Chemical Classification and Synthesis of Diuretics

SUBJECT- PHARMACEUTICAL CHEMISTRY-VII (4T2)

PRESENTED BY:

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ASST. PROF. (CONTRACT)

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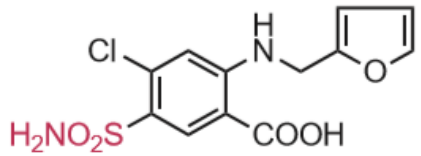
Chemical Classification

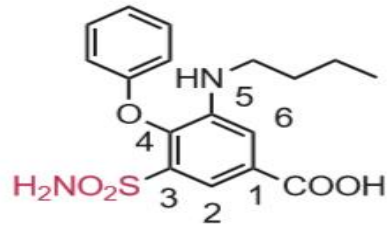
1. Loop diuretics-

(i) Furosemide



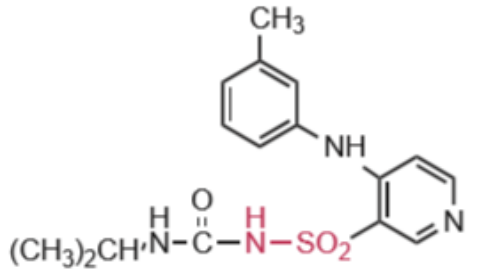
Furosemide

(ii) Bumetanide



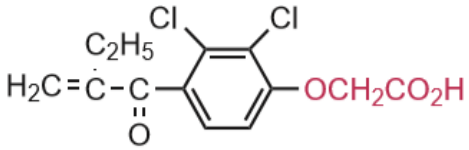
Bumetanide

(iii) Torsemide



Torsemide

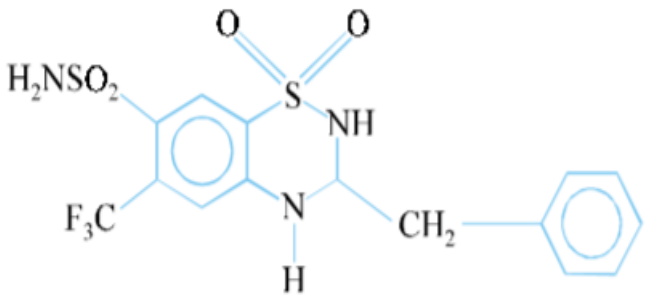
(iv) Ethacrynic acid



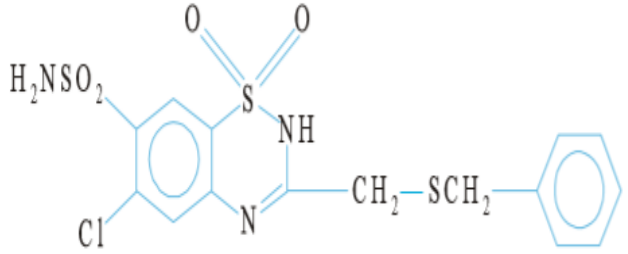
Ethacrynic acid

2. Thiazide diuretics-

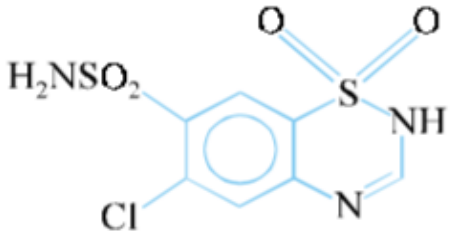
(i) Bendroflumethiazide



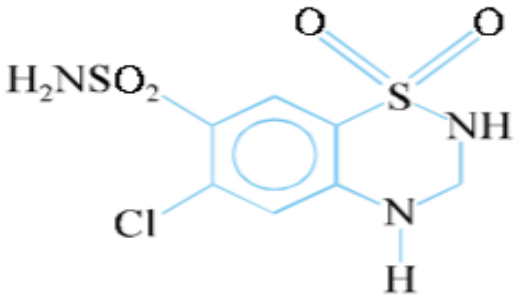
(ii) Benzthiazide



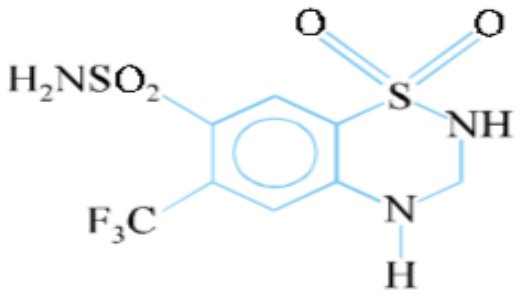
(iii) Chlorothiazide



(iv) Hydrochlorothiazide

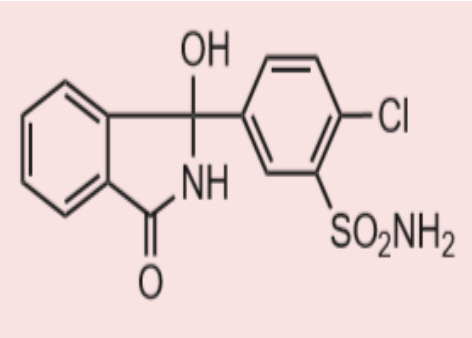


(v) Hydroflumethiazide

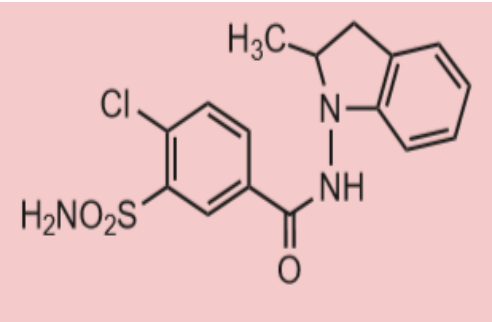


3. Thiazide-like diuretics-

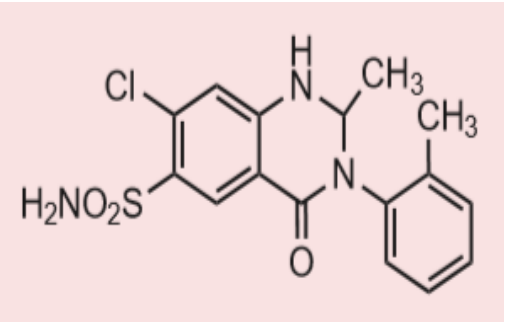
(i) Chlorthalidone



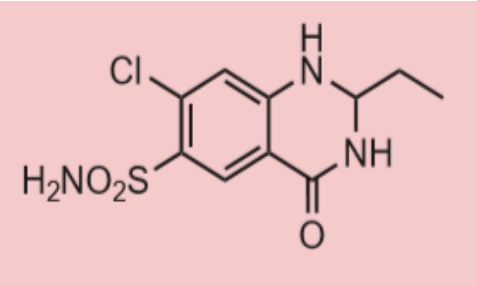
(ii) Indapamide



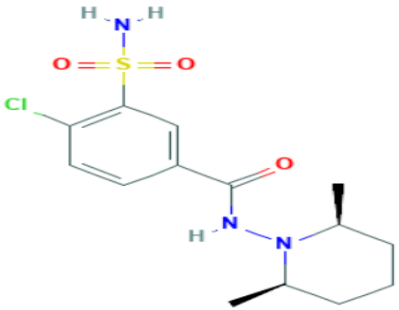
(iii) Metolazone



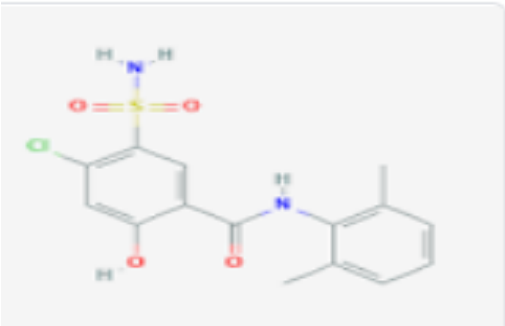
(iv) Quinethazone.



(v) Clopamide

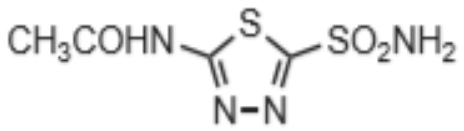


(vi) Xipamide



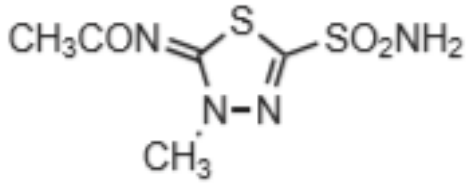
4. Carbonic anhydrase inhibitors-

(i) Acetazolamide



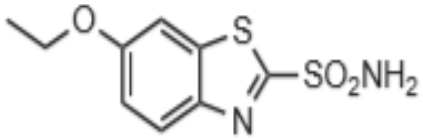
Acetazolamide

(ii) Methazolamide



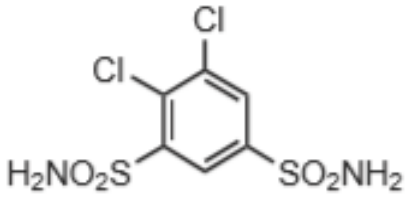
Methazolamide

(iii) Ethoxzolamide



Ethoxzolamide

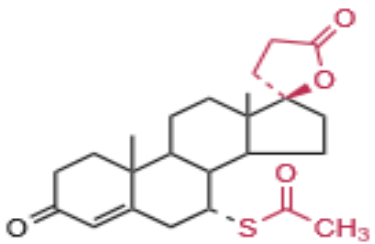
(iv) Dichlorphenamide



Dichlorphenamide

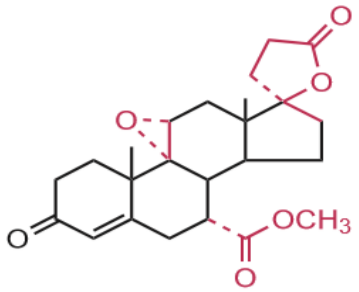
5. Aldosterone antagonists (mineralocorticoid receptor antagonists)-

(i) Spironolactone

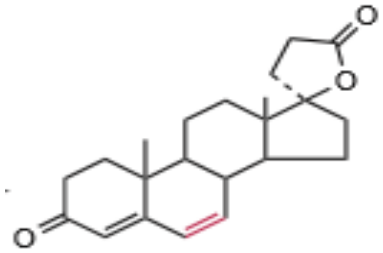


Spironolactone

(ii) Eplerenone



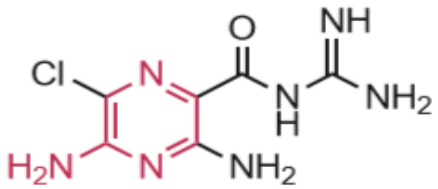
(iii) Canrenone



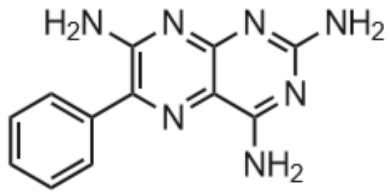
Canrenone

6. Potassium-sparing diuretics-

(i) Amiloride



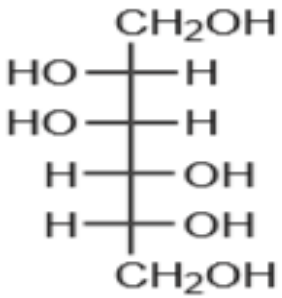
(ii) Triamterene.



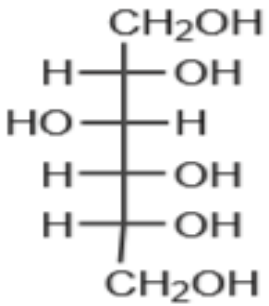
Triamterene

7. Osmotic diuretics-

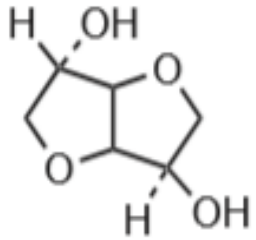
(i) Mannitol (ii) Sorbitol (iii) Isosorbide (iv) Glycerine (v) Urea



Mannitol



Sorbitol



Isosorbide

Synthesis of Acetazolamide

Structure-

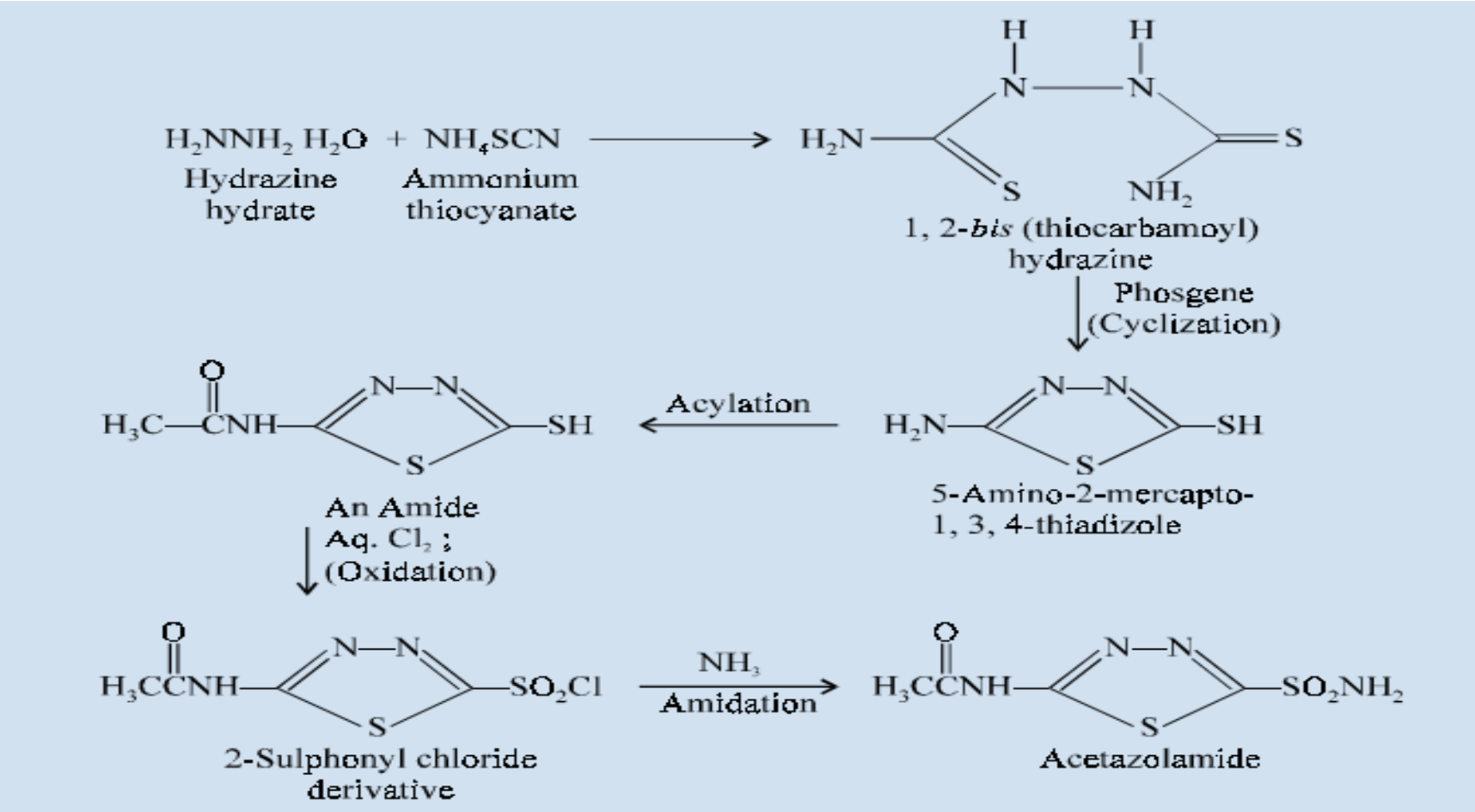
IUPAC Name- *N*-(5-sulfamoyl-1,3,4-thiadiazol-2-yl) acetamide. **Or**

Acetamide, N-[5-(amino-sulphonyl)-1, 3, 4thiadiazol-2-yl].

Properties-

- Acetazolamide appears as white to yellowish-white fine crystalline powder. No odour or taste.
- It is sparingly soluble in cold water, slightly soluble in alcohol and acetone.
- It is Insoluble in chloroform, diethyl ether, carbon tetrachloride; readily soluble in 1 N sodium carbonate solution.
- It is Stored in between 15 and 30 °C, in a well-closed container.
- Oral Absorption: nearly complete; Plasma Half-Life: 6-9 hours; and Route of Elimination: renal excretion of intact drug.
- It is an orally effective diuretic, with a therapeutic effect that lasts approximately 8 to 12 hours.

Synthesis-


$H_2NNH_2\,H_2O$ + NH_4SCN
Hydrazine hydrate
Ammonium thiocyanate
1, 2-*bis* (thiocarbamoyl) hydrazine
Phosgene (Cyclization)
5-Amino-2-mercapto-1, 3, 4-thiadizole
Acylation
An Amide
Aq. Cl_2 ; (Oxidation)
2-Sulphonyl chloride derivative
NH_3
Amidation
Acetazolamide

Mechanism of action-

- Acetazolamide is a sulfonamide derivative with diuretic, antiglaucoma, and anticonvulsant properties. Acetazolamide is a non-competitive inhibitor of carbonic anhydrase, an enzyme found in cells in the proximal tube of the kidney. Inhibition of this enzyme in the kidney prevents excretion of hydrogen ions for active transport in the renal tubule lumen. This leads to alkaline urine and an increase in the excretion of bicarbonate, sodium, potassium, and water.
- Acetazolamide reduces the concentration of bicarbonate, resulting in a decreased synthesis of aqueous humor in the eye, thereby lowering intraocular pressure. The anticonvulsant activity of Acetazolamide may depend on a direct inhibition of carbonic anhydrase in the CNS, which decreases carbon dioxide tension in the pulmonary alveoli, thus increasing arterial oxygen tension.

Uses-

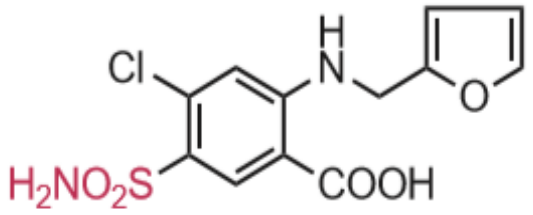
- Anticonvulsants; Carbonic Anhydrase Inhibitors; Diuretics.
- Its diuretic action is limited because of the systemic acidosis it produces.
- Acetazolamide has also been used as a diuretic in the treatment of edema due to congestive heart disease and drug-induced edema; centrencephalic epilepsies; chronic simple (open-angle) glaucoma.

Dose-

- The dose is 250 mg to 1 g per day in divided doses.

Synthesis of Furosemide

Structure-

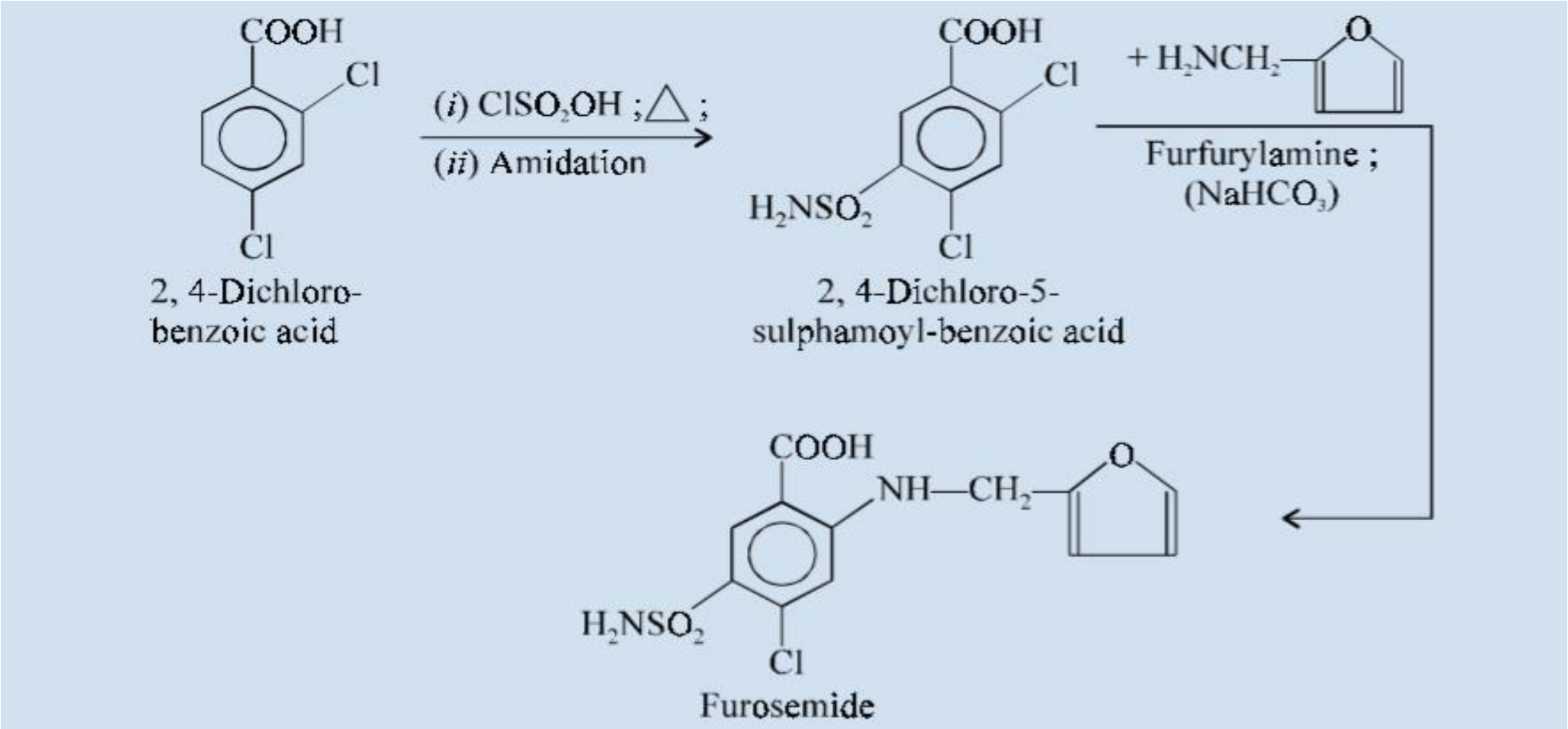


IUPAC Name- Benzoic acid, 5-(amino-sulphonyl)-4-chloro-2-[(2-furanylmethyl) amino]

Properties-

- Furosemide is an odourless white to slightly yellow crystalline powder. Keep container tightly closed in a dry and well-ventilated place
- Slightly soluble in water, chloroform, ether. Soluble in acetone, methanol, DMF, Soluble in methanol, acetone, dilute NaOH. Freely soluble in alkali hydroxide.
- Following oral administration, furosemide is absorbed from the gastrointestinal tract. the onset of the diuretic effect is about 1 and 1.5 hours, and the peak effect is reached within the first 2 hours.
- The duration of effect following oral administration if about 4-6 hours but may last up to 8 hours. The onset of effect is within 5 minutes following intravenous administration. The peak effect is reached within 30 minutes, and lasts for approximately 6 hours.

Synthesis-


COOH
Cl
Cl
2, 4-Dichloro-
benzoic acid
(i) ClSO2OH ; △ ;
(ii) Amidation
COOH
Cl
H2NSO2
Cl
2, 4-Dichloro-5-
sulphamoyl-benzoic acid
+ H2NCH2
O
Furfurylamine ;
(NaHCO3)
COOH
NH—CH2
O
H2NSO2
Cl
Furosemide

Mechanism of action-

- Furosemide, like other loop diuretics, acts by inhibiting the luminal Na+/ K+/2Cl− symporter in the thick ascending limb of the loop of Henle, by binding to the chloride transport channel, thus causing sodium, chloride, and potassium loss in urine. This inhibition results in increased excretion of water along with sodium, chloride, magnesium, calcium, hydrogen, and potassium ions. High-ceiling diuretics are characterized by a quick onset and short duration of activity.

Uses-

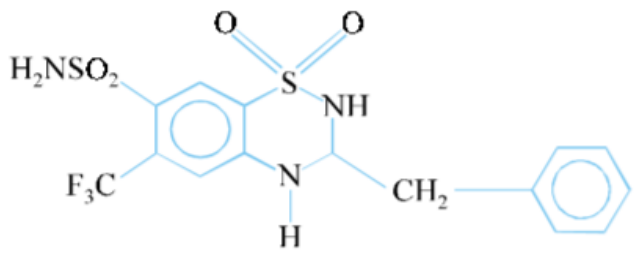
- It is used for the treatment of oedema associated with renal disease, nephrotic syndrome, cirrhosis of the liver.
- Furosemide is a diuretic used in the treatment of congestive heart failure, hypertension and edema.

Dose-

- Oral, 40 to 600 mg per day ; usual, 40 to 80 mg per day ; i.m. or i.v., 20 to 40 mg.

Synthesis of Bendrofluazide / Bendroflumethaizide

Structure-

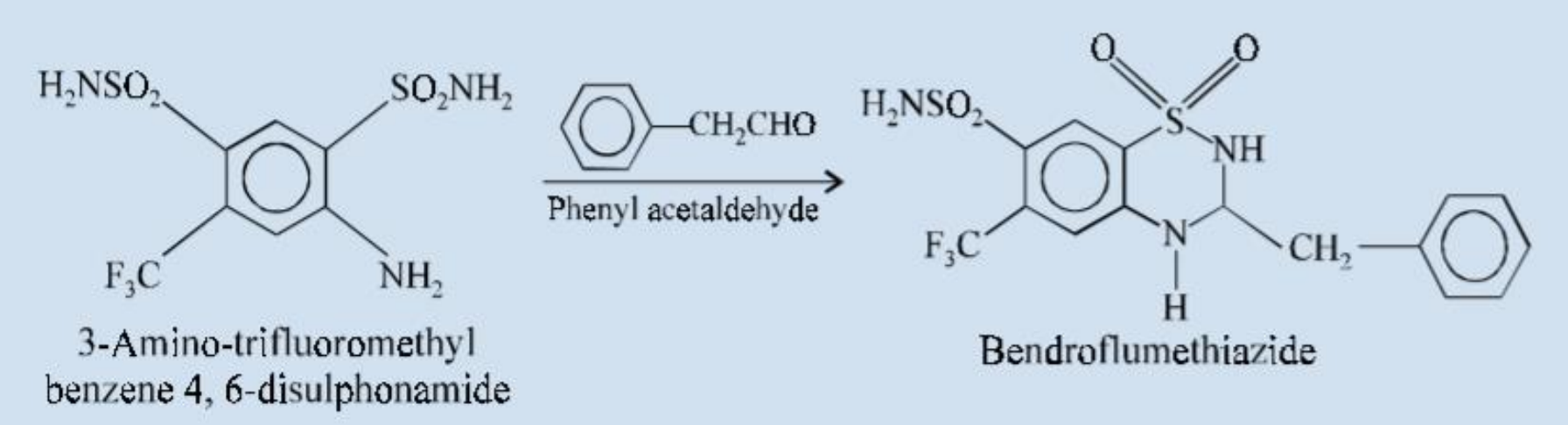


IUPAC Name- 3-Benzyl-3, 4-dihydro-6-(trifluoromethyl)-2H, 1, 2, 4-benzo-thiadiazine-7 sulphonamide 1, 1dioxide.

Properties-

- It is white to cream-colored, finely divided, crystalline powder, and has odourless or slight, characteristic floral odour.
- It is freely soluble in ethanol, acetone, insoluble in chloroform, benzene, ether.
- When heated to decomposition it emits toxic fumes of hydrogen fluoride, sulfoxides, and nitroxides.
- Bendroflumethiazide appears to be well absorbed from the GI tract. the drug is excreted unchanged in urine, and excretion is essentially complete within 24 hours.

Synthesis-



Uses-

- Diuretics, Antihypertensive Agents.

Dose-

- Initial, diuretic, 5 to 20 mg per day ; maintenance, 2.5 to 5 mg daily ;
- as antihypertensive, initial, 5 to 20 mg per day, maintenance, 2.5 to 15 mg per day.

Mechanism of action-

- Bendroflumethiazide, a thiazide diuretic, It inhibits Na^+/Cl^- reabsorption from the distal convoluted tubules in the kidneys, resulting in an increase in the excretion of sodium, chloride, and water. Thiazides also cause loss of potassium and an increase in serum uric acid.
- Bendroflumethiazide also inhibit sodium ion transport across the renal tubular epithelium through binding to the thiazide sensitive sodium-chloride transporter. This results in an increase in potassium excretion via the sodium-potassium exchange mechanism.
- Thiazides are often used to treat hypertension, but their hypotensive effects are not necessarily due to their diuretic activity.

Thank You...