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3CLpro of SARS-CoV-2 in Drug Development Against COVID-19

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Abstract

Coronaviruses cause acute infections of the upper and lower respiratory tracts with SARS-CoV-2 is the virus responsible for COVID-19. SARS-CoV-2 is one of the largest positive-sense, single-stranded RNA viruses and belongs to the genus Betacoronavirus. The main protease of SARS-CoV-2, 3C-like protease (3CLpro), is one of two proteases responsible for processing two polypeptides to liberate 16 non-structural proteins (nsps) that are important for replication, transcription, and virus recombination during infection. Inhibiting the proteases will block the release of nsps and progression of COVID-19, making 3CLpro an attractive target for the design of antivirals against COVID-19.

We characterized the functional and chemical properties of 3CLpro protease with optimum conditions for the high throughput screening of small molecules to screen existing FDA drugs for the identification of small molecules that can inhibit 3CLpro of SARS-CoV-2. Small molecule inhibitors that reduce the activity of 3CLpro can be characterized further for enhance inhibition effect and binding specificity against 3CLpro of SARS-CoV-2. Best small molecule inhibitors with highest efficacy giants 3CLpro of SARS-CoV-2 will make potential therapeutics for COVID-19.

3CLpro of coronaviruses have identical structural folds with homodimer constructed by the two perpendicular monomers. Studies of 3CLpro from different coronaviruses has suggested the dimer to be the catalytically active form, making the dimerization interface a target for antiviral development. Guided by structural analysis, single amino acid substitutions were introduced at nine residues at three key sites of the dimer interface to assess their impact on dimerization and activity. Four residues in two sites have been identify to be important for the activity of the protease. These results provide insights on two allosteric sites, R4/E290 and S10/E14, that may promote the design of antiviral compounds that target the dimer interface rather than the active site of SARS-CoV-2 3CLpro for higher efficacy and specificity.