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Review

A Contemporary Chemical Entities Infiltrating in the Antimalarial Therapy Era: A Comprehensive Review

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Abstract

Malaria, a life-threatening disease, is caused by parasitic single-celled microorganisms. It is specifically transmitted by the anopheles female mosquito of the Plasmodium family. There are a lot of drugs available in the market to treat this life-challenging disease. Chloroquine, a cheaper molecule that is available worldwide, is one of them. Drug resistance has been observed with chloroquine as well as with some other quinine derivatives and with artemisinin derivatives in the southeast region of Asia in countries like Cambodia, Thailand, Myanmar, and Vietnam country since 1957. After 1970, the drug resistance has been further increased and it has been expanded in several localities of India. Also, antimalarial agents, particularly chloroquine, have so many side effects such as nausea, vomiting, blurred vision, abdominal cramps, diarrhea, headache, appetite loss, deprivation of hearing, skin color change, baldness, reduced body weight, and seizures. Furthermore, this drug cannot be given to pregnant women. Hence, it is the right time to design and develop newer antimalarial agents so that this kind of drug resistance, as well as side effects of the drugs, can be overcome.

Keywords

clinical trial, drug resistance, malaria, *P. falciparum*, prophylaxis, treatment

Abbreviations used in the article

P. falciparum: *Plasmodium falciparum*	**CDRI:** Central Drug Research Institute
P. vivax: *Plasmodium vivax*	**LC-ESI-MS/MS:** Liquid Chromatography-Electrospray Ionization-Mass Spectrometry
P. ovale: *Plasmodium ovale*	**ATP4 Na-H pump:** Adenosine Triphosphate 4 Sodium-Hydrogen pump
P. malariae: *Plasmodium malariae*	**DHFR:** Dihydrofolate reductase
P. knowlesi: *Plasmodium knowlesi*	**DXR:** 1-deoxy-D-xylulose-5-phosphate reductoisomerase
RBC: Red Blood Cells	**USFDA:** United States Food and Drug Administration
CHMI: Controlled Human Malaria Infection	**USA:** United States of America
EF2: *Plasmodium falciparum* Elongation Factor 2	**G6PD:** Glucose-6-phosphate dehydrogenase

INTRODUCTION

Malaria is a life-threatening infectious disease that occurs due to biting of anopheles female mosquito. Mosquito biting leads to the introduction of parasites from the mosquito saliva into host blood. The parasites then shift to the infected host liver and go through maturation and reproduction stage. A total of five *Plasmodium* species has been summarized that can infect and be spread by a human. Among these, *P. falciparum* can cause death whereas *P. vivax*, *P. ovale* and *P. malariae* can cause a benign form of malaria. *P. knowlesi* species barely cause disease in humans. These microorganisms can affect both humans and animals.

Signs and symptoms of malaria can be seen in a person ten to fifteen days after being bitten by mosquitos. Typically, malaria can cause fever, headache, vomiting, tiredness, joint pains, shivering, jaundice, hemolytic anaemia, and haemoglobin in urine-like symptoms. Whereas in severe condition, it can cause retinal damage, yellow skin, seizures and coma, and if it is not cured, it may lead to death. In some cases, some other conditions like sepsis, gastroenteritis, and viral diseases can also be seen.

Malaria disease can be well treated with combination therapy. The combination of this antimalarial medication includes an artemisinin derivative with the second medication will be either chloroquine or mefloquine or lumefantrine or sulfadoxine/pyrimethamine. In some cases, when the artemisinin derivative is not available, then a combination therapy of quinine with doxycycline can also be used. Chloroquine and other quinine derivative enter the host RBC and accumulate there forming a complex with heme (toxic to the parasite). These inhibit the conversion step of heme into hemozoin (nontoxic to the parasite). So the concentration of heme will be increased that will destroy the malarial parasite. **Fig. 1** shows structures of antimalarial drugs currently available in the market.[1-3]

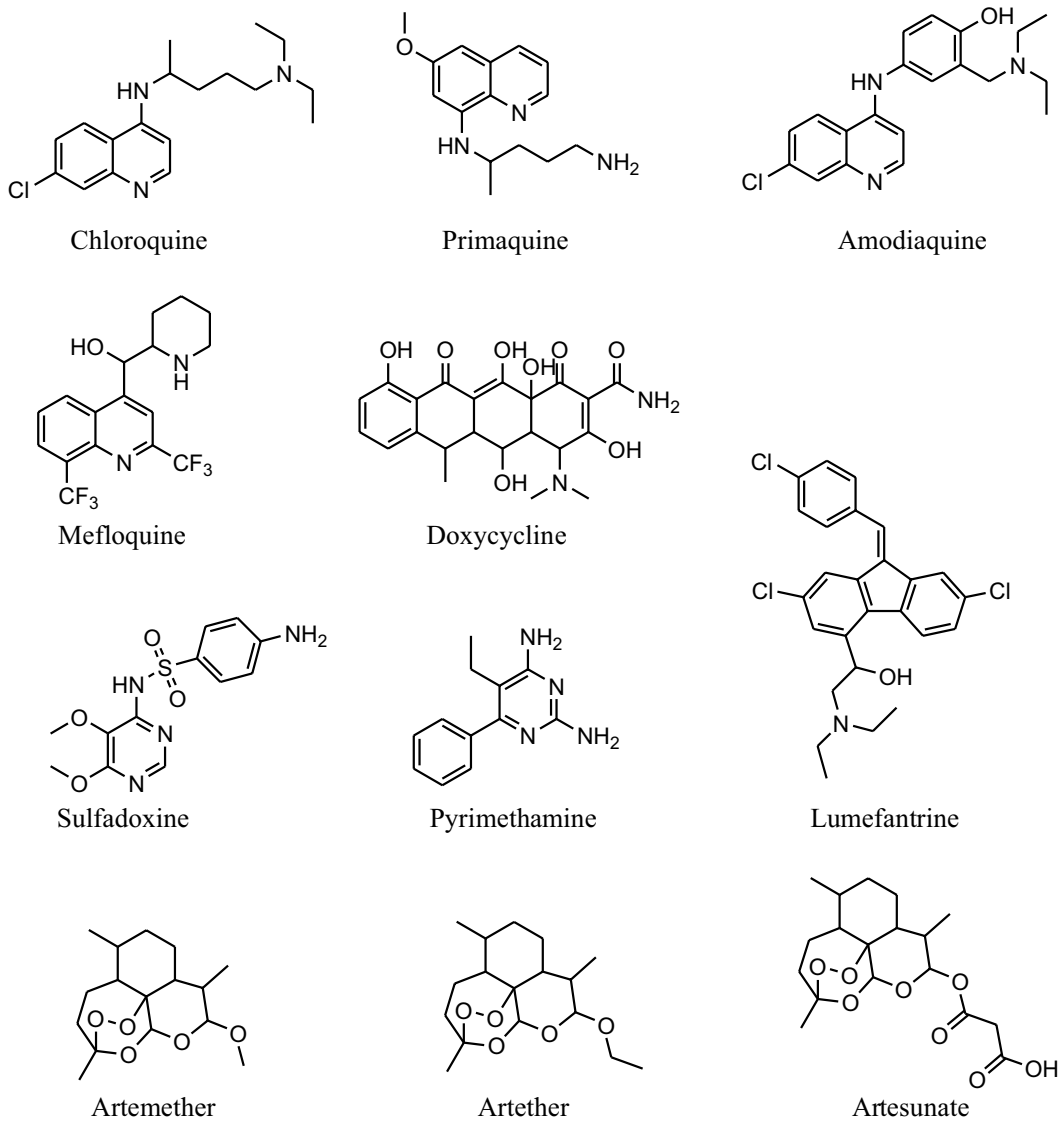

Figure 1. Structures of drugs currently available in the market.

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Development of resistance of *Plasmodium falciparum* to chloroquine and other quinine derivatives as well as artemisinin derivatives

Chloroquine, discovered in 1934, is employed as prophylaxis and treatment of malaria very effectively. In 1957, drug resistance was developed in Colombia-Thailand border. In Venezuela and other regions of Colombia, drug resistance was seen around 1960, in Papua New Guinea in the mid-1970s, whereas in Africa, drug resistance was developed in 1978, in Kenya, Tanzania, Sudan, Zambia, Uganda and Malawi by 1983. As of now, chloroquine, as well as artemisinin drug resistance, has been developed by approximately 40 countries. So it is extremely necessary that newer antimalarial agents should be designed and developed so that this kind of side effects and drug resistance can be overcome.[4-6]

The purpose of the study

In the present review, we have included many anti-malarial agents under a clinical trial. The main purpose of current studies is to open the new directions of antimalarial drug discovery and development. Researcher can take an advantage of agents which are under the clinical trials. Researchers have identified various scaffolds and heterocyclic rings for development of antimalarial agents. Various heterocycles like pyridine, triazolo[1,5-a]pyrimidine, quinolines, piperazines, pyrrolidine, morpholine, phenothiazine, tetrahydropyrido[3,4-b]indole, and dimethylimidazo[1,2-a]pyrazine have shown their importance in the antimalarial research. During upcoming decade, researchers can take the advantage of several scaffolds for the investigation purpose.

Antimalarial agents in clinical trials

Molecules under Phase 1 clinical trials

Pyridine derivatives

(+)SJ733 (SJ000557733)

(+)SJ733 is chemically N-(3-Cyano-4-fluorophenyl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydro-1-oxo-3-(pyridine-3-yl)isoquinoline-4-carboxamide **(Fig. 2)**. Jimenez-Diaz et al. have reported that SJ733 gives its potential activity on the target *Plasmodium* cation-transporting ATPase, ATP4. (+)SJ733 clears parasites in vivo with the same potency as that given by artesunate.[7] Gaur et al. have studied the safety, tolerability, pharmacokinetics and antimalarial activity of SJ733 in humans and concluded that favourable profile of SJ733 as well as rapid activity gives support for the development as fast acting candidate for combination antimalarial therapy.[8]

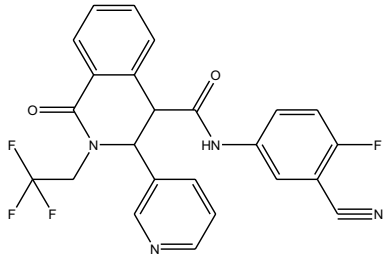

Figure 2. Structure of (+)SJ733 (SJ000557733).

MMV390048

It is chemically 3-(6-(Trifluoromethyl)pyridine-3-yl)-5-(4-(methylsulfonyl)phenyl)pyridine-2-amine **(Fig. 3)**. Paquet et al. have screened a small molecule library against human *P. falciparum* parasite and invented a newer 2-aminopyridine derivative, MMV390048, which was active against multiple parasite life cycle stages. They have reported that the drug is active against drug resistant parasites also. They have summarized the molecular mechanism of this drug which blocks the phosphatidylinositol 4-kinase (PI4K) and stated that this drug may be used for malaria control as a single dose combination treatment.[9] Sinxadi et al. have assessed the safety, tolerability, pharmacokinetics and antimalarial activity of MMV390048 in healthy human subjects of Ethiopia. After observing all the results they have reported that this drug is well tolerated in humans and by checking pharmacokinetic properties, they have concluded that it has a potential for prophylaxis of malaria as well as treatment of malaria in a single dose.[10]

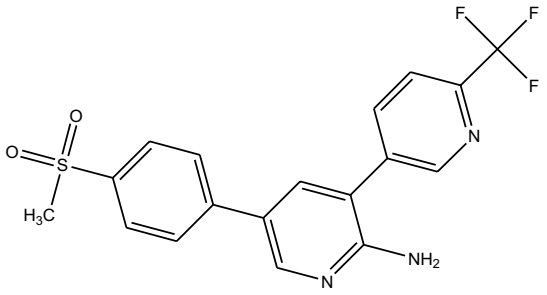

Figure 3. Structure of MMV390048.

Triazole derivative

DSM 265

DSM 265 is chemically 2-(1,1-Difluoroethyl)-5-methyl-*N*-[4-(pentafluoro-λ^6-sulfanyl)phenyl]-[1,2,4]triazolo[1,5-a]pyrimidin-7-amine **(Fig. 4)**. It is under phase 1 clinical trial study. McCarthy et al. have addressed that DSM 265 is a novel antimalarial agent that inhibits dihydroorotate dehydrogenase enzyme only in malarial parasite and inhibits pyrimidine biosynthesis. They have reported that in a single dose, DSM 265 has a potential to treat and protect against malaria.[11] Sulyok et al. have assessed the prophylactic activity of DSM 265 against controlled human

malaria infection (CHMI). They have reported that this drug shows in vitro activity against liver and blood stages of *P. falciparum*.[12]

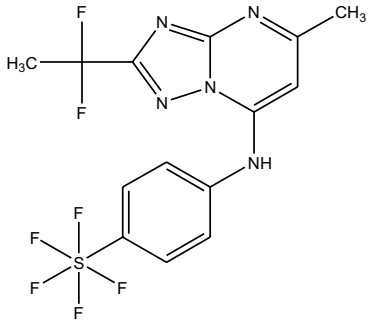

Figure 4. Structure of DSM 265.

Quinoline derivatives

Ferroquine (SR97193)

Ferroquine is chemically 7-Chloro-N-[[2-[(dimethylamino)methyl]cyclopenta-1,4-dien-1-yl]methyl]quinolin-4-amine;cyclopenta-1,3-diene; iron (2+) (**Fig. 5**). It is under phase 1 clinical trial. Dubar et al. have addressed a novel antimalarial drug ferroquine that currently is in development at Sanofi-Aventis. They have reported FQ, the first organometallic molecule containing ferrocenyl group that covalently linked with 4-aminoquinoline and a basic alkylamine. They have communicated that FQ can overcome the resistance problem of chloroquine. This drug targets lipids and inhibits hemozoin formation and generate reactive oxygen species.[13] Kondratskyi et al. have reported that the anticancer ferroquine can be the next generation potential antimalarial agent.[14]

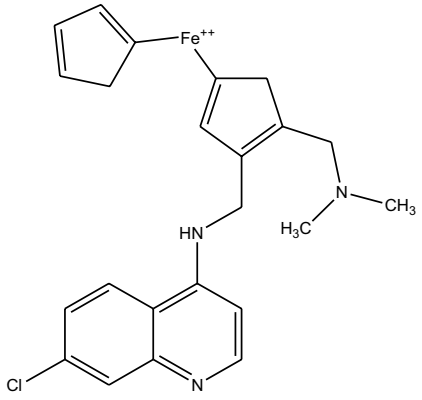

Figure 5. Structure of ferroquine (SR97193).

AQ13

It is chemically 7-Chloro-N-(3-(diethylamino)propyl) quinoline-4-amine (**Fig. 6**). Mengue et al. have reported a newer in development 4-aminoquinoline derivative drug. It is under phase 1 clinical trial and has structural similarity with chloroquine. It contains shorter diaminoalkyl side chain and it can be used for the patients suffering from malaria that is resistant to chloroquine and other antimalarial agents.[15] Koita et al. have addressed AQ13 that contains 4-aminoquinoline ring with modified side chains. They have compared the activity of AQ13 with artemether plus lumefantrine combination to treat uncomplicated *P. falciparum* malaria and concluded that this drug was active against resistant parasites.[16]

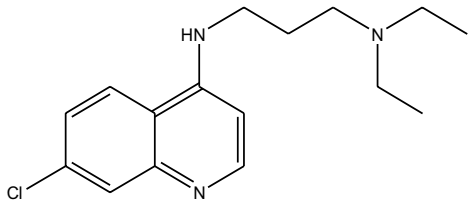

Figure 6. Structure of AQ13.

M5717 (DDD107498, DDD498, MMV121)

It is chemically 6-Fluoro-2-(4-(morpholinomethyl)phenyl)-N-(2-(pyrrolidin-1-yl)ethyl)quinoline -4-carboxamide (**Fig. 7**). It is used to treat malaria with single exposure radical cure as well as resistant management. Rottmann et al. have performed an antimalarial combination study of this drug with pyronaridine, which is hemozoin formation inhibitor, and reported that this drug works on the novel mechanism that it inhibits *P. falciparum* elongation factor 2 (EF2).[17]

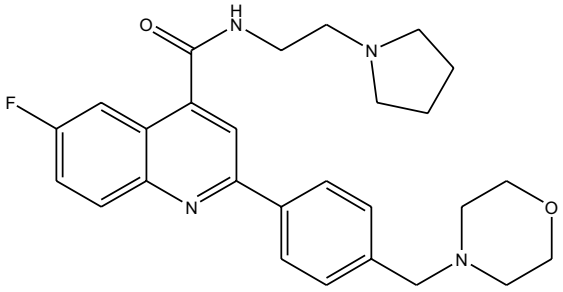

Figure 7. Structure of M5717.

Piperazine derivatives

ACT 451840

It is chemically 4-(4-Cyanobenzyl)-N-((E)-5-(4-*tert*-buutyphenyl)-1-(4-(4-acetylpiperazin-1-yl) phenyl)-3-oxopent-4-en-2-yl)-N-benzylpiperazine-1-carboxamide (**Fig. 8**). It is under Phase 1 clinical trial and works on the mechanism that it inhibits aspartic endopeptidase. Bihan et al. have assessed spectrum of activities of ACT 451840 against multiple stages of the life cycle of *P. falciparum* and *P. vivax*. They have summarized that the drug is

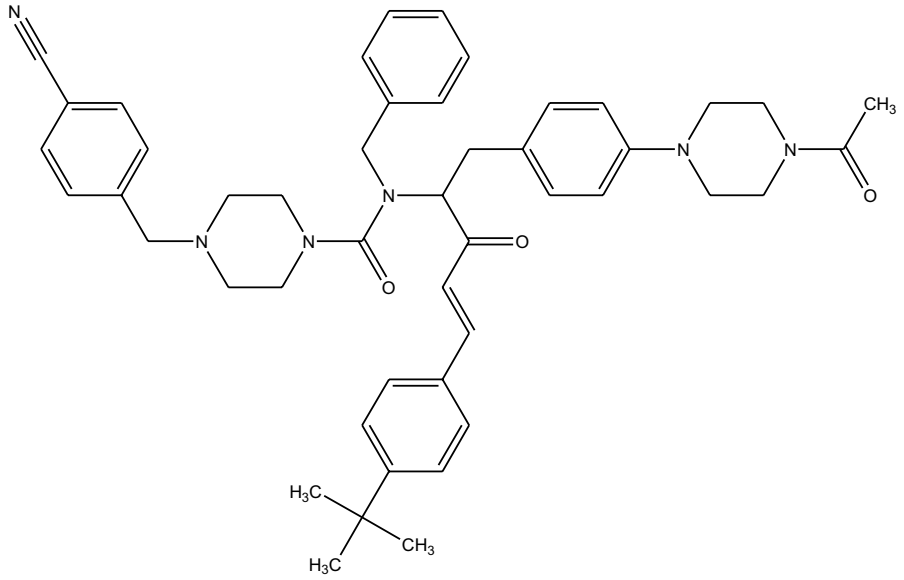

Figure 8. Structure of ACT 451840.

active against asexual and sexual stages of *P. falciparum* and *P. vivax*. They have concluded ACT 451840 has the potential to be a specific target compound that can replace artemisinin derivatives.[18]

Trioxane derivatives

CDRI 97/78

It is chemically a trioxane peroxide which is water soluble synthetic derivative of artemisinin (**Fig. 9**). It was developed by CDRI and Ipca laboratories. Shafiq et al. have performed a detailed study of CDRI 97/78 on 50 healthy volunteers in ascending single doses, randomized, placebo-controlled and double-blind design. They reported that this drug was found to be pharmacologically and toxicologically safe and effective.[19]

CDRI 99/411

It is chemically a trioxane peroxide which is highly efficacious and orally active agent (**Fig. 10**). It was developed by CDRI and Ipca laboratories. Taneja et al. have assessed the pharmacokinetic compatibility of this short acting CDRI 99/411 with long acting antimalarials, lumefantrine and piperaquine by LC-ESI-MS/MS analytical methods. They have found that in the presence of lumefantrine, absorption of CDRI 99/411 increases 1.37 times and also no change in metabolism of this drug. They summarized that this drug could be a good alternative to artemisinin derivatives for the combination treatment with lumefantrine.[20]

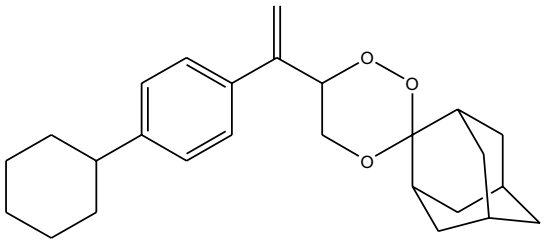

Figure 10. Structure of CDRI 99/411.

Molecules under Phase 2 clinical trials

Phenothiazine derivative

Methylene blue

It is chemically [7-(Dimethylamino)phenothiazin-3-ylidene]-dimethylazanium;chloride (**Fig. 11**). It is under phase 2 clinical trial. Schirmer et al. have reported intrinsic activity of methylene blue and concluded that this drug can

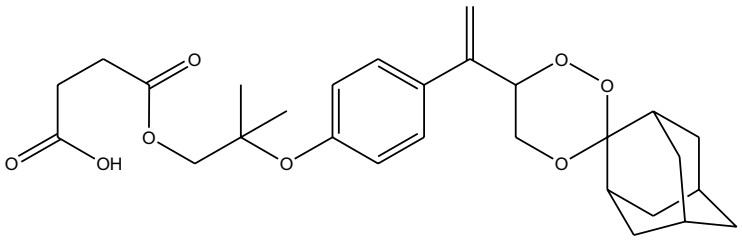

Figure 9. Structure of CDRI 97/78.

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act as chloroquine sanitizer. They have addressed that methylene blue prevents methemoglobunemia that is a serious complication of malarial anemia. Methylene blue inhibits glutathione reductase in malarial parasites.[21] Garavito et al. have reported the increased potential activity of methylene blue on combination with the non-curative dose of chloroquine or pyrimethamine or quinine.[22]

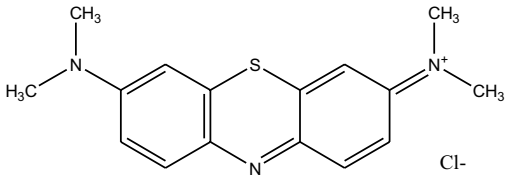


Figure 11. Structure of methylene blue.

Trioxolane derivatives

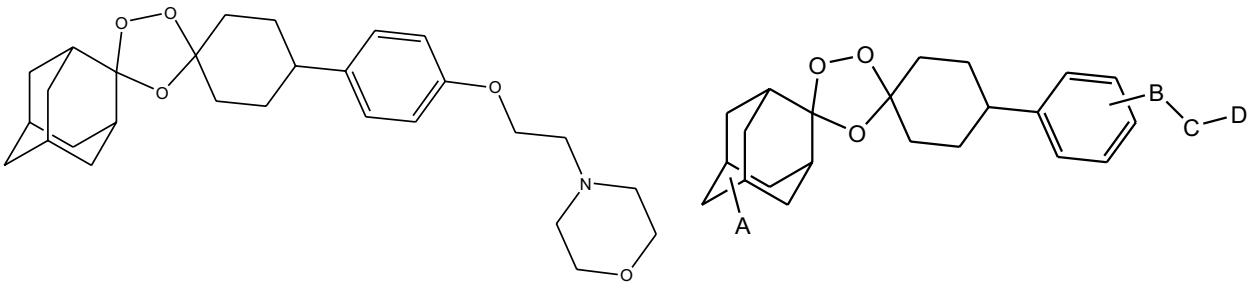
Artefenomel (OZ439, PQP)

It is chemically cis-4-[2-[4-(Dispiro[cyclohexane-1,3'-[1,2,4]trioxolane-5',2''-tricyclo[3.3.1.1(3,7)]decan]-4-yl)phenoxy]ethyl]morpholine methanesulfonate (**Fig. 12**). After the discovery of antimalarial arterolane (OZ2777), Dong et al. studied the structure-activity relationship (SAR) of artefenomel (OZ439, PQP) as an antimalarial agent. They have reported that primary and secondary amino ozonides have higher metabolic stabilities compared with the tertiary one. In the secondary amino ozonoids, addition of the polar functional groups leads to a decrease of the antimalarial efficacy. They found that primary and tertiary amino ozonoids with cycloalkyl and heterocyclic groups can give better activity than having acyclic group.[23] Phyo et al. have assessed efficacy, tolerability and pharmacokinetics of artefenomel at variable doses in patient with *P. falciparum* and *P. vivax*. They reported that that this drug could be well tolerated in volunteers at the dose of 1600 mg. They have summarized that artefenomel is a novel synthetic trioxolane having improved pharmacokinetic properties.[24]

Heparin analogue

Sevuparin (DF02)

It is developed from heparin. It is a polysaccharide of heparin analogue (**Fig. 13**). It has the antiadhesive activities of heparin without the antithrombin properties. Saiwaew et al. have reported that sevuparin has been designed to maintain antiadhesive properties with reducing the anticoagulant activity. This drug can disrupt the formation of *P. falciparum* rosette in a single dose and inhibits cycloadherence to endothelial cells.[25] Leitgeb et al. revealed that sevuparin blocked invasion of merosoite and transiently de-sequesters infected erythrocytes in humans with *P. falciparum* malaria. They have concluded that the drug was safe and well tolerated in malaria patients.[26]



Artefenomel

A = H, F
B = O, CH_2, CONR, SO_2NR
C = alkyl, cycloalkyl
D = weak base ± polar functional groups

Figure 12. Structure of artefenomel (OZ439, PQP) and derivatives of artefenomel.

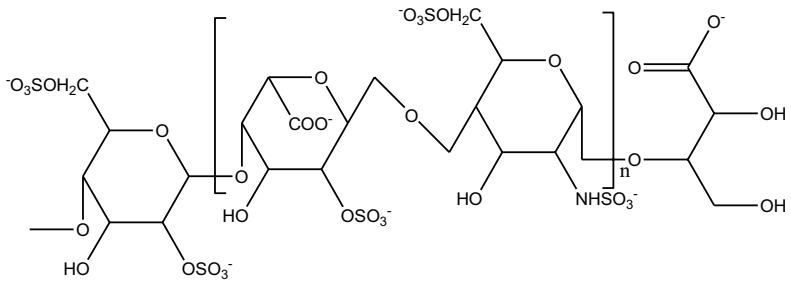


Figure 13. Structure of sevuparin (DF02)

Pyrido[3,4-b]indole derivative

Cipargamin (KAE 609, NITD 609)

Cipargamin is chemically (1R,3S)-5',7-Dichloro-6-fluoro-3-methyl-spiro[2,3,4,9-tetrahydropyrido[3,4-b]indole-1,3'-indoline]-2'-one (**Fig. 14**). Suzan et al. have demonstrated that cipargamin is very fast acting antimalarial agent belonging to the novel spiroindolone class and currently under phase 2 clinical trial. It has a gamatocitocidal activity and is active against all intra-erythrocytic stages of the malarial parasite.[27] White et al. have communicated that cipargamin is a newly synthesized compound with potent and dose-dependent antimalarial activity against asexual and sexual stages of *Plasmodium falciparum*. They have reported that cipargamin at the dose of 30 mg daily for 3 days in adults can clear *P. vivax* and *P. falciparum* malarial parasites more rapidly.[28] Likewise (+) SJ733, this drug inhibits *Plasmodium falciparum* ATP4 Na-H pump.

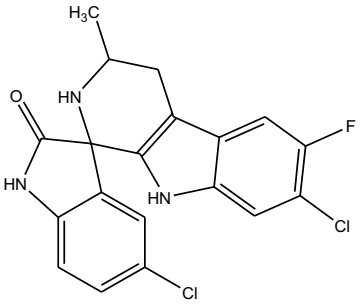


Figure 14. Structure of cipargamin (KAE 609, NITD 609).

Pyrimidine derivatives

P218

P218 is chemically 3-(2-(3-(2,4-Diaminopyrimin-5-yloxy) propoxy)phenyl)propanoic acid (**Fig. 15**). Chughlay et al. have reported first-in-clinical trial of P218 that assessed the safety, tolerability, pharmacokinetics and food effects in healthy individuals. They have addressed a short half-life of P218 so a long acting formulation must be required for the treatment of malaria.[29] Yuthavong et al. have reported the molecular mechanism of P218 that likewise pyrimethamine and cycloguanil, this drug is *P. falciparum* dihydrofolate reductase (DHFR) inhibitor.[30]

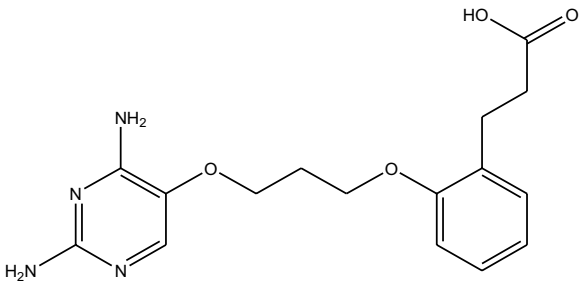


Figure 15. Structure of P218.

Imidazole derivative

Ganaplacide (KAF 156, GNF-156)

Ganaplacide is chemically 1-(3-(4-Fluorophenylamino)-2-(4-fluorophenyl)-5,6-dihydro-8,8-dimethylimidazo[1,2-a]pyrazin-7(8-*H*)-yl)-2-aminoethanone (**Fig. 16**). White et al. have reported a newer antimalarial drug KAF 156, belonging to imidazolopiperazines class. They addressed that the drug gives activity against sexual and asexual stages of blood and pre-erythrocytic liver stages of malarial parasites.[31]

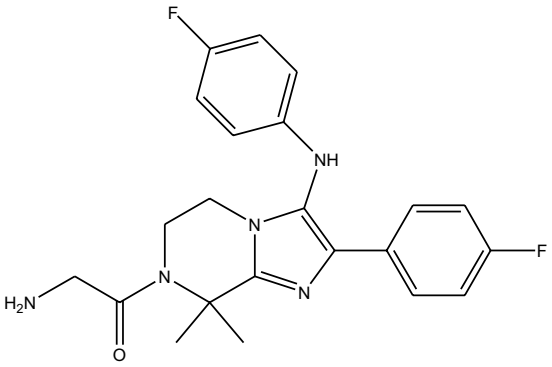


Figure 16. Structure of ganaplacide (KAF 156, GNF-156).

Molecules under Phase 3 clinical trials

Fosmidomycin

It is chemically 3-[Formyl(hydroxy)amino]propylphosphonic acid **(Fig. 17)**. Lell et al. have addressed the previous antimalarial study of fosmidomycin on mouse models and assessed 20 adults for the treatment of uncomplicated *P. falciparum* in Gabon and Thailand. They have taken an uncontrolled trial taking fosmidomycin at an oral dose of 1200 mg every 8 hours for 7 days and concluded that this drug is efficient as an antimalarial drug for the clearance of asexual parasitemia at both countries.[32] Umeda et al. have communicated the molecular mechanism of fosmidomycin that this drug inhibits 1-deoxy-D-xylulose-5-phosphate reductoisomerase (DXR) in malarial parasites. DXR is the enzyme of nonmevalonate pathway and it is absent in humans.[33]

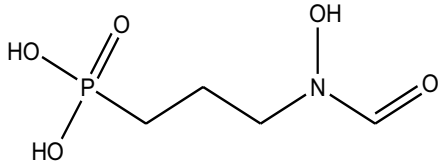


Figure 17. Structure of fosmidomycin.

Discovery and development of antimalarial agents (2014-2020)

Tafenoquine (SB-252263, WR238605)

It is chemically N-[2,6-Dimethoxy-4-methyl-5[3-(trifluoromethyl)phenoxy]quinoline-8-yl]pentane-1,4-diamine (**Fig. 18**). The USFDA has approved this drug for prophylaxis of malaria and radical cure of *P. vivax* malaria. It is prepared under the brand name of Krintafel by Sun pharmaceuticals, India and in Washington, USA it is prepared under the brand name of Arakoda. It has been approved for medical use in Australia and in the United States in 2018. Duparc et al. have reported that tafenoquine, an 8-aminoquinoline antimalarial drug has been approved as a single-dose therapy (300 mg) for prevention of *P. vivax* relapse when coadministered with chloroquine. They summarized that 200 mg of tafenaquine weekly after a loading dose has been approved as travelling prophylaxis.[34] Commons et al. have informed that this drug cannot be given to person with glucose-6-phosphate dehydrogenase (G6PD) deficiency as it can cause hemolytic anemia. Also, it cannot be given to pregnant women breast feeding an infant with G6PD deficiency as well as patient with a history of psychiatric disorder.[35]

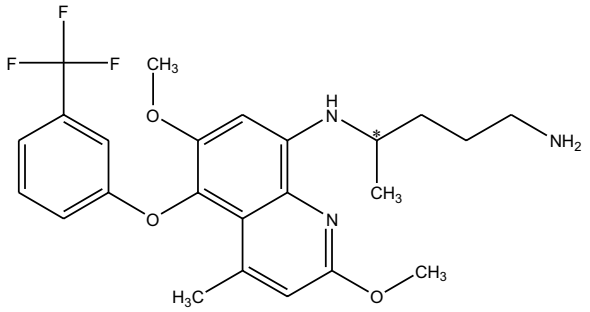


Figure 18. Structure of tafenoquine (SB-252263, WR238605).

Arterolane (OZ 2777, RBx 11160)

Arterolane is chemically N-(2-Amino-2-methylpropyl)-2-((1R,3R,4"S,5R,5'S,7R)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1"-cyclohexan]-4"-yl)acetamide (**Fig. 19**). This drug contains trioxolane (ozonide) and adamantane nucleus. Ranbaxy has completed phase 3 clinical trial of arterolane and piperaquine combination therapy and it is available in the market under the brand name of 'Synriam' (Arterolane maleate-150 mg and piperaquine phosphate-750 mg) manufactured by Sun pharmaceuticals. In 2012, this combination was approved as potential antimalarial agents in India. In Nigeria, Uganda, Senegal, Cameroon, Guinea, Kenya and Ivory Coast this combination was approved in 2014. Dong et al. have reported antimalarial testing of arterolane by Ranbaxy laboratories.[36] Patil et al. have reported a fixed dose combination therapy of arterolane and piperaquine as a newer aspect in the treatment of malaria.[37] Uhlemann et al. have communicated that arterolane is active against all erythrocytic stages of *P. falciparum*. This drug inhibits heme detoxification and Pf-encoded sarcoplasmic endoplasmic reticulum calcium ATPase (PfATP6).[38]

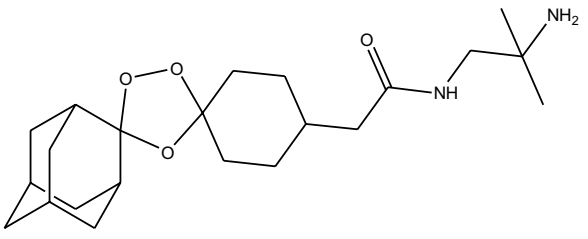


Figure 19. Structure of arterolane (OZ 2777, RBx 11160).

CONCLUSIONS AND FUTURE PERSPECTIVES

The developed chloroquine and artemisinin drug resistance has created the need to design and develop potential antimalarial agents so that the side effects as well as the developed resistance can be overcome. Here we present a detailed review of newer potential antimalarial agents. This review reveals the molecules, effective against *P. falciparum* parasites, that are under different clinical trials. Amongst these all tafenoquine and arterolane have passed clinical trial 3 and now are available at the market. The remaining candidates are still studied to find whether they are effective as potent antimalarial agents and could be released in the society for better treatment.

Human and animal rights

No animals/humans were used in the studies analysed in this research.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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Современные химические препараты, проникающие в эпоху противомалярийной терапии: всесторонний обзор

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Резюме

Малярия, опасное для жизни заболевание, вызывается паразитическими одноклеточными организмами. Оно передаётся, в частности, самкой комара Anafelesi из рода *Plasmodium.* На рынке есть множество препаратов для лечения этого опасного для жизни заболевания. Хлорохин, дешёвая молекула, доступная во всём мире, является одним из них. При хлорохине наблюдается лекарственная устойчивость, как и при ряде некоторых других производных хлорохина и производных артемизинина в регионе Юго-Восточной Азии в таких странах, как Камбоджа, Таиланд, Мьянма и Вьетнам с 1957 года. С 1970 года лекарственная устойчивость возросла и распространилась на несколько частей страны Индия. Кроме того, противомалярийные препараты, особенно хлорохин, имеют множество побочных эффектов, таких как тошнота, рвота, нечёткость зрения, спазмы в животе, диарея, головная боль, потеря аппетита, потеря слуха, изменение цвета кожи, облысение, потеря веса и судороги. Также препарат не назначают беременным. Таким образом, сейчас подходящее время для разработки и внедрения новых противомалярийных препаратов для преодоления этой лекарственной устойчивости, а также побочных эффектов препаратов.

Ключевые слова

клиническое испытание, лекарственная устойчивость, малярия, *P. falciparum*, профилактика, лечение