New antimalarial flavones active against artemisinin-resistant strains of P. falciparum: a chemical-biology approach to target discovery

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Résumé

Malaria is one of the most predominant parasitic diseases in the world and especially in tropical and developing countries. Accordingly, to the last WHO report, malaria affects 263 million people annually, with 608 000 deaths primarily from *Plasmodium falciparum*. Climate changes and emergence of resistance to artemisinin, the most potent antimalarial drug used today, urge for the development of new drug candidates to treat malaria. Preventive treatment such as insecticides and vaccines (MosquirixTM) show still insufficient efficacy.
In a previous ethnopharmacological approach followed by pharmacomodulation, the laboratory identified a new class of antiplasmodial synthetic flavones. These molecules showed an unmet *in vitro* target candidate profile: *in vitro*activity on resistant *P. falciparum* strains, no cross resistance with reference drugs, rapidity of action on all stages of the intraerythrocytic cycle, inability to select resistant parasites, putative efficacy on hepatic stages. Physicochemical and pharmacokinetic parameters must be improved for an increased *in vivo* activity. Moreover, the molecular target(s) of these flavone-based compounds to date are unknown.

In this work we aim to apply a chemical-biology approach to answer these questions. We synthetize flavone-fluorophore conjugate as tools to identify the subcellular localization of the lead compound in the parasite and to pursue proteomic studies to identify the parasitic proteins with which flavones could interact. Three aspects have been explored: 1/the synthesis of the flavone moiety; 2/ the synthesis of appropriate linkers; 3/the coupling with a fluorophore by using Sonogashira cross-coupling reaction.

Then, incubation of the synthetized probe with *P. falciparum*-infected blood cells is envisioned as well as the application of confocal microscopy coupled with chemoproteomic studies to identify the molecular target.

Mots-Clés: Malaria, synthetic flavones, chemo, biology, flavone, fluorophore conjugates, metal, catalyzed cross, coupling reactions

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