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Inhibitors of UDP-Galactopyranose Mutase from Mycobacterium tuberculosis, a Potential Antimycobacterial Drug Target

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Mycobacterium tuberculosis, the causative agent of tuberculosis, has developed multiple antibiotic resistance mechanisms against many of the available drugs. Targeting new biosynthetic pathways; therefore, represents a promising therapeutic strategy. UDP-galactopyranose mutase (UGM), an essential enzyme for M. tuberculosis involved in bacterial cell wall synthesis, is not present in mammalian cells, and is thus an attractive potential drug target. MS208 was previously identified as an allosteric inhibitor of MtUGM. A model, to better understand the binding pattern of MS208 within the allosteric site, is needed for prospective drug design. Attempts to crystallize MS208 with MtUGM were unsuccessful in the lab. As a result, an indirect method to understand how this molecule binds to MtUGM was required. This method involved developing MS208 analogues, testing these analogues for their ability to inhibit MtUGM, and understanding which structural features are important for binding using a preliminary structure activity relationship (SAR). My research focused on the design, synthesis, and analysis of MS208 analogues. Most of these analogues showed both inhibition against MtUGM, as well as antituberculosis activity. There was unexpected result regarding the effect of MS208 on MtUGM in the presence of a detergent. To provide other insights regarding the behavior of MS208 with MtUGM, biophysical techniques, such as DLS and 1H-NMR, were used. This research produced novel results that provided further understanding to the behavior of MS208 with MtUGM.

Biography

Dalia Ahmed is PhD candidate at Sanders Group, Chemistry Department, University of Saskatchewan, Canada. She earned her Bachelor degree of Pharmaceutical Sciences with distinction of honor from Ain Shams University in Egypt , where she continued her studies and earned her Master's degree in Pharmaceutical Chemistry from the same University. During her masters degree , she developed molecules with anti-inflammatory effects. She also collaborated with two research groups to develop molecules as potential anticancer agents. She joined Sanders group to have more understanding about small molecule-enzyme interactions. She has been awarded many scholarships during her PhD project from the Government of Saskatchewan, University of Saskatchewan and the Chemistry Department. During her research journey, she developed skills in many areas like organic synthesis of small molecules, computational study of drug target interactions, kinetic assay of enzymatic activity, binding assay of small molecules to target enzyme, protein purification , characterization and crystallization