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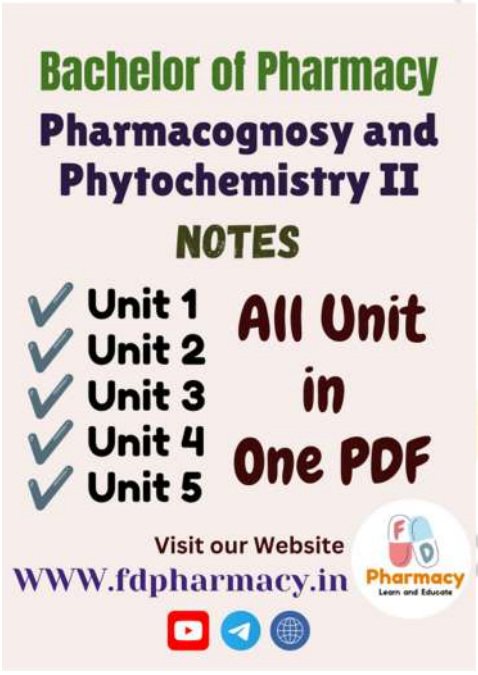
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MEDICINAL CHEMISTRY - II

UNIT 2

TOPIC :

- **Diuretics:**

  Carbonic anhydrase inhibitors : Acetazolamide, Methazolamide, Dichlorphenamide.

  Thiazides : Chlorthiazide, Hydrochlorothiazide, Hydroflumethiazide, Cyclothiazide,

  Loop diuretics : Furosemide*,Bumetanide, Ethacrynicacid.

  Potassiumsparing

  Diuretics : Spironolactone, Triamterene, Amiloride.

  Osmotic Diuretics : Mannitol

Diuretics

Diuretics are drugs that increase the excretion of water and electrolytes (mainly sodium and chloride) from the kidneys, leading to increased urine output (diuresis).

Clinical relevance :

- Management of hypertension
- Treatment of edema associated with heart failure, liver cirrhosis, or kidney disease
- Treatment of hypercalcemia
- Used in acute renal failure and glaucoma (specific diuretics)

Classification

- **Carbonic anhydrase inhibitors :** Acetazolamide*, Methazolamide, Dichlorphenamide.
- **Thiazides :** Chlorthiazide*, Hydrochlorothiazide, Hydroflumethiazide, Cyclothiazide,
- **Loop diuretics :** Furosemide*,Bumetanide, Ethacrynicacid.
- **Potassium sparing Diuretics :** Spironolactone, Triamterene, Amiloride.
- **Osmotic Diuretics :** Mannitol

Carbonic Anhydrase Inhibitors (CAIs)

Carbonic anhydrase inhibitors are a class of diuretics that inhibit the enzyme carbonic anhydrase in the kidneys, eye, and other tissues.

- Primary site of action: Proximal convoluted tubule of the nephron
- Effect: Reduce reabsorption of bicarbonate (HCO_3^-), sodium (Na^+), and water, leading to mild diuresis.
- Additional use : Decrease aqueous humor production in the eye, reducing intraocular pressure in glaucoma.

Mechanism of Action

1. Inhibition of carbonic anhydrase
    - Carbonic anhydrase catalyzes the conversion:

      CO2+H2O↔H2CO3↔H++HCO3−CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-CO2+H2O↔H2CO3 ↔H++HCO3−

    - Inhibition prevents H^+ secretion into tubular lumen → decreases Na^+ reabsorption via Na^+/H^+ exchanger.
2. Reduced bicarbonate reabsorption
    - Excess bicarbonate is excreted in urine → alkaline urine
3. Mild diuresis
    - Sodium, potassium, and water are excreted along with bicarbonate

Example

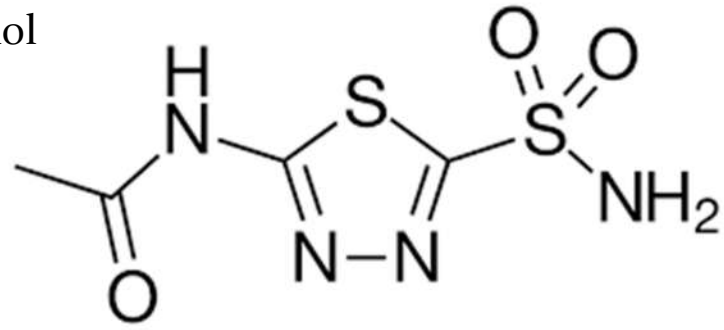
- Acetazolamide*,
- Methazolamide,
- Dichlorphenamide.

Acetazolamide

- Acetazolamide is a carbonic anhydrase inhibitor.
- It reduces aqueous humor formation, cerebrospinal fluid (CSF) production, and renal bicarbonate reabsorption.
- Used in glaucoma, altitude sickness, edema, and occasionally as a diuretic.
- Administered orally (tablets, capsules) or intravenously for acute conditions.

Chemical Structure

- IUPAC Name: N-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide
- Molecular Formula: $C_4H_6N_4O_3S_2$
- Molecular Weight: 222.24 g/mol
- Structure



Mechanism of Action

1. Carbonic anhydrase inhibition:
   - Inhibits carbonic anhydrase in proximal renal tubules, eye, and CNS.
2. Renal effects:
   - ↓ reabsorption of bicarbonate, sodium, and water → mild diuretic effect.
3. Ocular effects:
   - ↓ aqueous humor formation → reduces intraocular pressure (IOP).
4. Other effects:
   - ↓ CSF production → useful in idiopathic intracranial hypertension.
   - Alters systemic pH → used prophylactically in altitude sickness.

Synthesis

- Starting materials: thiadiazole derivatives and acetamide precursors.
- Stepwise outline:
    1. Formation of 1,3,4-thiadiazole ring with sulfonamide group.
    2. Acetylation of amino group to form acetamide substitution.
    3. Purification via recrystallization to obtain pharmaceutically pure acetazolamide.

Uses

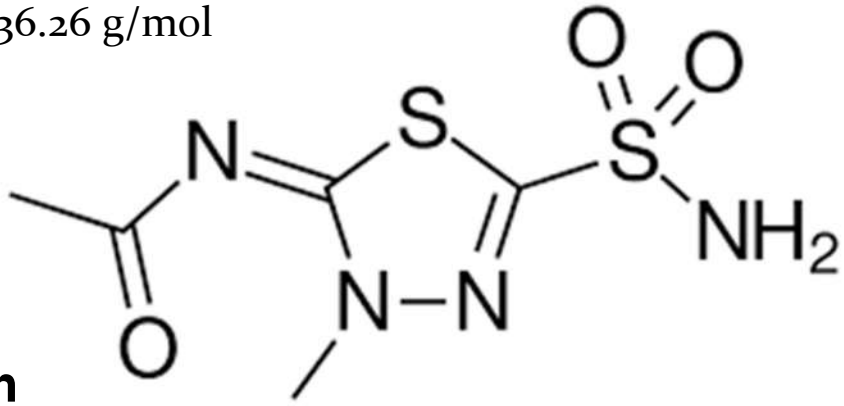
1. Glaucoma :
    - Reduces intraocular pressure by decreasing aqueous humor formation.
2. Edema :
    - Adjunctive therapy for fluid retention associated with heart failure or diuretic resistance.
3. Altitude sickness :
    - Prevents acute mountain sickness by acidifying blood and stimulating respiration.
4. Other uses :
    - Idiopathic intracranial hypertension, certain seizure disorders (as adjunct therapy).
5. Side effects :
    - Common: tingling in extremities, polyuria, fatigue, nausea.
    - Rare: metabolic acidosis, kidney stones, hypokalemia, hypersensitivity reactions.

Methazolamide

- Methazolamide is a carbonic anhydrase inhibitor.
- Structurally and pharmacologically related to acetazolamide, but more potent and longer-acting.
- Used primarily in glaucoma to reduce intraocular pressure (IOP).
- Administered orally in tablet form.
- It also has mild diuretic activity.

Chemical Structure

- IUPAC Name: N-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)-N-methylacetamide
- Molecular Formula: $C_5H_6N_4O_3S_2$
- Molecular Weight: 236.26 g/mol
- Structure:



Mechanism of Action

1. Carbonic anhydrase inhibition:
   - Inhibits carbonic anhydrase in ciliary body of the eye, kidney, and CNS.
2. Ocular effects:
   - ↓ aqueous humor formation → reduces intraocular pressure (IOP).
3. Renal effects:
   - Mild inhibition of bicarbonate reabsorption in proximal renal tubules → mild diuresis.
4. Other effects:
   - Alters systemic pH → sometimes useful for prophylaxis of altitude sickness.

Synthesis

- Starting materials: thiadiazole derivatives and methylacetamide precursors.
- Stepwise outline:
    1. Formation of 1,3,4-thiadiazole ring with sulfonamide substitution.
    2. N-methylation of acetamide group at position 2.
    3. Purification via recrystallization to obtain pharmaceutically pure methazolamide.

Uses

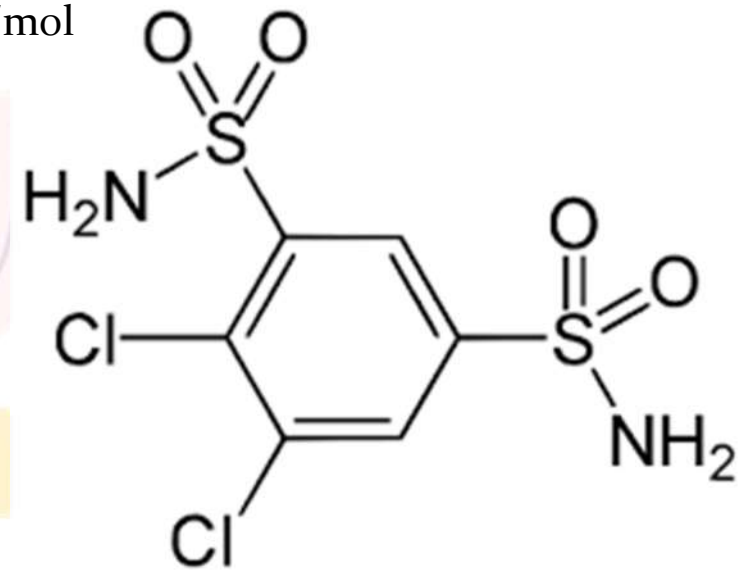
1. Glaucoma:
    - Reduces intraocular pressure in chronic open-angle glaucoma and ocular hypertension.
2. Other uses:
    - Mild diuretic effect in edema or altitude sickness prophylaxis (less common).
3. Side effects:
    - Tingling in extremities, nausea, fatigue, headache.
    - Rare: metabolic acidosis, kidney stones, hypersensitivity reactions, electrolyte imbalance.

Dichlorphenamide

- Dichlorphenamide is a carbonic anhydrase inhibitor.
- It is used primarily for glaucoma to reduce intraocular pressure (IOP).
- Also used in some cases for periodic paralysis and edema, though its primary use is ophthalmic.
- Administered orally as tablets.
- It is structurally related to acetazolamide and methazolamide.

Chemical Structure

- IUPAC Name: N-(5,6-dichloro-1,3,4-thiadiazol-2-yl)acetamide
- Molecular Formula: $C_4H_3Cl_2N_3O_2S$
- Molecular Weight: 207.05 g/mol
- Structure:



Mechanism of Action

1. Carbonic anhydrase inhibition:
   - Inhibits carbonic anhydrase in the ciliary body of the eye, kidneys, and CNS.
2. Ocular effects:
   - ↓ aqueous humor production → reduces intraocular pressure (IOP).
3. Renal effects:
   - Mild inhibition of bicarbonate reabsorption → mild diuresis.
4. Other effects:
   - Can alter systemic acid-base balance; used in some cases for periodic paralysis.

Synthesis

- Starting materials: dichlorothiadiazole derivatives and acetamide precursors.
- Stepwise outline:
    1. Formation of 1,3,4-thiadiazole ring with dichloro substitution.
    2. Acetylation to form acetamide group at position 2.
    3. Purification via recrystallization to obtain pharmaceutically pure dichlorphenamide.

Uses

1. Glaucoma:
    - Reduces intraocular pressure in chronic open-angle glaucoma and ocular hypertension.
2. Other uses:
    - Periodic paralysis (as prophylaxis).
    - Mild diuretic in fluid retention (less common).
3. Side effects:
    - Paresthesia, fatigue, nausea, headache.
    - Rare: metabolic acidosis, kidney stones, hypokalemia, hypersensitivity reactions.

Thiazide Diuretics

Thiazides are a class of diuretics that inhibit sodium and chloride reabsorption in the distal convoluted tubule of the nephron.

- They are moderately potent diuretics
- Commonly used in hypertension, edema, and certain kidney disorders
- They also reduce urinary calcium excretion, making them useful in prevention of kidney stones

Mechanism of Action

1. Inhibit Na^+-Cl^- symporter in the distal convoluted tubule → decreased sodium and chloride reabsorption
2. Increase water excretion along with sodium → mild diuresis
3. Reduce peripheral resistance with chronic use → antihypertensive effect
4. Decrease urinary calcium excretion → beneficial in preventing calcium-containing kidney stones

Example

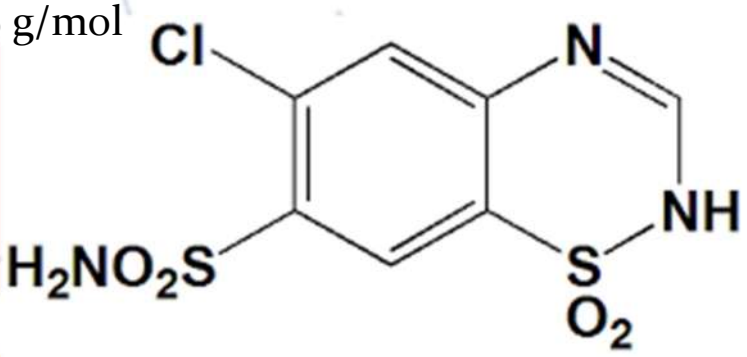
- Chlorthiazide*,
- Hydrochlorothiazide,
- Hydroflumethiazide,
- Cyclothiazide

Chlorthiazide

- Chlorthiazide is a thiazide diuretic.
- It acts on the distal convoluted tubule of the nephron to promote sodium, chloride, and water excretion.
- Used in the management of hypertension, edema associated with heart failure, renal, or hepatic disease, and sometimes in nephrolithiasis.
- Administered orally (tablets, capsules) and also available intravenously for acute fluid overload.

Chemical Structure

- IUPAC Name: 6-chloro-1,1-dioxo-1,2-benzothiazine-7-sulfonamide
- Molecular Formula: $C_7H_6ClN_3O_4S_2$
- Molecular Weight: 295.79 g/mol
- Structure:



Chlorothiazide

Mechanism of Action

1. Inhibition of Na^+/Cl^- symporter:
   - Blocks sodium and chloride reabsorption in the distal convoluted tubule.
2. Diuretic effects:
   - Increases excretion of sodium, chloride, potassium, and water → reduces extracellular fluid volume.
3. Antihypertensive effects:
   - ↓ blood volume → ↓ cardiac output and peripheral vascular resistance → lowers blood pressure.
4. Other effects:
   - Mild calcium-sparing effect → may reduce risk of kidney stones.

Synthesis

- Starting materials: substituted benzothiadiazine derivatives.
- Stepwise outline:
    1. Formation of 1,2-benzothiazine ring.
    2. Introduction of sulfonamide group at position 7.
    3. Chlorination at position 6.
    4. Oxidation to form sulfonyl (S=O) groups.
    5. Purification via recrystallization to yield pharmaceutically pure chlorthiazide.

Uses

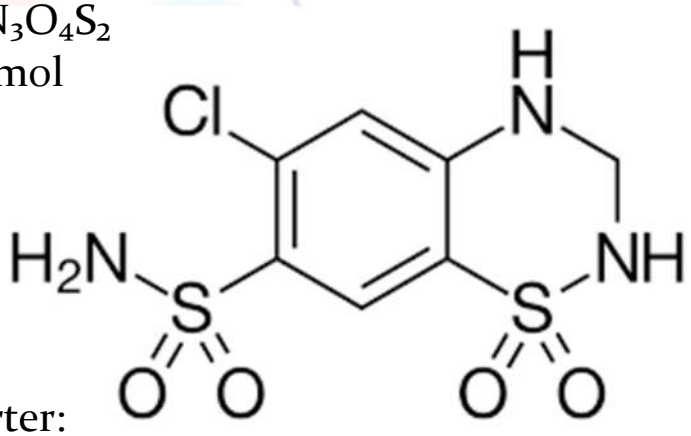
1. Hypertension:
    - First-line therapy in mild-to-moderate hypertension.
2. Edema:
    - Associated with heart failure, nephrotic syndrome, or hepatic cirrhosis.
3. Nephrolithiasis prevention:
    - Reduces urinary calcium excretion.
4. Side effects:
    - Common: hypokalemia, hyponatremia, hypotension, dizziness, headache.
    - Less common: hyperuricemia, hyperglycemia, photosensitivity, allergic reactions.

Hydrochlorothiazide

- Hydrochlorothiazide (HCTZ) is a thiazide diuretic.
- Acts on the distal convoluted tubule of the nephron to increase excretion of sodium and water, with accompanying loss of chloride and potassium.
- Used for hypertension, edema associated with heart failure, renal, or hepatic disease, and sometimes for nephrolithiasis prevention.
- Administered orally as tablets, usually once or twice daily depending on formulation.

Chemical Structure

- IUPAC Name: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide
- Molecular Formula: $C_7H_8ClN_3O_4S_2$
- Molecular Weight: 297.73 g/mol
- Structure:



Mechanism of Action

1. Inhibition of Na^+/Cl^- symporter:
    - Blocks sodium and chloride reabsorption in the distal convoluted tubule.
2. Diuretic effects:
    - Increases excretion of sodium, chloride, potassium, and water → reduces extracellular fluid volume.
3. Antihypertensive effects:
    - ↓ blood volume → ↓ cardiac output and peripheral vascular resistance → lowers blood pressure.
4. Other effects:
    - Mild calcium-sparing effect → may reduce the risk of kidney stones.

Synthesis

- Starting materials: substituted benzothiadiazine derivatives.
- Stepwise outline:
    1. Formation of 1,2-benzothiadiazine ring.
    2. Introduction of sulfonamide group at position 7.
    3. Chlorination at position 6.
    4. Oxidation to form sulfonyl (S=O) groups.
    5. Purification via recrystallization to yield pharmaceutically pure hydrochlorothiazide.

Uses

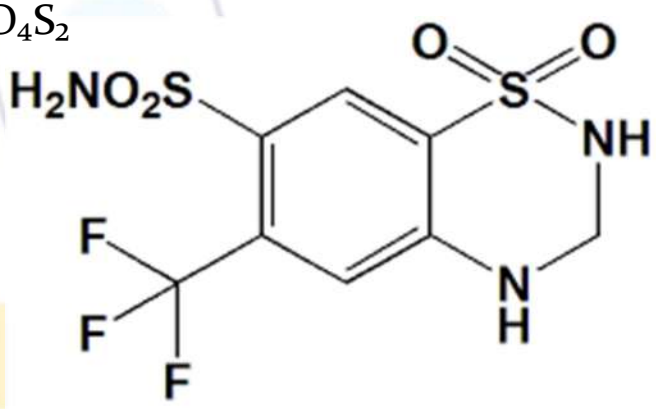
1. Hypertension:
    - First-line therapy for mild-to-moderate hypertension, alone or in combination.
2. Edema:
    - Associated with heart failure, nephrotic syndrome, or hepatic cirrhosis.
3. Nephrolithiasis prevention:
    - Reduces urinary calcium excretion.
4. Side effects:
    - Common: hypokalemia, hyponatremia, hypotension, dizziness, headache.
    - Less common: hyperuricemia, hyperglycemia, photosensitivity, allergic reactions.

Hydroflumethiazide

- Hydroflumethiazide is a thiazide-like diuretic.
- Acts on the distal convoluted tubule of the nephron to increase excretion of sodium, chloride, and water.
- Used primarily for hypertension and edema associated with heart failure, renal, or hepatic disorders.
- Administered orally in tablet form.
- Structurally similar to hydrochlorothiazide but with enhanced potency and longer duration of action.

Chemical Structure

- IUPAC Name: 6-chloro-3-(trifluoromethyl)-1,1-dioxo-3,4-dihydro-1,2,4-benzothiadiazine-7-sulfonamide
- Molecular Formula: $C_8H_6ClF_3N_3O_4S_2$
- Molecular Weight: 387.66 g/mol
- Structure:



hydroflumethiazide

Mechanism of Action

1. Inhibition of Na^+/Cl^- symporter:
   - Blocks sodium and chloride reabsorption in the distal convoluted tubule.
2. Diuretic effects:
   - Increases excretion of sodium, chloride, potassium, and water → reduces extracellular fluid volume.
3. Antihypertensive effects:
   - ↓ blood volume → ↓ cardiac output and peripheral vascular resistance → lowers blood pressure.
4. Other effects:
   - Mild calcium-sparing effect → may reduce risk of kidney stones.

Synthesis

- Starting materials: substituted benzothiadiazine derivatives.
- Stepwise outline:
    1. Formation of 1,2-benzothiadiazine ring.
    2. Introduction of sulfonamide group at position 7.
    3. Chlorination at position 6.
    4. Trifluoromethylation at position 3.
    5. Oxidation to form sulfone groups.
    6. Purification via recrystallization to yield pharmaceutically pure hydroflumethiazide.

Uses

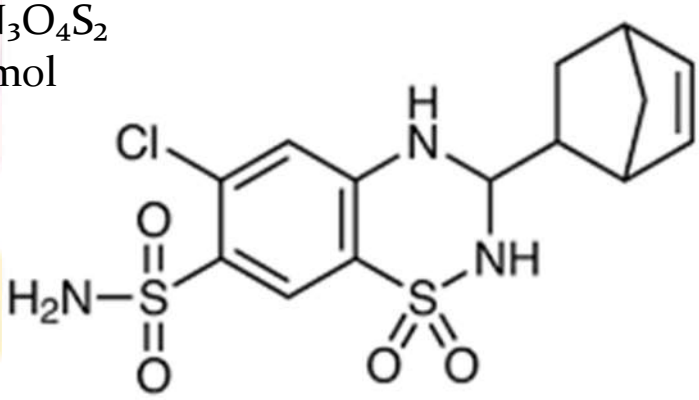
1. Hypertension:
    - First-line therapy, often used in combination with other antihypertensives.
2. Edema:
    - Associated with heart failure, nephrotic syndrome, or hepatic cirrhosis.
3. Side effects:
    - Common: hypokalemia, hyponatremia, hypotension, dizziness.
    - Less common: hyperuricemia, hyperglycemia, photosensitivity, allergic reactions.

Cyclothiazide

- Cyclothiazide is a thiazide diuretic and a positive allosteric modulator of AMPA-type glutamate receptors (used in neuroscience research).
- In clinical pharmacology, it acts as a diuretic by inhibiting sodium and chloride reabsorption in the distal convoluted tubule.
- Used for hypertension and edema associated with heart failure, renal, or hepatic disorders.
- Administered orally in tablet form.
- Structurally related to hydrochlorothiazide but has cyclization on the benzothiadiazine ring, enhancing pharmacological potency.

Chemical Structure

- IUPAC Name: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide, 1,1-dioxide, cyclized derivative
- Molecular Formula: $C_8H_8ClN_3O_4S_2$
- Molecular Weight: 341.68 g/mol
- Structure:



Mechanism of Action

1. Inhibition of Na^+/Cl^- symporter:
   - Blocks sodium and chloride reabsorption in the distal convoluted tubule.
2. Diuretic effects:
   - Increases excretion of sodium, chloride, potassium, and water → reduces extracellular fluid volume.
3. Antihypertensive effects:
   - ↓ blood volume → ↓ cardiac output and peripheral vascular resistance → lowers blood pressure.
4. Other effects:
   - Mild calcium-sparing effect → may reduce risk of kidney stones.

Synthesis

- Starting materials: substituted benzothiadiazine derivatives.
- Stepwise outline:
    1. Formation of cyclized 1,2-benzothiadiazine ring.
    2. Introduction of sulfonamide group at position 7.
    3. Chlorination at position 6.
    4. Oxidation to form sulfone groups.
    5. Purification via recrystallization to obtain pharmaceutically pure cyclothiazide.

Uses

1. Hypertension:
    - Used for mild-to-moderate hypertension, sometimes in combination therapy.
2. Edema:
    - Associated with heart failure, nephrotic syndrome, or hepatic cirrhosis.
3. Research use:
    - As an AMPA receptor modulator in neuroscience studies (non-clinical).
4. Side effects:
    - Common: hypokalemia, hyponatremia, dizziness, headache.
    - Less common: hyperuricemia, hyperglycemia, photosensitivity, allergic reactions.

Loop Diuretics

Loop diuretics are potent diuretics that act on the thick ascending limb of the loop of Henle to inhibit sodium, potassium, and chloride reabsorption.

- They are more powerful than thiazides and carbonic anhydrase inhibitors.
- Used in conditions requiring rapid and significant fluid removal.

Mechanism of Action

1. Inhibit Na^+-K^+-$2Cl^-$ symporter in the thick ascending limb of the loop of Henle
2. Increase excretion of sodium, chloride, potassium, calcium, and magnesium
3. Reduce medullary osmotic gradient, impairing water reabsorption in the collecting ducts
4. Leads to rapid diuresis and decreased blood volume

Example

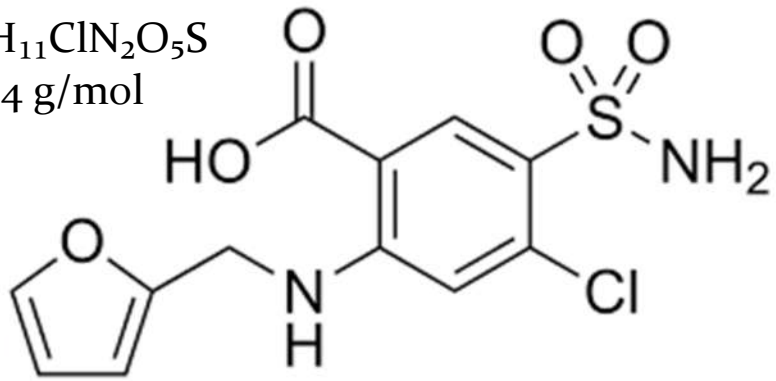
- Furosemide*,
- Bumetanide,
- Ethacrynicacid.

Furosemide

- Furosemide is a loop diuretic belonging to the sulfonamide class.
- It acts on the thick ascending limb of the loop of Henle, producing potent diuresis and natriuresis.
- It is stronger than thiazides, hence called a “high-ceiling diuretic”.
- Administered orally (tablets, solution) or parenterally (IV/IM) in acute conditions like pulmonary edema.
- It is commonly used in hypertension, edema, and conditions of fluid overload.

Chemical Structure

- IUPAC Name: 4-chloro-2-[(furan-2-ylmethyl)amino]-5-sulfamoylbenzoic acid
- Molecular Formula: $C_{12}H_{11}ClN_2O_5S$
- Molecular Weight: 330.74 g/mol
- Structure:



Mechanism of Action

1. Inhibition of Na^+-K^+-$2Cl^-$ symporter:
    - Blocks sodium, potassium, and chloride reabsorption in the thick ascending limb of loop of Henle.
2. Potent diuretic action:
    - Large amounts of sodium, chloride, potassium, calcium, and magnesium are excreted → strong diuresis.
3. Hemodynamic effects:
    - Rapid venodilation → decreases preload in acute pulmonary edema.
4. Secondary antihypertensive action:
    - Volume depletion reduces cardiac output and blood pressure.

Synthesis

- Starting materials: substituted chlorobenzoic acid derivatives.
- Stepwise outline:
    1. Synthesis of 4-chloro-5-sulfamoylbenzoic acid.
    2. Introduction of furan-2-ylmethylamino group at position 2.
    3. Purification through crystallization to obtain pure furosemide.

Uses

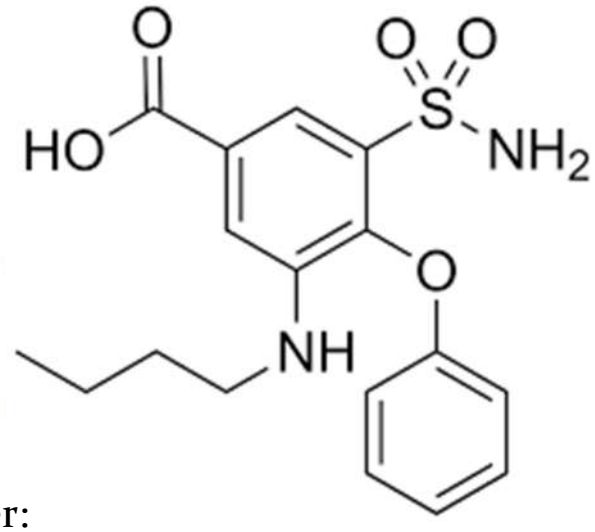
1. Edema:
    - Congestive heart failure, cirrhosis of liver, renal diseases, nephrotic syndrome.
2. Hypertension:
    - Moderate-to-severe cases, especially in patients with renal insufficiency.
3. Acute pulmonary edema:
    - IV furosemide gives rapid relief.
4. Hypercalcemia & hyperkalemia:
    - Promotes calcium and potassium excretion.

Bumetanide

- Bumetanide is a loop diuretic, structurally related to sulfonamides.
- It acts on the thick ascending limb of the loop of Henle, producing potent diuresis (40 times more potent than furosemide).
- Used mainly in the management of edema due to congestive heart failure, hepatic cirrhosis, renal disease, and sometimes in hypertension.
- Available in oral (tablet) and parenteral (IV/IM) formulations.
- Rapid onset and short duration of action compared to furosemide.

Chemical Structure

- IUPAC Name: 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoic acid
- Molecular Formula: $C_{17}H_{20}N_2O_5S$
- Molecular Weight: 364.41 g/mol
- Structure



Mechanism of Action

1. Inhibition of Na^+-K^+-$2Cl^-$ symporter:
    - Blocks reabsorption of sodium, potassium, and chloride in the thick ascending limb of the loop of Henle.
2. Diuretic action:
    - Causes excretion of sodium, chloride, potassium, calcium, and magnesium → strong diuresis.
3. Hemodynamic effects:
    - Decreases blood volume → reduces preload and cardiac output.
4. Antihypertensive action:
    - Long-term blood pressure reduction due to extracellular fluid volume depletion.

Synthesis

- Starting material: substituted benzoic acid derivatives.
- Stepwise outline:
    1. Preparation of sulfamoylbenzoic acid.
    2. Substitution with phenoxy group.
    3. Introduction of butylamino substituent at position 3.
    4. Purification through crystallization → yields Bumetanide.

Uses

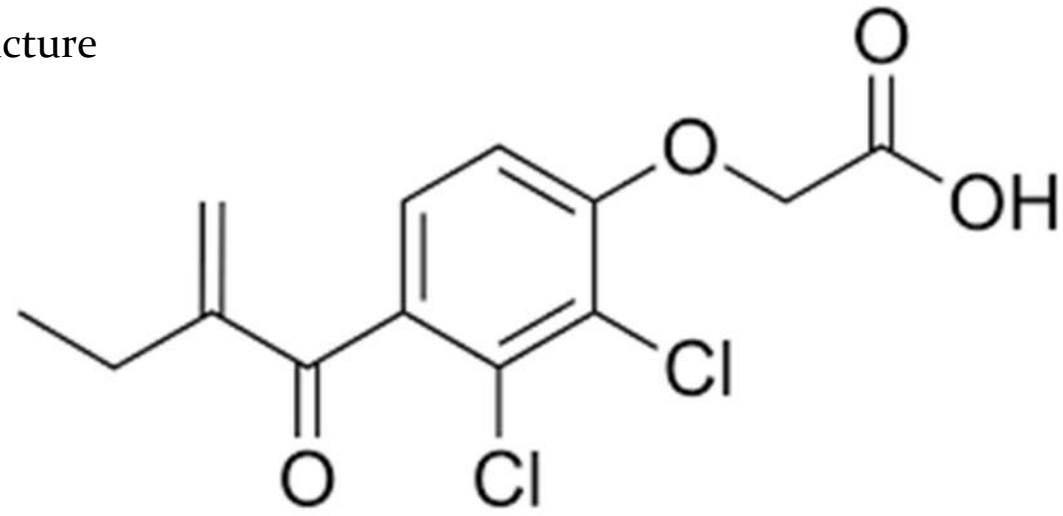
1. Edema:
    - Due to CHF, liver cirrhosis, renal disease (including nephrotic syndrome).
2. Hypertension:
    - In resistant cases or patients with renal impairment.
3. Acute pulmonary edema:
    - Rapid IV administration provides quick relief.
4. Hypercalcemia:
    - Increases calcium excretion.

Ethacrynic Acid

- Ethacrynic acid is a loop diuretic that belongs to the class of phenoxyacetic acid derivatives.
- Unlike other loop diuretics (like furosemide, bumetanide, torsemide), it is not a sulfonamide derivative, making it useful in patients with sulfonamide allergy.
- It is a potent diuretic but less commonly used due to risk of ototoxicity and toxicity.

Chemical Structure

- Chemical name: 2,3-dichloro-4-(2-methylenebutanoyl)phenoxyacetic acid
- Structure



Mechanism of Action

- Ethacrynic acid inhibits $Na^+/K^+/2Cl^-$ symporter in the thick ascending limb of the loop of Henle.
- This leads to:
  - Increased excretion of sodium, potassium, chloride.
  - Increased excretion of calcium and magnesium.
  - Strong diuretic effect.
- It decreases water reabsorption → produces profuse diuresis.
- Unlike thiazides, it remains effective even in patients with renal impairment.

Pharmacological Actions

- Diuretic effect: Very strong and rapid.
- Antihypertensive effect: Due to reduction in plasma volume.
- Vasodilation: Some mild direct vascular effect.

Uses

1. Edema associated with:
    - Congestive heart failure (CHF)
    - Chronic kidney disease (CKD)
    - Liver cirrhosis
    - Nephrotic syndrome
2. Pulmonary edema (emergency situations).
3. Hypertension (when other diuretics are not effective).
4. Sulfonamide allergy patients who cannot take furosemide/bumetanide.

Potassium-Sparing Diuretics

Potassium-sparing diuretics are mild diuretics that act on the collecting ducts and late distal tubules of the nephron.

- Unlike loop and thiazide diuretics, they do not cause potassium loss; instead, they help conserve potassium.
- Often used in combination with other diuretics to prevent hypokalemia.

Mechanism of Action

Potassium-sparing diuretics act via two main mechanisms:

1. Aldosterone antagonists
    - Block aldosterone receptors in the distal tubule and collecting duct
    - Reduce Na^+ reabsorption and K^+ excretion
    - Examples: Spironolactone, Eplerenone
2. Sodium channel blockers
    - Inhibit epithelial sodium channels (ENaC) in collecting ducts
    - Reduce Na^+ reabsorption → decrease K^+ excretion
    - Examples: Amiloride, Triamterene

Effect :

- Mild diuresis
- Potassium retention
- Decrease in sodium reabsorption

Example

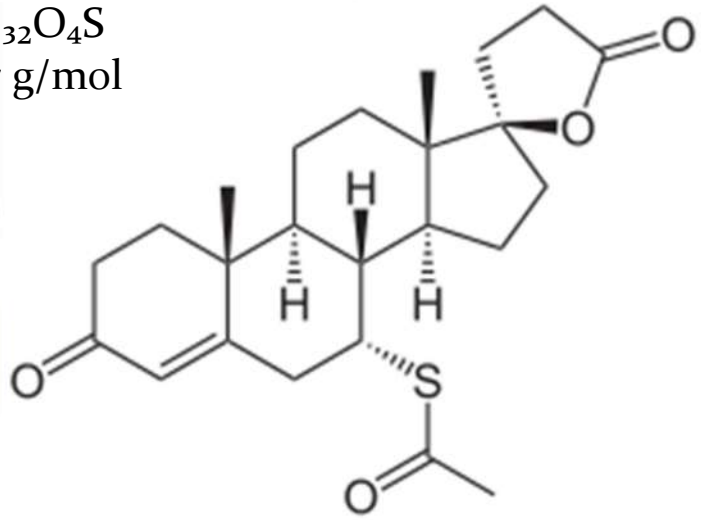
- Spironolactone,
- Triamterene,
- Amiloride

Spironolactone

- Spironolactone is a potassium-sparing diuretic and a synthetic steroid.
- Belongs to the class of aldosterone antagonists.
- It acts on the distal convoluted tubule and collecting duct of the nephron.
- Used in edema, hypertension, congestive heart failure (CHF), hyperaldosteronism, and hypokalemia prevention.
- Unlike amiloride and triamterene, spironolactone's activity is dependent on aldosterone levels.
- Available as oral tablets and capsules.

Chemical Structure

- IUPAC Name: 7α-acetylthio-3-oxo-17α-pregn-4-ene-21,17-carbolactone
- Molecular Formula: $C_{24}H_{32}O_4S$
- Molecular Weight: 416.57 g/mol
- Structural



Mechanism of Action

- Acts as a competitive antagonist of aldosterone at mineralocorticoid receptors in the distal nephron.
- Prevents aldosterone-induced synthesis of Na^+ channels and Na^+/K^+-ATPase pumps.
- Results in:
  - ↓ Na^+ reabsorption.
  - ↓ K^+ and H^+ excretion (potassium-sparing).
- Causes mild diuresis, but important for its potassium-conserving effect.
- Also has anti-androgenic activity (binds to androgen receptors and inhibits testosterone synthesis).

Synthesis

Start from steroidal precursors (pregnane derivatives).

1. Introduce a lactone ring at C-17.
2. Add a thioacetyl substituent at C-7.
3. Final oxidation and purification → spironolactone obtained.

Uses

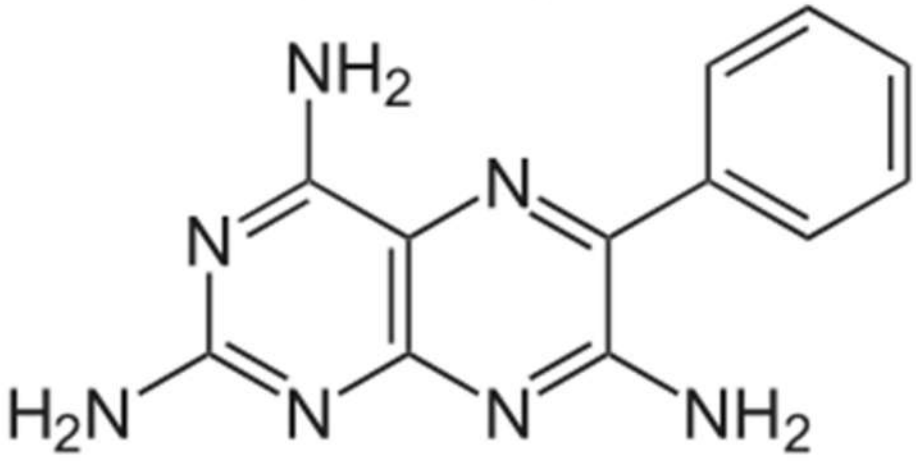
1. Edema (CHF, liver cirrhosis, nephrotic syndrome).
2. Hypertension (often in combination with other diuretics).
3. Primary hyperaldosteronism (Conn's syndrome) – diagnostic & therapeutic use.
4. CHF (NYHA class III & IV) – reduces mortality when added to standard therapy.
5. Hypokalemia prevention – adjunct with thiazides/loop diuretics.
6. Endocrine uses:
    - Polycystic ovary syndrome (PCOS).
    - Hirsutism, acne (due to anti-androgenic activity).

Triamterene

- Triamterene is a potassium-sparing diuretic.
- It belongs to the pteridine derivative class of diuretics.
- Unlike loop diuretics and thiazides, it does not cause potassium loss.
- Acts on the late distal tubule and collecting ducts of the nephron.
- Usually used in combination with thiazides (e.g., hydrochlorothiazide) to counteract hypokalemia caused by other diuretics.
- It is available in oral dosage forms (capsules, tablets).

Chemical Structure

- IUPAC Name: 2,4,7-triamino-6-phenylpteridine
- Molecular Formula: $C_{12}H_{11}N_7$
- Molecular Weight: 253.27 g/mol
- Structural



Mechanism of Action

- Site of action: Late distal convoluted tubule and collecting ducts.
- MOA:
  - Blocks epithelial sodium channels (ENaC) on the luminal membrane.
  - Prevents sodium reabsorption → sodium remains in urine.
  - Reduces potassium excretion (since sodium entry is reduced, exchange with potassium is decreased).
- Effect: Mild diuresis with potassium retention.

Synthesis

- Starting material: Pteridine derivatives.
- Steps:
    1. Construction of the pteridine ring system.
    2. Substitution at the 6-position with a phenyl group.
    3. Introduction of amino groups at positions 2, 4, and 7.
- Final product: Triamterene obtained after crystallization and purification.

Uses

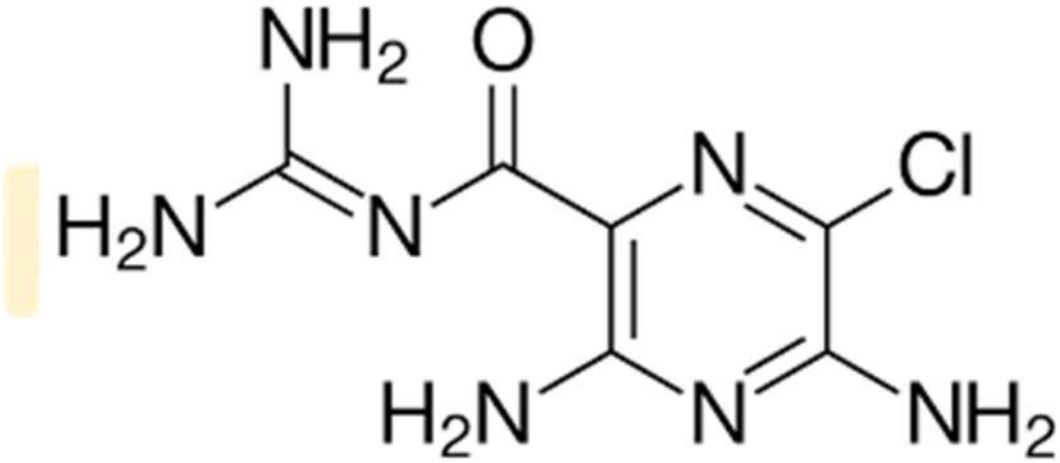
- Edema (due to CHF, liver cirrhosis, nephrotic syndrome, chronic kidney disease).
- Hypertension (usually in combination with thiazide diuretics).
- Hypokalemia prevention when used with thiazide or loop diuretics.

Amiloride

- Amiloride is a potassium-sparing diuretic.
- Belongs to the pyrazinoylguanidine class.
- Produces mild diuresis, mainly used to conserve potassium.
- Acts on the late distal tubule and collecting ducts of the nephron.
- Often given in combination with thiazides or loop diuretics to prevent hypokalemia.
- Available as oral tablets (commonly as Amiloride HCl).

Chemical Structure

- IUPAC Name: 3,5-diamino-6-chloro-N-(diaminomethylene)pyrazine-2-carboxamide
- Molecular Formula: $C_6H_8ClN_7O$
- Molecular Weight: 229.63 g/mol
- Structural



Mechanism of Action

- Site of action: Late distal convoluted tubule and collecting ducts.
- MOA:
  - Blocks epithelial sodium channels (ENaC) on the luminal surface.
  - Prevents sodium reabsorption → increases sodium excretion.
  - Potassium retention occurs (since sodium-potassium exchange is reduced).
- Effect: Mild diuresis with significant potassium-sparing action.

Synthesis

- Starting material: Substituted pyrazine derivatives.
- Steps:
    1. Synthesis of a pyrazine-2-carboxamide framework.
    2. Introduction of amino groups at positions 3 and 5.
    3. Substitution with chlorine at position 6.
    4. Addition of guanidine ($-C(=NH)NH_2$) side chain.
- Final step: Purification and crystallization → yields Amiloride.

Uses

- Edema (associated with CHF, liver cirrhosis, nephrotic syndrome).
- Hypertension (mild, usually in combination with thiazides).
- Hypokalemia prevention (due to thiazide or loop diuretics).
- Cystic fibrosis (off-label: reduces sodium absorption in airways).

Osmotic Diuretics

- Osmotic diuretics are a class of drugs that increase the osmolarity of the renal tubular fluid. This osmotic effect prevents water reabsorption in the nephron, primarily in the proximal tubule and loop of Henle, leading to increased urine output (diuresis). They do not significantly alter electrolyte transport directly but cause water to be retained in the tubular lumen.

Mechanism of Action

1. Osmotic diuretics are freely filtered by the glomerulus but not reabsorbed in the nephron.
2. Their presence increases the osmotic pressure of tubular fluid.
3. Water follows the osmotic gradient and remains in the lumen, increasing urine volume.
4. This results in reduced intracranial and intraocular pressure due to osmotic withdrawal of water from tissues.

Sites of Action:

- Proximal convoluted tubule: Major site of action.
- Loop of Henle: Contributes to diuresis by reducing medullary hypertonicity.
- Collecting ducts: Minor effect; mainly water excretion.

Example

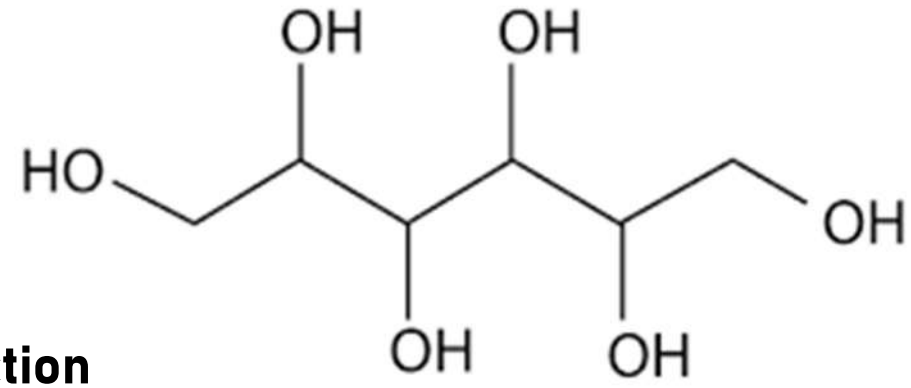
- Mannitol

Mannitol

- Mannitol is a osmotic diuretic.
- It is a sugar alcohol (polyol), highly water-soluble and pharmacologically inert.
- Primarily used to increase urine output, reduce intracranial pressure, and decrease intraocular pressure.
- Administered intravenously (IV); not effective orally due to poor absorption.
- Rapid onset of action, short duration (~3–6 hours).

Chemical Structure

- Chemical Name: Mannitol (or D-mannitol)
- Molecular Formula: $C_6H_{14}O_6$
- Molecular Weight: 182.17 g/mol
- Structural



Mechanism of Action

- Site of action: Primarily in the proximal tubule and loop of Henle.
- MOA:
    1. Filtered freely at glomerulus, poorly reabsorbed in renal tubules.
    2. Increases osmotic pressure in tubular fluid → reduces water reabsorption.
    3. Produces osmotic diuresis (increased excretion of water, sodium, chloride, and other electrolytes).
    4. Draws water from tissues into plasma (plasma expansion effect).

Synthesis

- Starting material: D-fructose or D-glucose (sorbitol).
- Steps:
    1. Hydrogenation of D-fructose using nickel catalyst (Raney Ni) under high pressure.
        - Fructose → Mannitol.
    2. Alternatively, D-glucose → hydrogenation → sorbitol → isomerization → Mannitol.
    3. Purification: Crystallization from water to obtain pure Mannitol.

Uses

- Acute renal failure / oliguria: Maintains urine output and prevents tubular obstruction.
- Raised intracranial pressure (ICP): Cerebral edema from trauma, stroke, or surgery.
- Acute glaucoma: Reduces intraocular pressure rapidly.
- Forced diuresis: Enhances excretion of toxic substances.
- Plasma volume expansion: Short-term use in shock or hypovolemia.