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A new approach toward PTP-1B inhibition

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Signaling pathways for cellular metabolism, growth, proliferation, differentiation, immune response, motility, and tissue homeostasis is regulated by the phosphorylation of protein tyrosine residues on target proteins in the relevant signal transduction pathways. Phosphorylation levels of tyrosine residues are controlled by the opposing actions of two enzymes: protein tyrosine kinases and protein tyrosine phosphatases (PTPs). Protein tyrosine kinases add phosphoryl groups while PTPs catalyze their removal. PTPs are emerging as potential drug targets for the treatment of type 2 diabetes, autoimmune diseases, osteoporosis, and cancer. PTP-1B is the archetypal PTP and its inactivation may be a viable treatment for type 2 diabetes and obesity. PTP-1B is regulated by endogenous hydrogen peroxide (H2O2), which is a known cellular signaling agent. H2O2 oxidatively-inactivates PTP-1B, and its activity is regenerated by free thiols within the cell such as glutathione. In order to facilitate enzyme regeneration the aforementioned thiol must have access to the enzyme active site. We are testing the hypothesis that small molecules can inhibit thiol-mediated reactivation of redoxinactivated PTPs. Molecules with such a property would decrease the activity of target PTPs in cells, thus enhancing cellular response to external stimuli that act through receptor protein kinases.