Organic Colloquium

Exploiting Natural Products to Design Protein-Protein Interaction (PPI) Stabilizers

Abstract. The association of proteins into protein complexes is a dynamic process involved in the regulation and execution of most biochemical processes. As such, targeted manipulation of PPIs has emerged as a cutting-edge area of research at the chemistry-biology interface. Small-molecule-based approaches for PPI modulation have focused largely on inhibiting PPIs, typically via peptidomimetics designed to replicate a conformational binding epitope involved in molecular recognition at the PPI interface. However, in comparison, the antithetical strategy of developing small-molecule PPI stabilizers remains underexplored in drug discovery.

Research in the Frederich Lab focuses on the chemistry and biology of natural products that function as PPI stabilizers. The objective of our program is to refine these scaffolds into selective chemical tools with optimized pharmacological profiles. This work is exemplified by fusicoccin A (FC-A), a structurally complex diterpene glycoside that targets 14-3-3 functions in vivo. Upon entering cells, FC-A binds to a select group of 14-3-3 client phosphoprotein complexes and enhances the lifetime of these PPIs by forming simultaneous contacts with both proteins. This biology inspired the design of ISIR-05, a semi-synthetic analog of FC-A with peripheral structural modifications that alter binding affinity and selectivity for 14-3-3 PPIs in human cell culture. These observations led us to hypothesize that FC-A can scaffold a new class of 14-3-3 PPI stabilizers with enhanced specificity profiles. However, the structural complexity of highly oxidized diterpene limits practical entry to synthetic FC-A variants. To address this limitation, we have developed a strategy to prepare fusicoccin that can also support deep-seeded structural investigations. This lecture will describe the evolution of strategies and tactics explored en route to fusicoccin and our efforts to characterize the structural features of FC-A that impart selectivity for certain 14-3-3 client protein PPI interfaces in vitro.