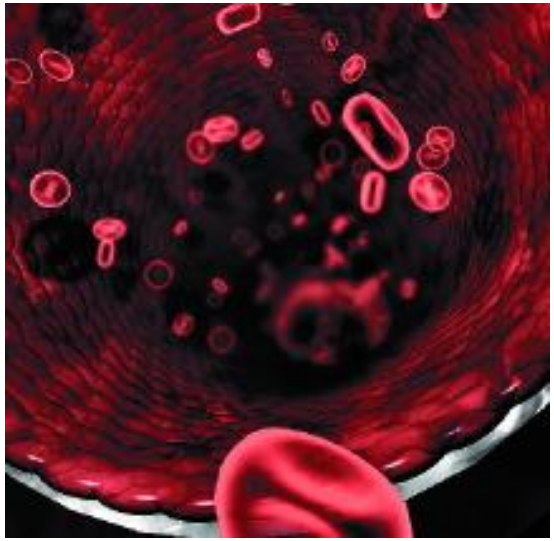


ESTATINAS HIPOLIPÊMICAS

Profa. Dra. Mônica T. Pupo
Química Farmacêutica I

livros

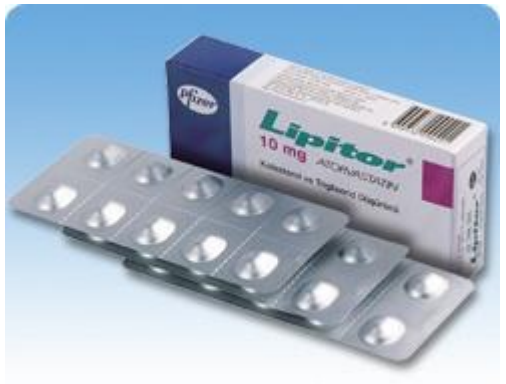
Foye´s Principles of Medicinal Chemistry
D. A. Williams, T. L. Lemke, eds. 7th Ed., Lippincott Williams & Wilkins, Baltimore, 2013
Cap. 25., M. Harrold, p. 815-840.
"Antihyperlipoproteinemics and inhibitors of cholesterol biosynthesis"

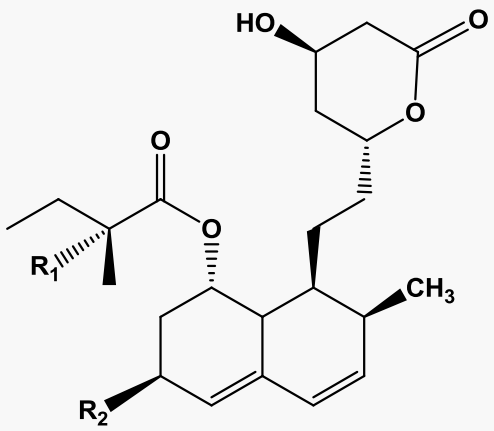
Ou: Foye´s Principles of Medicinal Chemistry 6th Ed., 2008, Cap. 30., M. Harrold, p. 797-819

artigos

Campo, V.L., Carvalho, I. Estatinas hipolipêmicas e novas tendências terapêuticas. *Química Nova* 2007, *30*, 425-430.

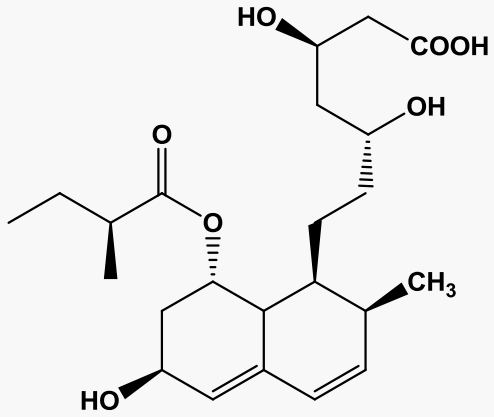
Istvan, E. S., Deisenhofer, J. Structural mechanism for statin inhibition of HMG-CoA reductase. *Science* 2001, *292*, 1160-64.



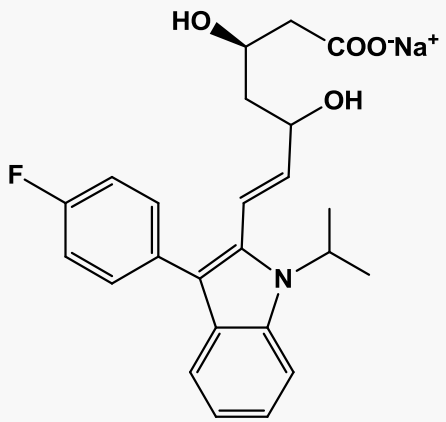


Lovastatina R_1=H; R_2=CH_3

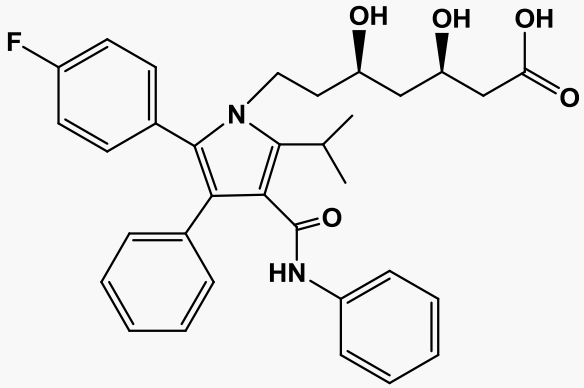
Sinvastatina R_1=R_2=CH_3



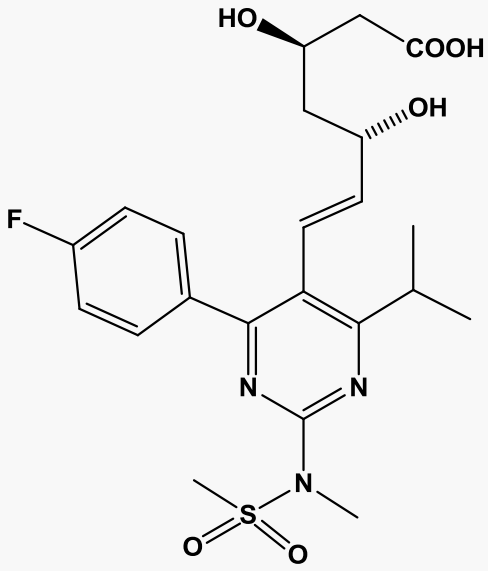
Pravastatina



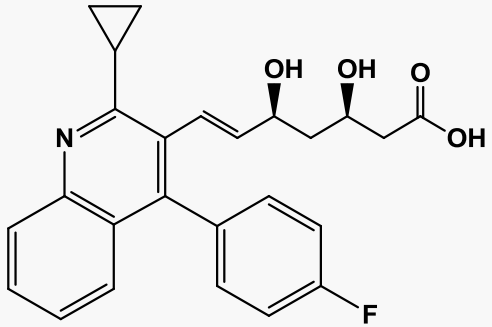
Fluvastatina



Atorvastatina



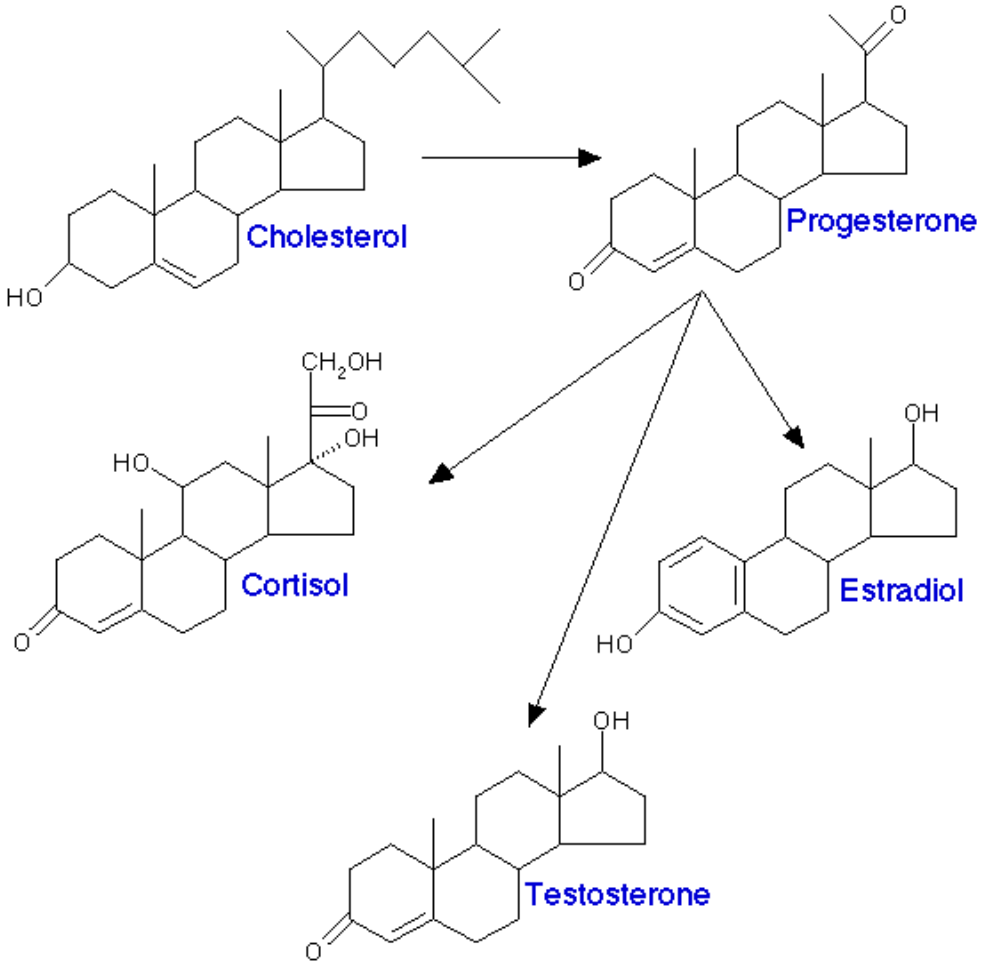
Rosuvastatina



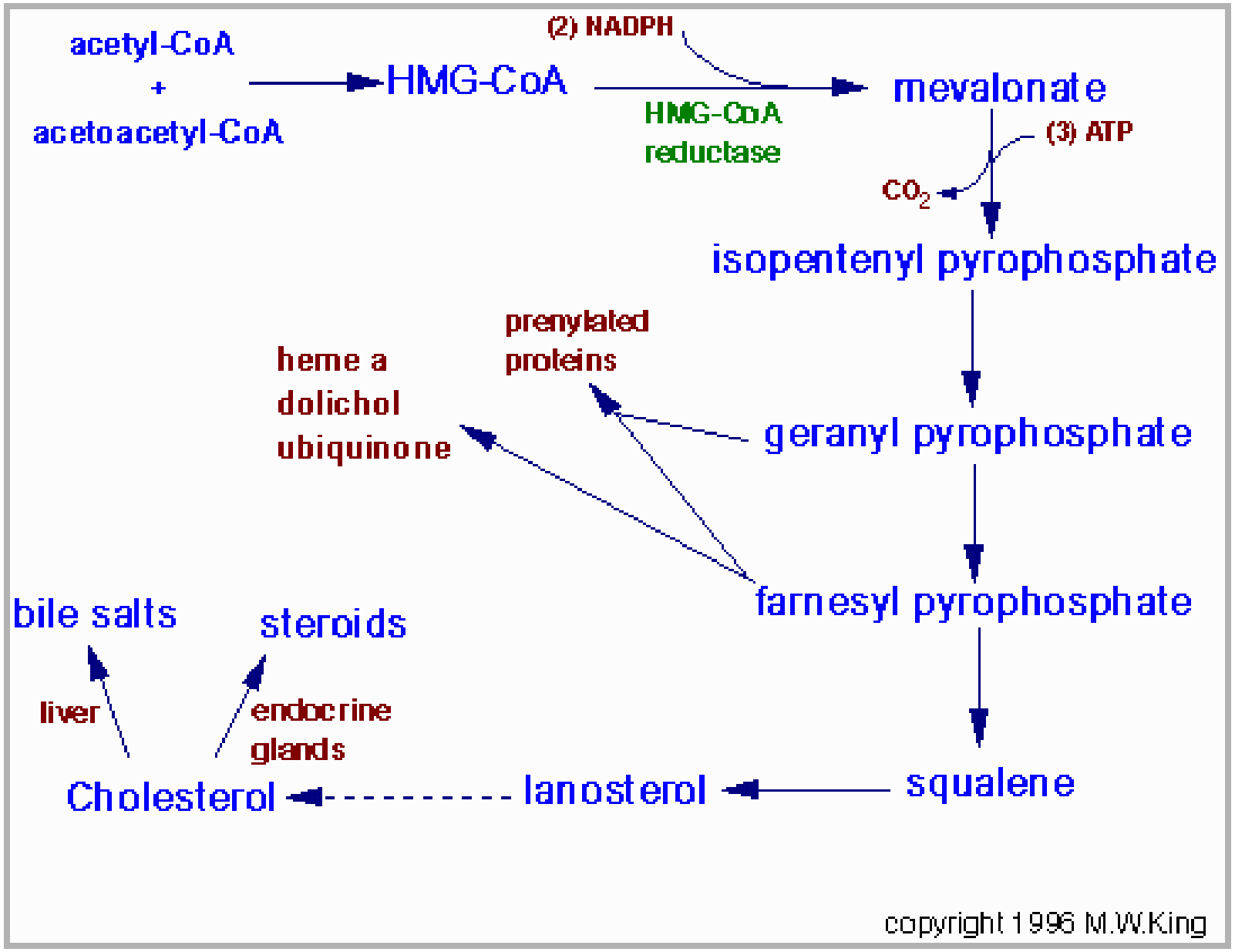
Pitavastatina

Importância do colesterol:
Aumento de estabilidade e modulação de permeabilidade das membranas celulares

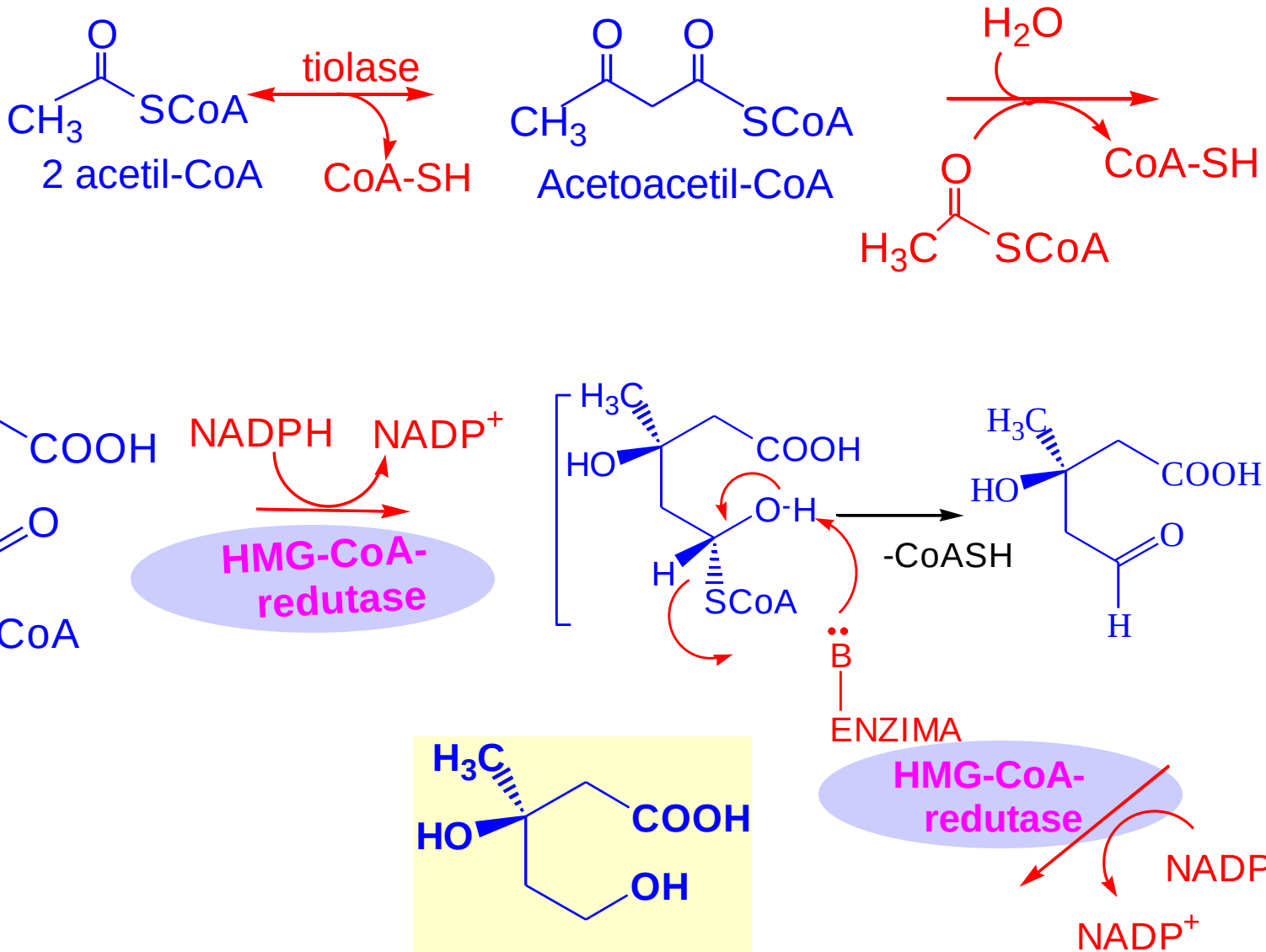
Colesterol é precursor dos hormônios esteroidais, além da Vitamina D

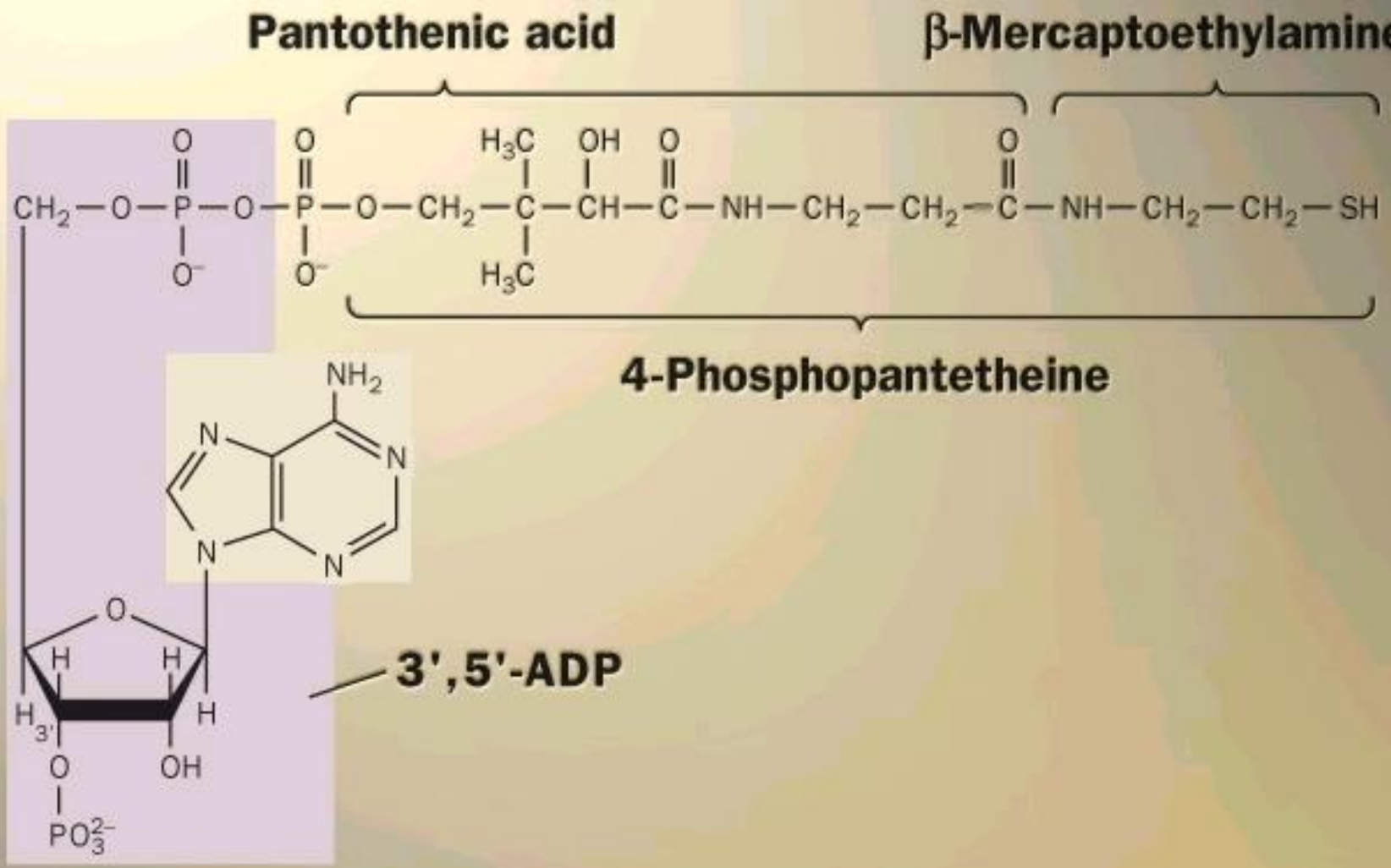


Biossíntese do colesterol



Etapa inicial de formação de ácido mevalônico

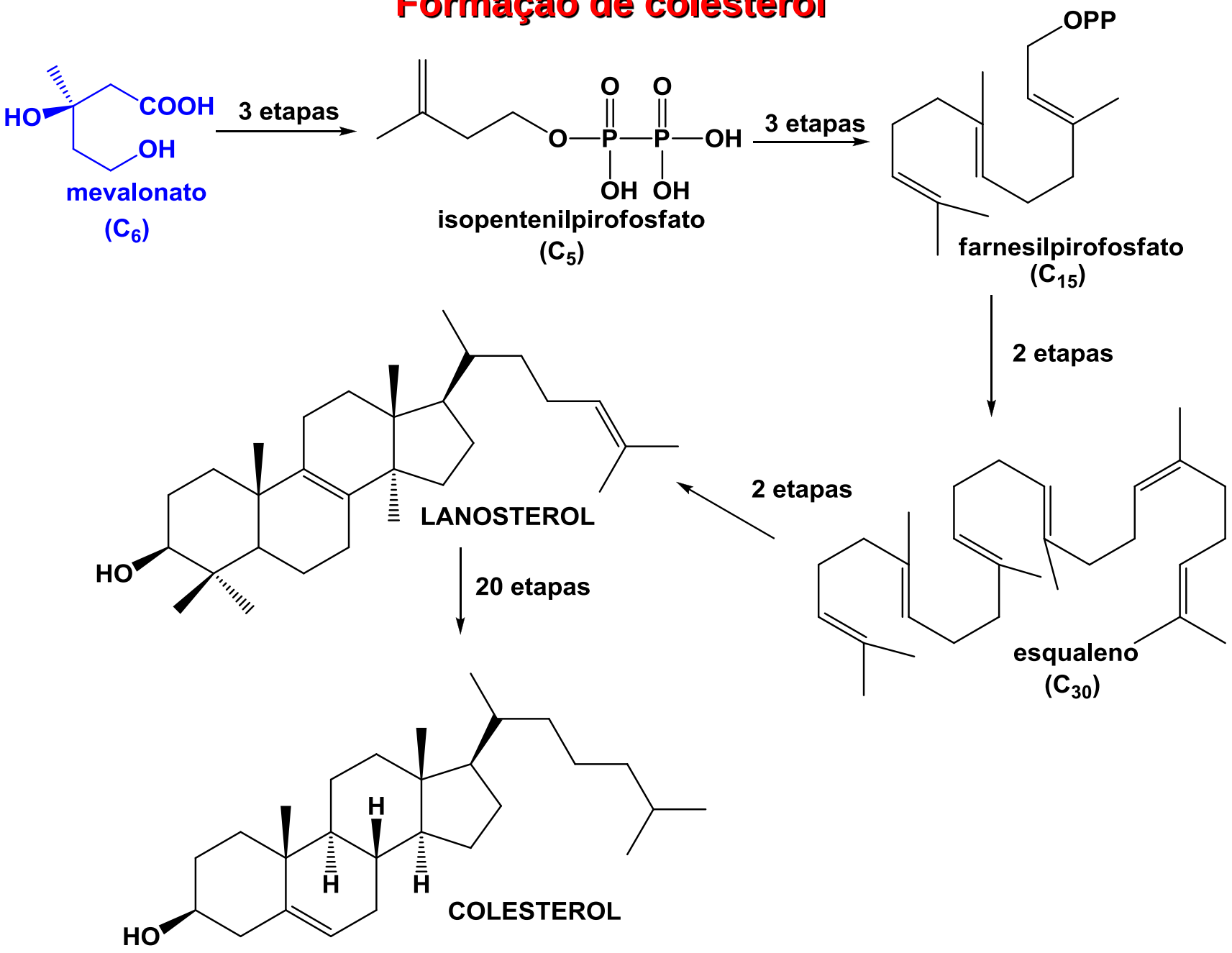




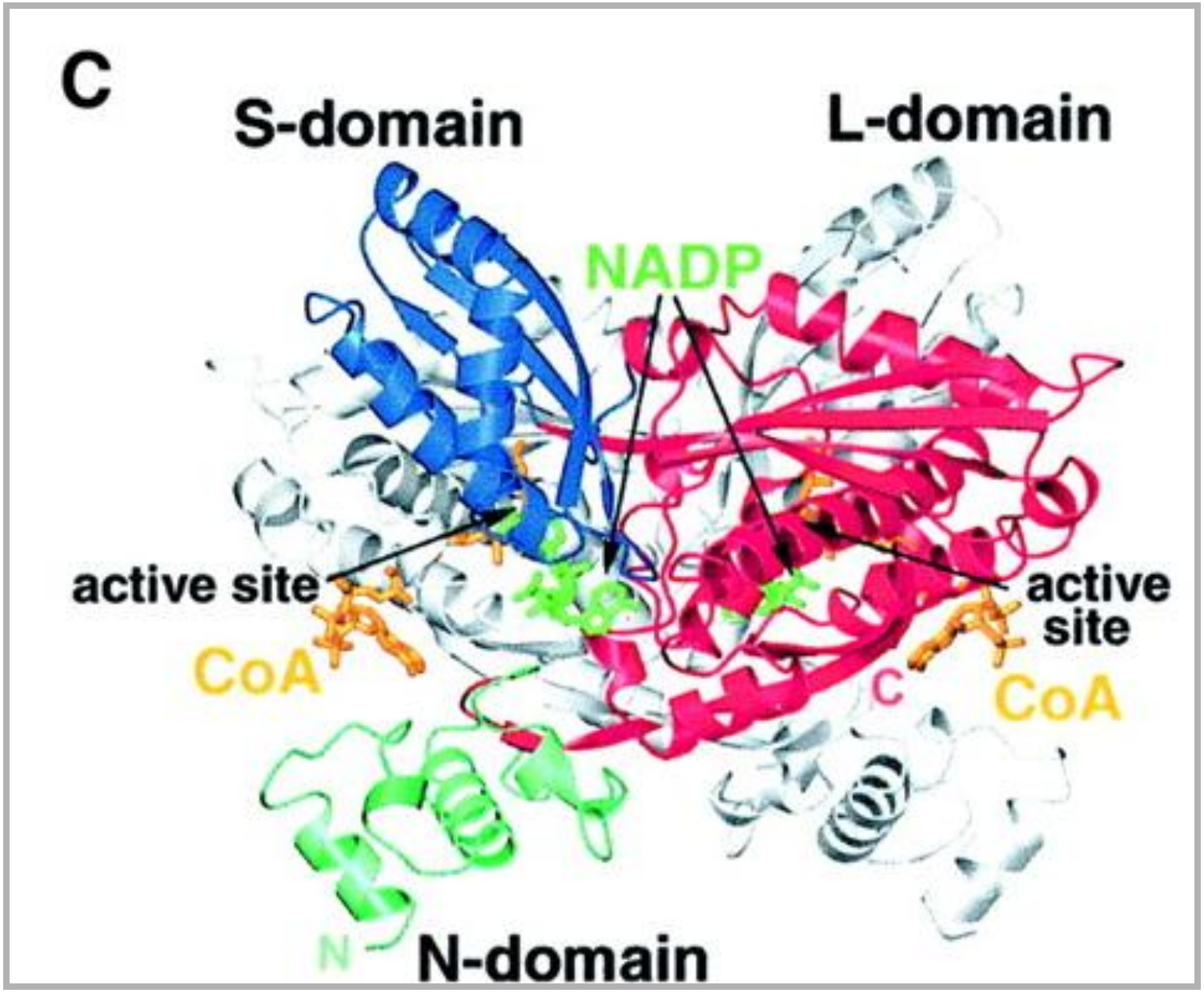
COENZYME A (CoA)

tiff29.mov

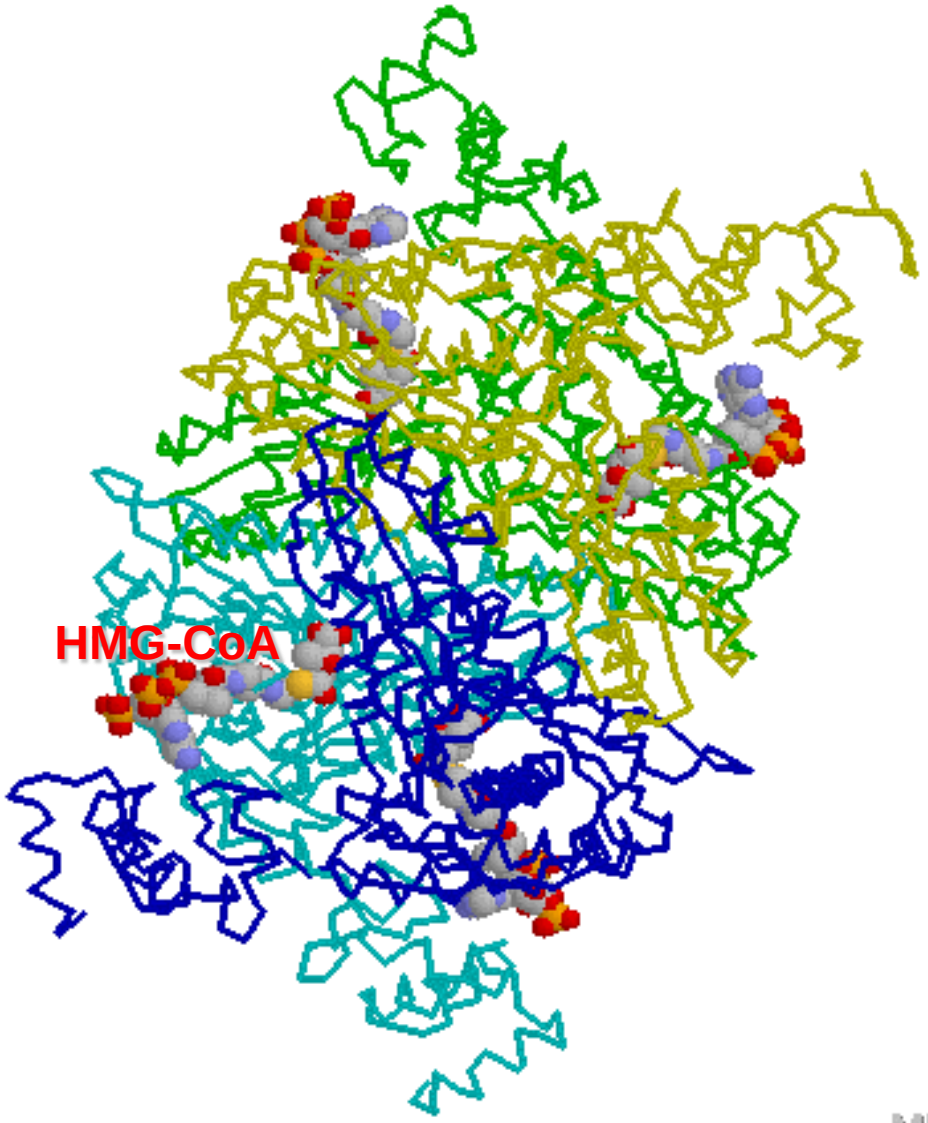
Formação de colesterol



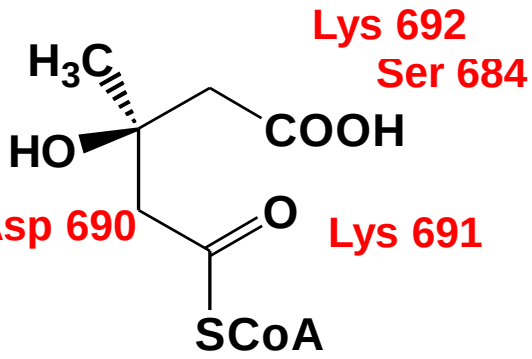
HMG CoA redutase



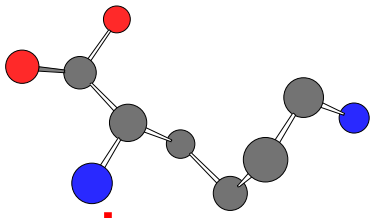
Sítio ativo da HMGCoA redutase



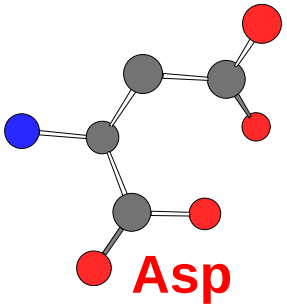
SÍTIOS DE INTERAÇÃO DA HMG-CoA REDUTASE COM HMG-CoA



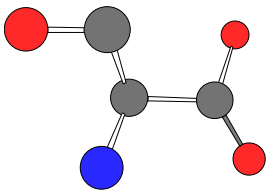
3-hidroxi-3metilglutaril-coenzimaA (HMG-CoA)



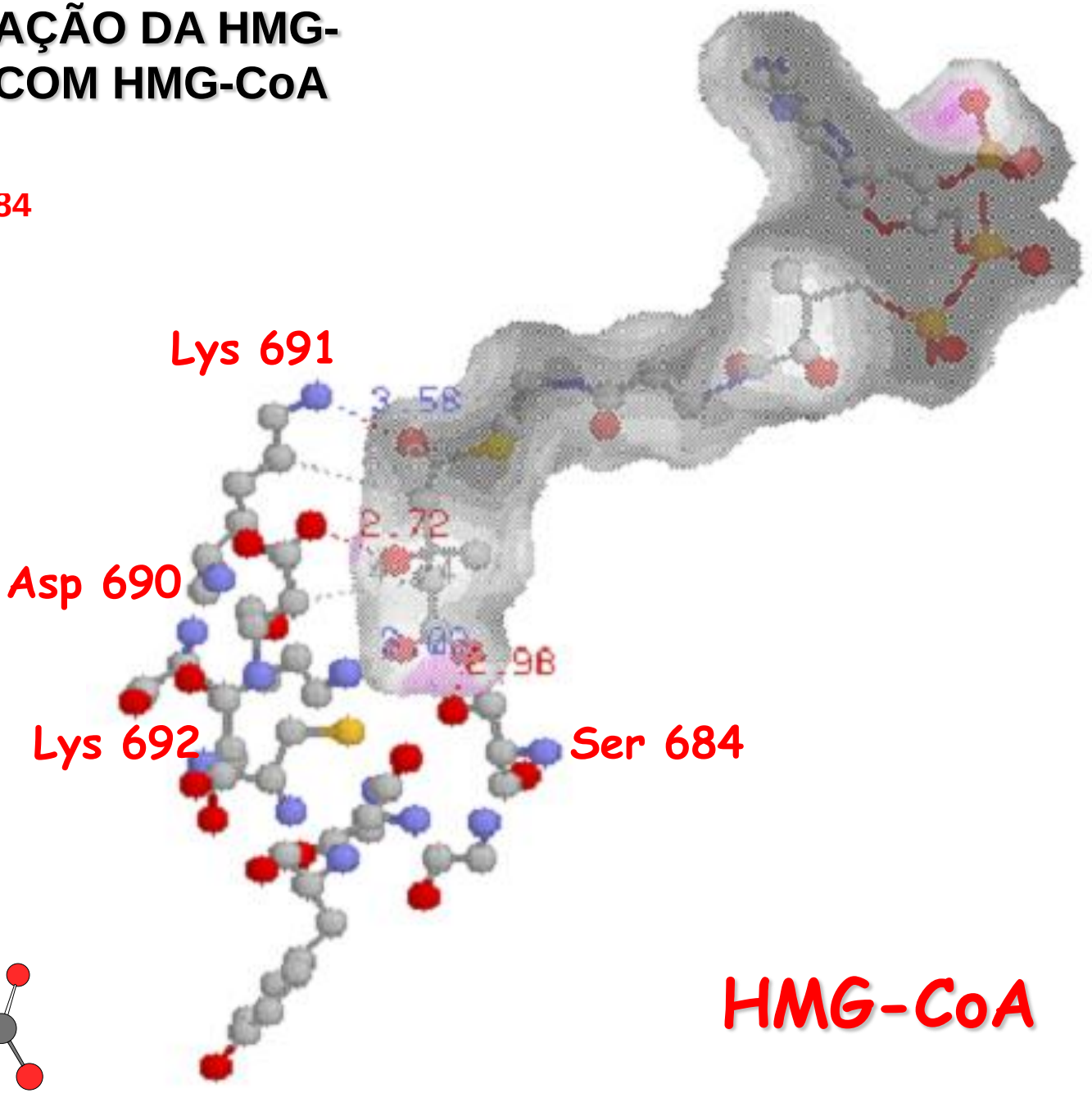
Lys



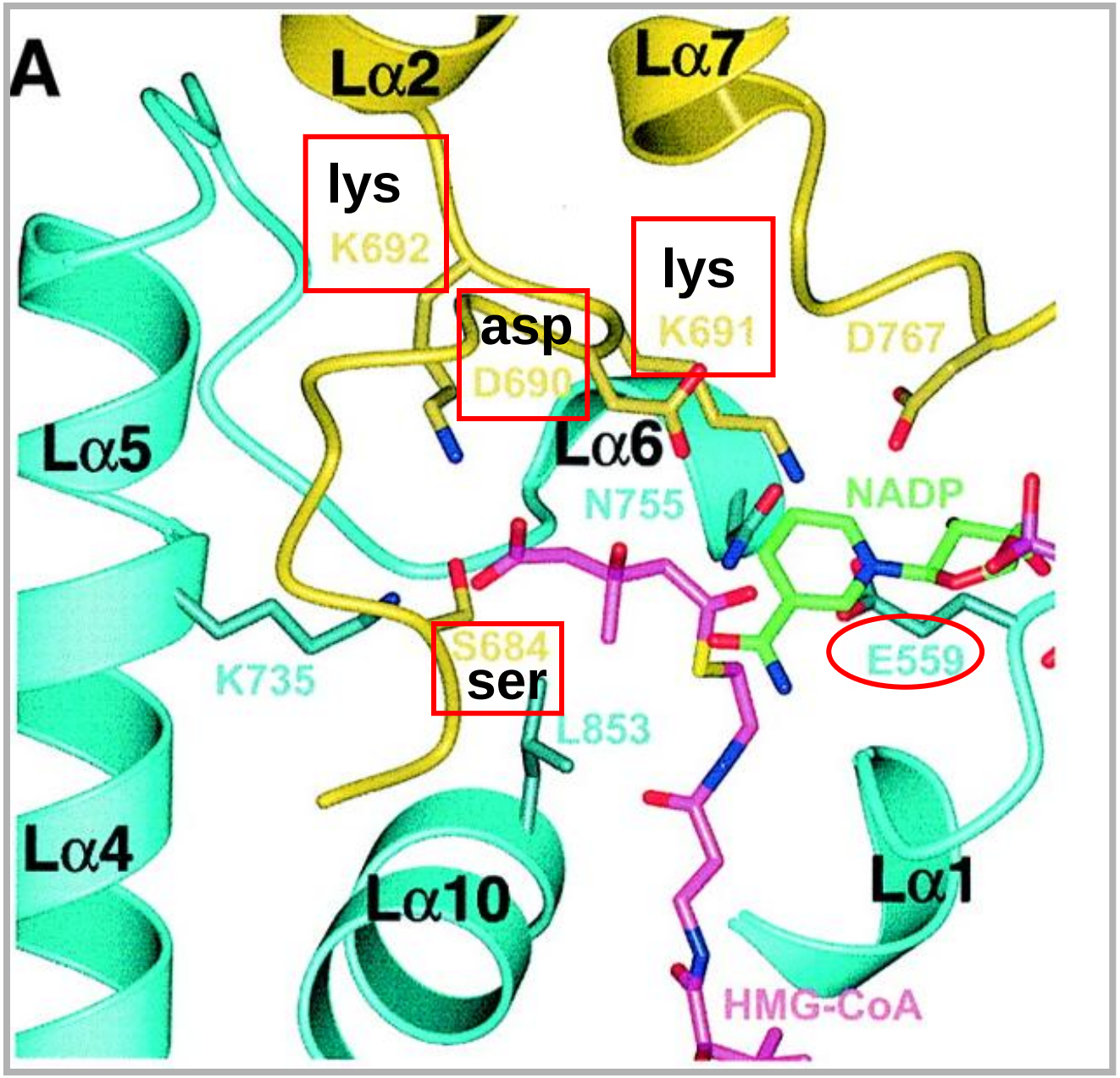
Asp

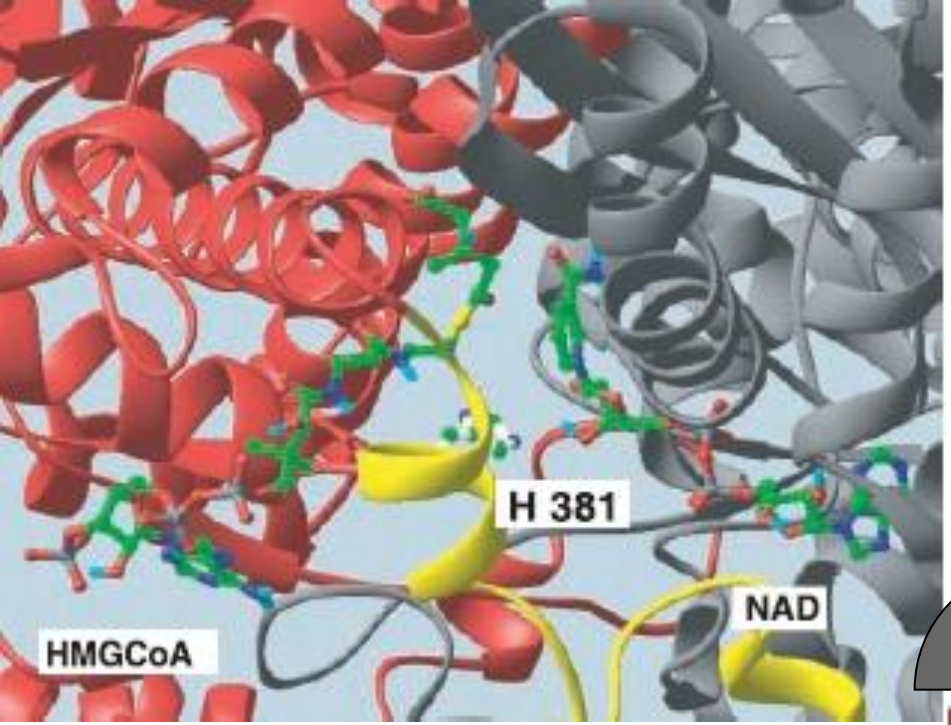


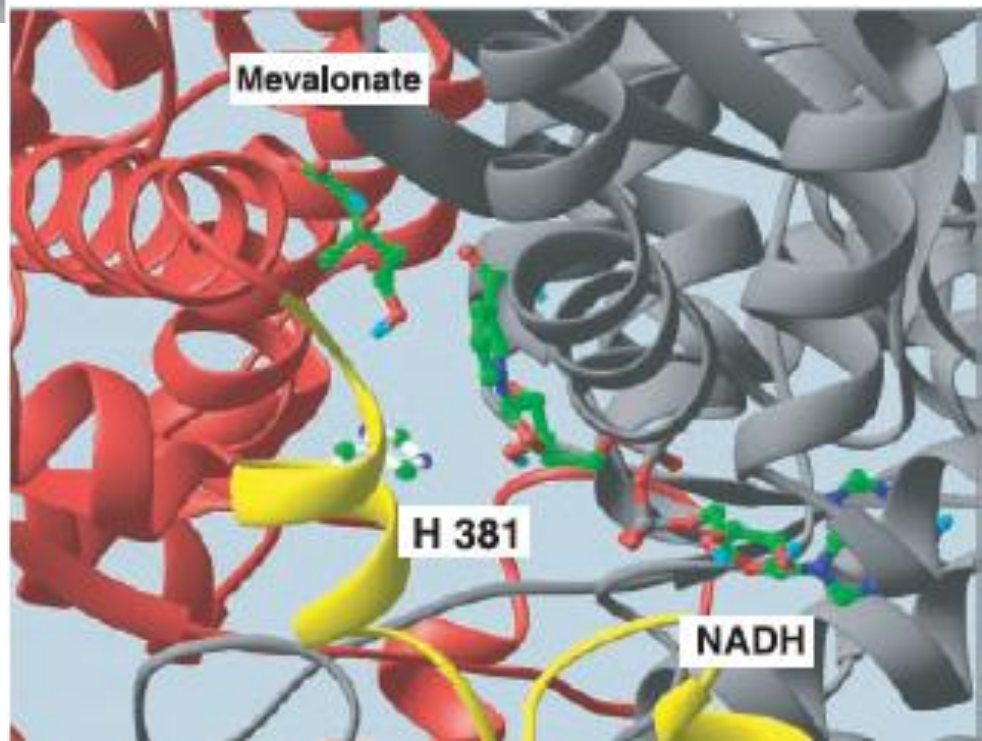
Ser



HMG-CoA


A
Lα2
Lα7
lys
K692
lys
K691
asp
D690
D767
Lα5
Lα6
N755
NADP
S684
ser
K735
E559
L853
Lα4
Lα10
Lα1
HMG-CoA

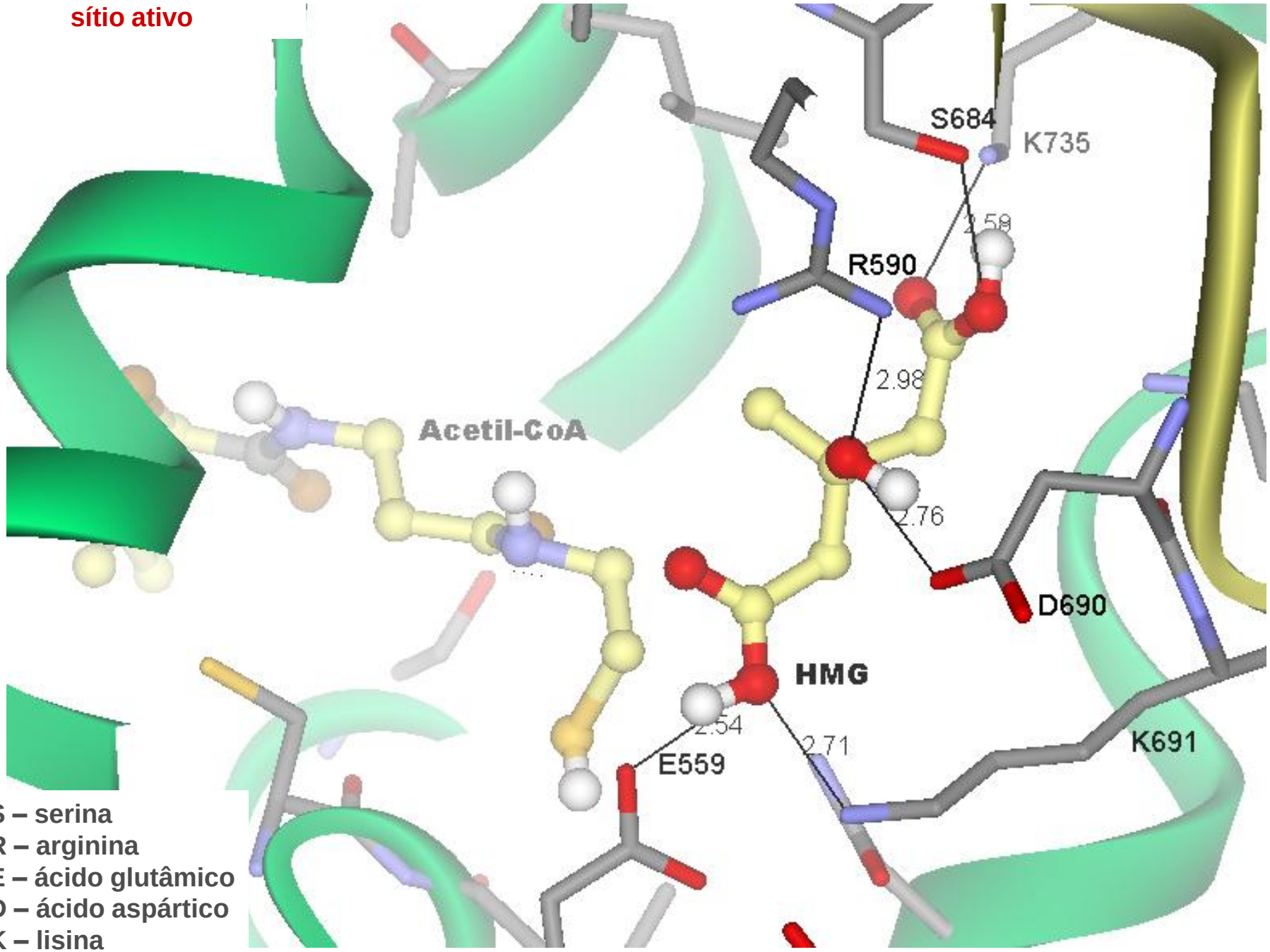




Tabernero et al.

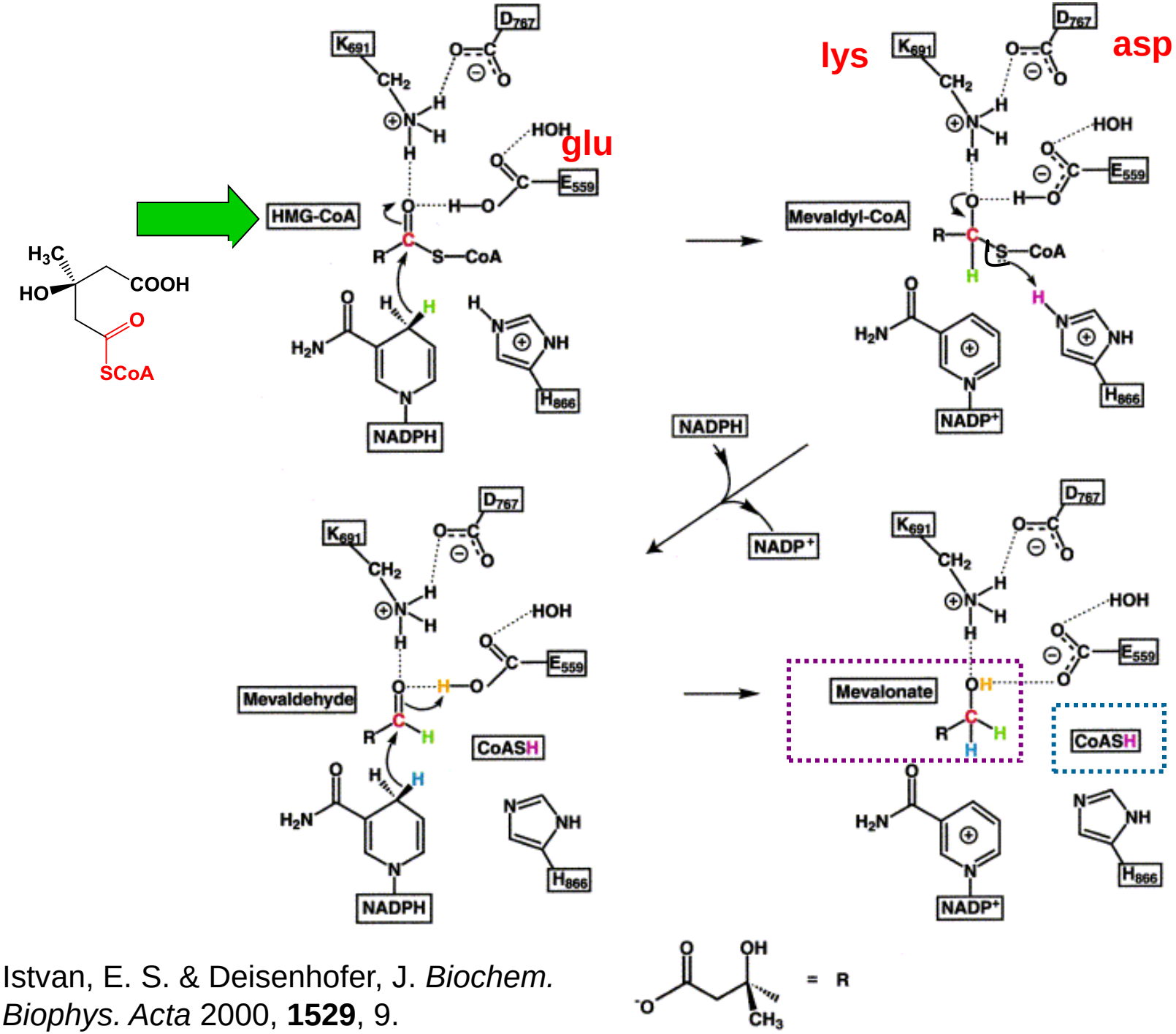
Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 7167–7171, June 1999

Interações do HMG no sítio ativo



S – serina
R – arginina
E – ácido glutâmico
D – ácido aspártico
K – lisina

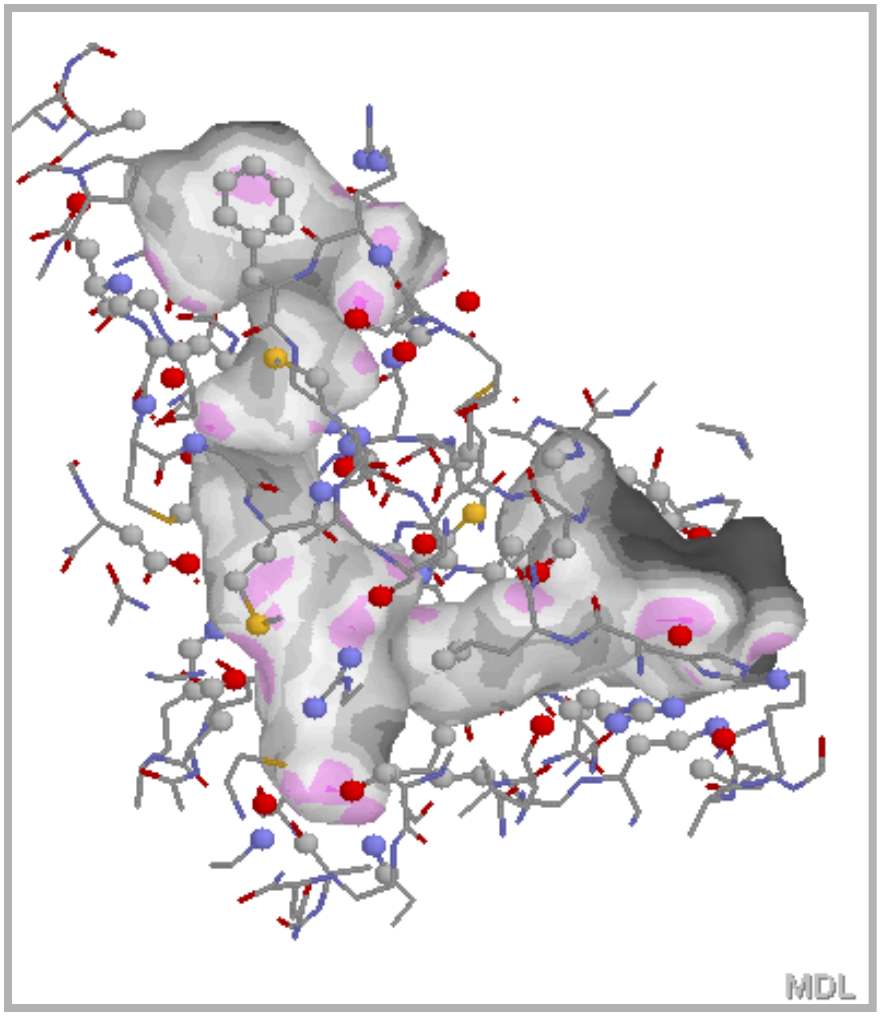
Grupo funcional do substrato	Resíduo que realiza interação	Força de Interação	Comentários
1-C=O	Glu559, Lys691*	ligação de hidrogênio	Promovem a polarização da carbonila para subsequente transferência de hidreto
3-C-OH	Asp690, Arg590	Ligação de hidrogênio	
3-C-CH_3	Leu853	Van der Waals	
5-C-OH	Lys735	Ponte salina	Região terminal COO^-, cuja carga é estabilizada por ambos resíduos
5-C=O	Ser684	ligação de hidrogênio	
-SH (CoA)	**His866**	Ligação de hidrogênio	Posicionado adequadamente próximo ao sítio para doar hidrogênio ao grupo tiol de CoA

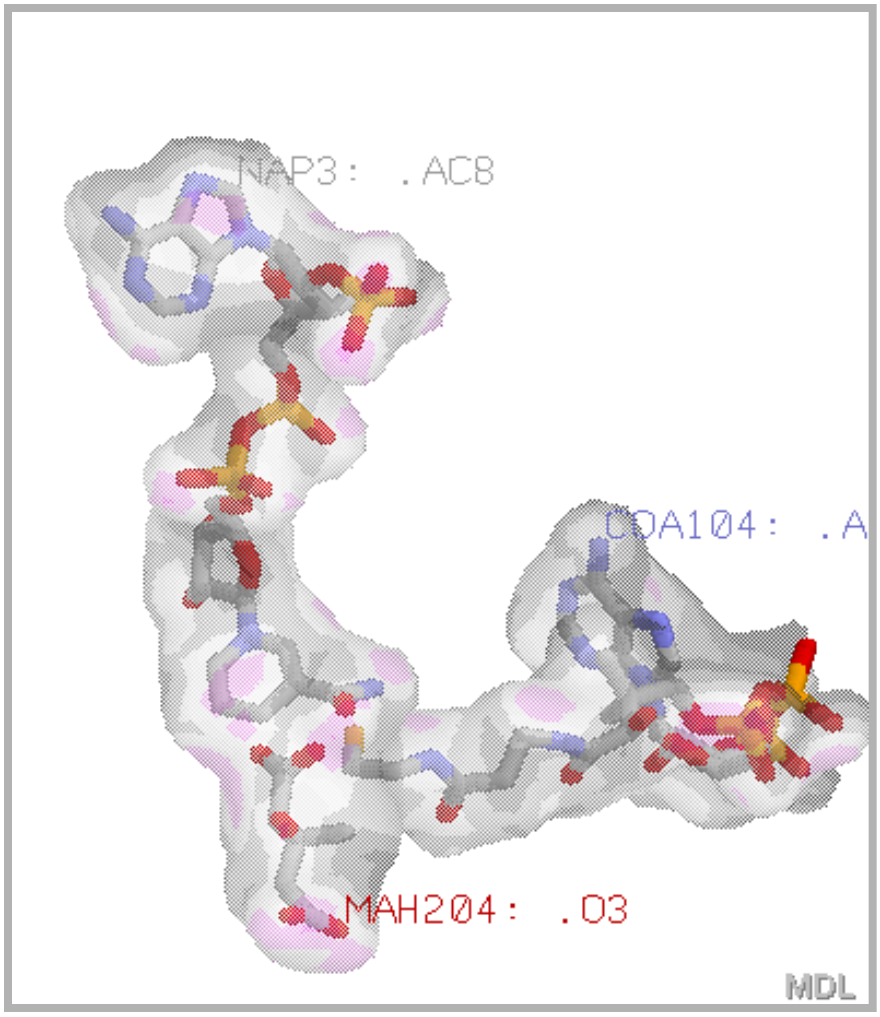


Istvan, E. S. & Deisenhofer, J. *Biochem. Biophys. Acta* 2000, **1529**, 9.

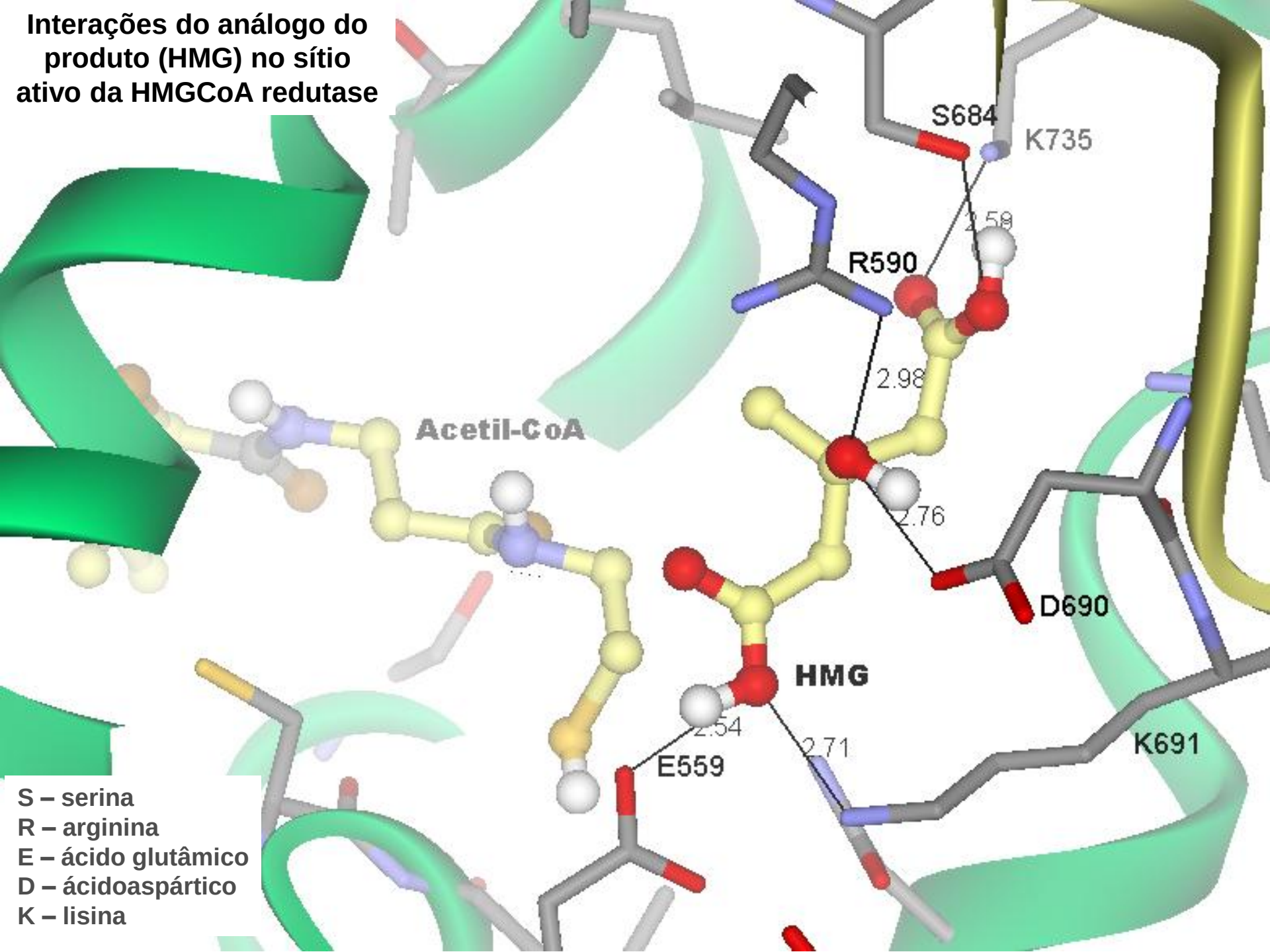
HMG CoA-REDUTASE:

ligantes ác hidroxi-metilglutárico (análogo do produto), Acetil-CoA e NADPH



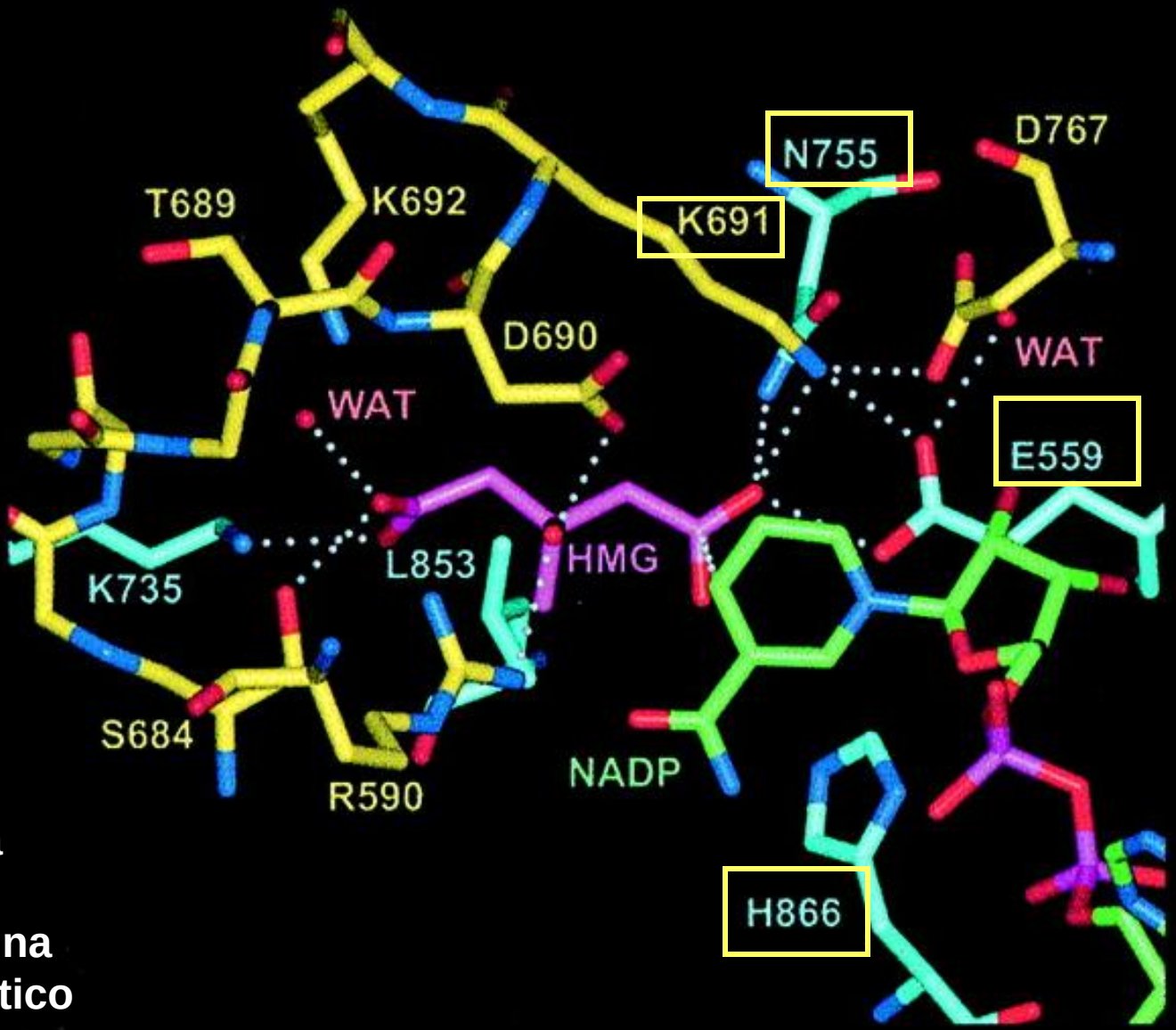


Interações do análogo do produto (HMG) no sítio ativo da HMGCoA redutase

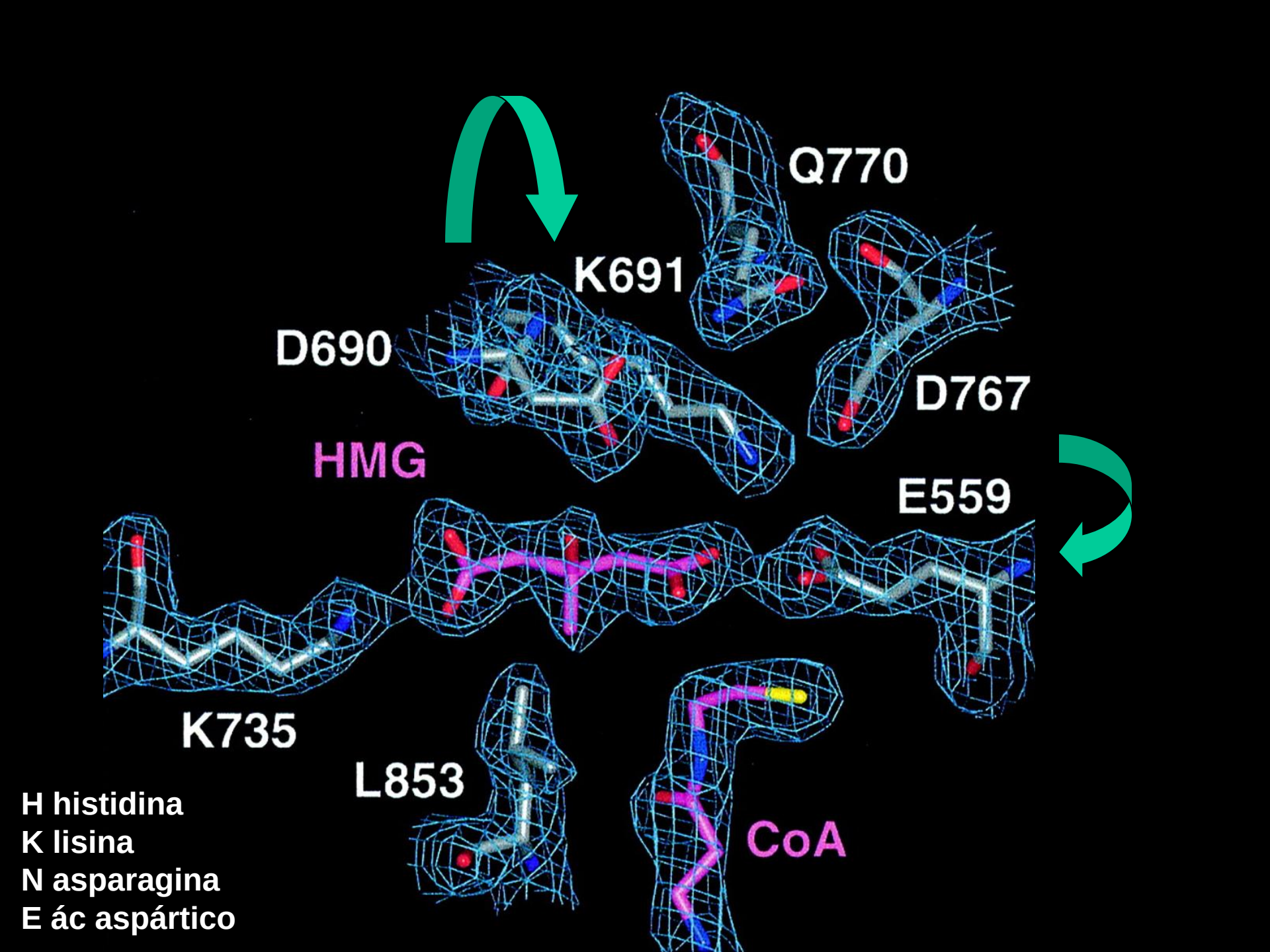


S – serina
R – arginina
E – ácido glutâmico
D – ácidoaspártico
K – lisina

INTERAÇÃO DOS LIGANTES NO SÍTIO CATALÍTICO



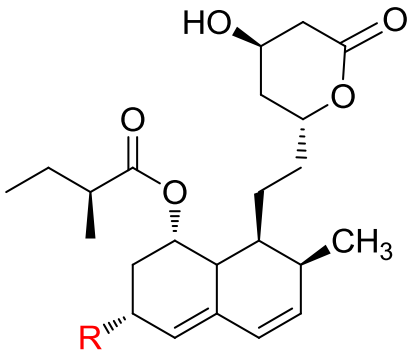
H histidina
K lisina
N asparagina
E ác aspártico



H histidina
K lisina
N asparagina
E ác aspártico

Lovastatina / Mevastatina

Mevastatina
Penicillium citrinum
(Sankyo Pharmaceuticals)

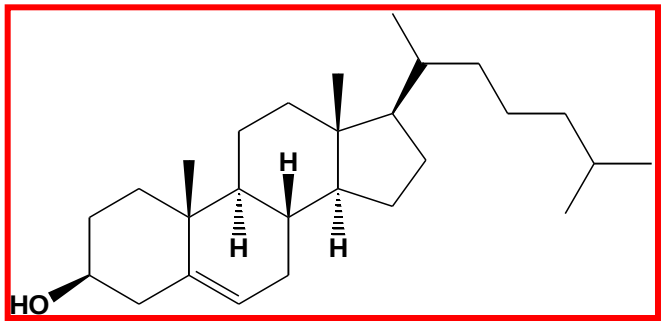


R = CH_3 lovastatina (Mevacor)
R = H mevastatina (Compactin)

Lovastatina
Aspergillus terreus
(Merck)

Estatinas
Novo e único mecanismo de ação

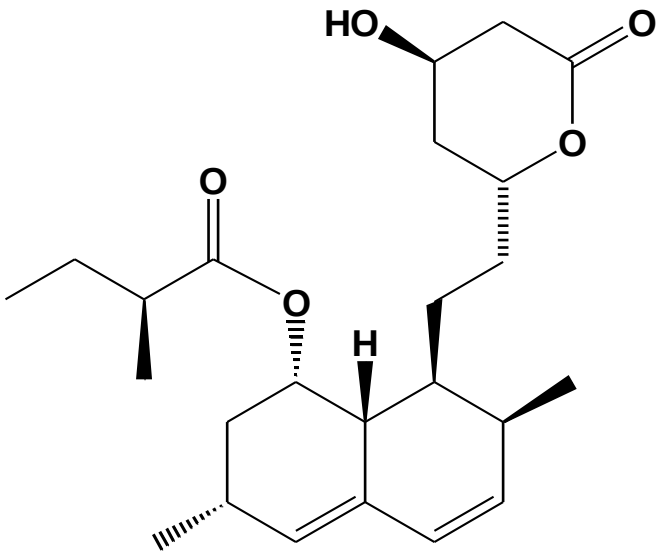
1987: introduzida no mercado



Colesterol – componente de membranas celulares e precursor de androgênios, estrogênios, progesterona e adrenocorticóides

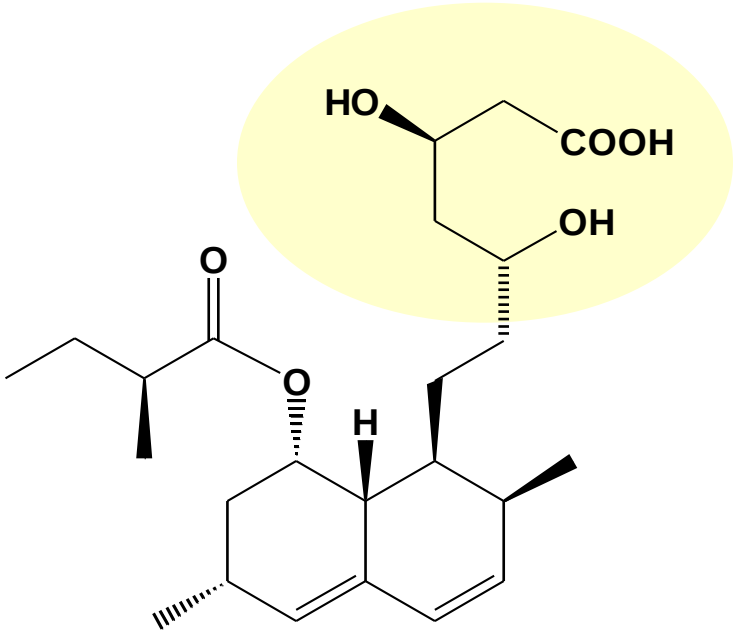
✓ **nova possibilidade de intervenção terapêutica para redução dos níveis sanguíneos de colesterol;**

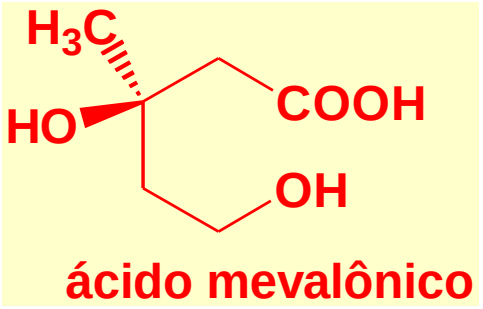
✓ **inibição da enzima HMG-CoA redutase de forma altamente potente, bloqueando a biossíntese de colesterol**



Lovastatina

Pró-fármaco



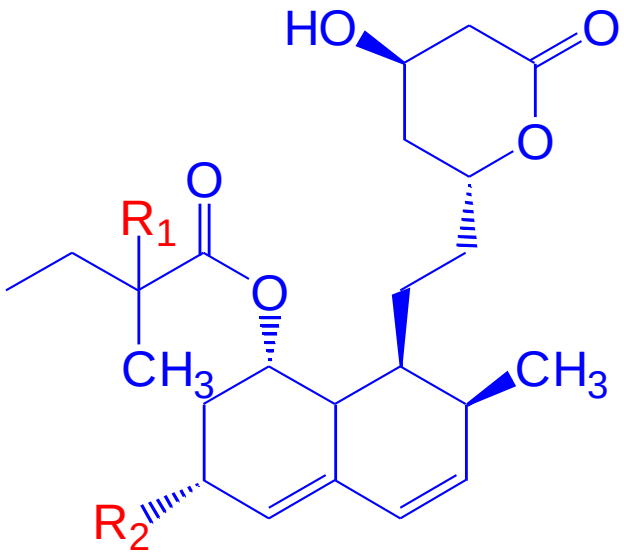


ácido mevalônico

ESTATINAS

Outras ações: anti-neoplásica, inib. de reabsorção óssea, aumento de NO endotelial, relaxamento da musc. vascular, etc

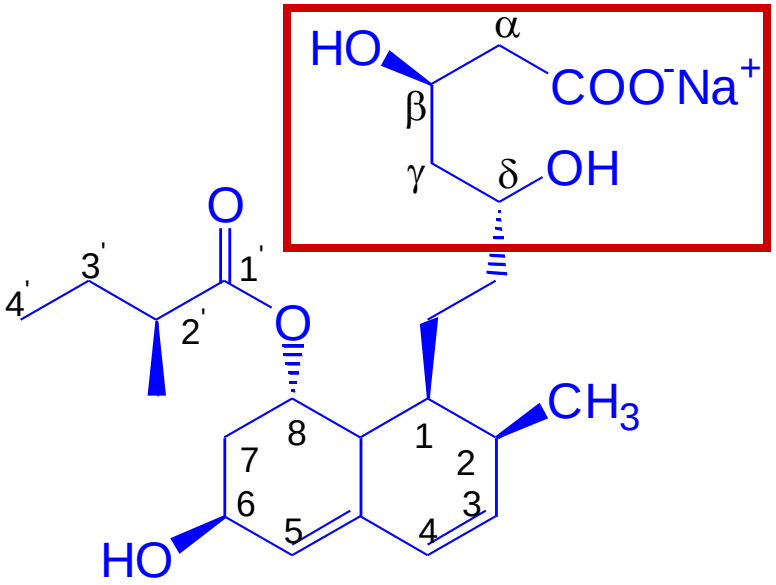
Primeira geração de fármacos:



Mevastatina $R_1=R_2=H$

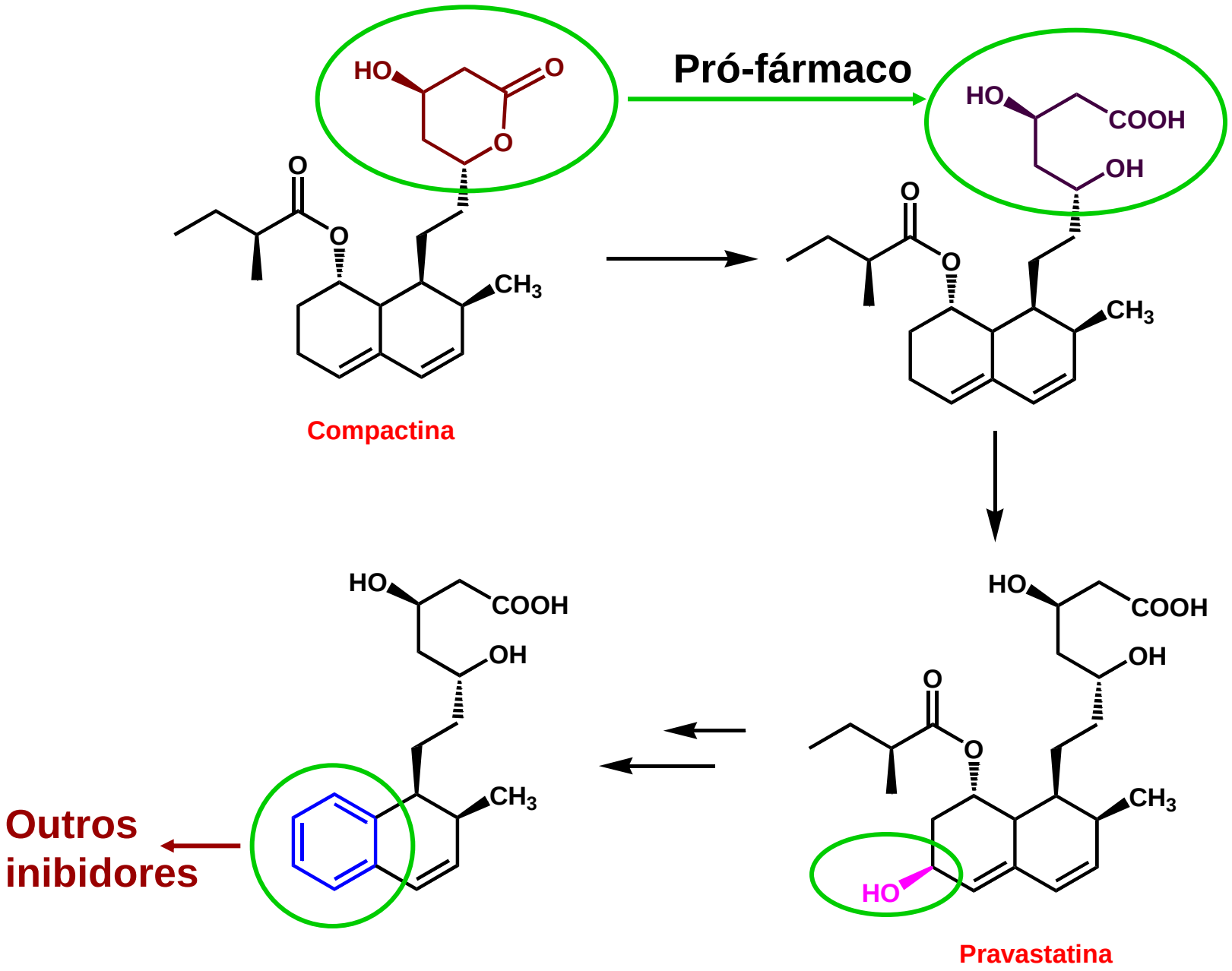
Lovastatina $R_1=H$; $R_2=CH_3$

Sinvastatina $R_1=R_2=CH_3$

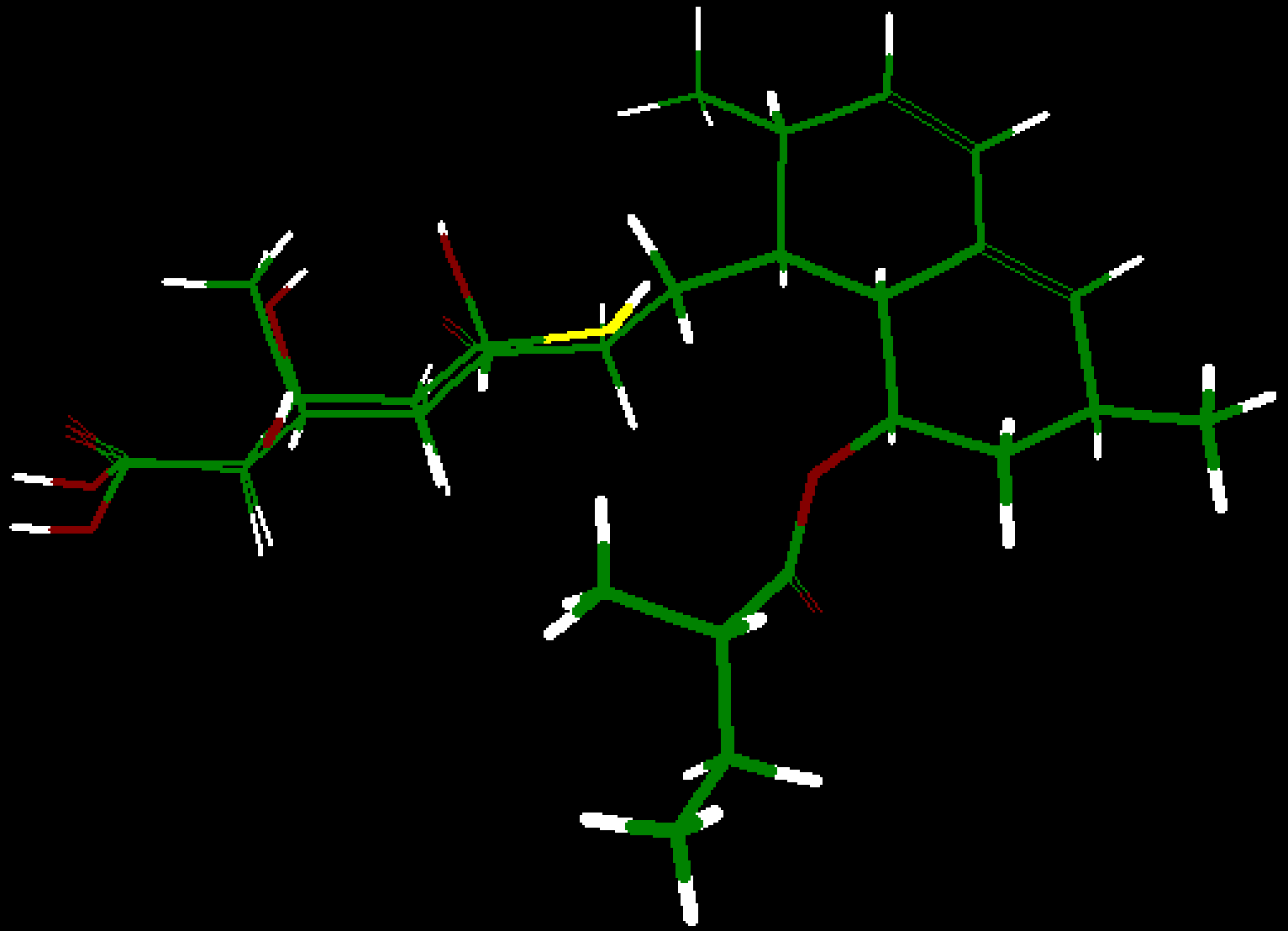


Pravastatina

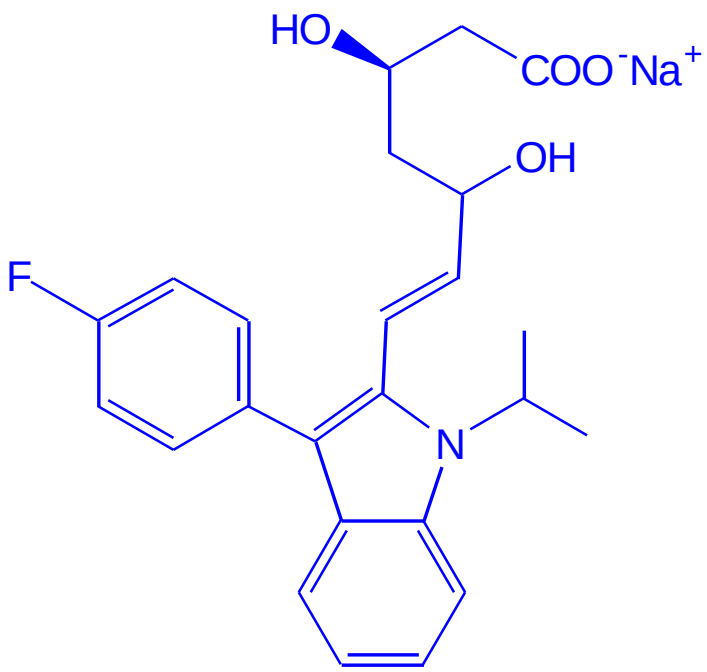
Mevastatina, lovastatina, pravastatina
Sinvastatina:


Pró-fármaco
HO
O
O
HO
COOH
OH
O
O
CH3
Compactina
HO
COOH
OH
O
O
CH3
HO
COOH
OH
O
O
CH3
HO
Pravastatina
HO
COOH
OH
CH3
Outros
inibidores

Sobreposição HMG CoA e Lovastatina

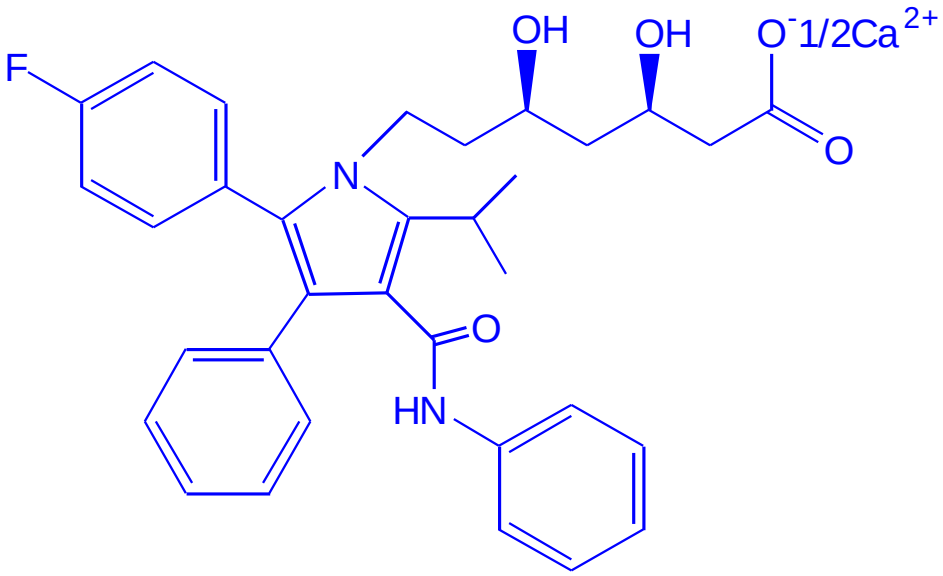


Segunda geração:



Fluvastatina

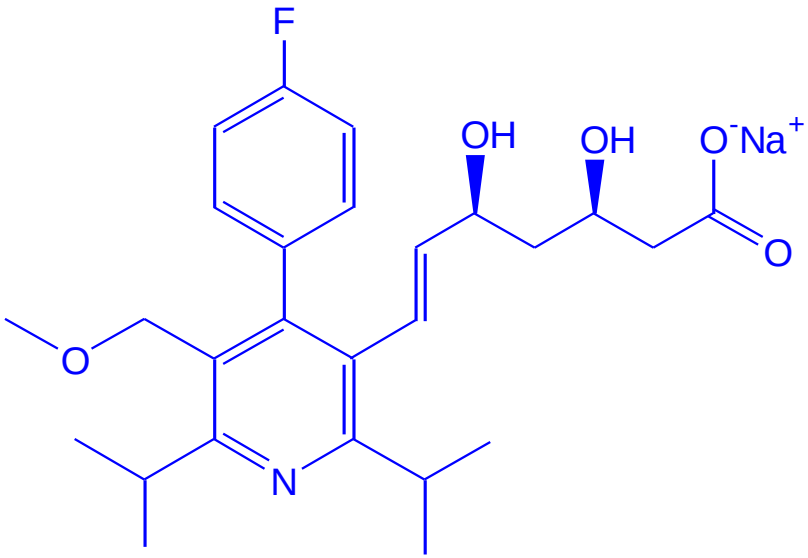
Terceira Geração:



Atorvastatina

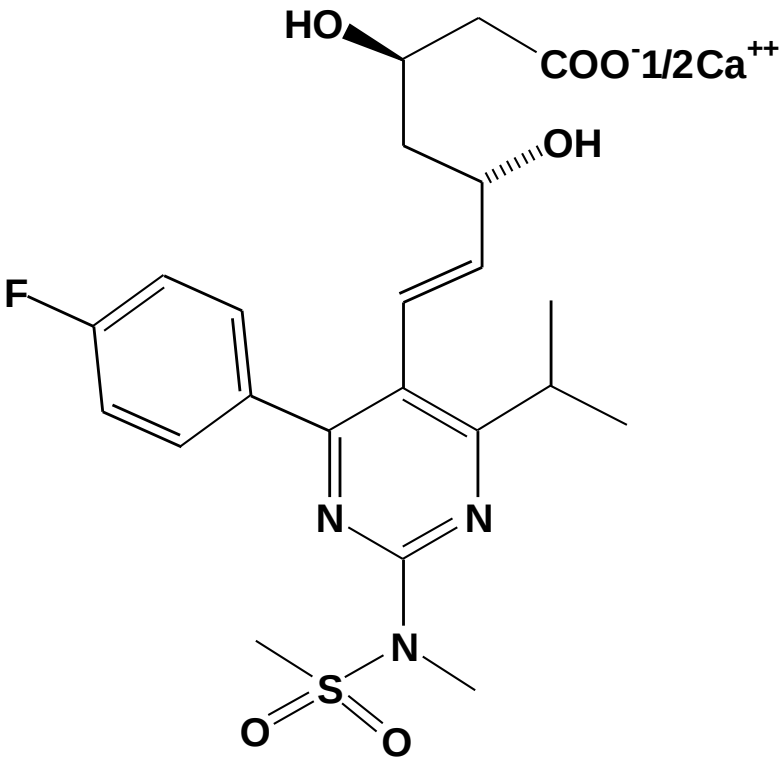
Sintéticos – enantiomericamente puros

Cerivastatina

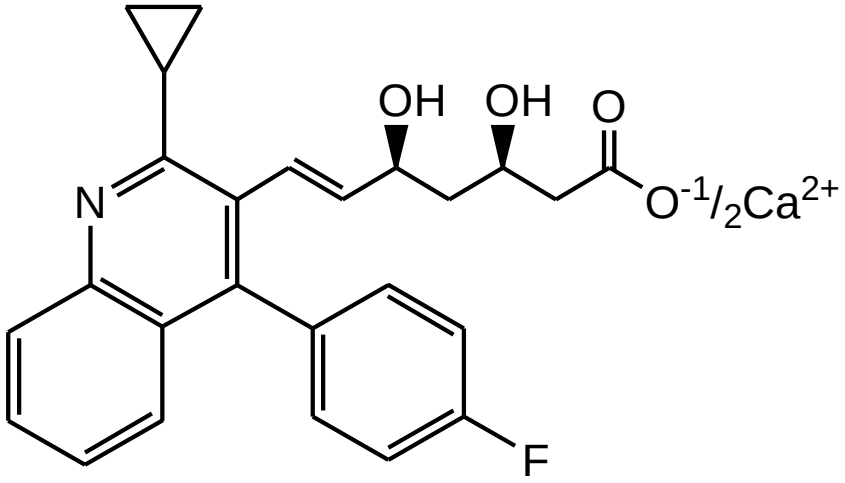


Cerivastatina

Terceira Geração:



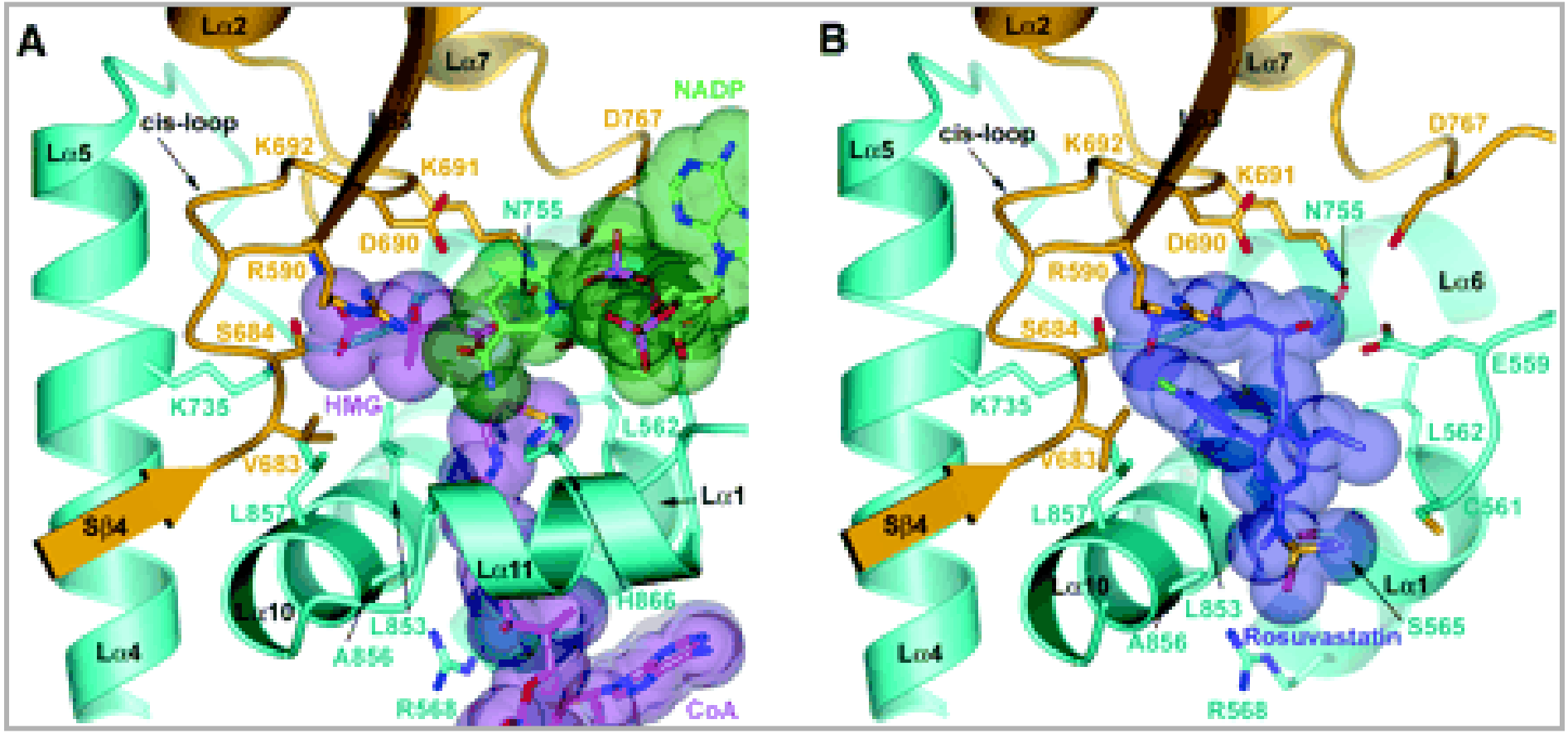
ROSUVASTATINA



PITAVASTATINA

Estatinas exploram a flexibilidade conformacional da HMGR (COOH term)

Não ocupam a região do NADP(H)
Ocupam parcialmente a região da CoA
Inibição competitiva com HMG-CoA



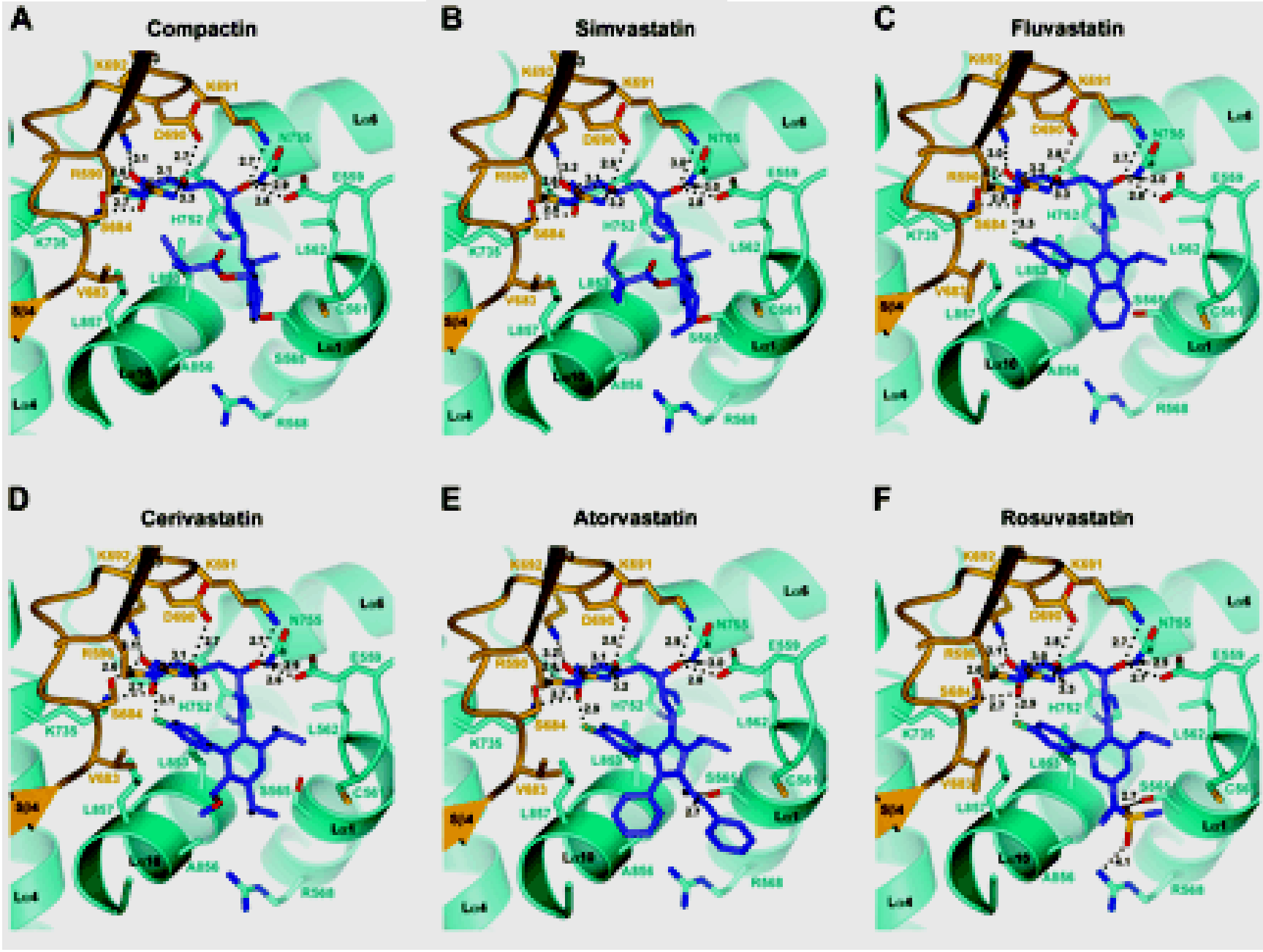
Sítio ativo da HMGR complexada com HMG, CoA e NADP

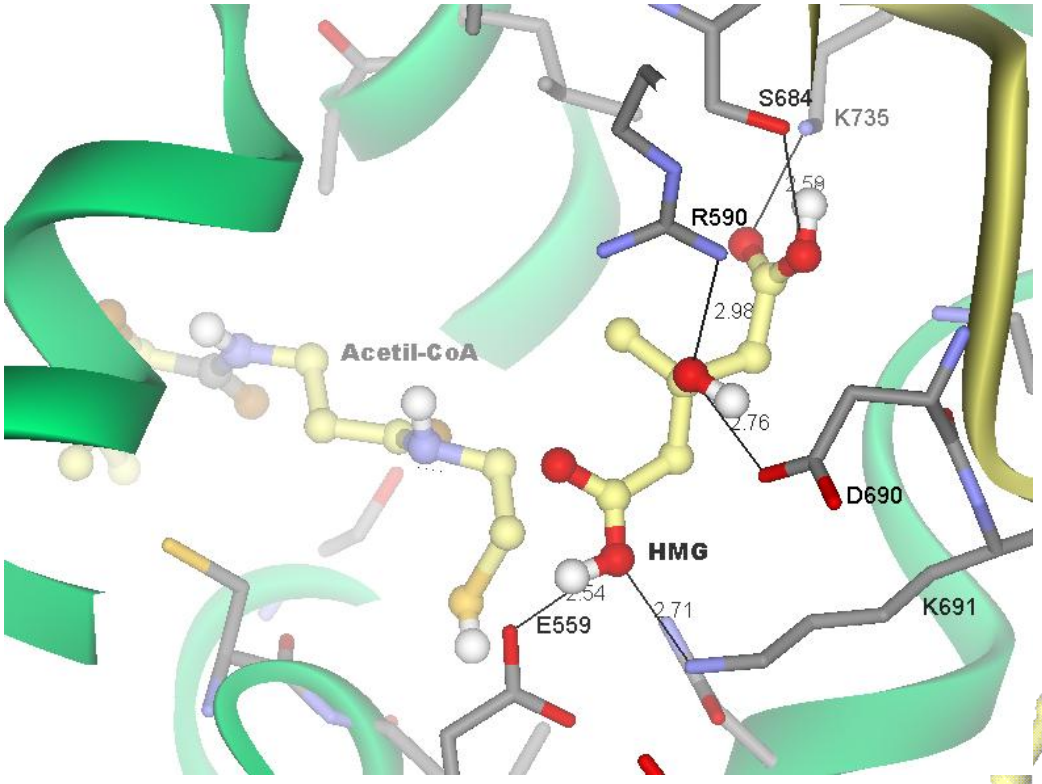
Sítio ativo da HMGR complexada com rosuvastatina

Istvan, E. S., Deisenhofer, J. *Science* (2001), **292**, 1160.

Resíduos de interações polares
Ser684, Asp690, Lys691, Lys692

Resíduos de interações VDW: Leu562, Val683, Leu853, Ala856, Leu857

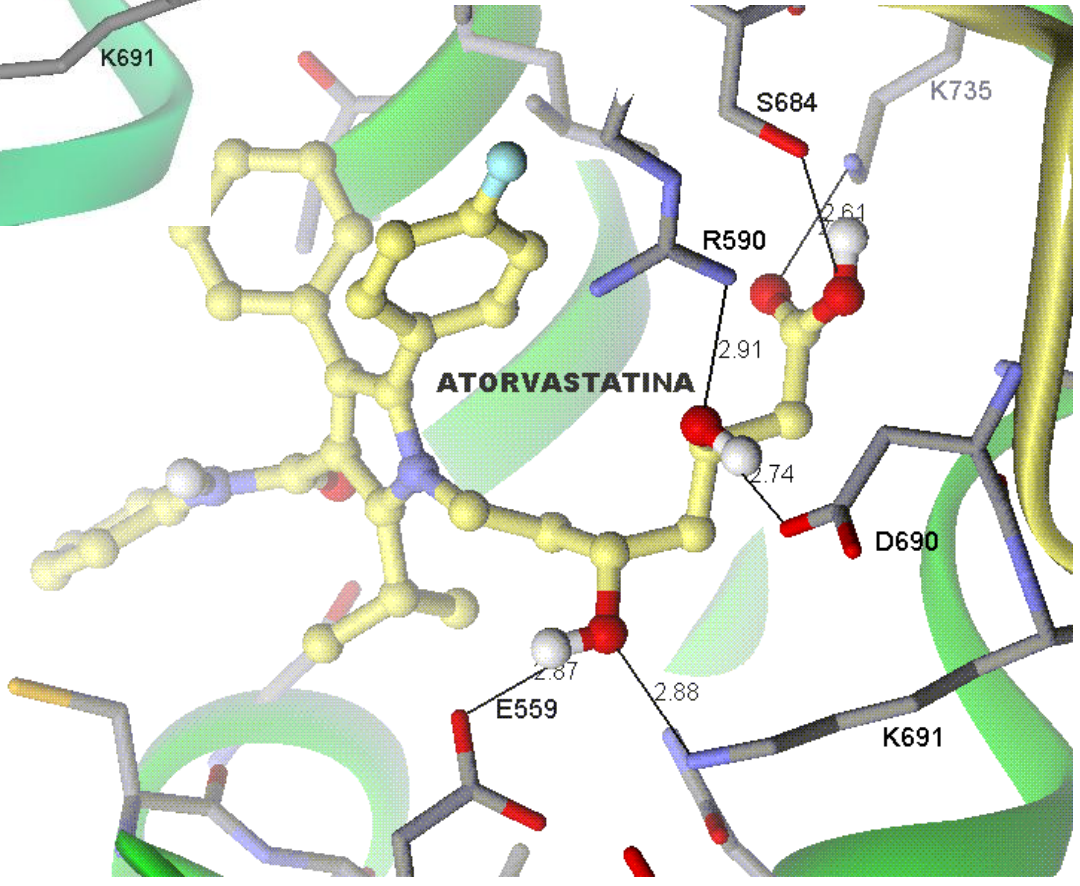


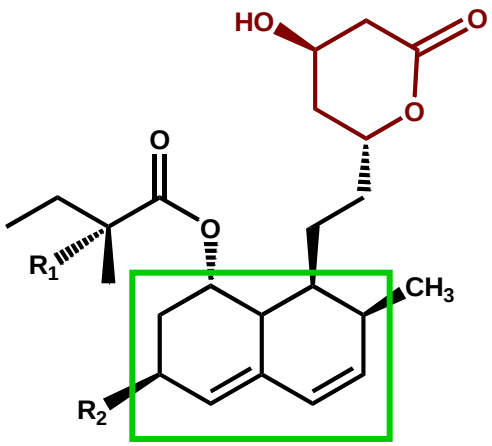


Interações do análogo do produto (HMG) no sítio ativo da HMGCoA redutase

S – serina
R – arginina
E – ácido glutâmico
D – ácido aspártico
K – lisina

Interações da Atorvastatina no sítio ativo da HMGCoA redutase

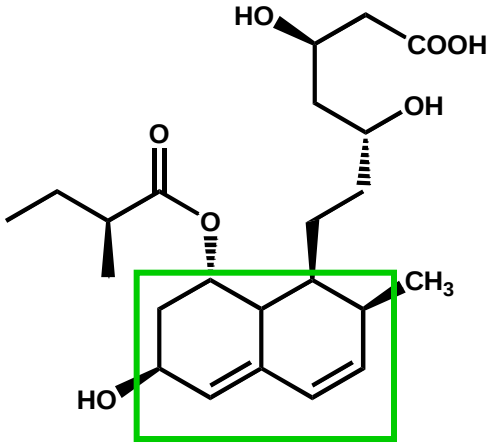




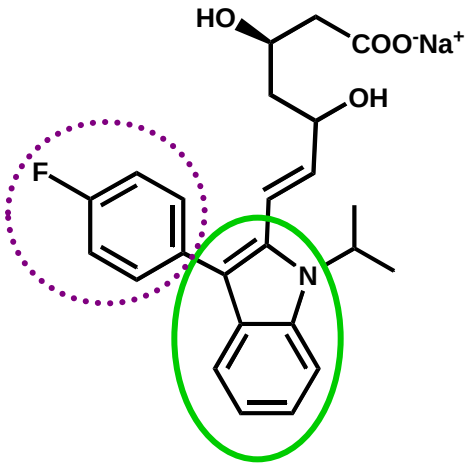
Lovastatina
(Mevacor)
Sinvastatina
(Zocor)

R_1=H; R_2=CH_3

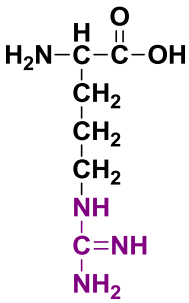
R_1=R_2=CH_3



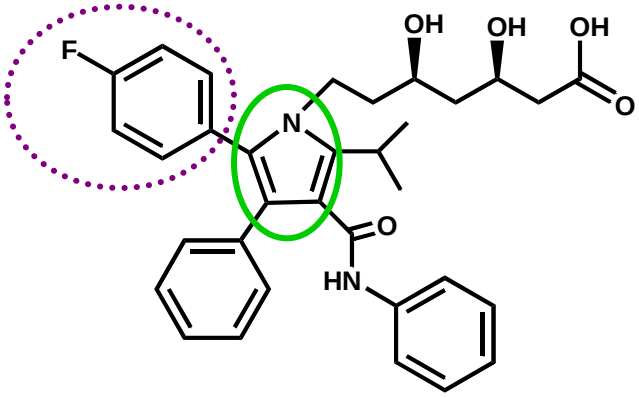
Pravastatina
(Pravachol, Mevalotin)



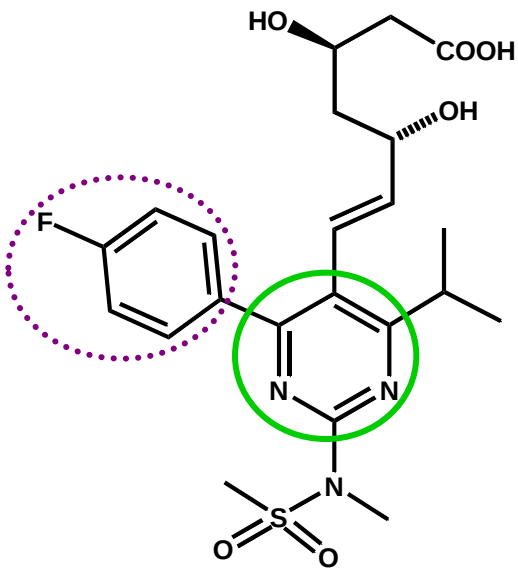
Fluvastatina
(Lescol)



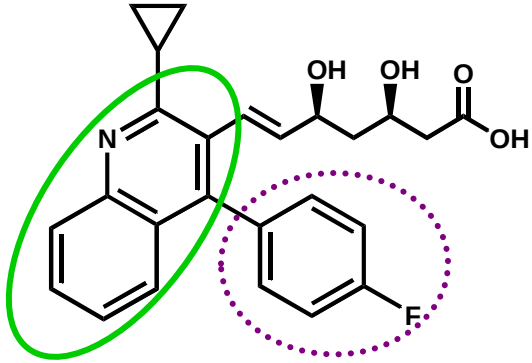
Grupo 4-fluorfenil nas estatinas sintéticas estabelece interações adicionais com o grupo guanidínico da Arg590



Atorvastatina
(Lipitor)



Rosuvastatina
(Crestor)



Pitavastatina
(Livalo)

Afinidades de algumas estatinas e do substrato HMG-CoA pelo sítio ativo da enzima HMG-CoA redutase

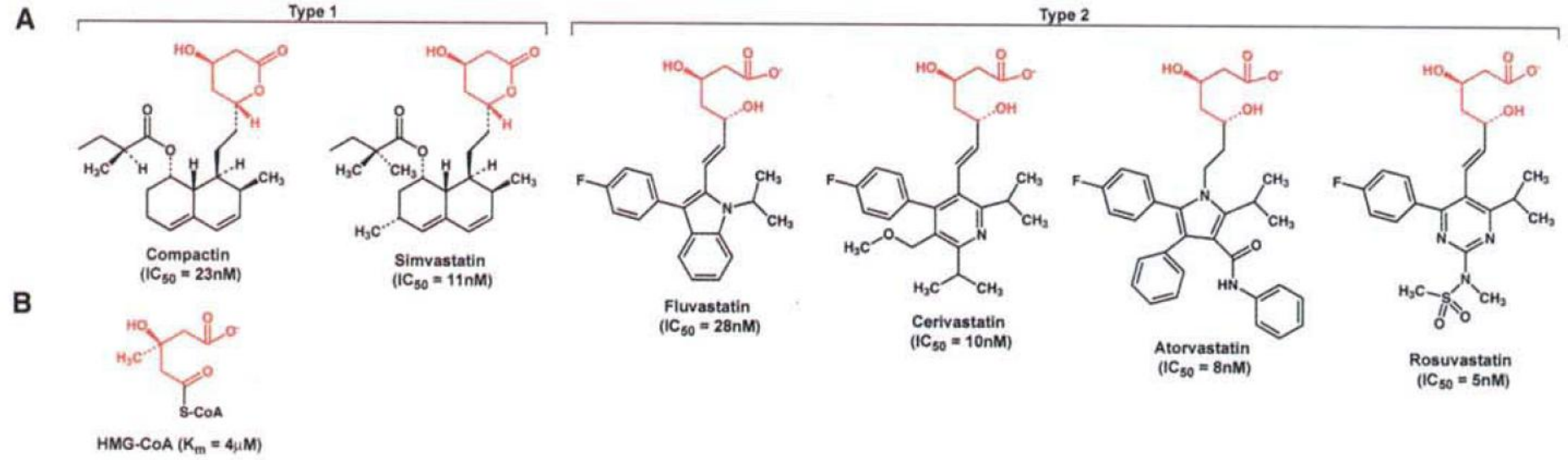


Fig. 1. Structural formulas of statin inhibitors and the enzyme substrate HMG-CoA. (**A**) Structure of several statin inhibitors. Compactin and simvastatin are examples of type 1 statins; not shown are the other type 1 statins, lovastatin and pravastatin. Fluvastatin, cerivastatin, atorvastatin, and rosuvastatin are type 2 statins. The HMG-like moiety that is conserved in all statins is colored in red. The IC_{50} (median inhibitory concentration) values of the statins are indicated (*21*). (**B**) Structure of HMG-CoA. The HMG-moiety is colored in red, and the K_m value of HMG-CoA is indicated (*7*).

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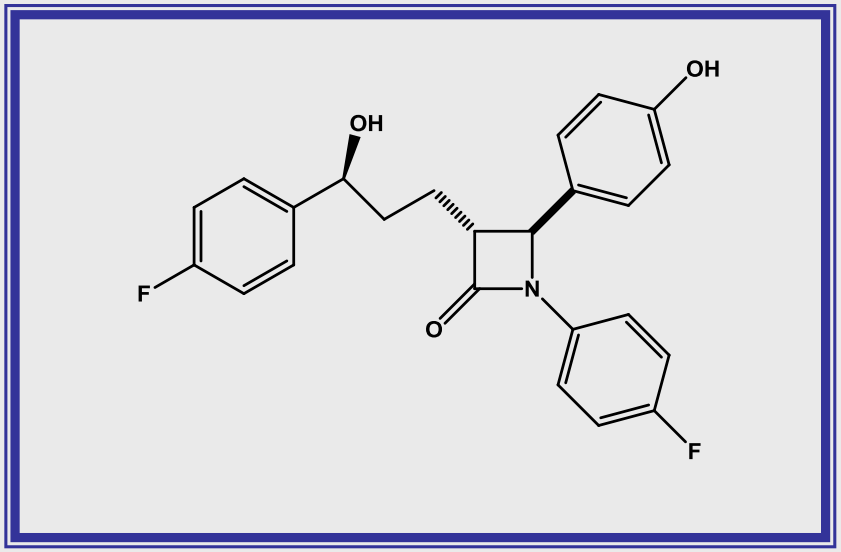
Istvan, E. S., Deisenhofer, J. *Science* (2001), **292**, 1160.



Ezetimiba é um medicamento aprovado em 2002 pelo FDA e usado para tratamento de dislipidemias, visando a redução dos níveis de colesterol e lipídeos no sangue.

Atua reduzindo a absorção de colesterol no intestino

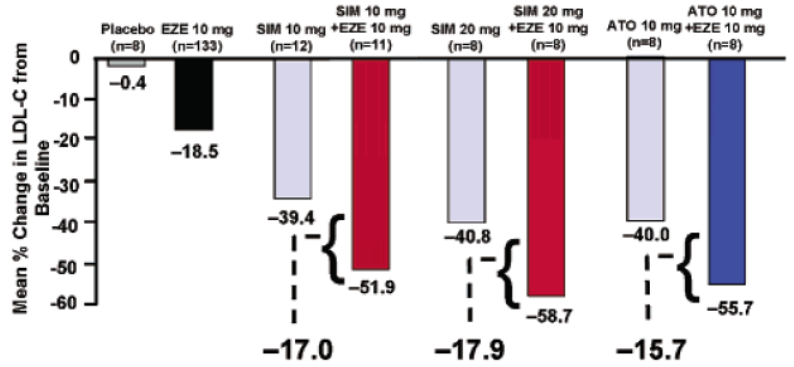


Figure 10. Ezetimibe coadministered with simvastatin or atorvastatin.

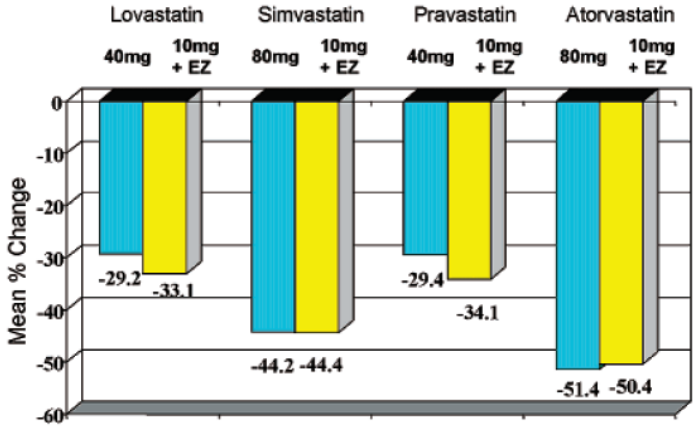


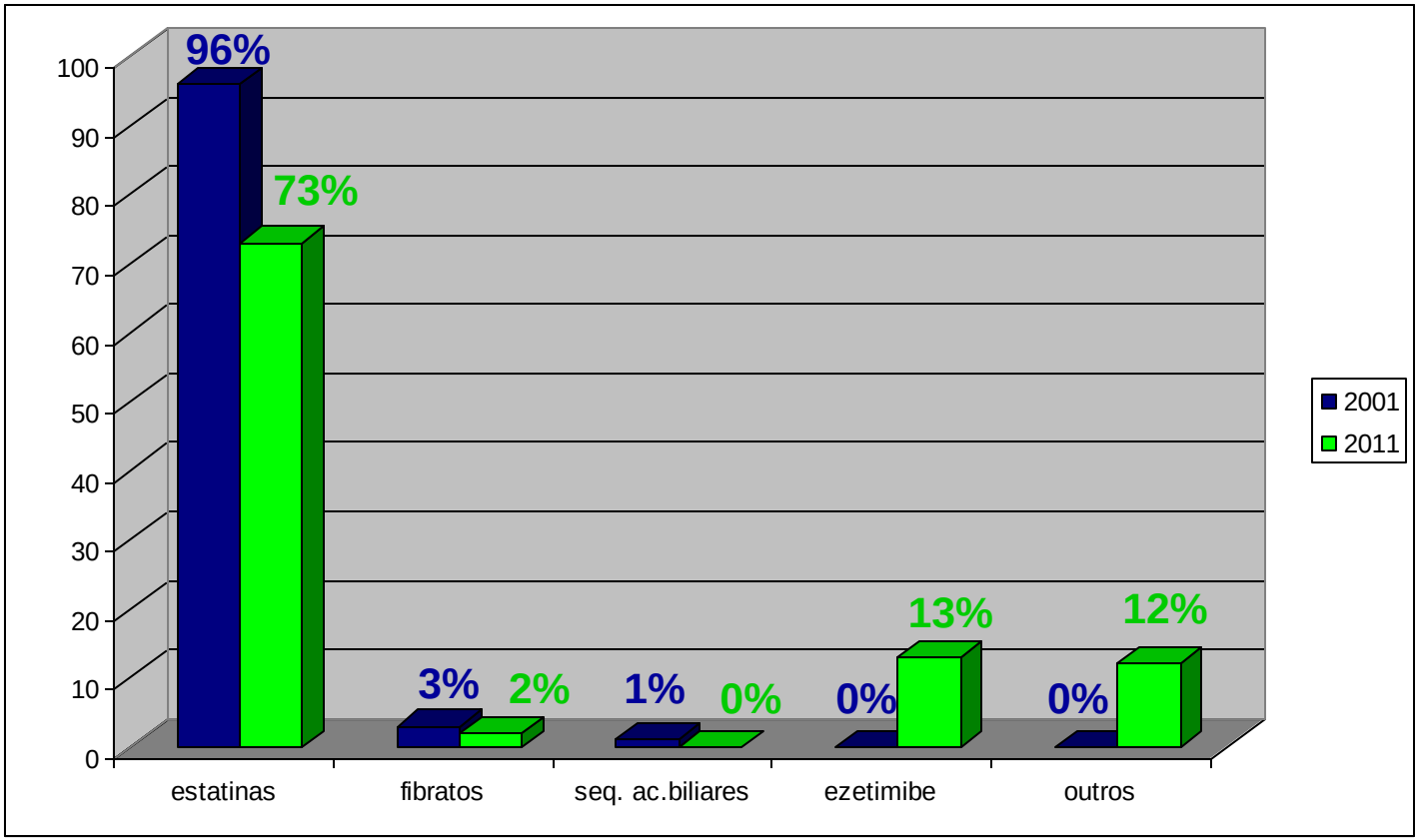
Figure 11. Effect of high- and low-dose statin coadministered with ezetimibe.

Clader, JW. *J. Med. Chem.* **2004**, 47, 1-9

Pode ser usado isoladamente quando outras medicações para reduzir o colesterol não são toleradas, ou em conjunto com estatinas (p.ex. ezetimiba/sinvastatina) quando os níveis de colesterol não são adequadamente controlados com estatinas isoladamente.

O medicamento é comercializado pela Schering-Plough e pela Merck Sharp and Dohme com os nomes *Ezetrol*, *Zetia* e *Ezemibe*.

Usos de classes fármacos para controle de dislipidemias



J. Earl & P. Kirkpatrick *Nature Rev. Drug Discov.* **2003**, 2, 97-98