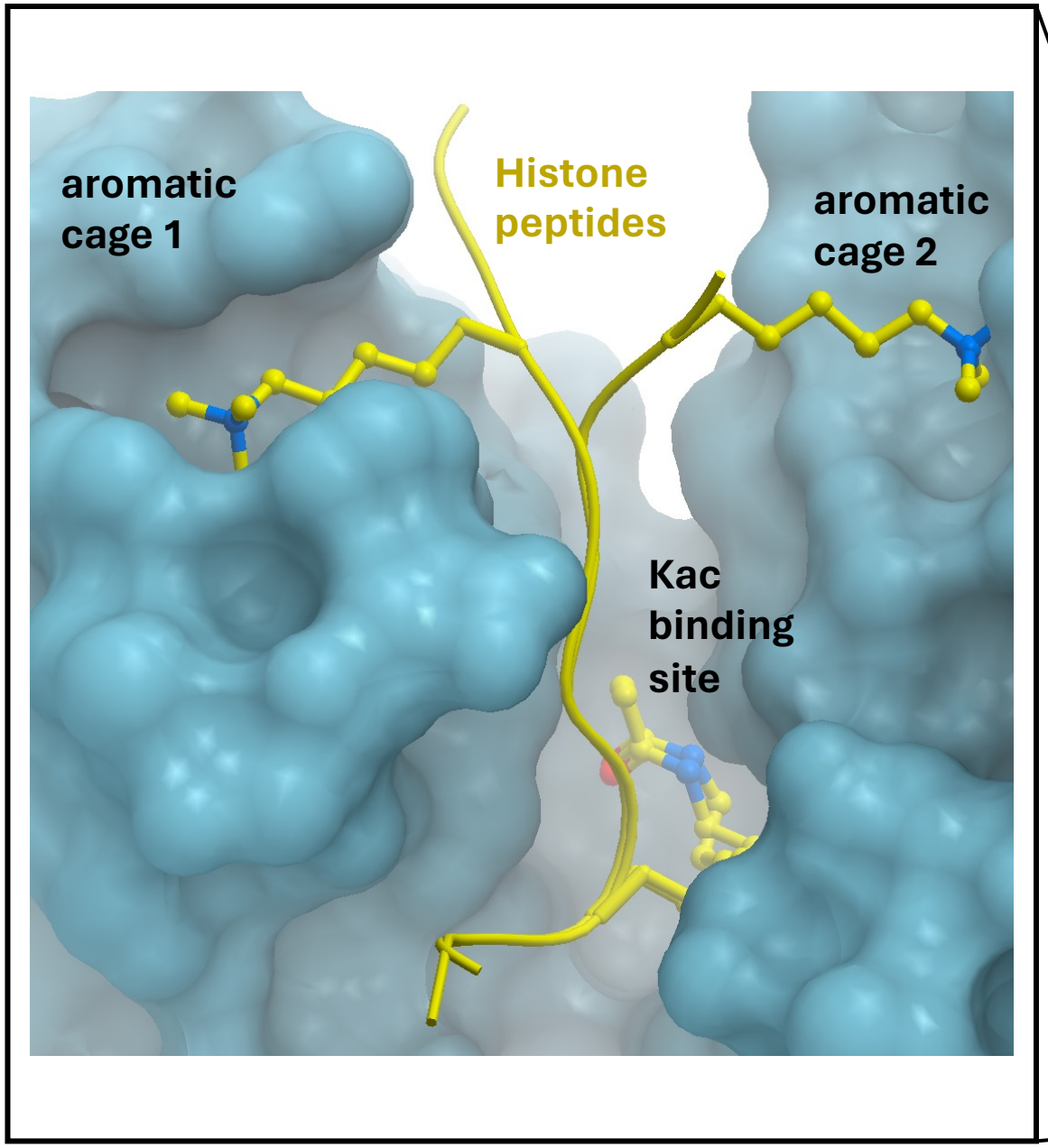
SETDB1 STRUCTURE OVERVIEW

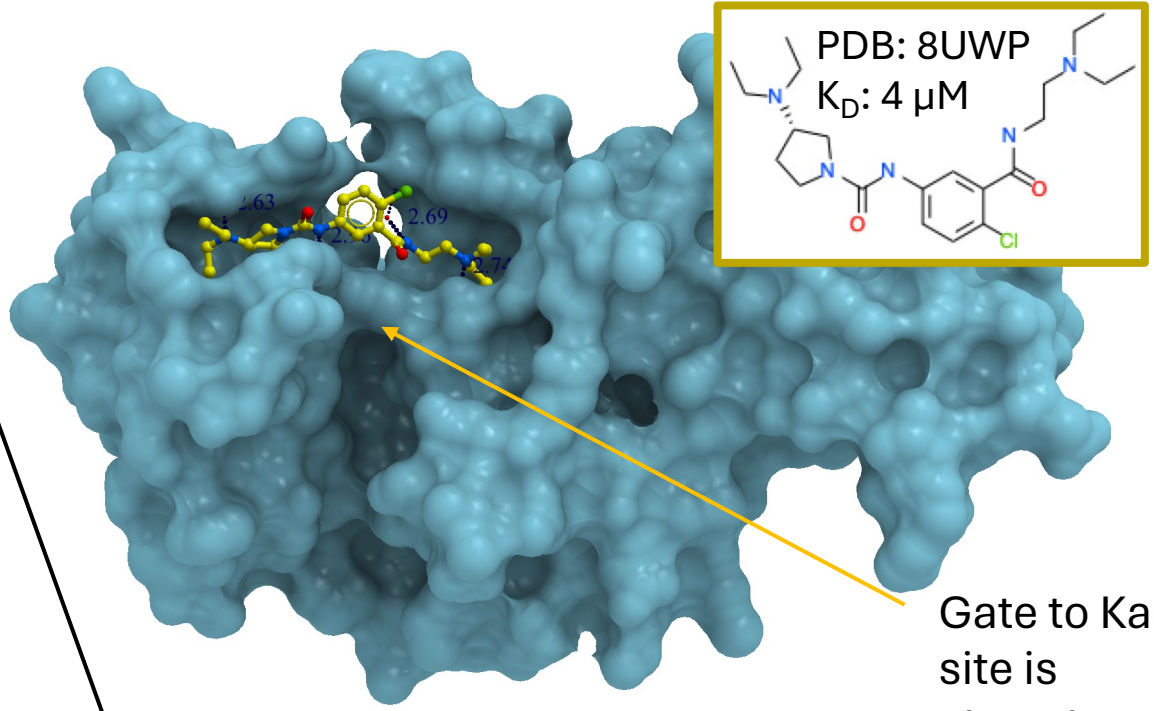
Methylated lysine sidechains from histone peptides occupy two aromatic cages that are sometimes occluded in the absence of ligand. An acetylated lysine occupies a third cavity in the peptide binding groove.

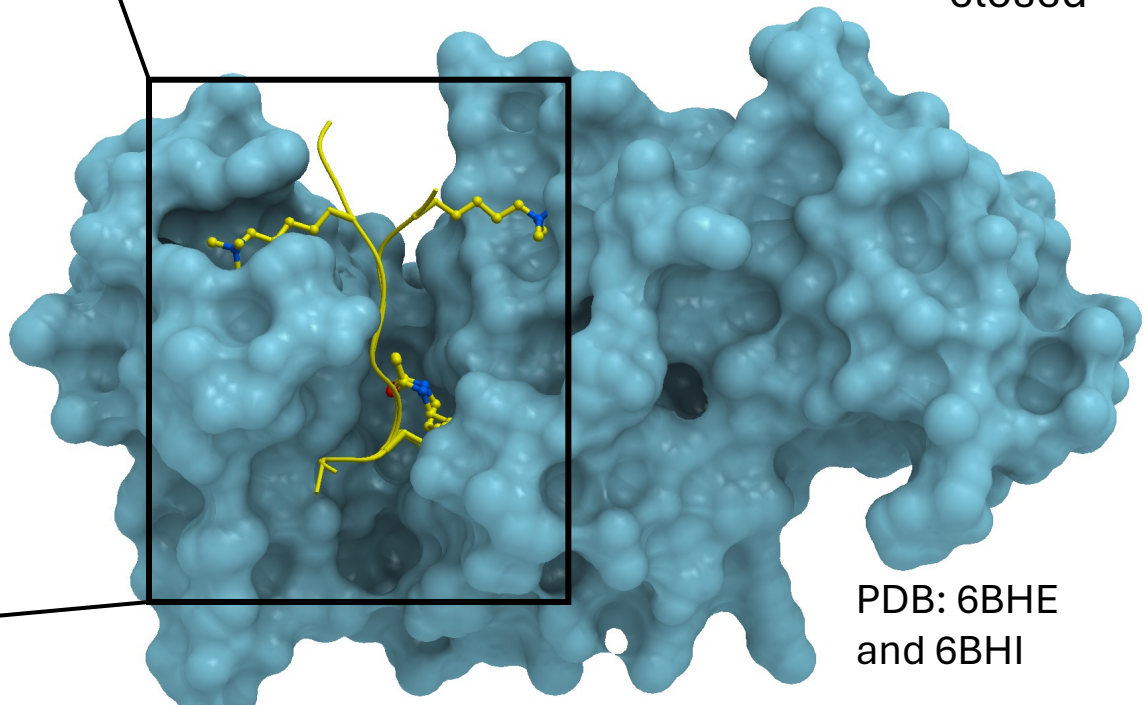
The 100 nM ligand in 7CJT exploits one of the aromatic cages and sits at the opening of the Kac binding site.

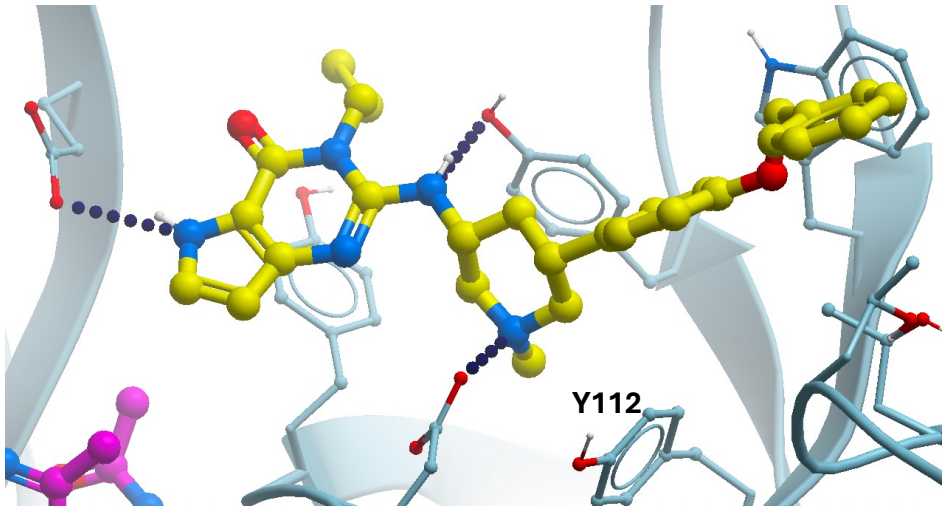
The 4 μM ligand in 8UWP exploits both aromatic cages. Access to the Kac binding pocket is partially blocked by Y112 but is open in other crystal structures (ex: PDB 6BHE, 6BHI or 7CJT).

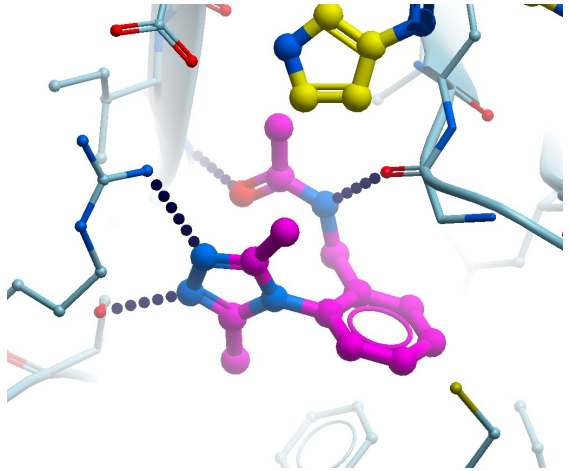
Efforts to optimize the 3 mM ligand in 6AU3 were unsuccessful, which may reflect underlying conformational strains associated with the plasticity of the binding site.

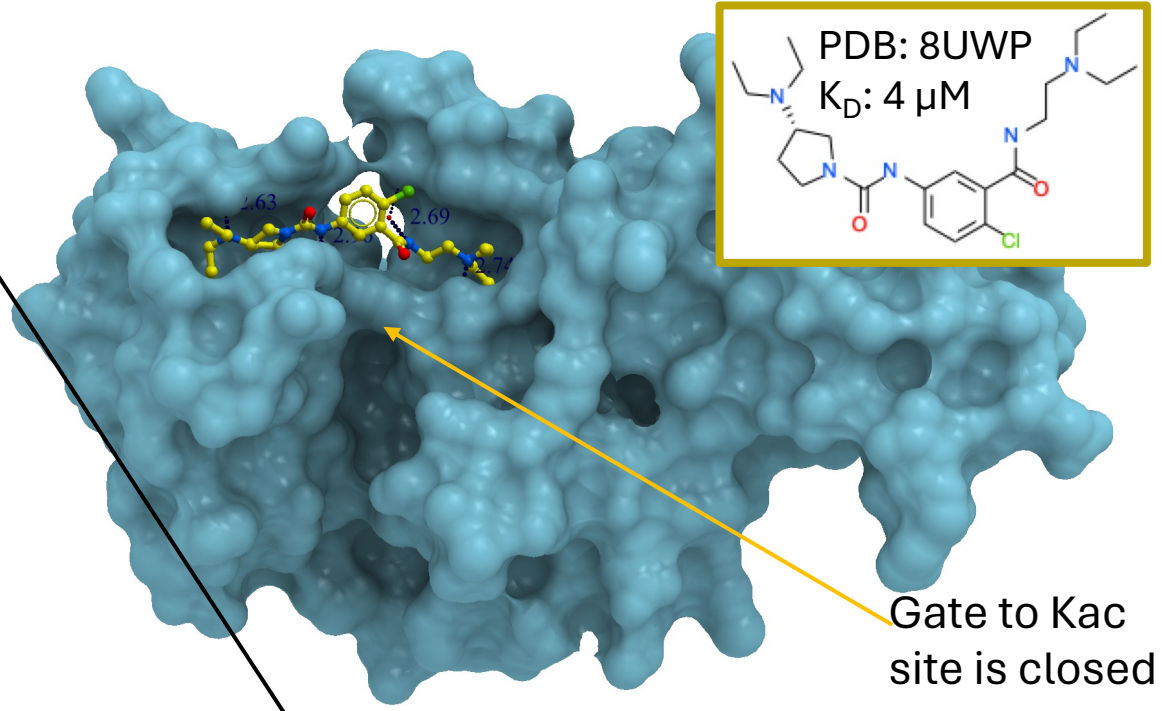

aromatic
cage 1
Histone
peptides
aromatic
cage 2
Kac
binding
site

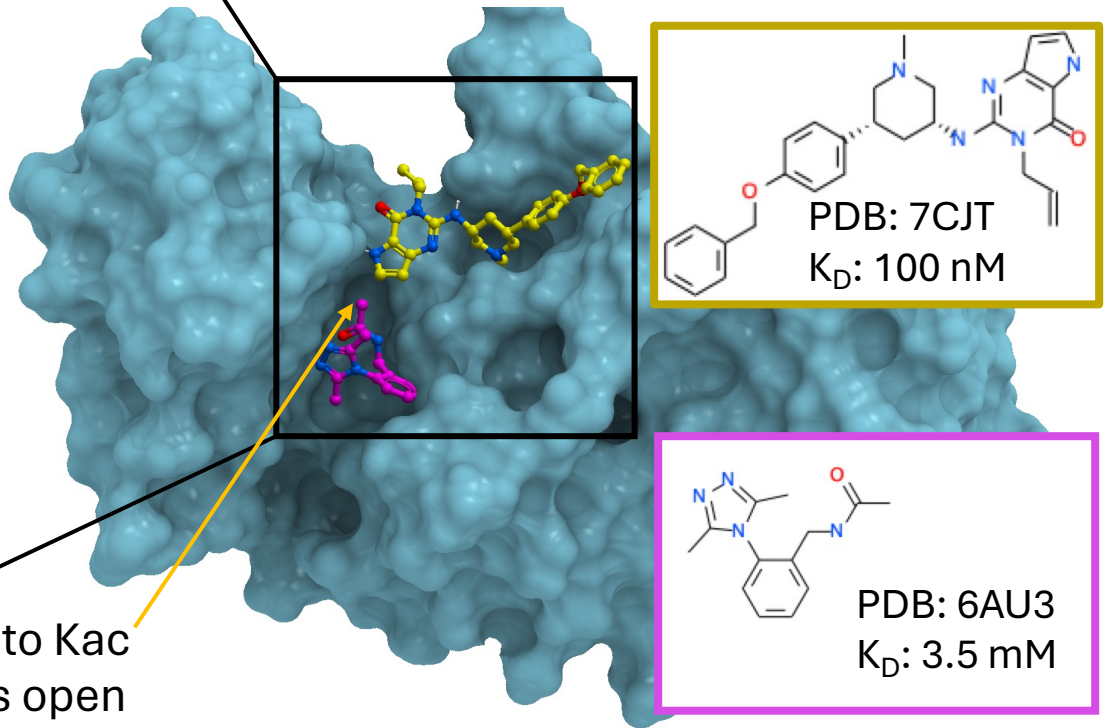

PDB: 8UWP
K_D: 4 µM
Gate to Kac
site is
closed

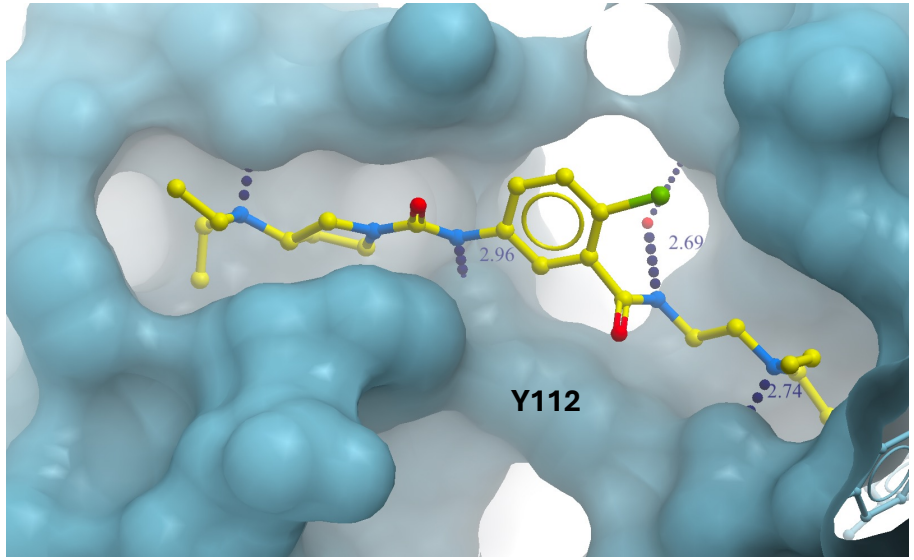

PDB: 6BHE
and 6BHI

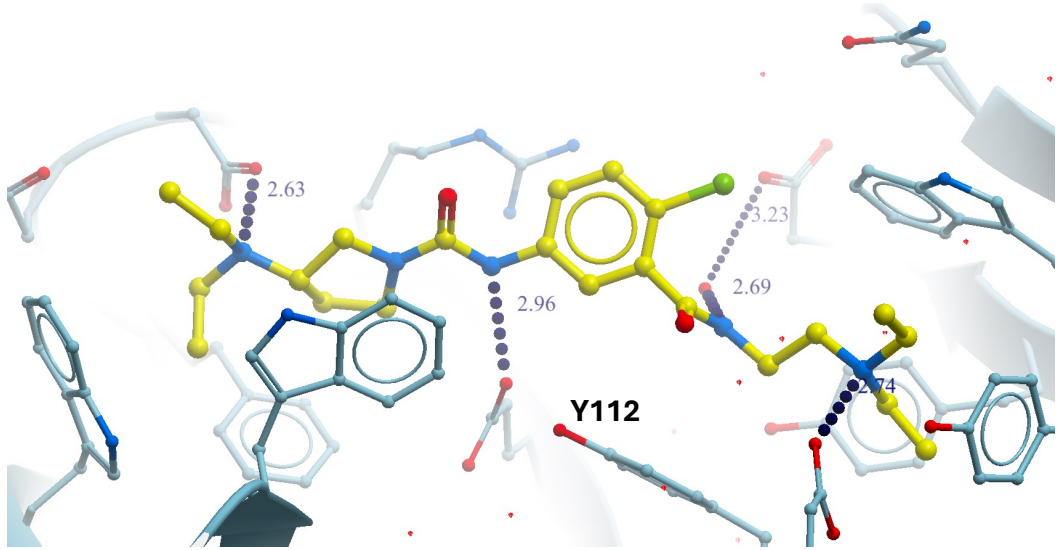

Y112

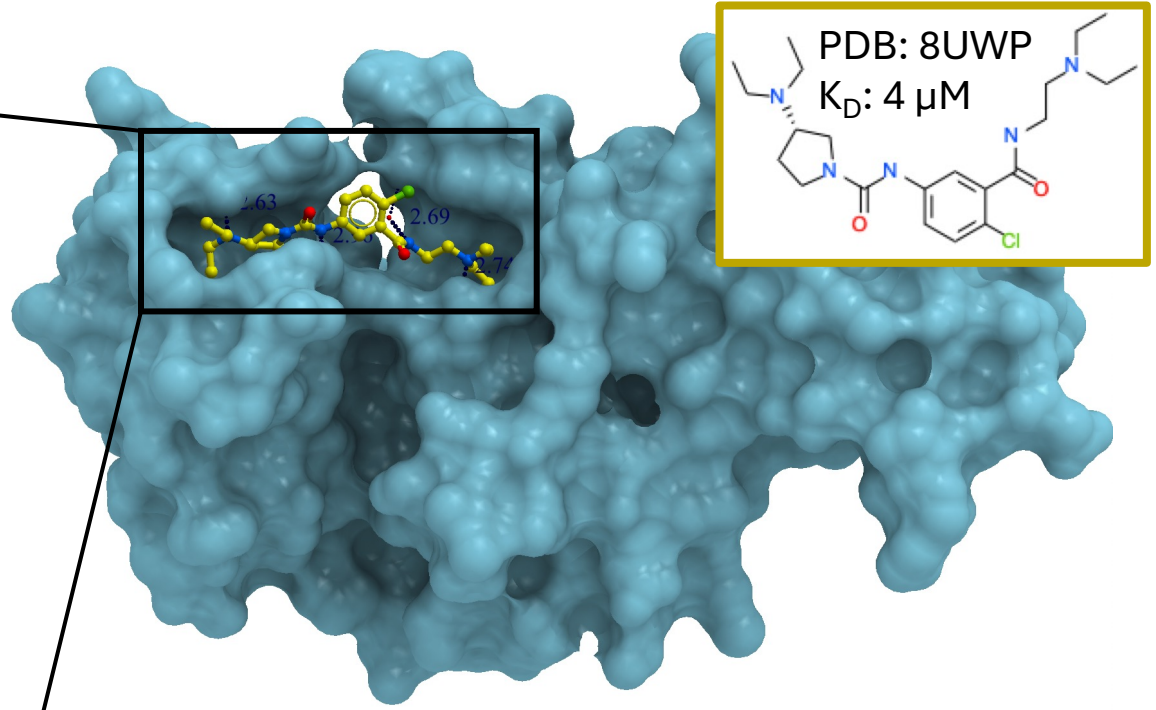


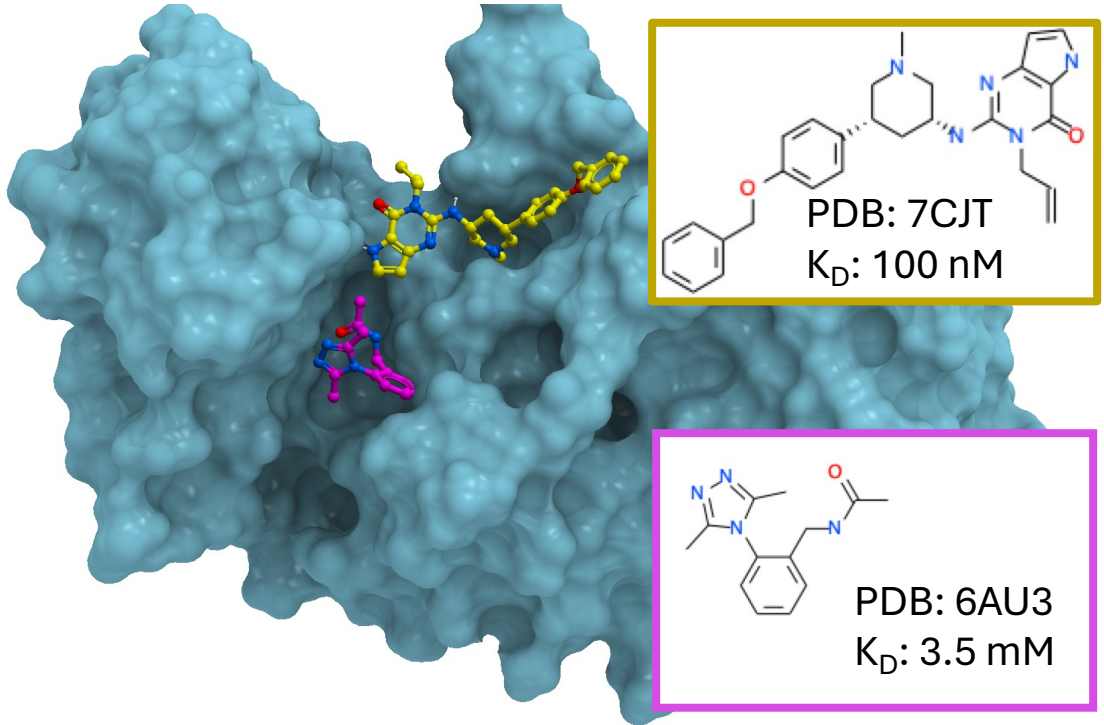

PDB: 8UWP
K_D: 4 µM
Gate to Kac site is closed


PDB: 7CJT
K_D: 100 nM
PDB: 6AU3
K_D: 3.5 mM
Gate to Kac site is open


2.96
2.69
2.74
Y112


2.63
3.23
2.69
2.96
2.74
Y112


PDB: 8UWP
K_D: 4 µM


PDB: 7CJT
K_D: 100 nM
PDB: 6AU3
K_D: 3.5 mM