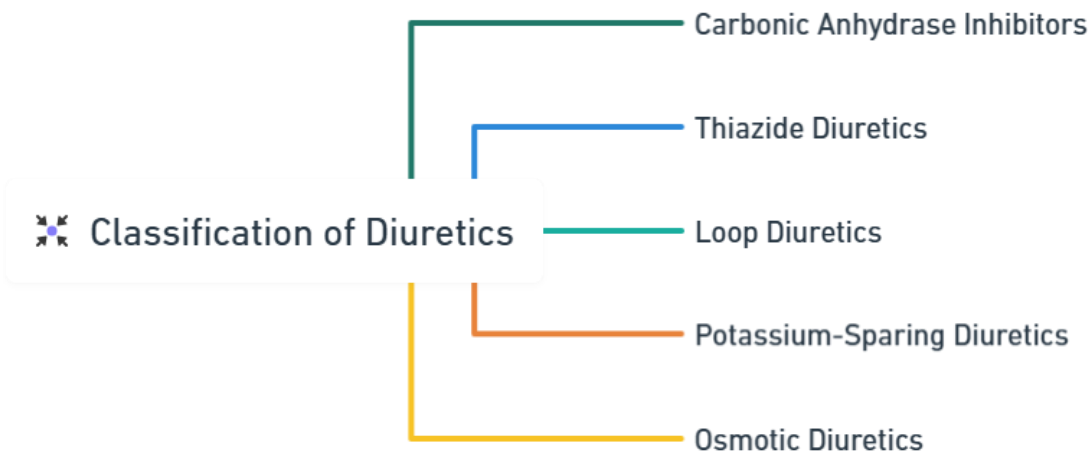
Diuretics

Diuretics: Overview and Classification

- Diuretics are a class of medications that promote the excretion of water and electrolytes (such as sodium and potassium) through the kidneys.
- They are primarily used to manage conditions like hypertension (high blood pressure), heart failure, kidney disorders, and certain cases of edema (fluid retention).
- By increasing urine output, diuretics help reduce blood volume, thereby lowering blood pressure and decreasing the workload on the heart.

Classification of Diuretics

- Diuretics can be categorized based on their mechanism of action and the specific segment of the nephron (the functional unit of the kidney) they act upon.
- Below is a concise classification of diuretics along with common examples and their primary mechanisms:



1. Carbonic Anhydrase Inhibitors

Examples:

- *Acetazolamide*
- *Methazolamide*
- Dichlorphenamide

Mechanism of Action:

- Inhibit the enzyme carbonic anhydrase in the proximal tubule of the nephron.
- Reduce reabsorption of bicarbonate, leading to increased excretion of bicarbonate, sodium, potassium, and water.

Clinical Uses:

- Treatment of glaucoma.
- Prevention of altitude sickness.

- Metabolic alkalosis.

2. Thiazide Diuretics

Examples:

- Chlorthiazide
- Hydrochlorothiazide
- Hydroflumethiazide
- Cyclothiazide

Mechanism of Action:

- Act on the distal convoluted tubule.
- Inhibit the sodium-chloride symporter, reducing sodium and chloride reabsorption.
- Increase excretion of sodium, chloride, and water, while promoting potassium retention.

Clinical Uses:

- Hypertension management.
- Edema associated with heart failure or nephrotic syndrome.
- Prevention of calcium-containing kidney stones.

3. Loop Diuretics

Examples:

- Furosemide
- Bumetanide
- Ethacrynic acid

Mechanism of Action:

- Target the ascending limb of the loop of Henle.
- Inhibit the sodium-potassium-chloride (Na^+-K^+-$2Cl^-$) cotransporter.
- Significantly increase excretion of sodium, chloride, potassium, calcium, and magnesium.

Clinical Uses:

- Acute and chronic heart failure.
- Pulmonary edema.
- Hypertension.
- Acute kidney failure.

4. Potassium-Sparing Diuretics

Examples:

- Spironolactone
- Triamterene
- Amiloride

Mechanism of Action:

- Act on the collecting ducts and late distal tubule.
- Spironolactone: Aldosterone receptor antagonists; block sodium reabsorption and potassium excretion.
- Triamterene and Amiloride: Inhibit epithelial sodium channels (ENaC), reducing sodium reabsorption and potassium loss.

Clinical Uses:

- Heart failure.
- Hypertension.
- Prevention of hypokalemia in patients taking other diuretics.
- Primary hyperaldosteronism (Spironolactone).

5. Osmotic Diuretics

Examples:

- Mannitol

Mechanism of Action:

- Remain in the lumen of the nephron and inhibit water reabsorption by increasing the osmolarity of the filtrate.
- Do not undergo significant reabsorption, thus drawing water into the urine.

Clinical Uses:

- Reduction of intracranial pressure in cases of cerebral edema.
- Treatment of acute kidney failure.
- Prevention of renal toxicity in certain poisoning cases.

Summary Table

Category	Medications	Primary Mechanism
Carbonic Anhydrase Inhibitors	*Acetazolamide*, *Methazolamide*, Dichlorphenamide	Inhibit carbonic anhydrase in proximal tubule; increase excretion of bicarbonate, sodium, potassium, water

Thiazide Diuretics	*Chlorthiazide*, *Hydrochlorothiazide*, Hydroflumethiazide, Cyclothiazide	Inhibit Na^+-Cl^- symporter in distal convoluted tubule; increase excretion of sodium, chloride, water
Loop Diuretics	*Furosemide*, *Bumetanide*, Ethacrynic acid	Inhibit Na^+-K^+-$2Cl^-$ cotransporter in ascending limb of loop of Henle; increase excretion of Na^+, Cl^-, K^+, Ca^{2+}, Mg^{2+}
Potassium-Sparing Diuretics	Spironolactone, Triamterene, Amiloride	Spironolactone: Aldosterone antagonists; Triamterene & Amiloride: ENaC inhibitors; reduce Na^+ reabsorption and K^+ loss
Osmotic Diuretics	Mannitol	Increase osmolarity of filtrate; inhibit water reabsorption

Brand Names Of Important Marketed Products

Increase urine output; used in **hypertension, edema, heart failure**.

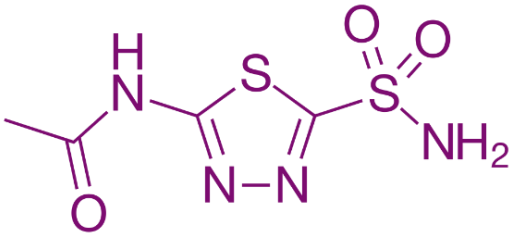
Class	Drug Name	Brand Name(s)	Use
Thiazide	Hydrochlorothiazide	*Esidrex*, *Aquazide*	HTN, edema
Loop	Furosemide	*Lasix*, *Frusemide*	Pulmonary edema, CHF
K+ Sparing	Spironolactone	*Aldactone*, *Spiroactin*	HTN, ascites
Osmotic	Mannitol	*Osmitrol*	Cerebral edema, glaucoma

Various Carbonic Anhydrase Inhibitors

1. Acetazolamide

Structure

- Acetazolamide is a sulfonamide derivative with a central sulfonamide group attached to a benzene ring and a dithiocarbamate moiety.
- Chemical Formula: $C_4H_6N_2O_3S_2$



Mode of Action

- **Carbonic Anhydrase Inhibition:** Acetazolamide inhibits the enzyme carbonic anhydrase, which is pivotal in the reversible hydration of carbon dioxide.

- **Renal Effects:** In the proximal tubules of the kidneys, this inhibition leads to decreased reabsorption of bicarbonate, resulting in increased excretion of bicarbonate, sodium, potassium, and water.
- **Metabolic Acidosis:** Causes a mild metabolic acidosis by reducing bicarbonate levels in the blood.

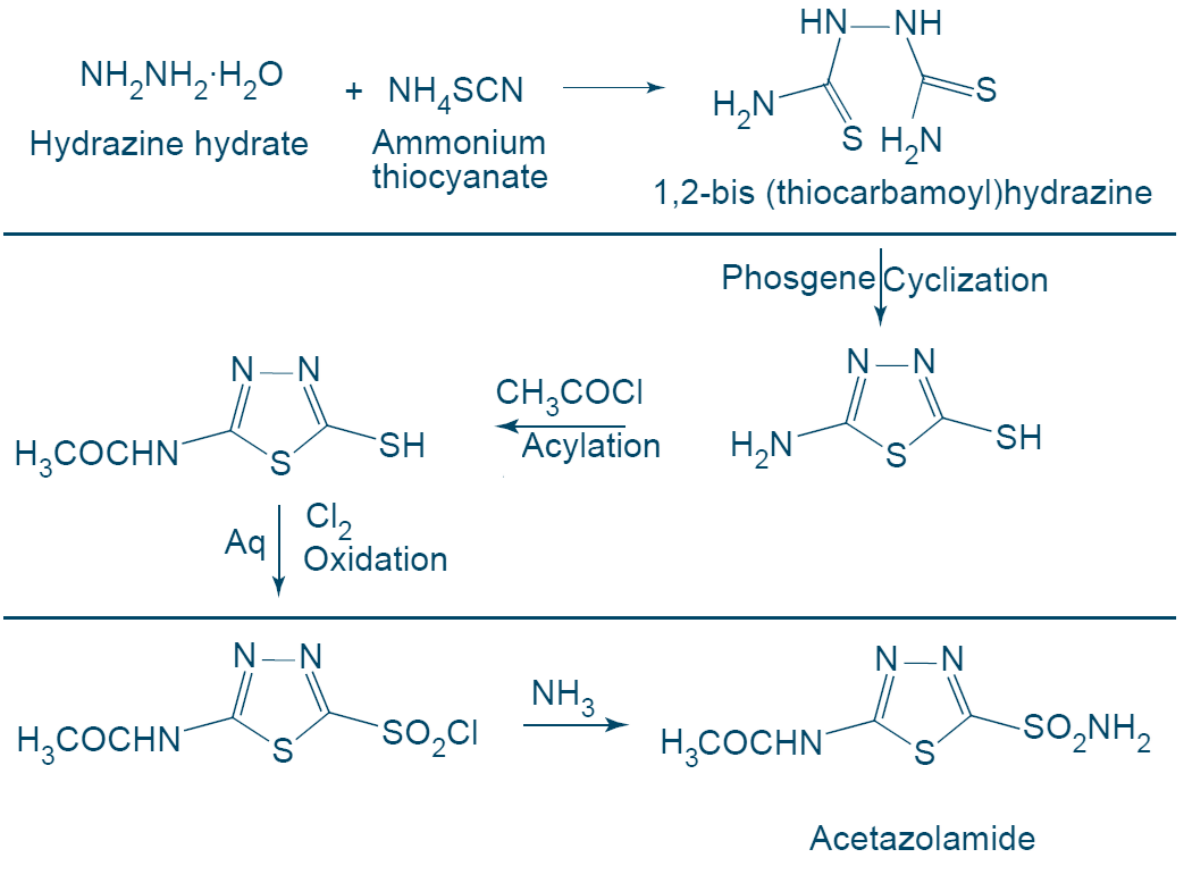
Uses

- **Glaucoma:** Reduces intraocular pressure by decreasing aqueous humor production.
- **Epilepsy:** Used as an adjunctive therapy in certain types of seizures.
- **Altitude Sickness:** Prevents and treats acute mountain sickness by inducing diuresis and metabolic acidosis.
- **Metabolic Alkalosis:** Corrects metabolic alkalosis by promoting bicarbonate excretion.
- **Diuretic:** Employed in cases where other diuretics are ineffective.

Structure-Activity Relationship (SAR)

- **Sulfonamide Group:** Essential for binding to the active site of carbonic anhydrase.
- **Dithiocarbamate Moiety:** Enhances binding affinity and specificity for the enzyme.
- **Benzene Ring:** Provides structural stability and facilitates proper orientation for enzyme interaction.
- **Substituents:** Electron-withdrawing groups on the benzene ring can increase inhibitory potency by enhancing binding interactions.

Synthesis



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