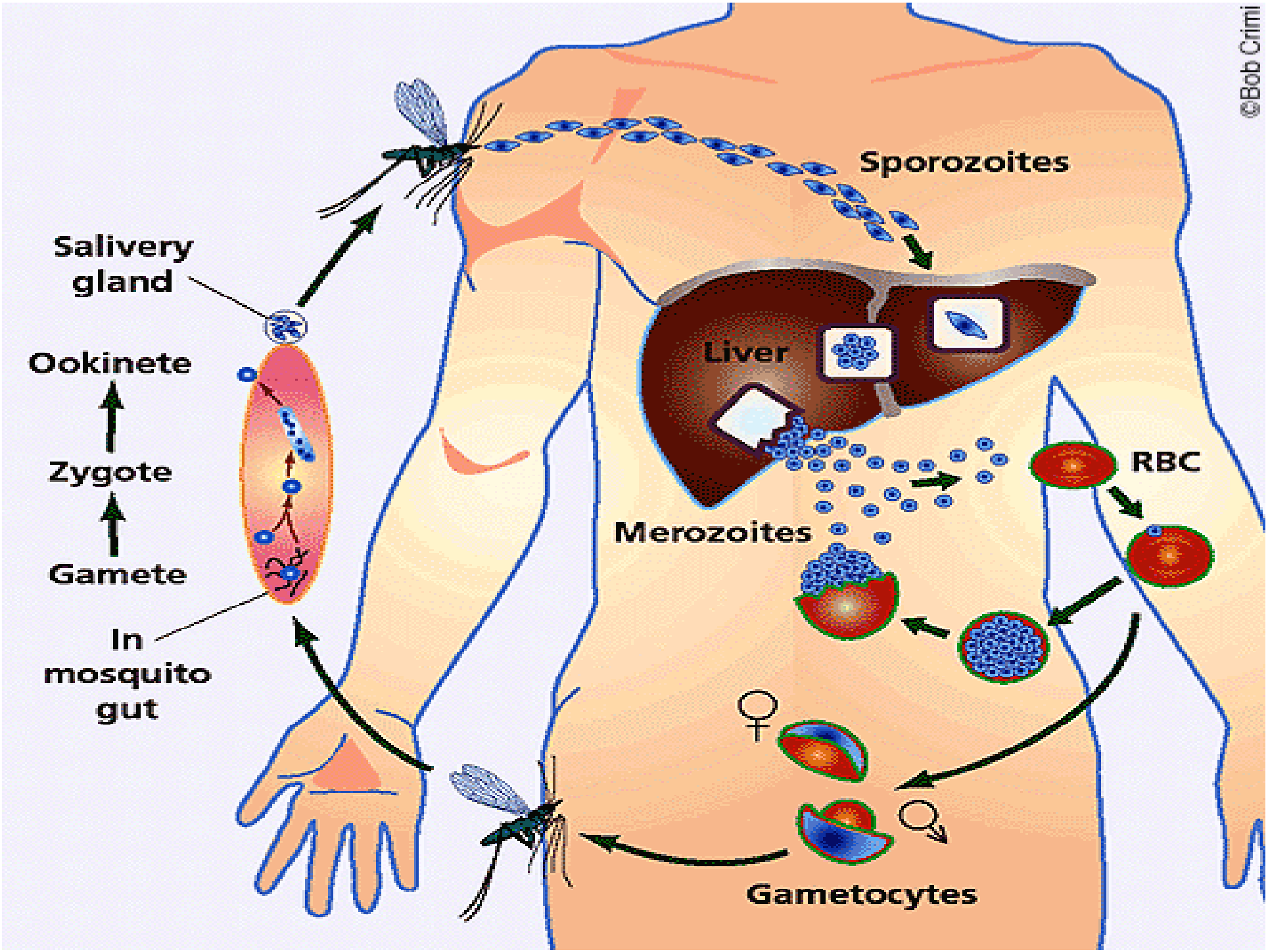
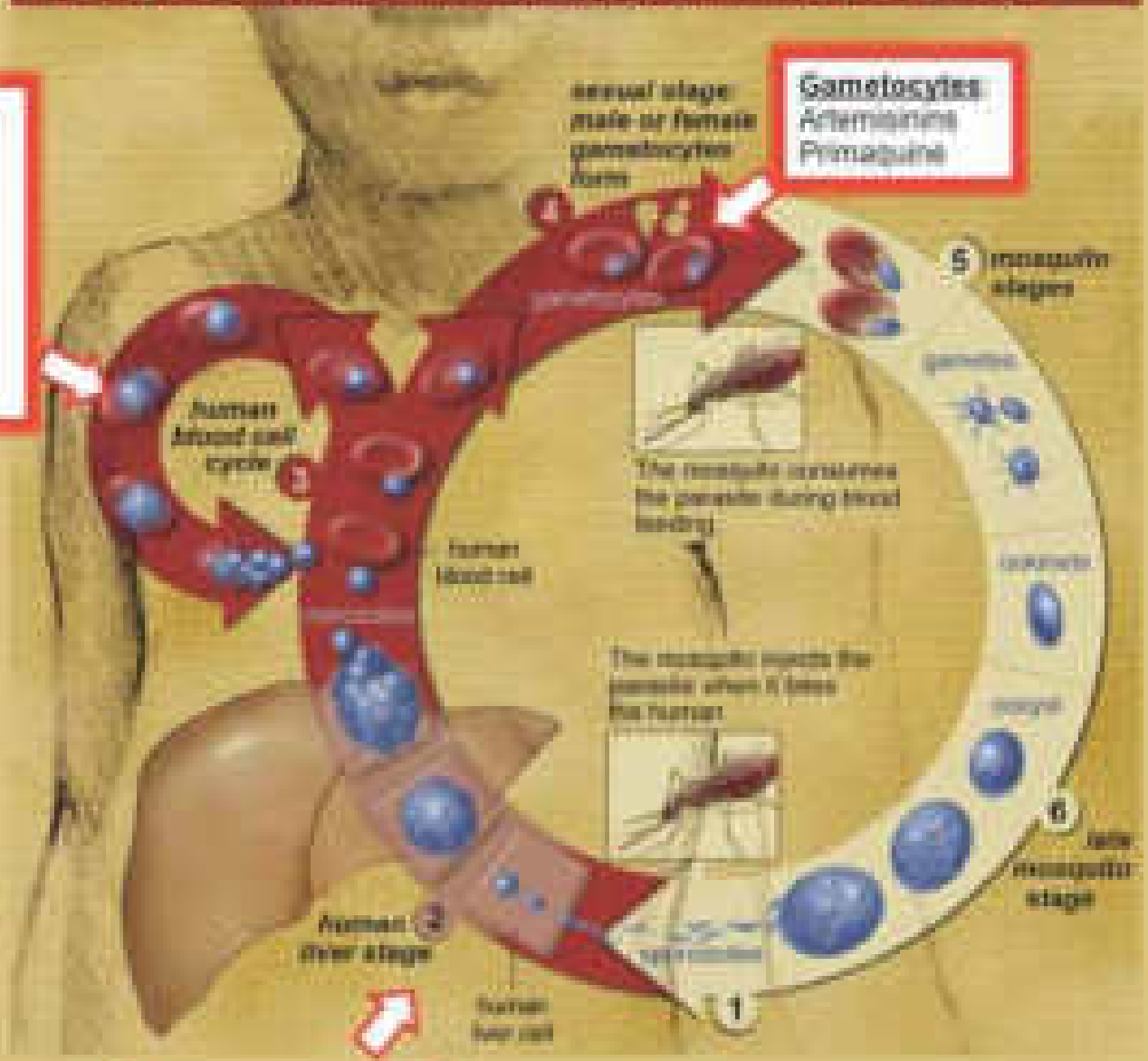
ANTI MALARIAL DRUGS

T.RADHIKA
G.P.R.C.P


Sporozoites
Salivery gland
Liver
Ookinete
Zygote
Gamete
In mosquito gut
Merozoites
RBC
Gametocytes
©Bob Crimi

Life Cycle of Malarial Parasites & Antimalarial Effects

Blood stage (schizonticides):
Artemisinins
Antifolates
Antimicrobials
Quinolones
(chloroquine, quinine, quinidine, mefloquine, lumefantrine)'
Primaquine (P vivax only)



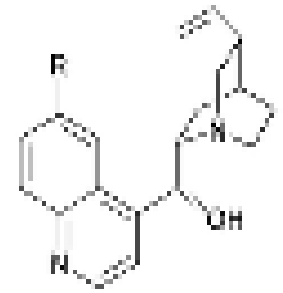
Gametocytes:
Artemisinins
Primaquine

Liver stage:
Atovaquone-proguanil
Primaquine

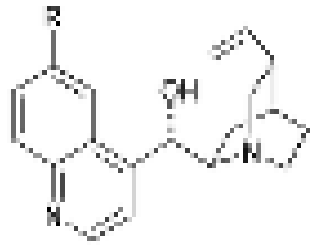
CLASSIFICATION OF ANTIMALARIAL DRUGS

1. **Cinchona Alkaloid** – Quinine, Quinidine
2. **4-Aminoquinolines** – Chloroquine, Amodiaquine, Piperaquine
3. **Diaminopyrimidines** – Pyrimethamine
4. **8-Aminoquinoline** – Primaquine, bulaquine
5. **Sulfonamides & Sulfone** – Sulfadoxine, sulfamethopyrazine, Dapsone
6. **Sesquiterpine Lactones** – Artesunate, artemeter, arteether
7. **Quinoline -Methanol** – Mefloquine
8. **Tetracyclines** – Tetracycline, Doxycycline
9. **Amino Alcohols** – Halofantrine, Lumefantrine
10. **Mannich base** – Pyronaridine
11. **Naphthoquinone** – Atorvaquone
12. **Biguanides** – Proguanil, chlorproguanil

Cinchona alkaloids

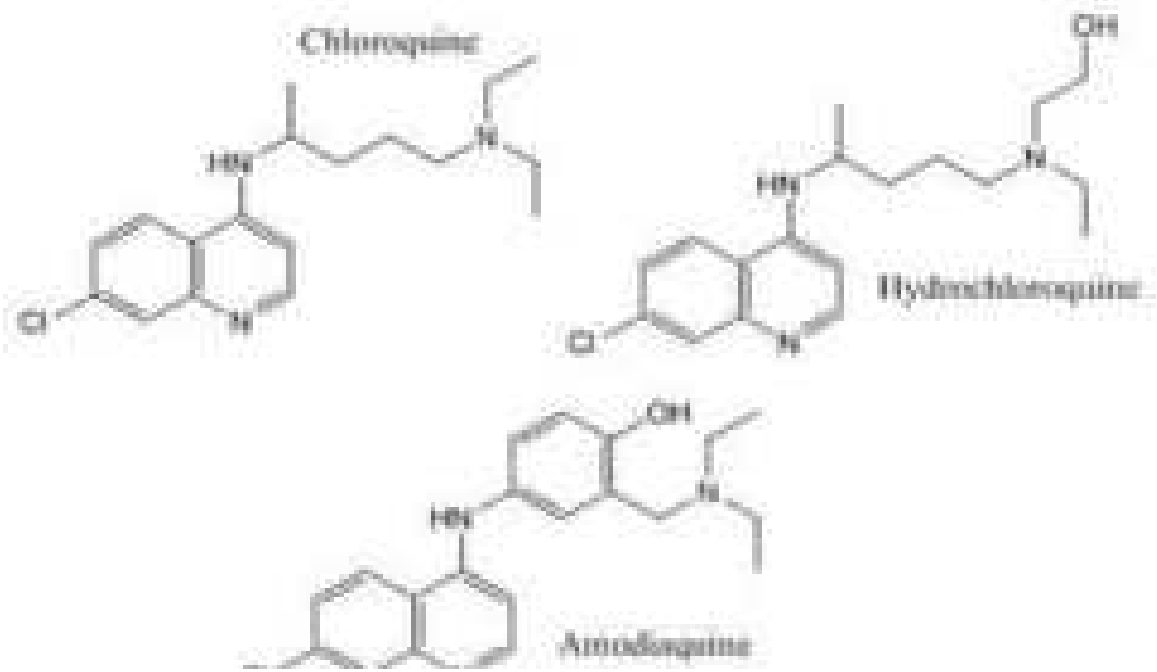


Quinine (R = OMe)
Cinchonine (R = H)

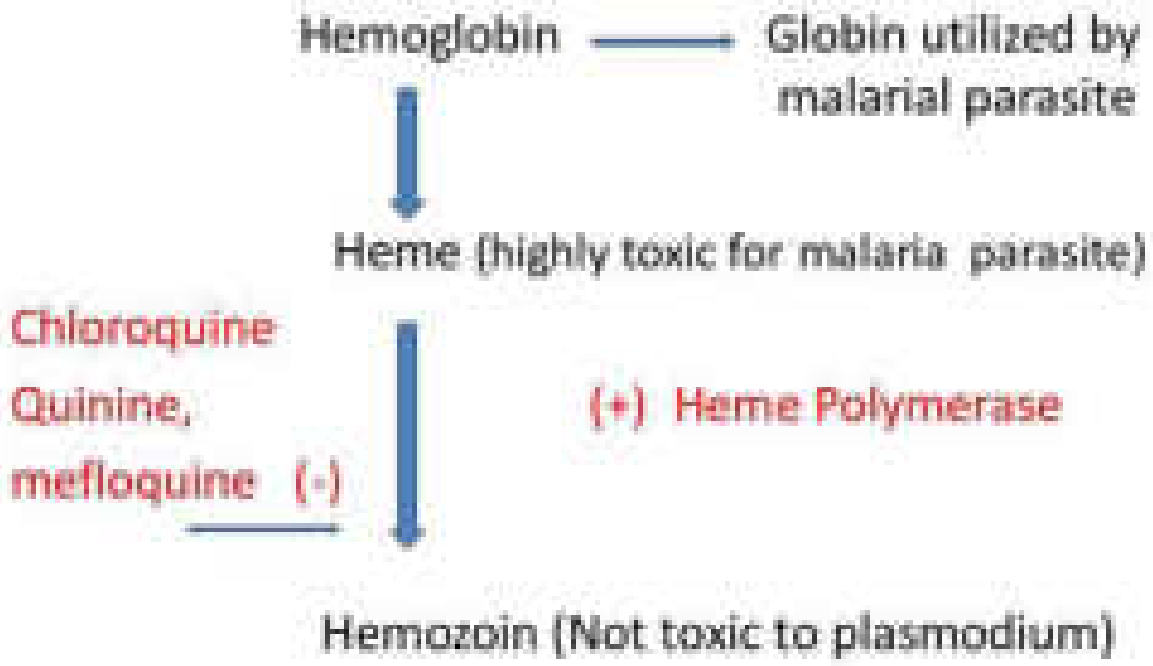


Quinidine (R = OMe)
Cinchonine (R = H)

4-Aminoquinolines



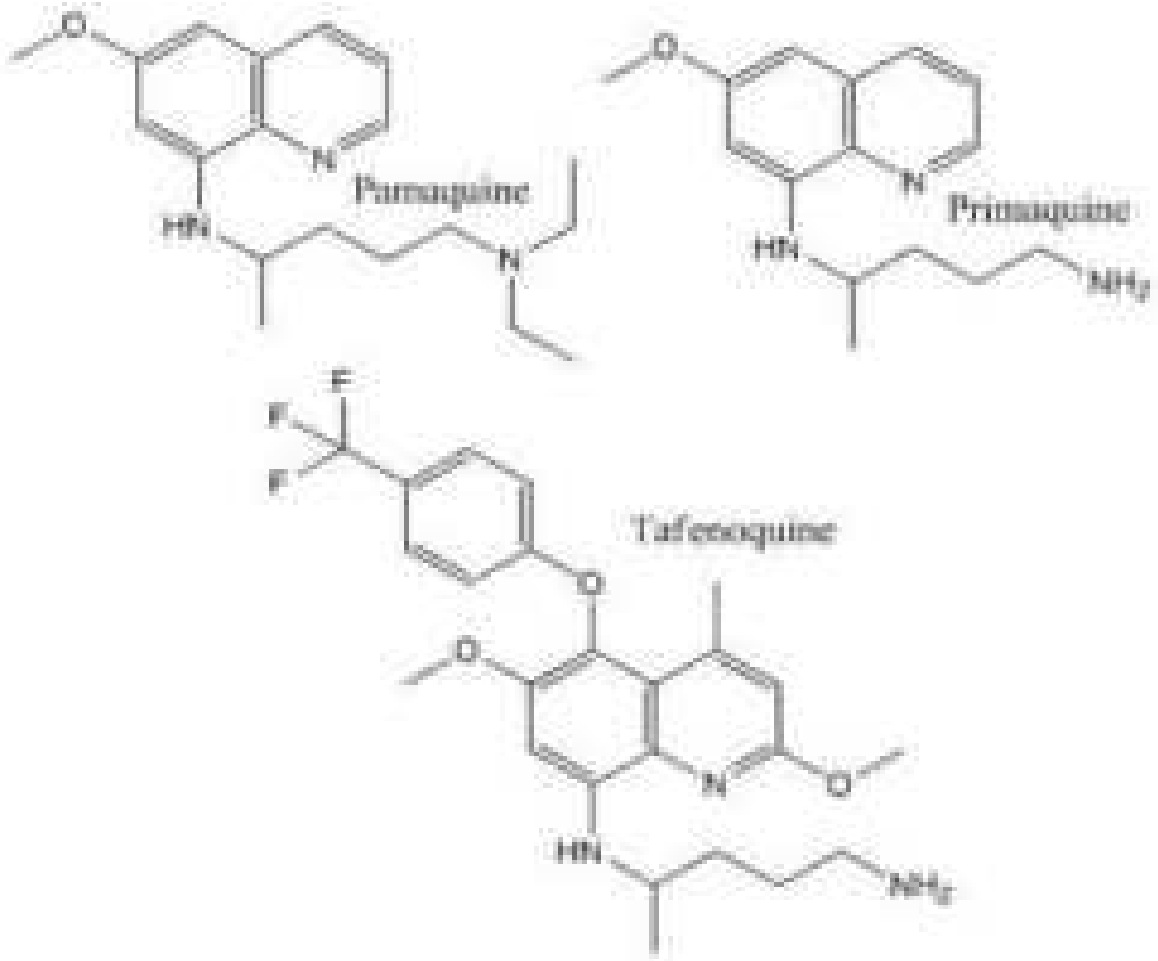
Mechanism of action



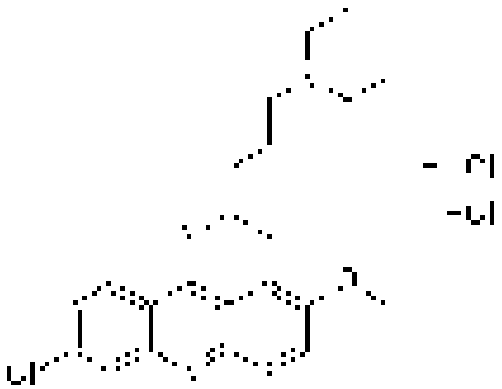
Antimalarial Drugs: Mechanism of Action

- 4-Aminoquinoline derivatives: chloroquine and hydroxychloroquine
  - Bind to parasite nucleoproteins and interfere with protein synthesis; also alter pH within the parasite
  - Interfere with parasite's ability to metabolize and use erythrocyte hemoglobin
  - Effective only during the erythrocytic phase

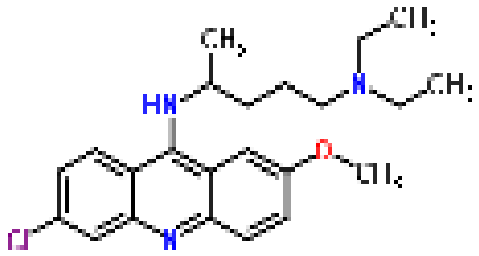
8-Aminoquinolines



9-Amino acridine

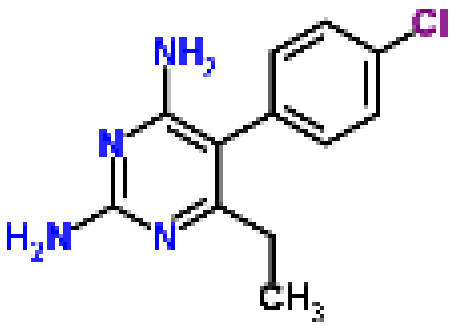


Quinacrine

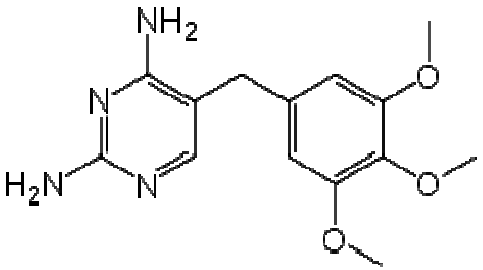


Mepacrine

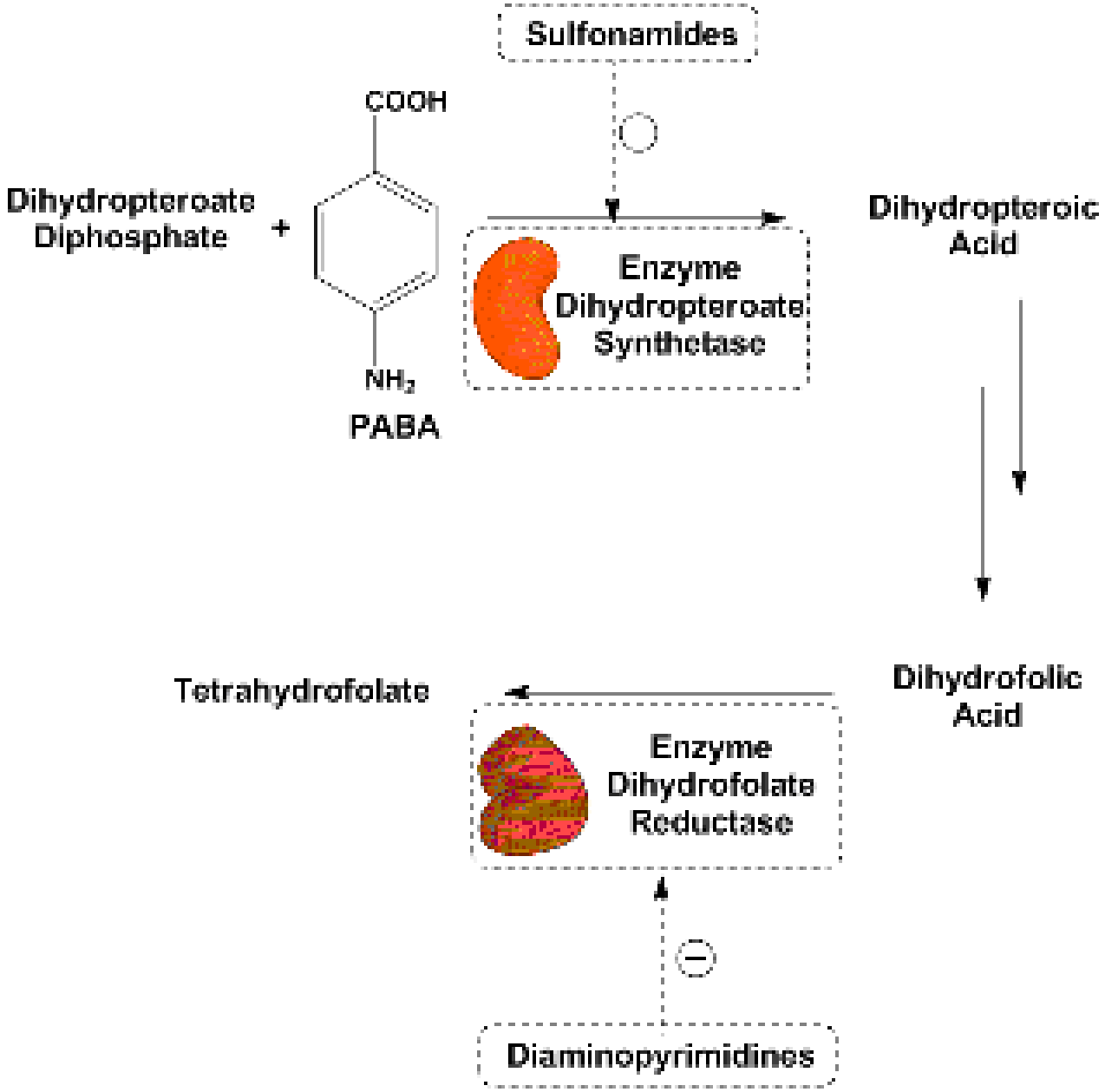
2,4-diamino Pyrimidines



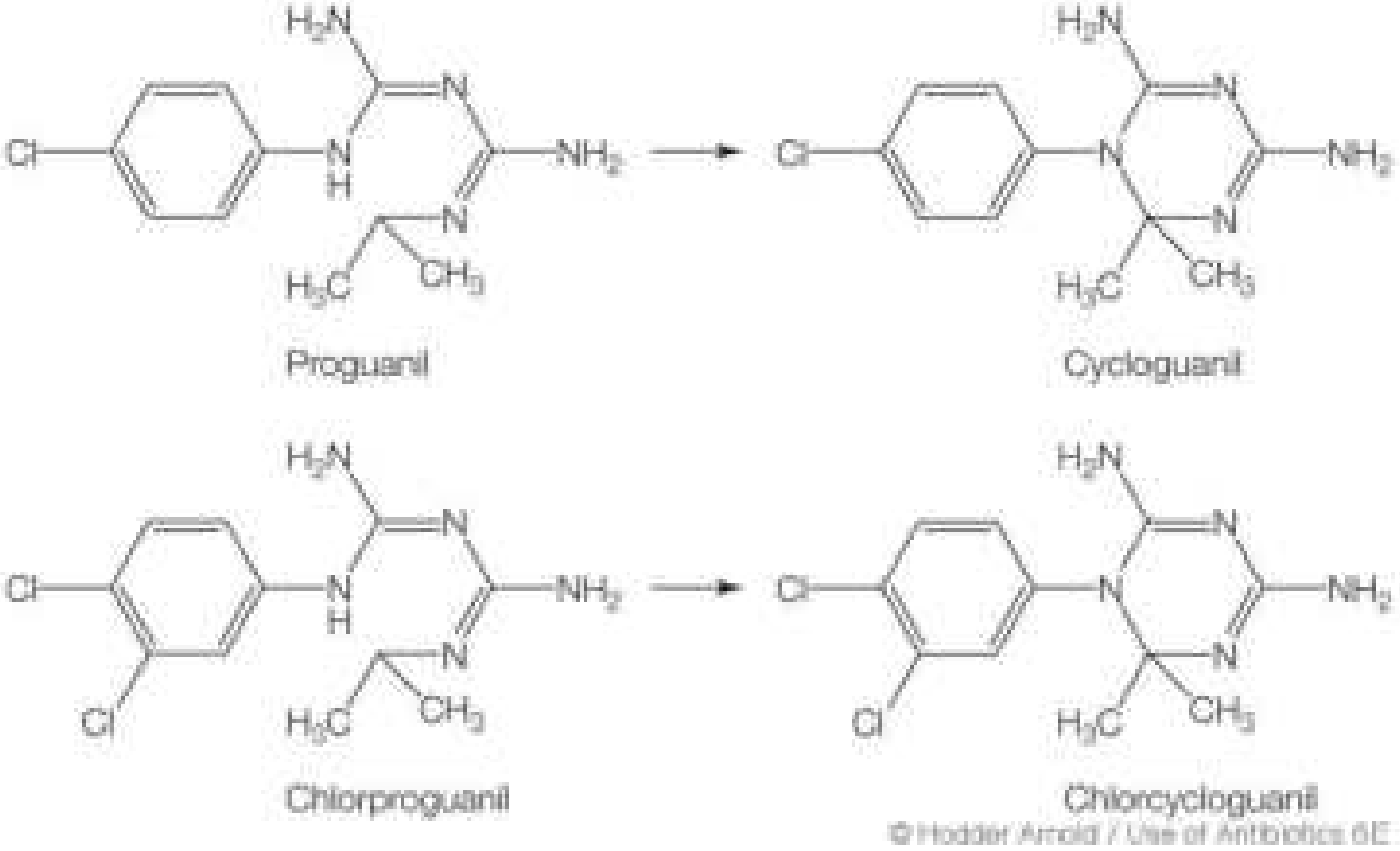
Pyrimethamine



Trimethoprim


Sulfonamides
COOH
Dihydropteroate
Diphosphate
+
NH2
PABA
Enzyme
Dihydropteroate
Synthetase
Dihydropteroic
Acid
Dihydrofolic
Acid
Tetrahydrofolate
Enzyme
Dihydrofolate
Reductase
Diaminopyrimidines

Biguanides



PROGUANIL (chloroguanide)

- Proguanil is a biguanide derivative
- Antimalarial action due to metabolite-cycloguanil
- Inhibit plasmodial dihydrofolate reductase-thymidylate synthetase- inhibiting DNA synthesis as well as depletion of folate cofactors
- Adequately absorbed – given orally
- In combination with atovaquone for chemoprophylaxis

Sulphones and Sulphonamides

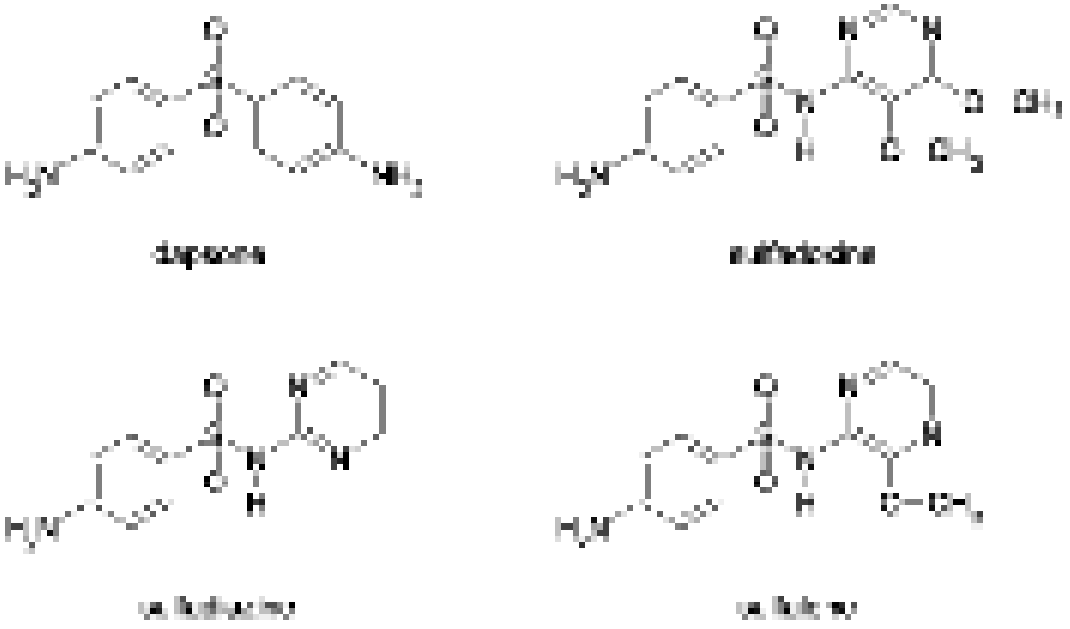
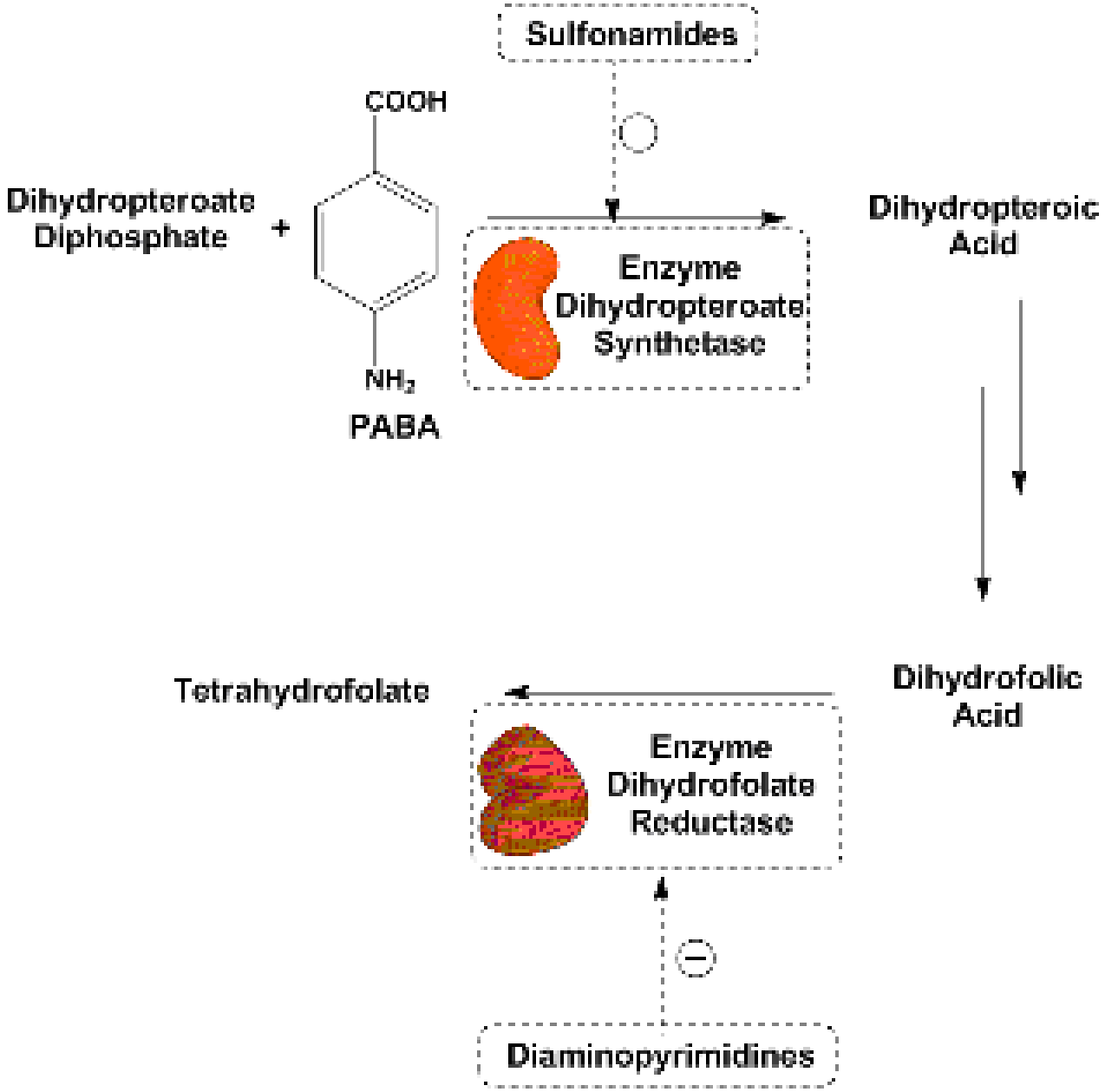


Figure 9. Structures of the four Type-I sulfones.


Sulfonamides
COOH
Dihydropteroate
Diphosphate
+
NH2
PABA
Enzyme
Dihydropteroate
Synthetase
Dihydropteroic
Acid
Dihydrofolic
Acid
Tetrahydrofolate
Enzyme
Dihydrofolate
Reductase
Diaminopyrimidines

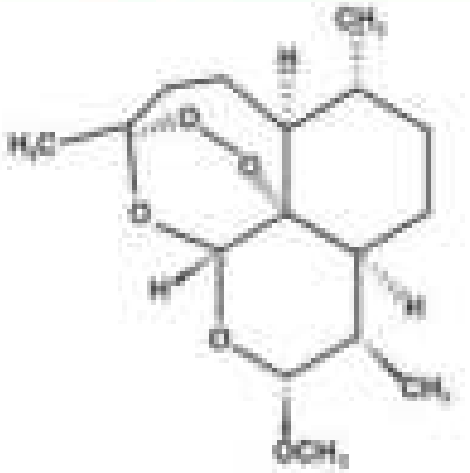
Artemisinins

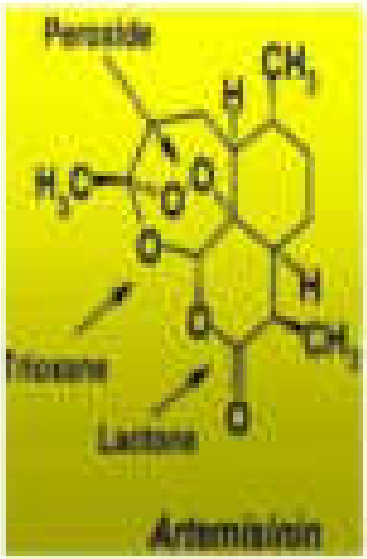
STRUCTURE OF ARTEMETHER

Molecular formula - $C_{16}H_{26}O_5$

Molecular Mass- 298.374

ARTEMETHER





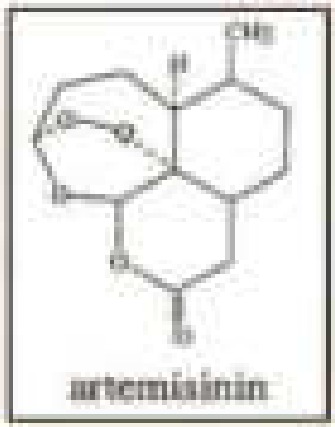
Mechanism of action

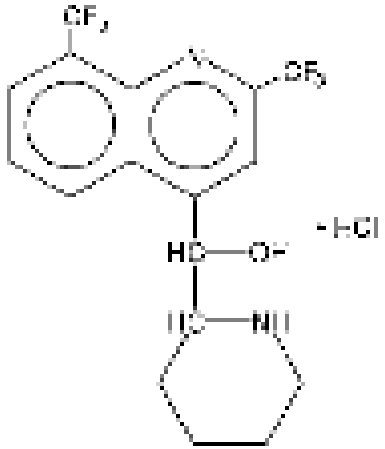
These compounds have presence of endoperoxide bridge

Endoperoxide bridge interacts with heme in parasite

Heme iron cleaves this endoperoxide bridge

There is generation of highly reactive free radicals which damage parasite membrane by covalently binding to membrane proteins





4-quinoline
carbinolamine

Mefloquine

Miscellaneous drugs:

Clindamycin and Doxycycline