

Metal complexes in the management of parasitic diseases: *In vitro* antiprotozoal studies of metal complexes of some antimalarial drugs

Parasitic infections are common in developing areas of the world, where the poorest of the poor live and affect an estimated 3.5 billion people. The three infections which constitute the highest disease burden are malaria caused by *Plasmodium* spp., African human trypanosomiasis caused by *Trypanosoma brucei rhodesiense* and *T. b. gambiense*, and Chagas disease caused by *Trypanosoma cruzi*. Malaria was successfully reduced after World War II because of easy access to cheap insecticide and readily available drugs. At present, there are an estimated 300–500 million cases, and up to 2.7 million deaths each year^{1,2}. The genus *Trypanosoma* contains a large number of parasitic species which infect wild and domesticated animals and humans. Only four drugs are in use for the treatment of trypanosomiasis. All of them have to be administered parenterally and frequently cause serious side effects^{3,4}. The emergence and spreading of parasites resistant to drugs in use for their treatment indicates that novel compounds need to be developed by identification of novel chemotherapeutic targets. Hence, the search for new anti-malarial therapies is a high priority for control of the disease. In the search for novel drugs against resistant parasites, the use of metal complexes has received considerable attention in recent years^{5–7}. In our effort to contribute to the search for novel chemotherapeutic drugs against parasitic diseases, we present the antiplasmodial and antitrypanosomal screening of metal complexes of some antimalarial drugs.

The metal complexes were synthesized as reported in the literature^{8–11}. The tests were performed as micro plate assays using *T. b. rhodesiense* (STIB 900), *T. cruzi* (Tulahuenc C4), *Leishmania dono-*

vani (MHOM-ET-67/L82) and K1 strain of *Plasmodium falciparum* (resistant to chloroquine and pyrimethamine). A description of these assays is reported elsewhere¹². The following were used as standard: melarsoprols (*T. b. rhodesiense*), Benznidazole (*T. cruzi*), Miltefosine (*L. donovani*) and chloroquine (*P. falciparum*).

The exact IC₅₀ values for the anti-parasitic assays and cytotoxicity of the complexes are presented in Table 1. The Cu(II) complex of trimethoprim [Cu(TMP)₂(CH₃COO)₄] exhibited the highest antiplasmodial activity (IC₅₀ = 3.7231 μM). It is more active than trimethoprim (IC₅₀ = 4.733 μM) and less toxic than trimethoprim (IC₅₀ = 46.474 μM), and the widely used chloroquine (IC₅₀ = 188.5 μM)¹³. All the metal complexes showed some level of activity against *T. b. rhodesiense*, with two Cu(II) complexes being the most active. The Cu(II) complexes of trimethoprim [Cu(TMP)₂(CH₃COO)₄] showed the highest activity (IC₅₀ = 3.411 μM), while the Cu(II) complex of sulphadiazine [Cu(SD)₂(H₂O)₂], (IC₅₀ = 15.063 μM) was the least toxic of all the complexes. The Cu(II) complex of trimethoprim (IC₅₀ = 16.3 μM) was the only active compound against *T. cruzi*, while the Pt(II) (IC₅₀ = 11.9 μM) and Pd(II) (IC₅₀ = 16.6 μM) complexes of trimethoprim were the only active compounds against axenic *L. donovani*.

The incorporation of metals into the drugs has improved the antiprotozoal activities of some of the metal complexes. The Cu(II) complex of trimethoprim showed enhanced antiplasmodial activity against the resistant strain of *P. falciparum*, while both Cu(II) complexes of sulphadiazine and trimethoprim showed activity against *T. b. rhodesiense*, and were far less toxic than chloroquine. Al-

though the activities of the complexes are not yet a challenge for the current generation of drugs in use, they will serve as leads for further structural modifications in the search for alternative therapy.

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Table 1. *In vitro* antiplasmodial and antitrypanosomal tests

Compound	<i>Plasmodium falciparum</i> K ₁ (μM)	<i>Trypanosoma brucei rhodesiense</i> (μM)	<i>Trypanosoma cruzi</i> (μM)	<i>Leishmania donovani</i> axenic (μM)	Cytotoxicity (μM)
[Cu(SD) ₂ (H ₂ O) ₂]	>5	15.05	>30	>30	19.90
[Cu(TMP) ₂ (CH ₃ COO) ₄]	3.72	3.41	16.3	>30	40.83
[Pd(TMP)(H ₂ O)Cl ₂].H ₂ O	>5	43.64	>30	16.60	>90
[Co(TMP) ₂ Cl ₂]	>5	63.18	>30	>30	>90
[Pt(TMP)(H ₂ O)Cl ₂].H ₂ O	>5	37.91	>30	11.90	>90
[Co(SD) ₂ (H ₂ O) ₂]	>5	50.50	>30	>30	>90