

Antihyperlipidemics

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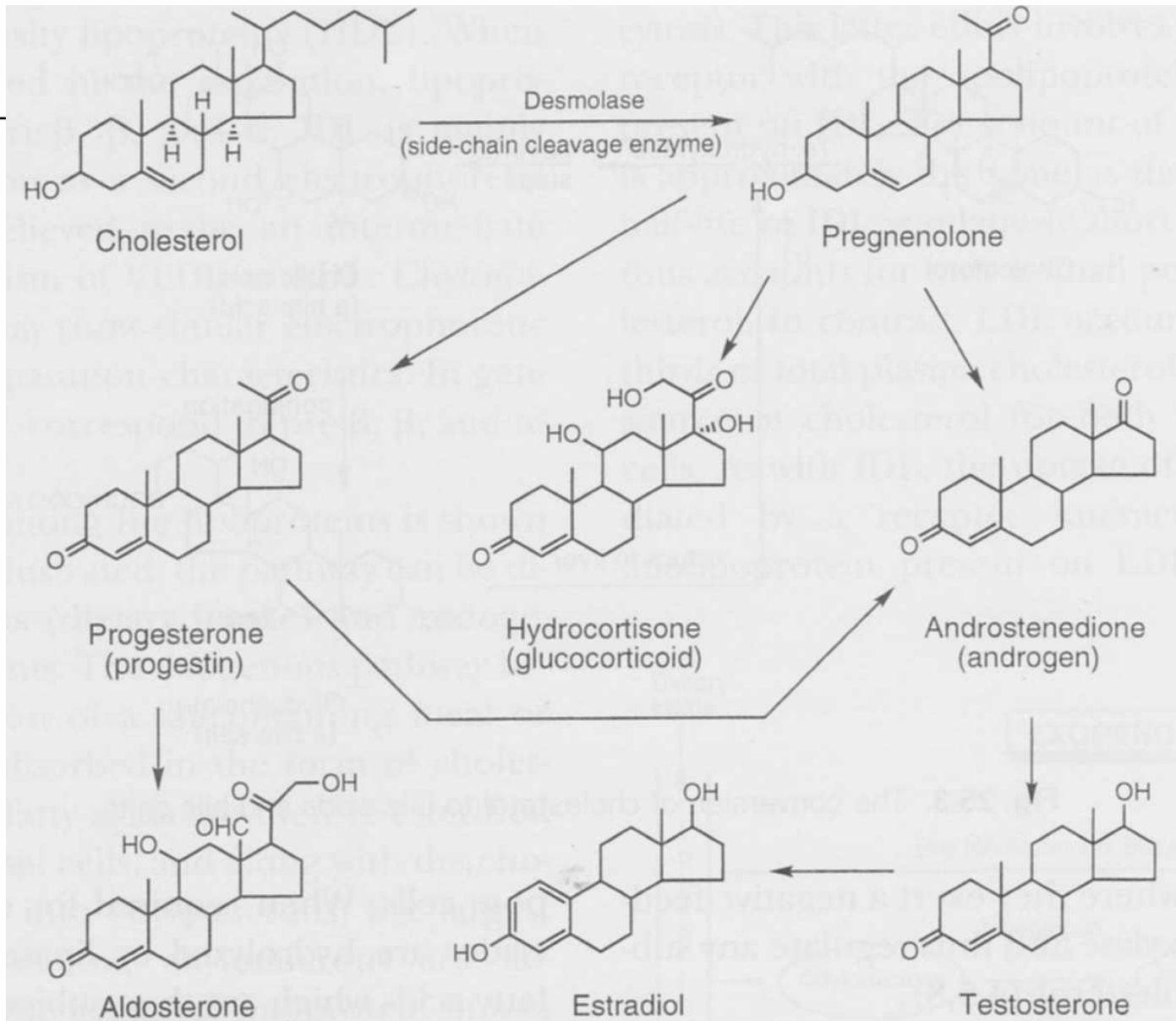
7.11.2011

Major lipids in blood stream

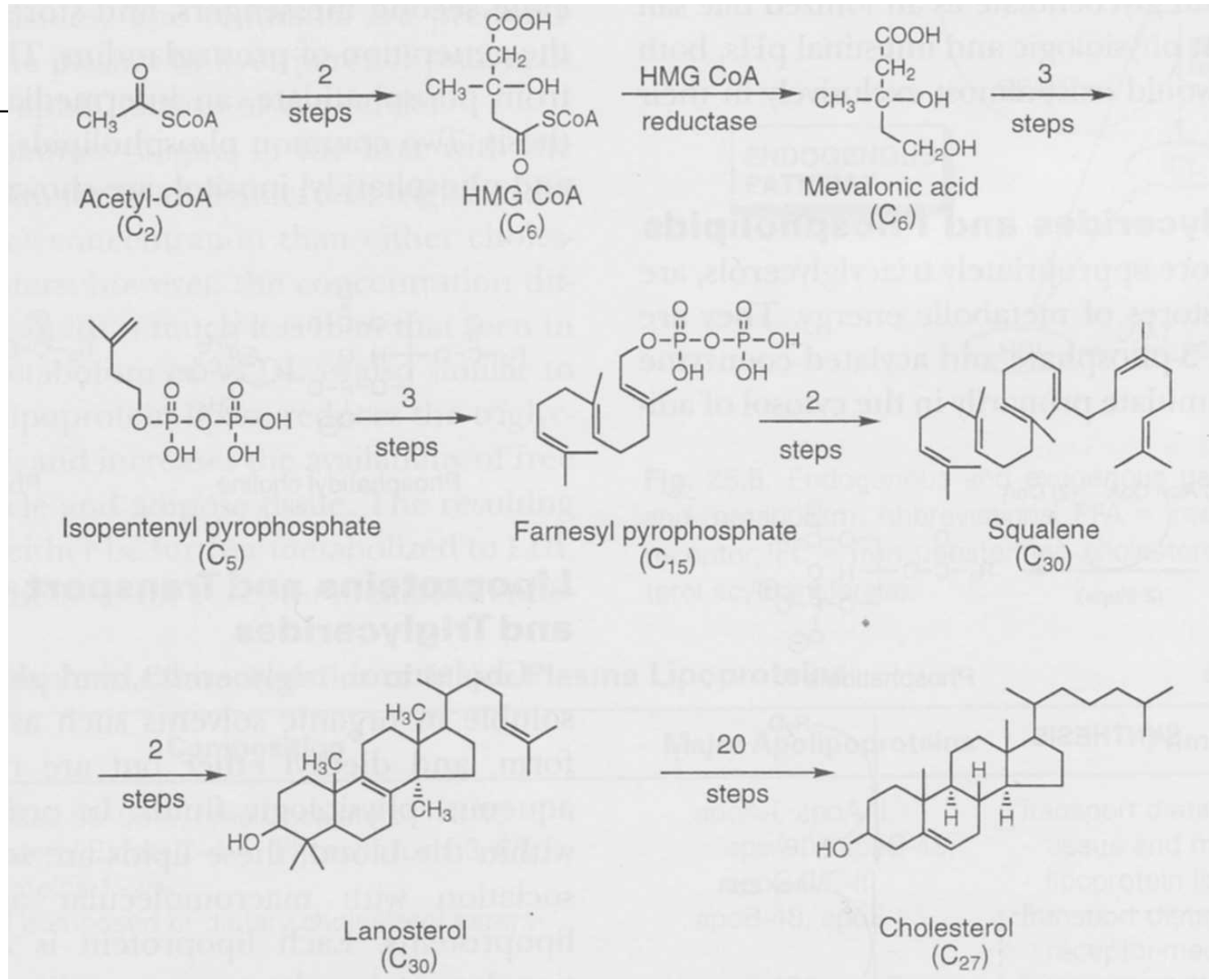
- Cholesterol and its esters
- Triglycerides
- Phospholipids

- Excess of one or more of these fractions = hyperlipidaemia

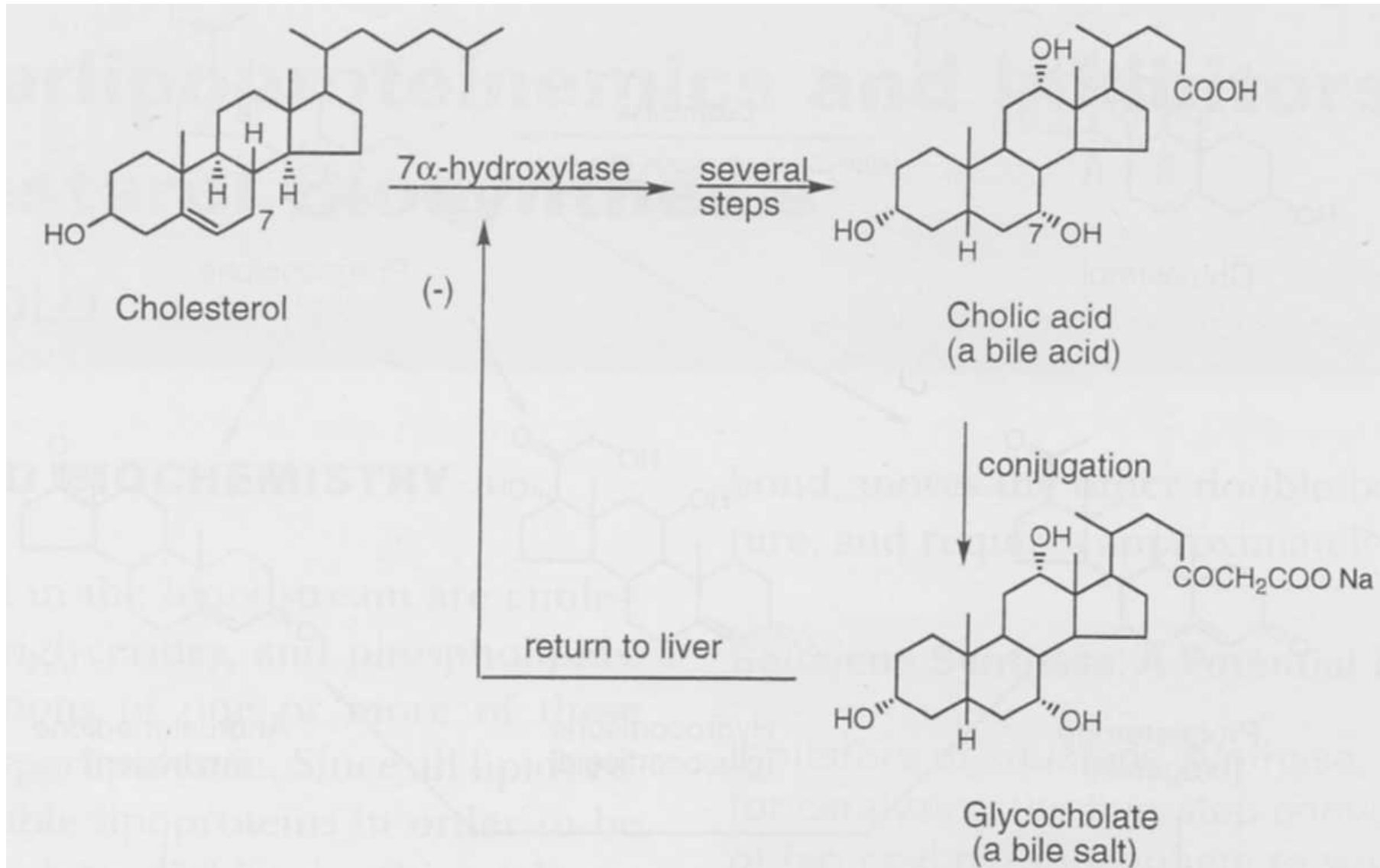
Cholesterol



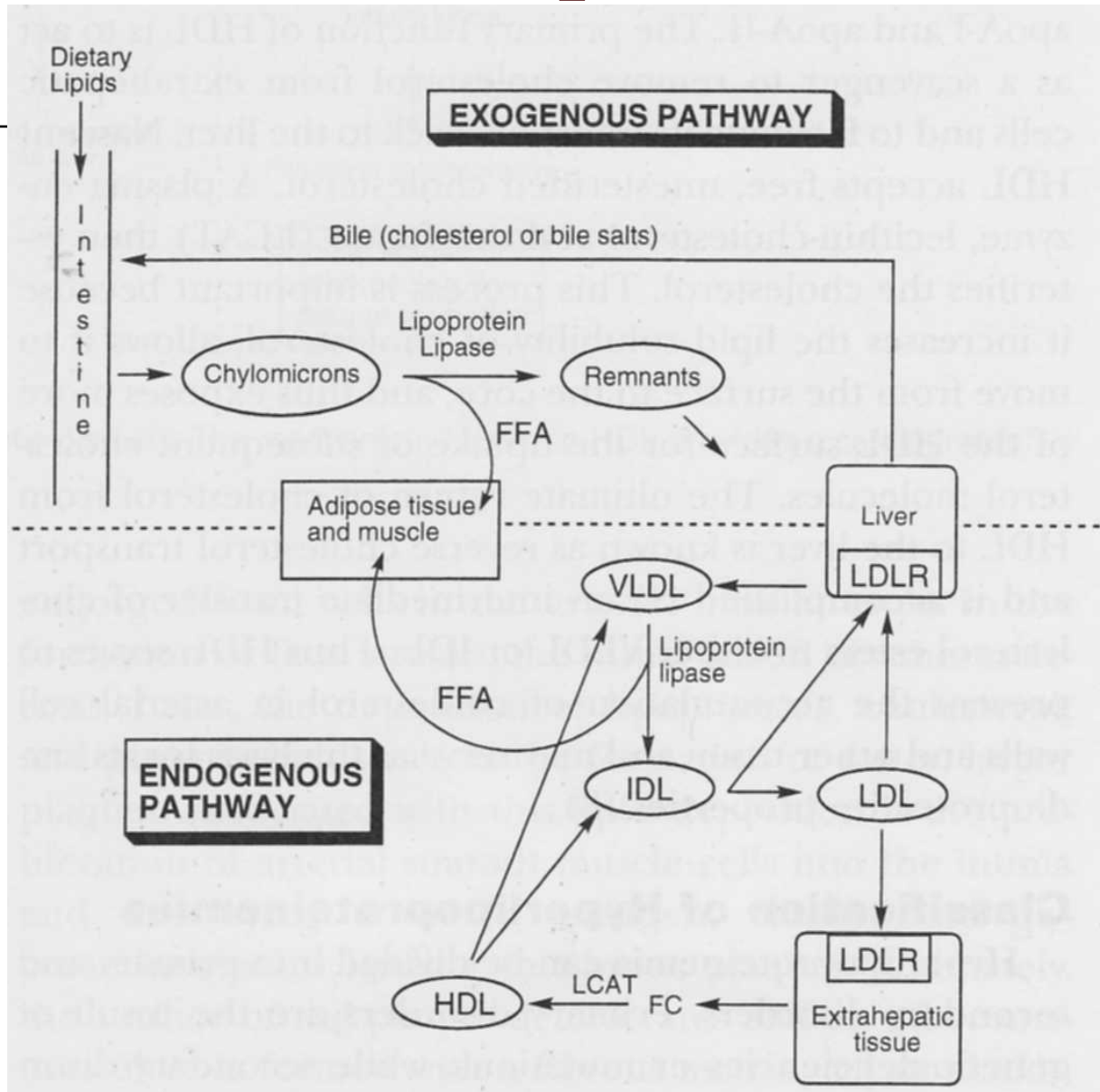
Cholesterol biosynthesis



Cholesterol – hepatobiliar circulation



Lipoproteins and lipid circulation

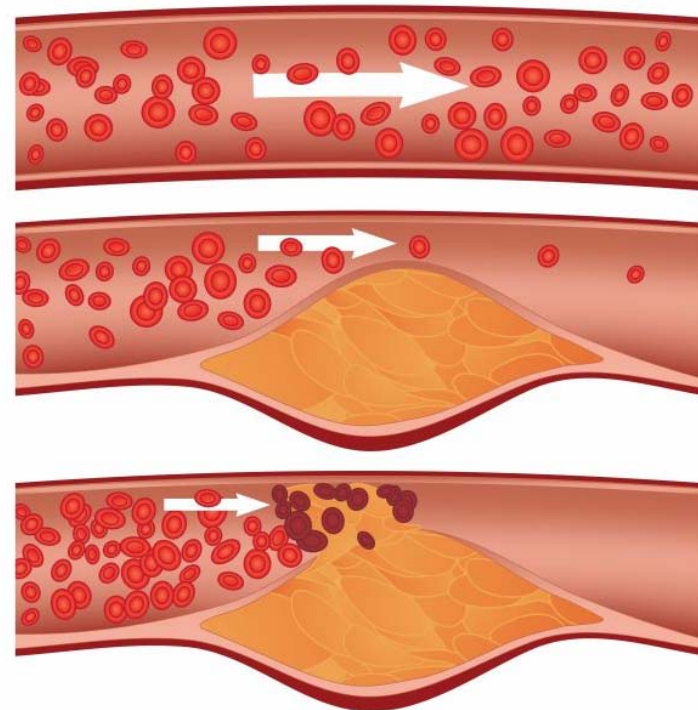
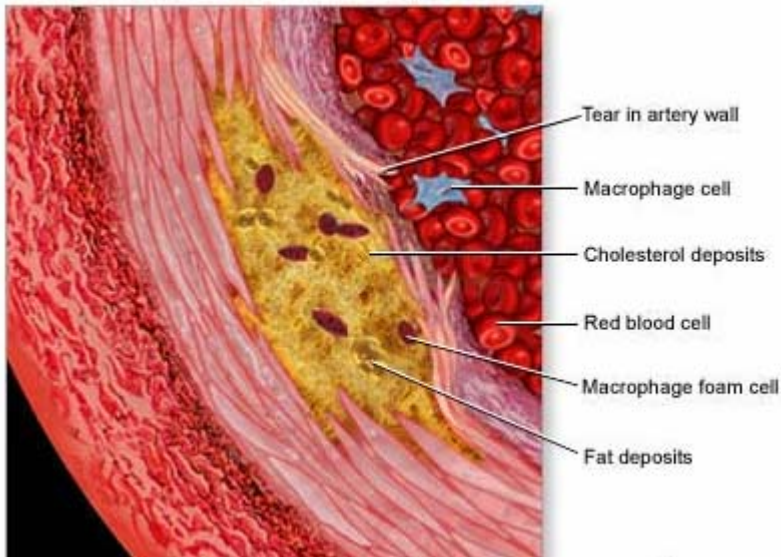


Hyperlipoproteinaemias

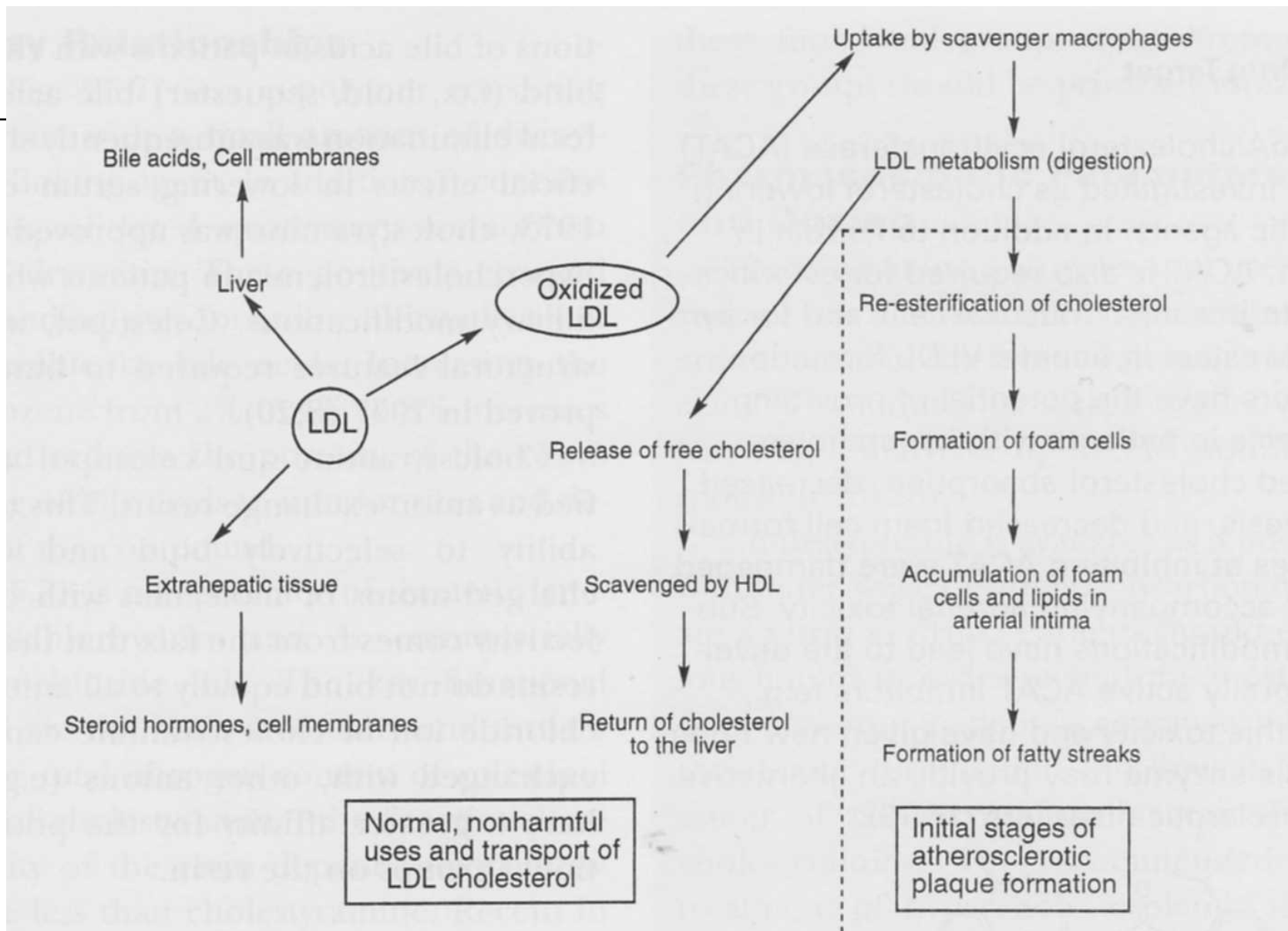
- primary – result of genetic mutations / insufficiencies of APO-lipoproteins and their tissue receptors
- secondary – result of insufficient biosynthesis of APO-lipoproteins and their tissue receptors
Associated with diabetes II, hypothyroidism, renal and liver diseases

Diseases and disorders caused by hyperlipoproteinaemias

- Coronary heart disease (myocardial infarction, ischemic heart disease, angina pectoris)



Role of LDL cholesterol in atherosclerosis



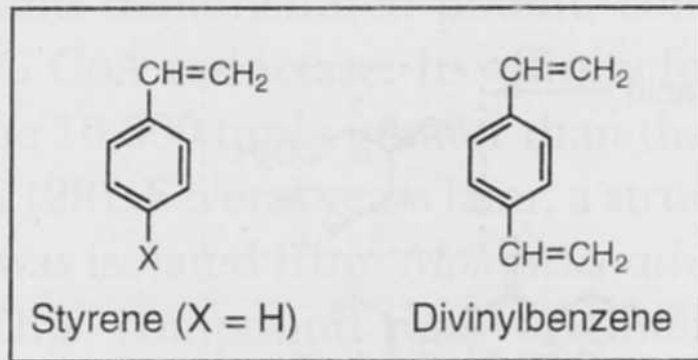


Drugs affecting lipoprotein metabolism

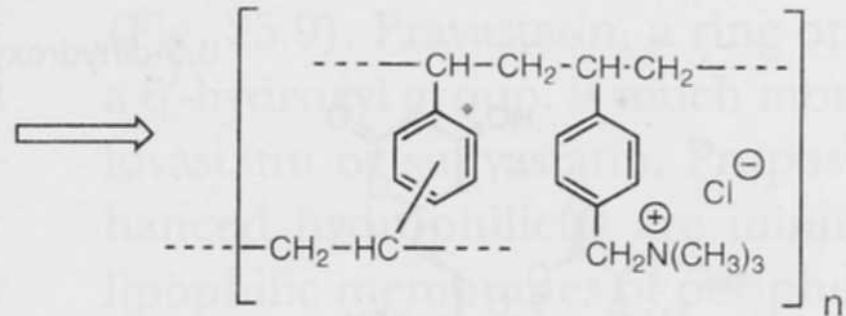
- bile acid sequestrants
- HMGCoA reductase inhibitors
- fibrates
- niacin and its derivatives

- often used in combination

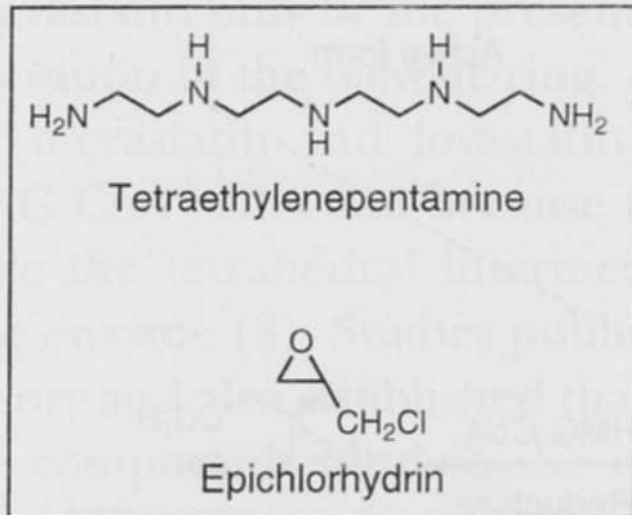
Bile acid sequestrants



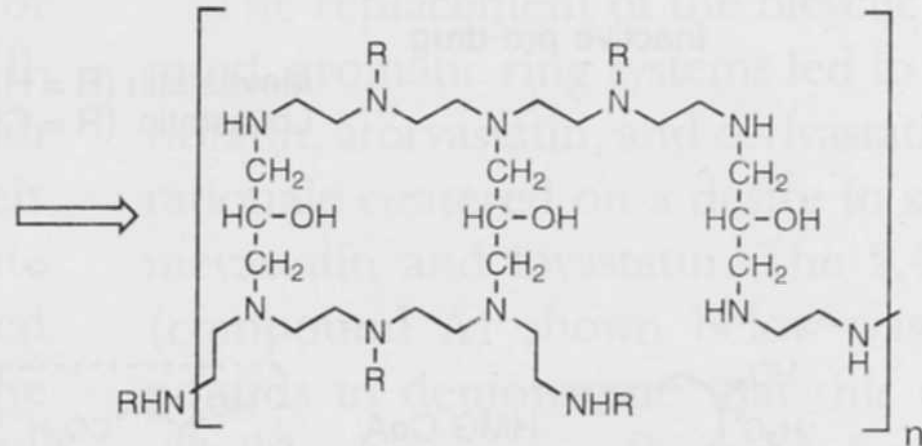
Precursors for cholestyramine



Cholestyramine



Precursors for colestipol



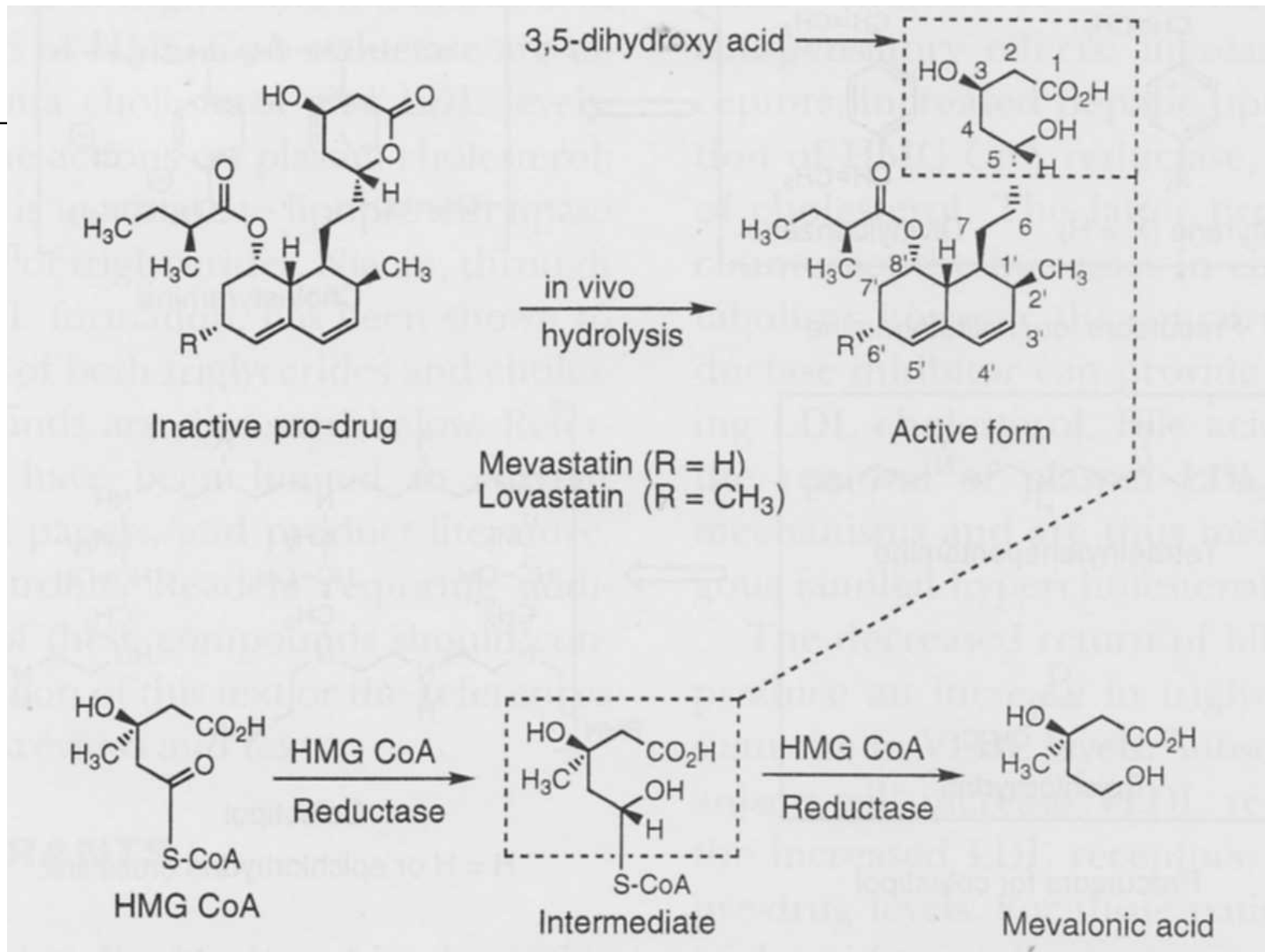
Colestipol

R = H or epichlorhydrin cross link

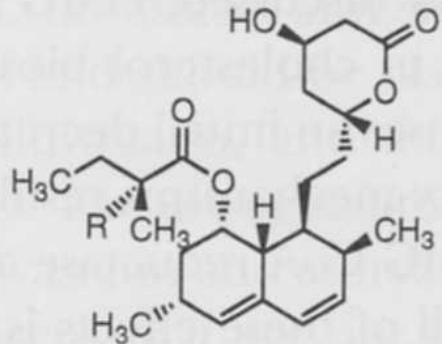
Bile acid sequestrants – mechanism of action

- basic nitrogens binds bile acids and together are excreted in the feces
- lower uptake of bile acids leads to increased LDL receptor expression and increased liver uptake of LDL fraction
- contraindicated in patients with cholelithiasis or biliary obstruction
- minimal side effects – decrease oral absorption of some drugs and lipid soluble vitamins

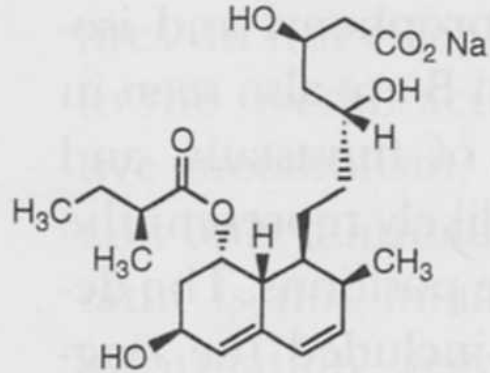
HMGCoA reductase inhibitors



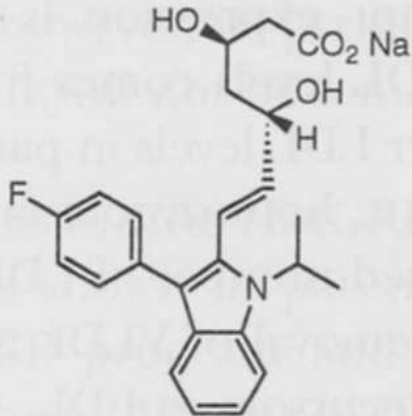
HMGCoA reductase inhibitors



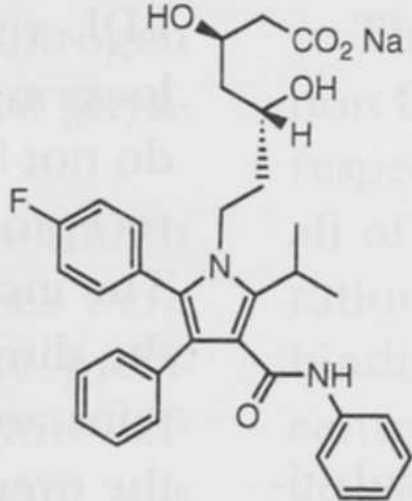
Lovastatin (R = H)
Simvastatin (R = CH₃)



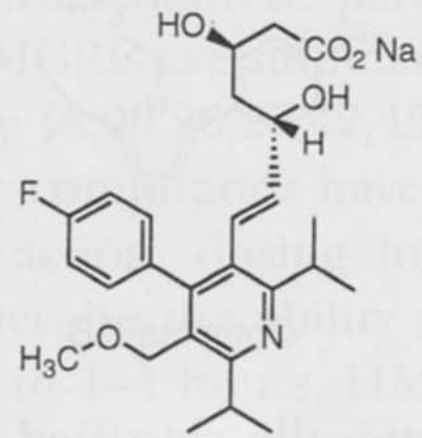
Pravastatin



Fluvastatin



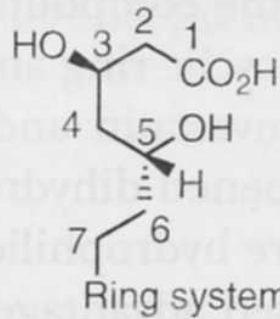
Atorvastatin



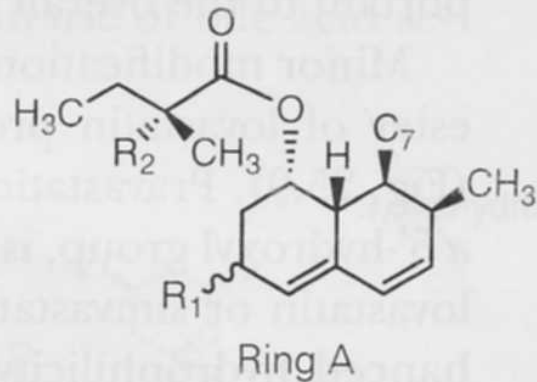
Cerivastatin

HMGCoA reductase inhibitors: Structure-activity relationships

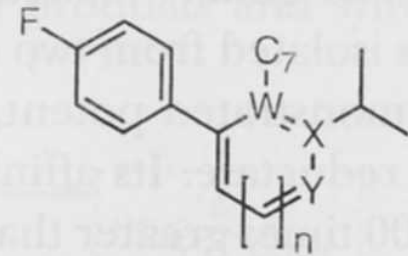
- Two main structural types



7-substituted-3,5-dihydroxyheptanoic acid



Ring A

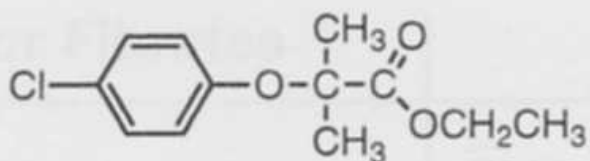


Ring B

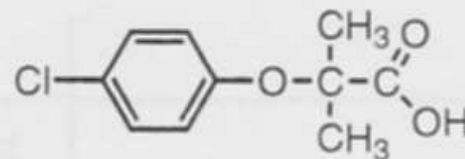
HMGCoA reductase inhibitors

- rare but serious adverse effect:
rhabdomyolysis (massive muscle necrosis) –
life threatening state
- clinical monitoring necessary
- 2001 Cerivastatin withdrawn from the market

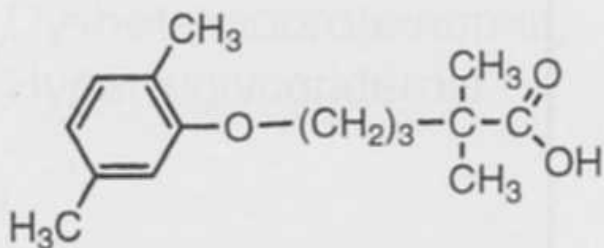
Fibrates



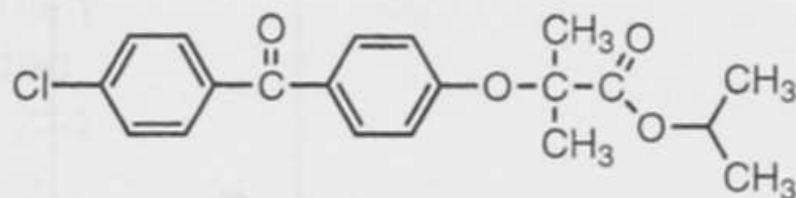
Clofibrate
(ethyl *p*-chlorophenoxyisobutyrate)



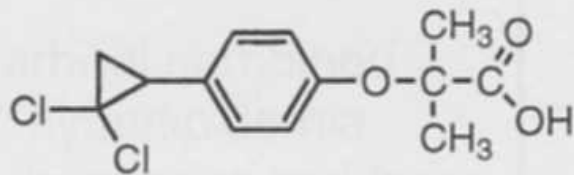
Clofibrate acid
(*p*-chlorophenoxyisobutyric acid)



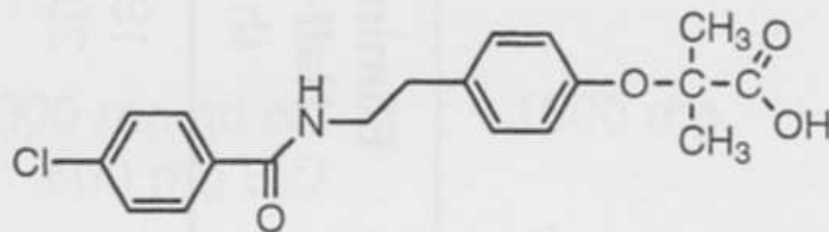
Gemfibrozil



Fenofibrate



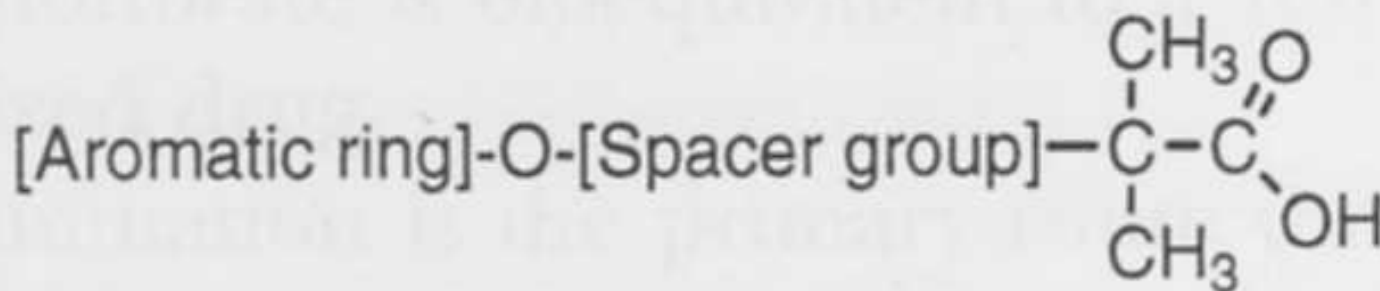
Ciprofibrate



Bezafibrate

Fibrates

– structure-activity relationship



- essential isobutyric acid group
- p-chloro substituted aromatic cycle prolongs biological half-time

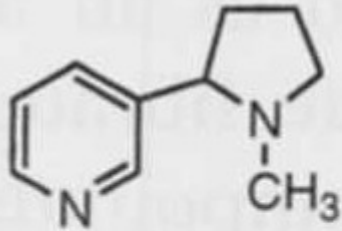
Fibrates – mechanism of action

- not fully elucidated yet
- PPARs (peroxisome proliferator activated receptors) activators
- decreases VLDL (significantly)
- increases HDL (moderate)
- variable effect on LDL

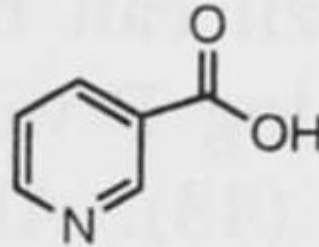
Fibrates

- serious adverse effects
- long-term administration of clofibrate increases morbidity and mortality
- all fibrates may cause myopathy and rhabdomyolysis

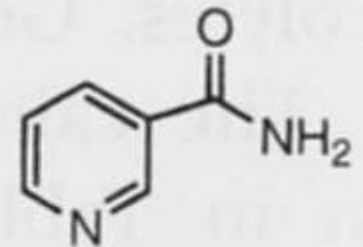
Nicotinic acid (niacin)



Nicotine



Nicotinic acid



Nicotinamide

- niacin is a nicotinic acid metabolite

Nicotinic acid – mechanism of action

- NA acts via its specific tissue receptor (NA receptor)
- inhibits lipolysis in adipose tissue
- decrease all lipid fractions (VLDL, triglycerides and LDL)

Nicotinic acid – side effects

- often side effects (20 – 50% patients)
- flushing and pruritus
- gastrointestinal intolerance