Platinum and Palladium Mononuclear Complexes Endowed with Potent Antiplasmodial and Antiamoebic Activities

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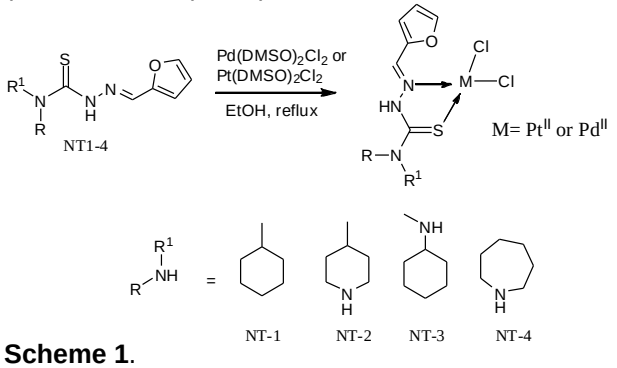
Introduction

Metallic complexes are highly active antiparasitic agents.[1] In light of this, we decided to turn our attention to the investigation of the antiprotozoal properties of a new set of mononuclear metal-thiosemicarbazone complexes. In our structural design, the furfuryl ring was explored, in view of previous observation of its antiparasitic and antimicrobial properties.[2] We thus selected Platinum and Palladium, in search of complexes bearing one ligand on each coordination sphere($MLCl_2$), thereby aiming to investigate how the ligand sphere contributes to antiprotozoal activity.

Results and Discussion

As depicted in **Scheme 1**, Pt (**NT1Pt**, **NT2Pt**) and Pd (**NT1Pd**-**NT4Pd**) complexes were obtained as monomers by heating the ligand and appropriate metallic precursor under reflux. From IR spectra, bands in the region of low wave-number (472–522 and 347–435 cm^{-1}) were tentatively assigned to *v*M–N and *v*M–S, respectively. NMR, EPR and electronic spectral were indicatives that an *N*,*S*-bidentate coordination is involved in these complexes. Besides, electronic spectral and *g* values (EPR) were suggestive that a square planar geometry is involved for both the Pt^{II} (**NT1Pt**, **NT2Pt**) and Pd^{II} (**NT1Pd-NT4Pd**) complexes.



Scheme 1.

The analysis of the pharmacological results showed that the **NT1-4** ligands were only weak *P. falciparum* inhibitors. Likewise, they were only modestly active against *E. histolytica*, the most potent being **NT2**, which is still four times less potent than **MNZ**. With regard to the metal complexes, we first analyzed the Pt and Pd series. The two complexes (**NT1Pt** and **NT2Pt**) showed near IC_{50} values against *P. falciparum*. On the one hand, these Pt complexes showed improved potency against *P. falciparum* compared with than the metal–free ligands (**NT1** and **NT2**). On the other hand, the replacement of Pt by Pd led to only a slight increase in potency against *P. falciparum*, far lower than the potency of **MQN**, which is active in nM range. Apart from **NT1Pd**, which was cytotoxic at low doses, the other Pt and Pd complexes retained their low cytotoxicity in mammalian cells. Noticeably, most of Pt and Pd complexes were highly potent in inhibiting the growth of *E. histolytica*, exhibiting the same range of potency as the reference drug, **MNZ**. A comparison of the inhibitory activity of ligand **NT2** and the **NT2Pd** complex, the latter proved to be 13 times more potent.

Table 1: *In vitro* screening.

Comp	*P. falciparum* IC_{50} (μM)	*E. histolytica* IC_{50} (μM)	Cytotoxicity (μg mL^{-1})
NT1	20.3 ± 0.2	10.12±00.5	33
NT2	36.2 ± 0.06	8.02±00.1	100
NT3	21.8 ± 0.4	9.07±00.4	>100
NT4	35.8 ± 0.9	12.08±00.3	>100
NT1Pt	37.0 ± 0.1	3.47±00.1	33
NT2Pt	42.3± 0.6	1.44±00.3	>100
NT1Pd	10.0 ± 0.08	0.99±00.3	3.3
NT2Pd	10.9 ± 0.1	0.6±00.5	33
NT3Pd	18.3 ± 0.3	2.42±00.5	33
NT4Pd	20.5 ± 0.01	1.66±00.1	33
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.

Conclusões

Overall, the major statement of this study is have demonstrated for the first time that mononuclear metal-thiosemicarbazone complexes are endowed with plasmodicidal properties.

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[1] Dive, D.; Biot, C. *ChemMedChem* **2008**, *3*, 383-391. [2] Sanchez-Delgado, R. A.; Anzellotti, A. *Mini. Rev. Med. Chem.* **2004**, *4*, 23–30.