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Investigation of the mode of action underlying brussonol's antiplasmodial activity

BARBOSA, Camila de Souza[1]; MALUF, Sarah El Chamy[1]; AHMAD, Anees[2]; BURTOLOSO, Antonio[3]; DUTRA, Marcos Leoni Gazarini[4]; LEHANE, Adele[5]; AGUIAR, Anna Caroline Campos[4]; GUIDO, Rafael Victorio Carvalho[1]

camilasbarbosa@ifsc.usp.br

[1]Instituto de Física de São Carlos - USP; [2]Instituto de Química - UNICAMP; [3]Instituto de Química de São Carlos - USP; [4]Instituto de Saúde e Sociedade - UNIFESP; [5]Australian National University - ANU

Malaria is an infectious disease that affects millions of people worldwide, mainly in developing countries. According to the World Health Organization (WHO), it was estimated that 241 million cases were responsible for approximately 627 thousand deaths globally in 2020. During the coronavirus disease (COVID-19) pandemic, WHO and partners collaboratively work to avoid service disruptions, so many campaigns to prevent and control this disease were completed.(1) Despite these efforts, the increase in malaria cases and malaria incidence was associated with the disruption of the services, thereby highlighting the importance of surveillance to tailor rapid responses to these changes. Malaria is a complex disease to eliminate and eradicate. Because of that, changes in how new antimalarial drugs are discovered and developed have been made. Currently, the antimalarial research is focused on discovering active molecules against resistant parasite strains, including parasites with reduced susceptibility to artemisinin, which are a great concern in the WHO African Region. Moreover, molecules capable of breaking the cycle of disease transmission are prioritized, which corresponds to compounds targeting parasite gametocytes (TCP-5), the insect vector (TCP-6), and active against hypnozoites (TCP-3).(2) Historically, natural products (NP) have been an attractive source of molecules for drug discovery. According to Newman and Cragg, from January 1981 to September 2019, over 68% of all small molecule approved drugs, and specifically, 60% of antiparasitic drugs, including antimalarial agents, were directly or indirectly derived from NPs. Plants are rich sources of new chemical scaffolds due to the development of molecules to fight off animal and environmental attacks. Examples of successful antimalarial agents inspired on plant metabolites are quinine and artemisinin. The icetexanes diterpenoids are a family of NPs that have been isolated from different terrestrial plants with diverse biological activities. These compounds have a 6-7-6 tricyclic framework, which is a key feature of the icetexane skeleton. In addition, the wide degree of oxygenation and oxidation in each ring of these compounds leads to diverse structures and biological activity.(3) In this research project, we investigated brussonol and synthetic derivatives as P. falciparum growth inhibitors. In this sense, we conducted extensive biological profiling to assess the antiplasmodial properties of brussonol that indicated the natural compound as a new antiplasmodial lead candidate.

Palavras-chave: Antimalarial activity. Brussonol. Mode of action.

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