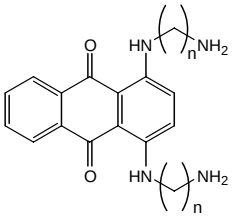
Cellular Distribution of New Antitumor-Active Dinuclear Platinum Complexes with N,N'-bis(aminoalkyl)-1,4-aminoanthraquinones in Different Types of Cancer Cells

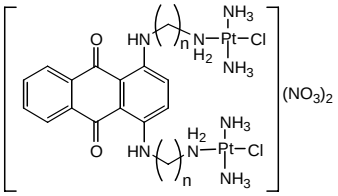
Ganna V. Kalayda[1], Bart A. J. Jansen[1], Chris Molenaar[2], Peter Wielaard[1], Hans J. Tanke[2], and Jan Reedijk[1]

[1]Leiden Institute of Chemistry, Gorlaeus Laboratories, Leiden University, The Netherlands, and [2]Laboratory for Cytochemistry and Cytometry, Department of Molecular Cell Biology, Leiden University Medical Center, The Netherlands

New dinuclear platinum complexes with fluorescent N,N'-bis(aminoalkyl)-1,4-diaminoanthraquinones have been synthesized as potential antitumor drugs. These complexes are highly cytotoxic in A2780 human ovarian carcinoma cell line and U2-OS human osteosarcoma cell line. The dinuclear platinum complexes overcome resistance in the cisplatin-resistant U2-OS/Pt osteosarcoma subline. However, they show cross-resistance with cisplatin in the resistant A2780cisR ovarian carcinoma cell line. Cellular distribution of the platinum complexes and the respective anthraquinones in A2780 and U2-OS sensitive/resistant pairs of cell lines has been studied over time using fluorescence microscopy. Different cellular processing in A2780cisR and U2-OS/Pt cells explain the different activity of the complexes in these two cell lines. In A2780cisR cells, the complexes are sequestered in lysosomes and are thereby kept away from nuclear DNA. This is not the case in the U2-OS/Pt cell line. The difference in cellular distribution is a result of different resistance profiles of A2780cisR and U2-OS/Pt cell lines. Sequestration of the platinum complexes in lysosomes appears to be an independent resistance mechanism in A2780cisR cells and might be related to the defect in lysosomal acidification.



n=2-4



n=2-4