Hypertension

It is a condition in which systolic & diastolic blood pressure exceeds above 140/90 mm.Hg

Types of Hypertension

1. Primary / Essential hypertension

- Definite cause is not known
- This is the common form of hypertension
- This may be due to Dietary intake of more sodium & less potassium
- In some cases, it may be hereditary.
- Advancement of age.
- Decreased vascular synthesis of nitric oxide (NO)(is useful in vasodilatation)

2. Secondary / Malignant hypertension

This is due to renal, endocrine & vascular disorders

Antihypertensive agents

These are the agents that lower the blood pressure

Classification of Antihypertensive agents

1. Drugs acting on Renin-Angiotensin Aldosterone axis

(a) Angiotensin Converting enzyme (ACE) inhibitors

1. **Sulfhydryl containing inhibitor**
   Captopril
2. **Dicarboxylate containing inhibitor**
   Enalapril, Lisinopril, Quinapril, Ramipril, Trandolapril, Spirapril, Moxeipril, Benazepril
3. **Phosphate containing inhibitor**
   Fosinopril

(b) Angiotensin II receptor blockers

Azilsartan, Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, valsartan

(c) Renin inhibitor

Aliskiren

2. **Endothelin receptor antagonists**

Ambrisentan,
Bosentan,
Sitaxsentan sodium,
Daxusenten

3. **Agents depleting neurotransmitter stores**

Powdered rauwolfia serpentina
Reserpine
Guanethidine monosulphate
Guanadrel sulphate

4. **Selective alpha adrenergic antagonists**

Prazosin HCl
Terazosin HCl
Doxazosin

5. **Beta adrenergic blockers**

Propranlol
Atenolol
Metoprolol
Timolol

6. **Mixed alpha & beta adrenergic blockers**

Labetolol
Carvedilol

7. **Centrally acting adrenergic drugs**

Methyldopate HCl
Clonidine HCl
Guanabenz acetate
Guanafacine HCl

8. **Vasodilators acting on smooth muscle**

Hydralazine HCl
Sodium nitro prusside

9. **Phosphodiesterase type 5 inhibitors**

Silenafil citrate
Verdenafil HCl
Tadalafil

10. **Potassium channel agonists**

Diazoxide
Minoxidil

11. Positive inotropic agents

Digoxin
Digitoxin
Amrinone
Milrinone
Dopamine
Dobutamine

12. Calcium channel blockers

(1) 1,4-dihydro pyridines

Amlodipine
Felodipine
Clevidipine
Nifedipine
Nimodipine
Nicardipine
Nisoldipine

(2) Phenyl alkyl amines

Verapamil

(3) Benzothiazepines

Diltiazem

(4) Diamino propranolol ether

Bepridil

13. Diuretics

(1) Thiazide type

Hydrochlorthiazide
Chlorthalidone
Bendroflumethiazide
Trichlormethazide

(2) Potassium sparing diuretics

Spironolactone
Amiloride
Triamterene

(3) Loop diuretics

Furosemide
Ethacrynic acid
Bumetanide
Torasemide

Angiotensin Converting Enzyme

- Zinc containing glycoprotein
- Molecular weight – 1,30,000
- Nonspecific peptidyldipeptide hydrolase
- It cleaves dipeptides from the carboxy terminus of several endogeneous peptides.
- The minimum structural requirement for binding & cleavage of substrate by ACE is that it is a tripeptide with a free carboxylate group
- A general exception is that this enzyme does not cleave peptides with a penultimate prolyl residue.

Renin

- Aspartyl protease enzyme
- Source – kidney
- Molecular weight – 35,000 – 40,000
- Converts Angiotensinogen to Angiotensin I

Angiotensinogen

- Glycoprotein
- Molecular weight – 58,000 – 61,000
- Synthesized primarily in liver & brought into circulatory system.
- Renin cleaves Leu-Val bond from the aspartic acid end of the angiotensinogen into angiotensin I.

Angiotensin I

- Decapeptide
- Inactive
- ACE cleaves Phe-His bond from the carboxy terminal of angiotensin I to Angiotensin II

Angiotensin II

- **Octapeptide**
- **Potent vasoconstrictor**
- **Glutamyl amino peptidase cleaves Asp- Arg bond of angiotensin II to angiotensin III**

Angiotensin II (in kidneys)

It constricts glomerular arterioles

↓

Effects are greater on efferent arterioles than afferent ones

↓

Constriction of afferent arterioles results in increased arteriolar resistance

↓

which raises systemic arteriolar B. P

Angiotensin II (in Hypothalamus)

Angiotensin II

↓

Stimulates the release of vasopressin from hypothalamus

↓

because this peptide hormone is typically released to conserve water when body is dehydrated

↓

in kidneys, it increases the permeability to water of the distal convoluted tubules and collecting tubules in the nephrons

↓

Concentrating the urine & reducing the urine volume

↓

By inducing moderate vasoconstriction, this peptide results in increase in B.P

Angiotensin II (in Vascular endothelium)

Angiotensin II

↓

Stimulates the production of endothelin

↓

endothelin is a 21 amino acid peptide (ie) produced in vascular endothelium

↓

Endothelin plays a role in the regulation of smooth muscle contraction

↓

Which contributes to blood pressure regulation

Angiotensin II (in Adrenal Cortex)

Angiotensin II

↓

Plays a primary role in regulating aldosterone secretion

↓

By stimulating, renin-angiotensin system, aldosterone is secreted by the adrenal cortex

↓

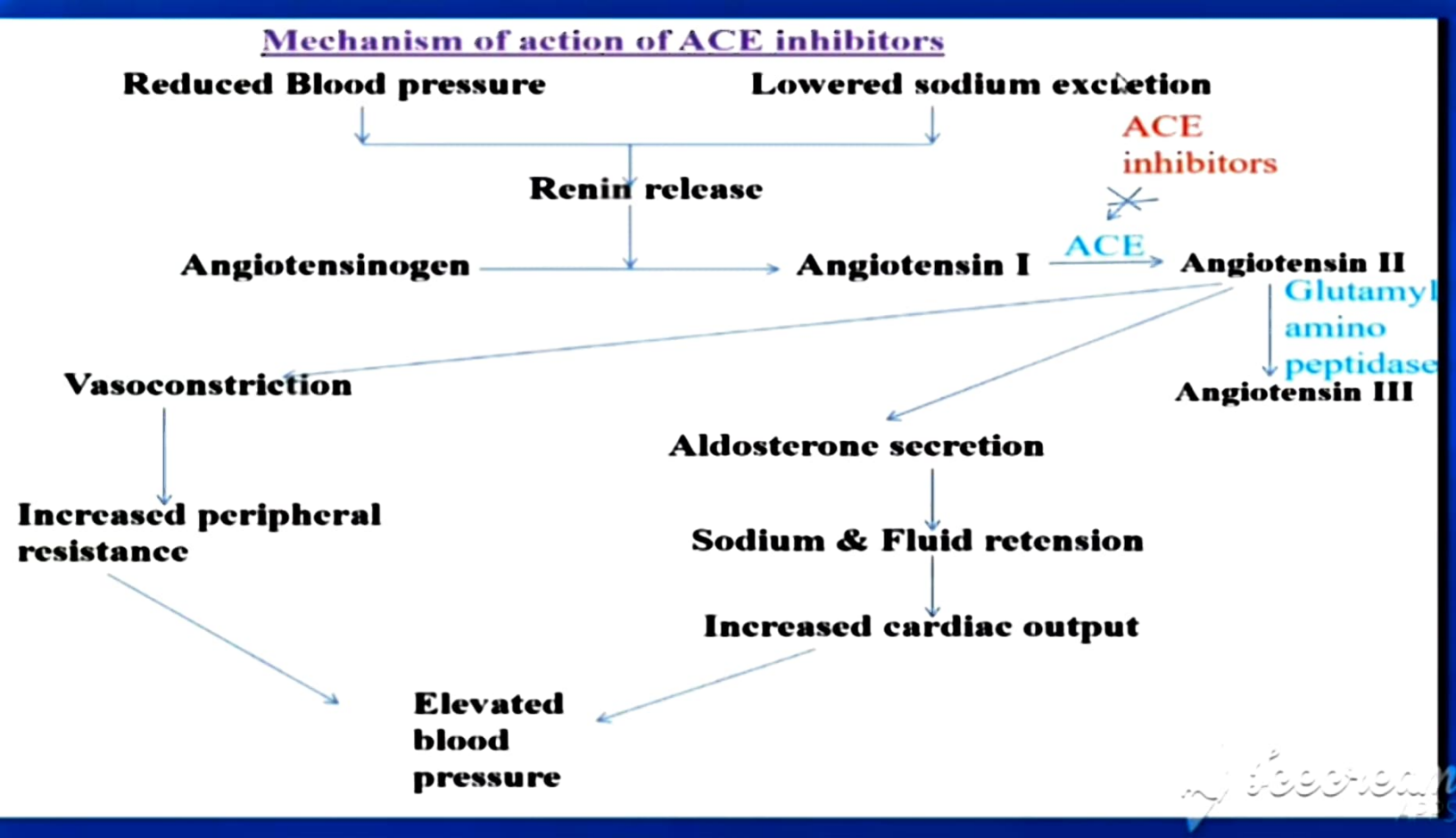
It is responsible for the reabsorption of sodium into the bloodstream

↓

This results in increases levels of sodium in the plasma

↓

Which results in increased blood volume & vascular resistance


Mechanism of action of ACE inhibitors
Reduced Blood pressure
Lowered sodium excretion
ACE inhibitors
Renin release
Angiotensinogen
Angiotensin I
ACE
Angiotensin II
Glutamyl amino peptidase
Angiotensin III
Vasoconstriction
Aldosterone secretion
Increased peripheral resistance
Sodium & Fluid retension
Increased cardiac output
Elevated blood pressure

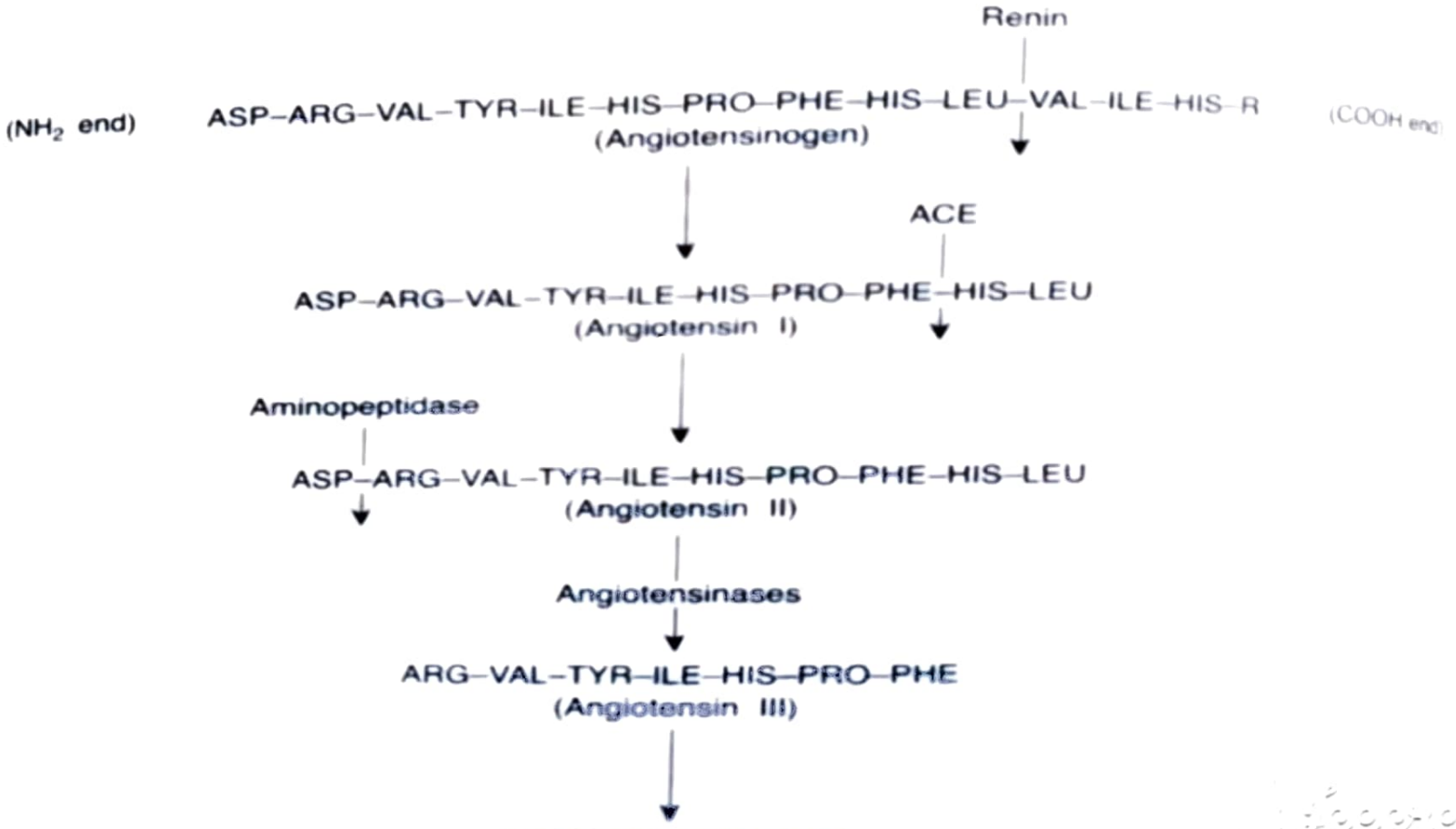

Renin
(NH2 end)
ASP–ARG–VAL–TYR–ILE–HIS–PRO–PHE–HIS–LEU–VAL–ILE–HIS–R
(Angiotensinogen)
(COOH end)
ACE
ASP–ARG–VAL–TYR–ILE–HIS–PRO–PHE–HIS–LEU
(Angiotensin I)
Aminopeptidase
ASP–ARG–VAL–TYR–ILE–HIS–PRO–PHE–HIS–LEU
(Angiotensin II)
Angiotensinases
ARG–VAL–TYR–ILE–HIS–PRO–PHE
(Angiotensin III)
INACTIVE PRODUCTS

Figure 18.2

ACE inhibitors

- Angiotensin converting enzyme(ACE) inhibitors inhibit the enzyme ACE
- Because of that , Angiotensin I would not be converted into Angiotensin II
- If Angiotensin II will not be there, there will be no increased blood pressure.

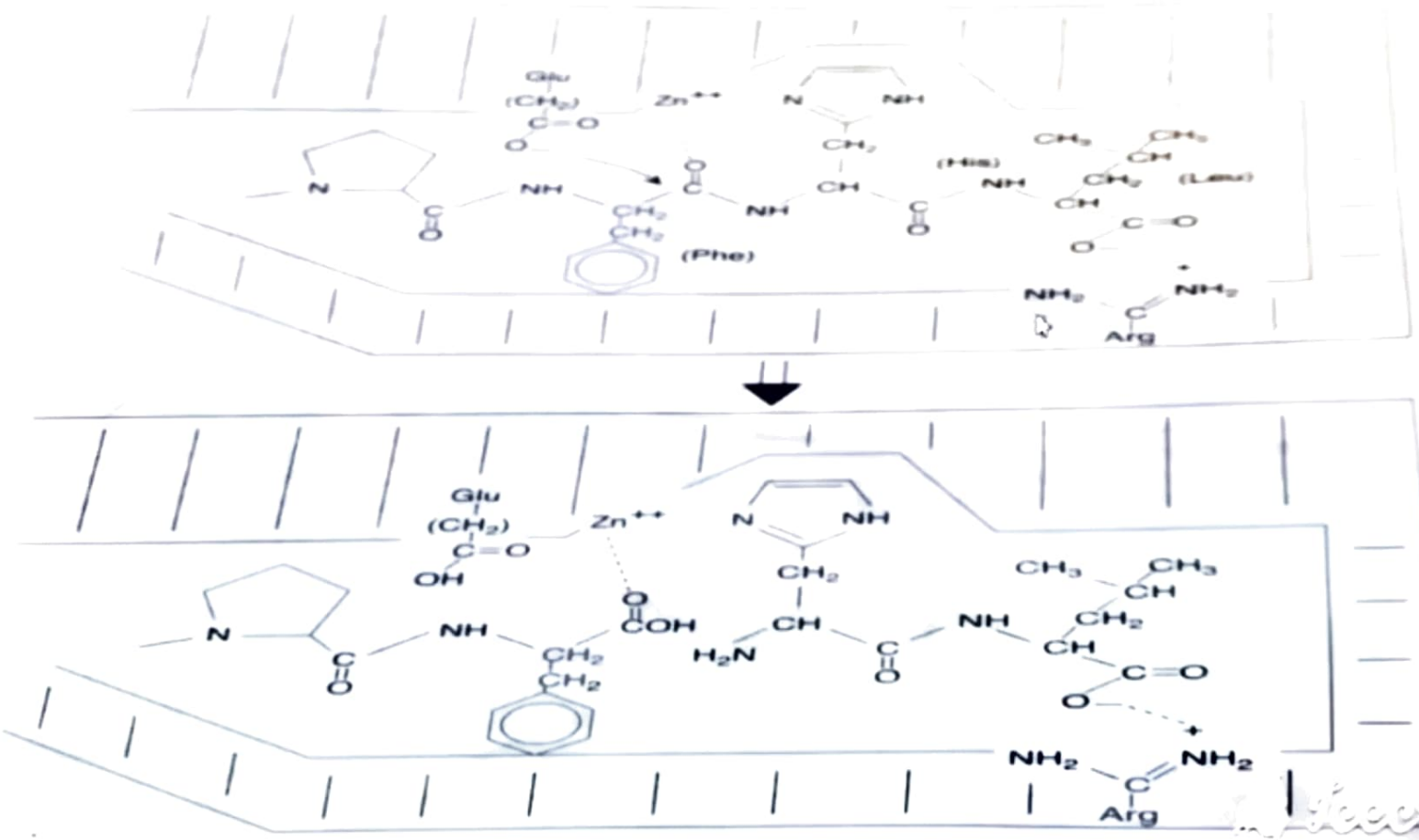
Types of ACE inhibitors

- These ACE inhibitor prodrugs are bioactivated by means of esterase to its active metabolite.
- Here the ester is hydrolysed to form an acid derivative. Eg .,
- Enalapril —hepatic esterase→ Enalaprilat
- Benazepril —hepatic esterase→ Benazeprilat
- Quinapril —hepatic esterase→ Quinaprilat
- Ramipril —hepatic esterase→ Ramiprilat
- Fosinopril —hepatic esterase→ Fosinoprilat
- Trandolapril —hepatic esterase→ Trandolaprilat
- All the ACE inhibitor prodrugs are not having any mutagenicity even though these drugs cross the placenta.

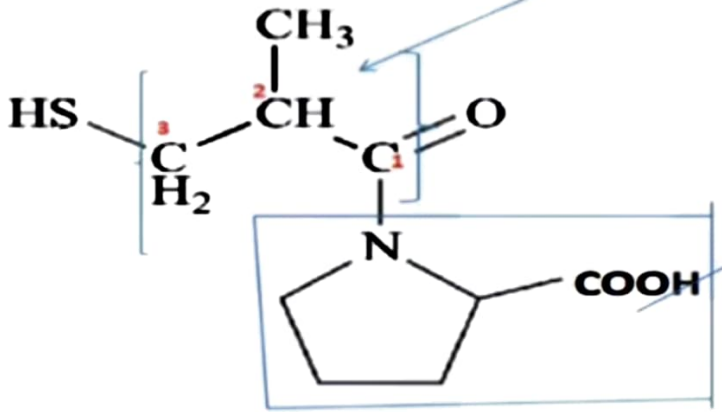
Binding sites of ACE

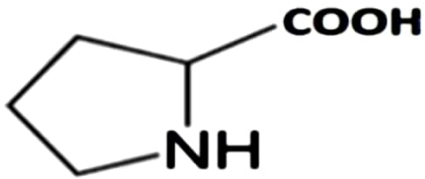
The important binding points at the active sites of ACE are

- **A cationic site** - to attract a carboxylate ion
- **A Zinc ion** – that can polarize a carbonyl group of amide function to make it more susceptible to hydrolysis.
- **In the active site, there is a nucleophilic attack of the amide carbonyl by the gamma carbonyl group of the glutamic acid residue to cause hydrolysis of the peptide.**
- **Hydrophobic pockets lie between these groups in the active site (as does a functional group that forms a hydrogen bond with an amide carbonyl)**


Glu
(CH2)
C=O
O
Zn++
N
NH
CH2
(His)
CH3
CH3
CH
CH2
(Leu)
NH
CH
C=O
O
N
C
O
NH
CH2
CH2
(Phe)
C
O
NH
CH
C
O
NH2
NH2
C
Arg
Glu
(CH2)
C=O
OH
Zn++
N
NH
CH2
CH3
CH3
CH
O
COOH
NH
CH2
CH2
H2N
CH
C
O
NH
CH2
CH
C=O
O
N
C
O
NH2
NH2
C
Arg

1. Captopril





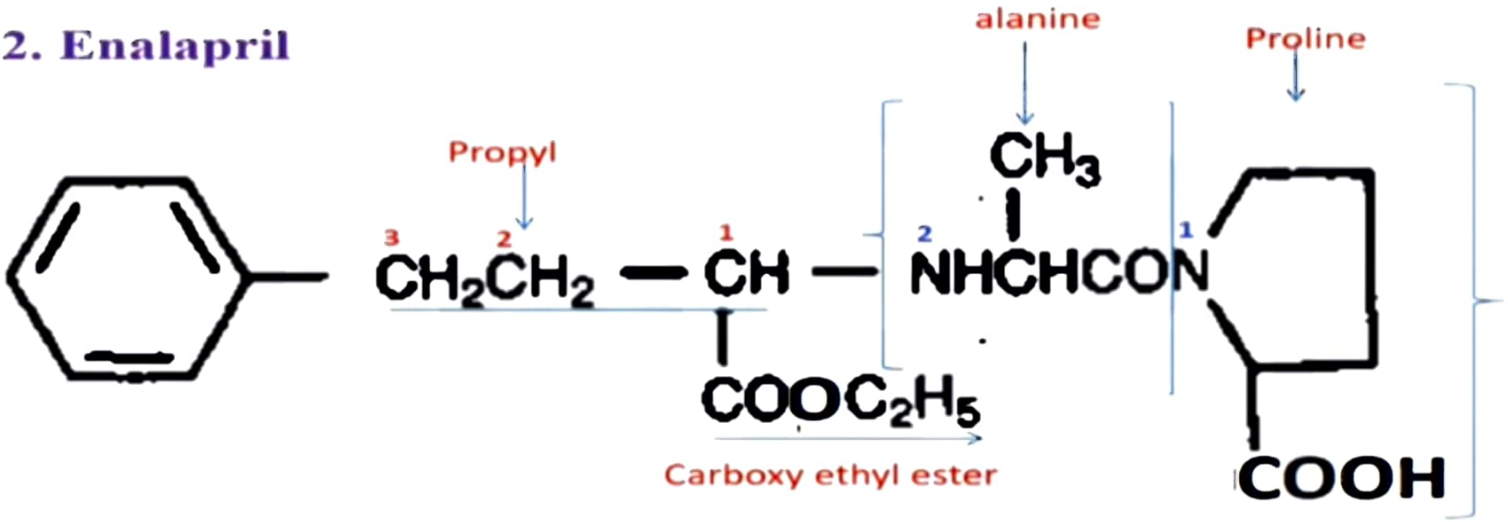
Proline
(Pyrrolidin-2-carboxylic acid)

1 – ((2S) 3 – mercapto – 2 – methyl – 1– propionyl) proline

Side effects :
Skin rashes &
Taste disturbances

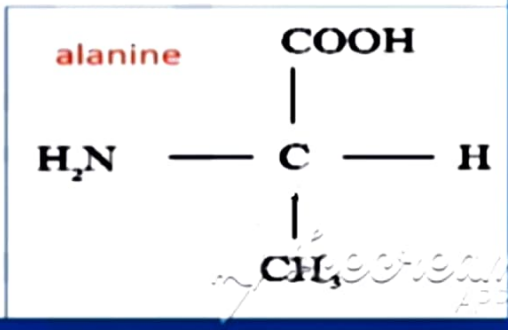
Used in the treatment of
Hypertension
Congestive heart failure
Myocardial infarction
Preservation of kidney function in diabetic neuropathy

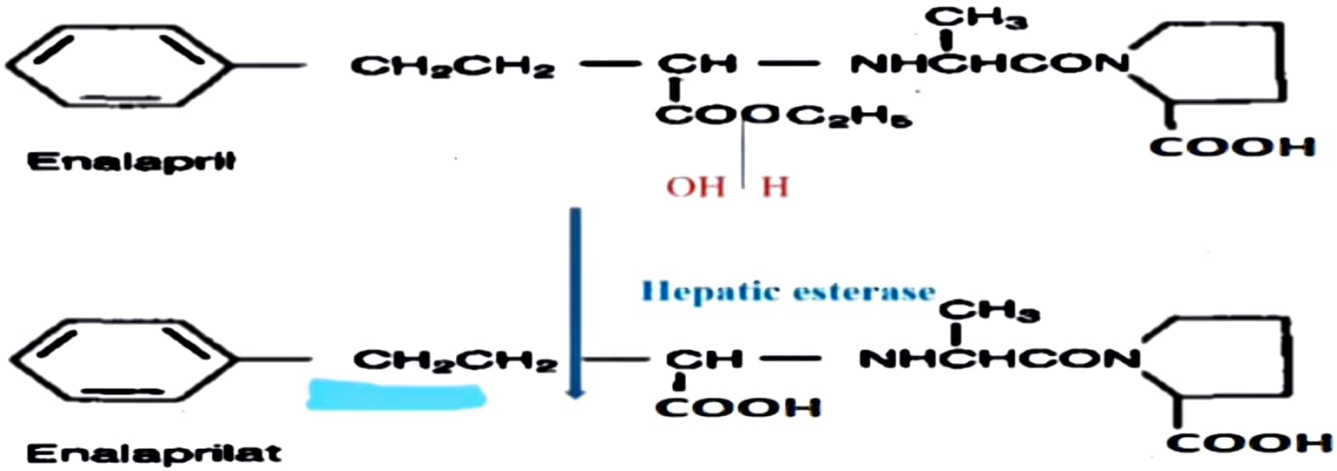
2. Enalapril



1[N ² (S) – 1- carboxy – 3- phenyl propyl]-1- alanyl – L- Prolin – 1- ethyl ester

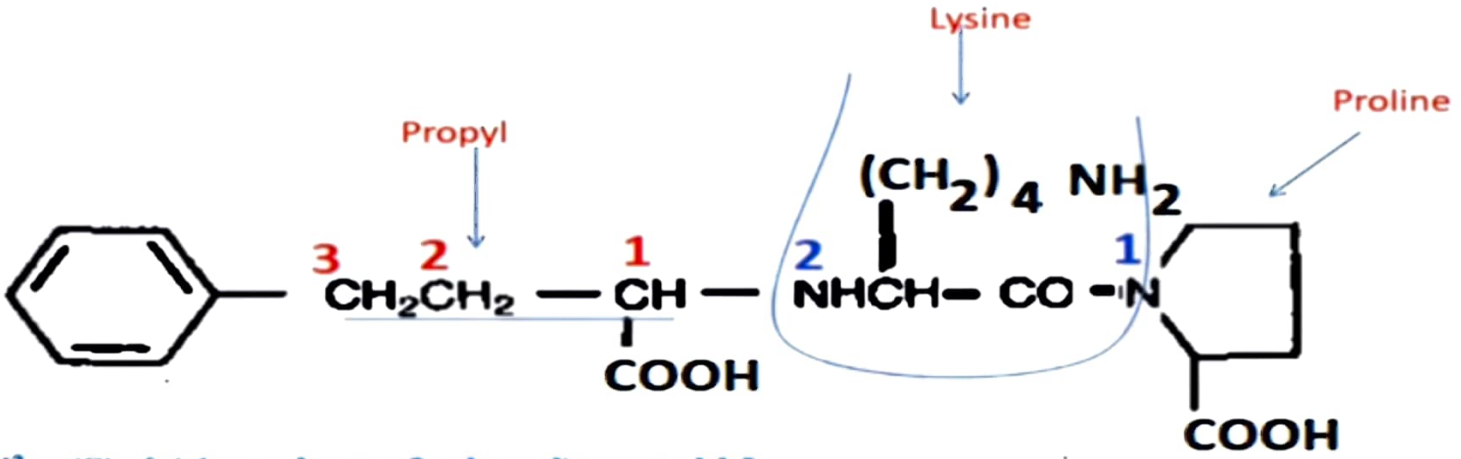
Available as a maleate salt.





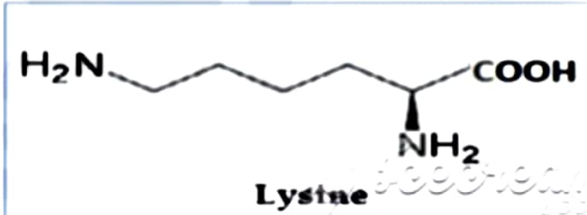
- It is a prodrug. Its active metabolite is Enalaprilat.
- It is devoid of side effects of rashes & taste disturbances (seen with captopril)
- Used in the treatment of hypertension , heart failure,
- For reduction of proteinuria and renal disease in patients with nephropathies, and
- For the prevention of stroke, myocardial infarction, and cardiac death in high-risk patients.

3. Lisinopril



1- [N^2 – (S)- [(1- carboxy- 3-phenyl) propyl] L-lysyl]–L-proline

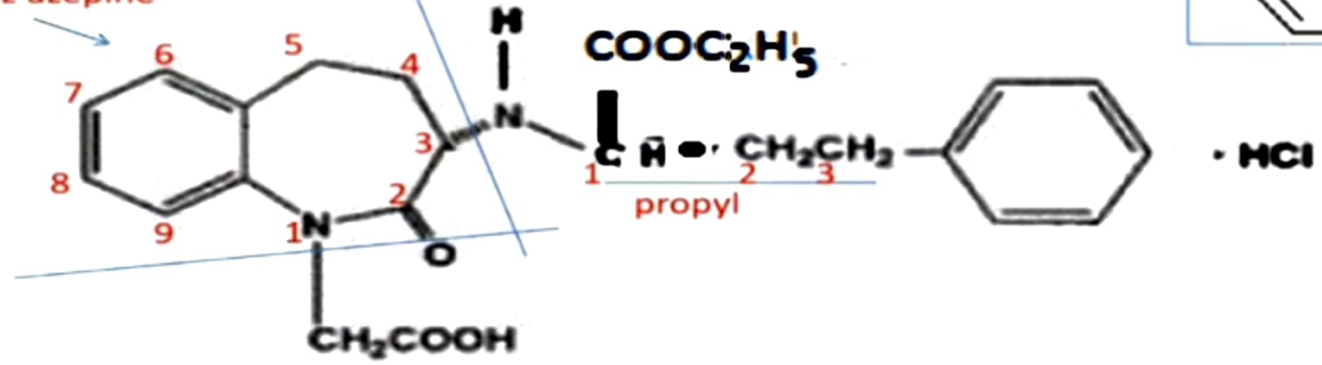
- **It is a lysine derivative of Enalaprilat**
- **Used in the treatment of hypertension & heart failure**



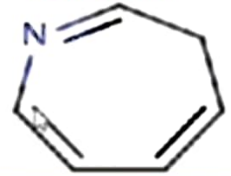
Lysine

4. Benazepril

2,3,4,5-tetrahydro-
1 H-benz azepine

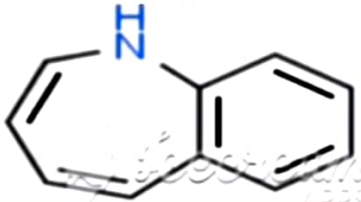


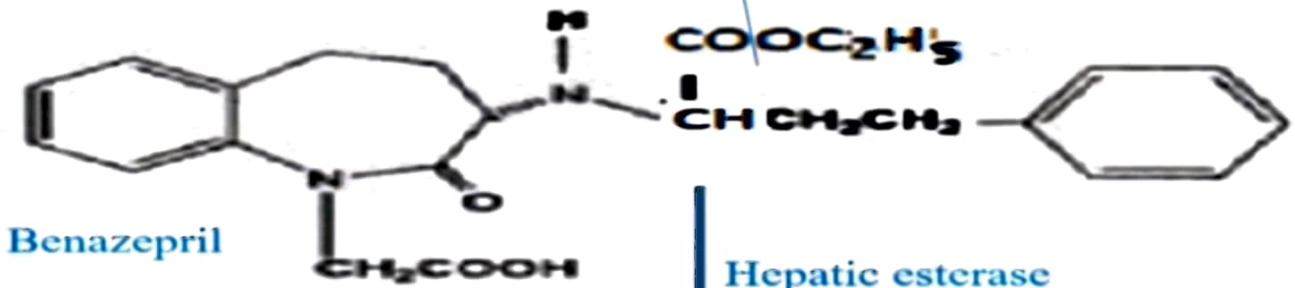
Azepine



**(3S) – 3 [[(1S) – 1- carbethoxy -3- phenyl propyl] amino]
2,3,4,5 – tetrahydro -2-oxo- 1H – 1- benzaepin – acetic acid –
3- ethyl ester**

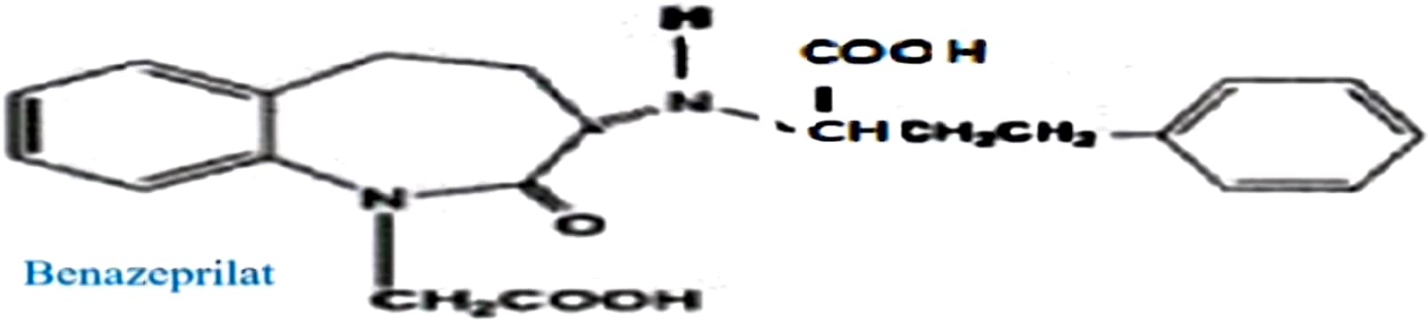
benzazepine





Benazepril

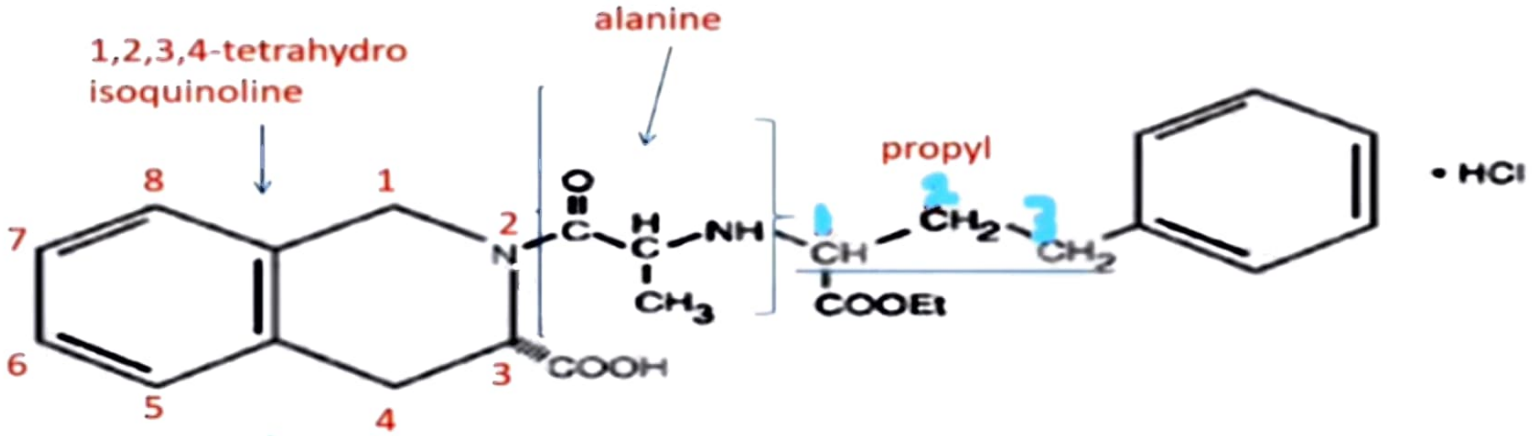
Hepatic esterase



Benazeprilat

- It is a prodrug
- It is metabolized rapidly to active diacid benazeprilat.
- All the ACE inhibitor prodrugs are not having mutagenicity

5. Quinapril

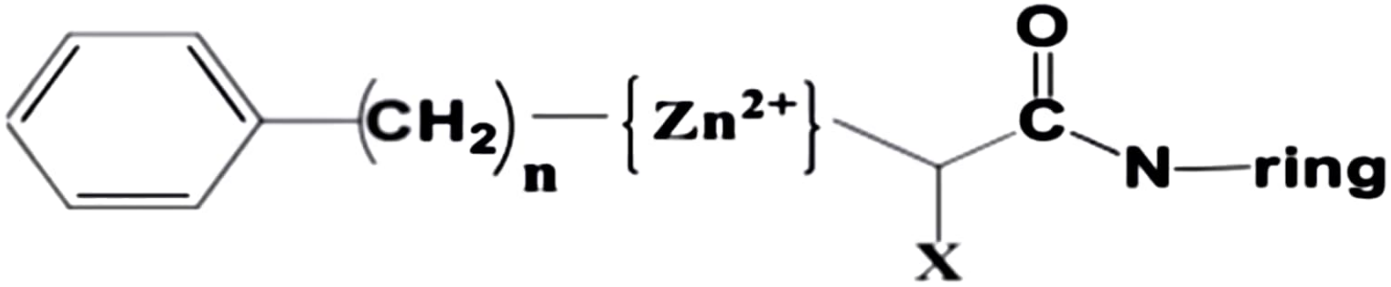


(S) – [(S) N^2 [(S) – 1- carboxy – 3- phenyl- propyl-] alanyl] -1,2,3,4- tetrahydro isoquinolin-3-carboxylic acid -1- ethyl ester

- **It is a prodrug**
- **It is metabolized by hepatic esterases into diacid quinaprilat in the body**
- **More potent than captopril**
- **Equipotent to the active form of enalapril**

SAR of ACE inhibitors

- **The general structure of ACE inhibitors is**

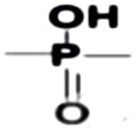


- **Zinc ion binding groups may be either**

1. Sulfhydryl group

2. Carboxylate group

3. Phosphinic acid group



SAR of ACE inhibitors

- **Among the zinc ion binding groups sulfhydryl shows superior binding to zinc** (side chain mimicking the Phe in carboxylate and Phosphinic acid compounds for the lack of sulfhydryl group).

- **Sulfhydryl compounds produce high incidence of skin rashes & taste disturbances.**

- **They can form dimers or disulphides which may shorten the duration of action.**

- **Compounds that bind to zinc through either a carboxylate or phosphinate mimic the peptide hydrolysis trasition state & enhance binding.**

- **Esterification of the carboxylate / phosphinate produces an orally bioavailable prodrug.**

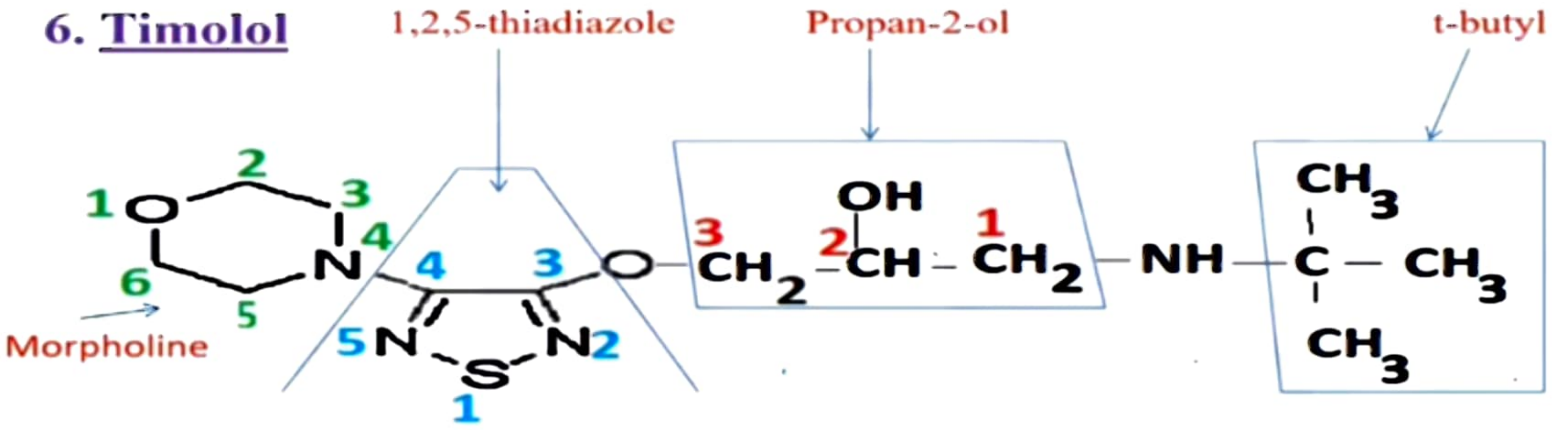
- **The N-ring must contain a carboxylic acid to mimic the C- terminal carboxylate of ACE substrate.**
- **Large hydrophobic heterocyclic rings in the N-rings, increases the potency & alter pharmacokinetic properties.**
- **X is usually a methyl group to mimic the side chain of alanine.**
- **Within the dicarboxylate series, when X equals n-butylamine (lysine side chain), this produces a compound that does not require prodrug for oral activity.**
- **Optimum activity occurs when stereochemistry of inhibitor is consistent with L-amino acid stereochemistry present in normal substrates.**

Therapeutic uses of ACE inhibitors

Used in the treatment of

- **High blood pressure**
- **Heart failure**
- **Heart attack**
- **Preventing kidney damage associated with high blood pressure & diabetes**

6. Timolol



(S) – 1- (t-butyl amino) – 3 [(4 – morpholin -4-yl) 1,2,5 – thiadiazol -3-yl) oxy] propan-2-ol

- **Non selective beta adrenergic blocker**
- **It was the first beta blocker approved for topical use in the treatment of glaucoma.**
- **It should be avoided in patients with pulmonary disease.**

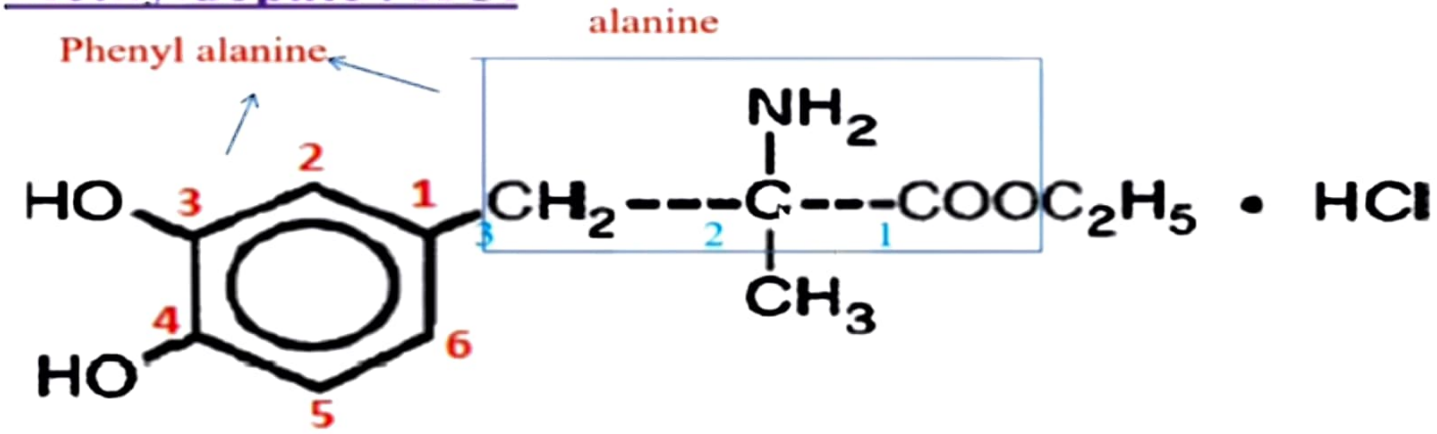
Timolol

Blocks the actions of sympathetic (adrenergic) nervous system

So in the heart, it causes a reduction of the pressure within the eye (intraocular pressure)

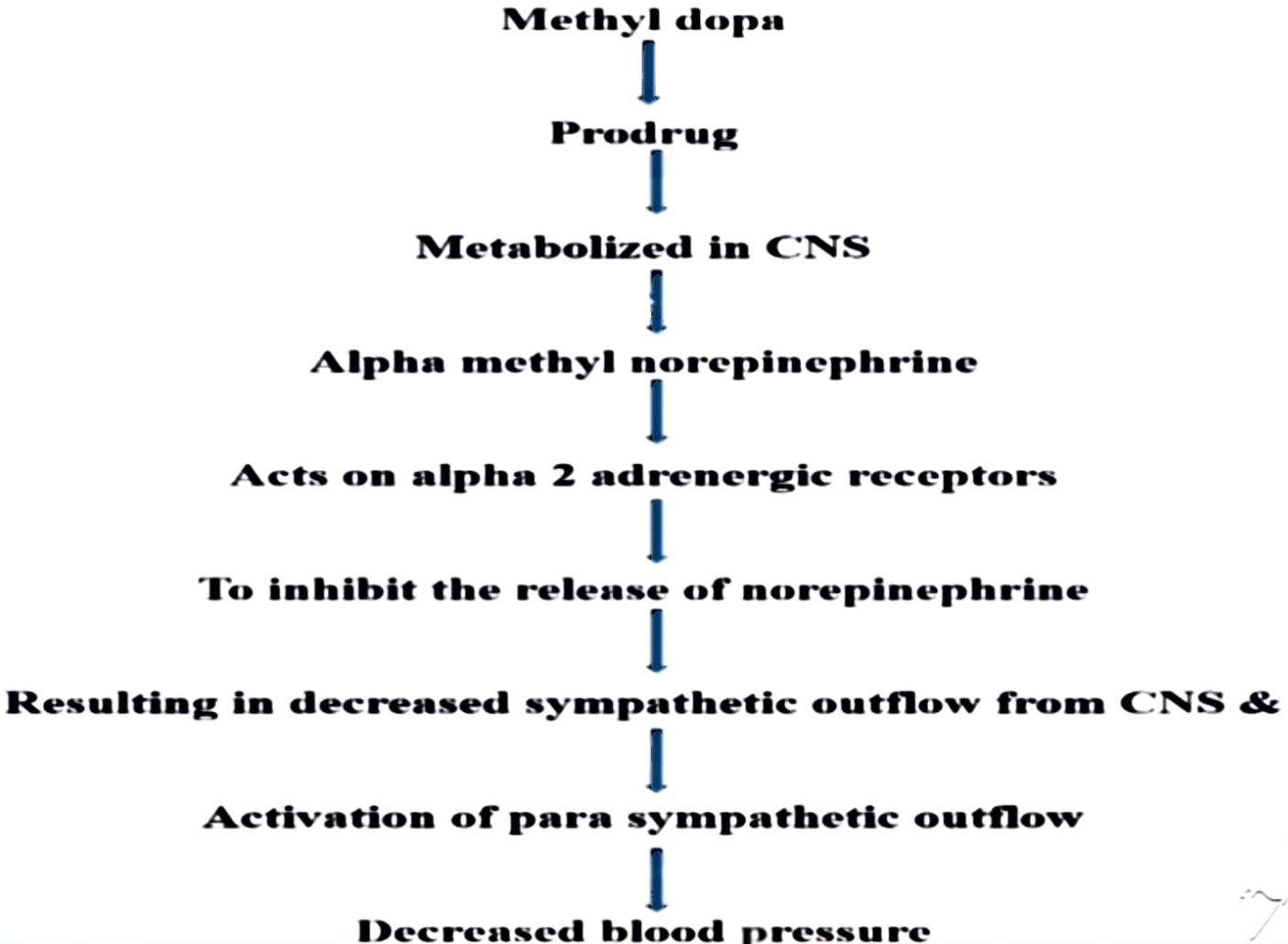
- Available as Timolol **hemihydrate** or **maleate**
- **Used to treat Ocular hypertension & Chronic open angle glaucoma**

7. Methyldopate . HCl

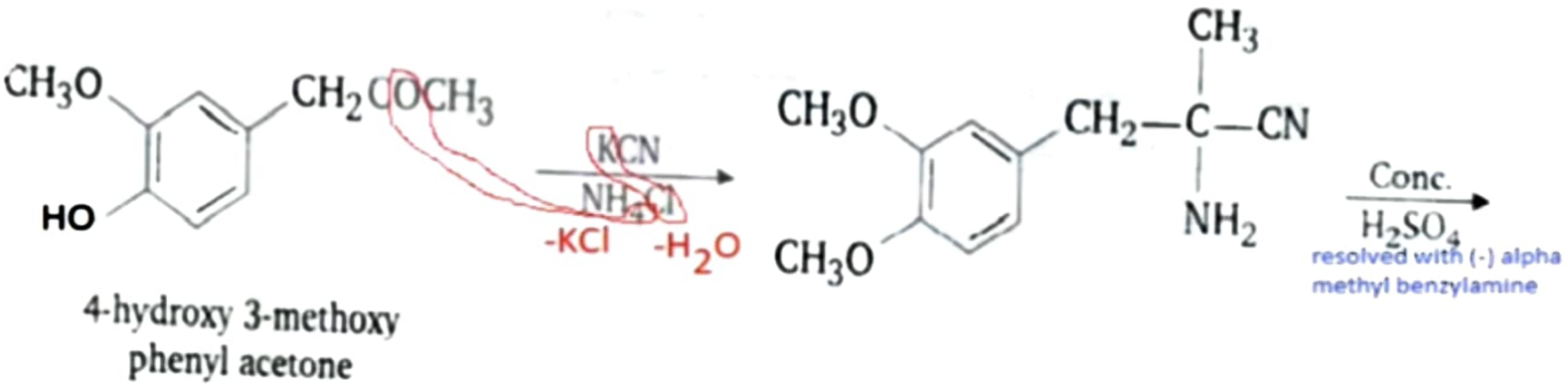


L – 3 (3,4 – dihydroxy phenyl) -2 – methyl – alanine ethyl ester hydrochloride

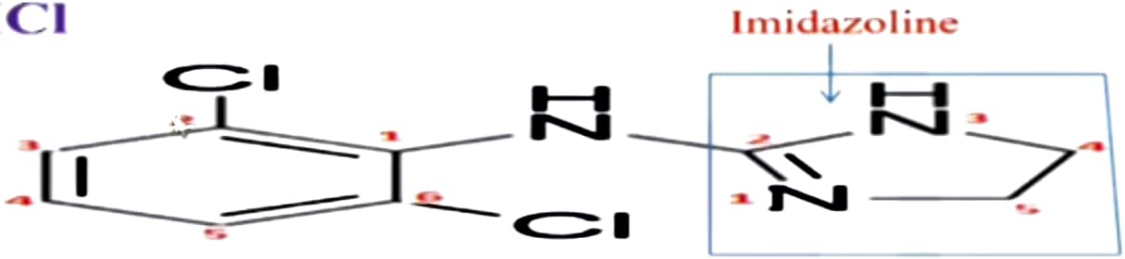
- **It is a central sympatholytic**
- **Phenyl alanine derivative**
- **Aromatic amino acid decarboxylase inhibitor with antihypertensive activity.**


Methyl dopa
Prodrug
Metabolized in CNS
Alpha methyl norepinephrine
Acts on alpha 2 adrenergic receptors
To inhibit the release of norepinephrine
Resulting in decreased sympathetic outflow from CNS &
Activation of para sympathetic outflow
Decreased blood pressure

Synthesis of Methyldopate HCl



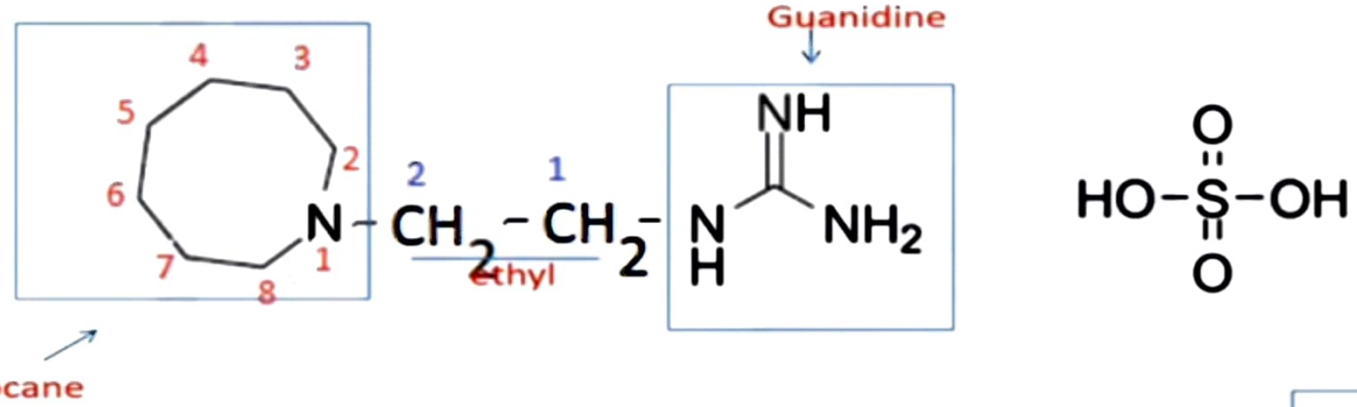
8. Clonidine HCl



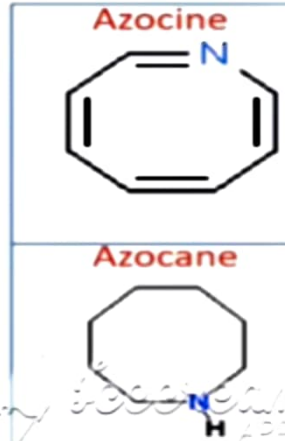
2 – (2,6- dichloro phenyl) imino imidazoline

- **First antihypertensive known to act on CNS**
- **Effective in the treatment of mild to severe hypertension**
- **It was synthesized as a derivative of known alpha sympathomimetic drugs Naphazoline & Tolazoline**
- **It is metabolized by the body to form two major metabolites p-hydroxy clonidine & its glucuronide.**
- **P-hydroxy clonidine does not cross BBB and has no hypotensive effect in humans**

9. Guanethidine monosulphate



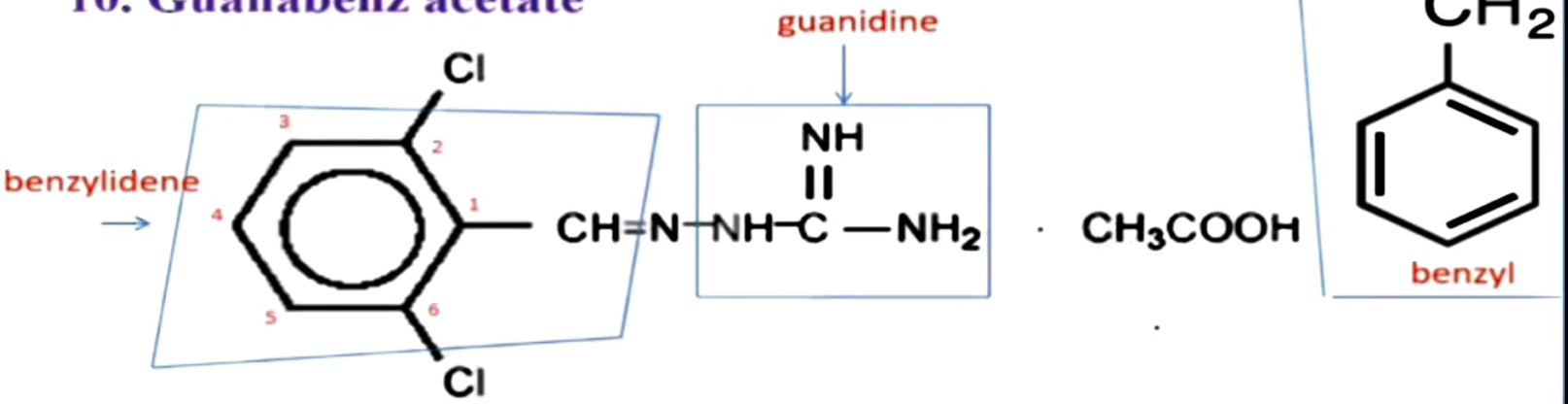
2-[2-(azocan-1-yl) ethyl] guanidine



- **Agent depleting neurotransmitter stores**
- **Reduces the release of catecholamines such as norepinephrine**

- Used as an antihypertensive,
- an adrenergic antagonists &
- Sympatholytic agent.
- As an antihypertensive agent, it acts by inhibiting selectively transmission in post ganglionic adrenergic nerves.
- It is believed to act mainly by preventing the release of NE at nerve endings &
- causes depletion of norepinephrine in peripheral sympathetic nerve terminals as well as in tissues.

10. Guanabenz acetate



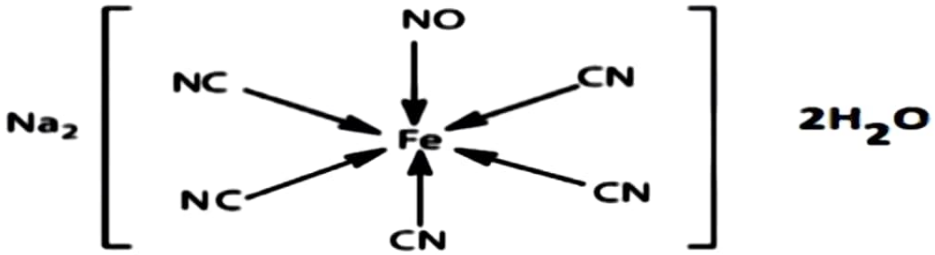
[(2,6 – dichloro benzylidene) amino] guanidine. monoacetate

- **Reduces the release of norepinephrine from the neuron when stimulated.**
- **The drug does not produce orthostatic hypotension.**

- Used as a step 2 agent
- Recommended for patients with high blood pressure who are not responsive to diuretic therapy alone.
- It is suitable for oral use.
- It is a zwitter ion & is not soluble enough for parenteral use. (The problem was solved by making the ester, leaving the amine free to form the water soluble HCl salt)
- It is supplied as a stable buffered solution, protected with antioxidants & chelating agents.

11. Sodium nitro prusside

$[\ Na_2Fe\,(CN)_5\,NO\ ]\ .\ 2\ H_2O$



- **Sodium nitro ferricyanide**
- **Disodium penta cyano nitrosyl ferrate (II)**
- **This differs from other vasodilators in that vasodilation occurs in both venous & arterial vascular beds**

Sodium nitroprusside

↓

breaks down in circulation to release nitric oxide (NO).

↓

By binding to oxyhaemoglobin to release cyanide, methaemoglobin and nitric oxide.

↓

NO activates guanylate cyclase in vascular smooth muscle and increases intracellular production of cGMP.

↓

cGMP activates protein kinase G

↓

which activates phosphatases

↓

which inactivate myosin light chains.

↓

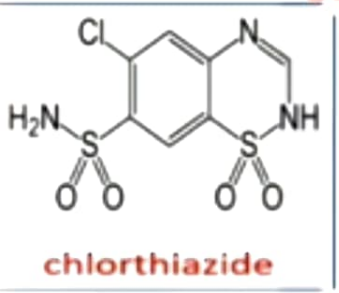
Myosin light chains are involved in muscle contraction.

↓

The end result is vascular smooth muscle relaxation,

↓

which allow vessels to dilate.

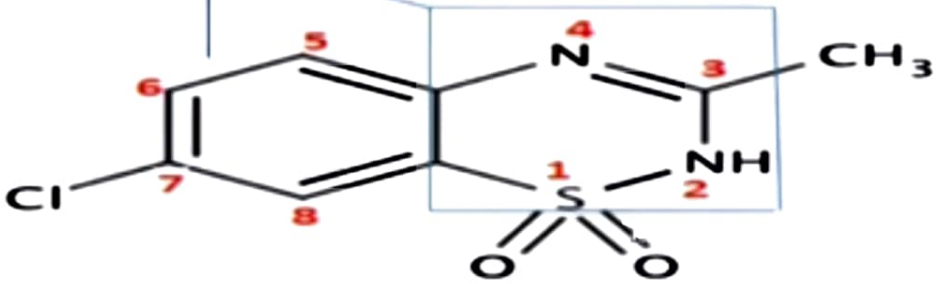


chlorthiazide

2H - 1,2,4-benzothiadiazine

12. Diazoxide

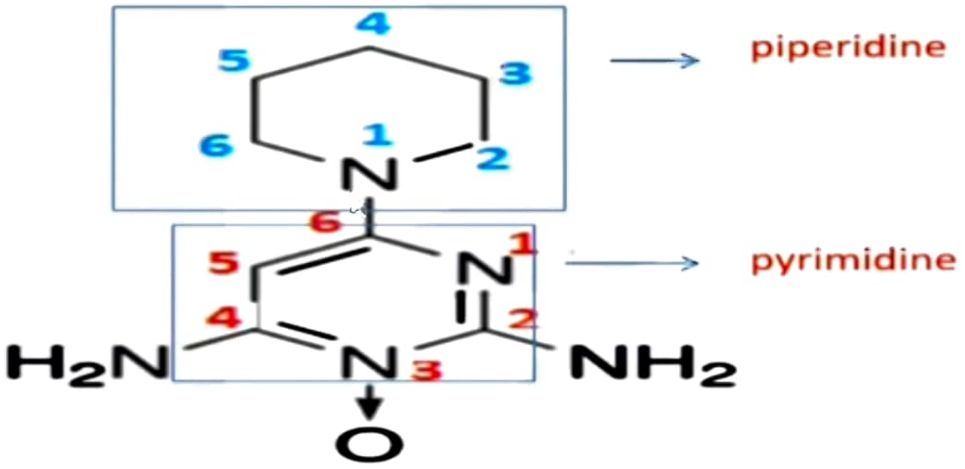
2H - 1,2,4-thiadiazine



7- chloro- 3- methyl – 2H – 1,2,4- benzothiadiazin -1,1- dioxide

- **Available as a sodium salt**
- **This is a des - sulfamoyl analogue of the benzothiadiazine diuretics**
- **Has a close structural similarity to chlorthiazide.**
- **(It was developed intentionally to increase the antihypertensive actions of the thiazides and to minimize the diuretic effect)**

13. Minoxidil



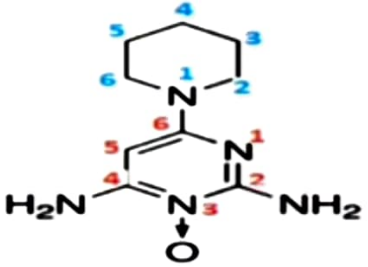
2,4 – diamino – 6- (piperidin-1-yl) pyrimidine-3-oxide

Note:

The triazines were inactive in humans because of the inability to form N-oxide metabolites. This led to the discovery of minoxidil

It is the only direct acting vasodilator that requires metabolic activation to produce its antihypertensive effects.

Minoxidil

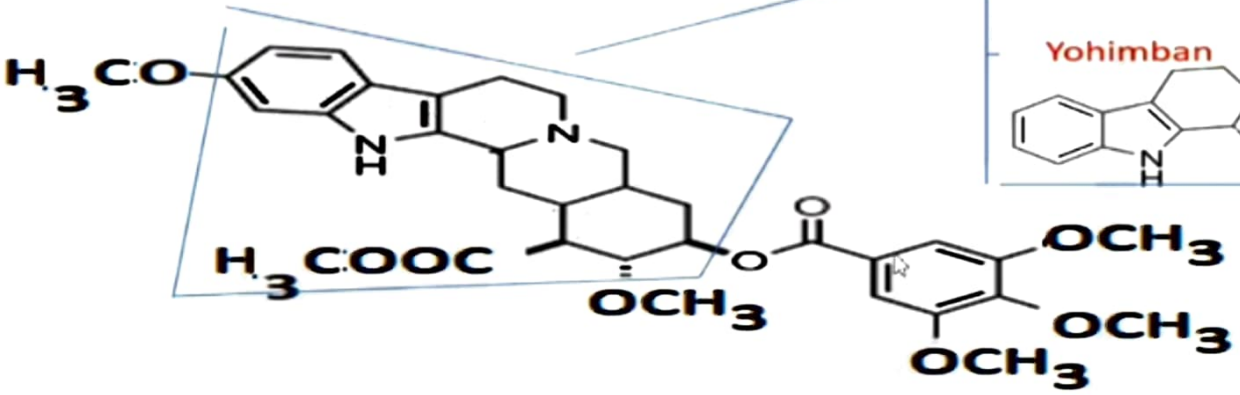


sulfotransferase

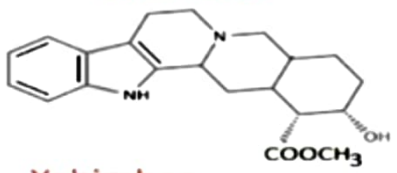
Minoxidil sulphate

- Used for severe hypertension i.e. difficult to control with other antihypertensive agents.
- It has vasodilatory effects.
- It causes sodium & water retention and may require coadministration with a **diuretic.**
- Causes reflux tachycardia which can be controlled by the use of a **beta adrenergic blocking** agent.
- To treat **alopecia androgenitica** (male pattern baldness)
- Topical minoxidil -increase cutaneous blood flow, which may stimulate **hair growth.**

14. Reserpine



Yohimbine

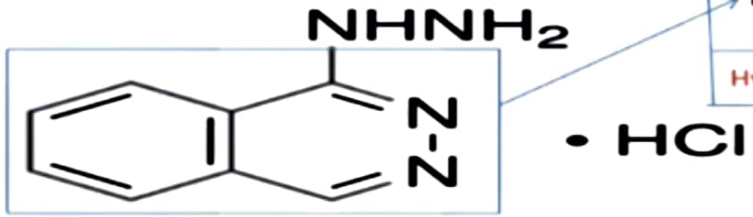


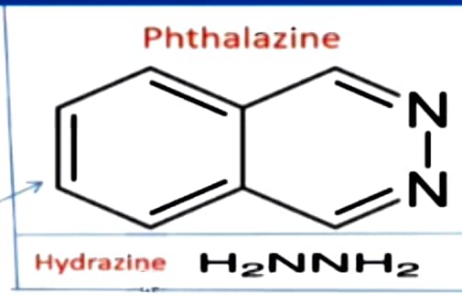
Yohimban

- Alkaoid, derived from the roots of Rauwolfia serpentina & vomitoria
- Adrenergic uptake inhibitor with antihypertensive effects
- This compound belongs to the class of organic compounds known as yohimbine alkaloids.
- These are alkaloids containing the pentacyclic yohimban skeleton.

15. Hydralazine HCl

1- hydrazino phthalazine monohydrochloride





- Treatment of moderate to severe hypertension.
- Often used in conjunction with less potent antihypertensive agents.
- It has a unique property of increasing renal blood flow, an important consideration in patients with renal insufficiency.
- More effective clinically when coadministered with drugs that antagonize adrenergic transmission (eg., Beta adrenergic antagonists, reserpine, guanethidine monosulphate, methyl dopa and clonidine HCl)
- When given with **diuretics**, it is useful in the treatment of **CHF**.
- Combines with **isosorbide** for African Americans with **CHF**.