Thesis Title	Mechanism-Based Development of Artemisinin-Derived Antimalarials
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Date of Graduation	8 May B.E. 2540 (1997)

ABSTRACT

Artemisitene (***10***), a naturally occuring endoperoxide closely related to artemisinin (***1***) bearing an *exo*-cyclic double bond at C-9 position, was chemically synthesized in a high yield, one-pot, reaction from ***1***. Originally, artemisitene was obtained as a minor component from *Artemisia annua* or from chemical reaction of artemisinin *via* a photochemical approach. Our synthetic route to artemisitene (***10***) involved a "one-pot" phenylselenenylation of the lactone ring in ***1*** followed by hydrogen peroxide induced oxidation-selenoxide rearrangement. The *exo*-cyclic double bond in ***10***, *via* a 1,4-(Michael) addition reaction, was reacted with various nucleophiles provided new C-16 functionalized artemisinin derivatives. The antimalarial activity of these newly synthesized and currently used artemisinin derivatives, against *Plasmodium falciparum* strain K1 *in vitro*, showed a correlation with their affinity of binding with ferroprotoporphyrin IX, as measured from the spectral change of the latter. The correlation points to the

biological significance of the interaction of these derivatives with ferroprotoporphyrin IX and may provide a basis for primary screening of peroxidic antimalarials of similar structures.