Biosinteza holesterola
Hipolipemiki

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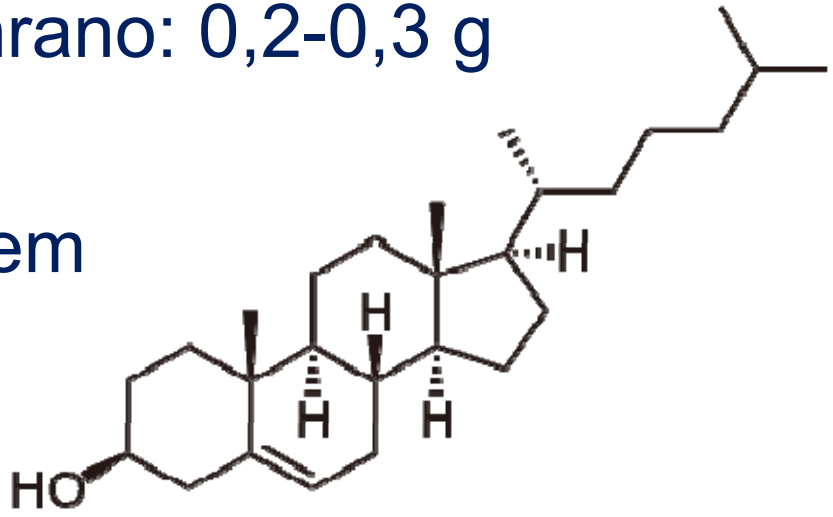
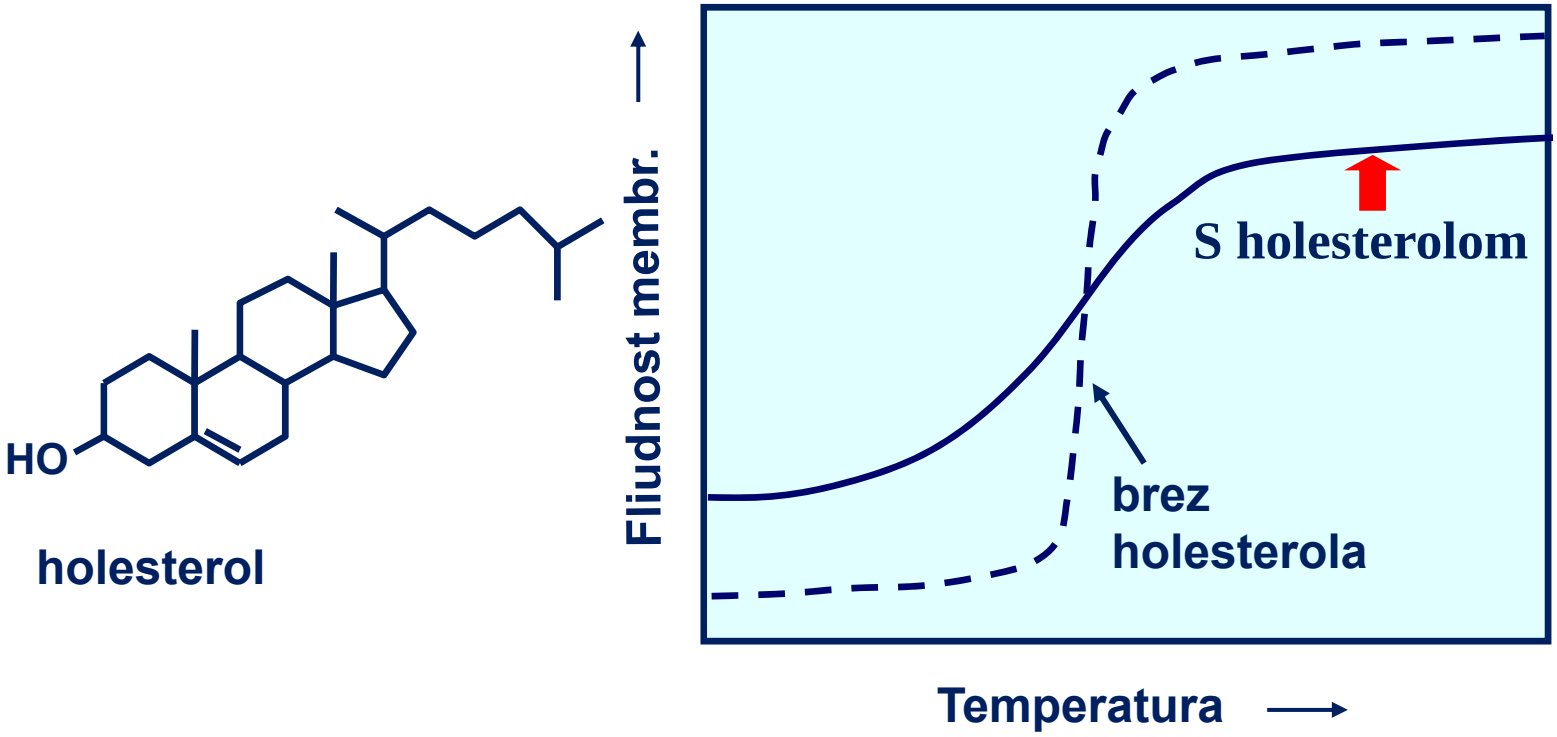
17. januar 2013

Holesterol

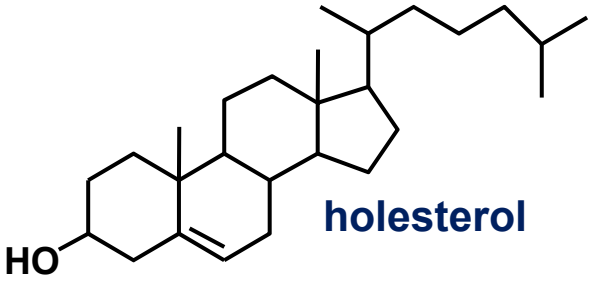
- Biosinteza v jetrih
- 1g/dan (sinteza)
- Dnevni vnos s hrano: 0,2-0,3 g
- 37 stopenj!
- Izločanje z žolčem



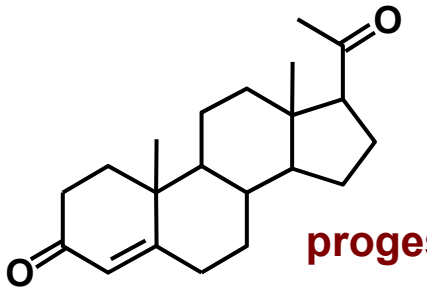
Vpliv holesterola na fosfolipidno membrano: dodatek “razvleče” temperaturo faznega prehoda



Holesterol kor prekurzor za steroidne hormone in žolčne kisline

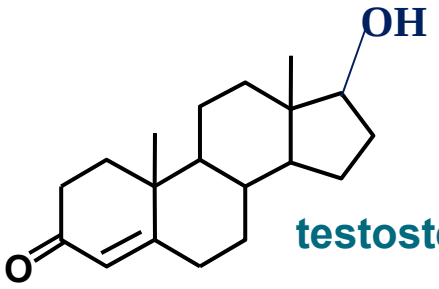


holesterol



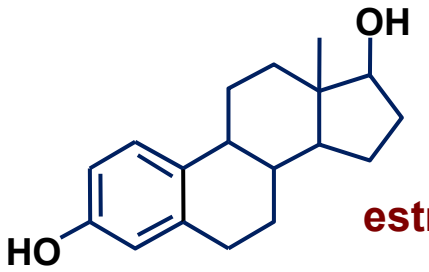
ž. hormon

progesteron



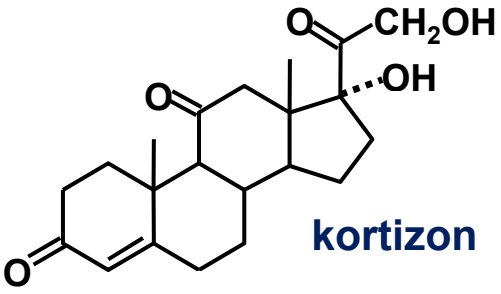
m. hormon

testosteron

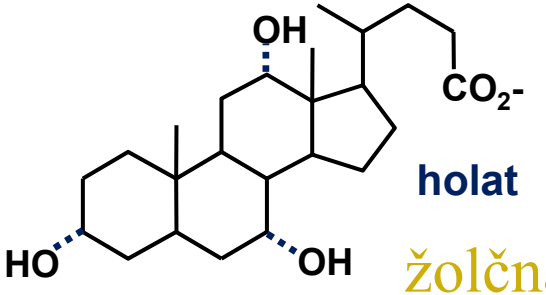


ž. hormon

estradiol



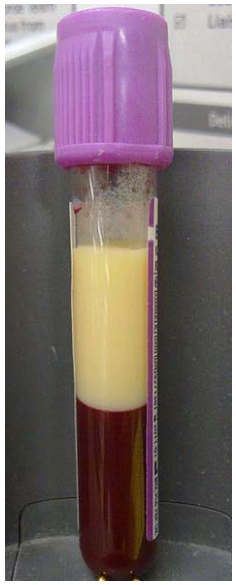
kortizon



holat

žolčna kislina

Hiperlipidemija



http://vizita.si/clanek/holesterol/povisan-holesterol-povzroca-bolezni-srca-in-ozilja.html

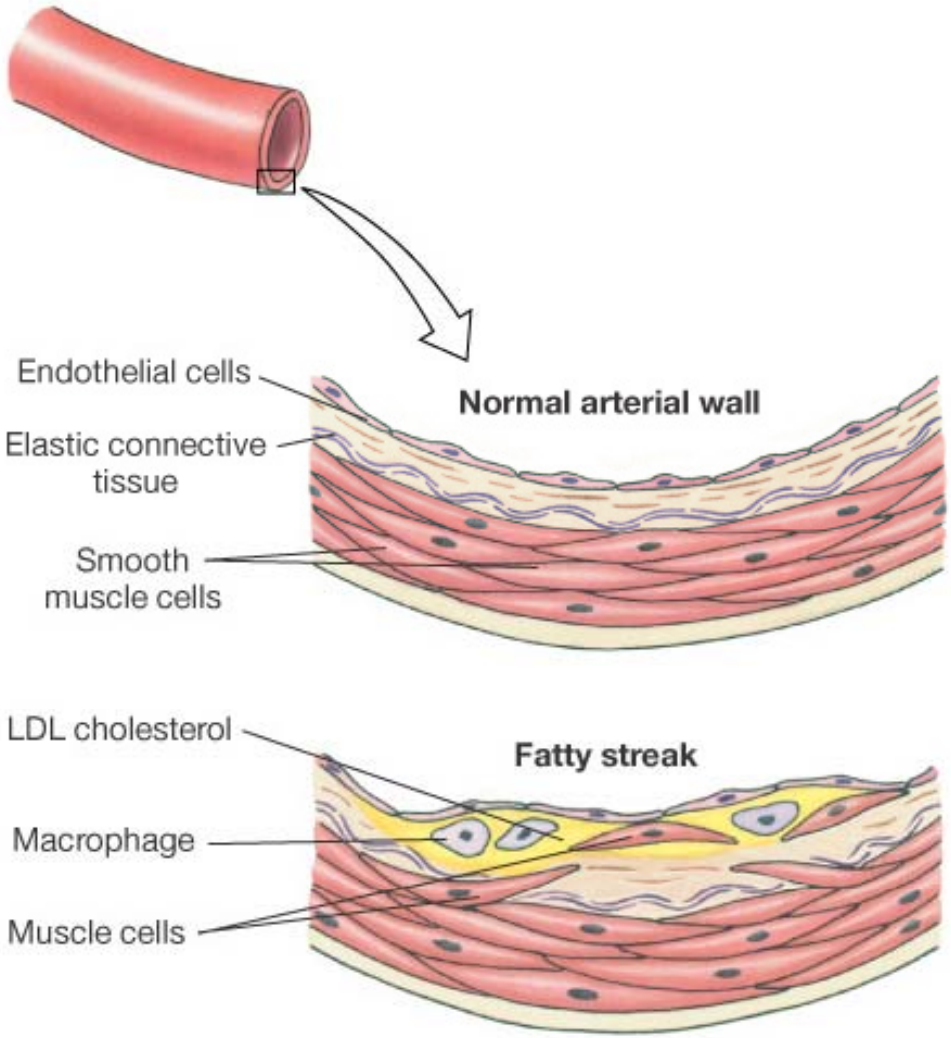
Hiperlipidemija

- nenormalno zvišana koncentracija ene lipidne frakcije ali več lipidnih frakcij v krvni plazmi
- hiperholesterolemija, hipertrigliceridemija, kombinirana

Nevarnost hiperlipidemij

- **ateroskleróza -e ž**; pogosta oblika arterioskleroze, pri kateri se v intimi aorte, arterij, včasih tudi ven ter v srčnih zaklopkah najprej naredijo ateromi, ki pozneje sklerozirajo (Slovenski medicinski slovar)

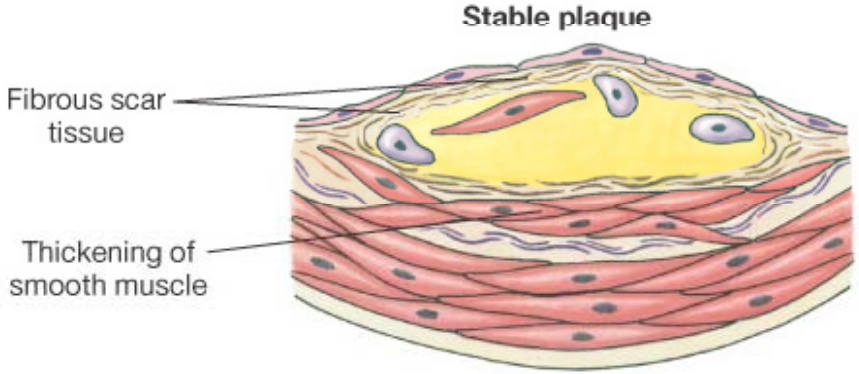
Nastanek ateroskleroze 1



(a) The normal arterial wall consists of smooth muscle and connective tissue with an endothelial cell lining.

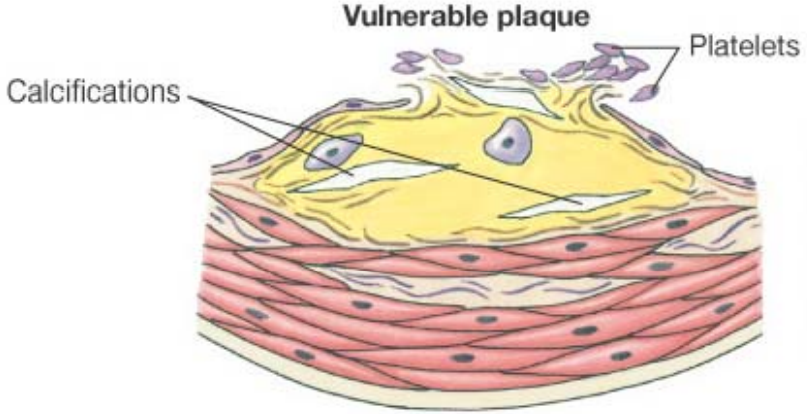
(b) In early stages, excess LDL-cholesterol accumulates between the endothelium and connective tissue. There, it is oxidized and phagocytosed. The macrophages produce paracrines that attract smooth muscle cells. At this stage, the lesion is called a fatty streak.

Nastanek ateroskleroze 2



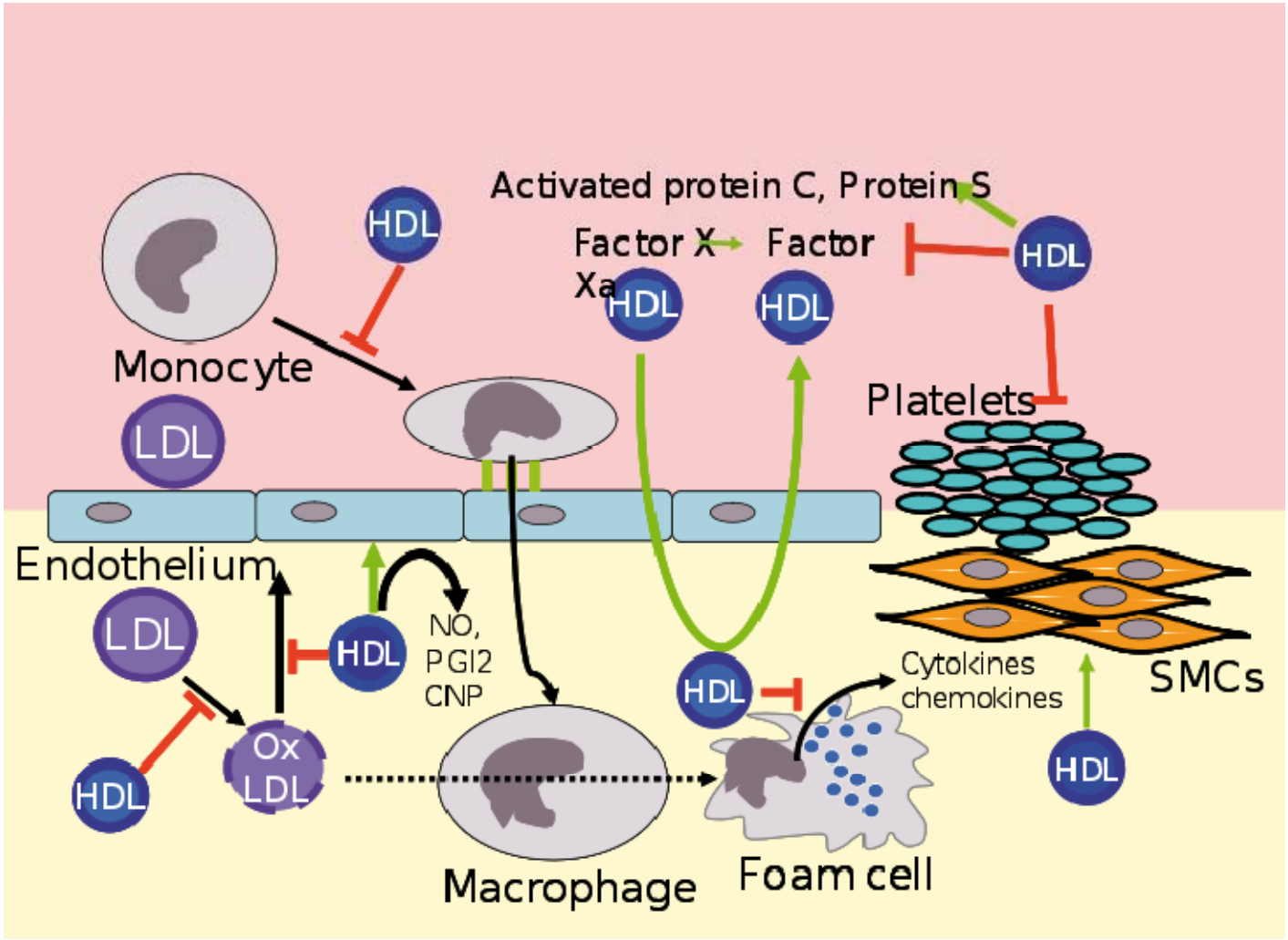
(c) As cholesterol accumulates, fibrous scar tissue forms around it. Migrating smooth muscle cells divide, thickening the arterial wall and narrowing the lumen of the artery. This stage is known as a fibrous plaque.

plak = leha
aterosklerotična leha = aterom

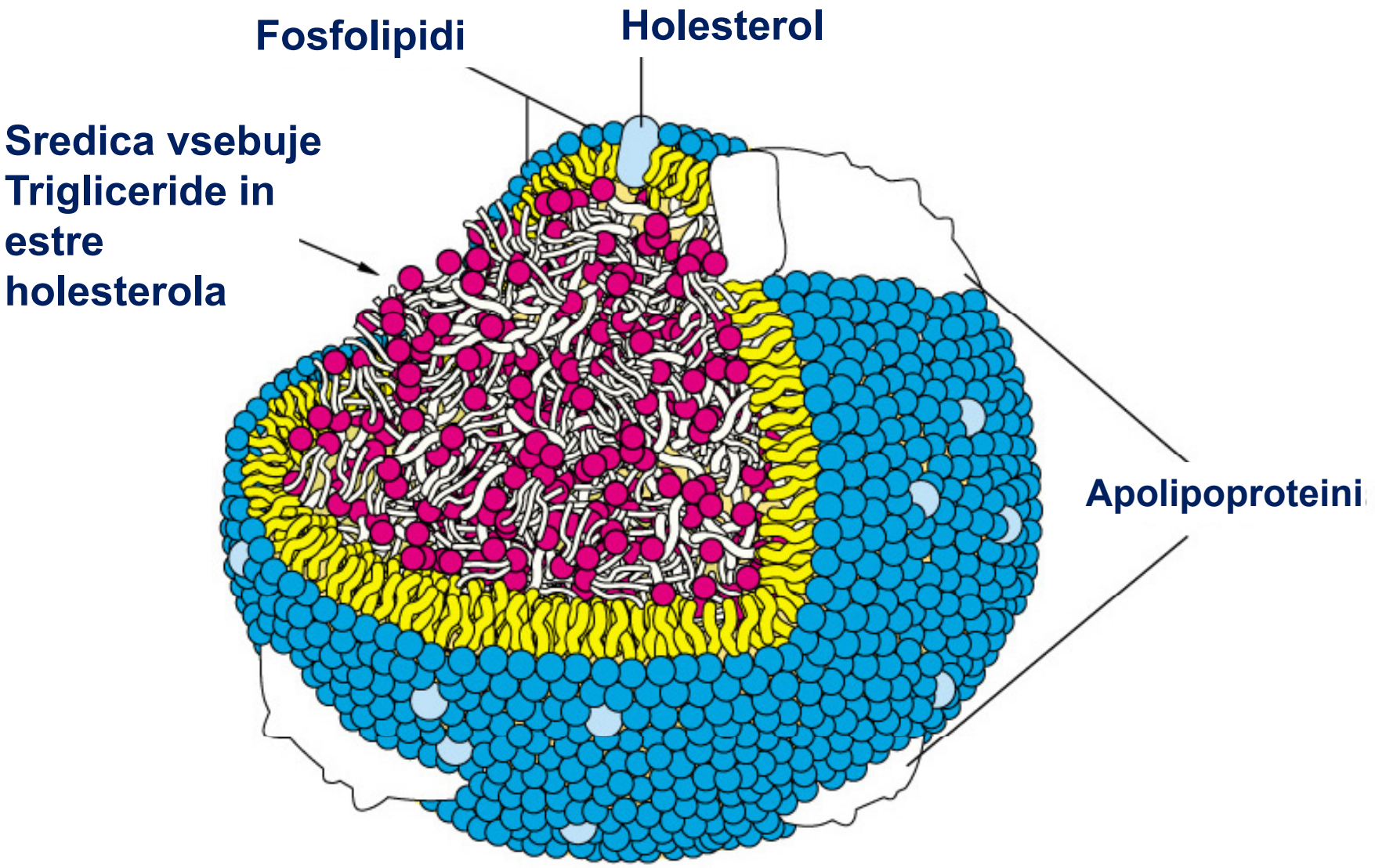


(d) In the advanced stages of atherosclerosis, calcified scar tissue will form. If the endothelium is damaged and collagen is exposed, platelets stick to the damaged area and a blood clot (thrombus) forms. If blood flow in the coronary blood vessel is stopped, a heart attack is the result.

Ateroskleroza na molekularnem nivoju



Lipoproteini - struktura



Lipoproteini

- LDL – transport endogenega holesterola (iz jeter, v jetra)
- HDL – transport endogenega holesterola (nazaj v jetra)
- VLDL – transport “endogenih”trigliceridov
- Hilomikroni – transport eksogenega holesterola

- Fredricksonova delitev hiperlipidemij:
- http://en.wikipedia.org/wiki/Hyperlipidemia

Lipoproteini

	VLDL	LDL	HDL
Gostota (g/mL)	0.95 - 1.006	1.006 - 1.063	1.063 - 1.210
Sestava (wt%)			
proteini	10	23	55
fosfolipidi	18	20	24
holesterol	7	8	2
estri holesterola	12	37	15
trigliceridi	50	10	4

Mejne vrednosti “holesterola”

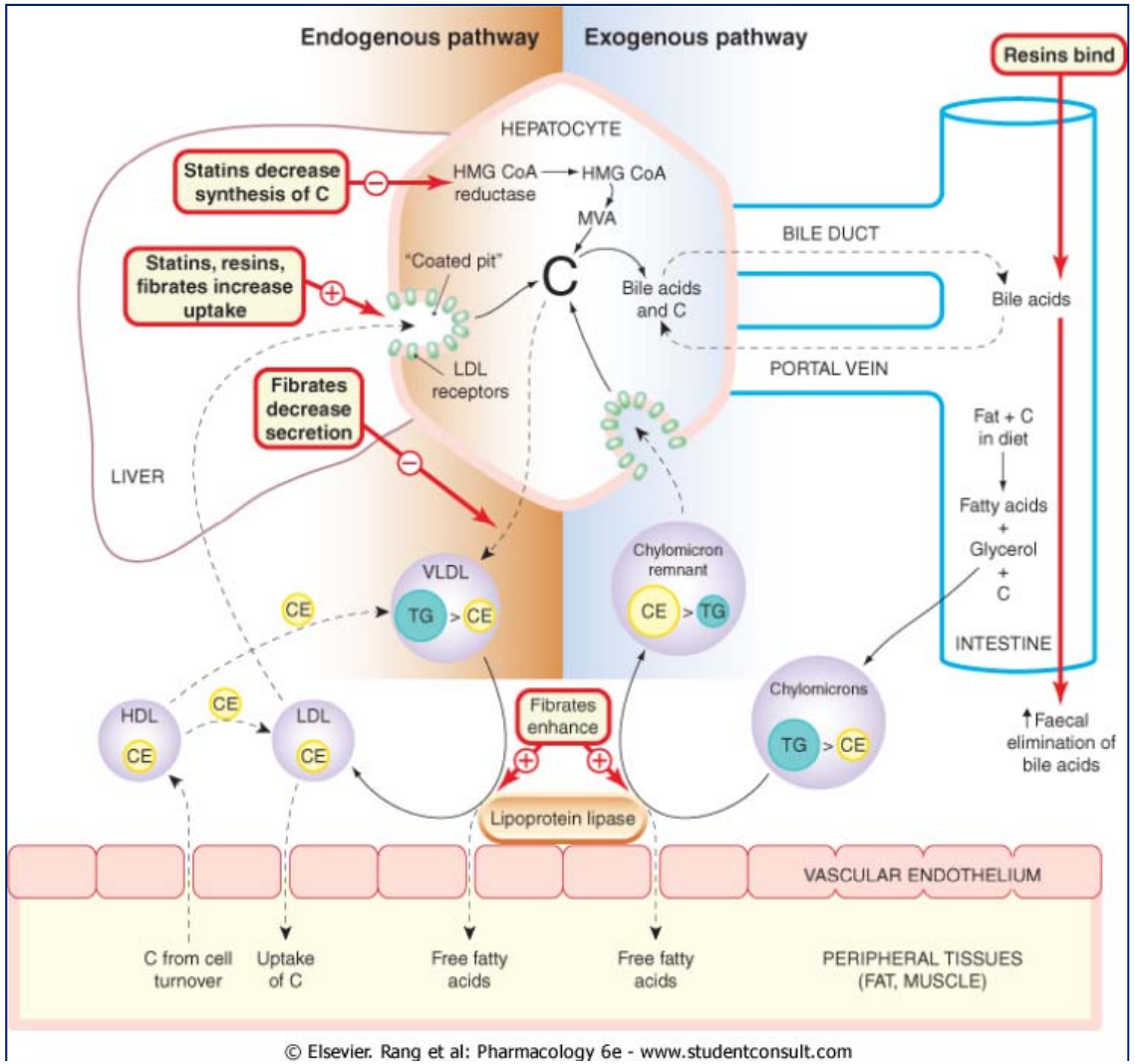
- nižje od 5.2 mmol/L NORMALNE VREDNOSTI
- 5.2 - 6.2 mmol/L MEJNE VREDNOSTI
- nad 6.2 mmol/L PREVISOKE VREDNOSTI

Holesterol v krvi	LDL holesterol	HDL holesterol	trigliceridi
Ugodno < 5,0	< 3,0	> 1,0	< 2,0
Mejne vrednosti 5,2 do 6,5	3,5 do 4,5	0,9 do 1,1	2,3 do 4,6
Previsoko > 6,5	> 4,5	< 0,9	> 4,6

Vplivi hormonov na raven holesterola

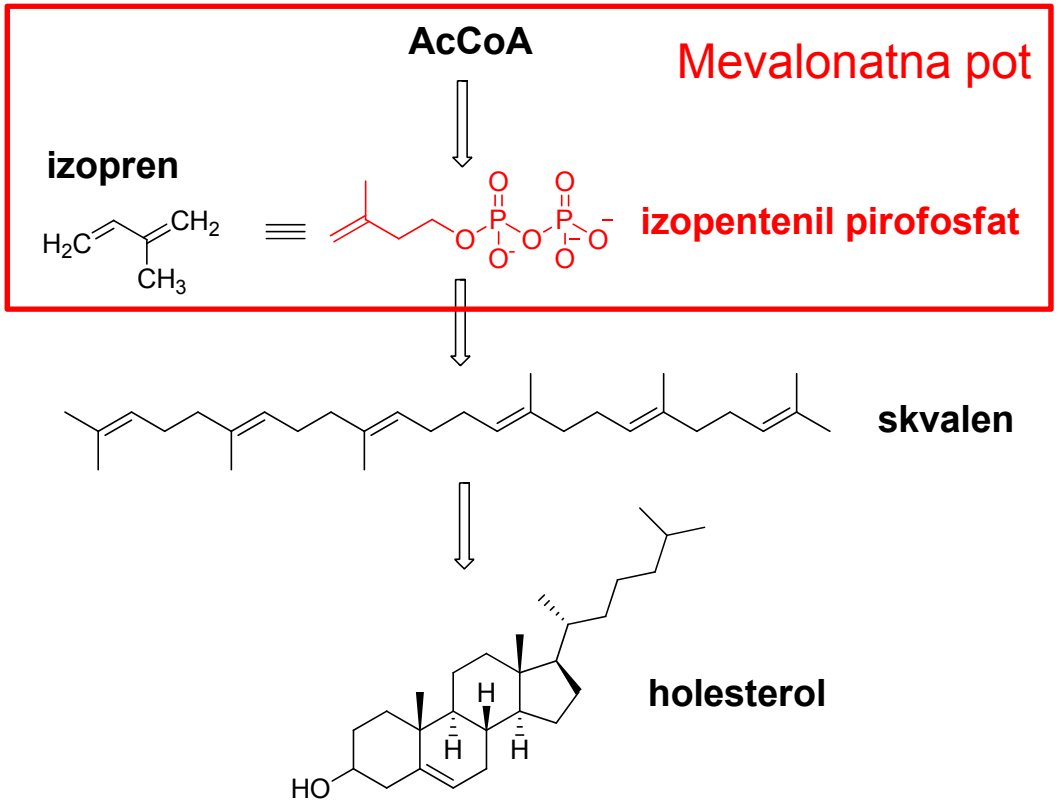
- Estrogeni: LDL↓, HDL↑
- Progestini: HDL ↓
- Androgeni: HDL ↓
- Glukokortikoidi: TG ↑, holesterol ↑
- Tiroidni hormoni: lipidi ↓

Prijemališča hipolipemikov



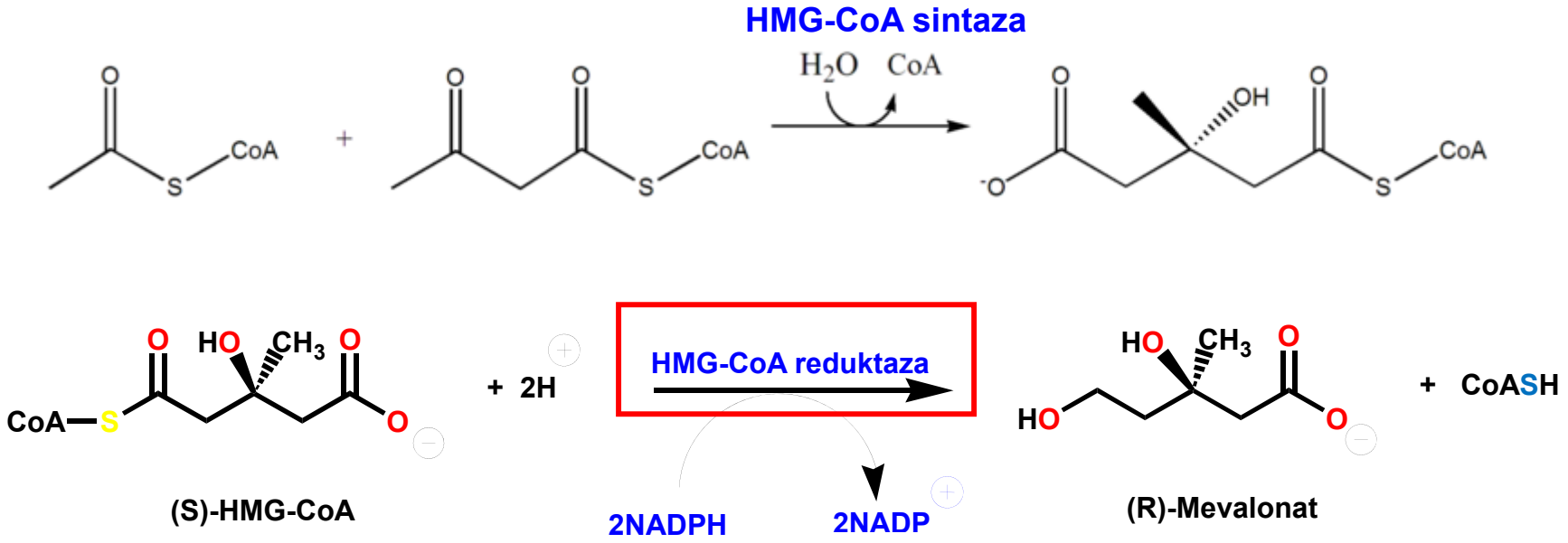
Biosinteza holesterola

- V jetrih
- Sestavljen iz izoprenskih enot



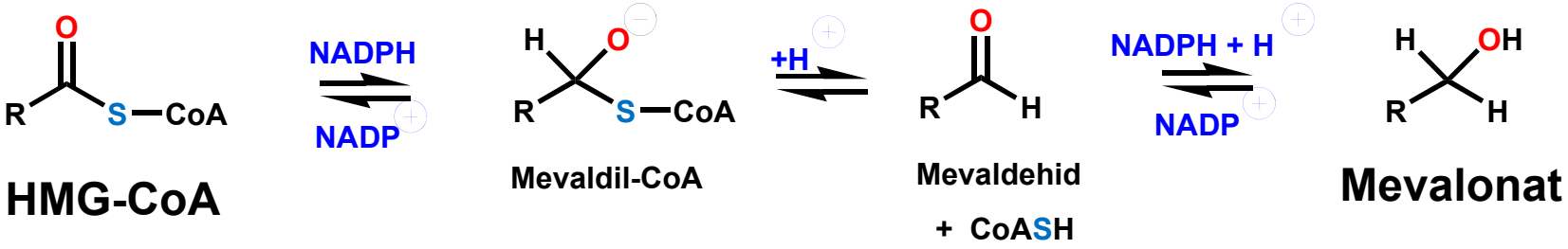
Mevalonatna pot

- Tarčni encim: HMG-CoA reduktaza
- Encim, ki določa hitrost biosinteze holesterola
- Inhibicija biosinteze, ne vnosa s hrano



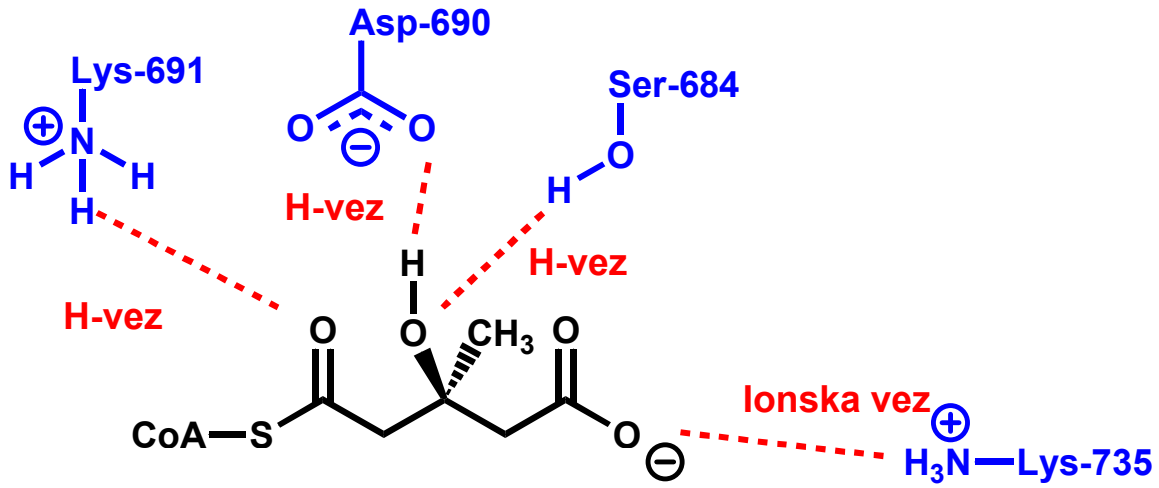
Katalitični mehanizem HMG-CoA

- 2x NADPH



Katalitični mehanizem HMG-CoA

- Vezava substrata



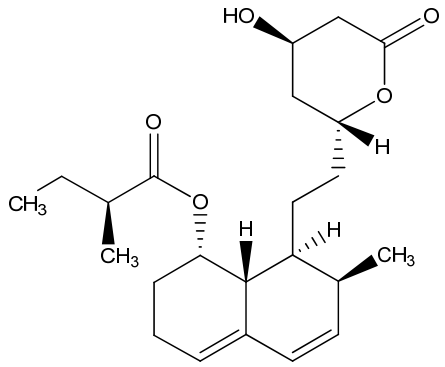
Odkritje statinov

Mevastatin (*Penicilium citrinum*)

• inhibitor hidroksimetilglutaril-koencim A reduktaze (HMG-CoA reduktaza)

• Akira Endo (1971); iskanje inhibitorjev HMG-CoA kot potencialnih antimikotikov

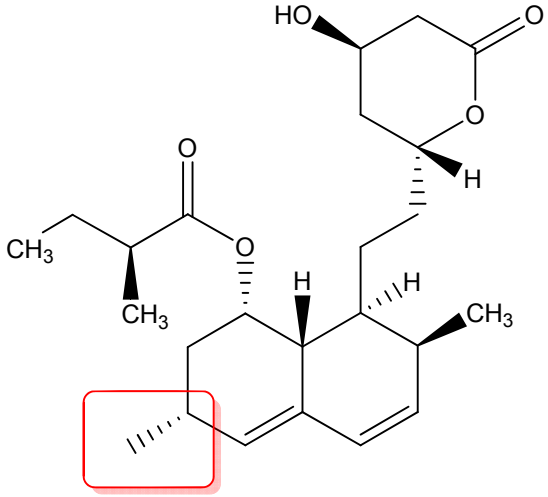
• Michael Brown, Joseph Goldstein; inhibicija endogene HMG-CoA → inhibicija biosinteze holesterola



Mevastatin IC_{50} = 24 nM, 1000x afiniteta substrata

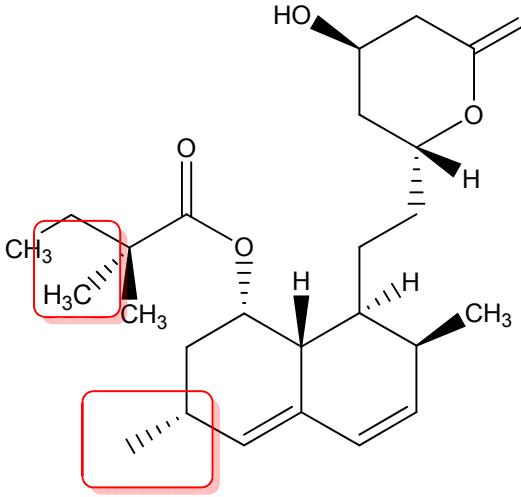
Prvi statini

- Lovastatin iz *Aspergillus terreus* (1987, Merck)
- Simvastatin – polsintezni analog
- Pravastatin – biotransformacija mevastatina



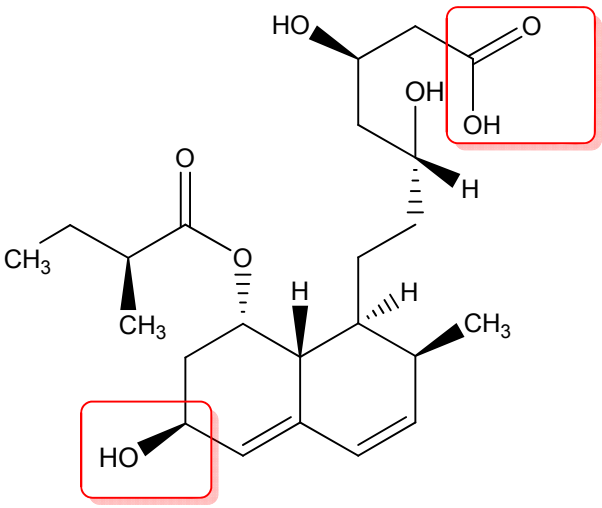
Lovastatin
IC_{50} = 24 nM

BU<5%



Simvastatin
IC_{50} = 24 nM

BU 5%

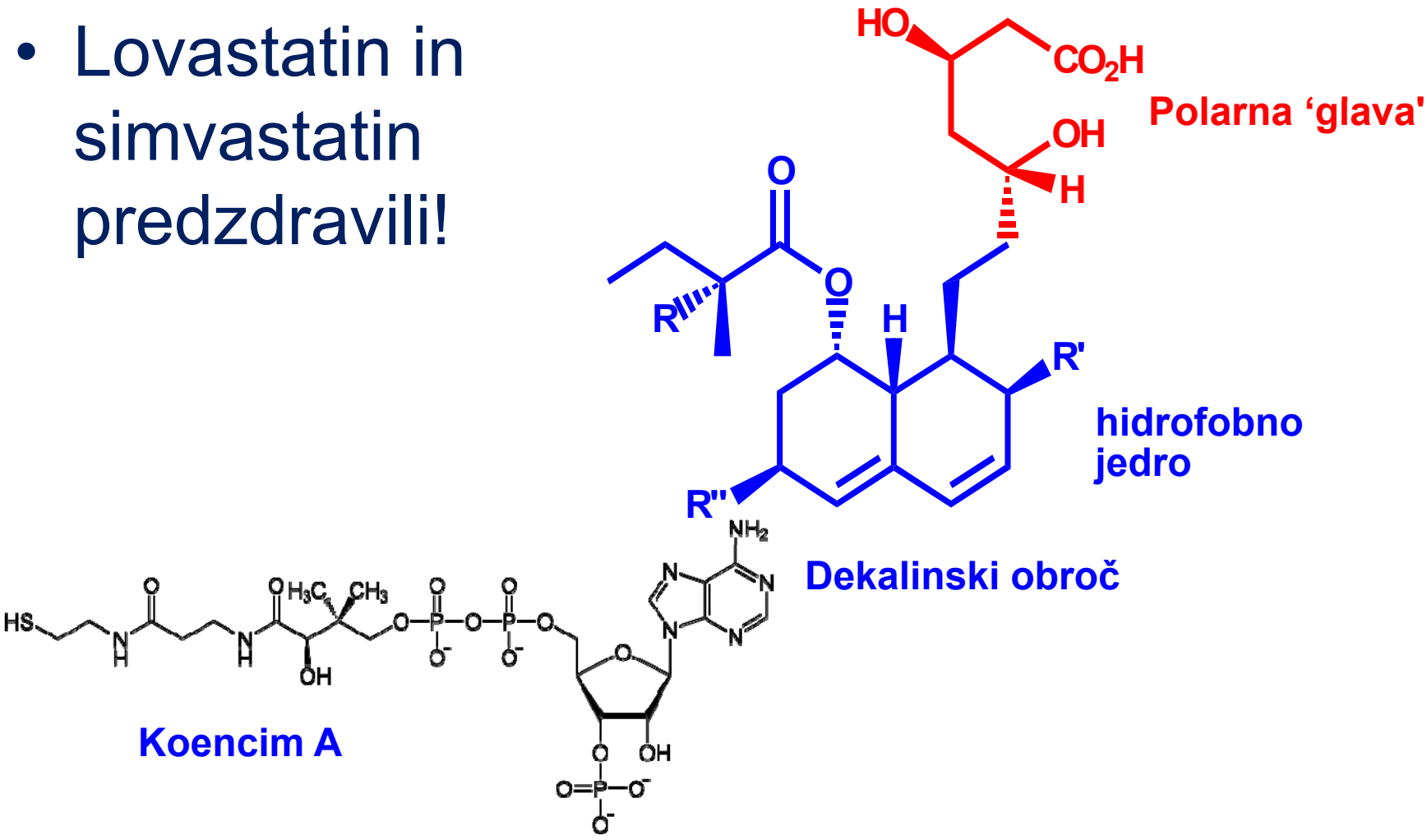


Pravastatin
IC_{50} = 19000 nM

BU 17%

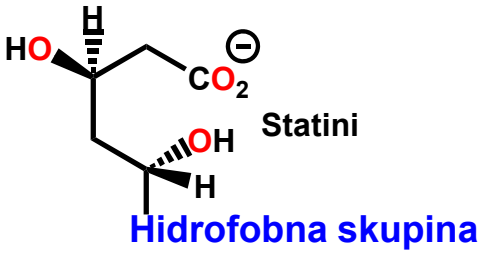
SAR prvih statinov

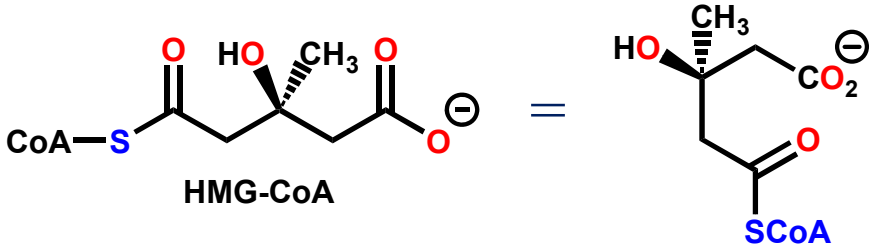
- Lovastatin in simvastatin predzdravili!



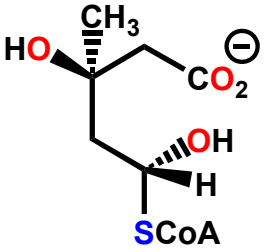
Mehanizem delovanja

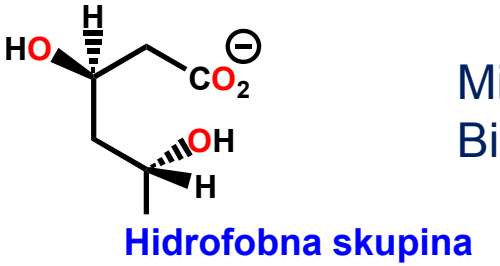
- Kompetitivna inhibicija HMGCoA





- Posnemajo substrat, ni reakcije (ni CoA)



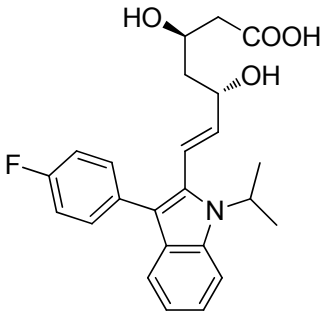


Mimetiki prehodnega stanja!
Bistveno višja afiniteta kot substrat

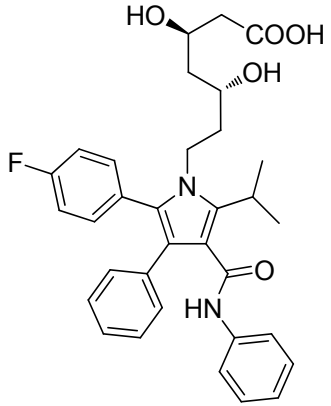
Slabosti prvih statinov

- Težavna sinteza
- Asimetrični centri
- Stranski učinki – mialgija, krči, povišani nivoji jetrnih encimov, rabdomioliza, ginekomastija, nevropatije

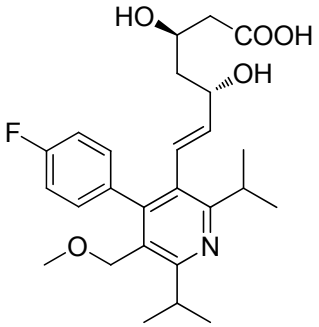
Sintezni statini



Fluvastatin
IC_{50} = 28 nM
BU 20-30%



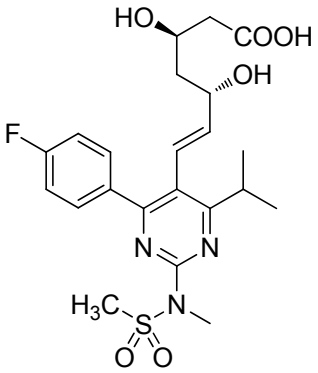
Atorvastatin
IC_{50} = 8 nM
BU 12-14%



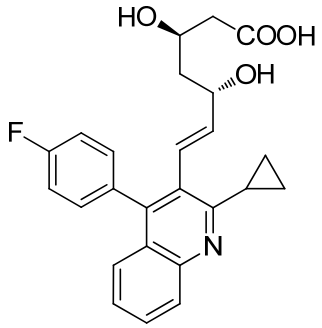
Cerivastatin
IC_{50} = 10 nM

- Hidrofobno jedro brez asimetričnih centrov
- fluvastatin (1994), atorvastatin (1997), cerivastatin (1998), rosuvastatin (2003)

Sintezni statini



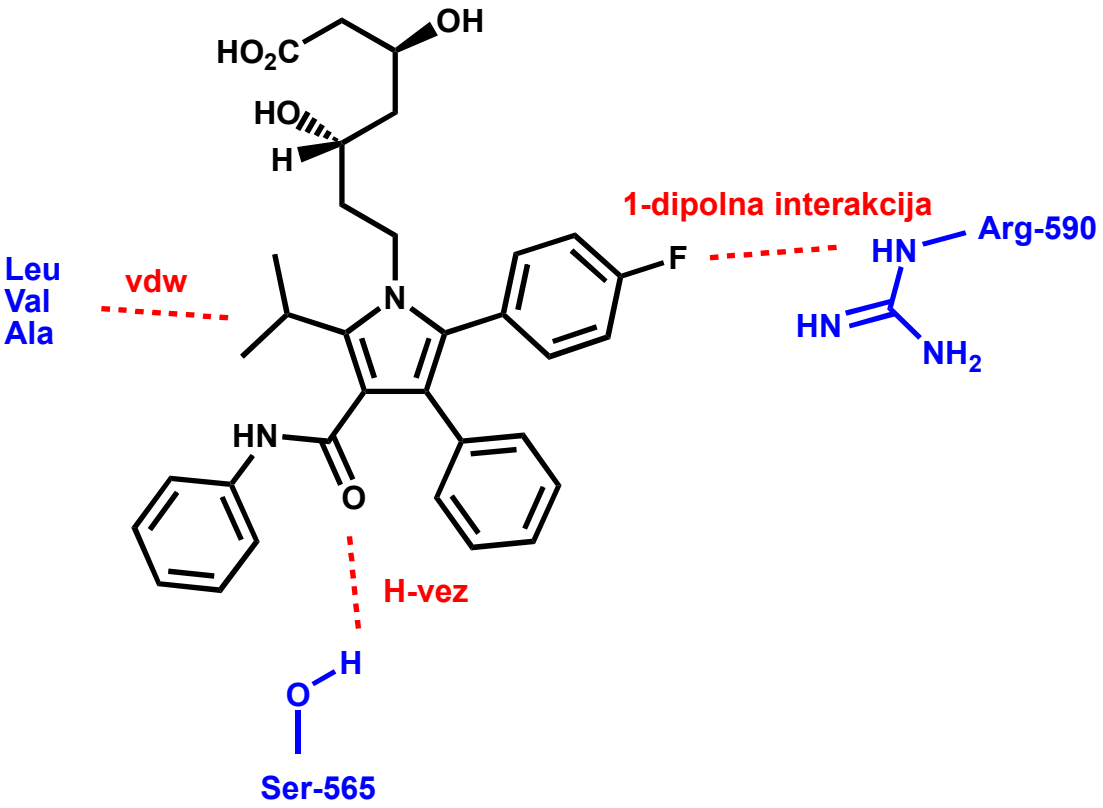
Rosuvastatin
IC_{50} = 5 nM
BU 20%



Pitavastatin
IC_{50} = 6,8 nM
BU 60%!!!

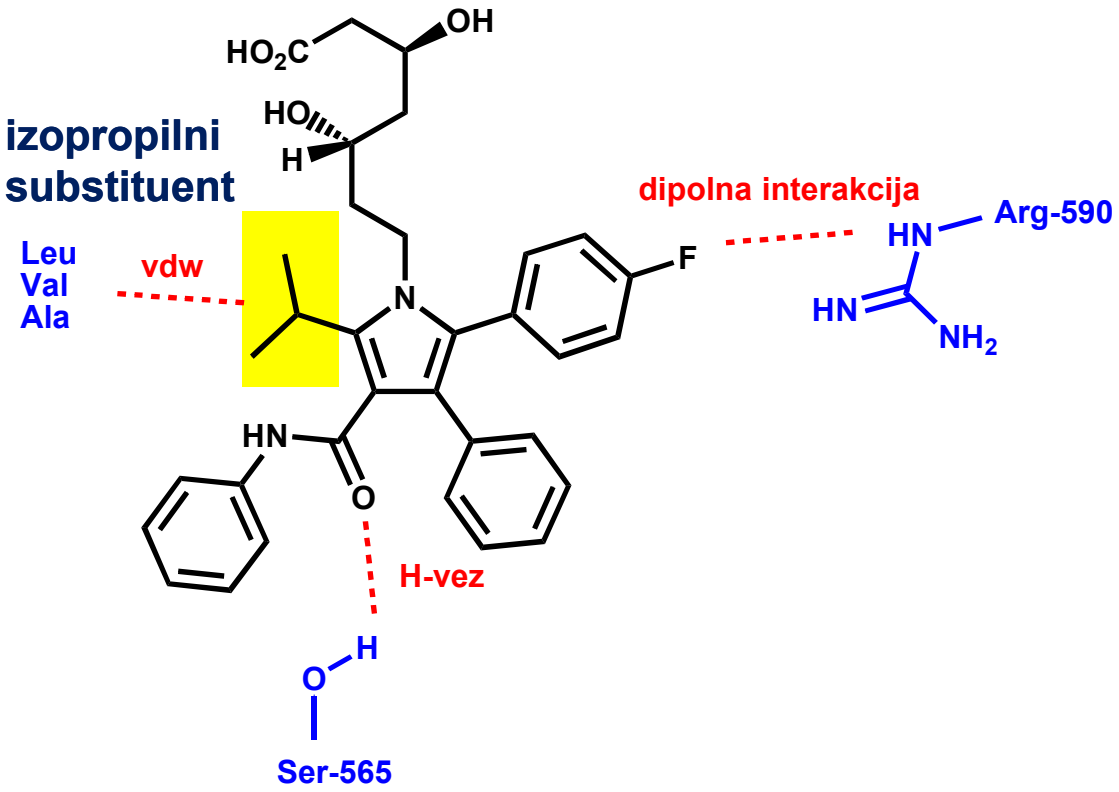
- Hidrofobno jedro brez asimetričnih centrov
- fluvastatin (1994), atorvastatin (1997), cerivastatin (1998), rosuvastatin (2003)
- “me too” učinkovine
- cerivastatin! – Baycol (Lipobay)

Statini - vezava



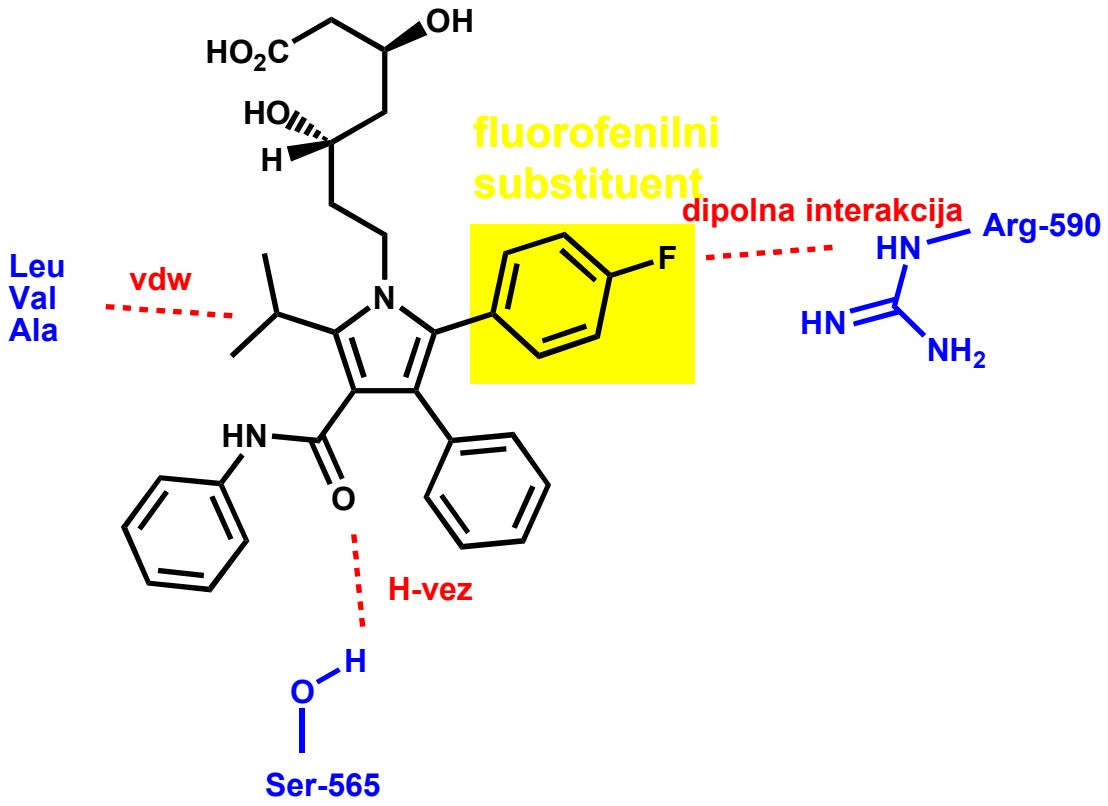
- **Polarna glava – mevalonat**
- **Hidrofobni del ni posnetek CoA, fleksibilnost encima**

Statini - vezava



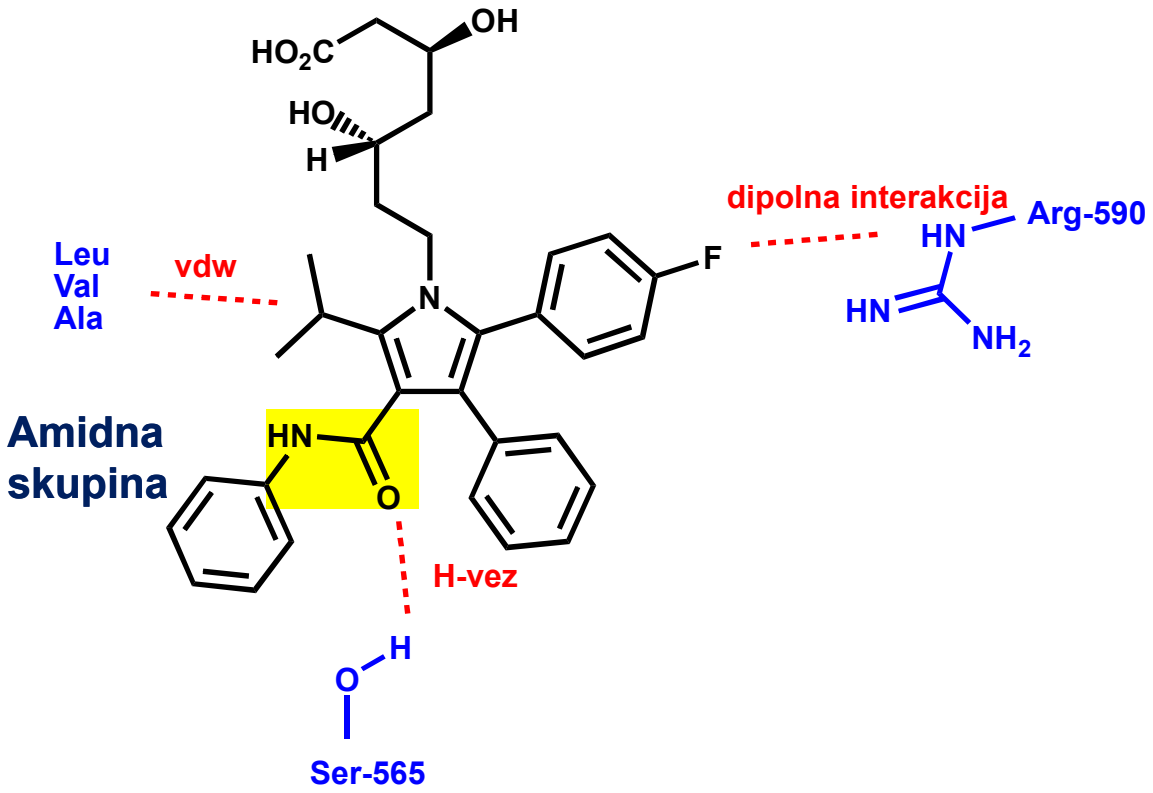
Izopropilni substituent – podobno kot dekalin pri tipu 1

Statini - vezava



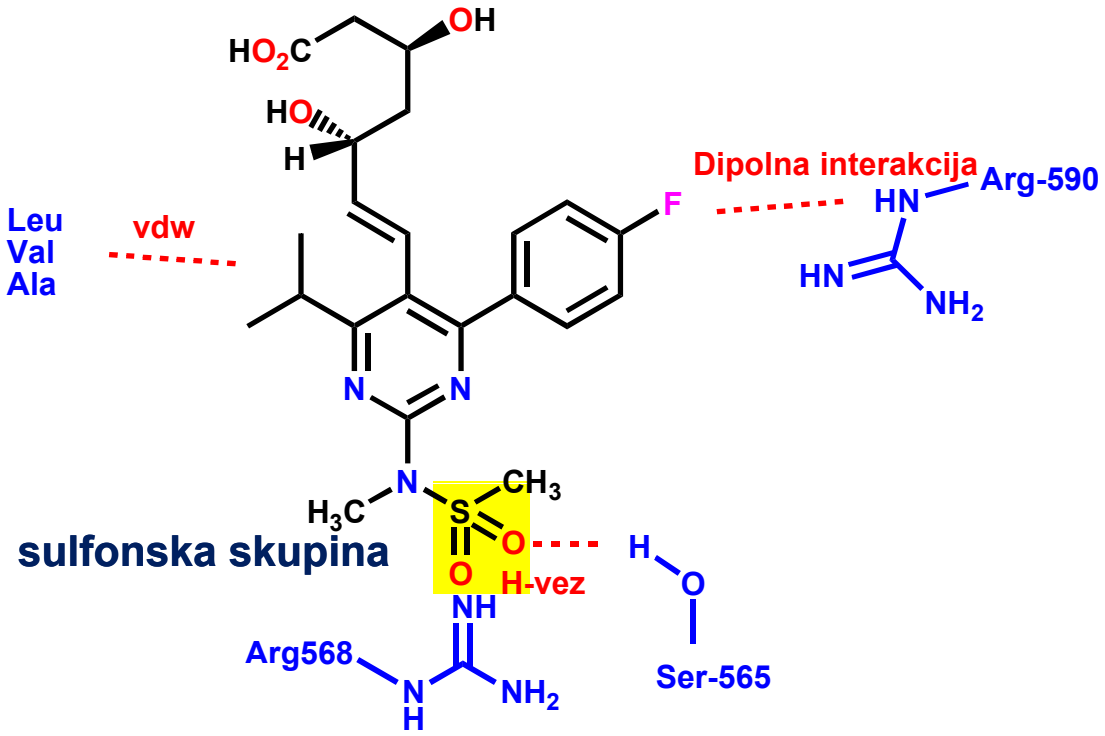
4-fluorofenilni substituent – dipolne interakcije, π-kation interakcije z gvanidinom

Statini - vezava



Amidna vez – dodatne interakcije,
π-kation interakcije z gvanidinom

Statini - vezava



Rosuvastatin – dodatna vodikova vez s sulfonamidom
-dodatne interakcije sulfonskega dela z argininom 568

SAR statinov

Fiz-kem lastnosti

- Karboksilne kisline, pKa 2,5-3,5
- Šibko bazična – rosuvastatin, pitavastatin, ni ionizacije bazične skupine pri fiziološkem pH

Statini FK lastnosti

TABLE 25.4 Pharmacokinetic Parameters of HMG-CoA Reductase Inhibitors

Drug	Calculated LogP[a]	Oral Bioavailability (%)	Active Metabolite(s)	Protein Binding (%)	Time to Peak Concentration (h)	Elimination Half-Life (h)	Major Route(s) of Elimination
Atorvastatin	4.13	12–14	*ortho*- and *para*-hydroxylated	98	1–2	14–19	Biliary/fecal (>90%) Renal (<2%)
Fluvastatin	3.62	20–30	None	98	0.5–1.0	1	Biliary/fecal (95%) Renal (5%)
Lovastatin	4.07 (4.04)[b]	5	3,5-Dihydroxy acid	>95	2	3–4	Fecal (83%) Renal (10%)
Pravastatin	1.44 (0.5)[b]	17	None	43–55	1.0–1.5	2–3	Fecal (70%) Renal (20%)
Pitavastatin	3.45	51	None	>99	1	12	Fecal (79%) Renal (15%)
Rosuvastatin	0.42	20	*N*-Desmethyl	88	3–5	19–20	Fecal (90%) Renal (10%)
Simvastatin	4.42 (4.2)[b]	5	3,5-Dihydroxy acid	95	4	3	Fecal (60%) Renal (13%)

[a]A commercial program was used for calculated values (47).
[b]Calculated using the CLOG program (40).

Statini FK lastnosti

TABLE 25.5 Dosing Information for HMG-CoA Reductase Inhibitors

Generic Name	Brand Name(s)	Dosing Range	Maximum Daily Dose	Dose Reduction with Renal Dysfunction	Tablet Strengths (mg)
Atorvastatin	Lipitor	10–80 mg once daily	80 mg	No	10, 20, 40,80
Fluvastatin	Lescol Lescol XR	20–80 mg once daily or b.i.d.	80 mg	Caution in severe impairment	20, 40, 80 (XR)
Lovastatin	Mevacor Altoprev (XR)	10–80 mg once daily or b.i.d.	80 mg (60 mg if XR) (20 mg with fibrate)	Yes	10, 20, 40, 20 (XR), 40 (XR), 60 (XR)
Pitavastatin	Livalo	1-4 mg once daily	40 mg	Yes	1, 2, 4
Pravastatin	Pravachol	10–80 mg once daily	80 mg	Yes	10, 20, 40, 80
Rosuvastatin	Crestor	5–40 mg once daily	40 mg (10 mg with fibrate)	Only with severe impairment	5, 10, 20, 40
Simvastatin	Zocor	5–40 mg once daily	80 mg (10 mg with fibrate)	Only with severe impairment	5, 10, 20, 40, 80

b.i.d., twice a day; XR, extended release.

Metabolizem

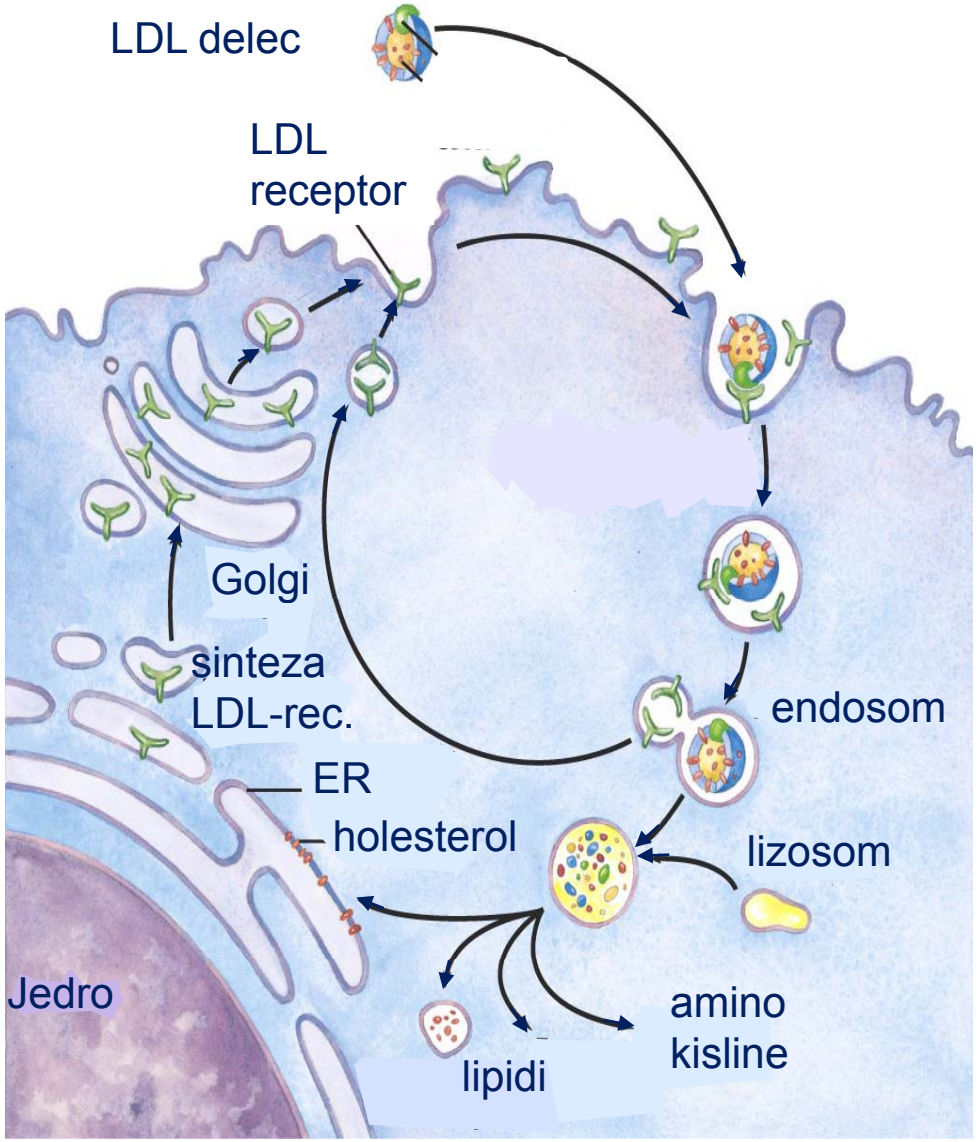
- Intenziven! Razlog za nizko BU – npr. fluvastatin obseg abs. 90%, BU 20-30%
- Lovastatin, simvastatin – 3,5-dihidroksi derivati
- Atorvastatin – aromatska hidroksilacija
- Rosuvastatin – N-demetiliranje
- Metaboliti atorvastatina in rosuvastatina so učinkoviti – izjemno dolg učinek

Stranski učinki

- Statini z nižjo lipofilnostjo – selektivni privzem v jetrih, manj stranskih učinkov
- Jetrne celice imajo transportni sistem za statine, ostale ne – pasivna difuzija skozi membrane (lipofilnost!)
- Večina sinteze holesterola v jetrih, vendar ne le tam!
- Stranski učinki (rabdomioliza) posledica zaviranja HMG-CoA reduktaze v mišicah
- Rabdomioliza je lahko fatalna
- Cerivastatin – odpoklic s trga 200, rabdomioliza, 50 smrtnih primerov

Dodatni učinki statinov

- Povečana ekspresija jetrnih LDL receptorjev
- Povečano število LDL receptorjev v jetrih
- izločanje LDL iz plazme



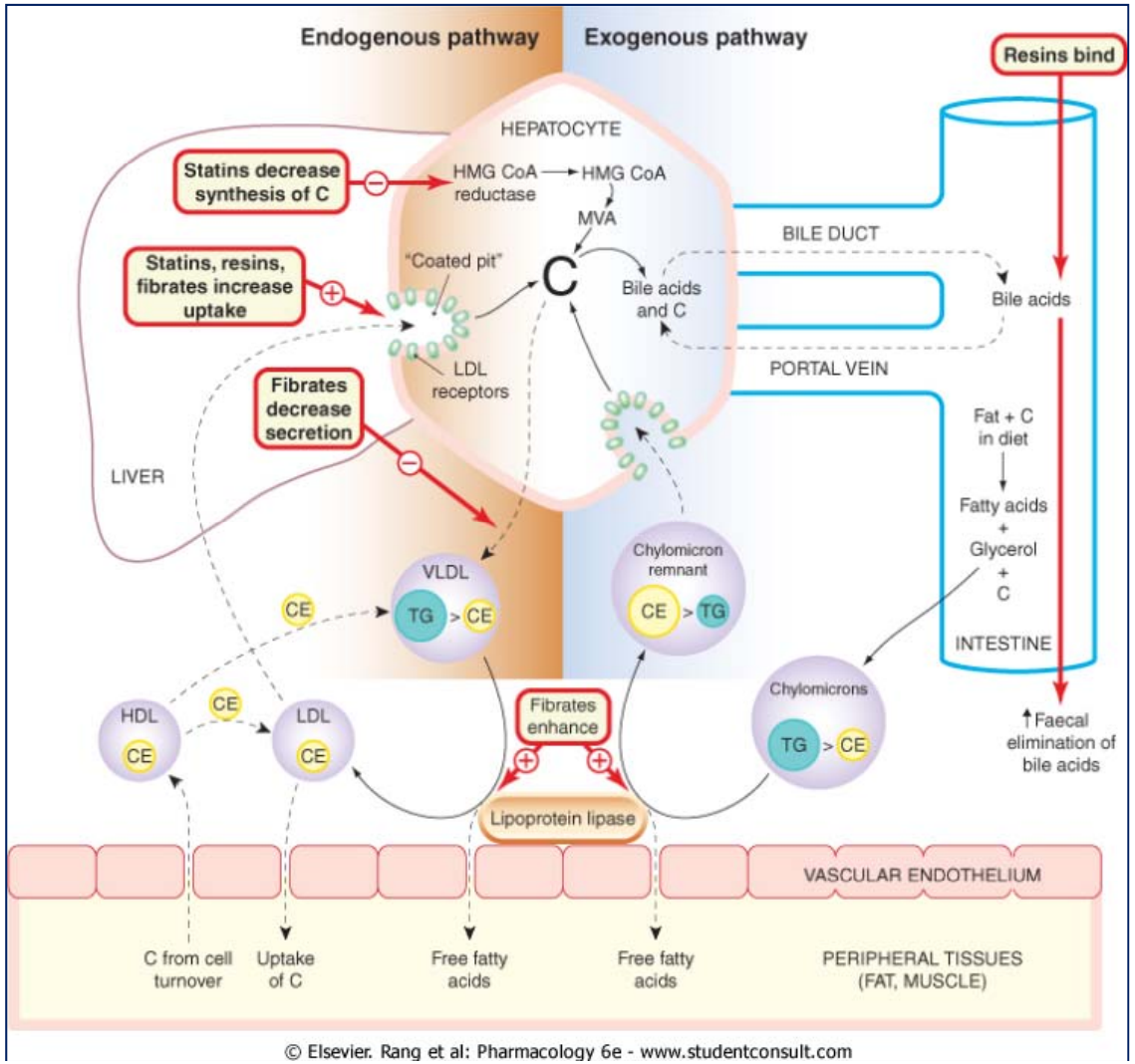
Fibrati

- Zdravila 2. izbora pri hiperholesterolemijah
- Učinkoviti pri hipertrigliceridemijah

Večplasten mehanizem

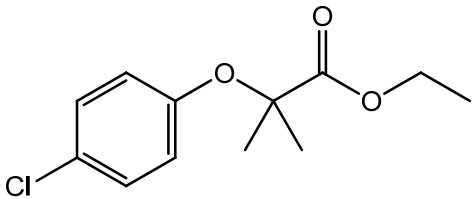
- aktivirajo specifične transkripcijske faktorje iz naddružine jedrnih hormonskih receptorjev (PPARα); indukcija sinteze apoA-I in apoA-II, preko HDL zniža serumsko koncentracijo holesterola
- stimulirajo celice za privzem maščobnih kislin in njihovo pretvorbo v Ac-CoA (β-oksidacija)
- povečano izločanje HDL
- zmanjšano izločanje VLDL
- +modulacija lipoprotein lipaze

Prijemališča hipolipemikov

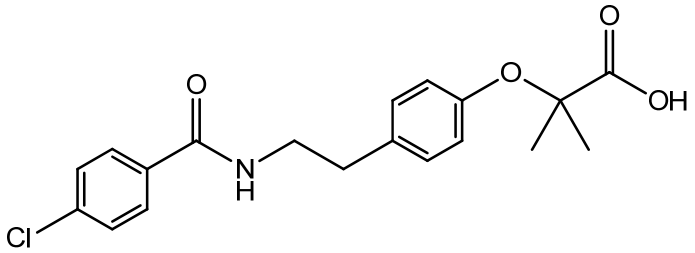


Fibrati

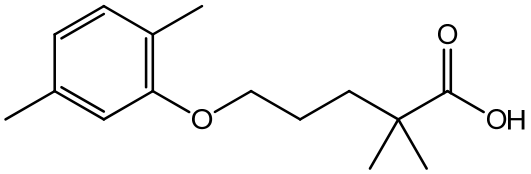
- Klofibrat



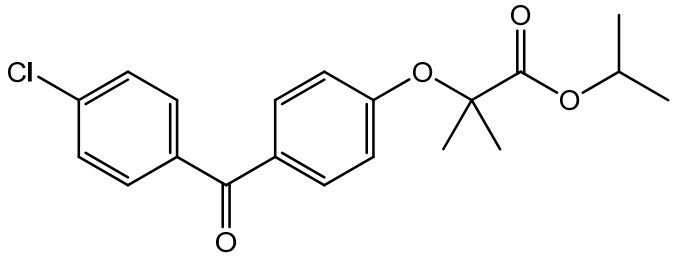
- Bezafibrat



- Gemfibrozil



- Fenofibrat



SAR fibratov

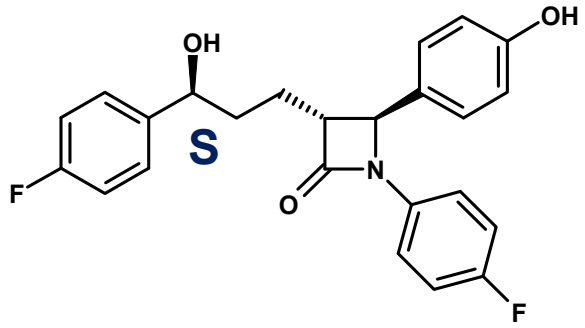
FK lastnosti fibratov

TABLE 25.9 Pharmacokinetic Parameters of Fibrates

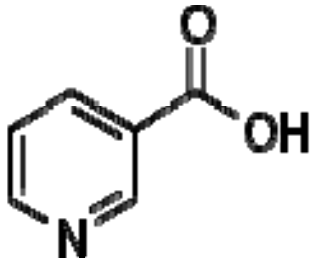
Drug	Calculated LogP	Oral Bioavailability (%)	Active Metabolite	Protein Binding (%)	Time to Peak Concentration (h)	Elimination Half-Life (h)	Major Route(s) of Elimination
Fenofibrate	5.24	60–90	Fenofibric acid	99	4–8	20–22	Renal (60%–90%) Fecal (5%–25%)
Gemfibrozil	3.9	>90	None	99	1–2	1.5	Renal (70%) Fecal (6%)

Ezetimib

- V uporabi od oktobra 2002
- Reducira serumski LDL, in TG, poveča HDL
- Preprečuje absorpcijo holesterola iz hrane – vezava na “Niemann-Pick C1-Like 1” (NPC1L1) protein



- “Problem” – niacin (nikotinska kislina, vitamin B3) veliko bolj učinkovit!



Mejne vrednosti holesterola

- nižje od 5.2 mmol/L NORMALNE VREDNOSTI
- 5.2 - 6.2 mmol/L MEJNE VREDNOSTI
- nad 6.2 mmol/L PREVISOKE VREDNOSTI

Smernice

- http://www.sfd.si/?mod=aktualno&action=viewOne&ID=229
- http://www.sfd.si/?mod=aktualno&action=viewOne&ID=51
- http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3037084/

Prodaja zdravil

- http://www.drugs.com/top200.html
- http://en.wikipedia.org/wiki/Annual_pharmaceutical_drug_sales
- http://www.nybooks.com/articles/archives/2004/jul/15/the-truth-about-the-drug-companies/?pagination=false

Literatura predavanj

Foye's Principles of Medicinal Chemistry, 6. izdaja:

- 30. poglavje