THE SEARCH FOR BIOLOGICALLY ACTIVE, PARTICULARLY ANTIMALARIAL, MARINE NATURAL PRODUCTS.

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Abstract

In the following paper some aspects of the current status of antimalarial agents with blood schizonticidal activity are given. Strategies employed for the discovery of new sources of antimalarials are outlined and the marine environment is proposed as a still unexploited resource, in terms of novel antimalarial agents or lead structures. A discussion of some of the authors' sponge derived in vitro antimalarial compounds serve as examples in the discussion of approaches suitable for the isolation and identification of active natural products. Some of our newest finds, which include a series of tri- and tetracyclic diterpene formamides, which are new natural products, some dibromopyrroles, and 4α-methyl-5α-cholest-8-en-3β-ol, are also reported.

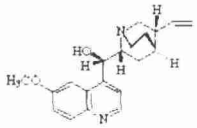
Key-words : biotechnologies, antibiotics, natural products

Introduction

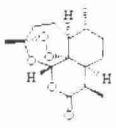
An estimated 1.5 x 10^9 people live in regions where malaria is endemic, and in excess of 2 million people die from it each year, the majority being under 5 years of age. The disease is caused by protozoan parasites, *Plasmodium* sp., which are transmitted by the female Anopheles mosquito. Of the four species of *Plasmodium* known to infect man (*P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*), *P. falciparum*, responsible for the cerebral form of the disease, is by far the most dangerous.

Malaria is currently restricted to mainly economically poor, tropical and sub-tropical regions of the world, where people can ill afford to pay for the high technology facilities needed to do adequate research into these types of health problems. In the last two decades, malaria has regained its status as one of the foremost threats to the health and economic prosperity of the human race. The main reasons for this being, the emergence of drug resistant strains of *Plasmodium* and insecticide resistant mosquitoes, as well as a general apathy on the part of Western Governments, and their associated health-care organisations to acknowledge that malaria represents a real health problem, and to provide adequate funding for research into a disease that does not affect them directly.

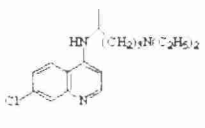
It is hoped that in the not too distant future, funding for malaria research will come to reflect the severe threat that this disease represents to us as a world population, more so than is currently the case. If reports concerning global warming are to be believed, the regions of the globe that will become havens for this dreadful disease will increase markedly in the next century. Although there have been a number of serious attempts at the development of antimalarial vaccines, to date they have proven to be unsuccessful, even though a recent report suggests this may not be the case for much longer [1]. It is also clear, that irradication of the transmitting vector is difficult, hence, there will always be a need for new antimalarial agents, particularly those that may have a novel mode of action.



1 Quinine



2 Artemisinin



3 Chloroquine

Research into the discovery of new natural sources of potential antimalarial agents has been restricted mainly to terrestrial organisms, which have in the past yielded a number of natural agents effective in the treatment of malaria *e.g.*, quinine (**1** [2]) and artemisinin (qinghaosu) (**2** [3]), and as lead structures for the development of synthetic/semisynthetic antimalarial drugs (**3, 4, 6**). Researchers working with higher plants have been able to make use of local knowledge to aid in the selection of natural materials for pharmacological and chemical investigations, particularly in regions of the world where malaria is endemic and where folk remedies are used as a matter of course in the treatment of malaria. While this approach has worked in the past and is still successfully applied [4, 5], it is clear, however, that new sources of antimalarial agents are desperately needed. One of the still unexploited resources for antimalarial agents being the marine environment.

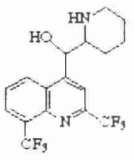
Life Cycle of the Malaria Parasite

Infected mosquitoes introduce sporozoites of *Plasmodia*, through their "bite", into the blood stream of the human host. Once infective forms of *Plasmodium* have entered the host, they quickly find their way to parenchymal cells of the liver, where they reproduce asexually to form merozoites. After an incubation period of 1-2 weeks the liver cells rupture releasing the merozoites back into the host's blood stream where they attach to and enter erythrocytes. Once in the red cells, the merozoites continue to reproduce asexually, eventually causing these cells to rupture, releasing more merozoites, which invade further erythrocytes. In the phase between being released from erythrocytes and reinvading, some of the merozoites differentiate into sexually reproducing gametocytes which can be ingested by the mosquito vector. The sexual forms reproduce both sexually and asexually to generate more gametocytes and sporozoites, hence completing the life cycle.

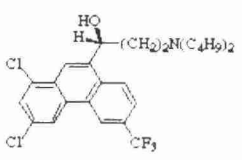
Current and Potential Antimalarial Agents (Blood Schizonticides) from Higher Plants

Traditionally, natural products play a major role in the treatment of malaria. In many malaria stricken regions of the world the local inhabitants still rely on remedies based on plant extracts, as they are either too poor or too far from medical facilities to enable them to utilise pharmaceutically proven antimalarial preparations. To use this local knowledge is certainly a very sound starting point for identifying plants and plant preparations which may prove efficacious in malaria treatment [6].

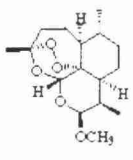
The efficacy of the extract of bark from various species of *Cinchona* trees, the active component of which is mainly quinine (**1**), in the treatment of malaria/intermittent fevers has been known in Peruvian Indian folklore for centuries [2]. The use of quinine was supplanted over the years by synthetic derivatives which had/have improved potency and selectivity *e.g.*, mefloquine (**4**) and chloroquine (**3**). Chloroquine itself has in the last ten years been found to be an inadequate treatment against certain strains of *Plasmodium* which have developed resistance to this drug, and in such cases quinine has been applied with good effect. The natural product quinine is today once again the drug of choice in cases of multi-drug resistant cerebral malaria. Another approach to overcome resistance has been to use other synthetic quinine based drugs *e.g.*, mefloquine (**4**), which, unfortunately, has already proven to be ineffective against some strains of Plasmodium, which have developed mefloquine resistance [7]. Thus, other drugs have been applied that are structurally different to the quinoline based ones, a recent example being halofantrine (**5**). The use of halofantrine is, however, restricted, since it has been shown to have some serious side effects [8]. In reality, no one drug represents an ideal treatment, and so, combinations of two or more drugs are often applied when drug resistance may be considered to be a problem.



4 Mefloquine



5 Halofantrine



6 Artemether