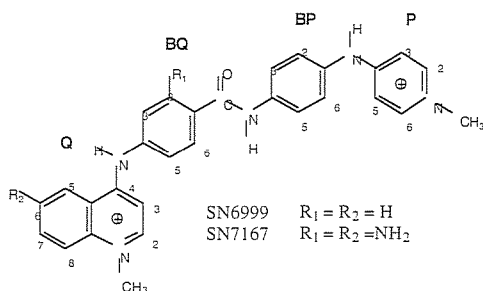


PS04.04.20 THE STRUCTURE OF AN RNA DODECAMER WITH NONCANONICAL BASE PAIRS DOES CHANGES LITTLE UPON CRYOCOOLING. Kurt F. Schaefer, Cindy L. Barnes, Susan E. Lietzke, and Craig E. Kundrot. Department of Chemistry and Biochemistry, University of Colorado, Boulder, CO 80309-0215

The structure of an RNA dodecamer duplex, r(GGCGCUUGCGUC), has been determined at room temperature (RT) at 2.9 Å resolution and ≈100 K at 2.4 Å resolution. The structure contains tandem U-U base-pairs. Previous studies with proteins indicate that the unit cell volumes decrease from 1% to 7% upon cryocooling, and similar results have been observed with cryocooled DNA duplexes. With the exception of one DNA octamer displaying a range of helical conformations, similar DNA structures were observed at room temperature and 100K. The recent use of cryocooling to determine the structures of RNA duplexes, the hammerhead ribozyme and the P4/P6 region of a Group I intron, has prompted us to examine how cryocooling affects the structure of an RNA duplex. The unit cell volume of the dodecamer crystals decreases 7% increase upon cryocooling. But a partially refined model (R=22.2% and R-free =22.9%) shows that the structures have a r.m.s.d. of only 0.2 Å. The results of comparing the fully refined RT structure to the 100 K structure will be presented.

PS04.04.21 CONFORMATIONAL CHANGES ON GROOVE BINDING TO DNA : MOLECULAR STRUCTURE OF SN7167 COMPLEXED WITH d(CGCGAATTCGCG)₂. Christopher J. Squire⁺, George R. Clark⁺, William A. Denny[±], ⁺Chemistry Department, [±]Cancer Research Laboratory, University of Auckland, Auckland, New Zealand.



The X-ray crystal structure of the synthetic antitumour and antiviral minor groove binding drug SN7167 and the DNA oligonucleotide d(CGCGAATTCGCG)₂ has been determined to an R factor of 20.0% at 2.6 Å resolution. The SN7167 molecule binds in the minor groove over the AATTCG sequence with the methylpyridinium (P) ring near to the G10-C15 base pair and the bulky methylquinolinium (Q) extending as far as the A5-T20 base pair. The drug binds weakly to the DNA as evidenced by long-range contacts and shallow penetration into the groove. We are in the process of analysing the nature of these weak interactions.

This structure will be compared with that of the complex between the parent drug SN6999 and the alkylated DNA d(CGC[e⁶G]AATTCGCG)₂ [Y. Gao, M. Sriram, W. A. Denny, A. H.-J. Wang, (1993). *Biochemistry*, 32, 9639-9648]. There are significant differences between the two structures in the extent of DNA bending, drug conformation and groove binding.

PS04.04.22 STRUCTURE AND FUNCTION OF ANTITUMOR DRUG ACTINOMYCIN D. Fusao Takusagawa, Shigehiro Kamitori, Miho Shinomiya, Wenhua Chu, Robert F. Weaver, Departments of Chemistry and Biochemistry, University of Kansas, Lawrence, KS 66045-0046

A group of compounds called intercalators bind intercalatively to DNA, and interrupt RNA synthesis (transcription) and/or DNA synthesis (replication). Some intercalators have been used as anticancer drugs and others are carcinogens. There are several important questions to be answered in order to understand the biological activities of useful intercalators. Some of the questions are: how intercalators bind to DNA, how intercalators distort DNA structures, and how intercalators recognize their binding sequence. Three-dimensional structures of DNA drug complexes, in which a drug intercalates between the middle base pairs of a relatively long DNA fragment, has been sought as a more practical model for biological systems.

Actinomycin D (AMD) is known to bind intercalatively on DNA and severely inhibits RNA polymerase activity. It has been employed clinically as an antitumor agent for treat of highly malignant tumors. However, its selective toxicity is poor because it is an extremely potent, specific inhibitor of DNA-directed RNA synthesis. Recently, we have determined the three crystal structures of the complexes between d(GAAGCTTC)₂ and AMD and its analogues, in which AMD intercalated between the middle 5'-GC-3' base pairs (Kamitori, et al, *JMB*, 225, 445 (1992); Kamitori, et al., *JACS*, 116, 4154 (1994); Shinomiya, et. al., *Biochemistry*, 34, 8481 (1995)). These crystal structures of the complexes show how the drug interacts with DNA. On the basis of the structures, we have synthesized series of AMD analogues and characterized the physical and biological properties. At the meeting, the structure and activity relationship will be discussed.

PS04.04.23 CRYSTAL STRUCTURES OF TWO FURAN DERIVATIVES OF BERENIL AND d(CGCGAATTCGCG)₂. John O. Trent, Stephen Neidle, George R. Clark⁺, and David W. Boykin⁺⁺. The CRC Biomolecular Structure Unit, The Institute of Cancer Research, Sutton, Surrey, SM2 5NG, U.K.; ⁺Chemistry Department, University of Auckland, New Zealand; ⁺⁺Department of Chemistry and Biotechnology and Drug Design, Georgia State University, U.S.A.

DNA minor groove binding bis-benzamidine derivatives such as berenil, propamidine, and pentamidine have been shown to bind to AT-rich base-pair regions. Two furan derivatives of berenil with alkyl substituted benzamidines complexed with d(CGCGAATTCGCG)₂ have been determined to 2.2 Å resolution and refined to R factors of 16.9 and 18.6%.

The cyclopropane and isopropyl substituents are orientated away from the floor of the minor groove with no penalty to binding. The drugs are located in the minor groove by two strong amidine hydrogen bonds to the O₂ of the thymines situated at the ends of the AT-rich region. The isopropyl substituted derivative has a tight hydrogen bonded water network in the minor groove at one amidine site which changes the orientation of the isopropyl substituent. The overall effect of this alkyl benzamidine substitution is to increase the binding of the drugs to the minor groove.