Unit-2
Medicinal Chemistry - III

B.Pharma 6th Sem Notes

Unit: 2

Antibiotics

Historical background, Nomenclature, Stereochemistry, Structure activity relationship, Chemical degradation classification and important products of the following classes.

- Macrolide: Erythromycin Clarithromycin, Azithromycin.
- Miscellaneous: Chloramphenicol*, Clindamycin.
- Prodrugs: Basic concepts and application of prodrugs design.
- Antimalarials: Etiology of malaria. Quinolines: SAR, Quinine sulphate, Chloroquine*, Amodiaquine, Primaquine phosphate, Pamaquine*, Quinacrine hydrochloride, Mefloquine. Biguanides and dihydro triazines: Cycloguanil pamoate, Proguanil.
- Miscellaneous: Pyrimethamine, Artesunete, Artemether, Atovoquone.

Macrolide Antibiotics:

Introduction:

- Macrolide antibiotics are a class of drugs that inhibit bacterial protein synthesis, primarily used to treat mild to moderate bacterial infections.
- They are known for their broad spectrum of activity against many gram-positive bacteria and some gram-negative bacteria.
- Common macrolides include erythromycin, azithromycin, and clarithromycin.
- The macrolides are a class of natural products that consist of a large macrocyclic lactone ring to which one or more deoxy sugars, usually cladinose and desosamine, may be attached.
- The lactone rings are usually 14-, 15-, or 16-membered.
- Macrolides belong to the polyketide class of natural products.

History:

- They were first discovered in the early 1952s, beginning with **Erythromycin**, isolated from *Streptomyces erythraeus* (now *Saccharopolyspora erythraea*).
- Developed as an alternative to **penicillin**, especially useful in **penicillin-allergic patients**.
- Later macrolides developed, including azithromycin and clarithromycin, stemmed from chemically modifying erythromycin; these compounds were designed to be more easily absorbed and have fewer side-effects (erythromycin caused gastrointestinal side-effects in a significant proportion of users).

Classification:

Macrolides

- Erythromycin
- Clarithromycin
- Azithromycin
- Roxithromycin
- Spiramycin

Ketolides

- Telithromycin

Mechanism of action:

- Macrolides are protein synthesis inhibitors.
- The mechanism of action of macrolides is inhibition of bacterial protein biosynthesis, and they are thought to do this by preventing peptidyltransferase from adding the growing peptide attached to tRNA to the next amino acid (similarly to chloramphenicol as well as inhibiting bacterial ribosomal translation. Another potential mechanism is premature dissociation of the peptidyl-tRNA from the ribosome.
- Macrolide antibiotics do so by binding reversibly to the P site on the 50S subunit of the bacterial ribosome. This action is considered to be bacteriostatic.
- Macrolides are actively concentrated within leukocytes, and thus are transported into the site of infection.

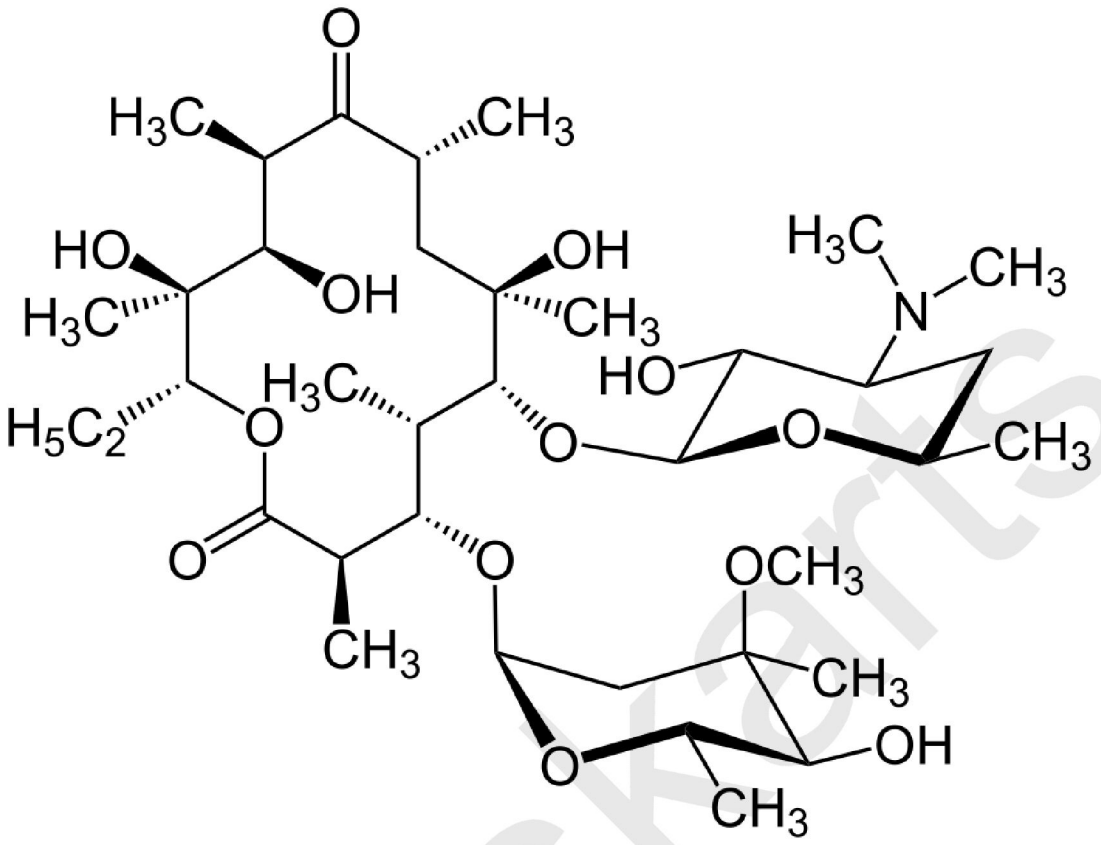
Uses:

- They are used to treat infections caused by Gram-(+) bacteria (Streptococcus pneumoniae) and limited Gram-(-) bacteria (Bordetella pertussis, Hoemophilus influenzae), and some respiratory tract and soft-tissue infections, Legionella pneumophila, mycoplasma, mycobacteria, some rickettsia, and chlamydia.

Structure of Macrolide Antibiotics:

They are characterized by five common chemical features

1. A macrocyclic lactone usually has 12-17 atoms, hence the name macrolide.
2. A ketone group.
3. One or two amino sugars glycosidically linked to the nucleus.
4. A neutral sugar linked either to amine sugar or to nucleus.
5. The presence of dimethyl amino moiety on the sugar residue, which explains the basicity of these compounds, and the formation of salts.



Erythromycin

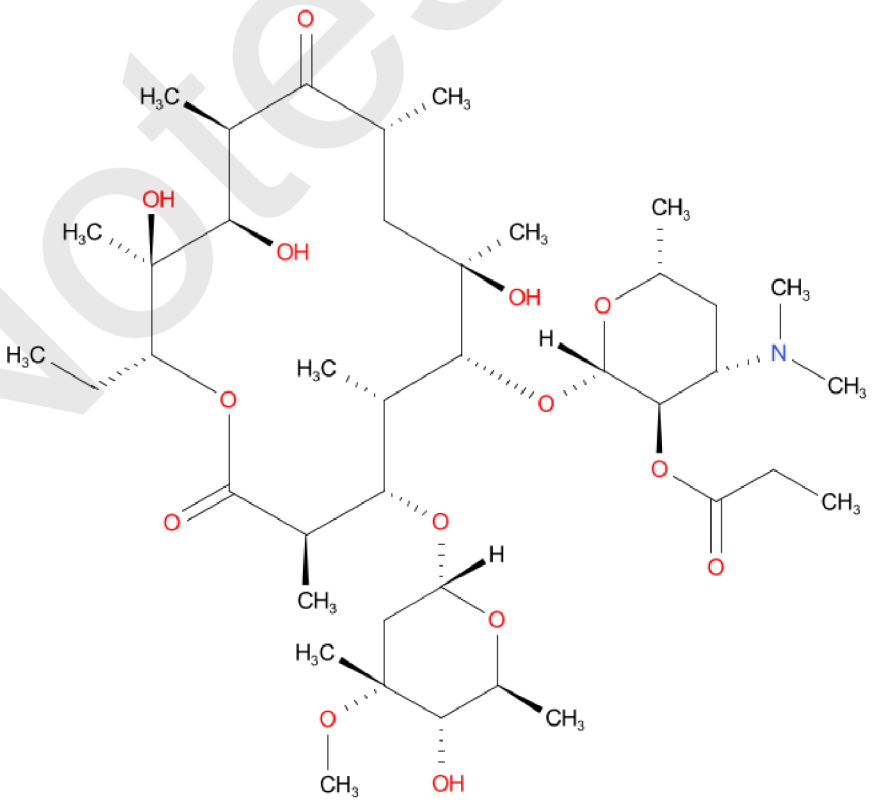
Introduction

- Erythromycin is the first macrolide antibiotic discovered in **1952**, produced by *Streptomyces erythraeus*.
- It consists of a **14-membered lactone ring** with attached deoxy sugars (desosamine and cladinose).
- It is a **broad-spectrum antibiotic**, effective against **Gram-positive bacteria** and some Gram-negative bacteria.
- It is mainly used as an alternative in patients allergic to **penicillin**.

Mechanism of Action

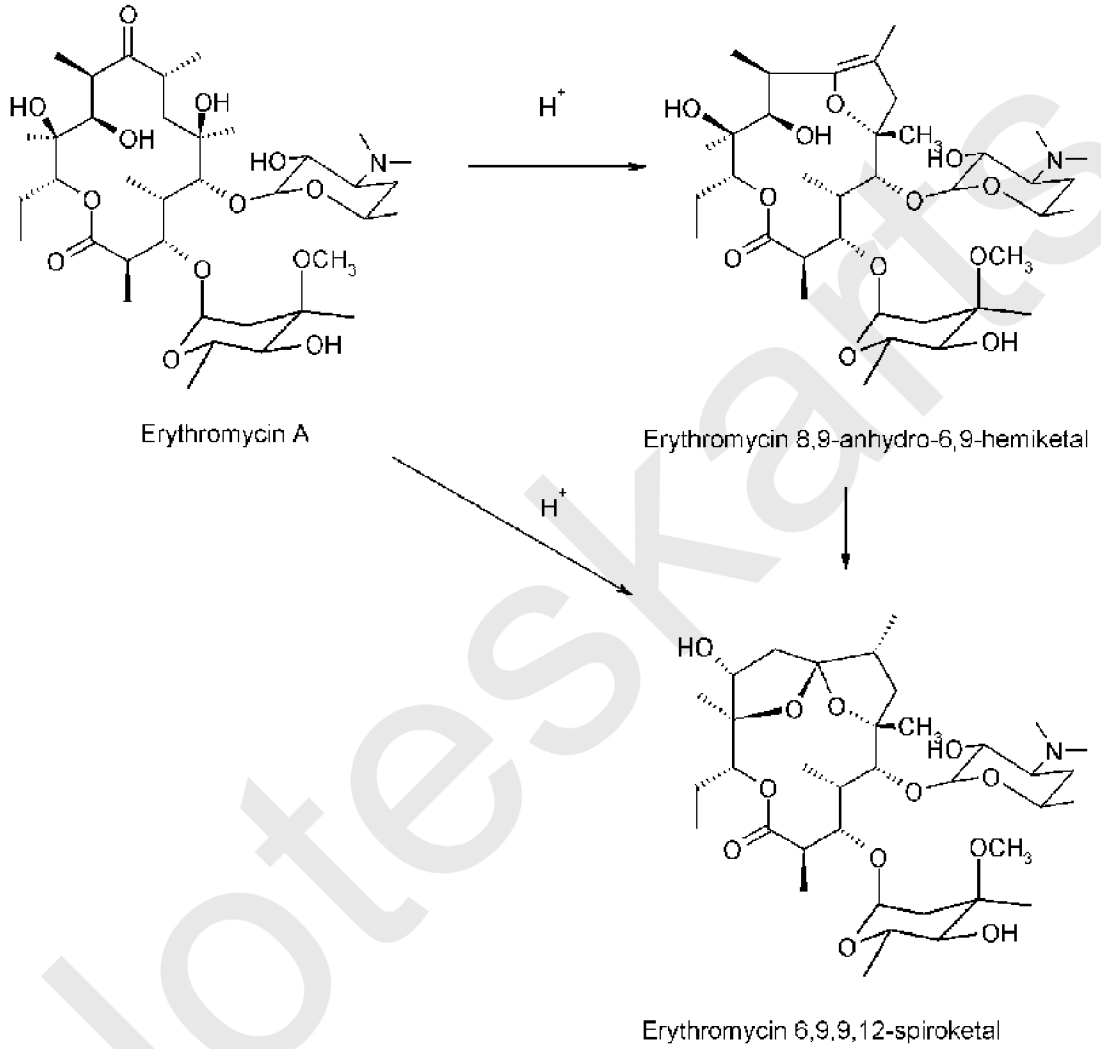
- Erythromycin binds to the **50S ribosomal subunit** of bacteria.
- It **inhibits translocation of peptidyl-tRNA** from the acceptor site to the donor site during protein synthesis.
- This prevents elongation of the peptide chain → leading to **inhibition of bacterial protein synthesis**.
- It is **bacteriostatic**, but at high concentrations can be bactericidal.

Structure of Erythromycin



Acid Degradation of Erythromycin

Erythromycin degradation, under acid conditions, results in intramolecular cyclizations yielding the biologically inactive hemi-and spiroketals. Two main products are shown as examples.



Uses

- **Respiratory tract infections**: pneumonia, bronchitis, pertussis (whooping cough).
- **Skin and soft tissue infections**: acne, cellulitis.
- **Sexually transmitted diseases**: chlamydia, syphilis (in penicillin-allergic patients).
- **Diphtheria and pertussis prophylaxis**.
- **Mycoplasma pneumonia** treatment.
- **Alternative to penicillin** in allergic patients.

Adverse Drug Reactions (ADR)

- **Gastrointestinal irritation** (nausea, vomiting, abdominal cramps, diarrhea) due to motilin receptor stimulation.
- **Hepatotoxicity**: cholestatic hepatitis (especially with estolate form).
- **Ototoxicity**: reversible hearing loss in high doses.
- **Cardiac effects**: prolongation of QT interval → risk of arrhythmia (torsades de pointes).
- **Drug interactions**: inhibits **CYP3A4 enzyme**, increasing toxicity of drugs like theophylline, carbamazepine, warfarin.

Clarithromycin

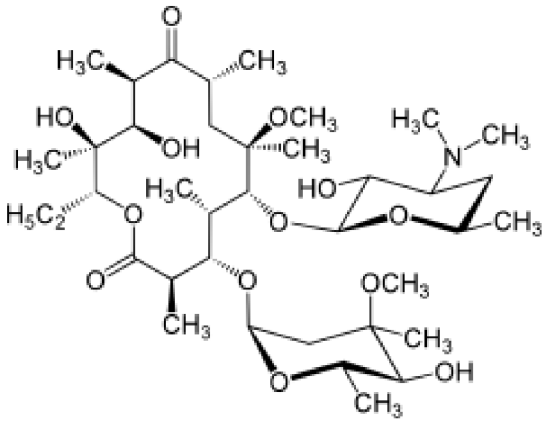
Introduction

- Clarithromycin is a **semisynthetic macrolide antibiotic**, made by modifying erythromycin.
- It has a **14-membered lactone ring** like erythromycin but with a **methyl group at position 6 (C6-OH → OCH_3)**.
- This small change makes it **more stable in acid** and **better absorbed** than erythromycin.
- It is active against **Gram-positive and Gram-negative bacteria**.

Mechanism of Action

- Works similar to erythromycin.
- Binds to the **50S subunit of bacterial ribosome**.
- Stops **protein synthesis** by blocking the translocation step.
- This prevents bacteria from growing → **bacteriostatic** (stops growth), but in higher dose can be **bactericidal** (kills bacteria).

Structure



Advantages of Clarithromycin over Erythromycin

1. **Better acid stability** → does not degrade in stomach acid.
2. **Higher oral bioavailability** → better absorbed from stomach.
3. **Longer half-life** → needs to be taken only **twice daily** (erythromycin requires 4 times).
4. **Less stomach irritation** (milder GI side effects).
5. **More potent** against some bacteria (e.g., *Mycobacterium avium complex*).

Uses

- **Respiratory infections**: pneumonia, bronchitis, sinusitis, tonsillitis.
- **Skin infections**: acne, cellulitis.
- **Helicobacter pylori infection** (part of triple therapy for peptic ulcer).
- **Mycobacterial infections** (*Mycobacterium avium complex* in AIDS patients).
- **Alternative in penicillin allergy** (e.g., throat infections).

Azithromycin

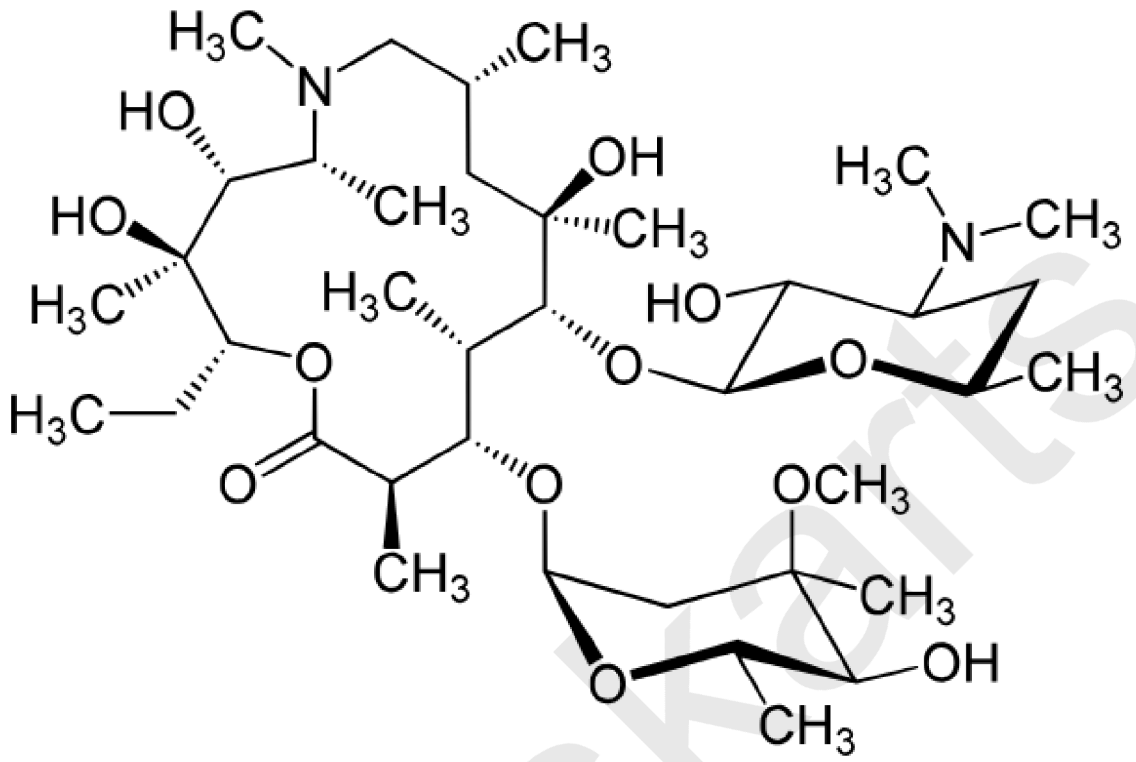
Introduction

- Azithromycin is a **semisynthetic macrolide antibiotic**, derived from erythromycin.
- Unlike erythromycin (14-membered ring), azithromycin has a **15-membered lactone ring** (called an **azalide**, because one nitrogen atom is inserted in the ring).
- It is **more stable in acid**, **better absorbed**, and has a **longer half-life** than erythromycin.
- Needs to be taken **once daily** → improves patient compliance.

Mechanism of Action

- Binds to the **50S ribosomal subunit** of bacteria.
- Blocks **translocation of peptides** → stops **bacterial protein synthesis**.
- Works as **bacteriostatic**, but at higher doses can be **bactericidal**.

Structure



Uses

- **Respiratory tract infections**: pneumonia, bronchitis, sinusitis, pharyngitis.
- **Skin and soft tissue infections**: acne, impetigo.
- **Sexually transmitted diseases**: chlamydia, gonorrhea.
- **Typhoid fever** (alternative to fluoroquinolones).
- **Traveler's diarrhea**.
- **Mycobacterium avium complex (MAC) infections** in HIV/AIDS patients.

Miscellaneous: Chloramphenicol*, Clindamycin

Chloramphenicol

Introduction

- Chloramphenicol is a **broad-spectrum antibiotic**.
- It was the **first antibiotic to be produced synthetically** on a large scale.

- It is highly effective but its use is limited due to serious toxicity (especially **bone marrow suppression**).

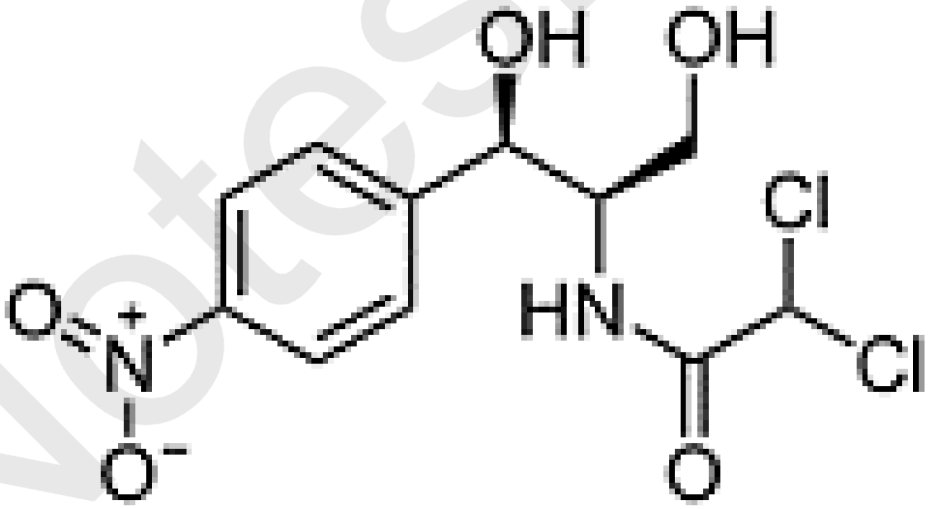
Historical:

- Discovered in **1947** from *Streptomyces venezuelae* by David Gottlieb.
- First antibiotic to be **chemically synthesized (1949)**.
- Initially used widely due to low cost and oral effectiveness.
- Later restricted because of **fatal aplastic anemia** cases.

Mechanism of Action:

- It **inhibits bacterial protein synthesis**.
- Binds to the **50S ribosomal subunit** → prevents **peptidyl transferase activity** → no peptide bond formation.
- Bacteriostatic for most organisms, but **bactericidal** for *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae*.

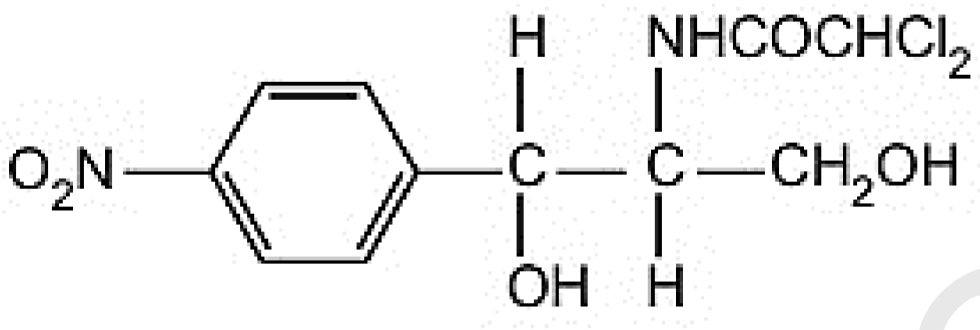
Structure:



Stereochemistry

- Has **two chiral centers**.
- Four possible stereoisomers.
- Only the **D-threo isomer** is biologically active.

SAR (Structure-Activity Relationship)



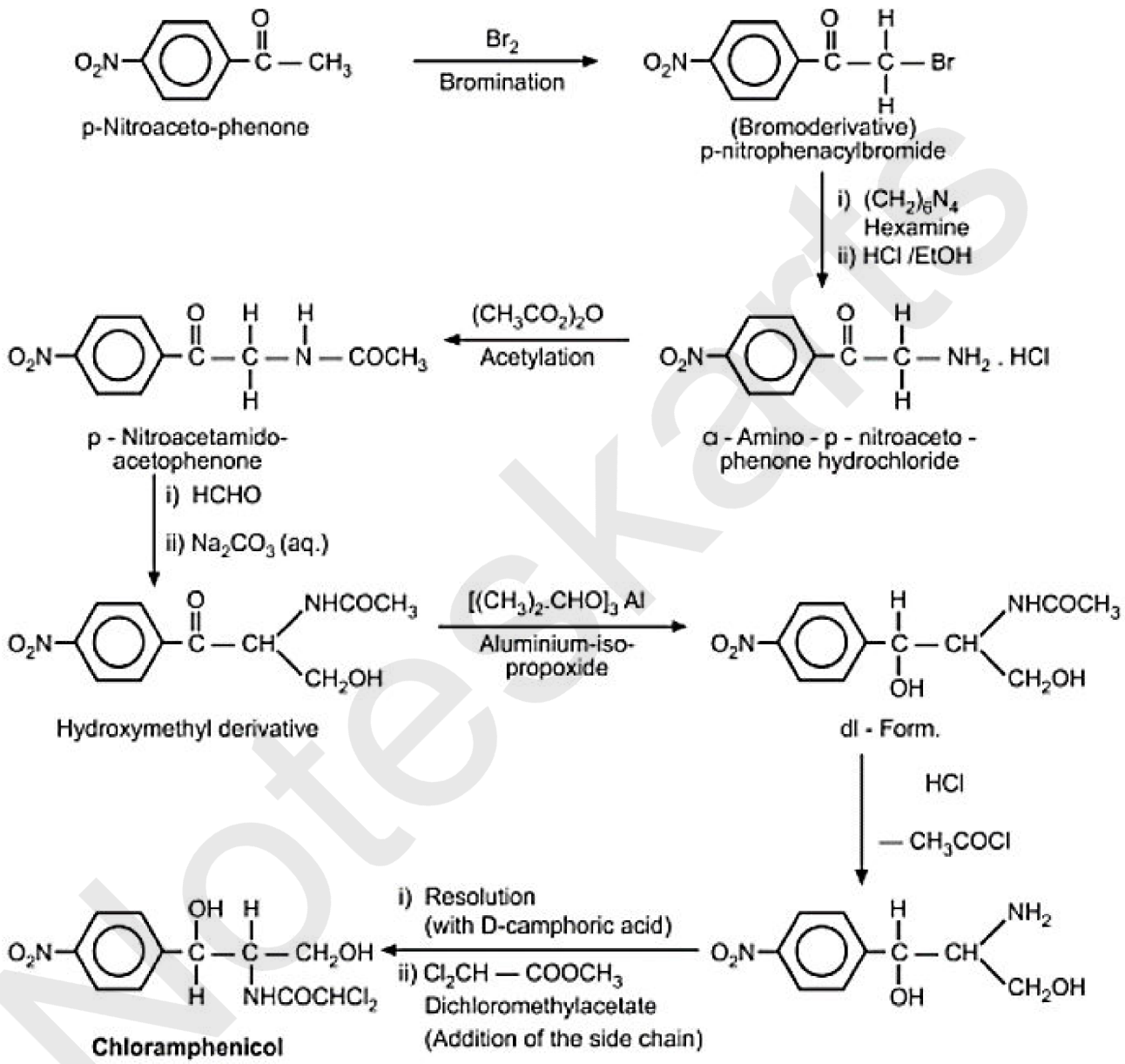
- Modification of *p*-nitrophenyl group.
- Modification of dichloroacetamide side chain.
- Modification of 1, 3-prepanediol.
- **Modification of *p*-nitrophenyl group:** The *p*-nitrophenyl group may be modified through the following ways:
- Replacement of the nitro group by other substituents leads to a reduction in activity.
- Shifting of the nitro group from the para position also reduces the antibacterial activity.
- Replacement of phenyl group by the alicyclic moieties results in less potent compounds.
- **Modification of dichloroacetamido side chain:** Other dihalo derivatives of the side chain are less potent although major activities are retained.
- **Modification of 1,3-propanediol:** If the primary alcoholic group on C-1 atom is modified, it results in a decrease in activity; hence, the alcoholic group seems to be essential for activity.

Chemical Properties

- White to grayish-white crystalline powder.
- Bitter taste.
- Soluble in alcohol, slightly soluble in water.
- Stable in air but decomposes by light and alkali.

Synthesis:

Chloramphenicol



Adverse Drug Reactions

1. **Bone marrow suppression** (dose-dependent, reversible).
2. **Aplastic anemia** (rare but fatal, irreversible).
3. **Gray baby syndrome** (in newborns due to immature liver → drug accumulates → cyanosis, hypotension, death).
4. GI disturbances: nausea, vomiting, diarrhea.
5. Allergic reactions (skin rashes, fever).

Uses

- Restricted due to toxicity, but still used in special cases:

1. **Typhoid fever** (if resistant to safer drugs).
2. **Meningitis** caused by *H. influenzae*, *N. meningitidis*, *S. pneumoniae*.
3. **Rickettsial infections** (when tetracyclines contraindicated).
4. **Topically** in eye infections (conjunctivitis, keratitis).
5. Alternative for **anaerobic infections** when metronidazole not suitabl

Clindamycin:

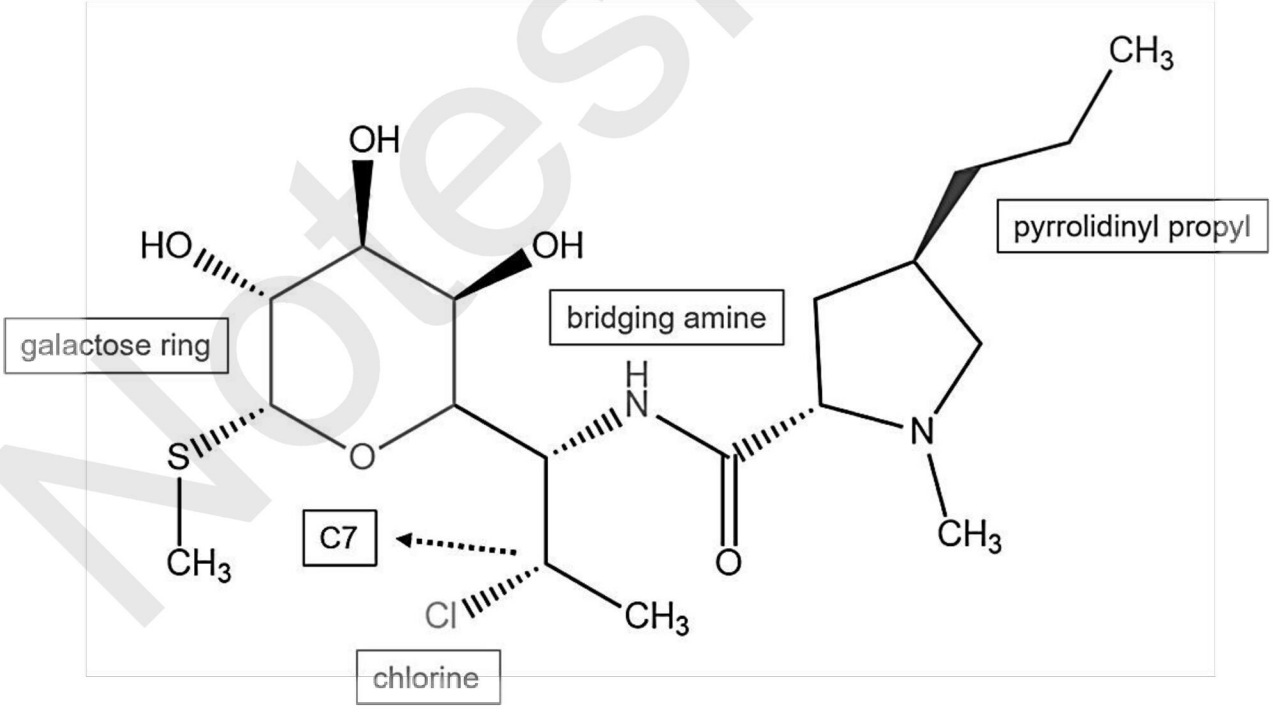
Introduction:

- Clindamycin is a **semi-synthetic antibiotic**.
- Belongs to **Lincosamide class** of antibiotics.
- It is derived from **Lincomycin** (natural antibiotic).
- Broad-spectrum activity mainly against **Gram-positive cocci** and **anaerobic bacteria**.

Mechanism of Action:

- Clindamycin binds to the **50S ribosomal subunit** of bacteria.
- Inhibits **protein synthesis** by blocking translocation and peptide bond formation.
- It is **bacteriostatic**, but can be **bactericidal** at high concentrations against susceptible organisms.

Structure of Clindamycin:



Properties:

- White, crystalline, bitter-tasting powder.
- Soluble in water and alcohol.
- Stable in solid form but aqueous solutions should be freshly prepared.

- Available as **oral capsules, IV injection, and topical formulations** (gel, lotion, cream).

Adverse Effects:

1. **Gastrointestinal:** Nausea, vomiting, abdominal pain.
2. **Pseudomembranous colitis** (serious, due to *Clostridium difficile* overgrowth).
3. Skin rashes, itching.
4. Hepatotoxicity (rare).
5. Local irritation at injection site.

Uses:

- **Alternative to penicillin** in allergic patients.
- **Anaerobic infections**: intra-abdominal, pelvic, lung abscess.
- **Bone and joint infections** (osteomyelitis).
- **Skin and soft tissue infections** (caused by staphylococci & streptococci).
- **Dental infections** (oral anaerobes).
- **Toxoplasmosis** (with pyrimethamine).
- **Acne vulgaris** (topical gels/lotions).

Prodrugs: Basic concepts and application of prodrugs design.

Prodrugs

Definition:

- A **prodrug** is a pharmacologically inactive derivative of a drug molecule that undergoes **enzymatic or chemical transformation inside the body** to release the active drug.

Purpose:

- Prodrugs are designed to **overcome limitations** of active drugs, such as poor absorption, low solubility, instability, poor targeting, or high toxicity.

Key Features:

- Inactive or less active form.
- Requires **biotransformation** (e.g., hydrolysis, oxidation, reduction).
- Improves **drug delivery, stability, or safety**.

Prodrug Classification

1. **Carrier-linked prodrugs**
   - Active drug is linked with a temporary group (carrier).
   - After enzymatic cleavage, the active drug is released.
   - Example: **Aspirin** (prodrug of salicylic acid).
2. **Bioprecursors**
   - Inactive compound is directly converted to active drug by metabolic transformation.
   - Example: **Levodopa → Dopamine** (by decarboxylation).

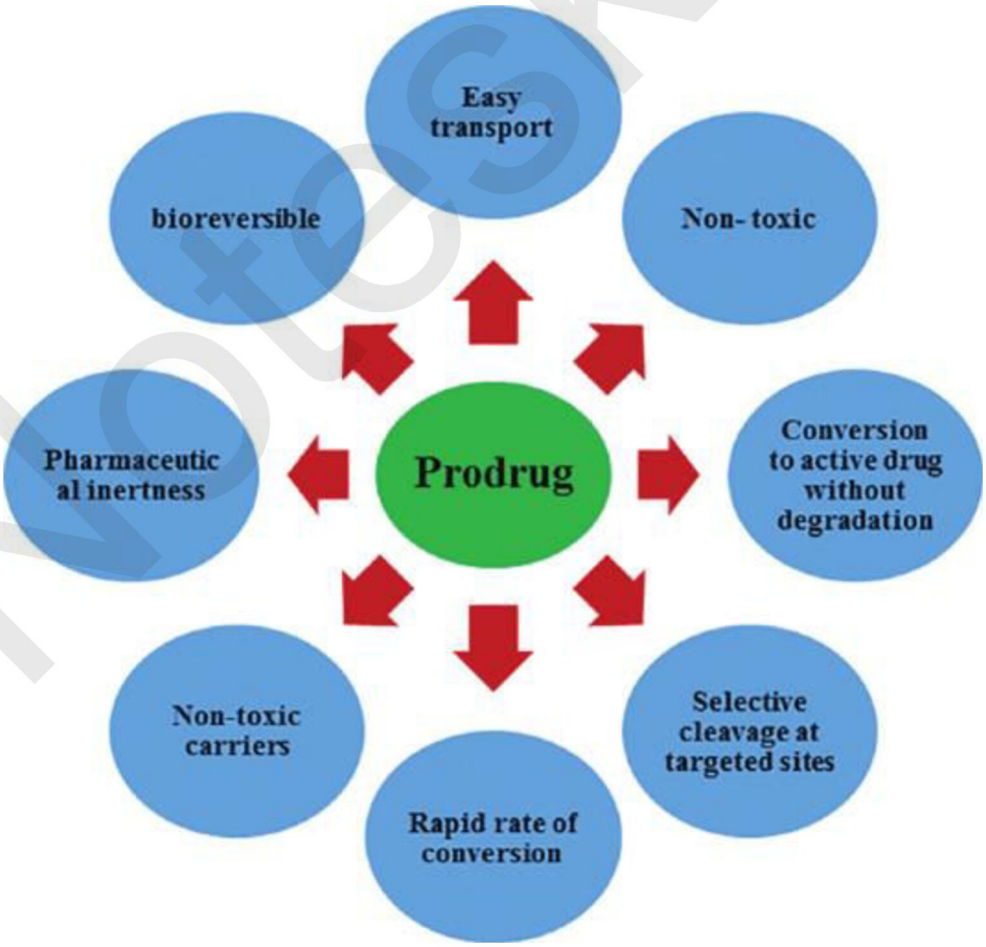
Applications of Prodrug Design

1. **Improving Absorption and Bioavailability**
   - Some drugs have poor solubility or membrane permeability.
   - Example: **Enalapril (prodrug) → Enalaprilat** (better oral absorption).
2. **Enhancing Solubility**
   - Poorly soluble drugs can be made more soluble.

- Example: **Prednisolone phosphate → Prednisolone** (increases aqueous solubility).

3. **Prolonging Drug Action**
   - Prodrugs may release the active drug slowly for sustained effect.
   - Example: **Fluphenazine decanoate** (long-acting antipsychotic).
4. **Reducing Toxicity or Side Effects**
   - Prodrug is less toxic until converted.
   - Example: **Cyclophosphamide** (activated in liver to cytotoxic metabolites used in cancer therapy).
5. **Site-Specific Drug Delivery**
   - Prodrugs can target specific organs or tissues.
   - Example: **Sulfasalazine → 5-Aminosalicylic acid** (activated in colon for ulcerative colitis).
6. **Improving Patient Compliance**
   - By reducing dosing frequency or taste masking.
   - Example: **Chloramphenicol palmitate** (better taste for oral use).

Ideal characteristics of prodrugs:



Antimalarials: Etiology of malaria. Quinolines: SAR, Quinine sulphate, Chloroquine*, Amodiaquine, Primaquine phosphate, Pamaquine*, Quinacrine hydrochloride, Mefloquine. Biguanides and dihydro triazines: Cycloguanil pamoate, Proguanil.

Antimalarials

Introduction

- Malaria is a protozoal disease caused by *Plasmodium* species (P. vivax, P. falciparum, P. malariae, P. ovale).
- Spread by the bite of female Anopheles mosquito.
- Antimalarial drugs are agents used for prevention, treatment and eradication of malaria.

Classification of Antimalarials

1. Based on Site of Action in Parasite Life Cycle

1. **Tissue schizontocides (for exoerythrocytic stage)**
   - Act on liver stages.
   - Example: Primaquine, Proguanil
2. **Blood schizontocides (for erythrocytic stage)**
   - Act on parasites in RBC.
   - Example: Chloroquine, Quinine, Mefloquine, Artemisinin, Pyrimethamine
3. **Gametocides**
   - Destroy gametocytes in blood, prevent transmission to mosquitoes.
   - Example: Primaquine, Artemisinin
4. **Sporontocides**
   - Prevent sporozoite development in mosquito.
   - Example: Primaquine (partial).

Etiology of Malaria:

The four species that affect humans are;

1. Plasmodium falciparum
2. Plasmodium vivax
3. Plasmodium malariae
4. Plasmodium ovale

1. Plasmodium falciparum

- **Most dangerous and virulent species**.
- Causes **malignant tertian malaria** (fever every 48 hours but irregular in onset).
- **Geographical distribution**: Predominant in Africa, Southeast Asia, and South America.
- **Incubation period**: 9–14 days.
- **Clinical features**:
  - Severe anemia due to rapid destruction of RBCs.
  - Cerebral malaria (coma, convulsions) due to sequestration of infected RBCs in brain capillaries.
  - Renal failure (blackwater fever due to hemoglobinuria).
- **Mortality rate**: Highest among all species; responsible for majority of malaria-related deaths.

2. Plasmodium vivax

- Causes **benign tertian malaria** (fever every 48 hours, usually regular).
- **Most common species worldwide**.
- **Geographical distribution**: Widely found in Asia, Latin America, and some parts of Africa.
- **Incubation period**: 12–17 days.
- **Clinical features**:
  - Moderate anemia.
  - Enlargement of spleen and liver.
  - Characteristic relapsing fever.
- **Severity**: Less severe than *P. falciparum* but more recurrent.

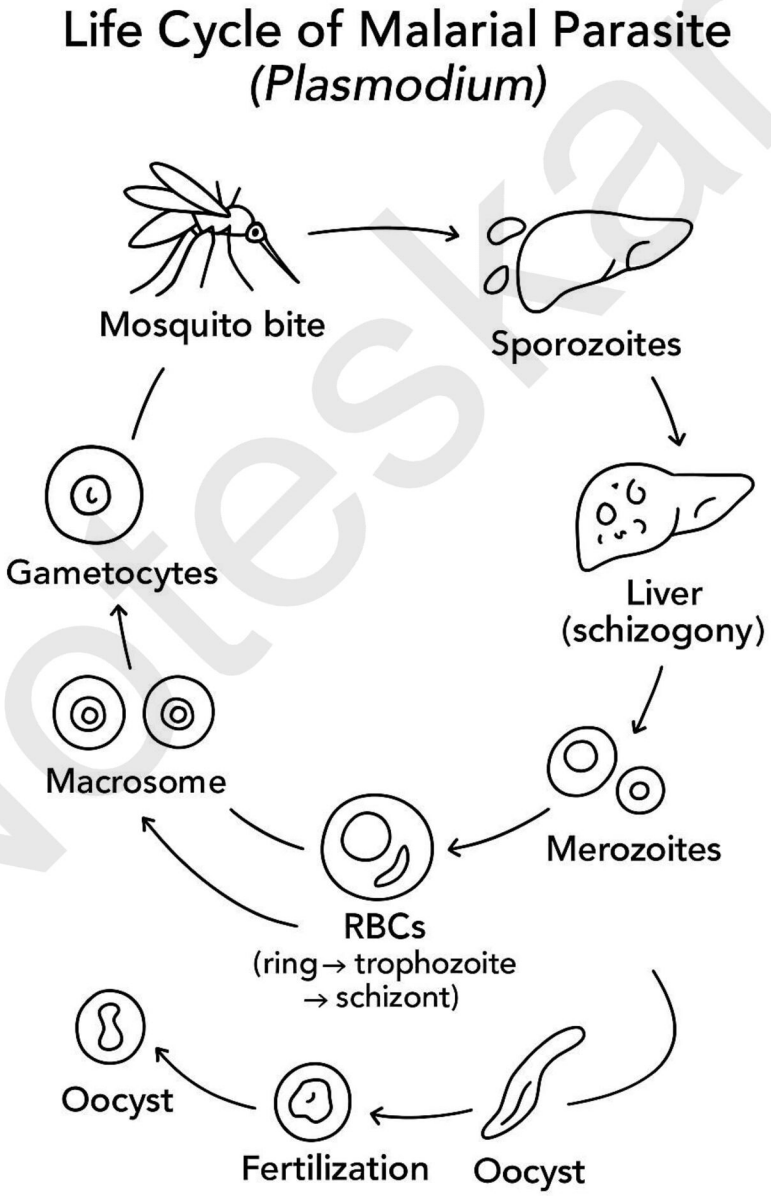
3. Plasmodium malariae

- Causes **quartan malaria** (fever every 72 hours).
- **Geographical distribution**: Patchy distribution, found in Africa, Southeast Asia, South America.
- **Incubation period**: 18–40 days.
- **Clinical features**:
  - Milder infection, low-grade chronic malaria.
  - May persist for many years (chronic infection).
  - Associated with **nephrotic syndrome** (immune complex deposition in kidneys).

4. Plasmodium ovale

- Causes **benign tertian malaria** (similar to *P. vivax*).
- **Less common species**, found mainly in West Africa and some Pacific islands.
- **Incubation period**: 12–20 days.
- **Clinical features**:
  - Generally mild malaria, low parasite density.
  - Fever pattern every 48 hours.
  - Enlarged spleen and anemia.

Life Cycle of Malarial Parasite:



Types of Malaria:

1. Uncomplicated Malaria: The most common symptoms of uncomplicated malaria are:

- Fever and chills
- Headaches
- Nausea and vomiting
- General weakness and body aches
- Sweating chest or abdominal pain
- Cough

2. Complicated or Severe Malaria:

This occurs when malaria affects different body systems. The most common symptoms of complicated malaria are:

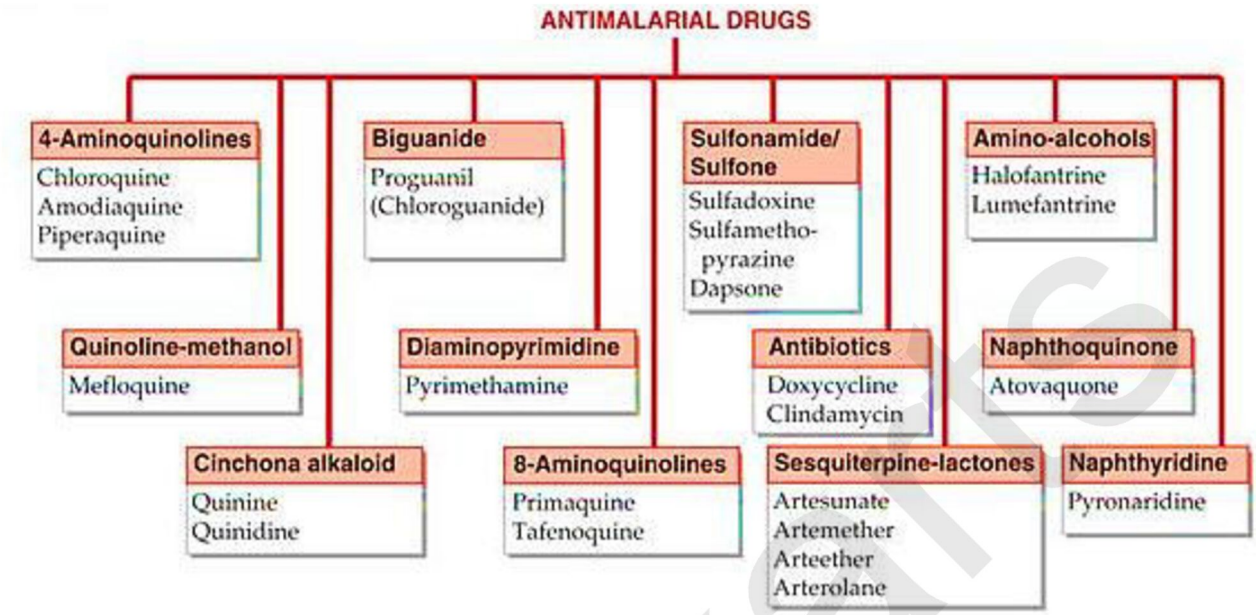
- Severe anemia (due to destruction of red blood cells). Kidney failure.
- Cerebral malaria - seizures, unconsciousness, abnormal behavior, or confusion.
- Cardiovascular collapse.
- Low blood sugar (in pregnant women after treatment with quinine).

Objectives and Use of Antimalarial drugs:

The aims of using drugs in relation to malarial infection are:

- To prevent clinical attack of malaria (prophylactic).
- To treat clinical attack of malaria (clinical curative).
- To completely eradicate the parasite from the patient's body (radical curative).
- To cutdown human-to-mosquito transmission (gametocidal).

Classification of Antimalarial Drugs:

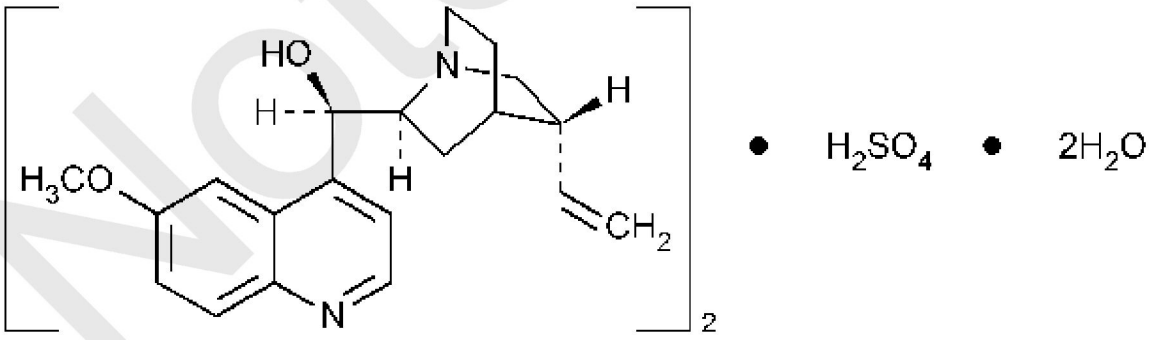


I. QUINOLINES

1. Quinine Sulphate

- **Class**: Natural alkaloid (Cinchona alkaloid, quinoline derivative).

Structure:



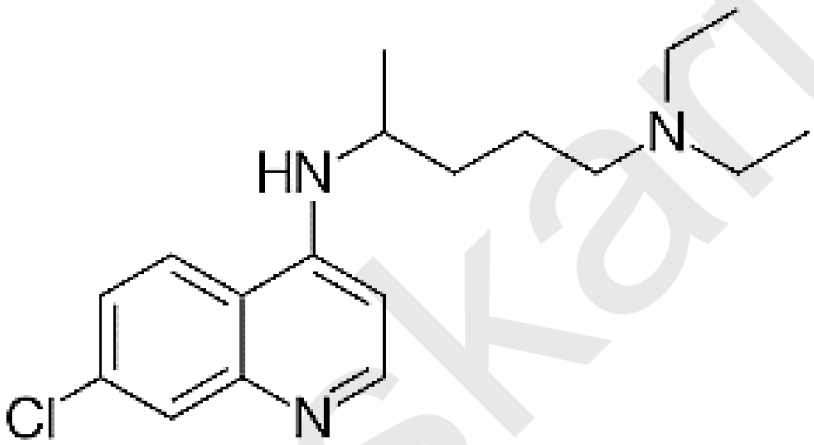
- **Mechanism of Action**: Inhibits heme polymerase → accumulation of toxic heme in parasite → parasite death.
- **Indications**: Severe falciparum malaria, resistant malaria strains, nocturnal leg cramps (off-label).
- **Administration**: Oral, IV (as dihydrochloride).

- **Side Effects**: Cinchonism (tinnitus, vertigo, headache), hypoglycemia, arrhythmias.
- **Contraindications**: Pregnancy (relative), G6PD deficiency, optic neuritis.

2. Chloroquine*

- **Class**: 4-aminoquinoline.

Structure:

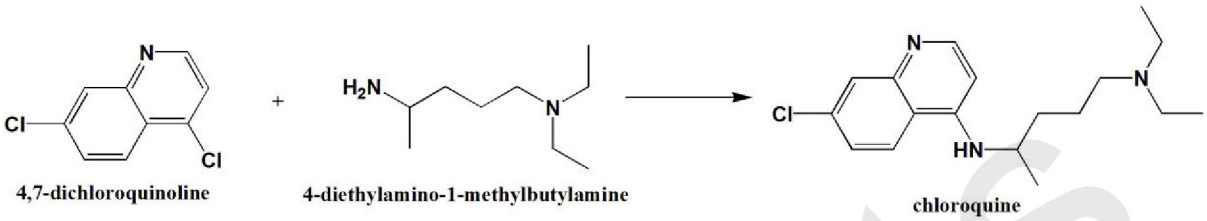


Structure Activity Relationship

- Chloroquine is crucial for heme binding.
- Nitrogen of the amine attached with the chloroquine entity is responsible for the basic nature of the drug.
- There is no major role of having the secondary alkyl group attached with the carbon next to the amino group near the chloroquine entity.
- Tertiary amine at the terminal is very important for the activity of the drug.
- The length of spacer between the terminal nitrogen and 4-amino group is sensitive towards the parasite resistance. Compounds having shorter chains or longer chains retains the activity against the resistant species of the parasite.
- Small electron withdrawing group at 7^{th} position of the quinoline ring is important for the inhibition of hmozoin formation.

Method of synthesis

Chloroquine can be synthesized by reaction of 4,7-dichloroquinoline with 4-diethylamino-1-methylbutylamine at 180 °C.

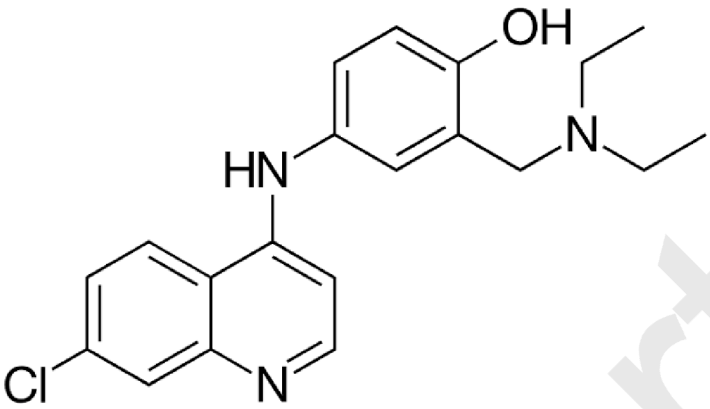


4,7-dichloroquinoline — 4-diethylamino-1-methylbutylamine — chloroquine

- **Mechanism of Action**: Concentrates in parasite food vacuole, prevents heme detoxification.
- **Indications**: Acute attacks of vivax, ovale, malariae malaria; prophylaxis of malaria; extraintestinal amoebiasis; autoimmune diseases (RA, SLE).
- **Administration**: Oral, IM, IV.
- **Side Effects**: Nausea, headache, visual disturbances, retinopathy (long term), pruritus.
- **Contraindications**: Psoriasis, retinal disease, epilepsy.

3. Amodiaquine:

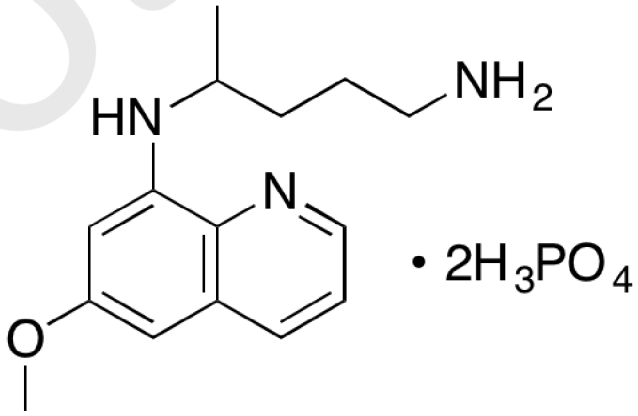
Structure:



- **Class**: 4-aminoquinoline.
- **Mechanism of Action**: Similar to chloroquine (heme polymerase inhibition).
- **Indications**: Uncomplicated falciparum malaria (esp. in chloroquine-resistant areas).
- **Administration**: Oral.
- **Side Effects**: Agranulocytosis, hepatotoxicity.
- **Contraindications**: Liver disease, previous history of neutropenia.

4. Primaquine Phosphate

Structure:

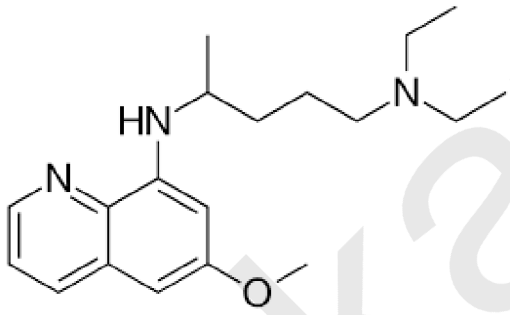


- **Class**: 8-aminoquinoline.
- **Mechanism of Action**: Destroys dormant hypnozoites in liver (*radical cure* for vivax and ovale); gametocytocidal against falciparum.

- **Indications**: Radical cure of vivax/ovale; prevention of relapse; gametocidal activity.
- **Administration**: Oral.
- **Side Effects**: Hemolysis in G6PD deficiency, abdominal pain, methemoglobinemia.
- **Contraindications**: Pregnancy, G6PD deficiency.

5. Pamaquine*

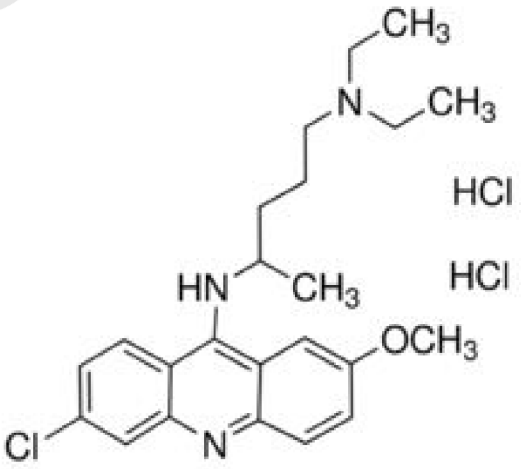
Structure:



- **Class**: 8-aminoquinoline (older, less used).
- **Mechanism**: Similar to primaquine (hepatic schizonticide).
- **Indications**: Previously used for radical cure, now obsolete due to toxicity.
- **Side Effects**: Severe hemolysis, CNS toxicity.
- **Contraindications**: G6PD deficiency, pregnancy.

6. Quinacrine Hydrochloride

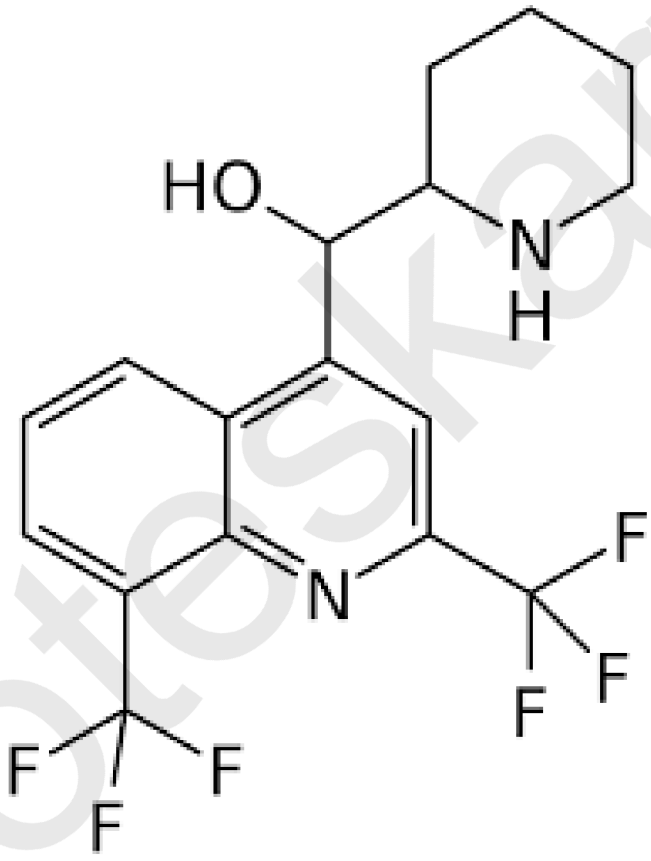
Structure:



- **Class**: 9-aminoacridine derivative (synthetic).
- **Mechanism of Action**: Similar to chloroquine; intercalates DNA.
- **Indications**: Rarely used; some resistant malaria cases, giardiasis.
- **Administration**: Oral.
- **Side Effects**: Yellow discoloration of skin, GI upset, psychosis.
- **Contraindications**: Psychiatric illness, liver disease.

7. Mefloquine

Structure:

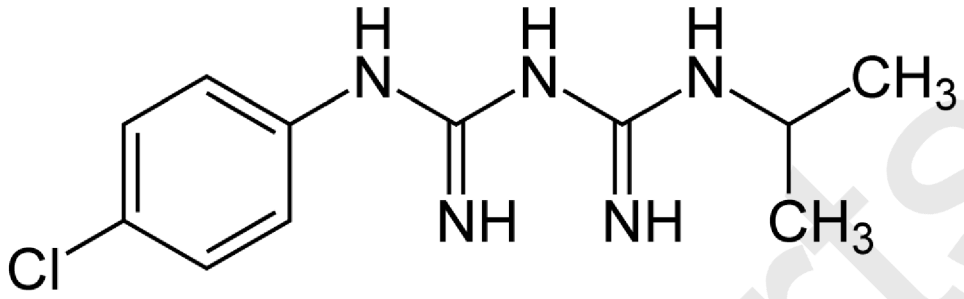


- **Class**: Quinoline-methanol derivative.
- **Mechanism of Action**: Blocks hemozoin formation → toxic heme accumulation.
- **Indications**: Chloroquine-resistant falciparum malaria (prophylaxis & treatment).
- **Administration**: Oral.
- **Side Effects**: Neuropsychiatric (depression, psychosis), vertigo, GI upset.
- **Contraindications**: Epilepsy, psychiatric disorders, cardiac conduction defects.

II. BIGUANIDES & DIHYDROTRIAZINES

1. Proguanil

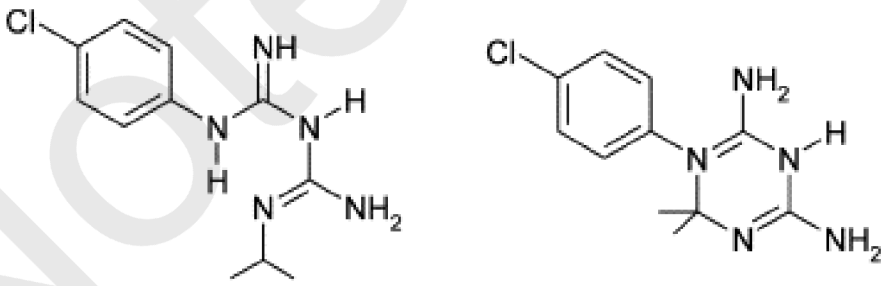
Structure:



- **Class**: Biguanide derivative.
- **Mechanism of Action**: Converted to **cycloguanil**, inhibits parasite **dihydrofolate reductase (DHFR)** → blocks DNA synthesis.
- **Indications**: Malaria prophylaxis, combined with atovaquone.
- **Administration**: Oral.
- **Side Effects**: Mouth ulcers, alopecia, GI upset.
- **Contraindications**: Severe renal impairment.

3. Cycloguanil Pamoate

Structure:



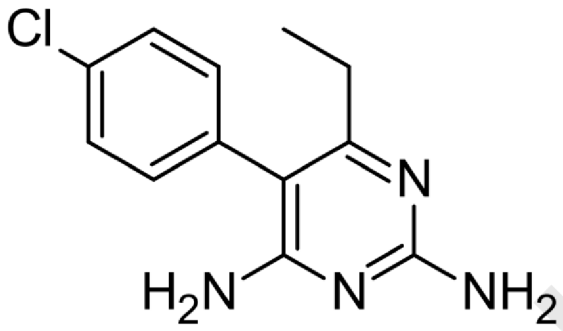
proguanil cycloguanil

- **Class**: Active metabolite of proguanil (biguanide).
- **Mechanism of Action**: DHFR inhibitor → inhibits DNA replication.
- **Indications**: Used experimentally; not widely marketed.
- **Side Effects**: Similar to proguanil.
- **Contraindications**: Same as proguanil.

Miscellaneous: Pyrimethamine, Artesunete, Artemether, Atovoquone

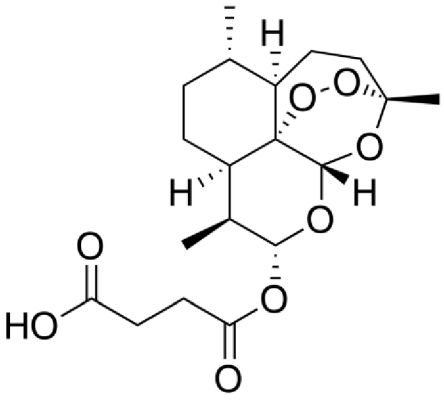
Pyrimethamine:

Structure:



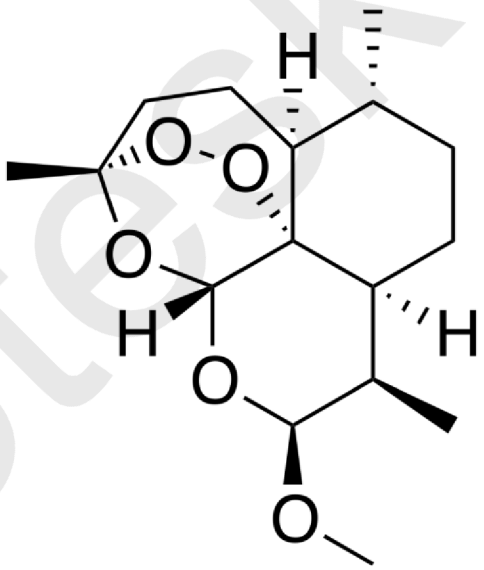
- **Class**: Diaminopyrimidine derivative.
- **Mechanism of Action**:
  - Inhibits **plasmodial dihydrofolate reductase (DHFR)** → blocks folic acid synthesis → inhibits DNA & RNA synthesis.
- **Indications**:
  - Used with sulfadoxine (Fansidar) in *falciparum malaria*.
  - Prophylaxis in resistant malaria areas.
  - Also used in toxoplasmosis (with sulfadiazine).
- **Administration**: Oral.
- **Side Effects**:
  - GI upset, megaloblastic anemia (due to folate deficiency), hypersensitivity.
- **Contraindications**:
  - Pregnancy (teratogenic in high doses).
  - Severe hepatic or renal impairment.

Artesunate



- **Class**: Artemisinin derivative (semi-synthetic).
- **Mechanism of Action**:
  - Contains **endoperoxide bridge** → generates free radicals in parasite → damages proteins & membranes.
  - Very rapid schizonticidal action.
- **Indications**:
  - Severe falciparum malaria (especially cerebral malaria).
  - Used in **Artemisinin-based combination therapy (ACT)** with lumefantrine, mefloquine, etc.
- **Administration**: Oral, IV, IM, rectal.
- **Side Effects**:
  - Nausea, vomiting, dizziness, bradycardia.
  - Rare: Hemolysis, hypersensitivity.
- **Contraindications**:
  - First trimester of pregnancy (relative).

Artemether

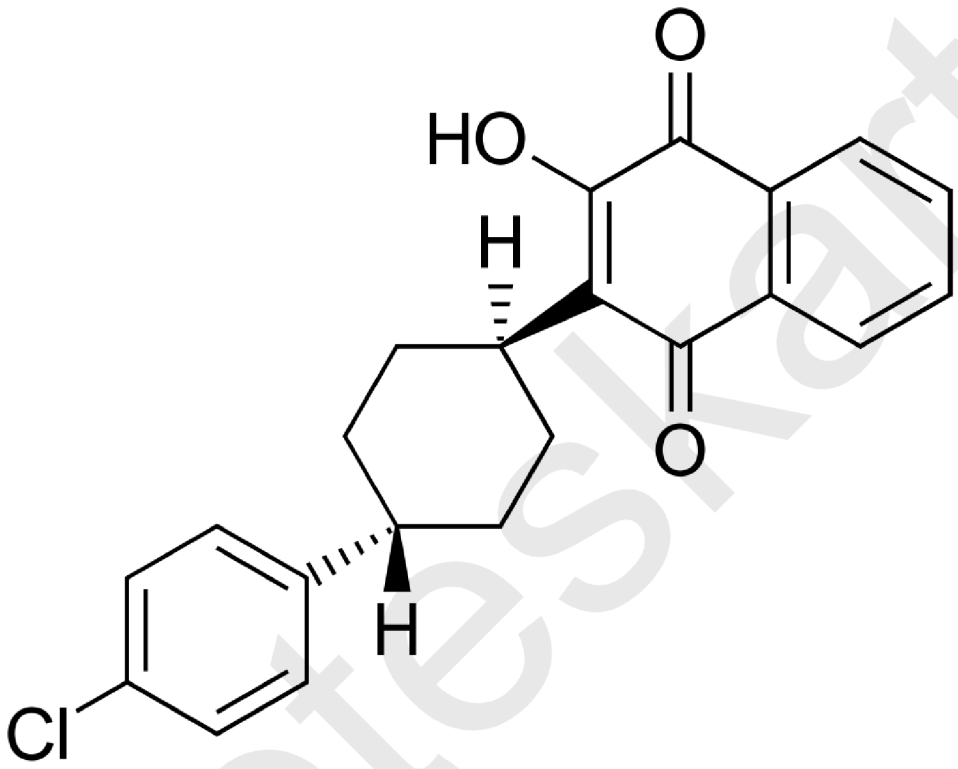


- **Class**: Artemisinin derivative.
- **Mechanism of Action**:
  - Similar to artesunate → free radical formation via endoperoxide bridge.
- **Indications**:
  - First-line treatment for multidrug-resistant falciparum malaria.
  - Used in **ACT (e.g., Artemether + Lumefantrine)**.
- **Administration**: Oral, IM.
- **Side Effects**:

- Headache, dizziness, GI upset.
- Rare: Neurotoxicity, QT prolongation.

- **Contraindications**:
  - Caution in pregnancy (especially 1st trimester).

Atovaquone



- **Class**: Hydroxy-naphthoquinone derivative.
- **Mechanism of Action**:
  - Inhibits **mitochondrial electron transport (cytochrome bc1 complex)** in parasite → collapse of mitochondrial membrane potential → inhibits ATP & pyrimidine synthesis.
- **Indications**:
  - Malaria prophylaxis & treatment (with proguanil = **Malarone**).
  - Pneumocystis jirovecii pneumonia (PCP).
  - Babesiosis, Toxoplasmosis (alternative).
- **Administration**: Oral (with fatty food for better absorption).
- **Side Effects**:
  - Rash, abdominal pain, diarrhea, fever.
- **Contraindications**:
  - Pregnancy, breastfeeding, severe renal impairment.

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