TOWARDS SELECTIVE INACTIVATION OF PROTEIN TYROSINE PHOSPHATASE 1B VIA EXO-AFFINITY LABELING AGENTS

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ABSTRACT

Protein tyrosine phosphatase 1B (PTP1B) is a validated drug target for type II diabetes, obesity, and cancer. However, no traditional non-covalent inhibitors have been FDA approved for PTP1B due to problems with selectivity or bioavailability. Exo-affinity labeling agents are compounds that gain selectivity by binding non-covalently to the active site of a protein and covalently modifying outside of the active site. Here we describe a novel exo-affinity labeling strategy for inactivation of PTP1B. Towards this end we designed and synthesized several compounds containing the known inhibitor 1,2,5-thiadiazolidin-3-one-1,1-dioxide (TDZ). We evaluated the kinetics for our TDZ containing exo-affinity labeling agent. The exo-affinity agent had a k_{inact} of 18 x10^{-4} s^{-1} for inactivation of PTP1B and a K_I of 1.7 x10^{-4} M. We then determined the apparent second order rate constant to be 10.6 $M^{-1}s^{-1}$. Using mass spectrometry we also determined that our exo-affinity agent primarily modifies Cys121 on PTP1B. Using our design and characterization methods, we can develop exo-affinity labeling agents that are specific for PTP1B and other PTPs. Eventually exo-affinity labeling agents can be used to study PTP signal transduction pathways or design drug candidates.