# The *in Vitro* Antiplasmodial and Antiproliferative Activity of New Ferrocene-Based α-Aminocresols Targeting Hemozoin Inhibition and DNA Interaction

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The conjugation of organometallic complexes to known bioactive organic frameworks is a proven strategy revered for devising new drug molecules with novel modes of action. This approach holds great promise for the generation of potent drug leads in the quest for therapeutic chemotypes with the potential to overcome the development of clinical resistance. Herein, we present the *in vitro* antiplasmodial and antiproliferative investigation of ferrocenyl α-aminocresol conjugates assembled by amalgamation of the organometallic ferrocene unit and an α-aminocresol scaffold possessing antimalarial activity. The compounds pursued in the study exhibited higher toxicity towards the chemosensitive (3D7) and -resistant (Dd2) strains of the *Plasmodium falciparum* parasite than to the human HCC70 triple-negative breast cancer cell line. Indication of cross-resistance was absent for the compounds evaluated against the multi-resistant Dd2 strain. Structure-activity analysis revealed that the phenolic hydroxy group and rotatable σ bond between the α-carbon and NH group of the α-amino-o-cresol skeleton are crucial for the biological activity of the compounds. Spectrophotometric techniques and *in silico* docking simulations performed on selected derivatives suggest that the compounds show a dual mode of action involving hemozoin inhibition and DNA interaction via minor-groove binding. Lastly, compound **9a**, identified as a possible lead, exhibited preferential binding for the plasmodial DNA isolated from 3D7 *P. falciparum* trophozoites over the mammalian calf thymus DNA, thereby substantiating the enhanced antiplasmodial activity of the compound. The presented research demonstrates the strategy of incorporating organometallic complexes into known biologically active organic scaffolds as a viable avenue to fashion novel multimodal compounds with potential to counter the development drug resistance.



## Introduction

The development of resistance to clinical drugs by diseases is a grave concern that is threatening the outlook of current medicines as effective treatments in modern drug discovery and it requires innovative strategies to address. In cancer, clinical resistance develops when malignant tumour cells undergo changes at genomic and biochemical levels to counteract the effects of an administered anticancer drug. Various hypotheses explaining the processes underpinning the mechanisms that promote anticancer resistance have been proposed and are extensively presented in literature.[1,2] Succinct reviews by Housman et al. and Nikolaou et al. on cancer clinical resistance comprehensively summarize the six common mechanisms leading to development of tumoral drug resistance, of which metabolic drug deactivation and drug efflux by transmembrane proteins of cancer cells are the most prevalent.[3,4] Similarly, antimalarial drug resistance predominantly involves drug efflux and alteration of the therapeutic biomolecular target, whereby the effectiveness of the drug molecule is diminished through its accelerated removal from the active site and reduced affinity for the therapeutic target, respectively.[5,6] This is best demonstrated by the case of chloroquine resistance. The development of chloroquine resistance is postulated to be caused by altered transmembrane proteins of the parasite's digestive vacuole (DV), that is, the active site where the drug

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