Electronic Supplementary Information

MoS_2 nanosheets effectively binds to the receptor binding domain of SARS-CoV-2 spike protein and destabilizes the spike-human ACE2 receptor interactions

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Table S1 Description of the hotspot region of the Spike and ACE2 receptor protein[1]

Protein	Hotspot region	Function
Spike glycoprotein	319-541	Receptor binding domain (RBD)
	437-508	Receptor binding motif (RBM)
ACE2	30-42 82-84 353-357	SARS-CoV-2 spike glycoprotein interacting amino acid

Table S2 List of all the systems for MD simulation

S. No.	System	Time (ns)
1	RBD-MoS_2-1	100
2	RBD-MoS_2-2	200
3	ACE2-MoS_2-1	100
4	ACE2-MoS_2-2	100
5	RBD-ACE2-MoS_2-1	100
6	RBD-ACE2-MoS_2-2	100
7	RBD-ACE2-MoS_2-3	100

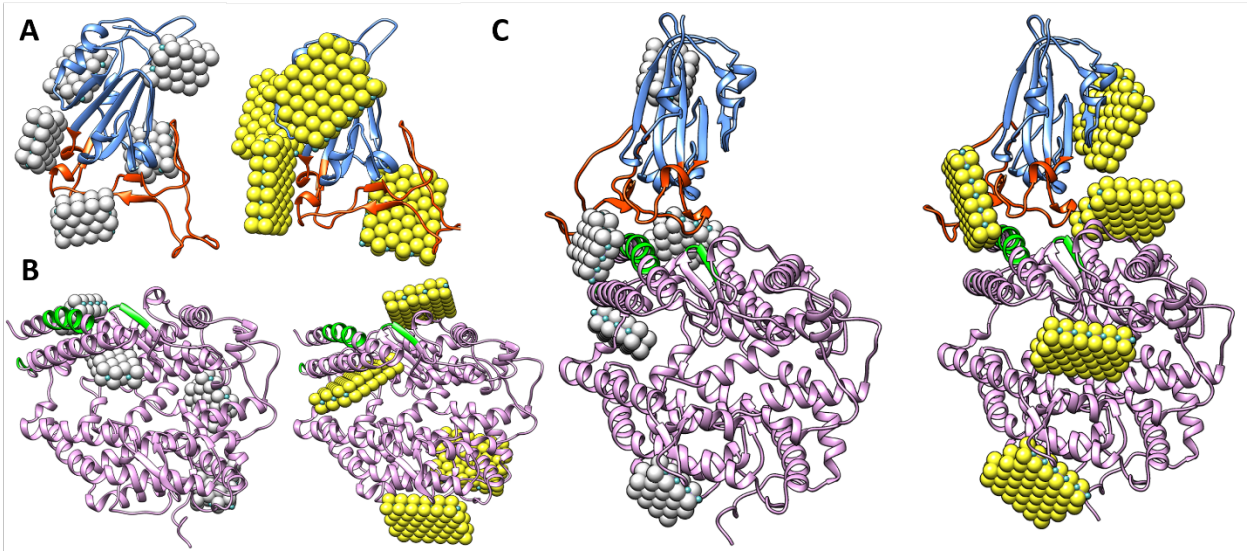

Figure S1. Docking conformation of smaller, 10×10×6 Å (in white) and larger, 17×16×6 Å (in yellow) MoS_2 nanosheets with A) RBD, B) ACE2 and, C) RBD/ACE2 complex.

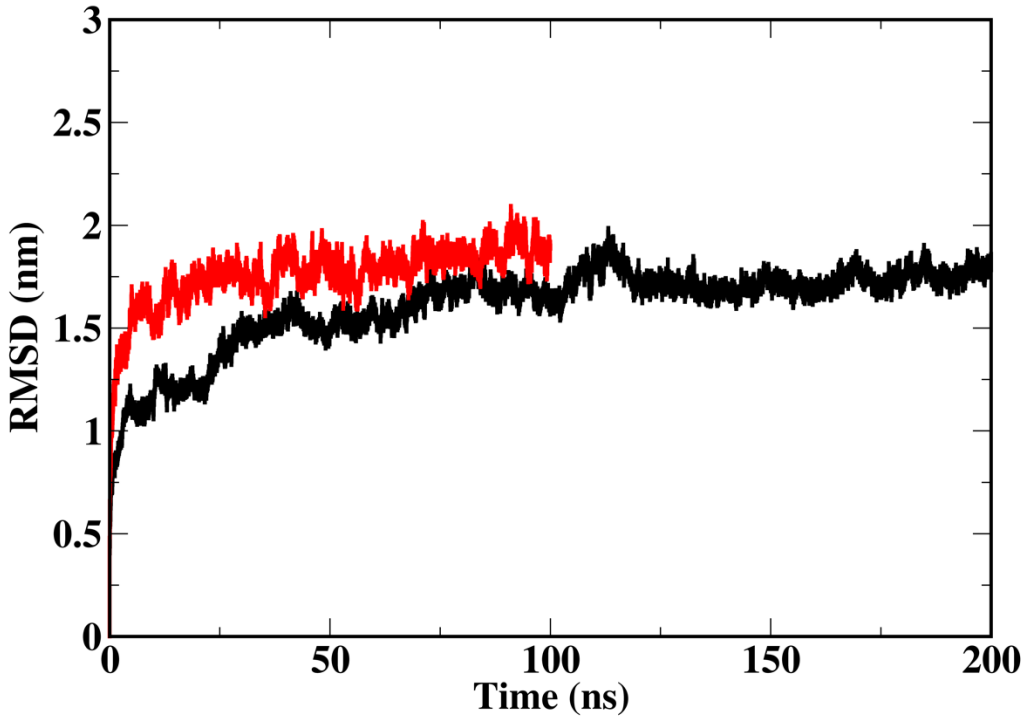

Figure S2 Time evolution of the RMSD of Spike RBD showing protein stability when bound to MoS_2 nanosheet. (Color: RBD- MoS_2-1 is shown in red and RBD- MoS_2-2 is shown in black).

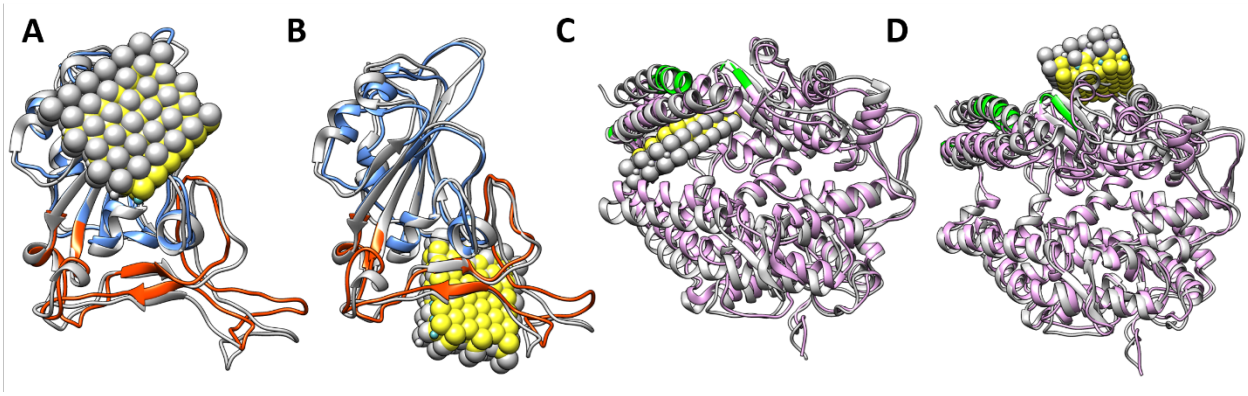

Figure S3 Superimposed structures of the initial and final conformations of A) RBD-MoS_2-1 B) RBD-MoS_2-2 C) ACE2-MoS_2-1 and, D) ACE2-MoS_2-2, showing the relative position of protein and larger MoS_2 nanosheet (17×16×6 Å).

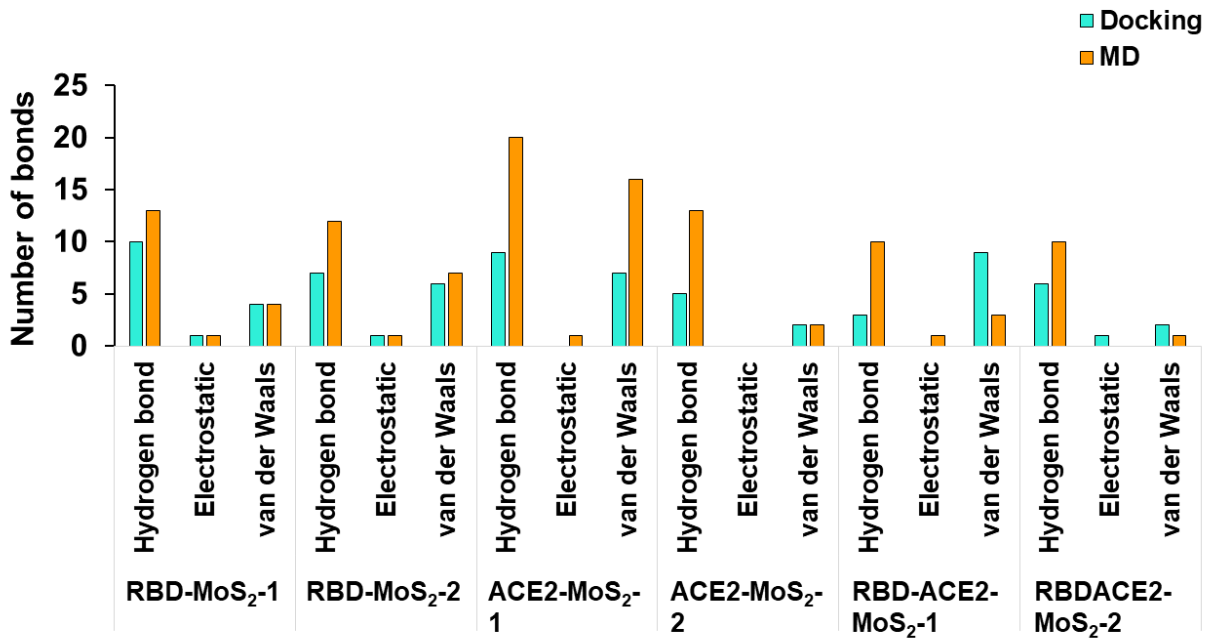

Figure S4 The total number of Hydrogen bonds, electrostatic and van der Waal's interaction before (in sea-green) and after simulation (in orange).

Table S3(A) Interactions in Docking and MD simulation for RBD and MoS_2*

System	Nanosheet	Type of bond	Docking		MD simulation	
			Donor	Acceptor	Donor	Acceptor
RBD-MoS_2-1	**17×16×6**	hydrogen bond	TYR369:HH	MD07:S7	:MD01:S3	:GLY381:O
			TYR380:HH	MD06:S7	:MD03:S3	:ASP427:O
			GLY381:HN	MD02:S7	:MD04:S5	:CYS379:O
			GLY381:HN	MD04:S1	:MD06:S1	:PRO412:O
			GLY381:HN	MD05:S3	:MD06:S1	:ASP427:O
			GLN414:HE22	MD06:S5	:MD06:S5	:PRO412:O
			MD01:S5	GLY381:O	:MD07:S1	:CYS379:O
			MD03:S5	ASP427:O	:MD09:S5	:ARG408:O
			MD06:S1	PRO412:O	:MD09:S5	:GLN414:OE1
			MD06:S5	PRO412:O	:LYS378:HZ3	:MD08:S7
					:GLY381:HN	:MD01:S5
					:GLY381:HN	:MD02:S7
					:GLY381:HN	:MD04:S1
		metallic	MD06:MO2	PRO412:O	:MD09:MO2	:GLN414:OE1
		pi-donor hydrogen bond	MD05:S5	TYR380		
		sulfur-x	MD05:S1	TYR380	:MD03:S7	:ASP427:O
		pi-sulfur	MD06:S3	TYR380	:MD05:S3	:TYR380
			MD06:S5	TYR380	:MD05:S5	:TYR380
					:MD08:S1	:TYR380
RBD-MoS_2-2	**17×16×6**	hydrogen	THR470:HG1	MD01:S5	:MD02:S1	:TYR351:OH

		GLU484:HN	MD07:S3	:MD02:S3	:THR470:OG1
		MD04:S3	GLY482:O	:MD03:S3	:TYR351:OH
		MD04:S7	GLY482:O	:MD03:S5	:SER349:OG
		MD06:S5	TYR449:O	:MD04:S1	:THR470:O
		MD07:S1	GLU484:OE2	:MD04:S3	:GLY482:O
		MD07:S7	GLU484:O	:MD04:S7	:GLY482:O
				:MD06:S5	:TYR451:O
				:MD07:S5	:GLU484:OE2
				:MD08:S3	:GLU484:OE2
				:SER349:HG	:MD03:S1
				:GLU484:HN	:MD07:S3
	metallic	MD06:MO2	TYR449:O	:MD06:MO2	:TYR449:O
	pi-donor hydrogen bond			:MD05:S5	:PHE490
	pi-sulfur	MD02:S7	PHE490	:MD02:S1	:TYR351
		MD03:S3	TYR351	:MD02:S5	:TYR351
		MD04:S1	PHE490	:MD03:S3	:TYR351
		MD05:S1	PHE490	:MD03:S5	:TYR351
		MD05:S7	PHE490	:MD05:S7	:PHE490
		MD09:S5	TYR449	:MD09:S5	:TYR449

*MD0X: here MD=MoS_2, 0X=0 chain number

Table S3(B) Interactions in Docking and MD simulation for ACE2 and MoS_2*

System	Nanosheet	Type of bond	Docking		MD simulation	
			Donor	Acceptor	Donor	Acceptor
ACE2-MoS_2-1	**17×16×6**	hydrogen bond	SER47:HG	MD04:S8	: MD01:S2	: ASN63:O
			SER70:HG	MD02:S8	: MD01:S4	: MET62:O
			SER106:HN	MD03:S5	: MD01:S4	: ASN63:O
			ASN117:HD22	MD02:S1	:MD02:S2	:ASP67:OD1
			ASP350:HN	MD07:S8	:MD03:S1	:SER105:O
			MD01:S6	ASP67:OD 1	:MD03:S6	:SER106:OG
			MD07:S7	ALA348:O	:MD04:S4	:SER47:OG
			MD08:S5	A:ASN394 :OD1	:MD07:S3	:ALA348:O
			MD09:S8	LEU391:O	:MD07:S4	:ALA348:O
					:MD07:S7	:ALA348:O
					:MD07:S8	:ALA348:O
					:MD09:S6	:LEU391:O
					:SER43:HG	:MD01:S8
					:SER43:HG	:MD04:S4
					:TRP69:HE1	:MD05:S4
					:TRP69:HE1	:MD05:S8
					:ASN117:HD21	:MD02:S1
					:ASN117:HD22	:MD03:S3
					:ASP350:HN	:MD07:S4
					:ASN394:HD21	:MD08:S7
		metallic			:MD03:MO2	:SER106:OG

		pi-sulfur	MD05:S4	TRP69	:MD04:S2	:TRP69
			MD05:S6	TRP69	:MD04:S3	:TRP349
			MD07:S6	PHE40	:MD04:S4	:TRP349
			MD08:S2	TRP69	:MD04:S6	:PHE40
			MD08:S2	TRP69	:MD04:S6	:TRP69
			MD08:S4	PHE40	:MD04:S8	:PHE40
					:MD04:S8	:TRP349
					:MD04:S8	:TRP349
					:MD05:S8	:TRP69
					:MD05:S8	:TRP69
					:MD07:S4	:PHE40
					:MD08:S2	:TRP69
					:MD08:S2	:TRP69
					:MD08:S2	:PHE390
					:MD08:S4	:PHE390
					:MD08:S6	:PHE390
		sulfur-x	MD02:S8	SER70:OG		
ACE2-MoS_2-2	**17×16×6**	hydrogen	ASN322:HD21	MD06:S5	:MD01:S3	:ALA384:O
			ASN322:HD21	MD09:S1	:MD03:S1	:THR548:O
			GLN325:HN	MD08:S5	:MD03:S5	:GLY319:O
			GLN325:HN	MD08:S7	:MD04:S3	:MET383:O
			MD07:S7	LYS353:O	:MD06:S5	:ASN322:OD1
					:MD07:S7	:GLN325:OE1
					:MD07:S7	:GLY354:O
					:MD07:S8	:GLN325:OE1
					:MD08:S1	:ASN322:O
					:MD08:S5	:MET323:O
					:ASN322:HN	:MD05:S5

					:ASN322:HN	:MD06:S7
					:GLN325:HN	:MD07:S5
		pi-sulfur	MD01:S1	PHE555	:MD01:S3	:PHE555
			MD01:S5	PHE555	:MD02:S3	:PHE555

*MD0X: here MD=MoS_2, 0X=0 chain number

Table S3(C) Interaction in Docking and MD simulation for RBD/ACE2 complex and MoS_2*

Protein name	Nanosheet	Type of bond	Docking		MD simulation	
			Donor	**Acceptor**	**Donor**	**Acceptor**
RBD-ACE2-MoS_2-1	**17×16×6**	hydrogen bond	CYS344:HN	MD03:S7	A:TRP349:HE1	X:MD03:S5
			MD03:S5	ALA342:O	A:VAL404:HN	X:MD07:S3
			MD06:S1	CYS344:SG	A:GLY405:HN	X:MD07:S7
					A:ARG518:HH12	X:MD04:S8
					A:GLN522:HE21	X:MD07:S8
					X:MD03:S1	A:ASN51:OD1
					X:MD06:S1	A:PRO346:O
					X:MD06:S5	A:PRO346:O
					X:MD07:S4	A:GLU402:O
					X:MD07:S7	A:GLY405:O
		metallic			X:MD03:MO1	A:ASN51:OD1
		pi-donor hydrogen bond;pi-sulfur			X:MD03:S3	A:TRP349
		pi-donor hydrogen bond	MD07:S8	PHE274	MD03:S3	TRP349

	pi-sulfur	MD01:S4	TYR127	MD03:S1	TRP48
		MD01:S4	PHE504	MD09:S7	HIS374
		MD01:S7	PHE504		
		MD01:S8	TYR127		
		MD04:S5	HIS345		
		MD05:S3	HIS345		
		MD05:S7	HIS345		
		MD07:S7	PHE274		
	hydrogen bond	ASN322:HD22	MD04:S1	A:ASN322:HN	X:MD02:S7
		MD01:S1	GLN325:OE1	A:ASN322:HN	X:MD02:S5
		MD03:S5	MET383:O	X:MD01:S1	A:MET323:O
		MD09:S1	GLY319:O	X:MD01:S1	A:GLN325:OE1
		MD09:S3	GLY319:O	X:MD02:S3	A:MET323:O
		MD09:S5	GLN552:OE1	X:MD02:S1	A:ASN322:O
				X:MD02:S5	A:ASN322:O
RBD-ACE2-MoS_2-2				X:MD04:S1	A:ASN322:OD1
				X:MD05:S5	A:LEU320:O
				X:MD09:S1	A:GLN552:OE1
	metallic	MD09:MO2	GLN552:OE1		
	pi-donor hydrogen bond;pi-sulfur	MD06:S5	PHE555	X:MD06:S5	A:PHE555
	(pi-sulfur)	MD03:S1	PHE356		

*MD0X: here MD=MoS_2, 0X=0 chain number

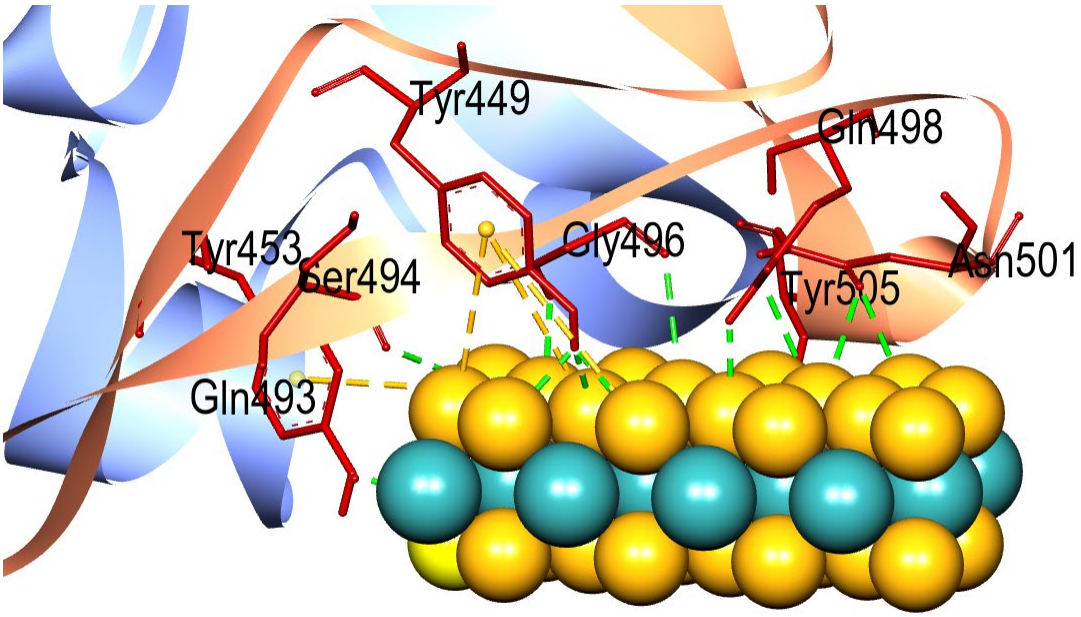

Figure S5. Interacting amino acid residues of RBD with smaller the MoS_2 nanosheet (10×10×6 Å). MoS_2 is shown in spheres where Mo is shown in teal and S in yellow colors. Amino acid residues are labelled. Dashed Green lines- Hydrogen bonds; Dashed Yellow lines - van der Waal's interactions.

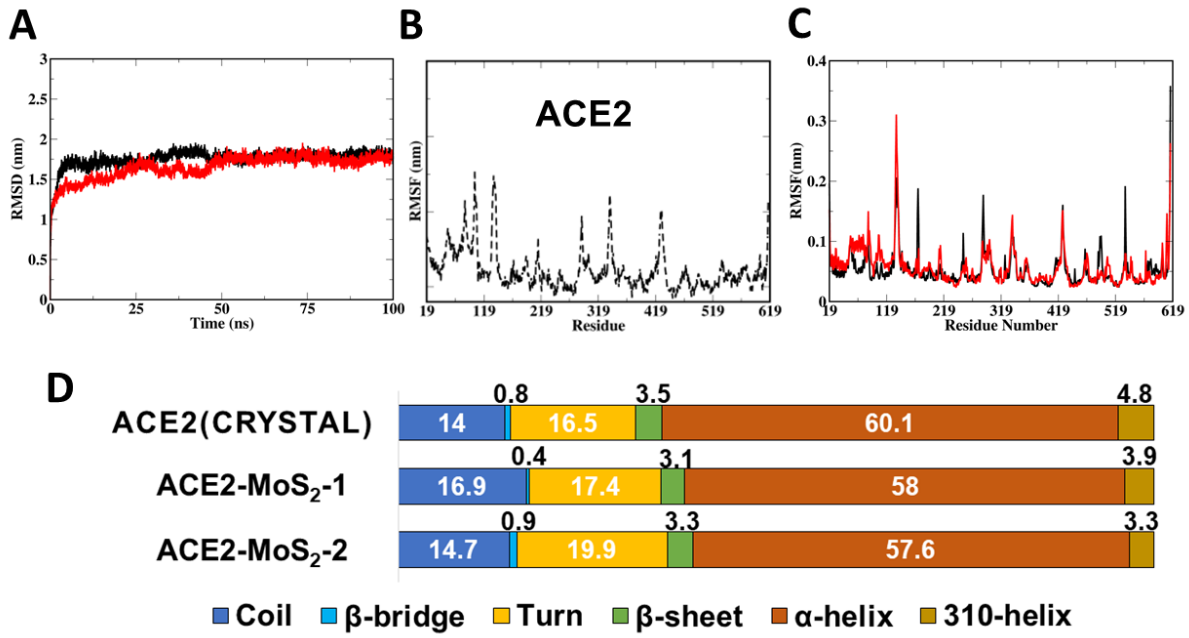

Figure S6 A) Time evolution of RMSD of human ACE2 receptor bound to larger MoS_2 nanosheet (17×16×6 Å) and its corresponding B) Atomic fluctuation of Cα atoms of ACE2 from the crystal structure 6M0J C) Root Mean Square Fluctuations (RMSF) of system ACE2-MoS_2-1 and ACE2-MoS_2-2 (color: ACE2-MoS_2-1 in black ACE2-MoS_2-2 in red) C) Distribution of secondary structure elements in different ACE2 complexes.

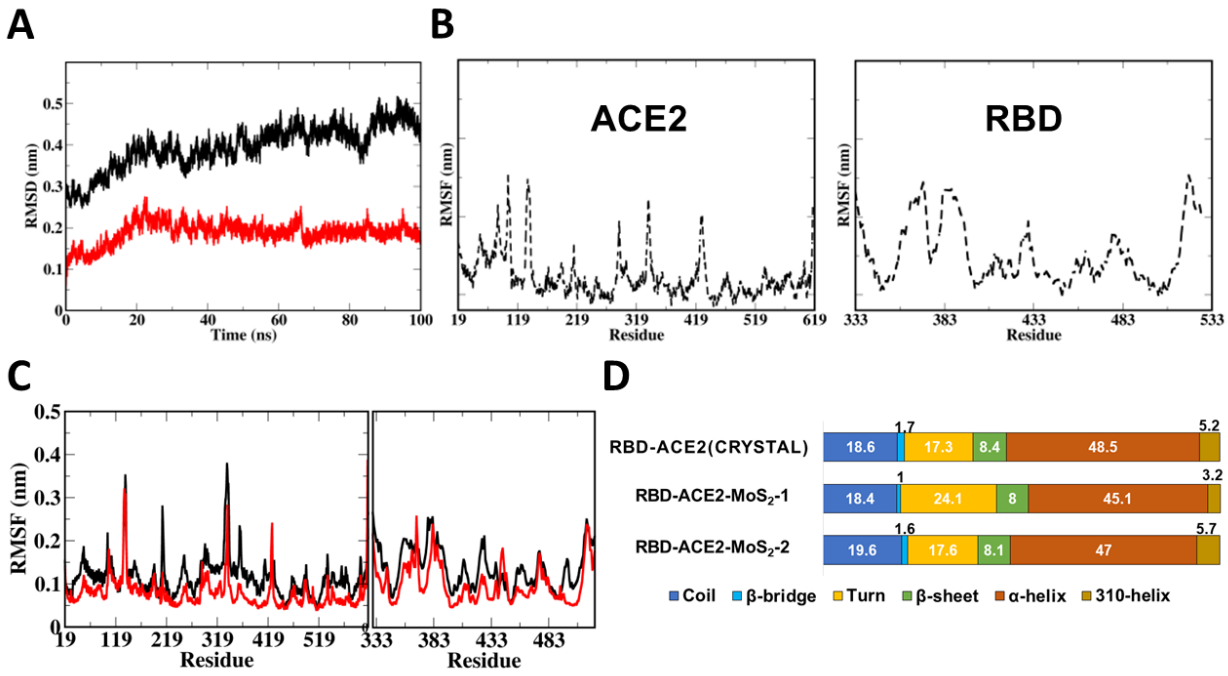

Figure S7 A) Time evolution of RMSD of RBD/ACE2 complex bound to larger MoS_2 nanosheet (17×16×6 Å) and its corresponding B) Atomic fluctuation of Cα atoms of RBD-ACE2 from the crystal structure 6M0J C) Root Mean Square Fluctuations (RMSF) of system RBD-ACE2-MoS_2-1 and RBD-ACE2-MoS_2-2 (color: RBD-ACE2-MoS_2-1 in black and RBD-ACE2-MoS_2-2 in red) D) The distribution of secondary structure elements in different RBD-ACE2 systems after simulation.

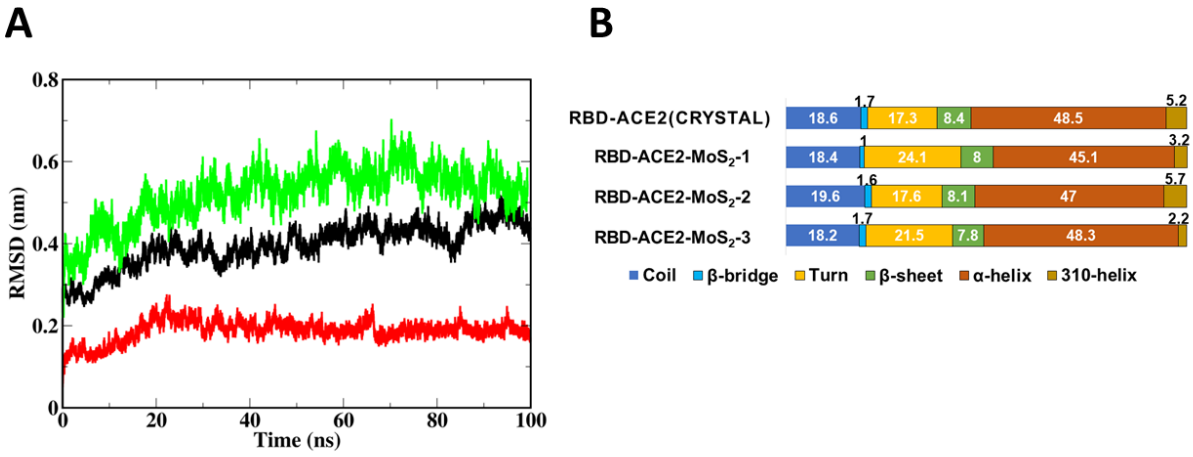

Figure S8 A) The time evolution of RMSD of RBD/ACE2 complex bound to larger MoS_2 nanosheet (17×16×6 Å) (color: RBD-ACE2-MoS_2-1 in black; RBD-ACE2-MoS_2-2 in red and RBD-ACE2- MoS_2-3 in green) and the distribution of B) secondary structure elements in the three RBD-ACE2 systems considered for the study.

MATERIALS AND METHODS

The docking studies were performed using AutoDock which uses semi empirical method which evaluates the binding in two steps. In step one, the energy is estimated from the unbound to bound state and the second step involves the calculation of intermolecular energetics of protein and ligand.

$$\Delta G = (V_{bound}^{L-L} - V_{unbound}^{L-L}) + (V_{bound}^{P-P} - V_{unbound}^{P-P}) + (V_{bound}^{P-L} - V_{unbound}^{P-L} + \Delta S_{conf})$$

$$V = W_{vdw}\sum_{i,j}\left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}}\right) + W_{hbond}\sum_{i,j}E(t)\left(\frac{C_{ij}}{r_{ij}^{12}} - \frac{D_{ij}}{r_{ij}^{10}}\right) + W_{elec}\sum_{i,j}\frac{q_i q_j}{e(r_{ij})r_{ij}} + W_{sol}\sum_{i,j}\left(S_i V_j + S_j V_i\right)e^{(-r_{ij}^2/2\sigma^2)}$$

Here, L refers to the "ligand" and P refers to the "protein" in a ligand-protein docking calculation. Further details can be found in the user manual of Autodock which is freely available[2].

References

1. Unal, M. A.; Bayrakdar, F.; Nazir, H.; Besbinar, O.; Gurcan, C.; Lozano, N.; Arellano, L. M.; Yalcin, S.; Panatli, O.; Celik, D., Graphene Oxide Nanosheets Interact and Interfere with SARS-CoV-2 Surface Proteins and Cell Receptors to Inhibit Infectivity. *Small* **2021,** *17* (25), 2101483.

2. User Guide, AutoDock Version 4.2, https://autodock.scripps.edu/wp-content/uploads/sites/56/2021/10/AutoDock4.2.6_UserGuide.pdf