# New powerful toolkit accelerates creation of potential new drugs

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Yuta Fujiwara (left) and Fionn O'Hara, research associates in the laboratory of Scripps Research Institute Professor Phil Baran, were among the lead authors of the new *Nature* paper. Credit: Photo courtesy of The Scripps Research Institute.

Scientists at The Scripps Research Institute (TSRI) have invented a set of chemical tools that is radically simplifying the creation of potential new drug compounds.

Pharmaceutical chemists frequently seek to generate dozens or even hundreds of variations of a given compound to see which works best. The new toolkit—described in the November 28, 2012 issue of the journal *Nature*—makes this process easier and cheaper, enabling

previously time- and cost-prohibitive chemical modifications. This fundamental innovation is already being adopted by drug companies and is expected to speed the development of new compounds in other industries as well.

"Feedback from companies that have started to use this toolkit indicates that it solves a real problem for them by boosting their chemists' productivity and by expanding the realm of compounds that they can feasibly generate," said Phil S. Baran, PhD, a professor in the Department of Chemistry and a member of the Skaggs Institute for Chemical Biology at TSRI who led the work.

Robert Lees, PhD, of the National Institutes of Health's National Institute of General Medical Sciences, which partially funded the work, added, "Methods to predictably, selectively and efficiently functionalize a given C-H site are difficult to invent but highly significant for developing new therapeutic and diagnostic agents, and studying biomolecules. Practical chemistry for introducing fluorine atoms into organic compounds is also an important current need in medicinal chemistry. The new reagents developed by Professor Baran address both goals, and they will likely be widely utilized in both academic and industrial laboratories."

## A Common and Useful Structure

The toolkit is a set of newly invented chemicals and methods for attaching functional groups of molecules to a series of common chemical structures known as nitrogen-containing heterocycles—flat molecules with rings made of carbon atoms and at least one nitrogen atom. Though their name might seem esoteric, these structures are common in both natural and synthetic chemicals, and they are found in most drugs that are taken in pill form.

"Ironically, the properties that make nitrogen-containing structures so useful in medicines are what also make them so hard to modify," said Baran. The resistance of nitrogen heterocycles to modification by traditional techniques has slowed drug discovery and has put many potential modifications out of reach.

But Baran envisioned a different scenario. "The ideal for discovery chemists would be a method that works in water, in an open flask, with procedures that are simple enough to be automated," he said.

A few years ago Baran began to glimpse the possibility of achieving such a method. His lab had just succeeded in synthesizing a complex natural nitrogen heterocycle, palau'amine, a toxin made by sea sponges in the Western Pacific that has shown anticancer, antibacterial and antifungal pharmaceutical promise. "As we developed an understanding of how that compound reacts, we recognized that it might help us solve this larger problem that discovery chemists face," he said.

The nitrogen atoms in heterocycles are what make them so tricky to handle. Traditional methods of modification typically aim to block their influence before the addition of any modifying molecules, but this approach can be cumbersome and expensive. The experience with palau'amine, which features an extremely challenging nine nitrogen atoms per molecule, led Baran and his team to try to find chemical reagents—tools, in effect—that would modify heterocycles directly.

## A More Direct Route

Direct methods already had existed, but they often require extreme temperatures as well as expensive and hazardous reagents. During 2010 and 2011, Baran's lab experimented with several comparatively safe chemical reagents that can work in mild conditions to make commonly desired heterocycle modifications, such as the addition of a

difluoromethyl group. One of these new reagents, a zinc dialkylsulfinate salt (DFMS) designed to transfer the difluoromethyl group, turned out to work particularly well. "We quickly realized that we might be able to make related zinc sulfinate salts that would attach other functional groups to heterocycles," Baran said.

In the new report in *Nature*, Baran and his colleagues describe an initial toolkit consisting of ten of these zinc-based salts, each of which attaches a different functional group to a heterocycle framework. "We selected these groups because they are commonly used by medicinal chemists," said Fionn O'Hara, PhD, a postdoctoral researcher in the Baran laboratory who was a first author of the new report with postdoctoral researcher Yuta Fujiwara, PhD, and technician Janice A. Dixon.

"In many cases, chemists will be able to use these reagents sequentially to make more than one modification to a starting compound," noted Fujiwara. The groups that can be attached with the new reagents include trifluoromethyl, difluoromethyl, trifluoroethyl, monofluoromethyl, isopropyl and triethylene glycol monomethyl ether.

To demonstrate the ability of the reagents to work in biological media, Baran's team used them to difluoromethylate or trifluoromethylate heterocycles in a solution of cell lysate—the contents of cells—as well as to serve as a buffer medium, Tris, commonly used in lab-dish tests. To underscore the general robustness of the reagents, the team even carried out such modifications in a paper cup containing Oolong tea.

Baran's laboratory collaborated in the research with scientists from the pharmaceutical company Pfizer Inc. "They provided insight into the types of compounds that would be valuable, assistance with optimization, and, most importantly, testing of the chemistry in their drug discovery laboratories, where it is meant to be used," Baran said.

The first of the zinc sulfinate salts, DFMS, now also known as Baran difluoromethylation reagent, is already being manufactured in bulk and marketed by chemical suppliers, including Sigma-Aldrich Corporation. "There has been a lot of demand for that product from the first day we listed it, which is very rare," said Troy Ryba, manager of academic chemistry strategy at the firm Sigma-Aldrich.

Baran currently is working to expand his lab's initial toolkit to provide more heterocycle-modifying choices to chemists in the pharmaceutical industry and beyond. "We have a whole slew of new reagents in the pipeline," he said.

**More information:** Practical, innate C-H functionalization of heterocycles" *Nature*, 2012.

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