Scientists break barrier to creating potential therapeutic molecules

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Scientists from The Scripps Research Institute have created a novel technique that for the first time will allow the efficient production of a molecular structure that is common to a vast array of natural molecules. This advance provides a means to explore the potential of this molecular substructure in the search for new therapies.

The study was published on May 23, 2010 in an advance online edition of the journal *Nature Chemistry*.

The structures in question, called "skipped polyenes," are shared by a large class of molecules that play a critical role in human health, including polyunsaturated fatty acids, which are vital to blood pressure regulation, inflammation, and immune response. The structures are also shared by a number of potent antibiotic, antifungal, and cytotoxic (toxic to living cells) compounds.

Simple and efficient methods for the preparation of skipped polyenes have generally been lacking, creating a significant barrier to exploring their potential as drugs. Currently, the production of molecules that contain simple variants of this substructure is quite labor intensive.

"Our study identifies a novel chemical reaction that will enable the accelerated production of this type of structural motif," said Associate Professor Glenn Micalizio, who authored the new study with a member of his Scripps Florida lab, Research Associate Todd K. Macklin. "This new reaction provides a means to explore the medicinal potential of

molecules bearing complex skipped polyenes - something that we simply haven't been able to do until now."

Chemical Short Cuts

In essence, the new chemical method provides a means to replace long, step-by-step sequences of reactions that would have otherwise been required to prepare skipped polyenes. The new chemical process defines a fundamentally novel pathway (a new carbon-carbon bond forming process) to these complex structures that proceeds in just a fraction of the number of chemical steps previously required.

As such, the new method not only saves time, but greatly increases efficiency for the production of molecules that house the skipped polyene core. In chemistry, each of the steps (or reactions) used to prepare a complex structure typically proceeds with less than 100 percent efficiency, notes Micalizio—maybe 80 to 90 percent of the initial material can successfully be advanced to the next chemical step. As a result, the requirement of long sequences of reactions, where yields per step are compounded mathematically through the sequence, typically result in poor overall efficiency.

"If one can invent reactions that decrease the length of sequences required to prepare complex structures, great enhancements of efficiency can result," said Micalizio. "A central focus of our laboratory is designing new chemical reactions that do just that. Since 2005, we have been advancing a large class of chemical transformations that can be seen as 'chemical short cuts' - so that ultimately scientists can better explore the therapeutic potential of molecules inspired by the vast and diverse structures that we see in nature."

The new technique described in the *Nature Chemistry* paper proceeds by bond formation between two specific classes of molecules,

vinylcyclopropanes and alkynes (or vinylsilanes), using a metal-promoted cross-coupling reaction to assemble the key structural motif.

"That initial metal-promoted coupling leads to a very unstable intermediate molecule," Micalizio said. "Actually, the chemical intermediate spontaneously rearranges to stabilize the structure, through a process that establishes all of the complex architecture of the skipped polyene product."

The research for the paper, "Convergent and Stereospecific Synthesis of Complex Skipped Polyenes and Polyunsaturated Fatty Acids," was supported by the American Cancer Society, the Arnold and Mabel Beckman Foundation, Boehringer Ingelheim, Eli Lilly & Co., and the National Institutes of Health.

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