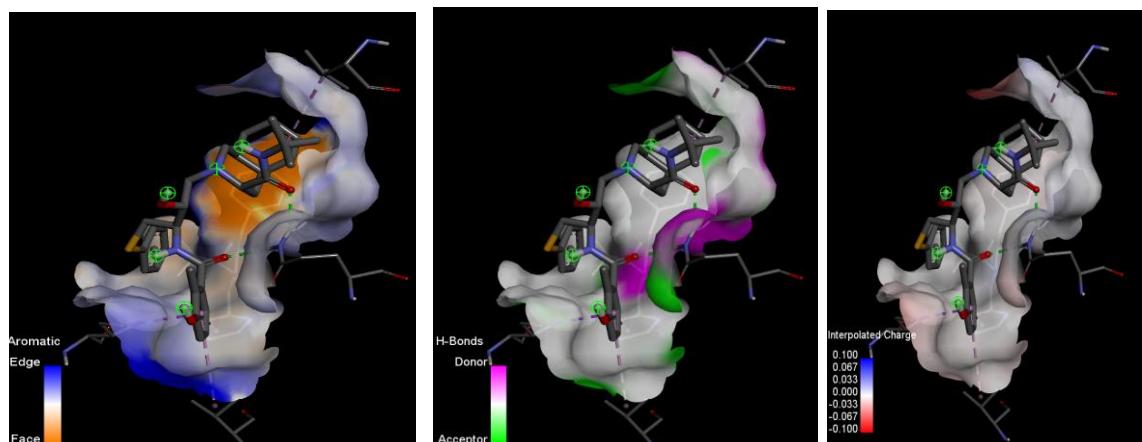
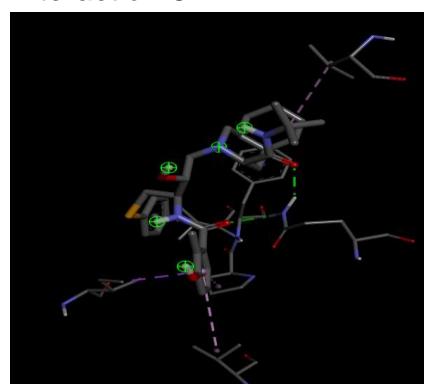
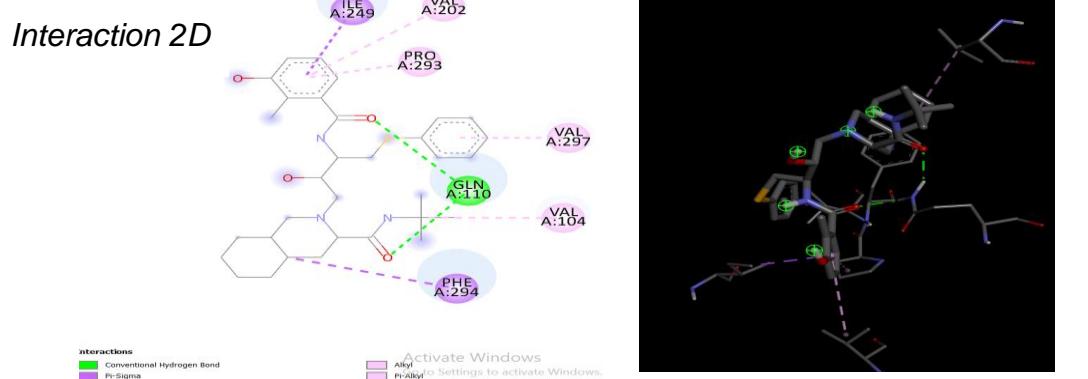


Choose Model





Interaction 3D



Rhein ligand Paper work

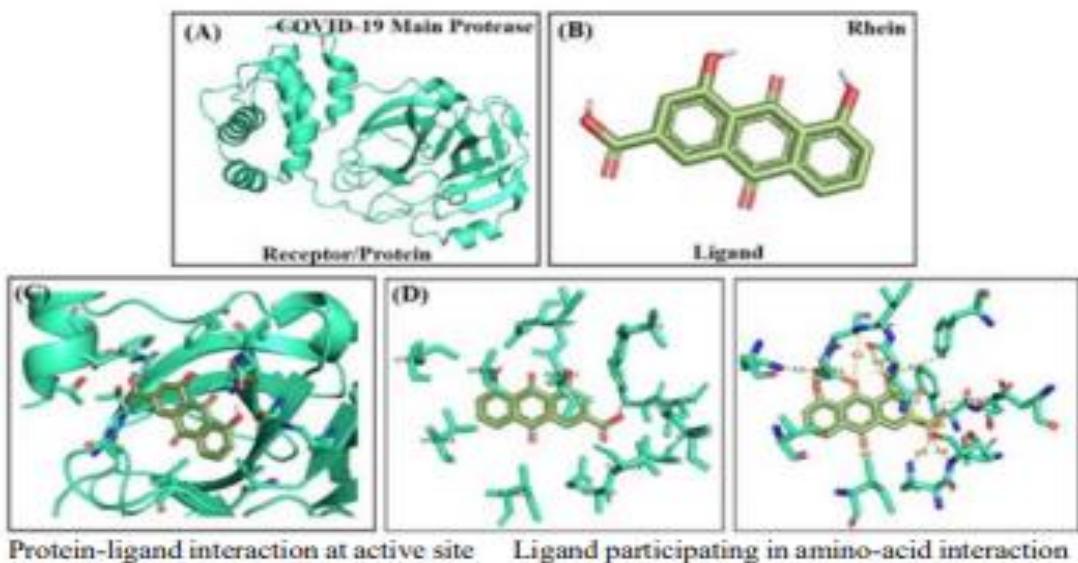
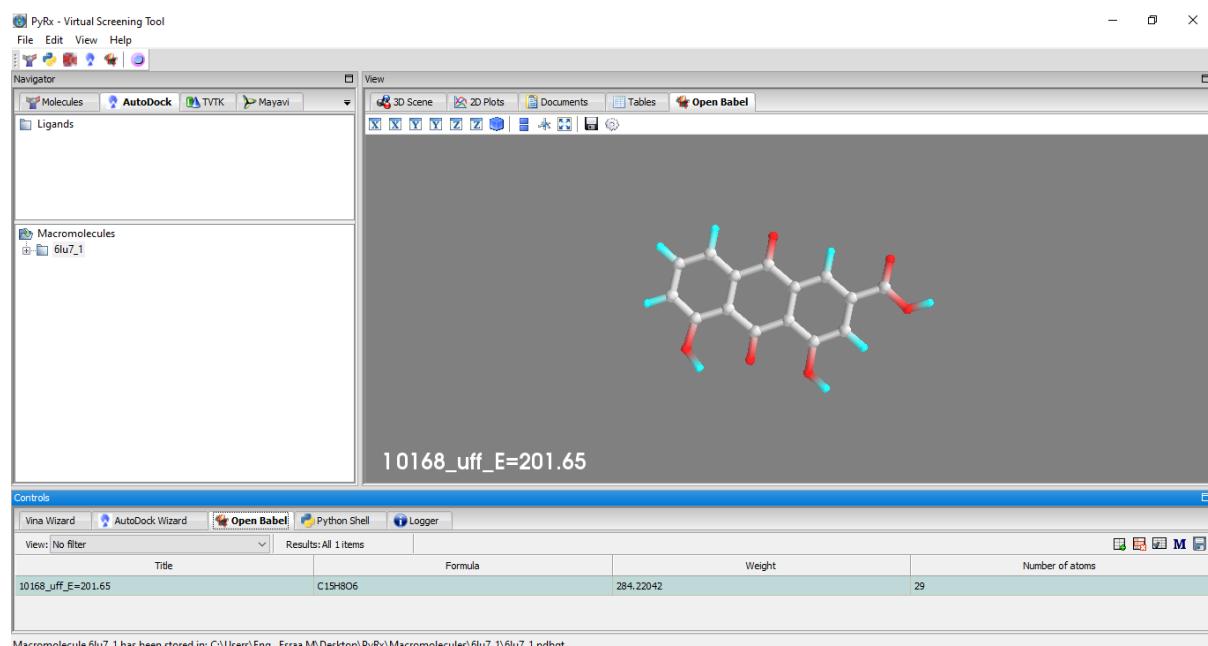
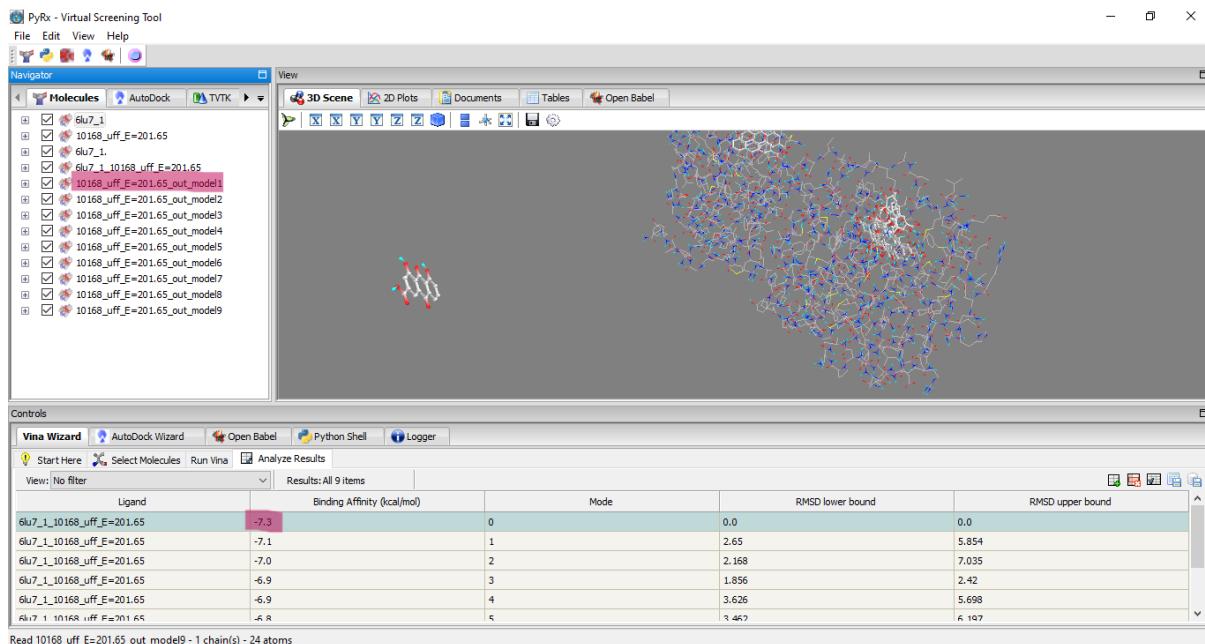


Figure 7: Molecular docking analysis between 6LU7 and Rhein. (A) 3D ribbon structure of Receptor/Protein (6LU7). (B) 3D ligand structure (Rhein). (C) Protein-ligand Interaction. (D) Interaction between the active site residues of the protein and ligand.

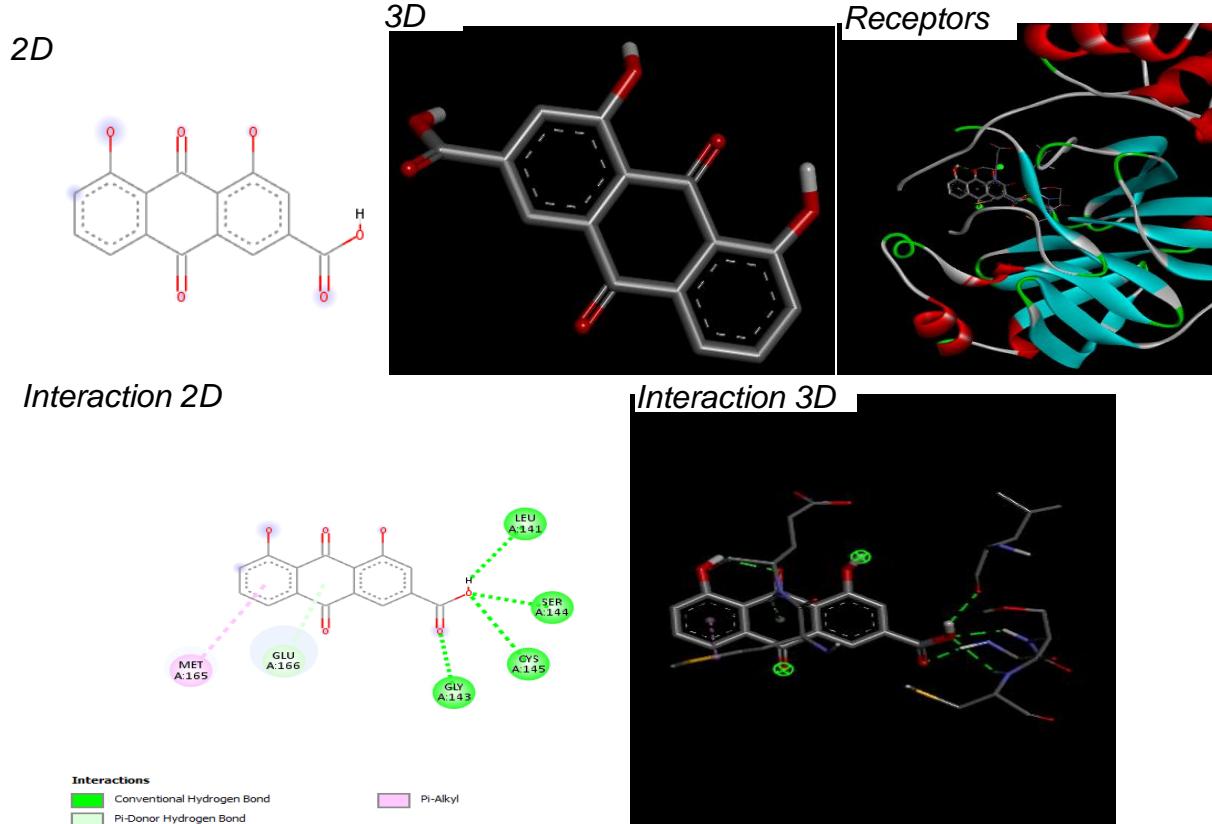
Our Work Minimize Energy

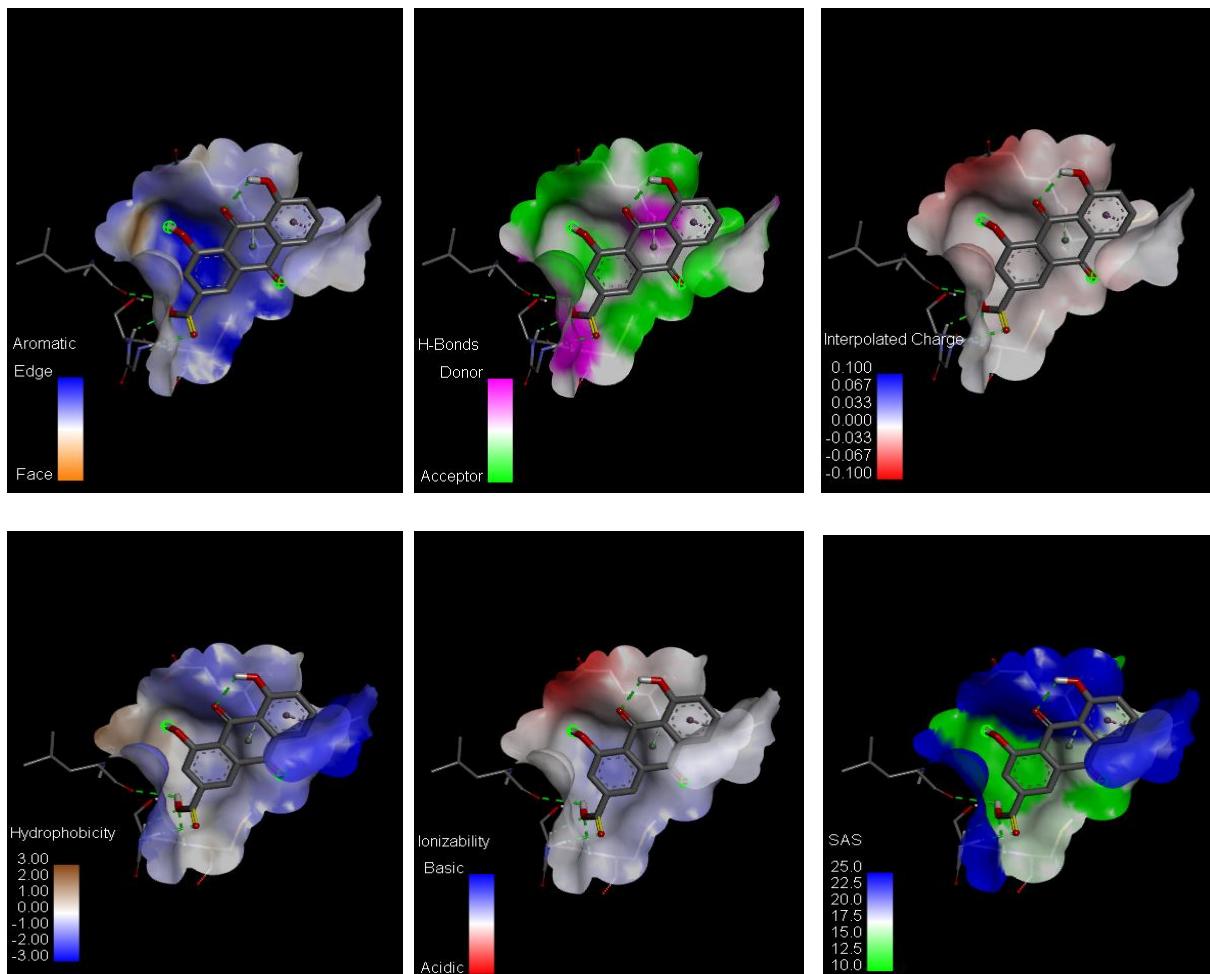


Choosing model



Read 10168_uff_E=201.65_out_model9 - 1 chain(s) - 24 atoms





Withaferin A Paper Work

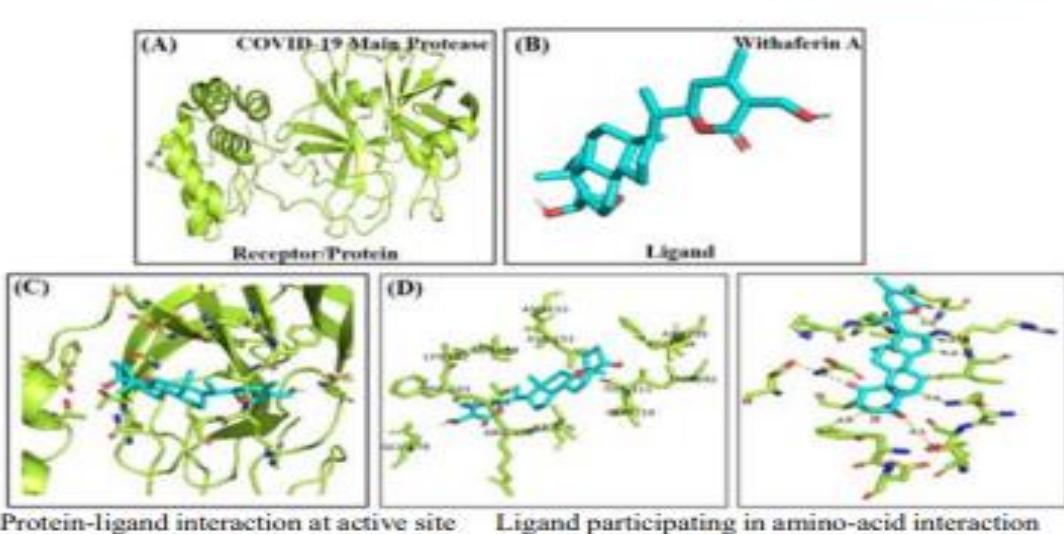
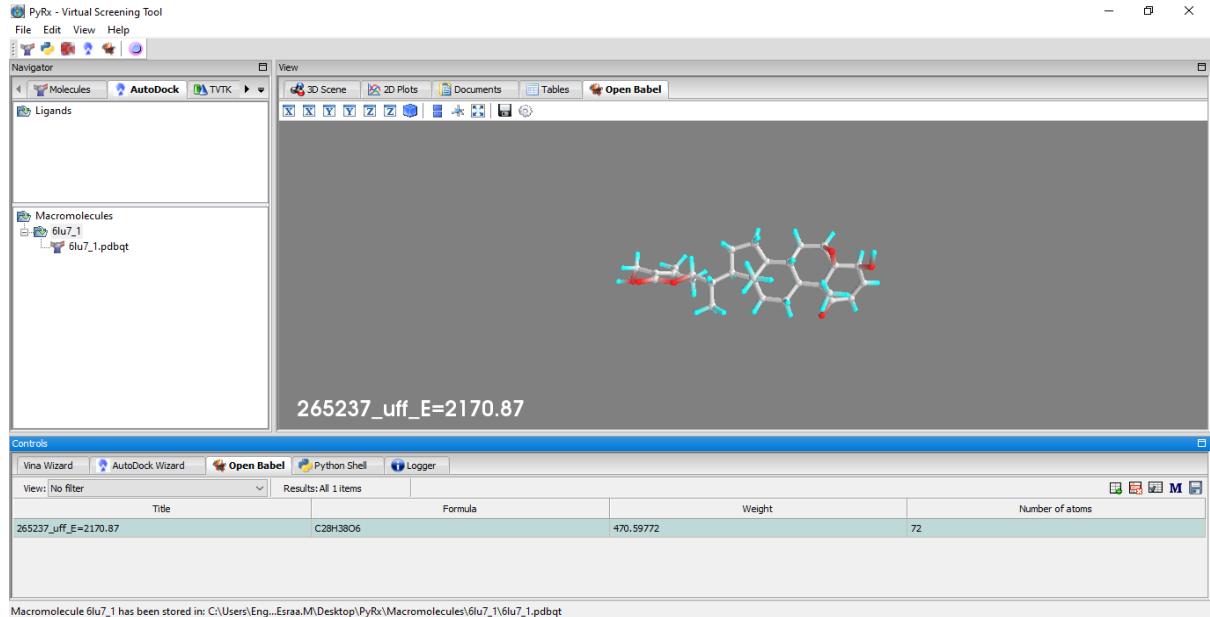


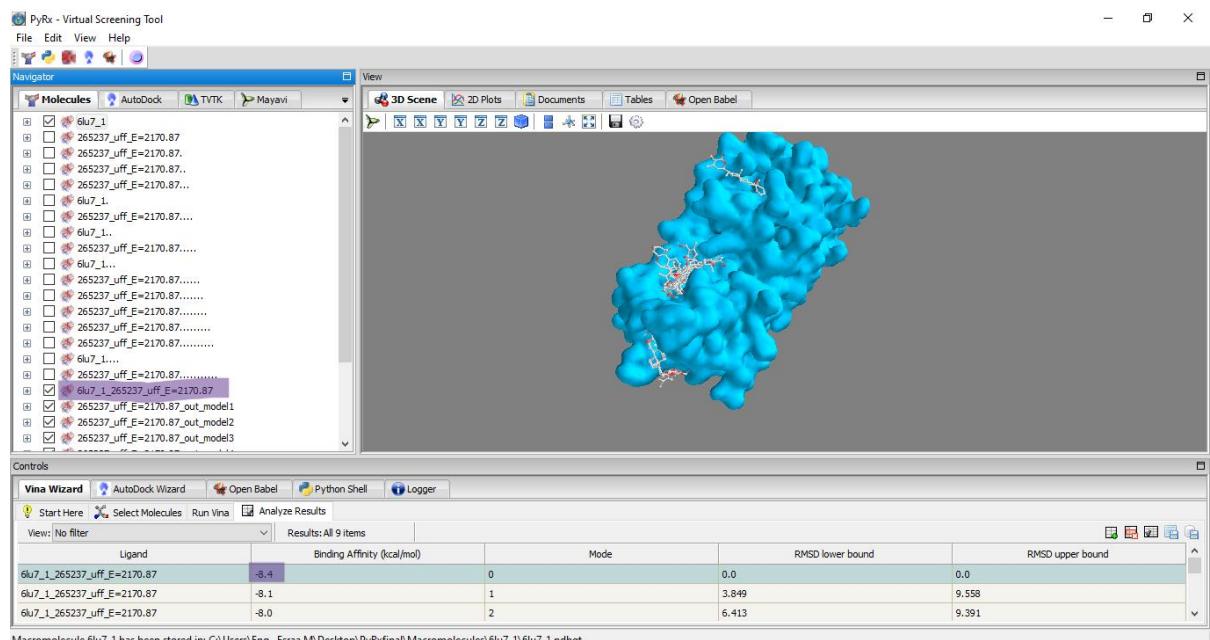
Figure 8. Molecular docking analysis between 6LU7 and Withaferin A. (A) 3D ribbon structure of Receptor/Protein (6LU7). (B) 3D ligand structure (Withaferin A). (C) Protein-ligand Interaction. (D) Interaction between the active site residues of the protein and ligand.

Withaferin A Our work

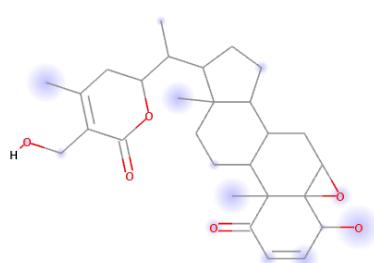
Minimize energy



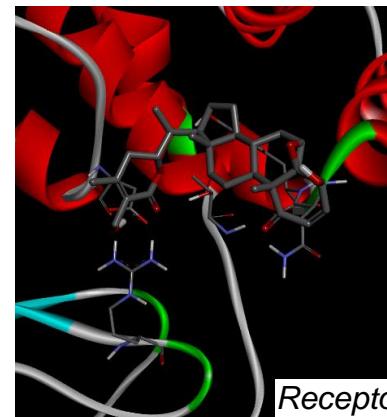
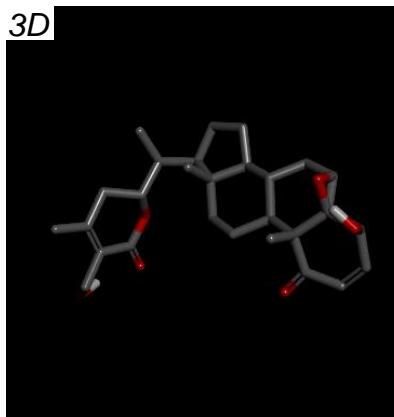
Choosing model



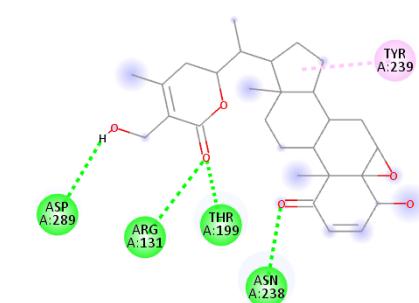
2D



3D



Interaction 2D

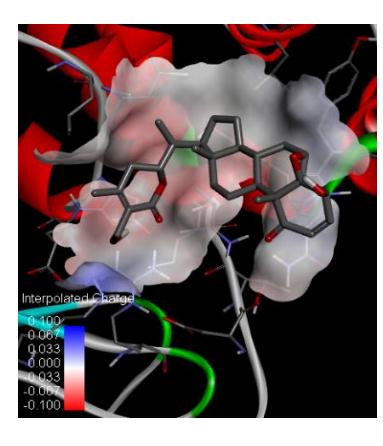
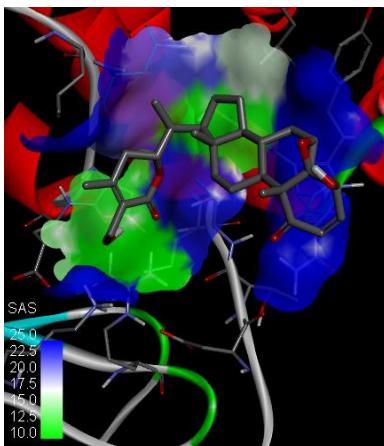
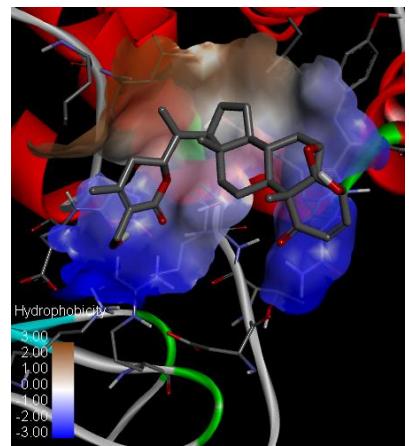
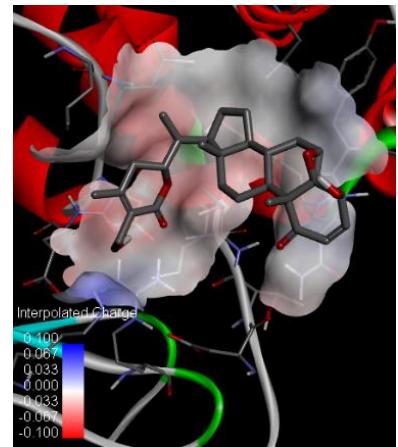
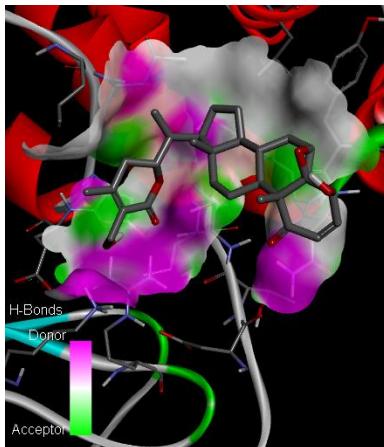
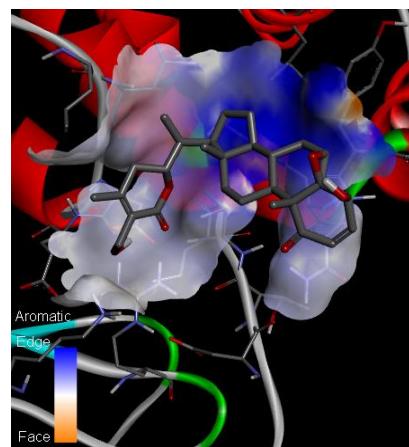
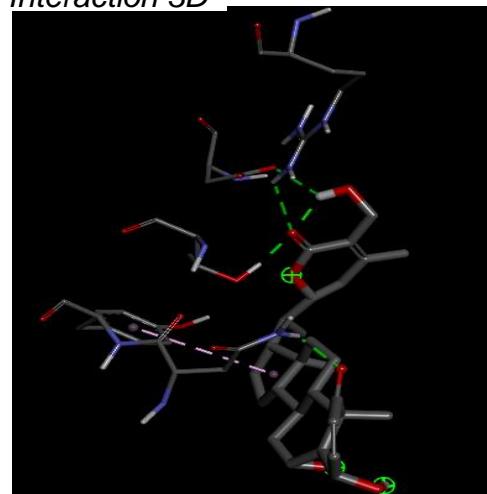


Interactions

Conventional Hydrogen Bond

Pi-Alkyl

Interaction 3D



Withanolide D

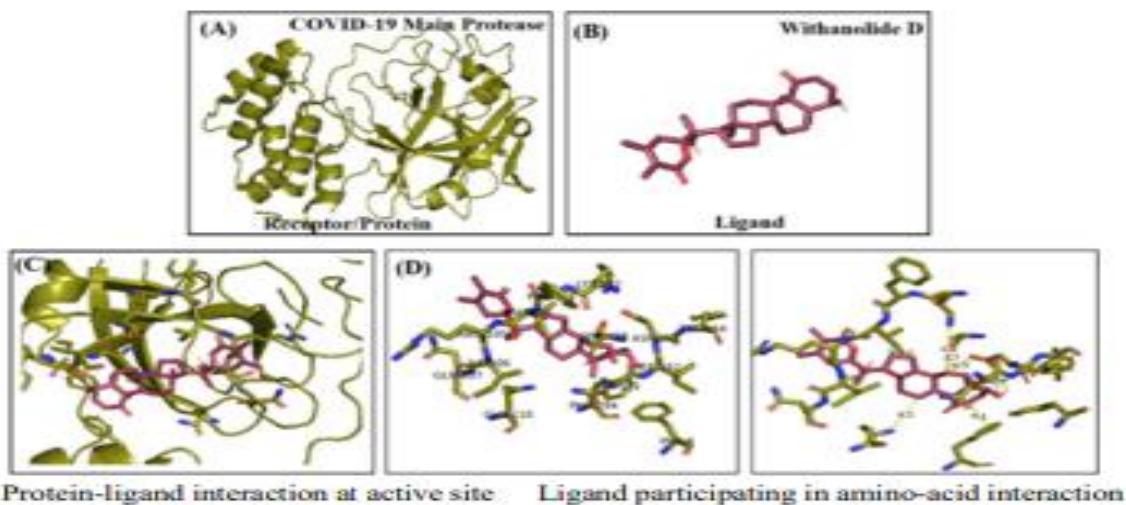
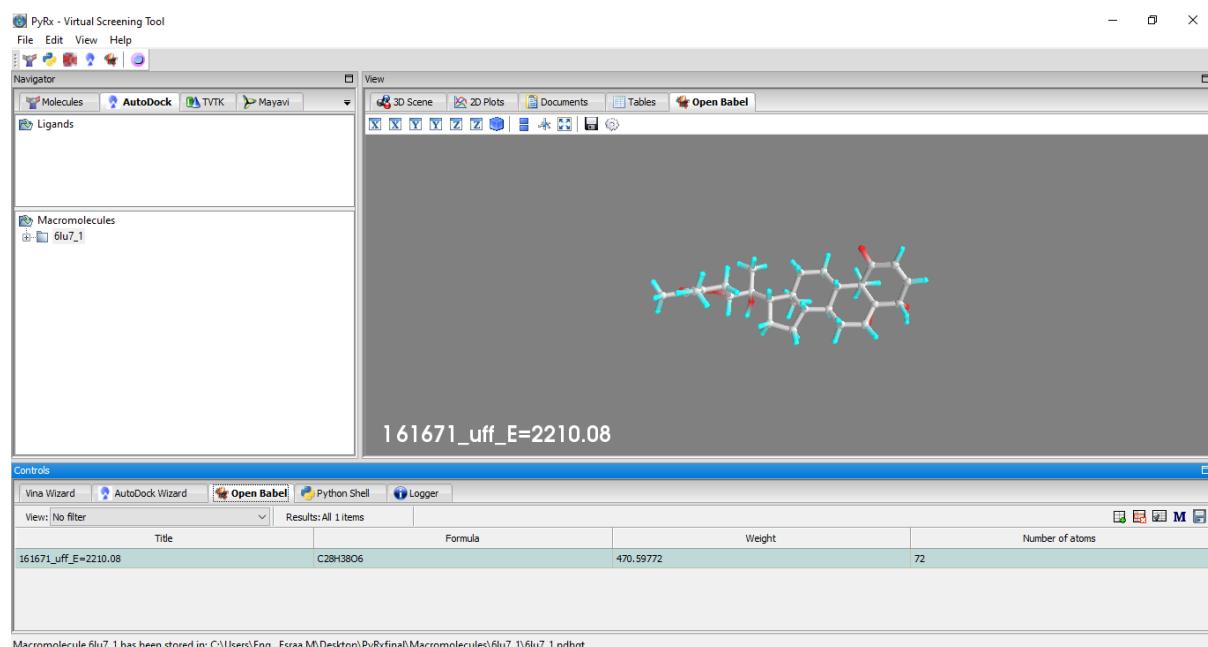


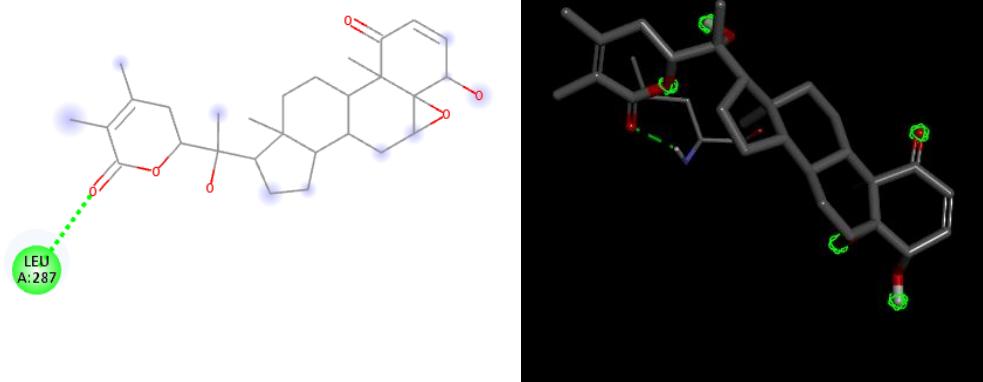
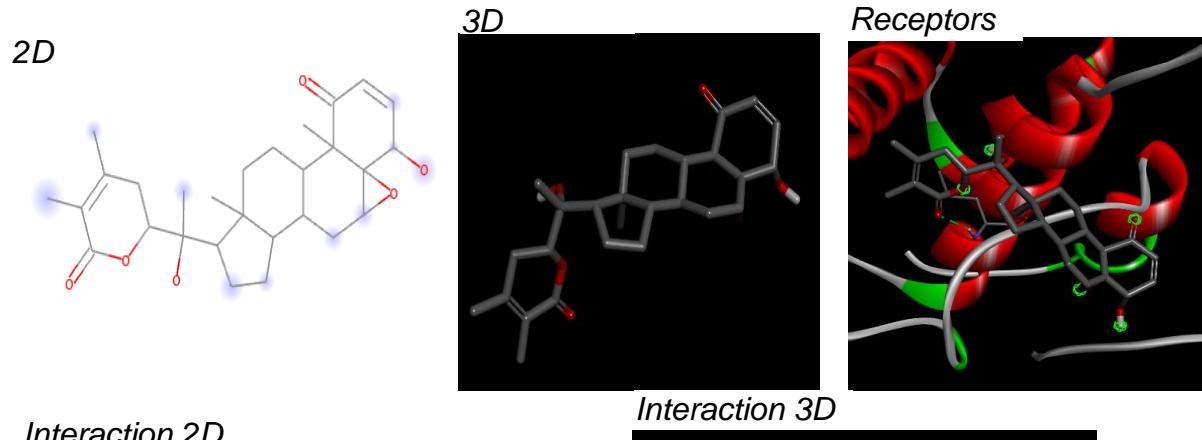
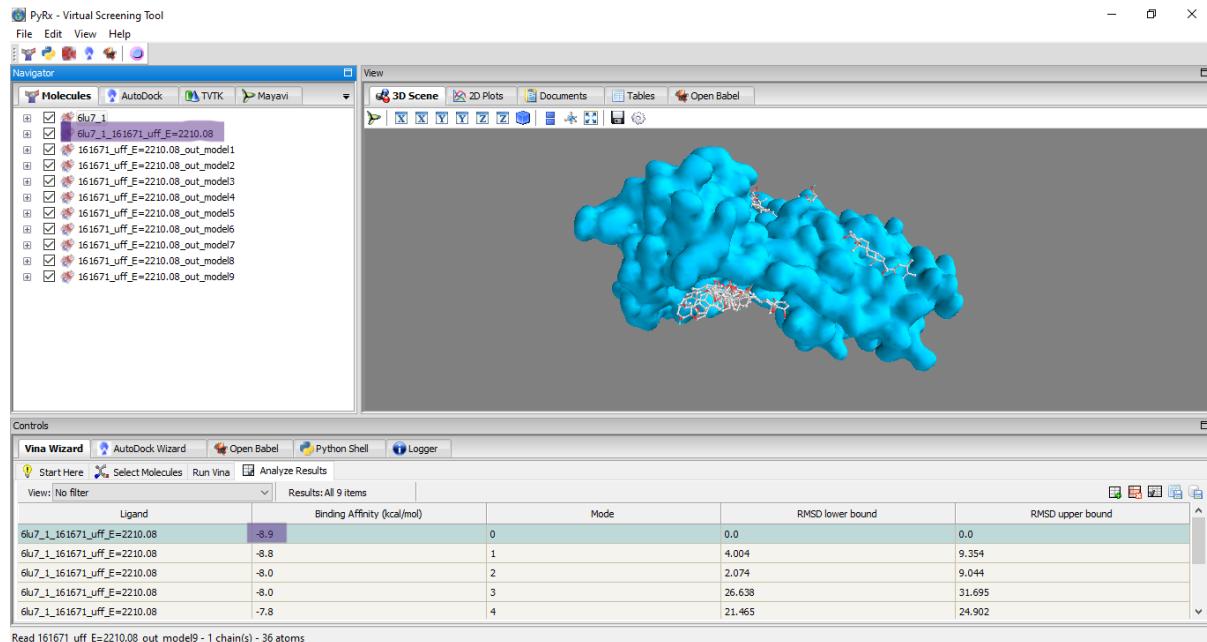
Figure 6. Molecular docking analysis between 6LU7 and Withanolide D. (A) 3D ribbon structure of Receptor/Protein (6LU7). (B) 3D ligand structure (Withanolide D). (C) Protein-ligand Interaction. (D) Interaction between the active site residues of the protein and ligand.

Our Work

Minimize energy



choosing model



Binding Affinity

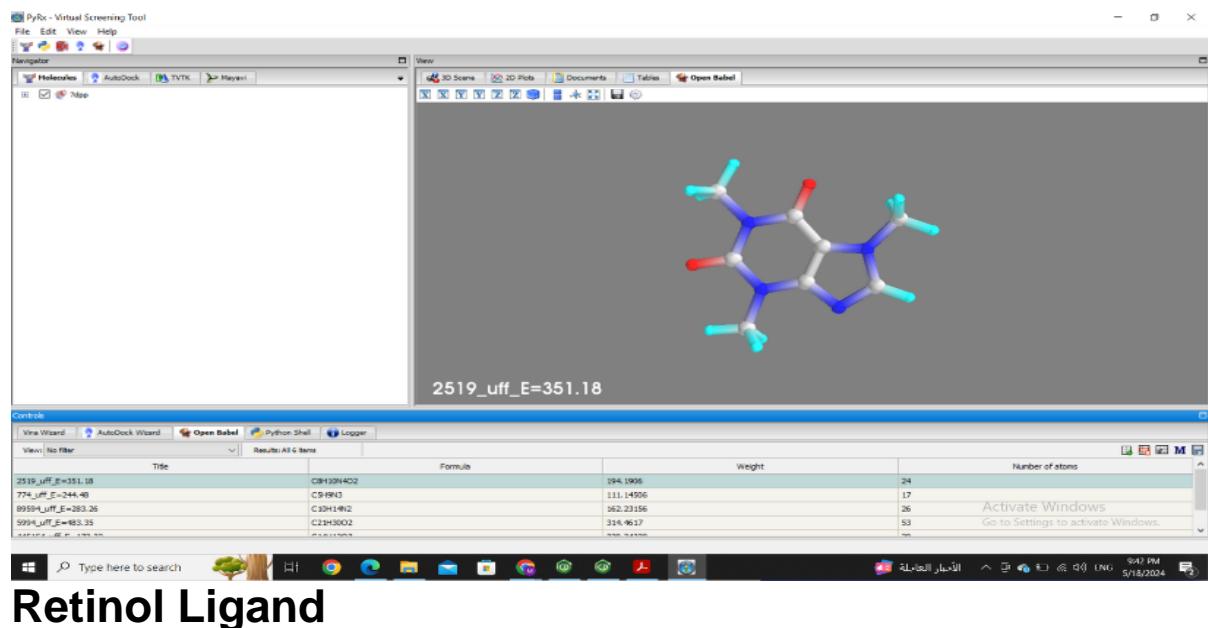
compound	Paper BA	Our BA
Aloe-emodin	-7.4	-7.5
Enoxacin	-7.4	-7.1
Nelfinavir	-8.4	-8.4
Rhein	-8.1	-7.3
Withaferin A	-7.7	-8.4
Withanolide D	-7.8	-8.9

The binding affinities in our study differ from those reported by the author due to methodological differences. The author manually drew the compounds and used their own calculations, while we used PyRx to automatically find the lowest energy conformations. This resulted in different energy values, highlighting the variability between manual and automated methods and emphasizing the benefits of using tools like PyRx for consistent and accurate results.

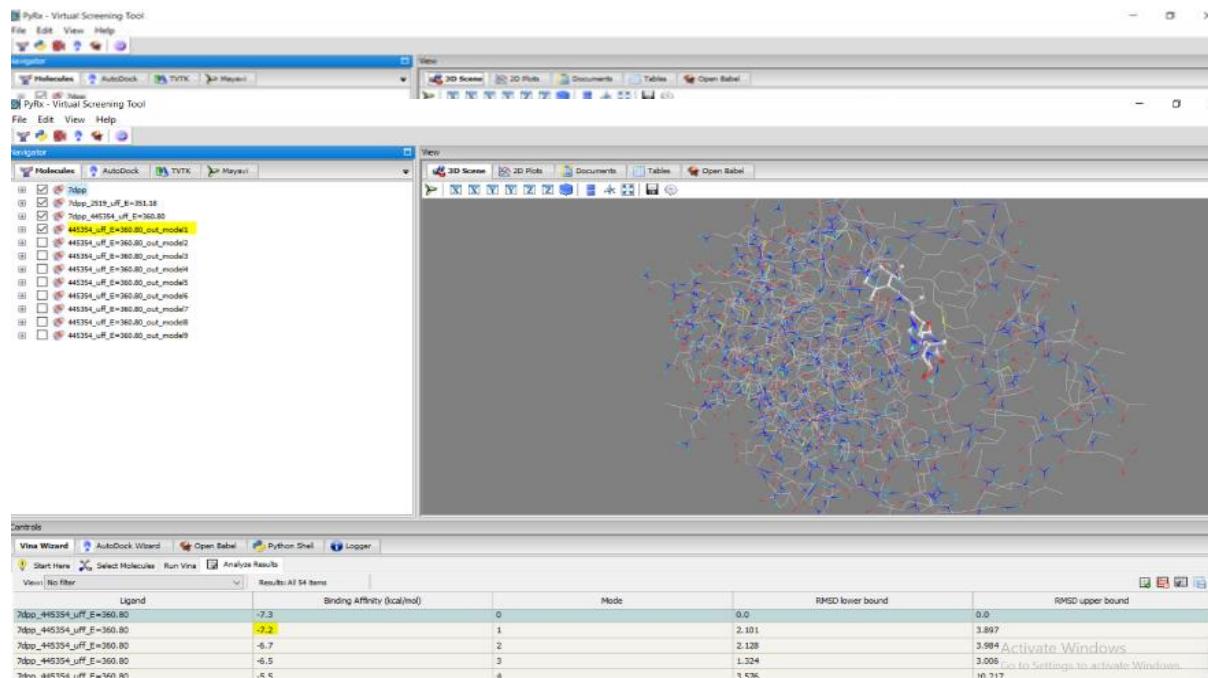
7DPP Experiment:

- The study of SARS-CoV-2 3CL protease is crucial for understanding virus replication and developing antiviral drugs.
 - Compounds like myricetin, which bind to and inhibit 3CLpro, are potential therapeutic agents against COVID-19.
 - This information can be used to guide the design of more potent inhibitors based on the myricetin scaffold or similar compounds.
 - PDB entry 7DPP provides insights into inhibitory action and design of potent inhibitors.

Minimize All Ligands Energy



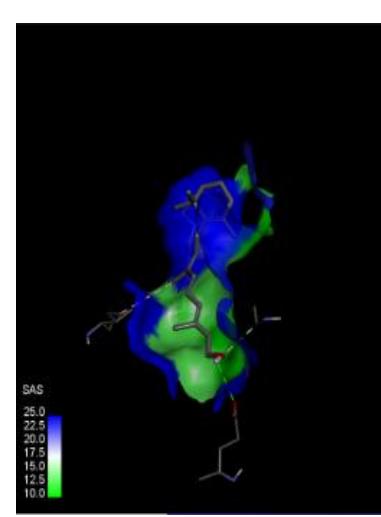
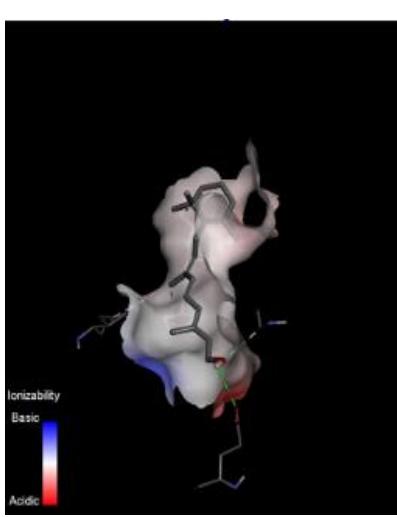
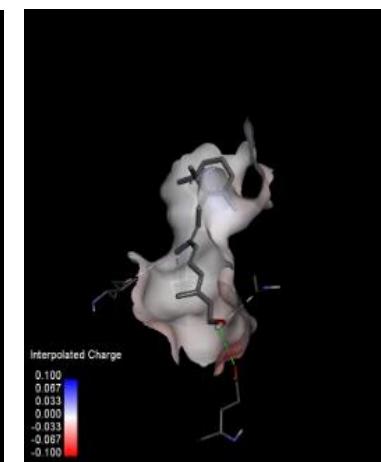
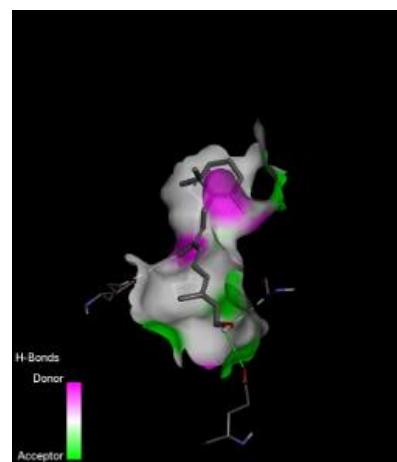
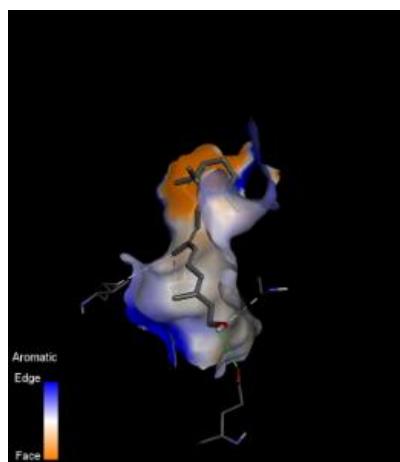
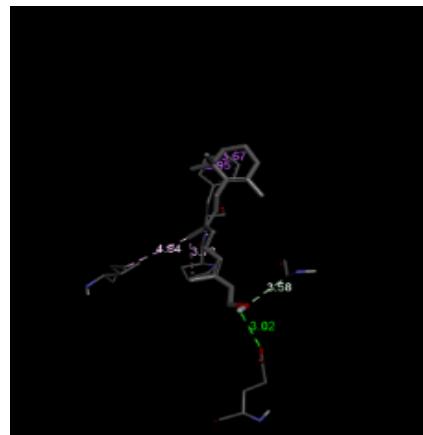
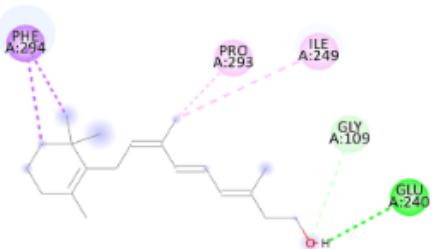
Choose Ligand



Choose Model

Retinol Ligand-Interaction





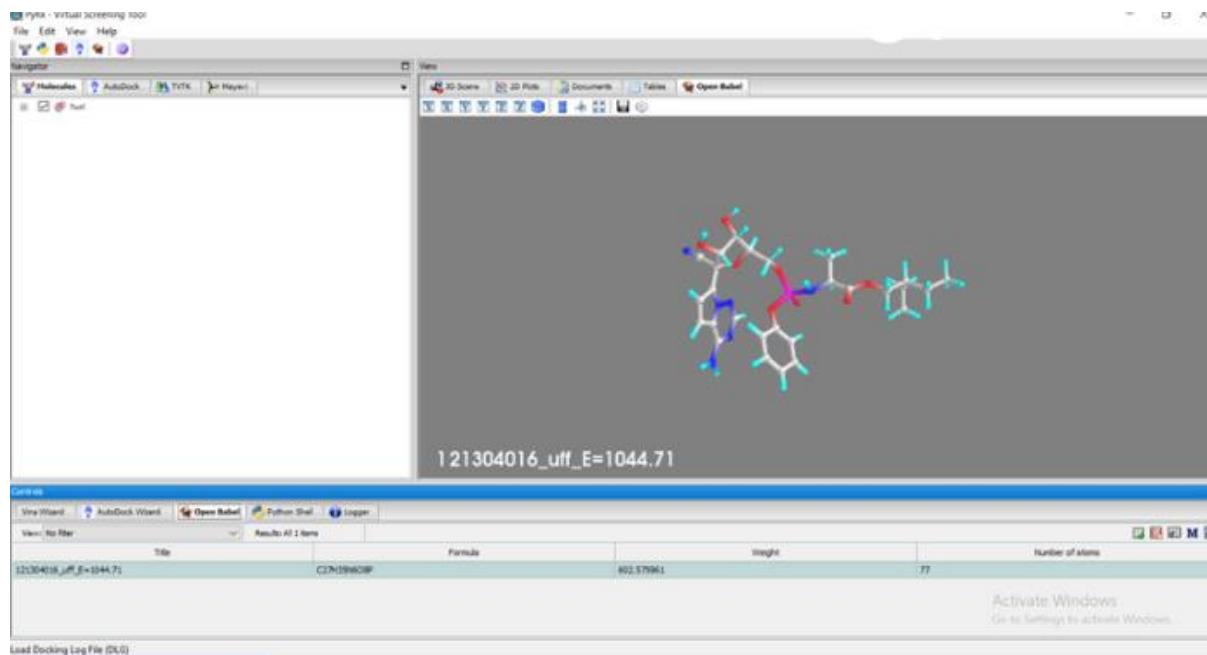
7WRL Experiment:

- Represents the local structure of the BD55-1239 Fab fragment in complex with the SARS-CoV-2 Omicron variant receptor-binding domain (RBD).
- Omicron RBD: has several mutations compared to the original strain. These mutations enhance its ability to bind to the ACE2 receptor on human cells and may affect its susceptibility to neutralising antibodies.
- The BD55-1239 Fab fragment, a fragment antigen-binding region, is crucial for understanding antibody neutralisation and can inform the design of therapeutic antibodies or vaccines by revealing the complex formation between the fragment and the RBD.
- Providing valuable structural insights into the interaction between an antibody fragment and the SARS-CoV-2 Omicron variant RBD, contributing to the ongoing efforts to combat COVID-19 through therapeutic and vaccine development.

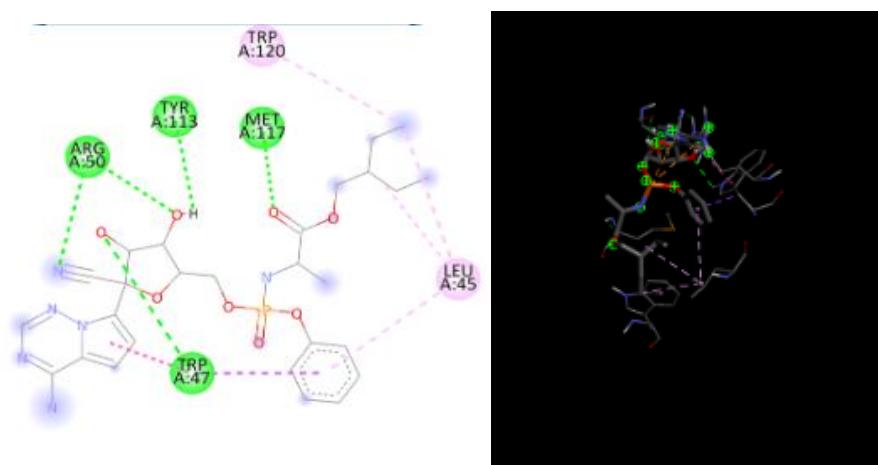
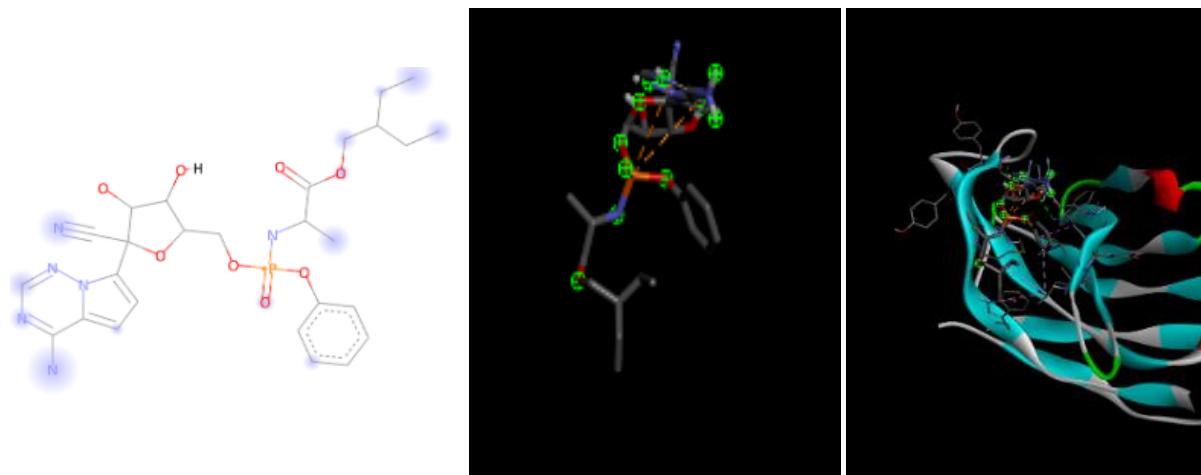
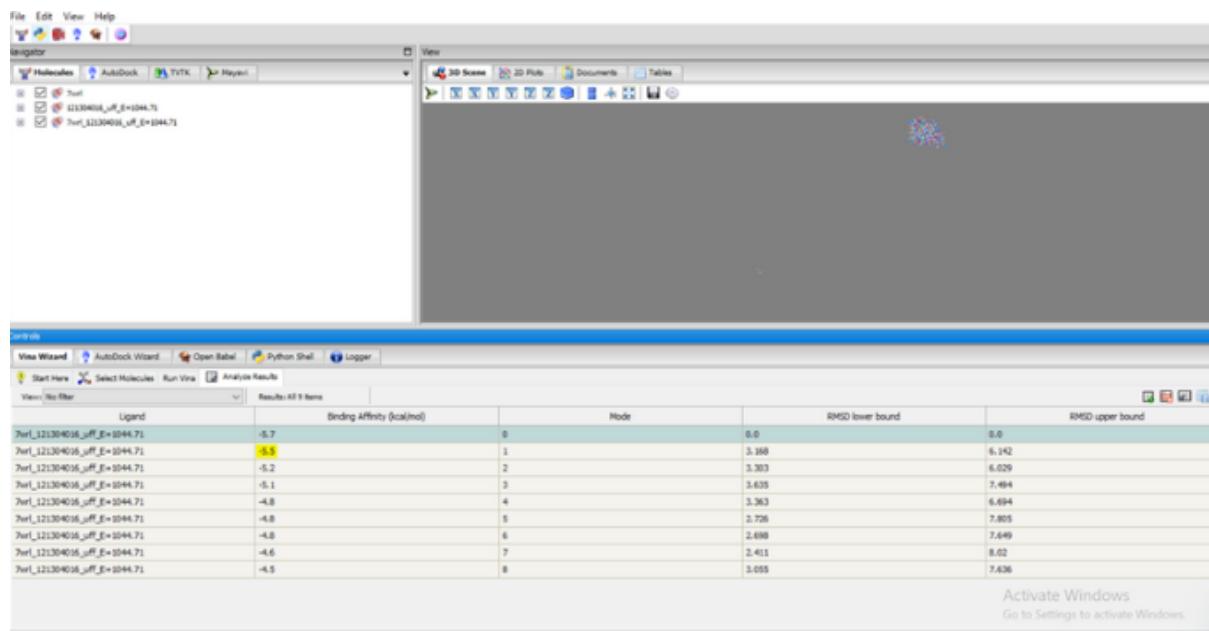
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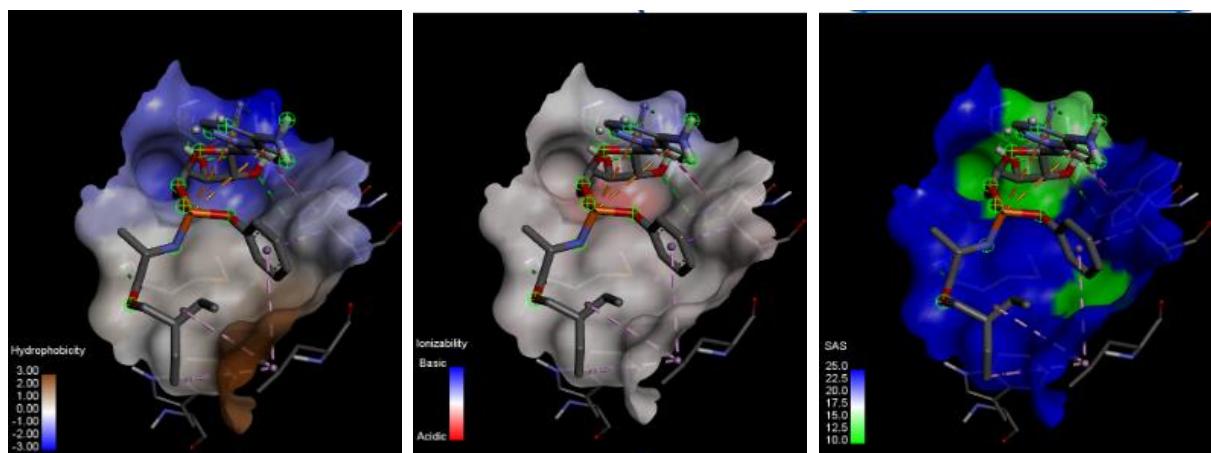
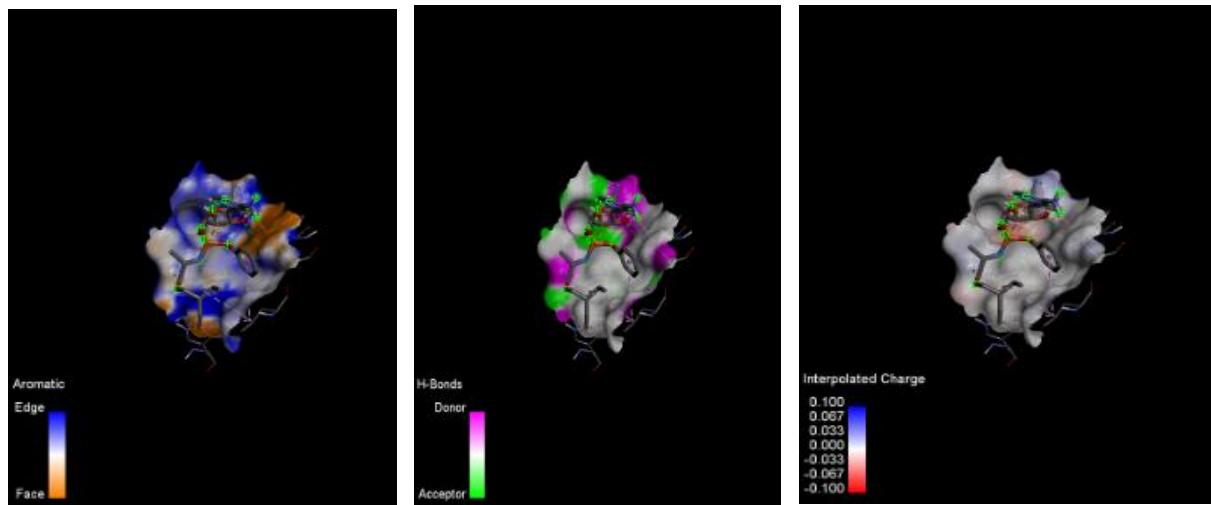
Remdesivir Ligand

Minimize Energy



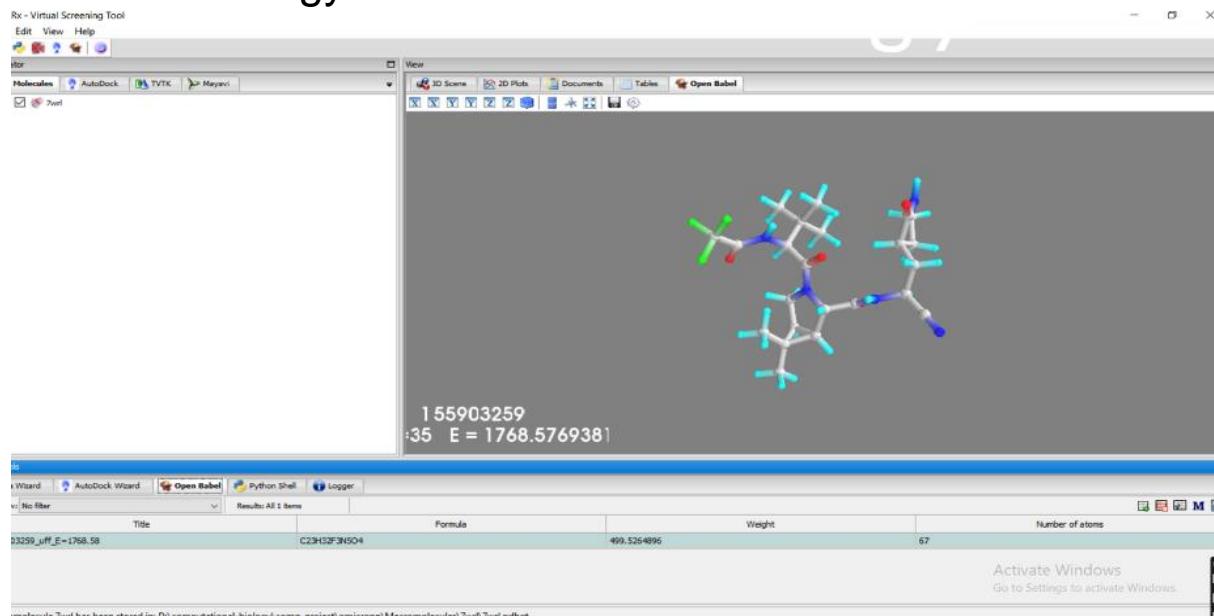
Choose Model



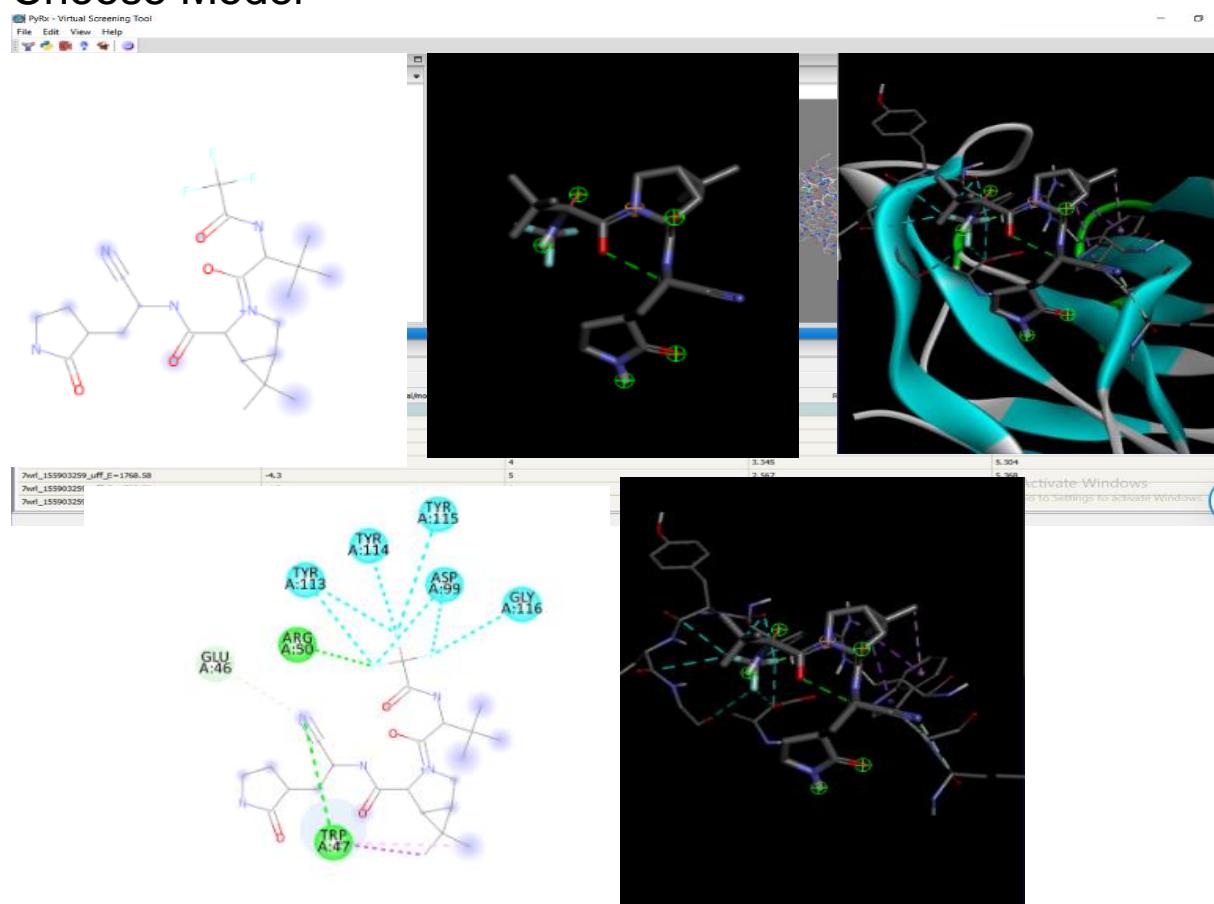


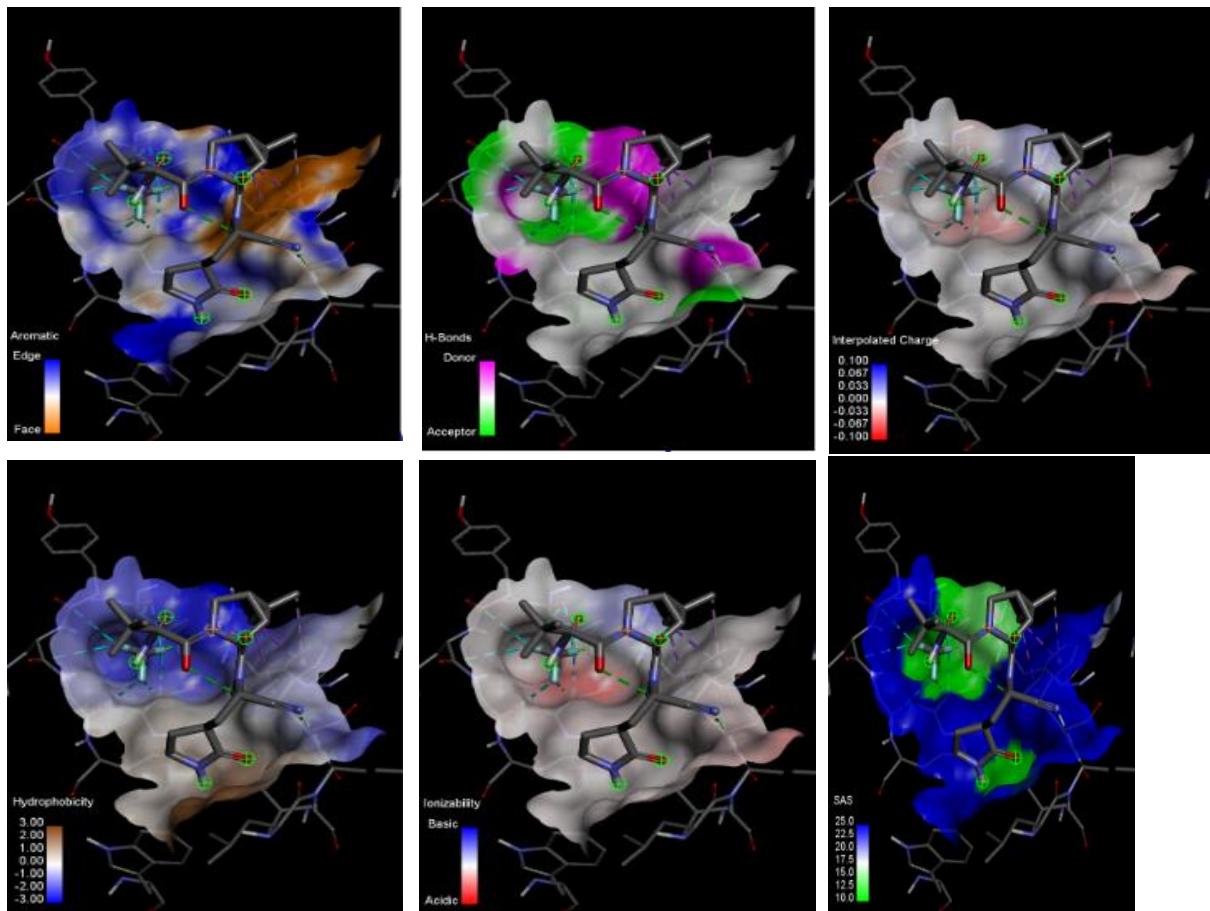
Nirmatrelvir Ligand

Minimize Energy



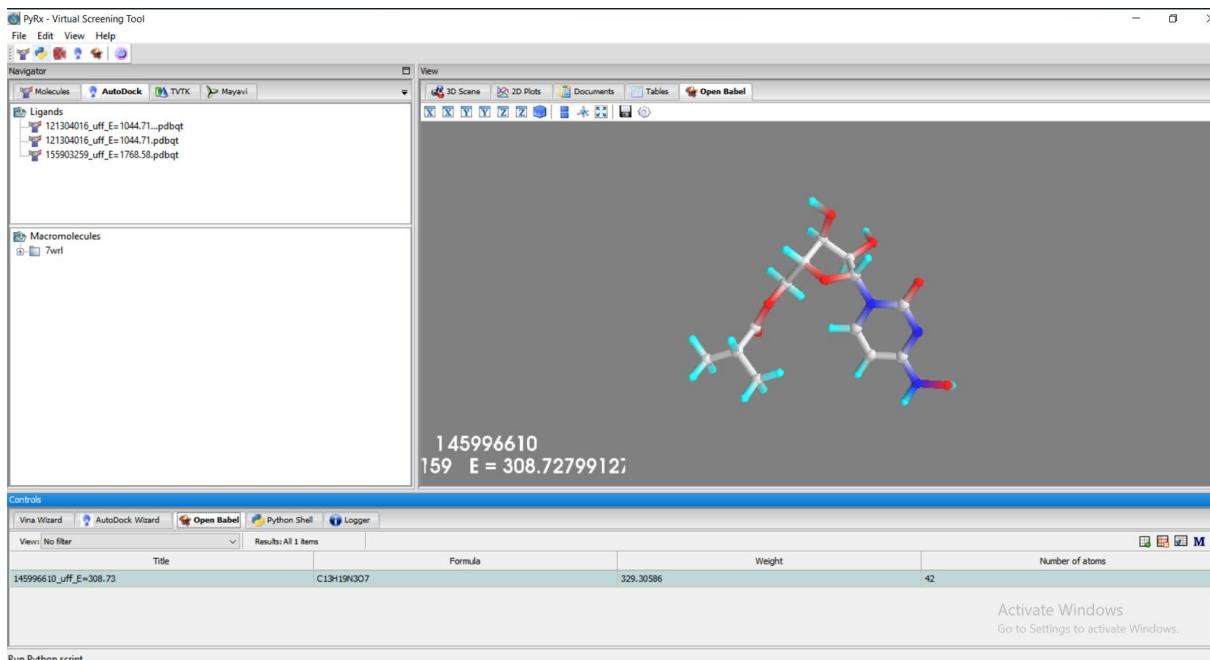
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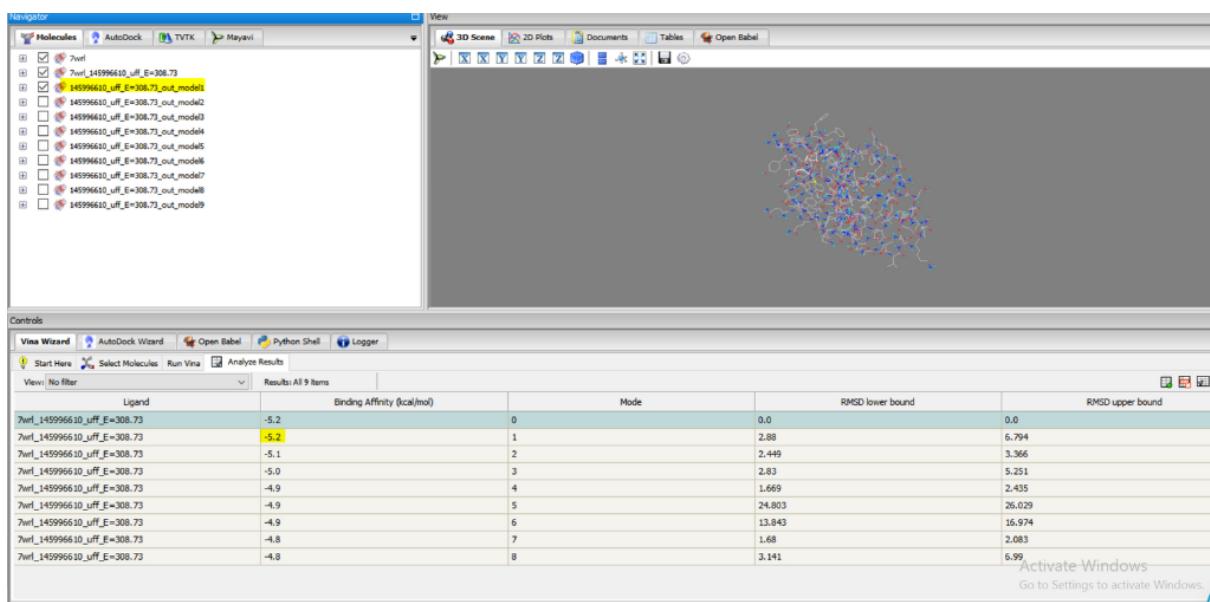


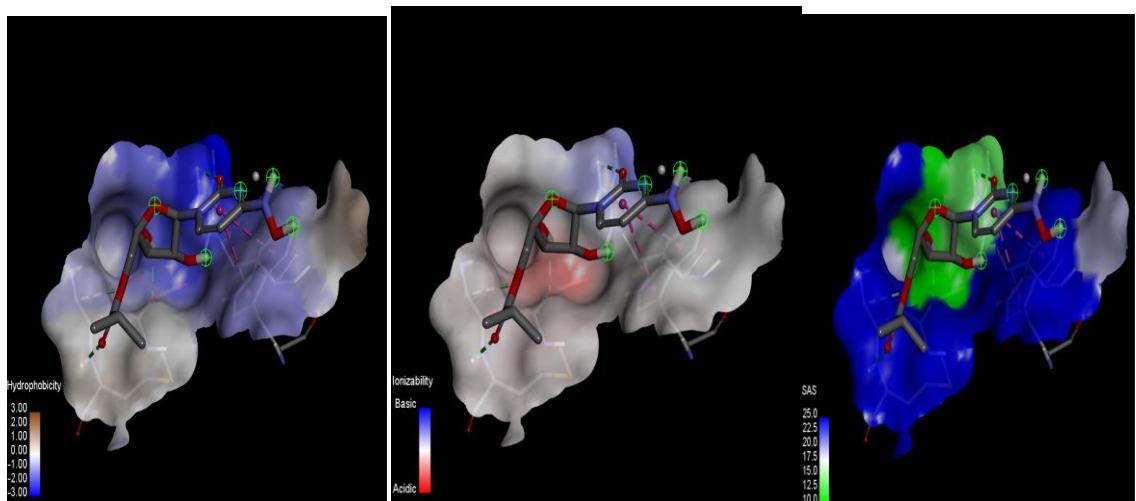
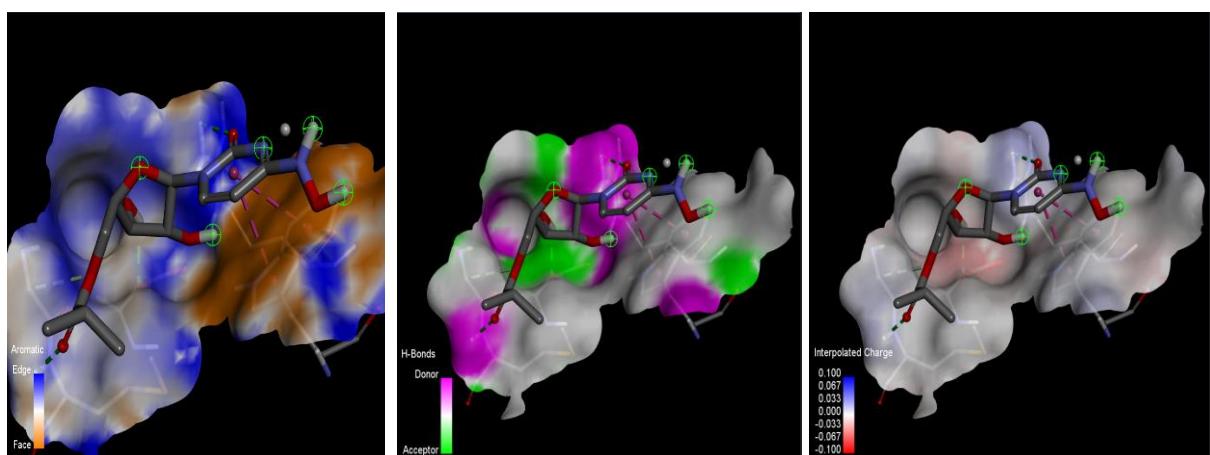
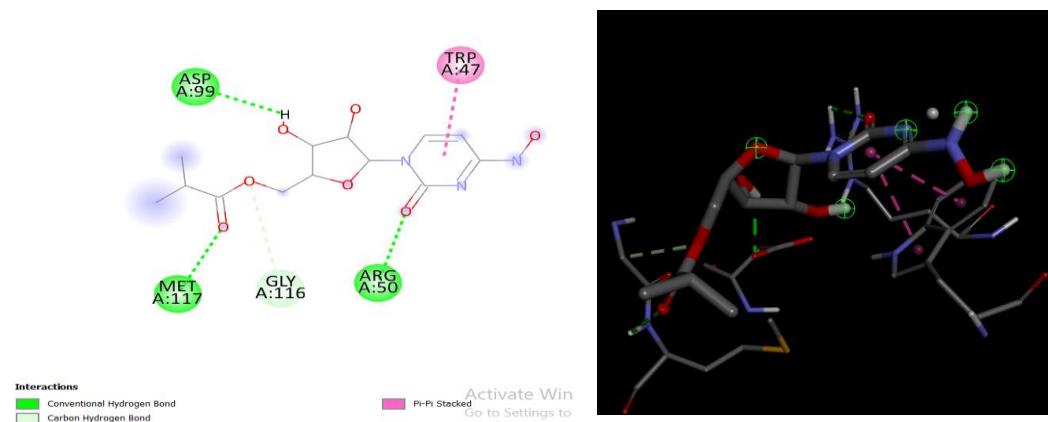
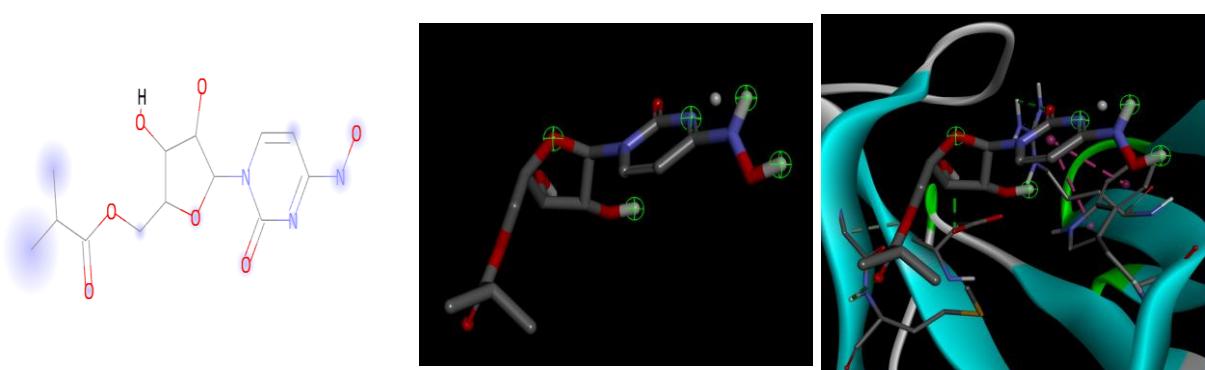
Molnupiravir Ligand

Minimise Energy



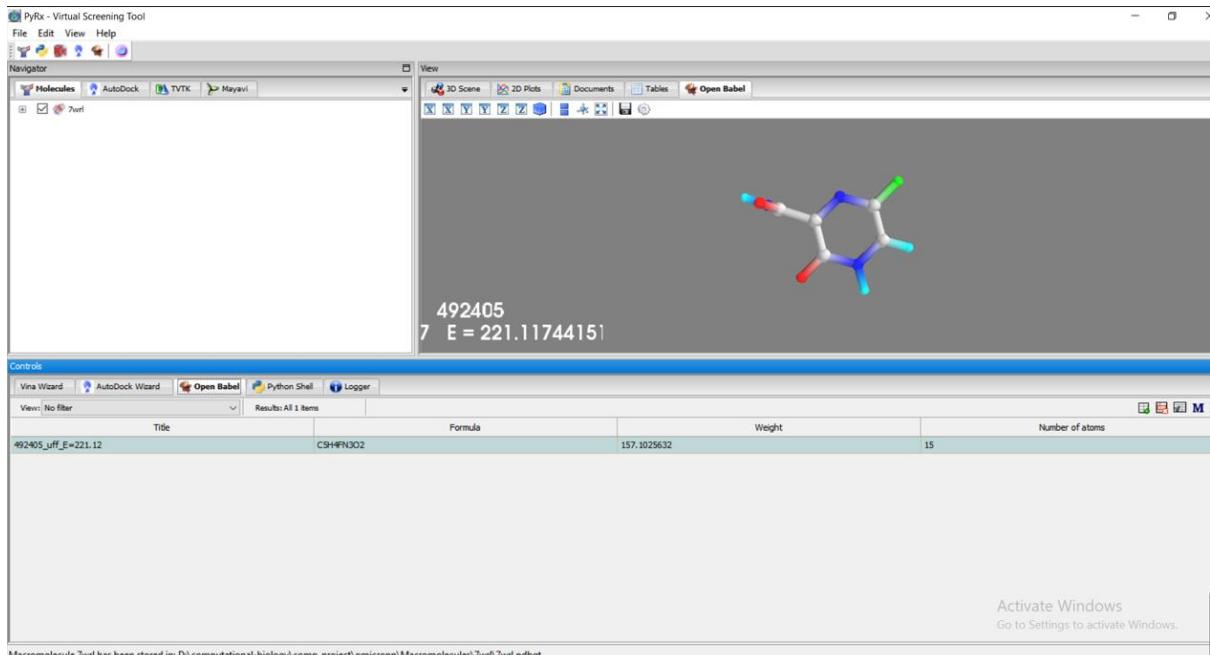
Choose Model



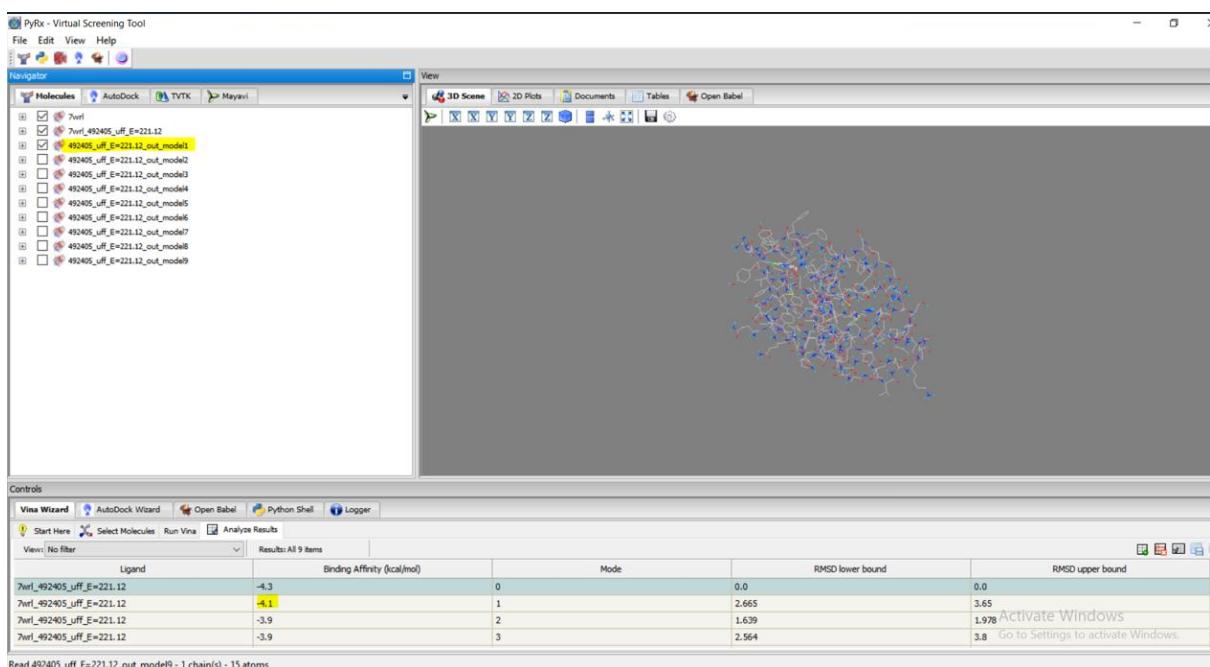


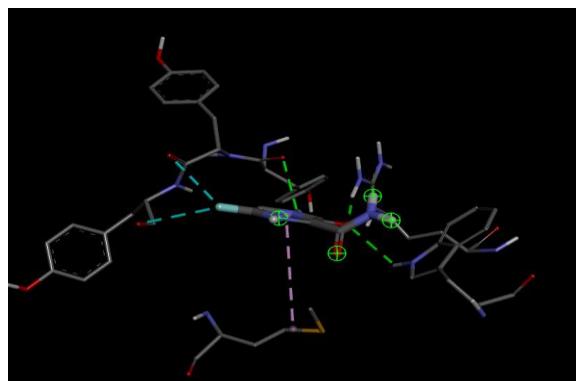
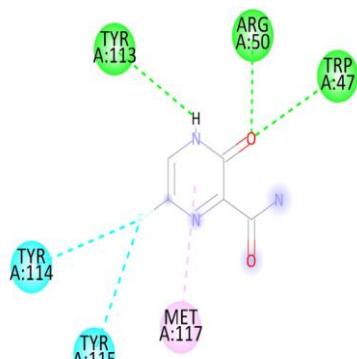
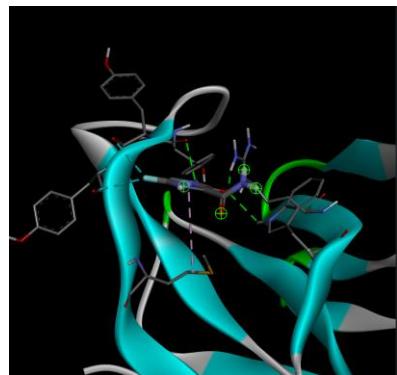
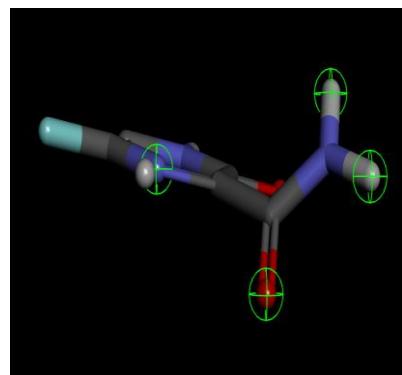
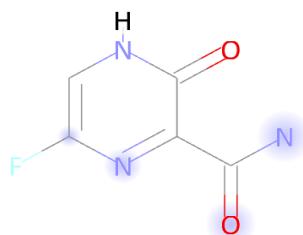
Favipiravir Ligand

Minimise Energy



Choose Model





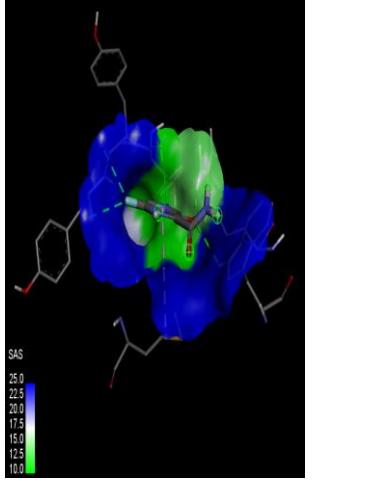
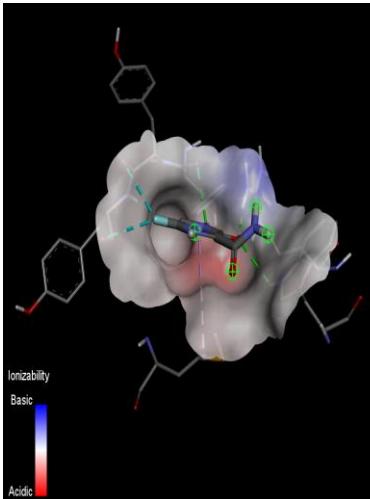
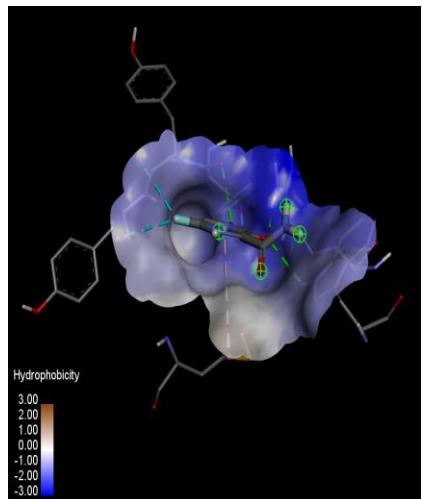
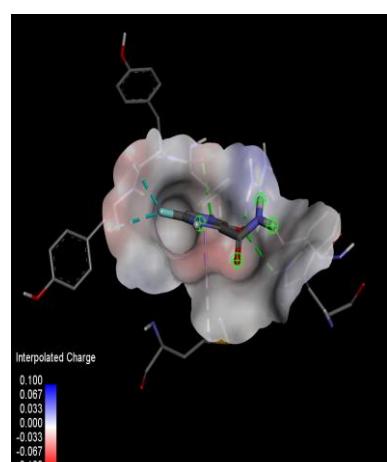
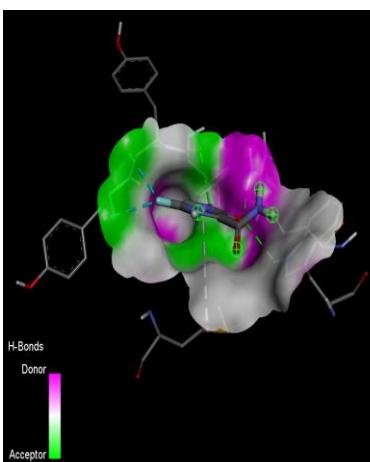
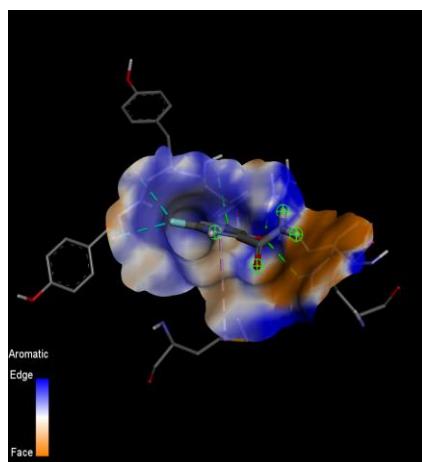
Interactions

Conventional Hydrogen Bond

pi-Alkyl

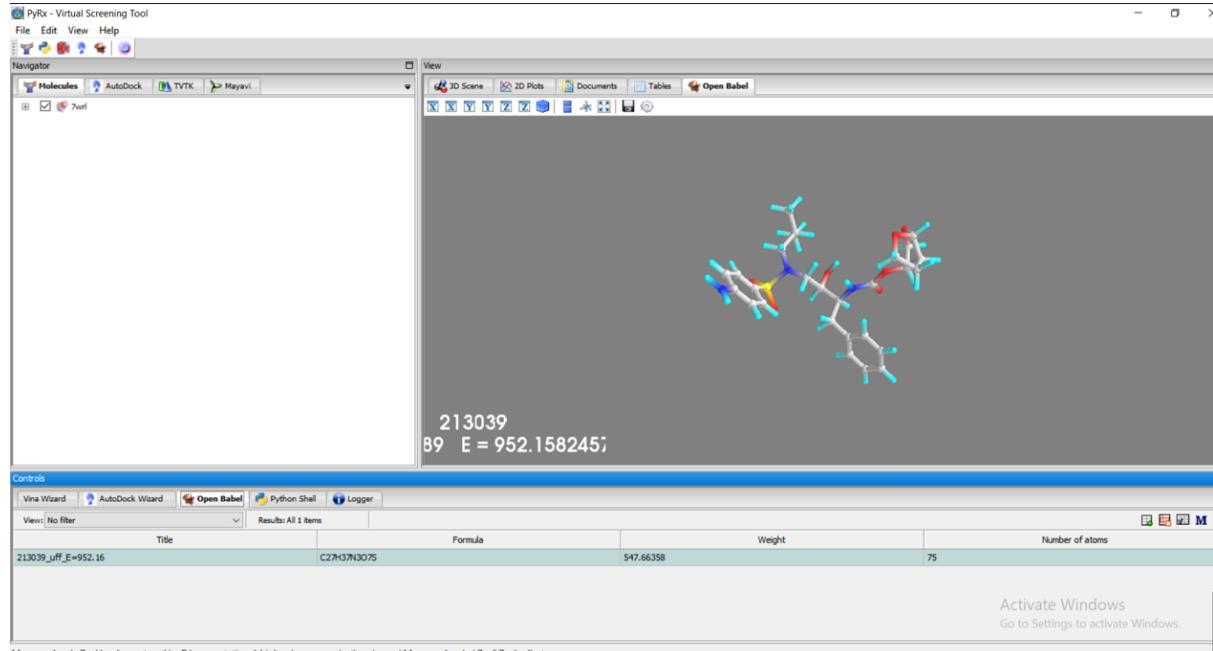
Activate W

Go to Settings

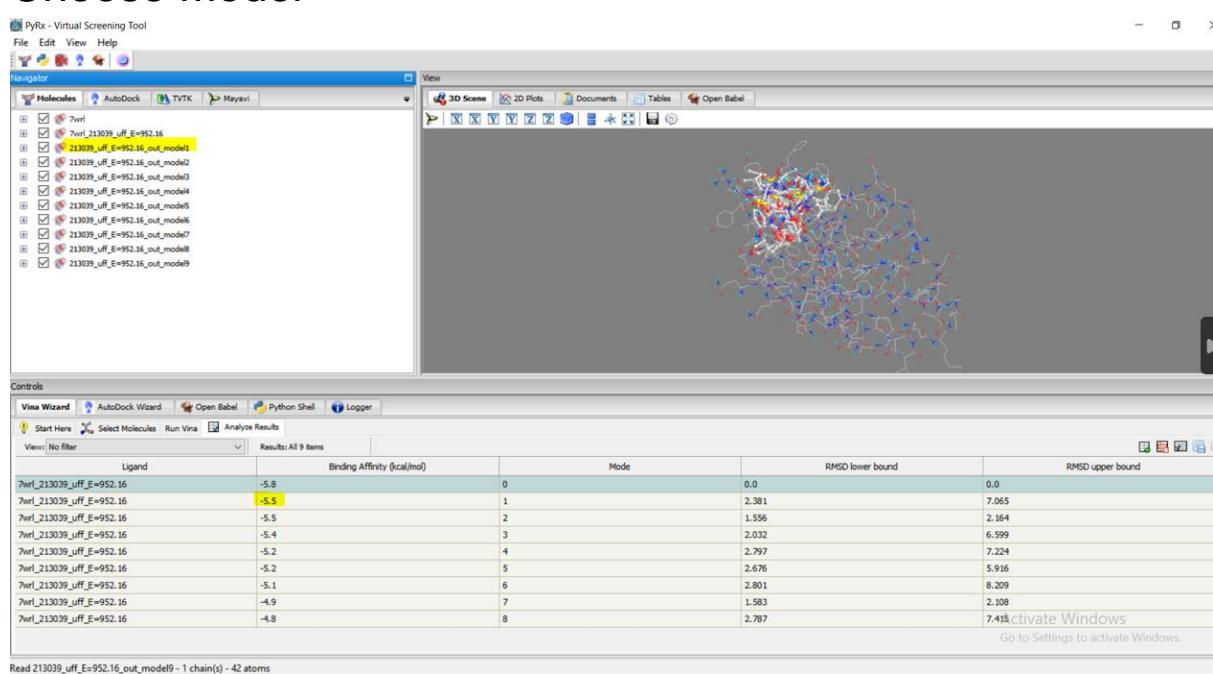


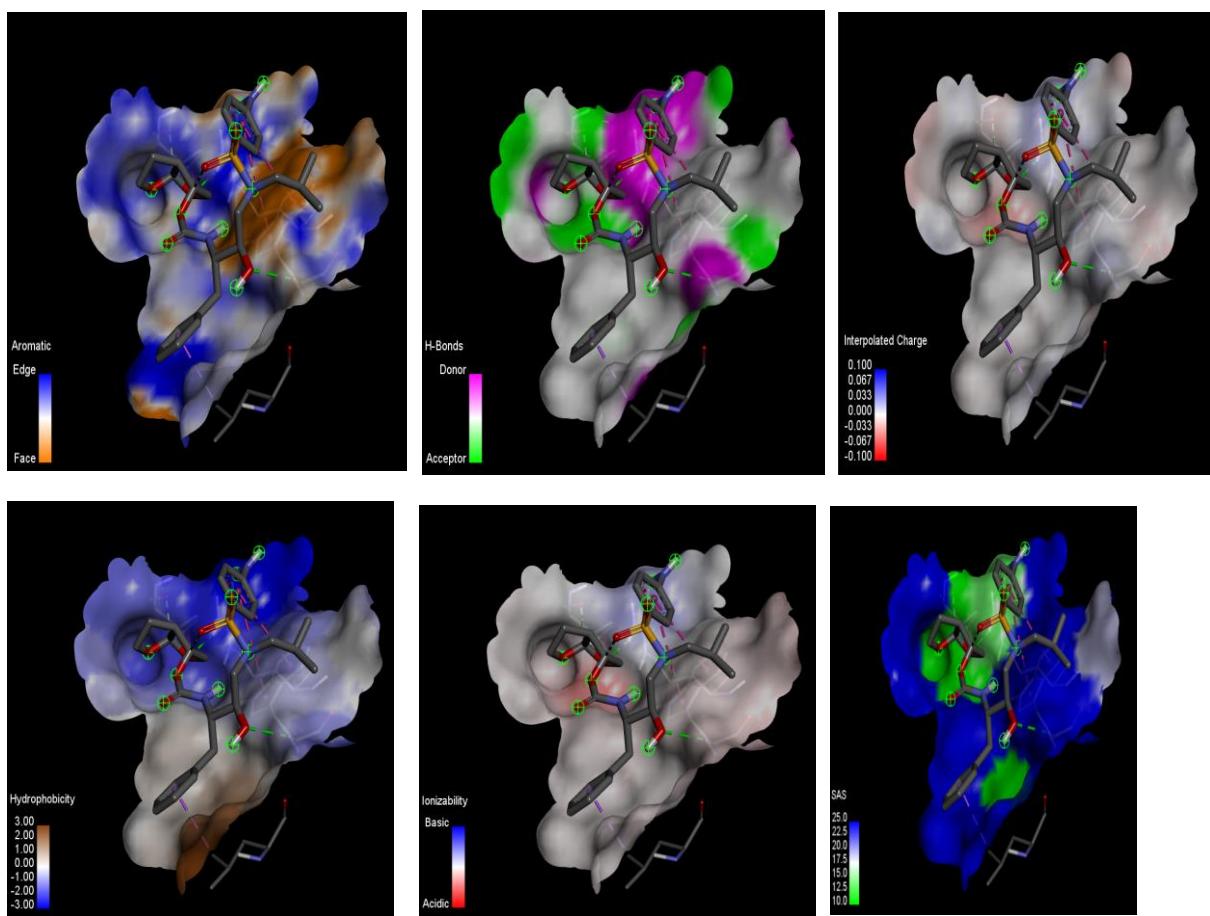
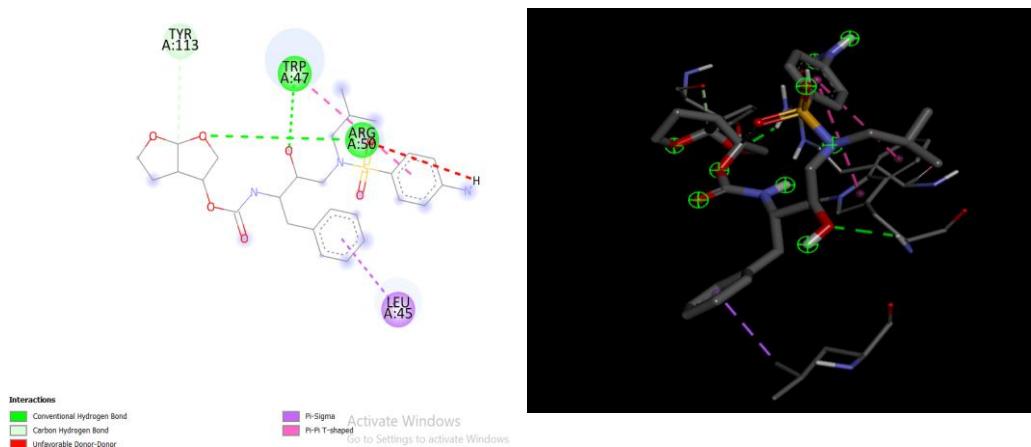
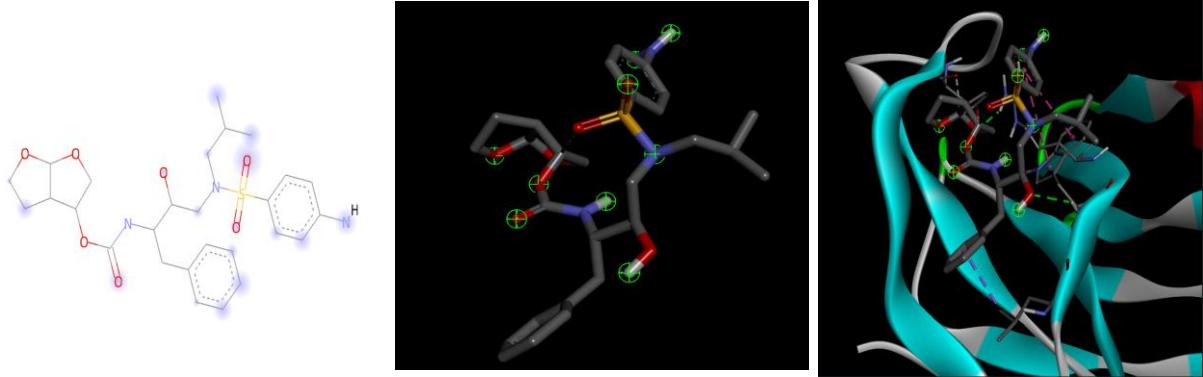
Darunavir Ligand

Minimise Energy



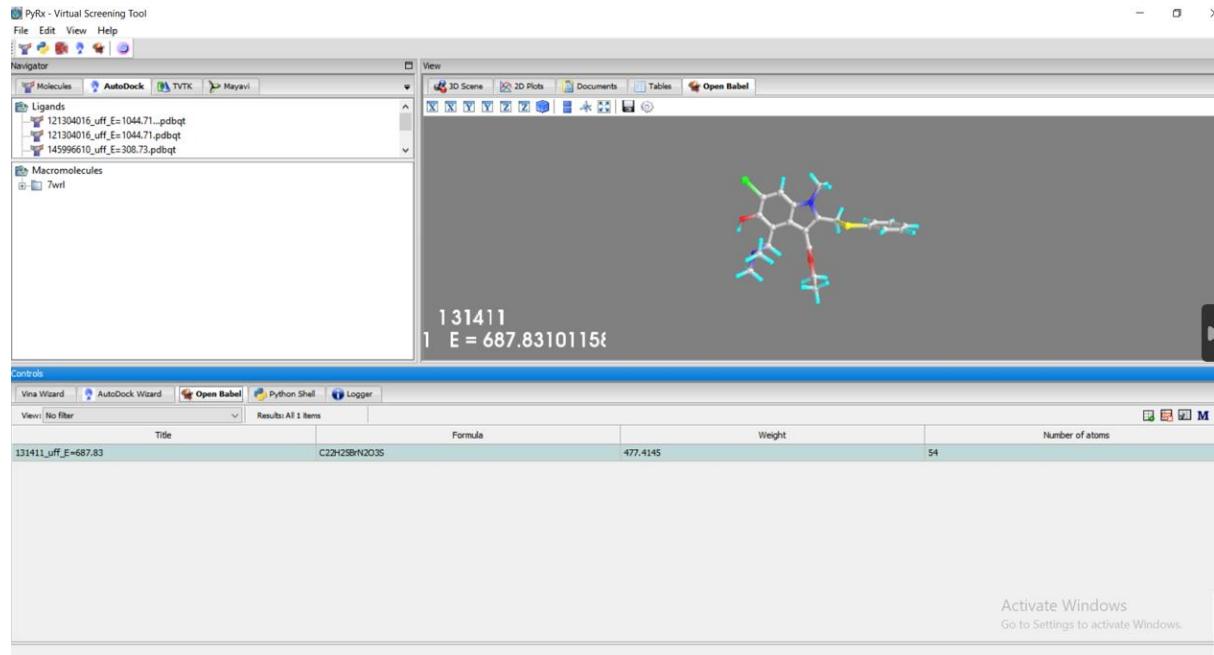
Choose Model



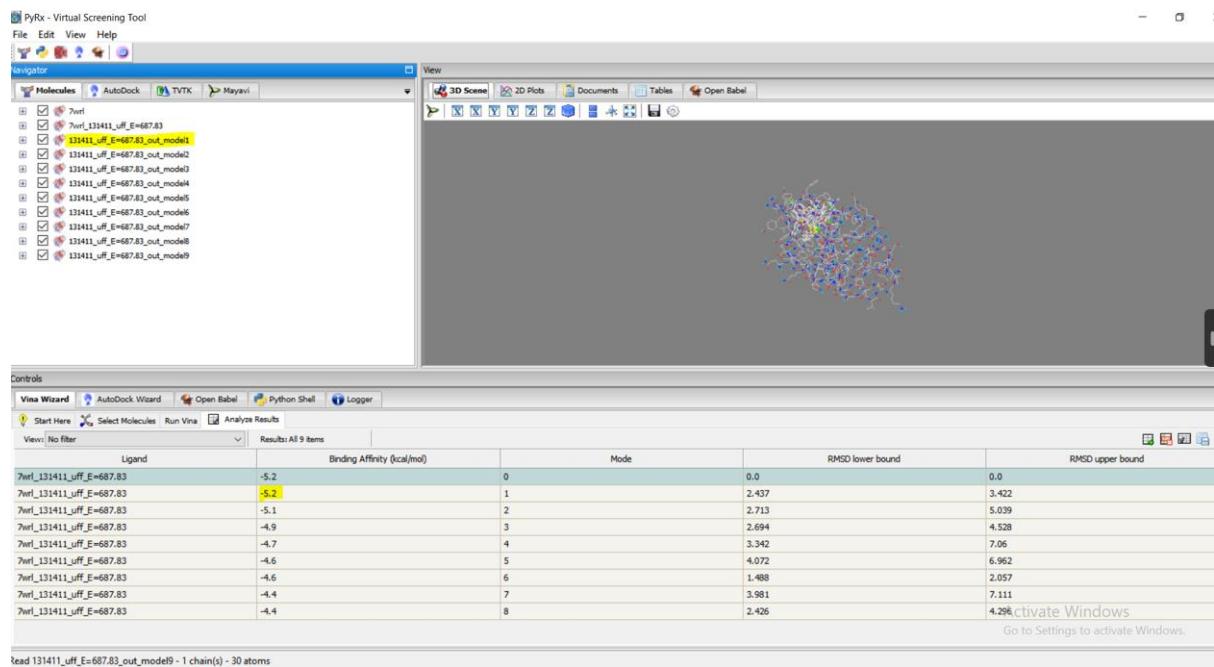


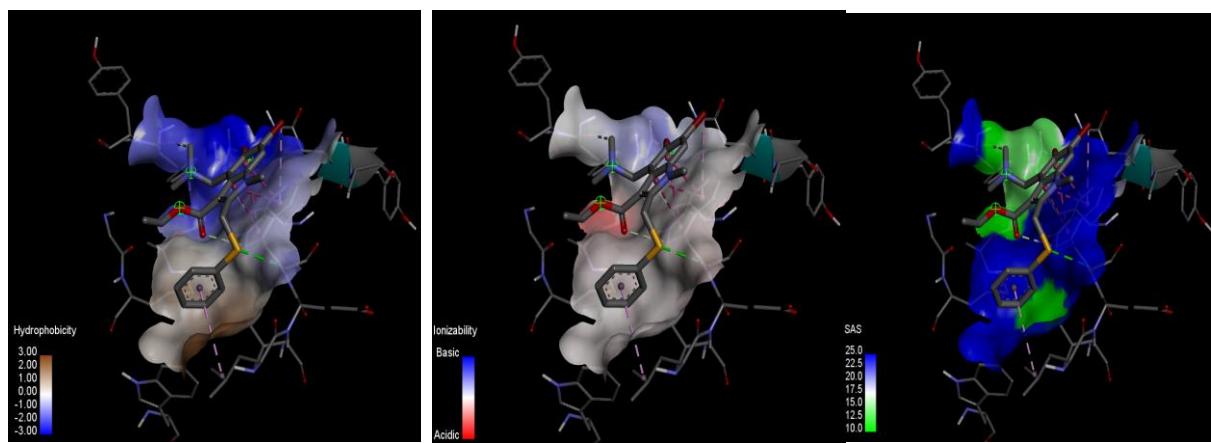
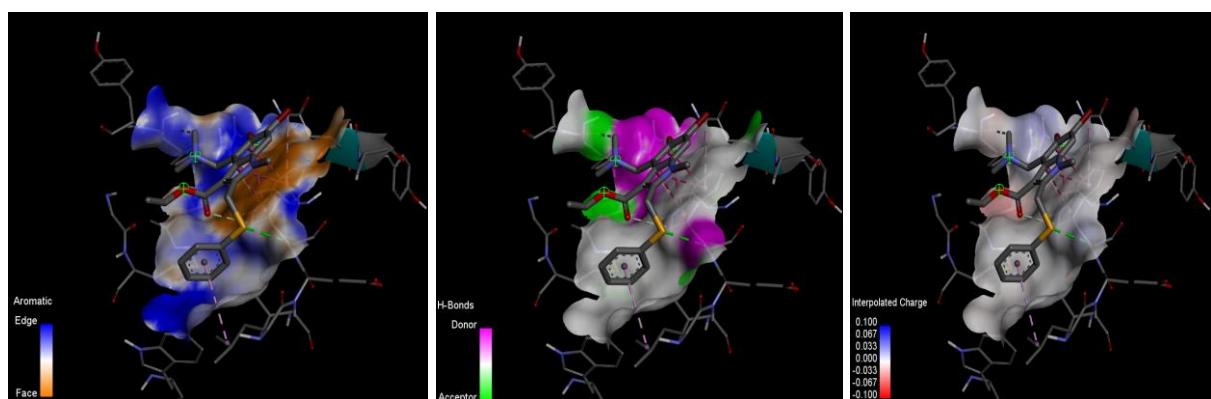
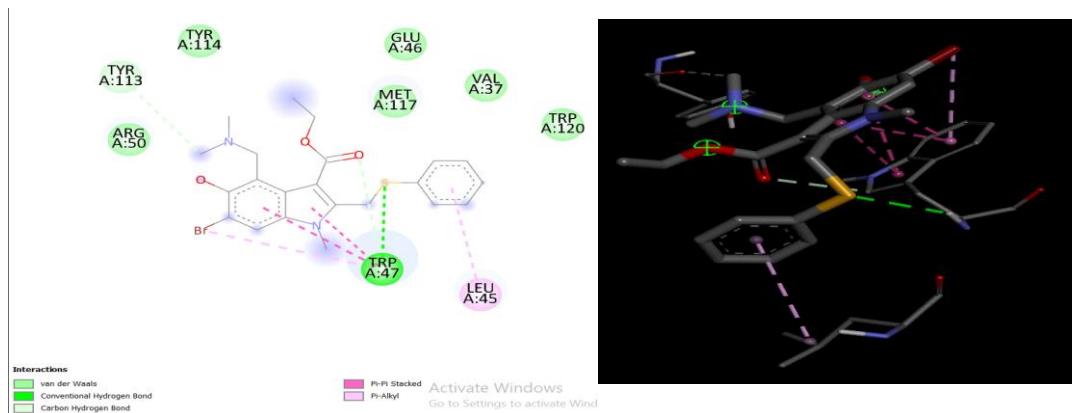
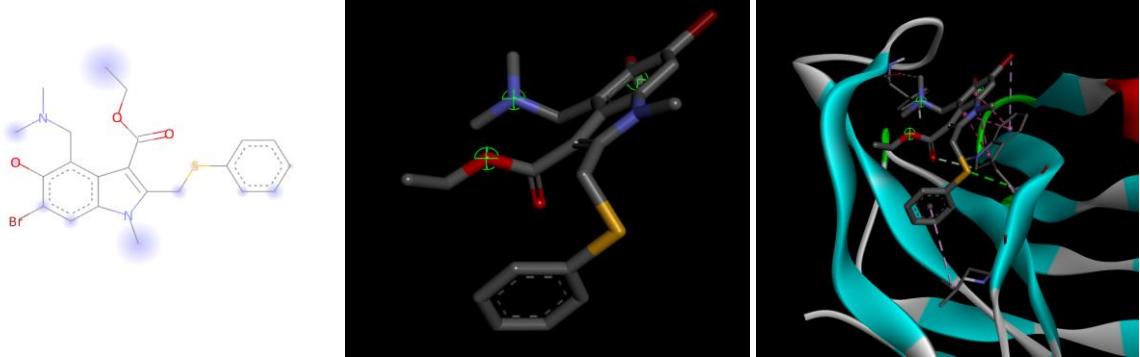
Arbidol Ligand

Minimise Energy



Choose Model





Conclusion

In this project, we've covered the process of molecular docking using PyRx and Biovia, highlighting their applications in drug discovery, particularly for targeting SARS-CoV-2.

Key Points:

PyRx Overview: PyRx is a versatile virtual screening tool that helps dock small molecules with proteins, aiding in computational chemistry.

Biovia Docking: Biovia offers advanced molecular docking tools, enabling detailed simulations and accurate interaction predictions.

Experimental Results:

6LU7 Protein: Docking experiments identified potential inhibitors that could block SARS-CoV-2 replication.

7DPP Protein: Studies revealed compounds that might disrupt the virus's function.

BD55-1239 Fab and Omicron RBD: Analyzed the interaction between an antibody and the Omicron variant, providing insights for antibody-based therapies.

Takeaways:

Computational Docking Efficacy: PyRx and Biovia are effective in finding potential therapeutic compounds, crucial for drug discovery.

Impact on SARS-CoV-2 Research: Our experiments demonstrate the importance of adaptable computational methods to tackle evolving viral threats.

Future Directions: Ongoing research with these tools is essential for developing new treatments and understanding viruses, aiding in pandemic management.