SL05 **Libraries Based on Natural Products and Peptides: Methods to Hits to Biology**

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A goal of library construction is to provide new chemical matter for screening and other biological applications. One way to accomplish this is to develop new synthetic methods that provide attractive routes to small molecules. This laboratory has a long-standing interest in such activities, notably involving the reactions of alkyl azides with electrophiles such as Lewis acid-activated ketones (the azido-Schmidt reaction). Recent work has led to the development of a number of domino processes that combine the azido-Schmidt with other Lewis acid-mediated reactions such as the Diels–Alder or the aldol reactions.

This presentation will show how such synthetic methodology work can be applied to the construction of libraries that are based on natural products or peptides. For the former, several libraries of compounds based on five different classes of alkaloids has been designed and prepared. The cheminformatic analysis of this library will be discussed, along with biological screening that has resulted in the discovery of a novel class of synthetic binders to the sigma-1 receptor.

Two different approaches to libraries based on peptides will then be discussed: one in the field of gamma turn analogs and the second much more liberally evolved from a beta turn motif. Screening of these compounds has uncovered novel chemotypes of molecules that bind tightly and selectively to several targets, including the kappa opioid receptor. The pharmacology of these compounds has been examined in collaboration with the laboratory of Professor Laura Bohn of the Scripps Research Institute in Jupiter, FL, and Professor Thomas Prisinzano of the University of Kansas. Recent results of these studies will be disclosed.