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Prioritizing Commercial Analogues of Previous USP5 ZnF-UBD Hits

Objective: To expand the chemical series of previous hits of USP5 zinc finger ubiquitin binding domain (ZnF-UBD) by docking commercially available chemical analogs and prioritizing chemical analogues to exploit new interactions in the binding pocket of USP5 ZnF-UBD

Experiment & Results:

Commercial analogs of compounds DAT00000194a and DAT00000201a (Table 1) (see attached enamine_194.sdf, enamine_201.sdf) and fragments from Molecular Forecaster selection (MFI.sdf) were docked to USP5 ZnF-UBD with GLIDE.

1. PDB files of co-crystal structures were uploaded in Molsoft ICM-Pro (PDB: 6NFT, 6DXH) and missing side chains were added. The structure file was saved as a PDB and opened in Schrodinger Maestro.
2. The protein was prepared using 'Protein Preparation Wizard'. The structure was preprocessed for H-bond assignment, and H-bonds were optimized and minimized at pH 7.3.
3. 2D sdf files of ligands to be docked against the protein were prepared from substructure searches against Enamine's REAL database of 700 million chemically accessible compounds.
4. Ligprep: sdf files of the ligands were converted to 3D format
5. Receptor Grid Generation: receptor, and size of the grid for the site of docking was chosen. H-bond constraints: NH side chain R221, NH backbone R221, OH side chain Y261
6. Ligand Docking: sdf files of ligands from LigPrep uploaded
   a) Setting: SP (standard precision); ligand sampling: flexible
   b) Enhance planarity of pi groups
   c) Core comparison; core molecule: COO-
   d) Tolerance: 1.0
   e) Constraints: H-bond (NH side chain R221, NH backbone R221, OH side chain Y261)
7. Docking results were exported to an sdf file and opened in ICM-pro and clustered. Compounds were selected based on docking pose, score, chemical groups, and cost (Figure 1). Please see attached .icb file for details. 20 compounds were ordered (finalcpdorder.xlsx/finalcpdorder.sdf).

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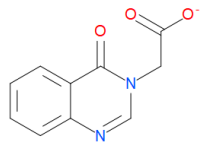
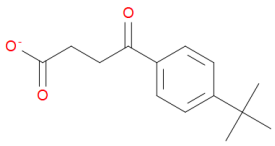
Table 1. USP5 ZnF-UBD Hits

SGC ID	Compound Structure	PDB	SMILES
DAT00000194a		6NFT	C(C([O])=O)N1C=Nc2ccccc2C1=O
DAT00000201a		6DXH	CC(C)(C)c1ccc(cc1)C(CCC([O])=O)=O

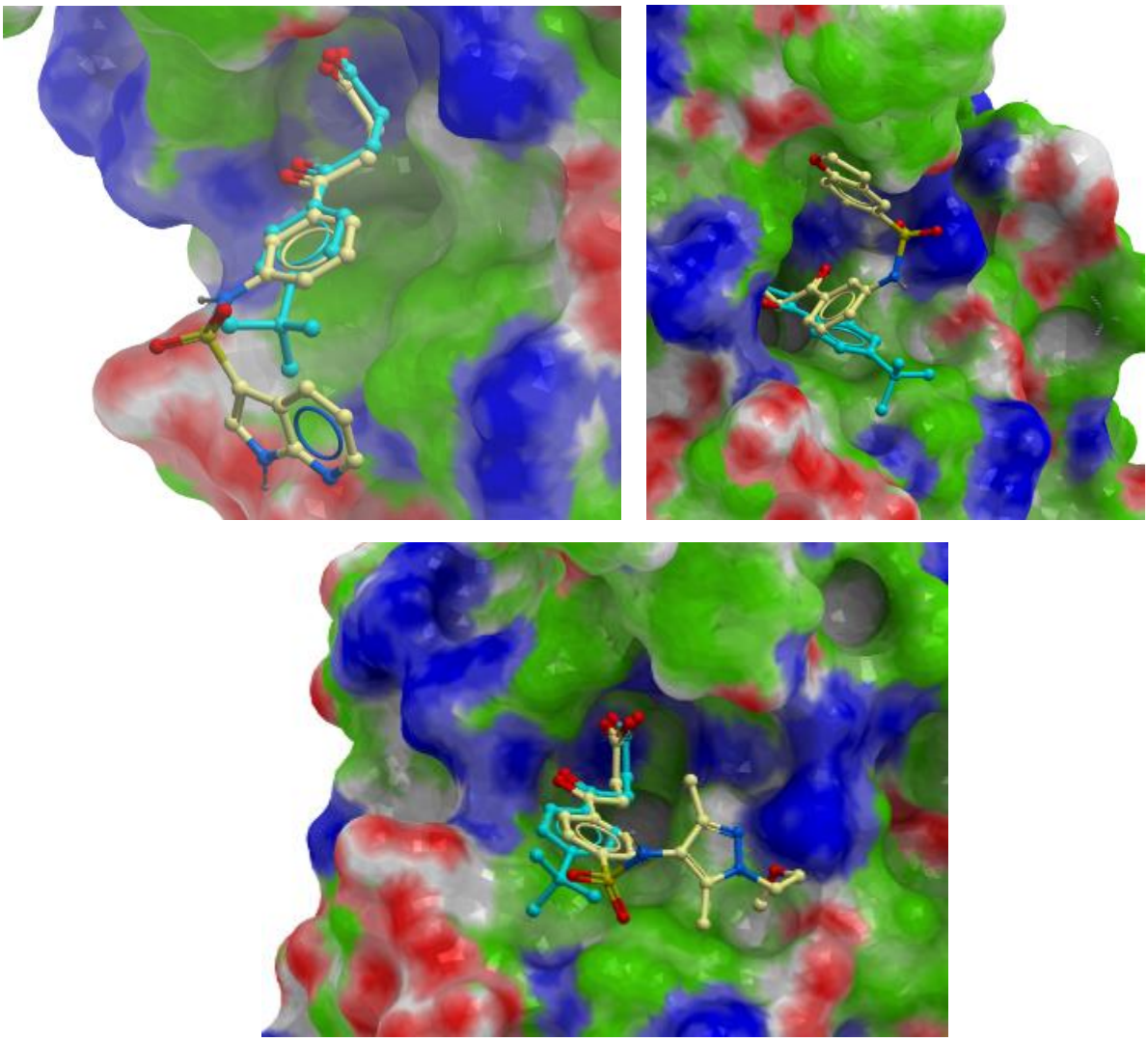


Figure 1. Surface representation of docked poses of DAT00000201 analogues making diverse sets of interactions in the binding pocket of USP5 ZnF-UBD (PDB: 6DXH)

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Conclusions:

Selected compounds from the docking study have been ordered. I'll be testing these compound against USP5 ZnF-UBD in a surface plasmon resonance assay in a few weeks and if the compounds bind to the protein domain with improved affinity, I will be co-crystallizing the ligands with the protein domain to investigate if the protein-ligand interactions are similar to the docked poses.