Antimalarial Activity of Metal Complexes of Cross-Bridged Tetraazamacrocyclic Ligands
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Purpose
The compounds with metal complexes have shown promising antimalarial properties. Recent discovery of antimalarial cyclen analogs at our lab prompted us to synthesize and examine the antimalarial activity of several new metal complexes with cross-bridged and side-bridged tetraazamacrocyclic ligands namely, cyclen and cyclam – analogs with benzyl groups.

Methods
The compounds were screened for in vitro antimalarial activity against W2 (chloroquine resistant) and D6 (chloroquine sensitive) strains of Plasmodium falciparum. The selectivity index (SI) of antimalarial activity of these compounds and in vitro cytotoxicity to mammalian cells were also determined.

Results
The free ligands tested showed little to no antimalarial activity. The manganese complex of dibenzyl cross-bridged cyclam based ligands exhibited very potent antimalarial activity with IC50s of 67.4 and 83.8 ng/ml against the D6 and W2 strains of P. falciparum strains, respectively. The iron complex of this same ligand displayed IC50s of 227.1 and 172.6 ng/ml against the D6 and W2 strains, respectively. The manganese complex of the dibenzyl cross-bridged cyclen ligand displayed IC50s of 274.4 and 133.7 ng/ml against the D6 and W2 strain respectively. The copper complex of this ligand exhibited a much better antimalarial activity than the iron complex whereas the Zn, Ni, and Co complexes were mostly inactive.

Conclusion
The bisbenzyl hydrophobic ligands showed better antimalarial activity possibly because of their better cell penetration ability. The higher antimalarial activity displayed by the manganese complex for the cyclam ligand in comparison to that of the cyclen underpins the larger pocket of cyclam compared to that of cyclen to produce more stable complex with the Mn2+. Some of the Cu and Fe complexes also showed improvement in activity but Ni, Co and Zn complexes were not very intriguing for antimalarial development.