4 DIURETICS

OBJECTIVES

Carbonic Anhydrase Inhibitors
Thiazide Diuretics
Loop Diuretics
Potassium Sparing Diuretics
Osmotic Diuretics

INTRODUCTION

Diuretics are the chemical agents which increase the excretion of urine by kidneys. They lead to the secretion of excess water and salt that accumulate in tissues and urine, results in decrease in body fluids especially the extracellular fluid. So, diuretics are used in management of heart failure, odema or hypertension.

The functional unit of kidney is nephron where urine is formed. Nephron consists of two anatomical parts i.e. glomerulus and tubule. The glomerulus part is closed, cup shaphed and known as Bowman's capsule. The tubule consists of three parts namely proximal convoluted tubule, the loop of Henle and the distal convoluted tubule, leading into a collecting tubule.

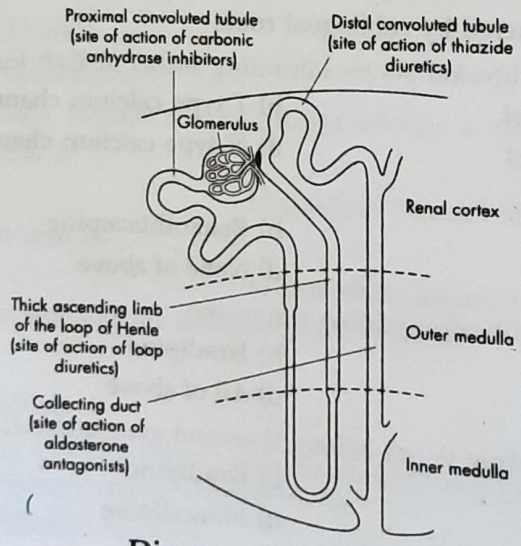


Diagram of Nephron

As the blood reaches at glomerular, it is filtered by Bowman's capsule. After filteration, the filterate reaches at proximal convoluted tubule where the reabsorption of sodium, chloride, calcium ions, bicarbonate and phosphate ions, amino acids and low molecular weight proteins takes place. Loop of Henle is the place where filterate becomes diluted due to half of the sodium and chloride ions are reabsorbed. The another site where sodium ions are reab-

sorbed is distal convoluted tubule by cation exchange which is under the control of aldosterone. The last and final site where the sodium ions reabsorption takes place is collecting tubule. Here, sodium ions from renal tubular fluid is exchanged for potassium ions and to a lesser extent with hydrogen ions from blood.

The tubule normally reabsorb over 90% of the glomerular filterate, the rest of the filterate and tubular secretions pass into the bladder and are voided as urine.

CLASSIFICATION

Diuretics are classified as follows :

DIURETICS

Carbonic Anhydrase Inhibitors
- Acetazolamide
- Methazolamide
- Dichlorphenamide

Thiazides
- Chlorthiazide
- Hydrochlorthiazide
- Hydroflumethiazide
- Cyclothiazide
- Bendro fluazide
- Poly thiazide
- Indapamide
- Chlortalidone
- Quinethazone
- Metolazone

Loop Diuretics or High Ceiling Diuretics
- Furosemide
- Bumetamide
- Ethacrynic acid

Potassium Sparing Diuretics
- Spironolactone
- Triameterene
- Amiloride

Osmotic Diuretics
- Mannitol
- Urea
- Glycerol
- Isosorbide

A) CARBONIC ANHYDRASE INHIBITORS

Carbonic anhydrase is an enzyme which is involved in the conversion of CO_2 and H_2O into H^+ and HCO_3^-. H^+ gets exchanged with sodium ions while the HCO_3^- gets reabsorbed

$$CO_2 + H_2O \underset{\text{Anhydrase}}{\overset{\text{Carbonic}}{\rightleftharpoons}} H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

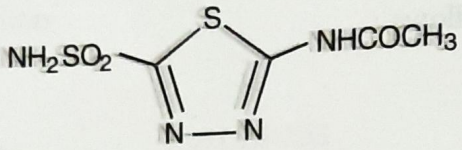
Blockage of this enzyme decreases the exchange of H^+–Na^+ ions and hence make the urine more alkaline and there is large excretion of Na^+ and HCO_3^- ions. Inhibition of carbonic anhydrase inhibits reabsorption of HCO_3^- and there is accumulation of HCO_3^- in the tubular lumen. There is decrease in amount of H^+ ions available for exchange with Na^+. So large amount of Na^+ ions retained in the tubule and gets excreted by the kidney with an increased volume of water. There is also significant loss of K^+. The urine which is normally acidic becomes alkaline and systemic acidosis occurs. During acidosis, the carbonic anhydrase inhibitors are not effective till the acid-base balance is restored.

The carbonic anhydrase is also present in number of intraocular structures including the ciliary processes which produce high concentrations of bicarbonate in aqueous humour. So

the inhibition of carbonic anhydrase reduces the rate of aqueous humour formation and causes reduction of intraocular pressure.

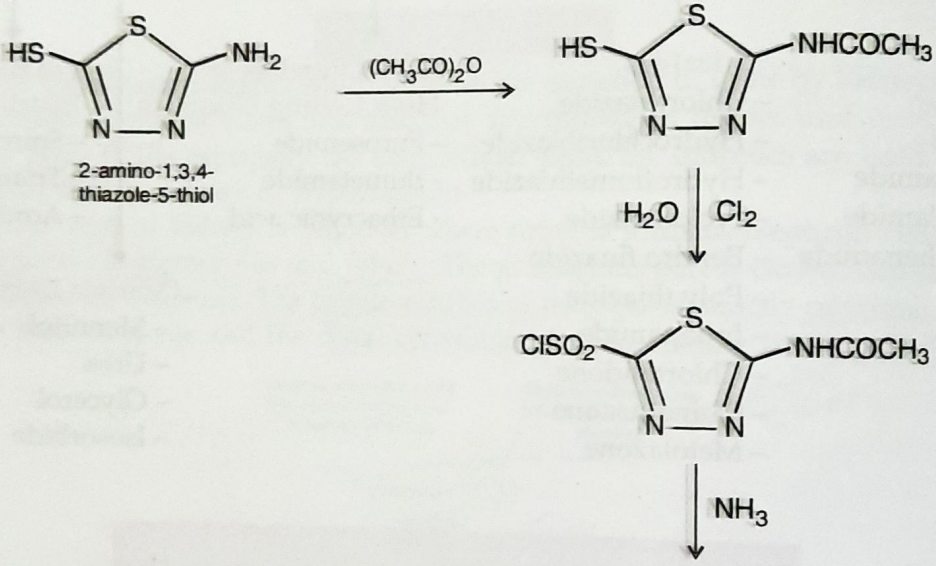
Mostly all the carbonic anhydrase inhibitors have unsubstituted sulphamoyl group (RSO_2NH_2). Substitution on the sulphamoyl group gives inactive compounds. Moreover for high carbonic anhydrase inhibition the unsubstituted sulphamoyl group is attached to an aromatic ring. The drugs belonging to this category are described as follows :

1) Acetazolamide



IUPAC Name : N–(5-sulphamoyl-1,3,4-thiadiazol-2-yl)acetamide.

Synthesis :



Properties : It is a white crystalline powder, slightly soluble in water. It is rapidly absorbed after oral administration. It is not metabolised and excreted unchanged in urine.

Mechanism of Action :

1. It inhibits carbonic anhydrase, causing reduction of hydrogen ions for active transport in the tubule lumen which leads to excretion of bicarbonate, sodium, potassium and water.
2. The anticonvulsant activity of this drug depends on direct inhibition of carbonic anhydrase in the CNS, which decrease carbon dioxide tension in the pulmonary alveoli thus increases arterial oxygen tension.

Uses :

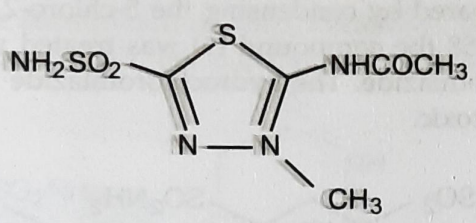
1. It is used in the treatment of glaucoma and drug induced edema.
2. It is also used as an anticonvulsant for treatment of epilepsy.

3. It has also been used in the treatment of Meniere's disease (disorder of inner ear), attitude sickness and neuromuscular disorders.

Structure Activity Relationship (SAR)

1. The unsubstituted sulphamoyl group is essential for the activity.
2. The sulphamoyl group must attached to aromatic ring.
3. Substitution of a methyl group on one of the acetazolamide's ring nitrogens yields methazolamide which also retain carbonic anhydrase inhibitor activity.

2) Methazolamide



IUPAC Name : N-[5-(amino sulphonyl)-3-methyl 1,3,4-thiadiazol-2-ylidene] acetamide.

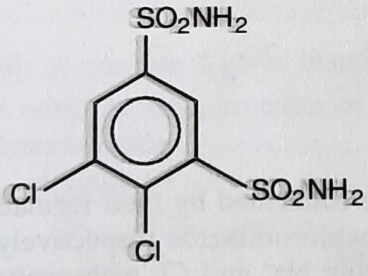
Properties : It is white crystalline solid having melting point 213.5°C. It is freely soluble in water. Methazolamide is well absorbed from the G.I.T. when given orally. It's metabolism and route of excretion is unknown. It should be stored in well closed containers at 15° to 30°C.

Mechanism of Action : It is a potent carbonic anhydrase inhibitor in the cilliary muscle which results in decrease aqueous humor secretion by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport.

Uses :

1. It is used as a diuretic.
2. It is used in the treatment of glaucoma.
3. It is also having antineoplastic activity.

3) Dichlorphenamide



IUPAC Name : 4,5-dichloro-1,3-benzenedisulphonamide.

Properties : It is a white or almost white crystalline powder, having m.pt. 228.5°C, slightly characteristic odor, practicaly insoluble in water and soluble in alkaline solution. It is freely soluble in pyridine, 1N NaOH, in alcohol and in 2N sodium carbonate solution. Its absorption, metabolism and route of excretion is not well known.

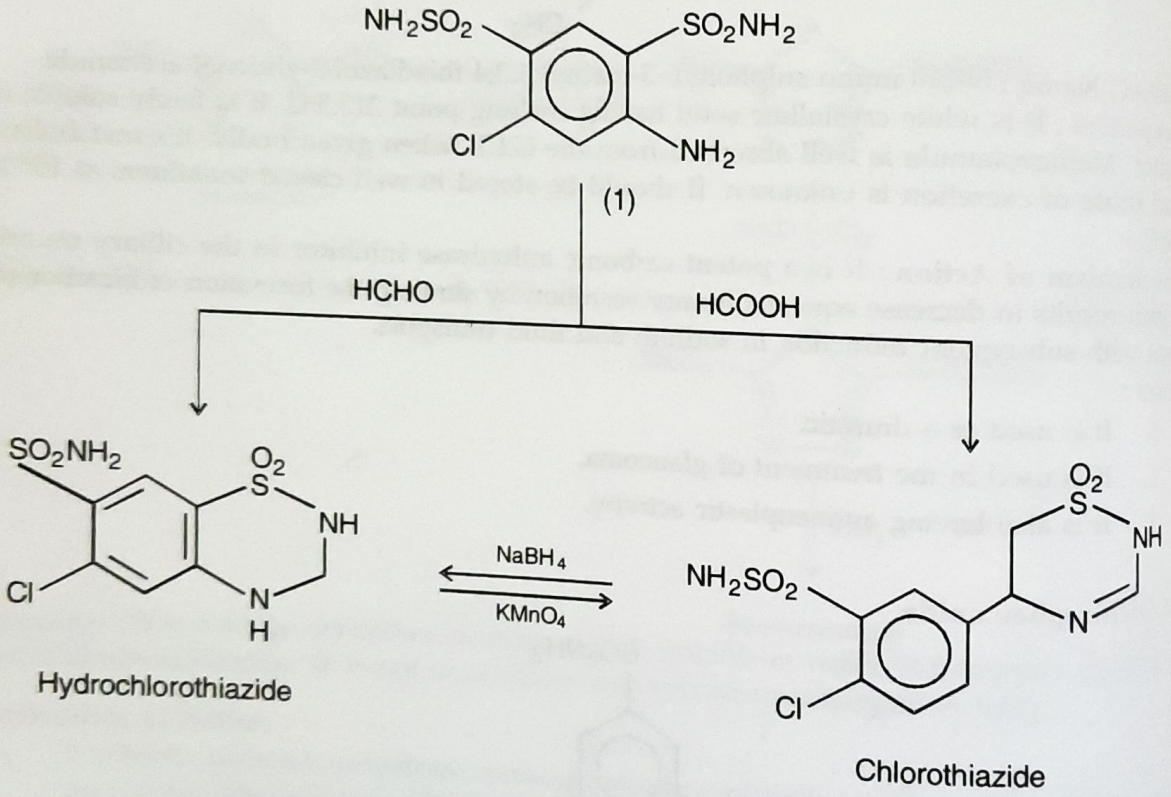
Mechanism of Action : Its action is similar to acetazolamide but causes excretion of less bicarbonate and more chloride ions along with sodium ions.

Uses :

1. It is used in the treatment of glaucoma.
2. It is found effective in cases of therapy resistant epilepsy.
3. It is also used as diuretic.

B) THIAZIDE DIURETICS

In 1955, chlorothiazide was prepared by condensing the 5-chloro-2,4-disulphamoyl aniline (1) with formic acid. Later in 1958 the compound (1) was treated with formaldehyde and gets cyclized to give hydrochlorothiazide. The hydrochlorothiazide was much more potent than chlorthiazide and was less toxic.



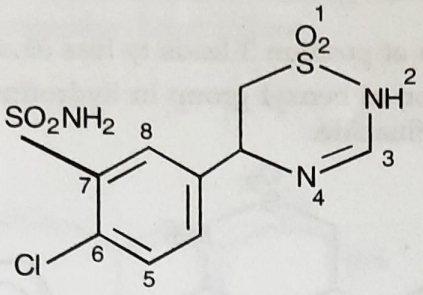
Hydrochlorothiazide

Chlorothiazide

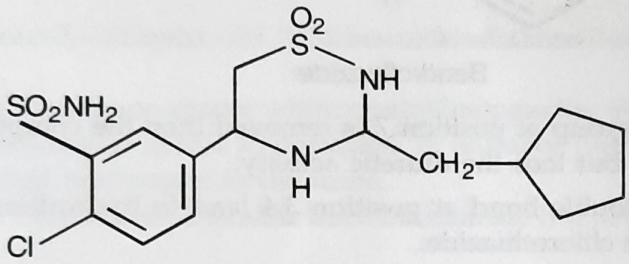
Both the thiazide structures were confirmed by their formation by the reduction and oxidation of chlorothiazide and hydrochlorothiazide respectively.

Thiazide diuretics acts by inhibiting Na^+ and Cl^- reabsorption at distal tubules. This inhibition increases Ca^{2+} reabsorption in the distal tubule and thus increases the activity of Na^+-Ca^{2+} exchanger and ultimately inhibits the entery of Na^+ iions and decreases plasma volume which results in increase in excretion of sodium chloride, water, potassium and bicarbonate ions.

STRUCTURE ACTIVITY RELATIONSHIP (SAR)

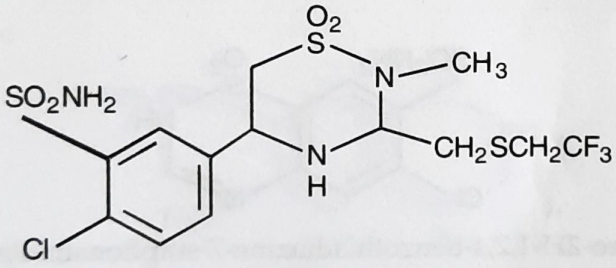


1. At position 3 the substitution of alkyl, cycloalkyl, haloalkyl and oralkyl groups give potent diuretic compound. For e.g. Cyclopenthiazide.



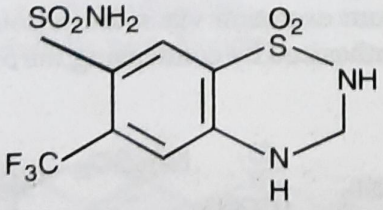
Cyclopenthiazide

2. Substitution at position 2 and 3 gives highly potent compound for e.g. Polythiazide.



Polythiazide

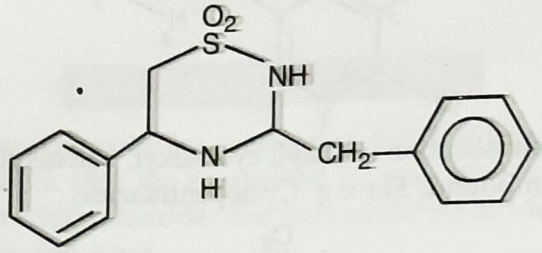
3. Substitution of alkyl group at position 4 gives inactive compound.
4. Substitution at position 6 with chlorine, bromine or fluorine give highly active compound. For e.g. Hydroflumethiazide.



Hydroflumethiazide

5. At position 7 free sulphamoyl group (NH_2SO_2) is essential for diuretic activity.

6. If methylation or acylation iis done at position 7, it decreases or completely loose the activity.
7. Introduction of oxygen at position 3 leads to loss of activity.
8. Further the introduction of benzyl group in hydroflumethazide gives highly active compound i.e. Bendrofluazide.

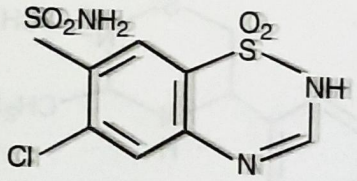


Bendrofluazide

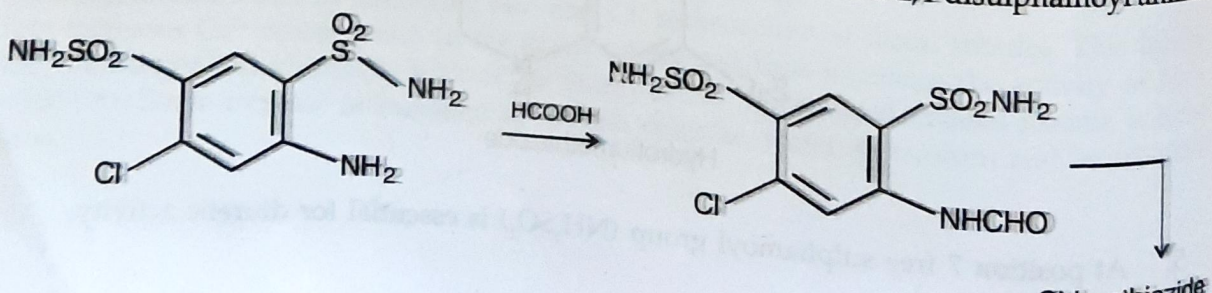
9. If Sulphamido group at position 7 is removed then the compound retain antihypertensive activity but loos the diuretic activity.
10. Reduction of double bond at position 3,4 lead to hydrothiazides which are more potent than the chlorothiazide.

The official drugs in this category are described as follows :

1) Chlorothiazide



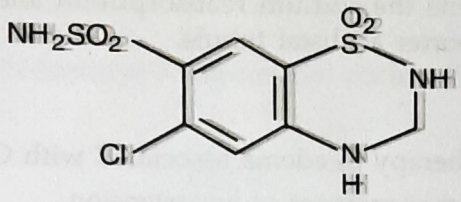
IUPAC Name : 6-chloro-2H-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide.
Properties : It is a white or almost white crystalline powder, very slightly soluble in water and soluble in alkali hydroxide solutions. It is partially or incompletely absorbed and excreted unchanged in the urine.
Mechanism of Action : Chlorothiazide inhibits chloride reabsorption at distal tubule results in an increase of sodium, chloride and water excretion. It also inhibit sodium ion transport across the renal tubule by binding to the thiazide sensitive sodium chloride transport which results in an increase in potassium excretion via sodium potassium exchange mechanism.
Synthesis : Chlorothiazide is synthesized by condensing the 5-chloro-2,4-disulphamoyl aniline with formic acid.



Chlorothiazide

Use : Chlorothiazide is used as diuretic and as an antihypertensive. It is also used to manage excess fluid associated with congestive heart failure.

2) Hydrochlorothiazide



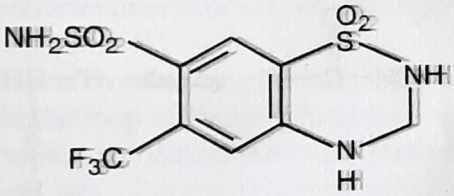
IUPAC Name : 6-chloro-3,4-dihydro-2H,1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide

Properties : This drug is white or almost white crystalline powder, slightly soluble in water, soluble in dilute solutions of alkali hydroxides. It is fairly rapidly absorbed but not metabolised and excreted unchanged in the urine.

Mechanism of Action : It's action is similar to chlorothiazide but it is more potent than the chlorothiazide.

Use : It is used as a diuretic or as an antihypertensive drug. It is given with potassium supplements due to excessive loss of potassium ions in the routine treatment of hypertension.

3) Hydroflumethiazide



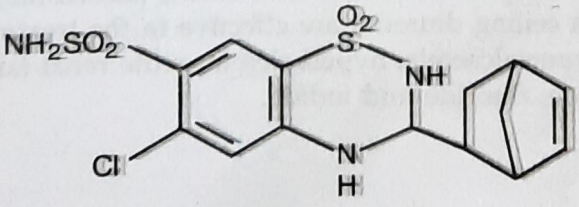
IUPAC Name : 3,4-Dihydro-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide.

Properties : It is a white or almost white crystalline powder, practically insoluble in water. It is fairly rapidly absorbed orally and produces a metabolite which binds to the red blood cells. It is excreted in urine.

Mechanism of Action : Similar to chlorothiazide.

Use : It is used as an antihypertensive and diuretic.

4) Cyclothiazide



IUPAC Name : 3-(bicyclo [2,2,1] hept-5-en-2-yl)-6-chloro-3,4-dihydro-2H-1,2,4 bennzothiadiazine-7-sulphonamide-1,1-dioxide.

Properties : It is a white or almost white powder odorless in nature, having m.pt. 230°C. It is practically insoluble in water, chloroform and ether but freely soluble in acetone, methanol and ethyl acetate.

Mechanism of Action : It inhibits the sodium reabsorptionn and water reabsorption by inhibiting sodium chloride symporter at distal tubule.

Uses :

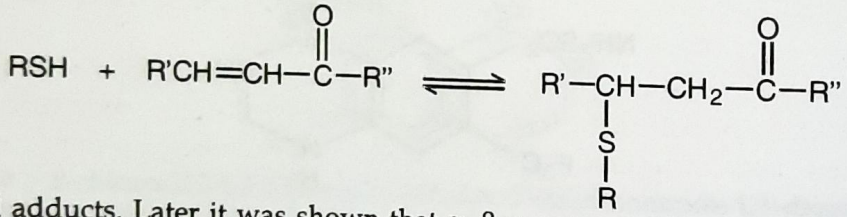
1. It is used as diuretic.
2. It is given as adjunctive therapy in edema associated with CHF.
3. It is also indicated in the management of hypertension.

C) LOOP DIURETICS (HIGH CEILING DIURETICS)

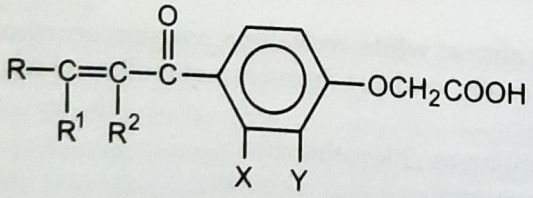
Loop diuretic acts mainly at thick ascending limb of the loop of Henle. These diuretics produce peak diuresis which is much greater than other diuretics.

Loop diuretics inhibit reabsorption of Na^+, Cl^- and K^+ ions by inhibiting $Na^+/K^+/2Cl^-$ symport of the thick ascending limb of loop of Henle. By inhibiting $Na^+/K^+/2Cl^-$ symport, these agents also inhibit reabsorption of Ca^{++} and Mg^{++}.

Earlier it was investigated that organomercurial diuretics acted by blocking renal enzymes possessinng sulphadryl (–SH) groups.

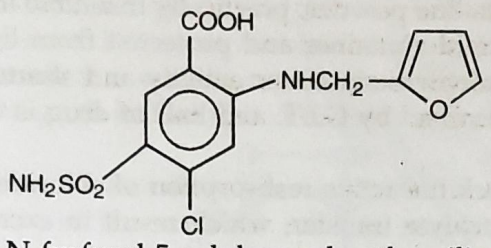


It makes thiol adducts. Later it was shown that α, β unsaturated ketones derivatives having a carboxylic acid group had significant diuretic activity.



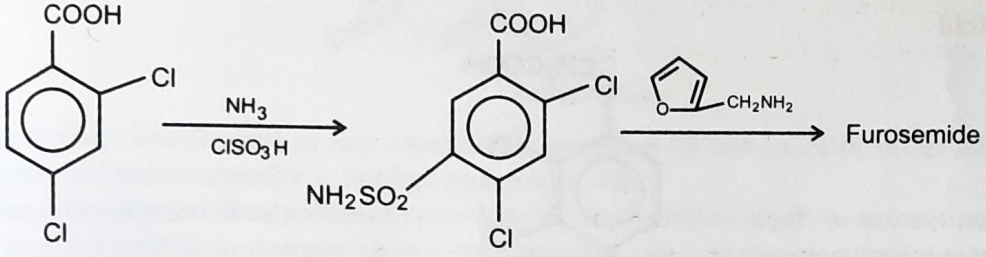
The most effective compounds in this category are ethacrymic acid, furosemide and Bumentanide. The other Loop diuretics are torasenide, azosemide, muzolimine, tripamide and piretanide. The high ceiling diuretics are effective in the treatment of acute pulmonary odema, hypertension, hypercalcaemia, hyperkalemia, acute renal failure and in treatment of toxic ingestion of bromide, fluoride and iodide.

1) Furosemide



IUPAC Name : 4-chloro-N-furfuryl-5-sulphamoyl anthranilic acid.

Synthesis :



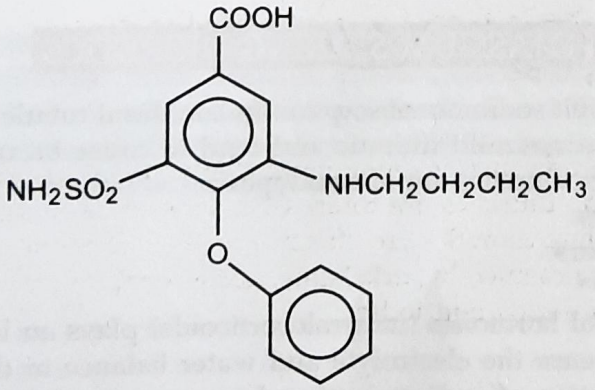
2,4-Dichloro benzoic acid

Properties : Furosemide is a white or almost white crystalline powder, practically insoluble in water and stored in well closed light resistant container. It is readily absorbed from the G.I.T. with bioavailability 60 to 70%. It is excreted unchanged and to a lesser extent as a glucuronide conjugate in urine. Furosemide has shorter time of onset and duration of action as compared to thiazides diuretics.

Mechanism of Action : Furosemide acts by inhibiting electrolyte reabsorption in the nephron by blocking $Na^+/K^+/2Cl^-$ symport in the loop of Henle which results in more hypertonic and interstition becomes less hypertonic, so diminishes the osmotic gradient for water reabsorption throughout the nephron.

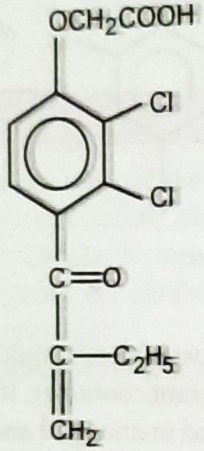
Use : It is used as a diuretic for the treatment of odema, hypertension and congestive heart failure. It is having weak carbonic anhydrase inhibitor activity.

2) Bumetanide



IUPAC Name : 3-Butylamino-4-phenoxy-5-sulphamoylbenzoic acid.
Properties : It is a white crystalline powder, practically insoluble in water, soluble in alkali solutions. It is stored in air-tight container and protected from light. Like furosemide, it also having weak carbonic anhydrase inhibitor activity and shorter onset of time and duration of action. It is readily absorbed by G.I.T. and half of drug is excreted unchanged in urine with some metabolites.
Mechanism of Action : It block the active reabsorption of chloride and sodium in ascending loop of Henle and alter electrolyte transfer, which result in excretion of sodium, chloride and water and hence reduces diuresis.
Use : Bumetanide is used in treatment of oedema and hypertension.

3) Ethacynic Acid



IUPAC Name : [2,3-Dichloro-4-(2-ethylacryloyl)phenoxy]acetic acid.
Properties : It is a white or almost white crystalline powder, slightly soluble in water, soluble in alkali hydroxide and carbonate solution. It is readily absorbed by G.I.T. and two thirds of it is excreted by the kidney and the rest by the liver. It is excreted as unchanged or as conjugate with sulphadryl compounds mainly cysteine and N-acetylcysteine. It does not have any carbonic anhydrase inhibitor activity.
Mechanism of Action : It's action is similar to furosemide and bumetanide.
Use : It is used as diuretic to treat oedema and hypertension.

D) POTASSIUM SPARING DIURETICS

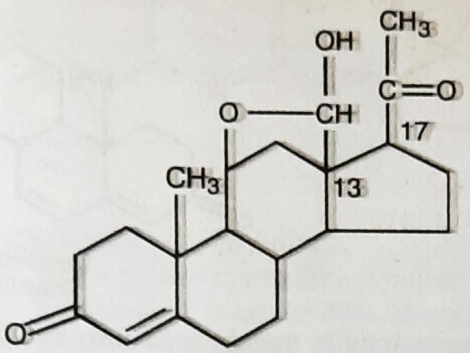
These type of diuretics inhibit sodium reabsorption in late distal tubule and indirectly spare potassium excretion. These are mild diuretic and tend to cause bicarbonate loss but not chloride. Potassium sparing diuretics are of two types :

1) Aldosterone Antagonists
2) Sodium Channel Inhibitors

1) Aldosterone Antagonists

The adrenal cortex steroidal hormones (mineralocorticoids) plays an important role in the body. Some of them influence the electrolyte and water balance in the body. These hormones increase the absorption of sodium ions and increase the urinary excretion of both

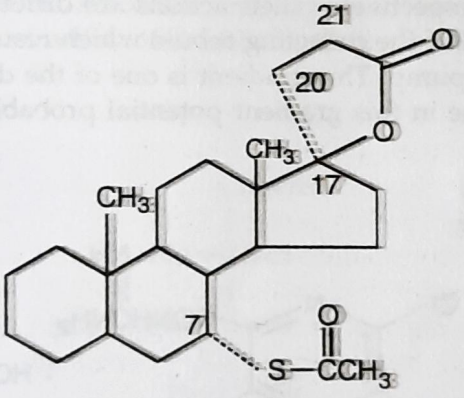
potassium and hydrogen ions. Among all the adrenal cortex hormones, aldosterone is most potent.



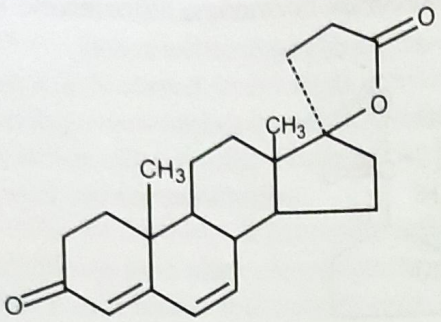
Aldosterone

Aldosterone has formyl group attached to position 13 where as in other natural occuring steroids there is normally a methyl group at C-18.
It was investigated that spironalctone was the drug which binds to mineralocorticoid receptor and prevent it to assume active confirmation, since these receptors exists in active and inactive allosteric confirmations. So, spironolactone act as a competitive antagonist and spare the potassium ions, increase the excretion of sodium, water and calcium ions.

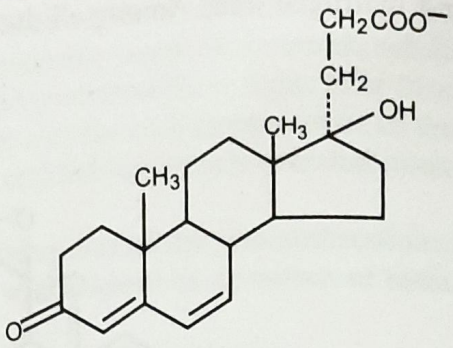
1) Spironolactone



IUPAC Name : 7α-Acetylthio-3-oxo-17α-pregn-4-ene-21,17β-carbolactone.
Properties : It is a yellowish white coloured powder, odourless and exhibits polymorphism. It is practically insoluble in water and stored in well closed light resistant container. It is fairly rapidly absorbed from G.I.T. Spironolactone is metabolised to canrenone and canrenoate in which canrenone is the active metabolite.



Canrenone
(Active)



Canrenoate
(Inactive)

Mechanism of Action : Spironolactone is metabolised into canrenone which compete with aldosterone for binding to aldosterone receptors which results in excretion of sodium and decrease in potassium excretion.

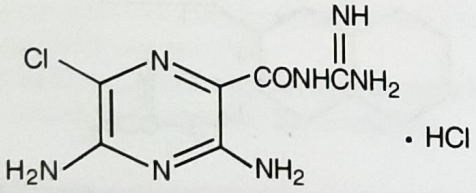
Uses :

1. It is used in the treatment of refractory oedema associated with nephrotic syndrome, CHF and cirrhosis of liver.
2. It is used to spare the potassium ions with other diuretic agents.

2) Sodium Channel Inhibitors

Amiloride and Triamterene are the two drugs in this class. These drugs are the derivatives of pyrazine and pteridine respectively. Their actions are different than the spironolactone. They inhibit sodium channel of the collecting tubule which results in fall of electro-chemical gradient created by sodium pump. This gradient is one of the driving forces for secretion of potassium ions. The decrease in this gradient potential probably decreases the secretion of potassium ions.

1) Amiloride Hydrochloride



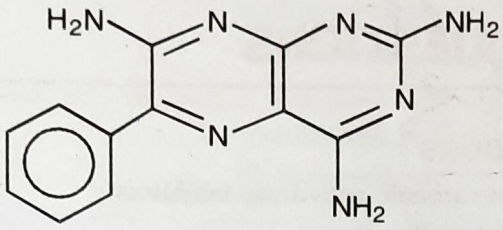
IUPAC Name : N-Amidino-3,5-diamino-6-chloropyrazine-2-carboxamide hydrochloride

Properties : It is a pale yellow to greenish yellow powder, slightly soluble in water and kept in well closed light resistant container. Aniloride is a strong base (pKa 8.67). Aniloride is given orally and about half of the drug is absorbed. It is not metabolised and excreted unchanged in urine.

Mechanism of Action : Amiloride inhibits sodium reabsorption at distal convoluted tubule and collecting duct, thus decreases the potential gradient and reduces both potassium and hydrogen secretion.

Use : In conjunction with other diuretics it is used in the treatment of refractory oedema associated with nephrotic syndrome, cirrhosis of liver and CHF.

2) Triamterene



IUPAC Name : 2,4,7-Triamino-6-phenyl-peteridine.

Properties : It is a weak base. It is a yellow crystalline powder, slightly soluble in water, kept in well closed light resistant container. It is about 50% absorbed when given orally, extensively metabolised and is excreted unchanged in urine and some gets metabolised.

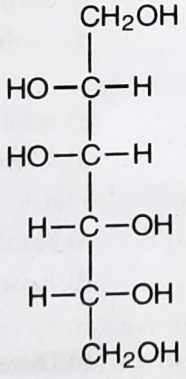
Mechanism of Action : Its action is similar to Amiloride hydrochloride.

Use : It is used as diuretic in treatment of refractory oedema.

E) OSMOTIC DIURETICS

Osmotic diuretics acts by increasing the osmotic pressure of tubular fluid. These agents are freely filterable at the glomerulus and have limited tubular reabsorption. When these agents are administered in high concentration, it results in passing of large quantity of water from the body into the tubule and this results in diuresis. Some exmaples of osmotic diuretics include Urea, Mannitol, Sorbitol, Isosorbide and Glycerol. Isosorbide and glycerol are used mainly in glaucoma. The site of action of osmotic diuretics is proximal tubule, loop of Henle and collecting tubule.

1) Mannitol



IUPAC Name : (2R, 3R, 4R, 5R)-Hexane-1,2,3,4,5,6-hexol

Properties : It is a white crystalline powder freely soluble in water. It is absorbed in small amount from G.I.T. After intravenous administration it is rapidly excreted in the urine.

Uses :

1. Mannitol is used as diagnostic agent for kidney function.
2. It is often used in the management of cerebral oedema.
3. It is used to increase urine volume in patient with acute renal failure.

REVIEW QUESTIONS

SHORT ANSWER QUESTIONS

Q.1. Write a short note on carbonic anhydrase inhibitors.
Q.2. Explain SAR of Thiazide diuretics.
Q.3. Write synthesis off furosemide and chlorthiazide.
Q.4. What are loop diuretics? Write a note on furosemide.
Q.5. Give a short note on Aldosterone antagonist.

LONG ANSWER QUESTIONS

Q.1. What are diuretics? Classify them. Explain carbonic anhydrase inhibitors.
Q.2. Write structure, mechanism of action and uses of-
1) Acetazolamide 2) Hydrochlorothiazide
3) Mannitol 4) Furosemide
5) Spironolactone
Q.3. Write a note on-
a) Carbonic anhydrase inhibitors
b) Potassium sparing diuretics

MULTIPLE CHOICE QUESTIONS

Q.1. Bumetanide belongs to which class-
a) Loop diuretics b) Osmotic diuretics
c) Potassium sparing diuretics d) Carbonic - Anhydrase inhibitors

Q.2. Mechanism of action of furosemide is-
a) Osmotic diuretic b) Inhibits $Na^+/K^+/2Cl^-$ symport
c) Inhibits carbonic anhydrase d) Competitive inhibit aldosterone

Q.3. Which of the following diuretic compete with aldosterone?
a) Furosemide b) Amiloride
c) Spironolactone d) Isosorbide

Q.4. Thiazide diuretics acts on-
a) Loop of Henle b) Distal tubule
c) Collecting tubule d) Proximal tubule

Q.5. Which one of the following act on loop of Henle?
a) Ethacrynic acid b) Dichlorophenamide
c) Spironolactone d) Acetazolamide

Q.6. Which one of the following is osmotic diuretic-
a) Glycerol b) Mannitol
c) Isosorbide d) All of above

Q.7. Which of the following is carbonic anhydrase inhibitor?
a) Triamterene
b) Chlorthiazide
c) Acetazolamide
d) Amiloride

Q.8. All of the following diuretics are used in treatment of glaucoma except-
a) Glycerol
b) Methazolamide
c) Acetazolamide
d) Furosemmide

Q.9. Which of the following diuretics is appropriate for treating acute pulmonary oedema?
a) Osmotic diuretics
b) Potassium sparing diuretics
c) Loop diuretics
d) Triazide diuretics

Q.10. Among the following which is having furfural moiety
a) Acetazolamide
b) Furasemide
c) Bumetanide
d) Spironolactone

Q.11. Potassium sparing diuretics inhibits the-
a) Sodium reabsorption
b) Potassium reabsorption
c) Chloride reabsorption
d) Calcium reabsorption

Q.12. Which of the following metabolite of spirono ketone is active?
a) Canrenoate
b) Canrenone
c) 7-methyl cysteine
d) Both a) and b)

Q.13. Sodium channel inhibitors acts by-
a) Increasing potential gradient
b) Decreasing potential gradient
c) Inhibit sodium channel
d) Both b) and c)

Q.14. Which of the following is pteridine derivative-
a) Amiloride
b) Triamterene
c) Mannitol
d) Isosorbide

Q.15. Which of the following have benzothiadiazine moiety-
a) Chloro thiazide
b) Hydro flumethiazide
c) Cyclo thiazide
d) All of above

ANSWERS

1.a)	2.b)	3.c)	4.b)	5.a)	6.d)
7.c)	8.d)	9.c)	10.b)	11.a)	12.b)
13.d)	14.b)	15.d)			