Synthesis of a Small Library of Potential Poly(ADP-ribose)glycohydrolase (PARG) Inhibitors

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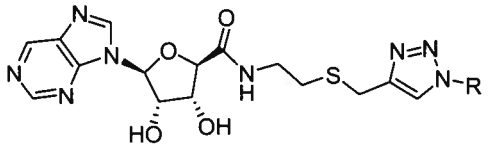
Poly(ADP-ribosyl)ation of proteins, catalyzed by the enzyme poly(ADP-ribose) polymerase (PARP), is a posttranslational modification that occurs in response to DNA damage. The enzyme poly(ADP-ribose) glycohydrolase catabolizes these ADP-ribose polymers (PAR), producing monomeric ADP-ribose units, and works in conjunction with PARP to regulate the concentration of PAR within the cell. Small molecule inhibitors of both PARP and PARG have been demonstrated to decrease cell death caused by oxidative insult and show promise as agents for the treatment of neurodegenerative disorders such as Parkinson's disease. Unfortunately due to issues with cell permeability, toxicity, and size, no biologically relevant PARG inhibitor has yet been developed. Thus, we have set out to produce a small library of PARG inhibitors with potential to work in vivo.



Substrate Specificity on Catalytic Reactions Between Two Distantly Related Enzymes in the Enolase Superfamily: "Promiscuous Enzymes Moonlighting in Different Metabolic Pathways"

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ortho-Succinylbenzoate synthase (OSBS) and *N*-acyl-amino acid racemase (NAAAR) are homologous members of the enolase superfamily. Although NAAAR from *Amycolatopsis* catalyzes the racemization of *N*-acyl-amino acids, it can moonlight as OSBS, an enzyme found in the menaquinone biosynthetic pathway and required for anaerobic growth. Although OSBS in *E. coli* and NAAAR in *Amycolatopsis* share a low sequence identity (19%), they have conserved quaternary structures and superimposable catalytic active site residues. Thus, while *Amycolatopsis* does not have the menaquinone biosynthetic pathway, the presence of OSBS activity in the NAAAR scaffold leads us to question the original function of this "promiscuous" enzyme. We have discovered more organisms that can catalyze both the OSBS and NAAAR reactions, even though some of them do not have the full complement of genes required for menaquinone biosynthesis. With both liganded and unliganded crystal structures of these OSBS and NAAAR enzymes, studies on the structure-function relationships in the OSBS and NAAAR scaffolds will be presented, and a focus on the substrate specificity and metabolic context for a number of NAAARs will be made to highlight the divergent evolution of enzymatic activities inherent in the enolase superfamily.