Structural elucidation of SARS-CoV-2 vital proteins: computational methods reveal potential drug candidates against Main protease, Nsp12 RNA-dependent RNA polymerase and Nsp13 helicase

Muhammad Usman Mirza[1], Matheus Froeyen[1*]

[1] Department of Pharmaceutical and Pharmacological Sciences, Rega Institute for Medical Research, Medicinal Chemistry, University of Leuven, B-3000 Leuven, Belgium

Corresponding author:

Prof. Matheus Froeyen

Department of Pharmaceutical and Pharmacological Sciences

Rega Institute for Medical Research,

Medicinal Chemistry, University of Leuven, B-3000 Leuven, Belgium

Email: mathy.froeyen@kuleuven.be

Supplementary information

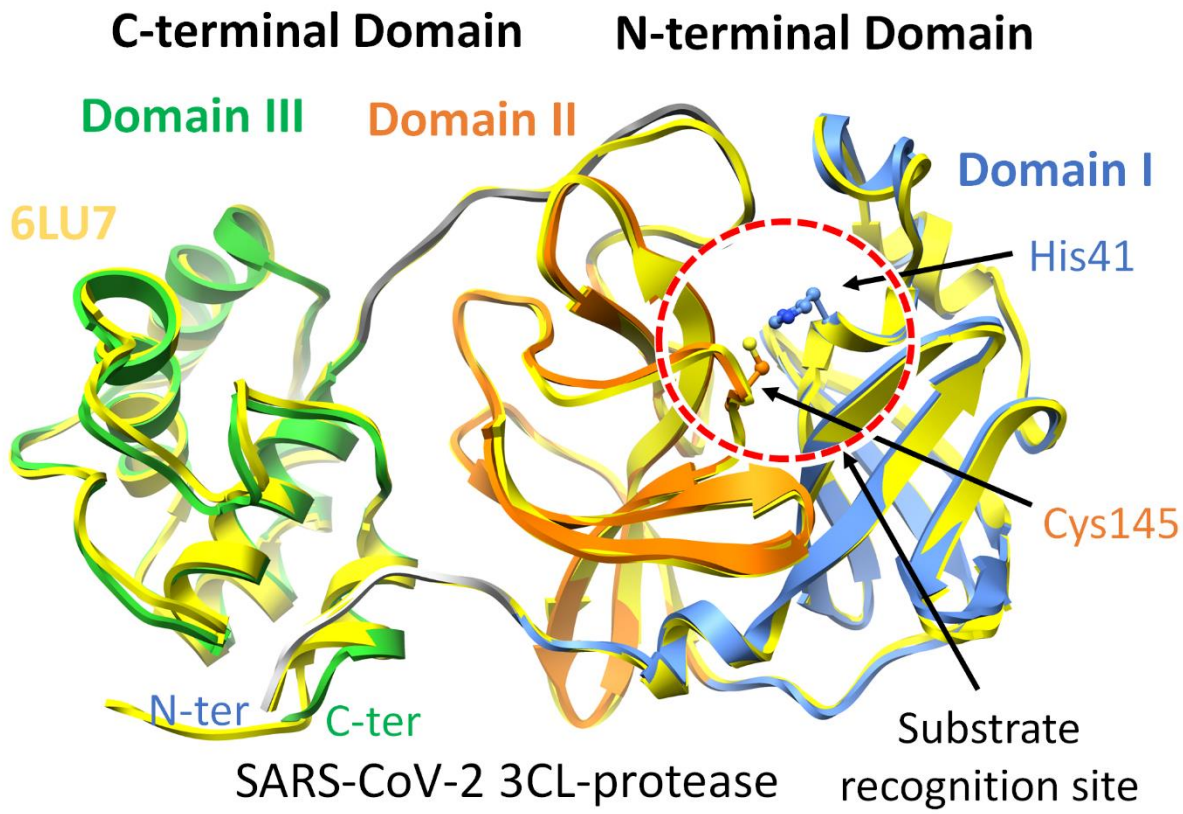

Figure S1: Overall ribbon representation of SARS-CoV-2 main protease monomer superimposed on co-crystalized structure in golden ribbon (PDB ID: 6LU7) composed of N-terminal domain I (cornflower blue) and domain II (orange), and C-terminal domain III (green). Substrate recognition site is circled and catalytic dyad residues, His41 and Cys145 are highlighted and labelled

Table S1: Detailed Pharmacokinetics and ADMET profile of top hits

Parameters	SARS-CoV-2 Mpro					SARS-CoV-2 NSp12 RdRp			SARS-CoV-2 Nsp13 Helicase			
	cmp3	cmp12	cmp14	cmp17	cmp18	cmp2	cmp17a	cmp21	cmp1	cmp3a	cmp11	cmp15
MW	340.38	463.58	555.03	502.56	509.45	566.63	529.59	566.52	560.47	578.71	596.7	598.47
#Heavy atoms	25	32	41	38	37	42	40	40	42	42	43	45
#Aromatic heavy atoms	14	21	38	29	23	26	28	15	24	42	21	36
Fraction Csp3	0.39	0.32	0.03	0.13	0.12	0.32	0.19	0.46	0	0	0.27	0.03
#Rotatable bonds	3	5	6	4	7	6	4	7	8	6	6	4
#H-bond acceptors	5	5	5	4	7	7	5	9	9	4	6	10
#H-bond donors	1	1	1	3	4	3	2	2	2	0	0	0
MR	97.01	127.67	161.71	150.82	133.06	165.06	158.26	141.69	147.88	171.28	176.42	164.01
TPSA	98.39	143.02	100.33	114	98.91	126.92	106.73	103.33	175.81	117.9	100.54	172.7

Consensus Log P	2.39	3.84	5.52	4.43	4.66	3.79	3.48	3.66	1.21	7.12	3.36	3.24
GI absorption	High	Low	Low	Low	Low	Low	High	High	Low	Low	High	Low
BBB permeant	No	No	No	No	No	No	No	No	No	No	No	No
Pgp substrate	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes
CYP1A2 inhibitor	Yes	No	No	No	Yes	No	Yes	No	No	No	No	No
CYP2C19 inhibitor	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	No
CYP2C9 inhibitor	Yes	Yes	No	No	No	Yes	Yes	No	No	No	Yes	No
CYP2D6 inhibitor	No	Yes	No	No	Yes	Yes	Yes	Yes	No	No	No	No
CYP3A4 inhibitor	Yes	No	No	No	No	No	No	Yes	No	No	Yes	No
log Kp (cm/s)	-6.53	-5.8	-5.11	-6.18	-6.46	-6.84	-7.46	-7.63	-8.72	-3.68	-7.45	-7.36
Lipinski #violations	0	0	2	1	1	1	1	1	2	2	1	2
Veber #violations	0	1	0	0	0	0	0	0	1	0	0	1
Egan #violations	0	1	1	0	1	0	0	0	1	1	0	1
Muegge #violations	0	0	1	0	0	0	0	0	1	2	0	2
Bioavailability Score	0.55	0.55	0.17	0.55	0.55	0.55	0.55	0.55	0.17	0.17	0.55	0.17
PAINS #alerts	0	0	0	0	0	0	0	0	0	0	1	0
Brenk #alerts	0	0	0	0	0	0	0	0	1	0	1	0
Leadlikeness #violations	0	2	2	2	2	2	1	1	2	2	2	2
Synthetic Accessibility	3.71	4.15	3.99	3.45	3.43	4.26	3.87	4.62	3.18	4.19	4.46	3.55

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 ($-1 \geq logp \leq 6$).