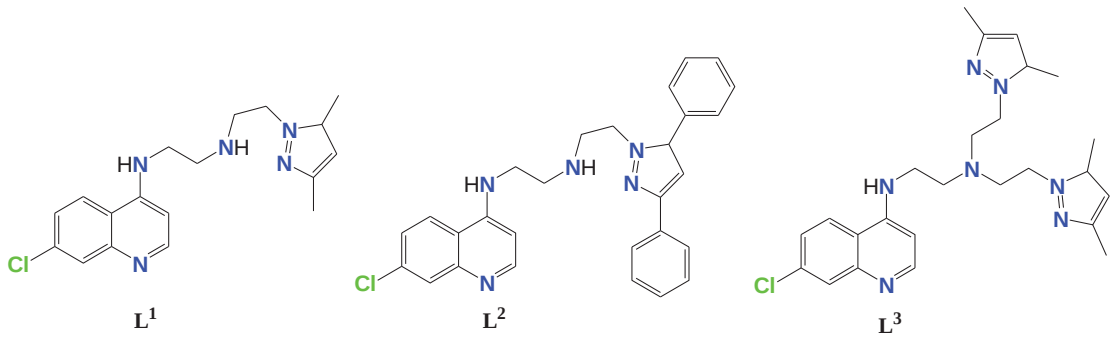
# Synthesis, characterization, and molecular docking of novel 4-aminoquinolines as potential antimalarial agents

Asanda V. Busa*, Erik Ekengard, Ebbe Nordlander, Phumlane S. Mdluli and Martin O. Onani
*University of Western Cape, South Africa*

In the 21st century with enormous advancement in modern medicine, malaria remains one of the greatest problems facing developing nations, especially in sub-Saharan Africa. The battle against malaria is intensified by the constant development of resistance to current treatments hence there is a large drive to develop novel antimalarial compounds.[1,2]

The focal point of the chemistry that has been studied in the present study can be viewed as a summation of four principal aspects, viz.: (i) Synthesis, (ii) Characterization (iii) Molecular Docking and (iv) Antiplasmodial Activity. Synthesis of designed chloroquine analogue ligands bearing a pyrazole scaffold resulted in ligands with an attractive secondary site for metal coordination in addition to the quinoline nitrogen. All ligands were synthesized from the primary amine N-(7-chloroquinolin-4-yl)ethane-1,2-diamine and different symmetric pyrazoles. The ligands were reacted with different palladium, platinum, iridium and rhodium starting materials to afford the targeted complexes. Thorough characterization of the complexes was done using various spectroscopic (UV-VIS, IR, NMR, ESI-mass) techniques in combination with elemental (C, H, N) analysis.

Three new ligands based on a 4-amino-7-chloroquinoline moiety with a pendant symmetric pyrazole arm N-(2-(2-(3,5-dimethyl-1H-pyrazol-1-yl)ethylamino)ethyl)-7-chloroquinolin-4-amine (**L¹**) , N-(2-(2-(3,5-diphenyl-1H-pyrazol-1-yl)ethylamino)ethyl)-7-chloroquinolin-4-amine (**L²**) and N-(2-(bis(2-(3,5-dimethyl-1H-pyrazol-1-yl)ethyl) amino)ethyl)-7-chloroquinolin-4-amine (**L³**) were synthesized. The reaction of the ligands (**L¹-L³**) with Pd2+, Pt2+, Ir3+ and Rh3+ metal precursors has been investigated. The characterization of the complexes was carried out by using the FT-IR, 1H/13C NMR, UV-Vis, ESI and elemental analysis. This study focused on the preliminary investigation of the antimalarial activity of the designed chloroquine analogous ligands **L¹-L³** as well as the corresponding metal complexes **C1-C6** against NF54, a chloroquine sensitive (CQS) strain of *P. falciparum*. **L¹** and **L³** exhibited the highest activity of the ligands tested and the complexes **C¹** and **C²** exhibited the highest activity of the metal complexes with the $IC_{50}$ values below 20 nM. Molecular docking studies were in agreement with the experiment data as **L¹** and **L³** exhibited highest number of interaction with the residues of the parasite active site.




**L¹** **L²** **L³**

## References

1. Carter, R. and Mendis, K. N. *Clin. Microbiol. Rev.* 2002, **15**, 564.
2. WHO Malaria Report, http:// http://www.who.int/malaria/publications/world_malaria_report_2013/en/