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Identification of the 3,4-Dihydro-2H,6H-Pyrimido[1,2-c][1,3]Benzothiazine-6-imine Derivatives as Novel selective Inhibitors of the *Plasmodium falciparum* Dihydroorotate Dehydrogenase

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Plasmodium falciparum is an apicomplexan parasite that is responsible for the development of malaria. The parasite has evolved resistance to conventional antimalarial drugs used in many endemic areas rendering development of novel antimalarial drugs as an urgent issue. Mitochondria carry out biochemical functions essential for almost all eukaryotic cells such as homeostasis calcium, signaling for cell death and survival also ATP production. In addition to that, mitochondria are also important organelle for de-novo pyrimidine biosynthesis. Studies of antimalarial drug target identified dihydroorotate dehydrogenase (DHODH) as potential drug target which involve in the fourth step of pyrimidine biosynthesis. PfDHODH is belong to Family 2 enzyme that catalyze the oxidation of dihydroorotate to orotate and the electrons are transferred to ubiquinone in the respiratory mitochondrial chain via the involvement of cofactor, flavin mononucleotide (FMN). The inhibitor binding site of *P. falciparum* DHODH is known to be structurally divergent from the mammalian orthologue. Its characteristic and functionalities allow development of pathogen-specific inhibitors. In this study, we screened around 40,000 compounds from Kyoto University's library in 384-well plates against recombinant PfDHODH. The screening identified PD 404182 and its derivatives as rPfDHODH inhibitors and among them ten compounds showed IC₅₀ of under 1 μ M. The average Z'-factor was 0.875 ± 0.088 and the coefficients of variation was 2.38% indicating excellent performance of the screening systems. Finally, PD 404182 and its derivative also inhibited the growth of *P. falciparum* 3D7, providing new starting points for antimalarial drug development.

Keywords: *Plasmodium falciparum*, dihydroorotate dehydrogenase, inhibitors

Biography:

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