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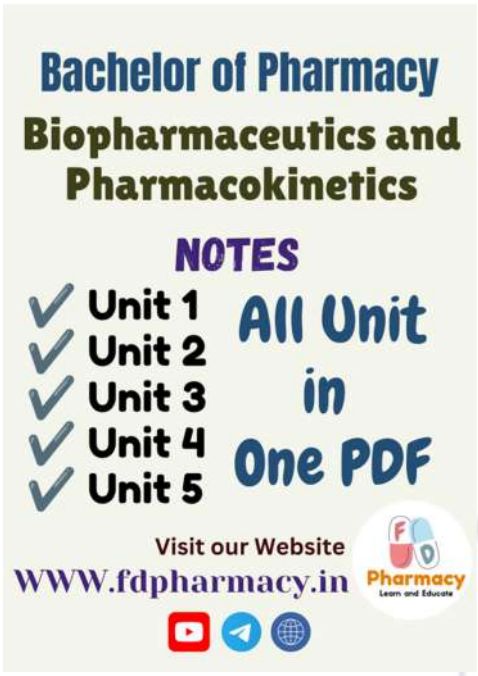
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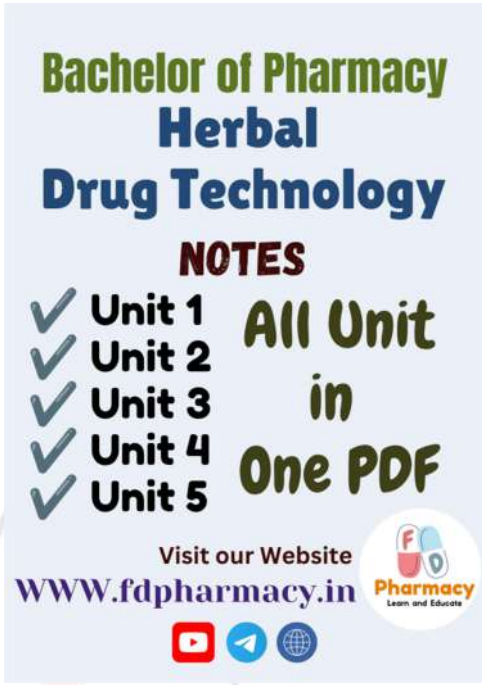
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MEDICINAL CHEMISTRY - III

UNIT 2

TOPIC :

- **Biguanides and dihydro triazines :** Cycloguanil pamoate, Proguanil.

Biguanides And Dihydrotriazines

- ⇨ Biguanides and dihydrotriazines are synthetic antimalarial drugs that act mainly as tissue schizonticides.
- ⇨ They interfere with folate metabolism of Plasmodium by inhibiting dihydrofolate reductase (DHFR).

Classification

A. Biguanides

Proguanil (Chloroguanide)

B. Dihydrotriazines

Cycloguanil *(active metabolite of proguanil)*

Mechanism of Action

- Proguanil is a prodrug.
- It is metabolized in the liver to cycloguanil.
- Cycloguanil inhibits dihydrofolate reductase (DHFR) enzyme.
- This prevents conversion of dihydrofolic acid to tetrahydrofolic acid.
- DNA synthesis in the parasite is inhibited.
- Parasite growth is stopped.
- Hence, these drugs are slow-acting antimalarials.

Stage of Action

- Act mainly on hepatic (tissue) schizonts
- Weak action on blood schizonts
- Also act as sporontocidal drugs

Spectrum of Activity

- *Plasmodium vivax*
- *Plasmodium falciparum*
- *Plasmodium malariae*

Therapeutic Uses

- Malaria prophylaxis
- Treatment of uncomplicated malaria (in combination)
- Used with atovaquone for resistant malaria
- Prevention of transmission of malaria

Adverse Effects

- Nausea and vomiting
- Abdominal pain
- Mouth ulcers (rare)
- Mild bone marrow suppression (high dose)

Advantages

- Safe for prophylactic use
- Acts on liver stages
- Useful in combination therapy
- Lower toxicity compared to other antimalarials

Resistance

- Resistance occurs due to:
- Mutation of DHFR enzyme
- Resistance reduced by combination therapy

Cycloguanil Pamoate

→ Cycloguanil pamoate is a synthetic antimalarial drug and the active metabolite of proguanil.

→ It acts as a blood schizonticide against the erythrocytic stages of Plasmodium species.

→ Cycloguanil is primarily used in combination therapy, often with atovaquone, to treat and prevent malaria.

Classification

Based on Chemical Class

- Biguanide derivative

Based on Antimalarial Action

- Blood schizonticide

Based on Origin

- Synthetic antimalarial

Structure

→ Cycloguanil is a triazine derivative with a p-chlorophenyl group.

Important structural features:

- 1,3,5-triazine nucleus
- Dichloro-substituted phenyl ring
- Biguanide moiety

Molecular formula: $C_{11}H_{12}ClN_5 \cdot C_{20}H_{14}O_6$ (as pamoate salt)

Structural Characteristics

- Forms water-insoluble pamoate salt for sustained release
- Lipophilic, allowing tissue distribution
- Orally active

Nomenclature

- Cyclo → cyclic triazine ring
- Guanil → biguanide moiety
- Marketed as cycloguanil pamoate (oral formulation)

Stereochemistry

- Cycloguanil has no chiral centers
- Activity depends on triazine nucleus and biguanide substitution

Mechanism of Action

- Cycloguanil inhibits dihydrofolate reductase (DHFR) enzyme in *Plasmodium*.
- Prevents conversion of dihydrofolate to tetrahydrofolate.
- Blocks DNA synthesis and parasite replication in RBCs.
- Parasite death occurs.
- Hence, cycloguanil acts as a blood-stage antimalarial (blood schizonticide) via antifolate action.

Spectrum of Activity

- Erythrocytic stages of:
  - *Plasmodium falciparum*
  - *Plasmodium vivax*
- Especially effective against sensitive strains

Uses

- Treatment of malaria in combination therapy (with atovaquone)
- Prophylaxis of malaria (as proguanil metabolite)
- Alternative in chloroquine-resistant malaria

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- Headache, dizziness
- Rare: allergic reactions, skin rash

Chemical Degradation

1. Acid Degradation

- Relatively stable

2. Alkaline Degradation

- Sensitive to 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)

Triazine Ring

- Essential for DHFR inhibition

Biguanide Moiety

- Required for binding to enzyme active site

p-Chlorophenyl Substitution

- Enhances antimalarial potency

Pamoate Salt

- Improves oral bioavailability and sustained release

Lipophilicity

- Promotes tissue penetration and sustained activity

Proguanil

→ Proguanil is a synthetic biguanide antimalarial.
→ It is a prodrug, which is metabolized in the liver to cycloguanil, the active metabolite responsible for antimalarial activity.
→ Proguanil is effective as a blood schizonticide and is commonly used in combination therapy, especially with atovaquone, for prophylaxis and treatment of malaria.

Classification

Based on Chemical Class

- Biguanide derivative

Based on Antimalarial Action

- Blood schizonticide (via metabolite cycloguanil)

Based on Origin

- Synthetic antimalarial (prodrug)

Structure

Proguanil contains:

- 1,2,4-triazine ring
- Biguanide side chain
- Chlorophenyl substitution

Important structural features:

- Metabolized to cycloguanil by hepatic CYP450
- Biguanide moiety essential for DHFR inhibition

Molecular formula: $C_{11}H_{16}ClN_5$

Structural Characteristics

- Lipophilic prodrug
- Orally active
- Forms salts for improved solubility

Nomenclature

- Pro → prodrug
- Guanil → biguanide moiety
- Available as proguanil hydrochloride (oral tablet)

Stereochemistry

- Proguanil has no chiral centers
- Activity depends on conversion to cycloguanil
- Racemic mixture is used clinically

Mechanism of Action

- Proguanil is absorbed orally and metabolized in the liver to cycloguanil.
- Cycloguanil inhibits dihydrofolate reductase (DHFR) in *Plasmodium*.
- Prevents tetrahydrofolate formation, blocking DNA synthesis.
- Parasite replication in RBCs is inhibited.
- Hence, proguanil is a blood-stage antimalarial (blood schizonticide) via its metabolite.

Spectrum of Activity

Erythrocytic stages of:

- *Plasmodium falciparum*
- *Plasmodium vivax*

- Effective mainly in combination therapy
- Less effective alone against resistant strains

Uses

- Malaria prophylaxis (especially with atovaquone)
- Treatment of chloroquine-resistant *P. falciparum* malaria
- Often used in combination therapy to enhance efficacy and prevent resistance

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- Headache, dizziness
- Rare: skin rash, mild hematological effects
- Generally well tolerated

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 degradation

Prevention

- Store in **cool, dry place**
- Protect from **light**

Structure–Activity Relationship (SAR)

Triazine Ring

- Essential for DHFR inhibition

Biguanide Moiety

- Required for active metabolite cycloguanil formation

Chlorophenyl Substitution

- Enhances antimalarial potency

Prodrug Nature

- Oral absorption and liver metabolism are critical for activity

Combination Therapy

- Synergistic effect with atovaquone improves efficacy