Identification of novel human USP2 inhibitor: might involve in SARS-CoV-2 papain-like (PLpro) protease deubiquitination activity

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Table S1: AutoDock Vina and of MMGBSA value (total binding free energy calculated after 5ns MD simulations) of known human-USP2 binders. pIC_{50} values are converted from the IC_{50} in order to generate correlation plot.

CHEMBL-ID	IC50 (µM)	pIC50 (-log IC50)	AD Vina score ΔG (kcal/mol)	MM-GBSA ΔGtol (kcal/mol)
CHEMBL3392809	1.2187	5.91	-7.3	-34.35
CHEMBL275938	1.0399	5.98	-7.2	-36.9
CHEMBL3392821	1.9314	5.71	-7.2	-38.47
CHEMBL1587630	7.0795	5.15	-7.1	-31.54
CHEMBL3197687	12.5893	4.9	-7.1	-28.17
CHEMBL3392782	3.4347	5.46	-7.1	-34.2
CHEMBL1730100	10	5	-7	-30.14
CHEMBL1439048	5.0119	5.3	-6.9	-33.7
CHEMBL1424694	4.4668	5.3	-6.9	-24.45
CHEMBL1473896	12.5893	4.9	-6.7	-24.25
CHEMBL1538730	10	5	-6.7	-32.14
CHEMBL1308447	12.5893	4.9	-6.7	-24.3
CHEMBL3192701	10	5	-6.5	-33.71
CHEMBL1304024	11.6681	4.93	-6.5	-29.54
CHEMBL3392890	1.7214	5.76	-6.4	-36.54
CHEMBL1598108	12.5893	4.9	-6.3	-29.45
CHEMBL1488249	11.2202	4.95	-6.3	-24.35
CHEMBL496	3.1623	5.5	-6.2	-36.1
CHEMBL1542331	7.9433	5.1	-6.2	-34.23
CHEMBL1577635	13.0918	4.88	-6.1	-27.32

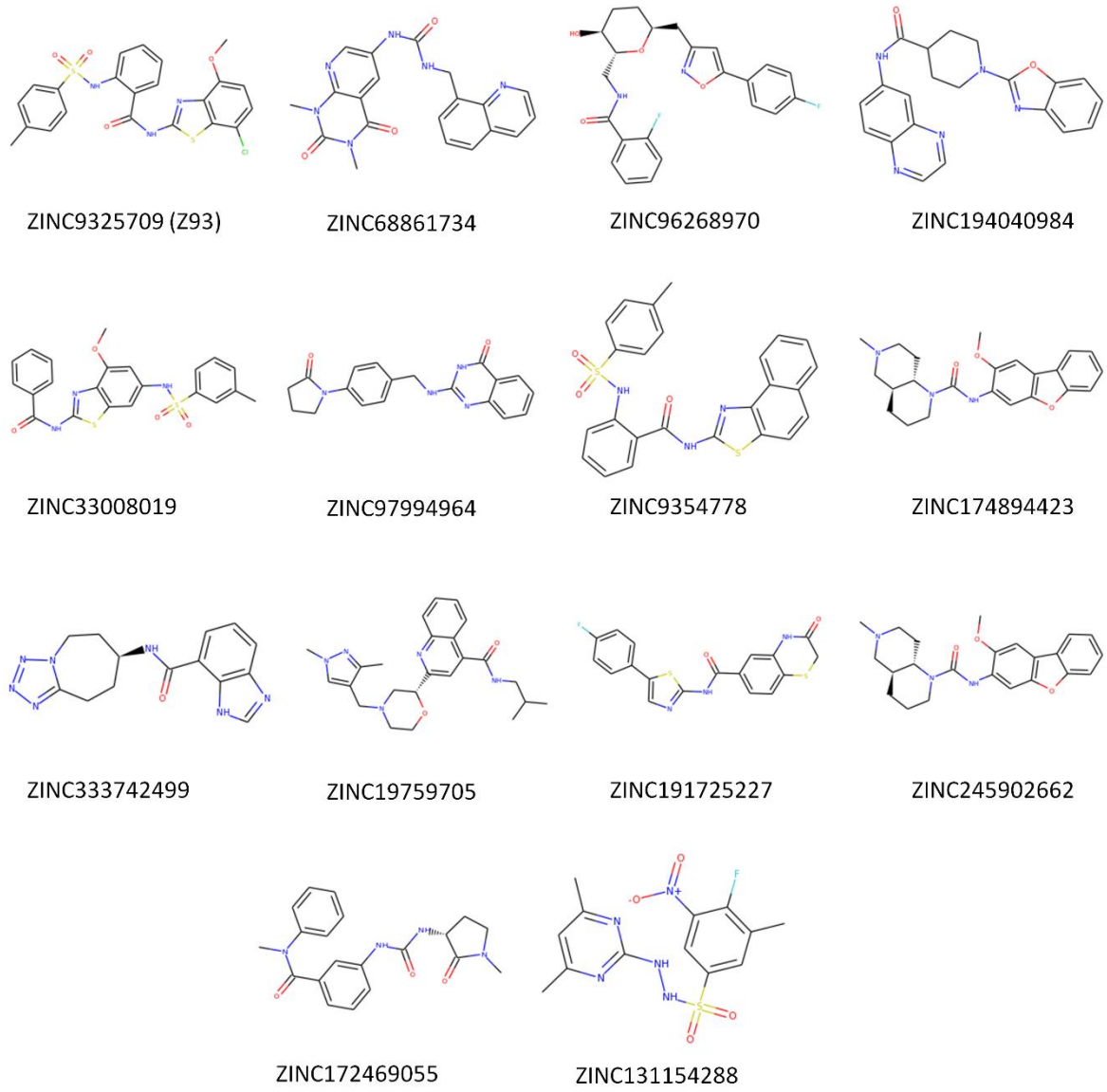

Figure S1: Structural representations of top 14 hits after step-wise integrated virtual screening workflow.

Table S2: AutoDock Vina and of MMGBSA value (total binding free energy calculated after 20ns MD simulations) of top 14 compounds from *in silico* screening. A total of 4.2 million molecules were screened. The docking results for CHEMBL3392809 (USP2 potent inhibitor) are included for comparison. The tested compound is presented bold.

Sr. number in VS	IDs	AD Vina score ΔG (kcal/mol)	MM-GBSA ΔGtol (kcal/mol)
7	**ZINC9325709 (Z93)**	**-7.9**	**-38.07**
22	ZINC68861734	-7.3	-36.8
11	ZINC33008019	-7.8	-35.4
31	ZINC97994964	-7.6	-34.65
8	ZINC9354778	-7.9	-34.25
29	ZINC174894423	-8	-33.61
2	ZINC333742499	-7.7	-32.7
20	ZINC19759705	-7.8	-32.58
23	ZINC191725227	-8.2	-31.83
3	ZINC245902662	-7.4	-29.45
34	ZINC172469055	-7.6	-28.4
14	ZINC131154288	-8.1	-27.54
9	ZINC96268970	-7.7	-26.7
18	ZINC194040984	-8.2	-26.45
	CHEMBL3392809 (Cut off)	-7.3	-34.35

Table S3: Detailed Pharmacokinetics and ADMET properties of top hits. All 3 hits have passed series of PAINS filter.

Parameters	ZINC9325709 (Z93)	ZINC68861734	ZINC33008019
MW	487.98	390.4	453.53
#Heavy atoms	32	29	31
#Aromatic heavy atoms	21	20	21
Fraction Csp3	0.09	0.15	0.09
#Rotatable bonds	7	5	7
#H-bond acceptors	5	5	5
#H-bond donors	2	2	2
Molar reractivity	127.42	110.08	122.41
TPSA	134.01	110.91	134.01
iLOGP	2.33	2.24	2.94
XLOGP3	5.59	0.84	4.41
WLOGP	6.02	1.16	5.37
MLOGP	3.13	1.46	2.38
Silicos-IT Log P	4.54	1.25	3.9
Consensus Log P	4.32	1.39	3.8
GI absorption	Low	High	Low
BBB permeant	No	No	No
Pgp substrate	No	Yes	No
CYP1A2 inhibitor	No	No	No
CYP2C19 inhibitor	Yes	No	Yes
CYP2C9 inhibitor	Yes	No	Yes
CYP2D6 inhibitor	No	No	No
CYP3A4 inhibitor	Yes	No	Yes
log Kp (cm/s)	-5.31	-8.09	-5.94
Lipinski #violations	0	0	0
Veber #violations	0	0	0
Egan #violations	1	0	1
Muegge #violations	1	0	0
Bioavailability Score	0.55	0.55	0.55
PAINS #alerts	0	0	0
Brenk #alerts	0	0	0
Synthetic Accessibility	3.49	2.89	3.45

Note: BBB, blood–brain barrier; HIA, human intestinal absorption; CYP450, cytochrome P450; Veber Rule, Bad or Good oral bioavailability rule (rotatable bonds ≤ 10) and (TPSA ≤ 140 Å or H-Bonds Donors + H-Bonds Acceptors ≤ 12); Egan Rule, Bad or Good oral bioavailability rule ($0 \geq TPSA \leq 132$) and ($-1 \geq logp \leq 6$).

Table S4: Binding affinities and contributing energies of the Z93 calculated through MMGBSA module of AMBER after 20 ns MD simulations

	Human-UPS2/Z93	**SARS-CoV-2 PLpro/Z93**
ΔE ele	-22.36	-18.45
ΔE vdw	-36.4	-39.45
ΔE MM	-58.76	-57.9
ΔG p	29.25	32.87
ΔG np	-8.56	-8.02
ΔG sol	20.69	24.85
ΔG tol	-38.07	-33.05