

# UNDERSTANDING THE MECHANISM OF ACTION OF ANTIMALARIAL DRUGS: INSIGHTS FROM SOLUTION NMR

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## ABSTRACT

Malaria is one of the most devastating global health issues today. The mechanism of action of commonly used quinoline antimalarial drugs such as chloroquine, quinine and amodiaquine is not completely understood. Quinoline antimalarials are thought to prevent the formation of hemozoin in the digestive vacuole of the parasite, allowing toxic heme or drug-heme complexes from the digestion of host red blood cell hemoglobin to accumulate. This thesis attempts to further the understanding of how these drugs function using solution nuclear magnetic resonance (NMR) experiments. First, the molecular structure of the complex formed between amodiaquine and heme in solution is determined by using measured NMR  $T_1$  relaxation times as distance restraints in molecular dynamics simulations. Second, the self-association and interaction between pairs of some representative drugs are investigated by comparing measured and *ab initio* chemical shift changes between the monomer and dimer forms of drug. Third, the  $\sigma(11)$  principal component of the chemical shielding tensor at each quinoline carbon is used as a measure of relative  $\pi$ -electron density at that particular carbon site, and a quantitative structure-activity relationship is developed between calculated  $\sigma(11)$  and heme binding strength for a series of chloroquine-like compounds with different substituents at the 7-position. Fourth, the equilibrium between heme monomer and  $\mu$ -oxo dimer in solution, and the effect of adding different drugs on this equilibrium, is examined by measuring the magnetic susceptibility of the heme iron as a function of pH using Evans' method. Last, partitioning of drugs and heme between the aqueous and various lipid environments is explored by using pulsed gradient experiments to measure the diffusion coefficients of drugs and lipid micelles, and by measuring the paramagnetic relaxation enhancement on drug and lipid protons to determine the location of heme. These experiments provide information that is useful in the design of future antimalarial drugs, to circumvent parasite resistance to known drugs.