Structure-Guided Repurposing of SARS-CoV-2 Compounds Identifies Putative Inhibitors of Mpox Viral Enzymes

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Molecular Modelling Equations

Glide docking results show a correlation between good poses and good scores for the docked complexes. However, to determine the most reliable binding mode of the lead analogues to the target, the free binding energy is calculated using molecular mechanics generalized born surface area (MM-GBSA) with the Prime module in Maestro (Schrödinger). A summary of the respective G_{score} values and their decomposition is shown in Eq. 1 (Metuge et al. 2024):

$$G_{score} = 0.065E_{vdw} + 0.130E_{coul} + E_{lipo} + E_{hbond} + E_{Metal} + E_{BuryP} + E_{rotb} + E_{site} \quad (1)$$

From Eq. 1, E_{vdw} represents the van der Waals energy, E_{coul} represents the Coulomb energy, E_{lipo} represents the lipophilic term which is derived from hydrophobic grid potential and rewards favourable hydrophobic interactions, E_{hbond} represents the H-bonding term, which is separated into differently weighted components that depend on whether the donor and acceptor are neutral, E_{Metal} represents the metalbinding term, in which only the interactions with anionic or highly polar acceptor atoms are included, E_{BuryP} represents the penalty for buried polar groups, E_{rotb} represents the penalty for freezing rotatable bonds, while E_{site} takes into consideration the polar interactions in the active site, in which polar but non-H-bonding atoms in a hydrophobic region are rewarded.

The value for ΔG_{bind} is computed according to Eq. 2 below:

$$\Delta G_{bind} = \Delta G_{solv} + \Delta E_{MM} + \Delta G_{SA} \quad (2)$$

where, ΔG_{solv} is computed as the difference in GBSA solvation energy of the protein–ligand complex and the sum of the GBSA solvation energies for unbound protein and ligand, according to Eq. 3 below:

$$\Delta G_{solv} = G_{solv}{}^{complex} - \{\Delta G_{solv}{}^{protein} + \Delta G_{solv}{}^{ligand}\} \quad (3)$$

The ΔE_{MM} is computed as the difference in the minimised energies between the protein–ligand complex and the sum of the energies of the unbound protein and ligand, according to Eq. 4, below:

$$\Delta E_{MM} = E_{minimized}{}^{complex} - \{\Delta E_{minimized}{}^{protein} + \Delta E_{minimized}{}^{ligand}\} \quad (4)$$

ΔG_{SA} is computed as the difference in the surface area energies of the complex and the sum of the surface area energies for the unbound protein and ligand.

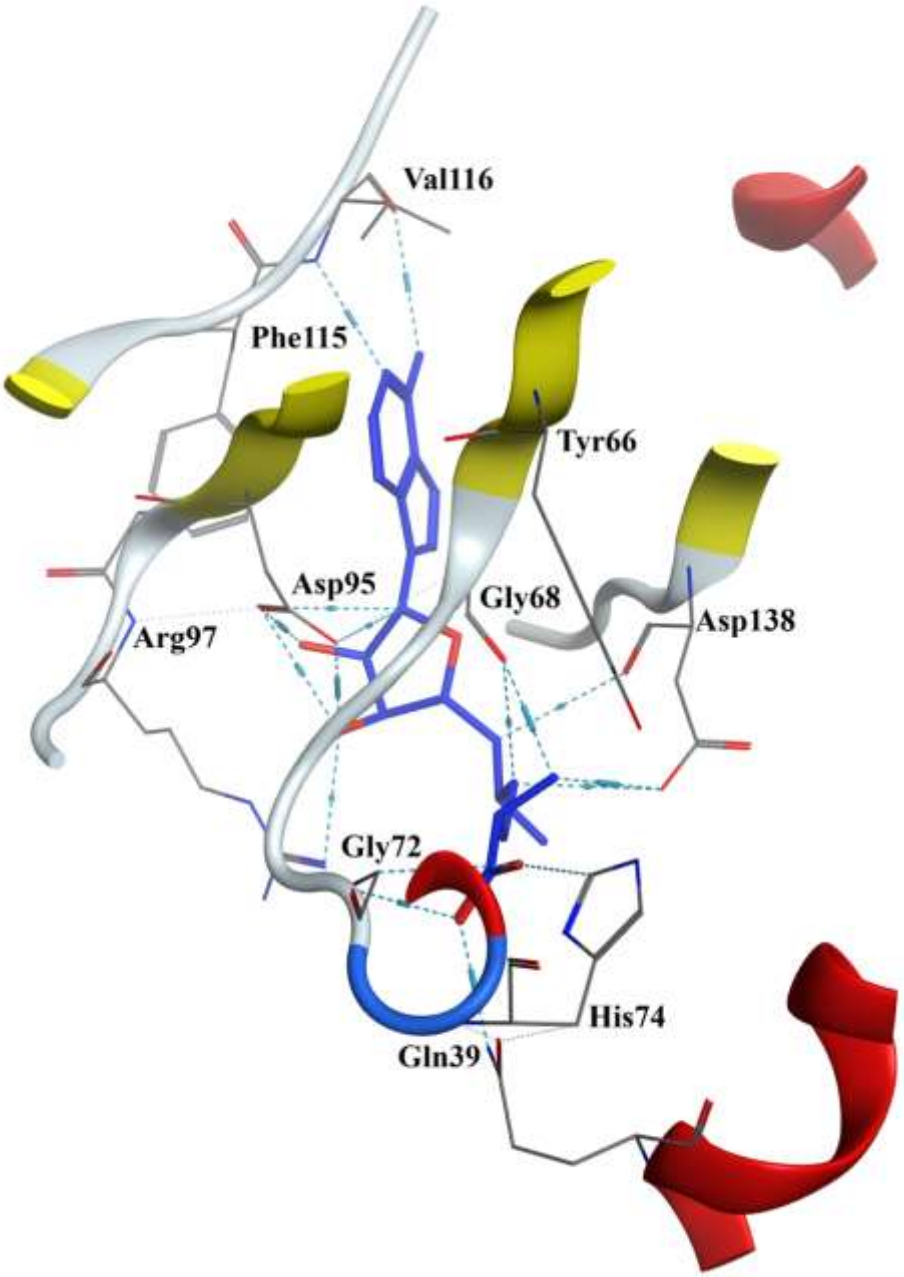


Fig. S1 Mpox viral methyltransferase VP39 in complex with its co-crystallised ligand highlights the interaction of the co-crystallised ligand with ten binding site residues cited for significantly contributing to ligand binding (Silhan et al. 2023)

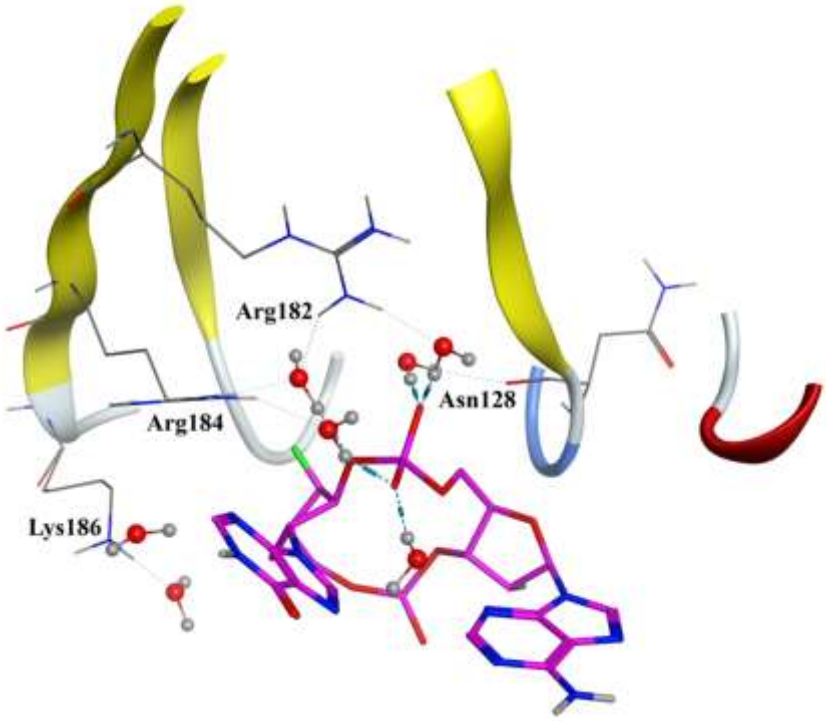


Fig. S2 Mpox viral poxin in complex with its co-crystallised ligand, MD1203 (pink), highlighting the interaction of the co-crystallised ligand with five binding site residues

Table S1. Representative scaffolds in the UB-CeDD SARS-CoV-2 compound library

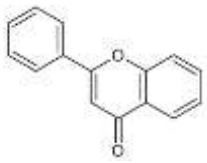
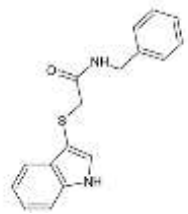
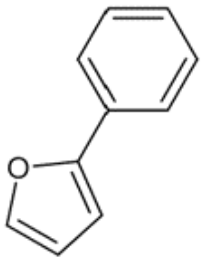
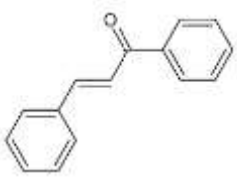
Scaffold Index	Scaffold Structure	Number of Molecules	Number of Rings	Number of Heteroatoms	Scaffold Name
1		26	3	2	Flavone
2		23	3	4	N-benzyl-2-(1H-indol-3-ylsulfanyl)acetamide
3		16	2	1	2-phenylfuran
4		16	2	1	Chalcone

Table S2. Structure-based virtual screening results of UB-CeDD SARS-CoV-2 library against Mpox viral core protease

Index	**Compound Name / ID**	**G_{score}**	**E_{vdw}**	**E_{coul}**	**L_{EFF}**
1.	78097010	-8.93	-27.51	-23.41	-0.11
2.	J02_11	-6.88	-22.73	-12.56	-0.27
3.	**Co-crystallised Ligand**	**-6.33**	**-29.94**	**-15.51**	**-0.26**
4.	Favipiravir	-6.16	-11.86	-5.75	-0.56
5.	J08_67	-6.06	-16.48	-17.60	-0.25
6.	J01_08	-5.99	-12.00	-18.90	-0.27
7.	J03_04	-5.98	-37.40	-12.35	-0.12
8.	J04_02	-5.49	-20.50	-15.47	-0.16
9.	JBB39_0009.mol	-5.43	-28.45	-16.65	-0.14
10.	J11_12	-5.37	-13.14	-13.73	-0.32
11.	J02_14	-5.07	-31.80	-15.81	-0.13
12.	11302670	-5.04	-24.49	-9.68	-0.19

KEY: See Eq. 1 above, L_{EFF}**:** Ligand Efficiency. The co-crystallised ligand is in **bold**

Table S3. Structure-based virtual screening results of UB-CeDD SARS-CoV-2 library against Mpox viral VP39 enzyme

Index	**Compound Name / ID**	**G_{score}**	**E_{vdw}**	**E_{coul}**	**L_{EFF}**
1.	JBB43_0001	-11.98	-34.90	-22.30	-0.44
2.	J08_51	-10.60	-49.33	-21.60	-0.19
3.	J14_04	-10.56	-39.90	-25.97	-0.30
4.	J01_05	-9.87	-56.97	-22.71	-0.17
5.	SV_J16_0011	-9.82	-45.08	-16.56	-0.24
6.	Cefiderocol	-9.78	-46.35	-17.94	-0.19
7.	JBB19_0002.mol	-9.44	-44.44	-13.09	-0.34
8.	JBB19_0006.mol	-9.41	-50.89	-12.72	-0.27
9.	Cangrelor	-9.40	-42.06	-27.55	-0.21
10.	**Co-crystallised Ligand**	**-9.34**	**-28.23**	**-18.49**	**-0.35**
11.	SV_J29_0002	-9.12	-49.69	-13.24	-0.17
12.	JBB39_0009	-8.55	-43.70	-22.30	-0.22

KEY: See Eq. 1 above, L_{EFF}**:** Ligand Efficiency. The co-crystallised ligand is in **bold**

Table S4. Structure-Based Virtual Screening Results of UB-CeDD SARS-CoV-2 Library against Monkeypox Viral Poxin

Index	**Compound Name / ID**	**G_{score}**	**E_{vdw}**	**E_{coul}**	**L_{EFF}**
1.	SA40_0002	-9.45	-31.12	-32.11	-0.141
2.	J02_14	-8.51	-24.39	-34.11	-0.213
3.	J02_16	-8.42	-27.75	-28.59	-0.162
4.	FAD	-7.75	-21.26	-39.73	-0.146
5.	Cangrelor	-7.70	-30.05	-29.97	-0.175
6.	JBB39_0009	-7.22	-29.24	-32.24	-0.188
7.	**Co-crystallised Ligand**	**-6.63**	**-32.97**	**-36.49**	**-0.151**
8.	J18_15	-6.12	-9.20	-19.18	-0.51
9.	3,4-Dihydroxymandelic acid	-6.10	-9.14	-24.26	-0.469
10.	MCSJ21_0009	-5.60	-15.41	-14.38	-0.229
11.	J11_21	-5.36	-19.66	-21.78	-0.19
12.	J11_56	-5.33	-17.01	-26.79	-0.25

KEY: See Eq. 1 above, L_{EFF}**:** Ligand Efficiency. The co-crystallised ligand is in **bold**

Representative two-dimensional (2D) and three-dimensional (3D) orientations of selected top-scoring docked Mpox core protease complexes from the UB-CeDD SARS-CoV-2 Library **(Fig. S3)**

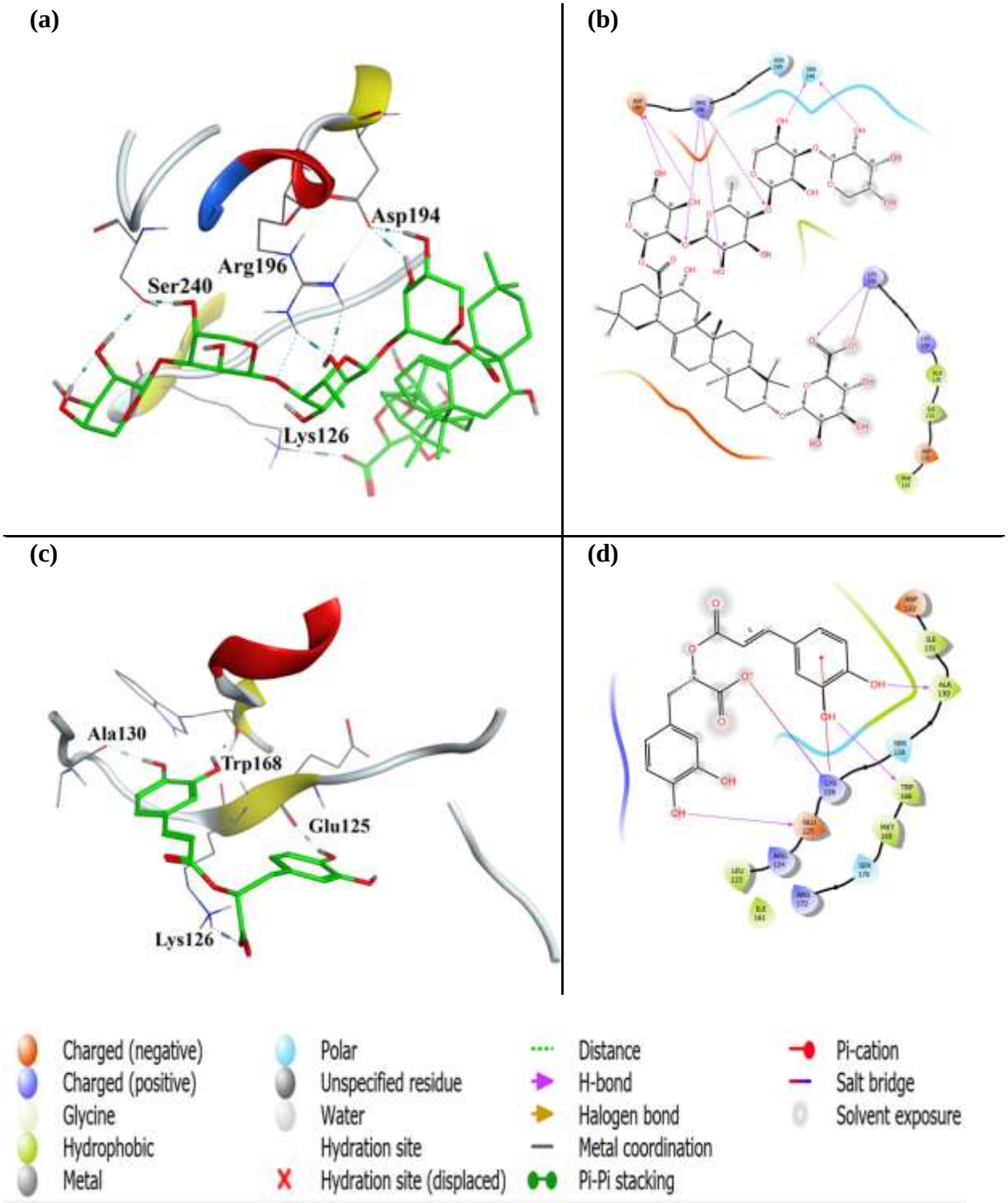


Fig. S3 3D (**a**, **c**) and 2D (**b**, **d**) interacting plots of top-scoring Mpox core protease complexes with 78097010 and J02_11, respectively

Table S5. Analysis of Binding Free Energy for Top-scoring compounds against Mpox Viral Poxin

	Compound ID	**G $_{score}$**	**ΔG_{Bind}**	**ΔG_{bind} Coul**	**ΔG_{bind} Hbond**	**ΔG_{bind} Lipo**	**ΔG_{bind} Solv GB**	**ΔG_{bind} vdW**	**Lig Strain Energy**
1.	**Co-crystallised Ligand**	**-6.63**	**-45.69**	**2.49**	**-7.09**	**-6.69**	**4.06**	**-35.13**	**2.58**
2.	J02_14	-8.51	-38.44	-33.53	-6.20	-7.06	31.30	-22.85	10.43
3.	FAD	-7.75	-35.74	-15.50	-6.99	-7.44	21.90	-27.06	3.74
4.	JBB39_0009	-7.22	-31.88	-44.87	-7.08	-8.50	53.23	-25.54	5.80
5.	J02_16	-8.42	-26.84	-55.57	-6.84	-8.87	57.29	-23.36	28.77
6.	Cangrelor	-7.70	-16.63	-46.80	-5.35	-7.77	77.35	-39.89	6.38
7.	SA40_0002	-9.45	6.64	-62.52	-9.10	10.65	89.00	-30.94	27.31

KEY: See Eq. 2 – 4. The co-crystallised ligand is in **bold.**

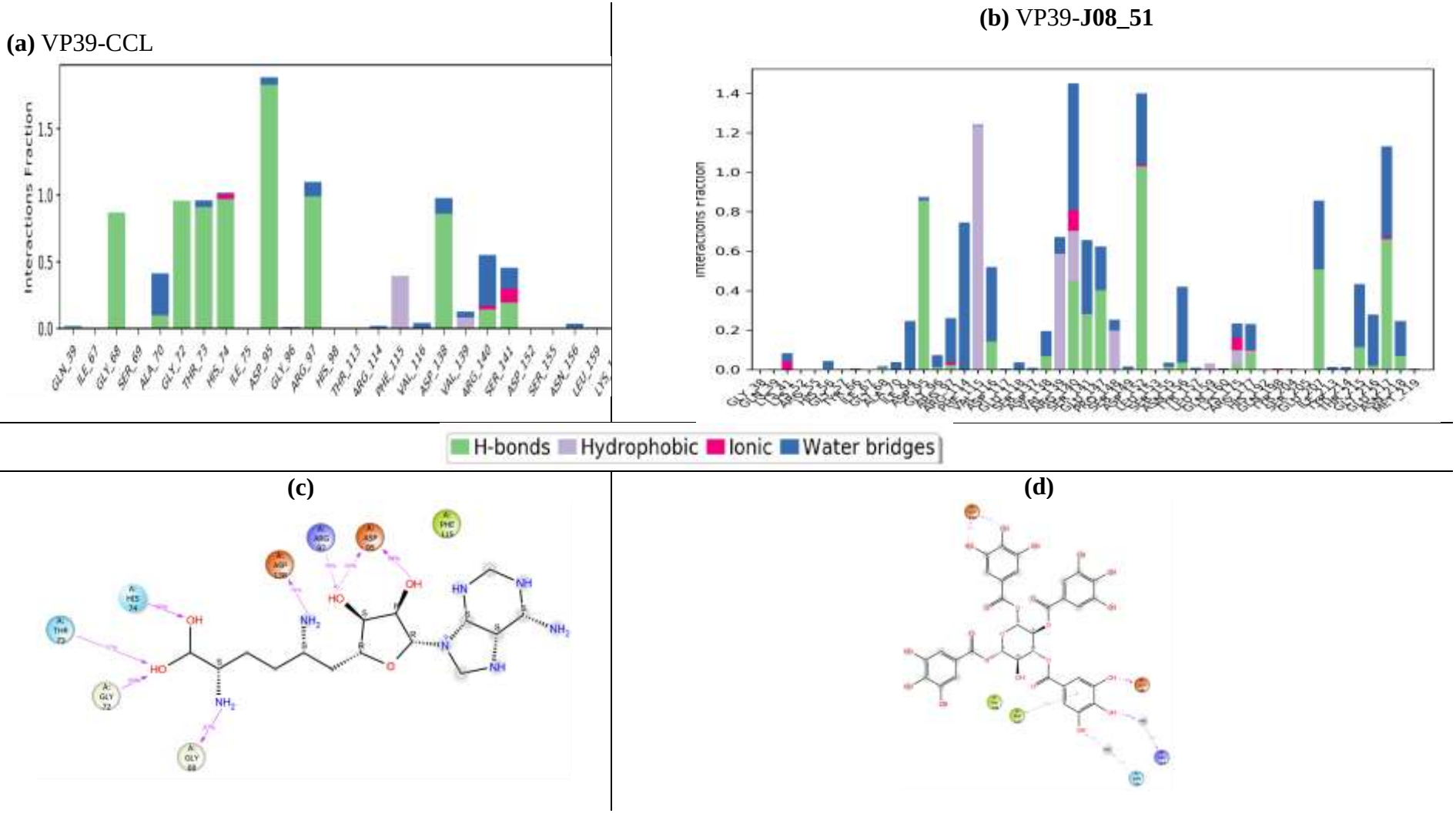


Fig. S4 Comparison of Mpox VP39 methyltransferase protein-ligand contacts between the co-crystallised ligand and top hit **J08_51**

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Silhan J, Klima M, Otava T, Skvara P, Chalupska D, Chalupsky K, Kozic J, Nencka R, Boura E (2023) Discovery and structural characterization of monkeypox virus methyltransferase VP39 inhibitors reveal similarities to SARS-CoV-2 nsp14 methyltransferase. Nat Commun 14(1):2259. https://doi.org/10.1038/s41467-023-38019-1