New oxindolimine metal-complexes capable of binding to DNA, but that are non-toxic to cells

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Introduction - Copper and zinc complexes coordinated to indole derivatives have been studied in our laboratory. Most of them have activity in the presence of biomolecules such as DNA, and showed to be promising pro-apoptotic agents, constituting potential metallodrugs [1]. Two new copper (CuL) and analogous zinc (ZnL) complexes were prepared, with oxindolimine ligands obtained from the reaction of aminoguanidine with indole-7-carboxaldehyde, and characterized by spectroscopic techniques (UV/Vis, IR). We investigated the interaction of these compounds with DNA, to verify its stability in biological environment and elucidate differences in its reactivity towards biomolecules, depending on its structure. The cytotoxicity of these compounds was tested against human MES-SA and resistant MES-SA/Dx5 sarcoma cells, in comparison to non-tumor fibroblast P4 cells.

Methods - The synthesis of the ligand was performed by reaction of indole-7-carboxaldehyde with aminoguanidine, under reflux for 1,5 hours, in the presence of triethylamine and using ethanol as solvent. Copper(II) or zinc(II) perchlorate was added dropwise to the solution of the ligand, obtaining a red and a pink solid, respectively, after slow evaporation. Interactions of the complexes with DNA were monitored by UV, through the titration of each complex solution (10 μM) with DNA, in the range of molar ratio 0.3 to 2.0. Cell viability was estimated by the MTT assay as the number of viable cells, compared to control measurements.

Results - The new complexes, isolated as perchlorate, showed characteristic band υC=N at 1647 cm^{-1} in infrared spectra, indicating coordination of a Schiff base ligand to the metal. UV/Vis spectra of CuL complex showed characteristic bands at: 286, 350 and 530 nm, ε= 5.46 x 10^3, 3.84 x 10^3 and 2.35 x 10^3 M^{-1} cm^{-1}, respectively. For the corresponding ZnL complex, bands appeared at: 264 and 332 nm, with ε= 3.48 x 10^3, and 4.89 x 10^3 M^{-1} cm^{-1}, respectively. In the studies of interactions with DNA, monitored by electronic spectroscopy, a pronounced effect of hypochromism was observed, indicating probably an intercalation of the compounds at DNA. The determined IC_{50} values towards P4 cells were 76.40 μM for ZnL_4 and > 100 μM for CuL_4, after 24 h incubation. For the uterine sarcomas, the IC_{50} for CuL_4 was > 100 μM for both MES-SA and MES-SA/Dx5. On the contrary, ZnL complex showed a selectivity vs. strains of uterine sarcoma, since the determined IC_{50} was 82.12 μM for MES-SA, while for MDR cell MES-SA/Dx5 the IC_{50} was > 100.

Conclusion - New oxindolimine-copper(II) and zinc(II) complexes were synthesized, showing strong interaction with DNA, but low toxicity towards both non-cancer and tumor cells.

References:

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