Biosciences, Biotechnology Research Asia Vol. **5**(1), 121-123 (2008)

Inducement of antimalarial biological activity in some S-based ligands by Cu(II) and Zn(II) ions

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(Received: November 30, 2007; Accepted: February 05, 2008)

ABSTRACT

Some sulphur-based ligands and their corresponding Cu(II) and Zn(II) complexes were tested in vitro against malaria parasite. The ligands were found to be devoid of biological activity. However, the corresponding metal complexes have been found to exhibit modest biological activity against the parasite when bound to Cu(II) and Zn(II) metal ions. On the other hand, the copper(II) complex containing a ligand with thiophenecarboxylic hydrazide fragment showed quite high biological activity towards the malaria parasite. This implies that the Cu(II) and Zn(II) metal ions induced the biological activity into the ligands in question.

Key words: Antimalarial, Sulphur based ligands, biological activity.

INTRODUCTION

In our earlier studies, we discovered that a non-active sulphur-based ligand LH when bound selected metal ions, the complexes so generated are highly active against malaria parasites[1]. Although the ligand was kept constant, the biological activity varied dramatically from metal to metal. The order of the biological activity varied in the order[1] Cd>Zn>Mn>Co>Ni>standard>Fe. On the other hand, the biological activities of certain thiosemicarbazone ligand complexes of Cu(II), Ni(II) and Fe(III) were found to be less active against malaria parasites than the corresponding ligands[2]. Also relatively recently, some diacetylferrocene-derived thiosemicarbazone ligands and their Co(II), Ni(II), Zn(II), and Cu(II) complexes[3] showed good biological activity against the bacterial species *E. coli, B. subtillis, S. aureus, P. aeruginosa,* and *S. typhi* as well as the fungal species *T. longifusus, C. albicans, A. flavus, M. canis, F. solani,* and *C. glaberata.* It is interesting to note that the biological activity of the ligand systems was found to be enhanced when coordinated to the metal ions[3]as we have found in our studies. Earlier, we discussed the paramagnetic shift influence found in the complexes $Cu(LH)_2Cl_2$, CuACl, and CuBCl relative to their corresponding ligands[4-5]. In our continued search for biologically active compounds against malaria parasite, monoacetylferrocene-derived thiosemicarbazones ligands shown in Figs. 1-3 (LH, AH, and TH) and their metal complexes [$Cu(LH)_2Cl_2$, CuACl, and ZnT_2) as well as the copper complex (CuBCl) of the 2-acetylpyridine containing thiophenecarboxylic hydrazide moiety ligand (see Fig. 4) were synthesized and tested for the biological activity. We hereby report the findings.

EXPERIMENTAL

The synthesis and characterization of the ligand systems, LH, AH, BH and the complexes,

$Cu(LH)_2Cl_2$, CuACl, and CuBCl have already been published[4-5]. The synthesis and characterization of the ligand system TH and its corresponding metal complexes will be published elsewhere.

RESULTS AND DISCUSSION

The results of the biological tests are shown in Table 1. The biological tests against the

Table 1:Biological activity ligand and metal complex systems

Compound	reading(nM)	sd*	comment on activity
LH	>20,000	-	negligible
$Cu(LH)Cl_2$	11,485	1,138	modest
BH	not done	not done	not available
CuBCl	669.9	6	quite active
AH	> 20,000	-	negligible
CuACl	14,580	1,329	modest
TH	> 20,000	-	negligible
ZnT_2	11,055	1,209	modest
CQ	90.535	24	standard

* SD = standard deviation

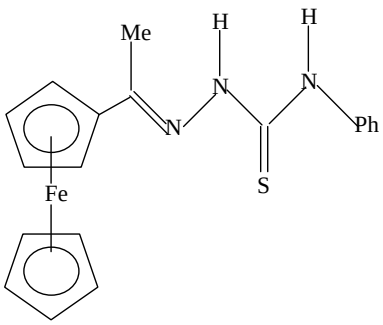

Fig. 1: The structure of ligand LH

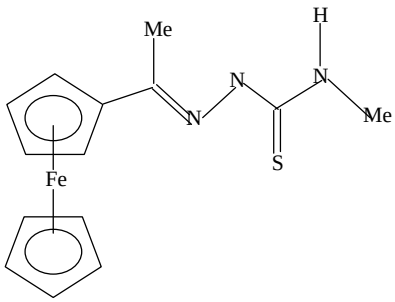

Fig. 2: The structure of ligand AH

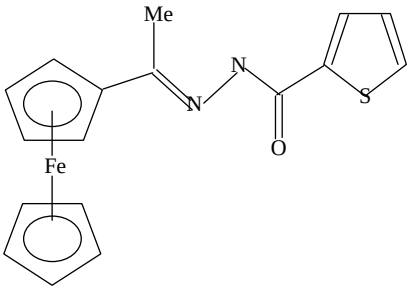

Fig. 3: The structure of ligand TH

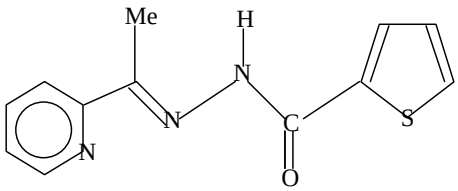

Fig. 4: The structure of ligand BH

malaria parasite were conducted in *in vitro* medium. Whereas the ligand systems LH, AH, and TH showed no biological activity, the corresponding metal complexes $Cu(LH)_2Cl_2$, CuACl and ZnT_2 exhibited modest biological activity. This clearly indicates that in this case, the binding of the metal ions to the ligands either in their protonated or deprotonated forms enhances or activates the biological activity of the ligand. The copper(II) complex of the 2-acetylpyridine containing thiophenecarboxylic hydrazide moiety ligand, CuBCl was found to have very good biological activity against the malaria parasite. The mechanisms by which the metal ions activate the ligands are unclear. The search for more novel complexes with sulphur-based ligands particularly the thiosemicarbazone type must be intensified.

ACKNOWLEDGMENTS

We wish to acknowledge the University of Namibia and Petrofund Namibia for funding the work. In addition, we wish to thank the University of Cape Town for providing facilities for the spectroscopic measurements and the University of California, San Francisco, for conducting the biological tests.

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