BIOREDUCTION AND CYTOTOXICITY OF Co^{3+} COMPLEXES CANDIDATES FOR PRODRUGS ACTIVATED BY HYPOXIA

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Solid tumors present regions of low oxygen (hypoxia) controlled by the irregular growth of blood vessels, which usually become resistant to chemo and radiotherapies. This characteristic has been explored for the development of hypoxia target-specific prodrugs, since this region of the tumor is a reducing environment. Then, cobalt complexes have been exploited as drug delivery, specially because of two oxidation states with different labilities, Co^{3+} that is inert, and Co^{2+} which is more labile. In order to evaluate a series of complexes to act as bioreductively activated prodrugs[1,2], here is presented the potential of biomolecules, like ascorbic acid and cysteine, to reduce the complexes of the series $[Co(bepi\text{-}R)_2]^+$ (R= H, OCH_3, Cl, Br and NO_2). In addition, their cytotoxicity activities were evaluated against the tumor cell lines MCF-7 and A549, with and without previous reduction. Ligands were synthesized reacting 2-(2-aminoethyl)pyridine with 5-R-salicilaldehydes (R= H, OCH_3, Cl, Br, NO_2), and treated with cobalt salts affording the desired complexes. After recristalization, single crystals were obtained, caracterizated,[3] and then used for bioreduction and cytotoxicity analyses. Bioreductions were spectroscopically monitored using complexes solutions ($1x10^{-4}$ M). The LMCT bands were monitored before and after the addition of ascorbic acid (or cysteine) in two different concentrations (5×10^{-4} M and 1×10^{-3}M) during 1/2, 1, 3/2, 2, 20, 24, 44, 48 and 120h. The best results were achieved with ascorbic acid (10^{-3}M) for complexes $[Co(bepi\text{-}Br)_2]^+$ and $[Co(bepi\text{-}NO_2)_2]^+$. The cytotoxicity analyses has shown that, in this series of complexes, the best cytotoxic activity was observed for complex $[Co(bepi\text{-}Br)_2]^+$, whose IC_{50} values were 91.4 μM in the MCF-7 cell line and 112.7 μM in A549, similar values, or even lower, than those obtained for cisplatin 91.2 μM (MCF-7) and 121.6 μM (A549) in the same conditions.

[1] SOUZA, E. T.; *Journal of Inorganic Biochemistry*, **2009**, 103, 1355-1365.
[2] SOUZA, E. T.; *Journal of Inorganic Biochemistry*, **2011**, 105, 1767-1773.
[3] Personal information (data not published).
CNPq, FAPERJ, CAPES, PRONEX2010, PRONEM2011.