

Quinolines

Introduction

- Quinolines are a group of synthetic antimicrobial agents primarily used in the treatment and prophylaxis of malaria and other protozoal infections.
- They differ from fluoroquinolones, which are used against bacterial infections. Quinolines act mainly by interfering with heme detoxification in parasites or DNA replication, depending on the specific agent.
- Many quinoline derivatives are antimalarial agents, widely used in both blood and tissue stages of *Plasmodium* species.
- Some members of this class are also active against amoebiasis and other protozoal diseases.

Classification

1. 4-Aminoquinolines

- Chloroquine
- Hydroxychloroquine
 - → Act on **blood schizonts** of *Plasmodium* species

2. 8-Aminoquinolines

- Primaquine
- Tafenoquine
 - → Active against **liver stages** (hypnozoites) of *P. vivax* and *P. ovale*

3. Quinoline-Methanols

- Quinine
- Quinidine
 - Used in **severe falciparum malaria**

4. Related Quinoline Derivatives

- Mefloquine
- Lumefantrine (used in combination therapy with artemether)

Note: **Fluoroquinolones** (e.g. ciprofloxacin) are structurally related but primarily antibacterial, not antimalarial. They are discussed separately.

Mechanism of Action

1. Chloroquine and related agents:

- Act by accumulating in the parasite's food vacuole.
- Inhibit the polymerization of toxic heme (from hemoglobin digestion) into non-toxic hemozoin.

- Accumulation of free heme is toxic to the parasite → leads to oxidative damage and parasite death.

2. Primaquine (8-aminoquinolines):

- Generates reactive oxygen species (ROS) that damage parasite mitochondria.
- Active against liver stages and gametocytes.

3. Quinine and Mefloquine:

- Similar to chloroquine in interfering with heme detoxification, but exact mechanism is not fully understood.

Pharmacokinetics (ADME)

Chloroquine:

- **Absorption:** Well absorbed orally
- **Distribution:** Extensive tissue binding (especially in liver, spleen)
- **Half-life:** Long (1–2 months)
- **Excretion:** Renal

Primaquine:

- **Absorption:** Good oral bioavailability
- **Metabolism:** Hepatic
- **Excretion:** Renal
- **Half-life:** ~4–6 hours

Quinine:

- **Absorption:** Rapid oral absorption
- **Distribution:** Wide
- **Metabolism:** Hepatic (CYP3A4)
- **Excretion:** Renal

Mefloquine:

- **Absorption:** Oral; well absorbed
- **Half-life:** Long (~20 days)
- **Metabolism:** Liver
- **Excretion:** Bile and feces

Pharmacodynamics

- Stage-specific activity:
 - **Chloroquine, quinine, mefloquine:** Blood schizonticides

- **Primaquine, tafenoquine:** Tissue schizonticides (liver stage)
- **Rapid onset** with chloroquine and quinine
- **Slow onset** with mefloquine due to long half-life

Therapeutic Uses

Chloroquine:

- **Treatment of uncomplicated malaria** caused by *P. vivax*, *P. ovale*, *P. malariae*
- **Prophylaxis** in areas with chloroquine-sensitive strains
- **Extraintestinal amoebiasis**
- **Autoimmune diseases:** Lupus, rheumatoid arthritis (hydroxychloroquine)

Primaquine:

- Radical cure of *P. vivax* and *P. ovale* (kills liver hypnozoites)
- **Gametocidal** against all Plasmodium species
- **Prophylaxis** in some cases

Quinine:

- Severe falciparum malaria
- Chloroquine-resistant malaria
- Often combined with doxycycline or clindamycin

Mefloquine:

- Prophylaxis and treatment of chloroquine-resistant falciparum malaria

Tafenoquine:

- Similar to primaquine, used for radical cure and prophylaxis

Adverse Effects

Chloroquine:

- GI upset, headache, pruritus
- High doses: retinal toxicity, cardiotoxicity
- Long-term use: retinopathy (monitor vision)

Primaquine:

- GI distress
- Hemolysis in G6PD-deficient patients (screen before use)
- Methemoglobinemia

Quinine:

- **Cinchonism:** Tinnitus, headache, nausea, dizziness
- Hypoglycemia
- Hypotension (IV use)
- Hemolysis (rare)

Mefloquine:

- Neuropsychiatric effects: anxiety, depression, hallucinations
- GI disturbances
- Contraindicated in psychiatric disorders

Contraindications

Chloroquine:

- Retinal or visual field abnormalities
- Psoriasis

Primaquine / Tafenoquine:

- G6PD deficiency
- Pregnancy (due to fetal hemolysis risk)

Mefloquine:

- History of seizures or psychiatric illness

Quinine:

- Hypersensitivity
- Avoid in **pregnancy** unless benefit outweighs risk (can be used for severe malaria)

Drug Interactions

Chloroquine:

- Inhibits CYP2D6
- May increase plasma levels of digoxin and cyclosporine

Quinine:

- Interacts with **warfarin, digoxin, and antacids**
- Risk of QT prolongation with other QT-prolonging drugs

Mefloquine:

- Additive CNS toxicity with other psychotropic drugs
- Increases risk of seizures with anticonvulsants

Primaquine:

- Additive hemolysis risk with sulfa drugs
- Interacts with myelosuppressive agents

Dose and Route of Administration

Chloroquine phosphate (oral):

- **Treatment:** 600 mg base initially, then 300 mg base at 6, 24, and 48 hours
- **Prophylaxis:** 500 mg once weekly (starting 1–2 weeks before travel)

Primaquine (oral):

- 15 mg base once daily for 14 days (P. vivax/ovale radical cure)
- Screen for G6PD deficiency before administration

Quinine sulfate (oral):

- 600 mg every 8 hours for 7 days
- Used with doxycycline or clindamycin

Quinine dihydrochloride (IV):

- 20 mg/kg loading dose, then 10 mg/kg every 8 hours

Mefloquine (oral):

- **Treatment:** 1250 mg single dose (split into two doses 6–8 hrs apart)
- **Prophylaxis:** 250 mg once weekly, start 1–2 weeks before travel

Tafenoquine (oral):

- 300 mg once weekly for prophylaxis
- 300 mg daily for 3 days for radical cure (followed by weekly dosing)



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