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<sub>pro</sub>) of betacoronaviruses and alphacoronaviruses were recently reported by Hilgenfeld and co-workers (<i>J. Med. Chem.</i> 2020, DOI: 10.1021/acs.jmedchem.9b01828). X-ray crystallography and structure-based design led to the discovery of submicromolar α-ketoamide inhibitor 13b, which has now been developed specifically against SARS-CoV-2 M<sub>pro</sub> 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. γ-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<sub>pro</sub> with IC<sub>50</sub> = 0.67±0.18 μM and displays promising lung tropism and inhalation tolerance in mice.