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Chagas075- **Evaluation of anti-*Trypanosoma cruzi* activities of nitrosyl/nitro ruthenium complexes *in vitro* and *in vivo***

1Bastos T. M., 2Barbosa M. I. F., 1Meira C. S., 1Guimarães E. T., 2Batista A. A., 1,3Soares M. B. P.
1CPqGM-Fiocruz, Salvador - Brazil, 2Universidade Federal de São Carlos, Departamento de Química, São Carlos - Brazil, 3CBTC – Hospital São Rafael, Salvador - Brazil.

Benznidazole has been used to treat Chagas disease since the decade of 70ies. Both drugs are effective in acute phase or recent chronic phase of the disease, but they can induce side effects for the patients. Therefore, more efficient drugs with lower toxicity are need for the treatment of this disease. Synthesis of transition metal compounds, especially ruthenium, has increased over the years and data have shown many biological applications of these compounds. The discovery of pharmacological functions of nitric oxide (NO), mainly on infection by protozoa, has led the development of NO donor compounds as therapeutic agents. This study aimed to evaluate the anti-*T. cruzi* activity of the nitrosyl/nitro ruthenium complexes, *cis*-[RuCl(NO2)(dppb)(5-mebipy)], *cis*-[Ru(NO2)2(dppb)(5-mebipy)], *ct*-[RuCl(NO)(dppb)(5-mebipy)](PF6)2 and *cc*-[RuCl(NO)(dppb)(5-mebipy)](PF6)2; (dppb=1,4-bis(diphenylphosphino)butane; 5-mebipy=5,5´-dimethyl-2,2´-bipyridine). The cytotoxicity assay was performed using splenocytes from BALB/c mice in the presence of the compounds at different concentrations. Trypanocidal effects were evaluated *in vitro* and *in vivo*. The evaluation of anti-*T. cruzi* activity *in vitro* was performed by incubating trypomastigotes and epimastigotes forms in the presence of the complexes. *In vivo* experiment was performed using female BALB/c mice infected with 104 parasites per mouse and orally treated with 25 mmol/kg/day of each compound, daily, for 5 consecutive days. Scanning electron microscopy was performed to evaluate ultrastructural effects of the most active compound. The LC50 values of *cis*-[RuCl(NO2)(dppb)(5-mebipy)], *cis*-[Ru(NO2)2(dppb)(5-mebipy)], *ct*-[RuCl(NO)(dppb)(5-mebipy)](PF6)2 and *cc*-[RuCl(NO)(dppb)(5 -mebipy)](PF6)2 were 34.43 μM, 16.34 μM, 34.05 μM and 27.96 μM, and the IC50 values for trypomastigotes were 8.38 μM, 2.87 μM, 2.08 μM and 5.85 μM, respectively. The first compound was not active against epimastigote form and the IC50 values of the other complexes were 16.64 μM, 5.69 μM, 26.66 μM, respectively. IC50 values of benznidazole, under the same conditions, were 11.41 μM and 10.68 μM. *In vivo* treatment with the compounds reduced parasitaemia and the groups treated with the compounds *cis*-[RuCl(NO2)(dppb)(5-mebipy)] and *ct*-[RuCl(NO)(dppb)(5-mebipy)](PF6)2 increased the survival of BALB/c mice in acute phase of the Chagas disease. The complex *ct*-[RuCl(NO)(dppb)(5-

mebipy)](PF6)2 presented the best results *in vitro* and *in vivo*. Scanning electron microscopy demonstrated that the treatment of trypomastigotes with this compound caused membrane fragmentation, surface discontinuities and shrinkage of the parasites. In conclusion, we observed that ruthenium complexes were effective against *T. cruzi* using *in vitro* and *in vivo* experimental models. **Supported by:** CNPq, CAPES, PRONEX and FAPESP. **E-mail:** taniramatutino@aluno.bahia.fiocruz.br