Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supporting Information

Title

Antiviral Drug Design Based on the Opening Mechanism of Spike Glycoprotein in SARS-CoV-2

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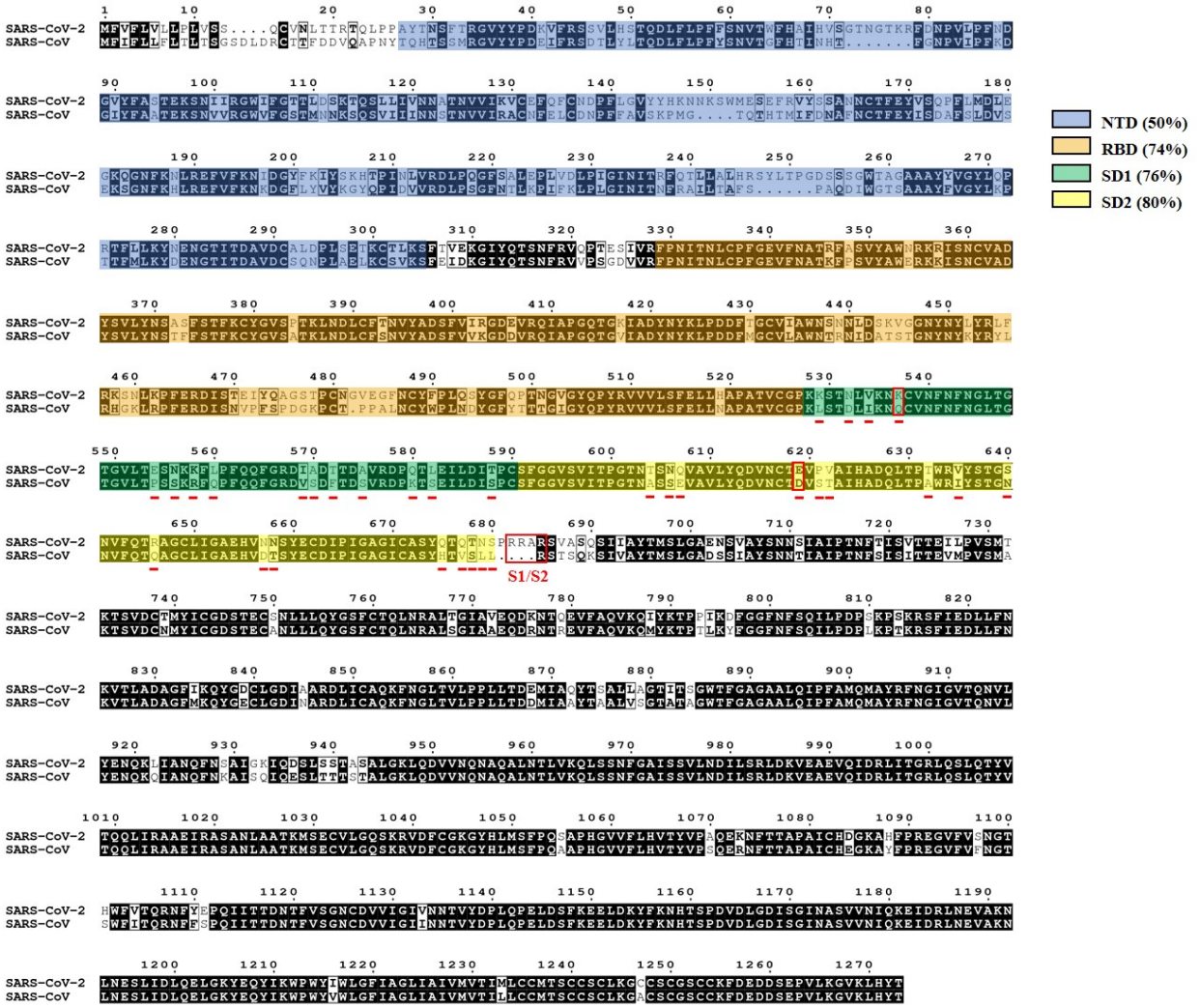

Figure S1. Sequence alignment of the S glycoproteins in SARS-CoV-2 and SARS-CoV. Each domain of S1 subunit is represented by the color corresponding to Figure 1. Residues 537 and 619, as well as the S1/S2 cleavage site are highlighted with red boxes. The brackets in the legend show the amino acid sequence identity of the corresponding domains. The mutations in the SD1 and SD2 of the S protein for SARS-CoV-2 were marked with red underlines.

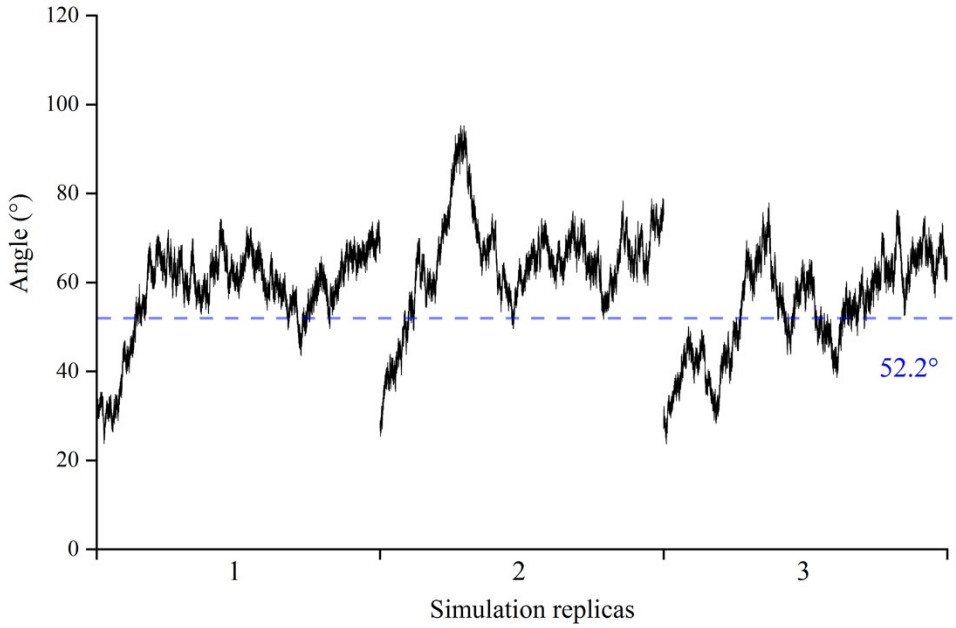

Figure S2. Interdomain angle for the non-glycosylated S protein during the course of three MD simulations.

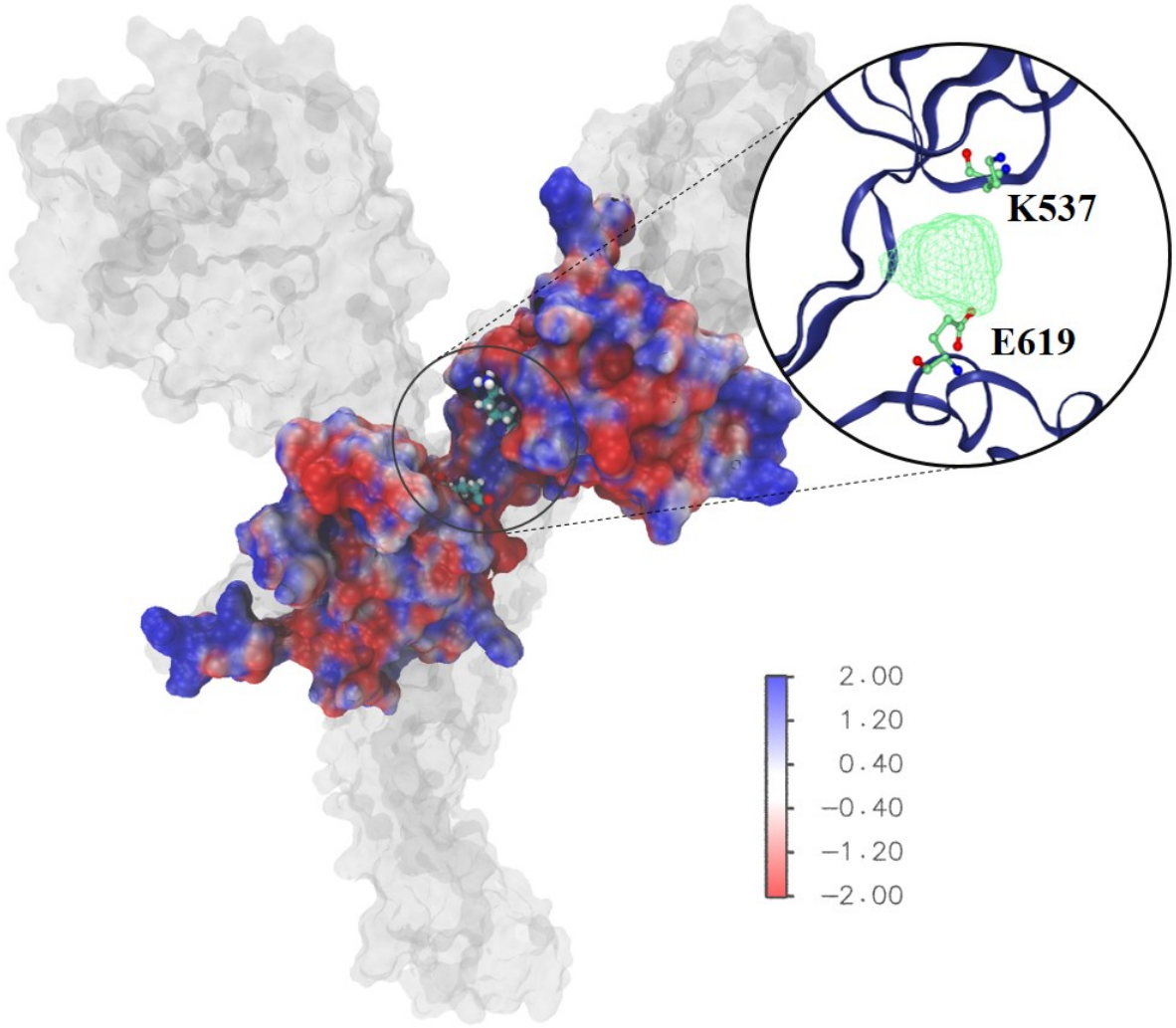

Figure S3. Schematic diagram of drug binding pocket. The protein surface for SD1 and SD2 domains is colored based on the electrostatic potentials (kT/e), where the residues with positive potential were in blue, and those in negative potentials were in red. The illustration shows the drug binding pocket predicted by DoGSiteScorer online tool (https://proteins.plus/).

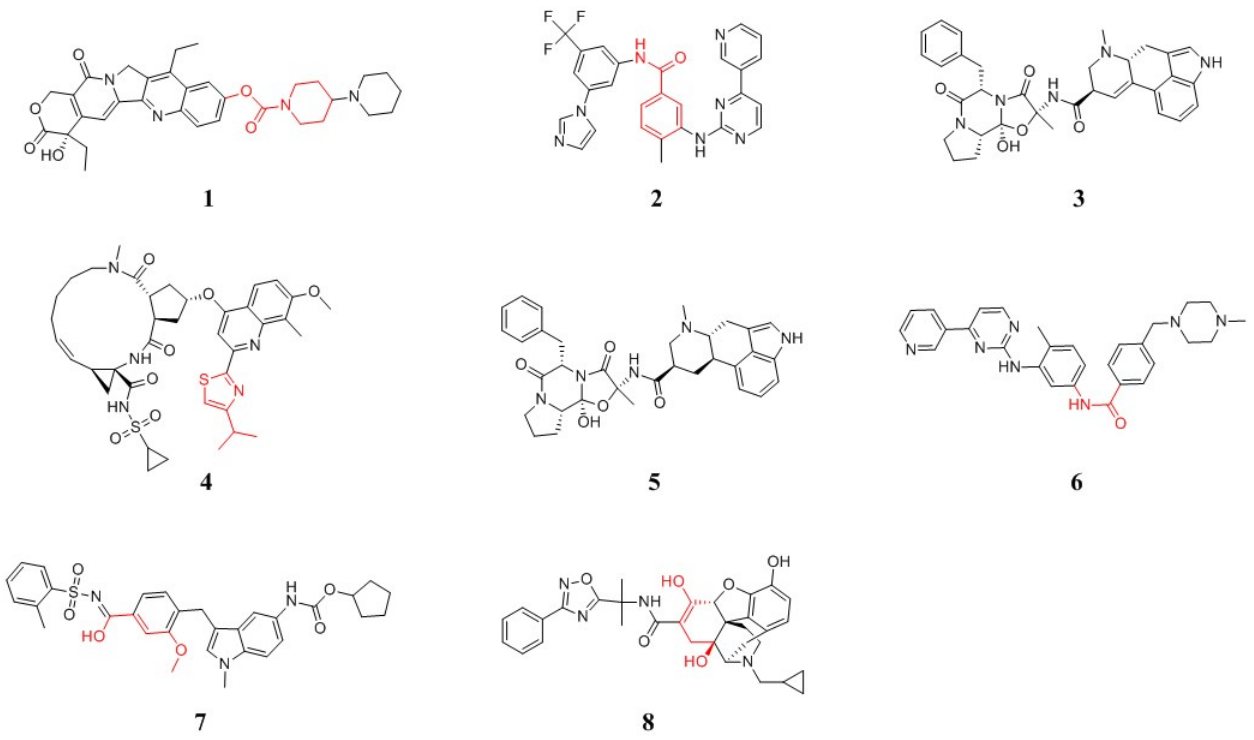

Figure S4. Chemical structures for the screened drug molecules. Atoms located between K537 and E619 were colored in red.

Table S1. Mutations of residues in SD1 and SD2 domains of the S protein in SARS-CoV to the corresponding ones in SARS-CoV-2.

Domain	Mutations	Charge[a]	Interface[b]
SD1	L529K	Yes	No
	D532N	Yes	No
	I534V	No	No
	Q537K	Yes	Yes
	P554E	Yes	Yes
	S556N	No	Yes
	R558K	Yes	No
	Q560L	No	No
	V569I	No	No
	S570A	No	No
	F572T	No	No
	S575A	No	No
	K580Q	Yes	No
	S582L	No	No
	S588T	No	Yes
SD2	A604T	No	No
	S606N	No	No
	E607Q	Yes	No
	D619E	Yes	Yes
	S621P	No	Yes
	T622V	No	Yes
	A632T	No	No
	I635V	No	No
	N640S	No	No
	Q646R	Yes	No
	D657N	Yes	No
	T658N	No	No
	H675Q	Yes	No
	V677Q	No	No
	S678T	No	No
	L679N	No	No
	L680S	No	No

[a]change of the net charge; [b]located at the interaction interface.

Table S2. Distance and occupancy for hydrogen bond interactions during the MD simulations.

System	Donor	Acceptor	Distance(Å) (Occupancy (%))
1	Lig-O40	P322-O	2.7 (89)
	Lig-N14	E619-Oε	2.8 (47)
2	C538-N	Lig-O10	3.2 (33)
	Lig-N39	E619-Oε	2.9 (53)
	Lig-N39	E619-Cδ	3.3 (31)
4	Q321-N	Lig-O39	3.0 (96)
	R319-N	Lig-O23	3.1 (97)
	Lig-N16	R319-O	2.9 (99)
6	C538-N	Lig-O8	2.9 (98)
	Lig-N14	E619-O	2.9 (95)
	Lig-N6	E619-Oε	2.9 (82)
7	C538-N	Lig-N8	3.2 (65)
	S591-N	Lig-O10	3.0 (60)
	C538-N	Lig-S9	3.4 (56)
8	Q321-N	Lig-N44	3.2 (75)
	Q321-N	Lig-O45	3.3 (52)
	Lig-N4	E619-O	2.9 (99)
	Lig-O10	E619-Oε	2.6 (95)
	Lig-N29	N536-O	3.0 (91)
	Lig-N29	N536-Oδ	3.1 (47)

Table S3. The positions of the drug molecules relative to K537 and E619 in MD simulations. The moieties of the drug molecules located between K537 and E619 were indicated by Figure S3.

Drug molecule	Distance (Å)		Angle (°)[c]
	Ligand-K537[a]	Ligand-E619[b]	
1	7.8±1.7	5.5±0.7	138.3±13.8
2	7.6±1.3	7.0±1.2	143.8±14.6
4	11.5±1.8	8.8±1.2	143.0±11.5
6	6.9±1.4	2.2±0.3	141.4±13.1
7	5.5±1.5	6.8±1.2	129.3±13.9
8	10.3±0.8	3.4±0.2	150.2±7.2

[a]The distances between the terminal nitrogen atom in the side chain of K537 and the mass center for the chosen moiety in these drug molecules (red region in Figure S3).

[b]The distance between the center of the oxygen atoms in the terminal carboxylate group in the side chain of E619 and the mass center for the chosen moiety in these drug molecules (red region in Figure S3).

[c]The angle formed by the previous three points with the pivot in the drug molecule.