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New ruthenium(II) complexes bearing 8-hydroxyquinolines derivates and their biological applications

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Ruthenium(II)-based complexes have been investigated as promising metallodrug candidates. An interesting strategy can be the synergic effect of using an active molecule as a ligand to improve the pharmacological response. De Sousa *et al*. demonstrated the antileishmanial activity of clioquinol (CLQ) against two relevant species of *Leishmania* [1]. These studies represent an opportunity for developing new metal complexes with ruthenium [2]. The synthesis, characterization, and evaluation of biological activities of two novel ruthenium(II) complexes with CLQ and 8-hydroxyquinoline (8HQ), are presented here. The complexes with formula $Ru(CLQ)(PPh_3)_2(bipy)]PF_6$ **(complex I)** and $Ru(8HQ)(PPh_3)_2(bipy)]PF_6$ **(complex II)** have molar conductivity of 71 and 95 Scm^2mol^{-1}, in methanol, attributed to a 1:1 electrolyte. The FT-IR spectra have bands at 1550 (νC=N), 1490 ($\nu C=C_{ring}$), 1090 (νC-P), and 833 (νP-F) cm^{-1} representing the major functional groups in the complexes. The complexes exhibited bands at 257 nm, 362 nm, and 470 nm related to intraligand $\pi \rightarrow \pi^*$ and MLTC transitions. Furthermore, elemental analysis, cyclic voltammetry, and NMR spectroscopy were used to characterized the complexes. The Ru(II) metal center present Ru(II)/Ru(III) oxidation potentials around 858 mV for **complex I** and 713, 842 mV for **complex II**. The $^{31}P\{^1H\}$ NMR spectra present one simplet signal around 25 ppm, refiring to the equivalent P atoms on the complexes. The structures of the complexes were confirmed as a distorted octahedral structure (with bond angles different from 90°) by single-crystal X-ray diffraction. The complexes have the P atoms of the PPh_3 in a *trans* position and the two N atoms of the bipy in a *trans* position to the N-O atoms of the CLQ and 8HQ ligands. Spectrophotometric titrations, DNA viscosity measurements, and electrophoresis experiments were performed to understand the interaction of the complexes with DNA. The intrinsic binding constants Kb are around 10^4-10^5 M^{-1}. These suggests a moderate interaction with CT-DNA as non-covalent, including intercalation, hydrogen bonding, or hydrophobic interactions. Cytotoxicity studies show IC_{50} values on *Leishmania infantum* of 35.56 and 3.289 µM for **complex I** and **II**, respectively. **Complex II** is more cytotoxic on *Leishmania infantum* than the free ligand 8HQ (IC_{50} > 200 µM). This result is in agreement with data reported in the literature for similar complexes with structure $[Ru(8HQs)(dppf)(NN)]PF_6$ [3]. In this study, the IC_{50} values in *Leishmania infantum* are between 3.0–4.8 µM. In this sense, our **complex II** becomes a promising candidate for drug development studies.

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