

# Active Novel Artemisinin–chloroquinoline Hybrid Compounds On B-hematin Formation, Parasite Morphology And Endocytosis In Plasmodium Falciparum.

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## Abstract:

4-Aminoquinolines were hybridized with artemisinin and 1,4-naphthoquinone derivatives via the Ugi four-component condensation reaction, and their biological activities investigated. The artemisinin-containing compounds **6a** and its salt **6c**-citrate were the most active target compounds in the antiplasmodial assays. However, despite the potent in vitro activities, they also displayed cytotoxicity against a mammalian cell-line, and had lower therapeutic indices than chloroquine. Morphological changes in parasites treated with these artemisinin-containing hybrid compounds were similar to those observed after addition of artemisinin. These hybrid compounds appeared to share mechanism(s) of action with both chloroquine and artemisinin: they exhibited potent b-hematin inhibitory activities; they caused an increase in accumulation of hemoglobin within the parasites that was intermediate between the increase observed with artesunate and chloroquine; and they also appeared to inhibit endocytosis as suggested by the decrease in the number of transport vesicles in the parasites. No cross-resistance with chloroquine was observed for these hybrid compounds, despite the fact that they contained the chloroquinoline moiety. The hybridization strategy therefore appeared to be borrowing the best from both classes of antimalarials.