Anti-Parasitic Agents:
Anti-Malarial Agents

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CHAPTER 32

Drugs Used to Treat Parasitic Infections

Thomas L. Lemke

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

TREATMENT OF MALARIA:

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

ANTIMALARIALS

- Artemisinins (arteether, artemether, artesunate, dihydroartemisinin)
- Atovaquone–proguanil
- Chloroquine
- Halofantrine
- Lumefantrine
- Mefloquine
- Pyrimethamine
- Quinine

Drug Classification for Anti-malarial Agents

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

Life Cycle for Malarial Protozoa

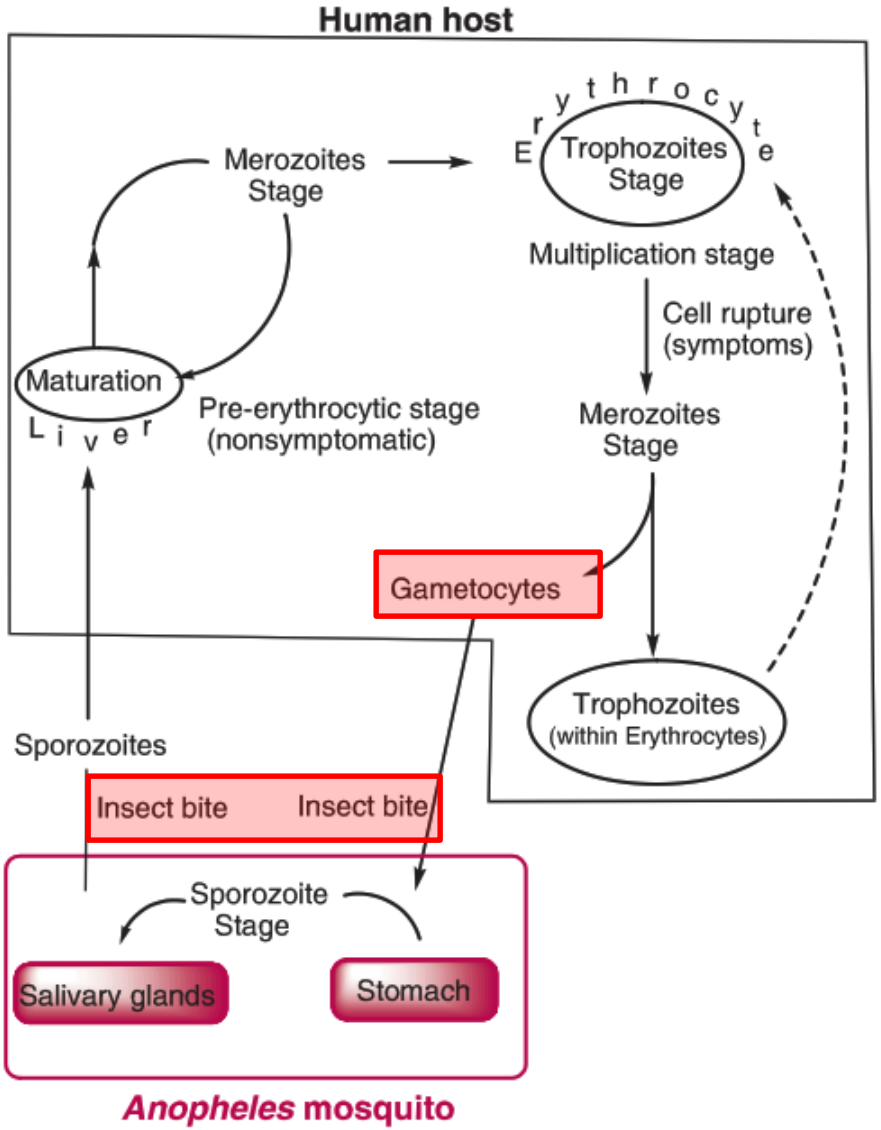


Figure 32.1 Life cycle of malarial protozoa.

Life Cycle for Plasmodium

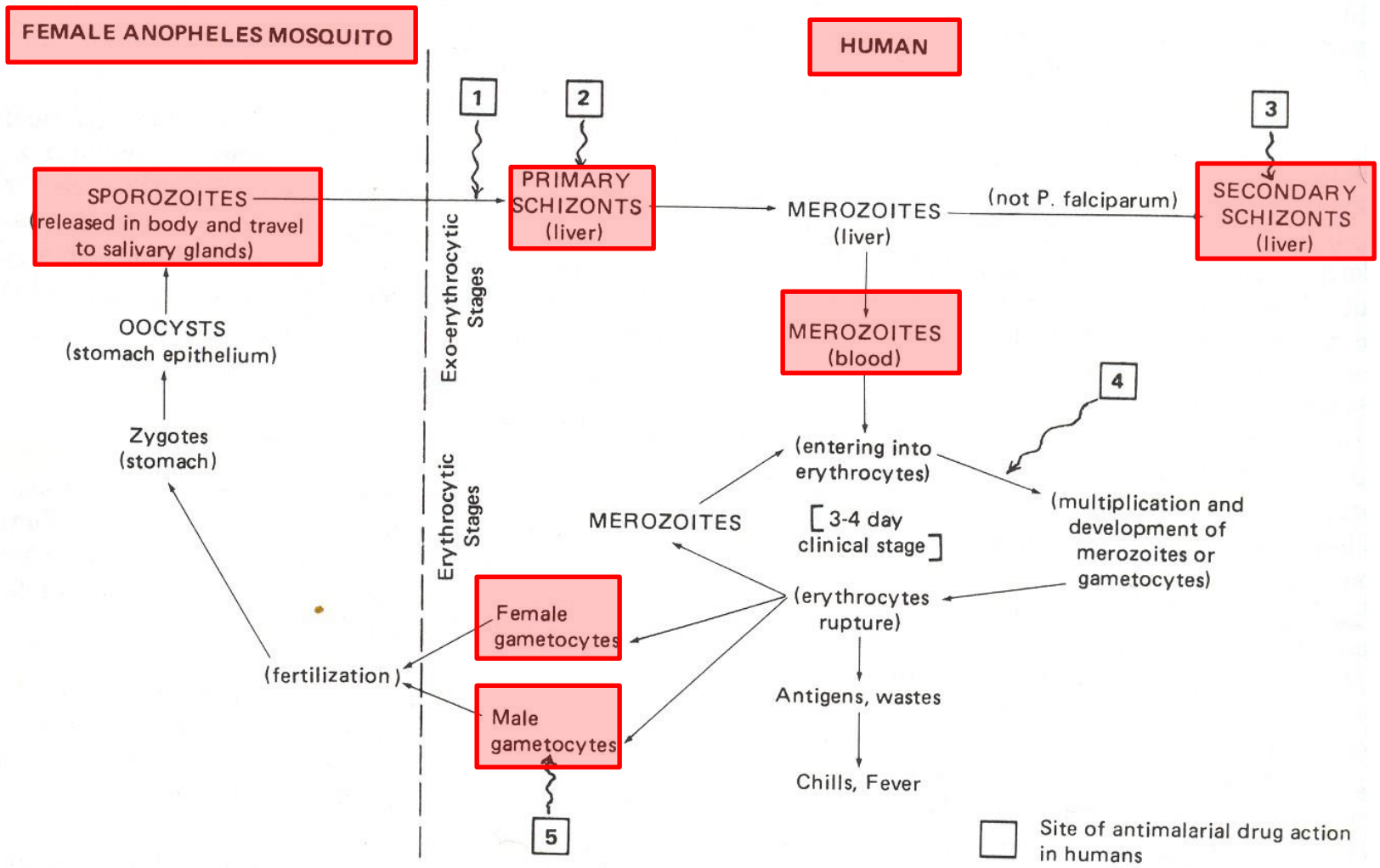


FIG. 6-1. *Life cycle of Plasmodium: (1) sporozoitocide — no drugs effective; (2) primary (exoerythrocytic) schizonticide — primaquine, pyrimethamine, chloroguanide, cycloguanil pamoate; (3) secondary (exoerythrocytic) schizonticide — primaquine; (4) erythrocytic schizonticide (fast-acting — chloroquine,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

- Wilson & Gisvold's 1991-p206

Sites of Action for Anti-malarial Agents in Plasmodium Parasite

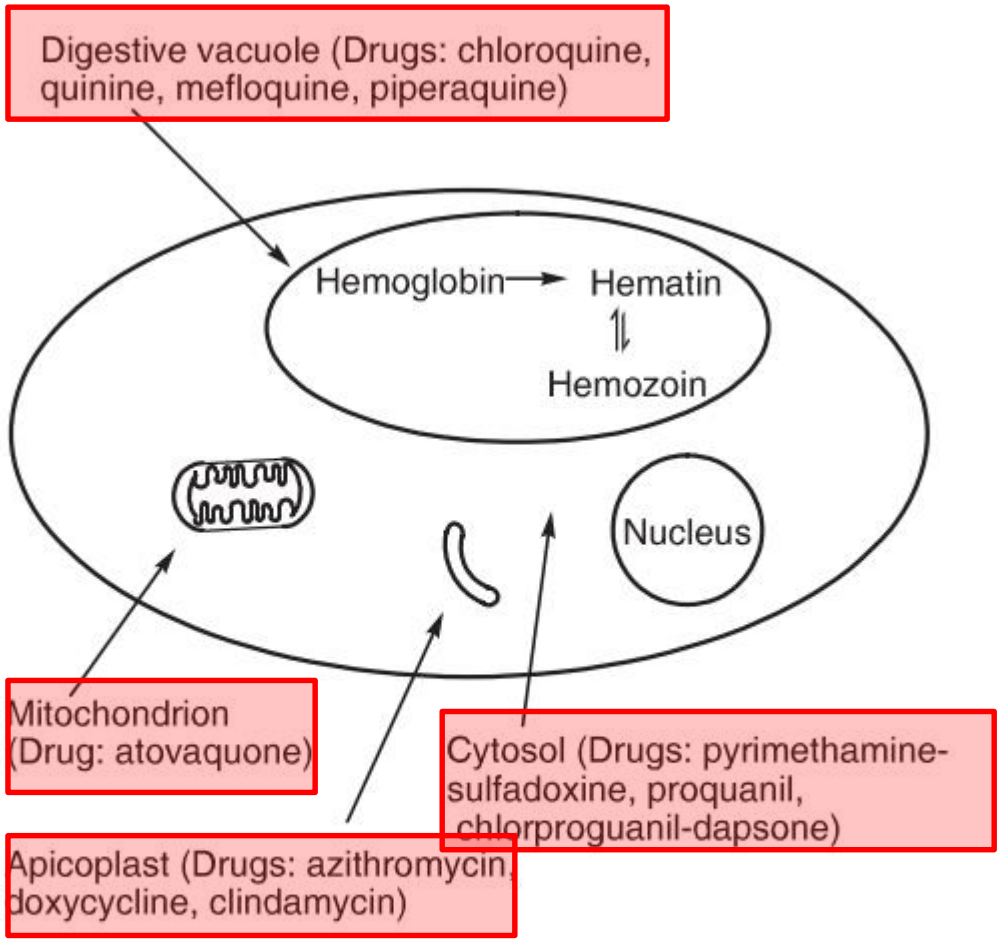


Figure 32.12 *Plasmodium* parasite cell as present within the erythrocyte and sites of drug action.

Proteolytic Degradation of Hemoglobin by Plasmodium

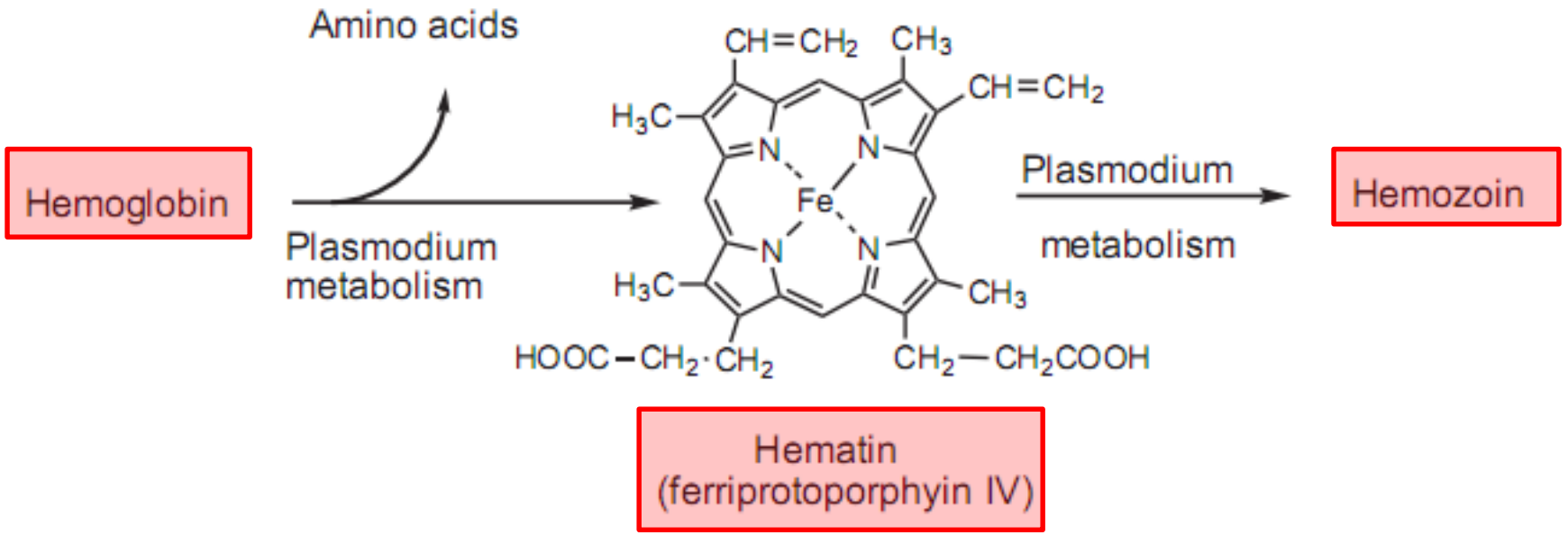


FIGURE 34.14 Proteolytic degradation of hemoglobin by the *Plasmodium* organism to the potentially toxic hematin and then to the nontoxic dimer hemozoin.

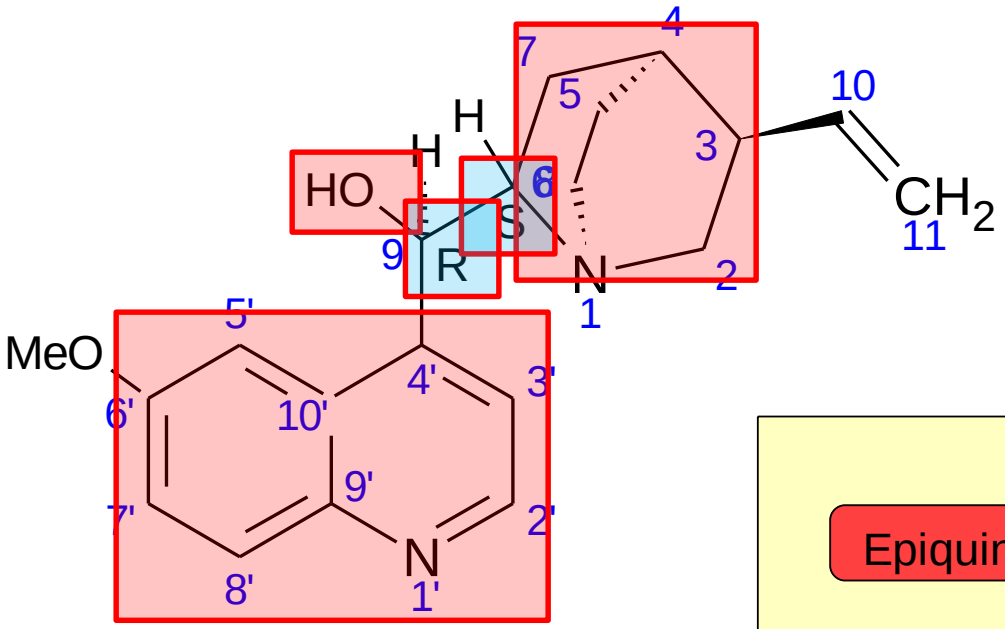
Sites of MOA for Anti-malarial Agents

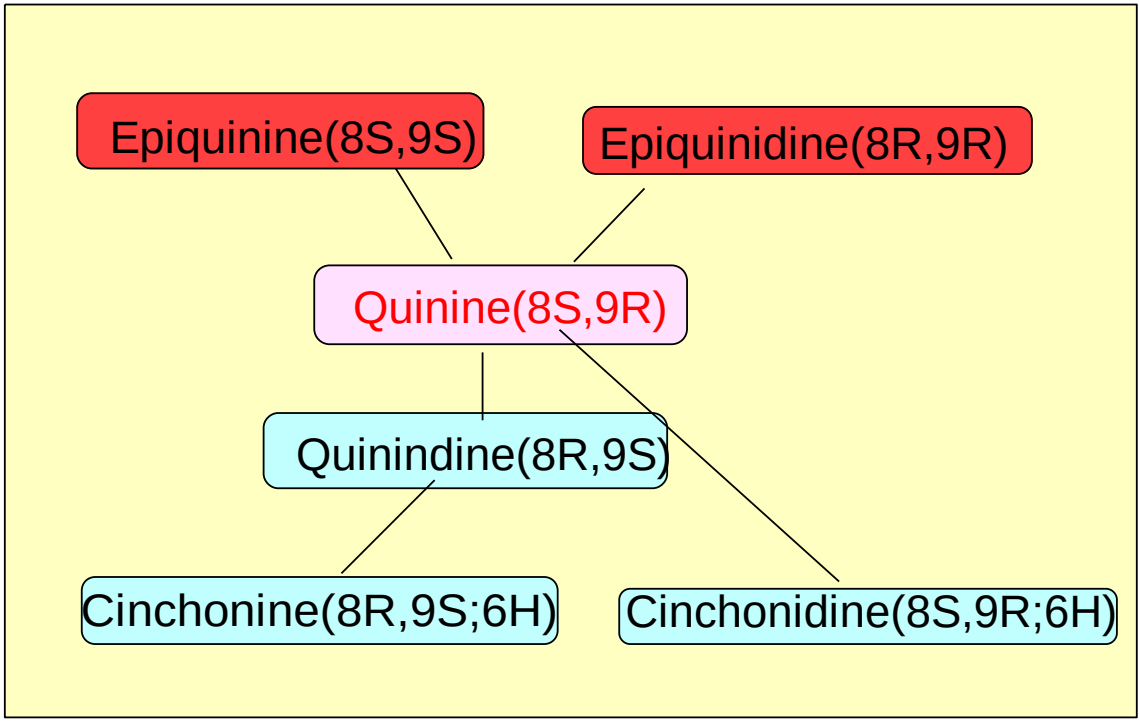
- DNA intercalation:
  - ✓ quinoline-methanols
  - ✓ Acridines
  - ✓ 4-amino-quinolines
  - ✓ 8-amino-quinolines
- Dihydrofolate reductase inhibitors:
  - ✓ trimethoprim, pyrimethamine
- Dihydropteroate synthase inhibitors:
  - ✓ sulfadoxine, dapsone
- Protein synthesis inhibitors:
  - ✓ tetracyclines, others…
- Free radical mechanism & endoperoxide activation: alter Ca^{2+} stores
  - ✓ sesquiterpene lactone

Chemical Classifications of Anti-malarial Agents

- 4-Quinoline-methanols
- Acridines: 9-amino-acridine: quinacrine
- 4-amino-quinolines
- 8-amino-quinolines
- Artemisines: sesquiterpene lactones
- Biguanides
- Diaminopyrimidines
- Imidazole
- Lincosamides
- Macrolides
- 1,4-naphthoquinones
- Sulfonamides
- Sulfones
- Tetracyclines
- Miscellaneous

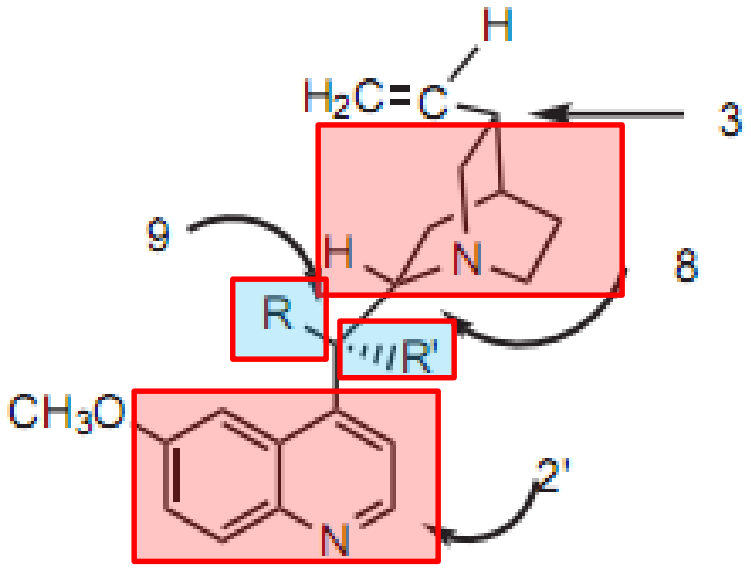
Quinoline Methanols



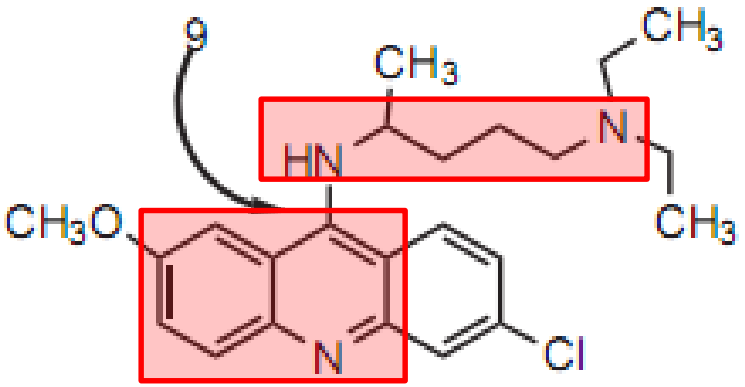


Quinoline-Methanols: Chemistry & SAR

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



Quinine (R = OH, R' = H)
Quinidine (R = H, R' = OH)



Quinacrine

Modification to Get New Simple Anti-malarial Agents

Development of Anti-malarial Agents Following Quinine as Lead Compound

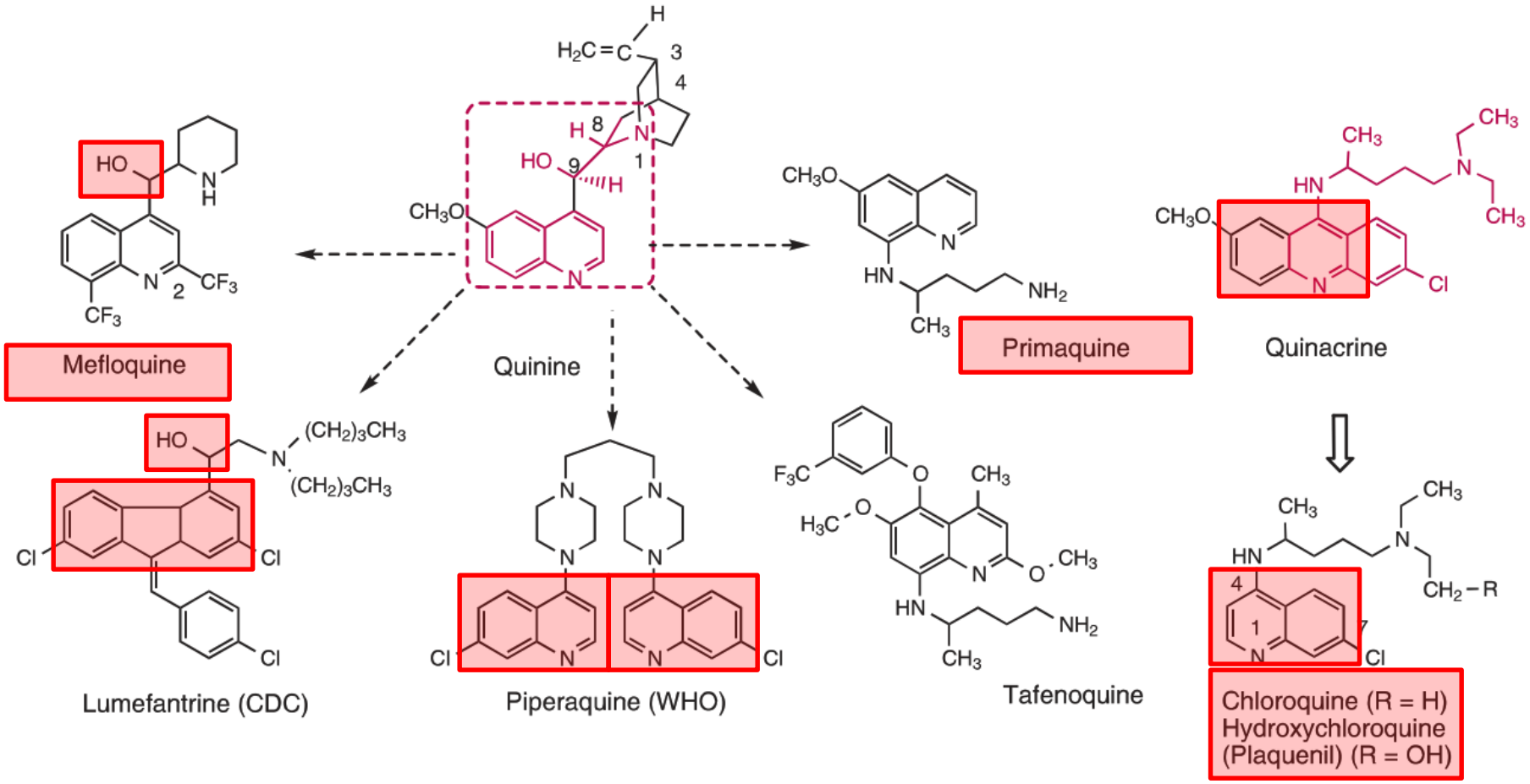


Figure 32.10 Structure similarity between the lead antimalarials (quinine and quinacrine) and the available antimalarials. *CDC*, Center for Disease Control; *WHO*, World Health Organization.

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

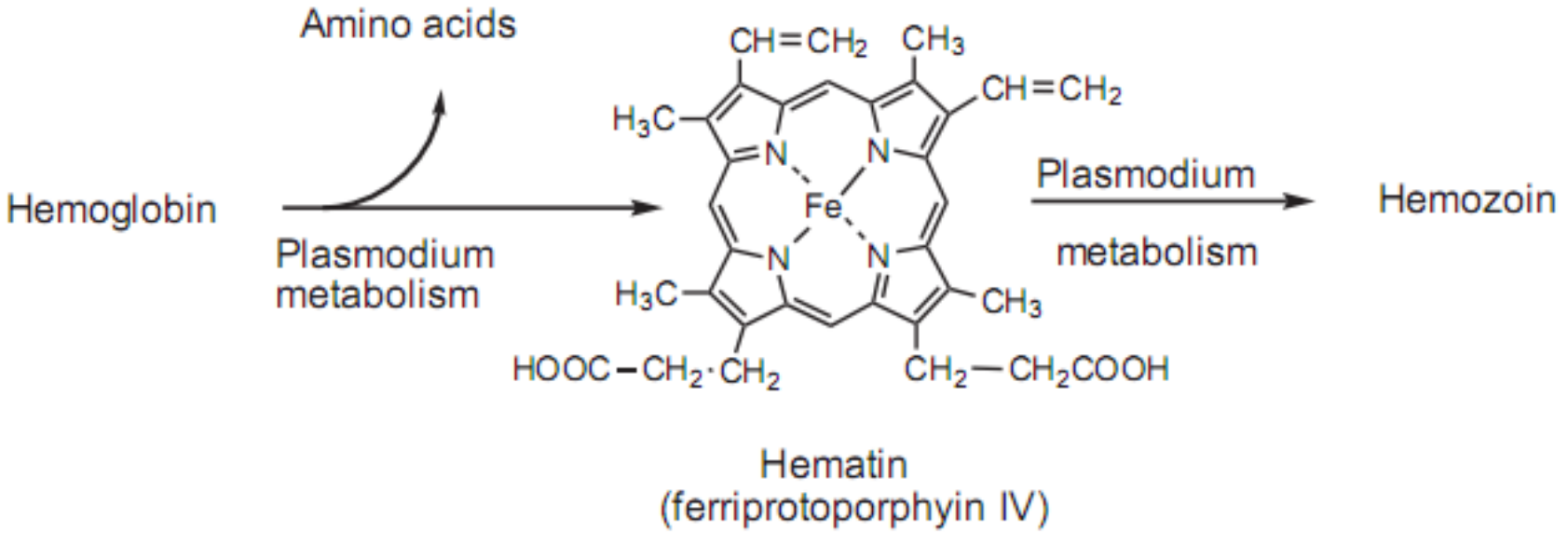


FIGURE 34.14 Proteolytic degradation of hemoglobin by the *Plasmodium* organism to the potentially toxic hematin and then to the nontoxic dimer hemozoin.

Metabolism of Primaquine

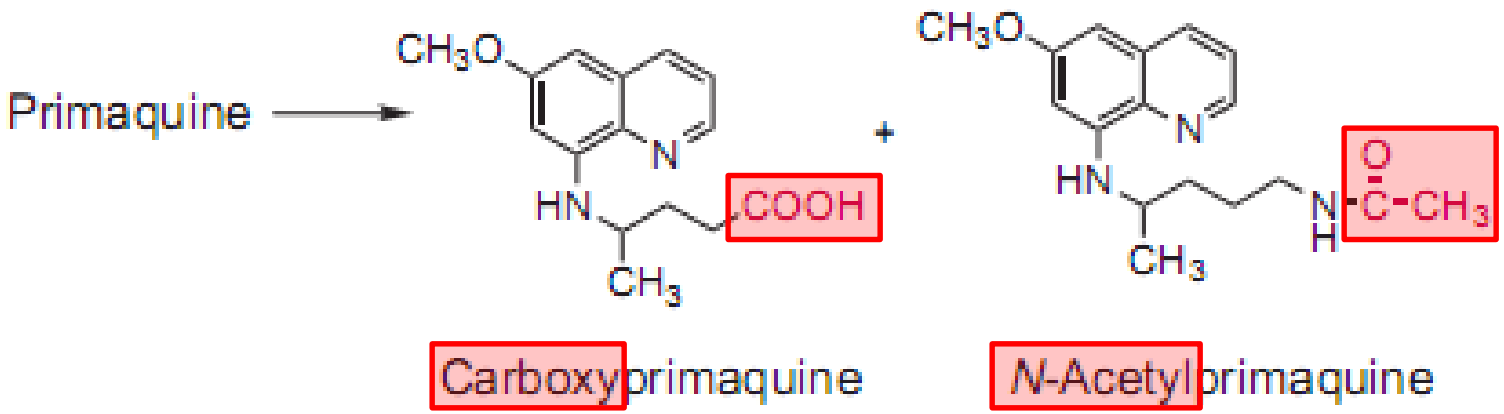


FIGURE 34.17 Metabolism of primaquine.

Metabolism for Piperaquine

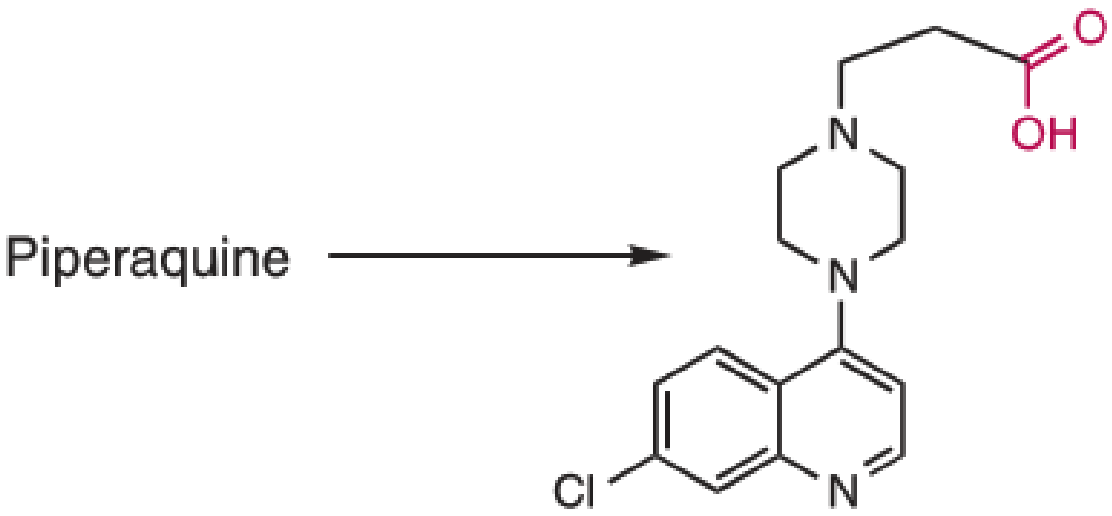
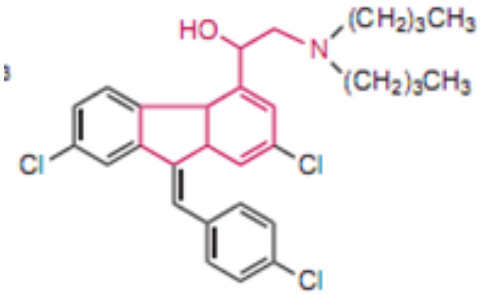


Figure 32.15 Metabolism of piperaquine.

Lumefantrine: Chemistry & MOA

- Chemistry: modified aryl methanols:
- ✓ Ring: fluorene

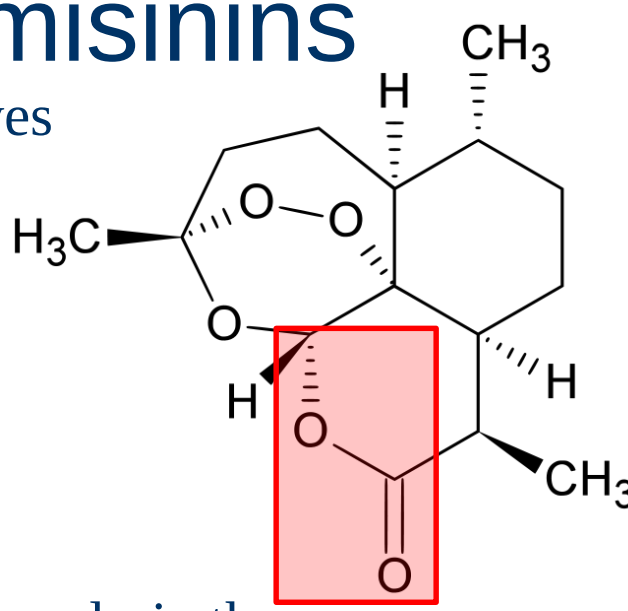


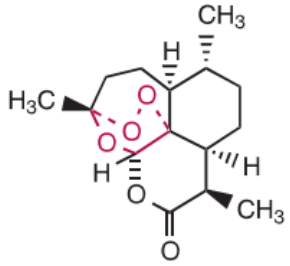
Lumefantrine

- Fat soluble: after fat meal has better oral absorption.
- MOA:
- ✓ erythrocytic schizonticide
- ✓ in combination with artemether (artemisinin)

Sesquiterpenes: Artemisinins

- Chemistry: sesquiterpene lactone: salts & derivatives
- ✓ 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



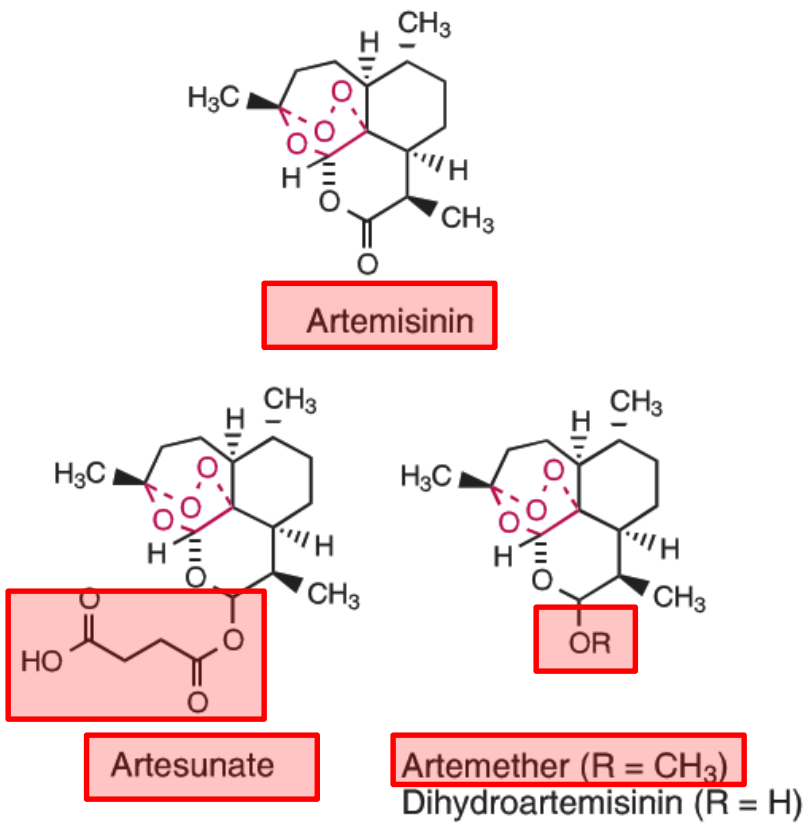


Artemisinin

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



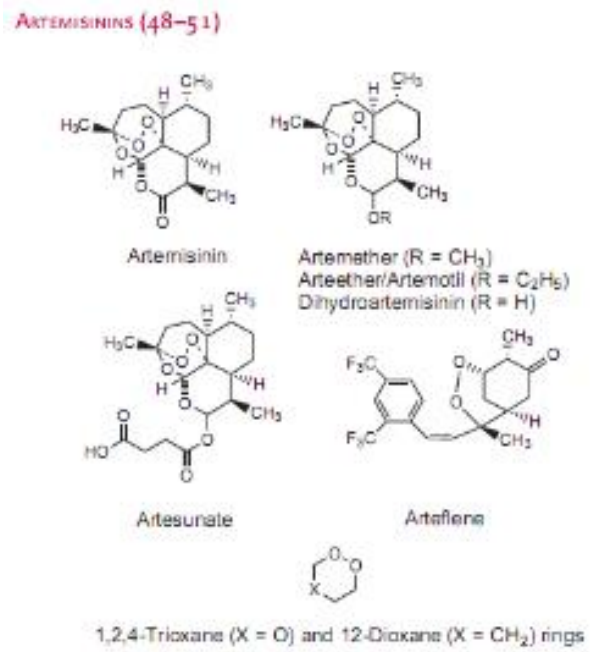
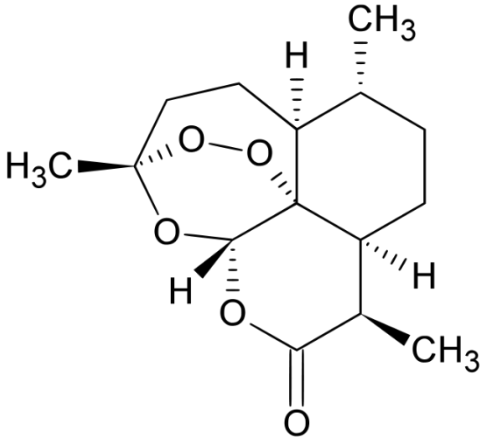


Figure 32.11 Structures of artemisinin and artemisinin derivatives.

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