Chapter 7: Antimalarial Drugs

(Medicinal Chemistry & Pharmacology)

Syllabus:

Antimalarials: Etiology of malaria.

Quinolines: SAR, Quinine sulphate, Chloroquine*, Amodiaquine, Primaquine phosphate, Pamaquine*, Quinacrine hydrochloride, Mefloquine.

Biguanides and dihydro triazines: Cycloguanil pamoate, Proguanil.

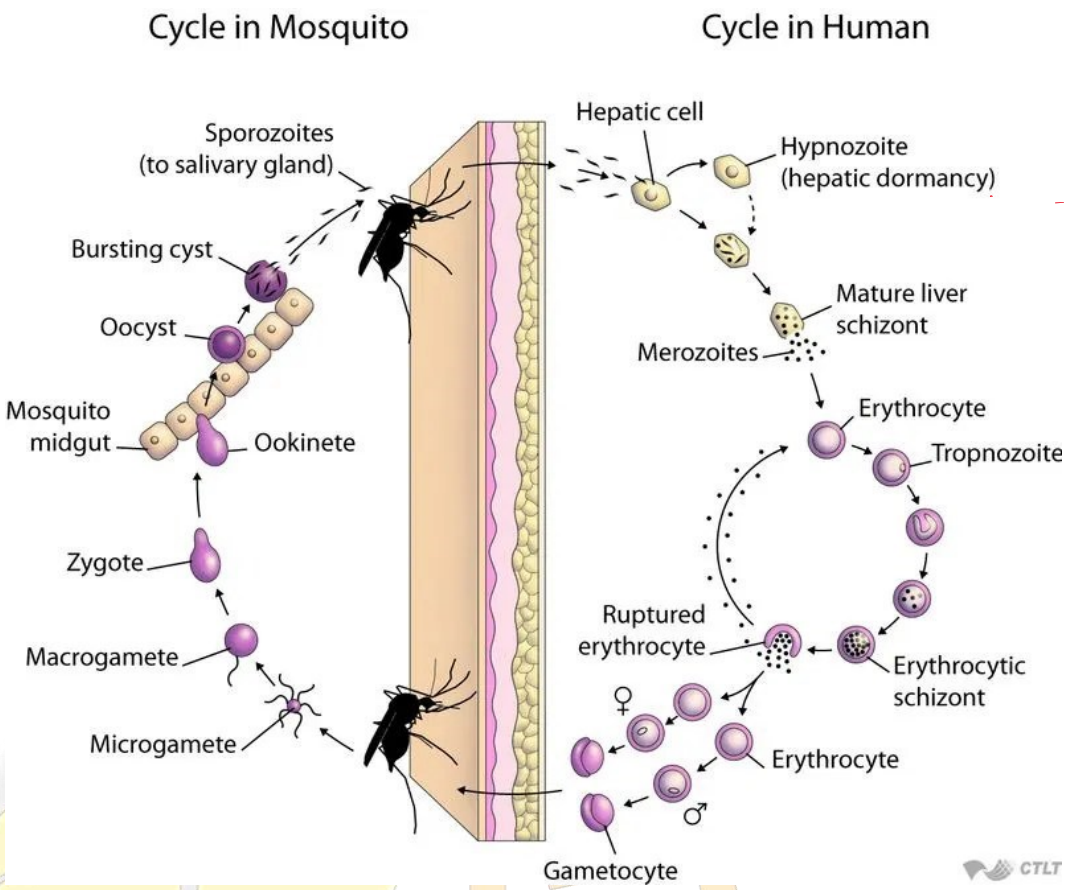
Miscellaneous: Pyrimethamine, Artesunete, Artemether, Atovoquone.

7.1. MALERIA

- Malaria is a protozoal disease infected by *Plasmodium specieses* (*P. falciparum, P. vivex, P. malariae* and *P. ovale*).
- Malaria is transmitted in human via a bite from an infected female *Anopheles* mosquito (Vector).
- *P. vivex, P. malariae* and *P. ovale* produce the mild forms of malaria by destroying red blood cells in peripheral capillaries and thus, causing anaemia
- The most dangerous is the *P. falciparum*. In this case, the infected red blood cells become sticky and form lumps in the capillaries of the deep organs of the body and cause microcirculatory arrest
- This disease still affects about 200 million people and causes at least 2 million deaths per year.
- **Symptoms:** Fever, Shivering, Joint pain, headache, vomiting, convulsion and coma. After mosquito bite, Symptoms occurs at 7-9 days

Two important phases of the parasite life cycle are the following:

1. Asexual cycle—occurs in the infected host.
2. Sexual cycle—occurs in the mosquito.



Source: https://www.malariasite.com/life-cycle

7.2. ANTIMALARIAL DRUGS

Based on Clinically Uses of Drugs

I) **Sporozoitocides (caused prophylaxis):** Primaquine, Chloroguanil, Pyrimethamine* (*reserve for *P. falciparum*)

II) **Tissue Schizonticides, Radical curative & Preventing Relapse:** Primaquine

III) Blood Schizontocides:

a. Slow Acting: Proguanil, Pyramethamine

b. Rapid Acting: Chloroquine, Mefloquine, Quinine, Atovaquone

IV) Used in Prophylaxis: Proguanil, Chloroquine, Mefloquine, Atovaquone

V) Use in Clinical Attack: Chloroquine, Mefloquine, Quinine, Atovaquone

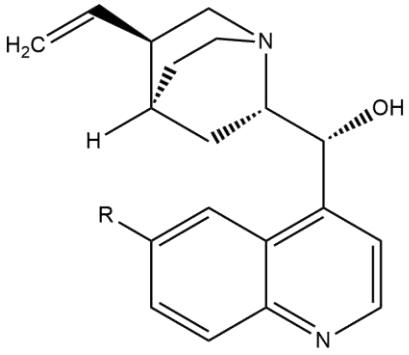
VI) Gametocytocides: to prevent transmission

a. For *P. vivex, P. malariae* and *P. ovale:* Chloroquine, Quinine

b. For *P. falciparum:* Primaquine

Based on Chemical Nature

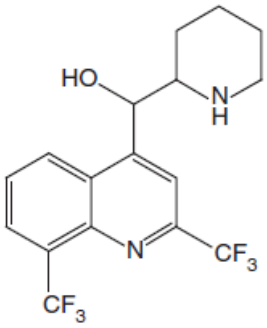
1) **Cinchona alkaloid:** Quinine, Quinidine, Cinchonine



Cinchona Alkaloids

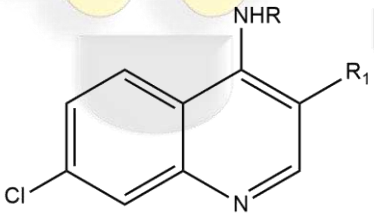
Quinine	-OCH3 (-) isomer
Quinidine	-OCH3 (+) isomer (antiarrhythmic)
Cinchonine	-H (+) isomer
Cinchonidine	-H (-) isomer

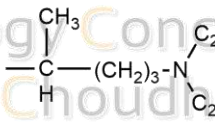
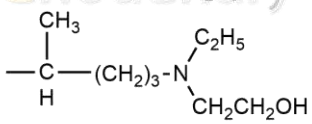
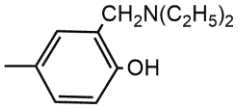
2) Quinoline-methenol: Mefloquine, Cinchona alkaloids (Quinine and Quinidine).



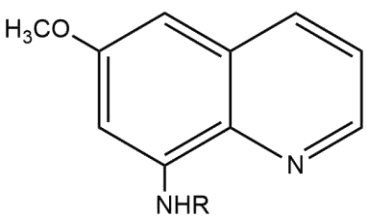
Mefloquine

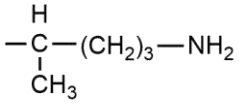
3) 4-Aminoquinolines: Chloroquine, Amodiaquine, Piperaquine.

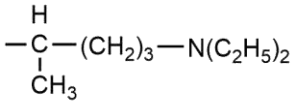


	R	R1
Chloroquine		—H
Hydroxychloroquine		—H
Amodiaquine		—H

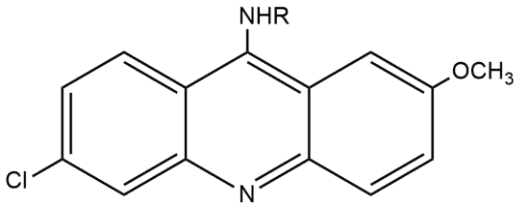
4) **8-Aminoquinolines:** Primaquine, Pamaquine, Bulaquine.

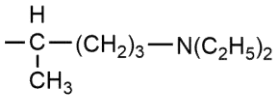


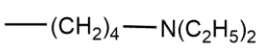
Primaquine 

Pamaquine 

5) 9-Amonoquinoline (Acridines): Quinacrine, Mepacrine

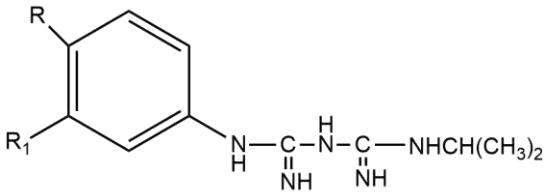


Quinacrine 

Acriquine 

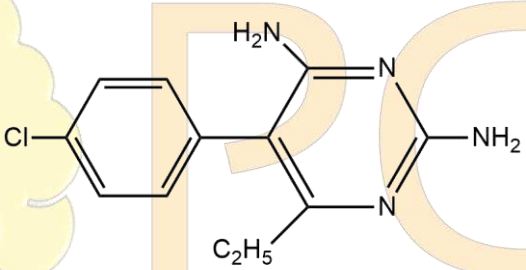
6) **Nephthoquinone:** Atovaquone.

7) **Biguanides:** Proguanil, Chlorproguanil.



	R	R1
Proguanil	—Cl	—H
Chloroguanil	—Cl	—Cl

8) **Diaminopyrimidines:** Pyramithamine.



Pyrimethamine

9) **Sulfones and Sulfonamides:** Dapsone, Sulfamethopyrazine, Sulfadoxine.

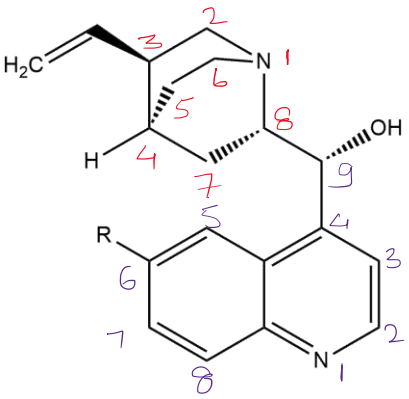
10) **Endoperoxides:** Artemether, Artesunate, Arteether- **Sesquiterpine lactones**

11) **Amino alcohols:** Halofantrine, Lumefantrine.

12) **Tetracyclines:** Tetracycline, Doxycycline

13) **Mannich Base**: Pyronaridine.

7.3. SAR of Quinoline



Cinchona Alkaloids

Quinine	-OCH3 (-) isomer
Quinidine	-OCH3 (+) isomer (antiarrhythmic)
Cinchonine	-H (+) isomer
Cinchonidine	-H (-) isomer

Quinine (-) 8S9R; Quinidine (+) 8R9S

Cinchonine (+) 8R9S; Cinchonidine (-) 8S9R

a) Asymmetry at 3 & 4 is not essential for antimalarial activity.

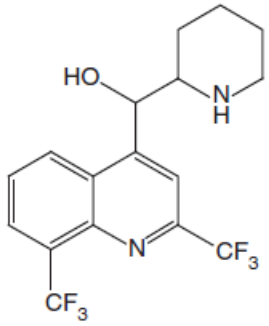
b) At C-8: addition of halogen (Cl, F, Br), enhance the activity

c) At C9 (2° alcohol): modification of 2° alcohol by oxidation (=O) or esterification (-OR) diminishes activity

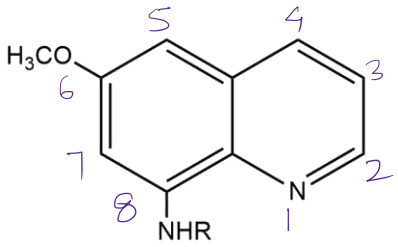
d) At C4: Quinuclidine portion is not essential for activity, so it can be replaced. E.g., 4-amino quinolines (Chloroquine, Amodiaquine, Piperaquine)

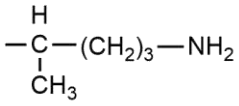
e) At C6: -OCH3 or -H replaced with -Cl, -CF3 increase the activity

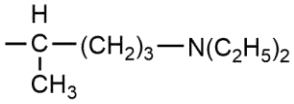
f) introduce a phenyl (not alkyl) group at C-2 position in quinoline ring increase the activity by blocking the metabolic oxidation (Quinoline→2hydroxy quinoline). But it may enhance the phototoxicity. Therefore, recently discover a highly active drug without phototoxic by addition of -CF3 at C-2 position (Mefloquine)



7.4. SAR of 8-Amino Quinoline



Primaquine 

Pamaquine 

Pentaqione $-(CH_2)_5-NH-CH(CH_3)_2$

Quinoclide $-(CH_2)_3-CH(CH3)-NH(C_2H_5)_2$

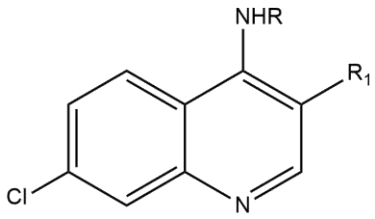
a) At C-6 position, -OCH3 (methoxy) group has high therapeutic index, it may be substituted by -H, -OH group.

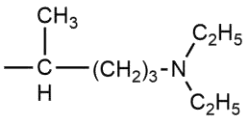
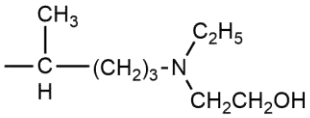
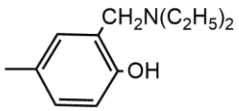
b) Introduce of 2nd methoxy group at C-5 or C-2 position increases the therapeutic index.

c) optimal activity was obtained with 2-6 (-CH2-) group between (NH------NH). Even no. of -CH2 group is lesser toxic than odd no.

d) Extent substitution of the terminal amine (-NR2) is not critical as 4-amino quinoline. Terminal aliphatic amino group may be 1° 2° and 3°. e.g., primaquine (1° amine)

7.5.SAR of 7-Chloro 4-Amino Quinoline



	R	R1
Chloroquine		—H
Hydroxychloroquine		—H
Amodiaquine		—H

- ✓ The D-isomer of chloroquine is less toxic than its L-isomer

C-4 Position

a) At C-4 position, the dialkylamino alkyl side chain has 2-5 carbon atoms between the nitrogen atoms, particularly the 4-diethylamino methyl butyl amino side chain that is optimal for activity, as in chloroquine and quinacrine.
b) The substitution of a hydroxyl group on one of the ethyl groups on the tertiary amine (hydroxy quinoline), reduces toxicity.
c) Incorporation of an aromatic ring in the side chain (e.g. amodiaquine) gives a compound with reduced toxicity and activity.
d) The tertiary amine in the side chain is important.
e) The introduction of an unsaturated bond in the side chain was not detrimental to activity.

C-7 Position

f) The 7-chloro group in the quinoline nucleus is optimal

C-3 Position

g) the methyl group in position 3 reduces activity,

C-8 Position

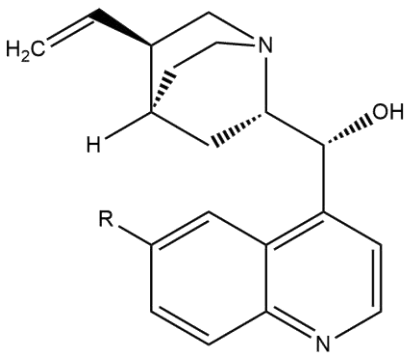
h) additional methyl group in position 8 abolishes activity.

7.6.Selected Drugs Pharmacology & Medicinal Chemistry

Quinoline Derivatives

Quinine sulphate, Chloroquine*, Amodiaquine, Primaquine phosphate, Pamaquine*, Quinacrine hydrochloride, Mefloquine

1) Quinine sulphate



Cinchona Alkaloids

Quinine	-OCH3 (-) isomer
Quinidine	-OCH3 (+) isomer (antiarrhythmic)
Cinchonine	-H (+) isomer
Cinchonidine	-H (-) isomer

6-(methoxy quinoline-4yl)-5-(venyl quinuclidine-2yl)-methenol

Mode of Action: Quinine (l-isomer) intercalates the DNS of the parasite. It inhibits the ability of haemoglobin digestion of parasite thus parasite starve and build up toxic level of partially degraded haemoglobin in itself.

The Possible Mode of Action of Quinoline derivatives

- ***DNA interaction***: Quinine intercalates the DNS of the parasite
- ***Ferriprotoporphyrin IX*:** The plasmodium parasite utilizes host haemoglobin as a source of amino acid. On digestion of the haemoglobin, the haem is released as ferriprotoporphyrins IX and it produces haemolysis of the erythrocyte parasites. Therefore, ferriprotoporphyrin that is released is converted into nontoxic products and they, in turn, to haemozoites by the polymerase enzyme. The steps involved in the conversion to haemozoites are inhibited by the chloroquine.
- ***Weak base hypothesis***: The 4-substituted quinolines have weak base and because of this pKa they are thought to accumulate in a location, which is acidic (parasite lysosome pH 4.8–5.2). As the extracellular fluid of the parasite is at pH 7.4, the weak base will move towards a more acidic pH of lysosome. Once the acid–base reaction occurs, elevating the pH in the lysozome, that in turn reduces the parasite's ability to digest haemoglobin, thus reducing the availability of amino acids.

Pharmacology

- ✓ Quinine is an erythrocytic schizontocide for all species of plasmodia, but less effective and more toxic than chloroquine. Resurgence of interest in quinine is due to the fact that most CQ and multidrug-resistant strains of *P. falciparum* still respond to it.
- ✓ Doxycycline or clindamycin is mostly added to it for complete parasite clearance.
- ✓ Quinine has no effect on preerythrocytic stage and on hypnozoites of relapsing malaria, but kills vivax gametes
- ✓ **Other Action:** Local irritant and anaesthetics, systemically it enhances GI secretion, Quinine is a weak analgesic and antipyretic, Cardiodepressant, antiarrhythmic and hypotensive actions are similar to quinidine

Pharmacokinetics

- ✓ Rapidly and complete absorbed orally
- ✓ PB- 70%, to alfa-acid glycoprotein, which increases during acute malarial infection
- ✓ Low CSF concentration
- ✓ Large fraction metabolized in liver by CYP3A4 and excreted in urine (t1/2 – 10-12h)

- ✓ **Metabolism:** Metabolism of liver, Quinine → 2-hydroxy quinine → 2,3-dihydroxy quinine

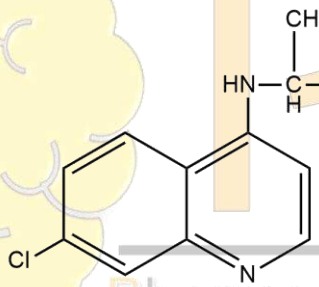
Therapeutic Uses

- ✓ Treatment of sever P. falciparum malaria
- ✓ Quinidine: may also use in Supraventricular and ventricular and other arrhythmias

ADR

- ✓ Toxicity of quinine is high and dose related; 8–10 g taken in a single dose may be fatal.
- ✓ *Cinchonism* A large single dose or higher therapeutic doses taken for a few days produce a syndrome called 'cinchonism'. It consists of ringing in ears, nausea, vomiting (due to both gastric irritation and CTZ stimulation), headache, mental confusion, vertigo, difficulty in hearing and visual defects (due to direct neurotoxicity as well as constriction of retinal and auditory vessels). Diarrhoea, flushing and marked perspiration may also appear. The syndrome subsides completely if the drug is stopped.

2) Chloroquine



N^4-(7-chloroquinolin-4-yl)-N^1,N^1-diethylpentane-1,4-diamine

7-chloro-4-(diethyl amino 1-methyl butyl) amino-quinoline

MOA

- ➢ It interferes haemoglobin digestion ability of plasmodia species. It actively concentrated in infected RBCs. Accumulating in the acidic vecuoles of the parasite and because of its weakly basic nature.
- ➢ Polymerization of toxic haeme generated from digestion of haemoglobin to nontoxic parasite pigment haemozoin is inhibited by the formation of CQ-haeme complex.
- ➢ Chloroquine also damages the plasmodial membranes
- ➢ Additionally, it interferes the protein and nucleic acid synthesis.

Pharmacology

- ✓ It is a rapidly acting erythrocytic schizontocide against all species of plasmodia; controls most

- ✓ clinical attacks in 1–2 days with disappearance of parasites from peripheral blood in 1–3 days.
- ✓ Therapeutic plasma concentration- 15-30 ng/ml
- ✓ No effects on primary and secondary hepatic stages of the parasite—does not prevent relapses in vivax and ovale malaria
- ✓ It has no clinically useful gametocidal activity
- ✓ Chloroquine-resistance among *P. falciparum* is now widespread in India. Resistance in *P. falciparum* is associated with a decreased ability of the parasite to accumulate CQ and increase encoding of efflux transport system (*pfcrt:* P.f. chloroquine-resistance transporter gene).
- ✓ Presently, Chloroquine-resistance among *P. vivax* was first reported from Papua New Guinea in 1989. It has now been confirmed from many countries, including India.
- ✓ It manifests as recurrence within 1–3 weeks of treating vivax malaria with standard dose of chloroquine. Such cases can be treated by quinine given along with doxycycline/clindamycin or by ACT, followed by primaquine to effect radical cure.
- ✓ However, CQ given in standard doses remains the first line treatment of vivax malaria as per National vector borne diseases control programme (NVBDCP) guidelines.
- ✓ *Other actions:* Chloroquine is active against *Entamoeba histolytica* and *Giardia lamblia* as well. It has anti-inflammatory, local irritant and local anaesthetic (on injection), weak smooth muscle relaxant, antihistaminic and antiarrhythmic properties.

Pharmacokinetics

- ✓ Orally well absorbed. 50% protein bound; It has high affinity for melanin and nuclear chromatin: gets tightly bound to these tissue constituents and is concentrated in liver, spleen, kidney, lungs (several hundred fold), skin, leucocytes and some other tissues.
- ✓ Its selective accumulation in retina is responsible for the ocular toxicity seen with prolonged use.
- ✓ Chloroquine is partly metabolized by liver and slowly excreted in urine.
- ✓ The early plasma t½ varies from 3–10 days. Because of tight tissue binding, small amounts persist in the body with a terminal t½ of 1–2 months

ADR

- ✓ Toxicity of CQ is low, but side effects like nausea, vomiting, anorexia, uncontrollable itching, epigastric pain, uneasiness
- ✓ Prolonged use of high doses (as needed for rheumatoid arthritis, DLE, etc.) may cause loss of vision due to retinal damage.

- ✓ Loss of hearing, rashes, photoallergy, mental disturbances, myopathy and graying of hair can occur on long-term use.
- ✓ Intravenous injection of CQ (rarely given now) can cause hypotension, cardiac depression, arrhythmias and CNS toxicity including seizures (more likely in children).

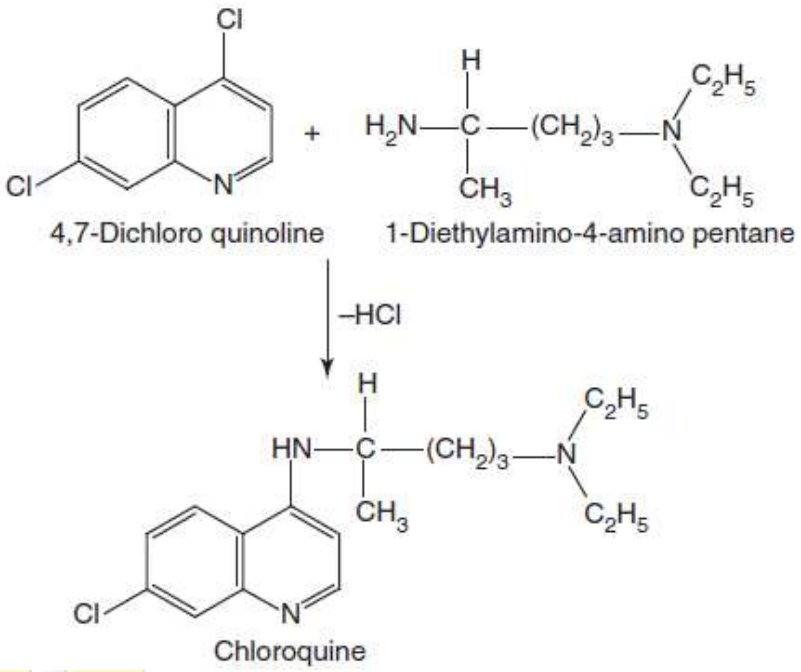
Contraindicated

- ✓ Caution In Liver damages, neurological, retinal and haematological diseases. Attacks of seizures, porphyria and psoriasis may be precipitated
- ✓ CQ can be used for treatment of malaria during pregnancy: no abortifacient or teratogenic effects have been reported.
- ✓ CQ should not be coadministered with mefloquine, amiodarone and other antiarrhythmics

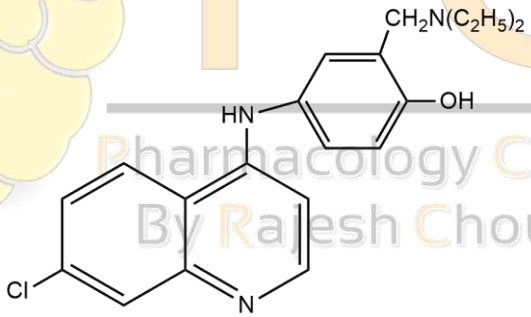
Uses:

- ✓ Treatment of Malaria (all species). It causes rapid fever clearance and disappearance of parasitaemia in patients of malaria
- ✓ Extraintestinal amoebiasis
- ✓ Rheumatoid arthritis
- ✓ Discoid lupus erythematosus—very effective;
- ✓ Lepra reaction
- ✓ Photogenic reactions.
- ✓ Infectious mononucleosis: affords symptomatic relief.

Synthesis



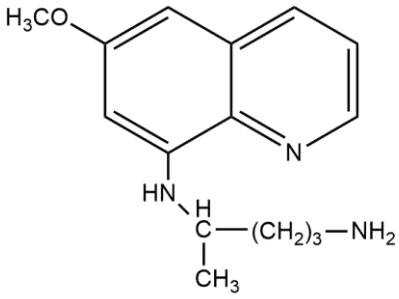
3) Amodiaquine



4-((7-chloroquinolin-4-yl)amino)-2-((diethylamino)methyl)phenol

- ✓ Amodiaquine has similar action as chloroquine. Amodiaquine has tended to be administered in areas of **chloroquine resistance** while some patients prefer its tendency to cause less itching than chloroquine.
- ✓ **Amodiaquine** is now available in a combined formulation with **artesunate** and is among the artemisinin-combination therapies recommended by the World Health Organization.
- ✓ It is used for chloroquine resistance falciparum malaria.

4) Primaquine phosphate

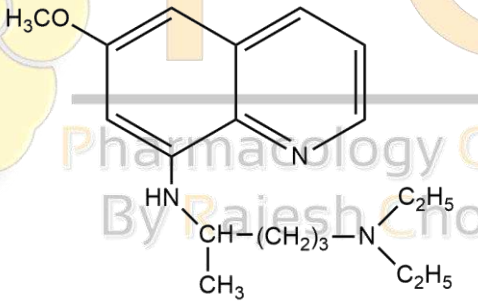


N^4-(6-methoxyquinolin-8-yl)pentane-1,4-diamine

Primaquine is most effective against gametocytes but also acts on hypnozoites, blood schizonticytes and the dormant plasmodia in *P. vivax* and *P. ovale*. It is the only known drug to cure both **relapsing malaria infections** and **acute cases.**

The mechanism of action is not fully understood but it is thought to block oxidative metabolism in Plasmodia and binds with the nucleoproteins and interferes with protein synthesis and intercalates readily into double-standard DNA and Inhibit both DNA and RNA polymerase.

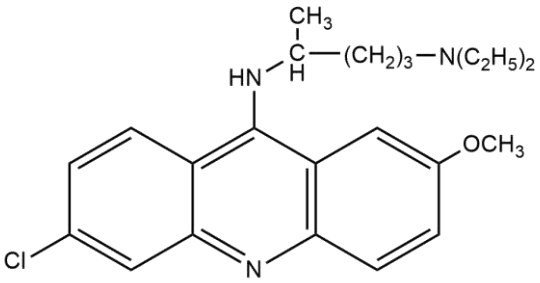
5) Pamaquine



N^1,N^1-diethyl-N^4-(6-methoxyquinolin-8-yl)pentane-1,4-diamine

Pamaquine act similar as primaquine, and used in treatment of malaria caused by *P. vivex* and *P. ovale*

6) Quinacrine



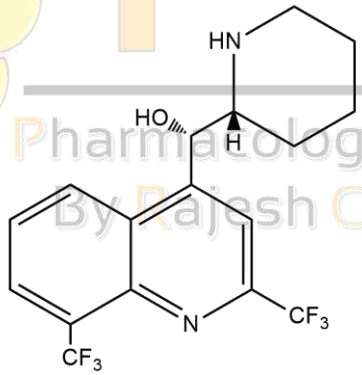
N^4-(6-chloro-2-methoxyacridin-9-yl)-N^1,N^1-diethylpentane-1,4-diamine

MOA: It intercalates DNA and inhibits succinate oxidation and interfere with electron transport.

Uses:

- ✓ Mainly used in treatment of malaria caused by *P. vivex* and *P. ovale*.
- ✓ Also used in Giardiasis caused by *Giardia lamblia*
- ✓ It is also used transcervically as a female sterilizing agents

7) Mefloquine



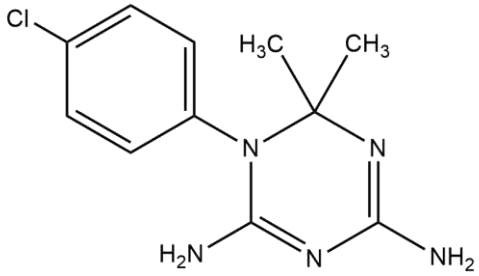
(*S*)-(2,8-bis(trifluoromethyl)quinolin-4-yl)((*R*)-piperidin-2-yl)methanol

- ✓ **MOA**: Mefloquine is a very potent blood schizonticide with a long half-life. It is thought to act by forming toxic heme complexes that damage parasitic food vacuoles and interfere the ability to metabolize and utilize erythrocyte hemoglobin.

  Uses:
- ✓ It is now used solely for the prevention of resistant strains of ***P. falciparum*** despite being effective against *P. vivax*, *P. ovale* and *P. marlariae*.
- ✓ Mefloquine is effective in prophylaxis and for acute therapy. It is now strictly used for resistant strains (and is usually combined with Artesunate).

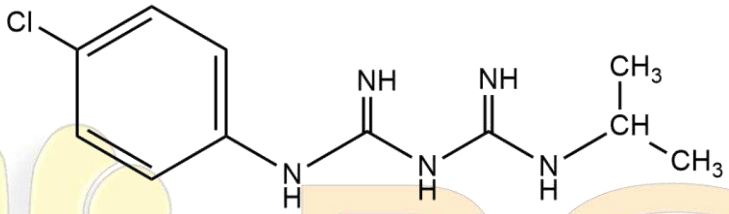
Biguanides and dihydro triazines

A) Cycloguanil pamoate



1-(4-chlorophenyl)-6,6-dimethyl-1,6-dihydro-1,3,5-triazine-2,4-diamine

B) Proguanil

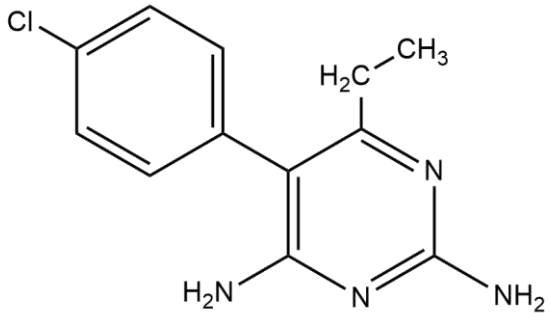


1-[amino-(4-chloro anilino)methylidene]-2-propane-2yl guanidine

- ✓ Proguanil (chloroguanide) is a biguanide; a synthetic derivative of **pyrimidine**.
- ✓ It has many mechanisms of action but primarily is mediated through conversion to the active metabolite cycloguanil.
- ✓ **MOA**: This inhibits the malarial **dihydrofolate reductase enzyme** (an enzyme essential for production of folic acid).
- ✓ **Uses**: Its most prominent effect is on the primary tissue stages of *P. falciparum, P. vivax* and *P. ovale*. It has no known effect against hypnozoites therefore is not used in the prevention of relapse.

Other Derivatives

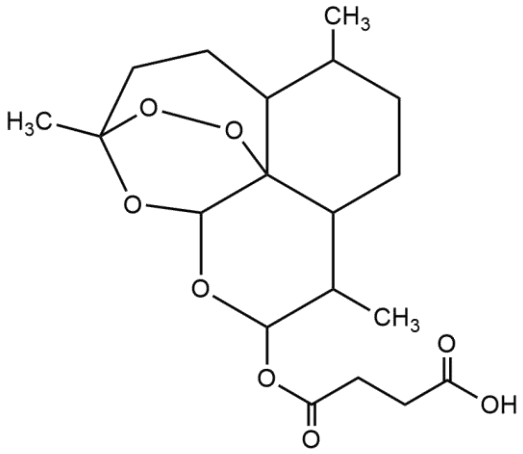
A) Pyrimethamine



5-(4-chlorophenyl)-6-ethylpyrimidine-2,4-diamine

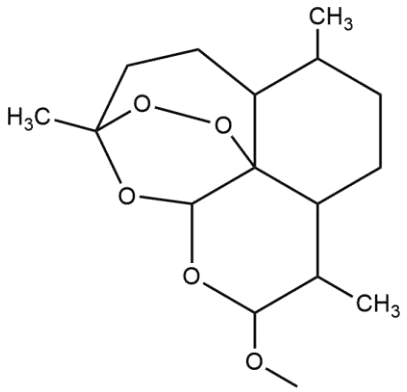
- ✓ Pyrimethamine is used in the treatment of uncomplicated malaria. It is particularly useful in cases of chloroquine-resistant *P. falciparum* strains when combined with sulfadoxine.
- ✓ It acts by **inhibiting dihydrofolate reductase** in the parasite thus preventing the biosynthesis of purines and pyrimidines, thereby halting the processes of DNA replication, cell division and reproduction.
- ✓ It acts primarily on the schizonts during the erythrocytic phase, and nowadays is only used in concert with a sulfonamide.
- ✓ It is used for suppression or chemoprophylaxis of malaria
- ✓ Also used along with sulfadiazine or azithromycin for the treatment of toxoplasmosis.

B) Artesunete



4-oxo-4-((3,6,9-trimethyldecahydro-3*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl)oxy)butanoic acid

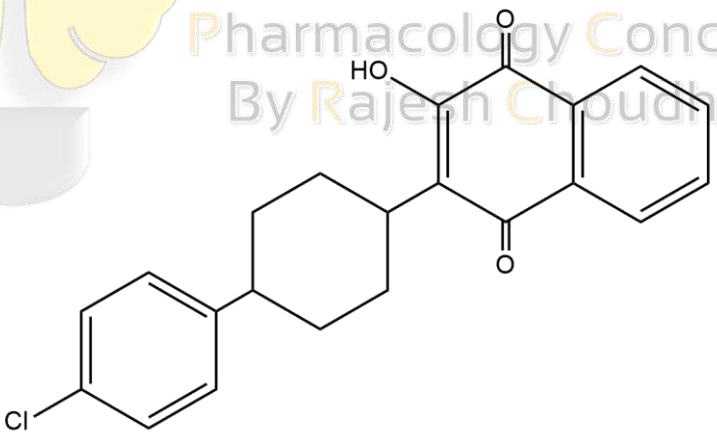
C) Artemether



10-methoxy-3,6,9-trimethyldecahydro-3*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromene

- ✓ It is derived from the plant ***Artemisia annua*** used in Chinese traditional medicine as 'Quinghaosu'**.**
- ✓ It is a sesquiterpene lactone with a chemically rare peroxide bridge linkage (**Endoperoxide bridge**).
- ✓ It is active against multidrug-resistant *P. falciparum.* The endoperoxide bridge interact with heam in the parasite, finally leads to inhibit protein synthesis and ultimately results in lysis of parasitesa and it also arrest the cell cycle.
- ✓ It is used for suppression or chemoprophylaxis of maleria

D) Atovoquone



2-(4-(4-chlorophenyl)cyclohexyl)-3-hydroxynaphthalene-1,4-dione

MOA: Atovaquone blocks the mitochondrial electron transport system at a complex III of the respiratory chain of protozoa, thereby inhibiting pyrimidine synthesis and preventing the nucleic acid or DNA synthesis

Uses: It is used for suppression or chemoprophylaxis of malaria and also has antipneumocystic properties.