CHAPTER I

INTRODUCTION

Malaria ranks among the major health a development challenges of the world. The disease is prevalent in almost 100 counties, accounting for 40% of the world's population. It affects an estimated three to five hundred million people, causing more than a million deaths per year. Malaria kills one child every 30 seconds. In absolute numbers, malaria kills 3000 children younger than five years of age day. Although the disease is spread in most tropical countries, Sub-Saharan Africa, with more that 80% of the world's malaria cause, is the focus of most efforts in combating the disease due to the high morbidity and mortality rates. Southeast Asia and South America are of interest because of the early development of drug resistance malaria parasite in regions. The mortality is concentrated among children younger than five years, travelers, migrants from non-malaria into malaria regions[1].

The problems of controlling malaria in malaria countries are aggravated by inadequate health structures and poor socioeconomic conditions. The situation has become even more complex over the last few years with the increase in resistance to the drugs normally used to combat the parasite that causes the disease. Because of worsening problems of drug resistance in many part of the word[2], adequate treatment of malaria is becoming increasingly difficult. This led to the introduction of artemisinin, which has more efficacies than conventional malaria chemotherapy.

Artemisinin is a sesquiterpene endoperoxide that has been isolated as the active principle of the Chinese antimalarial herb, *Antemisia annua.* Clinical trials have demonstrated that artemisinin is an effective antimalarial and can be used to treat infections of multidrug resistant strains. Since artemisinin is poorly soluble in either water or oil and has short elimination half-life, these led to search for derivatives,

which have improved pharmaceutical properties as well as better antimalarial activity. Reduction of artemisinin to the lactone-reduced dihydroartemisinin has led to the preparation of a series of semisynthetic first generation analogues. To date, aretmisinin, the water-soluble artesunate and the artemether, lipophilic alkylether are being used for treatment of malaria [3].

Artemisinin and its derivatives are converted to DHA in the body. Artesunate and artemether can be considered as prodrugs because biotransformation into the active metabolite DHA occurs rapidly almost immediately for artesunate[4]. Since DHA can be made from artemisinin so it is easy to produce with less synthetic steps and thus a lower cost. The use of DHA instead of the substitute compounds such as artesunate or artemether, has these advantages as described before. To date, oral DHA is available in China.

From clinical study of oral DHA for the treatment of acute, uncomplicated, falciparum malaria in Thailand, it was found that treatment with oral DHA is effective and well tolerated and that DHA may be suitable as an alternative treatment for acute, uncompleted, falciparum malaria [5].

Since the present of endoperoxide bridge, DHA is unstable. In stress condition, high temperature or long time storage, the amount of degradation product is higher than the minimal limit of regulation. Consequently, the analysis of chemical structure and toxicity of these compounds has to be done before DHA can go for the process of drug development.

1.1 The objectives of this research

The purpose of this work were

1. To identification of chemical structure of degradation products of DHA
2. To study cytotoxicity activity of these compounds
3. To study acute toxicity of these compounds
4. To study antimalarial activity of these compounds

Therefore, this work many provide a useful information for decide to develop DHA, treatment of life-threatening disease.