



تفريغ ميديسينال

Diuretics

محاضرة:

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الصيدلانية:



لجان الرفعات



ANTI-HYPERTENSIVE AGENTS

part 2 (adjuvant therapy)

كيف رح تطلع السوائل؟

الاستمى اكي رح يخلي السوائل تطلع من

Diuretics

الجسم هو خروج الـ electrolytes زي Ca^{2+} و Mg^{2+} ...

➤ Diuretics are chemicals that increase the volume of the urine excreted by the kidney through increase the rate of urine formation.

➤ Reduce the extracellular fluid volume by promoting the excretion of Na^+ , Cl^- or HCO_3^- ions which constitute the main electrolytes of the extracellular fluid.

diuretic رح تزيد الـ Urin output

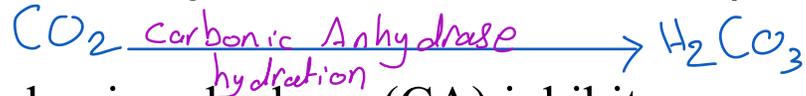
Diuretics are used mainly in the

1- Relief of edema: زي السوائل من الرشح والسوائل ابي تتجمع باليدية والرجلين

2- As adjuvant in the management of hypertension as well as other disorders including; congestive heart failure, chronic and acute renal failure, glaucoma, hypercalcemia, diabetes insipidus, and liver cirrhosis with ascites.

اسباب لحدوث الـ edema

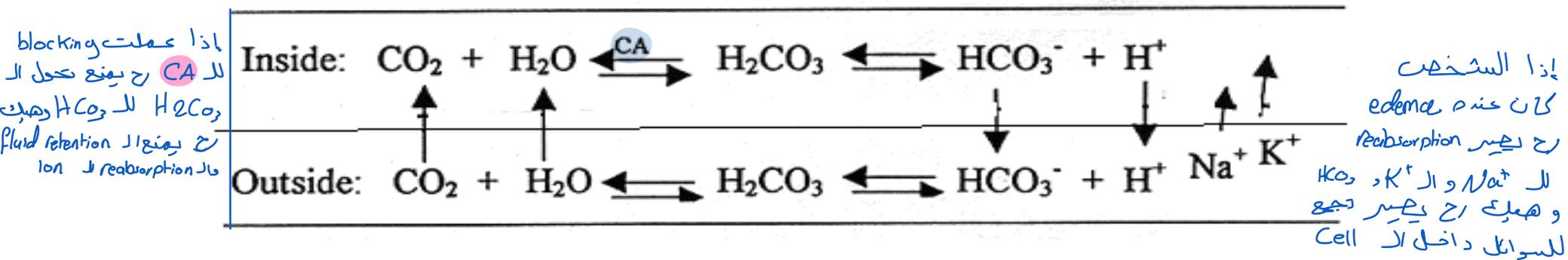
1) Carbonic Anhydrase Inhibitors (CA inhibitors).



- Carbonic anhydrase (CA) inhibitors are derived from the sulphonamide antibacterials.
 - Sulfonamide group ($-\text{SO}_2\text{NH}_2$) is essential for its activity.

➤ Carbonic anhydrase is an enzyme responsible for the hydration of CO_2 and its conversion to H_2CO_3

➤ The net result of carbonic anhydrase inhibition is increased excretion of Na^+ , K^+ , HCO_3^-

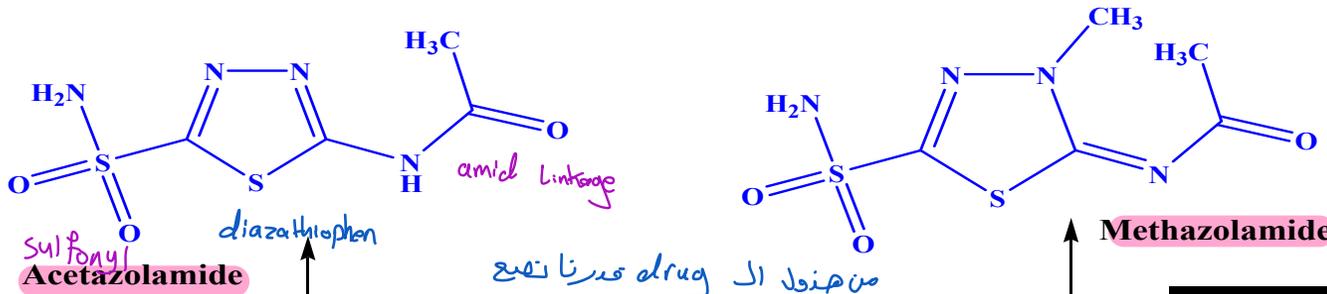


Carbonic anhydrase inhibitors contain free **sulfamoyl group $-\text{SO}_2\text{NH}_2$** which is essential for activity.

The SO_2NH_2 is isosteric with H_2CO_3 and is able to occupy the receptor site of carbonic acid formation and thus it must be un-substituted.

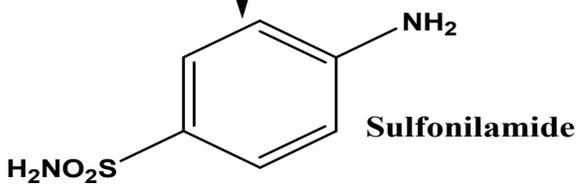
Development of two classes of carbonic anhydrase inhibitors based on the actions of sulfanilamide

الـ SO_2/H_2 راح يحل محل الـ H_2CO_3
 يصير راح يمنحوا انما تتفكك وصلح
 راح تمنع الـ CO_2 / reabsorption



من ههنا الـ drug ميرنا نتبع
 الـ meta-disulfamoylbenzen
Heterocyclic sulfonamide

كلمة **isosteric** (ايزوستيريك) في الكيمياء تعني "متشابه في الحجم أو الشكل" أو "له نفس عدد الذرات أو نفس البنية الهندسية".
 ببساطة، مركبان **isosteric** يكونان متشابهين في الحجم أو الشكل أو التركيب بحيث يمكن أن يحل أحدهما محل الآخر في جزيء دون تغيير كبير في خصائصه الكيميائية أو الفيزيائية.
 هل تريد شرح أكثر تفصيلاً أو أمثلة؟



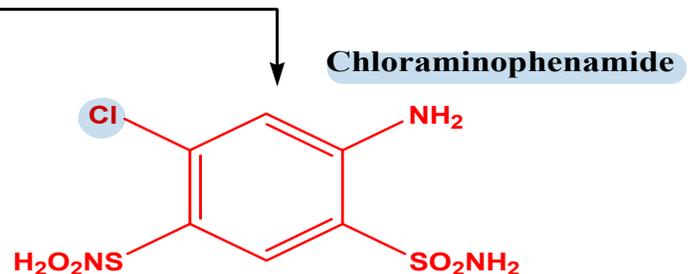
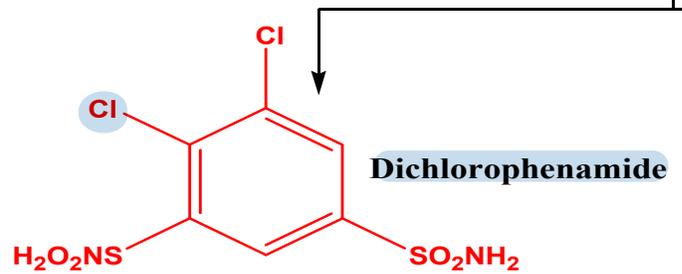
meta-Disulfamoylbenzenes

Maximal diuretic activity is observed when the position is substituted with: Cl-, Br-, CF₃-, or NO₂-

Substitution with amino(-NH₂) group increases saluretic activity but decrease carbonic anhydrase activity.

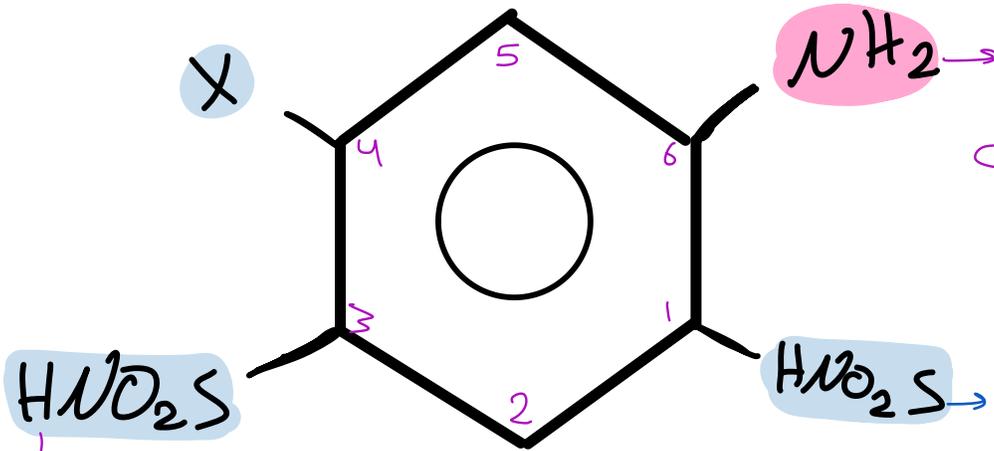
H₂NO₂S (An unsubstituted sulfamoyl moiety is of paramount importance

SO₂NH₂ can be replaced with similarly electrophilic group (e.g. Carboxyl, Carbonyl) that may increase diuretic potency while decreasing carbonic anhydrase inhibitory activity



هذه الـ diuretic effect اذا بدلنا بـ group ثانية صفت تزيد الـ Potency بس الـ diuretic effect رح تقل

بغير ابدلنا بـ electrophile group ثاني لازم تكون acidic



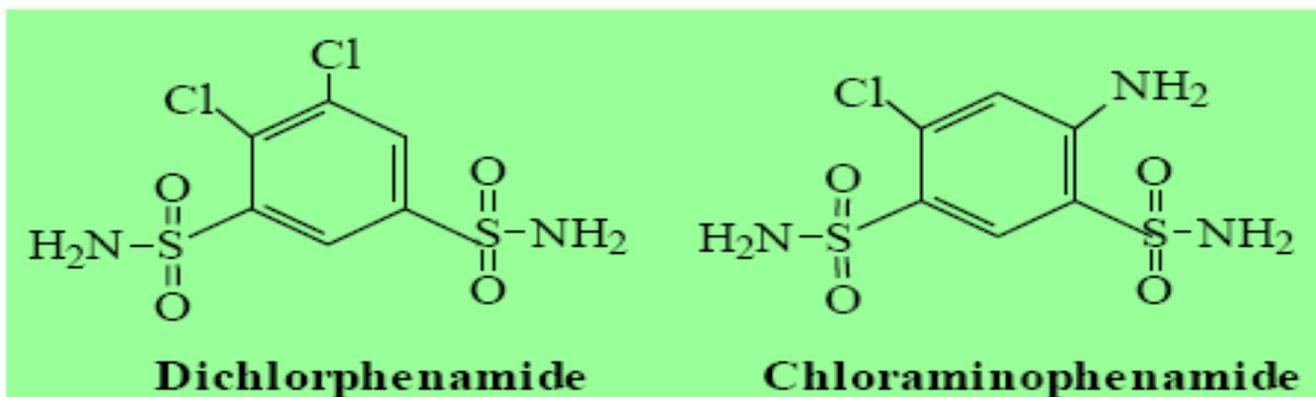
لازم تقل موجودة عنان ما أخسر الـ activity

اذا substitution في الـ 4 و 5 اهم! شبيء في الـ 3 رقم 4 صحت يكون فيه

اذا خسرت الـ substitution رح اخسر الـ activity ممكن الـ substitution يكون في الـ 3 بس الـ 4 الـ 4

Metadisulfamoylbenzene derivatives series SAR:

- The parent 1,3 meta-disulfamoylbenzene lacked diuretic activity.
- Key substitutions in 4 and 5 positions lead to compounds with diuretic activity.



* Side effects of carbonic anhydrase inhibitors

1- systemic acidosis. Due to renal loss of HCO₃

2- hypokalemia. Due to renal loss of K⁺

3- hypersensitivity .such as urticaria, drug fever, blood dyscrasias, and interstitial nephritis.

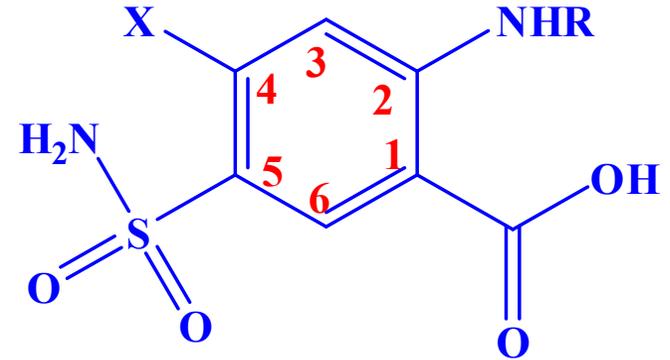
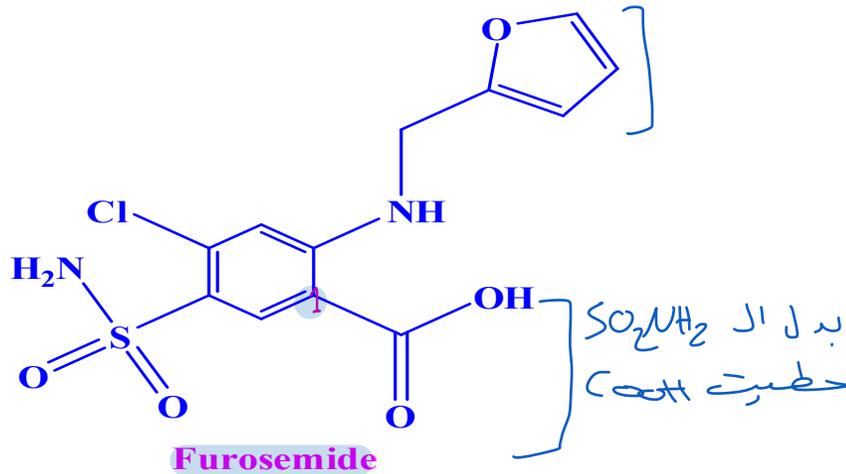
2) High Ceiling Diuretics (Site 2 Diuretics)

- They inhibit co-transport system located on the thick ascending limb of Henle's loop (1Na⁺, 1K⁺, 2 Cl⁻). Approximately, 20-25% of the filtered load of Na⁺ is reabsorbed in this segment. They cause **hypokalemia**, *hyponatremia*
كبحوا رج الامتصاص لـ Cl⁻, K⁺, Na⁺ rapid onset of diuresis : Their onset of action in about 30 minutes and lasts for 6 hours.
- Used largely to treat edema associated with heart, liver or kidney failure
- Potential for a transient or permanent loss of hearing *ما يقدر استخدمهم لفترة طويلة*
- The pronounced diuretic effect can result in severe fluid and electrolyte depletion if not monitored

Chemically, high-ceiling diuretics are classified into:

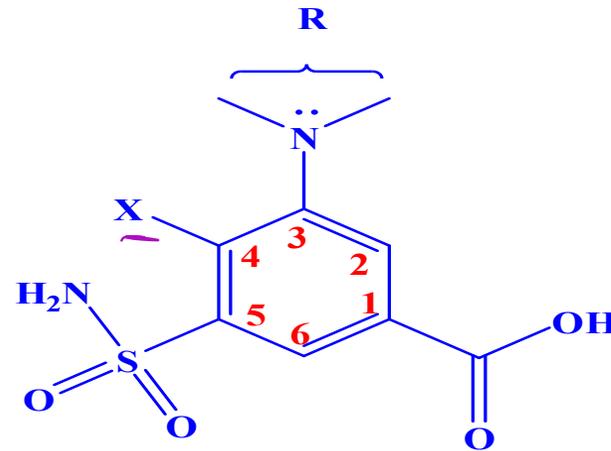
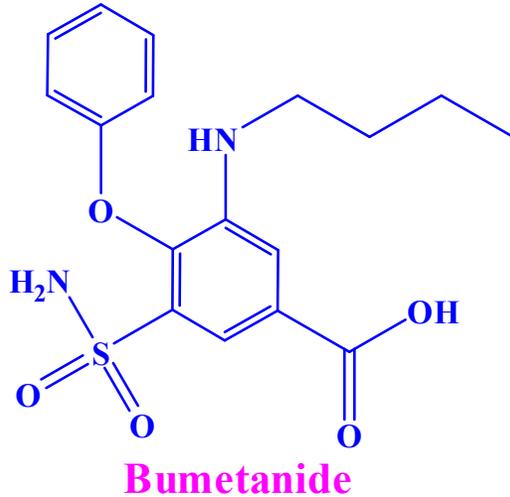
- A) 2-Aminobenzoic acid derivatives. sulfonamide derivatives
- B) 3-Aminobenzoic acid derivatives. sulfonamide derivatives
- C) Phenoxyacetic acid derivatives non-sulfonamide.

A) 2-Aminobenzoic acid (Anthranilic acid) derivatives



* Furosemide (LASIX) 8 – 10 x more potent than most thiazides and related agents

B) 3-Aminobenzoic acid derivatives → غير موقع ال amin ليست

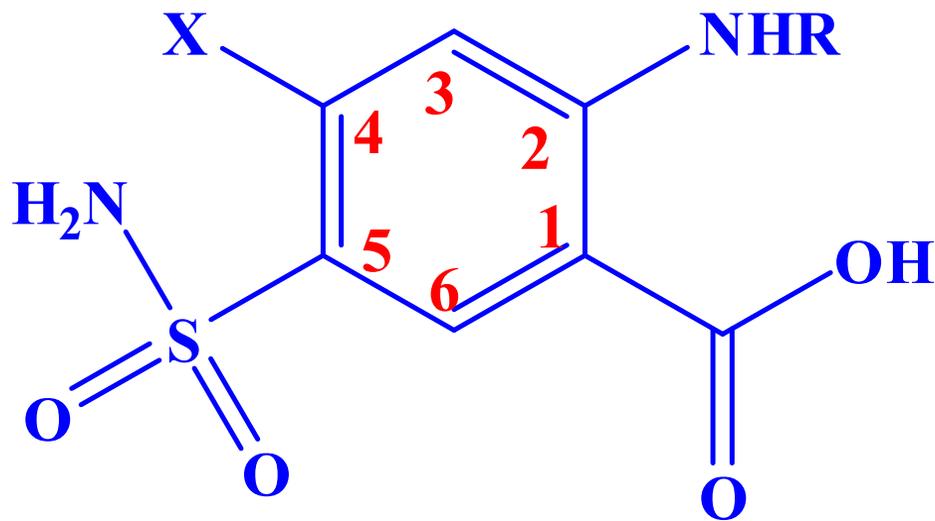


Bumetanide (BUMEX) less frequent ototoxic side effects than other loop diuretics

Bumetanide is 50 times more potent than furosemide with shorter duration of action.

* SAR of Aminobenzoic Acid Derivatives:

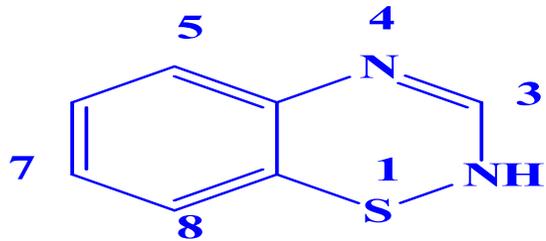
- 1- Position-1 must be acidic (optimal activity with COOH).
- 2- Sulfamoyl group at 5-must be free.
- 3- Activating group at position 4- as Cl or CF₃.



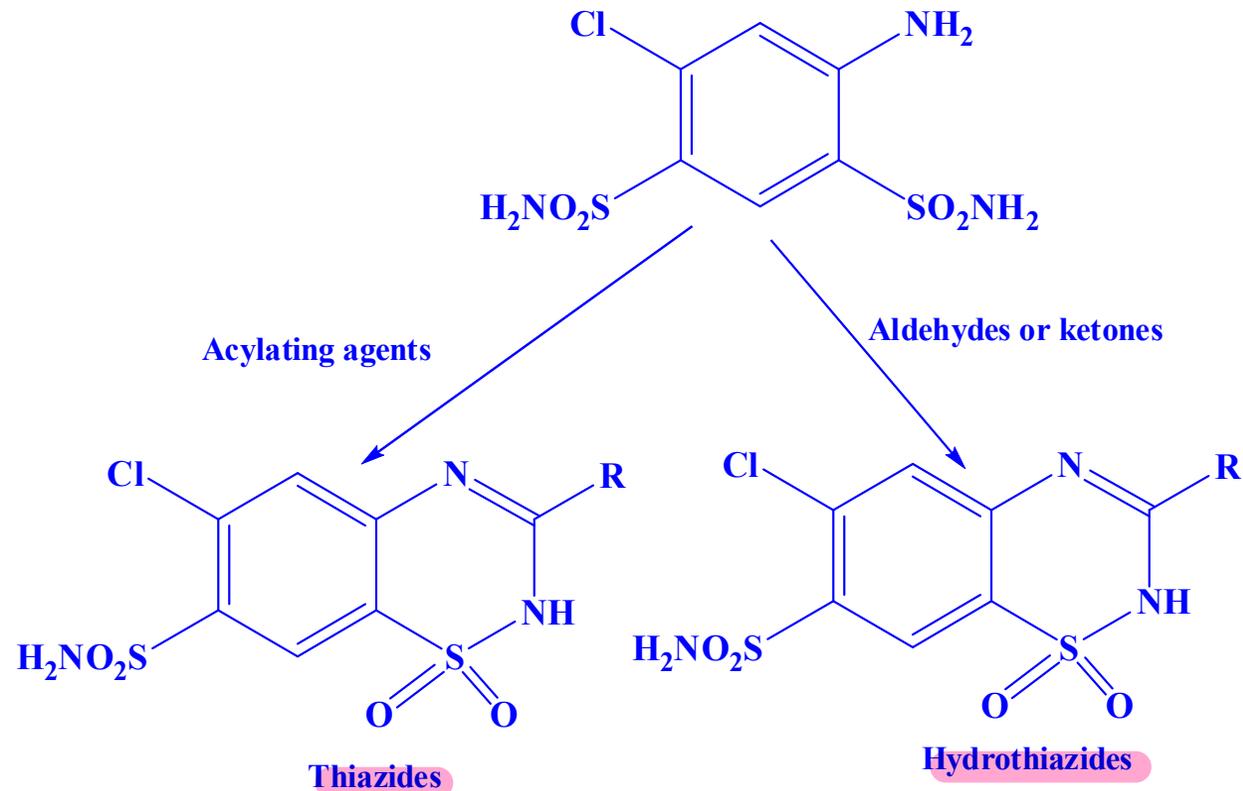
3-The Thiazides diuretics (Site 3 Diuretics)

A new series of compounds possessing important diuretic activity was developed by acetylation the amino group of **chloraminophenamide**, This group is a series of **benzothiazide derivatives**, **without** the undesirable effects of carbonic anhydrase inhibitors. **inhibit re-absorption of Na⁺ and consequently Cl⁻ in the distal convoluted tubule** via inhibition of the **Na⁺-Cl⁻ symporter** located in the distal convoluted tubule (**saluretic**). They lead to loss of 5-8% of the followed load of sodium.

يُقدر استخدامهم لفترة طويلة وبالعادة يكونوا من أدوية الـ HTN

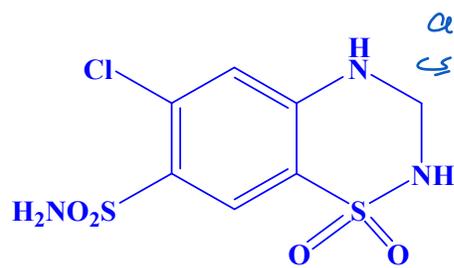


Benzothiadiazine (Benzothiazide)



Members of Thiazide diuretics

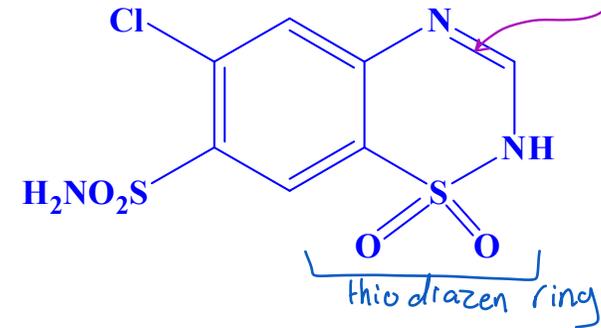
Hydrochlorothiazide (Esidrix)



الختلاف هو انه هتفتت ب group (acyl) كل لا amin و بهر يت مار كتي cyclization واعطاي هتول ال diuretic 2 type

The duration of action up to **18** hours

Chlorothiazide (Diuril)



The duration of action from **6-12** hours

Frequently are first line drugs for treating mild to moderate hypertension

- Used extensively to treat edema associated with congestive heart failure (CHF) and cirrhosis of the liver.

- Very often combined with other antihypertensive agents

- Usually given orally

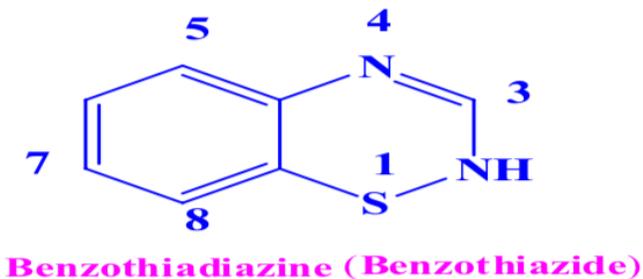
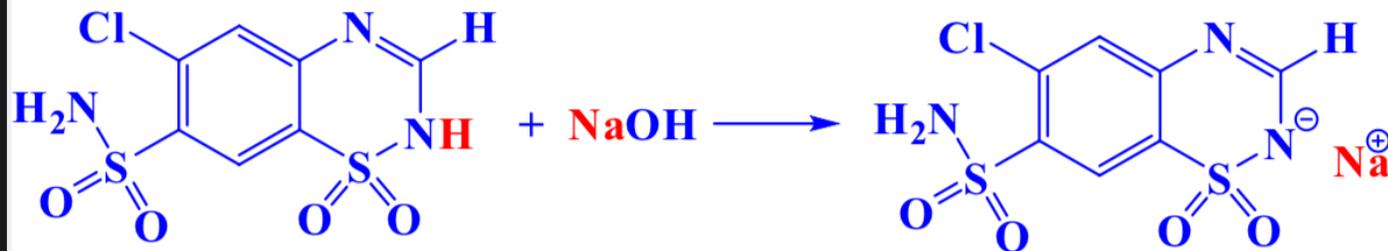
- most thiazides are excreted unchanged. → highly hydrophilic لازم

SAR of Thiazide Diuretics

- 1) The 2-position can tolerate relatively small alkyl group as CH_3 .

N.B. NH at 2-position is acidic can form sod. Salt and can be used for IV administration (in drugs with free NH at 2-position.

کشان اقدر اعلمه salt
 ال Na⁺ و اقدر استخبره
 IV salt



- 2) Substitution at 3-position affect **potency and duration of action**, when H is replaced by CH_2Cl gives activity up to 24h and 4-positions increases the potency 3-10 times.
 • **C-3: The lipophilicity of the C.** while $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CF}_3$ increase up to 48h and benzyl (18h).
- 3) Loss of the =double bond between the 3- ~~3~~⁴ **substituent governs potency and duration**
- 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 (electron withdrawing group here increases activity and electron donating groups at C-6 will cause a decrease in activity)
- 6) The **sulfamoyl group in the 7-position is essential for diuretic activity**
C-7 MUST have an unsubstituted sulfonamide & it must be directly attached to the aromatic ring

إذا العريف عند HTN و عند نقص K^+ يعطوه هذا النوع

Potassium-Sparing Diuretics (Na^+ Channel Blockers)

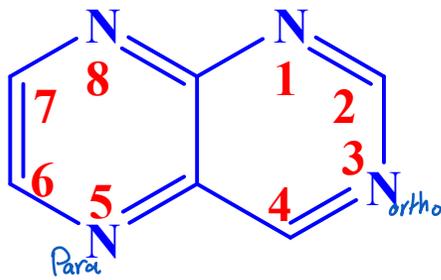
- Act mainly on the **late distal convoluted tubule** and **early collecting tubule**.
- Block about **2–3%** of Na^+ reabsorption by inhibiting **Na^+ channels** in the luminal membrane.

$dec^+ K^+$ excretion

•Result:

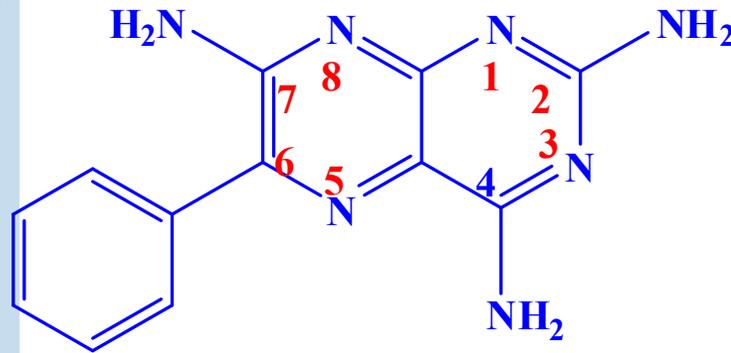
- $\downarrow Na^+$ reabsorption $\rightarrow \downarrow Na^+/K^+$ ATPase activity.
- $\downarrow K^+$ secretion (potassium is **spared**).

من هذا النوع موجوده بال drug

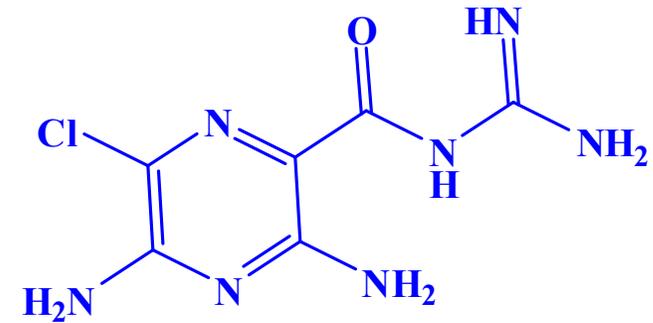


Pteridine

2 aromatic ring
فيهم 20



Triamterene



Amiloride

هو derivated من هذا

•Triamterene:

- Blocks Na^+ reabsorption and K^+ excretion **independently of aldosterone**.
- Inhibits cationic exchange in the distal tubule.
- These agents **increase Na^+ and Cl^- excretion** without causing **K^+ depletion** (unlike other diuretics).

ال Aldosteron عبارة عن Hormon يرتبط بال Mineralcorticoid receptor وظيفته يرتبط

مع زيادة excretion لل Na⁺ و هذا يقل ال BP ، فتمتصوا ادوية تشبه ال Aldosteron لتعطي نفس ال effect

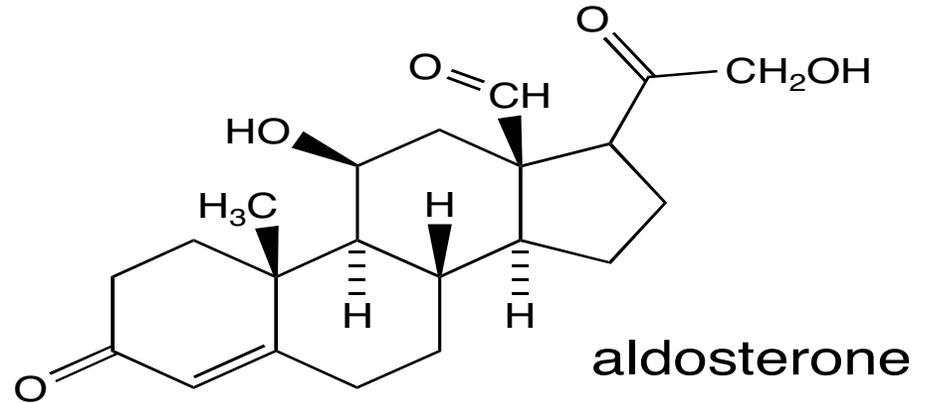
B. Aldosterone antagonists

Spirolactone (Aldactone)

↳ ↑ Na⁺ + excretion

↓ K⁺ + excretion

- Aldosterone is a mineralocorticoid hormone that binds to a soluble cytosolic receptor and causes transcriptional activation of genes for the synthesis of ion transport proteins.
- Progesterone was observed to inhibit the effects of aldosterone
 - Lead to the search for compounds with the antialdosterone activity of progesterone w/o other steroidal hormone side effects
- Spirolactone is a direct aldosterone receptor antagonist
- commonly prescribe in fixed combination with hydrochlorothiazide (Aldactazide)
- spironolactone is tumorigenic in long term oral studies in rats



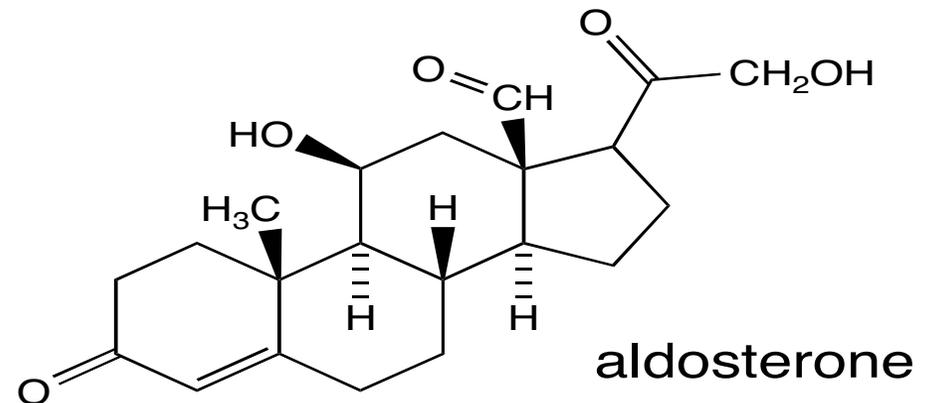
Aldosterone antagonists",

- which refers to a class of potassium-sparing diuretics that block the action of aldosterone at its receptor in the distal nephron (specifically in the collecting duct).
- Progesterone was observed to inhibit the effects of aldosterone: Lead to the search for compounds with the antialdosterone activity of progesterone w/o other steroidal hormone side effects



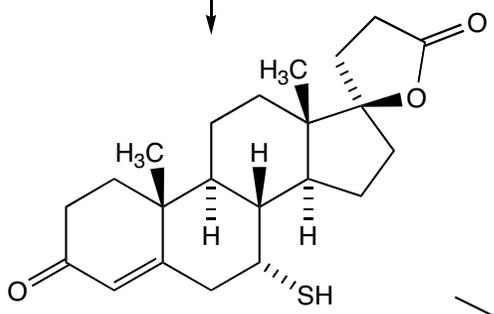
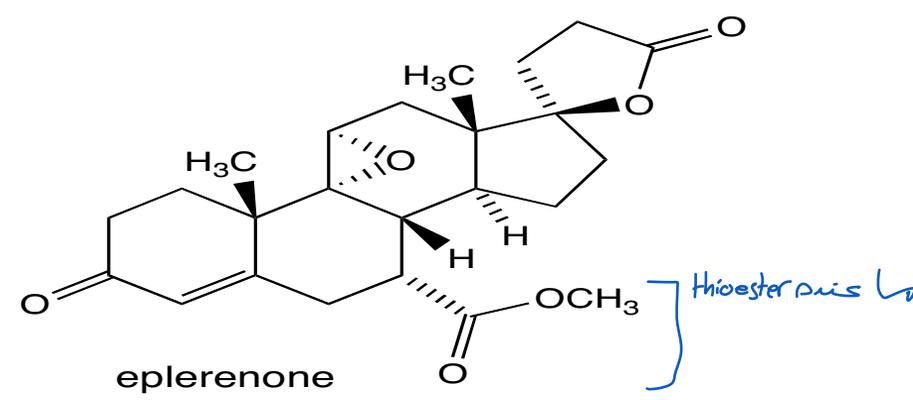
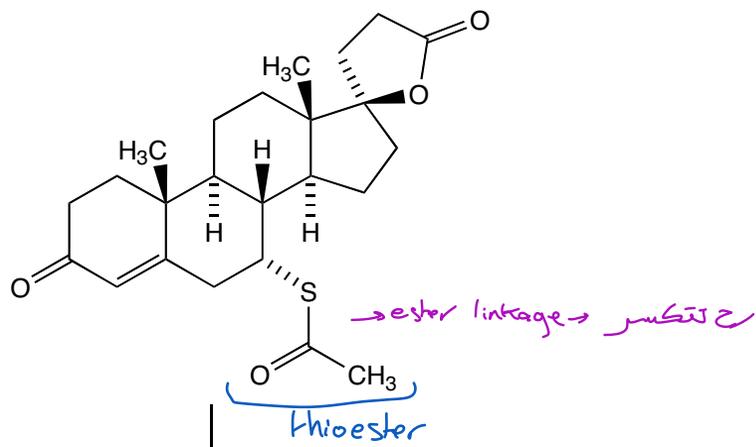
Mechanism of Action:

- Aldosterone normally increases sodium reabsorption and potassium excretion by acting on mineralocorticoid receptors.
- Aldosterone antagonists (like spironolactone and eplerenone) block these receptors.
- Result:
 - ↓ Sodium reabsorption → Natriuresis (sodium loss)
 - ↓ Potassium excretion → Potassium retention
- *← مشاكل هرمونية* Spironolactone has antiandrogen effects (e.g., gynecomastia التثدي عند الرجال)
- Eplerenone More selective for aldosterone receptor (fewer hormonal side effects)

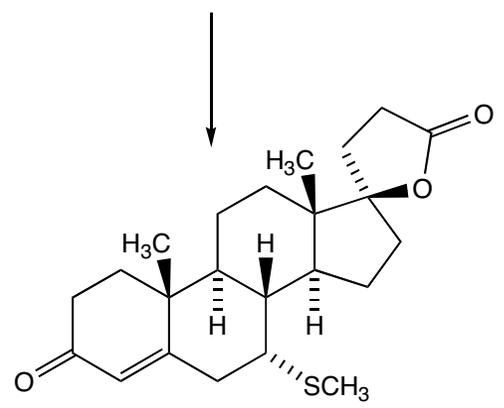


Spironolactone (Aldactone)

Eplerenone (Inspra®)



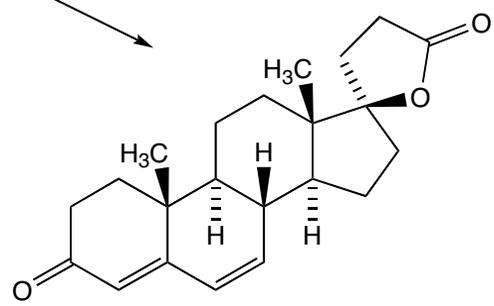
7α-thiol-spironolactone



7α-thiomethyl-spironolactone

- note the 'opposite sense' of the 7a methyl ester compared to the thioester of spironolactone metabolized by CYP3A4
- no active metabolites identified
No hormonal side effect

Major metabolite



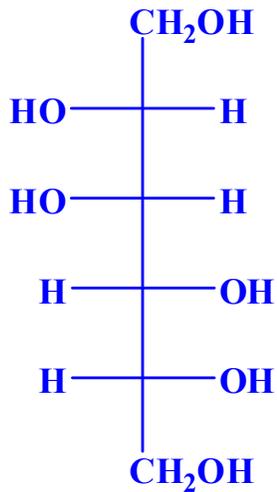
canrenone (active metabolite)

osmotic pressure ← رح زيديدا او **Osmotic diuretics** → hydrophilic compound بكونوا

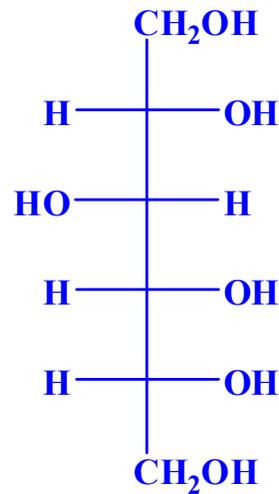
Osmotic diuretics are **low-molecular-weight** compounds that are not extensively metabolized and are **passively filtered through Bowman's Capsules into the renal tubules**. (Chemistry. Osmotic diuretics are the agents that mobilise fluids by increasing the osmotic pressure in tubules

اغلبهم sugar ويطلعوا
كل اشياء مع ال fluid

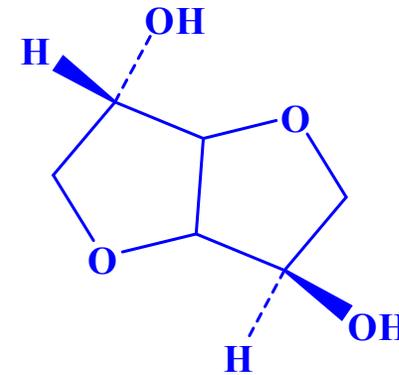
- **Polyols** such as **mannitol**, **sorbitol** and **isosorbide** provide this effect. Mannitol and sorbitol are used intravenously in solutions of 5-50%.



Mannitol



Sorbitol



Isosorbide is used orally to cause a reduction in intraocular pressure.

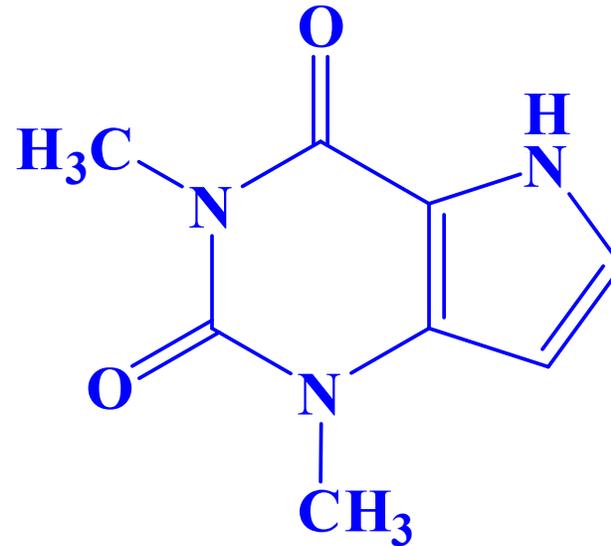
The primary sites of action for osmotic diuretics are the Loop of Henle and the proximal tubule where the membrane is most permeable to water.

← رح زيديدا او water permeability ل

Miscellaneous Diuretics:

Theophyllin موجود بالشاعی

It is a xanthine derivative that promote a weak diuresis by stimulation of cardiac function (increases the glomelular filtrate) and by direct action on the nephron.

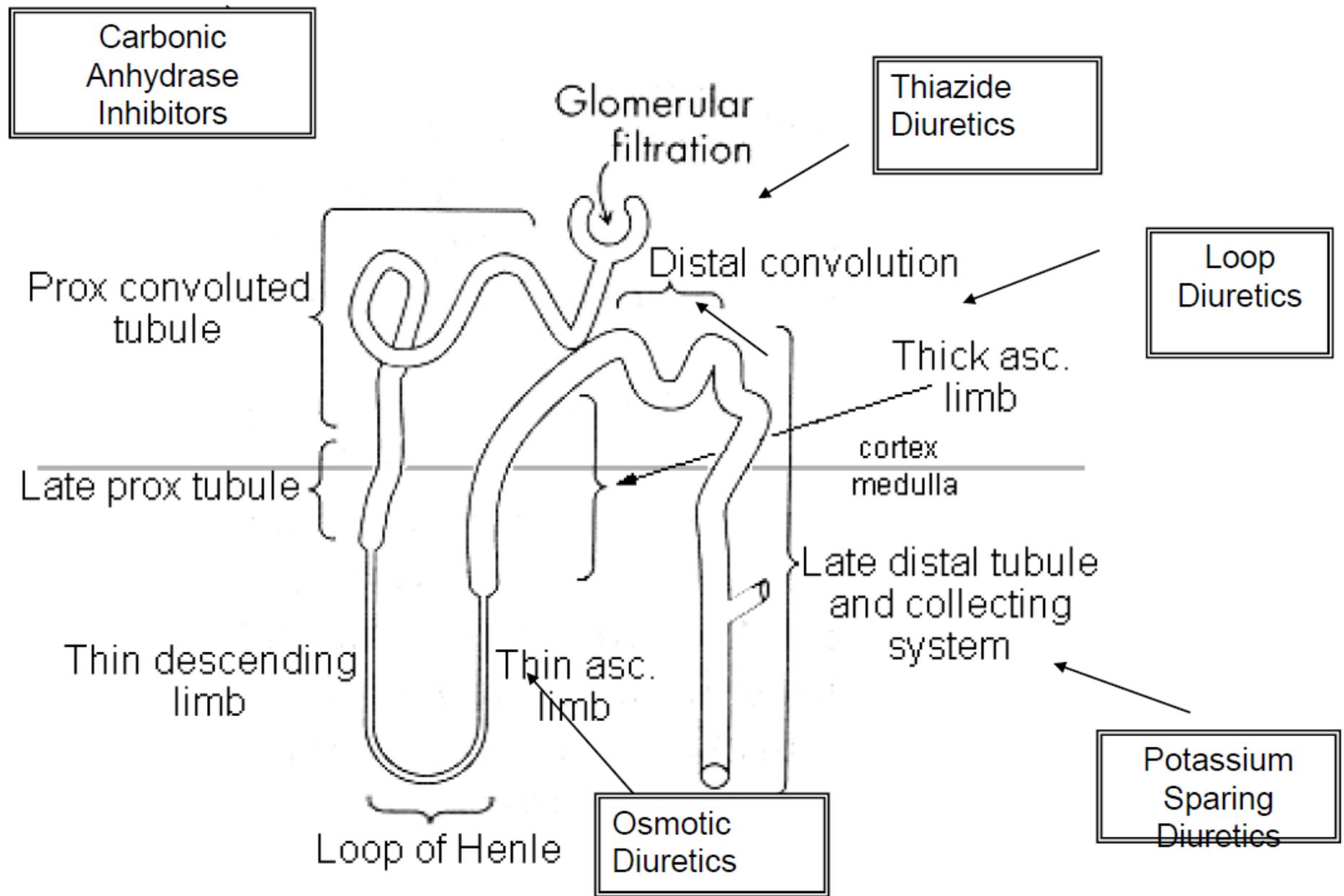


Mixtures of Diuretics

Hydrochlorothiazide and Amiloride (Moduretic).

Hydrochlorothiazide and spironolactone (Aldactazide).

Principal Sites of Action of Diuretics in the Nephron



لا تنسوا زميلنا ايهم من دعائكم



