Public Abstract

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Title:Biologically Relevant Chemistry of Sulfur Heterocycles: From Redox Regulation of PTP1B to the Biological Activity of S-deoxy Leinamycin

Protein tyrosine phosphatase 1B (PTP1B) is an important member of a tyrosine phosphatase family of enzymes. PTP1B acts as a negative regulator of insulin signaling cascade, as inhibition of PTP1B has been shown to increase the insulin mediated glucose uptake in cells. Hence understanding the molecular processes and chemical mechanisms that govern the activity of PTP1B becomes very important towards the treatment of type II diabetes. A key feature of insulin mediated glucose metabolism involves an oxidative inactivation of PTP1B in cells through endogenously produced hydrogen peroxide. Recent evidences suggest the formation of a novel sulfenyl amide crosslink during the oxidative inactivation of PTP1B. However, the chemical mechanisms leading to the formation of the sulfenyl amide is not clear. In this work, we designed an organic model compound to understand the chemical mechanism for the formation of this unique sulfenyl amide. In addition, we provided evidences that our model can mimic the redox chemistry seen at the active site of PTP1B. Furthermore, we obtained insights into the functional consequences of the formation and further oxidation of sulfenyl amide at the enzyme backbone, through our model studies. Our results suggested the formation of a novel sulfinyl amide intermediate (a hydrolytically labile but thiol reversible) upon over-oxidation of sulfenyl amide. Consistent with the understanding from our model studies, we indeed observed the formation of sulfinyl amide during the oxidative inactivation of PTP1B under biologically relevant conditions. Overall, our understanding of chemical properties of the novel intermediates may help design a better target for PTP1B and may aid in treating type II diabetes. In a different context, we gained insights into the possible chemical mechanism underlying the biological activity of S-deoxy leinamycin. We synthesized a crucial small molecule triggering unit (dithiolanone) mimic of the natural product and studied its reaction with thiols. Our results suggest that the biological activity of S-deoxy leinamycin may arise from the thiol-mediated generation of cell killing reactive oxygen species and hydrogen sulfide.