Synthesis and Evaluation of Desmethyl Azumamide Analogs

Histone deacetylases (HDACs) are a group of epigenetic modulators, which catalyze the removal of e-Nacetylated lysine residues. Histones are the most studied targets, however, the acetylated state of a variety of other proteins are also modified by HDACs. Aberrant epigenetic processes have been associated with various types of cancer and HDACs have therefore been a target in the development of anticancer drugs. So far, two HDAC inhibitors have been approved by the food and drug administration (FDA) and several compounds are in clinical trials.

Macrocyclic HDAC inhibitors are interesting compounds, as they can interact with a variety of amino acids on the surface near the binding site; these interactions may be used to obtain selectivity for specific HDAC isozymes. The azumamides are potent HDAC inhibitors and since they possess a relatively weak zinc-binding group (ZBG), the activity must arise from interactions with the large cap group. The natural compounds have been used as an inspiration to synthesize new HDAC inhibitors.

A small structure activity relationship (SAR) study was conducted in collaboration with Jesper S. Villadsen. Aromatic substituents in the cyclic peptide were explored, while the primary modifications were done to the b-amino acid. Removal of the methyl group in the 2-position and changes to the unsaturation in the side at the 3-position, afforded six compounds. These were tested against HDAC enzymes from class I, IIb, and IV.

Minor changes in activity were observed among the azumamide analogs; however, removal of the methyl group had a significant impact relative to the natural products. To understand this effect, the NMR structure was solved with the assistance from Casper Hoeck and Charlotte H. Gottfredsen and docked conformations were obtained from Niels J. Christensen and Peter Fristrup. Compared to the natural compounds, the 3Dstructure of the scaffold in the azumamide analogs were similar. Although a conclusion was not found, the preliminary docking results indicated favorable lipophilic interaction with the methyl group in the azumamides.

Largazole is another macrocyclic natural product with HDAC inhibitory activity. The compound has a thioester functionality in the side chain, which is hydrolyzed before interaction with the enzymes. In the attempt to mimic the prodrug nature of largazole, compounds containing a thiol group were designed, as it was hypothesized that acylation with different lipids could generate compounds with improved cell penetrating properties. A desmethylated azumamide analog containing a thiol side chain was synthesized and tested against HDAC3. A low activity was observed, which was explained by the unfavorable linker length.

In the work performed at CalTech, five 2-a-phenylpyrroloindolines were synthesized; utilizing an NCS mediated cyclization as the key step. Chris Marotta and Christina McCleary Daeffler tested their effect against a variety of ligand-gated ion-channels. Among these, one compound proved to be an agonist for the GABAA receptor.