Abstract

Acetylated adenosine diphosphoribose (*O*AADPR) is a product of protein deacetylation catalysed by class III of histone deacetylases called sirtuins. Sirtuins deacetylate histones and other proteins by unique mechanism coupled with consumption of stoichiometric amount of NAD^+. Sirtuins and *O*AADPR are implicated in the regulation of gene transcription, signalling and metabolic pathways and lifespan extension, thus preventing the development of age-related diseases. Even though, sirtuins are well studied, the exact biological role of *O*AADPR remains mainly unknown. Its further exploration is restricted by *O*AADPR's proneness to enzymatic hydrolysis. Therefore, non-hydrolysable analogues of *O*AADPR are needed to establish its biological function. These analogues are also expected to be competitive inhibitors of sirtuins, which may reveal their potential as therapeutic agents.

A series of *O*AADPR analogues in which the acetate moiety was replaced with alkylcarbonate functionality has been synthesized. The studies of alkylcarbonate migration on furanoside scaffold have established the stability of alkylcarbonate vs. acetate under various conditions. Generally, alkylcarbonates are more stable than acetate under acidic or neutral conditions whereas under basic conditions they seem to be less stable. Alkylcarbonates are also extremely prone to form cyclic carbonates under either acidic or basic conditions. Prepared alkylcarbonate furanosides were next phosphorylated. Several phosphorylation methods were examined revealing that only the phosphoramidite method with benzyl protected phosphite reagent gave satisfactory results. An employment of recently published procedure using a ball mill for the final coupling of unprotected monophosphofuranosides with AMP morpholidate proved to be high yielding. The synthesized *O*AADPR analogues have been tested for their inhibitory activity on two human sirtuin homologues, SIRT1 and SIRT3. Cytotoxicity of these compounds was evaluated on five carcinoma cell lines.

For inhibitory activity on yeast sirtuin homologue, yHst2, were tested the potential sirtuin inhibitors, piperidinyltriazolide nucleosides, simulating the elongation of the nucleosidic bond between C-1' and the nitrogen of the pyridine ring which occurs during the enzymatic reaction. These nucleosides were designed based on molecular modelling. They were synthesized from appropriate 1-azido-ribosides and alkyne-pyridines by Huisgen cycloaddition. Hydrogenation of the pyridine ring then afforded the final piperidinyltriazolide nucleosides.