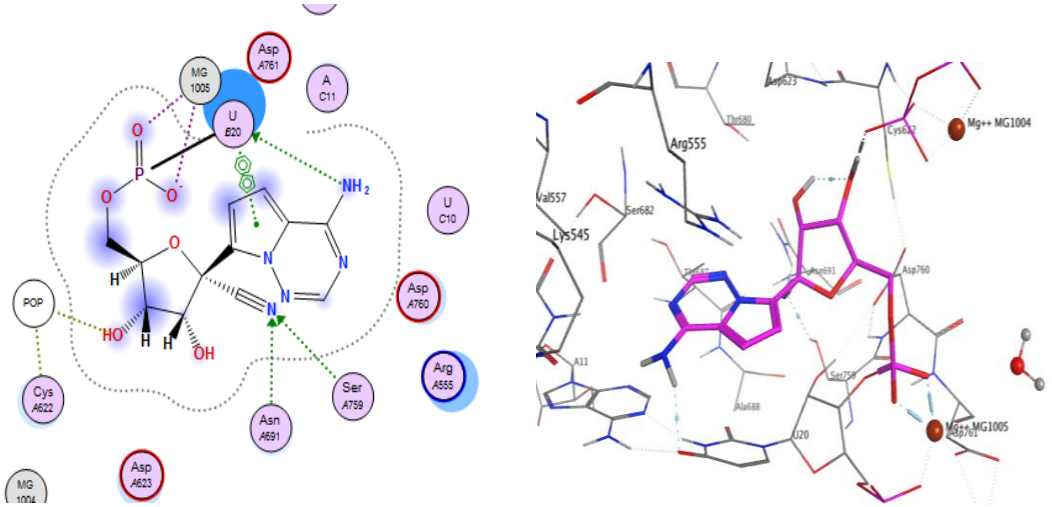
Supplementary Information

Repurposing drugs for treatment of SARS-CoV-2 infection: Computational design insights into mechanisms of action

Shubhangi Kandwal, Darren Fayne

(A) **(B)**



(C) **(D)**

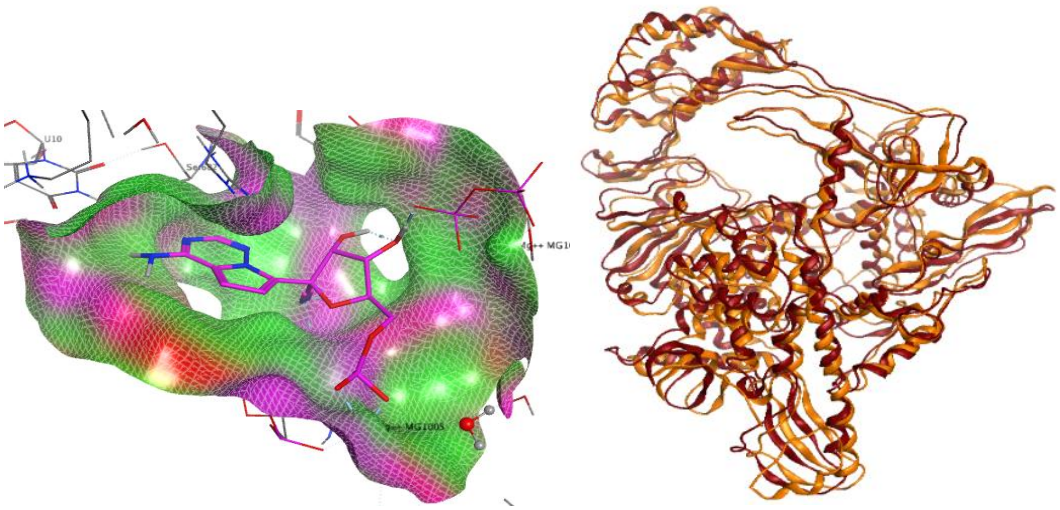
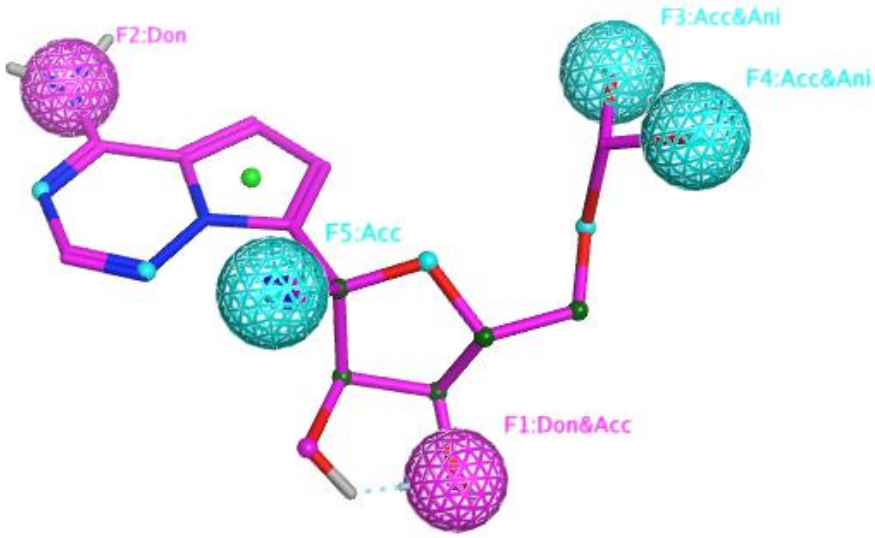


Figure S1. (A) 2D representation of the nsp7-nsp8-nsp12 ligand-binding pocket showing hydrogen bond interaction between F86 and amino acid residues. (B) 3D representation of ligand F86 (pink colour) interactions with amino acids. (C) Ligand inside the binding pocket with surface representation. (D) Superposition of 7BV2 and 7BW4 showing the structural similarity between them (Maroon colour- 7BW4, Orange colour- 7BV2).

(A)



(B)

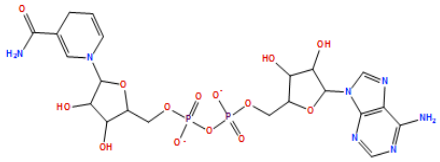
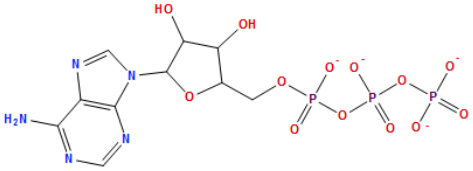
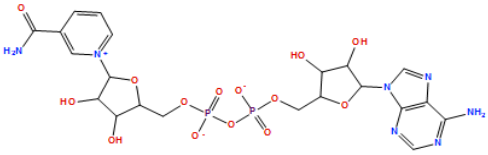
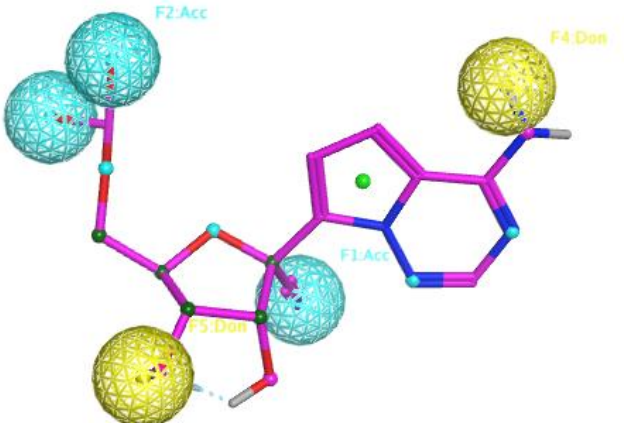
Name of hit molecule	Structure of hit molecule
1. Coenzyme-I	
2. Adenosine-triphosphate	
3. Nadide	

Figure S2, (A) First Pharmacophore features on F86 ligand (pink colour) of 7BV2 protein structure. (B) Structures of selected hit (Coenzyme-I, adenosine triphosphate and nadide) molecules obtained after VS.

(A)



(B)

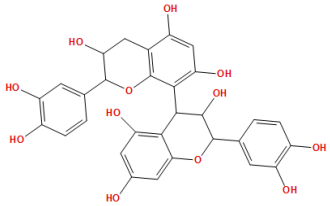
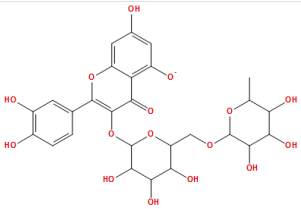
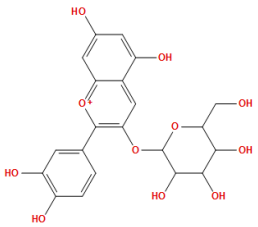
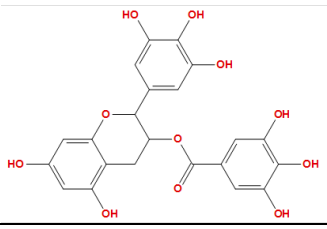
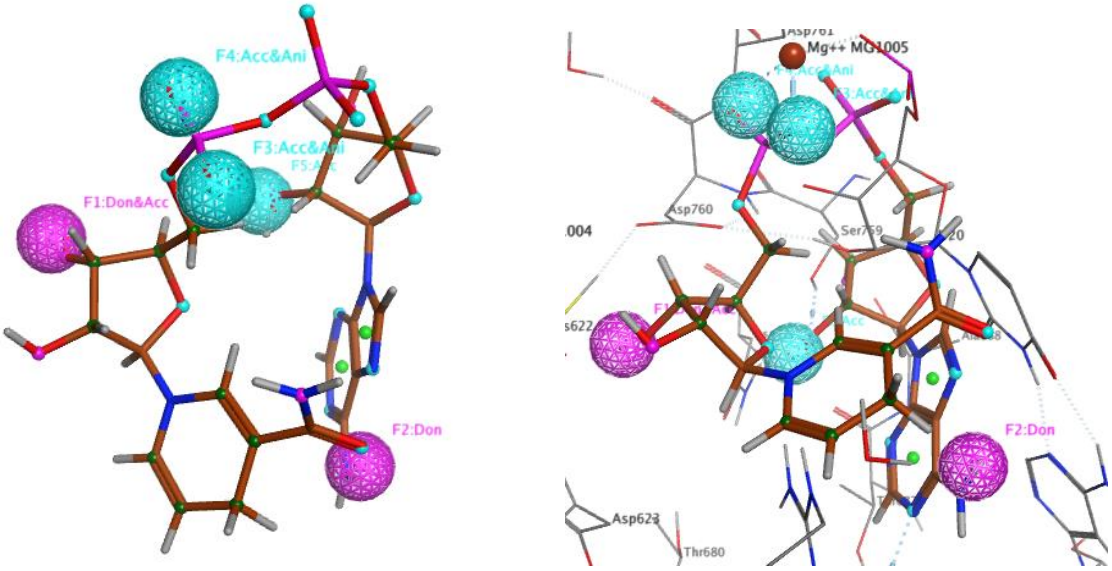
Name of hit molecule	Structure of hit molecule
1. Procyanidin-b-2	
2. Rutin	
3. Kuromanin	
4. Epigallocatechin-gallate- (-)	

Figure S3. (A) Second Pharmacophore features on F86 ligand (pink colour) from 7BV2 protein structure. (B) Structures of select hits (Procyanidin-b-2, rutin, kuromanin and epigallocatechin-gallate-(-)) obtained after VS.

(A)



(B)

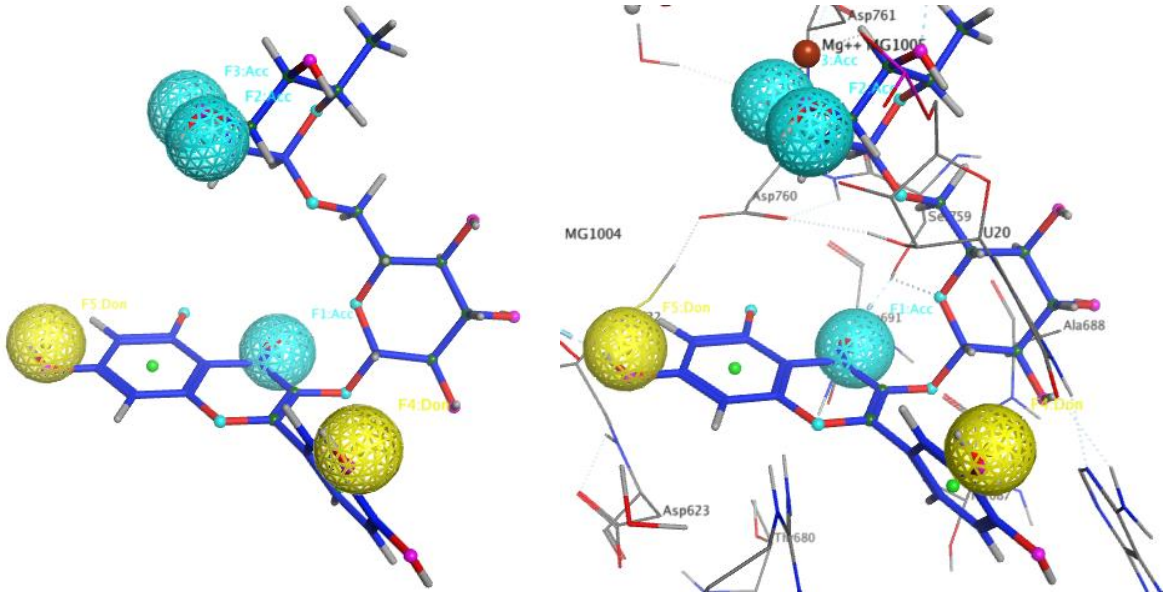
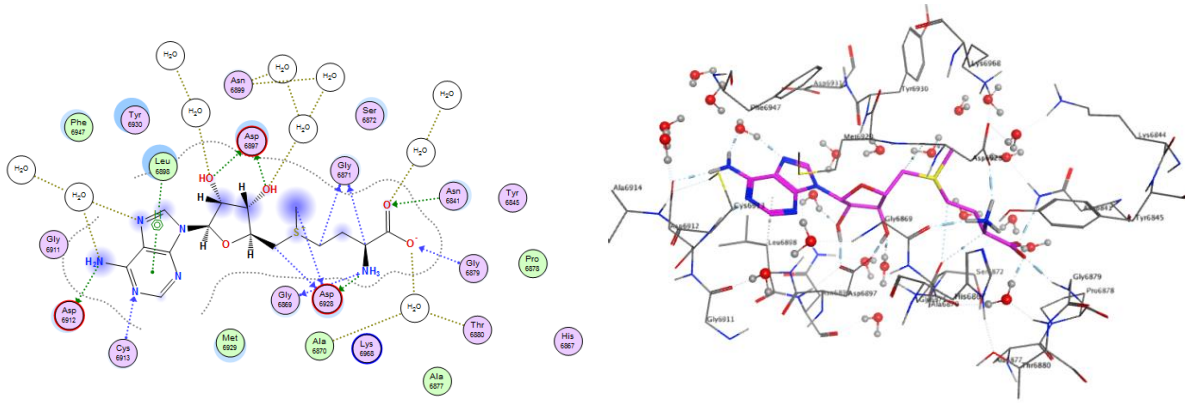


Figure S4. (A) First pharmacophore features around the hit molecule Coenzyme-I (brown colour) and interactions with the amino acids of the binding pocket. (B) Second pharmacophore features around the hit molecule rutin (dark blue colour) and its interactions with the binding pocket amino acids.

(A) **(B)**



(C) **(D)**

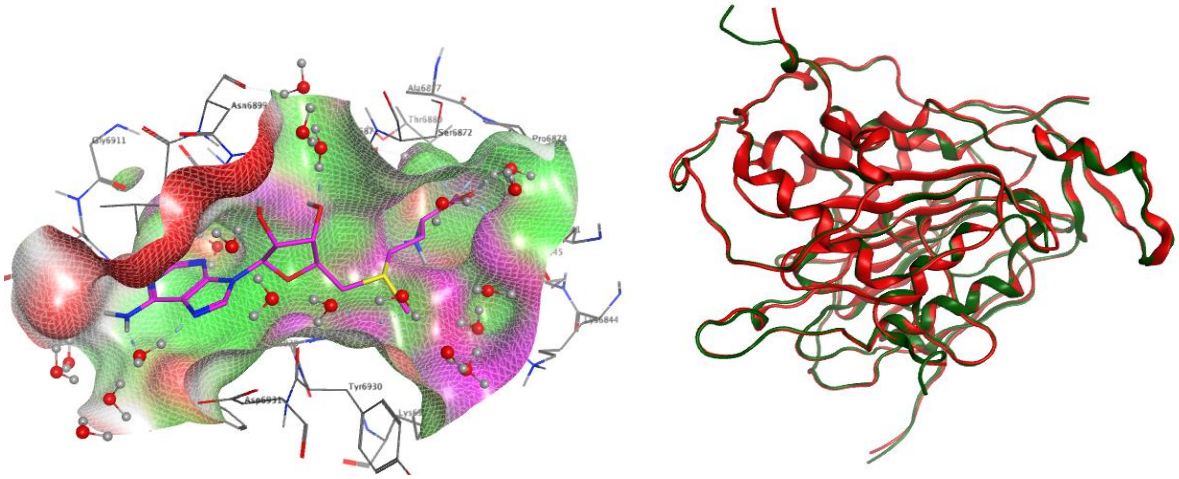
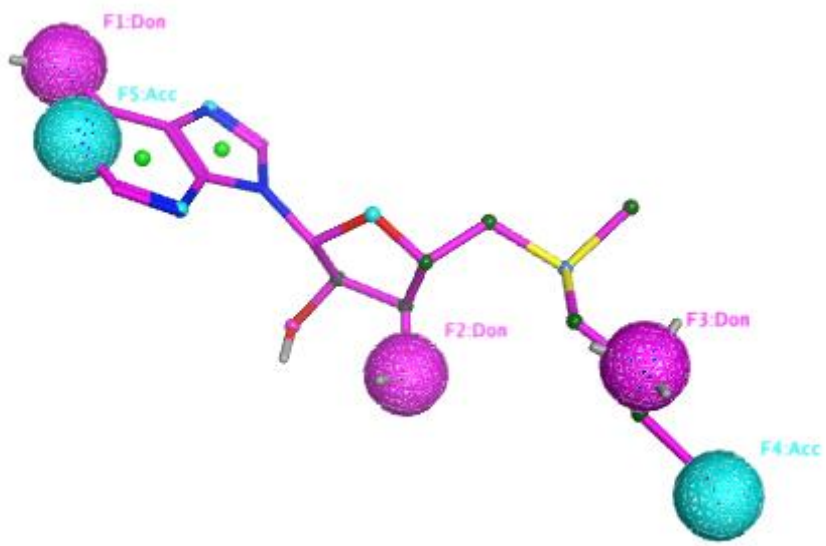


Figure S5. (A) 2D representation of nsp10-nsp16 (6W4H) ligand-binding pocket showing hydrogen bond interactions between SAM and amino acids. (B) 3D representation of ligand SAM (pink colour) interactions with amino acids. (C) Ligand inside the binding pocket with surface representation. (D) Superposition of 6W4H and 7BQ7 showing the structural similarity between them (Red colour- 7BQ7, Dark green colour- 6W4H).

(A)



(B)

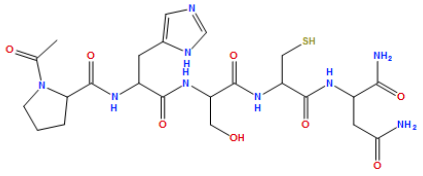
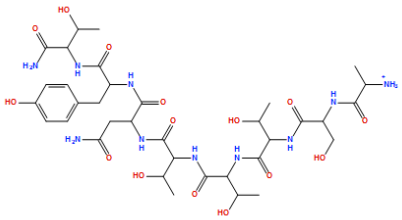
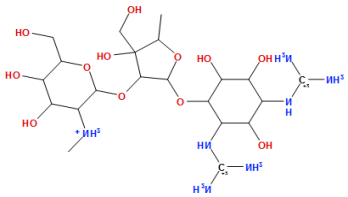
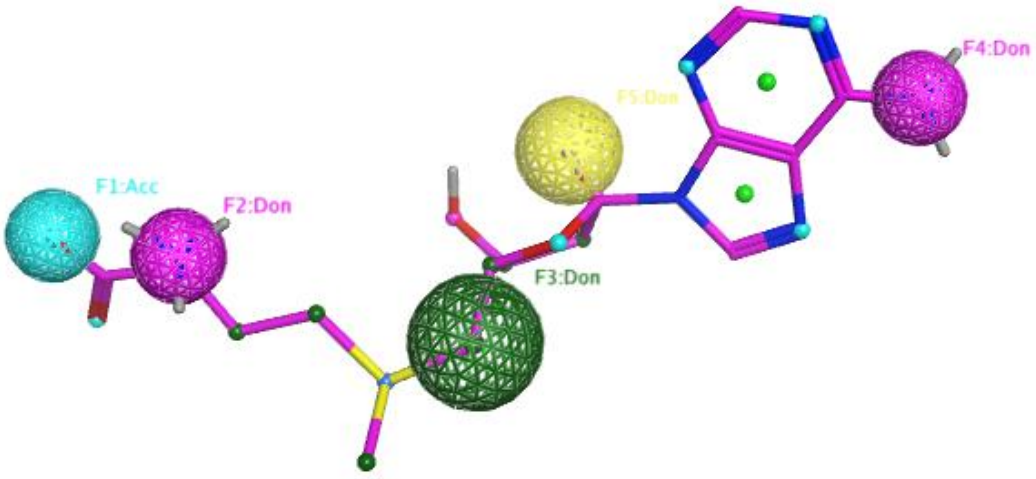
Name of hit molecule	Structure of hit molecule
1. ATN-161	
2. Adaptavir	
3. Dihydrostreptomycin	

Figure S6. (A) First Pharmacophore features on SAM ligand (pink colour) of 6W4H protein structure. (B) Structures of select hits (ATN-161, adaptavir and dihydrostreptomycin) obtained after VS.

(A)



(B)

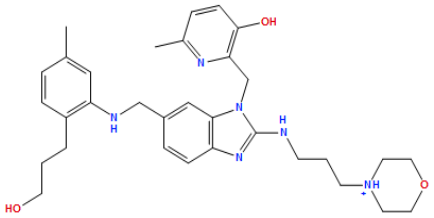
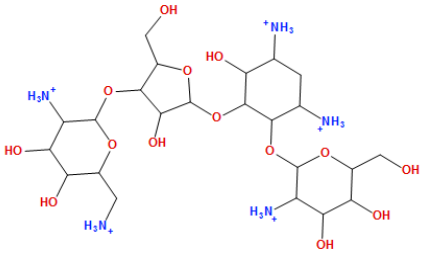
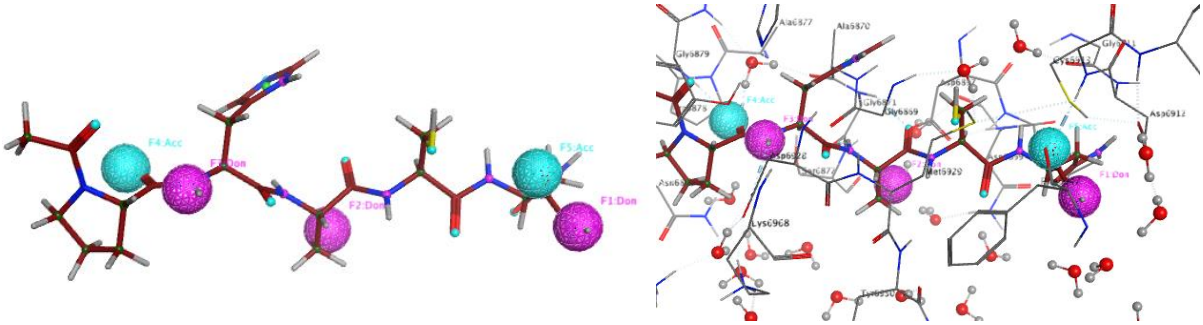
Name of hit molecule	Structure of hit molecule
1. TMC-353121	
2. Paromomycin	

Figure S7. (A) Second Pharmacophore features on SAM ligand (pink colour) of 6W4H protein structure. (B) Structures of hits (TMC-353121 and paromomycin) obtained after VS.

(A)



(B)

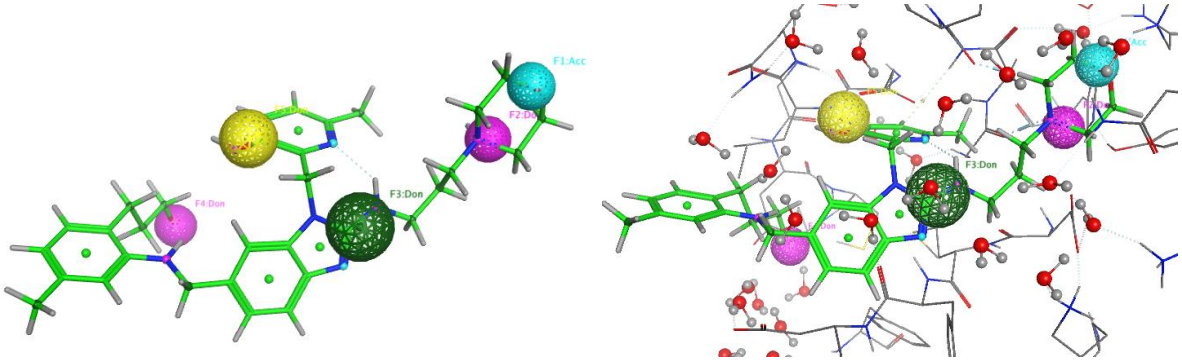


Figure S8. (A) First pharmacophore features around the hit molecule ATN-161 (brown colour) and interactions with the amino acids of the binding pocket. (B) Second pharmacophore features around the hit molecule TMC-35121 (green colour) and interactions with the amino acid of the binding pocket.

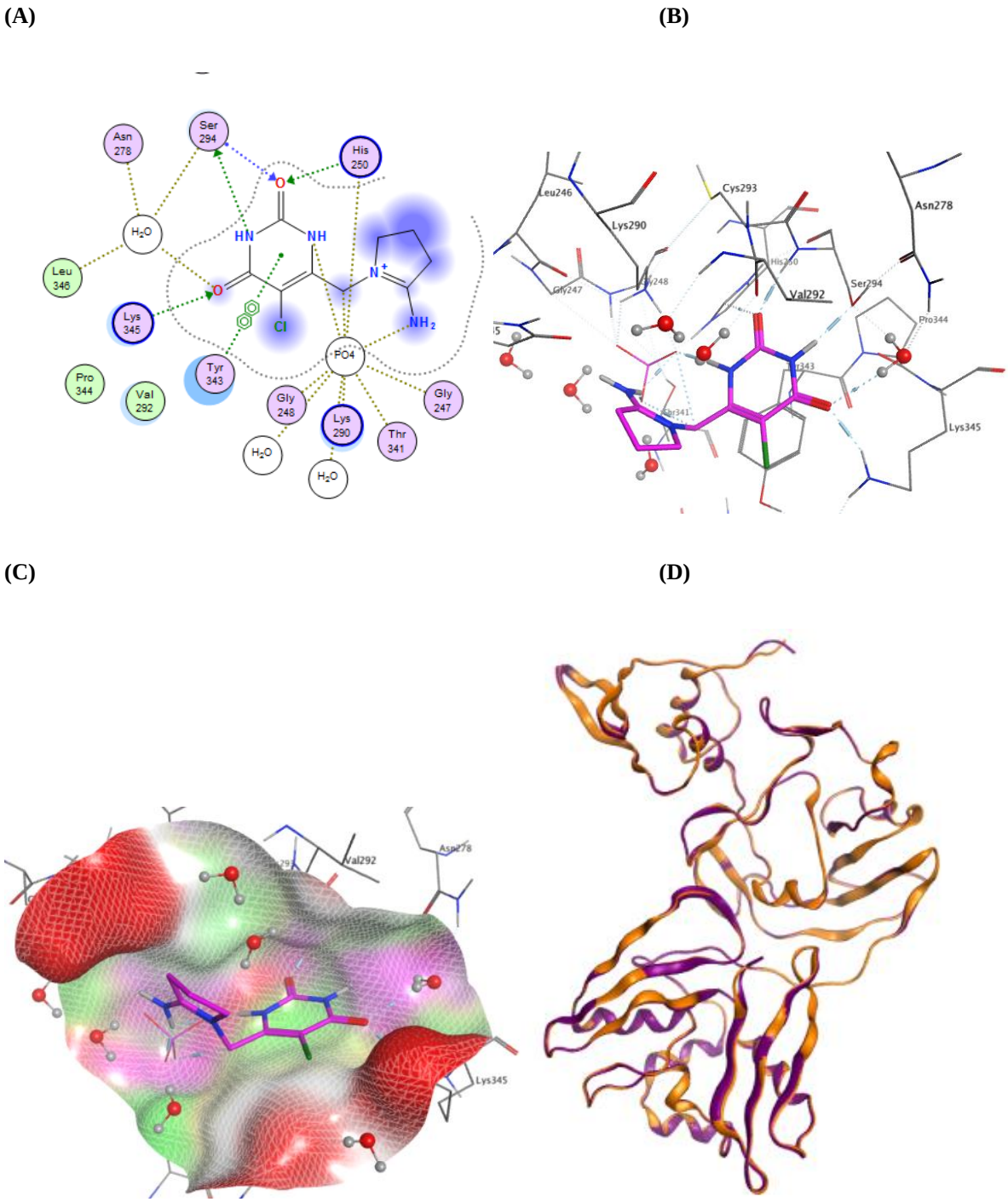
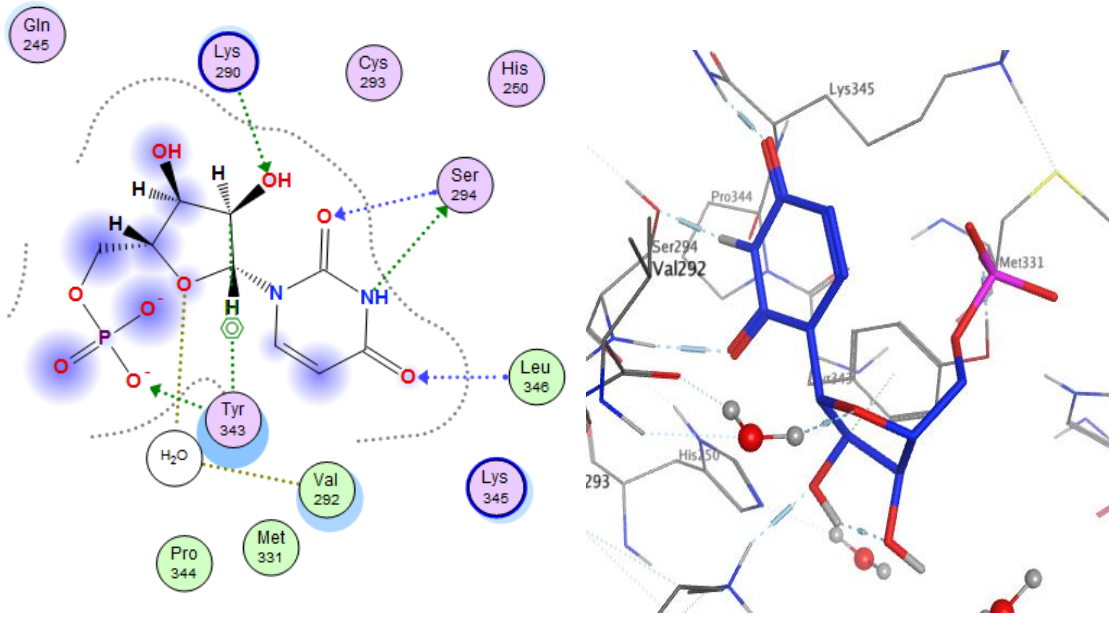


Figure S9. (A) 2D representation of the nsp15 ligand-binding pocket showing hydrogen bond interactions between tipiracil and amino acid. (B) 3D representation of ligand tipiracil (pink colour) interactions with amino acids. (C) Ligand inside the binding pocket with surface representation. (D) Superposition of 6WLC and 6WXC showing the structural similarity between them (Purple colour- 6WXC, Orange colour- 6WLC).

(A) **(B)**



(C)

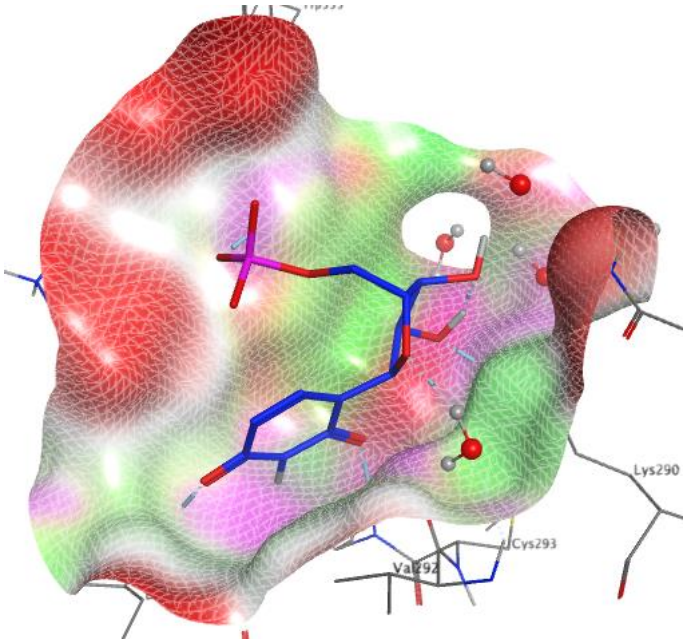
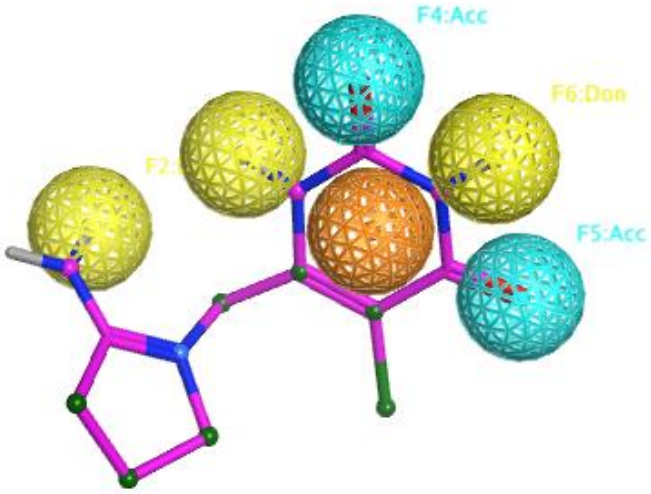


Figure S10. 2D representation of nsp15 ligand-binding pocket showing hydrogen bond interactions between U5P and amino acids. (B) 3D representation of ligand U5P (blue colour) interactions with amino acid. (C) Ligand inside the binding pocket with surface representation.

(A)



(B)

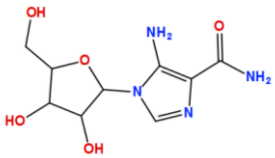
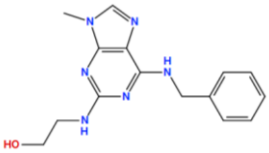
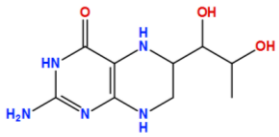
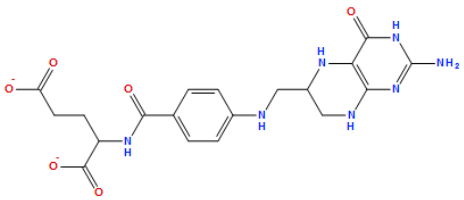
Name of hit molecule	Structure of hit molecule
1. Acadesine	
2. Olomoucine	
3. Sapropterin	
4. Tetrahydrofolic acid	

Figure S11. (A) First Pharmacophore features on tipiracil ligand (pink colour) from 6WXC protein structure. (B) Structures of select hits (acadesine, olomoucine, sapropterin and tetrahydrofolic acid) obtained after VS.

(A) **(B)**

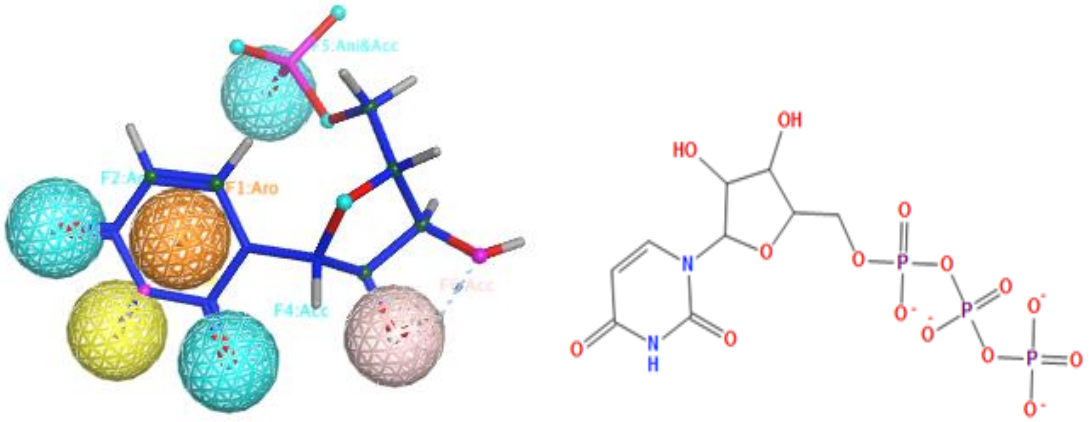
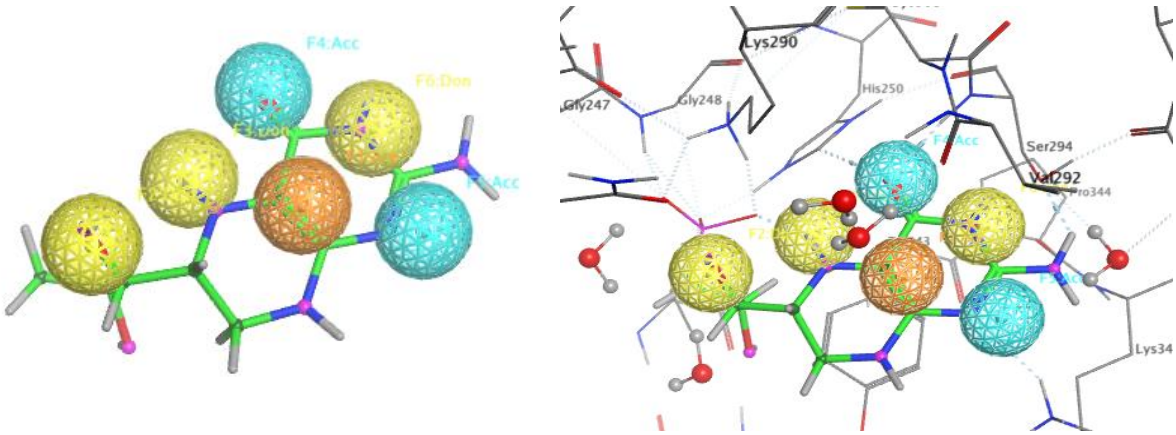


Figure S12. (A) Second Pharmacophore features on U5P ligand (blue colour) from 6WLC protein structure. (B) Structures of hit molecule (INS316) obtained after VS.

(A)



(B)

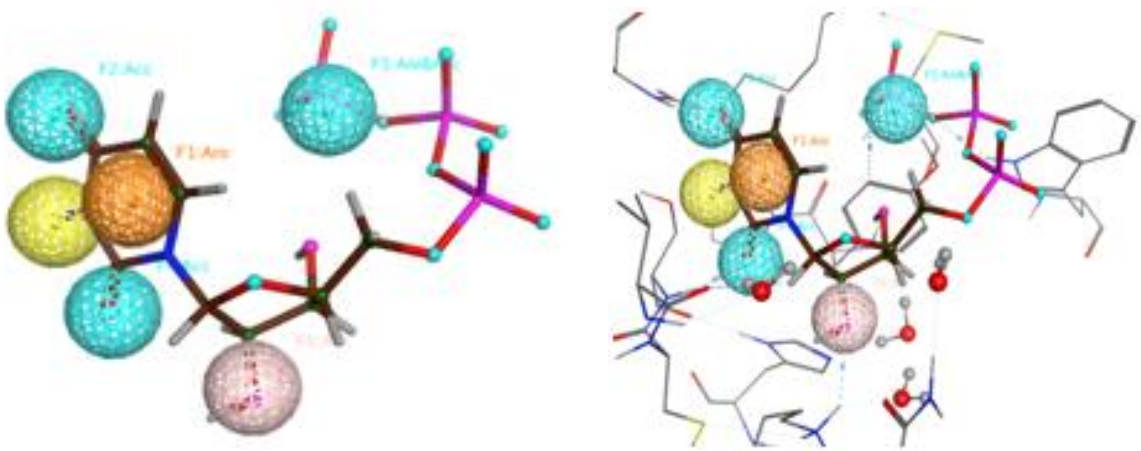


Figure S13. (A) First pharmacophore features around the hit molecule sapropterin (green colour) and its interactions with the amino acids of the binding pocket. (B) Second pharmacophore features around the hit molecule INS316 (brown colour) and interactions with the amino acids of the binding pocket.

(A) **(B)**

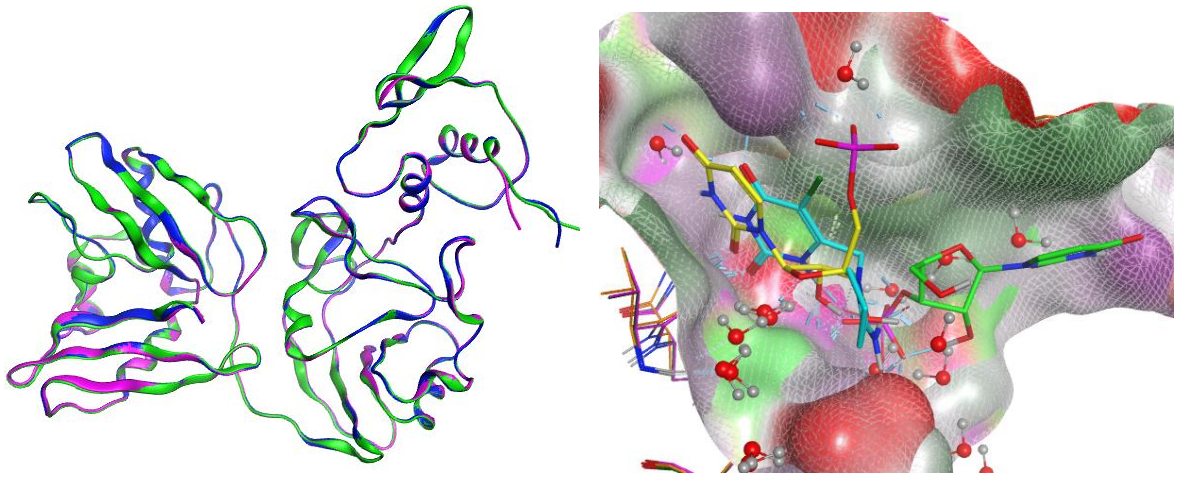
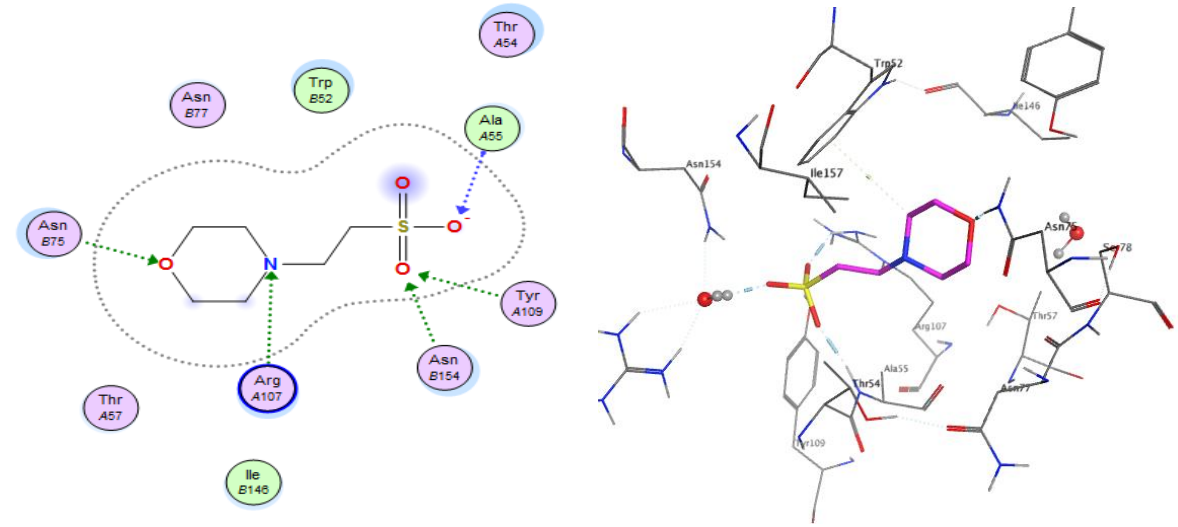


Figure S14. (A) Superposition of 6WLC, 6WXC and 6X4I showing the structural similarity between them. (B) Three different ligands in the binding site of nsp15 making different interactions (6WLC- yellow U5P, 6WXC-blue tipiracil, 6W4I-green U3P).

(A) **(B)**



(C) **(D)**

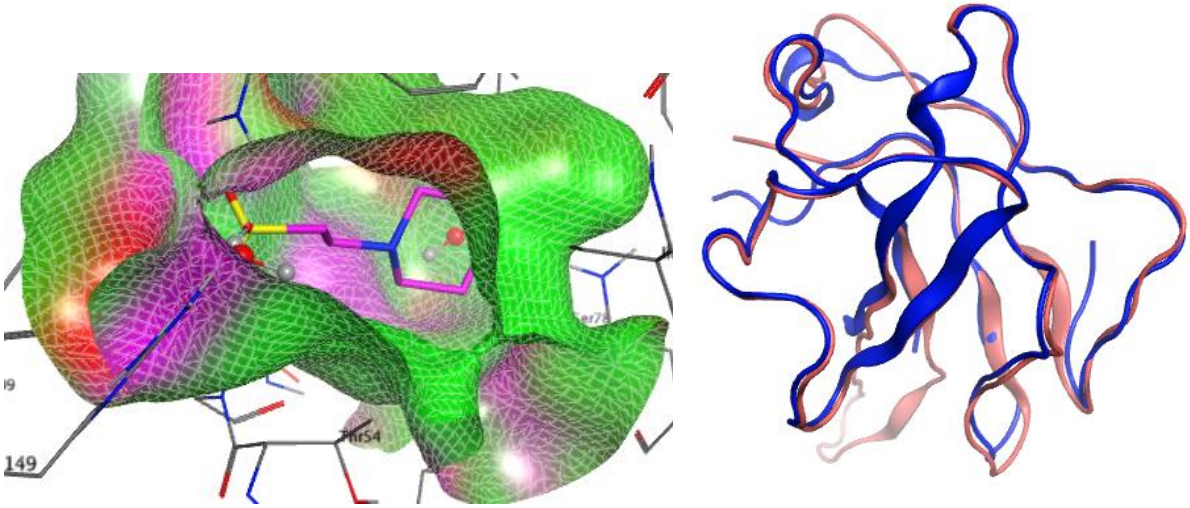
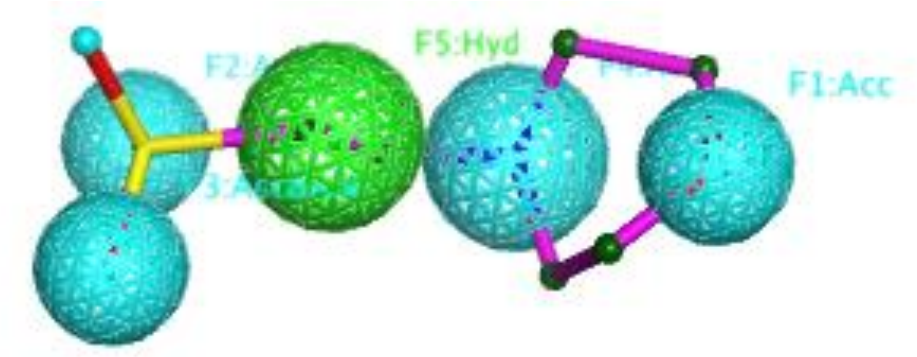


Figure S15. (A) 2D representation of nucleocapsid ligand-binding pocket showing hydrogen bond interactions between MES and amino acids. (B) 3D representation of ligand MES (pink colour) interactions with amino acids. (C) Ligand inside the binding pocket with surface representation. (D) Superposition of 6WKP and 6M3M showing the structural similarity between them (Blue colour- 6WKP, Pink colour- 6M3M).

(A)



(B)

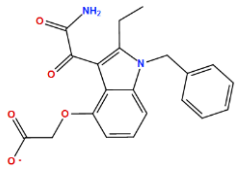
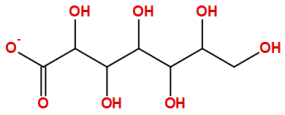
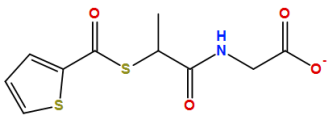
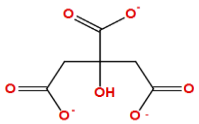
Name of hit molecule	Structure of hit molecule
1. Varespladib	
2. Calcium gluceptate	
3. Stepronin	
4. Citric acid	

Figure S16. (A) First Pharmacophore features on MES ligand D chain (pink colour) of 6WKP protein structure. (B) Structures of select hits (varespladib, calcium gluceptate, stepronin and citric acid) obtained after VS.