Learning Objectives

Upon completion of this presentation students are able to…understands

- General aspects of designing of the antimalarial drugs and their history.
- Classification of the antimalarial drugs and their nomenclature.
- Structure activity relationship (SAR) of the drug.
- Mechanism of action of drug, therapeutic uses and their adverse effects.
- Recent development in the antimalarial drugs.

INTRODUCTION

- Malaria is an infectious disease known since ancient times.
- The name comes from the word “mala aria” meaning bad air.
- Malaria was associated with regions that are badly drained, swamps, and marshes.
- The disease is caused by a protozoal Parasite (genus plasmodium), which Is carried by female mosquitos (genus Anopheles).
- Species of genus plasmodium associated with malaria include

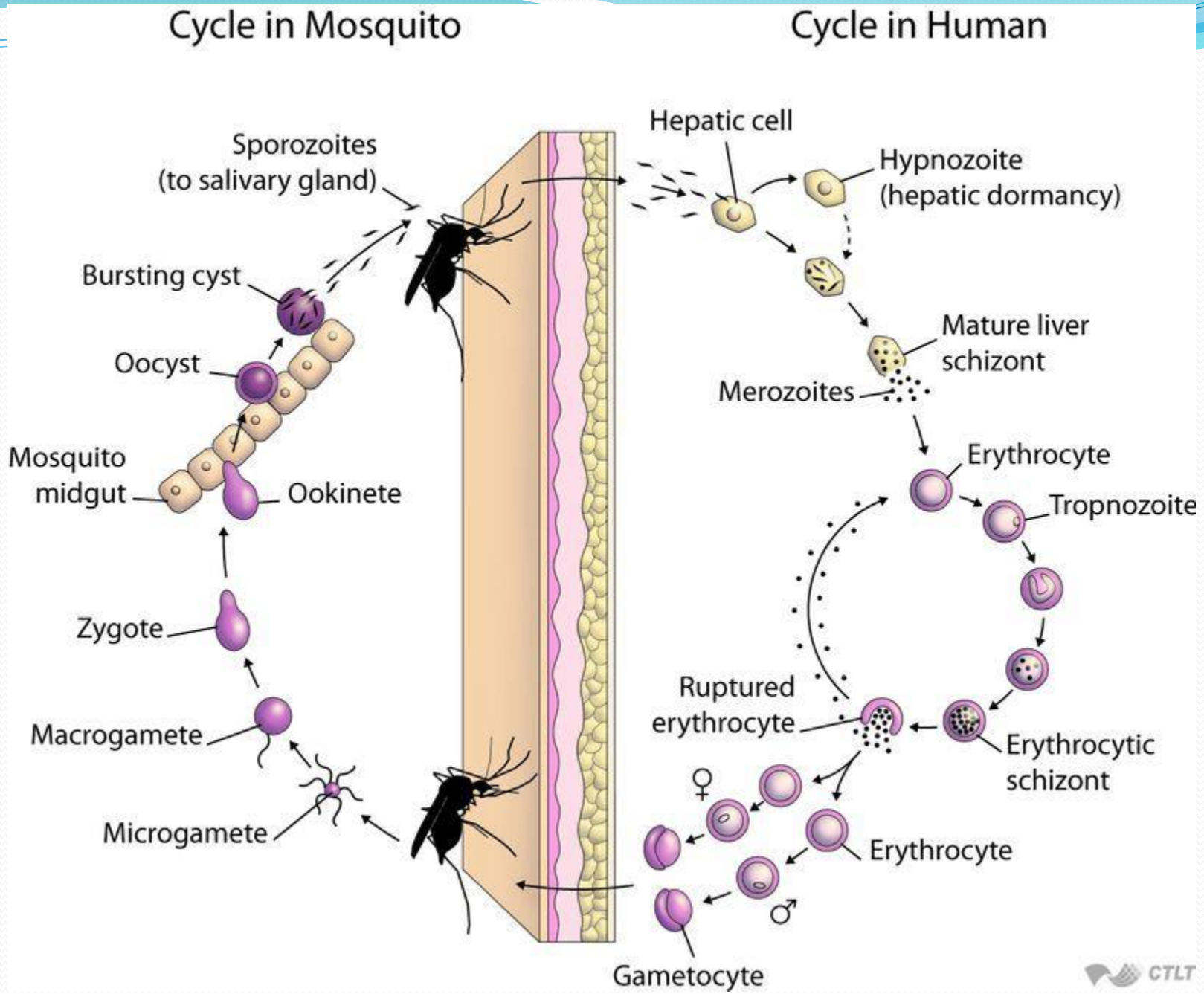
  Plasmodium **Vivax,**

  Plasmodium **Malariae,**

  Plasmodium **Falciparum, and**

  Plasmodium **Ovale.**

Malarial Life Cycle



Symptoms

- Fever
- Shivering
- Pain in joints
- Headache
- Repeated vomiting
- Severe convulsions, coma

Classification of Antimalarials

1. **On the basis of site of action/ depending upon stage of development**

   a. Tissue schizonticides for casual prophylaxis- e.g. Primaquine and Pyrimethamine.

   b. Tissue schizonticides for preventing relapse- e.g. Primaquine.

   c. Blood schizonticides- e.g. Halofantrine, Pyrimethamine, Sulfadoxine, Sulfones.

   d. Gametocyotocides- e.g. Chloroquine and Quinine.

   e. Sporontocides- e.g. Primaquine.

2. On the basis of Chemical structure (Chemical Classification)

a. Aryl amino alcohol e.g. Quinine, quinidine (Cinchona alkaloids), mefloquine

b. 4-aminoquinolines e.g. Chloroquine, amodiaquine.

c. 9-amino acridines e.g. Quinacrines

d. 8-aminoquinolines e.g. Primaquine, Pamaquine

e. Pyrimidines: e.g. Pyrimithamine, Trimethoprim

f. Sulphones: Dapsone, Sulphonamides

g. Biguanides: Proquanil, Chloroproguanil

h. Peroxides e.g. Artemisinin, artemether

i. Miscellaneous agents e.g. Mefloquine, Halofantrine.

j. Antimicrobials e.g. Tetracycline, doxycycline, clindamycine, azithromycin.

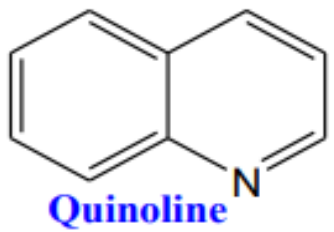
Aryl amino alcohol e.g. Quinine, quinidine (cinchona alkaloids), mefloquine

CINCHONA ALKALOIDS:

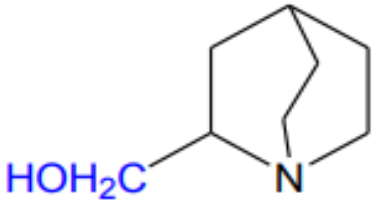
Cinchona officinalis is a South American tree in the family Rubiaceae. The bark contains alkaloids, including quinine, quinidine, cinchonidine, and cinchonine as the major members constitute a unique class of quinoline alkaloids with tremendous impact on human civilization.

- The bark of the cinchona tree contains antimalarial compounds, most notably the highly fluorescent compound, **quinine**.
- The bark of the cinchona tree, if made into an aqueous solution was able to treat most cases of malaria.
- The active principle quinine was first isolated from the bark during the early 19th century.
- Quinine is the compound that contributes to the bitter taste of tonic water.

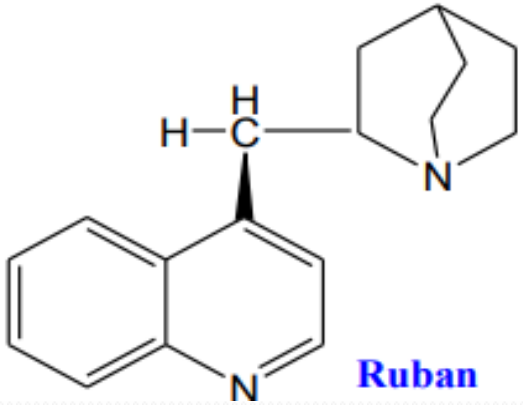
- The basic skeleton is ruban-9-Ol (derived from the parent compound ruban, named after Fam. Rubiaceae).
- Ruban nucleus is a combined skeleton formed from a quinoline ring attached through a methylene group to a quinuclidine ring (a bicyclic ring contains N).
- In Rubanol, the methylene group is oxidized to a secondary alcoholic group and the carbon atom becomes asymmetric.



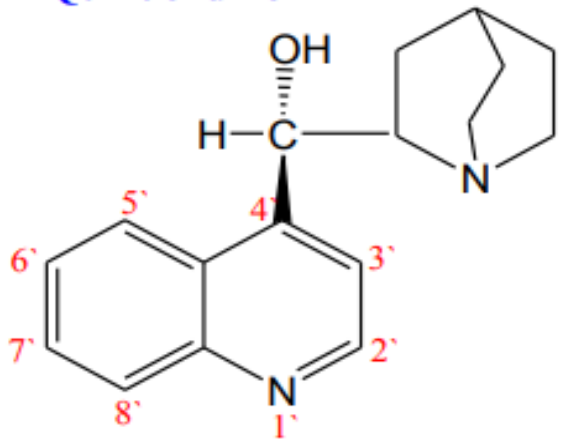
Quinoline



Quinuclidine



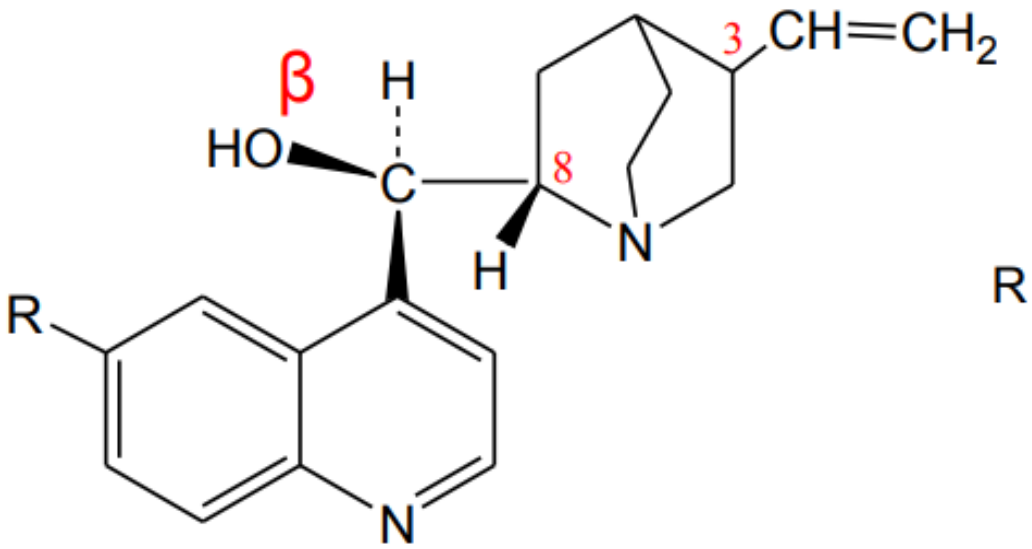
Ruban

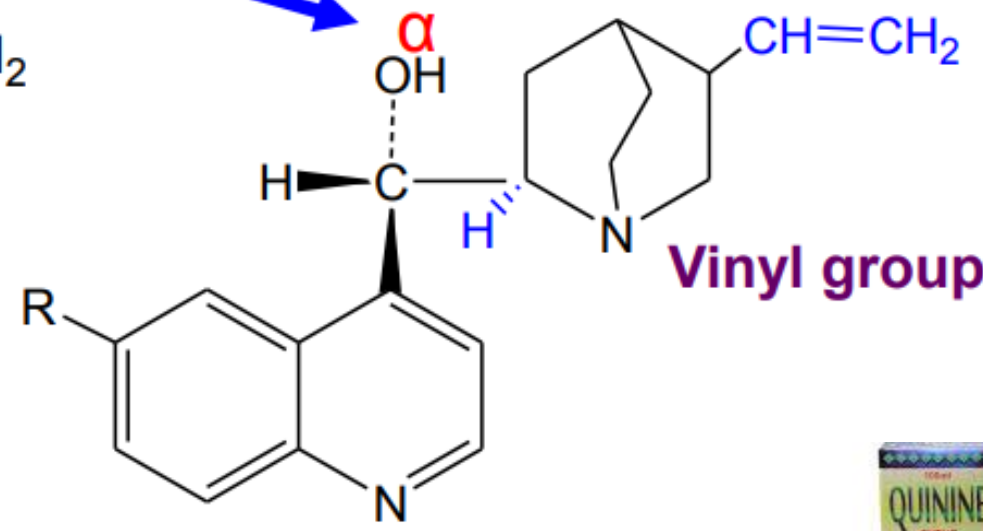


Ruban-9-ol

SAR

SAR





Vinyl group

R = OCH_3: (-) **Quinine**

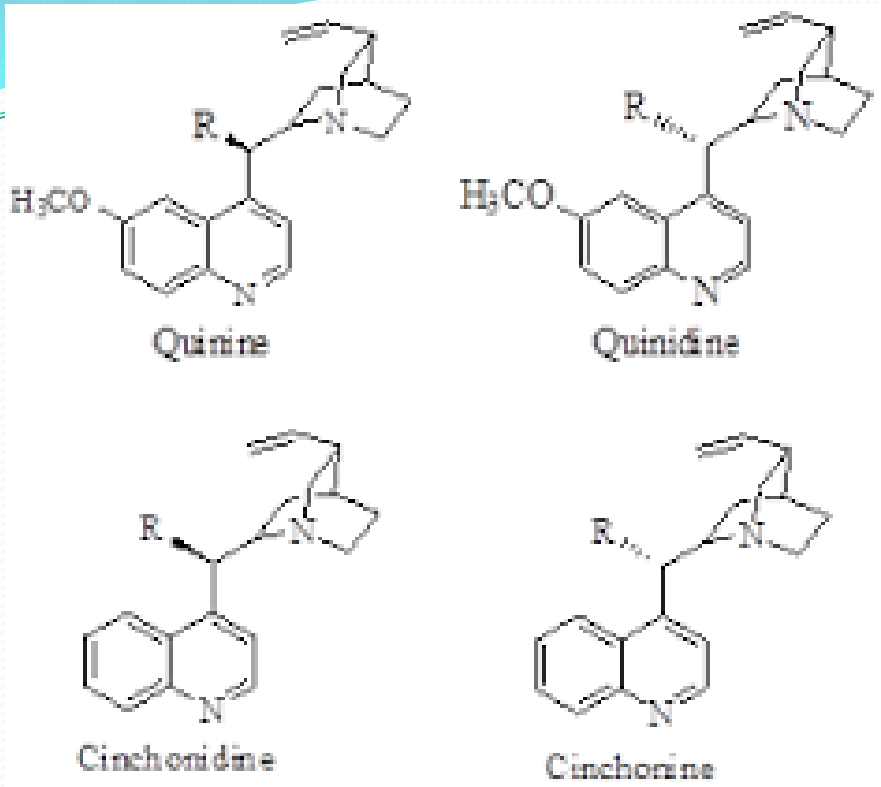
R = H: (-) **Cinchonidine**

R = OCH_3: (+) **Quinidine**

R = H: (+) **Cinchonine**

- Quinine and quinidine have opposite configurations at two centers.
- Cinchonidine and cinchonine are demethoxy analogues

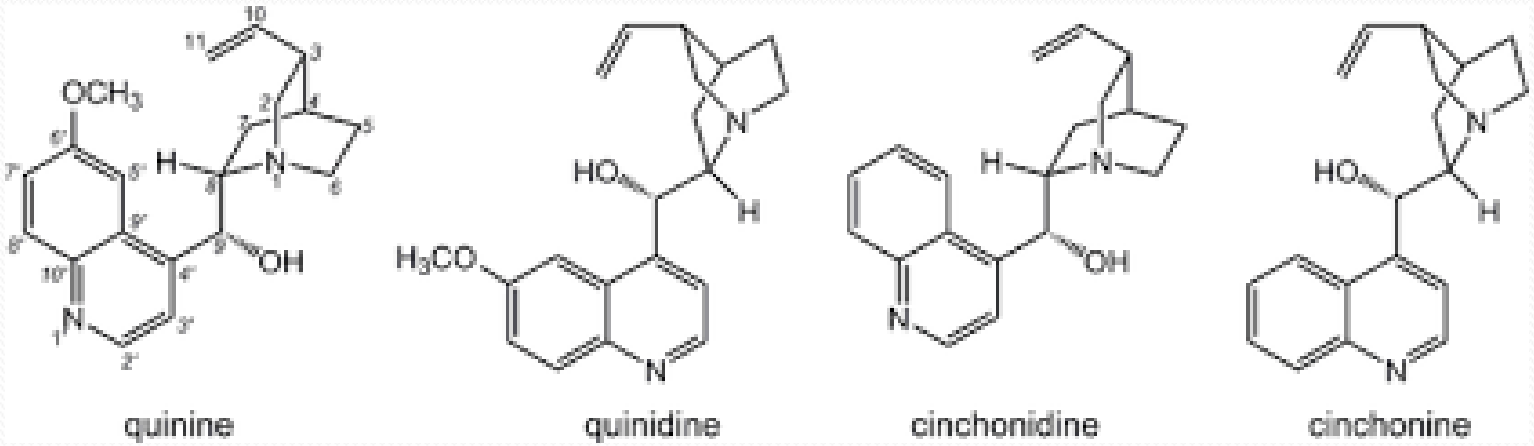
4 pairs of steroismoers: (-)-quinine and its dihydroform, (+)-quinidine (+)-cinchonine and its dihydroform, (-)-cinchonidine



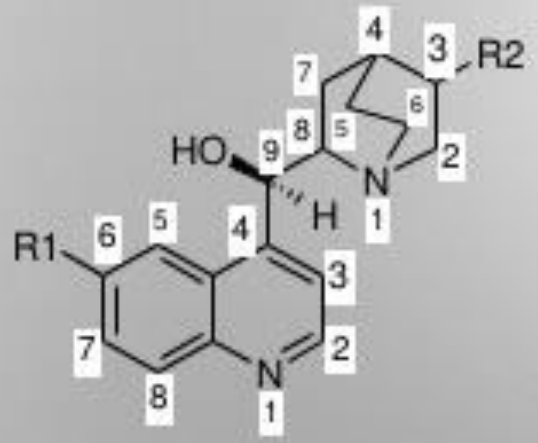
The cinchona alkaloids are rigid molecules containing four chiral carbons.

Quinine and cinchonidine has the absolute configuration 3(*R*),4(*S*),8(*S*),9(*R*) while quinidine and cinchonine has 3(*R*),4(*S*),8(*R*),9(*S*).

It is at the positions 8 and 9 that the chiral recognition is believed to take place due to hydrogen bonding groups, and the exchange of quinine for quinidine reverses the retention order of some enantiomers



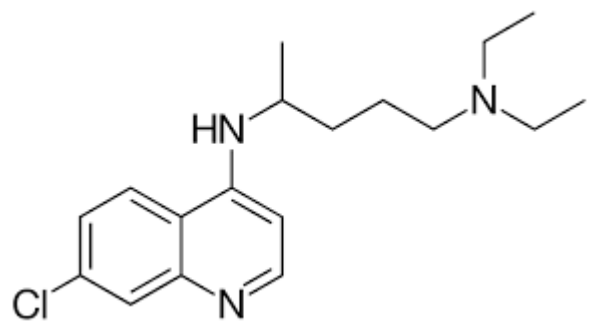
3. CINCHONA ALKALOIDS



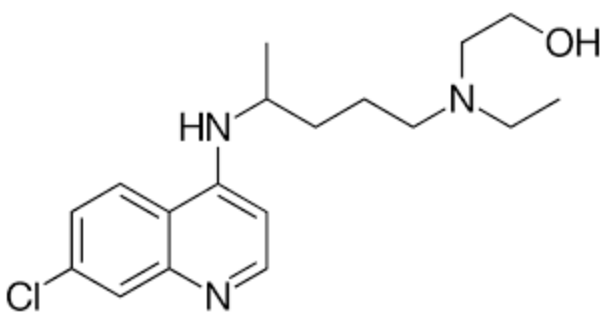
Quinine :	$R_1 = OCH_3 ; R_2 = -CH=CH_2$; (–) 8S : 9R isomer
Quinidine :	$R_1 = OCH_3 : R_2 = -CH=CH_2$; (+) 8R : 9S isomer
Cinchonine :	$R_1 = H ; R_2 = -CH=CH_2$; (+) 8R : 9S isomer
Cinchonidine :	$R_1 = H ; R_2 = -CH=CH_2$; (–) 8S : 9R isomer

- 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).

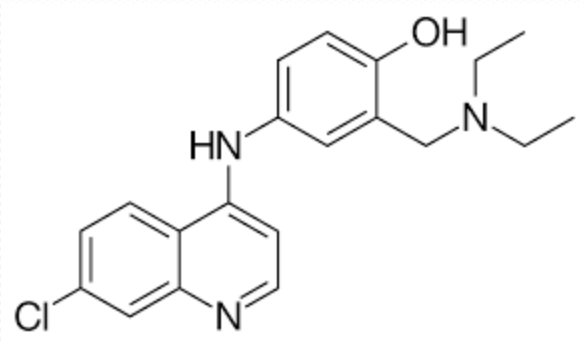
4-Amino quinolines



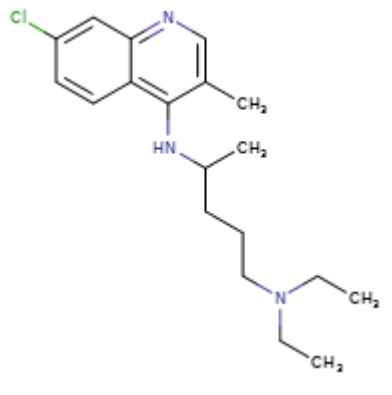
Chloroquine



Hydroxy chloroquine



Amodiaquine

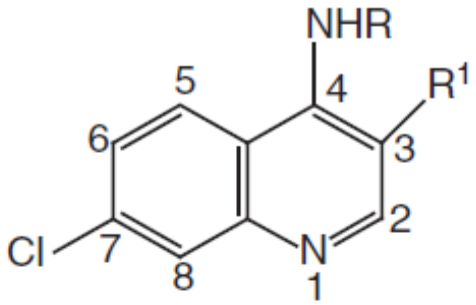


Santoquine

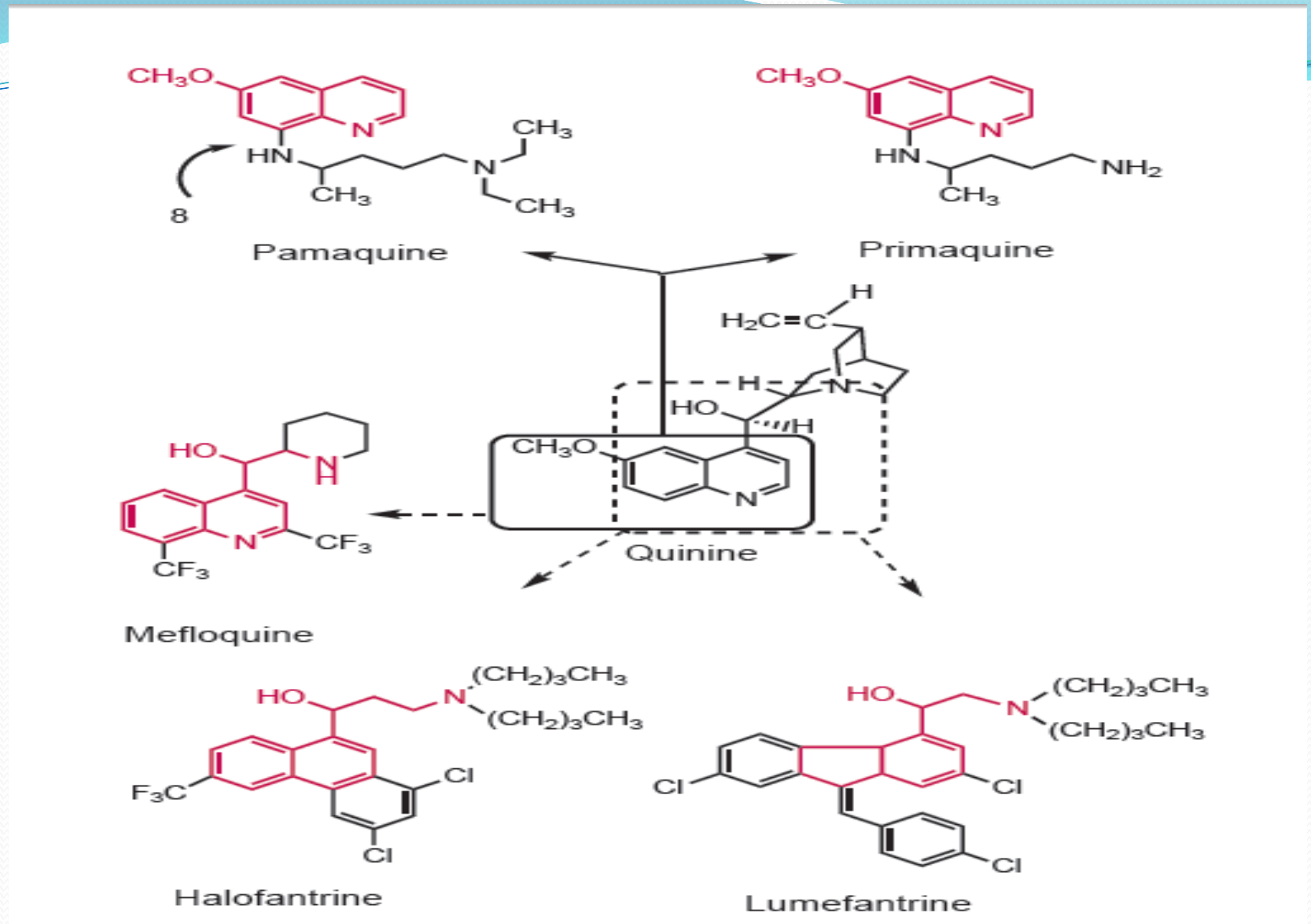
7-chloro-N-[5-(diethylamino)pentan-2-yl]quinolin-4-amine

Mechanism of Action:

The **mechanism of action** is interference with the parasite's ability to digest haemoglobin. Quinine and quinidine also inhibit the spontaneous formation of beta-haematin (haemozoin or malaria pigment) which is a toxic product of the digestion of haemoglobin by parasites.

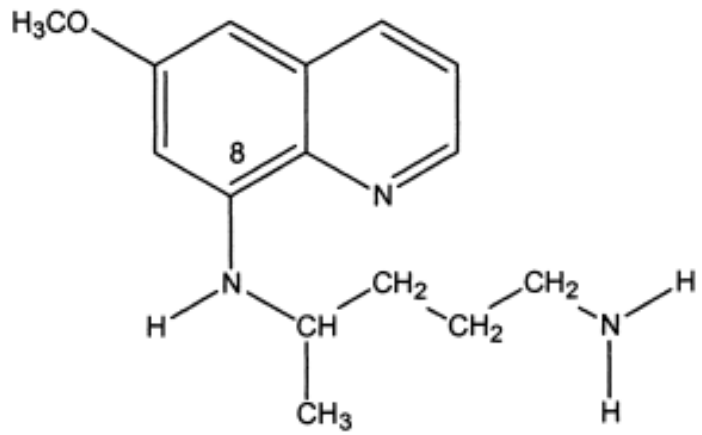


- At C-4 position, the dialkylaminoalkyl side chain has 2-5 carbon atoms between the nitrogen atoms, particularly the 4-diethylaminomethyl butyl amino side chain that is optimal for activity, as in chloroquine and quinacrine.
- The substitution of a hydroxyl group on one of the ethyl groups on the tertiary amine (hydroxy quinoline), reduces toxicity.
- Incorporation of an aromatic ring in the side chain (e.g. amodiaquine) gives a compound with reduced toxicity and activity.
- The tertiary amine in the side chain is important.
- The introduction of an unsaturated bond in the side chain was not detrimental to activity.
- The 7-chloro group in the quinoline nucleus is optimal, the methyl group in position 3 reduces activity, and an additional methyl group in position 8 abolishes activity.
- The D-isomer of chloroquine is less toxic than its L-isomer.

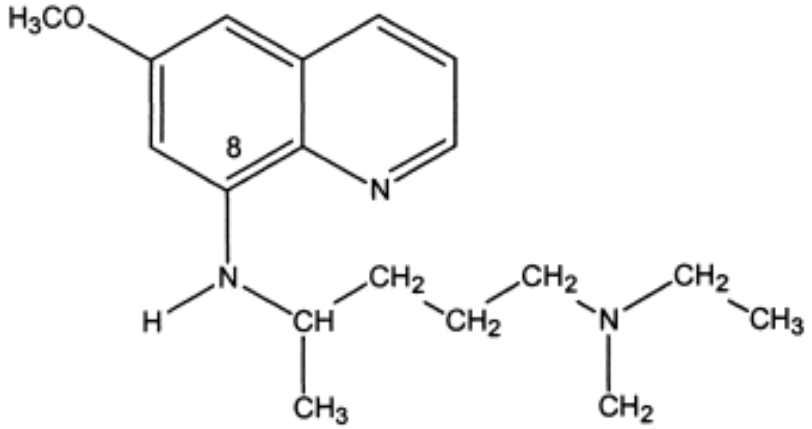


Structural similarity between quinine and the 8-aminoquinolines and between quinine and the quinoline-4-methanols .

8-aminoquinolines

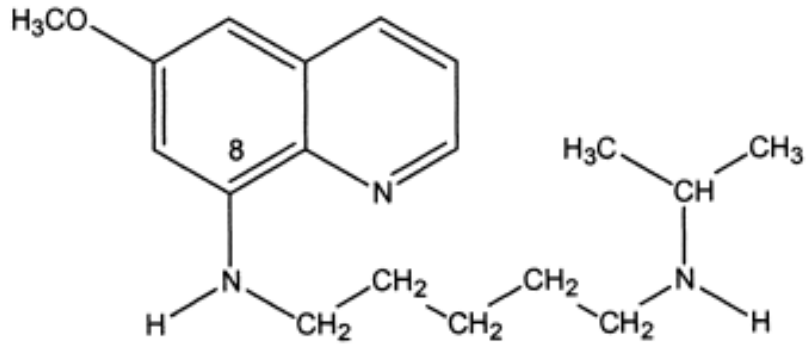


Primaquine

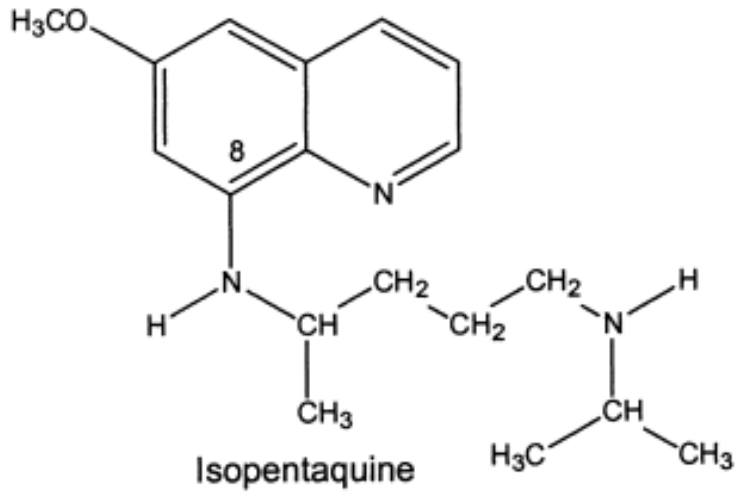


Pamaquine

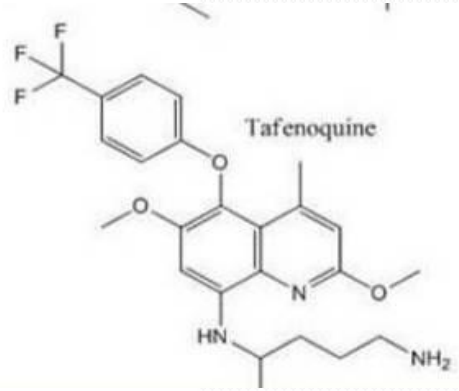
4-*N*-(6-methoxyquinolin-8-yl)pentane-1,4-diamine



Pentaquine

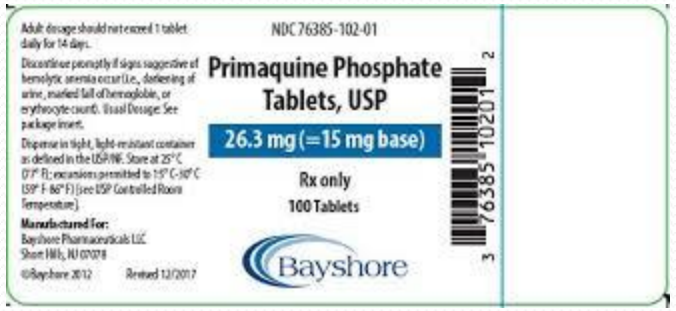


Isopentaquine



Mode of action:

While the mechanism of action of the 8-amino quinolines is unknown, it is known that primaquine can generate reactive oxygen species via an autoxidation of the 8-amino quinoline group with the formation of radical anion. As a result, cell destructive oxidants, such as hydrogen peroxide, super oxide, and hydroxyl radical can be formed.



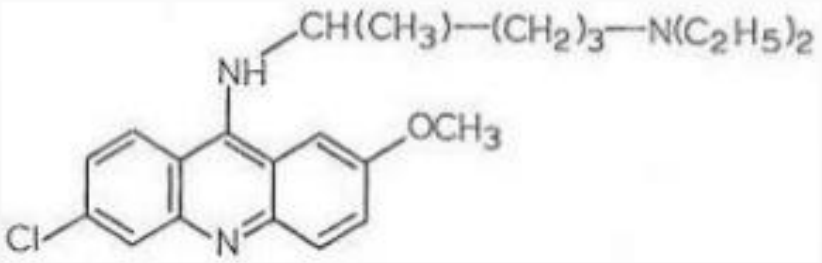
SAR

- 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

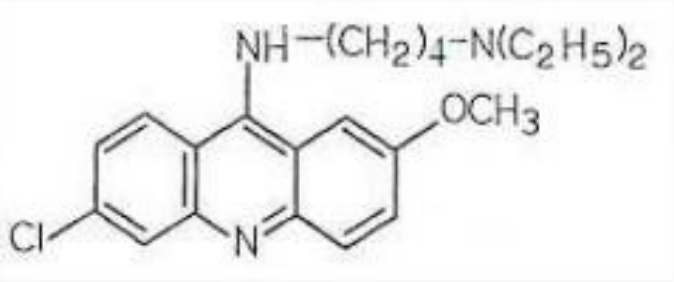
- Pentyl side chain gives maximum activity, increase or decrease of chain result is reduction of activity.
- The branched side chain when converted into straight chain pentaquine is obtained

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

9- Amino acridines



Quinacrine



Acriquine

Uses : More effective & less toxic than quinine.
Also pocess anti convulsant activity.

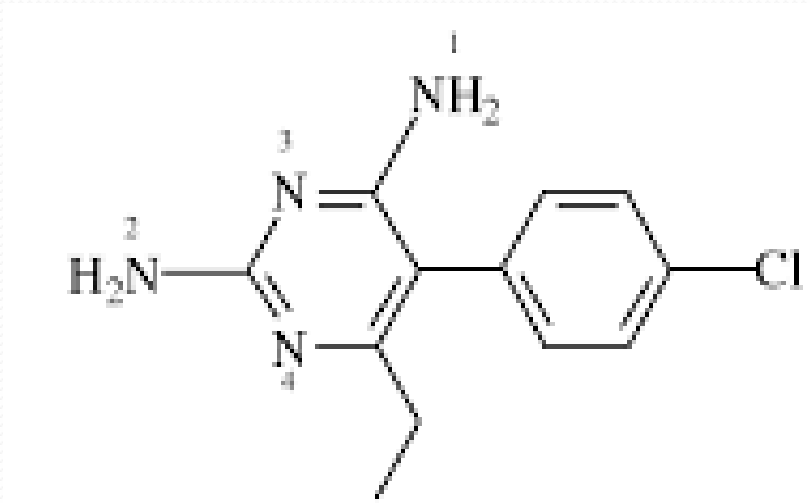
Adverse effects : Gastric irritation ,
Staining of tongue & skin.

FOR ILLUSTRATION PURPOSE ONLY. ACTUAL PRODUCT MAY VARY.

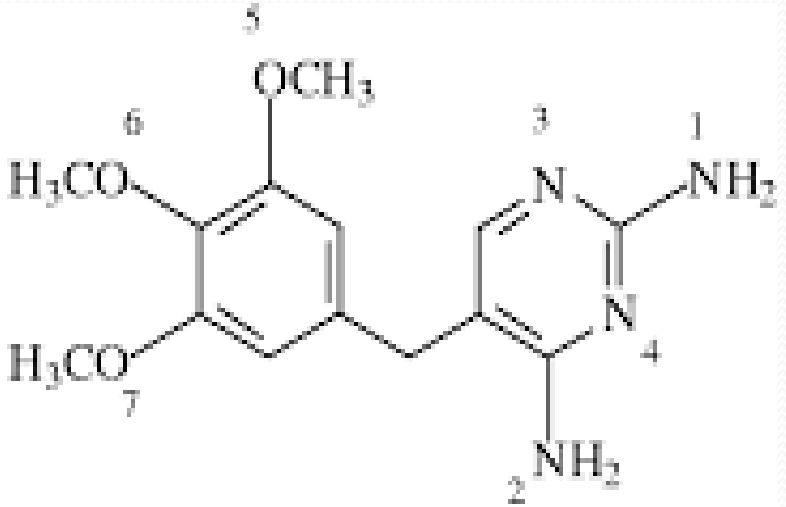
It acts at many sites within the cell including intercalation of DNA strands, succinic dehydrogenase and mitochondrial electron transport, and cholinesterase.

Pyrimidines: e.g. Pyrimithamine, Trimethoprim

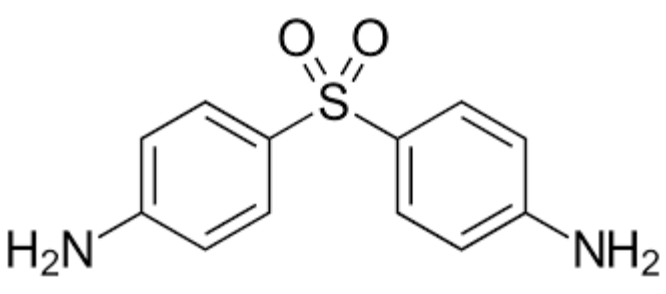
Sulphones: Dapsone, Sulphonamides



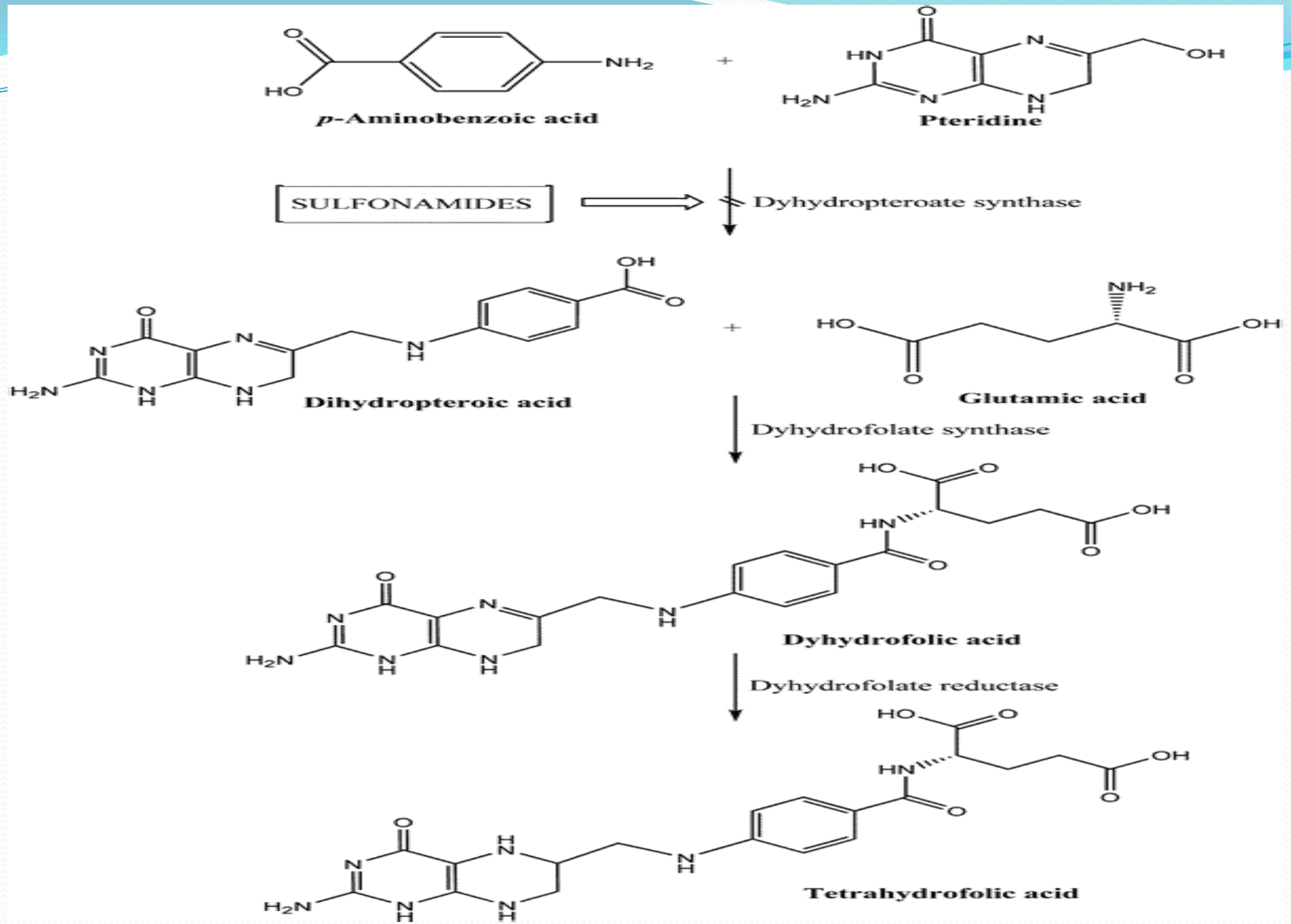
Pyrimethamine



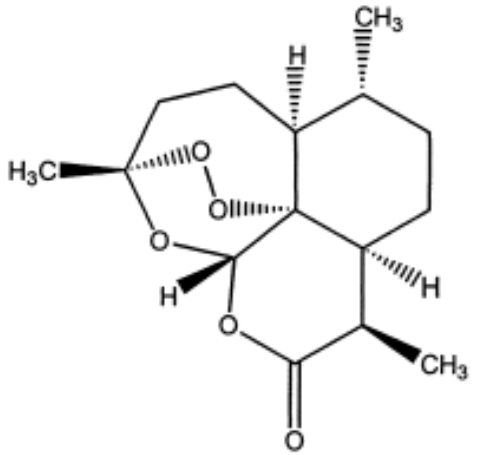
Trimethoprim



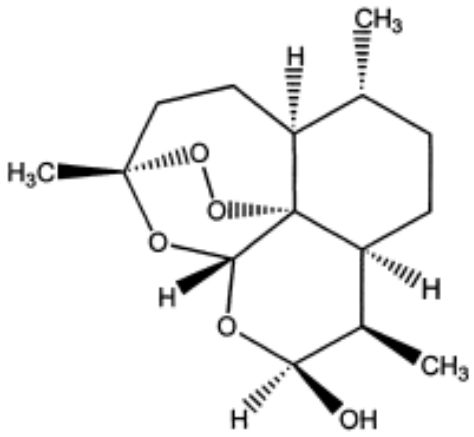
Dapsone


p-Aminobenzoic acid
Pteridine
SULFONAMIDES
Dyhydropteroate synthase
Dihydropteroic acid
Glutamic acid
Dyhydrofolate synthase
Dyhydrofolic acid
Dyhydrofolate reductase
Tetrahydrofolic acid

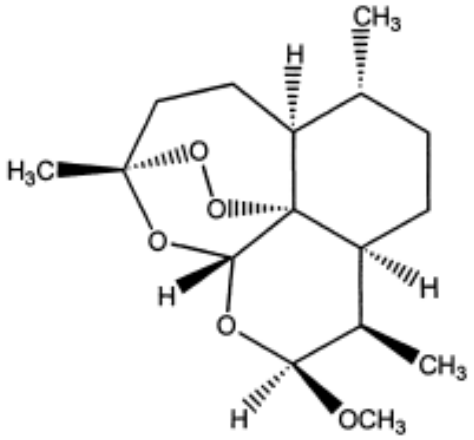
Peroxides e.g. Artemisinin, artemether



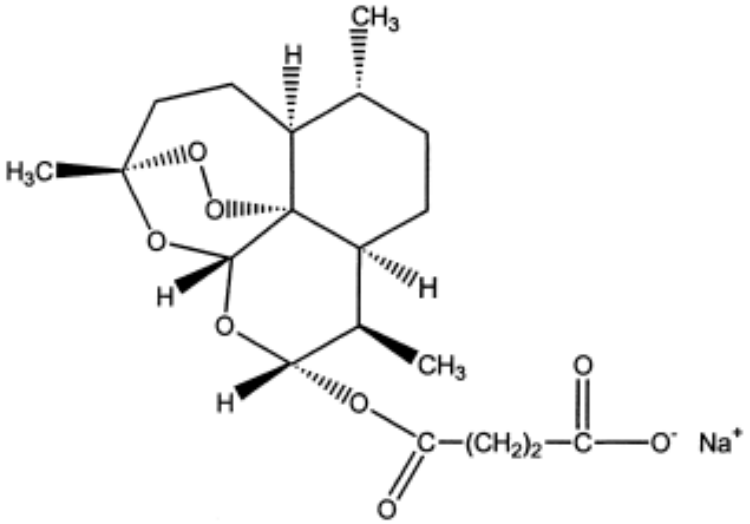
Artemisinin



Dihydroartemisinin



Artemether (oil soluble) R = CH_3
Artemotil (oil soluble) R = CH_2CH_3



Artesunate (water soluble)

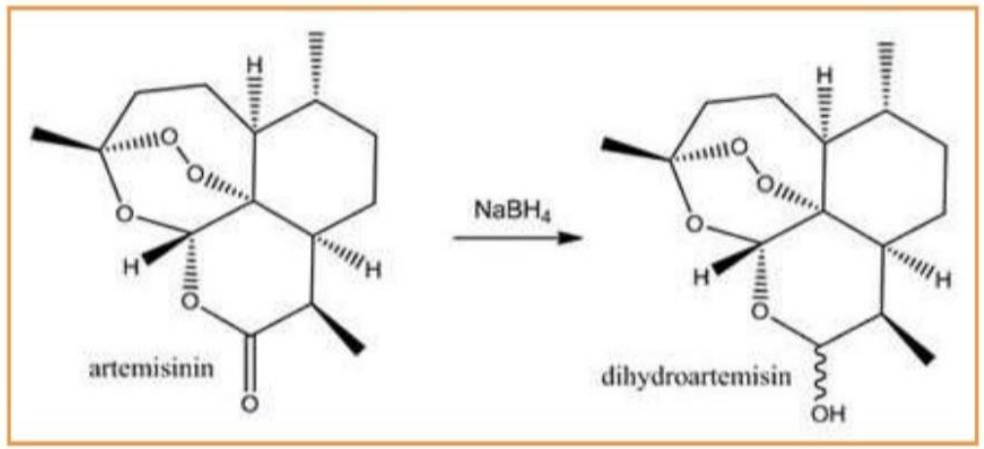
MOA :

The artemisinins appear to kill the parasite by a free radical mechanism—not by the generation of ROS but, rather, by virtue of a free radical associated with the endoperoxide, possibly involving a carbon radical. It is proposed that the heme in the form of hemozoin within the digestive vacuole is a source of FeII, which reacts with the peroxide to generate an oxy radical and FeIII.

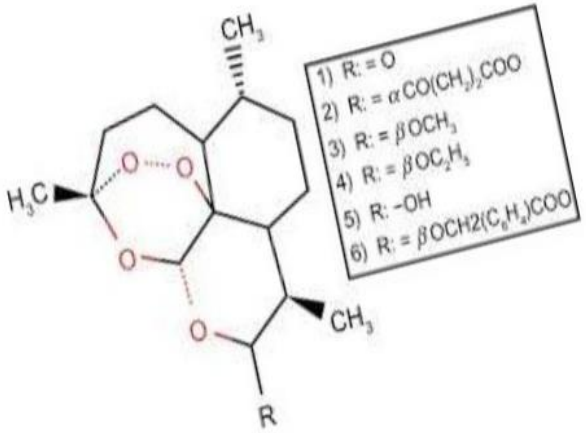
SAR

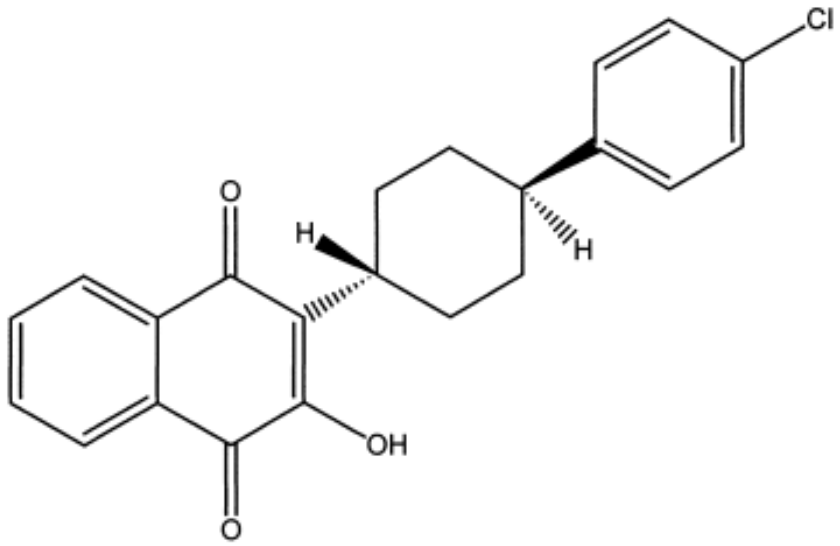
Artemisinin serve as a lead compound for the development of new antimalarials with improved properties

- The lactone group can be reduced & form dihydroartemisinin which is used to prepare semi synthetic prodrug that are more water & oil soluble

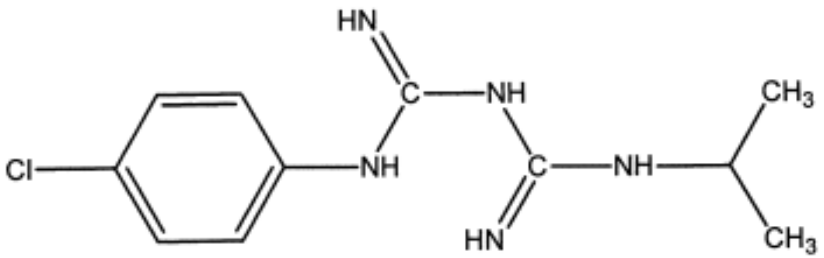


- The hydroxyl group can be alkylated to give oil soluble ether derivatives such as artemether & arteether
- Esterification of the hydrooxyl with succinic acid gives the water soluble derivative , artesunate



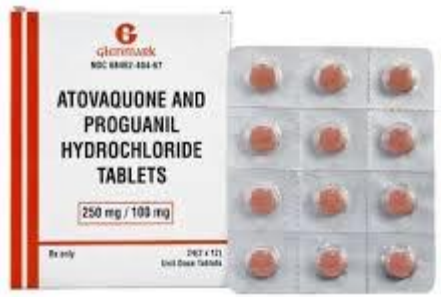


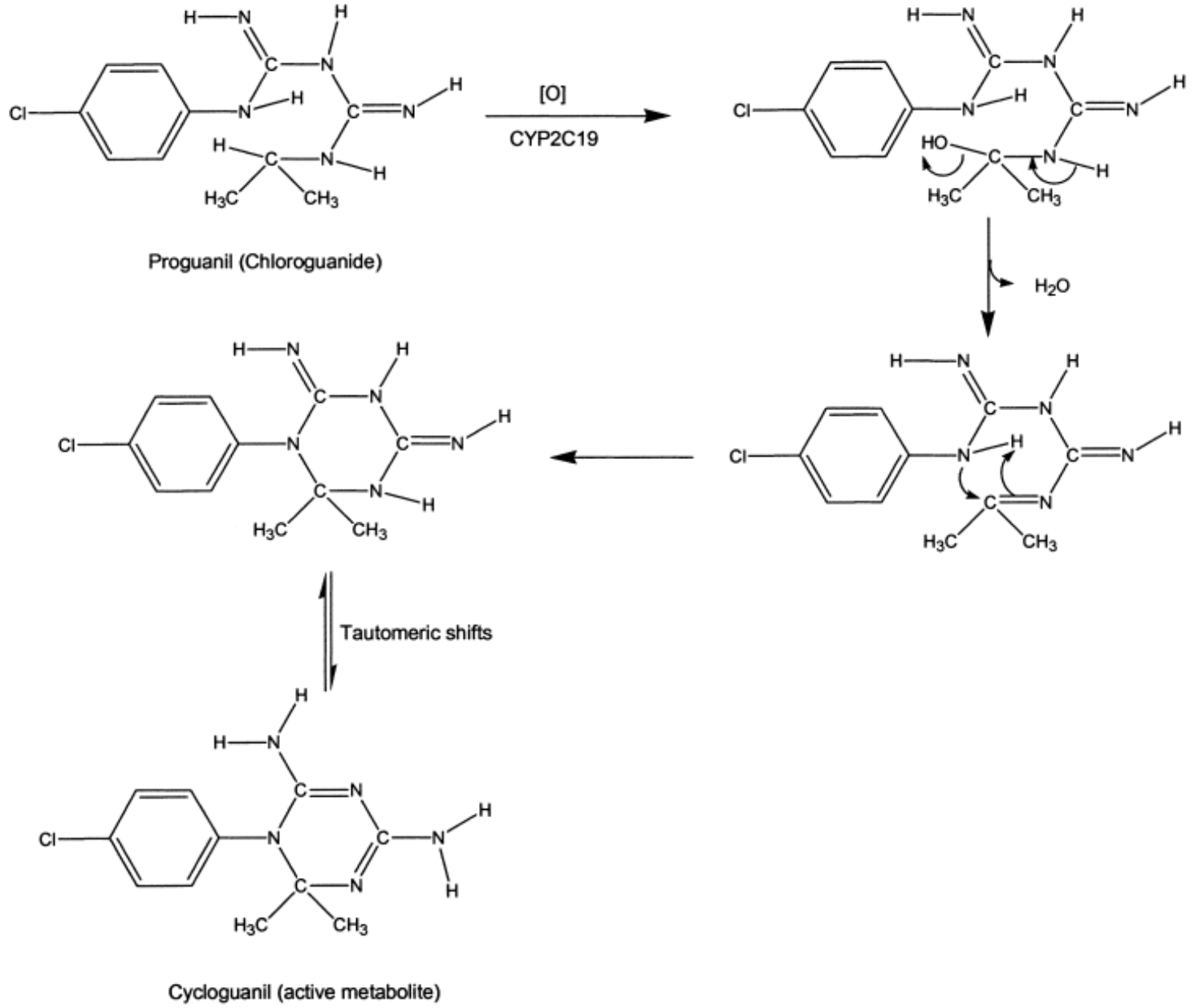
Atovaquone



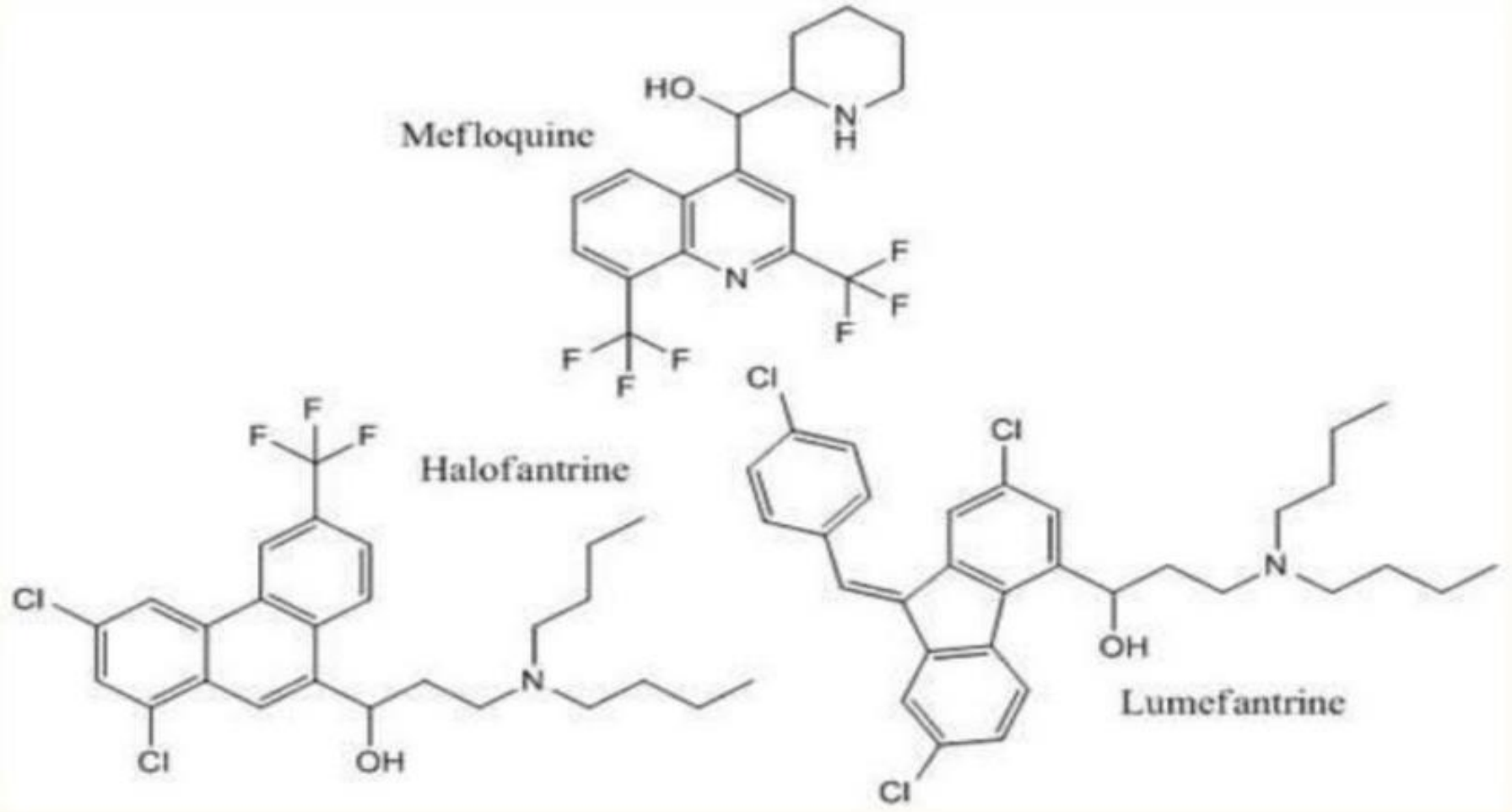
Proguanil

Biguanides: Proquanil, Chloroproguanil



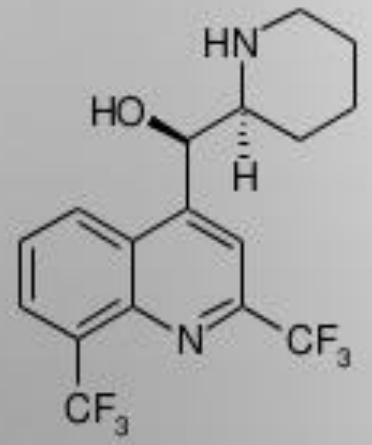

[O]
CYP2C19
Proguanil (Chloroguanide)
H_2O
Tautomeric shifts
Cycloguanil (active metabolite)

Miscellaneous Agents



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,