Drug design and synthesis of novel antitumor agents

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Phosmidosine was found as a new type of antifungal antibiotic isolated from a culture filtrate of *Streptomyces durhameusis* by Uramoto and Isono *et al*. Later, it was found by mass spectrometry and NMR spectroscopy that phosmidosine is a novel nucleotide-type antibiotic having a N-acyl phosphoramidite linkage which connects a nucleoside analogue, 8-oxoadenosine, with a L-proline residue. A new antitumor active phosmidosine A was successfully synthesized by a series of reactions involving construction of the N-acyl phosphoramidate linkage which was achieved by the reaction of the 5'-O-phosphoramidate derivative in the presence of 5-(3, 5-dinitrophenyl)-1*H*-tetrazole. The growth inhibitory effect of phosmidosine A and its N-acetyl analogue on the various human cell lines was examined. These results showed that the compounds have a significant growth inhibitory activity and that the 6-amino group is not required for the growth inhibitory activity of phosmidosine A. Phosmidosine B is a demethylated phosmidosine derivative with no chirality on the phosphorus. Phosmidosine B was successfully synthesized by the reaction of an N-acetyl-8-oxoadenosine 5'-O-phosphoramidite derivative with an N-protected prolinamide in the presence of 5-(3, 5-dinitrophenyl)-1*H*-tetrazole. The growth inhibitory activity of phosmidosine B and its derivatives in various tumor cell lines was evaluated by the MTT assay. As the result, phosmidosine B showed high antitumor activities and both the diastereomers of phosmidosine were found to have similar but approximately 10 times higher antitumor activity than phosmidosine B. Moreover, it turned out that these phosmidosine derivatives showed characteristic inhibitory activity against tumor cells independent of their p53 phenotypes. These results suggest that phosmidosine and its related compounds would be promising as a new type of antitumor agents having a wide range of inhibitory activities against tumor cells.

Sialic acids are commonly present at the non-reducing terminal positions of carbohydrate chains of glycoproteins and glycolipids on the cell surface and their crucial roles played in biological processes involving cell to cell recognition and interaction masking effects for cell surface antigen, differentiation of cells, and neoplastic transformation have been well studied. Recently, we have synthesized novel 5-deazaflavin substituted with the sialosylalkyl group at the amino group and their physicochemical properties as well as antitumor effects on KB and L1210 cells have been investigated. It has been found that these conjugate molecules show significant antitumor activity. Combination of an 8-amino-5-deazaflavin with the sialosylalkyl group has been found to give rise to significant increase in antitumor activity of the compound. Antitumor effects of 6-nitro-5-deazaflavin-sialic acid conjugate molecules were similar or rather weak in comparison with those of the 6-nitro-5-deazaflavin derivatives without sialosylalkyl group.

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