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Antiplasmodial profiling of peptide-like molecules as lead candidates for malaria

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Malaria is one of the most prevalent infectious diseases caused by *Plasmodium*.genus parasites. Artemisinin resistance has been arising in some affected areas. (1-2) Hence, the development of new compounds against *Plasmodium*.is highly needed. Small peptides have been reported as strong antimicrobial agents and their antiplasmodial activity has been investigated in the last few years. (3) This work focused on the parasitological profile of tri- and dipeptides against *P. falciparum*. We assessed the inhibitory activity of 15 tri- and dipeptides derivatives against the *P. falciparum*.3D7 strain. The most potent compound (Neq1153) showed an IC50 value of 0.6 $\pm$ 0.1 μM and a selectivity index against HepG2 cells of SI = 350. The time of action assay showed that Neq1153 is a slow-acting inhibitor with pronounced inhibitory activity over the mature forms of the parasite. The presence of Neq1153 caused a swallow of the digestive vacuole (Figure 1A), suggesting a possible mode of action. Next, we assessed the combination profile of Neq1153 with standard antimalarials (e.g., artesunate, chloroquine, atovaquone, and proguanil). Neq1153 showed an antagonistic profile when combined with artesunate and chloroquine. Conversely, the combination of the inhibitor with atovaquone and proguanil showed an additive profile. Finally, the assessment of Neq1153 against a panel of resistant strains of the parasite indicated that the compound showed no cross-resistance with K1 (RI = 1), Dd2 (RI = 0.1), TM90C6B (RI = 1), 3D7RMMV848 (RI = 1) and Dd2RDSM265 (RI = 0.1) strains (Figure 1C). Interestingly, Neq1153 exhibited a 10-fold increase in potency against Dd2 strain (chloroquine-resistant) when compared to the potency against 3D7 strain (chloroquine-sensitive). Modifications in R1 position led to a loss of potency, indicating that the aldehyde substituent in this position is essential for antiplasmodial activity against both the 3D7 and Dd2 strains. Modifications in R2 and R3 position were tolerated. Di- and tripeptides showed submicromolar potency against the chloroquine-sensitive strain of Plasmodium falciparum as well as a pronounced selectivity index (SI = 350). Neq1153 is a slow-acting P. falciparum inhibitor with activity peak in trophozoite forms, causing a swallow of the digestive vacuole. Moreover, Neq1153 showed no cross-resistance against a representative panel of resistant strains. These findings highlight the importance of an in-depth investigation to indicate the true potential of a new series of compounds as antimalarial candidates and that small peptide-like derivatives are attractive hits for an antimalarial drug discovery program.

Palavras-chave: Malaria. Peptide-like. Antiplasmodial.

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