Overview of DoD Antimalarial Use Policies

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Outline

- Historical Perspective
- Specific Medications
- DoD Policies
- Ethical Issues
- Epidemiologic Challenges

Historical Perspective—Malaria

- WWII: 695,000 cases
  - Pacific theater, Italy
  - Rate exceeded 4/person/year in the Pacific
- Korea: 390,000 cases
  - Malaria rate 600/1000/year
  - 3000+ vivax cases in returning troops
- Viet Nam: 50,000 cases
  - Hospital admissions: 27/1000/year
  - 2000+ vivax cases (1970) in returning troops
- Somalia: 48 cases, 243 vivax cases after return
- Afghanistan: 300 cases 2008-2017

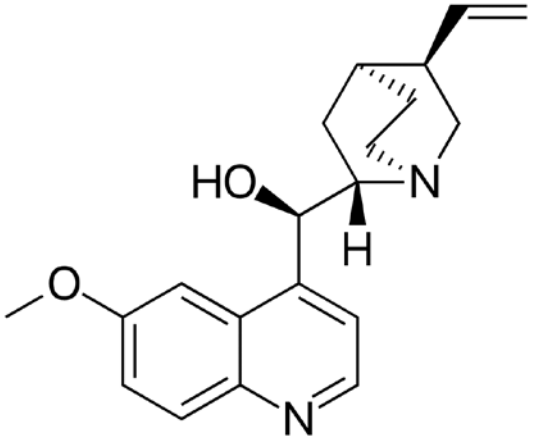
Anti-malarials (year introduced)

- Quinine sulfate (1632)
- Mepraquine (Quinacrine or Atabrine) (1942)
- Chloroquine (1945)*
- Primaquine (1946)*
- Hydroxychloroquine (1955)
- Diaminodiphenyl sulfone (Dapsone) (1966)
- Doxycycline (1967)*
- Sulfadoxine-pyrimethamine (Fansidar) (1967)*
- Halofantrine (Halfan) (1975)*
- Mefloquine (Larium) (1977)*
- Atovaquone-Proguanil (Malarone) (1997)*
- Tafenoquine (2018)*

* IND with FDA filed by DoD Anti-malarial drug program

Quinine

- First used to treat malaria in Rome (1631)
- Extracted from bark of the cinchona tree
- Allies lost supply (Java) during WWII, spurring development of alternatives



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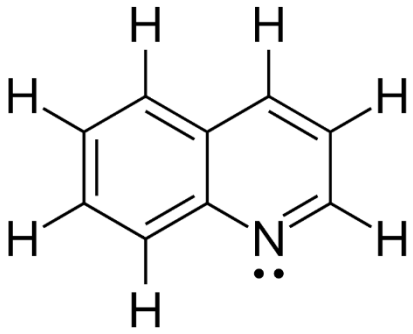
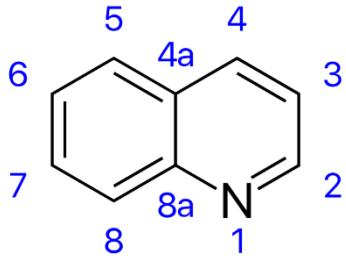
Quinolines

Quinoline





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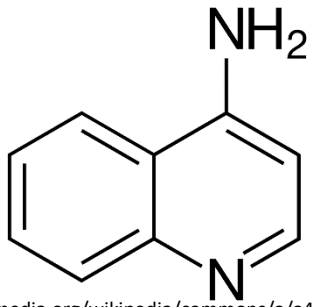
4-amino quinoline
(Chloroquine)



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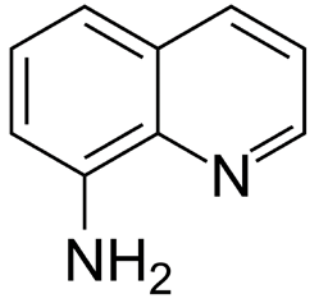
8-amino quinoline
(Primaquine,
Tafenoquine)



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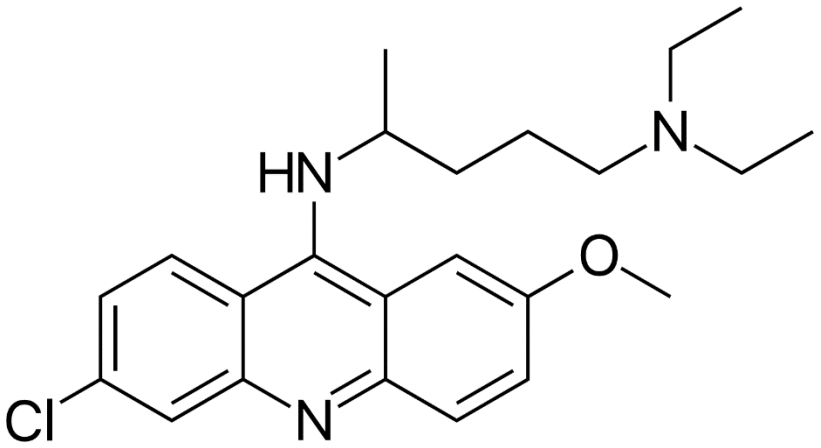
Mepraquine/Quinacrine/Atebrine

- Developed by Germany (Bayer) in 1931
- First substitute for quinine
- Toxicity and dosing difficulty limited utility
- Used during WWII by Allied and Axis forces



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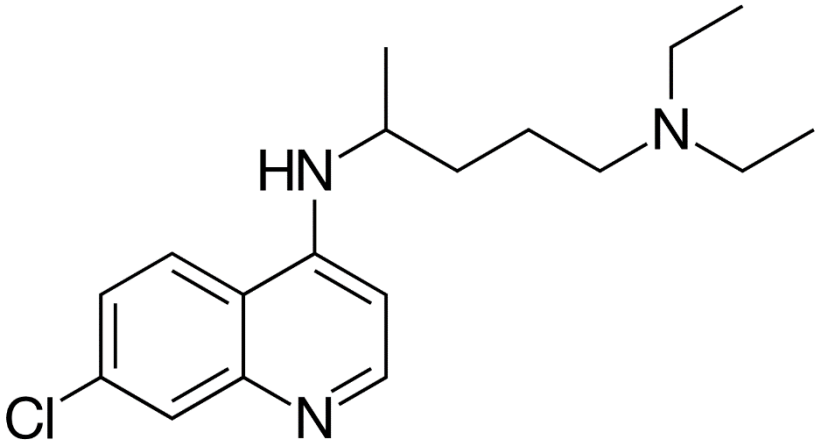
Chloroquine

- Synthetic alternative to quinine
- Lower toxicity, weekly dosing
- Introduced at the end of WWII
- Class: 4-aminoquinolone
- Resistance widespread by 1960s



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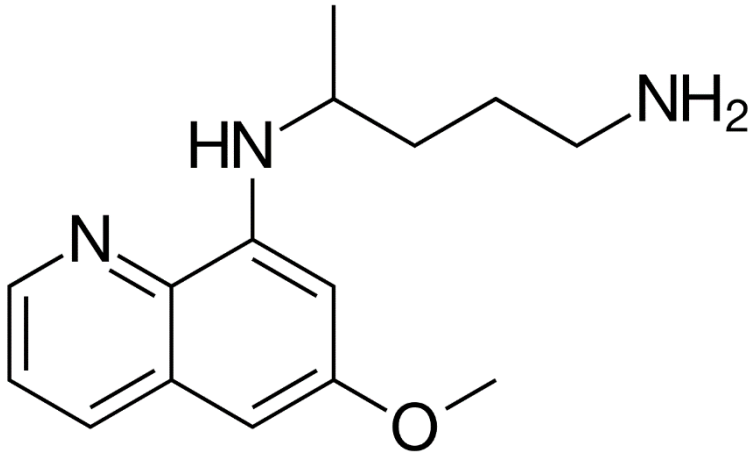
Primaquine

- Active against tissue forms of *P.vivax* and *P. ovale*
- Class: 8-aminoquinolone
- Associated with hemolysis (G6PD deficiency)
- Combined with chloroquine (*CP tablets*) as prophylactic (Viet Nam)



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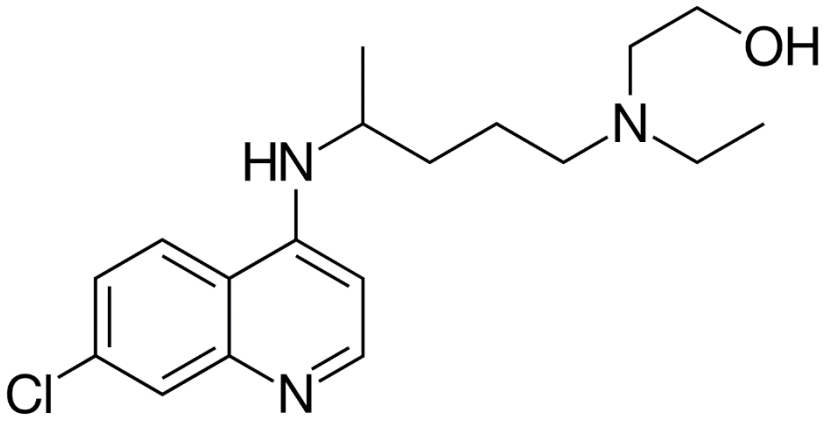
Hydroxychloroquine (Plaquenil)

- Primarily used as in treatment of rheumatologic disorders
- Similar profile to chloroquine
- Class: 4-aminoquinolone



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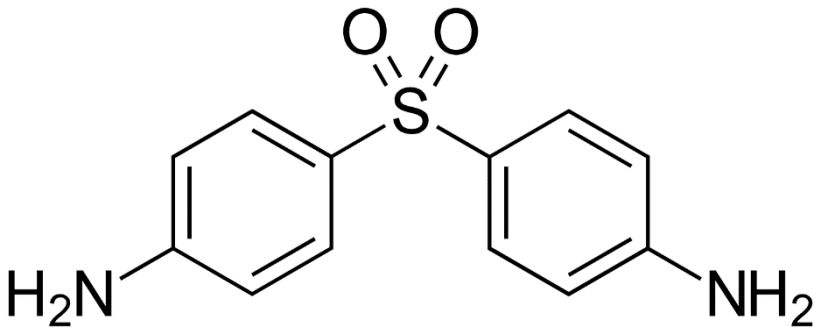
Diaminodiphenyl sulfone (Dapsone)

- Developed as an antibiotic in 1930s
- Used for treatment of leprosy
- Used prophylactically in conjunction with C-P tablets (suspected risk of chloroquine-resistant P. falciparum) during Viet Nam War
- Associated with hemolytic anemia (G6PD deficient)



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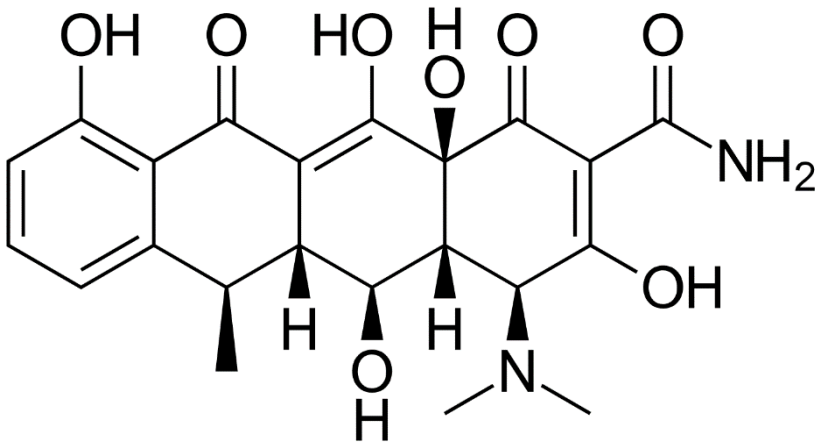
Doxycycline

- Broad spectrum antibiotic (tetracycline class)
- Class shown to be effective against drug-resistant malaria (1970s)
- New Drug Application for prophylaxis (1994)
- Limited by gastrointestinal side effects, photosensitivity, adherence (daily dosing)
- Primary prophylactic medication for OIF (2003-2007), OEF (2001-present)



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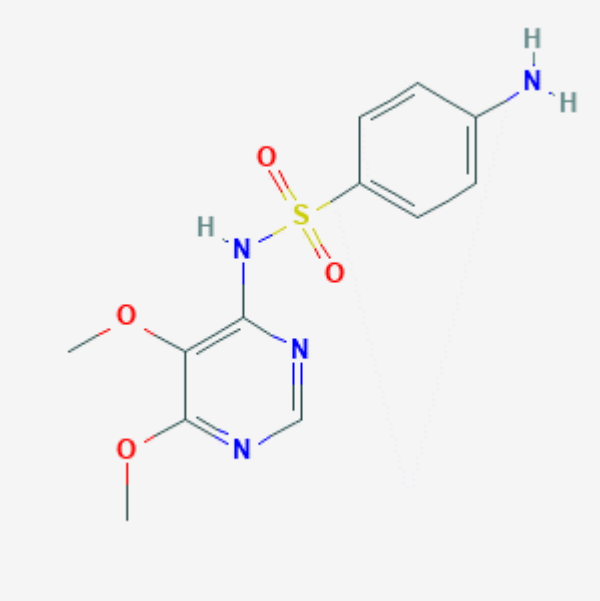
Sulfadoxine-pyrimethamine (Fansidar)

- Combination agent (sulfa plus anti-protazoal
- Limited by toxicity (hypersensitivity, Stevens-Johnson syndrome)
- No history of use as a prophylactic agent by DoD (treatment only)



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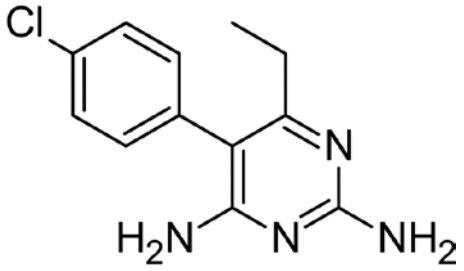

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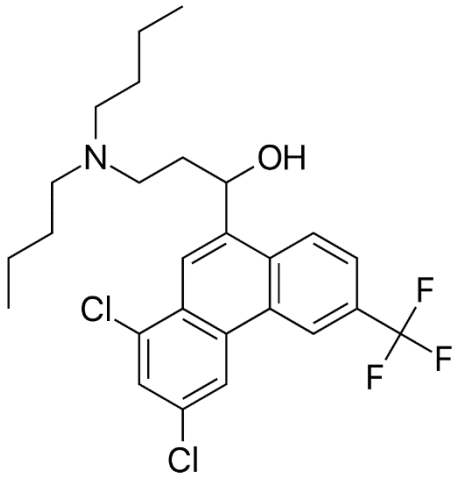
Halofantrine (Halofan)

- Developed for the Walter Reed Army Institute of Research (WRAIR)
- Indicated only for treatment, not prophylaxis
- Associated with cardiotoxicity, similar to quinidine (QT prolongation)



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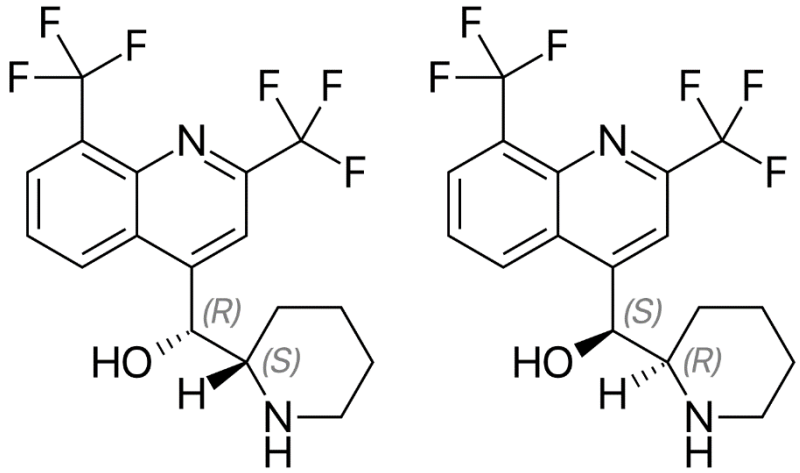
Mefloquine

- Developed at WRAIR during Viet Nam, transferred to La Roche/Smith-Kline
- FDA approved for prophylaxis 1989
- Used as second line agent (OIF/OEF) for prophylaxis
- Primary prophylactic agent for certain high-risk deployments (Liberia/Africa) prior to development of Malarone
- Current use limited to those who cannot tolerate other drugs



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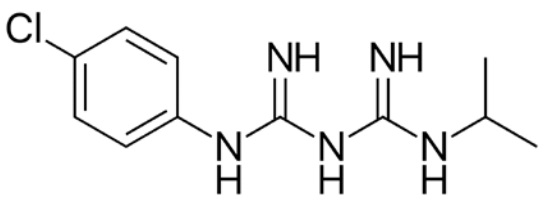
Atovaquone-Proguanil (Malarone)

- Combination agent against parasitic mitochondria
- Class: 2-hydroxynaphthoquinone
- Approved for treatment and prophylaxis in 1999
- Recommended, along with doxycycline, as first line agent prophylaxis in areas of chloroquine resistance
- Far fewer side effects than other anti-malarials
- First line agent for military personnel in Afghanistan (OEF)



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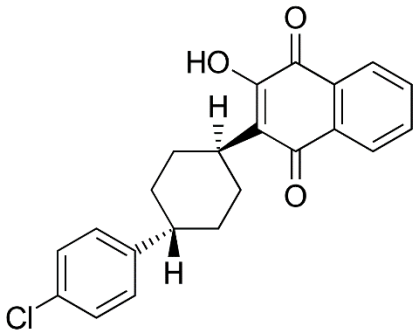

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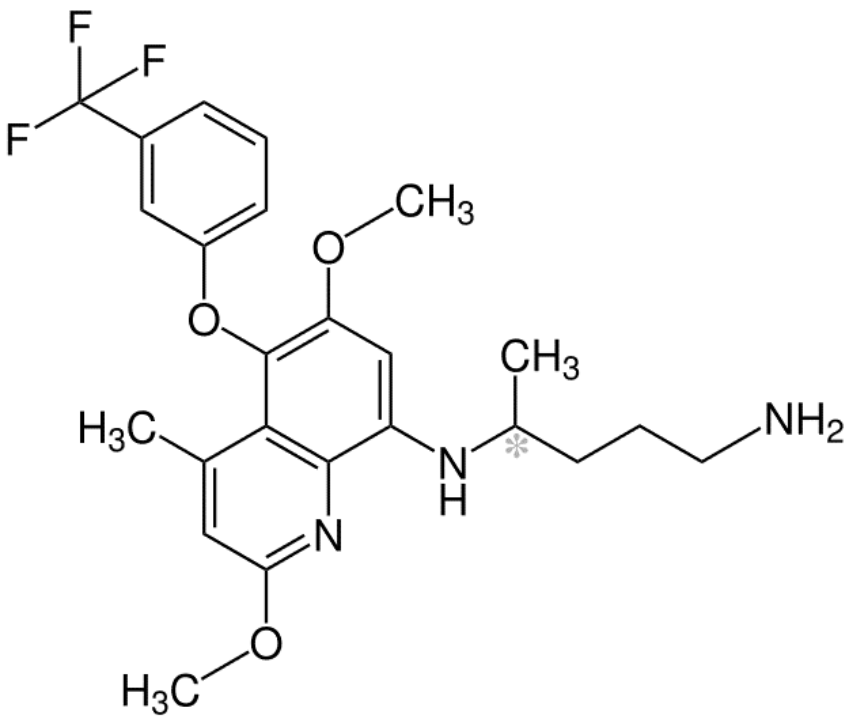
Tafenoquine

- Received FDA approval for prophylactic use in 2018
- Class: 8-aminoquinolone (like primaquine)
- Active against tissue and blood forms
- Contraindicated in G6PD deficiency



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DoD Policy
Malaria Prophylaxis

- DoD issues guidance through Health Affairs (HA)
  - HA Policy 13-002 “Guidelines on Medications for Prophylaxis of Malaria” (April 2013)
  - HA Policy 09-017 “Policy Memorandum on the Use of Mefloquine (Larium) in Malaria Prophylaxis (September 2009)
- Geographic Combatant Commanders set requirements for entry
  - Based on HA policy
  - Example: CENTCOM Individual Protection and Individual Unit Deployment Policy (Modification 13)

DoD Policy
Non-FDA Approved Medical Products

DoD Policy 6200.02 (February 2008)

- Covers medications, immunizations, devices
- Requires approval from Health Affairs when used for Force Protection purposes
- Must be accomplished through
  - Emergency Use Authorization
  - Investigational New Drug/Device application

Causal Criteria (adapted from Hill)

- Strength of association
- Consistency of effects
- Specificity between a single exposure and a unique effect
- Temporality
- Dose response
- Experimental evidence
- Biologic plausibility
- Coherence
- Analogy

Challenges to Establish Causation: Long term effects from anti-malarials

- Accurate assessment of exposure (who, when, how much, for how long)
- Objectively definable, measurable case definition
- Assessment of those exposed but who did not experience an adverse outcome
- Long time delay between exposure and effects
- Potential confounding factors (age, gender, other anti-malarials, other medications, other medical conditions)

Conclusions

- The DoD is committed to providing the best protection available to Service members and their families
- The DoD fully supports FDA efforts to evaluate risk and safety of approved and investigational medical products

Contact Information

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