Melatonin-Based Indole Compounds as Promising Antimalarials Targeting the Parasite Melatonin Pathway in *Plasmodium falciparum*

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The emergence of resistance to artemisinin-based combination therapies highlights the urgent need for new antimalarial strategies. Because host-derived melatonin regulates the intraerythrocytic developmental cycle of *Plasmodium falciparum* through PLC–IP_3–Ca^{2+} signaling, compounds capable of modulating this pathway may represent novel therapeutic tools. In this study, melatonin- and tryptamine-derived indole compounds were synthesized using copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) and evaluated for anti-plasmodial activity. Antimalarial activity was assessed against the *P. falciparum* 3D7 strain and a PfSR25 knockout line, while cytotoxicity was evaluated in HEK293T cells and gametocidal activity was tested using luciferase-expressing late-stage gametocytes. To investigate interference with melatonin signaling, parasites were incubated with sub-therapeutic concentrations of compounds (500 nM) alone or in combination with melatonin (100 nM). Several compounds increased parasitemia when tested alone, suggesting melatonin-like agonistic activity. In particular, compounds (3), (12), and (13) significantly enhanced parasitemia, indicating possible activation of melatonin-related signaling pathways. In contrast, compounds (7) and (8), which showed measurable antiplasmodial activity (IC_{50} ≈ 32 µM and 12 µM), displayed no agonistic effect but strongly inhibited melatonin-induced increases in parasitemia when co-incubated, suggesting competitive antagonism. Compound (13) also demonstrated significant gametocidal activity, reducing late-stage gametocyte viability by approximately 63%. These findings reveal that melatonin-derived indole compounds can either mimic or antagonize melatonin signaling in *P. falciparum*, highlighting their potential as chemical probes to study parasite synchronization and as promising scaffolds for the development of new antimalarial strategies targeting parasite signalling pathways.