2025
12(1), 1251

Chemical Biology
LETTERS

Beyond trial and error: Leveraging advanced software for Therapeutic discovery

Vanshika Rustagi[1#], Shradheya R R Gupta[1#], Archana Singh[2], Indrakant Kumar Singh[1,3*]

[1]Molecular Biology Research Lab, Department of Zoology & DBC i4 Centre, Deshbandhu College, University of Delhi, Kalkaji, New Delhi, 110019, India. [2]Department of Plant Molecular Biology, University of Delhi South Campus, Benito Juarez Road, Dhaula Kuan, New Delhi 110021, India. [3]Delhi School of Public Health, Institute of Eminence, University of Delhi, Delhi, 110007 India

Review

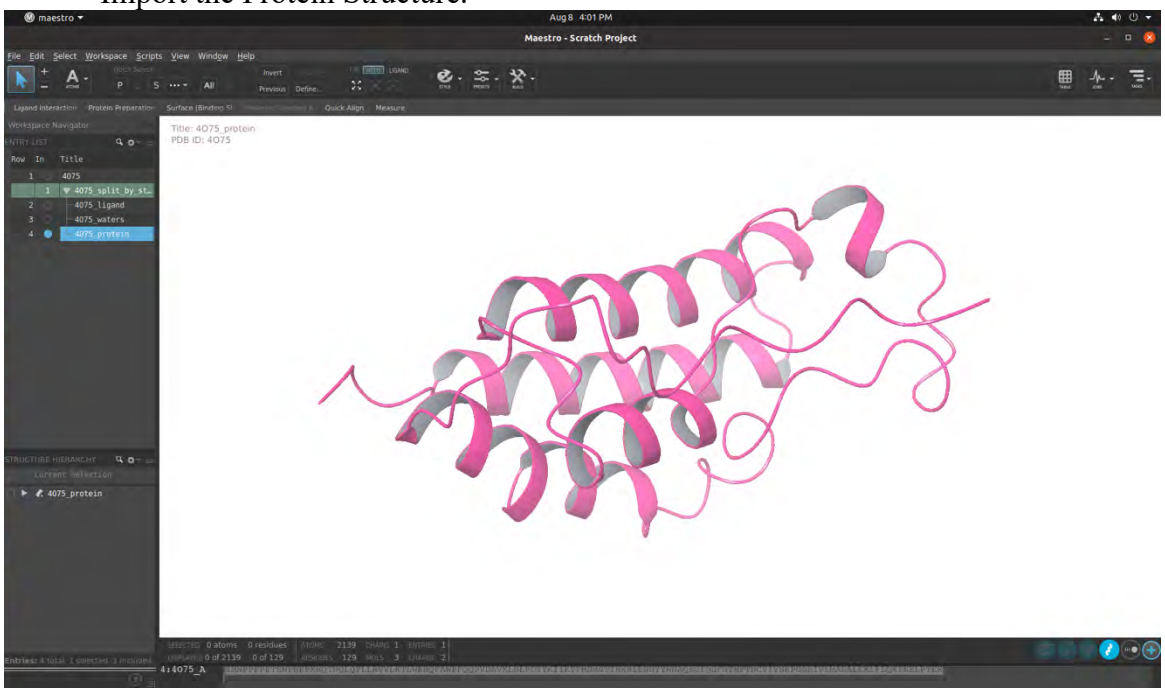
Supplementary Information

# Equal Contribution * Corresponding author: iksingh@db.du.ac.in

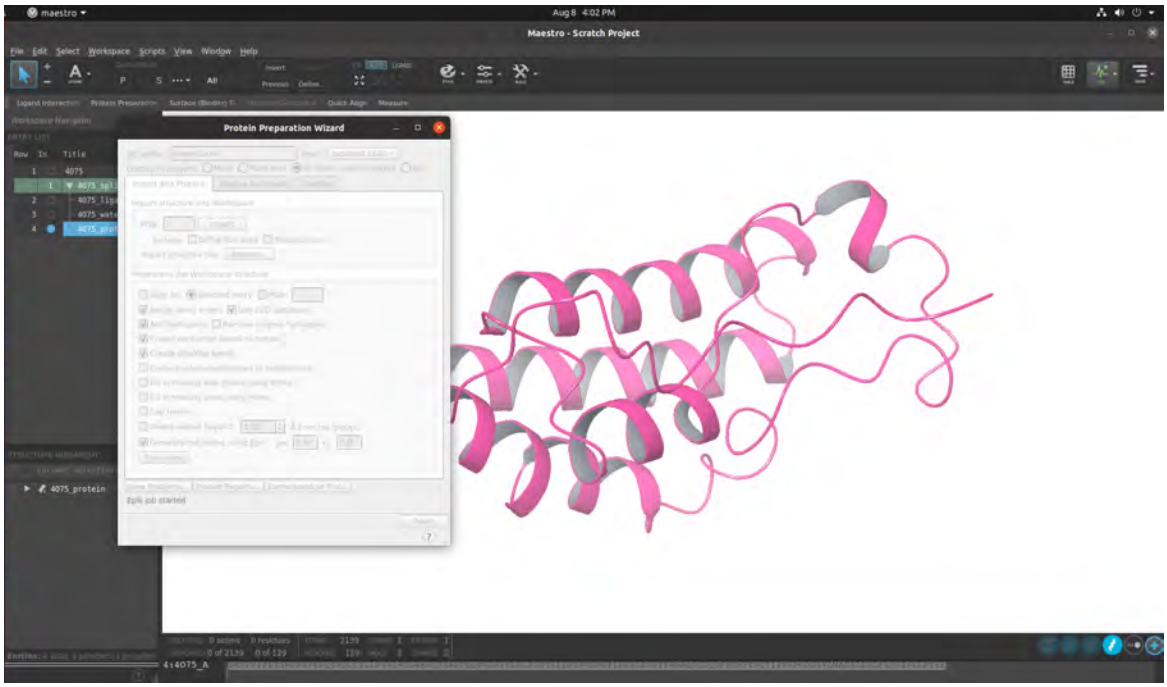
URN:NBN:sciencein.cbl.2025.v12.1251
DOI:10.62110/sciencein.cbl.2025.v12.1251

https://pubs.thesciencein.org/cbl

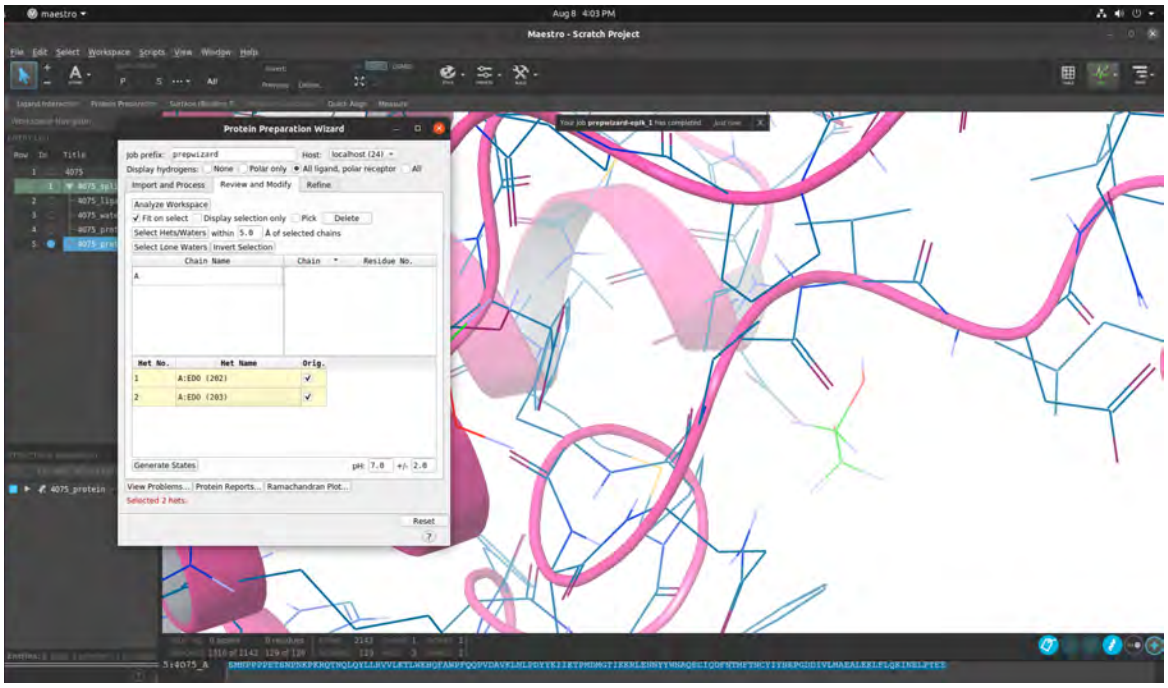
1. **Step 1: Protein Preparation:**
   - Import the Protein Structure.



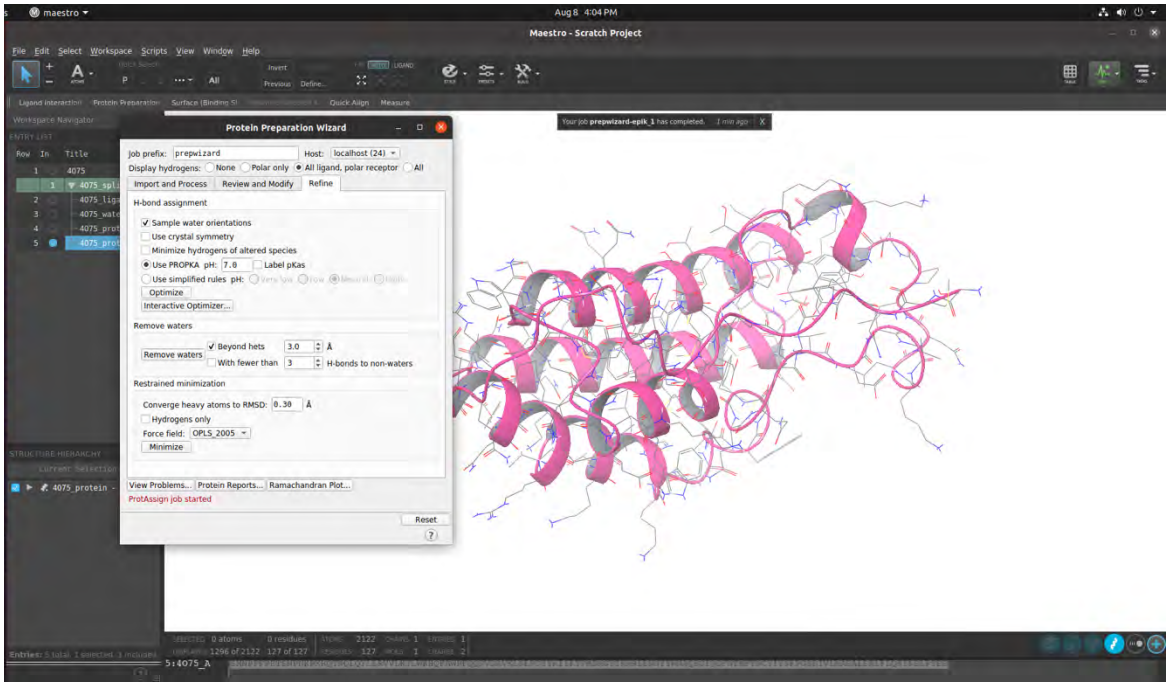
2. Go to Workflows > Protein Preparation Wizard.
   - Assign bond orders, Add hydrogens, Create disulfide bonds if necessary and select Cap termini if the protein is incomplete.
   - Click **Preprocess** to execute the initial steps.



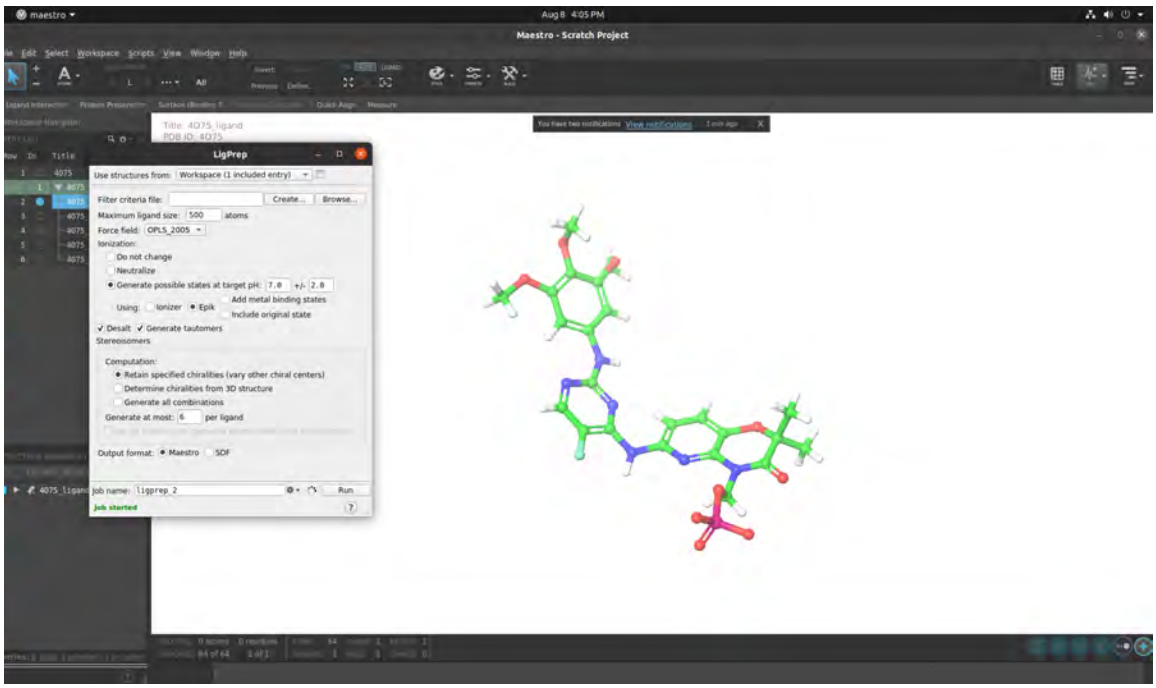
3. Click Analyze workspace and delete extra chains and water atoms.



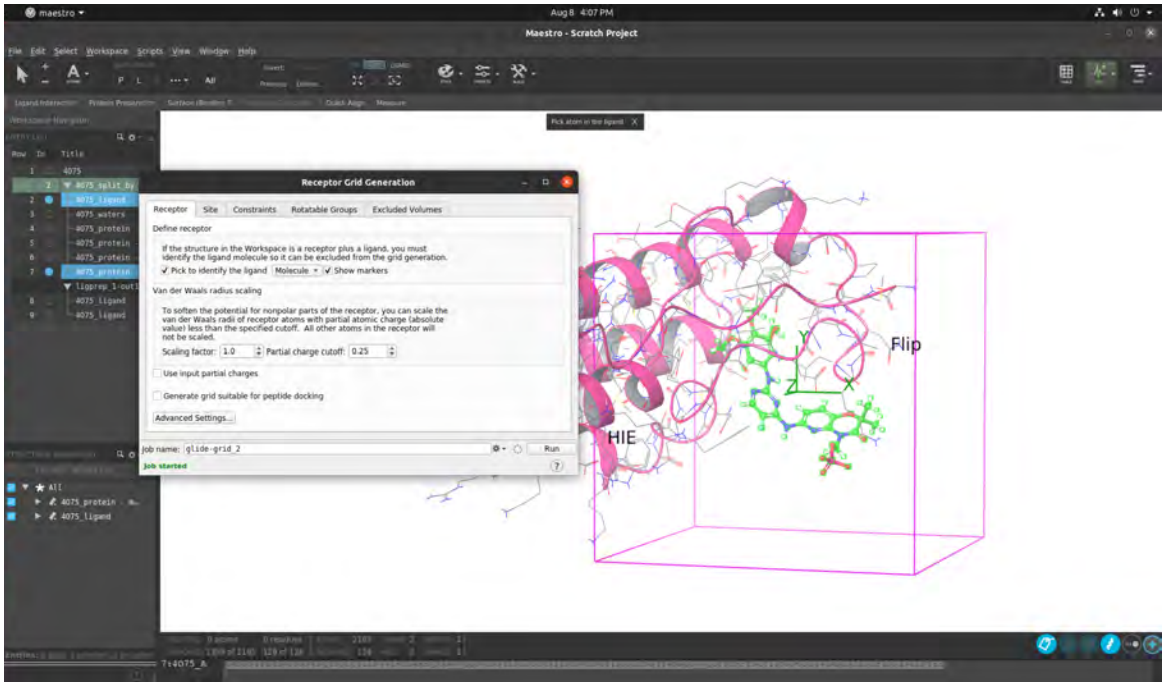
4. Generate het states, optimize hydrogen bonds and minimize the structure using the OPLS2005 force field.



5. **Step 2: Ligand Preparation**
   - Use the **LigPrep** module for ligand preparation.
   - Import the ligand structure
   - Generate tautomers and ionization states
   - Use the OPLS2005 force field for minimization.
   - Run the LigPrep job to obtain the prepared ligands.

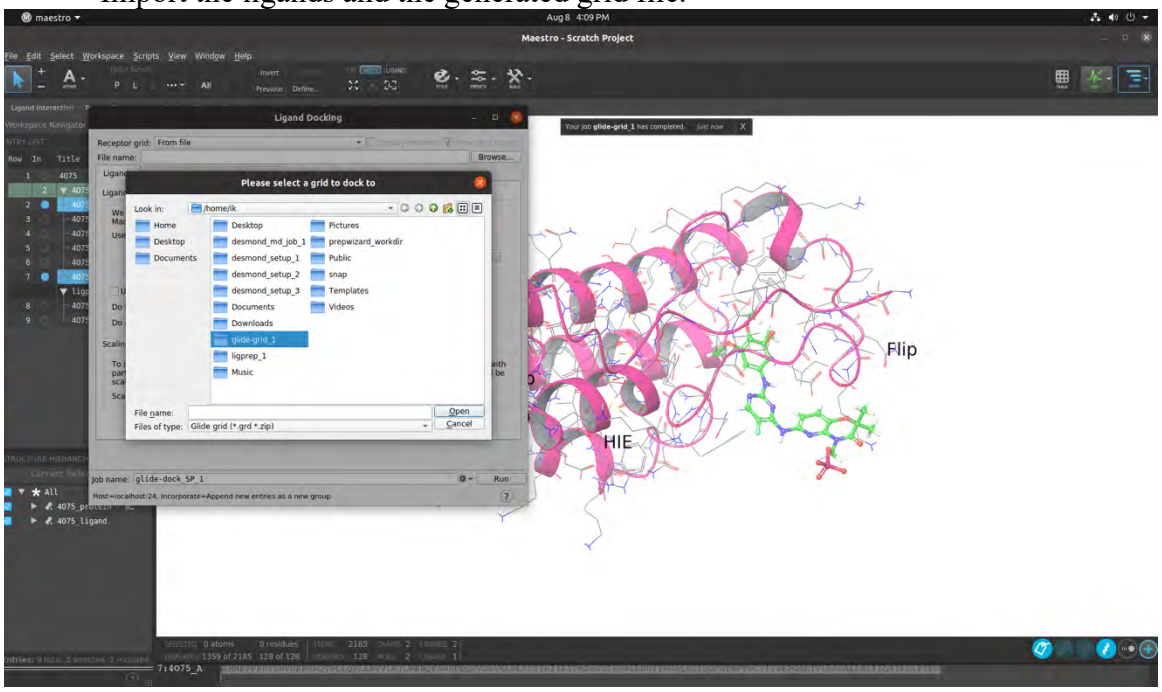


6. **Step 3: Grid Generation**
   - Define the Binding Site.
   - Import the prepared protein structure.
   - Define the receptor grid box by centering it on the ligand if a co-crystallized ligand is present or by selecting the active site residues.
   - Set Grid Parameters
   - Generate the Grid

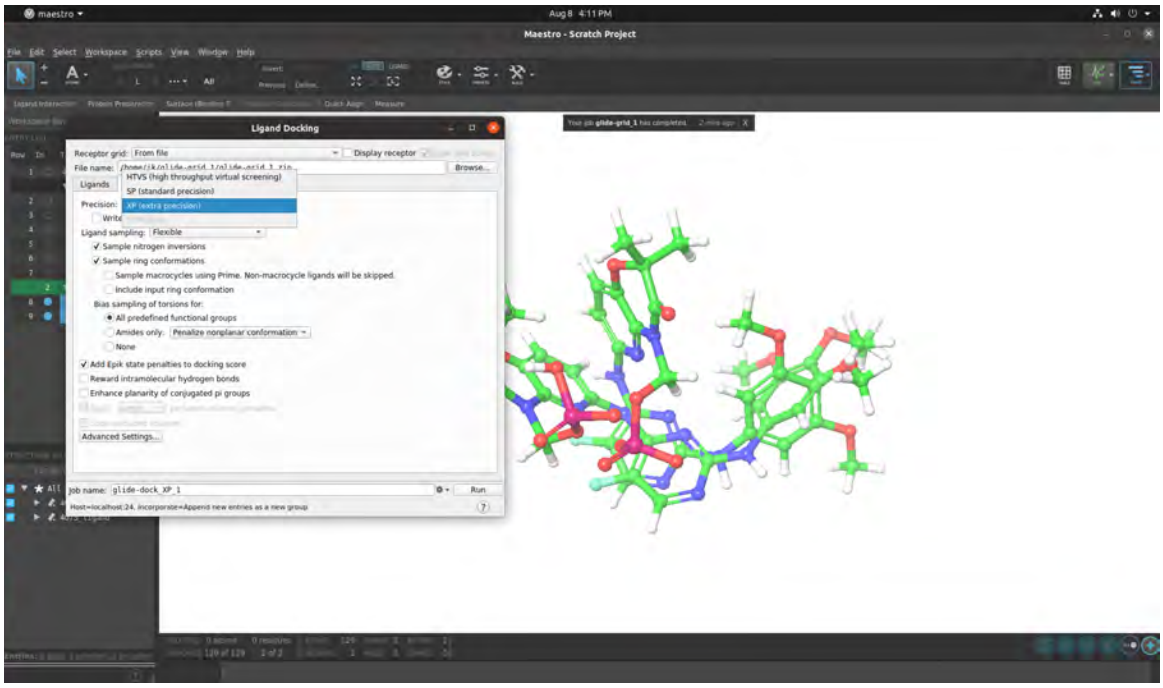


7. **Step 4: Docking (XP Docking)**

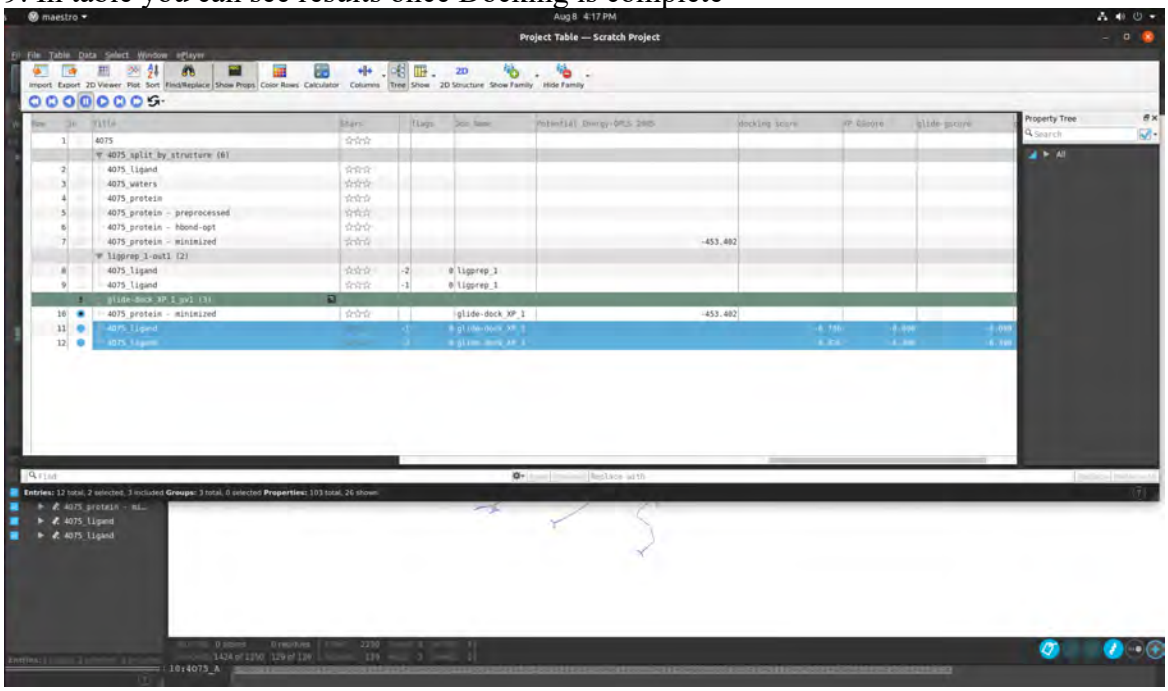
- Go to Applications > Glide > Ligand Docking
- Import the ligands and the generated grid file.



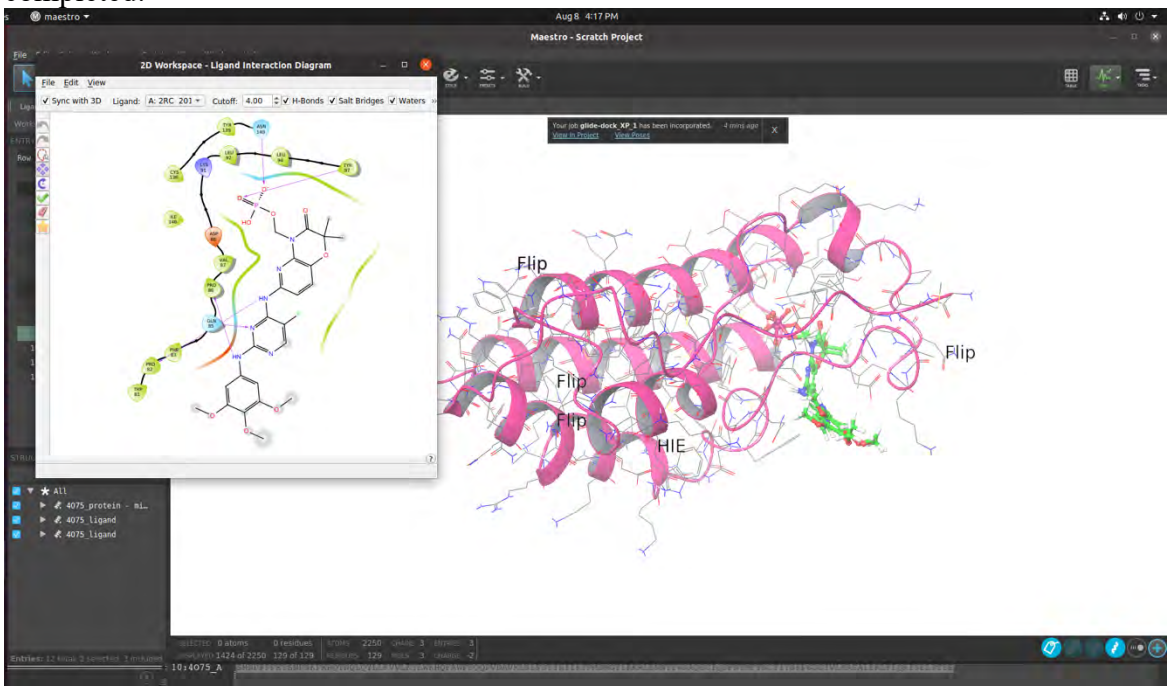
8. Configure Settings and Run the Docking Job



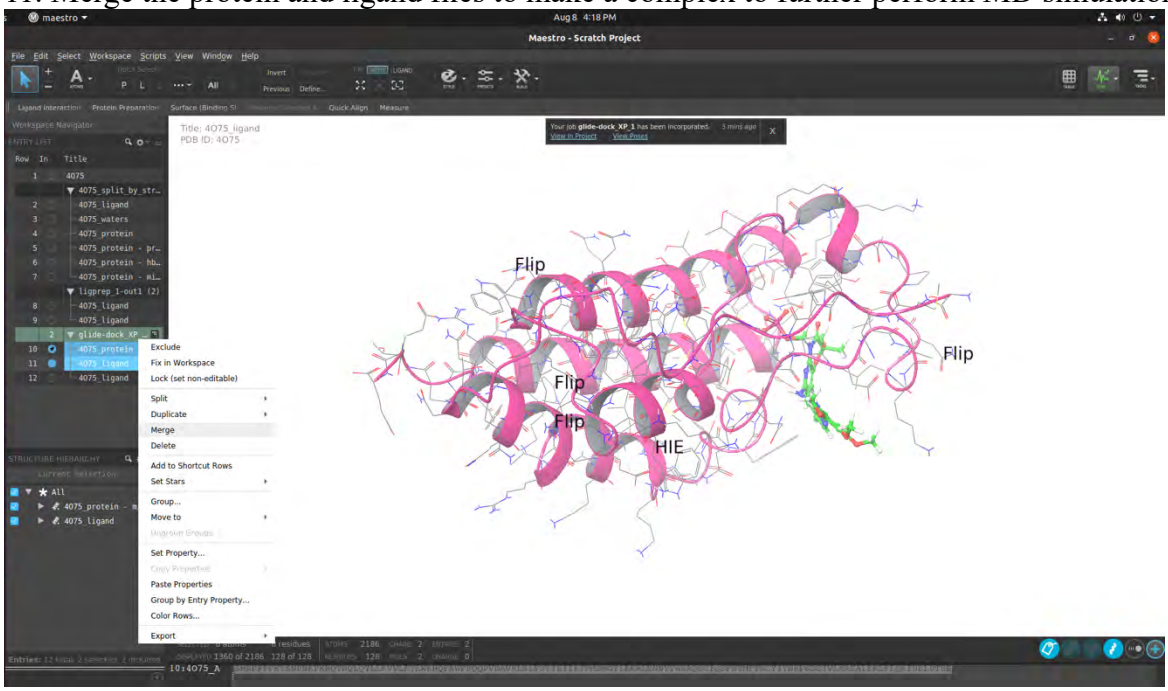
9. In table you can see results once Docking is complete



10. Further Docking interactions between protein and ligand can be seen once the job is completed.

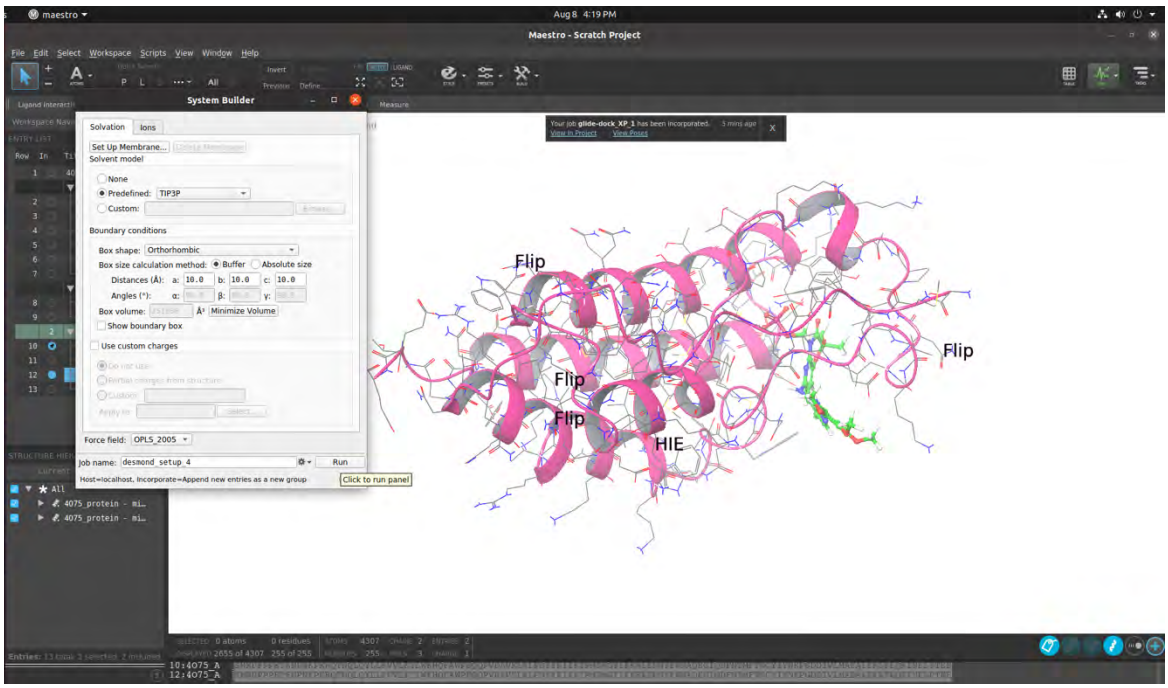


11. Merge the protein and ligand files to make a complex to further perform MD simulation



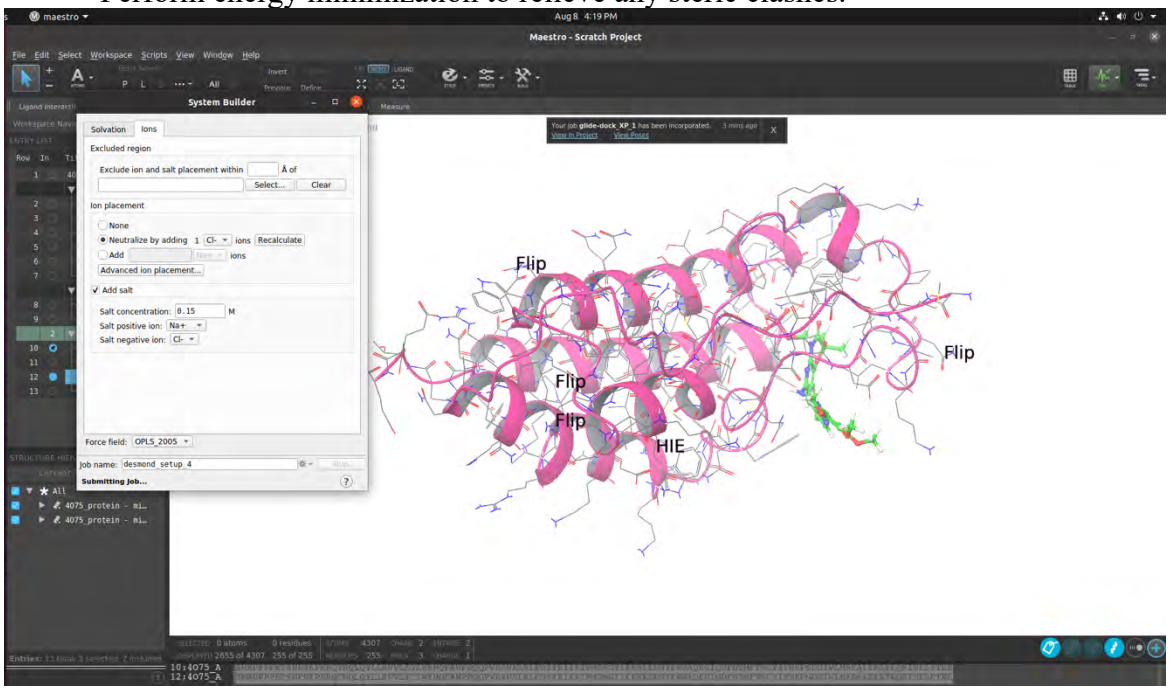
12. **Step 5: System Preparation for MD Simulation**

- Import Docked Complex
- Go to Applications > Desmond > System Builder**.**
- Define the solvation model:
- Choose a suitable solvent model (e.g., TIP3P water).
- Minimize volume.

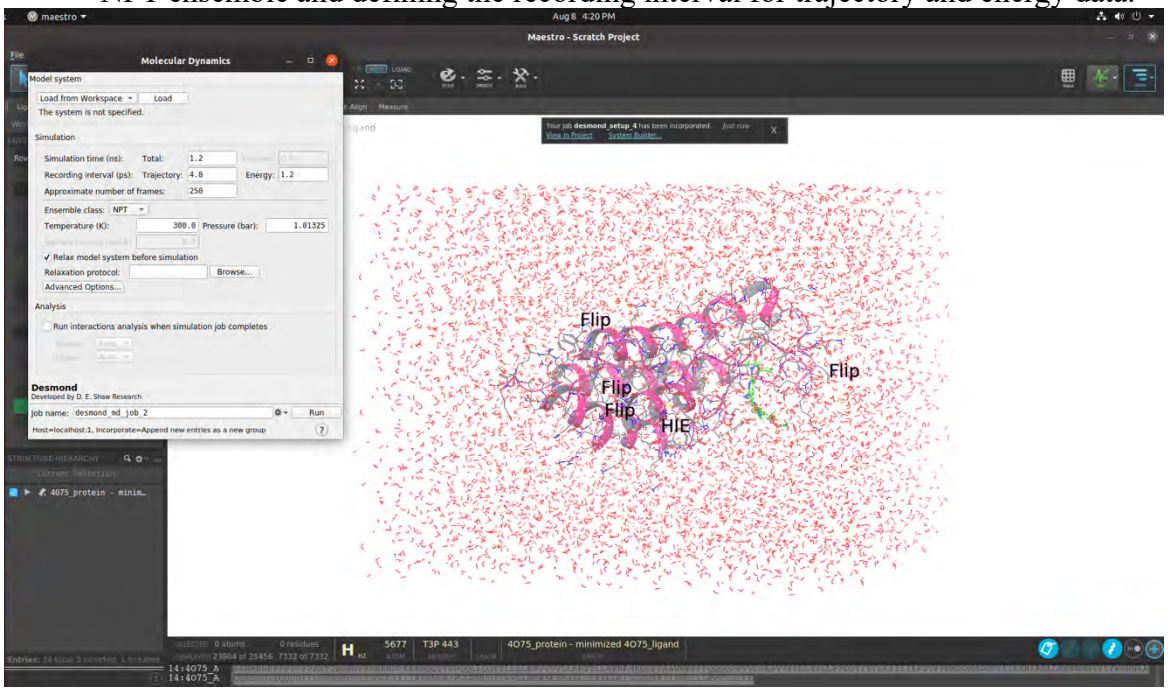


13. Set the buffer distance (e.g., 10 Å around the complex).

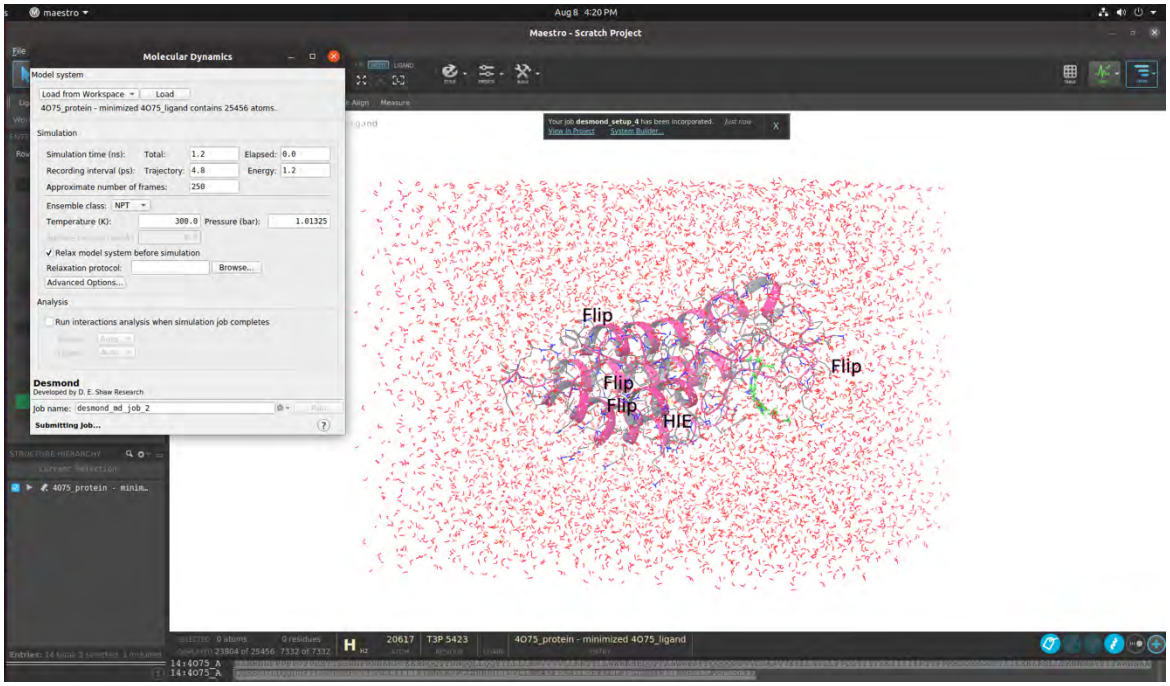
- Add counterions (e.g., Na+ or Cl-) to neutralize the system.
- Add salt (e.g., 0.15 M NaCl) to mimic physiological conditions.
- Perform energy minimization to relieve any steric clashes.



14. **Step 6: Molecular Dynamics Simulation**
    - Go to Applications > Desmond > Molecular Dynamics.
    - Define Simulation Parameters. Such as simulation time, temperature, selecting the NPT ensemble and defining the recording interval for trajectory and energy data.



15. Perform equilibration runs
    - After equilibration, run the production MD simulation.



16. **Step 7: Post-Simulation Analysis**
    - Use the Simulation Interaction Diagram tool to analyze interactions, RMSD, RMSF, and other properties