Organic Chemistry & Chemical Biology Seminar

Professor William Pomerantz

Department of Chemistry

University of Minnesota

Fluorinated bromodomains: Choosing the right halogen for small molecule discovery

Protein-protein interaction inhibitor discovery has proven difficult due to the large surface area and dynamic interfaces of proteins. To facilitate the early lead discovery rate, I will first describe a rapid protein-based ^{19}F NMR method for detecting protein-ligand interactions by screening low complexity molecules (fragments) as well as higher complexity molecules. We label the aromatic amino acids with the highly sensitive fluorine atom, due to the high conservation of aromatic residues at protein interfaces. We have tested the sensitivity, accuracy, and speed of this method with the protein interaction domain of CBP, KIX, screening 508 small molecule fragments. In the second part of the talk, I will describe an extension and improvements in our method for the field of epigenetics targeting bromodomain-containing proteins Brd4, BrdT and BPTF. These studies have led to the discovery of some of the first selective ligands for the bromodomain BPTF and new submicromolar ligands for Brd4. Finally, I will address the synthesis, development, and application of two of our new chemical probes for studying epigenetic protein function, including a new role for BPTF regulation of the oncogene, c-Myc. The speed, ease of interpretation, and low concentration of protein needed for binding experiments affords a new method to discover and characterize both native and new ligands for bromodomains and may find utility in the study of additional epigenetic "reader" domains.

Thursday, March 9, 2017 - 11:00 AM

Chemistry Room #1315

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