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New 4-aminoacridine-cinnamic acid conjugates as multi-stage antimalarial hits

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The eradication of malaria remains to be achieved, mainly due to the continued spread of drug-resistant parasites. To overcome this, multi-stage drugs have been prioritized in antimalarial drug discovery, since targeting more than one process in the *Plasmodium*'s life cycle may increase efficiency, while decreasing the chances of resistance emergence by the parasite [1]. Quinacrine (QN) was the first synthetic antiplasmodial drug active against blood forms of the *Plasmodium* parasite but was rapidly superseded by chloroquine (CQ) which has greater safety, efficiency, and bioavailability [2]. Analysing the QN structure, its acridine core is a fusion between the heterocycle core of CQ and primaquine (PQ), another antiplasmodial drug active against liver forms of the parasite, and able to block malaria transmission. A new family of QN derivatives reported by us, 4-aminoacridines, corresponding to the merge of CQ core and PQ, showed moderate dual-stage antimalarial activity [3,4]. We have now developed a second generation of 4-aminoacridines (**Fig.1**) through their conjugation to cinnamic acids (CA) of natural origin that have been reported to enhance antimalarial activity when conjugated to antimalarials [5]. In this communication, we will present the chemical synthesis of this new family of *N*-cinnamoyl-4-aminoacridines and the *in vitro* assessment or their activity against a) liver stages of *P. berghei*, b) erythrocytic forms of *P. falciparum*, and c) early and mature gametocytes of *P. falciparum*. Results demonstrate that the conjugation of the CA moiety to the 4-aminoacridine core delivers new compounds with enhanced *in vitro* activity against all three stages of the malaria parasite lifecycle inside mammalian hosts.

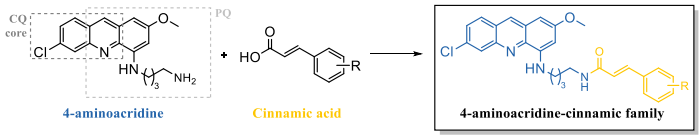

Fig.1. Chemical structure of the N-cinnamoyl-4-aminoacridines family.

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