Supplementary Figure Legends.

Supplementary Figure S1. The docking and MD procedure reveals stable binding between PLpro and rac5c. a) The time dependence of the heavy-atom RMSD of rac5c and the time dependence of the distance between the donor and acceptor (e.g. the N atom of rac5c peptide-backbone and the backbone oxygen of Y268) of the key hydrogen bond. The reference structure for RMSD calculation is taken from the trajectory at 76.1 ns and is plotted to the upper right corner with the same coloring as in Fig. 3a. b) The time dependence of the distance between the center of mass of the naphthalene fragment (with the attached methyl group, marked as NAP) and that of PLpro residues P247, P248, T301, M208 and Y268. c) The time dependence of the distance between the center of mass of the piperidine fragment (marked as PIP) and that of PLpro residues Y273, Y264, and Y268. d) The time dependence of the distance between the center of mass of the pyridine fragment (marked as PYR) and that of PLpro residues Q269 and L162.

Supplementary Figure S2. Original anti-ISG15 blotting data for Tanshinone IIA sulfonate sodium treatment.

Supplementary Figure S3. Original anti-ISG15 blotting data for chloroxine treatment.

Fig. S1

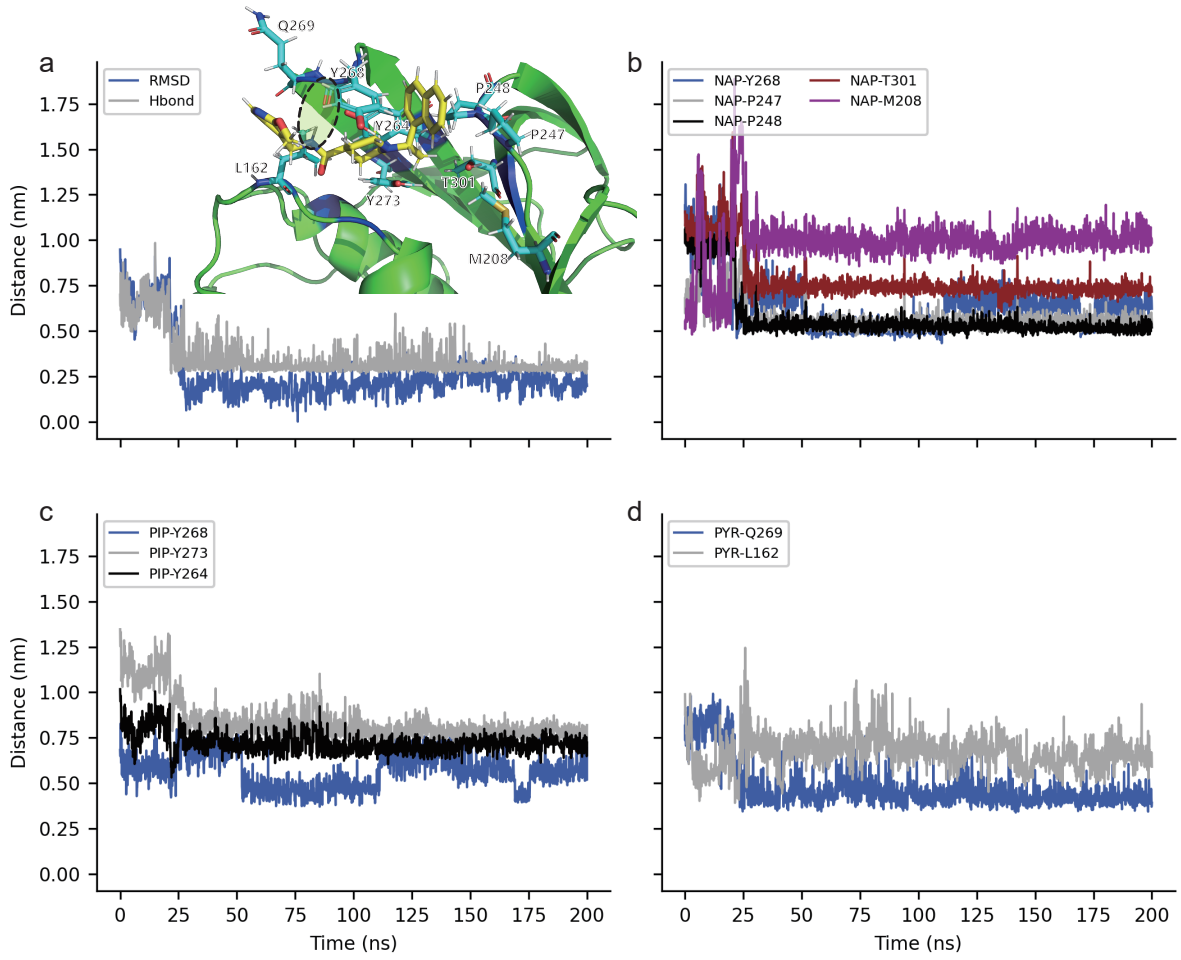
a
RMSD
Hbond
Distance (nm)
Q269
Y268
Y264
P248
P247
L162
T301
Y273
M208
b
NAP-Y268
NAP-P247
NAP-P248
NAP-T301
NAP-M208
c
PIP-Y268
PIP-Y273
PIP-Y264
Distance (nm)
Time (ns)
d
PYR-Q269
PYR-L162
Time (ns)

Fig. S2

ISG15	-	+	+	+	+	+	+
E1/E2/E3	-	-	+	+	+	+	+
GFP-PLpro	-	-	-	+	+	+	+
Tanshinone IIA sulfonate sodium	-	-	-	-	10	100	200 μM

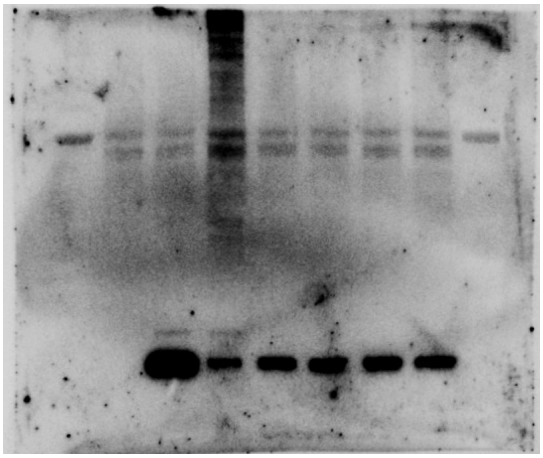

Fig. S3