Heme-binding as a biodereplication method for the discovery of antimalarial compounds in minute amounts of natural extracts

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Résumé

The principal antiplasmodial drugs mechanism consists in interrupting heme crystallization in erythrocytic phase, thus perturbating parasite's waste-sorting strategy. We improved our previously described method which identifies heme-binding molecule in a complex extract (m/z for heme = 616) by mass spectroscopy (ESI-Q-TOF instrument). This *in vitro* miniaturized (384 wells plates) biodereplication is based on a medium mimicking the parasite digestive vacuole (pH= 4.8). Correlation of the method with *in vitro* bioassays was assessed for synthetic compounds and natural methoxyflavones and showed reproducible results. Our screening method was applied on an ethanolic extract of *Piper coruscans*, used in the Peruvian traditional medicine as antimalarial (IC50 of extract on *P. falciparum* 3D7 chloroquine-sensible strain = 1.36 ± 0.06 μg/mL). Potentially active compounds were identified by m/z of adducts [two compounds with $m/z = 299$, one compound with $m/z = 285$] and visualized using molecular networking. Isolation of the target products from 500 mg of plant powder was performed by silica flash chromatography and preparative C18 HPLC. Structural identification was performed by 600 MHz cryo-probe NMR. 5,7-Dimethoxyflavanone (1), 5-Hydroxy-7-methoxy-6,8-dimethylflavanone (2) and aurentiacin (3) were identified, giving an example of biodereplication method for the fast targeting of active compounds against malaria.

Mots-Clés: Biodereplication, heme, binding, malaria, natural products

*Intervenant