Synthesis of Cleavable Acetal Antibody Drug Conjugate

Luis Salazar Guzman

Dr. Elizabeth M. Thomas.

Berea College

The design of a hydrophilic heterobifunctional linker with the functionality to conjugate to a monoclonal antibody, mAb, was our research goal. When drug toxins are bound to the linker that is conjugated to a mAb, these molecules are known as antibody drug conjugates, ADC’s. Linking drug toxins to mAbs is a way to deliver drug molecules specifically to cancer cells without targeting the healthy cells within the body. This minimizes the toxic effects of chemotherapy treatments. A heterobifunctional linker is functionalized on two separate ends of the small organic molecule. One end of the linker facilitates covalent bonding to the mAb while the other end facilitates covalent bonding to a toxin drug molecule. The mAbs that we are interested in bind specifically to the extracellular matrix (outside cell surface) of cancer cells; in particular antibody CD-55. Our desired linker consisted of a uridine molecule covalently bonded to malemide through an acetal moiety. The importance of the acetal is that this functional group is cleavable at a pH of 5.5 and therefore, once endocytosed (brought inside the cell membrane) within the cancer cell, should cleave to release the drug toxin. Outside the cell membrane is a pH of 7.2. Acetal functions are stable at pH of 7.2 and therefore would remain intact outside the cancer cell. The simulated cancer drug is uridine, however, 5-fluorouridine is a known cytotoxin that can be attached to the heterobifunctional linker in place of uridine once the chemistry has been established. We successfully synthesized the final intermediate precursor to the desired product containing the uridine group. Ideally, once the final product is synthesized, further research would be conducted to demonstrate the cleavage efficiency of the desired compound and then the synthesis of the 5-fluorouridine ADC for evaluation as a cytotoxin specific towards CD-55.