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Antiplasmodial activity assessment of the natural compound batzelladine L and synthetic derivatives as lead candidates for malaria

BERLINCK, Roberto Gomes de Souza[1]; BORGES, Natália Menezes Moreira[2]; GUIDO, Rafael Victorio Carvalho[2]; MENDES, Giovana Rossi[2]; NORONHA, Anderson de Rienzo[1]; JURBERG, Igor Dias[3]; PINHEIRO, Roberto do Carmo[3]; MOURA, Igor Mota Rodrigues de[2]; SOUZA, Ronei Messias Silva[3]; BARBOSA, Camila de Souza[2]; GOULART, Tales Antonio Camargo[3]

giquimica017@usp.br

[1]Instituto de Química de São Carlos - USP; [2]Instituto de Física de São Carlos - USP; [3]Instituto de Química - UNICAMP

Malaria is a parasitic disease caused by the pathogenic protozoa *Plasmodium*.spp., which has a significant global impact on human health. (1) The increasing resistance of *P. falciparum*.strains to approved drugs highlights the urgent need for the discovery of new antimalarial candidates. Guanidine alkaloids emerged as promising natural products with antiparasitic activity. Batzelladines are tricyclic guanidine derivatives that exhibit potent biological activities, including antiparasitic. (2-3) In this investigation, we aimed at to investigate the parasitological profile of the natural alkaloid batzelladine L against *P. falciparum*. as well as of 43 synthetic guanidine derivatives as potential anti-plasmodial agents. The inhibitory activity of batzelladine L was first evaluated against chloroquine-sensitive *P. falciparum*.3D7 strain. The natural alkaloid exhibited *P. falciparum*.inhibitory activity in the submicromolar range (IC503D7 = 0.4 $\pm$ 0.1 μM), consistent with the previous report on the antiplasmodial activity of batzelladine L against a FcB1 chloroquine-resistant *P. falciparum*.strain (IC50 = 0.3 μM). (3) Furthermore, batzelladine L presented moderate cytotoxicity against HepG2 cells (IC50HepG2 = 14 μM) with a selectivity index (SI) of 35. We subsequently investigated the parasitological profile of batzelladine L. Assessment of time of action revealed that the compound is a fast-acting inhibitor, exhibiting pronounced activity against *P. falciparum*.ring and trophozoite stages. Combination of batzelladine L with artesunate exhibited an antagonistic profile. Additionally, the inhibitory activity of batzelladine L was evaluated against a panel of *P. falciparum*.resistant strains. Results indicated no cross-resistance with the Dd2 (RI = 1.5), K1 (RI = 2.0), and Dd2RDSM265 (RI = 2.0) strains. Finally, we assessed the in vivo antimalarial activity of batzelladine L using *P. berghei*.NK65 strain in an animal model. The treated group showed a 33% reduction in parasitemia at day 5 post-infection. Such promising results led us to develop the synthesis of batzelladine L simplified analogues. Therefore, 43 guanidine derivatives were synthesized and tested against the *P. falciparum*.3D7 strain. Among these derivatives, 24 exhibited significant antiplasmodial activity (IC503D7 $\leq$ 10 μM). One derivative RCPA37P displayed inhibitory activity in the similar range of batzelladine L (IC503D7 = 0.21 $\pm$ 0.08 μM) with improved selectivity against HepG2 cells (SI = 58). These findings suggest that both natural and synthetic guanidine derivatives hold promise as attractive compounds for the development of future lead candidates against malaria.

Palavras-chave: Malaria. Guanidine. *P. falciparum*.

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