








# Chapter 4. Anti-Anginal Drugs





## Syllabus:

-  **Vasodilators:** Amyl nitrite, Nitroglycerin\*, Pentaerythritol tetranitrate, Isosorbidedinitrite\*
-  Dipyridamole
-  **Calcium channel blockers:** Verapamil, Bepridil hydrochloride, Diltiazem hydrochloride, Nifedipine, Amlodipine, Felodipine, Nicardipine, Nimodipine

## 4.1. ANGINA PECTORIS

-  Angina pectoris is a condition of myocardial ischemia.
-  Angina occurs due to imbalance between myocardial oxygen demand and myocardial oxygen supply.
-  Oxygen supply not meet as per demand lead to hypoxia condition resulting in myocardial tissue injury and followed to myocardial infarction.
-  Main reason is the coronary vasospasm and atherosclerosis that impaired the blood flow to the heart

### 4.1.1. Classification of Angina Pectoris

-  **Classical Angina:** occurs due to increase cardiac workload by exercise, emotional stress and cold condition. Atherosclerosis is the main reason. Depressed S-T segment in ECG. Treated by antiplatelet drugs and thrombolytics.
-  **Unstable Angina:** attack in rest condition (Pre-Infarct). Occurs due to extensive coronary artery blockage due to atheroma and vasospasm. Treated by vasodilators and antiplatelet drugs.
-  **Variant or Prinz metal Angina:** unpredictable and attack during sleep and rest. Coronary vasospasm is the main reason which is caused by stress, cold, smoking, etc. Elevation of S-T segment in ECG. Treated by vasodilators.
-  **Silent Angina:** Ischemia without symptoms.


### Pharmacology/Pathophysiology lectures of Angina Pectoris

Pathophysiology: <https://youtu.be/0BgkxP-SY0I>

Drug Classification and MOA: <https://youtu.be/7xUAuwGYNMk>

Antiplatelet drugs: [https://youtu.be/EnuW\\_tOm0Yc](https://youtu.be/EnuW_tOm0Yc)

## 4.2. ANTIANGINAL DRUGS

 Drugs which are used to treatment of angina pectoris are known as antianginal drugs.

 The basic goal is to improve the coronary blood flow and discard the atheroma.

### Drug Classifications

#### A. Vasodilators

##### 1. Nitrates:

(a) *Short acting*: Glyceryl trinitrate (GTN, Nitroglycerine)

(b) *Long acting*: Isosorbide dinitrate (short acting by sublingual route), Isosorbide mononitrate, Erythryl tetranitrate, Penta erythritol tetranitrate

2.  $\beta$  Blockers: Propranolol, Metoprolol, Atenolol and others.

##### 3. Calcium channel blockers:

(a) *Phenyl alkylamine*: Verapamil

(b) *Benzothiazepine*: Diltiazem

(c) *Dihydropyridines*: Nifedipine, Felodipine, Amlodipine, S(-) Amlodipine, Nitrendipine, Lacidipine, Benidipine, Lercanidipine


4. **Potassium channel opener**: Nicorandil


#### B. Others


Dipyridamole, Trimetazidine, Ranolazine, Ivabradine, Oxyphedrine

### 4.2.1. Medicinal Chemistry of Antianginal Drugs

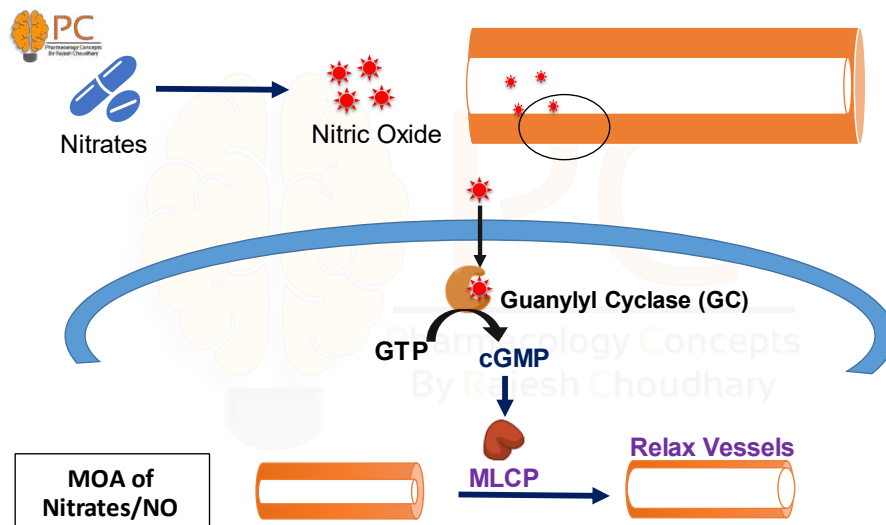
#### 1. Nitrates:

 Organic Nitrates are the polyester of nitric acid ( $-C-O-NO_2$ ), which donate NO a potent vasodilator

 **MOA**: NO activates the soluble guanylyl cyclase enzyme which is responsible for production of cGMP and further cGMP promotes the vasodilation by activation of myosin light chain phosphatase (MLCP).

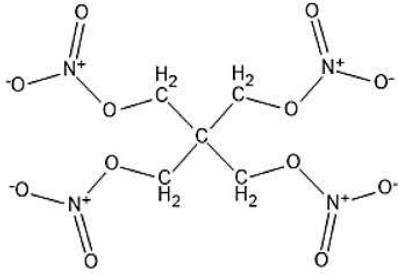
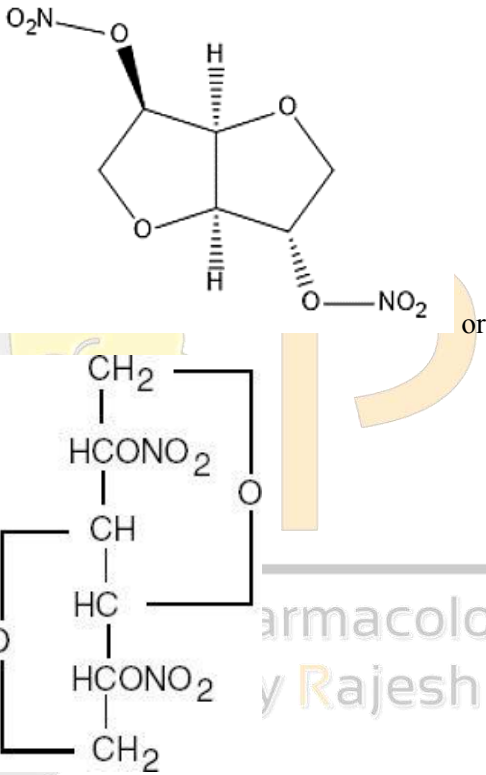
 **Uses**: Angina pectoris, myocardial ischemic diseases, cerebral or peripheral vascular disorders.

 **Pharmacology**: <https://youtu.be/2pJfCrtgYK8>

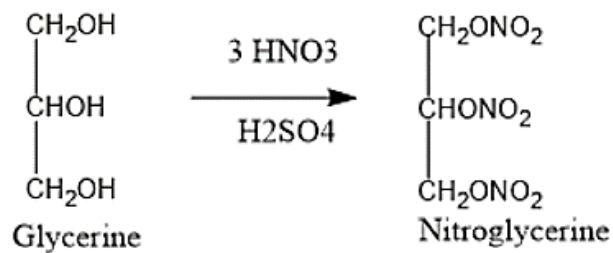


Animated Video link: <https://youtu.be/OxOHprGvbpk>

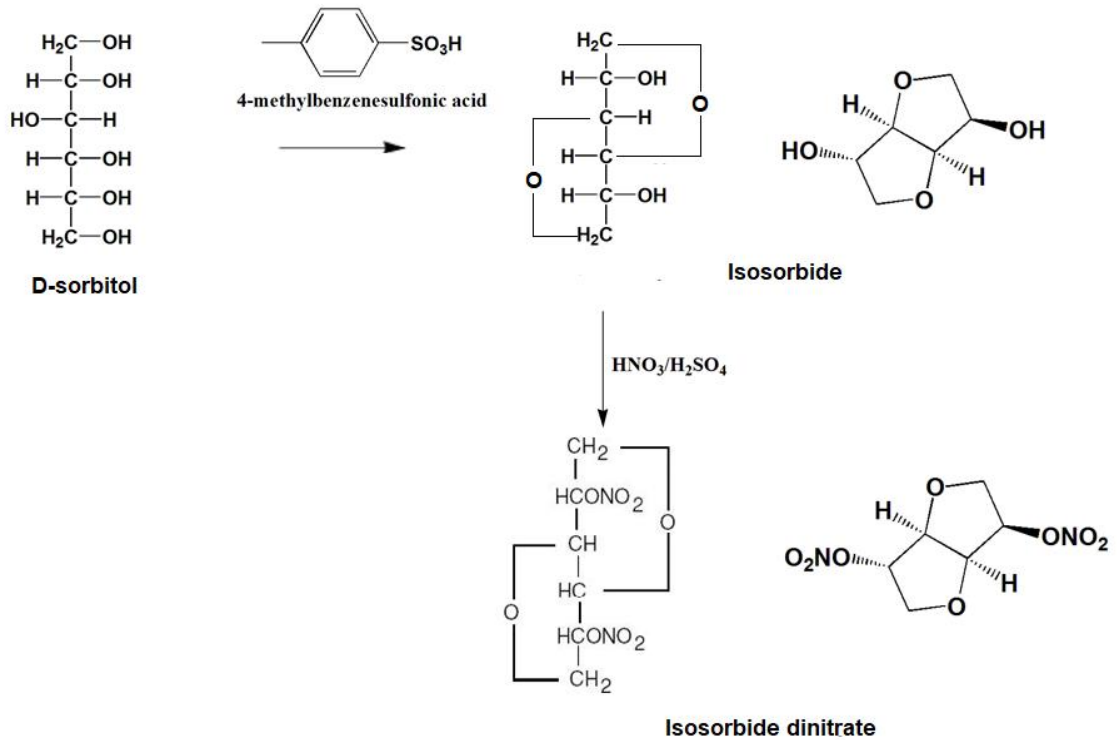
Name	Structure and IUPAC name	Uses
<b>Amyl Nitrite</b>	$  \begin{array}{c}  \text{CH}_3 \\    \\  \text{H}_3\text{C}-\text{CH}-\text{C}-\text{H}_2-\text{O}-\text{NO} \\    \\  \text{H}_2  \end{array}  $ 3-methyl-1-nitrosoxy butane	<ul style="list-style-type: none"> <li>Ischemic heart diseases</li> <li>Antidotes for Cyanide poisoning by oxidation</li> <li>In industries used as a cleaning agent</li> </ul>
<b>Amyl Nitrate</b>	$  \begin{array}{c}  \text{H}_3\text{C}-\text{C}-\text{H}_2-\text{C}-\text{H}_2-\text{O}-\text{N}^+=\text{O} \\    \quad   \\  \text{H}_2 \quad \text{H}_2  \end{array}  $ Pentyl nitrate	<ul style="list-style-type: none"> <li>Ischemic heart diseases</li> </ul>
<b>Nitroglycerine (Glyceryl trinitrate; GTN)</b>	$  \begin{array}{c}  \text{CH}_2-\text{O}-\text{NO}_2 \\    \\  \text{CH}-\text{O}-\text{NO}_2 \\    \\  \text{CH}_2-\text{O}-\text{NO}_2  \end{array}  $ 1,2,3-Trinitroxypropane	<ul style="list-style-type: none"> <li>Ischemic heart diseases</li> <li>Heart failure</li> <li>Taken sublingually in acute angina condition</li> </ul>

<p><b>Pentaerythritol tetranitrate</b></p>	 <p>3-nitrooxy-2,2-bis(nitrooxymethyl)propyl] nitrate</p>	<ul style="list-style-type: none"> <li>Ischemic heart diseases</li> <li>Also used as an explosive by military</li> </ul>
<p><b>Isosorbide dinitrate</b></p>	 <p>1,4:3,6-dianhydro-2,5-di-O-nitro-D-glucitol.</p>	<ul style="list-style-type: none"> <li>Ischemic heart diseases</li> <li>Taken sublingually in acute angina condition</li> </ul>

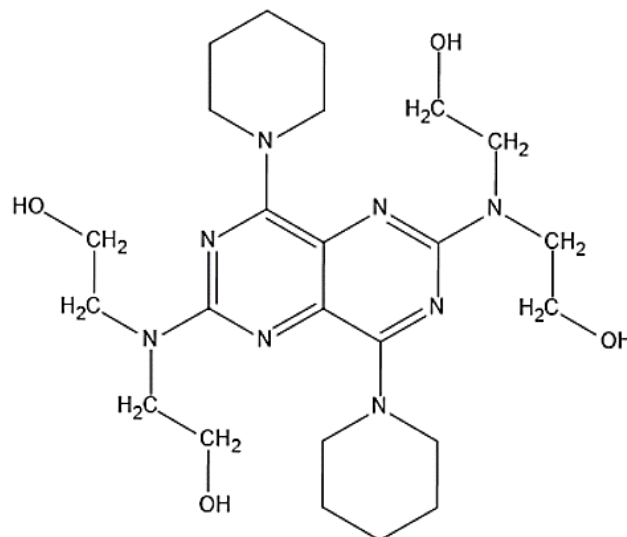
### Synthesis of Nitroglycerine



## Synthesis of Isosorbide dinitrate



## 2. Dipyridamole



2-[[2-[bis(2-hydroxyethyl)amino]-4,8-di(piperidin-1-yl)pyrimido[5,4-d]pyrimidin-6-yl]-(2-hydroxyethyl)amino]ethanol

2,2',2'',2'''-[(4,8-dipiperidin-1-yl)pyrimido[5,4-d]pyrimidine-2,6-diyl]dinitrilo]tetraethanol

**MOA:** Dipyridamole acts by two pathways

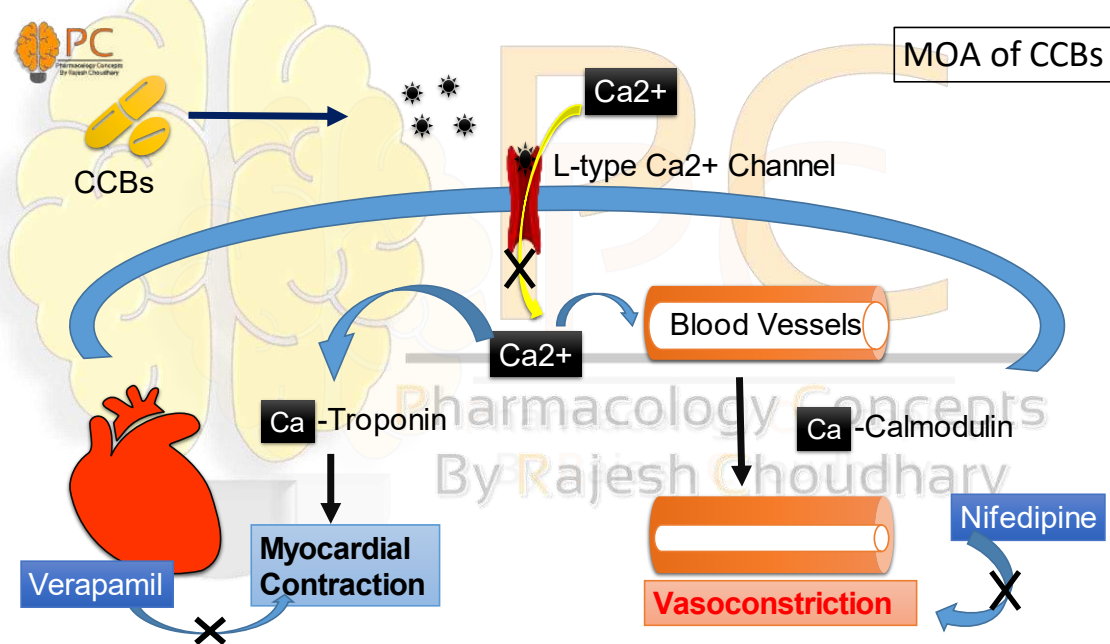
- 1) Inhibit the phosphodiesterase (PDE) enzyme and potentiate the cGMP & cAMP dependent effects.
- 2) Inhibit the cellular uptake of adenosine

**Uses:** It is an antiplatelet drug used along with anticoagulant drugs. it also dilate the blood vessels including coronary artery. It can be used in ischemic heart disease, pulmonary hypertension and thromboembolism.

### 3. Calcium Channel Blockers

- (a) *Phenyl alkylamine*: Verapamil
- (b) *Diaryl amino propyl amine*: Bepridil
- (b) *Benzothiazepine*: Diltiazem
- (c) *Dihydropyridines*: Nifedipine, Amlodipine, Felodipine, Nicardipine, Nimodipine

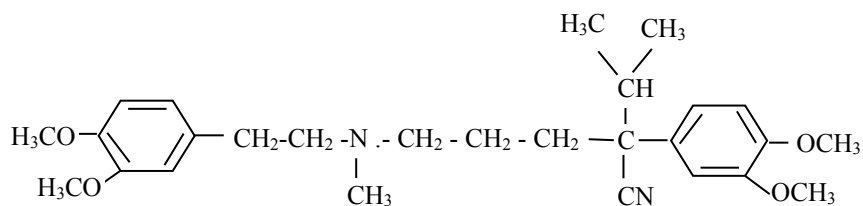
Pharmacology of CCBs: <https://youtu.be/7wRm1OY8bT8>



Animated Video Link: <https://youtu.be/9UMzJjXiNDM>

#### A) Phenyl alkylamine:

##### Verapamil



2-(3,4-dimethoxyphenyl)-5-[2-(3,4-dimethoxy phenyl)ethyl-methylamino]-2-propan-2-yl pentane nitrile

**MOA:** It blocks the L-type calcium channel mainly in myocardiocyte and suppress the cardiac activity. It also dilates arterioles and has some  $\alpha$ -adrenergic activity.

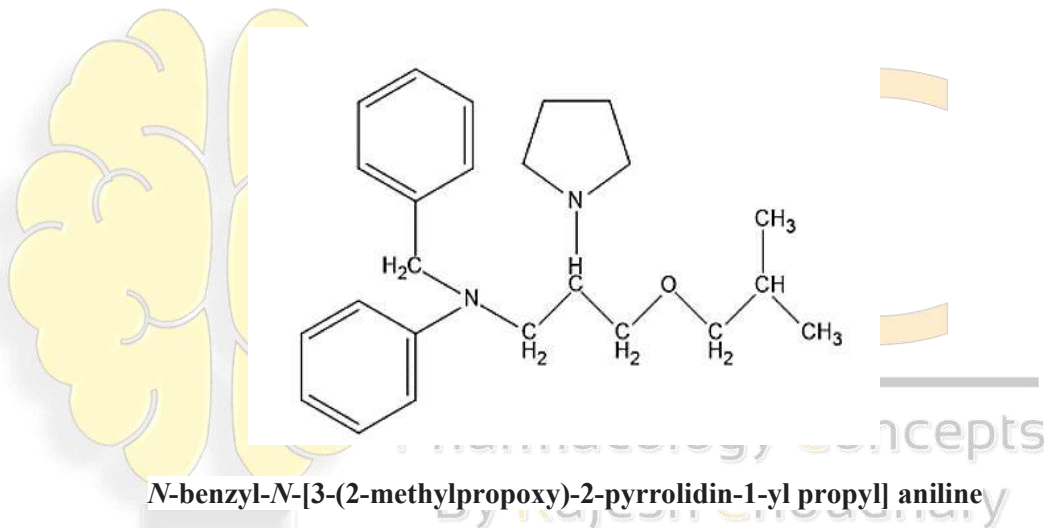
**Uses:** It has been used in the treatment of hypertension, angina pectoris, cardiac arrhythmia, and most recently, cluster headaches.

**Dose :** 40 – 120 mg TID (oral).

**\*\*The R-enantiomer is more effective at reducing blood pressure compared to the S-enantiomer. However, the S-enantiomer is 20 times more potent than the R-enantiomer at prolonging the PR interval in treating arrhythmias.**

### B) Diaryl amino propyl amine:

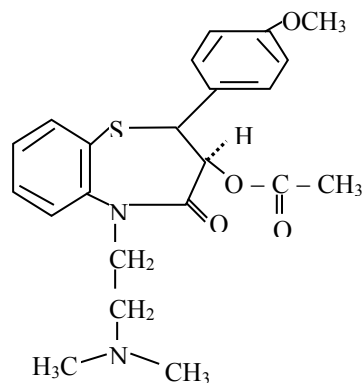
#### Bepridil



✓ Used in the treatment of Angina pectoris

### C) Benzothiazepine

#### Diltiazem



**(+) cis-3-(acetyloxy)-5-[2-dimethyl amino)ethyl]-2, 3-dihydro-2-(4-methoxy phenyl)-benzothiazepin-4(5H)-one**




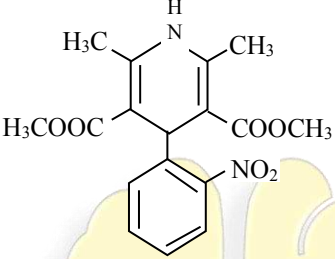
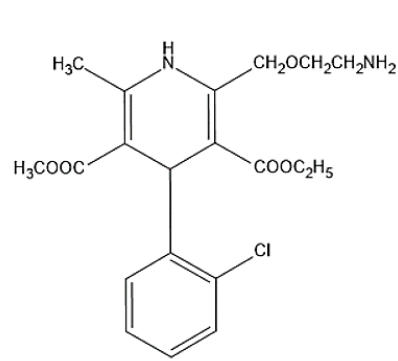
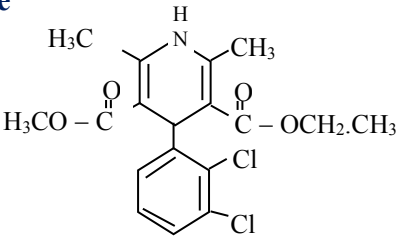
**MOA:** It blocks the L-type calcium channel in myocardiocytes and blood vessels. Less potent than verapamil and nifedipine

**Dose:** 30 – 60 mg TID/QID (oral).

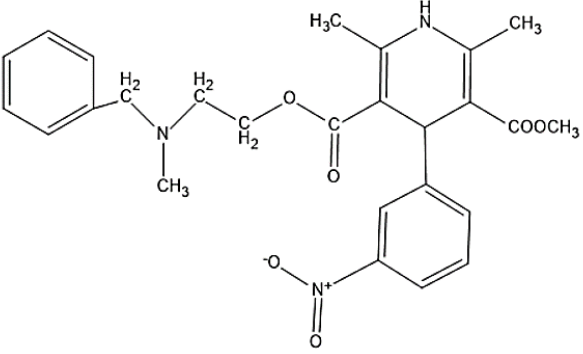
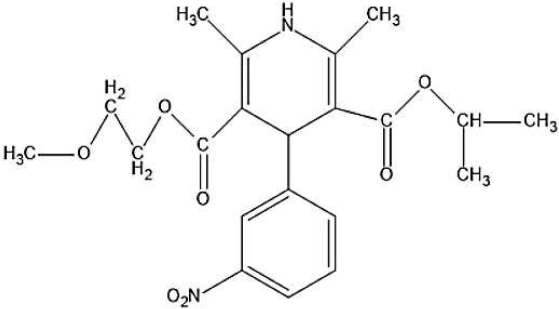
**Uses:** As an antihypertensive, antiarrhythmic & antianginal.

### D) Dihydropyridines

 They are **Vaso-selective** L-type calcium channel blockers, and not or little effects on heart

<p><b>Nifedipine</b></p>  <p>Dimethyl 1, 4-dihydro-2, 6-dimethyl-4-(2-nitrophenyl) pyridine-3, 5-dicarboxylate</p>	<ul style="list-style-type: none"> <li>▪ It dilates arterioles.</li> <li>▪ Nifedipine has no antiarrhythmic activity</li> <li>▪ It is used alone or in combination with diuretics or <math>\beta</math>-blockers in the management of hypertension.</li> <li>▪ It is also used in the prophylaxis of angina &amp; in the treatment of Raynaud's disease.</li> </ul>
<p><b>Amlodipine</b></p>  <p>3-O-ethyl 5-O-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydro pyridine-3,5-dicarboxylate</p>	<ul style="list-style-type: none"> <li>▪ Used in hypertension</li> <li>▪ and stable angina</li> </ul>
<p><b>Felodipine</b></p> 	<ul style="list-style-type: none"> <li>▪ Used in hypertension</li> <li>▪ and stable angina</li> </ul>



<p>5-<i>O</i>-ethyl 3-<i>O</i>-methyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate</p>	
<p><b>Nicardipine</b></p>  <p>5-<i>O</i>-[2-[benzyl(methyl) amino] ethyl] 3-<i>O</i>-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate</p>	<ul style="list-style-type: none"> <li>▪ It is a potent vasodilator, dilate the coronary artery and improve the blood flow</li> <li>▪ Used in ischemic heart disease</li> <li>▪ Also used in hypertension</li> </ul>
<p><b>Nimodipine</b></p>  <p>3-<i>O</i>-(2-methoxyethyl) 5-<i>O</i>-propan-2-yl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate</p>	<ul style="list-style-type: none"> <li>▪ It effectively dilates the cerebral blood vessels</li> <li>▪ Used in treatment of cerebral vascular disease</li> </ul>

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