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New plasmepsin inhibitors targeting multiple life stages of the malaria parasite

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Regardless of the several advances, malaria still remains one of the causatives for millions of deaths yearly, particularly in the endemic regions. The failure of frontline treatments and the paucity of new effective drugs together create the added burden to the global public health. Majority of the current antimalarial drugs selectively target blood-stage malaria infection. However, the renewed malaria eradication guidelines recommended the discovery of new drugs, which can target the liver, asexual and sexual blood stages (that is, multistage activity). Bearing in mind these facts, we decided to build a library of new compounds of chemical diversity based on the synergistic association of high-valued heterocycles with phthalimide and hydroxyethylamine scaffolds. Our studies suggested a few potential molecules that exhibited noteworthy growth inhibition of *Plasmodium falciparum* in culture and *P. berghei* infection in a mouse model with nominal cytotoxicity. Few hits were evaluated as notable multistage growth inhibitors (liver, asexual blood and gametocyte stages) of the parasite in low micromolar inhibitory concentrations. Added experiments presented synergistic interactions with chloroquine and dihydroartemisinin in culture and *P. berghei* infected mice model. Selected hits were examined for their target deification and found to inhibit the activity of plasmepsin (II, IV and V), enzymes found in the digestive vacuole of *the Plasmodium* parasite. The interesting observations will be presented.

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