Jordan university of science and technology
Faculty of pharmacy

Medicinal chemistry II

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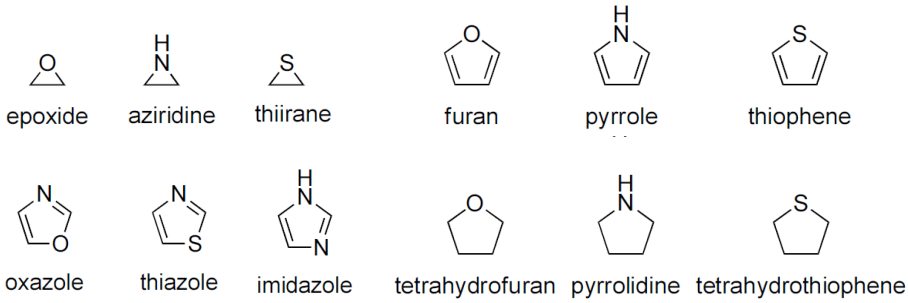
Before we start

Before we start this course you need to review some previous courses of high relevance to this one. Such things you need to review include:

- Important heterocycles frequently encountered in medicinal chemistry.
- Drug metabolism.

Examples of common heterocycles.



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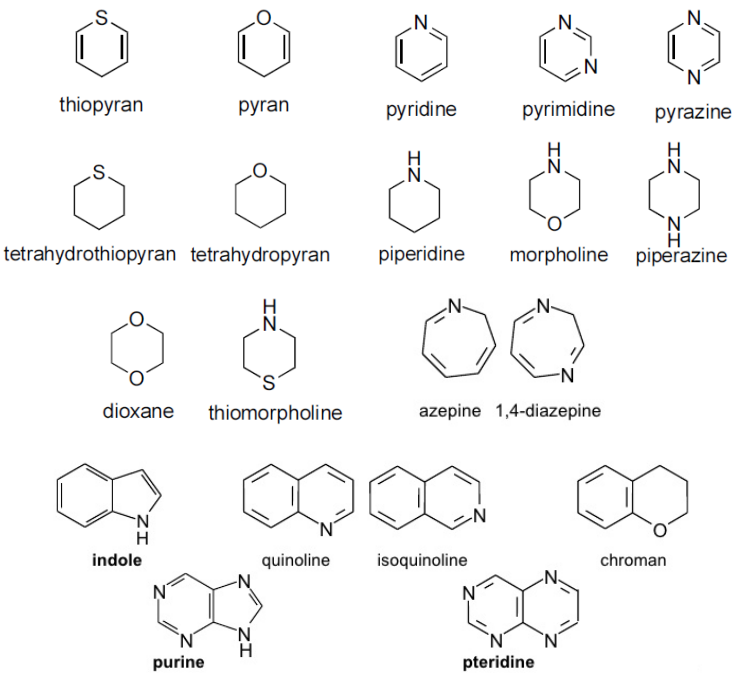

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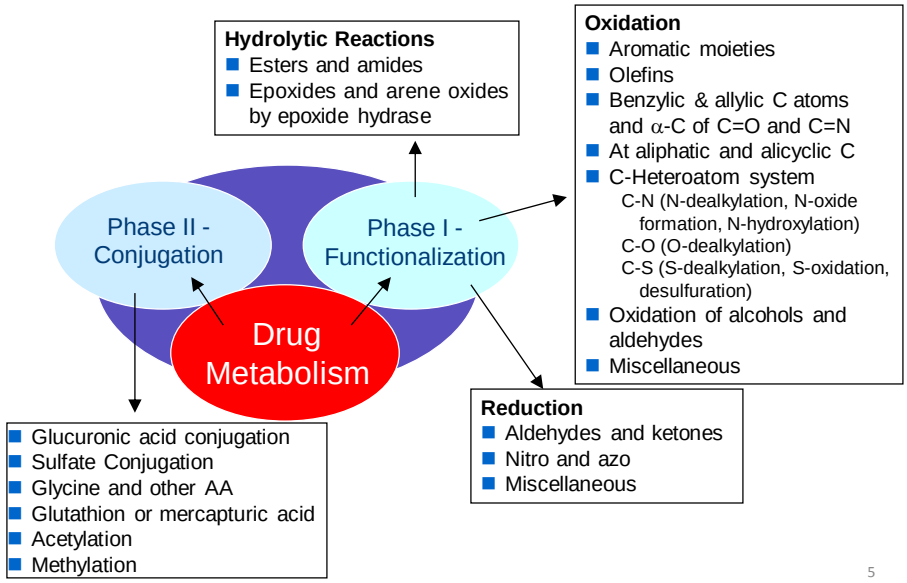
Summary of phase I and II biotransformations



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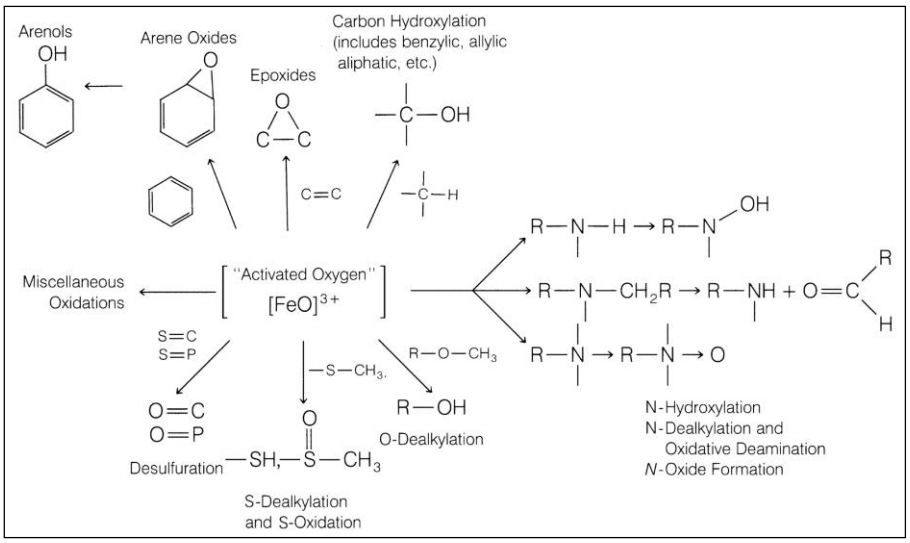
Summary of the many types of oxidative reaction carried out by CYP.



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1. Drugs affecting cardiovascular system

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A. Antihypertensive drugs

Drug classes that are used to treat hypertension (classified according to their mechanism of action) include:

1. **Diuretics**
2. **Angiotensin converting enzyme inhibitors**
3. **Angiotensin II receptor antagonists**
4. **Calcium channel blockers**
5. **Beta-adrenergic blockers**

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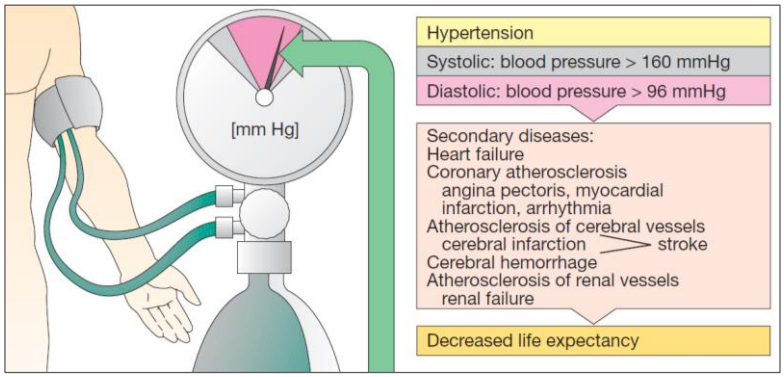
1.1 Overview of hypertension

Arterial hypertension (high blood pressure) generally does ***not*** impair the well-being of the affected individual; however, in the long term it leads to ***vascular damage*** and secondary complications. The aim of antihypertensive therapy is to ***prevent*** the complications and, thus, to prolong life expectancy. Hypertension infrequently ***results*** from another disease, such as a catecholamine-secreting tumor of the adrenal medulla (*pheochromocytoma*), renal artery stenosis, and excessive secretion of aldosterone by the adrenal cortex, often because of adenomas. In most cases the cause is unknown, ***essential (primary) hypertension*.**



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Hypertension is generally defined as ***mild*** when the diastolic pressure is between 90 and 104 mm Hg, ***moderate*** when it is 105 to 114 mm Hg, and ***severe*** when it is above 115 mm Hg. Antihypertensive drugs are ***indicated*** when blood pressure cannot be sufficiently controlled by means of weight reduction or a low salt diet.

Arterial blood pressure is ***regulated*** by several physiological factors, such as heart rate, stroke volume, peripheral vascular network resistance, blood vessel elasticity, blood volume, and viscosity of blood. Endogenous chemicals also play an important part in the regulation of arterial blood pressure. The peripheral vascular system is influenced greatly by the sympathetic–parasympathetic balance of the ***autonomic*** nervous system, the control of which originates in the CNS. Enhanced ***adrenergic*** activity is a principal contributor to primary (essential) hypertension. In principle, lowering of either cardiac ***output*** or peripheral ***resistance*** may decrease blood pressure. The available drugs influence ***one or both*** of these determinants. The therapeutic utility of antihypertensives is determined by their efficacy and tolerability.

The ***choice*** of a specific drug is determined on the basis of a benefit: risk assessment of the relevant drugs, in keeping with the patient's individual needs.

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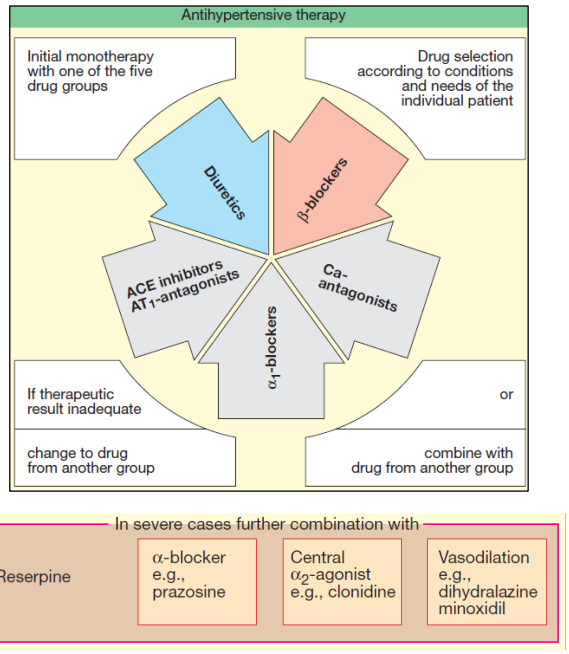

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1.2 Diuretics

Diuretics are chemicals that increase the ***rate*** of urine formation. By increasing the urine flow rate, diuretic usage leads to increased ***excretion*** of electrolytes (especially sodium and chloride ions) and water from the body without affecting protein, vitamin, glucose, or amino acid reabsorption.

Normal physiology of urine formation:

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.

In the ***PCT*** (50% to 60%) of filtered sodium is reabsorbed osmotically which is coupled with the reabsorption of glucose, phosphate, amino acids, and bicarbonate. The reabsorption of sodium and bicarbonate is facilitated by the enzyme ***carbonic anhydrase***, which catalyzes the formation of carbonic acid from water and carbon dioxide that provides the hydrogen ion, which drives the reabsorption of sodium bicarbonate. In the ***TALH*** approximately 20% to 25% of the filtered sodium and chloride ions are reabsorbed via a ***cotransport*** system ($Na^+/K^+/2Cl^-$) on the luminal membrane. In the ***CD*** sodium is reabsorbed in exchange for hydrogen and potassium ions, and this process is partially controlled by ***mineralocorticoids*** (e.g., aldosterone) and accounts for the reabsorption of between 2% and 3% of filtered sodium ions.

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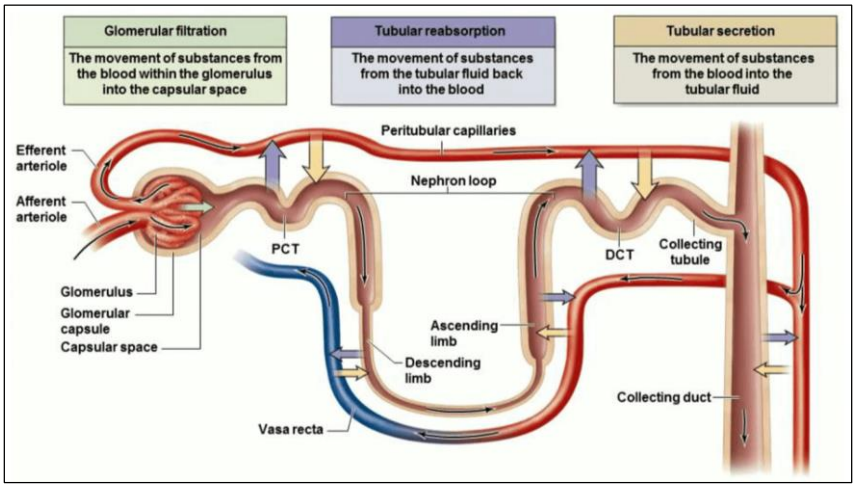
Normal physiology of urine formation



The nephron. BC, Bowman's capsule; CD, collecting duct; DCT, distal convoluted tubule; DLH, descending limb of the Loop of Henle; G, glomerulus; PCT, proximal convoluted tubule; PST, proximal straight tubule; TALH, thick ascending limb of the loop of Henle.

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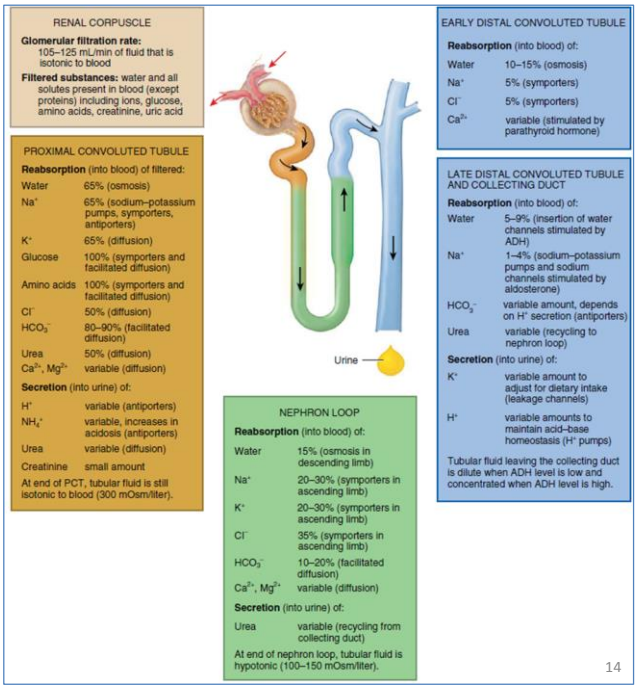
The urine formed during this process represents only approximately **1% to 2%** of the original glomerular filtrate, with more than 98% of electrolytes and water filtered at the glomerulus being reabsorbed during passage through the nephron. Thus, a **change in urine output of only 1% to 2% could double urine volume.**



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The diuretic class of antihypertensive drugs is comprised of the following subgroups:

A. *Osmotic diuretics*
B. *Carbonic anhydrase inhibitors*
C. *Thiazide diuretics*
D. *Thiazide-like diuretics*
E. *Loop diuretics*
F. *Aldosterone antagonists (mineralocorticoid receptor antagonists)*
G. *Potassium-sparing diuretics*

The diuretics currently in use are ***classified by*** their chemical class (thiazides), mechanism of action (carbonic anhydrase inhibitors and osmotics), site of action (loop diuretics), or effects on urine contents (potassium-sparing diuretics). These drugs vary widely in their efficacy (i.e., their ability to increase the rate of urine formation) and their site of action within the nephron.

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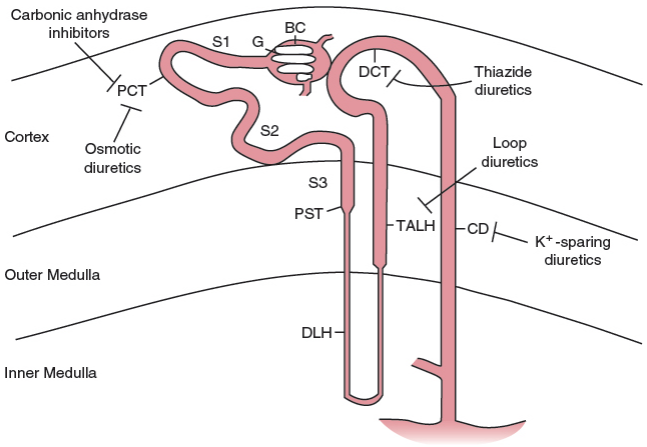
The site of action of the different diuretic drugs:



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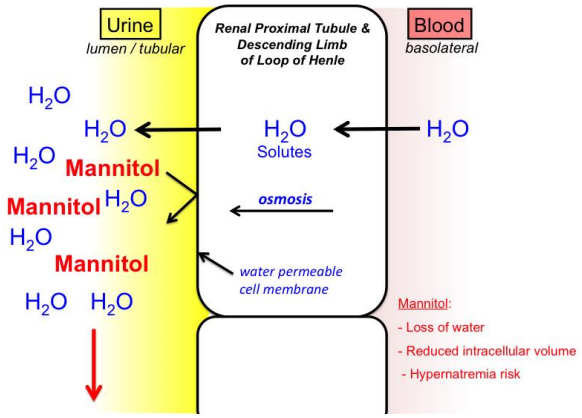
A. Osmotic Diuretics

Mechanism of action:

Are ***low*** molecular weight compounds that are ***freely*** filtered through the Bowman's capsule into the renal tubules, and because of their ***high*** water solubility they are ***poorly*** reabsorbed. Also, are ***not*** extensively metabolized.



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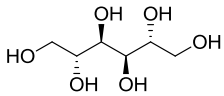
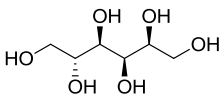
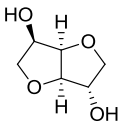
When administered as a ***hypertonic*** (hyperosmolar) solution, they increase intraluminal osmotic pressure, causing water to pass from the body into the tubule causing a diuretic effect. Osmotic diuretics ***increase*** the volume of urine and the excretion of water and almost all of the electrolytes. Polyols, such as mannitol, sorbitol, and isosorbide, provide this effect.



Mannitol



Sorbitol



Isosorbide

Mannitol is the agent most commonly used as an osmotic diuretic and is given via ***IV*** route. ***Isosorbide*** is used orally mainly to cause a reduction in intraocular pressure in glaucoma cases.

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B. Carbonic Anhydrase Inhibitors

Mechanism of action:

Carbonic anhydrase inhibitors induce diuresis by inhibiting the formation of carbonic acid within proximal (PCT, S2) and distal tubular cells to limit the number of ***hydrogen*** ions available for exchange with sodium. Sodium ions, along with bicarbonate ions, and associated water molecules were then excreted, and a diuretic effect was noted. For a diuretic response to be observed, more than ***99%*** of the carbonic anhydrase must be inhibited.

$$CO_2 + H_2O \xrightarrow[\text{anhydrase}]{\text{Carbonic}} H_2CO_3 \longrightarrow H^{\oplus} + HH_2CO_3^{\ominus}$$

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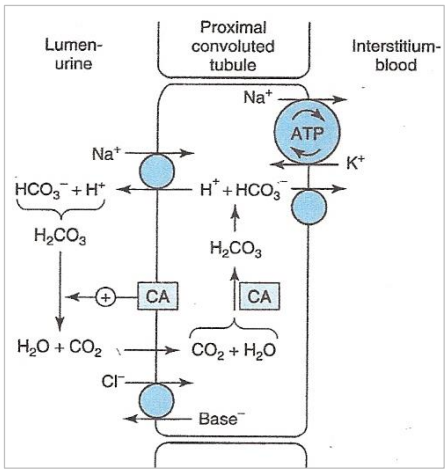
Although carbonic anhydrase activity in the proximal tubule regulates the reabsorption of approximately 20% to 25% of the filtered load of sodium, the carbonic anhydrase inhibitors are ***not highly efficacious diuretics***. An increased excretion of only ***2% to 5%*** of the filtered load of sodium is seen with carbonic anhydrase inhibitors ***because*** of increased reabsorption of sodium ions by the ascending limb of the loop of Henle and more distal nephron segments.



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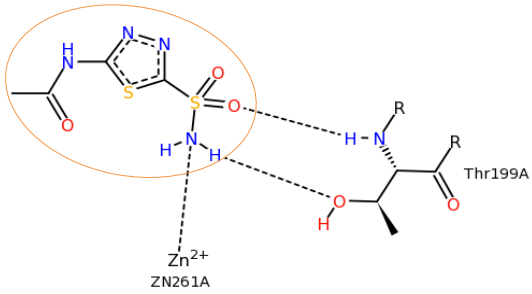
It was observed that ***sulfanilamide*** rendered the urine of dogs alkaline because of the inhibition of carbonic anhydrase. It was soon learned that the sulfonamide portion of an active diuretic molecule ***could not*** be monosubstituted or disubstituted. The unsubstituted sulfonamide acts as an ***isostere*** for carbonic acid.

It was reasoned that a ***more acidic sulfonamide*** would bind more ***tightly*** to the carbonic anhydrase enzyme. Synthesis of more highly acidic sulfonamides produced compounds with activities greater than 2,500-fold that of sulfanilamide.



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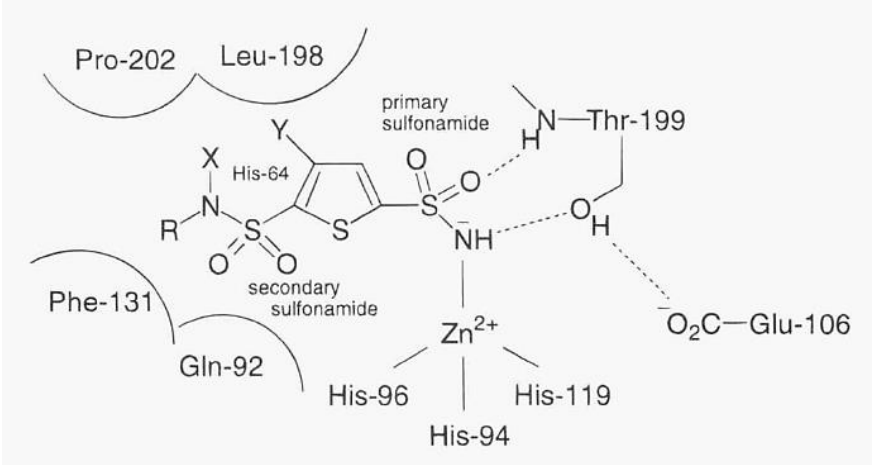

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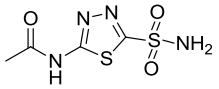
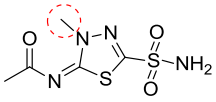
With ***prolonged*** use of the carbonic anhydrase inhibitor diuretics, the urine becomes more ***alkaline***, and the blood becomes more ***acidic***, because of the inhibition of the Na^+/H^+ exchange. When acidosis occurs, the carbonic anhydrase inhibitors ***lose*** their effectiveness. For this reason, their use as diuretics are ***limited***, they are most commonly used in the treatment of ***glaucoma***, to reduce intraocular pressure.

Products:



Acetazolamide (pKa=7.4)



Methazolamide (pKa=7.2)

Methazolamide is more ***lipophilic*** with better penetration into the ocular fluid.

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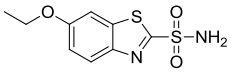
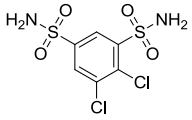
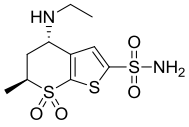


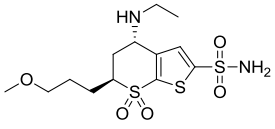
Ethoxzolamide (pKa=8.0)



Dichlorphenamide (pKa=8.3)



Dorzolamide (pKa=8.4)



Brinzolamide (pKa=8.2)

Brinzolamide and dorzolamide contain ***ionizable*** amino groups and are the result of efforts to develop water-soluble carbonic anhydrase inhibitors that retain sufficient lipophilicity to penetrate the cornea. These two drugs are for ***topical*** use only, while all other CAI are given ***orally***.

http://www.rcsb.org/3d-view/4M2U/1

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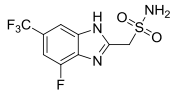
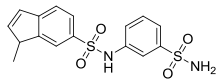
Exam type question:

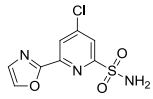
Which of the following drugs is the most potent topical CAI? And which is the most active CAI?



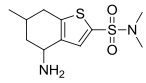
A



B



C



D

The most potent topical CAI is compound **B**, and the most active CAI is compound **C.**

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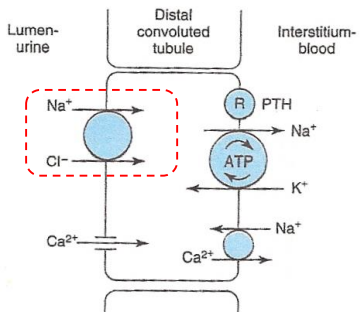
C. Benzothiadiazine or thiazide diuretics

Mechanism of action:

Further study of the ***benzene disulfonamide*** derivatives was undertaken to find more efficacious carbonic anhydrase inhibitors. These studies provided some compounds with a ***high*** degree of diuretic activity. ***Chloro and amino*** substitution 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.

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 **DCT**, 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.



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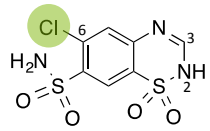
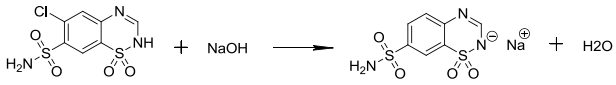
Products:

Chlorothiazide is the simplest member of this series, having a ***pKa*** of ***6.7 and 9.5***. The hydrogen atom at the ***2-N*** is the most acidic because of the electron-withdrawing effects of the neighboring amino group (the emine). The sulfonamide group that is substituted at C-7 provides an additional point of acidity in the molecule but is less acidic than the 2-N proton. These acidic protons make possible the formation of a water-soluble sodium ***salt*** that can be used for intravenous administration of the diuretics.



Chlorothiazide (pka=6.7 and 9.5)



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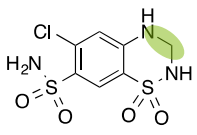
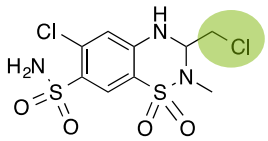
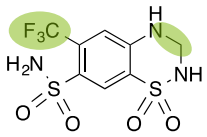


Hydrochlorothiazide
10-fold more active

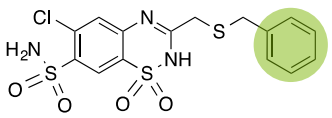


Methyclothiazide

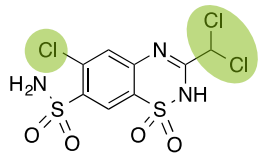


Hydroflumethiazide
longer duration

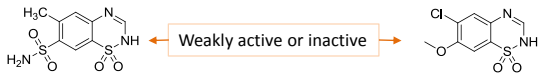
Increase in potency and duration



Benzthiazide



Trichloromethiazide



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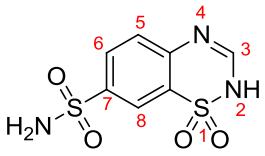
Structure-Activity Relationship:



1. 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 a chloro or trifluoromethyl substitution are highly active.
   - The trifluoromethyl-substituted diuretics are more lipid-soluble and have a longer duration of action than their chloro-substituted analogs.
   - Electron-releasing groups, such as methyl or methoxyl, markedly reduce the diuretic activity.

2. Replacement or removal of the sulfonamide group at position 7 yields compounds with little or no diuretic activity (it is essential).

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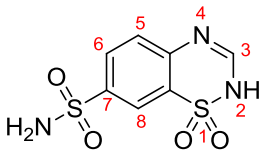

3. Saturation of the double bond to give a 3,4-dihydro derivative produces a diuretic that is 10-fold more active than the unsaturated derivative.

4. Substitution with a lipophilic group at position 3 gives a marked increase in the diuretic potency and duration of action.
   - Haloalkyl, aralkyl, or thioether substitution increases the lipid solubility of the molecule and yields compounds with a longer duration of action.

5. Alkyl substitution on the 2-N position also decreases the polarity and increases the duration of diuretic action.

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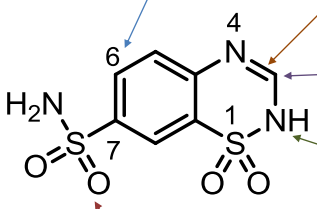
Summary of thiazides SAR:

No substitution → Little diuretic activity
EDG (Me, OMe) → decreases activity
EWG (Cl, CF_3) → necessary for activity
CF_3 → highly lipid soluble → longer duration of action

Saturation of 3,4-double bond → 10-fold increase in activity

lipophilic Substitution → higher potency and longer duration of action (e.g. haloalkyl, aralkyl or thioether substitution).

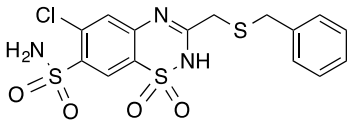


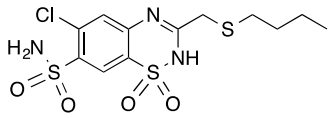
Substitution increases lipophilicity → increases duration of action

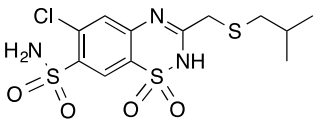
Replacement or removal of sulfonamide → little or no activity

31

Exam type question:
Substitution with a lipophilic group at C-3 leads to higher potency, why?

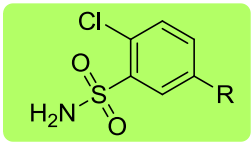






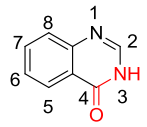
32

D. Thiazide-like diuretics

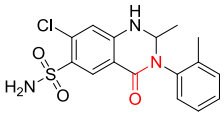


- Their mechanism of action is similar to thiazide diuretics.
- All thiazide-like drugs have an ***unsubstituted*** sulfonamide and an electron withdrawing ***chloride*** group present.

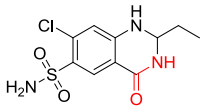
Quinazolinone derivatives:



Quinazolin-4-one



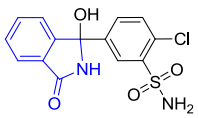
Metolazone



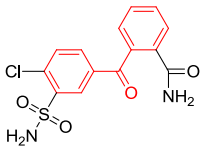
Quinethazone

Phthalimidine Derivatives: Chlorthalidone

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 quinazolinone series of diuretics.



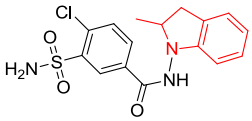
phthalimidine form



benzophenone form

Indolines: Indapamide

It is rapidly and completely absorbed from the GIT, with a duration of action of up to 8 ***weeks***. This prolonged duration of action is associated with its extensive binding to carbonic anhydrase in the ***erythrocytes***.

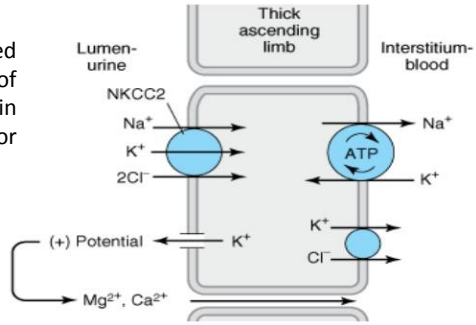


E. High-Ceiling or Loop Diuretics

Mechanism of action:

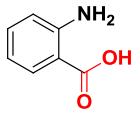
This class of drugs is characterized more by its ***pharmacologic*** similarities than by its chemical similarities. These drugs produce a peak diuresis much greater than that observed with the other commonly used diuretics, hence the name high-ceiling diuretics. Their main site of action is on the thick ascending limb of the loop of Henle ***(TALH),*** where they ***inhibit*** the luminal ***$Na^+/K^+/2Cl^-$ symporter*** resulting in significant Na^+ and Cl^- loss along with Ca^{2+} and Mg^{2+} loss. These diuretics are commonly referred to as ***loop diuretics***.

High-ceiling diuretics are characterized by a ***quick*** onset and ***short*** duration of activity. Their diuretic effect appears in approximately 30 minutes and lasts for approximately 6 hours.

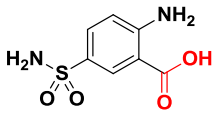


35

Furosemide is an example of a high-ceiling diuretic and may be regarded as a derivative of anthranilic acid or o-aminobenzoic acid.

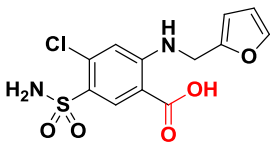


Anthranilic acid



5-Sulfamoyl-anthranilic acid

Because the molecule possesses a free carboxyl group, furosemide is a stronger acid than the thiazide diuretics (pKa = 3.9).



Furosemide

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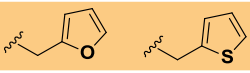
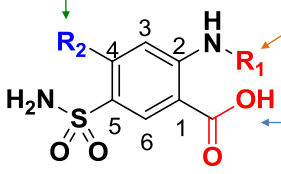
SAR of 5-sulfamoyl-anthranilic acid:

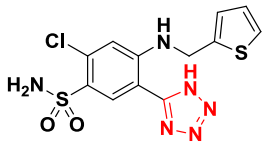
R_2= EWG such as Cl or phenoxy group

R_1= 



5-Sulfamoyl-anthranilic acid

Can be isosterically replaced by a tetrazole 



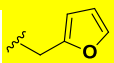
Azosemide

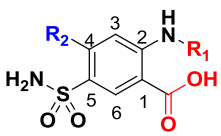
It exerts a comparable diuretic effect to furosemide with oral dosing but is 5.5 to 8 times more potent following ***intravenous*** administration. Its low oral bioavailability (~10% to 15%) could be a consequence of high first-pass metabolism in the liver.

37

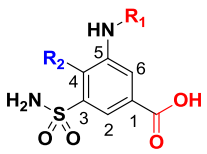
SAR of furosemide analogs:

R_2=EWG ⟶ Cl or phenoxy
Phenoxy could be replaced by C_6H_5S- or C_6H_5N- also result in favorable activity

R_1=Replacement of butyl group by furanylmethyl group ⟶ not favorable 

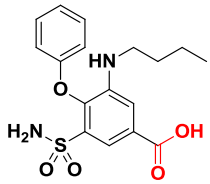


5-Sulfamoyl-anthranilic acid



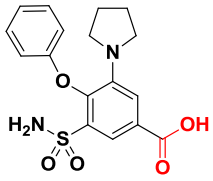
Marked increase in diuretic potency

38



Bumetanide

Bumetanide is 50-fold more potent than furosemide.

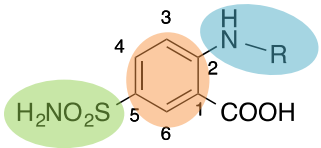


Piretanide

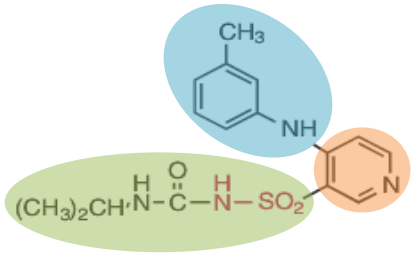
Like bumetanide, piretanide is a sulfamoylbenzoic acid derivative. It exhibits diuretic potency greater than furosemide but lower than bumetanide.

39

Further modification of furosemide-like structures has led to the development of torsemide. Instead of the sulfonamide group found in furosemide and bumetanide, torsemide contains a ***sulfonylurea*** moiety.



5-Sulfamoyl-anthranilic acid



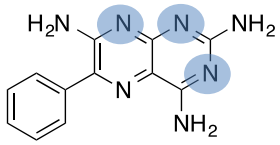
Torsemide

40

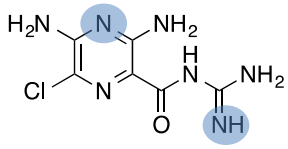
F. Potassium-Sparing Diuretics

Mechanism of action:

Two drugs in this class of diuretics are triamterene and amiloride. Individually, amiloride and triamterene exert a ***mild*** diuretic effect and are usually used in ***combination*** with thiazides or loop diuretics. In vitro experiments have shown that they exert a diuretic effect by ***blocking*** an epithelial sodium channel (***ENaC***) in principal cells of the late ***DCT*** and ***CD***.



Triamterene



Amiloride

Both drugs are weak organic ***bases*** and inhibit ENaC in a pH-dependent manner, where they ***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 (p*K*a = ***8.7***) and is therefore more extensively protonated at physiologic pH than triamterene (p*K*a = ***6.2***). Amiloride is an aminopyrazine structurally related to triamterene as ***an open-chain analog***.

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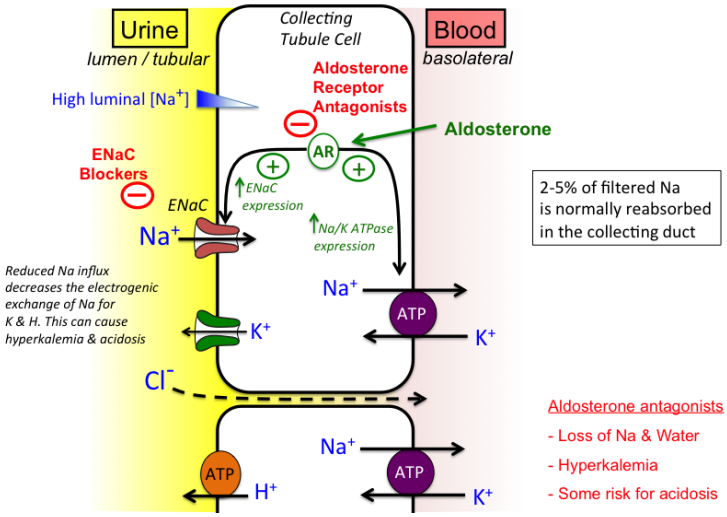
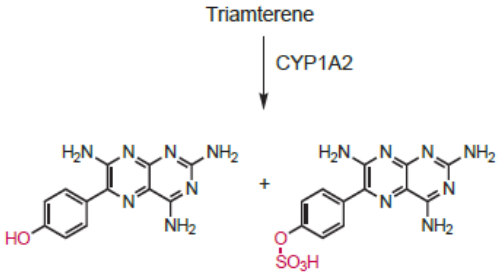
Sodium channel inhibitors ***block*** the reabsorption of ***sodium*** ion and ***inhibit*** the secretion of ***potassium*** ion. The ***net result*** is increased sodium and chloride ion excretion in the urine and almost ***no*** potassium excretion. As a consequence, amiloride and triamterene can be used to ***offset*** the effect of other diuretics that result in loss of potassium.



42

Triamterene is extensively metabolized to 4'-hydroxytriamterene and its sulfate conjugate, both of which (major metabolite) are still ***active*** as diuretics.



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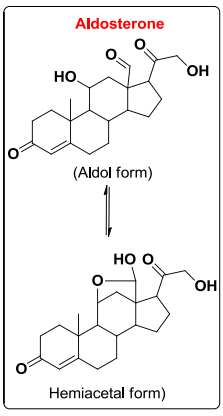
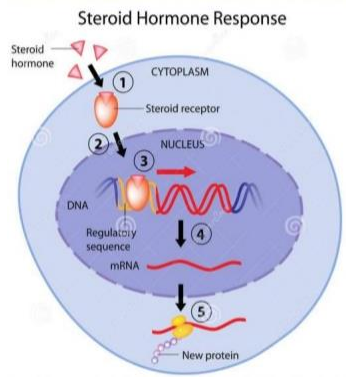
G. Mineralocorticoid Receptor Antagonists

Mechanism of action:

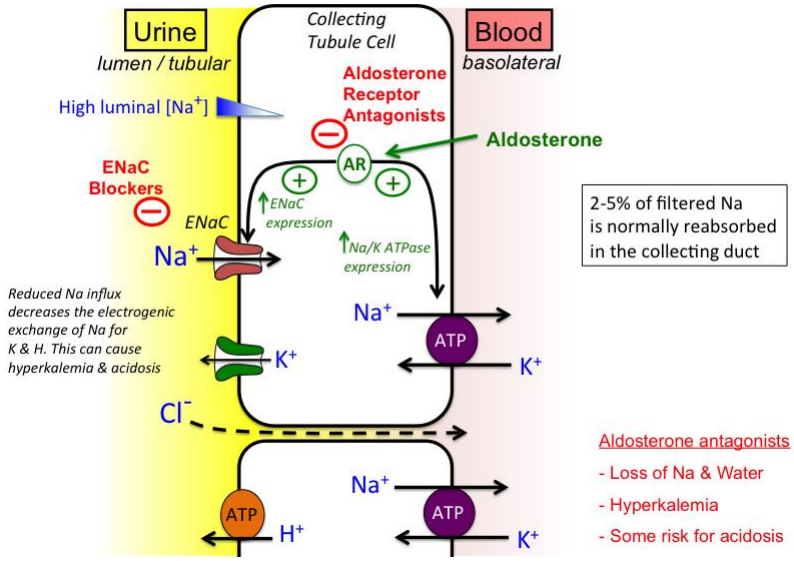
The ***adrenal cortex*** secretes a potent mineralocorticoid called ***aldosterone***, which promotes salt and water ***retention*** and potassium and hydrogen ion ***excretion***. Aldosterone exerts its biologic effects through binding to the mineralocorticoid receptor (***MR***), a nuclear transcription factor. Aldosterone-MR complex ***translocate*** to the nucleolus and initiates expression of gene products leading to the to ***protein synthesis***.





1. Steroid crosses cell membrane into cytoplasm
2. Steroid binds cytosolic receptor which is kept inactive by heat-shock proteins (HSPs)
3. Binding alters receptor confirmation, releasing HSPs
4. Active receptors bind directly to DNA and initiate transcription
5. mRNA enters cytoplasm and a new protein is synthesized.

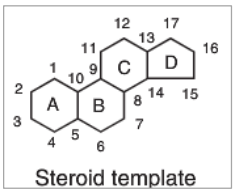
44

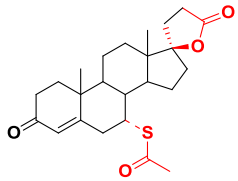


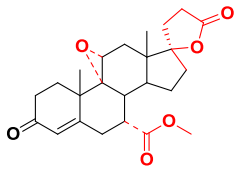
45

A substance that ***antagonizes*** the effects of aldosterone could conceivably be a good diuretic drug. MR antagonists ***competitively inhibit*** aldosterone binding to MR, interfering with NaCl transporter protein synthesis, and reducing Na^+, Cl^-, and water reabsorption (K^+ sparing activity).

Spironolactone and ***eplerenone*** are examples of such antagonists. These drugs are also classified as ***potassium sparing diuretics***. the primary site of action of spironolactone, is in the late ***DCT*** and ***CD***.



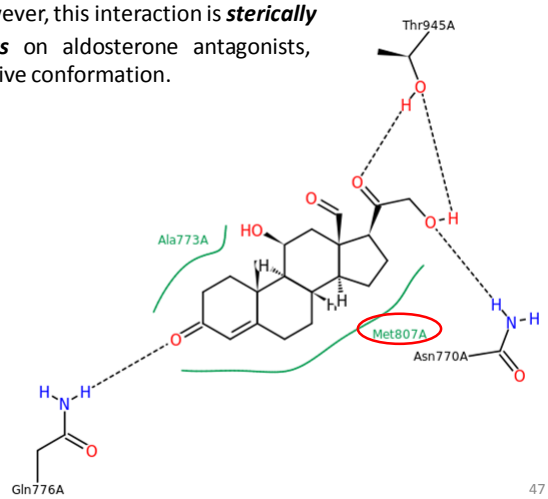

Spironolactone


Eplerenone

46

1. Spironolactone:

MR antagonists ***require*** the presence of a ***γ-lactone ring at C17*** and a ***substituent on C7*** (the unsubstituted C7 position is required for aldosterone binding to MR). 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.



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Pharmacokinetics:

On ***oral*** administration, approximately ***90%*** of the dose of spironolactone is absorbed and is ***significantly*** metabolized during its first passage through the liver to its major active metabolite and has a very short terminal half-life of 1.4 hours. The major metabolites of spironolactone are 7α-thiomethylspironolactone (7α-TMS), 6β-hydroxy-7α-thiomethylspironolactone (6β-OH-7α-TMS), and canrenone. These metabolites have much longer elimination half-lives than spironolactone of 13.8 hours, 15.0 hours, and 16.5 hours, respectively, and are ***responsible for the therapeutic effects*** of the medication. As such, spironolactone is a ***prodrug***.

Canrenone is interconvertible with its canrenoate anion. Canrenone is an ***antagonist*** to aldosterone and exists in equilibrium with its ring-opened form, canrenoate. The canrenoate anion is not therapeutically active but acts as an aldosterone antagonist because of its conversion back to canrenone, which exists in the lactone form.

Side effects:

Hyperkalemia, which can be fatal. Spironolactone ***Sexual*** side effects (i.e., gynecomastia, decreased libido, and impotence) can also occur and are due to nonselective binding of spironolactone to the androgen receptor (AR), glucocorticoid receptor (GR), or progesterone receptor (PR).

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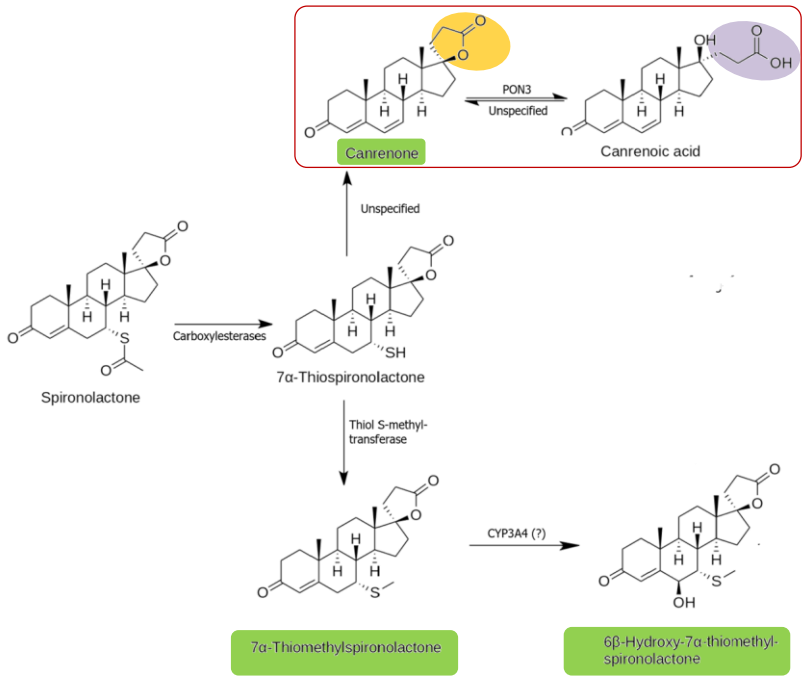
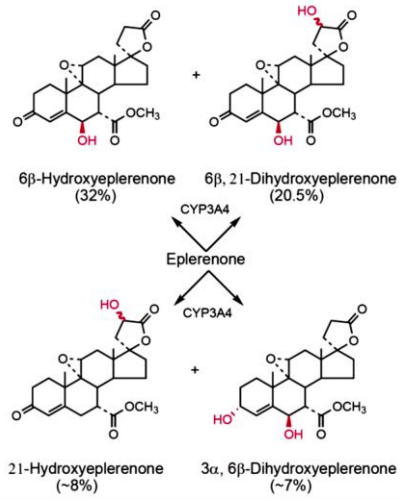


2. Eplerenone:

Eplerenone was designed in an attempt to ***lower*** the side effects. In addition to the lactone ring and C-7 substituent, eplerenone has a ***9α,11α-epoxy*** group as part of its structure. 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.

Eplerenone has a half life of approximately 5 hours and undergoes extensive metabolism by hepatic ***CYP3A4*** to inactive metabolites. Combination with potent inhibitors of CYP3A4 (i.e., ketoconazole or erythromycin) can alter eplerenone pharmacokinetics.



Side effects:

Hyperkalemia which could be fatal. In contrast to spironolactone, it has limited or no inhibitory effects on AR, GR, and PR and is, therefore, a more ***selective*** aldosterone antagonist with ***fewer*** sexual side effects.

General summary of diuretics:

Class of Diuretic	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) and blockade of sodium channel at the luminal membrane (triamterene and amiloride)

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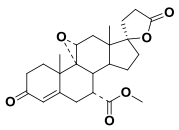
SBTE: Diuretics

SY is a ***63-year-old*** man who presents to the emergency room complaining of breathlessness for the past 3 days. His medical history shows that he had a myocardial infarction (***MI***) 3 years ago, which was followed by successful bypass surgery. SY has been asymptomatic since surgery with no complaints of chest pain. SY runs a small neighborhood grocery store and over the last 3 months has experienced shortness of breath while unloading groceries and climbing stairs. Two weeks ago he was unable to complete his daily 1-mile walk at the high school track, and 4 days ago he woke at 2 AM short of breath and had to sleep in his recliner the rest of the night. Yesterday, he became breathless walking from one room to another. He presents today with ***extreme shortness of breath and swelling*** in his feet and ankles, and he denies chest pain. A diagnosis of congestive heart failure (***CHF***) is made based on SY's symptoms, history of MI, and chest X-ray revealing cardiomegaly. ***The physician wants to initiate treatment with a diuretic to reduce edema before beginning treatment with digoxin for CHF. Evaluate the following three choices for appropriate use in this case.***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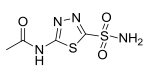
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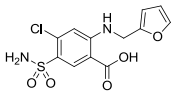
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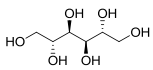
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1. Conduct a thorough and mechanistic SAR analysis of the three therapeutic options in the case. **2.** Apply the chemical understanding gained from the SAR analysis to this patient's specific needs to make a therapeutic recommendation.

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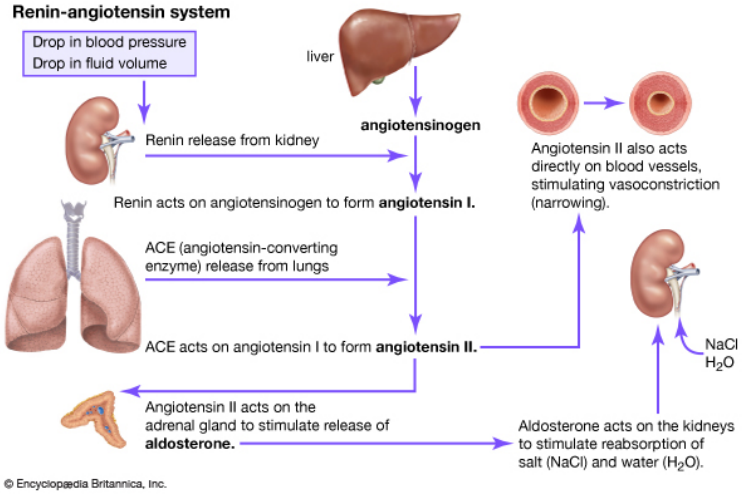
1.3 Drugs Acting on the Renin-Angiotensin Pathway

Introduction:

The renin-angiotensin pathway is an important biochemical pathway for maintaining ***cardiovascular homeostasis*** including blood volume, arterial blood pressure, and electrolyte balance.



53

Overproduction of renin and especially angiotensin II can result in hypertension and/or heart failure. ***Excess angiotensin II*** contributes to high blood pressure and heart failure through both ***fast*** and ***slow*** pressor responses including direct vasoconstriction, increasing proximal tubule sodium reabsorption, stimulating release of aldosterone, hypertrophy, and remodeling of vascular and cardiac cells.

The renin-angiotensin pathway consists of ***two main enzymes***: ***renin*** and angiotensin-converting enzyme (***ACE***) whose purpose is to release angiotensin II from endogenous angiotensinogen.

- ***Angiotensinogen*** is an α_2-globulin (452 amino acids) and found in the plasma and continually synthesized and secreted by the liver.
- ***Renin*** is an aspartyl protease (use an activated water molecule bound to one or more aspartate residues for catalysis of their peptide substrates) that cleaves the leucine-valine bond in ***angiotensinogen*** to form ***angiotensin I***.
- ***ACE*** (also known as kininase II) is a zinc-containing dipeptidyl carboxypeptidase. It converts ***angiotensin I*** to ***angiotensin II.***

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Angiotensin II is the dominant peptide produced by the renin-angiotensin pathway. It is a potent vasoconstrictor that increases total peripheral resistance through a variety of mechanisms: direct vasoconstriction, enhancement of both catecholamine release and neurotransmission within the peripheral nervous system, and increased sympathetic discharge.

Renin is substrate-specific and the rate limiting step in the formation of angiotensin II.

ACE is relatively nonspecific and only requires a tripeptide sequence as substrate, the only structural feature required by ACE is that the penultimate amino acid in the peptide substrate ***cannot*** be *proline*. The nonspecific nature of ACE gives it additional proteolytic activity. ACE degrades ***bradykinin*** which is a vasodilator, a bronchoconstrictor, stimulates natriuresis, stimulates prostaglandin synthesis, and increases vascular permeability.

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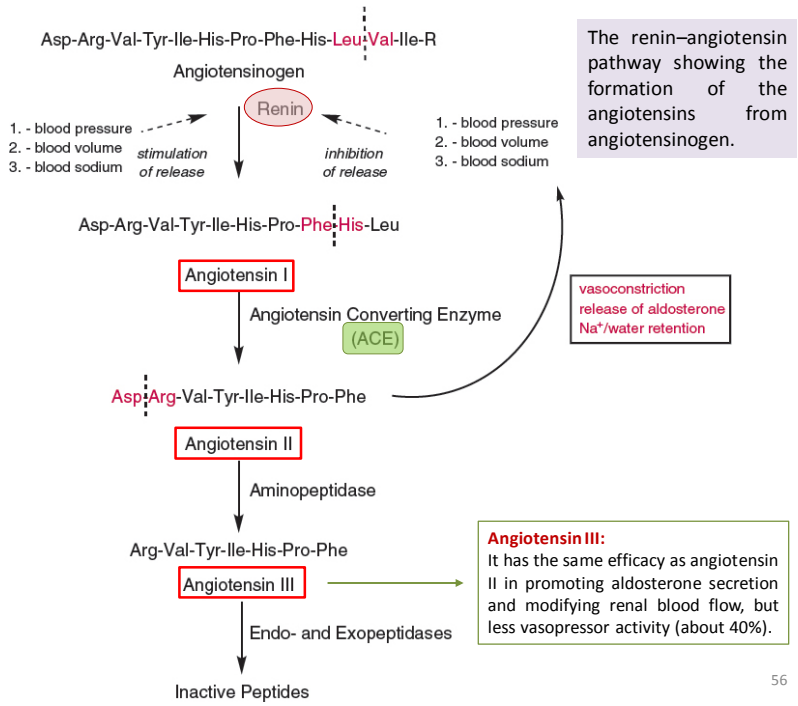
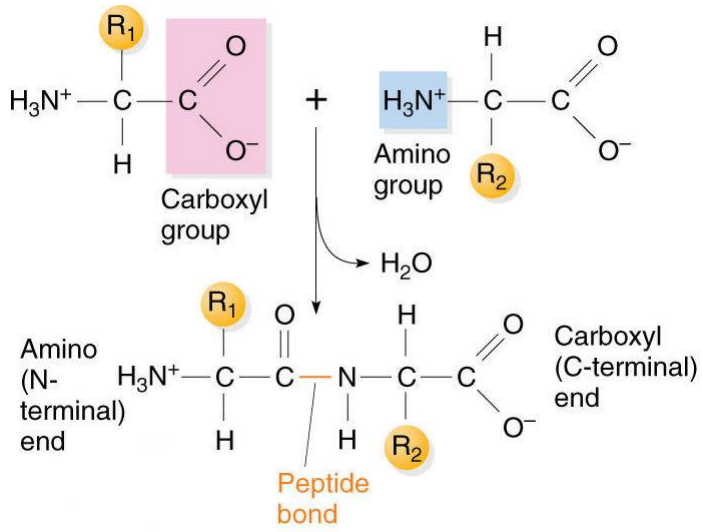


The renin–angiotensin pathway showing the formation of the angiotensins from angiotensinogen.

56

Peptides, protein primary structure, and peptidases:

Peptide bonds:



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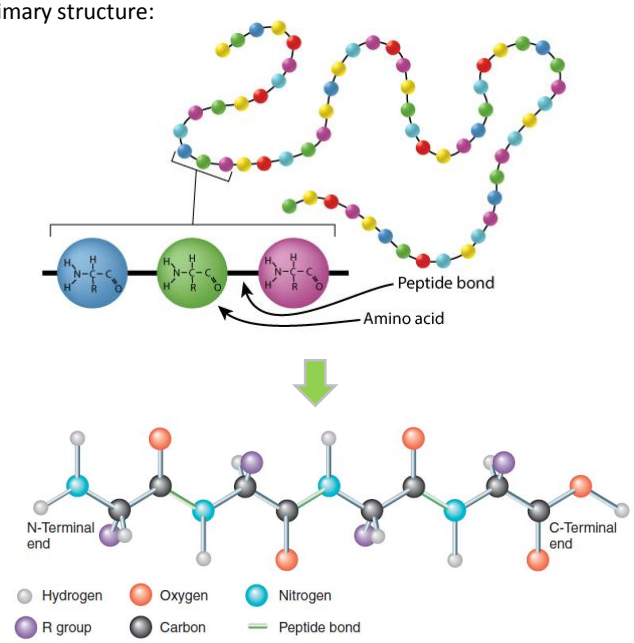
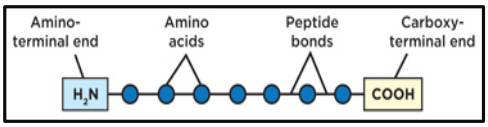
Protein primary structure:

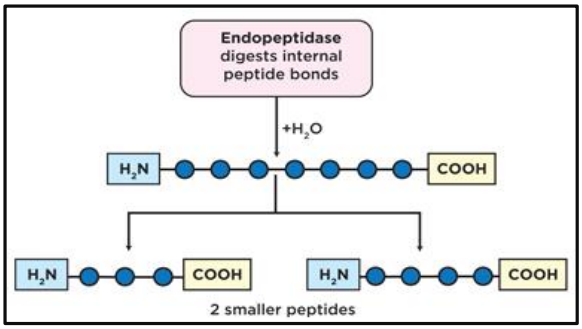


58

Peptidases: hydrolysis of peptides



Endopeptidase is an enzyme which breaks peptide bonds other than terminal ones in a peptide chain.



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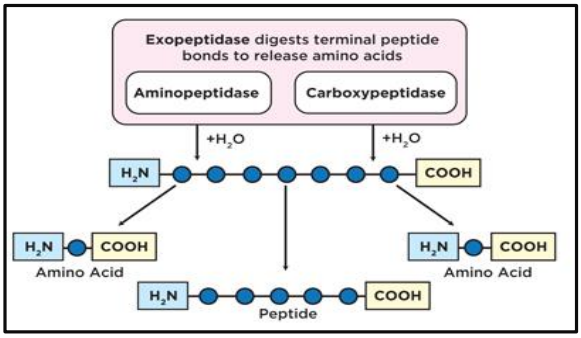
An ***exopeptidase*** is any peptidase that catalyzes the cleavage of the terminal (or the penultimate) peptide bond; the process releases a single amino acid or dipeptide from the peptide chain

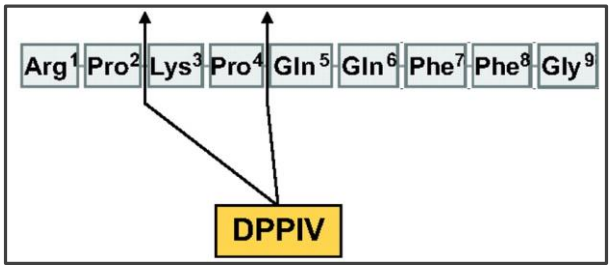


A ***carboxypeptidase*** is a protease enzyme that hydrolyzes (cleaves) a peptide bond at the carboxy-terminal (C-terminal) end of a protein or peptide

Aminopeptidases are enzymes that catalyze the cleavage of amino acids from the amino terminus (N-terminus) of proteins or peptides

60

Dipeptidases hydrolyze bound pairs of amino acids, called dipeptides



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Renin–angiotensin pathway as drug target:

Since the renin–angiotensin pathway produces a large number of effects on the cardiovascular system, therefore, compounds that can ***inhibit*** the effects of renin or ACE, as well as blocking the binding of angiotensin II to its receptors, would be important drugs for the treatment of hypertension and other cardiovascular diseases.

Antihypertensive drugs ***acting on the renin-angiotensin pathway*** that will be discussed in this chapter include the following classes:

A. *Angiotensin-converting enzyme inhibitors*
B. *Angiotensin II receptor blockers*
C. *Renin inhibitor*

Inhibitors of ACE were the first class of compounds to be marketed. This occurred in 1981 with the approval of ***captopril***. 14 years later, ***losartan*** was approved as the first angiotensin II receptor blocker, and in 2007, ***aliskiren*** was approved as the first orally active renin inhibitor.

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A. Angiotensin-Converting Enzyme Inhibitors

ACEIs can be subclassified into three groups based on their chemical structures:

- Sulfhydryl-containing (Captopril).
- Dicarboxylate-containing (majority of ACEIs)
- Phosphonate-containing inhibitors (Fosinopril).

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Sulfhydryl-Containing Inhibitors: Development of Captopril:

Do we really need to study this? Why shall we?!!

The story goes like this: In 1965, it was reported that the venom of a South American snake contained factors that potentiated the action of bradykinin (***BPFs***). These BPFs were isolated and found to be a family of ***peptides*** containing 5-13 amino acid residues. Their actions in potentiating bradykinin were linked to their ability to ***inhibit*** the enzymatic ***degradation*** of ***bradykinin***. Soon thereafter, it was reported that these peptides also ***inhibited*** the enzymatic ***conversion*** of angiotensin ***I*** to angiotensin ***II***. ***Therefore***, BPFs were seen as ***lead*** compounds for the development of new antihypertensive agents, because they possessed ***dual*** activities, inhibition of the degradation of bradykinin, a potent vasodilator, and inhibition of the biosynthesis of angiotensin II, a potent vasoconstrictor.

A nonapeptide, SQ 20,881 (***teprotide***), isolated from the original BPFs, had the greatest in vivo potency in inhibiting ACE and was shown to consistently lower blood pressure in patients with essential hypertension. However, because of its ***peptide*** nature and ***lack of oral activity***, it had limited activity in the therapeutic treatment.

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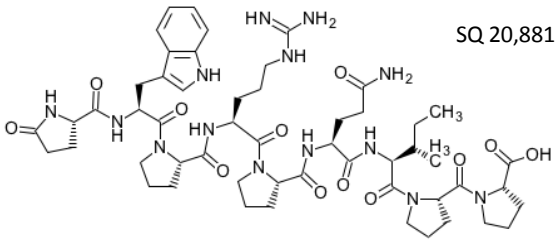
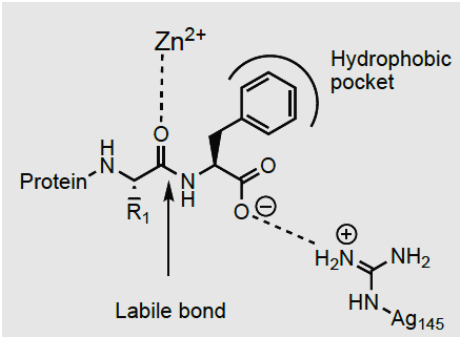
SQ 20,881



SQ 20,881 and other peptide analogs were used to provide an enhanced ***understanding*** of the enzymatic properties of ACE. ***ACE*** is similar to ***pancreatic carboxypeptidase A*** and both are zinc-containing exopeptidase. Based on these similarities, a ***hypothetical model of the ACE binding site*** was developed.

65

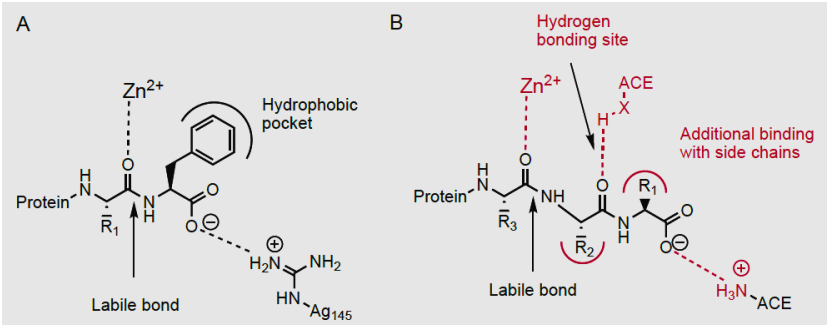
The ***binding*** of a substrate to ***carboxypeptidase A*** involves ***three*** major interactions (ionic, hydrophobic, interaction with zinc atom). Aromatic rings are found to bind strongly to the hydrophobic pocket and this explains the specificity of the enzyme towards peptide substrates containing an aromatic amino acid at the *C* –terminus, (ACE is nonspecific).The ***zinc*** atom is ***located*** close to the labile peptide bond and plays a crucial role in the mechanism by ***polarizing*** the carbonyl group and making the amide group more susceptible to hydrolysis, and it also ***stabilize*** the negatively charged tetrahedral intermediate during peptide hydrolysis.



A model of substrate binding to carboxypeptidase A.

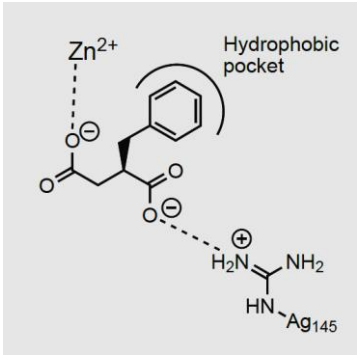
66

Similarly, the ***binding*** of substrates to ***ACE*** was proposed to involve ***three or four*** major interactions (ionic, zinc interactions, hydrogen bonding, and additional binding with side chains). ***Because*** ACE cleaves dipeptides the position of the zinc atom was assumed to be located **two** amino acids away from the cationic center.

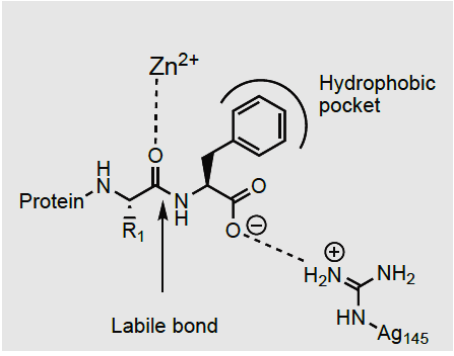


A model of substrate binding to carboxypeptidase A (A) and ACE (B). ACE substrate binding sites are highlighted in red.

The development of an effective drug began with ***D-2-benzylsuccinic*** acid a potent inhibitor of ***carboxypeptidase A***. The binding of this compound to carboxypeptidase A is very ***similar*** to that seen for substrates with the ***exception*** that the zinc ion binds to a carboxylate group instead of the labile peptide bond. Most of the structural features of the compound are ***identical*** to the terminal amino acid of the substrate, whereas the additional ***carboxylate*** group is able to ***mimic*** the carboxylate group that would be produced during peptide hydrolysis.

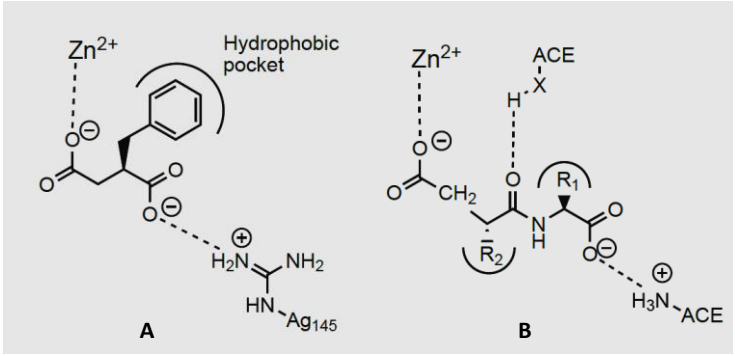


D-2-benzylsuccinic acid



Binding site of carboxypeptidase A

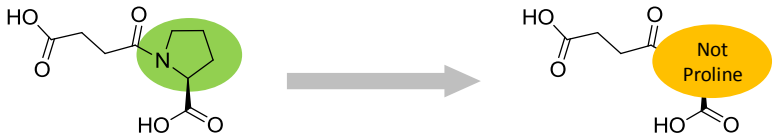
Applying this concept to the hypothetical model of ***ACE*** resulted in the synthesis and evaluation of a ***series*** of succinic acid derivatives.



Inhibitor binding models of (A) D-2-benzylsuccinic acid to carboxypeptidase A and (B) succinic acid derivatives to ACE.

69

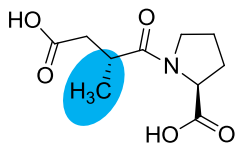
Because ***proline*** was present as the C-terminal amino acid in SQ 20,881 it was included in the structure of newly designed inhibitors. The first inhibitor to be synthesized and tested was ***succinyl-l-proline***. This compound proved to be somewhat disappointing. Although it provided reasonable ***specificity*** for ACE, it was only approximately 1/500 as potent as SQ 20,881. Substitution of ***other amino*** acids in place of proline produced compounds that were even ***less*** potent; hence, ***all*** subsequent SAR studies were conducted using analogs of l-proline.



Succinyl-l-proline (1/500)

Less potent

The addition of a ***methyl*** group to the 2-position of succinyl-l-proline to mimic the amino acid side chain, **R2**, of the substrate ***enhanced*** activity, but only marginally. ***D-2-Methylsuccinyl-L-proline*** had effects similar to SQ 20,881 but was still only 1/300 as potent.

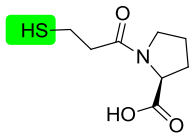


D-2-methylsuccinyl-L-proline

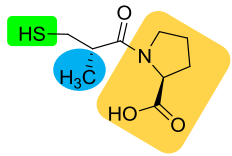
70

One of the ***most important alterations*** to succinyl-L-proline was the ***replacement*** of the succinyl carboxylate with other groups having enhanced affinity for the zinc atom bound to ACE. Replacement of this carboxylate with a ***sulfhydryl*** group produced 3-mercaptopropanoyl-l-proline. The IC_{50} of this compound was ***200*** nM and is greater than 1,000-fold more potent than succinyl-l-proline. Additionally, it is ***10- to 20-fold*** more potent than SQ 20,881.

Addition of a ***2-D-methy***l group further enhanced activity. The resulting compound, ***captopril*** is a competitive inhibitor of ACE with a *K*i value of 1.7 nM and was the first ACE inhibitor to be marketed.



3-Mercaptopropanoyl-l-proline



Captopril

The ***sulfhydryl*** group of captopril proved to be responsible not only for the ***excellent*** inhibitory activity of the compound but also for the two most common ***side effects***, skin rashes and taste disturbances (e.g., metallic taste and loss of taste).

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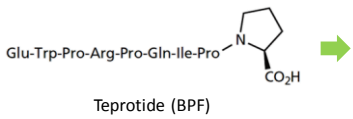
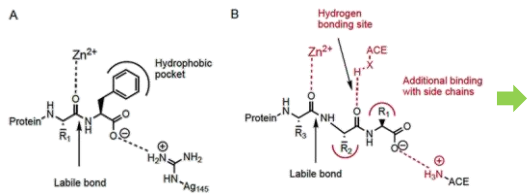
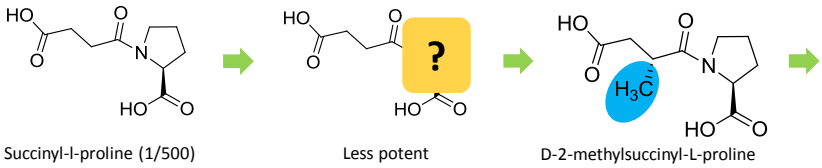
Summary of captopril development:



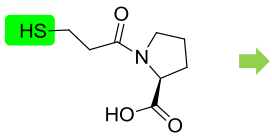
Teprotide (BPF)



A. A model of substrate binding to carboxypeptidase A. **B.** ACE hypothetical substrate binding sites



Succinyl-l-proline (1/500) | Less potent | D-2-methylsuccinyl-L-proline



3-Mercaptopropanoyl-l-proline

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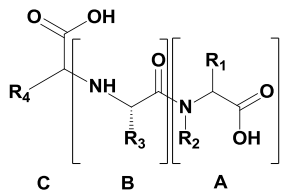
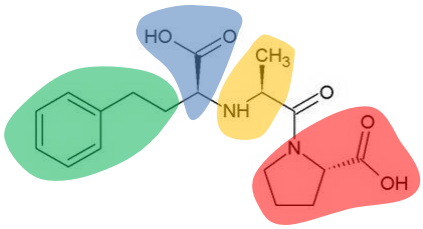
Dicarboxylate-Containing Inhibitors: Development of Enalapril

Researchers at Merck sought to develop compounds that ***lacked*** the ***sulfhydryl*** group of captopril yet maintained some ability to ***chelate*** zinc. Compounds having the shown general structure were designed to meet this objective.

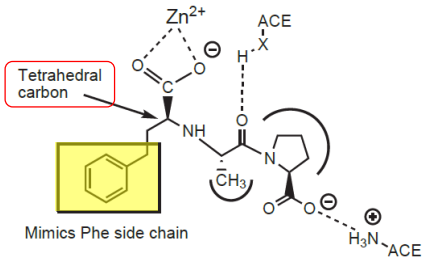


These compounds are ***tripeptide substrate analogs*** in which the C-terminal (A) and penultimate (B) amino acids are ***retained*** but the third amino acid is ***isosterically*** replaced by a substituted ***N-carboxymethyl*** group (C). Similar to the results seen in the development of captopril, C-terminal ***proline*** analogs provided optimum activity. The use of a methyl group at ***R3*** (i.e., B = Ala) and a phenylethyl group at ***R4*** resulted in ***enalaprilat*** which was ***10-fold*** more potent than captopril.

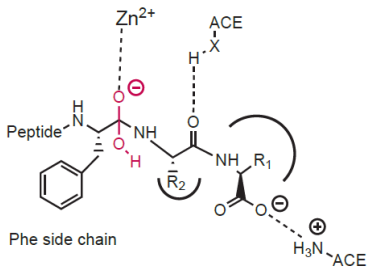


Enalaprilat

Studies investigating the ***binding*** of ***enalaprilat*** revealed that its ability to ***chelate*** the enzyme-bound zinc atom was significantly ***less*** than that of captopril. The enhanced binding was proposed to be caused by the ability to ***mimic the transition state*** of angiotensin I hydrolysis. Enalaprilat possess a ***tetrahedral carbon*** in place of the labile peptide bond.



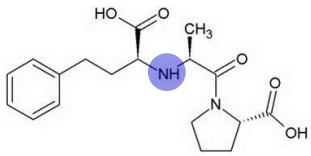
Enalaprilat



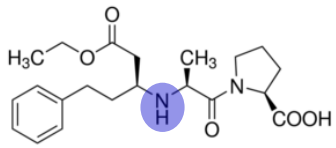
Transition state (**red**) of angiotensin I hydrolysis by ACE (R1 and R2= side chains of Leu and His).

Why do transition state analogues are very tight binders?

Despite excellent intravenous (***IV***) activity, enalaprilat has very poor ***oral*** bioavailability. ***Esterification*** of enalaprilat produced enalapril, a compound with superior ***oral*** bioavailability.



Enalaprilat



Enalapril

The ***combination*** of structural features in enalaprilat, especially the two ***carboxylate*** groups and the secondary ***amine***, is ***responsible*** for its overall low lipophilicity and poor oral bioavailability. ***Zwitterion*** formation also has been suggested to contribute to the low oral activity, and a comparison of the p*K*a values for the secondary amine of enalaprilat and enalapril supports this explanation. ***Ionization*** of the adjacent carboxylate in enalaprilat greatly enhances the basicity of the secondary amine such that the p*K*a of the amine in this compound is ***8.02***, whereas in enalapril, it is only ***5.49***. Thus, in the small intestine, the amine in enalaprilat will be primarily ionized and form a ***zwitterion*** with the adjacent carboxylate, but the amine in enalapril will be primarily ***un-ionized***.

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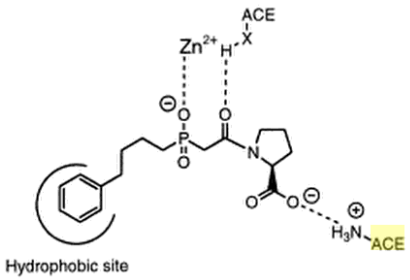
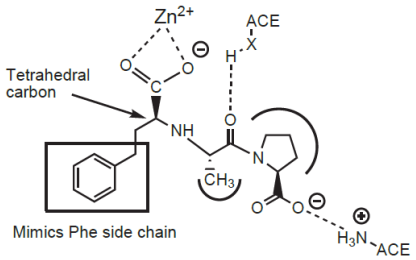
Phosphinate-Containing Inhibitors: The Development of Fosinopril

The search for ACE inhibitors that ***lacked*** the ***sulfhydryl*** group also lead to the investigation of ***phosphorous*** containing Compounds. A feature ***unique*** to this compound is the ability of the phosphinic acid to more ***truly mimic*** the ionized, tetrahedral intermediate of peptide hydrolysis. Unlike enalapril and other dicarboxylate analogs, however, the ***spacing*** of this tetrahedral species is ***shorter***, being only two atoms away from the proline nitrogen. Additionally, the ***spacing*** between the proline nitrogen and the ***hydrophobic phenyl*** ring is one atom ***longer*** than that seen in the dicarboxylates.



The binding of phosphonate analogs to ACE



Enalaprilat

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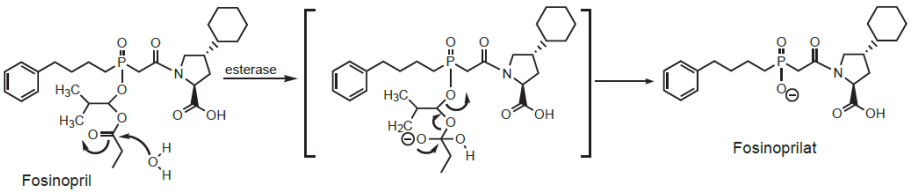
Structural modification to investigate more hydrophobic, C-terminal ring systems, similar to that described earlier for the dicarboxylate compounds, led to a ***4-cyclohexylproline*** analog of the original phosphinic acid. This compound, ***fosinoprilat***, was more potent than captopril but less potent than enalaprilat. The previously mentioned ***differences*** in the ***spacing*** of the ***phosphinic acid*** and ***phenyl*** groups may be ***responsible*** for this latter difference in potency.

Similar to the dicarboxylates, fosinoprilat was ***too hydrophilic*** and exhibited ***poor*** oral activity. The ***prodrug*** fosinopril contains an (acyloxy)alkyl group that allows better lipid solubility and improved bioavailability. ***Bioactivation*** via esterase activity in the intestinal wall and liver produces fosinopril.



Bioactivation via esterase activity in the intestinal wall and liver.

77

Mechanism of action of ACEIs:

ACEIs ***block*** the conversion of angiotensin I to angiotensin II by interacting with ***three*** major sites in the catalytic pocket:

1. a ***cationic*** site for binding to the anionic carboxylate terminus of the peptide substrate.

2. a ***zinc*** atom located close to the labile peptide bond and serves to ***polarize*** the carbonyl group and making the amide group more susceptible to hydrolysis, and ***stabilize*** the negatively charged tetrahedral intermediate.

3. a ***hydrophobic*** pocket that provides some specificity for the C-terminal aromatic or nonpolar residue.

Studies of ***indoline*** analogues of captopril indicated that ACE binding site contained a ***hydrophobic pocket*** similar to carboxypeptidase. Thus the model was modified and inhibitors with ***larger*** hydrophobic ring systems were developed

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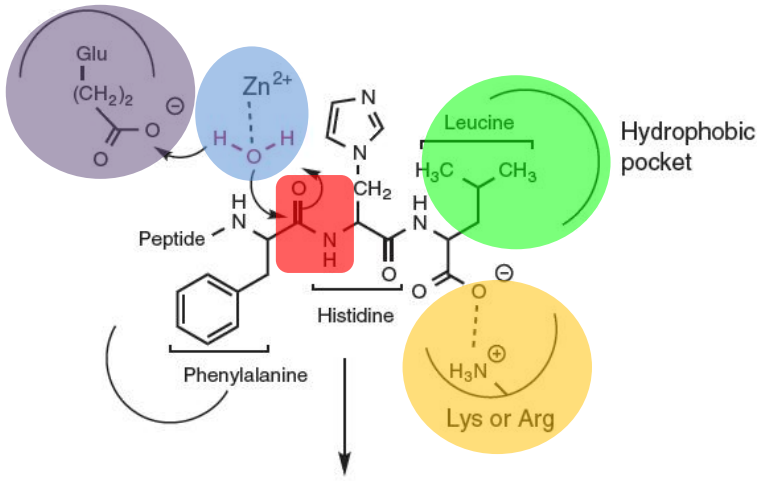
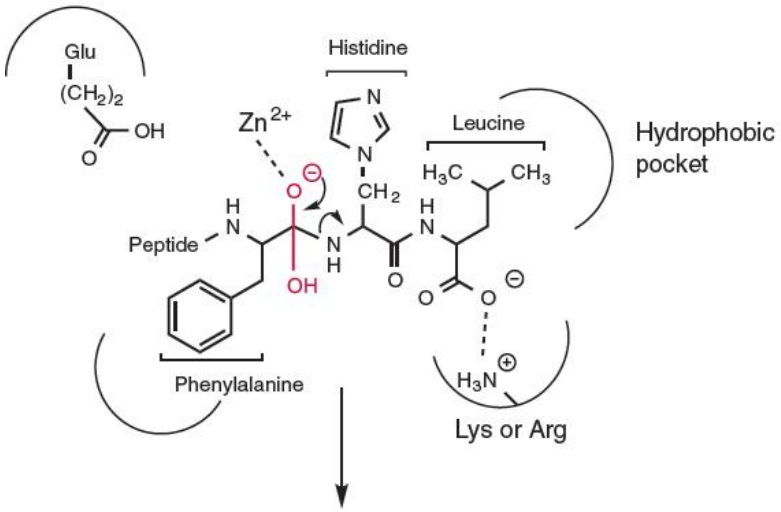
The binding of ***angiotensin I*** to key residues in ACE showing the formation of the ***tetrahedral*** transition state and the role of water and Glu in the hydrolysis process.

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe⋮His-Leu



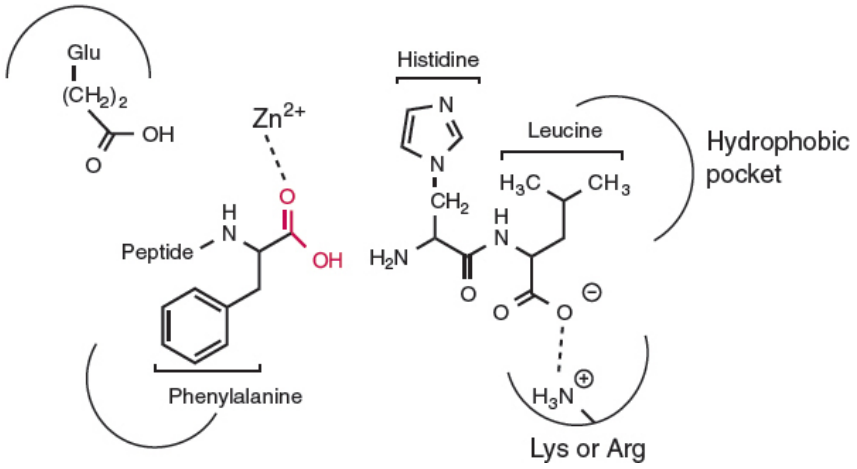
79

Transition state (tetrahedral intermediate)



80

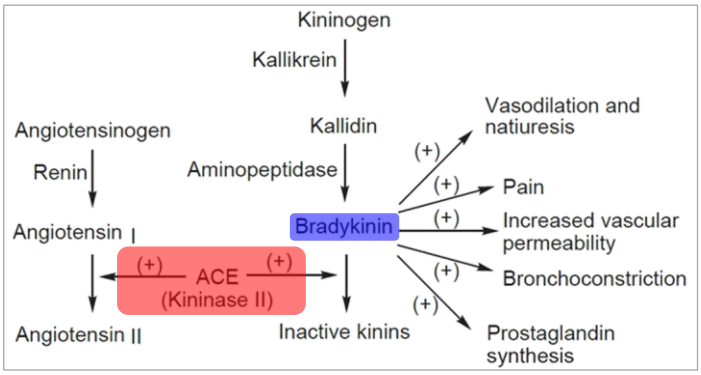
Hydrolysed peptide



81

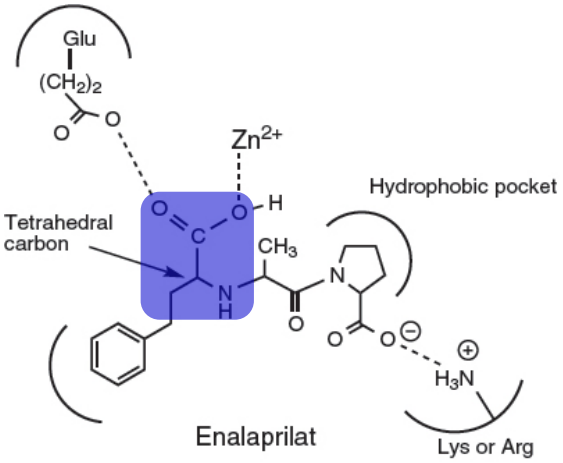
In addition, ACEIs ***mimic the tetrahedral*** transition state of peptide hydrolysis and are ***resistant*** to hydrolysis. Since ACE is a relatively ***nonspecific*** dipeptidyl carboxypeptidase, ACEIs also ***inhibit*** the metabolism of ***bradykinin*** which leads to a number of physiological effects:

- Vasodilation potentiating the hypotensive action of the ACEIs
- Bronchoconstriction is manifested by a dry cough
- Increased prostaglandin synthesis contributing to vasodilation, vascular permeability, and the production of some types of pain and inflammation.



82

Examples of inhibitor binding to ACE demonstrating the ***tetrahedral transition state*** are enalaprilat and captopril.



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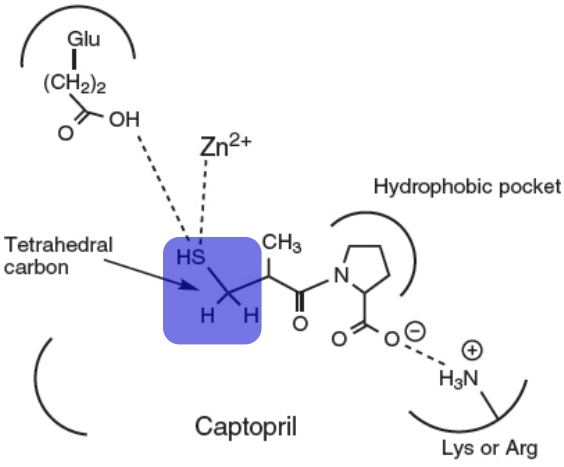

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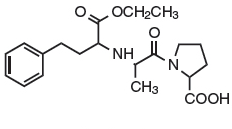
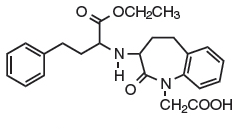
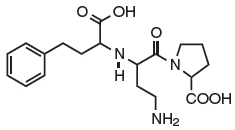
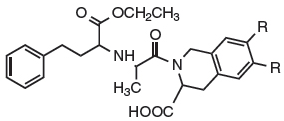
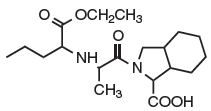
Products:

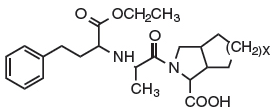

Enalapril

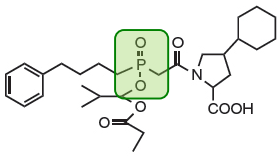

Benazepril

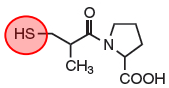

Lisinopril


Moexipril (R = OCH_3)
Quinapril (R = H)


Perindopril

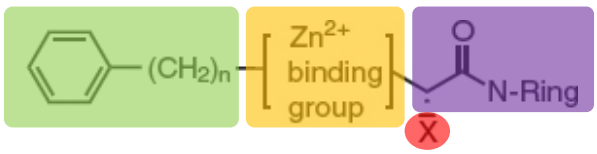

Ramipril (X = 1)
Trandolapril (X = 2)

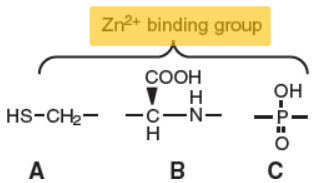

Fosinopril


Captopril

SAR of ACEIs:

Because currently approved ACE inhibitors act as either ***di- or tripeptide substrate analogs***, they must contain a ***stereochemistry*** that is consistent with the ***L-amino*** acids present in the natural substrates.





- The ***N-ring*** portion must contain a carboxylic acid for binding to the cationic site in ACE (to mimic the C-terminal carboxylate of ACE substrates). It is a ***common*** structural feature in all ACEIs.

- ***Large heterocyclic*** rings in the N-ring portion increase potency and alter pharmacokinetics.
- The ***zinc binding group*** can be either (A) sulfhydryl, (B) carboxylate, or (C) phosphinate.
- ***-SH*** group shows superior binding to Zn^{2+}. (The side chain mimicking the Phe in carboxylate and phosphinic acid compounds partially compensates for the lack of a sulfhydryl group).
- ***-SH*** containing compounds produce a high incidence of skin rashes and a loss of taste. They can also form ***disulfides*** and ***dimers*** which may ***shorten*** the duration of action.
- Binding of Zn^{2+} through either a carboxylate or phosphinate (O=P-OH) ***mimics*** the peptide hydrolysis transition state and enhance binding.
- ***X*** is usually a methyl group to mimic the side chain of alanine. Within the dicarboxylate series, when X equals n-butylamine (***lysine*** side chain), this produces a compound that does ***not*** require prodrug for oral activity. ***Stereochemistry*** mimicking the stereochemistry of L-amino acid is optimal (present in normal substrates).
- ***Esterification*** of the carboxylate or phosphinate produces orally bioavailable prodrugs. Nomenclature is designated as …***pril*** (ester prodrug) versus …***prilat*** (active drug). ***Lisinopril and captopril*** are the only two ACE inhibitors that are ***not*** prodrugs.

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Physicochemical and Pharmacokinetic Properties:

- All ACEIs are ***amphoteric*** except captopril and fosinopril which are ***acidic***.
- The carboxylic acid attached to the N-ring has a ***pKa*** range from 2.5 to 3.5 and is ionized at physiological pH.
- The ***second carboxylic acid*** in the dicarboxylate series is ionized in the active form but unionized when in the prodrug (ester) form.
- The ***pKa*** and ***ionization*** of the secondary ***amine*** in the dicarboxylate series ***depend*** on whether the adjacent functional group is in the prodrug or active form.

  In the ***prodrug*** form, the ***amine*** is adjacent to an ester, is less basic (pKa= 5.49), and is primarily un-ionized at physiologic pH. Following ***bioactivation***, the amine is adjacent to an ionized carboxylic acid that enhances both the basicity and ionization of the amine (pKa=8.02).

  Similarly, the ***basic nitrogen enhances*** the acidity of the adjacent ***carboxylic*** acid such that it usually has a lower pKa than the carboxylic acid attached to the N-ring. ***As an example***, the pKa values of enalaprilat are 3.39 and 2.30. These values correspond to the carboxylic acid on the N-ring and the carboxylic acid adjacent to the amine, respectively.

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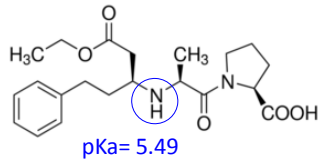
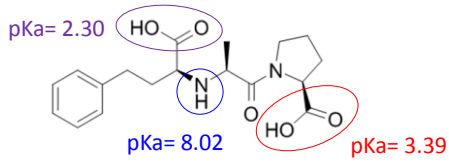
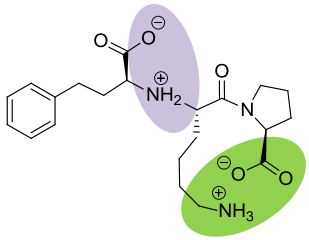




- ***All*** possess ***good lipid solubility*** with the ***exception*** of captopril, enalaprilat, and lisinopril. Compounds that contain hydrophobic ***bicyclic*** ring systems are more lipid soluble than those that contain proline.

- ***Lisinopril*** exhibits good ***oral*** bioavailability even though it is the ***most*** hydrophilic, because in the duodenum, lisinopril most likely exists as a ***di-zwitterion*** in which the ionized groups are ***internally*** bound to one another and is able to pass through the lipid bilayer with an overall net neutral charge.



Side effects of ACEIs:

Hypotension, ***hyperkalemia*** (due to inhibition of aldosterone release), ***dry cough***, rash (captopril), taste disturbances (captopril). Dry cough is by far most prevalent and is likely the result of the increase in the combination of bradykinin and prostaglandins.

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Pharmacokinetic Parameters of ACE Inhibitors

Drug	Calculated LogP	Oral Bioavailability (%)	Effect of Food on Absorption	Active Metabolite	Protein Binding (%)	Onset of Action (hours)	Duration of Action (hours)	Major Route(s) of Elimination
Benazepril	5.50	37	Slows absorption	Benazeprilat	>95	1	24	Renal (primary) Biliary (secondary)
Captopril	0.27	60–75	Reduced	NA	25–30	0.25–0.50	6–12	Renal
Enalapril	2.43	60	None	Enalaprilat	50–60	1	24	Renal/fecal
Enalaprilat	1.54	NA	NA	NA	—	0.25	6	Renal
Fosinopril	6.09	36	Slows absorption	Fosinoprilat	95	1	24	Renal (50%) Hepatic (50%)
Lisinopril	1.19	25–30	None	NA	25	1	24	Renal
Moexipril	4.06	13	Reduced	Moexiprilat	50	1	24	Fecal (primary) Renal (secondary)
Perindopril	3.36	65–95	Reduced	Perindoprilat	60–80	1	24	Renal
Quinapril	4.32	60	Reduced	Quinaprilat	97	1	24	Renal
Ramipril	3.41	50–60	Slows absorption	Ramiprilat	73	1–2	24	Renal (60%) Fecal (40%)
Spirapril	3.16	50	—	Spiraprilat	—	1	24	Renal (50%) Hepatic (50%)
Trandolapril	3.97	70	Slows absorption	Trandolaprilat	80	0.5–1.0	24	Fecal (primary) Renal (secondary)

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B. Angiotensin II Receptor Blockers

Overview and mechanism of action:

Angiotensin II produces its biological effects by interacting with two receptor subtypes, AT1 and AT2. The AT1 receptors are located in brain, neuronal, vascular, renal, hepatic, adrenal, and myocardial tissues. AT2 receptors are found in the brain, CNS, and myocardial and renal tissue.

- ***AT_1*** effects include vasoconstriction, aldosterone and vasopressin secretion, sodium reabsorption, catechol release, and left ventricular remodeling. ***AT_2*** interaction results in ***cardioprotective*** effects, for example, vasodilation, release of nitric oxide (NO), regression of hypertrophy, and apoptosis.
- All currently available ARBs are 10,000 times more ***selective for AT_1*** subtype and are ***competitive*** antagonists.
- It is more ***desirable*** to have a ***selective*** AT_1 blocker since blocking AT_2 would reduce or eliminate its apparent cardioprotective effects.

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Development of Losartan:

- Initial research focused on ***peptide analogs of Angiotensin II***. The prototypic compound that was developed was ***saralasin***, an octapeptide in which the Asp^1 and Phe^8 residues of angiotensin II were replaced by ***Sar*** (sarcosine, N-methylglycine) and Ala, respectively.

Asp^1–Arg—Val—Tyr^4–Ile^5–His^6—Pro—Phe^8
Angiotensin II

Sar—Arg—Val–Tyr—Ile—His—Pro—Ala
Saralasin

- Saralasin however ***lacks oral*** bioavailability and expresses ***partial agonist*** action.
- This lead to the development of ***peptide mimetics*** to circumvent these peptide-based drug drawbacks.
- A series of ***imidazole-5-acetic acid*** analogs exemplified by **S-8308** and were later found to block the angiotensin II receptor ***specifically***.

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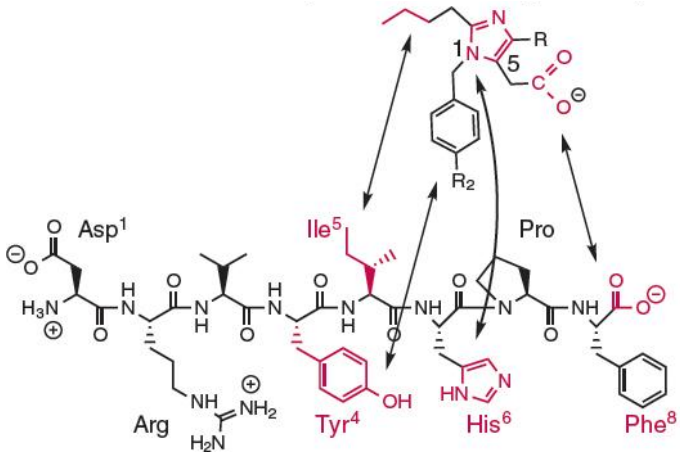
- A ***computerized*** molecular modeling ***overlap*** of angiotensin II with the structure of S-8308 revealed common structural features. The ***peptidomimetic 1-benzyl-5-acetyl-imidazoles mimic*** the ***key*** amino acid residues (Tyr^4, Ile^5, His^6, Phe^8) crucial for blocking the action of angiotensin II.

1-benzyl-5-acetyl-imidazole (**S-8308**)



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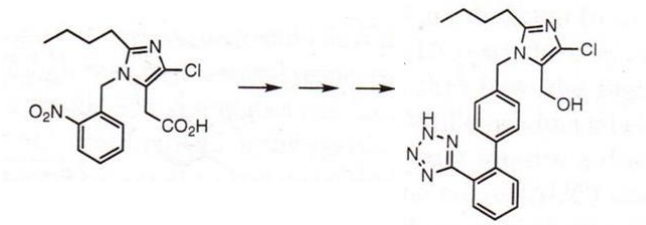
- From S-8308, a number of molecular ***modifications*** were carried out in an attempt to ***improve*** receptor ***binding*** and ***lipid solubility***, with the latter being important to assure adequate oral absorption. These changes resulted in the preparation of ***losartan***, a compound with high receptor affinity (IC_{50} = 19 nM) and oral activity.



(S-8308, IC_{50} = 15 μM) (Losartan, IC_{50} = 19 nM)

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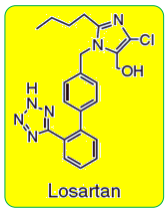
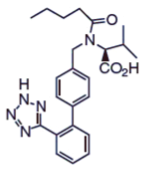
Additional Angiotensin II Receptor Blockers:

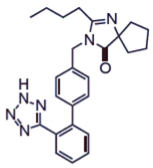
Valsartan, irbesartan, telmisartan, candesartan, olmesartan, and azilsartan are ***biphenyl*** analogs of losartan. These compounds possess structural features that are ***similar*** to those seen in losartan.



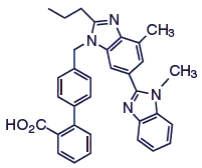
Losartan



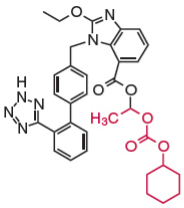
Valsartan



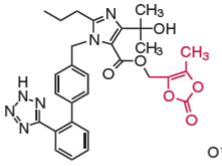
Irbesartan



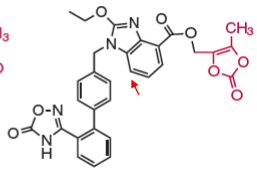
Telmisartan



Candesartan cilexetil



Olmesartan medoxomil



Azilsartan medoxomil

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Valsartan, named for the ***valine*** portion of the compound, is the first ***nonimidazole-containing*** ARB and is slightly more potent (IC50 = 0.0089 µmol/L) than losartan. The ***amide carbonyl*** of valsartan is isosteric with the imidazole nitrogen of losartan and can serve as a HBA similar to the imidazole nitrogen.

Irbesartan is a ***spiro-compound*** that ***lacks*** the primary alcohol of losartan but that has a 10-fold greater binding affinity (IC50 = 0.0013 µmol/L) for the angiotensin II receptor. Hydrogen bonding, or ion-dipole binding, of the ***carbonyl*** group can ***mimic*** the interaction of the primary alcohol of losartan, whereas the spirocyclopentane can provide enhanced ***hydrophobic*** binding.

Azilsartan medoxomil, ***candesartan*** cilexetil, and ***telmisartan*** contain ***benzimidazole*** rings that provide some enhanced ***hydrophobic*** binding, similar to that seen with the spirocyclopentane ring of irbesartan. All are ***prodrugs*** that are rapidly and completely hydrolyzed during absorption from the GIT to their active carboxylic acid metabolites, azilsartan, candesartan, and olmesartan, respectively in the intestinal wall. These carboxylic acids lie in exactly the ***same locations*** as the hydroxyl group of losartan, the carboxylic acid of valsartan, and the ketone of irbesartan and can participate in both ionic and dipole interactions.

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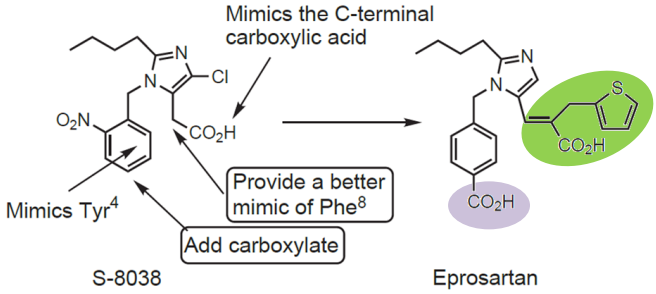
Eprosartan was developed using a ***different*** hypothesis than that for losartan. Similar to the rationale for losartan, the carboxylic acid of S-8308 was thought to mimic the Phe8 (i.e., C-terminal) carboxylate of angiotensin II. Thus, the ***major*** structural change was not an extension of the *N*-benzyl group but, rather, an enhancement of the compound's ability to ***mimic the C-terminal end of angiotensin II***. This was accomplished by ***substituting*** the ***5-acetic acid*** group with an ***α-thienylacrylic acid***. In addition, a ***para-carboxylat***e also was added. The thienyl ring isosterically mimics the Phe8 phenyl ring of angiotensin II and, along with the para-carboxylate, is responsible for the excellent potency (IC50= 0.0015 µmol/L) of this compound.



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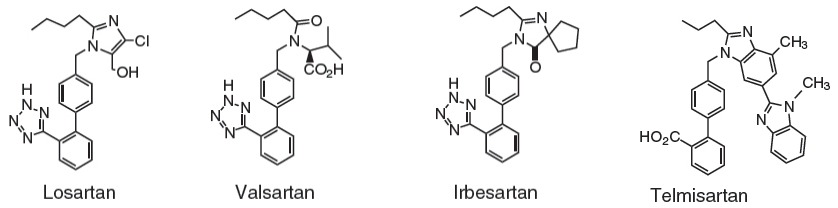
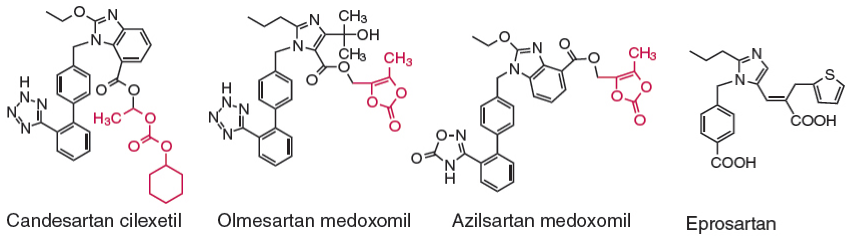
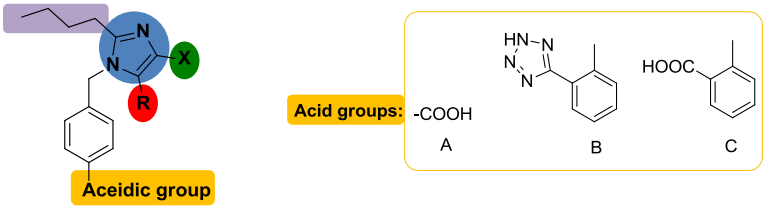




98

SAR of ARBs:

All commercially available ARBs are analogs of the following general structure:



- **X** can be an H, a Cl or varies.
- ***Acidic group*** is thought to mimic either the Tyr4 phenol or the Asp1 carboxylate of angiotensin II. In the biphenyl series, the tetrazole and carboxylate groups must be in the ortho position for optimal activity (the tetrazole group is superior in terms of metabolic stability, lipophilicity, and oral bioavailability).
- ***R*** can be carboxylic acid, a hydroxymethyl group, a ketone, or a benzimidazole ring, that are thought to interact with the AT1 receptor through either ionic, ion-dipole, or dipole-dipole bonds.

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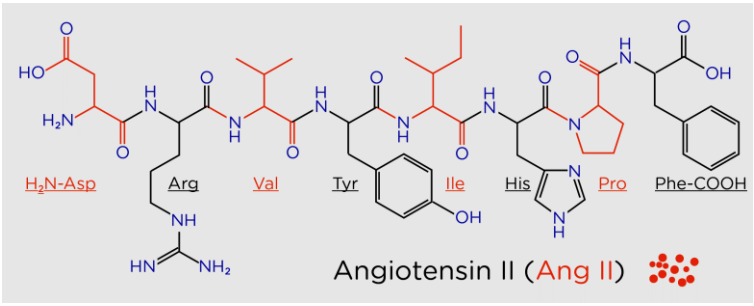
- ***The n-butyl chain*** provides hydrophobic binding and, most likely, mimics the side chain of Ile5 of angiotensin II. Can be either an ethyl ether or an *n*-propyl group.
- ***The imidazole*** ring or an isosteric equivalent is required to mimic the His6 side chain of angiotensin II.



100

Physicochemical and Pharmacokinetic Properties:

- All ARBs are acidic due to the tetrazole ring (pKa = 6) and carboxylate groups (pKa = 3-4).
- The tetrazole (at least 90%) and carboxylic acid groups are ionized at physiologic pH.
- The tetrazole ring containing ARBs have ***greater*** binding affinity than those without the tetrazole ring and are more ***lipophilic***. The four nitrogen atoms present in the tetrazole ring can create a greater ***charge distribution*** than that available for a carboxylic acid.
- All have low but adequate oral bioavailability (15% to 33%).
- Exceptions are irbesartan (60% to 80%) and telmisartan (42% to 58%).
- All are highly protein bound.
- Similar to ACE inhibitors, the ***stereochemistry*** of valsartan is consistent with the l-amino acids in the natural agonist.

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- Approximately 14% of a dose of losartan is oxidized by the isozymes ***CYP2C9*** and ***CYP3A4*** to produce ***EXP-3174***, a ***noncompetitive*** AT1 receptor antagonist that is ***10- to 40-fold more potent*** than losartan. The overall cardiovascular effects seen with losartan result from the combined actions of the parent drug and the active metabolite; thus, losartan should ***not*** be considered to be a ***prodrug***.

Losartan EXP-3174

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C. Renin Inhibitors

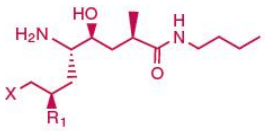
Developed as ***peptide mimetics*** to the ***octapeptide*** sequence (Pro7-Phe8-His9-Leu10-Val11-Ile12-His13-Asn14) of ***angiotensinogen*** recognized by renin. Currently, ***aliskiren*** is the only renin inhibitor available in the market. Aliskiren is based on an amino-amide ***nonpeptide*** template.

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-R

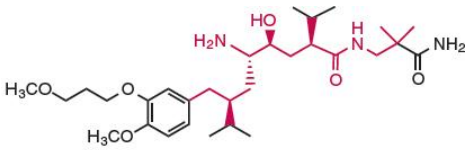
Angiotensinogen

Mechanism of action:

Aliskiren directly ***inhibits*** the formation of both angiotensin I and angiotensin II. Renin hydrolysis of angiotensinogen is the ***rate limiting*** step in this pathway and is regulated by hemodynamic, neurogenic, and humoral signals. Unlike ACEIs and ARBs, aliskiren does ***not*** cause a compensatory increase of renin in the plasma. ***Renin*** inhibitors and ***ARBs*** are ***peptide mimics*** that resemble the natural peptide substrates yet have no peptide bonds and therefore have ***better*** bioavailability and are ***stable*** to proteolytic degradation.



Nonpeptide Template



Aliskiren

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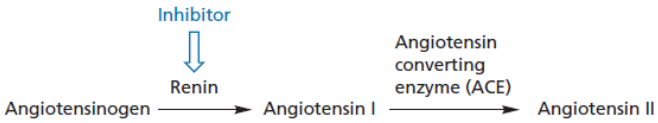
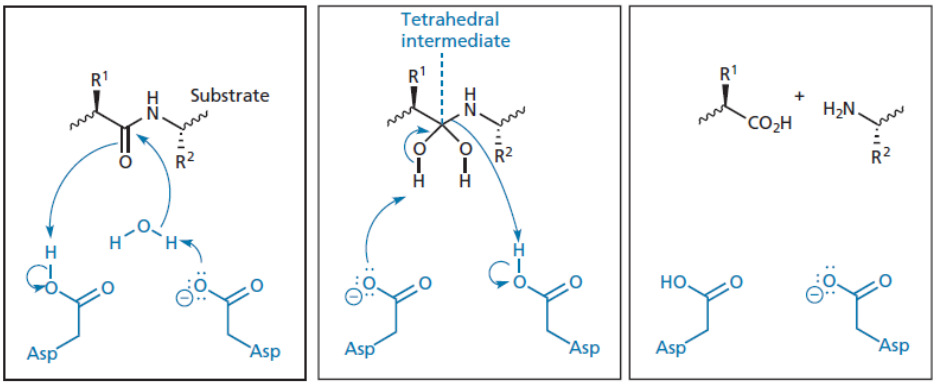
Renin inhibitors: Enzymes Transition State Inhibitors



Renin is an aspartyl protease enzyme



1.4 Calcium channel blockers

Overview:

Calcium is a ***key*** component of the ***excitation-contraction*** coupling process that occurs within the cardiovascular system. the concentration of Ca^{2+} outside cells is normally about ***10000-fold*** higher than the concentration inside cells. It acts as a cellular ***messenger*** to link internal or external excitation with cellular response. Embedded in the membrane of some cells are ***calcium channels***. When these cells receive a certain signal, the channels ***open***, letting calcium rush into the cell.

Increased cytosolic concentrations of Ca^{2+} result in the binding of Ca^{2+} to a ***regulatory*** protein, either ***troponin C*** in cardiac and skeletal muscle or ***calmodulin*** in vascular smooth muscle. This initial binding of Ca^{2+} ***uncovers*** myosin binding sites on the actin molecule, and subsequent ***interactions*** between actin and myosin result in muscle ***contraction***. ***All*** of these events are ***reversed*** once the cytosolic concentration of Ca^{2+} decreases. In this situation, Ca^{2+} binding to troponin C or calmodulin is diminished or removed, myosin binding sites are concealed, actin and myosin can no longer interact, and muscle contraction ceases.

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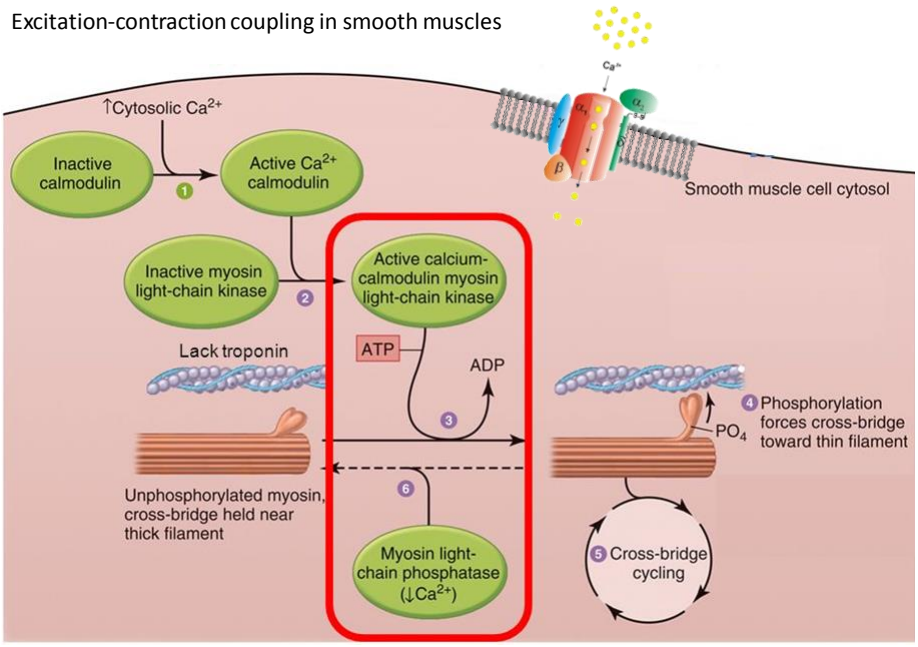
Excitation-contraction coupling in smooth muscles



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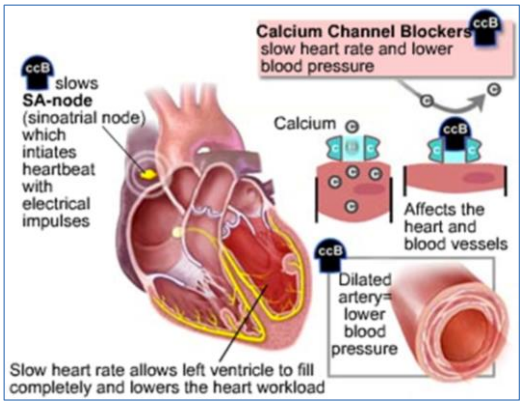
Voltage-dependent calcium channels are ***responsible*** for excitation-contraction coupling of skeletal, smooth, and cardiac muscle and for regulating aldosterone and cortisol secretion in endocrine cells of the adrenal cortex. In the ***heart***, they are also involved in the conduction of the pacemaker signals. Therefore, calcium (Ca^{2+}) channel blockers are prescribed for several disease states, the most important of which is ***hypertension***. Also they are used in the prevention and treatment of ***IHD*** or ***angina***.

The ***effectiveness*** of the Ca^{2+} channel blockers in treatment of hypertension is associated with selectivity for ***VSM*** (vascular smooth muscle), while action on myocardial tissue as well as VSM opens their use in treatment of IHD. Most of the antihypertensive Ca^{2+} channel blockers are members of the 1,4-dihydropyridines (***1,4-DHPs***) class of drugs.



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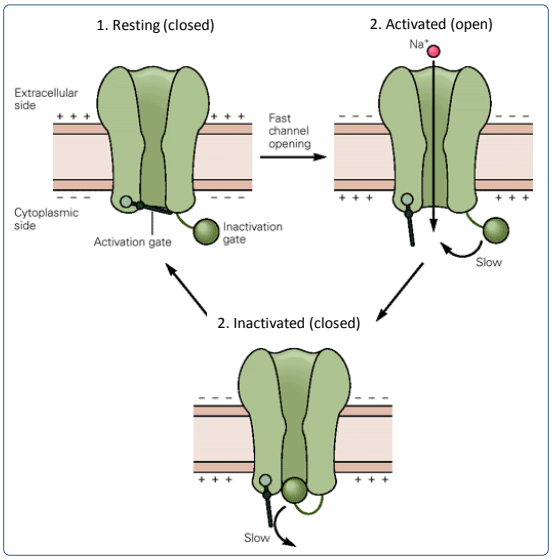
Several types of calcium channels occur, with a number of classes of blockers, but almost all of them preferentially or exclusively block the ***L-type voltage-gated calcium channel***. Potential-dependent channels (voltage-gated) can exist in one of ***three*** conformations: a ***resting*** state; an ***open*** state, which allows the Ca^{2+} to enter; and an ***inactive*** state, which is refractory to further depolarization.



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CCBs used as medications primarily have ***four effects***:

1. By acting on ***vascular smooth muscle***, they reduce contraction of the arteries and cause an increase in arterial diameter, vasodilation (CCBs do not work on venous smooth muscle).
2. By acting on ***cardiac muscles*** (myocardium), they reduce the force of contraction of the heart.
3. By ***slowing*** down the conduction of ***electrical*** activity within the heart, they slow down the heart beat.
4. By blocking the calcium signal on ***adrenal cortex*** cells, they directly reduce aldosterone production, which correlates to lower blood pressure.

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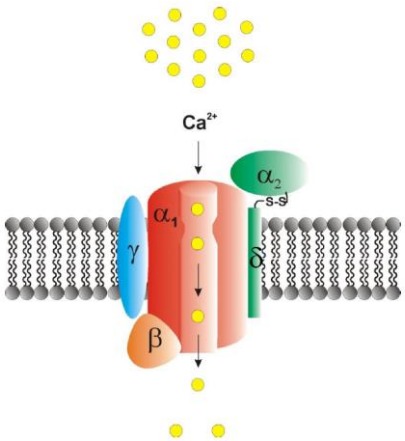
Mechanism of action:

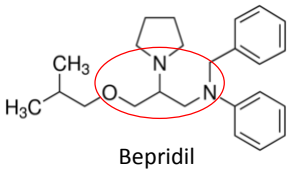
- Ca^{2+} channel blockers exert their effects by ***binding*** to specific receptor sites located within the ***central α_1*** subunit of L-type slow channels.
- Ca^{2+} channel blockers preferentially bind to Ca^{2+} channel in either the ***open*** or ***inactive*** state reducing Ca^{2+} flux.
- The 1,4-DHPs are primarily ***vasodilators*** although an ***increased heart*** rate may be seen resulting from a ***reflex*** mechanism tied to the vasodilation.



110

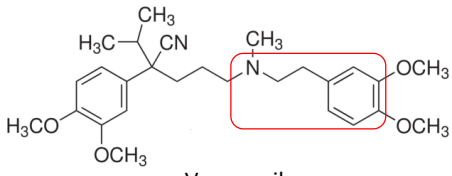
Calcium channel blockers are ***classified*** (depending on chemical structure) into:

1. Diaminopropanol ether:



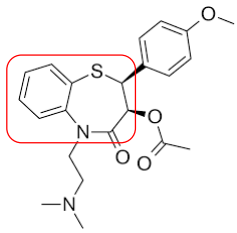
Bepridil

2. Phenylalkylamine:



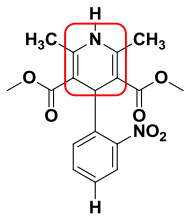
Verapamil

3. Benzothiazepine:



Diltiazem

4. 1,4-Dihydropyridine:



Nifedipine

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The ***majority*** of calcium channel blockers are 1,4-DHPs, and a detailed description of the SAR for this chemical class is provided below. In contrast, verapamil, diltiazem, and bepridil are the ***lone*** representatives of their respective chemical classes.

Bepridil is a ***nonselective*** agent. its actions are not based solely on its ability to block potential-dependent L-type (i.e., slow) Ca^{2+} channels. It ***also blocks*** fast Na^{+} channels as well as receptor-operated calcium channels. These additional actions are ***responsible*** for bepridil's ability to inhibit cardiac conduction, to slow AV nodal conduction, to increase the refractory period, to slow the heart rate, and to prolong the QT interval. It also should be noted that ***bepridil was never highly prescribed***, most likely because of the significant number of cardiovascular ***warnings*** and ***contraindications*** associated with its use.

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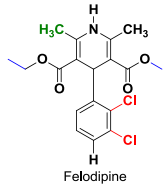
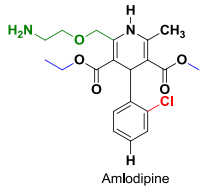
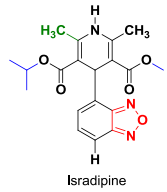
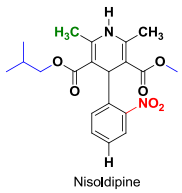
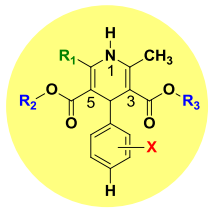
1,4-Dihydropyridine products:

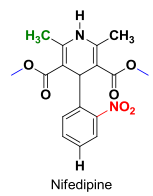

Felodipine

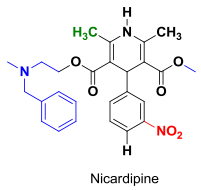

Amlodipine

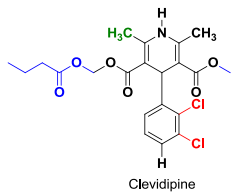

Isradipine

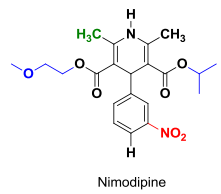

Nisoldipine




Nifedipine


Nicardipine


Clevidipine


Nimodipine

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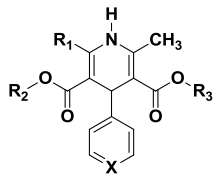
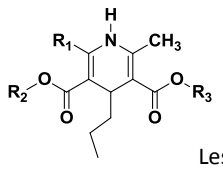
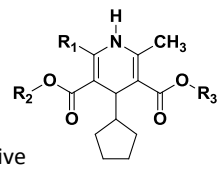
Structure-activity relationships: for 1,4-DHP derivatives.

1. ***A substituted phenyl ring at the C4 position optimizes activity*** (heteroaromatic rings, such as pyridine, produce similar therapeutic effects but are not used because of observed animal ***toxicity***), and C4 substitution with a small nonplanar alkyl or cycloalkyl group ***decreases*** activity.


Active but toxic




Less active

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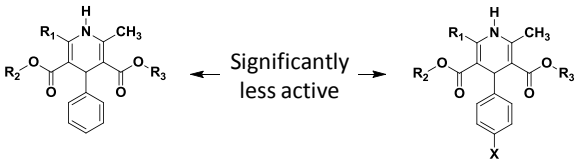
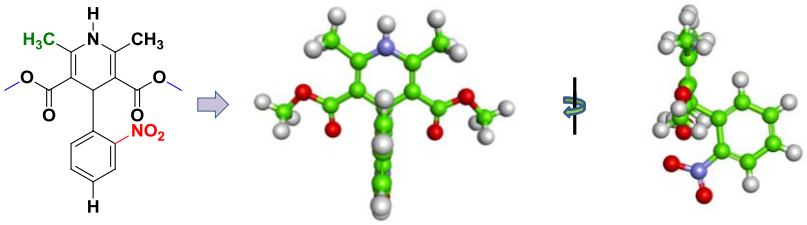
2. ***Phenyl ring substitution (X) is important for size and position rather than for electronic nature.*** Compounds with ***EDG*** at these same positions also have demonstrated good activity. Compounds with ***ortho*** or ***meta*** substitutions possess ***optimal*** activity, whereas those that are ***unsubstituted*** or that contain a ***para*** substitution show a significant ***decrease*** in activity. The importance of the ortho and meta substituents is to provide sufficient bulk to "***lock***" the conformation of the 1,4-DHP such that the C4 aromatic ring is ***perpendicular*** to the 1,4-DHP ring. This perpendicular conformation has been proposed to be ***essential for the activity*** of the 1,4-DHPs.





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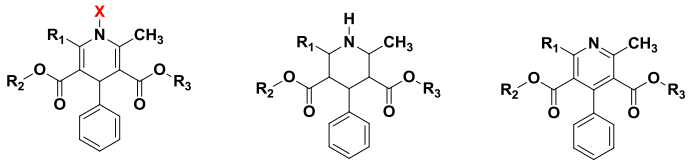
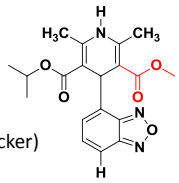
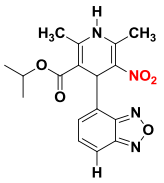
3. ***The 1,4-DHP ring is essential for activity***. Substitution at the N1 position or the use of reduced (piperidine) or oxidized (pyridine) ring systems greatly ***decreases*** or ***abolishes*** activity.



4. ***Ester groups at the C3 and C5 positions optimize activity***. Other ***EWG*** show decreased antagonist activity and may even show ***agonist*** activity. ***For example***, the replacement of the C3 ester of isradipine with a NO_2 group produces a calcium channel activator, or agonist. Thus, the term "***calcium channel modulators***" is a more appropriate classification for the 1,4-DHPs.

Isradipine
(Calcium channel blocker)





PN 202.791
(Calcium channel activator)

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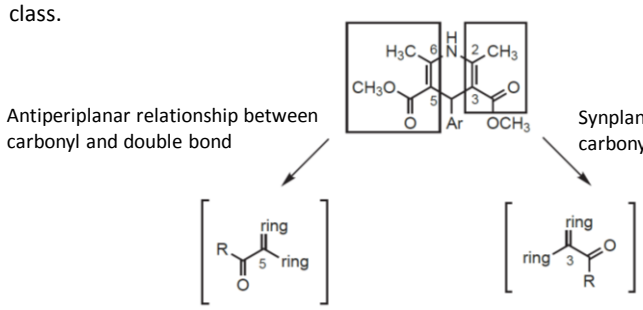
5. When the esters at C3 and C5 are ***nonidentical***, the C4 carbon becomes ***chiral***, and ***stereoselectivity*** between the enantiomers is observed. Additionally, evidence suggests that the C3 and C5 positions of the dihydropyridine ring are ***not equivalent*** positions. Crystal structures of nifedipine, a symmetrical 1,4-DHP, have shown that the C3 carbonyl is ***synplanar*** to the C2-C3 bond but that the C5 carbonyl is ***antiperiplanar*** (anti-coplanar) to the C5-C6 bond. ***Asymmetrical*** compounds have shown ***enhanced selectivity*** for specific blood vessels and are being preferentially developed. Nifedipine, the first 1,4-DHP to be marketed, is the only symmetrical compound in this chemical class.



6. With the ***exception*** of ***amlodipine***, ***all*** 1,4-DHPs have C2 and C6 ***methyl*** groups. The enhanced potency of amlodipine (vs. nifedipine) suggests that the 1,4-DHP receptor can ***tolerate larger*** substituents at this position and that ***enhanced*** activity can be obtained by altering these groups.

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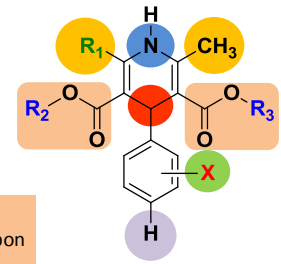
Summary for SAR of the 1,4-DHPs.



- N1 unsubstituted is essential
- 1,4-DHP receptor can tolerate larger substituents at C2 and C6 positions enhancing activity.
- Esters at C3 and C5 positions optimize activity.
- Nonidentical esters at C3 and C5 result in C4 chiral carbon (asymmetrical compounds enhancing selectivity).
- Other EWGs could lead to agonistic activity.
- Substituted phenyl ring at the C4 position optimizes activity (nonplanar alkyl or cycloalkyl group decreases activity).
- ortho or meta substituents for optimal activity.
- If X is bulky it will "lock" the conformation such that the C4 aromatic ring is perpendicular to the 1,4-DHP.
- can be EDG or EWG
- Para position must be unsubstituted

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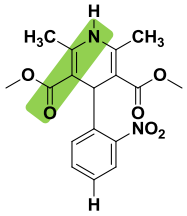
Physicochemical and Pharmacokinetic Properties:

- The N1 nitrogen of the 1,4-DHPs is part of a conjugated carbamate and as a result is ***not basic***.



- The 1,4-DHPs are all marketed as their ***racemic*** mixtures.
- The 1,4-DHPs possess ***good lipid solubility*** and excellent oral absorption, however ***rapid*** first-pass metabolism results in variable oral bioavailability depending on the extent of metabolism.

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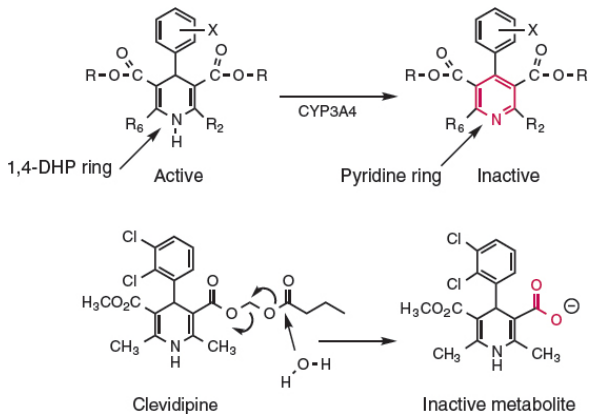
Metabolism:

- With the ***exception of clevidipine***, the 1,4-DHPs are oxidatively metabolized to ***inactive pyridine analogues***, followed by additional transformations (e.g., ester hydrolysis and conjugation).
- ***Nisoldipine*** also is subject to hydroxylation of the isobutyl ester producing a weakly active metabolite (~10% of the activity of the parent compound).



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1.5 Beta-adrenergic blockers

This class of drugs has been fully discussed in MedChem-I course within the topic "Drugs Acting on Peripheral Nervous System - the adrenergic system". Refer to that chapter to refresh your memory.

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