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Chemical Tools from Biology-Oriented Synthesis

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DOI 10.1016/j.chembiol.2007.04.002

Leßmann et al. present a chiral natural-product-derived library of α,β-unsaturated δ-lactones obtained through stereoselective synthesis on a solid support [1]. Phenotypic screening of this compound collection provided new modulators of cell cycle progression and of viral cell entry with high hit rates.

In this issue of *Chemistry & Biology*, Waldmann and colleagues report on the discovery of new modulators of cell cycle progression and viral entry through cellular screening of a natural-product-derived compound library [1]. This library was built around a α,β-unsaturated δ-lactone scaffold, which is a frequently encountered structural motif in biologically active natural products (Figure 1). Screening was conducted using fluorescence-based cellular assays that scored for effects on the actin or microtubule cytoskeleton, or, in a second case, for inhibition of cellular entry of the vesicular stomatitis virus (VSV). Remarkably, several compounds with activities in the low μM concentration range could be identified in both assay systems, in spite of a library size of only 50 compounds. Compared to conventional HTS campaigns, this is a spectacular hit rate. Two of the compounds that scored positive in the cell cycle progression assay were subsequently demonstrated to inhibit tubulin polymerization in vitro, thus linking the activity observed at the cellular level to a specific molecular target (although other targets may still contribute to the overall cellular phenotype).

Based on this short factual summary, the paper would appear to describe what nowadays might be called a "typical" chemical biology project, namely the screening of a library of low-molecular-weight synthetic compounds in fluorescence-based, phenotypic cellular assays followed (sometimes) by the analysis of hit compounds in target-specific systems. However, the paper is not just a "typical" (yet important) manifestation of modern chemical biology research. It is particularly notable for the conceptual framework that forms the basis for library design and synthesis and for Waldmann's research in general [2, 3]. The dissection of the overall concept underlying Waldmann's approach to the identification of new tool compounds for chemical biology research and new lead structures for drug discovery reveals three essential ingredients (apart from the use of powerful screening technology), whose combination now has been demonstrated repeatedly to enable the efficient identification of potent and specific inhibitors of various biological targets [2, 3].

The first of these ingredients is the idea that natural products represent prevalidated lead structures for chemical biology and medicinal chemistry research, due to an inherent propensity for protein binding. In other words, natural products are good starting points for the discovery of ligands for virtually any protein, as they have evolved to do precisely this, bind to proteins, either during their own biosynthesis or through their involvement in the modulation of a vast array of

biological processes. Of course, this does not mean that just any natural product will bind to just any protein, and even if this is the case, the binding may often not be strong or specific enough to be practically useful. However, what it does mean is that the structures of natural products can guide the design of screening libraries with a higher potential for hit identification than simple random compound collections. In order to provide a systematic basis for the implementation of this concept, Waldmann and coworkers have elaborated a tree-like classification system for natural products, termed "SCONP" for *s*tructural *c*lassification *o*f *n*atural *p*roducts, which provides a collection of possible scaffolds for library design [2]. One of these scaffolds is a α,β-unsaturated δ-lactone ring and this is the core structure of the library investigated in the current report [1].

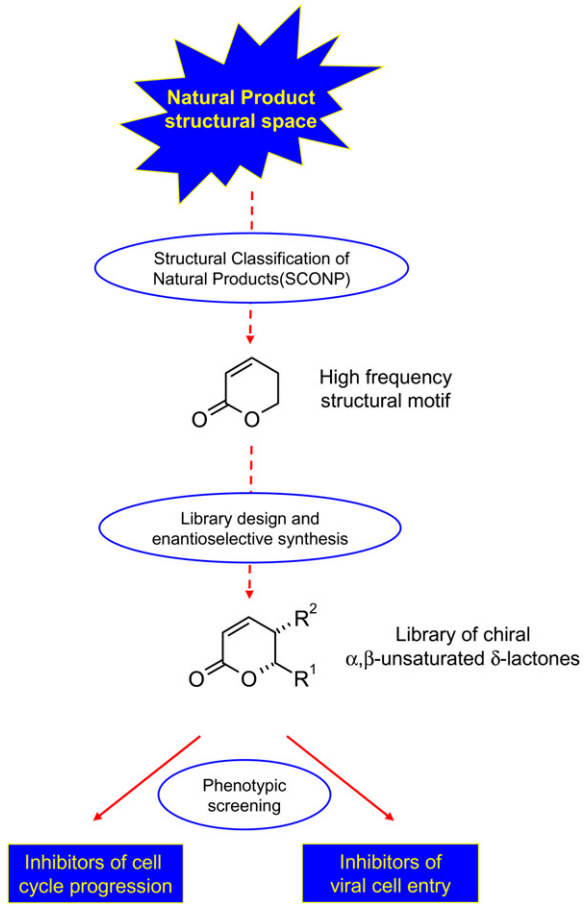

Figure 1. A Natural Product-Derived Structural Motif as Template for New Cell Cycle Modulators and Inhibitors of Viral Entry

The classification of overall natural product space leads to high-frequency structural motifs, such as α,β-unsaturated δ-lactones, which provided the core structure for the enantioselective solid-phase synthesis of a high-potential screening library. Phenotypic screening identified several hit compounds interfering either with cell cycle progression or viral cell entry. Two actives from the cell cycle progression screen were subsequently shown to be new inhibitors of tubulin polymerization.

The second essential element of Waldmann's approach to lead and tool compound identification is the idea that only a limited number of binding site topologies for small molecule ligands exists across all protein families, termed "ligand-sensing cores of protein domains (PSSC)" [4]. As a consequence, compounds binding to a given protein may be useful as starting points for ligand identification for another protein with similar ligand binding site topology. Waldmann and coworkers have clearly shown that the concept even holds for proteins with different overall structural features, i.e., similarities in the ligand sensing cores can exist independent of similarities in overall protein folding topology [5]. Although the screens discussed in Leßmann et al. [1] are not directed toward individual isolated targets, the concept of PSSC's was still an implicit part of the library design process. For example, α,β-unsaturated δ-lactone rings frequently occur in natural products that are phosphatase inhibitors, which are likely to play important roles in the regulation of cell cycle progression and viral entry. Thus, the current library indeed had a significant a priori potential to provide hits for the modulation of these cellular processes. The concept of developing new lead structures from existing ligands for other proteins is not entirely new, but before Waldmann's work these ideas were mostly limited to proteins from the same target family (e.g., kinases) [6, 7]. Most importantly, Waldmann's work on ligand binding site similarity together with the development of a natural product classification system for the first time has provided a systematic conceptual framework, which enables the rational design of natural-product-derived screening libraries with high hit potential.

The third essential ingredient in the mix is, of course, the synthesis of appropriate compound libraries. It is self-evident that Waldmann's approach requires the screening of "custom-made" structures and (for the most part) cannot rely on the use of commercially available libraries. In a most appropriate way, Waldmann refers to the synthesis of compound libraries based on the premises outlined above as "biology-oriented synthesis", i.e., synthesis that is guided by biology-derived structural principles and the biological characteristics of the system to be investigated. He also stresses in the paper that the full exploitation of biology-oriented synthesis will require a comprehensive set of methods for the enantioselective construction of screening libraries of stereochemically homogeneous compounds, in particular on solid-phase, and he correctly points out that the corresponding methods development, although not unexplored, still is an underdeveloped area of research in organic chemistry. The synthesis of the α-pyrone library investigated in the current paper is based on a highly enantioselective catalytic oxa Diels-Alder reaction, which was adapted to solid-phase synthesis, but Waldmann's group has also developed stereoselective methods for the elaboration of other natural product scaffolds on solid-phase (referenced in [1]). It is worth noting at this point that the work

presented in Leßmann et al., in spite of its success in identifying interesting new modulators of cellular processes, does not even fully exploit the power of the synthetic methodology developed. All library members screened exhibit the *R*-configuration at C-6 of the α-pyrone ring, whereas at least one of the natural products shown in the paper as examples of structures incorporating a α,β-unsaturated δ-lactone ring has an *S*-configuration at that position. Obviously, *S*-configured products are equally accessible by the Diels-Alder methodology developed as those with *R*-configuration.

Biology-oriented synthesis as defined by Waldmann is not to be confused with and has to be distinguished from "diversity-oriented synthesis" or DOS [8], which entails the synthesis of large libraries of structurally complex molecules in a minimum number of steps. Based on their structural complexity, the members of these DOS libraries are meant to have "natural-product-like" characteristics, but library design is not guided primarily by the structural characteristics of real natural products. Biology-oriented and diversity-oriented syntheses should be considered as complementary approaches toward the identification of biologically active molecules in cellular or target-based screening assays, each of which will be found to have its own merits and limitations.

In the current paper, the screening of a library of only 50 compounds sufficed to identify modulators of two unrelated biological processes, cell cycle progression through mitosis and viral entry into host cells, with the majority of hits not exhibiting any "cross-reactivity" between the two assays. In principle, such compounds could also represent structural entry points for the discovery of new drugs, but, obviously, even in the best of cases, this would require a significant amount of optimization work. Nevertheless, the potential exists and biology-oriented synthesis undoubtedly will deliver many more tool compounds for chemical biology and drug discovery research, and, in individual cases, also lead structures for medicinal chemistry.

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