

## ANTI-HYPERTENSIVE AGENTS $\Rightarrow$

Hypertension or high blood pressure is a most common of all cardiovascular diseases with a great number of people suffering from this. It is defined as either a sustained systolic blood pressure (SBP) of greater than 140 mmHg or a sustained diastolic blood pressure (DBP) of greater than 90 mmHg. It is the number one cause of stroke and heart attack.

Normal blood pressure in healthy adult is 120/80. Patients with as high as 200/120 needs immediate treatment. Consistent high blood pressure can damage the brain, eyes and kidney. It is often called the "Silent killer" this because it really exhibits symptoms even as it inflicts serious damage on the body. Hypertension is referred as essential or primary, when a specific cause cannot be identified. This occurs in up to 95% patients. Genetic factor appears to play a major role in essential hypertension. These genes regulate a group of hormones collectively known as the angiotensin-renin system and that regulates the sympathetic nervous system.

Secondary hypertension has recognizable causes that can be treated or reversed. Some medical conditions that can contribute to temporary hypertension are pregnancy, cirrhosis, kidney disease or cushings disease. Certain prescriptions and over the counter medications can cause the blood pressure to rise. Abuse of alcohol can lead to hypertension. Excessive consumption of coffee, stress etc also causes high B.P.

Anti-hypertensive drugs are referred to as drugs that are used to decrease the elevated blood pressure (Hypertension). The pressure exerted by blood on the walls of blood vessels is called blood pressure. The pressure produced due to the blood pushing into the aorta by left ventricle is called systolic blood pressure. The time at which the heart rests after ejection of the blood, then the pressure within the arteries is called diastolic blood pressure.

## CLASSIFICATIONS OF ANTI-HYPERTENSIVE AGENTS<sup>3</sup>

Numerous Anti-hypertensive agents are in use currently.

They can be majorly categorized as :

1. Angiotensin - Converting enzyme inhibitors  
That reduce the production of angiotensin II  
and III chemicals that cause arterioles to constrict

2. Sympathetic Nervous System Depressants  
including Vasodilators and Calcium  
channel blockers each of which dilates  
of blood vessels resulting to reduction  
of peripheral vascular resistance .

E.g. Verapamil, <sup>calcium channel blo</sup> Hydralazine, <sup>vasodilators</sup> Minoxidil  
diltiazem etc. Clonidine, Methyldopa  
~~and Central Sympatholytics~~

3. Diuretics that cause the body to excrete  
water and salt producing anti-hypertensive  
effects ..

Thiazides (Chlorothiazide) Loop: Furosemide (Bumetanide)  
Potassium sparing (Triamterene)

$\beta$ -Adrenergic blockers: Propranolol, atenolol  
 $\alpha$ -Adrenergic blockers: Timolol, mainly for ocular pressure

$\alpha + \beta$  Adrenergic blockers: Prazosin, terazosin  
Phentolamine, phenoxybenzamine

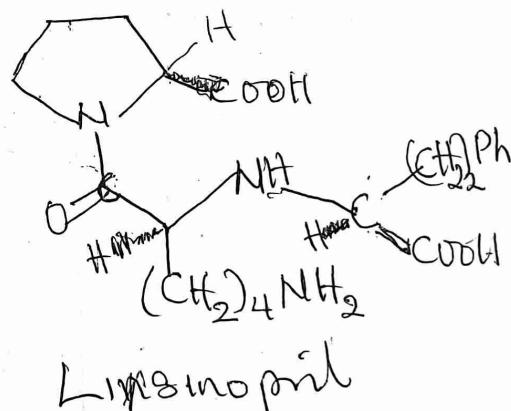
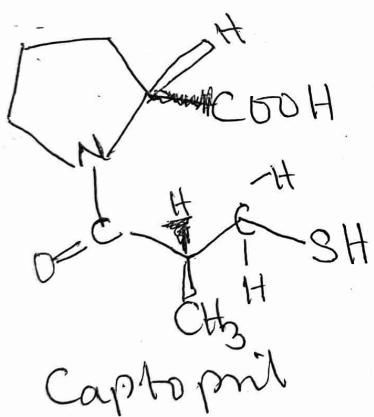
Cangiotrope blockers: Labetalol  
Pentaadrinum

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## Angiotensin-Converting Enzyme (ACE) Inhibitors

Captopril and Lisinopril

ACE Inhibitors containing a carboxylate group that recognize the cationic site, arginine, inactive site of the enzyme. The thiol group was incorporated to Captopril in the hope of enhancing its binding to zinc. However it introduces some side effects such as rashes and loss of taste. Both agents are stoichiometric inhibitors. Lisinopril is a lysine derivative and its metabolite, enalaprilat is active.

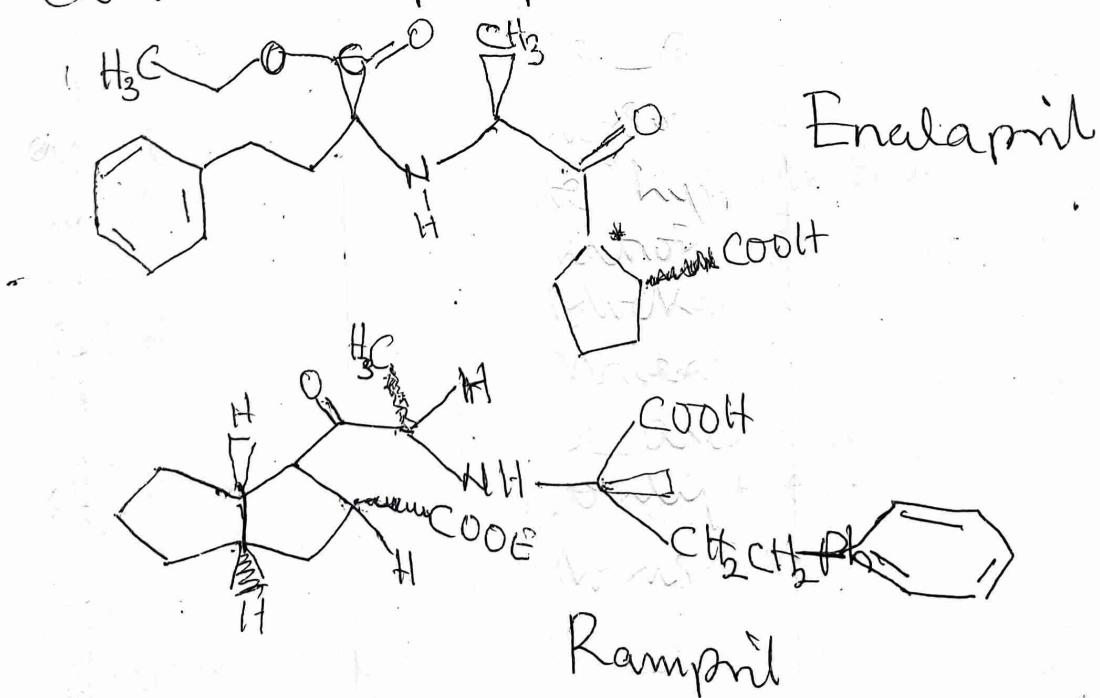


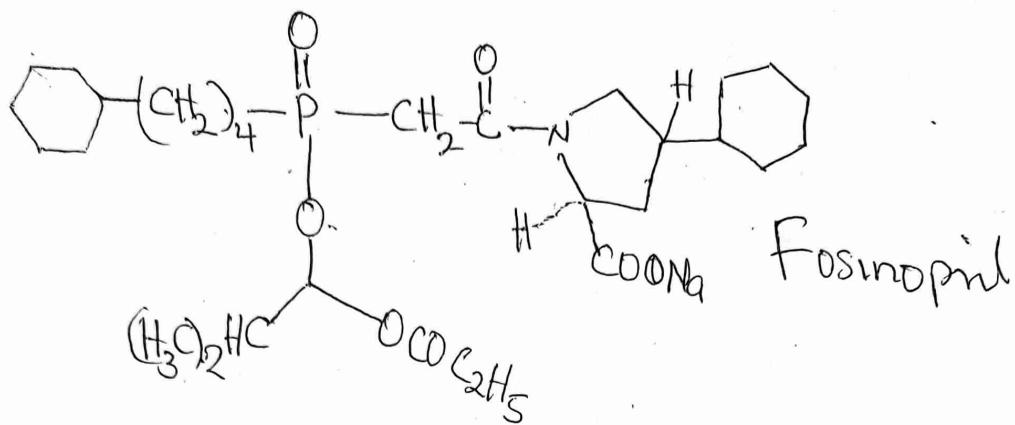
Captopril is a selective ACE inhibitor.

Common mode of action of drug ACE Inhibitors  
 ACE is also responsible for the breakdown of bradykinin levels, Vasodilation occurs.  
 ACE Inhibitors also decrease the secretion of aldosterone, resulting in decreased sodium and water retention.

Enalapril, Benazepril and Ramipril...  
...as per TTS as on

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### Direct-Acting Vasodilatory Drugs

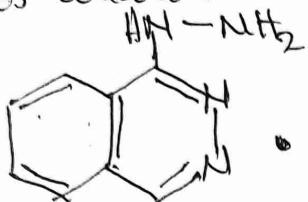
Drugs that act directly to induce dilation of the smooth muscle cells are useful in treating hypertension e.g hydralazine, Sodium nitroprusside, Calcium channel blockers and potassium channel openers.

Hydralazine is useful in the treatment of moderate to severe hypertension and is used in combination with other anti-hypertensive drugs. It dilates the vascular & smooth muscle fibers, as a result of its action on the cells, reducing the resistance to blood flow and thus decreasing the pressure.

Additionally, it improves renal blood flow and thus is especially useful for patients with renal dysfunction. Its exact mechanism is unknown. It is a stable yellow solid with low water solubility. It reaches peak plasma concentrations within 1 hour and rapidly metabolizes by hepatic oxidation, glucuronidation and N-*acetylation*.

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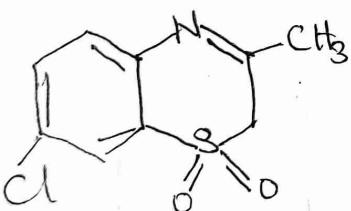
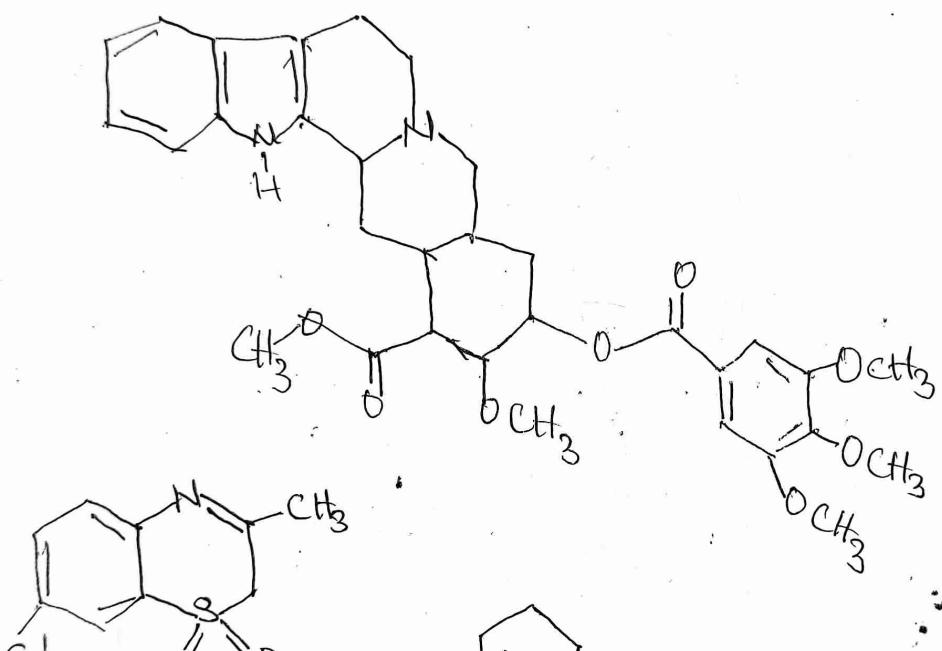
It is available as drug in its hydrochloride form



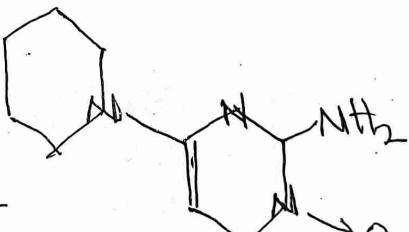
• HCl

Hydralazine

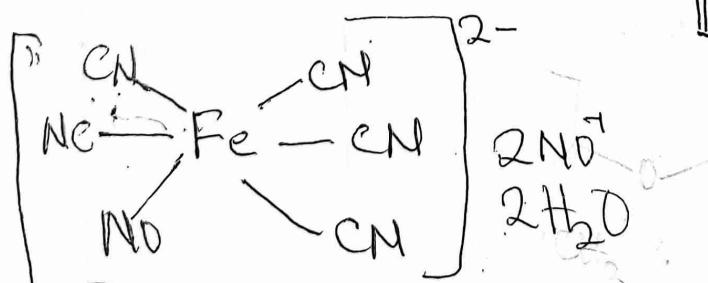
Reserpine



Diazoxide



Minoxidil



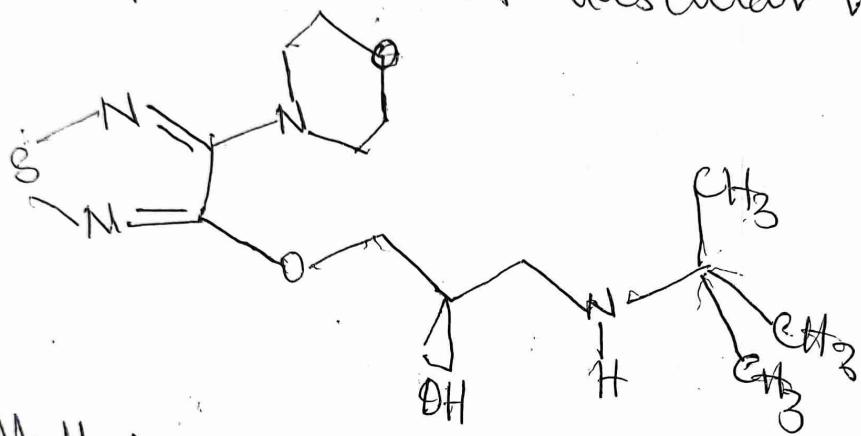
Sodium Nitroprusside

$\text{Na}_2[\text{Fe}(\text{CN})_5\text{NO}]$

Sodium Nitroprusside:- Sodium nitroferricyanide is one of the most potent blood pressure lowering drugs. It is useful only in emergencies because of its short action span. Relaxation of both the arterial and venous smooth muscle cells occurs. The physiological effect arises due to its decompaction and formation of nitric oxide in the plasma.

Diazoxide and Minoxidil : Both are potassium channel agonists that decrease the concentration of  $\text{Ca}^{2+}$  ions within the cells and thus reduce the excitability of smooth muscle cells. Diazoxide lowers the peripheral vascular resistance and so does Minoxidil. However, Minoxidil requires activation by sulfotransferase to minoxidil sulfate before it becomes functionally active. Diazoxide is intravenous injection at pH 11.5 that converts the drug to its soluble sodium form. The drug is highly protein bound and can displace other drugs. Minoxidil is useful in severe hypertension that is difficult to control with other drugs.

Timolol is a nonselective beta adrenergic receptor blocker that is widely used for the therapy of hypertension, angina pectoris and preventions of vascular headaches.



Methyldopa and Clonidine are central sympatholytics.

Most of Methyldopa converts into its metabolite  $\alpha$ -methyl-norepinephrine which stimulates the central inhibitory  $\alpha$ -adrenergic receptors.

It leads to reduction in sympathetic tone Bp and total peripheral resistance.

Inhibition of decarboxylation of dihydroxy-phenylalanine (Dopa) and 5-hydroxytryptophan in the CNS which produces anti-hypertensive effects.

nitrode

Catena

Stich

angie

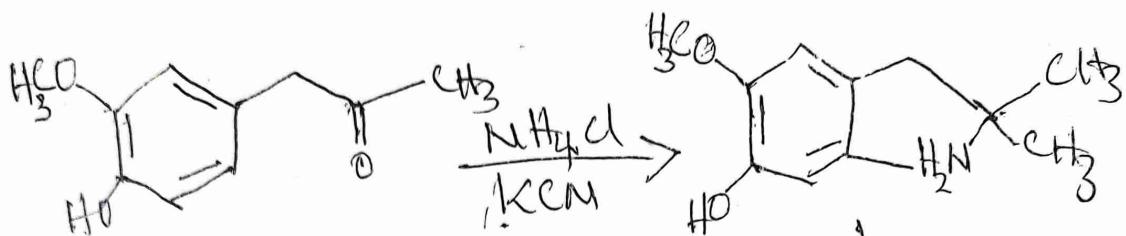
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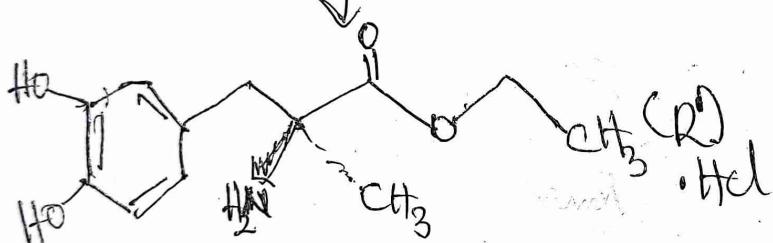
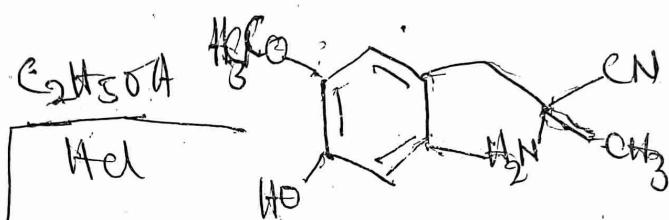
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Synthesis :-



(3-methoxy-4-hydroxyphenyl  
acetone)

Resolution



SAR

When R<sup>1</sup> is increased in size; activity of α-receptors decreases and activity of β-receptors increases but both receptors is maximum when R<sup>1</sup> is methyl group.  
Decrease in activity if R<sup>1</sup> substituted with larger group than methyl.