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Review Article
Quinazolinone Derivatives as a Potential Class of Compounds in Malaria Drug Discovery

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Abstract

Malaria causes over a million deaths each year (2 percent of the global total of deaths), with hundreds of millions of clinical episodes per annum. The greatest challenge to malaria control and eradication is the emergence of malaria parasites that are resistant to antimalarial drugs. The development of resistance to conventionally used anti-malarial drugs, such as chloroquine (CQ) and Sulfadoxine-Pyrimethamine (SP) has been documented. To counter this WHO recommended that artemisinin-based combination therapy (ACT) should be used for treating uncomplicated *Plasmodium falciparum* malaria to ensure efficacy and reduce the emergence of drug-resistant parasites. Currently available antimalarial drugs are ineffective and their number is declining because of the widespread resistance. Thus, the new antimalarial agent is in urgent demand; however, the development of new antimalarial drug presents challenges due to resistance, toxicity, minimal efficacy of those on the pipeline and high cost of drug research. Identification of novel drug targets and design of new chemical compounds acting on new targets is important to control the emergence of resistance to existing drugs. In this regard, a natural product derived synthetic analogs of febrifugine containing quinazolinone scaffold can be considered best. Therefore, quinazolinones are potential compounds in seeking for novel drugs that act against the malarial pathogen. Hence, in this review compounds containing quinazolinone structure and possessing antimalarial activities are covered.

Key words: Quinazolinone, malaria, *Plasmodium falciparum*, drug discovery, active compounds

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Malarial symptoms are described in ancient Chinese and Sanskrit medical texts and Hippocrates referred to the disease in the 4th Century BC[1]. It was associated with 'bad air' by the 18th century Italians meaning malaria from where the name malaria is derived[2,3]. In children under age five malaria accounts for almost 1 in 10 deaths worldwide and 1 in 5 deaths in Sub-Saharan Africa (SSA), which makes it one among the leading killers[4]. More than 80% of deaths due to malaria occurs in SSA where 90% accounts for children under five[5]. Malaria causes over a million deaths each year (2 percent of the global total of deaths), with hundreds of millions of clinical episodes per annum[3]. Malaria also places a tremendous burden on national health systems and individual families[6]. In the governmental budget proportions allocated to health system ranges from 5% in Africa, Asia and the Eastern Mediterranean Region, to well over 20% in some countries in Americans[7]. The economic impact of malaria is disproportionately felt by the poor. A study in Tanzania indicated that the death due to acute fever among children of the poorest families was 39% higher than among the wealthiest children[3]. The Plasmodium parasite, responsible for causing malaria, is a protozoan with four identified species which causes human malaria via a female Anopheles mosquito as a vector, namely: *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*[2]. Even though these four species of plasmodium parasite can infect human and cause malaria, *P. falciparum* is the riskiest and potentially threatening[8]. However, Plasmodium vivax also creates significant human morbidity, suffering and economic loss, being responsible for 70 million to 80 million cases of the global malaria burden each year[9].

Epidemiology of malaria: There are 109 malaria endemic countries in tropical and subtropical zones, across all countries except Antarctica and Australia. In these countries, the intensities of transmission vary from very low to extremely high[10]. Human malaria infections caused an estimated 214 million clinical cases and 438,000 deaths in 2015. The relatively low case-fatality rate, even for the most virulent species, *P. falciparum*, is partly due to patient immunity acquired after repeated infections but is also attributable to the timely provision of effective malaria drugs[11]. The SSA region is the hardest hit by malaria comprising endemic areas of stable transmission[12]. The millennium development goal Target 8 "Global partnership for development" ("Have halted by 2015 and begin to reverse the incidence of malaria and other major diseases [including TB]") were to be met before 2015[13]. Whereas, the target set under Millennium Development Goal 6 was to be reached by 55 countries that are on track to reduce their malaria burden by 75%. Despite progress in the reduction of malaria morbidity and mortality in recent years, malaria remains one of the leading health problems in endemic countries[14]. Global malaria death estimates in the 1980s and 1990s range from 800 000 to almost 2·5 million; in the 2000s, the range is from 650 000 to more than 1 million. Studies showed that malaria is the underlying cause of death for 1.24 million individuals, including 714 000 children younger than 5 years and 524 000 individuals aged 5 years or older in2010[15]. Children in sub-Saharan Africa and Southeast Asia have the highest risk of contracting and dying from malaria[16]. Being a curable disease, early diagnosis and prompt treatment is a key strategy to reduce morbidity and mortality from malaria. A core component of any malaria elimination program is to ensure that all patients with malaria are rapidly diagnosed, have access to highly effective antimalarial drugs[14]. Much of this morbidity and mortality could be avoided if drugs available to patients were efficacious, high quality and used correctly[16]. During the past 5 years, substantial progress has been made in the fight against malaria, with a 31% reduction in global malaria deaths[15].

Life cycle of malaria: Malaria parasites live in mosquito and human hosts and go through several developmental and transmission phases on the way to causing disease in humans [17]. Malaria is a mosquito-borne infectious disease transmitted by a parasitic protozoan in the Plasmodium genus[18]. The malaria parasite is a single-cell protozoan (plasmodium). Members of the genus Plasmodium have a complex life cycle, Fig. 1. A sexual stage occurs within the Anopheles mosquito, while asexual stages take place in the host. Malaria is transmitted from one human to another through the insect vector, the female Anopheles mosquito[19,20]. Only the female mosquito bites because it needs blood to produce eggs. Mosquitoes bite a variety of hosts-birds, dogs, horses, cattle and people[18]. The infection of human erythrocytes is ultimately responsible for all the clinical pathologies associated with the disease[17].

Initially, when female Anopheles mosquito bites an infected human, it gets infected and intakes gametocytes. The sexual transformation of gametocytes into ookinetes and ookinetes into oocyst takes place inside the midgut of

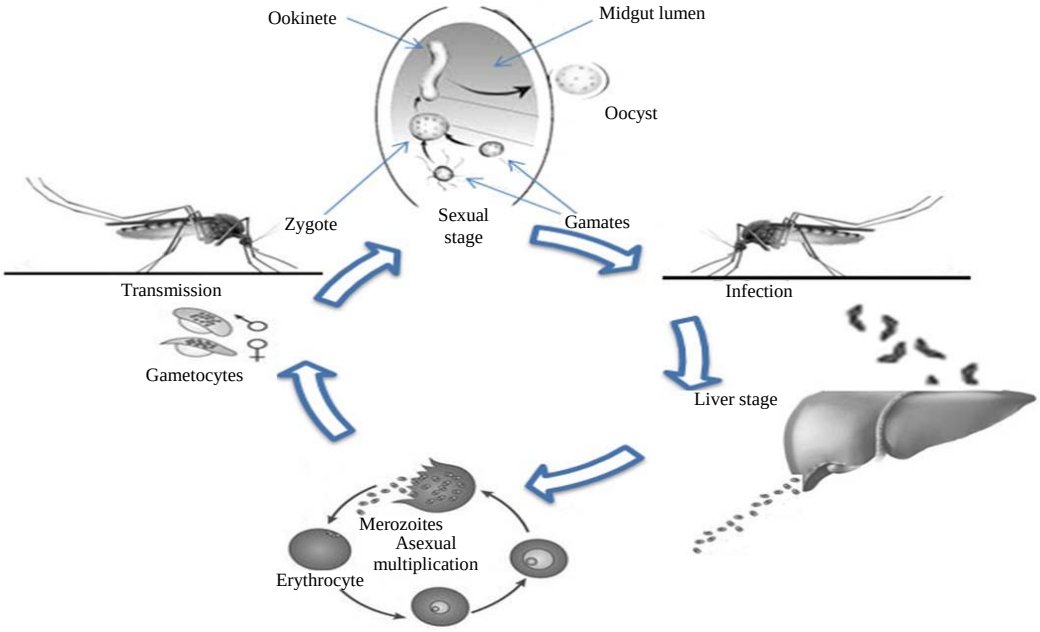


Fig. 1: Life cycle of the malaria parasite

mosquito. Finally, sporozoites are developed from oocysts, which eventually burst, releasing sporozoites into the salivary gland[21]. At the mosquito's next feeding, the sporozoites are injected into the blood stream of another human to begin the asexual stages. Once the mosquito inoculates the parasites (sporozoites) into the bloodstream, the parasites invade the liver within 30 min and start replicating there (schizonts). Also, *P. vivax* and *P. ovale* can remain dormant in the liver (hypnozoites, not shown in Fig. 1) and cause relapses years after the initial infection[22]. After a relatively brief residence (less than an hour) in the systemic circulation, the sporozoites invade liver parenchymal cells, where they divide and develop asexually into multinucleated schizonts. These are the primary exoerythrocytic tissue forms of the parasite. When this primary stage of development is completed (6-2 days), the schizonts will rupture, releasing merozoites into the blood. These latter forms invade host erythrocytes, where they again grow and divide asexually (erythrocytic schizogony) and become red cell schizonts. Some of the parasites differentiate into sexual (male and female) forms or gametocytes. If the diseased human is bitten by a mosquito at this time, the gametes will be taken up into the organism's gut to repeat the reproductive cycle[19].

Prevention and control of malaria: Since the launch of the Roll Back Malaria initiative by WHO in 1998 and particularly in the past few years, malaria control has intensified in endemic countries, supported by a greatly increased investment of financial resources and technical assistance from the international community[10]. Three main strategies are presently attempting to control the disease: Vaccination, vector control and parasitical drugs. Of these, parasitical drugs are currently the main line of disease control until vaccination or mosquito control can be implemented more successfully[23]. To eradicate malaria, achievable milestones must be set. The publication of the Global Malaria Action Plan (GMAP) by the WHO set some of those milestones; for example, a tenfold reduction in malaria incidence and deaths by 2030 (compared with 2015). The first GMAP was published in 2008 and covered the period until 2015. More recently, input and consultations are being sought from experts and regions for GMAP2. Both GMAP2 and the Global Technical Strategy for Malaria (coordinated by the WHO) will cover the 10 years between 2016 and 2025[24]. On Oct 17, 2007, Bill and Melinda Gates called for complete eradication to be adopted as the new goal for the age-old fight against malaria, with the Director-General of WHO, Margaret Chan, promptly echoing their conviction. Two crucial questions stand out for those organizations that will now begin striving towards malaria eradication. When and how can it be achieved?[24,25].

During the past decade, a range of organizations has led a global movement to combat malaria. Accurate assessments of the levels and time trends in malaria burden are crucial for the evaluation of progress towards goals and the focusing of future efforts[15]. A report released by WHO finds that the global burden of malaria remains enormous but that access to malaria control interventions, especially bed nets in Africa,

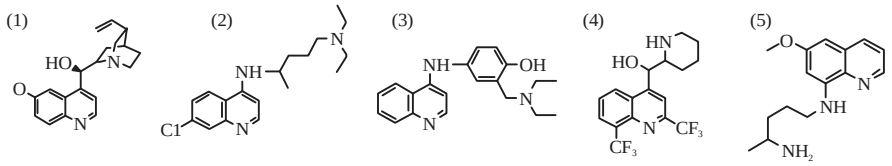


Fig. 2: Chemical structures of some quinoline derivatives

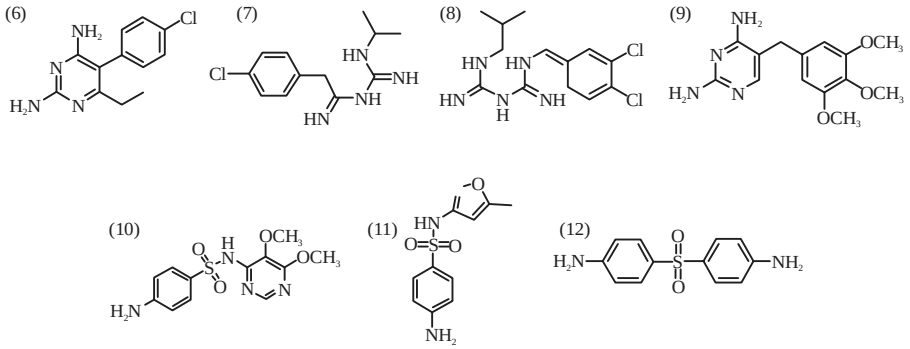


Fig. 3: Chemical structures of antifolate drugs

increased sharply between 2004 and 2006[26]. As a result of malaria control efforts across the world, 80 countries are now in the phase of malaria control; 12 countries are making the program transition to elimination; 11 countries are operating malaria elimination programs and 6 countries are actively engaged in preventing re-introduction of malaria[10]. Despite extensive control efforts, the incidence of the disease is not decreasing in most malaria-endemic areas of the world and some it is increasing[27].

Drugs for treatment of malaria: Currently available antimalarial agents comprise classes of drugs classified based on their chemical structures and mechanism of action[28]. The number of antimalarial drugs in use today is limited due to the wide spread of resistance. Those in use to date are the quinine derivatives, the artemisinins and antifolate combination drugs.

Quinoline derivatives: The quinoline derivatives have long been used for the treatment of malaria, the first one being quinine which is isolated from the bark extract of Cinchona trees. In the 17th century, the pulverized bark was widely used in Europe. As the quest for new compounds for treating malaria was on the rise the first 4(8), -aminoquinolines derivatives were developed[29]. The success of the antimalarial aminoquinoline drugs has been based on excellent clinical efficacy, limited host toxicity, ease of use and simple, cost-effective synthesis [30]. The 4-aminoquinoline derivatives of quinine (1), shown in Fig. 2 are chloroquine (2), amodiaquine (3) and mefloquine (4), whereas primaquine (5) is an 8-aminoquinoline derivative of quinine[31]. The mode of action and mechanism of resistance of these derivatives is not fully understood since much of the focus is directed to the identification of novel chemotherapeutic agents[32]. The quinolones are known to inhibit the polymerization of heme and prevent disposal of polymers from the food vacuole to the cytoplasm where hemozoin is formed. This leads to antiparasitic accumulation of free heme, which is highly toxic to the parasite[33].

Antifolate combination drugs: Antifolates are various combinations of dihydrofolate reductase inhibitors (proguanil (6), pyrimethamine (7), chlorproguanil (8) and trimethoprim (9)) and sulfa drugs (sulfadoxine (10), sulfamethoxazole (11), dapsone (12) and others), Fig. 3. Most commonly used combinations include sulfadoxine-pyrimethamin and sulfamethoxazole-trimethoprim. Currently, an antifolate combination drug, dapsone and chlorproguanil was tested and has a more potent synergistic antimalarial action than other drugs such as sulfadoxine-pyrimethamine[31].

Antibiotics: Tetracyclines (13 and 14) Fig. 4, usually in conjunction with quinine (1), have been reported to be suppressive in human malaria and proved to be of value as an additional drug for the radical cure of chloroquine-resistant falciparum infections. Clindamycin (15),

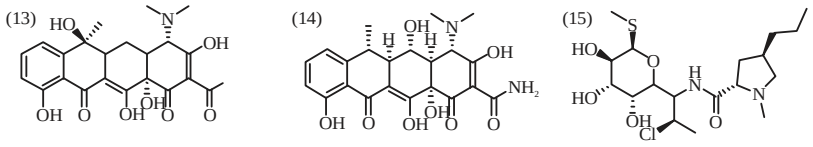


Fig. 4: Chemical structures of antimalarial antibiotics

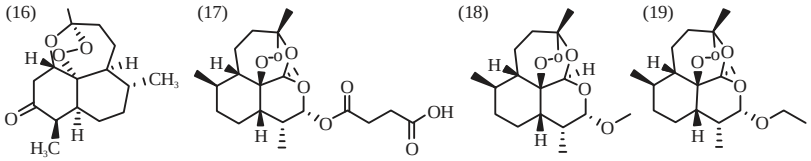


Fig. 5: Chemical structures of artemisinin and related compounds

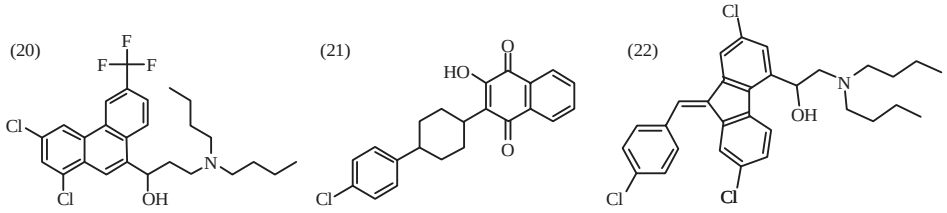


Fig. 6: Chemical structures of napthoquinone, phenanthrene and fluoromethanol derivatives

alone or in combination with quinine, has also been used for the treatment of CQR falciparum malaria in Thailand with good results, despite the side effects. In non-immune individuals, its efficacy has not been fully established [34].

Artemisinin compounds: Artemisinin (qinghaosu) (16), artesunate (17), artemether (18) and arteether (19) have all been used alone or in combination therapy as antimalarial agents[35]. Artemisinin (16) Fig. 5, which is present in the extracts of the aerial parts of the plant Artemissia annua, has been utilized for more than a millennia for fever and rediscovered as antimalarial agent[36]. The emergence of multidrug-resistant strains of *P. falciparum* and chloroquine-resistant strains of *P. vivax* in malaria endemic areas emphasize on preparing new, efficient and affordable antimalarial medications. Thus, Artemisinin Combination Therapy (ACT) was recommended by WHO for successful treatment of uncomplicated malaria[37].

Other compounds with antimalarial activity: Halofantrine (20), which consists phenanthrene-methanol and illustrated in Fig. 6, is active against the erythrocytic stage of malaria. In areas of multi-drug resistant falciparum malaria, halofantrine is mainly recommended. Atovaquone (21), which is a hydroxynaphthoquinone, is most widely used for treating opportunistic infections in immune-compromised patients. It is also effective against CQR *P. falciparum*. However, it is usually given in combination with proguanil to avoid the development of resistance. Lumefantrine (22), a fluoro methanol compound, is being produced as a fixed combination tablet with artemether [25][31].

Antimalarial drug resistance: Malaria continues to pose a challenge given its resurgence and problem of drug resistance. Chloroquine resistance in *P. falciparum* was first detected in Thailand in 1962 and India in 1973[38]. Since 2000, malaria-associated mortality has been reduced by more than 50% but emerging drug- and insecticide-resistance continues to pose a major threat[24]. The development drug resistance has jeopardized the efficacy of every antimalarial drug in use today. In fact, the history of malarial drug developments parallels the history of drug resistance development[39]. The WHO defined antimalarial drug resistance as the "ability of a parasite strain to survive and multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within a tolerance of the subject[21]". Broadly, there are two ways in which malaria parasites have become resistant to antimalarial drugs. Resistance against antifolates and atovaquone has arisen by mutations in drug targets that reduce their sensitivity; in these examples, an understanding of the molecular basis of drug action has been a prerequisite for

elucidating the mechanism of drug resistance. Other drugs such as chloroquine and mefloquine may not have parasite-derived protein targets that can mutate, allowing parasites to escape from therapies. For these classes of antimalarial drugs, the parasite has become resistant through mutations in transporters involved in determining drug disposition within the intraerythrocytic parasite and its organelles. This effectively reduces drug concentrations at critical (presumed) target sites[40].

The development of resistance to conventionally used anti-malarial drugs, such as chloroquine (CQ) and Sulfadoxine-Pyrimethamine (SP) has been documented[14]. Chloroquine strength and high-level sulfadoxine-pyrimethamine resistance in P. falciparum both originated in South-East Asia and subsequently spread to Africa[37]. Currently, scientists reported that they had found the first evidence of resistance to the world's most efficient drug coartem (lumefantrine and artemether) for treating malaria in western Cambodia[31]. Consequently, another change to artemether-lumefantrine was suggested in 2004[41]. WHO recommended that artemisinin-based combination therapy (ACT) should be used for treating uncomplicated Plasmodium falciparum malaria to ensure efficacy and reduce the emergence of drug-resistant parasites[14,24]. Several ACT combinations available include artemether-lumefantrine (AL), artesunate-amodiaquine (AS/AQ), artesunate-mefloquine (AS/MQ), artesunate-chlorproguanil-dapsone (AS/CD), artesunate-sulphadoxine-pyrimethamine (AS/SP), dihydroarte misinin-piperaquine (DA/PQ), artesunatepiperazine (AS/PZ) and artesunate-atovaquone-proguanil (A/AP). Out of these ACT combinations WHO recommended AL, AS/MQ, AS/AQ and AS/SP. Several countries have now adopted ACTs as the first line agents for uncomplicated malaria[42].

The concept of combination therapy relies on the rapid onset of schizonticidal action to rapidly reduce parasitaemia, leaving the residual parasitaemia to be cleared by high concentrations of the partner drug[14]. However, there is a constant threat of malaria evolving resistance to available drugs and recent observations that resistance may have arisen to the most widely used antimalarial drug class, the artemisinins[11]. Although ACTs are designed to reduce the chance of artemisinin drug resistance development, there are considerable concerns that this may already have occurred. For instance, there is now mounting evidence that the efficacy of artemisinin derivatives is reduced in Southeast Asia, where artemisinin derivatives have been used for a long time as monotherapies[43].

The greatest challenge to malaria control and eradication is the emergence of malaria parasites that are resistant to antimalarial drugs[21]. The major drug resistance problem occurs with *P. falciparum*, which is of particular concern because of the enormous burden of disease caused by this species, its lethal potential, the propensity for epidemics and the cost of candidate replacement drugs for areas with established drug resistance[37]. Whereas, other less lethal strains, *P. ovale* and *P. vivax*, can exist as latent hypnozoites in the liver which can initiate a relapse months to years after the initial infection[44]. Plasmodium falciparum can be clinically resistant to all monotherapy with current antimalarial drugs. In South-East Asia, the combination of quinine and tetracycline is the treatment of choice for multidrug-resistant *P. falciparum* infections[45].

Future drug candidates that are developed with the aim to circumvent or stall resistance will help produce the next generation of therapies that prevent or reduce mortality[39]. Any new antimalarial drug that is developed will ultimately be delivered as a combination therapy to delay the likely emergence of parasite resistance. Compounds in combinations should ideally act against different cellular targets to offset the likelihood that a single parasite genome-amplification event could render parasites resistant to both drugs[46]. Furthermore, poor-quality antimalarial drugs are very likely to jeopardize the unprecedented progress and investments in control and elimination of malaria made in the past decade. Of the many public health consequences of poor-quality antimalarial drugs, drug resistance is a particular concern. Low concentrations of active pharmaceutical ingredient in a bad quality antimalarial drugs can result in sub-therapeutic concentrations of drug *in vivo*, which contributes to the selection of resistant parasites [16]. Thus, we need to protect the medicines we have by ensuring correct deployment and continual vigilance to stop the production and distribution of counterfeit medicines. Even with fixed-dose combinations, there remains a risk of resistance emerging and therefore a need for new medicines. New molecules should shorten the duration of treatment and increase compliance and also prevent the transmission of the parasite back to the insect vector[24]. Therefore, there is an urgent need to gain information about the basic mechanisms through which antimalarial drugs act and resistance is generated in order not only to identify new targets and develop new drugs with novel mechanisms of action but also to take advantage of the mode of action of available drugs and make better use of them[47].

Recent advances in antimalarial drug development: Mefloquine is the only synthetic antimalarial agent discovered over the past 30 years. Whereas, artimisisin, which is

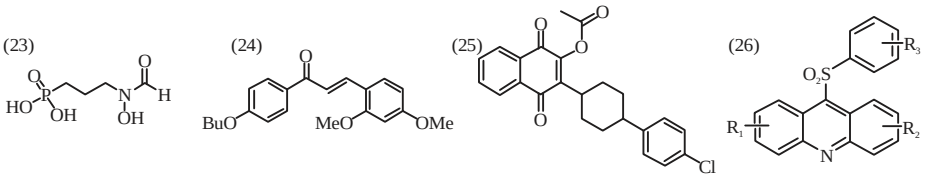


Fig. 7: Chemical structures of fosmidomycin, chalcone, naphthoquinone and arylsulfonyl acridinyl derivatives

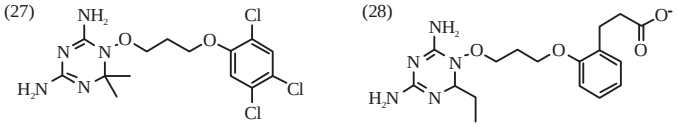


Fig. 8: DHFR inhibitors

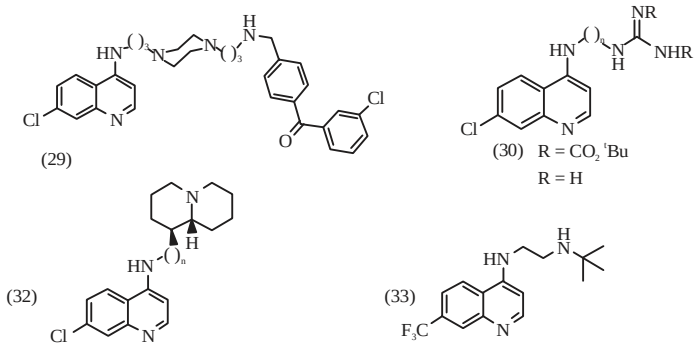


Fig. 9: 4-aminoquinoline antimalarials

discovered in this period is a natural product, whose medicinal actions have been known for over 2 millennia[48]. However, the sudden resurgence of malaria and emergence of malarial drug resistance in many countries of the world have made the synthetic efforts toward new antimalarial drugs very important[28]. Recently some synthetic compounds are reported to have potent antimalarial activity against different Plasmodium species.

Clinical trials conducted with fosmidomycin (23) in combination with clindamycin (15) or artesunate (17) have shown high efficiency in the treatment of acute, uncomplicated malaria[48]. Recently synthetic chalcone analog, 2,4-dimethoxy-4 butoxychalcone (24), was reported to have excellent antimalarial activity[49,50]. In addition to this, the antimalarial activity of naphthoquinone derivatives (25), Fig. 7, has been widely reported. Acylation of the hydroxy moiety of atovaquone (21) led to a compound exhibiting similar activity as atovaquone (21) and more active than chloroquine (2) and quinine (1) against *P. falciparum*[51]. Arylsulfonyl acridinyl derivatives (26), having an acridinic ring and aryl sulfone moiety together are also reported to have an antimalarial activity on *P. falciparum*[52]. Structure-based drug design resulted in P218 (28), a DHFR inhibitor active against all clinically relevant mutations. P218 (28) combines the pyrimidine ring of pyrimethamine (Fig. 8), which brings potency and the linker of the DHFR inhibitor WR99210 (27), which tolerates mutations due to its flexibility. The P218 is more potent than pyrimethamine against DHFR in the wild-type strain TM4 (IC50 = 4.6 and 58 nM, respectively) as well as in the quadruple mutant strain V1/S (IC50 = 56 and >100,000 nM, respectively)[22]. Recently, a series of bisquinolines (29, 30, 31, 32 and 33, Fig. 9), where the 4-aminoquinoline part of chloroquine was retained and bisamide links joined the two units, have been synthesized and screened against CQS and CQR strains of *P. falciparum in vitro*. The resistant indices for all the compounds were found to be lower than that of CQ. The position of attachment and length of the linker chain had marked effect on the activity[33].

Plasmepsins: Potential drug targets for antimalarial drugs: With the technological developments of the past few decades, the ability to search for new drug candidates has rapidly accelerated. Advances in robotic automation and liquid

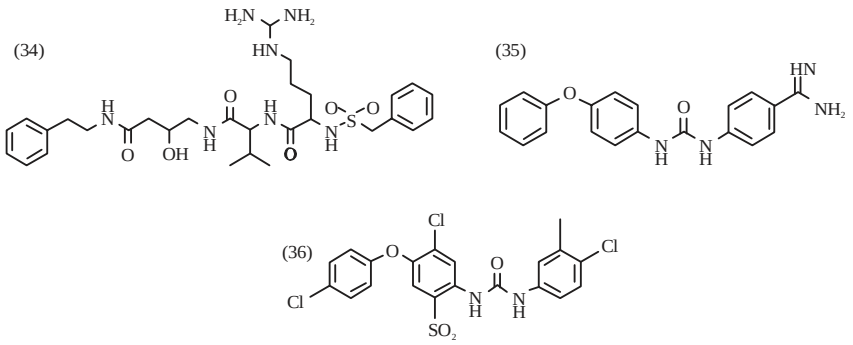


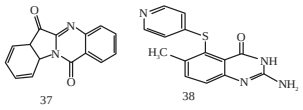
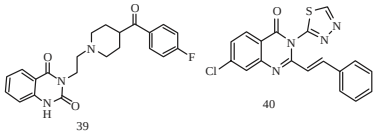
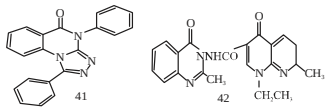
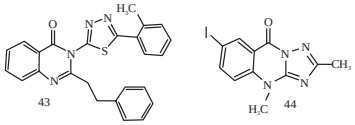
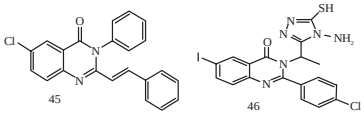
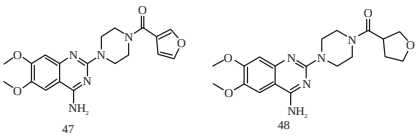
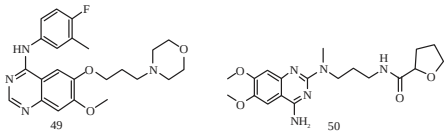
Fig. 10: Plasmepsin inhibitors

handling, coupled with the ever-shrinking scale at which these assays are performed, have facilitated ultra-HTS of enormous compound libraries[46]. Identification of novel drug targets and design of new chemical compounds acting on new targets is nowadays widely used approach all over the world to combat issue raised by the emergence of resistance to existing drugs. Therefore, investigating inhibitors specific for the new target proteins of malaria parasite has been exploited for drug target identification and currently studies are underway[53]. Thus far, the genetics underlying the new resistance against artemisinins are becoming increasingly understood and this knowledge is being used to set up panels of parasites against which new drug candidates can be tested[54]. Detecting the different genetic basis for malaria not only reveals the disease pathogenesis but also facilitates discovering new targets for anti-malaria drugs[55]. There is an argument to be made that hitting the sexual stages is useful- this blocks transmission and may delay resistance since there are several orders of magnitude fewer parasites from which to select mutants[56]. Given that the liver stage would be highly desirable for candidate drugs to have activity against hepatic and sexual forms of the malarial parasite, it is surprising that few clinical trials, to date, have examined whether gametocyte carriage can be reduced following drug treatment[57].

Because proteases play important roles during parasite infection of and development in the mosquito, they were considered as potential transmission-blocking targets. Transcriptomic data suggested that Plasmodium aspartic proteases, known as plasmepsins are expressed in sexual stage parasites[58]. There are 10 plasmepsins in *P. falciparum*. Other Plasmodium species have only seven; they have only one digestive vacuole plasmepsin instead of the four in falciparum[56]. Plms I-IV are the most studied isoforms owing to their expression and important role during the blood stage. Whereas Plm II remains the best-studied isozyme, Plms V-X remain considerably less understood; recent studies show that Plm V functions as Plasmodium export element (PEXEL)-cleaving protease for protein export from the food vacuole to the erythrocyte to enable the development of *P. falciparum* parasites[59,60]. Expression of Plm I, II, IV, V, IX, X and HAP occurs in the erythrocytic stage, whereas Plm VI, VII and VIII are expressed in the exo-erythrocytic stages. The digestive vacuole plasmepsins are 55-75% identical to each other but 10-25% identical to the other plasmepsins[61]. It has been shown that the general aspartic proteinase inhibitor isovaleryl pepstatin is a tight binding (sub-nanomolar K_i) inhibitor of plasmepsin I and plasmepsin II. However, this compound inhibits most aspartic proteinases and so has no value as a potential drug[62]. Plasmepsin V is an aspartic acid protease expressed by protozoan parasites of Plasmodium species and it has a crucial role in recognizing and processing effector proteins for export to host cells. The most potent plasmepsin V inhibitor to date, WEHI-916 (34), has a high affinity for the endogenous enzyme but has a modest ability to inhibit *P. falciparum* growth[63]. Other small nonpeptide inhibitors of Plm II based on a diphenylurea unit were discovered by a screening of compounds in the Walter Reed chemical database. BothP. Falciparum Plm II and P. Vivax plasmepsin were used in the screening assays. Compounds 35 and 36, Fig. 10, were identified as the lead inhibitors with great high-plasmepsin potency[61].

Review of quinazolinones: Various structural class of compounds has been reported to possess antimalarial activities such as chalcones[51], thienopyrimidinone[64], quinolones, quinazolins[47], enaminones[65], acridines[48]. Among the different heterocyclic structures which have been studied for their antiplasmodial properties, quinazoline has quite recently shown increasing interest[66]. Quinazolinones are versatile nitrogen heterocyclic compounds, displaying wide applications including anticonvulsant, sedative, tranquilizer, analgesic, antimicrobial[67], anesthetic, antioxidant[68], anticancer, antiviral[67], anti-TB[69], antihypertensive, anti-inflammatory,

Table 1: Some 4 (3H)-quinazolinone derivatives and their biological activity

4 (3H)-quinazolinone derivatives	Biological Activity Ref.
	(37) Antimalarial agents[74] (38) Anticancer agents[75]
	(39) 5-HT, receptor antagonist[76] (40) Diuretic[77]
	(41) Antimicrobial[71] (42) Antibacterial and antifungal agents[78]
	(43) CNS depressant and anticonvulsant[79] (44) Antihypertensive[80]
	(45) Antimitotic agents[81] (46) Analgesic and Anti-Inflammatory[82]
	(47), (48) Antihypertensive[67,73]
	(49) Anticancer[73] (50) Benign prostatic hyperplasia (BPH)[73]

antimalarial, diuretic and muscle relaxant properties, Table 1. Increased efforts in antimalarial drug discovery are urgent to develop safe and affordable new drugs to counter the spread of malaria parasites that are resistant to existing agents. Furthermore, quinazolinones substituted at 2 and 3-position plays a pivotal role in the antimalarial activity[70-72]. Moreover, there are marketed quinazoline derivatives such as prazocin and trazocin as antihypertensive agents[67,73] and Gentifib as anticancer[73] and alfuzosin for treating benign prostatic hyperplasia, which gives hope to research in classes of compounds[73].

Febrifugines derivatives and other important quinazolinones: The isomeric alkaloids (+)-febrifugine (51) and (+)-isofebrifugine (52), Figure 11 are found in the roots and leaves of the Chinese medicinal plant Dichroa febrifuga (also called Chinese quinine) belonging to the Saxifragaceae family[83]. Several bio-active natural products such as febrifugine (51) and isofebrifugine (52) contain quinazolinone moieties with potential antimalarial activity[83]. Compound 53 with an extra nitrogen atom in the position 5 or 6 of the aromatic ring (IC50= 1.2 nM) possessed antimalarial activity comparable to 51, while compound 54 (IC50 = 0.33 nM) with difluoride attached to C-5 and C-6 was superior to febrifugine. These compounds were 100 times less toxic than febrifugine[84]. In one study it was reported that antimalarial activity of a series of febrifugine derivatives bearing structural modifications at (i) the quinazoline ring, (ii) the linker or (iii) the piperidine ring. Thienopyrimidine analog 55 exhibited potent antimalarial activity and a high therapeutic selectivity both *in vitro* and *in vivo* [EC50 = 0.00306 lg mL^{-1} (*P. falciparum* FCR-3), ED_{50} = 2.95 mg kg^{-1}, LD_{50} = 88 mg kg^{-1} (*P. berghei*)][85]. The fluorinated analog 57, which was designed to prevent metabolic oxidation, actually showed higher antimalarial activity than that of (+)-febrifugine (51) but it also proved more toxic. On the other hand, analog 55 showed high *in vitro* and *in vivo* antimalarial activity. However, the other

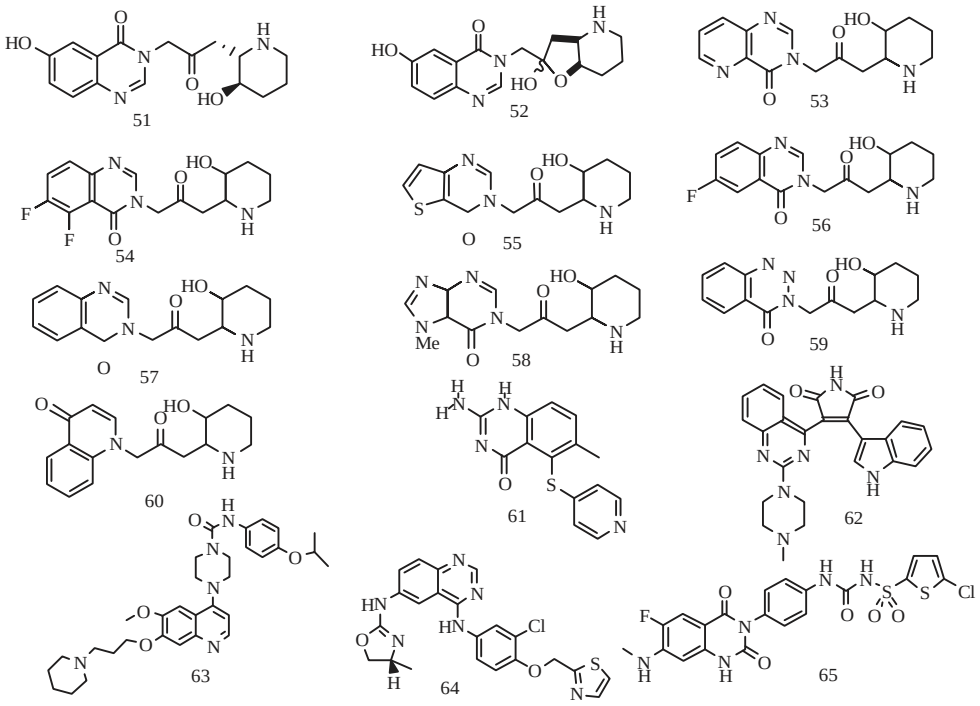


Fig. 11: Quinazolines, Quinazolinones, and analogs of febrifugine

analogs, 57-59, showed little antimalarial activity with total loss of antimalarial activity being observed for 60. The complete loss of antimalarial activity in analog 60 indicates that a basic nitrogen group within the heteroaromatic portion is essential for antimalarial activity[85-87]. Febrifugine acts by impairing hemozoin formation required for maturation of the parasite at the trophozoite stage. The use of febrifugine as an anti-malarial agent is initially appealing not only because of its rapid effect and no drug resistance but also because of its availability. Subsequent pre-clinical researchers have found that febrifugine possesses adverse side effects. Strong liver toxicity has precluded febrifugine as a clinical drug[22,69,88]. There are some available marketed drugs possessing quinazoline and quinazolinone ring such as the anti-solid tumor Nolatrexed (61), Sotrastaurin (62) used for psoriasis and ulcerative colitis, Tandutinib (63) for gloiblastoma, Varlitinib (64) for anticancer and Elinogrel (65) as antithrombosis[70].

CONCLUSION

Globally the importance fighting malaria is recognized. However, the burden of malaria is still high in developing countries, especially in the Sub-Saharan African region. Although decades-long efforts and academic engagements have been there, malaria continues to pose a challenge given its resurgence and problem of drug resistance. Most of the existing antimalarial drugs including chloroquine are brought to the sideline by the emergence of resistance. Currently, a combination therapy is recommended by WHO to reduce the risk of drug resistance. However, there are still reports indicating drug resistance even to those used in combination recommended by WHO such as artimisinin. Thus, malaria drug discovery is unquestionably urgent to battle against the disease. To minimize the likely hood of cross-resistance the focus of the drug discovery must be on newer drug targets, such as plasmepsin. In finding a novel antimalarial agent, a various library of chemicals has been investigated and heterocyclic compounds such as chalcones, thienopyrimidinone, quinolones, quinazolines, quinazolinones, enaminones and acridines have been reported to possess antimalarial activity. Further, assessment on quinazolinones has shown fruitful results and their activity as an antimalarial agent is appealing. In this regard, febrifugine and its derivatives have been reported to have excellent activity. Therefore, quinazolinones can be considered potential compounds in seeking for novel drugs that act against the malarial pathogen.

SIGNIFICANCE STATEMENTS

Quinazolinone derivatives possess broad spectrum activities including antimalarial, antibacterial, antifungal,

antiviral, anti-HIV, anti-inflammatory and many others. Owing to their inherent bioactive functionalities, quinazolinone derivatives have been extensively exploited in various biomedical sectors for different purposes with a particular reference to malaria drug discovery. With the advent of recent technologies, quinazolinone-based pharmaceuticals can be synthesized more efficiently through using various processing approaches. This review mainly focuses on quinazolinone-based bioactive compounds and their antimalarial potentialities.

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