Scientists find easier, cheaper way to make a sought-after chemical modification to drugs

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Scientists at The Scripps Research Institute have devised a much easier technique for performing a chemical modification used widely in the synthesis of drugs and other products.

Known as "trifluoromethylation," the modification adds a CF3 molecule to the original compound, often making it more stable—and, for a drug, keeping it in the body longer. With the new technique, chemists can perform this feat using a relatively simple, safe, room-temperature procedure and can even select the site of the modification on the target compound.

"I've been presenting this methodology at several pharma companies, and there's a lot of interest—so much so that their chemists are starting to use it," said Scripps Research Professor Phil S. Baran, senior author of the new study, scheduled for publication the week of August 15, 2011, in an advance online edition of the *Proceedings of the National Academy of Sciences.*

Standard procedures for trifluoromethylation involve gases and associated hardware, high heat, metal catalysts, and oxidants. "The procedures are often prohibitively complicated, and medicinal chemists often don't have the time or the resources to get into it," said Baran.

Inspired by frequent consulting visits to pharmaceutical companies, Baran and his lab began to look for simpler ways to perform trifluoromethylation. After running more than 500 different reaction

setups on a test compound, they found just one that delivered significant quantities of the desired reaction product. It was a simple setup that used a reagent known as sodium trifluoromethanesulfinate, an inexpensive chemical that is stable at room temperature.

Chemists had long believed that this reagent was unsuitable for trifluoromethylating a broad class of molecules frequently found in drug compounds, and also that the reagent required the use of catalyzing metal salts. But in this initial screening, the reagent, known as Langlois's reagent for its discoverer, the French chemist Bernard R. Langlois, seemed to work even without such constraints.

Baran and his team began collaborating with fellow Scripps Research chemistry Professor Donna Blackmond and members of her laboratory to study how Langlois's reagent works and to optimize its use, including the selection of trifluoromethylation sites on target compounds using certain solvents. With the optimized technique, they showed that they could directly and easily trifluoromethylate a variety of test compounds, including the natural malaria drug quinine and the synthetic anti-smoking drug varenicline (Chantix).

"The collaboration with Donna Blackmond and her lab was crucial in enabling us to improve the procedure and to understand why certain modifications led to those improvements," said Baran.

The new technique in principle makes it more feasible for pharmaceutical companies to modify and improve specific drug compounds of interest. It also means that these companies can expand the existing compound libraries they use for drug-discovery screening by making trifluoromethylated versions of these compounds quickly and easily.

"In one instance, a chemist at Pfizer told me that the trifluoromethylated

compound we made in one step with our technique would have taken at least eight steps using standard techniques," said Baran.

The Baran and Blackmond labs are now working on new reagents that may be used in this reaction and ways to enable fine control of trifluoromethylation sites. "The interplay of the two labs at the nexus of synthesis and mechanistic analysis is driving this project forward in new and exciting directions," Baran said.

More information: "Innate C-H Trifluoromethylation of Heterocycles," *Proceedings of the National Academy of Sciences.*

Provided by The Scripps Research Institute