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Antimalarial Agents

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ABSTRACT

Malaria is a major public health issue that affects people all around the world. Malaria's name came from the words mal-bad and aria-air. Malaria is a plasmodium infection caused by Plasmodium falciparum, *Plasmodium ovale, Plasmodium vivax, and Plasmodium malaria*, among others. Malaria infection can be treated with a variety of medications. Anemia and fever are both common signs of illness. Malaria has a life cycle. Malaria has an asexual and sexual phase, with the malaria parasite impacting the blood and hepatocytes (liver) of the host. The early stages of the life cycle do not create any symptoms, but fever or chills are developed when merozoites penetrate the host's liver. Because medication resistance is a serious issue for malaria patients, a combination therapy is used to treat malaria patient therefore; combination therapy is used instead of the single drug although it is used to overcome the drug resistance, side effect of drug as well. The focus of this review article is on classification, chemical structure and structural activity relationship of compounds, as well as new discovery and modification. The present article focused on recent development in malaria treatment.

Keywords: Malaria, Life cycle of malaria parasite, Chemistry of Antimalarial agent, structural activity relationship, recent advances in antimalarial agent.

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INTRODUCTION

Malaria is named after Mala aria, which meaning "bad air." Malaria is a major public health issue that affects people all around the world[1,2,3] Malaria has claimed the lives of more than half of the world's population. 450 million people are infected with the protozoan plasmodium falciparum[1]. Malaria is a virulent infectious disease marked by a high temperature, a neurological problem such as coma and brain impairment, and anemia [3,4]

Pregnant ladies are also affected. Children under the age of five years old account for 85 percent of all deaths. Plasmodium malaria, Plasmodium vivax, Plasmodium ovale, and Plasmodium falciparum are the parasites that cause malaria. Pseudomonas falciparum infection affects 95 percent of persons. Malaria is transmitted by the bite of the Anopheles mosquito, which carries sporozoites, a protozoan parasite. It does not have any locomotory organ but it has food vacuoles. Plasmodium is a digenic parasite. This means it requires two hosts for the completion of the life cycle. Antimalarial medications are drugs that are used to treat and prevent malaria. Because the symptoms are obvious at this stage, the majority of antimalarial drugs target the erythrocyte stage of illness. Because of its low cost, safety, and efficacy, chloroquine was developed after Second World War and is regarded useful against malaria[13]

Classification of the causative agent [7]

1. Plasmodium falciparum: Incubation period of 9-12 days.
2. Plasmodium vivax: This is the second common species of plasmodium and this infection is chronic because it reinfects to the liver cells. The incubation period of 11-14 days
3. Plasmodium malaria: these types of species causing 10% of all malarial cases. It may cause relapse in the patient. The incubation period of 18-22 days.
4. Plasmodium Ovale: This is the least common species of plasmodium. The incubation period of 9 days.

Life Cycle of Malaria parasite

- The different stages of the reproductive cycle of the malaria parasite and various drugs are effective at each stage
- stage I: No drug effective at this stage
- stage II: Primaquine, Pyrimethamine
- stage III: Primaquine effective at this stage because fever occurs at this stage
- stage IV: Chloroquine, amodiaquine, Proguanil
- stage V: Primaquine
- The life cycle of malaria involves two phases: Asexual Phase and Sexual Phase

- Sexual type of reproduction is anisogamous
- The asexual phase occurs in the infected host and the Sexual phase occurs in the mosquito
- When a healthy individual is bitten by an infected female anopheles mosquito, the sporozoite enters the bloodstream and goes to the liver, where it forms the primary schizont and thereafter the merozoites; therefore the Exoerythrocytic stage is formed. No symptoms appear at this time. Merozoites can injure other hepatocytes, cause liver failure, or enter the systemic circulation depending on the Plasmodium species. Furthermore, secondary schizonts are formed in P.ovale and P.vivax species but not in P.falciparum, and merozoites then enter the victim's systemic circulation (blood). While the merozoites are being injected into the blood so, this phase is known as the erythrocytic phase. The merozoites reside in the erythrocytes for 3-4 days before being burst. The person may experience chilly and fever-like symptoms as a result of the erythrocytes rupturing. The asexual phase is the name given to this stage.
- Some merozoites remain in the bloodstream of the victim, even though merozoites migrate from the blood to the salivary glands of the mosquito, where they create primary and secondary gametocytes, after being bitten by a healthy mosquito. The zygote is created in the mosquito's stomach after fertilization, and oocytes are formed in its stomach epithelium. Finally, the sporozoites that were expelled from the salivary glands of mosquito, inoculates the bloodstream. This phase is known as the Sexual phase.

Chloroquine is used as blood schizoticides whereas primaquine is used as tissue schizonticides or antirelapse drug[10].[11]

Classification of antimalarial agent

Most of the antimalarial agents are targeting the asexual phase of infection as it causes asymptomatic illness. The hepatic stage of infection is unreactive because the clinical symptoms not visible.[13]

Based on Chemical classification

4- Substituted quinolone

1. Cinchona alkaloids: e.g. Quinine, Quinidine, Cinchonine
2. 4-aminoquinoline e. g Primaquine, Pamaquine, Amodiaquine
3. 8-aminoquinoline: Chloroquine, 8-hydroxychloroquine
4. 4-quinoline methanol: e. g. Mefloquine
5. 4-aminoquinol atovaquone, amodiaquine
6. Sesquiterpene lactone: Artemisinin, artemether
7. 9-aminoacridine: e.g. Mepacrine

8. 2,4 -Diaminopyrimidine e.g. Pyrimethamine
9. Amino alcohol: Halofantrine, lumefantrine
10. Fixed-dose Combination

Trimethoprim + Sulphonamide

Arthemether + lumefantrine

Atovaquone + Proguanil

Biguanide : Proguanil, cycloguanil

Based on target site:

1. Tissue Schizonticide : e.g. Primaquine, tafequine
2. Blood schizonticides e. g. Chloroquine, mefloquine, doxycycline
3. Gametocytocides: These are the agent which kills the sexual forms of gametocytes g. Primaquine, artemisinin
4. Sporonticide : e. g Primaquine, Chloroquine

Based on therapeutic classification[14]

Casual Prophylaxis: Destroy the parasite in liver cells and prevent to inoculation of the erythrocytes. E. g. Primaquine, Proguanil

Suppressive prophylaxis : It suppresses the erythrocytic phase

e .g. Proguanil, Doxycycline, Chloroquine, Mefloquine

Clinical cure : It is used to cure the attack of malarial fever

Slow acting with low efficacy drugs: Proguanil, Pyrimethamine, tetracycline, sulfonamide

Fast acting with high efficacy: Chloroquine, Mefloquine, Atovaquone, quinine, Artemisinin

Life cycle of Malaria Parasite [1,3, 8,9,10,11]

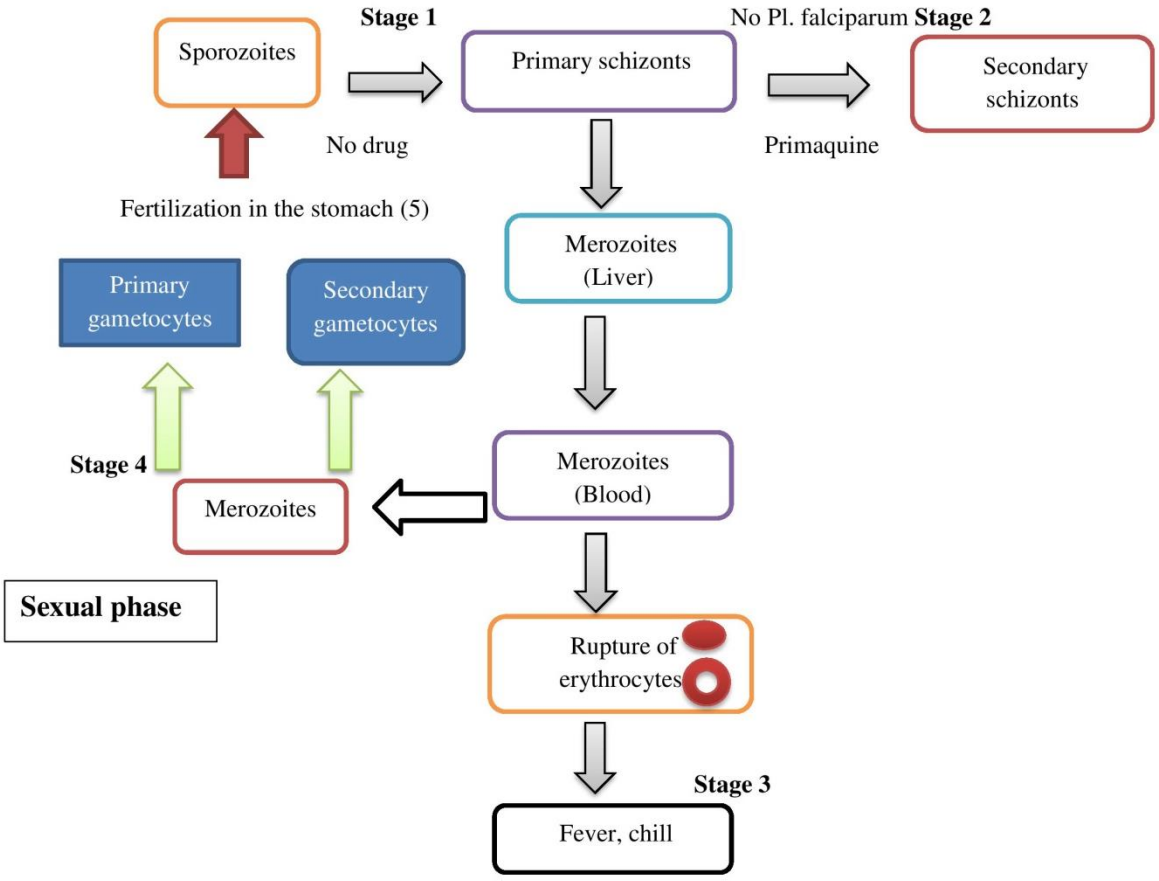
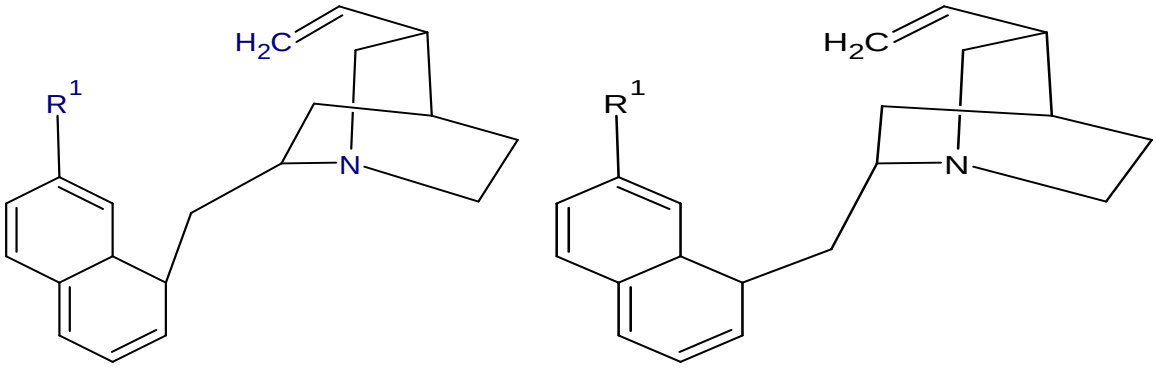


Figure 1: Life cycle of malaria Parasite

Quinine: Since 1600, it has been used in South America to treat fever. When the pure alkaloid was isolated from the natural plant in 1820 and it is renamed as quinine and quinidine. Quinine is a natural alkaloid derived from the bark plant *Cinchona ledgeriana*, and it was the first malaria treatment.[13] Quinidine is a quinine isomer with a higher toxicity than quinine. Quinidine is an isomer of quinine but it is more toxic than quinine. Quinine is toxic to plasmodium schizonts, gametocytes, and is effective against P.vivax and P.malariae, but not against P.falciparum. Quinine's mechanism of action is uncertain, however it is used to treat malaria induced by P. falciparum resistance to another medication. Depending on the situation, quinine is sometimes combined with sulfadoxine, doxycycline, and pyrimethamine. A vaccine would be a good treatment for malarial infection.

Quinine: Quinine compound undergoes metabolism in the liver to form 2- hydroxyl derivative the metabolite has low reactivity and it is excreted through urine.[12] Cinchonism is a quinine alkaloid adverse effect that causes nausea, vomiting, tinnitus, and hearing problems. Cardiovascular toxicity, respiratory disease, visual abnormalities, and idiosyncrasy are also side effects of the

medicine, and black water fever is induced by the presence of the methanol moiety in the quinine molecule.



Quinine R- OCH3, Quinidine R-CH3 **Cinchonine R- OCH3, Cinchonidine R-CH3**

Figure 2: Structure of quinine, quinidine and Cinchonine and Cinchonidine

Structural activity relationship[35]

1. Quinolone ring: In quinine drugs, the presence of a methoxy group at the 3' position is unimportant for antimalarial activity, but the presence of a halogen group at that position, such as chlorine, bromine, or iodine, boosts antimalarial activity.
2. The addition of a trifluoromethyl group to a medication may reduce its phototoxic effect while increasing its activity, leading to the production of mefloquine.
3. Quinuclidine is not required for antimalarial action, but the alkyl tertiary amine group is.
4. Addition of halogen group to the first position improves antimalarial action.
5. Antimalarial action is not dependent on asymmetry at the quinuclidine part.
6. Oxidation and esterification of quinuclidine's secondary alcohol results in a decrease in the amount of quinuclidine.

Sulphonamide is effective against malaria infection. It acts by inhibiting the absorption of Para amino benzoic acid of the malaria parasite. Primaquine and Pamaquine have the same effect but they have a slow duration of action because of the faster excretion of 8-aminoquinoline.

4- Substituted quinolone: The substitution occurs at 4 positions of quinolone

Chloroquine:

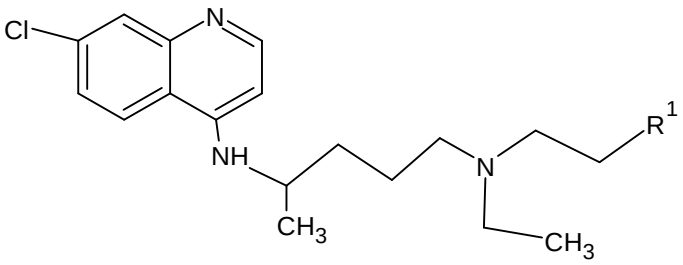
Mechanism of action

The mechanism of action of chloroquine is unknown. But 4- amino quinolone acts by three different mechanism

Drug intercalation: The drug-like quinine intercalated between the DNA strands of the parasite. It acts by taking into consideration that the concentration of inhibiting nucleic acid synthesis is higher than that of inhibiting the growth of the plasmodium parasite

Ferriprotoporphyrin IX: The plasmodium parasite utilizes haemoglobin as an amino acid. on digestion of haemoglobin, the heme is released as Ferriprotoporphyrin IX so, the Ferriprotoporphyrin IX is responsible for hemolysis of erythrocyte parasite therefore this Ferriprotoporphyrin IX is converted into the non-toxic compound by using heme polymerase enzyme and formation of haemozoin.

Weak base hypothesis: 4- substituted quinolone have a weak base and because of the pKa value of lysosomal enzyme it accumulates at the location and become more acidic.[12]



Chloroquine R-H, Hydroxychloroquine R-OH

Figure 3: Structure of chloroquine and hydroxychloroquine

Chemical Name: RS)-N'-(7-chloroquinolin-4-yl)-N,N-diethyl-pentane-1,4-diamine

Mechanism of action of chloroquine[15, 16]

Chloroquine targets the food vacuole. Food vacuoles in the malaria parasite are responsible for the hydrolysis of erythrocyte haemoglobin. Hemoglobin was metabolised into heme and globin in the food vacuole, therefore an antimalarial agent like chloroquine works by blocking the development of haemozoin, which leads to the generation of free radicals.

Structural Activity Relationship[9]

1. At 4 position dialkylamino, the alkyl side chain has 2-5 carbon atoms between nitrogen, it is essential for antimalarial activity. e. g. quinacrine, chloroquine
2. Substitution of the hydroxyl group on tertiary amine reduces toxicity
3. Substitution at 3-position by methyl group decreases the activity
4. The presence of two aromatic ring is essential for stacking of π-π interaction[33]
5. The presence of tertiary amine at the side chain essential for activity although nitrogen atom of amine is responsible for basic nature of drug
6. Substitution of electron withdrawing group at 7 position exhibits antimalarial activity it has essential role in inhibition of hemazoin formation however (chloroquine) 7- Chloro group is essential for antimalarial activity. Chlroquine has crucial role heme binding[37,38,39]

7. Incorporation of the aromatic ring at the side chain e.g. amodiaquine deceases the activity as well as toxicity.
8. D-isomer of chloroquine is less toxic than its L-isomer

Uses

Chloroquine has been used against all types of malaria

Chloroquine can be used in the treatment of malaria in pregnant condition

It is effective against rheumatoid arthritis

Chloroquine is active against Entamoeba histolytica, Giardia lamblia, antihistaminic, smooth muscle relaxant, and antiarrhythmic property.[17]

Alla osadchy, thirukumaran ratnapalan, and gideon koren:

In the treatment of malaria, chloroquine and hydroxychloroquine have been utilized, although the authors were studied that Chloroquine and hydroxychloroquine are effective during pregnancy; however they can cause toxicity, according to a thorough assessment of the literature. The safety of chloroquine and hydroxychloroquine during pregnancy was determined by looking at whether they cause ocular toxicity in offspring or not. A total of 770 abstracts were used, with 753 being discarded and the remaining 37 being used in the following order: Out of the 12 abstracts, 18,19 met all of the criteria. There were 588 infants born to mothers who were given chloroquine or hydroxychloroquine during pregnancy, and one clinical trial of chloroquine for malaria prophylaxis was conducted out of 11 trials on rheumatoid arthritis patient, mostly with hydroxychloroquine. The ocular toxicity studies on chloroquine and hydroxychloroquine treated women during pregnancy were examined using a randomised controlled trial, and the ocular toxicity was determined using an electroretinogram, and it was discovered that no ocular toxicity occurs in exposed children. There was no fatal eye toxicity seen in the study, according to the findings and conclusion, it was observed that no fatal ocular toxicity observed in antimalarial medication during pregnancy.

Side effect of chloroquine [18]

Chloroquine can produce side effect like headache, abdominal cramp, nausea, vomiting, tinnitus, after longer administration of chloroquine can produce visual impairment like retinal damage so, the condition is known as chloroquine retinopathy.

Drug interaction [18]

Chloroquine interacts with antibiotics and antacids and that alter the change in concentration of chloroquine.

Amodiaquine

Amodiaquine was developed in 1948 and frequently used in Africa and it has same structural interaction as that of chloroquine furthermore, its planar structure of quinolone ring is essential for antimalarial activity.[34]

Amodiaquine is effective against prophylaxis of malaria and it may causes agranulocytosis, hepatitis.

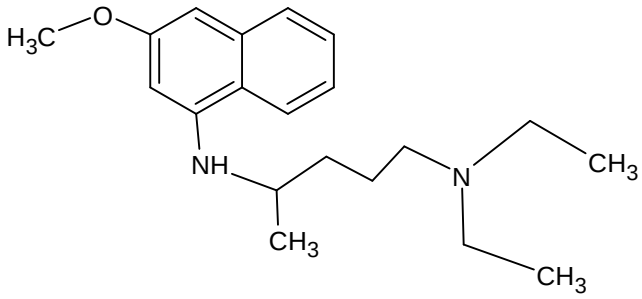


Figure 4: Structure of amodiaquine

Chemical name: 4-7-hloroquinolin-4-yl)amino)-2-(diethyl amino)methyl)Phenol

4-quinoline-methanol e. g Mefloquine

Mefloquine was came into the existence in 1820 and developed by United States army in response to increasingly the poor cure rate by chloroquine. Mefloquine has more half –life in malaria infected patient as well as in healthy host. Mefloquine is considered as effective treatment in chloroquine-resistant malaria and prophylaxis of malaria.

Halofantrine is an organic compound and it was came into the existence at the same time as was the mefloquine although it is used as second line agent but it has limited use due to its side effect like cardiotoxicity.

Mefloquine interacts with haeme by inhibiting the enzyme haeme polymerase but it is less potent enhancer of peroxidase activity of heme than chloroquine.[40,41, 42,43]

Nowadays mefloquine is no longer used due to its side effect like psychosis.

8-aminoquinoline

e. g. Primaquine and Pamaquine, tafenoquine.

The 8-aminoquinoline compounds have been reported to have antimalarial activity against the various type of causative agent. The 8-aminoquinoline is a first synthetic compound which has been used as antimalarial agent. Primaquine compound was approved by World Health Organization and it exhibits the antimalarial activity against the relapse of Plasmodium although effective against the *Pl.vivax, Pl ovale*. The use of 8-Aminoquinoline may produce the hemolysis of red blood cell in glucose-6-phosphate dehydrogenase deficiency patient therefore, for safety

purpose the patient with malarial infection should be screened for glucose-6-phosphate dehydrogenase deficiency and patient should be treated before these treatment[44, 45].

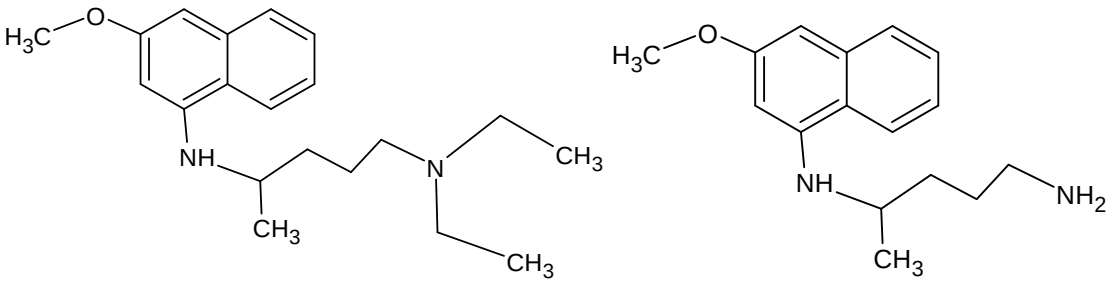


Figure 5: Structure of Pamaquine, Primaquine

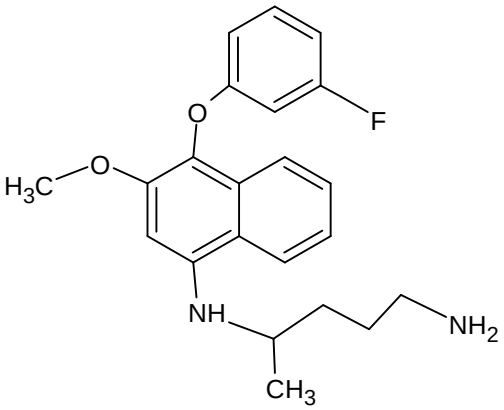


Figure 6: **Tafenoquine**

Chemical Name: Pamaquine: 8 - (4 - diethyl amino - 1 – methyl butyl)amino) -6-methoxyquinoline

Primaquine: 8 - (4 - amino - 1 - methybutylamino) -6-methoxyquinoline

Tafenoquine:4-N-{2,6-methoxy-4-methyl-{5-[3-trifluromehyl]Phenoxy]quinolin-8yl] pentane-1,4 diamine.

Miscellaneous

Artemisinin and its derivative

In 1970, the artemisinin drug was discovered for the first time. Although it has been used in Chinese traditional medicine, it is derived from the *Artemisinin anua* plant. [46]

Artemisinin derivatives (artemeter, artemether, Artesunuate) have been utilised in South Africa and China. It is efficient against the parasite Pseudomonas aeruginosa. Artemisinin is a sort of chemical that can be found in nature. This semi-synthetic derivative is a prodrug and it is converted into active metabolite like dihydroartemisinine.[47]

Although artemisinine has been shown to be effective against malaria, resistance to the drug was discovered in western Cambodia in 2008.[48]

Artemisinin has a variety of properties, including a short half-life and limited bioavailability. Because resistance to artemisinin has been established, the medicine is often used in conjunction with other drugs[49]Artemisinine is administered via rectal, intravenous and oral route of administration. If Artesunuate is used alone it must be administered for 5-7 days.

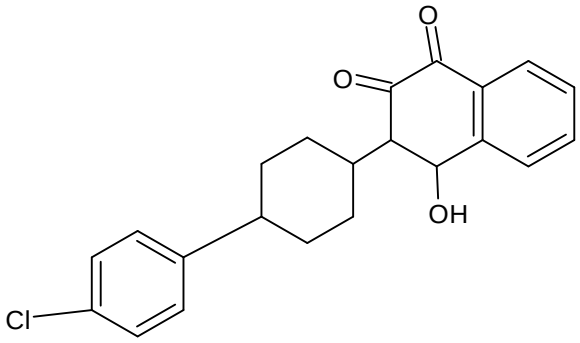


Figure 7: Structure of Atovaquone

9-aminoacridine

e. g. Quinacrine

Quinacrine isn't available in the United States of America anymore. Quinacrine is hazardous to the body because it affects DNA intercalation and mitochondrial electron transport via succinate dehydrogenase. Because of its acridine structure, it exerts harmful effects such as mutagenesis and sclerosing agents. It causes yellow discoloration in the urine or on the skin[36].

This is also known as Mepacrine and this was developed in 1933. It was developed when quinine became unavailable during World War II[50]**.** The artemisinin is an acridine derivative compound.

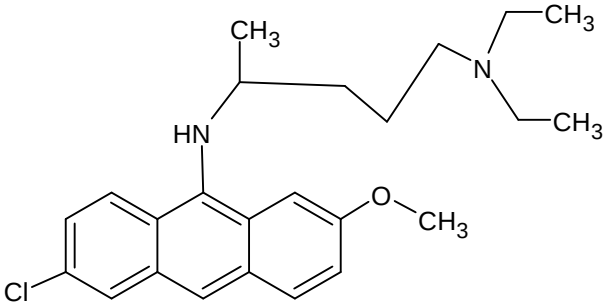


Figure 8: Structure of Quinacrine

Chemical name: 6-chloro-1-methoxy-9-(4-diethylamino-1-methylbuthylamino) acridine

Antibiotic: Tetracycline should be avoided in children and during pregnancy, however it is used in conjunction with quinine to treat chloroquine-resistant malaria, and it is effective against Plasmodium ovale.[51]

Tetracycline is used instead of doxycycline since doxycycline has a high resistance. For the treatment of chloroquine/mefloquine resistant malaria, 200 mg of doxycycline coupled with Artesunuate is used.

2, 4-diamino pyrimidine: Pyrimethamine

Pyrimethamine: It is a class containing 6- membered ring with 2 nitrogen atom.

There two types of antifolate antimalarial: Type 1 and Type 2

Type 1: (sulfonamide and sulfone)

The sulfonamide (mimic the P-amino benzoic acid) inhibits the formation of Dihydropteroate from Hydroxymethyl dihydropterin catalyzed by the dihydropterate synthase enzyme present in malarial parasite

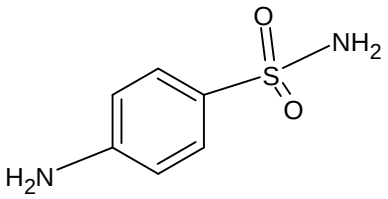


Figure 9: Structure of Sulfonamide

Type 2: Pyrimethamine:

The pyrimethamine inhibits the formation of tetrahydrofolic acid from dihydrofolic acid catalyzed by the dihydrofolate reductase enzyme which is bifunctional as thymidylate synthase enzyme present in malarial parasite.

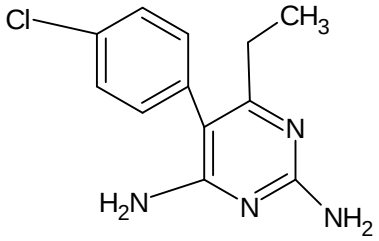


Figure 10: Structure of pyrimethamine

Mode of action

Hydroxymethyl dihydropterin

↓ Dihydropteroate synthase

Dihydropteroate

Dihydrofolic acid

↓ Dihydrofolate reductase

Terahydrofolic acid

In the production of pyrimidine and purine, folic acid plays a stimulating function. Pyrimethamine is an antifolate and a dihydrofolate reductase inhibitor. Pyrimethamine prevents the Plasmodium parasite from producing folic acid. By blocking dihydrofolate reductase, it prevents the formation of tetrahydrofolic acid from dihydrofolic acid. As a result, plasmodium replication is slowed. [51,52]

Fixed-dose combination

(Resistance is the common problem of treatment and prophylaxis of malaria so, the combination of the antimalarial drug is more preferred over a single dose of drug regimen. One of the drug from the combination, sometimes malarial parasite cannot survive without folic acid so, it acts by inhibiting the dihydrofolate reductase enzyme in malarial parasite hence it causes inhibition of folic acid synthesis of malarial parasite and another drug acts on malarial parasite mitochondria

Fansidar is containing a combination of Pyrimethamine 25 mg + sulphadoxine 500mg. This combination is effective against the prophylaxis of malaria. This combination is indicated for prophylaxis and treatment of chloroquine resistance P.falciparum and it may be used in combination with quinine) [36] Sulphonamide and dihydrofolate reductase inhibitor have the same pharmacokinetic properties. Resistance may occur due to mutation involving gene coding of thymidylate synthase and dihydrofolate synthase.

Atovaquone and Proguanil HCl is another fixed combination. Atovaquone is used in combination with proguanil in a ratio of 2.5 to 1 so, the proguanil is a prodrug and it is metabolized by CYP2C19 enzyme and converted into the cycloguanil. Atovaquone acts on mitochondria of plasmodial electron transport system of malarial parasite and Proguanil is a dihydrofolate reductase inhibitor.

Artemether and lumefantrine these combinations interfere with in formation of heme. Artemether acts by stopping the development of the malarial parasite in the erythrocyte stage[36]

Maloprim: Pyrimethamine 12.5 mg + Dapsone 10 mg[53]

Artesunate-Sulphadoxine + Pyrimathamine: This combination is effective against uncomplicated Plasmodium falciparum malaria infection although it is ineffective against the multidrug resistant strains of malaria. Proguanil was first report in 1945 against treatment of malaria infection while, atovaquone was reported for protozoa infection the combination of proguanil-atovaquone sold as Malarone

Recent development in antimalarial medication

Literature review

Bernhards O etal, the fixed dose of Artesunuate amodiaquine was developed by World Health Organization. Hence, the clinical trial was conducted .The open-label, randomized, Phase IIb clinical trial were conducted in Kenya's hospital. The study was started from November 2007 to June 2008. Kenya's adults were diagnosed for Plasmodium falciparum infection moreover; the fully informed and consented patients with age of 18-60 were selected who have infected with Pl. falciparum or Either who have history of fever though the exclusive criteria was taken into consideration like, the pregnant women, mixed infection of plasmodium, severe malaria, malnutrition, administrated artemissinin in previous three days, ingestion of sulfadoxine-pyrimethamine before 7 days. The randomization and treatment was given to them in the form of fixed and non-fixed dose. The computer based randomized trial was performed before the trial. The treated regimen is sealed in a closed cabinet. The infected patients were assigned for fixed dose of Artesunuate-amodiaquine. the total 26 number of patient were assigned for fixed drug combination of Artesunuate amodiaquine or for non-fixed combination were 28 although total dose of drug 600mg for fixed dose AS, or1620mg for fixed dose , 1836 mg for non-fixed combination so, the follow up extended over 28 days the pharmacokinetic data were collected. A repeat dose was administered if they vomiting and no concomitant food were given. The study was started by taking blood samples of patient like D0, D1, D2, D3, upto D28. The WBCs count was examined and blood sampling was started by taking merozoites and glycoproteins. The observation seen in a patient and the statistical analysis was performed. The plasma concentrations were analyzed by using liquid chromatography-mass spectroscopy mass spectroscopy and the Artesunuate and amodiaquine examined for reverse phase chromatography. The ECG were examined in D1, D2 to D20 therefore, from the result and conclusion it was observed that the Phase II clinical trial was conducted successfully and at therapeutic dose, the fixed dose of Artesunuate amodiaquine is safe for heart. The fixed dose of Artesunuate- amodiaquine is an effective treatment in malaria infected patient whereas the amodiaquine resistance is low or effective as compared to non-fixed Artesunuate amodiaquine.

ASAQ-Wintrop was developed by World Health Organization and came into the existence in 2008 furthermore; it is used for treatment of uncomplicated Plasmodium falciparum infection[54]

Tina S. Skinner-Adams,1 James S. McCarthy, Donald L. Gardiner, Petrina M. Hilton, and Katherine T. Andrews[55], were studied that the antiretroviral is used as an antimalarial agent by performing investigation with the use of 6 antiretroviral agents. Plasmodium falciparum parasite was maintained in a candle jar and saquinavir, ritonavir, nevirapine were prepared in dimethylsulfoxide solution at a concentration of 2 X 10^{-3}mol/L. Nelfinavir, amprenavir, and

indinavir were prepared at 2X 10 $^{-3}$ mol/L in methanol and chloroquine solution was prepared 10X 10^{-3} in PBS. Drug stock solution was diluted in RMPI with solution although dilution was prepared when required for the assay. DMSO, PBS did not use for the inhibition of microbes similarly, chloroquine was used as an internal control. Growth inhibition of the ring stage of P.falciparum was determined based on hematocrit incorporation. The effective concentrations were determined for inhibition of hypoxanthine incorporation. the 50% and 90% effective concentration of individual antiretroviral against the Pl.falciparum parasite were determined as follows:

Table 1 50% and 90% effective concentration of individual antiretroviral against the Pl. falciparum parasite

Drug	EC 50 %mol/L	EC 90%mol/L	Plasma Concentration	
			Maximum	Minimum
Saquinavir	0.4-0.8	2.0-4.1	3.3	0.1
Ritonavir	0.6-1.8	2.6-11.6	15.6	2.9
Indinavir	1-3.8	>7	12.6	0.2
Nelfinavir	Not achieved	>10	10	1.2
Amprenavir	Not achieved	>10	10.6	0.6
Nelvinapir	Not achieved	>10	25.1	3.0

Saquinavir and ritonavir was the most effective agent at concentration 0.4–0.8 and 0.6–1.8 mmol/L but Ampreavir, nelfinavir, and nevirapine did not show inhibition of growth of Pl. falciparum parasite, furthermore, it was suggested that this is a first report showing that though antiretroviral agent effective against drug-sensitive and drug-resistant Plasmodium falciparum[55].

Keshavarzi Arshadi Arash etal, Due to the evolution of drug resistance, antimalarial medicines are becoming less effective. All known malaria treatments, including artemisinin, have been reported to be resistant, necessitating a constant search for new therapeutic candidates. High throughput screening (HTS) of large chemical libraries for the identification of novel therapeutic leads is a time-consuming and resource-intensive approach to drug discovery. While virtual in-silico screening offers a solution to this problem, the models' generalization isn't perfect. In the realm of chemical property prediction, artificial intelligence (AI) has proven highly accurate results using either structure-based or ligand-based techniques. AI could be a viable alternative to blind-search HTS or fingerprint-based HTS by leveraging existing data. The AI programme would discover trends in the data and aid in the efficient search for hit compounds. We present Deep Malaria, a deep-learning-based method for predicting the anti-Plasmodium falciparum inhibitory effects of drugs based on their SMILES. A graph-based model was developed on 13,446 antiplasmodial hit chemicals from the public domain. Additional validation of an in-house independent dataset comprising largely of natural product chemicals is included in the in-silico pipeline for this

process. The deep learning model's performance was improved by using transfer learning from a big dataset. We employed a commonly used SYBR Green I fluorescence assay based phenotypic screening to validate the Deep Malaria generated hits. Deep Malaria detected all Nano molar compounds and 87.5 percent of compounds with higher than 50% inhibition. Further research into the mechanisms of action of the compounds has revealed that one of the hit compounds, DC-9237, not only suppresses all asexual phases of Plasmodium falciparum, but it is also a fast-acting drug, making it a good candidate for further optimization.[56,57]

António M. Mendes1 etal, The following reference lines of the ANKA strain of Pb were used: line cl15cy1, line 676m1cl1 (PbGFP-Luccon; see RMgm-29 in www.Pberghei.eu) and line 1596cl1 The GIMO-mutant has the hdhfr::yfcu positive–negative selection marker in the silent 230p locus, and PbGFP-Luccon produces a fusion protein of GFP and luciferase from the eef1a promoter. 30 Pf NF54 asexual and sexual blood stages were cultivated in a semi-automated culture system for Pf studies. Sporozoites were acquired by dissecting salivary glands from infected female Anopheles stephensi mosquitos raised at the iMM-Lisbon or the Radboud University.

A complete in silico prediction of CD8+ T cell epitopes in the proteomes of Pf and Pb was carried out to examine the potential of Pb to induce cross-species immunological responses against Pf. Our findings demonstrate that 24171 epitopes predicted in silico are common between species. These are encoded in 61 percent of Pf proteins (3371/5548) and 66 percent of Pb proteins (3332/5059). Both wild-type Pb and PbVac sporozoites infect and develop in human hepatocytes unabatedly, but are unable to infect and develop in human red blood cells. We show that PbVac generates cross-species cellular immune responses as well as PfCS-specific antibodies that effectively prevent Pf sporozoite liver invasion in human hepatocytes and mice with humanized livers in a rabbit model that is similarly vulnerable to Pb hepatic but not blood infection. As a result, preclinical investigations show that PbVac is safe and elicits functional immune responses, indicating that clinical testing and development are warranted.[58]

Garrido-Cardenas JA, Cebrián-Carmona J, González-Cerón L, Manzano-Agugliaro F, Mesa-Valle C, Malaria is one of the infectious diseases that scientists are most interested in that worldwide peoples are most concerned about Plasmodium falciparum, the parasite that causes the most severe type of malaria in Africa, has traditionally been the focus.

However, in the last two decades, the Plasmodium vivax parasite, which is responsible for a substantial number of cases in Latin America, the Middle East, South and Southeast Asia, the Horn of Africa, and Oceania, has sparked a lot of attention, thanks to published evidence, among other things. The Scopus database was used to assess international scientific publications on malaria and

P. vivax in order to try to determine global trends in this field of study. It has been demonstrated that factors such as the evolution of drug resistance can halt a trend. Non-malaria-endemic countries such as the United States and Switzerland play an essential role in malaria research. For the disease to be eradicated, worldwide collaboration will be critical. Furthermore, it was observed that, the bibliometric study of malaria caused by P. vivax is critical in this regard, as it helps to construct a picture of the current situation and inspire international collaboration and control efforts.[59]

Bioinformatics research suggested that sarcosine and aniline have antiplasmodial action. Sarcosine and aniline covalently linked can have a dual activity for suppressing plasmodial development, with separate ways of action. This claim was validated in this investigation due to the pressing necessity in drug development. The hypothesis was that a sarcosine-aniline hybrid could have dual inhibitory effects on pyrimidine and fatty acid production, circumventing parasite tolerance to ACTs. The following procedure was carried out to synthesize the sarcosine-aniline coupling in this process the thionyl chloride was added to the solution aniline and resulting solution was refluxed for 6 hrs. until it shows the clear yellow solution the excess of thionyl chloride is removed by vaccum pump and acid chloride solution added to the dichloromethane and kept at 0C 3-chloro-4-(4-chlorophenoxy) aniline was added to the triethylamine by using cannula. The solution was stirred at room temperature until it became the white precipitate the precipitate was washed with half saturated ammonium chloride solution and dried over magnesium sulphate however it, the hybrid of sarcosine-aniline was employed for the thin layer chromatography for monitoring of its coupling[60] and finally the hybrid compound was evaluated for cytotoxicity study and in-vitro toxicity study. From result and conclusion it was revealed that, thin layer chromatography was used to monitor and validate the production of 3-chloro-4-(4-chlorophenoxy) aniline pharmacophores, and the product was formed. Sarcosine-aniline hybrid drug is a promising antiplasmodial prodrug since it exhibited action in vitro and in vivo experiments with an IC50 of 44.80 4.70 ng/ml and an ED50 of 6.49 mg/kg, both of which are within acceptable ranges for medications used to treat severe malaria. According to this study, sarcosine-aniline hybrid drug is safe to vero cells with a CC50 of 50.18 3.53 g/ml, whereas doxorubicin is the most toxic with a CC50 of 1.96 0.59 g/ml. The acute toxicity results showed no dead mice up to a dosage of 2000 mg/kg administered orally for 14 days, and there was no significant weight loss in mice within and between groups with different sarcosine-aniline hybrid dosages, as well as in the control group.

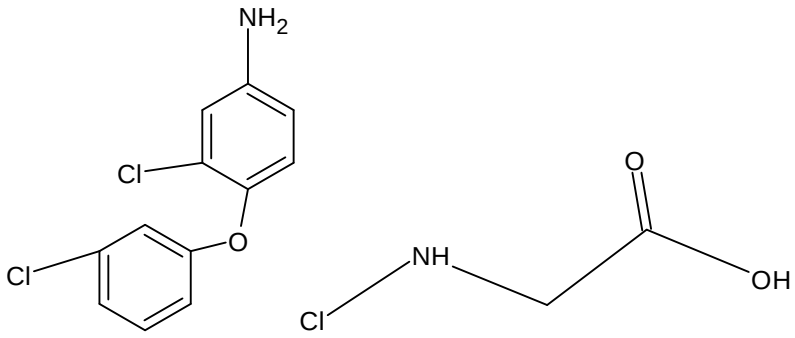


Figure 11: Structure of Aniline and sarcosine

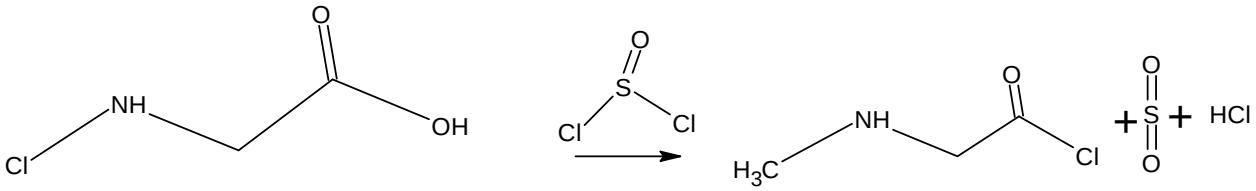


Figure 12: Reaction between sarcosine and thionyl chloride

Shackleford DM etal[62], 1,2, 4- trioxolone have been effective, oral antimalarial agent. It is first generation ozonide, arterolane in combination with piperaquine is approved in India similarly the second generation ozonide retains antimalarial agent although it have long duration of action, retain biological activity but it should combine with artemisinin. Metabolite was identified by LC/MS method. The synthesis of authentic metabolite were done out of which three sites have adamantane hydroxylation X ray diffraction study were conducted the 2 metabolite was detected by using chromatographic method like liquid chromatography and mass spectroscopy however the synthesized metabolite were screened against the chloroquine sensitive and chloroquine resistant strain of P.falciparum. The direct CYP inhibition assay was conducted using HLMs and a substrate-specific interaction.[63]

Antimalarials with a short half-life are essential for reducing parasite burden and relieving malaria symptoms as quickly as possible11. DDD01034957 was compared to artesunate (rapid kill), chloroquine (fast kill), pyrimethamine (medium kill), and atovaquone (slow kill) in an established parasite viability assay12 to determine its speed of action. DDD01034957 decreased parasite viability to baseline within 24 hours at 3.2 M (10xIC50) at a rate comparable to 10xIC50 artesunate and chloroquine confirming its fast acting antimalarial efficacy. Pyrimethamine and atovaquone, on the other hand, are slower acting antimalarial[64].

CONCLUSION

The Antimalarial agents are effective against the malarial infection but it may produce the resistance to the drug therefore the fixed dose combination is more effective drug therapy is effective against the malarial infection. The structure, chemical name, structural activity relationship of various drugs, uses was discussed.

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