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MEDICINAL CHEMISTRY - II

UNIT 2

TOPIC :

- **Calcium channel blockers** : Verapamil, Bepridil hydrochloride, Diltiazem hydrochloride, Nifedipine, Amlodipine, Felodipine, Nicardipine, Nimodipine.

Calcium Channel Blockers (CCBs)

Calcium channel blockers are drugs that inhibit the influx of calcium ions (Ca^{2+}) through voltage-gated L-type calcium channels in cardiac and smooth muscle cells.
By reducing intracellular calcium, they relax vascular smooth muscles, decrease myocardial contractility, and slow conduction through the heart, leading to vasodilation and reduced blood pressure.
Clinical relevance :

- Treatment of hypertension
- Angina pectoris
- Arrhythmias
- Raynaud's disease (selective vasodilation)

Mechanism of Action

1. Block Ca^{2+} entry into vascular smooth muscle → relaxation of arterioles → decreased peripheral resistance → lower blood pressure.
2. Block Ca^{2+} entry into cardiac muscle → decreased myocardial contractility (negative inotropic effect).
3. Slow conduction at AV node → useful in treating supraventricular tachyarrhythmias.
4. Coronary artery dilation → improves myocardial oxygen supply → useful in angina.

Examples

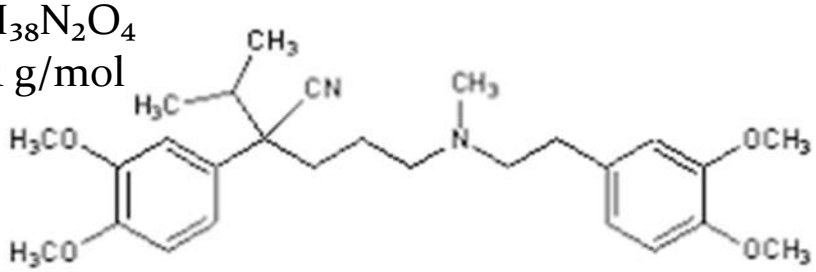
- Verapamil,
- Bepridil hydrochloride,
- Diltiazem hydrochloride,
- Nifedipine,
- Amlodipine,
- Felodipine,
- Nicardipine,
- Nimodipine.

Verapamil

- **Verapamil** is a **phenylalkylamine class calcium channel blocker (CCB)**.
- It primarily acts on **L-type calcium channels** in **cardiac and vascular smooth muscle**.
- Used in **hypertension, angina pectoris, and certain arrhythmias**.
- Administered **orally** (immediate- or sustained-release) and **intravenously** for acute management of arrhythmias.

Chemical Structure

- **IUPAC Name:** (RS)-2-(3,4-dimethoxyphenyl)-5-[2-(3,4-dimethoxyphenyl)ethylamino]-2-isopropylpentanenitrile
- **Molecular Formula:** $C_{27}H_{38}N_2O_4$
- **Molecular Weight:** 454.61 g/mol
- **Structure:**



Mechanism of Action

1. Calcium channel blockade:
   - Inhibits voltage-gated L-type calcium channels in cardiac and smooth muscle cells.
2. Cardiac effects:
   - ↓ AV node conduction → slows heart rate (negative chronotropic effect).
   - ↓ myocardial contractility (negative inotropic effect).
3. Vascular effects:
   - ↓ peripheral vascular resistance → vasodilation → reduced blood pressure.
4. Anti-anginal effects:
   - Reduces myocardial oxygen demand by decreasing heart rate, contractility, and afterload.
5. Anti-arrhythmic effects:

- Suppresses supraventricular tachyarrhythmias (e.g., atrial fibrillation/flutter, PSVT) via AV node conduction slowing.

Synthesis

- Starting materials: substituted phenylalkylamines and nitrile precursors.
- Stepwise outline:
  1. Synthesis of 3,4-dimethoxyphenylacetyl intermediates.
  2. Condensation with amine side chain to form phenylalkylamine skeleton.
  3. Introduction of nitrile group at the appropriate position.
  4. Purification via recrystallization or chromatographic methods.
- Industrial synthesis: multi-step and controlled for purity; exact conditions proprietary.

Uses

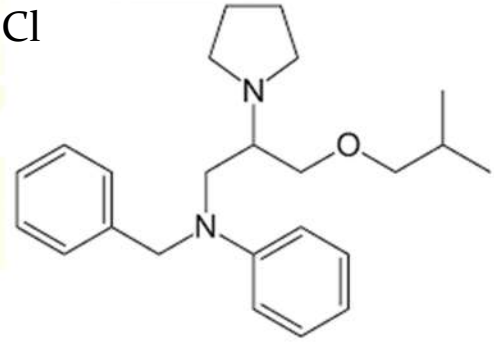
1. Cardiovascular disorders:
   - Hypertension (oral formulations).
   - Angina pectoris (chronic stable, vasospastic/Prinzmetal).
   - Coronary artery disease adjunct therapy.
2. Arrhythmias:
   - Supraventricular tachyarrhythmias (PSVT, atrial fibrillation/flutter).
   - Rate control in rapid ventricular response.
3. Side effects:
   - Headache, dizziness, hypotension, bradycardia.
   - Constipation (common).
   - Rare: AV block, heart failure exacerbation.

Bepridil Hydrochloride

- **Bepridil hydrochloride** is a **non-selective calcium channel blocker (CCB)**.
- It belongs to the **arylalkylamine class** of CCBs, like verapamil, but with **broader cardiovascular effects**.
- Used for **chronic stable angina pectoris** and historically for **supraventricular arrhythmias**.
- Administered **orally**, usually as **tablets**.
- Note: its clinical use is **limited due to risk of proarrhythmia** (particularly torsades de pointes).

Chemical Structure

- **IUPAC Name:** 2-(4-(3,4-Dimethoxyphenyl)butyl)-6-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride
- **Molecular Formula:** $C_{28}H_{34}N_2O_3 \cdot HCl$
- **Molecular Weight:** 488.05 g/mol
- **Structure:**



Mechanism of Action

1. Calcium channel blockade:
    - Inhibits L-type voltage-gated calcium channels in cardiac and vascular smooth muscle.
2. Cardiac effects:
    - ↓ AV node conduction (negative chronotropic effect)
    - ↓ myocardial contractility (negative inotropic effect)
3. Vascular effects:
    - Vasodilation of peripheral and coronary arteries → ↓ afterload and improved myocardial oxygen supply
4. Anti-anginal effects:
    - Reduces myocardial oxygen demand by decreasing afterload, heart rate, and contractility
5. Anti-arrhythmic effects:

- Blocks conduction in atrial and nodal tissues; historically used for supraventricular tachycardia

Synthesis

- Starting materials: methoxy-substituted aromatic aldehydes and amine precursors.
- Stepwise outline:
  1. Formation of tetrahydroisoquinoline nucleus via Pictet-Spengler cyclization.
  2. Alkylation with appropriate butylamine side chain.
  3. Formation of hydrochloride salt for oral stability.
- Industrial synthesis: multi-step process with purification by recrystallization.

Uses

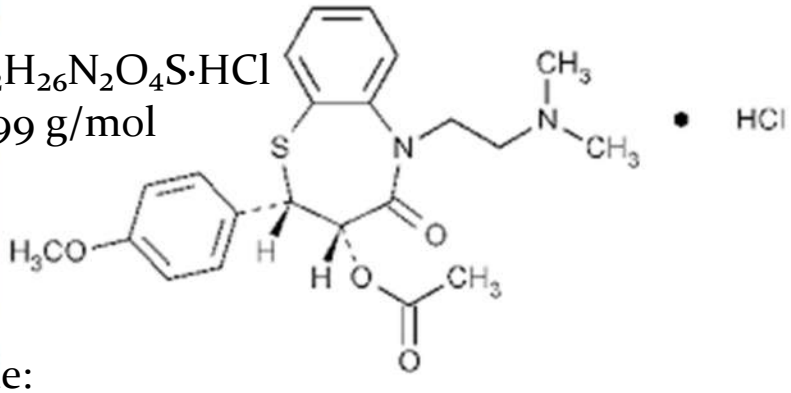
1. Chronic stable angina:
   - Reduces frequency and severity of angina attacks.
2. Supraventricular arrhythmias (historical):
   - Used to control heart rate in atrial fibrillation/flutter and paroxysmal supraventricular tachycardia.
3. Side effects:
   - Common: dizziness, hypotension, headache, constipation.
   - Serious: QT prolongation, torsades de pointes, AV block, heart failure exacerbation.

Diltiazem Hydrochloride

- **Diltiazem hydrochloride** is a **benzothiazepine class calcium channel blocker (CCB)**.
- It acts on **L-type calcium channels** in **cardiac and vascular smooth muscle**, producing **vasodilation and negative cardiac effects**.
- Used in **hypertension, angina pectoris, and supraventricular arrhythmias**.
- Administered **orally** (immediate or sustained release) and **intravenously** for acute arrhythmias.

Chemical Structure

- **IUPAC Name:** (2S,3S)-3-Acetoxy-5-[2-(dimethylamino)ethyl]-2-(3,4-dimethoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one hydrochloride
- **Molecular Formula:** $C_{22}H_{26}N_2O_4S{\cdot}HCl$
- **Molecular Weight:** 414.99 g/mol
- **Structure:**



Mechanism of Action

1. Calcium channel blockade:
   - Inhibits L-type voltage-gated calcium channels in cardiac and smooth muscle.
2. Cardiac effects:
   - ↓ AV node conduction (negative chronotropic effect)
   - ↓ myocardial contractility (negative inotropic effect)
3. Vascular effects:
   - Vasodilation of peripheral and coronary arteries → ↓ afterload and improved myocardial oxygen supply
4. Anti-anginal effects:
   - Reduces myocardial oxygen demand by decreasing heart rate, contractility, and afterload
5. Anti-arrhythmic effects:

- Slows conduction through AV node → effective in supraventricular tachyarrhythmias

Synthesis

- Starting materials: substituted benzothiazepine precursors and dimethoxyphenyl acetates.
- Stepwise outline:
  1. Formation of benzothiazepine ring via condensation/cyclization reaction.
  2. Alkylation with dimethylaminoethyl side chain.
  3. Esterification or acetylation at the hydroxyl group.
  4. Formation of hydrochloride salt for oral administration.
- Industrial process: multi-step and carefully controlled to ensure purity and stability.

Uses

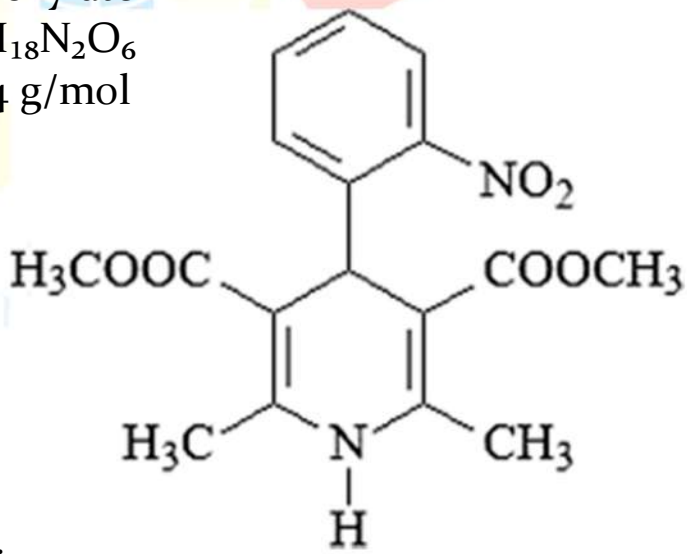
1. Cardiovascular disorders:
   - Hypertension (oral formulations).
   - Chronic stable angina and vasospastic (Prinzmetal) angina.
2. Arrhythmias:
   - Supraventricular tachyarrhythmias (PSVT, atrial fibrillation/flutter).
   - Rate control in rapid ventricular response.
3. Side effects:
   - Common: headache, dizziness, hypotension, edema.
   - Cardiac: bradycardia, AV block, worsening heart failure.
   - Gastrointestinal: nausea, constipation.

Nifedipine

- **Nifedipine** is a **dihydropyridine class calcium channel blocker (CCB)**.
- It acts mainly on **vascular smooth muscle** to cause **arterial vasodilation**.
- Used for **hypertension, chronic stable angina, and variant (Prinzmetal) angina**.
- Administered **orally** in immediate- or sustained-release formulations.
- Less effect on cardiac conduction compared to verapamil or diltiazem.

Chemical Structure

- **IUPAC Name:** 3,5-dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate
- **Molecular Formula:** $C_{17}H_{18}N_2O_6$
- **Molecular Weight:** 346.34 g/mol
- **Structure:**



Mechanism of Action

1. Calcium channel blockade:
    - Inhibits L-type voltage-gated calcium channels in vascular smooth muscle.
2. Vascular effects:
    - Arteriolar vasodilation → ↓ peripheral vascular resistance → ↓ blood pressure
3. Anti-anginal effects:
    - ↓ afterload → reduces myocardial oxygen demand
    - Coronary vasodilation improves oxygen supply in variant angina

4. Minimal cardiac conduction effects:
    - Slight negative inotropic/chronotropic effects; generally safe in patients with conduction disorders

Synthesis

- Starting materials: substituted aldehydes and β-ketoesters.
- Stepwise outline:
    1. Condensation of aldehyde with β-ketoester to form dihydropyridine ring (Hantzsch synthesis).
    2. Introduction of nitrophenyl group at position 4.
    3. Esterification to form 3,5-dicarboxylate esters.
    4. Purification via recrystallization for pharmaceutic use.

Uses

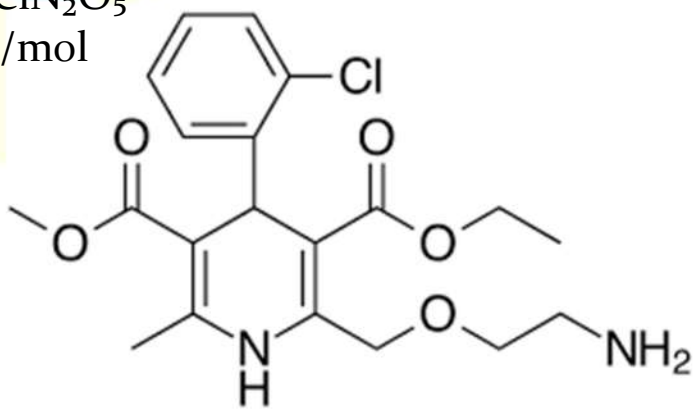
1. Hypertension:
    - First-line therapy for lowering blood pressure.
2. Chronic stable angina:
    - Reduces frequency and severity of angina attacks.
3. Variant (Prinzmetal) angina:
    - Relieves coronary vasospasm.
4. Side effects:
    - Common: headache, flushing, dizziness, peripheral edema.
    - Less common: hypotension, palpitations, nausea.

Amlodipine

- **Amlodipine** is a **dihydropyridine calcium channel blocker (CCB)**.
- Primarily acts on **vascular smooth muscle**, causing **arterial vasodilation**.
- Used for **hypertension, chronic stable angina, and vasospastic (Prinzmetal) angina**.
- Administered **orally**, typically as **once-daily tablets** due to long half-life (~30–50 hours).
- Compared to nifedipine, **amlodipine has slower onset and longer duration**, reducing reflex tachycardia.

Chemical Structure

- **IUPAC Name:** 3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylate
- **Molecular Formula:** $C_{20}H_{25}ClN_2O_5$
- **Molecular Weight:** 408.88 g/mol
- **Structure:**



Mechanism of Action

1. Calcium channel blockade:
    - Inhibits L-type voltage-gated calcium channels in vascular smooth muscle.
2. Vascular effects:
    - Causes arteriolar vasodilation → ↓ peripheral vascular resistance → ↓ blood pressure
3. Anti-anginal effects:
    - ↓ afterload → reduces myocardial oxygen demand
    - Coronary vasodilation improves oxygen supply in angina
4. Cardiac effects:

- Minimal negative chronotropic/inotropic effect → safer in patients with conduction disorders

Synthesis

- Starting materials: substituted aldehydes, β-ketoesters, and aminoethanol derivatives.
- Stepwise outline:
  1. Hantzsch condensation to form dihydropyridine ring.
  2. Introduction of 2-chlorophenyl group at position 4.
  3. Esterification at positions 3 and 5.
  4. Alkylation with aminoethoxymethyl group at position 2.
  5. Purification via recrystallization to obtain pharmaceutically pure amlodipine.

Uses

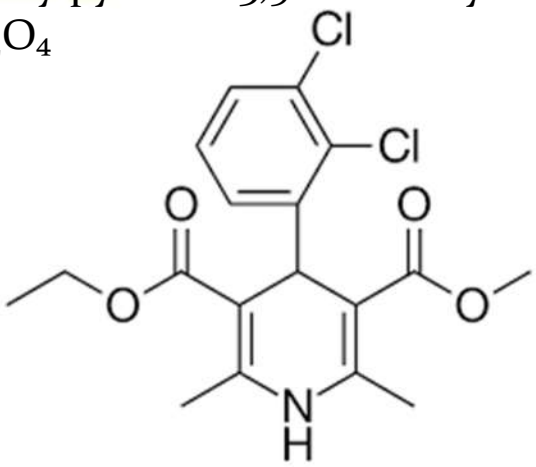
1. Hypertension:
   - First-line oral therapy; long duration allows once-daily dosing.
2. Chronic stable angina:
   - Reduces frequency and severity of angina attacks.
3. Variant (Prinzmetal) angina:
   - Relieves coronary vasospasm.
4. Side effects:
   - Common: headache, dizziness, flushing, peripheral edema.
   - Less common: palpitations, nausea, hypotension.

Felodipine

- **Felodipine** is a **dihydropyridine class calcium channel blocker (CCB)**.
- Primarily acts on **vascular smooth muscle**, causing **arterial vasodilation**.
- Used for **hypertension** and sometimes **chronic stable angina**.
- Administered **orally**, usually as **extended-release tablets** for once-daily dosing.
- Slower onset and longer duration reduce **reflex tachycardia** compared to short-acting dihydropyridines like nifedipine.

Chemical Structure

- **IUPAC Name:** 3-Ethyl 5-methyl 2-(2,3-dichlorophenyl)-4-(2,3-dichlorophenyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylate
- **Molecular Formula:** $C_{19}H_{20}Cl_2N_2O_4$
- **Molecular Weight:** 384.29 g/mol
- **Structure:**



Mechanism of Action

1. Calcium channel blockade:
    - Inhibits L-type voltage-gated calcium channels in vascular smooth muscle.
2. Vascular effects:
    - Predominantly arteriolar vasodilation → ↓ peripheral vascular resistance → ↓ blood pressure
3. Anti-anginal effects:
    - ↓ afterload → reduces myocardial oxygen demand
    - Improves coronary blood flow in patients with angina
4. Cardiac effects:

- Minimal negative chronotropic/inotropic effects → safer in conduction disorders

Synthesis

- Starting materials: substituted aromatic aldehydes, β-ketoesters.
- Stepwise outline:
  1. Hantzsch condensation to form 1,4-dihydropyridine ring.
  2. Introduction of dichlorophenyl groups at positions 2 and 4.
  3. Esterification at positions 3 and 5.
  4. Methyl substitution at position 6.
  5. Purification via recrystallization to yield pharmaceutically pure felodipine.

Uses

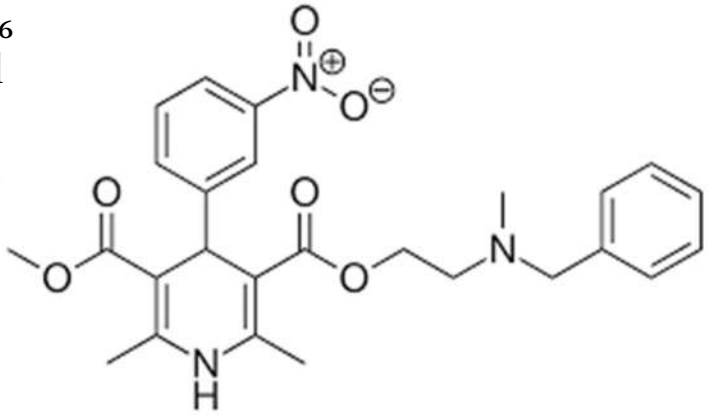
1. Hypertension:
   - First-line therapy; long-acting formulation allows once-daily dosing.
2. Chronic stable angina:
   - Reduces frequency and severity of angina attacks.
3. Side effects:
   - Common: headache, dizziness, flushing, peripheral edema.
   - Less common: palpitations, hypotension, nausea.

Nicardipine

- **Nicardipine** is a **dihydropyridine class calcium channel blocker (CCB)**.
- Primarily acts on **vascular smooth muscle**, causing **arterial vasodilation**.
- Used for **hypertension**, **chronic stable angina**, and occasionally **Raynaud's phenomenon**.
- Administered **orally** (immediate- or sustained-release tablets) and **intravenously** for acute hypertensive emergencies.
- Compared to nifedipine, nicardipine has **greater coronary vasoselectivity** and less reflex tachycardia.

Chemical Structure

- **IUPAC Name:** (±)-2-(2,2-Diphenylacetyl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylic acid dimethyl ester
- **Molecular Formula:** $C_{26}H_{29}N_3O_6$
- **Molecular Weight:** 475.53 g/mol
- **Structure:**



Mechanism of Action

1. **Calcium channel blockade:**
   - Inhibits **L-type voltage-gated calcium channels** in vascular smooth muscle.
2. **Vascular effects:**
   - Predominantly **arteriolar vasodilation** → ↓ peripheral vascular resistance → ↓ blood pressure
3. **Anti-anginal effects:**
   - Improves coronary blood flow → relieves ischemia in chronic stable angina
4. **Cardiac effects:**

- Minimal negative chronotropic/inotropic effect → safer in patients with conduction disorders

Synthesis

- **Starting materials:** substituted aldehydes and β-ketoesters.
- **Stepwise outline:**
  1. Hantzsch condensation to form **1,4-dihydropyridine ring**.
  2. Introduction of **3-nitrophenyl group** at position 4.
  3. Esterification at positions 3 and 5 (dimethyl ester).
  4. Addition of **diphenylacetyl substituent** at position 2.
  5. Purification via **recrystallization** to yield pharmaceutically pure nicardipine.

Uses

1. **Hypertension:**
   - First-line therapy; IV form used for **acute blood pressure control**.
2. **Chronic stable angina:**
   - Reduces frequency and severity of angina attacks.
3. **Side effects:**
   - Common: headache, flushing, dizziness, peripheral edema.
   - Less common: hypotension, palpitations, nausea.