Anti-Parasitic Agents:
Anti-Malarial Agents

SRAmini Oct2024

CHAPTER 32

Drugs Used to Treat Parasitic Infections

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Drugs covered in this chapter:

TREATMENT OF AMEBIASIS, GIARDIASIS, AND TRICHOMONIASIS:
- Metronidazole
- Nitazoxanide
- Tinidazole

TREATMENT OF PNEUMOCYSTIS:
- Atovaquone
- Penamidine isethionate
- Sulfamethoxazole-trimethoprim

TREATMENT OF TRYPANOSOMIASIS:
- Benznidazole
- Eflornithine
- Melarsoprol
- Niturtimox
- Pentamidine isethionate
- Suramin sodium

TREATMENT OF LEISHMANIASIS:
- Sodium stibogluconate
- Miltefosine

TREATMENT OF MALARIA:
- Artemisinins (artemether, artesunate, dihydroartemisinin)
- Atovaquone-proguanil
- Chloroquine
- Lumefantrine
- Mefloquine
- Piperaquine, primaquine, quinine
- Tafenoquine

TREATMENT OF HELMINTH INFECTIONS:
- Albendazole
- Ivermectin
- Mebendazole
- Moxidectin
- Praziquantel
- Pyrantel pamoate

TREATMENT OF SCABIES AND PEDICULOSIS:
- Benzyl alcohol
- Crotamiton
- Lindane
- Permethrin
- Spinosad

Table 32.3 Guidelines for Treatment of Malaria in the United States[a]

Clinical Diagnosis	Sensitivity	Drug Recommendation
Uncomplicated malaria *P. falciparum*	Chloroquine sensitive	Chloroquine phosphate
	Chloroquine resistant or unknown	A. Atovaquone-proguanil (Malarone) B. Artemether-lumefantrine (Coartem) C. Quinine sulfate + one of the following: Doxycycline Tetracycline Clindamycin D. Mefloquine
Uncomplicated malaria *P. malariae, P. knowlesi*	Chloroquine sensitive	A. Chloroquine phosphate B. Hydroxychloroquine
Uncomplicated malaria *P. vivax or P. ovale*	Chloroquine sensitive	Chloroquine phosphate + Primaquine phosphate
Uncomplicated malaria *P. vivax*	Chloroquine resistant	A. Quinine sulfate + Doxycycline or Tetracycline B. Atovaquone-proguanil + Primaquine phosphate C. Mefloquine + Primaquine phosphate
Severe malaria	Chloroquine sensitive/resistant	Quinidine gluconate (parenteral) + one of the following: Doxycycline Tetracycline Clindamycin

[a]Information taken from the CDC Guideline for Treatment of Malaria in the United States. Updated July 1, 2013. For more details including infectious region and dosing go to: www.cdc.gov/malaria/diagnosis_treatment/treatment and then CDC treatment guidelines.pdf.

Life Cycle for Malarial Protozoa

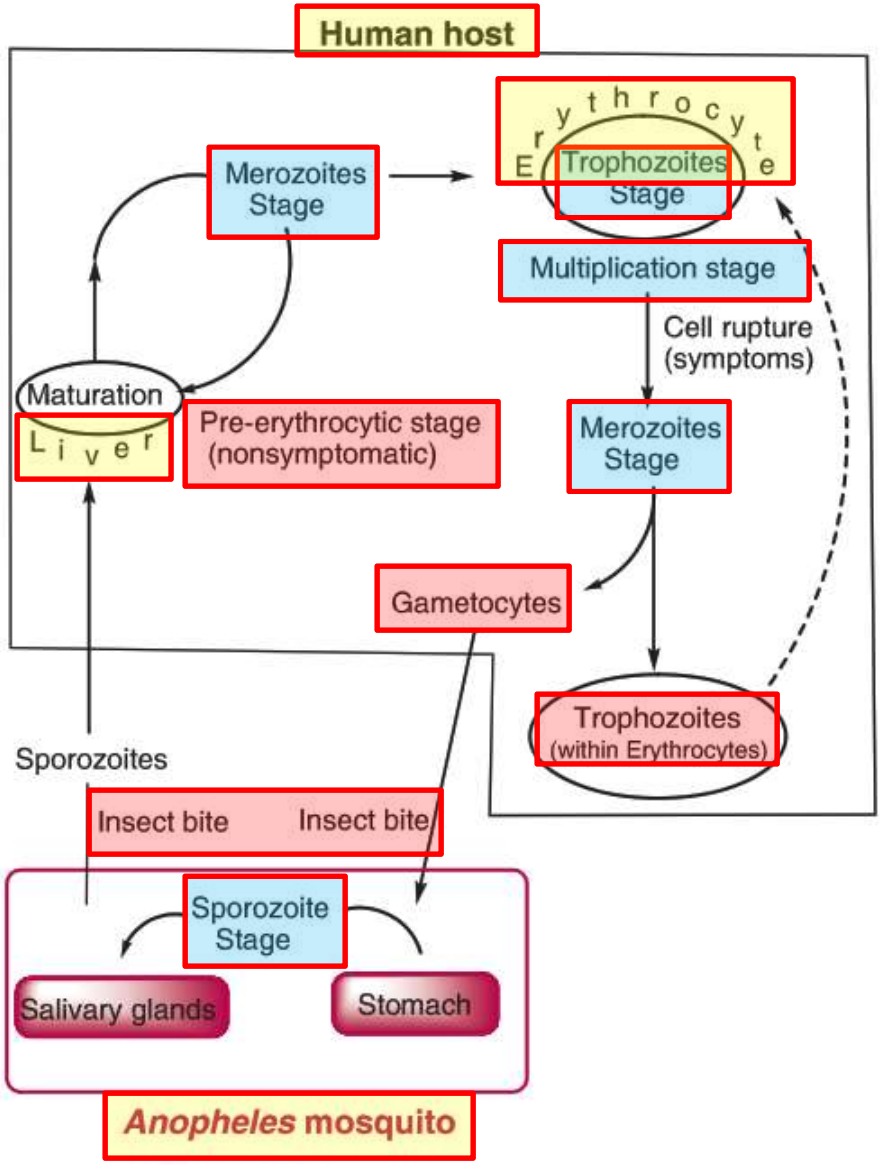


Figure 32.1 Life cycle of malarial protozoa.

Life Cycle for Plasmodium

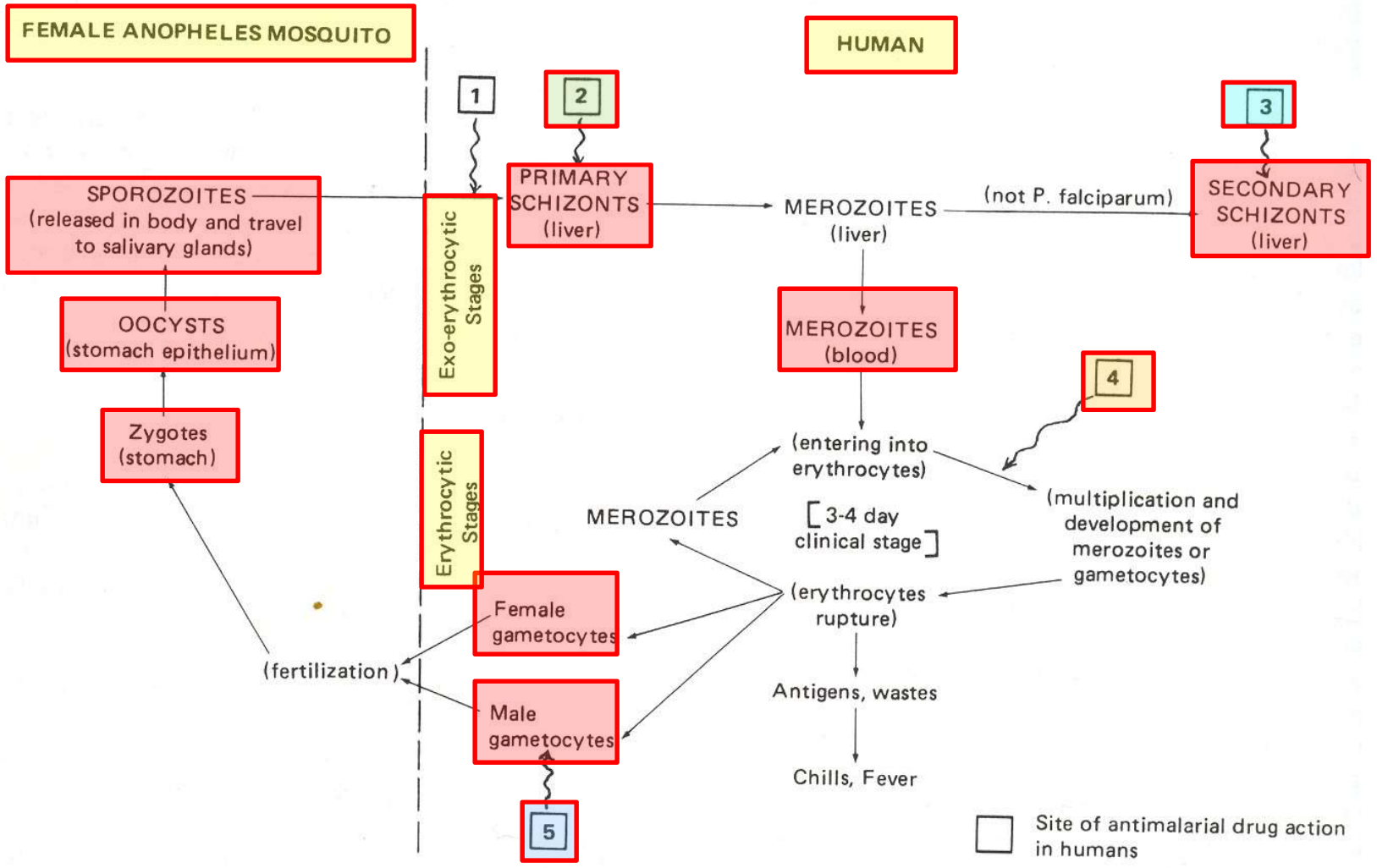


FIG. 6-1. *Life cycle of Plasmodium: (1) sporozoitocide — no drugs effective; (2) primary (exoerythrocytic) schizonticide — primaqui pyrimethamine, chloroguanide, cycloguanil pamoate; (3) secondary (exoerythrocytic) schizonticide — primaquine; (4) erythrocytic schizontici (fast-acting — chloroquine, quinine, amodiaquine; slow-acting — chloroguanide, pyrimethamine, sulfonamides, cycloguanil pamoate); (5) gan tocytocide — primaquine.*

- Wilson & Gisvold's 1991-p206

Drug Classification for Anti-malarial Agents

- Tissue schizonticide
- Blood schizonticide
- Gametocytocide
- Sporontocide (sporozooiticide)

Sites of Action for Anti-Malarial Agents in Plasmodium Parasite

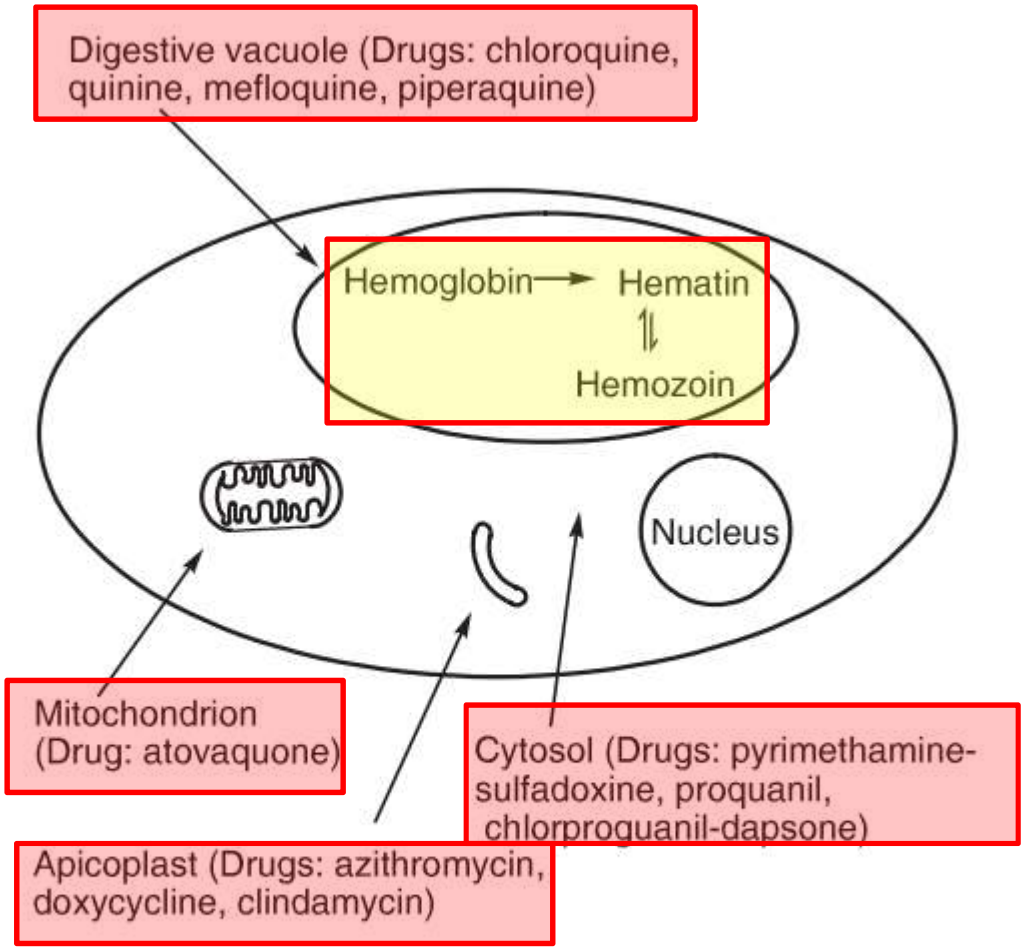


Figure 32.12 *Plasmodium* parasite cell as present within the erythrocyte and sites of drug action.

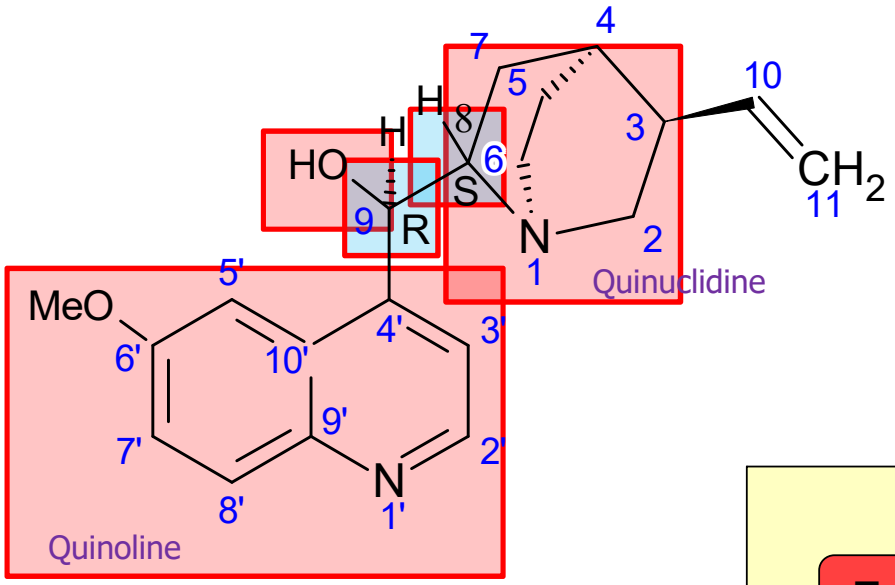
Sites & MOA for Anti-malarial Agents

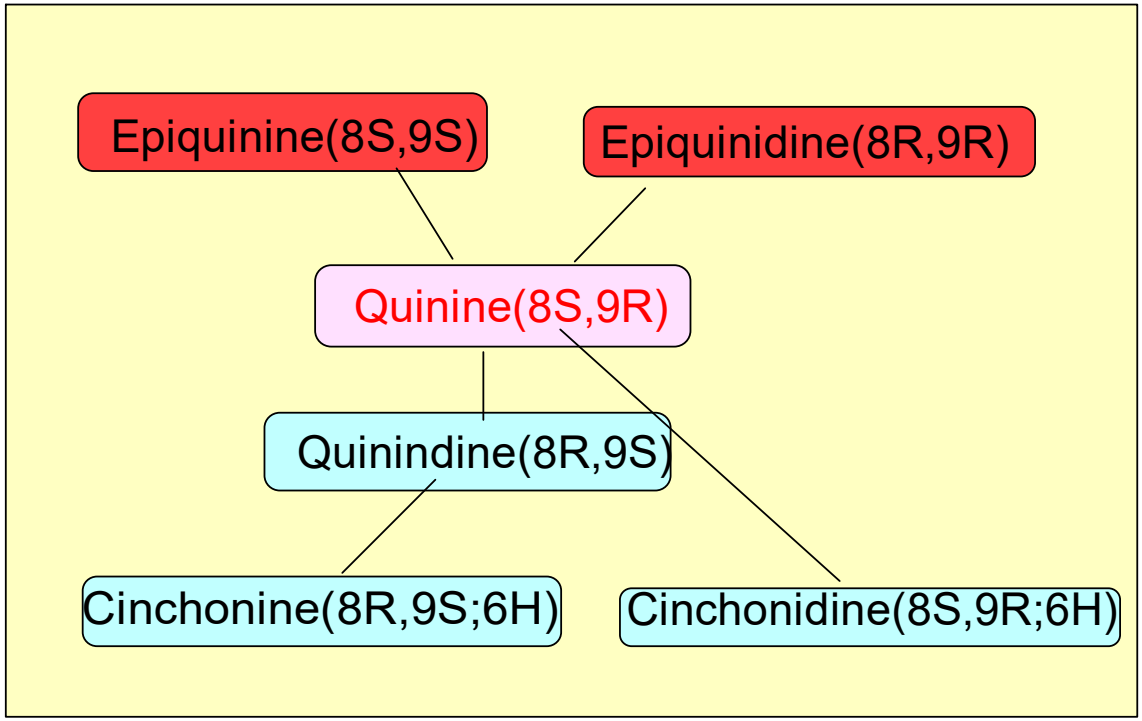
- DNA intercalation:
- ✓ quinoline-methanols
- ✓ acridines
- ✓ 4-amino-quinolines
- ✓ 8-amino-quinolines
- Dihydrofolate reductase inhibitors:
- ✓ trimethoprim, pyrimethamine, proguanil
- Dihydropteroate synthase inhibitors:
- ✓ sulfadoxine, dapsone
- Protein synthesis inhibitors:
- ✓ tetracycline (doxycycline), macrolide (azithromycin), lincosamide (clindamycin)
- Free radical mechanism & endoperoxide activation: alter Ca^{2+} stores
- ✓ sesquiterpene lactone: artemisinin

Chemical Classifications of Anti-malarial Agents

- 4-Quinoline-methanol
- Acridines: 9-amino-acridine
- 4-amino-quinoline
- 8-amino-quinoline
- Artemisines: sesquiterpene lactone
- Biguanide
- Diaminopyrimidine
- Imidazole
- Lincosamide
- Macrolide
- 1,4-naphthoquinone
- Sulfonamide
- Sulfone
- Tetracycline
- Miscellaneous

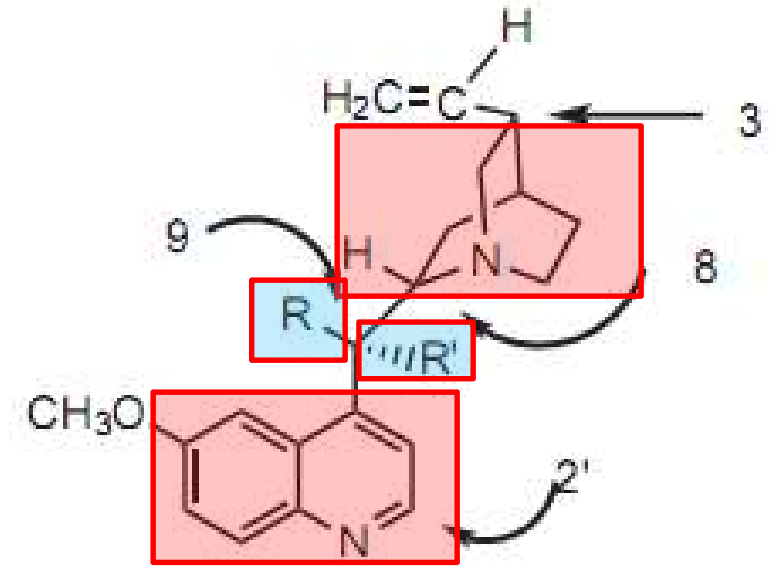
Quinoline Methanols

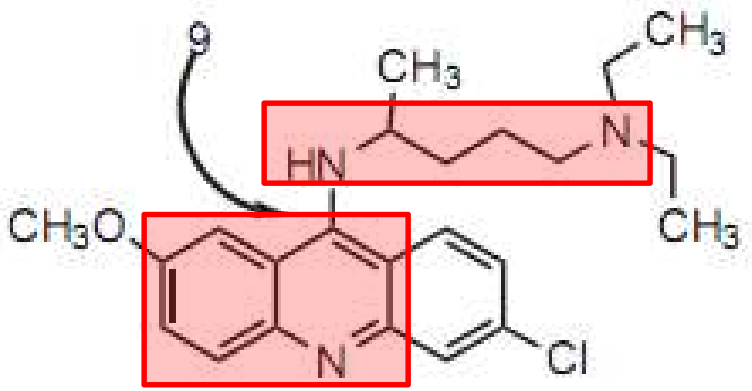




Quinoline-Methanols: Chemistry & SAR

- Quinuclidine + 4'-Quinoline-methanol (9R&9R′= OH & H)
- Compare toxicity & clinical application of quinine & quinidine
- Development of next synthetic agents following SAR





Quinacrine

Quinine (R = OH, R' = H) 8S, 9R
Quinidine (R = H, R' = OH) 8R, 9S

Modification to Get New Simple Anti-malarial Agents

Development of Anti-malarial Agents Following Quinine as Lead Compound

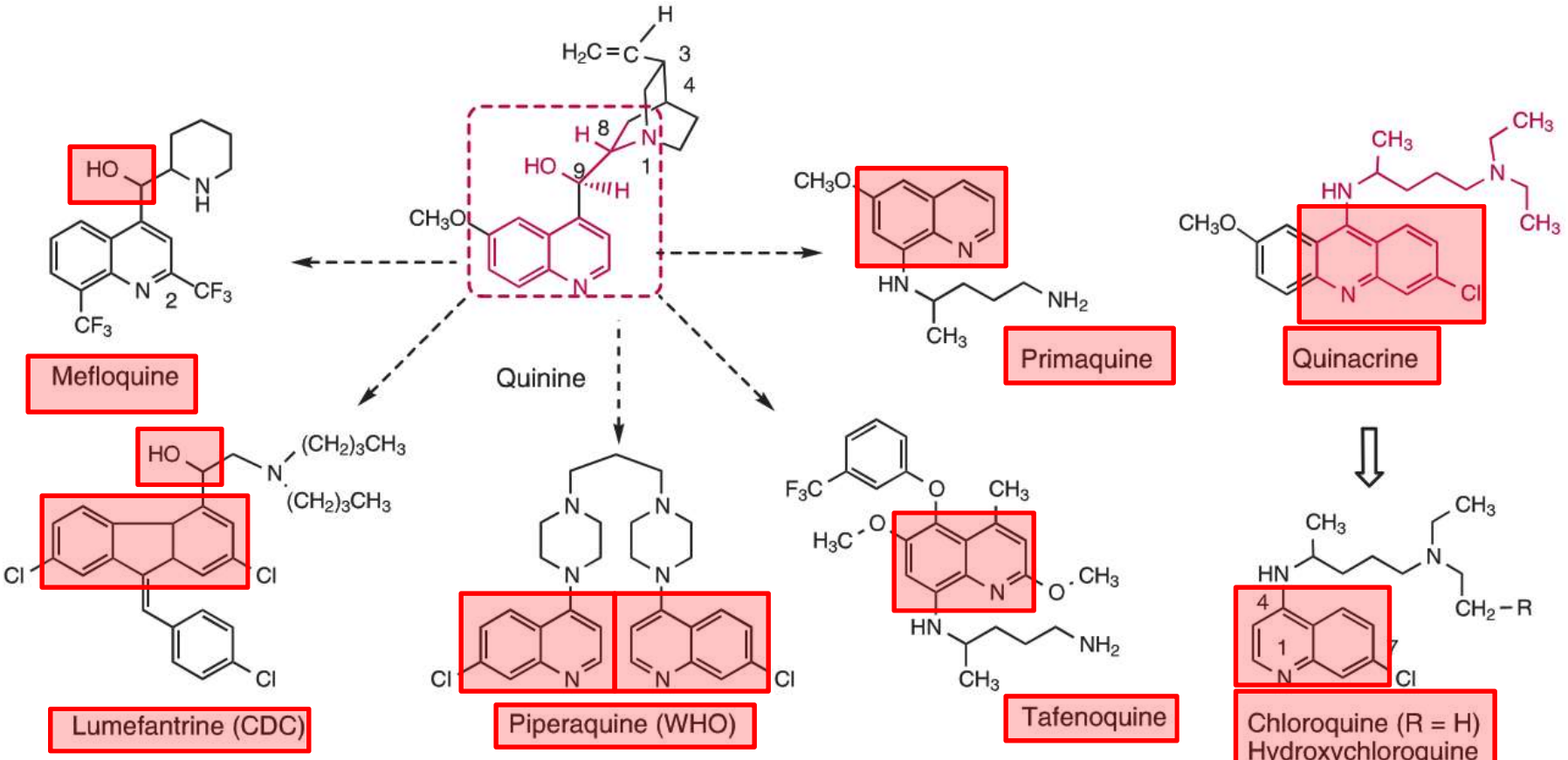


Figure 32.10 Structure similarity between the lead antimalarials (quinine and quinacrine) and the available antimalarials. *CDC*, Center for Disease Control; *WHO*, World Health Organization.

Quinacrine & Development of 4-AQ (CQ)

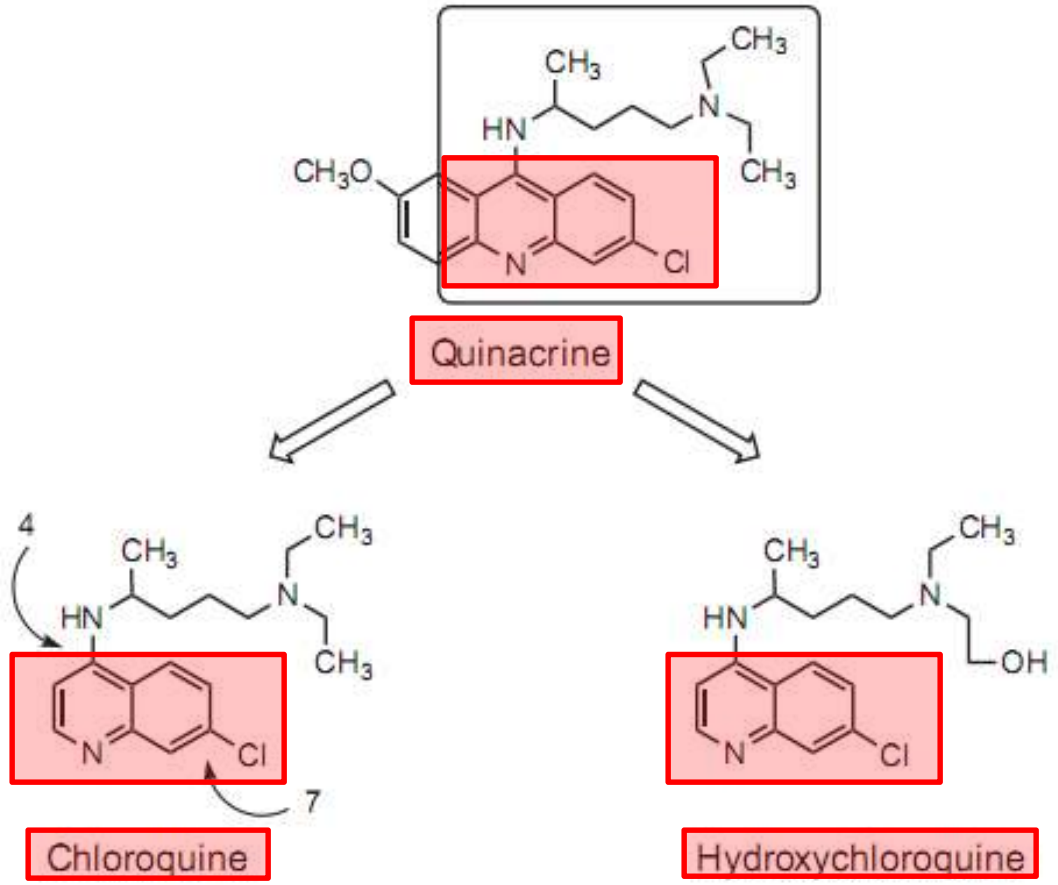


FIGURE 34.11 Structural similarity between quinacrine and the 4-aminoquinolines.

Developed 4-Substituted Quinolines from Quinine: Name & MOA

- Chloroquine
- Hydroxy-chloroquine
- Mefloquine
- Primaquine
- Tafenoquine
- Lumefantrine
- Piperaquine

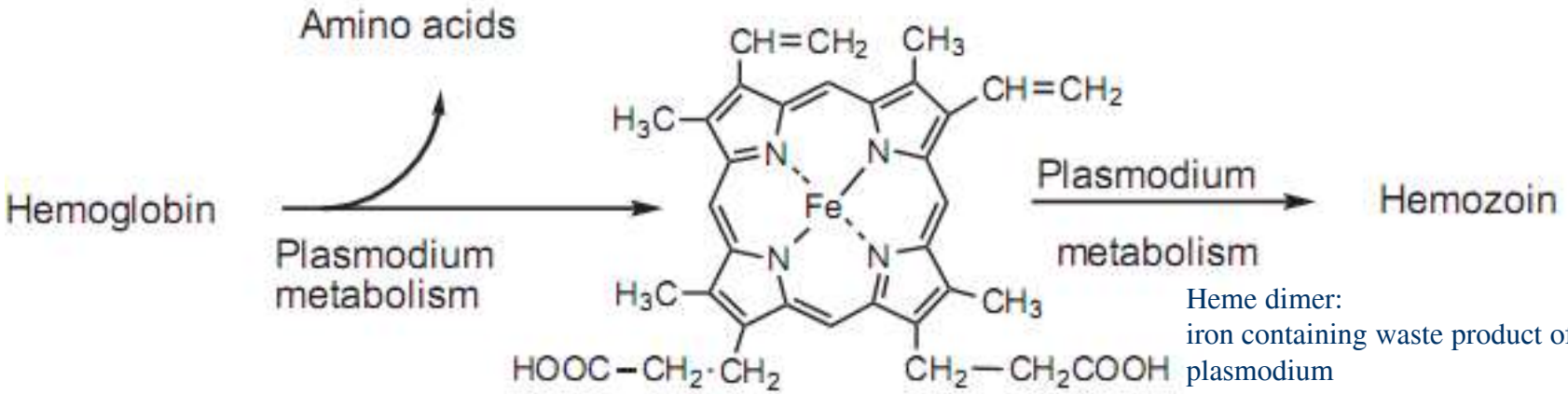
➢ MOA: DNA intercalation

✓ weak base hypothesis: accumulation in acidic vacuoles (pH=4.8-5.2)

✓ ferriprotoporphyrin hypothesis: π-stacking of quinoline to porphyrin

Proteolytic Degradation of Hemoglobin: Ferriprotoporphyrin Pathway

- Hematin: free heme: toxic
- Hemazoin:
- ✓ dimeric; biocrystal; insoluble: chemically inert: not-toxic



Heme dimer:
iron containing waste product of plasmodium
produced in heme detoxification
produced during intraerythrocytic digestio

FIGURE 34.14 Proteolytic degradation of hemoglobin by the *Plasmodium* organism to the potentially toxic hematin and then to the nontoxic dimer hemozoin.

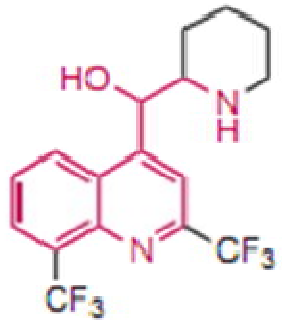
Quinoline Anti-malarials

Table 32.2 Pharmacokinetic of Quinoline Antimalarials

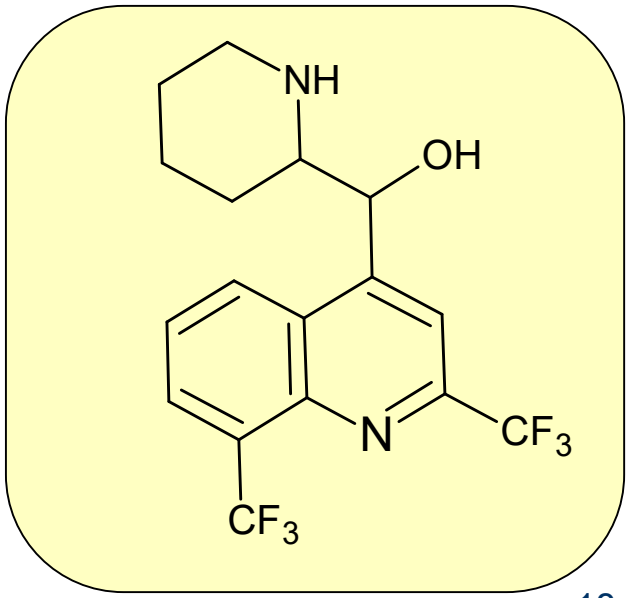
Generic Name	Protein Binding	Bioavailability	Half-Life (Days)	Route of Excretion
Quinine	69-92%	~85 %	~0.5	Urine
Chloroquine	~55%	75 %	3-9	Urine/feces
Hydroxychloroquine	30-40%	~74%	~40-50	Urine/feces
Mefloquine	>98%	~85%	20 median	–
Primaquine	NA	75%	~6 hr	Urine
Lumefantrine	99%	Low (5-11%)	3-6	Feces
Piperaquine	~97%	Not reported	20-30	Urine

4-Quinoline-methanol: Mefloquine

- One of quinine derived structures:
- Chemistry: 4-Quinoline-methanol
- The most promising of this group
- The 2nd choice in prophylaxis of multidrug resistant PIs

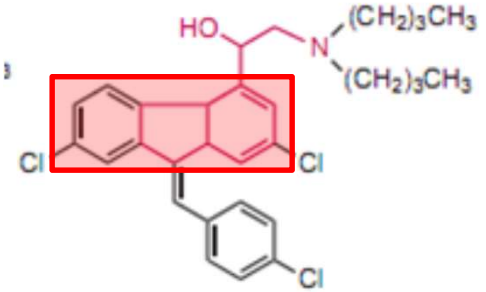


Mefloquine



Lumefantrine: Chemistry & MOA

- Chemistry: modified aryl methanols:
  - ✓ parent ring: fluorene



Lumefantrine

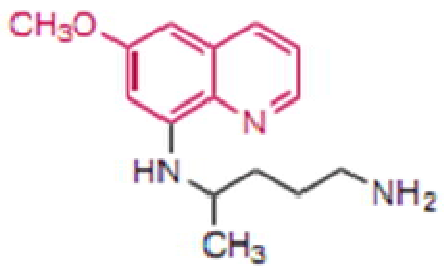
- Fat soluble: after fat meal has better oral absorption.

- MOA:
  - ✓ erythrocytic schizonticide
  - ✓ in combination with artemether (artemisinin)

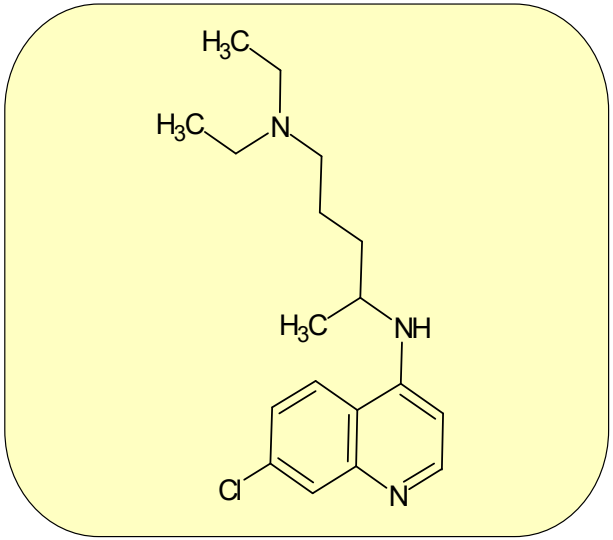
4-Aminoquinolines: Chloroquine (CQ)

- Chloroquine (CQ):
  - ✓ first choice for prophylaxis & acute attacks

- In combination with primaquine (8-aminoquinoline): in prophylaxis of all susceptible species
- *RESISTANCY !!!*



Primaquine



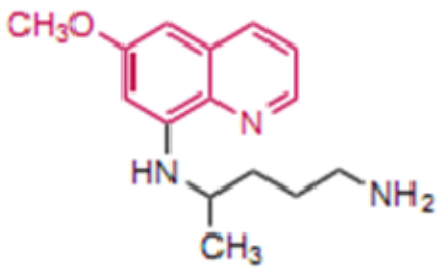
Optimized SAR of Quinoline Related Structures

- Chemistry:
- ✓ quinoline (4 methanol or 4 or 8-amino), acridine (9-amino), fluorene
- amine in the alkyl substituted at C4 or C8 of quinolone: secondary
- terminal amine in the alkyl substituted at C4 or C8 of quinoline: tertiary is preferred
- Optimum distance between two aminic nitrogen atoms: 2 to 4 carbons
- ✓ 4 is preferred: as chain or in piperazinyl form (bis-form)
- ✓ 4 atom might be inserted in part of an aromatic ring

- "OH" on "ethyl or ethylene" portion substituted at terminal amine:
- ✓ mimicking methanol in quinine
- Presence of electron withdrawing group at C2, C6, C7: improve the potency
- ✓ OCH_3; Cl; CF_3

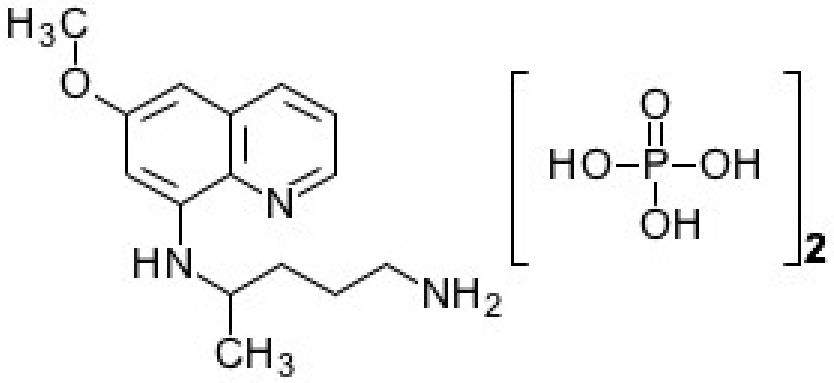
8-Amino-Quinolines: Primaquine

- Clinical use:
  - ✓ prophylaxis; prevent relapse
  - ✓ tissue schizonticide
  - ✓ radical cure of P.O & P. V.
  - ✓ gametocide



Primaquine

- SE: …



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Metabolism of Primaquine

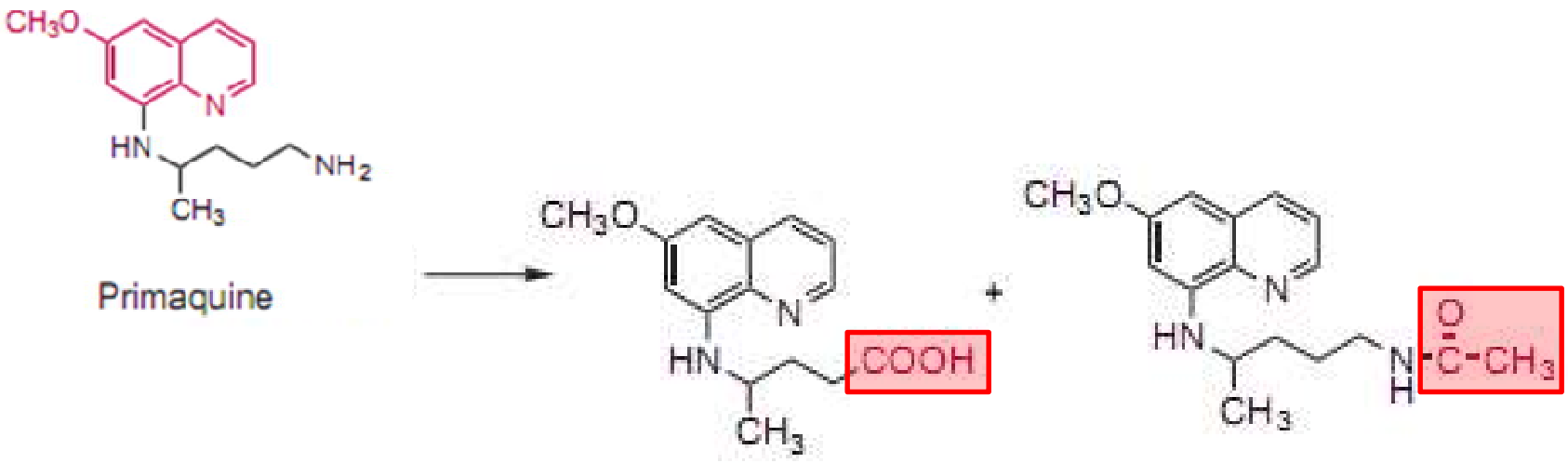


FIGURE 34.17 Metabolism of primaquine.

Metabolism for Piperaquine

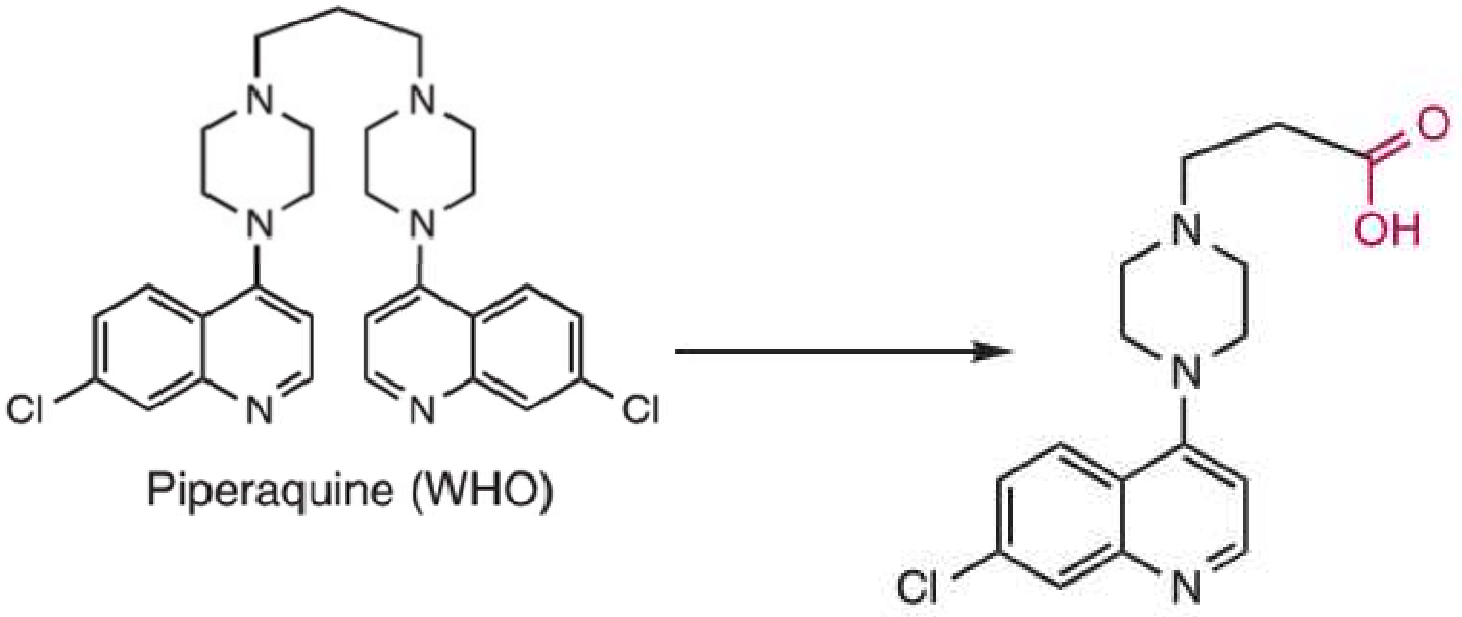
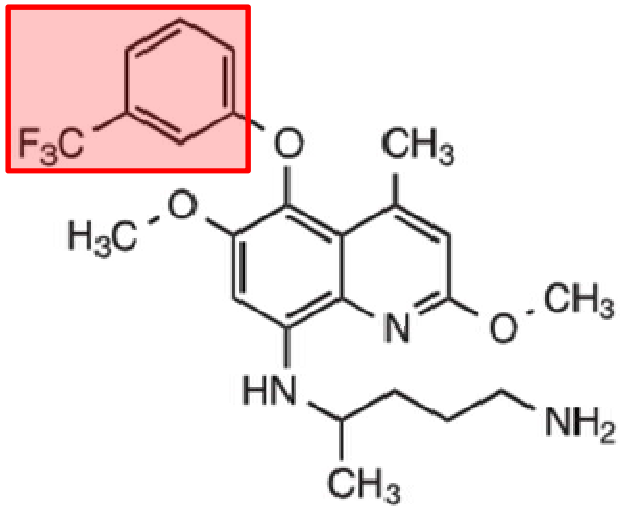


Figure 32.15 Metabolism of piperaquine.

Metabolism of Tafenaquine



Tafenoquine

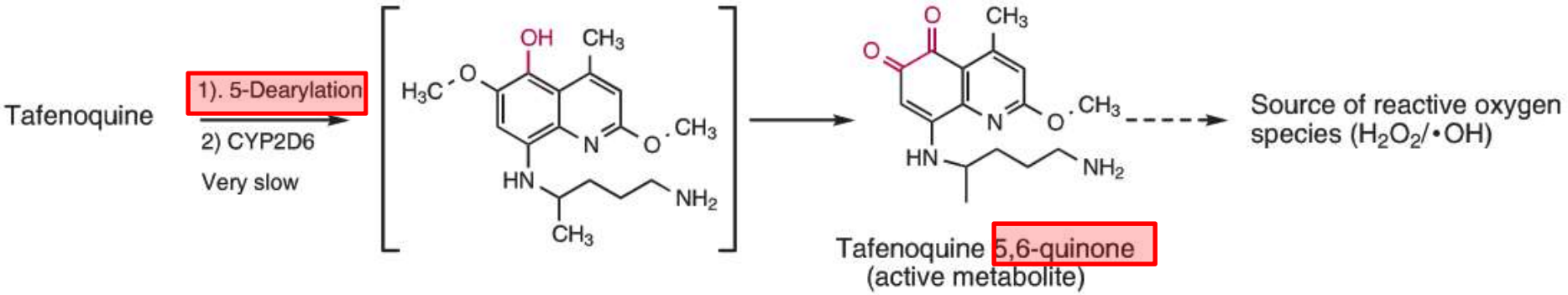
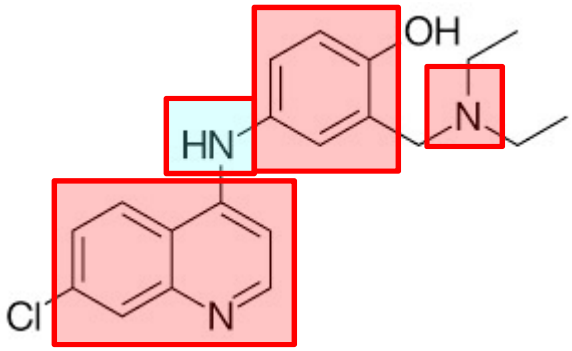


Figure 32.17 Metabolic activation of tafeoquine.

4-Amino-Quinoline: Amodiaquine

- Consider difference to original 4-aminoquinolines



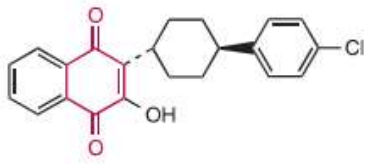
- Chemistry:
- ✓ 4-aminoquinoline
- ✓ 7-Cl
- ✓ possessing aromatic ring within two amines

Selective DHFRIs Against Plasmodium: Follow Next Slide

- Biguanides:

✓ proguanil (chloroguanide): in long term prophylaxis/ also was in use in CQ resistant strains of Plasmodium falciparum

✓ proguanil in combination with atovaquone



Atovaquone

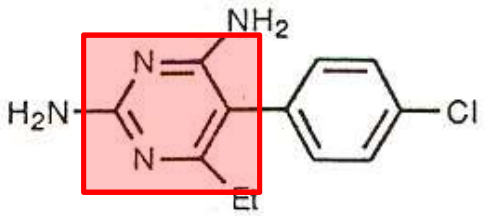
- Aryl-pyrimidine (aryl-diamino-pyrimidine):
- Pyrimethamine: tissue schizonticide (prophylaxis / prevent relapse)

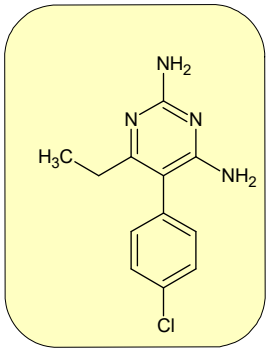
✓ pyrimethamine:sulfadoxine (1:20 = Fansidar): in prophylaxis of CQ resistant species; as 2nd choice in prophylaxis

✓ pyrimethamine:sulfadoxine:mefloquine (1:20:10): additive effect

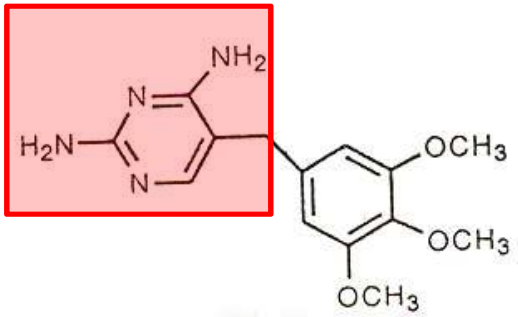
DHFRI: Aryl Pyrimidine & Biguanides

Pyrimethamine

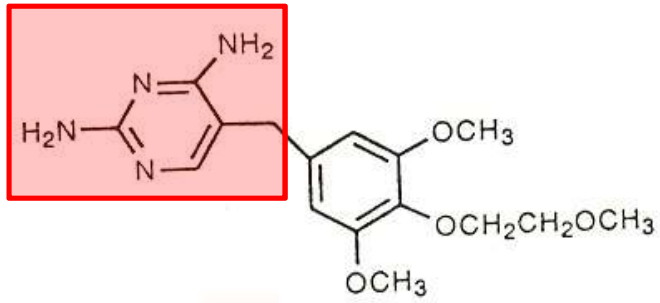




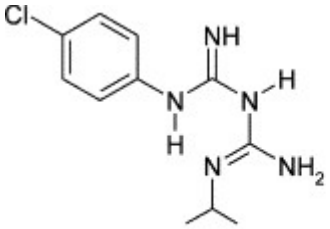
Trimethoprim



Tetroxoprim

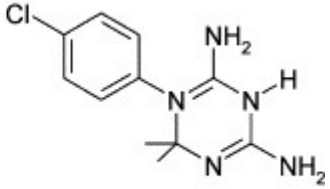


Proguanil

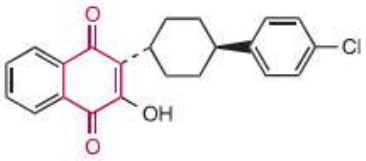


proguanil

Cycloguanil



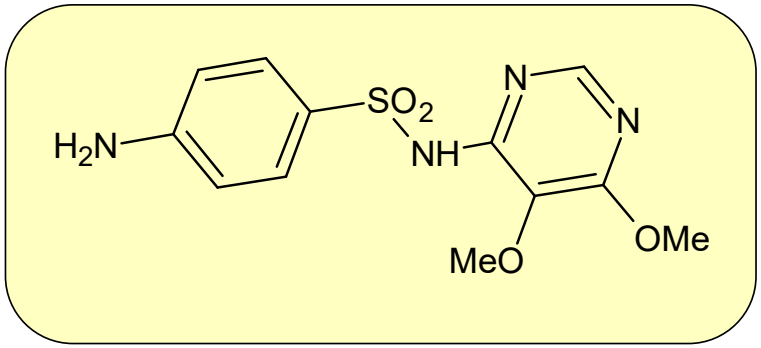
cycloguanil



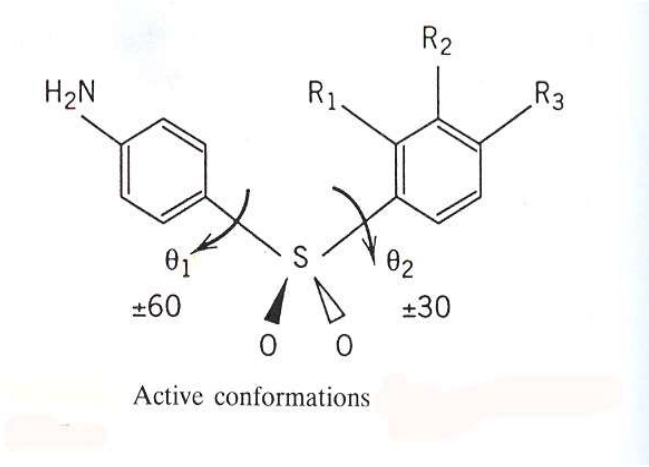
Atovaquone

Sulfonamides & Sulfones

- Sulfonamides: sulfadoxine
- ✓ only against erythrocytic site



- Sulfones: dapsone
- ✓ only against erythrocytic site

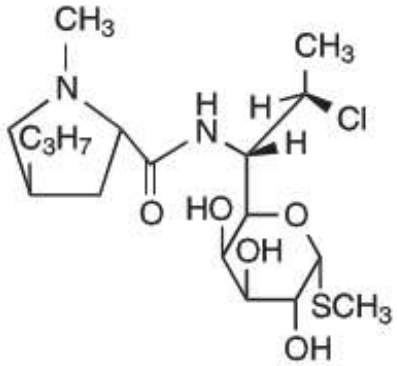


Miscellaneous Anti-Malarial ABs

Tetracycline

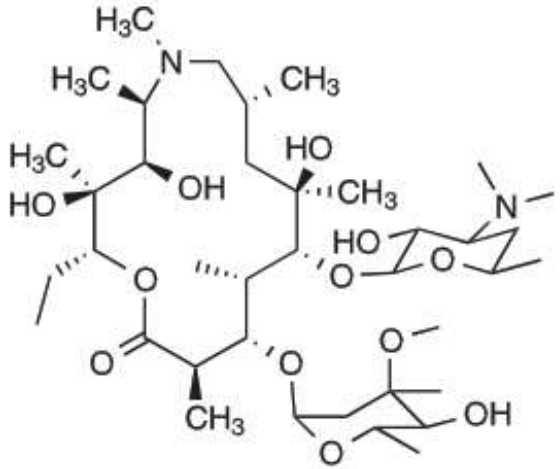
Doxycycline (Vibramycin)

Lincosamide



Clindamycin (Cleocin)

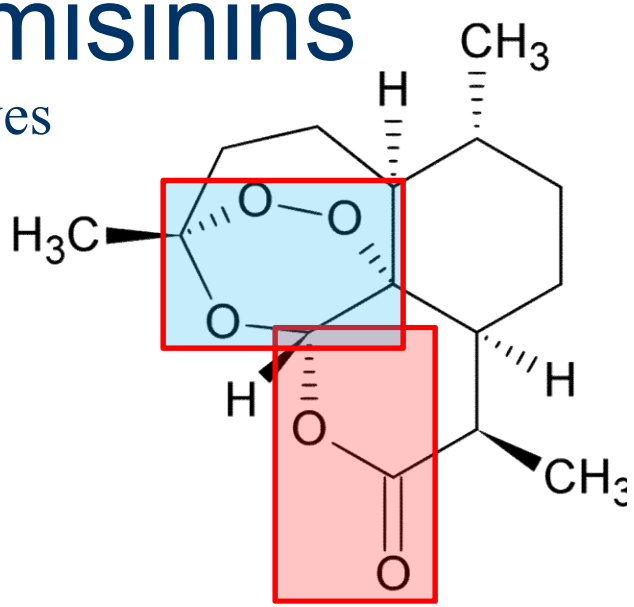
Macrolide

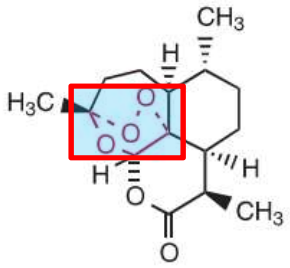


Azithromycin (Zithromax, Zmax)

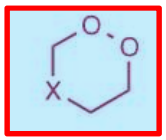
Sesquiterpenes: Artemisinins

- Chemistry: sesquiterpene lactone: salts & derivatives
- ✓ core nucleus: 1,2,4-trioxane; 1,2-dioxane
- ✓ derived from wormwood plant *qing hao*:
- ✓ applied in herbal Chinese medicine
- ✓ from *artemisia annua*
- Dosage forms: oral; IM; suppository
- MOA:
- Artemisinin-based Combination Therapy (ACT) in malaria therapy
- The 2015 Nobel Prize in Physiology & Medicine:
- ✓ development of artemisinin & dihydro-artemisinin in malaria therapy





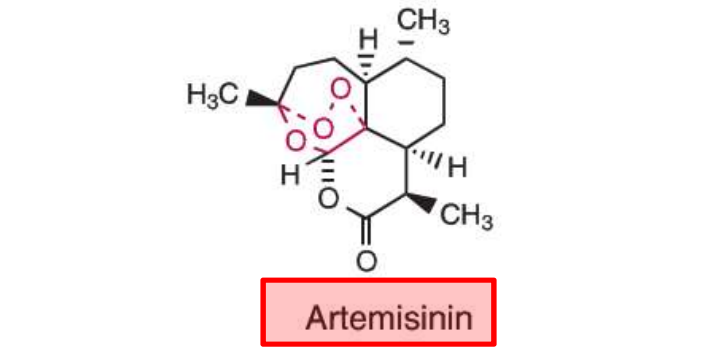
Artemisinin

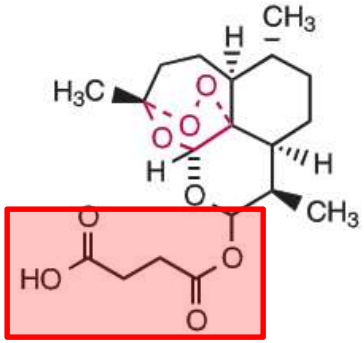


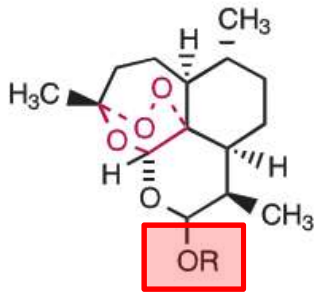
Core nucleus of the artemisinins
1,2,4-Trioxane (X = O)
1,2-Dioxane (X = CH_2) rings

Artemisinin Derivatives

- Compare water solubility of derivatives







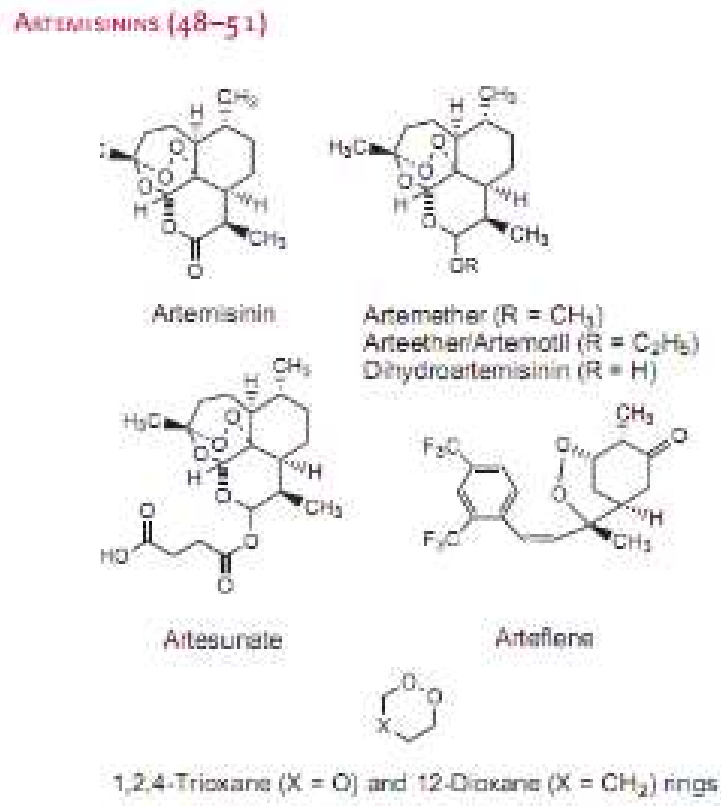
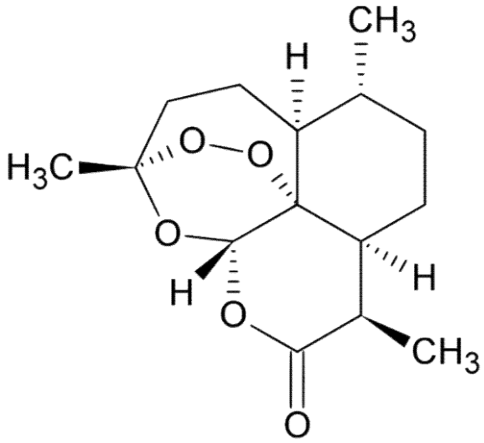


Figure 32.11 Structures of artemisinin and artemisinin derivatives.

MOA for Artemisinin & Derivatives



- Two proposed mechanisms:

1- free radical mechanism

not by ROS but by free radical mechanism

associated with endoperoxide involving a carbon radical

- ✓ heme in hemazoin form is a source of Fe^{2+}
- ✓ reacts with peroxide to generate oxy radical & Fe^{3+}: produce carbon radical

2- endoperoxide activation via iron dependent mechanism:

- ✓ activated artemisinin: targets sarcoplasmic/endoplasmic reticulum Ca-ATPase of the *Plasmodium falciparum*: altering Ca^{2+} stores
- ✓ form covalent adducts to specific membrane-associated proteins after concentrating in erythrocytes

Artemisinin Based Combined Dosage Forms in Anti-Malarial Drugs

Table 32.4 Artemisinins Used in Artemisinin-Based Combination Therapy (ACT)

Artemisinin	Second Component of ACT	Trade Name/ Alternative Name
Artemether	Lumefantrine	Coartem[a]
Artesunate	Amodiaquine	ASAOWinthrop
Artesunate	Mefloquine	ASMQ
Artesunate	Pyrimethamine/ Sulfadoxine	SPAQ-CO
Dihyroartemisinin	Piperquine	Eurartesim

[a]The only FDA-approved artemisinin in the United States.