# Scientists develop new class of small molecules through innovative chemistry

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Inspired by natural products, scientists on the Florida campus of the Scripps Research Institute have created a new class of small molecules with the potential to serve as a rich foundation for drug discovery.

Combining the power of synthetic chemistry with some advanced screening technologies, the new approach could eventually expand by millions the number of provocative synthetic compounds available to explore as potential drug candidates. This approach overcomes substantial molecular limitations associated with state-of-the-art approaches in small molecule synthesis and screening, which often serve as the foundation of current drug discovery efforts.

The study, led by Scripps Research Associate Professor Glenn Micalizio, was published Nov. 20, 2011, in an advanced online edition of the journal *Nature Chemistry*.

To frame the significance of this advance, Micalizio explains that high-throughput screening is an important component of modern drug discovery. In high-throughput screening, diverse collections of molecules are evaluated en masse for potential function in a biological area of interest. In this process, success is critically dependent on the composition of the molecular collections under evaluation. Modern screening centers maintain a relatively static collection of molecules, the majority of which are commercially available materials that have structures unrelated to natural products -- molecules that are appreciated as validated leads for drug development.

"This divergence in structure between natural products and commercially available synthetics lies at the heart of our inquiry," said Micalizio. "Why should we limit discovery of therapeutic leads to compound collections that are influenced by concerns relating to commercial availability and compatibility with an artificial set of constraints associated with the structure of modern screening centers?"

To expand the compounds available for investigation, the scientists embraced an approach to structural diversity that mimics nature's engine for the discovery of molecules with biological function. This process, termed "oligomerization," is a modular means of assembling structures (akin to the way that letters are used in a sequence to provide words with meaning) where a small collection of monomeric units can deliver a vast collection of oligomeric products of varying length, structure, and function (like the diversity of words presented in a dictionary).

Coupling this technique with a synthetic design aimed at generating molecules that boast molecular features inspired by the structures of bioactive natural products (specifically, polyketide-derived natural products, which include erythromycin, FK-506, and epothilone), the scientists established a new chemical platform for the discovery of potential therapeutics.

Micalizio points out: "The importance of oligomerization to drive discovery is well appreciated in chemistry and biology, yet a means to realize this process as an entry to small molecule natural product-inspired structures has remained elusive. The crux of the problem is related to challenges associated with the control of shape for each member of a complex oligomer collection -- the central molecular feature that defines biological function."

"It is the stability associated with the shape of these new compounds that lies at the heart of the practical advance," he continued. "The unique

features of this science now make possible the ability to synthesize large collections of diverse natural product-inspired structures that have predictable and stable three-dimensional shapes."

Micalizio said that the science described represents a first step toward revolutionizing discovery at the interface of chemistry, biology, and medicine by embracing nature's strategy for molecular discovery. Coupling this type of advance with modern screening technology that can handle the evaluation of large compound collections at low cost (such as work by Scripps Florida Professor Thomas Kodadek, a co-author of the new study), can dramatically enhance the future of pharmaceutically relevant science.

The potential of this vision was highlighted in the new study, in which a 160,000-member compound collection was employed to discover the first non-covalent small molecule ligand to the DNA binding domain of p53 -- an important transcription factor that regulates a variety of genes involved in cell cycle control and cell death.

**More information:** "A Biomimetic Polyketide-Inspired Approach to Small-Molecule Ligand Discovery," *Nature Chemistry*.

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