ANTIMALARIAL AGENTS

Disclaimer

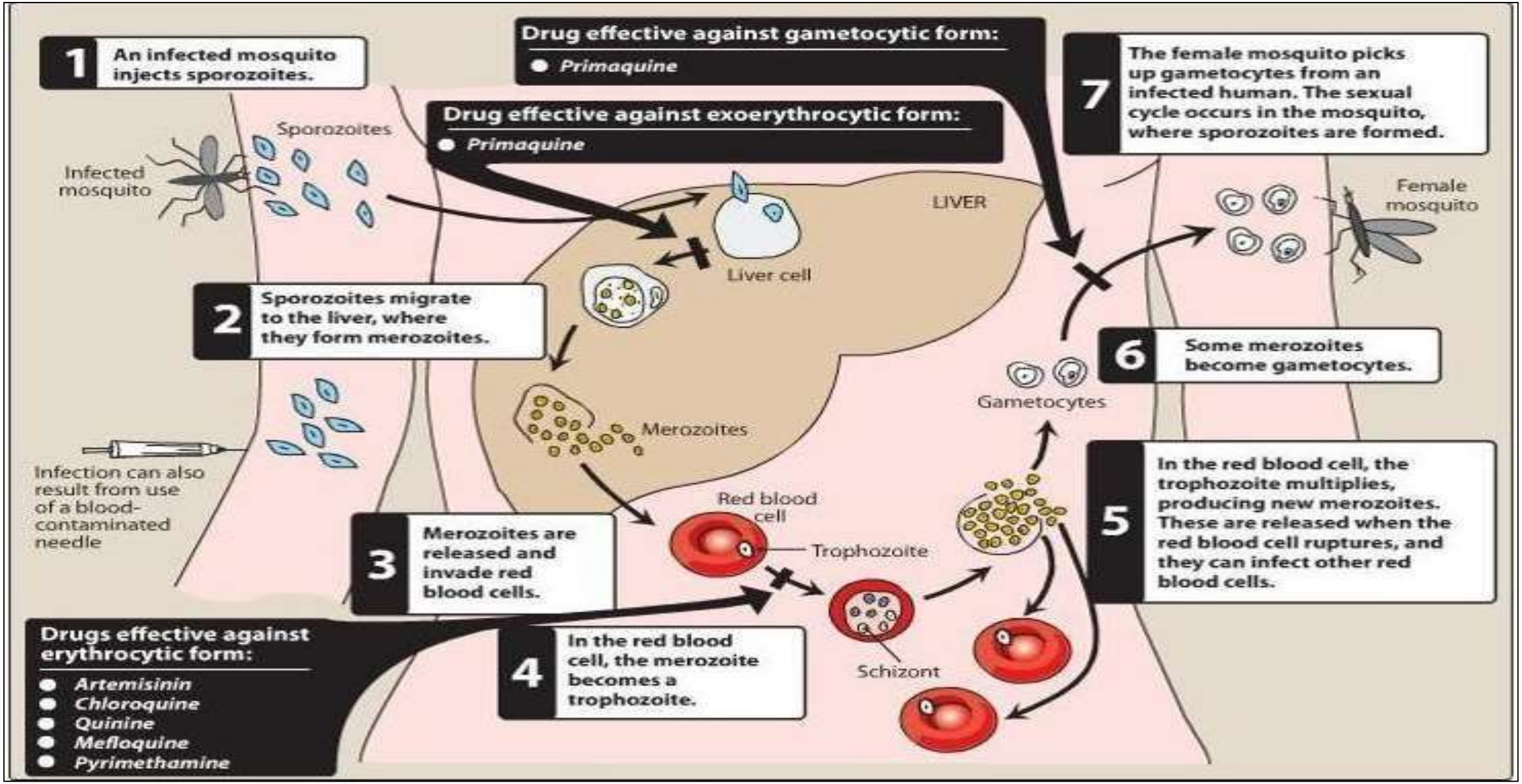
All the content material provided here is only for teaching purpose.

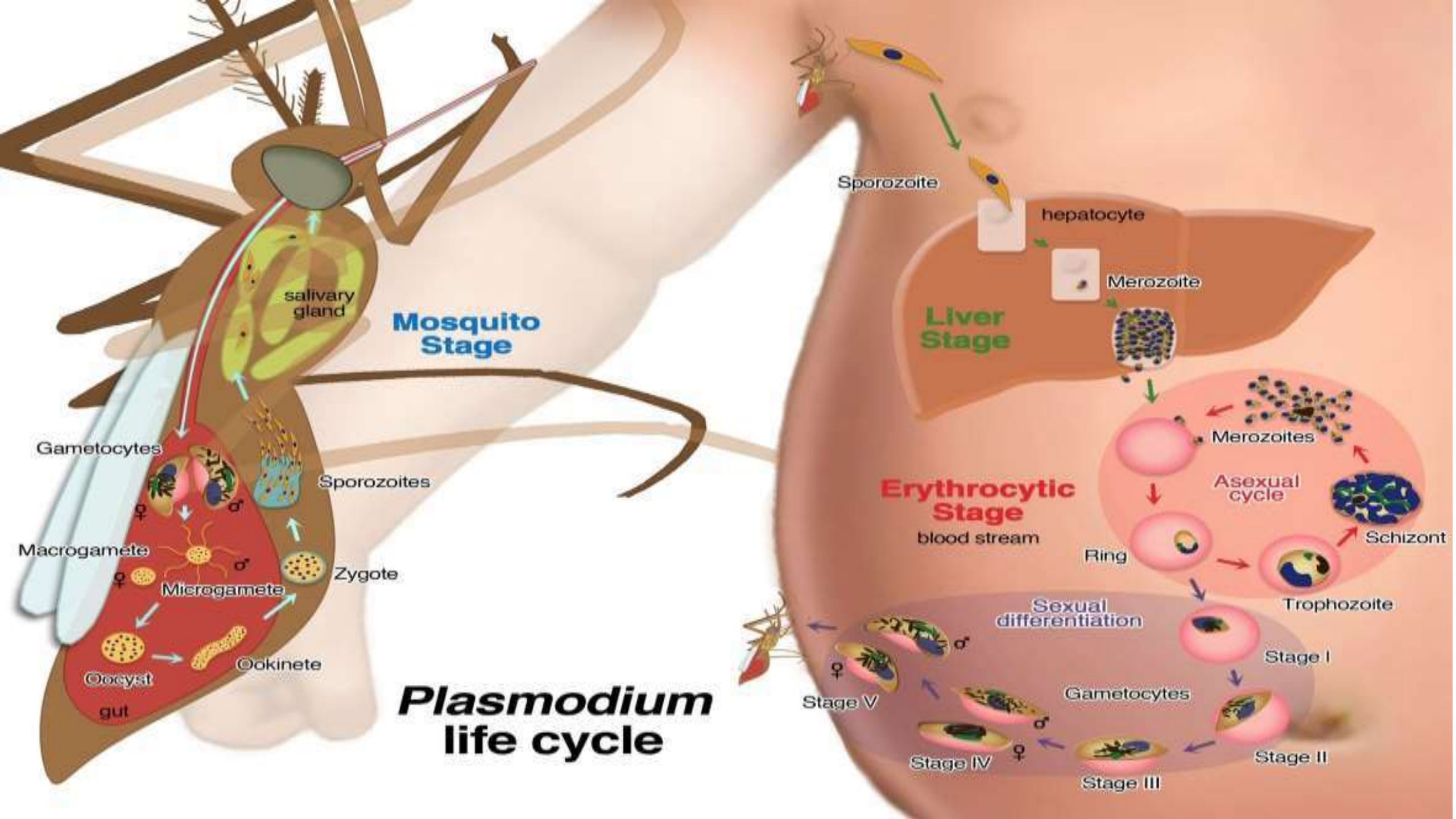
INTRODUCTION

- Malaria, one of the most widespread diseases, is caused by a *plasmodium* parasite and is transmitted to humans by the female *anopheles* mosquito. Plasmodium belongs to the class of protozoa known as sporozoa.
- Mainly four species of plasmodium typically cause human malaria are

  plasmodium falciparum, p. Vivax, P. Malariae and P. Ovale .
- A 5th species, *P. Knowlesi,* is primarily a pathogen of monkeys, but has recently been recognized to cause illness, including severe disease, in humans in asia.
- Although all species may cause significant illness, *p. Falciparum* is responsible for the majority of serious complications and death.

LIFE CYCLE OF THE MALARIAL PARASITE




salivary gland
Mosquito Stage
Gametocytes
Sporozoites
Macrogamete
Zygote
Microgamete
Oocyst
Ookinete
gut
Sporozoite
hepatocyte
Merozoite
Liver Stage
Merozoites
Asexual cycle
Erythrocytic Stage
blood stream
Schizont
Ring
Trophozoite
Sexual differentiation
Stage I
Stage V
Gametocytes
Stage II
Stage IV
Stage III
Plasmodium
life cycle

- An anopheles mosquito inoculates plasmodium sporozoites to initiate human infection. Circulating sporozoites rapidly invade liver cells, and exoerythrocytic stage tissue schizonts mature in the liver. Merozoites are subsequently released from the liver and invade erythrocytes.
- Only erythrocytic parasites cause clinical illness. Sexual stage gametocytes also develop in erythrocytes before being taken up by mosquitoes, where they develop into infective sporozoites.

THERAPEUTIC CLASSIFICATION

1. Causal prophylaxis: (primary tissue schizonticides)

- Drugs prevent the maturation of or destroy the sporozoites within the infected hepatic cell- thus prevent erythrocytic invasion
- Primaquine, proguanil
- Primaquine – for all species of malaria but not used due to its toxic potential
- Proguanil- primarily for *P. Falciparum* and not effective against *P. Vivax* (weak activity), rapid development of resistance

2. Supressives prophylaxis:

- Supress the erythrocytic phase and thus attack of malarial fever can be used as prophylactics
- Chloroquine, proguanil, mefloquine, doxycycline

3.Clinical cure: Erythrocytic Schizonticides

- Erythrocytic schizontocides are used to terminate episodes of malarial fever
- **Fast acting high efficacy drugs:**
  - Chloroquine, quinine, mefloquine, halofantrine, artemicinin
  - Used singly to treat malaria fever
  - Faster acting, preferably used in falciparum malaria where delayed treatment may lead to death even if parasites are clear from blood
- **Slow acting low efficacy drugs:**
  - Proguanil, pyrimethamine, sulfonamides, tetracyclines
  - Used only in combination

4. Radical curatives:

- Drug attack exoerythrocytic stage (hypnozoites) given with clinical curative for the total eradication of the parasite from the patient's body
- Radical cure of the *P. Falciparum* malaria can be achieved by suppressives only
- For radical cure of *P. Vivax* infection, primaquine and proguanil are effective

5. Gametocidal:

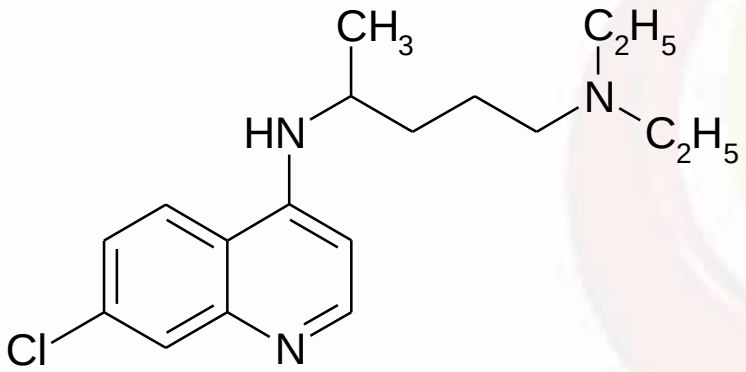
- Removal of male and female gametes of plasmodia formed in the patient's blood
- It has no benefit for treated patient
- Primaquine and artemisinins are highly effective against gametocytes of all species

CHEMICAL CLASSIFICATION

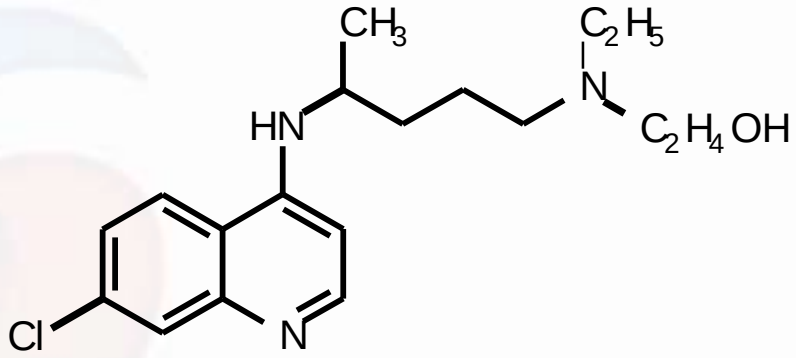
Classes	Drugs
1. 4-aminoquinolines	Chloroquine (CQ), amodiaquine (AQ), Piperaquine
2. Quinoline-methanol	Mefloquine
3. Cinchona alkaloid	Quinine, quinidine
4. Biguanide	Proguanil (chloroguanide)
5. Diaminopyrimidine	Pyrimethamine
6. 8-aminoquinoline	Primaquine, tafenoquine
7. Sulfonamides and sulfone	Sulfadoxine, sulfamethopyrazine, dapsone
8. Amino alcohols	Halofantrine, lumefantrine
9. Sesquiterpine lactones	Artesunate, artemether, arteether,

10. Naphthyridine	Pyronaridine
11. Naphthoquinone	Atovaquone
12. Antibiotics	Tetracycline, Doxycycline, Clindamycin

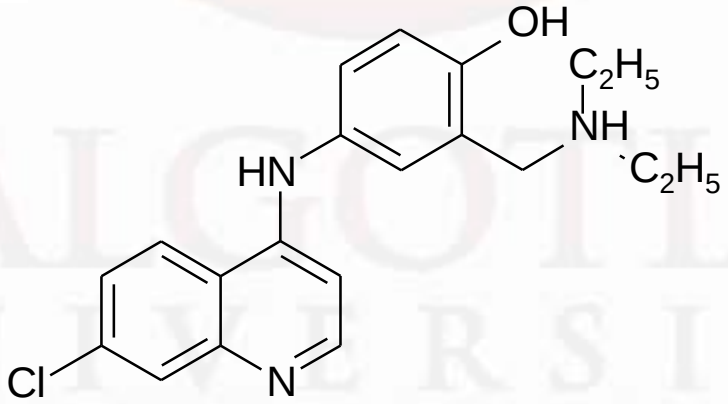
1. 4-AMINOQUINOLINES



Chloroquine



Hydroxychloroquine



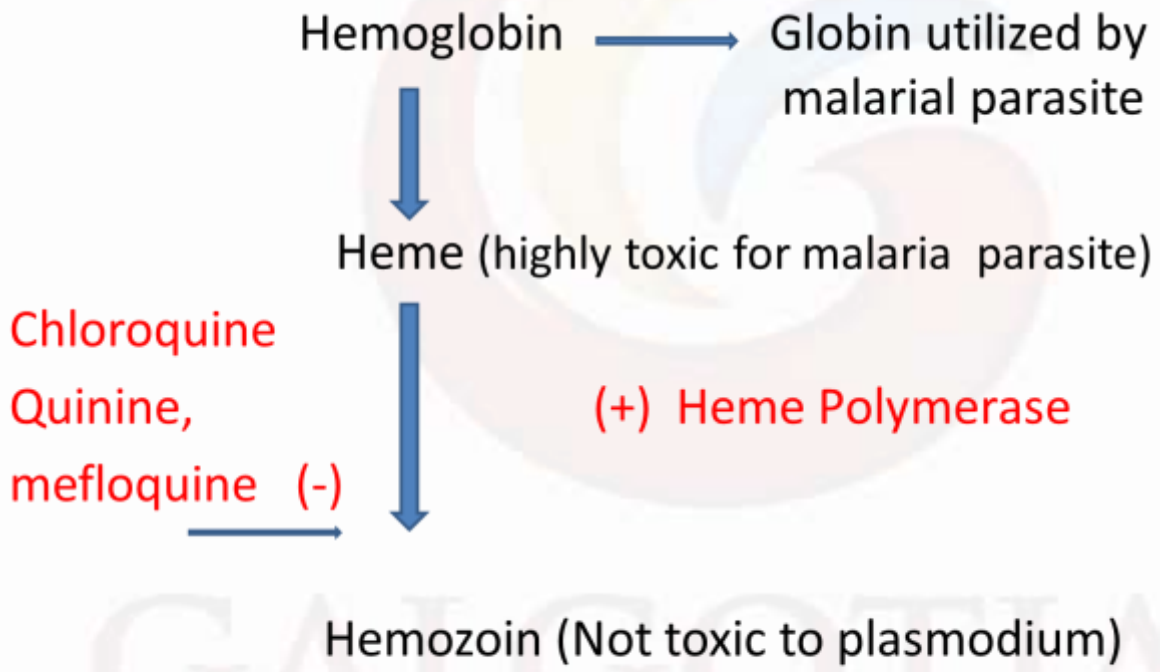
Amodiaquine

CHLOROQUINE:

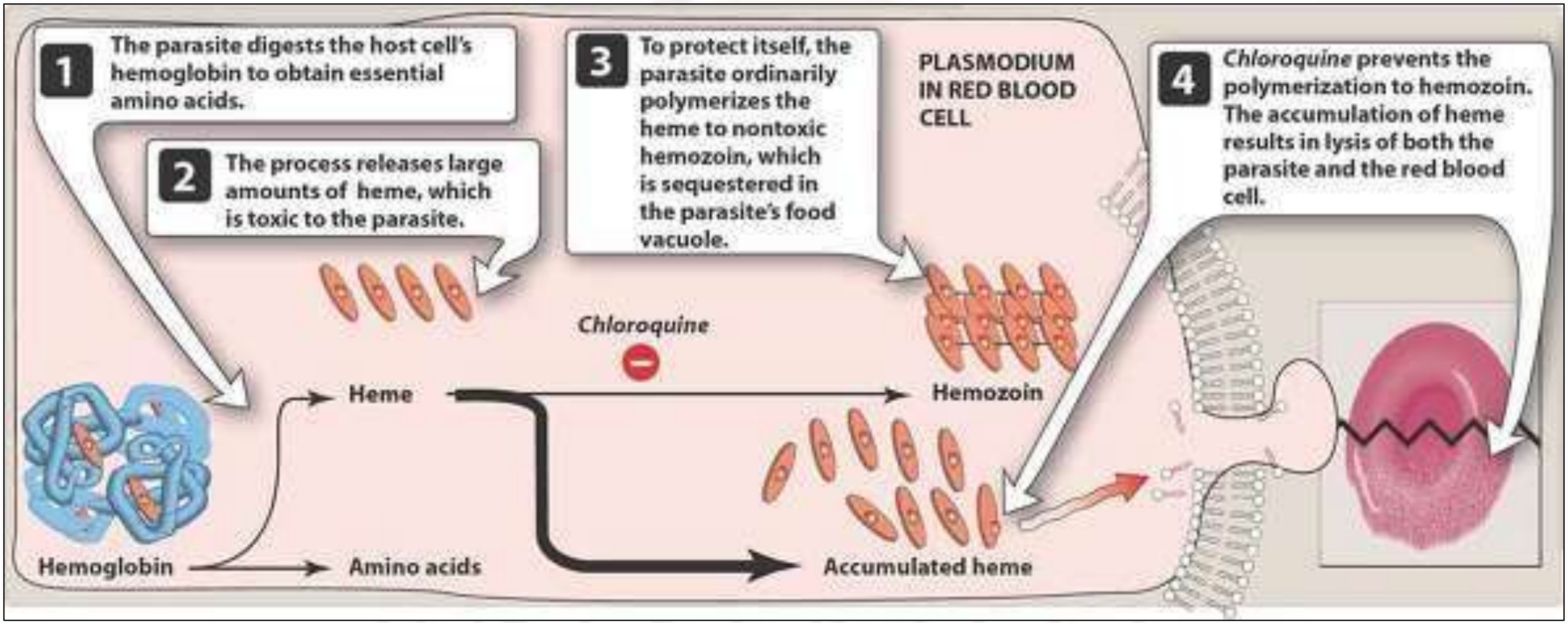
- It has activity against the blood stages of *plasmodium ovale, P. Malariae,* and susceptible strains of *P. Vivax and P. Falciparum.*
- Widespread resistance in most malaria-endemic countries has led to decline in its use for the treatment of p. Falciparum, although it remains effective for treatment of *P. Ovale, P. Malariae* and, in most regions, *P. Vivax*.
- **Mechanism of action :**
  - Binds to and inhibits dna and rna polymerase; interferes with metabolism and hemoglobin utilization by parasites; inhibits prostaglandin effects.
  - The parasite digests the human hemoglobin in order to get amino acid, but the problem here is that the heme part of hb is toxic to the parasite.

- To overcome this obstacle, the parasite has developed an enzyme responsible for polymerization of heme. To form insoluble crystals called hemozoin which are collected in vacuoles.
- Chloroquine enters parasite cell by simple diffusion. Chloroquine then becomes protonated as the digestive vacuole is known to be acidic (pH 4.7), chloroquine then cannot leave by diffusion. Chloroquine inhibits polymerization of heme and accumulation of heme.
- Chloroquine binds to heme (or fp) to form what is known as the fp-chloroquine complex, this complex is highly toxic to the cell and disrupts membrane function. Action of the toxic compound results in cell lysis and ultimately parasite cell autodigestion.

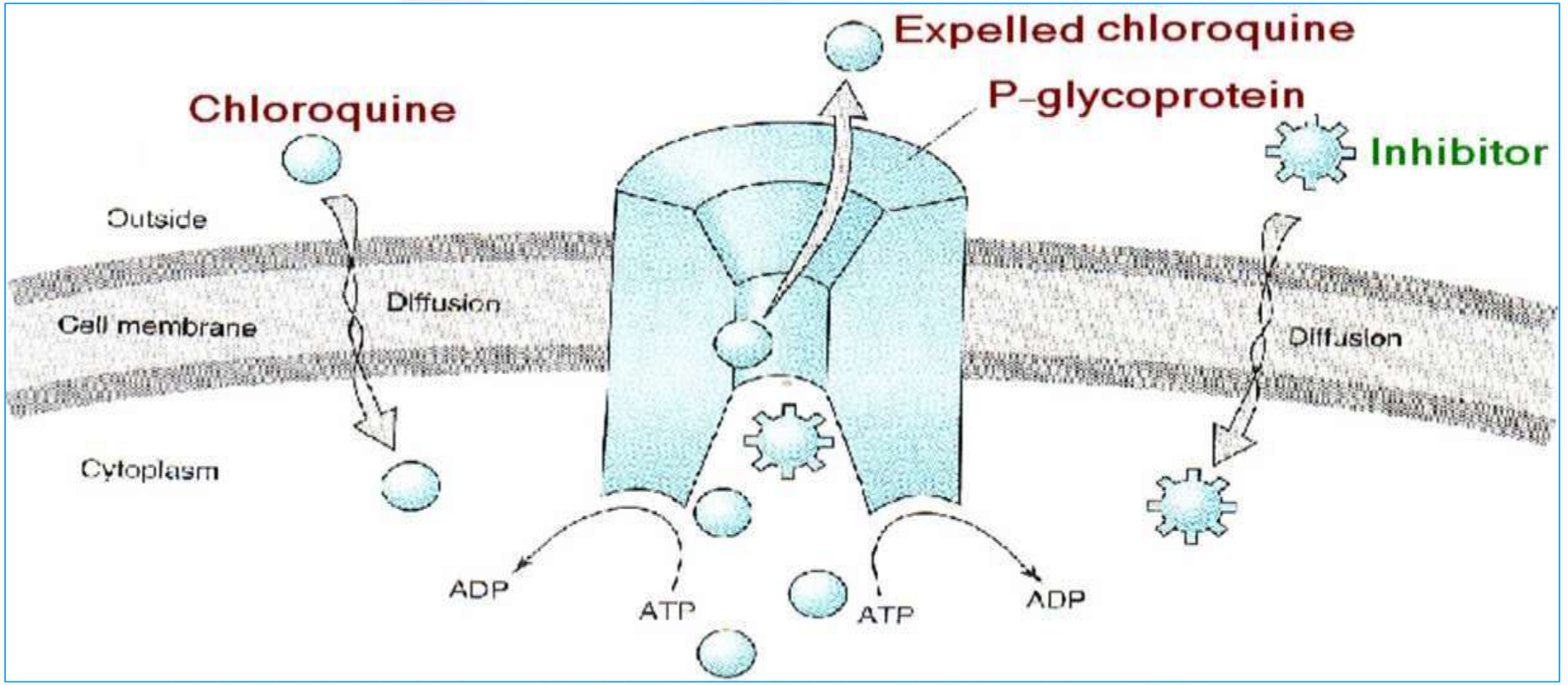
MECHANISM OF ACTION



MECHANISM OF ACTION :



- RESISTANCE RESULTS FROM ENHANCED EFFLUX OF THE PARASITE VESICLE EXPRESSION OF THE HUMAN MULTI DRUG RESISTANCE TRANSPORTER P-GLYCOPROTEIN.



PHARMACOLOGICAL ACTIONS

1. **Antimalarial activity:**
   - High against erythrocytic forms of vivax, ovale, malariae & sensitive strains of falciparum
   - Gametocytes of vivax
   - No activity against tissue schizonts
   - Resistance develops due to efflux mechanism
2. **Other parasitic infections:**
   - Giardiasis, taeniasis, extrainstestinal amoebiasis
3. **Other actions:**
   - Depressant action on myocardium, direct relaxant effect on vascular smooth muscles, antiinflammatory, antihistaminic , local anaesthetic

- **Hydroxy chloroquine:**
  - Less toxic, properties &uses similar
- **Amodiaquine:**
  - As effective as chloroquine
  - Pharmacological actions similar
  - Chloroquine resistant strains may be effective
  - Adverse events: GIT, headache , photosensitivity, rarely agranulocytosis
  - Not recommended for prophylaxis

- **Contraindications:**

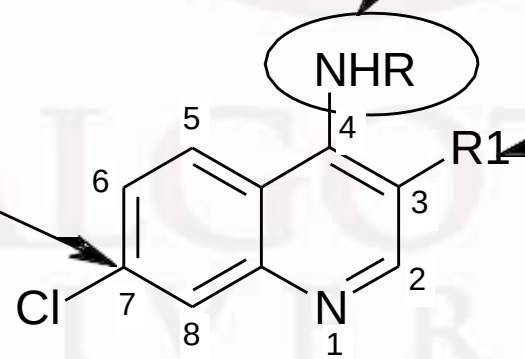
1. Psoriasis or porphyria
2. Visual field abnormalities or myopathy
3. Ca and mg containing antacid interfere with absorption
4. Used with caution in liver disease or neurologic or hematologic disorders.

SAR of 4-aminoquinolines

Dialkylaminoalkyl side chain

1. 2-5 carbon atoms between the nitrogen atoms,particularly 4-diethylamino-1-methylbutylamino side chain is optimal for activity as in chloroquine.
2. The tertiary amine is important.
3. Introduction of unsaturation in the side chain was not detrimental to activity.
4. Substitution of a hydroxy on one of the ethyl groups in tertiary amine (hydroxy quinoline) generally reduces toxicity and increases the plasma concentration. This is one of the metabolites of chloroquine.
5. Incorporation of an aromatic ring in the side chain e.g. in Amodiaquine, gives a compound with reduced toxicity and toxicity.

Introduction of chloro group at this position is optimal for activity

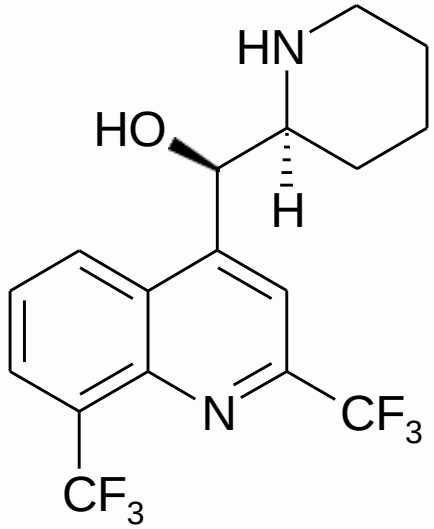


Introduction of methyl group at this position reduces activity

d-Isomer of chloroquine is somewhat less toxic than l-isomer

2. QUINOLINE-METHANOL

- Mefloquine, is marketed as the *R,S-isomer.*
- Mefloquine's effectiveness in the treatment and prophylaxis of malaria is due to the destruction of the asexual blood forms of the malarial pathogens that affect humans, *Plasmodium falciparum, P. vivax, P. malariae, P. ovale*.
- Used in chloroquine-resistant strains of *P. falciparum* and other species.
- Has strong blood schizonticidal activity against *P. falciparum* and *P. vivax*, it is not active against hepatic stages or gametocytes.

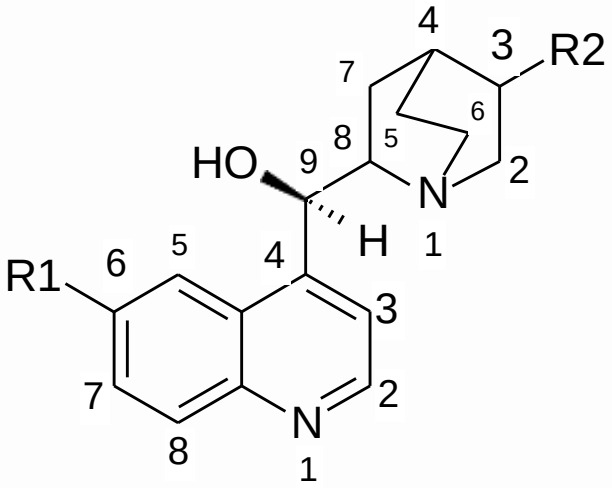


Mefloquine

Adverse effects

- ✓ Mefloquine is bitter in taste
- ✓ At high doses: Nausea, vomiting, diarrhea, abdominal pain,

3. CINCHONA ALKALOIDS



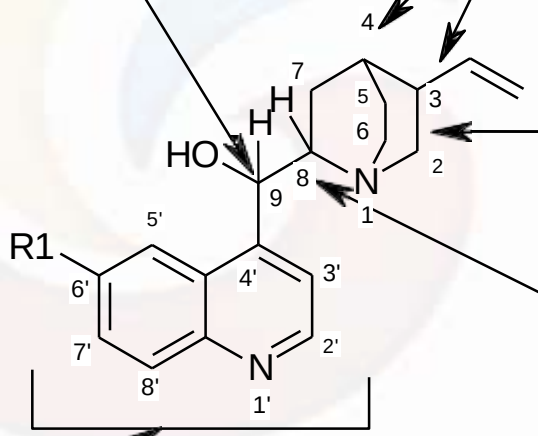
Quinine :	$R_1 = OCH_3$; $R_2 = -CH = CH_2$; (–) 8S : 9R isomer
Quinidine :	$R_1 = OCH_3$: $R_2 = -CH = CH_2$; (+) 8R : 9S isomer
Cinchonine :	$R_1 = H$; $R_2 = -CH = CH_2$; (+) 8R : 9S isomer
Cinchonidine :	$R_1 = H$; $R_2 = -CH = CH_2$; (–) 8S : 9R isomer

- Quinine is a *l-isomer* of alkaloid obtained from cinchona bark and quinidine (antiarrhythmic) is its *d-isomer.*
- An effective erythrocytic schizontocide as suppressive and used to prevent or terminate attacks of *vivax, ovale, malariae*, sensitive *falciparum. less effective and more toxic than chloroquine.*
- Moderately effective against hepatic form (pre-exoerythrocyte and gametocytes).

SAR Of Quinine

1. Modification of the secondary alcohol at C-9, through oxidation, esterification dim inishes activity.
2. The configuration at positions 8 and 9 affects the juxtaposition of the hydroxyl group and the non-arom atic nitrogen atom , a relationship that is associated with antim alarial activity.

Assym metry at this positions is not essential for antim alarial activity



Quinuclidine portion is not necessary for activity; however, an alkyl tertiary am ine attached at C-9 is im portant

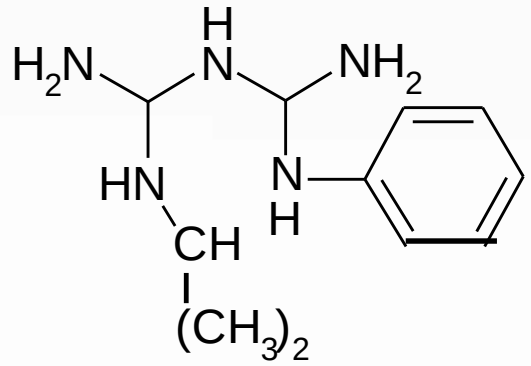
Activity usually enhanced by the introduction of a halogen at this position.

Quinoline Ring

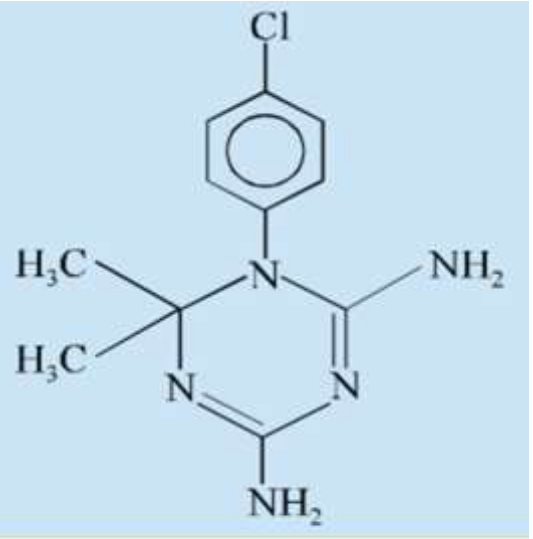
1. Presence of m ethoxy group in quinine is not essential.
2. R eplacem ent of m ethoxy group by a halogen, especially chlorine, enhances activity.
3. A further increase in activity resulted from the introduction of a phenyl group at position 2'.
4. It was discovered that high activity without phototoxicity could be attained by blocking position 2' with a trifluorom ethyl group, a finding that eventually led to developm ent of m efloquine.

4. BIGUANIDES

- ✓ It is an early example of a prodrug.
- ✓ It is a slow-acting erythrocytic schizontocide which also inhibits the preerythrocytic stage of *P. falciparum*. Gametocytes exposed to proguanil are not killed but fail to develop properly in the mosquito.
- ✓ It is cyclized in the body to a triazine derivative (cycloguanil) which inhibits plasmodial DHFRase in preference to the mammalian enzyme.
- ✓ Resistance to proguanil develops rapidly due to mutational changes in the plasmodial DHFRase enzyme.

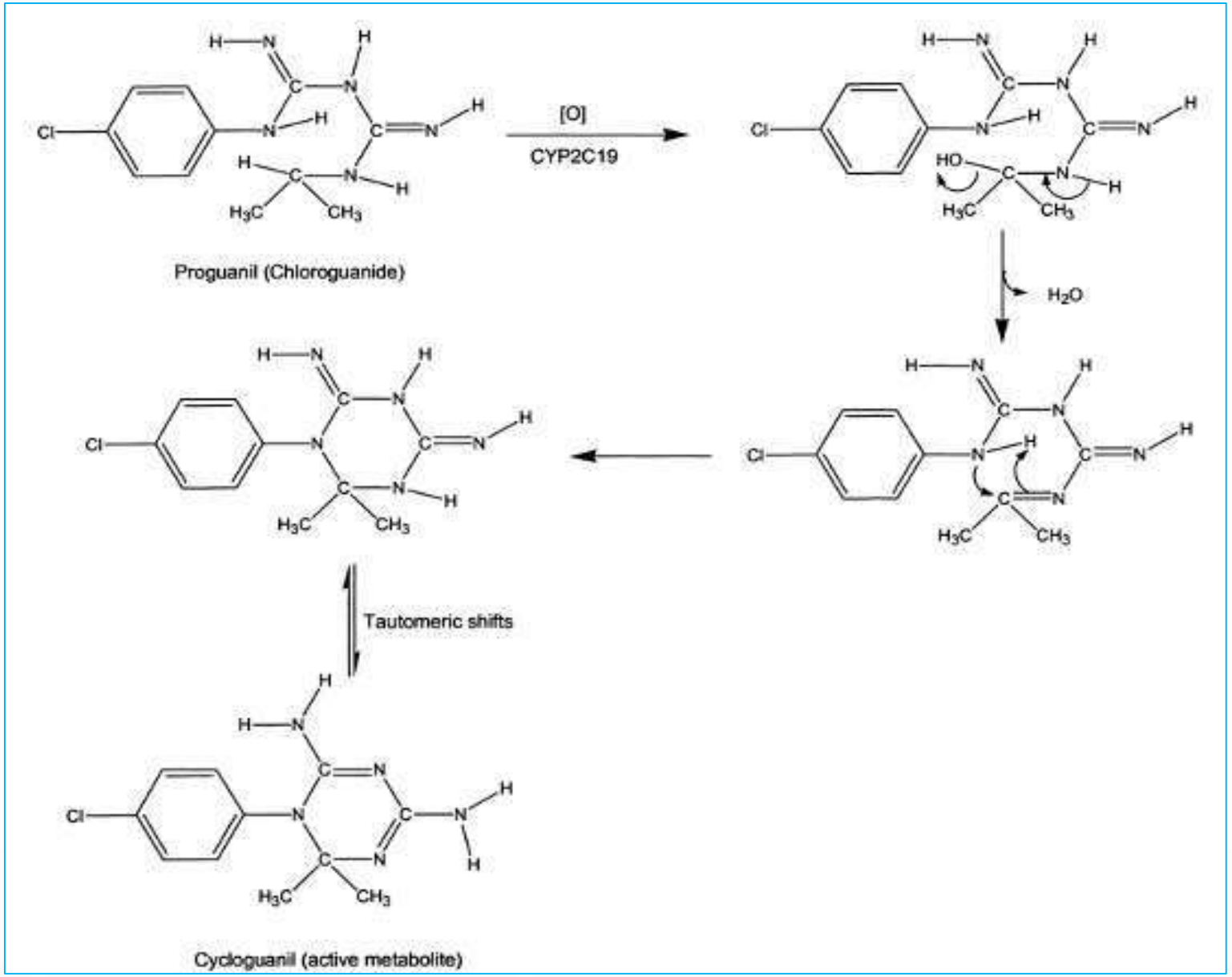


Proguanil

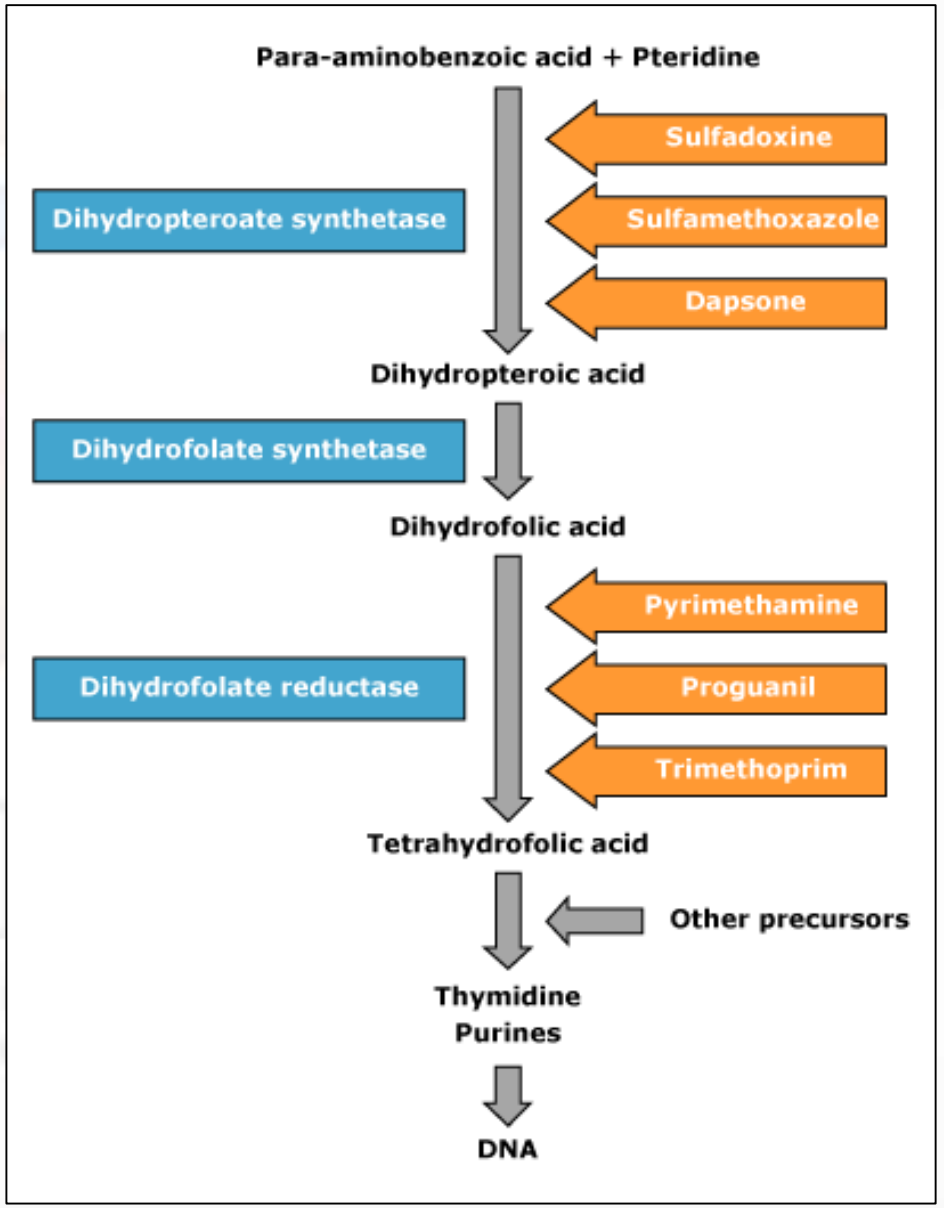


cycloguanil

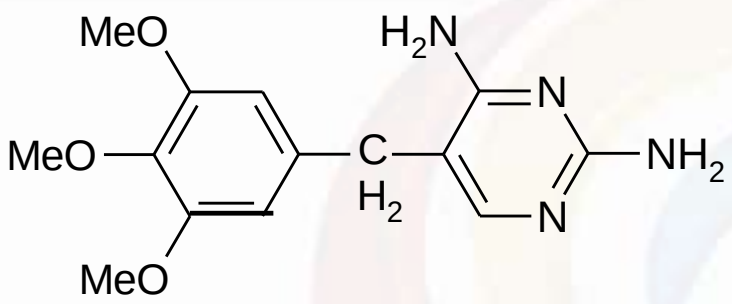
Conversion of proguanil to cycloguanil by CYP2C19



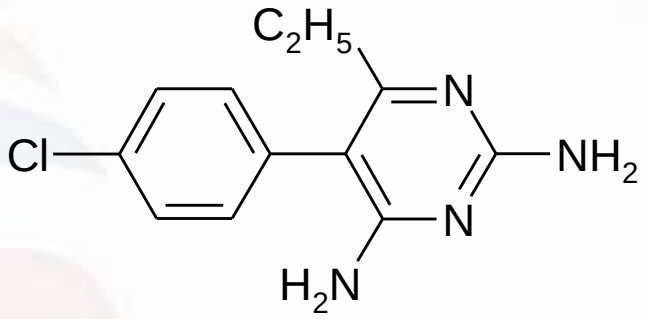
Mechanism of action of anti folates



5. DIAMINOPYRIMIDINE



Trimethoprim

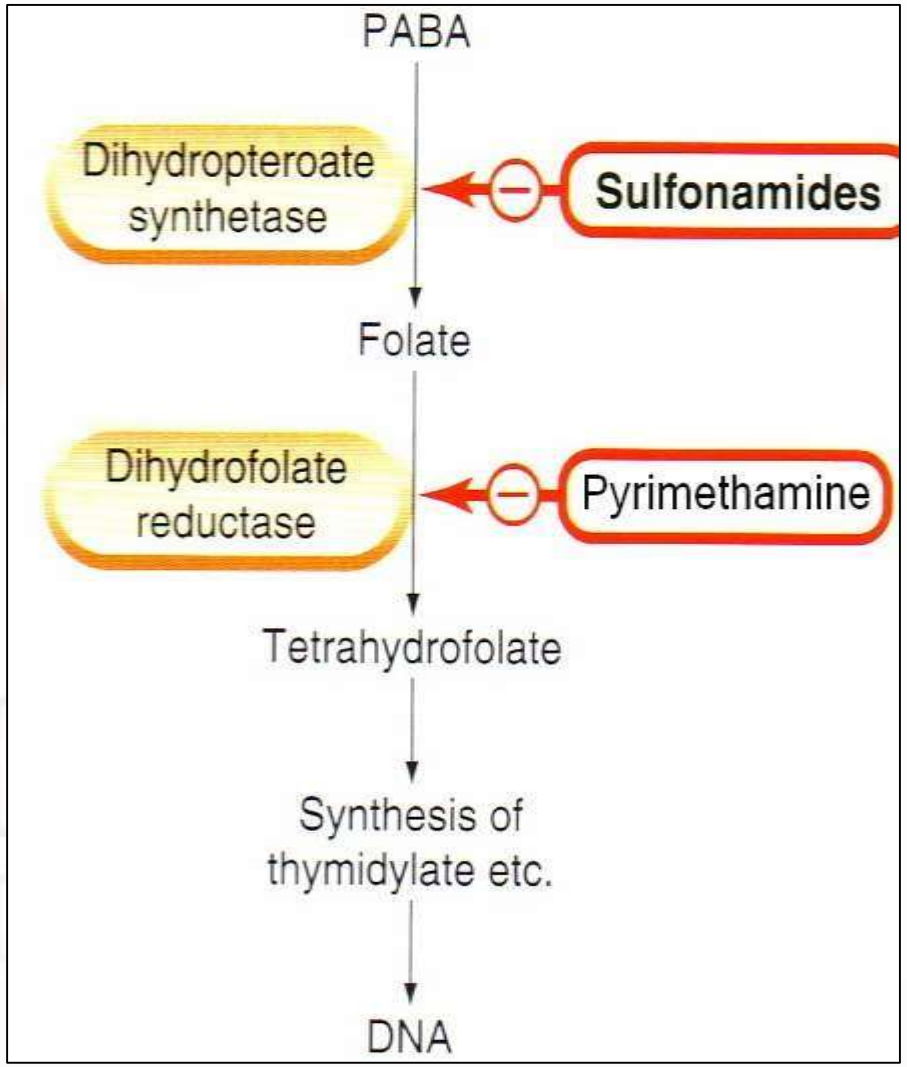


Pyrimethamine

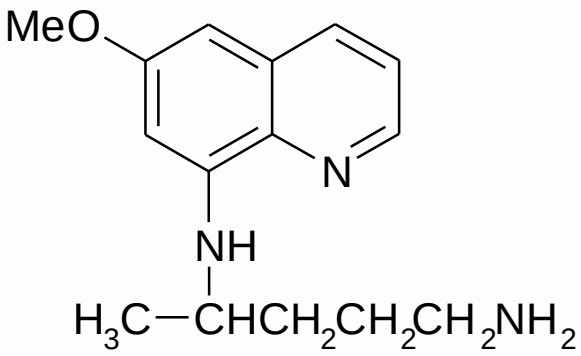
- ✓ Slow acting erythrocytic schizontocide
- ✓ Direct inhibitor of plasmodial dihydrofolate reductase (DHFRase)
- ✓ Conversion of dihydrofolic acid to tetrafolic acid is inhibited
- ✓ High doses inhibits *Toxoplasma gondi*
- ✓ Resistance develops by mutation in DHFRase enzyme
- ✓ Diaminopyrimidine more potent than proguanil & effective against erythrocytic forms of all species.

SULFADOXINE - PYRIMETHAMINE

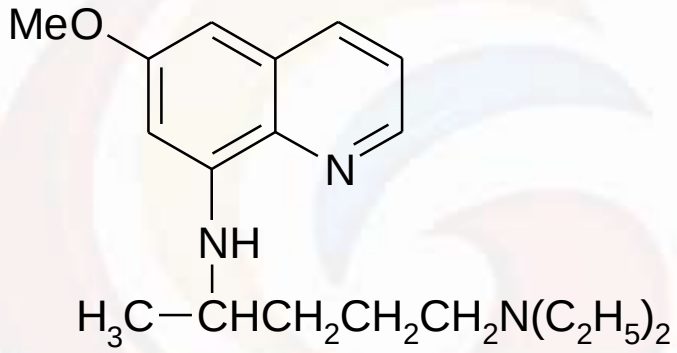
- Sequential blockade
- Sulfadoxine 500 mg + pyrimethamine 25 mg, 3 tablets once for acute attack
- Not recommended for prophylaxis
- Effective blood schizontocide against *plasmodium falciparum*
- Treatment and prophylaxis of *falciparum* malaria resistant to chloroquine



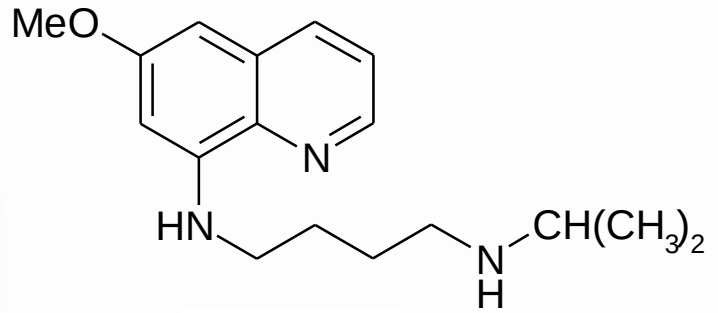
6. 8-AMINOQUINOLINE



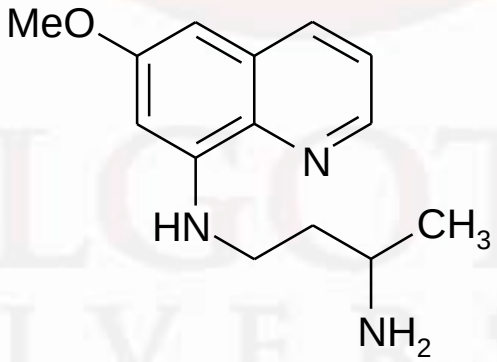
Primaquine



Pamaquine

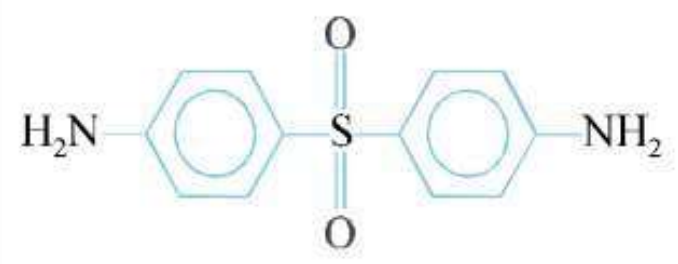


Pentaquine

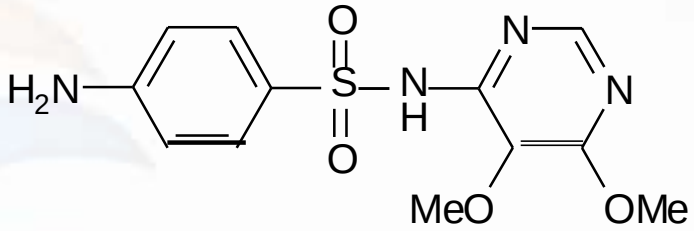


Quinocide

7. SULFONAMIDES AND SULFONE

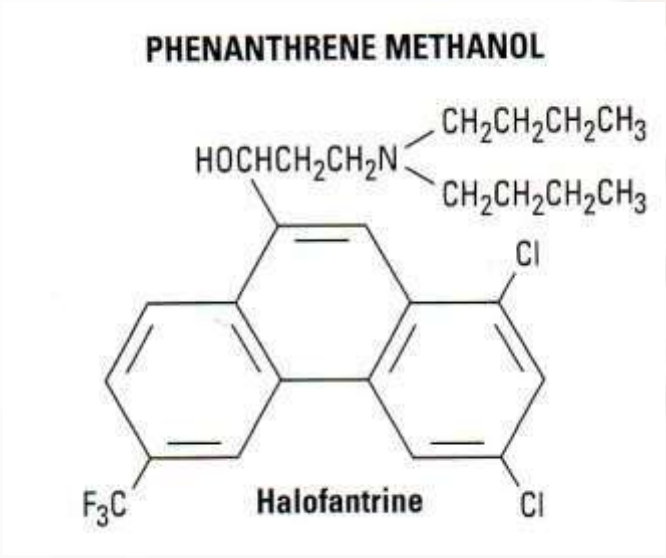


Dapsone

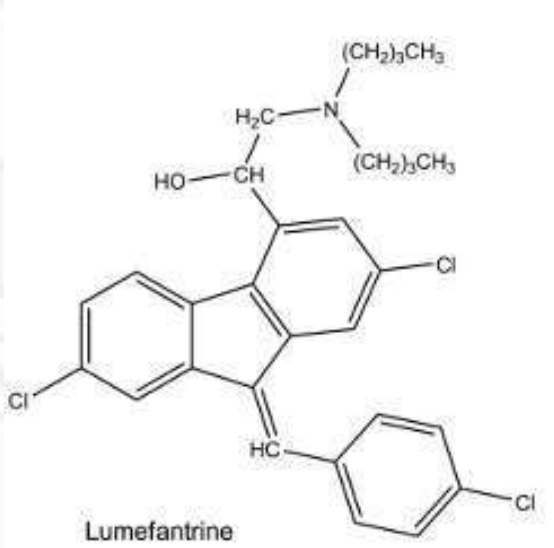


Sulfadoxine

8. Amino alcohols



Halofantrine



Lumefantrine

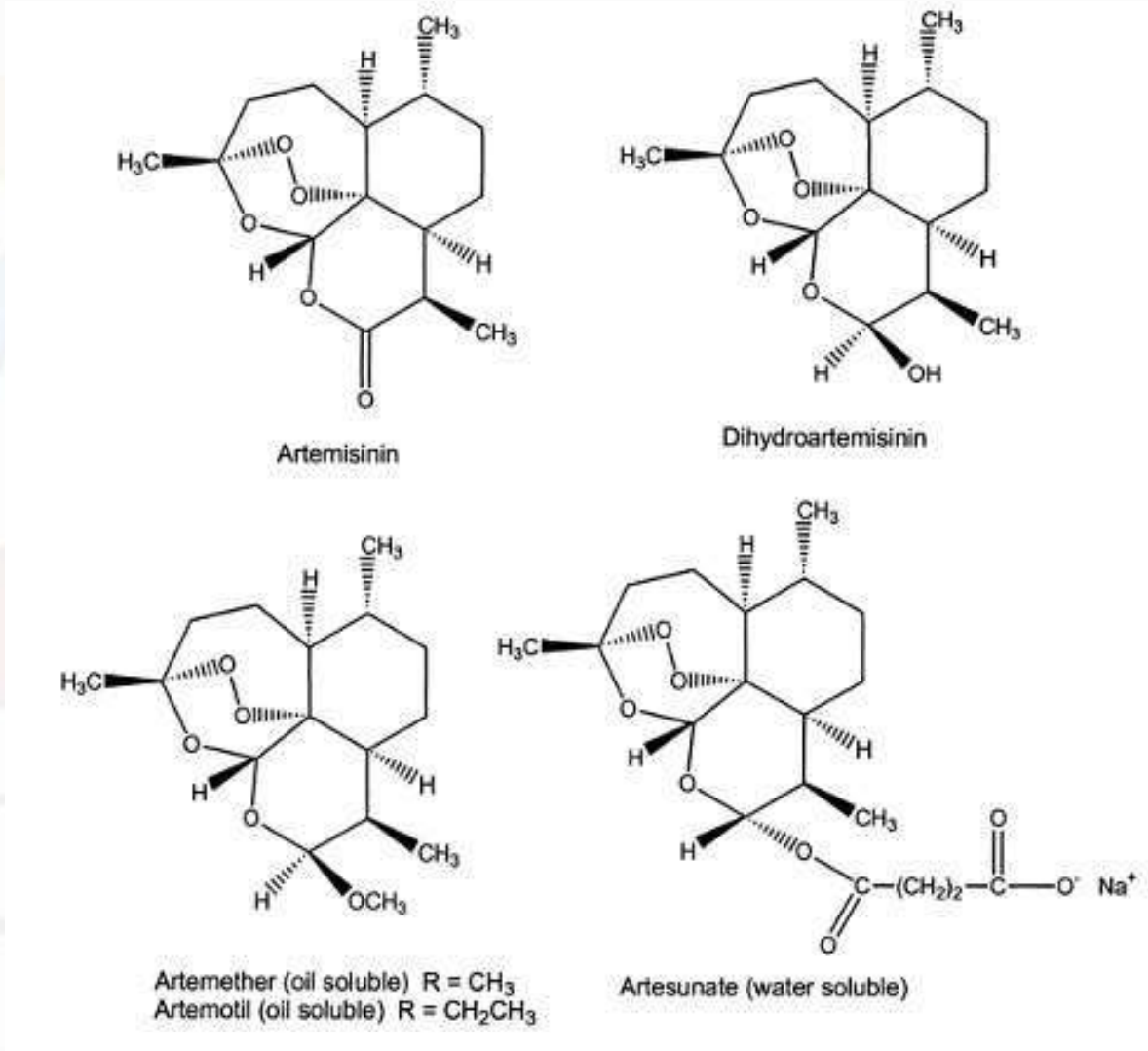
9. SESQUITERPINE LACTONES

- The artemisinin series are the newest of the antimalarial drugs and are structurally unique when compared with the compounds previously and currently used.
- The parent compound, artemisinin, is a natural product extracted from the dry leaves of *artemisia annua* (sweet wormwood).
- All of the compounds given in figure are active against the plasmodium genera that cause malaria.

PLANT– ARTEMISIA ANNUA

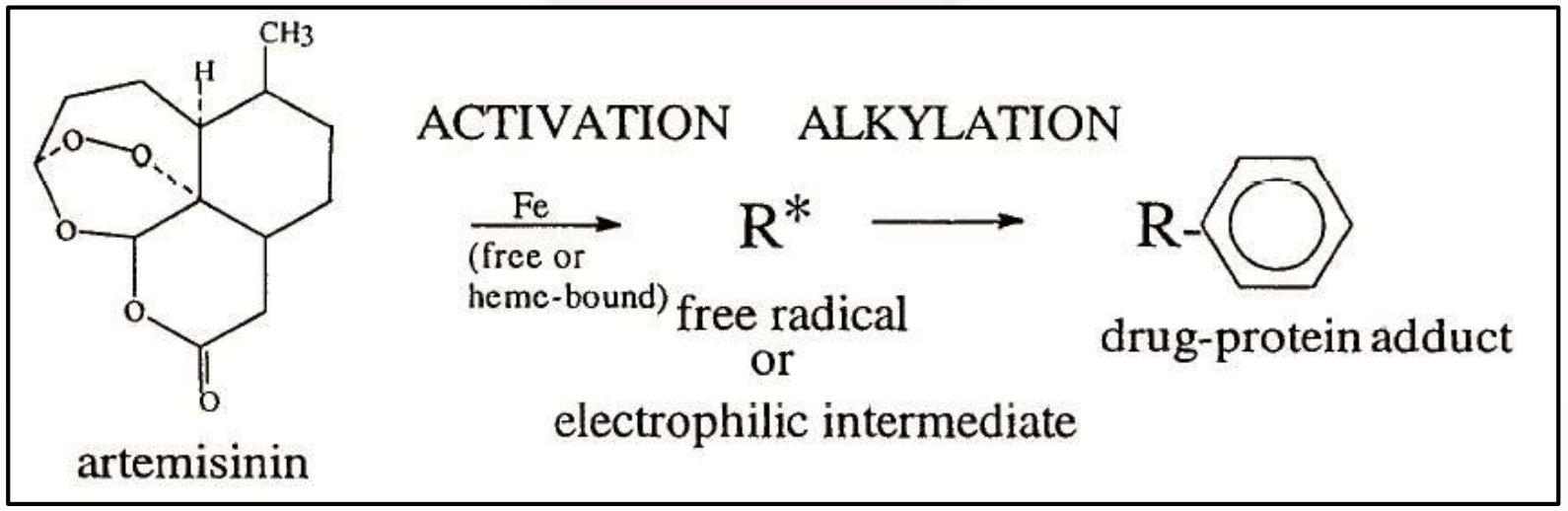
- The key structure characteristic appears to be a “trioxane” consisting of the endoperoxide and dioxepin oxygens.
- Note that the stereochemistry at position 12 is not critical.
- These are the artimisinin derivatives used in malaria:

1. Artesunate
2. Artemether
3. Arteether
4. Arterolane



MECHANISM OF ACTION

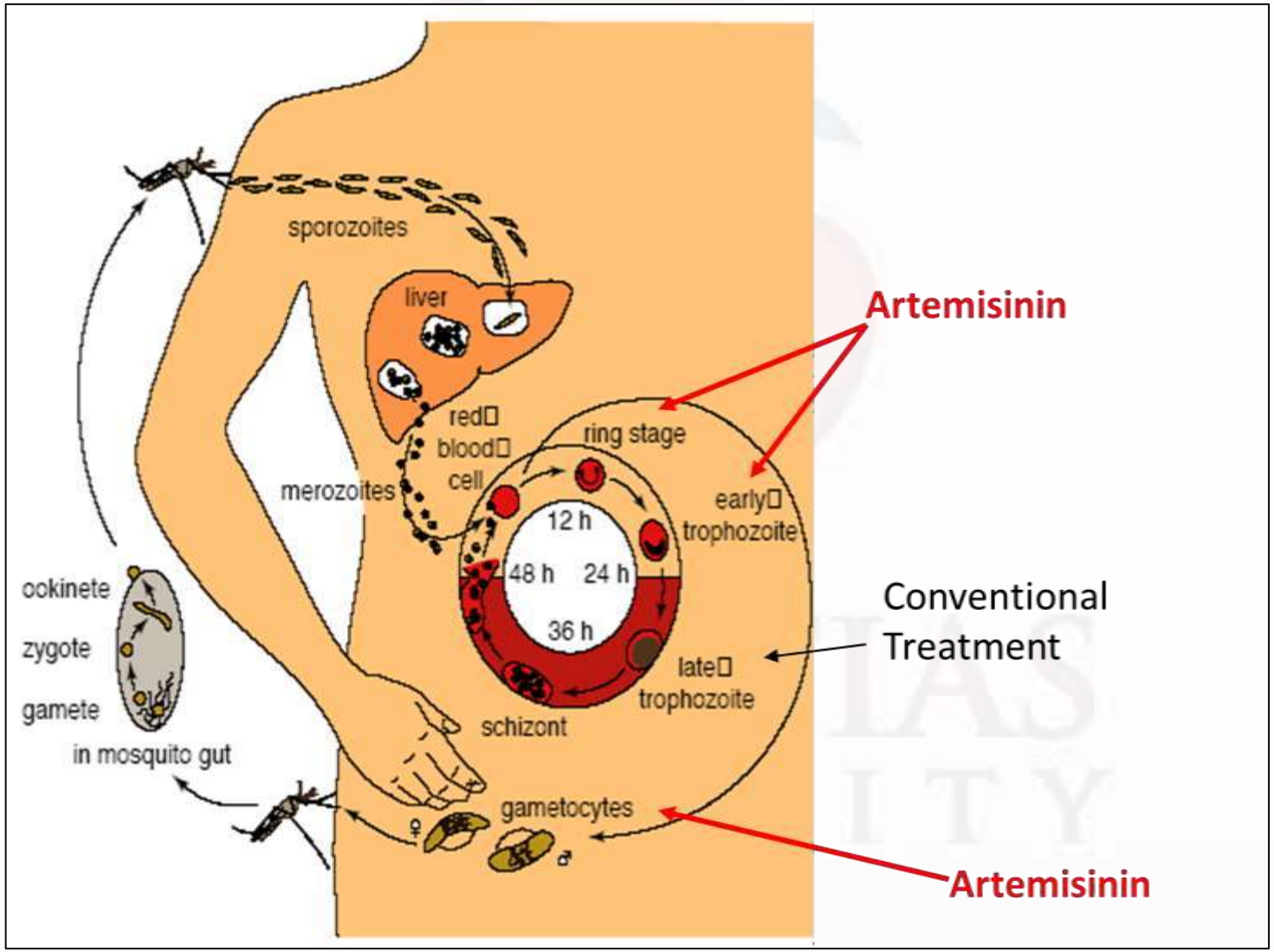
- These compounds contains endoperoxide bridge.
- Endoperoxide bridge interacts with heme in parasite.
- Heme iron cleaves this endoperoxide bridge.
- There is generation of highly reactive free radicals which damage parasite membrane by covalently binding to membrane proteins.



- They act rapidly, killing blood stages of all plasmodium species and reducing the parasite biomass.
- Artemisinins have the fastest parasite clearance times of any antimalarial.
- Artemisinins are active against gametocytes, the parasite form that is infectious to mosquitoes, and their use has been associated with reduced malaria transmission.
- Safe & 10-100 times potent compared to other antimalarials.

ANTIMALARIAL ACTION

ANTIMALARIAL ACTION

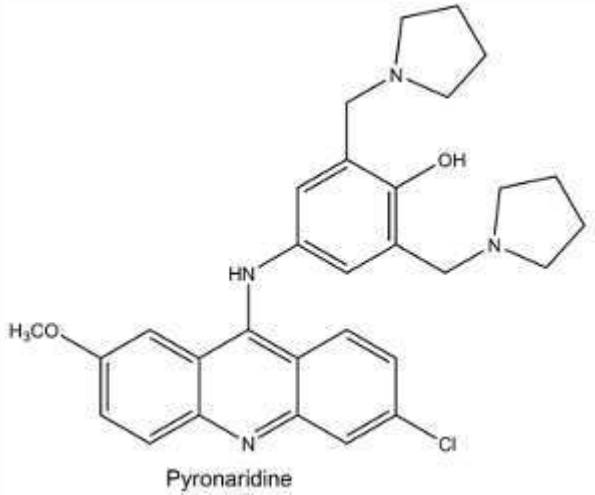


ARTEMISININ-BASED COMBINATION THERAPIES

- In general, artemisinins should not be used as a single agent, to prevent emergence of drug resistance and to avoid the need for prolonged therapy.
- Artemisinin-based combination therapy (acts) combine the highly effective short-acting artemisinins with a longer-acting partner to protect against artemisinin resistance and to facilitate dosing convenience.
- Acts are typically administered for 3 days and are often available in fixed-dose tablets.
- Four acts are recommended by the who for the treatment of uncomplicated malaria: artemether-lumefantrine, artesunate-amodiaquine, artesunate-mefloquine and artesunate-sulfadoxine-pyrimethamine.

10. NAPHTHYRIDINE

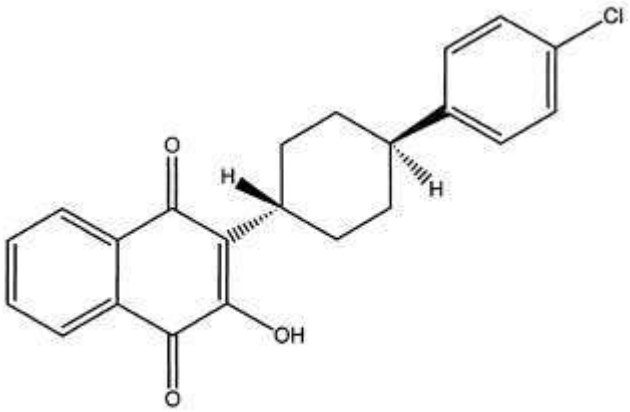
- Newer drug from Mepacrine developed in china.
- Mechanism similar to chloroquine.
- High effective erythrocytic schizonticide, effective against chloroquine sensitive & resistant vivax & falciparum malaria.
- Slow onset & long duration of action, concentrated in RBC.
- Water soluble, t1/2 : 7days
- Orally & parenterally used , well tolerated
- At high dose used analgesic/anti pyretic



Pyronaridine

11. NAPHTHOQUINONE

- ✓ Hydroxy naphthoquinone antiparasitic drug active against all Plasmodium species.
- ✓ Rapid acting erythrocytic schizontocide & inhibits pre-erythrocytic stage of falciparum.
- ✓ Also active against pneumocystis jiroveci & Toxoplasma gondii.
- ✓ Combined with proguanil Where its resistant, reduces relapse & which is synergistic.
- ✓ Collapses mitochondrial membrane interferes with cytochrome electron transport.



Atovaquone

12. ANTIBIOTICS

Tetracycline & doxycycline

- Erythrocytic schizonts are inhibited by all malarial parasite.
- Tetracycline used in combination with quinine in treatment of chloroquine resistant as well vivax malaria.
- Avoid in children & pregnant women.
- Doxycycline used in places where high resistance present.
- 200mg doxycycline combined with artesunate to treat mefloquine/chloroquine/s-p resistant malaria.
- 100mg/day of doxycycline used 2nd line prophylactic for short travels to chloroquine resistant p. Falciparum.

CLINDAMYCIN:

- Slow erythrocytic schizontocide, bacteriostatic
- With quinine used in treatment of resistant P.Falciparum
- Its used where tetracyclines can not be used in pregnancy & children less than 8 years old

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