

Supplemental Information for

Mechanistic insights into the inhibition of SARS-CoV-2 main protease by clovamide and its derivatives: in silico studies

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Figure S1

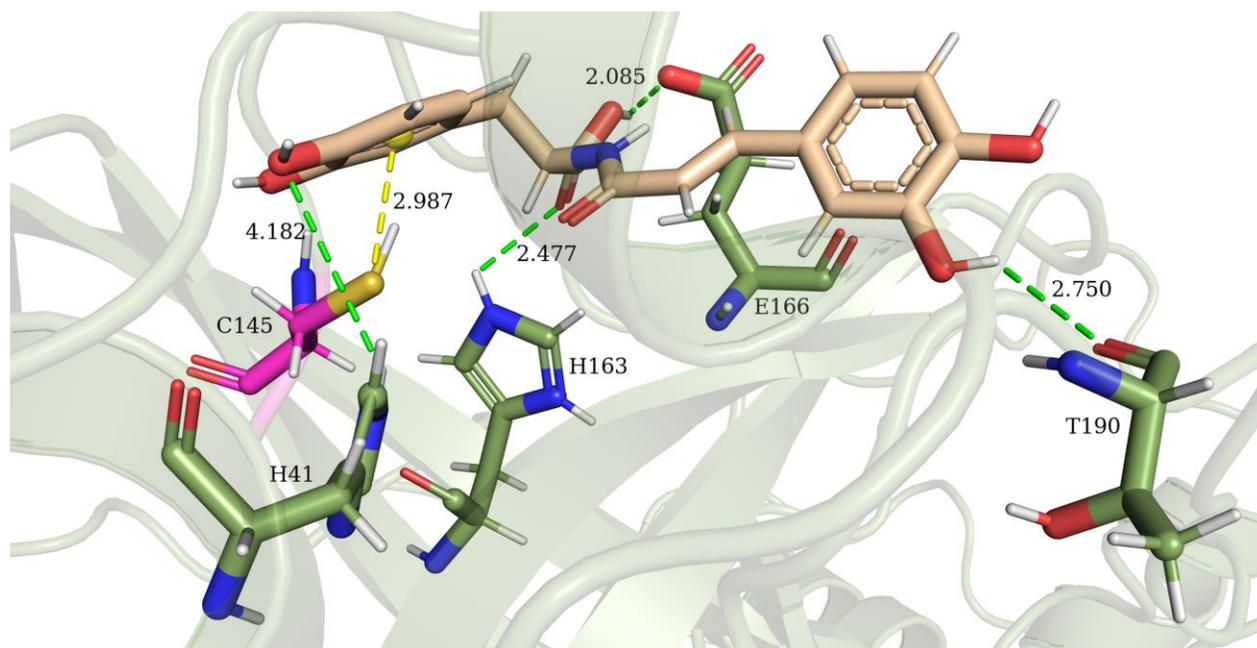


Figure S1. Pose 1 of the docking poses of clovamide to M^{pro} (PDB: 6LU7). S(C145) points to the catechol ring with an atom-to-centroid distance of 2.987 Å (yellow dash line), a strong interaction providing both stability to the complex and potentials for covalent reactions. Green dash lines represent hydrogen bonds providing non-covalent stabilizations towards the complex.

Figure S2

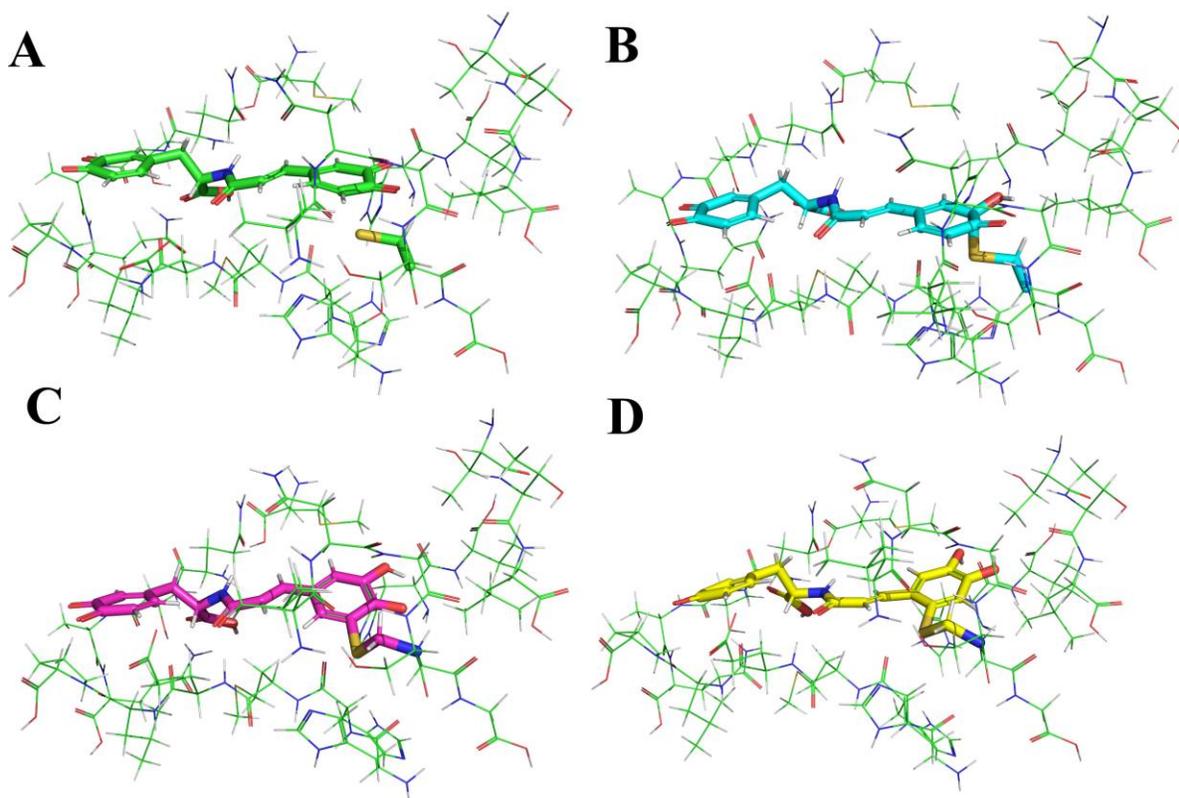


Figure S2. DFT geometric optimizations of three proposed M^{pro} inhibition mechanisms by clovamide quinone derivative C. The ligands and C145 residue are represented in sticks, while other surrounding amino acids are shown in lines. **A:** The deprotonated C145 thiolate and quinone derivative after geometry optimization. **B, C, D:** optimized product structures of the inhibited enzyme active site, showing covalent linkages between C145 and clovamide quinone derivative carbonyl carbon (**B**), α carbon (**C**), or β carbon (**D**). Detailed mechanisms leading to the formations of the products are illustrated in Scheme 5.

Figure S3

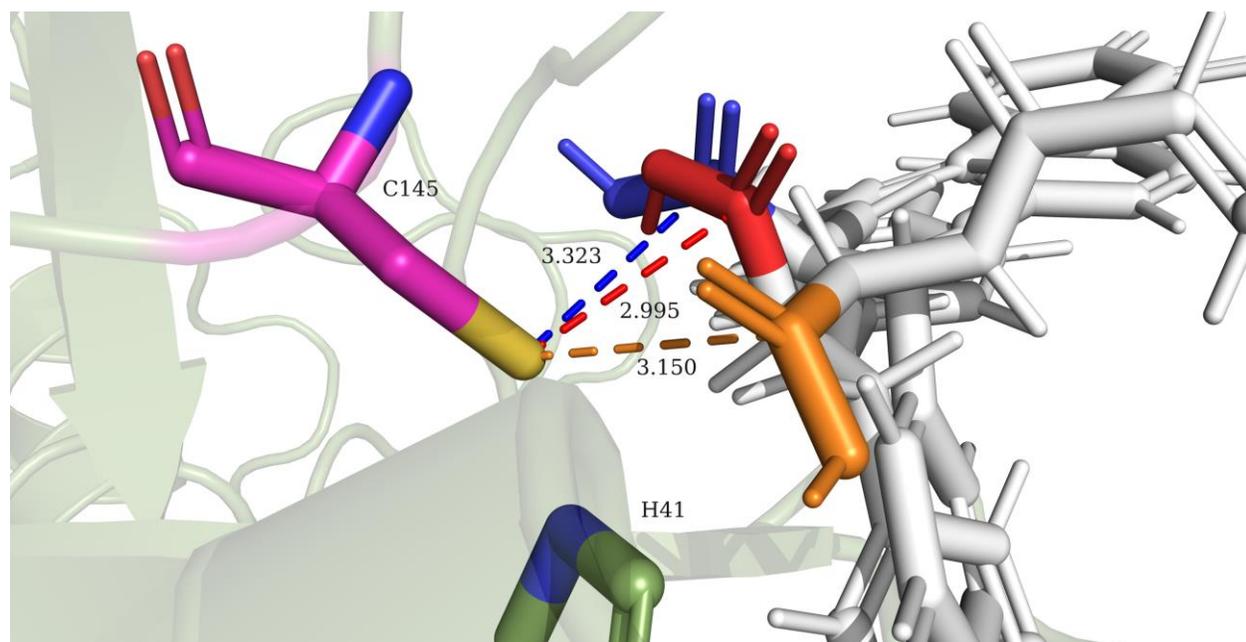


Figure S3. Potential thioester linkage formation by S(C145) attacking the carbonyl carbon of carboxylic acid groups. Protein hydrogen atoms are omitted; for substrates, only the carboxylic acid groups are colored for clarity. Orange compound is docking pose 12 of clovamide to M^{pro}; red compound is docking pose 3 of clovamide quinone derivative **B** to M^{pro}; blue compound is docking pose 1 of clovamide quinone derivative **C** to M^{pro}. Labels show distances between S(C145) to the carbonyl carbons of the acid groups.

Figure S4

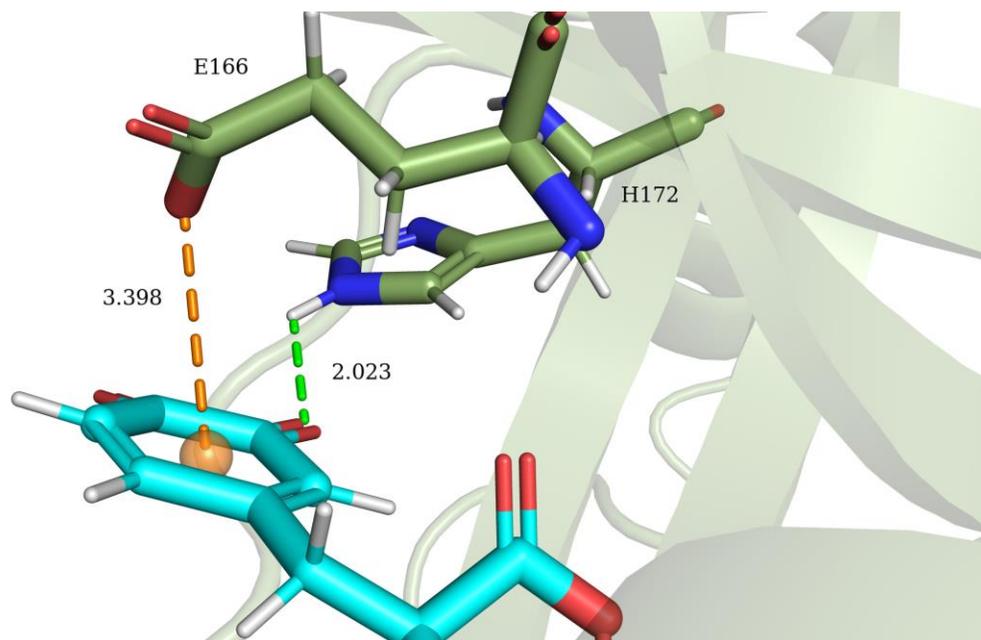


Figure S4. The π —anion interaction. This interaction (represented by orange dashed line) occurs between at the terminal of the negatively charged E166 residue and the π system of the ortho-quinone ring. The interaction distance is 3.398 Å. Green dash represents a strong hydrogen bond between quinone carbonyl oxygen and H172 residue.

Figure S5

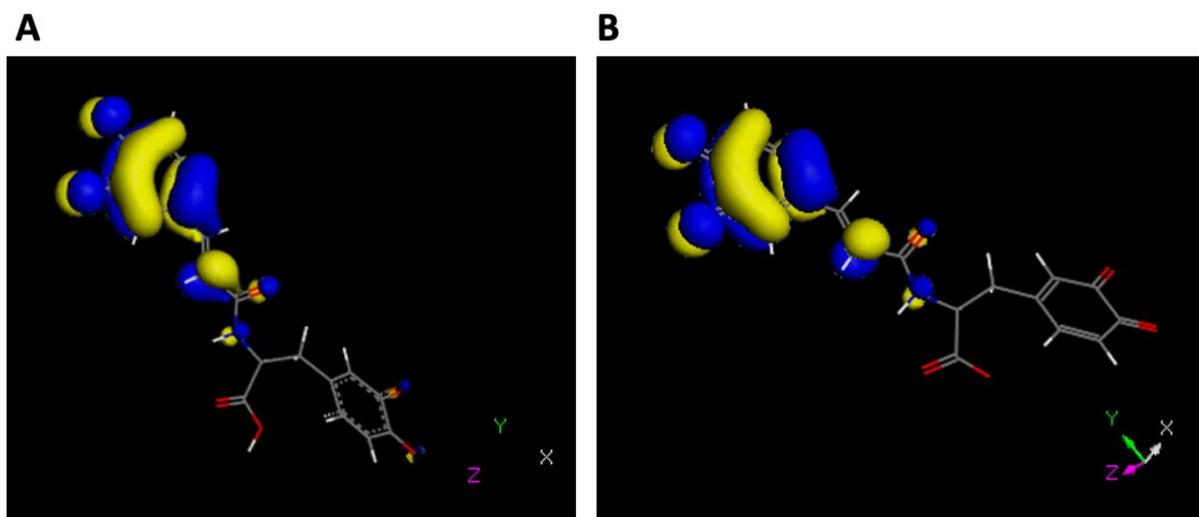
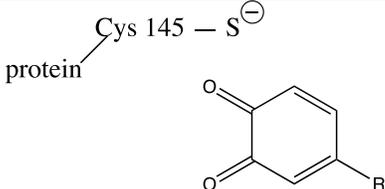
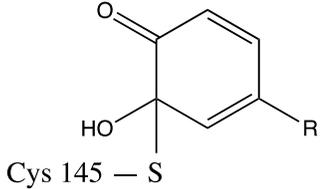
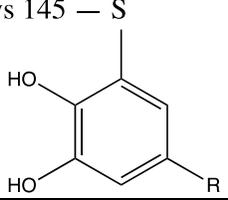
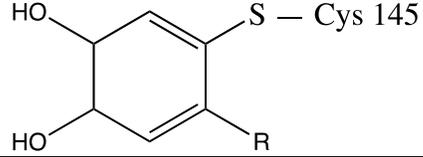


Figure S5. LUMO for the clovamide quinone derivative C, indicating reactivity at the ortho-quinone ring at the side with double-bond conjugation. **A:** natural molecule of clovamide derivative C; **B:** anionic form with deprotonated carboxylate group, total charge is -1.

Table S1: DFT geometry optimization free energy for the reactant and products of inhibition by clovamide quinone derivative. See Scheme 3 for mechanistic details

Mechanism	Structure of reactant/product	Energy (Hartree)	Energy (kJ/mol)
Reactant (thiolate C145)		-10861.731	-28517476.548
Mechanism A1 (carbonyl carbon addition)		-10861.711	-28517424.402
Mechanism A2 (α carbon addition)		-10862.134	-28518534.989
Mechanism A3 (β carbon addition)		-10862.067	-28518359.081