DIURETICS

Diuretics are drugs that increase the urine output by the kidney (i.e. promote diuresis). Diuretics are drugs which increases the rate of urine formation by increasing the excretion of sodium and water from the body.

If the kidney excretes more sodium, then water excretion will also increase. Most diuretics produce diuresis by inhibiting the reabsorption of sodium at different segments of the renal tubular system.

Sometimes a combination of two diuretics is given because this can be significantly more effective than either compound alone (synergistic effect).

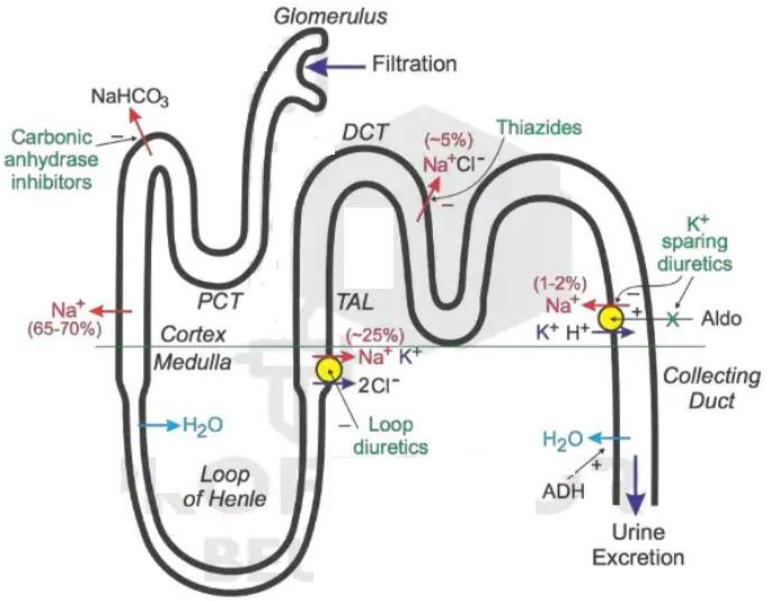
The reason for this is that one nephron segment can compensate for altered sodium reabsorption at another nephron segment; therefore, blocking multiple nephron sites significantly enhances efficacy.

Diuretics are used in

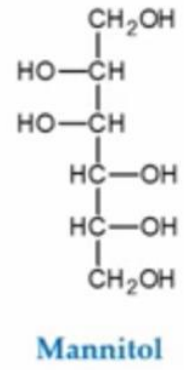
- Hypertension
- Congestive heart failure
- Kidney diseases
- Liver diseases
  which can cause retention of excess fluid (edema)

Classification of Diuretics

- Osmotic diuretics
- Carbonic anhydrase inhibitors (site 1 diuretics)
- Loop diuretics (site 2 diuretics)
- Thiazide and thiazide-like diuretics (site 3 diuretics)
- Potassium sparing diuretics (site 4 diuretics)

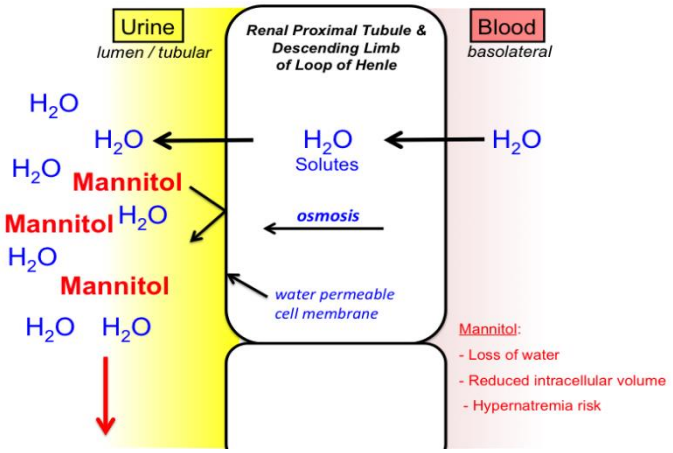


- **Osmotic diuretics**



Water has a tendency to move across the membrane from a region of lower osmolarity (dilute side) to a higher osmolarity (concentrated side).

MOA: Osmotic diuretics are filtered from glomerulus and increase the osmolarity of the tubular fluid and thus decrease water reabsorption.

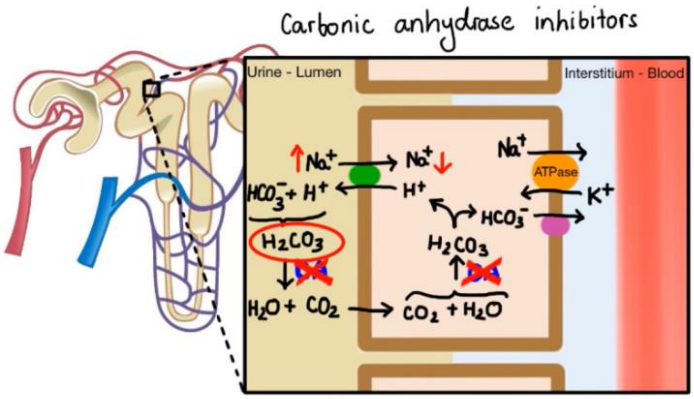


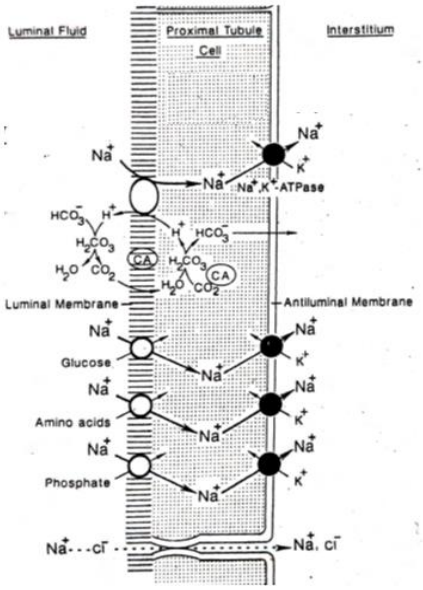
They are very water soluble or hydrophilic and they do not cross cell membrane. So they are administered intravenously.

Since osmotic diuretics increase water excretion rather than sodium excretion, they are not very effective to treat edema caused by sodium retention. Instead they are mainly used to reduce intracranial pressure, promotion of urinary excretion of toxic substances.

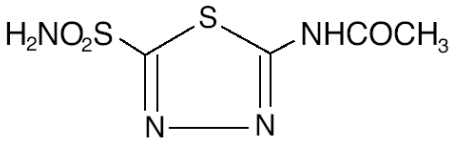
- **Carbonic anhydrase inhibitors (site 1 diuretics)**

MOA: Carbonic anhydrase inhibitors decrease proximal tubular reabsorption of HCO_3^- in the kidneys by non-competitive inhibition of luminal and cellular carbonic anhydrase.

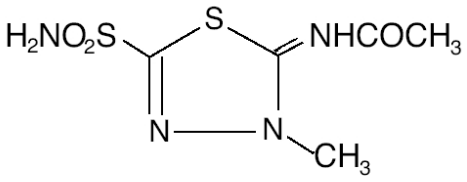




- This leads to less sodium reabsorption at this site and therefore greater sodium, bicarbonate and water loss in the urine.
- These are the weakest of the diuretics and seldom used in cardiovascular disease.
- Their main use is in the treatment of glaucoma.



Acetazolamide



Methazolamide

Acetazolamide reduces the rate of aqueous humor formation and is used to reduce the intraocular pressure in glaucoma.

Methazolamide has better penetration into the eye compared with acetazolamide.

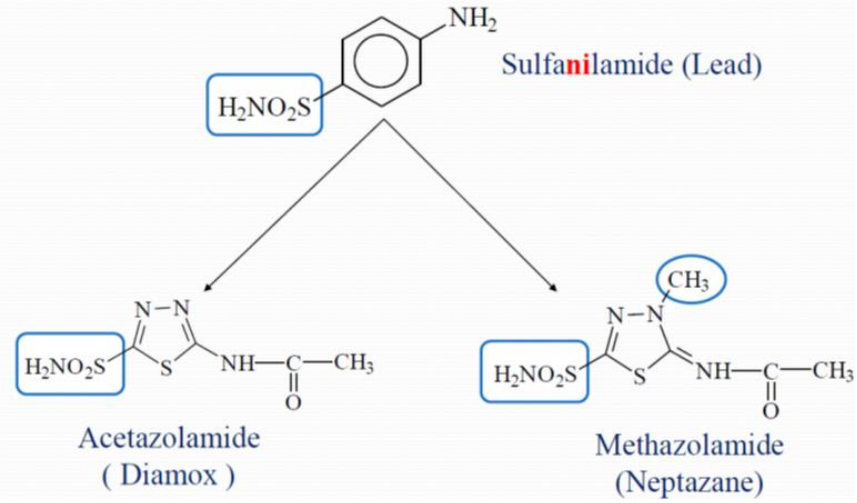
SAR

To improve the CA inhibitory property of sulfanilamide, many sulfamoyl containing ($-SO_2NH_2$) compounds were synthesized and screened for their diuretic activity and ability to inhibit CA.

Two groups of CA inhibitors emerged:

- Simple heterocyclic sulfonamides
- Metadisulfamoyl benzene derivatives

<u>Simple heterocyclic sulfonamides</u>

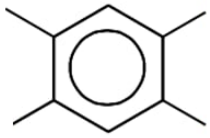


- The prototype is Acetazolamide.
- The sulfamoyl group is absolutely essential for the in vitro carbonic anhydrase inhibitory activity.
- The sulfamoyl moiety must be attached to a moiety that possess aromatic character.
- The sulfamoyl nitrogen atom must remain unsubstituted to both in vivo and in vitro activities (this feature explains why all of the antibacterial sulfonamides except sulfanilamide, are incapable of inhibiting carbonic anhydrase or exerting a diuresis).
- The derivatives with the highest lipid/water partition coefficient and lower pKa have the greatest CA inhibitory and diuretic activity.
- Substitution of a methyl group on one of the acetazolamide's ring nitrogens yield methazolamide, a product that retains carbonic anhydrase inhibitory activity and even more potent.

Metadisulfamoyl benzene derivatives

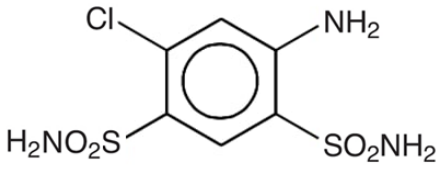
Maximal diuretic activity is observed When this position is substituted with Cl, Br, CF_3 or NO_2

Substitution with an amino group increases saluretic activity, but decreases CA inhibitory activity



SO_2NH_2 – this unsubstituted sulfamoyl group is of paramount importance

SO_2NH_2 – this sulfamoyl moiety can be replaced with a similar electrophilic group (carbonyl, carbamoyl) that may increase diuretic potency while decreasing CA inhibitory activity

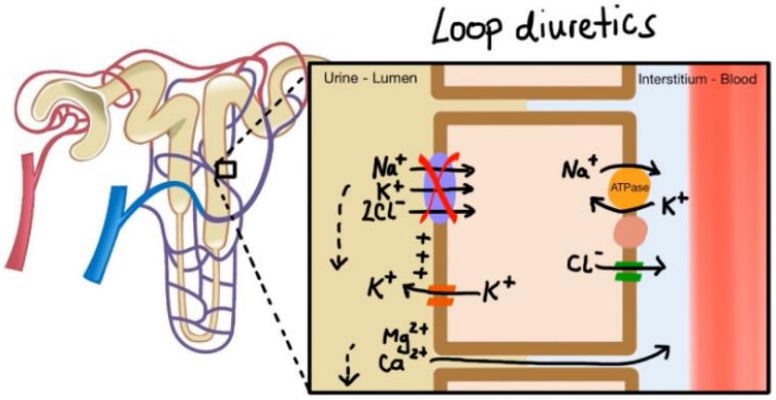


Chloraminophenamide

- **Loop diuretics (site 2 diuretics)**

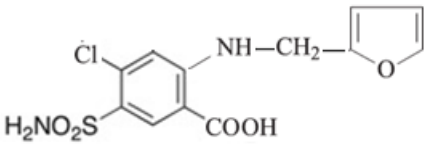
These diuretics produce a peak diuresis much greater than that observed with the other commonly used diuretics, hence the name high ceiling diuretics.

MOA: these diuretics inhibit the sodium-potassium-chloride ($Na^+/K^+/2Cl^-$) symporter located in the thick ascending limb of Loop of Henle leading to a sodium rich diuresis.

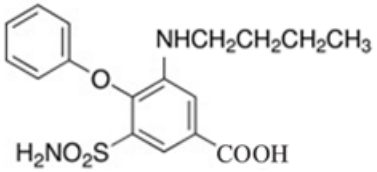


Loop diuretics include:

- The organomercurial diuretics
- The 5-sulfamoyl 2- and 3-amino benzoic acid derivatives
  e.g. Furosemide, Bumetanide

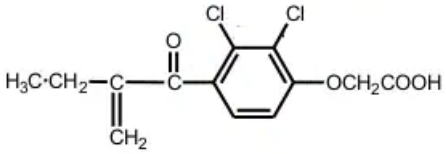


Furosemide



Bumetanide

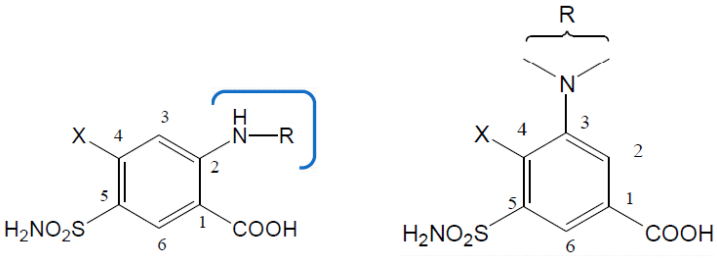
- Phenoxy acetic acid derivatives
  e.g. Ethacrynic acid



Ethacrynic acid

SAR

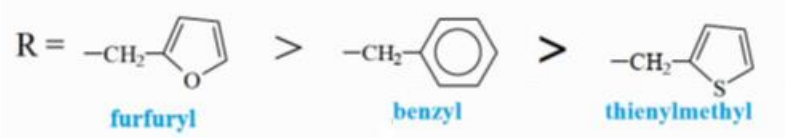
<u>5-sulfamoyl 2- and 3-amino benzoic acid derivatives</u>

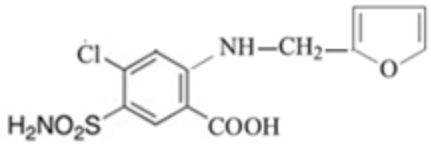


- The substituent at position 1 must be acidic. The carboxyl group provides optimal diuretic activity, but other groups, as tetrazole, may have respectable diuretic activity.
- A sulfamoyl group at the 5th position is essential for optimal high ceiling diuretic activity.
- The activating group (X) in the 4th position can be Cl- or CF_3-, a phenoxy-, alkoxy-, anilino-, benzyl- or benzoyl- group.

Major differences between the two series of 5-sulfamoyl benzoic acids is based in the nature of the functional groups that can be substituted into the 2 and 3 positions with the retention of maximum diuretic activity.

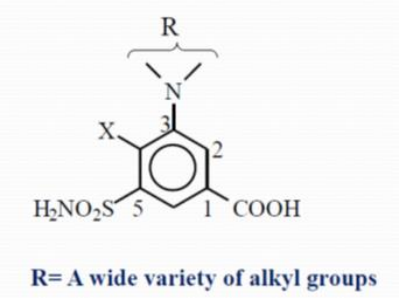
i. Substituents that can be tolerated at the 2-amino group of the 5-sulfamoyl-2-amino benzoic acid series are extremely limited, and no deviations are allowed on the few moieties that are acceptable.
For e.g. only furfuryl, benzyl and thienylmethyl (in decreasing order) yield derivatives with maximal diuretic activity.



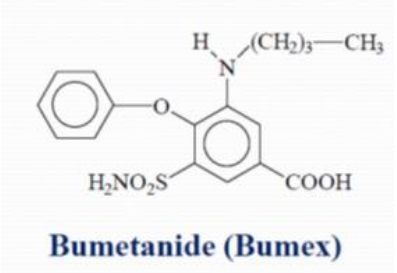


Furosemide

ii. Substituents at the 3-amino group of the 5-sulfamoyl-3-amino benzoic acid can vary widely without affecting optimal diuretic activity.

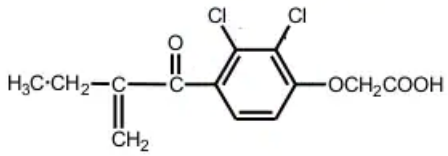


R= A wide variety of alkyl groups



Bumetanide (Bumex)

Phenoxy acetic acid derivatives



Ethacrynic acid

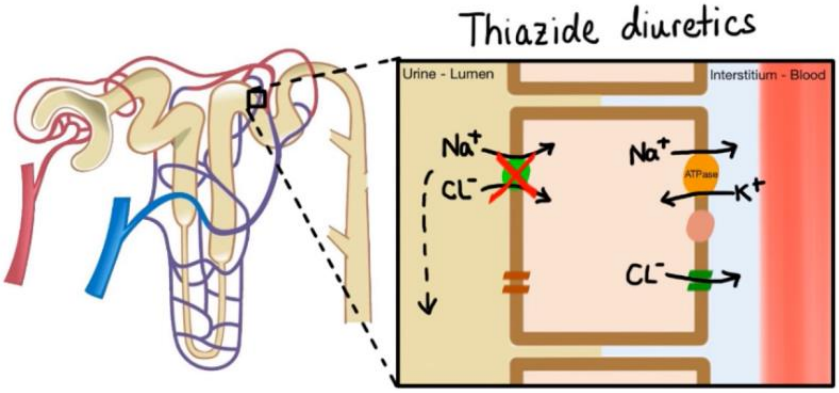
- Same uses as cited for furosemide and bumetanide.
- Ethacrynic acid is prescribed for individual who has a known hypersensitivity to sulfamoyl containing drugs

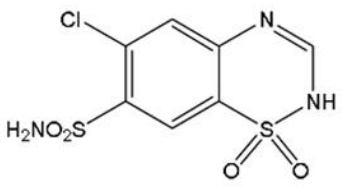
➢ Thiazide and thiazide-like diuretics (site 3 diuretics)

The thiazides were the first orally effective saluretic agents.
They were developed from cyclisation of chloraminophenamide CA inhibitor.
They inhibit the reabsorption of sodium and chloride ions. So they are referred to as saluretics.

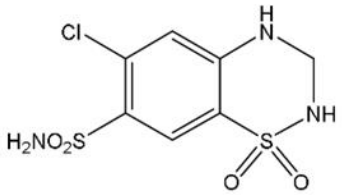
MOA

They inhibit the sodium-chloride (Na^+/Cl^-) symporter located in distal convoluted tubules.



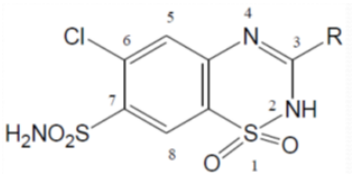


Chlorthiazide



Hydrochlorthiazide

SAR of Thiazide diuretics



- The position 2 can tolerate small alkyl groups as CH_3.
- Substituents at position 3 determine the potency and duration of action of the thiazides.
- Saturation of C-C bond between the 3 and 4 positions of the benzothiadiazine-1,1-dioxide nucleus increases the potency of this class of diuretics approximately 3-10 fold.
- Direct substitution of 4,5 or 8 positions with an alkyl group usually results in diminished diuretic activity.
- Substitution of the position 6 with an activating group is essential for diuretic activity. The best substituent include Cl, Br, CF_3 and NO_2 groups.
- The sulfamoyl group in the position 7 is essential for diuretic activity.

➢ Potassium sparing diuretics

This class of diuretics are characterized by their ability to increase Na^+ and Cl^- excretion without a concomitant increase in the urinary excretion rate of K^+ in the collecting duct.

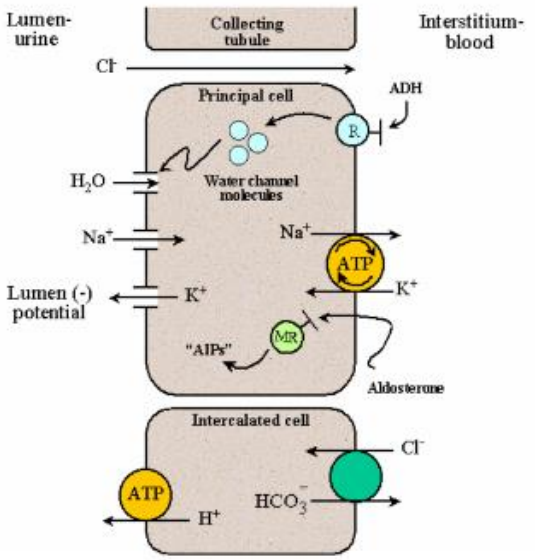
They are also known as antikaliuretic agents. They are classified into two:

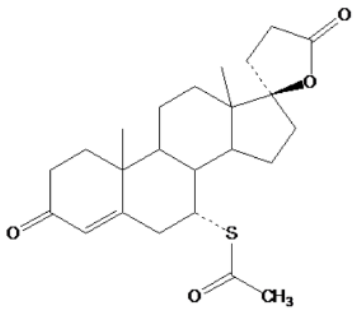
1. **Aldosterone antagonists**: Spironolactone
2. **Na^+ channel blockers**: Triamterene, Amiloride

<u>Aldosterone antagonists</u>

Aldosterone enhances the passage of Na^+ from the luminal fluid into the tubular cells and the passage of the intracellular K^+ into the luminal fluid.

These drugs antagonizes the effects of aldosterone and can be good diuretics.





Spironolactone

MOA: Spironolactone is a competitive antagonist to the mineralocortocoids such as aldosterone on its receptor. This lead to inhibition of reabsorption of Na^+ and Cl^- as well as the associated water.

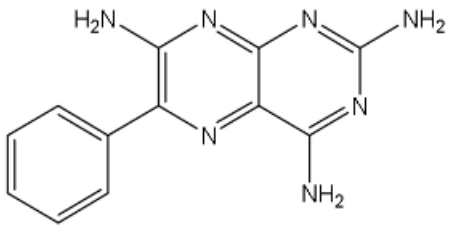
Use:

Particularly useful in primary aldosteronism and secondary aldosteronism.

It is the drug of choice in hepatic cirrhosis.

<u>Na^+ channel blockers</u>

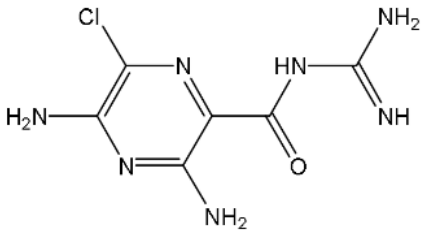
a. **Pteridine derivatives**



Triamterene

MOA: It interferes with the process of cationic exchange by blocking luminal Na^+ channel in the DCT. This blocks the reabsorption of Na^+ and also blocks the secretion of K^+ without antagonizing the aldosterone.

b. **Pyrazinoyl guanidines**

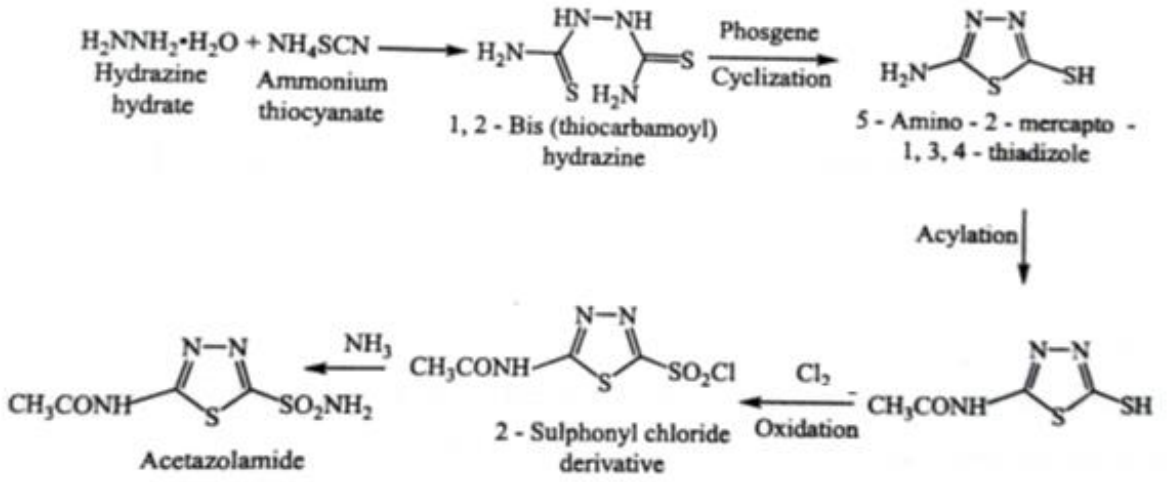


Amiloride

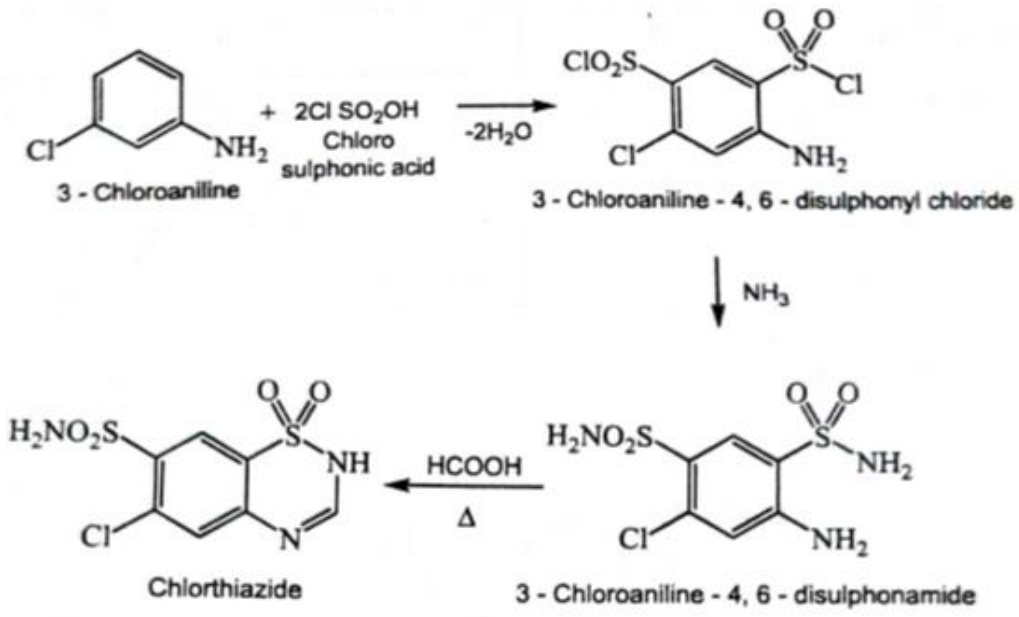
It is the open chain analog of triamterene acting with the same mode of action.

Synthesis

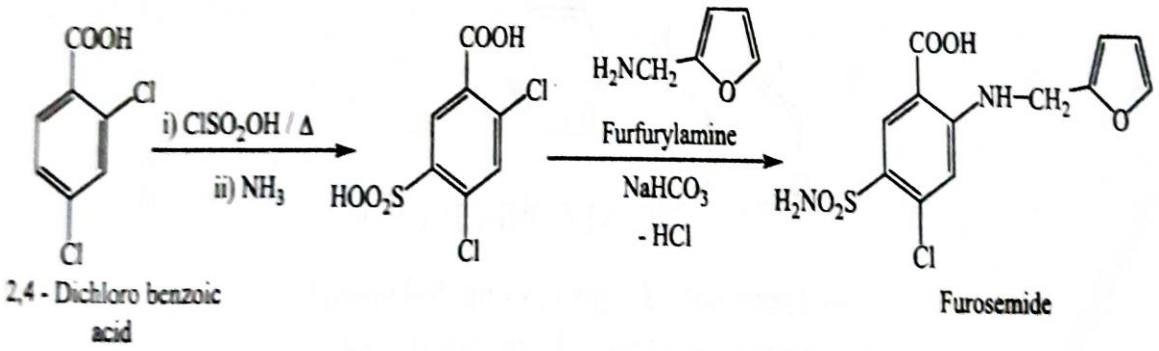
1. **Acetazolamide**



2. **Chlorthiazide**



3. Furosemide



2,4 - Dichloro benzoic acid

Furosemide