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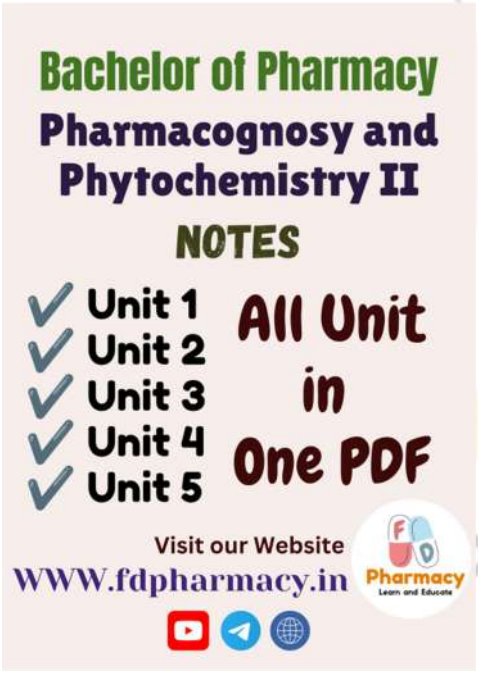
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MEDICINAL CHEMISTRY - II

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

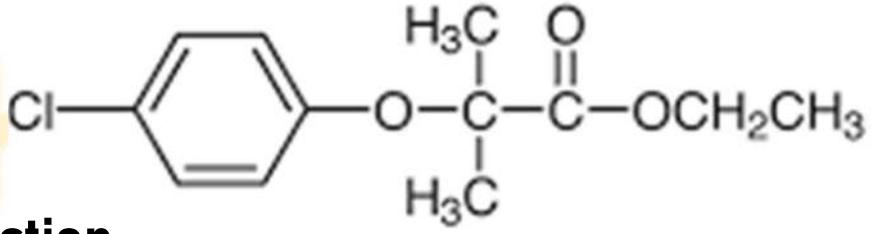
1. Primary Hyperlipidemia:
    - Familial hypercholesterolemia
    - Mixed dyslipidemia
2. Secondary Hyperlipidemia:
    - Obesity, diabetes, hypothyroidism, nephrotic syndrome, alcoholism
3. Cardiovascular Disease Prevention:
    - Atherosclerosis
    - Coronary artery disease
    - Stroke and peripheral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

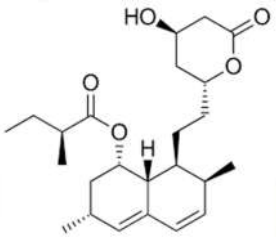
- Therapeutic Uses:
    1. Hypertriglyceridemia: High plasma triglyceride levels.
    2. Mixed hyperlipidemia: When triglycerides are predominant.
    3. Prevention of pancreatitis: In patients with severe hypertriglyceridemia.
    4. Adjunct therapy: Along with dietary management for dyslipidemia.

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

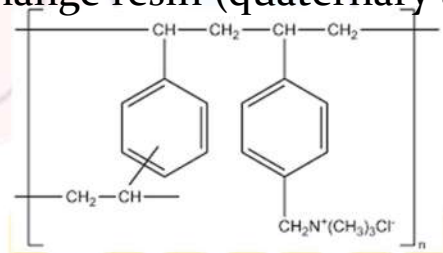
- Therapeutic Uses:
    1. Hypercholesterolemia: Elevated LDL cholesterol
    2. Mixed dyslipidemia: High LDL + triglycerides
    3. Primary and secondary prevention of cardiovascular disease
    4. Familial hypercholesterolemia: As part of combination therapy if diet alone is insufficient

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

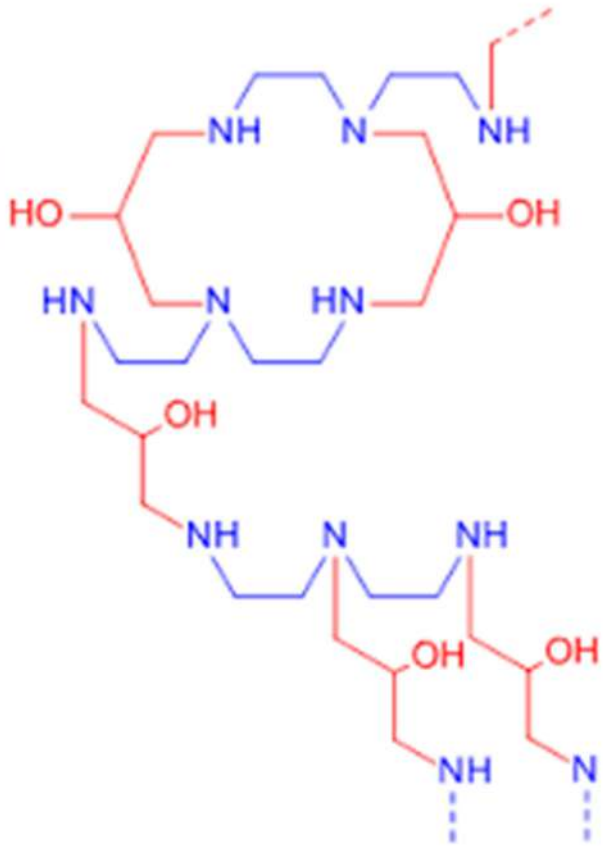
- Therapeutic Uses:
    1. Hypercholesterolemia: Especially elevated LDL cholesterol
    2. Bile acid malabsorption: For diarrhea associated with bile acid excess
    3. Pruritus in cholestasis: Binds bile acids to reduce skin itching
    4. Adjunct therapy with statins when further LDL reduction is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