A comprehensive derivative synthesis method for development of new antimicrobial drugs

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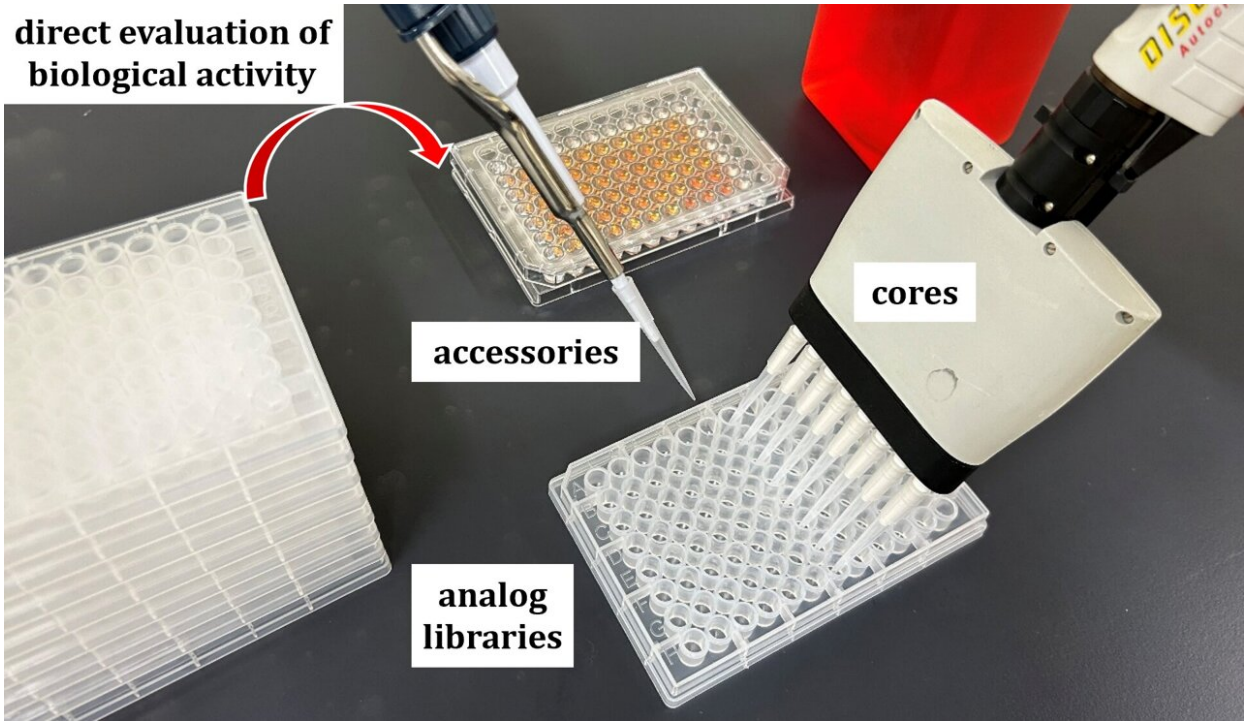

Preparation of the MraY inhibitor analog library. (Photo: Kazuki Yamamoto). Credit: Kazuki Yamamoto

Efforts to combat the increasing threat of drug-resistant bacteria are being assisted by a new approach for streamlining the search for antimicrobial drug candidates, pioneered by researchers at Hokkaido University, led by Assistant Professor Kazuki Yamamoto and Professor

Satoshi Ichikawa of the Faculty of Pharmaceutical Sciences.

Their methods, developed together with researchers elsewhere in Japan and in the U.S., are discussed in an article in the journal *Nature Communications*.

Antimicrobial resistance (AMR) in bacteria poses a major and ever-increasing challenge to health care worldwide, leaving clinicians struggling to treat a wide range of serious and potentially fatal infections.

One promising target for new drugs against a variety of AMR bacteria is an enzyme embedded in bacterial cell membranes called phospho-N-acetylmuramoyl-pentapeptide-transferase (MraY). This enzyme catalyzes formation of a specific lipid molecule, called lipid I, that is essential for bacteria to survive. Several inhibitors of MraY activity are already known, but improved versions are urgently required.

"In this study, we used four known classes of MraY inhibitors that are used as antibiotics," explains Yamamoto. "We developed a drug discovery platform (in situ build-up library method) that combines a comprehensive synthesis method for natural product derivatives and direct biological activity evaluation."

The team split known inhibitors into MraY binding regions (cores) and activity modulating regions (accessories). From seven cores and 98 accessories, they generated a library of 686 MraY inhibitor analogs. These analogs were tested against MraY, and eight analogs possessing strong MraY inhibitory and antibacterial activity were identified.

"After splitting the natural products, we attached aldehyde groups to the cores and hydrazine groups to the accessories. These groups react with each other to produce a hydrazone bond—allowing us to create the analog library in a straightforward manner," Yamamoto elaborates.

The eight analogs were resynthesized in stable forms and their effectiveness was verified. Analog 2 had the highest effectiveness against drug-resistant strains followed by analogs 3 and 6. Additionally, analog 2 was effective in mouse infection models—a very promising feature, as demonstrating efficacy in live animals is a key step towards developing successful new drugs.

Early indications also suggest the candidate drugs currently identified have low toxicity against cells other than the targeted bacteria, raising hopes that they could lead to a range of antimicrobials that could safely be used in patients.

"We have also demonstrated the wider potential of our drug discovery approach by applying it to identifying useful activity in the tubulin-binding natural products epothilone B, paclitaxel, and vinblastine (anti-cancer drugs)," adds Ichikawa. "We were able to construct a library of 588 analogs within just one month."

By showing that their method can be applied to other classes of medication, the researchers have opened a significantly more general new avenue in drug development.

More information: Kazuki Yamamoto et al, Development of a natural product optimization strategy for inhibitors against MraY, a promising antibacterial target, *Nature Communications* (2024). DOI: 10.1038/s41467-024-49484-7

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https://phys.org/news/2024-07-comprehensive-derivative-synthesis-method-antimicrobial.html