Using AI to navigate out of a COVID treatment supply issue

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It's 2021, and the world has a safe vaccine for COVID-19 as well as drugs to treat the disease. But now, we face a serious problem: How do we make billions of doses of the medicines?

Researchers fear that the same issues with supply chains that caused toilet paper shortages at the beginning of the pandemic in the United States may result in the same problem with the fine chemicals needed to synthesize COVID-19 therapeutics and vaccines.

Now, a University of Michigan team of medicinal chemists have used artificial intelligence to find alternative pharmaceutical building blocks for 12 drugs under investigation to treat COVID-19.

"The WHO has started to discuss who will be the first to receive vaccinations for COVID-19, should they become available," said U-M researcher Tim Cernak, an assistant professor of medicinal chemistry and chemistry.

"Just to hit that front group—the essential workers, the sick, the elderly—we will need 4.2 billion doses of a vaccine, because the dosing regimen is at least two doses per person and there will be wastage. For us synthetic chemists, the folks who actually produce the medicine, that number is mind boggling. We're in a supply chain crisis."

For example, the researchers say the only approved drug for treating COVID-19 is remdesivir. The drug, an antiviral nucleotide, had an availability of just 5,000 when the outbreak started. As of the week of July 13, the United States is adding approximately 60,000 cases of coronavirus infection a day.

Cernak and his lab were approached by chemical supplier MilliporeSigma to devise solutions to the supply issue. Cernak and his team combed the federal clinical trials database for drugs currently being considered for treatment of COVID-19, and then used the artificial intelligence software Synthia to determine new ways to piece the drugs together.

"A drug has a defined structure," Cernak said. "Let's say your drug has 12 atoms in it: three nitrogens and nine carbons. There is more than one way to put those three nitrogens and nine carbons in place.

"There's a process synthetic chemists use to break the target down to simple commercially available building blocks. You have to know which reactions will work in the forward direction, to stitch the building blocks together, but we tend to think of the breakdown of the complex drug molecule into simple pieces. We call that retrosynthesis."

Cernak and his team traced the synthetic sequences of 12 drugs currently under investigation for treating COVID-19. Those drugs include bromhexine, camostat, cobicistat, darunavir, favipiravir, galidesivir, nelfinavir, ritonavir, umifenovir, ribavirin, remdesivir and baricitinib.

The team used crowd-sourcing to survey the vast amount of published and patented synthetic routes to build the 12 drugs. Then, the researchers encoded these known routes into the AI software, and asked it to come up with new recipes.

This approach allowed the researchers to navigate around the starting materials that are already in the supply chain of the medicinal target compounds. Each search typically returned multiple proposals, which the researchers then winnowed down according to the overall economics of the starting materials and the overall sequence.

"The route we have found for some of these potential therapeutics might be longer than what's out there, but in most cases, such as umfenovir, we're actually finding routes that are shorter and starting materials that are cheaper than what's currently available," Cernak said. "We found a way to make the therapeutic bromhexine in one-step, which we are pretty stoked on."

Provided by University of Michigan