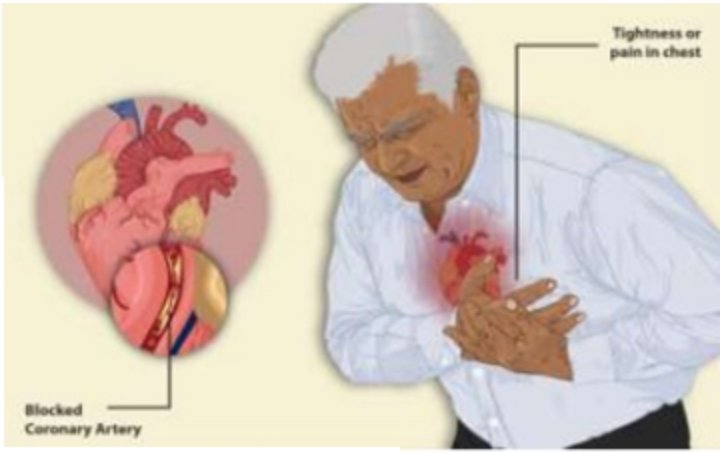
ANTI-ANGINAL

C351.2

Explain the structure activity relationship (SAR), mechanism of action, synthesis of drugs acting as diuretics, anti-anginal and antihypertensive agents.

What is Angina Pectoris...?



- It is chest pain or discomfort due to coronary heart disease
- It occurs when the heart muscle doesn't get as much BLOOD & OXYGEN as it needs
- This usually happens because one or more of the heart's arteries are narrowed or blocked, also called ischemia

Types of Angina Pectoris

- **Stable Angina / Angina Pectoris**
- **Unstable Angina**
- **Variant (Prinzmetal) Angina**
- **Microvascular Angina**

Tests:

- EKG (Electrocardiogram)
- Stress Testing
- Blood Tests
- Chest X-Rays
- Coronary Angiography and Cardiac Catheterization
- Computed Tomography Angiography

Treatment includes:

- Lifestyle changes
- Medicines
- Cardiac procedures
- Cardiac Rehab

Anti-anginal Agents

- **Vasodilators :**

Nitrates & Nitrites: **Amyl nitrite, Nitroglycerin, Pentaerythritol tetranitrate, Isosorbide dinitrite, Dipyridamole**

- **Calcium channel blockers:**

Verapamil, Bepridil hydrochloride, Diltiazem hydrochloride, Nifedipine, Amlodipine, Felodipine, Nicardipine, Nimodipine

- **Anti-hypertensive Agents:**

Timolol, Captopril, Lisinopril, Enalapril, Benazepril hydrochloride, Quinapril hydrochloride, Methyldopate hydrochloride, Clonidine hydrochloride, Guanethidine monosulphate, Guanabenz acetate, Sodium nitroprusside, Diazoxide, Minoxidil, Reserpine, Hydralazine hydrochloride

➢ Diuretics:

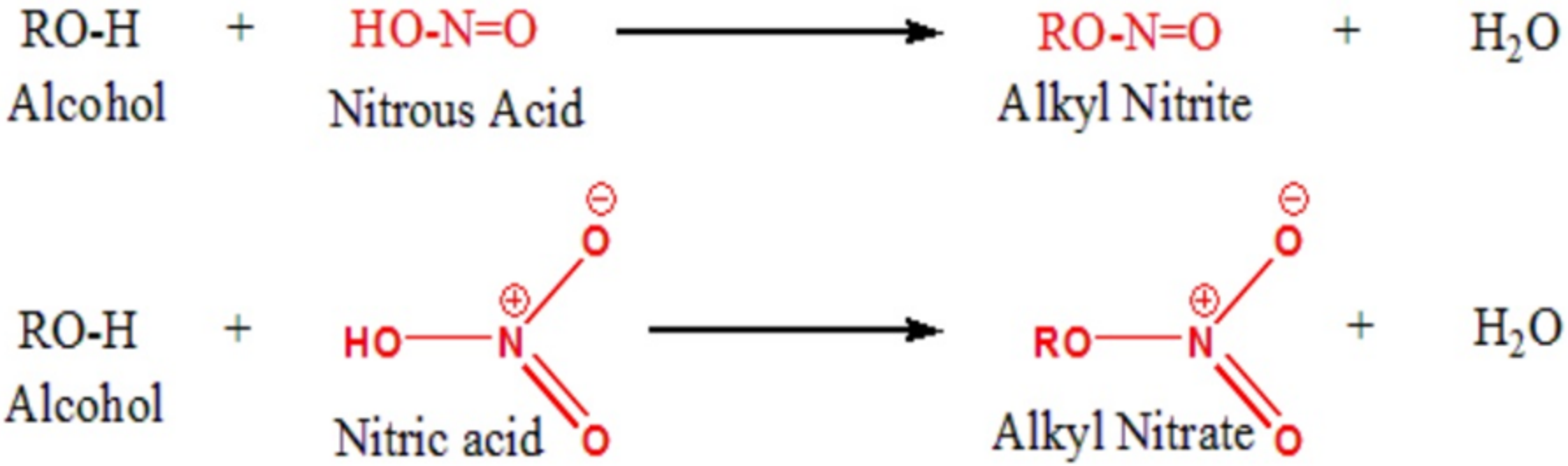
- **Carbonic anhydrase inhibitors:** Acetazolamide, Methazolamide, Dichlorphenamide
- **Thiazides:** Chlorthiazide, Hydrochlorothiazide, Hydroflumethiazide, Cyclothiazide
- **Loop diuretics:** Furosemide, Bumetanide, Ethacrynic acid
- **Potassium sparing Diuretics:** Spironolactone, Triamterene, Amiloride
- **Osmotic Diuretics:** Mannitol

Vasodilators

Nitrates & Nitrites:

- **Organic esters RCOOR' are esters of organic acids RCOOH with organic alcohols R'-OH**

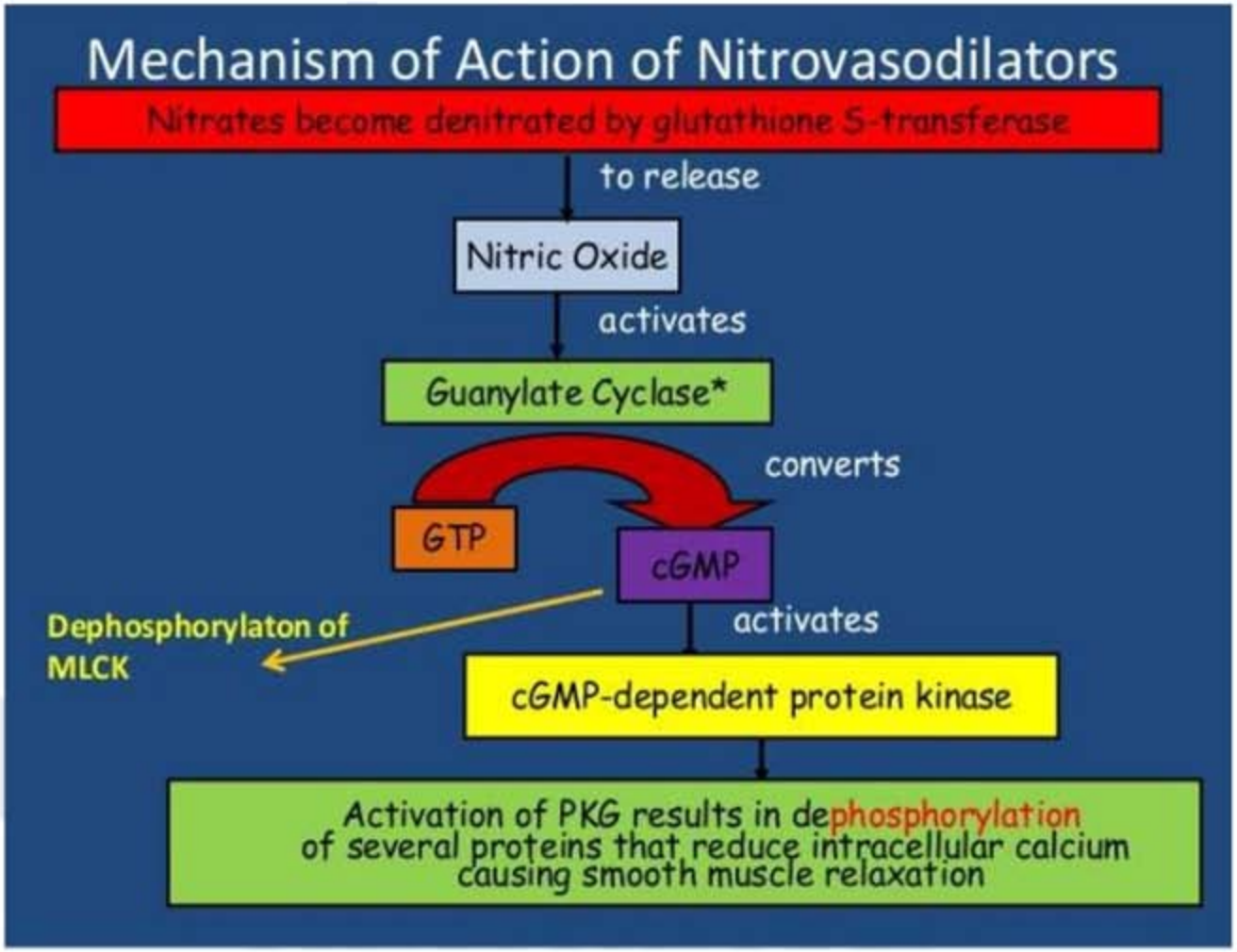
- **Organic nitrates($R'ONO_2$) & Organic nitrites(R'ON=O) are esters of nitrous acid (HNO_2) or nitric acid (HNO_3) with an organic alcohol R'OH where attachment of NO_2 is on Oxygen i.e.**

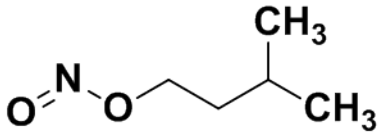


Mechanism of Action:

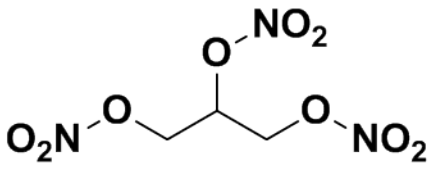
- Nitric oxide (NO) stimulates the formation of cGMP.
- Nitrodilators are the drugs, that mimic the actions of endogenous NO by releasing NO or forming NO within tissues.
- These drugs act directly on the vascular smooth muscle to cause relaxation and therefore serve as endothelial-independent vasodilators.
- There are two basic types of nitrodilators: those that release NO spontaneously (e.g., sodium nitroprusside) and organic nitrates that require an enzymatic process to form NO.
- Organic nitrates do not directly release NO, however, their nitrate groups interact with enzymes and intracellular sulfhydryl groups that reduce the nitrate groups to NO or to S-nitrosothiol, which then is reduced to NO.
- Nitric oxide activates smooth muscle soluble guanylyl cyclase (GC) to form cGMP.
- Increased intracellular cGMP inhibits calcium entry into the cell, thereby decreasing intracellular calcium concentrations and causing smooth muscle relaxation.

- NO also activates K^+ channels, which leads to hyperpolarization and relaxation.
- Finally, NO acting through cGMP can stimulate a cGMP-dependent protein kinase that activates myosin light chain phosphatase, the enzyme that dephosphorylates myosin light chains, which leads to relaxation.

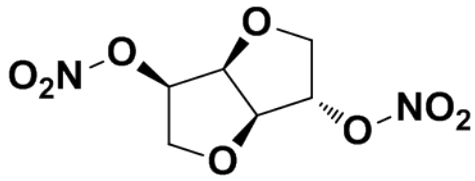




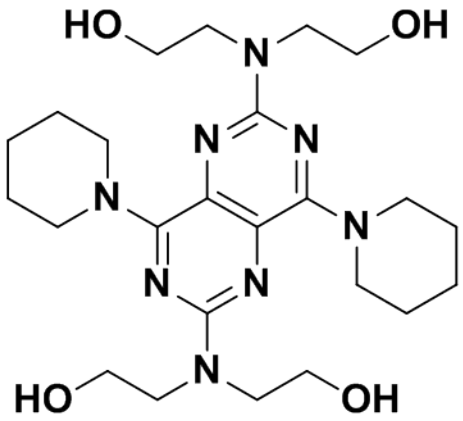
Amyl nitrite



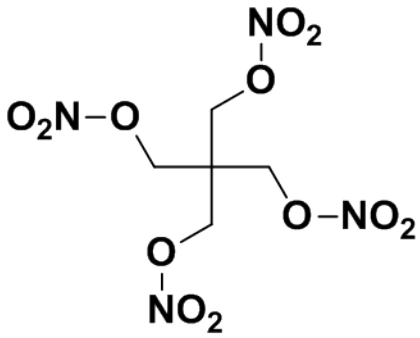
Nitroglycerin



Isosorbide dinitrate



Dipyridamole



Pentaerythritol tetranitrate

Calcium channel blockers

- Currently approved calcium-channel blockers (CCBs) bind to L-type calcium channels located on the vascular smooth muscle, cardiac myocytes, and cardiac nodal tissue (sinoatrial and atrioventricular nodes).

- These channels are responsible for regulating the influx of calcium into muscle cells, which in turn stimulates smooth muscle contraction and cardiac myocyte contraction.

- In cardiac nodal tissue, L-type calcium channels play an important role in pacemaker currents and in phase 0 of the action potentials.

- Therefore, by blocking calcium entry into the cell, CCBs cause vascular smooth muscle relaxation (vasodilation), decreased myocardial force generation (negative inotropy), decreased heart rate (negative chronotropy), and decreased conduction velocity within the heart (negative dromotropy), particularly at the atrioventricular node.

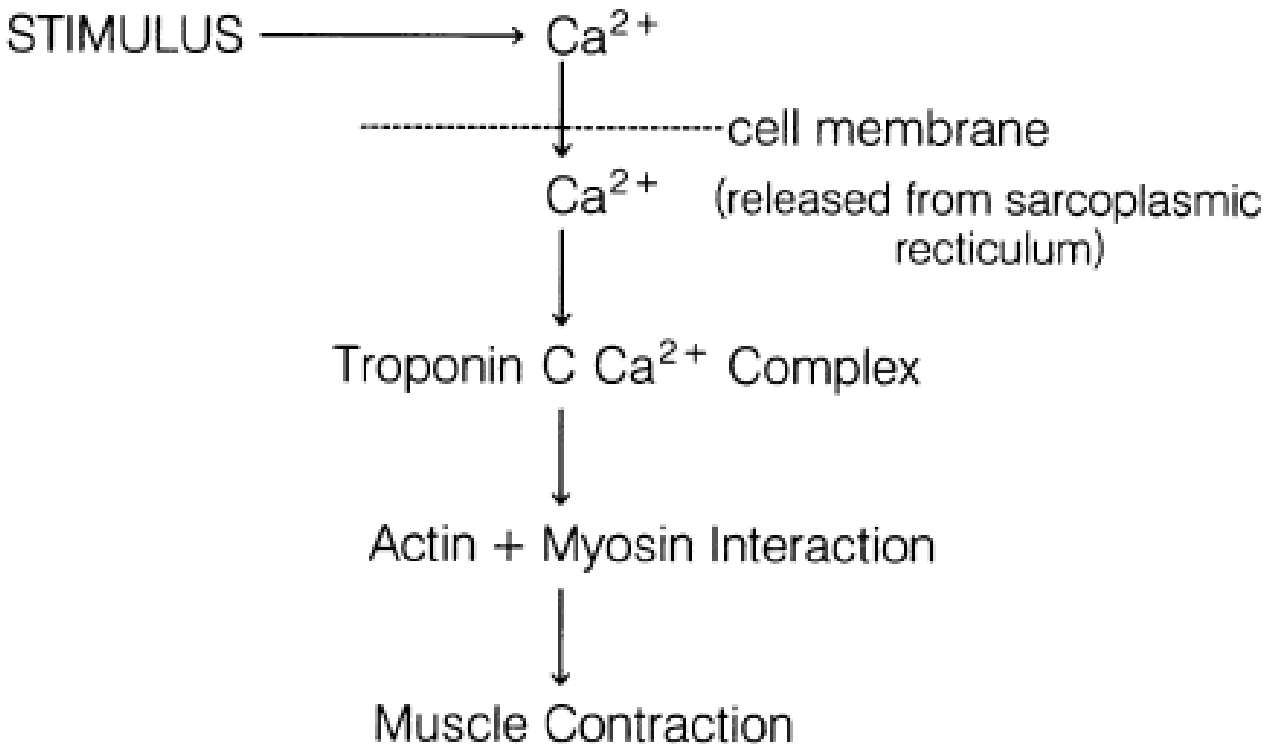
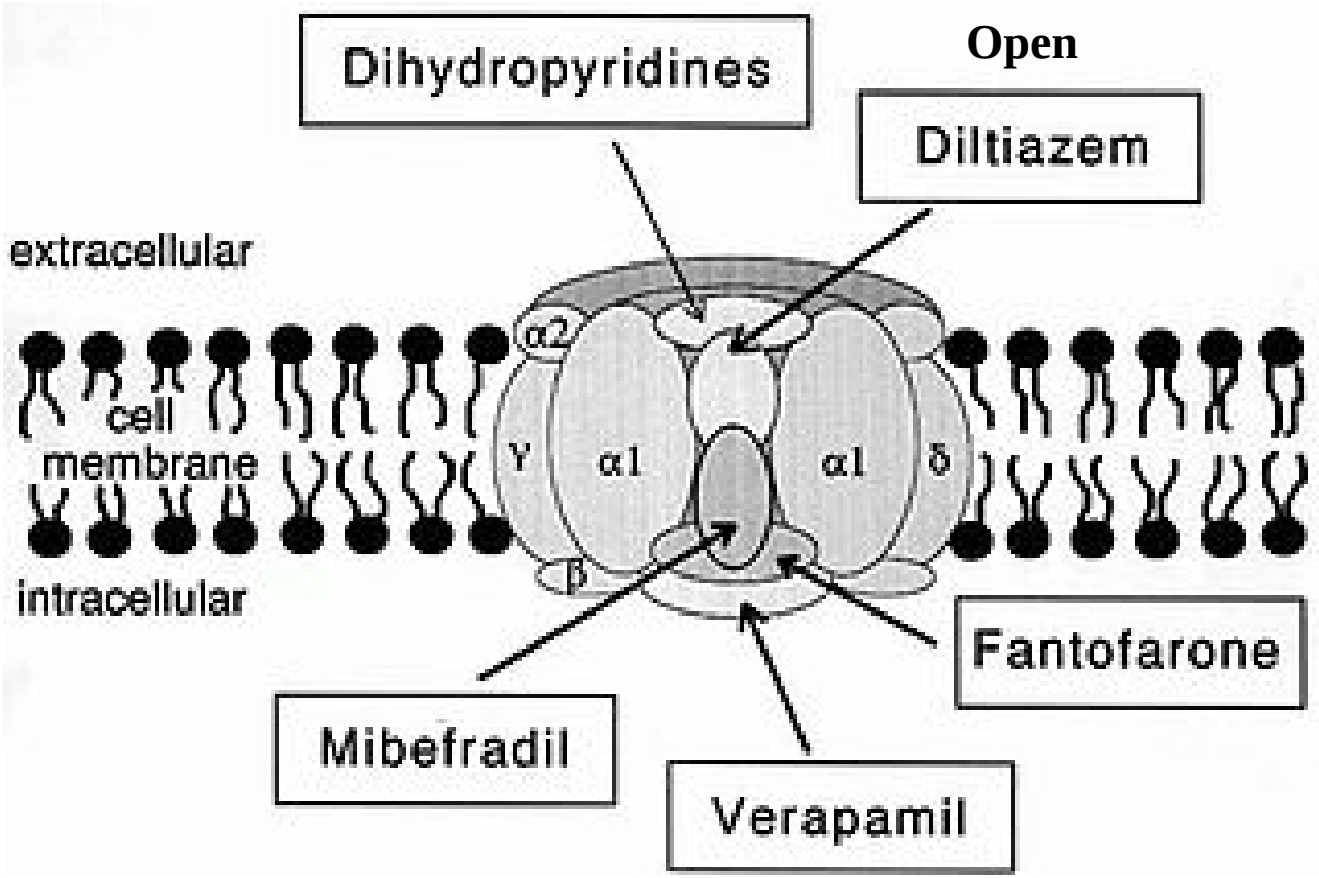


Figure 19.5 • Sequence of events showing excitation–contraction coupling in cardiac muscle.

Open or Closed



Open

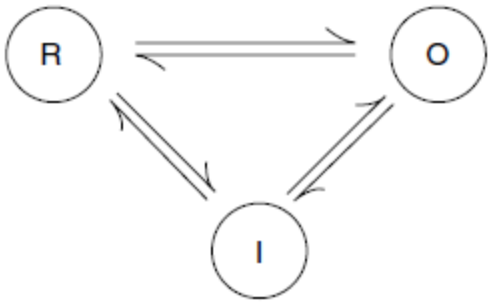
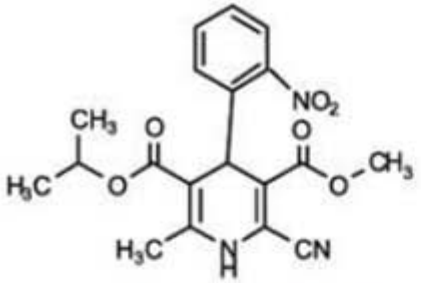


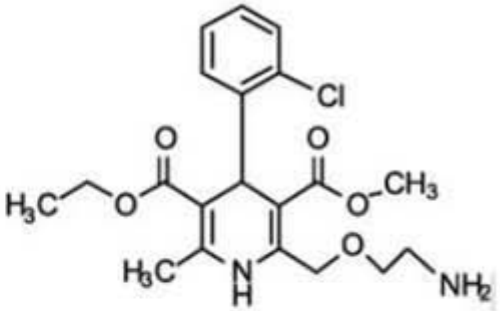
TABLE 19.3 First- and Second-Generation Calcium Channel Blockers

Chemical Classification	First Generation	Second Generation
Phenylalkylamines	Verapamil	Anipamil Bepridil
1,4-Dihydropyridine	Nifedipine	Amlodipine Felodipine Isradipine Nicardipine Nimodipine
Benzothiazepine	Diltiazem	—

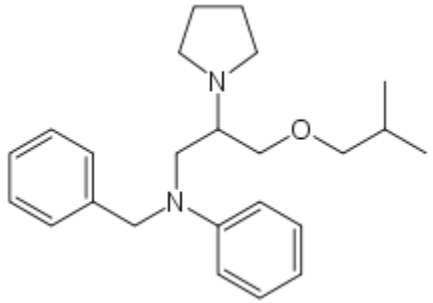
Structures



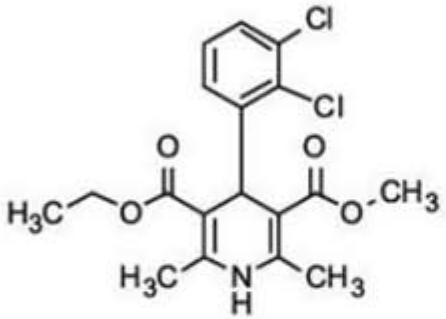
Nilvadipine



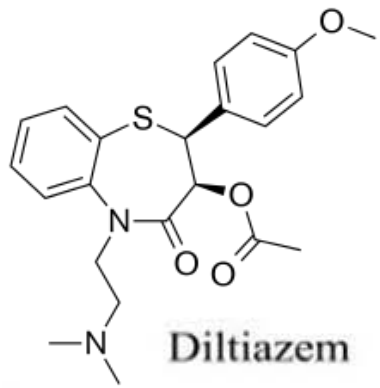
Amlodipine



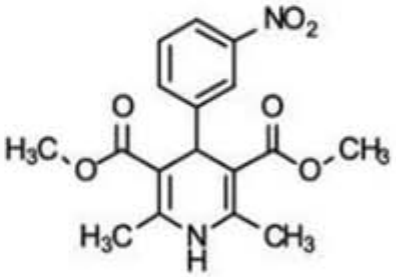
Bepridil



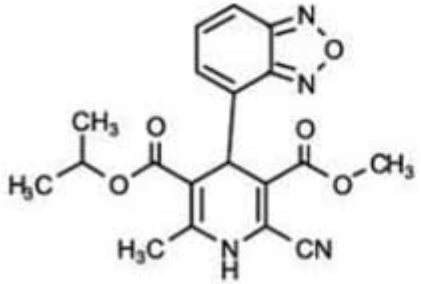
Felodipine



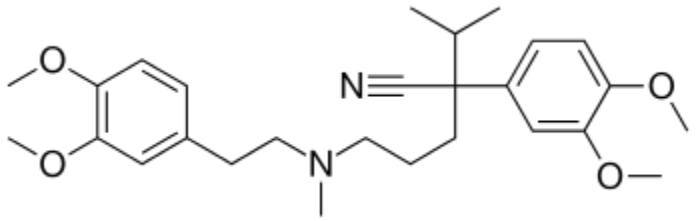
Diltiazem



Nifedipine



Isradipine



Verapamil

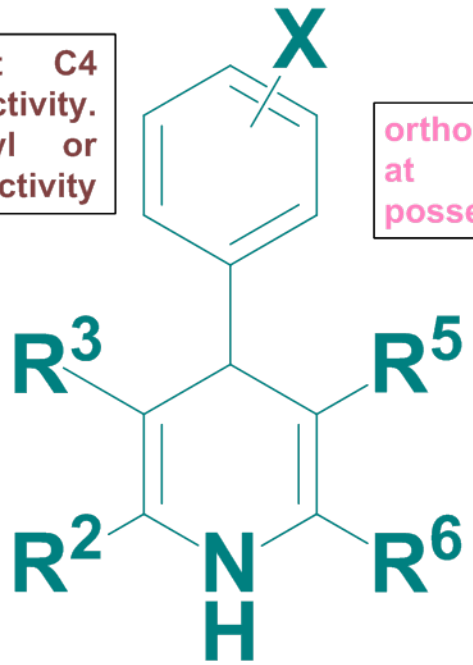
SAR

1,4-DIHYDROPYRIDINES

Substituted phenyl ring at C4 increases the activity. However, small planar alkyl or cycloalkyl group decreases the activity

ortho or para Substituent at C4 aromatic ring possesses optimum activity

Ester group at C3 & C5 optimize activity
Other EWG decreases antagonistic activity & may show agonist activity



All compounds have C2 & C6 methyl group, except Amlodipine. Amlodipine has bulky substituent and it suggests that methyl group can be replaced by bulky substituent

Alkyl group at C2 & C6 increases the antagonistic activity

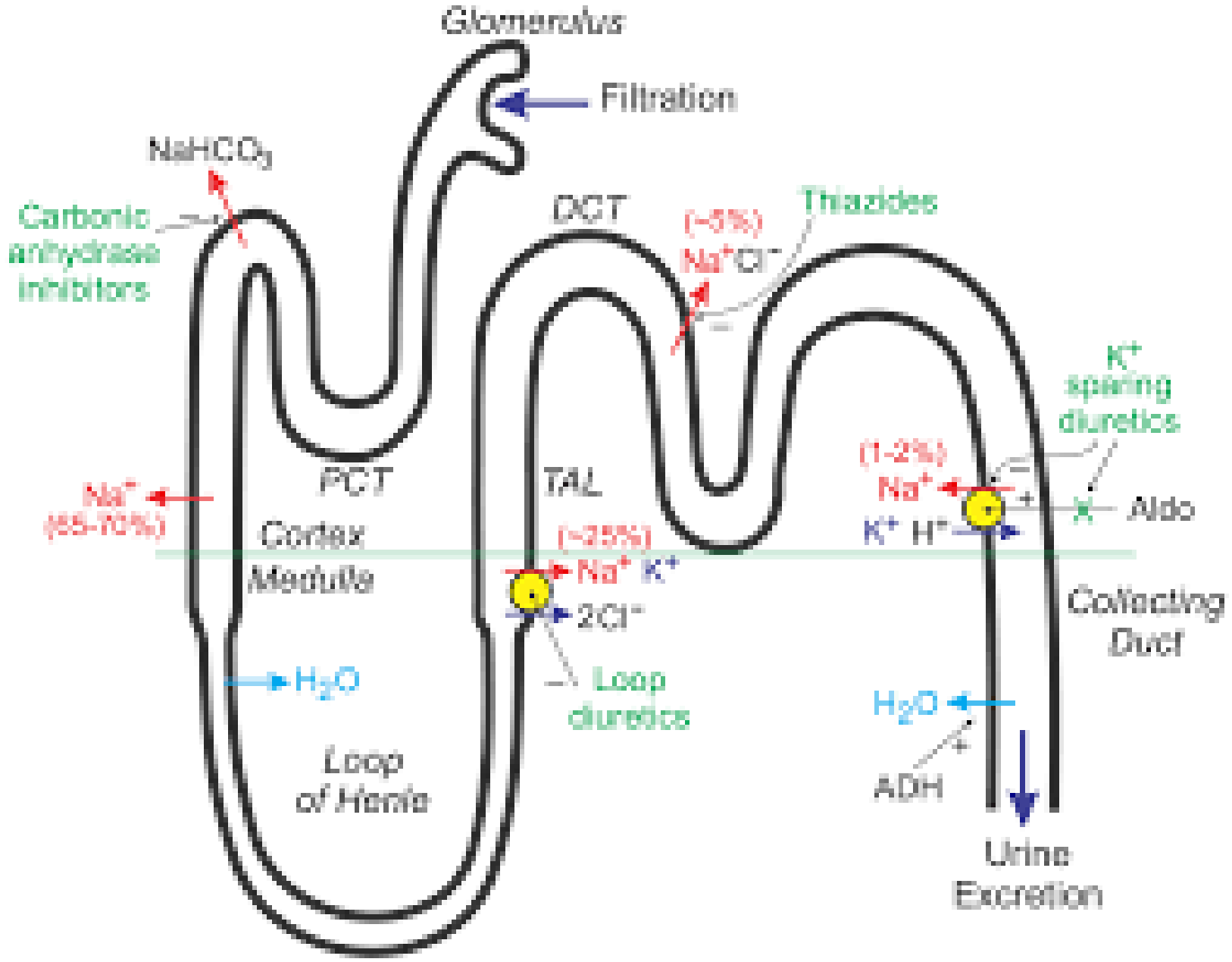
Substituent at N1 decreases the activity

1,4-Dihydropyridine ring is essential

Diuretics

Mechanisms of diuretic drugs

- Diuretic drugs increase urine output by the kidney (i.e., promote diuresis). This is accomplished by altering how the kidney handles sodium.
- If the kidney excretes more sodium, then water excretion will also increase.
- Most diuretics produce diuresis by inhibiting the reabsorption of sodium at different segments of the renal tubular system.
- Sometimes a combination of two diuretics is given because this can be significantly more effective than either compound alone (synergistic effect).
- The reason for this is that one nephron segment can compensate for altered sodium reabsorption at another nephron segment; therefore, blocking multiple nephron sites significantly enhances efficacy.


Glomerulus
Filtration
$NaHCO_3$
Carbonic anhydrase inhibitors
DCT
(~5%)
Na^+Cl^-
Thiazides
K^+ sparing diuretics
(1-2%)
Na^+
K^+ H^+
Aldo
Na^+ (65-70%)
PCT
TAL
Cortex
Medulla
(~25%)
Na^+ K^+
$2Cl^-$
Loop diuretics
Collecting Duct
H_2O
Loop of Henle
H_2O
ADH
Urine Excretion

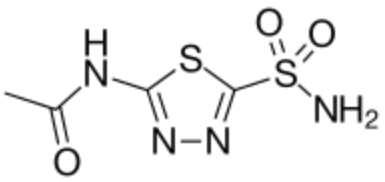
Carbonic anhydrase inhibitors

- **Inhibit the transport of bicarbonate out of the proximal convoluted tubule into the interstitium, which leads to less sodium reabsorption at this site and therefore greater sodium, bicarbonate and water loss in the urine**

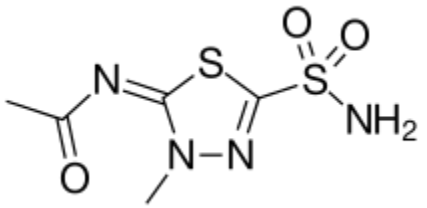
- **These are the weakest of the diuretics and seldom used in cardiovascular disease**

- **Their main use is in the treatment of glaucoma.**

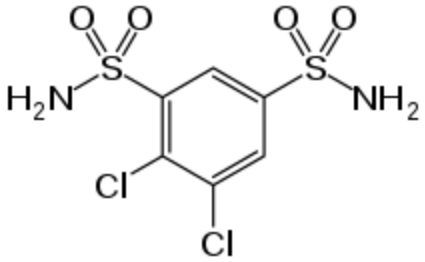
Carbonic anhydrase inhibitors



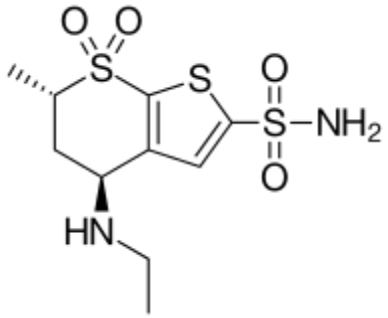
Acetazolamide



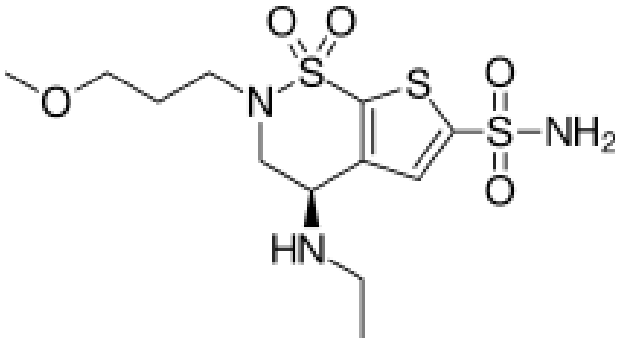
Methazolamide



Diclofenamide

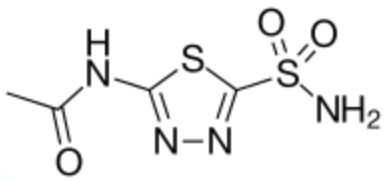


Dorzolamide



Brinzolamide

Structural Activity Relationship



Aliphatic sulfonamides are less active

Benzolamide with –$NHSO_2Ph$ is five times more active than Acetazolamide

Sulfamoyl group is essential

Aromatic Sulfonamides are most active

Carbonic Anhydrase Inhibitors

Benzothiazole derivatives are also active

Aryl groups can be further substituted with –SO_2NH_2 groups

1,3,4-thiadiazole & SO_2NH_2 group at C-2 Position=Max. activity

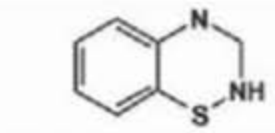
Thiazide Diuretics

- **Inhibit the sodium-chloride transporter in the distal tubule.**
- **Because this transporter normally only reabsorbs about 5% of filtered sodium, these diuretics are less efficacious than loop diuretics in producing diuresis and natriuresis.**
- **Nevertheless, they are sufficiently powerful to satisfy many therapeutic needs requiring a diuretic.**
- **Their mechanism depends on renal prostaglandin production.**

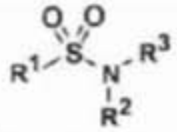
Because loop and thiazide diuretics increase sodium delivery to the distal segment of the distal tubule, this increases potassium loss (potentially causing *hypokalemia*) because the increase in distal tubular sodium concentration stimulates the aldosterone-sensitive sodium pump to increase sodium reabsorption in exchange for potassium and hydrogen ion, which are lost to the urine. The increased hydrogen ion loss can lead to *metabolic alkalosis*. Part of the loss of potassium and hydrogen ion by loop and thiazide diuretics results from activation of the renin-angiotensin-aldosterone system that occurs because of reduced blood volume and arterial pressure. Increased aldosterone stimulates sodium reabsorption and increases potassium and hydrogen ion excretion into the urine.

Thiazide diuretics: Structures

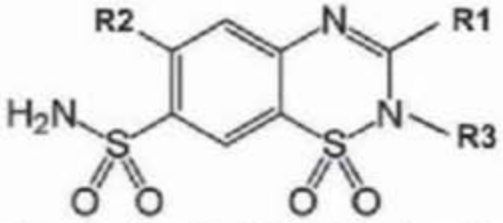
A.



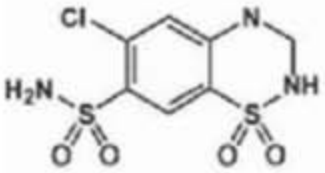
Benzothiadiazine ring



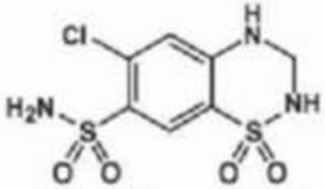
Sulfonamide group



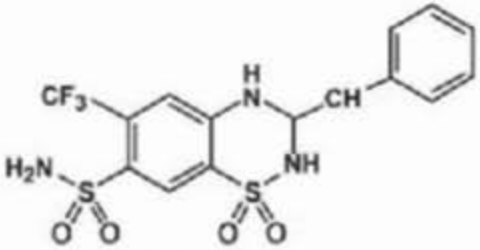
Structural unit of thiazide diuretics



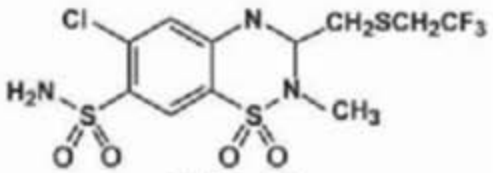
Chlorothiazide



Hydrochlorothiazide

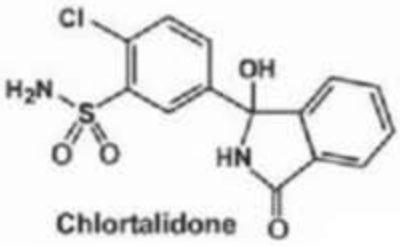


Bendroflumetiazide

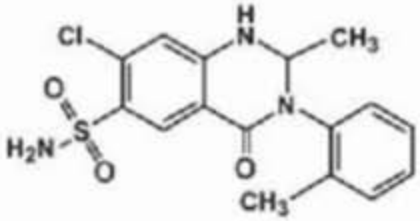


Politiazide

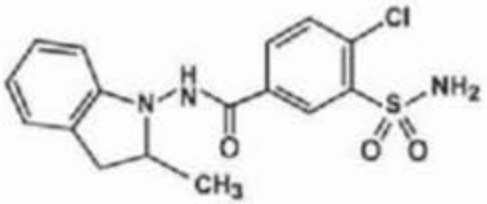
B.



Chlortalidone



Metolazone



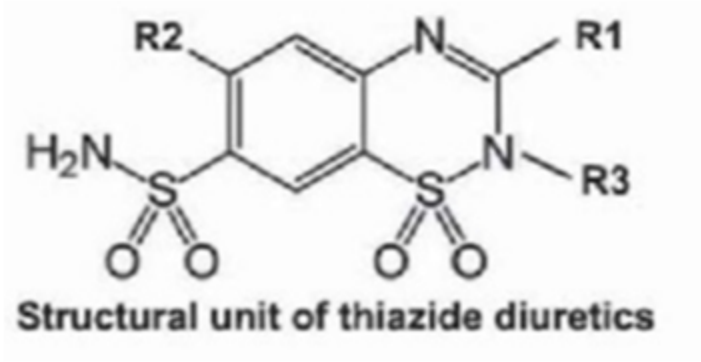
Indapamide

Structural Activity Relationship

Thiazide diuretics

Sub. on 6th position with electron withdrawing groups is essential for activity

Lipophilic Sub. At 3rd position increases the potency



Structural unit of thiazide diuretics

-SO_2NH_2 group at 7th Position is essential

2nd position can be sub. by –CH_3 group

Sub. On 4, 5 or 8th position with alkyl group, diminishes diuretic activity

H-atom at 2nd position is most acidic because of electron withdrawing –SO_2 group

3, 4, C-N double bond is not necessary, C-N single bonded compounds are more potent

Loop diuretics

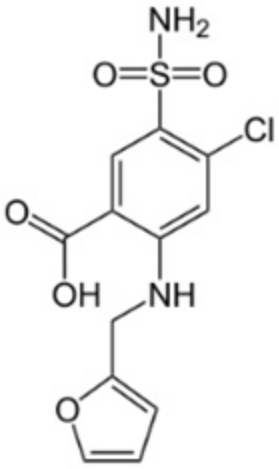
- **Inhibit the sodium-potassium-chloride cotransporter in the thick ascending limb.**

- **This transporter normally reabsorbs about 25% of the sodium load; therefore, inhibition of this pump can lead to a significant increase in the distal tubular concentration of sodium, reduced hypertonicity of the surrounding interstitium, and less water reabsorption in the collecting duct.**

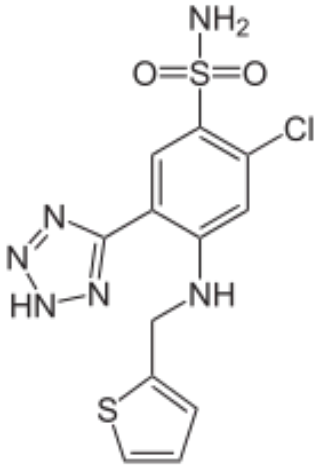
- **This altered handling of sodium and water leads to both diuresis (increased water loss) and natriuresis (increased sodium loss).**

- **By acting on the thick ascending limb, which handles a significant fraction of sodium reabsorption, loop diuretics are very powerful diuretics.**

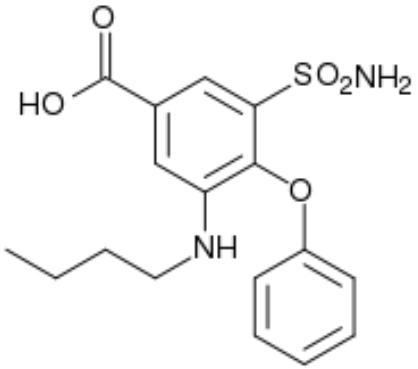
Loop diuretics: Structures



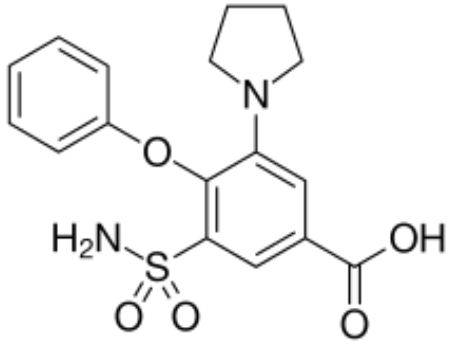
Furosemide



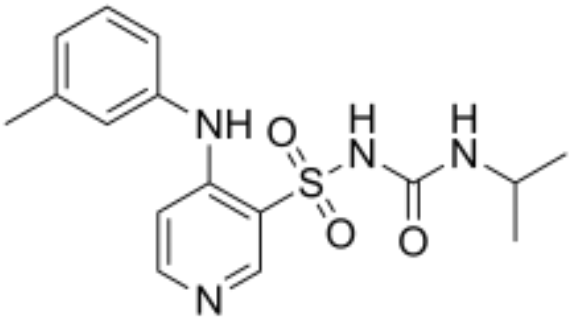
Azosemide



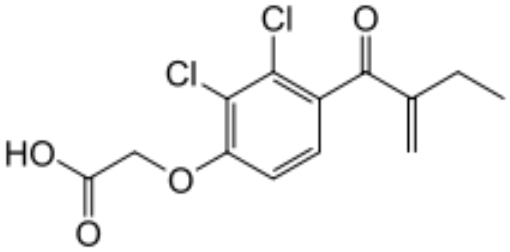
Bumetanide



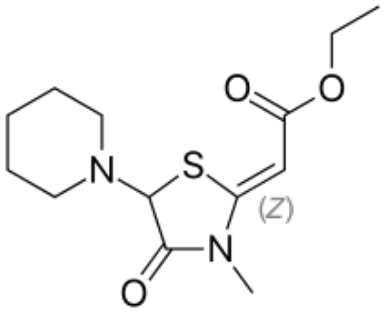
Piretanide



Torsemide



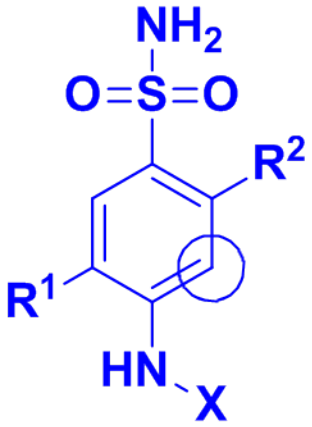
Ethacrynic acid



Etozolin

SAR
LOOP DIURETICS

-SO_2NH_2 Group on 5th position is essential for activity



Substitution at postion 1 must be acidic group E.g. -COOH, -tetrazole

Electron withdrawing group at 4th position can be -Cl, -CF, -OPh, -OR, aniline, -CH_2Ph

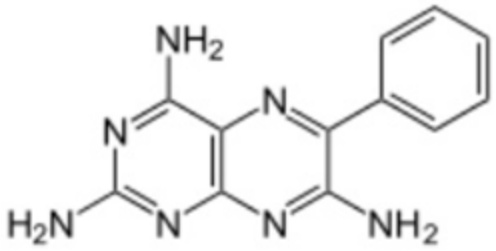
Aliphatic or heterocyclic bulky substituent at R^1 position increases activity

Amino group can be substituted at 2nd or 3rd postion

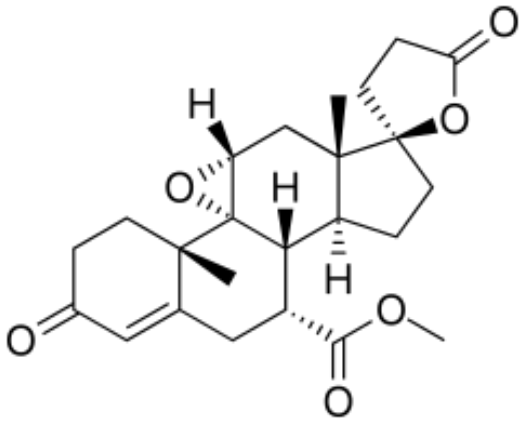
Potassium-sparing Diuretics

- Unlike loop and thiazide diuretics, some of these drugs do not act directly on sodium transport.
- Some drugs in this class antagonize the actions of aldosterone (aldosterone receptor antagonists) at the distal segment of the distal tubule.
- This causes more sodium (and water) to pass into the collecting duct and be excreted in the urine.
- They are called K^+-sparing diuretics because they do not produce hypokalemia like the loop and thiazide diuretics.
- The reason for this is that by inhibiting aldosterone-sensitive sodium reabsorption, less potassium and hydrogen ion are exchanged for sodium by this transporter and therefore less potassium and hydrogen are lost to the urine.

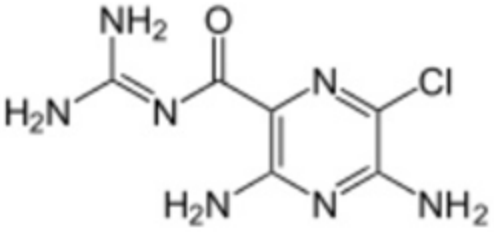
Potassium-sparing Diuretics: Structures



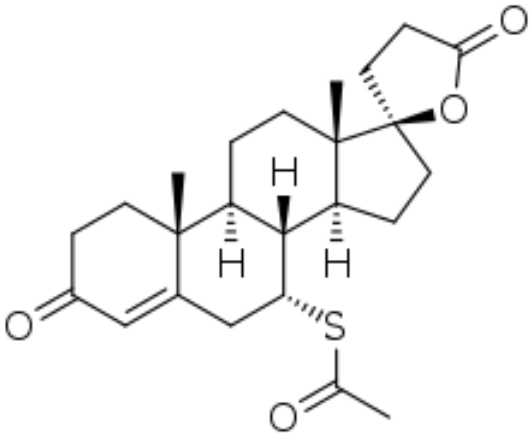
Triamterene



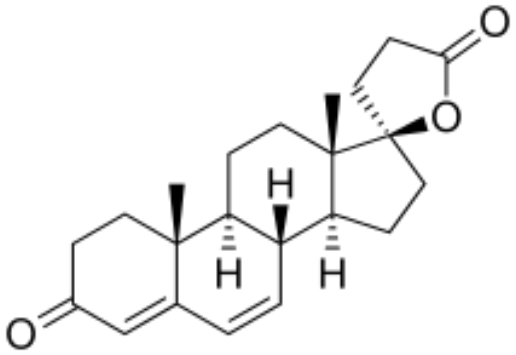
Eplerenone



Amiloride



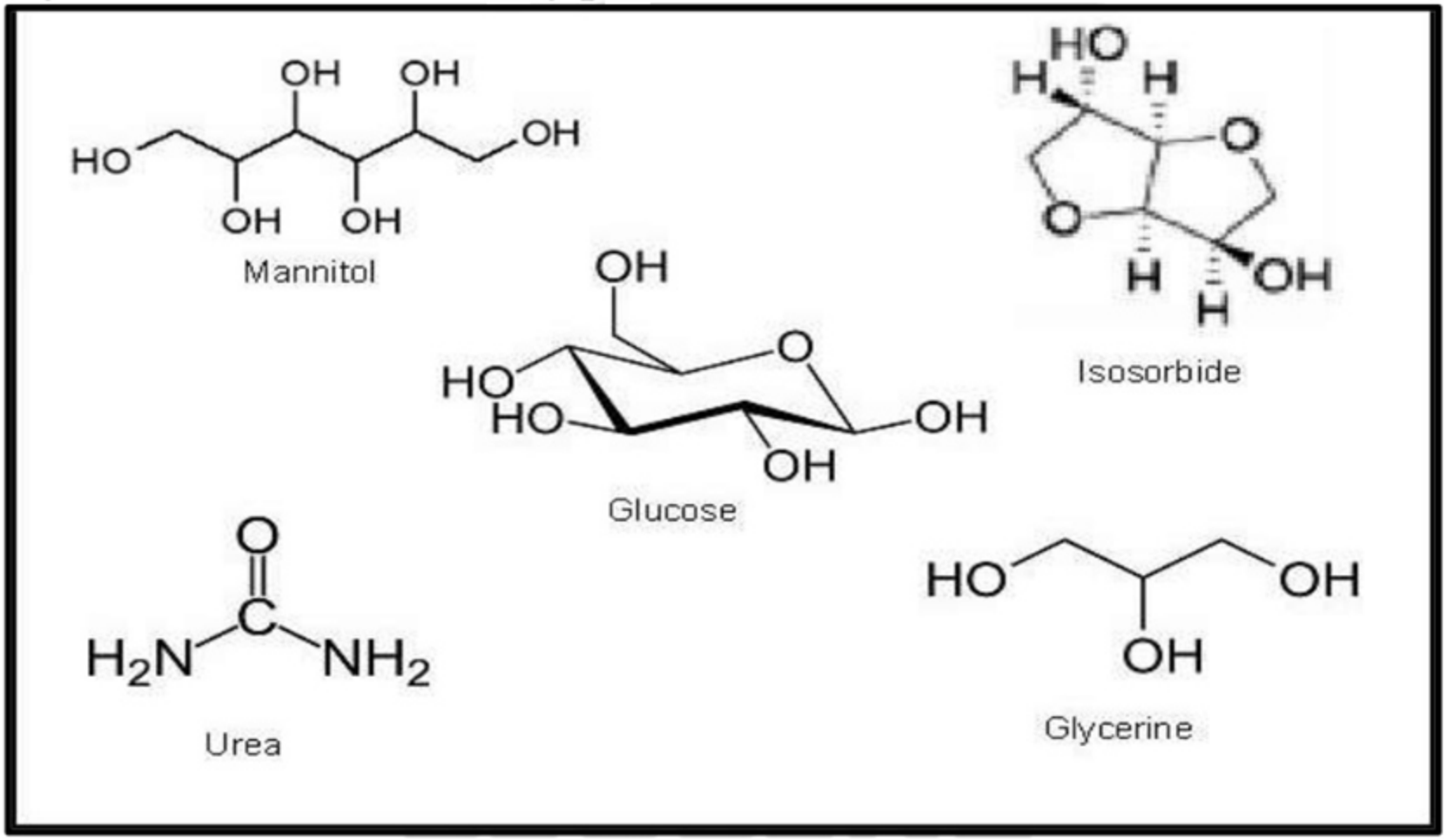
Spironolactone



Canrenone

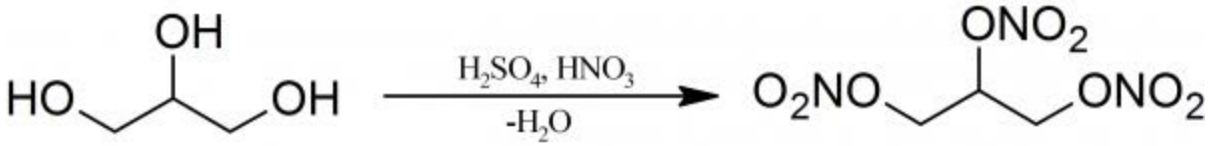
Osmotic Diuretics

- **By increasing the osmolality of the glomerular filtrate, they limit tubular reabsorption of water and thus promote diuresis**
- **They cause increase in urinary pH**



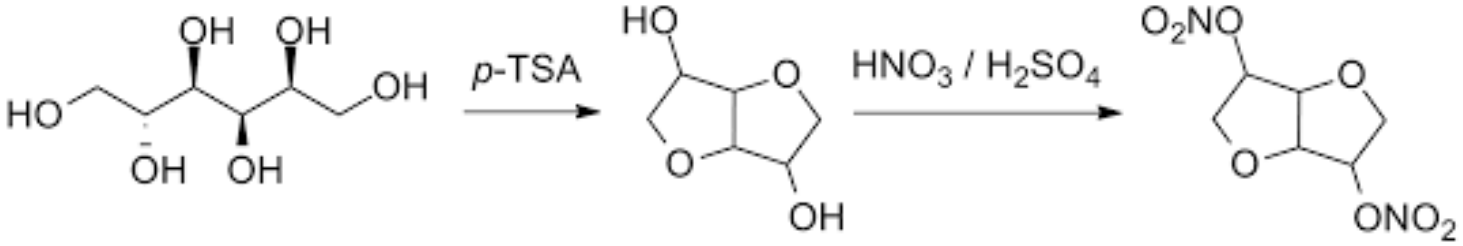
Synthesis of Drugs

Nitroglycerin



Glycerol

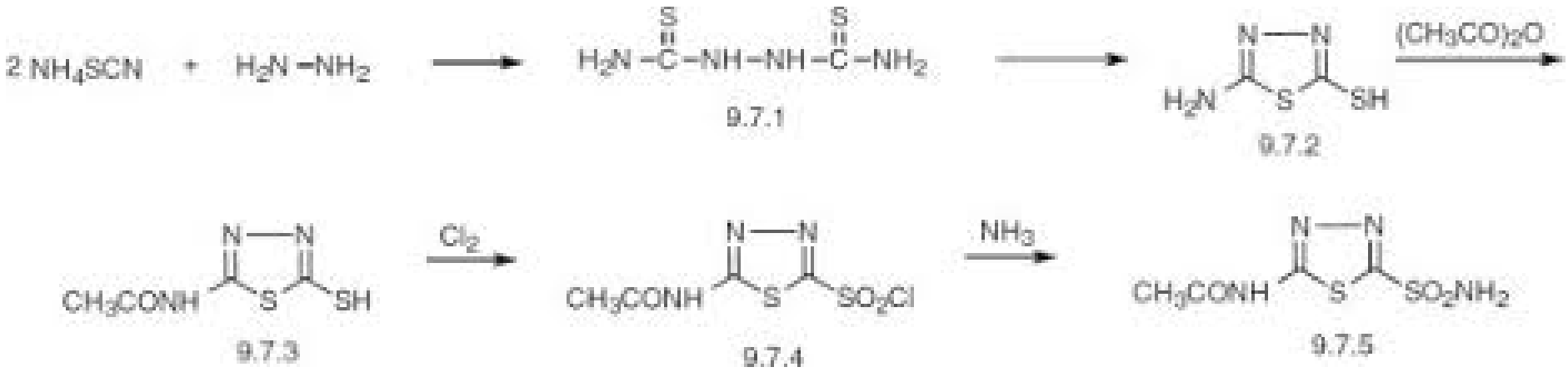
Isosorbide dinitrate



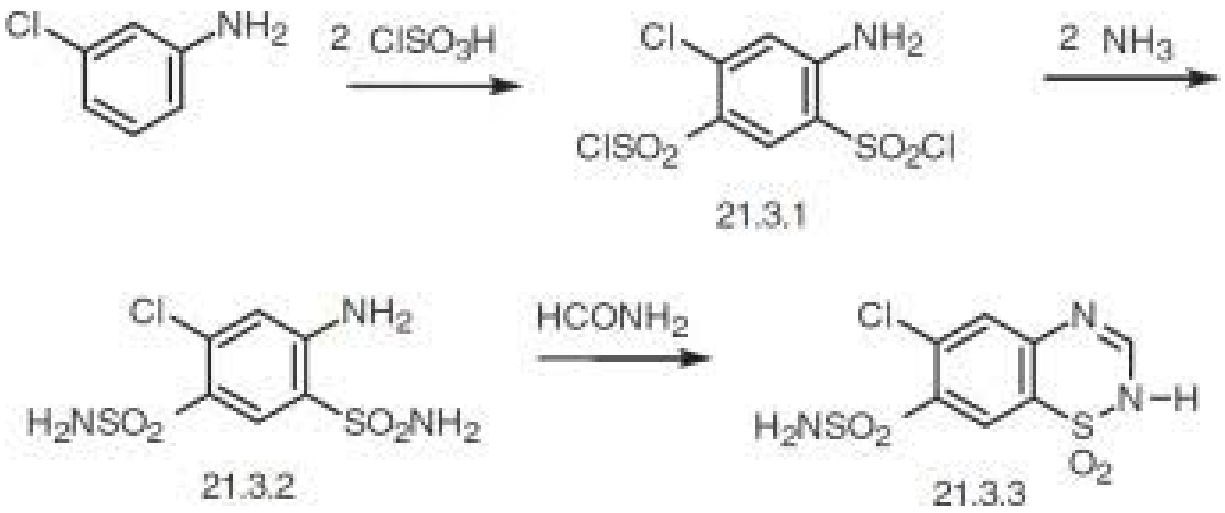
Sorbitol

Isosorbide

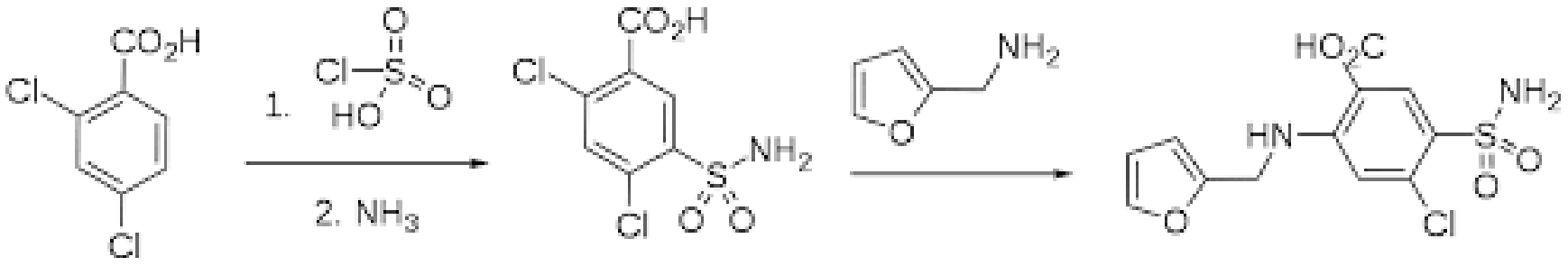
Acetazolamide



Chlorthiazide



Furosemide



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