Antihyperlipidemics

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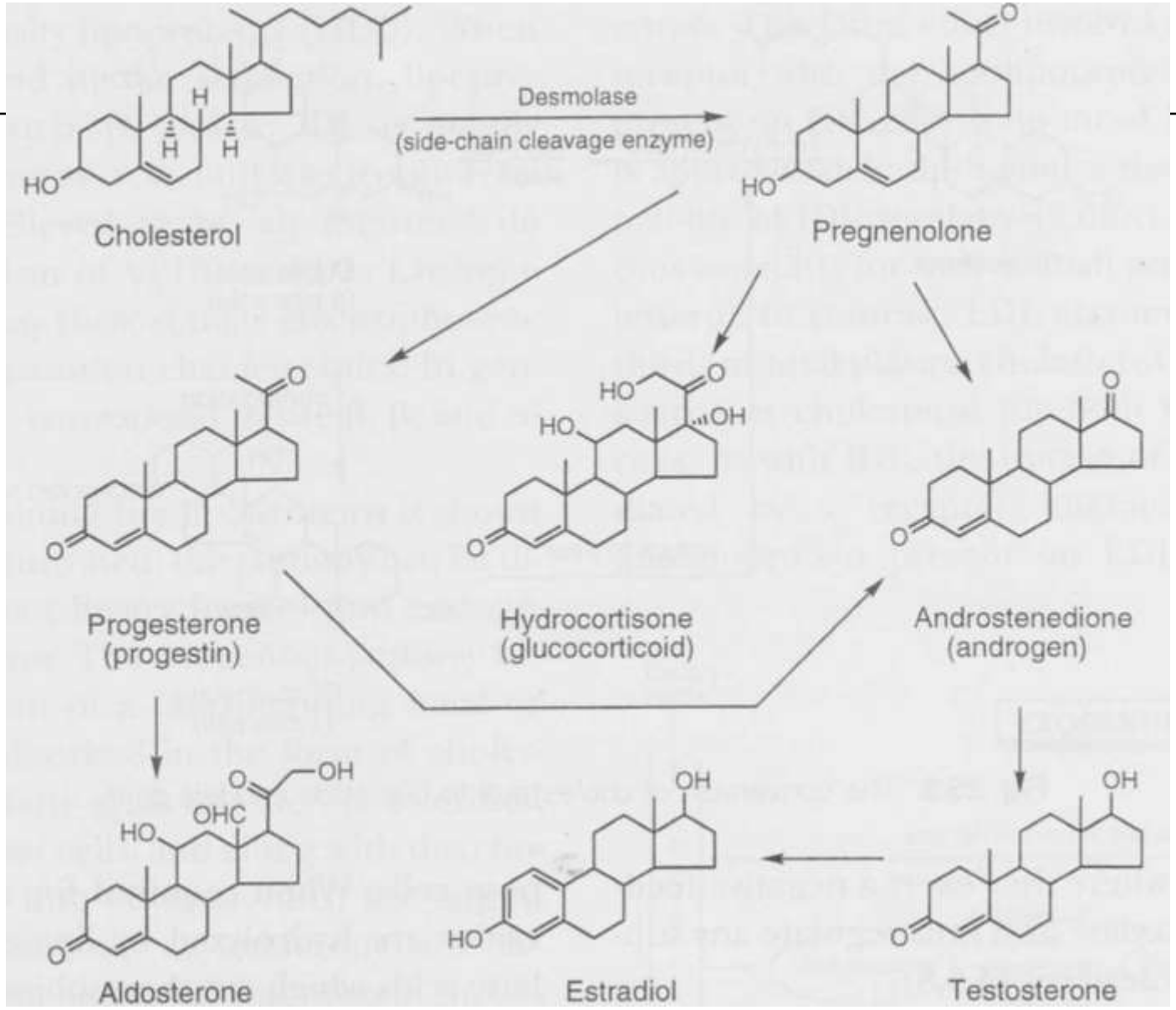
5.11.2012

Major lipids in blood stream

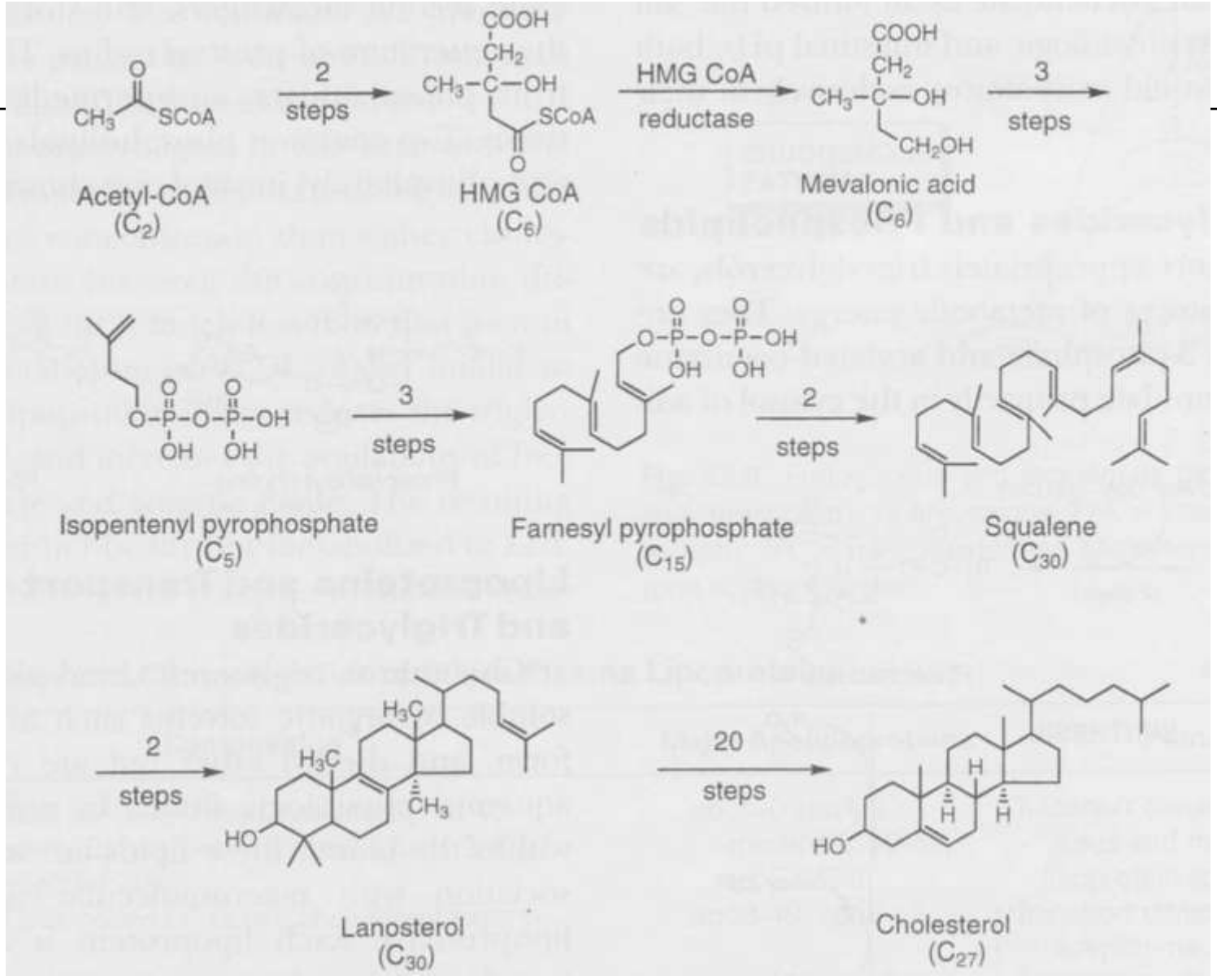
- Cholesterol and its esters
- Triglycerides
- Phospholipids

- Excess of one or more of these fractions = hyperlipidaemia

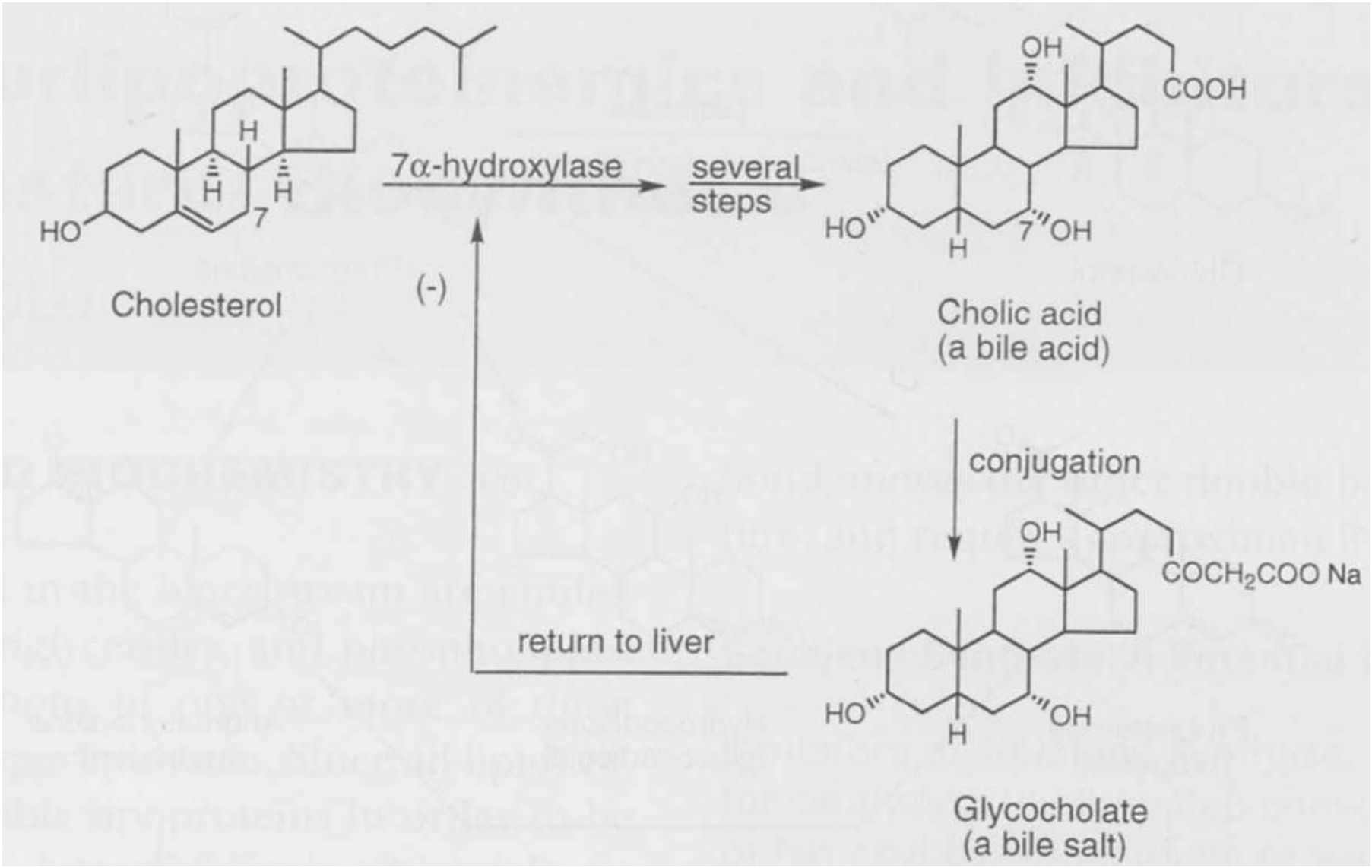
Cholesterol



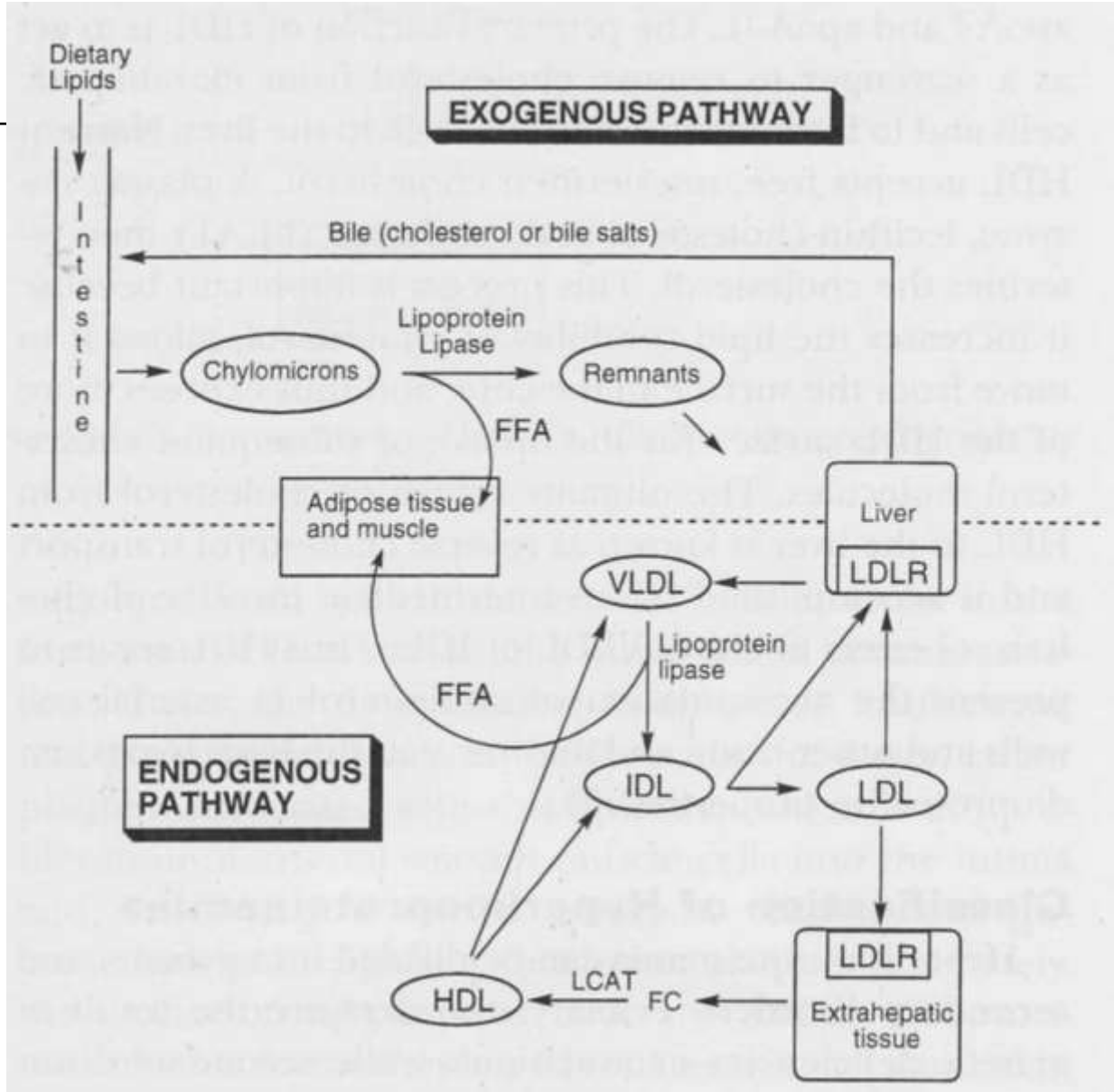
Cholesterol biosynthesis



Cholesterol – hepatobiliar circulation



Lipoproteins and lipid circulation

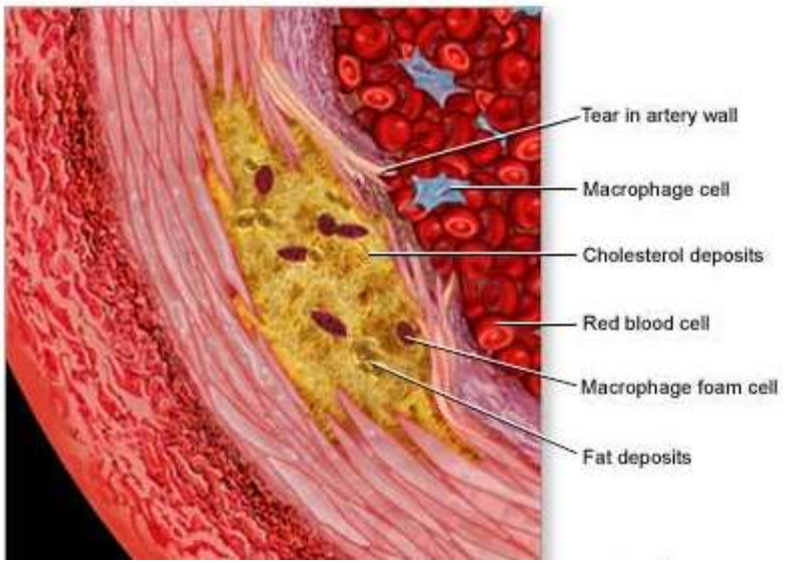


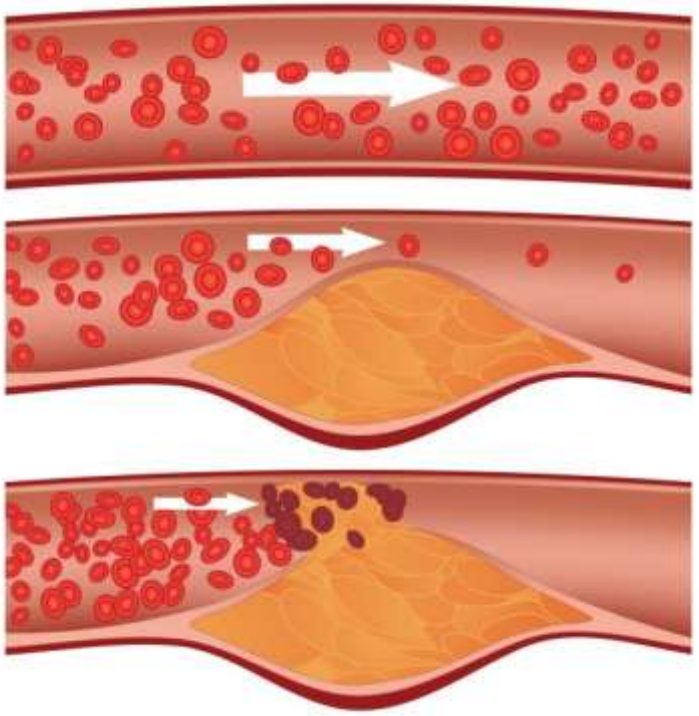
Hyperlipoproteinaemias

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

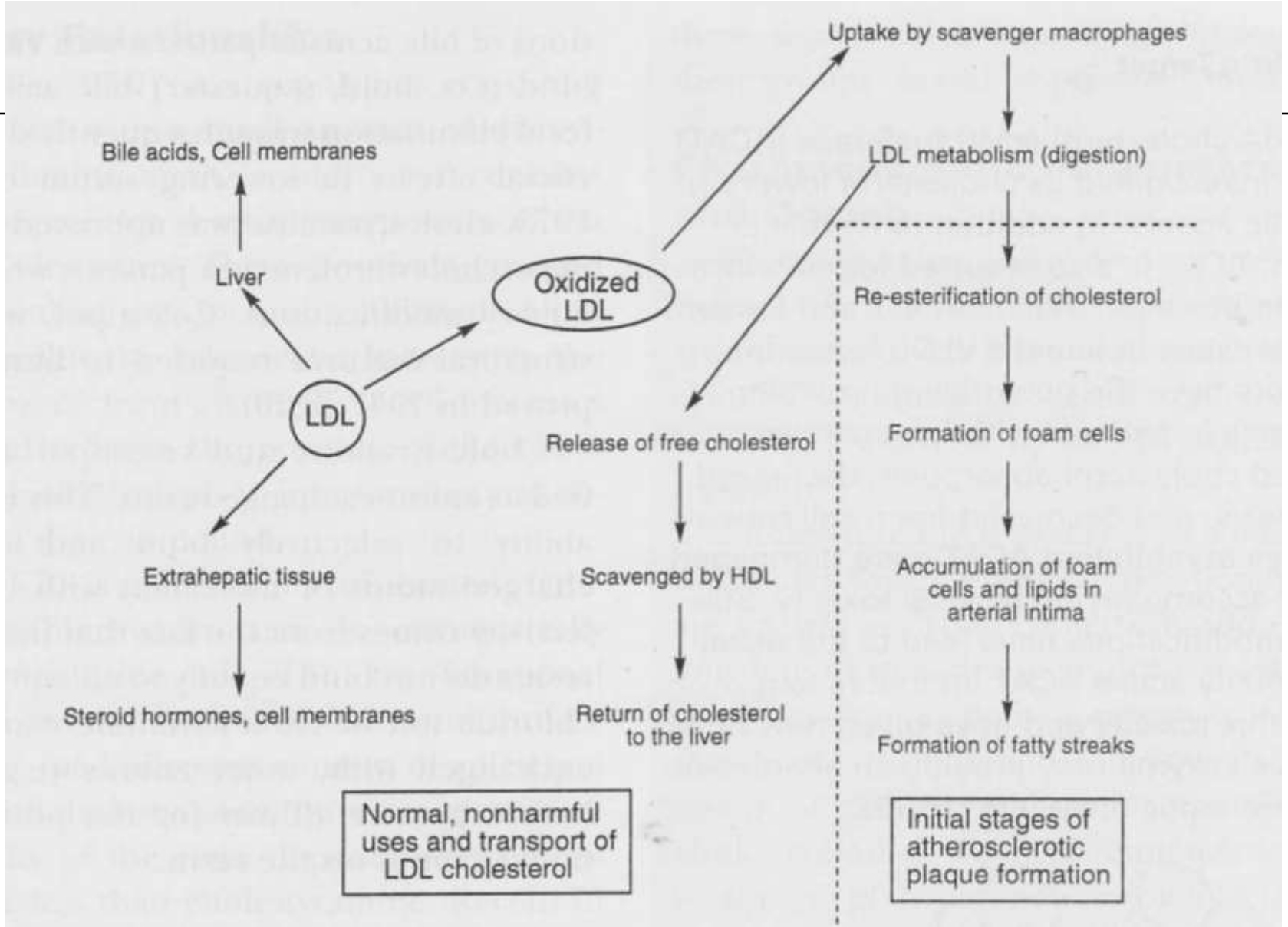
Diseases and disorders caused by hyperlipoproteinaemias

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





Role of LDL cholesterol in atherosclerosis

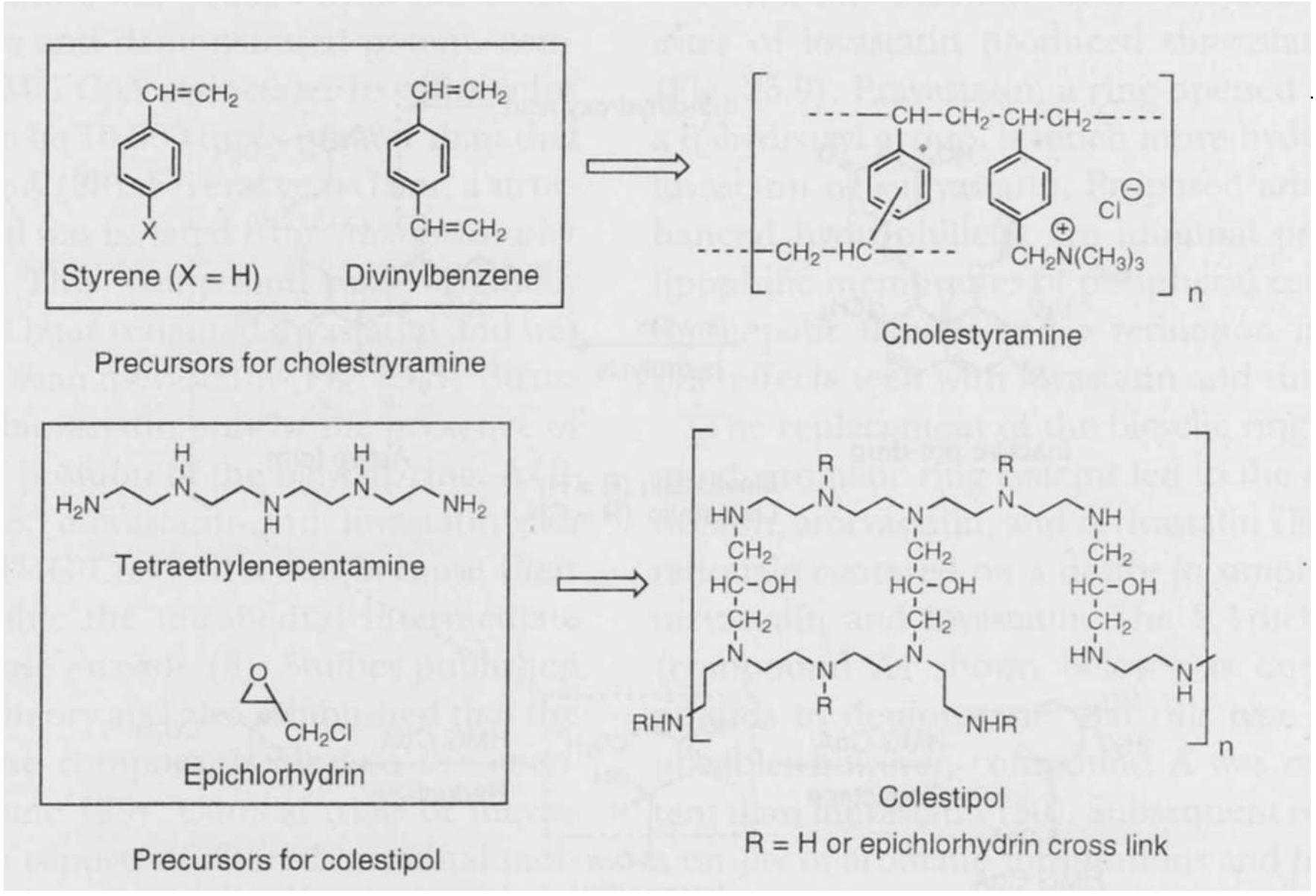


Drugs affecting lipoprotein metabolism

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

- often used in combination

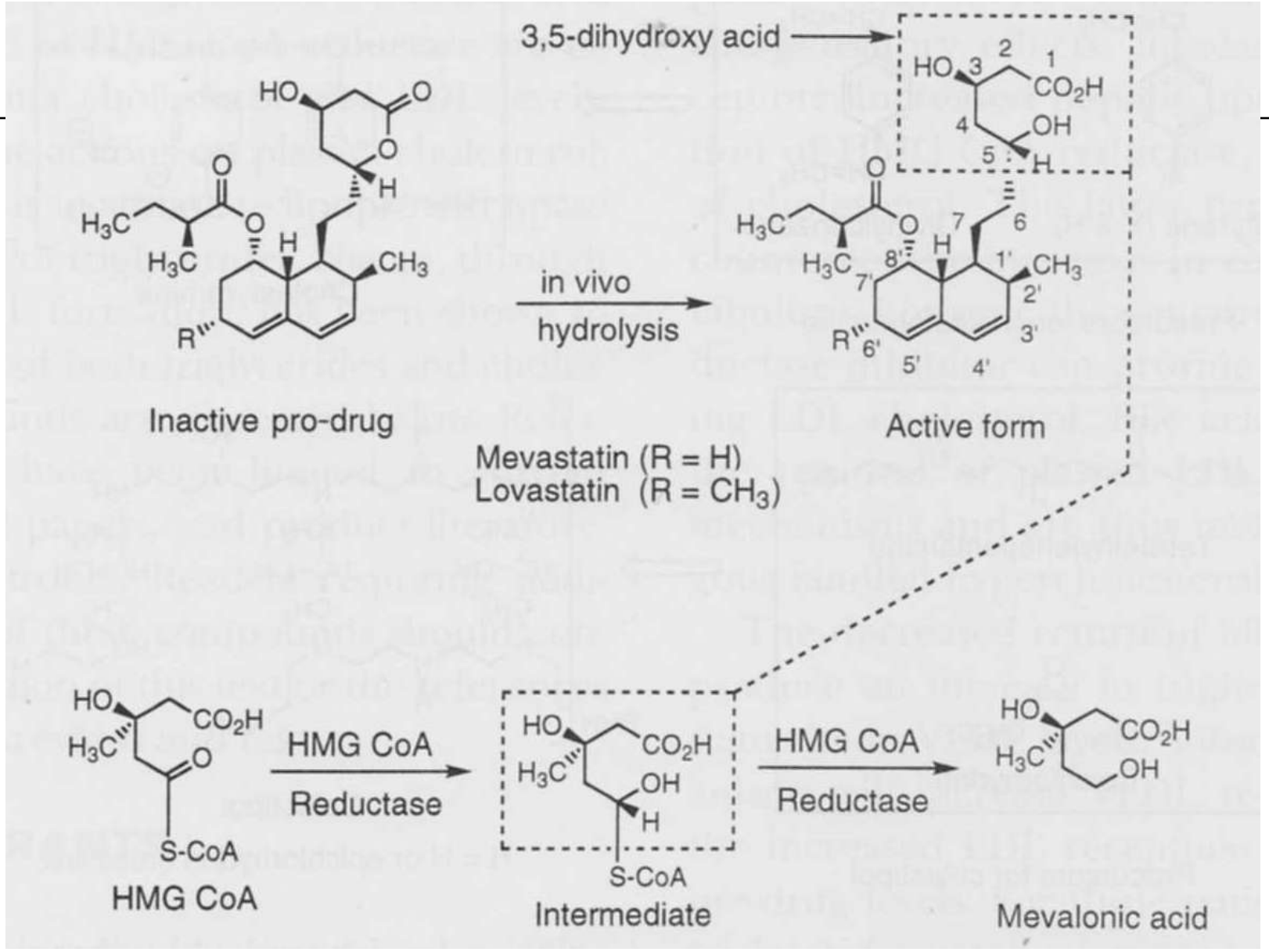
Bile acid sequestrants



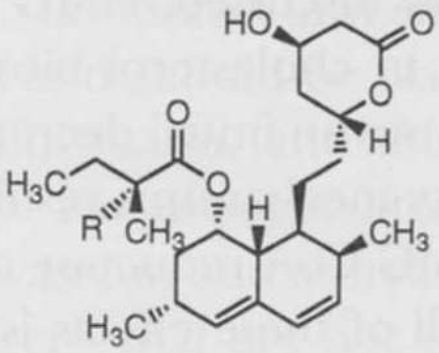
Bile acid sequestrants – mechanism of action

- 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

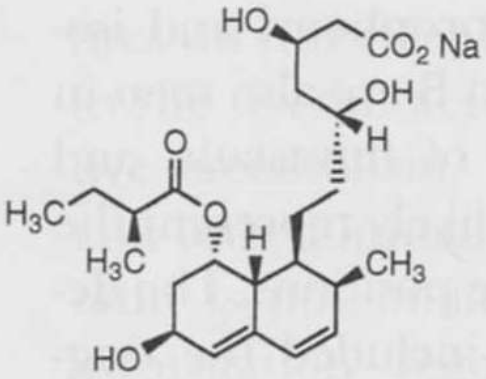
HMGCoA reductase inhibitors



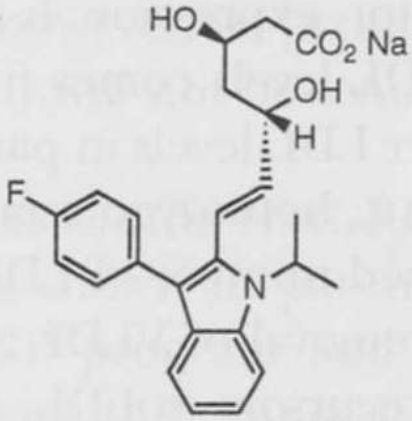
HMGCoA reductase inhibitors



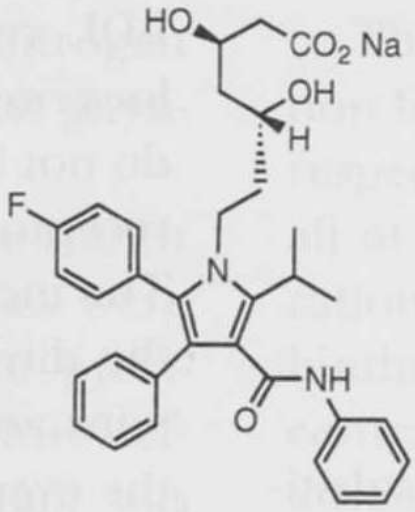
Lovastatin (R = H)
Simvastatin (R = CH_3)



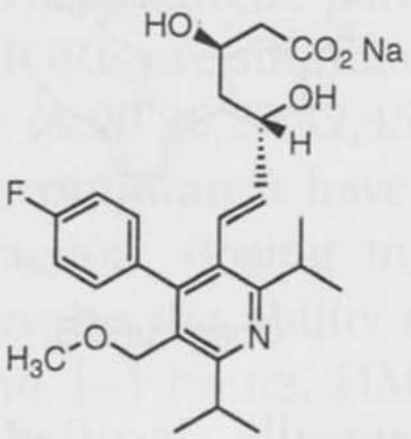
Pravastatin



Fluvastatin



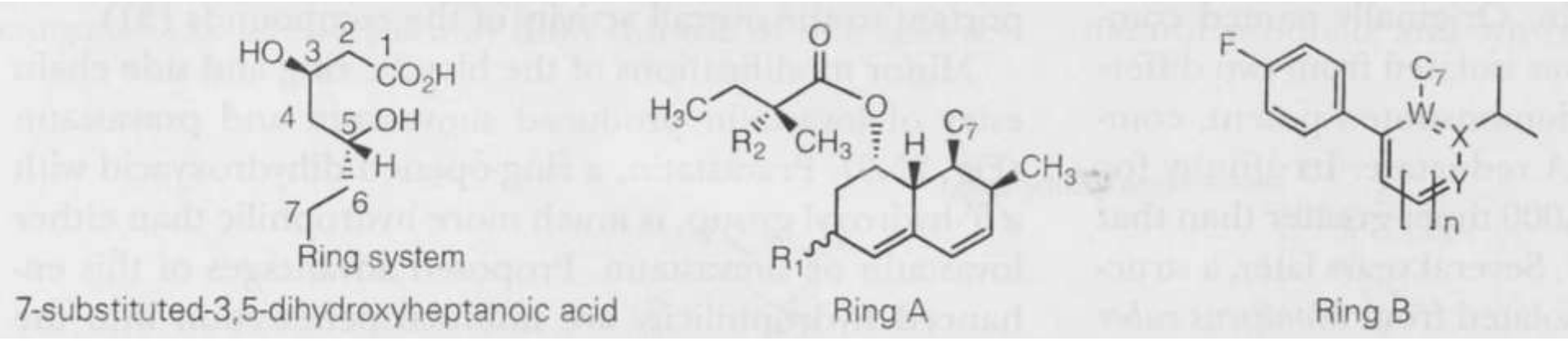
Atorvastatin



Cerivastatin

HMGCoA reductase inhibitors: Structure-activity relationships

- Two main structural types



A ring: OH in R_1 improves specifity
methyl in R_2 improves activity

B ring: 5 or 6 membered heterocycle with nitrogen in W or X orY
additional substitution with second phenyl improves activity

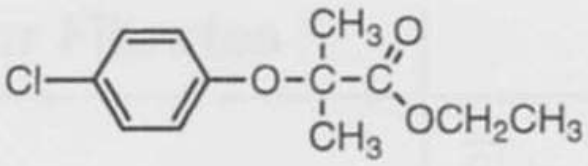
HMGCoA reductase inhibitors

- Lower plasma cholesterol levels
- Increase LDL uptake
- Reduces VLDL precursors

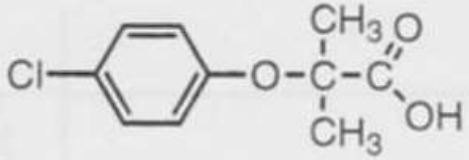
HMGCoA reductase inhibitors

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

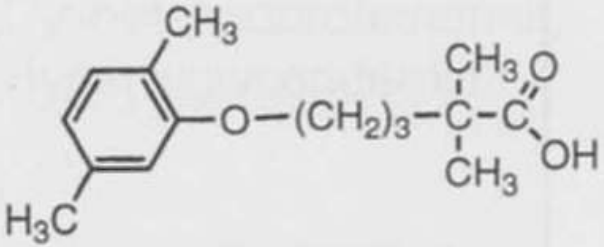
Fibrates



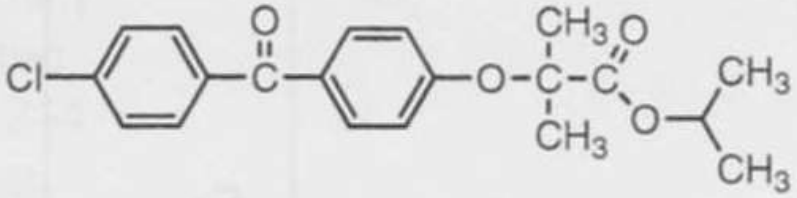
Clofibrate
(ethyl ρ–chlorophenoxyisobutyrate)



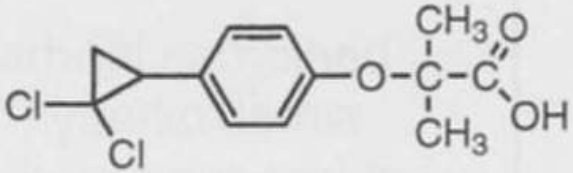
Clofibrate acid
(ρ–chlorophenoxyisobutyric acid)



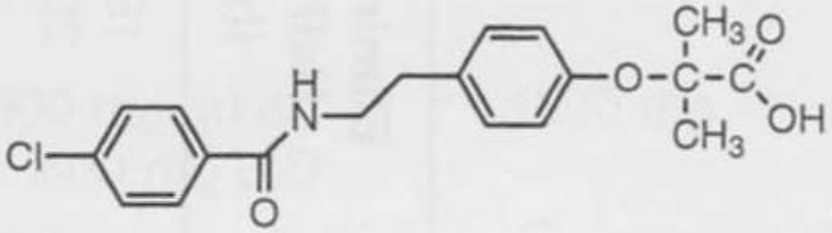
Gemfibrozil



Fenofibrate



Ciprofibrate



Bezafibrate

Fibrates
– structure-activity relationship

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

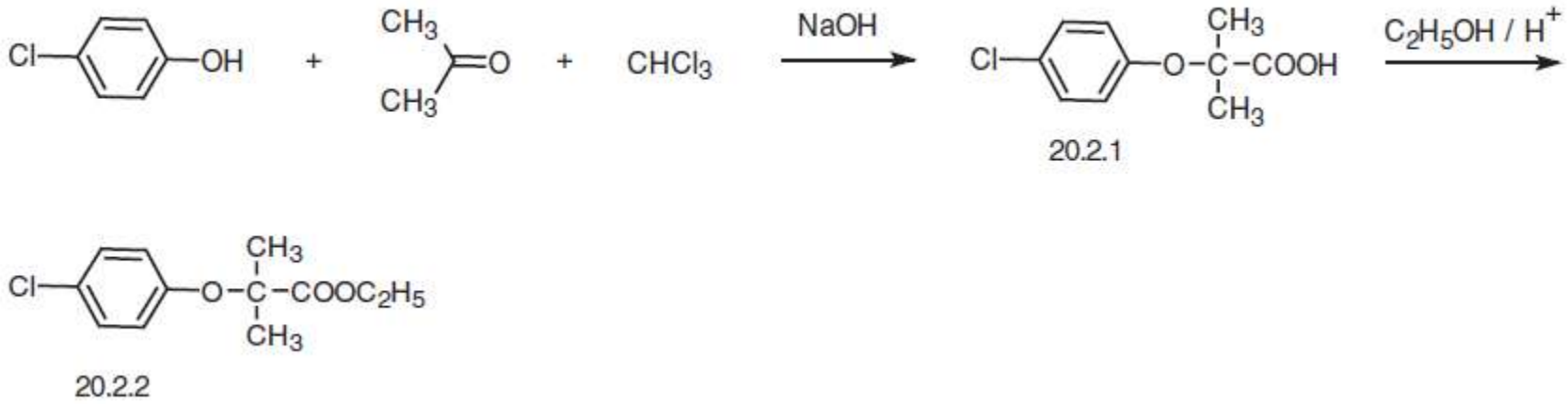
Fibrates – mechanism of action

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

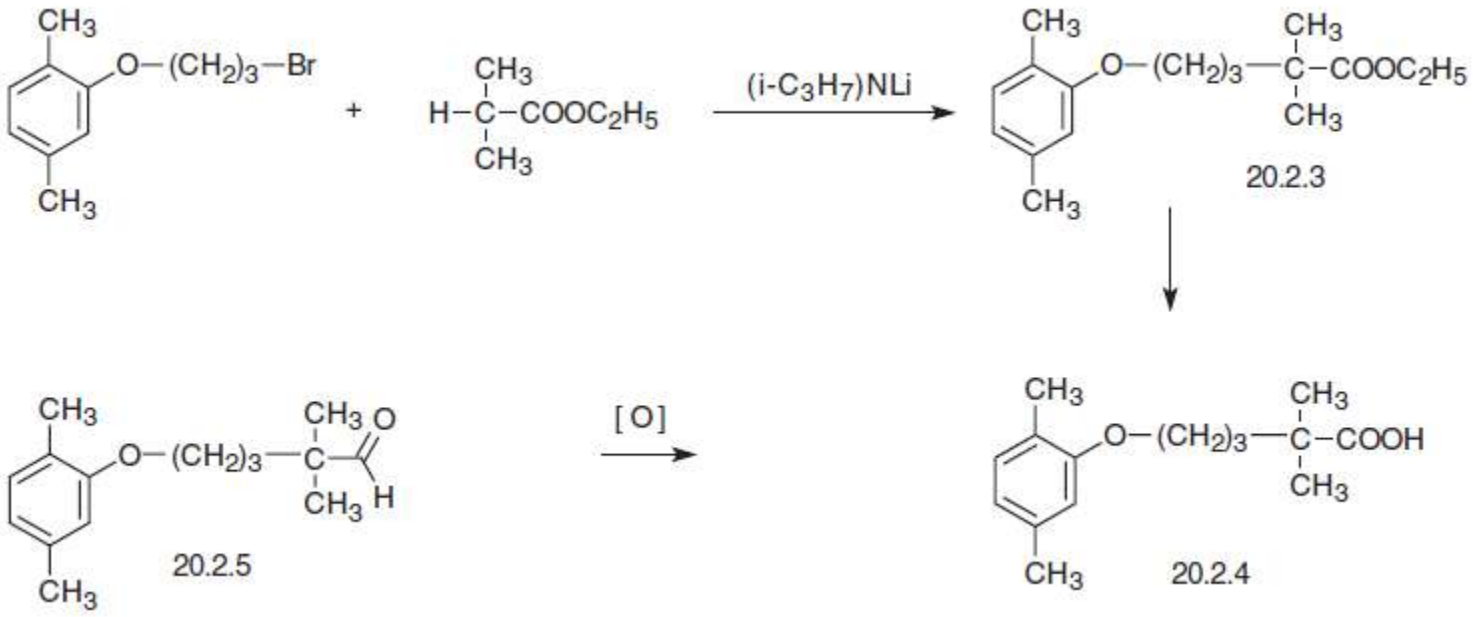
Fibrates

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

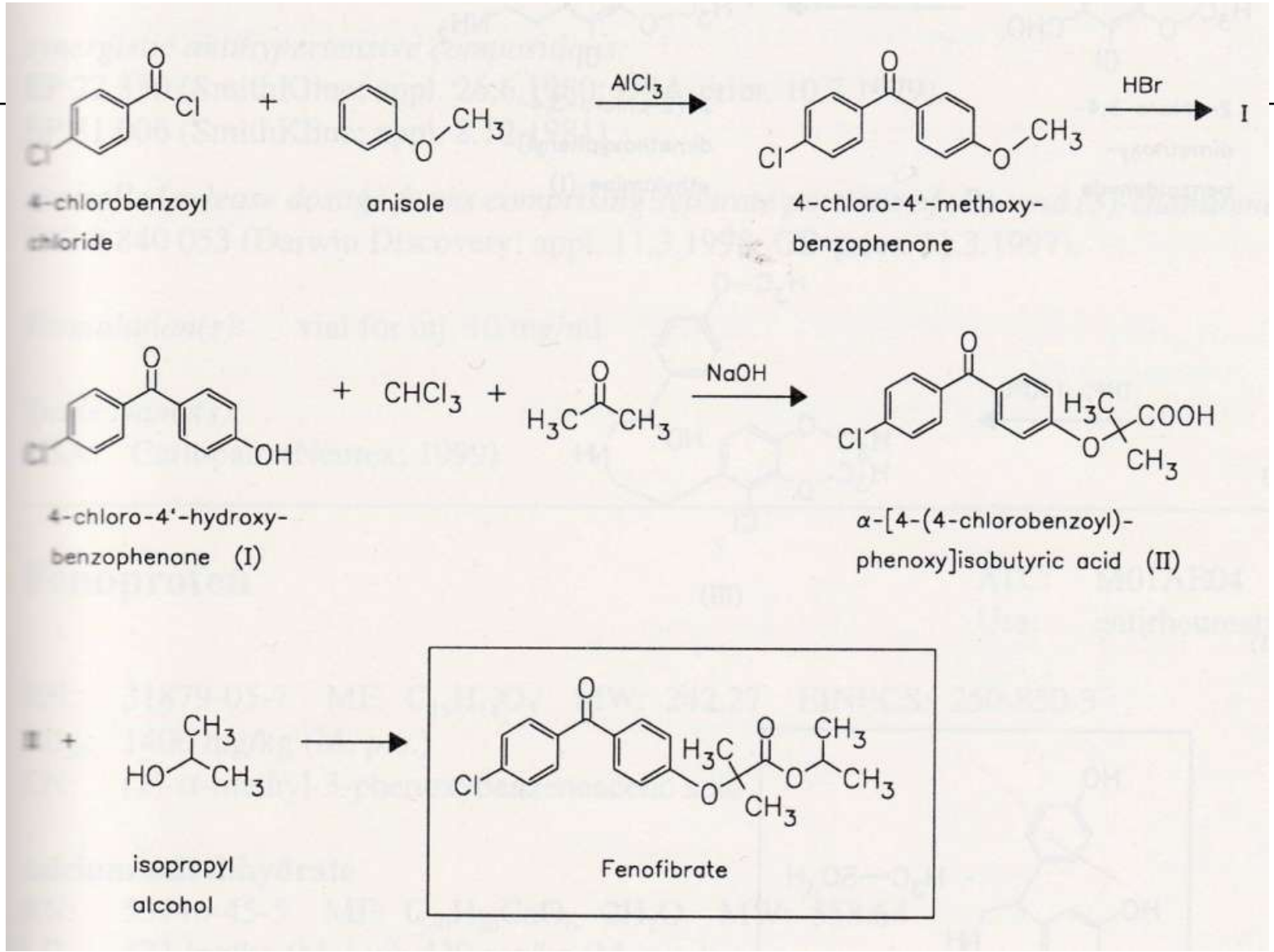
Clofibrate synthesis



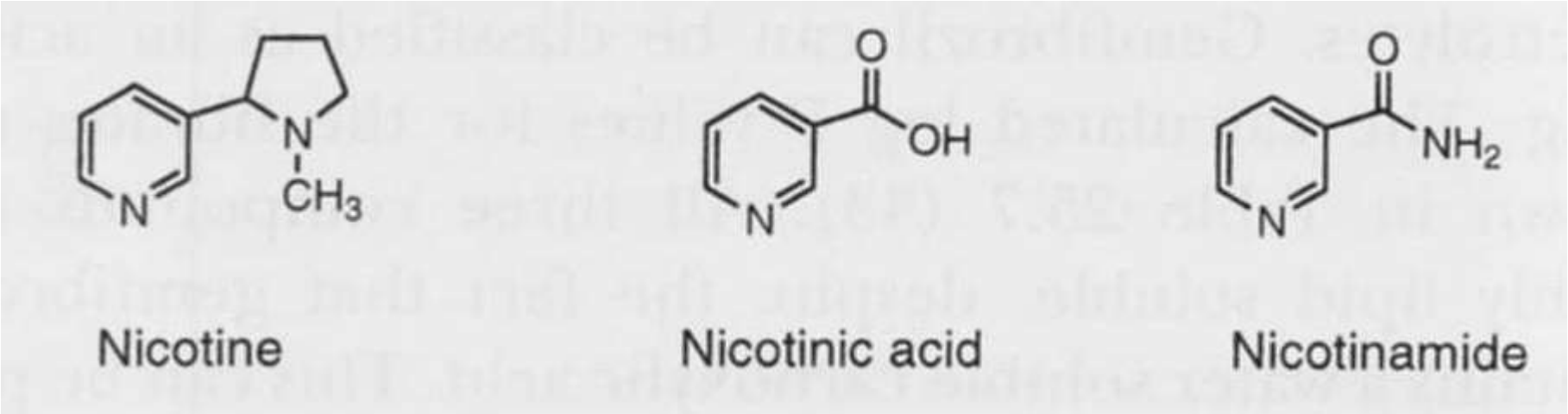
Gemfibrozil synthesis



Fenofibrate synthesis



Nicotinic acid (niacin)



- niacin is a nicotinic acid metabolite

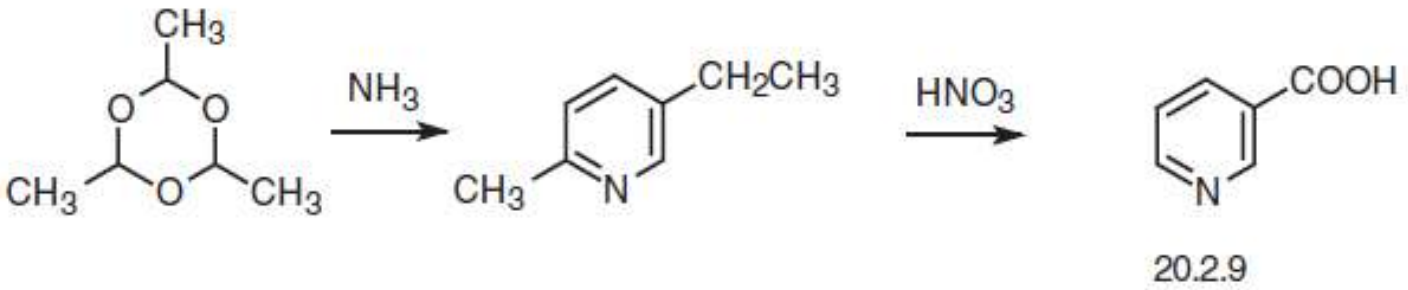
Nicotinic acid – mechanism of action

- 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

Nicotinic acid synthesis



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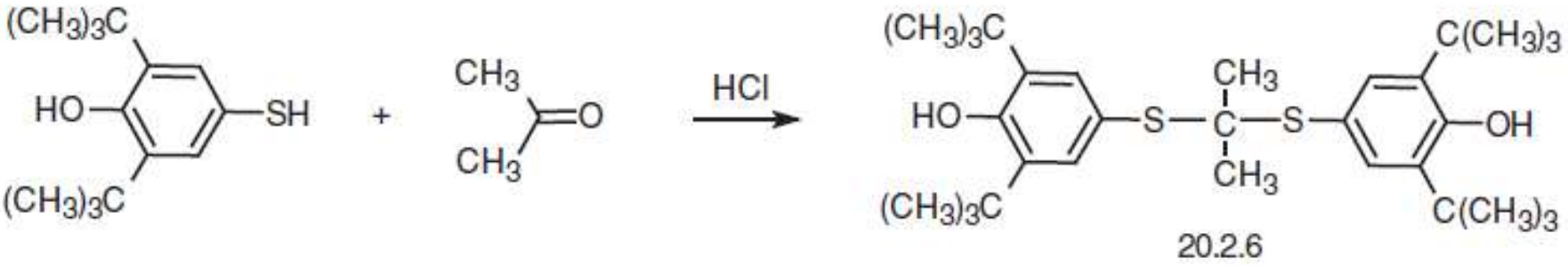
Probucol

- Unknown mechanism of action
- Decrease overall plasma level of cholesterol, primary LDL



20.2.6