Structure-activity relationship of ruthenium-catecholamines as promising complex to control tumoral angiogenesis. CAM assays

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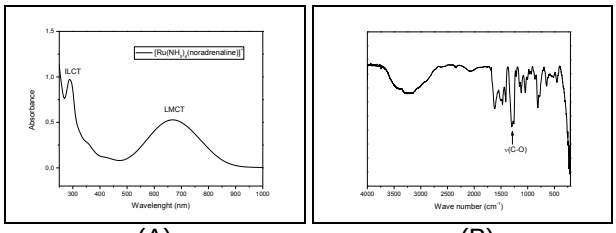
Introduction

Cancer kills people worldwide everyday. Tumor growth is related to its high rate of angiogenesis. Literature reports that catecholamines are involved in angiogenesis[1]. The understanding of catecholamines action in tumor development is substantial to control the formation and growth of the neovessels - thus it is possible to prevent increasing of a tumor. In this way, ruthenium complexes using catecholamines (noradrenaline, isoproterenol, adrenaline and dopamine) as ligands were synthesized and their angiogenic effect were evaluated in chicken eggs.

Results and Discussion

Compounds were characterized by several techniques, such as vibrational (FTIR), electronic and Raman spectroscopies; mass spectrometry; high performance liquid chromatography (HPLC); electrochemical analyzes and spectroelectrochemistry. Biological assays were developed in White Leghorn eggs. Electronic spectra of these complexes demonstrate caractheristics bands in the region of 670 (ligand-metal charge transfer) and 290 nm (intraligand). Vibrational spectra show peculiar bands of ammonia ligands and dioxolene substituents (Fig 1).



(A) (B)

Figure 1: A) Electronic spectrum of $[Ru(NH_3)_4(noradrenalinel)]^+$ 5×10^{-4} M in aqueous solution. B) FTIR of $[Ru(NH_3)_4(noradrenaline)]^+$ in CsI pellet.

Electrochemical processes involve reversible $Ru^{III/II}$-catechol (A) and Ru^{II}-quin/Ru^{II}-semiq (B) (Fig 2).

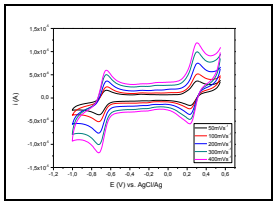


Figure 2: Cyclic voltammetry of $[Ru(NH_3)_4(noradrenaline)]^+$ in KCl – 0.1 M. Scan rates 50, 100, 200, 300 and 400 mV s^{-1}.

HPLC analyzes show that complexes were obtained in high level of purity:

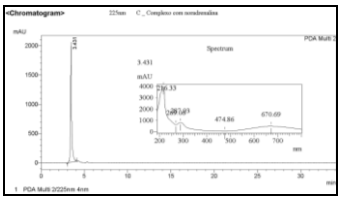
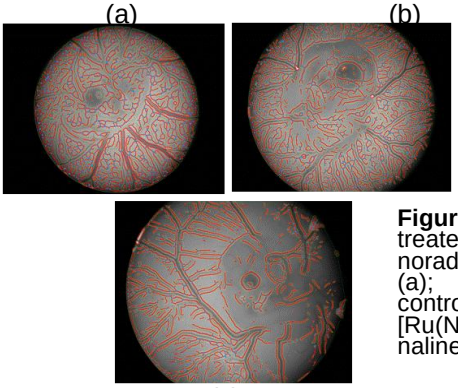


Figure 3: Chromatogram $[Ru(NH_3)_4(noradrenaline)]^+$: C18 (250cm x 4.6mm), 15% MeOH, 85% phosphate buffer 0.01 mol L^{-1}, pH 6.9, 1 mL min^{-1}, λ = 225 nm.

Results of free noradrenaline demonstrated that this catecholamine is proangiogenic, according to the literature[1]. However, eggs treated with $[Ru(NH_3)_4(noradrenaline)]^+$ presented only 47% of the quantity of negative control (PBS) vessels, while positive control (heparin) showed 23% of reduction related to negative control (PBS). Therefore, this ruthenium complex could be considerate an antiangiogenic compound.

(a) (b)



(c)

Figure 4: Eggs treated with: noradrenaline free (a); negative control (PBS) (b); $[Ru(NH_3)_4(noradrenaline)]^+$ (c)

Conclusions

Preliminary results showed that the proangiogenic mechanism of catecholamines is dependent on catechol site. Upon coordination, the $[Ru(NH_3)_4(catecholamine)]^+$ seems to control this mechanism and therefore could be a promising regulator of angiogenesis. Its excellent stability allows this metallic complex to become a future drug to cancer angiogenesis. This assay allows us also to understand better the action of catecholamines in tumor growth, as the site bonding.

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[1] Sarkar, C.; Chakroborty, D.; Basu, S. *J. Neuroimmune Pharmacol.* **2013**, *8*, 7.