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# MEDICINAL CHEMISTRY - III

# UNIT 4

TOPIC :

- Folate reductase inhibitors : Trimethoprim, *Cotrimoxazole.*

# Folate Reductase Inhibitors

→ Folate reductase inhibitors are antimicrobial and antiprotozoal drugs that inhibit the enzyme
→ dihydrofolate reductase (DHFR), thereby blocking folic acid → tetrahydrofolic acid conversion and inhibiting DNA synthesis.
→ Result: Inhibition of cell growth and multiplication

## Classification

A. Antibacterial DHFR Inhibitors

- Trimethoprim

B. Antiprotozoal / Antimalarial DHFR Inhibitors

- Pyrimethamine
- Proguanil (active form: cycloguanil)

C. Antifolate Anticancer Drug

- Methotrexate (mentioned in pharmacology overlap)

## Mechanism of Action

→ Folate is required for DNA and RNA synthesis
→ DHFR converts dihydrofolate → tetrahydrofolate
→ Folate reductase inhibitors block DHFR
→ DNA synthesis is inhibited
→ Cell division stops
→ Drugs are mainly bacteriostatic / protozoastatic

## Spectrum of Activity

| Drug | Effective Against |
|---|---|
| Trimethoprim | Gram-positive, Gram-negative bacteria |
| Pyrimethamine | *Plasmodium*, *Toxoplasma gondii* |
| Proguanil | *Plasmodium* species |

## Therapeutic Uses

Trimethoprim

- Urinary tract infections
- Respiratory infections
- Combined with sulphonamides (Co-trimoxazole)

Pyrimethamine

- Malaria (with sulfadoxine)
- Toxoplasmosis (with sulfadiazine)

Proguanil

- Malaria prophylaxis
- Used with atovaquone or chloroquine

## Adverse Effects

Common

- Nausea
- Vomiting
- Skin rash

Serious

- Megaloblastic anemia
- Leukopenia
- Thrombocytopenia

## Resistance

◈ Mutation of DHFR enzyme
◈ Decreased drug binding

# Trimethoprim

→ Trimethoprim is a synthetic antibacterial agent that belongs to the diaminopyrimidine class.
→ It is primarily used in urinary tract infections (UTIs), often in combination with sulfamethoxazole as co-trimoxazole.
→ Trimethoprim selectively inhibits bacterial dihydrofolate reductase (DHFR), blocking the conversion of dihydrofolic acid to tetrahydrofolic acid, which is essential for DNA, RNA, and protein synthesis.

## Classification

**Based on Chemical Class**

- Diaminopyrimidine derivative
- Synthetic antibacterial

**Based on Action**

- Bacteriostatic alone
- Bactericidal in combination with sulfonamides
- Mechanism: inhibition of bacterial dihydrofolate reductase (DHFR)

**Based on Use**

- Oral therapy – tablets, suspension
- Topical therapy – eye drops or creams (less common)

## Structure

➢ Pyrimidine ring with amino substitutions at C-2 and C-4

**Molecular formula:** $C_{14}H_{18}N_4O_3$

## Structural Characteristics

- Water-soluble → good oral absorption
- Lipophilic enough → penetrates tissues including urinary tract and respiratory tract
- Formulated as tablets, suspension, or topical preparations

## Nomenclature

⇨ Trimethoprim → generic name
⇨ Brand names: Primsol, Triprim, Proloprim
⇨ Formulations: oral tablets, suspension, eye drops/cream

## Mechanism of Action

- Trimethoprim selectively inhibits bacterial dihydrofolate reductase (DHFR).
- Prevents conversion of dihydrofolic acid to tetrahydrofolic acid.
- Blocks bacterial DNA, RNA, and protein synthesis.
- Results in bacteriostatic activity.
- When combined with sulfonamides, sequential blockade of folate pathway produces bactericidal effect.

## Spectrum of Activity

- Gram-positive bacteria: Staphylococcus aureus, Streptococcus spp.
- Gram-negative bacteria: Escherichia coli, Proteus spp., Klebsiella spp.
- Effective in urinary tract infections, respiratory infections, and certain gastrointestinal infections

## Uses

- Urinary tract infections (UTIs) – alone or with sulfamethoxazole
- Respiratory tract infections – bronchitis, pneumonia
- Gastrointestinal infections – Shigella, Salmonella
- Occasionally used topically in eye infections

## Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- Rash, urticaria, photosensitivity
- Rare: headache, dizziness, hypersensitivity reactions

## Chemical Degradation

- Sensitive to light, heat, and alkaline conditions
- Store in cool, dry place, protected from light
- Maintain proper formulation to ensure stability

## Structure–Activity Relationship (SAR)

- Diaminopyrimidine ring → essential for DHFR inhibition
- C-2 and C-4 amino groups → improve binding to bacterial DHFR
- Selective for bacterial DHFR over human DHFR → low toxicity
- Combination with sulfonamides → sequential blockade of folic acid pathway → bactericidal effect

# Cotrimoxazole

→ Cotrimoxazole is a combination antibiotic consisting of Sulfamethoxazole (SMX) and Trimethoprim (TMP) in a 5:1 ratio.
→ It is widely used for urinary tract infections (UTIs), respiratory infections, gastrointestinal infections, and prophylaxis of opportunistic infections in immunocompromised patients.
→ The combination exhibits synergistic bactericidal activity by sequential inhibition of bacterial folic acid synthesis.

## Classification

### Based on Chemical Class

- Sulfamethoxazole – sulfonamide derivative
- Trimethoprim – dihydrofolate reductase inhibitor

### Based on Antimicrobial Action

- Bactericidal (synergistic) – inhibits two sequential steps in folic acid metabolism
- Sulfamethoxazole: inhibits dihydropteroate synthase
- Trimethoprim: inhibits dihydrofolate reductase

### Based on Use

- Oral and parenteral therapy – tablets, suspension, injection

## Structure

### Sulfamethoxazole (SMX)

- Sulfonamide group attached to **heterocyclic isoxazole ring**
- Molecular formula: $C_{10}H_{11}N_3O_3S$

### Trimethoprim (TMP)

- Di-hydrofolate reductase inhibitor
- Pyrimidine derivative
- Molecular formula: $C_{14}H_{18}N_4O_3$

### Combination Characteristics

- Fixed 5:1 ratio (SMX:TMP)
- Synergistic bactericidal activity
- Formulated as tablets, oral suspension, and intravenous solution

## Nomenclature

- Cotrimoxazole → generic name
- Brand names: Septran, Bactrim, Cotrim
- Formulations: tablets, suspension, IV solution

## Mechanism of Action

- Sulfamethoxazole competitively inhibits dihydropteroate synthase → blocks conversion of PABA to dihydrofolic acid.
- Trimethoprim inhibits dihydrofolate reductase → prevents conversion of dihydrofolic acid to tetrahydrofolic acid.
- Sequential inhibition leads to complete blockade of bacterial folic acid synthesis.
- Results in synergistic bactericidal effect against susceptible bacteria.
- Hence, cotrimoxazole is bactericidal due to combination therapy, whereas each component alone is bacteriostatic.

## Spectrum of Activity

- Gram-positive bacteria: Staphylococcus aureus, Streptococcus pneumoniae
- Gram-negative bacteria: E. coli, Klebsiella, Proteus spp., Haemophilus influenzae
- Opportunistic pathogens: Pneumocystis jirovecii, Toxoplasma gondii

## Uses

- Urinary tract infections (UTIs)
- Respiratory tract infections – bronchitis, pneumonia
- Gastrointestinal infections – shigellosis, Salmonella infections
- Prophylaxis and treatment of opportunistic infections in HIV/AIDS – Pneumocystis pneumonia (PCP) and Toxoplasmosis
- MRSA infections (community-acquired)

## Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- Hypersensitivity: rash, urticaria, photosensitivity
- Hematologic: leukopenia, megaloblastic anemia, thrombocytopenia

- Rare: Stevens-Johnson syndrome, crystalluria, hepatotoxicity

## Chemical Degradation

- ❖ Sensitive to moisture, light, and extreme pH
- ❖ Store in cool, dry place, protected from light
- ❖ Stable in dry tablets and suspension formulations

## Structure–Activity Relationship (SAR)

- ➢ Sulfonamide group (SMX) → inhibits dihydropteroate synthase
- ➢ Trimethoprim pyrimidine ring → inhibits dihydrofolate reductase
- ➢ Combination → synergistic inhibition of folic acid pathway
- ➢ Fixed 5:1 ratio (SMX:TMP) maximizes bactericidal effect
- ➢ Effective against broad spectrum of Gram-positive, Gram-negative, and opportunistic pathogens