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In memory of Ben

Acknowledgments

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Abstract

Small molecules that bind specific DNA sequences may have powerful therapeutic applications by influencing the mechanisms of abnormal gene expression. Polyamides containing N-methylimidazole (Im) and N-methylpyrrole (Py) specifically bind the minor groove of DNA and have been shown to inhibit many protein-DNA complexes. However, some major groove-binding proteins can co-occupy the same DNA sequences as polyamides. Presented here are polyamide-intercalator conjugates that specifically bind target regions of DNA and deliver a non-specific intercalator to an adjacent site. The studies detail intercalative unwinding of specific DNA sequences to allosterically inhibit any protein:DNA complex. The evolution of sequence-specific polyamides to bisintercalate DNA and cause larger distortion of the helix is described. The success of hybrid molecules containing mixed DNA binding modes led to the development of a bis-polyamide-intercalator motif, modeled after the natural product actinomycin D, which is capable of specifically binding extended sequences of DNA. Also described is a polyamide-intercalator series which shows large fluorescence enhancement upon specific DNA binding and may be useful in detecting specific DNA sequences within living cells.

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