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Optimizing Molecular Toolkits for Inactivating Protease Activity in Coronaviruses: Advancing Pandemic Preparedness

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The recent COVID-19 pandemic has highlighted the urgent need for enhanced pandemic preparedness, as emphasized by WHO. Coronaviruses remain a major health threat, having crossed the zoonotic barrier multiple times in the past two decades to infect humans. Targeting coronaviral proteins is of interest, particularly the main protease (Mpro), which cleaves viral polyproteins, aiding viral maturation, replication, and infection. Mpro is highly conserved among coronaviruses making it an attractive target for pan-inhibitors. Here, we will discuss our efforts to understand Mpro's structure-function-ligand interactions. Using computational approaches and biochemical experiments, we identified a novel mutation that alters Mpro's conformational state, leading to oxidation and inactivation of its proteolytic activity. The X-ray crystal structure of this inactive Mpro state provides new insights into developing small-molecule inhibitors targeting this novel state. We also developed CoviProdigy, a user-friendly database for analyzing Mpro-ligand interactions. It enables comparative assessments of ligand binding, key interactions, and properties across thousands of Mpro structures in the Protein Data Bank. It benchmarks computationally designed complexes against crystal structures, identifying unique binding features. Our research provides tools to enhance pandemic preparedness.