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Disaccharide nucleosides as inhibitors of DNA repairing enzymes

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Motivation and Aim: Numerous drugs have been developed, which have or resemble nucleosidic structure. Disaccharide nucleosides is a group of natural compounds forming poly(ADP-ribose) (PAR) and found in tRNA, antibiotics, and other physiologically active compounds [1]. Earlier we have developed the synthetic methodology for the synthesis of 2′-O-α-D-ribofuranosyladenosine, a monomeric unit of PAR, which is an important biopolymer, participating in DNA repair [2]. Therefore, chemical synthesis of disaccharide analogues may be an advantageous area for the discovery of a novel compounds inhibiting DNA-repairing enzymes to increase the effectivity of anticancer therapy.

Methods and Algorithms: We have synthesized a series of disaccharide purine and pyrimidine nucleosides by the formation of an *O*-glycosidic bond between a nucleoside carrying one free hydroxyl group and an activated monosaccharide. All the compounds were characterized by NMR and UV spectroscopy and by LC-APCI and LC-HRMS. Inhibitory effect of disaccharide nucleosides was studied on two DNA-repairing enzymes – poly(ADP-ribose)polymerase 1 (PARP-1) and tyrosyl-DNA phosphodiesterase 1 (Tdp-1). PARP-1 inhibitory assay was performed using [^{3}H]-NAD$^+$. Tdp-1 activity was measured using real-time fluorescence assay in the presence of fluorophore-quencher containing oligonucleotides.

Results: In the series of disaccharide nucleosides pyrimidine derivatives were found to be effective Tdp-1 inhibitors, with IC_{50} being in low micro molar range, and weak PARP-1 inhibitors, with IC_{50} being $\sim 10^{-5}$ M. Disaccharide nucleosides did not demonstrate cytotoxic effects at concentration up to 1 mM against human cell lines.

Conclusion: Thus, the obtained results have revealed disaccharide nucleosides as a promising class of compounds, inhibiting key DNA-repairing enzymes: PARP and Tdp-1.

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References

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