Structure-assisted Design of Inhibitors Targeting Coronavirus Main Proteases

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Coronaviruses (CoVs) are important etiologic agents of upper respiratory and digestive tract diseases in humans and animals; especially, the severe acute respiratory syndrome (SARS). The viruses are characterized with a highly complex cascade of proteolytic processing the replicative polyproteins to control viral gene expression and replication, which was predominantly mediated by the viral main proteinase (M^{pro}, also called $3CL^{pro}$), therefore, an attractive target for drug development[1].

A series of novel compounds with Michael receptor was designed according to the crystal structures of 3 coronaviruses M^{pro}s. The solved structures of SARS-CoV and porcine transmissible gastroenteritis virus (TGEV) M^{pro}s individually complexed with these compounds revealed that inhibitors possessing α,β-unsaturated ester combined with peptidyl-binding elements specific for CoV M^{pro}s undergo a nucleophilic addition of the protease's catalytic Cys, resulting in covalent-bond formation and irreversible inactivation of the viral proteases. One compound in this series has exhibited potent and extensive inhibition effect on 6 CoV M^{pro}s covering all 4 groups within genus *Coronavirus*. Meanwhile, the novel small molecules showed low micromolar concentration of EC_{50} for inhibition of viral replication and very low cell toxicity. We suppose further modification of these compounds assisted with structural information might lead to discover drug candidates against all CoV-associated diseases, including SARS.

[1] Yang H., Yang M., Ding Y., Liu Y., Lou Z., Sun L., Zhou Z., Ye S., Pang H., Gao G., Anand K., Bartlam M., Hilgenfeld R., Rao Z., *Proc. Natl. Acad. Sci. USA*, 2003, **100(23)**, 13190-13195.

Keywords: SARS, main protease, drug design