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Discovery of brussonol as a lead candidate for malaria

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INTRODUCTION Malaria is a parasitic disease caused by Plasmodium. The spread of artemisinin resistance is a great concern, as artemisinin-based combination therapies (ACTs) are the first- and second-line treatment in many countries. (1) Therefore, it is imperative to discover and develop new antimalarial drugs. Plant extracts are an important source of new bioactive molecules. (2) The icetexanes are a family of diterpenoids that have been isolated from terrestrial plants. Antibacterial, antiprotozoal, and antiproliferative activities⁹ have been reported for some diterpenes. In this work, we investigated brussonol and synthetic derivatives as antiplasmodial lead candidates. **METHODS** Antiplasmodial activity against multiple Plasmodium strains: determination of IC₅₀ for each compound. Cytotoxic tests using immortalized cells: cells of the human hepatocellular carcinoma cell line (HepG2) were incubated with the compounds (IC₅₀Pf < 10 μ M) for 72 h. Chemical rescue assay: evaluation of the IC₅₀ value in the presence of IPP. Speed of action: verify if brussonol has a fast- or a slow-acting antiplasmodial activity. Combination profile assays: verify if brussonol has an additive, synergic or antagonistic profile when associated with artesunate. **RESULTS** In this work, 15 brussonol derivatives were synthesized and assessed against P. falciparum. Brussonol showed attractive antiplasmodial with low cytotoxic activity (IC₅₀Pf = 16 μ M, IC₅₀HepG2 = 67 μ M, SI = 4). The most potent derivatives showed increased potency and lower cytotoxic effect compared with brussonol (IC₅₀sPf $\sim$ 5 μ M, IC₅₀sHepG2 > 400 μ M, and SI > 70). Brussonol was selected as a representative compound of the series to assess the antiplasmodial activity profile. The resistant strains K1, Dd2, TM90C6B, and 3D7r_MMV848 were sensitive to brussonol, thereby indicating that brussonol showed no cross-resistance with standard antimalarials. Moreover, brussonol was a fast-acting inhibitor with an additive profile when associated with artesunate. Mechanism of action investigation indicated that brussonol did not interfere with the isoprenoid biosynthesis. **CONCLUSION** Brussonol represents a new molecular scaffold endowed with an attractive antiplasmodial activity profile. The biological properties of brussonol indicate that the natural product is a promising lead compound for antimalarial drug discovery.

Palavras-chave: Malaria. Natural products.. Brussonol

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