## New 5'-O- and 6-Substituted Purine Nucleoside Analogs: Synthesis and Cytotoxic Activity on Selected Human Cancer Cell Lines

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**Abstract :** Nucleoside analogs are a pharmacologically diverse family that includes cytotoxic compounds, antiviral agents, and immunosuppressive molecules. Purine nucleoside derivatives such as fludarabine, cladribine, and pentostatin are significant drugs used in chemotherapy for the treatment of solid tumors and hematological malignancies. In this study, we synthesized novel purine ribonucleoside analogs containing a 4-(4-substituted phenylsulfonyl) piperazine in the substituent at N6- and O-substituted sulfonyl group at 5'-position as putative cytotoxic agents. The newly obtained compounds were then characterized for their cytotoxicity in human cancer cell lines. The 5', 6-disubstituted 9-( $\beta$ -D-ribofuranosyl)purine derivatives (44-67) were readily obtained from commercially available inosine in seven steps in very cost effective synthesis approach. The newly synthesized compounds were first evaluated for their anti-tumor activities against human liver (Huh7), colon (HCT116) and breast (MCF7) carcinoma cell lines. The IC50 values were in micromolar concentrations with 5', 6-disubstituted purine nucleoside derivatives. Time-dependent IC50 values for each molecule were also calculated in comparison with known cytotoxic agents Camptothecin (CPT), 5-Fluorouracil (5-FU), Cladribine, Pentostatine and Fludarabine. N6-(4-trifluoromethyl phenyl) / N6-(4-bromophenyl) and 5'-O-(4-methoxybenzene sulfonyl) / 5'-O-(benzenesulfonyl) derivatives 54, 64 displayed the best cytotoxic activity with IC50 values of 8.8, 7  $\mu$ M against MCF7 cell line. The N6-(4-methylphenyl) analog 50 was also very active (IC50= 10.7  $\mu$ M) against HCT116 cell line. Furthermore, compound 64 had a better cytotoxic activity than the known cell growth inhibitors 5-FU and Fludarabine on Huh7 (1.5 vs 30.7, 29.9  $\mu$ M for 5-FU and Fludarabine).

Keywords : cytotoxic activity, Huh7, HCT116, MCF7, nucleoside, synthesis

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