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Crystal Structure of SARS-CoV-2 Main Protease Provides a Basis for Design of Improved α-Ketoamide Inhibitors Science 2020, 368, 409-412.

## α-Ketoamide Inhibitors of SARS-CoV-2 Main Protease

**Significance:** SARS-CoV-2 is the virus responsible for the coronavirus disease 2019 (COVID-19) pandemic. Potent, broad-spectrum α-ketoamide inhibitors of the main protease (M<sup>pro</sup>) of betacoronaviruses and alphacoronaviruses were recently reported by Hilgenfeld and co-workers (J. Med. Chem. 2020, DOI: 10.1021/acs.jmedchem.9b01828). X-ray crystallography and structure-based design led to the discovery of submicromolar  $\alpha$ -ketoamide inhibitor 13b, which has now been developed specifically against SARS-CoV-2 M<sup>pro</sup> to shut down the processing of polyproteins translated from viral RNA.

**Comment:** Starting from commercially available (R)-2-amino-3-cyclopropylpropanoic acid, Boc-protected pyridone **D** is synthesized in four steps.  $\gamma$ -Lactam B, a proxy for glutamine, is made using an asymmetric dianionic cyanomethylation of N-Boc-L-(+)-glutamic acid dimethyl ester (Q. Tian et al. Tetrahedron Lett. 2001, 42, 6807) and is coupled to the hydrolysis product of **D**. Five additional transformations yield 13b, which inhibits SARS-CoV-2  $M^{pro}$  with  $IC_{50} = 0.67 \pm 0.18 \,\mu M$  and displays promising lung tropism and inhalation tolerance in mice.

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Category

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## Key words

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