Synthetic and Structural studies of Complexes formed between Bis-intercalator molecules and higher order DNA motifs

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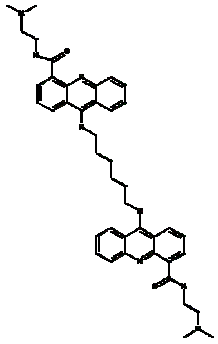
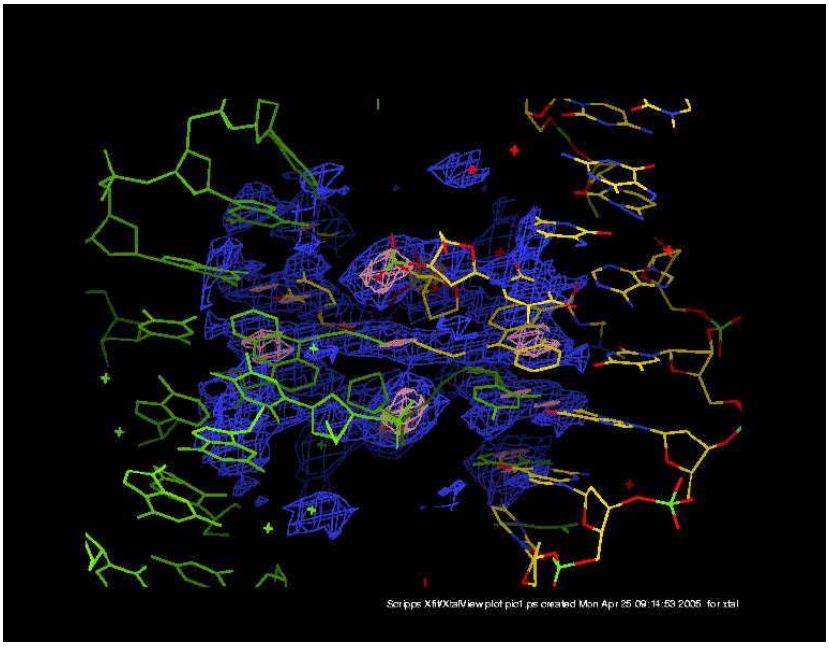
The work presented here describes the binding of small molecules to Holliday junction structures, which may have potential in the treatment of malignant disease. A series of bis(9-aminoacridine-4-carboxamides have been synthesised. Crystals have been grown with the C6 and C4 bis-intercalator molecules and $d(CGTACG)_2$ duplex DNA. Crystals have also been grown with the C6 bis-intercalator and $d(TCGGTACCGA)_4$, Holliday junction forming DNA. Initial structure solutions show two novel forms of DNA-drug binding with the C6 bis-intercalator forming complexes with both duplex and Holliday junction forming DNA. The complex formed between the C4 bis-intercalator and the $d(CGTACG)_2$ duplex DNA crystallised in a new trigonal lattice suggesting another novel binding mode.



The Holliday junction structure, containing four strands of d(TCGGTACCGA) with one molecule of the bisintercalator has currently been refined to 2.7 Å resolution using data from beamline X11 at EMBL-DESY Hamburg. This work has been supported by "European Community - Research Infrastructure Action under the FP6 "Structuring the European Research Area Programme" contract number RII3/CT/2004/5060008. Anna Brogden is supported by Xenova Ltd, The Univesity of Reading, and the London school of Pharmacy. Dr Nick Hopcroft is supported by BBSRC grant B19997.



Binding of the C6-diacridine drug to the Holliday junction structure at 2.7 Å resolution, displacing the adenine base from the AT base pairs at the junction.