Targeting the complement serine-protease MASP-2 as a therapeutic strategy for coronavirus diseases

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Supporting Information

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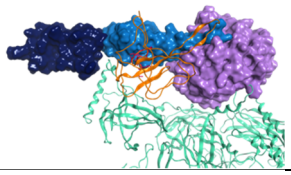
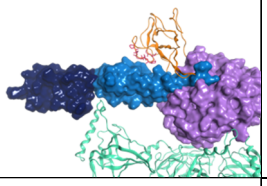
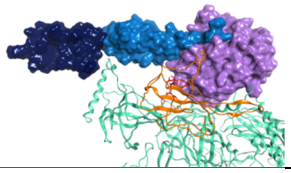
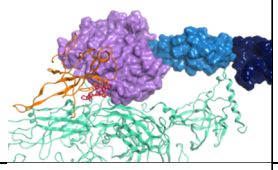
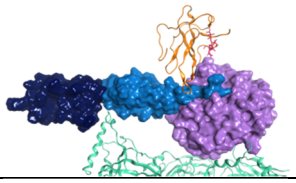
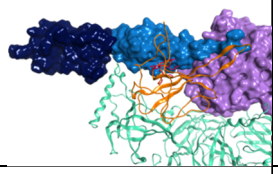
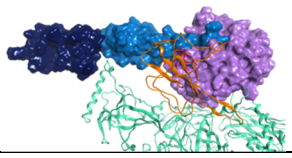
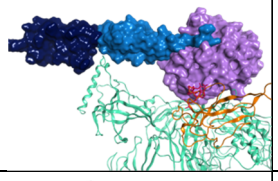
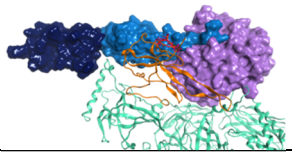
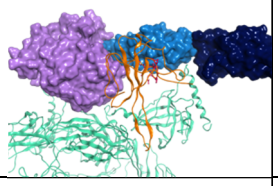
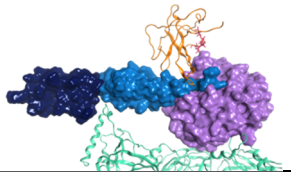
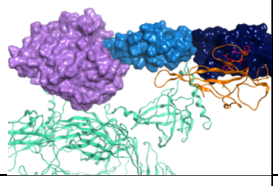
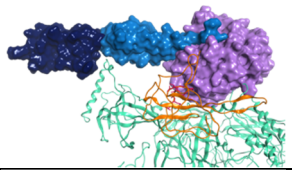
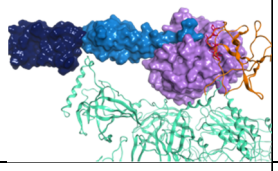
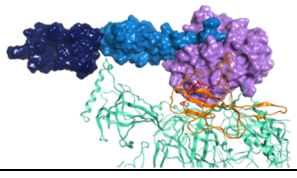
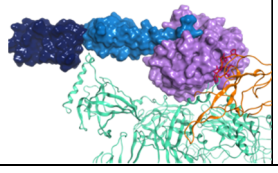
Table S1

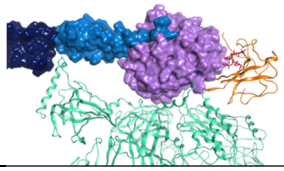
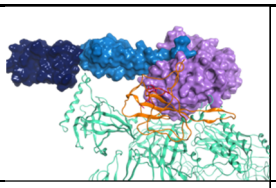
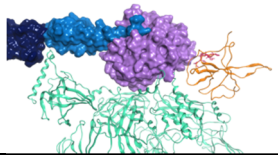
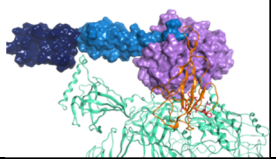
Rescoring values for the drug repurposing final choices for the catalytic site of MASP-2.

Compound	Rescoring values, kcal/mol			
	Glide XP	**PLANTS**	**FlexX**	**ScorePose**
Nafamostat	-8.4292631	-77.382202	-29.23	-14.948345
Furamidine	-7.6509728	-81.5009	-33.458	-10.458287
Skepinone-1	-7.4871306	-84.484703	-17.99	-11.943799
Tiotidine	-5.7613311	-74.677696	-29.006001	-11.650853
Ceritinib	-7.4828296	-85.0252	-23.82	-8.6786385
Guanfacine	-8.0983143	-69.356201	-19.563	-11.27206
ML324	-4.2543254	-82.982399	-22.639	-12.195214
Canertinib	-4.5961032	-85.014503	-21.056	-10.462101
Balaglitazone	-5.2521544	-79.750099	-19.941	-10.705989
CCT128930	-7.3585343	-71.544601	-19.858999	-9.128973
CB-5083	-4.5376992	-75.287498	-22.572001	-10.545598
Lucitanib	-7.5688577	-78.883698	-15.091	-8.9847565
SUN-11602	-5.1951108	-82.136597	-20.254	-8.5957499
Linifanib	-4.4032121	-72.777	-23.044001	-9.319706
JNJ-26481585	-5.3877602	-72.921402	-20.924999	-8.0121317
Paliperidone	-5.4913545	-73.477898	-15.971	-8.5497789
RP-001	-4.1750298	-76.439499	-17.313	-8.7906342
AZD1080	-4.2881861	-75.641899	-17.223	-8.4997702
VS-4718	-5.019186	-74.370102	-17.351	-7.714396
Revaprazan	-4.8230472	-70.754402	-16.761999	-8.5200548
Olmesartan	-4.8132172	-70.759399	-13.546	-8.795146
Sunitinib	-6.0446553	-74.079102	-19.391001	-12.049711

Table S2

Protein-protein docking results between MASP-2 (PDB ID 4FXG) and SARS-CoV-2 N protein (6M3M), obtained with MOE 2019.10.

Complex	Structure*	MOE Docking Score	Complex	Structure*	MOE Docking Score
1		-78.438843	11		-48.151939
2		-64.966309	12		-47.884235
3		-56.666553	13		-46.32021
4		-56.060783	14		-44.49239
5		-55.253914	15		-43.264782
6		-53.31538	16		-41.950214
7		-51.986874	17		-40.230049
8		-49.597775	18		-35.882229

9		-48.835548	19		-30.870058
10		-48.414017	20		-23.445593

***** MASP-2 domains are represented as molecular surface: CCP1 in dark blue, CCP2 in light blue and SP in lilac. C4 is represented as green ribbon. SARS-CoV-2 N protein is represented as orange ribbon, with atoms if the interacting sequence (res. 115-123) shown in pink.

Figure S1

Effect of serum heat-inactivation and DMSO on the MBL complement pathway activity. Positive standard non-heat inactivated (NHI) serum or heat inactivated (HI) serum as a negative control was 1:101 diluted with the Wieslab kit buffer and tested, in the presence and absence of different concentrations of DMSO, for their ability to activate the MBL complement pathway by the Wieslab ELISA kit. The complement activation of the MBL pathway was detected by an anti-C5b-9 antibody conjugated to alkaline phosphatase, followed by adding the substrate pNPP and the measurement of the absorbance at 405 nm. Diluent only was also tested as a blank control. Data shown represent the mean ± SD of experiments conducted in duplicate. Data from DMSO-treated NHI serum were statistically analysed for significant differences versus NHI untreated serum by a two-tailed unpaired Student t-test.

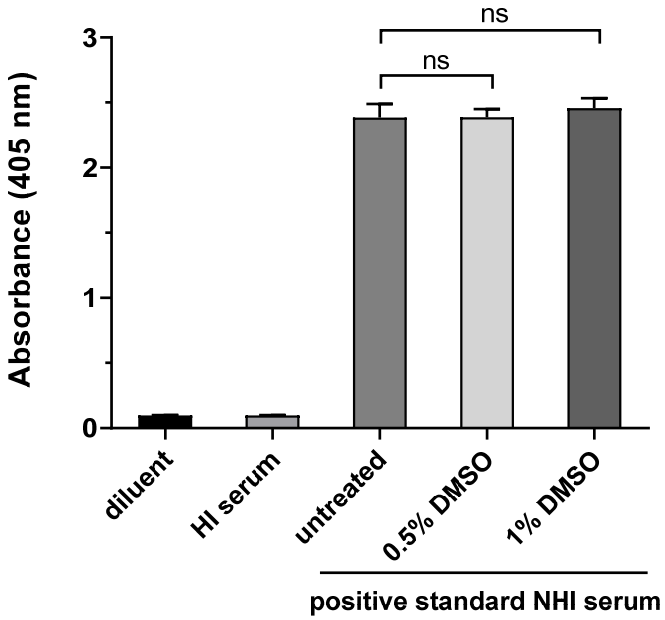


Figure S2

Plots of mean C-alpha RMSD (Å) values against simulation time for the complex of MASP-2 and SARS-CoV-2 N protein. After ~10 ns of equilibration, the system reaches stability and it is characterised by a small RMSD variation for the rest of the simulation. Colour legend: MASP-2 (blue), SARS-CoV-2 N protein (purple).

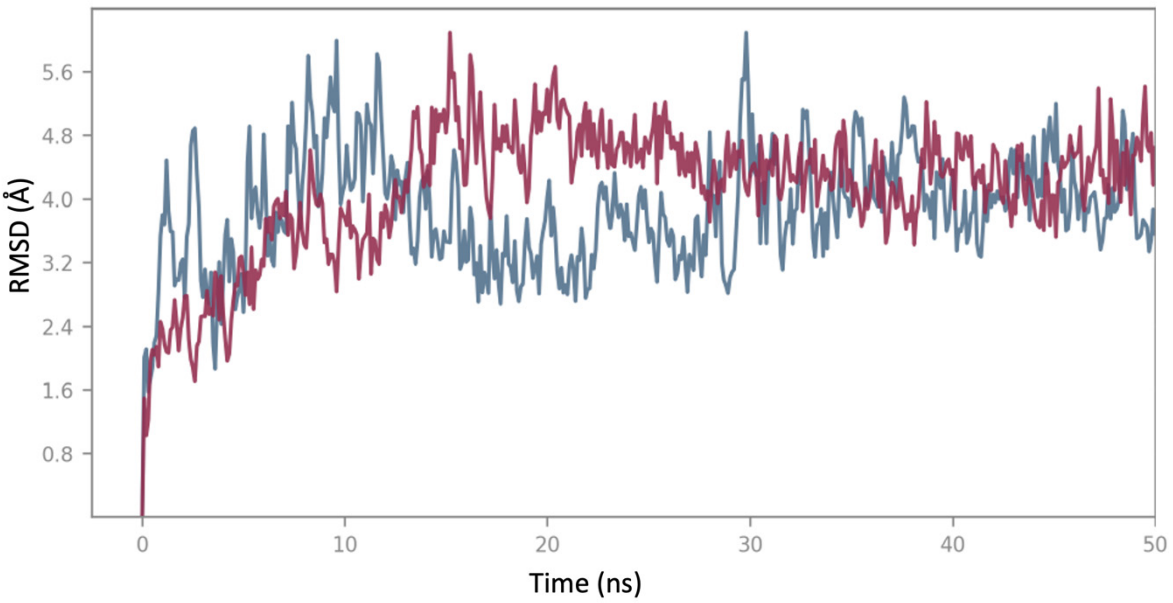


Figure S3

Interactions detected during the molecular dynamics simulation (representative graph), analysed with the Simulation Interaction Diagram function in Desmond. MASP-2 residues directly interacting with residues 115-123 of SARS-CoV-2 N protein are labelled, and the different interactions are shown as coloured bars: H-bonds (green), hydrophobic (lilac) and water bridges (blue). Fraction values over 1.0 indicate that the protein residue makes multiple contacts of the same subtype with the ligand.

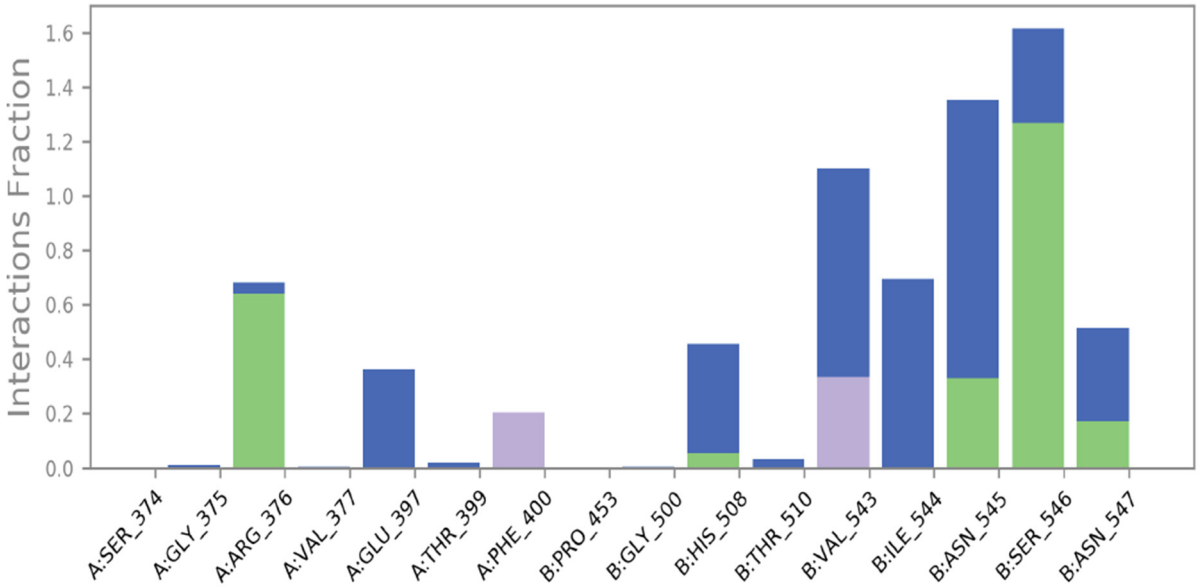


Table S3

Direct contacts observed in discrete frames from the molecular dynamics simulations, between the N protein target residues 115-123, with the addition of Tyr124 and Lys128, and MASP-2 residues forming the druggable site at the contact surface with the N protein.

Frame	MD 1			MD 2			MD 3		
	MASP-2 residues defining the interaction site in proximity to N-protein interacting sequence		*Direct interactions between MASP-2 and N-protein interacting sequence*[1]	*MASP-2 residues defining the interaction site in proximity to N-protein interacting sequence*		*Direct interactions between MASP-2 and N-protein interacting sequence*[1]	*MASP-2 residues defining the interaction site in proximity to N-protein interacting sequence*		*Direct interactions between MASP-2 and N-protein interacting sequence*[1]
	CCP2	*SP*		*CCP2*	*SP*		*CCP2*	*SP*	
0 ns (starting point)	T339 F400	M499 G500 Y509 T510 N545 S546 N547 I548	S546-G121 N547-P118 N547-E119 T510-K128	T339 F400	M499 G500 Y509 T510 N545 S546 N547 I548	S546-G121 N547-P118 N547-E119 T510-K128	T339 F400	M499 G500 Y509 T510 N545 S546 N547 I548	S546-G121 N547-P118 N547-E119 T510-K128
10 ns	T399 F400	M499 G500 H508 Y509 T510 N545 S546 N547 I548	T510-K128 N545-P118 N547 -118 N547-A120 V543 -L122	S374 C396 E397 F400 T401	M499 G500 H508 Y509 T510 Q511 V542 V543 I544 N545 N547 I548	R376-Y124 S546-A120 V543-L122	P369 D370 D371 L372 S374 G375 R376 V377 Y379 Y394 S395 C396 E397	-	-
20 ns	S374 E397 F400 Y401	G500 H508 Y509 Y510 N540 Y541 V542 V543 I544 N545 N547 I548	N547-A120 V543-L122	S374 G375 C396 E397 F400 Y401	V542 V543 I544 N545 N547 I548 G500 H508 Y509 T510	R376 -Y124 V543-L122 S546-A120	P373 S374 Y401 C430 E431 P432 V433	G454 P457 D475 K541 V542 V543 I544 N545 S546 T549	-
30 ns	-	M499 G500 H508 Y509 T510 N545 N547 I548	V543-L122	S374 C396 E397 F400 Y401	V543 I544 N545	R376-Y124 S546-A120 V543-L122	S374 G375 R376 S395 C396 E397 F400 Y401 C430 P432 V433	I544 N545 N546 T549	-

40 ns	S374 G375 R376 C396 E397 F400 Y401	D475 G500 T510 K541 V542 V543 I544 N545 I548	V543-L122	S374 G375 E378 S395 C396 E397 E398 Y401	K452 P453 G455 F456 P457 N459 V460 R498 M499 G500 T501 L502 K503 S506 H508 T510 N545 N547 I548 L585	R376-Y124 N545 -P118 V543-L122	S374 G375 R376 S395 C396 E397 F400 Y401 P432 V433 C434	I544 N545 S546 T549 P550	Y401-E119
45-50 ns	-	M499 G500 T501 H508 Y509 T510 G500 T510 V542 V543 N545 I548	-	S374 G375 R376 S395 C396 G397 G398 F400 Y401	-	N545-P118 V543-L122	S374 G375 R376 S395 C396 G397 F400 Y401 E431 P432 V433 C434 G435	D455 F456 P457 W458 I544 N545 S546 N547 T549 P550 T569 V638 W647	Y401-E119 S546-P118

[1] Residues forming hydrogen bonds are written in blue, residues forming hydrophobic interactions are written in red.

Table S4

Rescoring values for the drug repurposing final choices for the predicted interaction site between MASP-2 and SARS-CoV-2 N-protein.

Compound	Rescoring values, kcal/mol			
	Glide XP	**PLANTS**	**FlexX**	**ScorePose**
DB15048 (Licogliflozin)	-6.746119	-91.5084	-14.687	-4.6446152
Folic acid	-6.0690455	-74.758301	-13.853	-6.319243
DB11867	-5.1712122	-71.432701	-17.881001	-5.471735
DB08761	-6.1412387	-69.827003	-14.052	-5.589211
Tegobuvir	-4.4814105	-74.320297	-17.247999	-5.4427938
DB07971	-4.3589334	-72.345802	-16.893	-6.0400171
DB07796	-4.859621	-79.182297	-13.108	-5.5817342
Bromperidol	-4.1765733	-79.562798	-10.159	-7.3683848
DB13203	-5.8700581	-76.093102	-8.4429998	-5.7741981
BW-B70C	-6.1472735	-72.209297	-9.2720003	-5.4998498
Capadenoson	-4.9079962	-77.526497	-11.226	-4.6569052
DB06916	-4.0989428	-73.932999	-11.922	-5.3395009
DB09219 (Bisoxatin)	-4.137249	-71.463799	-12.289	-5.0380678
Amodiaquine	-4.6493254	-67.924103	-11.914	-5.1063619
Ketanserin	-4.1550202	-72.667801	-11.761	-4.655653
Org-27569	-3.9761355	-78.513802	-8.309	-5.0109782
INH1 (IBT-13131)	-5.4476967	-64.733704	-14.366	-8.0506153
Orantinib	-6.1413898	-56.3396	-15.549	-7.9078922
DB07975	-5.4642611	-62.1297	-14.867	-6.747962
Raltegravir	-5.8380814	-74.710999	-16.274	-3.3730099
DB08772	-5.4090199	-79.800102	-7.414	-5.7413182
TAK-632	-5.3757372	-75.660698	-13.504	-4.0465221
DB12524	-5.4703827	-73.684097	-12.623	-3.7325981
Oxyphencyclimine	-5.2495055	-71.639099	-7.632	-5.8837409