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Octahedral copper(II)-diimine complexes of triethylenetetramine: effect of stereochemical fluxionality and ligand hydrophobicity on Cu^{II}/Cu^{I} redox, DNA binding and cleavage, cytotoxicity and apoptosis-inducing ability†

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Octahedral copper(II) complexes of the type [Cu(trien)(diimine)]$(ClO_4)_2$ (**1–4**), where trien is triethylenetetramine and diimine is 2,2′-bipyridine (**1**), 1,10-phenanthroline (**2**), 5,6-dimethyl-1,10-phenanthroline (**3**), and 3,4,7,8-tetramethyl-1,10-phenanthroline (**4**), have been isolated. Single crystal X-ray structures of **1** and **2** reveal that the coordination geometry around Cu(II) is tetragonally distorted octahedral. The stereochemical fluxionality of the complexes illustrates the observed trend in Cu^{II}/Cu^{I} redox potentials and DNA binding affinity (K_b: **1**, 0.030 ± 0.002 < **2**, 0.66 ± 0.01 < **3**, 1.63 ± 0.10 < **4**, 2.27 ± 0.20 × 10^5 M^{-1}), determined using absorption spectral titration. All complexes effect oxidative DNA cleavage more efficiently than hydrolytic DNA cleavage. The bpy complex **1** with stereochemical fluxionality lower than its phen analogue **2** shows a higher cytotoxicity against both A549 lung (IC_{50}, 3.3 μM) and MCF-7 human breast (IC_{50}, 3.9 μM) cancer cells, and induces the generation of the highest amount of ROS in A549 cells. Complex **3** with a higher stereochemical fluxionality and higher ligand hydrophobicity exhibits a higher DNA binding and cleavage ability and higher cytotoxicity (IC_{50}, 2.1 μM) towards MCF-7 cells. Complex **4** with a still higher stereochemical fluxionality displays the highest DNA binding and cleavage ability but a lower cytotoxicity towards both A549 and MCF-7 cell lines due to its tendency to form a five-coordinated complex with the uncoordinated amine group. Annexin V.Cy3 staining and immunoblot analysis demonstrate the mechanism of cell death caused by **1** and **2**. The finding of the up-regulation of the pro-apoptotic Bax protein and down-regulation of PARP protein in western blot analysis confirms the induction of apoptosis by these complexes.

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Introduction

Cancer, the uncontrolled proliferation of cells, has become the based drug, is the most extensively used chemotherapeutic drug for the treatment of different types of cancers which include testicular cancer, cervical cancer, breast cancer,