Sunisa Akkarasamiyo 2014: Efficient Synthesis of Anti-influenza, Tamiflu®, Novel Anticancer and Antimalarial Naphthoquinone Amides, Antimalarial *N-O* Heterocycles and Other Bioactive Heterocycles. Doctor of Philosophy (Chemistry), Major Field: Chemistry, Department of Chemistry.
Thesis Advisor: Professor Ngampong Kongkathip, Ph.D. 362 pages.

Tamiflu® (Oseltamivir phosphate) is a potent neuraminidase inhibitor that is used for the treatment of influenza A (H5N1 and H1N1) infection. The total synthesis of Tamiflu® was accomplished in 20 steps with 1.9 % overall yield started from very cheap and abundant starting material, D-glucose. The synthesis represents a new and efficient modified Bernet-Vasella-Barbier reaction of 5-iodo-3-amino-1,2-*O*-isopropylidine furanoside to generate the corresponding diene. Ring closing metathesis was employed to construct the cyclohexene carboxylate core structure. Introduction of the amino function to perform S_N2 substitution with NaN_3 followed by azide reduction. Pentyl ether moiety was introduced through aziridine opening with 3-pentanol.

Rhinacanthins are naphthoquinone ester derivatives which were isolated from Thai herb, *Rhinacanthus nasutus*. In Thailand, *R. nasutus* is used for treatment of cancer. Synthesis of rhinacanthins and derivatives, novel naphthoquinone aromatic and aliphatic esters and naphthoquinone aromatic amides, and their anticancer and antimalarial evaluations were reported by our group. Therefore, novel naphthoquinone aliphatic amides were synthesized to compare their biological activities with those of aromatic amides and the esters. Fourteen novel naphthoquinone aliphatic amides were synthesized in nine steps with 9-25% overall yield from 1-hydroxy-2-naphthoic acid. They were evaluated for their anticancer activity against KB and NCI-H187 cell lines, antimalarial activity against *Plasmodium faciparum*, cytotoxicity to normal Vero cells and studies for the structure activity relationship. Interestingly, all compounds showed anticancer activity with IC_{50} value in the range of 4.83 to 101.86 μM. Four naphthoquinone aliphatic amides with long aliphatic chain length (C9-C18) showed antimalarial activity with IC_{50} values of 0.76 to 10.62 μM.

Malaria is a serious health problem in tropical and sub-tropical zones. Artemisinin and its derivatives are currently effective drugs for the treatment of malaria patients. The structure of artemisinin contains an unusual peroxide bridge (O-O) which is believed that it is responsible for the drug's mechanism of action. The heterocyclic spiro-compounds based on spiroacenapthenones and spirooxindole that contain an N-O bond instead of the O-O bond (peroxide) in artemisinin were synthesized to evaluate antimalarial and anticancer activities. Their compounds were obtained in two steps from 1,3-dipolar cycloaddition of azomethine ylides followed by oxidative Meisenheimer rearrangement. One of triple *N-O* heterocyclic compounds showed inhibition against *Plasmodium faciparum* malaria with a good activity (IC_{50} = 1.04 μM). Seven *N-O* heterocyclic compounds showed anticancer activity with IC_{50} values of 24.45 to 120.78 μM.

Palladium catalysed cascade reaction of allene is very useful for synthesis of biologically active complex structures. We also presented the regio and stereoselective catalytic synthesis of *Z,Z*-bisallylamines, isoquinoline and isoquinolinone from combination of complex allenes, containing purine and quinazolinone cores, with aryl/heteroaryl iodides and ammonium tartrate as a novel ammonium surrogate.

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