

# Compounds kill *C. diff*, don't affect other gut bacteria in vitro

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*C. diff*. Credit: Renee Fox

NC State researchers developed a drug-testing pipeline to help identify compounds that worked against the three stages of *Clostridium difficile* infection, and found that a compound that holds promise for treating antibiotic-resistant bacteria may also be able to control *C. difficile* infections by killing the harmful bacteria without affecting other bacteria in the gut.

*Clostridium difficile*, or *C. diff*, is a bacterium that can cause painful and sometimes fatal infections: it is responsible for over 450,000 infections and 29,000 deaths annually in the United States. *C. diff* exists in the environment as a dormant spore. In a healthy gut other microbes within the gut keep *C. diff* in check. However, when the [gut microbiota](#) fail to keep *C. diff* in check; for example, when someone has taken antibiotics that kill off the "good" gut [bacteria](#), the spores germinate, grow and produce toxins that damage the large intestine.

"The Catch-22 of *C. diff* is that the antibiotics that treat it exacerbate the problem by also eliminating bacteria that keep *C. diff* from growing," says Casey Theriot, an assistant professor of infectious

disease at NC State. "So when we look for compounds that can be effective against *C. diff*, we have to look at a number of factors, including the compound's effect on the rest of gut microbiota."

Theriot and her team, led by Rajani Thanissery, created a small molecule pipeline that addressed those factors to help researchers identify compounds that could be used against *C. diff*. The pipeline tested compounds against three different stages of the *C. diff* life cycle: growth, [toxin](#) production and sporulation, as well as against other gut bacteria. The goal was to screen and select compounds that could inhibit one or all of the steps in the *C. diff* life cycle.

One of the small molecules she tested – 2-aminoimidazole (2-AI) – gave her some surprising results. 2-AI was developed by former NC State professors John Cavanagh and Christian Melander. The compound, derived from sea sponges, is effective against [antibiotic-resistant bacteria](#) like MRSA. It works on these bacteria primarily by suppressing their ability to form biofilms or produce toxins, rather than killing the bacteria outright.

Thanissery screened eleven 2-AI molecules (compounds 1 through 11), provided by Daina Zeng and Raul Doyle at Agile Sciences, against *C. diff* in vitro. The molecules she screened were selected for their ability to inhibit *C. diff* growth, toxin activity and sporulation. Three molecules ([compounds](#) 1, 2, and 3) eliminated *C. diff*, but did not affect other bacteria. Compounds 4, 7, 9, and 11 inhibited toxin activity without affecting the growth of *C. diff* strains or the other microbiota.

"The results were both encouraging and surprising – we weren't expecting the molecules to kill *C. diff*, since they primarily inhibit virulence factors," Theriot says. "Our next steps will be to look more closely at the mechanisms by which 2-AI inhibits toxin activity."

"We were also pleased that our testing pipeline was able to successfully identify [molecules](#) that demonstrated activity against different aspects of C. diff infection. Hopefully other researchers can use our pipeline to screen future therapeutics in the lab before moving into preclinical animal models."

The research appears in *Frontiers in Microbiology*.

**More information:** Rajani Thanissery et al. A Small Molecule-Screening Pipeline to Evaluate the Therapeutic Potential of 2-Aminoimidazole Molecules Against Clostridium difficile, *Frontiers in Microbiology* (2018). DOI: [10.3389/fmicb.2018.01206](https://doi.org/10.3389/fmicb.2018.01206)

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