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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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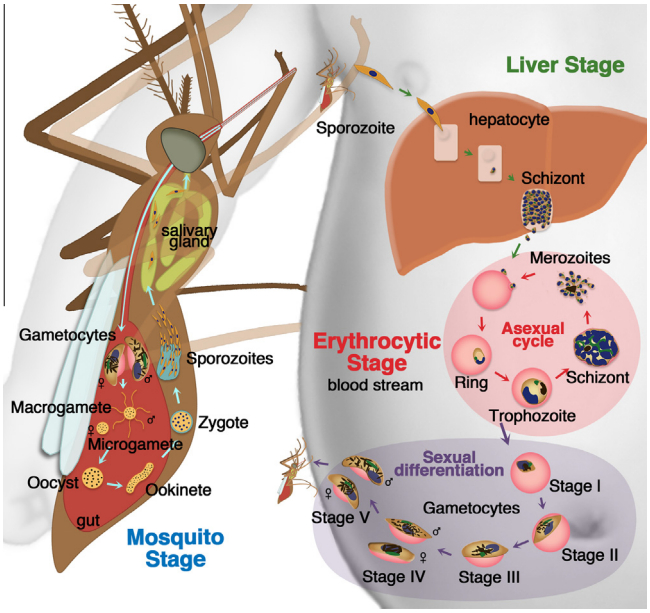
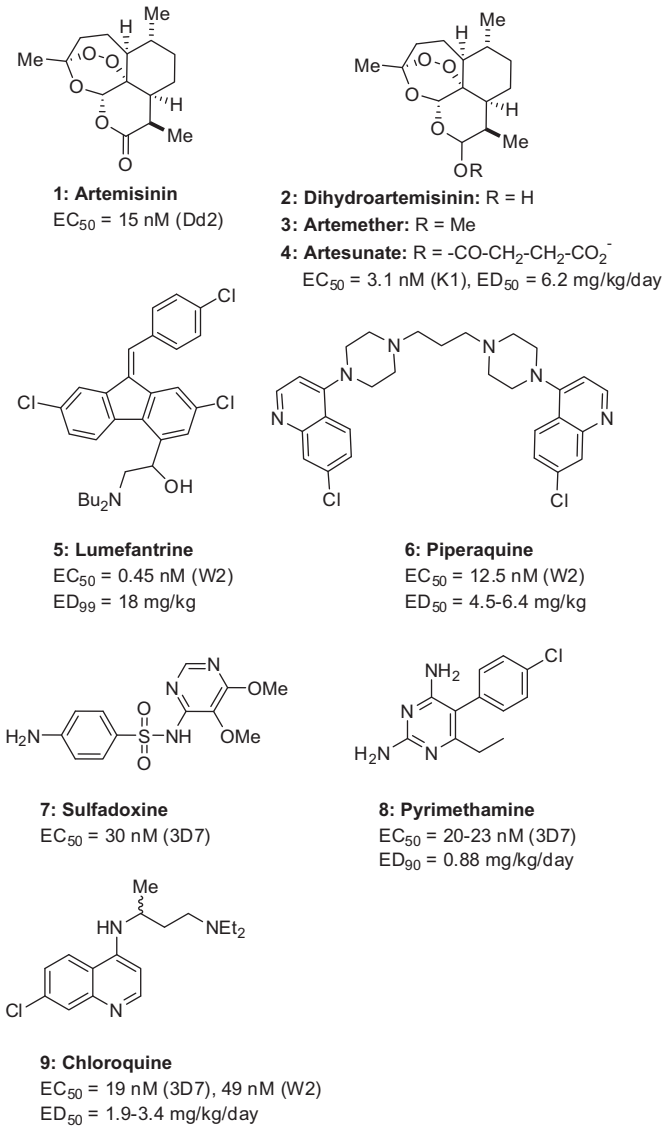


Scheme 1. *Plasmodium* life cycle. Liver, blood (= erythrocytic), transmission, and mosquito stages. See text for details.



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]

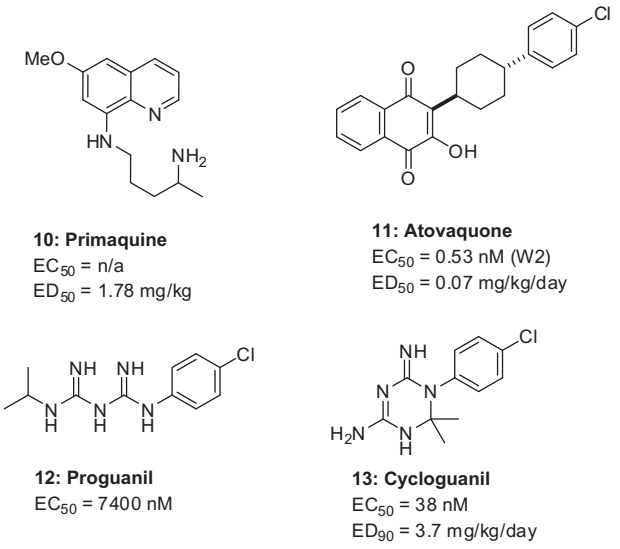
are important to prevent the infection of other humans, and would benefit an eradication agenda.

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]

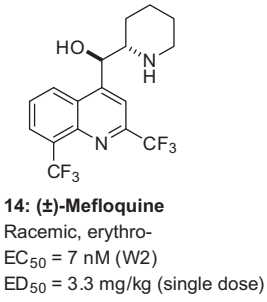
For the liver stages, primaquine (**10**, Scheme 3) is the only drug approved to eliminate hypnozoites. As for prophylactic treatment, atovaquone–proguanil (**11**/**12**) (Malarone, GlaxoSmithKline) is usually preferred because it is well tolerated, but is expensive. Incidentally, proguanil is a pro-drug, 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]

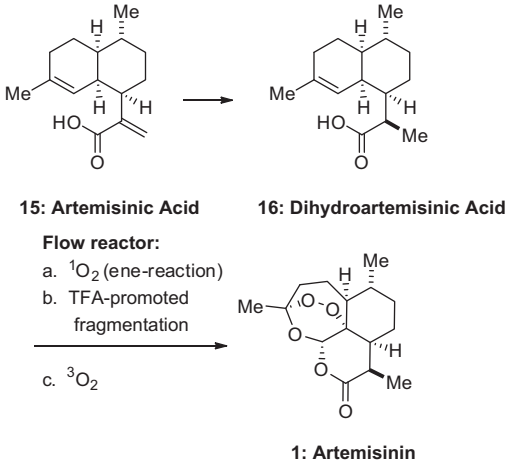
Artemisinin is commercially produced by extraction from sweet wormwood (*Artemisia annua*) at a cost of $400–1100/kg. A recent alternative production method involves a yeast fermentation process that delivers the biosynthetic precursor artemisinic acid (**15**, Scheme 5, Amyris). The latter is converted 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



Scheme 3. Preferred drugs for the elimination of hypnozoites (primaquine), preferred combination for prophylaxis (atovaquone–proguanil), and the active metabolite of proguanil (cycloguanil). Data are reported for primaquine,[40] atovaquone,[41,42] proguanil,[43] and its active metabolite cycloguanil.[44]



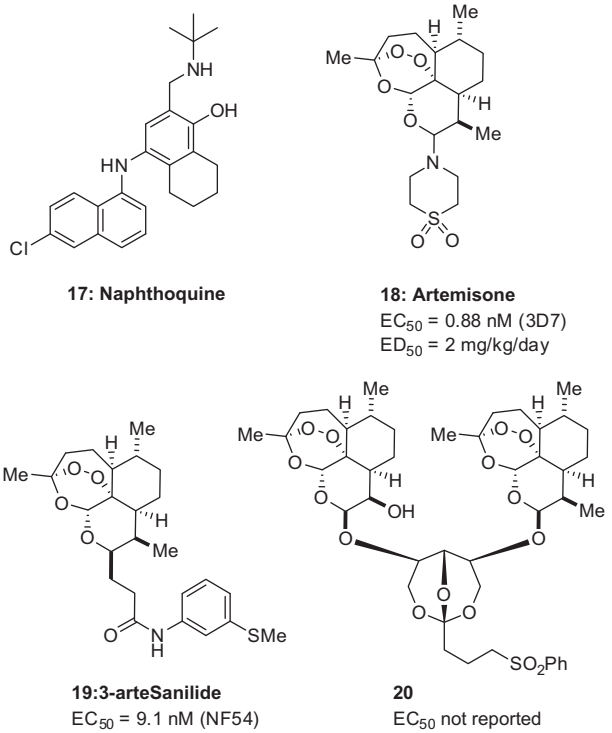
Scheme 4. Mefloquine, the only single-agent antimalarial active as a single-dose in human. The EC_{50} value is for the multi-drug resistant strain W2, and the ED_{50} data for a single p.o. administration to mice.[201] Mefloquine is a racemate, and the reported stereochemistry for mefloquine is relative, not absolute.



Scheme 5. Conversion of artemisinic acid into artemisinin.

five pots to the desired product, thus challenging the paradigm that total synthesis is not amenable to an industrially viable process.[56]

The combination of an artemisinin derivative with slow-clearing drugs can cure malaria in a single dose. The combination of

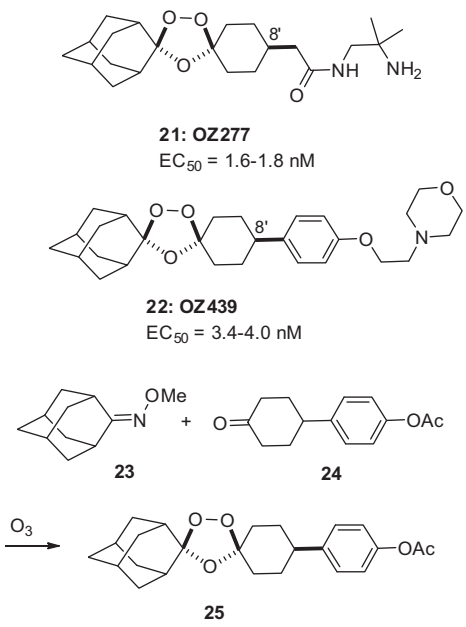


Scheme 6. Active ingredients used in combinations that have potential for single-dose cure. EC_{50} values are reported for the drug-sensitive strains 3D7 and NF54.

artemisinin (1000 mg) and naphthoquine (**17**, Scheme 6, 400 mg) introduced by the Chinese army, appears to be effective as a single dose of eight tablets (ARCO, Phase III).[57–63] Artemisone (**18**), a drug in Phase II trials, is 10 times more potent than artesunate (**4**) in vitro[64] and 4–10 times more potent in mice.[64] It provides a single-dose cure in *Aotus* monkeys infected with *P. falciparum* at 10 mg/kg when combined with mefloquine (5 mg/kg).[65] Artemisone is also active in a murine model of cerebral malaria.[66] Combining artemisinin derivatives **19**[32] or **20**[67] (6 or 30 mg/kg, respectively) with the longer-acting mefloquine hydrochloride (18 mg/kg) was found to be curative in a single dose.

The antimalarial action of artemisinin is thought to involve the cleavage of the peroxide bond by Fe(II) found in heme proteins, thus generating toxic oxygen radicals. Synthetic peroxides are proving to be useful substitutes for artemisinin. The first-generation ozonide OZ277 (**21**, Scheme 7), known as arterolane, inhibits the growth of chloroquine-resistant (K1) and chloroquine-sensitive (NF54) parasite strains with an IC_{50} = 1.6–1.8 nM.[68] In 2012, Ranbaxy launched the combination of arterolane maleate and piperaquine phosphate as a 3-day treatment in India.

The second-generation peroxide OZ439 (**22**, Scheme 7) (EC_{50} = 3.4–4.0 nM) is now in Phase IIa studies. It features an 8′-aryl rather than an 8′-alkyl group.[30] This seemingly inconspicuous modification has far-reaching consequences. The stability of the O–O bond towards Fe(II) increases by 50-fold, presumably because of steric reasons. This in turn translates into a much longer half-life in both rats ($t_{1/2}$ = 20 h for OZ439 vs. 1 h for OZ277) and humans ($t_{1/2}$ = 25–30 h for OZ439).[30,69] The improved pharmacokinetic profile renders OZ439 capable of completely curing mice of malaria in a single dose of 20 mg/kg, a feat that artemisinin derivatives cannot achieve without the addition of a second drug. Furthermore, OZ439 has significant prophylactic activity, and a single 30 mg/kg oral dose of OZ439 administered 48 h prior to parasite inoculation is protective. In rat, multiple doses of OZ439 are tolerated up to 300 mg/kg.[30] These ozonides are synthesized from an oxime (**23**) and a ketone (**24**) in the presence of ozone.

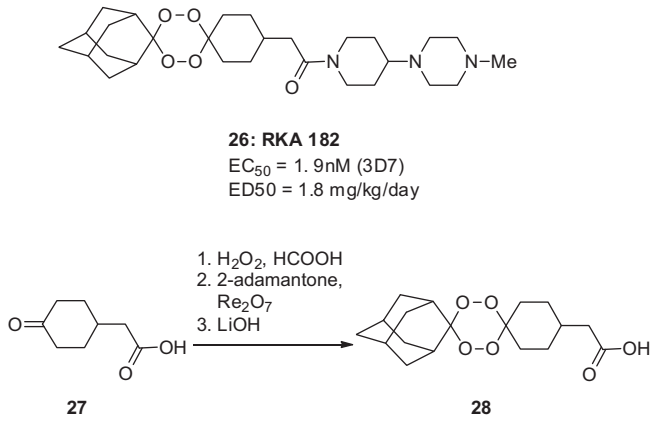


Scheme 7. The ozonides OZ277 (Arterolane) and OZ439.

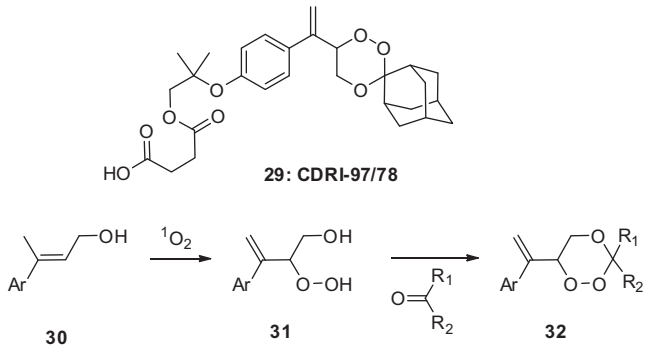
Another way of stabilizing the O–O bond is to form tetraoxanes, as was employed in the drug development candidate RKA 182 (**26**, Scheme 8),[70] which displays IC_{50} values of 4.9 nM against the *P. falciparum* 3D7 strain and of 1.9 nM against the K1 strain (chloroquine-sensitive and -resistant, respectively). In a mouse model of malaria, RKA 182 inhibits parasite growth with an ED_{50} of 1.8 mg/kg/day. The oral bioavailability of its tosylate salt is 42% in mouse and 38% in rat. The tetraoxane ring is made via a Re_2O_7-catalyzed step (**27**→**28**).[70] RKA 182 is not curative in a single dose.

The Central Drug Research Institute, Lucknow, India, is investigating the trioxane CDRI-97/78 (**29**, Scheme 9) in Phase I studies.[71–73] The key step in the construction of the trioxane core is an *ene* reaction between an allylic alcohol (**30**) and singlet oxygen, to give peroxide **31**. Additional artemisinin derivatives,[74] ozonides,[75] and 1,2,4-trioxanes[72,76] have been reported to have potencies comparable to artemether, but were not shown to possess obvious advantages.

The prototypical 4-aminoquinoline chloroquine has been widely used for treating malaria since World War II. Chloroquine



Scheme 8. The tetraoxane RKA182. EC_{50} values are reported for the drug-sensitive strain 3D7.



Scheme 9. The trioxane CDRI-97/78.

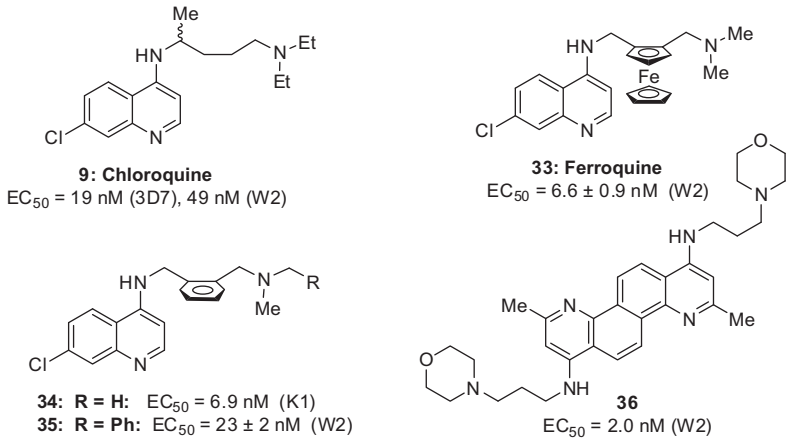
exerts its antimalarial action by interfering with the formation of hemozoin within the parasite's digestive vacuole. Hemozoin is a crystalline derivative of heme that the parasite makes as a way of disposing of toxic heme released upon hemoglobin digestion. Resistance to chloroquine is now found in all areas of the world, and involves multiple mutations in the *P. falciparum* chloroquine resistance transporter, PfCRT. These mutations result in an increased efflux of chloroquine from the acidic digestive vacuole to the cytosol of the parasite. Ferroquine (**33**, Scheme 10) was found to be active against chloroquine-resistant strains, and is currently undergoing Phase II clinical trials. Ferroquine, unlike chloroquine, accumulates in the digestive vacuole of the chloroquine-resistant parasites. This was demonstrated by X-ray fluorescence microscopy, a technique that allows visualizing the chlorine atom of both drugs.[77] It was also shown that replacing the expensive ferrocene moiety of ferroquine with a simple and inexpensive benzene ring as in **34** and **35** retains activity against chloroquine-resistant strains (K1, W2).[78] Because of its basicity, **35** is expected to accumulate like other 4-aminoquinolines in the acidic (pH = 5) environment of the food vacuole. In this organelle, the concentration of **35** is calculated to reach 370 μM at pharmacologically relevant doses, thus enabling PfCRT inhibition (IC_{50} = 69 μM) to become an operational second mode of action.[79] The fused 'dimeric quinoline' **36** is active in vitro against drug-resistant strains, and in mouse when administered orally at 80 mg/kg.[80]

Amodiaquine (**37**, Scheme 11) is also active against most chloroquine-resistant strains; however, hepatitis, myelotoxicity and agranulocytosis restrict its use to treating acute malaria. Amodiaquine is rapidly absorbed after oral administration in human, and rapidly metabolized, mostly, via N-deethylation. In addition, two reactive metabolites are formed, namely imine **38** and aldehyde **39**, and are the likely cause of the hepatotoxicity and agranulocytosis, respectively.

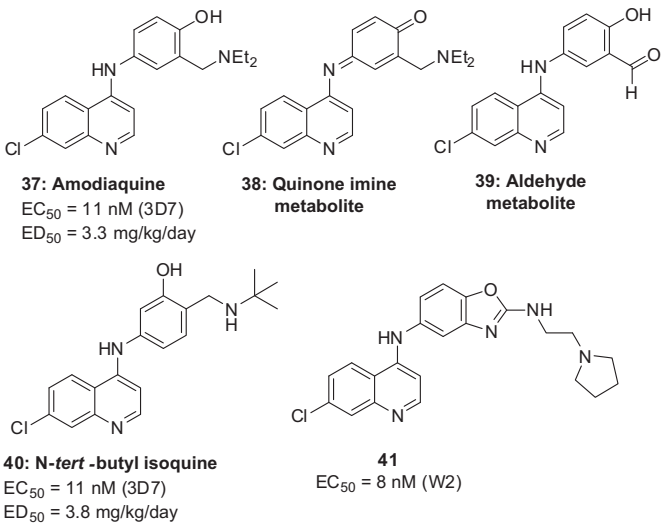
N-tert-Butyl isoquine (GSK369796, **40**, Scheme 11) was designed to avoid the formation of quinone imines, and entered Phase I studies. It is potent in vitro, including in the chloroquine-resistant strain K1 (EC_{50} = 13 nM) and is active in vivo with an ED_{50} = 3.8 mg/kg/day, thus being comparable to amodiaquine.[38,81,82] In spite of the excellent exposures and near quantitative oral bioavailabilities in animal models, its development was discontinued due to exposures insufficient to demonstrate drug safety superior to chloroquine.[17]

Analogs exemplified by **41** (Scheme 11) were also designed to prevent the formation of quinone imines, and were found to retain activity against chloroquine-resistant strains.[83]

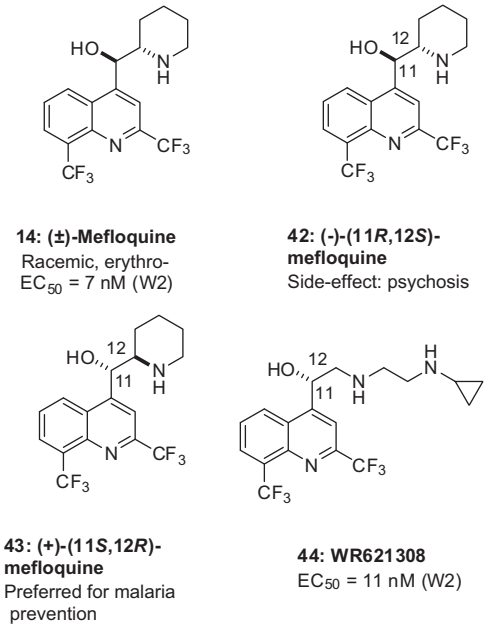
Mefloquine (**14**, Scheme 12) has been widely used for malaria prevention due to a long half-life (2–4 weeks in human) that necessitates only a once-weekly dosing. Mefloquine is sold as a racemate (Lariam), and causes a relatively high incidence of depression, psychosis, and nightmares. While both enantiomers



Scheme 10. 4-Aminoquinoline. EC_{50} values are reported for the drug-sensitive strain 3D7 and the multi-drug resistant strains W2 and K1.



Scheme 11. Amodiaquine and derivatives. EC_{50} values are reported for the drug-sensitive strain 3D7 and the multi-drug resistant strains W2.



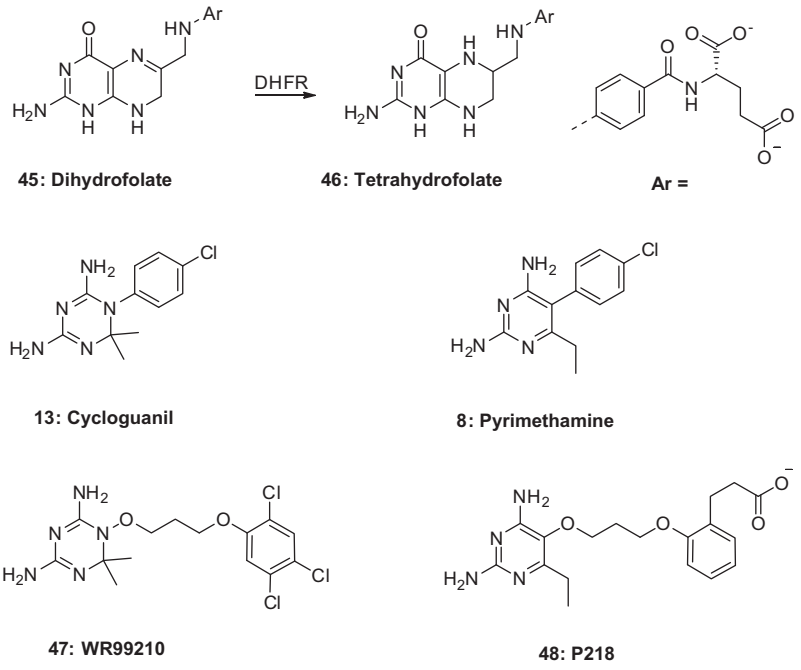
Scheme 12. 4-Hydroxymethylquinolines. Note that mefloquine is a racemate, and the reported stereochemistry for mefloquine is relative, not absolute. EC_{50} values are reported for the multi-drug resistant strain W2.[86]

are active, the (−)-enantiomer **42** is believed to cause the neurological side effects by binding the adenosine receptors in the brain.[84] In an effort to select the next generation of quinoline methanol derivatives that could serve as a replacement for mefloquine, the Walter Reed Army Institute of Research screened for analogs with a lower brain penetration, and identified WR621308 (**44**).[85,86] WR621308 has a substantially lower permeability across MDCK cell monolayers than mefloquine, suggesting lower brain exposures.

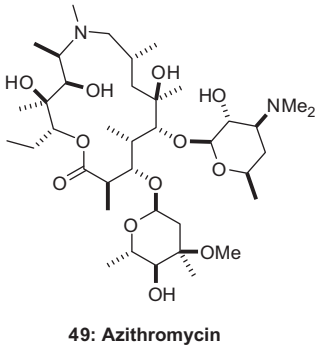
Some of the most important malaria drugs, cycloguanil (**13**) and pyrimethamine (**8**), are inhibitors of dihydrofolate reductase (DHFR). DHFR converts 7,8-dihydrofolate (**45**, Scheme 13) into tetrahydrofolate (**46**), a cofactor involved in one-carbon transfer reactions and in the biosynthesis of nucleic acids. Inhibition of DHFR therefore arrests DNA replication,[87] but resistance is widespread due to mutations in the enzyme.

Structure-based drug design resulted in P218 (**48**, Scheme 13), a DHFR inhibitor active against all clinically relevant mutations.[88] P218 combines the pyrimidine ring of pyrimethamine (**8**, Scheme 13), which brings potency, and the linker of the DHFR inhibitor WR99210 (**47**, Scheme 13), which tolerates mutations due to its flexibility. Furthermore, the terminal carboxylate group forms a salt bridge to the conserved Arg122 residue, thus mimicking the α-carboxylate of dihydrofolate (**45**). P218 is more potent than pyrimethamine against DHFR in the wild-type strain TM4 (IC_{50} = 4.6 and 58 nM, respectively) as well as in the quadruple mutant strain V1/S (IC_{50} = 56 and >100,000 nM, respectively). P218 is active against quadruple mutant *P. falciparum* in mice, with an ED_{50} = 0.3 mg/kg/day, orally. In rat, the oral bioavailability is 46%, and the oral $t_{1/2}$ is 7.3 h.[88]

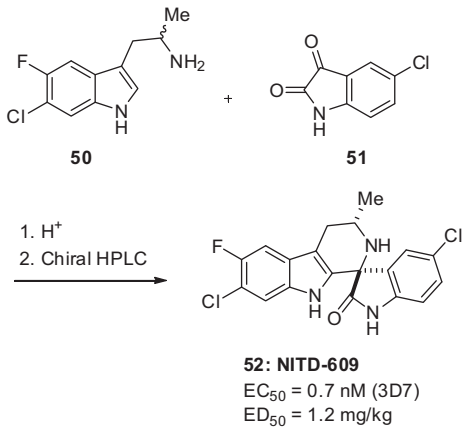
About 125 million pregnancies are at risk of malaria every year, and 10,000 women and 200,000 babies die as a result. An intermittent preventative treatment (IPT) is recommended for pregnant women, but drug-resistance to the currently adopted IPT (sulfadoxine–pyrimethamine) necessitates new and effective regimens. Both azithromycin (**49**, Scheme 14) and chloroquine have demonstrated safety in children and pregnant women over a number of years. Notably, the azithromycin–chloroquine combination is designed to be synergistic against chloroquine-resistant strains of *P. falciparum*,[89] and was shown to be synergistic in the treatment of symptomatic malaria in clinical trials.[89] By itself, azithromycin is



Scheme 13. DHFR inhibitors.



Scheme 14. Azithromycin.



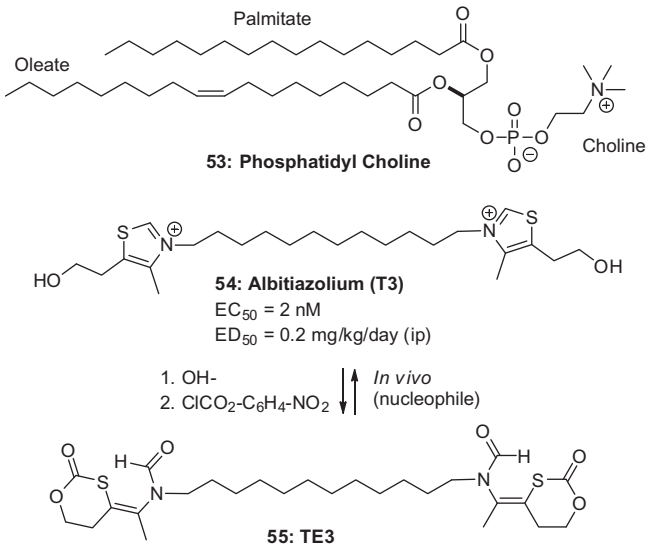
Scheme 15. The spiroindolone NITD-609. The EC_{50} value is for the drug-sensitive strain 3D7.

a slow-acting antimalarial, with a maximum antiparasitic effect occurring only after two cycles of intraerythrocytic development (one cycle of invasion, development, and egress lasts 42–48 h).[89,90] Finding azithromycin analogs with improved activity in mouse models of malaria has been challenging.[90–92]

The Novartis team screened its compound collection, identified spiroindolones as a novel chemotype, and optimized the series to deliver NITD-609 (**52**, Scheme 15), now in Phase II trials.[29] The target was identified by genomics using clones with decreased susceptibility and was found to be the cation channel PfATPase4.[29] In the medicinal chemistry route, the two enantiomers were separated by chiral chromatography.[93] NITD-609 has an excellent potency, with EC_{50} = 0.7 nM (3D7) and is 100% orally bioavailable in mouse and rat. Its oral $t_{1/2}$ is 10 h (mouse) and 27 h (rat). In mouse, NITD-609 has an ED_{50} = 1.2 mg/kg, and is thus more potent than artesunate (ED_{50} = 6.2 mg/kg) or chloroquine (ED_{50} = 1.9 mg/kg). Three daily doses of 50 mg/kg, or a single dose of 100 mg/kg, afforded a complete cure. NITD-609 is also a potent inhibitor of gametocytogenesis, and blocks transmission to mosquitoes.[94] The Medicines for Malaria Ventures (MMV) selected the spiroindolone project[6,7] as the Project of the Year 2009.

Albitiazolium (**54**, Scheme 16, also known as T3 or SAR97276) is a drug that has reached Phase II clinical trials (CNRS/University of Montpellier/Sanofi).[95] The understanding of its mechanism has recently been refined.[96,97] Albitiazolium acts primarily by inhibiting the transport of choline into the parasite.[97] The parasite requires choline to generate phosphatidylcholine (**53**), the main lipid of its cell membranes, as it replicates and forms new membranes. An important property of albitiazolium is that it accumulates irreversibly in the *Plasmodium* up to 1000-fold. Albitiazolium inhibits parasite growth (EC_{50} = 2 nM) and cures mice with an ED_{50} = 0.2 mg/kg/day (ip) without recrudescence. It is also active in severe conditions (ED_{50} ⩽0.5 mg/kg ip at 5–10% parasitemia). Notably, a single injection is curative (ED_{50} = 1 mg/kg ip at 0.5–1% parasitemia). A single-dose cure is observed even at high parasitemia levels (ED_{50} = 2.5 mg/kg ip at 5–10% parasitemia).[98,99]

Albitiazolium is also efficacious when given orally, but with a much lower ED_{50} = 13 mg/kg/day,[100] suggesting an oral bioavailability of the order of 2% (mouse). Because of its low oral bioavail-



Scheme 16. Albitiazolium and its pro-drug T3.

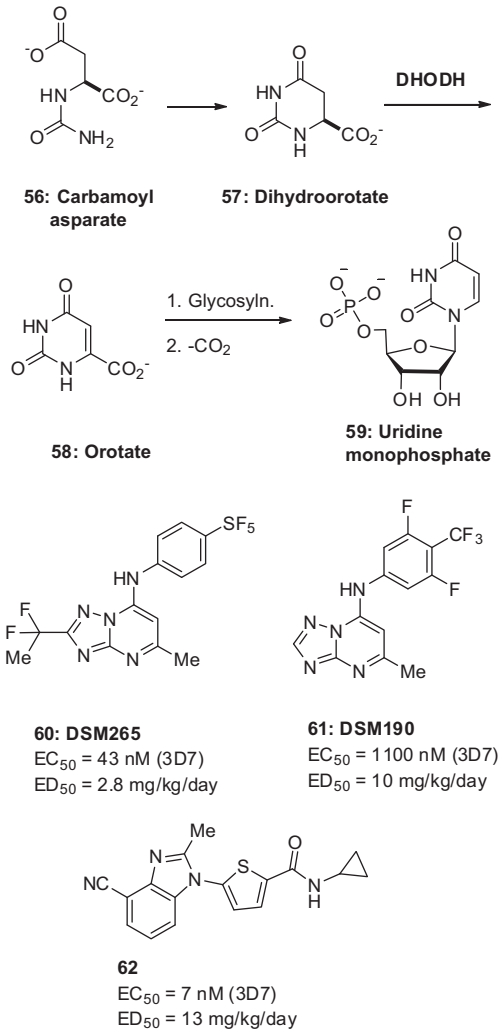
ability, the clinical trials have been conducted with intravenous or intramuscular injections. An oral version of albitiazolium would be highly desirable. The pro-drug TE3, reported in 2004–2005, has an oral ED_{50} = 5 mg/kg/day.[98,101] This indicates a 2–3-fold improvement in mouse oral bioavailability; the rat bioavailability is 15%.[100] In spite of numerous efforts made in the last few years,[37,102–105] the bioavailability of these bis-cations has not been improved yet.

Unlike its human host, *P. falciparum* cannot salvage pyrimidines, and therefore depends on their de novo biosynthesis. Dihydroorotate dehydrogenase (DHODH) is the enzyme which catalyzes the rate-limiting step of the de novo pyrimidine biosynthetic pathway (**56**→**59**, Scheme 17). Factors that affect the human versus *Plasmodium* DHODH selectivity have been investigated by crystallography.[106] The DHODH approach was awarded the MMV Project of the Year 2010.

A project coordinated by the MMV and involving the University of Texas Southwestern, the University of Washington, Monash University, and GlaxoSmithKline reported the preclinical candidate DSM265 (**60**, Scheme 17), expected to enter Phase I studies in 2013.[107] DSM265 inhibits PfDHODH selectively over its human counterpart (IC_{50} = 33 nM and 2500 nM, respectively). It is orally bioavailable (rat: F = 57–68%, $t_{1/2}$ = 12–28 h), and efficacious in vitro (EC_{50} = 43 nM (3D7)) and in mouse (ED_{50} = 2.8 mg/kg/day). A related effort identified triazolopyrimidine DSM190 (**61**, Scheme 17), which is less potent in vitro (IC_{50} = 190 nM, EC_{50} = 1.1 μM (3D7)) and in mouse (ED_{50} = 10 mg/kg/day), but has a bioavailability of 100% in rat.[36]

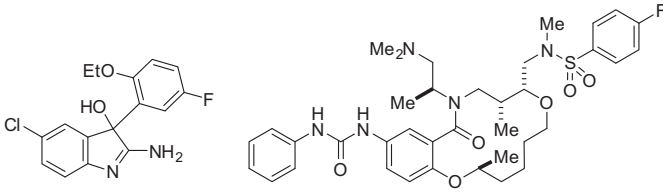
Genzyme reported DHODH inhibitor **62** (Scheme 17) as a potential drug development candidate.[108] Benzimidazole **62** inhibits PfDHODH (IC_{50} = 40 nM) and parasite growth (EC_{50} = 7–10 nM, 3D7, Dd2). It is bioavailable in rat (49%) and dog (19%) and is eliminated with $t_{1/2}$ = 0.85 h (rat) or 0.52 h (dog). In mouse, it is efficacious with an ED_{50} of 13 mg/kg/day.[108]

Most efforts use high-throughput phenotypic screens against the blood stage. GlaxoSmithKline,[109] Novartis,[110] and the St. Jude Children's Research Hospital[111] performed such screens and made 20,000 hits publically available. The MMV narrowed the list down to 400 compounds representing a diverse dataset with low toxicity. The resulting "Malaria Box" can be downloaded, and is available in plates from the MMV. The targets are not known and will require deconvolution.[112,113] Additional screens are reported below and a recent review of the patent literature is also available.[114]



Scheme 17. DHODH inhibitors. EC_{50} values are reported for the drug-sensitive strain 3D7.

Screening 70,000 compounds from the Broad Institute and the Harvard Medical School against the chloroquine resistant strain Dd2 led to Genzyme's Genz-668764 (**63**, Scheme 18, single enantiomer, absolute configuration not published).[115] Genz-668764 inhibits *P. falciparum* in vitro (EC_{50} = 28 and 65 nM, 3D7 and Dd2 strains, respectively) and is active in mouse at doses of the order of 100 mg/kg/day. Allometric scaling predicts a human dose of 6 mg/day qd for 3 days, which would maintain plasma trough lev-



Scheme 18. New scaffolds from phenotypic screens. EC_{50} values are reported for the drug-sensitive strain 3D7 and the multi-drug resistant strain Dd2.

els above the EC_{50} against *P. falciparum* for at least 96 h after the last dose. The predicted human therapeutic index is approximately 3, on the basis of the exposure in rats at the no observable adverse effect level (NOAEL).

A similar screen of the 8000 compounds from the Broad Institute's diversity-oriented synthesis (DOS) library led to the discovery of the extremely potent ML238 (**64**, Scheme 18, EC_{50} = 0.5 nM (Dd2)), which is also highly water soluble (120 μM) and not cytotoxic.[116]

Actelion reported ACT-213615 (**65**, Scheme 19).[117,118] The compound is fast-acting against all asexual erythrocytic stages. Although 30 times less potent against the murine *Plasmodium berghei* than against *P. falciparum*, ACT-213615 completely cured *P. berghei*-infected mice with three consecutive oral daily doses of 750 mg/kg (ED_{90} = 54 mg/kg/day). ACT-213615 was efficacious in the recently established SCID mouse *P. falciparum* model (ED_{90} = 8.4 mg/kg/day) with potencies comparable to chloroquine (ED_{90} = 6.4 mg/kg/day). No acute toxicity was observed.

Anacor[119] identified benzoxaborole (**66**, Scheme 19, EC_{50} = 26–44 nM) as a promising starting point (MW = 206, low clogP, solubility: 750 μg/mL at pH 7, and low to no cytotoxicity).[120,121] SAR studies suggested that an acidic side-chain is favored for high anti-malarial potency, and a number of compounds with EC_{50} values <100 nM were discovered, such as **67**. Further optimization is ongoing.

The screening network funded by the WHO Special Programme for Research and Training in Tropical Diseases (TDR) reported the results of a 10,000 compound screen against seven whole organism pathogens responsible for tropical diseases, including the intra-erythrocytic forms of *P. falciparum*.[122] The most potent screening hit was TDR84420 (**68**, Scheme 19) with an EC_{50} = 326 nM (K1).

The publically available screening data set from GSK has been analyzed to extract SAR trends[123] and GSK identified 47 high quality starting points for further follow-up.[124] Further manual filtering led to the selection of five series. One of them was deprioritized due to resistance issues. TCMDC-134142 (**69**, Scheme 19) represents one of the four remaining series.[125]

Amongst the targeted approaches, kinase inhibitors have been evaluated but so far are weak inhibitors (EC_{50} >100 nM)[8,126] and are therefore outside of the scope of this digest.

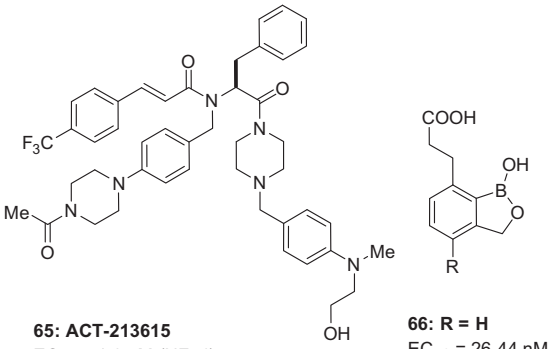
GSK reported a series of highly potent 2-pyrimidinecarbonitriles as inhibitors of falcipain-2 and falcipain-3, such as **70** (Scheme 20, EC_{50} = 1 nM).[127] Falcipains are cysteine proteases that hydrolyze the host hemoglobin to provide amino acids for parasite protein synthesis.

Harmine (**71**, Scheme 20) was reported to inhibit the *Plasmodium* heat shock protein 90 (Hsp90) and some selectivity over the human Hsp90 was observed. Its cellular activity is EC_{50} = 50 nM (3D7).[128] Hsp90 inhibitors have traditionally been pursued for cancer, and were found to have a limited therapeutic window.[129]

Epigenetic factors regulate the progression of the malaria parasite through its complex life cycle, and malarial histone acetyltransferase (HAT)[130] and histone deacetylase (HDAC)[131,132] inhibitors have been reported. Recently, the targeting of *P. falciparum* epigenetic factors was extended to include inhibitors of histone methyltransferases, such as BIX-01294[133] and TM2-115 (**72/73**, Scheme 20).[134] In an acute infection mouse model (highly virulent *P. berghei* ANKA strain), the compounds (dosed ip, 40 mg/kg) showed a rapid onset and a 2- and 18-fold parasite reduction.

Febrifugine (**74**, Scheme 21) is the active component of the Chinese herb Chang Shan (*Dichroa febrifuga*), and is an appealing anti-malarial because of its rapid effect and availability. However, strong liver toxicity has precluded its use as a clinical drug. Radix Pharmaceuticals discovered febrifugine analog **75** with a much improved therapeutic index in mouse (TI = 132 vs 3), thus exceeding the therapeutic index of artesunate (TI = 37).[135] The therapeutic index was defined as the ratio between the maximum tolerated dose (MTD), and the minimum clearance dose (MCD). Compound **75** is effective in mouse (EC_{50} = 0.3 mg/kg/day) and in *Aotus* monkeys (EC_{50} = 2 mg/kg/day).[135]

Several additional active compounds were identified by various approaches (Scheme 22), including the potent marine natural product salinosporamide A (**74**),[136] SSJ-183 (**75**),[137,138] prodiginine **74**,[139] tsitsikammamine C (**77**),[140] the berberine analog **78**,[141] quin-



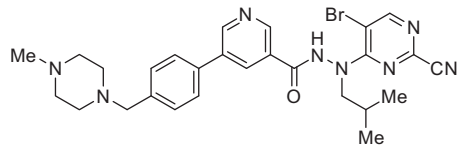
65: ACT-213615
EC_{50} = 1.0 nM (NF54)
ED_{90} = 8.4 mg/kg/day

66: R = H
EC_{50} = 26-44 nM
67: R = F
EC_{50} = 26 nM

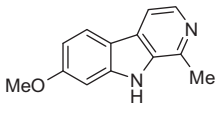
68: TDR84420
EC_{50} = 326 nM (K1)

69: TCMDC-134142
EC_{50} = 100 nM

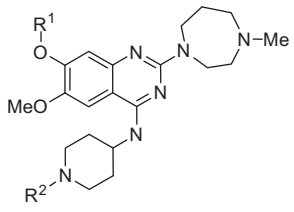
Scheme 19. New scaffolds from phenotypic screens (continued). EC_{50} values are reported for the drug-sensitive strain NF54 and the multi-drug resistant strain K1.



70: Falcipain inhibitor
IC_{50} < 0.5 nM
EC_{50} = 1 nM (W2)

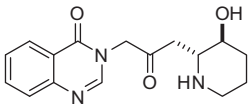


71: Harmine, PfHsp90 Inhibitor
EC_{50} = 50 nM (3D7)

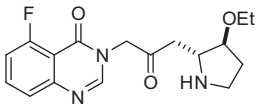


Histone methyl transferase inhibitors
72: BIX-01294 (R^1 = Me, R^2 = Bn)
EC_{50} = 75 nM (3D7)
73: TM2-115 (R^1 = Bn, R^2 = Me)
EC_{50} = 100 nM (3D7)

Scheme 20. New scaffolds from targeted approaches. EC_{50} values are reported for the drug-sensitive strain 3D7 and the multi-drug resistant strain W2.



74: Febrifugine
EC_{50} = 2.1 nM (Dd2)
ED_{50} = 2.3 mg/kg/day
MCD = 12 mg/kg/day
MTD = 35 mg/kg/day
TI = 3



75
EC_{50} = 0.26 nM (Dd2)
ED_{50} = 0.31 mg/kg/day
MCD = 1.9 mg/kg/day
MTD = 250 mg/kg/day
TI = 132

Scheme 21. Febrifugine and improved analog. MCD = minimum clearance dose. MTD = maximum tolerated dose. TI = therapeutic index = MTD/MCD. EC_{50} values are reported for the multi-drug resistant strain Dd2.

dolone **79**,[142] propafenone **80**,[143] sulfonamide **81**,[144] diamine **82**,[145] the iridoid **83** extracted from traditional African herbal remedies,[146] and iThemba's **84**.[147]

Currently, most approved malaria drugs target only the blood stages of the disease. The two exceptions are the combination of atovaquone/proguanil which is also effective in clearing parasites from the liver, and primaquine.[148] The latter clears not only liver schizonts but also hypnozoites, the dormant liver-stage parasites in *P. vivax* and *P. ovale* infections, thus providing what is known as a radical cure.[149] Hypnozoites are long-lasting reservoirs responsible for recurring malaria episodes in the absence of mosquito bites, and are a major health concern, especially in the case of *P. vivax*.

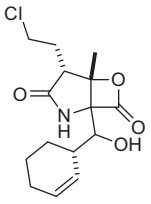
The search for liver stage drugs has been severely hampered by the lack of culture techniques and by cumbersome primate animal models. It has been suggested that for prophylactic treatment, compounds without blood stage activity might be preferred in order to minimize the risk of the emergence of drug-resistant parasites.

Primaquine is a drug that acts slowly,[150] and is therefore given together with other drugs, for example, chloroquine. Its mechanism of action is unclear, but is believed to be mediated by reactive metabolites which destroy the mitochondrial structure of the parasite. Primaquine, however, causes hemolytic anemia in people with glucose-6-phosphate dehydrogenase (G6PD) deficiencies, which occur in ~10% of the population,[151] and are particularly prevalent in malaria endemic countries.[202] In fact, the spatial extent of *P. vivax* malaria overlaps widely with that of G6PD deficiency.[202] Additionally, compliance with the primaquine 14-day treatment regimen is difficult.

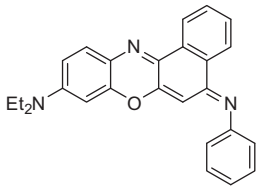
The primaquine analog tafenoquine (**85**, Scheme 23) is currently in Phase IIb/III clinical trials and has proven activity against hypnozoites. Tafenoquine has the same G6PD deficiency liability as primaquine, but has the advantage of being a single-dose treatment.

Recent drug discovery efforts have focused specifically on targeting the asymptomatic liver stage sporozoites and/or hypnozoites (possibly in addition to the blood stages) in order to provide novel, non-8-aminoquinoline drugs without the G6PD liability.[149,152,153] A new imaging technique of *Plasmodium* liver stages, described by The Scripps Research Institute and Novartis, constitutes a breakthrough, and was applied to prioritize 4000 compounds already possessing blood-stage activity.[154] Imidazolopiperazines emerged as a hit series, exemplified by GNF-Pf-5069 (**86**, Scheme 24), which was then optimized to provide GNF179 (**87**) and GNF156 (**88**). The latter is currently in Phase I clinical trials.[155,156]

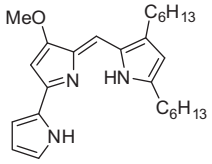
Most data was initially reported for the nonclinical compound GNF179,[155] which inhibits both the blood stages of *P. falciparum* (EC_{50} = 6 nM (3D7)) and the liver stages of the murine *Plasmodium*



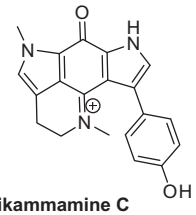
74: Salinosporamide A
EC_{50} = 11 nM
EC_{50} = 0.25 mg/kg/day



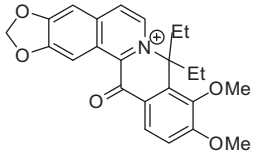
75: SSJ-183
EC_{50} = 7.6 nM (K1)
ED_{50} ~ 20 mg/kg/day



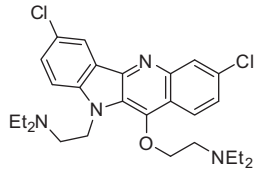
76
EC_{50} = 1.7 nM (D6)



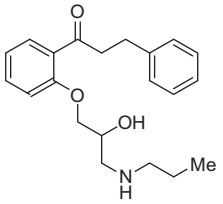
77: Tsitsikammamine C
EC_{50} = 13 nM (3D7)
EC_{50} = 18 nM (Dd2)



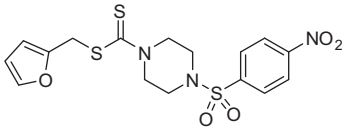
78
EC_{50} = 36 nM



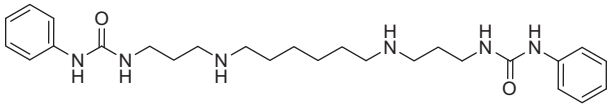
79
EC_{50} = 51 nM (W2)



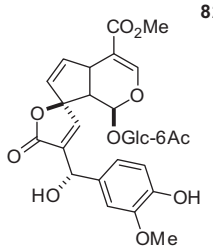
80: Propafenone
EC_{50} = 60 nM (3D7)



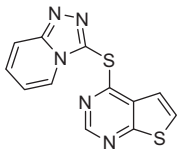
81
EC_{50} = 64 nM (3D7)
EC_{50} = 117 nM (Dd2)



82: EC_{50} = 88 nM (3D7)



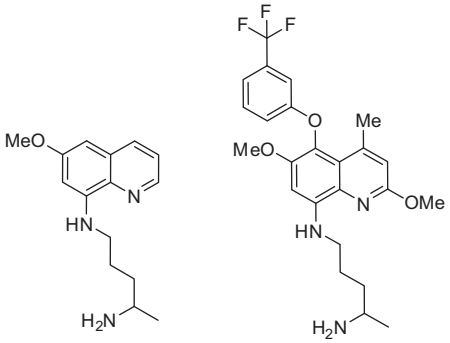
83
EC_{50} = 100 nM



84
EC_{50} = 150 nM (NF54)

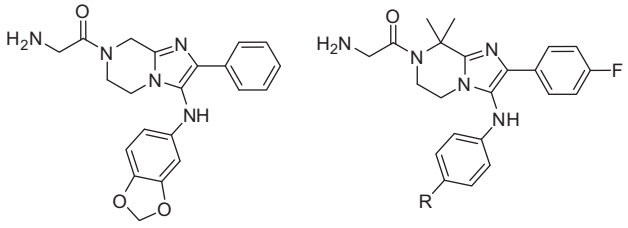
Scheme 22. New scaffolds from various approaches. EC_{50} values are reported for drug-sensitive (3D7, NF54) and multi-drug resistant (Dd2, K1) strains.

yoelii, (EC_{50} = 5 nM). GNF179 is orally bioavailable in mouse (F = 58%, $t_{1/2}$ = 8.9 h), and reduces *P. berghei* parasitemia in mice by 99.7% at 100 mg/kg. Importantly, a single dose of 15 mg/kg of



10: Primaquine **85: Tafenoquine**

Scheme 23. Primaquine and tafenoquine.

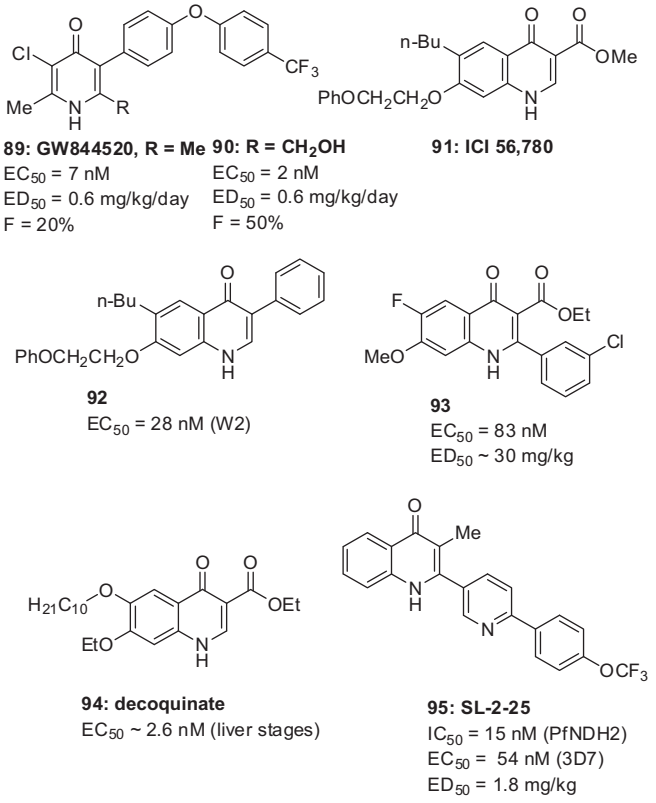


86: GNF-Pf-5069
EC_{50} = 462 nM (3D7)
EC_{50} = 221 nM (*P.yoelii* liver stage)
Poor exposure in animal models

87: GNF179 (R = Cl)
EC_{50} = 6 nM (3D7)
EC_{50} = ~5 nM (*P.yoelii* liver stages)
hERG (binding) IC_{50} = 6.6 μM
ED_{99} = 2.2 mg/kg

88: GNF156 (R = F)
EC_{50} = 6 nM (3D7 strain)
EC_{50} = N/A (*P.yoelii* liver stages)
hERG (binding) IC_{50} = 6.6 μM
ED_{99} = 2.2 mg/kg

Scheme 24. Imidazolopiperazines. EC_{50} values are reported for the drug-sensitive *P. falciparum* strain 3D7, and the hepatic stages of the murine *P. yoelii*.



89: GW844520, R = Me
EC_{50} = 7 nM
ED_{50} = 0.6 mg/kg/day
F = 20%

90: R = CH_2OH
EC_{50} = 2 nM
ED_{50} = 0.6 mg/kg/day
F = 50%

91: ICI 56,780

92
EC_{50} = 28 nM (W2)

93
EC_{50} = 83 nM
ED_{50} ~ 30 mg/kg

94: decoquinate
EC_{50} ~ 2.6 nM (liver stages)

95: SL-2-25
IC_{50} = 15 nM (PfNDH2)
EC_{50} = 54 nM (3D7)
ED_{50} = 1.8 mg/kg

Scheme 25. Pyridones with activity against liver stages. EC_{50} values are reported for the drug-sensitive strain 3D7 and multi-drug resistant strain W2.

GNF179 was shown to be completely protective in mice challenged with *P. berghei* sporozoites.

GNF156 was recently shown to be equally as potent as GNF179 against *P. falciparum* (EC_{50} = 6 nM (3D7)). The potency against *P. yoelii* liver stages has not been disclosed.[156] GNF156 is orally bioavailable in mouse (F = 72%, $t_{1/2}$ = 2.2 h) and rat (F = 20–57%, $t_{1/2}$ = 4.7–8.4 h).[156] It is noteworthy that GNF156 not only inhibits the liver stages, but also transmission.[156b]

It is not yet known whether these compounds are active against the hypnozoites of *P. vivax* and *P. ovale* and would thus be able to provide a radical cure.[154] The mechanism of action of the imidazolopiperazines remains unknown.

Atovaquone (**11**) targets the electron transport chain (ECT) of the mitochondrion, and specifically the cytochrome bc_1 complex. Additional quinones have been reported, without obvious advantage,[157,158] and most progress was made with pyridones.

GSK reported a back-up to pyridone GW844520 (**89**, Scheme 25), a molecule targeting cytochrome bc_1; hydroxymethyl derivative **90** remarkably improved the mouse oral bioavailability (50%) as compared to GW844520 (20%).[159]

The paucity of compounds with anti-relapse properties led to the reinvestigation of the quinolone ICI 56,780 (**91**, Scheme 25). The latter was discovered in the 1960s and a 7-day regimen of **91** prevents relapses for 120 days in rhesus monkeys infected with *Plasmodium cynomolgi*, suggesting potency against hypnozoites. It was abandoned because resistance was obtained after only a single passage in *P. berghei* infected mice. The group of Manetsch at the University of South Florida, reported compound **92** with an EC_{50} = 28 nM against the W2 strain, and of 31 nM against the atovaquone-resistant TM90-C2B strain (chloroquine-, mefloquine-, pyrimethamine-, and atovaquone-resistant).[41,160,161] The Guy group at St. Jude Children's Research Hospital, Memphis, reported compound **93** with an EC_{50} = 83 nM,[162] which has suppression activity in mice comparable to that of amodiaquine (57% suppression of parasitemia at 30 mg/kg) but is not curative. It remains to be investigated if activity against hypnozoites is maintained, and if resistance against **92** and **93** develops as fast as with ICI 56,780.

In a screen including 1037 compounds which have reached at least Phase I clinical trials (veterinary and/or human), decoquinate (**94**, Scheme 25), an approved veterinary drug, was identified to potently inhibit the *P. yoelii* liver stage (estimated EC_{50} of 2.6 nM) as well as the asexual (EC_{50} = 10 nM) and sexual (EC_{50} = 36 nM) *P. falciparum* blood stages.[163] The decoquinate-induced reduction of mosquito transmission has not been reported. Decoquinate (administered p.o., 10 mg/kg) was found to completely protect *P. berghei* infected mice from developing disease when treated 24 h after the infection. The molecular target is the parasitic cytochrome bc_1 complex (IC_{50} = 2 nM, >5000-fold selectivity over its human counterpart).[164] Unfortunately, decoquinate has so far only been tested in animals, which makes the repurposing of this drug challenging.

The O'Neill group, at the University of Liverpool, searched for compounds that would inhibit another enzyme involved in the ECT, namely NADH:ubiquinone reductase (PfNDH2). A succession of in silico screens, HTS, and medicinal chemistry activities led to CK-2-25 (**95**, Scheme 25), which is specific for PfNDH2 over bc_1, and is potent in mouse, with an ED_{50} = 1.8 mg/kg.[42,165]

The first screening examples have been reported, such as the imidazolopiperazines **86**–**88** described above.[154] Additionally, a set of ~5300 biologically active compounds, which included 640 FDA-approved drugs, was screened and 37 structurally diverse compounds with varied known biological functions were identified to also inhibit the malarial liver stages.[166] Screening a natural product library highlighted the secondary fungal metabolite cladosporin (**96**, Scheme 26), which potently inhibits the blood and liver stages in drug sensitive and multiple drug-resistant cell lines (IC_{50} ~40–90 nM).[167] The molecular target was identified to be cytoplasmic lysyl-tRNA synthetase. (*Pf*Krs1) Cladosporin is selective over human Krs1 (IC_{50} >20 μM).

In addition, there is a growing interest in signal peptide peptidases (SPP) such as NITD-731 (**97**, Scheme 26) which inhibits *P. yoelii* liver stages with EC_{50} = 7.8 nM.[168]

Since many different proteins are expressed during the liver and blood stages of the parasite's life cycle[169,170] and since the necessary medium- to high-throughput liver stages assays are continuously being developed and refined including assays which allow the assessment of hypnozoiticidal activities,[171–174] it is reasonable to believe that in the near future many new chemotypes and biological targets will emerge from these efforts.

Drugs that can reduce the formation of gametocytes (gametocytogenesis), or can kill them (gametocytocides), are highly desirable but have been underexplored because of the lack of quantitative high throughput assays.[175,176] These transmission-blocking drugs could target endpoints such as:

(1) The effective and complete killing of mature gametocytes once they are formed in the human host.
(2) The inhibition of the onward development of gametocytes into ookinetes and ultimately into sporozoites in the mosquito. This assumes that enough drug from the blood sample reaches the gut of the mosquito.[177]

Gametocyte development goes through five stages of maturation, with stage V being the only form which can infect mosquitoes (Scheme 1). For *P. falciparum*, these mature gametocytes start to be present ~12 days after disease symptoms, circulate on average for 2.5–6.5 days,[178] and persist for up to 22 days.[179] Thus, circulating gametocytes can sustain malaria transmission well after drug treatment has caused disease symptoms to disappear. For the other *Plasmodium* parasites, mature gametocytes appear much earlier, closer to 1 day after disease symptoms appear. This difference in biology represents an additional challenge when optimizing dosing regimens of transmission-blocking drugs in the clinic.

Most currently approved anti-malarial drugs, including ACTs, are only effective against blood stages and young gametocytes up to stage III and possibly stage IV of gametocyte maturation (stage III can be observed at day 4–6 and IV is observed at day 7–9; Scheme 1). This unfortunately does not result in complete clearance of mature gametocytes. To make matters worse, some drug treatments, for example, chloroquine[180] and sulfadoxine–pyrimethamine,[181] were found to induce gametocytogenesis, thus potentially contributing to increased numbers of transmissions and increased rates of new infections.[182]

The transmission-blocking potential of approved and clinical antimalarials has been reviewed.[9,183,184] Currently, the only fully effective gametocytocidal drug is primaquine (**10**, Scheme 3), which acts against gametocytes of all malaria species and represents the WHO recommended treatment option against *P. falciparum* gametocytes. Until recently, the WHO recommendation was a single primaquine dose of 0.75 mg/kg,[185] provided that the risk for acute hemolytic anemia (G6PD deficiency) had been evaluated prior to treatment. In 2012, the WHO recommended that the dose be lowered to 0.25 mg/kg, which is still effective at lowering transmission while being unlikely to cause serious toxicity in subjects with G6PD variants.[186,187] Thus, a single dose of primaquine (0.25 mg base/kg) should be given to all patients with parasitologically-confirmed *P. falciparum* malaria on the first day of treatment in addition to an ACT, except for pregnant women and infants <1 year of age.[186]

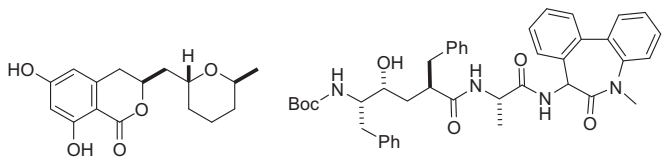
Because of the risks associated with primaquine, novel transmission-blocking drugs are being sought for achieving the goal of global malaria eradication. Large strides have recently been made in understanding the specifics of transmission-stage biology, and in developing in vitro assays focused on late-stage gametocyte development, lethality of mature gametocytes and the gametocyte–ookinete/sporozoite transition.[188–192]

Tafenoquine (**84**), NITD609 (**52**),[94] and GNF156 (**88**) were shown to have transmission-blocking activities in vitro. Tafenoquine was also found to delay sporozoite formation in *P. vivax*. Interestingly, a recently developed gametocyte drug screening assay identified methylene blue (**97**, Scheme 27), as a potent inhibitor of gametocyte development across all stages. Methylene blue is an approved injectable monoamine oxidase inhibitor[193] for methemoglobinemia, which almost fully abolishes *P. falciparum* transmission to mosquitoes at concentrations readily achievable in humans, highlighting the potential of this chemical class to reduce the spread of malaria.[194] Incidentally, methylene blue was the first antimalarial to be tested in man (1891), based on Ehrlich's observation that it could stain the malaria parasite.

Additional examples of compounds with transmission-blocking activities include, amongst others, trioxaquine DU1302 (**98**, Scheme 27), epoxomicin (**99**, nonselective over human cells),[189] HIV protease inhibitors such as tipranavir (**100**),[184,195] kinase inhibitor BKI1 (**101**),[196] ketotifen (**102**),[197,198] thiostrepton (**103**),[195] and cycloheximide (**104**).[199]

Anti-malarial strategies are ideally a balanced use of mosquito control, anti-*Plasmodium* treatments, and a general improvement of sanitation and awareness.[175,176] This is how malaria was eradicated from developed countries. Vaccines would also be extremely useful.[200] Nonetheless, there is an urgent need for developing new anti-malarial drugs. The new 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.

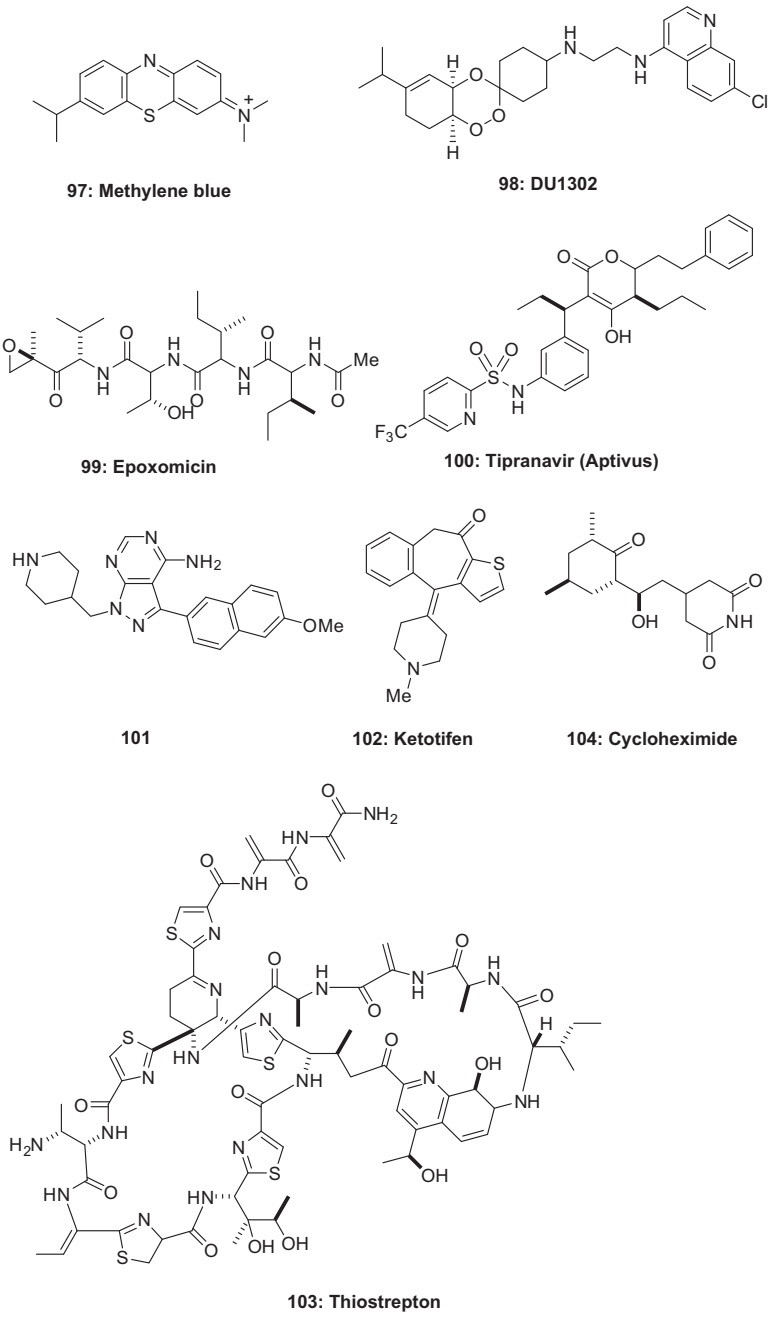
The pipeline for the blood stage is arguably the best in history, but still needs to be expanded. The last few years have seen an explosion of potent new chemotypes, and the new challenge is to assess the potential of these chemotypes. Ideally, the new drug should: (i) address drug-resistance issues, (ii) have a rapid onset of action, (iii) be safe, especially in children and pregnant women, and (iv) cure malaria in a single dose. The challenge is to find a drug that addresses all of these features. It is our hope that with the rich variety of new chemical entities, such a drug will be discovered. Nevertheless, drug discovery efforts should continue, as the artemisinins set a high standard of efficacy and safety.



96: Cladosporin
EC_{50} = 45 nM (3D7)
EC_{50} = 90 nM (D10)

97: NITD-731
EC_{50} = 17 nM (*Pf* blood stages)
EC_{50} = 7.8 nM (*P. yoelii* liver stage)

Scheme 26. Cladosporin and NITD-731 inhibit liver stages with novel mechanisms of action. EC_{50} values are reported for the drug-sensitive strains 3D7 and D10.



Scheme 27. Compounds with transmission blocking properties.

Drugs that target the liver and transmission stages have the potential to be transformational, but research efforts have been hampered by the absence of high-throughput screens. New imaging techniques are beginning to solve this problem and open up novel avenues, with an innovative clinical compound having liver stage activity. The field of transmission-blocking agents is in its infancy, but may be the most transformative of all in achieving the ultimate goal of eradicating malaria.

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