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New catalysis method can generate a library of novel molecules for drug discovery

Using reprogrammed biocatalysts, researchers are pushing the boundaries of enzymatic synthesis with a method that opens the door to a diverse array of valuable compounds. Reporting in the journal Science, UC Santa Barbara chemistry professor Yang Yang and collaborators detail an enzymatic multicomponent reaction, resulting in six distinct molecular scaffolds, many of which were not previously accessible by other chemical or biological methods.

"The ability to generate novelty and molecular diversity is particularly important to medicinal chemistry," Yang said. "For a long time, biocatalysis was considered as a field of relevance mainly to the large-scale production of valuable specialty chemicals. Our work suggests that new biocatalytic methods can now find applications in discovery chemistry, through accelerated combinatorial synthesis of novel molecules."

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Diversity-oriented synthesis

Diversity-oriented synthesis focuses on developing a structurally diverse library of molecules that can be screened for beneficial biological and chemical properties. In contrast to traditional, target-oriented synthesis that concentrates on a few specific targets, this method prepares an array of potential options that increase the chances of finding novel bioactive compounds and molecules that can effectively interact with biological targets or probe biological processes.

Underpinning these biologically active compounds is the carbon-carbon bond, the backbone of all organic chemistry, holding together biomolecules like proteins and DNA. Understanding how and where to make or break these bonds can yield powerful, novel molecules and compounds.

There are a number of ways to facilitate reactions that create carbon bond-based structures. Yang's UCSB team, with counterparts in University of Pittsburgh computational organic chemistry professor Peng Liu's research group, propose a combinatorial process that uses enzymes and sunlight-harvesting catalysts to produce novel molecular scaffolds with rich and well-defined stereochemistry, or 3D shapes.

“Enzymes are nature's privileged catalysts,” Yang said. Having evolved alongside their substrates over vast timescales, enzymes are generally powerful, efficient and specific with the molecules they work upon. However, these natural catalysts work on only a select number of substrates under certain conditions. Synthetic catalysts, meanwhile, can be broad and diverse, and function under a wide range of conditions but are not as efficient and as selective as enzymes.

The method seeks to leverage the best of both worlds: the efficiency and selectivity of enzymes with the versatility of synthetic catalysts. In a process of concerted chemical reactions, the photocatalytic reaction generates reactive species that participate in the larger enzymatic catalysis cycle to ultimately produce six novel products via carbon-carbon bond formation with outstanding enzymatic control.

“Through enzyme-photocatalyst cooperativity, using a radical mechanism, we developed novel multicomponent biocatalytic reactions which were both unknown in chemistry and biology,” Yang said. “These enzymes are surprisingly general and can function on a wide range of substrates. This allowed us to carry out one of the most complex multicomponent enzymatic reactions my team has developed.”

Research in this project was also conducted by Chen Zhang, Jun Zhou and Silvia M. Rivera at UCSB; Pei-Pei Xie and Turki M. Alturaifi at the University of Pittsburgh; and collaborators James Finnegan and Simon Charnock at Prozimix Ltd. in the UK.

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