

Dissertation Evaluation Report

Report No.	Diploma Number: D-BIO 1370	Applicant's Name	Endah Dwi Hartuti
Evaluators	Print name		
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Evaluation Report of Dissertation			
<p>1 . Evaluation of the research purpose.</p> <p>Malaria is one of the most devastating parasitic infections in tropical areas. Because malaria parasites undergo antigenic variation at high rates, they easily escape from the immune system and become resistant to conventional drugs. It is thus essential to develop novel classes of therapeutics with distinct mechanisms. The applicant sought to develop anti-malarial drugs targeting a unique malarial pyrimidine biosynthetic pathway. The research purpose is, therefore, appropriate.</p> <p>2 . Evaluation of the research methods.</p> <p>The target for the drug development was dihydroorotate dehydrogenase derived from <i>Plasmodium falciparum</i> (PfDHODH). The applicant expressed a SUMO-tagged PfDHODH in <i>E. coli</i>. After digestion with a SUMO protease, the enzyme was purified and examined for its specific activity. After the development of an assay system, a Kyoto University library consisting of more than 40,000 compounds was screened to obtain inhibitors of PfDHODH. Finally, the specificity of the inhibitors was examined by using parent and transgenic malaria parasite strains. The research method is, therefore, appropriate.</p> <p>3 . Evaluation of the analysis, interpretation and discussion.</p> <p>The applicant obtained a series of inhibitors of PfDHODH, which were categorized into two classes of compounds, 3,4-dihydro-2<i>H</i>,6<i>H</i>-pyrimido [1,2-<i>d</i>][1,3]benzothiazine-6-imine (DPBI) and 3,4-dihydro-2<i>H</i>-benzo[4,5]isothiazolo[2,3-<i>α</i>]pyrimidine (DBIP) derivatives and analyzed them chemically. The analysis, interpretation and discussion are well structured.</p> <p>As stated above, the dissertation will greatly contribute to the development of therapeutics for drug-resistant malaria parasites, and the evaluators uniformly agree that the dissertation is worthy of being approved for a Doctor of Philosophy in Medical Science.</p>			
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