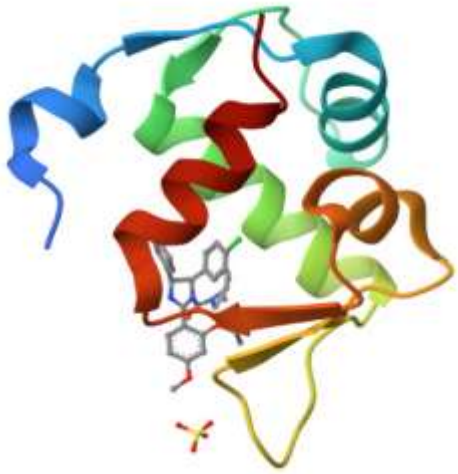
# Computational Molecular Docking Analysis of Ritonavir Binding to MDM2 Protein (PDB: 4HG7)

**INTRODUCTION**: MDM2 is a negative regulator of the tumour suppressor p53 and an attractive target in cancer drug discovery. In this project I performed molecular docking to evaluate the *possible* binding of Ritonavir (Drug Bank ID: DB00503) to MDM2 (PDB ID: 4HG7). These computational results are hypothesis-generating and require experimental validation.

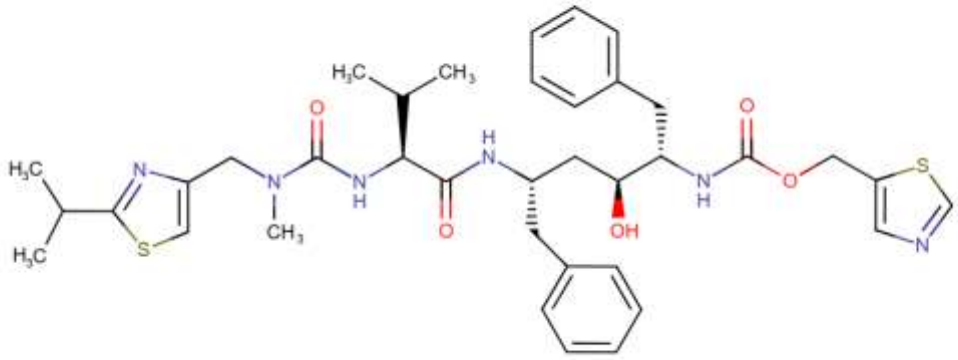
**TOOLS:** RCSB PDB, Drug Bank, ChemSketch, CB-Dock (online docking server).

**PROCEDURE:**

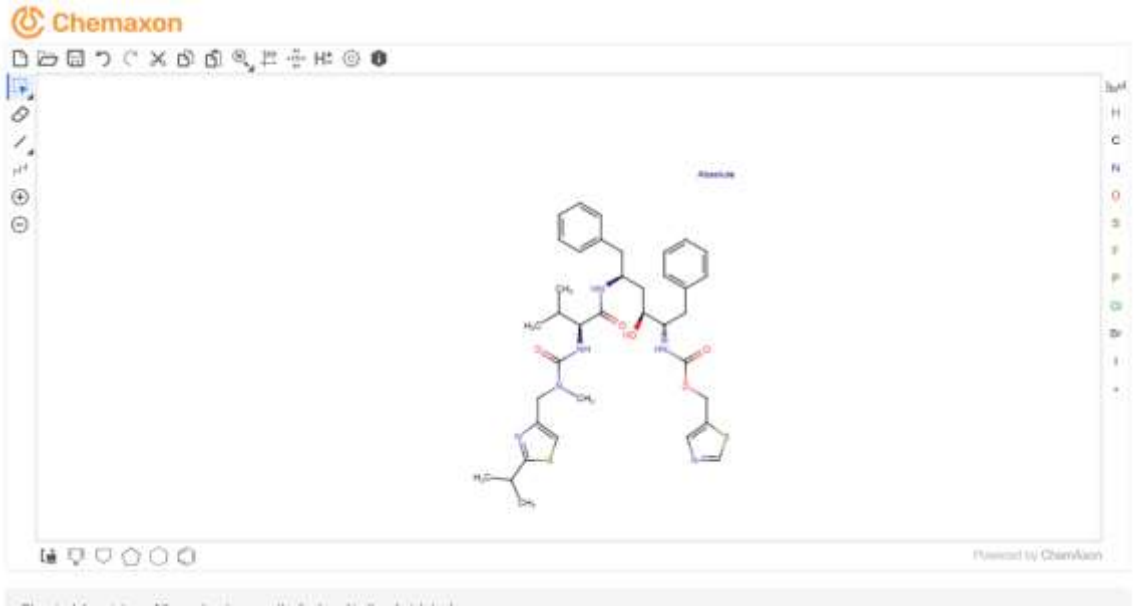
1. Protein selection: I choose this 4HG7



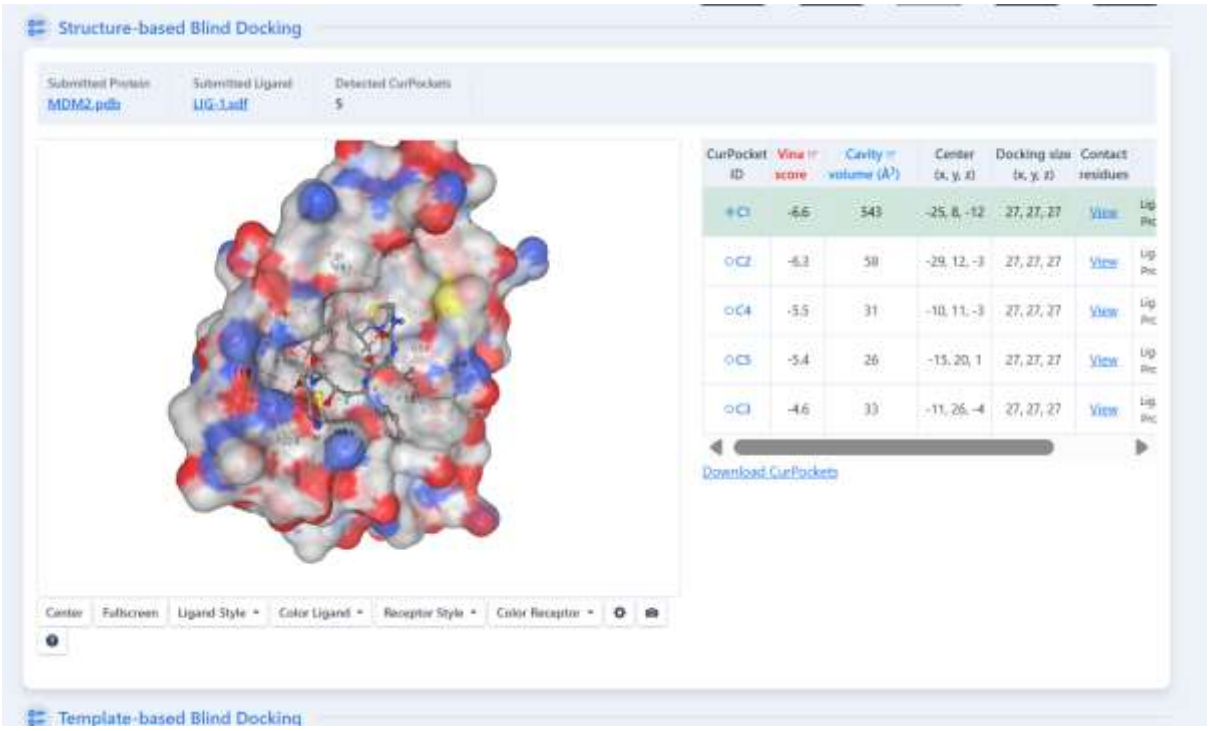
2. Ligand selection: the ligand choose is Ritonavir having drug bank id DB**00503**




3. **Structure analysis:** for the protein after taking PDB structure than visualize under pymol and remove water molecules and ligand and clean the molecule and also use chem sketch for the ligand molecule preparation using smile.




4. Docking: for this I use tool CB DOCK upload the protein structure and the ligand molecule and run the dock application and get the following docking result among them pocket c1 is the best as it has lower vina value which tell binding affinity and cavity volume is high.




**RESULT**: The docking study was performed using CB-Dock with Ritonavir (DB00503) docked into MDM2 (PDB ID: 4HG7). Among the predicted binding sites, pocket C1 showed the most favourable result with:

- Binding affinity (Vina score): –6.6 kcal/mol

- Cavity volume: 543 Å³
- Key interacting residues: (e.g., F55, V93, I99 – update based on your CB-Dock output)

**DISCUSSION:** The docking score of –6.6 kcal/mol suggests a moderate binding affinity of Ritonavir to MDM2. The large cavity volume of pocket C1 allowed the ligand to be accommodated without steric clashes, supporting stable binding. Since MDM2 is a negative regulator of the tumour suppressor p53, blocking MDM2 could restore p53 activity and promote apoptosis in cancer cells. Ritonavir, originally an HIV protease inhibitor, has been studied for repurposing in oncology due to its potential to interfere with signalling pathways. These results support further investigation of Ritonavir as a possible MDM2 inhibitor.

**CONCLUSION:** This docking study suggests that Ritonavir may bind to the C1 pocket of MDM2 with a predicted Vina score of –6.6 kcal/mol and contacts to key residues. These computational findings indicate a possible repurposing opportunity, but they are preliminary and require validation via molecular dynamics simulations and experimental assays.

**FUTURE WORK:**

- Perform MD simulations (e.g., 100 ns, 3 replicates) to evaluate binding stability (RMSD, H-bonds, contacts).
- Run MM-PBSA/MM-GBSA on MD snapshots for improved binding-energy estimates and per-residue decomposition.
- Compare Ritonavir's predicted binding/energetics to a known MDM2 inhibitor (e.g., Nutlin-3a) as a reference.
- If computational results are promising, propose experimental validation: SPR/ITC binding assays and cell-based p53 activation assays.