Probing Conformational Hotspots For The Recognition And Intervention Of Protein Complex By Lysine Reactivity Profiling

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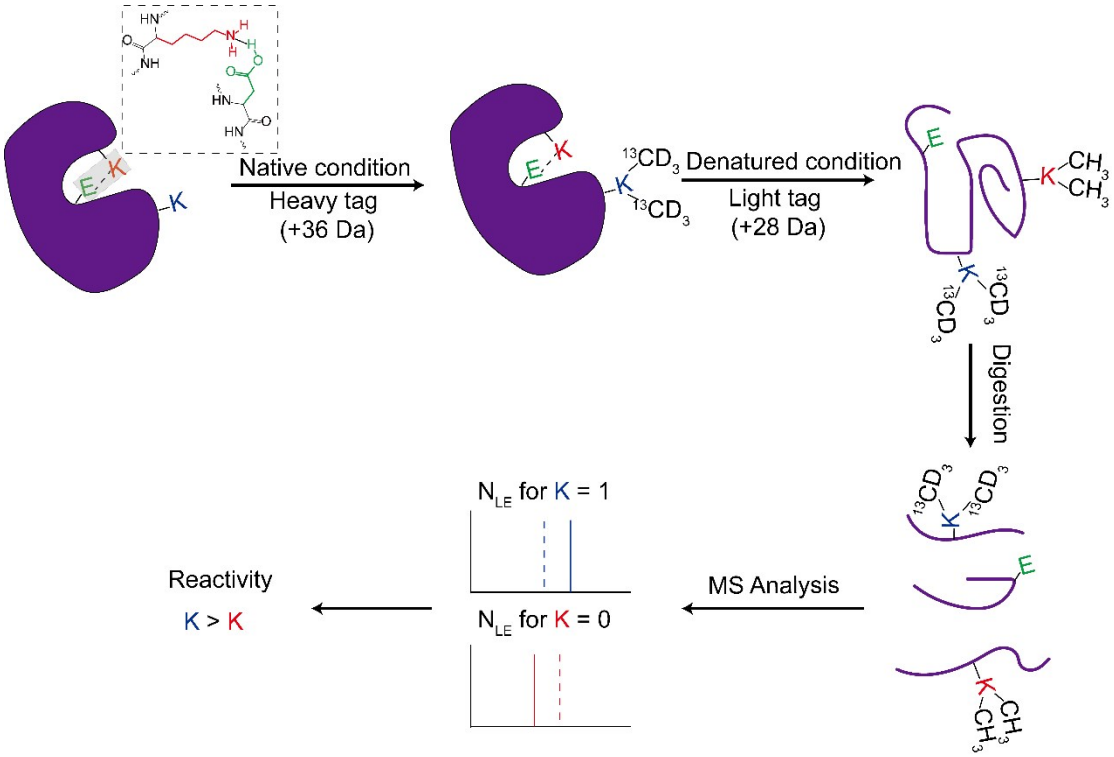

Fig. S1. The workflow of two-step isotope labeling-lysine reactivity profiling strategy. The first-step labeling is performed under native state with heavy isotope dimethyl tags. After denaturation, the second-step labeling is performed to completely labeled all of the lysine residues with light dimethyl tags.

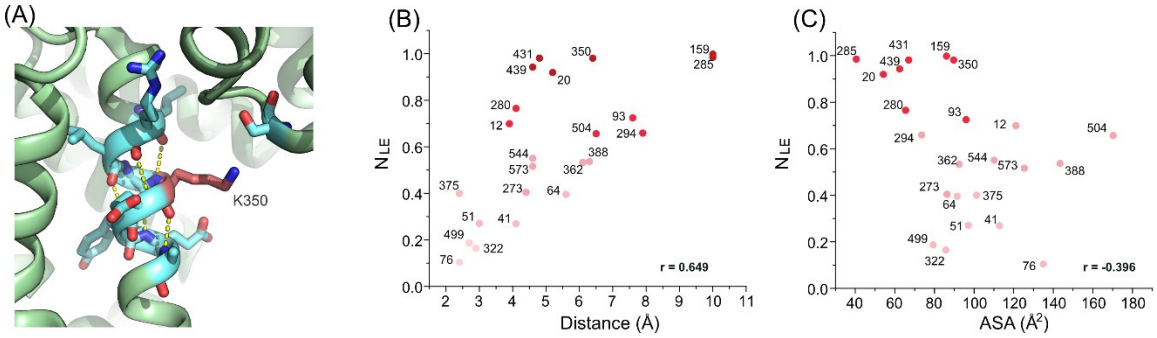

Fig. S2. Quantification of the relative lysine reactivities (N_{LE}) of purified BSA under native aqueous solution by TILLRP strategy. (**A**) The microenvironment of Lys^{350}; (**B**) The correlation between the lysine N_{LE} values and the distances between lysine residues and their proximal acidic residues (the correlation coefficient r is 0.649); (**C**) The correlation between the lysine N_{LE} values and the corresponding solvent-accessible surface areas (SASAs) (the correlation coefficient r is -0.396).

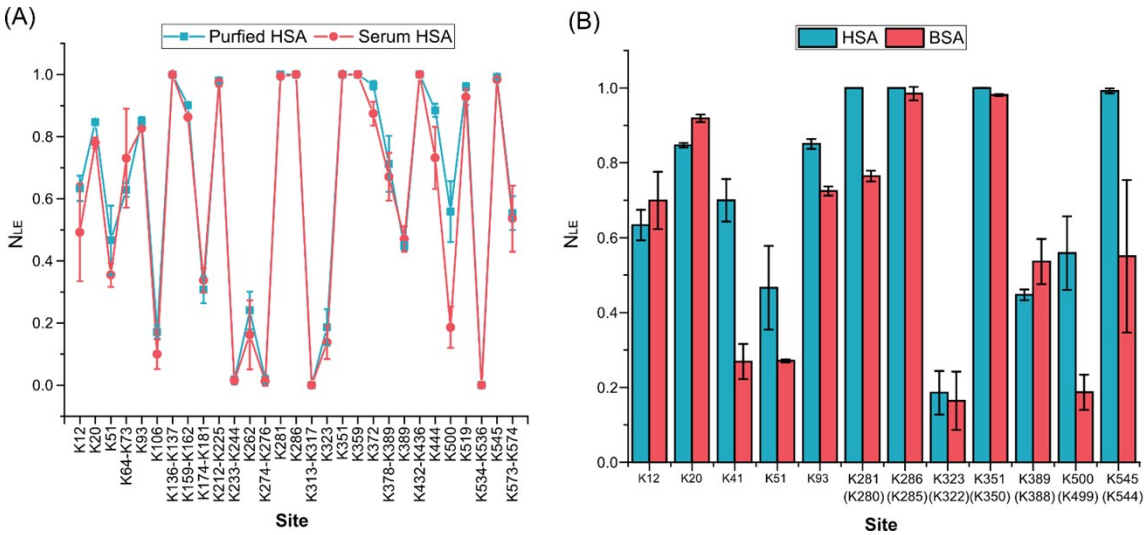

Fig. S3. Quantification of the relative lysine reactivity of HSA by TILLRP strategy. (**A**) The N_{LE} profiles of purified and serum HSA; (**B**) Comparison of the N_{LE} of conserved lysines in HSA and BSA, the lysines in brackets for BSA.

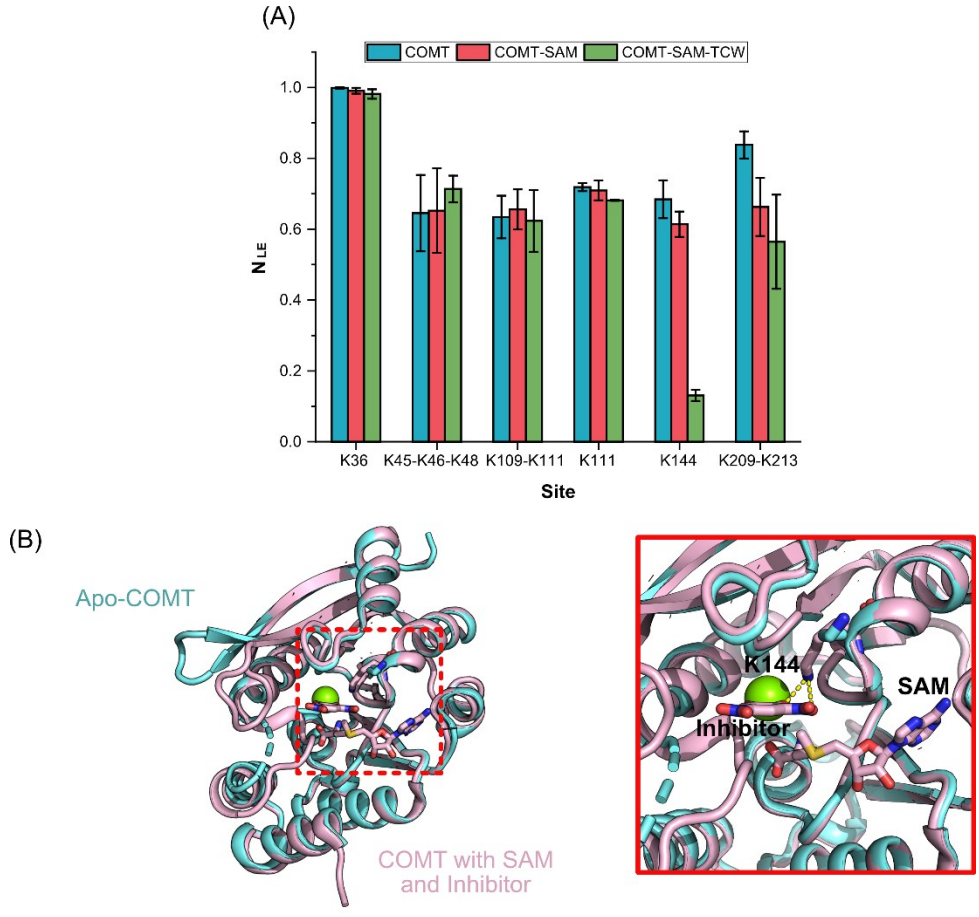

Fig. S4. Quantification of the lysine reactivity of COMT with/without ligand combination by TILLRP strategy. (**A**) comparison of the N_{LE} of lysine residues in COMT, COMT-SAM,

and COMT-SAM-TCW; (**B**) the microenvironments of Lys[144] in the crystal structure of apo-COMT (PDB: 4pyi) and COMT with ligands (PDB: 3bwy).

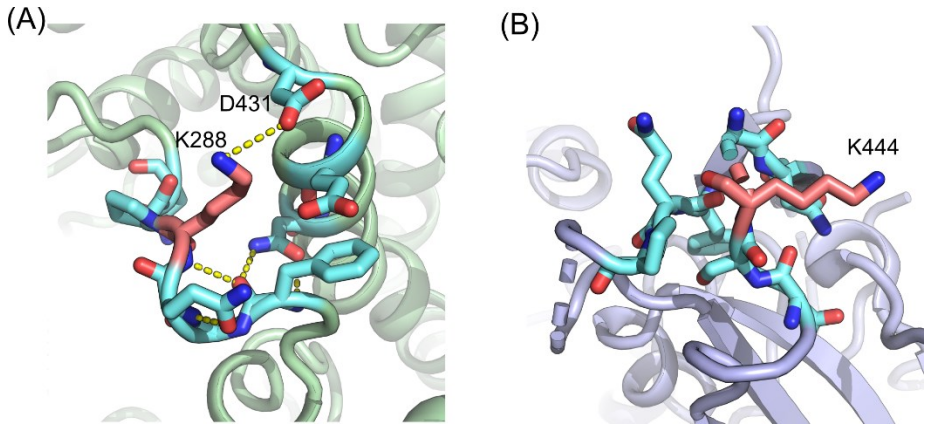

Fig. S5. The microenvironments of (A) ACE2 Lys[288] (PDB: 6m18) and (B) S1 Lys[444] (PDB: 6vxx). The salt bridge of lysine is shown as a yellow dashed line.

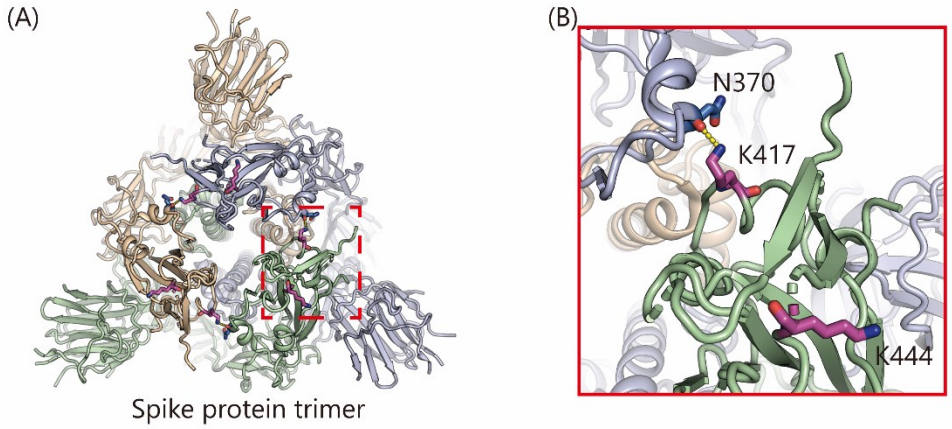

Fig. S6. The microenvironments of Lys[417] and Lys[444] at the closed trimer Spike glycoprotein conformation (PDB: 6vxx). The salt bridge of lysine is shown as a yellow dashed line.

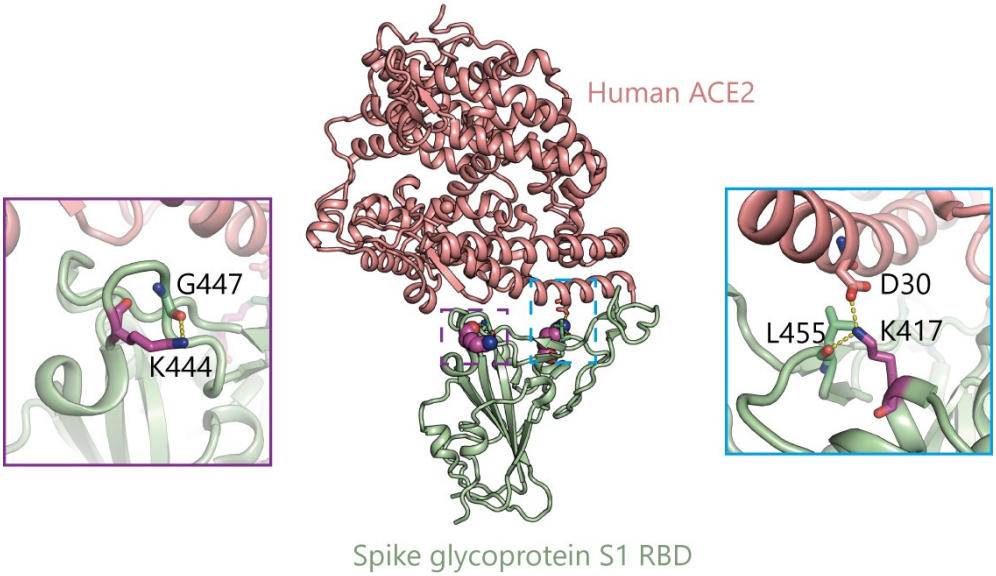

Fig. S7. The microenvironments of Lys^{417} and Lys^{444} in SARS-CoV-2 S1-ACE2 complex (PDB: 6lzg). The salt bridge of lysines are shown as yellow dashed lines.

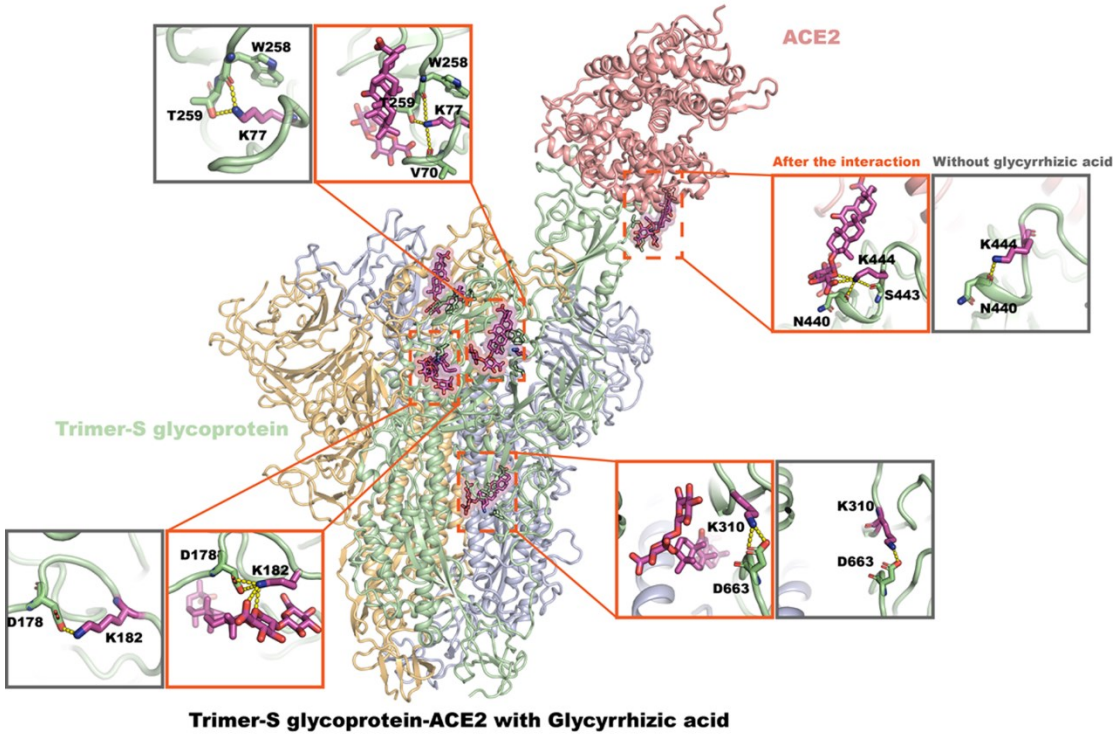

Fig. S8. Simulated docking conformation of the interactions of SARS-CoV-2 S1-ACE2 complex with glycyrrhizic acid. The gray and orange boxes represent the schematic diagram of lysine microenvironments before and after docking glycyrrhizic acid with S1-ACE2 complex. The salt bridges of lysines are shown as yellow dashed lines.

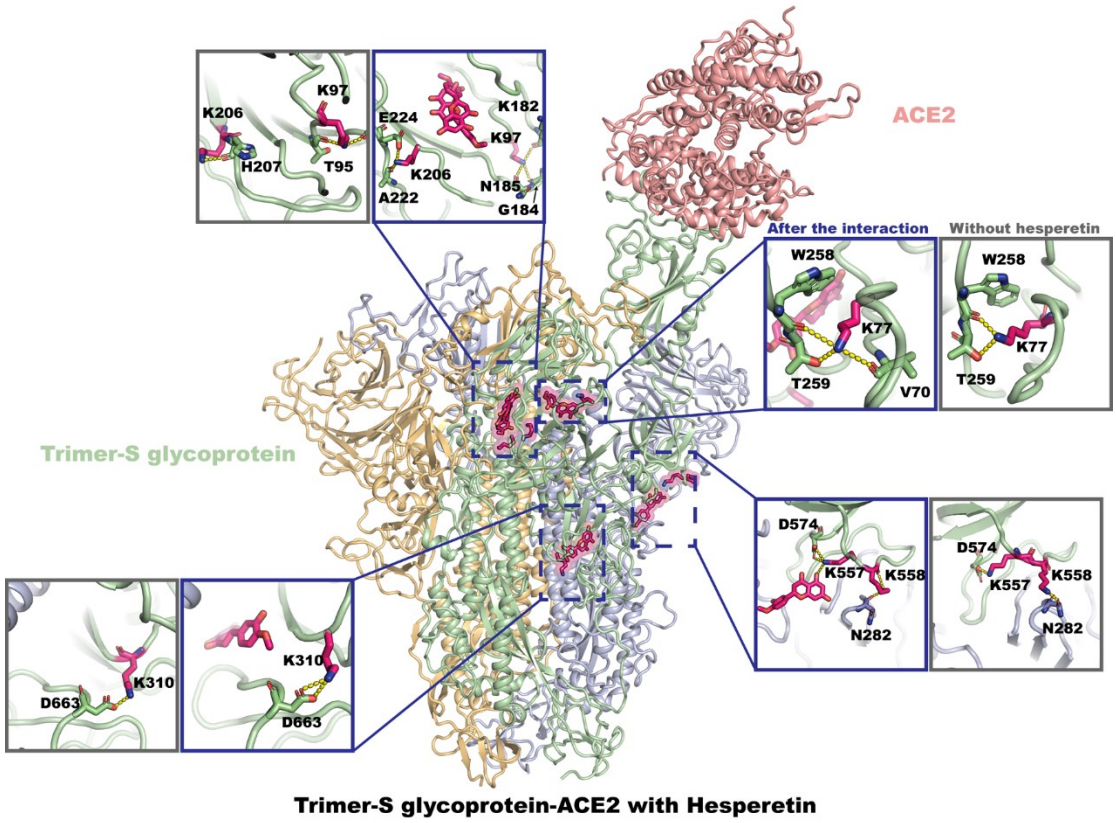

Fig. S9. Simulated docking conformation of the interactions of S1-ACE2 complex with hesperetin. The gray and blue boxes represent the schematic diagram of lysine microenvironments before and after docking hesperetin with S1-ACE2 complex. The salt bridges of lysines are shown as yellow dashed lines.

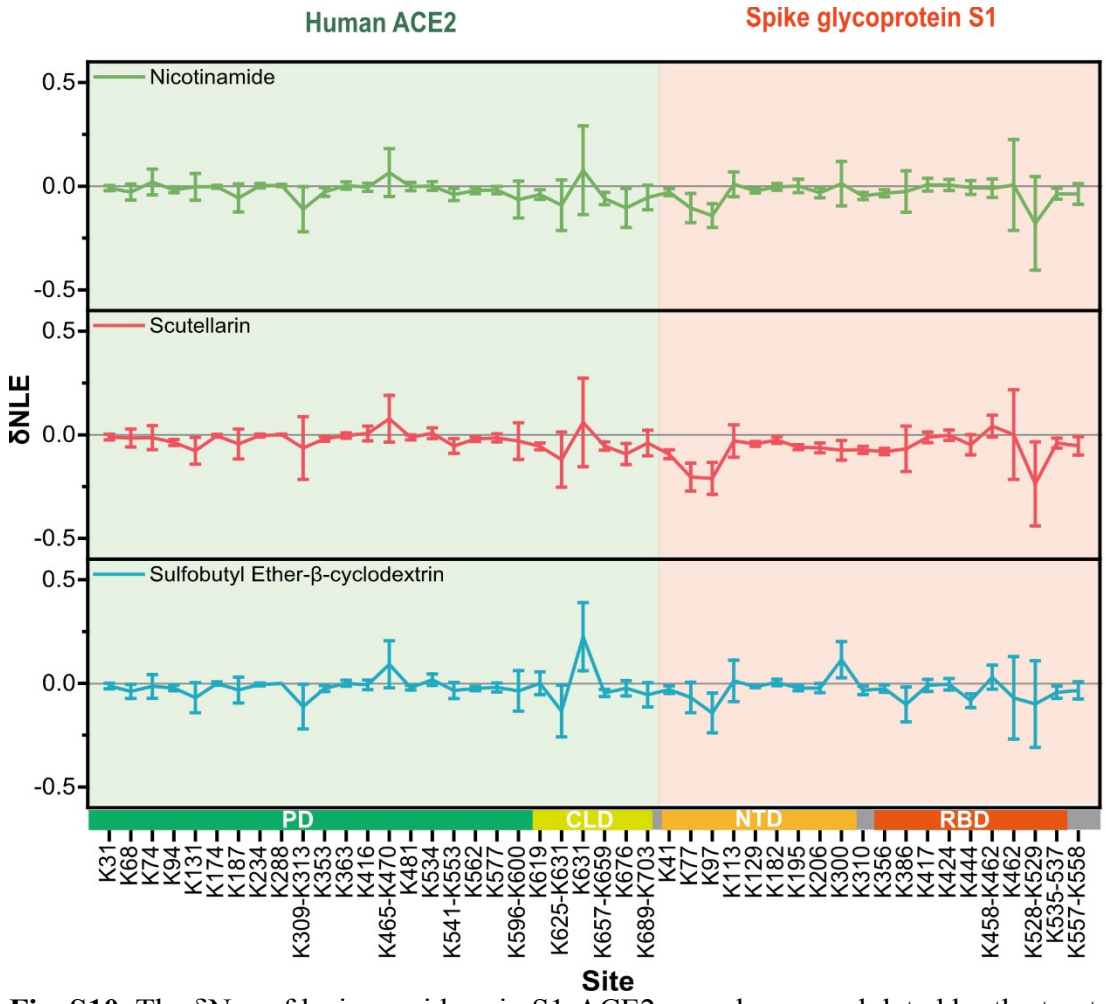

Fig. S10. The δN_{LE} of lysine residues in S1-ACE2 complexes modulated by the treatment of exogenous compounds nicotinamide, scutellarin, and sulfobutyl ether-β-cyclodextrin.