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MEDICINAL CHEMISTRY - II

UNIT 3

TOPIC :

- **Anti-hyperlipidemic agents :** Clofibrate, Lovastatin, Cholesteramine andCholestipol

Anti-Hyperlipidemic Agents

- **Anti-hyperlipidemic agents** are drugs used to **lower lipid levels** (cholesterol, triglycerides) in the blood.
- They are primarily used to **prevent or treat hyperlipidemia**, which is a major risk factor for **atherosclerosis, coronary artery disease (CAD), stroke**, and **peripheral vascular disease**.
- Hyperlipidemia can be **primary (genetic)** or **secondary** due to **obesity, diabetes, hypothyroidism, or diet**.
- These drugs work through **various mechanisms** to reduce **LDL cholesterol, triglycerides**, or **increase HDL cholesterol**.

Classification of Anti-Hyperlipidemic Agents

1. **HMG-CoA Reductase Inhibitors (Statins):**
    - **Examples:** Atorvastatin, Simvastatin, Rosuvastatin, Pravastatin
    - **Mechanism:** Inhibit **HMG-CoA reductase**, the rate-limiting enzyme in cholesterol synthesis → ↓ LDL and ↑ HDL.
    - **Uses:** Hypercholesterolemia, familial hyperlipidemia, atherosclerosis prevention.
2. **Bile Acid Sequestrants (Resins):**
    - **Examples:** Cholestyramine, Colestipol, Colesevelam
    - **Mechanism:** Bind **bile acids** in the intestine → prevent their reabsorption → liver converts cholesterol into bile acids → ↓ LDL.
    - **Uses:** Hypercholesterolemia, pruritus in cholestasis.
3. **Nicotinic Acid (Niacin):**
    - **Mechanism:**
        - ↓ Hepatic VLDL synthesis → ↓ LDL
        - ↓ triglycerides
        - ↑ HDL
    - **Uses:** Hypertriglyceridemia, mixed dyslipidemia, low HDL levels.
4. **Fibric Acid Derivatives (Fibrates):**
    - **Examples:** Gemfibrozil, Fenofibrate, Clofibrate
    - **Mechanism:**

        - Activate **PPAR-α** → ↑ lipoprotein lipase activity → ↓ triglycerides
        - Modest ↓ LDL, ↑ HDL
    - **Uses:** Hypertriglyceridemia, combined dyslipidemia.
5. **Cholesterol Absorption Inhibitors:**
    - **Example:** Ezetimibe
    - **Mechanism:** Inhibits **intestinal absorption of cholesterol** at the brush border → ↓ LDL
    - **Uses:** Primary hypercholesterolemia, combination therapy with statins.
6. **Omega-3 Fatty Acids:**
    - **Examples:** Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA)
    - **Mechanism:** Reduce hepatic triglyceride synthesis → ↓ VLDL → ↓ triglycerides
    - **Uses:** Hypertriglyceridemia, cardiovascular protection.
7. **PCSK9 Inhibitors (Monoclonal Antibodies):**
    - **Examples:** Alirocumab, Evolocumab
    - **Mechanism:** Inhibit **PCSK9 enzyme** → ↑ LDL receptor recycling → ↑ LDL clearance → ↓ LDL cholesterol
    - **Uses:** Familial hypercholesterolemia, statin-resistant hyperlipidemia.

Therapeutic Uses

1. **Primary Hyperlipidemia:**
    - Familial hypercholesterolemia
    - Mixed dyslipidemia
2. **Secondary Hyperlipidemia:**
    - Obesity, diabetes, hypothyroidism, nephrotic syndrome, alcoholism
3. **Cardiovascular Disease Prevention:**
    - Atherosclerosis
    - Coronary artery disease
    - Stroke and peripheral artery disease

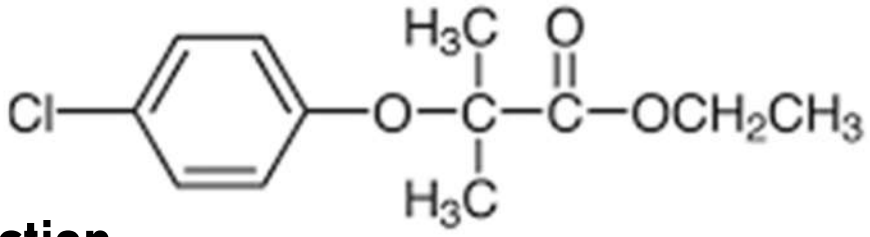
4. **Other Uses:**
    - Pruritus in cholestasis (bile acid sequestrants)
    - Pancreatitis risk reduction in severe hypertriglyceridemia

Clofibrate

- **Clofibrate** is a **lipid-lowering agent** belonging to the **fibrate class of drugs (fibric acid derivatives)**.
- It is primarily used for the **treatment of hyperlipidemia**, particularly **hypertriglyceridemia**.
- Clofibrate acts by **activating peroxisome proliferator-activated receptor alpha (PPARα)**, which modulates lipid metabolism in the liver.
- First synthesized in the 1950s, it was one of the earliest fibrates used clinically.
- It is administered orally as **tablets** and is **hydrolyzed in vivo** to the active metabolite, **clofibric acid**.

Chemical Structure

- **Chemical name:** Ethyl 2-(4-chlorophenoxy)-2-methylpropanoate
- **Molecular formula:** $C_{12}H_{15}ClO_3$
- **Molecular weight:** 238.70 g/mol
- **Chemical class:** Fibrate; derivative of fibric acid
- **Structural**



Mechanism of Action

- Clofibrate acts primarily via **PPARα activation** in the liver.

Stepwise Mechanism:

1. **Activation of PPARα** → transcription of genes involved in lipid metabolism.
2. **Increase in lipoprotein lipase activity** → enhanced hydrolysis of triglyceride-rich lipoproteins (VLDL).

3. **Reduction in VLDL and triglyceride levels** in plasma.
4. **Modest increase in HDL cholesterol** due to enhanced apolipoprotein A-I and A-II synthesis.
5. Minimal effect on LDL cholesterol; primary action is **triglyceride reduction**.

Synthesis of Clofibrate

Stepwise Synthesis (Simplified Overview):

1. **Starting material:** *4-Chlorophenol*
2. **Step 1 – Alkylation:**
    - React 4-chlorophenol with **2-chloroisobutyric acid ethyl ester** in the presence of base → forms **ethyl 2-(4-chlorophenoxy)-2-methylpropanoate (clofibrate)**.

Step 2 – Hydrolysis (in vivo):

- Clofibrate is hydrolyzed in the liver by **esterases** to **clofibric acid**, the pharmacologically active metabolite.

Uses

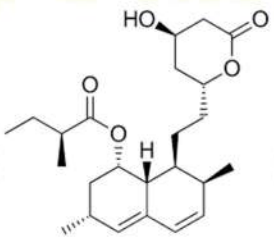
- **Therapeutic Uses:**
    1. **Hypertriglyceridemia:** High plasma triglyceride levels.
    2. **Mixed hyperlipidemia:** When triglycerides are predominant.
    3. **Prevention of pancreatitis:** In patients with severe hypertriglyceridemia.
    4. **Adjunct therapy:** Along with dietary management for dyslipidemia.

Lovastatin

- **Lovastatin** is a **HMG-CoA reductase inhibitor**, belonging to the **statin class of lipid-lowering agents**.
- It is a **prodrug**, hydrolyzed in vivo to its **active β-hydroxy acid form**.
- Lovastatin inhibits **cholesterol biosynthesis in the liver**, leading to **lower LDL cholesterol and total cholesterol levels**.
- Clinically, it is used for **hypercholesterolemia**, **mixed dyslipidemia**, and for **cardiovascular risk reduction**.
- It was the **first statin approved** for clinical use (by Merck, 1987).

Chemical Structure

- **Chemical name:** (1S,3R,7S,8S,8aR)-8-{2-methylbutyrate}-3,7-dihydroxy-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2-methylbutyrate
- **Molecular formula:** $C_{24}H_{36}O_5$
- **Molecular weight:** 404.55 g/mol
- **Chemical class:** Lactone prodrug; HMG-CoA reductase inhibitor (statin)
- **Structural**



Mechanism of Action

- **Target:** HMG-CoA reductase, the **rate-limiting enzyme in cholesterol biosynthesis**.

Stepwise Mechanism:

1. Lovastatin (prodrug) is hydrolyzed in vivo to **β-hydroxy acid (active form)**.
2. The active form **competitively inhibits HMG-CoA reductase**, blocking conversion of HMG-CoA to mevalonate.
3. This **reduces hepatic cholesterol synthesis**, leading to:
    - Upregulation of **LDL receptors** on hepatocytes → increased clearance of LDL from blood.
    - Decrease in **plasma LDL cholesterol** and **total cholesterol**.

4. Modest reduction of triglycerides and slight increase in HDL cholesterol.

Synthesis of Lovastatin

Biosynthetic/Semi-synthetic Approach:

1. **Fermentation method:**
    - Produced by **Aspergillus terreus** or **Monascus species** using polyketide biosynthesis.
2. **Chemical steps (semi-synthetic derivatization):**
    - Polyketide chain assembly → cyclization → lactone formation → side chain attachment.
    - Hydroxylation and stereochemistry controlled enzymatically to produce active lactone.

Uses

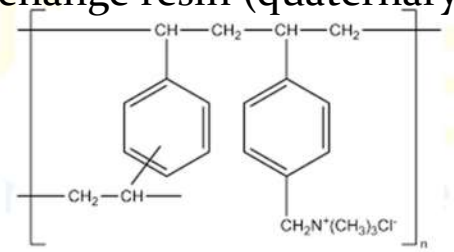
- **Therapeutic Uses:**
    1. **Hypercholesterolemia:** Elevated LDL cholesterol
    2. **Mixed dyslipidemia:** High LDL + triglycerides
    3. **Primary and secondary prevention of cardiovascular disease**
    4. **Familial hypercholesterolemia:** As part of combination therapy if diet alone is insufficient

Cholestyramine

- **Cholestyramine** is a **bile acid sequestrant (resin)** used to **lower plasma cholesterol levels**, particularly **LDL cholesterol**.
- It is a **non-absorbable, anion-exchange resin**, meaning it **binds bile acids in the intestine** and prevents their reabsorption.
- By reducing bile acid reabsorption, the liver **increases conversion of cholesterol to bile acids**, lowering plasma cholesterol.
- Cholestyramine is administered **orally** as a **powder or granules** and is **not absorbed systemically**.

Chemical Structure

- **Chemical name:** 2-[(2-methacryloyloxy)ethyl]trimethylammonium chloride copolymer with divinylbenzene
- **Molecular formula:** It is a **cross-linked copolymer**; no fixed molecular formula.
- **Chemical class:** Anion-exchange resin (quaternary ammonium polymer)
- **Structural**



Mechanism of Action

1. **Binding of bile acids:**
   - Cholestyramine binds bile acids in the **small intestine**, forming insoluble complexes.
2. **Prevention of enterohepatic recirculation:**
   - The bile acid–resin complex is excreted in **feces**, reducing bile acid pool.
3. **Increased hepatic cholesterol catabolism:**
   - Liver converts **more cholesterol into bile acids** to compensate, lowering **plasma LDL cholesterol**.
4. **Indirect effects:**
   - Slight increase in hepatic LDL receptor expression → increased LDL clearance from plasma.
   - Minimal effect on HDL; may slightly increase triglycerides in some patients.

Synthesis

Stepwise Overview:

1. **Polymer backbone formation:**
    - Copolymerization of **styrene** and **divinylbenzene** → forms cross-linked polystyrene resin.
2. **Quaternization:**
    - Functionalize with **trimethylamine or similar tertiary amines** → converts to **quaternary ammonium groups**.
3. **Bead formation and purification:**
    - Polymer beads are **washed, dried, and sieved** to form the final resin powder or granules.

Uses

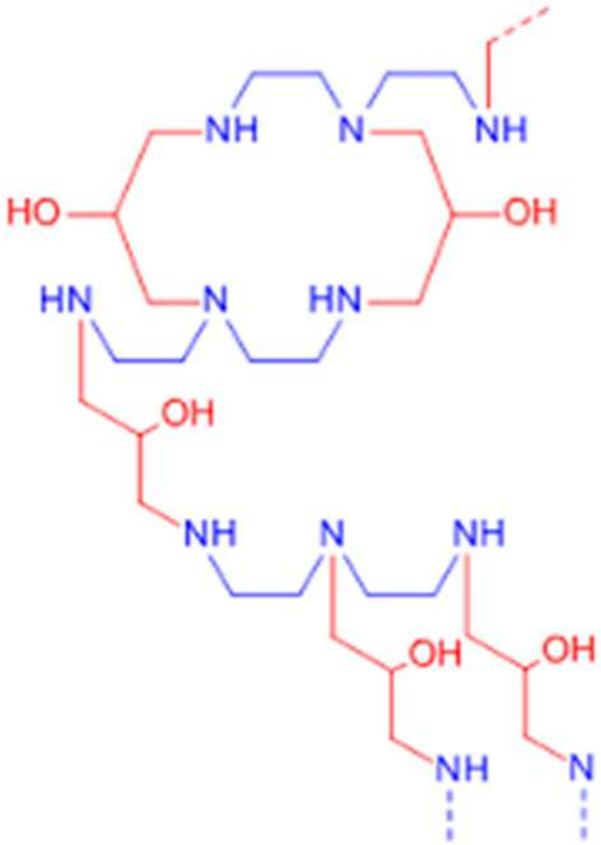
- **Therapeutic Uses:**
    1. **Hypercholesterolemia:** Especially elevated LDL cholesterol
    2. **Bile acid malabsorption:** For diarrhea associated with bile acid excess
    3. **Pruritus in cholestasis:** Binds bile acids to reduce skin itching
    4. Adjunct therapy **with statins** when further LDL reduction is required

Cholestipol

- **Cholestipol** is a **bile acid sequestrant (resin)** similar to cholestyramine.
- It is a **non-absorbable anion-exchange polymer** used to **reduce plasma LDL cholesterol**.
- By binding bile acids in the intestine, cholestipol **prevents their reabsorption**, forcing the liver to convert more cholesterol into bile acids.
- It is available as **oral granules or tablets** and is **not absorbed systemically**, making it relatively safe for long-term use.

Chemical Structure

- **Chemical name:** Copolymer of 4-vinylbenzyl chloride with divinylbenzene and quaternized with N,N-dimethyl-1,3-propane-diamine
- **Molecular formula:** Cross-linked copolymer (no fixed formula)
- **Chemical class:** Anion-exchange resin (quaternary ammonium polymer)
- **Structural**



Mechanism of Action

1. **Binding of bile acids:**
   - Cholestipol binds bile acids in the **small intestine**, forming insoluble complexes.
2. **Excretion:**
   - The bile acid–resin complex is excreted in **feces**, reducing the bile acid pool.
3. **Cholesterol catabolism:**
   - Liver converts more **cholesterol into bile acids**, lowering plasma LDL levels.
4. **Indirect effects:**
   - Slight upregulation of hepatic **LDL receptors** → increased clearance of LDL cholesterol from plasma.
   - Minimal effect on triglycerides; may slightly increase HDL cholesterol in some patients.

Synthesis

Stepwise Overview:

1. **Polymer backbone formation:**
   - Copolymerization of **4-vinylbenzyl chloride** with **divinylbenzene** → forms cross-linked polystyrene resin.
2. **Quaternization:**
   - Functionalize polymer with **N,N-dimethyl-1,3-propane-diamine** → forms quaternary ammonium groups.
3. **Bead formation and purification:**
   - Resin is **washed, dried, and sieved** to form oral granules or tablets.

Uses

- **Therapeutic Uses:**
  1. **Hypercholesterolemia:** Reduces elevated LDL cholesterol
  2. **Bile acid malabsorption:** Helps control diarrhea due to bile acid excess
  3. **Pruritus in cholestasis:** Binds bile acids to reduce itching
  4. Adjunct therapy with statins for **additional LDL reductio**