DNA Mismatch Binding and Antiproliferative Activity of Rhodium Metalloinsertors

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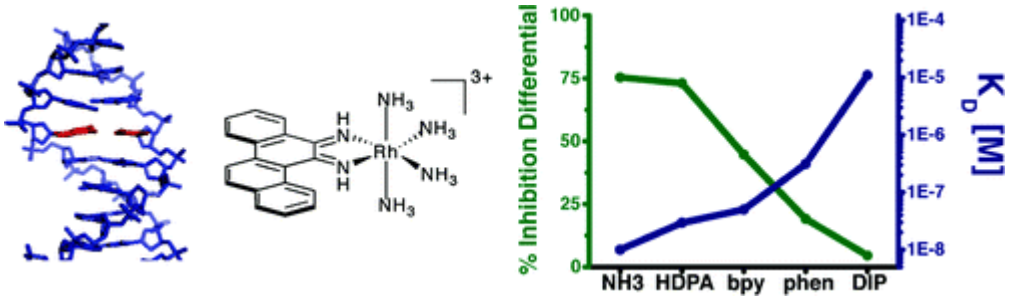
Abstract:



Deficiencies in mismatch repair (MMR) are associated with carcinogenesis. Rhodium metalloinsertors bind to DNA base mismatches with high specificity and inhibit cellular proliferation preferentially in MMR-deficient cells versus MMR-proficient cells. A family of chrysenequinone diimine complexes of rhodium with varying ancillary ligands that serve as DNA metalloinsertors has been synthesized, and both DNA mismatch binding affinities and antiproliferative activities against the human colorectal carcinoma cell lines HCT116N and HCT116O, an isogenic model system for MMR deficiency, have been determined. DNA photocleavage experiments reveal that all complexes bind to the mismatch sites with high specificities; DNA binding affinities to oligonucleotides containing single base CA and CC mismatches, obtained through photocleavage titration or competition, vary from 10^4 to 10^8 M^{-1} for the series of complexes. Significantly, binding affinities are found to be inversely related to ancillary ligand size and directly related to differential inhibition of the HCT116 cell lines. The observed trend in binding affinity is consistent with the metalloinsertion mode where the complex binds from the minor groove with ejection of mismatched base pairs. The correlation between binding affinity and targeting of the MMR-deficient cell line suggests that rhodium metalloinsertors exert their selective biological effects on MMR-deficient cells through mismatch binding *in vivo*.

Full text (subscription may be required):
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