SYNTHESIS OF ANTHRAQUINONE ANALOGUES AND THEIR ANTIPLASMODIAL ACTIVITY

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1. Letter of Report Submission

Wed 21 December, 2011

Prof. Dr. Abu Bakar bin Abdul Majeed
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Prof,

RE: SUBMISSION OF FINAL REPORT FOR FRGS PROJECT
PROJECT TITLE: SYNTHESIS OF ANTHRAQUINONE ANALOGUES AND THEIR ANTIPLASMODIAL ACTIVITY
RMI FILE NUMBER: 600-RMI/ST/DANA 5/3/Dst (252/2009)

With regards to the above, we are pleased to submit the final report of our project entitled "Synthesis of Anthraquinone Analogues and Their Antiplasmodial Activity", which was funded under the Dana Kecemerlangan (Danakep).

Please find the full report of the project herewith for your attention.

Thank you.

Yours Sincerely,

PROF. DR. NOR HADIANI ISMAIL

Project Leader

5. Report

5.1 Proposed Executive Summary

One of the major anthraquinones identified from the *R. elliptica* was reported to possess strong antiplasmodial activities. Quinone derivatives have been widely used as malaria drugs. Their mechanism of action is suggested to be through inhibition of the haemazoin formation during the pathogenic blood infection by *Plasmodium falciparum*, the protozoa that causes malaria disease. The evaluation of anthraquinones, one of quinone derivatives as antiplasmodial agents is not yet widely studied. Synthetic chemistry is a convenient tool to prepare synthetic analogues of natural anthraquinones possessing antiplasmodial activities. Evaluation of natural anthraquinones and their synthetic analogues for antiplasmodial activities is necessary to evaluate anthraquinone class of compounds as potential antiplasmodial candidate.

5.2 Enhanced Executive Summary

Several anthraquinones such as 2-formyl-3-hydroxyanthraquinone, damncanthal and emodin were known antiplasmodial agents. Anthraquinones like other aromatic substances may undergo bioreduction and produce oxygen radicals thereby rendering the malarial parasite more susceptible to oxidative stress leading to the death of parasites. Anthraquinones isolated from the roots of *Rennellia elliptica* demonstrated interesting antiplasmodial activity. The activity however, varies depending on substitution pattern of the anthraquinone skeleton. Thus, the synthesis of 9,10-anthraquinones mimicking natural anthraquinones from *R. elliptica* was warranted and their antiplasmodial activity was evaluated to examine the possible structure-activity relationship of 9,10-anthraquinones and their antiplasmodial activity. The analogues of bioactive anthraquinones were synthesized through Friedel-Craft reaction between phthalic anhydride and various benzene derivatives in the presence of eutectic mixture of aluminium chloride and sodium chloride. The antiplasmodial activity was determined based on inhibition of the compounds against *Plasmodium falciparum* (3D7) growth *in vitro*. Thirty two compounds were successfully synthesized throughout the study. The strongest inhibition against malarial parasite was shown by 1,3-dihydroxy-6-methyl-9,10-anthraquinone with IC_{50} value of 0.02 µM. In general, the arrangement of substituents in symmetrical manner is essential for effective antiplasmodial activity. For dihydroxylanthraquinones, the activity is favourable when the substituents are *meta*-arranged and symmetrical to methyl group at C-6. For dimethoxyanthraquinones, the activity is more potent when the substituents are *ortho*-arranged at C-1 and C-2 and symmeticaly to methyl substituent at C-6. This observation correlates well with anthraquinones substituted with hydroxyl and methyl substituents. Quantitative structure-activity relationship to further examine the potential of anthraquinones as antiplasmodial agent should be pursued.