3736289 SCBC/M : MAJOR : BIOCHEMISTRY ; M.Sc. (BIOCHEMISTRY)

KEY WORD : TOPOISOMERASE II / *PLASMODIUM FALCIPARUM* 9-ANILINOACRIDINE DERIVATIVES / KCl / SDS METHOD / TUNEL

SARANYA AUPARAKKITANON : STUDY ON THE MECHANISM OF ACTION OF *PLASMODIUM FALCIPARUM* DNA TOPOISOMERASE II INHIBITORS. THESIS ADVISOR : PRAPON WILAIRAT Ph.D., SUMALEE TANGPRADUBKUL Ph.D. 104 p. ISBN 974-589-307-2

Malaria is the most widespread infectious human disease in the world, causing a high degree of morbidity and mortality. Due to resistance to most of antimalarial drugs by *P. falciparum*, the most virulent strain of human malaria parasites, development of new effective antimalarial drugs is urgently needed.

Derivatives of 9-anilinoacridine, an antitumor drug, have been shown to inhibit *P. falciparum* growth in culture, and to inhibit parasite DNA topoisomerase II activity *in vitro*. Using KCl/SDS precipitation assay to detect the presence of protein-DNA complexes within parasite cells, an indicator of DNA topoisomerase II inactivation, derivatives containing 3,6-diNH_2 substitutions with 1′-electron donating (NMe_2, CH_2NMe_2, $NHSO_2Me$, OH, OMe), or 1′-electron withdrawing (SO_2NH_2.) groups produced protein-DNA complexes. However, pyronaridine, 9-anilino-aza-acridine antimalarial drug, did not produce protein-DNA complexes although it could inhibit *P. falciparum* DNA topoisomerase II activity *in vitro*.

During topoisomerase II-mediated DNA-protein complex formation, the enzyme forms a covalent link with the 5′-phosphate of DNA producing a free 3′-hydroxyl end. Terminal deoxynucleotidyl transferase was used to label to 3′- termini of fragmented DNA *in situ* (TUNEL technique). Derivatives of 9-anilinoacridines which produced DNA protein complexes as determined by KCl/SDS method also produced significantly higher $TUNEL^+$cells compared to control. Pyronaridine failed to stimulate an increase in $TUNEL^+$cells.