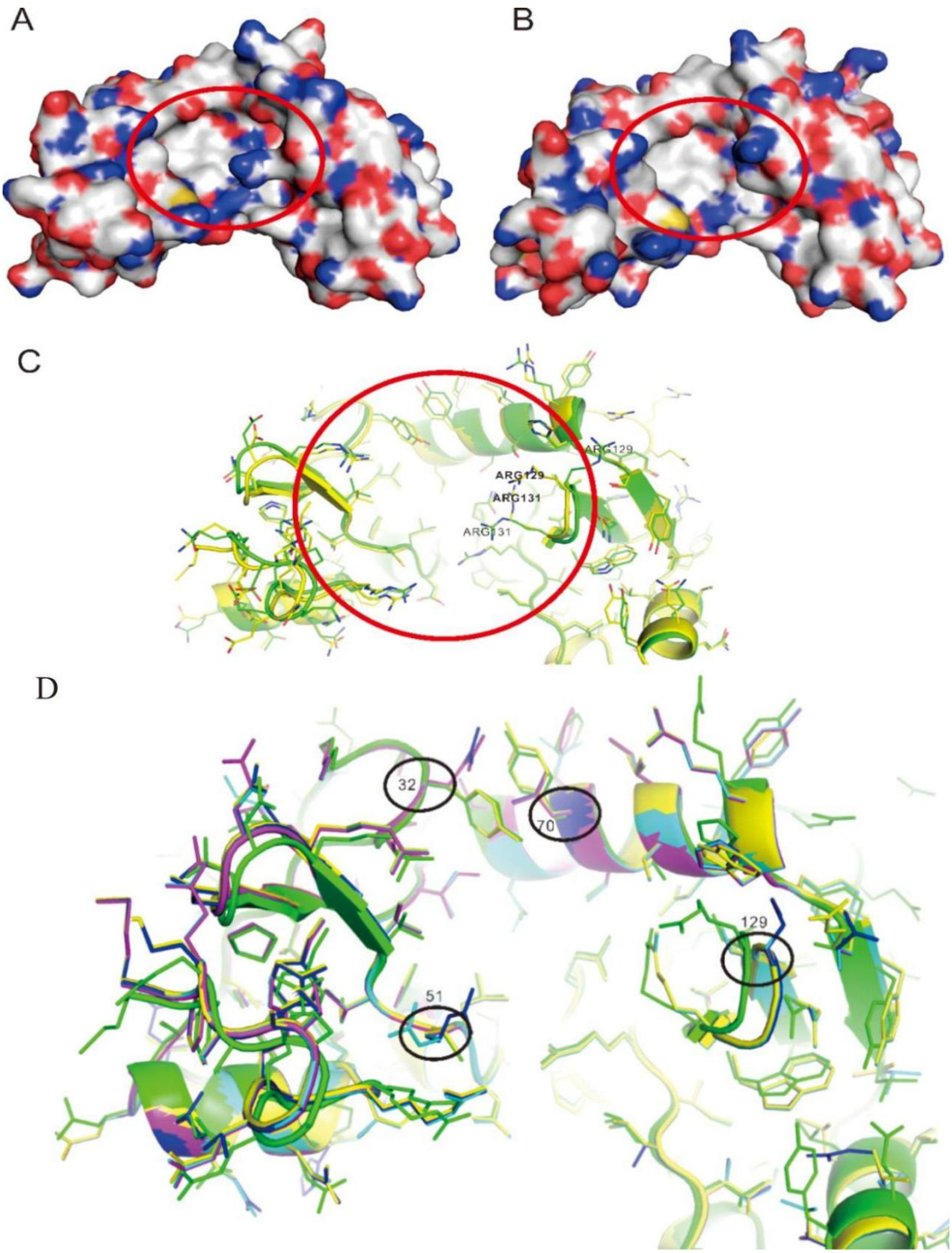
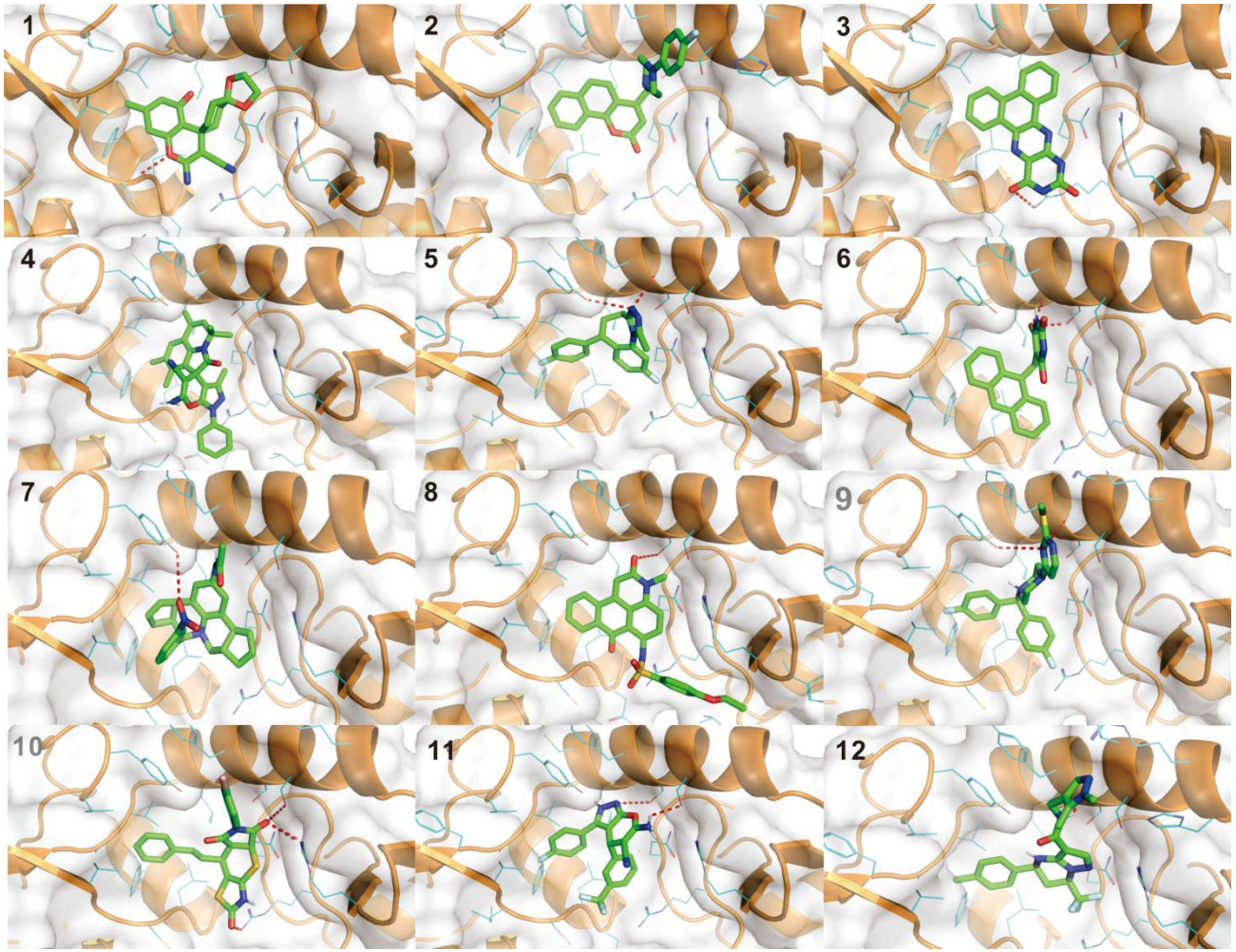


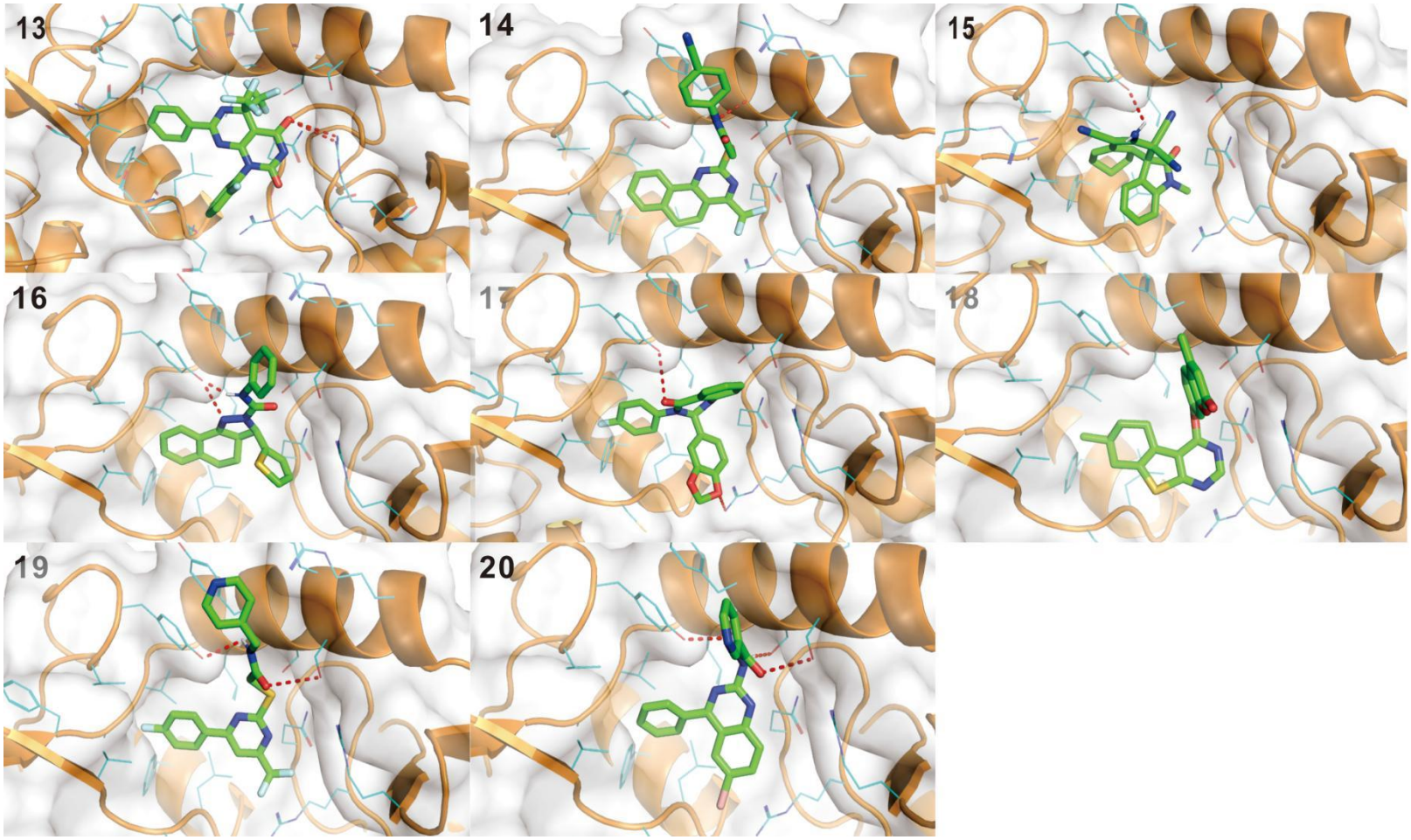
Supplementary Fig. 1 Crystal structure model of HPV-16 E6 and Superposition of α -9 HPV E6 structure model.

Note: A is the conformational surface model of E6 crystal in 4GIZ, and B is the conformational surface model of E6 crystal in 4XR8, C shows the superimposed effect of E6 crystal conformation in 4GIZ and 4XR8. D shows superposition of α-9 HPV E6 structure model; Green represents HPV-16; Yellow is HPV-31; Purple is HPV-33; Blue is HPV-52; Cyan is HPV-58; Black circles indicate sites with different residues near the "LXXLL" binding groove.



Supplementary Fig. 2 Candidate molecules binding pose for E6 and E6AP binding inhibitors

Note: E6 protein was represented by surface model and ribbon model, and the residue side chain of binding site was displayed in the form of thin lines. Small molecules are represented by rod model. These molecules are bound to the docking pocket of E6, and the red dotted lines represent hydrogen bonding interactions.



Supplementary continued Fig. 2 Candidate molecules binding pose for E6 and E6AP binding inhibitors

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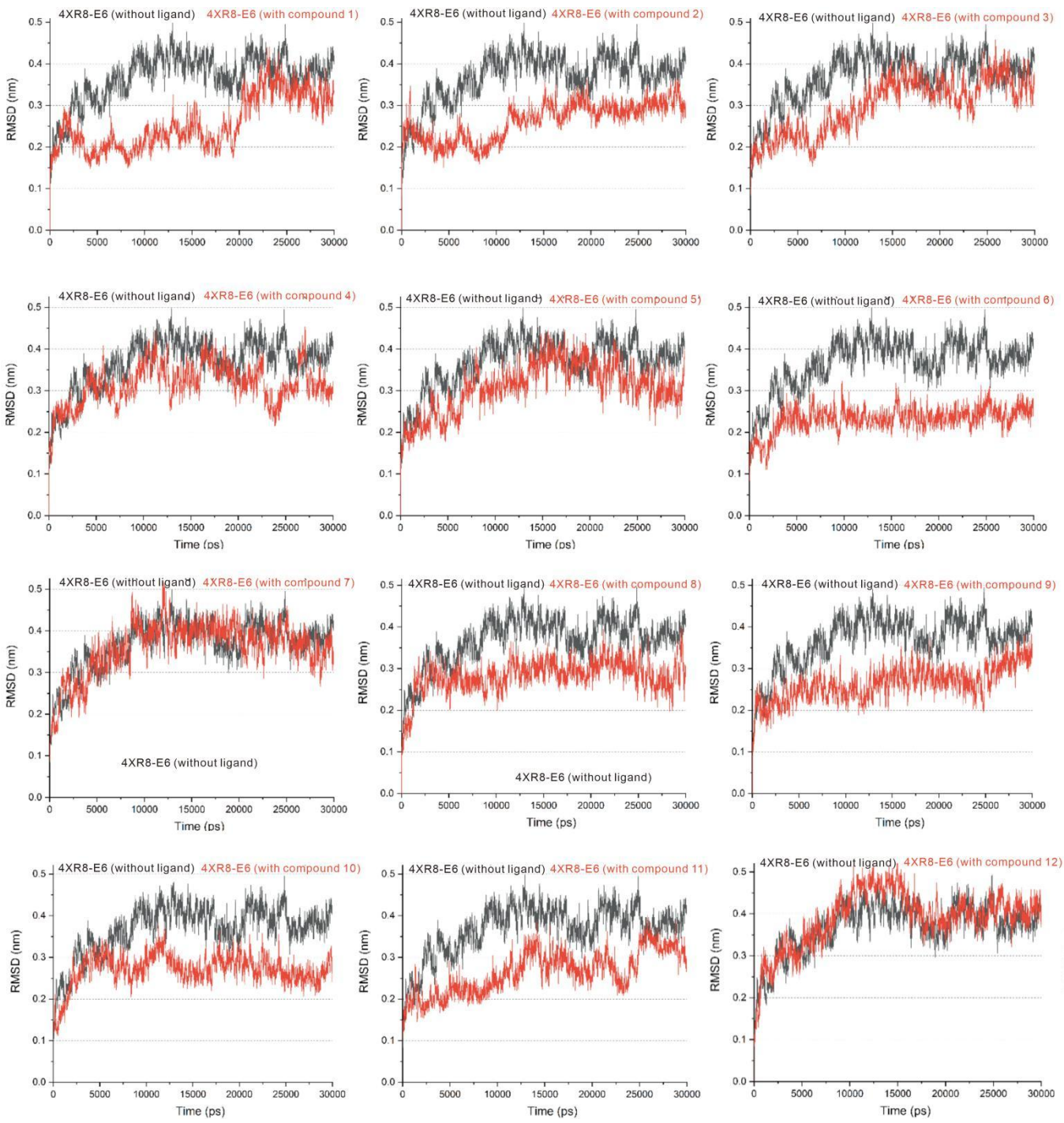
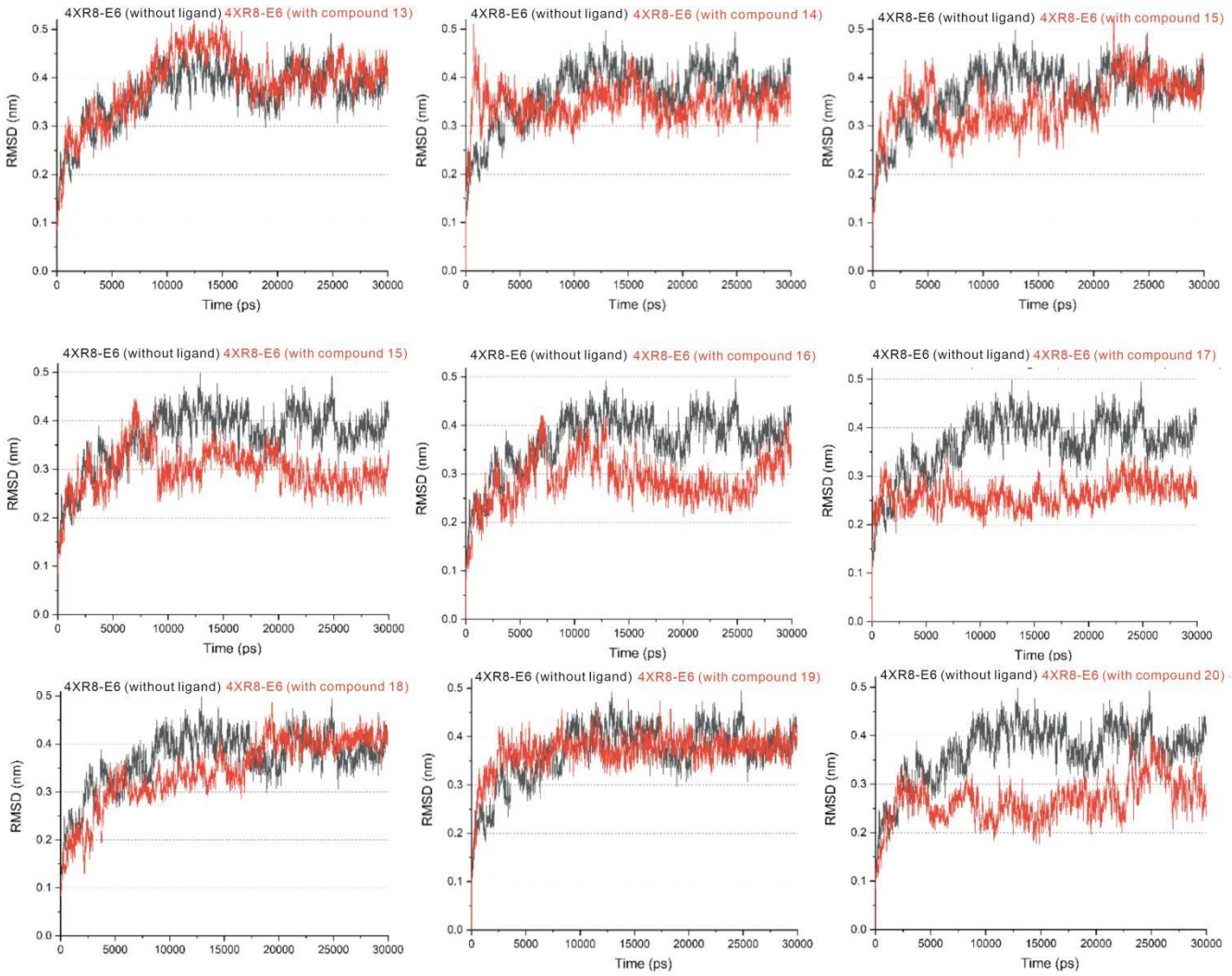


Supplementary Fig. 3 RMSD (Root-mean-square deviation) of all Cα atoms for the receptor 4XR8-E6 during MD simulations.

Note: The RMSD of 4xR8-E6 conformation without binding ligand is shown in black; The RMSD of 4xR8-E6 conformation with small molecules is red.



Supplementary continued Fig. 3 RMSD (Root-mean-square deviation) of all Cα atoms for the receptor 4XR8-E6 during MD simulations.

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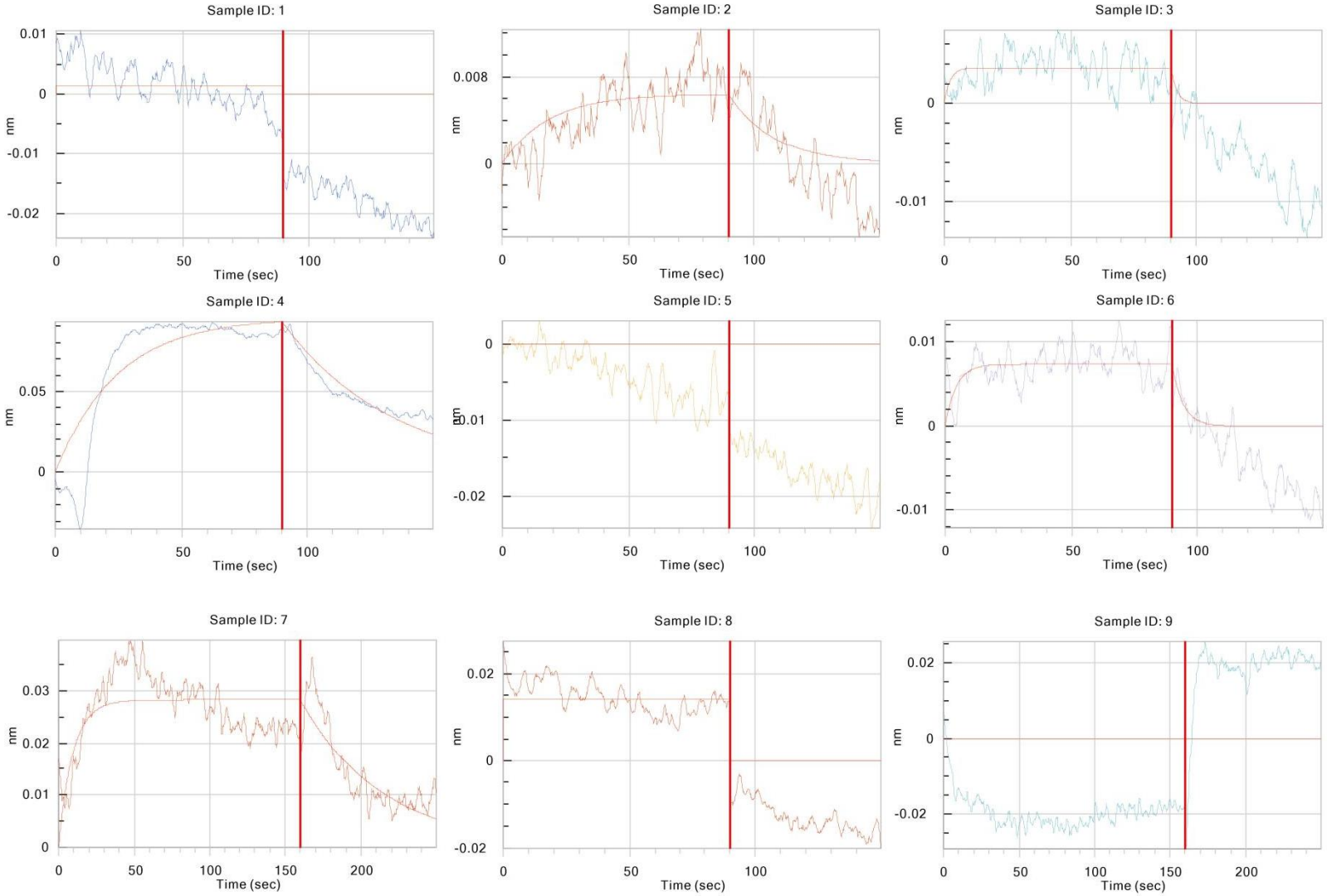
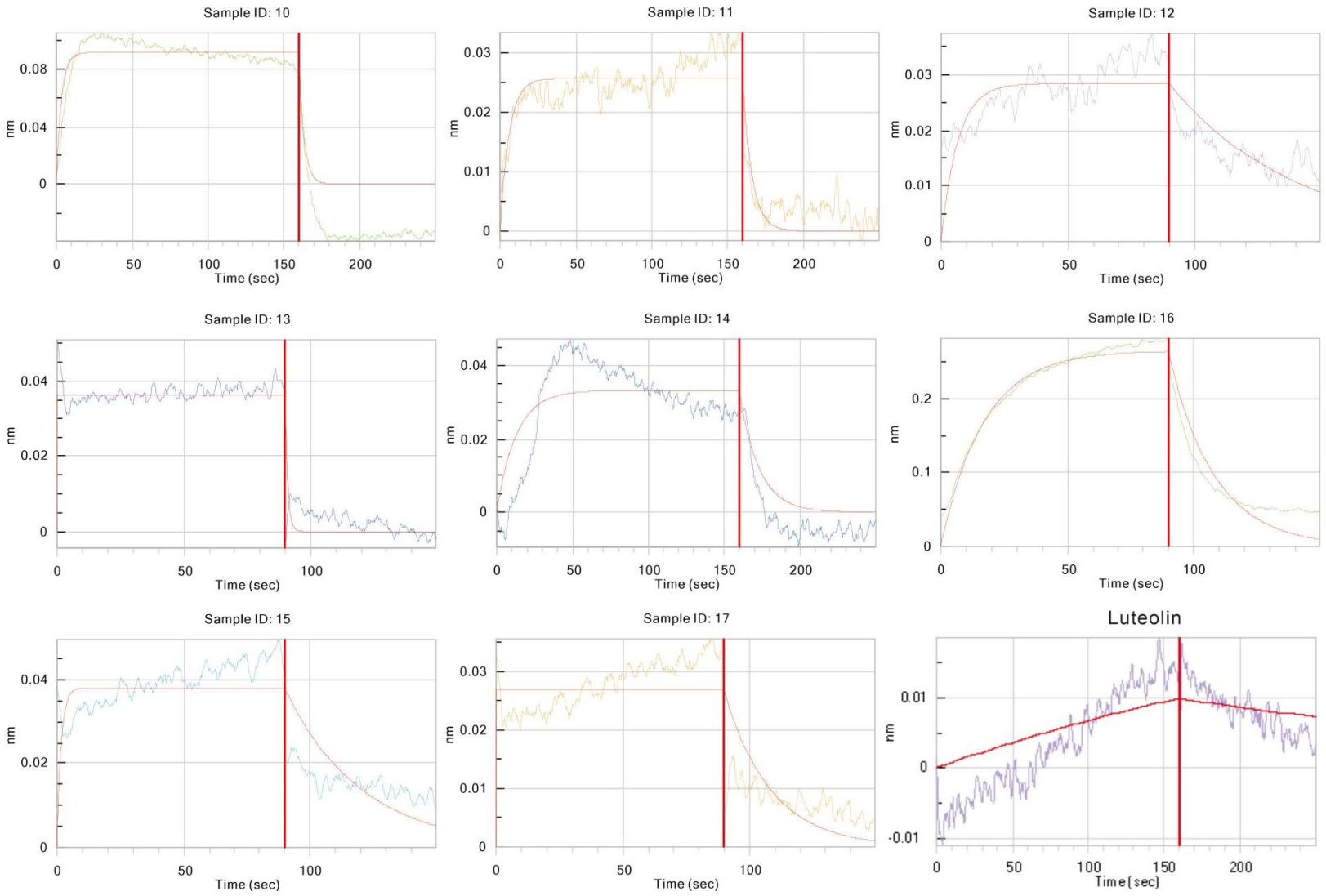


Supplementary Fig. 4 The Molecular interactions of E6 and E6-E6AP binding inhibitors candidate



Supplementary continued Fig. 4 The Molecular interactions of E6 and E6-E6AP binding inhibitors candidate