Simulation of Molecular Dynamics of SARS-CoV-2 S-Protein in the Presence of Multiple Arbidol Molecules: Interactions and Binding Mode Insights

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Supplementary materials

Molecular dynamics

Initial systems used for calculations

Hereinafter, the Arbidol molecule is shown in the form of the van der Waals model; RBD is red; ACE-2 is blue; sodium cation and chloride anion are shown green big and dark-red small balls, respectively.
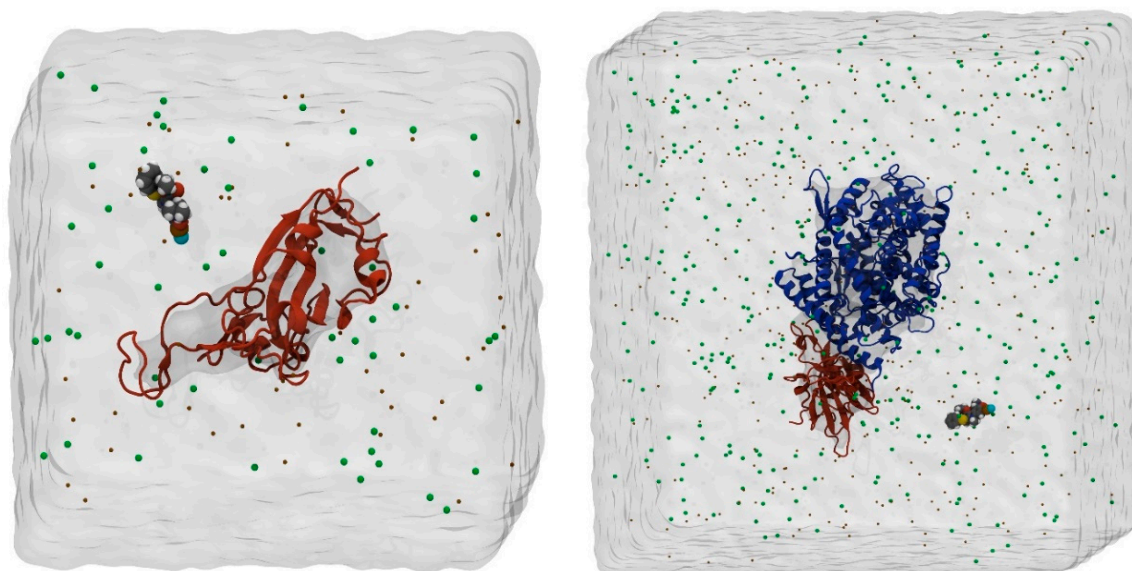

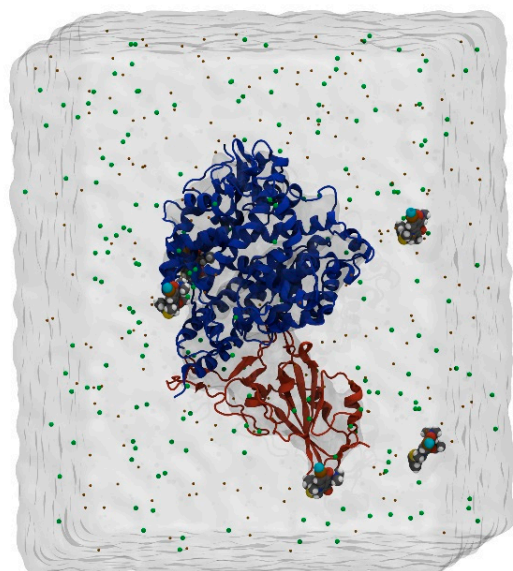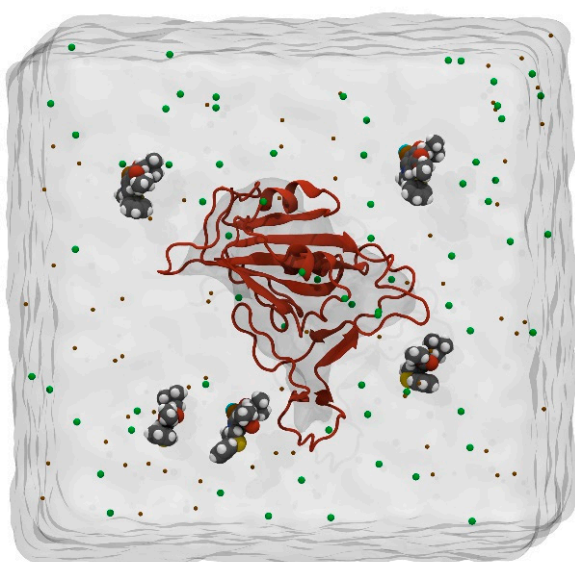**Figure-S1** RBD-1×Arb and ACE-2-RBD-1×Arb

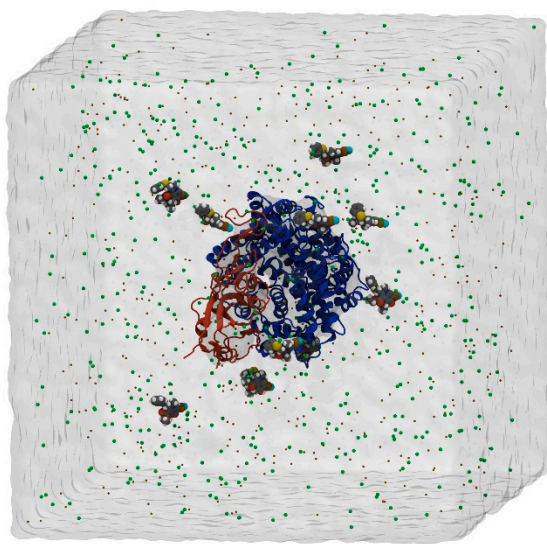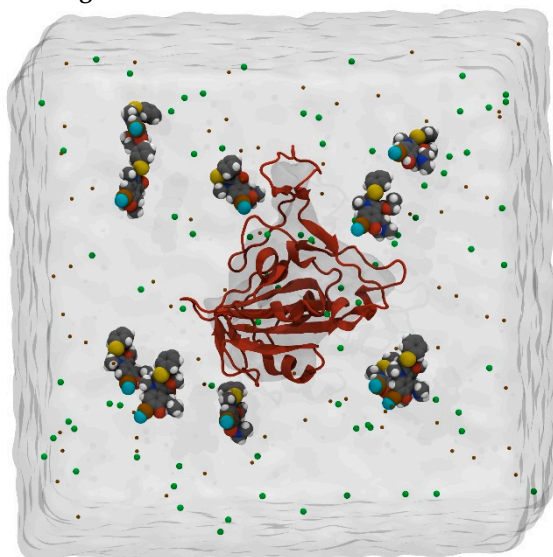**Figure-S2** RBD-5×Arb and ACE-2-RBD-5×Arb
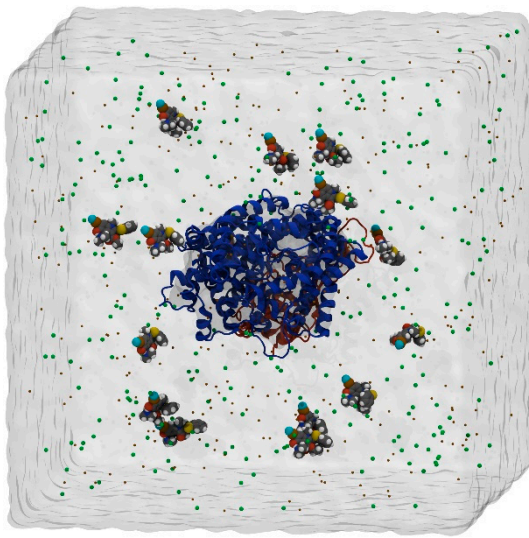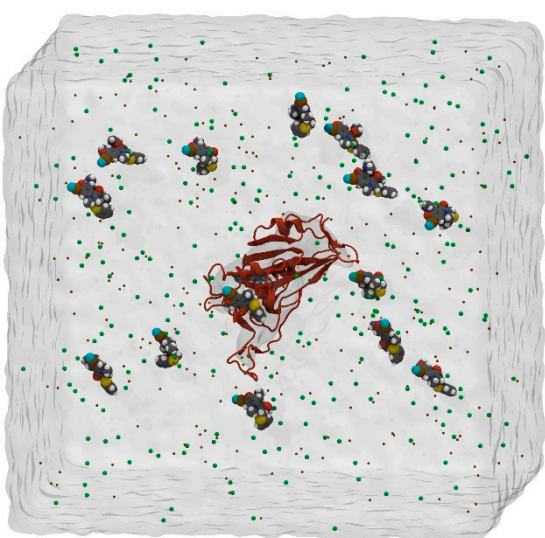

Figure-S3 RBD-10×Arb and ACE-2-RBD-10×Arb

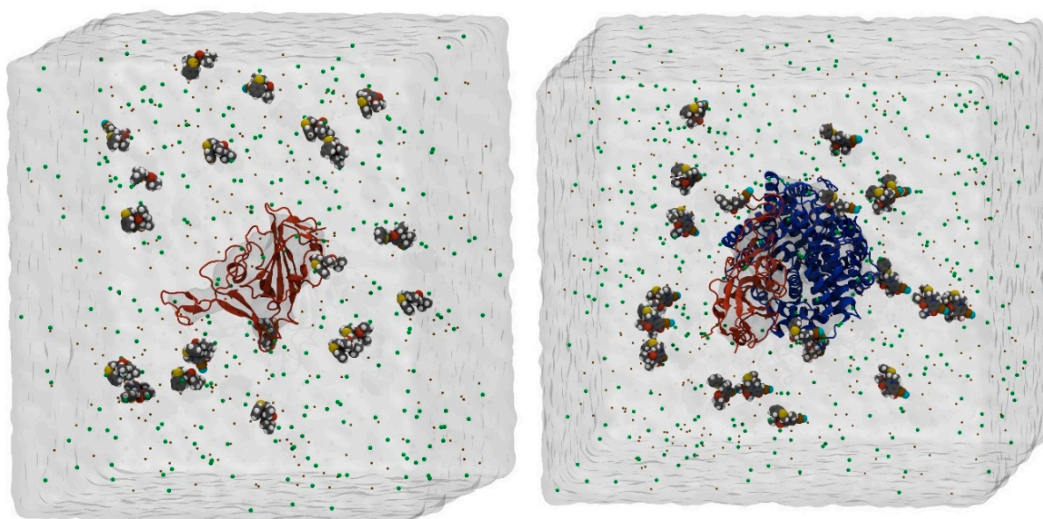**Figure-S4** RBD-15×Arb and ACE-2-RBD-15×Arb

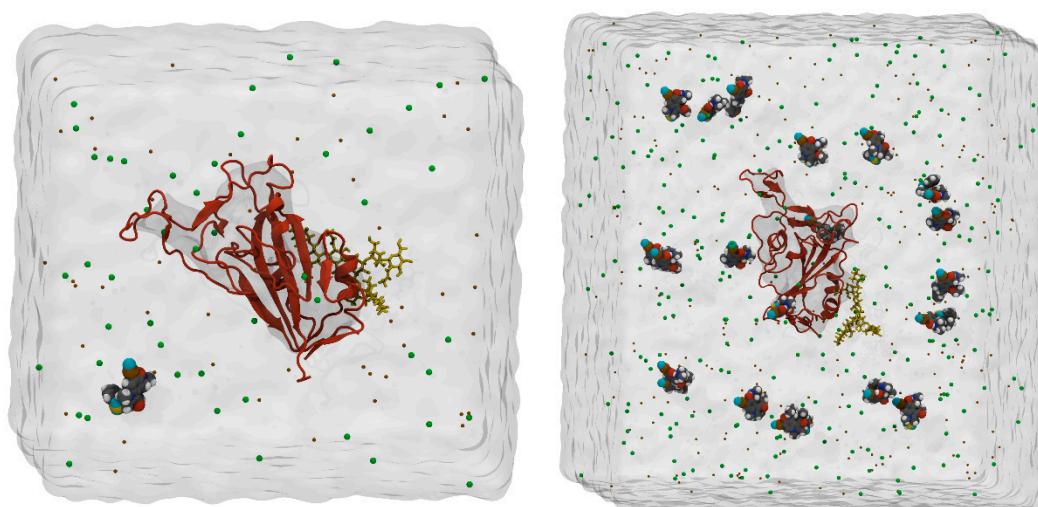**Figure-S5** RBD-20×Arb and ACE-2-RBD-20×Arb

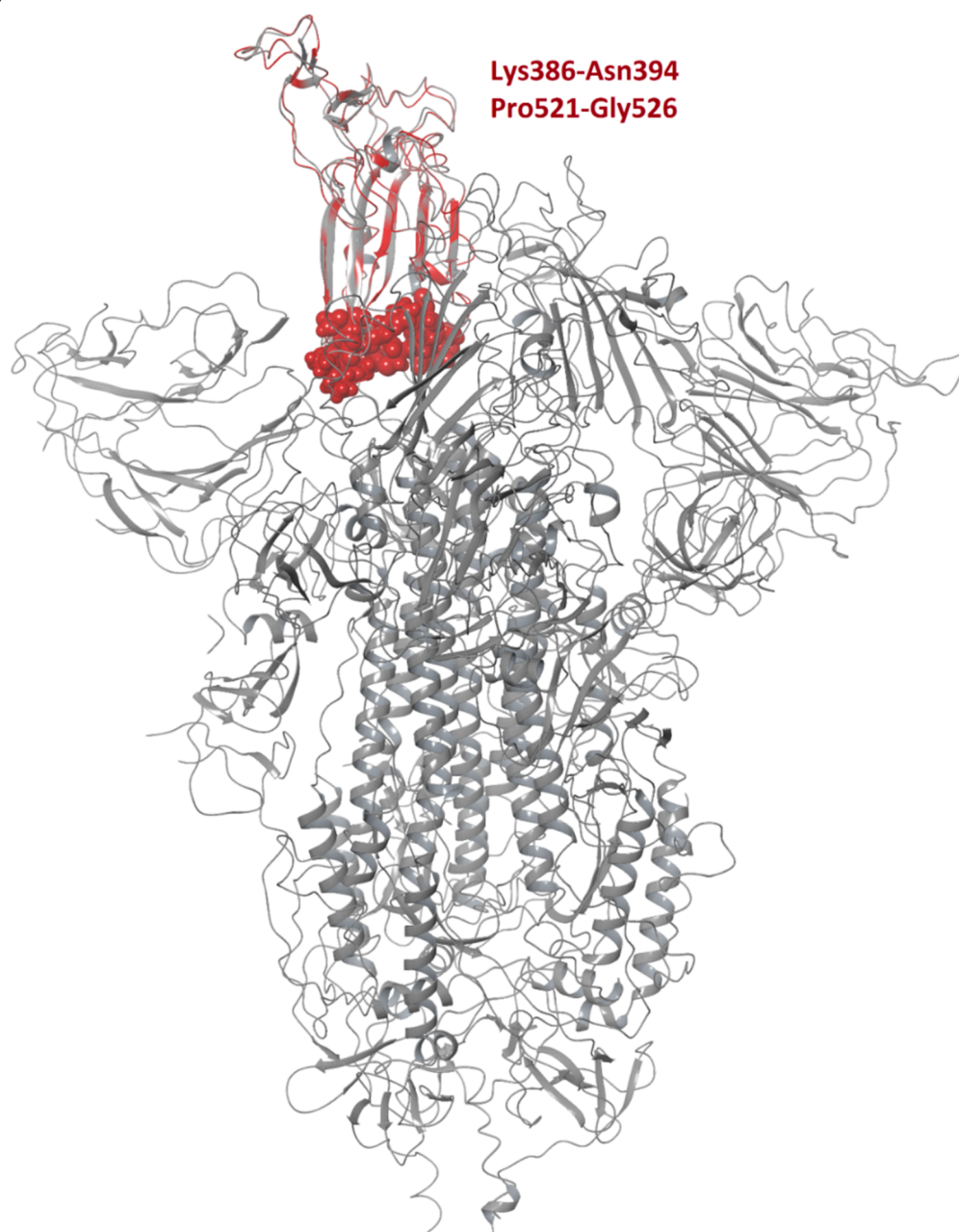**Figure-S6** RBD-20×Arb and ACE-2-RBD-20×Arb

Figure-S7 Spike-protein SARS-CoV-2 open conformation: hard-to-reach amino acids for Arbidol are shown with balls model

Root-mean-square deviation of atomic positions

        The results of molecular dynamics simulation for 300 ns at 310K are presented. In the case of ligands for systems containing 1 and 5 Arbidol molecules (RBD-n×Arb and ACE-2-RBD-n×Arb, n = 1, 5), perturbations in RMSD values are observed (Figures S 8-9), which fade with increasing numbers of Arbidol molecules (RBD-n×Arb and ACE-2-RBD-n×Arb, n = 10-20) (Figures S 10-12). At the same time, increasing the simulation time at an elevated temperature does not practically change the situation. The perturbations of the RMSD values of the ligand position in the RBD-1×Arb and ACE-2-RBD-1×Arb systems are significant (Figure S 13), while in RBD-20×Arb and ACE-2-RBD-20×Arb they are not significant (Figure S 14).

Figure-S8 RMSD of ACE-2-RBD – 1×Arb molecular dynamic simulation

Figure-S9 RMSD of ACE-2-RBD – 5×Arb molecular dynamic simulation

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Figure-S10 RMSD of ACE-2-RBD – 10×Arb molecular dynamic simulation

Figure-S11 RMSD of ACE-2-RBD – 15×Arb molecular dynamic simulation
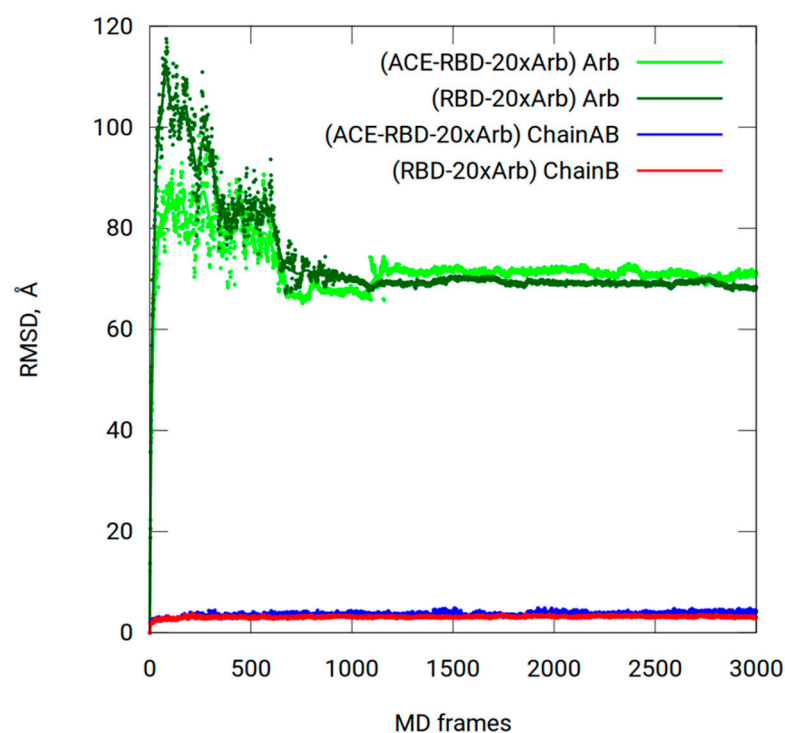
Figure-S12 RMSD of ACE-2-RBD – 20×Arb molecular dynamic simulation

The results of molecular dynamics simulation for 100 ns at 400K are presented.

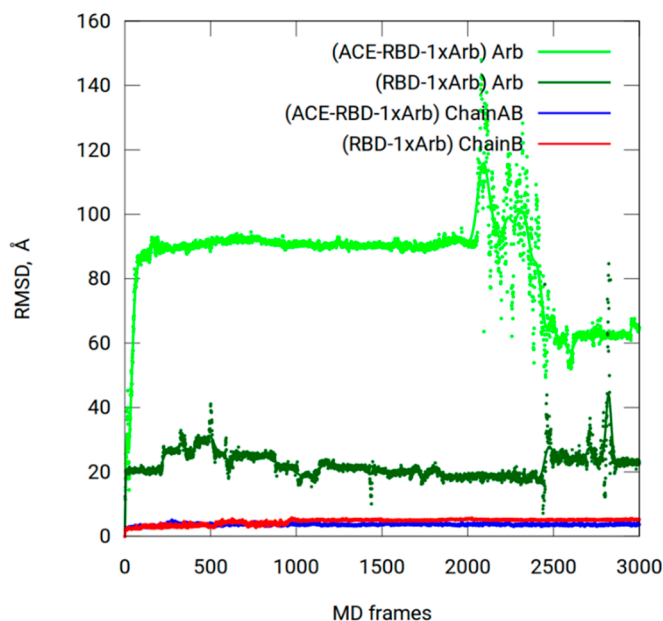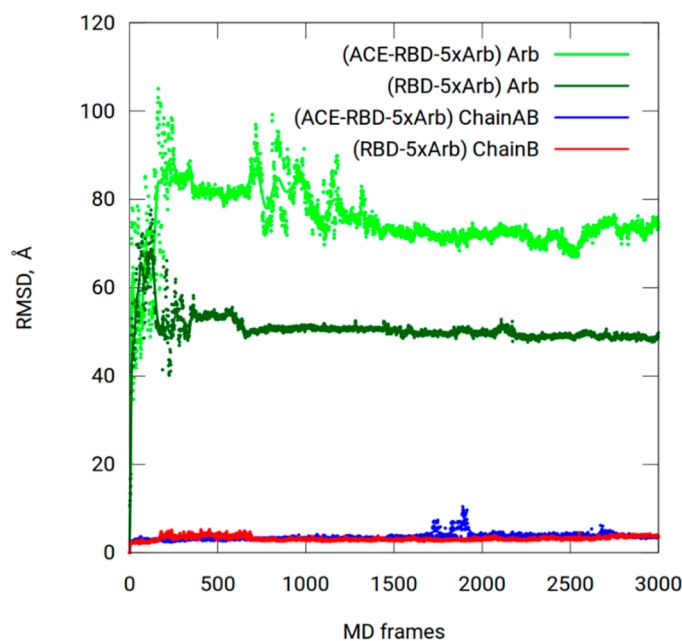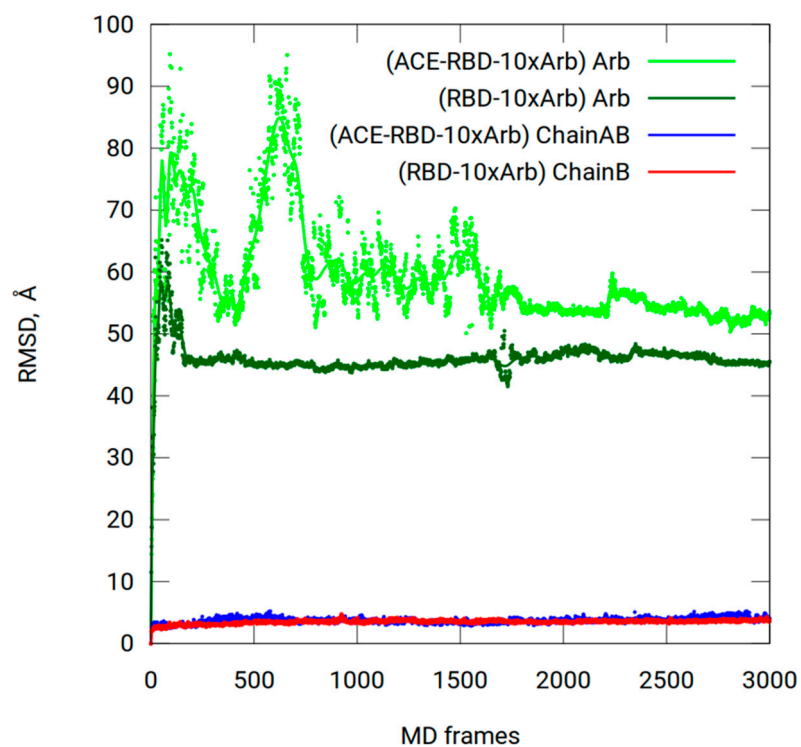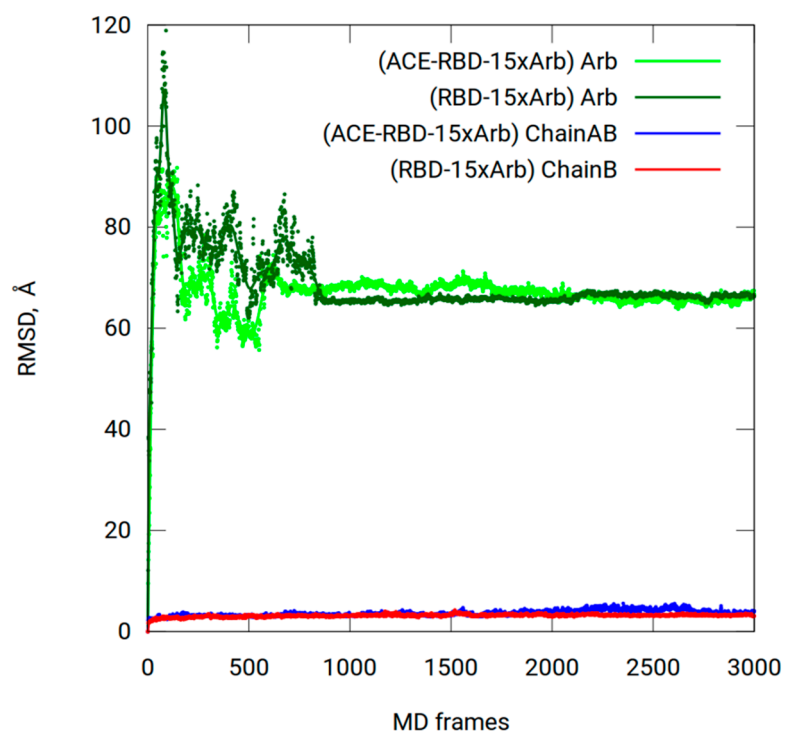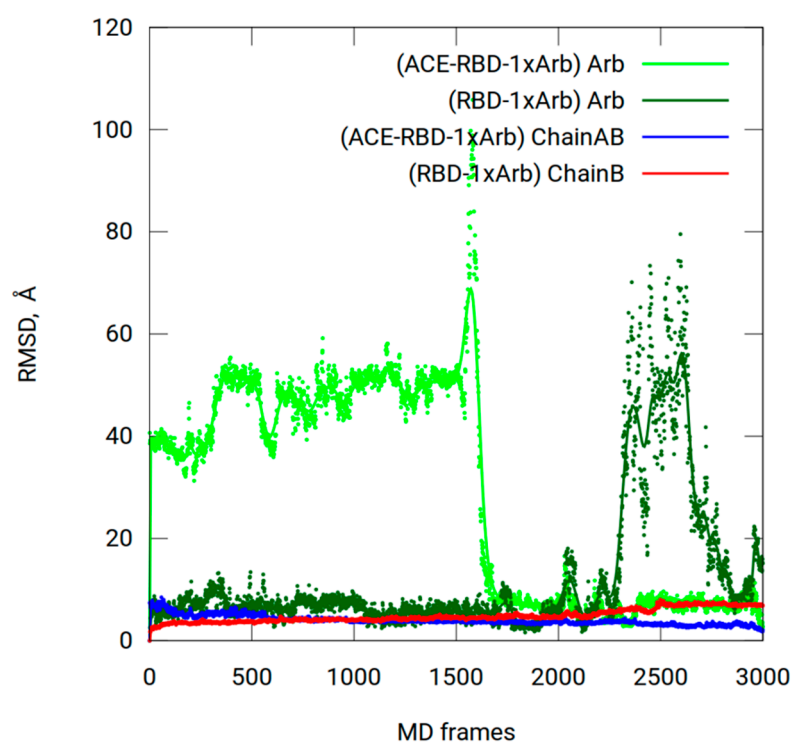**Figure-S13** RMSD of ACE-2-RBD – 1×Arb molecular dynamic simulation
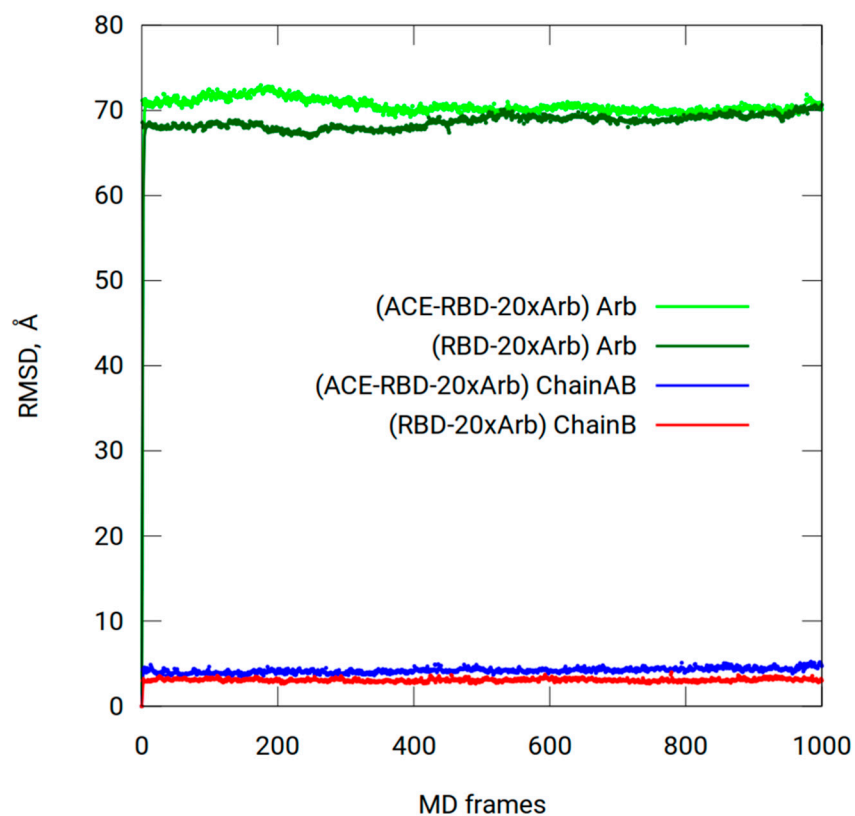
Figure-S14 RMSD of ACE-2-RBD – 20×Arb molecular dynamic simulation
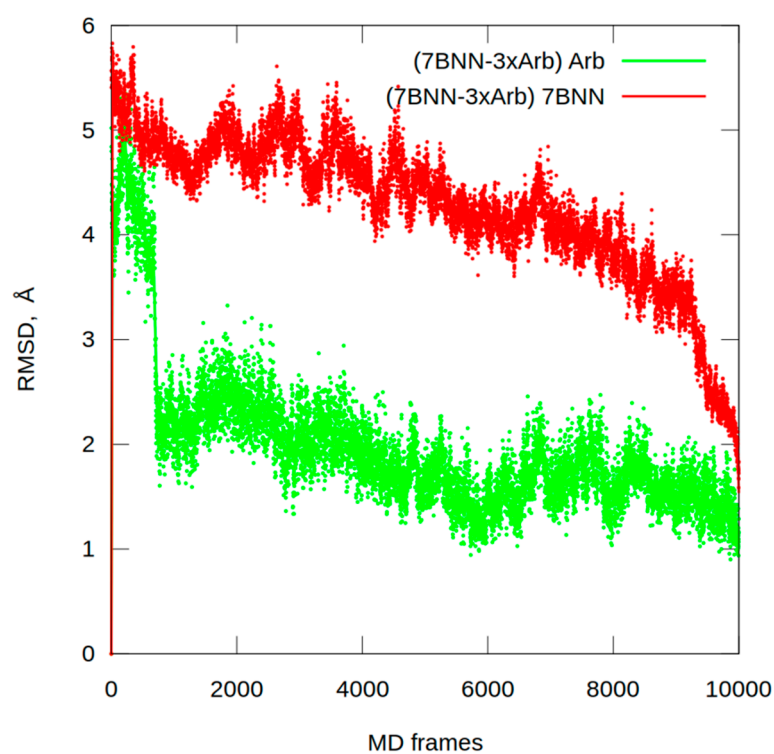
Figure-S15 RMSD of S-protein 3×Arb molecular dynamic simulation
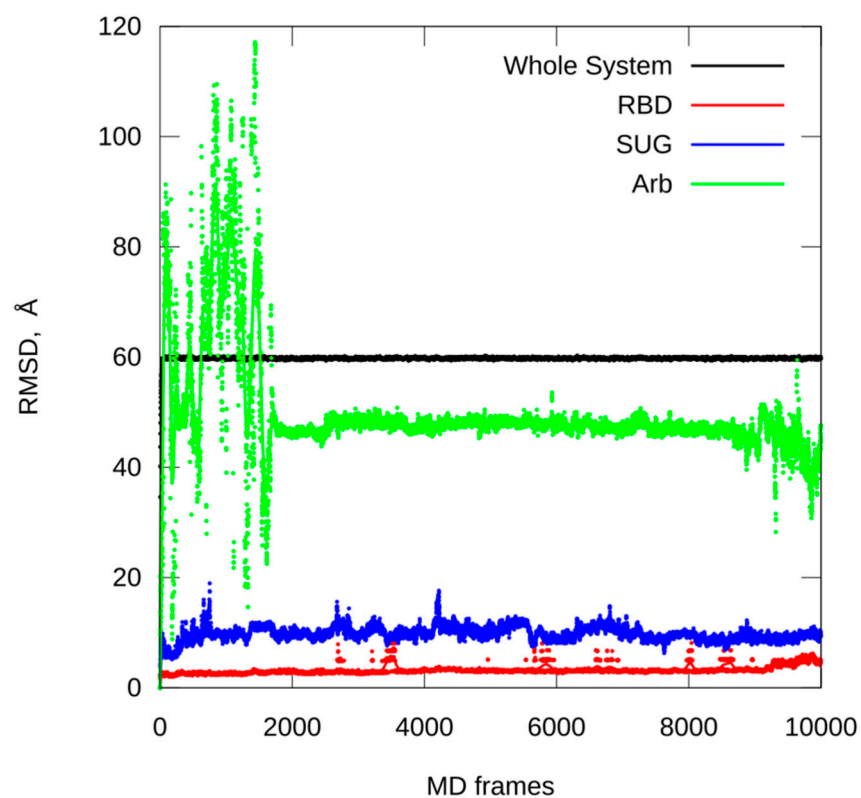
Figure-S16 RMSD of RBD-SUR-1×Arb molecular dynamic simulation
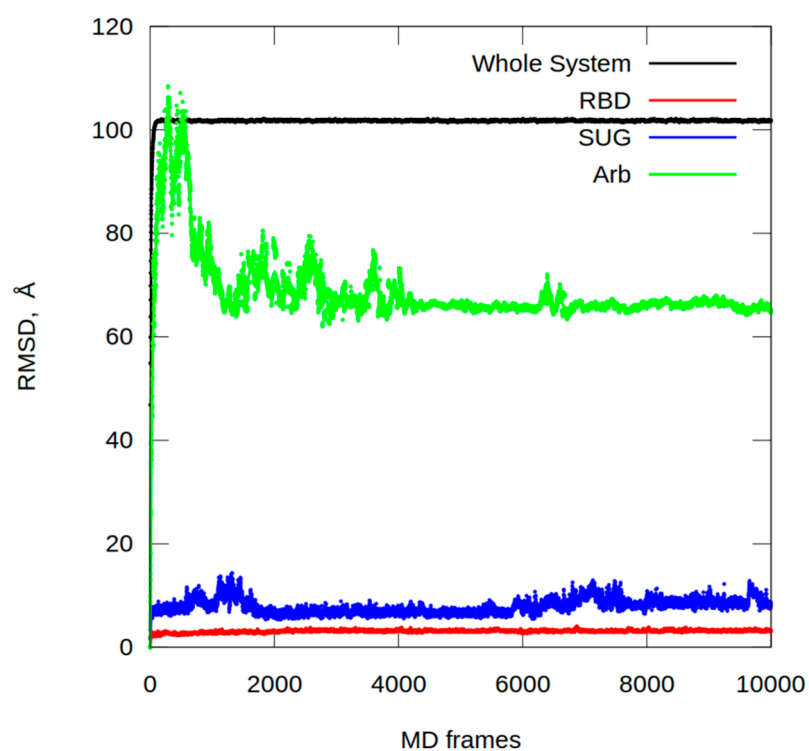
Figure-S17 RMSD of RBD-SUR-20×Arb molecular dynamic simulation
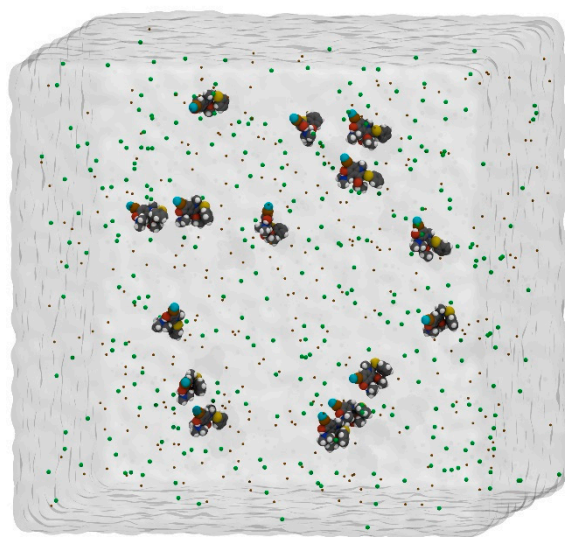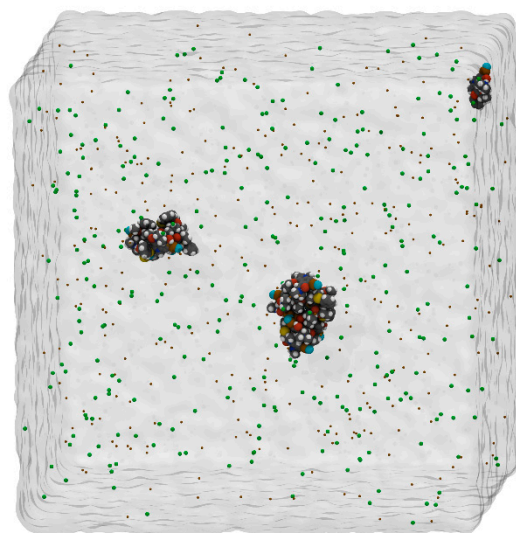
τ = 0 ns τ = 300 ns

Figure-S18

Population analysis

RBD-1xArb (T = 310 K)

Asn343 − 25.2%
Ser373 − 24.5%

ACE-2-**RBD**-1xArb (T = 310 K)

Asn546 − 35.1%
Pro263 − 29.4%
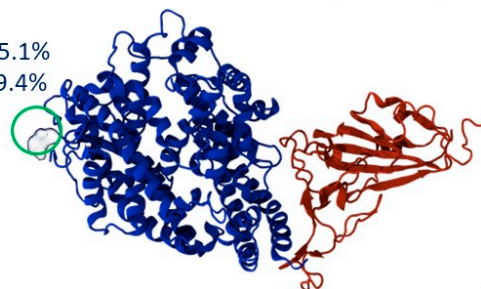
RBD-1xArb (T = 400 K)

Thr470 − 25.8%
Pro491 − 11.7%
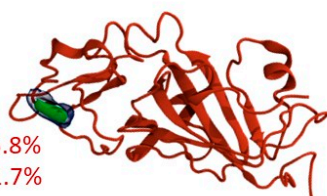
ACE-2-**RBD**-1xArb (T = 400 K)

Asn416 − 26.0%

Tyr380 − 7.6%
Arg408 − 5.6%

Figure-S19

RBD-5xArb

Asn370 – 18.6%
Ser373 – 7.8%

Gly496 – 35.8%
Gly446 – 13.8%

ACE-2-RBD-5xArb

Asn343 – 2.5%

Arg195 – 9.5%
Lys81 – 6.2%

Gln474 – 5.2%

RBD-10xArb

Lys378 – 9.4%
Asn343 – 5.1%

Gly414 – 2.7%

Thr393 – 9.9%
steric hindrance

ACE-2-RBD-10xArb

Leu585 – 23.9%

Glu171 – 9.7%

THR 21
TYR 83
ASN 487
PHE 486

Tyr83 – 0.5%

Asn487 – 0.4%

Figure-S 20

RBD-15xArb

Val362 – 16.0%
Asn360 – 15.9%

Pro491 – 2.2%

Asp389 – 6.5%
steric hindrance

ACE-2-RBD-15xArb

Ser425 – 2.9%

Ser349 – 26.6%
Asn354 – 14.6%

Asn194 – 3.6%

RBD-20xArb (T = 310K)

Val445 – 39.2%
Ser438 – 8.3%

ACE-2-RBD-20xArb (T = 310K)

Asn49 – 4.1%

Ser383 – 11.3%
Asn370 – 4.6%

Tyr83 – 1.9%

RBD-20xArb (T = 400K)

Val445 – 54.6%
Ser438 – 16.7%

ACE-2-RBD-20xArb (T = 400K)

Lys61 – 15.2%

Ser383 – 8.8%

Thr582 – 11.3%

Phe486 – 14.7%

Thr478 – 5.0%

Figure-S21

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Table S1 Molecular dynamics statistics for systems RBD-n×Arb, n = 1..20 and RBD-SUG-n×Arb, (n = 1, 20)

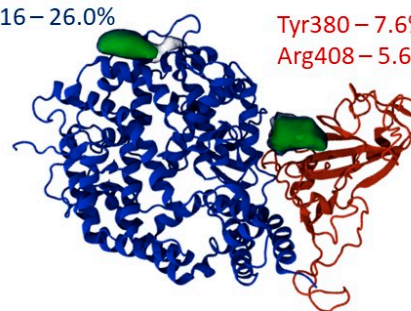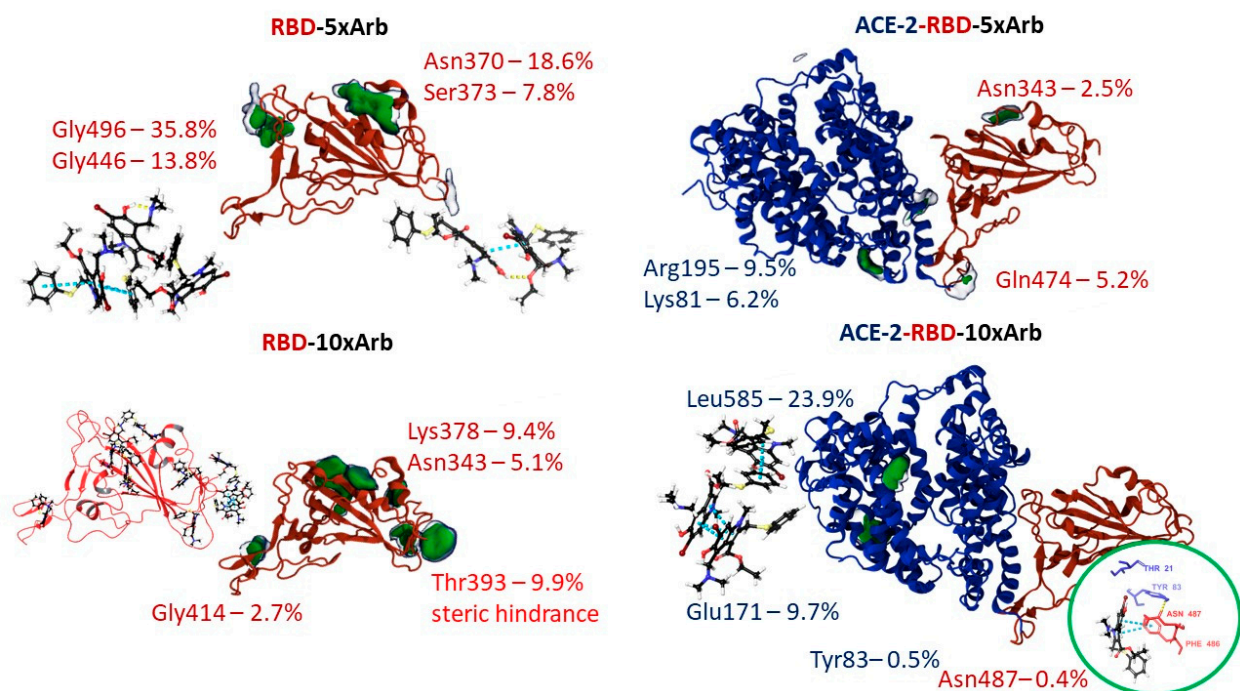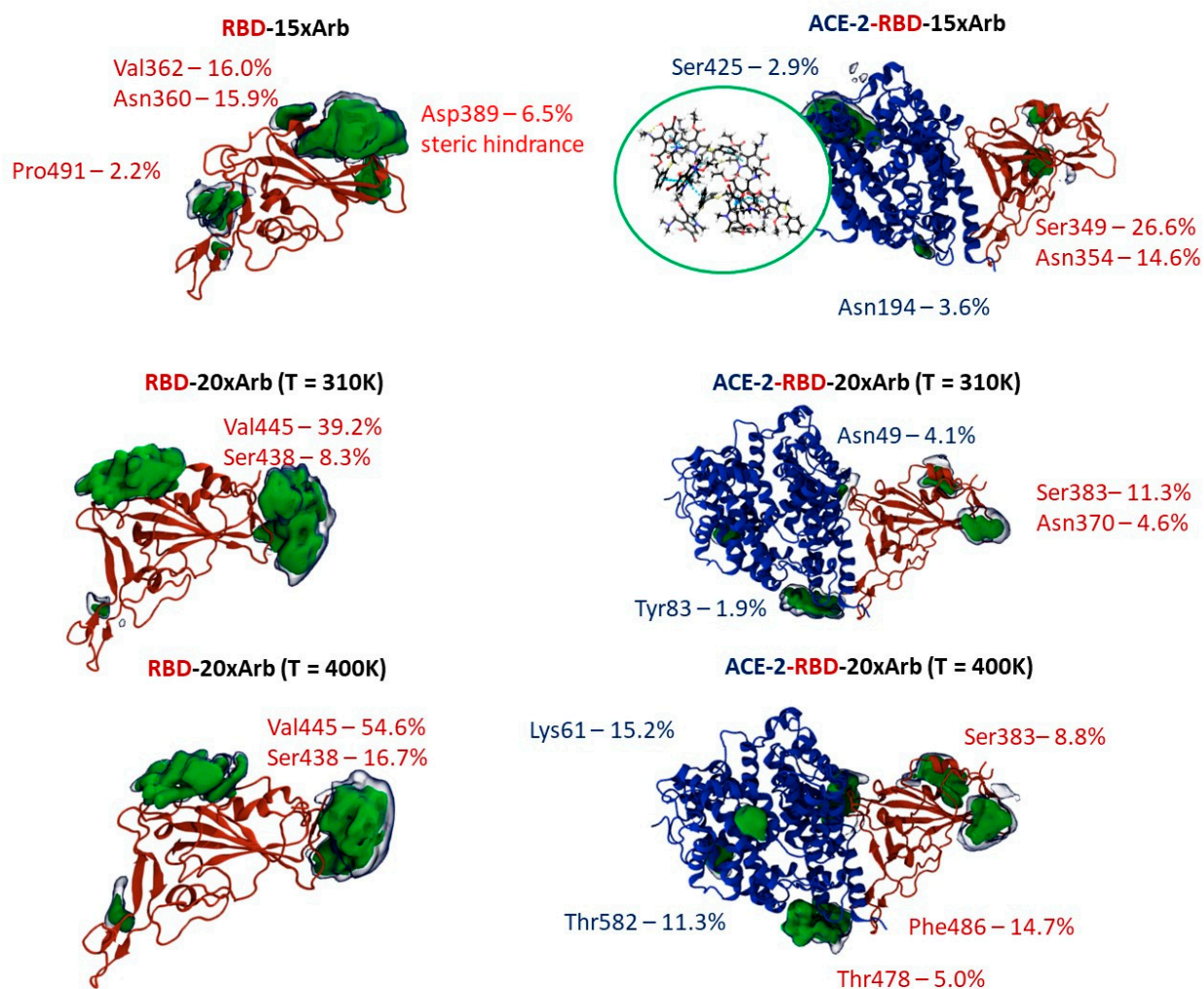| System	Amino acids	Donor-acceptor interaction	Descript of Arb	Occupancy, %	Probability of intramolecular interaction, %	Type of intramolecular interaction
RBD-1×Arb (310 K)	Asn343	Donor	O – acceptor	0.8	25.5	H-bond
	Ser371	Donor	O – acceptor	0.8	24.5	H-bond
	Asn370	Donor	O – acceptor	0.4	12.6	H-bond
RBD-1×Arb (400 K)	Thr470	Donor	O – acceptor	0.8	27.6	H-bond
	Pro491	Donor	Ring	0.3	10.3	π-cation
	Arg545	Donor	O – acceptor	0.3	10.3	H-bond
RBD-SUG-1×Arb (310 K)	Pro491	Donor	Acceptor	0.4	19.8	hydrophobic
	Tyr489	Donor	Acceptor	0.4	14.0	hydrophobic
	Tyr473	Donor	Acceptor	0.2	9.0	hydrophobic
RBD-5×Arb (310 K)	Gly496	Donor	O – acceptor	25.4	35.6	H-bond
	Asn370	Donor	O – acceptor	13.2	18.6	H-bond
	Gly446	Donor	O – acceptor	9.8	13.4	H-bond
RBD-10×Arb (310 K)	Thr393	Donor	Ring	3.7	9.9	π-cation
	Lys378	Donor	N - acceptor	3.5	9.4	H-bond
	Asn343	Acceptor	O - donor	1.8	5.1	H-bond
RBD-15×Arb (310 K)	Val362	Donor	Ring	6.3	16.0	π-cation
	Asn360	Donor	O - acceptor	6.3	15.9	H-bond
	Asp389	Donor	O - acceptor	2.6	6.5	H-bond
RBD-20×Arb (310 K)	Val445	Donor	O - acceptor	31.3	54.6	H-bond
	Ser438	Donor	Ring	9.6	16.7	π-cation
	Asn388	Acceptor	O - donor	2.6	4.5	H-bond
RBD-SUG-20×Arb (310 K)	Gly381	Donor	Acceptor	12.5	21.6	H-bond
	Gly339	Donor	Acceptor	7.4	12.5	hydrophobic
	Asn440	Donor	Acceptor	6.7	8.3	hydrophobic
RBD-20×Arb (400 K)	Val445	Donor	O - acceptor	29.3	39.2	H-bond
	Ser438	Donor	Ring	6.2	8.3	π-cation
	Gln93	Donor	O - acceptor	3.9	5.2	H-bond

Table S2 Molecular dynamics statistics for systems ACE-2-RBD-n×Arb, n = 1…20.

System	Amino acids	Donor-acceptor interaction	Descript of Arb	Occupancy, %	Probability of intramolecular interaction, %	Type of intramolecular interaction
ACE-2-RBD-1×Arb (310 K)	Asn456 (ACE-2)	Donor	O – acceptor	1.8	35.1	H-bond
	Pro263 (ACE-2)	Donor	Ring	1.4	29.4	π-cation
	Ala614 (ACE-2)	Donor	O – acceptor	0.6	12.0	H-bond
ACE-2-RBD-1×Arb (400 K)	Asn456 (ACE-2)	Donor	O – acceptor	1.7	26.0	H-bond
	Tyr380 (RBD)	Donor	O – acceptor	0.4	7.6	H-bond
	Pro590 (ACE-2)	Donor	Ring	0.3	5.6	π-cation
ACE-2-RBD-5×Arb (310 K)	Leu585 (ACE-2)	Acceptor	O - donor	5.9	23.9	H-bond
	Glu171 (ACE-2)	Acceptor	O - donor	2.4	9.7	H-bond
	Arg115 (Ace-2)	Donor	N - acceptor	1.4	5.5	H-bond
ACE-2-RBD-10×Arb (310 K)	Asn195 (ACE-2)	Donor	O – acceptor	6.0	9.5	H-bond
	Lys81 (ACE-2)	Donor	N - acceptor	3.9	6.2	H-bond
	Gln474 (RBD)	Donor	N - acceptor	3.3	5.3	H-bond
ACE-2-RBD-15×Arb (310 K)	Ser349 (RBD)	Donor	O – acceptor	18.5	26.6	H-bond
	Asn354 (RBD)	Donor	O – acceptor	10.2	14.6	H-bond
	Ser371 (RBD)	Donor	O – acceptor	2.9	4.3	H-bond
ACE-2-RBD-20×Arb (310 K)	Ser383 (RBD)	Donor	O – acceptor	11.1	11.6	H-bond
	Ala522 (RBD)	Donor	O – acceptor	8.2	8.5	H-bond
	Thr393 (RBD)	Donor	Ring	6.4	6.7	π-cation
ACE-2-RBD-20×Arb (400K)	Lys61 (ACE-2)	Donor	N – acceptor	13.0	15.2	H-bond
	Phe486 (RBD)	Donor	O – acceptor	12.6	14.7	H-bond
	Thr582 (ACE-2)	Donor	O – acceptor	9.6	11.3	H-bond

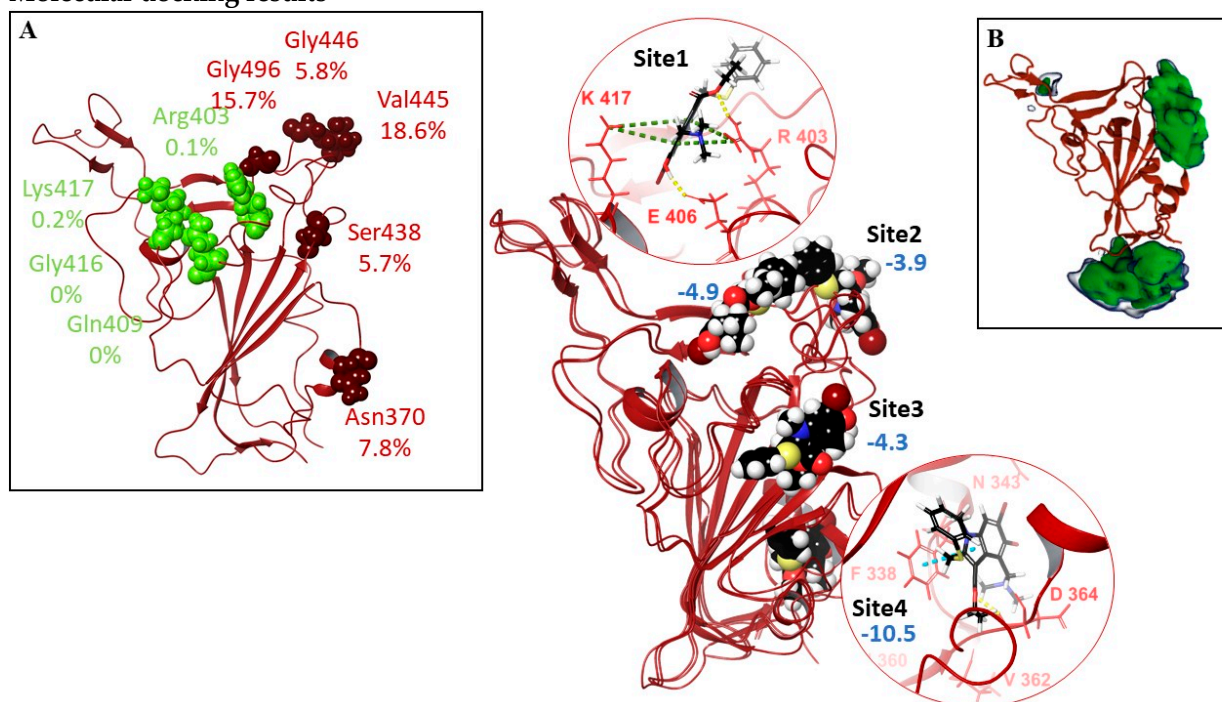| Amino acids	Descript of Arb	Occupancy, %	Probability of intramolecular interaction, %	Type of intramolecular interaction
Phe1042	hydrophobic	19.4	44.5	hydrophobic
Arg1019	O – donor	15.8	36.4	H-bond
Asn1023	N – acceptor	3.3	7.5	H-bond
Lys1028	O – donor	1.5	3.4	H-bond

Molecular docking results

Figure-S22 Molecular docking results to potential RBD binding sites: Numbers show glide score values (kcal/mol). Hydrogen and salt bridges are shown with yellow and purple dashed lines, π-cationic and π-π stacking interactions with green and blue lines, respectively. A - Amino acid residues with which Arbidol molecules are most likely to interact are shown in dark red; light green amino acid residues are described in [26] as the likely binding site of Arbidol. B   Weighted populations of Arbidol molecules on the protein surface because of statistical processing of molecular dynamic simulation data of the RBD-20×Arb system are shown.

Table S4 Docking results into the sites of PBD

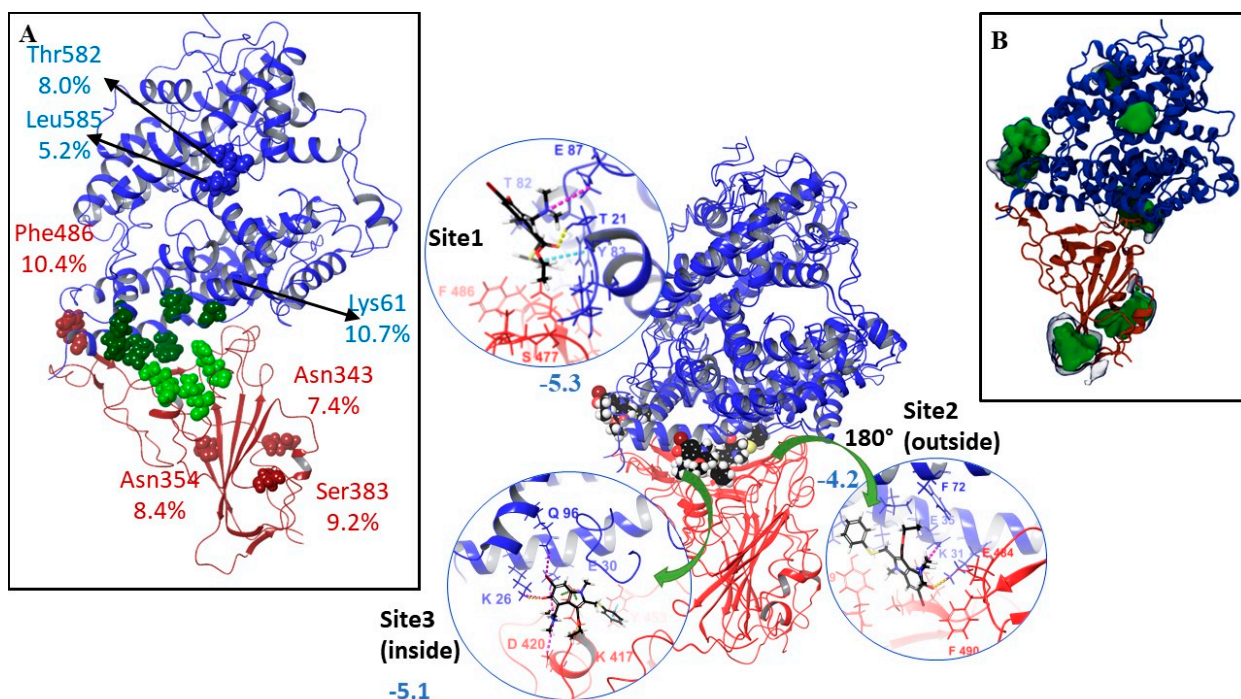| Binding site	Glide score	|LE|	Glide Emodel	IFS score	Interaction	
					H-bond	Others
Site 1	-4.94	0.17	-56.76	-379.01	Arg403 Glu406	Lys417 Arg403 π-cation
Site 2	-3.88	0.13	-42.53	-387.31	Val445	Asn439 – salt bridge
Site 3	-4.33	0.15	-47.60	-387.99		
Site 4	-10.48	0.36	-88.75	-397.31	Asp364	Phe338 π-π
Site 4* (RBD-SUG)	-9.94	0.34	-84.76	-411.04	NAG	Phe373 π-cation Phe374 π-π

Figure-S23 ACE-2-RBD-20 Arb. Molecular docking results to potential RBD binding sites. Numbers show glides score values. Hydrogen bonds and salt bridges are shown in yellow and purple dashed lines π-cationic and π-π-stacking interactions in green and blue lines, respectively. A amino acid residues with which Arbidol molecules are most likely to interact are shown in dark red; green amino acid residues are described in 26 as the likely binding site of Arbidol (dark green amino acids refer to ACE-2; light green to RBD). B - Weighted average of Arbidol molecules on the protein surface resulting from statistical processing of data from molecular dynamic simulations of the ACE-2-RBD-20×Arb system are shown.

Table S5 Docking results into the interface of RBD-ACE-2 complex

Binding site	Glide score	|LE|	Glide Emodel	IFD score	Interaction	
					H-bond	Others
Site 1	-5.28	0.18	-50.25	-1690.20	ACE-2: Thr21	ACE-2: Glu-87 salt Tyr83 - π-cation
Site 2 (outside)	-4.20	0.15	-46.62	-1684.09	ACE-2: Lys31	ACE-2: Lys31, Glu35
Site 3 (inside)	-5.11	0.17	-52.72	-1689.87	ACE-2: Lys26 RBD: Lys417	ACE-2: Gln96 halogen bond Lys26, Glu30 salt RBD: Lys417 π-cation Tyr453 π-π

Table S6 Docking results into the subunits2

Binding site	Glide score	|LE|	Glide Emodel	IFD score	Interaction	
					H-bond	Others
Subunits 2 (FP2)	-7.70	0.27	-67.63	-3605.20	Arg1019	Glu-780 salt Leu727, Val1040, Phe1042, Leu1024 hydrophobic