Update / Le point

Status of antimalarial drugs under development*

P.L. Olliaro[1] & P.I. Trigg[2]

Despite the urgent need for new antimalarial drugs, particularly those against multiresistant falciparum malaria, only a limited number of drugs are now at an advanced stage of preclinical or clinical development. They include artemisinin derivatives, pyronaridine and benflumetol (all originally developed in China), as well as new antifolate combinations, the hydroxynaphoquinone atovaquone which has a novel mode of action, and a new 8-aminoquinoline which appears more active and less toxic than primaquine. Some of these drugs may become available in the next few years. It is therefore essential to find mechanisms to ensure that they are made available at an affordable price to the populations that really need them.

Introduction

Increasing drug resistance in many parts of the world has aggravated the problem of deciding which antimalarial to use, particularly in countries where *Plasmodium falciparum* has developed resistance to chloroquine, sulfa/pyrimethamine combinations and, to some extent, quinine which previously was effective in the treatment of severe and complicated disease. In some areas, such as on the Thai/Cambodian and Thai/Myanmar borders, high levels of resistance to mefloquine led to the introduction in 1993 of artemisinin derivatives. Among the countries with endemic falciparum malaria, only those in Central America and the Caribbean have not recorded resistance to chloroquine. Chloroquine resistance of various levels is now common in practically all endemic countries of Africa, and in many of them, particularly in eastern Africa, high levels of resistance pose increasing problems for the provision of adequate treatment. This highlights the urgent need for new antimalarial drugs and formulations; those currently at the clinical stage of development are described in this article.

Artemisinin and related compounds

Artemisinin (qinghaosu) is the antimalarial principle isolated by Chinese scientists in 1972 from the aerial part of *Artemisia annua* L., a plant used in traditional Chinese medicine for over 2000 years. It is a sesquiterpene with a peroxide bridge linkage (Fig. 1), the peroxide moiety appearing to be responsible for the antimalarial activity. Artemisinin was formulated in China in both oil and water for intramuscular injections and as tablets and suppositories. However, the drug's poor solubility stimulated Chinese scientists to synthesize more soluble derivatives by the formation of dihydroartemisinin (Fig. 2) and its esterification or etherification to, for example, artesunate (Fig. 3) and artemether (Fig. 4). All these derivatives have a more potent antimalarial activity than the parent compound and appear to be the most rapidly acting of all antimalarial compounds developed so far.

The following formulations are produced in China: oral formulations of artemether, artesunate and, more recently, of dihydroartemisinin; injectable formulations of artemether in groundnut oil for intramuscular administration and of sodium artesunate for intravenous administration; and suppositories of artemisinin. An injectable formulation of artemether has been produced and registered by Rhone-Poulenc Rorer in conjunction with the Kunming Pharmaceuti-

* A French translation of this article will appear in a later issue of the *Bulletin*.

[1] Manager, Steering Committee on Drugs for Malaria, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, World Health Organization, 1211 Geneva 27, Switzerland. Requests for reprints should be sent to this author.

[2] Malaria Unit, Division of Control of Tropical Diseases, World Health Organization, Geneva, Switzerland.

Reprint No. **5634**

Fig. 1. **Artemisinin.**

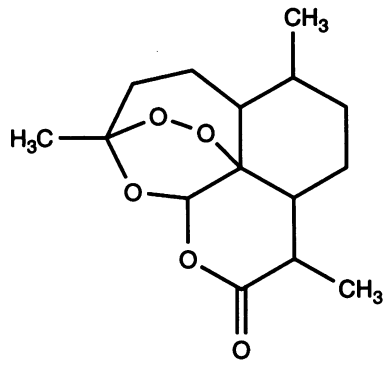
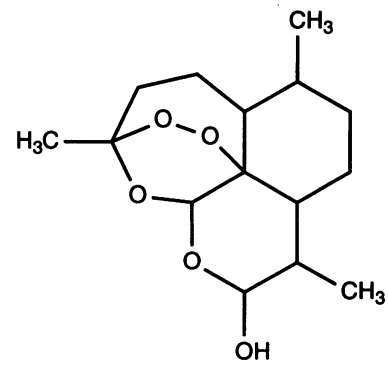


Fig. 2. **Dihydroartemisinin.**



cal Factory in China and the UNDP/World Bank/ WHO Special Programme for Research and Training in Tropical Diseases (TDR). In addition, oral artesunate has been produced and registered by Mepha A.G.[a] Viet Nam produces artemisinin tablets, capsules and suppositories as well as artesunate tablets and capsules for local use. A growing number of pharmaceutical companies now produce and market artemisinin and its derivatives, some of which have been registered for use in several countries of southeast Asia and in many other parts of the world. Recommendations for their use were made by WHO in 1993[b] and these will be reviewed again shortly.

Although oral formulations of artemether and dihydroartemisinin have been registered in China, only limited studies on oral artemether and none on dihydroartemisinin have been carried out in other countries. Most data on these formulations are either not at present available or are published in Chinese. Recent research in Viet Nam suggests that artemisinin suppositories may have a comparable efficacy to injectable parenteral artemether or artesunate but this has to be confirmed (*1*). Effective suppository formulations would have particular use at the periphery of the health care system, particularly in patients who are unable to swallow oral medications.

The development of an injectable formulation of arteether (Fig. 5) has been supported by the UNDP/ World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) in collaboration with the Walter Reed Army Institute of Research (WRAIR) and ACF Beheer bv.[c] Its spec-

Fig. 3. **Sodium artesunate.**

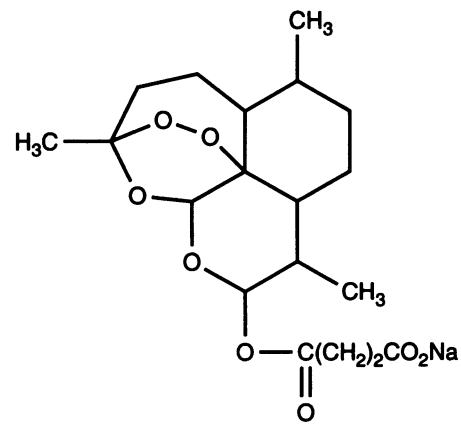
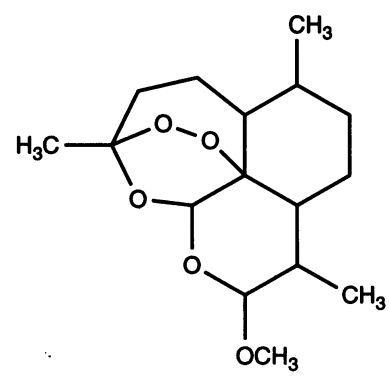


Fig. 4. **Artemether.**



[a] Mepha A.G., Aesch-Basle, Switzerland.

[b] *The role of artemisinin and its derivatives in the current treatment of malaria (1994–1995): report of an informal WHO consultation.* Unpublished WHO document WHO/MAL/94.1067, 1994.

[c] ACF Beheer bv, Maarssen, Netherlands.

Fig. 5. **Arteether.**

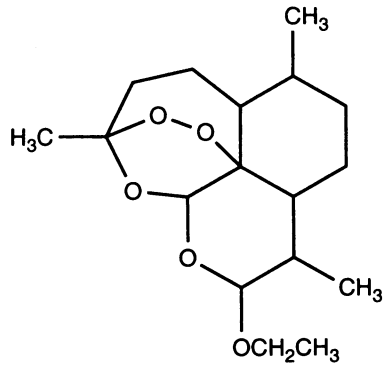
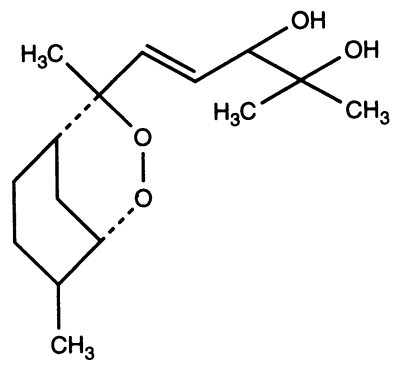


Fig. 7. **Yingzhaosu A.**



trum of activity is similar to artemether. Phase I clinical studies have shown the drug to be safe and well tolerated; the resorption from the intramuscular depot appears slow with a long elimination half-life. It is currently in Phase II trials (*2*).

Attempts to synthesize more soluble, stable and effective derivatives are continuing. Artelinic acid (Fig. 6) is being developed by WRAIR as a more water-soluble intravenous formulation than artesunate for the treatment of severe and complicated malaria (*3*). It is currently in Phase I trials in human volunteers.

The demonstration of antimalarial activity related to both the trioxane ring of the artemisinin molecule and the peroxide group of yinghaosu (Fig. 7), the antimalarial principle of *Atrobotrys uncinatus*, has led to the synthesis of a variety of peroxide, trioxane and tetraoxane analogues (*4–6*). Although several have shown antimalarial activity in *in vitro* and *in vivo* models, only Ro 42-1611 (arteflene), as an oral formulation, has so far reached human Phase I and II clinical trials (*7–9*). Arteflene shows an apparent lack of cross-resistance with chloroquine, mefloquine and quinine, and only a moderate level of cross-resistance with artemisinin in laboratory models (*10*).

Nevertheless, the development of arteflene has been discontinued by the company involved because of high recrudescent rates after one-day treatments. Although a longer duration of treatment and/or its combination with other antimalarials such as mefloquine might enhance the efficacy, the projected cost of such treatment was judged too high.

Pyronaridine

Pyronaridine (Fig. 8) was synthesized in China in 1970. It exhibits marked blood schizontocidal activity against chloroquine-sensitive and resistant para-

Fig. 6. **Artelinic acid.**

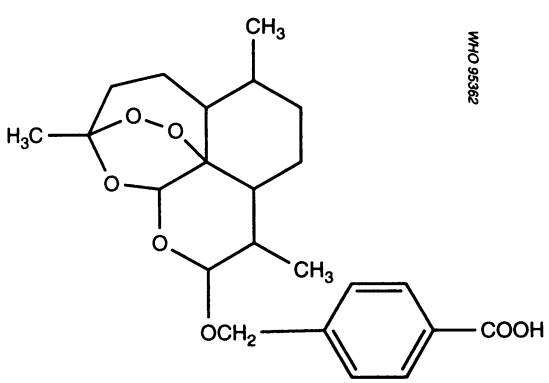
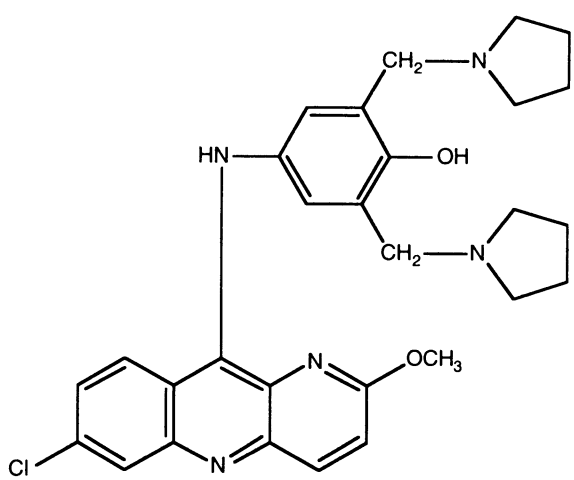


Fig. 8. **Pyronaridine.**



sites in both rodent malarias *in vivo* and *P. falciparum in vitro*. It has been used clinically in China since the 1970s and is now marketed in that country. In spite of the general consensus on its activity against chloroquine-resistant strains, its clinical effectiveness, its apparent tolerability, and the availability of oral and injectable formulations (*11*), the drug is not widely used and has only been used experimentally outside China.

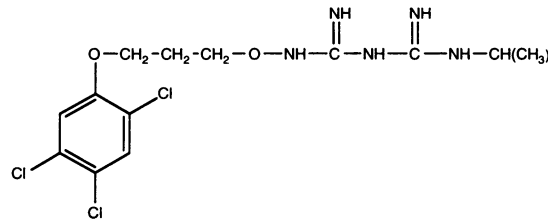
Pyronaridine may have potential as replacement for oral formulations of chloroquine in many areas. However, its entire development has taken place in China and most data, particularly on preclinical studies are either not available or published only in Chinese. Further pharmacokinetic and clinical studies are currently planned to assess the potential of this drug for wider use in malaria control.

Antifolates

Currently used antifolate combinations of sulfadoxine–pyrimethamine and sulfalene–pyrimethamine have long elimination half-lives, 81 h for sulfadoxine, 62 h for sulfalene and 116 h for pyrimethamine (*12, 13*). This has both advantages and disadvantages. On the one hand, it allows single-dose therapy and persistence of the drugs at effective blood levels might protect the patients from reinfections after cure of the initial disease. On the other hand, the latter would be only useful in high transmission areas and the slow elimination favours the selection of resistant parasites (*14*). There is also concern with adverse reactions to long-acting sulfonamides (*15*), especially in subjects concomitantly infected with human immunodeficiency virus (HIV) infections (*16*).

Alternative antifolate combinations, including the use of short-half-life sulfonamides and sulfones, are therefore being studied. These include the biguanides and triazines, the mechanism of resistance to which appears to be different from that to pyrimethamine (*17–20*) and the short-acting sulfonamides and sulfones. One of these, WR 250 417 (also known as PS-15), is an analogue of proguanil (Fig. 9). It was developed as a prodrug that would be transformed by hepatic cytochrome P-450 to the triazine WR 99210, thereby overcoming the gastric intolerance shown to occur in humans administered directly the triazine. WR 250 417 has been shown to be highly active against a pyrimethamine-resistant strain of *P. falciparum* in *Aotus* monkeys as well as against treatment failures with proguanil (*21*). The combination of the biguanide, chlorproguanil, with dapsone appears to have potential for the treatment of non-severe falciparum malaria (*22*) and is being evaluated in clinical trials.

Fig. 9. **WR250 417.**



Atovaquone

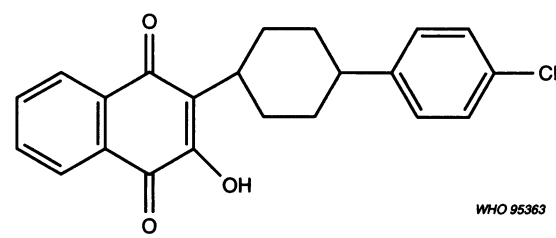
The hydroxynaphthoquinone, atovaquone (formerly designated as 566C80) (Fig. 10), has broad-spectrum antiprotozoal activity. It is currently licensed in North America for the treatment of *Pneumocystis carinii* pneumonia and as salvage therapy for cerebral toxoplasmosis (*23–25*).

Its potential as an antimalarial stems from its high intrinsic activity against erythrocytic stages of *P. falciparum in vitro*. It is also active against the primary liver stages. As an inhibitor of electron transport, it has a novel mode of action and is not cross-resistant with other antimalarials. In contrast to previous members of this series, it is metabolically stable with an elimination half-life of approximately seventy hours.

Despite this promising profile, its use as monotherapy in the treatment of acute uncomplicated falciparum malaria has been compromised by recrudescent rates of approximately 30%. These have been attributed, on the basis of susceptibility studies on paired clinical isolates, to the emergence of resistant parasites.

Interaction studies of atovaquone with other antimalarial drugs against *P. falciparum in vitro* have shown the three quinolines, chloroquine, qui-

Fig. 10. **Atovaquone.**



nine and mefloquine, as well as halofantrine and artesunic acid, to be antagonistic. In contrast, tetracycline and proguanil were synergistic and provided the context for the evaluation of atovaquone in combination therapy (C.J. Canfield & W.E. Gutteridge, personal communication, 1994).

Co-administration of atovaquone with either tetracycline or proguanil, in empirically selected regimens, has had a dramatic effect on the cure rates of patients with falciparum malaria who were followed up for 28 days. In a series of dose-ranging studies in Thailand, a cure rate of 93% was achieved following administration of atovaquone with proguanil in respective doses of 500 mg and 200 mg twice daily for three days (*26*). Rationalization of this dose to once daily resulted in a 100% cure rate.

In view of its acceptability for administration during pregnancy and to children, coupled with its impressive record of safety, proguanil has been selected as the preferred partner drug. Evaluation of the drug combination is being carried out within an integrated programme of comparative Phase III studies, sponsored by the Wellcome Foundation, with a view to international registration (D.B.A. Hutchinson, personal communication, 1994).

Benflumetol

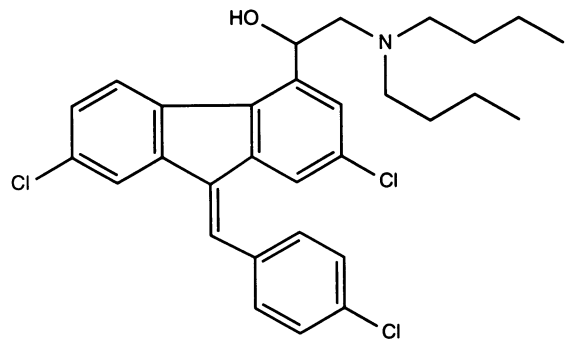
Benflumetol is a fluoromethanol (Fig. 11), synthesized by the Institute of Military Medical Sciences (IMMS), Beijing, in the 1970s and registered for use as an antimalarial drug in China in 1987. There is, at present, no published work on the compound outside China (*27*).

The compound, an active blood schizontocide, is poorly soluble in water and oils but is soluble in unsaturated fatty acids, such as oleic and linoleic acid. It has been formulated in the latter. Clinical studies of the drug as an oral formulation in capsules have been carried out in China since 1979, latterly being co-administered orally with artemether for the treatment of falciparum malaria infections. Preclinical studies are reported to show synergy between the two compounds. An oral formulation of the combination of benflumetol with artemether is being developed by Ciba-Geigy in collaboration with IMMS and the Kunming Pharmaceutical Factory in China.

New 8-aminoquinolines

WR 238 605, an 8-aminoquinoline (Fig. 12), is being developed by WRAIR. It is 13 times more active as a hypnozoitocidal drug than primaquine, as measured by the dose required to produce radical cure of *P. cynomolgi* infections in monkeys (B.G. Schuster,

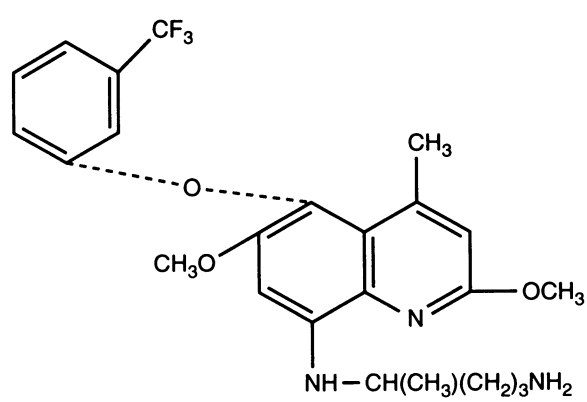
Fig. 11. **Benflumetol.**



personal communication, 1994). In contrast to primaquine, it also has appreciable blood schizontocidal activity, being 10–90 times more active than primaquine against *P. berghei* and 5–60 times more active against *P. yoelii* spp. Although originally designed as a causal prophylactic and radical curative drug to replace primaquine for the prevention of relapsing malarias, it may have clinical utility for the treatment of falciparum malaria (*28*). The drug is currently in Phase I trials in the USA.

Another primaquine analogue, denoted 80/53, is being developed by the Central Drug Research Institute (CDRI), Lucknow, India, and is currently in Phase II clinical trials for treatment of *P. vivax* infections (*29*). Although not as potent as WR 238 605, it is claimed to be significantly less toxic than primaquine.

Fig. 12. **WR 238 605.**



Resistance-modifiers or chemosensitizing compounds

There is evidence that chloroquine-resistant *P. falciparum* parasites accumulate significantly less chloroquine than susceptible parasites by an accelerated drug efflux (*30, 31*). Various drugs, including calcium-channel inhibitors (e.g., verapamil) and tricyclic compounds (e.g., desipramine) have been shown to "reverse" or "modify" chloroquine resistance *in vitro* (*32, 33*). Others, like penfluridol, modulate resistance to mefloquine and halofantrine.

Unfortunately, no compound has also yet proved effective in modulating resistance to chloroquine *in vivo* and there is some concern about potential host cell toxicity (*34, 35*). Newer compounds are now being tested, some of which have intrinsic antimalarial activity. The availability of such resistance modifiers or chemosensitizing compounds would have great practical repercussions by restoring the effectiveness of present first-line antimalarial drugs in areas where parasites are no longer susceptible.

Conclusions

The number of drugs currently at an advanced stage of preclinical or clinical development is limited and it may be several years before most, with few exceptions, can be made available for malaria control in view of the time and cost of this development. There is, therefore, a clear need both to use optimally the available drugs and to accelerate drug development. Priority in development should be given to research on drugs and drug combinations to treat multidrug-resistant falciparum malaria since this is a major operational problem in certain countries of South-East Asia and the Western Pacific and may arise in Africa in the not too distant future. When these new drugs become available, it will be a major challenge to ensure that they are affordable to those who need them.

References

1. **Hien TT et al.** Comparison of artemisinin suppositories with intravenous artesunate and intravenous quinine in the treatment of cerebral malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1992, **86**: 582–583.
2. **UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR).** *Tropical disease research—Progress 1991–1992. Eleventh programme report.* Geneva, 1993.
3. **Lin AJ, Klayman DL, Milhous WK.** Antimalarial activity of new water-soluble dihydroartemisinin derivatives. *Journal of medicinal chemistry*, 1987, **30**: 2147–2150.
4. **Peters W et al.** The chemotherapy of malaria. XLVIII. The activities of some synthetic 1,2,4-trioxanes against chloroquine-sensitive and chloroquine-resistant parasites. Part 1: Studies leading to the development of novel *cis*-fused cyclopenteno derivatives. *Annals of tropical medicine and parasitology*, 1993, **87**: 1–7.
5. **Peters W et al.** The chemotherapy of malaria. XLIX. The activities of some synthetic 1,2,4-trioxanes against chloroquine-sensitive and chloroquine-resistant parasites. Part 2: Structure-activity on *cis*-fused cyclopento-1,2,4-trioxanes (fenozans) against drug-sensitive and drug-resistant lines of *Plasmodium berghei* and *P. yoelii* spp NS *in vivo*. *Annals of tropical medicine and parasitology*, 1993, **87**: 9–16.
6. **Posner GH et al.** New, antimalarial, tricyclic 1,2,4-trioxanes: evaluations in mice and monkeys. *American journal of tropical medicine and hygiene*, 1994, **50**: 522–526.
7. **Weidekamm E, Dumont E, Jaquet C.** Tolerability and pharmacokinetics of Ro 42–1611 (arteflene) in man. *Tropical medicine and parasitology*, 1994, **45** (suppl. 3): 278–283.
8. **Salako LA et al.** Ro 42-1611 in the treatment of patients with mild malaria: a clinical trial in Nigeria and Burkina Faso. *Tropical medicine and parasitology*, 1994, **45** (suppl. 3): 284–287.
9. **Somo-Moyou R et al.** Efficacy of Ro 42-1611 (arteflene) in the treatment of patients with mild malaria: a clinical trial in Cameroon. *Tropical medicine and parasitology*, 1994, **45** (suppl. 3): 288–291.
10. **Jaquet C et al.** Antimalarial activity of the bicyclic peroxide Ro 42-1611 (arteflene) in experimental models. *Tropical medicine and parasitology*, 1994, **45** (suppl. 3): 266–271.
11. **Fu S, Xiao S-H.** Pyronaridine: a new antimalarial drug. *Parasitology today*, 1991, **7**: 310–313.
12. **Donno L et al.** Pharmacokinetic study of an antimalarial antifolic combination. *Current therapeutic research*, 1980, **27**: 346–355.
13. **Winstanley PA et al.** The disposition of oral and intramuscular pyrimethamine/sulfadoxine in Kenyan children with high parasitaemia but clinically non-severe falciparum malaria. *British journal of clinical pharmacology*, 1992, **33**: 143–148.
14. **Watkins WM, Mosobo M.** Treatment of *Plasmodium falciparum* malaria with pyrimethamine–sulfadoxine: selective pressure for resistance is a function of long elimination half-life. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1993, **87**: 75–78.
15. **Björkman A, Phillips-Howard PA.** Adverse reactions to sulfa drugs: implications for malaria chemotherapy. *Bulletin of the World Health Organization*, 1991, **69**: 297–304.
16. **Coopman SA et al.** Cutaneous disease and drug reactions in HIV infection. *New England journal of medicine*, 1993, **328**: 1670–1674.
17. **Knight DJ, Williamson P.** The antimalarial activity of *N*-benzyloxydihydrotriazines. II. The development

of resistance to clociguanil (BRL 50216) and cycloguanil by *Plasmodium berghei*. *Annals of tropical medicine and parasitology*, 1980, **74**: 405–413.
18. **Foote SJ, Galatis D, Cowman AF.** Amino acids in the dihydrofolate reductase-thymidylate synthase gene of *Plasmodium falciparum* involved in cycloguanil resistance differ from those involved in pyrimethamine resistance. *Proceedings of the National Academy of Sciences, USA*, 1990, **87**: 3014–3017.
19. **Peterson DS, Milhous WK, Wellems TE.** Molecular basis of differential resistance to cycloguanil and pyrimethamine in *Plasmodium falciparum* malaria. *Proceedings of the National Academy of Sciences, USA*, 1990, **87**: 3018–3022.
20. **Sirawaraporn W et al.** The dihydrofolate reductase domain of *Plasmodium falciparum* thymidylate synthase-dihydrofolate reductase. Gene synthesis, expression, and anti-folate-resistant mutants. *Journal of biological chemistry*, 1993, **268**: 21637–21644.
21. **Canfield CJ et al.** PS-15: a potent, orally active antimalarial from a new class of folic acid antagonists. *American journal of tropical medicine and hygiene*, 1993, **49**: 121–126.
22. **Watkins WM et al.** Chlorproguanil/dapsone for the treatment of non-severe *Plasmodium falciparum* malaria in Kenya: a pilot study. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1988, **82**: 398–403.
23. Atovaquone for *Pneumocystis carinii* pneumonia. *Medical letters and drug therapy*, 1993, **35**: 28–29.
24. **Artymowicz RJ, James VE.** Atovaquone: a new antipneumocystis agent. *Clinical pharmacology*, 1993, **12**: 563–570.
25. **Kovacs JA.** Efficacy of atovaquone in treatment of toxoplasmosis in patients with AIDS. *Lancet*, 1992, **340**: 637–638.
26. **Hutchinson DBA.** Clinical evaluation of atovaquone in the treatment of malaria. *13th International Congress for Tropical Medicine and Malaria*. Jomtien, Pattaya, Thailand, 1992. Abstract, Vol. 1, p. 201.
27. *Practical chemotherapy of malaria. Report of a WHO Scientific Group*. Geneva, World Health Organization, 1990 (WHO Technical Report Series, No. 805).
28. **Milhous WK et al.** Evaluation of WR 238 605 in rodent malaria models. *American journal of tropical medicine and hygiene*, 1992, **47** (suppl.): 89.
29. **Central Drug Research Institute.** *Annual report, 1993–1994*. Lucknow, 1994: 31.
30. **Krogstad DJ et al.** Efflux of chloroquine from *Plasmodium falciparum*: mechanism of chloroquine resistance. *Science*, 1987, **238**: 1283–1285.
31. **Cowman AF, Karcz S.** Drug resistance and the P-glycoprotein homologues of *Plasmodium falciparum*. *Seminars in cell biology*, 1993, **4**: 29–35.
32. **Martin SK, Oduola AMJ, Milhous WK.** Reversal of chloroquine resistance in *Plasmodium falciparum* by verapamil. *Science*, 1987, **235**: 899–901.
33 **Bitonti AJ et al.** Reversal of chloroquine resistance in malaria parasite *Plasmodium falciparum* by desipramine. *Science*, 1988, **242**: 1301–1303.
34. **Watt G et al.** Reversal of drug-resistant falciparum malaria by calcium antagonists: potential for host cell toxicity. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1990, **84**: 187–190.
35. **Watt G et al.** Amplification of quinine cardiac effects by the resistance-reversing agent prochlorperazine in falciparum malaria. *American journal of tropical medicine and hygiene*, 1993, **49**: 645–649.