Two series of semisynthetic triterpene derivatives: synthesis, cytotoxicity, antimalarial evaluation and structure-activity relationship

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Malaria is a devastating disease that remains a significant public health problem worldwide. The emergence and spread of resistance to antimalarial drugs plays an important role in the occurrence and severity of malaria, being a major problem that hinders the control of malaria. Aiming to improve the therapy of malaria, natural products could be a potential source of new drugs with high activity and low toxicity, which can be further optimized by chemical modulation. Ursolic acid (UA) and betulinic acid (BA) are pentacyclic triterpenoids extracted from several natural sources and have been reported a broad and promising spectrum of biological activities. Therefore, the search for new triterpene derivatives is a promising approach for to develop new drugs with antimalarial potential. This study aim to develop new potential semi-synthetic antimalarial compounds through different modifications at C-3 and C-28 positions of the UA and BA. UA was isolated from apple pomace (*Malus domestica*) and BA from barks of *Platanus acerifolia*. At C-3 position, a ketone and some esters groups (acetic, butyric and isobutyric) were inserted, and from these derivatives, were incorporated methyl and imidazole ring at C-28. The *in vitro* effects of two series of UA and BA derivatives against *P. falciparum* (W2) were measured using HRPII kit and the cytotoxicity through MTT method, using VERO and HepG2 cells. Twenty-four compounds comprised in two series of UA and BA derivatives were prepared with success. Esters at C-3 have relevant antiplasmodial activity (IC_{50} ranging from 3.4 to 13.32 µM), being that the 3-O-butyrilbetulinic acid was the more active compound. The study of structure-activity relationship indicated that the introduction of a methyl group at C-28 is not favorable, since annulling the activity (IC_{50} > 100 µM), and the imidazole ring showed not to be important for the antiplasmodial activity, increasing or not the IC_{50} value of the initial scaffold. These data suggest that a hydrogen donor group at C-28 position could be important for the antiplasmodial activity. Most compounds have not presented cytotoxic effect after 24, 48 and 72 h for mammalian and hepatic cancer cells (IC_{50} > 400 µM), showing good selectivity towards the parasites.

Keywords: *Plasmodium falciparum*, natural products, semisynthesis.

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