Unit-2
Medicinal Chemistry- II

B.Pharma 5th Sem Notes

Unit: 2

1. Anti-anginal

- **Vasodilators:** Amyl nitrite, Nitroglycerin*, Pentaerythritol tetranitrate, Isosorbide dinitrite*, Dipyridamole.
- **Calcium channel blockers:** Verapamil, Bepridil hydrochloride, Diltiazem hydrochloride, Nifedipine, Amlodipine, Felodipine, Nicardipine, Nimodipine.

2. Diuretics

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

3. Anti-hypertensive Agents

- Timolol, Captopril, Lisinopril, Enalapril, Benazepril hydrochloride, Quinapril hydrochloride, Methyldopate hydrochloride,* Clonidine hydrochloride, Guanethidine monosulphate, Guanabenz acetate, Sodium nitroprusside, Diazoxide, Minoxidil, Reserpine, Hydralazine hydrochloride.

1. Anti-anginal

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Anti-anginal:

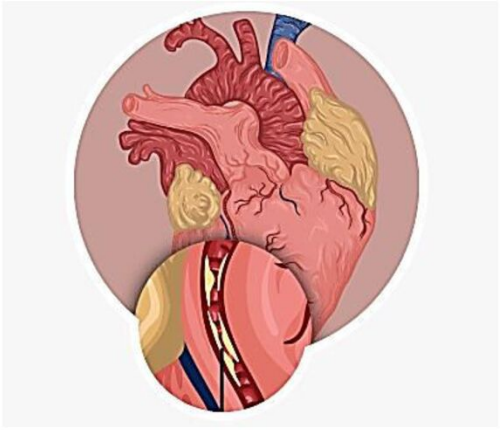
- Antianginal agents are medicinal drugs that treat or prevent conditions caused by poor blood flow to the heart, such as angina pectoris.
- They work by dilating blood vessels and reducing the heart's need for oxygen to improve blood flow.
- The three main classes of antianginal drugs are nitrates, beta blockers, and calcium channel blockers

Angina pectoris

Angina pectoris is chest pain or discomfort that occurs when the heart muscle doesn't receive enough oxygen-rich blood. It's often a symptom of coronary artery disease (CAD), where the arteries supplying blood to the heart become narrowed.

Symptoms:

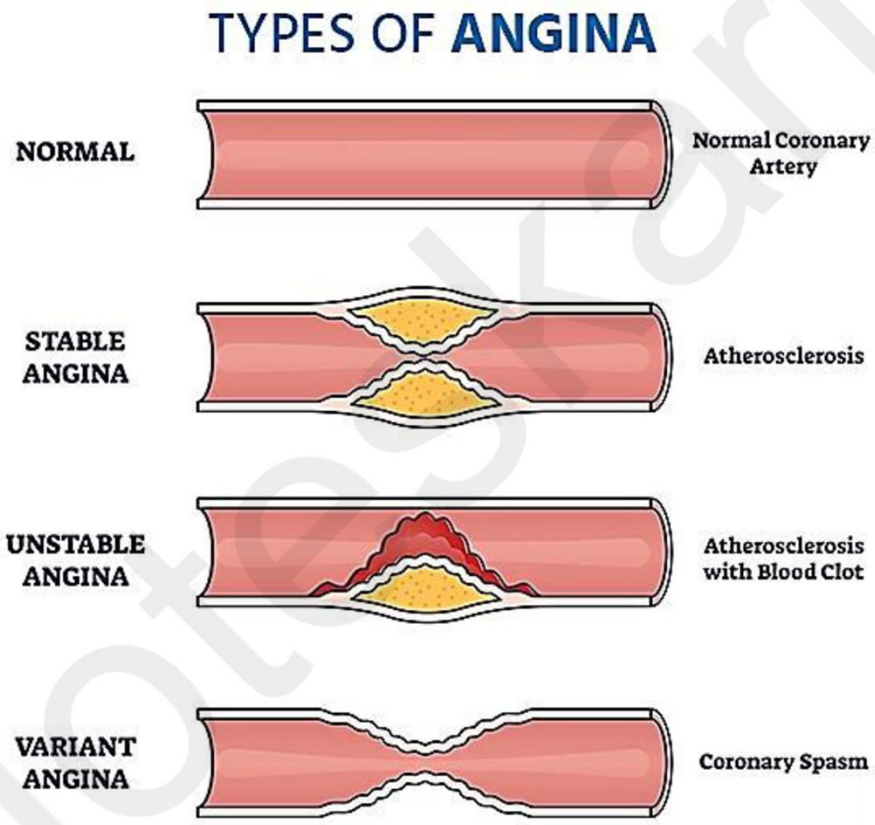
- Chest pain or discomfort (pressure, fullness, squeezing, or pain)
- Pain radiating to neck, jaw, shoulder, back, or arm
- Shortness of breath
- Fatigue
- Dizziness



Angina Types

There are many types of angina. The most prominent ones are:

- **Stable Angina** – Also known as Angina Pectoris.
- **Unstable Angina** – This condition is characterized by unexpected chest pain during rest. Unlike stable angina, unstable angina occurs unpredictably. It also changes in frequency and may get worse over time.
- **Variant Angina** – Also known as Prinzmetal's variant angina or Angina inversa. It is usually rare and typically occurs in younger patients who have other pre-existing heart conditions. It generally occurs while resting, specifically during the night or early morning.



Classification of Anti-anginal Agent

- **Vasodilators:** Amyl nitrite, Nitroglycerin*, Pentaerythritol tetranitrate, Isosorbide dinitrite*, Dipyridamole.
- **Calcium channel blockers:** Verapamil, Bepridil hydrochloride, Diltiazem hydrochloride, Nifedipine, Amlodipine, Felodipine, Nicardipine, Nimodipine.

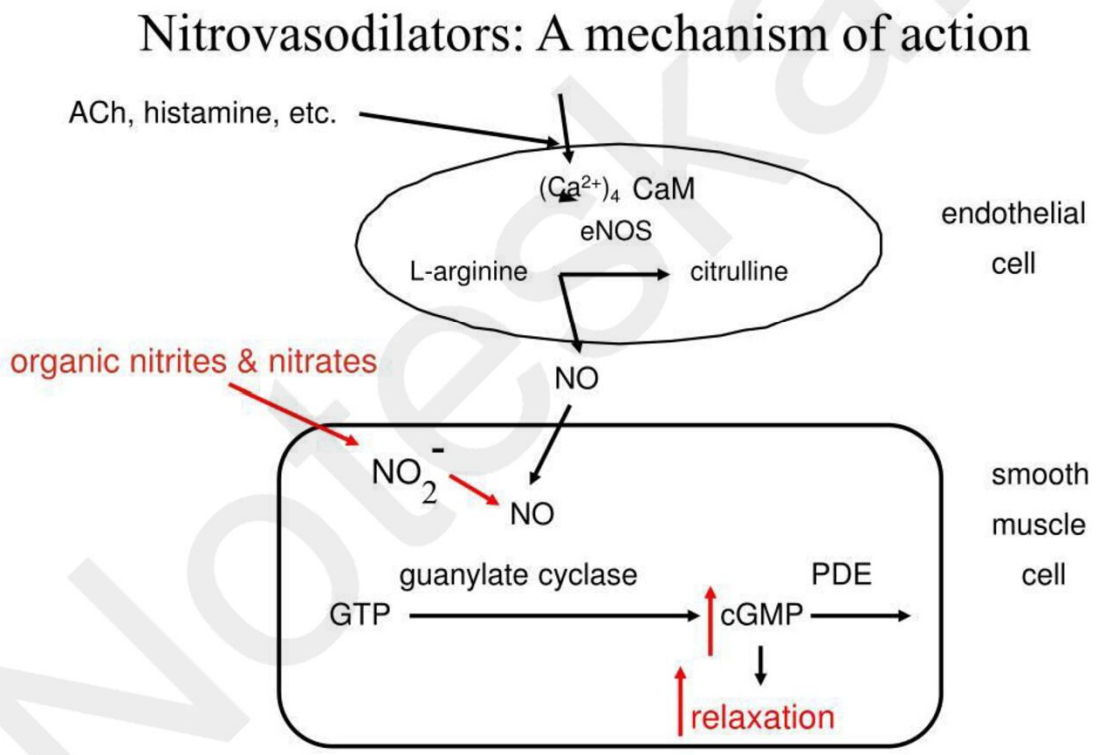
Vasodilators:

- Vasodilators are medicines that open blood vessels, also called dilate, to allow blood to flow more easily through the body.
- They work by relaxing the muscles in the walls of arteries and veins, preventing them from tightening and narrowing.

Nitro- Vasodilators:

- A nitrovasodilator is a pharmaceutical agent that causes vasodilation (widening of blood vessels) by donation of nitric oxide (NO), and is mostly used for the treatment and prevention of angina pectoris.

Mechanism of Action:

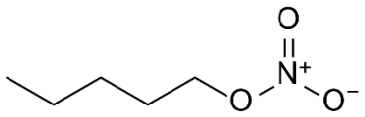
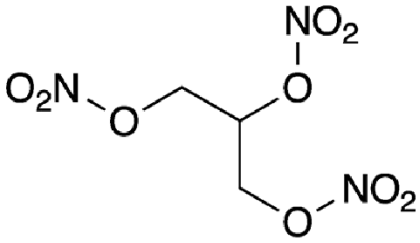
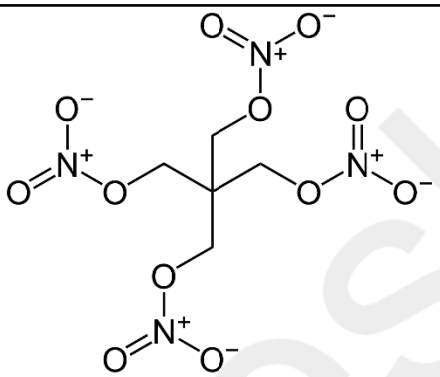
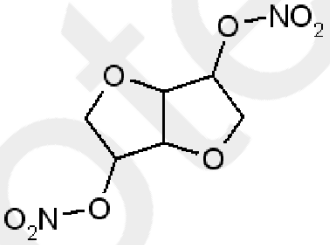
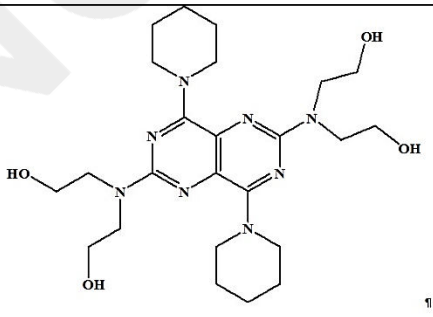


Use of Vasodilators:

They are used to treat and prevent many conditions that affect blood flow, including:

- High blood pressure, Heart failure, Angina, Pulmonary hypertension, Preeclampsia, and Postpartum preeclampsia

Vasodilators Drugs:

Vasodilator	Structure	Mechanism of Action	Uses
Amyl nitrite		Releases nitric oxide (NO), which activates guanylate cyclase and increases cGMP	Used in the treatment of angina, cyanide poisoning, and as a vasodilator
Nitroglycerin		Converted to nitric oxide (NO) in the body, which relaxes smooth muscles of blood vessels by increasing cGMP	Used primarily for angina pectoris, acute myocardial infarction, and heart failure
Pentaerythritol tetranitrate		Similar to nitroglycerin, it releases nitric oxide (NO) to increase cGMP levels and cause vasodilation	Used for angina pectoris and coronary artery disease
Isosorbide dinitrate		Prodrug that is converted to isosorbide mononitrate, which releases NO and increases cGMP	Used for angina pectoris, heart failure, and esophageal spasms
Dipyridamole		Inhibits the uptake of adenosine into platelets, endothelial cells, and erythrocytes, increasing local concentrations of adenosine	Used as an adjunct in the prevention of thromboembolism, and for pharmacologic stress testing in coronary artery disease

Nitroglycerin:

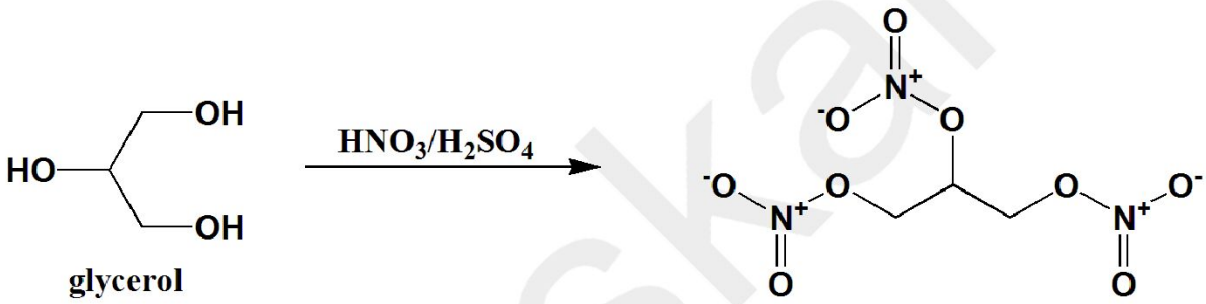
Structure Activity Relationship

General structure activity of organic nitrate antianginal drugs be summarized as:

- The number of nitrate groups determines the potency of organic nitrate for guanylate cyclase activation.
- Increase in nitric group increases the potency.
- Increase in lipophillicity doesn't have major effect over activation of drug.

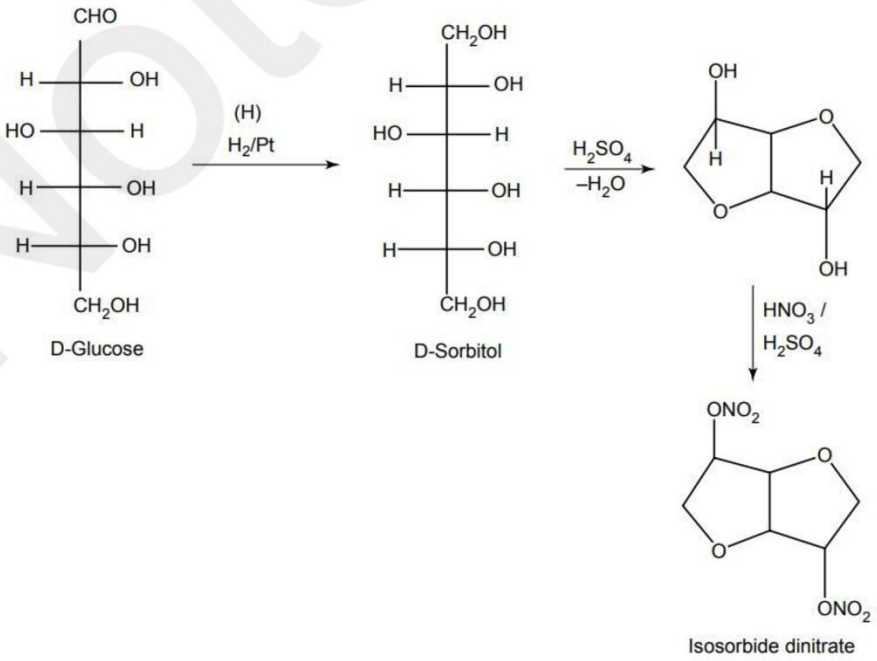
Method of synthesis

- Nitration of glycerol with nitric acid produces nitroglycerine.



Isosorbide dinitrate:(Imp)

Synthesis:



Calcium channel blockers: Verapamil, Bepridil hydrochloride, Diltiazem hydrochloride, Nifedipine, Amlodipine, Felodipine, Nicardipine, Nimodipine.

Calcium channel blockers:

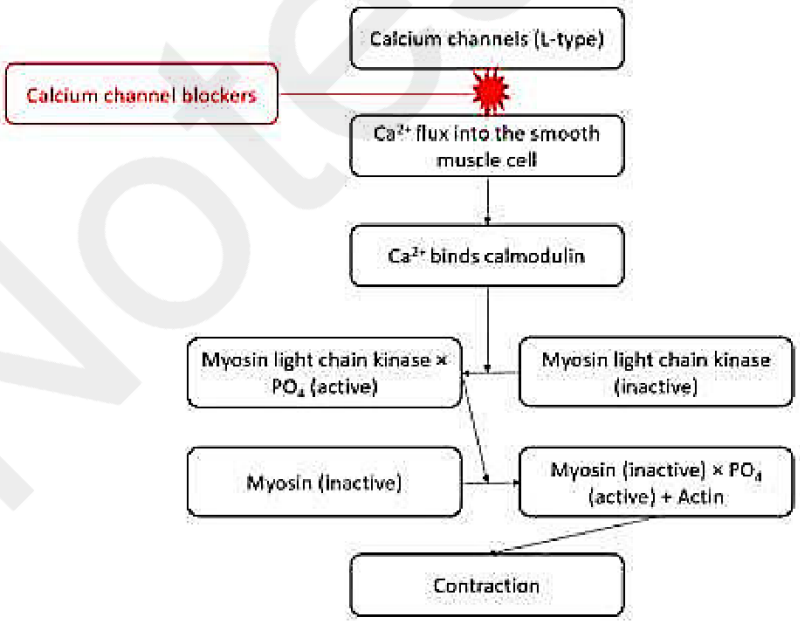
Calcium channel blockers are medicines used to lower blood pressure. They stop calcium from entering the cells of the heart and arteries.

Calcium causes the heart and arteries to squeeze more strongly. By blocking calcium, calcium channel blockers allow blood vessels to relax and open.

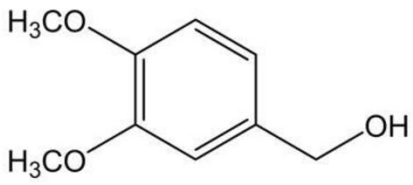
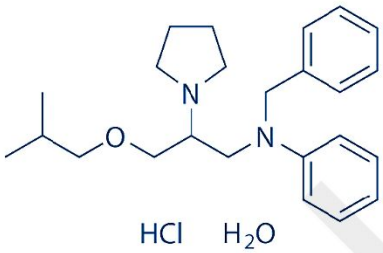
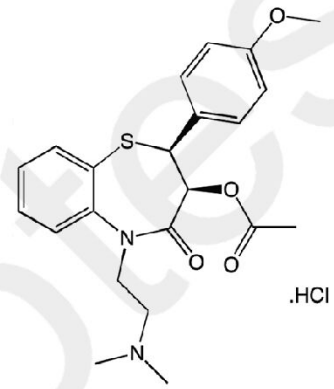
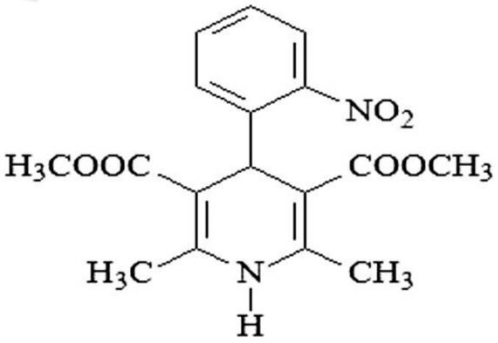
They are often prescribed to treat heart and blood vessel conditions, such as:

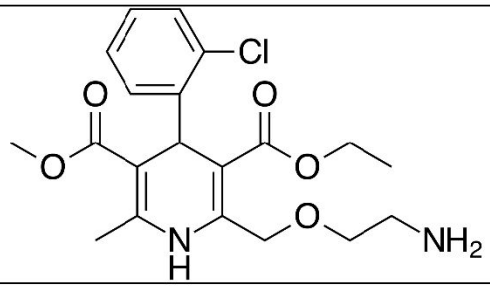
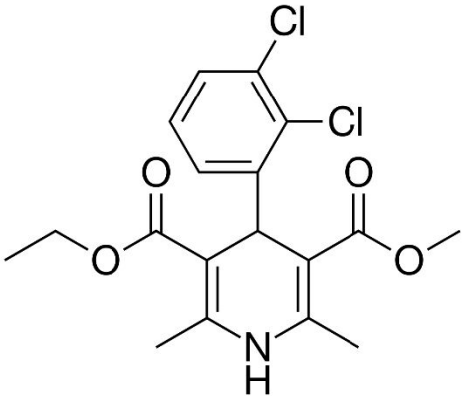
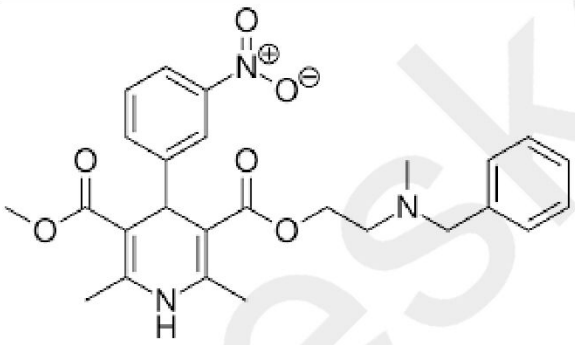
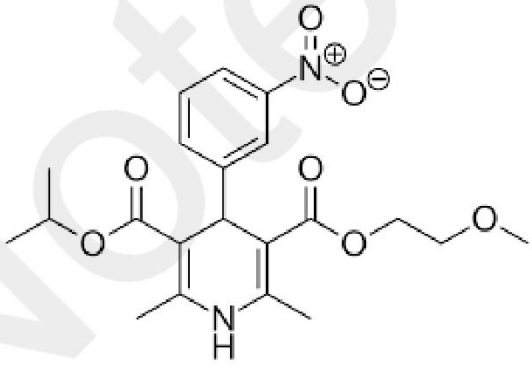
- High blood pressure: CCBs are vasodilators, which means they relax and widen blood vessels, which can help lower blood pressure.
- Angina: CCBs can help treat chest pain caused by heart disease.
- Arrhythmia: CCBs can help control irregular heartbeats.
- Raynaud's phenomenon: CCBs can help treat painful and cold fingers and toes caused by narrowing of the arteries in the hands and feet.

Mechanism of Action:



Calcium channel blockers Drugs:

Calcium Channel Blocker	Structure	Mechanism of Action	Uses
Verapamil		Inhibits L-type calcium channels, reducing calcium influx into cardiac and smooth muscle cells	Used for hypertension, angina, and certain arrhythmias
Bepridil hydrochloride		Blocks calcium channels as well as sodium channels, leading to vasodilation and decreased heart rate	Used for angina and certain arrhythmias
Diltiazem hydrochloride		Inhibits L-type calcium channels, reducing calcium influx in cardiac and vascular smooth muscle cells	Used for hypertension, angina, and certain arrhythmias
Nifedipine		Inhibits L-type calcium channels in vascular smooth muscle, causing vasodilation and reducing blood pressure	Used for hypertension and angina

Amlodipine		Inhibits L-type calcium channels in vascular smooth muscle, leading to vasodilation	Used for hypertension and angina
Felodipine		Inhibits L-type calcium channels in vascular smooth muscle, leading to vasodilation	Used for hypertension and angina
Nicardipine		Inhibits L-type calcium channels in vascular smooth muscle, leading to vasodilation	Used for hypertension and angina
Nimodipine		Selectively inhibits L-type calcium channels in cerebral arteries, causing vasodilation	Used for the prevention of cerebral vasospasm

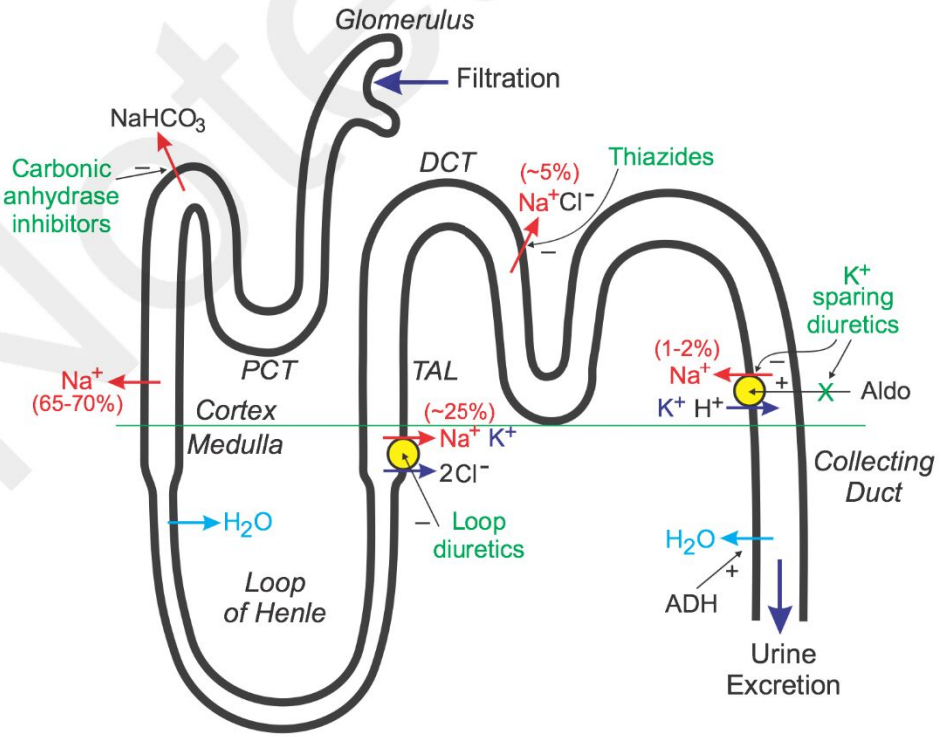
2. Diuretics

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

Diuretics

- A diuretic is any substance that promotes diuresis, the increased production of urine. This includes forced diuresis.
- A diuretic tablet is sometimes colloquially called a water tablet. There are several categories of diuretics.
- All diuretics increase the excretion of water from the body, through the kidneys.

Nephron:



It has basic five parts which have different functions:

1. Bowman's Capsule (Glomerulus)
2. PCT (Proximal Convoluted Tubule)
3. Loop of Henle
    - Descending Limb
    - Ascending Limb
4. Distal Convoluted tubule (DCT)
5. Collecting Duct

1. Bowman's Capsule (Glomerulus)

- **Structure:** Cup-shaped structure surrounding a network of capillaries called the glomerulus.
- **Function:** Filtration of blood. Blood pressure forces water, ions, and small molecules (filtrate) through the porous capillary walls into the Bowman's capsule.

2. Proximal Convoluted Tubule (PCT)

- It is the tubular segment of the nephron that connects the renal corpuscle to the proximal straight tubule and to the loop of Henle. It is located in the renal cortex of the medulla and functions in both reabsorption and secretion.

3. Loop of Henle

- **Structure:** U-shaped portion of the nephron divided into descending and ascending limbs.
- **Function:** Establishes a concentration gradient in the medulla of the kidney.
    - **Descending Limb:** Permeable to water, allowing water to move out of the tubule into the surrounding hypertonic environment.
    - **Ascending Limb:** Impermeable to water but actively reabsorbs sodium and chloride ions, contributing to the concentration gradient.

4. Distal Convoluted Tubule (DCT)

- The DCT, which is the last part of the nephron, connects and empties its contents into collecting ducts that line the medullary pyramids. The collecting ducts amass contents from multiple nephrons and fuse together as they enter the papillae of the renal medulla.

- Similar to PCT, DCT also secretes ions such as hydrogen, potassium, and NH_3 into the filtrate while reabsorbing the HCO_3^- from the filtrate. Conditional reabsorption of sodium ions and water takes place in DCT. Thus, it maintains the pH and sodium-potassium level in the blood cells.

5. Collecting Duct

- **Structure:** Large duct collecting filtrate from multiple nephrons.
- Collecting duct is a long, straight tube where H+ and K+ ions are secreted to maintain the electrolyte balance of the blood. This is also the region where the maximum reabsorption of water takes place to produce concentrated urine.

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

1. Carbonic anhydrase inhibitors:

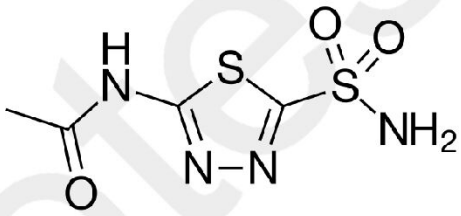
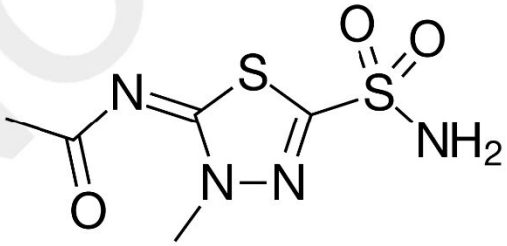
- These drugs give their effects in PTC (Proximal Convoluted Tubule) by inhibit reducing the reabsorption of biocarbonate.
- Carbonic anhydrase inhibitors are a medication used to manage and treat glaucoma, idiopathic intracranial hypertension, altitude sickness, congestive heart failure, and epilepsy, among other diseases.
- Carbonic anhydrase inhibitors are considered part of the diuretic class of medications.

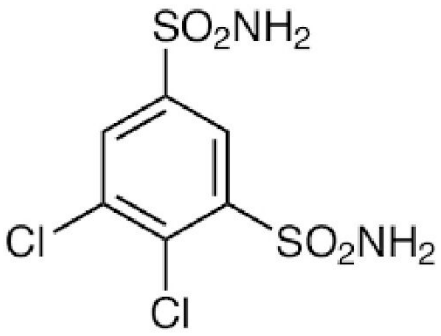
Mechanism of Action:

- The class of diuretics inhibit carbonic anhydrase enzyme in the membrane and intracelluaraly in PCT that causes the decrease reabsorption and increased excretion of sodium bicarbonates and potassium.

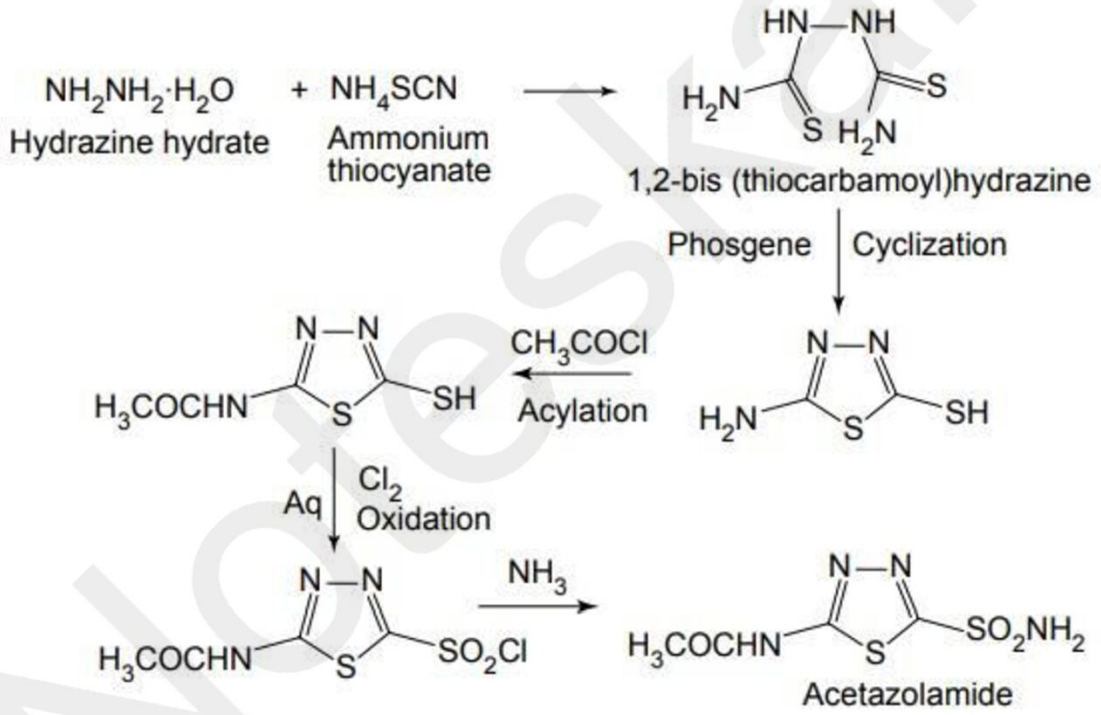
Drugs:

Acetazolamide*, Methazolamide, Dichlorphenamide

Drug	Structure	Mechanism of Action	Uses
Acetazolamide		Inhibits carbonic anhydrase, decreasing the formation of bicarbonate and reducing sodium reabsorption	Used for glaucoma, altitude sickness, epilepsy, and edema
Methazolamide		Similar to acetazolamide, it inhibits carbonic anhydrase, reducing intraocular pressure and diuresis	Used for glaucoma and as an adjunct for epilepsy and edema

Dichlorphenamide		Inhibits carbonic anhydrase, leading to decreased production of aqueous humor and reduction of intraocular pressure	Used for glaucoma and periodic paralysis

Acetazolamide Synthesis:



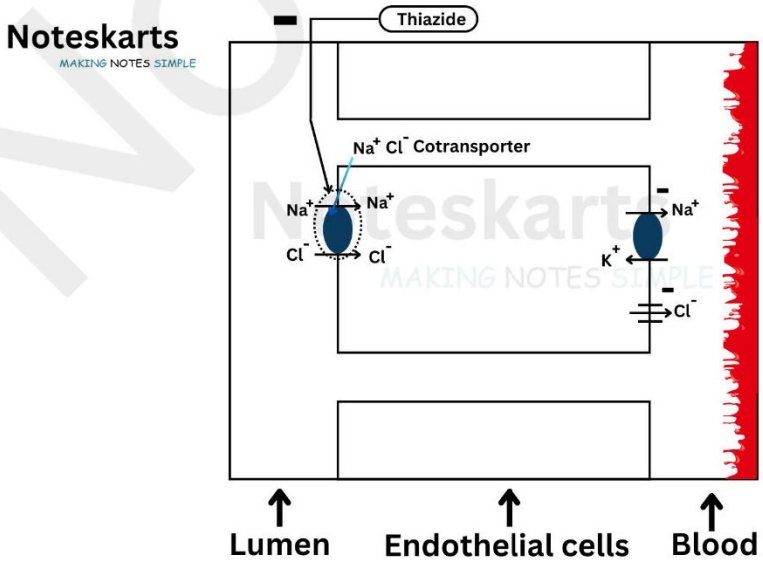
2. Thiazides: Chlorthiazide*, Hydrochlorothiazide, Hydroflumethiazide, Cyclothiazide

Thiazides Diuretics:

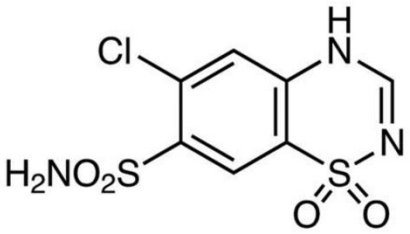
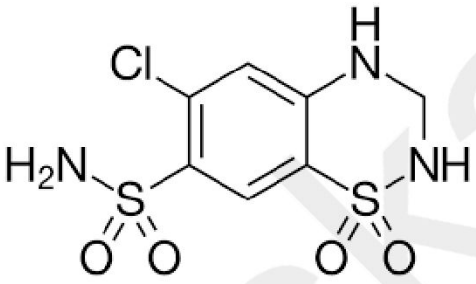
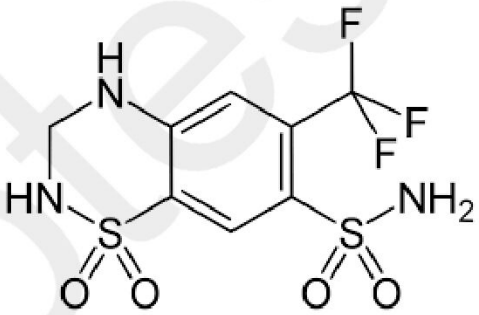
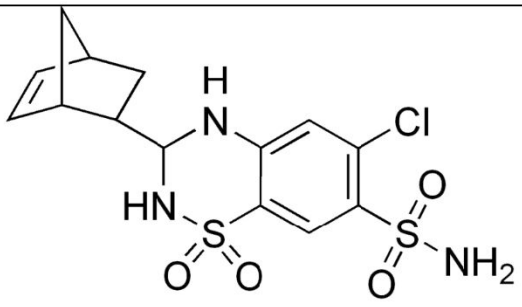
- Thiazides are also called as benzothiadiazides. Thiazides are sulfonamide derivatives.
- Thiazide diuretics are a class of drugs that treat high blood pressure, edema, and other conditions.
- They work by making the kidneys produce more urine, which helps the body get rid of extra fluid and salt. Thiazide diuretics are also known as water pills.

Mechanism of Action:

- These drugs give their effect by working in distal convoluted tubule (DCT) where they reduce the absorption of sodium chloride by inhibiting (Na^+ Cl^+ Cotransporter).
- Now In DCT there are Sodium Chloride cotransporter through which sodium and chloride get in the cell from lumen.
- Then sodium get transported to the blood via sodium potassium ATPase.
- Now when thiazide diuretics introduced they inhibits the Na^+ Cl^+ Cotransporter which decreased Na^+ Cl^+ reabsorption and increased urine output.

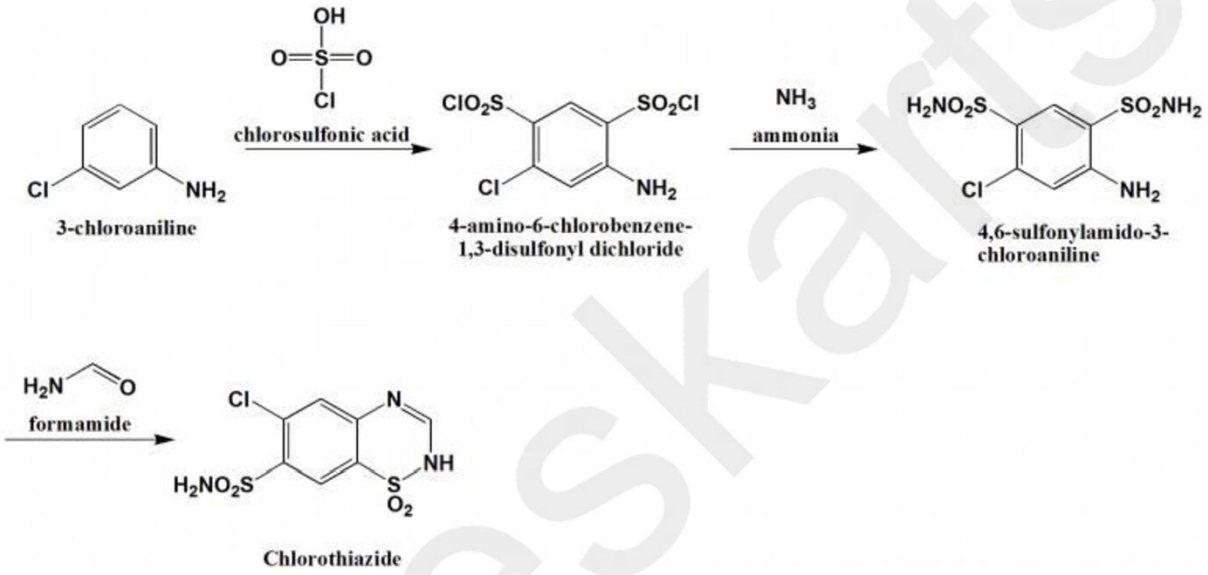


Drug:

Drug	Structure	Mechanism of Action	Uses
Chlorthiazide		Inhibits sodium and chloride reabsorption in the distal convoluted tubules of the kidney	Used for hypertension, edema, heart failure, and nephrogenic diabetes insipidus
Hydrochlorothiazide		Similar to chlorthiazide, inhibits sodium and chloride reabsorption in the distal convoluted tubules	Used for hypertension, edema, heart failure, and nephrogenic diabetes insipidus
Hydroflumethiazide		Inhibits sodium and chloride reabsorption in the distal convoluted tubules, with additional action from its fluorine atoms	Used for hypertension, edema, and heart failure
Cyclothiazide		Inhibits sodium and chloride reabsorption in the distal convoluted tubules of the kidney	Used for hypertension and edema

Chlorthiazide Synthesis:

- Sulfonylchlorination of 3-chloroaniline using chlorosulfonic acid to produce 4,6-sulfonochloride-3-chloroaniline.
- The last is reacted with ammonia to give 4,6-sulfonylamido-3-chloroaniline.
- Heating of the above formed compound with formamide produces chlorothiazide drug.



3. Loop diuretics: Furosemide*, Bumetanide, Ethacrynic acid.

Loop diuretics:

- **Loop diuretics** are used in the treatment of edema due to heart failure, liver disease and kidney disease.
- They may also be used to treat high blood pressure.
- Loop diuretics are pharmacological agents that primarily inhibit the Na-K-Cl cotransporter located on the luminal membrane of cells along the thick ascending limb of the loop of Henle.

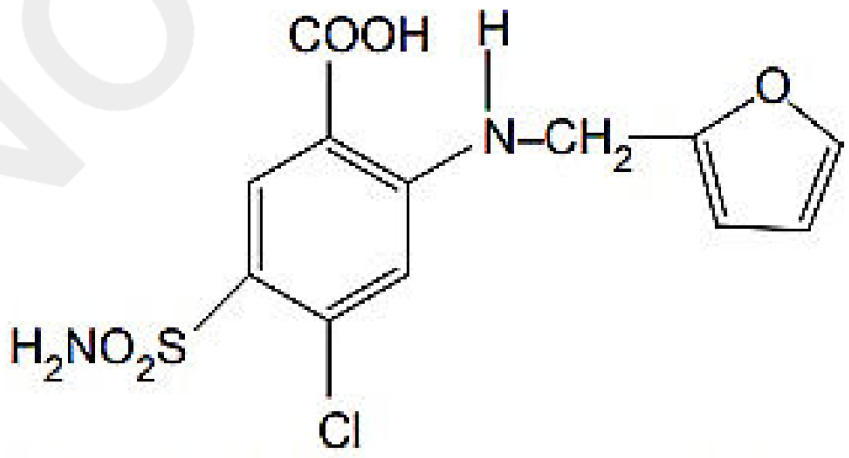
Mechanism of Action:

- Loop diuretics are the most potent diuretics and work by inhibiting the sodium-potassium-chloride symporter in the thick ascending limb of the loop of Henle.
- This prevents sodium reabsorption and increases the elimination of water, potassium, hydrogen ions, magnesium, and calcium from the kidneys.

Drug:

Furosemide

Structure:

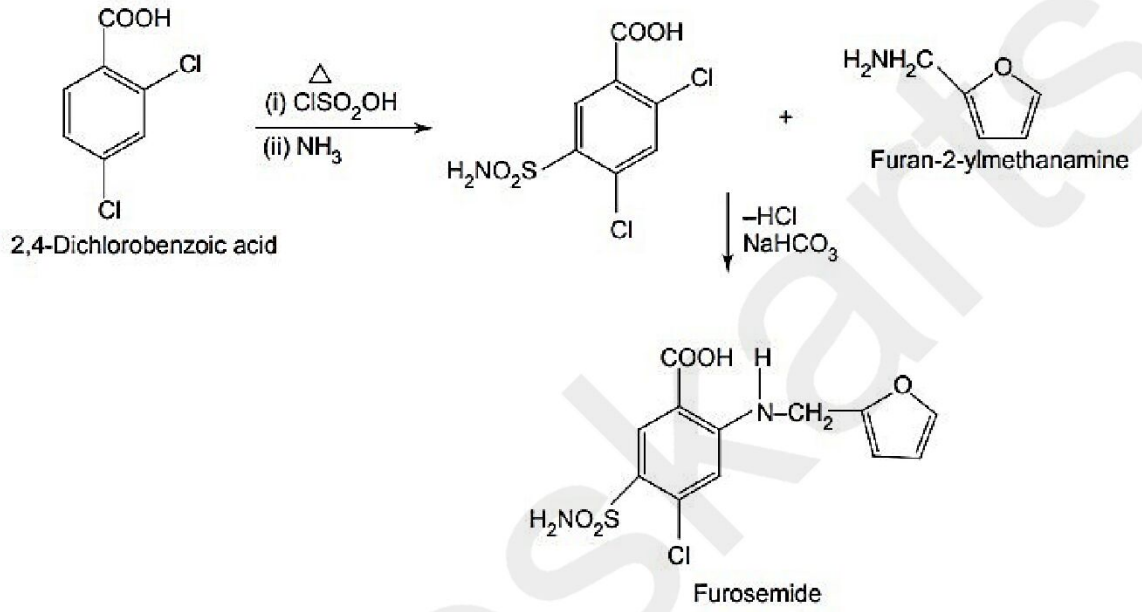


4-Chloro-*N*-furfuryl-5-sulphamoylanthranillic acid

Mechanism of Action:

- Furosemide works by inhibiting the Na-K-2Cl symporter in the thick ascending limb of the loop of Henle, leading to increased excretion of sodium, potassium, chloride, and water. This reduces fluid accumulation in tissues and blood vessels.

Synthesis:

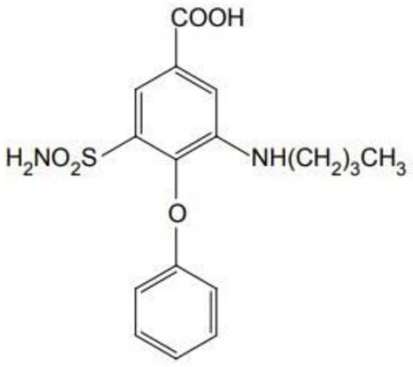


Uses:

- It is used for managing edema associated with congestive heart failure, liver cirrhosis, and renal disease, as well as for treating hypertension.

Bumetanide

Structure:



3-Butylamino-4-phenoxy-5-sulphamoylbenzoic acid

Mechanism of Action:

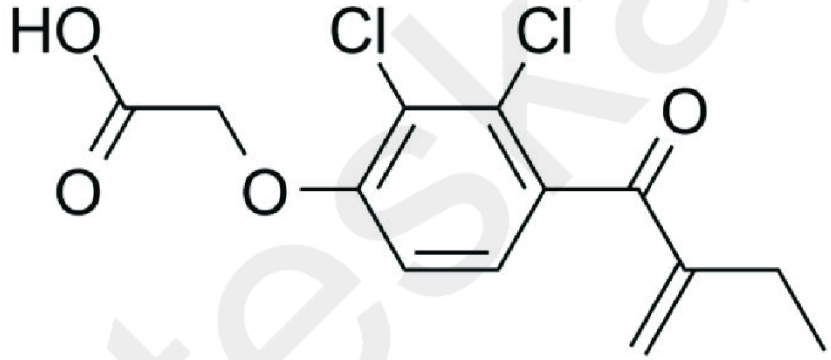
- Bumetanide has a similar mechanism to furosemide, inhibiting the Na-K-2Cl symporter in the thick ascending limb of the loop of Henle, but it is more potent.
- This results in increased excretion of sodium, potassium, chloride, and water.

Uses:

- It is used for the treatment of edema associated with congestive heart failure, liver cirrhosis, renal disease, and hypertension.

Ethacrynic Acid

Structure:



Mechanism of Action:

- Ethacrynic acid inhibits the Na-K-2Cl symporter in the thick ascending limb of the loop of Henle, similar to other loop diuretics, leading to increased excretion of sodium, chloride, and water.
- It does not contain a sulfonamide group, making it suitable for patients with sulfa allergies.

Uses:

- It is used for managing edema associated with congestive heart failure, liver cirrhosis, renal disease, and for patients who are allergic to sulfonamide diuretics.

4. Potassium sparing Diuretics: Spironolactone, Triamterene, Amiloride.

Potassium sparing Diuretics:

- These drugs give their effects by working in collecting duct where they inhibits Na^+ and K+ secretion.
- These are weak diuretics so mostly used in combination. Weak diuretics filtrate almost 90% reabsorbed before reached to collecting duct.

Mechanism of Action:

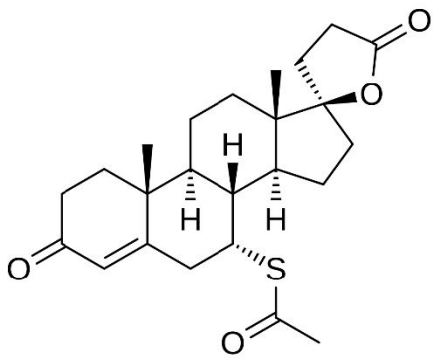
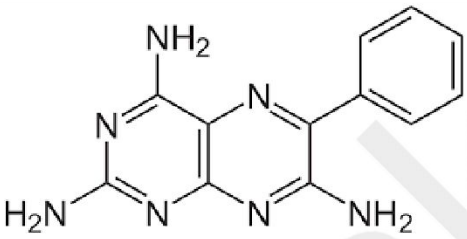
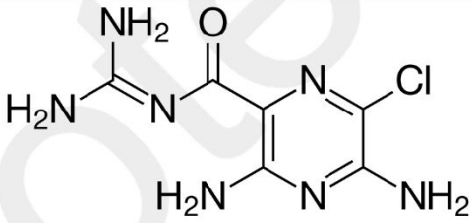
- The potassium sparing diuretics are divided into two groups on the basis of mechanism of action:

1. Na+ channel Inhibitors: Triamterene and Amiloride

2. Aldosterone Antagonists: Spironolactone.

Aldosterone Antagonists:

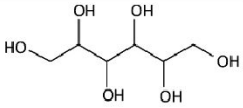
Aldosterone by binding to its receptor enhances the passage of Na+ from the luminal fluid into tubular cells (Na+ reabsorption) and the passage of intracellular K+ into the luminal fluid at site 4.

Drug	Structure	Mechanism of Action	Uses
Spironolactone		Aldosterone antagonist that blocks sodium reabsorption and potassium excretion in the distal tubule	Used for hypertension, heart failure, hyperaldosteronism, and edema associated with liver cirrhosis
Triamterene		Inhibits epithelial sodium channels in the distal tubules, reducing sodium reabsorption and potassium excretion	Used for hypertension and edema, often in combination with other diuretics to prevent hypokalemia
Amiloride		Inhibits epithelial sodium channels in the distal tubules and collecting ducts, reducing sodium reabsorption and potassium excretion	Used for hypertension, heart failure, and edema, often in combination with other diuretics to prevent hypokalemia

5. **Osmotic Diuretics:** Mannitol

Osmotic Diuretics:

- Osmotic diuretics are medications that increase urine production by preventing the kidneys from reabsorbing water and solutes.
- They work by increasing the osmolarity of blood and renal filtrate, which eventually becomes urine.

Drug	Structure	Mechanism of Action	Uses
Mannitol		Increases osmolarity of the glomerular filtrate, inhibiting reabsorption of water and electrolytes	Used for reducing intracranial and intraocular pressure, promoting diuresis in renal failure, and facilitating urinary excretion of toxic substances

3. Anti-hypertensive Agents

- Timolol, Captopril, Lisinopril, Enalapril, Benazepril hydrochloride, Quinapril hydrochloride, Methyldopate hydrochloride,* Clonidine hydrochloride, Guanethidine monosulphate, Guanabenz acetate, Sodium nitroprusside, Diazoxide, Minoxidil, Reserpine, Hydralazine hydrochloride.

Anti-hypertensive drugs

- These are those drugs which are used to in the treatment of Hypertension.

Hypertension

- Hypertension is define as either a sustained systolic Blood Pressure (BP) of greater then 140 mmHg or sustained diastolic BP of greater than 40mmHg.

$$\text{Normal} = \frac{120}{80} = \frac{\text{Systolic}}{\text{Diastolic}}$$

Stage of Hypertension:

Hypertension	Systolic	Diastolic
Stage-I	140-159	90-99
Stage-II	160-179	100-109
Severe	>180	>110

Hypertension Can Cause

- Heart Failure
- Brain Stroke
- Kidney Failure
- Vision loss
- Sexual dysfunction

Risk Factor

- NA+ Intake ↑
- Smoking ↑
- Stress ↑
- Obesity ↑

Anti-hypertensive drugs

- These are those drugs which are used to in the treatment of Hypertension.

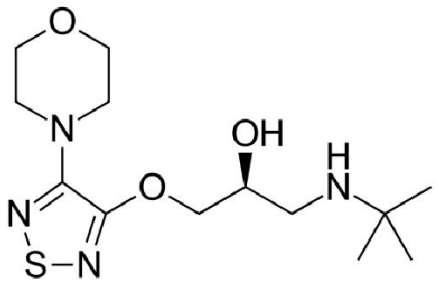
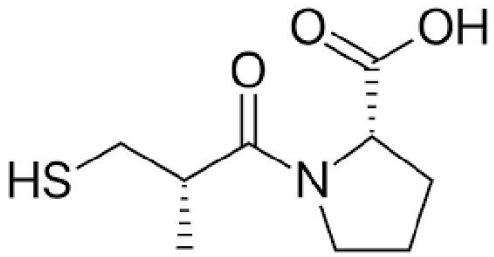
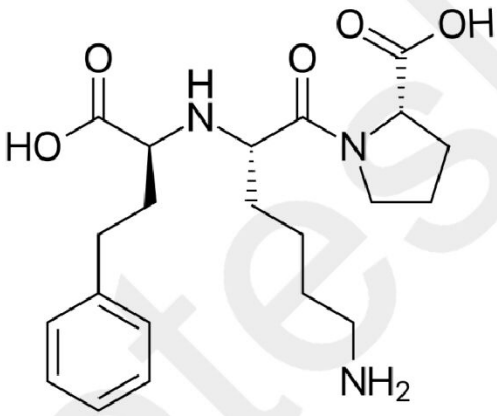
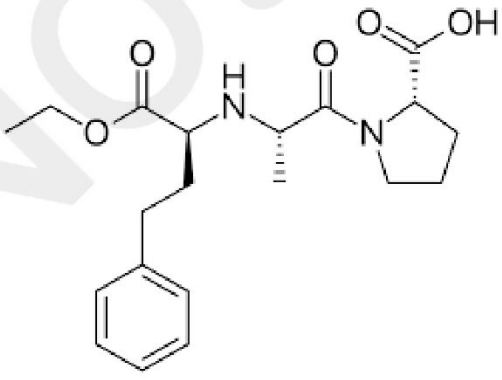
Or

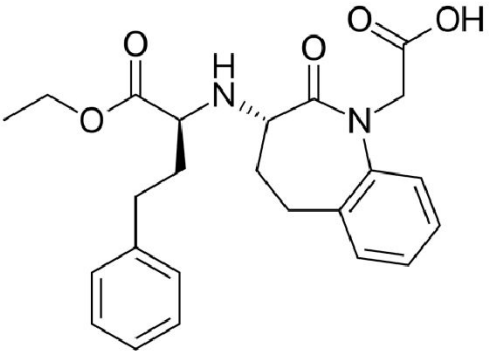
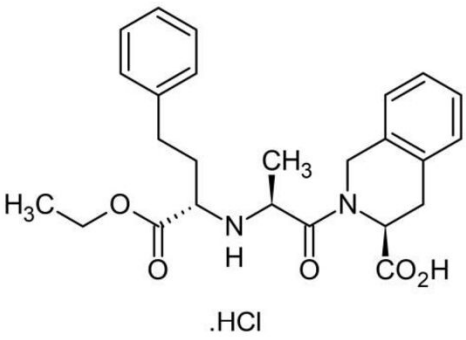
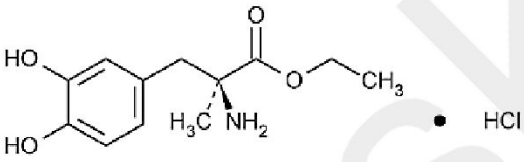
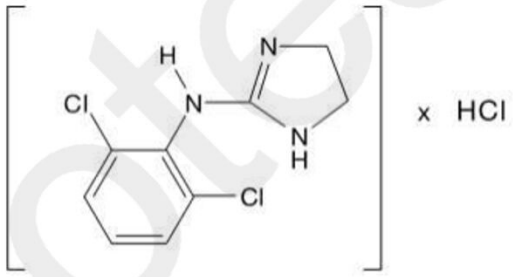
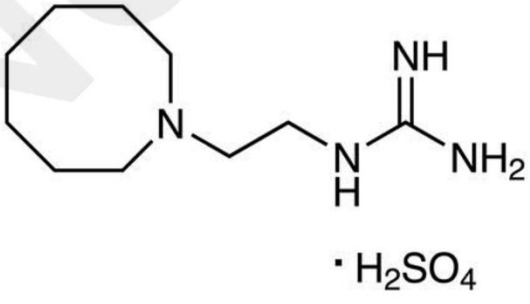
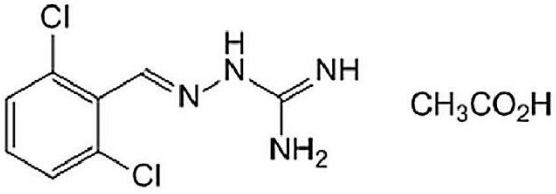
- The antihypertensive of the 1960-70s were methyldopa, B blockers, thiazide and high ceiling diuretics and clonidine.
- The status of ß blockers and diuretics was consolidated in the 1970s and selective α, blocker prazosin broke new grounds.
- The antihypertensive introduced in the 1980-90s were angiotensin II converting enzyme (ACE) inhibitors and calcium channel blockers.
- Angiotensin receptor blockers (losartan, etc.) were added soon after, and the direct renin inhibitor aliskiren is the latest drug.

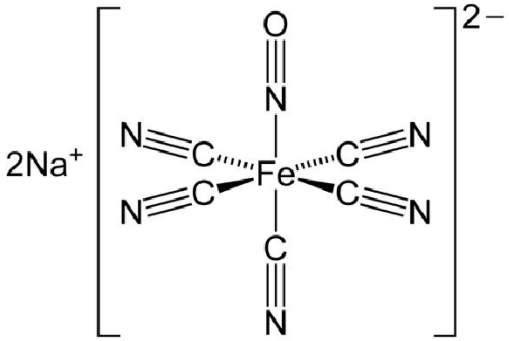
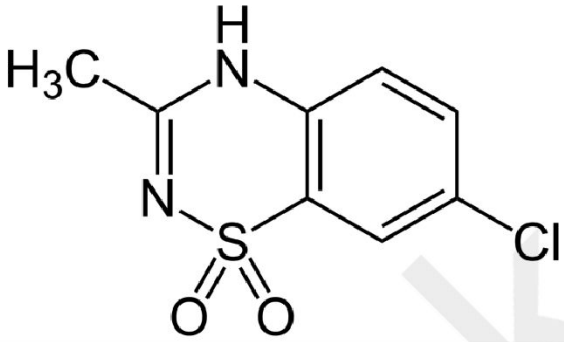
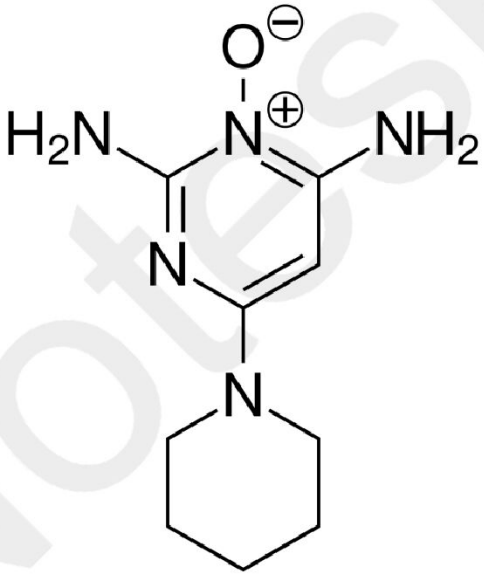
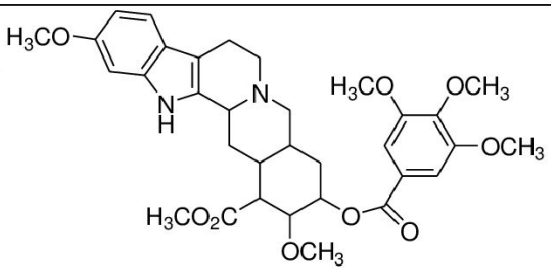
Classification Anti-hypertensive drugs:

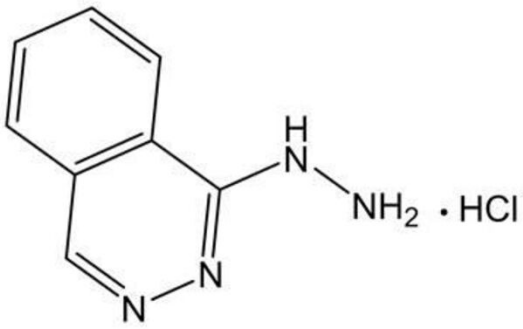
1. **Diuretics**
    - Furosemide
    - Thiazides
    - Eplerenone, etc.
2. **ACE Inhibitors**
    - Captopril
    - Lisinopril
    - Quinapril, etc.
3. **Beta Adrenergic blocker**
    - Atenolol
    - Metoprolol
    - Propranolol, etc.
4. **Calcium Channel Blockers**
    - Verapamil
    - Diltiazem
    - Nifedipine
    - Felodipine, etc

Drugs:

Drug Name	Structure	Mechanism of Action	Uses
Timolol		Decreases aqueous humor production and reduces intraocular pressure	Glaucoma, hypertension, myocardial infarction
Captopril		Inhibits angiotensin-converting enzyme, reducing angiotensin II and aldosterone	Hypertension, heart failure, diabetic nephropathy
Lisinopril		Inhibits angiotensin-converting enzyme, reducing angiotensin II and aldosterone	Hypertension, heart failure, acute myocardial infarction
Enalapril		Inhibits angiotensin-converting enzyme, reducing angiotensin II and aldosterone	Hypertension, heart failure

Benazepril hydrochloride		Inhibits angiotensin-converting enzyme, reducing angiotensin II and aldosterone	Hypertension
Quinapril hydrochloride		Inhibits angiotensin-converting enzyme, reducing angiotensin II and aldosterone	Hypertension, heart failure
Methyldopate hydrochloride		Stimulates alpha-2 adrenergic receptors, reducing sympathetic outflow	Hypertension (especially in pregnancy)
Clonidine hydrochloride		Stimulates alpha-2 adrenergic receptors, reducing sympathetic outflow	Hypertension, ADHD, pain management
Guanethidine monosulphate		Inhibits release of norepinephrine from sympathetic nerve endings	Hypertension
Guanabenz acetate		Stimulates alpha-2 adrenergic receptors, reducing	Hypertension

		sympathetic outflow	
Sodium nitroprusside		Releases nitric oxide, causing vasodilation	Hypertensive emergencies, acute heart failure
Diazoxide		Opens potassium channels, causing hyperpolarization and relaxation of vascular smooth muscle	Hypertensive emergencies, hypoglycemia
Minoxidil		Opens potassium channels, causing hyperpolarization and relaxation of vascular smooth muscle	Severe hypertension, hair growth (topical)
Reserpine		Depletes norepinephrine, serotonin, and dopamine from sympathetic nerve endings	Hypertension (historically)

Hydralazine hydrochloride		Directly relaxes arteriolar smooth muscle	Hypertension, heart failure

Methyldopate hydrochloride:

1. 4-hydroxy-3-methoxy phenylacetone is taken as starting material.
2. It undergoes reaction with ammonium chloride followed by reaction with potassium cyanide to α-amino nitrile compound.
3. L-isomer is separated out by rection with camphosulfonic acid.
4. On reating with sulfuric acid, we get methyldopa as final product.