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Unit-II/Part-B

Diuretics

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SPECIALIZATION:- PHARMACEUTICAL CHEMISTRY

Diuretics

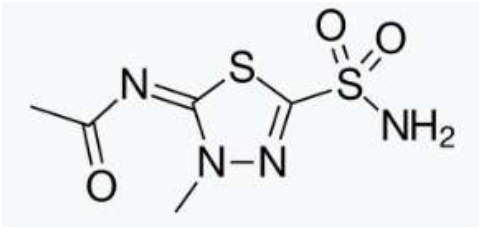
I. **Diuretics** are **medications that increase the excretion of water and electrolytes (mainly sodium and chloride) from the body through urine**.

II. They act on the kidneys to promote diuresis (urine production).

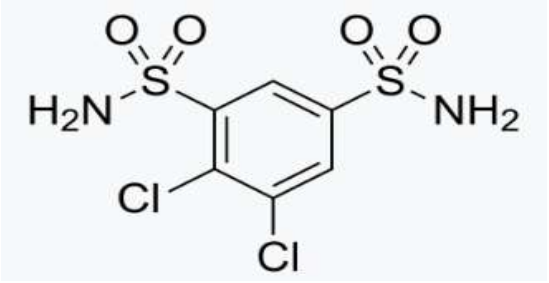
III. Diuretics are primarily used in the treatment of **hypertension, heart failure, edema, and certain kidney disorders.**

Classification of Diuretics

1. **Carbonic anhydrase inhibitors:-** Acetazolamide*, Methazolamide, Dichlorphenamide.
2. **Thiazides:-** Chlorthiazide*, Hydrochlorothiazide, Hydroflumethiazide, Cyclothiazide.
3. **Loop diuretics:-** Furosemide*, Bumetanide, Ethacrynic acid.
4. **Potassium sparing Diuretics:-** Spironolactone, Triamterene, Amiloride.
5. **Osmotic Diuretics:-** Mannitol.

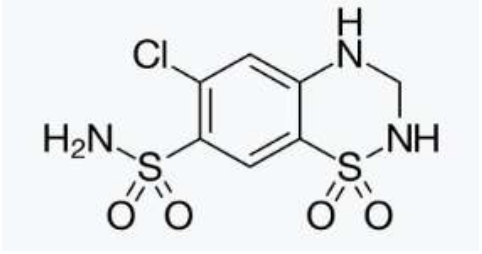


Methazolamide

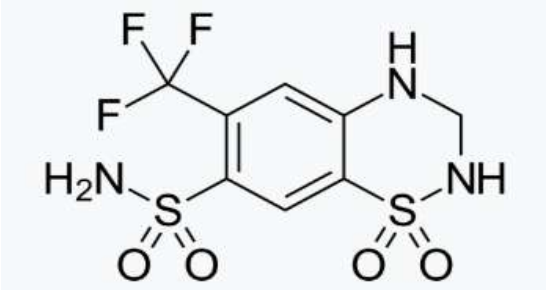


Dichlorphenamide

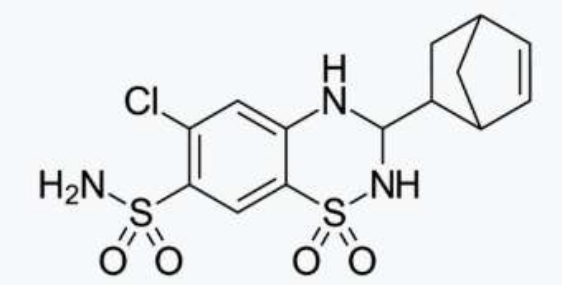
Amiloride



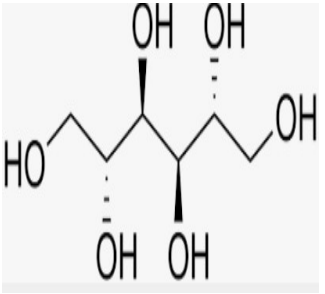
Hydrochlorothiazide



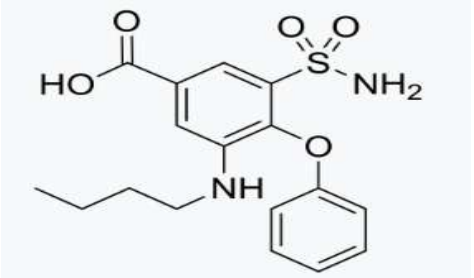
Hydroflumethiazide



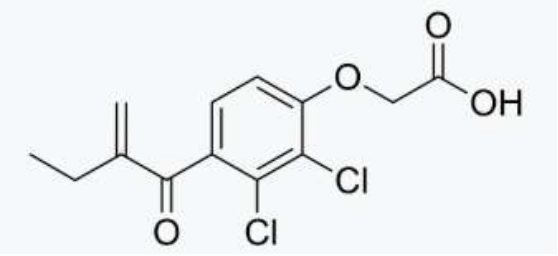
Cyclothiazide



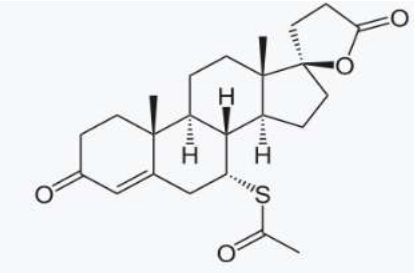
Mannitol



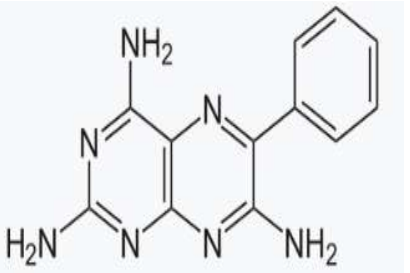
Bumetanide



Ethacrynic acid



Spironolactone



Triamterene

MOA of Each Category of Diuretics

1. **Carbonic Anhydrase Inhibitors:**
   - These diuretics inhibit the enzyme carbonic anhydrase, which plays a role in the reabsorption of bicarbonate (HCO_3^-) and hydrogen ions (H^+) in the proximal convoluted tubule of the nephron.
   - By inhibiting this enzyme, they increase the excretion of sodium (Na^+), bicarbonate, and water, making the urine more alkaline
   - Examples include acetazolamide and methazolamide.
2. **Thiazide Diuretics:**
   - Thiazides work by inhibiting the sodium-chloride symporter in the distal convoluted tubule, preventing the reabsorption of sodium and chloride ions.
   - This leads to increased excretion of sodium, chloride, and water, as well as potassium.
   - Examples include hydrochlorothiazide, chlorthalidone, and indapamide.
3. **Loop Diuretics:**
   - Also known as high-ceiling diuretics, they act on the thick ascending limb of the loop of Henle.
   - They inhibit the sodium-potassium-chloride cotransporter, preventing the reabsorption of these ions and increasing water excretion.
   - Examples include furosemide, bumetanide, and ethacrynic acid.
4. **Potassium-Sparing Diuretics:**
   - These diuretics act on the collecting duct, either by blocking aldosterone receptors (aldosterone antagonists) or by directly inhibiting sodium channels.
   - They promote sodium excretion and potassium retention, hence the name "potassium-sparing".
   - Examples include spironolactone (aldosterone antagonist) and amiloride (sodium channel blocker).
5. **Osmotic Diuretics:**
   - These agents are filtered by the glomerulus but are not reabsorbed by the tubules.
   - They create an osmotic gradient that draws water into the tubules, increasing urine volume.
   - Examples include mannitol, urea, and glycerol.

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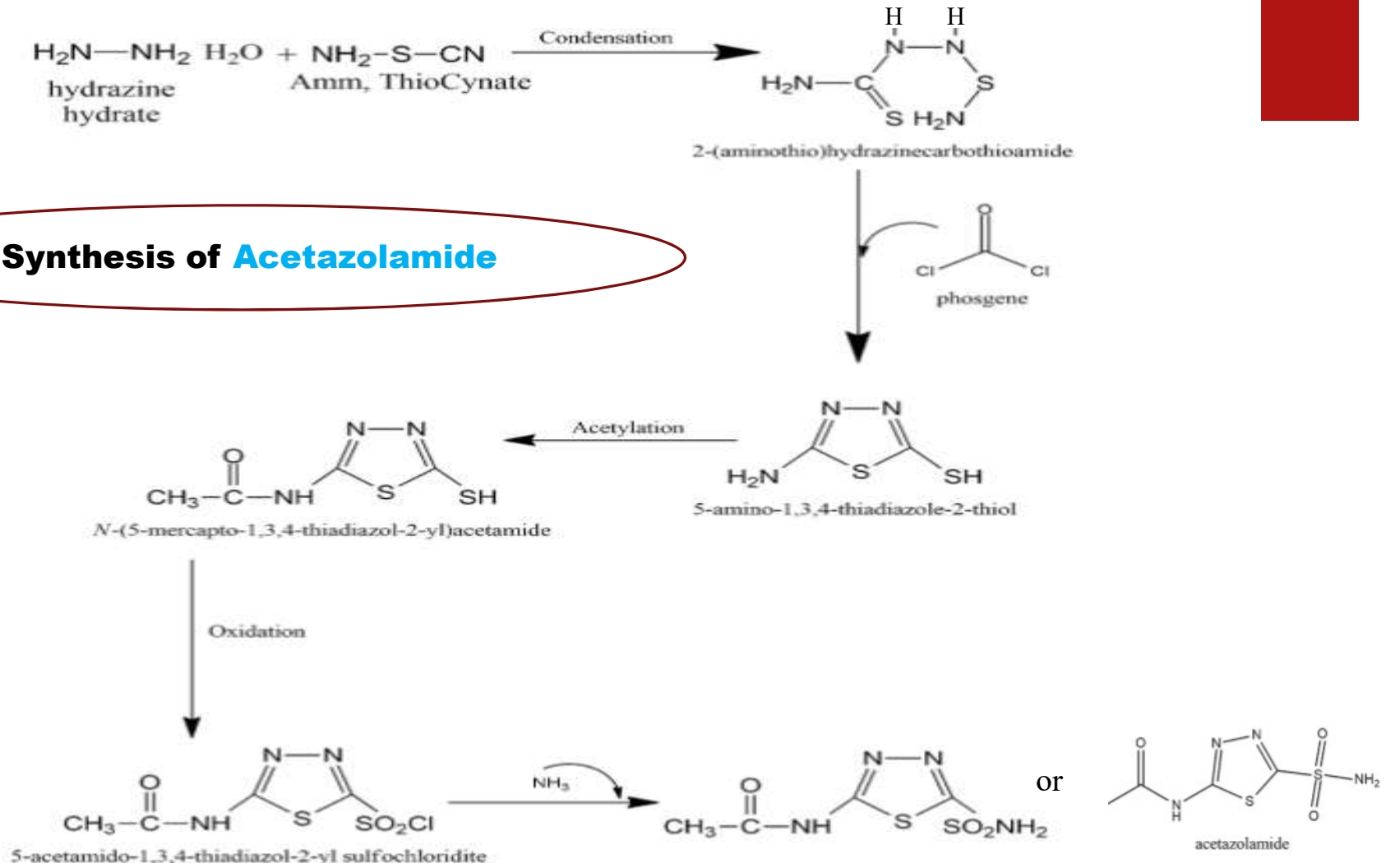
Synthesis of Acetazolamide



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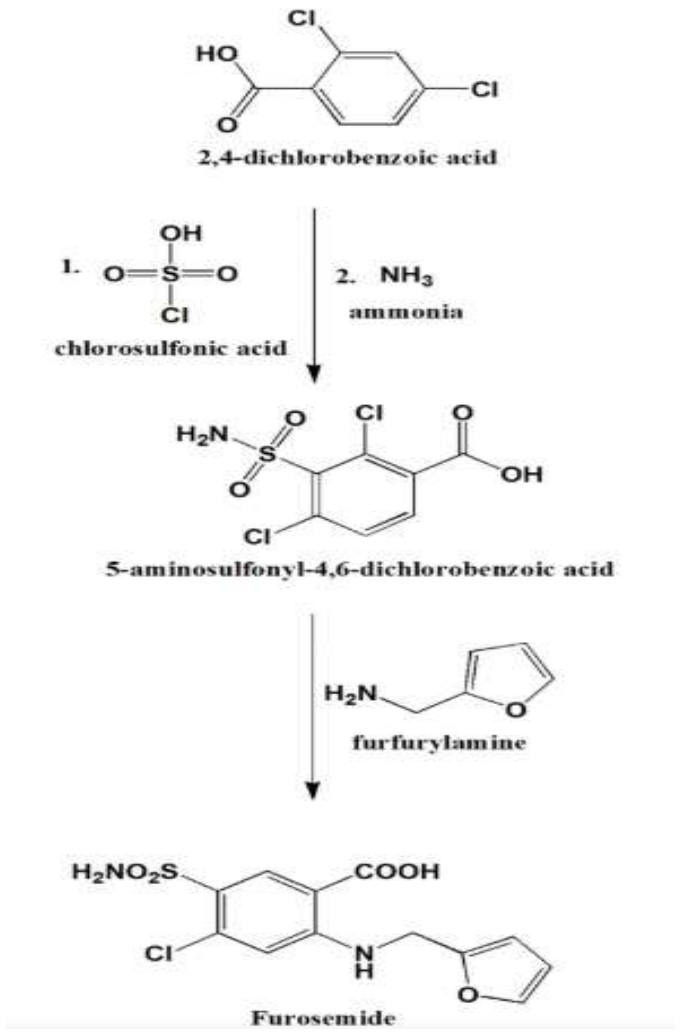
Synthesis of Furosemide



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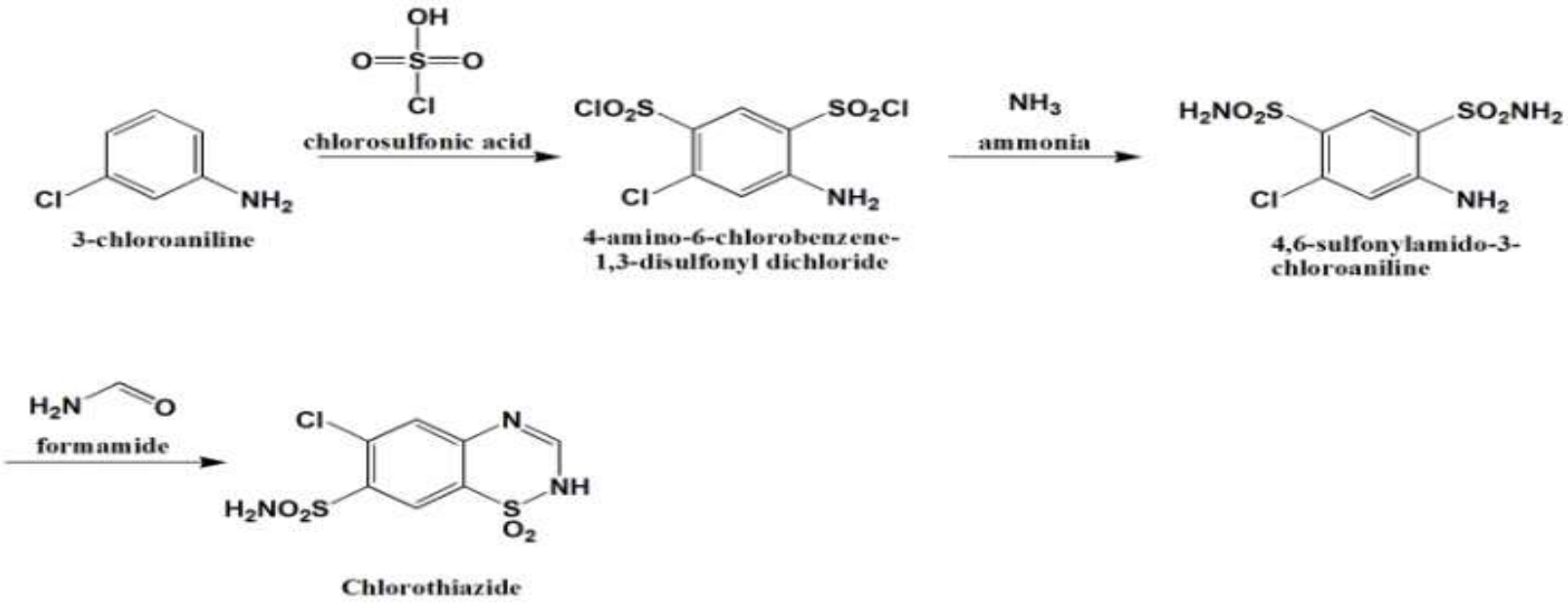
Synthesis of Chlorthiazide



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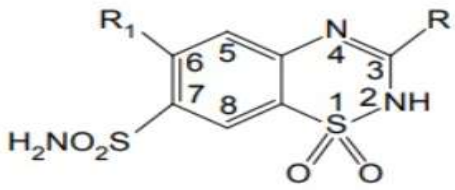
SAR of Thazides



General Structure

Position	Modification	Effect on Activity
2-Position	Introduction of an electron-withdrawing group (e.g., Cl, CF_3)	Essential for diuretic activity. Enhances potency.
3-Position	Sulfonamide ($-SO_2NH_2$) group is essential	Necessary for interaction with Na^+/Cl^- symporter.
3,4-Dihydro derivative (saturation of double bond)	Increases potency (e.g., hydrochlorothiazide)	More potent than unsaturated analogs.
6-Position	Substitution with Cl or CF_3 increases lipophilicity	Improves membrane permeability and potency.
7-Position	Unsubstituted or alkyl groups tolerated	Minor effect on activity.
Substitution at 1-N	Not favorable	Reduces activity
Modification of sulfonamide group	N^4-substitution can improve potency or alter kinetics	Some derivatives show increased duration of action

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THANK YOU