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Keywords: G4-quadruplexes, DNA-drug interactions, telomeres

P.04.05.4

Acta Cryst. (2005). A**61**, C219

Structural Studies on Acridine Derivatives Binding to Telomeric DNA

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Acridine derivatives are known to inhibit a variety of nuclear enzymes, such as topoisomerases and telomerases, by binding or intercalating to DNA. This class of compounds is of great interest in the development of novel anticancer agents, some of which are currently under clinical trial [1, 2].

Despite the obvious pharmaceutical interest and recent successes in determining the crystal structure of some of the compounds complexed with DNA [1,2,3], a lot is still unknown about the mechanisms of action, binding preferences and biological targets.

In this study a variety of techniques is employed to investigate the binding behaviour of a selection of drugs to DNA. Fiber diffraction is used to obtain information about sequence preferences and to analyze structural changes in the DNA upon drug binding using a continuous polymer. Data is usually obtained at lower resolution and complements crystal diffraction studies. Crystal diffraction is then used to analyze DNA-drug complexes in oligonucleotides at high resolution. With the information gained, neutron diffraction studies are planned to analyze the hydrogen bonding patterns of the DNA-drug complexes.

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Keywords: DNA-drug complexes, X-ray fiber diffraction, X-ray crystallography

P.04.05.5

Acta Cryst. (2005). A**61**, C219

Crystallographic Studies of *Homo sapiens* A-sites Complexed with Aminoglycosides

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Toxicity resulting from the clinical use of aminoglycoside antibiotic drugs is known to originate from the binding of these drugs to the *Homo sapiens* A-sites. In order to design antibiotics with higher selectivity for bacterial ribosomes and less toxicity to eukaryotes, further structural investigations have been carried out with a number of A-site complexes. In all cases, the structure solution by molecular replacement was not straightforward and required simultaneous applications of several programs and various approaches.

In the case of the cytoplasmic A-site with paromomycin, a $P2_12_12$ crystal with one RNA duplex in the asymmetric unit was obtained. The same solution was found with *AMoRe* using the bulk-solvent correction technique and with *PHASER*. After applying normal-mode refinement for only the central stem region in the 10-5.0 Å resolution range, R_{free} and CC_{free} values are 30.5% and 32.3%, respectively.

The crystal of the mitochondrial A-site with tobramycin (space group *P1*) contains two RNA duplexes in the asymmetric unit. Orientation of the duplexes has been found by combination of information from *PHASER*, the self-rotation function from *GLRF* and other sources. Position of the duplexes was obtained essentially from the packing analysis.

The solution of other similar complexes (1 or 2 strands in the A.U., trigonal unit cells) also required specific approaches.

Keywords: RNA structure, antibiotic binding, crystal structures

P.04.05.6

Acta Cryst. (2005). A**61**, C219

X-ray Analyses of DNA Dodecamers Containing 2'-Deoxy-5-formyluridine

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It is known that formylation of thymine base induces purine transition in DNA replication. In order to establish the structural basis for such mutagenesis, crystal structures of two kinds of DNA dodecamers d(CGCGRATf^{5}UCGCG) with f^{5}U=2'-deoxy-5-formyluridine and R=A or G have been determined. The f^{5}U residues form a Watson-Crick-type pair with A[1,2] and two types of pairs (wobble and reversed wobble) with G[3] (*see* figure), the latter being the first example. Structural modeling suggests that the DNA polymerase can accept the reversed wobble pair with G, as well as the Watson-Crick pair with A.

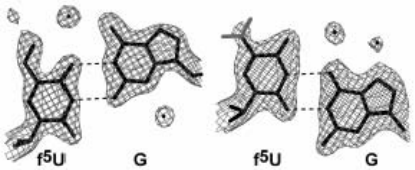

Figure 2|*Fo*|-|*Fc*| maps around the f^{5}U residues found in crystals of f^{5}U:G.

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Keywords: DNA crystallography, mutagenesis, novel structures

P.04.05.7

Acta Cryst. (2005). A**61**, C219

A 1:1 Binding Mode for Netropsin in the Minor Groove of d(GGCCAATTGG)

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The naturally occurring antitumor drug netropsin from *Streptomyces netropsis* binds preferentially to the minor groove of AATT-rich B-DNA. The decamer d(GGCCAATTGG) forms an octamer B-DNA double helix with 2 overhanging G-bases, able to form triple helices. This crystal engineering technique allows enhancing the resolution of minor groove binders such as DAPI [1], distamycin [2] and netropsin with approximately 0.5 Å.

A 98.5% complete dataset was collected at EMBL beamline BW7B (DESY in Hamburg). The structure was solved by molecular replacement using the decamer-DAPI structure [1] as a starting model and further refined to completion using Refmac5.1.24, R factor of 20.0% (including 68 water molecules). The enhanced resolution to 1.75 Å resulted in an unambiguous determination of the drug conformation and orientation.

Bifurcated hydrogen bonds are formed between the amide N-atoms of the drug and the N3(A) and (O2)T base atoms, cataloging the structure to Class I. As the bulky NH_2-group on G is believed to prevent binding of the drug, the detailed nature of several of the amidinium and guanidinium end contacts were further investigated by *ab initio* quantum chemical methods.

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Keywords: nucleic acids, netropsin, ab-initio calculations