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Review

Recent approaches in the drug research and development of novel antimalarial drugs with new targets

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ABSTRACT

Malaria is a serious worldwide medical issue that results in substantial annual death and morbidity. The availability of treatment alternatives is limited, and the rise of resistant parasite types has posed a significant challenge to malaria treatment. To prevent a public health disaster, novel antimalarial agents with single-dosage therapies, extensive curative capability, and new mechanisms are urgently needed. There are several approaches to developing antimalarial drugs, ranging from alterations of current drugs to the creation of new compounds with specific targeting abilities. The availability of multiple genomic techniques, as well as recent advancements in parasite biology, provides a varied collection of possible targets for the development of novel treatments. A number of promising pharmacological interference targets have been uncovered in modern times. As a result, our review concentrates on the most current scientific and technical progress in the innovation of new antimalarial medications. The protein kinases, choline transport inhibitors, dihydroorotate dehydrogenase inhibitors, isoprenoid biosynthesis inhibitors, and enzymes involved in the metabolism of lipids and replication of deoxyribonucleic acid, are among the most fascinating antimalarial target proteins presently being investigated. The new cellular targets and drugs which can inhibit malaria and their development techniques are summarised in this study.

Keywords: antimalarial drugs, protein kinases, dihydroorotate dehydrogenase

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INTRODUCTION

Malaria, an acute febrile illness primarily caused by five *Plasmodium* parasite species, of which *P. vivax* and *P. falciparum* are the deadliest, spreads among individuals by pricks from infected female *Anopheles* parasites, often called "malaria vectors" (1, 2) (life cycle is depicted in Figs. 1 and 2). As per the World Health Organization (WHO), in 85 malaria-endemic countries, there were about 241 million malaria cases in 2020 (compared to 227 million in 2019) (3). Notably, the WHO African region itself accounted for 95 % (228 million) of the estimated cases. As per the World Malaria Report 2021, approximately 627,000 deaths were associated with malaria, with a 12 % increase in cases since 2019. Undoubtedly, this rise in the death toll may be attributed to the disruptions to services during the Coronavirus disease 2019 (COVID-19), which was estimated to be 47,000 death cases. To illustrate, the current malaria mortality rate is 15 per 100,000 people at risk. Though globally about 1.7 billion cases and 10.6 million deaths associated with malaria were averted during the period 2000–2020, the burden of malaria infection in pregnancy (also in neonates and children) remains a concern. Nevertheless, considering the global technical strategy for malaria 2016–2030 (GTS) milestone, an estimated USD 3.3 billion (including USD 619 million in research and development) was funded in 2020 for malaria control and elimination. Mosquirix, a malaria vaccine, supplied to kids between six weeks to seventeen months of age, can potentially prevent them from *P. falciparum*-caused malaria (4). This vaccine must be used in *P. falciparum* prevalent places in accordance with government advice (5). Mosquirix vaccine can be used for a short period of time and is effective even in the most vulnerable age groups (6, 7).

Numerous investigations have demonstrated that the advent of drug-resistant *Plasmodium* species reduces the effectiveness of most antimalarial medications (8, 9). Almost all currently available antimalarial drugs have been found to be resistant, underscoring the urgent need for novel antimalarial treatments that target both proven and novel antimalarial targets (10).

Particularly in resistant parasite species, a new antimalarial therapy that targets both transmissible gametocyte phases and intra-erythrocytic proliferative asexual stages is required (11). Several enzymes, transporters, ion channels, red blood cell (RBC)-invasion

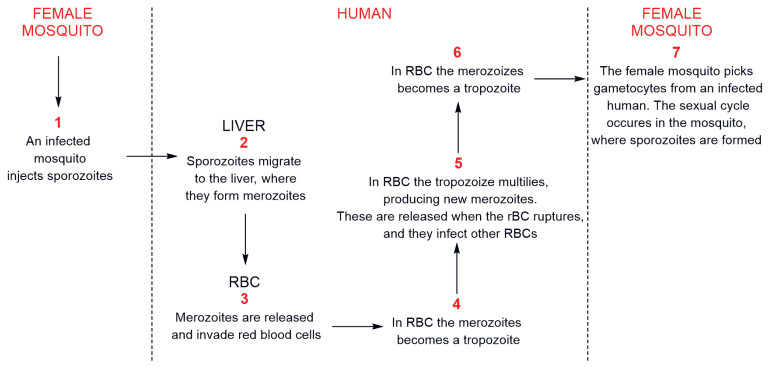

Fig. 1. Life cycle of malaria parasite in female *Anopheles* mosquito and human.

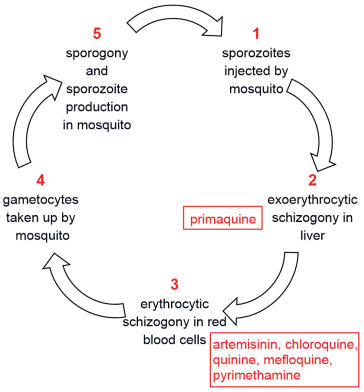

Fig. 2. The life cycle of *Plasmodium* parasite in humans: stages and forms of the parasite at which different types of antimalarial drugs act.

interacting molecules, inducing oxidative stress in the parasite, lipid metabolism and haemoglobin breakdown molecules, are all intriguing novel targets for creating new antimalarial medications against rapidly evolving malarial parasites (12). New mechanisms of action without cross-resistance to the present antimalarial drug, single-dose therapies, and effectiveness against both transmission-causing gametocytes and asexual blood stages are among the criteria used to assess a new antimalarial agent's potential (13). In addition, the new antimalarial medication should be able to both control disease and eliminate *P. vivax* hypnozoites from the liver (14).

Conventional medicinal research employs a variety of methods for developing new antimalarial medications. Some of the approaches being pursued are the combining of existing drugs and formulations (15), modification of active antimalarial drugs, analyzing natural compounds, isolation of resistance-reversing drugs, and exploitation of agents specified for different purposes [repurposing] (16). Understanding the *Plasmodium* genome and its biology has been shown to be a strong tool for revealing resistance mechanisms and has tremendous promise for developing innovative medicines with enhanced antimalarial efficacy and transmission-blocking capability for the complete eradication of malaria (17). Genetic screening of *P. falciparum* species revealed that 2680 genes are required for asexual blood-stage growth, leading to the discovery of important cellular mechanisms that are essential for the development of new medicines (18).

The new medication should tackle drug resistance, have a quick onset of action, be safer, particularly in pregnant women and kids, and treat malaria in a single dose (19). The issue is finding a medicine that possesses all these qualities (20). The purpose of this review is to give an overview of the current trends on novel antimalarial targets that are being researched by a variety of companies.

NOVEL ANTIMALARIAL TARGETS

The existing antimalarial drugs focus on the variations between the key metabolic pathways of *Plasmodium* species and their hosts. Heme detoxification, synthesis of fatty

acids and nucleic acids and oxidative stress, are the major metabolic processes that might be targeted for new drug development (21, 22). Despite the fact that most antimalarial drugs have been in use for several years, drug resistance has limited their usage. According to the literature, no antimalarial medication has been found that inhibits a specific drug target (23).

Rather, the majority of antimalarial medicines have been discovered based on *in vivo* or *in vitro* experiments. As a result, the mode of action of most antimalarial drugs is unknown. Furthermore, most antimalarial drugs' mechanisms of resistance are poorly known (22). Malaria prevention necessitates a multi-dimensional approach that includes vector management, efficacious and safe antimalarial drugs and vaccinations. Given the seriousness of malaria and associated mortality, the urgent need to combat drug resistance and the incompetency of currently accessible antimalarials against non-erythrocyte and sexual phases, it is critical to discover new antimalarial drugs by targeting the basic metabolic pathway of the parasite. Drug discovery must focus on new targets that have been verified in order to discover a new lead molecule to accomplish this aim.

There are numerous reasons for the need to find new metabolic targets. To begin with, most antimalarial medicines have no chemical diversity, with the exception of atovaquone- and artemisinin-derived medications, which can lead to cross-resistance. Secondly, many potential chemotherapeutic targets have not been confirmed due to the bewildering number of possibilities, verification of which may lead to the discovery of potent drug molecules. Detection of new targets and the development of novel derivatives that act on those targets is presently a commonly utilized strategy across the world to address challenges highlighted by the rise of drug resistance (23, 24).

As a result, therapeutic target discovery has been aided by looking for inhibitors specific to novel target proteins of the parasite. Since the publication of the *P. falciparum* genome, a number of new therapeutic targets have emerged. The essential metabolite production, membrane transport, and signalling systems, as well as the haemoglobin breakdown mechanisms, are all targets for these prospective antimalarial drugs (25). The following have emerged as promising targets:

- phosphatidylinositol 4-kinase (PfPI4K)
- P-type Na^+-ATPase (PfATP4)
- V-type H^+-ATPase
- choline transport
- dihydroorotate dehydrogenase (DHODH)
- isoprenoid biosynthesis
- *P. falciparum* translational elongation factor 2 (pfEF2)
- anti-adhesive polysaccharides
- *P. falciparum* glutathione reductase
- β-haemozoin.

The drug candidates targeting the above sites have been summarized in Fig. 3.

Phosphatidylinositol 4-kinase (PfPI4K) inhibitors

Phosphoinositide lipid kinases (PIKs) are the prevalent enzymes that control proliferation, survival, trafficking and intracellular signalling by phosphorylating lipids (26).

Phosphoinositide 3-kinase (PI3K) and phosphatidylinositol 4-kinase (PI4K) are the two most studied PIK classes. The suppression of these two enzymes has been recognized as a probable target for antimalarial drug development with a better activity profile for malaria prevention, cure and eradication (27).

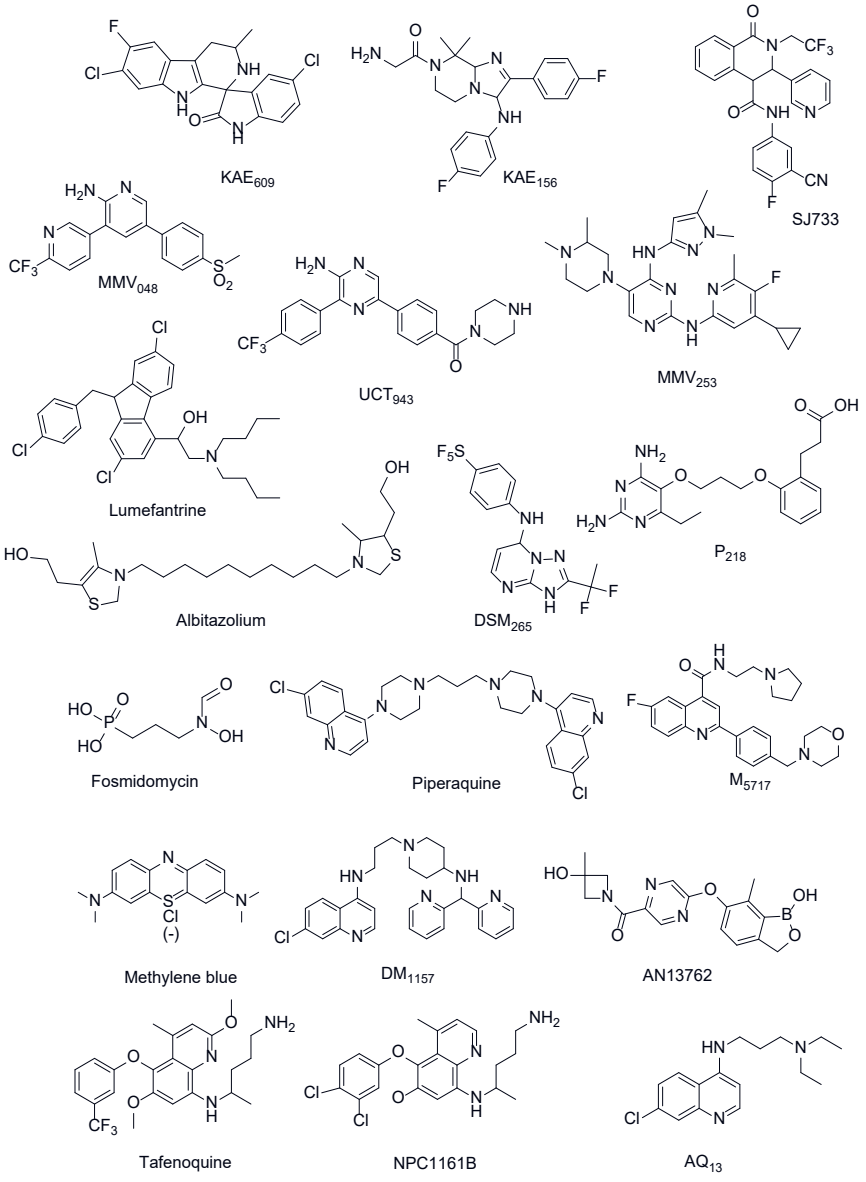

Fig. 3. Chemical structures of new antimalarial candidates in clinical trials.

UCT 943 (formerly MMV 642943)/MMV, H3D, is a novel antimalarial candidate that targets PI4K and was discovered by a group at the University of Cape Town in 2016. It is a crucial component of a new class of 2-aminopyrazines that added one more nitrogen atom to the pyridine ring (21, 22). It is active on both *P. falciparum* and *P. vivax* at different phases of the parasitic lifecycle (27). It has been proven to treat malaria in the *P. berghei* mouse model at dosages of 4–10 mg kg^{-1} and has an ED_{90} of 1 mg kg^{-1}. It was originally intended to serve as a backup to MMV048; however, it was discontinued owing to preclinical toxicity.

MMV048 is a 3,5-diaryl-2-aminopyridine that can inhibit PfPI4K (27). In the same campaign as UCT943, a group at the University of Cape Town in South Africa discovered a drug candidate that has strong preventive efficacy on *P. cynomolgi in vivo* and has the ability to inhibit the spreading of malaria (28). In the *P. berghei* mouse model, a single dose of 30 mg kg^{-1} resulted in a 99.3 % decrease in parasitaemia, with no evidence of parasites after 30 days (ED_{90} = 1.7 mg kg^{-1}). It works as a one-time therapy. Presently, it is undergoing Phase IIa clinical studies in Ethiopia (29).

These two drugs (UCT943 and MMV048) have been discovered to suppress the enzyme PfPI4K by cultivating resistant lines and detecting genomic alterations (27). Further, SAR studies indicated that substituting the methoxy group with a trifluoromethyl group might enhance MMV048's potency and strength.

Novartis and the Scripps Research Institute developed KAF156/ GNF156 in 2008, and it suppresses the intracellular growth of various *Plasmodium* species at every phase of the life cycle in humans by targeting PI4K (30). It was discovered during lead optimization of the imidazolopiperazine family, and it may have a new mode of action and perform well as a clinical candidate (31, 32). A single oral dose of 10 mg kg^{-1} given 2 hours prior to intravenous infection with *P. berghei* sporozoites was demonstrated to completely protect the causative prophylactic rodent malaria model. KAF156 is significantly less effective than KAE609, but it exhibits action against gametocytes and provides prophylactic protection in animal models (33). It is currently undergoing Phase IIb clinical studies and is being assessed in conjunction with lumefantrine [NCT03167242] (34).

Lumefantrine-KAF156 combines aryl-amino alcohol [which is already widely used in the artemether-lumefantrine (LUM) mixture], with the very powerful imidazolopiperazine KAF156, which has a 48.7-h half-life of elimination (35). This trial is looking at a novel lumefantrine formulation called lumefantrine-solid dispersion formulation, which can be administered once a day (36). Because lumefantrine absorption has been found to be fat-dependent and dose-restricted, this is an improvement over the widely used artemether-lumefantrine co-formulation, which is taken two times daily (37). As a result, targeting PI3K and PI4K may be considered novel pathways for antimalarial drug development.

P-type Na^+-ATPase (PfATP4) inhibitors

Erythrocytes, like other cell forms, have a low intrinsic Na^+ level. On the other hand, the parasite raises the penetrability of the erythrocyte cell membrane, allowing more Na^+ influx, thereby causing the erythrocyte's cytoplasm Na^+ content to rise to that of the extracellular medium. As the parasite is within the cell, it is in a high-Na^+ environment and must efflux Na^+ ions through its plasma membrane to maintain a low cytoplasmic Na^+ level in order to survive. The parasite's Na^+ influx is controlled by a P-type ATPase trans-

Table I. Antimalarial drugs in the market and their mechanism of action

No.	Class	Drug	Mechanism of action	Classification	Ref.
1	4-Quinolinemethanols	Quinine	Inhibits erythrocytic phase and rupture of the infected erythrocytes	Gametocides	123
		Chloroquine	It accumulates in the acidic food vacuoles of intraerythrocytic trophozoites and thereby prevent haemoglobin degradation	Blood schizonticides	124
2	4-Aminoquinolines	Amodiaquine (1948)	Inhibit heme polymerase activity	Blood schizonticides	125
		Piperaquine (1960)	Accumulating in the parasite digestive vacuole and interfering with the detoxification of heme into hemozoin	Blood schizonticides	126
3	8-Aminoquinolines	Primaquine	It interferes with the electron transport in the parasite during respiration process	Tissue schizonticides	127
		Tafenoquine (1978)	It is active against the liver stages including the hypnozoite (dormant stage) of *P. vivax*	Hypnozoiticides	127
4	4-Quinolinemethanols	Mefloquine	Prevents polymerization of Hb	Blood schizonticides	128
5	Aryl amino alcohol	Lumefantrine (1976)	It inhibits nucleic and fomarion of B-hematin by forming a complex with hemin	Blood schizonticides	129
6	Artemisinin derivatives	Artemisinin	Involves the heme-mediated decomposition of the peroxide bridge to produce carbon-centred free radicals	Blood schizonticides	130
7	Naphthoquinone	Atovaquone (1991)	Inhibition of cytochrome bc1in *Plasmodium*	Blood schizonticides	124
8	Diaminopyrimidine	Pyrimethamine (1950)	Inhibition of *Plasmodium* dihydropteroate synthase	Tissue schizonticides	131
9	Biguanide	Proguanil (chloroguanide) (1945)	Inhibition of dihydrofolate reductase-thymidylate synthase	Erythrocytic schizonticides	132
10	Tetracycline	Doxycycline and tetracycline	Inhibition of protein synthesis by binding to 30S ribosomal subunit	Blood-stage schizonticides	133

porter (PfATP4), which also acts as the parasite's principal Na^+-efflux pump. By blocking this transporter, more Na^+ is absorbed by the parasite, causing its death (38).

Research association with Novartis, the STPHI and the Wellcome Trust led to its discovery of cipargamin [KAE609] (39-42). It was discovered utilizing whole-genome sequencing and *in vitro* evaluation, and is the first potential chemical with a new mechanism [inhibits the P-type cation-translocating ATPase ATP4 of *P. falciparum* (PfATP4), disturbing parasite sodium homeostasis and causing osmotic dysregulation] to reach clinical trials in 20 years. It is equally efficient as artesunate against drug-resistant strains of *P. vivax* and *P. falciparum* isolates. It has a spectacle safety report, with minimal cardiotoxicity, cytotoxicity and mutagenicity, and can rapidly eliminate parasitaemia in people with naive *P. vivax* or *P. falciparum* malaria when given at a dose of 30 mg kg^{-1} for three days. Cipargamin is effective enough to cure *P. berghei*-infected mice and halt transmission with a single oral dose of 100 mg kg^{-1} (43), as evidenced by decreased oocyst counts assessed in a membrane--feeding experiment. It has low body clearance, a longer half-life ($t_{1/2}$ of elimination of 18.5 ± 4.7 h), and good bioavailability (44). This drug is postulated to target the P-type ATPase 4 (PfATP4) outer membrane transporter (45), which was formerly thought to be a Ca^{2+} ion pump, now found to be crucial for controlling Na^+ homeostasis in the parasite (46). Suppression of this PfATP4 by KAE609 was found to raise intracellular sodium levels, causing the parasite to enlarge and expire (47). It has advanced significantly from the transmission phase which started in 2007, through Phase IIa clinical studies, which began in 2013 (14, 48).

(+)-SJ733 is a new tetrahydroisoquinolone carboxanilide with remarkable *in vivo* antimalarial activity (49, 50). In 2010, St. Jude Children's Research Hospital in collaboration with Rutgers University discovered (+)-SJ733. It was shown to cure malaria in the *P. berghei* mouse model at doses of 4 × 100 mg kg^{-1} and had an ED_{90} of 1.9 mg kg^{-1}. It has been demonstrated to inhibit transmission in infected mice with an ED_{50} of 5 mg kg^{-1}. When compared to conventional drug regimens, such as chloroquine, artesunate and pyrimethamine, it has a favourable safety record, with minimal cytotoxicity, and has been shown to be more efficacious *in vivo* (50). PfATP4 has been identified as the molecular target of (+)-SJ733, and it has been characterized as a target for a variety of other structurally different molecules (51). Presently, (+)-SJ733 is undergoing Phase I clinical studies (52–54).

V-type H^+-ATPase inhibitors

Plasmodium species use a P-type ATPase transporter to regulate their Na^+ levels. A similar route is used to import H^+ ions. The malarial parasite employs a corresponding V-type ATPase transporter to efflux H^+ ions to maintain an intracellular pH of 7.3 and regulate the increasing H^+ ion content. It represents itself as a good target for new drug development. In 2015, AstraZeneca identified a potential series of TAPs (triaminopyrimidines) after a high-throughput assessment of five million derivatives from their collection on blood stages of *P. falciparum.*

MMV253 (formerly AZ13721412) is a new triaminopyrimidine blood schizonticide that inhibits the V-type H^+-ATPase as its mode of action (55, 56), by whole-genome and sequencing mutant selection. It is also a *Plasmodium* ATPase inhibitor that is currently in preclinical testing with the goal of being used in a single-dose radical treatment (57, 58). Cadila Healthcare, which acquired the licence for the chemical series in late 2016, is

continuing to work on the lead optimization process in order to develop the medicine through preclinical testing (59). It has a projected human half-life of 36 hours and has demonstrated high *in vitro* potential and *in vivo* efficacy (59, 60).

Choline transport inhibitors

Phospholipids act as an important part of *P. falciparum*'s intra-erythrocytic life cycle, both as structural parts of the membrane and as governing fragments that control a variety of enzymatic activities. They are necessary for parasite growth within RBCs. Phospholipid levels rise after RBC invasion, with phosphatidylcholine being the most abundant lipid in the cell membrane. The parasites use choline as a precursor for making phosphatidylcholine from scratch. This process is required for parasite survival and proliferation. Choline transport inhibition causes phosphatidylcholine production to be inhibited, resulting in parasite death (61).

Albitiazolium (SAR9727) has been studied in Phase II trials, at CNRS/University of Montpellier/Sanofi. It works by preventing choline from being transported into the parasite. It accumulates approximately about 1000-fold in the *Plasmodium* and suppresses parasite development without causing recurrence. At high parasitaemia levels, a single injection is curative (62, 63).

Dihydroorotate dehydrogenase (DHODH) inhibitors

The wide and fast separation of DNA of a parasite, which is dependent on the presence of critical metabolites like pyrimidines, is a crucial stage in *Plasmodium* species spreading in human hosts. Pyrimidine nucleotide is required for the production of DNA, phospholipids, and glycoproteins in the malaria parasite. The salvage process and the *de novo* pathway are the two primary mechanisms for nucleotide synthesis. The oxidation of dihydroorotate to orotate, which is a rate-limiting stage in the synthesis of *de novo* pyrimidine, is catalysed by the enzyme DHODH. As a result, DHODH might be an appropriate target for the development of potent antimalarials (64).

Human cells can get pyrimidines either by salvaging so far-produced pyrimidines or by synthesizing them from scratch. The cell will rely on the salvage route if the *de novo* biosynthesis pathway is blocked, and it will not perish. On the other hand, *de novo* pyrimidine synthesis in the parasite is inhibited resulting in cell death since the malarial parasite is deficient in the pyrimidine salvage pathway, making it sensitive to DHODH inhibition (65).

DSM265 is a triazolopyrimidine discovered by a team of scientists from the University of Washington, Monash University, and the University of Texas South-Western (66). It is a specific inhibitor of malarial DHODH, and is effective against liver and blood stages of *P. falciparum*, as well as drug-resistant parasite isolates. It is the earliest DHODH suppressor to undergo pre-clinical trials (elimination $t_{1/2}$ = 86–118 h) and is reported to be along-acting inhibitor (67). It was shown to exhibit strong action in whole-cell tests (IC_{50} in *P. falciparum* = 79 nmol L^{-1}) and >5000-fold specificity for parasite DHODH over human DHODH; however, in the *P. berghei in vivo* model, this class was ineffective (66). After a wide range of chemical alterations and evaluations of drug-enzyme co-crystal structures to optimise binding against drug-sensitive and drug-resistant *P. falciparum*, as well as

resistance to atovaquone, chloroquine and the antifolate, pyrimethamine, a potent lead compound with an IC_{50} of 40–50 nmol L^{-1}, was discovered (66–68). It has a reliable safety report and a low clearance rate, and an extended half-life (69). *In vitro* investigation shows that this medication has a low barrier to resistance selection; therefore, efforts to safeguard it, such as pairing it with a compound with identical elimination kinetics and only using it in a fixed-dose combination, would be critical (70, 71). In Peru, DSM265 (NCT02123290) completed Phase IIa studies in people with *P. falciparum* or *P. vivax*, in conjunction with OZ439 (NCT02389348) (72).

P218 is an antifolate antimalarial medication developed by BIOTEC Thailand in 2012 that resembles the 2,4-diaminopyrimidine parent structure of pyrimethamine (73). It was discovered by studying the co-crystal structures of known PfDHFR (*P. falciparum* dihydrofolate reductase) inhibitors and their substrates. The 2,4-diaminopyrimidine scaffold of P218 has been shown to bind deeply in the active site of both mutant and wild-type PfDHFR strains. Because P218 is almost completely contained inside the dihydrofolate binding site, the binding potency must be adequate to counter any amino acid changes, thus reducing the risk of drug-resistant mutations. It is able to overcome pyrimethamine resistance thanks to its unique two-stage mode of action for binding to PfDHFR. It has also demonstrated excellent selectivity for malarial binding over human DHFR, resulting in decreased toxicity. It was shown to be very effective against *P. chabaudi* and *P. falciparum* in mice models, with ED_{90} values of 0.75 mg kg^{-1} and 1 mg kg^{-1}, resp., in *in vivo* experiments (74). It was also shown to be more potent than pyrimethamine in all of the *in vivo* and *in vitro* potency tests that were conducted. It has the potential to replace pyrimethamine in conjunction with cycloguanil in cases where PfDHFR resistance has evolved due to its enhanced potency and favourable safety profile (75). It is a lead chemical that is selective for *Plasmodium* spp. DHFR, and possesses a nanomolar IC_{50} against *P. falciparum* that exhibits either mutant or wild-type DHFR. It has been studied in Phase I of clinical trials (NCT02885506) (67, 69). P218 displayed favourable safety, tolerability and pharmacokinetics. In view of its short half-life, a long-acting formulation will be needed for malaria chemoprotection (76).

Isoprenoid biosynthesis inhibitors

Isoprenoids are required for the asexual replication and post-translational lipid variation of proteins in *P. falciparum*. Isoprenoid may be made from either the 5C-precursor *iso*--pentyl diphosphate (IPP) or its isomer dimethyl allyl diphosphate (DMAPP), which can be made by either of the pathways, the 2C-methyl-D-erythritol-4-phosphate (MEP) route and the mevalonate pathway. In most microbes, the two routes are mutually exclusive. The MEP route is used solely by bacteria and *P. falciparum*, but not by humans (77). As a result, enzymes in the MEP pathway have been investigated as possible drug targets. 1-Deoxy-D--xylulose-5-phosphate reductoisomerase (PfDXR) in *P. falciparum* catalyses the rate-limiting step in the MEP pathway, projecting this enzyme as a desirable target for the development of new antimalarial drugs (78). *P. falciparum* growth was shown to be reduced by a PfDXR inhibitor that was not harmful to human cells, thus implicating PfDXR as a possible newer target for the development of antimalarial drugs. DOXP reductoisomerase, a crucial enzyme in the DOXP pathway that is absent in humans, is inhibited by fosmidomycin, MMV019313 and MMV008138. Because protein prenylation inhibition in the malarial parasite causes asexual parasite development to be disrupted, it is a potential antimalarial target.

In the 1980s, fosmidomycin was created as an antibacterial medication. This isoprenoid biosynthesis inhibitor has an excellent safety profile, although it has demonstrated mixed effectiveness as a monotherapy and in combination with clindamycin (79–81). In recent times, it has been combined with piperaquine, a bisquinoline discovered in the 1960s, which was previously used in conjunction with dihydroartemisinin in leading artemisinin--based combination therapies (ACT) (82). The dose of piperaquine is 16 mg kg^{-1}, which has been shown to be minimal in children under the age of 5 in the conventional DHA-piperaquine ACT (83). The above is likely to be of relevance for combining piperaquine with fosmidomycin, a less potent medication than DHA having an elimination half-life of around two hours. One of the characteristic features of Phase II combinations is that they always include one drug that may have lower efficacy in multidrug-resistant areas.

Fosmidomycin-piperaquine demonstrated good effectiveness in a short Phase IIb study in Gabon patients of various age groups (84). Because piperaquine resistance has already been reported in Thailand, Cambodia and Vietnam, this combo cannot be used to replace Southeast Asia's unsuccessful ACTs (85).

P. falciparum *translational elongation factor 2 (pfEF2) inhibitors*

The inhibition of the ribosome of *P. falciparum* and additional elements of the translational machinery responsible for the synthesis of protein is one of the most promising targets for creating a novel medication. There are three genomes in *Plasmodium* species: mitochondrial, nuclear and apicoplast. Translational machinery is required for all genomes to operate. Syntheses of proteins as strong antibiotics/inhibitors have had a lot of success in the clinic. Doxycycline, clindamycin and azithromycin are antimalarial drugs that act by inhibiting ribosomes in the mitochondria and apicoplast of *Plasmodium* species, causing these organelles to lose their function (86). The ribosomes of *P. falciparum* live in an evolutionary central ground between eukaryotic and prokaryotic, distinguishing them from the ribosomes of humans and providing a viable new target. PfEF2 is a ribosome constituent that catalyses the ribosome's GTP-dependent translocation along with mRNA and is essential for the synthesis of protein in eukaryotes. PfEF2 has been identified as a potential antimalarial therapeutic target (87, 88). The discovery of sordarin, a natural substance that inhibits the synthesis of fungal protein by blocking the yeast eukaryotic elongation factor 2, proved protein synthesis inhibition.

M5717 is a suppressor of 80S ribosome in interaction with PfEF2 and is presently in Phase I trial (67, 89). It is developed by Merck KGaA, Germany. A common mutation was discovered by whole-genome sequencing of these resistant lines, referring to PfEF2 as the target. This mechanism was discovered by cultivating blood-stage parasites with a five-fold higher EC_{50} than M5717, which resulted in resistance in the 7G8, 3D7 and Dd2 strains. This antimalarial is active against pre-erythrocytic stages, blood stages, and mature female and male gametocytes (90, 91).

Anti-adhesive polysaccharides

The major characteristics of acute malaria are inflammation, microvascular obstruction and parasite-infected erythrocytes. Heparan sulphate is used by the *P. falciparum* parasite to bind to the endothelium and additional blood cells, obstructing blood movement. The

use of drugs to inhibit these aberrant cells and pathogen contacts restores impeded blood flow and inhibits parasite development (92).

Sevuparin (DF02) is an antiadhesive polysaccharide compound. According to various studies, it retains the anti-adhesive qualities of heparin while lacking antithrombin capabilities. It is a sickle cell disease medication that has been found to prevent merozoite invasion into erythrocytes (93, 94). Furthermore, it has been associated with the Duffy-binding like domain 1 (DBL1), a crucial sponsor to the sequestration of infected erythrocytes, which is located at the N-terminal extracellular heparan sulphate binding structure of *P. falciparum* erythrocyte membrane protein 1. A Phase I study in healthy male volunteers revealed the drug was safe and well tolerated. In the Phase I/II clinical study, sevuparin was administered *via* short intravenous infusions to malaria patients with uncomplicated malaria who were also receiving atovaquone/proguanil treatment (94). However, it was discontinued due to non-promising results (NCT01442168) (95, 96).

P. falciparum *glutathione reductase inhibitors*

The malarial parasite contains various glutaredoxins and glutaredoxin-like proteins, which require GSH as co-factors. It offers a powerful redox buffer that maintains intracellular redox homeostasis and is mainly involved in detoxification reactions through GSTs and glyoxalases and provides regulation of protein functions *via* thiol-disulphide exchange reactions (97).

Methylene blue is a methemoglobinemia therapy medication. This drug is being improved at the University of Heidelberg as part of a plan to defend against the establishment of artemisinin resistance and to decrease transmission (98, 99). Methylene blue is an ancient anthelmintic drug that kills blood-stage parasites as well as mature female and male gametocytes of *P. falciparum*. It inhibits *P. falciparum* glutathione reductase and prevents haem polymerization. It exhibited substantial antimalarial activity against all types of malaria in various endemic areas and, in combination with other antimalarials, against *Falciparum* malaria in Africa. Though as a single drug it showed slow action against the asexual parasites of *P. falciparum*, it had a synergistic effect in combination with artemisinin in rapidly clearing the parasites. It is very effective in reducing gametocytes and consequently mosquito transmission. It revealed good tolerance and acceptance with mild gastrointestinal and urogenital symptoms, the major side effects. In 2017, a Phase II study assessed its combination with ACT in comparison with pamaquin-ACT (NCT02851108) (100). It was associated with a higher rate of vomiting and a slightly higher difference in haemoglobin values but there was no difference in the rate of adverse effects. However, asexual *P. falciparum* parasites were rapidly cleared, and a lower prevalence and density of *P. falciparum* gametocytes during follow-up was revealed.

β-haemozoin formation inhibition

In the trophozoite stage of the intra-erythrocytic life cycle, *P. falciparum* ingests 80 % of the host haemoglobin. It occurs *via* protozoan, phagocytic organelle, and cytostome. The cytostome transports haemoglobin into an acidic digestive vacuole where proteolytic enzymes break it down into small peptides in an ordered catabolic process. These peptides are used as nutrients by the parasite. Thereupon, for every molecule of haemoglobin that is consumed, four molecules of haem are released which is very much harmful to the

parasite. Hence, *Plasmodium* crystallizes haem into a non-toxic biomineral, known as haemozoin. Thus, inhibition of the formation of haemozoin is an attractive target to design novel moieties (101).

DM1157 belongs to a family of drugs called "reversed chloroquines" (RCQs), which are used to combat chloroquine-sensitive and chloroquine-resistant strains of malarial organisms. This drug was developed by Design Medix, after being discovered by a group at the State University of Portland in 2010. *In vivo* and *in vitro* reports have demonstrated that the compound is effective in malaria (101).

The *P. falciparum* chloroquine resistance transporter (PfCRT) is identified to be related to chloroquine resistance: alterations to this target promote chloroquine expulsion from the parasite. A family of chemicals known as "reversal agents" has been discovered that can block PfCRT, reducing chloroquine export from the parasite (102).When related to chloroquine (*c*log *P*= 5.1, D6 = 6.9 nmol L^{-1}, Dd2 = 102 nmol L^{-1}), DM1157 had a reduced *c*log*P* value of 3.6, while retaining efficacy (IC_{50}) against both chloroquine-resistant (Dd2 = 1.6 nmol L^{-1}) and chloroquine susceptible (D6 = 0.9 nmol L^{-1}) strains. DM1157 was found to be effective both orally and subcutaneously in a *P. berghei* rodent model. Most notably, an oral dose of 4 × 30 mg kg^{-1} resulted in a > 99.9 % decrease in parasitaemia, with 2/3 of animals cured 30 days after infection. In Indonesia, DM1157 was tested against multi-drug resistant *P. falciparum* and *P. vivax* field isolates and was found to be three times more effective than chloroquine in both species (103).

Chloroquine is recognized to attach to haem and prevent the production of β-haemozoin. Both in *in vitro* and *in vivo*, DM1157 and other RCQ derivatives have been found to act in the same way, although with significantly greater amounts of β-haemozoin suppression. It is now undergoing Phase I studies to assess its safety and pharmacokinetics (NCT03490162) (104).

Pf-encoded sarcoplasmic endoplasmic reticulum calcium ATPase [PfATP6/PfSERCA/ PfATPasa6]

PfATP6, also known as PfSERCA or PfATPase6, is a calcium ATPase gene encoded by the malaria parasite *P. falciparum*. The protein is thought to be a P-type ATPase involved in calcium ion transport (105).

OZ277, a 1,2,4 trioxolane, is a first-generation synthetic ozonide that is as potent as artesunate *in vitro* and has enhanced efficacy in the *P. berghei* mouse model, fully curing animals after three 10 mg kg^{-1} oral doses (105). It is also known as arterolane and RBx11160. OZ277 was the first synthetic ozonide to be tested in the hospital, but when Phase II findings revealed just 70 % effectiveness after a week of therapy, its priority in the development was lowered (106, 107). Nevertheless, since April 2012, OZ277 (RBx11160) has been authorized for use in India as Synriam (Ranbaxy Laboratories) (108), in the form of a mixture of OZ277 and piperaquine. In 2014 approval to market it in Nigeria, Uganda, Senegal, Cameroon, Guinea, Kenya and Ivory Coast has been received. The OZ277+ piperaquine was reported to suppress Pf-encoded sarcoplasmic endoplasmic reticulum calcium ATPase.

Unidentified targets

Actelion Pharmaceuticals and the Swiss Tropical and Public Health Institute (STPHI) collaborated on the development of ACT-451840, a phenylalanine-based molecule, in 2016

(109). It has been proven to cure malaria in the *P. berghei* mouse model at the dose of 3x300 mg kg^{-1} with an ED_{90} of 13 mg kg^{-1}. It had an ED_{90} of 3.7 mg kg^{-1} in the *P. falciparum* SCID mice model. *In vivo* studies revealed the relevance of the delivery route for this compound: a 60 mg dosage in maize oil was equally efficacious as a 100 mg dose in a 10:90 combination of Tween-EtOH/water. It has revealed effectiveness against several phases of the *P. falciparum* parasite and has the ability to be a fast-acting medication with a longer half-life. It has been demonstrated to be effective against many stages of the parasitic life cycle of both *P. falciparum* and *P. vivax* (110). The mode of action is thought to be new but is presently unidentified. The first-in-human investigations were finished in 2014 [NCT02223871] (111) and are pending a judgment on whether or not to move further.

AN13762 emerged as the lead compound in 2017 after Anacor Pharmaceuticals began a discovery process in 2010 with a new group of benzoxaborole antimalarial derivatives (111). It showed good activity *in vivo* and *in vitro*, multi-strain efficacy, and the capability to act as a fast-acting medicine. When compared to artesunate, the compound exhibits similar *in vivo* clearance rates. There is no intrinsic genotoxicity and cytotoxicity in human cell lines at doses up to 100 mol L^{-1} (112). The exact mechanism of action for AN13762 is uncertain; however, preliminary molecular docking investigations on the hit chemical AN3661 revealed the *P. falciparum* cleavage and polyadenylation specificity factor (PfCPSF3) as a possible target (113).

SC83288 is a derivative of amicarbalide with a unique chemotype for existing antimalarials, with a possible novel mode of action, and the capacity to treat severe malaria intravenously. It was created by a group at Heidelberg University in 2017; it is rapid-acting and may be administered by the parenteral route (114). It has been found to be effective against a variety of strains that are drug-resistant with IC_{50} values less than 20 nmol L^{-1}, as well as early phase (I–III) gametocytes (IC_{50} = 199 nmol L^{-1}), but not late-stage gametocytes (IV and V). It has a very good safety profile, with no cytotoxicity, genotoxicity or binding to hERG. It was capable of treating the infection completely in the *P. vinckei* rat malaria model when administered intraperitoneal at a dose of 20 mg kg^{-1} once per day; for four consecutive days fully cured the infection with no recurrence of infection. On the other hand, it is entirely ineffective against *P. berghei.* While the specific process is uncertain, PfATP6 has been identified as a possible target through the production of resistant clones. On the other hand, it has been demonstrated not to inhibit this target directly, indicating that PfATP6 may have a minimum direct function. Another potential mechanism of resistance has been discovered in PfMDR2, which aids in drug clearance from the parasite. SC83288 has been tested against artemisinins, and demonstrated no cross-resistance, emphasizing its ability as a substitute to artesunate to treat malaria in severe conditions of malaria (115). It is the lone medicine in preclinical development for severe malaria (114).

Tafenoquine is a 3-phenoxy-substituted 8-aminoquinoline (WR238605) that is 4–100 times more potent and has an extended half-life than primaquine. It was discovered in 1993, and is presently being tested as a single-dose anti-relapse drug in a dose range Phase II study (116).

NPC1161B, an 8-aminoquinonoline, appears to be an effective antimalarial; however, it is uncertain if it will have the same degree of side effects as primaquine. The University of Mississippi is developing this drug for relapse prevention in the late preclinical stages (117). Phase I study will determine whether this single enantiomer drug has a lower haematological toxicity profile than tafenoquine.

The substituted 4-aminoquinoline AQ-13 was originally discovered in 1946 (111). Although only the amine side-chain differs from chloroquine (CQ), this change has been associated with improved effectiveness against CQ-resistant bacteria (118). It has previously been in clinical trials for almost a decade. In symptomatic adult men in Mali, it was shown to be non-inferior to artemether-lumefantrine in a short proof-of-concept trial published in 2017 (119). It is expected to be comparable to ferroquine with regard to action and potency. In the Mali research (95 % CI in parentheses), the mean elimination half-life of AQ-13 was 3.9 days (2.4-5.3 days) in patients with malaria, in comparison to an earlier finding of 14.3 days (6.2–39.3 days) in healthy adult volunteers (120). It has a comparable mechanism and pharmacokinetic characteristics to chloroquine (120, 121). The most recent Phase II study for AQ-13 was completed in late 2017 (NCT01614964) at Tulane University and the University of Bamako (119, 122). As there is no indication of any subsequent active studies, the compound's position is unknown.

Summary

No single medication is effective against all *Plasmodium* species or malaria symptoms that can occur in various patient populations. Thus, population-specific tailoring is needed while considering malaria treatment. Various target product profiles are adapted to control and eliminate malaria in multiple populations. However, the main aim is to ensure a steady supply of effective blood schizonticides and to maximize their therapeutic life. Recent advancements in the development of technologies for screening for hypnozoiticidal and transmission-blocking compounds may result in the identification of more medicines in the coming years. The failure of ACTs in Southeast Asia has prompted a rethinking of malaria combination therapy. Thus, rather than relying solely on triple combinations of existing drugs to improve cure rates in areas where resistance has already developed, it is wise to introduce them (triple combination of existing drugs) in countries where resistance has yet to emerge. This ensures that all new combinations developed contain three or more drugs for increasing the rate of curing malaria. This can be the goal for future generations of novel antimalarial combination therapies.

The discovery of novel mechanisms of action (MoA) will open the road for future antimalarial drug development. The application of *in vitro* evolution and whole-genome analysis (IVIEWGA), which employs genome-based target discovery approaches on molecules found from more common phenotypic screens, has enabled the discovery of further new MoA. If individuals are to continue to be able to tackle this formidable disease, originality and ingenuity in hit-to-lead efforts will be required in all future developments.

CONCLUSIONS

The recent increase of malaria parasite resistance to current treatments is extremely alarming, as it is restricting the capacity to control this devastating illness. However, as discussed above, several innovative techniques for antimalarial drug development are now being evaluated. Recent advances in the rate of advancement in this domain imply that, with proper support for antimalarial drug discovery, innovative techniques should lead to the creation of new antimalarials with novel mechanisms of action in the near future.

After decades of clinical research, RTS,S/AS01 (Mosquirix) vaccine has reached a significant milestone as the first malaria vaccine to be evaluated in Phase III clinical trials and is currently being tested in implementation studies. When WHO, Gavi, and other organizations examine the risk/benefit, cost-effectiveness, and practical concerns of vaccine implementation capacity in resource-limited contexts, they should also address the possible effects on people living in endemic regions' health conditions, poverty and social justice.

High-throughput screens have found numerous new chemotypes that have turned into extremely promising antimalarial candidates in recent years. Besides effectiveness, pharmacokinetic compatibility, safety issues and drug resistance would all be important considerations in the development of a successful antimalarial agent. Understanding the processes causing antimalarial drug resistance might also aid us in preventing resistance to newer antimalarial drug generations in the near future.

Abbreviations, acronyms, symbols. PfPI4K – phosphatidylinositol 4-kinase, PIKs – phosphoinositide lipid kinases, PI3K – phosphoinositide 3-kinase, PI4K – phosphatidylinositol 4-kinase, PfATP4 – P-type cation-translocating ATPase ATP4 of *P. falciparum,* TAPs – triaminopyrimidines, PfDXR – *P. falciparum* 1-deoxy-D-xylulose-5-phosphate reductoisomerase, ACT – artemisinin-based combination therapies, pfEF2 – *P. falciparum* translational elongation factor 2, RCQs – reversed chloroquines, PfCRT – *P. falciparum* chloroquine resistance transporter, RBC – red blod cell.

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