Creating New Inhibitors To SARS-Cov-2 Macrodomain Using Fragments, Neutrons, And Entropy!

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) macrodomain within the nonstructural protein 3 counteracts host-mediated antiviral adenosine diphosphate-ribosylation signaling. This enzyme is a promising antiviral target because catalytic mutations render viruses nonpathogenic. We conducted a massive crystallographic screening and computational docking effort, identifying new chemical matter primarily targeting the active site of the macrodomain. X-ray data collection to ultra-high resolution and at physiological temperature enabled assessment of the conformational heterogeneity around the active site. Neutron diffraction data determined the precise orientations of active site water molecules and the protonation states of key catalytic site residues suggesting a catalytic mechanism for coronavirus macrodomains distinct from the substrate-assisted mechanism proposed for human MacroD2. Several hits have promising activity in solution and provide starting points for development of potent SARS-CoV-2 macrodomain inhibitors with cellular activity. The role of entropy in modulating binding affinity will also be discussed.