

INVESTIGATIONS INTO THE DNA-BINDING PROPERTIES OF FURGAMYCIN-RELATED ANTHRACYCLINE ANTIBIOTICS

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Anthracycline antibiotics are the best characterized of a group of agents which interact with DNA through intercalation and are widely used as anticancer drugs. However two principal factors limit the use of anthracycline antibiotics in chemotherapy: the cumulative cardiotoxicity and certain tumors develop resistance to these agents. In the last few years there has been increasing interest in different glycosylated forms of anthracyclines. The presence of sugar chains on anthracyclines, length and composition is an essential element which determines the cytotoxicity, the biological activity and the binding affinity of these compounds for double stranded DNA. No simple correlation has been established between DNA-binding affinity of anthracyclines and their antitumour activity, however the binding constant/affinity of the drug for the DNA is dependent upon the DNA base pair sequence and on the presence and the number of charged amino groups. We have isolated and characterized the anthracycline compound furgamycin from *Streptomyces olindensis* ICB20 (also known in the literature as cosmomycin D). Some preliminary work has been done in our laboratory in order to assess the interaction of cosmomycin D with DNA: stoichiometry of DNA/CosD complexes as well as some competitive binding experiments with daunomycin and doxorubicin. The structures of these anthracyclines and furgamycin are shown in Figure 1 A, B and C, respectively. The preliminary results from our lab have highlighted some interesting differences between CosD and other anthracyclines which warrant further investigation, especially since they may lead to beneficial effects on biological activity. The relative stabilities of the different complexes were assessed by tandem mass spectrometry (MS-MS) experiments using a Waters Q-ToF Ultima ESI mass spectrometer, and revealed interesting differences in the stabilities of complexes with the same stoichiometry but different overall charge.

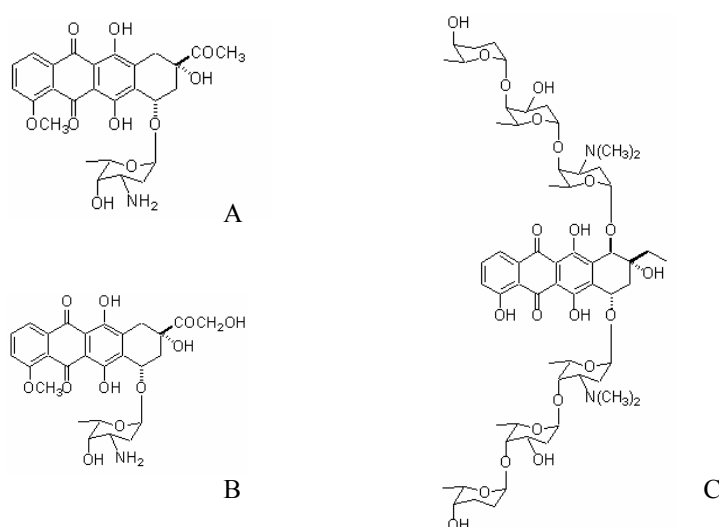


Figure 1: Anthracycline antibiotics A: Daunomycin (or Daunorubicin); B: Doxorubicin (or Adriamycin) and C: Furgamycin (Cosmomycin D)