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.

[1] Vlieghe D., Sponer J., Van Meervelt L., *Biochemistry*, 1999, **38**, 16443. [2] Uytterhoeven K., Sponer J., Van Meervelt L., *Eur. J. Biochem.*, 2002, **269**, 2868.

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