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\textsuperscript{144} in the crystal structure of apo-COMT (PDB: 4pyi) and COMT with ligands (PDB: 3bwy).

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

**Fig. S6.** The microenvironments of Lys\textsuperscript{417} and Lys\textsuperscript{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\textsuperscript{417} and Lys\textsuperscript{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 $\delta N_{LE}$ of lysine residues in S1-ACE2 complexes modulated by the treatment of exogenous compounds nicotinamide, scutellarin, and sulfobutyl ether-$\beta$-cyclodextrin.