Chapter 5. Diuretics

Diuretics:

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

5.1. DIURETICS

- Diuretics are drugs that promote the output of urine excreted by the kidneys. They are very effective in the treatment of cardiac oedema, specifically the one related with congestive heart failure.

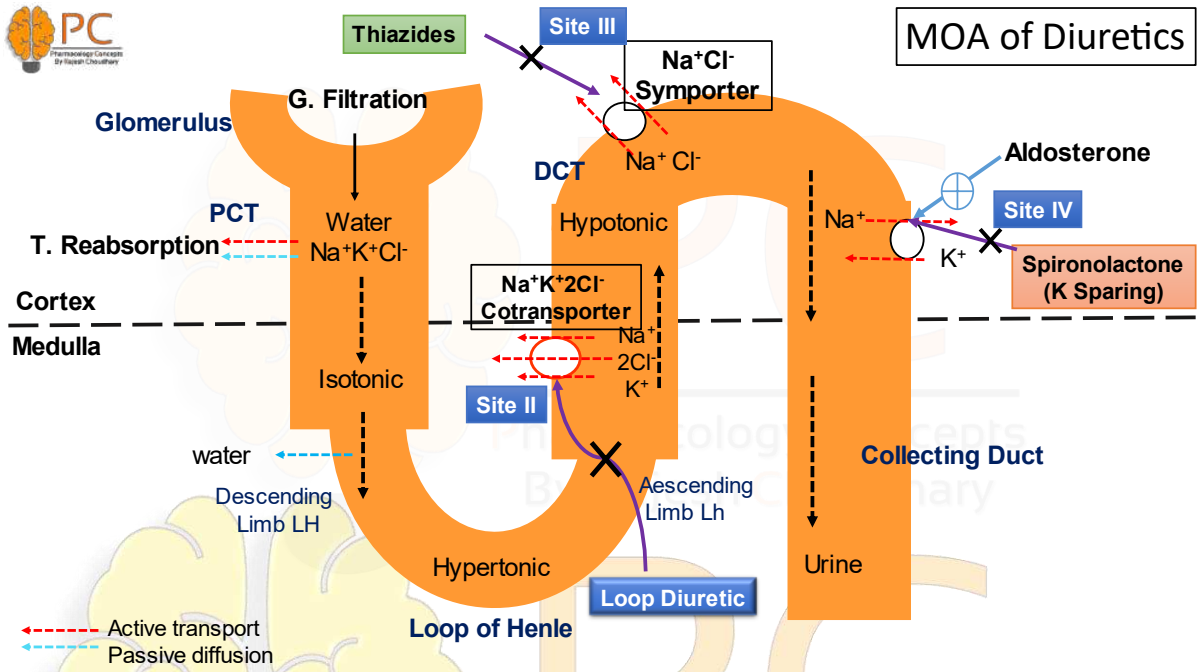
5.2. CLASSIFICATION

A. Mercurial diuretics: Chlormerodrin, Meralluride, Mercaptomerin sodium, Mersalyl etc.

B. Non-Mercurial diuretics:

1. **Thiazides (Benzothiadiazines):** Chlorthiazide, Hydrochlorthiazide, Benzthiazide, Hydroflumethiazide, cyclopenthiazide etc.
2. **Carbonic Anhydrase Inhibitors:** Acetazolamide, Ethoxzolamide, Methazolamide, Dichlorphenamide
3. **Potassium sparing diutetics:**
   (i) **Aldosterone antagonist:** Spironolactone
   (ii) **Directly acting:** Triamterene, Amiloride.
4. **'Loop' or High-Ceiling diuretics:** Furosemide, Bumetanide, Ethacrynic acid.
5. **Purine or Xanthine derivatives:** Theophylline, caffeine etc.
6. **Pyrimidine diuretics:** Aminometradine.
7. **Osmotic diuretics:** Urea, Mannitol etc.
8. **Acidotic diuretics:** Ammonium chloride.
9. **Miscellaneous diuretics:** Triamterene, Muzodimine, Chlorthalidone etc.

5.3. Mechanism of Action

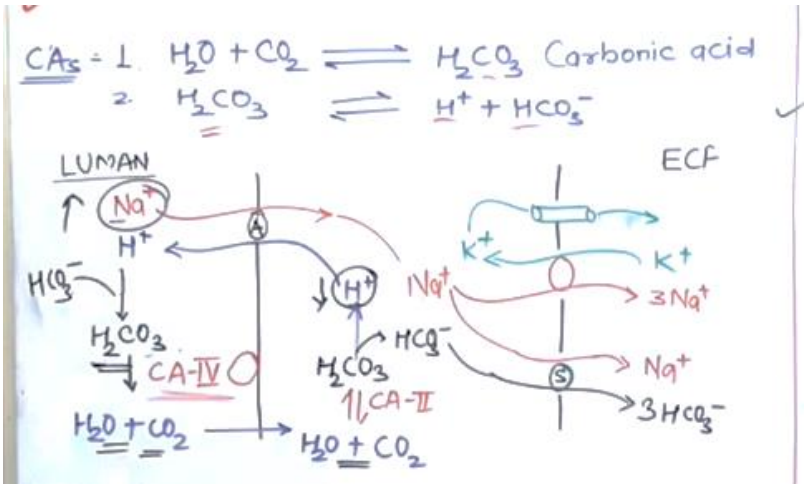


Animated Video Link: https://youtu.be/3L-G_aukQWk

5.4. Medicinal Chemistry of Diuretics

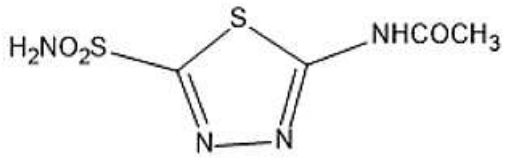
1. Carbonic anhydrase inhibitors:

MOA: CAIs inhibit the carbonic anhydrase enzyme at the proximal convoluted tubules (**SITE-I**) that important for NaHCO3 reabsorption and acid secretion. CAIs inhibit the formation of H^+ and decrease the exchange of H^+ with Na^+ thus enhance the excretion of Na^+ and $HCO3^-$ through urine.



- **Uses:** CAIs are used as the diuretic also used in glaucoma (reduce the intraocular pressure by inhibition of aqueous humor formation) and epilepsy
- **Drugs:** Acetazolamide*, Methazolamide, Dichlorphenamide.
- *Detail Pharmacology link: https://youtu.be/9w-ocA8idOM)*

A) Acetazolamide



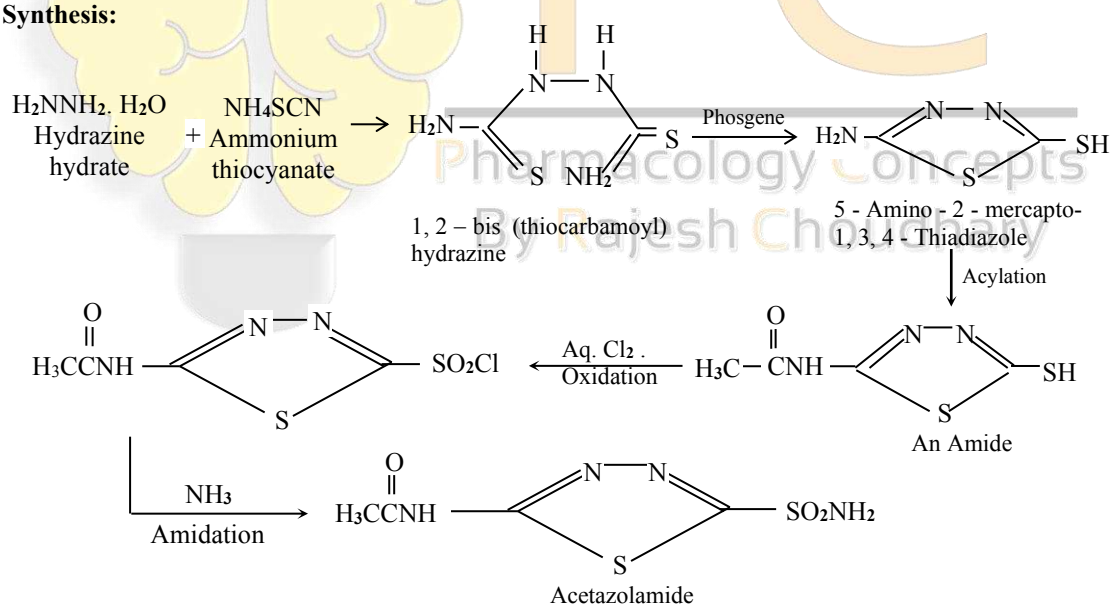
N-(5-Sulfamoyl-1, 3, 4-thiadiazol-2-yl) acetamide

MOA: Carbonic Anhydrase enzyme inhibitor

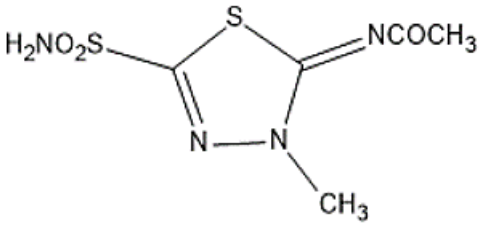
Uses:

- ✓ As a diuretics
- ✓ Used in open angle glaucoma, epilepsy and Meniere's disease (disease of internal ear)

Synthesis:



B) Methazolamide



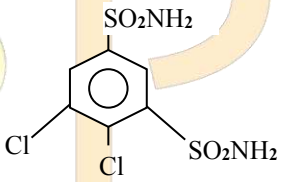
***N*-(3-methyl-5-sulfamoyl-1,3,4-thiadiazol-2-ylidene) acetamide**

MOA: Carbonic Anhydrase enzyme inhibitor

Uses:

- ✓ As a diuretics
- ✓ Used in open angle glaucoma and epilepsy

C) Dichlorphenamide (Diclofenamide)



4, 5-Dichloro-1,3-benzene disulphonamide

MOA: Carbonic Anhydrase enzyme inhibitor

Uses:

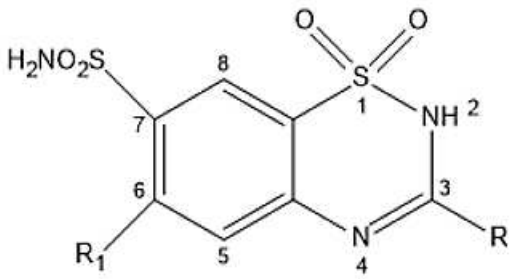
- ✓ As a diuretics
- ✓ Used in open angle glaucoma and epilepsy

2. Thiazides:

- These are the benzothiadiazine derivatives.
- **MOA**: They inhibit the Na^+Cl^- Symport pump at distal convoluted tubules (**SITE 3**) and enhance the excretion of Na^+, Cl^-, K^+, and Mg^{2+} ions and reduce the excretion of $Ca2^{2+}$,. It also decreases the plasma volume, ECF, cardiac output, and release of insulin. Not useful in renal failure condition.
- **Uses**: They are used as diuretic and treatment of hypertension, oedema, diabetes insipidus and hypocalsiurea.
- **Drugs:** Chlorothiazide*, Hydrochlorothiazide, Hydroflumethiazide, Cyclothiazide,
- **Detail Pharmacology**: https://youtu.be/VrGfeipWfeg

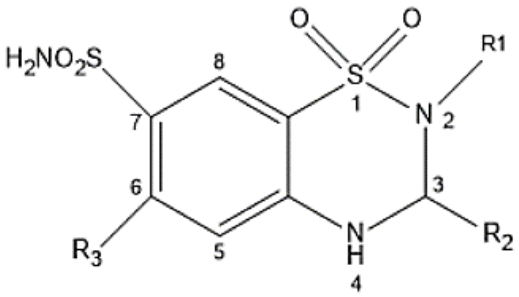
Structural Activity Relationship (SAR) of Thiazide

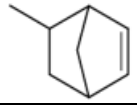
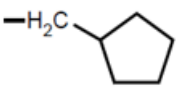
Thiazide Derivatives



Name	R	R1
Chlorthiazide	-H	-Cl
Flumethazide	-H	$-CF_3$
Benzthiazide	$-CH_2-S-CH_2-C6H_5$	-Cl

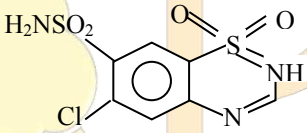
Hydro-thiazide Derivatives



Name	R1	R2	R3
Hydrochlorthiazide	-H	-H	-Cl
Cyclothiazide	-H		-Cl
Hydroflumethiazide	-H	-H	-CF3
Cyclopenthiazide	-H		-Cl
Polythiazide	-H	$-CH_2-S-CH_2-CF_3$	-Cl

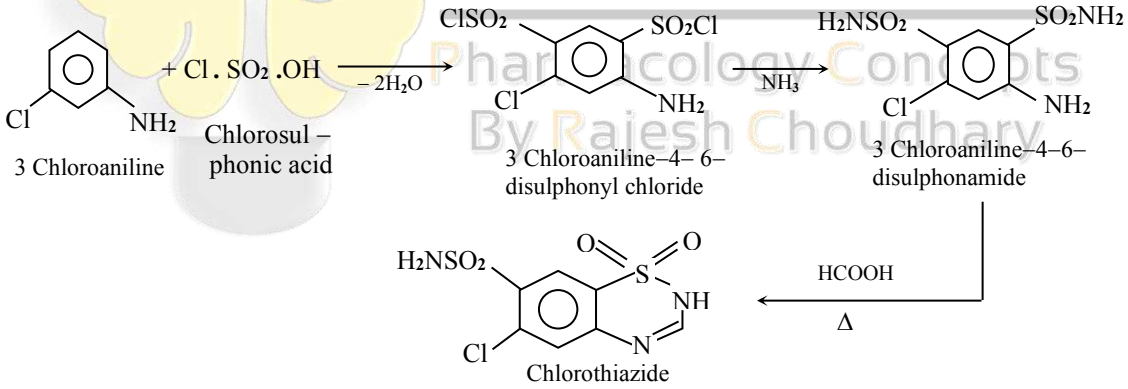
- Substituents with hydrophobic character (–CH2Cl, –CHCl2, –CH2C6H5, –CH2S, –CH2 –C6H5) in the 3rd position (-R) increases saluretic activity 1000 times. The increase in saluretic activity correlates with the lipid solubility. E.g., Benzthiazide
- Saturation of double bond between the 3rd and 4th position of nucleus increases the diuretic activity approximately 3-fold to 10-fold. Example— Hydrochlorthiazide.
- Hydrogen atom at the 2nd position (N-R1) is more acidic due to the presence of neighbouring electron withdrawing the sulphone group.
- A free sulphamoyl or potentially free sulphamoyl group at 7th postion is essential for activity.
- Direct substitution of the 4th, 5th, or 8th position with an ethyl group usually results in diminished diuretic activity
- At 6th position, an activating group is essential for diuretic activity. The substiutents include Cl, Br, and CF3 groups.

A) Chlorothiazide

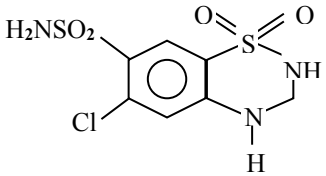


6-Chloro-2H-1,2,4-benzothiadiazine-7-sulphonamide 1, 1-dioxide

Synthesis :

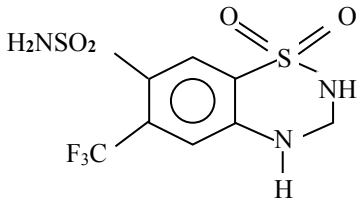


B) Hydrochlorothiazide



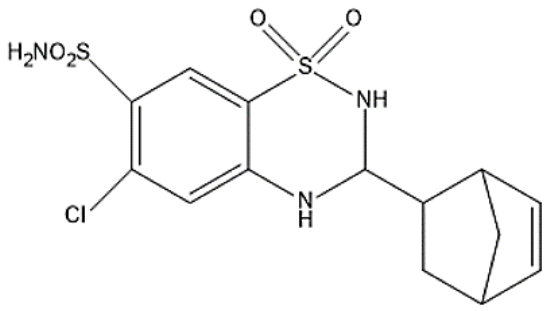
6-Chloro-3, 4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulphonamide 1, 1-dioxide

C) Hydroflumethiazide



3, 4-Dihydro-6-(trifluoromethyl)-2H-1, 2, 4-benzothiadiazine-7-sulphonamide, 1 1-dioxide

D) Cyclothiazide



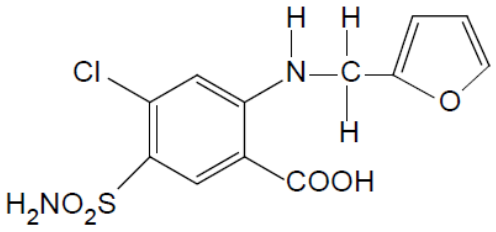
6-Chloro-3, 4-dihydro-3-(5-nor-bornen-2yl)-2H, 1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide

3. Loop Diuretic

- They are also known as **high ceiling diuretics.**
- **MOA:** They inhibit the $Na^+K^+2Cl^-$ cotransporter at the thick ascending loop of henle (ALH; Site II). They Also have some carbonic anhydrase inhibition properties.
- They show the maximum natriuretic effects (excretion of Na^+). They also cause the excretion of other ions like Cl^-, K^+, Mg^{2+}, Ca^{2+} ions. Improve the venous capacitance and reduce the filling at left ventricle.
- **Uses:** Oedema (Periferal, pulmonary, cerebral), CHF, Hypertension, and poisoning.
- Detail Pharmacology: **https://youtu.be/rhDUCOkb88k**
- **Loop diuretics**: Sulphomoyl benzoic acids (Furosemide*, Bumetanide), Phenoxyacetic acid (Ethacrynic acid)

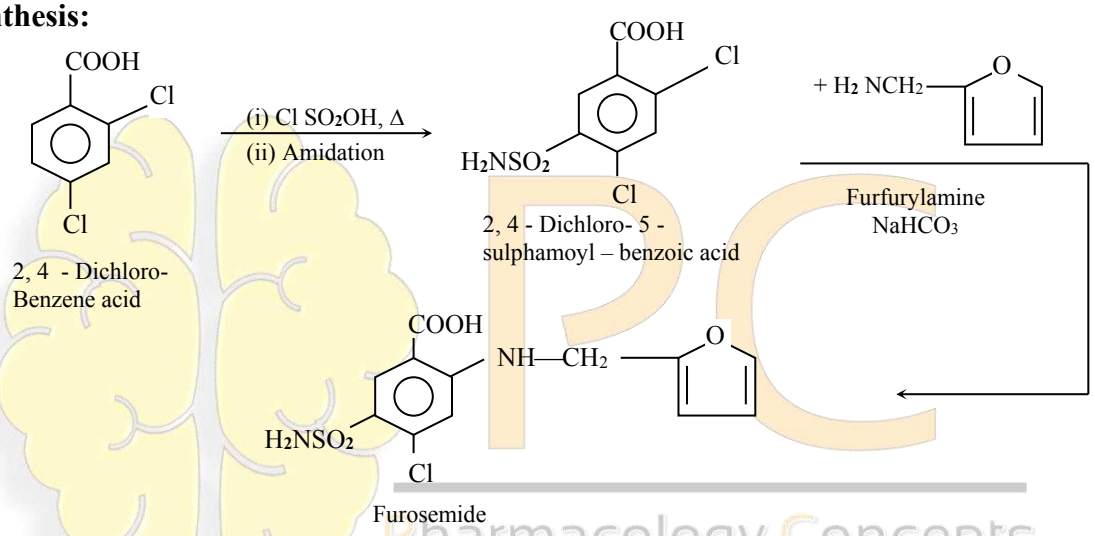
Sulphomoyl Benzoic Acids

A) Furosemide

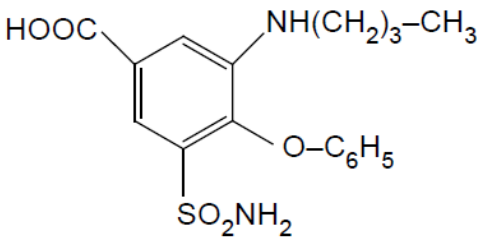


4-Chloro-N-furfuryl-5-sulphamoyl anthranilic acid

Synthesis:



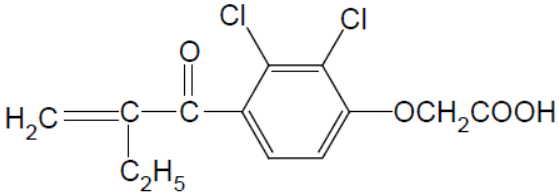
B) Bumetanide



3-butyl amino-4-phenoxy-5-sulphamoyl benzoic acid

Phenoxy acetic acid

C) Ethacrynic Acid

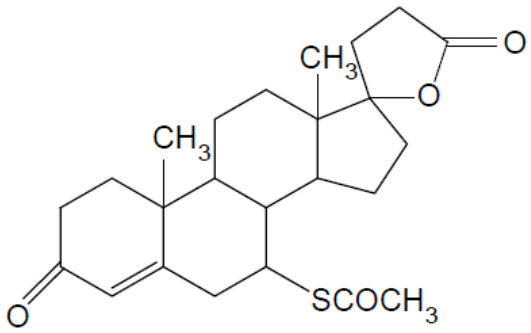


[2,3-Dichloro-4-(2-methylene butyryl) phenoxy] acetic acid

4. Potassium Sparing Diuretics

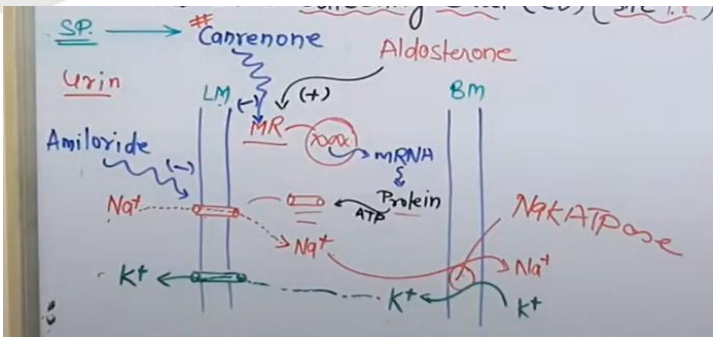
- They conserve K+ with mild natriuretic & saluretic effects.
- **Aldosterone Antagonist**: Spironolactone, Eplerenone
- **Renal epithelial Na+ Channel blockers**: Amiloride, Triameterene
- **Uses**: Diuresis, hypertension, CHF, hypokalemia
- Pharmacolgy: https://youtu.be/8348dSe7yFU

A) Spironolactone



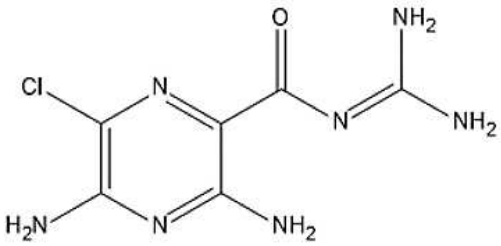
7α-Acetylthio-3-oxo-17α-pregn-4-ene-21,17β-carbolactone

MOA: Canrenone is the active metabolite which antagonize the aldosterone receptors that may lead to inhibition of Na^+ channel expression at late DCT and collecting duct (**SITE 4**), resulting in inhibition of Na^+ reabsorption.



Uses: Diuresis, hypertension, CHF, hypokalemia, hepatic cirrhosis with ascites, and nephrotic syndrome.

B) Amiloride

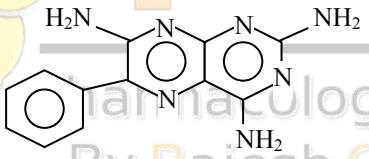


3,5-diamino-6-chloro-*N*-(diamino methylidene)pyrazine-2-carboxamide

MOA: It selectively block the Na^+ channel or sodium transport at late distal tubule and collecting duct (**SITE IV**) of the nephron, thereby inhibiting sodium-potassium exchange. The mechanism of action of amiloride is independent of aldosterone

Uses: It is a potassium-conserving drug with natriuretic diuretic and antihypertensive activity. It also used in oedema, CHF, hepatic cirrhosis with ascites, and nephrotic syndrome.

C) Triamterene

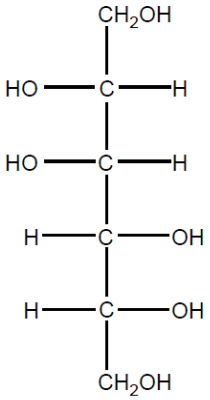


2,4,7-Triamino-6-phenylpteridine

MOA: Similar as Amiloride

Uses: It is a potassium-conserving drug with natriuretic diuretic. Used in hypertension, oedema, CHF, hepatic cirrhosis with ascites, and nephrotic syndrome.

5. Osmotic Diuretics: Mannitol



Hexane-1,2,3,4,5,6-hex-ol

MOA: It acts by increasing the osmotic pressure of tubular fluids and extract water from in tricellular cells. It easily filtered through glomerular filtration but limited to reabsorption. It increases the excretion of all ions like Na^{+}, Cl^{-}, K^{+}, Mg^{2+}, $Ca^{2+}$and $HCO3^{-}$.

Uses:

- ✓ It is most widely used for acute renal failure, cardiovascular operation, cerebral oedema, and glaucoma. And severe traumatic injury with nephrotoxic anticancer agents
- ✓ Used as diagnostic agent for kidney function

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