CHARPTER I

INTRODUCTION

1.1 Statement of the problem

1.1.1 Malaria

Malaria is caused by a parasite called *Plasmodium*, which is transmitted *via* the bites of infected *Anophelesis ssp*. At present time, there are more than 100 species of malaria parasites but only four species - *P. falciparum*, *P. ovale*, *P. vivax* and *P. malariae.* "*Plasmodium falciparum"* are the most dangerous species. Currently, the severe infection of malaria is widespread into other countries owing to more convenience and faster transportation. There are two species - *Plasmodium falciparum* and *Plasmodium vivax* that cause this severe infection in Thailand. Many studies have been aimed to develop several antimalarial drugs, for instance, quinine (**1**), chloroquine (**2**), pyrimathamine (**3**) and mefloquine (**4**).[1]

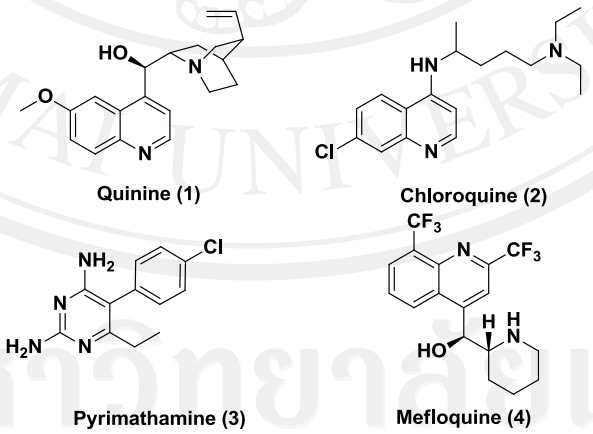


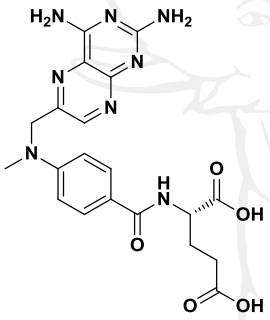
Figure 1.1 Chemical structure of antimalarial drugs : Quinine (**1**), Chloroquine (**2**), Pyrimathamine (**3**) and Mefloquine (**4**).[1]

A major obstacle to successful treatment of malaria is due to the remarkable resistance to antimalarial drugs of malaria parasites especially *P. falciparum*. The parasite has developed resistance to nearly all available antimalarial medicine, for example, choloroquine.[2] In recent years, *P. vivax*, particularly from Oceania and some parts of South-East Asia, has also developed resistance to chloroquine. Moreover, the resistance of *Plasmodium* to the other antimalarials has also been reported such as resistance to quinine, mefloquine and artemisinin compounds.[2,3] This drug resistance in malaria is widespread in many parts of the world which cause the treatment increasingly difficult. Hence, The development of antimalarial drugs is proving to be a challenging problem for the discovery of new drugs with novel mechanism of action against malaria parasites.

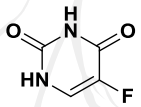
1.1.2 Cancers

Cancer is another life threatening diseases of human. It is a leading cause of death about 13% of all deaths (more than 6 million people) in 2004.[4] About one in three of common cancers may be protectable and two in three of leading cause of cancers related with smoking, food, obesity, lack of exercise and environmental occupations such as air pollution. In addition, cancer is the disease that takes several years before symptoms appear and it is a chronic disease that is not specific only one organ. The six most common cancers worldwide are lung cancer, stomach cancer, breast cancer, colorectal cancer and cervival cancer, respectively.[5] Treatment of cancer usually required a long period of time. As a result, loss of economic resources, personnel, including mental of patient and patient's family will occur. There are several types of treatment of cancer such as surgery, radiation therapy, hormone therapy and chemotherapy etc.

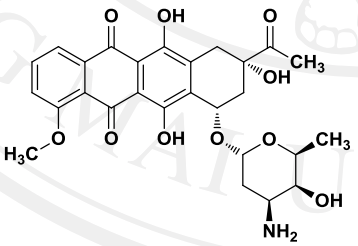
Chemotherapy is a cancer treatment that utilizes anticancer drugs to stop the growth of cancer cells. These drugs are administered most commonly either intravenously or by mouth such as methotrexate (**5**), 5-fluorouracil (**6**) daunorubicin (**7**) and doxorubicin (**8**).[6] In contrast, a wide variety of drugs that are used to treat cancers have side effects. Some side effects may be temporary and uncomfortable. Some can cause dose reductions and treatment delays or even be life-threatening.[7] Thus, there are many attempts to develop anticancer drugs for enhancing the efficacy of anticancer drug while reducing their side effects.



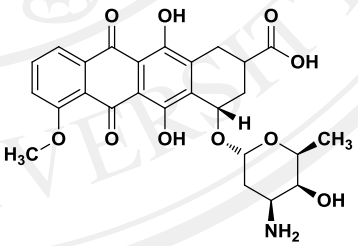
Methotrexate (**5**)



5-Fluorouracil (**6**)



Daunorubicin (**7**)

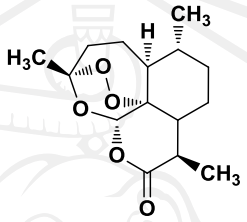


Doxorubicin (**8**)

Figure 1.2 Chemical structure of anticancer drugs.[6]

In 1971, artemisinin (**9**), discovered by Chinese chemist, was isolated from the leafy portion of the Chinese medicinal plants, *Artemisia annua Linn.* This compound is call quinghaosu (QHS, artemisinin) which has been used for the treatment of fever and malaria for more than 1000 years.[8] Artemisinin is a sesquiterpene trioxane lactone

containing a unique endoperoxide bridge responsible for the antimalarial activity as shown in Figure 1.3.[9] The mechanism of action of artemisinin has been proposed that involves the formation of free radical intermediates resulting from interaction of the endoperoxide moiety with heme. However, it is not entirely clear on how the free radicals cause the parasite death.[10]



Artemisinin (**9**)

Figure 1.3 Chemical structure of Quinghaosu (QHS, artemisinin)

Recently, artemisinin is under early research and testing for treatment of cancer, primarily by researchers at the University of Washington.[11,12] While its mechanism of action is unknown, it has been suggested that the antitumor activity of artemisinin is related to the peroxide lactone group in the structure. It has been proposed that artemisinin release reactive oxygens species (ROS) when the peroxide comes into contact with high iron concentration, which is common in cancerous cell. Furthermore, it was observed that artemisinin reduce angiogenesis and the expression of vascular endothelial growth factor in some tissue cultures.[13,14]

1.2 Research Objectives

1.2.1 To synthesize deoxoartemisinin derivatives as the starting materials for linear deoxoartemisinin-pseudo peptide backbone oligomers synthesis.

1.2.2 To synthesize cyclic deoxoartemisinin pseudo peptide backbone oligomers.

1.2.3 To explore the biological activities of linear deoxoartemisinin pseudo peptide backbone oligomers and cyclic deoxoartemisinin pseudo peptide backbone oligomers.

1.3 Usefulness of the research

Deoxoartemisinin pseudo peptide nucleic acid compounds may show interesting bioactivities that could be applied for medicinal use such as antimalarial, anticancer, and other biological activities.

1.4 Scope of the study

1.4.1 To synthesize deoxoartemisinin monomer, dimer, trimer and tetramer using pseudo peptide backbone as a linker.

1.4.2 To synthesize deoxoartemisinin monomer, dimer, trimer and tetramer using pseudo peptide backbone with lysine at N-terminus.

1.4.3 To synthesize cyclic pseudo peptide backbone of deoxoartemisinin monomer, dimer, trimer and tetramer.

1.4.4 To evaluate the biological activities of the synthesized compounds against malaria parasites and cancer cell lines.