The SARS-CoV-2 main protease as a target for antivirals: Crystal structures, new inhibitors, and mutants

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SARS coronavirus 2 (SARS-CoV-2) is the causative agent of the present COVID-19 pandemic, which started in early 2020. The SARS-CoV-2 main protease (Mpro) is one of the most attractive targets for the development of antiviral inhibitors for COVID-19 therapy. In February 2020, we determined the crystal structure of the SARS-CoV-2 Mpro and presented a powerful alpha-ketoamide inhibitor, compound 13b [1]. Using a structure-based approach, we have since optimized this compound further and now have inhibitors with IC50 down to 13 nM in the biochemical assay and EC50 < 400 nM in virus-infected cell culture. ADME and pharmacokinetic data will be discussed for the frontrunner compounds.
In preparing for future drug resistance mutations, which will likely emerge when the presently available SARS-CoV-2 Mpro inhibitor paxlovid [2] (and potential future candidate compounds such as 13b-K [3]) will be used in the clinic, we analyzed the natural evolution of the Mpro since the beginning of the pandemic. When cumulated, the most common mutations are L89F and K90R and we determined crystal structures for both. However, the frequency of L89F is declining and others are coming up, and we will also present structural studies on the most interesting ones. Most mutations are far from the substrate-binding site and the dimerization interface of the enzyme and the inhibitory potency of compound 13b-K is not affected. The Mpro mutation P132H is characteristic for the Omicron variant of concern of SARS-CoV-2 and we will present data on this protein as well.

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[3] Cooper MS, Zhang L, Zhang K, Sun X, Röske J, Sauerhering L, Becker S, Vangeel L, Jochmans D, Neyts J, Rox K, Marsh GP, Maple HJ, Hilgenfeld R. Diastereomeric resolution yields highly potent inhibitor of SARS-CoV-2 main protease. To be submitted.

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