

METHOD FOR THE TREATMENT OF MALARIA

GOVERNMENT RIGHTS

This invention was made with government support Under NO1-AI-72648 awarded by the National Institutes of Health. The government has certain rights in the invention.

This is a continuation of copending application(s) Ser. No. 334,590, filed on Apr. 6, 1989, now abandoned.

BACKGROUND OF THE INVENTION

Human malaria is caused by species of parasitic organisms of the genus *Plasmodium*. It is transmitted by mosquitoes which ingest sexual forms of the parasite in blood meals. Sporozoite forms of the parasite develop in the mosquito and are transmitted to new host individuals bitten by the insect. The major human pathogen is *Plasmodium falciparum*.

Malaria is one of the most important health problems in underdeveloped, tropical countries. It is estimated that more than a billion people in the world inhabit areas in which malaria is transmitted. Although chloroquine has been used as an effective drug, this drug has some side effects, but more importantly, malarial parasites have acquired a resistance to chloroquine.

Thus, malaria has become an increasing problem in the tropical zones with the advent of chloroquine resistant strains of malaria parasites coupled with a decreased effectiveness of long acting insecticides such as DDT. The magnitude of the problem is reflected in the fact that malaria is the largest infectious disease in the world. Of the one billion people residing in malaria endemic areas, approximately 25 to 200 million people are diseased at any given time.

There are estimates of a million malaria deaths a year in Africa, chiefly among children under five. Even after surviving childhood infection, a large proportion of adults nonetheless remain susceptible to infection and show periodic parasitemia, even though their serum contains "protective" antiplasmodial antibodies. In hyperendemic areas of Africa, it is believed that nearly all residents harbor a continuous series of *falciparum* infections of low to moderate pathogenicity throughout their lives.

The problem of malarial infection has become even more serious as more strains of malaria have become resistant to the major anti-malaria drug chloroquine. More and more chloroquine resistant strains of *Plasmodium falciparum* have emerged in Central and South America, Africa, and Southeast Asia.

Researchers have synthesized chemical variants of chloroquine to combat new resistant malaria strains; however, these strains have already become resistant to the new drugs. Recently a new drug, mefloquine, was introduced, but already resistant strains have appeared. A totally new drug having chemical properties different from chloroquine is needed to stem the increasing epidemic of resistant malaria strains.

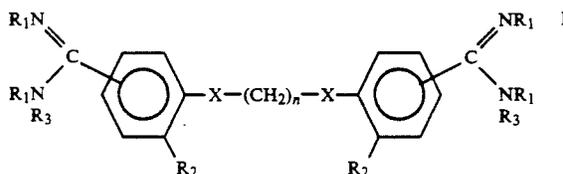
Pentamidine has been known for decades and was originally shown to be useful for the treatment of trypanosomiasis. Of more recent time, pentamidine has been found to be extremely useful in the treatment of pneumocystis carinii pneumonia, especially in immunocompromised patients suffering from the acquired immunodeficiency syndrome (AIDS). However, pent-

amidine has not heretofore been known to have utility in the treatment of malaria.

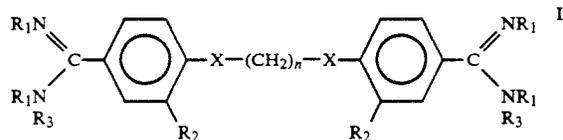
It goes without saying that in view of the magnitude of malaria infection throughout the world, and the lack of a satisfactory agent for the treatment thereof, an urgent need exists for a more-effective anti-Plasmodia agent having good therapeutic properties.

SUMMARY OF THE INVENTION

Surprisingly, it now has been discovered that malaria may be treated with pentamidine and analogues thereof. Accordingly, the present invention provides a method for treating malaria which comprising administering to an afflicted host a therapeutically effective amount of compound having the structure of formula I



wherein X is O, N or S; R₁ is H or two R₁ groups on the same amidine group together represent $-(CH_2)_m-$, wherein m=2, 3 or 4; R₂ is H, NH₂, OCH₃, Cl, or NO₂; R₃ is H, CH₃ or CH₂CH₃ and n=2-6, or pharmaceutically acceptable salts thereof, or more preferably a compound of formula II:



wherein X, R₁, R₂, R₃, m and n have the foregoing meanings, or a pharmaceutically acceptable salt thereof.

DESCRIPTION OF THE PREFERRED EMBODIMENTS DETAILED

The present invention provides a new method for treating malaria by administering compounds of formula I, above, or pharmaceutically acceptable salts thereof. Formula I encompasses pentamidine, along with various analogues or derivatives thereof, all of which are aromatic diamidines.

Obviously, the therapeutically effective dosage of any specific compound will vary somewhat from compound and patient to patient. As a general proposition, a dosage from about 0.1 to about 20 mg/kg will have therapeutic efficacy. However, toxicity concerns at the higher level may restrict the dosage to a lower level such as up to about 10 mg/kg, based upon the weight of free-base. Typically, a dosage from about 0.5 mg/kg to about 5 mg/kg will be employed. The duration for the treatment is usually once per day for a sufficient length of time for the patient to become asymptomatic. Depending upon the severity of the infection in the individual patient, this may last several weeks, or longer.

In accordance with the present method, a compound of Formula I (or preferably of Formula II), or a pharmaceutically acceptable salt thereof, may be administered orally as a solid, or may be administered orally, intramuscularly, or intravenously, as a solution, suspen-