Thesis Title	Evaluation of Bisquaternary Quinolinium Compounds Against *Plasmodium falciparum* In Culture
Name	Kunnika Kuaha
Degree	Master of Science (Biochemistry)
Thesis Supervisory Committee	
	Prapon Wilairat, Ph.D.
	Suman Nakornchai, M.Sc.
Date of Graduation	14 May B.E. 2540 (1997)

ABSTRACT

Malaria is an infectious disease that causes morbidity and mortality in many tropical areas, including the borders of Thailand with Cambodia and Myanmar. The most virulent human malaria parasite, *P. falciparum*, has become resistant to most of the antimalarial drugs in current use. Reversing drug resistance is difficult because of the mechanism of action of the drugs still are not known. Therefore, the development of new antimalarial drugs is urgently needed. In addition, drug targets and the mechanism of drug action should be identified.

Thirty-four derivatives of bisquaternary quinolinium compounds, DNA minor groove binding ligands, which had previously been studied in the treatment of human leukemia, were synthesized and tested against *P. falciparum* K1 (chloroquine-and pyrimethamine-resistant strain) in culture and against human Jurkat leukemia cell line in order to obtain *in vitro* therapeutic index (IVTI) for toxicity. Results showed that the derivative with a methyl group substitution at R1 and H at R2 and R3, 1-methyl-4-[4-[4-[4-(1-methyl-quinolinium)amino]benzamido]anilino]pyridinium salt (sn 6999), had high antiparasite activity (IC_{50} = 15 nM) and high IVTI (> 1333). Derivatives which had functional group substitution at C6, C7, or C8 of the quinoline ring or derivatives

with amino group substitution at R2 position of benzene ring also had high antimalarial activity (IC_{50} = 20 nM) and high IVTI (= 1000).

As a number of DNA minor groove binding agents have been shown to inhibit DNA topoisomerase I and II activity *in vitro*, tests with partially purified *P. falciparum* DNA topoisomerase I and II were performed. Results showed that bisquaternary quinolinium compounds could inhibit parasite DNA topoisomerase I and II. Derivatives with functional group substitutions at the quinoline ring showed more inhibitory effect on both enzymes. Compound 1-methyl-4-[4-[4-[4-(1-methyl-7-amino-quinolinium)amino]benzamido]anilino]pyridinium salt (sn 10005) had the most inhibitory effect (minimum inhibitory concentration (MIC) for topoisomerase I = 25 μM, and MIC for topoisomerase II = 5 μM).

When drug combinations of bisquaternary quinolinium derivative 1-methyl-4-[4-[4-[4-(1-methyl-7-chloro-quinolinium)amino]benzamido]anilino] pyridinium salt (sn 7678), or 1-methyl-4-[4-[4-[4-(1, 6-dimethyl-quinolinium)amino]benzamido]anilino] pyridinium salt (sn 8315) with antimalarial drugs (e.g., chloroquine, dihydroartemisinin, mefloquine, pyronaridine, quinacrine, quinine) were studied, no antagonistic effects could be observed for all combinations of drugs tested.