Identification and Evaluation of Novel PARG Inhibitors

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While several promising inhibitors of poly(ADP-ribose) polymerase (PARP) have been developed and fully characterized *in vivo* as anticancer and neuroprotective agents, no crystal structure of poly(ADP-ribose) glycohydrolase (PARG) is available, and therefore it has been difficult to intelligently design compounds to inhibit this enzyme. To date, the known inhibitors of PARG can be predominantly grouped into the three categories: DNA intercalators, tannins, and ADP-ribose analogues. While these compounds have proven valuable in the *in vitro* analysis of PARG, due to toxicity (intercalators), cell permeability issues (ADP-HPD), and nonspecific activity (tannins), few if any of these compounds have been useful for evaluating the effects of PARG inhibition in cell culture and *in vivo*. As compounds based on rhodanine scaffolds have been identified as inhibitors of enzymes utilizing pyrophosphate-containing substrates, we have screened a collection of rhodanine-containing small molecules for their ability to inhibit PARG. Through this screen several novel PARG inhibitors were identified, and subsequent derivative synthesis has elucidated structural features important for PARG inhibition. Furthermore, several of the compounds are cell permeable and induce the build-up of poly(ADP-ribose) in the cell. Details of the TLC-based screen, synthesis, and evaluation of hit compounds in cell culture will be discussed.