ANTIHYPERTENSIVE AGENTS

(Unit Objective - Student should able to understand the Chemistry of various classes of antihypertensive agents.)

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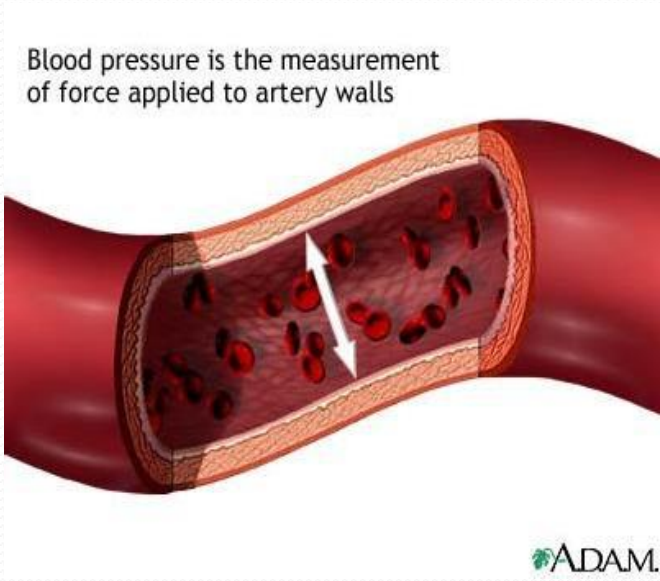
HYPERTENSION

It is defined as a physiologic condition where there is an increase in the arterial blood pressureabove normal.

- Normal B.P is **120/80** mm Hg.

- An individual is hypertensive when B.P is **>140/90** mm Hg.



Hypotension may be defined as a physiologic state where there is a

↓ In B.P than the normal.

An individual is said to be hypotensive when the B.P is< than $\frac{90}{60}$ mm of hg.

HYPERTENSION IS DEVIDED IN TO 2 TYPES:

1.PRIMARY HYPERTENSION OR ESSENTIAL HYPERTENSION

1.SECONDARY HYPERTENSION OR MALIGNANT HYPERTENSION.

In PRIMARY OR ESSENTIAL HYPERTENSION In majority of casses where etiology Is unknown cause and is known as primary hypertension.

The following factors may contribute to elevate of B.P

•Dietary intake of more sodium and less potassium.

In some cases primary hypertension may be herediatary.

Advancement of age.

Decreased vascular synthesis of Nitric oxide (No)(is useful in vasodialatation)

In SECONDARY HYPERTENSION where etiology can be identified.

Secondary hypertension is due to

¬Renal disease (kidney disorders (Chronic glomerular nephritis.)

¬Adrenal disease (endocrine disorders)

Pheochromocytoma (tumour on adrenal medulla) which secretes excessive catechol amines like adrenaline and nor adrenaline)

Hyper aldosteronism.

¬Muscular disorders:

Contraction (narrowing)of aorta.

Renal artery stenosis(narrowing of artery)

Toxemia of pregnancy (presence of toxins in the blood stream)

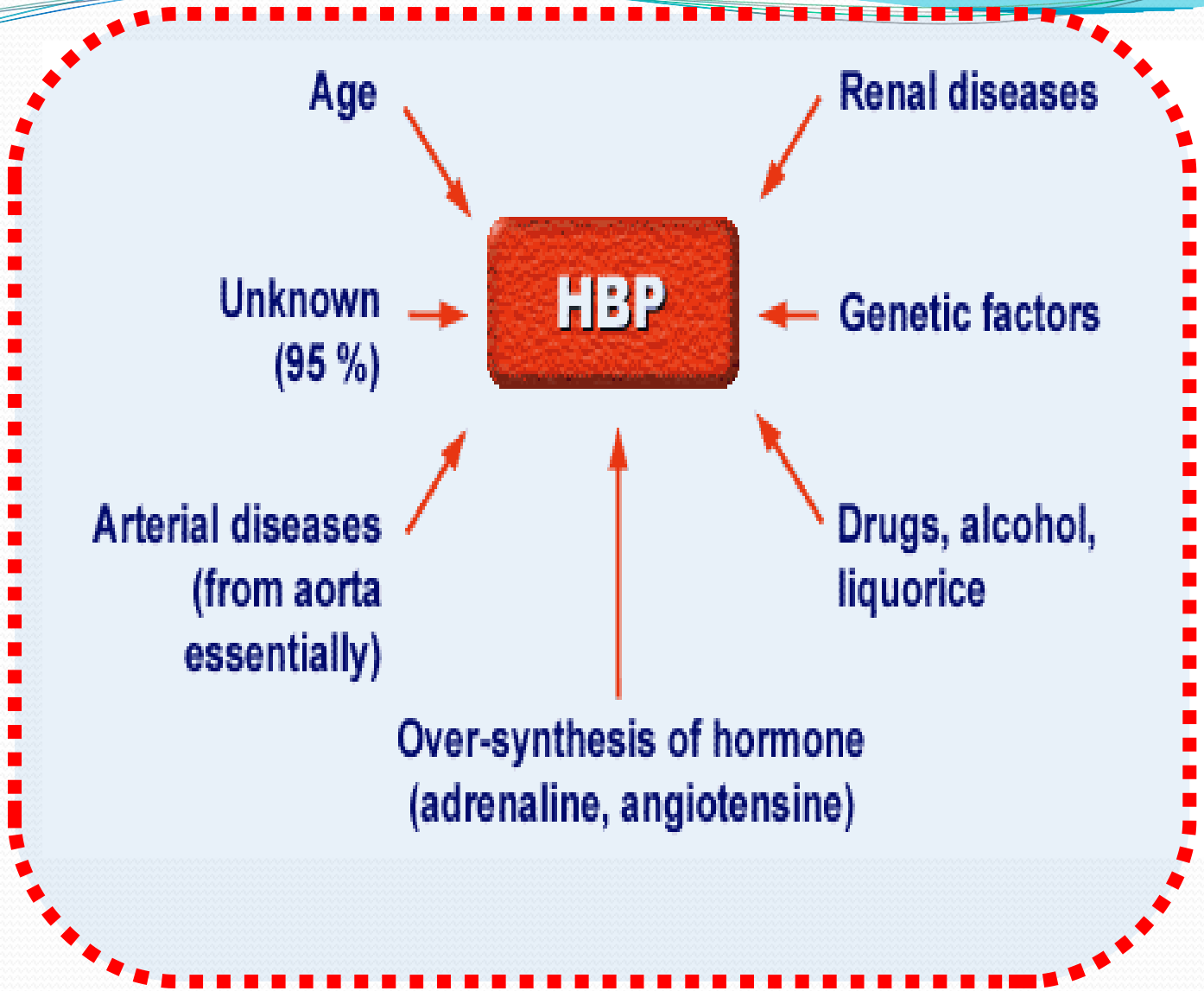
Encephalitis(inflammation of the briain)

Increased intra cranial pressure.

Thyrotoxicosis(toxic condition caused by over activity of thyroid gland)

oral contraceptives.

CAUSES OF HYPERTENSION



Classification (category of Hypertension)	Systolic Blood Pressure (mmHg)		Diastolic Blood Pressure (mmHg)
Normal (B.P)	120	and	80
Prehypertension	121-139	or	81-89
Stage 1 (mild) hypertension	140-159	or	90-99
Stage 2 hypertension (moderate)	160-179	or	100-109
Stage III (severe)	180-209		110-119.
Stage iV (very severe)	>210		>120.

Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42(6):1206–1252.

On etiological basis hypertension is divided into two types

1.Primary hypertension

A definite cause is not known in primary hypertension.

Following factors may contribute to elevation of B.P.

- Dietary intake of more sodium and less potassium.
- Decrease in vascular synthesis of nitric oxide responsible for vasodilation.
- In some cases it may be heriditary.

2.Secondary Hypertension

In some cases Hypertension may be secondary to other diseases like

a.Endocrine disorders

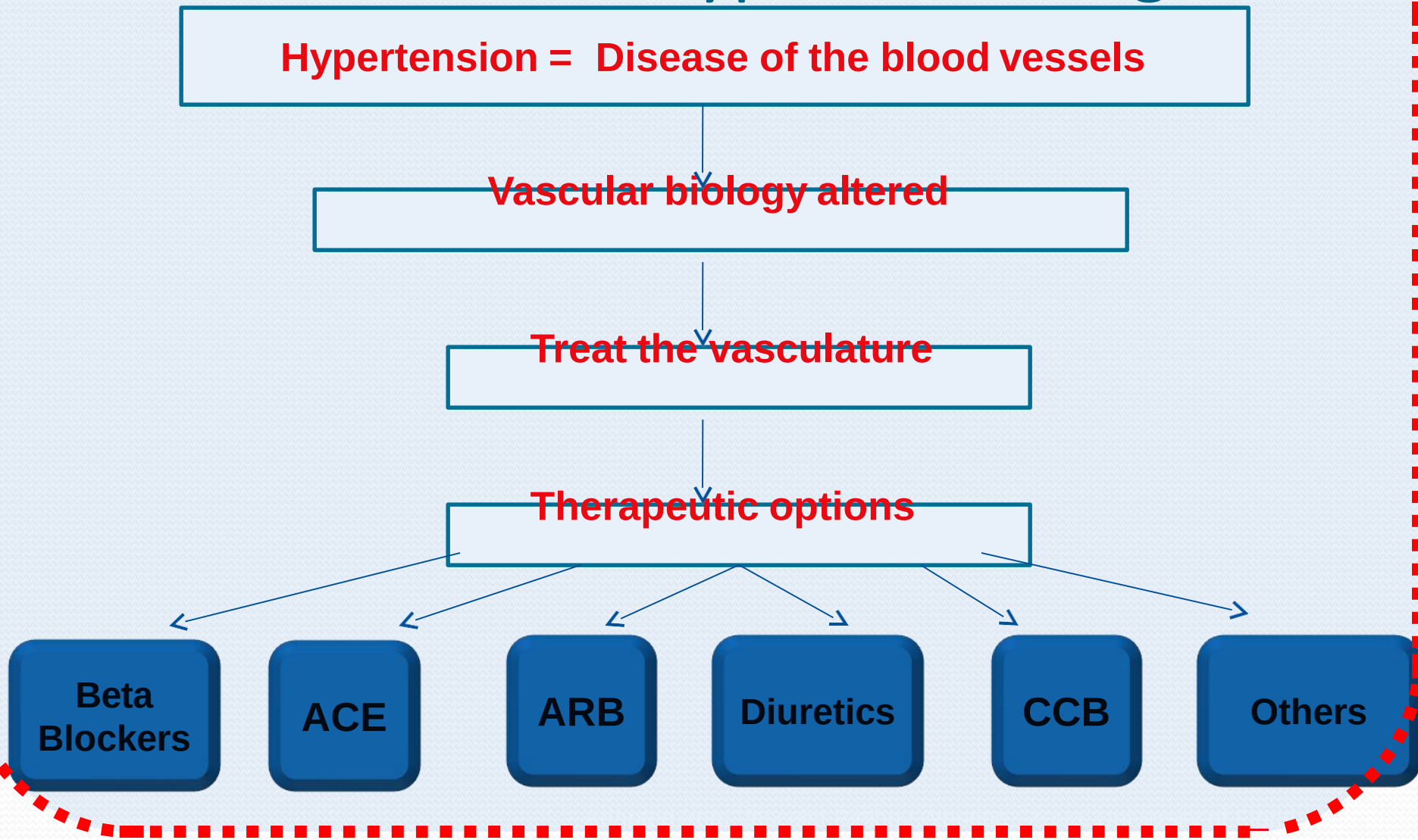
- Pheochromocytoma
- Hyperaldosteronism

b.Chronic glomerular nephritis

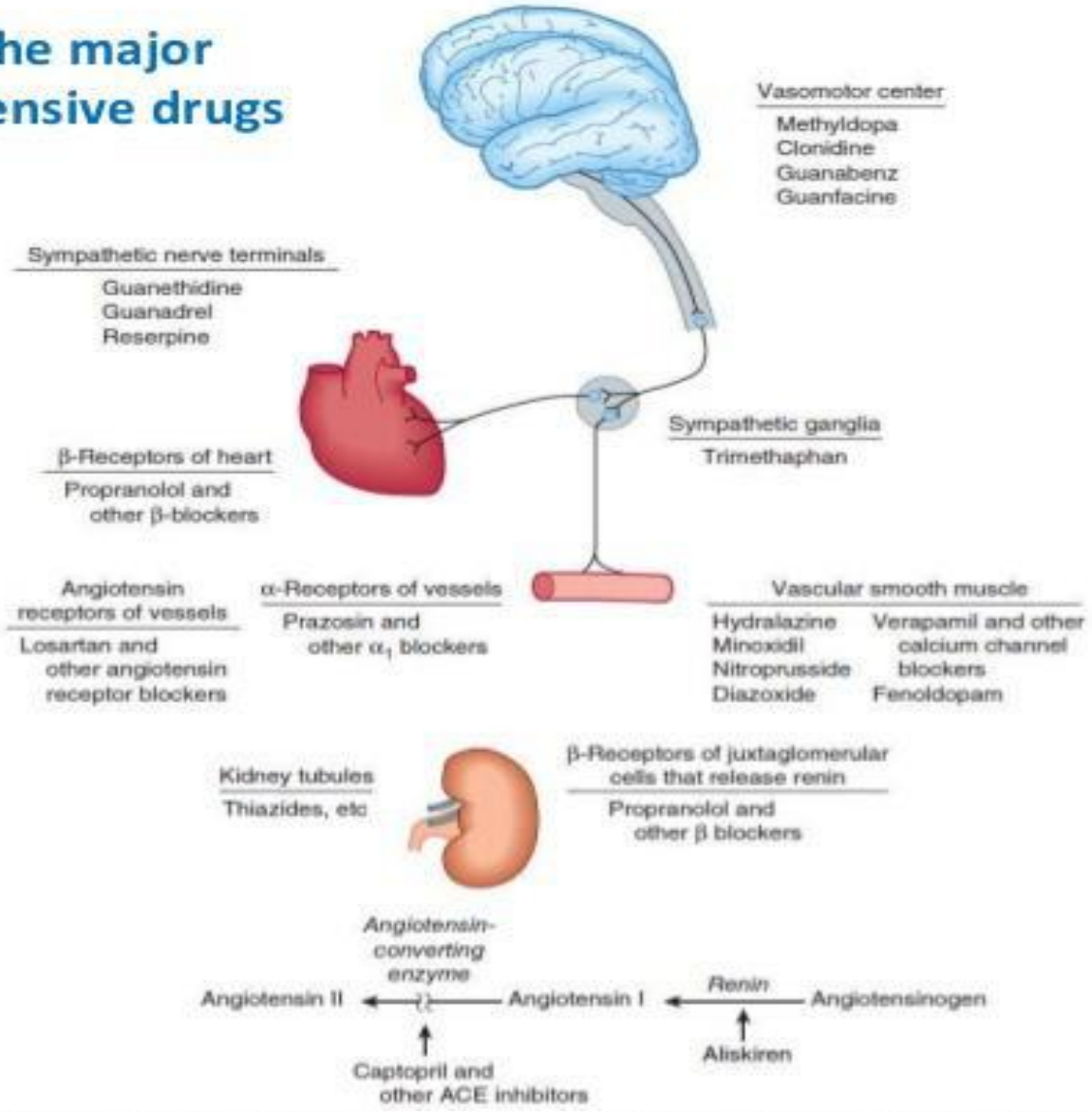
c.Muscular disorders

- Contraction of aorta
- Renal artery stenosis

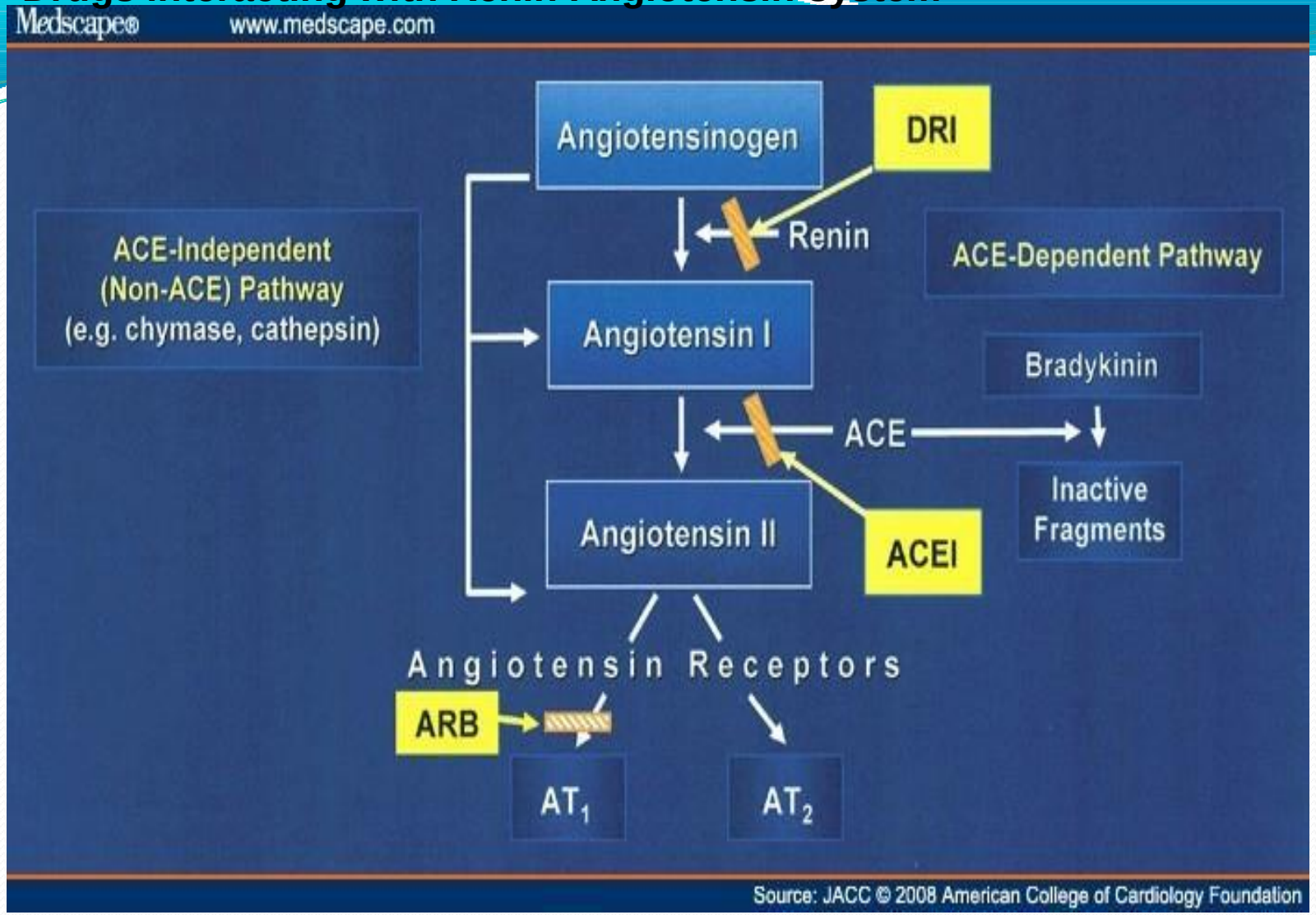
Classification of antihypertensive agents



Sites of action of the major classes of antihypertensive drugs

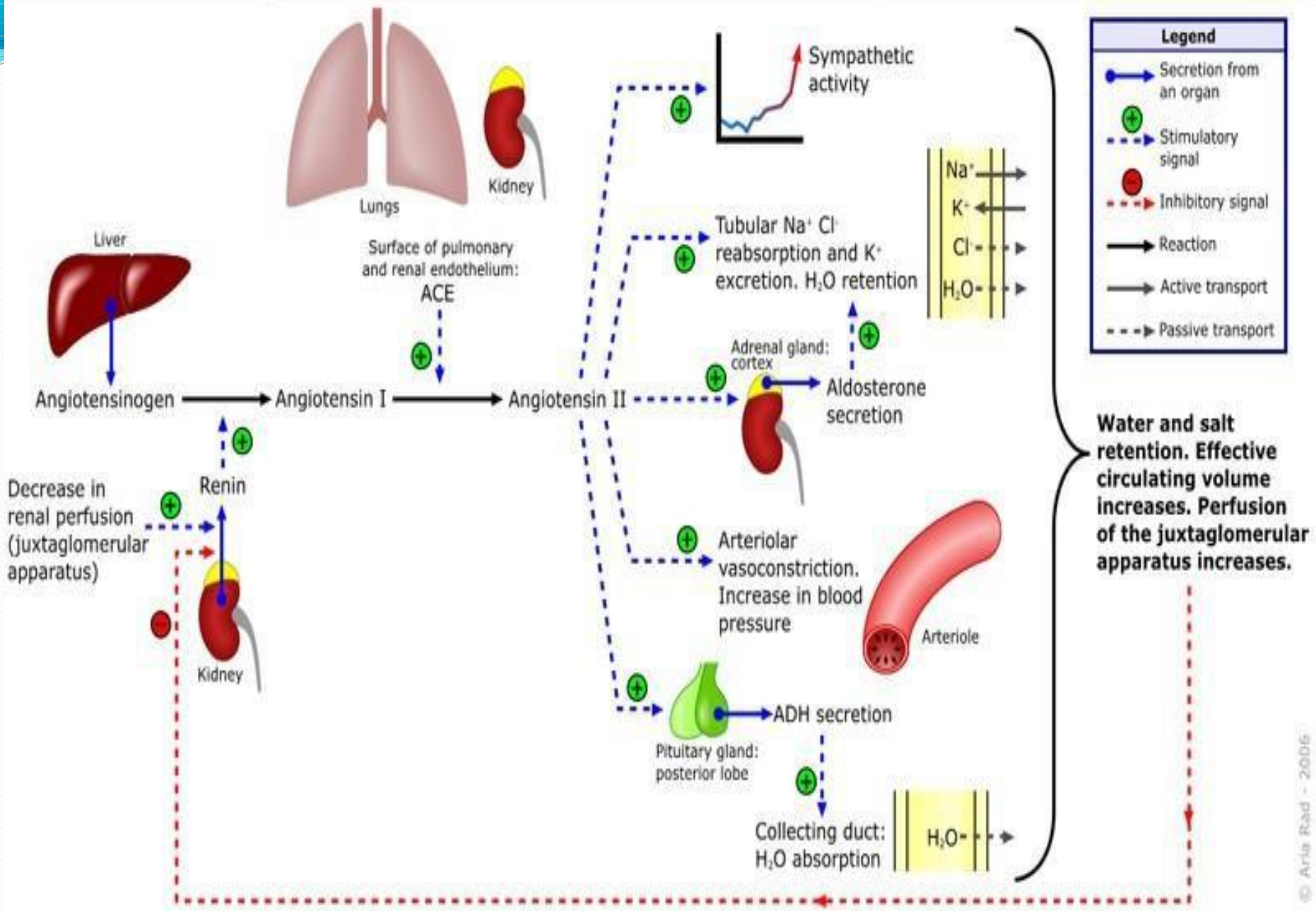


Drugs interacting with Renin-Angiotensin system

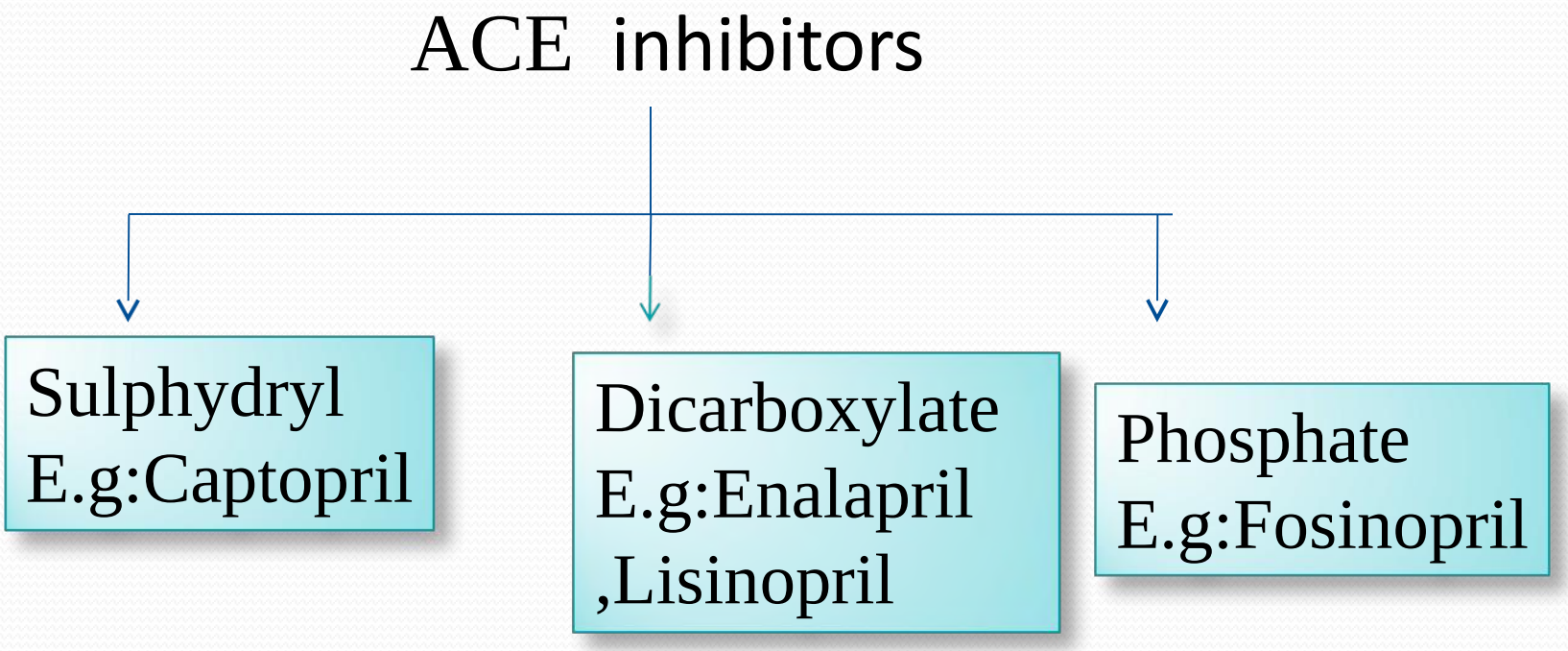


The Renin-Angiotensin Cascade and the 3 Available Approaches to Pharmacologic Inhibition of Production or Action of Angiotensin II. Direct renin inhibitors (DRI), angiotensin-converting enzyme inhibitors (ACEI), and angiotensin (AT) type 1 receptor blockers (ARB).

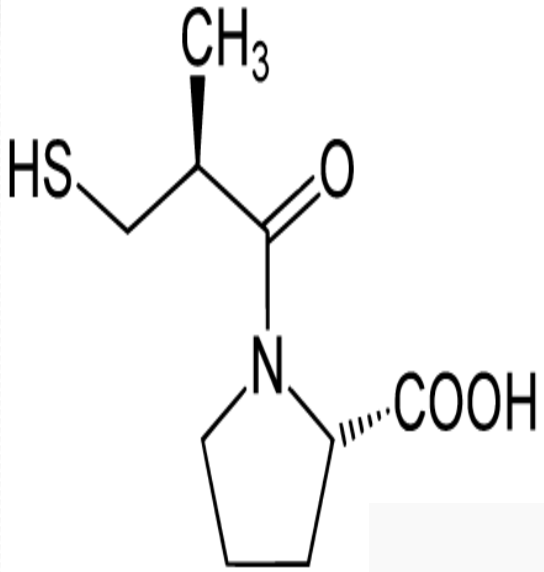
Renin-angiotensin-aldosterone system



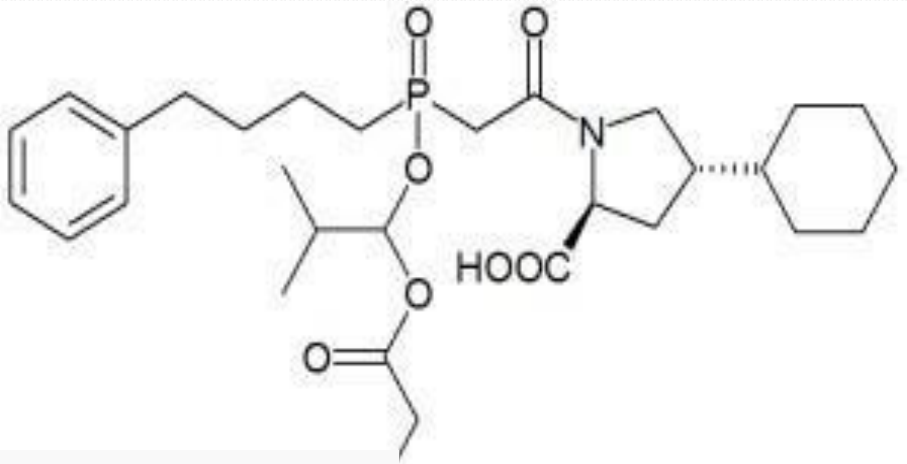
Depending on chemical classification

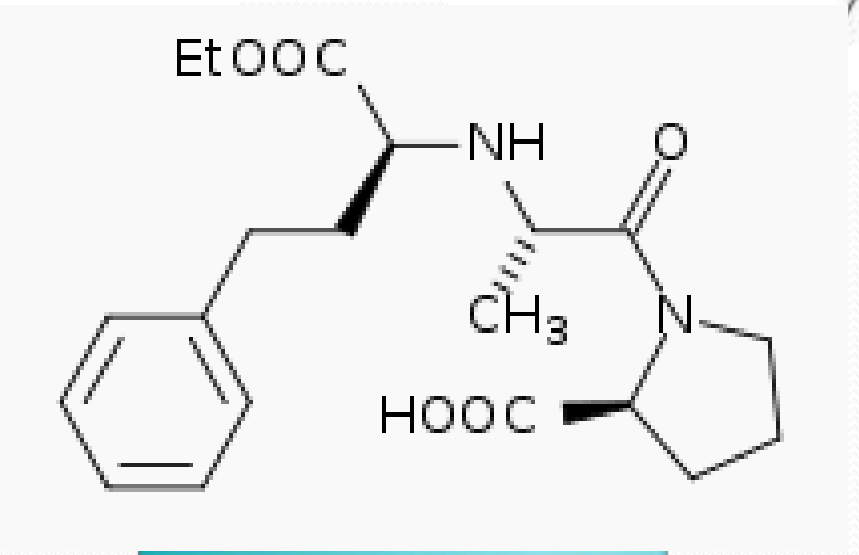


CAPTOPRIL

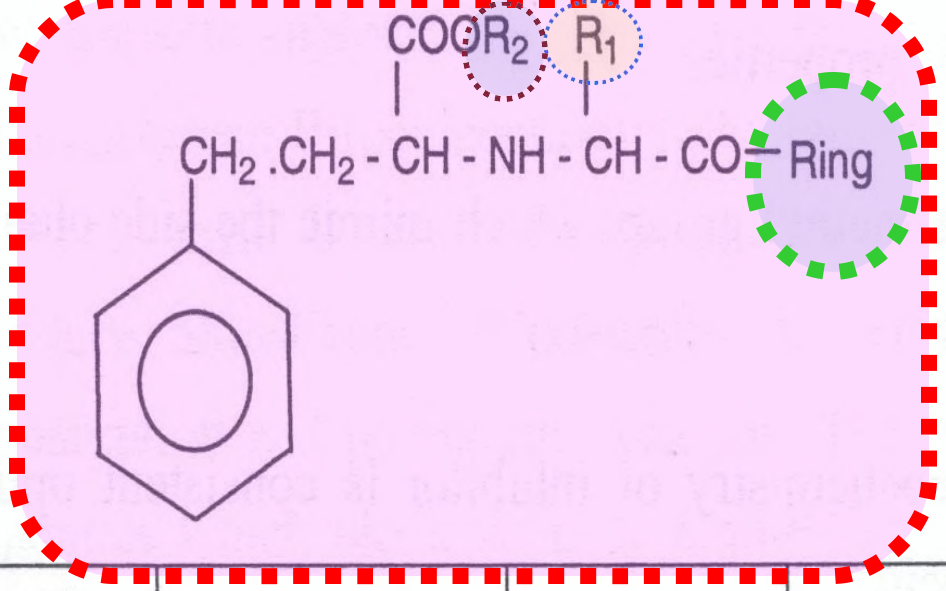


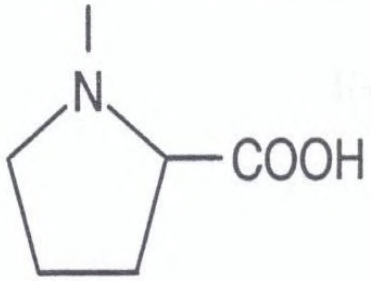
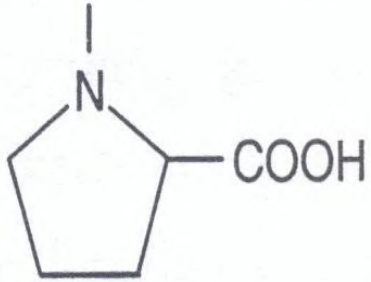
FOSINOPRIL

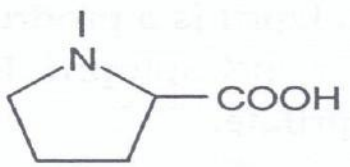
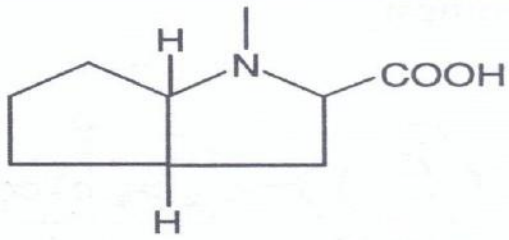
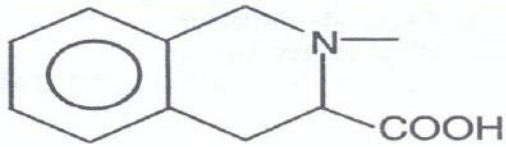
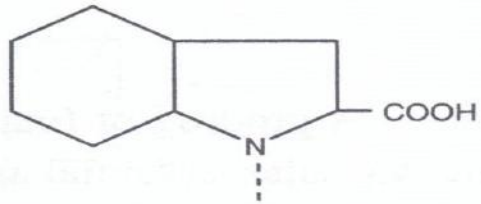
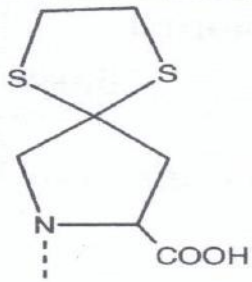
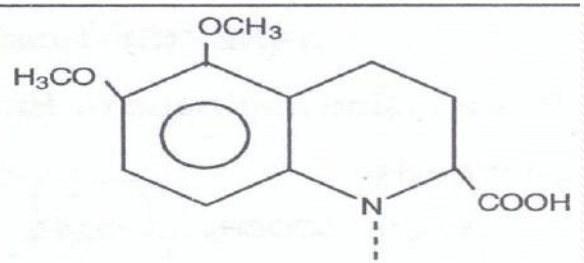




ENALAPRIL



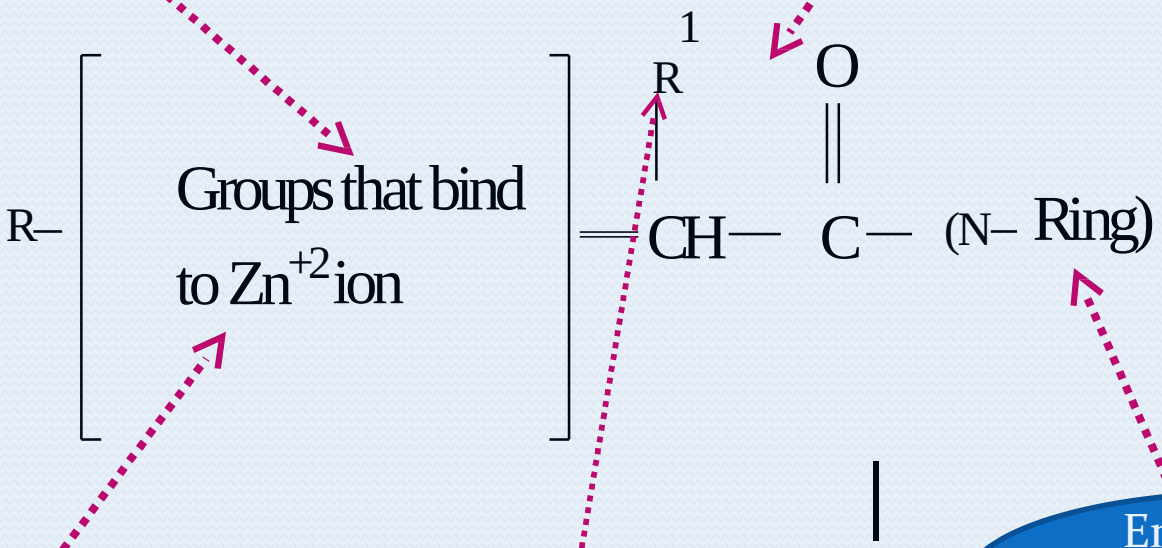
S.No.	Compound Name	R_1	R_2	Ring
1.	Enalapril	$-CH_3$	$-C_2H_5$	
2.	Enalaprilate	$-CH_3$	$-H$	

3.	Lisinopril	$-(CH_2)_4\,NH_2$	$-H$	
4.	Ramipril	$-CH_3$	$-C_2H_5$	
5.	Quinapril	$-CH_3$	$-C_2H_5$	
6.	Trandolapril	$-CH_3$	$-CH_2CH_3$	
7.	Sprapril	$-CH_3$	$-CH_2CH_3$	
8.	Moexipril	$-CH_3$	$-CH_2CH_3$	

Structure activity relationship[SAR]

Sulfhydryl group leads to shorter duration of action

Methyl group resembles side chain of alanine

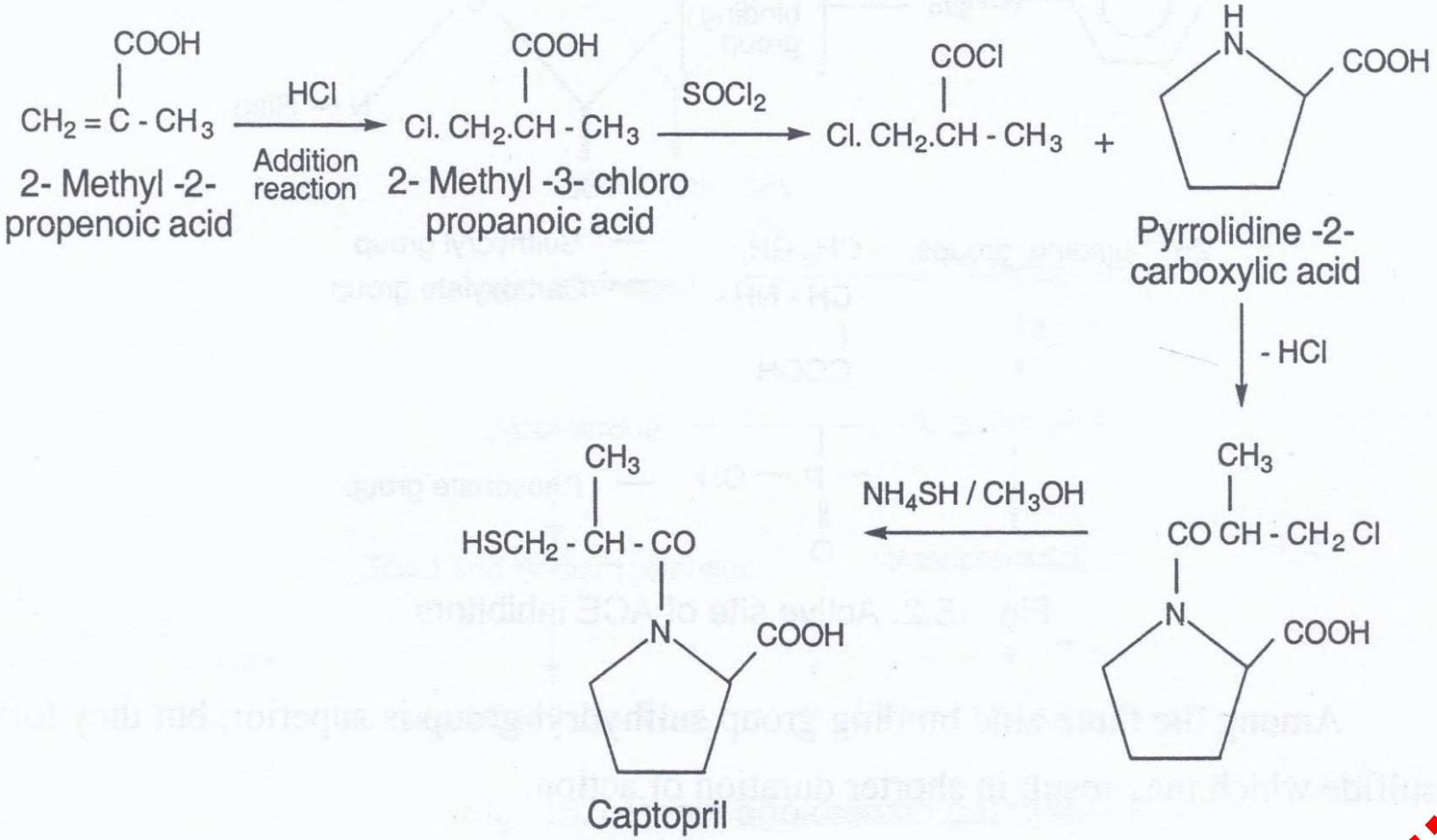


Essential for stabilisation

n-butylamine in dicarboxylate containing componds orally active.

Enhances the potency of the compound

Synthesis


COOH
CH2 = C - CH3
2- Methyl -2- propenoic acid
HCl
Addition reaction
COOH
Cl. CH2.CH - CH3
2- Methyl -3- chloro propanoic acid
SOCl2
COCl
Cl. CH2.CH - CH3
+
H
N
COOH
Pyrrolidine -2- carboxylic acid
- HCl
CH3
CO CH - CH2 Cl
N
COOH
NH4SH / CH3OH
CH3
HSCH2 - CH - CO
N
COOH
Captopril

Mechanism of action

They inhibit ACE which is involved in the conversion of AngI to Ang II.

- Which is a potent vasoconstrictor.

Adverse effects

- Dry cough
- Dysgysia
- Skin rashes
- Foetal toxicity

Uses

- First choice in treatment of Hypertension.
- In left ventricular failure
- In diabetic nephropathy
- In myocardial infarction

ACE Inhibitors

CAPTOPRIL:-

Mechanism of Action:

It decreases angiotensin II and increase bradykinin levels. Vasodilation is a result of decreased vasocontriction from diminished levels of angiotensin II and enhanced vasodilation from increase bradykinin. By reducing circulating angiotensin II levels, ACE inhibitors also decrease the secretion of aldosterone, resulting in decreased sodium and water retention.

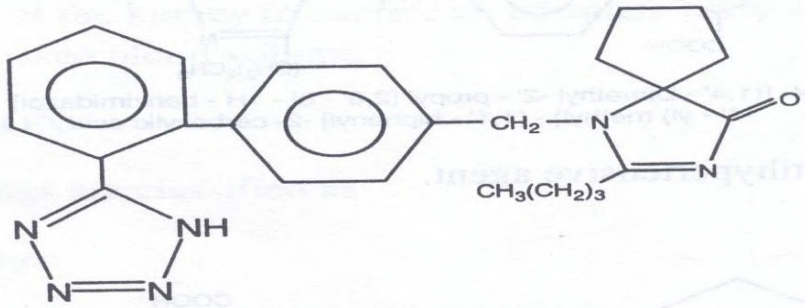
Captopril, 1-[(2*S*)-3-mercapto-2-methyl-1-oxopropionyl]proline (Capoten), blocks the conversion of angiotensinI to angiotensin II by inhibiting the convertingenzyme. The rational development of captopril as an inhibitorof ACE was based on the hypothesis that ACE and carboxypeptidaseA functioned by similar mechanisms. It was noted that *d*-2-benzylsuccinic acid7 was a potent inhibitor of carboxypeptidase A, but not ACE. By use of this small

ACE inhibitors

- Benazepril (Lotensin®)
- Captopril (Capoten®)
- Fosinopril (Monopril®)
- Lisinopril (Prinivil®,Zestril®)
- Enalapril (Vasotec®)
- Quinapril (Accupril®)
- Ramipril (Altace®)
- Trandolapril (Mavik®)

Angiotencin receptor Antagonists

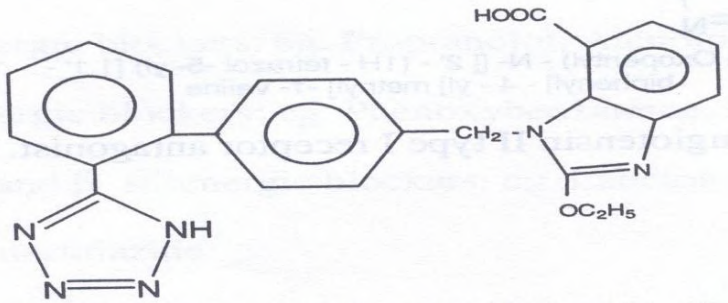
B. Irbesartan



2- Butyl -3-{[2' (1H - tetrazol -5- yl) [1,1' - biphenyl] -4 - yl] methyl} 1,3 - diazaspiro [4,4] non -1- en -4- one

Use: It is a angiotensin II type I receptor antagonist.

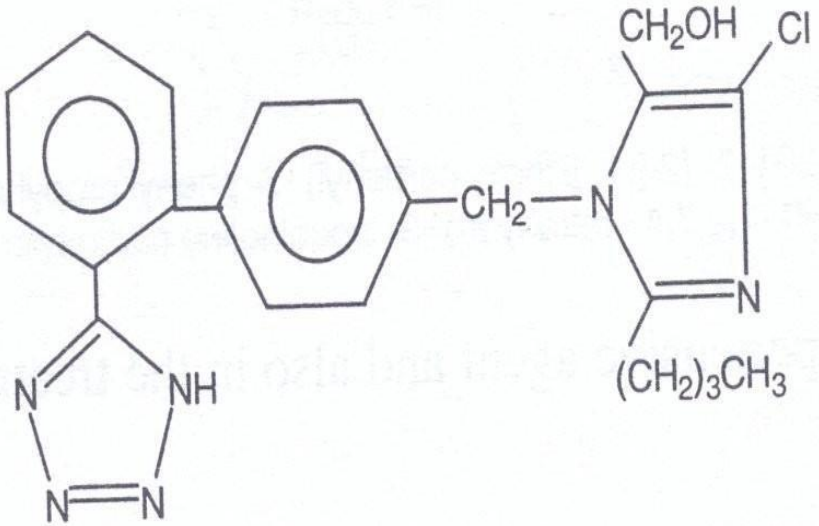
C. Candesartan



(+) -1- {[2' (1H - tetrazol -5- yl) [1,1' - biphenyl] -4- yl] methyl} -1H benzimidazole -7- carboxylic acid

Use: It is a angiotensin II type I receptor antagonist, used as antihypertensive agent.

A. Losartan



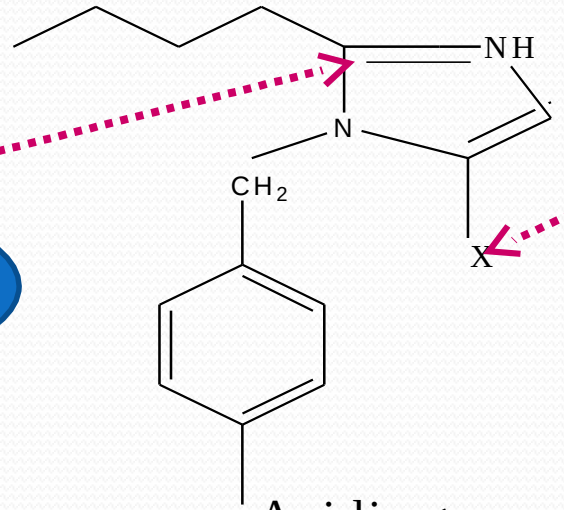
2- Butyl -4- chloro -5- hydroxy methyl -1- {[2'(1H - tetrazol - 5- yl) - biphenyl -4 - yl] methyl} imidazole

LOSARTAN:-

It is a competitive antagonist and inverse agonist, it is more selective for AT1 than for AT2 recetor it does not block any other receptor or ion channel except thromoxane A2 receptor .

Other action of ARBs blocker are vasocontriction, central and peripheral sympathetic stimulation, release of aldosterone and Adr from adrenals, renal action promoting salt and water reabsorption, central action like thirst, vasopressin release and growth promoting action on heart and blood vessels.

STRUCTURE ACTIVITY RELATIONSHIP[SAR]



Require to mimic the His side chain of Angiotensin-II

Substituted with ketones,cooH forms Ionic,dipole-dipole helps drug to interact with AT1

Essential for activity to mimic Asp1 carboxylate of Ang-II

Mechanism of action

They act by blocking the Angiotensin I which regulates the effects of angiotensin on B.P,heart and sodium and water balance.

Adverse effects

- ♣Hyperkalaemia
- ♣Angioedema
- ♣Foetal toxicity
- ♣Gidisturbances

Uses

In treatment of hypertension as an alternative to ACE Inhibitors.

Angiotensin receptor blockers

- Valsartan (Diovan®)
- Telmisartin (Micardis®)
- Candesartan (Atacand®)
- Losartin (Cozaar®)
- Irbesartin (Avapro®)

Diuretics

- **Diuretics ("water pills") increase the kidneys' excretion of salt (sodium) and water, decreasing the volume of fluid in the bloodstream and the pressure in the arteries. Diuretics are the oldest and most studied antihypertensive agents.**

CLASSIFICATION

Thiazide

chlorthalidone, hydrochlorothiazide (HCTZ), indapamide, metolazone

Loop

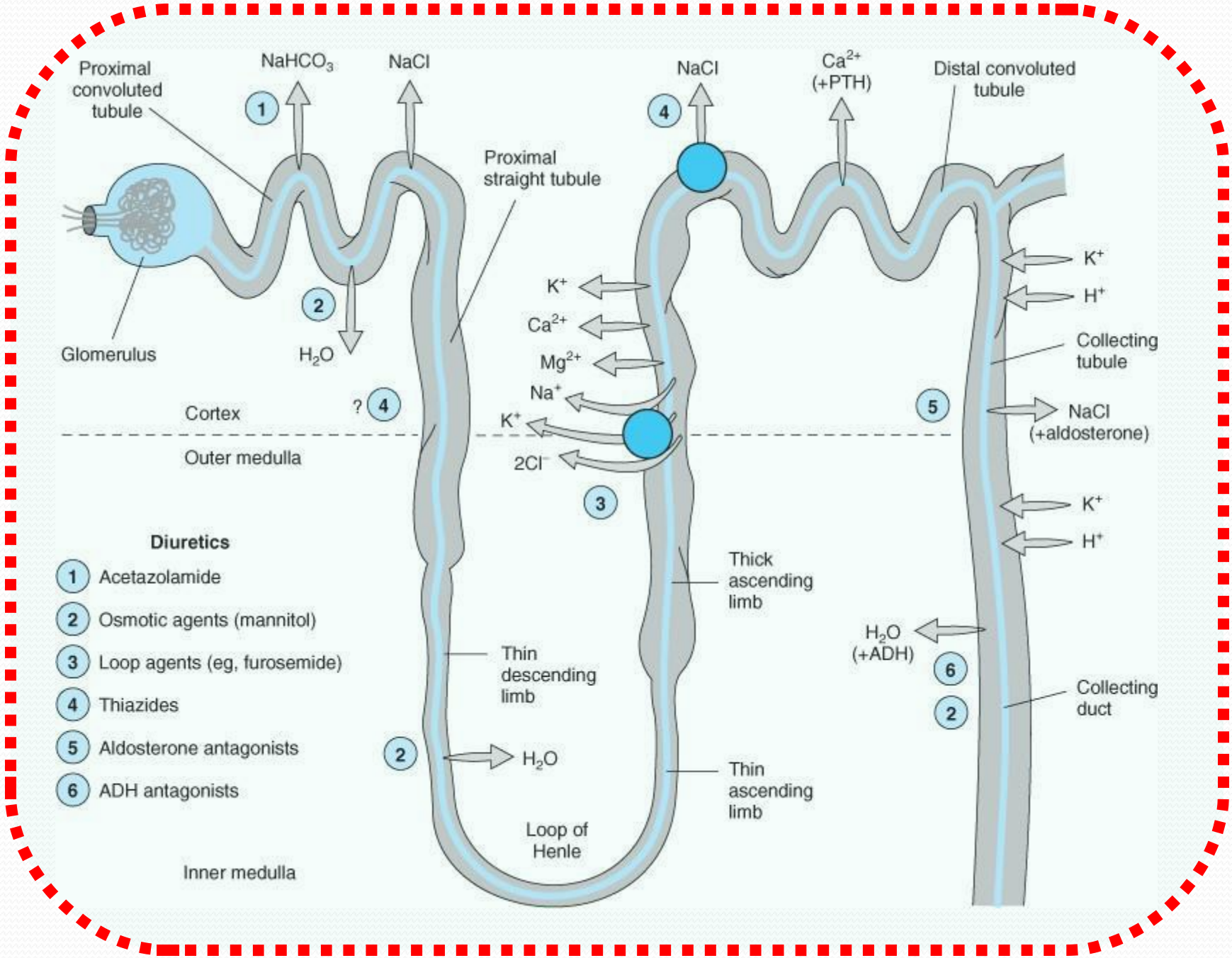
bumetanide, furosemide, torsemide

Potassium-sparing

amiloride, triamterene

Aldosterone antagonists

eplerenone, spironolactone


Proximal convoluted tubule
NaHCO3
NaCl
1
Glomerulus
2
H2O
Cortex
?
4
Outer medulla
Proximal straight tubule
NaCl
4
Ca2+ (+PTH)
Distal convoluted tubule
K+
Ca2+
Mg2+
Na+
K+
2Cl−
3
Thick ascending limb
Thin descending limb
2
H2O
Thin ascending limb
Loop of Henle
Inner medulla
K+
H+
Collecting tubule
5
NaCl (+aldosterone)
K+
H+
H2O (+ADH)
6
2
Collecting duct
Diuretics
1 Acetazolamide
2 Osmotic agents (mannitol)
3 Loop agents (eg, furosemide)
4 Thiazides
5 Aldosterone antagonists
6 ADH antagonists

Thiazide Diuretics

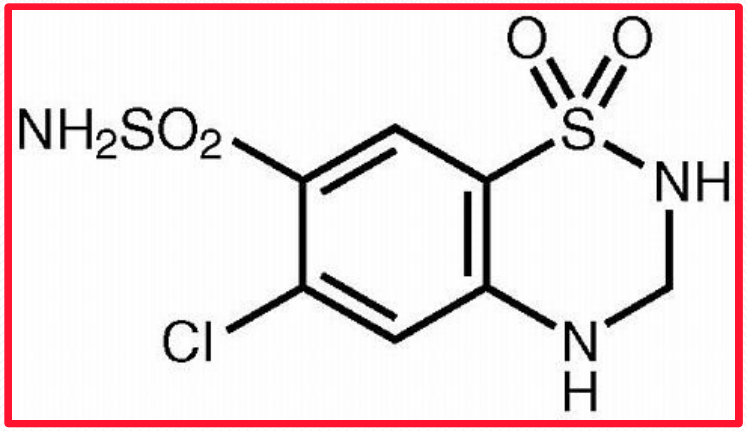
- Dose in morning to avoid nocturnal diuresis
- More effective antihypertensives than loop diuretics

. Chlorthalidone 1.5 to 2 times as potent as HCTZ

Adverse effects

- hypokalemia
- hypomagnesemia
- hypercalcemia
- sexual dysfunction
- lithium toxicity with

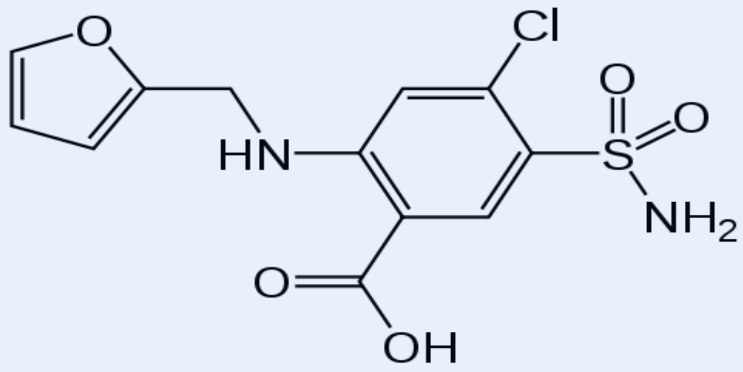
Concurrent adminstration.



Loop Diuretics

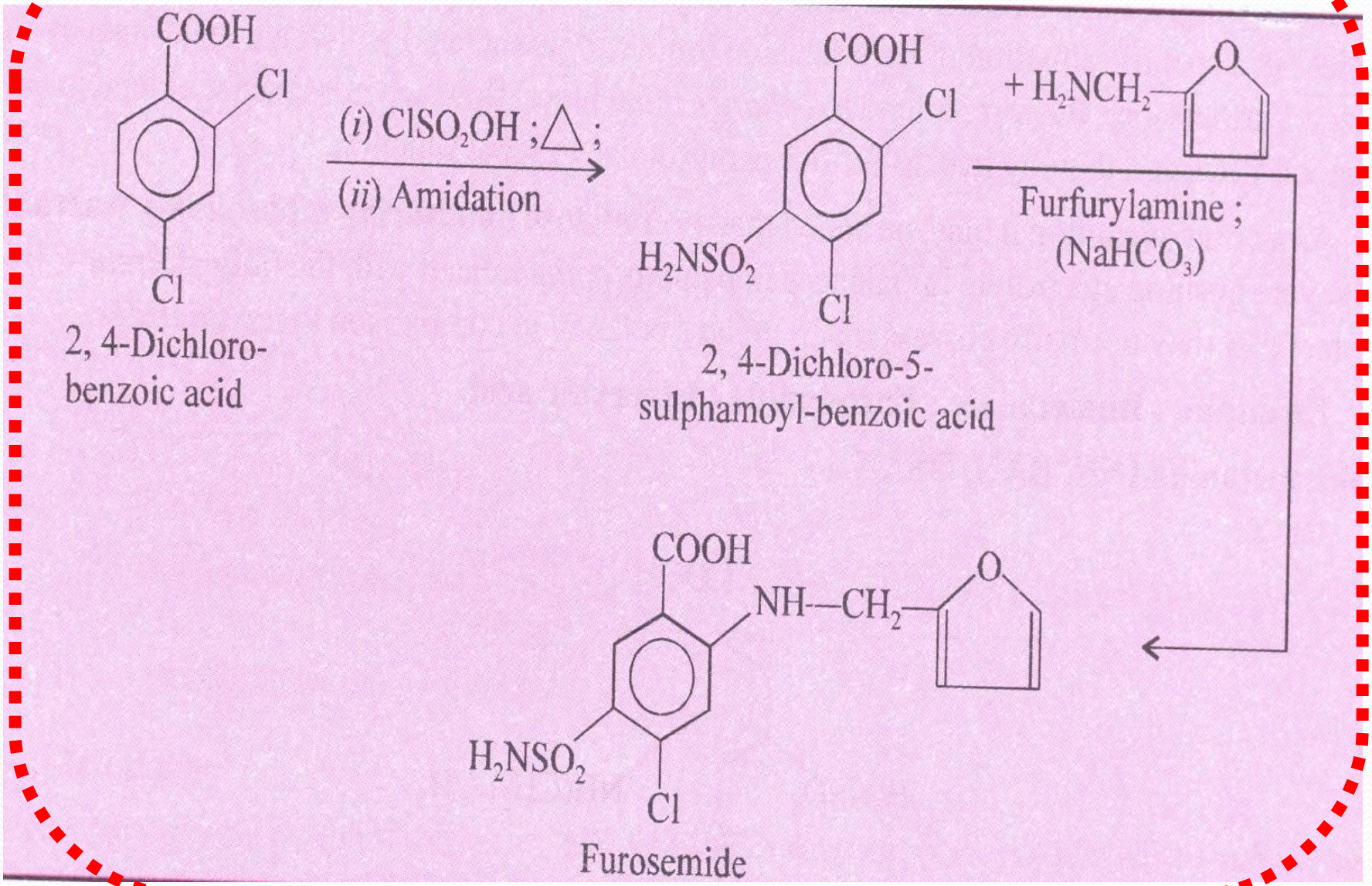
- Dose in AM or afternoon to avoid nocturnal diuresis
- Higher doses may be needed for patients with severely decreased glomerular filtration rate or heart failure

Furosemide



Adverse effects:

- hypokalemia,
- hypomagnesemia,
- hypocalcemia


COOH
Cl
Cl
(i) ClSO2OH ; △ ;
(ii) Amidation
2, 4-Dichloro-
benzoic acid
COOH
Cl
H2NSO2
Cl
2, 4-Dichloro-5-
sulphamoyl-benzoic acid
+ H2NCH2
O
Furfurylamine ;
(NaHCO3)
COOH
NH—CH2
O
H2NSO2
Cl
Furosemide

Mechanism of Action

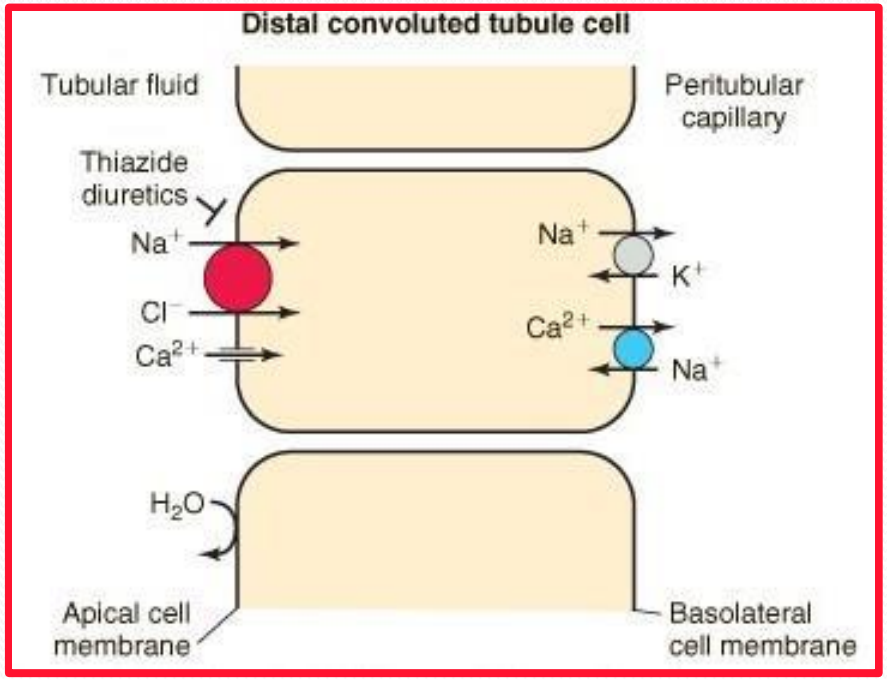
inhibit Na+ and Cl- transporter in distal convoluted tubules

increased Na+ and Cl- excretion

weak inhibitors of carbonic anhydrase, increased HCO3- excretion

increased K+/Mg2+ excretion

decrease Ca2+ excretion



Potassium-sparing Diuretics

- Dose in AM or afternoon to avoid nocturnal diuresis
- Generally reserved for diuretic-induced hypokalemia patients
- Weak diuretics, generally used in combination with thiazide diuretics to minimize hypokalemia

Adverse effects:

- may cause hyperkalemia especially in combination with an ACE inhibitor, angiotensin-receptor blocker or potassium supplements
- avoid in patients with diabetes

Aldosterone antagonists

- Dose in AM or afternoon to avoid nocturnal diuresis

- Adverse effects:
  - may cause hyperkalemia especially in combination with ACE inhibitor, angiotensin-receptor blocker or potassium supplements
  - Gynecomastia: up to 10% of patients taking spironolactone

Calcium channel blockers

Depending upon their chemical structure

Diphenylalkylamines

Eg:Verapamil

Benzothiazepines

Eg:Diltiazem

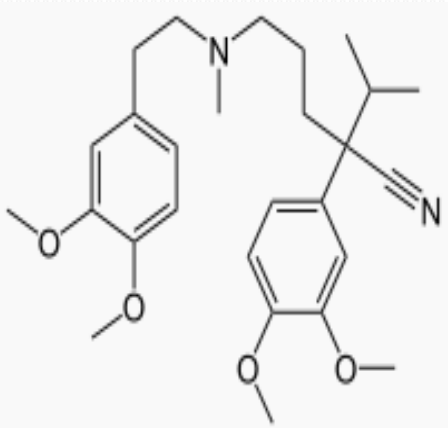
1,4-dihydropyridines

Eg:Nifedipine

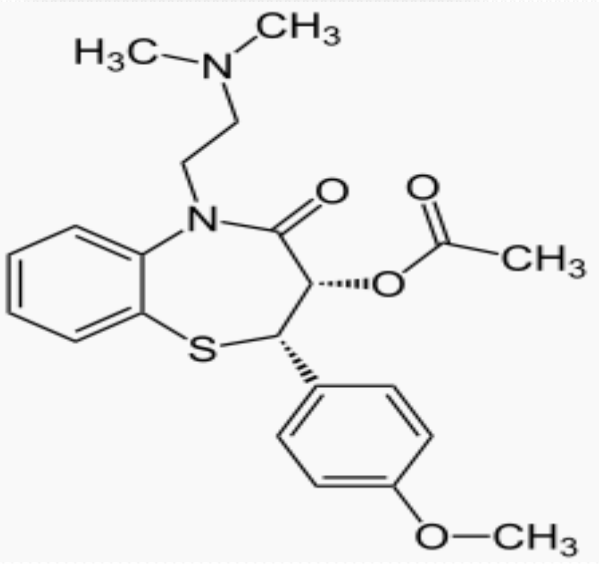
Diaminopropanol ether

Eg:Bepridil

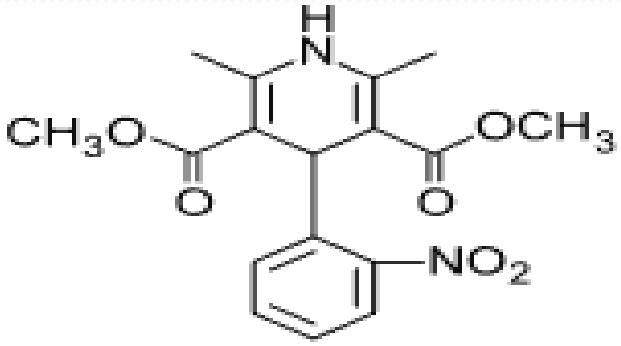
Verapamil



Diltiazem



Nifedipine



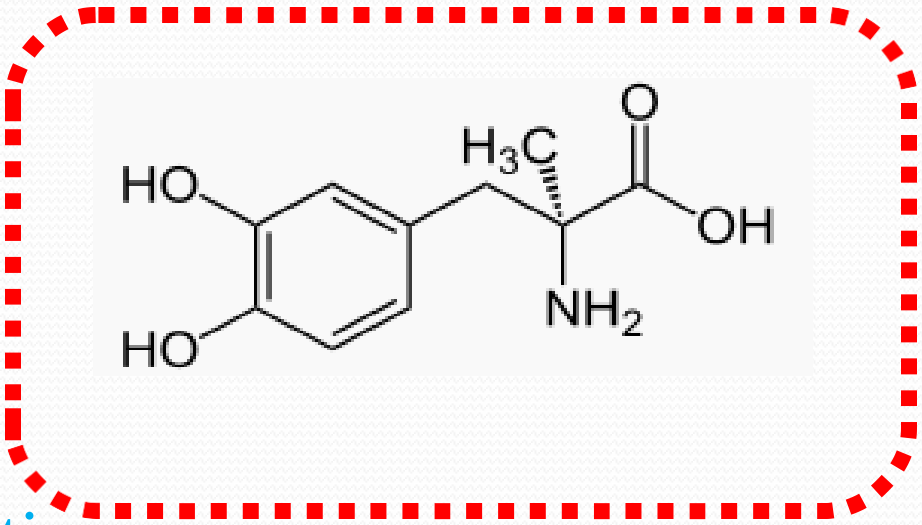
DRUGS	Mode of action	Adverse Drug reactions	Uses
Diltiazem	Acts by inhibiting Voltage sensitive Calcium channels in myocardium and vascular smooth muscles.	○Constipation ○Dizziness ○Oedema	○In arrythmias ○In Angina
Verapamil		○Flushing ○Oedema	•In Angina In Arrythmias
Nifedipine		○Tachycardia	In Angina

Calcium channel blockers

- Idradipine (DynaCirc®)
- Nicardipine (Cardene®)
- Nisoldipine (Sular®)
- Felodipine (Plendil®)
- Amlodipine (Norvasc®)

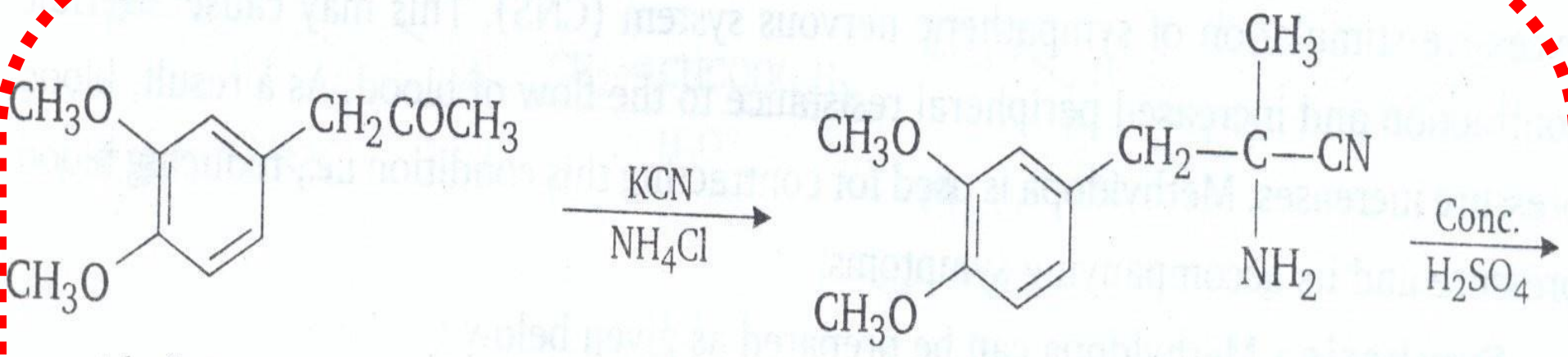
Centrally acting sympatholytics

Methyldopa

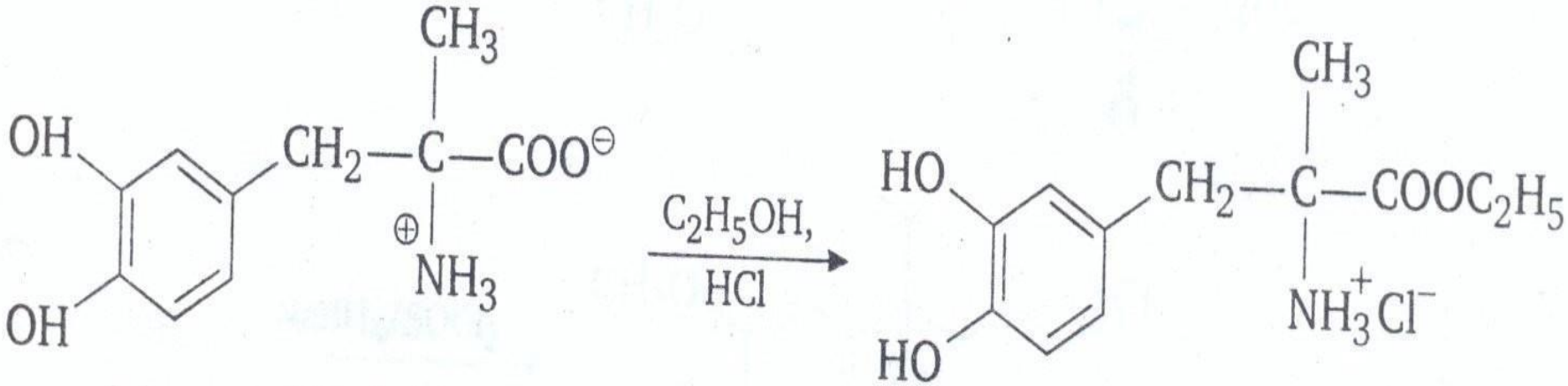


Mechanism of action

Methyldopa is an α2 adrenergic receptor agonist acts centrally by decreasing the sympathetic outflow which inturn lowers B.P.



4-hydroxy 3-methoxy phenyl acetone



L-isomer of Methyldopa

Methyldopa ethylester hydrochloride

Adverse effects

- Sedation and drowsyness
- Constipation
- Gynacomastia
- Sexual impotense

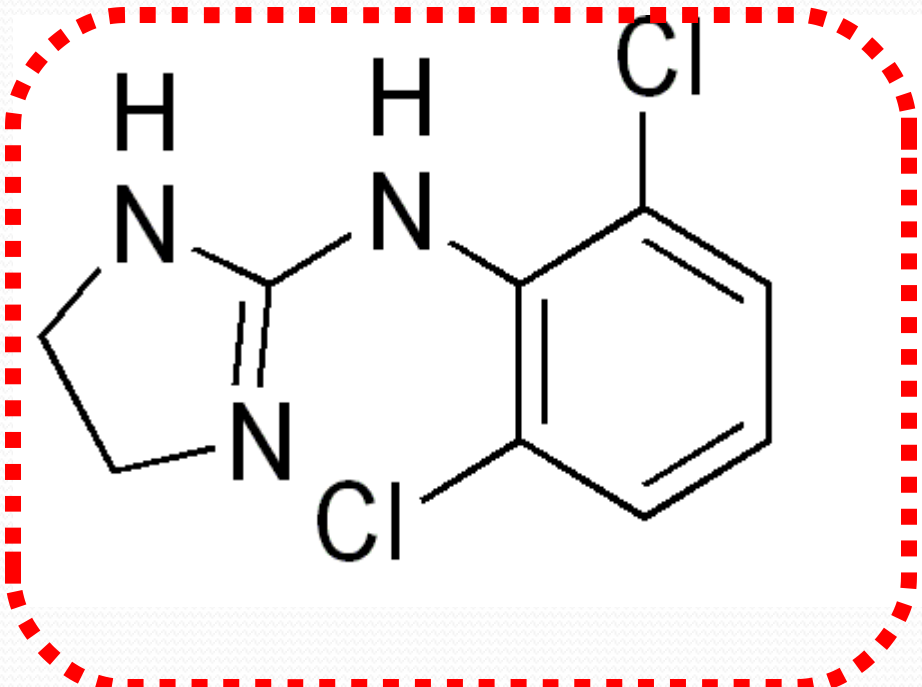
Uses

Treat of Hypertension in combination
With diuretics.

clonidine

Mode of action:

Its acts by stimulating α2-adrenergic receptros and thereby reducing sympathetic outflow and noradrenaline release



- ***Clonidine Hydrochloride.***
- 2-[(2,6-dichlorophenyl)imino]imidazolidine monohydrochloride(Catapres), was synthesized in 1962 as a derivative of the known -sympathomimetic drugs naphazoline and tolazoline, potential nasal vasoconstrictors, but instead it proved to be effective in the treatment of mild-to-severe hypertension. Clonidine hydrochloride acts by both peripheral and central mechanisms in the body to affect blood pressure. It stimulates the peripheral -adrenergic receptors to produce vasoconstriction, resulting in a brief period of hypertension. Clonidine hydrochloride acts centrally to inhibit the sympathetic tone and cause hypotension that is of much longer duration than the initial hypertensive effect. Administration of clonidine hydrochloride thus produces a biphasic change in blood pressure, beginning with a brief hypertensive effect and followed by a hypotensive effect that persists for about 4 hours. This biphasic response is altered by dose only. Larger doses produce a greater hypertensive effect and delay the onset of the hypotensive properties of the drug.

Adverse drug reaction

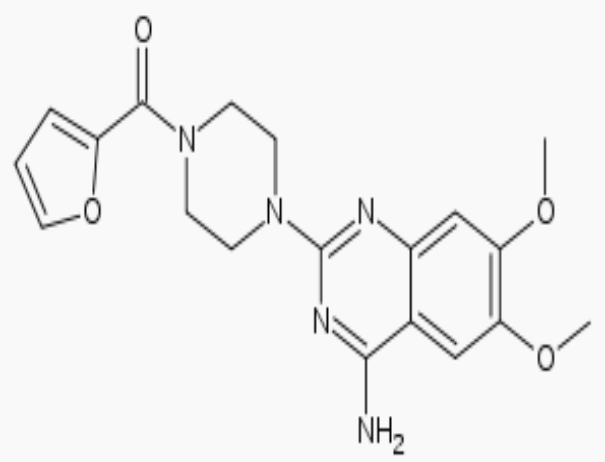
- Sedation and drowsiness
- Dryness of mouth and nase
- Constipation
- Bradycardia

uses

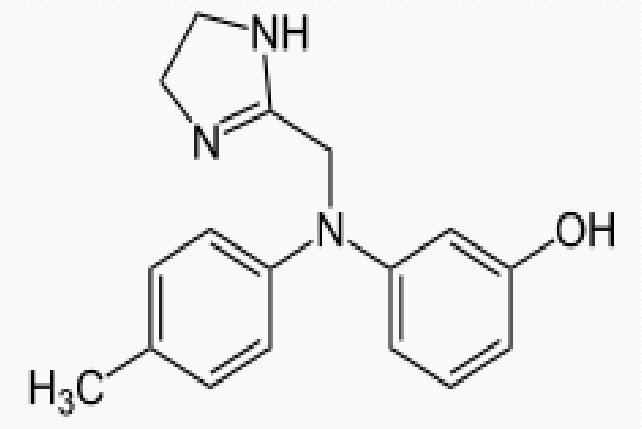
- In moderate to severe hypertension
- For withdrawl therapy of alcohol opioids
- To diagnose pheochromocytoma

Adrenergic receptor antagonist

Prazosin



phentolamine



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Adrenergic receptor antagonists

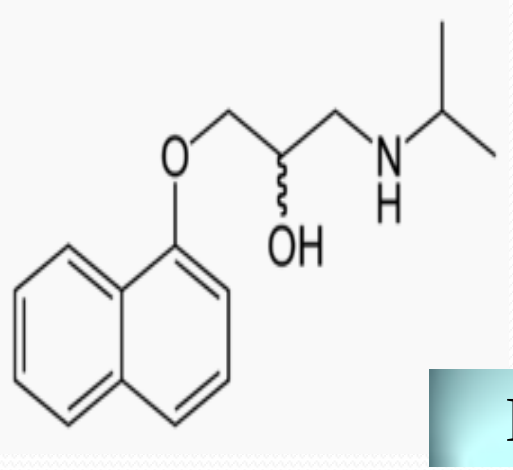
α-blockers

Drugs	Mode of action	Adverse drug reaction	Uses
prazosin	It acts by selective blocking of α-1 receptors in the peripheral blood vessels leading to vasodilation	First dose effect: ϖPostural hypotension and syncope ϖDrowsiness ϖHeadache ϖNasal congestion	In the treatment of moderate to serve hypertension in combinaton with a β-blocker and a diuretic

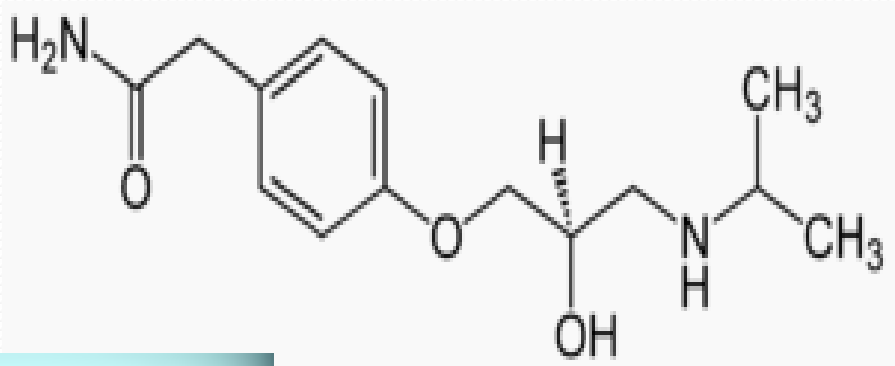
Drugs	Mode of action	Adverse drug reaction	Uses
Phentolamine	It blocks both α1 and α2-receptors leading to vasodilation and increase in noradrenaline release	ϖ Hypotension ϖTachycardia ϖIncrease in gastric acid secretion	ϖ Pheochromocytoma

β-adrenergic Blockers

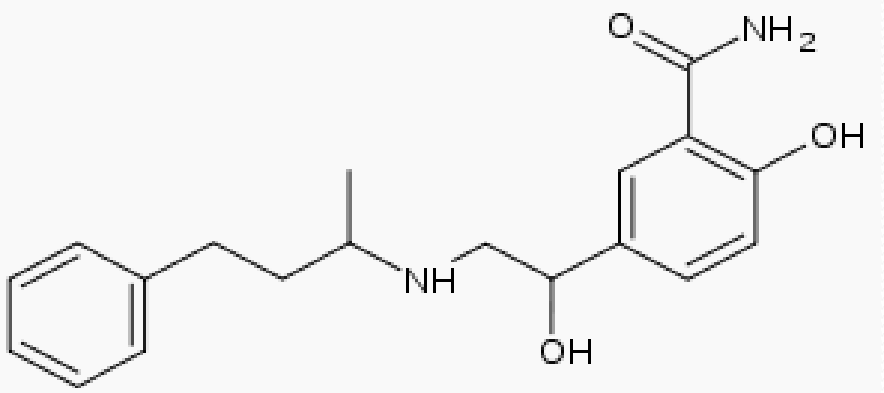
PROPANOLOL

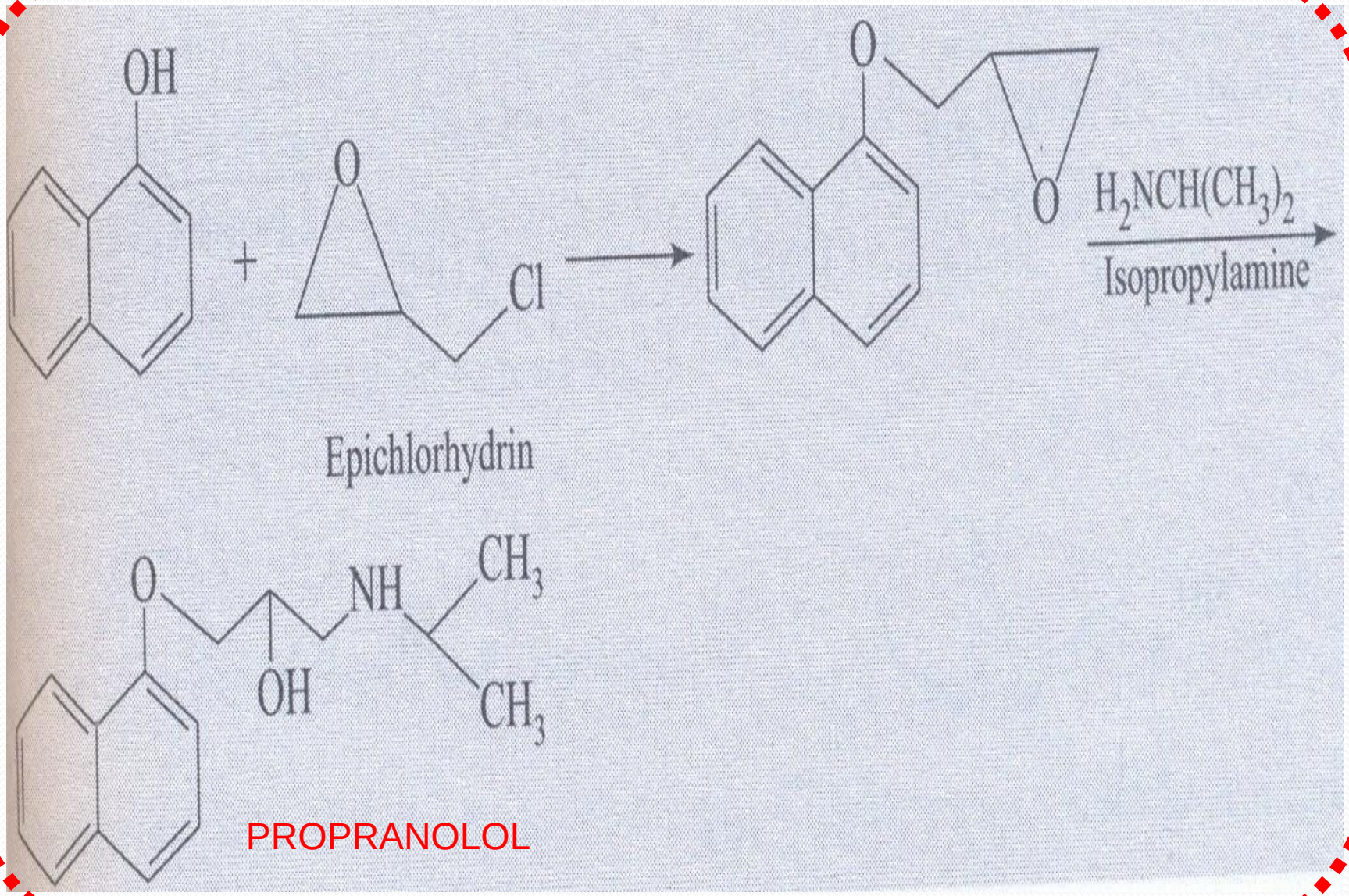


ATENOLOL



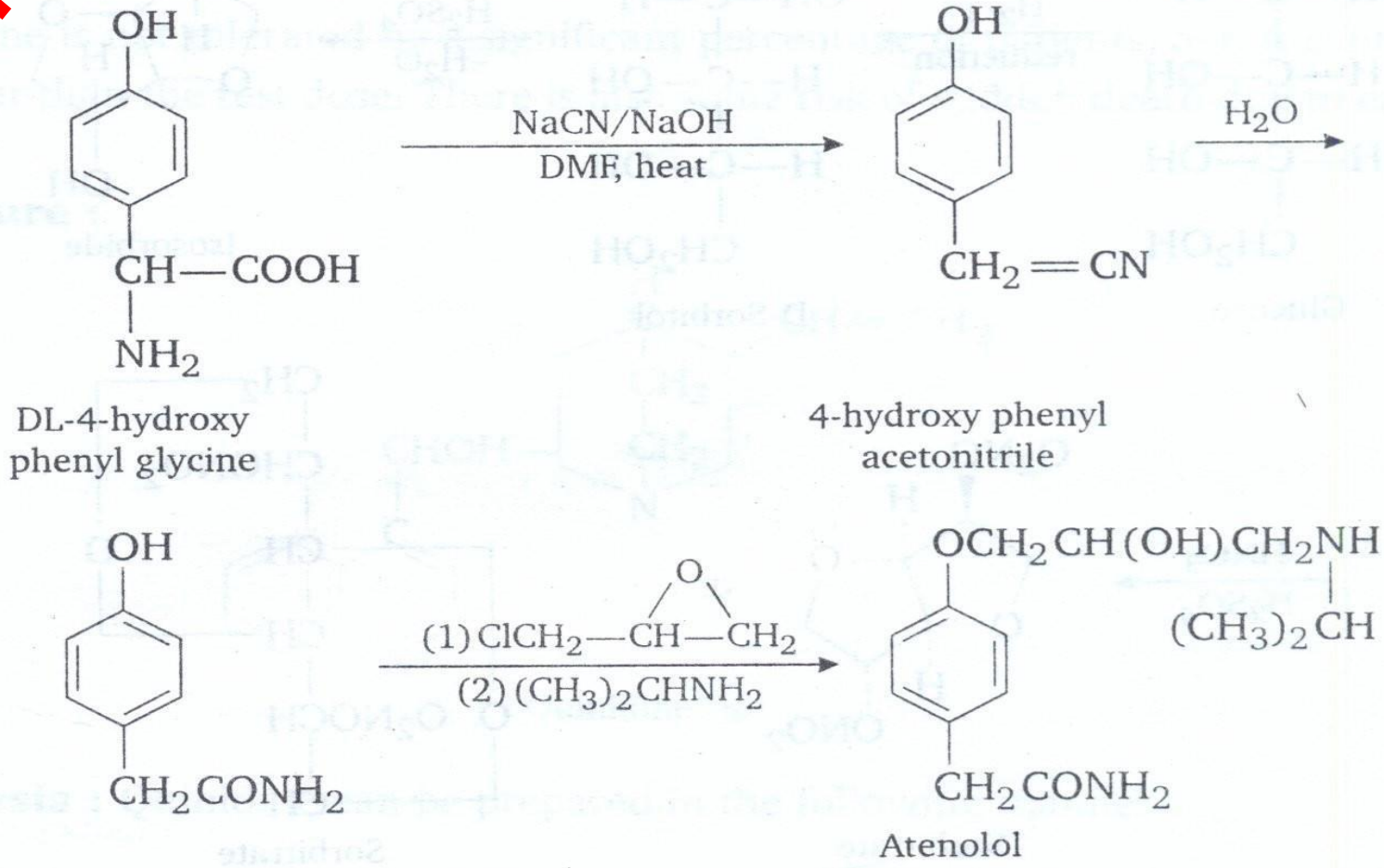
LABETOLOL




OH
O
Cl
O
O
$H_2NCH(CH_3)_2$
Isopropylamine
Epichlorhydrin
O
NH
CH_3
OH
CH_3
PROPRANOLOL

β-adrenergic Blockers

Drugs	Mode of action	Adverse drug effects	Uses
Propanolol	Inhibits sympathetic activity by blocking β1 and β2 receptors	•Fatigue •Bradycardia •Hypoglycemia	•In angina •In myocardial infarction •In arrythmias

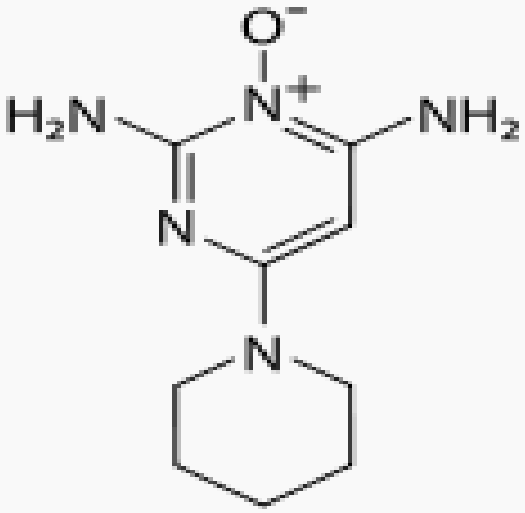

OH
CH—COOH
NH2
NaCN/NaOH
DMF, heat
OH
CH2 = CN
H2O
DL-4-hydroxy phenyl glycine
4-hydroxy phenyl acetonitrile
OH
CH2 CONH2
(1) ClCH2—CH—CH2
O
(2) (CH3)2CHNH2
OCH2 CH (OH) CH2NH
(CH3)2 CH
CH2 CONH2
Atenolol

Drug	Mode of action	Adverse drug reactions	Uses
Atenolol	Inhibit Sympathetic activity by selective blockage of β1 receptors.	•Fatigue •Bradycardia	In angina In arrythmias

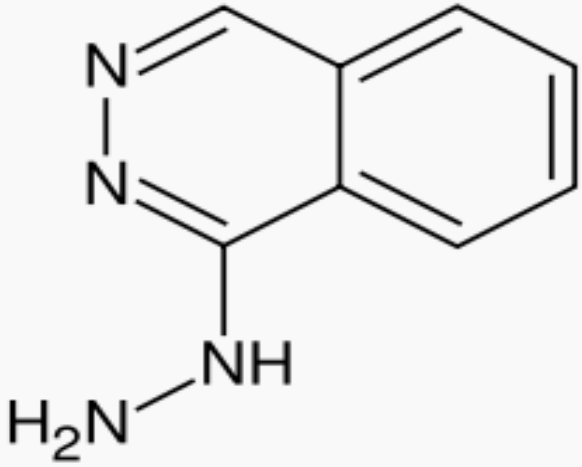
Drug	Mode of action	Adverse effects	Uses
•Carvedilol •Labetalol	They block β and α1 receptor there by inhibit sympathetic activity.	•Dry mouth •Gidisturbances •Sexual dysfunction	•Cavedilol-CHF •Labetalol-Emergencies

Direct vasodilators

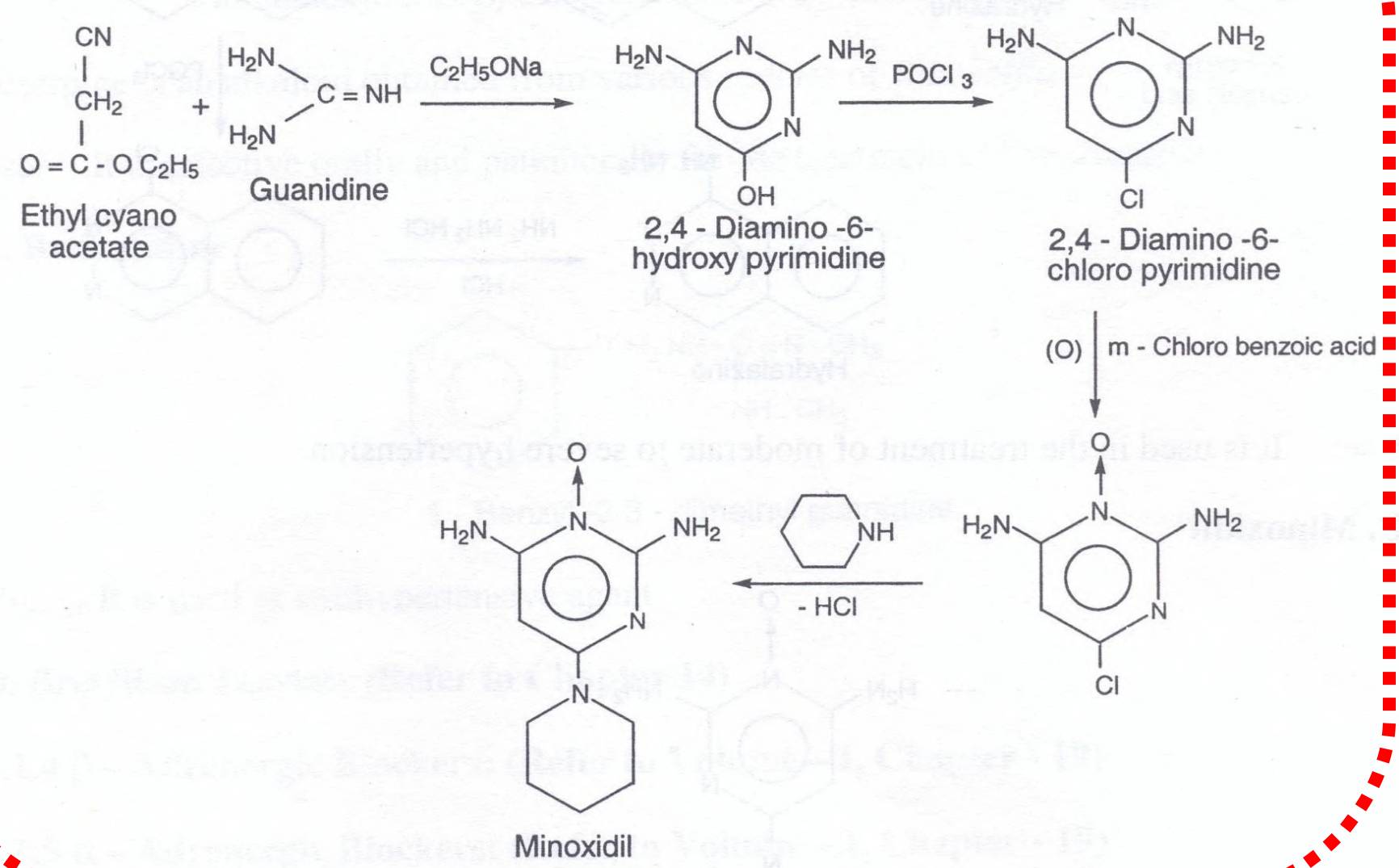
MINOXIDIL



HYDRALAZINE

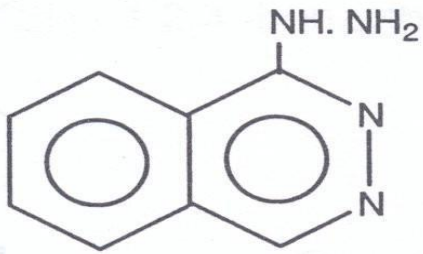


Synthesis


CN
CH2
O = C - O C2H5
Ethyl cyano acetate
+
H2N
C = NH
H2N
Guanidine
C2H5ONa
H2N
N
NH2
N
OH
2,4 - Diamino -6- hydroxy pyrimidine
POCl 3
H2N
N
NH2
N
Cl
2,4 - Diamino -6- chloro pyrimidine
(O)
m - Chloro benzoic acid
O
H2N
N
NH2
N
Cl
NH
- HCl
O
H2N
N
NH2
N
N
Minoxidil

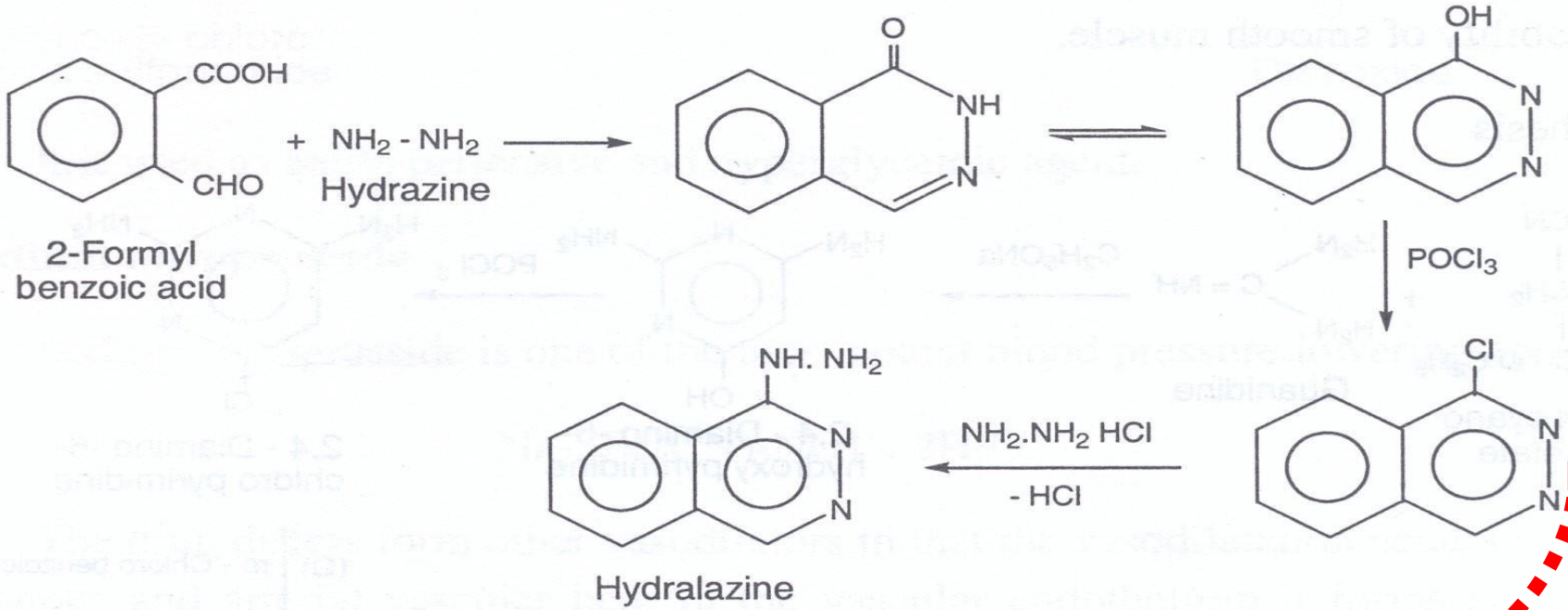
Direct Vasodilators

Drug	Mode of action	Adverse effects	Uses
Minoxidil	It opens the potassium channels and causes hyperpolarization.	•Tachycardia •Fluid retension •Hypertrichosis	•In treatment of Baldness



1- Hydrazino phthalazine

Synthesis



2-Formyl benzoic acid

Hydralazine

Drug	Mode of action	Adverse effects	Uses
Hydralazine	Direct relaxation of vascular smooth muscles by stimulating cGMP	•Flushing •Tachycardia •Fluid retension	Emergencies

CONCLUSION

"Saunders said. "Doctors are using ACE inhibitors, Calcium channel blockers, Beta-blockers, Angiotensin-receptor blockers (ARBs), Alpha-blockers and low-dose diuretics in ways that don't cause the sexual complications and other side effects of older therapies. Also, these new drugs only need to be taken once a day, instead of two or three times a day. This is a lot easier for patients." .

We need to make sure that we eat eight servings of fruits and vegetables a day, and get more exercise. We need to get ourselves and our children away from the television sets and the computers, and start them exercising early in their lives."

Acknowledgement

I would like to express my special thanks of gratitude to Power point presentation by PROF. RAVISANKAR, Vigyan Pharmacy college,Valdlamudi, Guntur Dist. A.P.

REFERENCES

Wilson and Gisvolds Text book of Organic Medicinal And Pharmaceutical chemistry

Principles of Medicinal chemistry Dr.S.S.Kadam
Dr.K.R..Mahadik
Dr.K.G.Bothara

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P.Valentine

Principles of Medicinal chemistry by William foeye

Advanced practical Medicinal chemistry by Ashutoshkar
Profiles in drug synthesis vol-1 Dr.v.N.GOGTE

The organic chemistry of drug synthesis vol-3 DANIEL LEDNISER,LESTER .A.MITSCHER

Medicinal chemistry D.SRIRAM,P.YOGEESWARI

Essentials of Medicinal chemistry II Edition – ANDREJUS KAROLKOVAS

Power point presentation by PROF. RAVISANKAR, Vigyan Pharmacy college,Valdlamudi, Guntur Dist. A.P.


THANK YOU