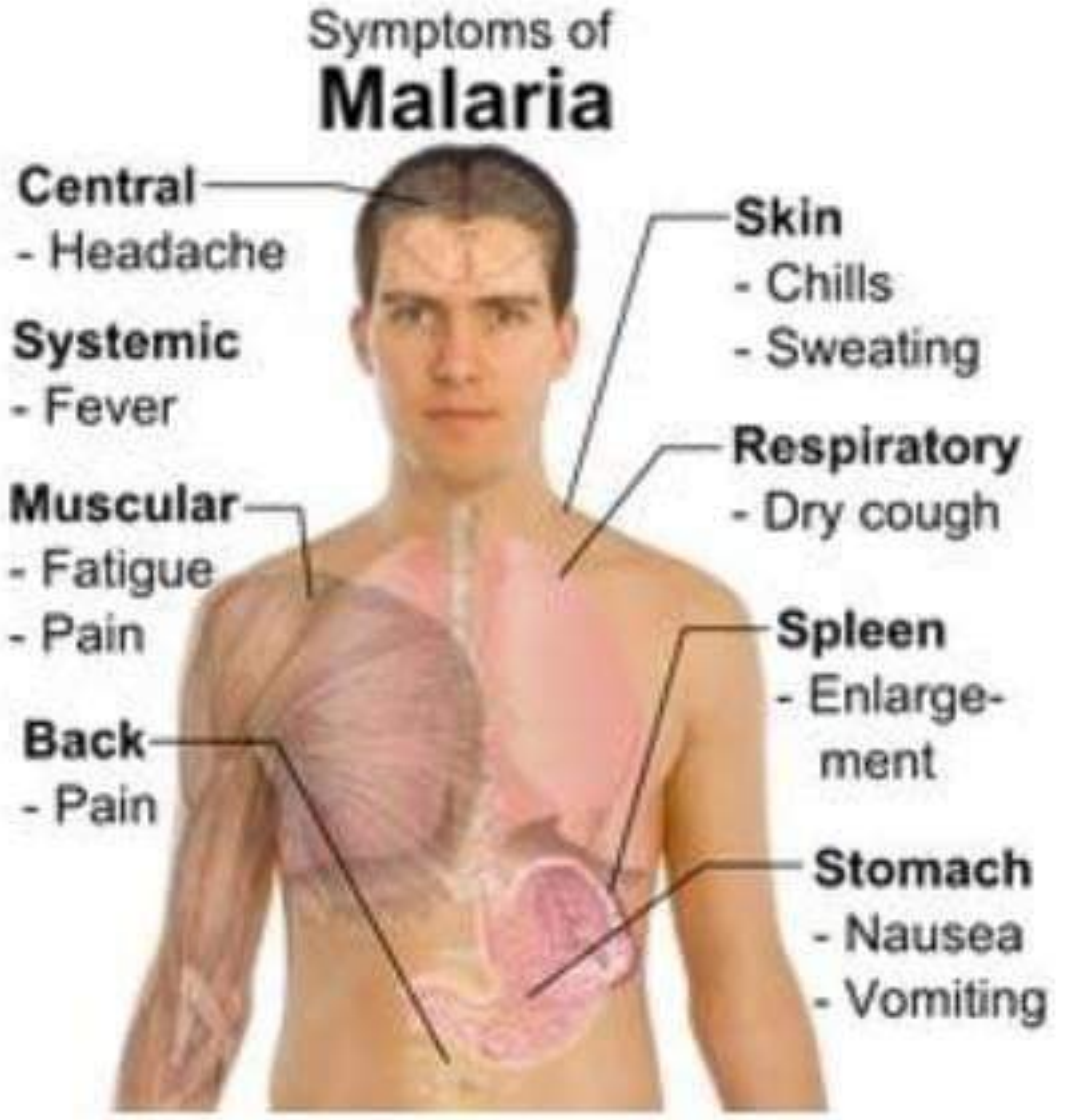
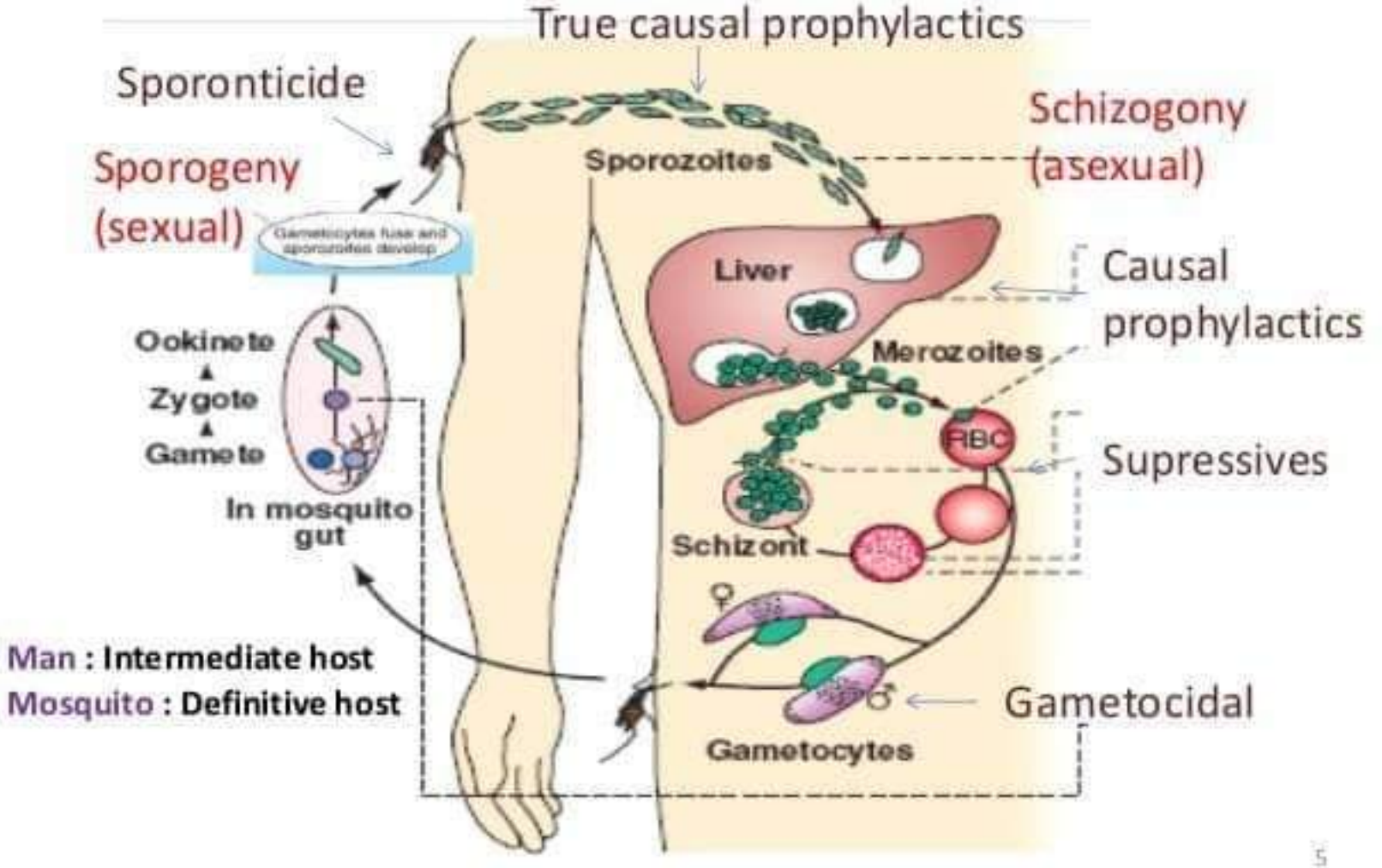
Antimalarial drugs

Introduction

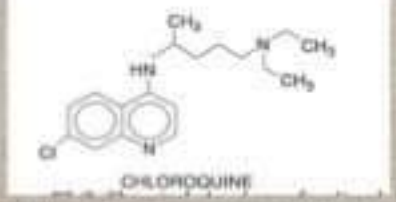
- Malaria is a protozoal disease, caused by
  - Plasmodium vivax
  - Plasmodium malariae
  - Plasmodium ovale
  - Plasmodium falciparum
- Most of the serious complications and death occur due to Plasmodium falciparum.


Symptoms of
Malaria
Central
- Headache
Systemic
- Fever
Muscular
- Fatigue
- Pain
Back
- Pain
Skin
- Chills
- Sweating
Respiratory
- Dry cough
Spleen
- Enlarge-
ment
Stomach
- Nausea
- Vomiting

Life cycle of the malarial parasite



Chloroquine



- Synthesized at Bayer laboratories, and named as "Resochin"

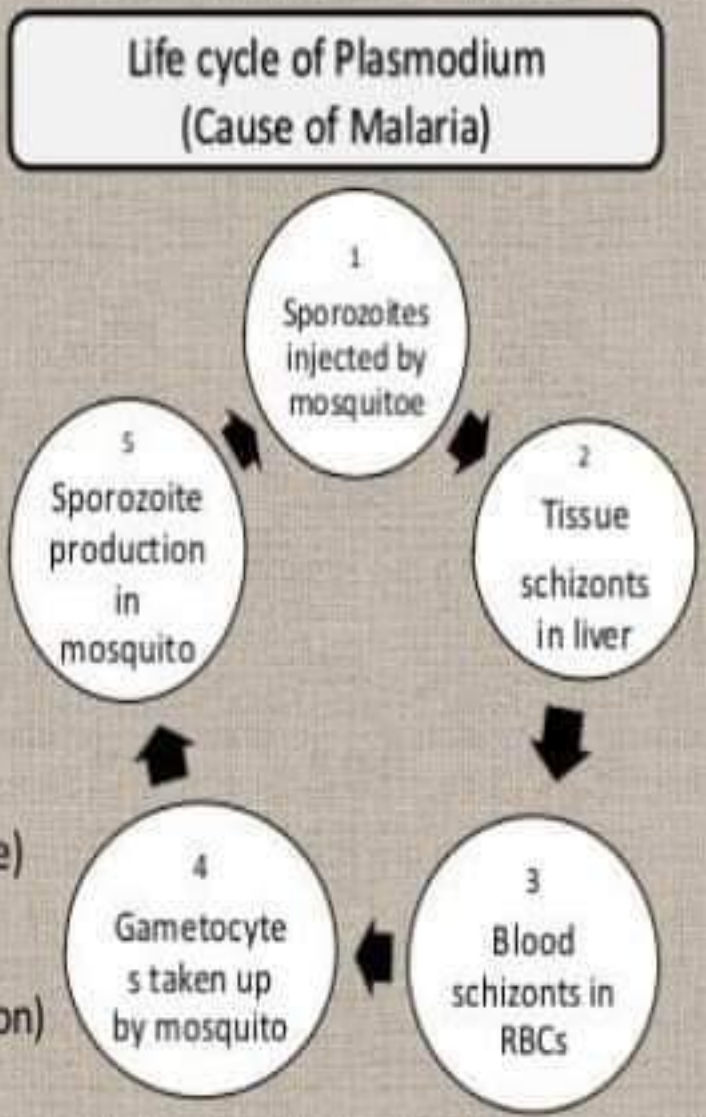
Classification:

Chemically ➟ 4-aminoquinoline

Therapeutically

➟ As Supressive prophylactic and in Clinical cure (erythrocytic schizonticide)

➟ Gametocidal for p.vivax (prevent transmission)



Malaria Life Cycle of Plasmodium HD Animation.mp4

- Classification of antimalarial drugs
  - Therapeutic classification
  - Chemical classification

Therapeutic classification

- Causal prophylaxis: (Primary tissue schizonticides)
  - Destroy parasite in liver cells and prevent invasion of erythrocytes
  - Primaquine, proguanil
- Supressives Prophylaxis:
  - Supress the erythrocytic phase and thus attack of malarial fever can be used as prophylactics
  - Chloroquine, proguanil, mefloquine, doxycycline

Therapeutic classification

- Clinical cure: erythrocytic schizonticides
  - used to terminate an episode of malarial fever
- Fast acting high efficacy
  - Chloroquine, quinine, mefloquine, atovaquone, artemisinin
- Slow acting low efficacy drugs
  - Proguanil, pyrimethamine, sulfonamides, tetracyclines

Therapeutic classification

- Radical curatives:
  - Eradicate (destroy completely) all forms of P.vivax & P.ovale from the body
  - Supressive drugs + hypnozoitocidal drugs
  - For vivax: primaquine 15 mg daily for 14 days
- Gametocidal:
  - Destroy gametocytes and prevent transmission
  - Primaquine, artemisinin – against all plasmodia
  - Chloroquine, quinine – Pl Vivax
  - Proguanil ,pyrimethamine – prevent development of sporozoites

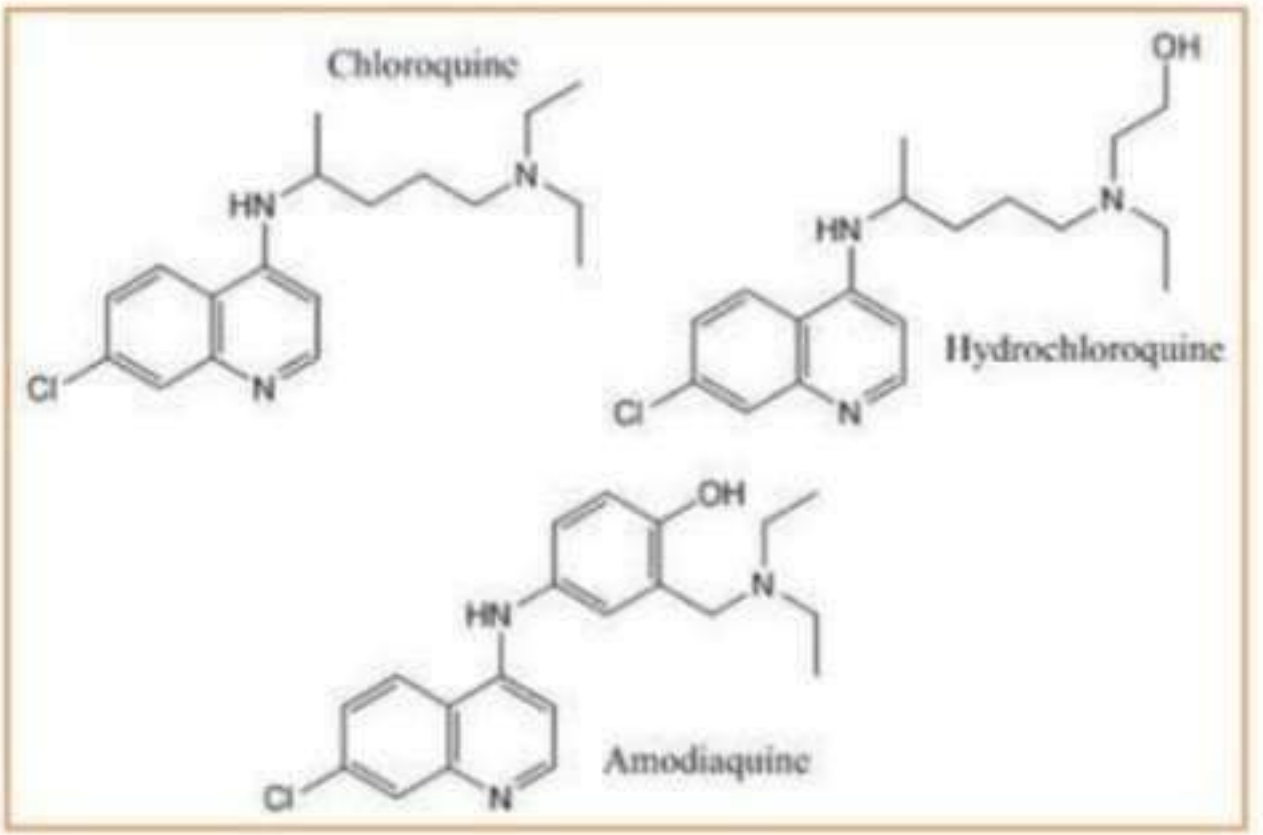
Chemical classification

- 4 aminoquinolines:
  - Chloroquine, Hydroxychloroquine, Amodiaquine, Pyronaridine
- 8 aminoquinolines:
  - Primaquine, Tafenoquine, Bulaquine
- Cinchona alkaloids:
  - Quinine, Quinidine
- Quinoline methanol:
  - Mefloquine
- Biguanides
  - Proguanil, Chlorproguanil

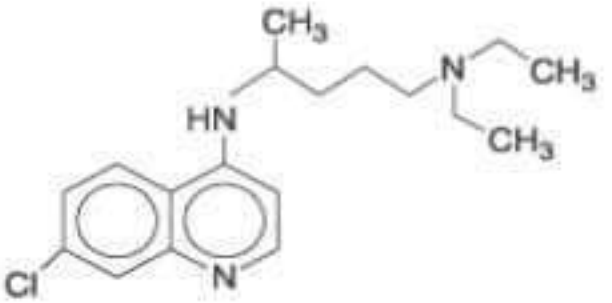
Chemical classification

- Diaminopyrimidines
  - Pyrimethamine
- Sulfonamides
  - Sulfadoxine, dapsone
- Tetracyclines:
  - tetracycline, doxycycline
- Naphthoquinone:
  - Atovaquone
- Sesquiterpene lactones:
  - Artesunate, artemether, arteether

4-aminoquinolines



- Chloroquine:
  - Synthesized by Germans in 1934 (resochin)



CHLOROQUINE

  - d & l isomers, d isomer is less toxic
  - Cl at position-7 give maximal antimalarial efficacy

Biochemistry of Plasmodium:

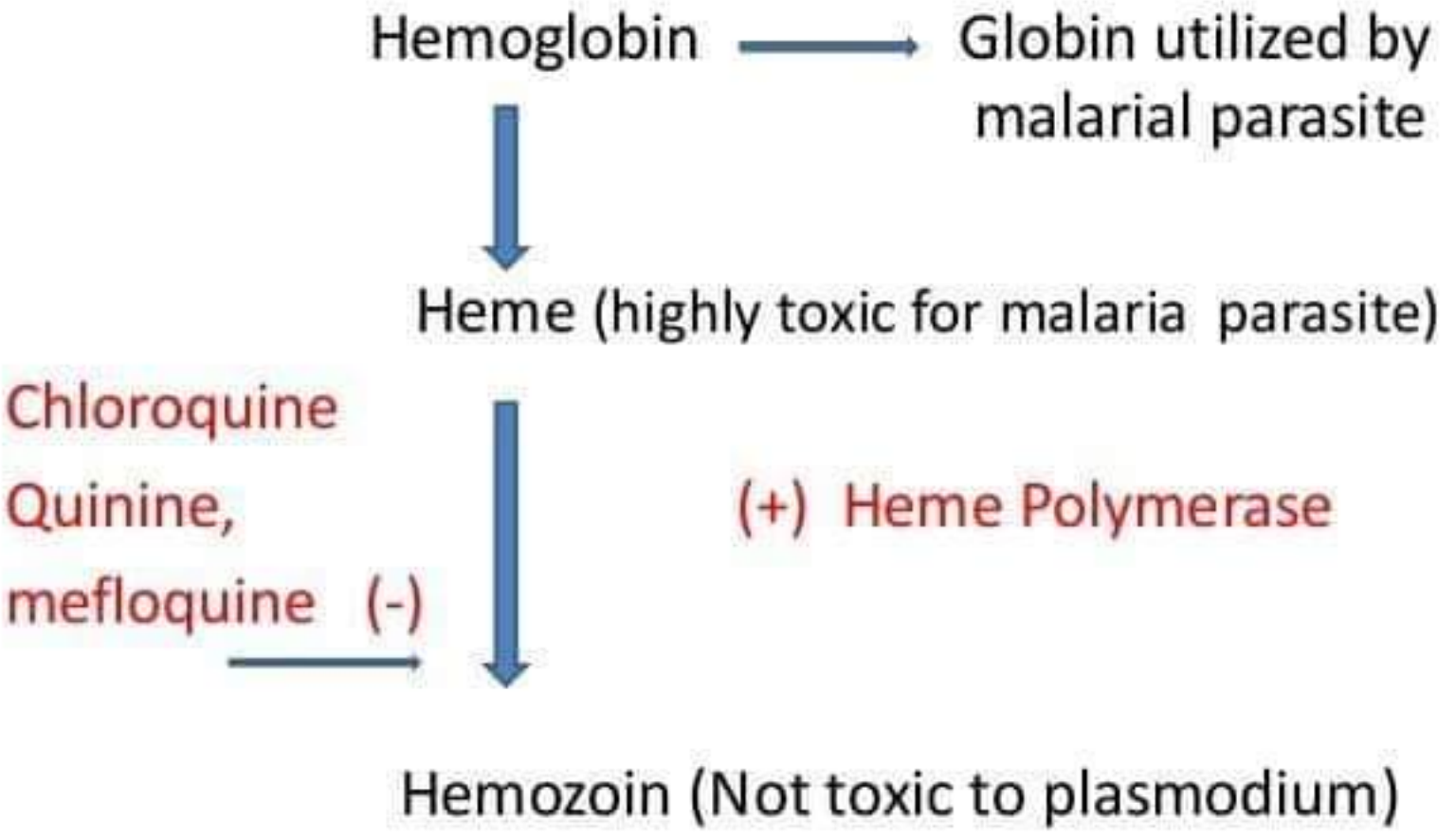
Human blood has **hemoglobin**

Parasite utilize it to get Aminoacids

Heme is released ⟶ toxic to parasite

Parasite do biocrystallization of heme into **Hemozoin** (insoluble crystals)

Mechanism of action



Mechanism of action

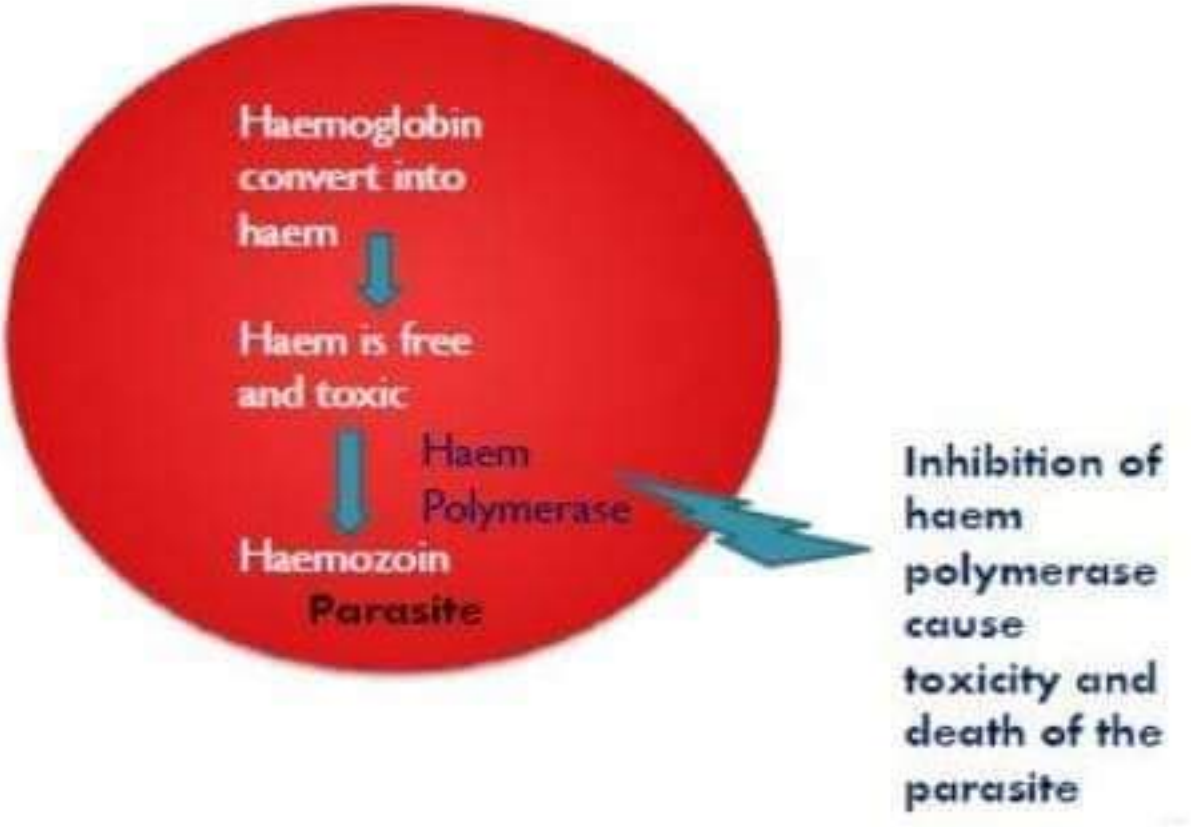
Chloroquine (basic) concentrates in parasite food vacuole (acidic).

Prevent heme polymerization into hemozoin causing heme accumulation (toxic to parasite).

Drug complex with heme ➡ disrupt cell membrane function.

Other mechanism include intercalating of parasite DNA, DNA synthesis inhibition.

Inhibition of haem polymerase

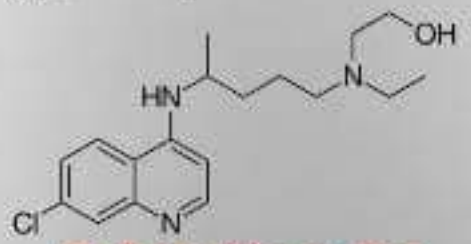


SAR of 4-aminoquinolines

Chloroquine

Dialkylaminoalkyl side chain

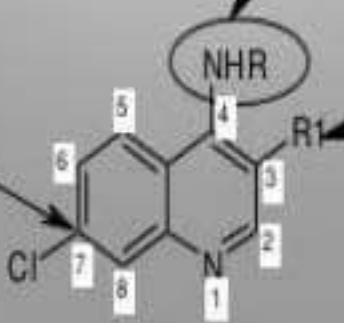
1. 2-5 carbon atoms between the nitrogen atoms,particularly 4-diethylamino-1-methylbutylamino side chain is optimal for activity as in chloroquine.
2. The tertiary amine is important.
3. Introduction of unsaturation in the side chain was not detrimental to activity.
4. Substitution of a hydroxy on one 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.

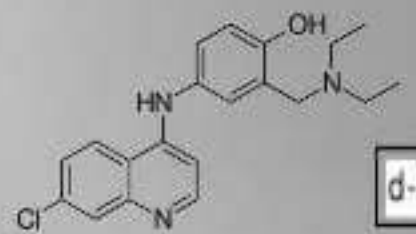


Hydroxychloroquine

Introduction of chloro group at this position is optimal for activity

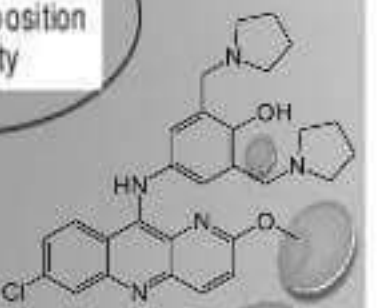
Introduction of methyl group at this position reduces activity





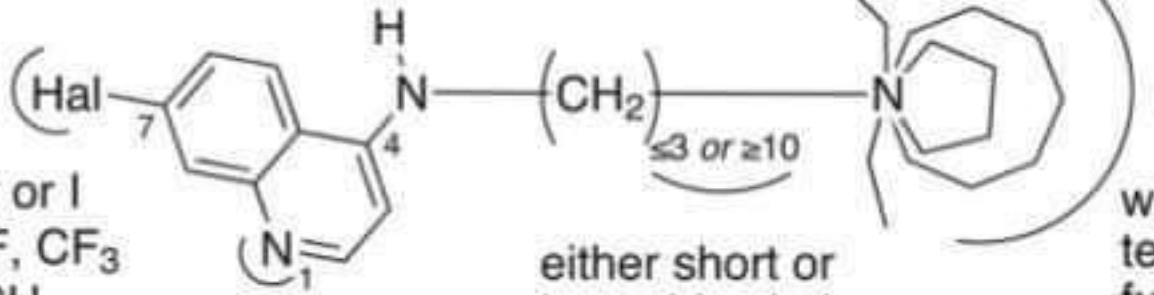
Amodiaquine

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



Pyronaridine

SAR of chloroquine

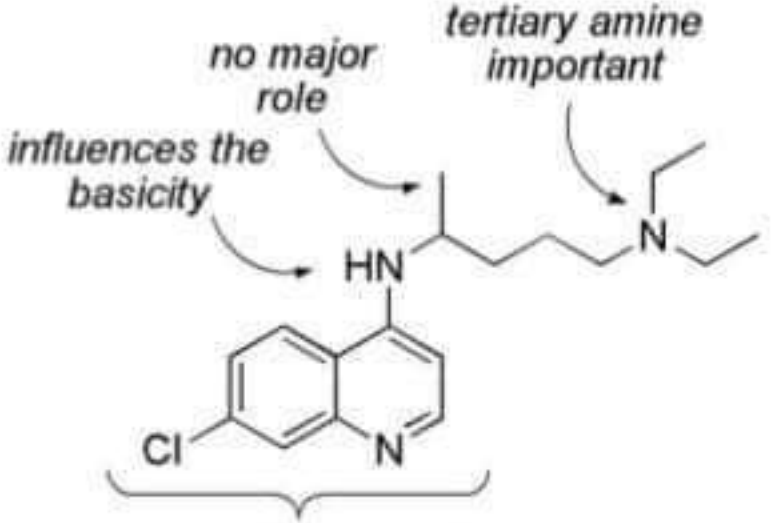


Cl, Br or I
Not F, CF_3
or OCH_3

amino
essential

either short or
long side chain

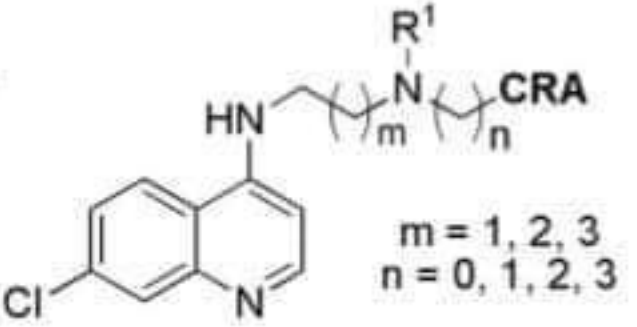
wide tolerance for
terminal 3° amine
functionality



crucial for heme binding

1 (chloroquine)

*attach CRA
and simplify*



m = 1, 2, 3
n = 0, 1, 2, 3

hybrid compound design

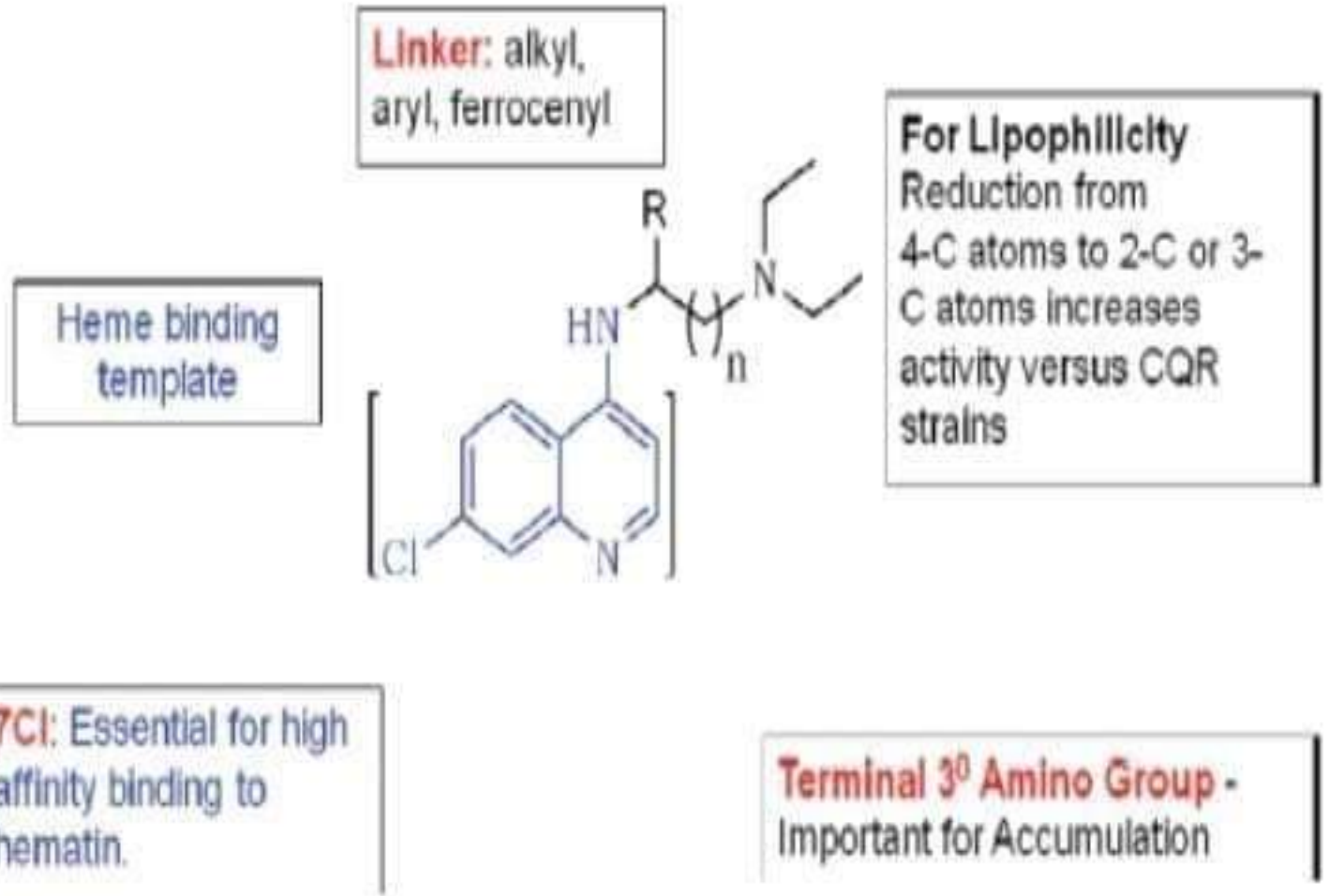
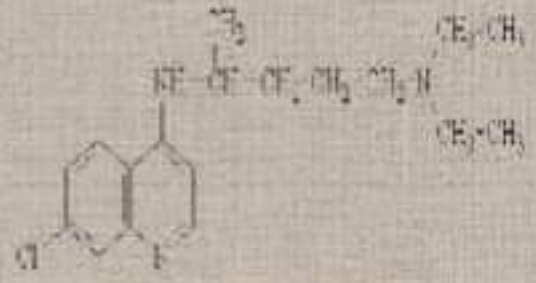


Figure 9: Structural requirements of 4-AQs for antimalarial activity.

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 (infection of the intestine), taeniasis, extrainstestinal amoebiasis
3. Other actions:
   - Depressant action on myocardium, direct relaxant effect on vascular smooth muscles, antiinflammatory, antihistaminic , local anaesthetic

Pharmacokinetics :



Chloroquine

Synthetically available as **chloroquine phosphate**

Rapidly and completely **absorbed** from **GIT**

Metabolised in liver

Peak conc. Achieved in 2-3 hrs after oral dose.

High **tissue distribution** esp in liver, spleen ,lung, kidney.

t½ 3-4days but terminal t½1-2months

Adverse Effects:

CVS

- Cardiomyopathy,abrupt fall in BP

CNS

- Insomnia
- Neuromyopathy
- Ototoxicity

Ocular toxicity

- Retinopathy
  Blue black pigmentation,edema

Long term use

- Myopathy
- Pheripheral neuropathy

Intolerance

- Nausea , vomiting
- Skinrashes,photosnsitivity

Dosage

- 600 mg of base stat
- 300 mg base after 8 hours
- 150 mg of base BD for 2 days

- 200 mg oral tablet of chloroquine phosphate consists of 150 mg base

Chloroquine is administered in loading dose in malaria

- Chloroquine is well absorbed after oral administration. It is extensively tissue bound and sequestrated by tissues particularly liver, spleen, kidney it has got large apparent volume of distribution
- So it is given in loading dose to rapidly achieve the effective plasma conc.

Therapeutic uses

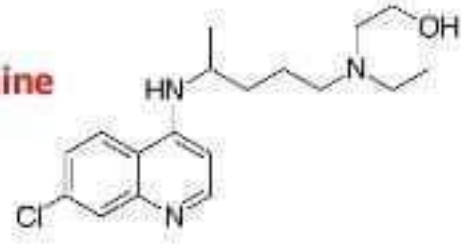
1. Hepatic amoebiasis:
2. Giardiasis
3. Clonorchis sinensis
4. Rheumatoid arthritis
5. Discoid Lupus Erythematosus
6. Control manifestation of lepra reaction
7. Infectious mononucleosis

Resistance

- Plsmodium falciparum is now resistant to chloroquine in most of the part.

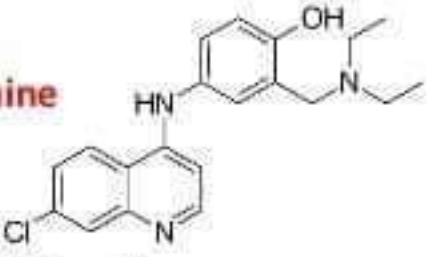
- Resistance appears to result from enhanced efflux of the drug from parasitic vesicles as result from enhanced efflux of the drug from parasitic vesicles as a mutation in plsmodium transporter genes. (pfcrt gene)

Hydroxychloroquine

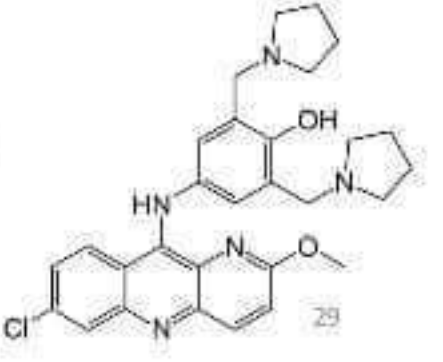


- Hydroxychloroquine:
  - Less toxic, properties &uses similar
- Amodiaquine:
  - As effective as chloroquine
  - Pharmacological actions similar
  - Chloroquine resistant strains may be effective
  - Adverse events: GIT, headache , photosensitivity, rarely agranulocytosis
  - Not recommended for prophylaxis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

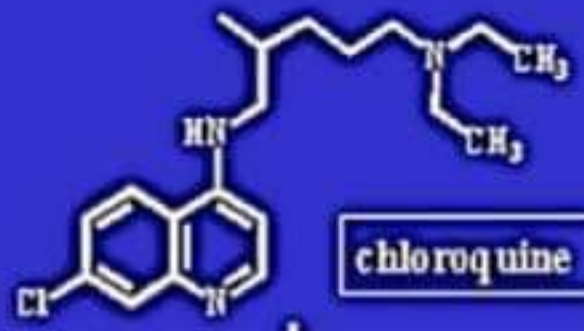
Amodiaquine



Pyronaridine

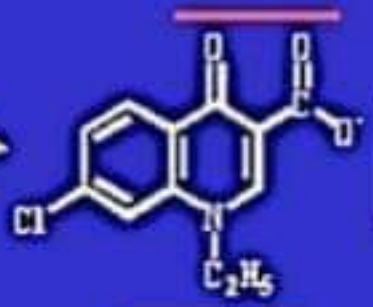


From chloroquine to nalidixic acid...



chloroquine

1939



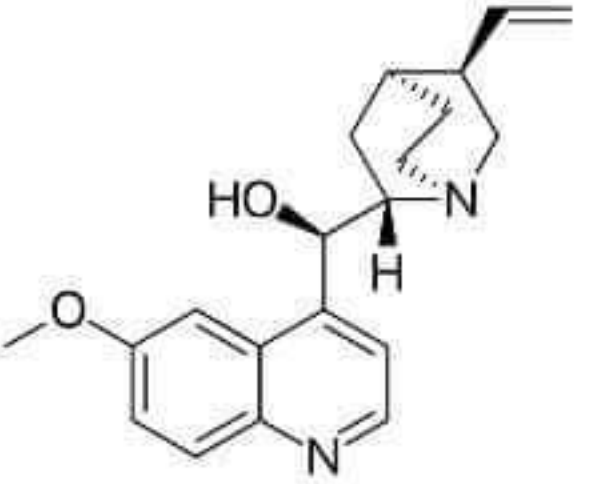
1958

7-chloroquinoline
(synthesis intermediate found to display antibacterial activity)

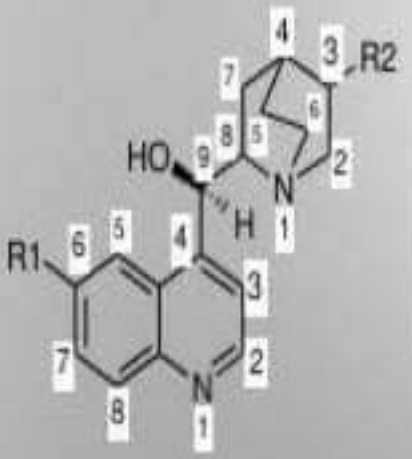
1962

Quinine

- 1820 Pelletier & caventou isolated quinine from cinchona bark.
- Mechanism of action:
  - Similar to chloroquine



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).

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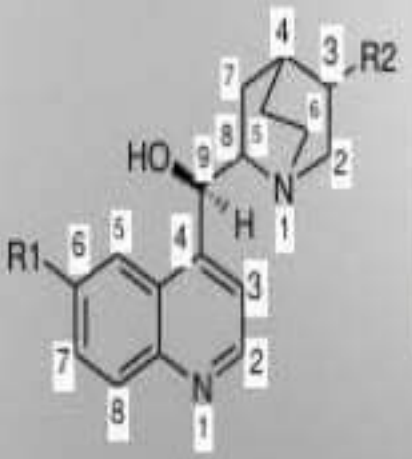

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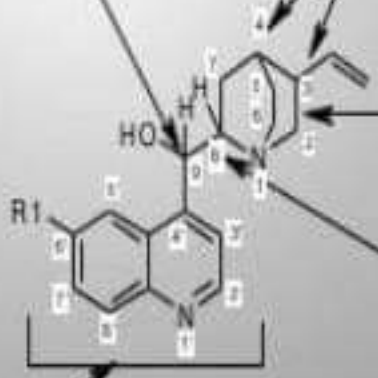
SAR Of Quinine

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.

Asymmetry 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.

Pharmacological actions

1. Antimalarial action:

- Erythrocytic forms of all malarial parasites including resistant falciparum strains .
- Gametocidal for vivax & malariae

2. Local irritant effect:

- Local pain sterile abcess.

3. Cardiovascular:

- depresses myocardium, ↓ excitability, ↓ conductivity, ↑ refractory period, profound hypotension IV.

4. Miscellaneous actions:

- Mild analgesic, antipyretic activity , stimulation of uterine smooth muscle, curare mimitic effect

Adverse drug reactions

Cinchonism:

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

Adverse drug reactions

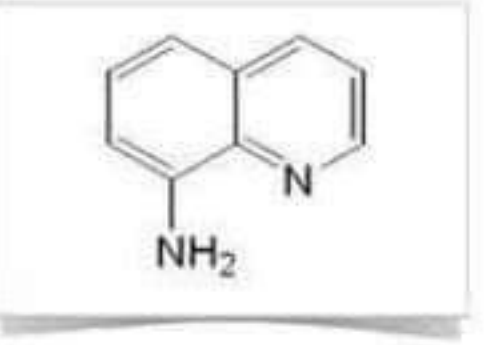
- Idiosyncrasy : similar to cinchonism but occurs in therapeutic doses
- Cardiovascular toxicity: cardiac arrest, hypotension ,fatal arrhytmias
- Black water fever:
- Hypoglycemia:

Uses

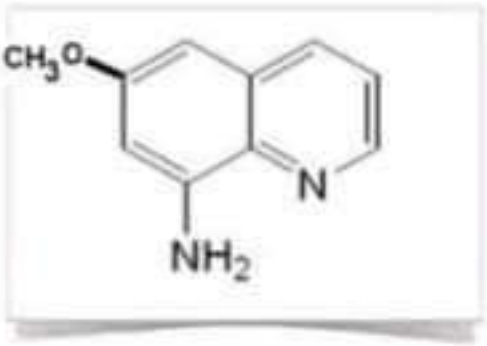
- Malaria:
  - uncomplicated resistant falciparum malaria
  - Cerebral malarial
- Myotonia congenita: 300 to 600 mg BD/ TDS
- Nocturnal muscle cramps: 200 – 300 mg before sleeping
- Spermicidal in vaginal creams
- Varicose veins: along with urethane causes thrombosis & fibrosis of varicose vein mass

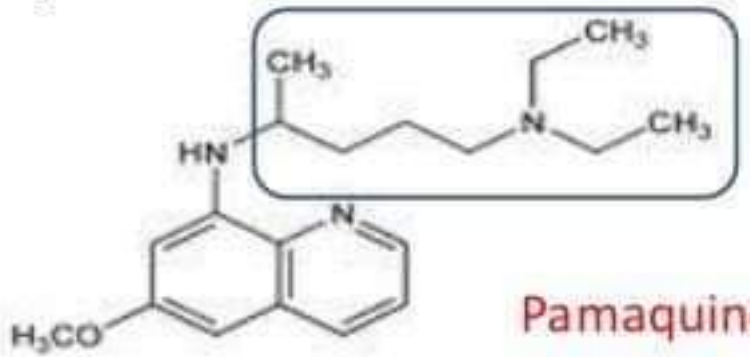
8-aminoquinolines

- Drugs in this group have amino group at position 8 of quinoline ring
- Important members of this family include
  1 Pamaquine
  2 Primaquine, etc.



- Such drugs have OCH_3 group at position 6
- This molecule has antimalarial activity but when side chain is introduced at amino group antimalarial activity is intensified e.g pamaquine
- It causes hemolysis of RBCs

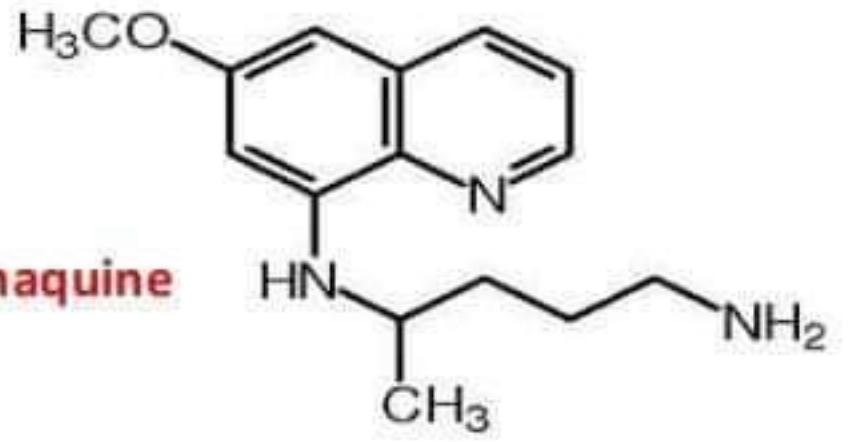




Pamaquine

Diethyl amino pentyl side chain

- It contains tertiary amino group and when it is converted into primary amino group the compound is called primaquine, which is
  - Less toxic

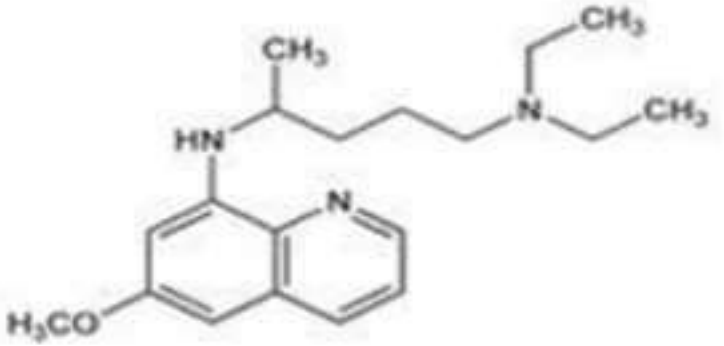


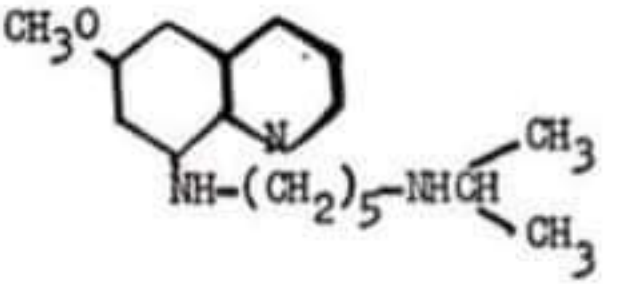
Primaquine

  - It is the most commonly used agent in this group in the treatment of malaria

- OCH_3 is not necessary for antimalarial activity but when replaced by OC_2H_5 the compound became
  - less active
  - Toxic in nature
- OCH_3 when replaced by CH_3 the compound become inactive
- Introduction of halogens increases toxicity
- Presence of quinoline ring is necessary for antimalarial activity. When pyridine ring is converted to piperidine (saturated) the compound became inactive

- Pentyl side chain gives maximum activity, increase or decrease of chain result is reduction of activity.
- The branched side chain when converted into straight chain pentaquine is obtained





- It has less antimalarial activity as compared to both pamaquine and primaquine