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Ruthenium(II)-diphosphine complexes as anticancer agents: synthesis, characterization and biological studies

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Chemotherapy is, probably, the main strategy to fight cancer. The use of metallodrugs as chemotherapeutic agents has been rising, initially, with the development of the cisplatin and consolidated by other Pt-based complexes.[1] Although several compounds have been studied as potential anticancer agents, ruthenium-based compounds are considered a promising alternative to platinum drugs.[2,3] In this work we describe three Ru(II)-based compounds containing both phosphine and mercapto ligands, with a general formula $[Ru(dppm)_2(N–S)]PF_6$ (**1–3**) [N–S are 1,3-thiazolidine-2-thione (Hmtz), mercapto-1-methylimidazole (Hmmi) and 4,6-diamino-2-mercapto-pyrimidine (Hdmp) and dppm is the 1,1`-bis(diphenylphosphino)methane]. These complexes were characterized by nuclear magnetic resonance (NMR) [^{1}H, $^{31}P(^{1}H)$, and ^{13}C], high resolution mass spectrometry (HR-MS), conductivity and infrared and UV-Vis spectroscopies. The cyclic voltammetry obtained in DCM for **1–3** revealed processes attributed to Ru^{II}/Ru^{III} redox couple, ranging from 1.04 to 1.32 V *vs* Ag/AgCl. Their distribution coefficients between *n*-octanol/water indicated the preference for the organic phase. As the stability of these complexes was confirmed in different media (DMSO and DMSO/DMEM) over 48 h, their cytotoxicity was tested in different cancerous and non-cancerous cell lines. Complex $[Ru(dppm)_2(mmi)]PF_6$ (**2**) [mmi = mercapto-1-methylimidazole] was found to be more cytotoxic and selective than cisplatin control, exhibiting IC_{50} = 0.28 ± 0.03 µM on MCF-7 breast cancer cells. In addition, **2** affects cell morphology and inhibits colony formation in these cells. DNA still represents the main target studied with medicinal purpose. In this scenario, the interaction modes between these complexes and DNA were investigated using different techniques, such as viscosity, circular dichroism, fluorescence and agarose gel electrophoresis. Our results revealed that **1–3** interact via electrostatic or minor groove contacts. Furthermore, Ames and micronucleus tests revealed the lack of mutagenicity for **2**, making it a promising anticancer agent.

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