Copper and Cobalt Complexes Endowed with Potent Antiplasmodial and Antiamoebic Activities

Amir Azam[1] (PQ), Deepa Bahl [1] (PG), Matheus S. de Sá[2] (PG), Milena B. P. Soares[2] (PQ), Lucas C. D. Coêlho[3] (PG), Suellen M. T. Cavalcanti[3] (PG), Paulo A. T. M. Gomes[3] (IC), Gevanio B. de O. Filho[3] (IC), Ana C. L. Leite[3*] (PQ)

*[1]Department of Chemistry, Jamia Millia Islamia, Jamia Nagar, New Delhi-110025 India. [2]Oswaldo Cruz Foundation, CPqGM, Salvador BA. [3]Pharmacy, UFPE, 50740-520, Recife, PE. *e-mail:* ana.leite@pq.cnpq.br*

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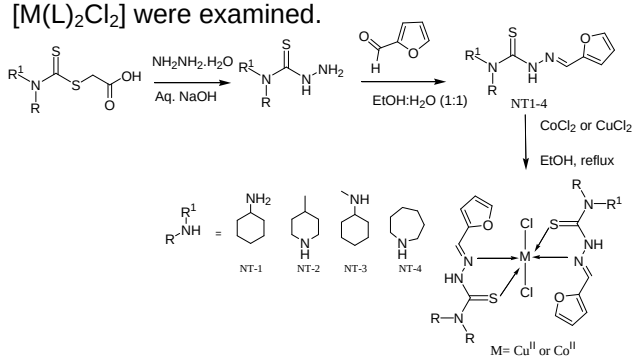
Introduction

A useful concept for the rational design of antiparasitic drug candidates is the complexation of bioactive ligands with transition metals.[1-3] In view of this, an investigation was conducted into a new set of metal complexes as potential antiplasmodium and antiamoebic agents, in order to examine the importance of metallic atoms, as well as the kind of sphere of coordination, in these biological properties.

Results and Discussion

To this end, a set of four functionalized furyl-thiosemicarbazones (**NT1-4**) treated with divalent metals (Copper and Cobalt) to form the mononuclear metallic complexes of general formula $[M(L)_2Cl_2]$ were examined.



Scheme 1.

The synthesis of ligands **NT1-4** was straightforward and produced moderate to good yields (41–90%). **NT1-4** were further used as chelating ligands to complex with $CoCl_2{\cdot}6H_2O$ or $CuCl_2{\cdot}2H_2O$. Co (NT1Co-NT4Co) and Cu complexes (NT1Cu-NT4Cu) were obtained as mononuclear and *bis*-chelated, by heating the ligand and appropriate metallic precursor under reflux. On the basis of NMR and IR analyzes, an *N*,*S*-bidentate coordination was suggested in these complexes, as proposed in Scheme 1**.** Moreover, data from electronic spectral and EPR were suggestive that Cu^{II} complexes (**NT1Cu**-**NT4Cu**) and Co^{II} complexes (**NT1Co**-**NT4Co**) probably are of octahedral geometry.

Regarding the metal-free thiosemicarbazones (IC_{50} of 20.3 to 36.2 μM), their Cu complexes were proven to be good antiplasmodial agents, exhibiting the following order of potency: **NT1Cu** = **NT4Cu** > **NT2Cu** > **NT3Cu**. Altering the structure of the cyclohexyl ring on the ligands of *C*-methyl (**NT2Cu**) to *N*-methyl (**NT3Cu**) produced a slight reduction in potency (IC_{50}= 5.2 *vs* 7.8 μM). Moreover, it was observed that, although the ring expansion of cyclohexyl (**NT1Cu**) by cycloheptane (**NT4Cu**) retains antiplasmodial activity, the latter proved to be cytotoxic against mammalian cells. These SAR suggest either a lipophilic property or a steric effect is occurring as a result of the impact of substituents on the structures of thiosemicarbazones. Our log*P* experiments produced the following values: **NT1Cu** (–1.73), **NT2Cu** (–1.54), **NT3Cu** (–1.49), and **NT4Cu** (–0.89). Such values suggest that, instead of a direct correlation between the antiprotozoal activity and lipophilicity, electronic and steric parameters that affect the geometry of complexes may be involved in determining bioactivity.

Table 1: *In vitro* screening.

Comp	*P. falciparum* IC_{50} (μM)	*E. histolytica* IC_{50} (μM)	Cytotoxicity (μg mL^{-1})
NT1Co	N.d.	2.28±00.1	33
NT2Co	41.0 ± 0.4	3.40±00.2	33
NT3Co	21.4 ± 0.2	7.50±00.5	33
NT4Co	58.7 ± 1.7	2.00±00.3	100
NT1Cu	4.6 ± 0.1	1.11±00.2	33
NT2Cu	5.2 ± 0.1	4.05±00.1	11
NT3Cu	7.8 ± 2.0	1.80±00.2	33
NT4Cu	4.6 ± 0.1	1.06±00.4	3.3
MQN	0.039 ± 0.01	–	N.d.
MNZ	–	1.80±00.3	N.d.

MQN is Mefloquine and MNZ is Metronidazole. Non-cytotoxicity concentrations from BALB\c mouse splenocytes.

Conclusions

As a result, SAR data were collected and steps were made towards the identification of new antiamoebic (**NT2Pd**, IC_{50} = 0.6 μM) prototype.

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