MEDICINAL CHEMISTRY-II

UNIT 2 NOTES

ANTI-ANGINAL DRUGS

- Vasodilators
- Calcium Channel Blockers
- Diuretics
- Anti Hypertensive Agents

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Ischemic Heart Disease

- Ischemic Heat Disease is also known as Coronary Artery Disease.
- It is a condition in which supply of oxygen to the muscles of heart get reduced.
- IHD/CAD develops when coronary artery become diseased or damaged.
- In IHD blood supply reduced according to demand of myocardium.
- Building of Plaque & Inflammation in arteries are the major causes of Ischemic Heart Disease.
- Ischemic Heat Disease is further responsible for following heart diseases as follows :

① Angina Pectoris
② Myocardial Infarction
③ Atherosclerosis

Angina Pectoris

- Angina is a term used for 'Chest Pain' caused by reduced blood flow to the heart muscles.
- It is a symptom or complication of 'Coronary Artery Disease'.
- It is a condition that arised when there is an imbalance between the demand for oxygen and its supply to myocardium.

Types Of Angina Pectoris

① Stable Angina
② Unstable Angina
③ Variant Angina

STABLE ANGINA

- It is also known as Chronic Angina.
- It generally occurs when heart is working harder than it works in normal conditions i.e., during exercises.
- It occurs due to building of plaque / fat deposition in Coronary Arteries.
- Pain of stable angina releived by proper rest or medication.

UNSTABLE ANGINA

- The pain of unstable angina occurs even during period of rest, sleeping or suddenly.
- It is considered more serious than stable angina as rest or medication is not enough for its relief.
- It generally occurs due to rupturing of coronary arteries.

VARIANT ANGINA

- It is a rare type of angina, its pain generally occurs at resting stage.
- It occurs due to narrowing of coronary arteries.
- This narrowing or spasm leads to decreased blood flow to the heart and increases the risk of Heart Attack.

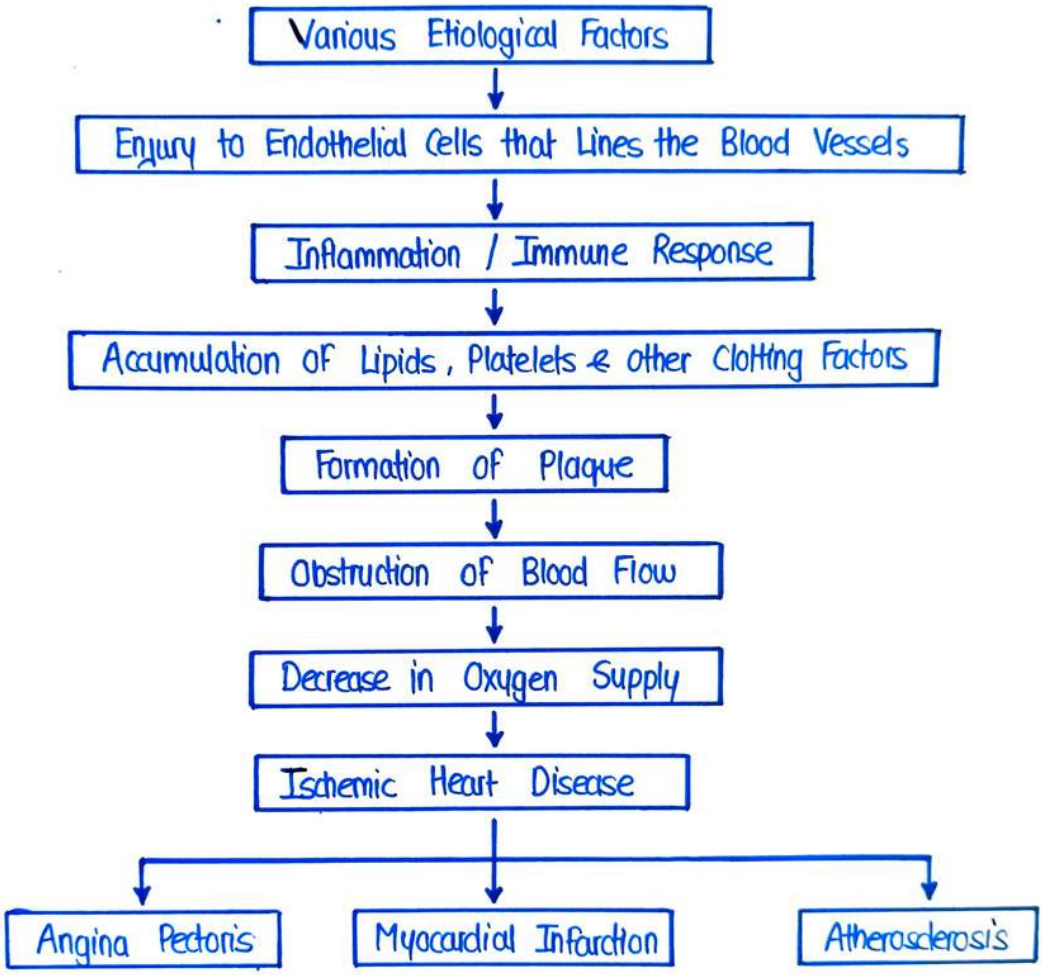
CAUSES

The various causes for Ischemic Heart Disease including Angina Pectoris, Myocardial Infarction & Atherosclerosis are as follows:

- Hypertension
- High Cholesterol
- Smoking
- Alcohol
- Obesity
- Diabetes
- Age
- Stress
- Genetics

PATHOGENESIS

The most common mechanism / pathogenesis behind all the Ischemic Heart Diseases are as follows :



Sign & Symptoms

- Chest Pain
- Fatigue
- Anxiety
- Headaches
- Shortness of Breath
- Irregular Heartbeat
- Blurred Vision

Complications

- Heart Attack
- Heart Failure
- kidney Failure
- Eye Problems
- Various Metabolic Disorders.

Treatment / Management

① Non Pharmacological

- Exercise
- Healthy Diet
- No Tobacco / Alcohol
- Healthy Lifestyle

② Pharmacological :

- Anticoagulants
- Beta Blockers
- ACE Inhibitors / Vasodilators

ANTI-ANGINAL DRUGS

- Anti-anginal drugs are medications used to relieve or prevent angina pectoris, which is chest pain caused by reduced blood flow to the heart muscle.
- These drugs work by improving blood flow, reducing heart workload, or both.

CLASSIFICATION

Anti-anginal drugs can be classified as follows :

① Vasodilators

- Amyl Nitrite
- Nitroglycerine *
- Pentaerythritol Tetranitrate
- Isosorbide Dinitrite *
- Dipyridamole

② Calcium Channel Blockers

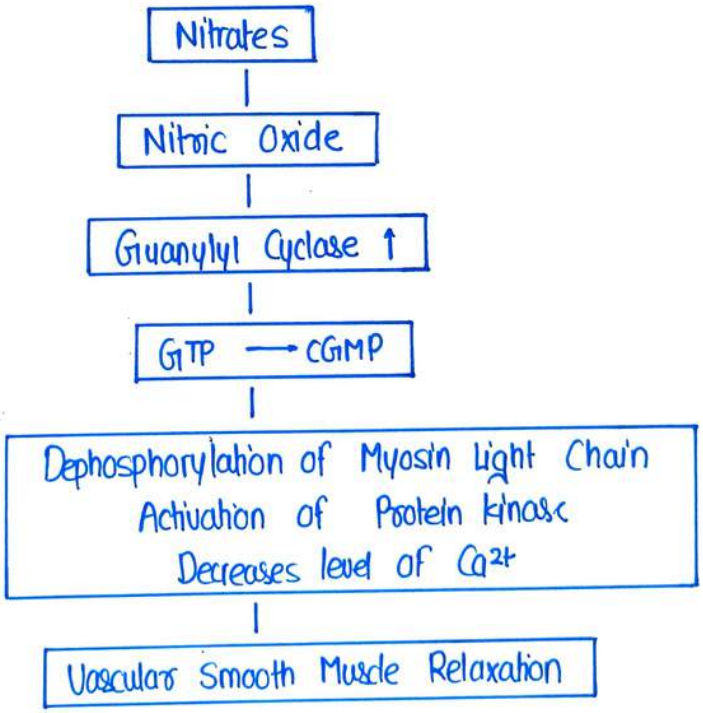
- Verapamil
- Bepridil Hydrochloride
- Diltiazem Hydrochloride
- Nifedipine
- Amlodipine
- Felodipine
- Nicardipine
- Nimodipine

① VASODILATORS

- Vasodilators are drugs that dilate the blood vessels results from relaxation of smooth muscles of blood vessels.
- The vasodilators used in treatment of Angina Pectoris are basically Nitrovasodilators or simply nitrates

Mechanism Of Action

Nitrates work by converting into Nitric Oxide, which is a potent vasodilator.
They reduced workload on heart which decreases heart's oxygen demand & dilates coronary artery, improving oxygen supply to heart.



① AMYL NITRITE

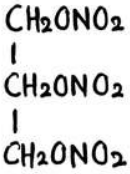
Amyl Nitrite belongs to the class of Alkyl Nitrite which is commonly used as a vasodilator.

Uses

- Angina Pectoris
- Cyanide Poisoning
- Oxidant

② NITROGLYCERINE *

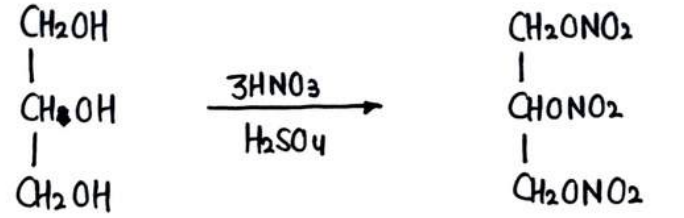
Nitroglycerine is a type of Nitroglycerol in which all three H atoms of glycerol is replaced by Nitro Groups.



Properties

- It is a dense, colourless, oily, explosive liquid.
- It is insoluble in water but soluble in alcohol.

Synthesis

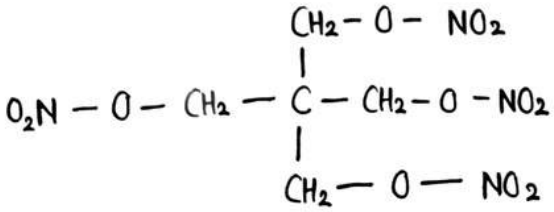


Glycerin — Nitroglycerin

Uses

- Angina Pectoris
- Acute Myocardial Infarction
- Heart Failure

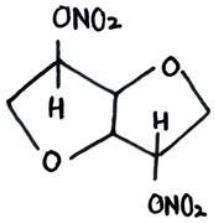
③ PENTAERYTHRITOL TETRANITRATE



Uses

- Angina Pectoris
- Myocardial Infarction

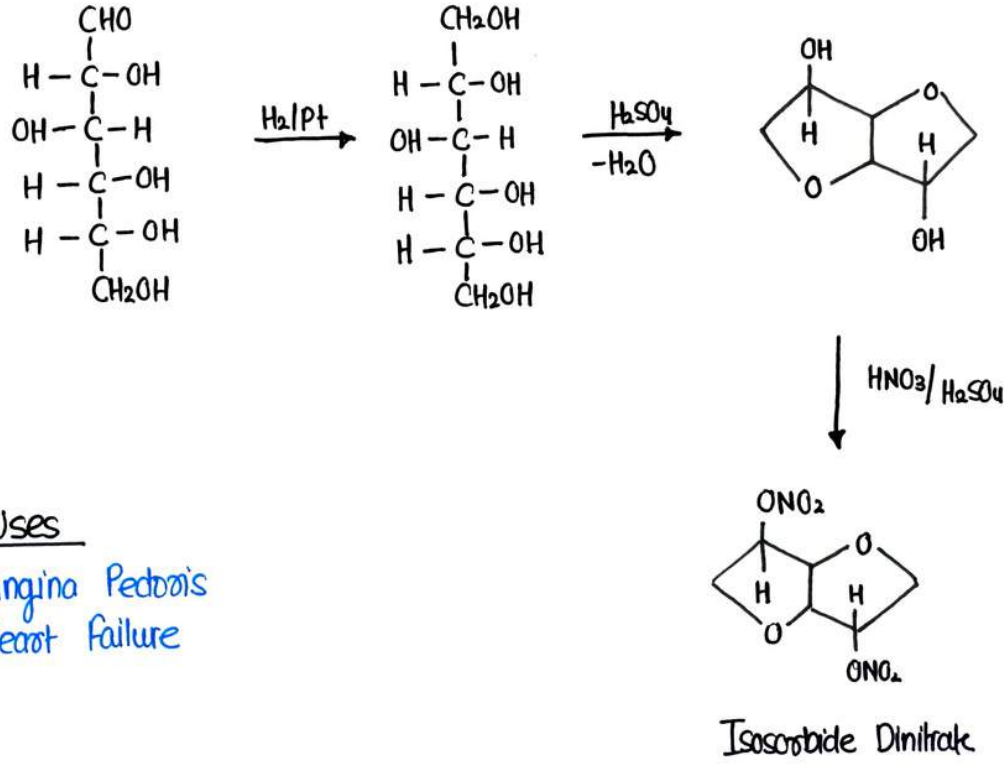
④ Isosorbide Dinitrate



Properties

- It is a fine white crystalline powder
- It is slightly soluble in water, well soluble in acetone

Synthesis

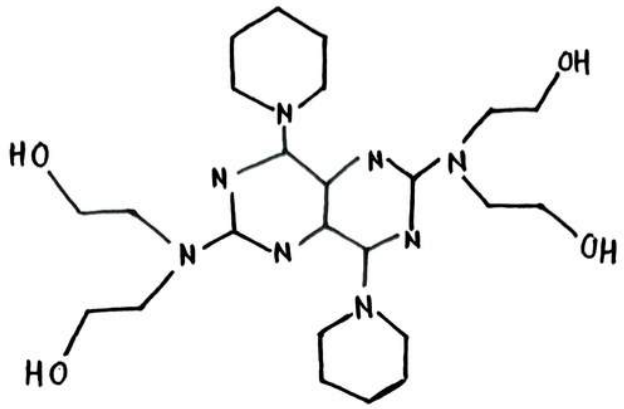


Isosorbide Dinitrate

Uses

- Angina Pectoris
- Heart failure

⑤ DIPYRIDAMOLE



Uses

- Antiplatelet Agent
- Vasodilator

MOA

- Dypyridamole increases the level of adenosine in blood stream
- Adenosine binds to receptors on surface of blood vessels, causing vasodilation, and improved blood flow particularly in coronary arteries.

② CALCIUM CHANNEL BLOCKERS

- Calcium Channel Blockers are class of medications used as an antianginal agents to treat angina pectoris.
- They work by blocking the entry of calcium ions into smooth muscle cells of heart and blood vessels.

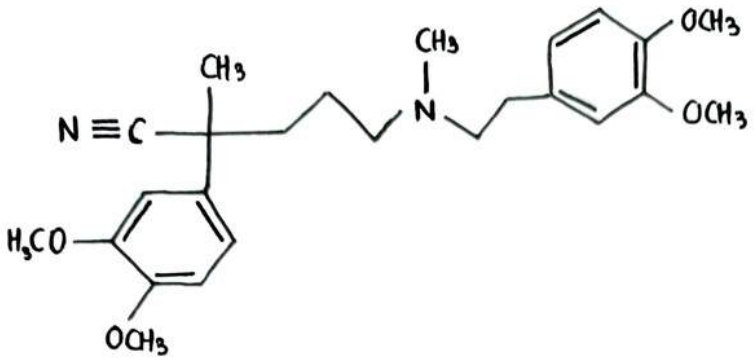
Mechanism of Action

- L-type calcium channels are found in smooth muscles of blood vessel, cardiac myocytes (heart muscle cells) & SA & AV node of heart.
- Normally, when calcium ions enter cells through these channels they trigger muscle contraction, in heart this increase force of contraction, while in blood vessels it leads to vasoconstriction.

Drugs

- Verapamil
- Bepridil Hydrochloride
- Diltiazem Hydrochloride
- Nifedipine
- Amlodipine
- Felodipine
- Nicardipine
- Nimodipine

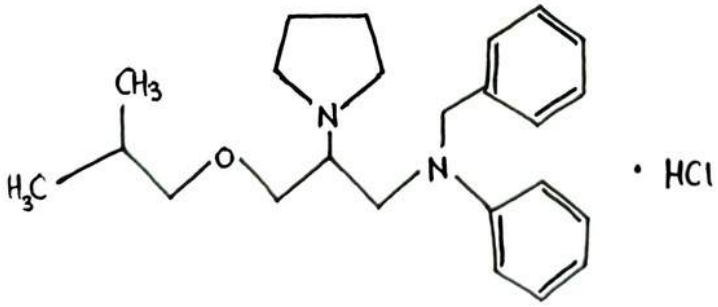
① VERAPAMIL



Uses

- Angina
- Hypertension
- Arrythmia

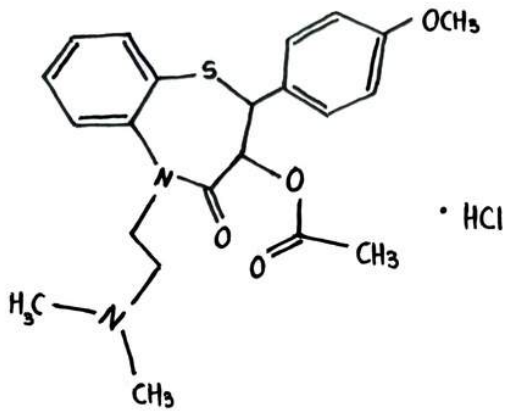
② BEPRIDIL HYDROCHLORIDE



Uses

- Angina
- Certain Arrythmias

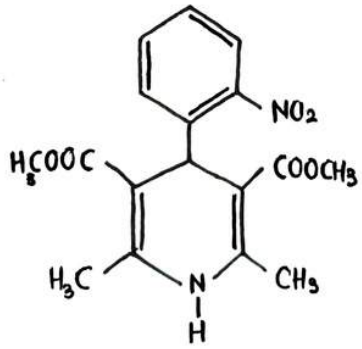
③ DILTIAZEM HYDROCHLORIDE



Uses

- Hypertension
- Angina
- Arrythmia

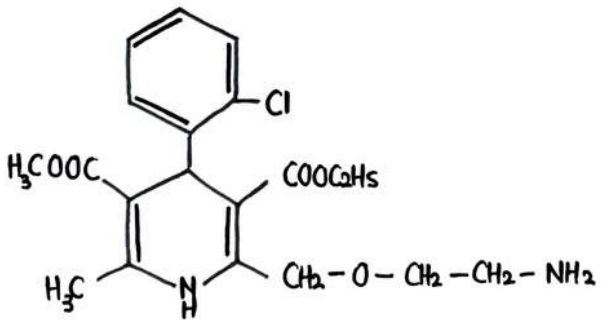
④ NIFEDIPINE



Uses

- Angina
- Hypertension

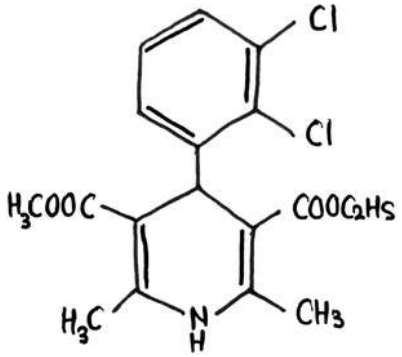
⑤ AMLODIPINE



Uses

- Angina
- Hypertension

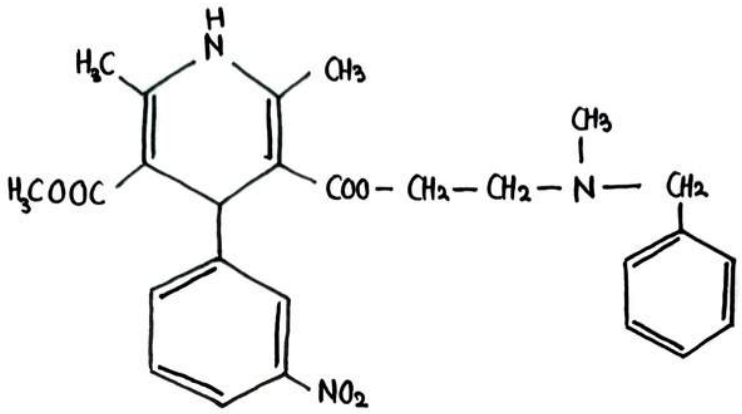
⑥ FELODIPINE



Uses

- Angina
- Hypertension

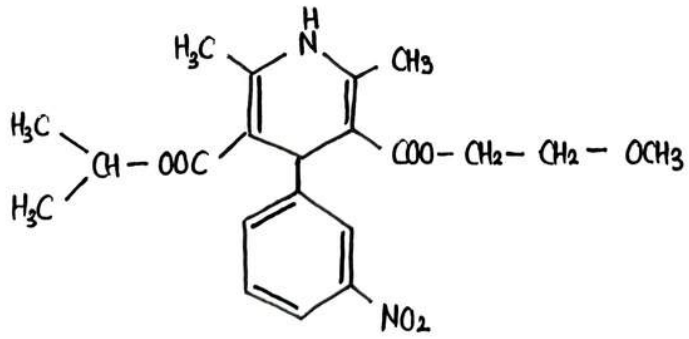
⑦ NICARDIPINE



Uses

- Hypertension
- Angina

⑧ NIMODIPINE



Uses

- Cerebral vasospasm

HYPERTENSION

- The term Hypertension referred to 'High Blood Pressure'.
- It is a chronic medical condition that arises when blood pressure is abnormally high.
- It occurs when blood vessels gets narrowed & cause blood to exert more pressure on heart's wall.
- Heart & Blood vessels can tolerate high blood pressure for months & years but eventually high B.P. ended up damaging walls of heart that leads to Heart Failure.
- As per the world health statistics, approx 1.5 billion adult population across the world is suffering from Hypertension.

STAGES OF HYPERTENSION

	STAGES	SYSTOLIC BP	DIASTOLIC BP
•	Normal	< 120 mm Hg	< 80 mm Hg
•	Pre- Hypertension	120-139 mm Hg	80-89 mm Hg
•	Stage I	140- 159 mm Hg	90-99 mm Hg
•	Stage II	≥ 160 mm Hg	≥ 100 mm Hg

TYPES OF HYPERTENSION

Hypertension is of mainly two types :

① Primary Hypertension
② Secondary Hypertension

Primary Hypertension

- It is also known as Essential Hypertension.
- 95% people with High B.P. suffered with Primary Hypertension.
- Generally causes behind this are unidentified.

Secondary Hypertension

- Secondary Hypertension is often arised by other medical conditions such as kidney, artery, heart or endocrine system disorders.
- It's less common than primary hypertension affecting 5-10% of Hypertensive patients.
- It's more common in younger people.

Etiology / Causes Of Hypertension

As we discussed early, it is very difficult to find the exact cause of Hypertension, but here are some following reasons that can be responsible for Hypertension.

- Inactive Life Style
- Stress
- Obesity
- High sodium (salt) diet
- Alcohol
- Smoking
- kidney Diseases.
- Diabetes
- Age
- Family History
- Certain Medications

PATHOGENESIS OF HYPERTENSION

Pathogenesis of hypertension is often multifactorial & complex, it can be described by following mechanism

- Increased Arteriolar Resistance
- Chronic Renal Failure
- Sympathic Activation
- Activation of RAAS System

① Increased Arteriolar Resistance

- An increase in arteriolar resistance can lead to Hypertension by raising blood pressure within arteries.
- An increase in arteriolar resistance can be occur due to many reasons including thining & fracturing of elastin, increased collagen deposition & increased wall thickness.
- It further increases risk of stroke, coronary artery disease & CHF.

② Chronic Renal Failure

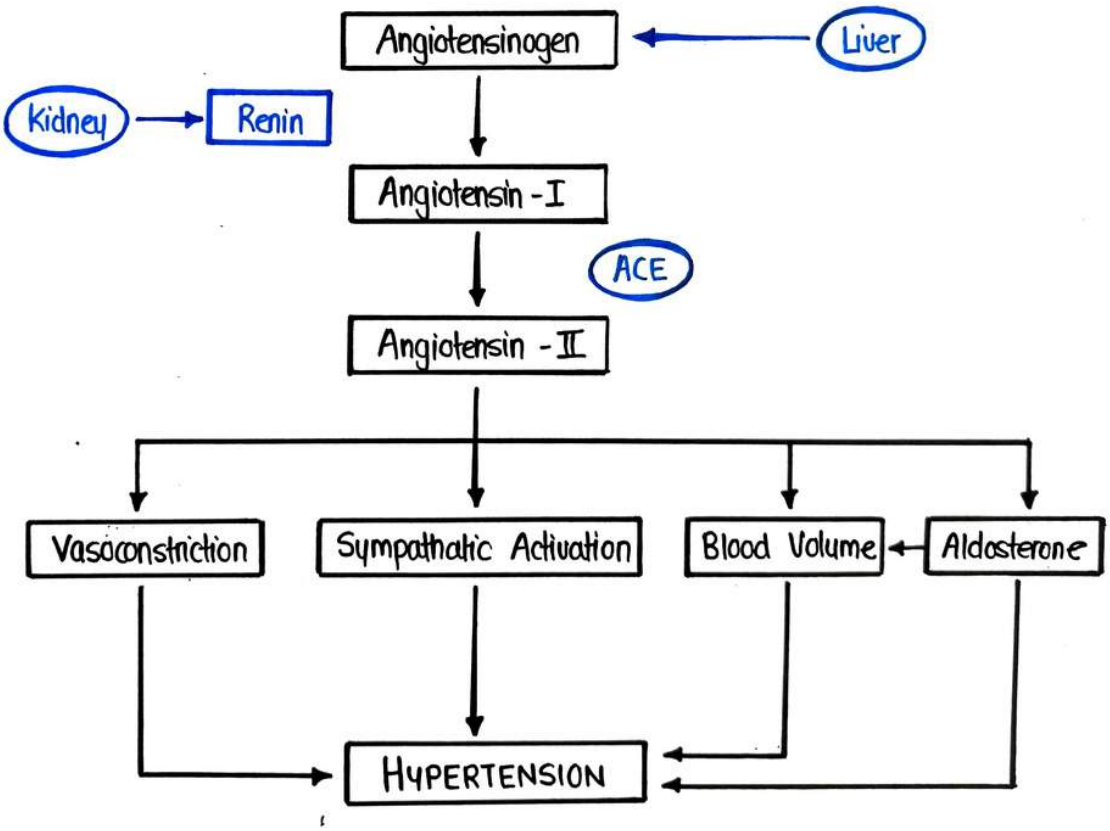
- When kidney doesn't function properly then it fails to excrete normal amount of sodium that leads to sodium retention.
- Now this sodium retention causes water retention that increases the blood volume that leads to Hypertension.

③ Sympathatic Activation

- Stress & various other factors leads to the activation of sympathatic nervous system that causes increased release of nor-epinephrine
- Now this leads to increase cardiac output & systemic vascular resistance.

④ Activation Of RAAS System

- RAAS stands for Renin Angiotensin Aldosterone System.
- Renin is a harmone released by kidney while Angiotensin is released by liver & when they both combines activates Aldosterone.



Sign & Symptoms

- Headache
- Dizziness
- Blurred Vision
- Nausea & Vomiting
- Fatigue
- Chest Pain
- Irregular Heartbeat

Complications

- Heart Attack
- Heart Failure
- kidney Failure
- Stroke
- Retinopathy

Treatment / Management

① Non Pharmacological

- Weight Loss
- Exercise
- Meditation
- Healthy Diet

② Pharmacological

- Diuretics
- α, β Blockers
- Vasodilators, ACE Inhibitors

ANTIHYPERTENSIVE AGENTS

- Antihypertensive Agents are class of medications used to treat Hypertension.
- They work through various mechanisms to lower the blood pressure, reduce the risk of cardiovascular events & prevent complications associated with chronic high blood pressure & kidney issues.

CLASSIFICATION

Antihypertensive Agents can be classified as follows :

① ACE INHIBITORS

- Captopril
- Lisnopril
- Enalapril
- Benzapril Hydrochloride
- Quinapril Hydrochloride

② Centrally Acting Adrenergic Agents

- Methyldopate Hydrochloride *
- Clonidine Hydrochloride
- Guanethidine Monosulphate
- Guanabenz Acetate
- Reserpine

③ Vasodilators

- Sodium Nitroprousside
- Diazoxide
- Minoxidil
- Hydralazine Hydrochloride

④ B-Blockers

- Timolol

① ACE Inhibitors

- Angiotensin- Converting- Enzyme Inhibitors are class of medications primarily used to treat Hypertension & Heart failure.
- The work by interfering with Angiotensin converting enzyme a enzyme involves in RAAS System.

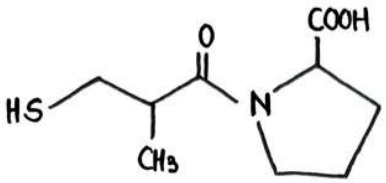
MOA

- It block the action of ACE enzyme, which is responsible for converting Angiotensin I to Angiotensin II.
- By inhibiting the formation of Angiotensin II, ACE Inhibitors leads to:
  - Vasodilation
  - Decreased Aldosterone secretion
  - Lowered Sympathetic activity.

DRUGS

- Captopril
- Lisnopril
- Enalapril
- Benzapril Hydrochloride
- Quinapril Hydrochloride

① CAPTOPRIL



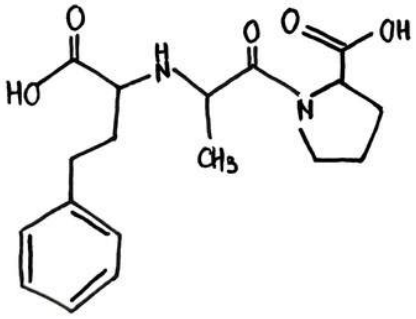
MOA

It inhibits ACE enzyme, reducing angiotensin II & aldosterone levels.

Uses

- Hypertension
- Heart failure
- Left Ventricular Dysfunction

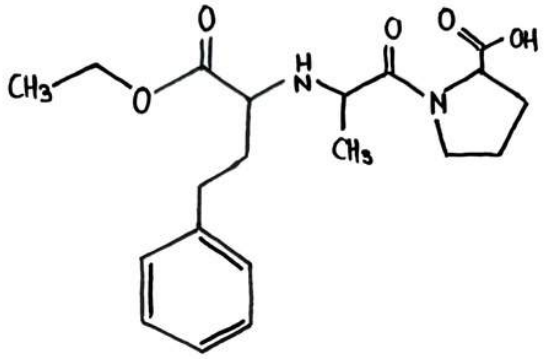
② LISINOPRIL



Uses

- Hypertension
- Heart failure
- Acute Myocardial Infarction

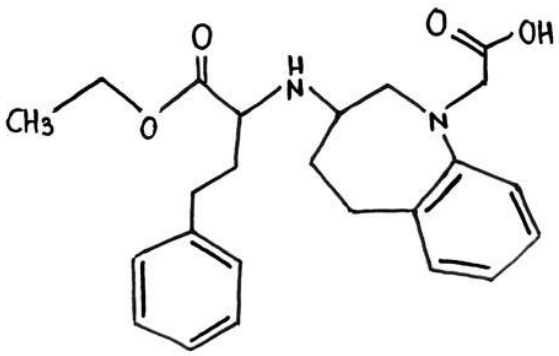
③ ENALAPRIL



Uses

- Hypertension
- Heart Failure

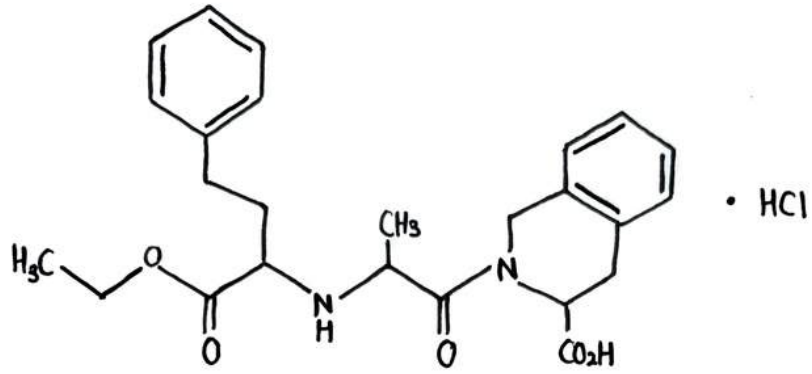
④ BENAZEPRIL HYDROCHLORIDE



Uses

- Hypertension
- Heart Failure

(S) QUINAPRIL HYDROCHLORIDE



Uses

- Hypertension
- Heart failure

② CENTRALLY ACTING ADRENERGIC AGENTS

Centrally acting adrenergic agents are medications that target the Central Nervous System to reduce sympathatic nervous system activity, leading to decreased blood pressure & other therapeutic effects.

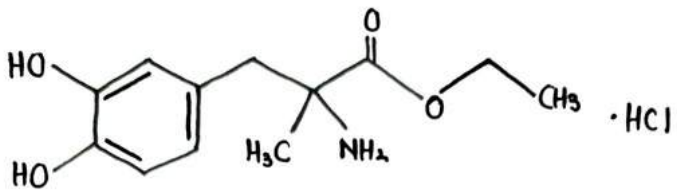
MOA

- These agents mainly stimulate α-2 adrenergic receptors in brain
- Activation of alpha-2 receptors inhibits the release of norepinephrine, leading to a decrease in sympathatic nervous system activity.
- This results in lowered heart rate and vasodilation.
- The overall effect of reduced sympathatic tone results in lower blood pressure.

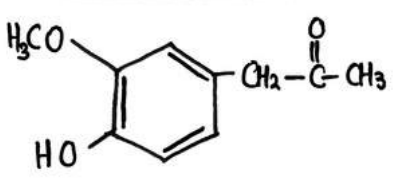
DRUGS

- Methyldopate Hydrochloride
- Clonidine Hydrochloride
- Guanethidine Monosulphate
- Guanabenz Acetate
- Reserpine

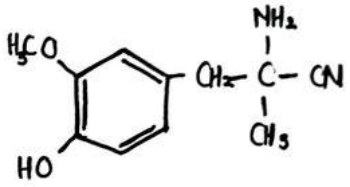
① METHYLDOPATE HYDROCHLORIDE *



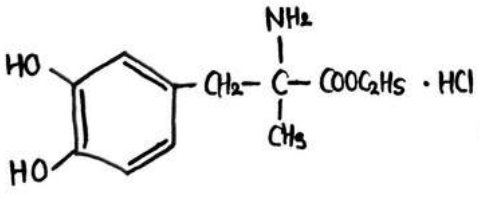
Synthesis



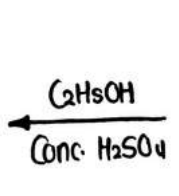
4-hydroxy-3 methoxy phenylacetone

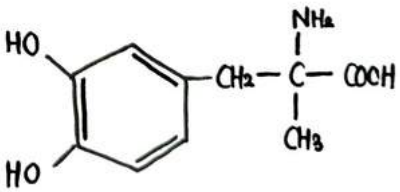


2-amino-3 (4-hydroxy-3 methoxyphenyl) - 2-methylpropanenitrile



Methyldopate Hydrochloride





Methyldopa

Mechanism Of Action

It stimulates alpha- 2 adrenergic receptors, reducing the activity of sympathetic nervous system.

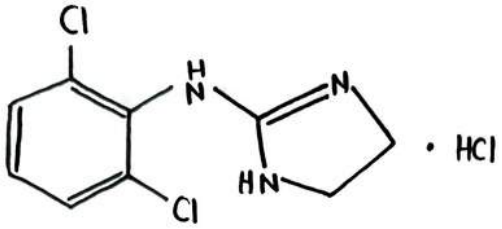
Properties

- It is a white crystalline powder
- It is freely soluble in water

Uses

- Hypertension

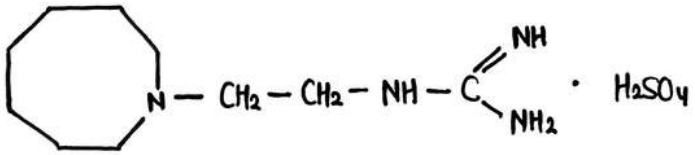
② Clonidine Hydrochloride



Uses

- Hypertension
- Attention Deficit Hyperactivity disorders

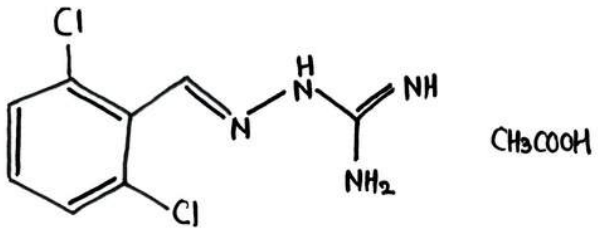
③ Guanethidine Monosulphate



Uses

- Hypertension

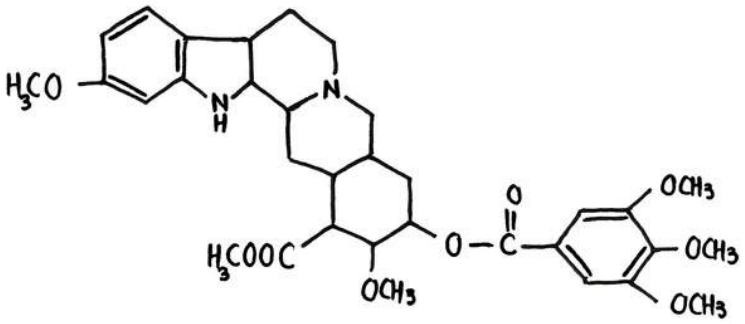
④ GUNABENZ ACETATE



Uses

Hypertension

⑤ Reserpine



Uses

Hypertension

③ VASODILATORS

Vasodilators are class of Antihypertensive Agents that work by relaxing the smooth muscles in blood vessels leading to vasodilation.

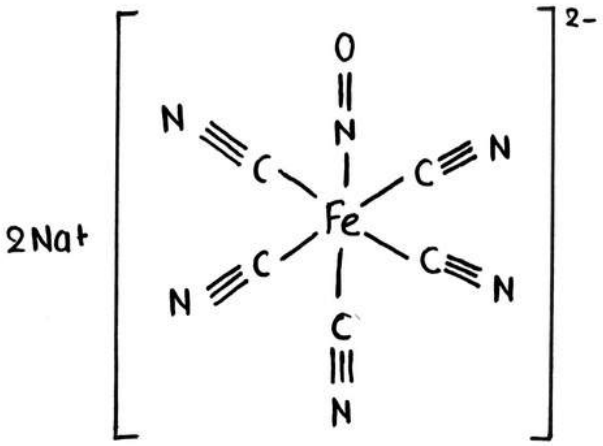
Mechanism Of Action

- Vasodilators cause vasodilation by directly relaxing the vascular smooth muscles that leads to :
  - Reduced peripheral vascular resistance
  - Lowering blood pressure.
- They also act by increasing level of Nitric Oxide which is a potent vasodilator & by opening potassium channels leading to hyperpolarization & relaxation of smooth muscles.

DRUGS

- Sodium Nitroprusside
- Diazoxide
- Minoxidil
- Hydralazine Hydrochloride

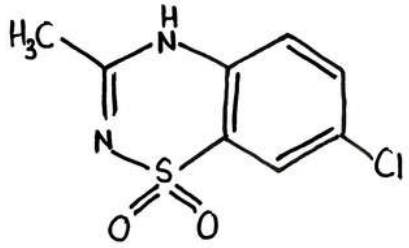
① Sodium Nitroprusside



Uses

- Hypertension
- Acute Heart failure

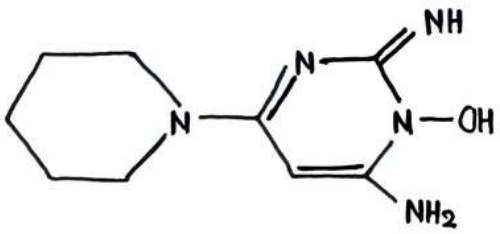
② Diazoxide



Uses

- Hypertension
- Hypoglycemia

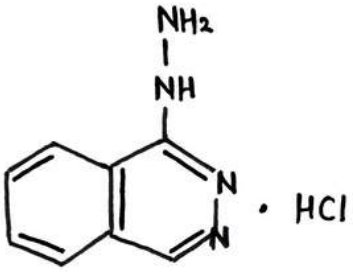
③ Minoxidil



Uses

- Severe Hypertension
- Hair Growth

④ Hydralazine Hydrochloride



Uses

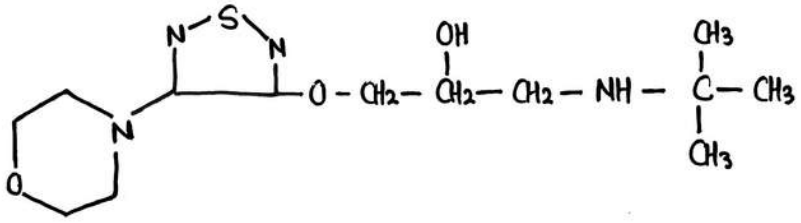
- Hypertension
- Heart failure

④ B- BLOCKERS

- Beta Blockers are a class of medications reduce the effects of adrenaline (epinephrine) on the body.
- They work primarily by blocking beta receptors in heart & blood vessels, which slows down heart rate, reduces force of contraction & lowers blood pressure.

TIMOLOL

It is a non-selective Beta blockers, blocks both β_1 & β_2 receptors



MOA

Timolol binds with β_1 & β_2 receptors & inhibits their action lowering blood pressure

Uses

- Glaucoma
- Hypertension
- Myocardial Infarction

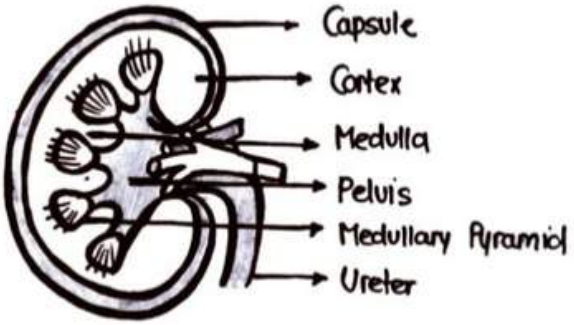
KIDNEY

- They are present in a pair in our body.
- kidneys are two bean shaped organ located on each side of vertebral column. (T-12 - L3).
- It is Reddish- brown in colour.
- It is about 10-12 cm long & 5-7 cm wide
- Its weight is about 120- 170 gram.

Layers of kidney

kidney mainly contains 3 layers :

① Outer Cortex
② Inner Medulla
③ Renal Pelvis



NEPHRONS

- Nephrons are the major functional unit of kidney.
- Nephron is mainly consist of two parts :

① Renal Corpuscle
② Renal Tubule

RENAL ~~CAPSULE~~ CORPUSCLE

- It is present in the cortex of kidney.
- The major function of renal corpuscle is filteration of blood.
- It can be further subdivided into two portions

① Glomerulus : Bunch of capillaries.
② Bowman's Capsule : Upper end of renal tubule.

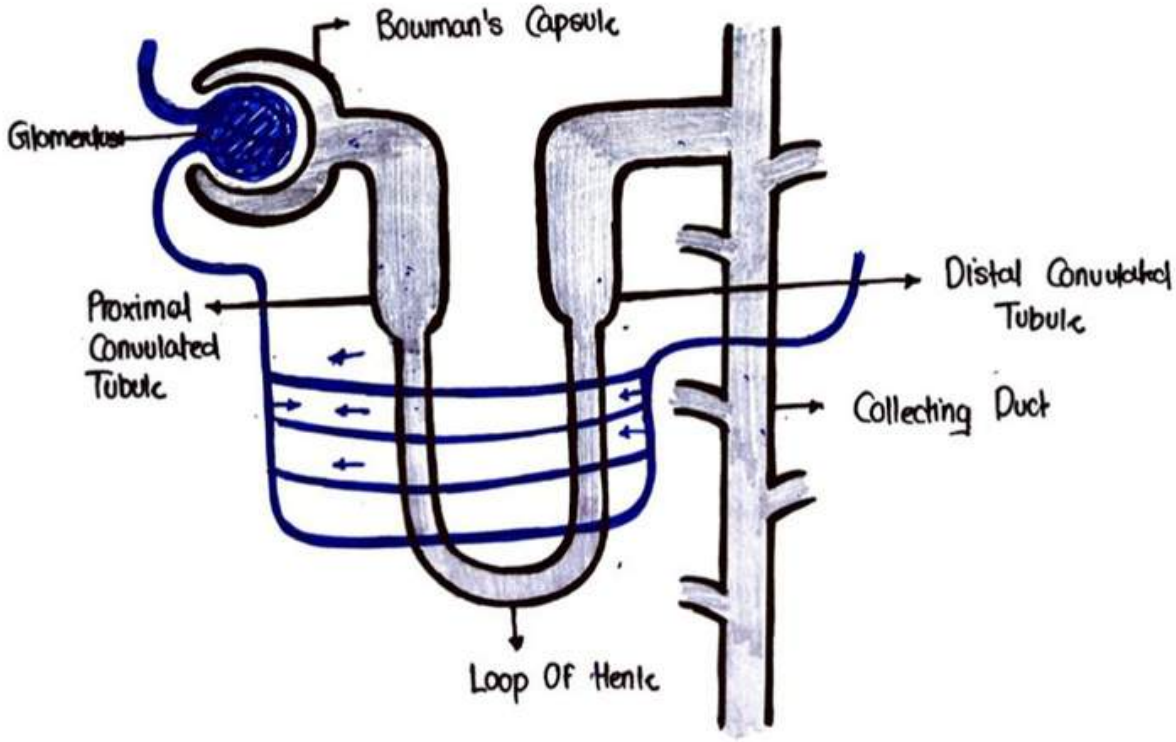
RENAL TUBULE

- It is a tube like structure and the continuation of Bowman's capsule.
- Proximal & Renal tubule mainly consist of 3 parts :

① Proximal Convoluted Tubule : Present in Cortex
② Loop of Henle : Present in Medulla
③ Distal Convoluted Tubule : Present in Cortex

- Loop of Henle can be further subdivided into 2 parts :

(i) Descending Limb
(ii) Ascending Limb



NEPHRON

Types Of Nephrons

Nephrons are of basically two types :

① Cortical Nephrons : 85%, short Loop of Henle

② Juxta - Medullary Nephrons : 15%, Long Loop of Henle.

PHYSIOLOGY OF URINE FORMATION

- Urine formation is a Blood Cleansing function.
- Normally about 1300 ml of blood enters into the kidney.
- kidney excreted the unwanted substances from the blood as Urine.
- Normal Urine output is 1 - 1.5 Litre / day.

Formation Of Urine

It mainly involves 3 steps :

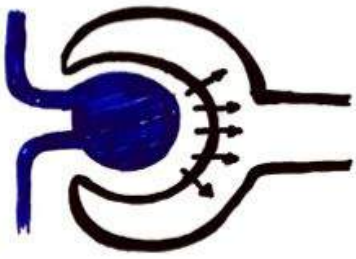
① Glomerular Filteration

② Tubular Reabsorbtion

③ Tubular Secretion

① GLOMERULAR FILTERATION

- It is a process by which blood is filtered while passing through glomerular capillaries by filteration membrane.
- It is first step of Urine formation.
- When blood passes through glomerular capillaries the plasma is filtered in bowman's capsule.



- All the substance of plasma filtered in glomerular filtrate except plasma protein & filtered fluid is known as Glomerular filterate.

Glomerular filteration Rate

- Glomerular filteration rate (GFR) is defined as total quantity of filterate formed in all the nephrons of both the kidney in the given unit of time.
- Normal GFR is 125 ml / minute or 180 L / day

Factors Affecting GFR

- Renal blood flow
- Glomerular capillary Pressure
- Colloidal Osmotic Pressure
- Hydrostatic pressure in bowman's capsule.

② TUBULAR REABSORBTION

- As we clearly saw that about 180 L filterate formed per day but only 1.5 litre urine is excreted out from our body that means about 99% part of filterate again reabsorbed in blood.
- It is the process by which water & other necessary substances are reabsorbed from Renal Tubule to Blood.
- The reabsorbed substances moves into the interstitial fluid of renal medulla & after that they moved into ~~cap~~ tubular capillaries.
- Tubular reabsorbtion is a selective reabsorbtion as the tubular cells reabsorbs only those substances that are necessary for our body.
- Essential substances get reabsorbed while unwanted substances excreted out from body.

Site of Reabsorbtion

PROXIMAL CONVULATED TUBULE	LOOP OF HENLE	DISTAL CO. TUBULE
Glucose, Amino Acids Sodium, Potassium Calcium, Bicarbonates Chlorides, Phosphates Urea, Uric Acid Water	Sodium Chloride	Sodium Calcium Bicarbonate Water

③ TUBULAR SECRETION

- It is process in which substance are transported from blood to renal tubules.
- The unwanted substances that are not get filtered from blood to Bowman's Capsule in first step are directly transported to renal tubules later in this process.

Substance secreted in different segment of renal ~~capsu~~ tubule

- Proximal Convulated Tubule : Potassium, Ammonia, H^+ ions.
- Loop of Henle : Urea
- Distal Convulated Tubule : Potassium, H^+ ions
- Collecting Ducts : Potassium

DIURETICS

- Diuretics are the medications that increases the rate of urine flow and sodium excretion
- They are commonly used to treat conditions like high blood pressure heart failure, kidney problems and edema (swelling caused by fluid retention)
- By promoting the removal of fluid, diuretics helps to reduce the volume of blood, which can lower blood pressure & workload on heart.

CLASSIFICATION OF DIURETICS

Diuretics can be classified as follows :

① Carbonic Anhydrase Inhibitors

- Acetazolamide *
- Methazolamide
- Dichlorophenamide

② Thiazides

- Chlorothiazide *
- Hydrochlorothiazide
- Hydroflumethiazide
- Cyclothiazide

③ Loop Diuretics

- Furosemide *
- Bumetanide
- Ethacrynic Acid

④ Potassium Sparing Diuretics

- Spironolactone
- Triamterene
- Amiloride

⑤ Osmotic Diuretics

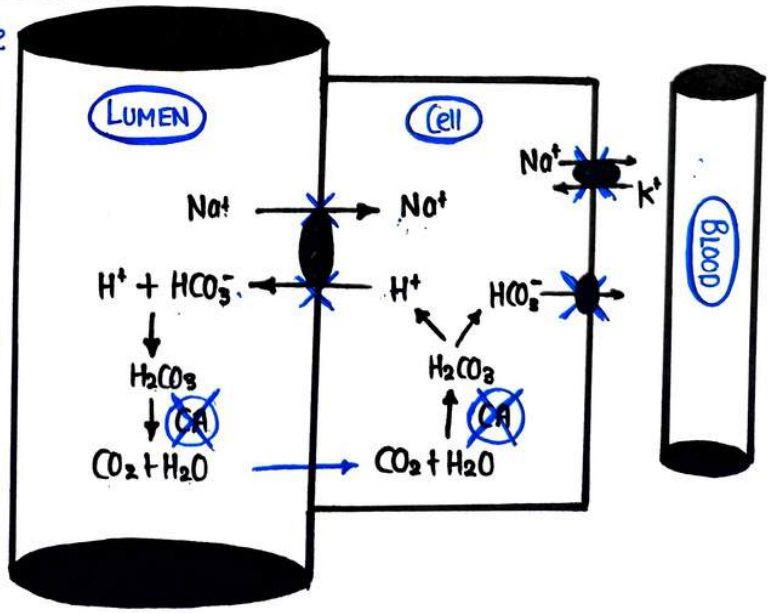
- Mannitol

① CARBONIC ANHYDRASE INHIBITORS

- Carbonic Anhydrase Inhibitors are class of diurehics that reduce the reabsorption of bicarbonate in kidneys by inhibiting the enzyme 'carbonic anhydrase'.
- These drugs give their effect on Proximal Convulated Tubule

Mechanism Of Action

Carbonic anhydrase inhibitors inhibits the carbonic anhydrase enzyme & decreases bicarbonate & sodium reabsorption thus increased excretion which leads to increased urine output



Pharmacokinetics

- Absorption : CAIs, like acetazolamide, are well absorbed orally
- Distribution : They are widely distributed in tissues, they ~~co~~ cross the blood brain barrier, making them effective for treating neurological conditions like certain types of seizures.
- Metabolism : These drugs are not extensively metabolized
- Excretion : They are mainly excreted by kidneys.

Therapeutic Uses

- Glaucoma
- Edema
- Epilepsy
- Metabolic Alkalosis

Adverse Effect

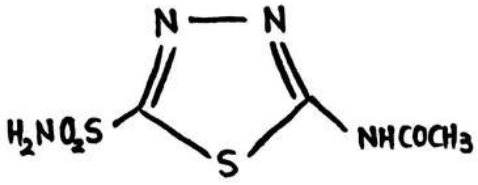
- Metabolic Acidosis
- Hypokalemia
- kidney Stones
- Allergic Reactions

SAR OF CARBONIC ANHYDRASE INHIBITORS

For understanding SAR, CAIs can be classified into two types:

① Heterocyclic Sulphonamides
② Meta- Disulphamoyl Benzene Derivatives

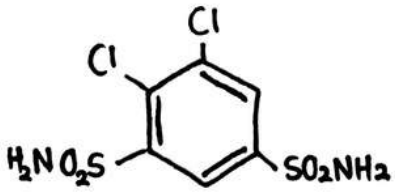
① Heterocyclic Sulphonamides



Acetazolamide

- The sulfamoyl group is essential for activity
- The sulfamoyl nitrogen atom must be unsubstituted.
- Substitution of methyl group on one of the ring nitrogen retains CA inhibitor activity, e.g. methazolamide.
- The moeity to which sulfamoyl group is attached must possess aromatic character.

② Meta- Disulphamoyl Benzene Derivative

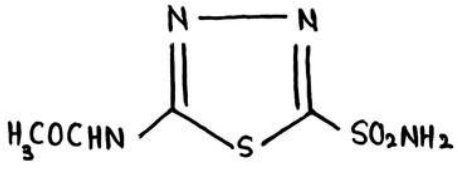


Dichlorphenamide

- Maximum diuretic activity is observed when position 4 is substituted with Cl, Br, NO_2 etc.
- An unsubstituted sulfonamoyl moeity at position 3 is essential for activity.
- Replacement of sufonamoyl moeity at position 1 with electrophilic group results in decrease CA inhibitor activity.

① ACETAZOLAMIDE

Acetazolamide is a carbonic anhydrase inhibitors primarily used to treat conditions such as glaucoma, altitude sickness and certain types of epilepsy



Mechanism Of Action

- Acetazolamide is a non-competitive inhibitor of Carbonic Anhydrase.
- It inhibits CA enzyme and prevents reabsorption of bicarbonate & sodium ions thus increases urine output.

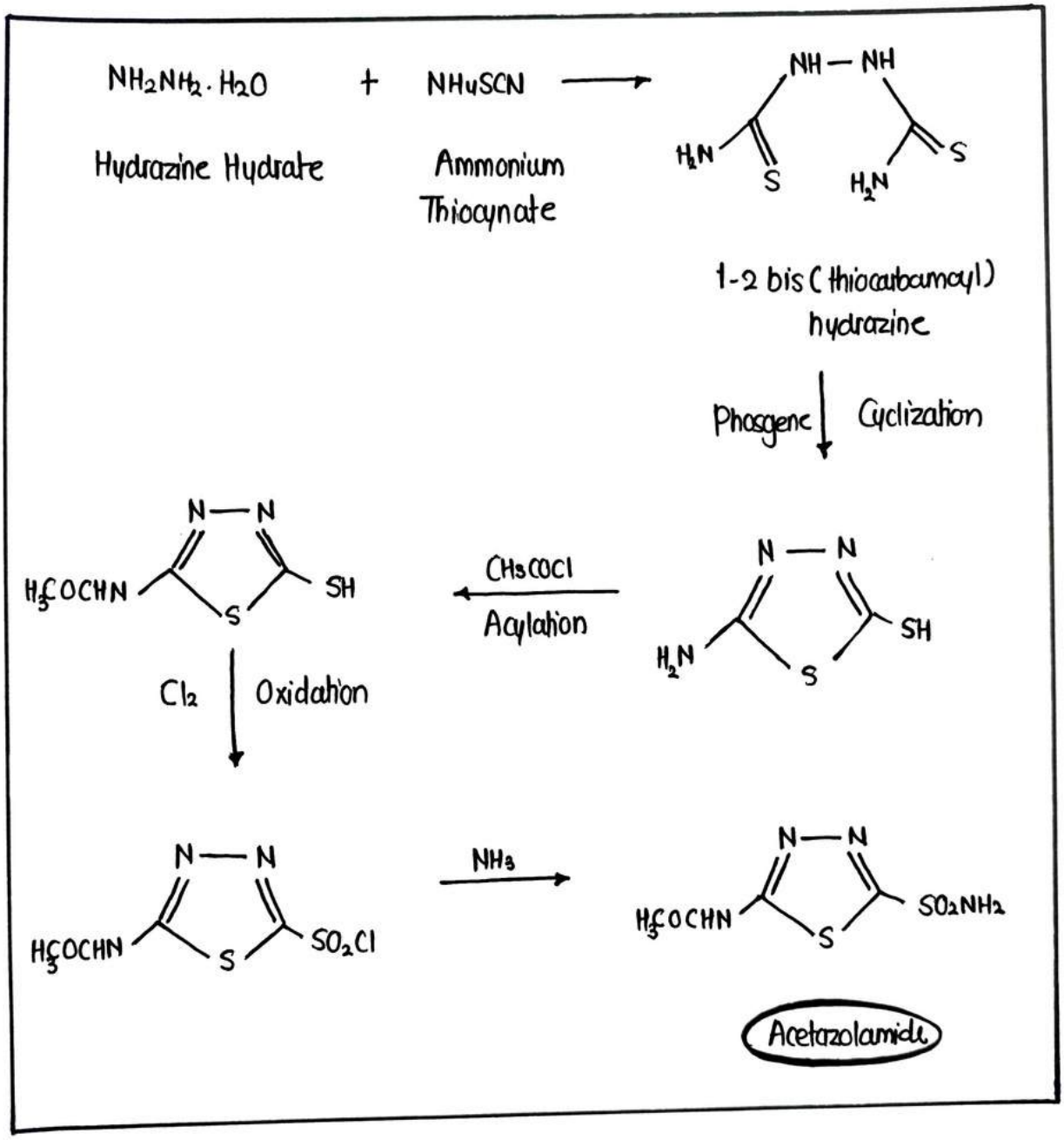
Properties

- It appears as white to yellowish crystalline powder.
- It doesn't have any odour or taste.
- It rapidly absorbed after oral administration.

Uses

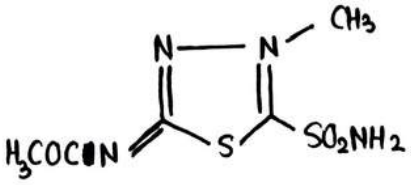
- Glaucoma
- Epilepsy
- Altitude Sickness
- Edema

Synthesis



② Methazolamide

- It belongs to group of carbonic anhydrase inhibitors

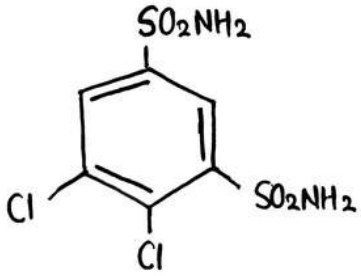


Uses

- Glaucoma
- Epilepsy
- Edema

③ Dichlorphenamide

It is a carbonic anhydrase inhibitors & commonly used as an antiglaucoma agent



Uses

- Glaucoma
- Occassional Paralysis

② THIAZIDES

- They are also known as benzothiazides, they are sulfonamide derivatives.
- These are class of drug that treat high blood pressure, edema and other conditions.

Mechanism Of Action

- Thiazides act mainly in the distal convulated tubule of nephron.
- They inhibit the sodium- chloride symporter, reducing the reabsorption of sodium and chloride.
- This leads to increased excretion of sodium, chloride and water, resulting in decreased blood volume & reduced blood pressure.

Pharmacokinetics

- Absorption : Thiazides are well absorbed orally, with peak plasma concentration occuring within 1-2 hours.
- Half Life : They typically have a half life of 6-15 hours
- Metabolism : They are minimally metabolized & primarily excreted unchanged in urine.

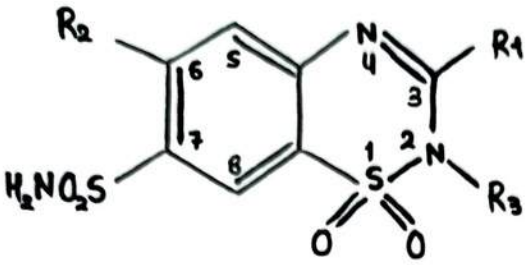
Uses

- Hypertension
- Edema
- kidney Stones

Side Effects

- Electrolyte Imbalance
- Metabolic Disorders
- Dizziness
- Headache

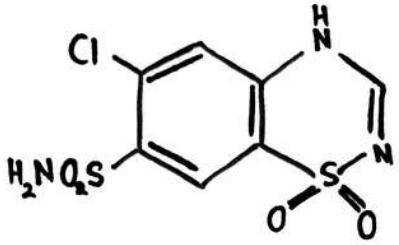
SAR OF THIAZIDE DIURETICS



- Sulphonyl group at position 1 is essential for activity
- Hydrogen atom at 2nd position give more potent effect
- 2nd position can tolerate the presence of small alkyl groups such as CH_3
- Substituents with hydrophobic character in 3rd position increases activity 1000 times.
- Saturation of double bond b/w 3rd & 4th position increases diuretic activity.
- Substitution of 6th position with electron withdrawing group is essential for diuretic activity i.e., Cl, Br etc.

① CHLORTHIAZIDE *

Chlorothiazide is a thiazide diuretic often used to treat high blood pressure and fluid retention due to conditions like heart failure, liver disease & kidney disorders etc.



Mechanism Of Action

It inhibits sodium & chloride reabsorption in distal convulated tubules of the kidney result in increase excretion of sodium, chloride & water.

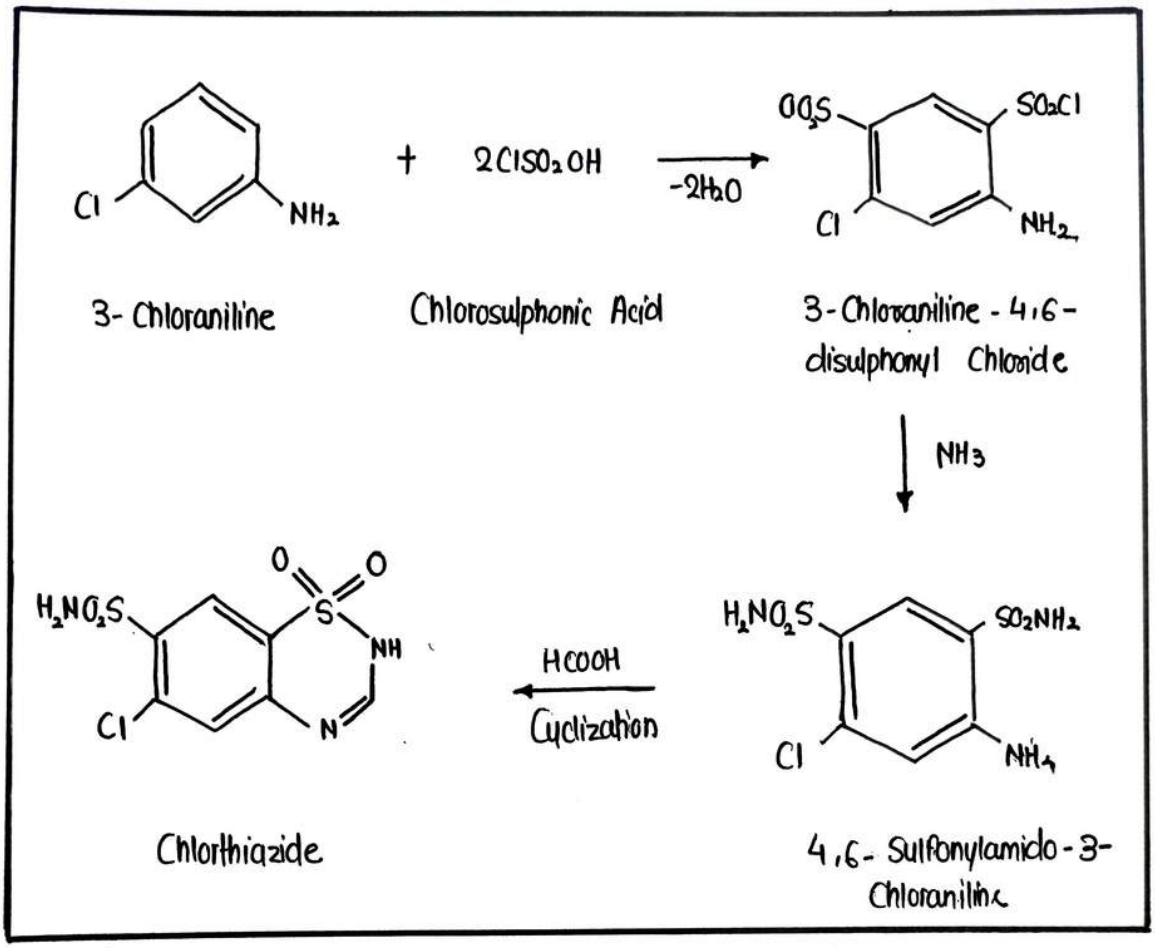
Properties

- It is a white crystalline powder
- It is slightly soluble in water & alcohol and sparingly soluble in Acetone

Uses

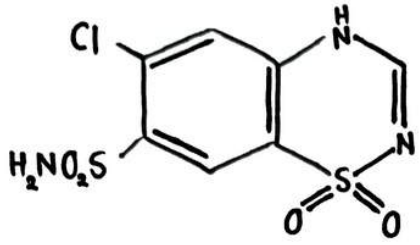
- Hypertension
- Edema
- Heart failure

Synthesis



② HYDROCHLORTHIAZIDE

Hydrochlorothiazide is a thiazide diuretic commonly used to treat high blood pressure & fluid retention



Uses

- Hypertension
- Edema
- Heart failure

③ HYDROFLUMETHIAZIDE

It is a thiazide diuretic used to treat Hypertension, edema etc.

Uses

- Hypertension
- Edema
- Heart failure

⑭ CYCLOTHIAZIDE

It is a thiazide diuretic used to treat high BP & Edema.

Uses

- Hypertension
- Edema

③ LOOP DIURETICS

Loop Diuretics are class of diuretics that act on the loop of henle in the kidney to increase urine output, effectively reducing blood pressure and fluid retention.

Mechanism Of Action

- Loop Diuretics inhibit the sodium-potassium-chloride cotransporter in the thick ascending limb of loop of henle
- Inhibition of sodium-potassium-chloride transporter leads to decreased reabsorption & increased excretion, water follows excreted sodium that ultimately increases urine output

PHARMACOKINETICS

- Absorption : Most loop diuretic absorbed from GIT.
- Distribution : They are widely distributed in body.
- Metabolism : They are metabolized in liver by cytochrome P450 enzyme
- Excretion : Loop diuretics primarily excreted through kidney

Uses

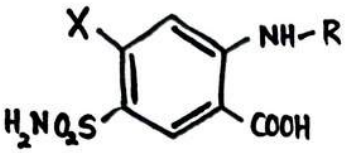
- Edema
- Hypertension
- Hypercalcemia

Side Effects

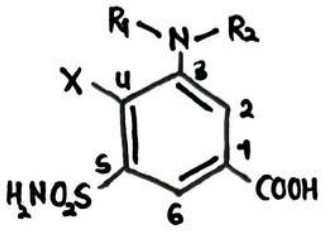
- Dehydration
- Hypotension
- Renal Impairment

SAR OF LOOP DIURETICS

- There are either 5- sulphamoyl - 2 amino benzoic acid or 5- sulphamoyl - 3 amino benzoic acid derivatives.



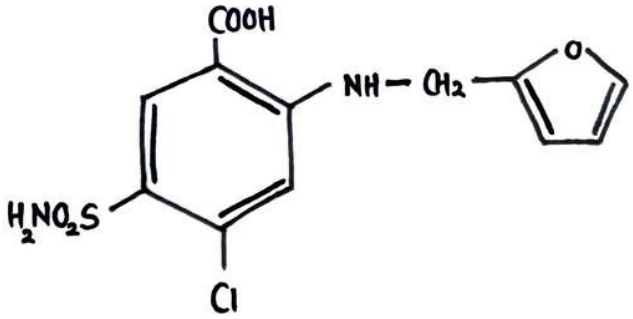
5- Sulphamoyl - 2- amino benzoic acid



5- Sulphamoyl- 3- amino benzoic acid

- The carbonyl group at C1 provides optimal diuretic activity.
- The substitution of activating group (X) in position 4 by Cl, alkoxy, aniline, benzyl or benzoyl group increases diuretic activity.
- The presence of sulphamoyl group in 5th position is essential for activity.
- The presence of furfuryl, phenyl and thienyl methyl group at 2nd amino group of 5- sulphomoyl - 2 amino benzoic acid gives maximum diuretic activity.

① FUROSEMIDE *



Mechanism Of Action

- Furosemide works by inhibiting the sodium - potassium & chloride transporter in thick ascending loop of henle, leading to increased excretion of sodium, potassium, chloride & water.
- This reduces fluid accumulation in tissues and blood vessels.

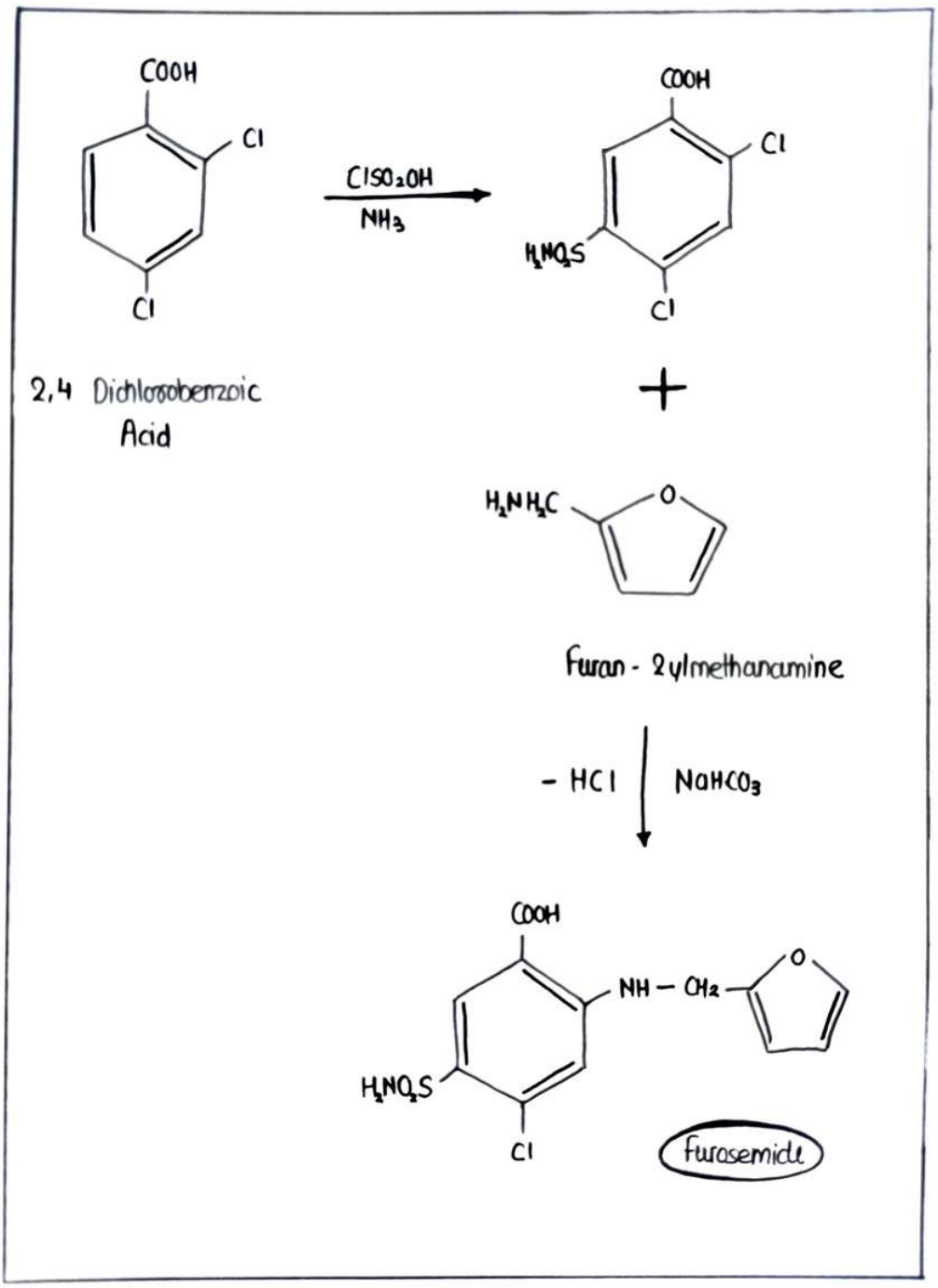
Properties

- It is a white crystalline powder.
- It is insoluble in water & soluble in acetone.

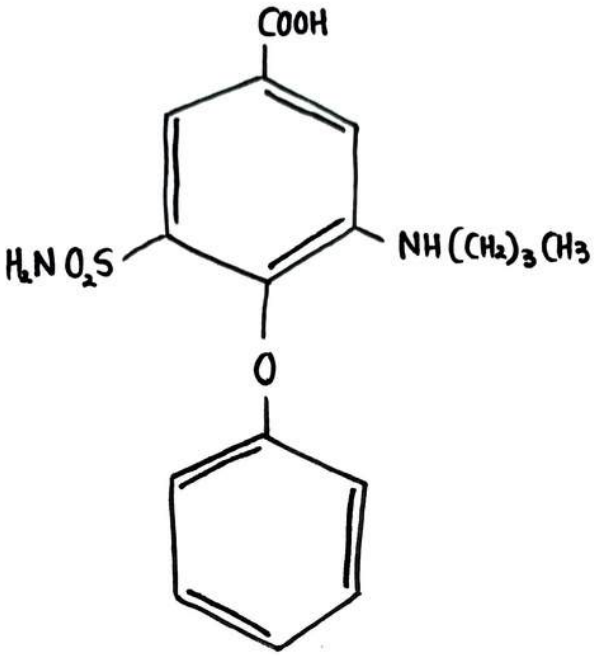
Uses

- Edema
- Congestive Heart failure
- Hypertension
- Nephrotic Syndrome

Synthesis



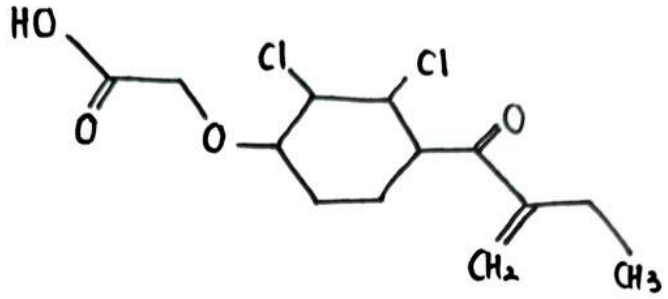
② BUMETANIDE



Uses

- Congestive Heart Failure
- Edema
- Liver Cirrhosis
- Renal Disease
- Hypertension

③ Ethacrynic Acid



Uses

- Edema
- Congestive Heart failure
- Liver Cirrhosis
- Renal Disease

④ Potassium Sparing Diuretics

Potassium sparing diuretics are class of diuretics that promotes excretion of sodium & water while decreasing excretion of potassium.

Mechanism Of Action

Mechanism of action of potassium sparing diuretics can be classified into two categories :

① Nat Channel Inhibitors : Triamterene & Amiloride
② Aldosterone Antagonist : Spironolactone

Pharmacokinetics

- Absorption : They are well absorbed orally
- Distribution : They are widely distributed throughout the body
- Metabolism : It is extensively metabolized (mainly spironolactone)
- Excretion : The drugs are excreted via urine.

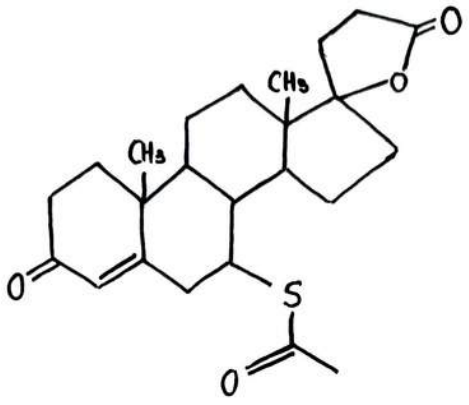
Uses

- Hypokalemia
- Hypertension
- Heart Failure

Adverse Effect

- Hyperkalemia
- Gastrointestinal Disturbances

① SPIRONOLACTONE



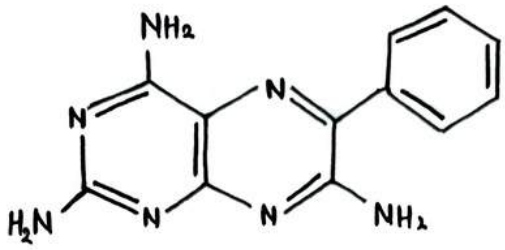
Mechanism of Action

It is an aldosterone antagonist that blocks sodium reabsorption and potassium excretion in distal convuluted tubule.

Uses

- Hypertension
- Heart failure
- Edema
- Liver Cirrhosis

② TRIAMTERENE



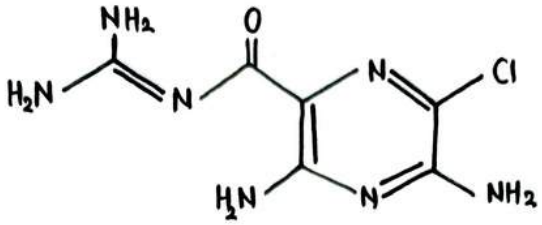
Mechanism Of Action

Inhibits epithelial sodium channels in the distal tubules, reducing sodium reabsorption and potassium excretion.

Uses

- Hypertension
- Edema
- Hypokalemia

③ AMILORIDE



Mechanism Of Action

It inhibits epithelial sodium channels in distal tubules and collecting duct, reducing sodium reabsorption & potassium excretion.

Uses

- Hypertension
- Heart failure
- Edema
- Hypokalemia

⑤ Osmotic Diuretics

- Osmotic Diuretics are class of medications that promote diuresis by increasing osmolarity of blood & renal filtrate.
- The major drug used as osmotic diuretic is mannitol.

Mannitol

Mannitol is a potent osmotic diuretic commonly used in clinical settings.

Mechanism of Action

- Mannitol increases osmolarity in renal tubules, preventing reabsorption of water in kidneys.
- It draws water from cells into the bloodstream, reducing cellular edema and increasing urine output.

Pharmacokinetics

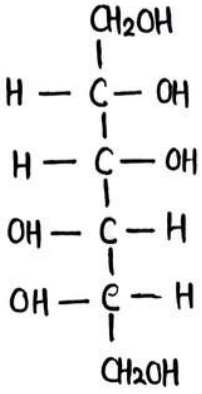
- Administration : Typically given intravenously due to poor oral absorption.
- Distribution : It rapidly distributes in extracellular space.
- Metabolism & excretion : It is not metabolized & is excreted unchanged urine.

Uses

- Cerebral Edema
- Acute kidney Injury

Side Effect

- Electrolyte Imbalance
- Dehydration



Mannitol

Properties

- It is white crystalline powder
- It is soluble in water & slightly soluble in ethanol

THANK YOU

FOR CHOOSING IMPERFECT PHARMACY AS YOUR STUDY PARTNER

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