TRITERPENOIDS AS INHIBITORS OF PLASMODIUM LIVER-STAGE DEVELOPMENT

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INTRODUCTION

Malaria is one of the foremost public health problems in Africa. It is endemic in 90 countries, affecting nearly 40% of the global population. The increasing prevalence of drug-resistant Plasmodium falciparum strains is one of the greatest challenges in malaria control. In order to overcome drug-resistance, new antimalarial drugs are urgently needed. Most of the available antimalarial agents kill blood stage parasites and only a limited number of drugs act on liver stages. In fact, the study of Plasmodium liver stage development (Fig. 1) has been hampered by limitations in the experimental approaches required to quantify hepatocyte infection by the parasite. Therefore, the development of new drugs targeting Plasmodium liver stages represents an important and under-exploited site of intervention [1, 2].

RESULTS AND DISCUSSION

Previously, bioassay-guided fractionation of the methanol extract of the aerial parts of Momordica balsamina led to the isolation of several cucurbitane-type triterpenoids. Many of these compounds and acylated derivatives displayed in vitro antimalarial activity against blood schizonts of chloroquine-sensitive and -resistant strains of Plasmodium falciparum [3-5].

In this study, compounds 1 – 5 (Fig. 3) were evaluated for their in vitro activity against liver stages of the rodent malaria parasite P. berghei, using a recently described bioluminescence imaging method [1]. This method uses a transgenic P. berghei parasite, PlGFP-Luc_conf expressing the bioluminescent reporter protein luciferase to visualize and quantify parasite development in Huh-7 cells, a human hepatoma cell line (Fig. 3 – bars). Compound toxicity was also assessed on the same cell line through the fluorescence measurement of cell confluency (Fig. 3 – line).

Compounds 1 - 4 exhibited activity against P. berghei liver stages in vitro (Fig. 4). Balsaminol F (1) and, in particular, Balsaminoside B (2) displayed significant toxicity against Huh-7 cells at 15 µM.

Triacetylalsaminol F (5) showed the most potent inhibitory activity against the liver stages of Plasmodium, with no detectable toxicity towards the Huh-7 cells, at the concentrations employed.

CONCLUSION

Triacetylalsaminol F (4) displayed higher in vitro efficacy than primaquine against P. berghei liver forms, warranting further exploitation of its mechanism of action.

REFERENCES