Ruthenium monocarbonyl complexes are antiparasitics by inducing oxidative stress and irreversible necrotic parasite death

Diogo R. M. Moreira,[1*] Marília I. F. Barbosa,[2,3] Tanira M. Bastos,[1] Rodrigo S. Correa,[2,4] Milena B. P. Soares[1] and Alzir A. Batista[2]

[1]FIOCRUZ, Salvador, BA, Brazil. [2]UFSCAR, São Carlos, SP, Brazil. [3]UNIFAL, Alfenas, MG, Brazil. [4]UFOP, Ouro Preto, MG, Brazil.

*e-mail: diogo.moreira@bahia.fiocruz.br

Chagas disease, caused by protozoan *Trypanosoma cruzi*, remains a major health problem in Latin America. Chemotherapy based on Benznidazole has long been a mainstay in the combat against Chagas disease, but limited efficacy an increasing emergence of drug resistance is limiting disease control.[1] We previously demonstrated that ruthenium complexes containing nitrosyl ligand are endowed with potent antiparasitic activity.[2] Based on this, here we examined the anti-*T. cruzi* activity of six new complexes containing carbonyl as ligand.

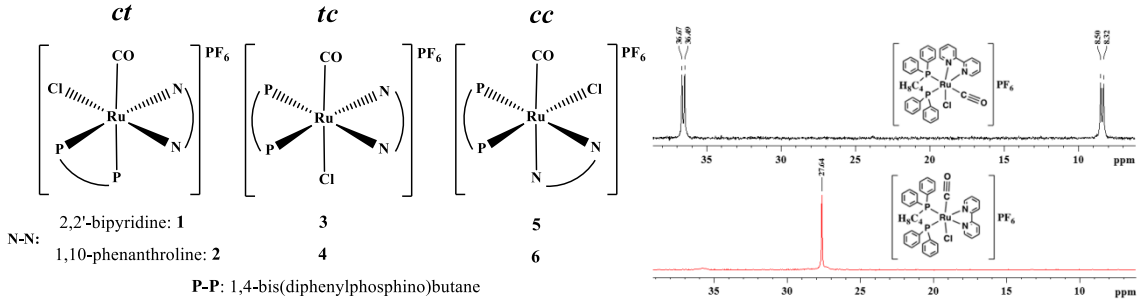

Figure: (*Left***)** Structures of complexes. (*Right*) ^{31}P NMR spectra of (**1**) and (**2**) complexes.

These complexes were fully characterized by conductivity, I.R., cyclic voltammetry, ^{1}H, ^{13}C and ^{31}P NMR and X-ray crystallography. In comparison to benznidazole, ruthenium complexes were more active antiparasitic agents, while metallic precursor lacking carbonyl was devoid of activity.

Table. Activity against *T. cruzi* and host cell cytotoxicity.

Compounds	Trypomastigotes Y strain, EC_{50} ±S.E.M.(μM)[a]	splenocytes, EC_{50} ±S.E.M.(μM)[b]
ct-[RuCl(CO)(dppb)(bipy)]PF_6 (**1**)	0.95 ± 0.1	1.21 ± 0.2
ct-[RuCl(CO)(dppb)(phen)]PF_6 (**2**)	N.D.	N.D.
tc-[RuCl(CO)(dppb)(bipy)]PF_6 (**3**)	0.9 ± 0.1	3.15 ± 0.10
tc-[RuCl(CO)(dppb)(phen)]PF_6 (**4**)	1.8 ± 0.1	0.53 ± 0.10
cc-[RuCl(CO)(dppb)(bipy)]PF_6 (**5**)	2.0 ± 0.4	0.66 ± 0.50
cc-[RuCl(CO)(dppb)(phen)]PF_6 (**6**)	3.3 ± 0.5	0.42 ± 0.10
Benznidazole	10.6 ± 2.3	> 100

[a] Determined 24 h after incubation with compounds. [b] Determined 72 h after incubation with compounds.

The underlying mechanism of action for *tc*-[RuCl(CO)(dppb)(bipy)]PF_6 (**3**) showed that this complex is a parasiticidal agent (killing), induces oxidative stress (MitoSOX staining) and causes cell death through a necrotic pathway (PI staining).

[1]Pérez-Molina, J. A.; Perez, A. M.; Norman, F. F.; Monge-Maillo, B.; López-Vélez, R. *Lancet Infect Dis.* **2015** *15*, 1347. [2]Bastos, T. M.; Barbosa, M. I.; da Silva, M. M.; Júnior, J. W.; Meira, C. S.; Guimaraes, E. T.; Ellena, J.; Moreira, D. R.; Batista, A. A.; Soares, M. B. *Antimicrob. Agents Chemother.* **2014**, *58*, 604.

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