

Biology Oriented Synthesis

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Relevance to nature is one of the most important criteria to be met by compound classes for chemical biology and medicinal chemistry research. The underlying frameworks of natural products (NPs) provide evolutionary selected chemical structures encoding the properties required for binding to proteins, and their structural scaffolds represent the biologically relevant and prevalidated fractions of chemical space explored by nature so far.

Biology oriented synthesis (BIOS) builds on these arguments. It employs core structures delineated from NPs as scaffolds of compound collections and creates focussed diversity around a biologically prevalidated starting point in vast structural space. BIOS, therefore, builds on the diversity created by nature in evolution and aims at its local extension in areas of proven biological relevance. Consequently BIOS offers a conceptual alternative to other guiding strategies for library design which for instance are based on mechanistic considerations, sequence or structure homology or on the creation of chemical diversity.

In the lecture the trains of thought leading to the BIOS concept will be detailed, including the development of a Structural Clustering of Natural Products (SCONP) in a tree-like arrangement and its combined use with Protein Structure Similarity Clustering (PSSC) as hypothesis generators for the development of NP-derived and –inspired collections, the chemical feasibility of their synthesis on the solid phase and in solution and the investigation of these compound collections in selected biochemical and biological assays.

References:

- (1) Breinbauer, R.; Vetter, I. R.; Waldmann, H. *Angew. Chem. Int. Ed.* **2002**, *41*, 2878.
- (2) Koch, M. A.; Wittenberg, L.-O.; Basu, S.; Jeyaraj, D. A.; Gourzoulidou, E.; Reinecke, K., Odermatt, A., Waldmann, H. *Proc. Natl. Acad. Sci.* **2004**, *101*, 16721.
- (3) Koch, M.; Schuffenhauer, A.; Scheck, M.; Wetzels, S.; Casaulta, M.; Odermatt, A.; Ertl, P.; Waldmann, H. *Proc. Natl. Acad. Sci.* **2005**, *102*, 17272.
- (4) Nören-Müller, A.; Reis Corrêa Jr., I.; Rosenbaum, C.; Schwalbe, H.; Vestweber, D.; Prinz, H.; Schiewe, H.; Waldmann, H. *Proc. Natl. Acad. Sci.* **2006**, *103*, 10606.