CHAPTER I

INTRODUCTION

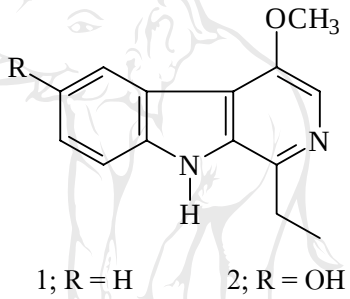
Malaria continues to be the most prevalent and deadly parasitic disease in the world, infecting more than 300 million people and causing more than 1 million deaths each year (WHO, 1998). Human malaria is caused by four species of parasitic protozoa (i) *Plasmodium falciparum*, (ii) *P. vivax* , (iii) *P. ovale* and (iv) *P. malariae*. Of the four species, *P. falciparum* is responsible for most severe and deadly forms of malaria. However there are only a few antimalarial drugs available for the treatment of *P. falciparum* infection. In addition, the resistance of *P. falciparum* to the classical antimalarial drugs such as quinine, chloroquine and mefloquine, has rapidly increased (Willems, 1991; Bray and Ward, 1993; Nosten and Price, 1995; Olliaro *et al*., 1996). These have triggered off a massive screening of new compounds from either synthetic, or from natural sources, for potential anti-malarial activity.

Based on traditional medicine, artemisinin (qinghaosu) has been isolated from Chinese herb *Artemisia annua* and its semisynthetic derivatives have been developed (Cumming *et al*., 1998). Although artemisinin is now effective in the treatment of malaria of both chloroquine-sensitive and resistant strains of *P. falciparum*, these parasites may rapidly develop resistance to the drugs. Therefore it is also necessary to search for new compounds as back-up antimalarial drugs.

The bark of medicinal plant *Picrasma javanica* Bl. was widely used for the treatment of malaria in the traditional medicine in Myanmar, Indonesia and Thailand (Old Style Doctor Association, 1962). In 1942, during second world war, 36 recipes of Thai Folk Medicine were used for treatment the soldiers who infected either falciparum or vivax malaria by Dr. Ketsusinh and staff (Ketusinh, 1948). One of the ingredients in these recipes was stembark of *P. javanica*. Pavanand *et al*. (1988) demonstrated that the chloroform extract of the bark possessed the high level of in vitro antimalarial activity against asexual stage *P. falciparum*. Further isolation and purification of the chloroform extract resulted in the identification of the pure alkaloids in the class 1-substituted-4-oxygenated-β-carbines (Figure 1.1), 1-vinyl-4-methoxy-β-carboline (1) and 1-vinyl-4-methoxy-6-hydroxy-β-carboline (2). The first compound was effective against *P.*

falciparum isolated with mean IC_{50} of 2.4 μg/ml, while the second one showed mean IC_{50} of 3.2 μg/ml.

In order to develop new candidate compounds for antimalarial originated from Thai medicinal plants, this thesis focused on fractional isolation of *P. javanica*. Isolated fractions with anti-malarial activity against *P. falciparum* were further purified. The structure of pure active compounds were elucidated. In addition, the lead structure was selected based on antimalarial activity and chemical structure. The lead structure then was modified and the structure-activity relationship was discussed.



1; R = H 2; R = OH

Figure 1.1 Chemical structure of 1-substituted-4-oxygenated-β-carbolines