A rhodium(III) complex for high-affinity DNA base-pair mismatch recognition

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A rhodium(III) complex, *rac*-$[Rh(bpy)_2phzi]^{3+}$ (bpy, 2,2'-bipyridine; phzi, benzo[*a*]phenazine-5,6-quinone diimine) has been designed as a sterically demanding intercalator targeted to destabilized mismatched sites in double-helical DNA. The complex is readily synthesized by condensation of the phenazine quinone with the corresponding diammine complex. Upon photoactivation, the complex promotes direct strand scission at single-base mismatch sites within the DNA duplex. As with the parent mismatch-specific reagent, $[Rh(bpy)_2(chrysi)]^{3+}$ [chrysene-5,6-quinone diimine (chrysi)], mismatch selectivity depends on the helix destabilization associated with mispairing. Unlike the parent chrysi complex, the phzi analogue binds and cleaves with high affinity and efficiency. The specific binding constants for CA, CC, and CT mismatches within a 31-mer oligonucleotide duplex are 0.3, 1, and 6×10^7 M^{-1}, respectively; site-specific photocleavage is evident at nanomolar concentrations. Moreover, the specificity, defined as the ratio in binding affinities for mispaired vs. well paired sites, is maintained. The increase in affinity is attributed to greater stability in the mismatched site associated with stacking by the heterocyclic aromatic ligand. The high-affinity complex is also applied in the differential cleavage of DNA obtained from cell lines deficient in mismatch repair vs. those proficient in mismatch repair. Agreement is found between photocleavage by the mismatch-specific probes and deficiency in mismatch repair. This mismatch-specific targeting, therefore, offers a potential strategy for new chemotherapeutic design.