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Diuretics

Medicinal Chemistry-II

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M. Pharm., Ph.D.

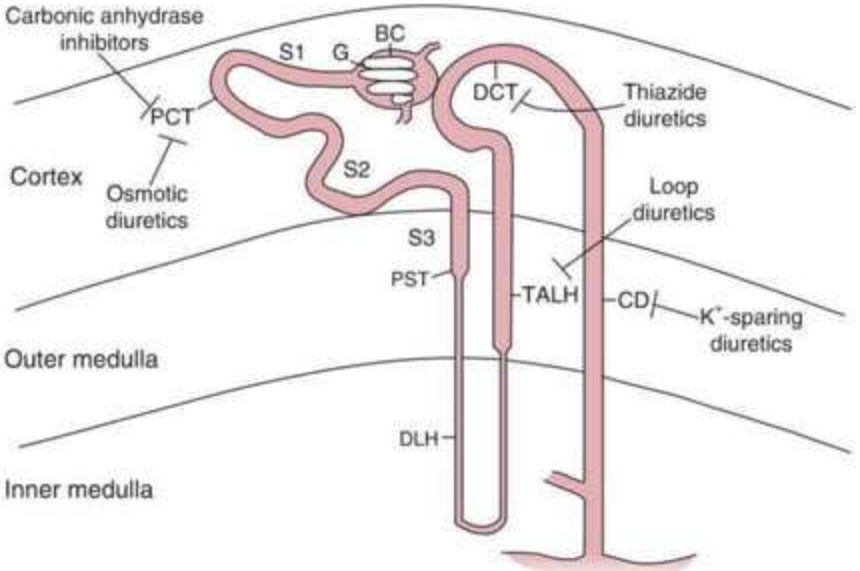
Diuretics

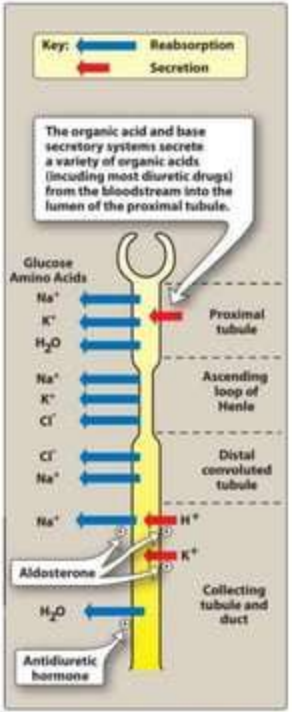
- Diuretics are chemicals that increase the rate of urine formation.
- Diuretic usage leads to increased excretion of electrolytes (especially sodium and chloride ions) and water from the body by increasing the urine flow rate, without affecting protein, vitamin, glucose or amino acid reabsorption.
- These pharmacological properties have led to the use of diuretics in the treatment of edematous conditions resulting from a variety of causes (e.g., congestive heart failure, nephrotic syndrome and chronic liver disease) and in the management of hypertension.
- Diuretic drugs also are useful as the sole agent or as adjunct therapy in the treatment of a wide range of other clinical conditions, including hypercalcemia, diabetes insipidus, acute mountain sickness, primary hyperaldosteronism, and glaucoma.

Diuretics

- The primary target organ for diuretics is the kidney, where these drugs interfere with the reabsorption of sodium and other ions from the lumina of the nephrons, which are the functional units of the kidney.
- The amount of ions and accompanying water that are excreted as urine following administration of a diuretic, however, is determined by many factors, including the chemical structure of the diuretic, the site or sites of action of the agent, the salt intake of the patient, and the amount of extracellular fluid present.
- In addition to the direct effect of diuretics to impair solute and water reabsorption from the nephron, diuretics also can trigger compensatory physiological events that have an impact on either the magnitude or the duration of the diuretic response.

Normal Physiology of Urine Formation





Normal Physiology of Urine Formation

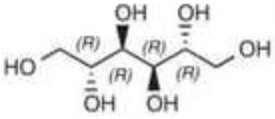
- **Two important functions of the kidney are (1) to maintain a homeostatic balance of electrolytes and water and (2) to excrete water-soluble end products of metabolism.**
- **The kidney accomplishes these functions through the formation of urine by the nephrons.**
- **The nephrons are composed of a specialized capillary bed called the glomerulus and a long tubule divided anatomically and functionally into the proximal tubule, loop of Henle, and distal tubule.**
- **Each component of the nephron contributes to the normal functioning of the kidney in a unique manner; thus, all are targets for different classes of diuretic agents.**

Table 17.4 Diuretics: Sites and Mechanisms of Action

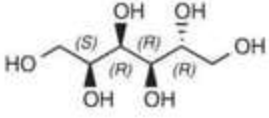
Diuretic Class	Site of Action	Mechanism of Action
Osmotics	Proximal tubule	Osmotic effects decrease sodium and water reabsorption
	Loop of Henle	Increases medullary blood flow to decrease medullary hypertonicity and reduce sodium and water reabsorption
	Collecting tubule	Sodium and water reabsorption decreases because of reduced medullary hypertonicity and elevated urinary flow rate
Carbonic anhydrase inhibitors	Proximal convoluted tubule	Inhibition of renal carbonic anhydrase decreases sodium bicarbonate reabsorption
Thiazides and thiazide-like	Cortical portion of the thick ascending limb of loop of Henle and distal tubule	Inhibition of Na^+/Cl^- symporter
Loop or high ceiling	Thick ascending limb of the loop of Henle	Inhibition of the luminal $Na^+/K^+/2Cl^-$ transport system
Potassium sparing	Distal tubule and collecting duct	Inhibition of sodium and water reabsorption by competitive inhibition of aldosterone (spironolactone) or blockade of sodium channel at the luminal membrane (triamterene and amiloride)

Osmotic Diuretics

- **MECHANISM OF ACTION:** Osmotic diuretics are low molecular-weight compounds that are freely filtered through the Bowman's capsule.
- Once in the renal tubule, osmotic diuretics have limited reabsorption because of their high-water solubility.
- When administered as a hypertonic (hyperosmolar) solution, these agents increase intraluminal osmotic pressure, causing water to pass from the body into the tubule.
- As the osmotic agent and associated water are not reabsorbed from the nephron, a diuretic effect is observed.
- Osmotic diuretics increase the volume of urine and the excretion of water and almost all electrolytes.



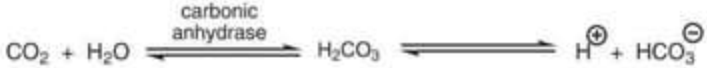
Mannitol



Sorbitol

Carbonic Anhydrase Inhibitors

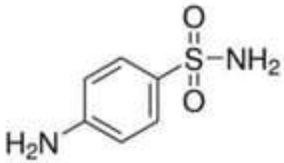
- **Carbonic anhydrase, which catalyzes the formation of carbonic acid from carbon dioxide and water.**
- **This inhibition of carbonic anhydrase resulted in a lesser exchange of hydrogen ions for sodium ions in the kidney tubule.**
- **Sodium ions, along with bicarbonate ions, and associated water molecules were then excreted, and a diuretic effect was noted.**



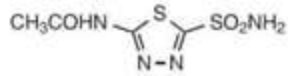
Carbonic Anhydrase Inhibitors

- **Carbonic anhydrase inhibitors induce diuresis by inhibiting the formation of carbonic acid within proximal (proximal convoluted tubule; S2) and distal tubular cells to limit the number of hydrogen ions available to promote sodium reabsorption.**
- **For a diuretic response to be observed, more than 99% of the carbonic anhydrase must be inhibited.**
- **Although carbonic anhydrase activity in the proximal tubule regulates the reabsorption of approximately 20%-25% of the filtered load of sodium, the carbonic anhydrase inhibitors are not highly efficacious diuretics.**

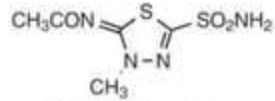
Carbonic Anhydrase Inhibitors



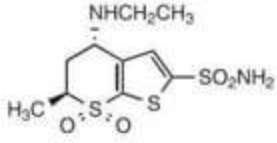
Sulfanilamide



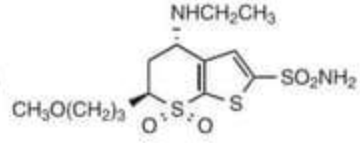
Acetazolamide



Methazolamide



Dorzolamide



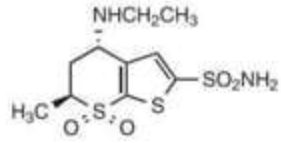
Brinzolamide

Carbonic Anhydrase Inhibitors

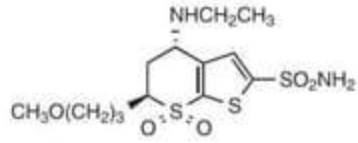
- **Sulfanilamide inhibits carbonic anhydrase; however, the large doses required for inhibition and the side effects associated with this compound prompted a search for more effective carbonic anhydrase inhibitors as diuretics.**
- **This led to the discovery that the sulfonamide portion of an active diuretic molecule could not be monosubstituted or disubstituted.**
- **Acetazolamide was introduced in 1953 as an orally effective diuretic drug.**
- **Methazolamide is a close structural analog of acetazolamide in which one of the active hydrogens in the thiadiazole ring has been replaced by a methyl group.**

Carbonic Anhydrase Inhibitors

- **This decreases polarity of the compound and permits a greater penetration into the ocular fluid, where it acts as a carbonic anhydrase inhibitor, reducing intraocular pressure.**
- **Brinzolamide and dorzolamide contain ionizable amino groups and are the result of efforts to develop water-soluble compounds that retain sufficient lipophilicity to penetrate the cornea.**
- **They are only indicated for topical eye administration in glaucoma patients.**



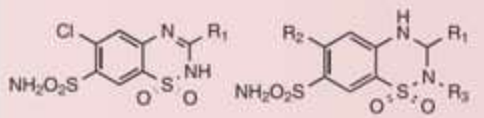
Dorzolamide



Brinzolamide

Thiazide Diuretics

- **Thiazide and thiazide-like diuretics are a main stay in the treatment of hypertension.**
- **They are used in monotherapy and in combination with other antihypertensive drugs, including ACE inhibitors, ARBs, and β-blockers.**
- **Chloro and amino substitution on benzene Disulfonamide gave compounds with increased activity, but these compounds were weak carbonic anhydrase inhibitors.**
- **When the amino group was acylated, an unexpected ring closure took place.**
- **These compounds possessed a diuretic activity independent of the carbonic anhydrase inhibitory activity, and a new series of diuretics called the benzothiadiazines was discovered.**

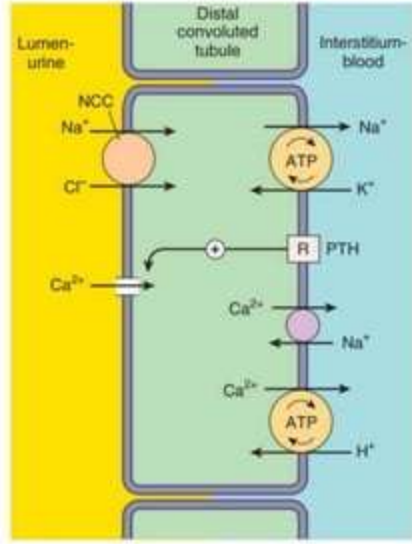


Thiazides: Structure I Thiazides: Structure II

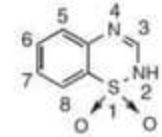
Generic Name	Trade Name	Structure
Bendroflumethiazide	Naturetin	Structure II: R_1 = benzyl; R_2 = CF_3; R_3 = H
Chlorothiazide	Diuril	Structure I: R_1 = H
Hydrochlorothiazide	HydroDiuril Esidrix	Structure II: R_1 = H; R_2 = Cl; R_3 = H
Hydroflumethiazide	Saluron Diucardin	Structure II: R_1 = H; R_2 = CF_3; R_3 = H
Methyclothiazide	Aquatensen	Structure II: R_1 = CH_2Cl; R2 = Cl; R3 = CH_3

Thiazide Diuretics: MOA

- **These diuretics are actively secreted in the proximal tubule and are carried to the loop of Henle and to the distal tubule.**
- **The major site of action of these compounds is in the distal convoluted tubule, where these drugs compete for the chloride binding site of the Na^+/Cl^- symporter and inhibit the reabsorption of sodium and chloride ions.**
- **For this reason, they are referred to as saluretics. They also inhibit the reabsorption of potassium and bicarbonate ions, but to a lesser degree.**
- **Hypersensitivity reactions, gastric irritation, and electrolyte imbalances, such as hyponatremia, hypokalemia, hypomagnesemia, hypochloremic alkalosis, hypercalcemia, and hyperuricemia.**

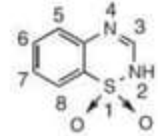


Thiazide Diuretics: SAR



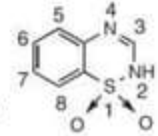
- **Thiazide diuretics are weakly acidic compounds, with common benzothiadiazine 1,1-dioxide nucleus.**
- **Chlorothiazide is the simplest member of this series, with pKa values of 6.7 and 9.5.**
- **The hydrogen atom at the N-2 is the most acidic because of the electron-withdrawing effects of the neighboring sulfone group.**
- **The sulfonamide group that is substituted at C-7 provides an additional point of acidity in the molecule but is less acidic than the N-2 proton.**
- **These acidic protons make possible the formation of a water-soluble sodium salt that can be used for intravenous administration of the diuretics**

Thiazide Diuretics: SAR



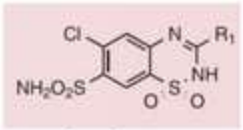
- **An electron-withdrawing group is necessary at position 6 for diuretic activity.**
- **Little diuretic activity is seen with a hydrogen atom at position 6, whereas compounds with either chloro (e.g., chlorothiazide, hydrochlorothiazide, and methyclothiazide) or trifluoromethyl (e.g., bendrofloumethiazide and hydroflumethiazide) substituents are highly active.**
- **The trifluoromethyl-substituted diuretics are more lipid soluble and have a longer duration of action than their chloro-substituted analogs.**
- **When electron-releasing groups, such as methyl or methoxyl, are placed at position 6, the diuretic activity is markedly reduced.**

Thiazide Diuretics: SAR



- **Replacement or removal of the sulfonamide group at position 7 yields compounds with little or no diuretic activity.**
- **Saturation of the double bond to give a 3,4-dihydro derivative (cf. chlorothiazide and hydrochlorothiazide) produces a diuretic that is 10-fold more active than the unsaturated derivative.**
- **Substitution with a lipophilic group at position 3 gives a marked increase in the diuretic potency.**
- **Haloalkyl, aralkyl, or thioether substitution increases the lipid solubility of the molecule and yields compounds with a longer duration of action.**
- **Alkyl substitution on the 2-N position also decreases the polarity and increases the duration of diuretic action**

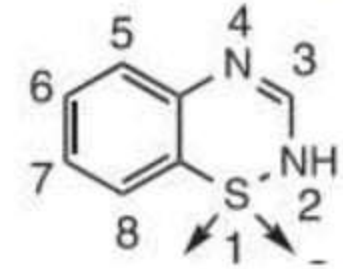
Thiazide-Like Diuretics

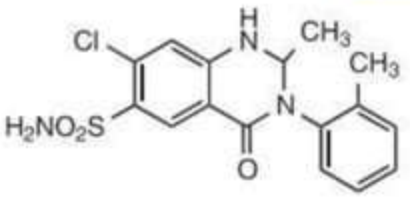


- This is a structurally diverse group of sulfonamide-containing compounds that are derivatives of quinazolin-4-one, phthalimidine, or indoline.
- In spite of their dissimilar structures and lack of a benzothiadiazine ring, these drugs have the same mechanism of action and similar therapeutic activities and adverse effects as the thiazide diuretics.
- However, in contrast to thiazide diuretics, metolazone (2.5-20 mg given as a single oral dose) maybe effective as a diuretic when the GFR falls below 40 mL/min.
- In addition, chlorthalidone has a long duration of action (48-72 hr).
- For example, although metolazone is administered daily, chlorthalidone may be administered in doses of 25-100 mg three times a week.
- Uses of indapamide include the treatment of essential hypertension and edema resulting from congestive heart failure.
- Like metolazone, indapamide is an effective diuretic drug when the GFR is below 40 mL/min

Medicinal Chemistry of Thiazide-Like Diuretics

- The quinazolin-4-one molecule has been structurally modified in a manner similar to the modification of the thiazide diuretics.
- Metolazone (pK_a= 9.7) is an example of this class of drug.
- The structural difference between the quinazolinone and thiazide diuretics is the replacement of the 4-sulfonegroup (-SO_2-) in the former with a 4-keto group (-CO) in the latter.
- Because of their similar structures, it is not surprising that the quinazolin-4-ones have a diuretic effect similar to that of the thiazides.

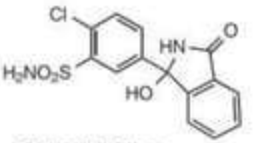




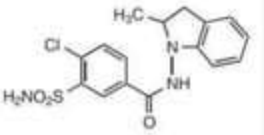
Metolazone

Medicinal Chemistry of Thiazide-Like Diuretics

- Chlorthalidone (pK_a = 9.4) may be named as a 1-oxo-isoindoline or a phthalimidine.
- Although the molecule exists primarily in the phthalimidine form, the ring may be opened to form a benzophenone derivative.
- The benzophenone form illustrates the relationship to the quinazolin-4-one series of diuretics.
- The prototypic indoline diuretic is indapamide, which contains a polar chlorobenzamide moiety and a nonpolar lipophilic methyl indoline group.
- In contrast to the thiazides, indapamide does not contain a thiazide ring, and only one sulfonamide group is present within the molecular structure of this drug (pK_a = 8.8).



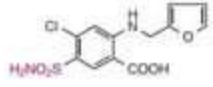
Chlorthalidone
(Thalitone)



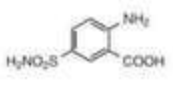
Indapamide

High-Ceiling or Loop Diuretics

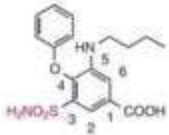
- This class of drugs is characterized more by its pharmacological similarities than by its chemical similarities.
- Examples include furosemide, bumetanide, torsemide, and ethacrynic acid.
- These drugs produce a peak diuresis much greater than that observed with the other commonly used diuretics, hence the name high-ceiling diuretics.
- Their diuretic effect appears in approximately 30 minutes and lasts for approximately 6 hours.



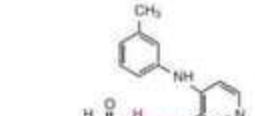
Furosemide



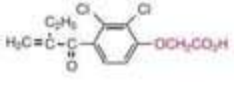
5-Sulfamoyl-anthranilic acid



Bumetanide



Torsemide



Ethacrynic acid

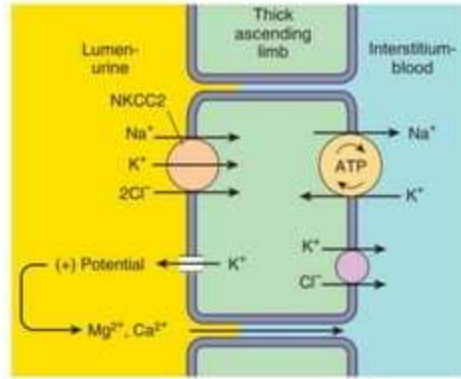
High-Ceiling or Loop Diuretics

- However, the loop diuretics are less effective in treating hypertension than thiazide diuretics.
- As they have a different mechanism of action, they may be used in combination with other diuretics for improved antihypertensive effects.
- Furosemide has a saluretic effect 8- to 10-fold that of the thiazide diuretics; however, it has a shorter duration of action (""6-8 hr).
- It can cause a marked excretion of sodium, chloride, potassium, calcium, magnesium, and bicarbonate ions, with as much as 25% of the filtered load of sodium excreted in response to initial treatment.
- It is effective for the treatment of edemas connected with cardiac, hepatic, and renal sites.

MECHANISM OF ACTION:

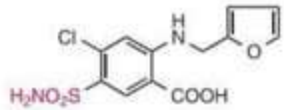
- The main site of action for the high-ceiling (loop) diuretics is believed to be on the thick ascending limb of the loop of Henle, where they inhibit the luminal $Na^+/K^+/2Cl^-$ symporter.
- Additional effects on the proximal and distal tubules also are possible.
- High ceiling diuretics are characterized by a quick onset and short duration of activity.

- The mechanism of action of ethacrynic acid appears to be more complex than the simple Michael addition of the α, β-unsubstituted ketone of the drug to enzyme sulfhydryl groups.
- When the double bond of ethacrynic acid is reduced, the resulting compound is still active, although the diuretic activity is diminished.
- The sulfhydryl groups of the enzyme would not be expected to add to the drug molecule in the absence of the α, β-unsubstituted ketone.

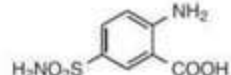


Medicinal Chemistry of High-Ceiling or Loop Diuretics

- Research on 5-sulfamoylanthranilic acids at the Hoechst Laboratories in Germany showed them to be effective diuretics.
- The most active of a series of variously substituted derivatives was furosemide.
- Chlorine and sulfonamide substituents are also found in other diuretics.
- Because the molecule possesses a free carboxyl group, furosemide is a stronger acid than the thiazide diuretics (pKa = 3.9).
- This drug is excreted primarily unchanged.
- A small amount of metabolism, however, can take place on the furan ring, which is substituted on the aromatic amino group

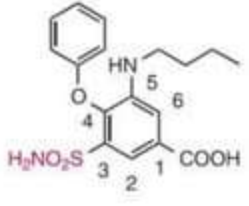


Furosemide

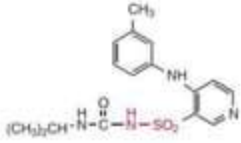


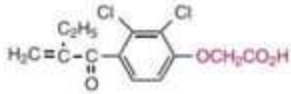
5-Sulfamoyl-anthranilic acid

- **In bumetanide, a phenoxy group has replaced the customary chloro or trifluoromethyl substituents seen in other diuretic molecules.**
- **The phenoxy group is an electron-withdrawing group similar to the chloro or trifluoro, methyl substituents.**
- **The amine group customarily seen at position 6 has been moved to position 5.**
- **These minor variations from furosemide produced a compound with a mode of action similar to that of furosemide, but with a marked increase in diuretic potency.**
- **The short duration of activity is similar, but the compound is approximately 50-fold more potent.**
- **Replacement of the phenoxy group at position 4 with a C_6H_5NH- or C_6H_5S- group also gives compounds with a favorable activity.**
- **When the butyl group on the C-5 amine is replaced with a furanylmethyl group, such as in furosemide, however, the results are not favorable.**



- Further modification of furosemide-like structures led to the development of torsemide.
- Instead of the sulfonamide group found in furosemide and bumetanide, torsemide contains a sulfonylurea moiety.
- Optimal diuretic activity was obtained when an oxyacetic acid group was positioned para to an α, β-unsubstituted carbonyl and chloro or methyl groups were placed at the 2- or 3-position of the phenyl ring.
- In addition, hydrogen atoms on the terminal alkene carbon also provided maximum reactivity.
- Thus, a molecule with a weakly acidic group to direct the drug to the kidney and an alkylating moiety to react with sulfhydryl groups and lipophilic groups seemed to provide the best combination for a diuretic in this class.

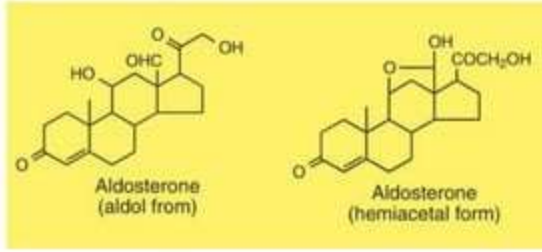




Mineralocorticoid Receptor Antagonists

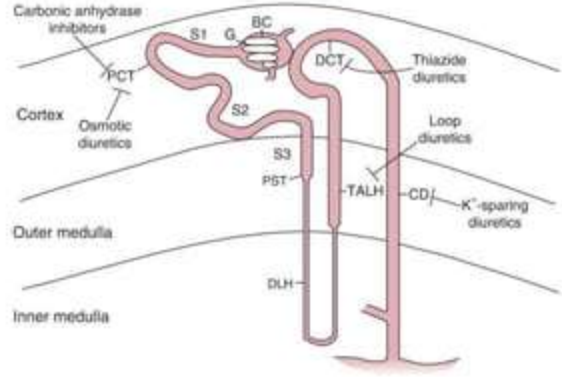
- The adrenal cortex secretes a potent mineralocorticoid called aldosterone, which promotes salt and water retention and potassium and hydrogen ion excretion.
- Aldosterone exerts its biological effects through binding to the mineralocorticoid receptor (MR), a nuclear transcription factor.
- Its ability to cause increased reabsorption of sodium and chloride ion and increased potassium ion excretion is approximately 3,000-fold that of hydrocortisone.

- A substance that antagonizes the effects of aldosterone could conceivably be a good diuretic drug.
- Spironolactone and eplerenone are examples of such antagonists.
- These drugs are also classified as potassium-sparing diuretics.



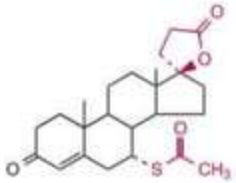
MECHANISM OF ACTION

- Spironolactone and eplerenone competitively inhibit aldosterone binding to the MR, thereby interfering with reabsorption of sodium and chloride ions and the associated water.
- The most important renal site of the MR receptors, and hence the primary site of action of spironolactone and eplerenone, is in the late distal convoluted tubule and collecting system (collecting duct).

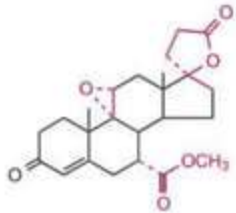


MECHANISM OF ACTION & SAR

- MR antagonist activity is dependent on the presence of a γ-lactone ring on C-17 and a substituent on C-7 in spironolactone and structurally related compounds.
- Interaction of C-7-unsubstituted agonists, such as aldosterone, with a methionine residue in the MR ligand binding domain is important for receptor activation and subsequent transcription.
- However, this interaction is sterically hindered by C-7 substituents on aldosterone antagonists, thereby leaving MR in an inactive conformation.

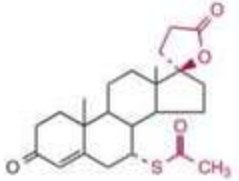


Spironolactone

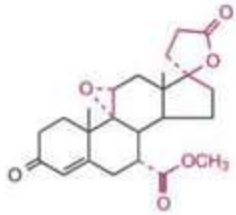


MECHANISM OF ACTION & SAR

- In addition to the lactone ring and C-7 substituent (in this case an acetyl group) that are important for MR antagonism, eplerenone has a 9α, 11α-epoxy group as part of its structure.
- Like spironolactone, it binds to the MR and is an aldosterone antagonist. However, it has a 20- to 40-fold lower affinity for the MR than spironolactone.
- This reduced binding is believed to be due to the epoxy group. Nevertheless, eplerenone is an effective diuretic and has certain therapeutic advantages over spironolactone.

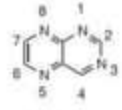


Spironolactone

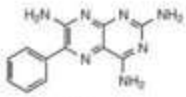


Potassium-Sparing Diuretics:

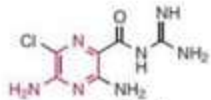
- Two drugs in this class of diuretics are triamterene and amiloride, which are derivatives of pteridine and aminopyrazine, respectively.
- Individually, amiloride and triamterene exert a mild diuretic effect and are usually used in combination with other diuretic agents.



Pteridine



Triamterene



Amiloride

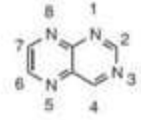
- Triamterene is useful in combination with a thiazide or loop diuretic in the treatment of edema or hypertension.

Mechanism of Action:

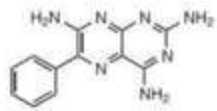
- In vitro experiments have shown that triamterene and amiloride exert a diuretic effect by blocking an epithelial sodium channel (ENaC) in principal cells of the late distal convoluted tubule and collecting duct.
- Both drugs are weak organic bases and inhibit ENaC in a voltage- and pH-dependent manner.
- Inhibition occurs because amiloride and triamterene bind to negatively charged regions of the sodium channel in the ENaC.
- The greater potency (approximately 100-fold in vitro) of amiloride is probably due to the fact that it is a stronger base (pKa = 8.7) and is therefore more extensively protonated at physiological pH than triamterene (pKa = 6.2).
- Sodium channel inhibitors block the reabsorption of sodium ion and inhibit the secretion of potassium ion.
- The net result is increased sodium and chloride ion excretion in the urine and almost no potassium excretion.
- Consequently, amiloride and triamterene can be used to offset the effect of other diuretics that result in loss of potassium.

RECEPTOR BINDING & SAR

- Pteridine ring-containing compounds have a marked potential for influencing biological processes.
- Early screening of pteridine derivatives revealed that 2,4-diamino-6,7-dimethylpteridine had diuretic activity.



Pteridine



Triamterene

- Structural modifications of the pteridine nucleus led to the development of triamterene.
- Further alterations of the triamterene structure are not usually beneficial in terms of diuretic activity.
- Activity is retained if an amine group is replaced with a lower alkylamine group.
- Introduction of a para-methyl group on the phenyl ring decreases the activity by approximately half.
- Introduction of a para-hydroxyl group on the phenyl ring yields a compound that is essentially inactive as a diuretic.
- Amiloride is an aminopyrazine structurally related to triamterene as an open-chain analog.