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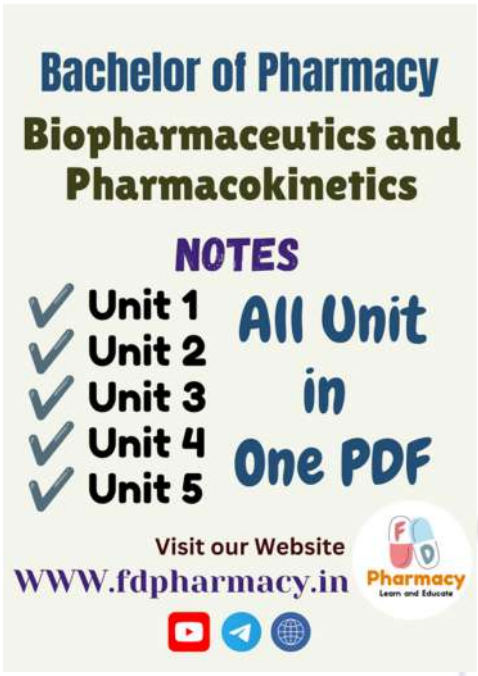
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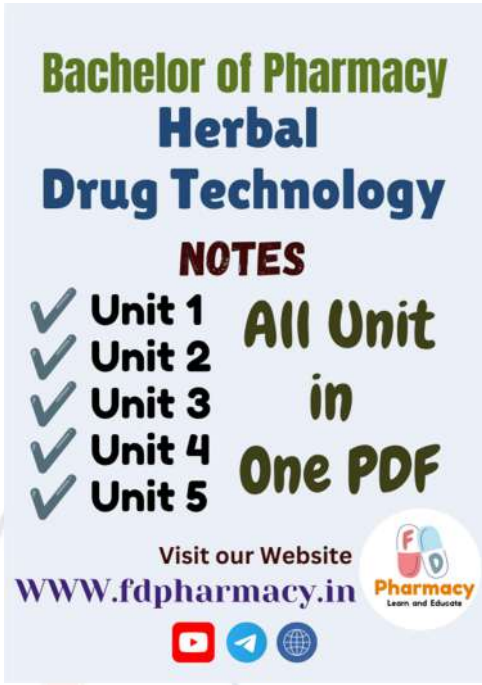
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MEDICINAL CHEMISTRY - III

UNIT 2

TOPIC :

- **Miscellaneous :** Pyrimethamine, Artesunete, Artemether, Atovoquone.

Miscellaneous Antimalarial Drugs

→ Miscellaneous antimalarials are drugs that do not belong to the major classes like quinolines, biguanides, or sulfonamides but are still effective against malaria.

→ They have different mechanisms of action and are often used in resistant malaria or in combination therapy.

Examples

- Artemisinin and derivatives – Artemether, Artesunate
- Sulfonamides – Sulfadoxine
- Atovaquone
- Mefloquine

Mechanism of Action

A. Artemisinin
- Endoperoxide bridge reacts with heme inside parasite
- Produces free radicals
- Damages parasite proteins and membranes
- Rapidly kills blood-stage parasites

B. Atovaquone
- Inhibits mitochondrial electron transport in parasite
- Blocks ATP production
- Parasite energy metabolism fails

C. Sulfadoxine
- Structural analogue of para-aminobenzoic acid (PABA)
- Inhibits dihydropteroate synthase → folate synthesis blocked

D. Mefloquine
- Disrupts heme detoxification in parasite
- Acts on blood schizonts

- **Stage of Action**

Drug	Stage of Action
Artemisinin	Blood schizonts (rapid)
Atovaquone	Blood schizonts
Sulfadoxine	Blood schizonts
Mefloquine	Blood schizonts

Therapeutic Uses

- Severe malaria – Artesunate, Artemether
- Drug-resistant malaria – Mefloquine, Atovaquone
- Combination therapy – Artemisinin + Mefloquine / Atovaquone-Proguanil
- Prophylaxis – Mefloquine, Atovaquone-Proguanil

Adverse Effects

Artemisinin

- Mild GI disturbances
- Dizziness, headache

Atovaquone

- Nausea, vomiting
- Rash

Sulfonamides

- Hypersensitivity
- Stevens-Johnson syndrome (rare)

Mefloquine

- Neuropsychiatric symptoms
- GI disturbances

Advantages

- Rapid parasite clearance (Artemisinin)
- Effective against drug-resistant strains
- Useful in combination therapy

Resistance

- Rare but increasing with Artemisinin monotherapy
- Combination therapy recommended to prevent resistance

Pyrimethamine

→ Pyrimethamine is a synthetic antimalarial drug belonging to the diaminopyrimidine class.

→ It acts as a blood schizonticide by inhibiting parasite folate metabolism.
Pyrimethamine is often used in combination therapy with sulfonamides (e.g., sulfadoxine) to treat chloroquine-resistant *Plasmodium falciparum*.

→ It is orally active and primarily targets the erythrocytic stages of the parasite.

Classification

Based on Chemical Class

- Diaminopyrimidine derivative

Based on Antimalarial Action

- Blood schizonticide (antifolate)

Based on Origin

- Synthetic antimalarial

Structure

Pyrimethamine contains:

- Pyrimidine ring
- Amino and chlorophenyl substitutions

Important structural features:

- 2,4-diaminopyrimidine nucleus
- 5-chlorophenyl group
- Weakly basic properties

Molecular formula: $C_{12}H_{14}ClN_5$

Structural Characteristics

- Lipophilic and orally absorbable
- Forms salts for improved solubility
- Inhibits parasite dihydrofolate reductase (DHFR)

Nomenclature

- Pyri → pyrimidine ring
- Methamine → amino substitution
- Available as pyrimethamine tablets or in combination with sulfadoxine

Stereochemistry

- Pyrimethamine is achiral
- Activity depends on 2,4-diaminopyrimidine nucleus

Mechanism of Action

- Pyrimethamine selectively inhibits parasite dihydrofolate reductase (DHFR).
- Blocks conversion of dihydrofolate to tetrahydrofolate.
- Prevents DNA synthesis in the erythrocytic stage of the parasite.
- Parasite replication is inhibited, leading to death of blood-stage parasites.
- Hence, pyrimethamine acts as a blood schizonticide via antifolate action.

Spectrum of Activity

- Erythrocytic stages of:
  - *Plasmodium falciparum* (including chloroquine-resistant strains)
  - *Plasmodium vivax*
- Limited effect on liver stages

Uses

→ Treatment of chloroquine-resistant *P. falciparum* malaria (with sulfadoxine)
→ Prophylaxis of malaria in combination therapy
→ Occasionally used for toxoplasmosis in combination with sulfadiazine

Adverse Effects

- Gastrointestinal: nausea, vomiting
- Headache, dizziness
- Rare: rash, hypersensitivity reactions
- Hematological: megaloblastic anemia (due to folate deficiency)
- Generally well tolerated at recommended doses

Chemical Degradation

1. Acid Degradation

- Stable in acidic medium

2. Alkaline Degradation

- Sensitive in strong alkali

3. Photodegradation

- Sensitive to light

4. Thermal Degradation

- Heat accelerates decomposition

Prevention

- Store in cool, dry place
- Protect from light and moisture

Structure–Activity Relationship (SAR)

2,4-Diaminopyrimidine Nucleus

- Essential for DHFR inhibition

Chlorophenyl Substitution

- Enhances binding to parasite DHFR
- Increases antimalarial potency

Lipophilicity

- Facilitates oral absorption and tissue penetration

Combination Therapy

- Synergistic effect with sulfonamides reduces resistance

Artesunate

→ Artesunate is a semi-synthetic derivative of artemisinin, extracted from the plant *Artemisia annua*.

→ It is a rapid-acting blood schizonticide effective against all erythrocytic stages of *Plasmodium*, including chloroquine- and multidrug-resistant *Plasmodium falciparum*.

→ Artesunate is widely used in severe malaria, combination therapy (ACT), and prophylaxis.

→ It is water-soluble, allowing intravenous, intramuscular, and oral administration.

Classification

Based on Chemical Class

- Artemisinin derivative (sesquiterpene lactone endoperoxide)

Based on Antimalarial Action

- Blood schizonticide
- Rapidly kills erythrocytic parasites

Based on Origin

- Semi-synthetic natural product

Structure

→ Artesunate is a hemisuccinate ester of artemisinin.

Important structural features:

- Endoperoxide bridge (-O-O-) (critical for activity)
- Lactone ring
- Succinate ester enhances water solubility

Molecular formula: $C_{20}H_{28}O_8$

Structural Characteristics

- Water-soluble derivative of artemisinin
- Rapidly hydrolyzed in vivo to dihydroartemisinin (active metabolite)
- Highly lipophilic, allowing fast tissue penetration

Nomenclature

- **Arte** → artemisinin derivative
- **Sunate** → hemisuccinate ester
- Available forms:
  - Artesunate sodium (for IV/IM injection)

Stereochemistry

- Artesunate contains multiple chiral centers
- Correct stereochemistry is essential for endoperoxide-mediated activity
- Semi-synthetic derivatives preserve the natural stereochemistry of artemisinin

Mechanism of Action

- Artesunate is rapidly converted to dihydroartemisinin in the body.
- The endoperoxide bridge reacts with heme iron in parasite food vacuoles.
- Generates free radicals that damage parasite proteins and membranes.
- Causes rapid death of erythrocytic parasites.
- Hence, artesunate is a fast-acting blood schizonticide.

Spectrum of Activity

- Active against all erythrocytic stages of:
  - *Plasmodium falciparum* (including resistant strains)
  - *Plasmodium vivax*
- Rapidly reduces parasitemia
- Ineffective against liver hypnozoites

Uses

- Treatment of severe *P. falciparum* malaria (IV/IM)
- Part of artemisinin-based combination therapy (ACT) for uncomplicated malaria
- Reduces parasite load quickly in high-risk patients
- Sometimes used in malaria prophylaxis in resistant areas

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- Headache, dizziness
- Mild hematological effects: transient hemolysis, anemia
- Rare: hypersensitivity reactions
- Generally well tolerated

Chemical Degradation

1. Acid Degradation
- Stable under normal acidic conditions

2. Alkaline Degradation
- Sensitive to strong alkali

3. Photodegradation
- Sensitive to light exposure

4. Thermal Degradation
- Heat accelerates decomposition

Prevention

- Store in cool, dry place
- Protect from light and moisture

Structure–Activity Relationship (SAR)

Endoperoxide Bridge (-O-O-)
- Critical for antimalarial activity

Lactone Ring
- Maintains structural stability and reactivity

Succinate Ester
- Increases water solubility and bioavailability

Lipophilicity
- Ensures rapid tissue penetration and fast action

Stereochemistry
- Preserves free radical generation and efficacy

Artemether

→ Artemether is a semi-synthetic derivative of artemisinin, obtained from *Artemisia annua*.

→ It is a rapid-acting blood schizonticide used primarily against erythrocytic stages of *Plasmodium falciparum*, including chloroquine-resistant strains.

→ Artemether is often used in artemisinin-based combination therapy (ACT), usually combined with lumefantrine.

→ It is lipophilic, allowing intramuscular and oral administration, and is rapidly converted to the active metabolite dihydroartemisinin (DHA).

Classification

Based on Chemical Class

- Artemisinin derivative (sesquiterpene lactone endoperoxide)

Based on Antimalarial Action

- Blood schizonticide
- Rapidly kills erythrocytic parasites

Based on Origin

- Semi-synthetic natural product

Structure

→ Artemether is a methyl ether derivative of dihydroartemisinin.

Important structural features:

- Endoperoxide bridge (-O-O-) (essential for activity)
- Lactone ring
- Methyl ether substitution enhances lipophilicity

Molecular formula: $C_{16}H_{26}O_5$

Structural Characteristics

- Lipophilic → rapid tissue penetration
- Converted in vivo to dihydroartemisinin, the active antimalarial
- Water-insoluble; usually administered with coformulation for oral absorption

Nomenclature

- Arte → from artemisinin derivative
- Mether → methyl ether
- Available forms:
  - Artemether tablets (oral)
  - Artemether injections (IM)

Stereochemistry

- Contains multiple chiral centers
- Correct stereochemistry is essential for endoperoxide-mediated activity
- Semi-synthetic process preserves natural stereochemistry

Mechanism of Action

- Artemether is rapidly converted to dihydroartemisinin in the body.
- The endoperoxide bridge reacts with heme iron inside the parasite food vacuole.
- Generates free radicals that damage parasite proteins and membranes.
- Leads to rapid parasite death in erythrocytic stages.
- Hence, artemether is a fast-acting blood schizonticide.

Spectrum of Activity

- Active against all erythrocytic stages of:
  - *Plasmodium falciparum* (including resistant strains)
  - *Plasmodium vivax*
- Rapidly reduces parasitemia
- Not effective against liver hypnozoites

Uses

- Treatment of severe and uncomplicated *P. falciparum* malaria
- Part of artemisinin-based combination therapy (ACT) (usually with lumefantrine)
- Rapid reduction of parasite load in high-risk patients
- Sometimes used in malaria prophylaxis in resistant areas

Adverse Effects

- Gastrointestinal: nausea, vomiting
- Headache, dizziness
- Mild hematological effects: transient hemolysis, anemia
- Rare: hypersensitivity reactions
- Generally well tolerated

Chemical Degradation

1. Acid Degradation

- Stable under normal acidic conditions

2. Alkaline Degradation

- Sensitive to strong alkali

3. Photodegradation

- Sensitive to light exposure

4. Thermal Degradation

- Heat accelerates decomposition

Prevention

- Store in cool, dry place
- Protect from light and moisture

Structure–Activity Relationship (SAR)

Endoperoxide Bridge (-O-O-)

- Critical for antimalarial activity

Lactone Ring

- Maintains structural stability and reactivity

Methyl Ether Substitution

- Increases lipophilicity → faster tissue penetration

Lipophilicity

- Ensures rapid absorption and quick action

Stereochemistry

- Preserves free radical generation and efficacy

Atovaquone

→ Atovaquone is a synthetic hydroxynaphthoquinone antimalarial.
→ It acts as a blood schizonticide and is highly effective against *Plasmodium falciparum*, including chloroquine-resistant strains.
→ Atovaquone is often used in combination therapy with proguanil (marketed as Malarone®) to improve efficacy and prevent resistance.
→ It is lipophilic, poorly water-soluble, and administered orally.

Classification

Based on Chemical Class

- Hydroxynaphthoquinone derivative

Based on Antimalarial Action

- Blood schizonticide
- Inhibits parasite mitochondrial electron transport

Based on Origin

- Synthetic antimalarial

Structure

Atovaquone contains:

- Hydroxynaphthoquinone ring
- Chlorophenyl substitution
- Lipophilic alkyl side chains

Important structural features:

- Quinone nucleus (essential for mitochondrial inhibition)
- Hydroxyl group for binding interactions

Molecular formula: $C_{22}H_{19}ClO_3$

Structural Characteristics

- Highly lipophilic → accumulates in parasite membranes
- Poorly water-soluble → oral absorption improved with fatty meals
- Selectively inhibits parasite mitochondrial cytochrome bc1 complex

Nomenclature

- Ato → hydroxynaphthoquinone derivative
- Vaquone → quinone nucleus
- Marketed as atovaquone tablets or in combination with proguanil

Stereochemistry

- Atovaquone is achiral
- Activity depends on quinone nucleus and hydroxyl substitution

Mechanism of Action

→ Atovaquone inhibits parasite mitochondrial electron transport by binding to the cytochrome bc1 complex.
→ Disrupts mitochondrial membrane potential.
→ Prevents ATP synthesis and pyrimidine biosynthesis.
→ Parasite replication in RBCs is halted → death of blood-stage parasites.
→ Hence, atovaquone is a blood schizonticide with mitochondrial inhibition.

Spectrum of Activity

→ Erythrocytic stages of:
  - *Plasmodium falciparum* (including chloroquine-resistant strains)
  - *Plasmodium vivax*

→ Sometimes used for pneumocystis prophylaxis (P. jirovecii)
→ Ineffective against liver hypnozoites

Uses

- Treatment of chloroquine-resistant malaria (with proguanil)
- Malaria prophylaxis in endemic regions (with proguanil)
- Alternative therapy in multidrug-resistant *P. falciparum* infections

Adverse Effects

⇨ Gastrointestinal: nausea, vomiting, diarrhea
⇨ Rash
⇨ Headache, dizziness
⇨ Rare: hepatotoxicity
⇨ Generally well tolerated

Chemical Degradation

1. Acid Degradation

- Stable in acidic medium

2. Alkaline Degradation

- Decomposes in strong alkali

3. Photodegradation

- Sensitive to light

4. Thermal Degradation

- Heat accelerates decomposition

Prevention

- Store in cool, dry place
- Protect from light

Structure–Activity Relationship (SAR)

Quinone Nucleus

- Essential for mitochondrial electron transport inhibition

Hydroxyl Substitution

- Required for binding to cytochrome bc1 complex

Lipophilicity

- Ensures accumulation in parasite membranes and oral absorption

Combination Therapy

- Synergistic with proguanil → reduces resistance and improves efficacy