ANTIMALARIAL AGENTS

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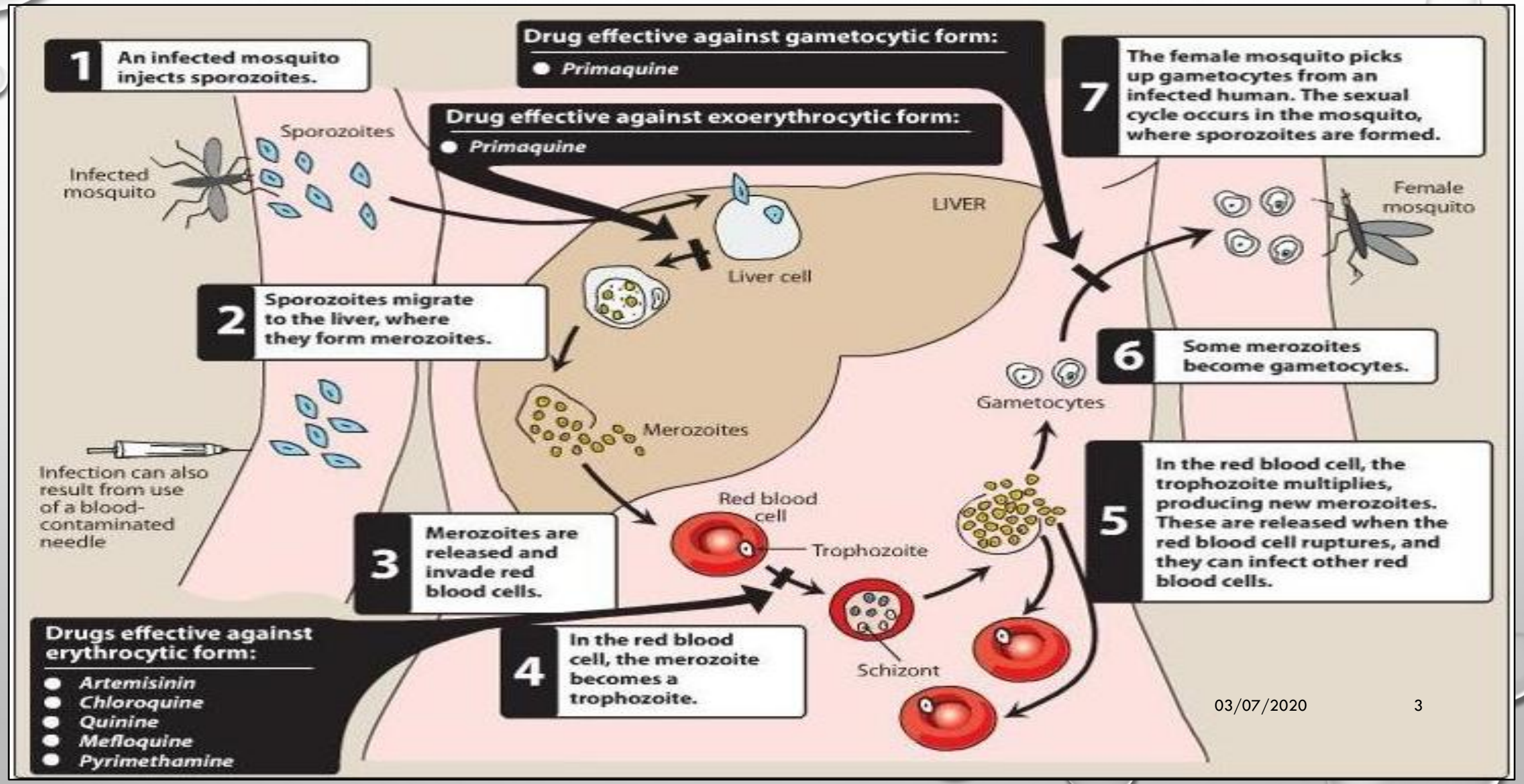
INTRODUCTION

- 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



- 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.

WHAT ARE THE SYMPTOMS OF MALARIA?

Symptoms of malaria occurs after 12-16 days after mosquito bite……

So pre-erythrocytic phase is free from symptoms and erythrocytic phase is responsible to have symptoms of malaria.

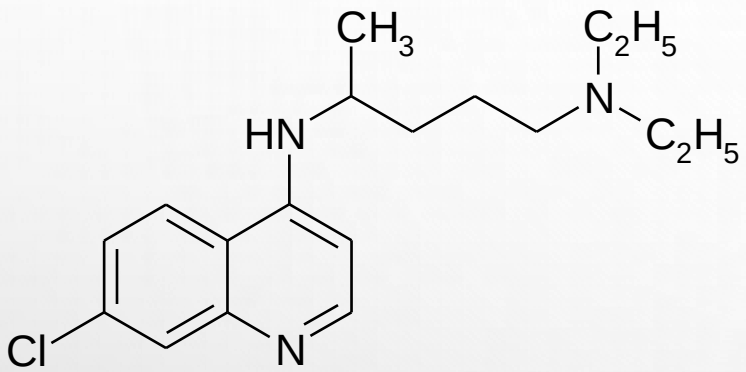
- **Nausea, vomiting, chills, delirium and fever may reaper every 3-4 days depends ontype of infection.**
- **Anaemia (breakdown of Hb to get bilirubin)**
- **Jaundice due to accumulation of bilirubin**
- **muscle pain**
- **Convulsions**
- **headache**

CHEMICAL CLASSIFICATION

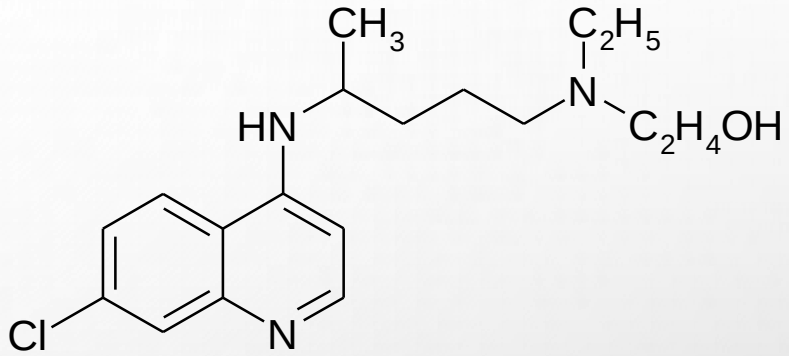
Classes	Drugs
1. 4-aminoquinolines	Chloroquine (CQ), amodiaquine (AQ), Piperaquine
2. Quinoline-methanol	Mefloquine
3. Cinchona alkaloid	Quinine, quinidine
4. Biguanide	Proguanil (chloroguanide)
5. Diaminopyrimidine	Pyrimethamine
6. 8-aminoquinoline	Primaquine, tafenoquine
7. Sulfonamides and sulfone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

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

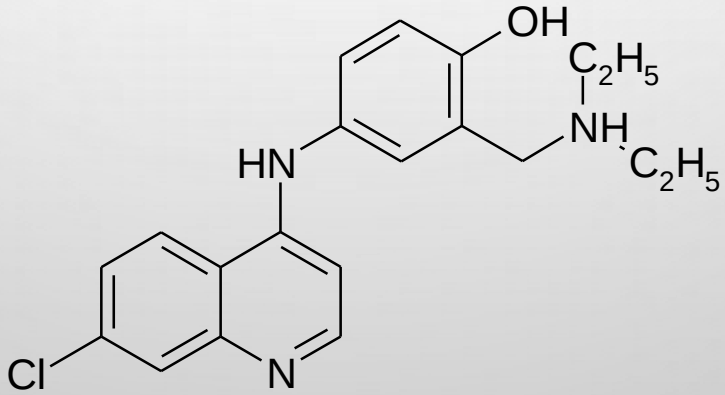
1. 4-AMINOQUINOLINES



Chloroquine



Hydroxychloroquine



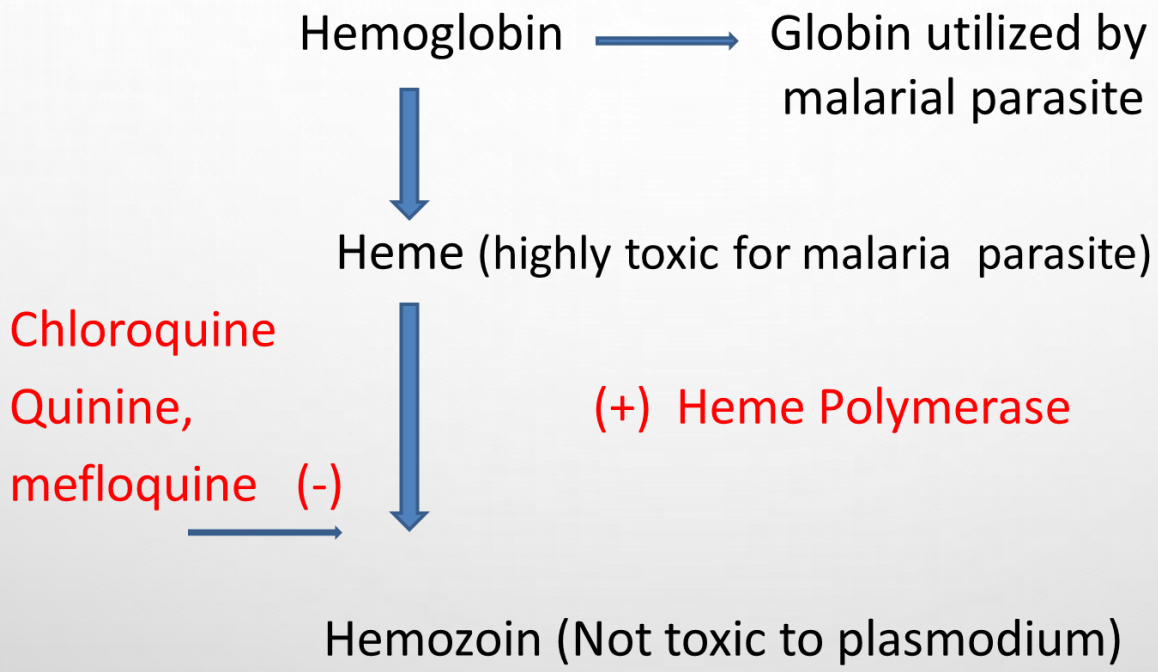
Amodiaquine

CHLOROQUINE:

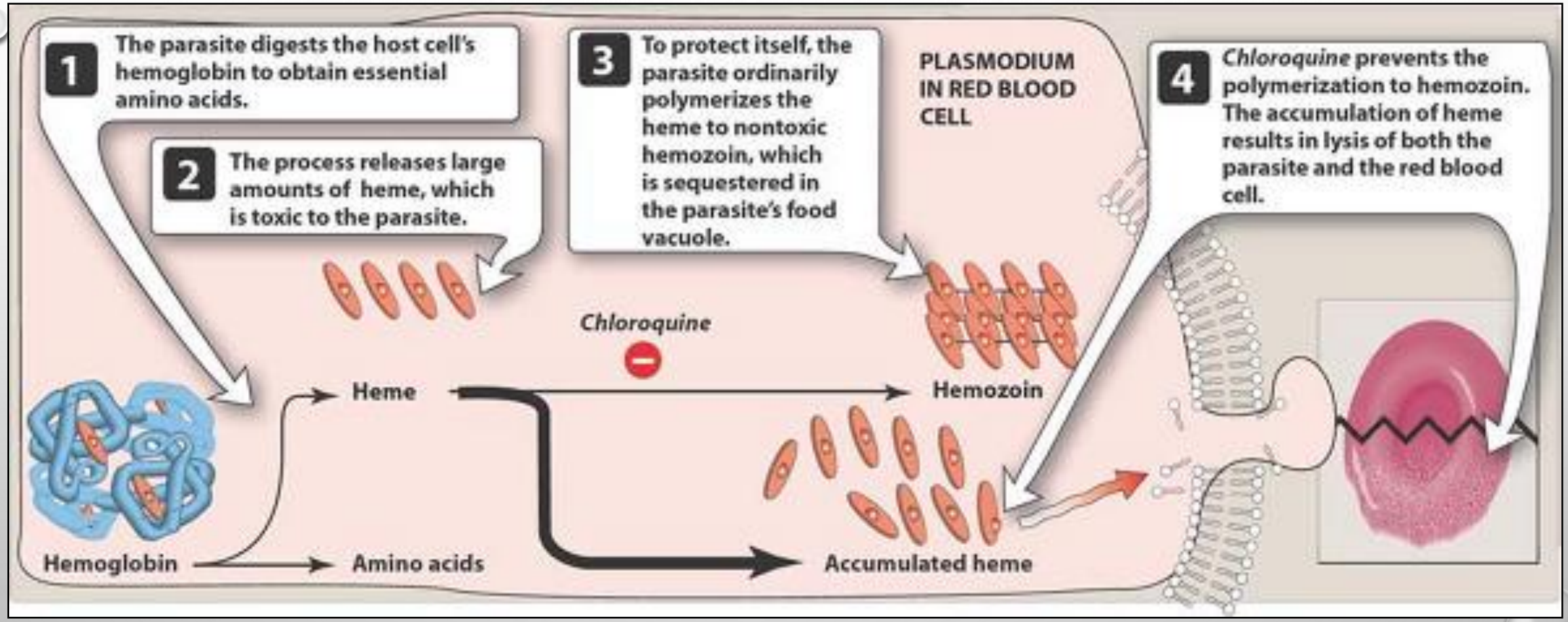
- It has activity against the blood stages of *plasmodium ovale, P. Malariae,* and susceptible strains of *P. Vivax and P. Falciparum*.
- Widespread resistance in most malaria-endemic countries has led to decline in its use for the treatment of p. Falciparum, although it remains effective for treatment 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 Form complex with Hb-----deficiency of food material.

- 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.

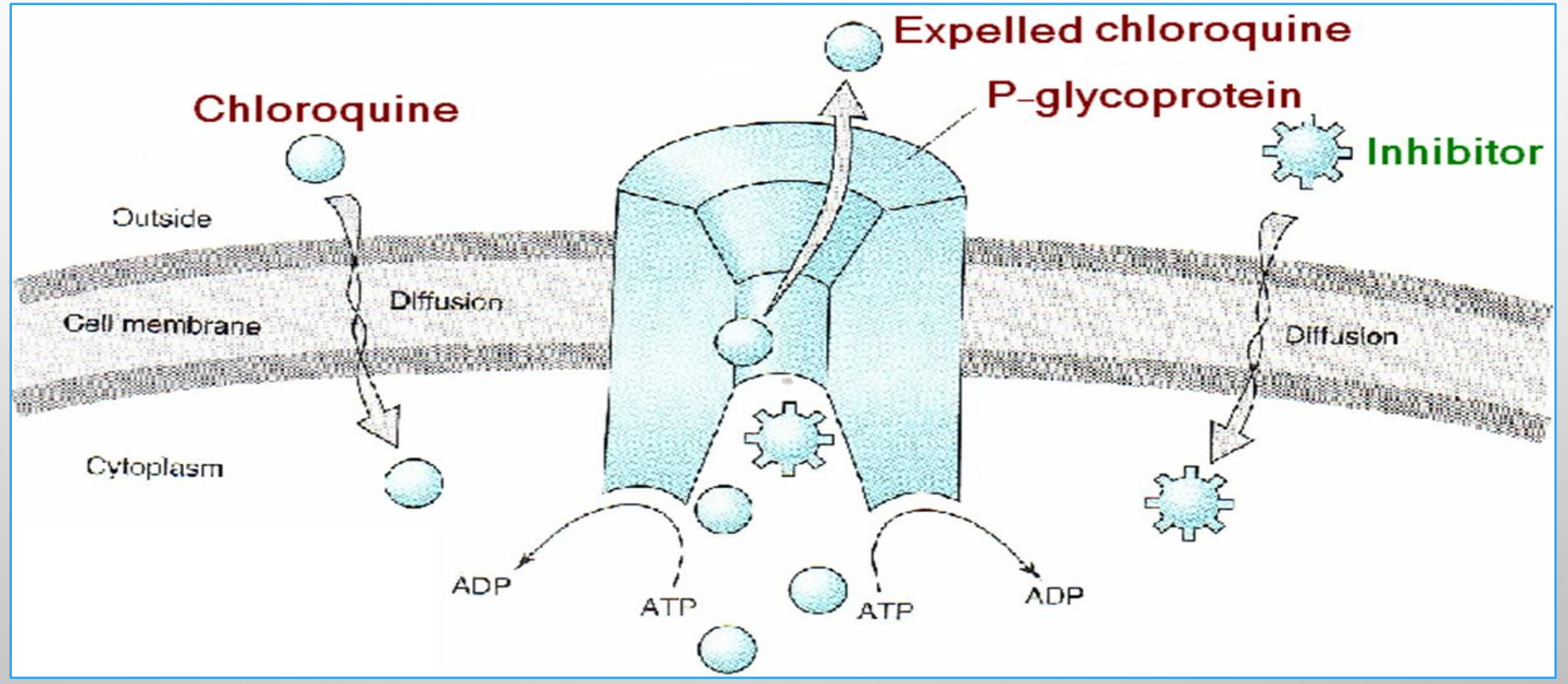
MECHANISM OF ACTION



MECHANISM OF ACTION :



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



Adverse drug reactions

Intolerance:

- Nausea, vomiting, anorexia
- skin rashes, angioneurotic edema, photosensitivity, pigmentation, exfoliative dermatititis
- Long term therapy may cause bleaching of hair
- Rarely thrombocytopenia, agranulocytosis, pancytopenia

Ocular toxicity:

- High dose prolonged therapy
- Temporary loss of accommodation

Adverse drug reactions

- **Retinopathy:**
  - Constriction of arteries, edema, blue black pigmentation, constricted field of vision.
- **CNS:**
  - Insomnia, transient depression seizures, rarely neuromyopathy & ototoxicity
- **CVS:**
  - abrupt fall in bp & cardiac arrest in children reported

- **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

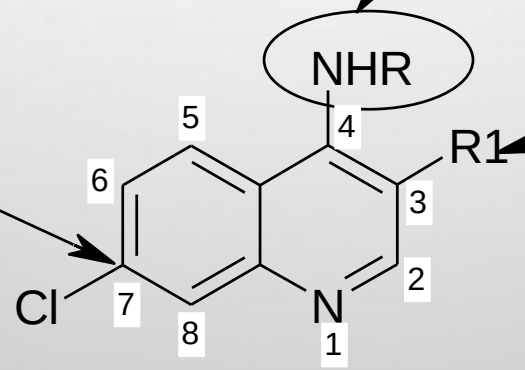
SAR of 4-aminoquinolines

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

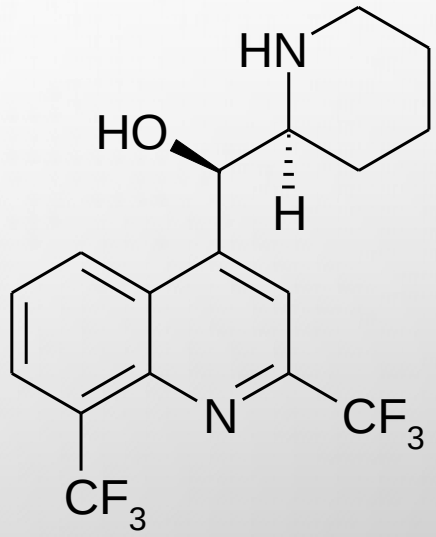
Introduction of methyl group at this position reduces activity



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.

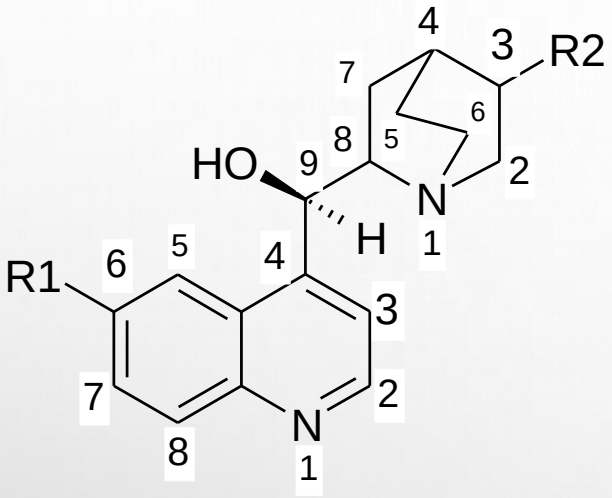


Mefloquine

Adverse effects

- ✓ Mefloquine is bitter in taste
- ✓ At high doses: Nausea, vomiting, diarrhea, abdominal pain, bradycardia, ataxia, hallucinations, depression.
- ✓ Mefloquine is safe in pregnancy

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).

Adverse drug reactions

Cinchonism:

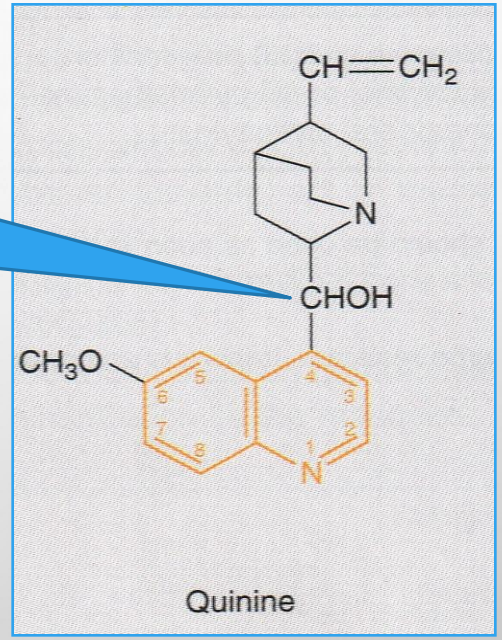
- Tinnitus, nausea & vomiting.
- Headache mental confusion, vertigo, difficulty in hearing & visual disturbances
- Diarrhoea , flushing & marked perspiration.
- Still higher doses, exaggerated symptoms with delirium, fever, tachypnoea, respiratory depression, cyanosis.

Idiosyncrasy: similar to cinchonism but occurs in therapeutic doses

Black water fever: a fatal condition in which acute hemolytic anemia is associated with renal failure.

Cardiovascular toxicity: cardiac arrest, hypotension ,fatal arrhythmias

Black water fever because of methanol group



Quinine

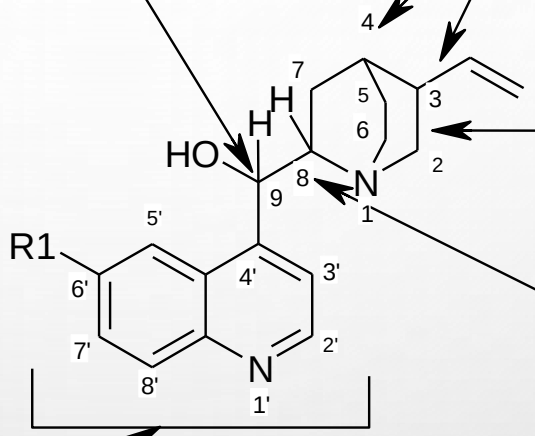
CONTRAINDICATIONS :

Hypersensitivity to quinine or any component of the formulation; hypersensitivity to mefloquine or quinidine (cross sensitivity reported); prolonged QT interval; myasthenia gravis; optic neuritis; G6PD deficiency; history of black water fever; thrombotic thrombocytopenia purpurea, hemolytic uremic syndrome, thrombocytopenia

SAR Of Quinine

1. Modification of the secondary alcohol at C-9, through oxidation, esterification diminishes activity.
2. The configuration at positions 8 and 9 affects the juxtaposition of the hydroxyl group and the non-aromatic nitrogen atom, a relationship that is associated with antimalarial activity.

Assymmetry at this positions is not essential for antimalarial activity



Quinuclidine portion is not necessary for activity; however, an alkyl tertiary amine attached at C-9 is important

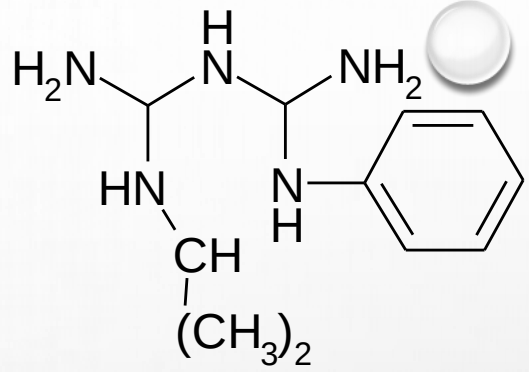
Activity usually enhanced by the introduction of a halogen at this position.

Quinoline Ring

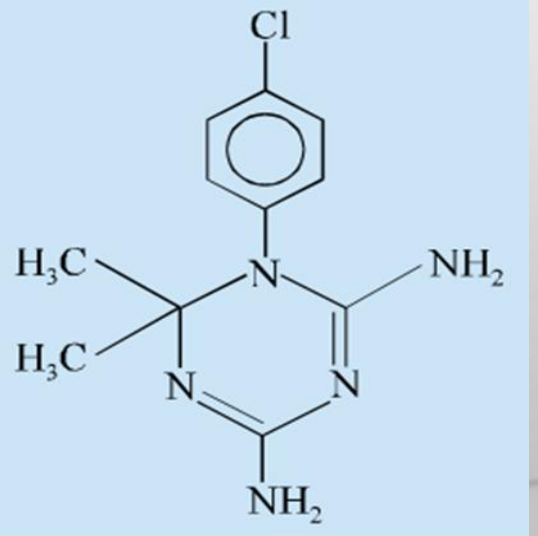
1. Presence of methoxy group in quinine is not essential.
2. Replacement of methoxy group by a halogen, especially chlorine, enhances activity.
3. A further increase in activity resulted from the introduction of a phenyl group at position 2'.
4. It was discovered that high activity without phototoxicity could be attained by blocking position 2' with a trifluoromethyl group, a finding that eventually led to development of mefloquine.

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 plas-modial DHFRase in preference to the mammalian enzyme.
- ✓ Resistance to proguanil develops rapidly due to mutational changes in the plasmodial DHFRase enzyme.

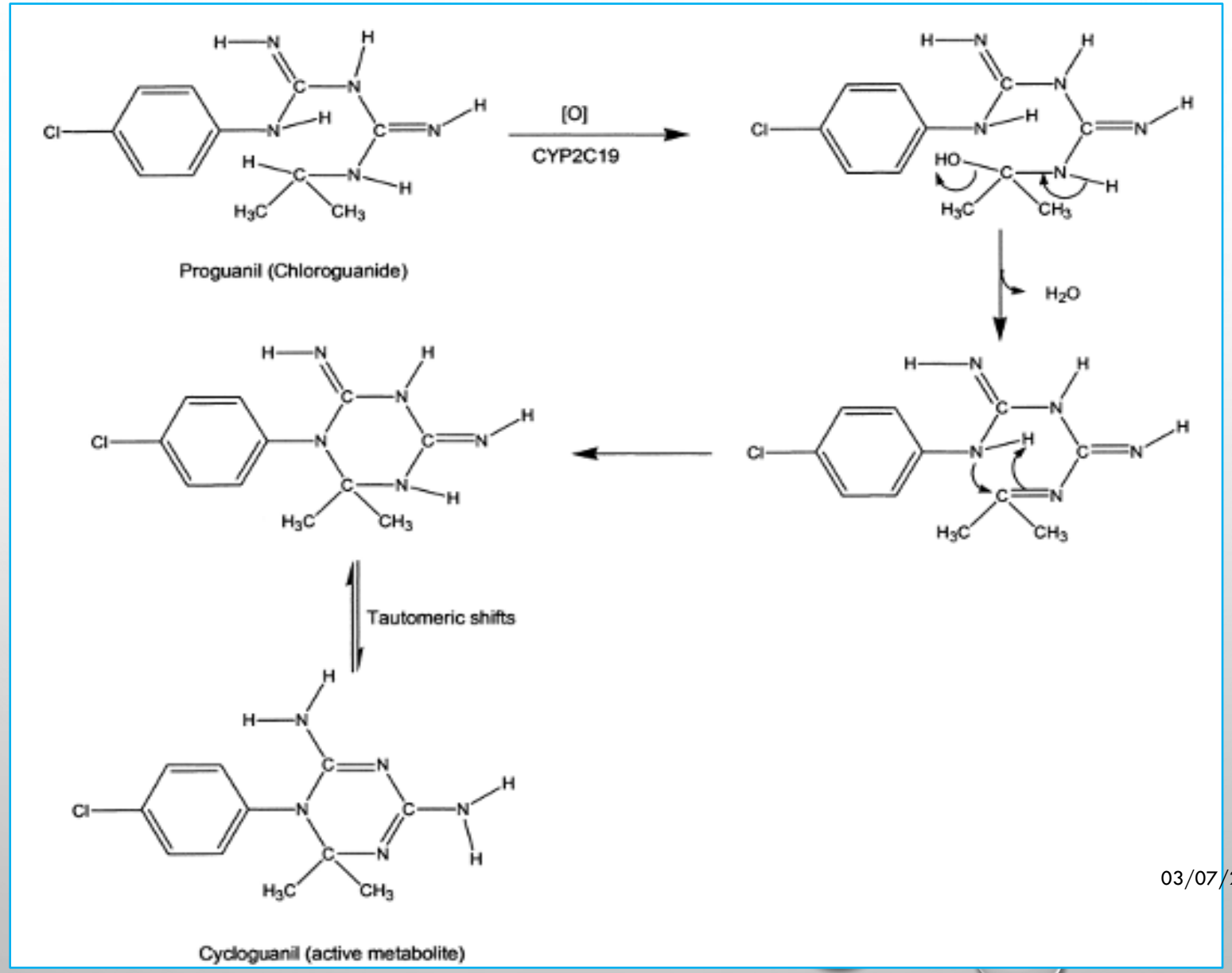


Proguanil



cycloguanil

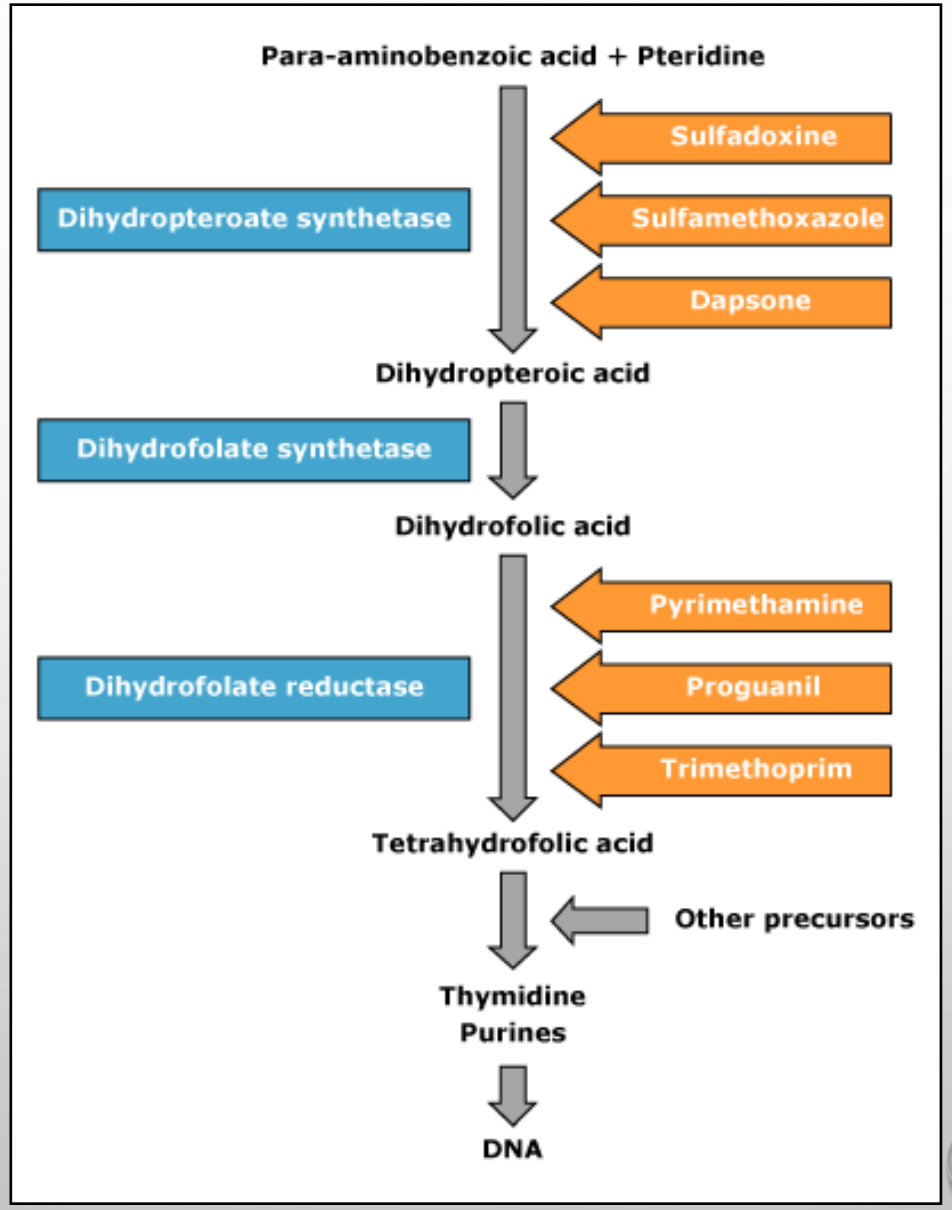
Conversion of proguanil to cycloguanil by CYP2C19



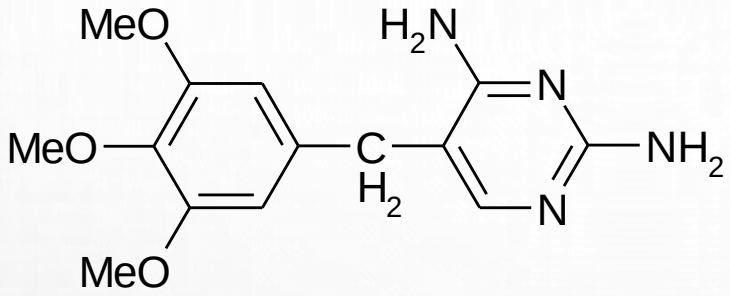
Adverse effects

- Mild abdominal upset, vomiting
- Occasional stomatitis
- Haematuria, rashes and transient loss of hair
- Note : safe during pregnancy

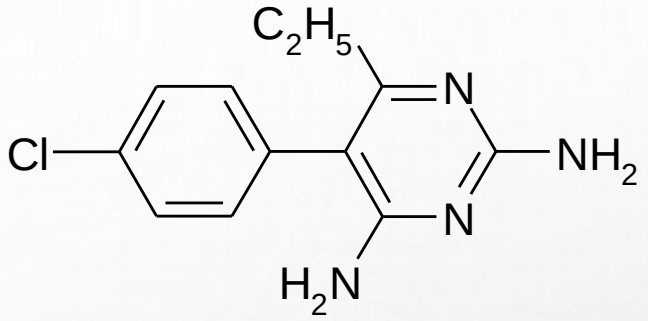
Mechanism of action of anti folates



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.

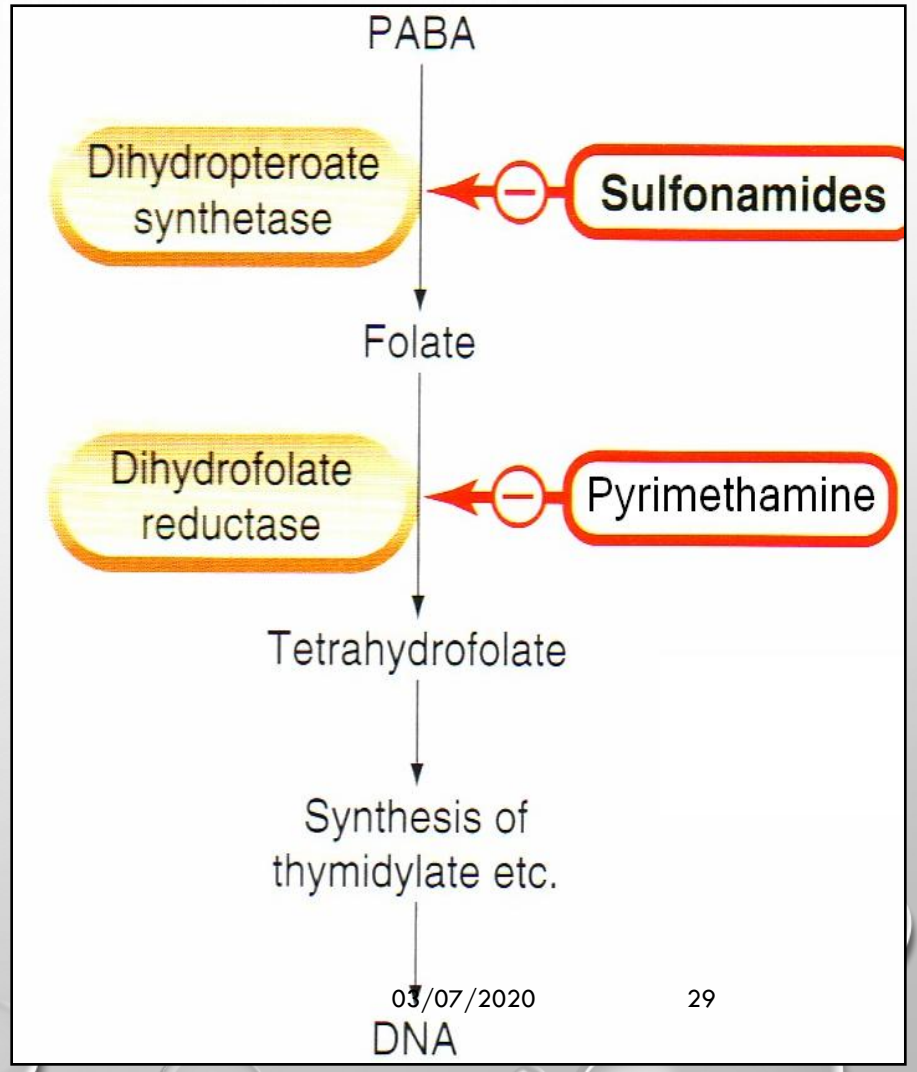
Pyrimethamine

Adverse effects

- Occasional nausea and rashes
- Folate deficiency rare
- Megaloblastic anaemia and granulocytopenia with higher dose
- Can be treated with folinic acid
- Combined with a sulfonamide (S/P) or dapsone for treatment of falciparum malaria

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



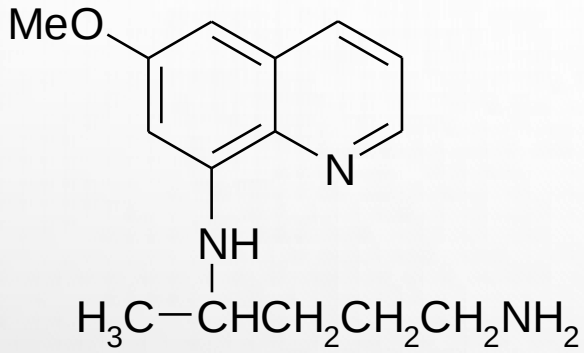
Adverse effects

- Mild GIT upset
- Megaloblastic anemia, bone marrow depletion
- Rashes, urticaria, serum sickness, drug fever
- Exfoliative dermatitis, stevens johnson syndrome
- Nephrotoxicity

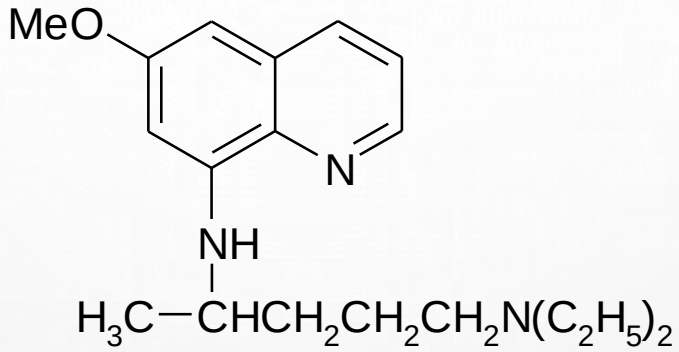
Uses:

- Single dose treatment of uncomplicated chloroquine resistant falciparum malaria
- Patients intolerant to chloroquine
- First choice treatment for toxoplasmosis

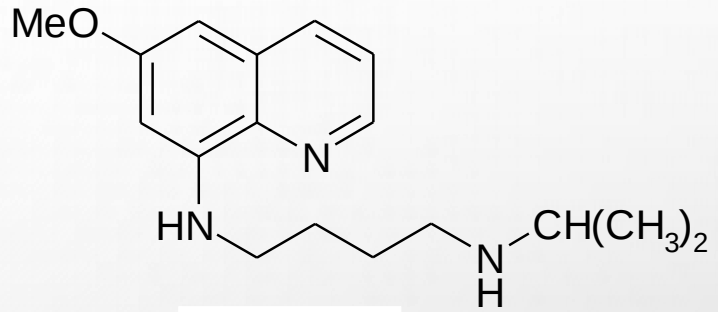
6. 8-AMINOQUINOLINE



Primaquine



Pamaquine



Pentaquine

Quinocide

Primaquine:

- It is the only 8-aminoquinoline in clinical use.
- It is largely used to prevent relapse of p. Ovale and P. Vivax malaria by eliminating dormant hypnozoites, and it also has activity against the pre-erythrocytic stage and gametocytes of P. Falciparum.
- It is not used for prophylaxis. Its spectrum of activity is one of the narrowest of the currently used antimalarial drugs being indicated only for exoerythrocytic P. Vivax malaria

Mechanism of action primaquine:

- Not clear, its converted & produces active oxygen interfere with plasmodial mitochondrial function

Uses of primaquine

1. Radical cure

A) P.Vivax & ovale :

- Given in acute attack or throughout incubation period
- Prevents relapse

Prophylactically: before & after leaving the endemic area to eradicate hepatic forms

- Effective vector control is possible or used in areas of low transmission

B) falciparum malaria:

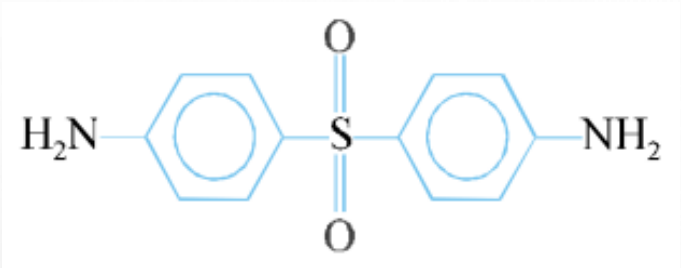
- 45mg with chloroquine used like gametocidal & cut down transmission or where effective control is needed.

Adverse drug reaction

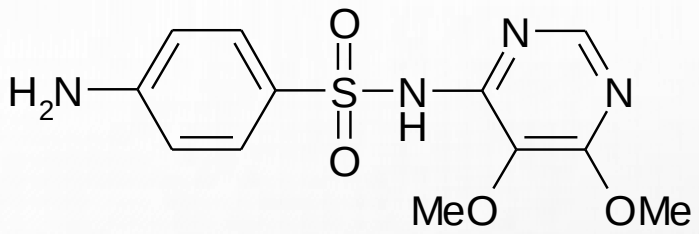
Therapeutic doses:

- Haemolysis & methaemoglobinaemia commonly seen in g6pd deficiency
- Causes nausea, headache, epigastric pain &abdominal cramps on empty stomach
- Rarely : leucopenia, leucocytosis & agranulocytosis
- Precaution – primaquine
- Should not be given during pregnancy because fetus is glucose-6-phosphate dehydrogenase (g-6-pd) deficient

7. SULFONAMIDES AND SULFONE

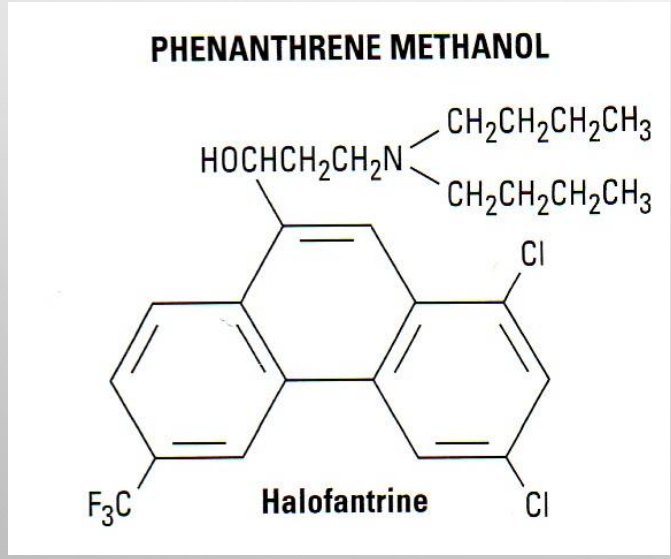


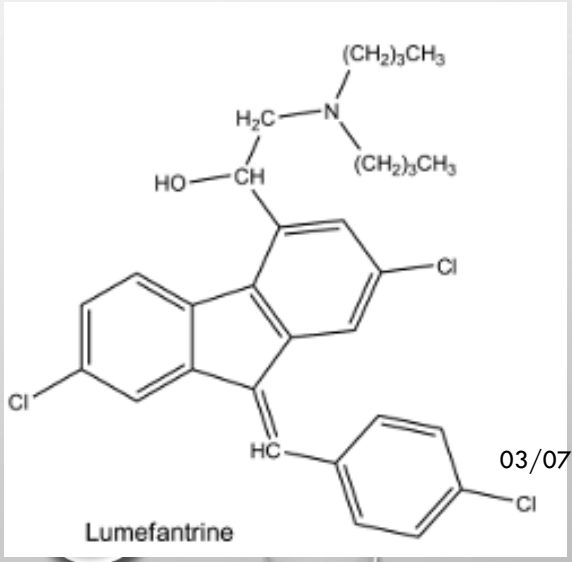
Dapsone



Sulfadoxine

8. Amino alcohols





- Structurally, halofantrine differs from all other antimalarial drugs. It is a good example of drug design that incorporates bioisosteric principles as evidenced by the trifluromethyl moiety.
- Halofantrine is a schizonticide and has no affect on the sporozoite, gametocyte,or hepatic stages.
- It is active against strains resistant to chloroquine, pyrimethamine, quinine.
- Cross-resistance in falicparum infection occurred .
- Erratic bioavailability, lethal cardio toxicity & cross resistance to mefloquine limited its use.
- Now a days used only when no other alternative available

ADR:-

- Abdominal pain, headache, transient increase in hepatic enzymes, cough, pruritus, lengthening of qt interval. May cause hemolytic anemia & convulsions. Reserved for infection caused by resistant organisms.

Contraindications: with mefloquine.

- Patients with cardiac conduction defects.
- In pregnancy → embriotoxic in animals

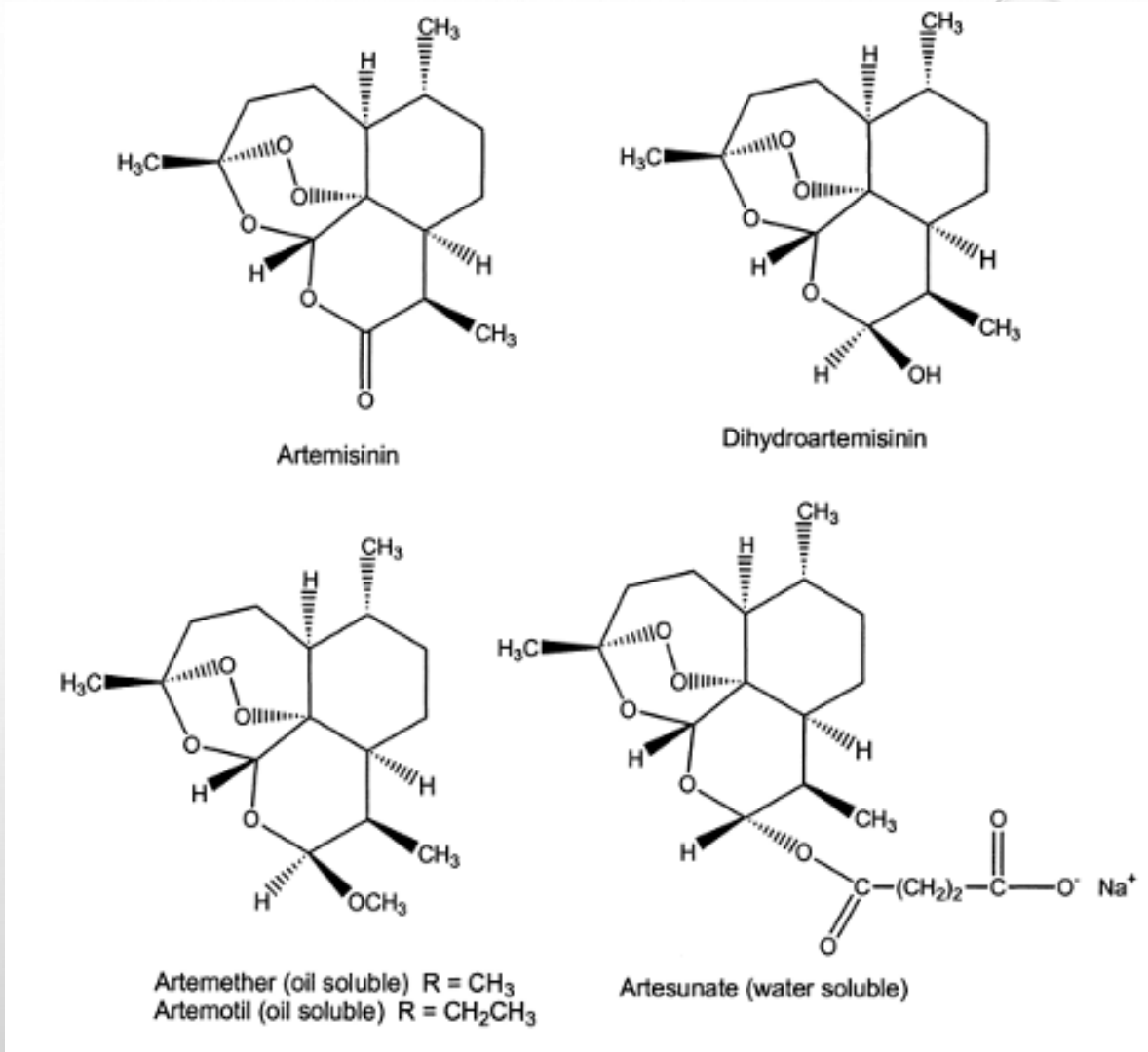
9. SESQUITERPINE LACTONES

- 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

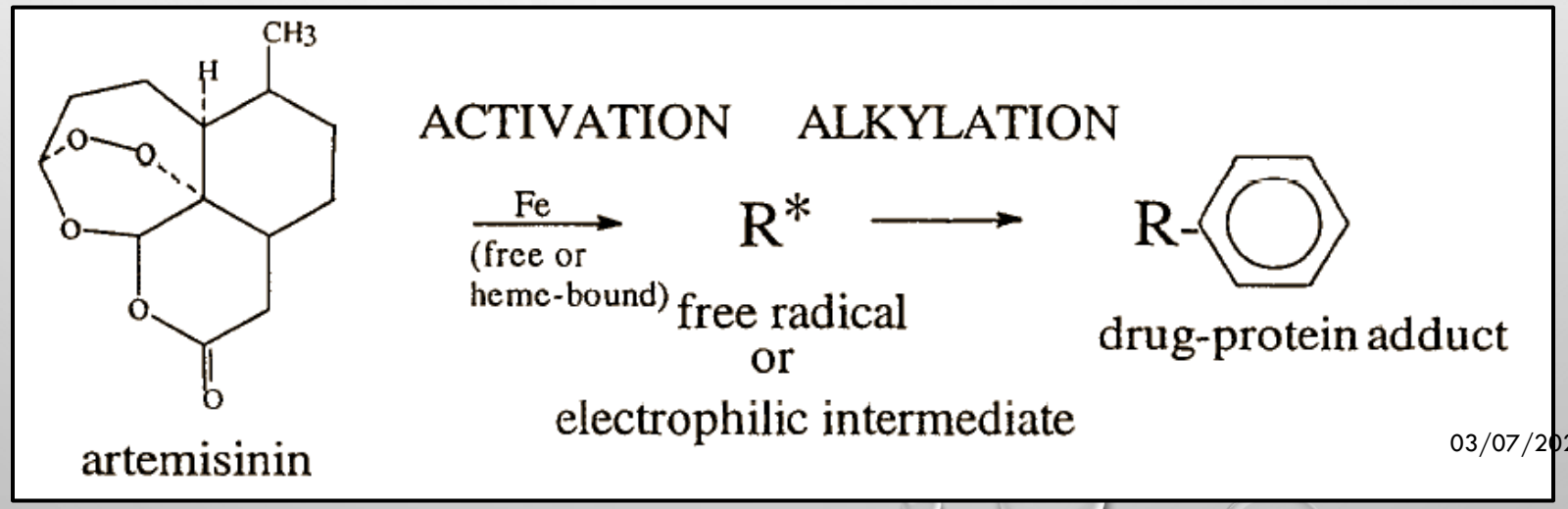
- The key structure characteristic appears to be a “trioxane” consisting of the endoperoxide and dioxepin oxygens.
- Note that the stereochemistry at position 12 is not critical.
- These are the artimisinin derivatives used in malaria:

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



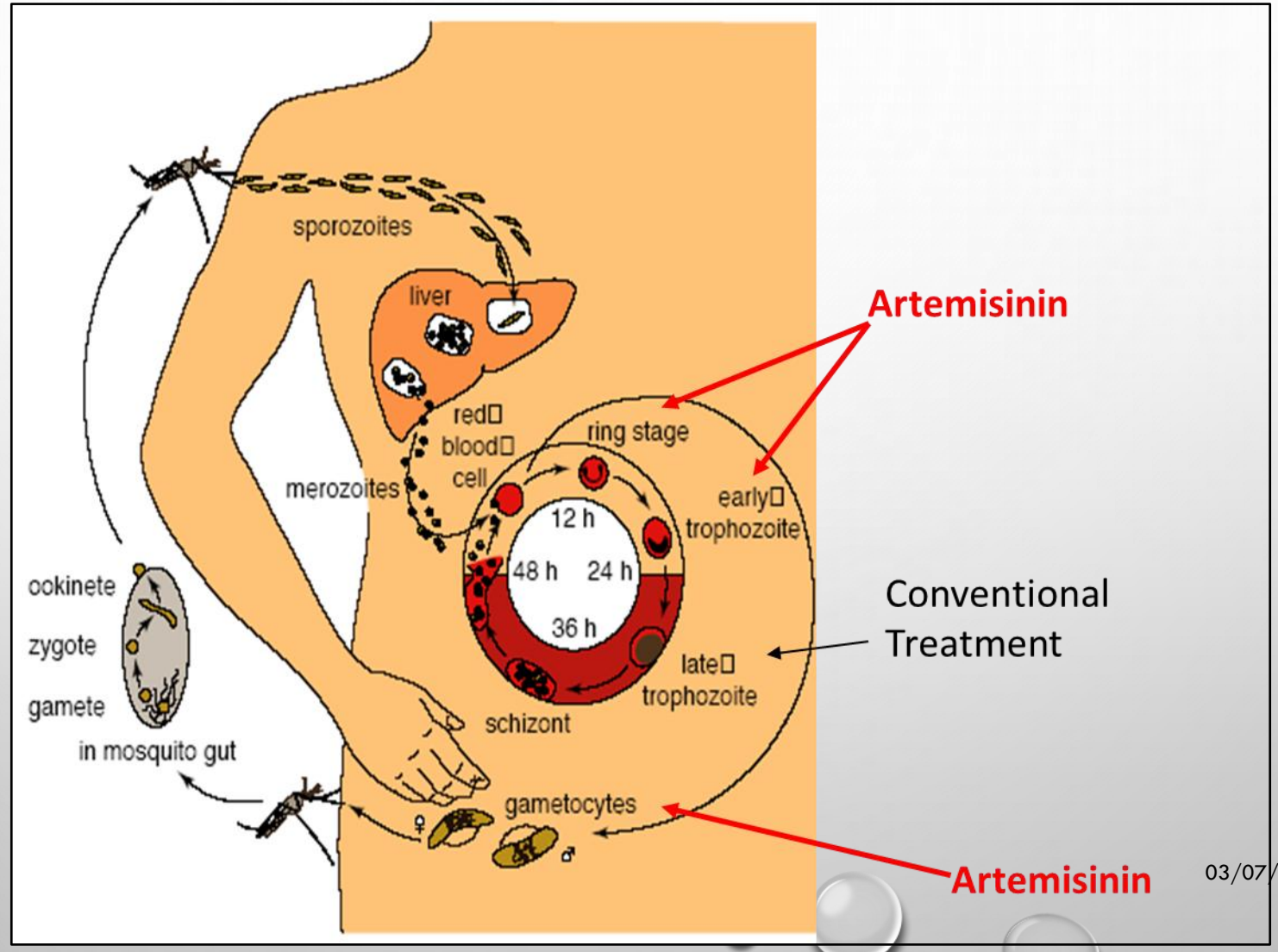
MECHANISM OF ACTION

- 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



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.

ARTEMISININS

- Intravenous artesunate is used for the treatment of severe malaria.
- It is superior to quinine for treatment of severe malaria with respect to clearing parasitemia and reducing mortality.
- Given the short half-life of artemisinins, intravenous therapy must be followed by a longer acting agent once the patient is able to tolerate oral medication.
- If used alone (via the parenteral, rectal or oral route), artesunate must be administered for 5-7 days.
- Treatment for less than 5 days results in recurrent parasitemia several weeks after therapy due to the very short duration of action, rather than to artemisinin resistance.

- Artemisinins are generally well tolerated.
- Type 1 hypersensitivity to the artemisinin compounds has been reported.
- Adverse effects of orally-administered artemisinins demonstrated transient neurological abnormalities (nystagmus and disturbances in balance); these effects resolved without lasting sequelae.

Advantages of act

- Rapid clinical and parasitological cure
- High cure rates(>95%) and low recrudescence rate
- Absence of parasite resistance
- Good tolerability profile
- Dosing schedule is simpler

1. ARTESUNATE - SULFADOXINE + PYRIMETHAMINE (AS-S/P)

- First line drug for uncomplicated *falciparum* malaria.
- Not effective against multidrug-resitant strains which are non responsive to s/p.
- Fewer side effects than as/mq.

2. Artesunate /mefloquine (AS/MQ)

- Highly effective and well tolerated in uncomplicated *falciparum* malaria

3. Artemether - lumefantrine (AS/LF)

- ✓ Clinical efficacy: 95-99%
- ✓ Must be administered with fatty food or milk to allow absorption and ensure adequate blood level of AS/LF
- ✓ Quickly reduces parasite biomass, resolve symptoms, prevent recrudescence, check gametocyte population

4. DIHYDROARTEMISININ (DHA)-PIPERAQUINE

- Used in dose ratio of 8:1 for multidrug resistant *plasmodium falciparum*.
- Good safety profile and even tolerated by children (>98% response rate).

5. ARTESUNATE-AMODIAQUINE(AS/AQ)

- First line therapy of uncomplicated *falciparum* malaria
- To be taken twice daily for three day treatment

Other recently developed ACT are:

6. ARTEROLANE-PIPERAQUINE

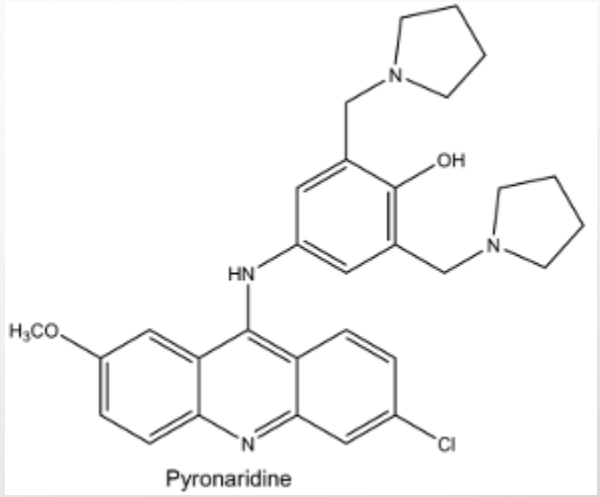
- Acts rapidly at all stages of asexual schizogony of malarial parasite including multidrug resistant *P. Falciparum*

7. ARTESUNATE-PYRONARIDINE

- **Under clinical trial**

10. NAPHTHYRIDINE

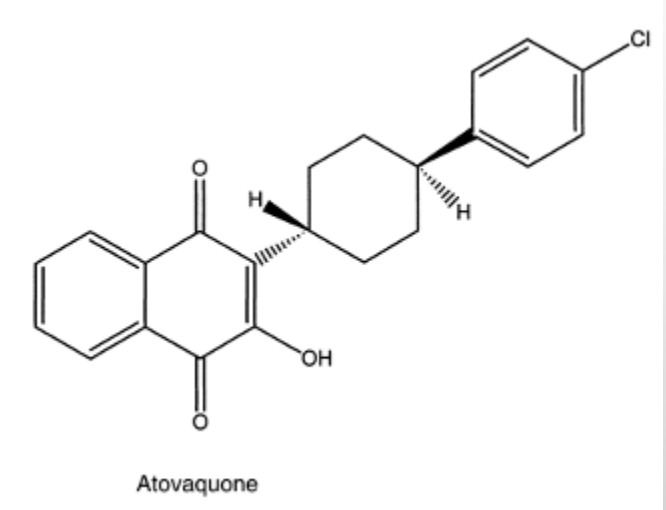
- Newer drug from **Mepacrine developed in china.**
- Mechanism similar to chloroquine.
- High effective erythrocytic schizonticide, effective against chloroquine sensitive & resistant vivax & falciparum malaria.
- Slow onset & long duration of action, concentrated in RBC.
- Water soluble, t1/2 : 7days
- 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

THANK YOU