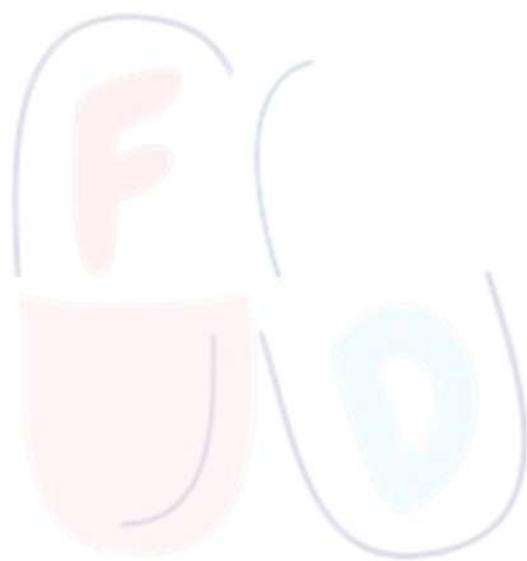


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MEDICINAL CHEMISTRY - III

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	<i>Plasmodium</i> , <i>Toxoplasma gondii</i>
Proguanil	<i>Plasmodium</i> 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

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