Study reports new compound that halts replication of COVID by targeting 'Mac-1' protein in cell models

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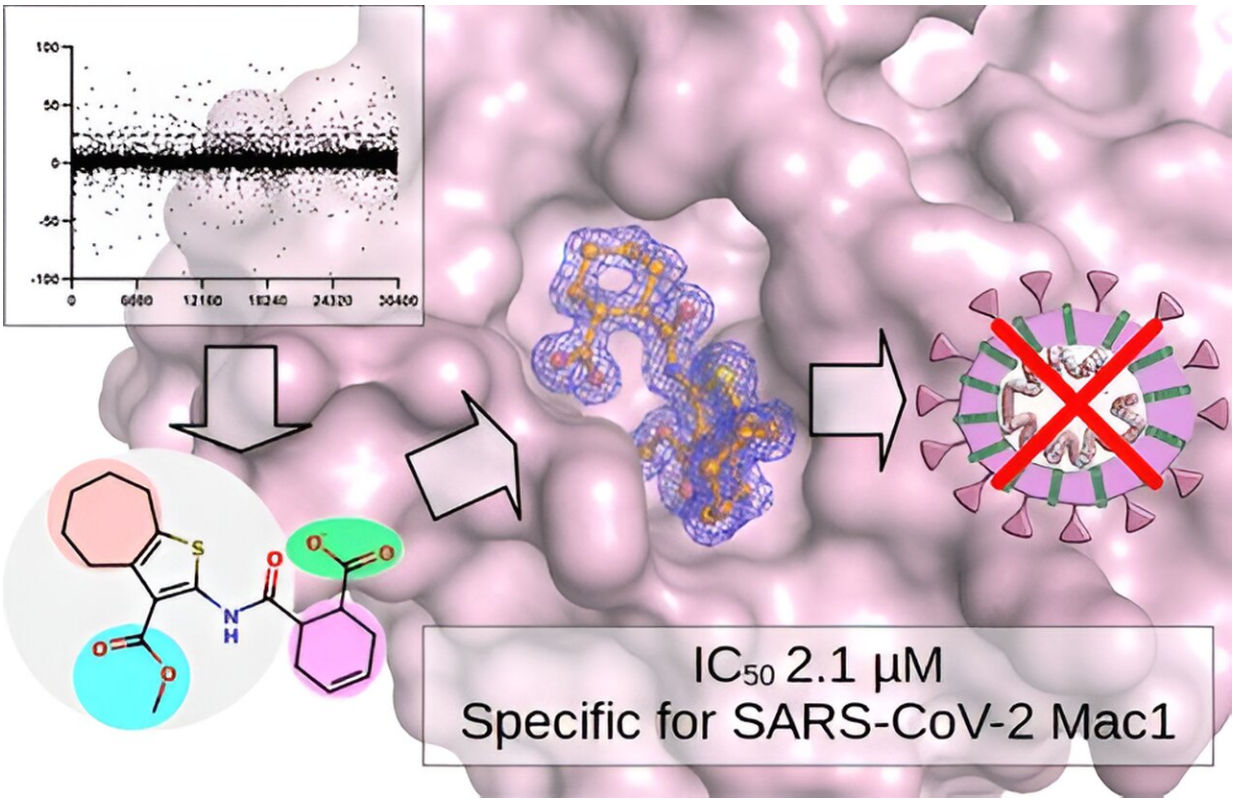

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Research appearing in the Journal of Medicinal Chemistry shows for the first time SARS-CoV-2, the virus responsible for COVID-19, can be inhibited from replicating in living cell cultures using a compound that targets "Mac-1," a protein key to defending SARS-CoV-2 against the human immune response.

University of Kansas researchers in the lab of Anthony Fehr, associate professor of molecular biosciences at KU, teamed with scientists at the University of Oulu in Finland and McDaniel College in Maryland to test a promising molecule called "Compound 27," that specifically inhibits the Mac-1 protein from SARS-CoV-2.

Compound 27 was isolated via a technique called high-throughput screening and then further modified by the Finnish team to target the Mac-1 protein precisely. Then, Fehr's KU lab tested the modified agent against the virus to gauge its effectiveness.

"Our lab really has analyzed Mac-1 in many ways over the years and laid the foundation that this is a good antiviral target," Fehr said. "If SARS-CoV-2 doesn't have this protein, it doesn't cause disease in mice. So, we believe compounds targeting Mac-1 should protect people from disease."

Compound 27 appears to be particularly effective against Mac-1. As the team reports in its new paper, "Compound 27 is the first Mac-1-targeted small molecule demonstrated to inhibit coronavirus replication in a cell model."

"When several of the high-throughput screening hits for Mac-1 inhibitors had the same core scaffold, we realized we had discovered something really promising," said senior author Lari Lehtiö of the University of Oulu.

"Experimental crystal structures showing the detailed binding mode to Mac-1 were key for designing new analogs, but there was also a component of luck and intuition that helped us to improve the potency of Compound 27. But—the time to actually celebrate was when we got an email from Kansas that the Mac-1 inhibitor indeed repressed SARS-CoV-2 replication."

Fehr said therapies based on Compound 27 or similar compounds with the potential to inhibit Mac-1 someday could join already existing SARS-CoV-2 medications like Remdesivir. What's more, Mac-1-based therapies could fight emerging coronaviruses beyond SARS-CoV-2.

"There's a distinct concern within the health and virus communities that other coronaviruses could trigger future pandemics, such as Middle East respiratory syndrome coronavirus, which is a major potential threat listed among pathogens with pandemic potential," he said. "MERS-CoV is somewhat related but distantly compared to SARS-CoV-2. Additionally, there are various coronaviruses that cause the common cold, although they're very distantly related to SARS-CoV-2."

Fehr said the question arises: When will one of these viruses evolve into a deadly threat?

"We're keen on developing coronavirus inhibitors targeting the Mac-1 across multiple coronaviruses," he said.

An additional benefit of Mac-1 targeted approaches is that coronaviruses seem to have trouble developing adequate resistance.

"It's a good therapeutic target because we're finding evidence that even if it tries to develop resistance, it's not going to be able to do so very easily," Fehr said. "Our evidence suggests the resistant viruses would not be able to cause disease."

For now, Fehr is eager to move the findings into additional coronaviruses to discover if Compound 27 and other related compounds targeting Mac-1 continue to show potential.

"We're keen to begin developing inhibitors targeting the Mac-1 across multiple coronaviruses," he said. "Furthermore, we aim to validate these inhibitors through testing in animal models. Currently, we're validating them in ex vivo cell cultures, but transitioning to in vivo systems would provide a more comprehensive understanding of their efficacy."

More information: Sarah Wazir et al, Discovery of 2-Amide-3-methylester Thiophenes that Target SARS-CoV-2 Mac1 and Repress Coronavirus Replication, Validating Mac1 as an Antiviral Target, *Journal of Medicinal Chemistry* (2024). DOI: 10.1021/acs.jmedchem.3c02451

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