Supporting Information

Effect of an Inhibitor on the ACE2-Receptor Binding Domain of SARS-CoV-2

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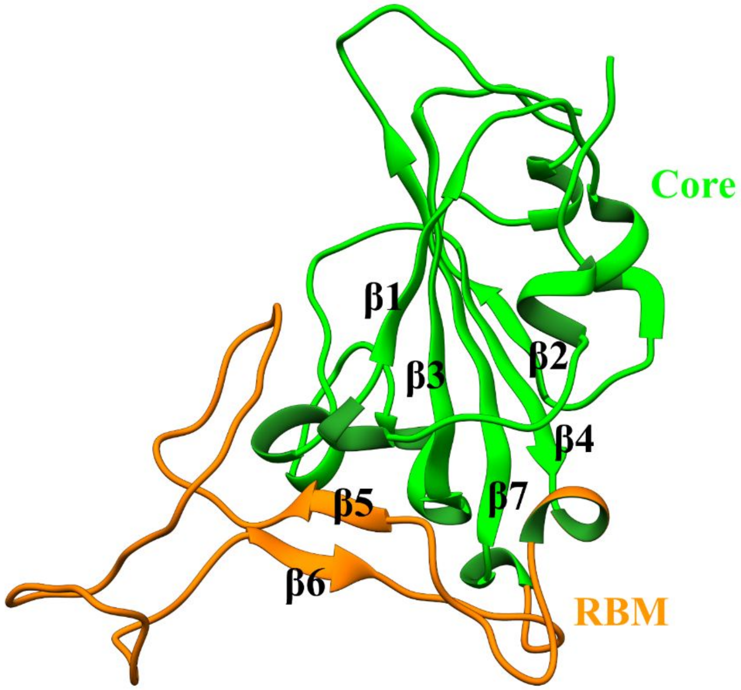


Figure S1: X-ray structure of RBD. The receptor binding membrane (RBM) is in orange and the core is in green color.

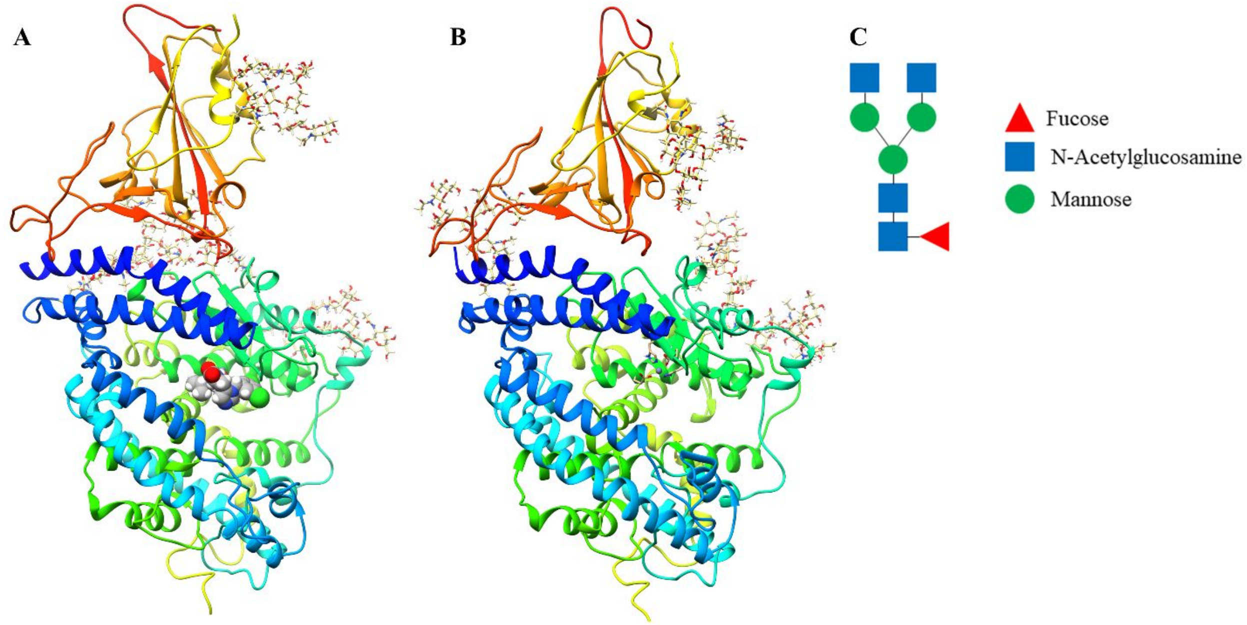


Figure S2: Equilibrated structure of ACE2-RBD-Inhibitor (A), ACE2-RBD (B) complex with larger N-Glycans, and structure of N-glycan (C).

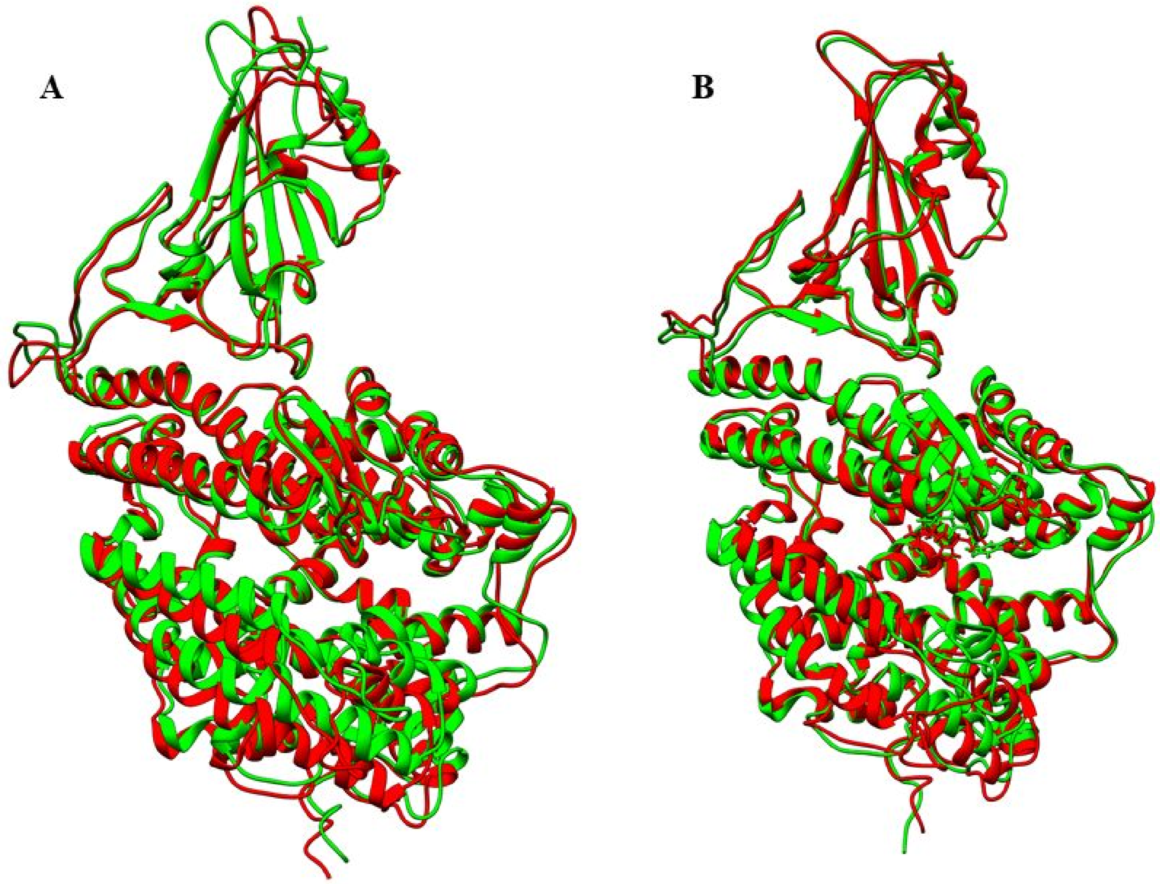


Figure S3: (A) Superimposed structure of ACE2-RBD (small N-glycan) in green and ACE2-RBD (large N-glycan) in red; (B) ACE2-RBD-Inhibitor (small N-glycan) in green and ACE2-RBD-Inhibitor (large N-glycan) in red.

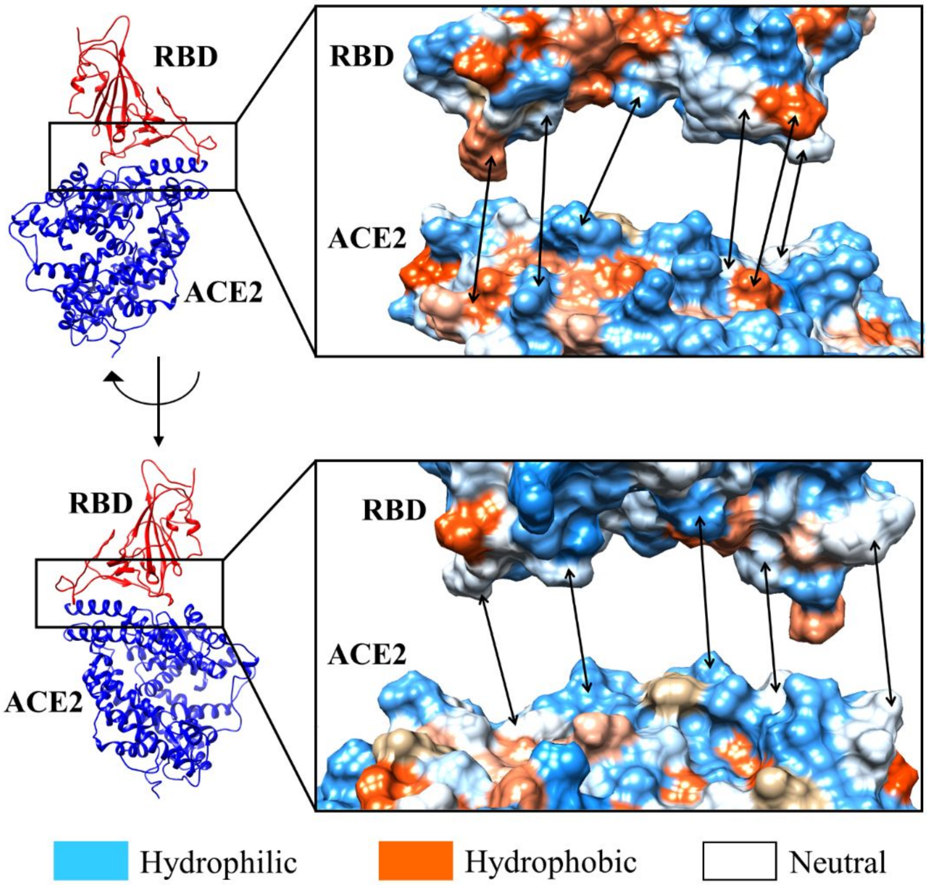


Figure S4: Hydrophobicity surface of ACE2 and RBD interface. Red represents hydrophobic, blue as hydrophilic, and white as neutral.

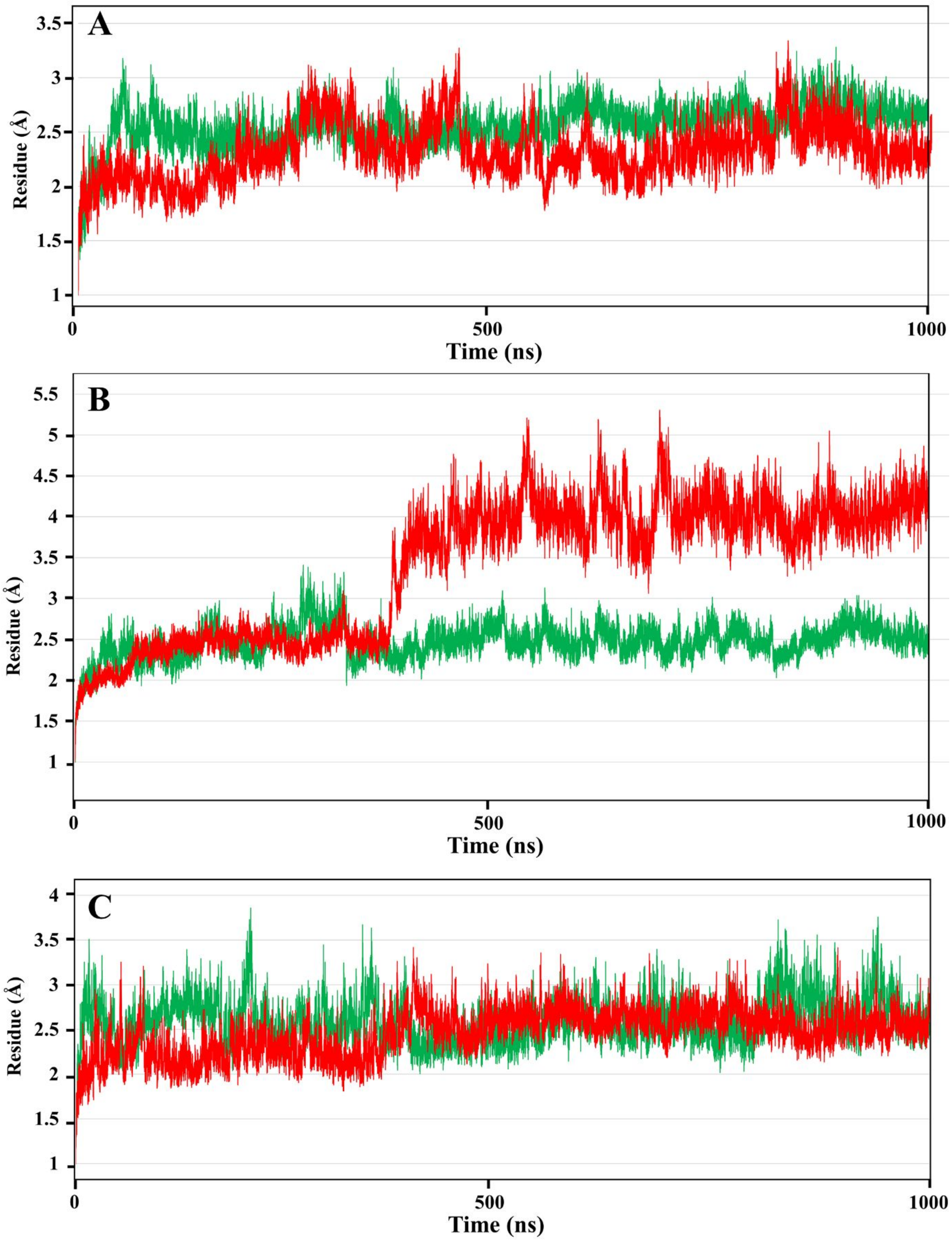


Figure S5: Per-residue root mean square deviation (RMSD) of; (A) $\mathbf{A_O}$ and $\mathbf{A'_O}$ (B) $\mathbf{A_C}$ and $\mathbf{A'_C}$; and (C) $\mathbf{RA_O}$ and $\mathbf{RA'_O}$ complex trajectories (Red = Inhibitor present, Green = Inhibitor absent).

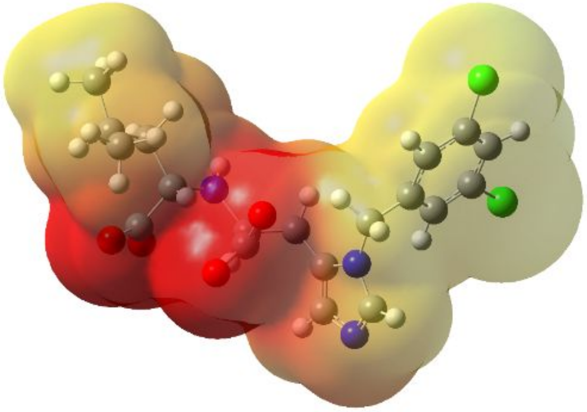


Figure S6: Electrostatic surface potential (ESP) of inhibitor MLN-4760.

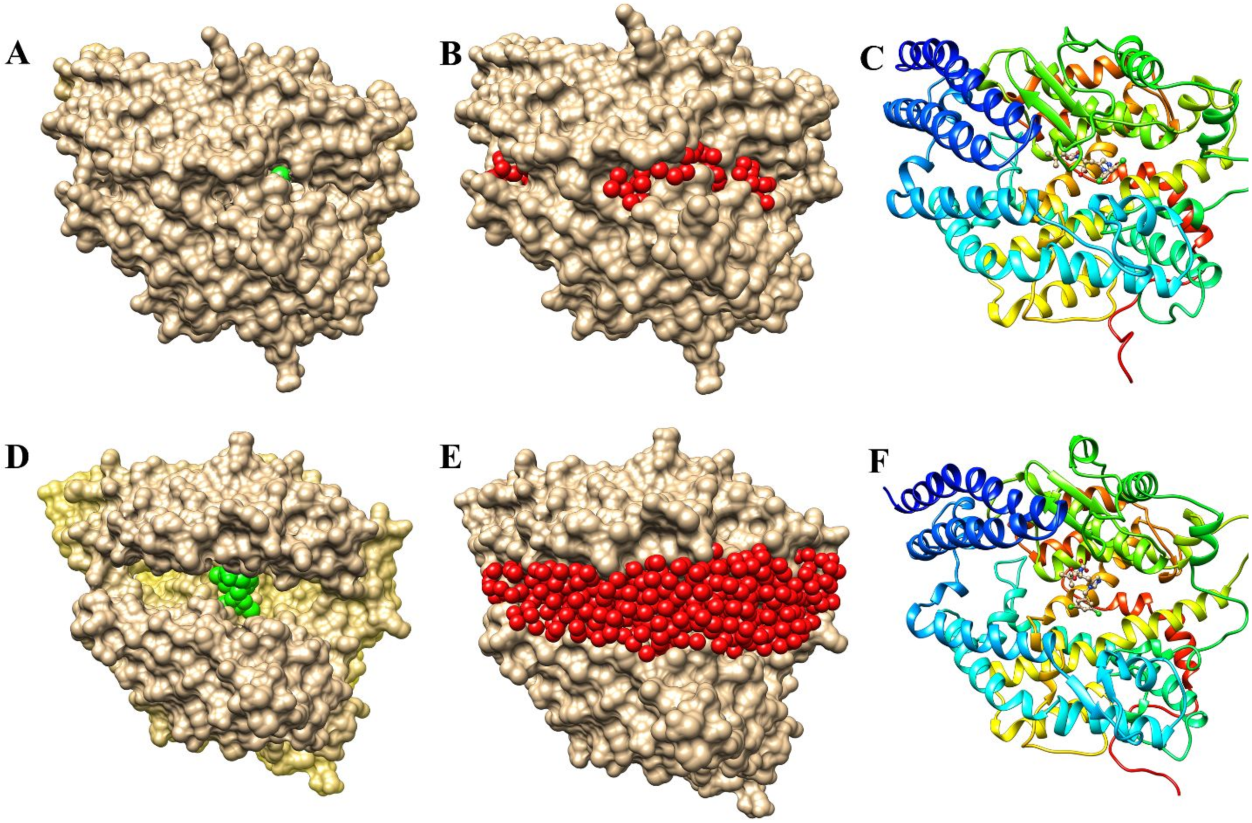


Figure S7: (A) ACE2 surface in a closed state; (B) water molecules trapped in the active site cleft of closed state ACE2 enzyme; (C) ribbon diagram for reference; (D) ACE2 surface in open state; (E) water molecules in the active site cleft of the open state ACE2 enzyme; and (F) ribbon diagram for reference.

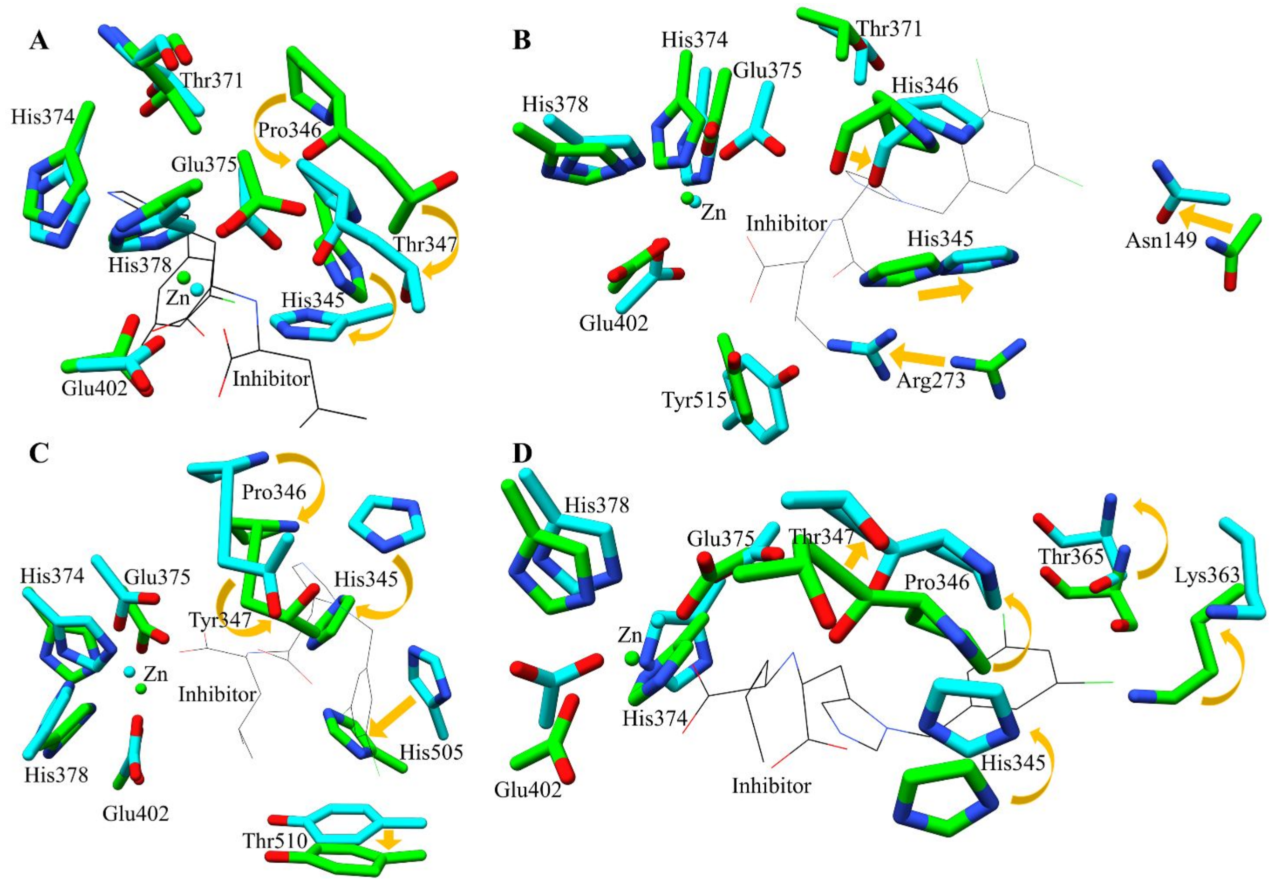


Figure S8: Superposition of the inhibitor bound (cyan carbons) and unbound (green carbons) structures; (A) $\mathbf{A_O}$ vs $\mathbf{A'_O}$; (B) $\mathbf{A_C}$ vs $\mathbf{A'_{C1}}$; (C) $\mathbf{A_C}$ vs $\mathbf{A'_{C2}}$; and (D) $\mathbf{RA_O}$ vs $\mathbf{RA'_O}$.

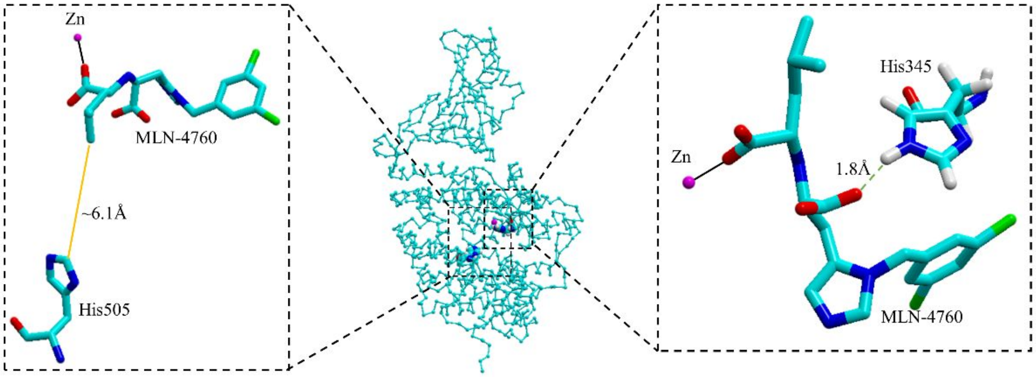


Figure S9: In $\mathbf{RA_O'}$ complex. H345 forms a hydrogen bond interaction with MLN-4760 while H505 was ~6.1 apart.

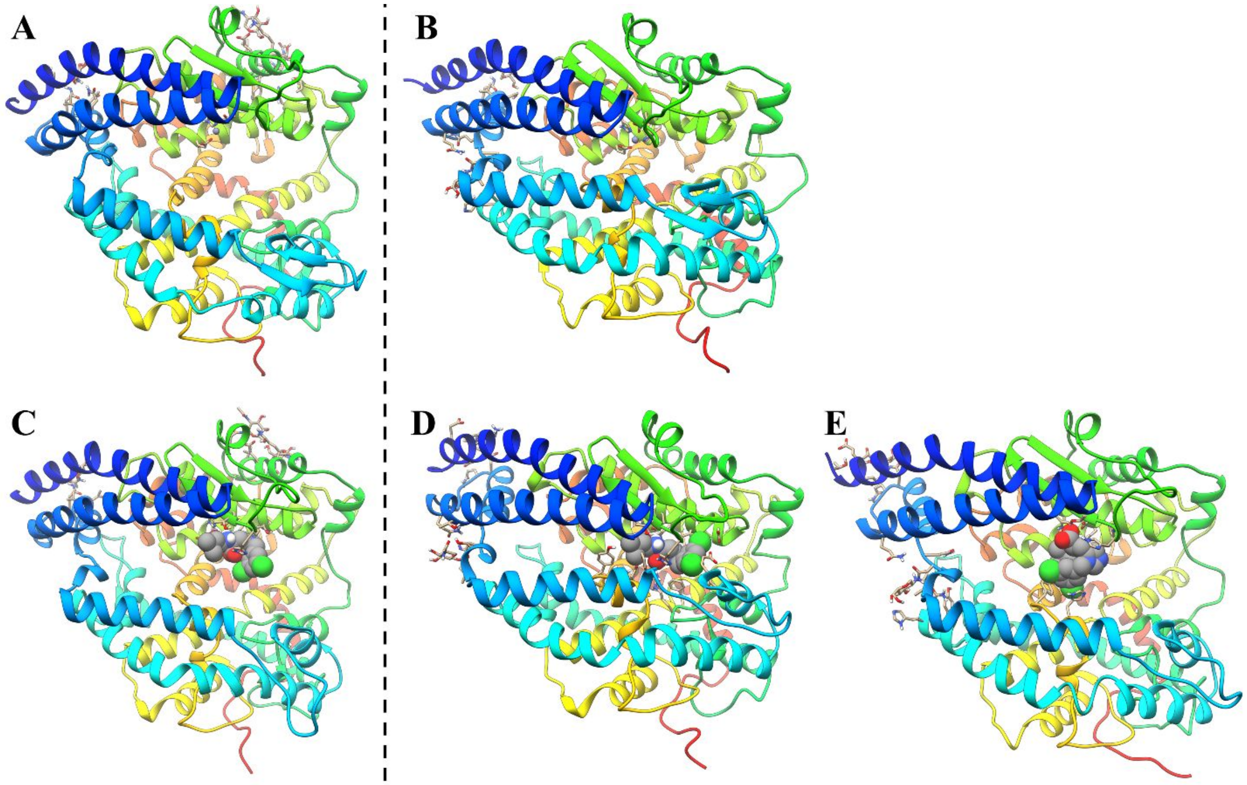


Figure S10: Most-representative structures of; (A, C) $\mathbf{A_O}$ and $\mathbf{A'_O}$ (B) $\mathbf{A_C}$; (D) $\mathbf{A'_{C1}}$; and (E) $\mathbf{A'_{C2}}$.

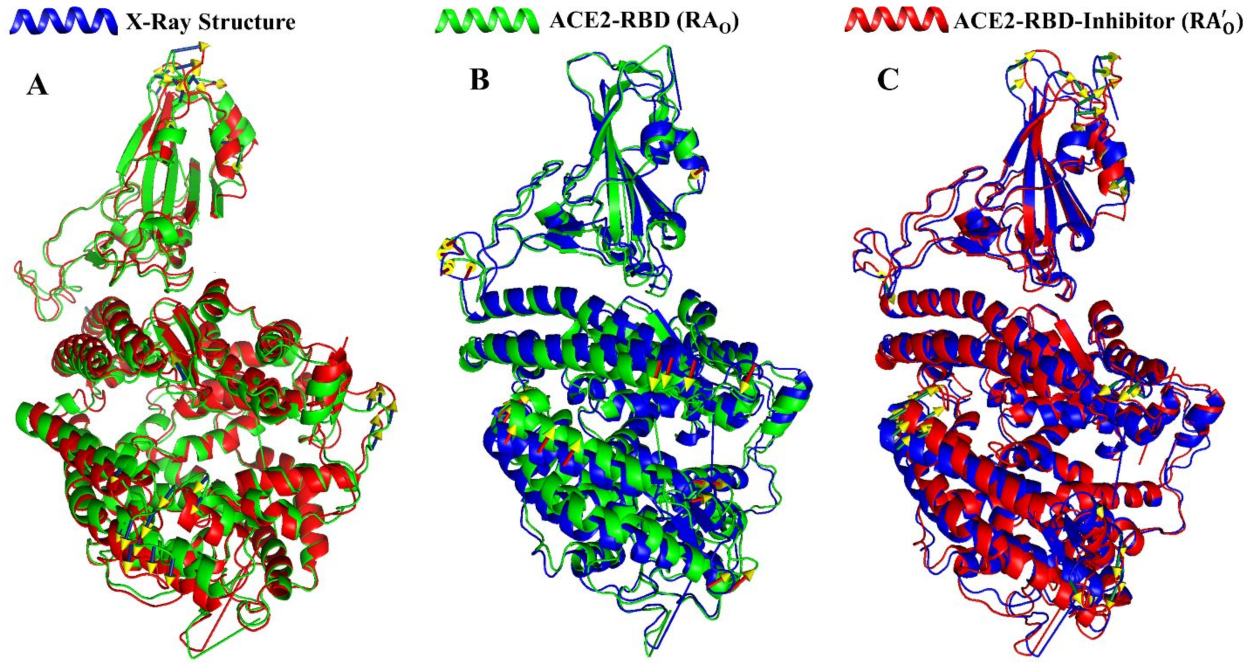


Figure S11: (A) Superimposed structure of ACE2-RBD ($\mathbf{RA_O}$) and ACE2-RBD-Inhibitor ($\mathbf{RA'_O}$); (B) X-Ray and ACE2-RBD ($\mathbf{RA_O}$); and (C) X-Ray and ACE2-RBD-Inhibitor ($\mathbf{RA'_O}$).

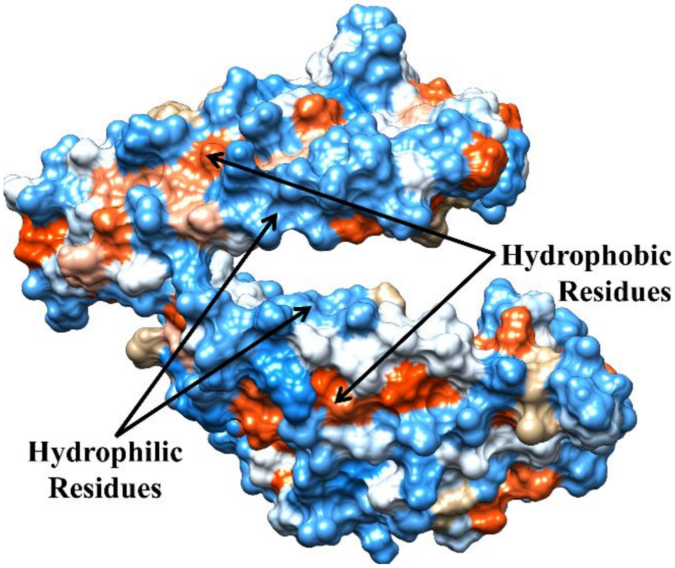
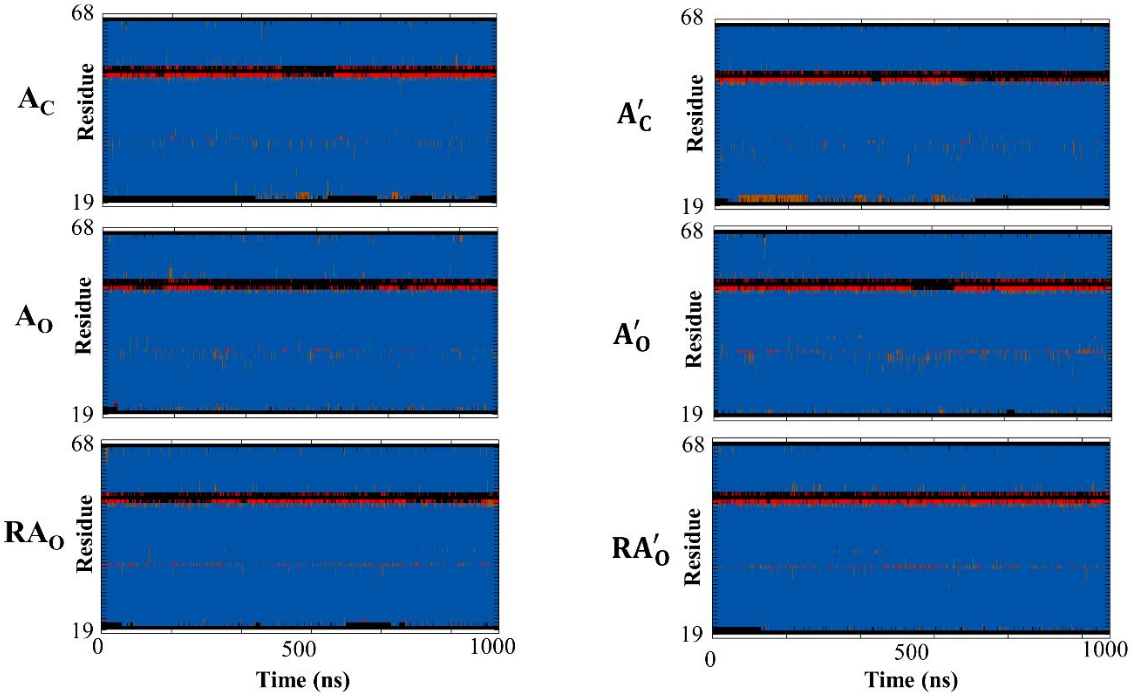
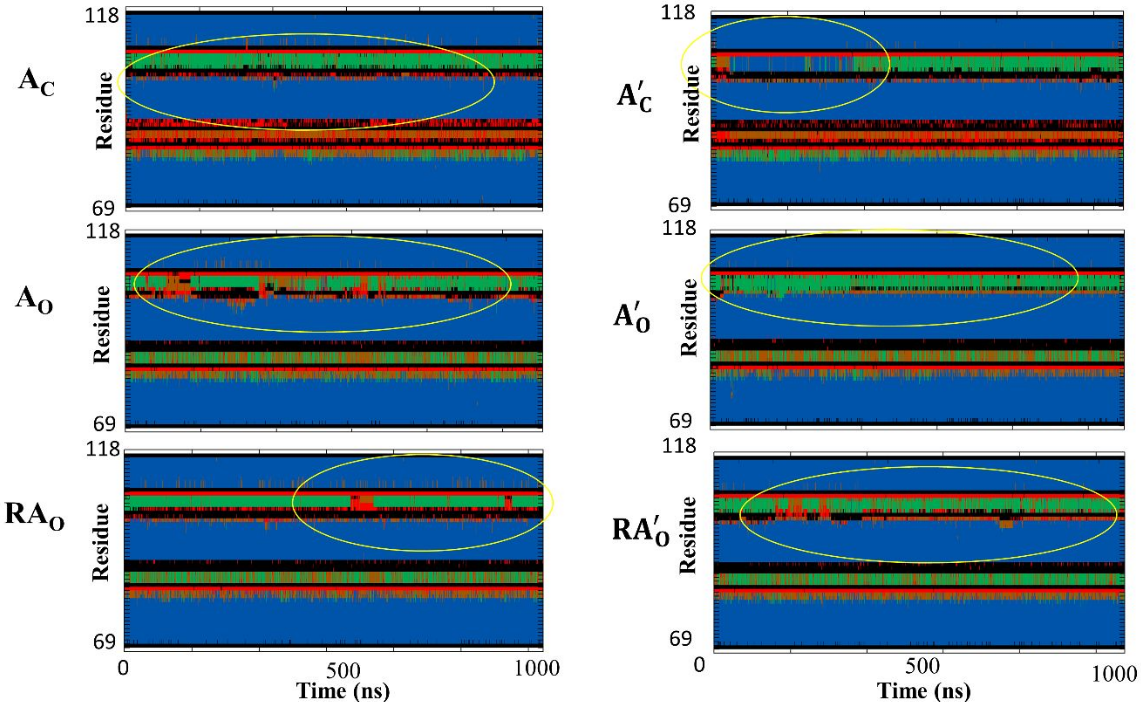
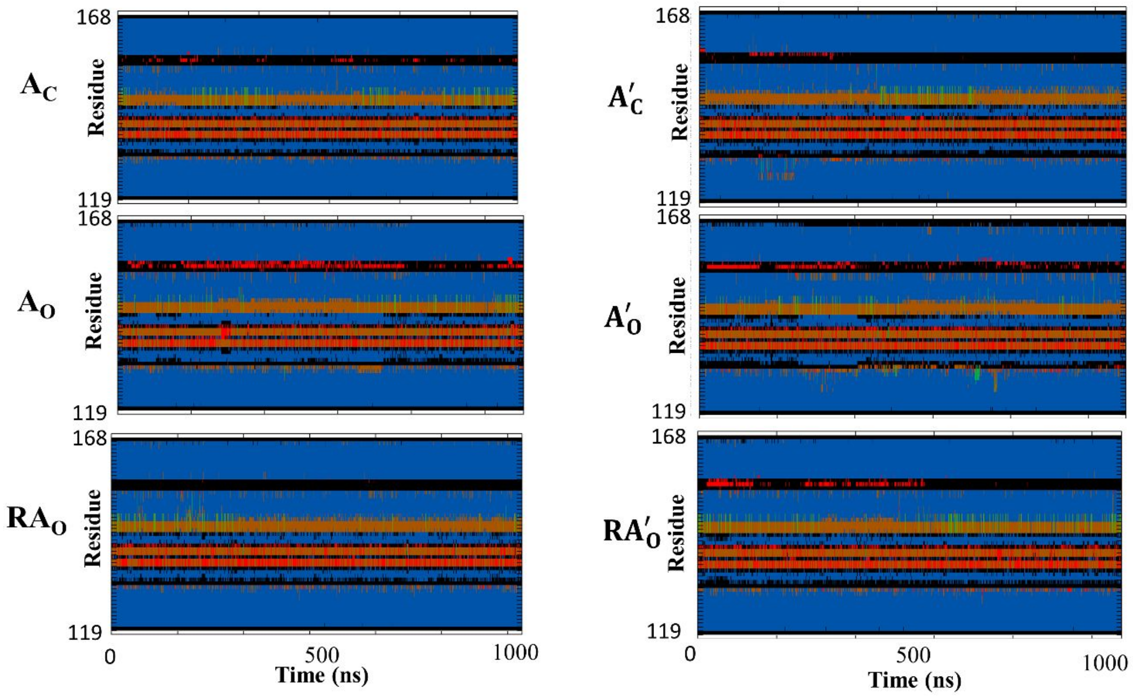


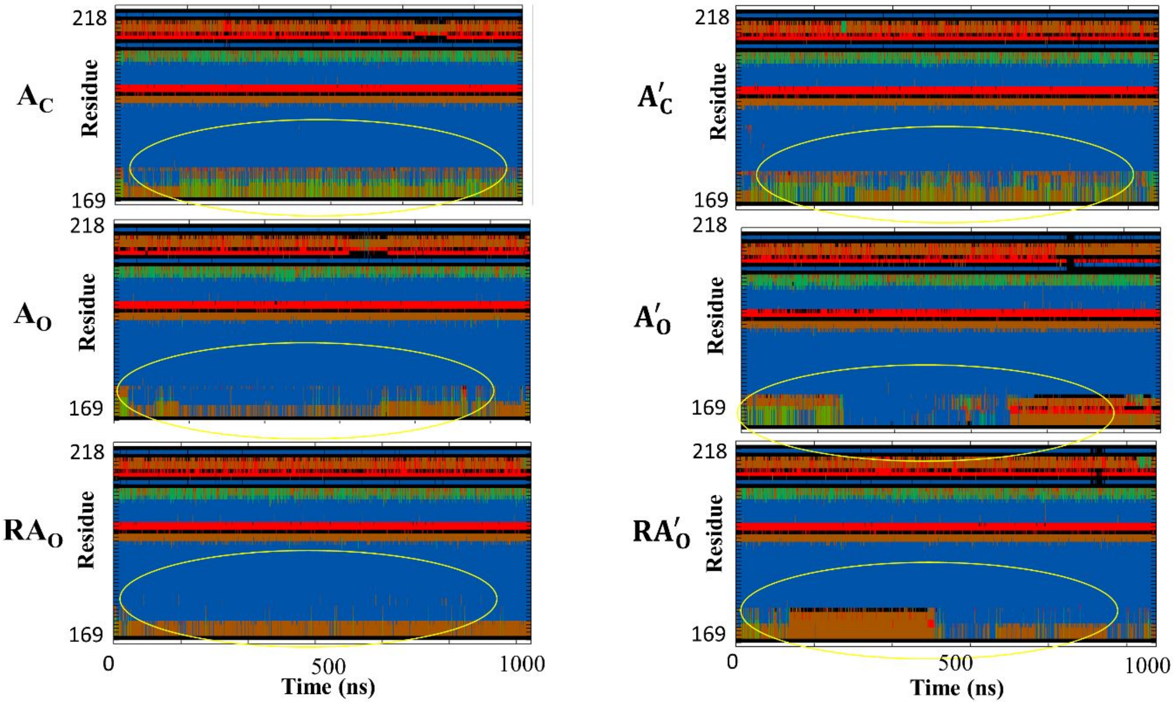
Figure S12: Hydrophobicity surface of ACE2. The hydrophilic residues present on α2 and α3 helixes are facing each other while hydrophobic residues are on the opposite side of the α2 and α3 helixes.


A_C
A'_C
A_O
A'_O
RA_O
RA'_O
Residue
68
19
0
500
1000
Time (ns)

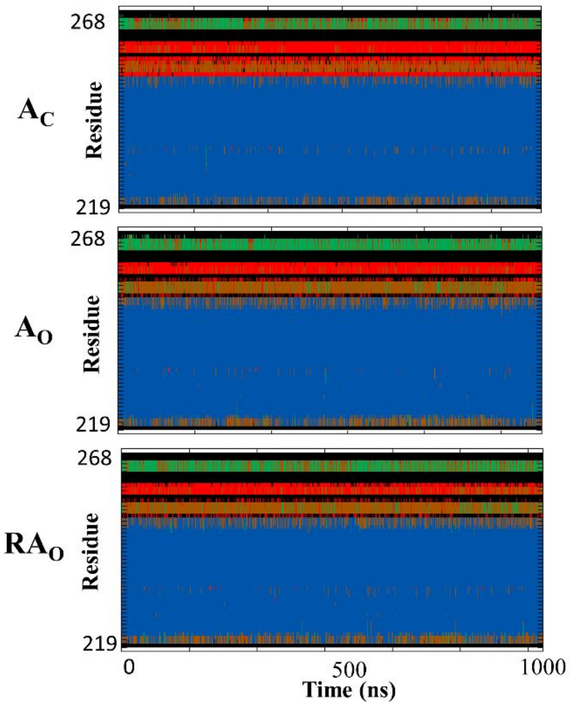

A_C
A'_C
A_O
A'_O
RA_O
RA'_O
Residue
118
69
0
500
1000
Time (ns)

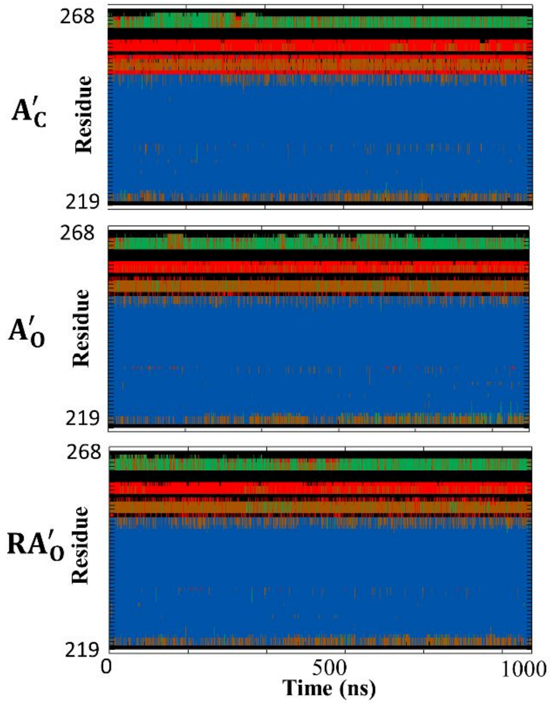


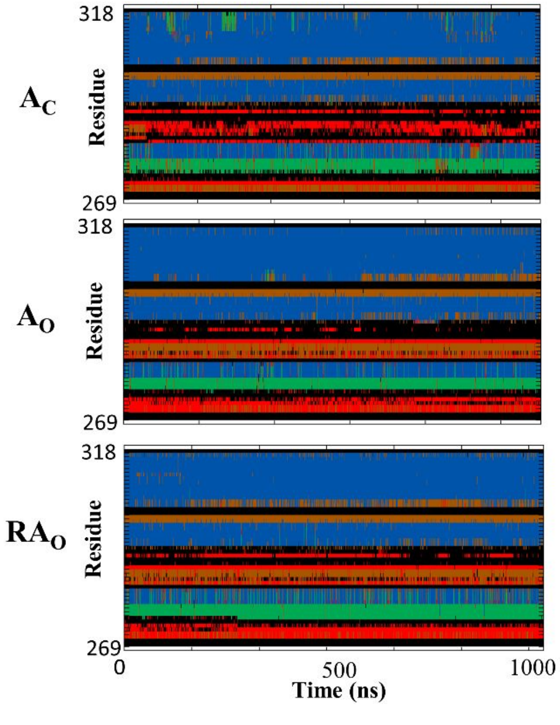
A_C
A'_C
A_O
A'_O
RA_O
RA'_O
Residue
168
119
0
500
1000
Time (ns)

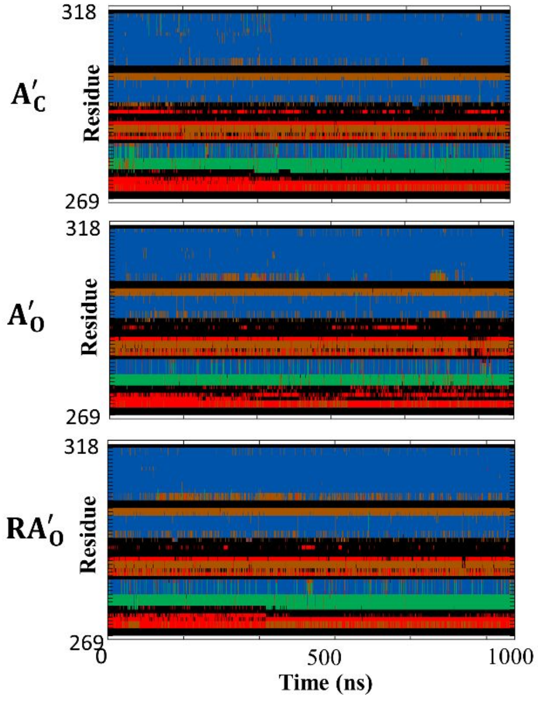


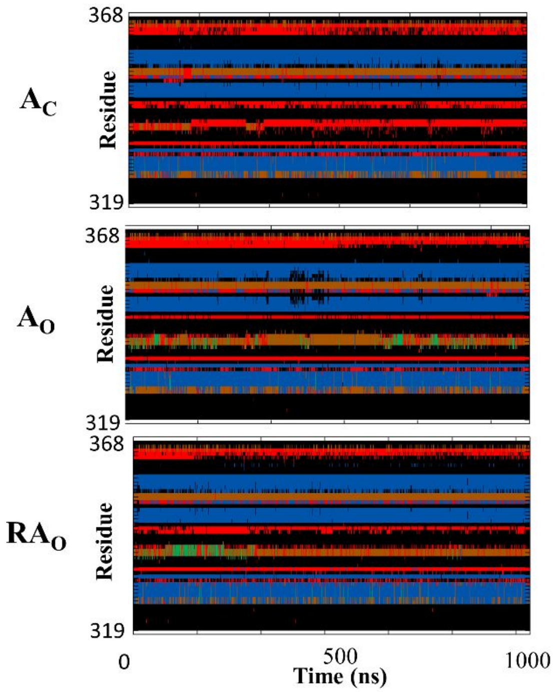
A_C
A'_C
A_O
A'_O
RA_O
RA'_O
Residue
218
169
0
500
1000
Time (ns)

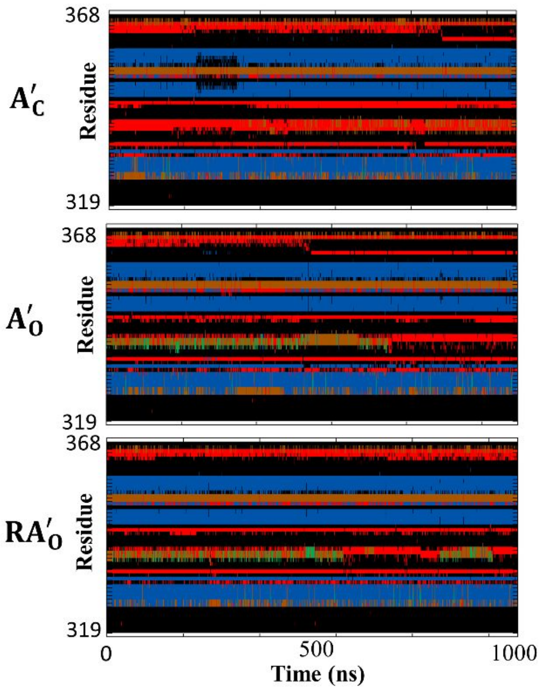

A_C
Residue
268
219
A_O
Residue
268
219
RA_O
Residue
268
219
0
500
1000
Time (ns)

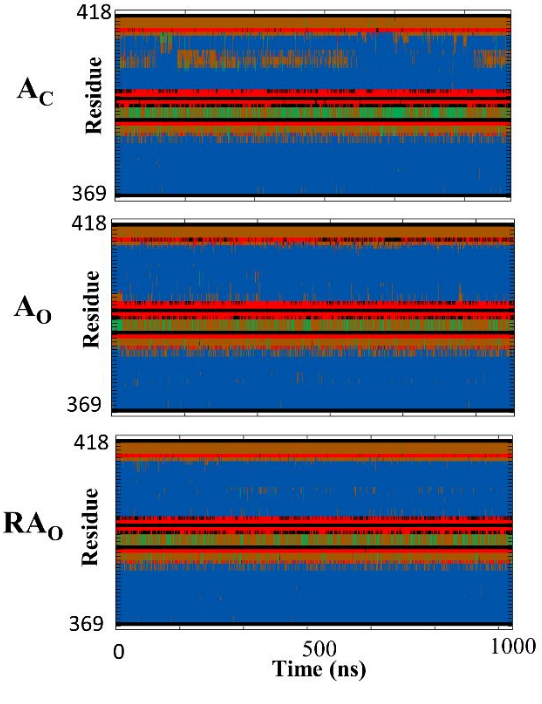

A'_C
Residue
268
219
A'_O
Residue
268
219
RA'_O
Residue
268
219
0
500
1000
Time (ns)

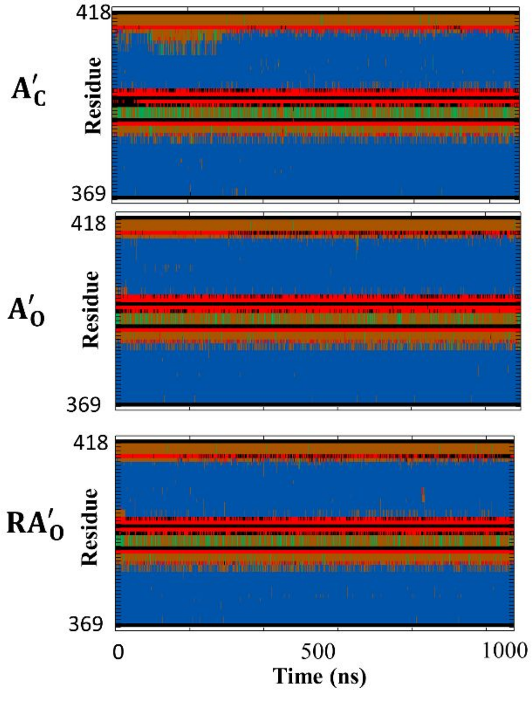

A_C
Residue
318
269
A_O
Residue
318
269
RA_O
Residue
318
269
0
500
1000
Time (ns)

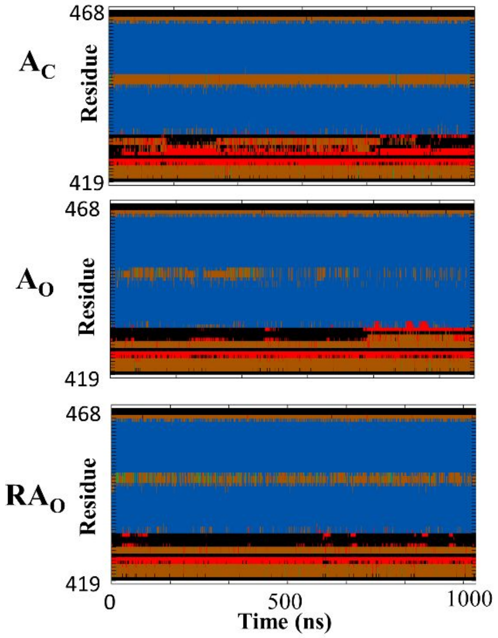

A'_C
Residue
318
269
A'_O
Residue
318
269
RA'_O
Residue
318
269
0
500
1000
Time (ns)

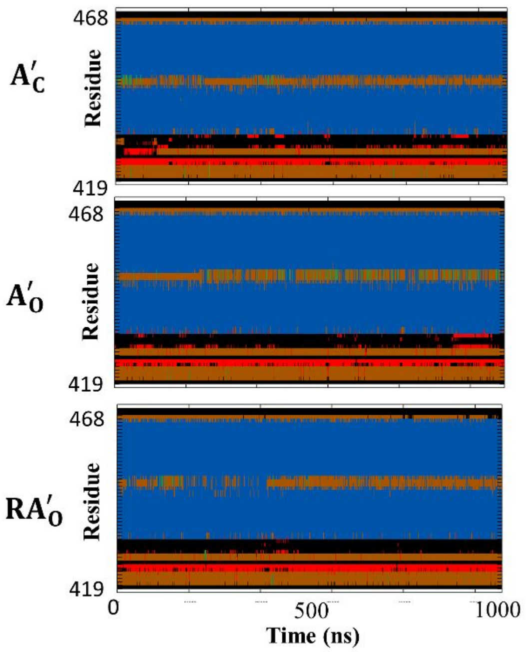

A_C
368
Residue
319
A_O
368
Residue
319
RA_O
368
Residue
319
0
500
1000
Time (ns)

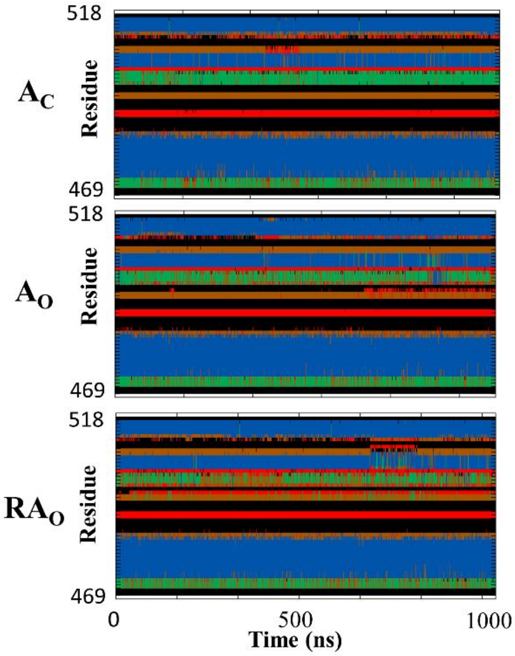

A′_C
368
Residue
319
A′_O
368
Residue
319
RA′_O
368
Residue
319
0
500
1000
Time (ns)

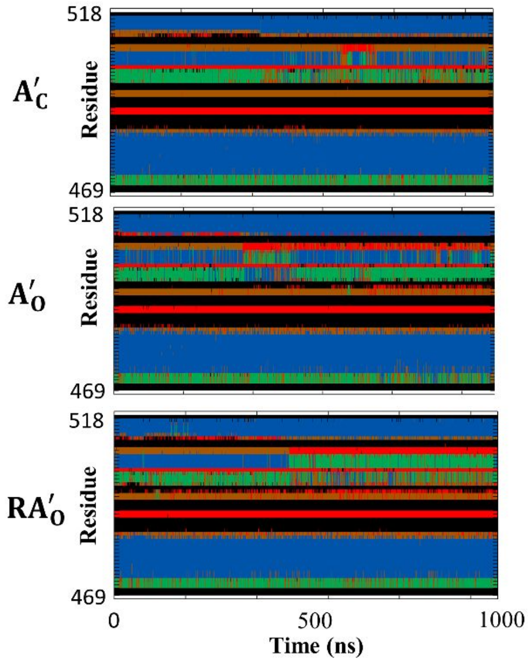

A_C
418
Residue
369
A_O
418
Residue
369
RA_O
418
Residue
369
0
500
1000
Time (ns)

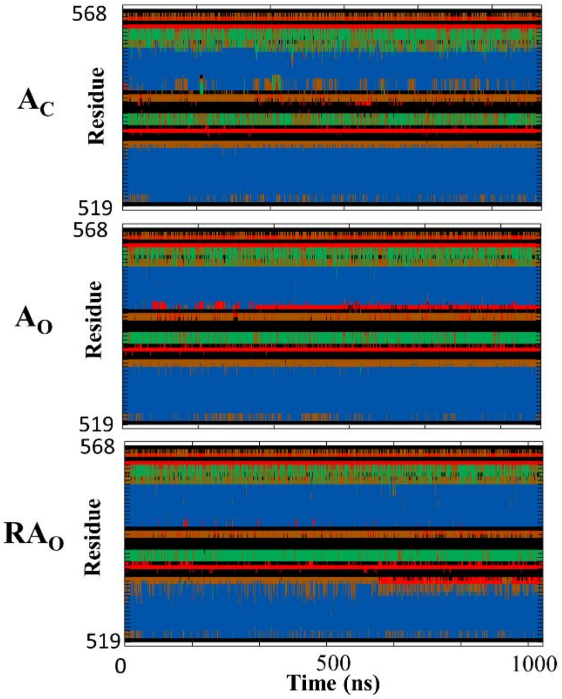

A′_C
418
Residue
369
A′_O
418
Residue
369
RA′_O
418
Residue
369
0
500
1000
Time (ns)


468
A_C
Residue
419
468
A_O
Residue
419
468
RA_O
Residue
419
0
500
1000
Time (ns)

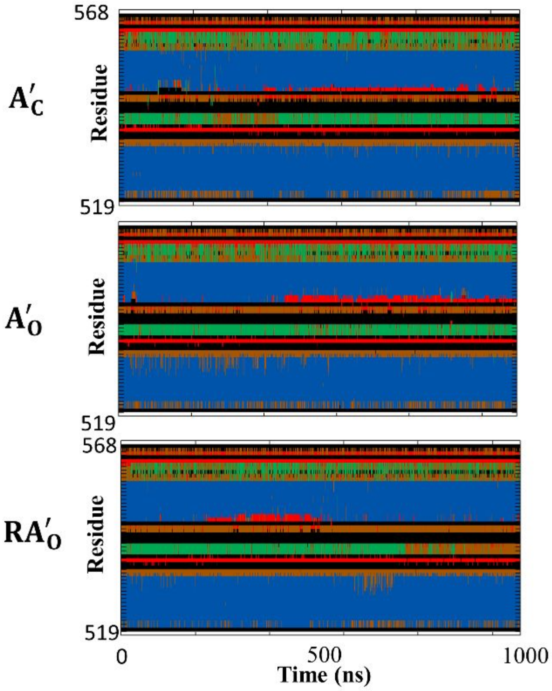

468
A'_C
Residue
419
468
A'_O
Residue
419
468
RA'_O
Residue
419
0
500
1000
Time (ns)


518
A_C
Residue
469
518
A_O
Residue
469
518
RA_O
Residue
469
0
500
1000
Time (ns)

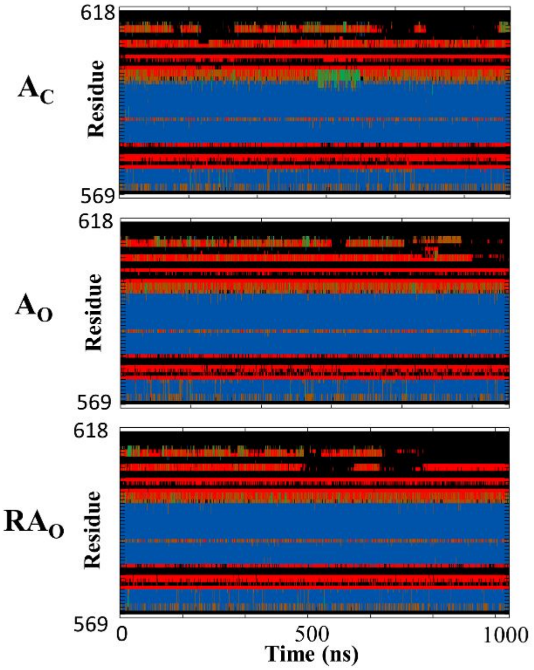

518
A'_C
Residue
469
518
A'_O
Residue
469
518
RA'_O
Residue
469
0
500
1000
Time (ns)



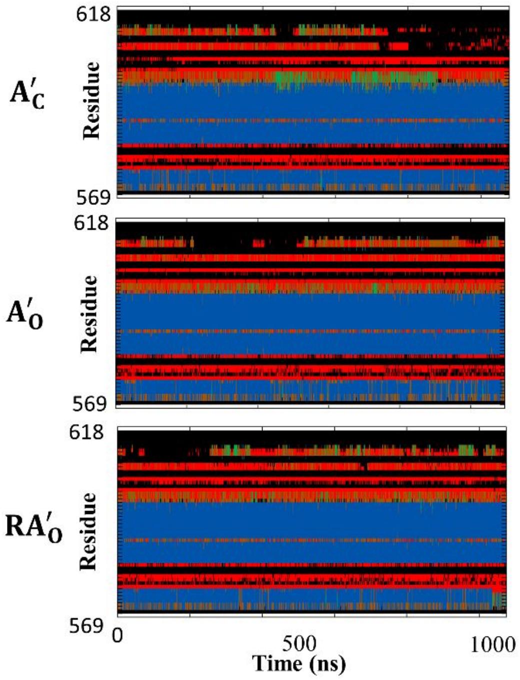
A_C
A_O
RA_O
Residue
568
519
0
500
1000
Time (ns)



A'_C
A'_O
RA'_O
Residue
568
519
0
500
1000
Time (ns)



A_C
A_O
RA_O
Residue
618
569
0
500
1000
Time (ns)



A'_C
A'_O
RA'_O
Residue
618
569
0
500
1000
Time (ns)

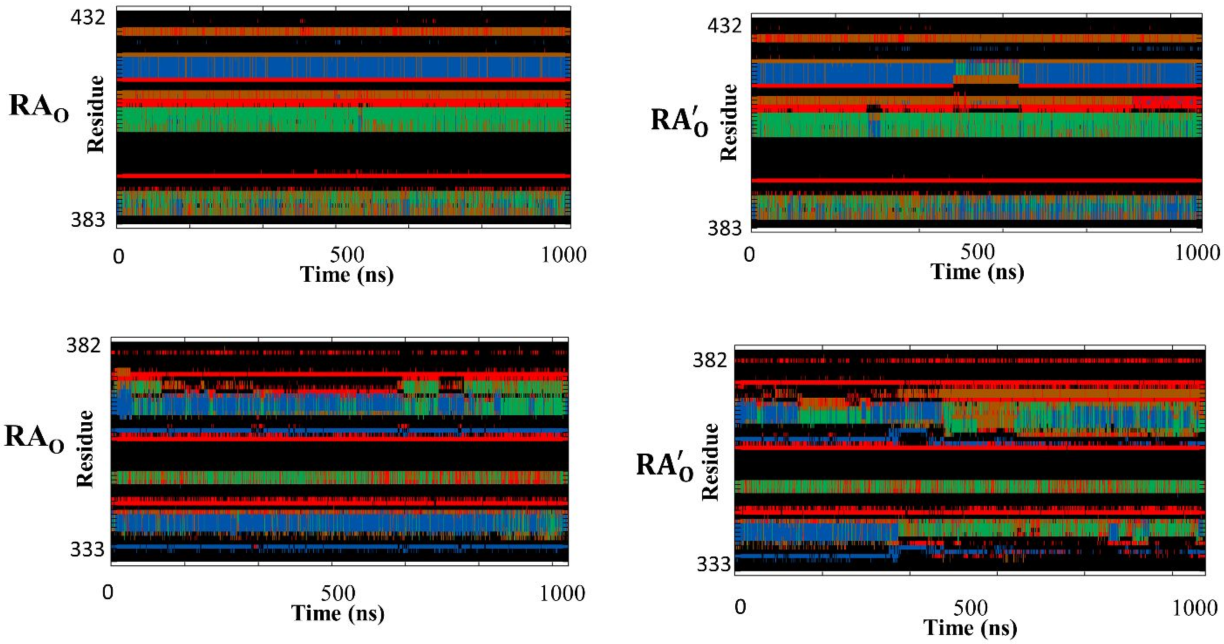


Figure S13: Secondary structure evolution (DSSP analysis) of six complexes throughout MD simulations.