Researchers cook up new recipe for pretzel-shaped peptides

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Dr Christoph Nitsche. Credit: Australian National University

Researchers from The Australian National University (ANU) have developed a new way to synthesize bicyclic peptides, with major implications for future research into drug treatments for a range of diseases including cancer, viruses and bacterial infections.

Bicyclic peptides are pretzel-shaped chains made of amino acid building

blocks. This pretzel shape allows them to attach to specific proteins, similar to antibodies, giving them immense potential for use in targeted pharmaceutical treatments.

However, a major roadblock in the development of pharmaceuticals from bicyclic peptides is looping them and getting them to bond in just the right locations to form the desired pretzel shape.

Led by Dr. Christoph Nitsche at the ANU, the new method developed by the team of researchers has overcome this challenge.

"Unlike previous methods, we have been able to take a natural peptide sequence and add the three amino acid building blocks on the peptide where we want the bonds to form in water, meaning we can now control the final product," said Dr. Nitsche.

Even more promising for future pharmaceutical research, the method developed by Dr. Nitsche's team can be automated, which he believes will "substantially increase" the accessibility of bicyclic peptides for researchers.

"Nowadays, we can make peptides using automated synthesizers. Our method can be programmed into these synthesizers to make bicyclic peptides, meaning biomedical researchers who have access to these machines, but who don't have access to highly sophisticated chemistry set-ups can now synthesize bicyclic peptides very easily," Dr. Nitsche said.

"This means more groups will be able to investigate the potential uses of bicyclic peptides for pharmaceutical treatments, meaning more treatments can be developed."

While Dr. Nitsche is careful to stress this new method contributes to the

early stages of research into the role of bicyclic peptides in pharmaceutical treatments, the team is already demonstrating potential applications.

"To showcase our method, we made a bicyclic peptide which can inhibit an enzyme of the Zika virus. This peptide isn't a drug, but it does show us the potential of this technology," he said.

"Bicyclic peptides can be engineered to bind to any protein, so theoretically, this method could be used to make any kind of drug, including cancer treatments, antimicrobial and antiviral medications to treat COVID-19 and other common diseases."

Significant barriers to the development of bicyclic peptide pharmaceuticals still need to be overcome. For example, bicyclic peptides aren't very good at crossing cell membranes, though Dr. Nitsche and his team have already begun to tackle this problem.

For now, Dr. Nitsche is excited that bicyclic peptide synthesis has become more reliable and more accessible.

"Bicyclic peptides are considered next-generation therapeutics, and our method means more researchers will be able to contribute to this field of pharmaceutical development."

The research is published in *Angewandte Chemie International Edition*.

More information: Sven Ullrich et al, Biocompatible and Selective Generation of Bicyclic Peptides, *Angewandte Chemie International Edition* (2022). DOI: 10.1002/anie.202208400

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