Medicinal Chemistry 2
PC810
Cardiovascular drugs
2015/2016
Cardiovascular drugs

List of References:
- Foy’s Medicinal Chemistry.
- Wilson and Gisvold’s Organic Medicinal and Pharmaceutical Chemistry.
- Burger’s Medicinal Chemistry.

ILO’S:
- Understand and have an overview about drugs acting on CVS.
- Recognize the chemical structure, nomenclature, pharmacophoric moieties and consequently the SAR of each mentioned class of cardiovascular drugs.
- Apply the given information to evaluate the activity of related compounds within the pharmacological class based on structure similarities and dissimilarities.
- Recognize the synthesis and metabolic pathways.
- Understand the role of molecular modification of prototypes in the design and development of new drugs.

Topics to be studied
Antihypertensive drugs
Diuretics
Antianginal
Antihyperlipidimics
Anticoagulants

Antihypertensive drugs

Blood pressure is a measure of the force of the blood pushing against the walls of the arteries Normal B.P 120/80

Hypertension is defined as a repeatedly elevated blood pressure exceeding 140/90 mm Hg. So antihypertensive drugs are medications used to treat High blood pressure.

Classification of antihypertensive according to MOA
I- Sympatholytics (Adrenergic receptors inhibitors)
   1. Adrenergic Neuron blockers (guanethidine)
   2. \( \alpha_1 \)-Adrenergic blockers. (quinazoline derivatives)
   3. \( \beta \)-adrenergic blockers
4. Centrally acting drugs (Methyl dopa, clonidine,……)

II- Vasodilators

1. Arterial (hydralazine, minoxidil, diazoxide)
2. Arterial and venous (sodium nitroprusside)

III- Angiotensin Converting Enzyme Inhibitors (ACE inhibitors)

IV - ACE antagonists

V- Endothelin receptor antagonists

VI- Diuretics

Adrenergic Neuronal Blocking agent (prototype reserpine)

Guanethidine (Ismelin)

MOA: Guanethidine can prevent the release of NE from postganglionic neurons in response to adrenergic stimulation, it is transported across the sympathetic nerve by the same mechanism that transports NE. Once guanethidine has entered the nerve, it is concentrated in transmitter vesicles, where it replaces norepinephrine. Once inside the terminal it blocks the release of norepinephrine in response to an action potential.
There is absence of CNS effects (compared to reserpine), such as depression ……why?
Because the drug is highly polar and does not cross BBB the presence the highly basic guanidine group means that at physiological pH the drug is completely protonated so not cross BBB

**b) \( \alpha_1 \)-Adrenergic Receptor blockers**

**MOA:**
\( \alpha_1 \)-adrenergic blocker that is specific for the alpha-1 receptors. These receptors are found on vascular smooth muscle, they produce peripheral vasodilatation without increase heart rate or cardiac output

- Prazosin (minipress) and trazosin are quinazoline derivatives.
- The 4- \( \text{NH}_2 \) groups are very important for \( \alpha_1 \) adrenergic receptor affinity.
- Piperazine ring could be replaced by other heterocyclic moieties
• Reduction of furan ring in prazosin to tetrahydrofuran in trazosin increases duration of action due to altering rate of metabolism. (36 h)
• These drugs also block $\alpha_{1A}$ being predominant in prostate gland and bladder neck, so blockade of these receptors relaxes the tissue. for this reason these agents are also used in treatment of BPH (benign prostatic hypertrophy, enlarged prostate), where they help improve urination. flow rates (Dexazosin: Cardura)

c) $\beta$-adrenergic receptor antagonists

Non selective $\beta$-blockers: (1st generation)

Aryloxypropanolamines (propranolol)

Non selective $\beta$-blockers:

Side effects: CNS effects (dizziness, dreams and sedation)

Bronchoconstriction in asthmatics (needs $\beta_2$- receptor agonists)

This is serious problem if the patient is asthmatic since its use could initiate asthmatic attack due to antagonism of $\beta_2$ receptor as well.

Selective $\beta_1$ blockers: 2nd generation
- Centrally-acting Sympathomimetics

**Selective α₂ Agoist**

A second approach to modify sympathetic influence on the cardiovascular system is through stimulating α₂-receptors which reduce the sympathetic outflow to the cardiovascular system and produce a hypotension effect.

1- Clonidine Hydrochloride (Catapress).

\[
\text{2-(2,6-Dichlorophenylamino)-imidazoline}
\]

Acts centrally as α₂ adrenoceptors agonist

**SAR:**

1-Halogen substituents produce maximum lipophilicity of the drug to cross CNS (greater than -CH₃).

2-Imidazoline ring is not essential for activity.

3-Bridged group may be single amino or methylene group

**Metabolism:**

4-Hydroxyclonidine inactive metabolite….why?

Open chain analogue of clonidine is…. ..........................
2-Methyldopate HCl (Aldomet ester)

\[
\begin{align*}
\text{R} &= \text{H} \quad \text{L- Methyldopa} \\
\text{R} &= \text{C}_2\text{H}_5 \quad \text{Methyldopate ethyl ester}
\end{align*}
\]

3-(3,4-Dihydroxyphenyl)-2-methylalanine ethyl ester

- The prodrug \(\alpha\)-methyldopa is an antihypertensive \(\alpha_2\) agonist acting in the CNS via its active metabolite \(\alpha\)-Methylnorepinephrine (\(\alpha\) MNE)
- The current hypothesis concerning the hypotensive activity of methyldopa involves \(\alpha\)-Methylnorepinephrine displaces NE in nerve terminals and act as a false transmitter.

Methyldopa, suitable for oral use, is a zwitterion and is not suitable enough for parenteral use. Masking -COOH group solved this problem by formation of ethyl ester, leaving the -NH\(_2\) free to form water-soluble hydrochloride salt.

Methyldopa used in the management of hypertension during pregnancy without adverse effects on fetus.

- **Vasodilators (Drugs Acting Directly on Smooth muscle)**

Directly acting vasodilators have the ability to relax smooth muscles in blood vessels lead to dilatation of vessels which results in reduction in systemic vascular resistance.

1-Minoxidil (Loniten)
Minoxidil sulfate is a potassium channel opener
It has effect on androgenic alopecia.
Metabolism:

2-Diazoxide (Hyperstat IV)

Sodium 7-Chloro-3-methyl-2H-1,2,4-benzothiadiazine-1,1-dioxide
Diazoxide is a non diuretic hypotensive agent
MOA : the same as Minoxidil (K⁺ channel opener)
Metabolism:
Used IV in hypertension crisis for emergency lowering of blood pressure also used in malignant hypertension

- Angiotensin Converting Enzyme Inhibitors (ACE inhibitors)
Renin angiotensin system, is a complex, highly regulated pathway that is integral in controlling bl volume, electrolyte balance and arterial B.P. It consists of 2 enzymes Renin and Angiotensin Converting enzyme (ACE) and the following scheme shows the role of ACE:

Mode of action (MOA) of ACE inhibitors:
Inhibit conversion of Angiotensin I to Angiotensin II which is a potent vasoconstrictor

![Diagram of Renin-Angiotensin System]

Figure 4: The renin–angiotensin system of blood pressure control. ACE inhibitors inactivate angiotensin – converting enzyme (ACE) thereby preventing the formation of peptides angiotensin II and III, agents that mediate the signal for increasing the systemic blood pressure.
ACE inhibitors are classified into:
ACE is Zinc containing enzyme so according to the group that binds with Zn$^{+2}$ ACE inhibitors are classified into;
Sulphydryl containing inhibitors (e.g. Captopril)
Carboxylate containing inhibitors (e.g. Enalapril)
Phosphonate containing inhibitors (e.g. Fosinopril)

SAR of ACE inhibitors

- N-ring must contain COOH group to mimic C-terminal carboxylate in ACE substrate.
- Compounds contain hydrophobic bicyclic rings are more lipid soluble than those which contain proline
- Groups A, B, or C can serve as zinc binding groups.
- -SH group show superior binding to zinc
- X is usually methyl to mimic the side chain of alanine. Within dicarboxylate series, when X equals n-butylamine (lysine side chain) this produces a compound which is orally active without being a prodrug

a) Sulphydryl-Containing Inhibitors
Captopril (Capoten)

1-[(2S)-3-Mercapto-2-methyl-1-oxopropionyl]L-proline
Captopril inhibits the ACE enzyme. The important binding points at the active site of ACE are shown in the following diagram.
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 & metallic taste. These side effects usually subsided upon dosage reduction or discontinuation of captopril. Duration of action 6h

b) Dicarboxylate containing inhibitors

Enalapril Maleate (Vasotec):

1-[2-(1-ethoxycarbonyl-3-phenyl-propyl) aminopropanoyl] pyrrolidine-2-carboxylic acid. It is free from thiol group thus doesn’t has the side effects of captopril.

Enalapril is a prodrug undergoes bioactivation by hepatic esterase to form diacid enalaprilat

The combination of structural features present in enalaprilat especially 2- COOH gps and NH are responsible for its overall low lipophilicity and poor oral bioavailability

In comparing the activity of captopril and enalaprilat, it was found that enalaprilat is 10 fold more potent than captopril why?
Other ACE inhibitors

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<thead>
<tr>
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<th>Chemical Structure</th>
<th>Name</th>
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<tbody>
<tr>
<td><img src="image" alt="Lisinopril" /></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Lisinopril (Zestril)</td>
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<tr>
<td><img src="image" alt="Ramipril" /></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Ramipril (Altace)</td>
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<td><img src="image" alt="Quinapril" /></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Quinapril (Accupril)</td>
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<td><img src="image" alt="Benazepril" /></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Benazepril (lotensin)</td>
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Lisinopril is probably the most hydrophilic inhibitor, but it is orally active. Why?

Lisinopril exists as a zwitterion in which ionized groups can internally bind with one another, so the drug is able to pass through the lipid membrane with an overall neutral charge.
c) Phosphonate containing inhibitors (fosinoprilat)

![Diagram of fosinoprilat](image)

**Fig. 23.11.** The binding of phosphinate analogs to ACE.

- **Angiotensin receptor Antagonist**

Angiotensin II (AT) receptor was the initial target for developing compounds which could inhibit the renin-angiotensin pathway.

Angiotensin II receptors exists at least in two 2 subtypes: type 1 (AT$_1$) & type 2 (AT$_2$)

**Structure Activity Relationship**

All commercially available angiotensin II antagonists are analogs of the shown general formula.

The acidic group may be either:

- a carboxylic acid (A)
- a phenyl tetrazole (B)
- a phenyl carboxylate (C).

- In the biphenyl series, the tetrazole and carboxylate groups must be in the ortho position for optimal activity (the terazole group is superior in terms of metabolic stability, lipophilicity, and bioavailability).
The n-butyl group of the model compounds provides hydrophobic binding and most likely mimics the side chain of angiotensin II. n-Bu could be replaced by benzimidazole ring.

The imidazole ring or an isosteric equivalent is required to mimic the His6 side chain of angiotensin II.

Substitution with a variety of -R groups including carboxylic acid, methyl alc., ether or alkyl chain, all these groups are thought to interact with AT1 receptor some through ionic or dipole bonds and others through hydrophobic interaction.

Losartan (Cozaar)

2-Butyl-4-chloro-1-[p-(o-1H-tetrazol-5-yl-phenyl)benzyl] imidazole-5-methanol

Valsartan is the first nonimidazole containing AGII antagonist amide carbonyl is isosteric with imidazole and serve as hydrogen bond acceptor similar to imidazole nitrogen.
Diuretics

Diuresis

• Increased formation of urine by the kidneys

A diuretic is defined as a substance that increases the rate of urine formation.

By increasing the urine flow rate diuretic usage leads to increase excretion of electrolytes (especially Na⁺ & Cl⁻) and water from the body without affecting protein, vitamins, glucose, amino acids reabsorption.

Diuretics are used mainly in:

1- The relief of edema
2- As adjuvant in the management of hypertension
3- Management of other disorders including; congestive heart failure, chronic and acute renal failure, glaucoma, & liver cirrhosis with ascites.

A diuretic usually possesses a combination of

| Natriuretic | Na⁺ |
| Chloruretic | Cl⁻ |
| Saluretic   | NaCl |
| kaliuretic  | K⁺ |
| Bicarbonaturetic | HCO₃⁻ |

Functions of the kidneys:

1- To maintain homeostatic balance of electrolytes and water
2- To excrete water soluble end products of metabolism

So the kidneys accomplishes these functions through the formation of urine by nephrons.

The kidney contains, approximately, two million nephrons. Nephrons routinely, filter water and electrolytes (such as NH₄⁺, Na⁺, K⁺, Ca²⁺, Mg²⁺, Cl⁻, HCO₃⁻, and H₃O⁺) and non-electrolytes (such as urea, creatinine, uric acid, glucose) through Bowman’s capsules.

Diuretics are acting at different sites in the nephron and are classified as:

1- Carbonic anhydrase inhibitors acting at the proximal convoluted tubule (site 1 diuretics).
2- Loop diuretics acting at the Henle’s loop (site 2 diuretics).
3- Thiazides and thiazide-like diuretics acting at distal convoluted tubule (site 3 diuretics).
4- Potassium-sparing diuretics acting at collecting tubule (site 4 diuretics).
5- Osmotic diuretics;
Carbonic Anhydrase inhibitors (CA inhibitors)

Carbonic anhydrase is an enzyme containing Zinc.

It catalyzes the formation of carbonic acid (H$_2$CO$_3$) from CO$_2$ and water.

$$\text{CO}_2 + \text{H}_2\text{O} \xrightarrow{\text{CA enzyme}} \text{H}_2\text{CO}_3 \xrightarrow{\text{enzymatic reaction}} \text{H}^+ + \text{HCO}_3^-$$

![Diagram of chemical interactions catalyzed by carbonic anhydrase (CA) and site of action inhibitors of this enzyme](image)

Figure 19.14: Diagram of chemical interactions catalyzed by carbonic anhydrase (CA) and site of action inhibitors of this enzyme.
MOA:
The carbonic anhydrase (CA) make H+ ions available for exchange with Na+ in the proximal tubules…
CAIs block this reaction, thus preventing the exchange of H+ ions with Na+ and decrease H+ ion concentration in renal tubules
As a result, there is increased excretion of bicarbonate, sodium, and water ………………… increased urine volume. So flow of alkaline urine & a mild metabolic acidosis.
These compounds contain free sulfamoyl group (-SO$_2$NH$_2$) that is essential for activity.
- SO$_2$NH$_2$ is isosteric with H$_2$CO$_3$, and is able to occupy the receptor site of carbonic acid formation and thus it must be non-substituted.

SAR of carbonic anhydrase inhibitors
1. The free sulfamoyl nitrogen is essential for diuretic activity. The mono and Di substituents at SO$_2$NH$_2$ abolish the activity.
2. Substitution of the methyl group on one of the ring nitrogen (Methazolamide) retains the activity
3. Attachment of the sulfamoyl group to aromatic system.

- **Acetazolamide (Diamox)**

![Acetazolamide Structure](image)

*Uses:*
Acetazolamide used orally as tablets to reduce the rate of aqueous humor formation, and is used primarily in reducing intraocular pressure in the treatment of glaucoma
- **Methazolamide (Neptazane)**

Methazolamide is a more potent derivative of acetazolamide due to more lipophilic properties. The increased lipophilicity is due to replacement of one of the active hydrogen by methyl group. This permits greater penetration into ocular fluids reducing intraocular pressure.

**Dichlorphenamide (Daranide)**

4,5-Dichloro-1,3-benzenedisulfonamide

Dichlorphenamide is a disulphonamide derivative has mode of action and uses similar to acetazolamide.

**Side Effects of CA inhibitors:**

1. Development of metabolic acidosis due to renal loss of bicarbonate (system becomes more acidic & urine becomes more alkaline)
2. Typical sulphonamide associated hypersensitivity reactions e.g. urticaria, drug fever, and interstitial nephritis

2- Site 3 Diuretics (Benzothiadiazines OR Thiazides and Thiazide-like diuretics)
The sodium transport systems that are responsible for the reabsorption of Na\(^+\) & Cl\(^-\) in (DCT). Thiazide and thiazide like diuretics (saluretic agents) are inhibitors of the luminal membrane bound Na\(^+\)/Cl\(^-\) system include

**SAR of thiazides & thiazides like diuretics:**

1- Hydrogen at N-2 is the most acidic because of the electron withdrawing effect of the neighboring sulfone group.

The acidic protons make possible the formation of water soluble sodium salts for I.V. administration

Alkyl substitution on N-2 results in decrease polarity and increase duration of action

2- Saturation of the double bond to give 3,4 dihydro drvs. give diuretic from 3-10 times more active than unsaturated drvs.

3- Substitution at position 3 with lipophilic group will affect potency and duration of action, (CHCl\(_2\),CH\(_2\)C\(_6\)H\(_5\), CH\(_2\)SCH\(_2\)CF\(_3\)) results in marked increase in potency & duration of action

4- Direct substitution at position 4,5 or 8 with alkyl group diminishes diuretic activity

5- Substitution at position 6 with electron withdrawing gp (activating gp) (Cl\(^-\), Br\(^-\), CF\(_3\),NO\(_2\)) is essential for activity.

Whereas substitution with electron releasing gp (CH\(_3\) –or -OCH\(_3\))results in marked reduction in diuretic activity.
6- The Sulfamoyl gp(-SO₂NH₂) at position 7 is a prerequisite for diuretic activity

Chlorthiazide 6-12h

Benzthiazide 12-18h

Hydrochlorothiazide
Esidrex
6-12 h

Hydroflumethiazide
Salturon
18-24h

Polythiazide
Renese
24-48 h

Thiazides like diuretics

The discovery that substitution of the sulfone group at position-1 in thiazide diuretics with another electronegative group para to the activating group as well as the opening of bicyclic hetero-system in benzothiadiazines do not affect the diuretic activity. That aids in the emergence of a group of diuretics known as thiazide-like diuretics. They are no longer benzothiadiazines, but site of action and efficacy and side effects are similar to thiazide diuretics.

a) Substituted meta disulfamoylbenzene

Mefruside (Baycaron)
b) Benzhydrazides  

*Indapamide (Natrilix)*

\[
\text{H}_2\text{NO}_2\text{S} \quad \text{Cl} \quad \text{C} \quad \text{H} \quad \text{2} \quad \text{N} \quad \text{O} \\
\text{H} \quad \text{N} \quad \text{O} \quad \text{2} \quad \text{S} \quad \text{H} \quad \text{C} \quad \text{H} \quad \text{3}
\]

Side effects of site 3 diuretics

1. Hypersensitivity due to -SO$_2$NH$_2$ group
2. Hypokalemia due to increase renal excretion of K$^+$

So potassium supplements are used (e.g. KCl, K gluconate, K citrate), also use food rich with K$^+$ as banana, or used in combination with other diuretics (potassium sparing diuretics)

**Drug –drug interactions of thiazides and thiazide like diuretics**

1. Administration of these diuretics with Non steroidal anti-inflammatory drugs (NSAIDs) which inhibit prostaglandin synthesis, can antagonize the diuretic effect of the former.
2. Concurrent administration of these drugs with large doses of Ca$^{2+}$ containing substances may result in hypercalceamia because of Ca$^{2+}$ retaining properties of these diuretics.
3. When these drugs are used with cardiac glycosides in treatment of congestive heart failure, serious toxicity can result if hypokalemia occurs.

3. (Site 2 Diuretics) loop diuretics – High ceiling diuretics

Diuretics that act on site 2 are the most efficacious of all because site 2 normally is responsible for reabsorption of 20-25% of filtered load of Na$^+$. Diuretics that act at site 3,4 are responsible for reabsorption of only 5-8% & 2-3% of the filtered load of Na$^+$, respectively.
Loop diuretics are very potent saluretic agents. They are called so because they inhibit \((1\text{Na}^+, 1\text{K}^+, 2\text{Cl}^-)\) co transport system located in the luminal membrane of the loop of Henle

**Classification:**

**A) 5-Sulfamoyl-2-aminobenzoic Acid drvs. & 5-Sulfamoyl-3-aminobenzoic Acid drvs.**

1- Substituents at position 1 must be acidic COOH provides optimal diuretic activity.

Other groups such as tetrazole may impart respectable diuretic activity.

2- \(\text{SO}_2\text{NH}_2\) group at position 5 is prerequisite for activity, must be free.

3- Activating group at position 4 could be Cl\(^-\) or CF\(^3\)- or better with phenoxy, alkoxy, anilino, benzyl or benzoxy.

4- They are characterized by rapid onset (within 30 min) and short duration (6 h)

**A) 2-Aminobenzoic acid (Anthranilic acid) derivatives**

5-Sulfamoyl-2-aminobenzoic Acids

**Furosemide (lasix)**

4-Chloro-N-furfuryl-5-sulfamoylanthranilic acid

Furosemide is stronger acid than benzothiadiazine

It promotes excretion of \(\text{Na}^+, \text{K}^+, \text{Cl}^- & \text{HCO}_3^-\)

Dose of furosemide is 20-80mg/day
B) 3-Aminobenzoic acid Derivatives

Bumetanide (Burinex) 0.5-2mg/day

\[
\text{\begin{align*}
\text{H}_2\text{N}-\text{(CH}_3\text{)}_3-\text{CH}_3 \\
\text{H}_2\text{NO}_2\text{S} \\
\text{COOH}
\end{align*}}
\]

3-(Butylamino)4- phenoxy-5- sulfamoylbenzoic acid

-\text{Cl}^- \text{in furosemide is replaced by Phenoxy group}

When the butyl gp is replaced with Furanylmethyl as that in furosemide ,there is loss of diuretic activity. The -\text{COO}^- \text{moieties of furosemide and bumetanide are thought to compete with Cl}^- \text{for Cl}^- \text{binding sites on (1Na}^+, 1 \text{K}^+, 2\text{Cl}^-\text{) co transport system}

Uses:
Treatment of pulmonary edema associated with congestive heart failure

Side Effects
1- -\text{SO}_2\text{NH}_2 \text{group hypersensitivity}
2- Ototoxicity So care must be noticed when used with aminoglycosides.
3- GIT disturbance(nausea, vomiting)

B. Phenoxyacetic acid derivatives

Ethacrynic acid (Edecrin)

\[
\text{\begin{align*}
\text{Cl} \\
\text{Cl} \\
\text{O-CH}_2\text{COOH}
\end{align*}}
\]

Mechanism of action:
Inhibition of SH-containing enzymes involved in solute reabsorption

Ethacrynic acid (Edecrin)

\text{SAR:1-} \text{Oxyacetic acid moiety at position para to } \alpha,\beta \text{ unsaturated carbonyl. This weakly acidic group directs the drug to the kidney}

2- Activating group (Cl or CH}_3^- \text{) occupy either 3 or 2 & 3 positions
3- Hydrogen atoms occupy the terminal alkene carbon
Side Effects:
1- greater incidence of ototoxicity
2- produce more serious GIT disturbances than sulfamoyl containing loop diuretics.

4-Site 4 diuretics (K⁺ sparing diuretics)

a) Antihormone K⁺ sparing diuretic:

The adrenal cortex secretes a potent mineralocorticoid hormone called aldosterone which promotes:

Na⁺& Cl⁻ reabsorption (salt retention)
K⁺ excretion

Spironolactone (Aldactone)that antagonizes the effects of aldosterone could be a good diuretic drug.

Spironolactone binds to the receptor and competitively inhibits aldosterone binding the receptor. (competitive antagonist)
The inability of aldosterone to bind to its receptor prevents reabsorption of Na⁺ & Cl⁻ and associated water.
The most important site of these receptors is in the late distal tubule and collecting system.
The drug is significantly metabolized during its first passage through the liver. The major metabolite is canrenone (active form), which can easily be converted to canrenoate anion.
Side Effects:
1- Hyperkalemia, therefore patients taking spironolactone should be warned not to take K⁺ supplements.
2- Antiandrogenic effects (i.e., gynecomastia, decreased libido, and impotence)
Preparations: Aldactone (Spironolactone)
                      Aldactazide (Spironolactone + HCT)

B) Pteridines

[Biochemical structure of Pteridine and Triamterene]

Site & MOA:
It blocks re-absorption of Na⁺ and blocks excretion of K⁺.
The net result is increased NaCl excretion in the urine and almost no K⁺ excretion
- Products: Triamterene alone
- Triamterene & Hydrochlorothiazide

c) Aminopyrazines

[SAR: 1- Optimum activity is obtained when position 6 is substituted with Cl⁻
2- NH₂ group at positions 3,5 are unsubstituted
Products: Amiloride + Hydrochlorothiazide (Moduretic)

Miscellaneous diuretics:

A) Osmotic diuretics
Osmotic diuretics are low-molecular-weight compounds that are not extensively metabolized and are passively filtered through Bowman’s Capsules into the renal tubules. Once in the renal
tubules they have limited reabsorption. **They form a hypertonic solution and cause water to pass from the body into the tubules, producing a diuretic effect.**

Polyols such as mannitol, sorbitol and isosorbide provide this effect.

Mannitol (osmitrol) and sorbitol are used intravenously in solutions of 5-50%. Isosorbide is basically a bicyclic form of sorbitol used orally to cause a reduction in intra-ocular pressure.

**Uses:**
1- Diagnosis & prophylaxis of acute renal failure
2- To promote urinary excretion of toxic substances
Angina is a disease affecting the coronary arteries which supply oxygenated blood from the ventricle to all heart tissues. When the lumen of the coronary arteries becomes less efficient in supplying oxygen to the heart, the heart is said to be ischemic. An antianginal is any drug used in the treatment of angina pectoris, a symptom of ischemic heart disease.

The two basic types of angina are:

- Acute or variant angina, which is caused by sudden spasm in the coronary artery, unrelated to atherosclerotic narrowing, can occur at rest.
- Stable or typical angina, which results from an advanced state of atherosclerosis and provoked by activity, food and emotional factors.

Classes of Antianginal drugs

- Antianginal nitrates
- Nitric oxide donor
- Calcium channel blockers
- Modulators of myocardial metabolism
- B -Adrenergic Blocking agents

a) Organic nitrates and nitrites

This class of compounds has a property of generating the unstable and lipophilic free radical nitric oxide (NO) in situ. NO activates Cyclic GMP synthesis which causes vascular smooth muscle relaxation both arterial and venous, vasodilatation, increase blood flow.

![Diagram of Organic Nitrates Action](attachment:image.png)
Rapid acting compounds
(Glyceryl trinitrate)

It is dispensed in sublingual, buccal, and trans-dermal preparations (patch).
Onset of action is 2 minutes and lasts for half an hour.
It is an effective antianginal because it causes redistribution of coronary blood flow to ischemic regions of the heart.

Slow acting compounds
Diluted Isosorbid dinitrate (Isordil)

Isosorbide dinitrate is used for prophylaxis or treatment of acute angina in the form of sublingual tablets.
Its onset of action is 3 min. and duration is one hour.
Synthesis isosorbide dinitrate
Metabolism of isosorbide dinitrate
5-isomer is still potent vasodilator, its plasma half life of about 4.5 hours is much longer than isosorbide dinitrate itself, the extended half life owing to the metabolite’s resistance to other metabolism indicates that it may be contributed to the prolonged duration of action of isosorbide

2-Nitric Oxide Donor

Molsidomine (Corvaton)

Molsidomine is an oral nitric oxide donor known as sydnone imine, a mesionic compound soluble in both water and organic solvents

Molsidomine has a slower onset and longer duration of action than conventional nitrates because the relatively slow rate of conversion to linsidomine which has rapid onset and shorter duration.

Used in treatment of stable angina

3-Calcium Channel Blockers

Calcium ions are known to play a critical role in many physiological functions. Inhibition of calcium ion influx into the myocardial cell may be advantageous in preventing angina. Calcium ions are known to play a critical role in many physiological functions. Because of the dependency of myocardium contraction on calcium ions, these drugs have a negative inotropic effect on the heart. Vascular smooth muscles also depend on calcium influx for contraction. The use of calcium channel blockers results in decreased heart work load and after load. The pre-load is not affected because of the lesser sensitivity of the venous bed to calcium channel blockers.
Chemistry of Calcium Channel Blockers

Dihydropyridine derivatives (e.g. Nifedipine)
Benthothiazepine derivatives (e.g. Diltiazem hydrochloride)
Phenyl alkylamine derivatives (e.g. Verapamil)

a) Dihydropyridine derivatives

The General SAR for 1,4-DHP drvs.

- 1,4-dihydropyridine ring is essential for the activity.
- Position 2,6 are substituted with alkyl gp that play a role in the drug duration of action.
- Substituted Phenyl ring at C4-position optimizes the activity [heteroaromatic rings (e.g. pyridine) show similar therapeutic activity but not used due to toxicity].
- substitution at C4-position with a small nonplanar alkyl or cycloalkyl gp decrease activity.

Phenyl ring substitution (X):
• compounds with \( O \)- or \( m \)- substitutions possess optimal activity, while those which are unsubstituted or contain \( p \)- substitution show a significant decrease in activity 

Despite the fact that all commercially available 1,4 DHPs have electron withdrawing \( O \)- & \( m \)- substituents, compounds with electron donating groups show good activity.

• The importance of \( o \)- & \( m \)- substituent is to provide sufficient bulk to “lock” the conformation of the 1,4DHP such that \( C_4 \) aromatic ring is perpendicular to the 1,4DHP. 

**This perpendicular conformation is essential for activity**

• Substitution at \( N_1 \) or the use of oxidized (piperidine) or reduced (pyridine) ring systems greatly decreases or abolishes activity.

• Ester gp at \( C_3 \) and \( C_5 \) positions optimizes activity, other electron withdrawing gp show decreased antagonist activity and may show agonist activity.

Nifidipine (Adalat)

Nifedipine inhibits \( Ca^{2+} \) dependant channels in the vascular smooth muscles but has little effect on that in the cardiac muscle

Metabolism of Nifedipine
These are examples of 2nd generation Ca\(^{2+}\) channel blockers, which are more selective for vascular smooth muscle than for cardiac tissue.

With the exception of amlodipine, all 1,4 DHP have C\(_2\)&C\(_6\) methyl groups. The enhanced potency of amlodipine (vs. nefidipine) suggests that 1,4 DHP receptor can tolerate larger substituents at this position and enhanced activity can be obtained by altering these groups.

**b) Benzothiazepine drvs.**

Deltiazem

The drug is used in patients with variant angina and is used also as antiarrhythmic agent.

Active metabolite is desacetyldeltiazem

c) Phenyl alkylamine drvs

Verapamil (Isoptin)

5-\{(3,4-Dimethoxyphenethyl)-methylamino\}-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile

Active metabolite: nor verapamil
Deltiazem & verapamil are both chiral, in each case the dextro (+) enantiomer is approximately one order of magnitude more potent as Ca\(^{2+}\) Channel blocker than levo (-) enantiomer. Verapamil and deltiazem have both cardiac and vascular effects so used as antianginal, antiarrhythmic and antihypertensive, while 1,4 DHP are more frequently used as antianginal and antihypertensive as it has much less effect on the cardiac tissue and higher specificity for vascular beds.

4) Modulators of myocardial metabolism

**Ranolazine (Ranexa)**

![Ranolazine Structure](image)

MOA: Metabolic modulator

Modulates myocardial metabolism by inhibition of fatty acid oxidation & increasing glucose oxidation thus generating more ATP per molecule of oxygen consumed.

Used for treatment of chronic angina in combination with amlodipine, B-blockers or organic nitrate.
Anticoagulants

Compounds that do not allow blood to clot are called anticoagulants.
The clotting cascade is a proteolytic enzyme cascade of 13 components.
The process of blood coagulation involves a series of steps that occur in a cascade and terminate in the formation of a fibrin clot.

Physical process of clotting

Anticoagulant drugs to treat thromboembolism
Anticoagulants inhibit the chemical process of proteolytic formation of fibrin polymer.
Anti-coagulants are classified into:
1- Natural compound : Heparin (parenteral)
2- Synthetic compounds : (oral)
classified chemically as:

<table>
<thead>
<tr>
<th>i) 4-Hydroxycoumarins</th>
<th>ii) 1,3 Indandiones</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
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</table>
Heparin is known as heparinic acid.

[Chemical structure image]

Heparin is a strongly acidic, high molecular weight mucopolysaccharide. The polysaccharide polymer chain is composed of sulfated D-glucosamine and D-glucuronic acid residue, linked by α-1→4 bonds.

Antidote is: Protamine sulfate

MOA of Heparin

**Fibrin Formation**

Extrinsic pathway

1. Factor Xa
2. Prothrombin (factor II)
3. Thrombin (factor IIa)
4. Fibrin monomers (soluble)
5. Fibrin polymers (insoluble)
6. Factor XIIIa

Intrinsic pathway

1. Factor Xa
2. Prothrombin (factor II)
3. Thrombin (factor IIa)
4. Fibrin monomers (soluble)
5. Fibrin polymers (insoluble)
6. Factor XIIIa

Antithrombin III works by forming 1:1 complex with both thrombin and factor Xa. The rates of these reactions are slow in absence of heparin, binding is accelerated 1000 fold when heparin is added.

Heparin accelerates binding of antithrombin III (ATIII) to thrombin and factor Xa.

So decreasing the availability of thrombin

**Heparin Forms**

Heparin is administered I.V, or subcutaneous but not by oral route because the polysaccharide chains are broken by gastric acid.

I.M route is not recommended as it results in high risk of hematoma.
ii) Vitamin K antagonists (Oral anticoagulant)
Vitamin K antagonists are classified chemically as
i) 4-Hydroxycoumarin derivatives
ii) Indandione derivatives.
Mechanism of action

MOA of Coumarins and 1,3-indandiones are
1-Competitive inhibitors of vitamin K in the biosynthesis of prothrombin.
2-Inhibit vitamin K 2,3 quinone reductase and vitamin K epoxide reductase, enzymes that play an important role in the oxidation – reduction process necessary for γ-carboxylation of prothrombin.

i) 4-Hydroxycoumarins
SAR of Coumarins
All coumarins are water insoluble lactones
3-Substituent greatly affect the pharmacokinetic and toxicological properties of warfarin.
-\text{OCH}_3\text{ gp at position }8\text{ increases anticoagulant activity}

**Warfarin Sodium (Coumadin)**

![Warfarin Sodium (Coumadin) structure]

**Warfarin Metabolism**

![Warfarin Metabolism diagram]

- 2- Dicumarol

- 3,3-Methylene bis[4-hydroxycoumarin]
Dicumarol is used alone or in combination with heparin in the prophylaxis and treatment of intravascular clotting.

**ii) Indandiones**

<table>
<thead>
<tr>
<th>1-Phenendione (Dindivan)</th>
<th>2- Anisindione (Miradon)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Chemical Structure" /></td>
<td><img src="image2" alt="Chemical Structure" /></td>
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</tbody>
</table>

Both are oral anticoagulant specifically designed to function as anti-metabolite for vitamin K. The urine will take an orange red tint.

**Antiplatelet Drugs**

(Inhibitors of platelet aggregation)

Another site of action for inhibition of the normal blood coagulation cascade is at the level of platelets. This is achieved through either reducing the formation or inhibiting the action of chemical signals that promote platelet aggregation.

Molecules that do not allow platelets to aggregate and thus prevent clotting, especially in the arteries, are called anti-platelet agents. They either reducing the formation or inhibiting the factors that promote platelet aggregation.

![Chemical Reaction Diagram](image3)

**Adenylate cyclase**

\[
\text{ATP} \xrightarrow{\text{Adenylate cyclase}} \text{cAMP} \xrightarrow{\text{Phosphodiesterase}} \text{AMP}
\]

**Kinase**

\[
\text{Protein + Phosphate} \xrightarrow{\text{Kinase}} \text{Chelator of Calcium (Bound Calcium)} \xrightarrow{\text{Chelator of Calcium}} \text{Calcium (Free Calcium)}
\]

**Necessary for aggregation**

\[
\text{Aspirin} \xrightarrow{\text{Inhibit platelets aggregation}} \text{COOH} \xrightarrow{\text{O}} \text{CH}_3
\]

\[
\text{Aspirin}
\]
Ticlopidine (Ticlid) and Clopidogrel (Plavix)

Clopidogrel (Plavix)  

Antihyperlipidimic Agents

The major lipids found in the blood stream are  
Cholesterol, Cholesterol esters, Triglycerides and Phospholipids

Hyperlipidemia is a term used to describe elevated plasma levels of lipids that are usually in the form of lipoproteins.

Lipoproteins (Transport lipids to be used or stored)

LDL  (Bad cholesterol) Delivers cholesterol to cells

HDL  (Good cholesterol) Clears cholesterol from circulation

IDLP

VLDL

Chylomicrons Produced by intestines, broken down by lipoprotein lipase

Total plasma cholesterol level $< 200 \text{ mg/dL}$ are considered desirable.

Levels between 200 and 239 mg/dL are considered border line

Levels $> 240 \text{ mg/dL}$ are considered high

Cholesterol sources, biosynthesis and degradation

Diet only found in animal fat

Biosynthesis primarily synthesized in the liver from acetyl CoA

biosynthesis is inhibited by LDL uptake by the liver

Degradation only occurs in the liver

cholesterol is converted to bile acids
There are several mechanisms by which lipid-lowering drugs can affect the metabolism of cholesterol and relative levels of various cholesterol-carrying lipoproteins in the plasma.

1) Inhibitor of de novo cholesterol biosynthesis (Statins)
2) Sequestering agents (Bile acids sequestrants)
3) Stimulation of lipoprotein lipase
4) Inhibition of cholesterol absorption
5) Miscellaneous.

**1- HMG-CoA Reductase inhibitors**

Drugs in this class inhibit the enzyme 3-Hydroxy 3-Methyl Glutaryl Reductase (HMG-CoA), responsible for the conversion of HMG-CoA to mevalonate in the synthetic pathway for the synthesis of cholesterol.

HMG-CoA reductase is the rate-limiting catalyst for the irreversible conversion of HMG-CoA to mevalonic acid in the synthesis of cholesterol.
**Biosynthesis of Cholesterol**

\[ \text{CH}_2-C-\text{SCoA} \rightarrow \text{3-hydroxy-3-methyl-glutaryl-CoA} \]

\[ \text{HMG CoA reductase} \]

**Intermediate**

\[ \text{Mevalonic acid} \]

**Mechanism of action**

\[ \text{HMG CoA} \rightarrow \text{Intermediate} \rightarrow \text{Mevalonic acid} \]
SAR:

Common to all HMGCoA reductase inhibitors:
1- 3,5 dihydroxy carboxylate is essential for inhibitory activity. Compounds containing a lactone ring are prodrugs.
2- Altering the 2-carbon distance between the ring system diminishes the activity.
3- 3R,5R stereoisomerism is required for activity.

Ring A Subclass:
1. The decaline ring is essential for anchoring the compound to the enzyme active site. Replacement with cyclohexane resulted in 10,000 fold decrease in activity
2. Conversion of ester to ether decrease the activity
3. Methyl substitution at R2 increases the activity
4. β-hydroxyl subst. at R1 enhances hydrophilicity and may provide cellular specificity

Ring B subclass:

7-Substituted-3,5-dihydroxyheptanoic acid

1 – Substitution W,X,Y could be C or N, n is equal to either zero or one (i.e five or six member heterocycle)
2- p- fluorophenyl cannot be coplanar with the central aromatic ring
3- R substitution with aryl gp, H-C chain, amides or sulphonamide enhance lipophilicity and inhibitory activity
2-Sequestring agents (Bile acids sequestrants)

Mode of action:
Cholestyramine and colestipol are basic anion exchange resins, which sequester bile acids in the intestine and prevent their re-absorption and their enterohepatic re-circulation.
The main side effects of these two agents is constipation

Cholestyramine Resin (Questran)
It is an inert styrene – divinylbenzene copolymer with quaternary ammonium functional groups
Increase amount of divinylbenzene from 2% to 4 to 8% increase cross linkage and reduce porosity of the resin this prevents binding of bile acids and decrease efficacy of the compound.
After oral ingestion, cholestyramine remains in GIT where it readily exchanges chloride ions for bile acids in the small intestine to be excreted as bile salts and feces.

3- Stimulation of lipoprotein metabolism Fibrates
MOA:
Fibrates decrease plasma triglycerides level more than cholesterol lipoprotein lipase activity, and thus increased VLDL clearance

SAR

- Isobutyric acid gp is essential for activity
- Compounds containing esters are prodrugs
- 3-Substitution at p-position of aromatic ring with Chloro or chlorine containing isopropyl ring produce compounds with longer half life
- compounds containing n-propyl as a spacer group results in an active drug.

<table>
<thead>
<tr>
<th>Clofibrate (Atromid S)</th>
<th>Gemfibrozil (Lopid)</th>
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**Fenofibrate (Artiflex)**

![Fenofibrate structure](image)

2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropanoic acid 1-methylethyl ester.

It has structural features represented in clofibrate. The primary difference involves the second aromatic ring which imparts a greater lipophilic character than exists in clofibrate, resulting in a much more potent hypocholesterolemic and triglyceride-lowering agent. 

$p$-chloro gp is less susceptible to oxidative metabolism than gemfibrozil
4-Inhibition of cholesterol absorption

Ezetimibe (Ezetrol)

It acts by decreasing cholesterol absorption in the small intestine. It may be used alone when other cholesterol-lowering medications are not tolerated, or together with statins. Active metabolite is phenolic glucuronide.