Examination of co-ligands in mefloquine–metal complexes reveals the structural determinants for activity against *Plasmodium falciparum*

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ABSTRACT

Malaria is a parasitic disease caused by protozoa of the genus *Plasmodium* spp. and remains one of the most prevalent tropical diseases worldwide. Although control strategies have significantly reduced burden and mortality in several regions, treatment efficacy is increasingly compromised by parasite resistance and the limited activity of current drugs against juvenile stages. Mefloquine (MQ) is widely used for malaria prevention and treatment, and is considered a drug with pleiotropic effects. Metal complexes have emerged as promising drug candidates, as they can interact with molecular targets inaccessible to organic ligands, offering an alternative strategy to overcome resistance. Thus, this study aimed to describe the synthesis of MQ-metal complexes with the general formula $[M(II)(L)(MQ)]PF_6$ and to evaluate their biological activity against *Plasmodium* spp. Complexes were synthesized by varying the metal center (platinum or palladium) and co-

ligands (phosphine or bipyridine). Biological assays were performed against *Plasmodium falciparum*, including in vitro and in vivo evaluations. Cellular accumulation of metals and inhibition of thioredoxin reductases were also investigated. All complexes showed MQ coordination as an N,O-bidentate ligand. Biological assays revealed that the metal center acts as a thioredoxin/glutathione-targeting moiety, while MQ targets the parasite directly. MQ-Pt complexes demonstrated enhanced in vivo efficacy. Accumulation of the metal inside parasite cells was observed, which contributes to the abrogation of biochemical pathways essential for parasite survival, such as thioredoxin reductases. Finally, this study establishes a novel structural framework for the development of metal-based antiparasitic drugs. The metallic complexes can preferentially target pathogens in the blood rather than host and mammalian cells, with potency, efficacy, and importantly, by interfering with parasite molecular targets not affected by MQ.

Keywords: *Plasmodium falciparum,* metal-based drugs, mefloquine, structure-activity relationships, platinum, palladium.