

A structure-guided, taxonomic-based approach to the design of broad-spectrum coronavirus protease inhibitors

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Human coronaviruses such as SARS-CoV, MERS and SARS-CoV-2 continue to emerge as significant threats to public health. Other human coronaviruses such as NL63, HKU1, 229E and OC43 continue to persist in the population but are significantly less deadly. Since the SARS-CoV epidemic emerged in 2003, we have worked to develop small-molecule inhibitors of coronavirus 3C-like protease (3CLpro, also known as main protease or Mpro) and the papain-like protease (PLP or PLpro). Initially, we focused on the proteases from SARS and then on NL63 and MERS. However, the differences in inhibitory potencies of our compounds and the taxonomic distance of the alpha and beta coronavirus genera taught us that approach of studying one virus at a time was too slow and provided to little molecular information to inhibit multiple coronaviruses. Moreover, it was not allowing us to predict how to inhibit emerging coronavirus pathogens. In the interest of pandemic preparedness, we are now taking what we call a taxonomically-driven approach to the structure-based design of coronavirus protease inhibitors. We targeted 12 different 3CLpros from the alpha-, beta- and gamma-coronavirus genera with a series of 50 compounds that we designed and synthesized using the Automated Synthesis and Purification platform at Eli Lilly. We identified inhibitor templates that potently inhibit the enzymes from the alpha and beta genera but not the gamma genus. To ascertain the structural basis of the selectivity, we utilized LS-CAT and LRL-CAT beamlines at the APS and performed a sparse-matrix sampling approach and determined multiple X-ray structures of 3CLpro from the different coronavirus genera in complex with different inhibitors. We identified precise structural regions that define inhibitor selectivity for different inhibitor scaffolds and we are now extending this approach to PLpro. We have been able to design and synthesize over 350 additional compounds against SARS-CoV-2 3CLpro. These compounds include potent non-covalent inhibitors, reversible-covalent and covalent inhibitors with low nanomolar to picomolar potency including inhibitors with broad-spectrum, i.e. pancoronavirus, activity against 12 different alpha, beta and gamma coronavirus.

Keywords: COVID-19, SARS-CoV-2, inhibitor, drug, structure

This work was supported in part by funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN272201700060C.