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Scientists unlock a massive new ‘color palette’ for biomedical research by synthesizing non-natural amino acids

Ozempic has been making headlines for its remarkable success in treating obesity and diabetes. Yet it is just one in a rapidly growing class of drugs called peptide therapeutics that sits between small molecules (like aspirin) and biologics (like antibodies).

A UC Santa Barbara research team has developed a technique for efficiently synthesizing non-natural amino acids and applying them to peptide construction. They hope that the methodology, published in the Journal of the American Chemical Society, will significantly advance peptide research, giving scientists greater access to amino acids beyond the 22 found in nature.

“The key advantage is that these amino acids come out of the process already in a form that can be used directly to make peptides, without extra modification steps,” said first author Phil Kohnke, a doctoral student in senior author Liming Zhang’s lab in the Department of Chemistry & Biochemistry. “Compared to existing approaches, this is one of the most straightforward and broadly useful methods reported so far.”

The machinery of life

Amino acids are the building blocks of proteins, making them among the most fundamental biological molecules. Linking together 10 to 50 amino acids produces a peptide. While proteins are longer, more complex and may consist of multiple peptides.

Similar to stacking cups, these building blocks fit together in only one orientation: The amino group of one always links to the carboxylic acid group of another. And just like making color patterns in the stack of cups, the order of amino acids is a defining characteristic of peptides and proteins.

Although there are hundreds of types of amino acids, only 22 are naturally used by lifeforms to build proteins. These include 20 canonical flavors that are coded for in our DNA, and two that are produced by other mechanisms. “Nature uses these to great effect,” said Zhang.

Scientists can already produce natural amino acids cheaply. “But we have developed an efficient chemical synthesis for making non-natural or noncanonical amino acids in a way that they can be used directly for peptide synthesis,” Zhang said.

A two-step technique

The recently published paper details a new technique for synthesizing amino acids and then binding them together into peptides using a resin scaffold. The team uses gold catalysis to create amino acids from cheap, readily available chemical ingredients. The technique is highly stereoselective, meaning that it can produce amino acids with a specific handedness instead of an undesired mixture of right-handed and left-handed ones.

Getting amino acids to link together requires exposing and priming the reactive sites. This fact is an asset to chemists, because it enables them to connect the molecules in the proper sequence for the peptide they intend to make. Current synthetic techniques require removing the constituent that shields the amino group as well as activating the acid group during peptide synthesis. However, their method produces amino acids where the acid group is already primed to react; only the

amino group requires unmasking.

Similar to the Zhang lab's recent work on oligosaccharides, the team used a resin scaffold to assemble peptides from the amino acids. The framework attaches to one side of the growing peptide, enabling them to add amino acids one by one to the molecule in a rinse-and-repeat process. “We basically attach things to resin and then just grow the chain,” he said.

This technique is popular in industry because it greatly simplifies the purification process. Rather than go through the tedious effort of purifying the peptides from a solution, the molecules can be cleaved from the scaffold and washed off. “Our method can be ported into this process with very little friction or accommodation,” Kohnke added.

Expanding availability and opening opportunities

Having access to more amino acids opens up entirely new possibilities for biochemists, medical researchers and materials scientists. It’s like swapping out a 22-color box of crayons for a palate of 500 different hues.

But making non-natural amino acids is often difficult, expensive or impractical. “Many existing methods either involve many time-consuming steps, only work for a narrow set of molecules, or require further manipulations before ready for peptide synthesis,” Kohnke said. The new technique mostly solves these problems, easily and cheaply producing amino acids that are immediately useful for peptides synthesis.

Zhang is particularly interested in developing new peptide therapeutics. Peptides have found use in over 80 drugs worldwide since insulin was first synthesized in the 1920s, which changed type 1 diabetes from a death sentence to an entirely manageable condition.

While natural peptides are effective, they are fragile — enzymes in the body can destroy them quickly. “By incorporating non-natural amino acids, drug designers can ‘armor-plate’ the peptide against enzymes or force it into a specific shape to lock onto a receptor better,” Zhang explained. Ozempic itself is one particular success of this approach, containing one non-natural amino acid, in addition to a fatty acid side

chain.

The Zhang lab is currently working to automate the process. Realizing the full potential of non-natural amino acids will require making them readily available to non-chemists. On that note, they are actively looking to collaborate with other research teams in making the technique more accessible to drug development and materials research.

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Health and Medicine

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