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Synthesis and Evaluation of Antiplasmodial Activity of 2,2,2-Trifluoroethoxychalcones and 2-Fluoroethoxy Chalcones against *Plasmodium falciparum* in Culture

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Abstract: A new class of compounds comprising two series of chalcones with 2,2,2-trifluoroethoxy group and 2-fluoroethoxy groups were synthesized and screened for in vitro antiplasmodial activity against *Plasmodium falciparum* (3D7) using the [^{3}H] hypoxanthine incorporation inhibition assay. Chalcones with 2,2,2-trifluoroethoxy groups substituted on the *p*- and *m*-positions of the 1-phenyl ring showed weak antiplasmodial activity, while compounds substituted on the *o*-position of the 1-phenyl ring displayed enhanced antiplasmodial activity, thus indicating that 2,2,2-trifluoroethoxy groups on the 1-phenyl ring of chalcones show position-dependent antiplasmodial activity. Of the 34 compounds synthesized, chalcones **3a** and **3f** exhibited significant inhibitory effects, with IC_{50} values of 3.0 μg/mL and 2.2 μg/mL, respectively. Moreover, these compounds **3a** and **3f** showed profound antiplasmodial activity in combination with artemisinin in vitro. The most active molecules, **3a**, and **3f**, were further assessed for their cytotoxicity towards mammalian Vero cells and the selectivity index (SI) values are 8.6, and 8.2 respectively, being considered non-toxic. We also studied the antiplasmodial activity of 2-fluoroethoxychalcones to discern the effect of the number of fluorine atoms in the fluoroethoxy group. Our results showed that chalcones with 2-fluoroethoxy group on the 1-phenyl ring exhibited more enhanced inhibitory effects on the growth of parasites than their trifluoro analogues, which reveals that monofluoroethoxy group is generally more effective than trifluoroethoxy group in the inhibition of parasite growth. Thus *o*-2,2,2-trifluoroethoxychalcones (Series 3) and 2-fluoroethoxychalcones may serve as good antiplasmodial candidates for future further development.

Keywords: fluoroethoxychalcones; antiplasmodial activity; *Plasmodium falciparum* (3D7); artemisinin combination therapy; cytotoxicity