Metal complexes of biologically relevant molecules with anticancer and cholinesterase inhibiting properties

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Two systems will be described and discussed in this contribution. Compounds containing the η^6-p-cymene-chloro-ruthenium(II) fragment are promising agents for the treatment of degenerative diseases.[1] Herein novel [(η^6-*p*-cymene)Ru(**L**)Cl]PF_6 complexes were prepared in good yields from aza-chalcones [N,O donors **L** = 3-R-1-(pyridin-2-yl)prop-2-en-1-one, R = 4-C_6H_4X (X = H **1a** and electron donor and electron withdrawing groups)] and their structures, established by spectroscopic and X-ray diffraction analyses (**Fig. 1**). Investigation of their aqueous solution chemistry (UV-Vis, ^{1}H NMR and ESI-TOF mass spectrometry) showed Ru–Cl bond hydrolysis with rates varying from 6.75 ± 0.3 x 10^{-4} to 4.28 ± 0.6 x 10^{-3} (298 K) and reversible hydration of the aza-chalcone double bond generating the coordinated corresponding alcohols. Strong interaction with DNA and inhibition of topoisomerase IIα at 100 mmol.L^{-1} were evidenced. *In vitro* cytotoxic activity of the compounds was investigated in a number of cancer cell lines. Best IC_{50} values <15 mmol.L^{-1} were obtained for WM35, WM793, WM1617, B16-F10, HL-60 and HeLa cell lines.

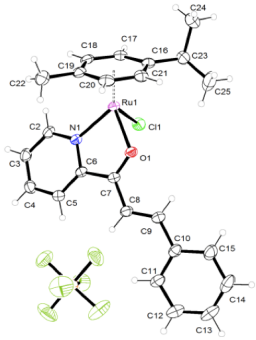
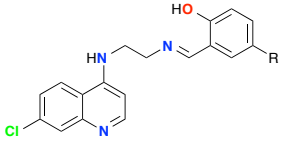


Figure 1. Structure of **1a**

The most promising currently available drugs for palliative treatment of Alzheimer's disease (AD) are acetylcholinesterase inhibitors (AChEI). In human brain regions affected by AD (with high levels of Aβ) evidence for Cu imbalance has been found, with an increase in labile Cu^{2+} ions. These ions are scavenged by amyloidogenic plaques, which thus become even more toxic. We describe the synthesis, molecular docking, cytotoxicity and anti-AChE activity of a series of 7-chloro quinoline candidates (**HL**, Fig. 2A) for the treatment of AD. Due to intrinsic relationship between Cu^{2+} and the amyloidogenic plaques these ligands were reacted with Cu^{2+} salts to analyze the species that could be formed *in vivo*. Dimeric species $[Cu(\mathbf{HL})_2]_2Cl_4$ were isolated in the solid state and fully characterized, including by an X ray diffraction study (Fig. 2B). According to EPR data, the compounds exist as monomers in DMSO. The inhibitory activity of all compounds was evaluated by spectrophotometric Ellman's method in AChE from EE. Schiff bases **HLa-HLe** were better inhibitors than their complexes **2a-e**, except for **2d** In AD-affected brain, **HLd** may scavenge the Cu^{2+} bonded to Aβ, possibly enabling its disaggregation and forming **2d**, which in turn inhibits AChE.



	R	IC_{50}(μM)
HLa	H	4.61 ± 0.48
HLb	Br	7.17 ± 0.43
HLc	NO_2	9.23 ± 0.36
HLd	OCH_3	9.31 ± 1.17
HLe	CH_3	7.34 ± 0.06
Cu2d		5.45 ± 0.70

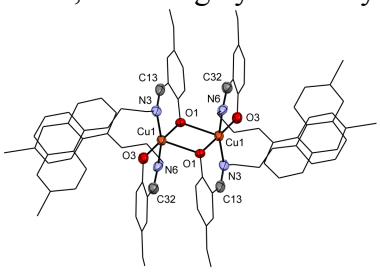


Figure 2. Structures of **HLa-e** and **Cu2d** (Cu(1)···Cu(1') = 3.262(4)Å

1. a) Dyson, P. J. et al, *Chem. Commun.*, **2001**, 1396; b) Sadler, P. J. et al, *J. Med. Chem.*, **2001**, *44*, 3616.
2. Faller, P., *Free Radical Biol. Med.,* **2012**, *52* 747

FAPERJ, CNPq, Capes; Josélia A. Lima (IME) and Ronny R. Ribeiro (UFPR) for measurements.