Flavone derivatives: a promising new class of fast-acting drug active against multi-resistant falciparum malaria parasites

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Résumé

P. falciparum malaria is the deadliest parasitic disease with 438.000 deaths in 2015. The increasing proportion of *P. falciparum* parasites resistant to artemisinin, the most potent antimalarial, is a major concern in Southeast Asia. Fast acting drugs with unaltered activity versus the current multi-drug resistant strains are urgently needed to replace artemisinin. We are developing new antimalarials based on the structure of an active natural product: a biflavonoid from *Campnosperma panamense* (IC50 = 480 nM *in vitro* on *P. falciparum*). One of the simplified synthetic analogs, MR70, is acting faster than artemisinin *in vitro* at 10 times the IC50. MR70 exhibit a partial *in vivo* antimalarial activity, reducing parasitemia by 35% at day 4 using Peter's model (*P. berghei* ANKA, 100 mg/kg for 4 days). As MR70 acts on early ring stage, which has been associated to artemisinin resistance, we assessed the *in vitro* susceptibility of artemisinin-resistant isolates to MR70 and found no cross-resistance between MR70 and artemisinins. These findings make flavone derivatives a promising new class of antimalarials. To optimize MR70 activity, we synthesized new derivatives and managed to increase its *in vitro* antiplasmodial activity and selectivity. We now have to assess if the activity is conserved *in vivo*.

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