Supplementary Data for

Bcr-Abl tyrosine kinase inhibitor imatinib as a potential drug for COVID-19

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This PDF file includes:

Table S1. Vina docking scores of the selected compounds.

Compounds	SARS-CoV template	SARS-CoV-2 template
	Docking Score (kcal/mol)	
DMSO	-2.10	-1.90
Antiviral825	-6.90	-6.30
Antiviral2038	-6.30	-6.20
Antiviral2981	-6.80	-6.00
ZINCFDA130 (ergotamine)	-8.00	-7.70
ZINCFDA515 (ponatinib)	-8.47	-7.63
ZINCFDA754 (imatinib)	-7.50	-6.80
ZINCFDA2083(glecaprevir)	-7.10	-7.20

Table S2. MM-GBSA binding free energies of the selected compounds during the 5-10 ns simulation.

Compounds	Binding free energy (kcal/mol)	Library	Standard deviation
DMSO	0.00832	Negative_control	0.07582208
Antiviral825	-32.07596	Enamine_antiviral	4.970953
Antiviral2038	-36.91549	Enamine_antiviral	3.323704
Antiviral2981	-26.22972	Enamine_antiviral	4.193055
ZINCFDA130 (ergotamine)	-40.26142	ZINC15_FDA	8.50835
ZINCFDA515 (ponatinib)	-43.19959	ZINC15_FDA	3.46693
ZINCFDA754 (imatinib)	-40.45192	ZINC15_FDA	4.660994
ZINCFDA2083 (glecaprevir)	-42.03294	ZINC15_FDA	4.354867

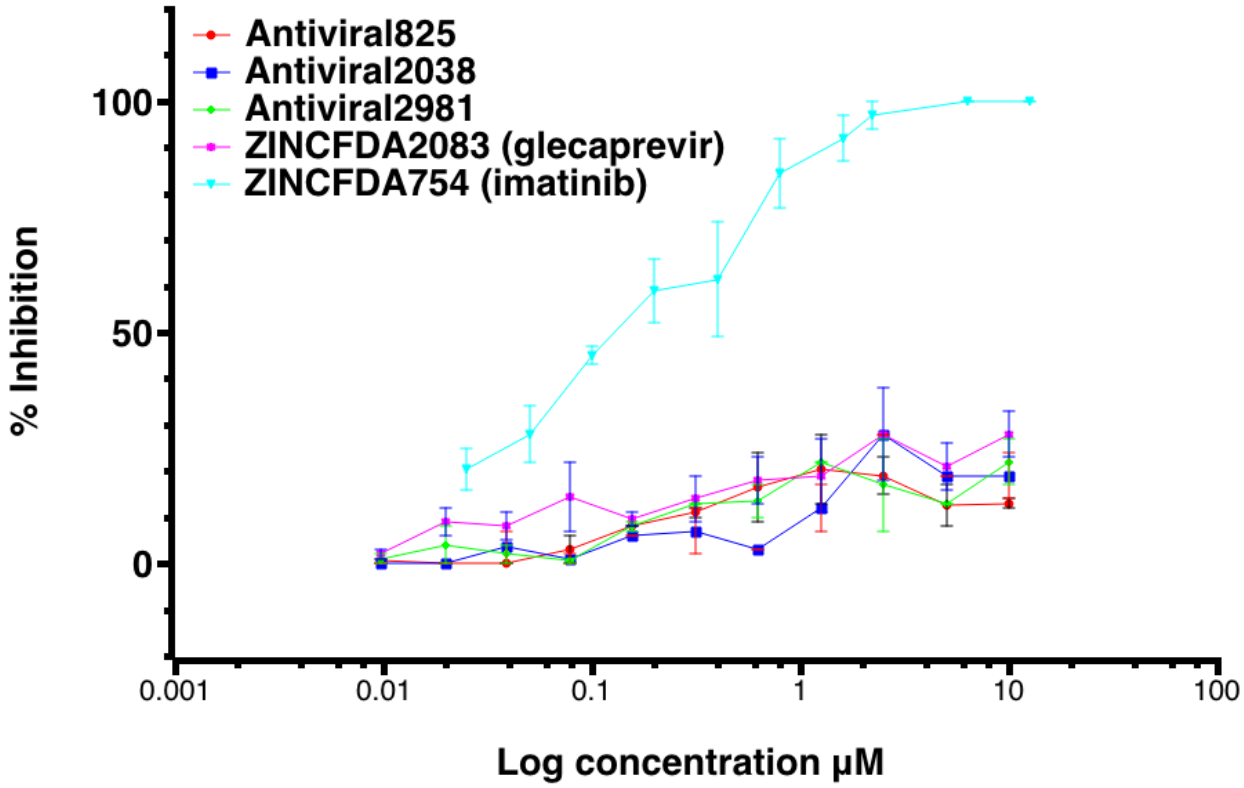
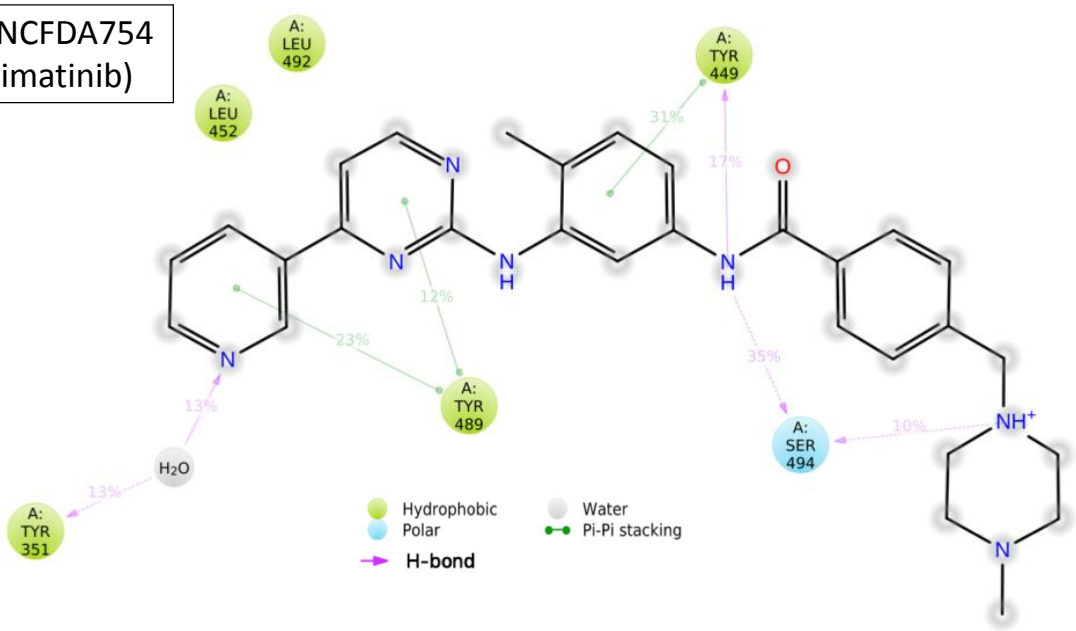
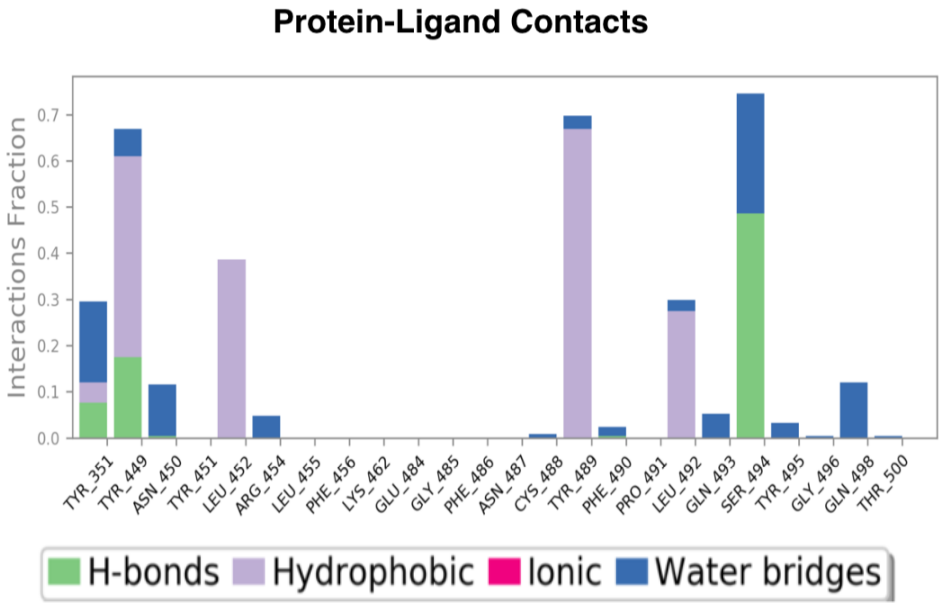


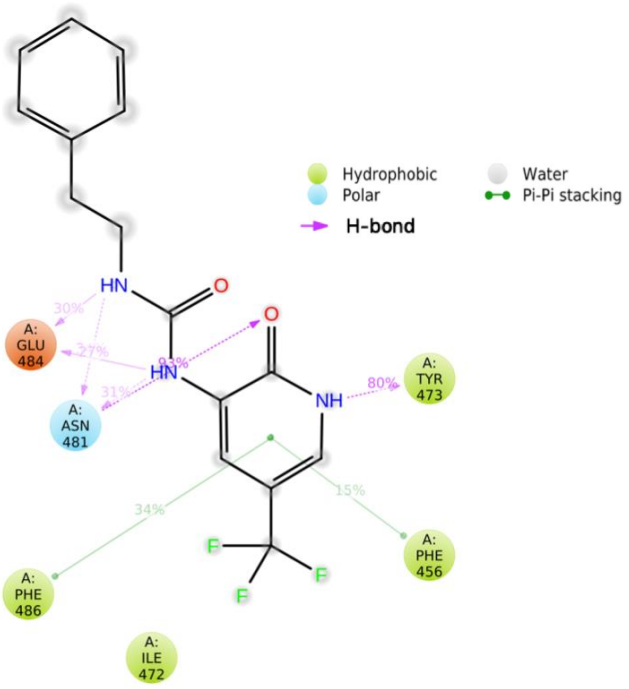
Fig. S1. Percent inhibition compared to the amount of plaques on cells. Here, 2-fold dilution of the compounds were done in duplo. Then 300 TCID50 of SARS-CoV-2 was added to each well, and plates were incubated at 37C for 1 hour. Then, the mixes were added onto vero cells and incubated for 8 hours at 37 C. Subsequently, cells were fixed for 15 min with 2% PFA, followed by another 15 min fixation with 70% ethanol. Fixed cells were stained with a monoclonal antibody, followed by AlexaFluor 488. Here imatinib shows significant % inhibition as compared to other compounds tested.

ZINCFDA754
(imatinib)

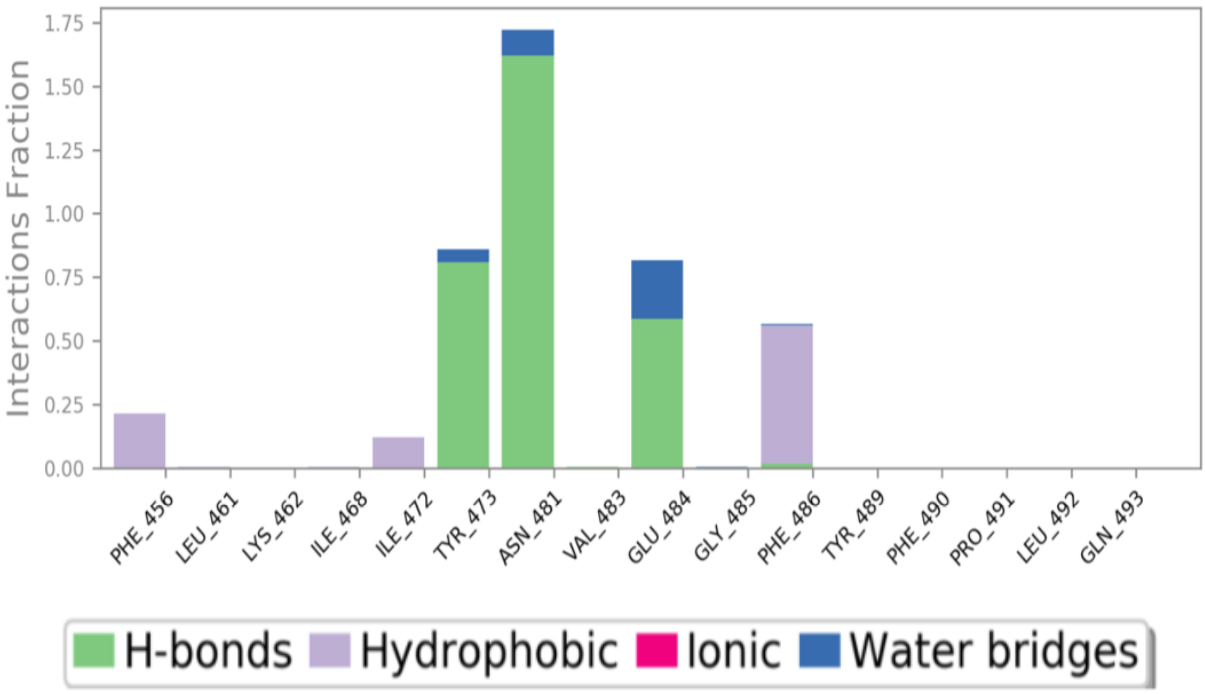




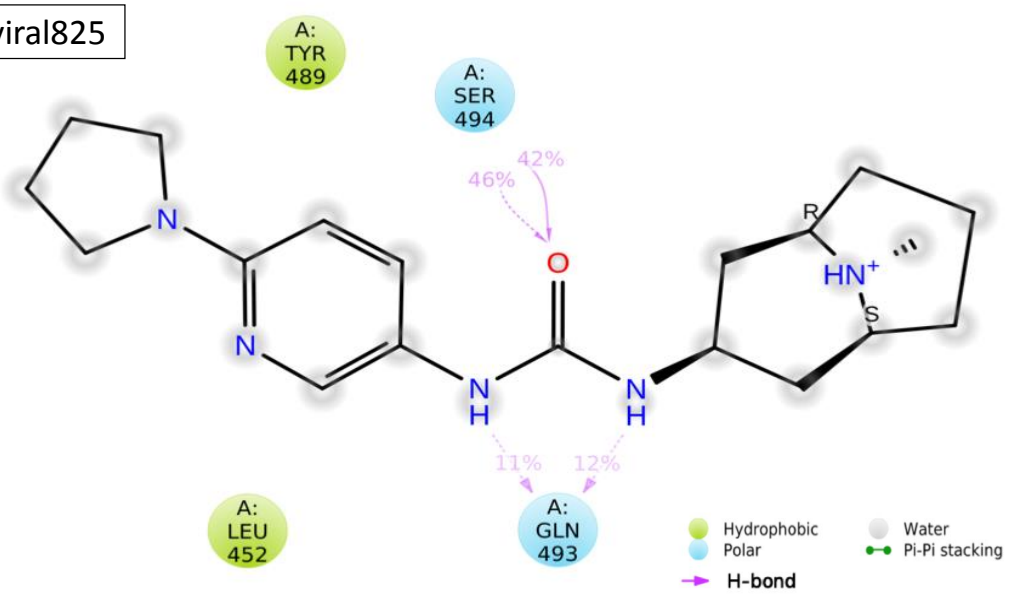
Antiviral2038

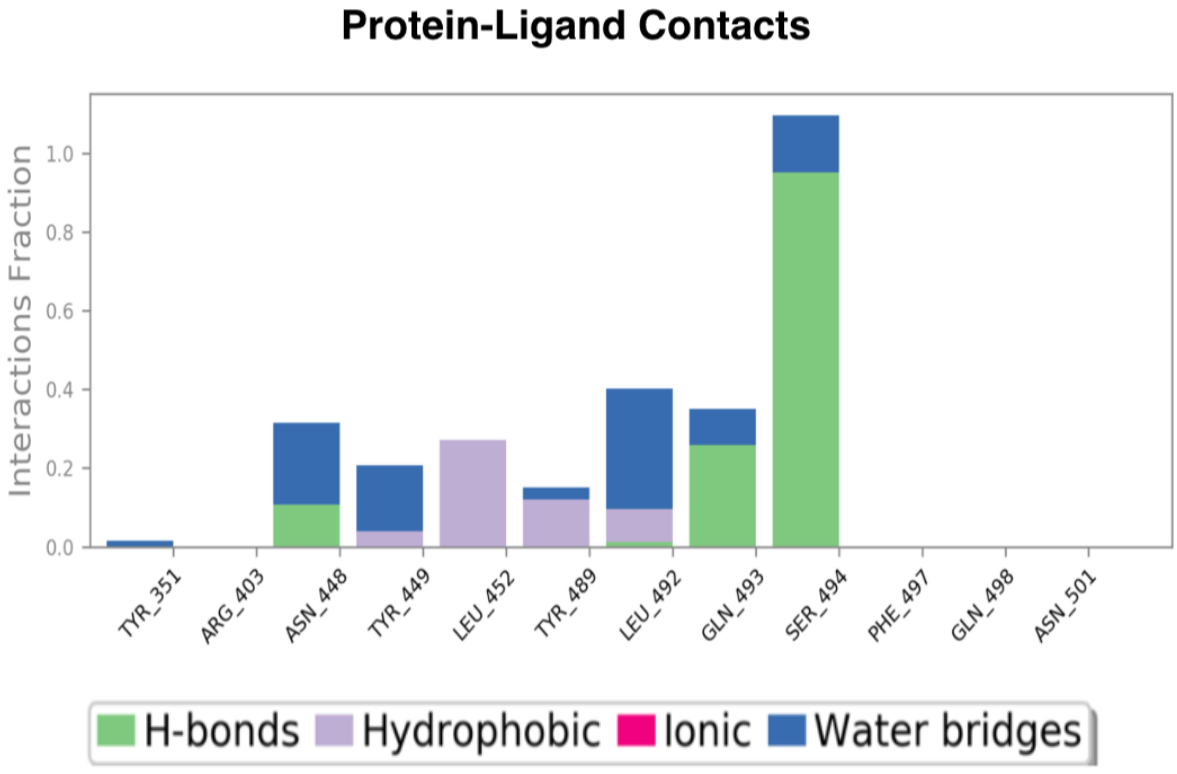


Protein-Ligand Contacts

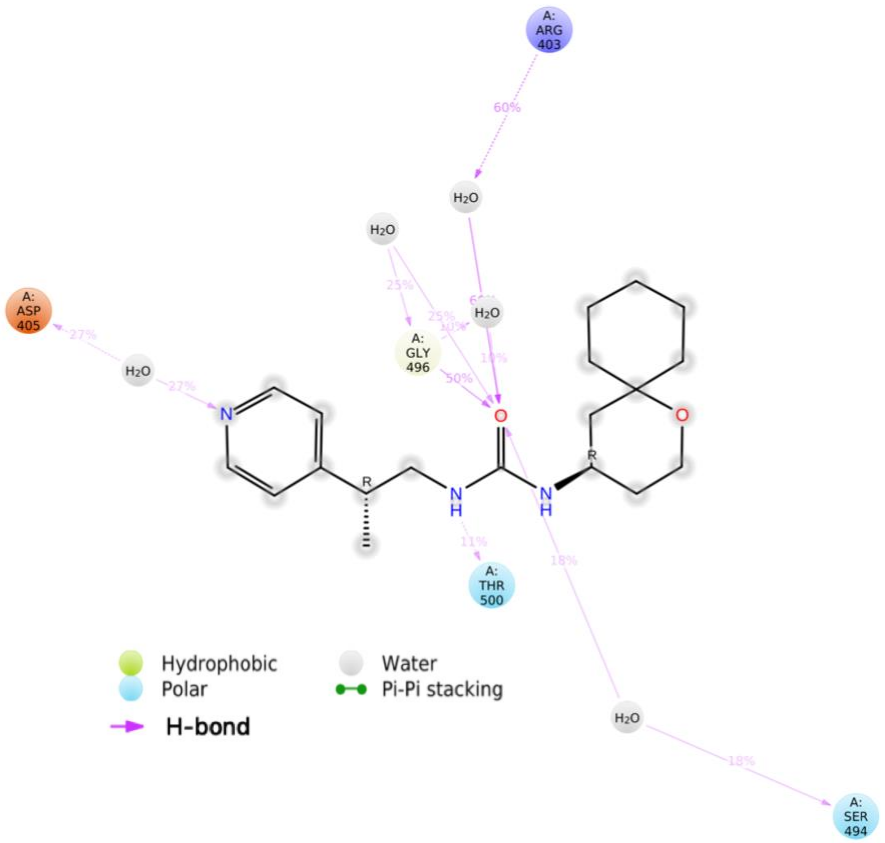


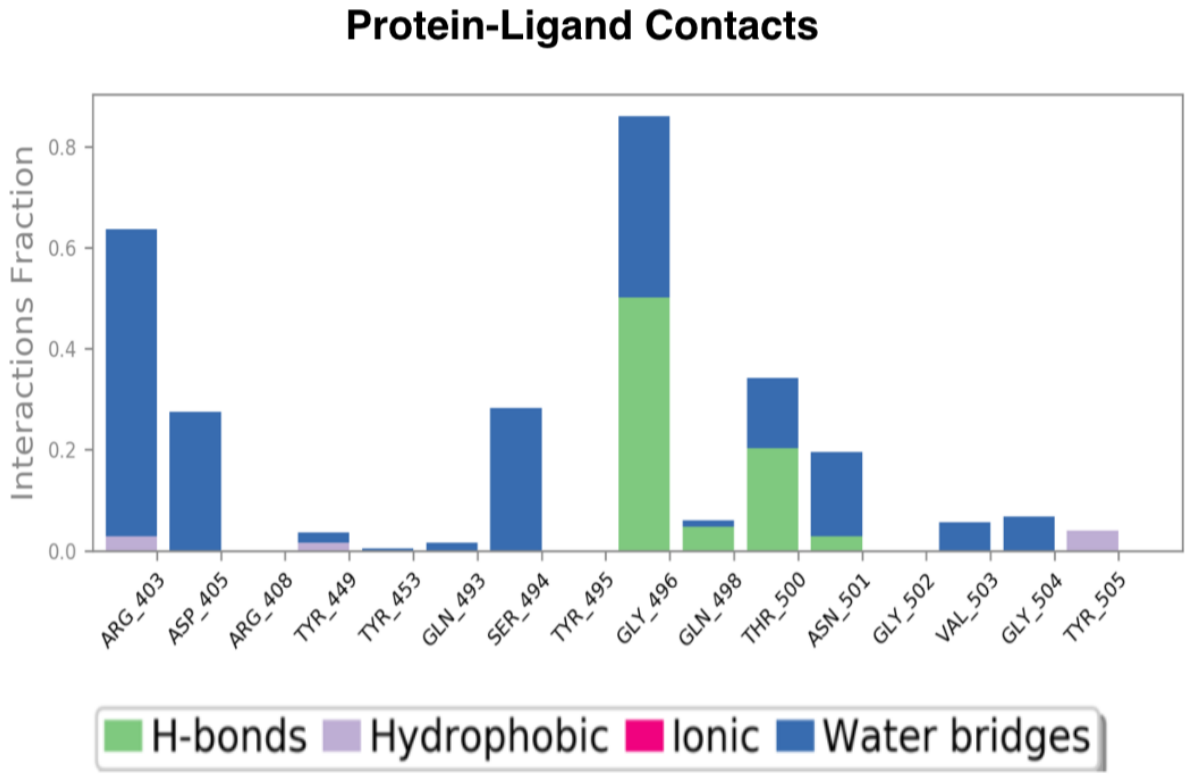
Antiviral825



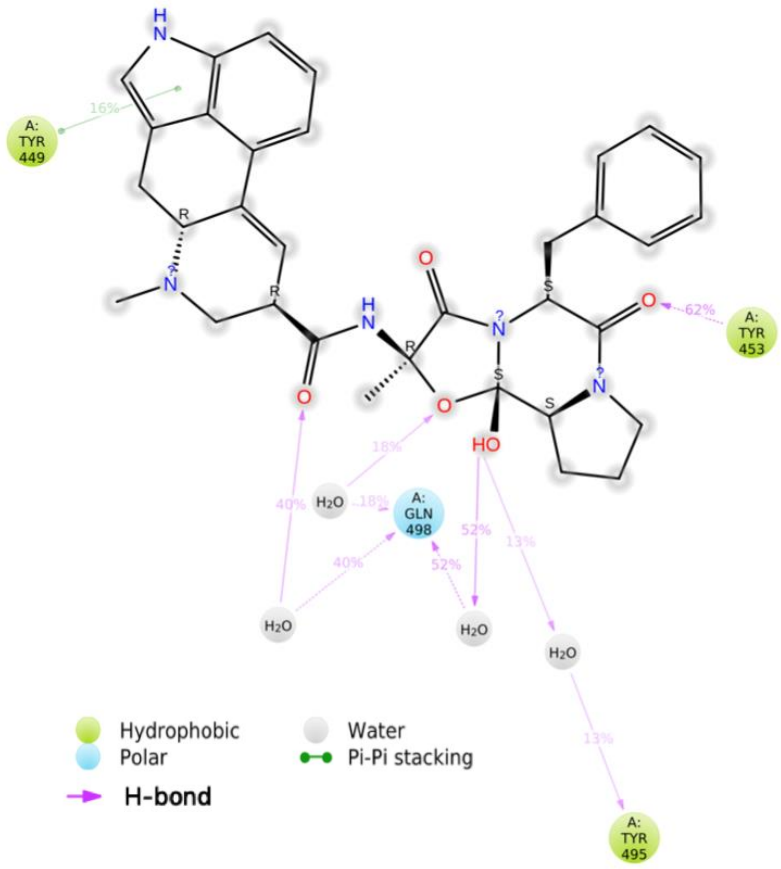


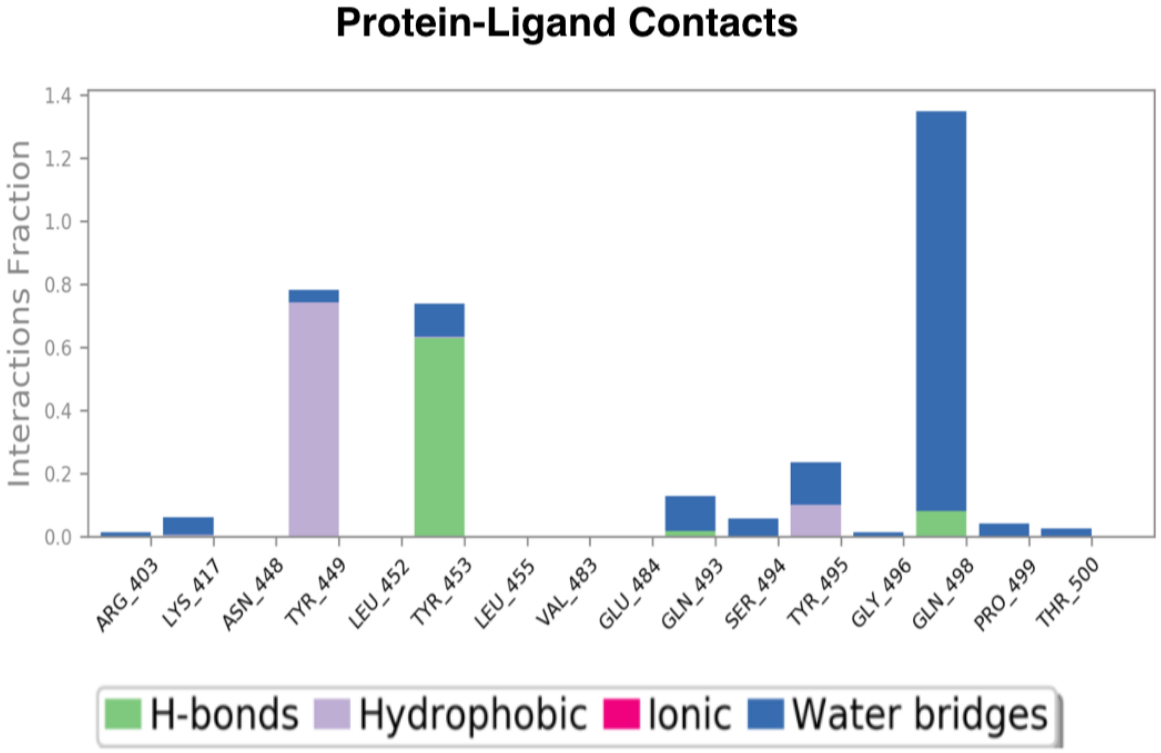
Antiviral2981



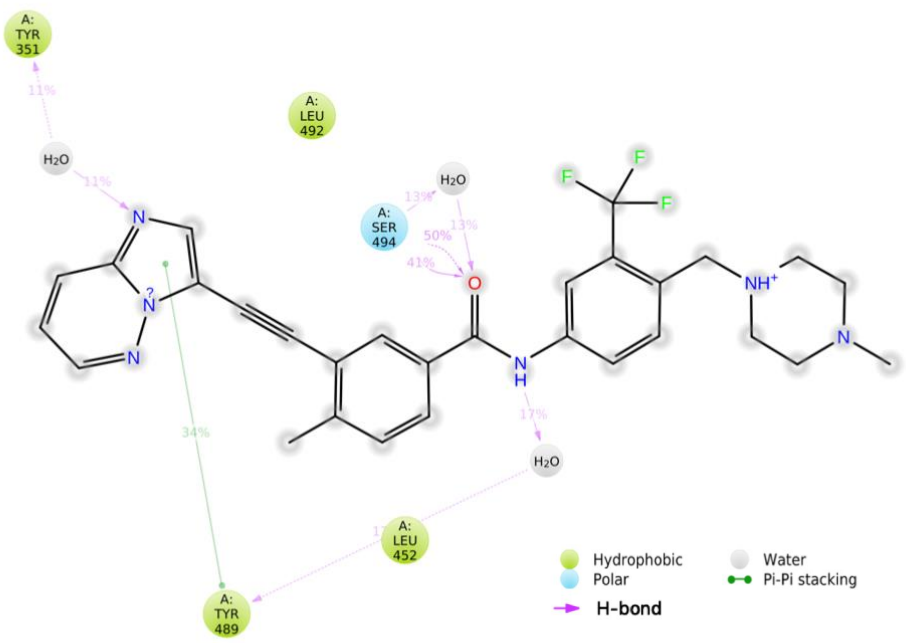


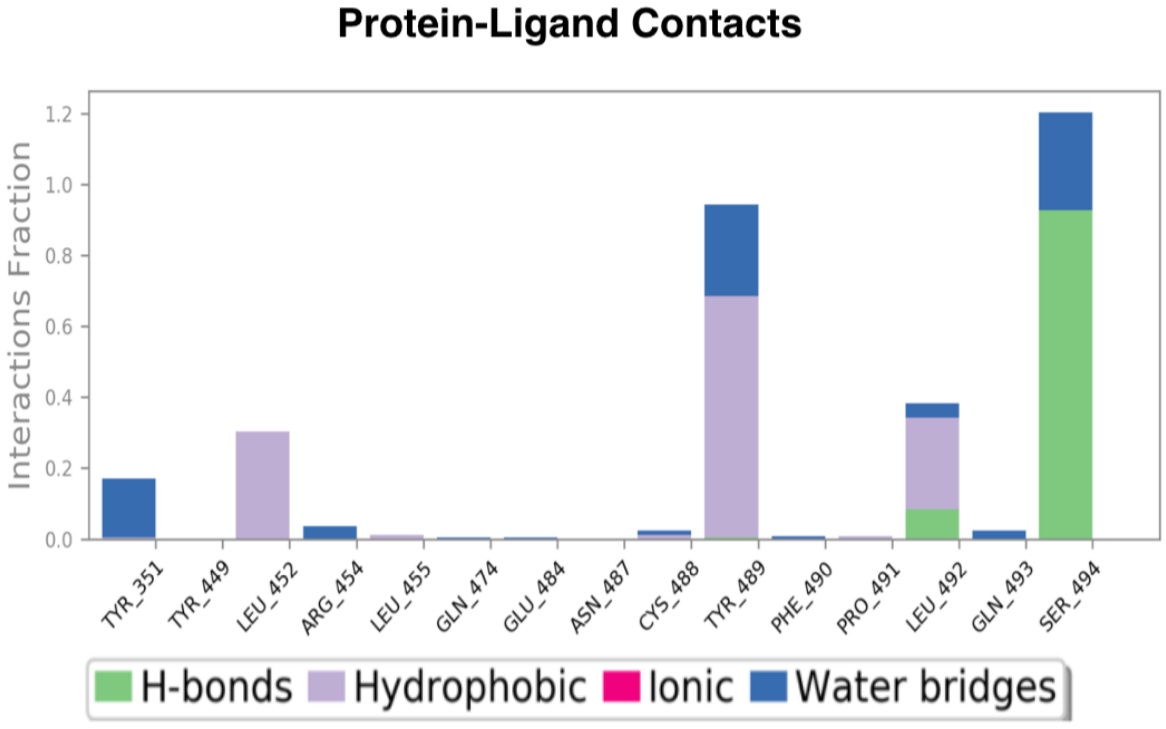
ZINCFDA130
(ergotamine)





ZINCFDA515
(ponatinib)





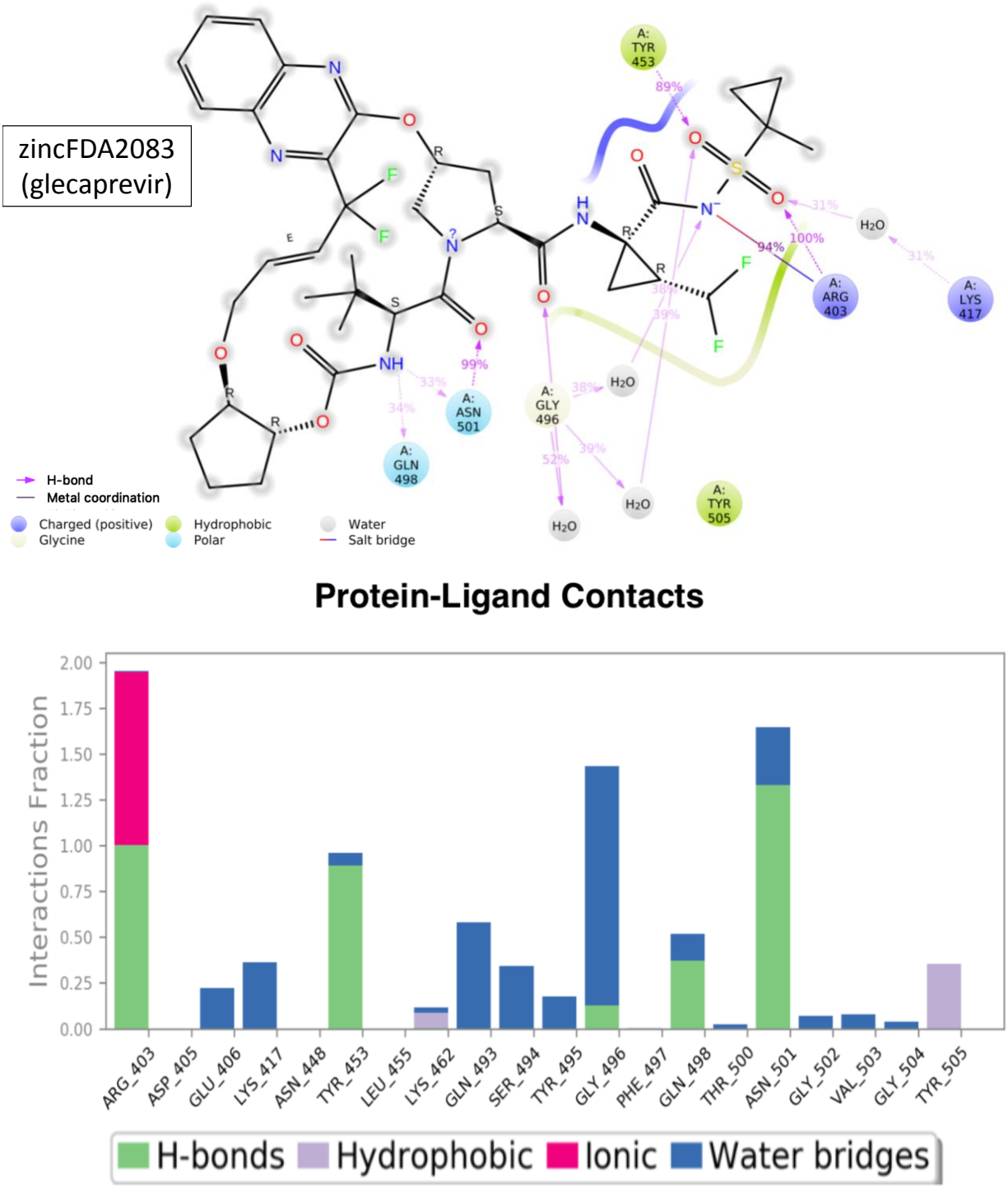
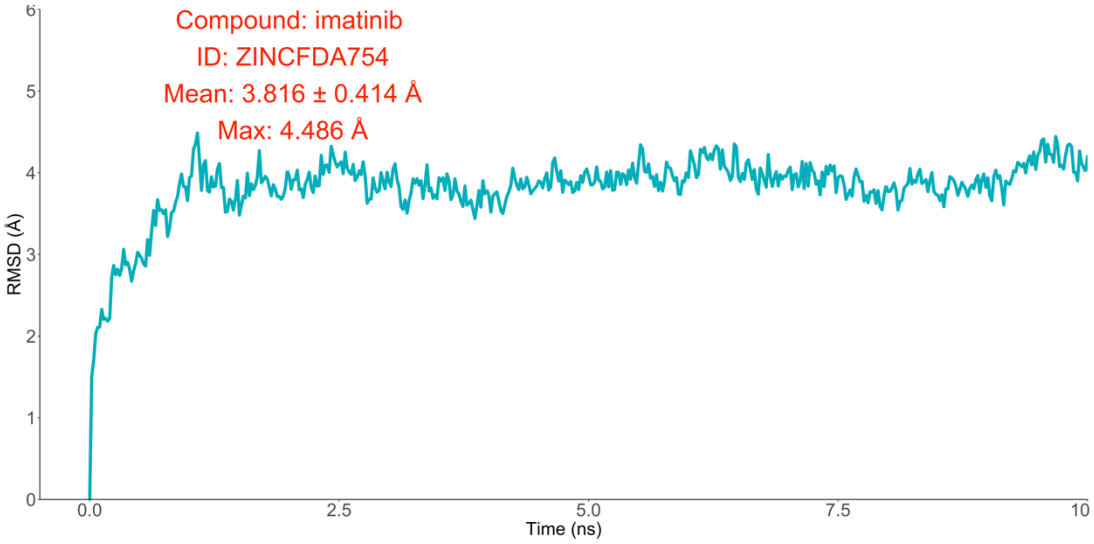
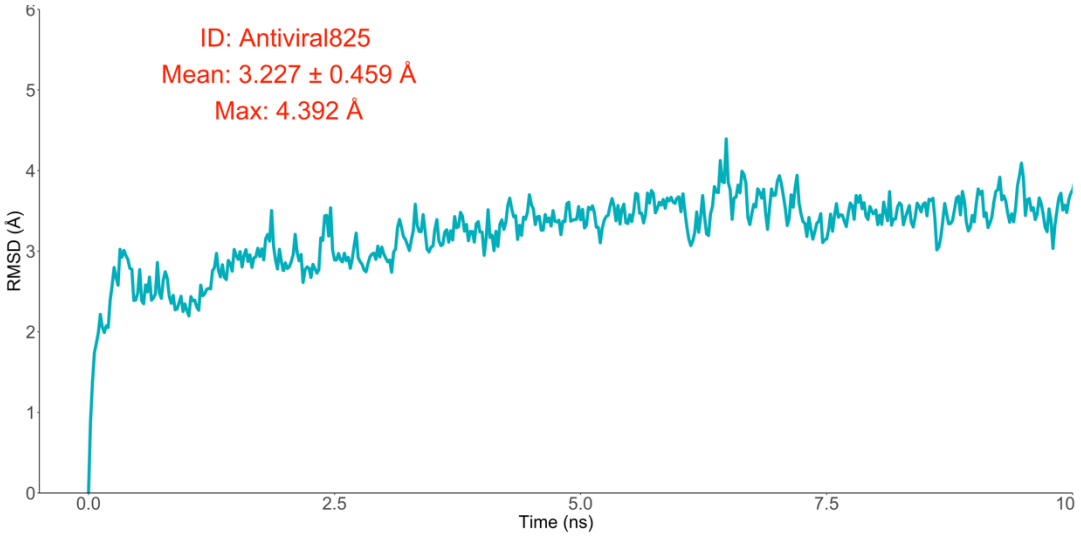
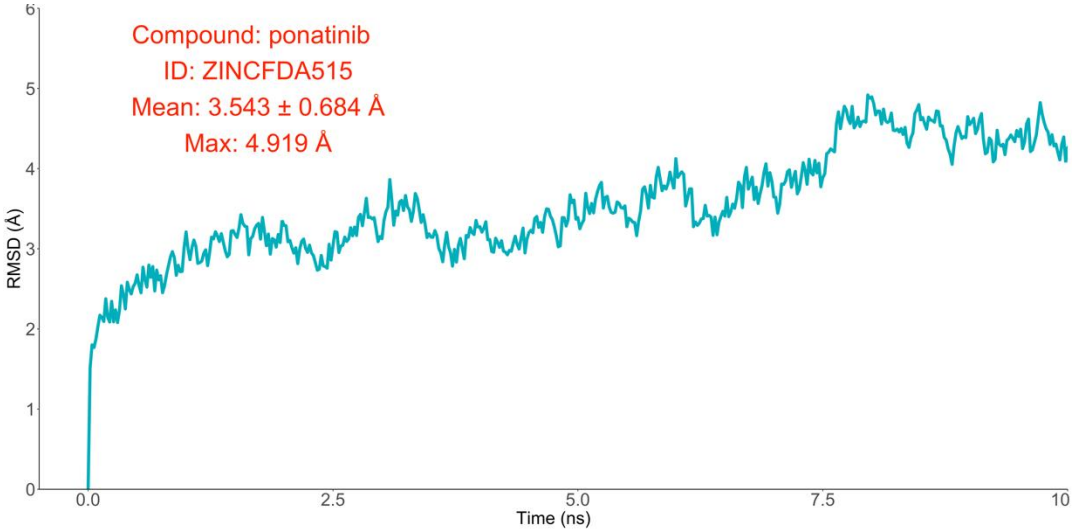
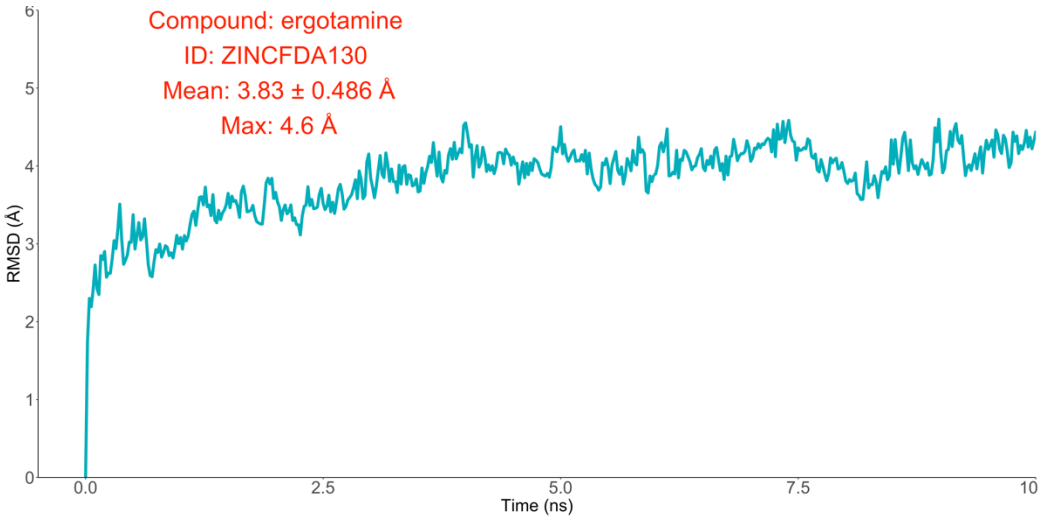


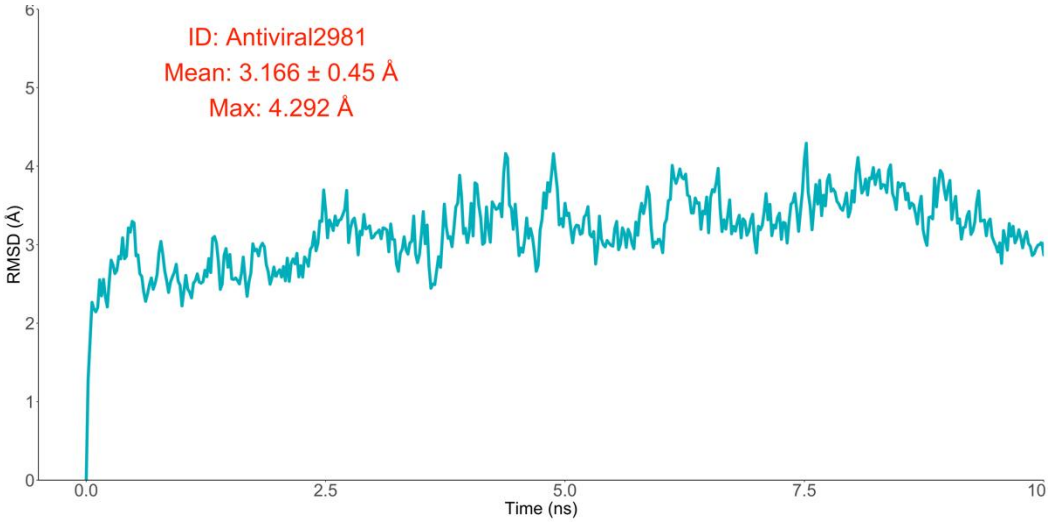
Fig. S2 Interactions of the seven selected compounds with the RBD of SARS-CoV-2 spike protein

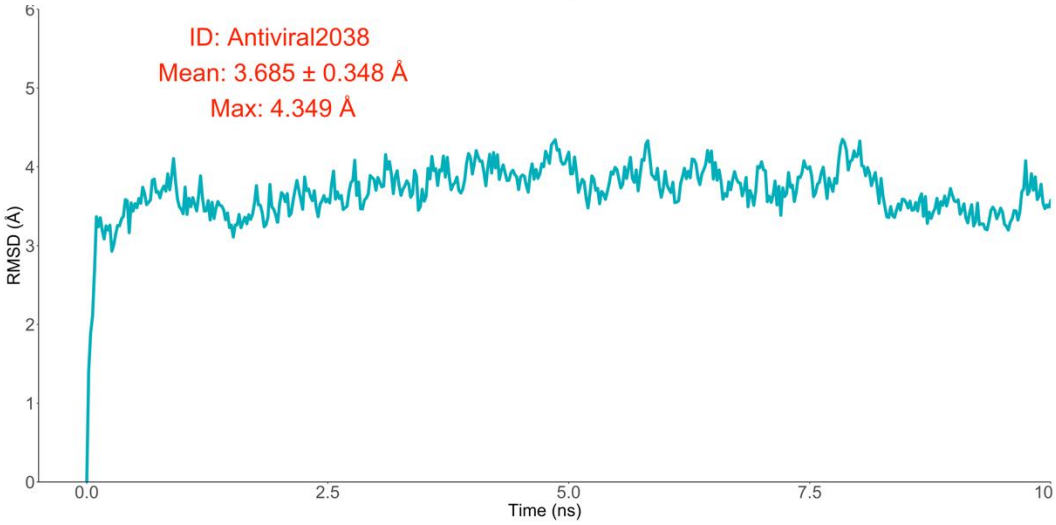

Compound: imatinib
ID: ZINCFDA754
Mean: 3.816 ± 0.414 Å
Max: 4.486 Å
RMSD (Å)
Time (ns)


ID: Antiviral825
Mean: 3.227 ± 0.459 Å
Max: 4.392 Å
RMSD (Å)
Time (ns)


Compound: ponatinib
ID: ZINCFDA515
Mean: 3.543 ± 0.684 Å
Max: 4.919 Å
RMSD (Å)
Time (ns)


Compound: ergotamine
ID: ZINCFDA130
Mean: 3.83 ± 0.486 Å
Max: 4.6 Å
RMSD (Å)
Time (ns)
0
1
2
3
4
5
6
0.0
2.5
5.0
7.5
10


ID: Antiviral2981
Mean: 3.166 ± 0.45 Å
Max: 4.292 Å
RMSD (Å)
Time (ns)
0
1
2
3
4
5
6
0.0
2.5
5.0
7.5
10


ID: Antiviral2038
Mean: 3.685 ± 0.348 Å
Max: 4.349 Å
RMSD (Å)
Time (ns)
0
1
2
3
4
5
6
0.0
2.5
5.0
7.5
10

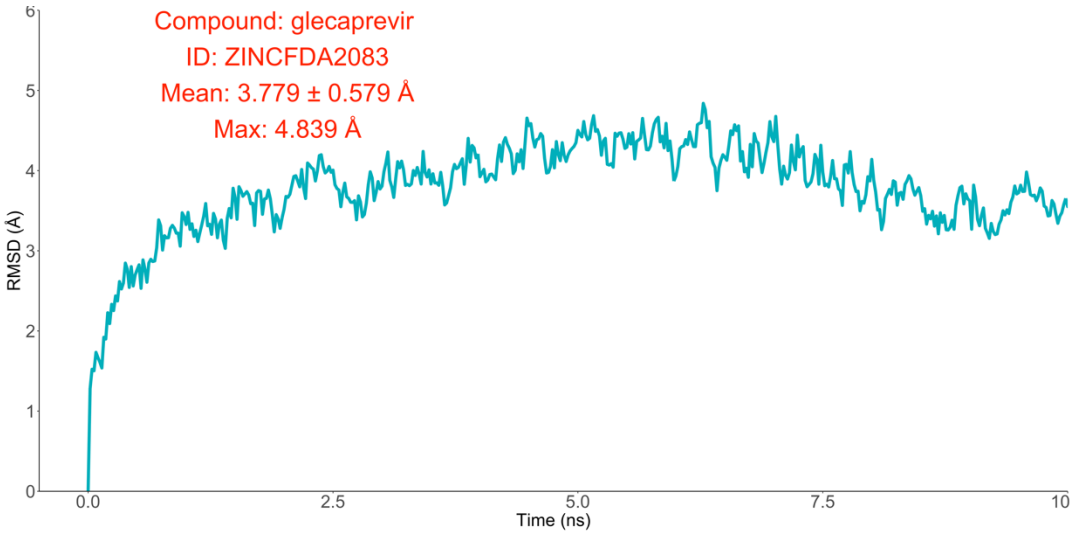
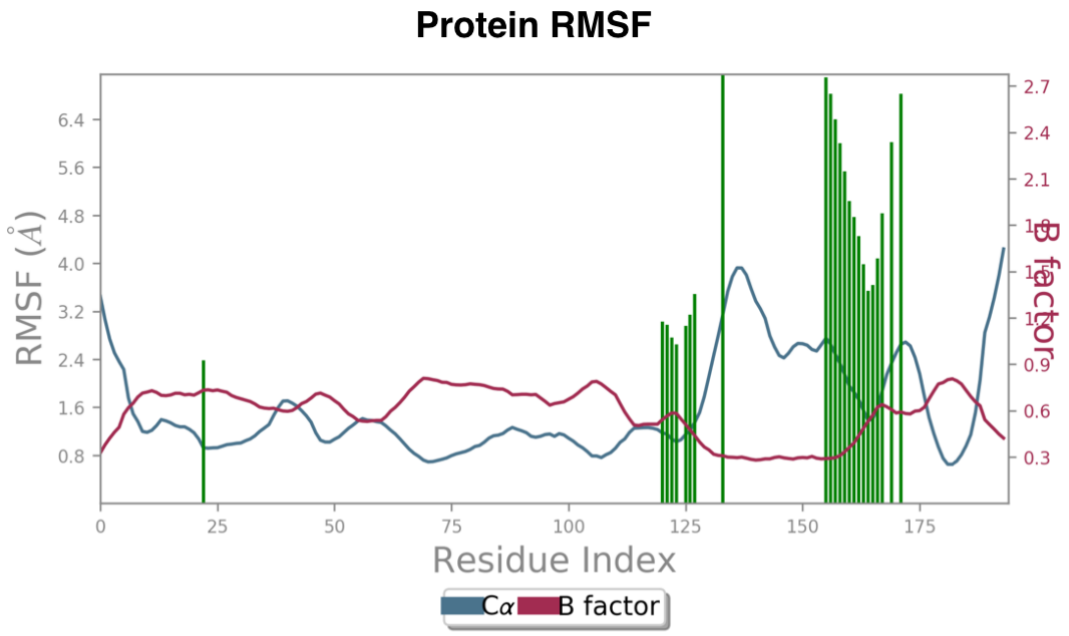
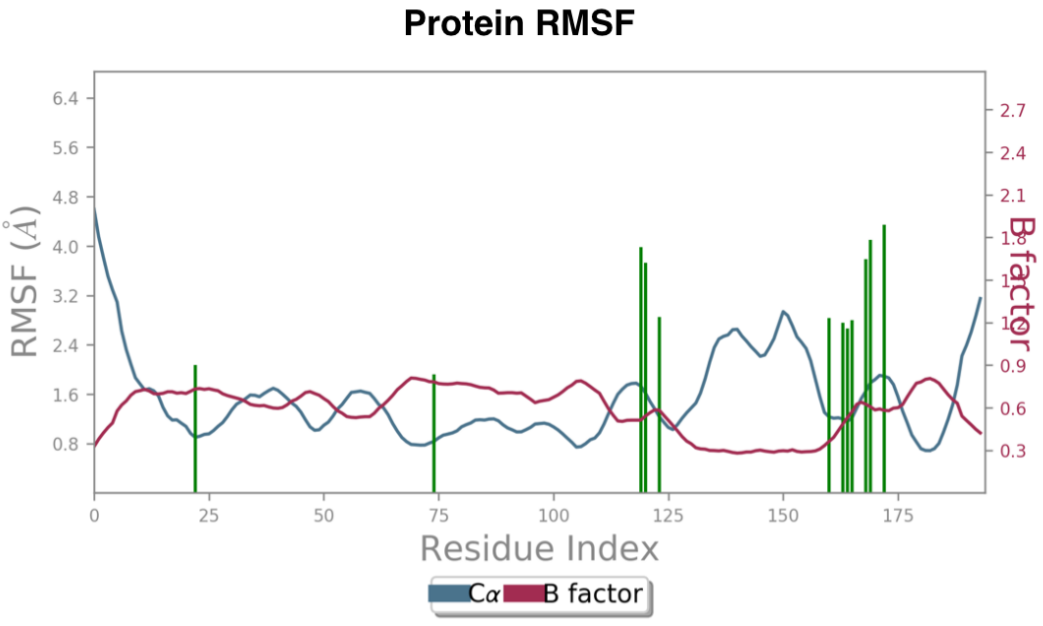


Fig. S3 RMSD Diagram for MD simulations of the seven selected compounds with the RBD of SARS-CoV-2 spike protein.

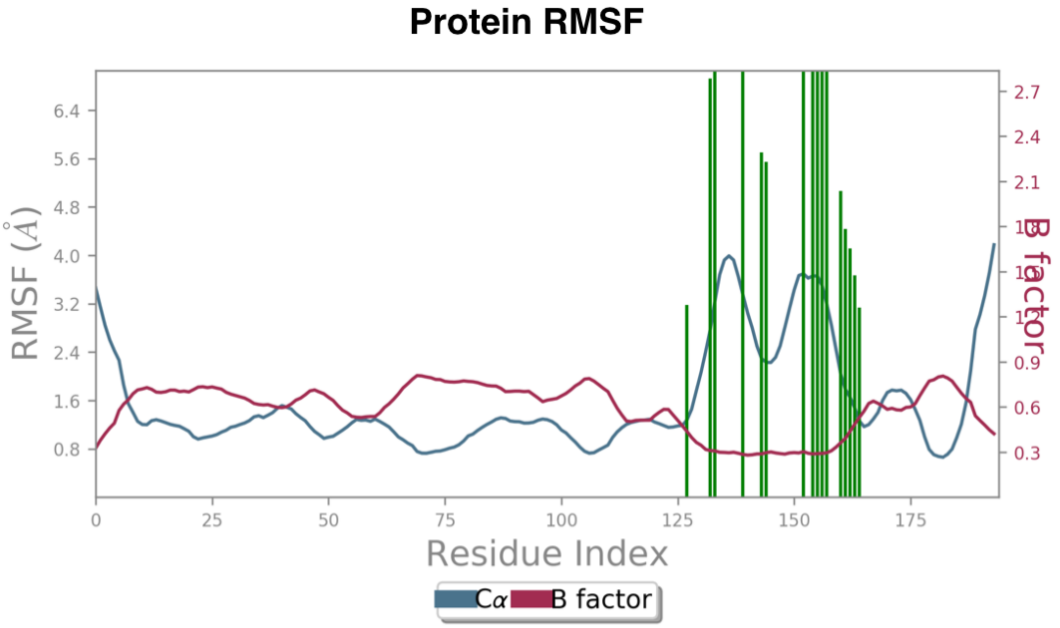
RMSF for ZINCFDA754 (imatinib):



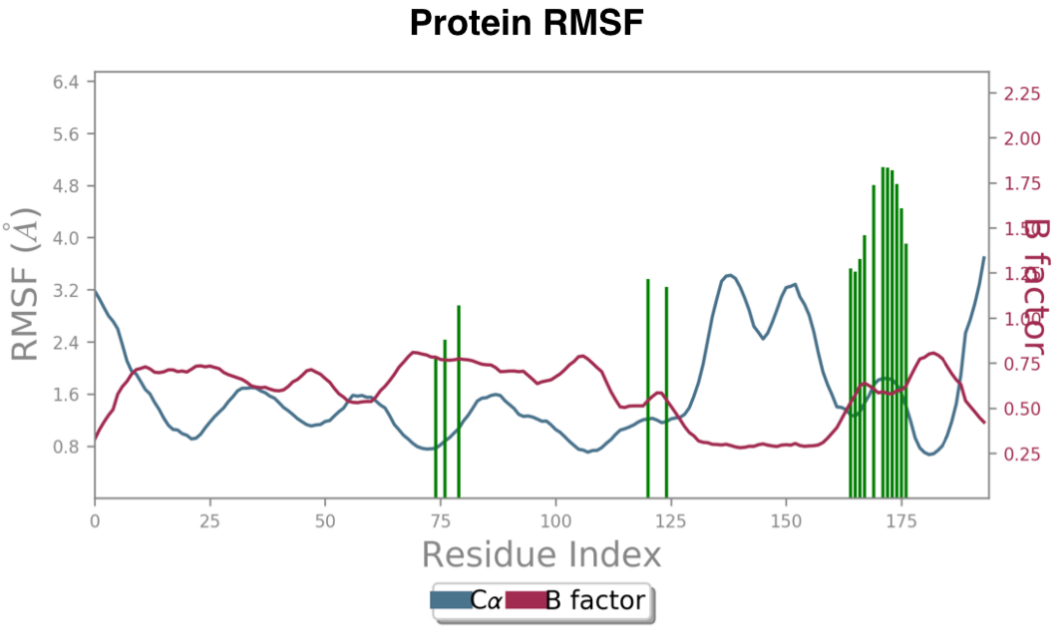
RMSF for Antiviral825:



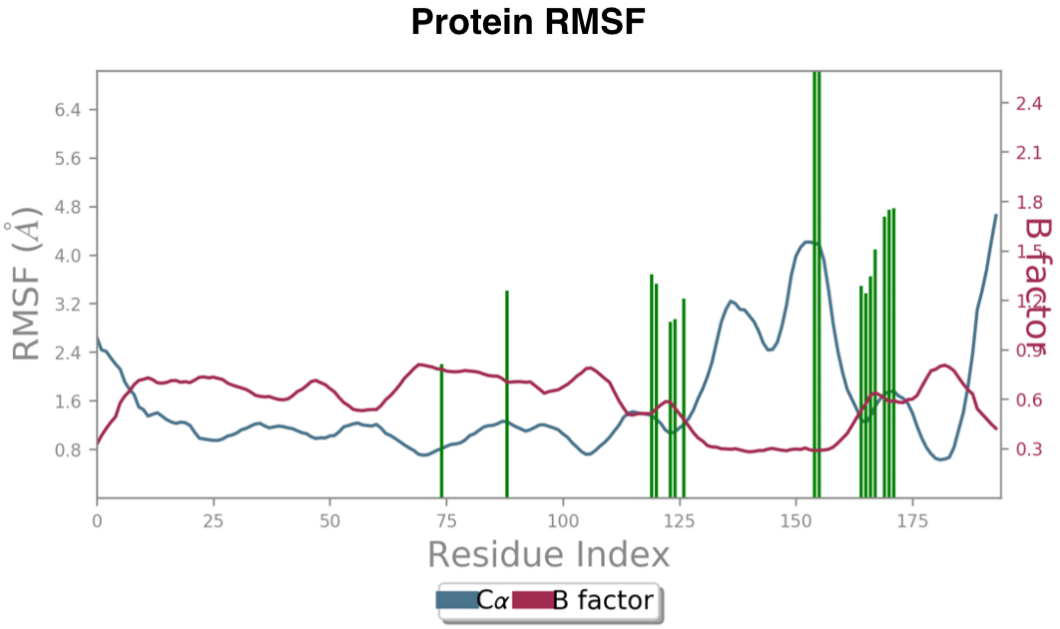
RMSF for Antiviral2038:



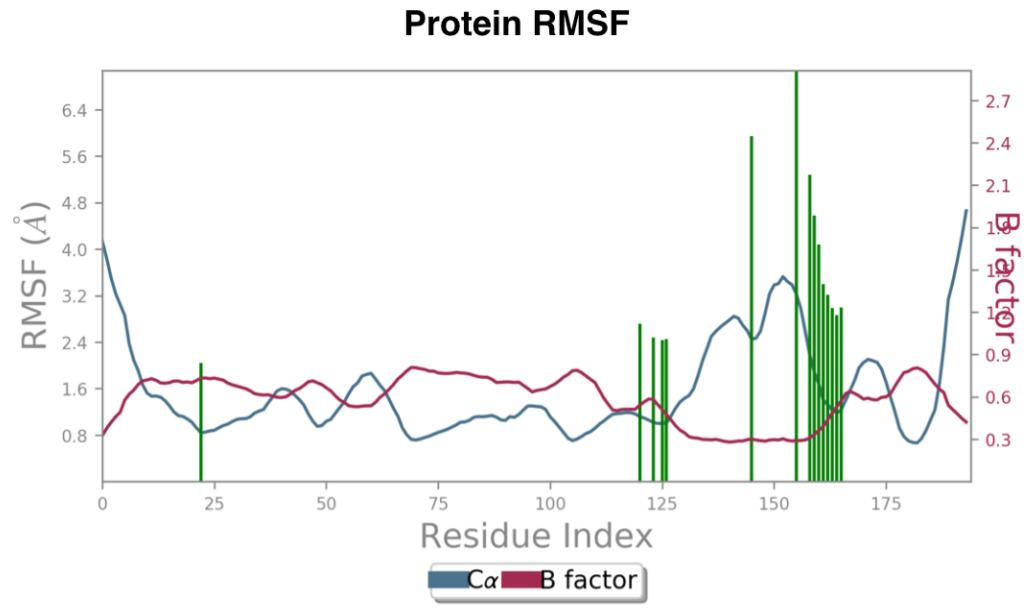
RMSF for Antiviral2981:



RMSF for ZINCFDA130 (ergotamine):



RMSF for ZINCFDA515 (ponatinib):



RMSF for ZINCFDA2083 (glecaprevir):

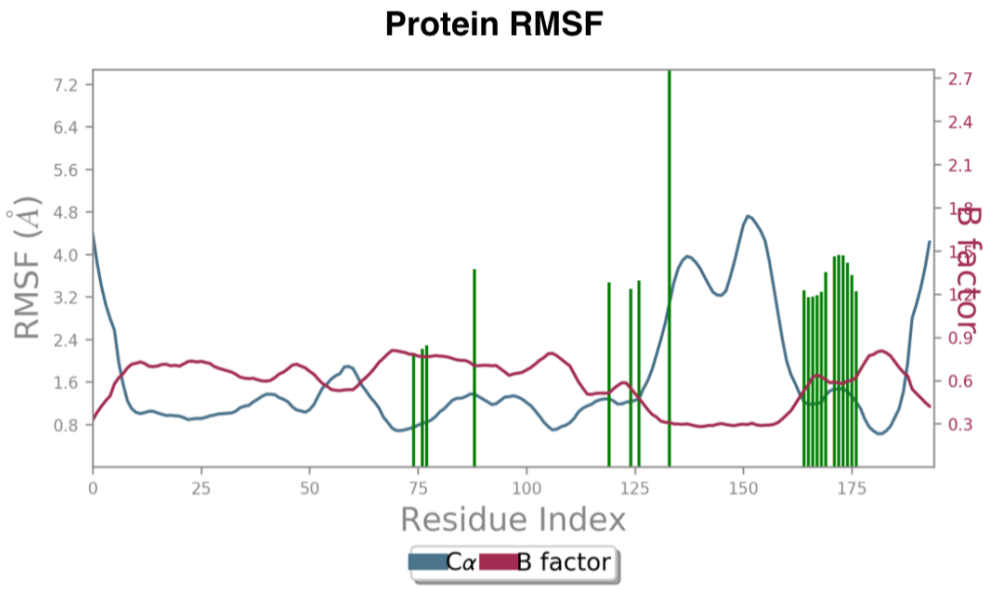
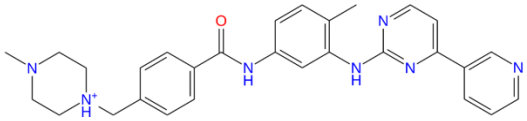
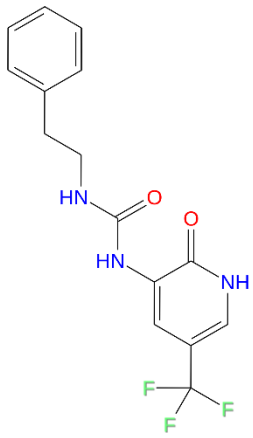
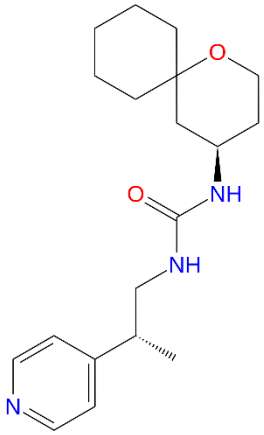
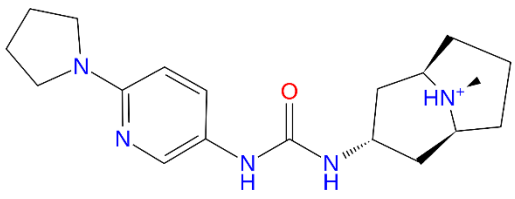
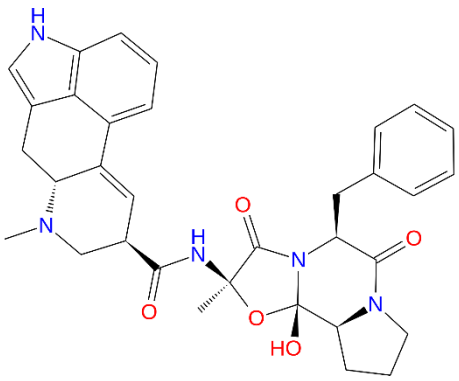
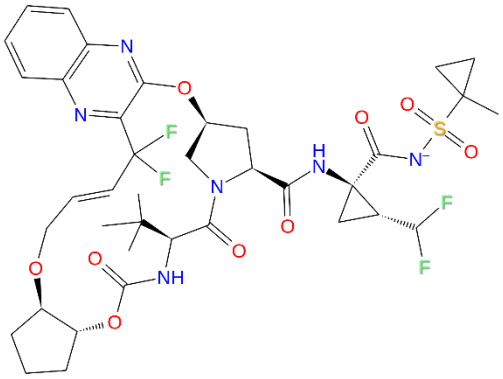
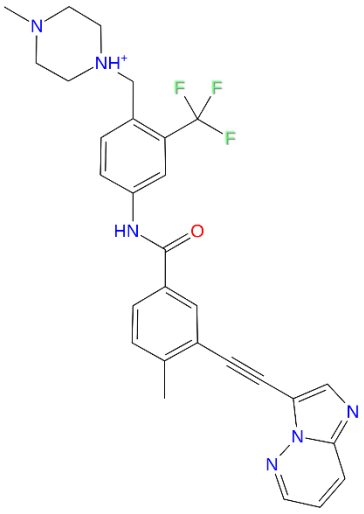


Fig. S4 RMSF Diagram for MD simulations of the seven selected compounds with the RBD of SARS-CoV-2 spike protein. Green columns are the ligand-protein interaction residues. The fluctuation (blue) was reasonable between 0.5 to 4 Å at the interacted protein residues (green).

Table S3 – Information of substances screened from initial docking studies.

Substance	2D structure	Applications and mechanism of action	References
ZINCFDA754/ imatinib/ ZINC000019632618		Leukemia treatment by inhibition of Bcr-Abl tyrosine kinase.	[1]
Antiviral2038 / Z787722876 / ZINC50038784		No reported bioactivity. Antiviral properties based on Enamine predictions.	
Antiviral2981 / Z1452532074 / ZINC170674881		Has a molinspiration bioactivity score of 0.35 as GPCR ligand	[1]
Antiviral825 / Z1277226201 / ZINC104169890		Has good molinspiration bioactivity scores as GPCR ligand (0.43), Ion channel modulator (0.38), kinase inhibitor (0.27) and enzyme inhibitor (0.2)	[1]

ZINCFDA130 / ergotamine/ ZINC000052955754		Migraine treatment via acting as an agonist to 5-HT1A, 5-HT1B, 5-HT1D, and 5-HT1F receptors	[2]
ZINCFDA2083 / glecaprevir/ ZINC164528615		Hepatitis C treatment by NS3/4 protease inhibition	[3]
ZINCFDA515 / ponatinib/ ZINC000036701290		Leukemia treatment by inhibition of Bcr-Abl tyrosine kinase	[4]

Movie S1. Molecular dynamics simulation video of SARS-CoV-2 spike protein (RBD) interacting with imatinib.

References:

1. Sisk, J.M., M.B. Frieman, and C.E. Machamer, *Coronavirus S protein-induced fusion is blocked prior to hemifusion by Abl kinase inhibitors.* The Journal of general virology, 2018. **99**(5): p. 619.
2. Silberstein, S.D., *The pharmacology of ergotamine and dihydroergotamine.* Headache, 1997. **37 Suppl 1**: p. S15-25.
3. Gane, E., et al., *Glecaprevir and pibrentasvir in patients with HCV and severe renal impairment.* New England Journal of Medicine, 2017. **377**(15): p. 1448-1455.
4. Goldman, J.M., *Ponatinib for chronic myeloid leukemia*. 2012, Mass Medical Soc.