Antimalarial drugs currently in development

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Introduction

There can be no doubt that the need for new antimalarial drugs is being taken very seriously both by the scientific community and the pharmaceutical industry. Even a cursory glance at the primary scientific literature reveals that a wide range of novel chemical structures are being assessed for such activity (see Table 1 for examples from the 1988 literature). Furthermore, examination of the patent literature suggests that some of the discoveries being made are being followed up (Table 2 contains extracts from the 1988 literature). However, the drug discovery and development process is not only expensive (about £100 million to allow for failures) and time-consuming (10-12 years), it is also highly speculative (only about 1 in 10 000 compounds synthesized becomes a pharmaceutical product)[11]. It is unlikely, therefore, that many of the examples given in Tables 1 and 2 will ever reach the market place. I shall, therefore, concentrate in this communication on those drugs that have been registered recently in at least one country but which are not yet generally available and on those compounds that have reached the full development process. Even so, my list will not be exhaustive: time constraints force me to focus on examples which, in my opinion, will be of most interest.

Table 1. Some chemical series with experimental antimalarial activity which were the subject of 1988 publications

artesunate, pyronaridine, hydroxypiperaquine (Lee & Huang)[1]
nitrosoureas (Zhang *et al.*)[2]
Spathodea campanulata stem bark extract (Makinde *et al.*)[3]
Mannich bases (Scott *et al.*)[4]
tinidazole (Sarma)[5]
trans (E) clopenthixol (Kurtzhals *et al.*)[6]
naphthoquinones (Carvalho *et al.*)[7]
doxycycline (Pang *et al.*)[8]
halogenated histidine analogues (Panton *et al.*)[9]
quinolones (Midgley *et al.*)[10]

Table 2. Some chemical series with antimalarial activitity published in the patent literature in 1988

(ethylpiperazinyl-1-phenyl amino) benzo (g) quinolines (Medic Parasit Tropi)
dihydroartemisinin derivatives (Dept of the Army, Washington)
2-acetyl and 2-propiony-pyridine thiosemicarbazones (US Sec of the Army)
N-alkoxy: carbonyl: alkyl-aminocarbonyl derivatives of deferrioxamine B (Ciba Geigy AG)
poly-oxo-artemisinin derivatives (SRI International)
7-chloro-3-phenyl acridone N-oxides derivatives (Hoechst AG)
1,2,4-trioxane derivatives (Jefford, CW)
amino acid derivatives of primaquine (IRE Celltarg SA)
peptide(s) having sequence that is substrate of protease of *Plasmodium falciparum* (Cnre Cent Nac Rech Sci)
pyridine-2-aldehyde N-heterocyclyl-hydrozones (Deuts Aussatz Hilf)

Antimalarial drugs are used in three distinct modes: as causal prophylactics to prevent the development of blood parasitaemia; as blood schizonticides to kill blood parasites; and as anti-relapse agents to kill the hypnozoite stages in the liver. Also, there are four species of human malaria parasite, including *P. falciparum* which causes acute disease and is responsible for most malaria deaths and *P. vivax* which causes a much more chronic disease, typified by frequent relapses. Within the many permutations of these two sets of parameters, most people would agree that there are three key priorities for the pharmaceutical industry:

(i) development of blood schizonticides for *P. falciparum*, if possible to include parenteral formulations for cases of cerebral malaria;
(ii) development of causal prophylactics for *P. falciparum*, preferably that can be taken weekly by the oral route;
(iii) development of a primaquine replacement with a better therapeutic window to prevent *P. vivax* relapse.

These priorities are dictated by the apparent absence (so far) of chloroquine-resistant strains of *P. vivax* and the adverse reaction experienced with primaquine, which is the only clinically useful drug with this type of activity. I will discuss antimalarial drugs currently in development under these three headings, with the exception of Wellcome's hydroxynaphthoquinone. Since the latter might have utility in all three modes of use, I will discuss it separately at the end.

Blood schizonticides in development

Real progress is being made in the development of novel blood schizonticides with activity against drug resistant *P. falciparum*. Initially, perhaps not surprisingly, such attempts focused on the synthesis of molecules with more than a passing chemical resemblance to chloroquine, which is a 4-amino-quinoline, and to quinine, which is a quinoline methanol and the original antimalarial drug (Figure 1). Such work led to the marketing of the quinoline methanol, mefloquine, in 1984, either alone as Lariam or in combination with pyrimethamine and sulphadoxine as Fansimef. More recently, in 1988, Smith, Kline and French Laboratories launched the phenanthrenemethanol, halofantrine, as Halfan, with a 12 h dosage regimen, for the treatment of both adults and children[12]. There are two problems with these compounds. First, neither is yet registered

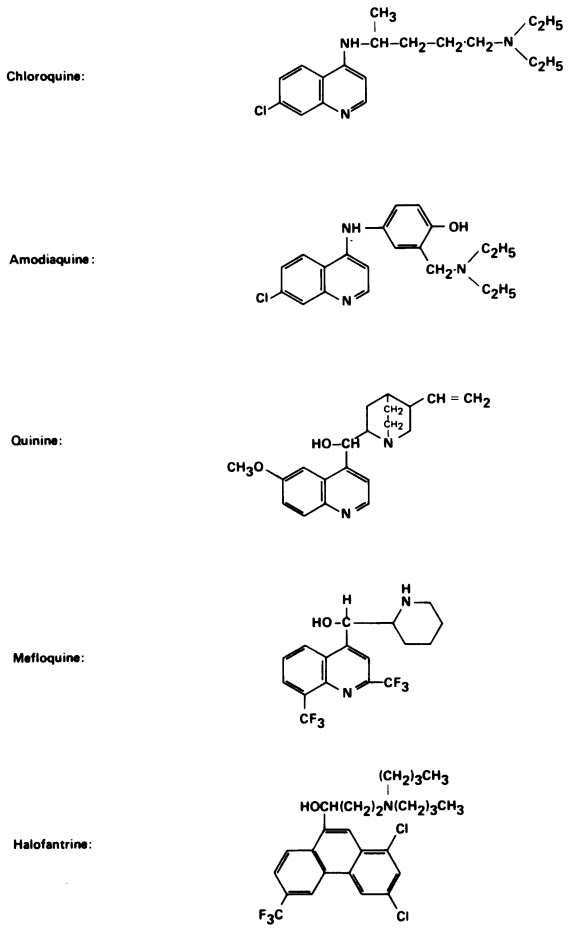

Figure 1. Chemical structures of antimalarials related to quinine

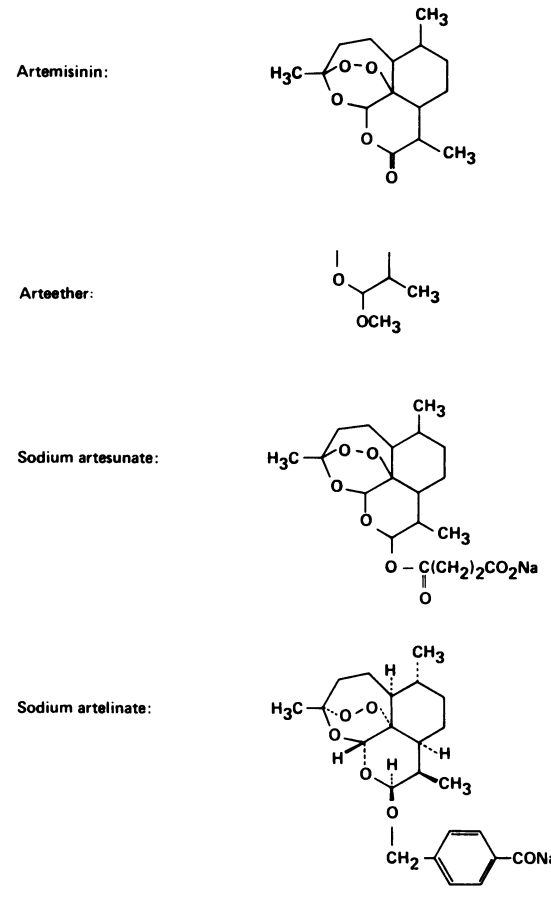

Figure 2. Chemical structures of antimalarials related to artemisinin

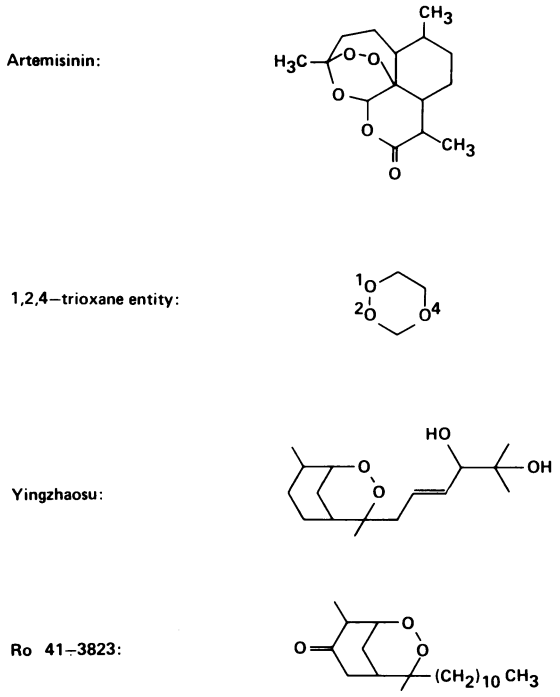

Figure 3. Chemical structures of synthetic antimalarials related to artemisinin and yingzhaosu

in many territories and is therefore not freely available. Second, the overall similarity of their chemistry to existing antimalarials, especially chloroquine, amodiaquine and quinine, suggests that they will rapidly be overcome by problems of multi-drug resistance.

Such criticism cannot be laid at the door of the sequeterpinoid series of antimalarials related to Qinghaosu, now known as artemisinin (Figure 2). The latter is a natural product from the plant *Artemisia annua* and was developed by the Chinese as a rapidly acting blood schizonticide with good activity against chloroquine and multi-drug resistant strains of *P. falciparum*. Problems with recrudescences and adverse reactions are likely to limit its use in this way in the West, although a semi-synthetic derivative, arteether (Figure 2), should begin Phase I trials soon. Another semi-synthetic analogue, artesunic acid (Figure 2), was found to have problems of aqueous stability. However, the Walter Reed Institute of Research (WRAIR) in Washington reported last year on the synthesis of sodium artelinate (Figure 2), the water soluble form of artelinic acid[13]. This compound not only shows negligible hydrolysis after two months storage in aqueous solution but also appears to be at least as potent an antimalarial as artemisinin and artesunic acid. Its development as a rapidly acting injectable for cerebral malaria will be followed with interest.

Artemisinin has been synthesized de novo but the route is complex and not commercially viable. It has, however, been used as a lead compound in the design of a series of 1,2,4-trioxanes (Figure 3) which are more potent against *P. falciparum* and have a wider therapeutic window than the parent compound[14]. A parallel series of bicyclic peroxide antimalarials (Figure 3) is in development by Roche Limited, based on Yingzhaosu, another traditional Chinese herbal medicine[15]. Their qualities have been summarized as follows[16]: chemical accessibility; low acute toxicity and absence of mutagenicity in the Ames test; in vitro activity against susceptible and drug resistant strains

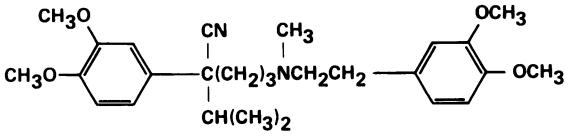

Figure 4. Chemical structure of verapamil

of *P. falciparum*; excellent blood schizontocidal activity in vivo against *P. berghei* with rapid onset of efficacy; activity after oral and parenteral administration; extended biological half-life in mice; absence of significant cross-resistance to chloroquine, mefloquine and artemisinin; suitability for use in drug combinations.

Further development of these two series as rapidly acting blood schizonticides is awaited with interest.

The WRAIR had also been involved in an alternative strategy to solve the problems of multi-drug resistant strains of *P. falciparum* malaria. During induction of resistance to drugs in cultured cancer cells, it was observed that cells made resistant to one drug became simultaneously resistant to other structurally and functionally unrelated drugs. This form of resistance is known as multi-drug resistance (MDR). The basis of MDR was later shown to be a failure of drugs to reach toxic levels within resistant cells. This is because such cells have acquired the capacity to actively extrude drug from the interior of the cell using the so-called MDR transporter. If MDR cells are temporarily deprived of energy, they accumulate as much drug as sensitive cells and manifest signs of drug toxicity. Other agents like calcium antagonists, calmodulin inhibitors and lysosomotropic agents are also able to prevent resistant cancer cells from eliminating toxic drugs, thereby reversing their resistance[17]. All such effects have been interpreted as being due to inhibition of the functioning of the MDR transporter. Chloroquine, a known lysosomotropic drug, reverses MDR in cancer cells. Therefore, it was suggested that the mechanism of chloroquine-resistance in malaria may be related to MDR[18]. Recent work has provided molecular evidence to substantiate this claim[19]: a gene which codes for a malaria homologue of the tumour MDR gene has been shown to be amplified in some chloroquine-resistant malaria strains. It has also provided a new strategy for circumventing chloroquine resistance in malaria[18]: in the presence of agents such as the calcium antagonist, verapamil (Figure 4), chloroquine-resistant falciparum malaria parasites become as sensitive to chloroquine as susceptible organisms. The undesirable effects to the host of presently known reversing agents precludes the direct in vivo application of this new strategy. Work is in progress in the WRAIR to find or develop more acceptable compounds.

Prophylactics in development

Less success has been achieved to date in the development of novel therapies for *P. falciparum* prophylaxis. The pharmacokinetics of both halofantrine and the sesqueterpenes do not lend themselves to a prophylactic mode of use. Mefloquine does not suffer from this limitation and indeed is recommended by the manufacturers for such use, though only as the single entity (Lariam), presumably because of the hazards now known to be associated with the sulphonamide component of Fansidar in the prophylactic mode. Registration in the UK is expected shortly.

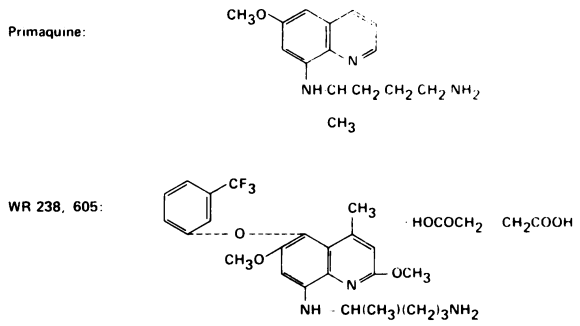

Figure 5. Chemical structure of WR 238,605

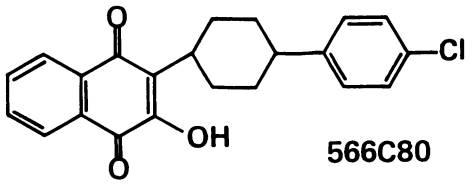

Figure 6. Chemical structure of hydroxynaphthoquinone, 566C80

Anti-relapse compounds in development

There is, however, at long last progress in the development of a possible replacement for primaquine. WR 238,605, another 8-aminoquinoline (Figure 5), is currently completing preclinical development at the WRAIR[20]. Experimental data suggest it is 7.4 times more active than primaquine as a tissue schizonticide, has reduced toxicity, good oral bioavailability and a longer half life. It is therefore an excellent potential candidate to replace primaquine.

Hydroxynaphthoquinone 566C80

Most exciting of all to me, however, is hydroxynaphthoquinone, 566C80 (Figure 6), which is in development at the Wellcome Research Laboratories. This compound has potential utility as a blood schizonticide, causal prophylactic and possibly an anti-relapse compound. It arose out of a programme of work specifically designed to exploit differences in ubiquinones and hence respiratory chain-linked electron transport between malaria and mammalian cells, using menoctone, a ubiquinone antagonist, as lead compound[21]. This drug is more active in vitro against *Plasmodium falciparum* than any of the standard antimalarials and shows very good activity in rodent models of malaria. Its activity in vivo in the *Aotus* model of *P. falciparum* is outstanding: infection is cured, without recrudescence, by seven daily oral doses of 1 mg/kg of drug or a single oral dose of 10 mg/kg.

566C80 is targeted to the mitochondrial respiratory chain of the malaria parasite where it blocks electron transport, most likely at Complex III, by virtue of it being a ubiquinone antagonist. Mammalian and malaria ubiquinoneous differ, explaining in part the selectivity of the compound. Malarial parasites are homolactate fermenters. Therefore inhibition manifests itself in terms of blockade of pyrimidine biosynthesis de novo, since the enzyme responsible for the dihydroorotate dehydrogenase step is in the form of a complex with the respiratory chain. Such a mode

of action is unique among existing blood schizonticides and causal prophylactics, suggesting that 566C80 should be active against all strains of malaria resistant to existing drugs, including multi-drug resistant strains. So far, this has been found experimentally to be the case.

There are more than three orders of magnitude of difference between the hydroxynaphthoquinone sensitivity of the malarial and mammalian dihydroorotate dehydrogenase complexes. In addition, mammalian cells can rescue themselves from any adverse reactions caused by blockade of pyrimidine biosynthesis by salvage of free pyrimidines; malaria parasites cannot do this. We are thus dealing with a compound with a potentially large therapeutic window. Pre-clinical toxicological studies have supported this contention. In addition, a Phase I human volunteer study has just been completed without significant adverse reactions. The compound has been shown, unlike earlier candidate drugs in this series, to be orally bioavailable and apparently metabolically stable in man, with a very satisfactory plasma half life of the order of three days. Plasma levels obtained should, on the basis of bioassay and extrapolation from the *Aotus* model, be more than sufficient to exert a therapeutic response. Phase II studies in patients with *P. falciparum* malaria will thus be approached with confidence.

Conclusions

There are major new series of antimalarial drugs at various stages of development and marketing: Roche's mefloquine; Smith, Kline and French's halofantrine; the Chinese's artemisinin and its analogues; Jefford's 1,2,4-trioxanes and Roche's bicyclic peroxides; WRAIR's MDR reversing agents; WRAIR's 8-aminoquinoline, WR 238,605; and Wellcome's hydroxynaphthoquinone, 566C80. It is too early to say which of these drugs will eventually occupy the niche being vacated by chloroquine, but surely, somewhere amongst them, is the answer to our current problems in malaria chemotherapy.

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Discussion
Chairman: Professor E H O Parry

Mr I Odidi (Nigeria & London): I feel that the lack of progress in the development of malaria vaccine is not because the technology is lacking but because of three factors: (1) a lack of social will; (2) the question of economics: the Third World countries do not have the buying power; (3) lack of political will. It is not a problem like acquired immune deficiency syndrome (AIDS).