Scientists find easier way to make new drug compounds

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Scientists at The Scripps Research Institute have developed a powerful new technique for manipulating the building-block molecules of organic chemistry. The technique enables chemists to add new functional molecules to previously hard-to-reach positions on existing compounds—making it easier for them to generate new drugs and other organic chemicals.

"This is a basic tool for making novel chemical compounds, and it should have a wide range of applications," said Jin-Quan Yu, PhD, a professor at Scripps Research and senior author of the new report, published in the June 28, 2012 issue of the journal *Nature*. The co-lead authors are Dasheng Leow, PhD, a former Yu lab member who is now a researcher at the A*Star Institute of Bioengineering and Nanotechnology in Singapore, and Gang Li, PhD, a postdoctoral fellow in the Yu laboratory.

"Controlled selectivity and reaction efficiency are important goals in synthetic chemistry methods for discovering and manufacturing therapeutic and diagnostic agents," said Robert Lees, PhD, who oversees chemical synthesis grants at the National Institutes of Health's National Institute of General Medical Sciences, which partially supported the work. "Professor Yu's work is an exciting example of progress toward those goals, and his novel methods are likely to find broad utility in pharmaceutical research."

The new advance is a method for "CH activation"—chemists' code for

the removal of a simple hydrogen atom from the carbon backbone of an organic molecule, and the replacement of that hydrogen atom with a functional chemical group. Compared to the traditional method, in which chemists modify only the existing functional groups on a compound, CH activation more directly boosts the complexity of a compound, giving it potentially valuable new properties.

Overcoming Technical Obstacles

Over the past decade, Yu has helped to pioneer the development of versatile CH-activation techniques. But the use of these techniques has been limited by important technical obstacles. For example, some strategies employ a specially designed molecule that contains the bond-cracking metal palladium; it can attach to an existing functional group on a chemical at an angle that puts the palladium in position to sever a particular CH bond nearby—enabling the attachment of a new functional group at that site. So far, such activation techniques have been useful only against CH bonds that are close to a functional group and that occupy the most accessible relative position (the ortho position) on an aromatic hydrocarbon's carbon-ring backbone.

"But what if a CH bond is in the middle of a desert, so to speak—far from the nearest functional group?" said Yu. "And what if it is also on the hard-to-access meta position, facing away from the nearest functional group in terms of geometry? How do you reach out so far and then around, to cut it?"

In the new study, Yu and his team showed just how to do this with a chemical structure that can deliver bond-breaking palladium to a relatively remote CH site, more than a dozen bonds distant from the nearest functional group. The lengthy, modifiable structure includes a nitrile (a carbon-nitrogen group) and has a flexibility that allows it to act like a crane swinging a wrecking ball. "It brings the palladium out and

around to the CH bond at the meta position, and it has the right length and angle so that it will not touch any other positions," said Li.

"It overwhelms the intrinsic preference for other usually more reactive and accessible CH bonds," said Leow.

'Just a Small Sample of the Possibilities'

The team used the technique to quickly modify a variety of compounds, including the amino acid phenylalanine and the neurotransmitter-mimicking drug baclofen. "These are from compound classes that chemists use routinely to synthesize new candidate drugs and other useful chemicals," Yu said. "And they represent just a small sample of the possibilities; we think that we can apply our technique to many compound classes and functional groups."

Yu has now established a collaboration with the pharma giant Bristol Myers Squibb to exploit the new technique in drug development and manufacturing. "The new method will certainly be adopted by pharmaceutical chemists, but I expect that polymer chemists, materials chemists, and others will find it useful too," he said.

More information: "Activation of Remote meta-C–H Bonds Assisted by an 'End-on' Template," *Nature*.

Provided by Scripps Research Institute