Review Article

A Brief History of Quinoline as Antimalarial Agents

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ABSTRACT

Development of new and more powerful antimalarial drugs has become more complex because of emergence of multidrug resistant strains of *P. falciparum*. Due to resistance of malaria parasite against well-known available drugs, the chemotherapy of malaria has become more complex and challenging. In this review we have discussed the life cycle of malaria parasite followed by quinoline based antimalarial drugs. Quinoline containing antimalarial compounds is the most effective class of drugs known for malaria chemotherapy. The list of commercially available antimalarial drugs along with their mode of action on different stages of parasite has been discussed in this review. A brief description of their mechanism of action and advantages and disadvantages are also reported. The combination chemotherapy and drugs under clinical trials and future strategies which are following are summarized in conclusion section. Aim of this review to summarize structure-activity relationship and medicinal chemistry developments in the field of therapeutic 4-amino quinoline derivatives.

Keywords: Malaria, *P. falciparum*, 4-amino quinoline, combination chemotherapy, structure-activity relationship.

INTRODUCTION

Malaria, one of the most infectious diseases of mankind in the world, is wide spread in more than 90 countries and affecting around 40% of the world's population. There are some 300-500 million cases and between 1.5-2.7 million deaths each year from malaria. It is a hematoprotozoan parasitic disease transmitted to humans by a particular species of *Anopheline* mosquitoes.[1] These insects inoculate *Plasmodium* sporozoites to humans *via* a blood feeding process. The genus *Plasmodium* can be classified into nine subgenera. *Plasmodium falciparum, P. vivax, P. ovale* and *P. malariae* are the species that infect humans. Malaria caused by *P. falciparum* is most critical and lethal. It accounts for 80% of all malaria infections and 90% of malaria related deaths. Infection with this parasite can lead to death within hours to days.[2-6]

The increasing resistance of malaria parasites particularly in *P. falciparum* is an important factor in the persistence of this disease as a major worldwide public health menace. The existing chemotherapy is not satisfactory in terms of lack of effectiveness and also due to the side effects associated to long-term treatments.[7, 8] Drug resistance and strain sensitivity to the existing drugs are other shortcomings for the clinically accessible chemotherapy. The drug discovery costs for the pharmaceutical industry to introduce new compounds into the market have risen dramatically from the last decades. In 1998, the World Health Organization, UNICEF, UNDP and the World Bank launched the Roll Back Malaria (RBM) initiative to offer a coordinated approach to fight against malaria but with little success so far.[9] Artemisinin based drugs are the only affordable treatment for malaria. However, some parasites isolated from French Guiana and Senegal recently showed diminished in vitro sensitivity to artemether.[10, 11] Therefore, it is an urgent need to find new natural or synthetic drugs before malaria parasite get resistance against artemisinin and its derivatives. Early discovery of potent drug is highly required to help in the prevention and control of this parasitic disease.

Quinoline and its derivatives represent a very important class of antimalarial drugs that function by parasite hemoglobin breakdown pathway.[12-14] Quinoline-containing antimalarials have long been used to combat malaria. In 1940s, synthetic Quinoline compound chloroquine was introduced (Loeb *et al.*, 1946)[15] and proved invaluable in the fight against the disease. However, only limited number of quinolines have evaluated for their antimalarial activity against malaria parasites. Thus, it is meaningful to re-look the antimalarial activity of existing quinoline libraries or synthesize some different quinoline derivatives with enhanced activity. A systematic and extensive study is required to discover effective antimalarial compound form 4-aminoquinoline based scaffold. In this chapter we have synthesised different analogs of 4,7-dichloroquinoine and screened against malaria parasite.

Life cycle of malaria parasite

The human malaria parasite requires both human hosts and insect hosts to complete its life cycle. In anopheles mosquito, the *Plasmodium* parasite sexually i.e., by combining sex cells, while in human parasite reproduces asexually, first in liver cells and then repeatedly in blood cells. Malaria infection in human host starts when the sporozoites injects into the blood during an infected mosquito bite. The mosquito takes meal to nourish her eggs. At the same time, she injects saliva that contains

infectious sporozoites. Although it is assumed than one single sporozoite is capable of initiating the infection in men, the number of sporozoites injected by a mosquito bite is supposed to vary from dozens to thousands. It is likely that this number strongly affects the clinical picture: the greatest the sporozoite load, the shortest the incubation period and the most serious the symptoms. The sporozoites remain into the circulation for a short period, calculated as 60 minutes at maximum, before they actively enter the liver of the host (Lopez-Antunano, 1980).[16] The Kupffer cells in the liver may be invaded (or the parasite may be phagocitated) but the sporozoites are not able to develop in those cells and die shortly after invasion. Most parasites however invade the hepatocytes and start the asexual exo-erythrocitic schizogonic cycle. The cycle has been studied in details in liver sections from a rodent model for malaria infection, but observations from liver biopsis in human volunteers are also available for *P. falciparum* and *P. vivax.* The liver trophozoite initially appears as a mononucleated round body into the cytoplasm of the host cell; subsequently it begins to develop and multiply asexually, a mature schizont(the multinucleated stage of the parasite) is formed, and finally a large number of merozoites are released**.**

The mature schizont is 30-70 µm large, has no pigment (there is no hemoglobin into the hepatocyte), and occupies the entire cell cytoplasm. The length of the schizogonic liver cycle is constant for each Plasmodium species to the extent that it can be considered a taxonomic character: this is the above mentioned prepatent period (5.5, 8, 9, and 15 days for *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae,* respectively).

The number of merozoites produced at the end of the cycle is also species dependant: it is estimated as 2,000 for *P. malariae*, 10,000 for *P. vivax/P. ovale*, and up to 30,000 for *P. falciparum* (Garnham, 1966).[17] The liver cycle ends when the mature schizont ruptures and releases the merozoites into the sinusoids of the liver. Released merozoites can only invade a red blood cell: the theory of the continuation of the liver cycle by invasion of a new hepatocyte by the merozoite, is not any more accepted at present (figure-1).[18, 19]

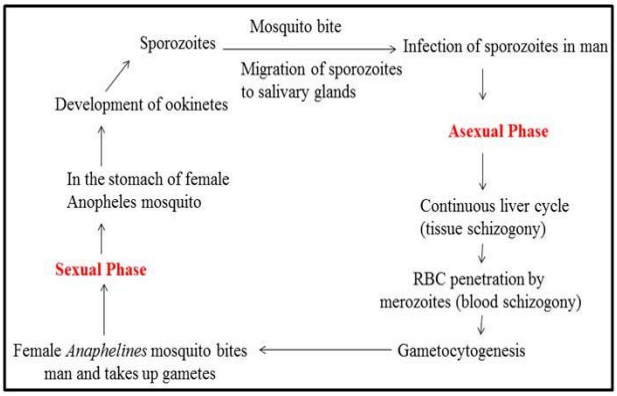

Figure 1: Lifecycle of malaria parasite

HISTORY OF QUINOLINE ANTIMALARIAL DRUGS

Quinine

The first quinoline antimalarial drug quinine was alkaloids extracted from the cinchona tree. The cinchona tree is named after the Countess of Chinchon, who according to legend was cured of malaria in 1630 by a powder made from its bark (figure 2). The powdered bark of the "fever tree" was widely distributed in Europe by the Jesuits during the 17th century (Wallace, 1996).[20] A crude mixture of crystalline alkaloids was extracted from cinchona bark in 1810 by Gomes in Portugal and quinine & cinchonine subsequently were isolated by Pelletier and Caventou in 1820 (Hofheinz and Merkli, 1984) (figure 3).[21] A pathway for the synthesis of quinine was described by Woodward and von Doering in 1944. Quinidine a stereoisomer of quinine is also used as antimalarial drug. After World War II, chloroquine and pyrimethamine largely replaced quinine for prophylaxis and routine treatment.

Figure 2: Cincona tree parts

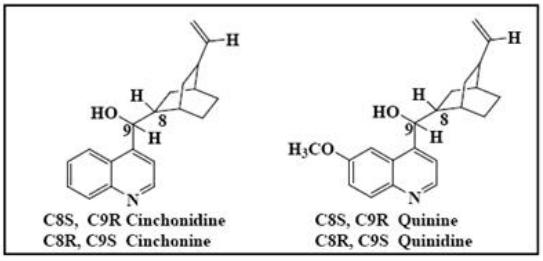

Figure 3: Chemical structure of quninine and quinidine

8-Aminoquinoline

The discovery of 8-aminoquinoline drugs came from the mild antimalarial activity of methylene blue. Various analogs of methylene blue were synthesised by replacing one methyl group with basic alkyl side chain to enhance activity.

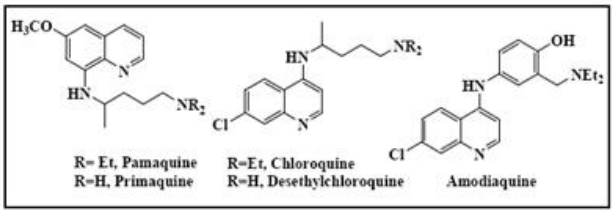

Figure 4: Chemical structure of pamaquine, primaquine, chloroquine & amodiaquine

The first analog which was synthesized in this series was plasmoquine which was also known as pamaquine (figure 4).[22] This compound was found too toxic to use therefore, to overcome this problem primaquine was synthesised. Primaquine was comparatively much less toxic analog of 8-amonoquinoline. Primaquine is still used to eradicate the hypnozoites of *P. ovale* and *P. vivax*.

4-Aminoquinole

Scientist at Bayer Institute in Germany synthesized 4-aminoquinoline Resochin by altering the basic side chain.[15, 23] Resochin was found to be safe for malaria treatment and renamed as chloroquine. Chloroquine became popular for clinical use due to its effectiveness and low risk of side effects. Unfortunately, chloroquine has not been used wisely and in early 1960s the cases of chloroquine resistance emerged.[24, 25] Amodiaquine was introduced as an alternative and has been used for the prophylaxis of *P. falciparum* for almost 40 years. Upon oral intake of amodiaquine rapidly absorbs and metabolizes. Even though AQ has a high absorption rate, it has a low bioavailability and is considered a pro-drug for desethylamodiaquine. The formation of DEAQ is rapid and its elimination very slow. In contradiction of the metabolism of CQ, AQ produces a toxic quinoneimine metabolite. The metabolites have been detected in vivo by the excretion of glutathione (GSH) conjugates (figure 5).

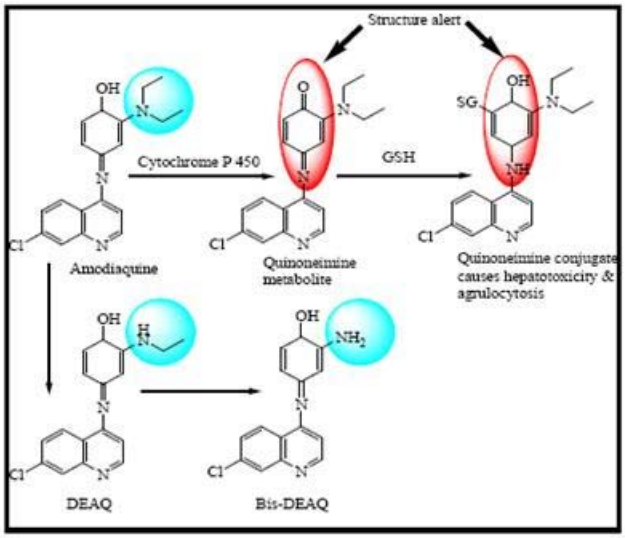

Figure 5: Chemical reactions involve in the formation of DEAQ and bis DEAQ

CQ still remains the treatment of choice in a few geographical areas where it can still be relied upon, although guidelines now instruct the use of combination chemotherapy to slow the development of resistance to the partner drug. In some resistance "hot spots", CQ was completely abandoned for a combination of Sulfadoxine - pyrimethamine almost two decades ago. In such cases, there is evidence to suggest that CQ sensitivity can be restored. The failure rate of CQ treatment can be decreased by giving the drug twice per day rather than as a once daily treatment regimen. Doubling the dosing frequency in this way achieved a high cure rate despite underlying CQ resistance and without any adverse side effects. This increase in efficacy can be explained by the pharmacokinetics of CQ; the second daily dose of CQ acting to raise plasma concentrations to levels where they have activity against resistant parasites. It has also been shown that the use of this type of treatment regimen can stabilize the spread of CQ resistance but major drawback in this is the narrow therapeutic index for chloroquine.

Quinoline methanol

The most promising compounds in this group were 4-aminoquinoline methanol structurally analogous to quinine.[21] These compounds were every effective for both *P. falciparum* and *P. vivax* but exhibited strong photosensitizing actions.

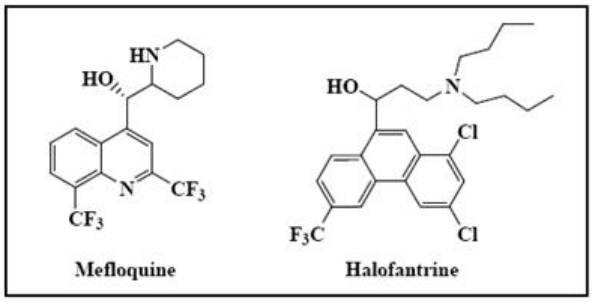

Figure 6: Chemical structure of mefloquine and halofantrine

Mefloquine (figure 6) was synthesized afterwards which was more potent with no appreciable photosensitizing effects.[26] Mefloquine was used in fields for almost 30 years especially for chloroquine resistant strains. But due to resistance and toxicity associated these are now limiting in use.[27-29]

Another major class of compounds emerged by replacing quinoline basic scaffolds of 4-aminoquinoline to various aromatic rings. Halofantrine (figure 6) synthesized in this class and used to treat chloroquine resistant malaria.[30-32] However, its use has been restricted due to serious cardiotoxic effects.[33, 34]

Quinoline and its derivatives: structure-activity relationship (SAR)

Quinine has been used for centuries in the treatment of malaria. It is a low-cost drug but has become limited due to a decrease in its sensitivity by parasites. However, it is still used parenteral to control acute cerebral malaria. The structure-activity relationships of chloroquine and related quinoline antimalarial compounds have been reviewed extensively.[35-38] Other derivatives of quinine include chloroquine, amodiaquine, mefloquine and halofantrine. These drugs act by decreasing the rate of hemozoin formation, rather than irreversibly blocking its formation.[39-41] An alternative mechanism of action of chloroquine has also been hypothesized. It is believed that it works through the generation of highly reactive radicals due to an electron transfer between the redox

couple Fe II heme/Fe III heme and the quinoline ring may be responsible for antimalarial action of chloroquine.[42]

The 7-halosubstituted compounds are the most active antimalarials in the 4-aminoquinoline series. Change of the halogen or disubstitution on the quinoline nucleus generally lowers activity as in 9-aminoacridine series. The inter-nitrogen separation (the molecular distance between the quinoline N and the alkylamino N) affects the level of activity of 4-aminoquinolines[43] and is important in defining the ability of drugs to bind to heme.[44] Structure-activity relationship studies of quinine analogs suggested that a hydroxyl group on C-9 is necessary for activity. *Erythro* configurations at the C-8 and C-9 positions of quinine analogs are more active than the *threo* isomers but not in all cases.[21] The orientations of the hydroxyl and amine groups of mefloquine are critical to antimalarial activity. 4-Aminoquinoline nucleus of chloroquine and related antimalarials is responsible for complexing free heme and the group at the 7-position of the quinoline ring appears to be vital in determining the antimalarial ability of 4-aminoquinolines to inhibit the formation of hemozoin. The aminoalkyl side chain of quinoline drugs is also accountable for strong antiplasmodial activity. However, change in the length of amino alkyl side chain has little influence on activity against chloroquine-sensitive strain of *P. falciparum* but has an intense influence on the activity especially against chloroquine-resistant strains.[45]

Quinoline drugs lacking 7-chloro group do not inhibit hemozoin formation although forming complexes with heme. Replacing 7-chloro group with a bromo or nitro group shows the inhibition of hemozoin formation. If a chloro atom is introduced at the 6-position on the quinoline ring, the interaction with hematin is completely disrupted.[43-45] If 7-chloro is replaced by 7-amino and 7-chloro derivatives, hemozoin formation is not inhibited. Aminoquinolines inhibiting hemozoin formation must have aminoalkyl side chain for its strong antimalarial activity. Replacement of aminoalkyl side chain to hydroxyl or other group causes severe reduction in activity. 4-Aminoquinolinedialkylamino side groups are liable for ideal activity.[46]

Heme detoxification pathway

The characteristic clinical symptoms produced during the intra-erythrocytic phase of the parasite life cycle within host. During this phase, hemoglobin is employed as a major source of amino acids to stimulate the parasite growth. When hemoglobin is degraded, potentially toxic iron containing heme group is released. Though, *Plasmodium* parasites develop a particular heme detoxification mechanism where heme is altered into a dimeric form and finally converted into polymeric non-toxic hemozoin (malaria pigment) through the formation of hydrogen bonds between dimeric heme units.[47]

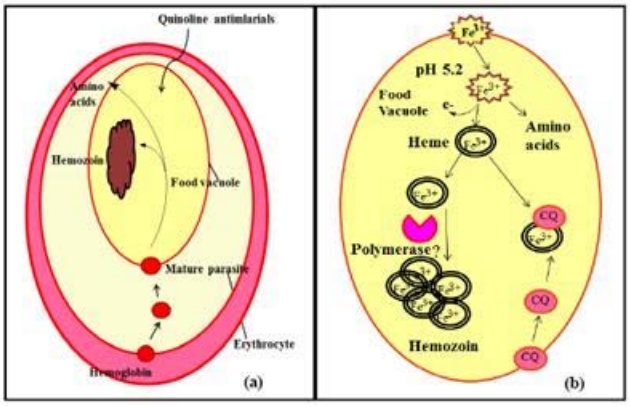

Figure 7: The digestive process in the malaria infected erythrocyte and the putative mode of action of chloroquine. **a.** Hemoglobin degradation; **b.** Inhibition of heme polymerisation. Foley *et al*., 1998.

The quinoline containing antimalarial drugs like chloroquine kills the parasite, causing swelling of the food vacuole, increasing granularity of the cell and ultimately cell death. Chloroquine is effective against the erythrocytic stages of malaria parasite but shows no effect against liver stages like pre erythocytic or hypnozoite stage.The sensitivity of the parasite towards chloroquine is much higher than the host cells. Chloroquine is a diprotic weak base (pK_{a1}=8.1, pK_{a2}=10.2) and its unprotonated from it diffuses through the membrane of parasitised erythrocyte and gets accumulated in the acidic food vacuole (pH=5-5.2). Acidic compartment in *P. falciparum* alsoknown as the digestive vacuole (DV) helps the function of digesting hemoglobin from the infected erythrocyte. A by-product hemozoin is produced after the degradation of haemoglobin. Free heme (ferriprotoporphyrin IX, Fp IX;Free FP) can lyse the cell and affect the function of lysosomal enzymes. Detoxification of FP is performed by the food vacuole, which converts it into hemozoin and an enzyme heme polymerase appears to be involved in this process (figure 7).[48] This pigment is not incorporated into the merozoites and is left behind with the shell of the parasitized red cell. Early studies implicated the importance of FP in the mechanism of action of chloroquine because it was noted that quinine was not effective against malaria which did not make pigment.[49-51]

Drug Resistance in malaria parasite

The ability of an organism to resist the action of drugs is known as drug resistance. The development of resistance is one of the greatest threats to malaria control. Generally, drug resistance occur through spontaneous mutations in genus that confer reduced sensitivity to a given drug or class of drugs. Drug resistance by malaria parasites has been defined as the ability of a parasite strain to survive or multiply despite the administration and absorption of a drug when given in doses equal to or higher than those normally recommended and within the limits of tolerance of the subject.

Two of the four species of malaria parasite that naturally infect humans are *P. falciparum* and *P. vivax*. *P. falciparum* has developed resistance to nearly all antimalarials in current use.[52]

Almost 80% malarial parasites are chloroquine resistant and spread all over world at present. Because of the digestion of hemoglobin, large amount of a toxic by-product are formed. The parasite polymerizes this by-product in its food vacuole, producing non-toxic hemozoin (malaria pigment). It is believed that resistance of *P. falciparum* to chloroquine is related to an increased capacity for the parasite to expel chloroquine at a rate that does not allow chloroquine to reach levels required for inhibition of heme polymerization.[53] The drug resistance against the antifolates has also been reporteddue to specific gene mutations encoding for resistance to both dihydropteroate synthase (DHPS) and dihydrofolate reductase (DHFR).[54] Recent reports on drug resistant malaria showed that malaria parasite had developed resistance against all class of drugs.Unfortunately, the emergence of malaria parasite strain resistant against effective and cheap chloroquine has eroded its efficacy.

Combination therapy

Combination therapy or polytherapy is the use of more than one medication or therapy. Foremost benefit of combination therapies is that it decreases the development of drug resistance, since a pathogen is less likely to have resistance to multiple drugs concurrently.[55] Due to resistance of malaria parasites to commonly accessible antimalarial drugs in market, combination therapy is promoted by world health organisation for malaria treatment with remarkable success.[56, 57] Sulfadoxine-pyrimethamine, an antifolate combination has been used all over the world, especially in areas where chloroquine has futile. It inhibits folate synthesis that is a key factor for parasite persistence. Pyrimethamine inhibits DHFR[58] and sulfadoxine prevents dihydropteroate synthase (DHPS).[59, 60] Although, the combination of sulfadoxine and pyrimethamine (SP) (figure 8) is still being used in Africa as first line treatment for non-severe *falciparum* malaria, however, increasing resistance has been reported in Africa.[61, 62] Several efforts are being made to get most effective combination from current or newly demonstrated drugs. A number of combination have been conveyed, out of which artemisinin based combination therapy is most effective.

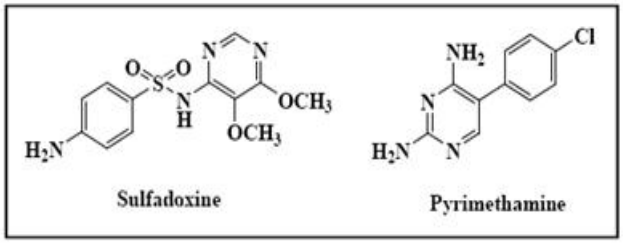

Figure 8

Artemisinin-based combination therapy (ACT) is being widely promoted to counteract the increase in *P. falciparum* antimalarial drug resistance.[63, 64] Artemisinin derivatives are potent, rapidly acting antimalarials which can reduce gametocyte carriage and patient infectivity.

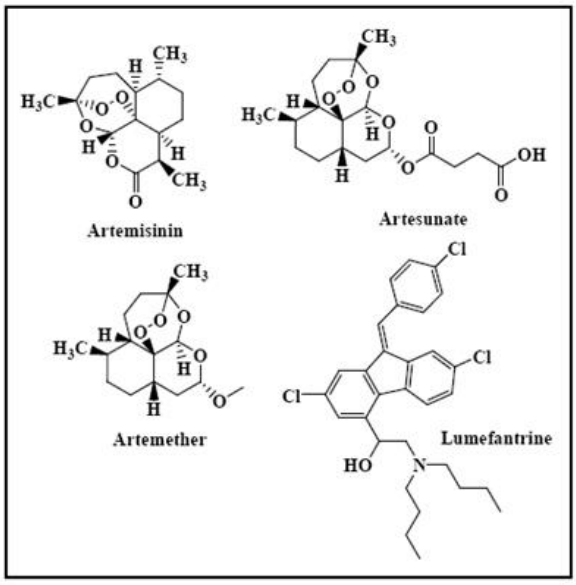

Figure 9: Chemical structure of Artemisinin and analogs

The most common artemisinin derivatives used in ACT are artesunate and artemether as shown in figure 9. The drugs used in combination with the artemisinin derivative are called the partner drugs (mefloquine, lumefantrine, amodiaquine etc.). ACTs are now accepted by the scientific community and WHO as the best strategy for the treatment of malaria caused by *Plasmodium falciparum*.[65]

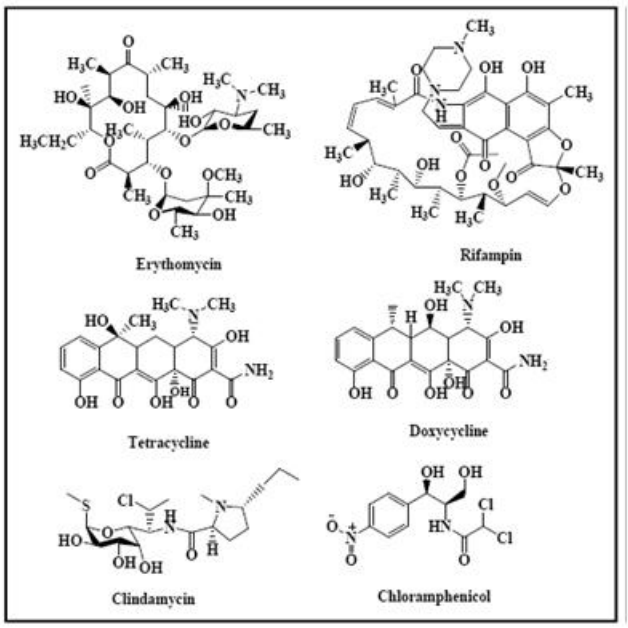

Figure 10

Various combinations of artemisinin and other drugs e.g. artemether + lumefantrine (A/L),[66] artesunate + sulfamethoxypyrazine + pyrimethamine,[67-71] dihydro-

artemisinin + piperaquine and artesunate + mefloquinehave been reported.The combination of artesunate + amodiaquine is therapeutically superior to a combination of chloroquine + pyrimethamine-sulfadoxine.[72]

Various classes of antibiotics also exhibit antimalarial activity. Sulphonamide and sulphones are well known scaffolds exhibiting antimalarial activity. They are very effective when used in combination with pyrimethamine. It is well established fact that antibiotics such as erythromycin, clindamycin, tetracycline, rifampin, and chloramphenicol (figure 10) displays antimalarial activity in vivo either alone or in combination with other commonly used antimalarial drugs.[73-76] Despite of slow antimalarial activity against malaria parasite, antibiotics such as doxycycline are used for antimalarial prophylaxis along with more efficient antimalarial drugs.[77] The fluoroquinolones are antimicrobial agents that are similar in structure to quinoline antimalarial drugs also exhibits antimalarial activity. Fluoroquinolones e.g. ciprofloxacin, norfloxacin and pefloxacin (figure 11) have been evaluated previously for antimalarial activity against *P. falciparum in vitro.*[78-80]

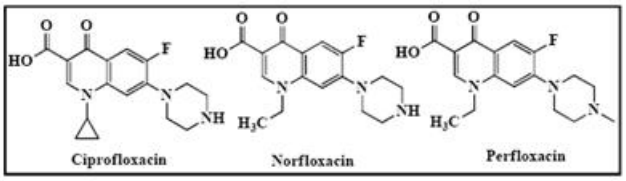

Figure 11

CONCLUSION

It is really apprehensive that resistance in malaria parasites continues to grow, increasingly limiting our ability to control this serious disease lead to an over dependence on artemisinin availability and may influence cost. So it is extremely important that 4-aminoquinoline drug development programmes continue. Increased understanding of 4-aminoquinoline SARs, mechanisms of toxicity and parasite resistance has aided development of what will hopefully be the next generation of 4-aminoquinolines. Recent increases in the pace of progress in this area suggest that, if support for antimalarial drug discovery is adequate, new approaches should lead to the development of valuable new strategies for antimalarial therapy in the near future.

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