New compounds thwart multiple viruses, including coronavirus

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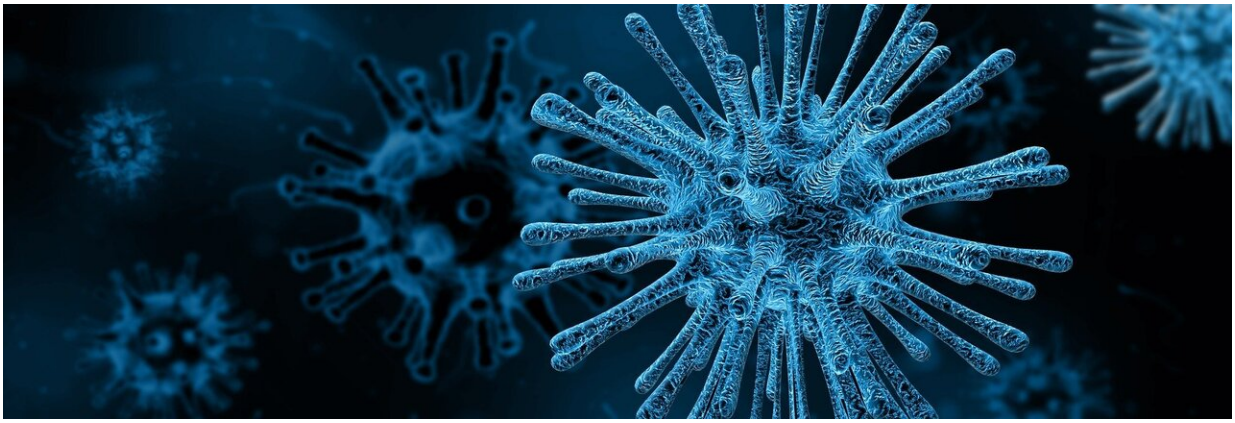

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According to a February 13 report from the World Health Organization, the Wuhan coronavirus has stricken more than 46,000 people and has caused over 1,300 deaths since the first cases in Wuhan, China, in December 2019. Now, researchers reporting in ACS' *Journal of Medicinal Chemistry* have designed compounds that block the replication of similar coronaviruses, as well as other disease-causing viruses, in the lab. The compounds have not yet been tested in people.

The Wuhan coronavirus, also known as SARS-CoV-2 or 2019-nCoV, is a close relative to the severe acute respiratory syndrome (SARS) virus that caused an outbreak in 2003 (SARS-CoV-1), as well as the Middle-

East respiratory disease virus (MERS-CoV) that emerged in 2012. All of these viruses cause flu-like symptoms and, frequently, pneumonia. However, no effective treatments have been developed, in part because the relatively small number of cases have not warranted large expenditures by pharmaceutical companies. Hong Liu, Rolf Hilgenfeld and colleagues envisioned a possible solution in the form of broad-spectrum antiviral drugs that target all coronaviruses, as well as enteroviruses—some of which cause conditions like the common cold; hand, foot and mouth disease; and the "summer flu." All of these viruses share a similar protein-cutting enzyme, called the "main protease" in coronaviruses and the "3C protease" in enteroviruses, that is essential for viral replication.

The researchers examined X-ray crystal structures of the proteases and then made a series of α-ketoamide compounds that were predicted to fit snugly in the enzymes' active sites, interfering with their function. By testing the molecules in the test tube and in human cells in petri dishes, they identified one versatile inhibitor that blocked multiple coronaviruses and enteroviruses, including SARS-CoV-1. Another molecule showed very strong activity against MERS-CoV, with moderate activity against the other viruses. Because the main proteases of SARS-CoV-2, MERS-CoV and SARS-CoV-1 are very similar, the inhibitors will most likely show good antiviral activity against the Wuhan coronavirus, the researchers say. Their next step will be to test the inhibitors in small-animal models of disease.

More information: Linlin Zhang et al. α-Ketoamides as Broad-Spectrum Inhibitors of Coronavirus and Enterovirus Replication: Structure-Based Design, Synthesis, and Activity Assessment, *Journal of Medicinal Chemistry* (2020). DOI: 10.1021/acs.jmedchem.9b01828

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