

Polynuclear Alkylamineplatinum(II) Complexes of [1,2-Bis(4-fluorophenyl)ethylenediamine]platinum(II): Synthesis and Investigations on Cytotoxicity, Cellular Distribution, DNA and Protein Binding

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During the last years polynuclear platinum complexes were identified as a very promising class of antitumor active compounds. They showed a different toxicity profile than cisplatin and a slightly different mode of action; they cross-link the DNA in an 1→4 instead of an 1→2 GG-pattern, as identified for cisplatin or carboplatin. Remarkable activity of polynuclear compounds was noticed in a wide panel of tumor cells. However, a relatively low activity was found for breast cancer cell lines especially the MCF-7 cell line. Therefore, we focussed our attention on the design of those drugs with increased selectivity for breast tumors. In this study, we combined the well known [1,2-bis(4-fluorophenyl)ethylenediamine]platinum(II) complex with alkylamins, alkylidiamines and the DAB(PA)₄ polyimine dendrimer and used either DMSO or Cl⁻ as leaving group.

The polynuclear complexes strongly bound to human serum albumin mainly through electrostatic interactions. If this inactivation was prevented by the use of serum free medium, a high accumulation in hormone dependent MCF-7 breast cancer cells and a high DNA-binding was observed. These effects were independent on the charge of the molecule but depended clearly on the length of the alkyl spacer. Furthermore, it was demonstrated that the tetranuclear complexes of DAB(PA)₄ polyimine dendrimer were the most efficient compounds. They showed a 20 fold higher cellular uptake and an about 700 fold higher DNA binding than cisplatin. Unfortunately, the complexes showed only marginal cytotoxicity. This can be related to the high inactivation reactions prior to transport into the tumor cells. Experiments to overcome this obstacle are in progress.