Imine complexes of essential metals showing antiparasite activity towards Chagas Disease and Leishmaniosis

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In this project, studies were carried out on the reactivity of imine ligands derived from isatin, an endogenous indole formed as a metabolite of tryptophan and serotonine, and its corresponding metal complexes towards parasite infections, particularly Chagas disease and Leishmaniosis. Chagas disease is caused by protozoa *T. cruzi*, and Leishmaniosis is triggered by more than 20 different *Leishmania* parasites. Both diseases are infectious, endemic on many countries and responsible for millions of infected people around the world, with a high ratio of mortality[1,2]. Drugs available nowadays to combat these infections have been developed many years ago, and present many disadvantages, including severe collateral effects. Since the metal complexes under study are capable of generating reactive oxygen species (ROS), especially hydroxyl radicals, and of inhibiting specific crucial proteins as kinases and topoisomerases, we intend to verify possible mechanisms of action of such complexes as antiparasite agents.

New metal compounds derived from isatin were synthetized seeking to enhance the activities shown by previous similar compounds studied. A novel compound was also synthesized, without the indole moiety, to provide a comparison with the ones that have oxindole group on their structure. These new compounds were characterized by several techniques, including UV-Vis, IR, elemental analysis, ICP-OES, and EPR. The structure and elemental analysis of some of the studied compounds are shown below.

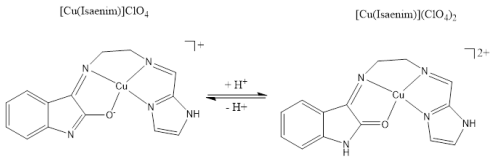

Fig. 1: Structure of $[Cu(isaenim)]ClO_4$ complex.

Table 1: Elemental analysis and ICP-OES results.

COMPLEXES	Elemental Analysis (% C/ H/ N)	ICP-OES (%Cu)
$[Cu(isaenim)]ClO_4$	36.14/ 3.47/ 15.05 35.58/ 3.07/ 14.26	13.66 (Calc.) 16.41 (Experim.)
$[Cu(isabmz)]\ ClO_4$	34.05/4.46/9.93 33.46/4.12/9.02	11.26 (Calc.) 15.74 (Experim.)
$[Cu(apybmz)]ClO_4$	33.94/3.04/10.56 35.78/3.17/10.61	11.97 (Calc.) 12.13 (Experim.)

Through the so called MTT method, based on tetrazolium dye, [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide], a faster and more accurate method to determine the dying rate of the parasites[3], several experiments were initially conducted in order to verify the best conditions for the MTT analysis. These experiments set out 3 h incubation, MTT 2.5 mg/mL and parasite concentration $6.25x10^5$ to $1.0x10^7$ parasites/mL as optimized conditions. Further experiments to determine IC_{50} values regarding the cytotoxicity of all the compounds are in progress.

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2 - G.A. Schmunis, *Mem. Inst. Oswaldo Cruz*, Rio de Janeiro 102 (2007) 75-85.
3 – S. Muelas-Serrano, J.J. Nogal-Ruiz, A. Gómez-Barrio, *Parasitol. Res.* 86 (2000) 999-1002.

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