Synthesis and Structure-Activity Relationship of Small-Molecule Inhibitors of Poly(ADP-ribose) Glycohydrolase

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The metabolism of poly(ADP-ribose) (PAR), a polymeric post-translational modification, is a key component of many cellular processes, including DNA maintenance, cellular replication, cell survival, and cell death. Poly(ADP-ribose) glycohydrolase (PARG), the enzyme that degrades PAR, is a promising target for anti-cancer and cytoprotective therapeutics due to its significant role in the determination of cell survival. However, there is currently a need for potent, specific, and cell-permeable inhibitors of PARG. ADP-HPD is the only known compound that specifically inhibits PARG; unfortunately, this compound is not cell permeable, due to its diphosphate group, a necessary functionality for activity. Recently, our laboratory investigated the use of rhodanine heterocycles, well-known phosphate replacements, as a strategy for developing new PARG inhibitors. From a focused library of rhodanine-containing compounds, we identified nine structurally similar compounds that inhibited PARG with IC_{50} values of less than 10 μM.

In this study, we sought to synthesize derivatives that would probe the role of various structural features and functional groups in PARG inhibition. The derivatives were evaluated for the ability to prevent degradation of ^{32}P-PAR using a TLC-based PARG assay. The results suggested that an appended protic functionality is required for activity and that a number of substituents are tolerated on the isatin and benzyl rings. Also, some of these new derivatives were active in cell lysate experiments and in cell culture. Overall, systematic modification of this new class of PARG inhibitors has expanded the structure-activity relationship and will provide further insight into the inhibition of PARG both *in vitro* and in cell culture.