Recipient of IOCD Travel Grant to Attend 2007 Winter Conference on Medicinal & Bioorganic Chemistry

THE POTENTIALS OF NATURAL PRODUCTS TO LESSEN THE MALARIA BURDEN IN AFRICA

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Malaria is a major problem in Africa, killing up to 3000 children per day. It is a disease burden for Africa resulting in an annual estimated loss in GDP of $12 billion. There are, besides the use of insecticide-impregnated bed nets, measures to deal with the malaria problem depending upon specific targets that may be identified as intervention strategies. Targeting one or more stages of the life cycle of the parasite, developing vaccines, as well as innovative ways of using methods to kill mosquitoes or mosquito larvae, are some of the approaches that are used to address the problem of malaria. One of the approaches we followed was to screen plants that are traditionally used for treating fevers. Accordingly, evaluation of plant extracts and natural products for anti-plasmodial activity has resulted in the isolation and characterization of many dimeric chalcones [1], flavonoids, quinones [2], sesquiterpenes [unpublished results]. One of the major factors for the increase in the global burden of malaria is due to the building up of resistance of the parasite to most of the drugs. Chloroquine (CQ) was once considered as the most effective and safe drug for the treatment of malaria while at the same time it was the least expensive and affordable drug for the developing world. The most recent strategy recommended by the WHO and adopted by many countries to overcome the development of resistance has been to use, what is known as, combination therapy. Unfortunately the drugs that are recommended under this new scheme are still too expensive and not affordable to the poorer population of the developing world. Our approach to contribute to the issue of resistance is in two fronts. The first is to find natural products that can potentiate chloroquine against the CQ resistant malaria parasite – *P. falciparum*. The second front is to discover natural products that would weaken the resistance of the malaria vector (*Anopheles gambae*) to the insecticide – DDT. Our hypothesis is based on the assumption that the resistance of *P. falciparum* to chloroquine is based on the parasites ability to produce Gluthathione transferase (GST) enzyme which binds heme more effectively than chloroquine. This assumption is consistent with the observation that resistant parasites have developed a new way of detoxifying heme as opposed to the non-resistant parasites which convert heme to the dimeric haemozoin (so called malaria pigment) [3]. It is possible to test this hypothesis since it is now possible to produce sufficient quantities of the enzyme using *E-coli*, isolate, purify it and then conduct binding studies. Heme (**1**) was used as a reference which demonstrated an IC_{50} at 4 _M concentration. Of the ten compounds tested in our preliminary trial, the most active compound, but still less active than heme is the sesquiterpene lactone **2**, followed by the polyprenylated benzophenone **3**. The IC_{50} for the known binder of human GST, ethacrynic acid (**5**) is 8 _M. Similarly we have also conducted binding studies of selected natural products using the mosquito enzyme *Anopheles gambiae* gluthathione transferase (AGGST) enzyme. It was found recently that _-class GSTs are expressed at higher levels in *Anopheles gambiae* mosquites that are resistant to DDT than in insecticide-susceptible individuals [4]. We have now found that the bicoumarin **6** has a remarkable low IC_{50} of 1.5 _M in binding these enzymes. Based on the binding studies further experiments were conducted to see if compounds **2-4** had any effects in potentiating chloroquine against CQ resistant parasite. As can be seen from the isobolograms (Fig. 1), the sesquiterpene lactone (IC_{50} at 4 _M) had a slightly synergistic or additive effect while the chalcone (**4**) clearly had an antagonistic effect. We are currently testing more

compounds to find natural products that may have greater binding ability than heme. Work is currently in progress to test the potentiating effects of bicumarin **6**, and other active compounds.

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