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OBSERVING NON-COVALENT DNA-DRUG INTERACTIONS USING ESI-MS

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The anthracycline antibiotics daunomycin and nogalamycin (figure 1) both exhibit potent antitumour activity. Whilst related in structure, nogalamycin differs from daunomycin in that both ends of the intercalating chromophore are substituted in nogalamycin resulting in a dumbbell-like structure. In contrast, the intercalating chromophore of daunomycin is only substituted at one end.

Both nogalamycin and daunomycin are thought to bind to DNA by intercalation primarily between CpG steps in the oligonucleotide structure. These interactions have been studied extensively using a variety of spectrometric techniques such as NMR, X-ray crystallography, fluorescence as well as UV-Vis. These techniques are, however, limited in that they can be time consuming and require large amounts of sample. The aim of this study is to use negative ion ESI-MS to study the interactions between the two anthracycline antibiotics and the duplex oligonucleotides (5' CGGCGCCG 3', 5' GGCTAGCC 3', 5' TGAGCTAGCTCA 3')

ESI-MS spectra were obtained using a VG Biotech Quattro mass spectrometer equipped with an electrospray ionisation source and a triple quadropole mass analyser. Oligonucleotide samples and their adducts were dissolved in aqueous 0.1 M NH_4OAc and annealed at a temperature 20°C higher than their respective melting temperatures. A ratio of drug to duplex of 5:1 was used for all experiments. A ramped skimmer potential was used in all experiments.

Ions owing to the double stranded oligonucleotides as well as those corresponding to the various drug-DNA complexes were observed in the ESI-mass spectra. The results of binding experiments with different oligonucleotides and either one or both drugs will be presented. The implications of these results for studying the binding of intercalating agents for which the binding has not been charactarised by other methods will also be discussed.