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Nucleoside 5'-phosphonates: synthesis, anti-HIV activities and reactions with DNA polymerases

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Synthesis of new modified 3'-fluorothymidine (FLT) 5'-phosphonates was carried out. Some of them have demonstrated anti-HIV properties in cell cultures. The most active were 5'-phosphofluoridate of FLT (ED_{50} 0.3 μM), fluorochloromethylphosphonate of FLT (ED_{50} 2.5 μM), difluoromethylphosphonate (ED_{50} 8 μM) and cyanomethylphosphonate (ED_{50} 24 μM). A series of nucleoside 5'-phosphonates proved to be less toxic in cell cultures than corresponding nucleoside precursors. Synthesis of some nucleoside 5'-(α-phosphonyl)-β,γ-diphosphates was performed. These compounds were shown to be weak substrates of several DNA polymerases and viral reverse transcriptases. Thus, it was demonstrated that some DNA polymerases could catalyze synthesis of uncharged phosphonoester bonds.

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Synthesis of Sangivamycin Derivatives as Potential Inhibitors of Protein Kinases.

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Previous reports have shown that inhibitors of protein kinase C (PKC) decrease HIV infectivity (Fields, A.P. et al. *Nature* **1988**, *333*, 278.) and the infectivity of several enveloped viruses (Constantinescu, S.N. et al. *FEBS Lett.* **1991**, *292*, 31.), including vesicular stomatitis, herpes simplex I and vaccinia, most likely at the virus-entry level. Thus, inhibition of protein phosphorylation could represent a potential target for antiviral agents. The antibiotic sangivamycin is an effective inhibitor of PKC and to a lesser extent of PKA, however, in intact cells, the antibiotic is phosphorylated affecting other targets including DNA and RNA. To preserve selective inhibitory activity for the protein kinases, analogs potentially resistant to phosphorylation were prepared by replacing the 5'-hydroxy group with O-nitro, O-sulfamoyl, O-methane-sulfonyl, azido, amino, or fluoro groups or by replacing the ribofuranosyl moiety with that of allofuranose. The newly prepared derivatives inhibited PKC and PKA at concentrations ranging from 6.5×10^{-5} M to 1.1×10^{-8} M.