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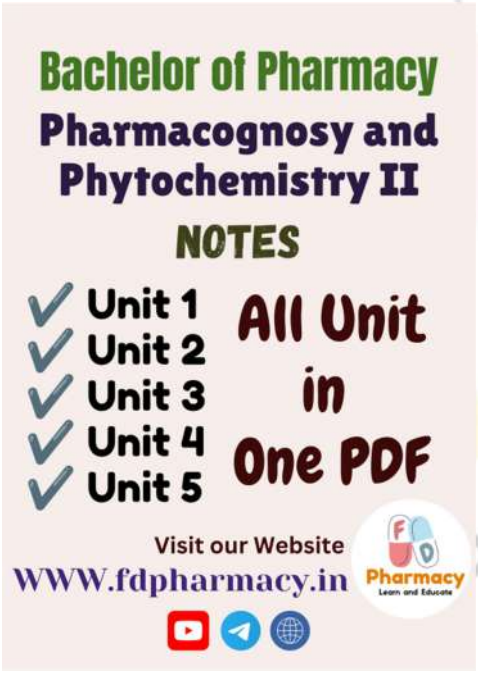
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MEDICINAL CHEMISTRY - II

UNIT 2

TOPIC :

- **Anti-anginal :**

  Vasodilators : Amylnitrite, Nitroglycerin, Pentaerythritol tetranitrate, Isosorbide dinitrite, Dipyridamole.

Angina Pectoris

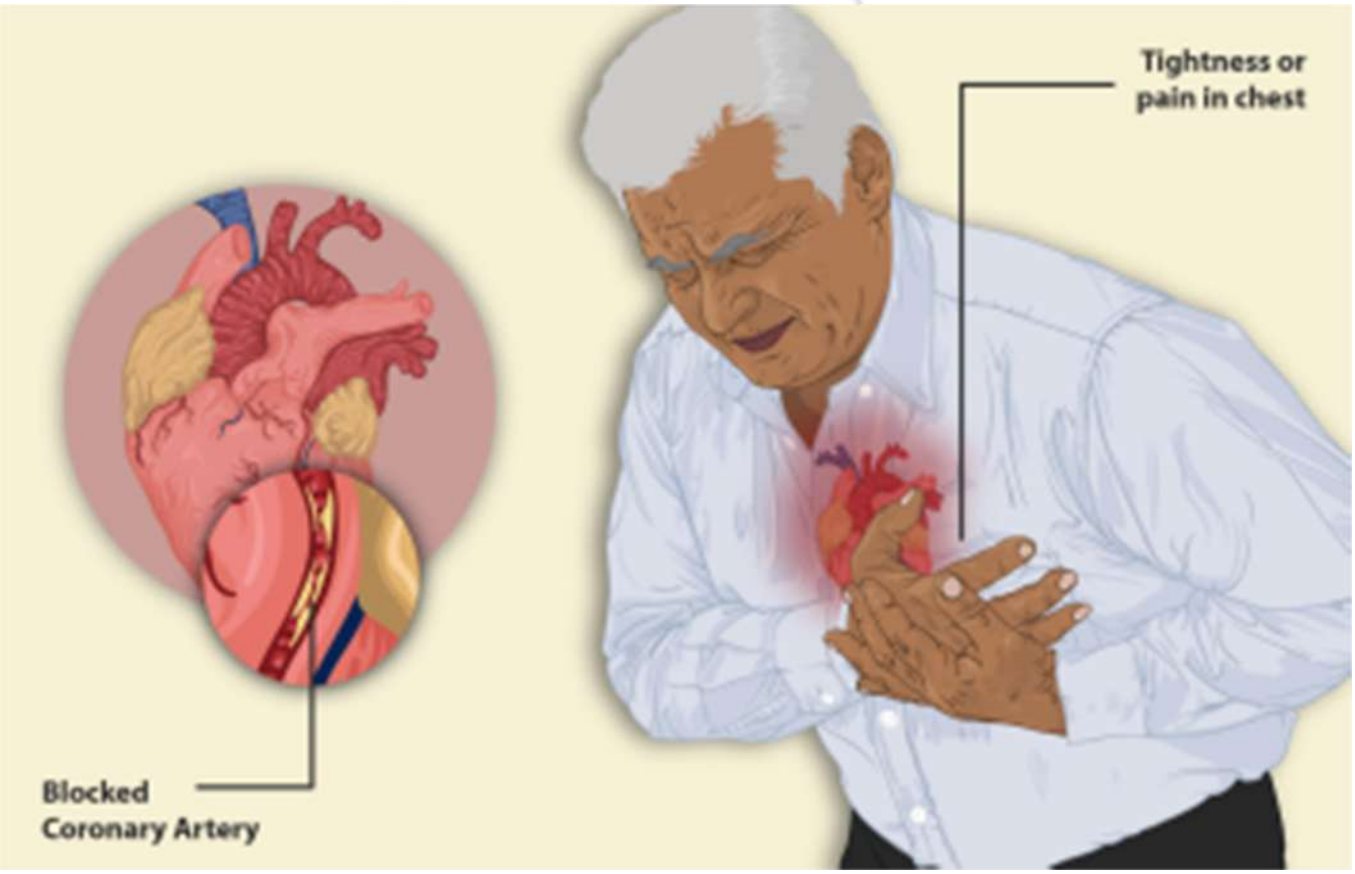
→ Angina is a term used for chest pain caused by reduced blood flow to the heart muscles.

→ It is a symptom of coronary artery disease, and is typically described as squeezing, pressure, heaviness, tightness, or pain in chest.

→ Angina is experienced during physical stress and relieved after rest, but in severe conditions, it may be observed on minimum physical work or at rest.

→ Generally it is indication of coronary artery disease.

→ It is a very strong sign that someone at high risk of cardiac arrest, heart attack, and sudden cardiac death.



Types of Angina Pectoris

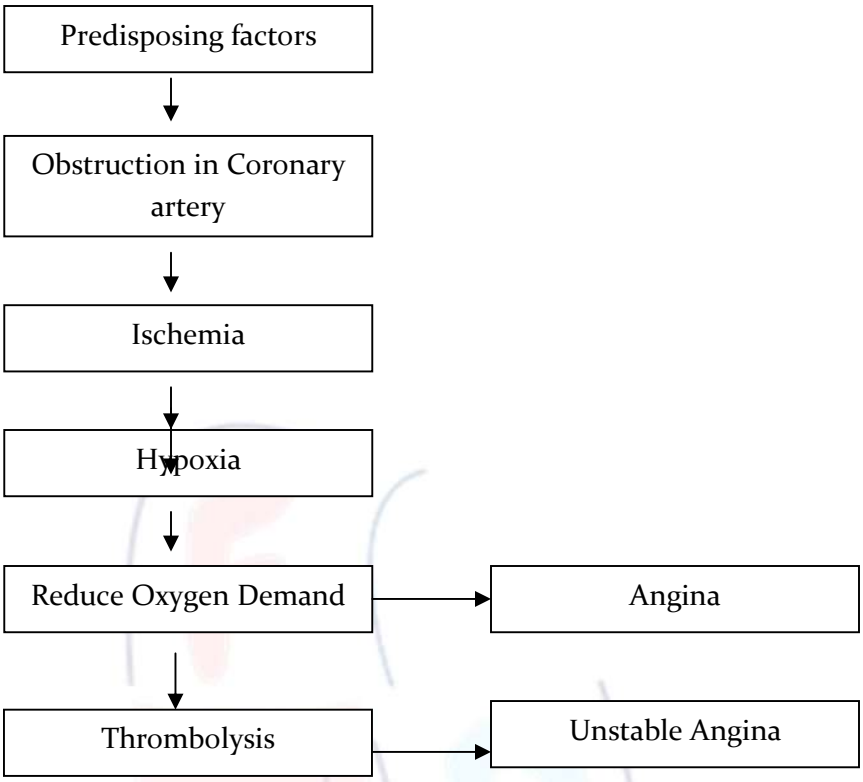
1. Stable / Chronic
2. Unstable Angina
3. Microvascular angina
4. Variant Angina
    1. **Stable / Chronic :** This type of angina follow a regular pattern due to stable plaque in coronary arteries and occurs when work load of heart increased due to any reason like exercise ,playing foot ball . It is less dangerous than unstable Angina . This is relieved by rest and medication.
    2. **Unstable Angina :** This type of angina does not follow a regular pattern due to unstable (dynamic) plaque in coronary arteries and occurs even at resting condition , rest and medication is not enough for its relief.
    3. **Microvascular Angina :** This type of angina occurs when any one more smallest coronary arteries are blocked , and it commonly occurs due to thrombosis part of unstable angina.
    4. **Variant Angina :** This type of angina occurs due to coronary spasm , and it follows a pattern , and spasm occurs due to external reasons like smoking , Cold weather , certain medicines , and stress . It is commonly occurs in younger people.

Etiology of Angina Pectoris

The main causes of angina pectoris are

- Coronary Artery diseases
- Plaque In Coronary arteries : (It is also called Athreosclerosis) More than 60 % of blocking of coronary arteries become unable to fulfill the demand of increased blood oxygen by the heart muscles.
- Narrowing of Coronary arteries.
- Spasm In coronary arteries.

Pathogenesis



Clinical Manifestations Angina pectoris

- Pain in Chest
- Weakness
- Heartburn
- Cramping.
- Sweating

Non Pharmacological Management of angina Pectoris

- To stop smoking
- Controlling Weight
- Avoiding heavy work in case of blockage .
- Controlling Hypertension
- Avoiding Heavy meals
- Adding fruits , vegetable , high density lipoproteins , in diet

Pharmacological management of angina Pectoris

- **Nitrates :** Nitroglycerine , Isosorbide Dinitrate , they open the coronary arteries , and are given by sublingual route to obtain one set of action .
- **ß Blockers :** Atenolol , propranolol , they decrease BP and slow down the heart rate.
- **Calcium Channel Blocker :** Amlodipine , Nifedipine , Verapamil . they also act like ß blockers.
- **Thrombolytic Drugs (Antiplatelet drugs) :** Steptokinase , Urokinase , prourokinase , they prevent blood clotting.

Anti Anginal Drugs

→ Angina is referred to chest pain due to low or no blood supply to the Heart muscles .

→ The Drugs are used to treat Angina pectoris are called anti anginal Drugs

Classification

- **Vasodilators :** Amylnitrite, Nitroglycerin*, Pentaerythritol tetranitrate, Isosorbide dinitrite*, Dipyridamole.
- **Calcium channel blockers :** Verapamil, Bepridil hydrochloride, Diltiazem hydrochloride, Nifedipine, Amlodipine, Felodipine, Nicardipine, Nimodipine.

Vasodilators

Vasodilators are drugs that widen (dilate) blood vessels by acting on the smooth muscles of the vessel walls, resulting in reduced vascular resistance and improved blood flow.

They are primarily used to treat cardiovascular conditions such as:

- Hypertension (high blood pressure)
- Angina pectoris (chest pain due to reduced coronary blood flow)
- Heart failure
- Peripheral vascular diseases

Mechanism of Action

→ Vasodilators work by relaxing vascular smooth muscle, which reduces afterload and preload on the heart.

Mechanisms include:

1. Direct relaxation of smooth muscle – Drugs like hydralazine act directly on arteriolar smooth muscle.
2. Release or mimicry of nitric oxide (NO) – Drugs like nitroglycerin increase NO, stimulating cGMP production, causing vasodilation.
3. Blockade of calcium channels – Calcium channel blockers (e.g., amlodipine) prevent calcium influx, reducing smooth muscle contraction.
4. Activation of potassium channels – Drugs like minoxidil open K^+ channels, hyperpolarizing smooth muscle and causing relaxation.
5. ACE inhibition / Angiotensin receptor blockade – Indirectly cause vasodilation by inhibiting vasoconstrictor pathways.

Examples

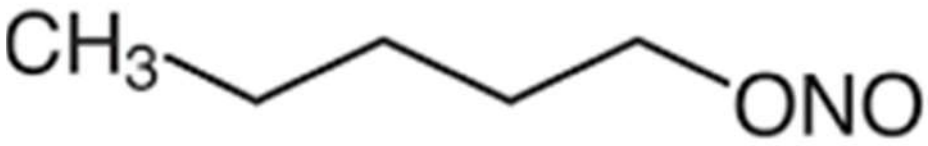
- Amylnitrite
- Nitroglycerin*,
- Pentaerythritol tetranitrate,
- Isosorbide dinitrite*,
- Dipyridamole.

Amyl Nitrite

- Amyl nitrite is a volatile liquid ester of nitrous acid and amyl alcohol.
- Chemically, it is pentyl nitrite ($C_5H_{11}ONO$).
- Historically used for angina pectoris due to its vasodilatory effects and also as an antidote for cyanide poisoning.
- Administered inhalation (vapors), not orally.

Chemical Structure

- IUPAC Name: Pentyl nitrite
- Molecular Formula: $C_5H_{11}NO_2$
- Molecular Weight: 117.15 g/mol
- Chemical Structure



Mechanism of Action

- Nitric Oxide (NO) Release:
  - Amyl nitrite releases NO in the blood → activates guanylate cyclase.
- cGMP-Mediated Vasodilation:
  - Increases cGMP levels → relaxes vascular smooth muscle, causing arterial and venous dilation.
- Cardiovascular Effects:
  - Reduces preload and afterload, decreases myocardial oxygen demand → relieves angina pain.
- Other Effects:
  - Vasodilation also causes headache, flushing, and hypotension as side effects.

Synthesis of Amyl Nitrite

1. Starting Material:
    - Amyl alcohol (pentanol)
2. Reaction:
    - React amyl alcohol with sodium nitrite in the presence of sulfuric acid → forms amyl nitrite ester.
3. Purification:
    - Fractional distillation → volatile liquid suitable for pharmaceutical use.

Uses

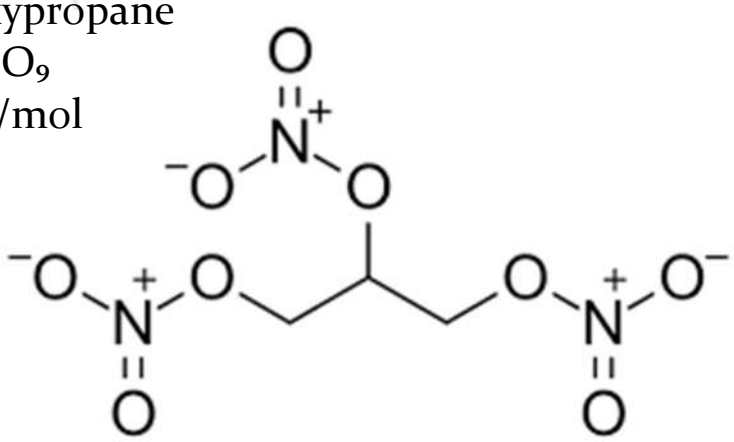
1. Cardiovascular:
    - Acute angina pectoris attacks (rapid relief).
2. Toxicology:
    - Antidote for cyanide poisoning → oxidizes hemoglobin to methemoglobin, which binds cyanide.
3. Other Uses:
    - Occasionally used recreationally as a vasodilator and euphoric agent (not recommended).
4. Side Effects:
    - Headache, dizziness, hypotension, flushing, tachycardia, methemoglobinemia (high doses), and syncope.

Nitroglycerin (Glyceryl Trinitrate)

- Nitroglycerin is a nitrate ester of glycerol, widely used as a vasodilator in cardiovascular therapy.
- It is primarily used for angina pectoris, acute myocardial infarction, and heart failure.
- Administered sublingually, orally, transdermally, or intravenously depending on the condition.
- Rapid onset of action due to conversion to nitric oxide (NO) in the body.

Chemical Structure

- IUPAC Name: 1,2,3-trinitroxypropane
- Molecular Formula: $C_3H_5N_3O_9$
- Molecular Weight: 227.09 g/mol
- Chemical Structure



Mechanism of Action

- Nitric Oxide (NO) Release:
  - Enzymatic metabolism in smooth muscle cells → releases NO.
- cGMP-Mediated Vasodilation:
  - NO activates guanylate cyclase → increases cGMP levels → relaxes vascular smooth muscle.
- Cardiovascular Effects:
  - Venous dilation → reduces preload (venous return)
  - Arterial dilation → reduces afterload
  - Decreases myocardial oxygen demand, relieving angina
- Other Effects:
  - Coronary artery dilation → improves oxygen supply to ischemic myocardium

Synthesis of Nitroglycerin

1. Starting Material:
    - Glycerol (1,2,3-propane-triol)
2. Nitration Reaction:
    - React glycerol with concentrated nitric acid in the presence of sulfuric acid (nitrating mixture) → forms nitroglycerin
3. Purification:
    - Dilution with cold water and careful extraction → obtain pharmaceutical-grade nitroglycerin

Uses

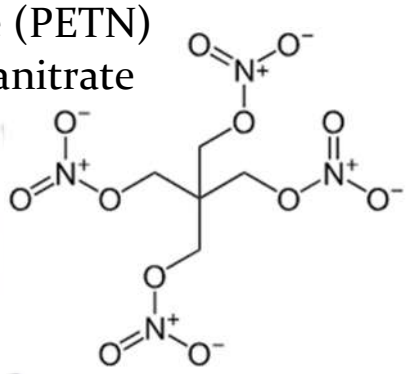
1. Cardiovascular:
    - Angina pectoris (acute and prophylactic)
    - Acute myocardial infarction
    - Heart failure (especially with pulmonary edema)
2. Other Uses:
    - Occasionally in hypertensive emergencies (IV form)
3. Side Effects:
    - Headache (most common), dizziness, hypotension, reflex tachycardia, flushing, syncope, tolerance with prolonged use

Pentaerythritol Tetranitrate (PETN)

- Pentaerythritol tetranitrate (PETN) is an organic nitrate ester of pentaerythritol.
- Two very different contexts of use: (A) an energetic material/explosive (most common and best known), and (B) a vasoactive nitrate used historically as an anti-anginal agent.
- PETN is highly lipophilic, stable at ordinary temperatures but sensitive to shock/heat under concentrated/industrial conditions.
- Because of its explosive properties, manufacture, storage and handling require specialised facilities and strict safety controls.

Chemical identity & physical data

- Common name: Pentaerythritol tetranitrate (PETN)
- IUPAC name (concise): pentaerythritol tetranitrate
- Molecular formula: $C_5H_8N_4O_{12}$
- Molecular weight: ≈ 316.15 g·mol^{-1}
- Structure



Mechanisms of Action

As a nitrate vasodilator (pharmacologic action):

- PETN, like other organic nitrates, acts as a source of nitric oxide (NO) or related NO-donor species in vascular smooth muscle.
- NO → activates guanylate cyclase, ↑ cGMP, causing vascular smooth muscle relaxation (venodilation > arteriolar dilation).
- Clinically this lowers preload (and to some extent afterload), decreasing myocardial oxygen demand and relieving angina.
- PETN appears to produce less tolerance development than some other nitrates in certain studies, but clinical use is limited and situational.

- As an explosive (chemical/energetic action):
  - PETN undergoes very rapid exothermic decomposition to gaseous products (N_2, CO_2, H_2O, etc.) — the rapid gas generation and heat produce blast and brisance.
  - The nitroester groups are the energetic functional groups that break and rearrange during detonation.

Synthesis

- **Starting material :** pentaerythritol (2,2-bis(hydroxymethyl)propane-1,3-diol; commonly written as $C(CH_2OH)_4$).
- **Nitration :** treat pentaerythritol with a nitrating mixture (concentrated HNO_3 in the presence of H_2SO_4 or equivalent nitrating agents) under well-controlled, low-temperature conditions. Each hydroxyl is converted to a nitrate ester → PETN.
- **Workup & purification :** careful quench, washing and crystallization under safe, controlled conditions (specialized plant procedures because of hazard).
- **Safety note :** nitration reactions for PETN are hazardous and potentially explosive; they must be performed only in industrial facilities designed for energetic materials.

Uses

A. Medical / pharmacologic (limited)

- Anti-anginal agent (historical/limited use): oral or topical formulations evaluated for chronic stable angina prophylaxis.
- Advantages claimed in some studies: potential for reduced nitrate tolerance compared with some nitrates.
- Reality: PETN is rarely a first-line nitrate; GTN, ISDN/ISMN and other antianginal classes are preferred clinically.

B. Energetic / industrial (primary worldwide use)

- Explosive / detonator applications: PETN is widely used in detonators, blasting caps, boosters, and plastic explosives (formulated in controlled matrices).
- Military & demolition: used where high brisance and small mass/large effect are required.

C. Research / niche

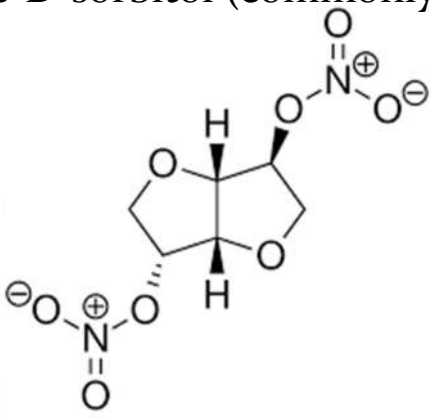
- Pharmacologic research: used experimentally to study nitrate pharmacology and tolerance mechanisms.
- Energetic materials research: formulation, desensitization, detection and handling studies.

Isosorbide Dinitrate

- Isosorbide dinitrate (ISDN) is an organic nitrate vasodilator.
- Used mainly for prophylaxis and management of angina pectoris, and as adjunct therapy in ischemic heart disease.
- Acts as a prodrug, metabolized to active mononitrate metabolites (notably isosorbide-5-mononitrate, ISMN) which contribute to sustained antianginal activity.
- Administered orally in immediate- or sustained-release formulations; sometimes historically used sublingually for acute relief.

Chemical Structure

- IUPAC Name: 1,4:3,6-Di-O-nitrate-D-sorbitol (commonly called dinitrate ester of isosorbide)
- Molecular Formula: $C_6H_8N_2O_8$
- Molecular Weight: 236.14 g/mol
- Structure:



Mechanism of Action

1. Bioactivation → NO donation:
    - ISDN is metabolized enzymatically to release nitric oxide (NO).
2. cGMP pathway:
    - NO activates guanylate cyclase → ↑ cGMP → ↓ intracellular Ca^{2+} → vascular smooth muscle relaxation.
3. Hemodynamic effects:
    - Predominantly venodilation → reduces preload.
    - At higher doses, arteriolar dilation → reduces afterload.
    - Net effect: reduced myocardial oxygen demand and relief of angina.
4. Tolerance:
    - Continuous use may lead to nitrate tolerance.
    - Daily nitrate-free interval (usually overnight) helps prevent tolerance.

Synthesis

- Starting material: Isosorbide (bicyclic diol from sorbitol).
- Reaction: Controlled nitration of the two secondary hydroxyl groups using concentrated nitric acid, often in the presence of sulfuric acid.
- Purification: Quenching, washing, crystallization to obtain pharmaceutically pure ISDN.

Uses

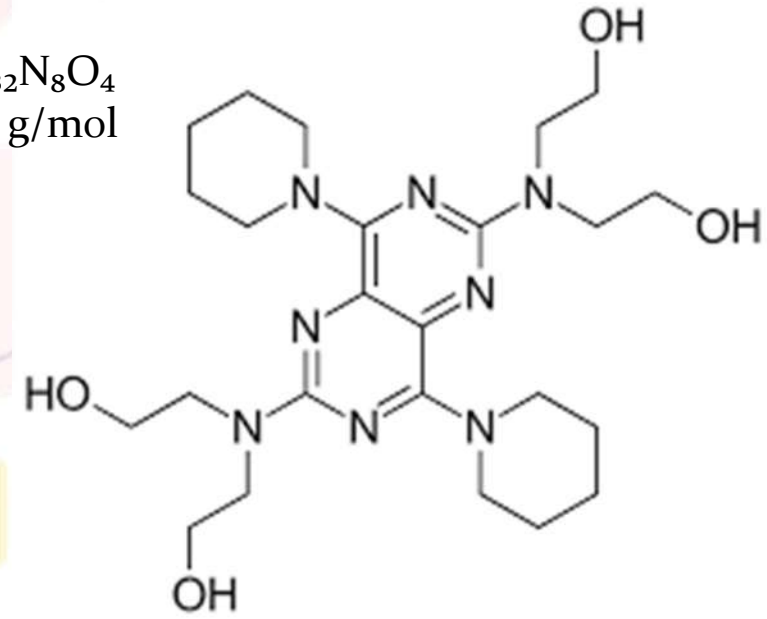
1. Angina prophylaxis:
    - Chronic management of stable angina pectoris.
2. Acute angina relief (historical / sublingual):
    - Sublingual forms occasionally used; GTN more commonly preferred for rapid relief.
3. Adjunct in ischemic heart disease / heart failure:
    - Reduces preload, beneficial in select heart failure patients.
4. Side effects:
    - Headache, dizziness, flushing, hypotension, reflex tachycardia, syncope.
    - Nitrate tolerance with continuous exposure; abrupt withdrawal may cause rebound angina.

Dipyridamole

- Dipyridamole is a vasodilator and antiplatelet agent.
- It is commonly used for prevention of thromboembolic disorders, such as stroke prophylaxis, often in combination with aspirin.
- It also has coronary vasodilator activity, historically used in diagnostic cardiac stress tests.
- Administered orally (tablets, sustained-release) or intravenously.

Chemical Structure

- IUPAC Name: 2,6-bis(diethanolamino)-4,8-dipiperidinopyrimido[5,4-d]pyrimidine
- Molecular Formula: $C_{24}H_{32}N_8O_4$
- Molecular Weight: 504.56 g/mol
- Structure



Mechanism of Action

1. Antiplatelet activity:
    - Inhibits phosphodiesterase (PDE) → prevents breakdown of cAMP in platelets → increased cAMP → inhibits platelet aggregation.
    - Enhances adenosine-mediated effects by blocking cellular uptake of adenosine → further inhibits platelet aggregation.
2. Vasodilation:
    - Increases cAMP in vascular smooth muscle → smooth muscle relaxation → coronary vasodilation.
3. Indirect effects:
    - Improves coronary blood flow, reduces myocardial ischemia, and provides protection against thrombotic events.

Synthesis

- Starting materials: Pyrimidine derivatives and suitable amine substituents.
- Stepwise outline:
    1. Formation of pyrimido[5,4-d]pyrimidine nucleus.
    2. Alkylation with diethanolamine and piperidine derivatives.
    3. Purification via recrystallization to obtain dipyridamole.

Uses

1. Antiplatelet therapy:
    - Prevention of thromboembolic events in stroke or TIA.
    - Often combined with aspirin for synergistic effect.
2. Coronary vasodilation:
    - Used in stress testing for ischemic heart disease (pharmacologic stress agent).
3. Adjunct therapy:
    - Sometimes used in heart valve replacement patients or other conditions with high thrombosis risk.
4. Side effects:
    - Headache (common), dizziness, hypotension, gastrointestinal disturbances (nausea, dyspepsia), and rarely, arrhythmias or bleeding.