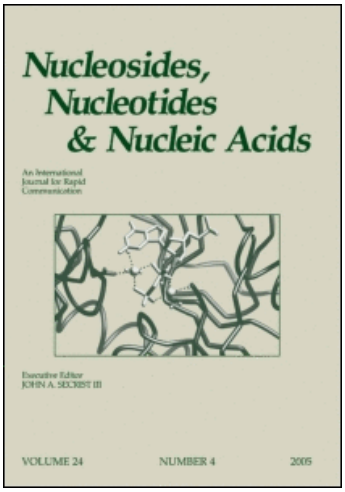

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Anticancer Activities of 7-, and 9-Substituted 3-Deazaguanine Derivatives

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NUCLEOSIDES & NUCLEOTIDES, 4(1&2), 253 (1985)

ANTICANCER ACTIVITIES OF 7-, AND 9-SUBSTITUTED 3-DEAZAGUANINE DERIVATIVES

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Summary: Interesting differences in anticancer activities of 7- and 9-substituted derivatives of 3-deazaguanine are described.

3-Deazaguanine (DG) is a potent inhibitor of a variety of experimental mammary tumors and is about to undergo clinical trial in USA.[1] The antitumor activity of DG has been ascribed to its incorporation into tumor cell DNA as its 2'-deoxyriboside.[2] Syntheses of 7- and 9-substituted ribosides (7-DGR and 9-DGR, respectively) and 7- and 9-substituted 2'-deoxyribosides (7-DGdR and 9-DGdR, respectively) of DG has been reported.[3,4] DG, 9-DGR and 9-DGdR, at concentrations of 7.5, 6.0 and 8.0 μM caused a 50% inhibition in the growth of leukemia L1210 cells in culture. DG and 9-DGdR also were active against C3H/16C mammary adenocarcinoma system in $B6C3F_1$ female mice; 9-DGR was toxic and lacked therapeutic activity in this system. 7-DGR and 7-DGdR at concentrations of 2000 and 900 μM, respectively, caused 50% inhibition of the growth of L1210 cells in culture; both of these derivatives were inactive in C3H/16C tumor system, in vivo. The apparent lack of antitumor activity of 7-DGR and 7-DGdR was ascribed to the inability of the mammalian nucleoside phosphorylase to degrade these derivatives to DG.

Recently we have found that the 7-tetrahydropyranyl-3-deazaguanine (7-THPDG) is active (ED_{50}, 45 μM) in leukemia L1210 system, in vitro, and in C3H/16 tumor system, in vivo. The 9-tetrahydropyranyl-3-deazaguanine (9-THPDG) was inactive, in vitro (ED_{50}, 3000 μM), as well as, in vivo. The studies on mechanism of action of these analogs are in progress.

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0732-8311/85/0401-0253$3.50/0