ANTIANGINAL AGENTS

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How Does the Heart Function?

- https://www.youtube.com/watch?v=_qmNCJxpsr0

Types of Cardiovascular Diseases

Diseases of the Heart, Blood, and Blood Vessels

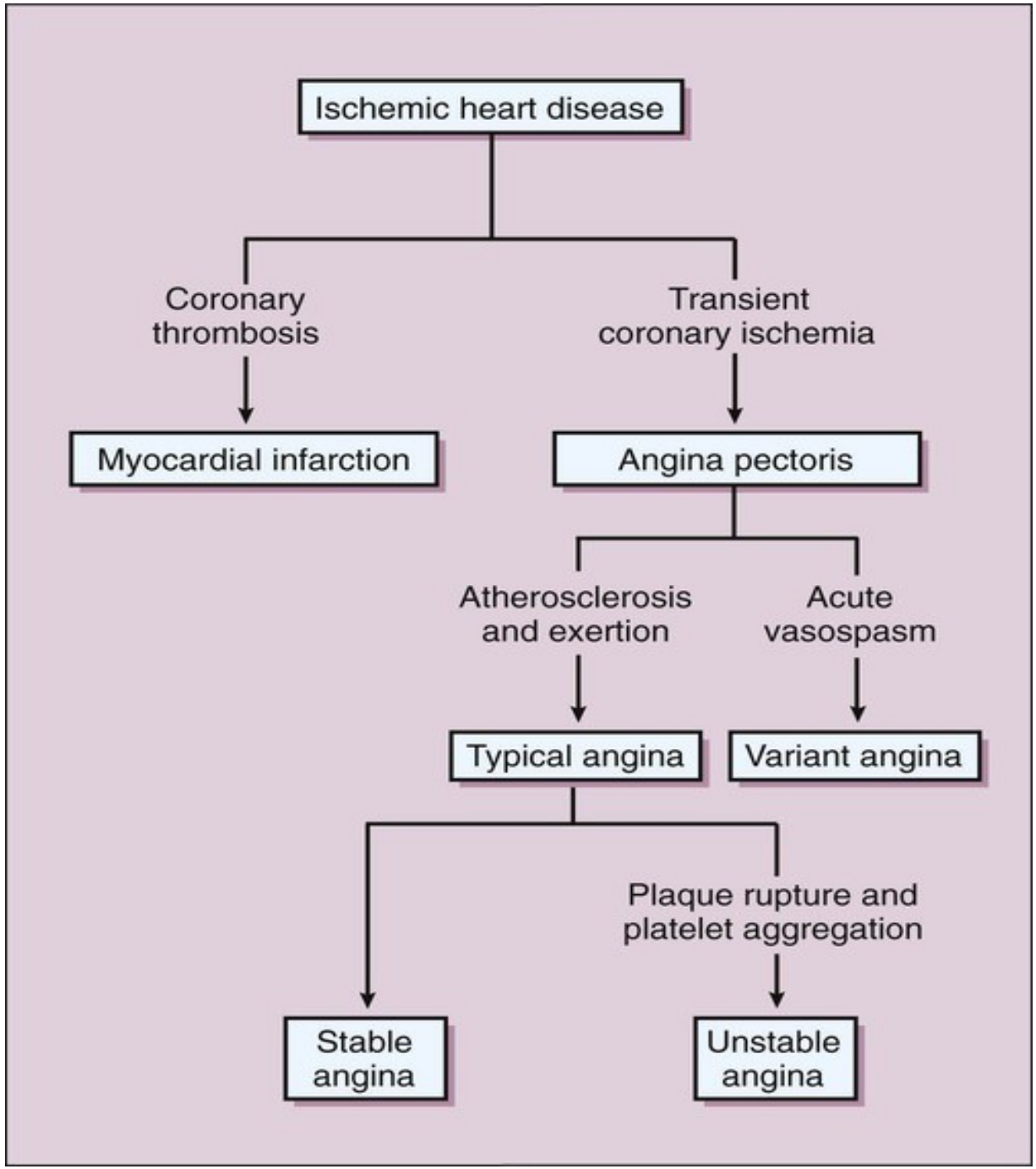
- **Hypertension**
- **Atherosclerosis**
- **Angina Pectoris**
- **Arrhythmias**
- **Heart Attack**
- **Congestive Heart Failure**
- **Stroke**

OUTLINE

- **Anti-anginal:** Introduction and Definition
- **Vasodilators:** Amyl nitrite, Nitroglycerin*, Pentaerythritol tetranitrate, Isosorbide dinitrite*, Dipyridamole.
- **Calcium channel blockers:** Verapamil, Bepridil hydrochloride, Diltiazem hydrochloride, Nifedipine, Amlodipine, Felodipine, Nicardipine, Nimodipine.

Introduction and Definition

- ***Antianginal drugs*** are those that prevent, abort or terminate attacks of angina pectoris.
- **Angina pectoris:** Angina pectoris, commonly known as angina, is severe chest pain due to ischemia (a lack of blood, hence a lack of oxygen supply) of the heart muscle, generally due to obstruction or spasm of the coronary arteries (the heart's blood vessels).
- It is caused by coronary blood flow that is insufficient to meet the oxygen demands of the myocardium, leading to ischemia.
- The imbalance between oxygen delivery and utilization may result during exertion, from a spasm of the vascular smooth muscle, or from obstruction of blood vessels caused by atherosclerotic lesions.


Ischemic heart disease
Coronary thrombosis
Transient coronary ischemia
Myocardial infarction
Angina pectoris
Atherosclerosis and exertion
Acute vasospasm
Typical angina
Variant angina
Plaque rupture and platelet aggregation
Stable angina
Unstable angina

Types of Angina

Two principal forms are recognized:

- ***Classical angina (common form):*** *Attacks* are predictably provoked (stable angina) by exercise, emotion, eating or coitus and subside when the increased energy demand is withdrawn.
- The underlying pathology is—severe arteriosclerotic affliction of larger coronary arteries (conducting vessels) which run epicardially and send perforating branches to supply the deeper tissue (Fig.1).
- The blood flow fails to increase during increased demand and ischaemic pain is felt.
- Drugs that are useful, primarily reduce cardiac work (directly by acting on heart or indirectly by reducing preload hence end diastolic pressure, and afterload).
- They may also cause favourable redistribution of blood flow to the ischaemic areas.

(b)***Variant/Prinzmetal/Vasospastic angina:*** (uncommon form)
Attacks occur at rest or during sleep and are unpredictable. They are due to recurrent localized (occasionally diffuse) coronary vasospasm (Fig.2)

Drugs are aimed at preventing and relieving the coronary vasospasm.

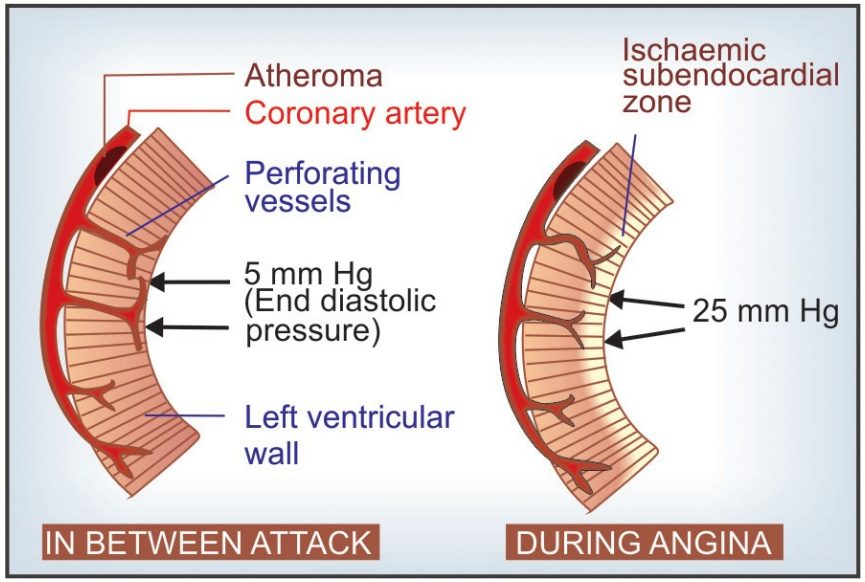


Fig.1 Attack of Angina

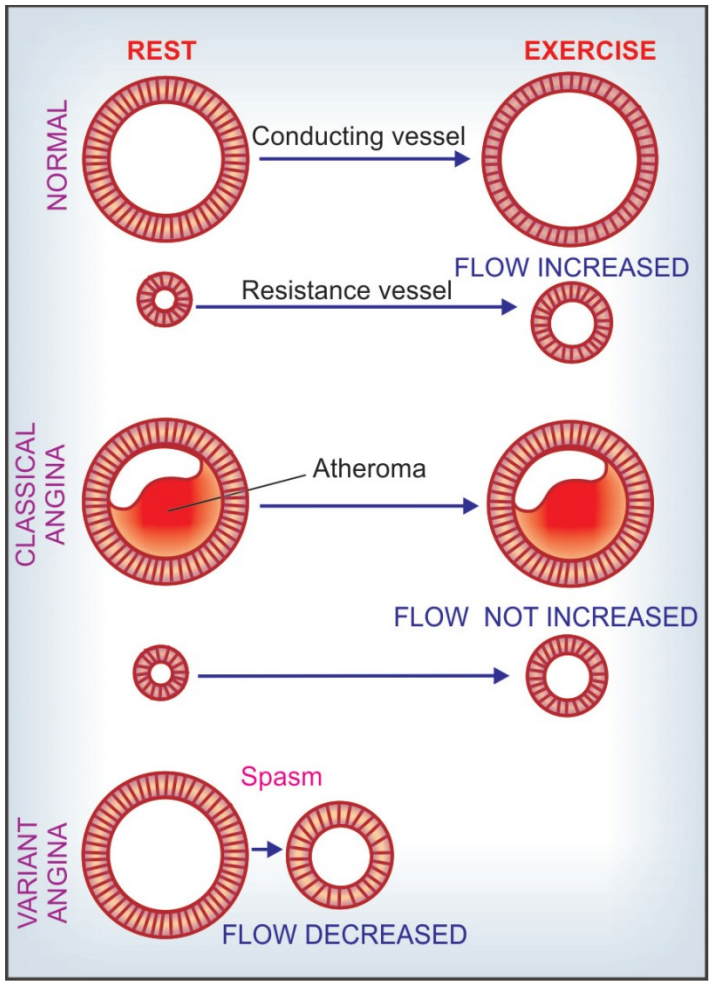


Fig.2 Types of Angina

- ***Unstable angina (UA)*** *with rapid increase in* duration and severity of attacks is mostly due to rupture of an atheromatous plaque attracting platelet deposition and progressive occlusion of the coronary artery; occasionally with associated coronary vasospasm.
- Chronically reduced blood supply causes atrophy of cardiac muscle with fibrous replacement (reduced myocardial work capacity → CHF) and may damage conducting tissue to produce unstable cardiac rhythms.
- Antianginal drugs relieve cardiac ischaemia but do not alter the course of coronary artery pathology: no permanent benefit is afforded.
- On the other hand, aspirin, ACE inhibitors and statins (hypocholesterolaemic) can modify coronary artery disease and improve prognosis

Major risk factors

- Age (≥ 55 for men, ≥ 65 for women)
- Cigarette smoking
- Diabetes mellitus (DM)
- Dyslipidemia
- Family History
- Hypertension (HTN)
- Kidney disease
- Obesity
- Physical inactivity
- Medications

CLASSIFICATION

1. *Nitrates*

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

(b) *Long acting:* *Isosorbide dinitrate (short* acting by sublingual route), Isosorbide mononitrate, Erythrityl tetranitrate, Pentaerythritol tetranitrate

2. β *Blockers* Propranolol, Metoprolol, Atenolol and others.

3. *Calcium channel blockers*

(a) *Phenyl alkylamine:* *Verapamil*

(b) *Benzothiazepine**:*** *Diltiazem*

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

(d) Diamino propanol ethers: Bepridil

4. *Potassium channel opener* *Nicorandil*

5. *Others* *Dipyridamole, Trimetazidine, Ranolazine, Ivabradine,Oxyphedrine*

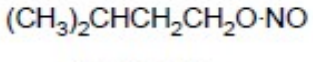
Clinical classification

A. *Used to abort or terminate attack* *GTN,* Isosorbide dinitrate (sublingually).

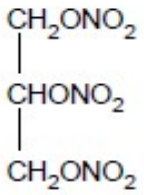
B. *Used for chronic prophylaxis* *All other drugs*

Classification

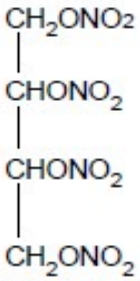
I. Nitrites and Nitrates



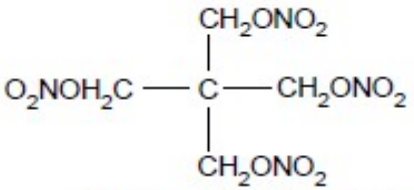
Amyl nitrite



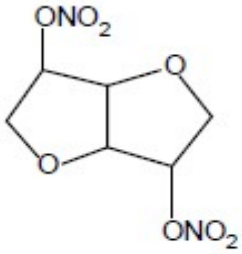
Nitroglycerine



Erythrityl tetranitrate



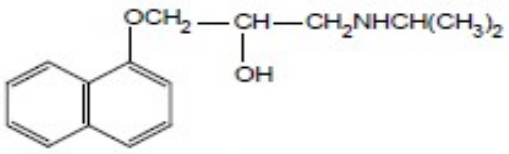
Pentaerythritol tetranitrate



Isosorbide dinitrate

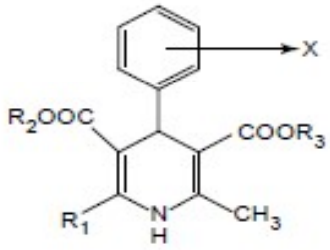
Classification

II. β-Adrenergic blocking agents



Propranolol

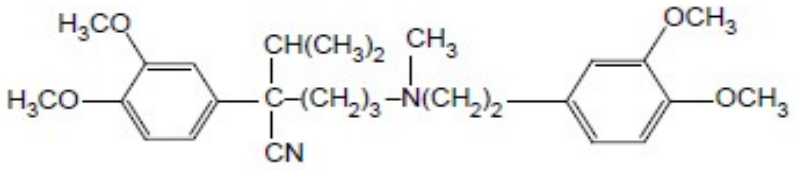
III. Calcium channel blockers
a. 1,4-Dihydro Pyridines



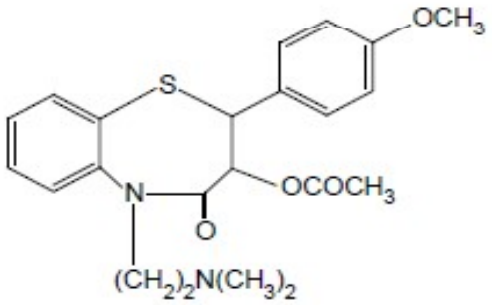
S. No.	Compound	R_1	R_2	R_3	X
1	Amlodipine	$-CH_2O(CH_2)_2NH_2$	$-C_2H_5$	$-CH_3$	2–Cl
2	Felodipine	$-CH_3$	$-C_2H_5$	$-CH_3$	2,3–Cl
3	Nifedipine	$-CH_3$	$-CH_3$	$-CH_3$	2–NO_2
4	Nitrendipine	$-CH_3$	$-CH_3$	$-C_2H_5$	3–NO_2
5	Nimodipine	$-CH_3$	$-CH_2CH_2OCH_3$	$-CH(CH_3)_2$	3–NO_2
6	Nisoldipine	$-CH_3$	$-CH_2CH(CH_3)_2$	$-CH_3$	2–NO_2

Classification

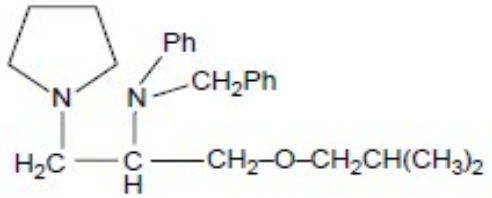
b. Diphenyl alkylamines
i. Verapamil



c. Benzothiazepine derivatives
i. Diltiazem

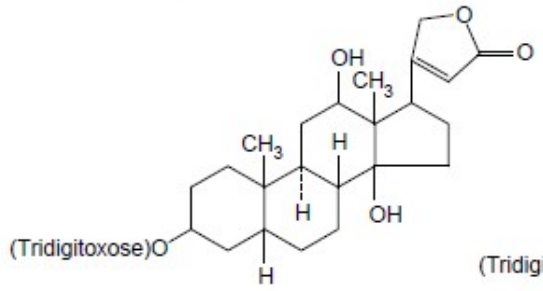


d. Diamino propanol ethers
i. Bepridil

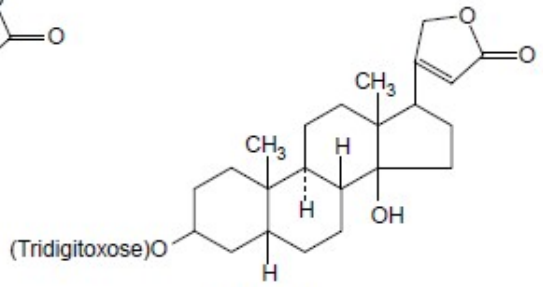


Classification

IV. Cardiovascular glycosides



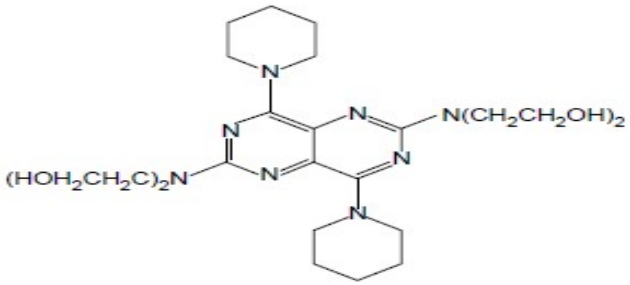
Digoxin



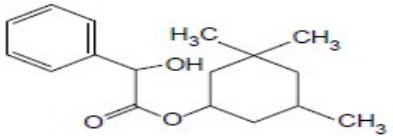
Digitoxin

V. Miscellaneous

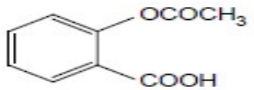
i. Dipyridamole



ii. Cyclandelate



iii. Aspirin



Treatment

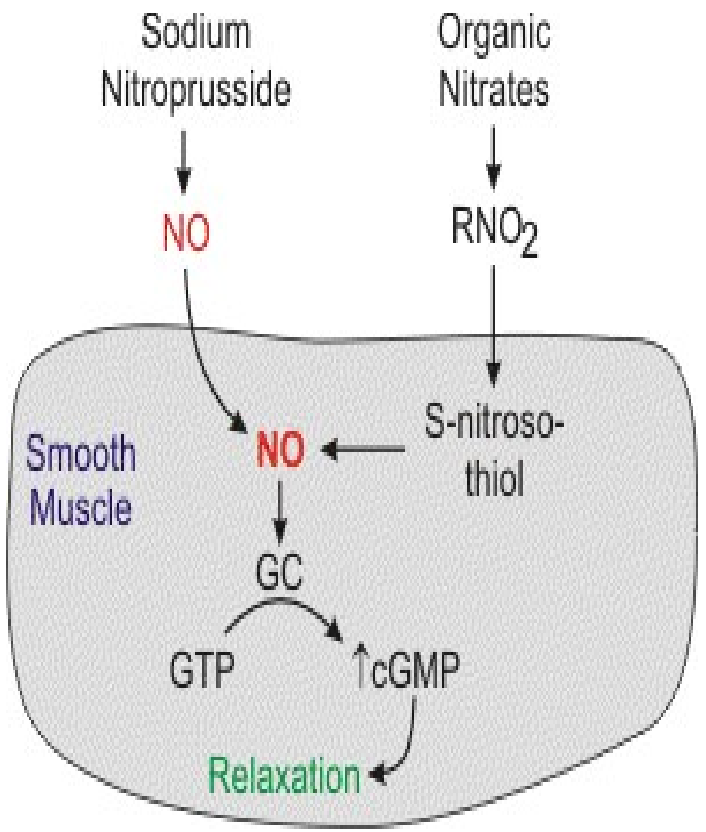
- Different classes of drugs, used either alone or in combination, are effective in treating patients with angina.
- These agents lower the oxygen demand of the heart by affecting blood pressure, venous return, heart rate, and contractility.

VASODILATORS: Organic Nitrates

- Organic nitrates (and nitrites) used in the treatment of angina pectoris are simple nitric and nitrous acid esters of glycerol.
- These compounds cause a rapid reduction in myocardial oxygen demand, followed by rapid relief of symptoms.
- They are effective in stable and unstable angina as well as in variant angina pectoris.
- All these agents are effective, but they differ in their onset of action and rate of elimination
- For prompt relief of an ongoing attack of angina precipitated by exercise or emotional stress, sublingual (or spray form) nitroglycerin is the drug of choice

MOA: Organic Nitrates

- Nitrates decrease coronary vasoconstriction or spasm and increase perfusion of the myocardium by relaxing coronary arteries.
- In addition, they relax veins, decreasing preload and myocardial oxygen consumption.
- Organic nitrates, such as nitroglycerin, which is also known as glyceryltrinitrate, are thought to relax vascular smooth muscle by their intracellular conversion to nitrite ions, and then to nitric oxide, which in turn activates guanylatecyclaseand increases the cells' cyclic guanosinemonophosphate(GMP).
- Elevated cGMP ultimately leads to dephosphorylation of the myosin light chain, resulting in vascular smooth muscle relaxation



MOA: Organic Nitrates

- At therapeutic doses, nitroglycerin has two major effects:
- **First,** it causes dilation of the large veins, resulting in pooling of blood in the veins. This ***diminishes preload*** (venous return to the heart) and reduces the work of the heart.
- **Second,** nitroglycerin dilates the coronary vasculature, providing an increased blood supply to the heart muscle.
- Nitroglycerin decreases myocardial oxygen consumption because of decreased cardiac work.

Organic Nitrates

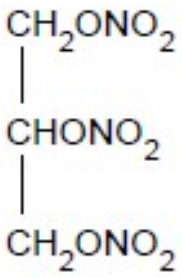
- The time to onset of action varies from 1 minute for nitroglycerin to more than 1 hour for isosorbidemononitrate
- Significant first-pass metabolism of nitroglycerin occurs in the liver. Therefore, it is common to take the drug either sublingually or via a transdermal patch, thereby avoiding this route of elimination.
- Isosorbidemononitrate owes its improved bioavailability and long duration of action to its stability against hepatic breakdown
- Oral isosorbidedinitrate undergoes denitration to two mononitrates, both of which possess antianginal activity.

Amyl nitrite

(CH3)2CHCH2CH2O.NO

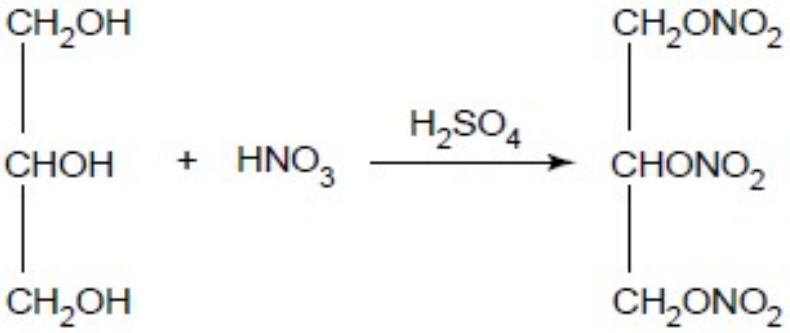
- **Properties and uses**: It is a clear yellowish liquid with an ethereal, fruity odour, and pungent, aromatic taste. It is insoluble in water, but miscible with alcohol, chloroform, or ether.
- It is a mixture of isomeric amyl nitrites, but is principally isoamyl nitrite. It is mainly used to treat angina pectoris. It is also effective in the emergency management of cyanide poisoning by causing the oxidation of haemoglobin to the compound methemoglobin.
- **Dose:** The usual dose of amyl nitrite 0.18 or 0.3 ml.

Nitroglycerin*
(Glyceryl trinitrate)



1,2,3-Propanetriol trinitrate

Synthesis



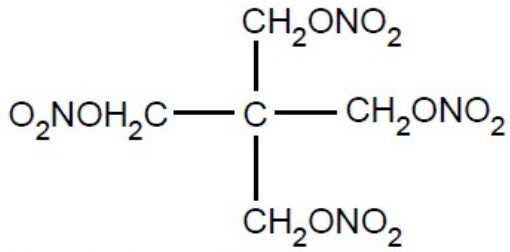
Propane-1,2,3-triol

Nitroglycerine

Nitroglycerin

- **Properties and uses:** It is a colourless, odourless liquid with a sweet taste.
- Glyceryl trinitrate is the trinitrate ester of glycerol.
- Nitroglycerine is used in angina pectoris and extensively as an explosive in dynamite.
- A solution of the ester, if spilled or allowed to evaporate, will leave a residue of nitroglycerine.
- To prevent an explosion of the residue, the ester must be decomposed by addition of alkali. Even then the material dispensed is so dilute that the risk of explosions does not exist.

Pentaerythritol tetranitrate



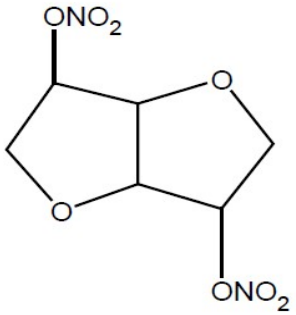
2,2-bis(hydroxy methyl)-1,3-propane diol tetranitrate

Properties and uses:

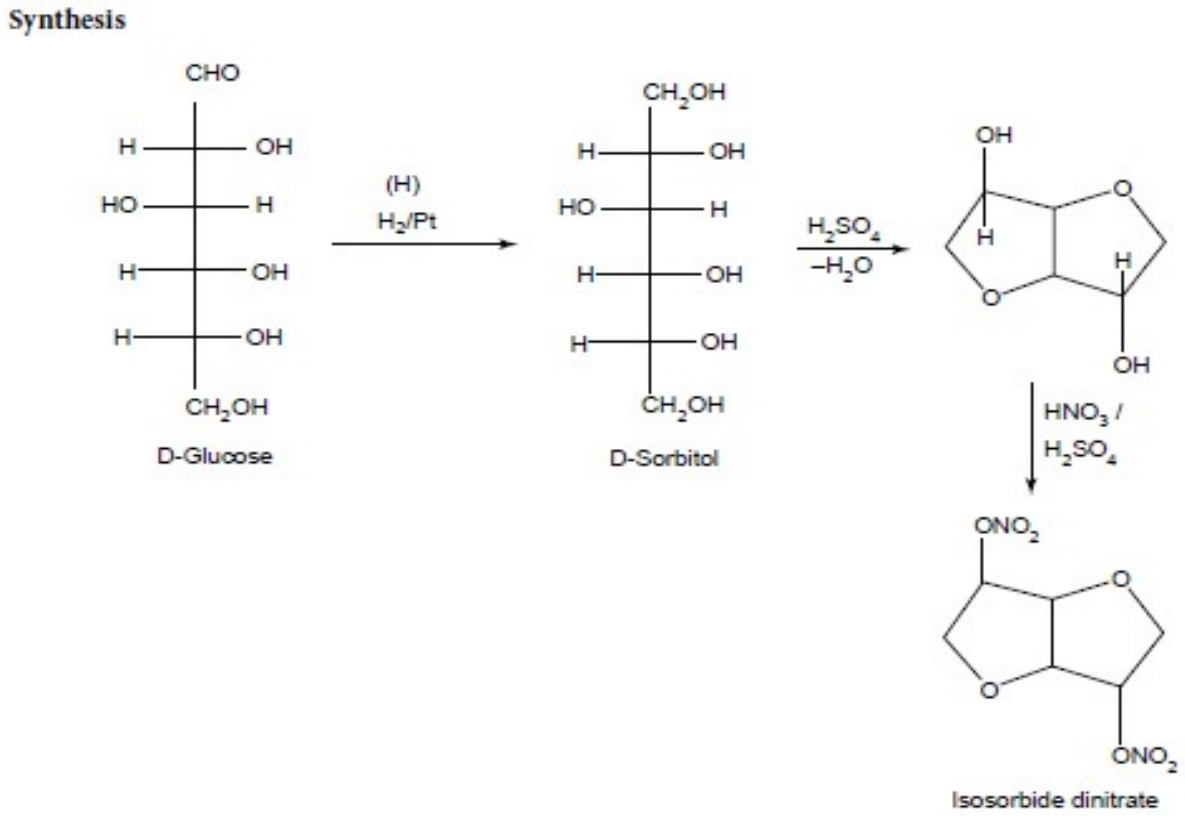
•It is a white or slightly yellowish powder that is practically insoluble in water, soluble in acetone, and slightly soluble in alcohol. It is used in the treatment of angina pectoris.

• It relaxes the smooth muscle of smaller vessels in the coronary vascular tree.

Isosorbide dinitrite*



[(3*S*,3*aS*,6*R*,6*aS*)-3-nitrooxy-2,3,3*a*,5,6,6*a*-hexahydrofuro[3,2-b]furan-6-yl] nitrate



Isosorbide dinitrite

Properties and uses:

- It is a fine white crystalline powder, slightly soluble in water, well soluble in acetone, but sparingly soluble in alcohol.
- It is effective in the treatment of acute angina attack.

Storage: It should be stored in well-closed airtight containers and protected from light.

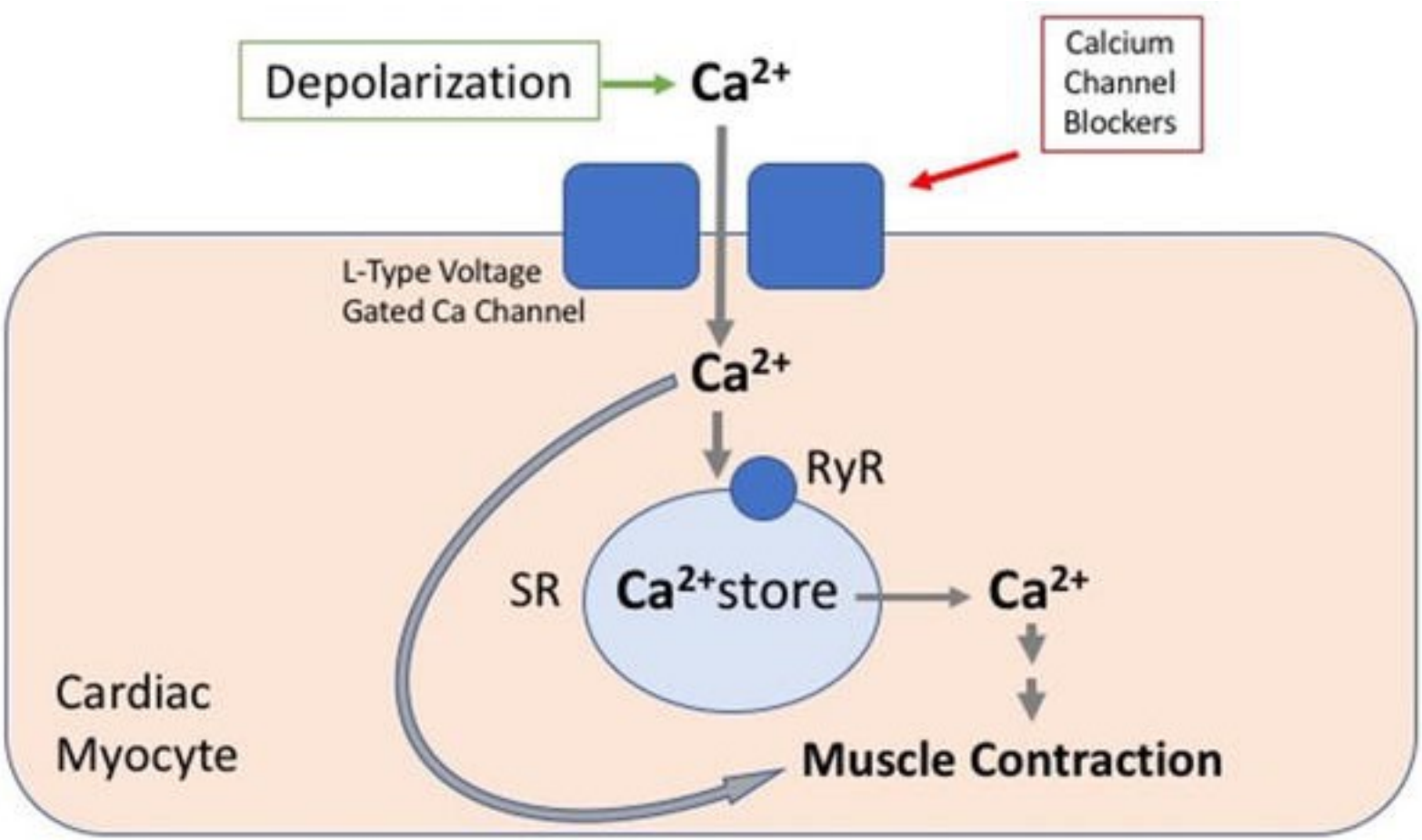
Dose: Sublingual: 5–10 mg every 2–3 h, Oral: 5–60 mg every 4–6 h; chewable tablet: 5–10 mg every 2–4 h.

Dosage forms: Isosorbide dinitrate tablet B.P. (Isordil Tablets)

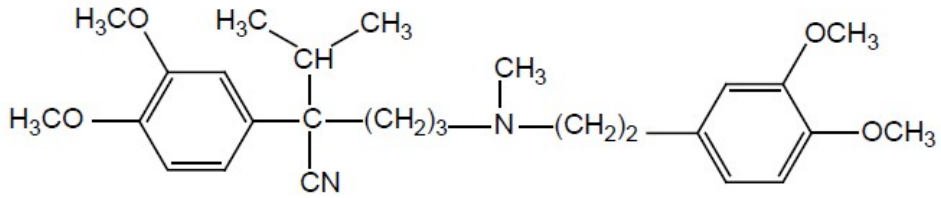
Calcium Channel Blockers

- Calcium is essential for muscular contraction. Calcium influx is increased in ischemia because of the membrane depolarization that hypoxia produces.
- In turn, this promotes the activity of several adenosine triphosphate consuming enzymes, thereby depleting energy stores and worsening the ischemia.
- The calcium-channel blockers protect the tissue by inhibiting the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds.
- All calcium-channel blockers are therefore **arteriolar vasodilators** that cause a decrease in smooth muscle tone and vascular resistance.

MOA: Calcium Channel Blockers



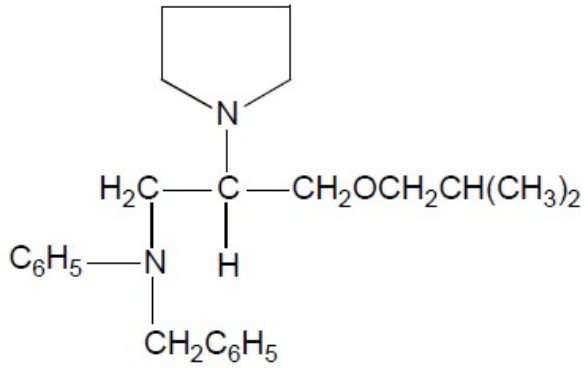
Verapamil



2-(3,4-dimethoxyphenyl)-5-[2-(3,4-dimethoxyphenyl)ethyl-methylamino]-2-propan-2-ylpentanenitrile

- Verapamil is a first generation calcium channel blocker used for treatment of hypertension, angina pectoris and superventricular tachyarrhythmias.
- Also known as rapam or isoptin, Verapamil belongs to the class of organic compounds known as phenylbutylamines.
- Phenylbutylamines are compounds containing a phenylbutylamine moiety, which consists of a phenyl group substituted at the fourth carbon by an butan-1-amine.
- Verapamil exists as a solid and is considered to be practically insoluble (in water) and relatively neutral.
- Verapamil has been found throughout most human tissues, and has also been detected in multiple biofluids, such as urine and blood.
- Within the cell, verapamil is primarily located in the membrane (predicted from logP.
- Verapamil is a drug which is used for the treatment of hypertension, angina, and cluster headache prophylaxis.

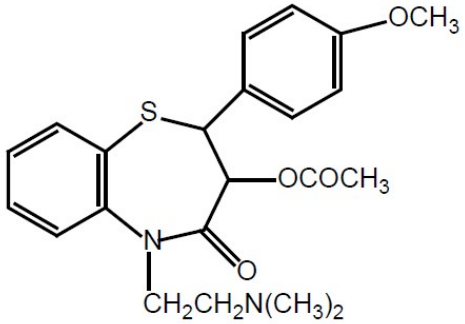
Bepridil hydrochloride



N-benzyl-*N*-(3-isobutoxy-2-(pyrrolidin-1-yl)propyl)benzenamine

- Bepridil is Second-Generation Alkyl Amine type Calcium Channel Blockers-a tertiary amine in which the substituents on nitrogen are benzyl, phenyl and 3-(2-methylpropoxy)-2-(pyrrolidin-1-yl)propyl.
- It is a tertiary amine and a member of pyrrolidines.
- Bepridil is considered to be a practically insoluble (in water) and relatively neutral molecule.
- Bepridil has been detected in multiple biofluids, such as urine and blood. Within the cell, bepridil is primarily located in the cytoplasm and membrane (predicted from logP). Bepridil can be converted into bepridil hydrochloride and bepridil hydrochloride monohydrate.
- It has a role as a vasodilator agent, an anti-arrhythmia drug, an antihypertensive agent and a calcium channel blocker.

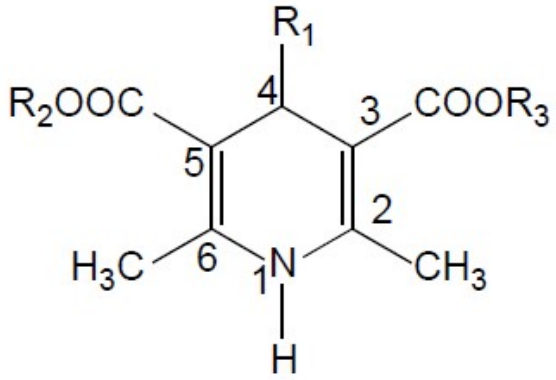
Diltiazem hydrochloride



[(2*S*,3*S*)-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3-dihydro-1,5-benzothiazepin-3-yl] acetate;hydrochloride

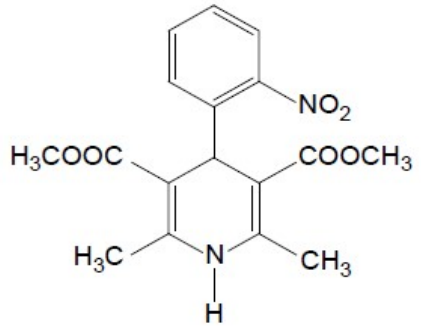
- Diltiazem Hydrochloride is a benzothiazepine calcium channel blocking agent.
- It inhibits the transmembrane influx of extracellular calcium ions into select myocardial and vascular smooth muscle cells, causing dilatation of coronary and systemic arteries and decreasing myocardial contractility.
- Because of its vasodilatory activity, this agent has been shown to improve the microcirculation in some tumors, thereby potentially improving the delivery of antineoplastic agents to tumor cells. (NCI04)
- A calcium-channel blocker and vasodilator, it is used in the management of angina pectoris and hypertension.

SAR of Dihydropyridines



- 1, 4-Dihydro pyridine ring is essential for activity. Substitution at N or oxidation or reduction of the ring reduces or abolishes the activity.
- A phenyl substitution at the 4th position is optimum for the activity. Substitution at para or unsubstituted phenyl ring reduces the activity.
- The 3rd and 5th position ester group optimizes activity. Placement of electron withdrawing substitution results in agonistic activity.
- When the ester at C3 and C5 are non-identical, the C4 become chiral and stereo selectivity is observed.
- S-enantiomers found to be more effective.

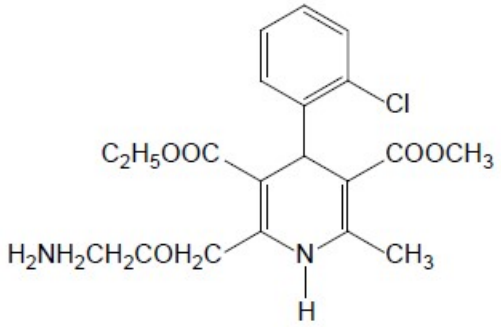
Nifedipine



3,5-Dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

- Nifedipine is a dihydropyridine calcium channel blocking agent: a first generation calcium channel blocker used to treat hypertension and angina pectoris.
- It belongs to the class of organic compounds known as dihydropyridinecarboxylic acids and derivatives. Dihydropyridinecarboxylic acids and derivatives are compounds containing a dihydropyridine moiety bearing a carboxylic acid group.
- Nifedipine inhibits the transmembrane influx of extracellular calcium ions into myocardial and vascular smooth muscle cells, causing dilatation of the main coronary and systemic arteries and decreasing myocardial contractility.
- This agent also inhibits the drug efflux pump P-glycoprotein which is overexpressed in some multi-drug resistant tumors and may improve the efficacy of some antineoplastic agents. (NCI04)
- Nifedipine is a drug which is used for the management of vasospastic angina, chronic stable angina, hypertension, and raynaud's phenomenon. may be used as a first line agent for left ventricular hypertrophy and isolated systolic hypertension (long-acting agents).

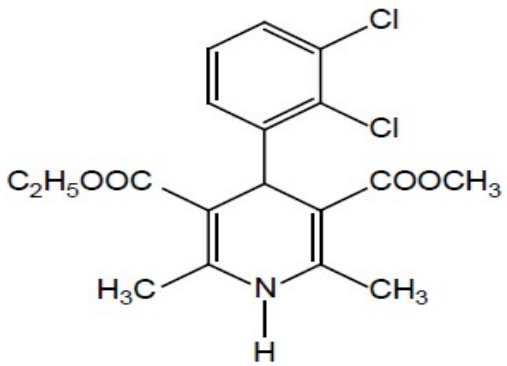
Amlodipine



3-Ethyl-5-methyl-2-((2-aminoethoxy)methyl)-4-(2-chlorophenyl)
-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate

- Amlodipine is a fully substituted dialkyl 1,4-dihydropyridine-3,5-dicarboxylate derivative, which is used for the treatment of hypertension, chronic stable angina and confirmed or suspected vasospastic angina.
- It is a dihydropyridine, a member of monochlorobenzenes, an ethyl ester, a methyl ester and a primary amino compound.
- Amlodipine inhibits the influx of extracellular calcium ions into myocardial and peripheral vascular smooth muscle cells, thereby preventing vascular and myocardial contraction. This results in a dilatation of the main coronary and systemic arteries, decreased myocardial contractility, increased blood flow and oxygen delivery to the myocardial tissue, and decreased total peripheral resistance.
- It has a role as an antihypertensive agent, a calcium channel blocker and a vasodilator agent.

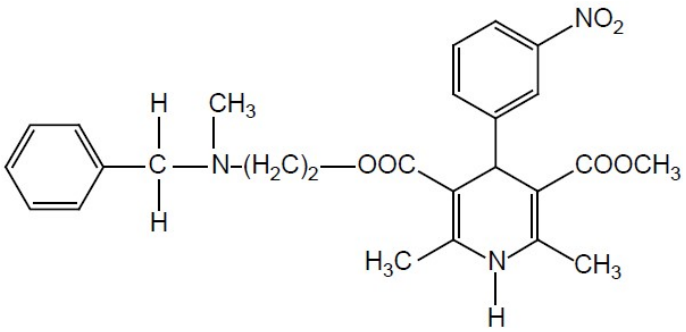
Felodipine



3-Ethyl 5-methyl 4-(2,3-dichlorophenyl)
-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

- Felodipine, also known as plendil or felo biochemie, belongs to the class of organic compounds known as dihydropyridinecarboxylic acids and derivatives.
- Dihydropyridinecarboxylic acids and derivatives are compounds containing a dihydropyridine moiety bearing a carboxylic acid group.
- Felodipine is a second generation calcium channel blocker and commonly used antihypertensive and antianginal agent.
- Felodipine inhibits the influx of extracellular calcium ions into myocardial and vascular smooth muscle cells, causing dilatation of the main coronary and systemic arteries and decreasing myocardial contractility.
- This agent also inhibits the drug efflux pump P-glycoprotein which is overexpressed in some multi-drug resistant tumors and may improve the efficacy of some antineoplastic agents. (NCI04)

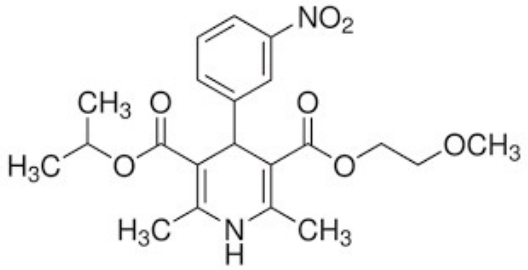
Nicardipine



5-*O*-[2-[benzyl(methyl)amino]ethyl] 3-*O*-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

- Nicardipine is a synthetic derivative of nitrophenyl-pyridine and potent calcium channel blocker.
- Nicardipine (Nifedipine Family) blocks calcium ions from certain cell walls and inhibits contraction of coronary and peripheral arteries, resulting in lowered oxygen requirements for heart muscle and decreased arterial contraction and spasm. It is used clinically as a cerebral and coronary vasodilator.
- Nicardipine is used for the management of patients with chronic stable angina and for the treatment of hypertension.

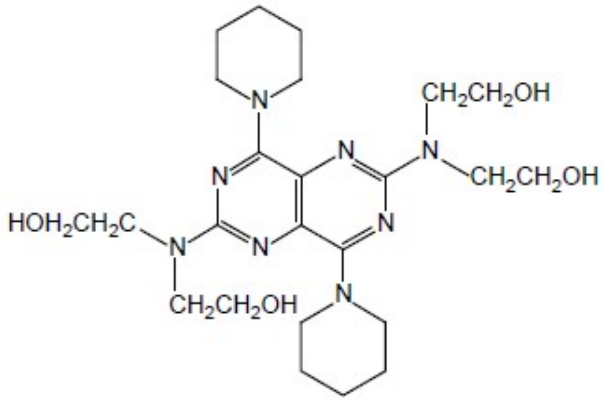
Nimodipine



3-*O*-(2-methoxyethyl) 5-*O*-propan-2-yl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

- Nimodipine is a dihydropyridine that is 1,4-dihydropyridine which is substituted by methyl groups at positions 2 and 6, a (2-methoxyethoxy)carbonyl group at position 3, a m-nitrophenyl group at position 4, and an isopropoxycarbonyl group at position 5.
- Nimodipine inhibits the transmembrane influx of calcium ions in response to depolarization in smooth muscle cells, thereby inhibiting vascular smooth muscle contraction and inducing vasodilatation. Nimodipine has a greater effect on cerebral arteries than on peripheral smooth muscle cells and myocardial cells, probably because this agent can cross the blood brain barrier due to its lipophilic nature.
- An L-type calcium channel blocker, it acts particularly on cerebral circulation, and is used both orally and intravenously for the prevention and treatment of subarachnoid hemorrhage from ruptured intracranial aneurysm.
- It has a role as an antihypertensive agent, a calcium channel blocker, a vasodilator agent and a cardiovascular drug.

Misc. Agents: Dipyridamole



2,2-*bis* [diethanol amino]-4,8-dipiperidine pyrimido-[5,4-d]-pyrimidine

Properties and uses:

•It is a bright yellow crystalline powder, which dissolves in dilute solutions of mineral acids, but insoluble in water, soluble in acetone and ethanol.

•The drug inhibits adenosine deaminase in erythrocytes and interacts with the uptake of vasodilator adenosine by erythrocytes.

•These actions potentiate the effect of prostacyclin, which acts as an inhibitor to platelet aggregation. It is a long-acting vasodilator.

•Its vasodilating effect is selective for the coronary system. It is also used to treat angina pectoris.

Thank you