

new dimension
for drug discovery



Enamine Computational Services Report

**Customer – Customer
Project – SETDB1**

September 15th, 2025

Demo Material – For Illustration Purposes

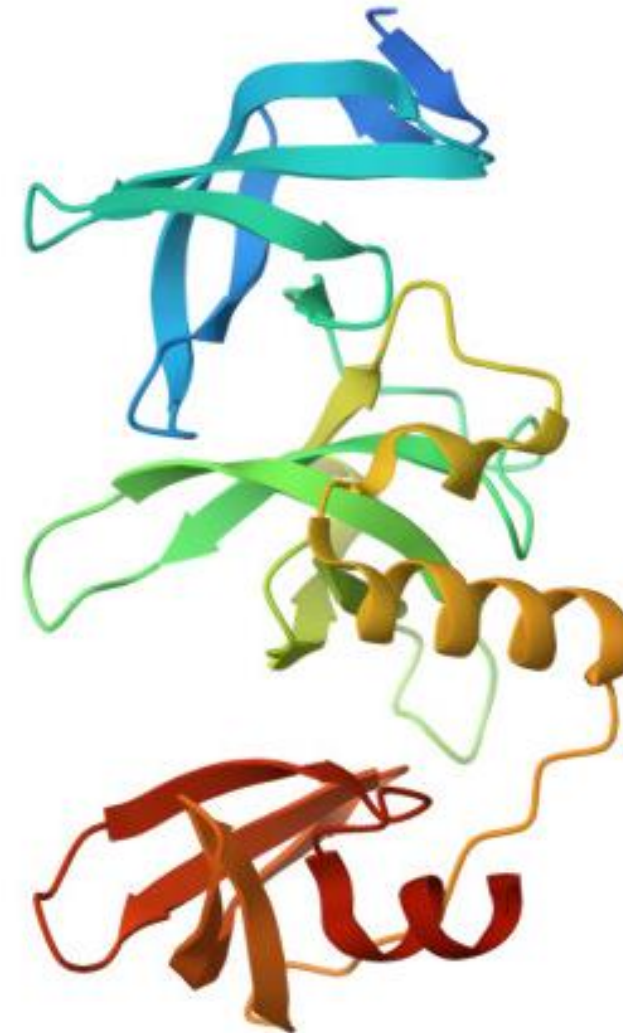
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Our evaluation and proposal

SETDB1

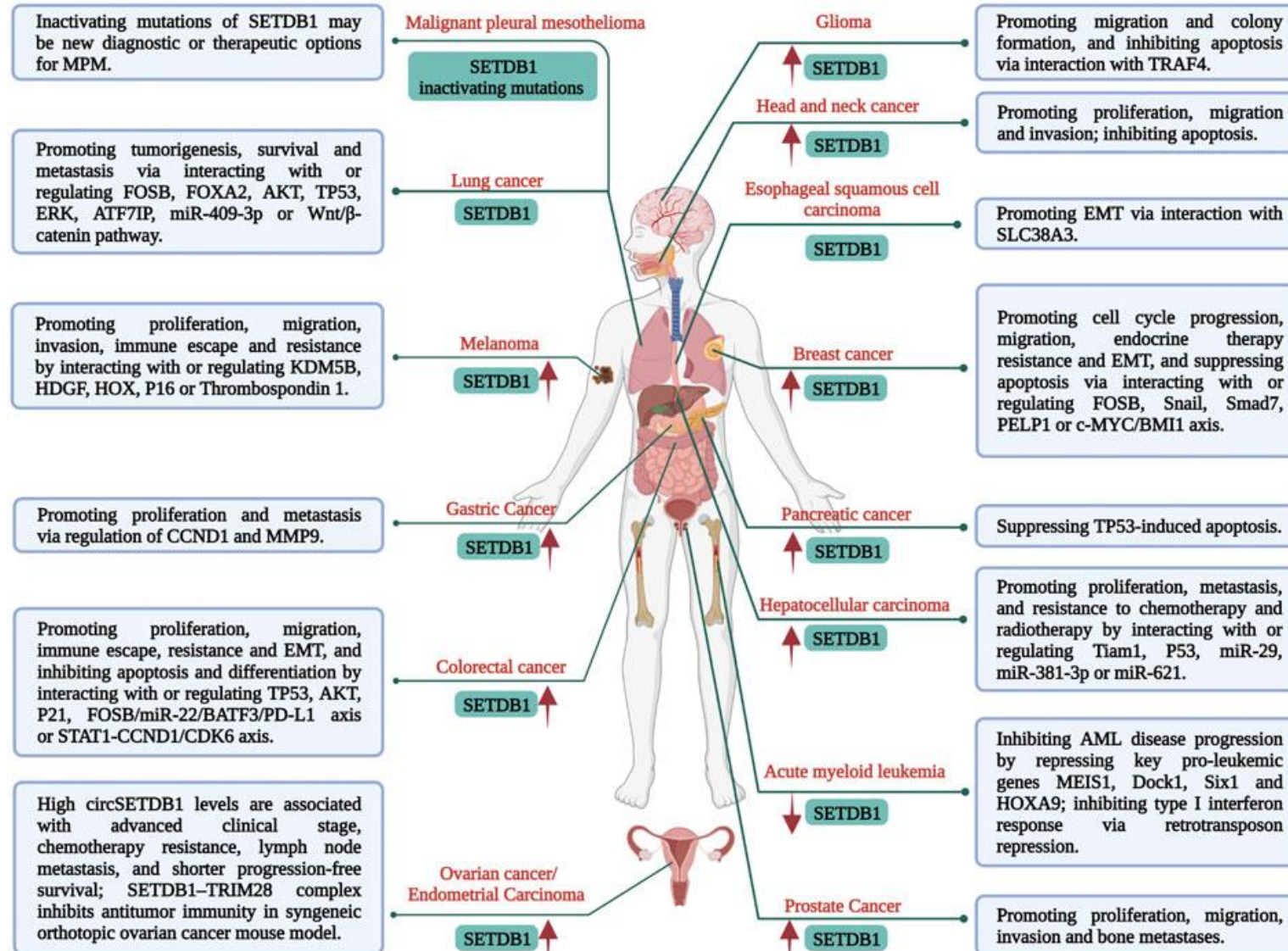
The SET Domain Bifurcated Histone Lysine Methyltransferase 1 (SETDB1) is a prominent member of the Suppressor of Variegation 3-9 (SUV39)-related protein lysine methyltransferases (PKMTs), comprising three isoforms that differ in length and domain composition. SETDB1 is widely expressed in human tissues, methylating Histone 3 lysine 9 (H3K9) residues, promoting chromatin compaction and exerting negative regulation on gene expression.

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Multiple functions and mechanisms of SETDB1 regulation in malignancies

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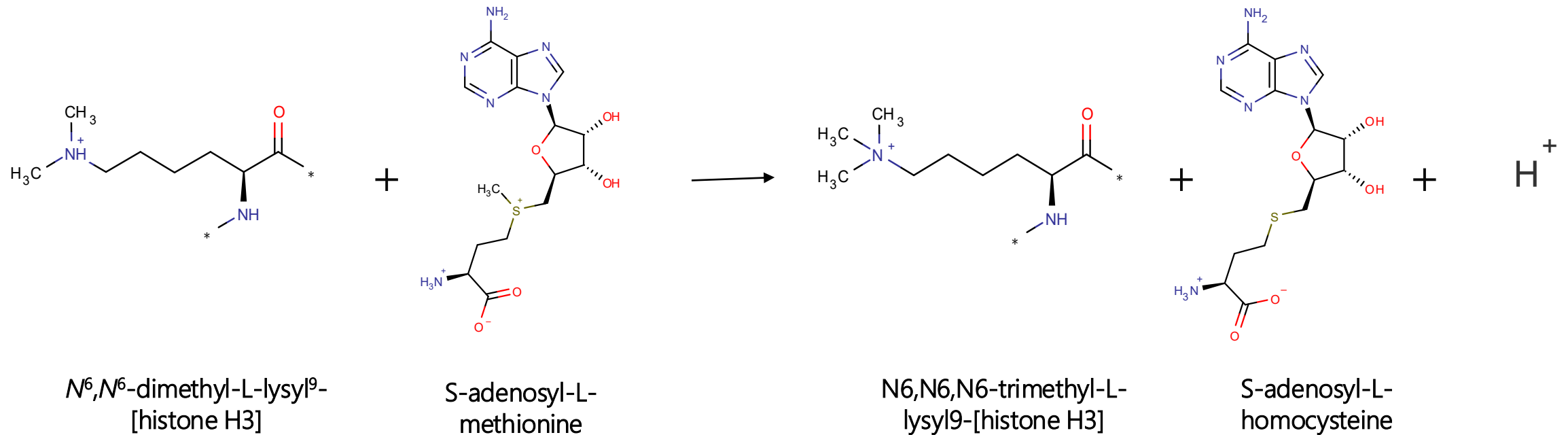


SETDB1 amplification plays pivotal roles in tumourigenesis and progression, such as promoting cell proliferation, migration, invasion, epithelialmesenchymal transition (EMT), metastasis, resistance, and immune evasion.

Catalytic activity

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SETDB1 regulates gene expression by di-/trimethylating lysine 9 (K9) of H3 protein across various chromatin regions. As a chromatin regulator, it mediates H3K9 methylation, a repressive modification that compacts chromatin by recruiting Heterochromatin protein 1 (HP1), reducing accessibility and impacting gene expression. This compaction inhibits transcription factor binding, thus repressing transcription.



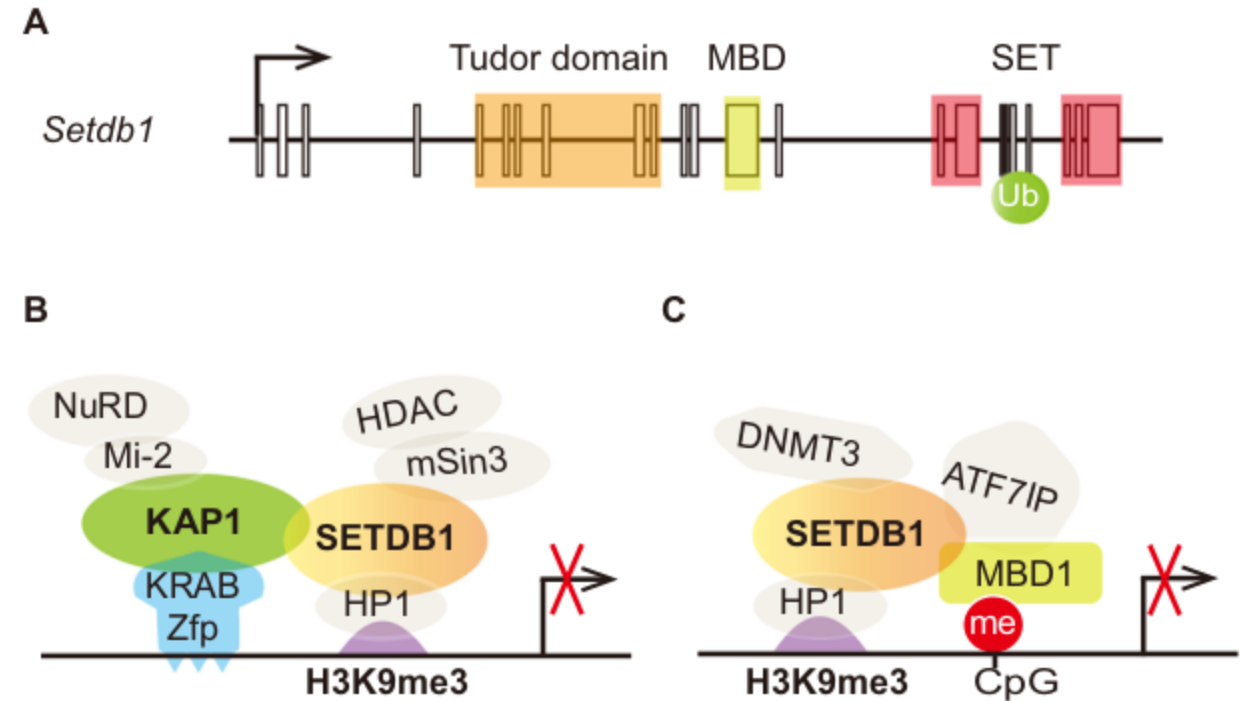
SETDB1-associated chromatin repressive complex

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a Setdb1 gene structure containing a Tudor domain, encoding protein MBD binding domain. The SET domain contains a ubiquitination (Ub) site on lysine-867.

b SETDB1/KAP1/ KRAB-Zfp complex. SETDB1 interacts with KAP1 and is recruited by KRAB-Zfp in a sequence specific manner. The H3K9me3 signal is established and recognized by HP-1; together with other repressive signals from the SIN3A/HDAC1/2 corepressor complex and the Mi-2/ NuRD (nucleosome remodeling deacetylase) local transcriptional repression is established.

c SETDB1/MBD-1/ATF7IP complex mediates the interaction between H3K9me3 and DNA methylation. DNA methyltransferases (DNMTs) also interacts with SETDB1.



SETDB1

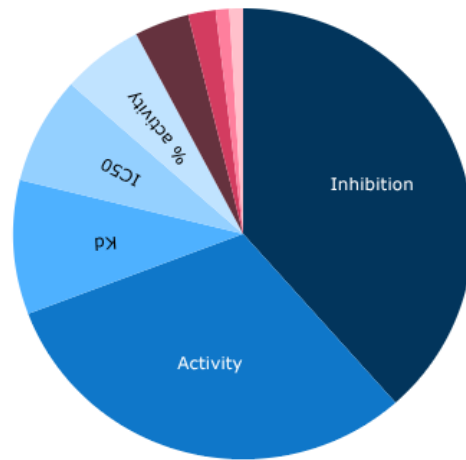
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Uniprot: Q15047

Protein: Histone-lysine N-methyltransferase SETDB1

Gene: SETDB1

ChEMBL: ChEMBL2321646



Total
104

■ Inhibition
 ■ Activity
 ■ Kd
 ■ IC50
 ■ % activity
 ■ % of activity
 ■ EC50
 ■ % activity remaining
 ■ dTagg



Triple Tudor Domain

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Tudor Domain 1: 201-251

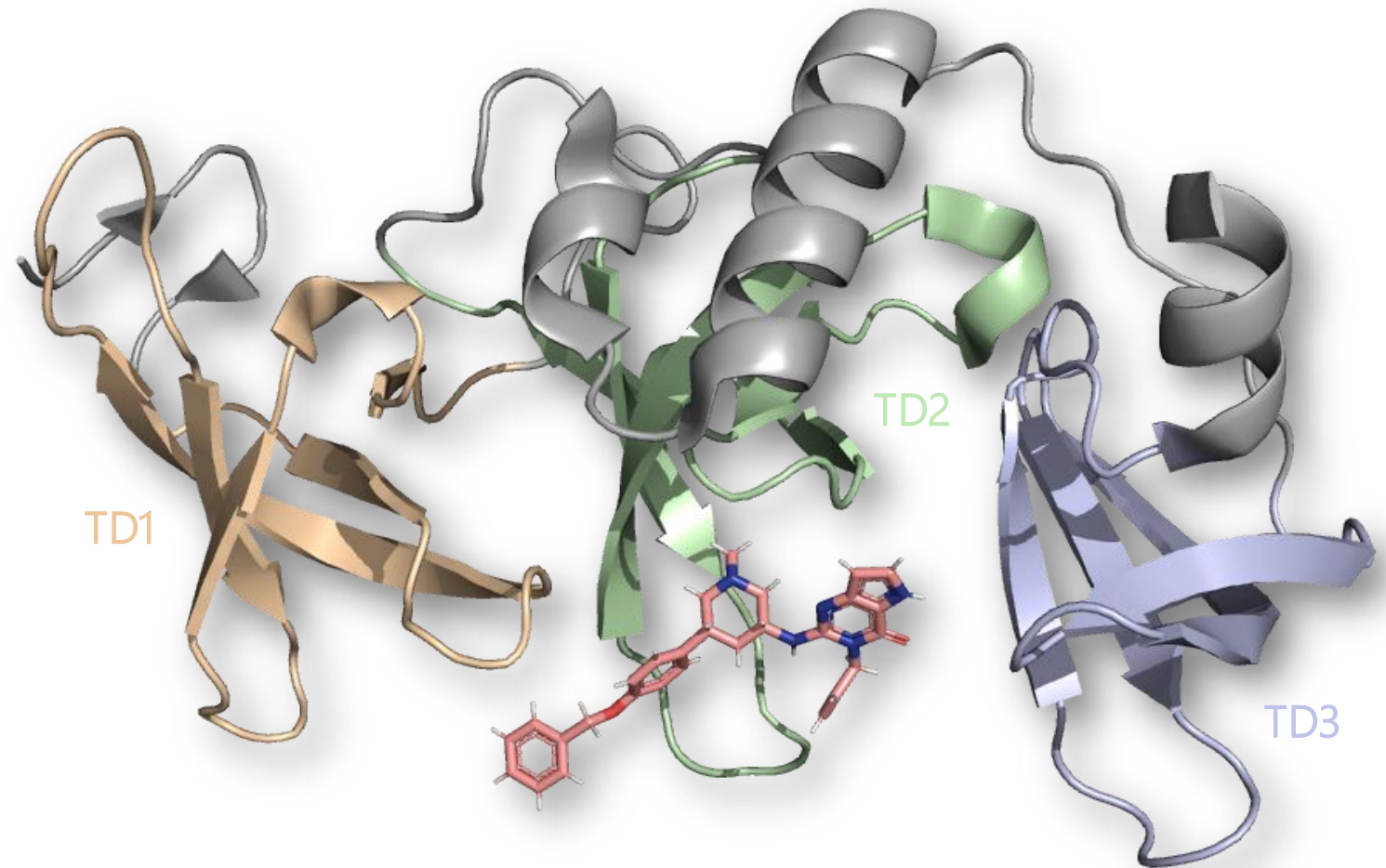
Tudor Domain 2: 261-314

Tudor Domain 3: 350-395

PDB – 7CJT

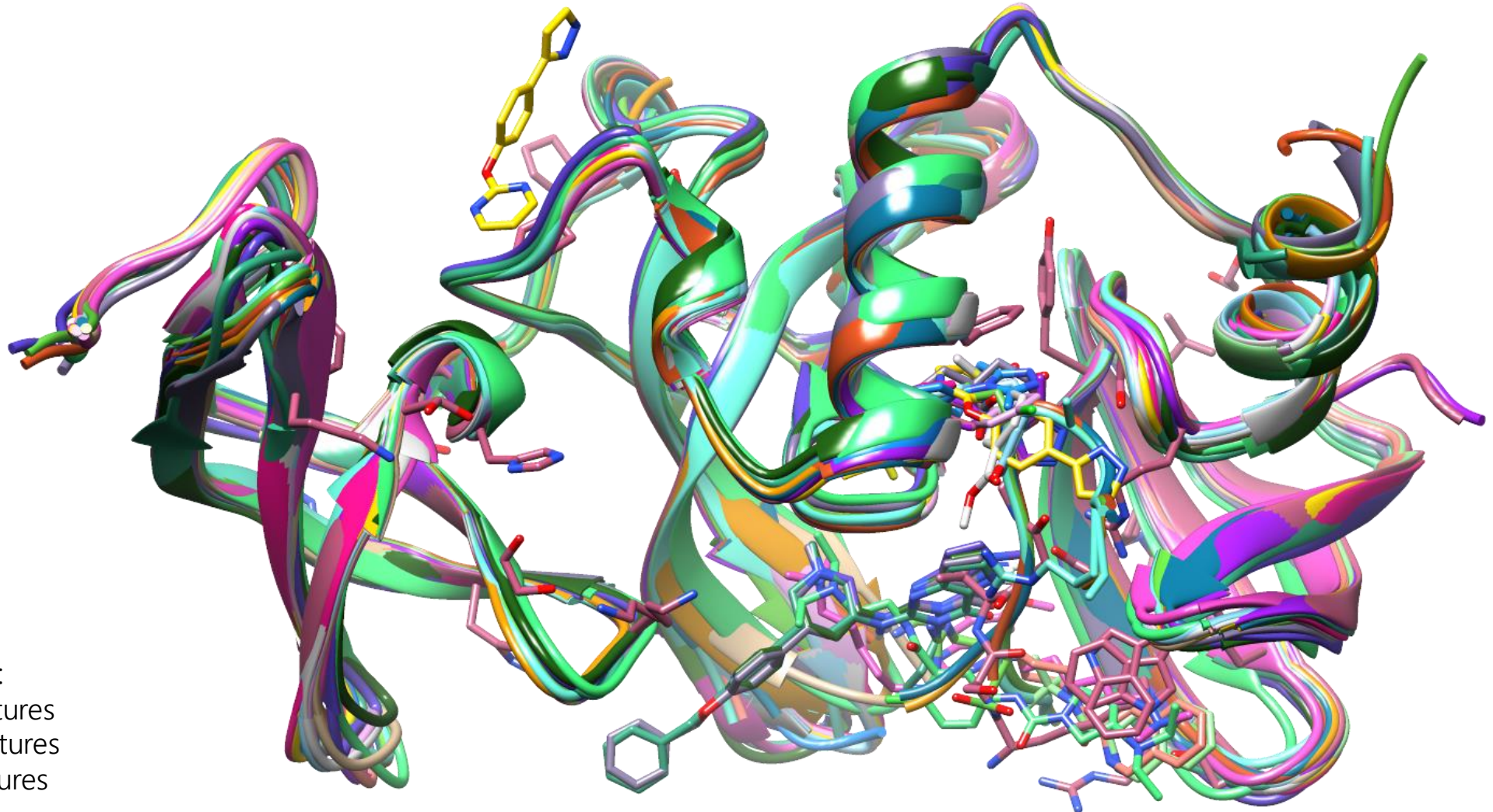
Interacts with already methylated histones, stabilizing them and ensuring proper positioning for further methylation.

Inhibition of Tudor-domain-mediated interactions is a promising approach for the treatment of diseases associated with epigenetic disorders.



PDB SETDB1

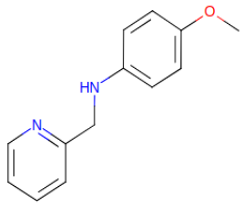
Demo Material – For Illustration Purposes



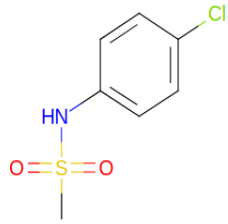
UniProt: Q15047
Structures – 23

Ligand-contained:
Pocket 1 – 7 structures
Pocket 2 – 8 structures
Peptide – 6 structures

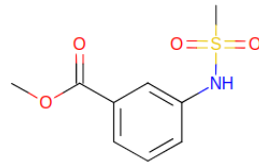
Pocket 1



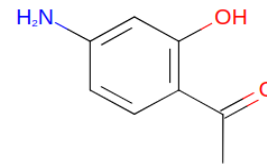
5KCH



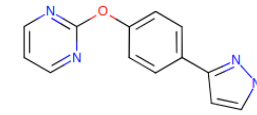
5KCO



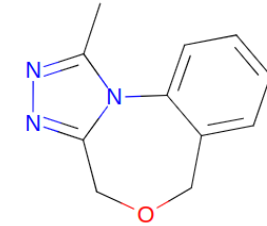
5KH6



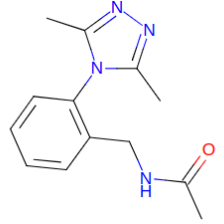
5QT1



5QT2



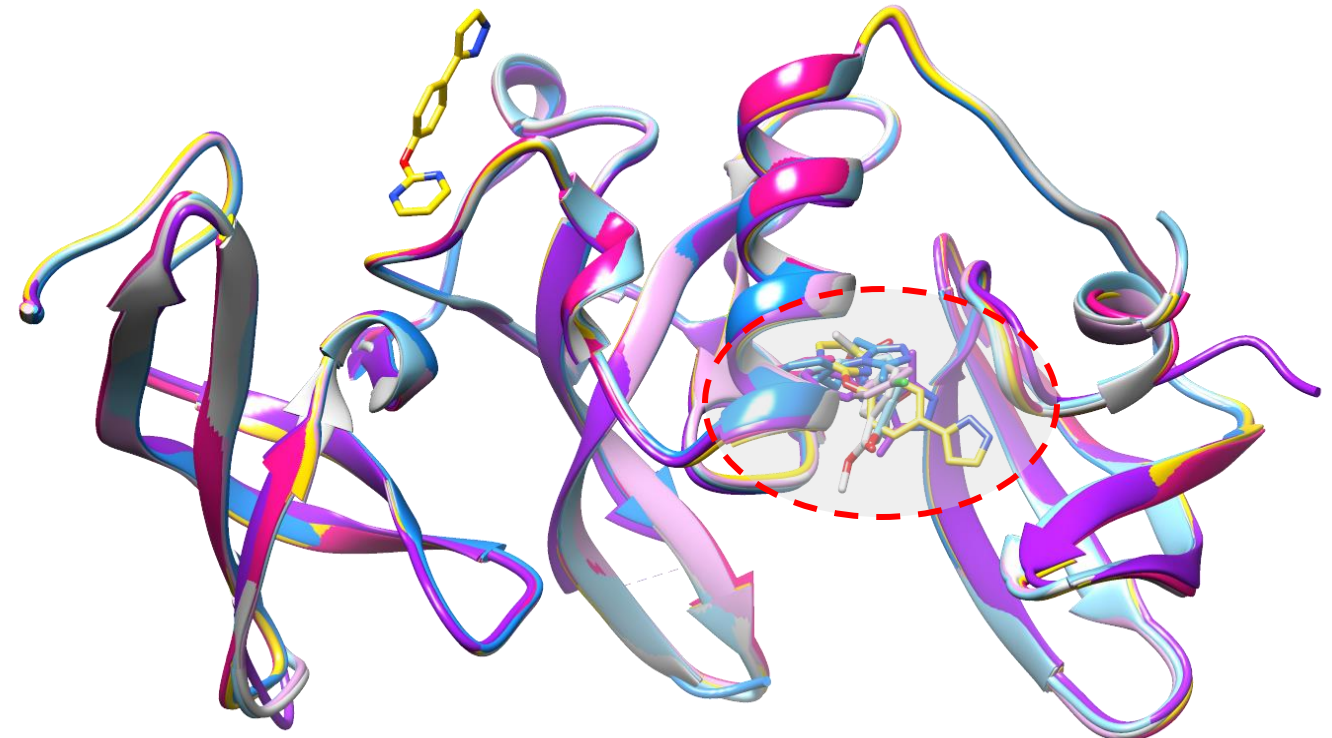
6AU2



6AU3

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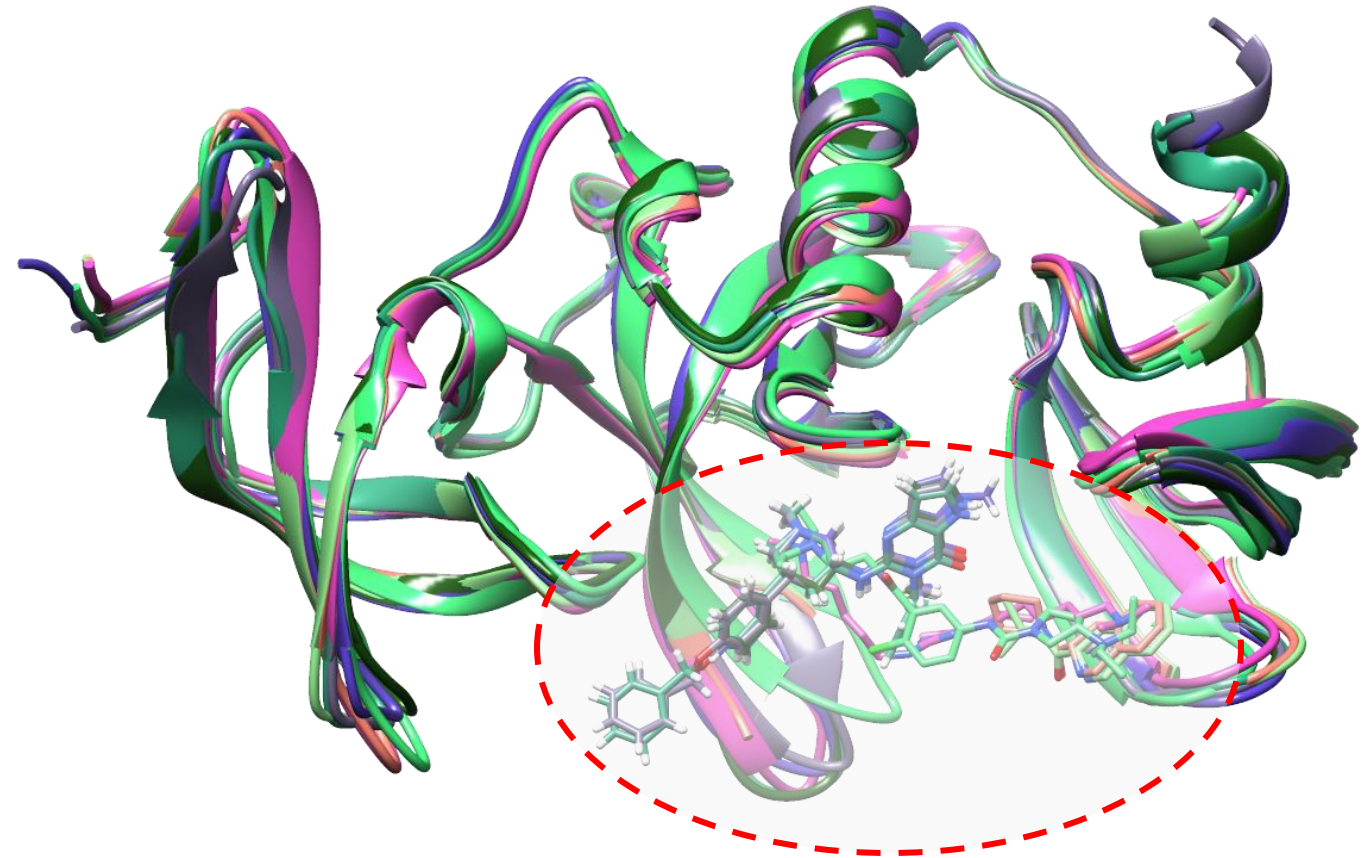
Identifier	Color	Resolution	Chain	Ligand
5KCH		1.70 Å	A	Fragment candidate
5KCO		1.47 Å	A	Fragment candidate
5KH6		2.05 Å	A	fragment candidate
5QT1		1.58 Å	A	FMOMB000017a
5QT2		1.59 Å	A	FMOPL000074a
6AU2		1.63 Å	A	Triazole fragments
6AU3		1.80 Å	A	Aryl triazole fragments



Pocket 2

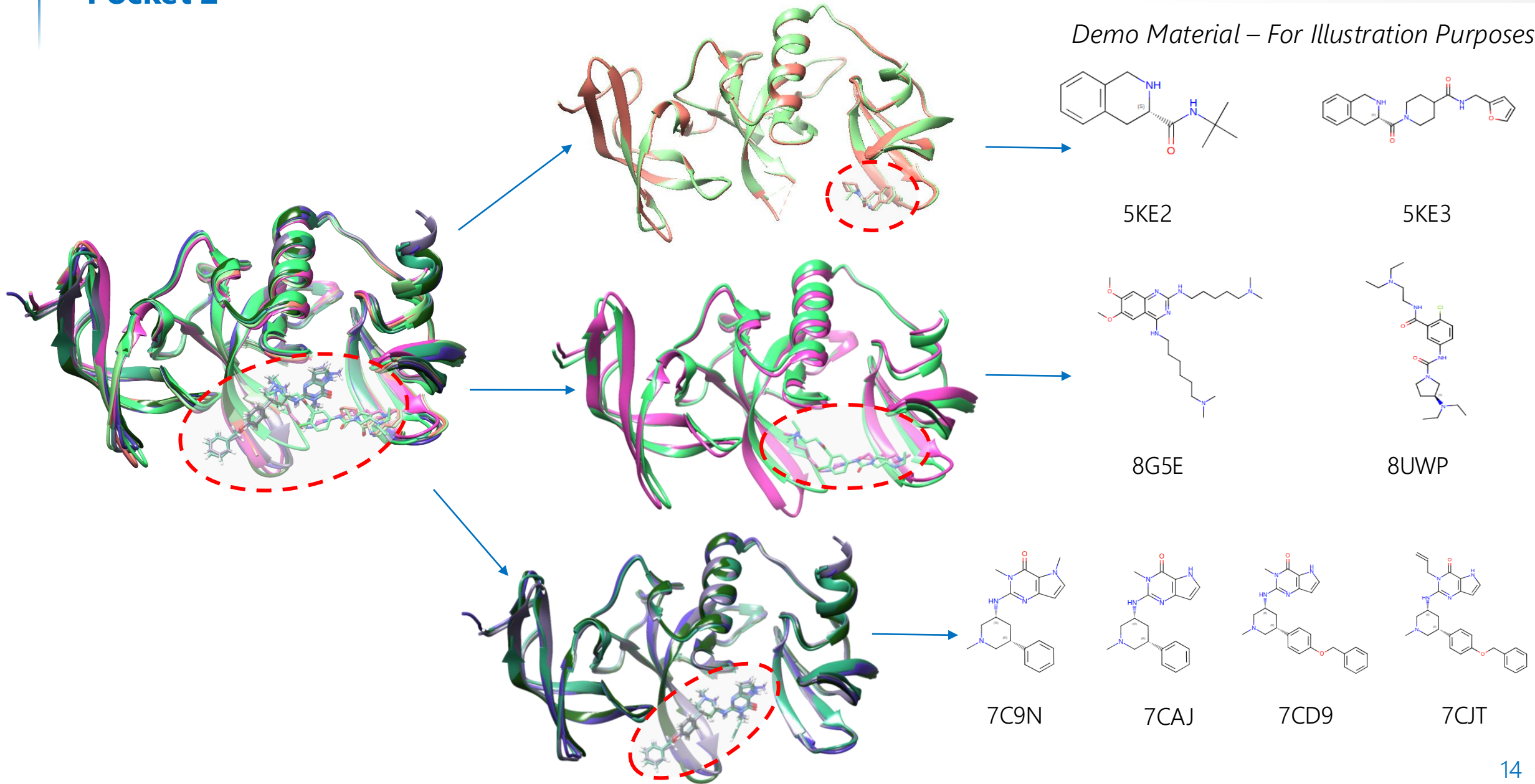
Demo Material – For Illustration Purposes

Identifier	Color	Resolution	Chain	Ligand
5KE2		1.56 Å	A	inhibitor XST06472A
5KE3		1.70 Å	A	fragment MRT0181a
7C9N		2.47 Å	A/B	Compound 1
7CAJ		2.20 Å	A/D	Compound 2
7CD9		1.60 Å	A/B	Compound 6
7CJT		2.47 Å	A/B/C/D	(R,R)-59
8G5E		1.98 Å	A	UNC6535
8UWP		1.77 Å	A/B	MR46747



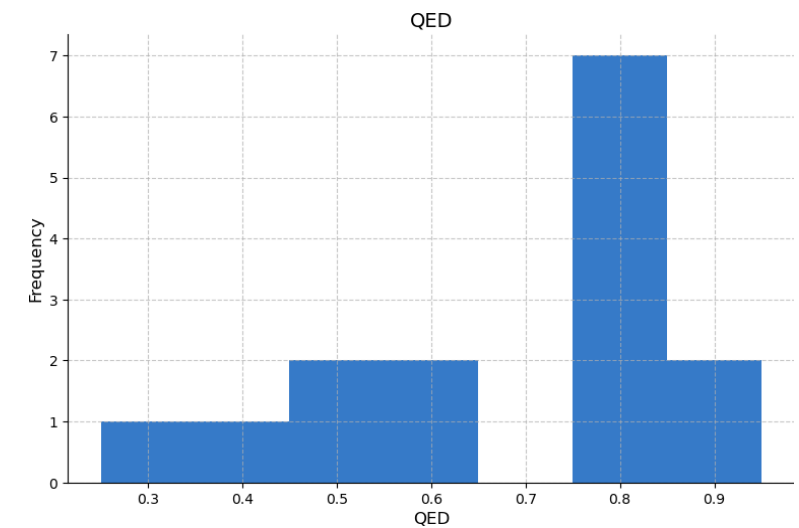
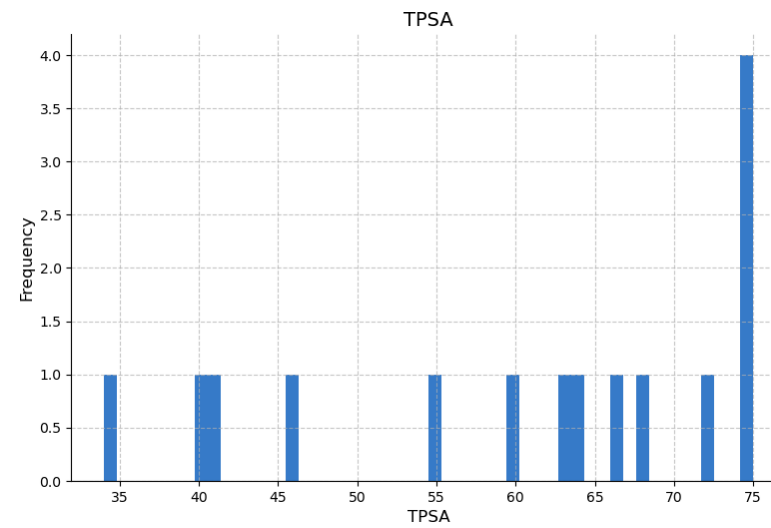
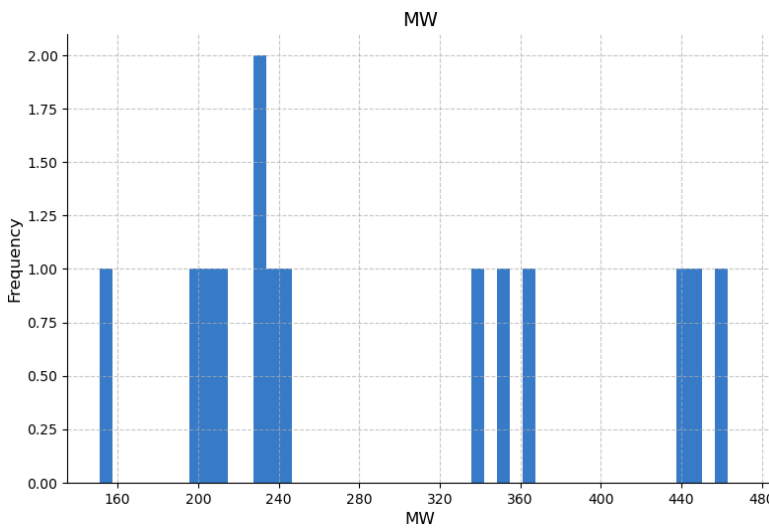
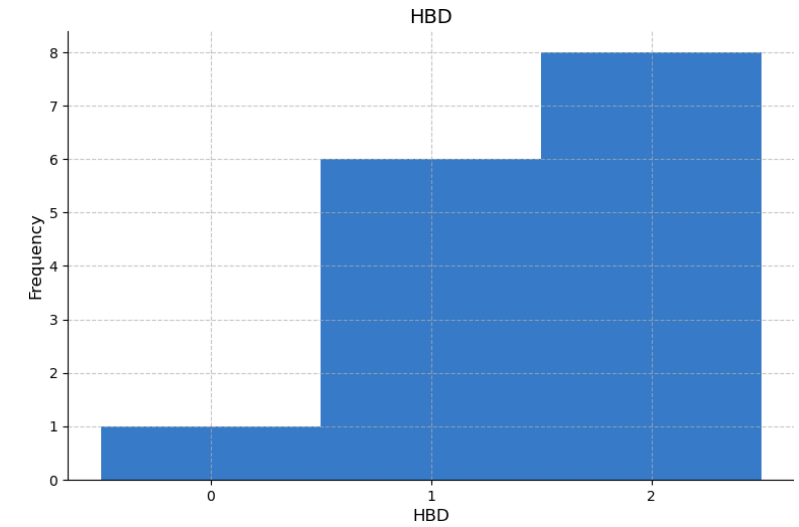
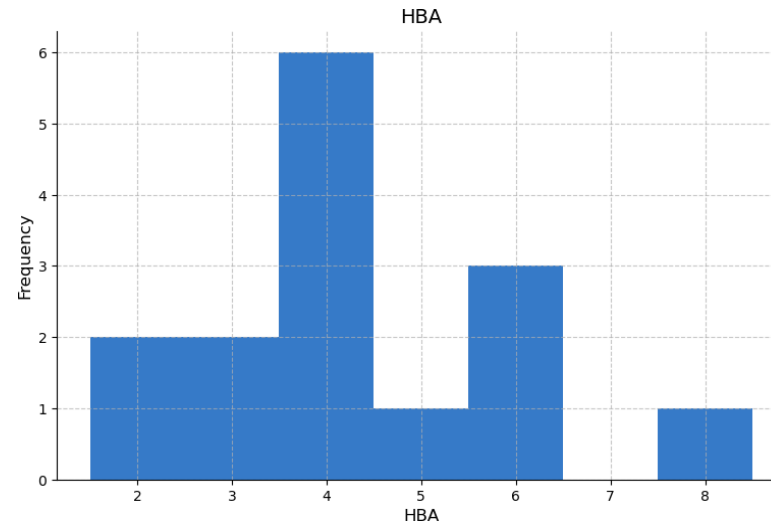
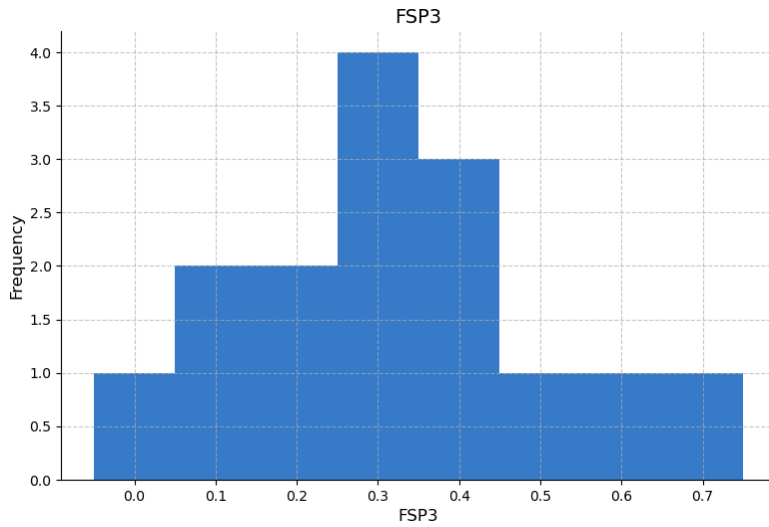
Pocket 2

Demo Material – For Illustration Purposes


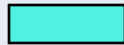






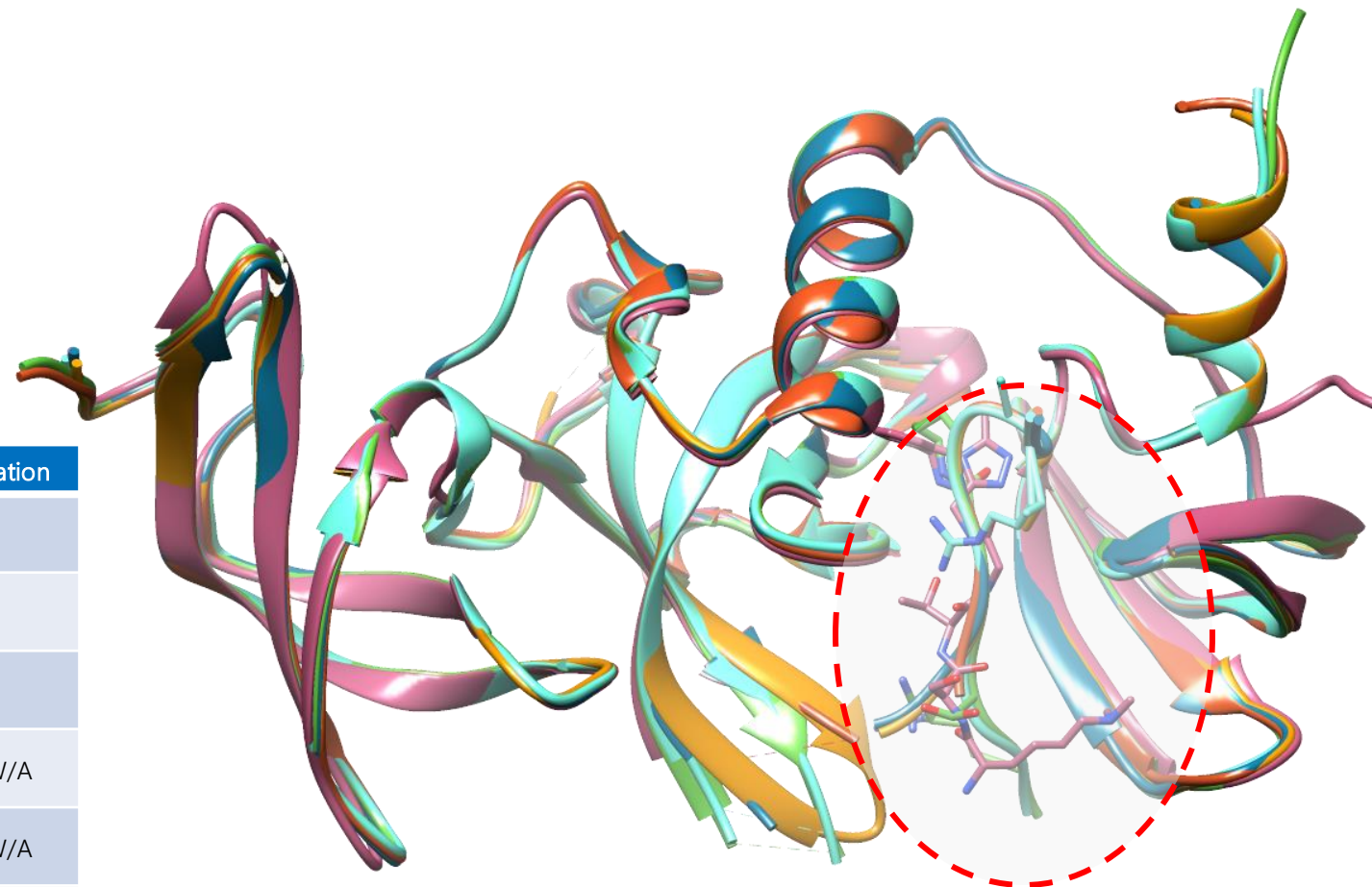
Physicochemical properties of ligand

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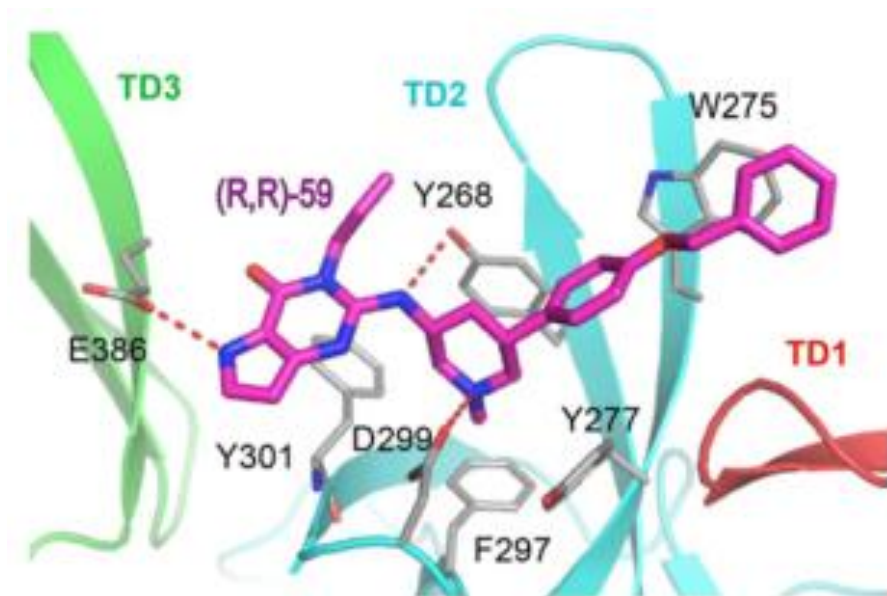


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Identifier	Color	Resolution	Chain	Ligand	Mutation
6BHD		1.25 Å	A	modified H3 peptide	
6BHE		1.35 Å	A	modified H3 peptide	
6BHG		1.45 Å	A	modified H3 peptide	
6BHH		1.85 Å	A	modified H3 peptide	1 W/A
6BHI		1.40 Å	A	modified H3 peptide	1 W/A
6BPI		1.64 Å	A	aryl triazole fragment peptide conjugates	



Binding modes of (R,R)-59 with SETDB1-TTD

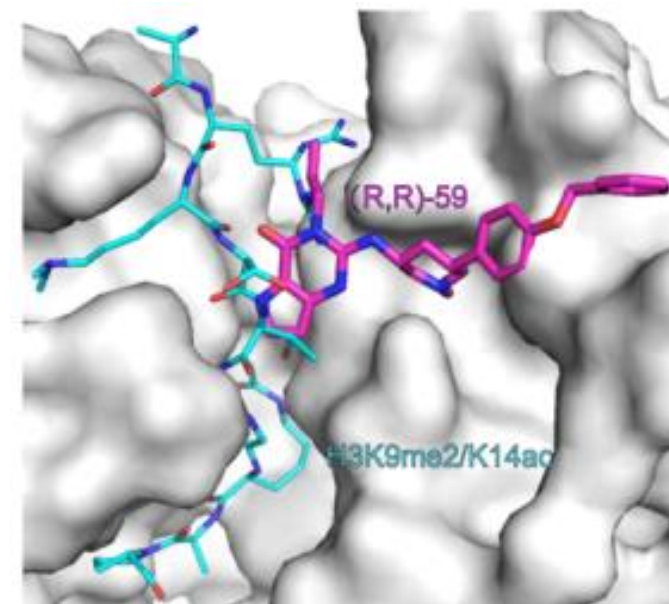


The (R,R)-59 molecule is located in the binding site between the TD2 and TD3 domains.

Main interactions:

- Location in the aromatic "pocket" formed by the amino acid residues Y301, Y268, W275, Y277 and F297.
- Hydrogen bond with the phenolic oxygen of Y268.

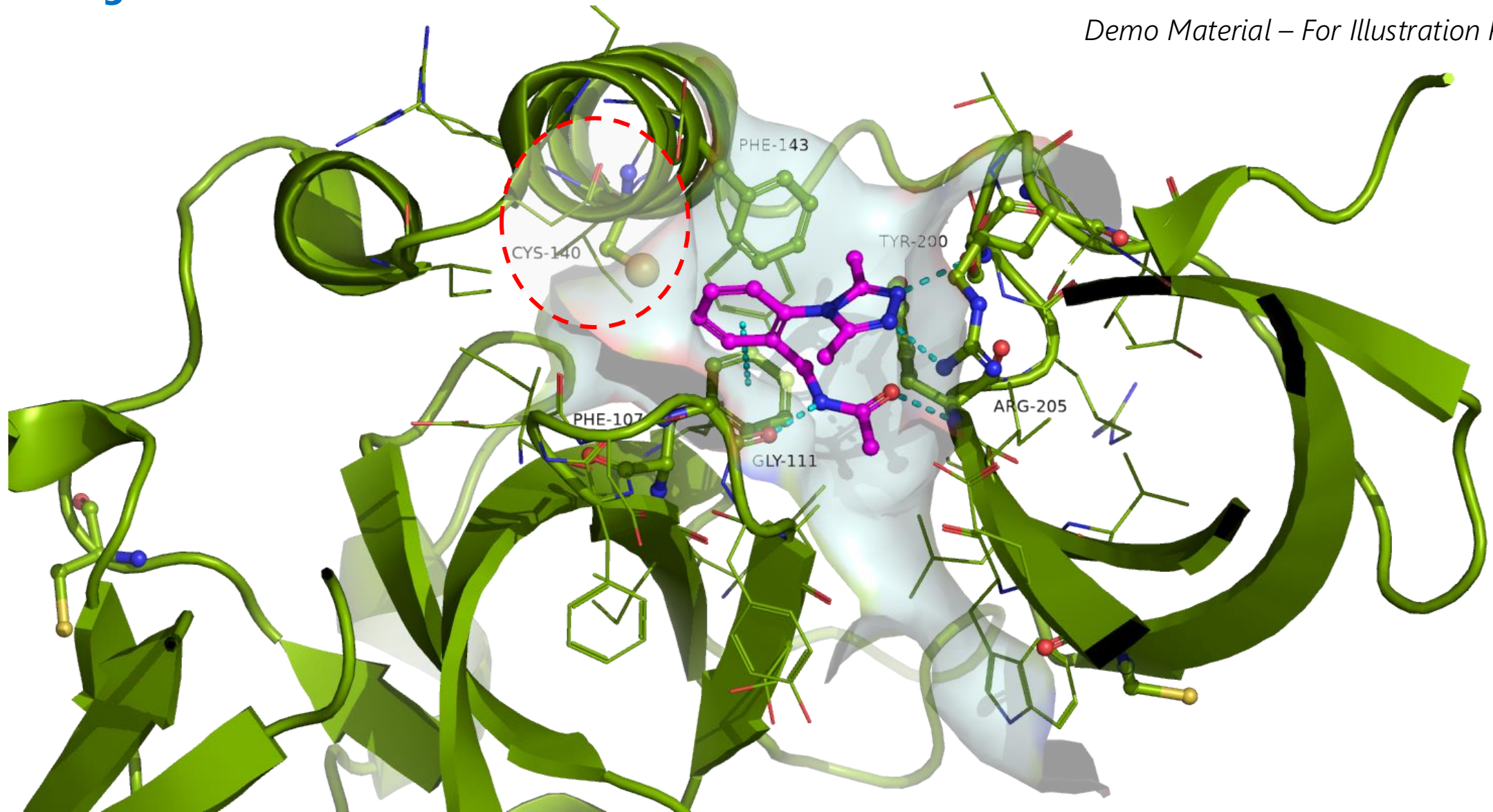
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A superposition of crystal structures of the TTD-(R,R)-59 complex (PDB entry: 7CJT) and TTD-H3 peptide (PDB ID: 6BHD). Structural superposition demonstrates that (R,R)-59 and the H3 peptide occupy the same binding site on the protein surface.

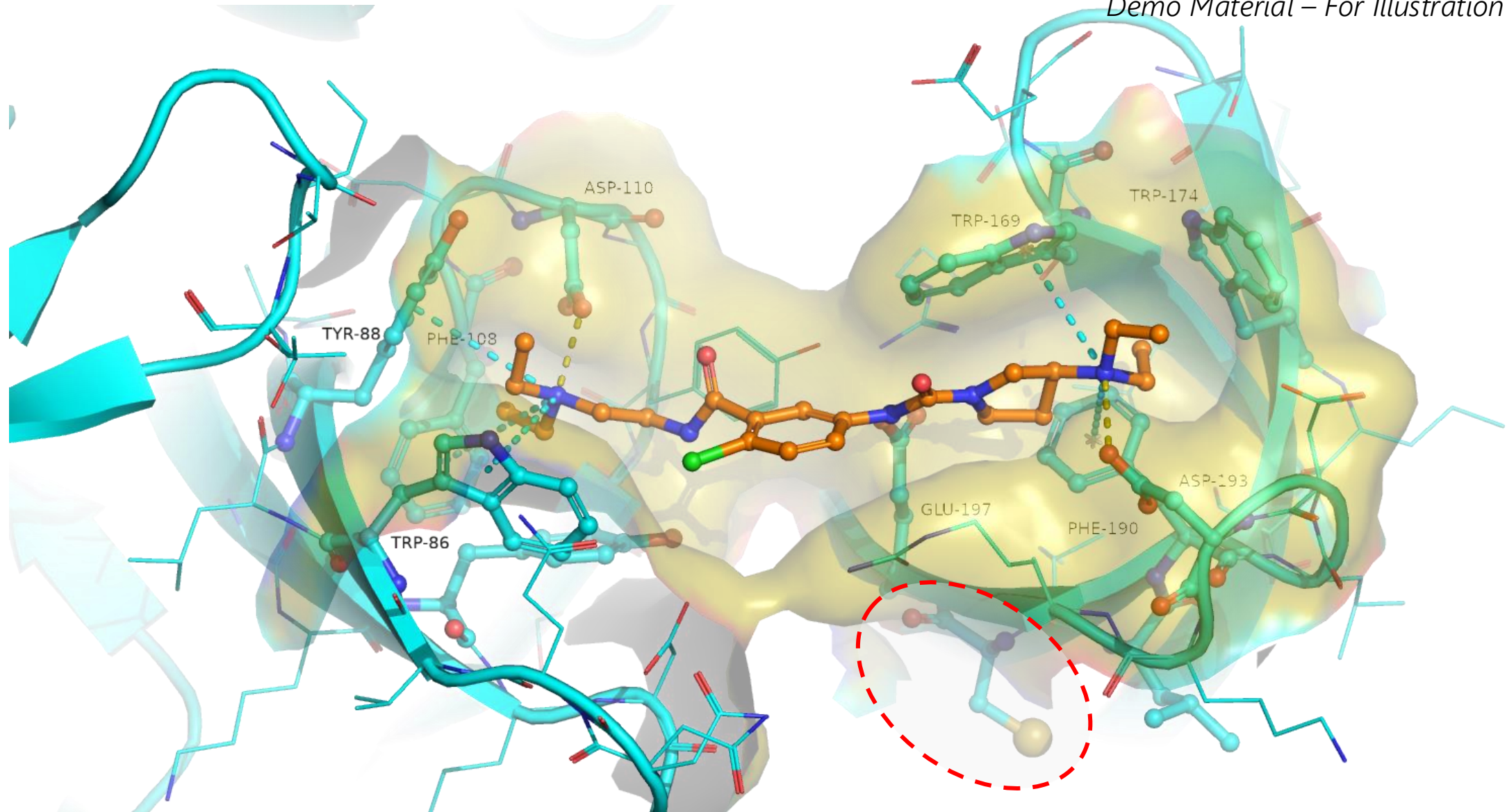
Binding mode 6AU3

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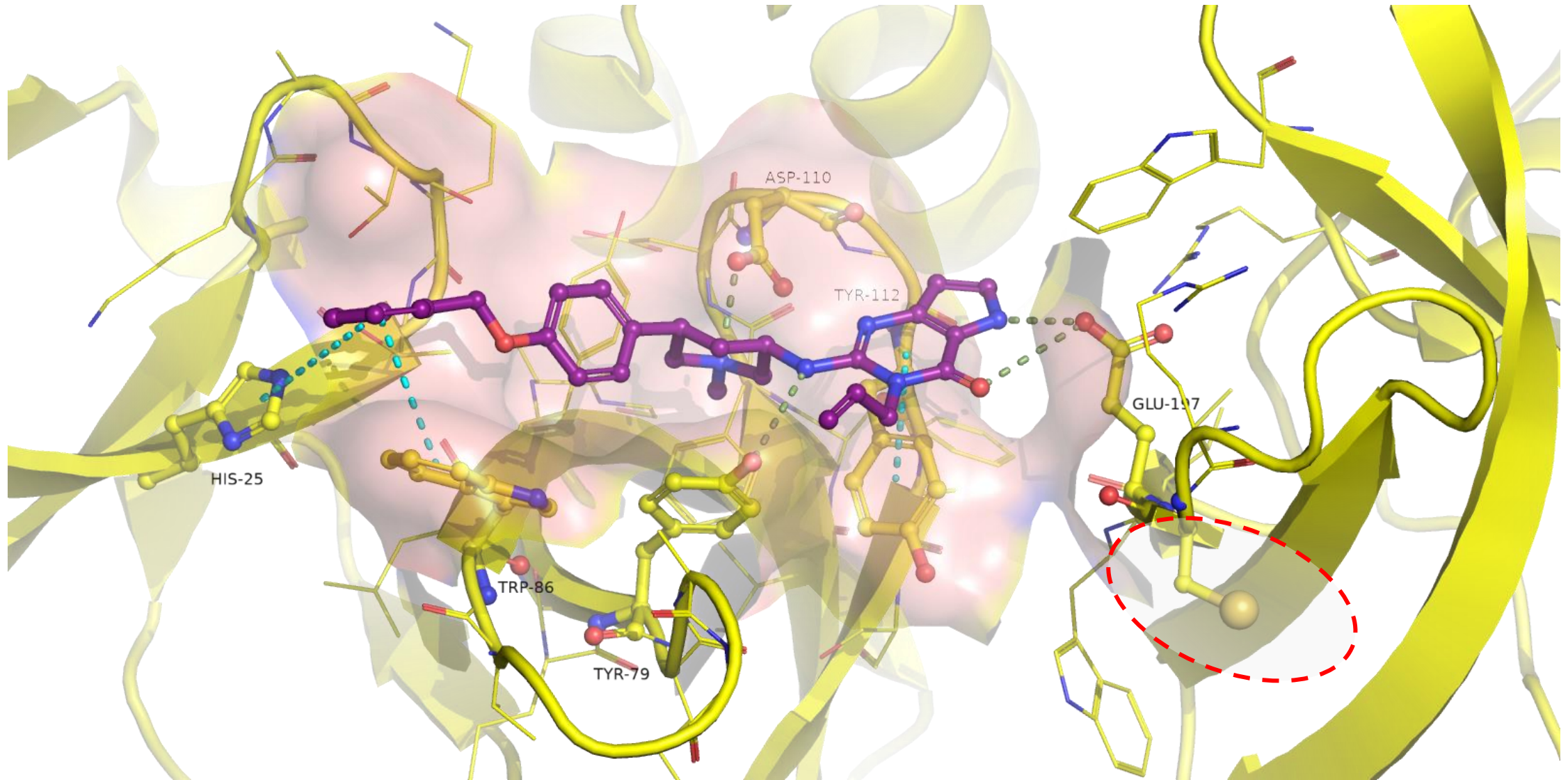
Binding mode 8UWP

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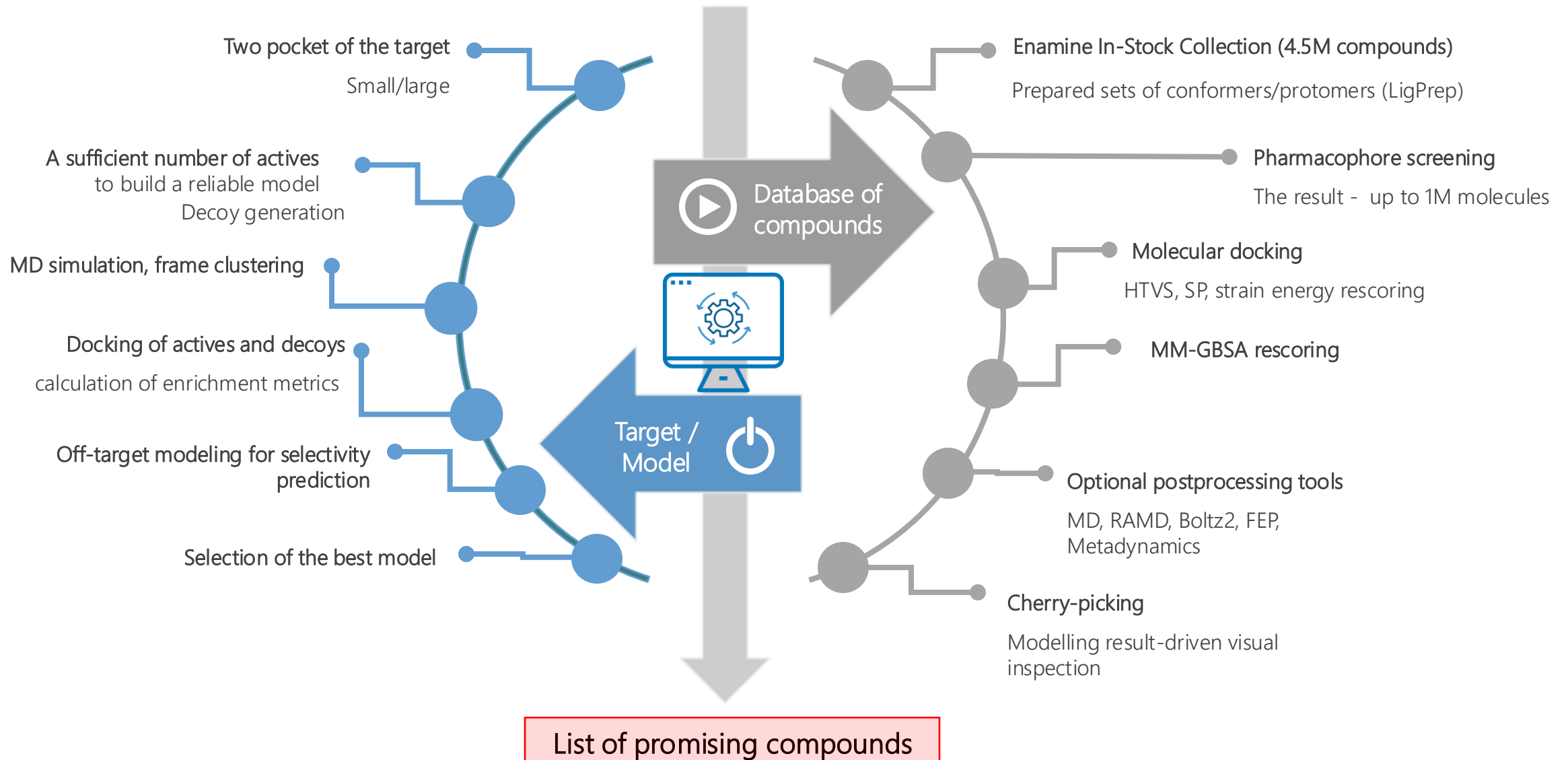
Binding mode 7CJT

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Our proposed workflow

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Thank you!

CADD project was performed by the CADD team at Enamine