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BMCL Digest

Recent advances in malaria drug discovery

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ABSTRACT

This digest covers some of the most relevant progress in malaria drug discovery published between 2010 and 2012. There is an urgent need to develop new antimalarial drugs. Such drugs can target the blood stage of the disease to alleviate the symptoms, the liver stage to prevent relapses, and the transmission stage to protect other humans. The pipeline for the blood stage is becoming robust, but this should not be a source of complacency, as the current therapies set a high standard. Drug discovery efforts directed towards the liver and transmission stages are in their infancy but are receiving increasing attention as targeting these stages could be instrumental in eradicating malaria.

Malaria remains one of the most prevalent and deadly infectious diseases across Africa, Asia, and the Americas. The World Health Organization (WHO) estimates 154–289 million malaria cases in 2010, with 660,000 associated deaths.[1,2] An independent study suggests that the mortality is twice as high when including cases of malaria that are undiagnosed or untreated.[3] Eighty percent of the estimated cases occur in sub-Saharan Africa and 86% of deaths occur in children less than 5 years of age.[1] In Africa, the economic burden is estimated at $12 billion/year, but the sales of antimalarial drugs are orders of magnitude lower.[4] Advances in malaria research are often reviewed[2,5–16] and a recent monograph[17] will prove useful to the medicinal chemist. This digest covers some of the most relevant progress in malaria drug discovery from 2010 to 2012, and limits itself to compounds with EC_{50} values <100 nM in a parasite proliferation assay. We cover the blood stage, the liver stage, and the transmission stage of the disease. Each section contains several scaffolds, and within each scaffold the compounds are arranged, when possible, with the marketed drugs first and the research compounds last.

Several species of *Plasmodium* cause malaria in humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and the simian *Plasmodium knowlesi*. The most lethal species is *P. falciparum*, found predominantly in Africa.[18] If left untreated, *P. falciparum* causes organ failures (severe malaria) and accumulates in the brain capillaries (cerebral malaria), leading to coma and eventually death. Furthermore, there is growing evidence that the lethality of *P. vivax* has been underestimated.[19]

The parasite has a complex life cycle and in order to eradicate the disease, every stage should be considered for treatment (Scheme 1):

1. Liver stage. Once the mosquito inoculates the parasites (sporozoites) into the blood stream, the parasites invade the liver within 30 min and start replicating there (schizonts). In addition, *P. vivax* and *P. ovale* can remain dormant in the liver (hypnozoites, not shown in Scheme 1) and cause relapses years after the initial infection. Drugs that target the liver stages are important to prevent the disease from developing (prophylactic treatment) and to provide what is known as a "radical cure" for *P. vivax* and *P. ovale*.

2. Blood stage. After approximately 5–10 days, the liver cells burst and merozoites invade the red blood cells where they rapidly proliferate, causing the symptomatic high fevers and the pathology. In their intraerythrocytic phase, the merozoites go through various forms (rings, trophozoites, schizonts) to form an average of 20 daughter merozoites that are released into the bloodstream and infect new red blood cells. Drugs that target the blood stages are important to control the symptoms of the disease and associated mortality.

3. Transmission stage. After several cycles of asexual reproduction, some parasites further differentiate into male and female gametocytes, which contain only a half set of chromosomes.

4. Mosquito stage. When ingested by mosquitoes, the male and female gametocytes fuse in the midgut to form a zygote that further develops into new sporozoites ready for the next human host.[20] Drugs that target the transmission and mosquito stages

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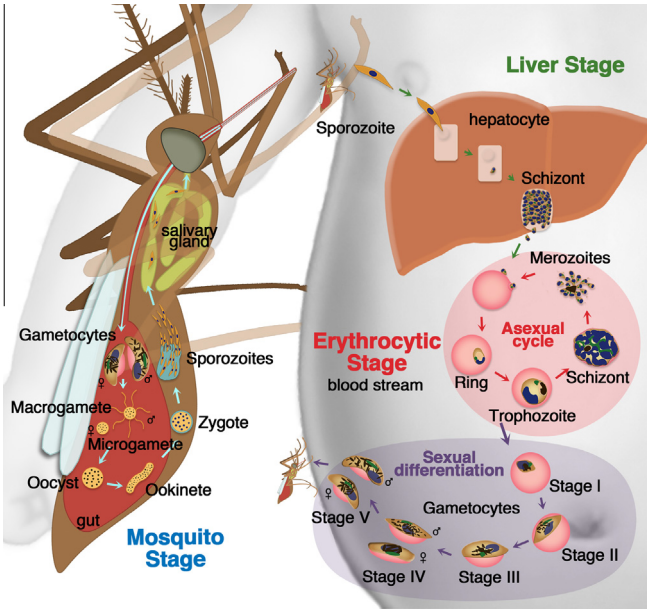
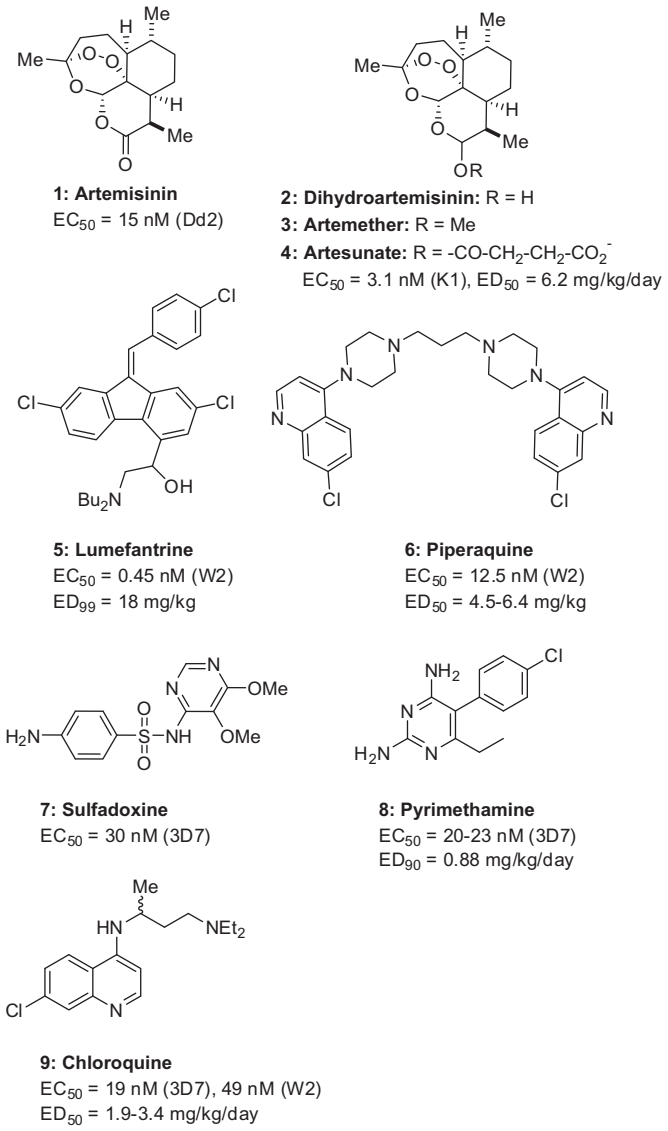


Scheme 1. *Plasmodium* life cycle. Liver, blood (= erythrocytic), transmission, and mosquito stages. See text for details.



Scheme 2. Current standard of care (artemisinin derivatives, combined with lumefantrine or piperaquine) and previous first-line therapies (sulfadoxine–pyrimethamine and chloroquine). In vitro potency data (EC_{50} values) are reported for proliferation assays using different strains of *P. falciparum* that are either drug-sensitive (3D7) or multi-drug resistant (Dd2, K1, W2). The in vivo efficacy data (ED_{50} and ED_{90} values) are reported for rodent models of malaria. Data are reported for artemisinin,[29] artesunate,[29,30] lumefantrine,[31,32] piperaquine,[31,33] sulfadoxine,[34] pyrimethamine,[35,36] and chloroquine.[29,37,38]

are important to prevent the infection of other humans, and would benefit an eradication agenda.

Artemisinin-based combination therapies (ACTs) are the current standard of care for uncomplicated malaria. Artemisinin (**1**, Scheme 2) and its derivatives (**2**–**4**) have a fast onset of action but are cleared rapidly (human $t_{1/2}$ ~1 h),[21] and are therefore combined with slow-clearing drugs to kill residual parasites. Typical partner drugs include lumefantrine (**5**, human $t_{1/2}$ = 3–4 days)[22] and piperaquine (**6**, human $t_{1/2}$ = 8–16 days).[23] The most popular combination consists of tablets containing artemether (**3**, 20 mg) and lumefantrine (**5**, 120 mg) sold as Coartem™ (Novartis).[24] Adults take four tablets twice a day for 3 days,[25] but compliance to this six-dose regimen is variable.[26] In 2011, the European Medicines Agency (EMA) approved the combination of dihydroartemisinin (**2**) and piperaquine (**6**) which is taken once a day for 3 days (Eurartesim™, Sigma-Tau).[27] The ACTs have supplanted the previously recommended sulfadoxine–pyrimethamine (**7**/**8**, Fansidar™, Roche), which in turn replaced chloroquine (**9**). Parenteral artesunate (**4**) is the drug of choice for severe malaria.[28]

For the liver stages, primaquine (**10**, Scheme 3) is the only drug approved to eliminate hypnozoites. As for prophylactic treatment, atovaquone–proguanil (**11**/**12**) (Malarone, GlaxoSmithKline) is usually preferred because it is well tolerated, but is expensive. Incidentally, proguanil is a pro-drug, of which cycloguanil (**13**) is the active metabolite. For the transmission stages, primaquine (**10**) is the only registered drug active against the mature gametocyte.[39]

Resistance against the many existing antimalarials is well documented,[45] and especially troubling is the emerging resistance to artemisinins.[45–48] Combining drugs can limit the emergence of resistance, but this technique is not infallible. For instance, in parts of Cambodia, the proportion of patients who were still parasitemic after 3 days of treatment with the dihydroartemisinin–piperaquine combination increased from 26% in 2008 to 45% in 2010.[49] The problem of drug resistance requires new drugs. The challenge is that drug resistance is not the only feature. New, innovative drugs should also (i) be fast acting, (ii) be safe for children and pregnant women, and (iii) ideally be amenable to a single-dose administration. An example of how difficult it is to combine all these features is seen in mefloquine. It is the only registered drug effective in a single dose (**14**, Scheme 4, human $t_{1/2}$ = 2–4 weeks, adult dose = 1250 mg);[50] however, drug resistance is problematic.[51] Similarly, the only marketed antimalarial drug combination effective as a single dose is sulfadoxine–pyrimethamine, but it also suffers from drug resistance.[45,52,53]

Artemisinin is commercially produced by extraction from sweet wormwood (*Artemisia annua*) at a cost of $400–1100/kg. A recent alternative production method involves a yeast fermentation process that delivers the biosynthetic precursor artemisinic acid (**15**, Scheme 5, Amyris). The latter is converted to artemisinin in 62% yield using a photochemical oxidation process being implemented by Sanofi.[54] An independent group adapted the process to a continuous flow reactor, better suited for conducting photochemistry at an industrial scale, thus potentially reducing production costs.[55] In addition, Zhu and Cook published a remarkably concise synthesis of (+)-artemisinin, where cyclohexenone is converted in only