Design and Synthesis of Novel Nucleoside Derivatives

Yuichi Yoshimura
(Tohoku Pharmaceutical University)

Nucleoside derivatives are playing an important role in the field of cancer chemotherapy as well as treatment of virus causing disease, *e.g*. AIDS. Thus, many efforts have been made for the development of novel nucleoside derivatives. 4’-Thionucleoside containing a sulfur atom instead of furanose ring oxygen is a unique class of nucleoside analogues and is a good target molecule for searching novel antiviral and antitumor agents. We have focused on the design and synthesis of novel 4’-thionucleoside derivatives. Our first target was 4’-thioDMDC, a 2’-methylene analogue of 2’-deoxy-4’-thiocytidine, designed as an antineoplastic nucleoside. At the beginning, we have developed a facile synthetic route to access 4-thiosugar skeleton starting from D-glucose. The synthesis of 4’-thioDMDC was achieved by developing a novel coupling reaction of N^3-acetylcytosine and the 4-thiosugar portion based on the Pummerer reaction. Our method could successfully be applied to the synthesis of the other 2’-substituted 4’-thionucleosides derivatives. Among them, 2’-fluoro-4’-thio-arabinonucleosides are quite interesting. 2’-Fluoro-4’-thioarabinosylcytosine (4’-thio-FAC) has prominent antitumor activities which are more potent than those of 4’-thioDMDC. The guanine counterpart, 4’-thioFAG, proved to have potent anti-herpes virus activities. The Pummerer-type thioglycosylation reaction developed by us was applied to the synthesis of various 4’-thionucleosides including 4’-thio-*ribo*-nucleosides and novel 4’-thio-*apio*-nucleoside derivatives. We have also achieved to synthesize a novel nucleoside derivative, designed as a potential anti-HIV agent, which was constructed on a 2-oxa-6-thiabicyclo[3.2.0]heptane scaffold.