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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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Abstract

Plasmodium falciparum is an apicomplexan parasite that is responsible for the development of malaria. 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. The inhibitor binding site of P. falciparum DHODH is known to be structurally divergent from the mammalian orthologue. The screening identified PD 404182 and its derivatives as rPfDHODH inhibitors and among them ten compounds showed IC50 of under 1 µM. 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.

Biography

Endah Dwi Hartuti, Apt, M.Biomed is a PhD student, Graduate School of Biomedical Science, Nagasaki University, Japan. Biochemistry with experience designing and performing experiments with a focus on protein characterization, Production technology of bio-based product with experience in utilization of Indonesian microbial resource for creating products in health and food fields. Drug discovery with experience in establishment of screening methods from natural and synthetic compounds.

Speaker Publications:

1. “Structural and Biochemical Features of Eimeria tenella Dihydroorotate Dehydrogenase, a Potential Drug Target.”
2. “Identification of Plasmodium falciparum Mitochondrial Malate: Quinone Oxidoreductase Inhibitors from the Pathogen Box”
3. “Biochemical studies of membrane bound Plasmodium falciparum mitochondrial L -malate:quinone oxidoreductase, a potential drug target”

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