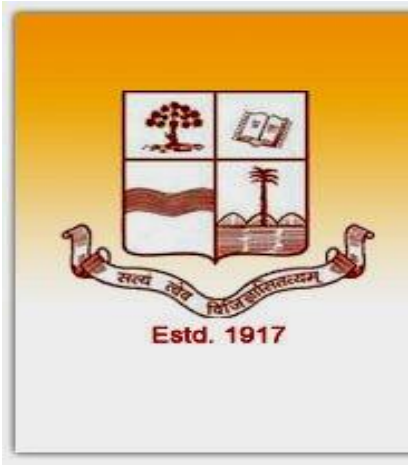
CARDIOVASCULAR DRUGS



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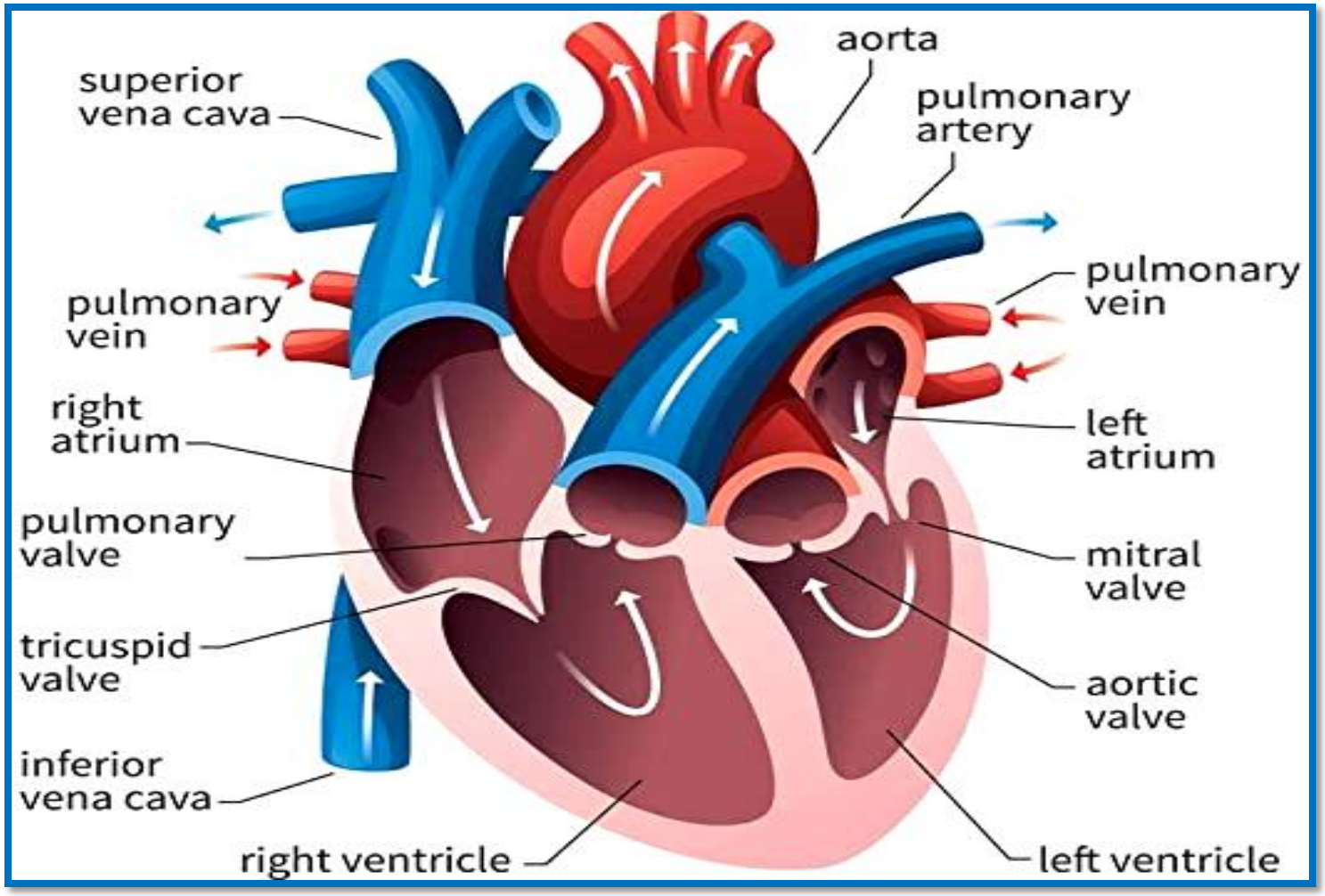
OBJECTIVES

Learning Basics of CVD's and Drugs Used

- Types of Cardiovascular Diseases
- Classes of Drugs Used for treatment
- Inhibition of Drugs by Various Factors
- Synthesis of Some Important Drugs

OVERVIEW OF HEART



DEFINING CARDIOVASCULAR DISEASE

Cardiovascular disease is name of the group of the disorders related to the heart and the blood vessels which include :

- Hypertension (High blood pressure)
- Coronary heart disease (Heart attack)
- Cerebrovascular disease (Stroke)
- Heart failure (Sudden non-working of heart)
- Cardiomyopathies (Heart muscle dysfunction)

CVD'S ARE GLOBAL THREAT TO HUMANS

- According to World Health Organization the CVD's are largest cause of death globally.
- As an estimate about 17.3 million people died of CVD in 2008, 30% of all global deaths : 7.3 million suffered coronary heart disease and 6.2 million due to stroke.
- By 2030 almost 23.6 million people are expected to suffer badly of CVD's.
- It is becoming a matter of serious concern.

OUR HEART NEEDS PROPER OXYGEN SUPPLY

- Like any other muscle in the body heart also needs adequate blood supply to provide oxygen so that the muscle can contract and pump blood to the rest of the body and to itself, of course.
- A blocked coronary artery supplies inadequate blood and thus oxygen that ultimately hinders the electrical impulses to propagate.
- Various symptoms related to cardiovascular diseases arise due to reasons mentioned above.

CORONARY ARTERY DISEASE

- Coronary arteries supply blood to the heart muscles and when there is buildup of **cholesterol plaque** inside the artery walls, it partially of largely blocks the artery, leading to a decreased blood flow through it.
- Rupture of plaque and subsequent formation of clot in the artery results in blockage and the part of heart muscle which is denied the blood supply begins to die.

I. ANGINA AND ANTI-ANGINAL DRUGS

- Angina is the principal symptom of an ischemic heart creating a sudden, severe pain that originates in the chest and radiates through the left shoulder down the arm.
- Coronary arteries maintain cardiac function and are expected to adapt to sudden demands on the heart due to enhanced activity.
- Arteries respond to this sudden demand by dilatation.

- The heart has to exert more to increase the blood flow through such atheroslerotic arteries. In this situation the heart is deprived of oxygen and feels suffocated, a condition called ischemic.
- ANTI-ANGINAL DRUGS mainly alleviate the pain by reducing the oxygen requirements of the heart.
- Three main classes of such drugs are

  (a) O*rganic nitrates.*

  (b) Calcium channel antagonists.

  (c) β-*adrenergic antagonists.*

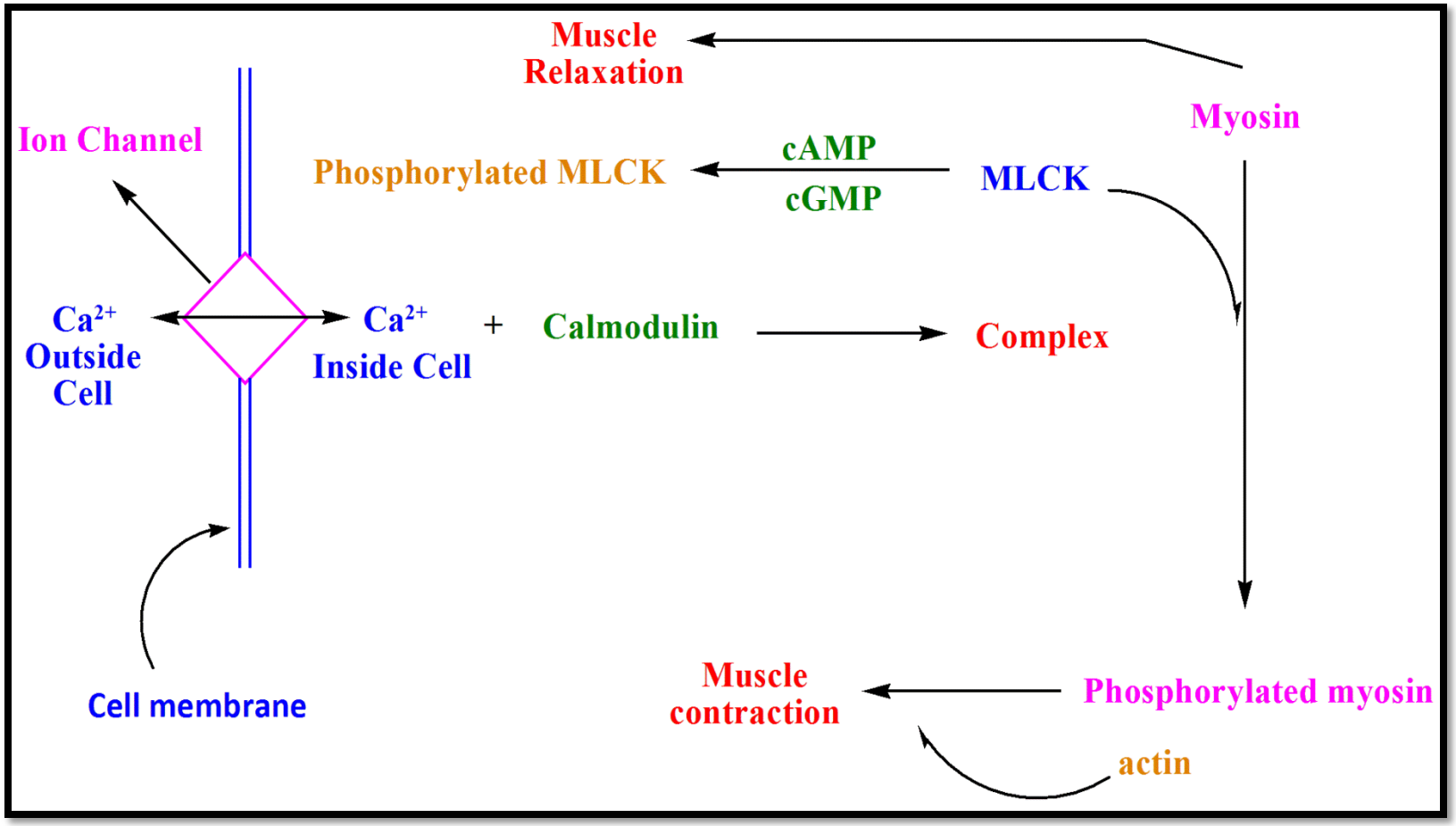
(a) ORGANIC NITRITES AND NITRATES

- Organic nitrites as well as nitrates remain the drugs of choice for treating spasmatic episodes of angina.
- Among organic nitrites called nitrovasodilators discovered, amyl nitrite (1) was the first (1867).
- Because of their non-polar nature these agents exhibit very high lipid permeability thus highly suitable for rapid treatment.
- Smaller molecules have higher activity.

HOW ORGANIC NITRITES WORK ?

- Organic nitrates are rapidly metabolized by their reaction with cysteine-containing proteins resulting in the release of nitric oxide (NO) that is responsible for the vasodilating effect on the arteries and hence these are regarded as pro-drugs.
- The state of muscle (contraction or relaxation) is controlled by the action of myosin-actin pair of proteins.
- Depending on whether myosin is phosphorylated or not, the action of actin results in either contraction or relaxation of the muscle.

MECHANISM OF MUSCLE CONTRACTION AND RELAXATION

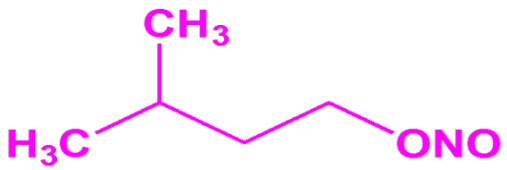


cAMP and cGMP stand for cyclic adenine of guanosine respectively

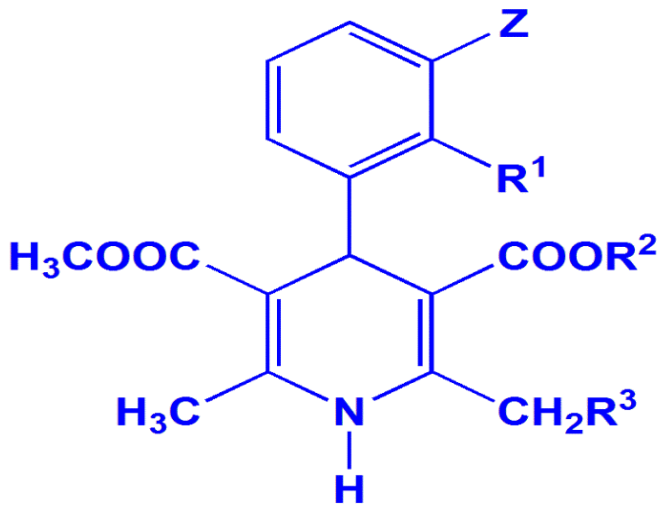
(b) CALCIUM CHANNEL BLOCKERS (ANTAGONISTS)

- It can be concluded that molecules that block the passage of Ca^{+2} ions from the outside to the inside of the muscle cell, will prevent the contraction of muscles leading to reduced work load and lowered oxygen demand.
- Specific calcium channel antagonists that bind L-type channels cause antagonism and are effective as anti-anginal agents. These agents do not physically block the channel, but bind at specific sites in the open form of the channel.

STRUCTURES OF DRUG MOLECULES 1,2,3,4



(1) Amyl nitrite



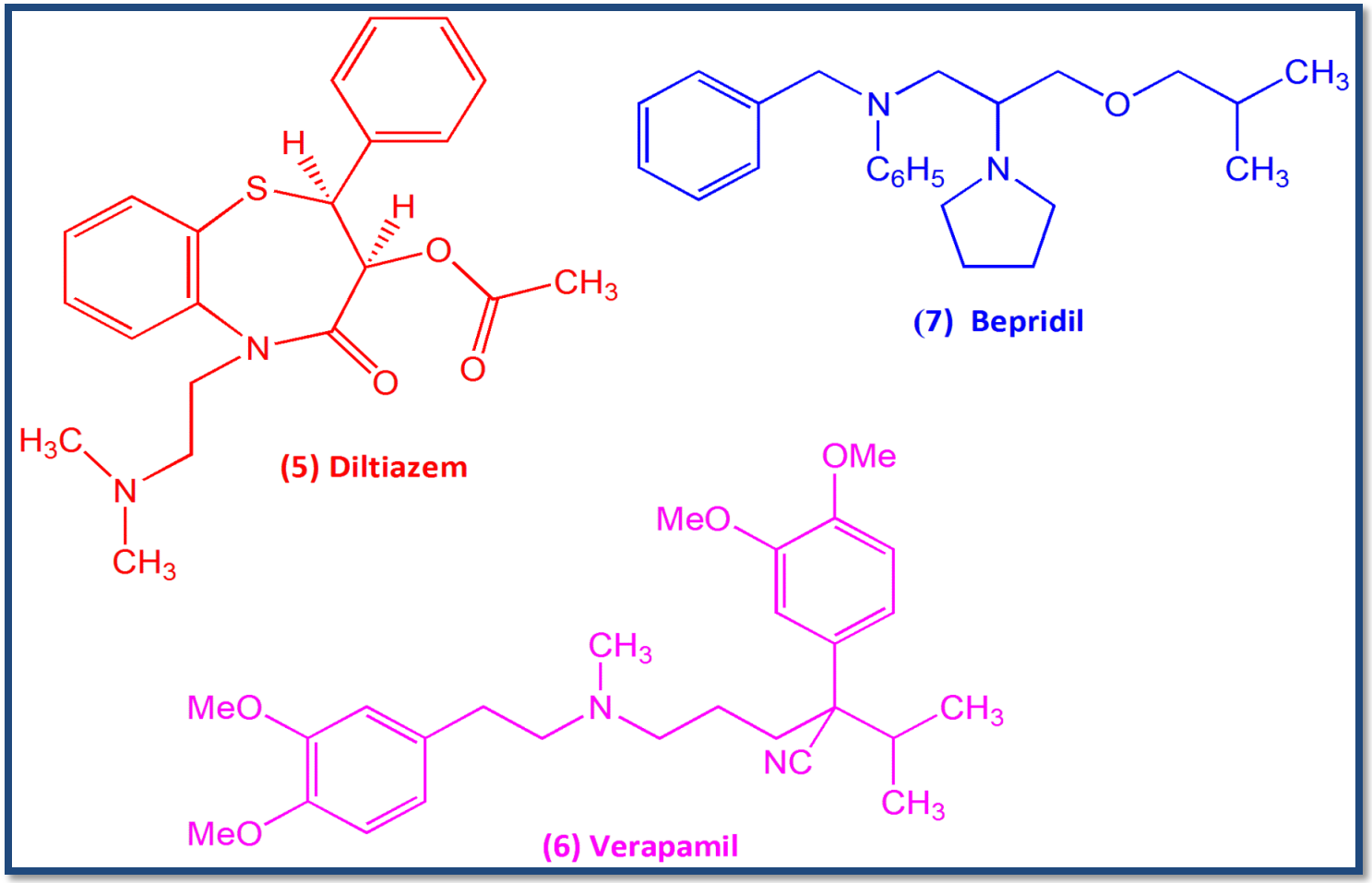
Structures of 2,3,4

Substituents	R^1	R^2	R^3	Z
2. Nifedipine	NO_2	CH_3	H	H
3. Amlodipine	Cl	C_2H_5	$O(CH_2)_2NH_2$	X
4. Nicardipine	H	$(CH_2)_2N(CH_3)CH_2Ph$	H	NO_2

SOME CHANNEL BLOCKER DRUG MOLECULES

1. Dihydropyridines include the drug molecules Nifedipine (2), Amlodipine (3), Nicardipine (4).
2. Benzothiazepines drug molecules examplified by Diltiazem ; [benzo[*b*-1,5]-thiazepine] (5).
3. Aralkylamines are Verapamil(6), and bepridil(7).
4. No structural similarities exist between these classes of compounds, suggesting that the activity profile of each class is distinct from the other.

STRUCTURES OF DRUG MOLECULES 5,6,7



(C) β-ADRENERGIC ANTAGONISTS

- Drugs with β-blocking activity slow the heart rate and decrease the force of contraction of muscles, thus these drugs are useful in treating hypertension and **cardiac arrythmias**, in addition to angina.
- Propranolol (8) is a common nonselective β-blocker of both cardiac and bronchial adrenergic receptors.
- In addition to angina, Propanolol is also typically used in combination with organic nitrates or calcium channel blockers to enhance its anti-anginal efficacy.

II. ARRHYMTHIC CARDIOVASCULAR DISEASES

- Arrhythmia is a disease in which the rhythmic contraction of the heart is disturbed or altered. Rhythmic contractions are caused by a sequence of electrical impulses.
- Cardiac arrhythmias can originate from a disturbed origin of the impulse (pacemaker cells) and concerned with diseases such as hypertension, atherosclerosis, hyperthyroidism, or lung disease.
- These are also known as ectopic arrhythmias.

SOME ANTI-ARRHYMTHIC DRUGS

1. Quinidine and Quinine **:** These are Obtained from *Cinchona* plant trivially. Quinidine is a dextrorotatory diastereoisomer of quinine.
2. Procainamide **:** It is major anti-arrhythmic drug used in the treatment of cardiac arrhythmias.
3. Disopyramide **:** Used orally and intravenously.
4. Lidocaine : It was initially introduced as a local anesthetic, but is now routinely used for treatment of arrhythmias arising from acute myocardial infarction and cardiac surgery.

III. HYPERTENSION

- Hypertension, or high blood pressure, is the most common of all cardiovascular diseases .
- Consistent high blood pressure (normal 120/80) can damage the brain, eyes, and kidneys. Hypertension is often called the silent killer.
- Apart from irregular and unhealthy life style, genetic factors play a major role in inducing hypertension.
- Abuse of alcohol, drinking excessive coffee increases excretion of calcium that plays an important role in disturbing the normal blood pressure.

ANTI-HYPERTENSIVE DRUGS

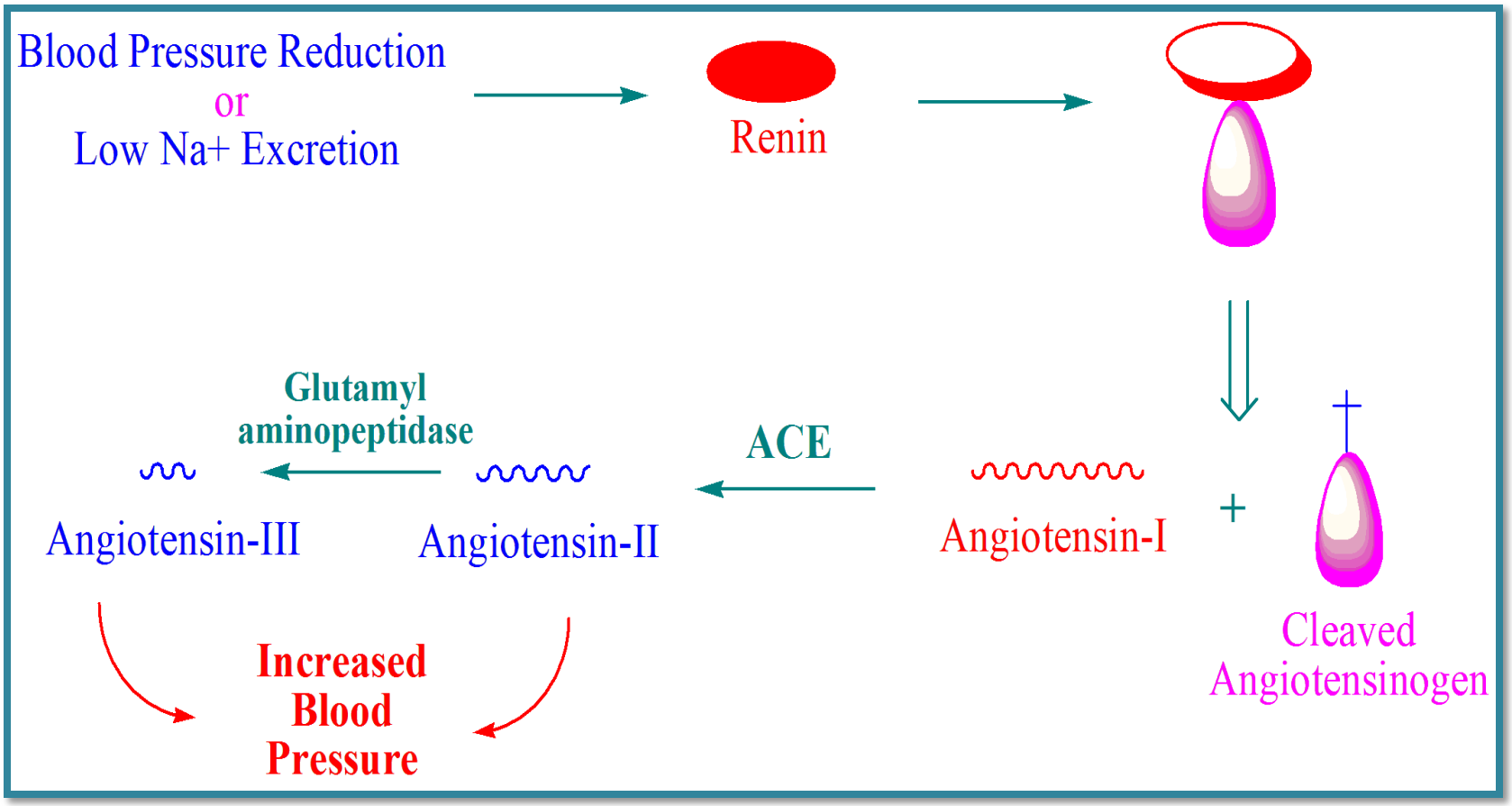
They can be categorized as follows:

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

DRUG INHIBITION OF PERIPHERAL SYMPATHETIC FUNCTION : THE RENIN-ANGIOTENSIN SYSTEM

- The Renin-Angiotensin system is a hormonal regulatory mechanism controlling the excretion of sodium and maintains body fluids.
- Lowering of blood pressure results in the release of renin which is in fact an aspartyl protease that cleaves angiotensinogen, a plasma glycoprotein.
- A generalized mechanism regarding the role of the Renin-Angiotensin in blood pressure regulation by contraction and relaxation is given below :

RENIN-ANGIOTENSIN MECHANISM OF BLOOD PRESSURE CONTROL



ANGIOTENSIN-CONVERTING ENZYME (ACE)

- This releases angiotensin-I, a decapeptide, from the carboxy terminal end of angiotensinogen.
- Angiotensin-I is further cleaved at its carboxy terminal to form an octapeptide, angiotensin-II, utilizing angiotensin-converting enzyme (ACE).
- Angiotensin-II is the first peptide that is a potent vasoconstrictor.
- The release of angiotensin-II thus results in an increased blood pressure.

ANGIOTENSIN-II AND ANGIOTENSIN-III

- Further reaction of angiotensin-II with glutamyl aminopeptidase results in angiotensin-III that is slightly less potent as a vasoconstrictor but possesses significant regulatory effect on sodium excretion.
- Thus, action of ACE increases the secretion of angiotensin-II and -III, constricting peripheral blood vessels, thereby raising blood pressure.
- Angiotensin–converting enzyme (ACE) is a membrane bound enzyme that utilizes zinc for optimal enzymatic hydrolysis of the second peptide.

IV. THE ACE-INHIBITORS

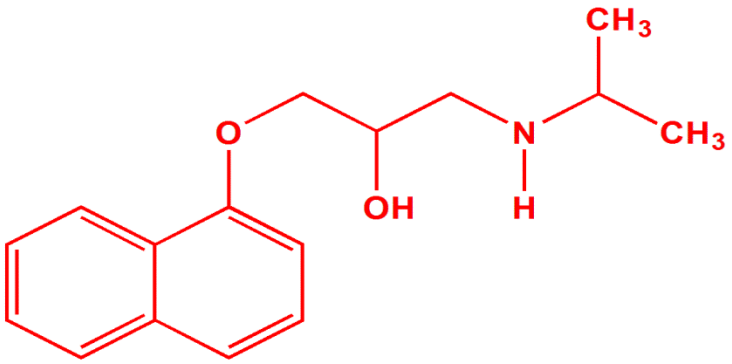
Captopril (9) and Lisinopril (10)

- These drugs are ACE inhibitors containing a carboxylate group that recognizes the cationic site, arginine, in active site of the enzyme.

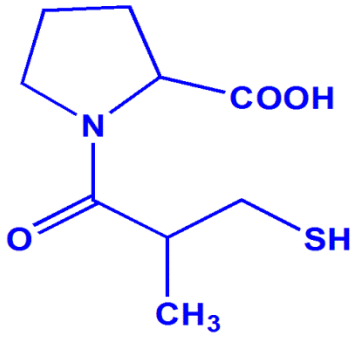
  Enalapril(11), Benazepril(12), Quinapril(13) and Ramipril(14).

- Each of these drugs functions as an ACE inhibitor prodrug. They contain a 2-(S)-aminophenylbutryic acid ethyl ester moiety. These drugs are converted to the active enzyme inhibitor following absorption and metabolism by liver and intestinal enzymes.

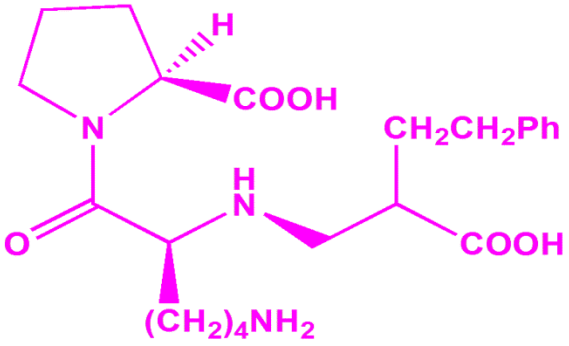
STRUCTURES OF DRUG MOLECULES 8,9,10,11



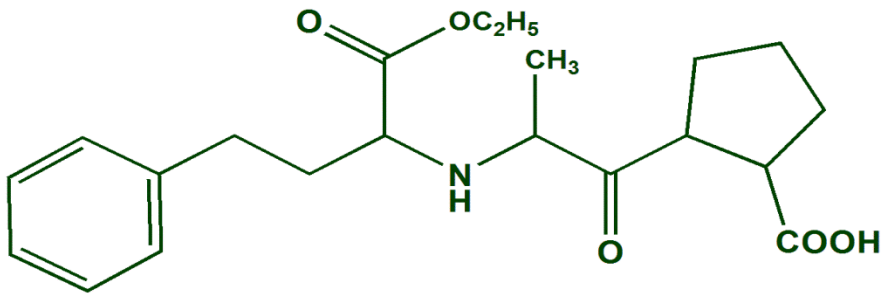
(8) Propranolol



(9) Captopril

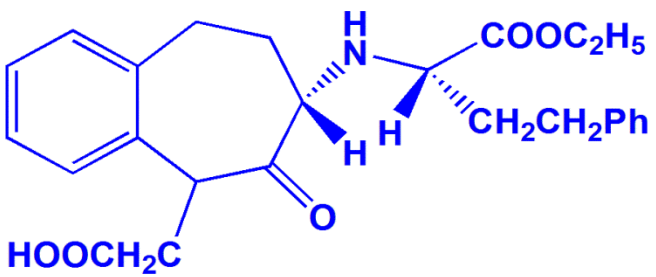


(10) Lisinopril

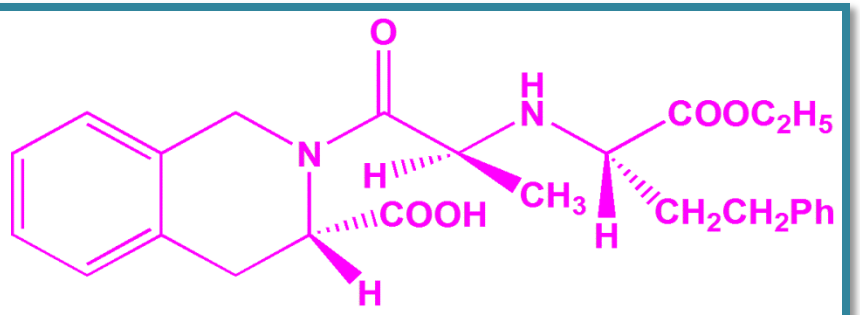


(11) Enalapril

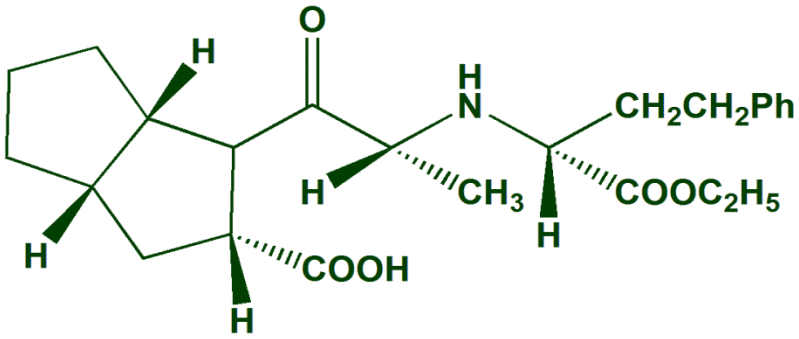
STRUCTURES OF DRUG MOLECULES 12,13,14



(12) Benzapril

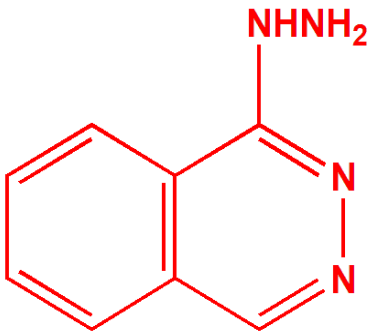


(13) Quinapril

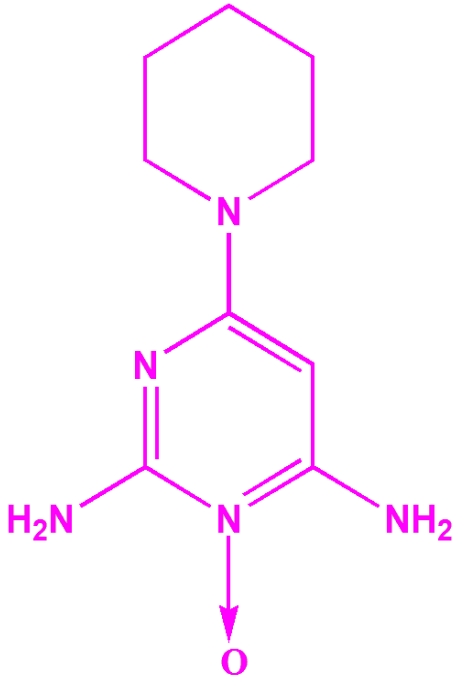


(14) Ramipril

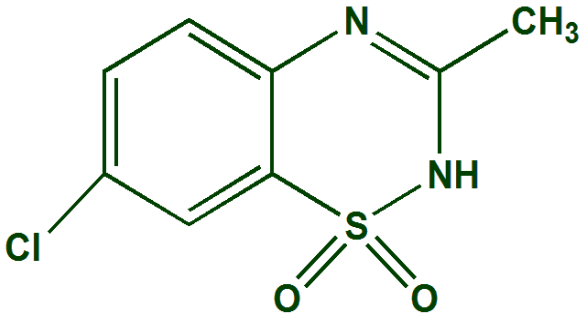
STRUCTURES OF DRUG MOLECULES 15,16,17,18



(15) Hydralazine



(18) Minoxidil



(17) Diazoxide

$Na_2[Fe(CN)_5NO]$

(16) Sodiumnitroprusside

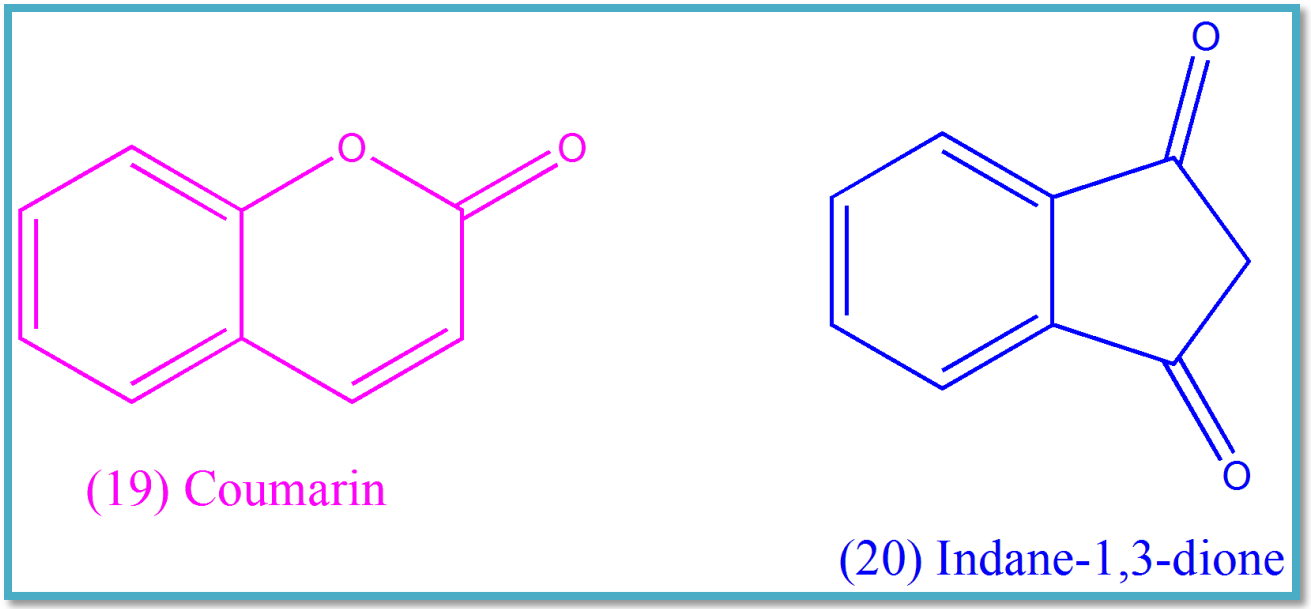
IV. DIRECT-ACTING VASODILATORY DRUGS

Drugs that induce dilation of the smooth muscle cells are useful in treating hypertension. These include

1. Hydralazine(15).
2. Sodium nitroprusside(16).
3. Calcium channel blockers and
4. Potassium channel openers.
5. Diazoxide(17) and Minoxidil(18).

   Both these drugs are potassium channel agonists that decrease the concentration of Ca^{2+} ions within the cells and thus reduce the excitability of the smooth muscle cells.

STRUCTURES OF DRUG MOLECULES 19, 20.



VI. ANTICOAGULANTS

- All the most catastrophic bleeding is rapidly stopped, in a process known as hemostasis.
- Hemostasis is a combination of many events arising from physical and chemical interactions between soluble components of the plasma.
- Clotting is the formation of a highly cross-linked insoluble hard mass containing cells, enzymes, and other proteins at the site of injury that prevents blood loss.
- Blood clot is medically known as thrombus.

THROMBOSIS : BLOOD CLOTTING

- Clot formation may also occur within the vasculature and without any external injury. Intravascular clotting or thrombosis can be caused by vascular injury or blood hypercoagulability.
- The clotting cascade is a sequence of chemical reactions mediated by enzymes present in the plasma.
- Anti-coagulants are molecules that prevent blood from clotting. They inhibit the chemical process of proteolytic formation of the three-dimensional fibrin polymer. These include heparin, low molecular weight heparin, coumarins(19) and 1,3-indanediones(20).

THANKS FOR WATCHING