Diuretics

(Unit Objective - Student should able to understand the Chemistry of various classes of Diuretic agents.)

Prof. S. G. Jawarkar

Department of Pharmaceutical Chemistry
Vidyabharati College of Pharmacy,
Camp Road, Amravati

Contents

- Introduction of diuretics
- Normal Physiology of Urine
- Classification of Drugs
- Mechanism of Action Of Drugs
- Structure Activity Relationship Of Drugs
- Synthesis
- Uses
- Adverse Effects
- References

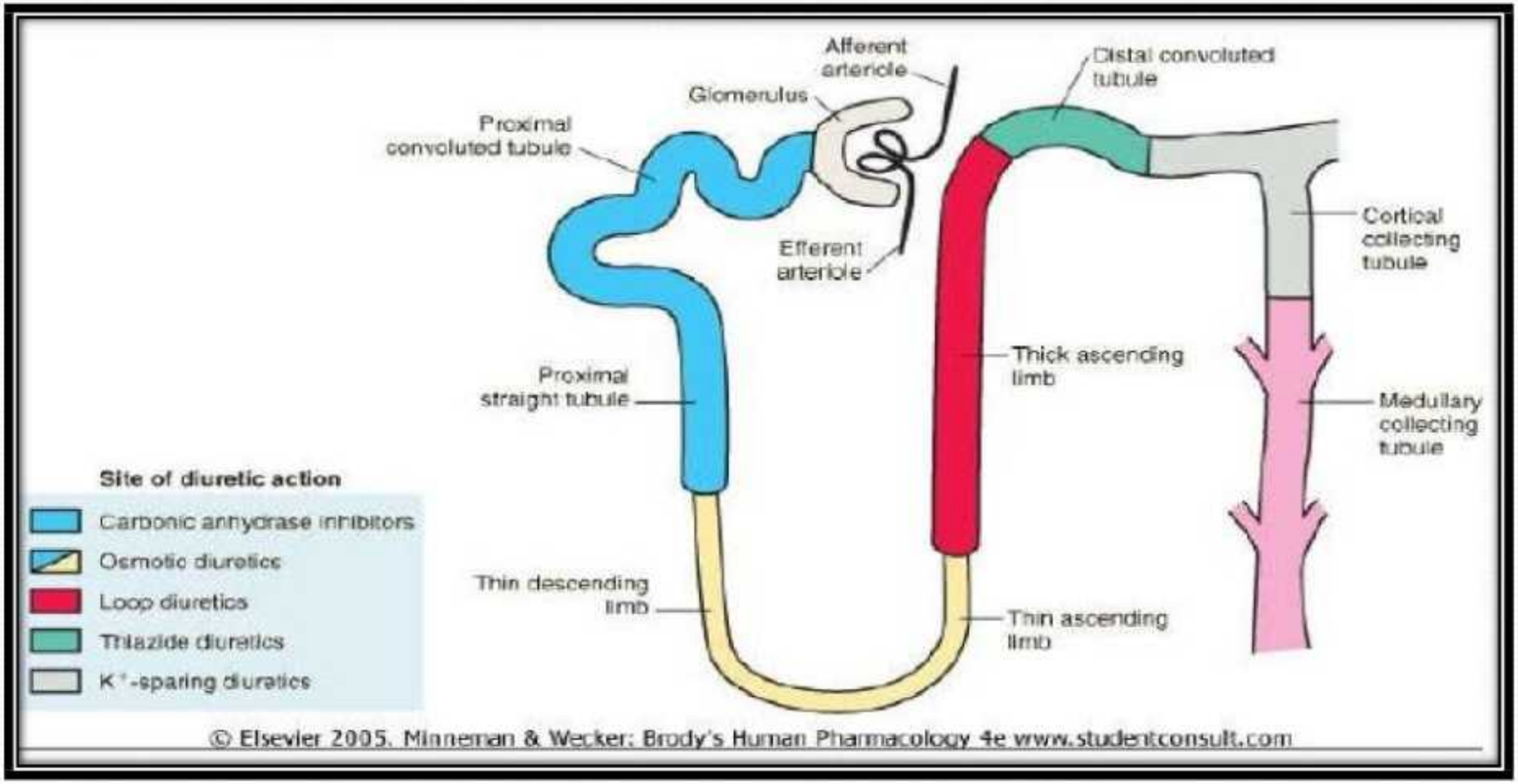
Diuretics

- A diuretic is a drug that **increases the secretion of urine** (ie, water, electrolytes, and waste products) by the kidneys.

- **Many conditions or diseases**, such as hypertension, congestive heart failure, endocrine disturbances, and kidney and liver diseases can **cause retention of excess fluid (edema).**

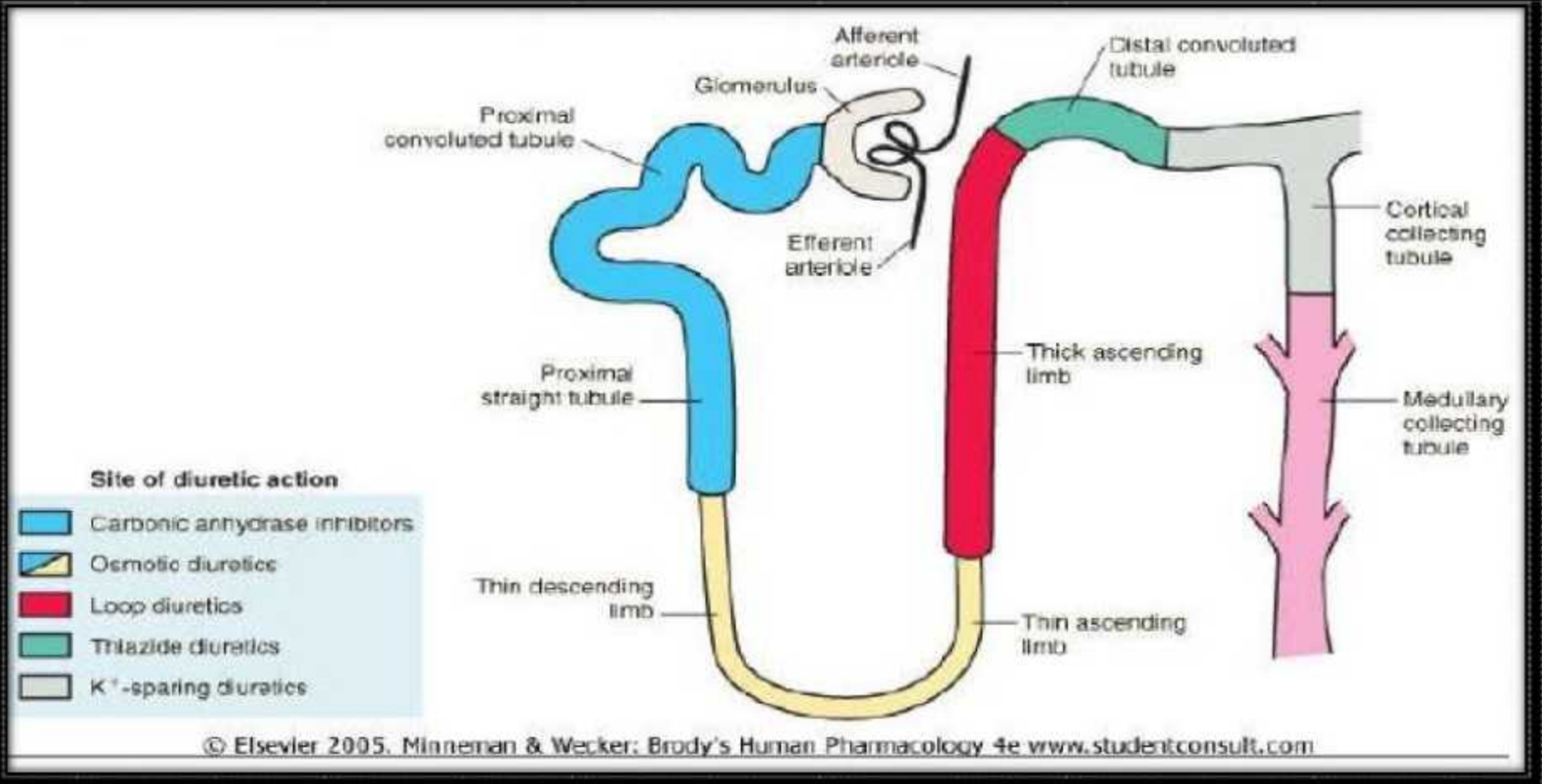
- **A diuretic is used when the patient shows signs of excess fluid retention.**

- Reabsorption of Na in the kidney results in the reabsorption of water. It follows that inhibition of Na reabsorption will result in diuresis. Because of this, the term diuretic has come **to mean any agent that will inhibit the tubular reabsorption of sodium.**


Afferent arteriole
Glomerulus
Proximal convoluted tubule
Efferent arteriole
Distal convoluted tubule
Cortical collecting tubule
Thick ascending limb
Proximal straight tubule
Medullary collecting tubule
Thin descending limb
Thin ascending limb
Site of diuretic action
Carbonic anhydrase inhibitors
Osmotic diuretics
Loop diuretics
Thiazide diuretics
K+-sparing diuretics
© Elsevier 2005. Minneman & Wecker: Brody's Human Pharmacology 4e www.studentconsult.com

SITE 1 DIURETICS
(Work in Proximal Tubule)

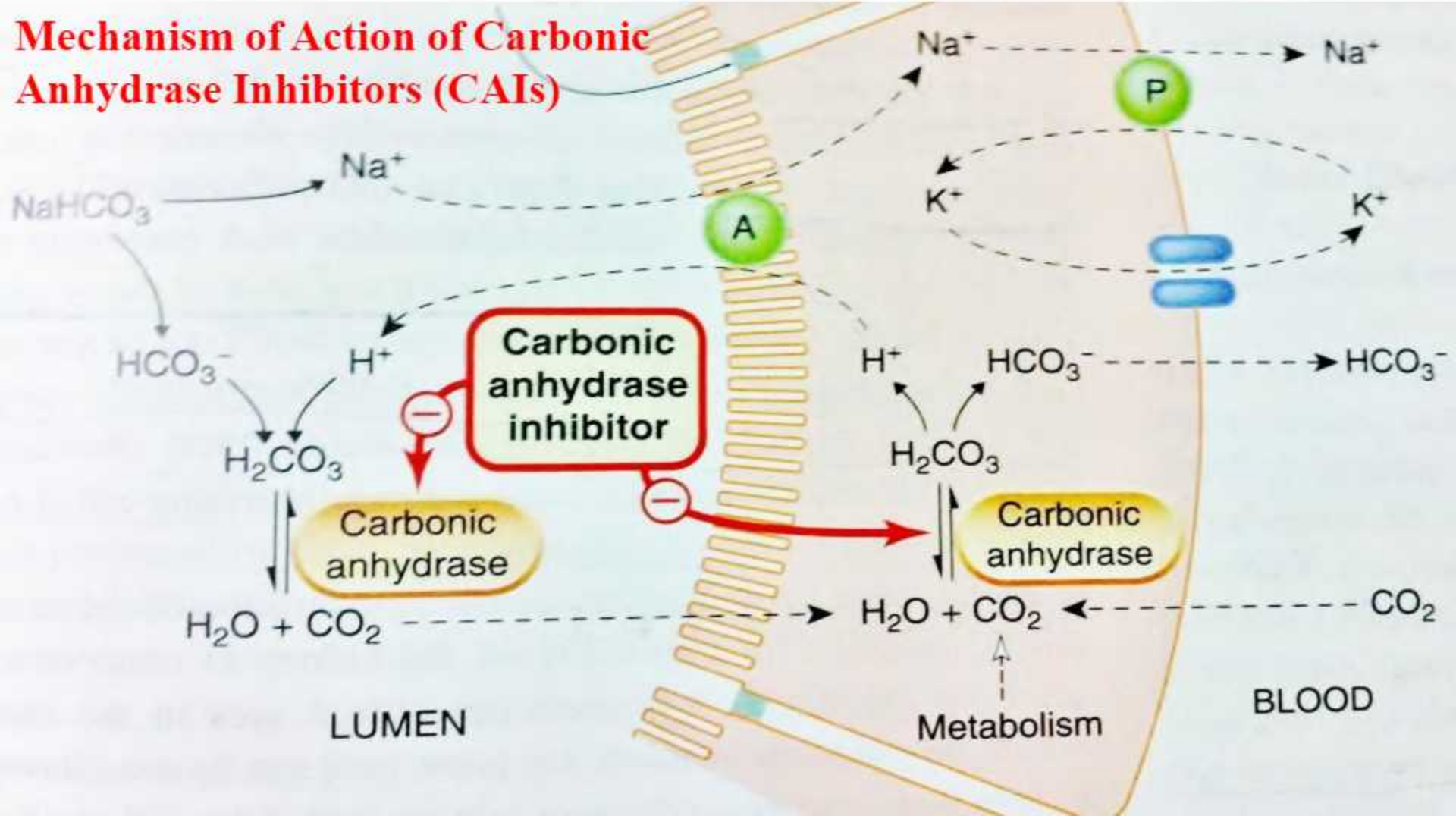
Carbonic Anhydrase Inhibitors (CAIs)



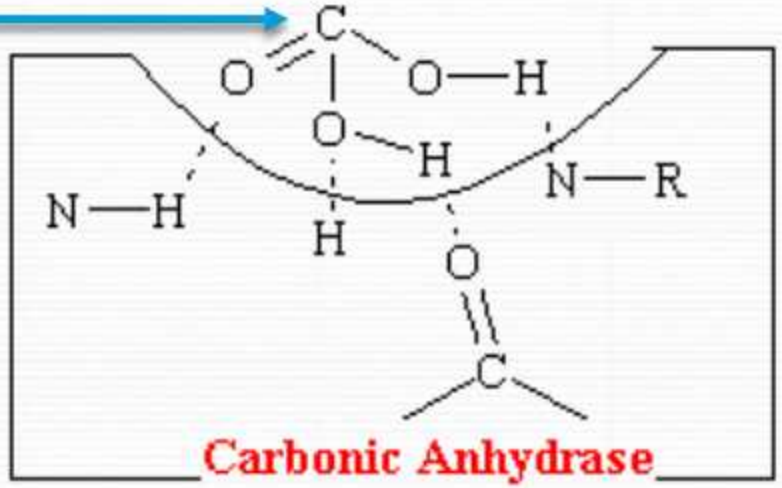
CARBONIC ANHYDRASE (CA)

The **carbonic anhydrases** form a family of enzymes that catalyze the rapid **inter-conversion** of carbon dioxide(CO_2) and water to bicarbonate (HCO_3^-) and protons (or vice versa).

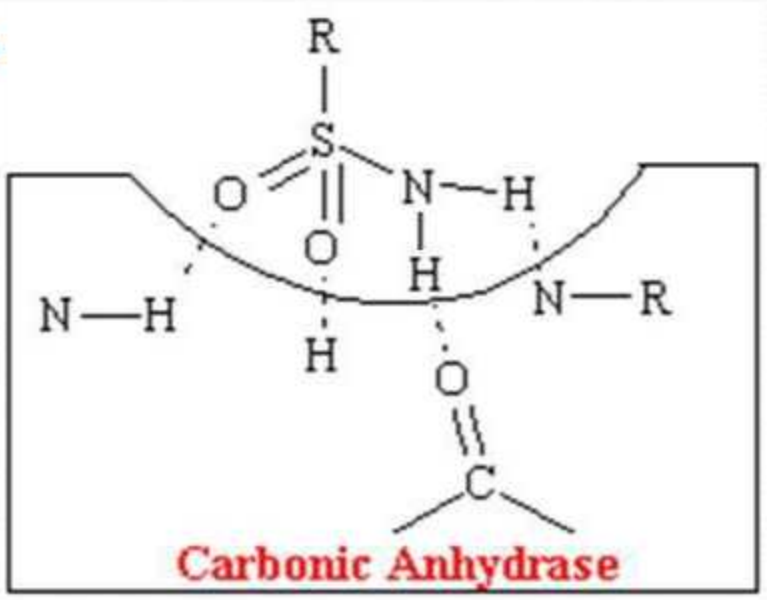
Mechanism of Action of Carbonic Anhydrase Inhibitors (CAIs)



(H_2CO_3)



(Inhibitors)



SULFANILAMIDE

- It was introduced for the treatment of **bacterial infections**, BUT observed to produce a **mild diuresis** through inhibition of renal Carbonic Anhydrase (CA).

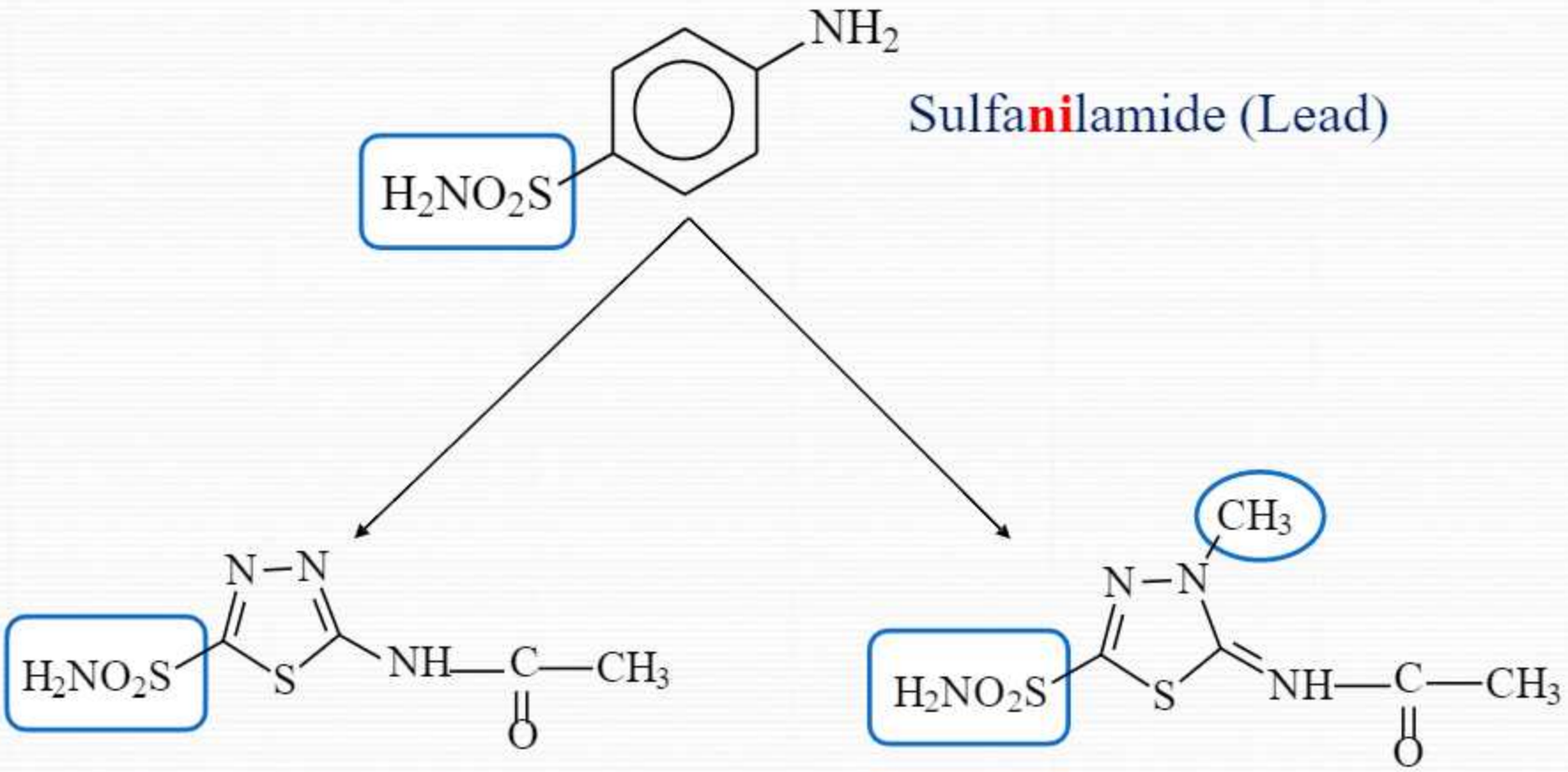
- It was also found to have severe side effects.

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:

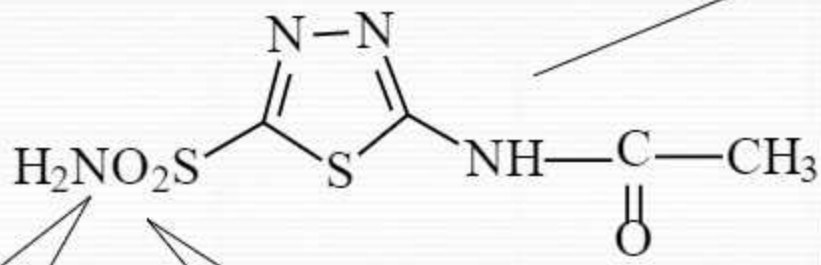
1. **Simple heterocyclic sulfonamides.**
2. **Metadisulfamoylbenzene derivatives.**

HETEROCYCLIC SULFONAMIDES



STRUCTURE- ACTIVITY RELATIONSHIPS

-The prototype is Acetazolamide .



The derivatives with the **highest lipid / water** partition coefficient and **lowest pKa** have the **greatest CA inhibitory** and **diuretic activity**.

The **sulfamoyl group** is **essential** for the production of diuresis

The sulfamoyl **nitrogen** atom must remain **unsubstituted** to retain the activity .

Structure – activity relationships

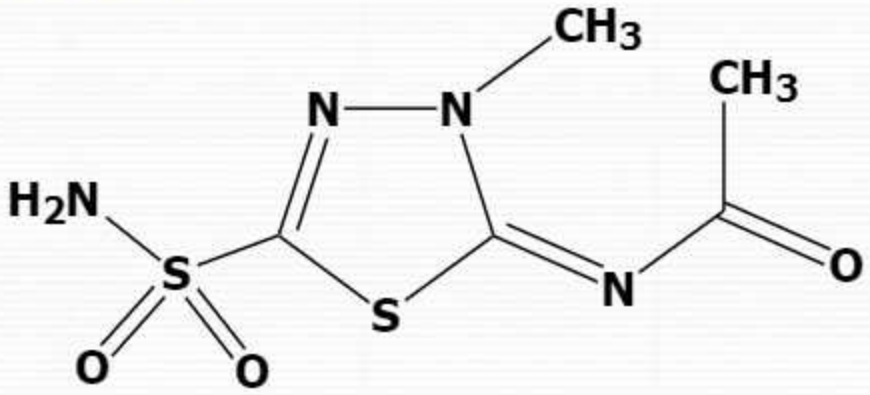
1. The **sulfamoyl group** is absolutely **essential** for the *in vitro* carbonic anhydrase inhibitory activity.

1. 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.)

2. Substitution of a methyl group on one of acetazolamido's ring nitrogens yields methazolamide, a product that retains carbonic anhydrase inhibitory activity & even more potent.

3. **Sulfamoyl group must be attached** to a moiety that possess **aromatic character.**

Methazolamide, USP



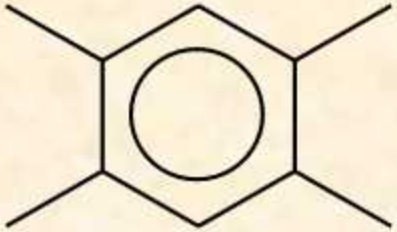
N-(3-Methyl-5-sulfamoyl-1,3,4-thiadiazol-2(3H)-ylidene)-acetamide

Methazolamide is **more potent** carbonic anhydrase inhibitor than acetozolamide (the prototype), but is rarely used as diuretic. It is used in treatment of **glaucoma**, because it displays **improved penetration into the eye.**

Metadisulfamoylbenzene derivatives SAR

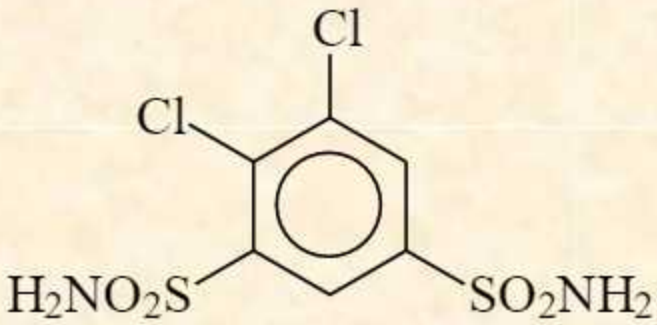
Maximal diuretic activity is observed
When this position is substituted with:
Cl , Br , CF_3 or NO_2

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

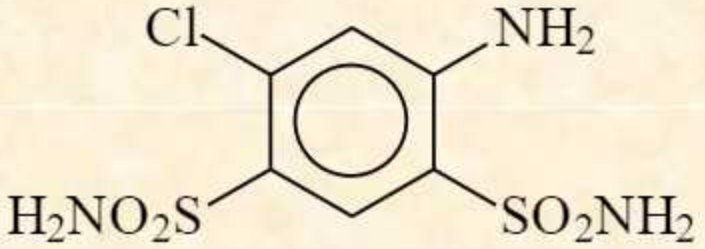


SO_2NH_2 - **unsubstituted sulfamoyl** is of paramount importance

SO_2NH_2 - the **sulfamoyl moiety can be replaced with a similar electrophilic Group** (carbonyl, carbamoyl) that may **increase diuretic potency** while **decreasing CA inhibitory activity**



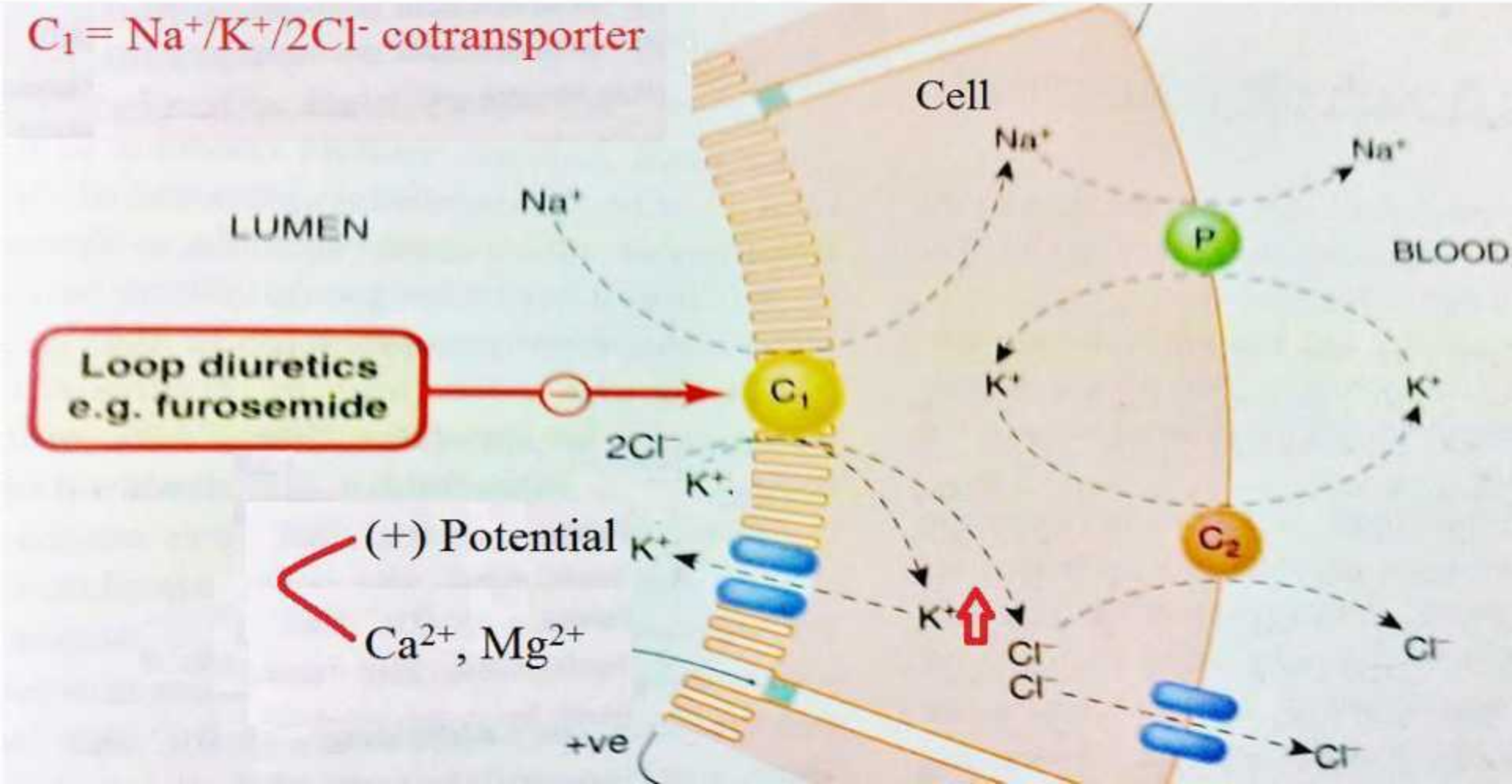
Dichlorphenamide
(Daranide)



Chloraminophenamide

Loop Diuretics: Mechanism of Action

TAL contains **Na^+ / K^+ / $2Cl^-$ cotransporter** from lumen to TALcells.
Loop diuretic blocks this cotransporter and **increases the excretion of sodium and chloride** by inhibiting their reabsorption in **TAL**. *The diuretic action of this drug is not limited by the development of acidosis, as is the case with CAIs.*



LOOP DIURETICS

The loop diuretics are of extremely diverse chemical structure such as

1. The **organomercurial diuretics**
2. The **5-Sulfamoyl-2- and -3-aminobenzoic acid derivatives**. For example, furosemide and bumetanide respectively.
3. **Phenoxyacetic acid derivatives** as ethacrynic acid

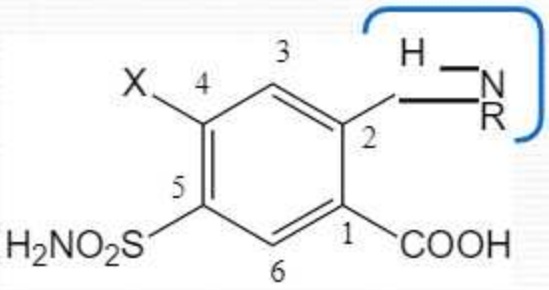
1) Organomercurials:

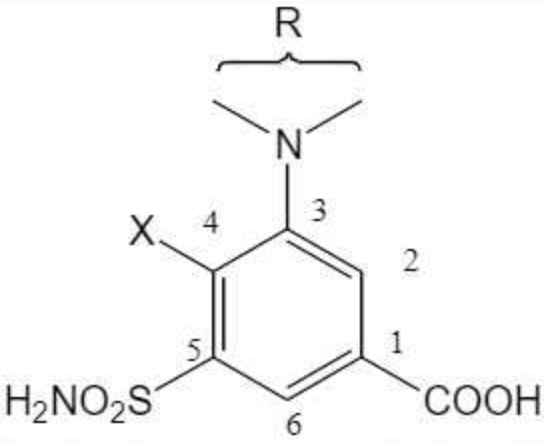
They were the main diuretic therapy from 1926 to the early 1950s.

Limitations of the organomercurials

- They cannot be given orally because of poor and erratic absorption.
- After their parenteral administration there is a one- to two-hour lag in the onset of the diuresis.
- Their activity depend on the acid-base status of the individual (i.e., they are ineffective when the urine is alkaline).
- They are cardio- and nephro-toxic.

2) 5-Sulfamoyl-2- and -3-aminobenzoic acid derivatives

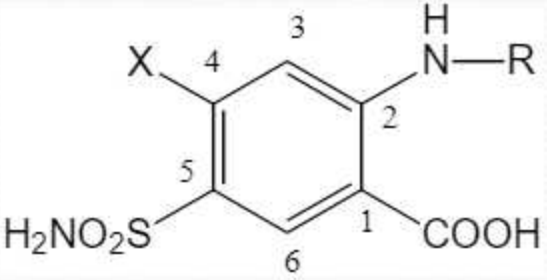


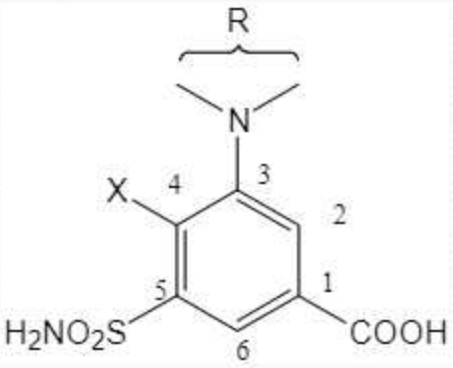


Uses:

- **Edema**,
- **Hypertension**
- **Hypercalciuria** (i.e., an elevated urinary concentration of calcium) are prone to the formation of calcium-containing stones within the urinary tract.

Structure Activity Relationship (SAR)
5-Sulfamoyl-2- and -3-aminobenzoic acid derivatives



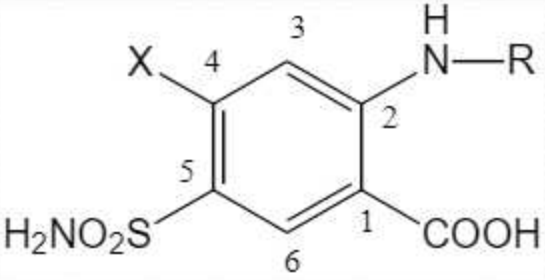


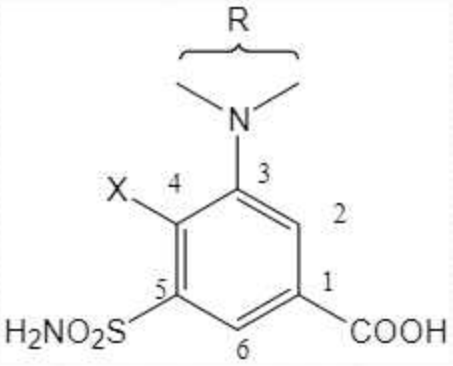
1. The substituent at the **1-position must be acidic**, The **carboxyl group** provides optimal diuretic activity, but other groups, as **tetrazole**, may have respectable diuretic activity.

2. A **sulfamoyl group in the 5-position is essential** for optimal high-ceiling diuretic activity.

3. The activating group (x-) in the 4-position can be Cl- or CF_3-, a phenoxy-, alkoxy-, anilino-, benzyl-, or benzoyl- group

SAR of 5-Sulfamoyl-2- and -3-aminobenzoic acid derivatives:



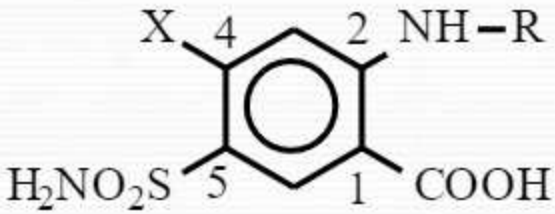


Major differences between the two series of 5-sulfamoyl-benzoic acids is based in the **nature of the functional groups** that can be substituted into the **2-and 3-positions** with the retention of maximal diuretic activity:

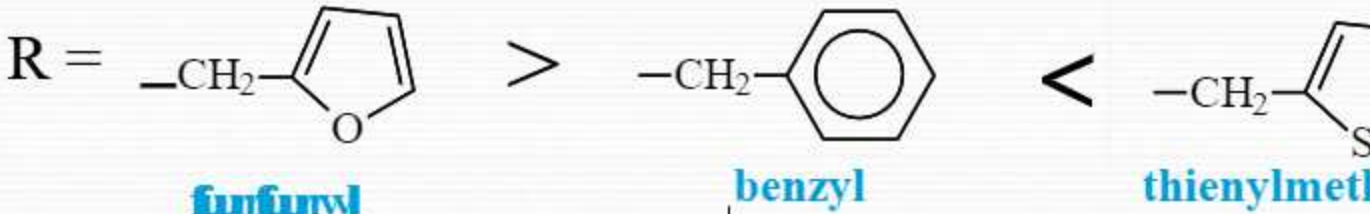
i. **Substituents** that can be **tolerated at the 2-amino group** of the 5-sulfamoyl-2-aminobenzoic acid series are **extremely limited**, and no deviations are allowed on the few moieties that are acceptable. For example, only **furfural-, benzyl-,** and **thienylmethyl** (in decreasing order) yield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

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

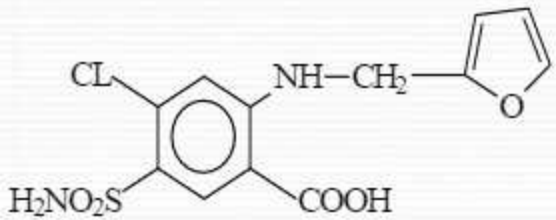
5-SULFAMOYL-2-AMINOBENZOIC ACID



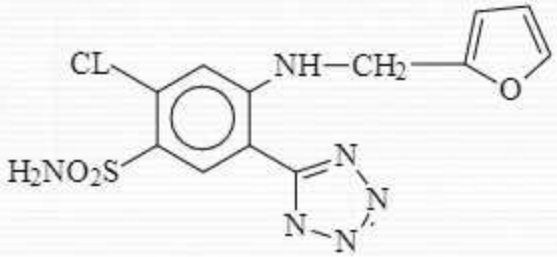
- The substituents that can be tolerated on the 2- amino group are limited and no deviation are allowed on the few moieties that are acceptable.
- Only **furfuryl**, **benzyl** and **thienylmethyl** yield derivatives of diuretic activity.



furfuryl **benzyl** **thienylmethyl**

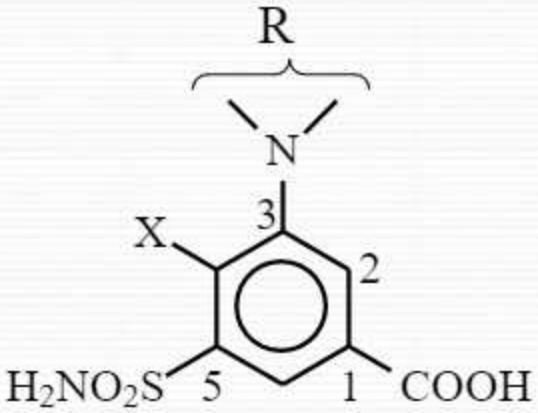


Furosemide (Lasix)

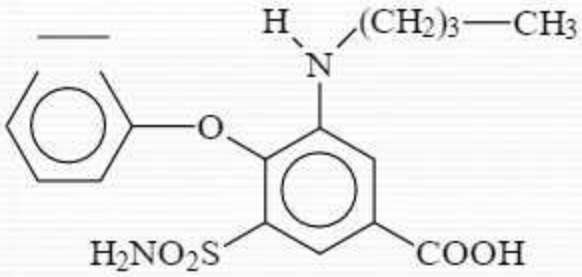


Azosemide

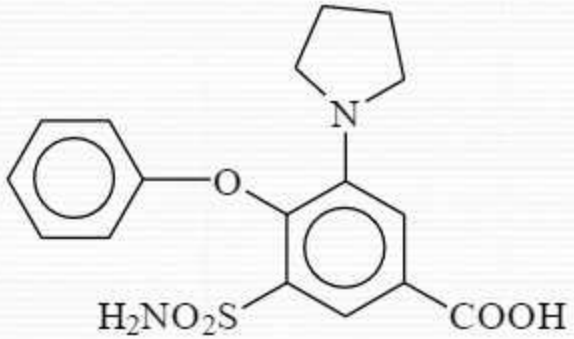
5-SULFAMOYL-3-AMINOBENZOIC ACID



R= A wide variety of alkylgroups

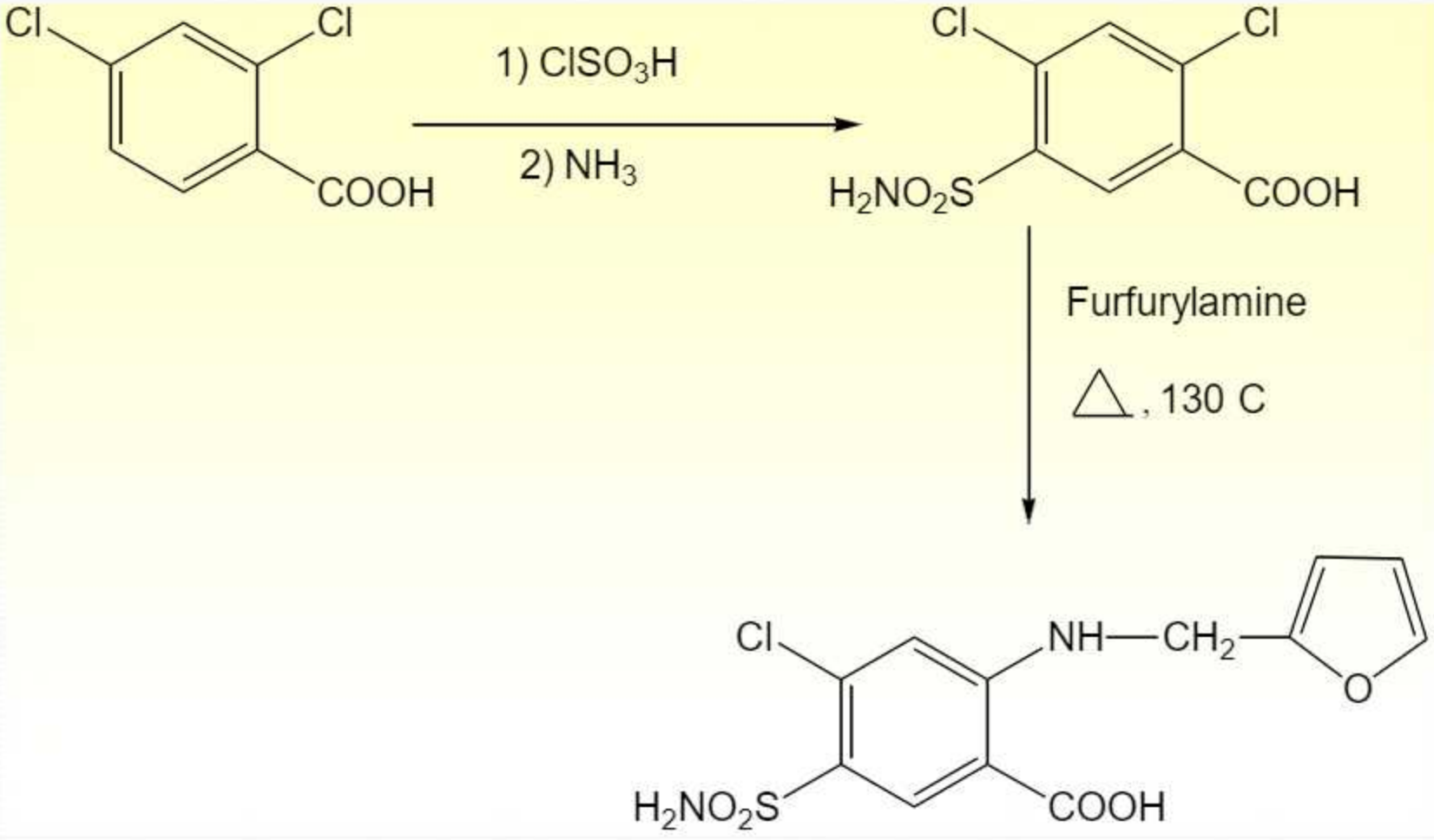


Bumetanide (Bumex)

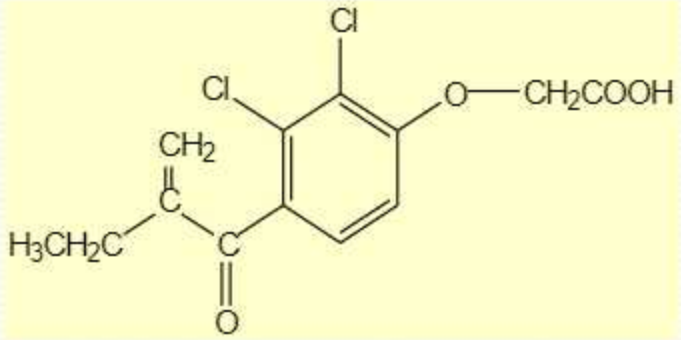


Piretanide

Synthesis of Furosemide



Phenoxyacetic acids
Ethacrynic Acid, (Edecrin)



2,3-Dichloro-4-(2-methylene-1-oxobutyl)phenoxyacetic acid

Uses:

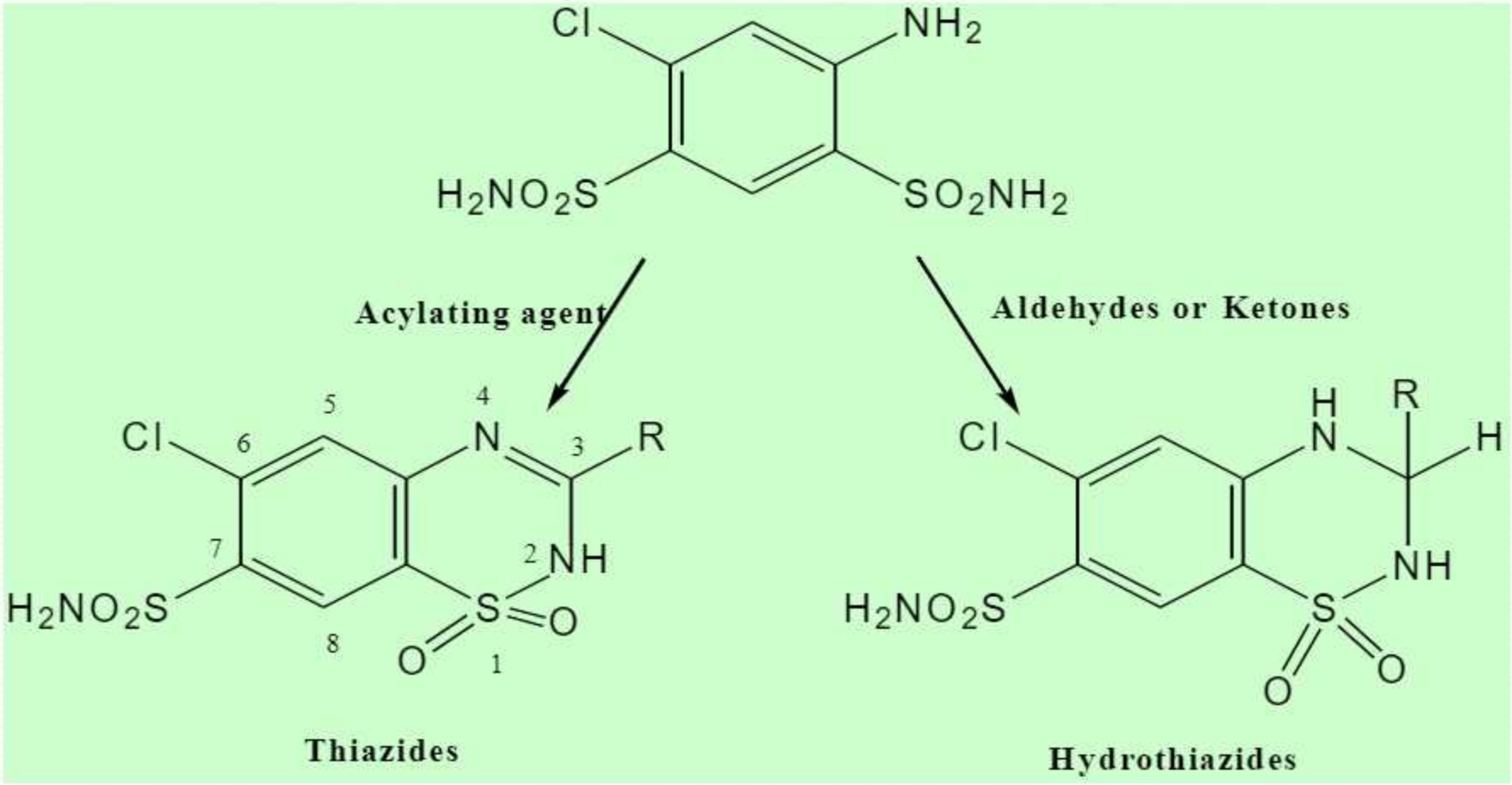
1. Same uses as cited for furosemide and bumetanide.
2. **Ethacrynic acid is prescribed for individual who has** a known **hypersensitivity to Sulfamoyl containing drugs.**

Adverse Effects:

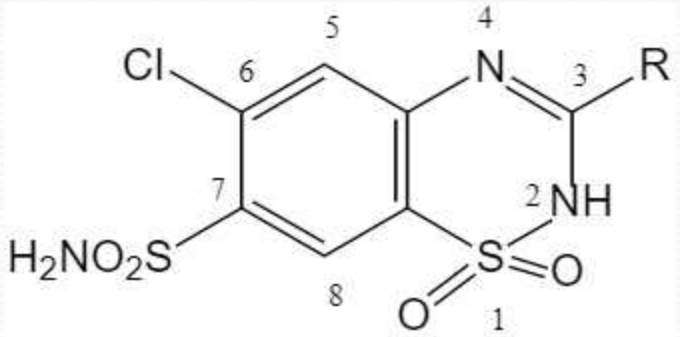
1. Same adverse effects as noted with Furosemide and bumetanide except those related to sulfamoyl group.
2. Ototoxicity and GIT effects (GIT hemorrhage) more than furosemide and bumetanide.

Site 3 Diuretics: Thiazide and Thiazide-like Diuretics

Thiazides and related **diuretics inhibit the reabsorption of sodium and chloride ions** in the **ascending THIN portion of the loop of Henle** and the early **distal convoluted tubule** of the nephron. This **action results in the excretion of sodium, chloride, and water.**

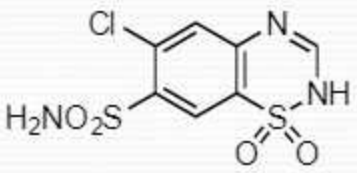


Structure-Activity Relationships: Thiazide Diuretics

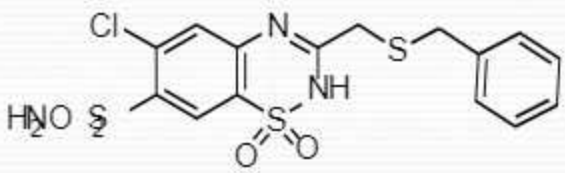


1. The 2-position can tolerate small alkyl groups as CH_3.
2. Substitutents at the **3-position determine the potency and duration of action** of the thiazides.
3. **Saturation of C-C bond between the 3 and 4 positions** of the benzothiadiazine-1,1-dioxide nucleus **increases the potency** of this class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

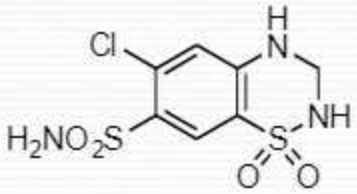
Examples of Thiazide Diuretics



Chlorothiazide



Benzthiazides

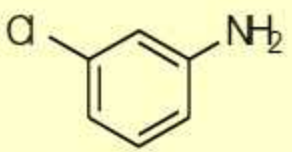


Hydrochlorothiazide

Bendroflumethiazide

- **Chlorothiazide:** 6-Chloro-2*H*-1, 2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
- **Benzthiazide (Hydrex):** 6-Chloro-3-[(phenylmethyl) thio]methyl]-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
- **Hydrochlorothiazide, (Esidrix):** 6-Chloro-3, 4-dihydro-2*H*-1, 2,4-benzothiadiazine-7-sulfonamide 1,1 -dioxide
- **Bendroflumethiazide:** 3-Benzyl-3,4-dihydro-6 (trifluoromethyl)-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1, 1-dioxide

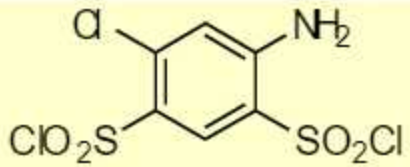
Synthesis of Thiazides



3-chlorobenzenamine

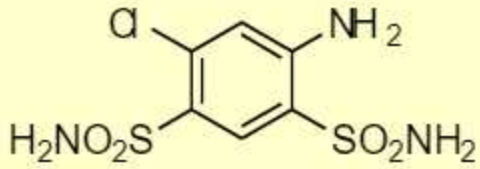
+ $ClSO_2OH$

sulfurochloridic acid



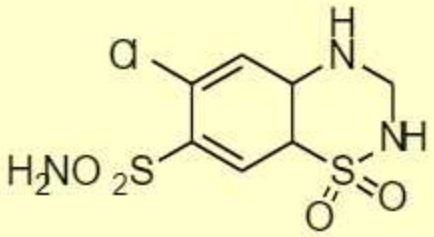
4-amino-6-chlorobenzene-1,3-disulfonyl dichloride

NH_3



4-amino-6-chlorobenzene-1,3-disulfonamide

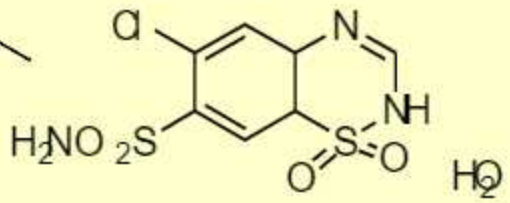
HCHO



Hydrochlorothiazide

H_2

HOCl HCOOH



H_2O

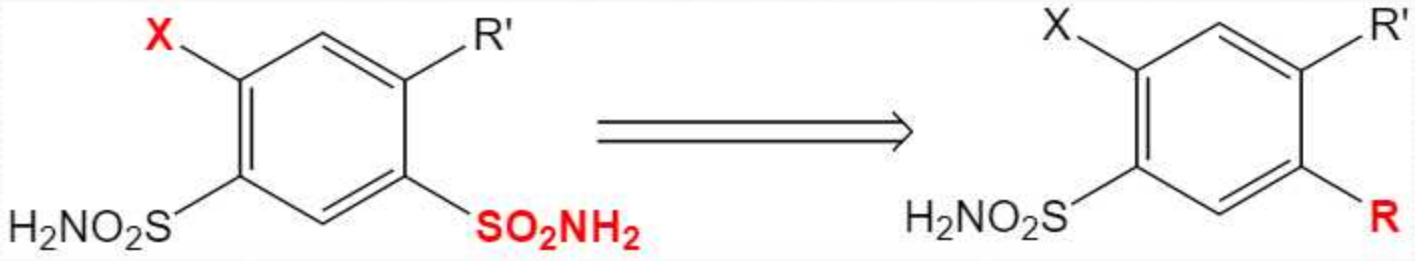
Chlorothiazide

Thiazide-like Diuretics

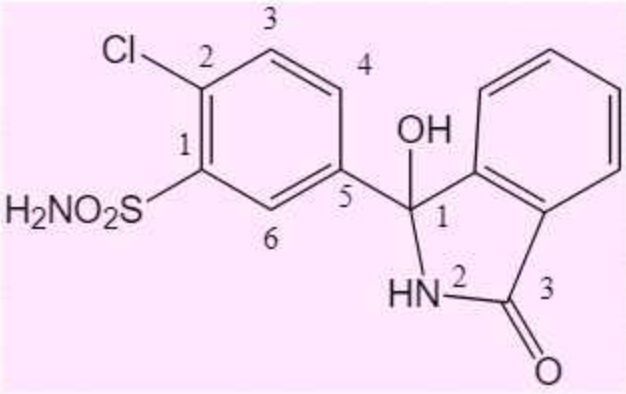
- The **sulfamoyl group para to the activating group of thiazides could be replaced by several other electronegative groups** (X-) with retention of diuretic activity (as R = amide, carbonyl, carboxyl groups, etc) in the meta-disulfamoylbenzene.

- These diuretics known as thiazide-like diuretics.

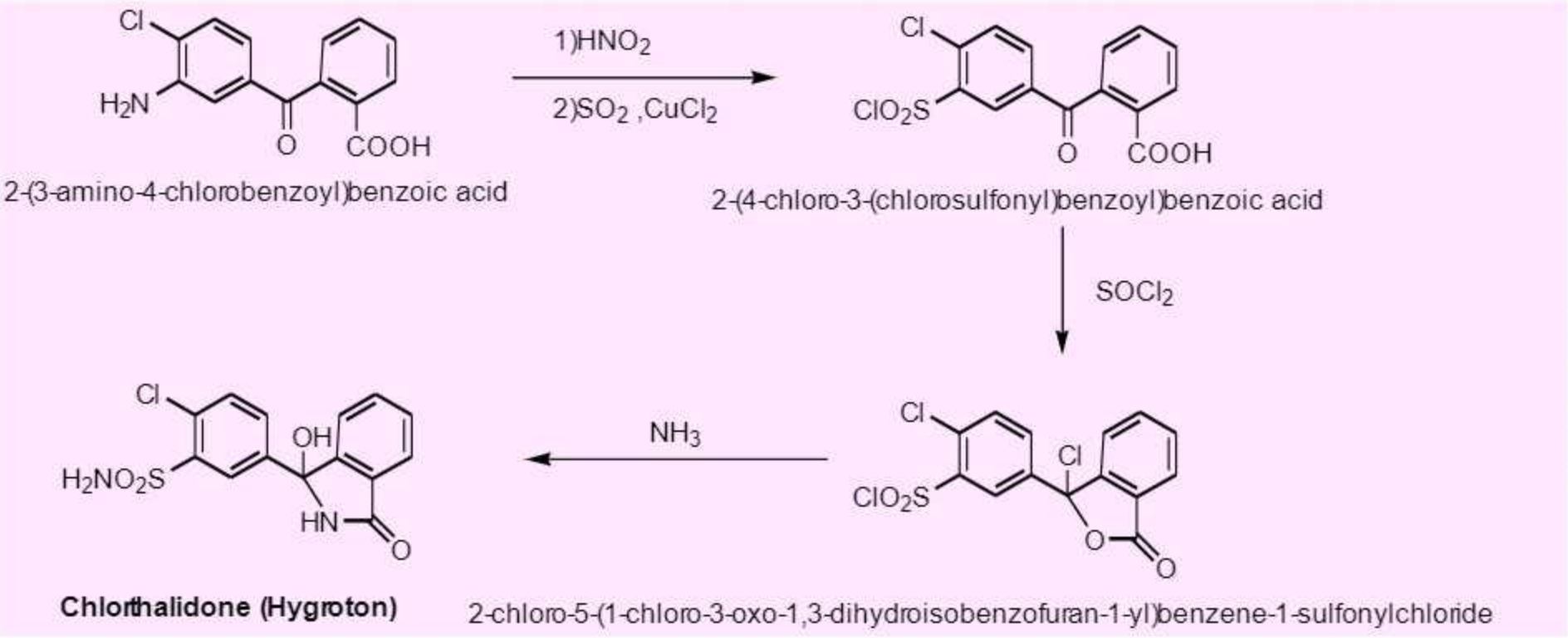
- Their site of action, efficacy, electrolyte excretion pattern, and adverse effects resemble the thiazides.



Chlorthalidone (Hygroton): 2-Chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzenesulfonamide



Synthesis



Site 4 Diuretics: Potassium-sparing diuretics

- Diuretics that increase sodium and chloride excretion, **without a concomitant increase in the urinary excretion rate of potassium.** These agents are known as potassium-sparing (or potassium- saving) diuretics or anti-kaliuretic agents. They work in in the **distal convoluted tubules** of the kidney.

Classification:

1. Aldosterone antagonists (e.g. Spironolactone)
2. Direct-acting diuretics (e.g. triamterene and amiloride)

Properties and uses:

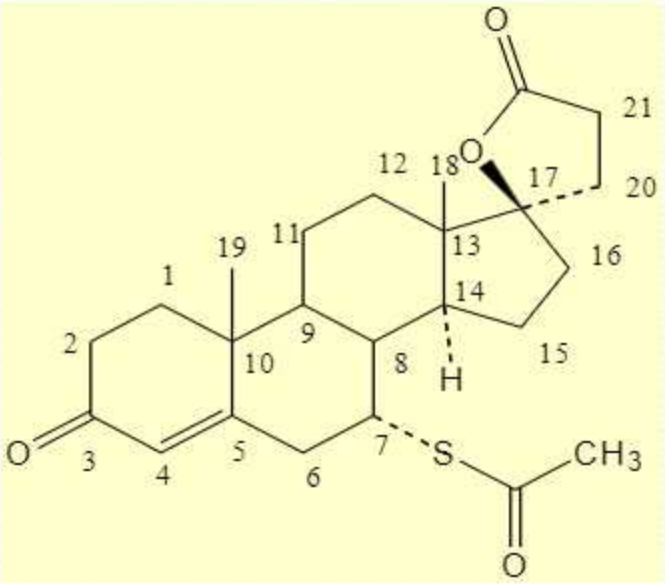
- These agents are **not potent diuretics when used alone** but, when combined with a thiazide - eg, Aldactizide
- They **reduce potassium loss**, increase sodium excretion
- Minimize alkalosis.
- The **onset of diuresis with combination therapy** is much more **rapid than with spironolactone alone**.

Aldosterone antagonists:

Aldosterone, a hormone produced by the adrenal cortex, **enhances the reabsorption of sodium in the distal convoluted tubules** of the kidney.

Spironolactone (Aldactone) antagonizes the action of aldosterone.

When this activity of **aldosterone is blocked, sodium (but not potasium)** and **water are excreted.**



Spironolactone (Aldactone):

7α-(Acetylthio)-17β-hydroxy-3-oxopregn-4-ene-21-carboxylic acid γ-lactone

Uses

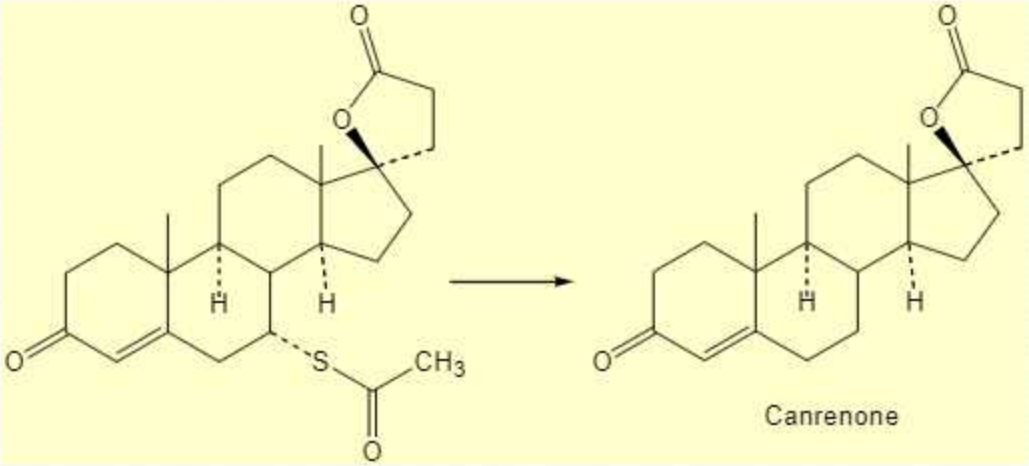
- Treatment of edema
- Antihypertensive agent.
- Primary use is in combination with diuretics that act at site 2 or 3 **to reduce the hypokalemic effect of the latter groups of diuretics**.

Adverse Effects

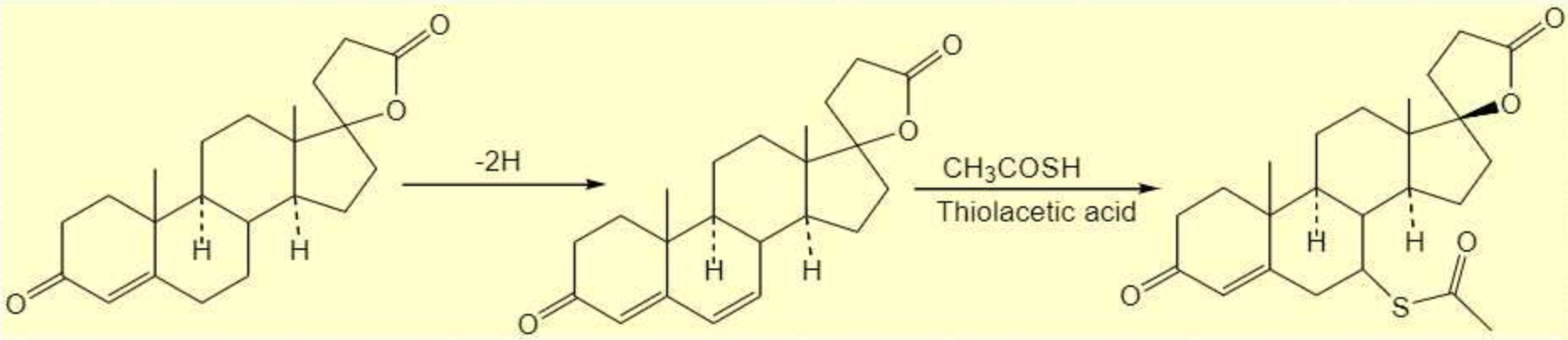
- **Hyperkalemia**
- Metabolic acidosis.
- **Gynecomastia in men** and Breast tenderness and menstrual disturbances in women because of its residual hormonal activity.
- Minor GIT symptoms.

Metabolism:

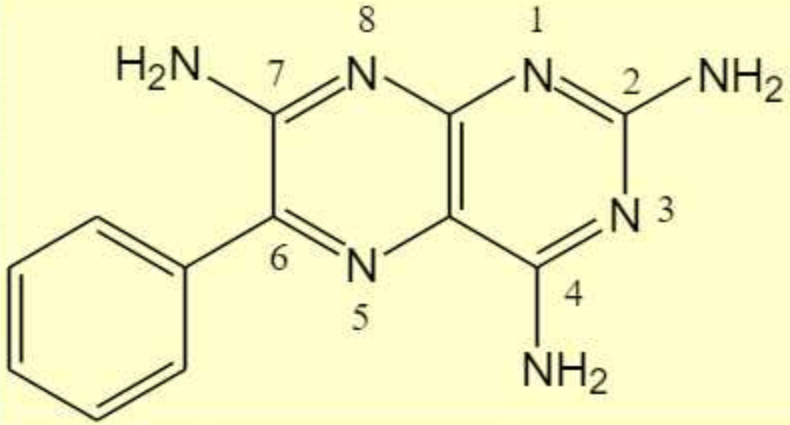
Spironolactone is metabolized to **Canrenone** **which is an active aldosterone antagonist.**



Synthesis



Triamterene: 2,4,7-triamino-6-arylpteridines



SAR:

- **Para-substitution of phenyl ring** with (**-OH group**) **increases activity**
- The phenyl group can be replaced by small heterocyclic rings
- The **amino groups must be un-substituted.**
- It has a structural similarity to folic acid and certain dihydrofolate reductase inhibitors, but it has little, if any, of their activities.

Uses:

- Treatment of edema, hypertension.
- Used in combination with other diuretics that act at site 2 or 3 to prevent hypokalemia.

Adverse Effects:

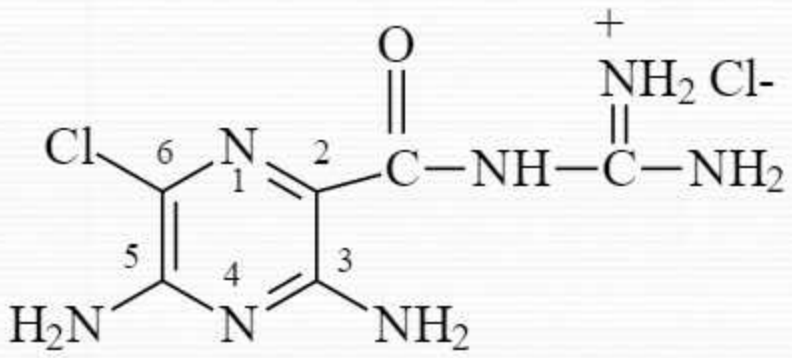
- Hyperkalemia, renal stones formation, GIT symptoms.

Pyrazinoylguanidines

Mechanism of Action:

"Plugs" the sodium channels preventing electrogenic reabsorption of 2-3% of the filtered Na^+.

Directly blocks Na+ entry through sodium-selective ion channels, which directly alters the Na+/K+ exchange mechanism in the distal nephron.



Amiloride Hydrochloride
(Midamor, Moduretic)

Uses and Adverse effects as triametrine

SAR:

-Optimal diuretic activity is observed when

1. The 6 position is substituted with chlorine.
2. The **amino group at 3, 5 position are unsubstituted**.
3. The **guanidino nitrogen are not substituted** with alkyl group.

- Moderately plasma protein bound, oral bioavailability 15-20%,
- Used in combination with hydrochlorthiazide (Moduretic®).
- **Side effects:** hyperkalemia,, nausea, vomiting, headache, diarrhea

Osmotic diuretics

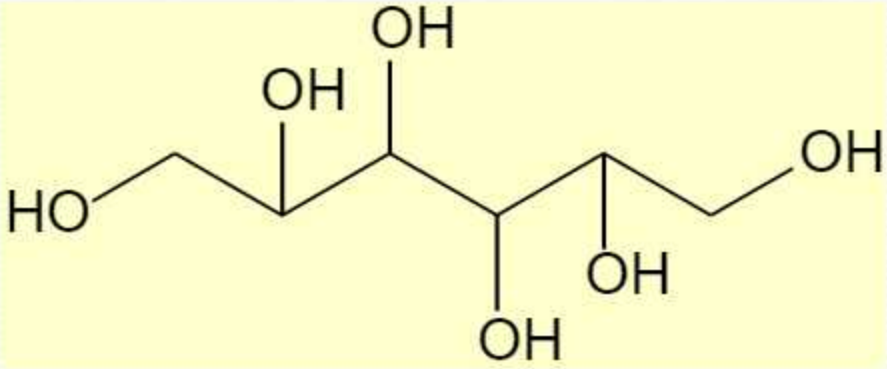
Osmotic diuretics increase the density of the filtrate in the glomerulus. This **prevents selective reabsorption of water**, which allows the water to be excreted. **Sodium and chloride excretion is also increased**.

They have the following key features:

1. They are passively filtered by glomerular filtration.
2. They undergo limited reabsorption in the renal tubules
3. They are metabolically and pharmacologically inert,
4. They have a high degree of water solubility

Examples, Mannitol, Theophylline

Mannitol

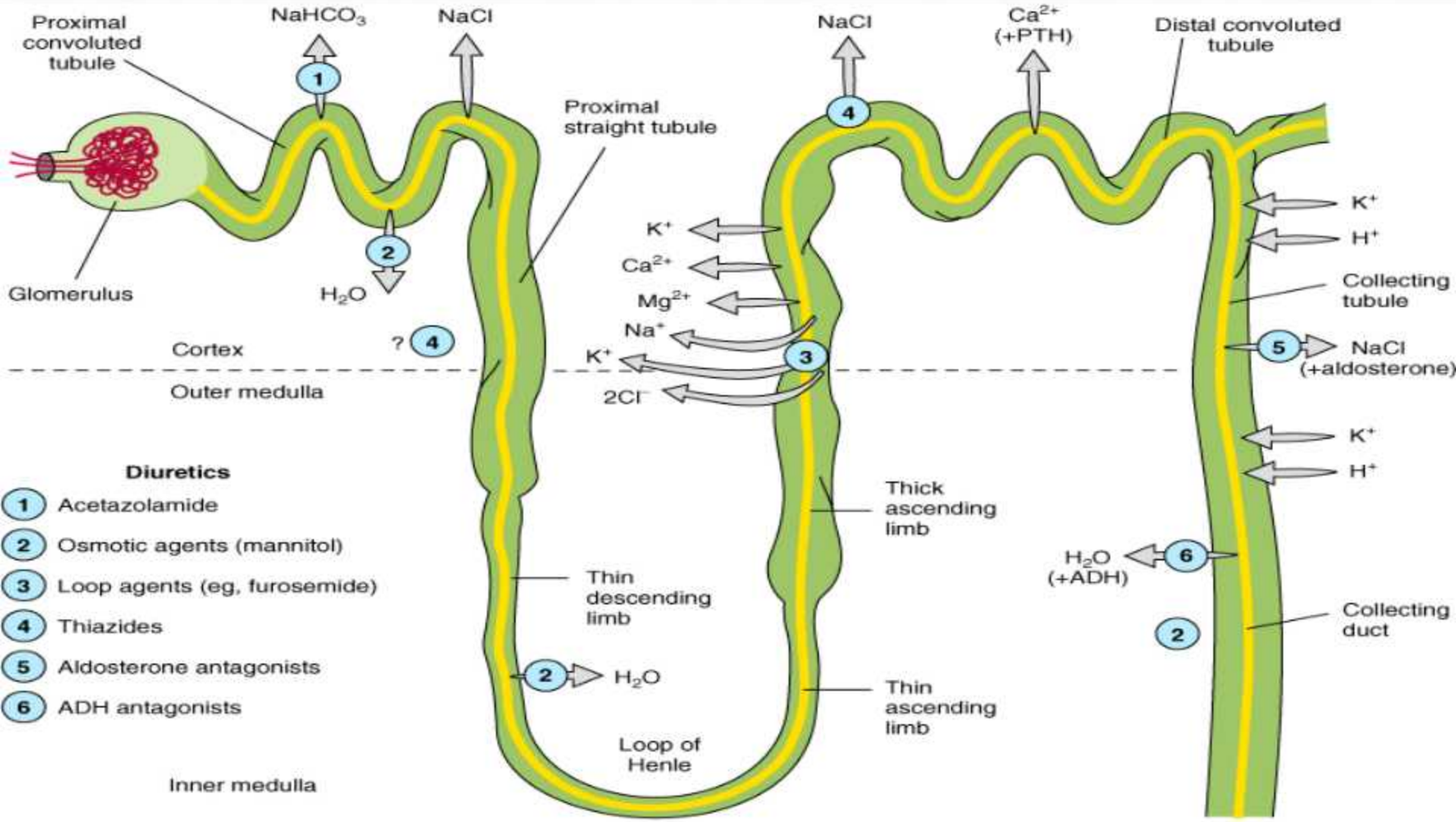


- The prototypic osmotic diuretic,
- D-Mannitol is a water-soluble, lipid-insoluble hexahydroxy alcohol. It does not diffuse GIT or renal tubule epithelium. Mannitol should be given by the **intravenous (IV) route**.
- Mannitol enters renal luminal fluid only by glomerular filtration. Its **high luminal fluid concentration creates an osmotic effect that may prevent the reabsorption of up to 28% of the filtered load of water**.
- Mannitol may be employed prophylactically to avoid acute renal failure or the reduction of CSF volume and pressure.
- Because solutions of mannitol may expand the extracellular fluid volume, they should not be used in patients with severe renal disease or cardiac decompensation.

Theophylline

The prototypic xanthine, is known to promote a **weak diuresis** by stimulation of cardiac function and by a direct action on the nephron. Although theophylline is **infrequently used as a diuretic**, a diuresis may be an observed side effect when it is used as a bronchodilator.

Summary of Diuretics



References

Wilson & Gisvold's Text Book of Organic Medicinal And Pharmaceutical Chemistry 11th edition.

Bertran G. Katzung- Basic & Clinical Pharmacology 12th edition.

Thomas L Lemke/ David A Willams- Foye's principle of Medicinal Chemistry 6th edition

Lippincott Williams & wilkins- Remington The Science And Practice Of Pharmacy 21st edition

D. Sriram, P. Yogeeswari – Medicinal Chemistry.

Volume 2 by Dr. S.S. Kadam, Dr. K. R. Mahadik, Dr.K.G. Bothara