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Expansion of UBTR012574 Chemical Series Pt. II

Objective: Docking analogues of UBTR012574 against the USP5 zinc finger ubiquitin-binding domain (ZnF-UBD) to prioritize compound synthesis.

Previous expansion of the chemical series shed some insight into the structural activity relationship (SAR) (Figure 1). UBTR020988a which has an amide resulted in weaker potency for USP5 but is 6-fold selective for USP5 over HDAC6. Keeping the SAR in mind, we hope to improve potency and retain selectivity for USP5 ZnF-UBD.

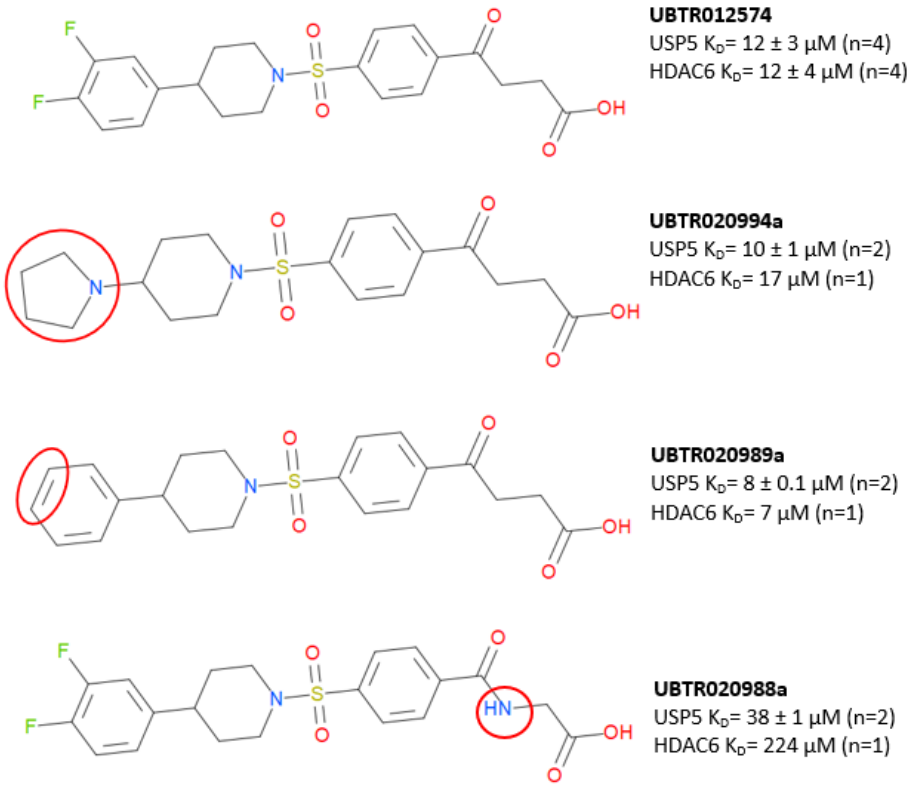

Figure 1. UBTR012574 chemical series

Methods and Results:

1. PDB file of co-crystal structure of USP5 ZnF-UBD with UBTR012574 (UBTR012574.pdb) was uploaded in Molsoft ICM-Pro and converted to an ICM object and missing side chains were added. The resulting 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 was prepared based on available chemistry materials and was generated by chemists at OICR: Dr. Carlos Zepeda and Hector Gonzalez-Alvarez (usp5v1.sdf, usp5v2.sdf) and converted to 3D format using GLIDE's Ligprep. It should be noted that all docked analogues are amides, to retain selectivity based on SAR (UBTR20988) as well as easier chemistry.
4. Receptor Grid generation: receptor, and size of the grid for the site of docking as chosen.

5. Ligand docking:
    a. Setting: SP (standard precision); ligand sampling: flexible
    b. Tolerance: 1.0
    c. H-bond constraints: NH-side chain of R221, NH backbone of R221
6. Docking results were exported as sdf file (glide_docked_1_2.sdf) and poses were viewed with ICM-pro (docked_analogues.icb).

Conclusions & Future Directions

Of the docked analogues, there were two docking poses where (1) an aromatic ring makes pi-stacking interactions with Y223 (Figure 2- cyan) or (2) an ammonium group forms an H-bond with D264 (Figure 2- green).

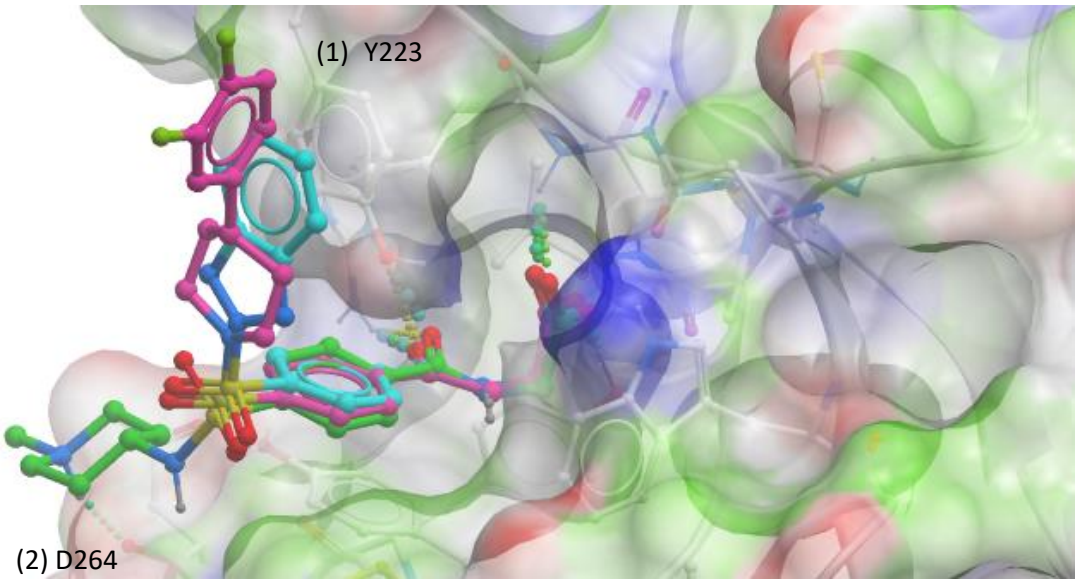

Figure 2. USP5 ZnF-UBD co-crystal structure with UBTR012574 (magenta) and docked poses of analogues (cyan & green)

This data was shared with chemists to be used to prioritize the synthesis of the first subset of analogues. The compounds with the best docking scores and poses will be synthesized in the first instance. Starting materials have been ordered; however, synthesis has been put on hold for COVID-19 related lab closures. Once labs re-open, we hope to get started on synthesizing and testing some of these compounds.