New chemistry approach promises less expensive drugs

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With a newly discovered method of assembling organic molecules, a team of Princeton University chemists may have found a way to sidestep many of the expensive and hazardous barriers that stand in the way of drug development.

The new approach allows scientists to synthesize molecules without employing toxic catalysts, and it also does not generate alternate versions of drug molecules that can damage the body, two perennial issues that plague the manufacturing process. David MacMillan, one of the researchers on the team, said the discovery is important not only for its industrial applications, but also because of the new research possibilities it opens up.

"This is a new type of chemistry that could expand the way people think about making biologically active molecules," said MacMillan, who holds Princeton's A. Barton Hepburn Chair of Chemistry and directs the chemistry department's Merck Center for Catalysis. "We've found more than a new chemical reaction. It's a common mode of molecule activation that allows a whole group of reactions to take place."

Broadly stated, the discovery will open up new possibilities for working with ketones and aldehydes, two chemical groups that are found on a large percentage of the substances in which organic chemists are interested. "They form a big region of the reaction landscape," MacMillan said.

The paper, which MacMillan cowrote with first author Teresa Beeson, Anthony Mastracchio, Jun-Bae Hong and Kate Ashton, all members of his research group, appears in the March 29 issue of the journal *Science*. John Schwab, a chemist at the National Institutes of Health (NIH), applauded the work for the new possibilities it could provide.

"One sometimes hears that organic chemistry is a mature field, but MacMillan's work shows that there still are rich veins waiting to be mined," said Schwab, also a program director at the NIH's National Institute of General Medical Sciences, which supported the work. "What's particularly exciting to me is the depth and rigor of the analysis that enabled this very creative breakthrough. Equally important, MacMillan has discovered new reactions that will streamline the synthesis of compounds that are relevant to human health."

Most drug molecules that pharmaceutical companies produce can exist in two different forms, which are mirror images of one another. Though both forms of an organic molecule -- known in the chemistry world as "enantiomers" -- have the same chemical formula, their effect on the body can differ dramatically.

"The two enantiomers are like keys with the same number of teeth, but which have different orientation," MacMillan said. "One key fits in with our biology very well, opening the correct doors in our body and helping us to heal. But the other key doesn't fit the same doors because its teeth are in opposing locations."

The two forms are indistinguishable by most modern lab tests, yet our bodies can tell the difference. Where one enantiomer might be the basis for a helpful drug, its mirror image might do nothing for the body, or even damage it.

"This was the problem in the 1960s with the drug phthalidomide,"

MacMillan said. "One of its enantiomers helped pregnant women overcome morning sickness. Its mirror image, however, caused birth defects."

In the vast majority of cases, the Food and Drug Administration now requires that drug companies create only the beneficial enantiomer during the manufacturing process. While this requirement keeps any of these helpful molecules' "evil twins" from reaching our systems, it also places heavy demands on the drug companies.

Building large quantities of a drug molecule often requires a catalyst, a substance that permits a chemical reaction to take place without itself being affected. Until recently, however most catalysts would create both enantiomers simultaneously, MacMillan said. In cases where the catalyst can create only the helpful enantiomer -- a process called asymmetric catalysis -- they are often expensive, capricious and difficult to work with.

"That is one reason why for several years our lab has been looking for catalysts based on organic molecules rather than metals," MacMillan said. "Organic catalysts are generally inexpensive, robust to water and air and environmentally friendly. Organic catalysts, it turns out, are proving more capable than most people expected."

Since the year 2000, MacMillan's work has enabled the discovery of a new family of organic catalysts, which can be used to produce only beneficial enantiomers. These catalysts have proven desirable because they are based on organic substances, and are therefore not harmful either to patients or to the environment. But his team's latest paper does more than offer chemists a new set of organic catalysts with which to work.

"This discovery does not yield merely more organic catalysts, but makes

a whole new type of chemical reactions available to us," MacMillan said. "It's almost like a new airport hub that allows you to extend the range of your air travel. You can reach destinations that were not open to you before."

Gregory Fu of the Massachusetts Institute of Technology said that these destinations would likely prove important to the pharmaceutical industry.

"This work adds an important new dimension to efforts to achieve asymmetric catalysis," said Fu, a professor of chemistry. "It will no doubt have a substantial impact on the discovery of new bioactive compounds for the benefit of society."

MacMillan said he hopes the findings would eventually make drugs both more useful and widely available.

"The big payoff here is that the discovery will allow new chemical reactions to be developed that are powerful yet unprecedented in the field of chemistry," MacMillan said. "They will allow access to single enantiomers, and they will do it using cheap, environmentally friendly small organic molecules as catalysts. It's a double whammy."

Source: Princeton University