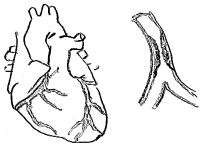
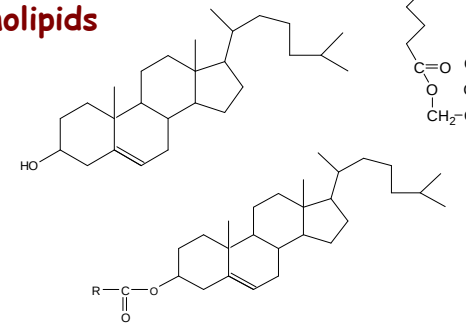
I. Hyperlipidemias

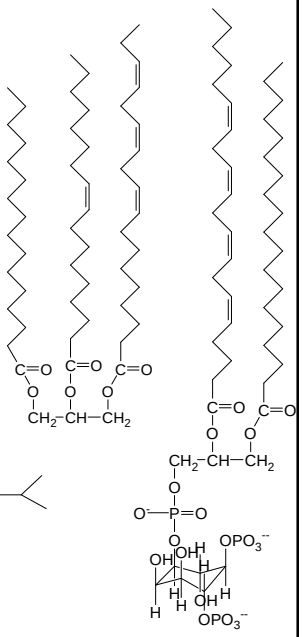
Hyperlipidemia means the serum concentration of one of the following is higher than the normal range:

a) Cholesterol
b) Cholesterol esters
c) Triglycerides
d) Phospholipids

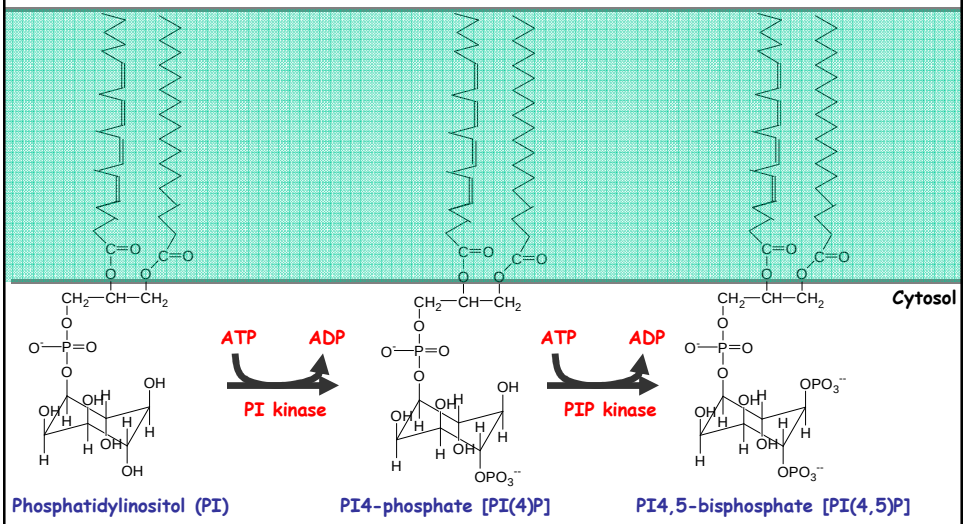


Plaque
(Coronary artery)



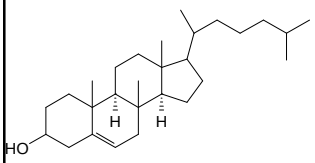


Phospholipids-signal transduction
e.g. Formation of PIP_2, or Phosphatidylinositol-4,5,-bisphophate

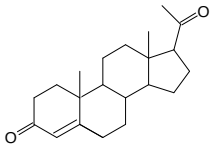


Phosphatidylinositol (PI) | PI4-phosphate [PI(4)P] | PI4,5-bisphosphate [PI(4,5)P]

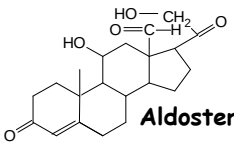
Cholesterol is a precursor of many endogenous hormonal molecules



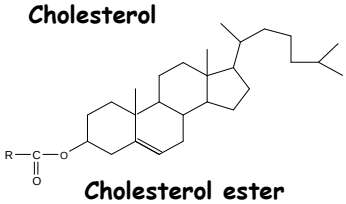
Cholesterol



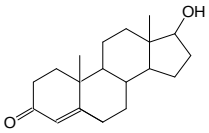
Progesterone



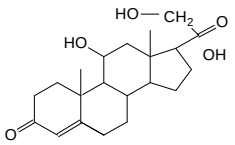
Aldosterone



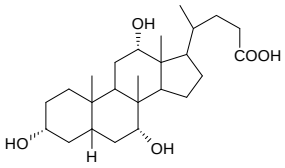
Cholesterol ester



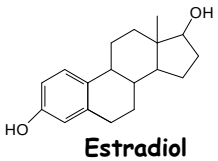
Testosterone



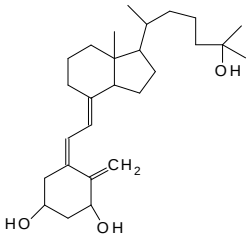
Cortisol



Cholic acid (a bile acid)



Estradiol



1, 25-$(OH)_2$-Vitamin D_3
(Calciferol, biologically potent)

Classification of major plasma lipoproteins

- Based on mode of separation (preparative ultracentrifugation/protein density)
- Very low density lipoproteins (VLDLs);Intermediate density lipoproteins (IDLs); Low density lipoproteins (LDLs);High density lipoproteins (HDLs)

Classification	Triglycerides (%)	Free cholesterol (%)	Cholesterol esters (%)	Phospholipids (%)	Apoproteins (%)
Chylomicrons	80-95	1-3	2-4	3-9	1-2
Chylomicron remnants	Primarily composed of dietary cholesterol esters				
VLDL	50-65	4-8	16-22	15-20	6-10
IDL	Intermediate between VLDL and LDL				
LDL	4-8	6-8	45-50	18-24	18-22
HDL	2-7	3-5	15-20	26-32	45-55

- Hypercholesterolemias: LDL↑
- Hypertriglyceridemias: VLDL↑; chylomicrons↑

II. Drug therapies for hyperlipidemias

A. Bile acid sequestrants

↓LDL; →VLDL

B. HMG-CoA reductase inhibitors

↓LDL; ↓VLDL

C. Squalene synthase inhibitors

↓VLDL; ↓LDL

D. Cholesterol absorption inhibitors

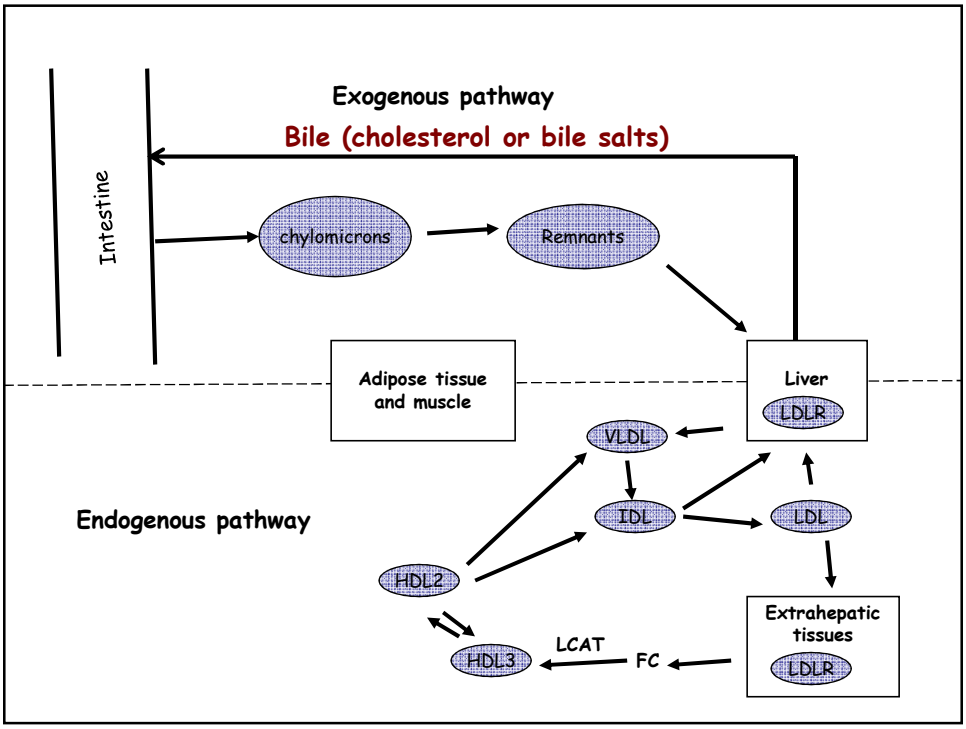
↓LDL

E. Fibrates

↓VLDL; ↓LDL

F. Nicotinic acid

↓VLDL; ↓LDL



A. HMG-CoA reductase inhibitors

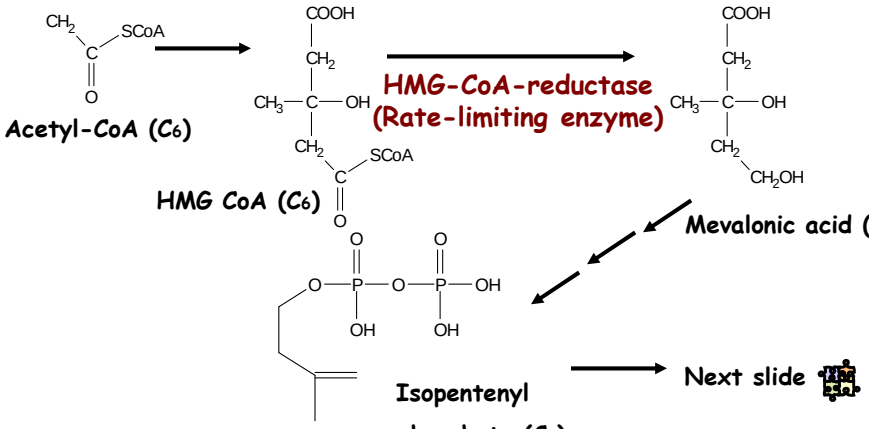
a. Importance
b. Mechanism of action
c. Lead discovery
d. Lead modification
e. Structure/activity relationships

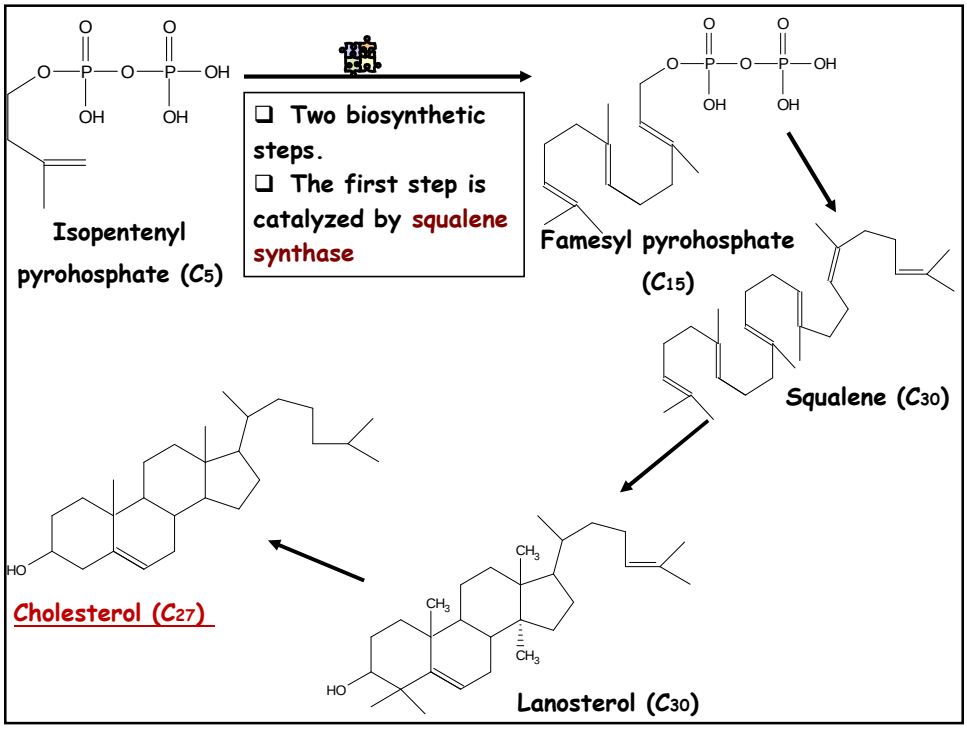
a. Importance

- Coronary disease-Leading cause of death in US
  - Atherosclerosis
    - Plaque (fatty deposits) on the inner walls of arteries
    - Cholesterol is the major component of atherosclerotic plaque
- Top selling drug
  - Lipitor
  - Zocor

b. Mechanism of action

- Biosynthesis of cholesterol
  - More than 20 enzyamtic steps starting from acetyl CoA
    - The rate-limiting step is the conversion of 3-hydroxy-3-thylglutaryl coenzyme A (HMG-CoA) to mevalonic acid by HMG-CoA reductase





c. Lead discovery

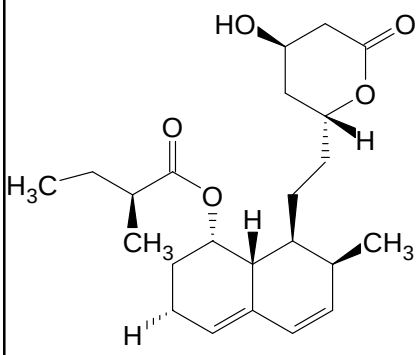
(1). History

- Endo and coworkers at the Sankyo Company in Tokyo
  - First tested 8000 strains of microorganisms for metabolites inhibiting sterol biosynthesis
  - Three metabolites in the culture broths of the fungus *Penicillium citrinum*
- Brown and coworker at Beecham Pharmaceutical in England
  - Isolated mevastatin (compactin) from the culture broth of *Penicillium brevicompactum*
- Endo and coworkers at the Sankyo Company in Tokyo
  - Isolated monacolin K from the fungus *Monascus ruber*
- Scientists in Merck
  - Isolated monacolin K from the fungus *Aspergillus terreus and* name it mevinolin (Lovastatin, or Mevacor)
- Other active fungal metabolites: Dihydrocompactin (P.citrinum); dihyromevinolin (A. terreus; dihyromonacolin L (M. ruber)

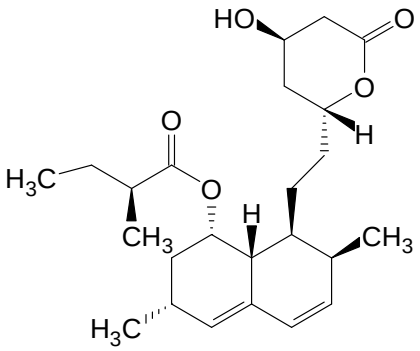
c. Lead discovery

(2). Mechanism of action

- Both mevastatin and lovastatin are competitive reversible inhibitors of HMG-CoA reductase



Mevastatin, or compactin
(Beecham Pharmaceutical)



Lovastatin, or mevinolin
(Merck)

- Competitive reversible inhibitor of HMG-CoA
- Highly potent

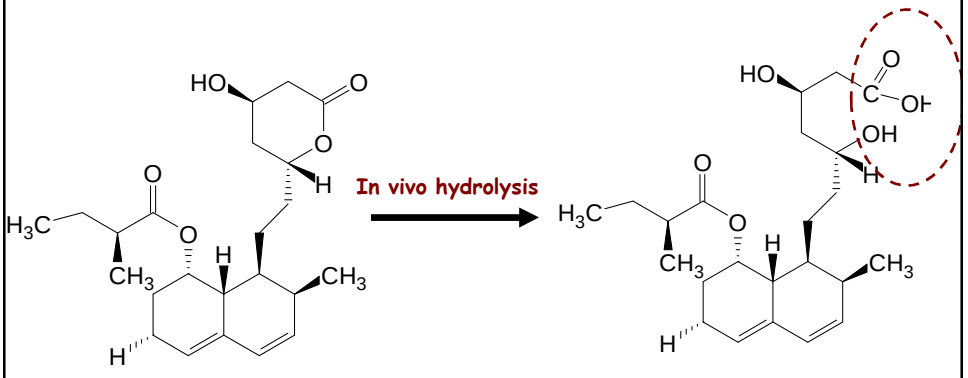
Compactin	$K_i = 1.4 \times 10^{-9}$ M
Lovastatin	$K_i = 6.4 \times 10^{-10}$ M
HMG-CoA reductase	$K_m = 10^{-5}$ M

How many folds higher is the affinity of HMG-CoA reductase for lovastatin and compactin than for HMG-CoA?

Kd for inhibitor = ([E][I])/[EI]

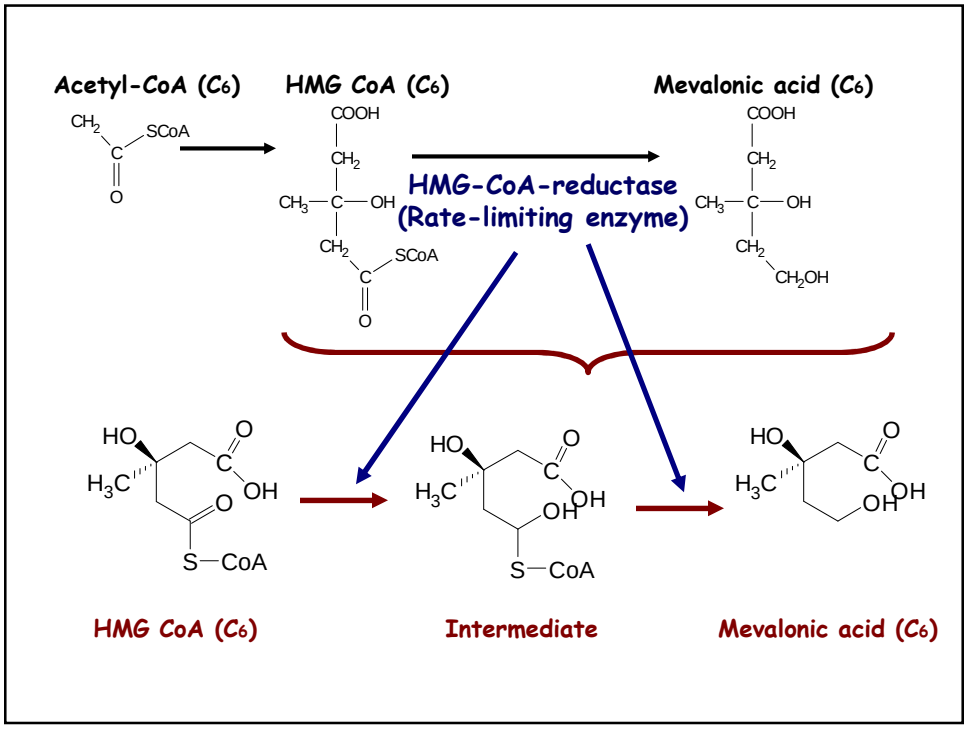
Kd for substrate = ([E][S])/[ES]

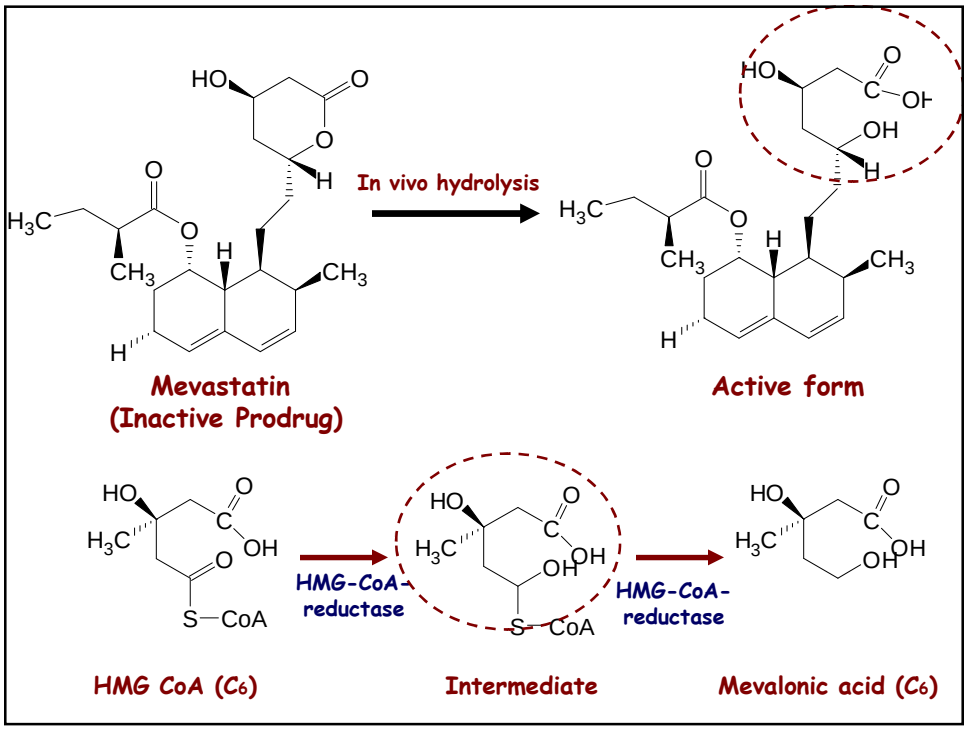
- In vivo activation

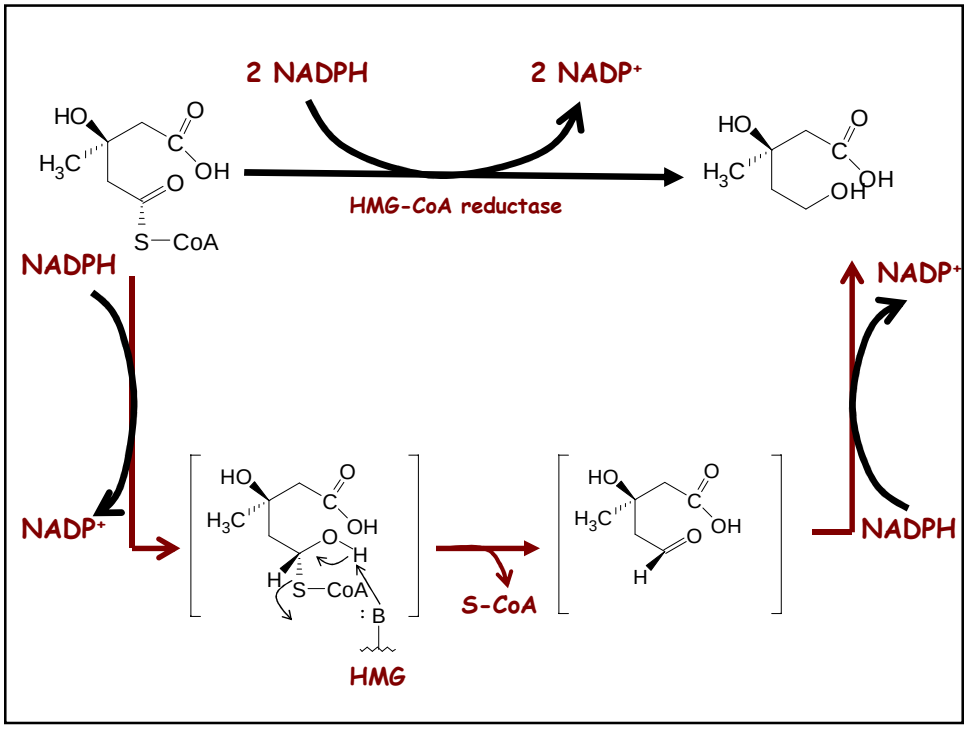


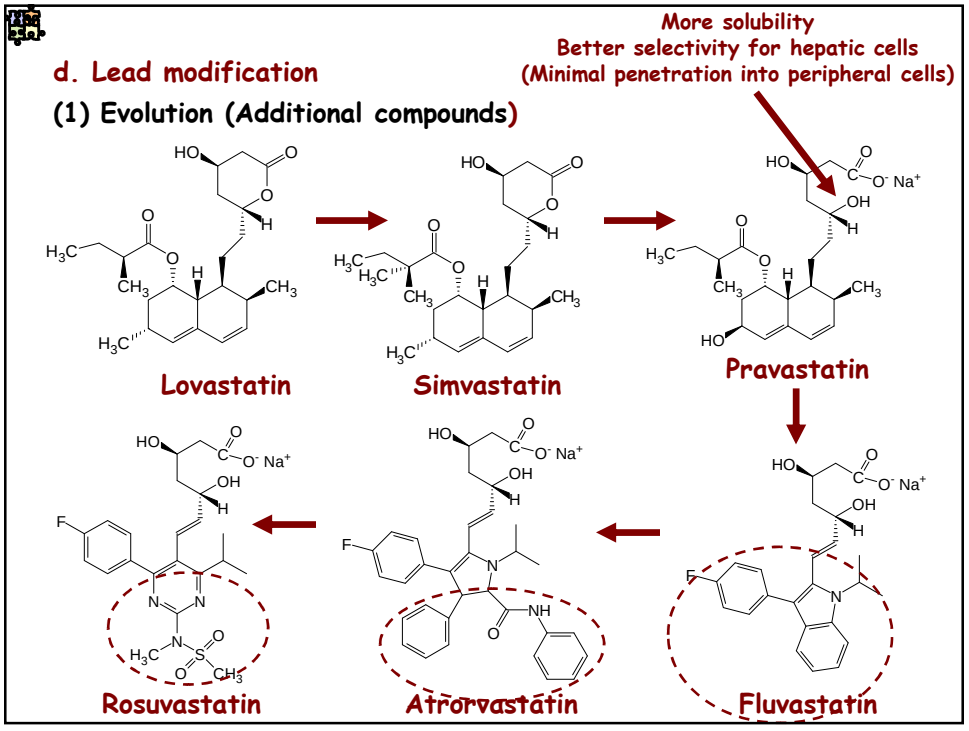
Mevastatin
(Inactive Prodrug)

Active form


Acetyl-CoA (C6)
HMG CoA (C6)
Mevalonic acid (C6)
HMG-CoA-reductase
(Rate-limiting enzyme)
HMG CoA (C6)
Intermediate
Mevalonic acid (C6)

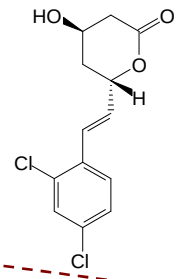

In vivo hydrolysis
Mevastatin
(Inactive Prodrug)
Active form
HMG-CoA-
reductase
HMG-CoA-
reductase
HMG CoA (C6)
Intermediate
Mevalonic acid (C6)


2 NADPH
2 NADP+
HMG-CoA reductase
NADPH
NADP+
NADP+
NADPH
S-CoA
HMG


More solubility
Better selectivity for hepatic cells
(Minimal penetration into peripheral cells)
d. Lead modification
(1) Evolution (Additional compounds)
Lovastatin
Simvastatin
Pravastatin
Fluvastatin
Atrorvastatin
Rosuvastatin

Compound A

- 2,4-dichlorophenyl analogue
- But less potent than mevastatin

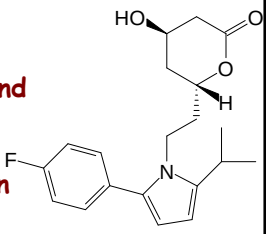


Compound B

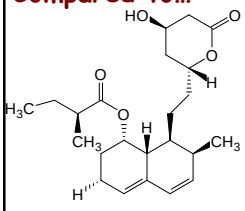
- Pyrrole with fluorophenyl and isopropyl substitutions
- A key intermediate in the development of atorvastatin
- The fluorophenyl and isopropyl substitutions are also present in Fluvastatin and rosuvastatin

d. Lead modification

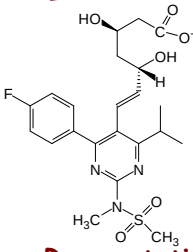
(2) Simplification



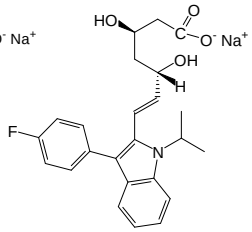
Compared to…



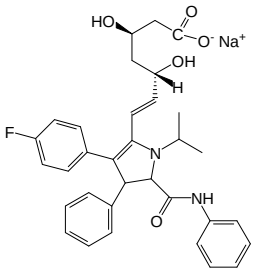
Mevastatin



Rosuvastatin



Fluvastatin



Atrorvastatin

d. Lead modification

(3) Other experiments that have been done

- Efforts have been made to determine
  - The importance of the lactone moiety and its stereochemistry
  - The ability of the lactone moiety to be opened to the dihydroxy acid
  - The optimal length and structure of the moiety bridging the lactone and the lipophilic groups
  - The size and shape of the lipophilic group

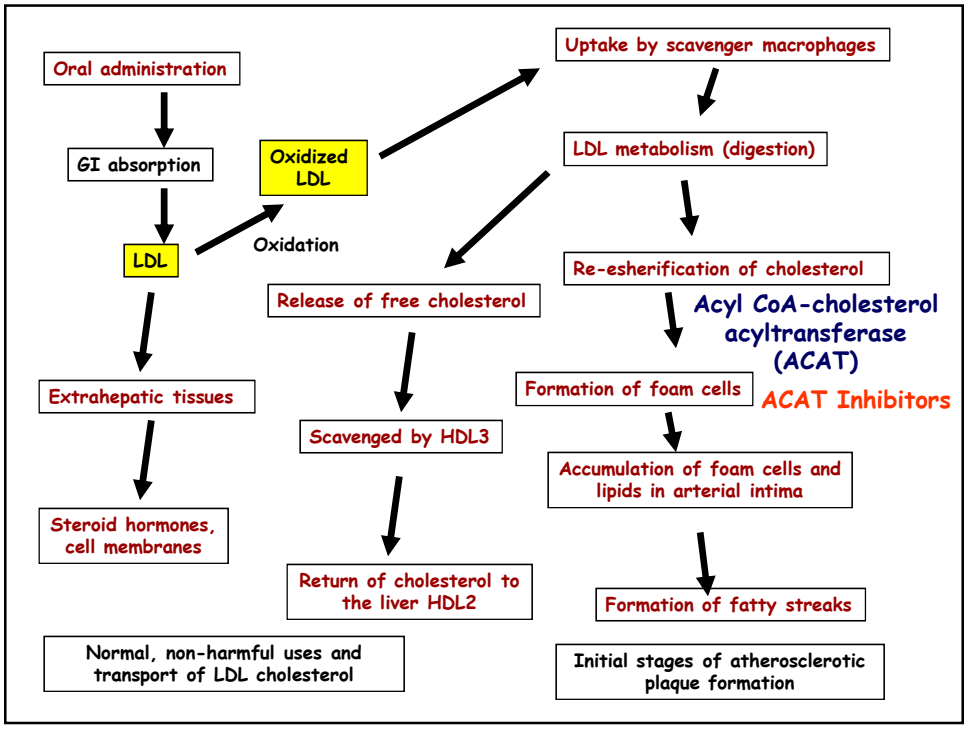
e. Structure/activity relationships

- The activity of HMGRIs is sensitive to
- Lactone
  - The stereochemistry of the lactone ring
  - The ability of the lactone ring to be hydrolyzed
  - The length of the bridge between the lactone ring and the bicyclic ring
- Carboxylic acid
  - pKa 2.5-3.5
  - Ionized at physiological pH
- Nitrogens in the indole and pyrrole rings
  - Not ionized

B. Cholesterol absorption inhibitors-Ezetimibe

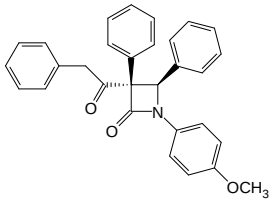
a. Mechanism of action

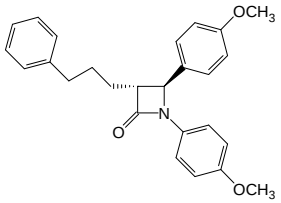
- The initial idea was to develop ACAT inhibitors
  - Decreased foam cell formation
- Lowers plasma cholesterol by inhibiting the absorption of cholesterol at the intestine



b. Development of ezetimibe

- Schering-Plough (now Merck) wanted to develop ACAT inhibitors
  - Cholesterol-fed hamster
    - Model with high liver cholesterol level
    - Sensitive to ACAT inhibitors

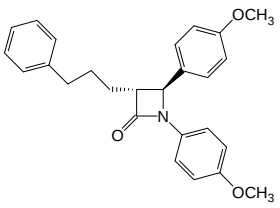


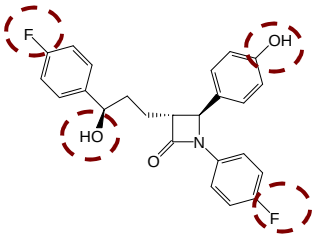


SCH compound #1
ACAT IC50=7.5 μM
Hamster 100mg/kg
Serum Cholesterol: -10%
Liver cholesterol ester:-26%

SCH compound #2
ACAT IC50=26 μM
Hamster 10mg/kg
Serum Cholesterol: -43%
Liver cholesterol ester:-93%

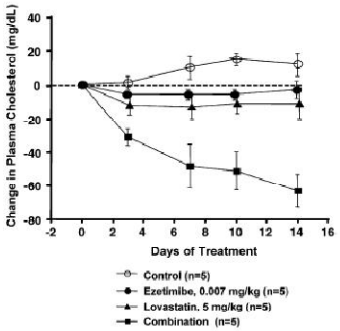
J Med Chem (2004) 47:1-9





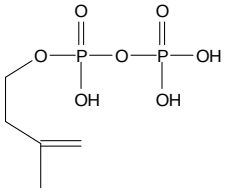
SCH compound #2
Hamster ED50 = 2.2 mg/kg

Ezetimibe
Hamster: ED50 = 0.04 mg/kg



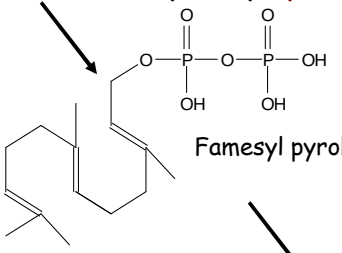
Clader J Med Chem (2004) 47:1-9 Figure 9. Effect of ezetimibe and lovastatin in chow-fed dogs.

C. Squalene synthase inhibitors

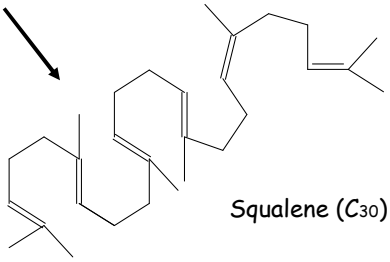


Isopentenyl pyrohosphate (C_5)

Two biosynthetic steps. The first step is catalyzed by squalene synthase



Famesyl pyrohosphate (C_{15})



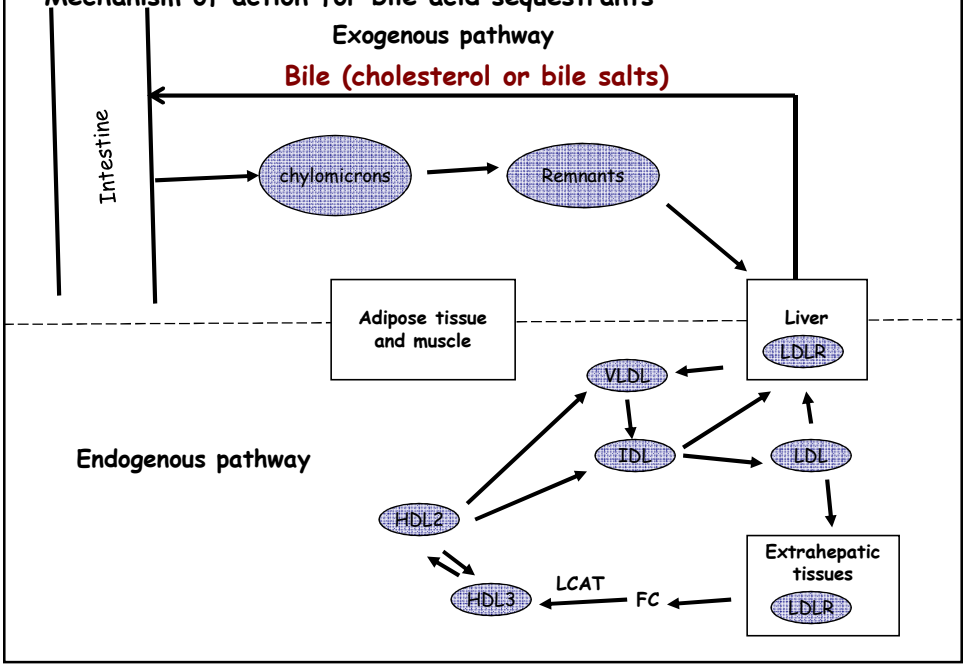
Squalene (C_{30})

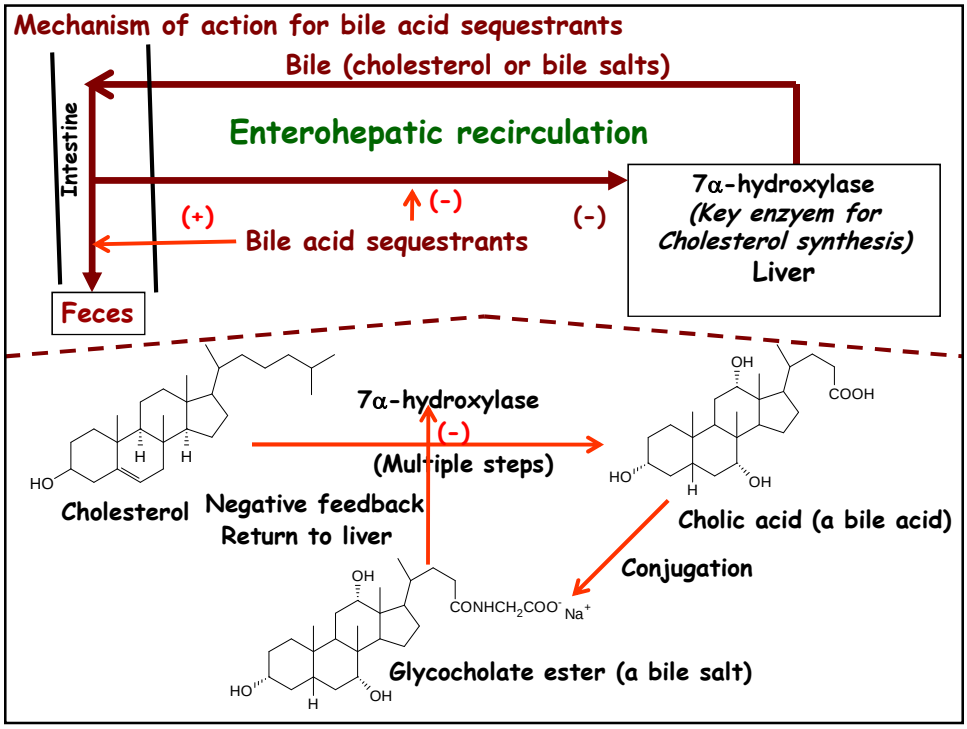
Squalene synthase is a potential drug target.

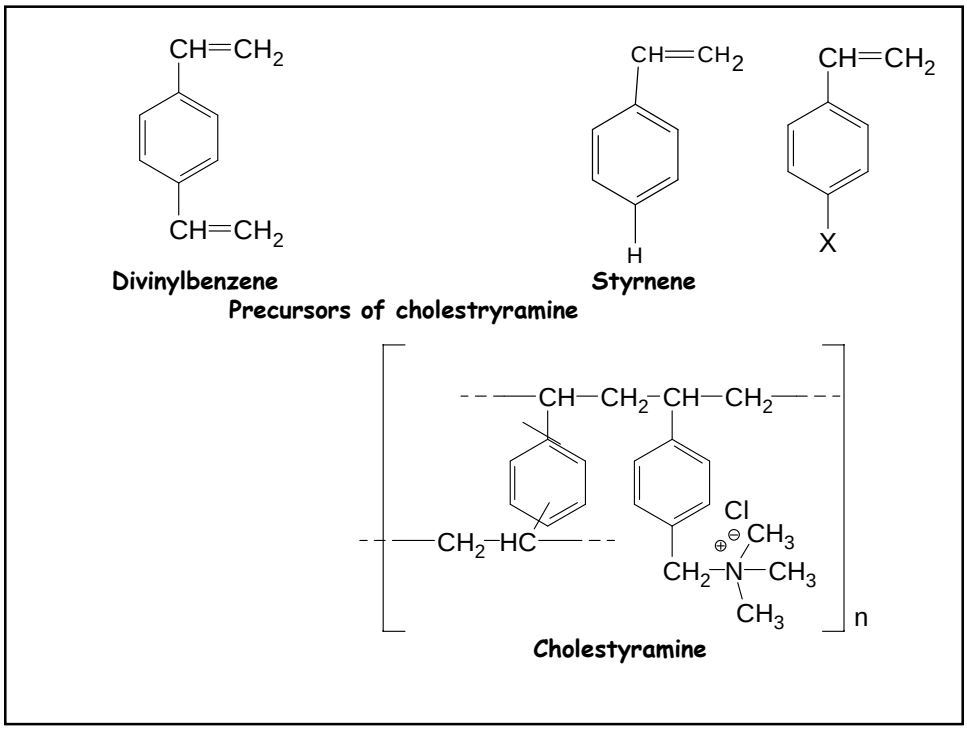
squalestatin isolated from the fermentation products produced by the fungus *Phoma*

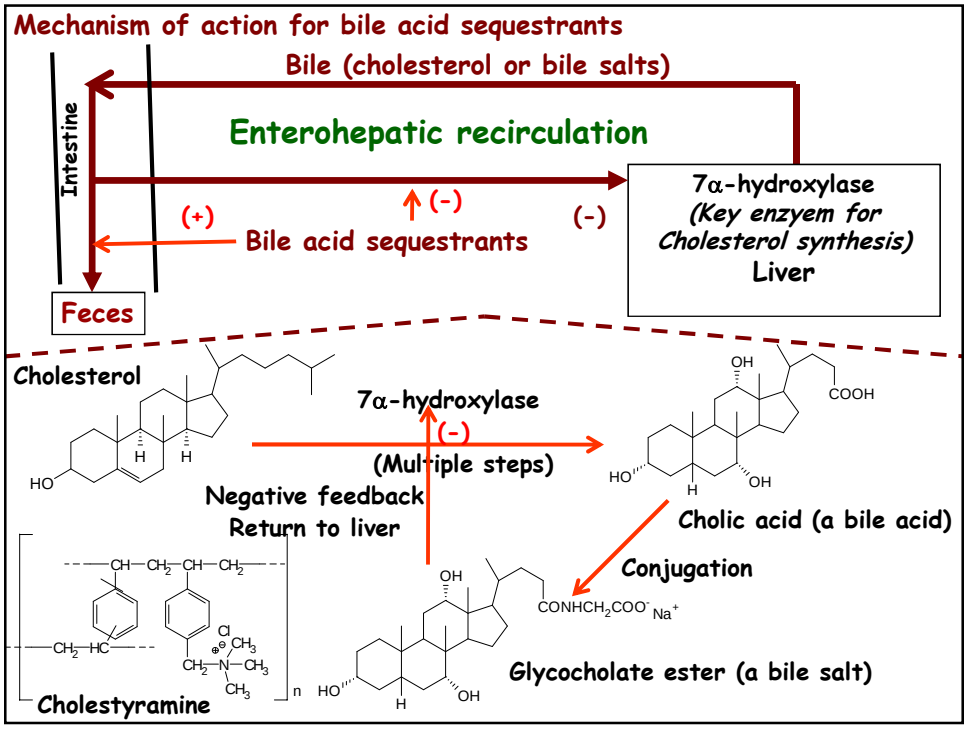
D. Bile acid sequestrants

Mechanism of action for bile acid sequestrants



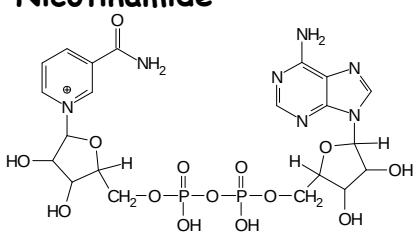

Mechanism of action for bile acid sequestrants
Bile (cholesterol or bile salts)
Intestine
Enterohepatic recirculation
7α-hydroxylase
(Key enzyem for Cholesterol synthesis)
Liver
(+)
(-)
(-)
Bile acid sequestrants
Feces
7α-hydroxylase
(-)
(Multiple steps)
Cholesterol
Negative feedback
Return to liver
Cholic acid (a bile acid)
Conjugation
Glycocholate ester (a bile salt)


Divinylbenzene
Styrene
Precursors of cholestryramine
Cholestyramine

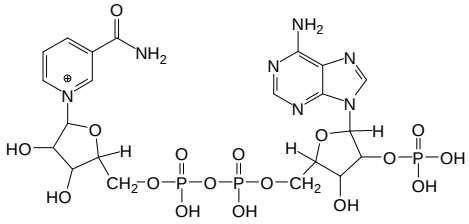


E. Nicotinic acid

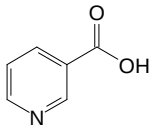
- ❑ Nicotine
- ❑ Nicotinic acid
- ❑ Nicotinamide

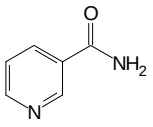


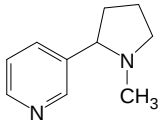
Nicotinamide Adenine Dinucleotide (NAD+)



Nicotinamide Adenine Dinucleotide Phosphate (NADP+)



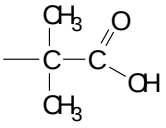




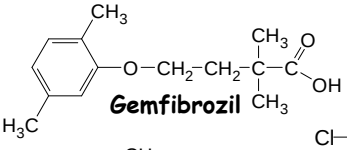
F. Fibrates

- MOA-Activation of peroxisome proliferator-activated receptors (PPARs)
- ↓↓Plasma triglyceride levels
- ↓Plasma cholesterol levels
- General chemical structure:

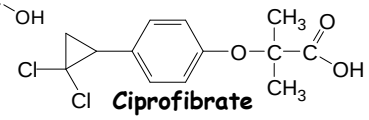
[Aromatic ring]-O-[spacer group]



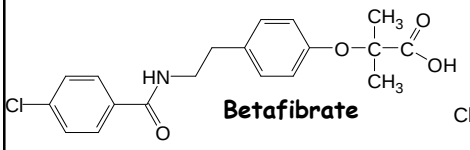
- For examples



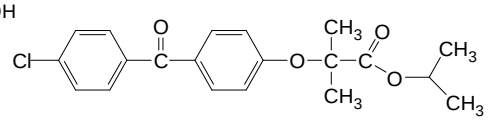
Gemfibrozil



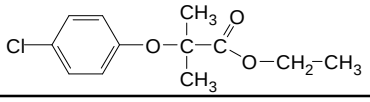
Ciprofibrate



Betafibrate

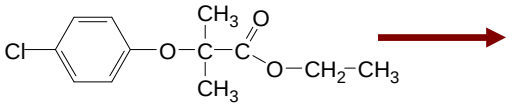


Fenofibrate

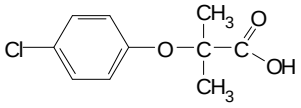


Clofibrate

- Bioactivation



Clofibrate
(ethyl-ρ-chlorophenoxyisobutyrate)



Clofibrate acid
(ρ-chlorophenoxyisobutyrate)

- Structure and pharmaceutical properties

Drug	Calculated Log P	Oral Bioavailability	Active Metabolite	Time to Peak Conc. (hrs)	Elimination half-life (hrs)
Fenofibrate	5.24	60-90	Fenofibric acid	4-8	20-22
Gemfibrozil	3.9	>90	None	1-2	1.5