ANTIMALARIALS

- Malaria, one of the most widespread diseases, is caused by a plasmodium parasite. Its name is derived from **mala aria** (Bad air) , and it has been called ague, intermittent fever, marsh fever and The fever.
- Laveran , (Army physician) should that malaria is caused by Plasmodium protozoan.
- Ronald Ross , (Army surgeon) demonstrated that the Anopheles mosquito is the transmitter of the disease.

PLASMODIUM AND LIFE CYCLE

- In man , the infective Protozoa are **Plasmodium falciparum, P. vivax , P. malariae** and **P. ovale.**
- Plasmodium falciparum causes 50 percent malingnant tertian malaria (most dangerous form of human malaria)
- Plasmodium vivax causes 40 percent benign tertian malaria.
- Plasmodium malariae causes 10 percent quartan malaria.
- Plasmodium ovale causes rare malarial infection and it is milder and more rapidly caured.
- Man gets infected by the bite of infected mosquitoes which inject sporozoits into the circulation.

DIAGNOSIS OF LIFE CYCLE

There are four possible sites for drug therapy at this stage of disease.

1) Kill the sporozoites injected by the mosquito and or prevent the sporozotis from entering the liver.

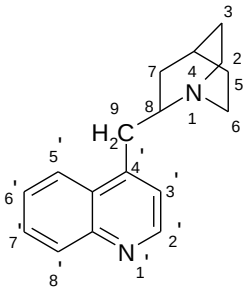
2) Kill the schizonts responding in hepatocytis and or prevent them from becoming merozoites.

3) Kill the merozoites in blood and or prevent the from developing into gametocytes.

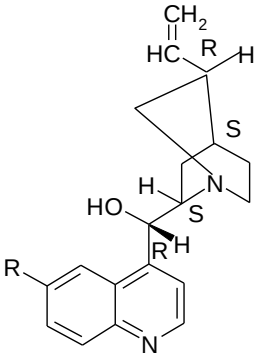
4) Kill the gametocytes before they can enter the mosquito and reproduce into zygotes.

CLASSIFICATION

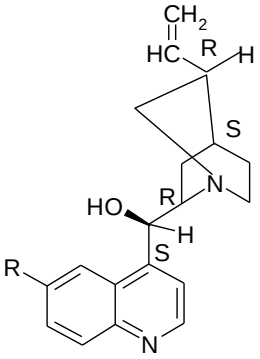
A) **CINCHONA ALKALOIDS** – These alkaloids are the enantiomeric pair quinine and quinidine and their desmethoxy analogoues , cinchonadine (for quinine) and for cinchonine (for quinidine) . their numbering system is based on urbane. The stereochemistry differs at positions 8 and 9 , with quinine and (cinchonidine) being S,R and quinidine (cinchonine) being R,S. (Quinine is the main treatment for malaria until the advent of world war second.)



Rubane

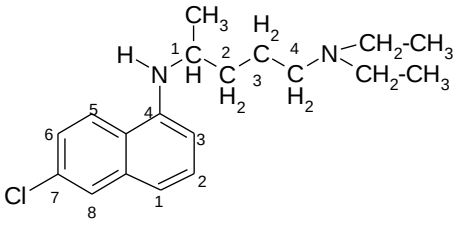


Quinine R = OCH3
Cinchonadine R = H



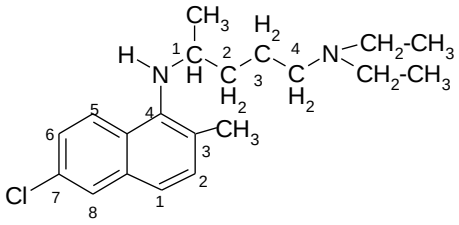
Quinidine R=OCH3
Cinchonine R= H

B) **4 –AMINOQUINOLINES**

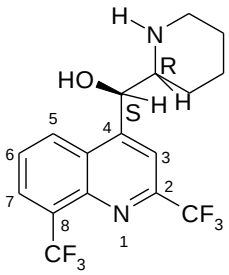


7-chloro-4-(diethylamino-1-methylbutylamino)

Quinoline (chloroquine)



Sontoquine



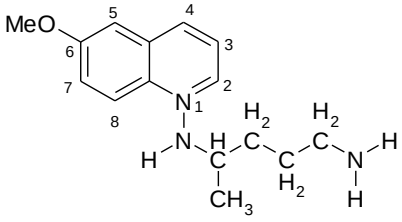
Mefloquine

Note- 1- Newest drug in this series, mefloquine, only R,S isomer is markted.

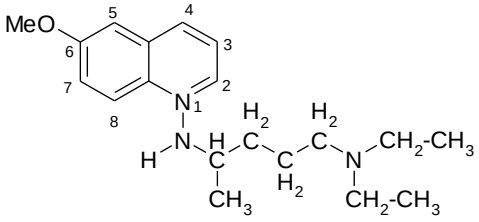
2-Recently, chloroquine was the main antimalarial drug used both for prophylaris and Treatment.Its main siteof action appears to involve the lysosome of Parasite –injected lrythrocyte..

Mecanism of action- A very complain mechanism is based on ferriprotoporphyrin IX Which is realeased by plasmodium - containing erthrotes, acting as a chloroquine receptor. The combination of ferriprotoporphyrin IX and chloroquine caused lysisi of the parasites or the erythrosites membrane.

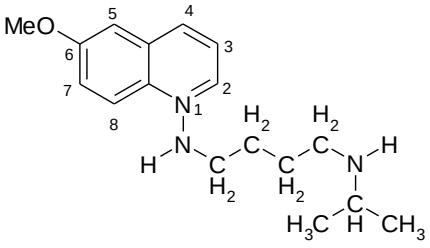
C) **8-AMINOQUINOLINES –** The first compound introduced in the series was paraquine . During world war 2 , Pentaquine , isopentaquine and primaquine become available. Only primaquine , used during the Korean war , is in wide today . all of the 8-aminoquinolines can causes haemolytic anemia in erythrocytic glucose-6-phosphate dehydrogenase deficient patients.



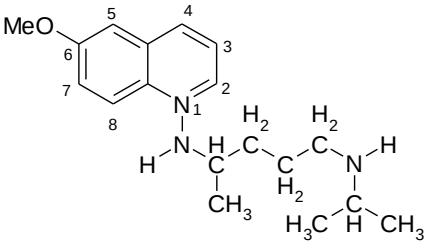
Primaquine



Pamaquine



Pentaquine

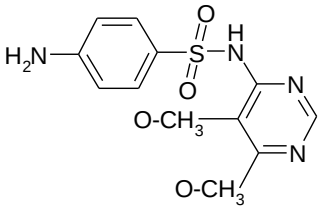


Isopentaquine

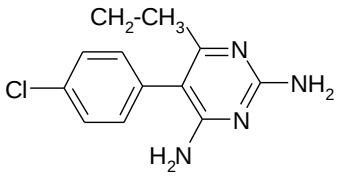
- Paraquine appears to disrupt the parasites mitrochondria.
- Primaquine kills primary and secondary erythrocytic forms of the plasmodium.

D) **COMBINATIONS**

1- Sulfadorine and pyrimethamine



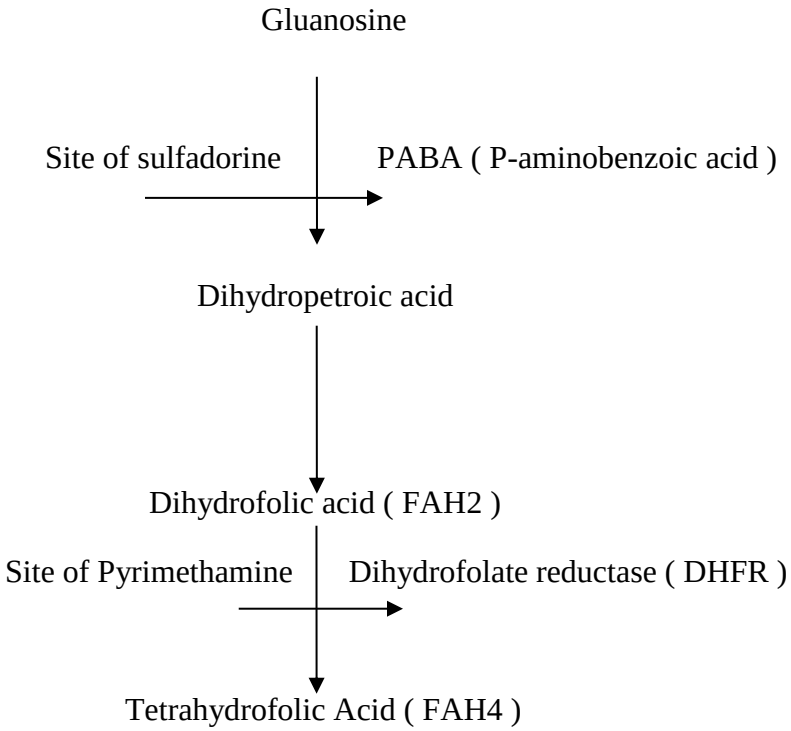
Sulfadorine



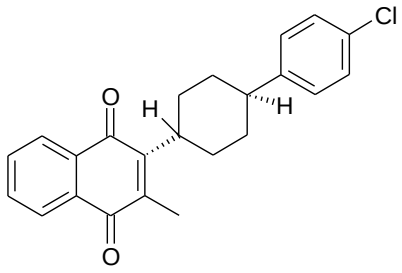
Pyrimethamine

- The combination considered Schizonticidal (site 2)
- The combination of sulfadorine and pyrimetamine used as a drug from the sulphonamide antibacterial group and pyrimidine diamine similar to trimethoprime.
- The sulphonamide , sulfadorine interfere with the parasites ability to synthesize folic acid and pyrimidinediene.
- Pyrimethamine ,inhibits the reduction of folic acid to its active tetrahydrofolate co-enzyme form.
- The first combination contains 500mg of sulfadorine and 25mg of pyrimethamine.

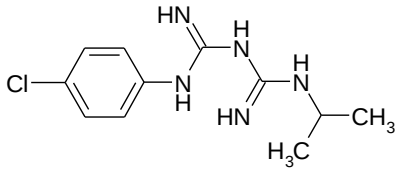
FOLIC ACID SYNTHESIS PATHWAYS



2- ATOVAQUONE AND PROGQUANIL **(2:5:1) –**



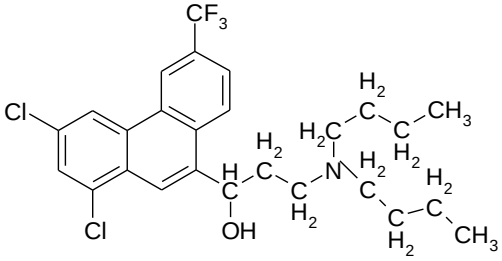
Atovaquone



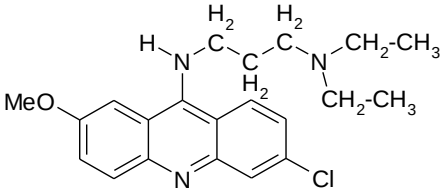
Proquanil

- Proquanil metabolized to cycloquanil at the presence of CYP2C19.

E) –POLYCYCLE ANTIMALARIAL DRUGS

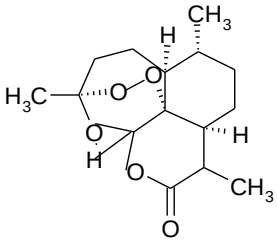


Halofantrine



Quinocrine

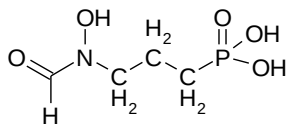
F) – NEW ANTIMALARIAL DRUGS



Artemisinin

NOTE-

- Artemisinin is a natural product extracted from the dry leaves of Artemisia annua (sweet warmwood)



Fosmidomycine

- Fosmidomycine was isolated from a streptomyces fermentation broth in 1980.
- Replacement of fosmidomycine N-aldehyde with an acetate produce a very active antimalarial agent that has been designated FR900098