



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May 20, 2014

LEGO-Style Chemistry to Build Thousands of Small Molecule Drug Candidates

While making and improving medicines may never be child's play, chemists are always looking for simpler ways to build complex molecules. And chemists often succeed, especially when they emulate natural systems that accomplish biosynthesis via the iterative coupling of a few chemical building blocks. Already, chemists have devised generalized synthesis platforms that are analogous to biosynthetic systems for constructing polypeptides, oligonucleotides, and oligosaccharides. Most recently, chemists at the [University of Illinois](#) have emulated nature's building block chemistry to build polyenes, which number in the thousands, including many that have potential as drugs.

These scientists, led by Martin Burke, M.D., Ph.D., a professor of chemistry at the university and early career scientist at the [Howard Hughes Medical Institute](#), reported that the polyene motifs found in >75% of all known polyene natural products can be synthesized by means of a systematic building block technique. The scientists detailed their findings May 11 in *Nature Chemistry*, in an article entitled "Synthesis of most polyene natural product motifs using just 12 building blocks and one coupling reaction."

"Using the same general retrosynthetic algorithm and reaction conditions, this platform enabled both the synthesis of a wide range of polyene frameworks that covered all of this natural-product chemical space and the first total syntheses of the polyene natural products asnipyrone B, physarigin A, and neurosporaxanthin β -D-glucopyranoside," the authors wrote.

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"We want to understand how these molecules work, and synthesis is a very powerful engine to drive experiments that enable understanding," said Dr. Burke. "Once you have the pieces in a bottle, you can make naturally occurring molecules, or you can change the pieces slightly to make them better. Usually, that's such a herculean task that it slows down research. But if that part becomes on-demand, you can make anything you want, and it can powerfully accelerate the drug discovery process."

To demonstrate their findings, the researchers synthesized several compounds representing a wide variety of polyene molecules using only the dozen designated building blocks. Many of these building blocks are available commercially thanks to a partnership between Dr. Burke's group and Sigma-Aldrich.

Dr. Burke hopes that identifying the required building blocks and making them widely available will speed understanding of polyene natural products and their potential as pharmaceuticals, particularly compounds that until now have been left unexplored because they were too costly or time-consuming to make.

Burke's group hopes eventually to identify and manufacture a set of building blocks from which any researcher—trained chemist or not—can build any small molecule. "Now that we have this quantifiable result, that with only 12 building blocks we can make more than 75% of polyenes, we are committed to figuring out a global collection of building blocks—how to make them, how to put them together—to create a generalized approach for small molecule synthesis."

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