DIURETICS

Presented By:

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OUTLINE

- **Introduction and Definition**
- **Relevant Physiology of Urine Formation**
- **Classification: different ways**
- **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

Introduction and Definition

- Diuretics (natriuretics) are drugs which cause a net loss of Na^+ and water in urine and hence increase the urine output (or) urine volume.
- The primary action of most diuretics is the direct inhibition of Na^+ reabsorption (increased excretion) at one or more of the four major sites along the nephron.
- An increased Na^+ excretion is accompanied by anion like Cl^- Since NaCl is the major determinant of extracellular fluid volume; Diuretics reduce extracellular fluid volume (decrease in oedema) by decreasing total body NaCl content.

Introduction and Definition

- Diuretics are very effective in the treatment of conditions like:
  - chronic heart failure
  - nephrotic syndrome
  - chronic hepatic diseases
  - hypertension
  - Pregnancy associated oedema
  - Cirrhosis of the liver.

Relevant Physiology of Urine Formation

- Kidneys are the organs responsible for urine formation. Two important functions of the kidney are:
  - To maintain a homeostatis balance of electrolytes and water.
  - To excrete water soluble end products of metabolites.
- Each kidney contains approximately one million nephrons and is capable of forming urine independently.
- Urine formation starts from glomerular filtration (g.f.) in a prodigal way.
- Normally, about 180 L of fluid is filtered everyday: all soluble constituents of blood minus the plasma proteins (along with substances bound to them) and lipids, are filtered at the glomerulus.

Relevant Physiology of Urine Formation

- More than 99% of the glomerular filtrate is reabsorbed in the tubules; about 1.5 L urine is produced in 24 hours.
  - Ions such as sodium, chloride, calcium are reabsorbed.
  - Total amount of glucose, amino acids, vitamins, proteins are reabsorbed. (If the urine contains these ions, it represents the disorders. For example proteins such as albumin in higher amounts causes albuminuria.)
- The diuretics act primarily by inhibiting tubular reabsorption: just 1% decrease in tubular reabsorption would more than double urine output.

Relevant Physiology of Urine Formation

There are **four major sites** along the nephron that are responsible for reabsorption:

- ❑Site 1: Proximal Convoluted Tubule (PCT)
- ❑Site 2: Ascending Loop of Henle (AscLH)
- ❑Site 3: Cortical diluting segment of loop of Henle
- ❑Site 4: Distal Tubule (DT) and Collecting Duct (CD)

Relevant Physiology of Urine Formation

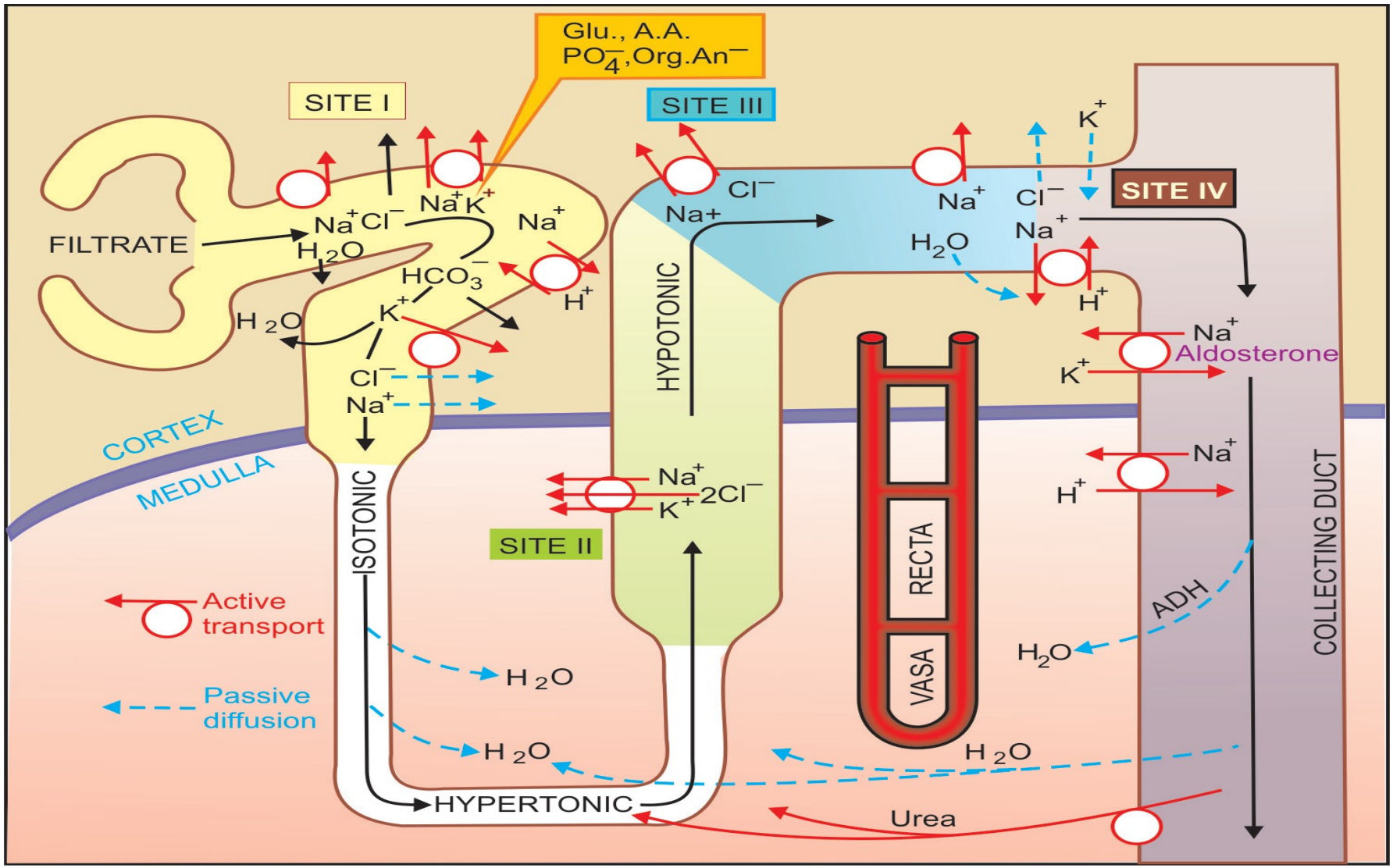


Fig. 1: Diagrammatic representation of nephron showing the four sites of solute reabsorption.

The thick ascending limb of loop of Henle is impermeable to water; Glu.—Glucose; A.A.—Amino acid;Org. An.—Organic anions.

Relevant Physiology of Urine Formation

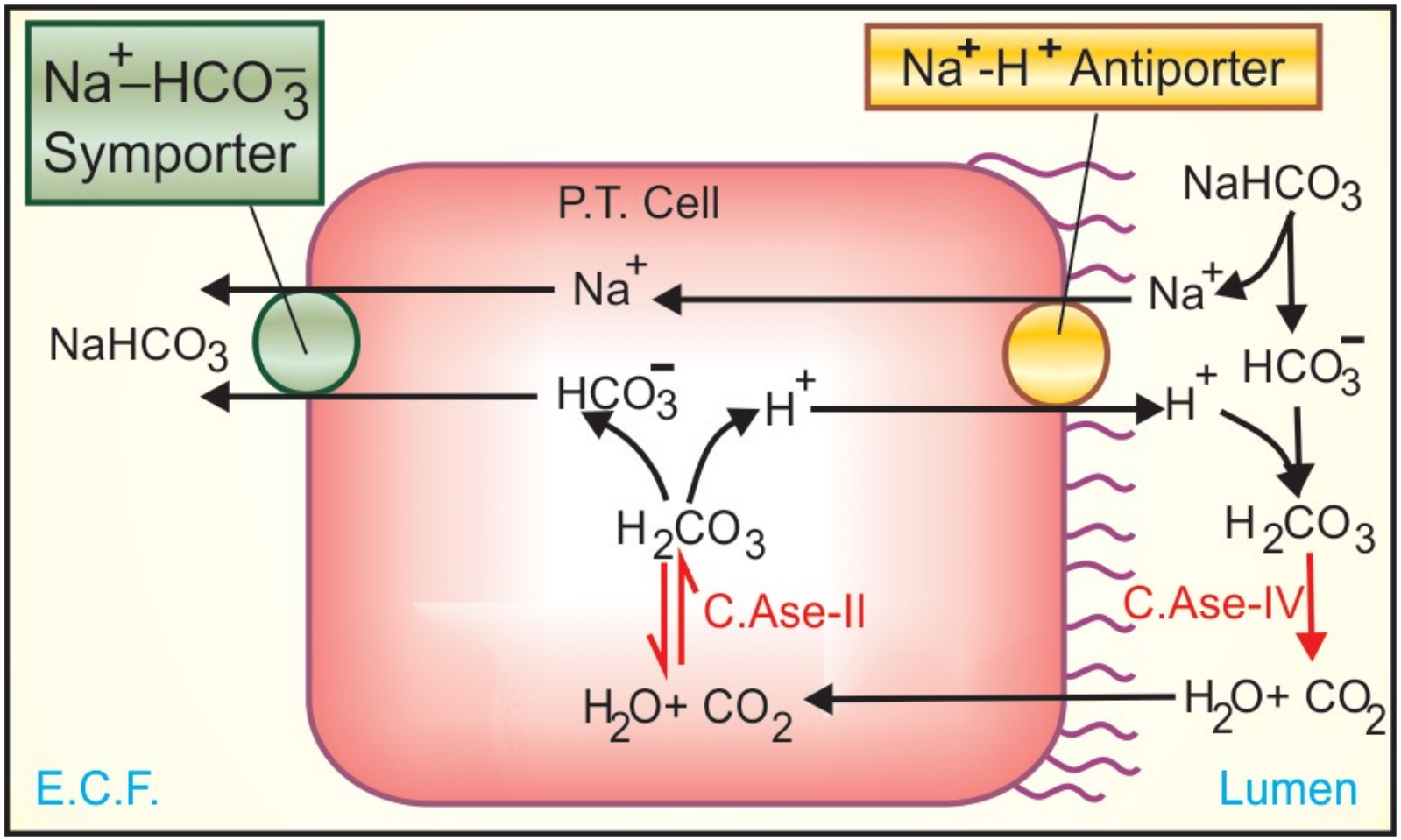
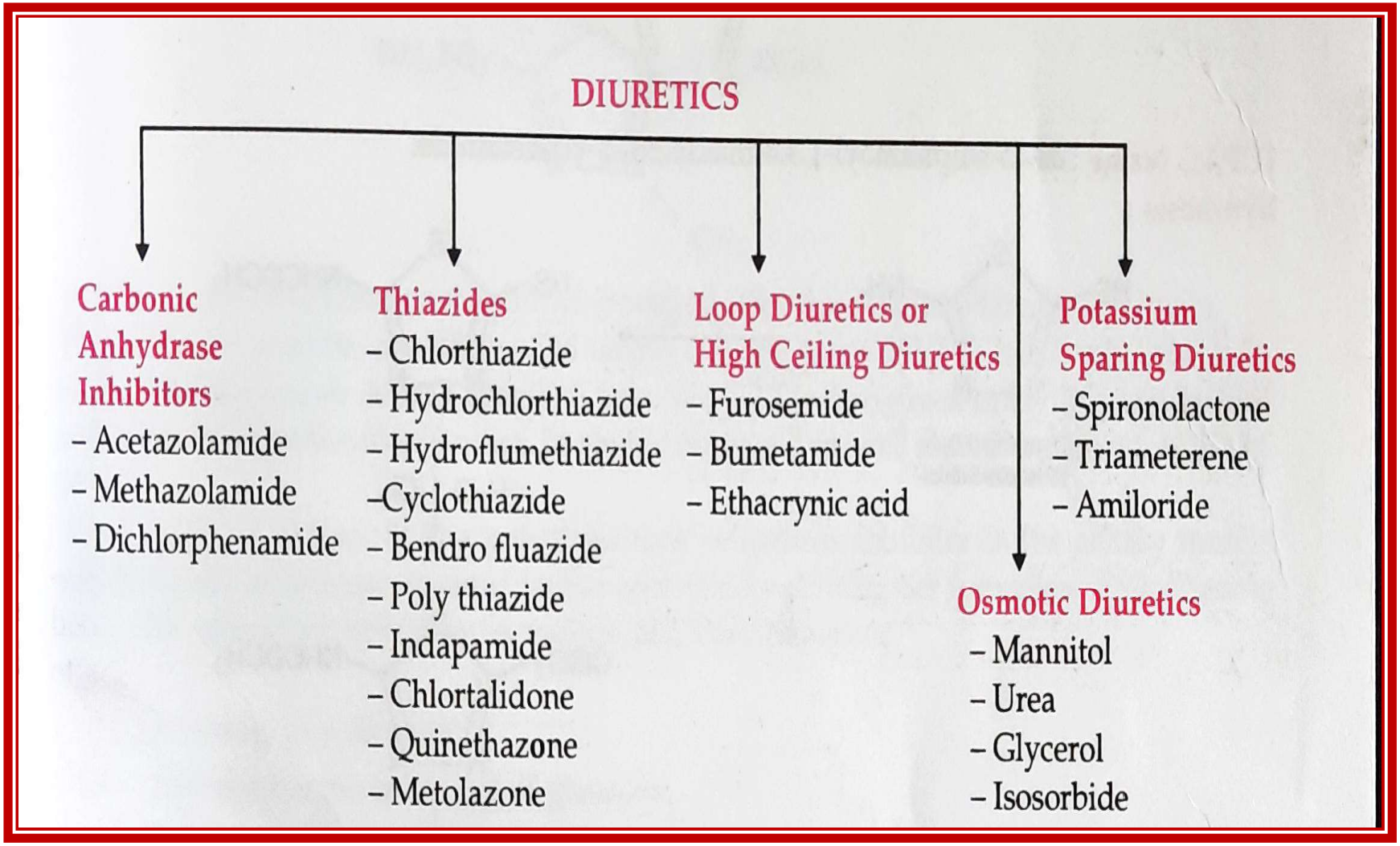


Fig. 2: The carbonic anhydrase (CAse) mediated bicarbonate absorption in proximal tubule (P.T.)

Classification



Classification according to efficacy

1. *High efficacy diuretics (Inhibitors of Na^+- K^+-$2Cl^-$ cotransport)*

Sulphamoyl derivatives: Furosemide, Bumetanide, Torasemide

2. *Medium efficacy diuretics (Inhibitors of Na^+-Cl^- symport)*

(a) *Benzothiadiazines (thiazides):* Hydrochlorothiazide, Benzthiazide, Hydroflumethiazide, Bendroflumethiazide

(b) *Thiazide like (related heterocyclics):* Chlorthalidone, Metolazone, Xipamide, Indapamide, Clopamide

3. *Weak or adjunctive diuretics*

(a) *Carbonic anhydrase inhibitors:* Acetazolamide

(b) *Potassium sparing diuretics*

(i) Aldosterone antagonist: Spironolactone, Eplerenone

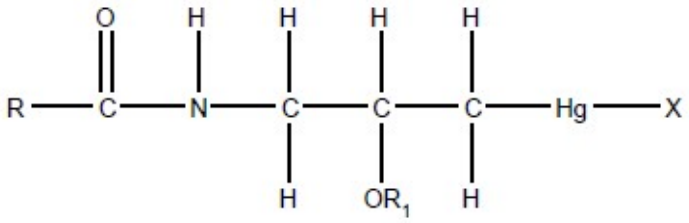
(ii) Inhibitors of renal epithelial Na^+ channel: Triamterene, Amiloride.

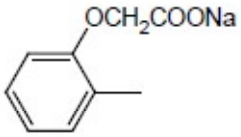
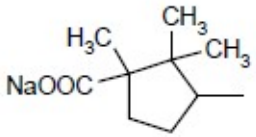
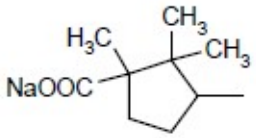
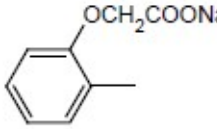
(c) *Osmotic diuretics:* Mannitol, Isosorbide, Glycerol

Chemical Classification

- Chemically, Diuretics can be classified into two categories:
    1. Mercurials
    2. Non-mercurials

Mercurial Diuretics



Name	R	R_1	X
Mersalyl		$-CH_3$	Theophylline
Mercurophyllin		$-CH_3$	Theophylline
Mercaptomerin		$-CH_3$	$-SCH_2COOH$
Chloromerodrin	$-NH_2$	$-CH_3$	$-Cl$
Merethoxyline		$-CH_2CH_2OCH_3$	$-OH$
Meralluride	$NaOOCCH_2CH_2CONH-$	$-CH_3$	$-OH$

Non-mercurial Diuretics

The non-mercurial diuretics may be classified on the basis of their chemical structure as follows:

a. Thiazide derivatives

b. Hydrothiazides

c. *Carbonic Anhydrase inhibitors*

d. Sulphonamide diuretics

e. Aldosterone inhibitors

f. Pteridine derivatives and related compounds

g. sulphomoyl benzoic acid derivatives

h. Phenoxyacetic acid derivatives

i. Purine or Xanthine derivatives

j. Osmotic diuretics

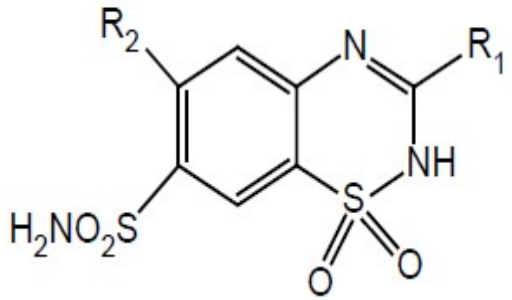
k. Acidic diuretics

l. Uricosuric diuretics

m. Miscellaneous

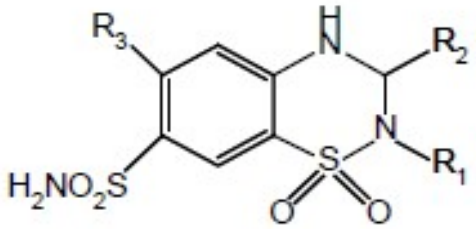
Non-mercurial Diuretics

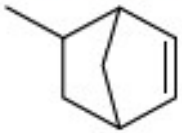
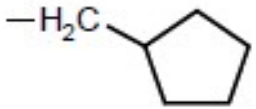
a. Thiazide derivatives



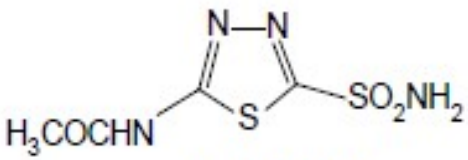
Name	R_1	R_2
Chlorthiazide	–H	–Cl
Benzthiazide	$-CH_2-S-CH_2-C_6H_5$	–Cl
Flumethiazide	–H	$-CF_3$

b. Hydrothiazides

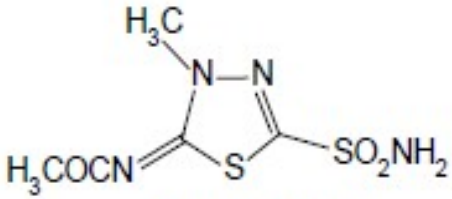


Name	R_1	R_2	R_3
Hydrochlorothiazide	–H	–H	–Cl
Bendroflumethiazide	–H	$-CH_2C_6H_5$	$-CF_3$
Cyclothiazide	–H		–Cl
Hydro flumethiazide	–H	–H	$-CF_3$
Cyclopenthiazide	–H		–Cl
Trichloromethiazide	–H	$-CHCl_2$	–Cl
Buthiazide	–H	$-CH_2CH(CH_3)_2$	–Cl
Methyclothiazide	$-CH_3$	$-CH_2Cl$	–Cl
Polythiazide	$-CH_3$	$-CH_2-S-CH_2-CF_3$	–Cl

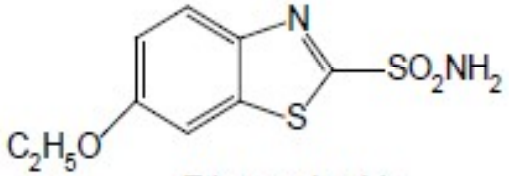
c. *CAse* inhibitors



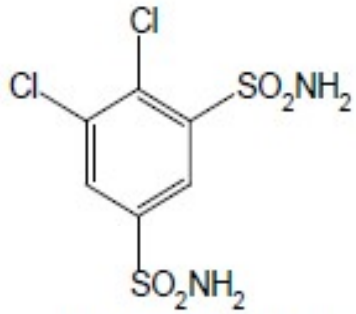
Acetazolamide



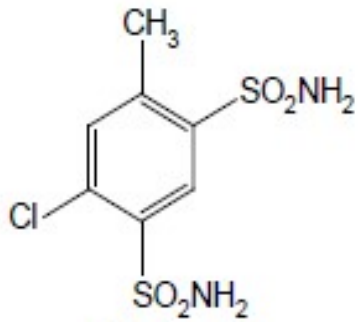
Methazolamide



Ethoxozolamide

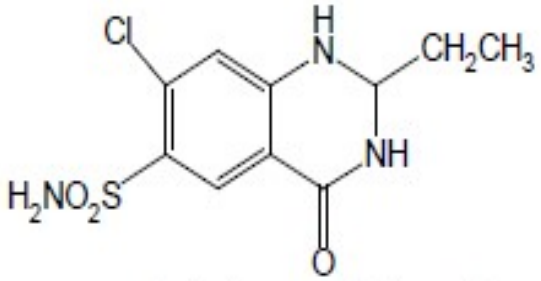


Dichlorophenamide

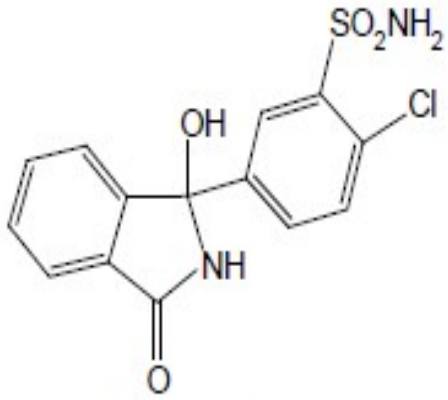


Disulfamide

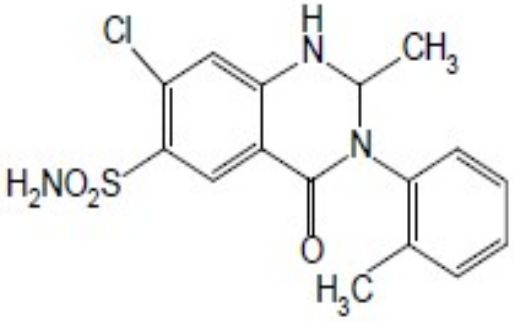
d. Sulphonamide diuretics



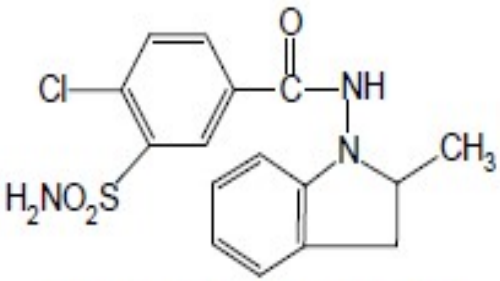
Quinethazone (Quinazolinones)



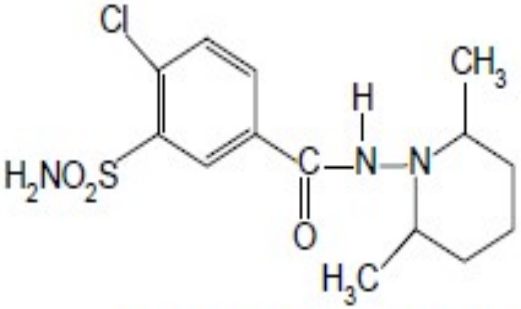
Chlorothalidone



Metolazone

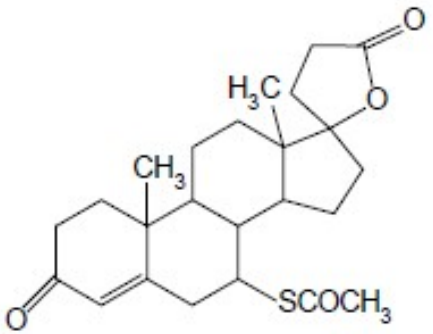


Indapamide (Benzhydrazide)

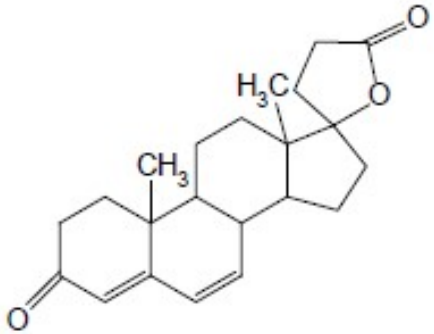


Clopamide (Benzhydrazide)

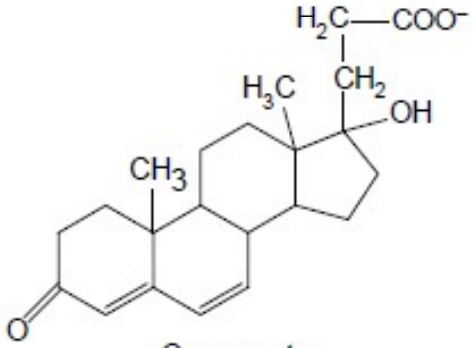
e. Aldosterone inhibitors



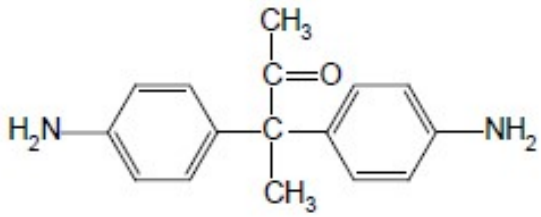
Spironolactone



Canrenone

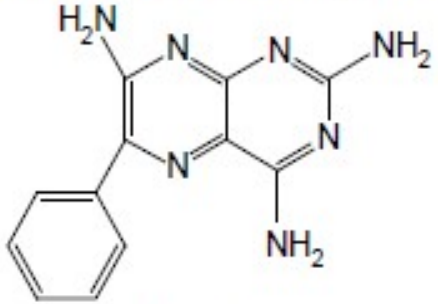


Canrenoate

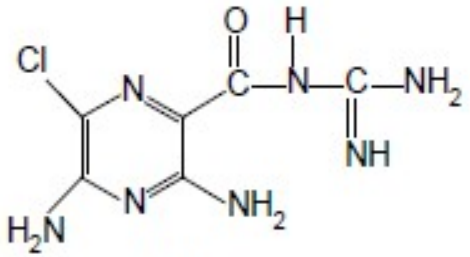


Amphenone B

f. Pteridine derivatives and related compounds

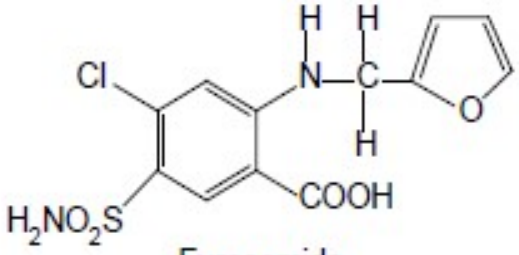


Triamterene

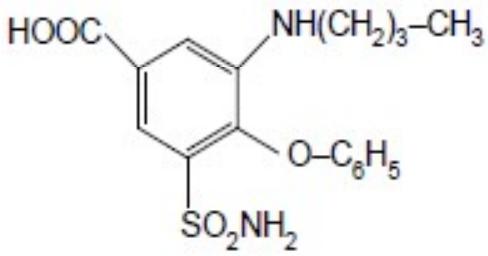


Amiloride

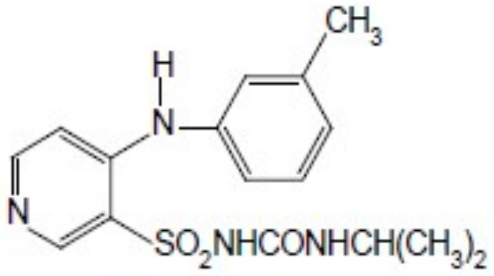
g. sulphomoyl benzoic acid derivatives



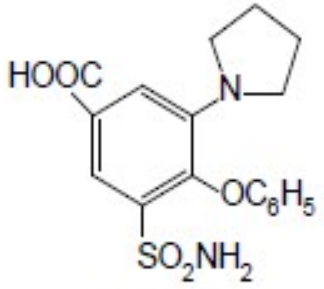
Furosemide



Bumetanide

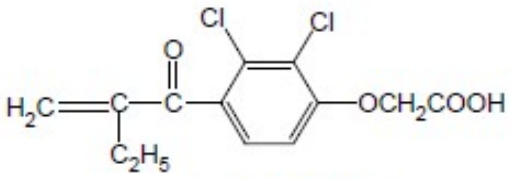


Toresemide

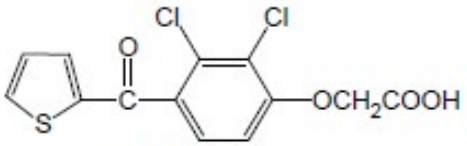


Piretanide

h. Phenoxyacetic acid derivatives

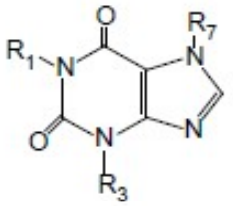


Ethacrynic acid



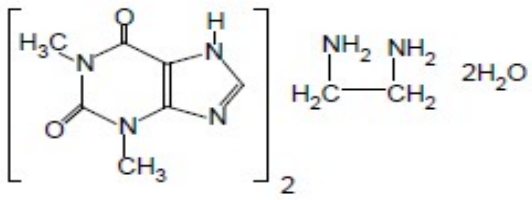
Ticrynafen

i. Purine or Xanthine derivatives



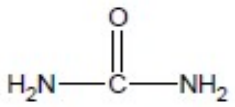
Name	R_1	R_3	R_7
Caffeine	$-CH_3$	$-CH_3$	$-CH_3$
Theophylline	$-CH_3$	$-CH_3$	$-H$
Theobromine	$-H$	$-CH_3$	$-CH_3$

Aminophylline

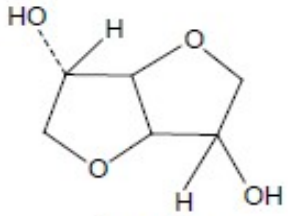


j. Osmotic diuretics

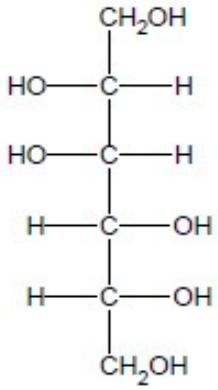
Sodium and potassium salt, urea, sucrose, mannitol, trometamol, sodium acid phosphate, potassium acetate, and glycerine are the osmotic diuretics.



Urea



Isosorbide



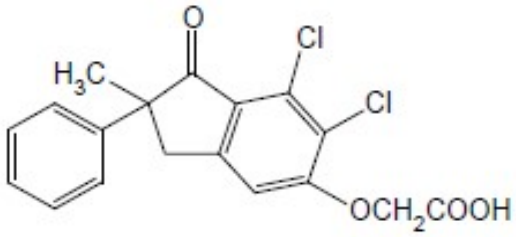
Mannitol

k. Acidic diuretics

Ammonium chloride is a acidic diuretic.

l. Uricosuric diuretics

i. Indacrinone



m. Miscellaneous
Example: Muzolimine

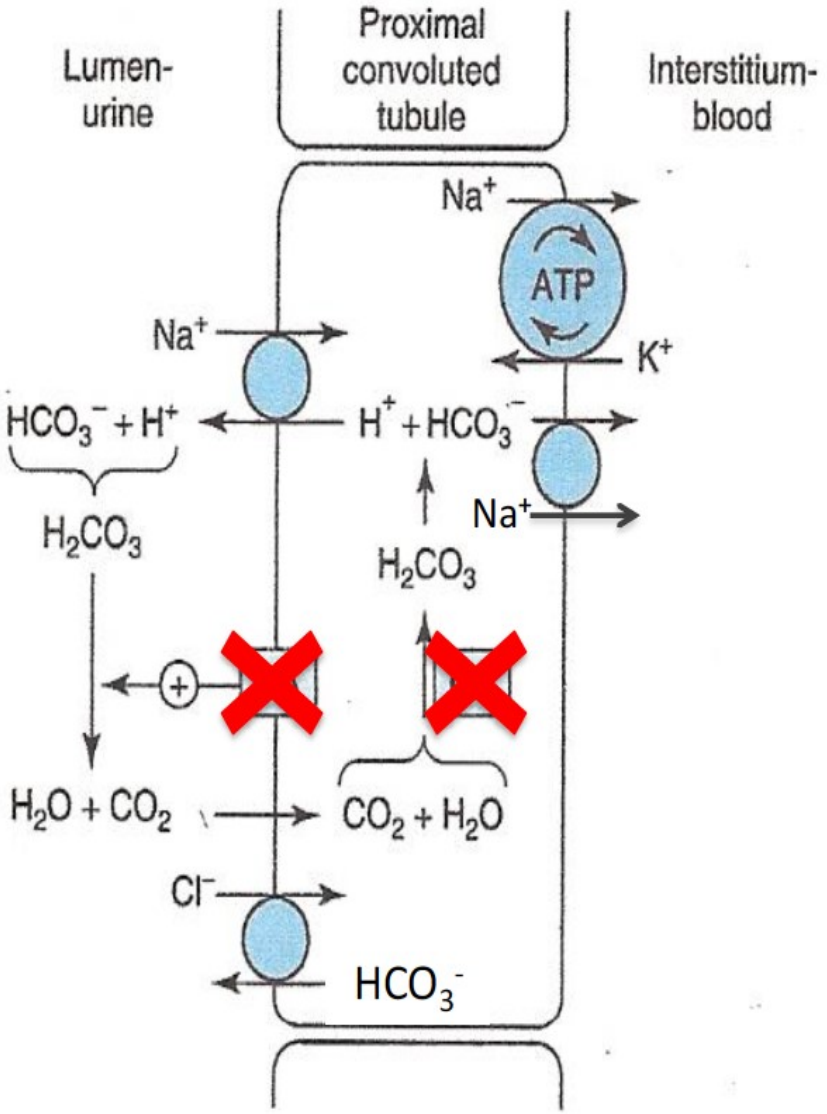
Carbonic Anhydrase inhibitors

Mechanism of Action

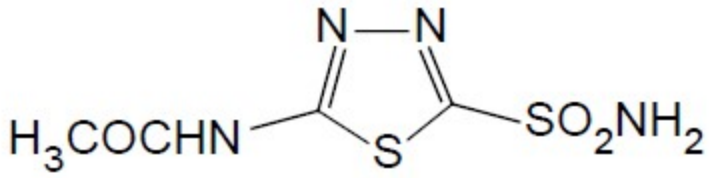
- Developed from **sulfanilamide** (caused metabolic acidosis and alkaline urine), these are weak/adjunctive diuretics.
- Case inhibitors inhibit carbonic anhydrase in renal proximal tubule cells.
- Carbonic anhydrase catalyzes formation of $HCO3^-$ and H^+ from H_2O and CO_2
- inhibition of carbonic anhydrase decreases $[H^+]$ in tubule lumen.
- less H^+ for for Na^+/H^+ exchange
- increased lumen Na+, increased H_2O retention, increased urine volume

Carbonic Anhydrase inhibitors

- Loop of Henle and other distal sites reabsorb the Na^+, therefore CAIs are not very effective diuretics
- Loss of HCO_3^- in urine can result in reduced plasma acid buffering capacity and lead to metabolic acidosis
- Increased distal urine delivery of HCO_3^- results in increased urine K^+ excretion and hypokalemia



Acetazolamide*

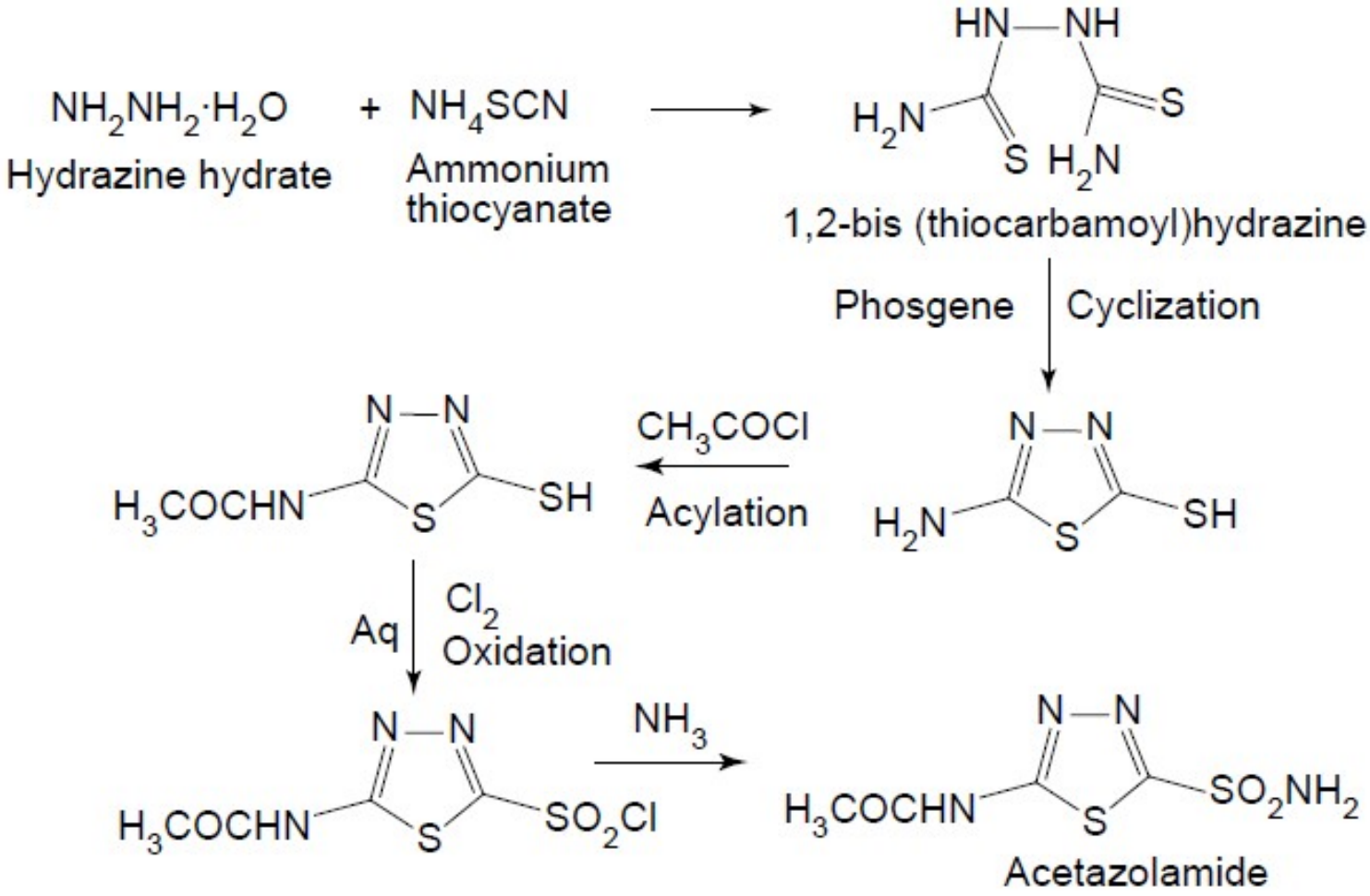


N-(Sulphonamido-1,3,4-thiadiazol-2-yl)acetamide

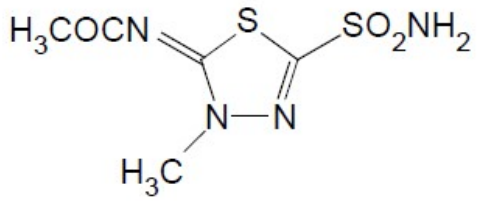
- Acetazolamide belongs to the class of organic compounds known as thiadiazole sulfonamides.
- These are heterocyclic compounds containing a thiazole ring substituted by at least one sulfonamide group.
- Acetazolamide is a sulfonamide derivative with diuretic, antiglaucoma, and anticonvulsant properties.
- It is a non-competitive inhibitor of carbonic anhydrase, an enzyme found in cells in the proximal tube of the kidney, the eye, and glial cells.
- Inhibition of this enzyme **in the kidney** prevents excretion of hydrogen, leading to increased bicarbonate and cation excretion and increased urinary volume, which results in an alkaline diuresis.

- Acetazolamide reduces the concentration of bicarbonate, resulting in a decreased synthesis of aqueous humor **in the eye**, thereby lowering intraocular pressure.
- Although its mechanism of action is unknown, acetazolamide has **anti-convulsant properties** resulting from indirect effects secondary to metabolic acidosis or direct effects on neuronal transmission.
- Acetazolamide also produces **respiratory stimulant** effects in response to changes to both carbon dioxide and oxygen tension levels within the lungs.
- Acetazolamide exists as a solid, slightly soluble (in water), and a very weakly acidic compound (based on its pKa).
- It has been detected in multiple biofluids, such as urine and blood. Within the cell, acetazolamide is primarily located in the cytoplasm.
- Acetazolamide is used for adjunctive treatment of: edema due to congestive heart failure; drug-induced edema; centrencephalic epilepsies; chronic simple (open-angle) glaucoma.

Synthesis of Acetazolamide



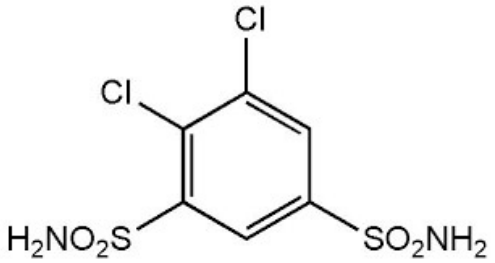
Methazolamide



N-(4-methyl-2-sulphonamido-1,3,4-thiadiazolin-5-ylidene)acetamide

- Methazolamide is a member of thiadiazoles and a sulfonamide: a carbonic anhydrase inhibitor with potential antineoplastic activity.
- Methazolamide inhibits tumor-associated carbonic anhydrase IX (CAIX), which may result in increased cell death in hypoxic tumors.
- As a hypoxia-inducible transmembrane glycoprotein, CAIX catalyzes the rapid interconversion of carbon dioxide and water into carbonic acid, protons, and bicarbonate ions, helping to maintain acidification of the tumor microenvironment and enhance resistance to cytotoxic therapy in some hypoxic tumors.
- Primarily used as diuretics and in the therapy of glaucoma.

Dichlorphenamide



4,5-dichlorobenzene-1,3-disulfonamide

- Diclofenamide is a sulfonamide that is benzene-1,3-disulfonamide in which the hydrogens at positions 4 and 5 are substituted by chlorine.
- An oral carbonic anhydrase inhibitor, it partially suppresses the secretion (inflow) of aqueous humor in the eye and so reduces intraocular pressure.
- Dichlorphenamide is used for adjunctive treatment of: chronic simple (open-angle) glaucoma, secondary glaucoma, and preoperatively in acute angle-closure glaucoma where delay of surgery is desired in order to lower intraocular pressure.

Thiazides

Thiazide Diuretics: Mechanism of Action

- These are medium efficacy diuretics (sulfonamide derivatives) with primary site of action in the cortical diluting segment or the early DT (Site III).
- Here they inhibit Na^{+}–Cl^{-} symport at the luminal membrane.
- Under thiazide action, increased amount of Na+ is presented to the distal nephron, more of it exchanges with K+ $\longrightarrow$ urinary K+ excretion is increased in parallel to the natriuretic response (Hypokalemia).

- Thiazides are secreted by proximal tubules but works in DCT – Inhibit Na^+-Cl^- symporter from the lumen to tubular cells
- They increase Na^+, Cl^- excretion (and water)
- Some thiazides have weak Carbonic Anhydrase Inhibitory effect.

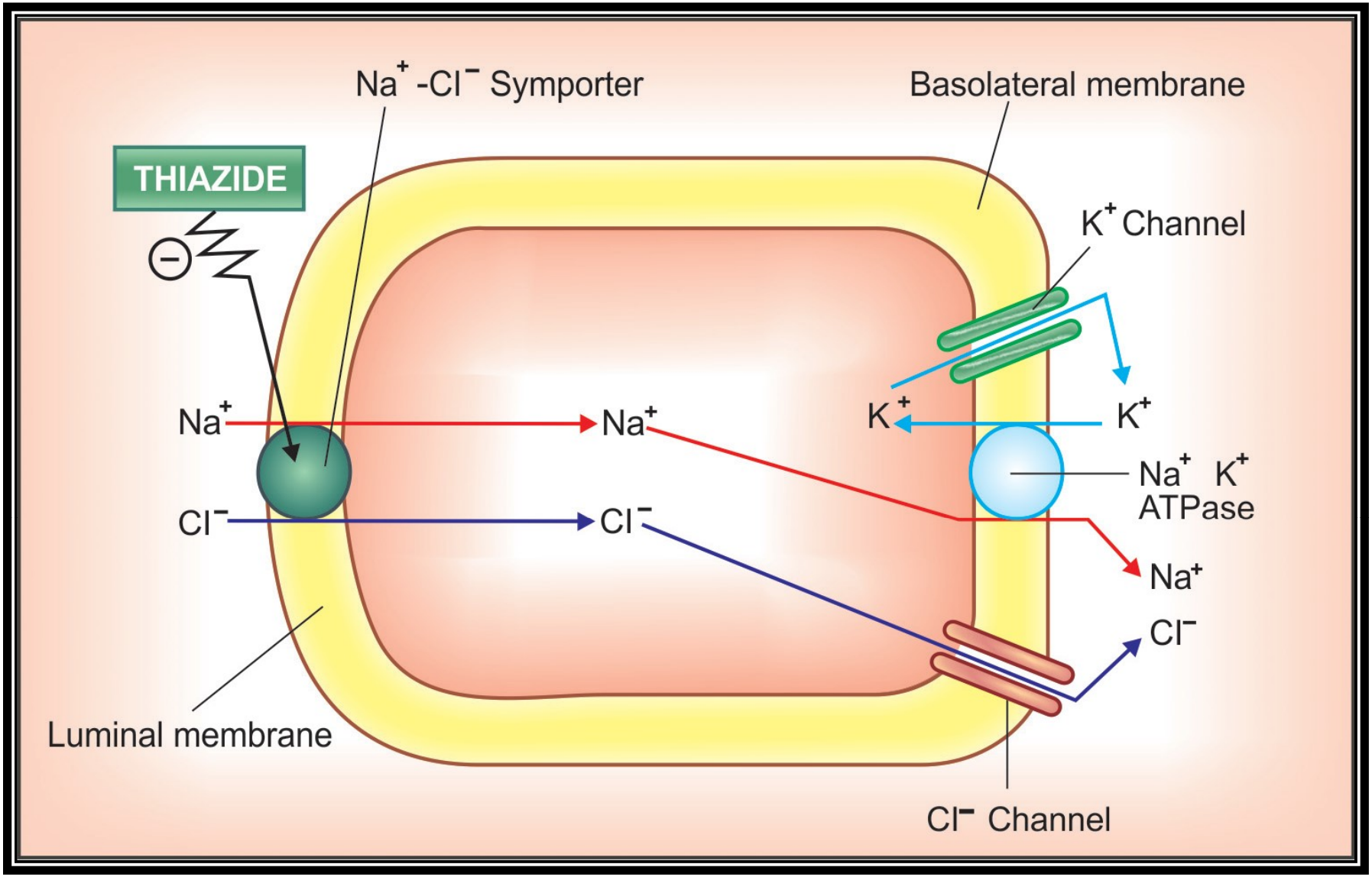
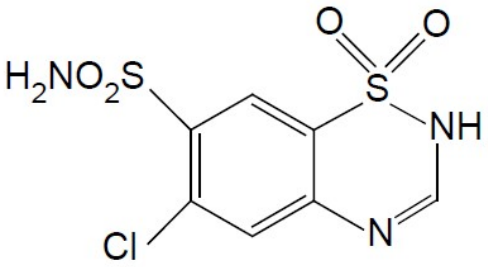


Fig.3 : Mechanism of salt reabsorption in early distal tubular cell and site of action of thiazide diuretics on Na^+ Cl^- symporter

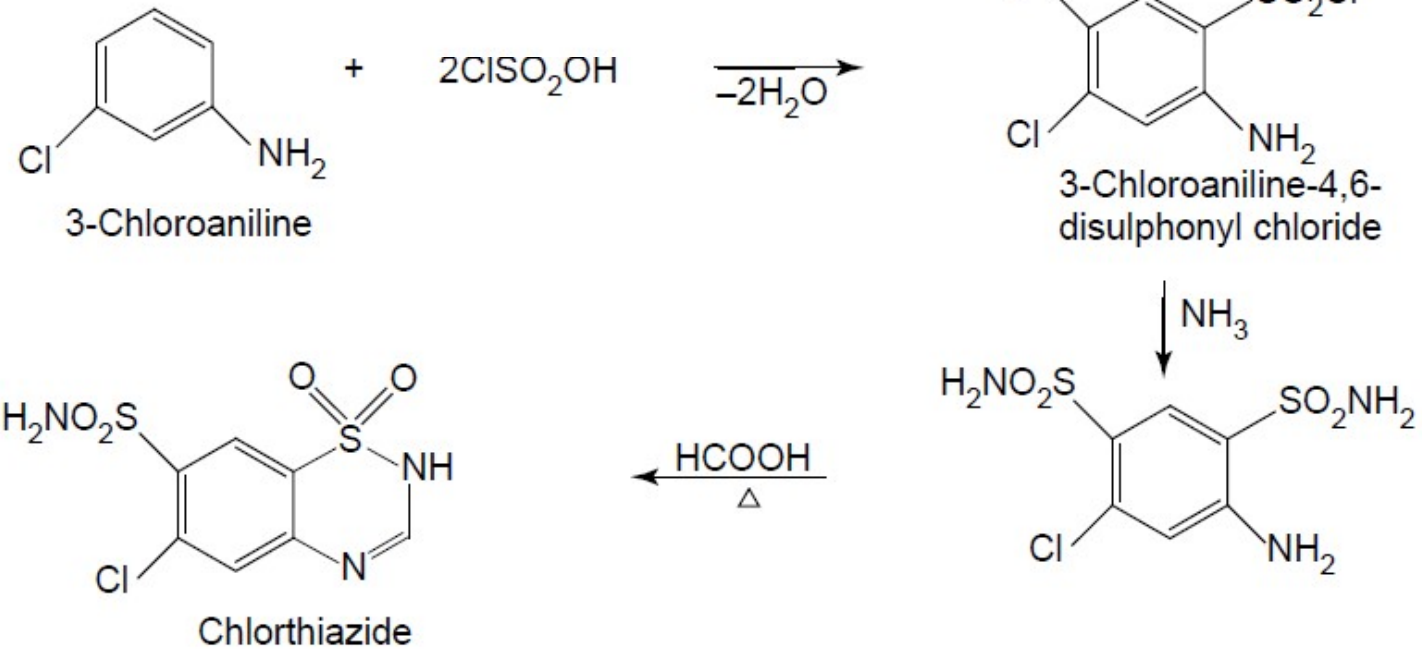
- Effect of thiazides on the proximal convoluted tubule is less.
- The acid-base balance is not usually affected.
- These drugs must be excreted into the tubular lumen to be effective. Therefore with decreased renal function thiazides are not effective.
- Thiazide diuretics decrease the Ca^{2+} content of urine by promoting the reabsorption of Ca^{2+}.

Chlorthiazide*



6-Chloro-1,2,4-benothiazine-7-sulphonamide-1,1-dioxide

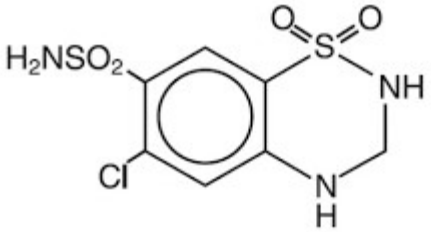
Synthesis:



Chlorthiazide

- Chlorthiazide is a short-acting, benzothiadiazinesulfonamide derivative and prototypical thiazide diuretic.
- These are aromatic heterocyclic compounds containing a 1, 2, 4-benzothiadiazine ring system with two S=O bonds at the 1-position.
- Chlorthiazide exists as a solid and is considered to be practically insoluble (in water) and relatively neutral.
- It has been detected in multiple biofluids, such as urine and blood. Chlorothiazide is excreted unchanged by the kidneys.
- A diuretic, it is used for treatment of oedema and hypertension. It has a role as a diuretic and an antihypertensive agent.

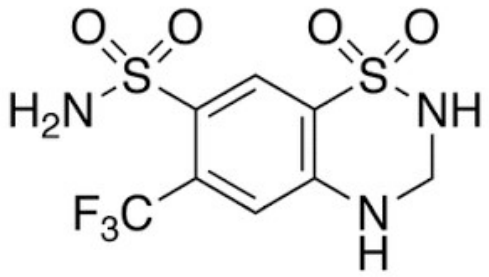
Hydrochlorothiazide



6-chloro-1,1-dioxo-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide

- Hydrochlorothiazide is a short acting thiazide diuretic.
- These are aromatic heterocyclic compounds containing a 1, 2, 4-benzothiadiazine ring system with two S=O bonds at the 1-position.
- Hydrochlorothiazide exists as a solid, slightly soluble (in water), and a very weakly acidic compound (based on its pKa).
- It has been found in human adipose tissue and kidney tissues, and has also been detected in multiple biofluids, such as feces, urine, and blood. Within the cell, hydrochlorothiazide is primarily located in the cytoplasm.
- Hydrochlorothiazide is widely used to treat hypertension and edema.

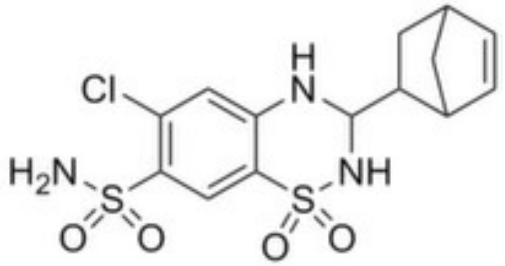
Hydroflumethiazide



1,1-dioxo-6-(trifluoromethyl)-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide

- Hydroflumethiazide is an intermediate-acting benzothiadiazine sulfonamide derivative belonging to the class of the thiazide diuretics.
- These are aromatic heterocyclic compounds containing a 1, 2, 4-benzothiadiazine ring system with two S=O bonds at the 1-position.
- Hydroflumethiazide is a drug which is used as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy. also used in the management of hypertension either as the sole therapeutic agent or to enhance the effect of other antihypertensive drugs in the more severe forms of hypertension.

Cyclothiazide



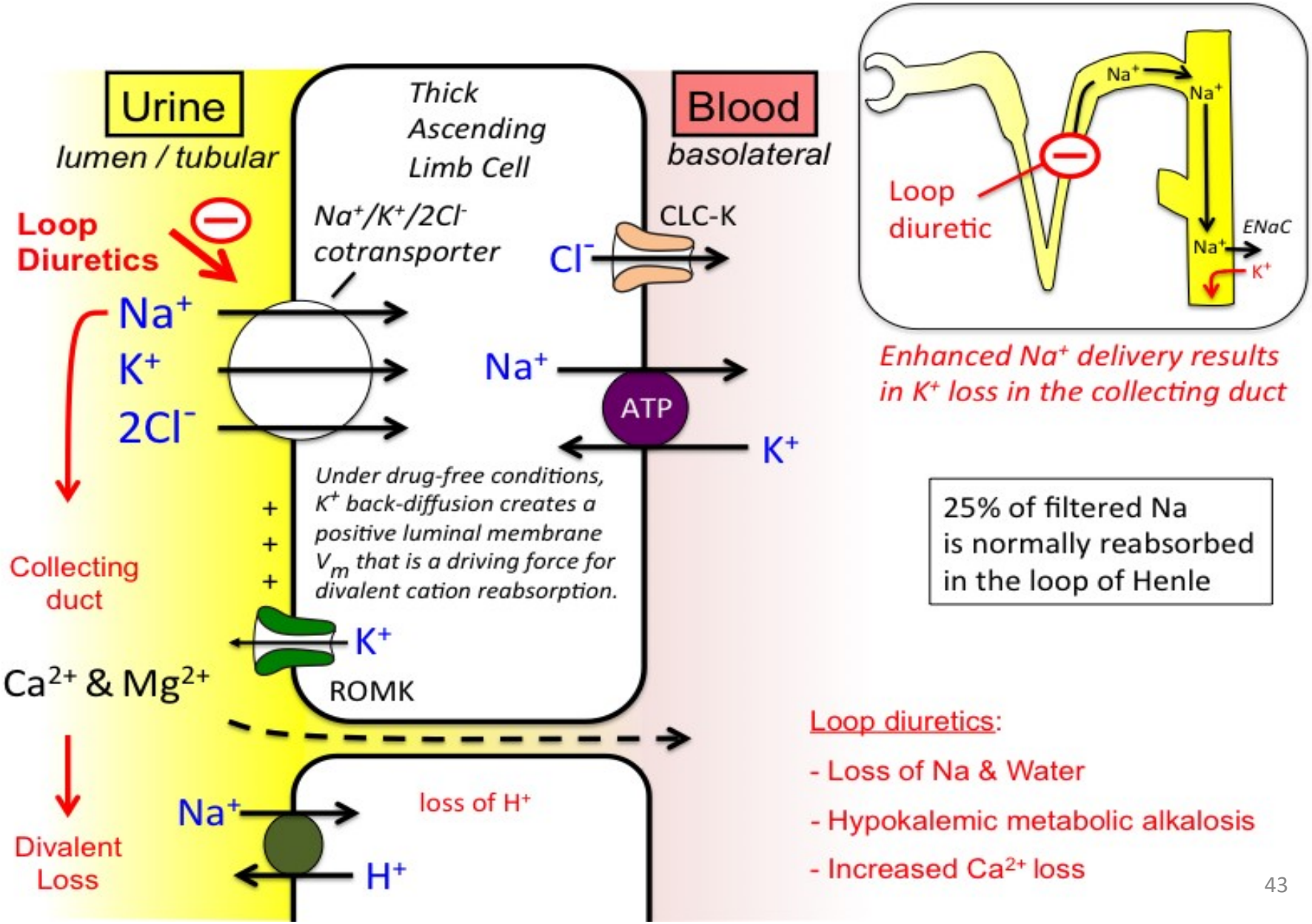
3-(2-bicyclo[2.2.1]hept-5-enyl)-6-chloro-1,1-dioxo-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide

- Cyclothiazide is a benzothiadiazide belonging to the class of thiazide diuretics.
- These are aromatic heterocyclic compounds containing a 1, 2, 4-benzothiadiazine ring system with two S=O bonds at the 1-position.
- Cyclothiazide is indicated as adjunctive therapy in edema and in the treatment of hypertension.
- In addition, this agent is capable of inhibiting rapid desensitization of the ionotropic alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)-type glutamate receptors, thereby potentiating glutamate responses which may induce seizures activity. Cyclothiazide was also found to inhibit gamma-aminobutyric acid (GABA)-A receptors.

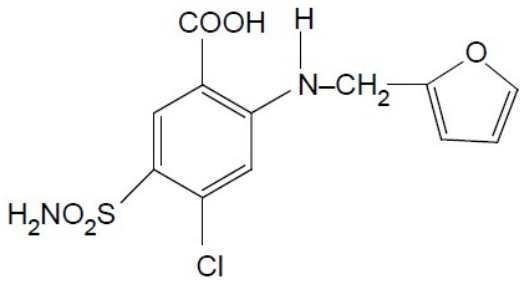
Loop Diuretics

- **Loop diuretics** (or **High ceiling diuretics**) are diuretics that act at the ascending limb of the **loop of Henle** in the kidney (Site II) where they **inhibit Na^+-K^+-$2Cl^-$ cotransport** $\longrightarrow$ significantly increase the excretion of Na^+, K^+, and Cl^-
- Their maximal natriuretic effect is much greater than that of other classes.
- Osmotic gradient for water reabsorption is also decreased $\longrightarrow$ increasing water excretion.
- Ca^{2+} and Mg^{2+} are excreted as well.
- It is secreted in PT by organic anion transport and reaches AscLH where it acts from luminal side of the membrane.
- A minor component of action on PT has also been indicated.

Mechanism of action of loop diuretics

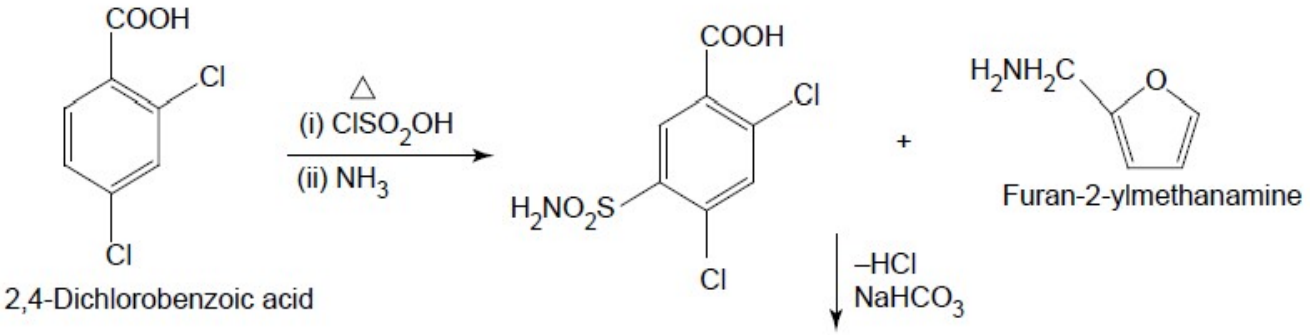


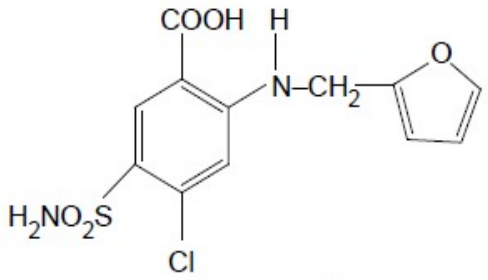
Furosemide*



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

Synthesis



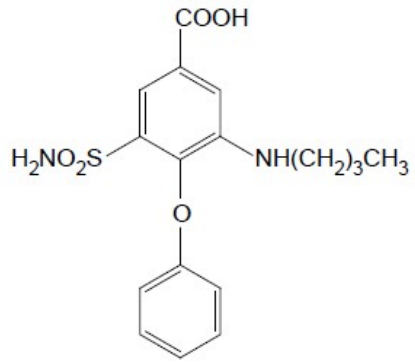


Furosemide

Furosemide

- Furosemide (also known as frusemide) is a sulfamoylanthranilic acid derivative, and potent loop diuretic.
- These are organic compounds containing a benzenesulfonamide moiety with an amine group attached to the benzene ring.
- This agent is highly bound to albumin and is largely excreted unchanged in the urine.
- Furosemide is a drug which is used for the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome.
- Also for the treatment of hypertension alone or in combination with other antihypertensive agents.

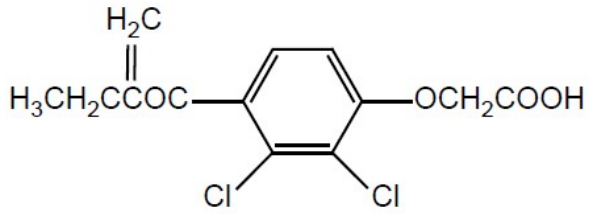
Bumetanide



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

- Bumetanide is a potent sulfamoylanthranilic acid derivative belonging to the class of loop diuretics.
- These are aromatic compounds containing two benzene rings linked to each other through an ether group.
- Bumetanide is a drug which is used for the treatment of edema associated with congestive heart failure, hepatic and renal disease including the nephrotic syndrome.
- In the brain, bumetanide may prevent seizures in neonates by blocking the bumetanide-sensitive sodium-potassium-chloride cotransporter (NKCC1), thereby inhibiting chloride uptake thus, decreasing the internal chloride concentration in neurons and may block the excitatory effect of GABA in neonates.

Ethacrynic acid



2,3-Dichloro-4-(2-methylene butyryl)phenoxy acetic acid

- Ethacrynic Acid is an unsaturated ketone derivative of aryloxyacetic acid without a sulfonamide substituent belonging to the class of loop diuretics.
- Comes under the chemical class of Chlorophenoxyacetates which are compounds containing a phenoxyacetate that carries one or more chlorine atoms on the benzene ring.
- Ethacrynic acid is extensively bound to plasma proteins; both ethacrynic acid in its unchanged form as well as its metabolites are excreted in bile and urine.
- Ethacrynic acid is used for the treatment of high blood pressure and edema caused by diseases like congestive heart failure, liver failure, and kidney failure.

Potassium Sparing Diuretics

Potassium Sparing Diuretics

1. Na^+ channel inhibitor (Amiloride, triamterene)
   → Inhibit Na^+ reabsorption → Na^+ excretion
   → Reduced K^+ secretion → K^+ retention
2. Aldosterone antagonist (Spironolactone, eplerenone) Steroid derivatives
   – Aldosterone induces the expression of Na/K-ATPase and Na^+ channel
   – Spironolactone and eplerenone blocks aldosterone receptor → reduces Na^+ reabsorption and K^+ secretion

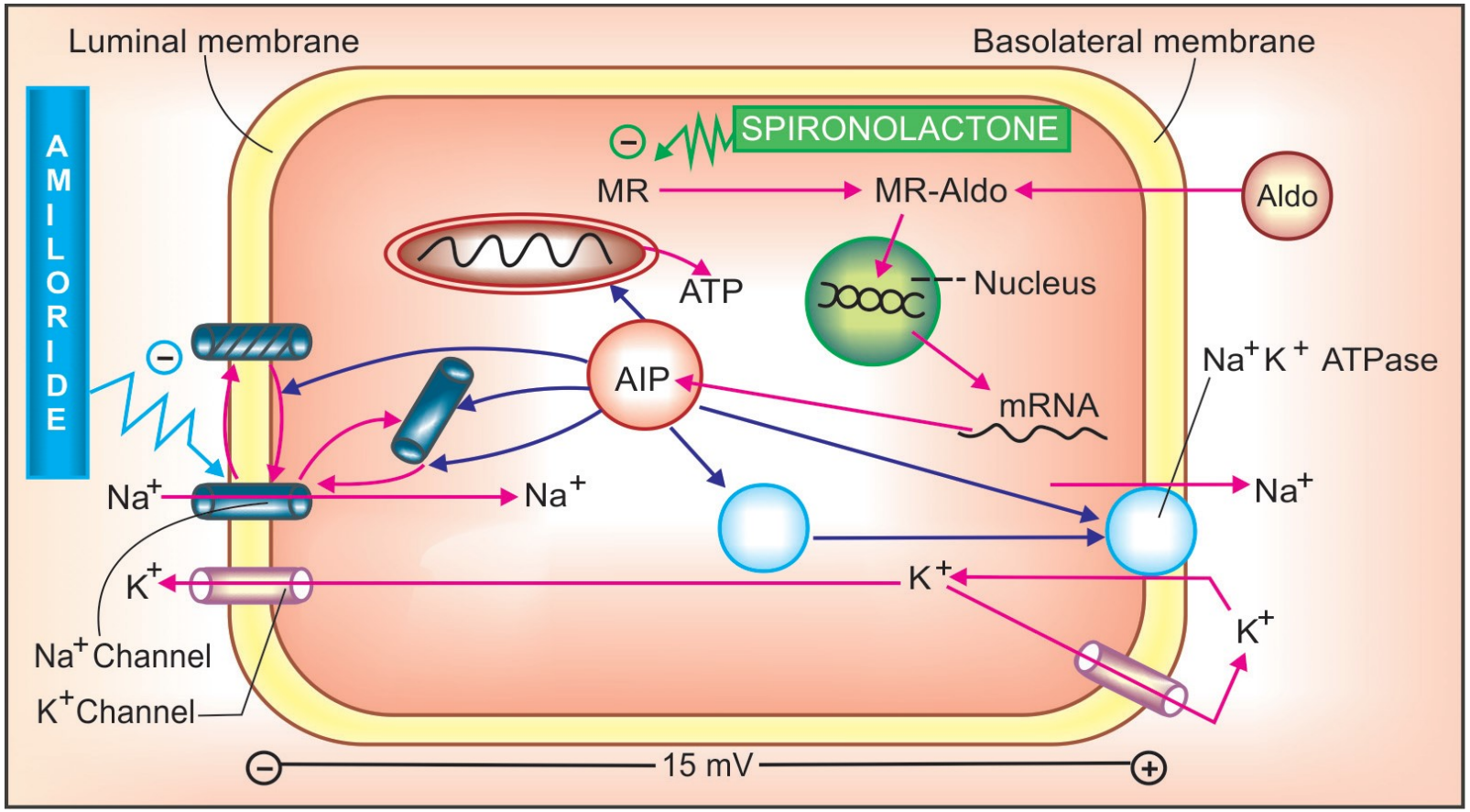
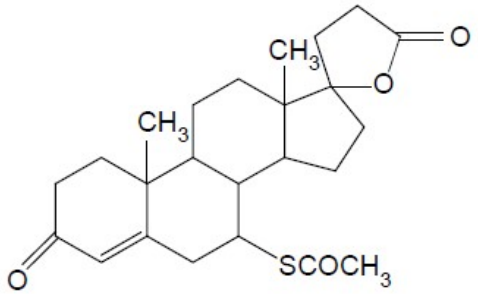


Fig. 4: Site and mechanism of action of potassium sparing diuretics on the late distal tubule/collecting duct cell Aldosterone (Aldo) penetrates the cell from the interstitial side and combines with the mineralocorticoid receptor (MR). The complex translocates to the nucleus—promotes gene mediated mRNA synthesis. The mRNA then directs synthesis of aldosterone induced proteins (AIPs). The AIPs include Na+K+ ATPase and renal epithelial (amiloride sensitive) Na+ channels. More of these proteins are synthesized. The AIPs also activate these Na+ channels and, translocate them from cytosolic site to luminal membrane. They also translocate Na+K+ATPase to the basolateral membrane. AIPs also increase ATP production by mitochondria. All these changes promote Na+ reabsorption. More K+ and H+ is secreted indirectly. Spironolactone binds to MR, prevents Aldo action and produces opposite effects.

Amiloride approaches the Na+ channel from the luminal side and blocks it—reducing the lumen negative transepithelial potential difference which governs K+ and H+ secretion

- Potassium sparing diuretic has a weak diuretic action
- Usually used in combination with other diuretic for:
  - Potentiation of diuretic and antihypertensive effects
  - Prevention of hypokalemia
- Spironolactone is metabolized to its active metabolite, canrenone.
- Long term use of spironolactone can prevent myocardial hypertrophy and myocardial fibrosis Potassium Sparing Diuretics

Spironolactone (Aldosterone antagonist)



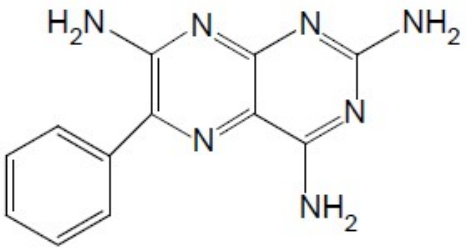
S-[(7*R*,8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-10,13-dimethyl-3,5'-dioxospiro[2,6,7,8,9,11,12,14,15,16-decahydro-1*H*-cyclopenta[a]phenanthrene-17,2'-oxolane]-7-yl] ethanethioate

- Spironolactone is a synthetic 17-spironolactone corticosteroid, chemically related to the mineralocorticoid **aldosterone.**
- Aldosterone penetrates the late DT and CD cells (Fig. 4) and acts by combining with an intracellular mineralocorticoid receptor (MR) ⟶ induces the formation of *aldosterone-induced proteins' (AIPs).*
- *The AIPs* promote Na^+ reabsorption by a number of mechanisms and K^+ secretion.
- Spironolactone acts from the interstitial side of the tubular cell, combines with MR and inhibits the formation of AIPs in a competitive manner.

Spironolactone

- It has no effect on Na^+ and K^+ transport in the absence of aldosterone, while under normal circumstances, it increases Na^+ and decreases K^+ excretion.
- Spironolactone is a mild saluretic because majority of Na^+ has already been reabsorbed proximal to its site of action. However, it antagonises K^+ loss induced by other diuretics and slightly adds to their natriuretic effect
- This agent may inhibit the pathophysiologic effects of aldosterone produced in excess by various types of malignant and benign tumors.
- Used as an adjuvant along with thiazide/ loop diurtics in the treatment of edema, hypertension, CHF, and to counteract the K^+ loss due to thiazide/ loop diurtics.

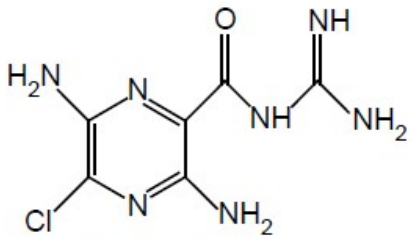
Triamterene



2,4,7-Triamino-6-phenylpteridine

- Triamterene is a pteridine derivative with potassium-sparing diuretic property.
- It blocks the sodium-potassium exchange pump (Na-K-ATPase) in the luminal membrane of principal cells in the late distal tubule, cortical collecting tubule and collecting duct in the kidney.
- This reversible inhibition of the electrogenic sodium transport decreases the lumen-negative transepithelial potential difference and thus reduces the driving force for K^+ movement into the tubular lumen resulting in the inhibition of sodium reabsorption in exchange for K^+ and H^+.
- Triamterene is used for the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and the nephrotic syndrome; also in steroid-induced edema, idiopathic edema, and edema due to secondary hyperaldosteronism.

Amiloride

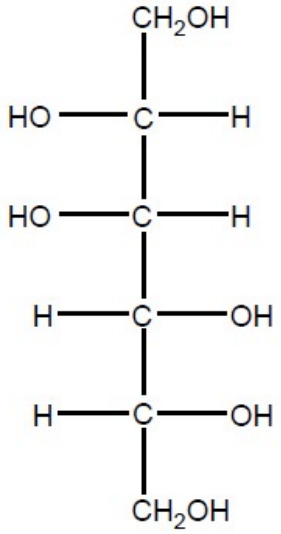


N-Amidino-3,5-diamino-6-chlorpyrazine carboxamide

- Amiloride is a synthetic pyrazine derivative with potassium-sparing diuretic properties.
- Amiloride inhibits sodium channels (Amiloride sensitive channels) located in the distal tubules and collecting ducts of the kidney, thereby preventing the absorption of sodium and increasing its excretion along with water, to produce naturesis.
- In response to the hypernatremic conditions in the kidney, the plasma membrane becomes hyperpolarized and electrochemical forces are reduced, which then prevents the excretion of potassium and hydrogen into the lumen.
- Amiloride is used in the therapy of edema often in combination with thiazide diuretics.

Osmotic Diuretics

Mannitol



2*R*,3*R*,4*R*,5*R*)-hexane-1,2,3,4,5,6-hexol

- Mannitol is a nonelectrolyte of low molecular weight (182) that is pharmacologically inert— can be given in large quantities sufficient to raise osmolarity of plasma and tubular fluid.
- It is a naturally occurring alcohol found in fruits and vegetables and used as an osmotic diuretic.
- It is minimally metabolized in the body; freely filtered at the glomerulus and undergoes limited reabsorption: therefore excellently suited to be used as osmotic diuretic.

Mechanism of action

Mannitol appears to limit tubular water and electrolyte reabsorption in a variety of ways:

1. Retains water iso-osmotically in PT—dilutes luminal fluid which opposes NaCl reabsorption.
2. Inhibits transport processes in the thick AscLH by an unknown mechanism. Quantitatively this appears to be the largest contributor to the diuresis.
3. Expands extracellular fluid volume (because it does not enter cells, mannitol draws water from the intracellular compartment)— increases g.f.r. and inhibits renin release.
4. Increases renal blood flow, especially to the medulla—medullary hypertonicity is reduced (due to washing off)—corticomedullary osmotic gradient is dissipated—passive salt reabsorption is reduced.

Though the primary action of mannitol is to increase urinary volume, excretion of all cations (Na^+, K^+, Ca^{2+}, Mg^{2+}) and anions (Cl^-, HCO_3^-,PO_4^{3-}) is also enhanced.

- **Mannitol is used**

1. To reduce the Increased intracranial or intraocular tension (acute congestive glaucoma, head injury, stroke, etc.): by osmotic action it encourages movement of water from brain parenchyma, CSF and aqueous humour.
2. To counteract low osmolality of plasma/e.c.f. due to rapid haemodialysis or peritoneal dialysis (dialysis disequilibrium).
3. To maintain g.f.r. and urine flow in impending acute renal failure.

Summary: Site and Mechanisms of action of diuretics

Diuretics	Site of Action	Mechanism
Osmotic Diuretic	1. Proximal tubules 2. Loop of Henle 3. Collecting duct	Inhibition of water and Na+ reabsorption
Carbonic Anhydrase Inhibitor (CA-I)	Proximal tubules	Inhibition of bicarbonate reabsorption
Loop Diuretic	Loop of Henle (*thick ascending limb*)	Inhibition of Na^+, K^+, Cl^- cotransport
Thiazide	Early distal tubule	Inhibition of Na^+, Cl^- cotransport
K^+ sparing diuretics	Late distal tubule Collecting duct	Inhibition of Na+ reabsorption and K^+ secretion

Thank You.....

Keep learning