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MEDICINAL CHEMISTRY - III

UNIT 4

TOPIC :

- **Sulphonamides and Sulfones**

Historical development, chemistry, classification and SAR of Sulfonamides:

Sulphamethizole, Sulfisoxazole, Sulphapyridine, Sulphamethizine, Sulfacetamide, *Sulfamethoxazole*, Sulphadiazine, Mefenide acetate, Sulfasalazine



Sulfonamides

- Sulfonamides are synthetic antibacterial agents that act by inhibiting folic acid synthesis in bacteria.
- They are bacteriostatic drugs and are structural analogues of para-aminobenzoic acid (PABA).

Classification

A. Systemic Sulfonamides

1. Short-acting

- Sulfamethoxazole
- Sulfisoxazole

2. Intermediate-acting

- Sulfadiazine

3. Long-acting

- Sulfadoxine
- Sulfametomidine

B. Poorly Absorbed (Intestinal) Sulfonamides

- Sulfasalazine
- Phthalylsulfathiazole

C. Topical Sulfonamides

- Silver sulfadiazine
- Mafenide acetate
- Sulfacetamide (ophthalmic)

Mechanism of Action

- Sulfonamides resemble PABA
- They competitively inhibit dihydropteroate synthase
- Folic acid synthesis is blocked
- DNA and RNA synthesis is inhibited
- Bacterial growth is stopped
- Therefore, sulfonamides are bacteriostatic

Spectrum of Activity

- Gram-positive bacteria
- Gram-negative bacteria
- *Chlamydia*
- *Toxoplasma*
- Some protozoa

Therapeutic Uses

- + Urinary tract infections
- + Respiratory tract infections
- + Gastrointestinal infections
- + Toxoplasmosis
- + Burns (silver sulfadiazine)

Adverse Effects

Common

- Nausea
- Vomiting
- Skin rashes
- Photosensitivity

Serious

- Stevens–Johnson syndrome
- Hemolytic anemia (G6PD deficiency)
- Crystalluria
- Bone marrow suppression
- Kernicterus in newborns

Drug Interactions

- ❖ Increase effect of warfarin
- ❖ Increase effect of phenytoin
- ❖ Increase hypoglycemic effect of sulfonylureas

Resistance

- ❖ Increased PABA production

- ◇ Altered dihydropteroate synthase
- ◇ Decreased drug uptake

Sulfamethizole

- Sulphamethizole is a synthetic sulfonamide antibiotic.
- It is primarily used for urinary tract infections (UTIs) caused by Gram-positive and Gram-negative bacteria.
- Sulfonamides act as competitive inhibitors of dihydropteroate synthase, interfering with folic acid synthesis in bacteria, which is essential for DNA and RNA synthesis.

Classification

Based on Chemical Class

- Sulfonamide derivative (heterocyclic sulfonamide with a methylthiazole group)

Based on Antimicrobial Action

- Bacteriostatic – inhibits bacterial growth by preventing folic acid synthesis

Based on Use

- Oral therapy – tablets or suspension
- Mainly for urinary tract infections

Structure

⇒ Sulfonamide group attached to a heterocyclic methylthiazole ring

Molecular formula: $C_8H_8N_4O_2S_2$

Structural Characteristics

- Water-soluble → well absorbed orally
- Excreted primarily by the kidneys → effective for UTIs
- Formulated as tablets or oral suspension

Nomenclature

- ◇ Sulphamethizole → generic name
- ◇ Brand names: Thiosulfon, Urodes, Sulphin
- ◇ Formulations: oral tablets, oral suspension

Mechanism of Action

- ⇒ Sulphamethizole competitively inhibits bacterial dihydropteroate synthase.
- ⇒ Blocks the conversion of para-aminobenzoic acid (PABA) to dihydrofolic acid.
- ⇒ Disrupts folic acid synthesis, which is essential for DNA, RNA, and protein synthesis.
- ⇒ Leads to inhibition of bacterial growth.
- ⇒ Hence, sulphamethizole is bacteriostatic.

Spectrum of Activity

- Gram-positive bacteria: Staphylococcus spp., Streptococcus spp.
- Gram-negative bacteria: E. coli, Klebsiella, Proteus spp.
- Mainly effective for urinary tract infections

Uses

- ▲ Uncomplicated urinary tract infections
- ▲ Prophylaxis of recurrent UTIs
- ▲ Sometimes combined with trimethoprim for synergistic effect (co-trimoxazole)

Adverse Effects

- ▲ Gastrointestinal: nausea, vomiting, diarrhea
- ▲ Hypersensitivity reactions: rash, urticaria, photosensitivity
- ▲ Avoid in patients with G6PD deficiency

Chemical Degradation

- ❖ Sensitive to light and moisture
- ❖ Store in cool, dry place, protected from light
- ❖ Degraded in alkaline or acidic conditions

Structure–Activity Relationship (SAR)

- Sulfonamide group → essential for inhibition of dihydropteroate synthase
- Heterocyclic methylthiazole → enhances urinary excretion and activity in UTIs
- Modifications of the aromatic ring → affect potency and solubility
- Rapid renal excretion → makes it ideal for urinary tract infections

Sulfamethizole

- Sulphamethizole is a synthetic sulfonamide antibiotic.
- It is primarily used for urinary tract infections (UTIs) caused by Gram-positive and Gram-negative bacteria.
- Sulfonamides act as competitive inhibitors of dihydropteroate synthase, interfering with folic acid synthesis in bacteria, which is essential for DNA and RNA synthesis.

Classification

Based on Chemical Class

- Sulfonamide derivative (heterocyclic sulfonamide with a methylthiazole group)

Based on Antimicrobial Action

- Bacteriostatic – inhibits bacterial growth by preventing folic acid synthesis

Based on Use

- Oral therapy – tablets or suspension
- Mainly for urinary tract infections

Structure

- Sulfonamide group attached to a heterocyclic methylthiazole ring

Molecular formula: $C_8H_8N_4O_2S_2$

Structural Characteristics

- Water-soluble → well absorbed orally
- Excreted primarily by the kidneys → effective for UTIs
- Formulated as tablets or oral suspension

Nomenclature

- ◇ Sulphamethizole → generic name
- ◇ Brand names: Thiosulfon, Urodes, Sulphin
- ◇ Formulations: oral tablets, oral suspension

Mechanism of Action

- Sulphamethizole competitively inhibits bacterial dihydropteroate synthase.
- Blocks the conversion of para-aminobenzoic acid (PABA) to dihydrofolic acid.
- Disrupts folic acid synthesis, which is essential for DNA, RNA, and protein synthesis.
- Leads to inhibition of bacterial growth.
- Hence, sulphamethizole is bacteriostatic.

Spectrum of Activity

- ▲ Gram-positive bacteria: Staphylococcus spp., Streptococcus spp.
- ▲ Gram-negative bacteria: E. coli, Klebsiella, Proteus spp.
- ▲ Mainly effective for urinary tract infections

Uses

- Uncomplicated urinary tract infections
- Prophylaxis of recurrent UTIs

Adverse Effects

- ✚ Gastrointestinal: nausea, vomiting, diarrhea
- ✚ Hypersensitivity reactions: rash, urticaria, photosensitivity
- ✚ Rare: crystalluria, hematuria, Stevens-Johnson syndrome, blood dyscrasias
- ✚ Avoid in patients with G6PD deficiency

Chemical Degradation

- ❖ Sensitive to light and moisture
- ❖ Store in cool, dry place, protected from light
- ❖ Degraded in alkaline or acidic conditions

Structure–Activity Relationship (SAR)

- Sulfonamide group → essential for inhibition of dihydropteroate synthase
- Heterocyclic methylthiazole → enhances urinary excretion and activity in UTIs
- Modifications of the aromatic ring → affect potency and solubility
- Rapid renal excretion → makes it ideal for urinary tract infections

Sulfamethizine

- Sulphamethizine is a synthetic sulfonamide antibiotic.
- It is mainly used for urinary tract infections (UTIs) and certain systemic bacterial infections.
- Sulfonamides act as competitive inhibitors of dihydropteroate synthase, disrupting folic acid synthesis in bacteria, which is essential for DNA, RNA, and protein synthesis.

Classification

Based on Chemical Class

- Sulfonamide derivative (aromatic sulfonamide with a methylthiazole group)

Based on Antimicrobial Action

- Bacteriostatic – inhibits bacterial growth by interfering with folic acid synthesis

Based on Use

- Oral therapy – tablets or suspension

Structure

Sulfonamide group attached to a heterocyclic methylthiazole ring

Molecular formula: $C_{10}H_{12}N_4O_2S$

Structural Characteristics

- Water-soluble → well absorbed orally
- Excreted primarily via renal route → effective for UTIs
- Formulated as tablets or oral suspension

Nomenclature

- ◇ Sulphamethizine → generic name
- ◇ Brand names: Thiosulphin, Sulphin-S
- ◇ Formulations: tablets, oral suspension

Mechanism of Action

- ⇒ Sulphamethizine competitively inhibits bacterial dihydropteroate synthase.
- ⇒ Blocks the conversion of para-aminobenzoic acid (PABA) to dihydrofolic acid.
- ⇒ Inhibits folic acid synthesis, essential for DNA, RNA, and protein production.
- ⇒ Results in bacteriostatic effect.
- ⇒ Hence, sulphamethizine is bacteriostatic.

Spectrum of Activity

- Gram-positive bacteria: Staphylococcus spp., Streptococcus spp.
- Gram-negative bacteria: E. coli, Klebsiella, Proteus spp.
- Mainly effective for urinary tract infections

Uses

- ▲ Uncomplicated and complicated UTIs
- ▲ Systemic bacterial infections (less commonly used)
- ▲ Occasionally combined with trimethoprim for enhanced activity

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- Hypersensitivity reactions: rash, urticaria, photosensitivity
- Rare: crystalluria, hematuria, blood dyscrasias
- Avoid in patients with G6PD deficiency

Chemical Degradation

- Sensitive to light, moisture, and extreme pH
- Store in cool, dry place, protected from light
- Stability decreases in alkaline or acidic conditions

Structure–Activity Relationship (SAR)

- ✚ Sulfonamide group → essential for competitive inhibition of dihydropteroate synthase
- ✚ Methylthiazole substitution → improves urinary excretion and UTI activity
- ✚ Modifications of the aromatic ring → affect potency, solubility, and spectrum

- + Rapid renal excretion → makes it ideal for urinary tract infections

Sulfacetamide

- Sulfacetamide is a synthetic sulfonamide antibacterial.
- It is primarily used for ocular infections such as conjunctivitis and sometimes for dermatological conditions like acne vulgaris.
- Sulfacetamide acts by inhibiting bacterial folic acid synthesis, essential for nucleic acid and protein production.

Classification

Based on Chemical Class

- Sulfonamide derivative
- Synthetic antibacterial

Based on Action

- Bacteriostatic – inhibits bacterial growth
- Mechanism: competitive inhibition of dihydropteroate synthase (DHPS) → blocks folic acid synthesis

Based on Use

- Topical therapy – ophthalmic drops, ointments
- Oral therapy – less commonly used

Structure

- Sulfonamide nucleus with acetamide substitution

Molecular formula: $C_8H_{10}N_2O_3S$

Structural Characteristics

- Water-soluble → suitable for ophthalmic preparations
- Acetamide group → improves antibacterial activity and solubility
- Formulated as eye drops, eye ointments, creams

Nomenclature

- ◇ Sulfacetamide → generic name
- ◇ Brand names: Bleph-10, Sulamyd
- ◇ Formulations: ophthalmic solution, ointment, topical creams

Mechanism of Action

- ⇒ Sulfacetamide competes with para-aminobenzoic acid (PABA).
- ⇒ Inhibits dihydropteroate synthase, preventing formation of dihydrofolic acid.
- ⇒ Blocks folic acid metabolism, inhibiting bacterial DNA, RNA, and protein synthesis.
- ⇒ Leads to bacteriostatic effect.

Spectrum of Activity

- Gram-positive bacteria: *Staphylococcus aureus*, *Streptococcus* spp.
- Gram-negative bacteria: *Haemophilus influenzae*, *Neisseria* spp., some *E. coli*
- Effective mainly for ocular and topical infections

Uses

- ▲ Bacterial conjunctivitis – ophthalmic drops or ointment
- ▲ Blepharitis – eyelid infections
- ▲ Acne vulgaris – topical creams (alone or in combination with sulfur)
- ▲ Minor skin infections

Adverse Effects

- Local irritation: burning, stinging, redness in the eye
- Allergic reactions: rash, urticaria, pruritus
- Rare: systemic absorption → headache, gastrointestinal upset
- Avoid prolonged use in patients with sulfonamide hypersensitivity

Chemical Degradation

- Sensitive to light and alkaline conditions
- Store in a cool, dry place, protected from light
- Ophthalmic solutions often buffered to maintain pH and stability

Structure–Activity Relationship (SAR)

- ✚ Sulfonamide group ($-\text{SO}_2\text{NH}_2$) → essential for DHPS inhibition
- ✚ Acetamide substitution → improves water solubility and antibacterial activity
- ✚ Topical formulations → minimizes systemic absorption, increases local effect
- ✚ Effective mainly against ocular and superficial skin infections

Sulphapyridine

- Sulphapyridine is a synthetic sulfonamide antibiotic.
- It was historically used to treat systemic bacterial infections such as rheumatic fever, streptococcal infections, and meningococcal infections.
- Sulfonamides act as competitive inhibitors of dihydropteroate synthase, interfering with folic acid synthesis in bacteria, essential for DNA, RNA, and protein synthesis.

Classification

Based on Chemical Class

- Sulfonamide derivative (aromatic sulfonamide with pyridine ring)

Based on Antimicrobial Action

- Bacteriostatic – inhibits bacterial growth by blocking folic acid synthesis

Based on Use

- Oral therapy – tablets or suspension
- Historically used for systemic infections

Structure

- Sulfonamide group attached to a pyridine ring

Molecular formula: $C_{11}H_{11}N_3O_2S$

Structural Characteristics

- Water-soluble → well absorbed orally
- Distributed systemically → effective for blood-borne infections
- Formulated as tablets or oral suspension

Nomenclature

- ◇ Sulphapyridine → generic name
- ◇ Brand names: Gantrisin (historical), Sulfapyri
- ◇ Formulations: oral tablets, oral suspension

Mechanism of Action

- ⇒ Sulphapyridine competitively inhibits bacterial dihydropteroate synthase.
- ⇒ Blocks the conversion of para-aminobenzoic acid (PABA) to dihydrofolic acid.
- ⇒ Disrupts folic acid synthesis, which is required for DNA, RNA, and protein synthesis.
- ⇒ Leads to inhibition of bacterial growth.
- ⇒ Hence, sulphapyridine is bacteriostatic.

Spectrum of Activity

- Gram-positive bacteria: Streptococcus spp., Staphylococcus spp.
- Gram-negative bacteria: Neisseria spp., E. coli
- Historically used for meningococcal infections and rheumatic fever prophylaxis

Uses

- ▲ Rheumatic fever – prevention and early treatment
- ▲ Streptococcal infections
- ▲ Meningococcal infections
- ▲ Currently largely replaced by newer sulfonamides and antibiotics

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- Hypersensitivity: rash, photosensitivity, urticaria
- Rare: hemolytic anemia, crystalluria, blood dyscrasias

Chemical Degradation

- + Sensitive to light, moisture, and extreme pH
- + Store in cool, dry place, protected from light
- + Degradation occurs in alkaline or acidic conditions

Structure–Activity Relationship (SAR)

- Sulfonamide group → essential for competitive inhibition of dihydropteroate synthase
- Pyridine substitution → improves systemic absorption and distribution
- Modifications of the aromatic ring → affect potency and spectrum

- Systemic distribution → effective for blood-borne infections

Sulfamethoxazole (SMX)

- Sulfamethoxazole is a synthetic sulfonamide antibacterial commonly used in combination with trimethoprim (as co-trimoxazole).
- It acts by inhibiting bacterial folic acid synthesis, which is necessary for DNA, RNA, and protein synthesis.
- The combination with trimethoprim provides synergistic bactericidal activity against a broad spectrum of bacteria.

Classification

Based on Chemical Class

- Sulfonamide derivative
- Synthetic antibacterial

Based on Action

- Bacteriostatic alone
- Bactericidal in combination with trimethoprim
- Mechanism: competitive inhibition of dihydropteroate synthase (DHPS) → blocks folic acid synthesis

Based on Use

- Oral therapy – tablets, suspension
- Often combined with trimethoprim for enhanced effect

Structure

- Sulfonamide nucleus with methoxazole substitution

Molecular formula: $C_{10}H_{11}N_3O_3S$

Structural Characteristics

- Poorly water-soluble → absorption enhanced with oral formulations
- Methoxazole ring → improves antibacterial potency and spectrum
- Formulated as tablets, oral suspension, or combination with trimethoprim

Nomenclature

- ◇ Sulfamethoxazole → generic name
- ◇ Brand names: Gantanol, Bactrim (in combination with trimethoprim)
- ◇ Formulations: oral tablets, suspension, combined preparations

Mechanism of Action

- ⇒ Sulfamethoxazole competes with para-aminobenzoic acid (PABA).
- ⇒ Inhibits dihydropteroate synthase, preventing synthesis of dihydrofolic acid.
- ⇒ Combination with trimethoprim inhibits dihydrofolate reductase, producing synergistic bactericidal effect.
- ⇒ Hence, sulfamethoxazole alone is bacteriostatic, but bactericidal with trimethoprim.

Spectrum of Activity

- ▲ Gram-positive bacteria: *Staphylococcus aureus*, *Streptococcus pneumoniae*
- ▲ Gram-negative bacteria: *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Haemophilus influenzae*
- ▲ Effective against urinary tract infections, respiratory infections, and some GI infections

Uses

- Urinary tract infections (UTIs)
- Respiratory tract infections – bronchitis, pneumonia
- Gastrointestinal infections – *Shigella*, *Salmonella*

Adverse Effects

- + Gastrointestinal: nausea, vomiting, diarrhea
- + Hypersensitivity: rash, urticaria, photosensitivity
- + Rare: Stevens-Johnson syndrome

Chemical Degradation

- ❖ Sensitive to light, moisture, and alkaline conditions
- ❖ Store in cool, dry place, protected from light

Structure–Activity Relationship (SAR)

- Sulfonamide group ($-\text{SO}_2\text{NH}_2$) → essential for DHPS inhibition
- Methoxazole ring → improves potency and spectrum
- Combination with trimethoprim → blocks sequential steps in folic acid pathway, enhancing bactericidal effect
- Effective for systemic and urinary infections due to good oral absorption and tissue penetration

Sulphadiazine

- Sulphadiazine is a synthetic sulfonamide antibiotic.
- It is primarily used for systemic bacterial infections and protozoal infections, especially in combination with pyrimethamine for toxoplasmosis.
- Sulfonamides act as competitive inhibitors of dihydropteroate synthase, interfering with folic acid synthesis in bacteria and protozoa, essential for DNA, RNA, and protein synthesis.

Classification

Based on Chemical Class

- Sulfonamide derivative (heterocyclic sulfonamide with pyrimidine-like substitution)

Based on Antimicrobial Action

- Bacteriostatic – inhibits bacterial growth by blocking folic acid synthesis
- Active against protozoa when combined with dihydrofolate reductase inhibitors

Based on Use

- Oral therapy – tablets or suspension
- Used in combination therapy for toxoplasmosis

Structure

- Sulfonamide group attached to a heterocyclic pyrimidine-like ring

Molecular formula: $C_{10}H_{10}N_4O_2S$

Structural Characteristics

- Water-soluble → well absorbed orally
- Systemically distributed → effective for blood-borne infections and protozoal infections
- Formulated as tablets, oral suspension, and injectable forms

Nomenclature

- ◇ Sulphadiazine → generic name
- ◇ Brand names: Daraprim (in combination), Silvadene (topical for burns)
- ◇ Formulations: oral tablets, suspension, topical cream

Mechanism of Action

- Sulphadiazine competitively inhibits bacterial dihydropteroate synthase.
- Blocks the conversion of para-aminobenzoic acid (PABA) to dihydrofolic acid.
- Disrupts folic acid synthesis, required for DNA, RNA, and protein synthesis.
- Results in bacteriostatic effect.
- When combined with pyrimethamine, it becomes synergistically parasitocidal against *Toxoplasma gondii*.

Spectrum of Activity

- ⇒ Gram-positive bacteria: *Staphylococcus* spp., *Streptococcus* spp.
- ⇒ Gram-negative bacteria: *E. coli*, *Salmonella* spp., *Shigella* spp.
- ⇒ Protozoa: *Toxoplasma gondii* (in combination with pyrimethamine)
- ⇒ Used in systemic bacterial and protozoal infections

Uses

- ▲ Systemic bacterial infections – UTIs, meningococcal infections
- ▲ Toxoplasmosis – in combination with pyrimethamine

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- Hypersensitivity: rash, photosensitivity, urticaria
- Monitor renal and hepatic function for prolonged therapy

Chemical Degradation

- ✚ Sensitive to light, moisture, and extreme pH
- ✚ Store in cool, dry place, protected from light
- ✚ Degraded under strongly acidic or alkaline conditions

Structure–Activity Relationship (SAR)

- ✓ Sulfonamide group → essential for competitive inhibition of dihydropteroate synthase
- ✓ Heterocyclic pyrimidine substitution → enhances systemic absorption and distribution
- ✓ Rapid renal excretion → effective for urinary tract infections

- ✓ Combination with dihydrofolate reductase inhibitors → synergistic anti-protozoal effect

Mefenide Acetate

- Mefenide acetate is a synthetic sulfonamide antibacterial used primarily as a topical agent in burn wounds.
- It prevents bacterial infections in second- and third-degree burns and is effective against Gram-positive and Gram-negative organisms.
- It acts by inhibiting bacterial folic acid synthesis, which is essential for DNA, RNA, and protein synthesis.

Classification

Based on Chemical Class

- Sulfonamide derivative
- Topical antibacterial

Based on Action

- Bacteriostatic – inhibits bacterial growth
- Mechanism: competitive inhibition of dihydropteroate synthase (DHPS) → blocks folic acid synthesis

Based on Use

- Topical therapy – cream for burn wound infections

Structure

- Sulfonamide nucleus with acetamide substitution

Molecular formula: $C_{12}H_{14}N_2O_2S$

Structural Characteristics

- Water-soluble → suitable for topical formulations
- Lipophilic properties → penetrates burn eschar
- Formulated as 2% cream

Nomenclature

- Mefenide acetate → generic name
- Brand names: Sulfamylon
- Formulations: topical cream (2%)

Mechanism of Action

- ❖ Mefenide acetate competitively inhibits para-aminobenzoic acid (PABA).
- ❖ Blocks dihydropteroate synthase (DHPS) → prevents dihydrofolic acid formation.
- ❖ Inhibits bacterial DNA, RNA, and protein synthesis.
- ❖ Results in bacteriostatic effect in the wound area.
- ❖ Hence, mefenide acetate is bacteriostatic.

Spectrum of Activity

- ⇒ Gram-positive bacteria: *Staphylococcus aureus*, *Streptococcus pyogenes*
- ⇒ Gram-negative bacteria: *Pseudomonas aeruginosa*, *E. coli*
- ⇒ Effective in burn wound infections and prevention of sepsis

Uses

- Topical treatment of burn wounds (2nd and 3rd degree)
- Prevention of infection in extensive burns
- Sometimes used for minor skin infections in sensitive areas

Adverse Effects

- ▲ Pain or burning sensation on application
- ▲ Allergic reactions: rash, itching
- ▲ Metabolic: rare metabolic acidosis when applied to large areas
- ▲ Generally well tolerated for topical use

Chemical Degradation

- ✚ Sensitive to light and moisture
- ✚ Store in cool, dry place, protected from light
- ✚ Maintain proper formulation to ensure stability in cream

Structure–Activity Relationship (SAR)

- ❖ Sulfonamide group ($-\text{SO}_2\text{NH}_2$) → essential for DHPS inhibition
- ❖ Acetamide substitution → improves lipophilicity and penetration of burn eschar
- ❖ Effective topically due to local antibacterial action and limited systemic absorption

- ❖ Prevents infection in deep burn wounds without significant systemic toxicity

Sulfasalazine

- Sulfasalazine is a synthetic sulfonamide derivative with anti-inflammatory and antibacterial properties.
- It is primarily used in the treatment of inflammatory bowel disease (IBD) such as ulcerative colitis and rheumatoid arthritis.
- Sulfasalazine acts by inhibiting prostaglandin synthesis and reducing inflammation, while its sulfonamide component provides mild antibacterial activity in the gut.

Classification

Based on Chemical Class

- Sulfonamide derivative linked to 5-aminosalicylic acid (5-ASA)

Based on Pharmacological Action

- Anti-inflammatory – reduces prostaglandin and leukotriene synthesis
- Mild antibacterial – acts locally in the gut
- Metabolized in the colon to 5-ASA (active anti-inflammatory) and sulfapyridine

Based on Use

- Oral therapy – tablets, enteric-coated formulations

Structure

- Prodrug composed of sulfapyridine linked to 5-aminosalicylic acid via an azo bond (-N=N-)

Molecular formula: $C_{18}H_{14}N_4O_5S$

Structural Characteristics

- Poorly absorbed in the small intestine → reaches colon where bacterial azoreductases cleave it
- Active moiety 5-ASA reduces inflammation locally
- Formulated as tablets or enteric-coated tablets

Nomenclature

- ❖ Sulfasalazine → generic name
- ❖ Brand names: Azulfidine, Salazopyrin

- ◇ Formulations: tablets, enteric-coated tablets

Mechanism of Action

- ▲ Sulfasalazine is poorly absorbed in the small intestine.
- ▲ In the colon, bacterial azoreductases cleave the azo bond → releases 5-ASA (mesalazine) and sulfapyridine.
- ▲ 5-ASA: inhibits prostaglandin and leukotriene synthesis, reducing inflammation.
- ▲ Sulfapyridine: mild antibacterial activity in the colon.
- ▲ Reduces symptoms of ulcerative colitis and rheumatoid arthritis.
- ▲ Hence, sulfasalazine acts as a prodrug with anti-inflammatory and antibacterial action.

Spectrum of Activity

- Anti-inflammatory: colonic mucosa in ulcerative colitis
- Mild antibacterial: acts on intestinal bacteria producing the azo reduction
- Not effective systemically as an antibiotic

Uses

- + Ulcerative colitis – induction and maintenance of remission
- + Crohn's disease – limited use for colonic involvement
- + Off-label: juvenile idiopathic arthritis

Adverse Effects

- ◇ Gastrointestinal: nausea, vomiting, abdominal discomfort
- ◇ Hypersensitivity: rash, fever, urticaria
- ◇ Hematological: rare agranulocytosis, hemolytic anemia, leukopenia

Chemical Degradation

- + Sensitive to light and moisture
- + Store in cool, dry place, protected from light
- + Azo bond is stable in tablet form but cleaved by intestinal bacteria

Structure–Activity Relationship (SAR)

- ❖ Azo linkage ($-N=N-$) → prodrug design allowing colon-specific release
- ❖ 5-ASA moiety → responsible for anti-inflammatory activity
- ❖ Sulfapyridine moiety → provides local antibacterial effect
- ❖ Poor absorption in the small intestine → acts locally in the colon

