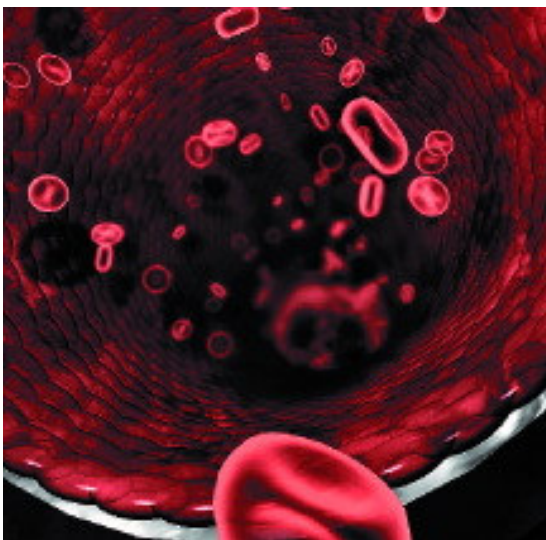




ESTATINAS HIPOLIPÊMICAS

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”

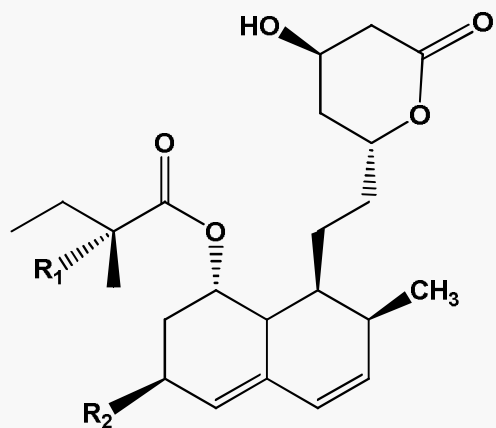
Ou: Foye's Principles of Medicinal Chemistry 6th Ed., 2008, Cap. 30., M. Harrold, p. 797-819

artigos

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

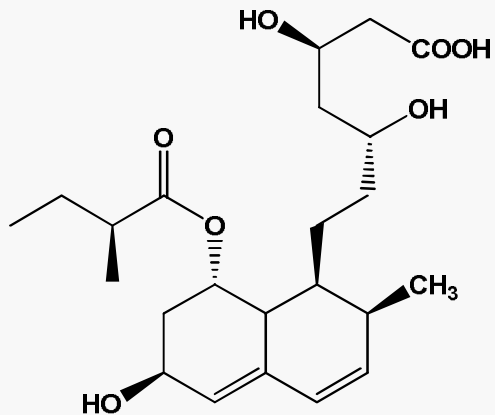
Istvan, E. S., Deisenhofer, J. Structural mechanism for statin inhibition of HMG-CoA reductase. *Science* 2001, 292, 1160-64.



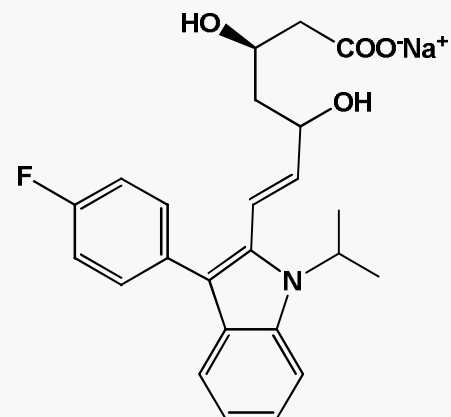


Lovastatina $R_1=H$; $R_2=CH_3$

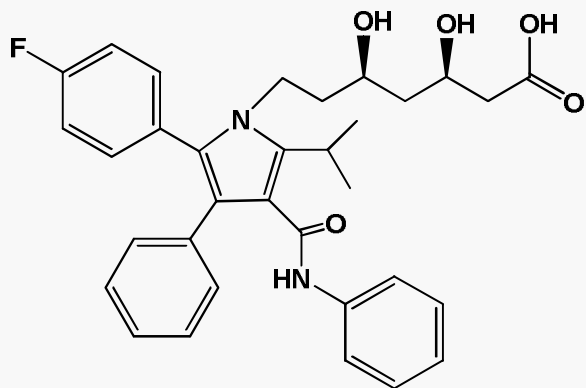
Sinvastatina $R_1=R_2=CH_3$



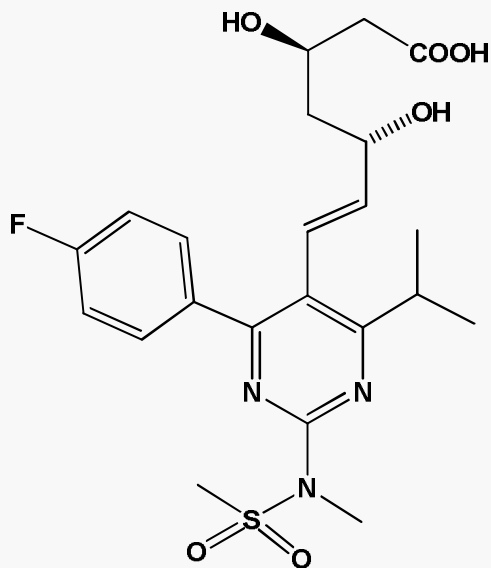
Pravastatina



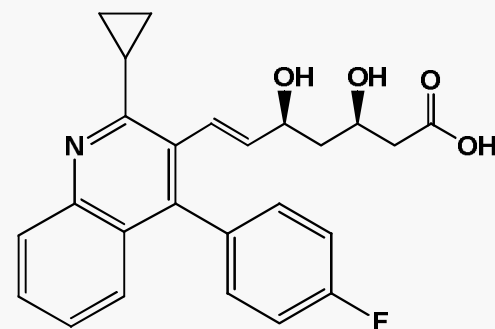
Fluvastatina



Atorvastatina



Rosuvastatina

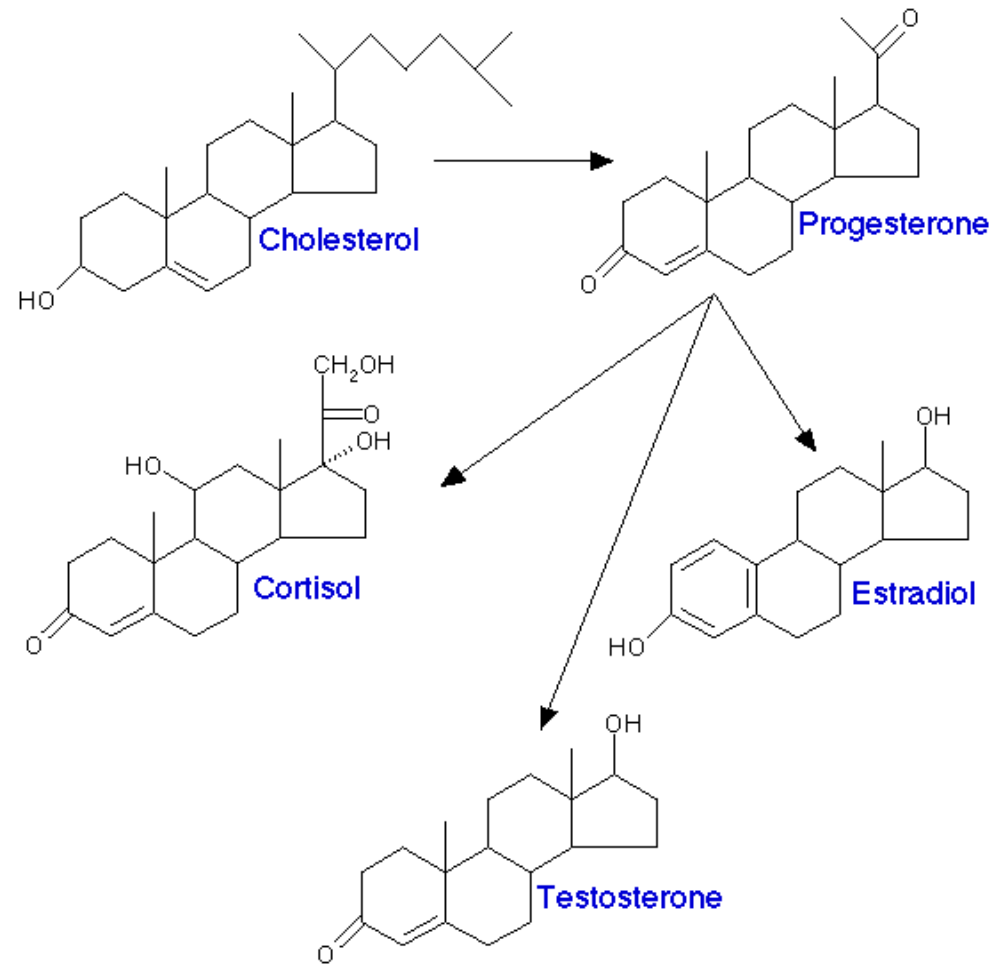


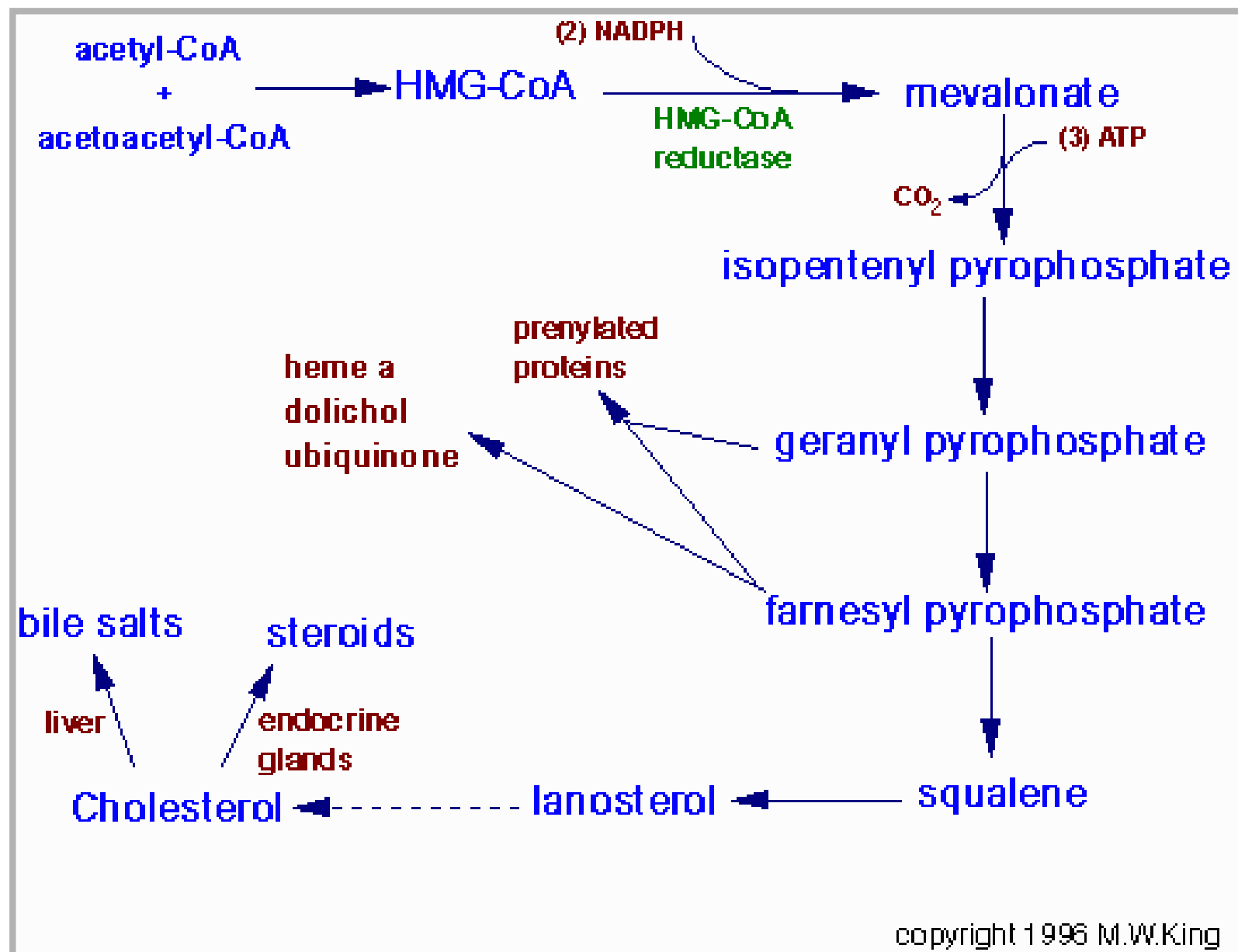
Pitavastatina

Importância do colesterol:

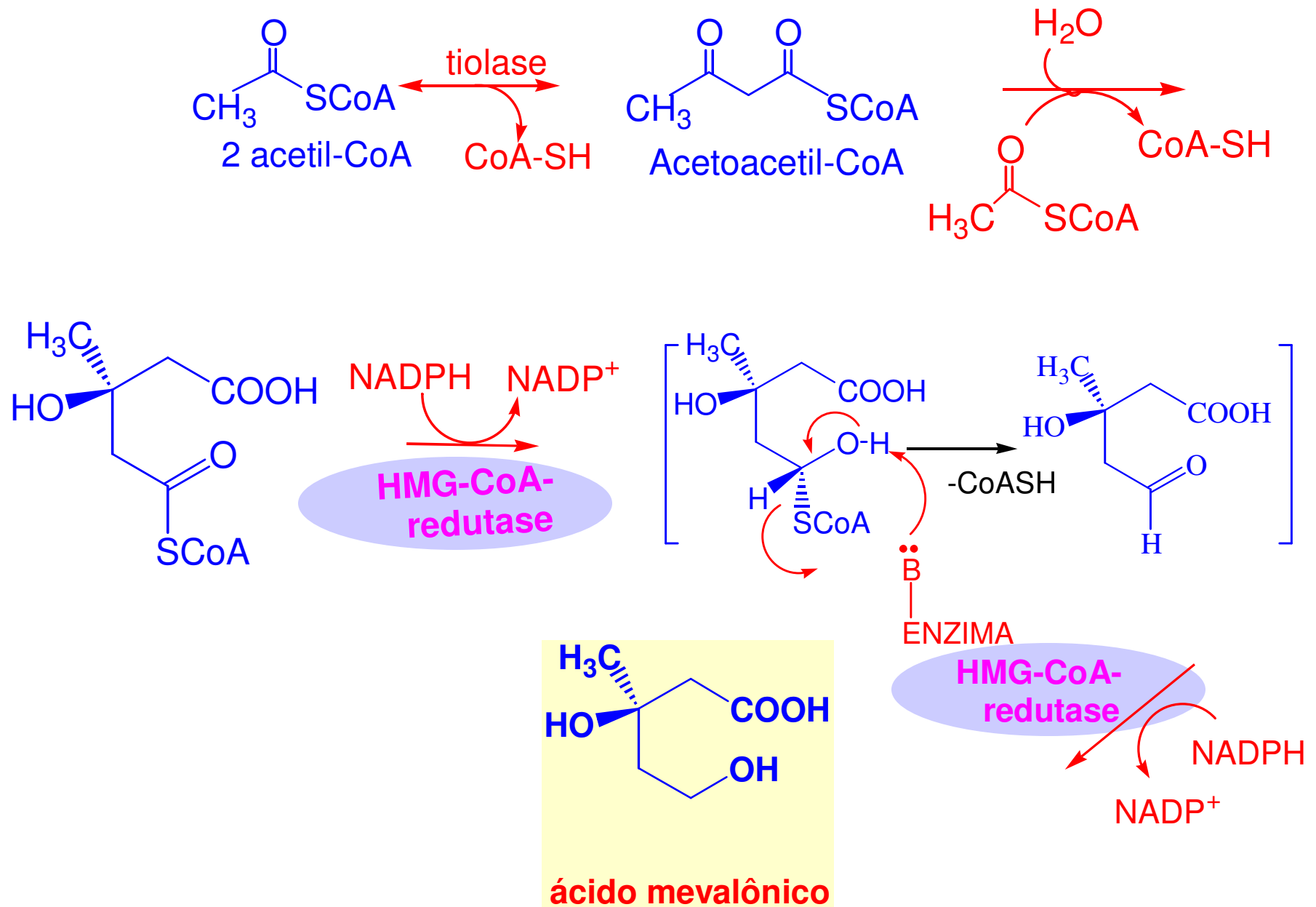
Aumento de estabilidade e modulação de permeabilidade das membranas celulares

Colesterol é precursor dos hormônios esteroidais, além da Vitamina D



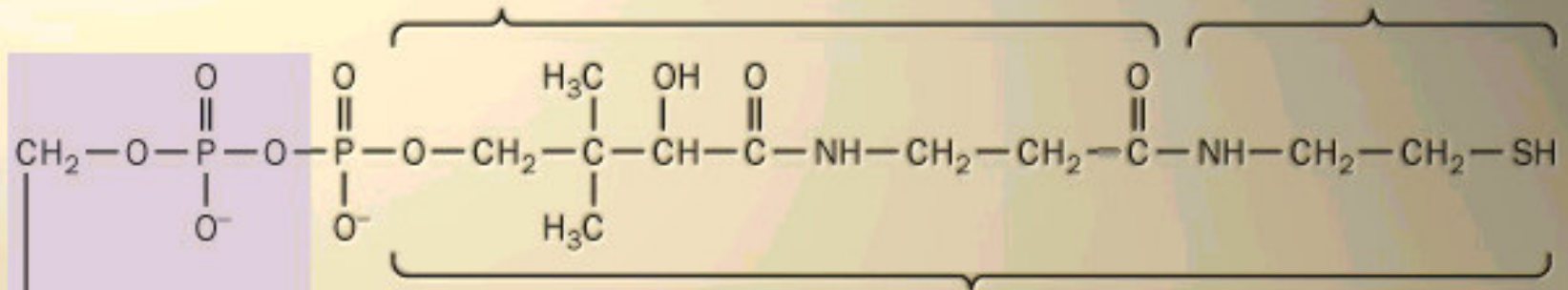


Etapa inicial de formação de ácido mevalônico

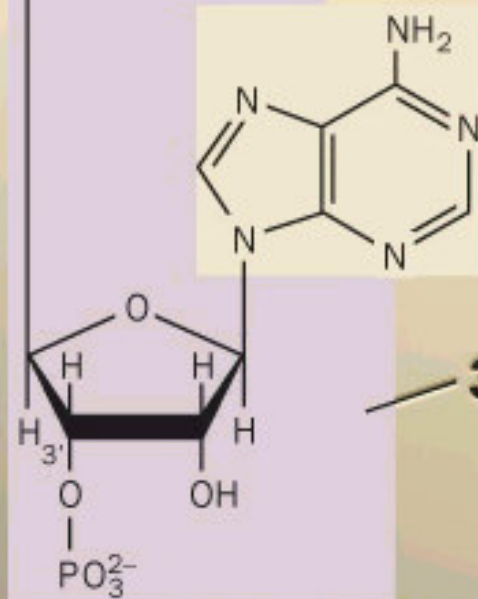


Pantothenic acid

β-Mercaptoethylamine



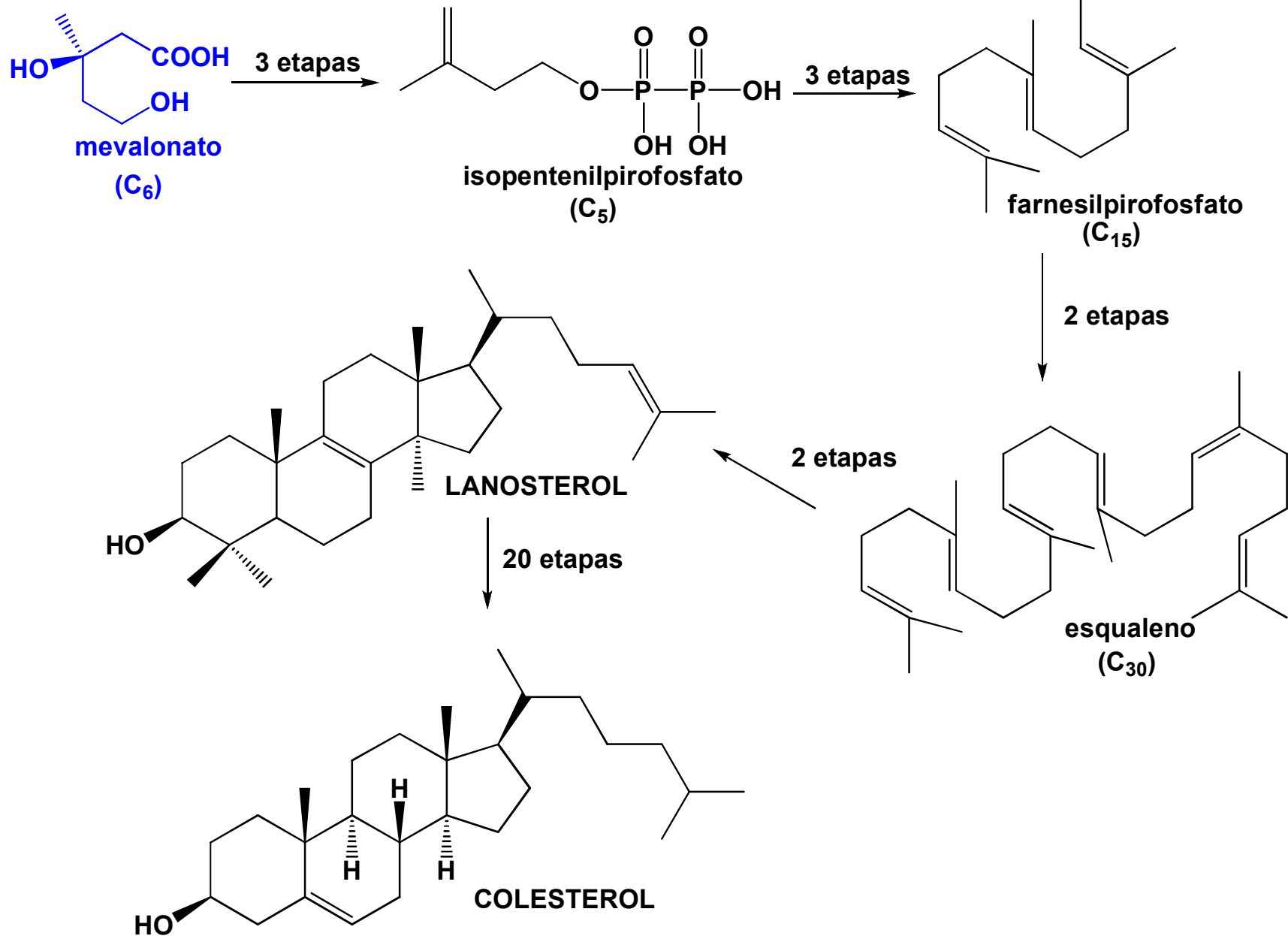
4-Phosphopantetheine



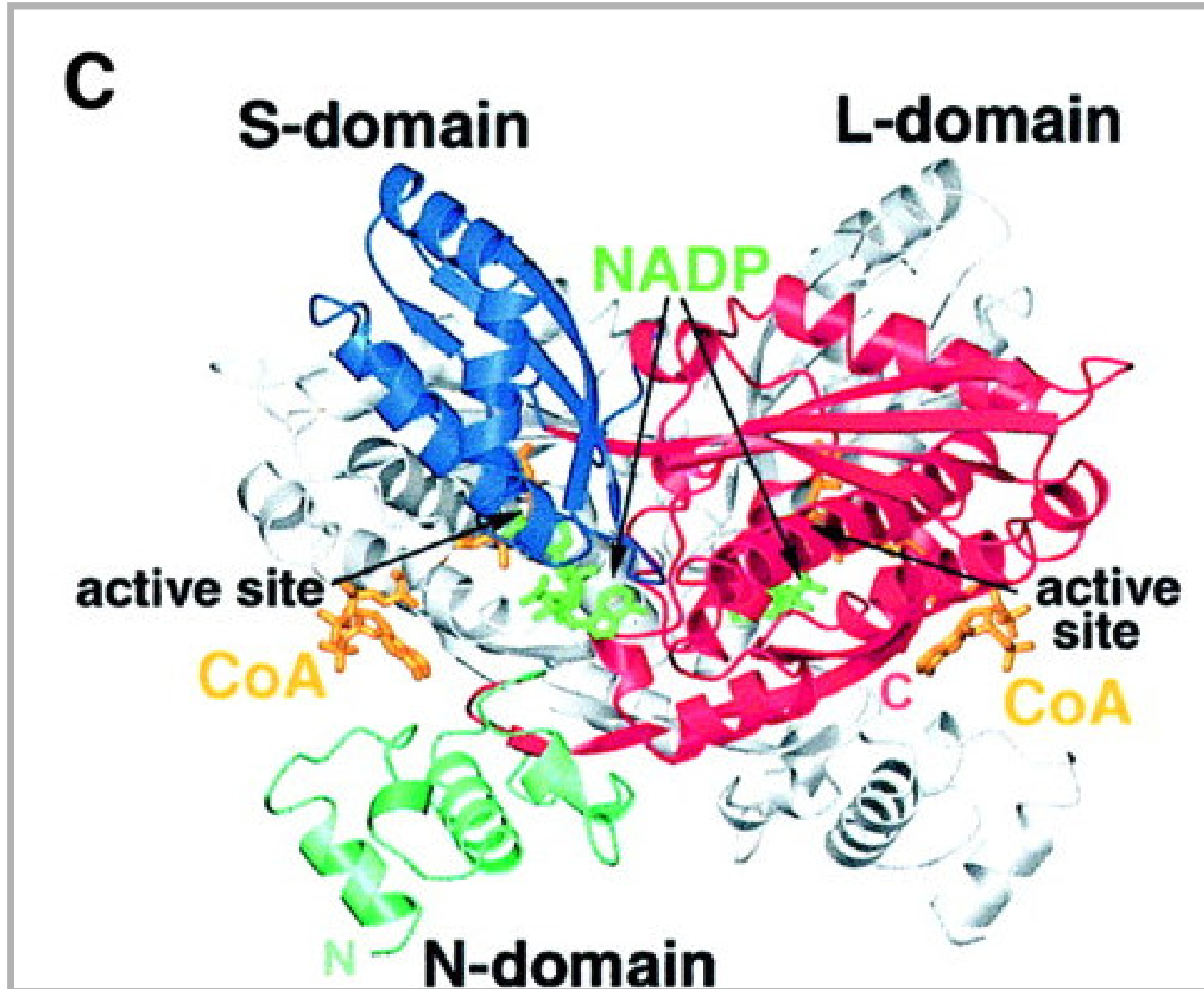
3',5'-ADP

COENZYME A (CoA)

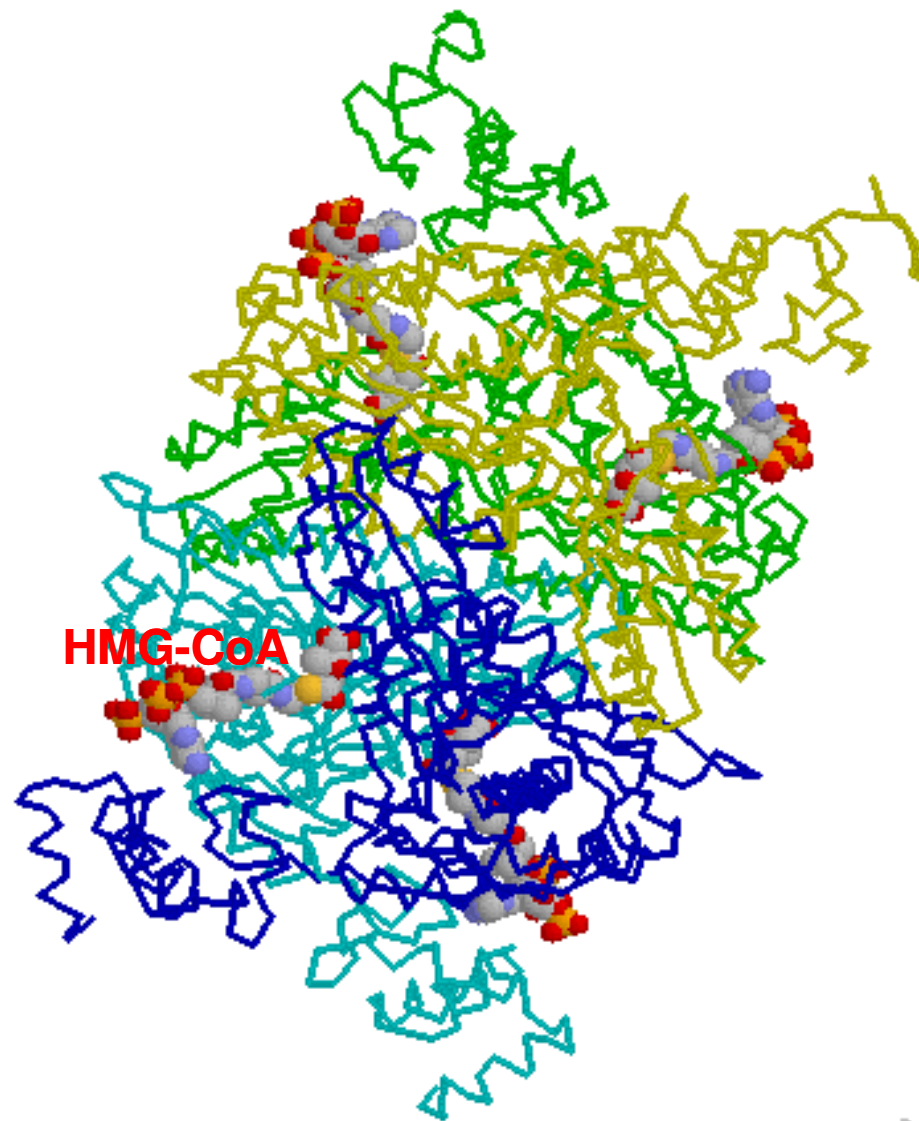
Formação de colesterol



HMG CoA reductase

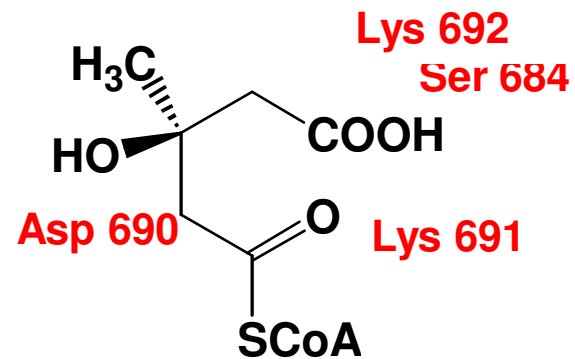


Sítio ativo da HMGCoA redutase

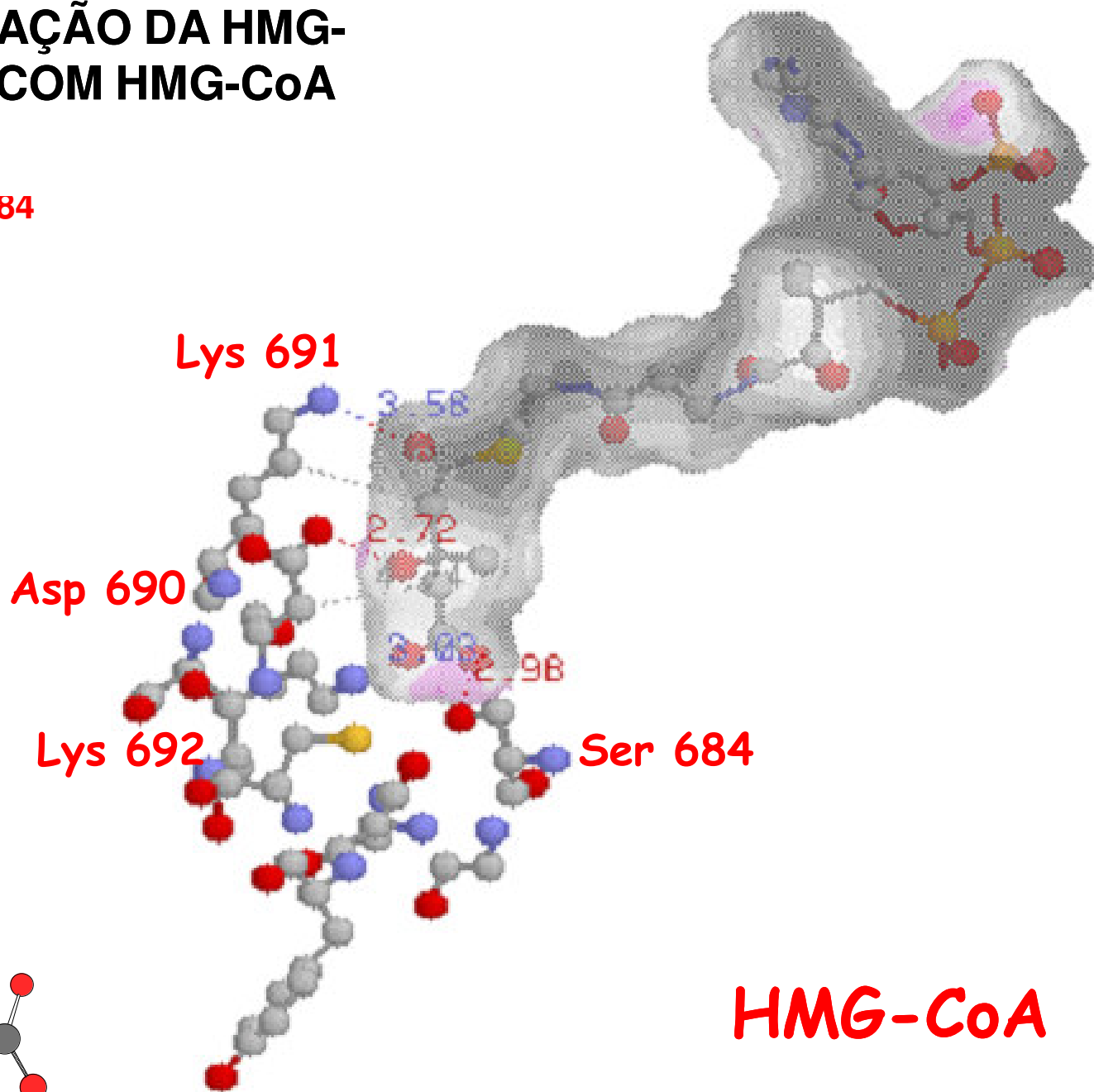
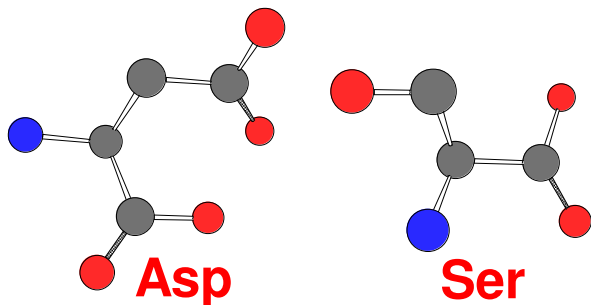
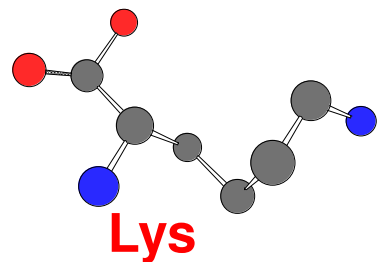


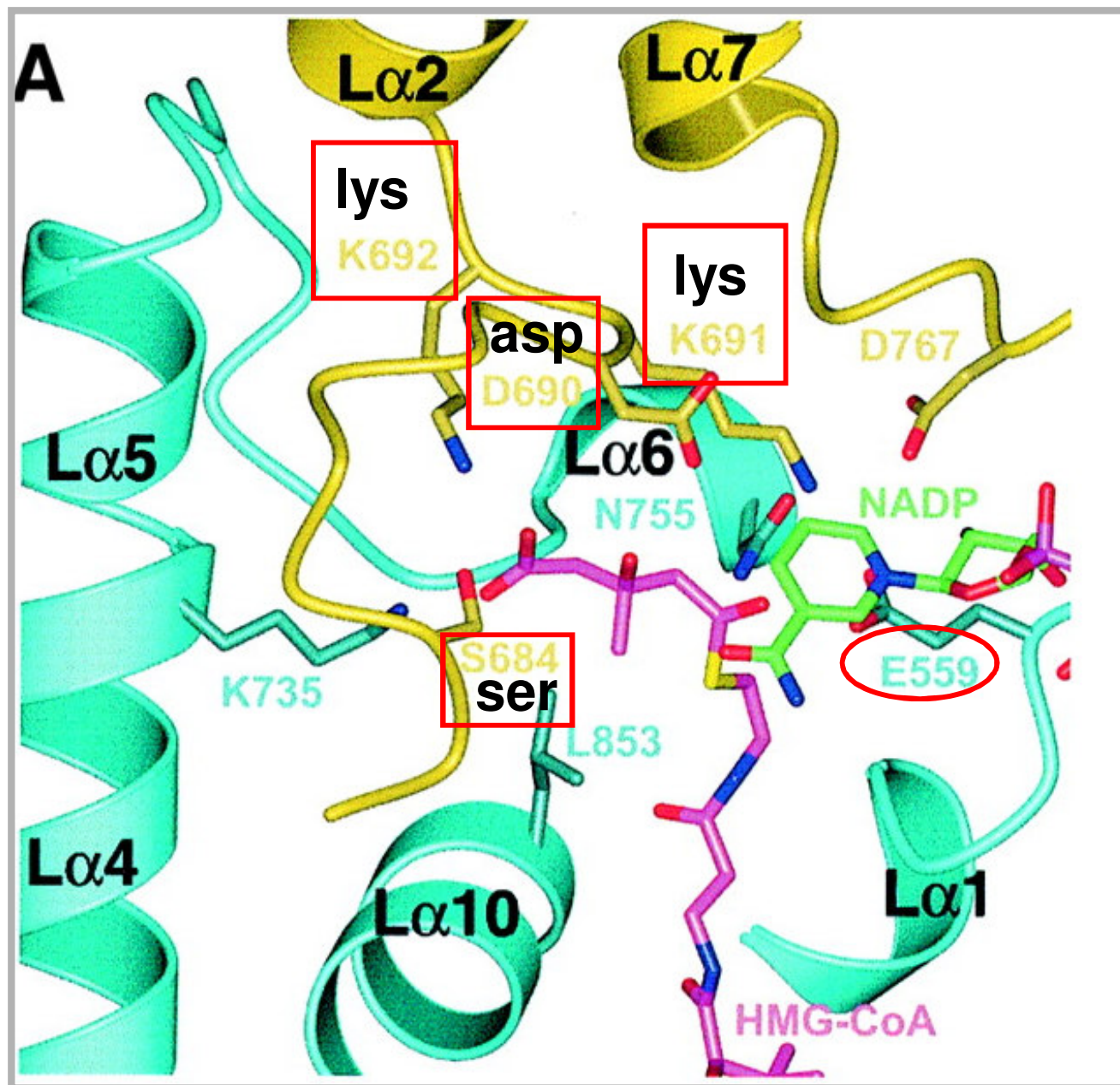
MDL

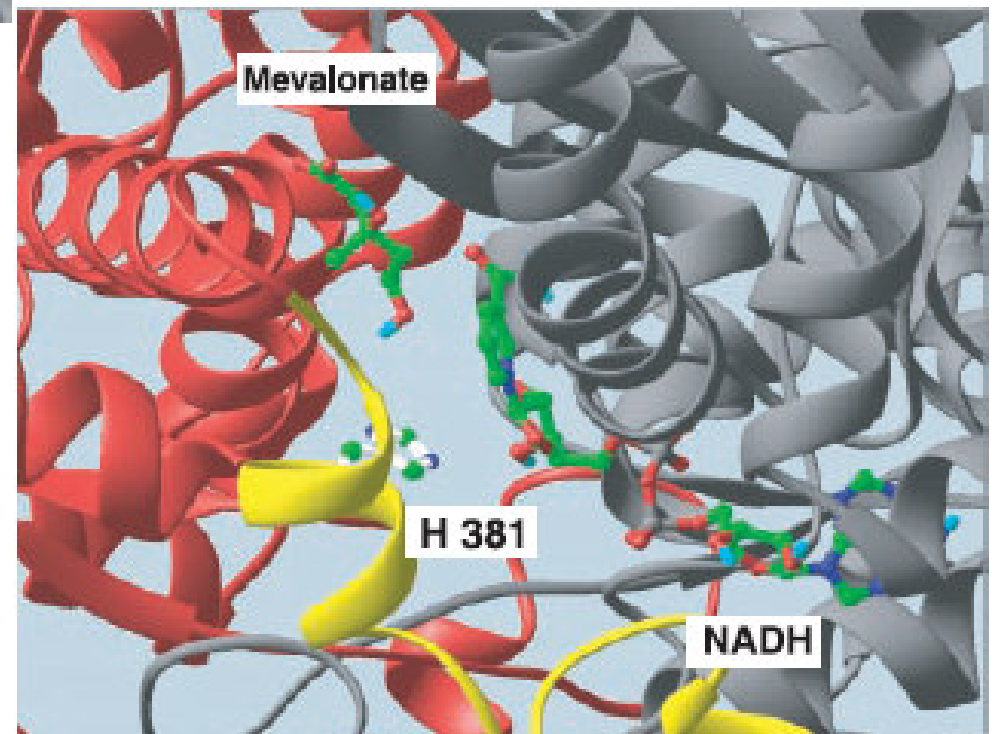
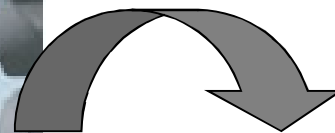
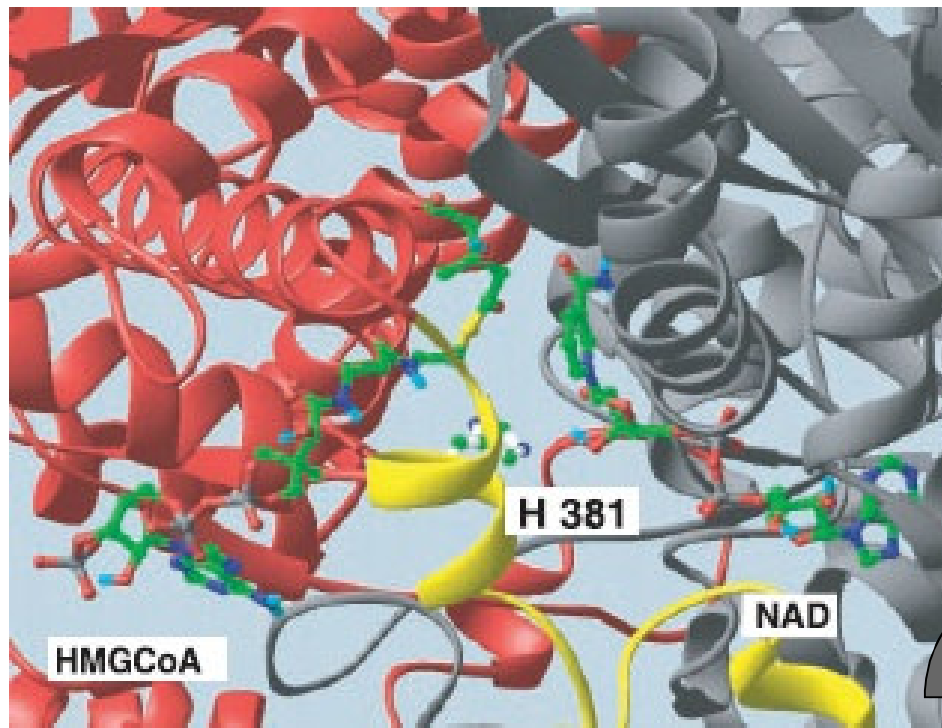
SÍTIOS DE INTERAÇÃO DA HMG-CoA REDUTASE COM HMG-CoA



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



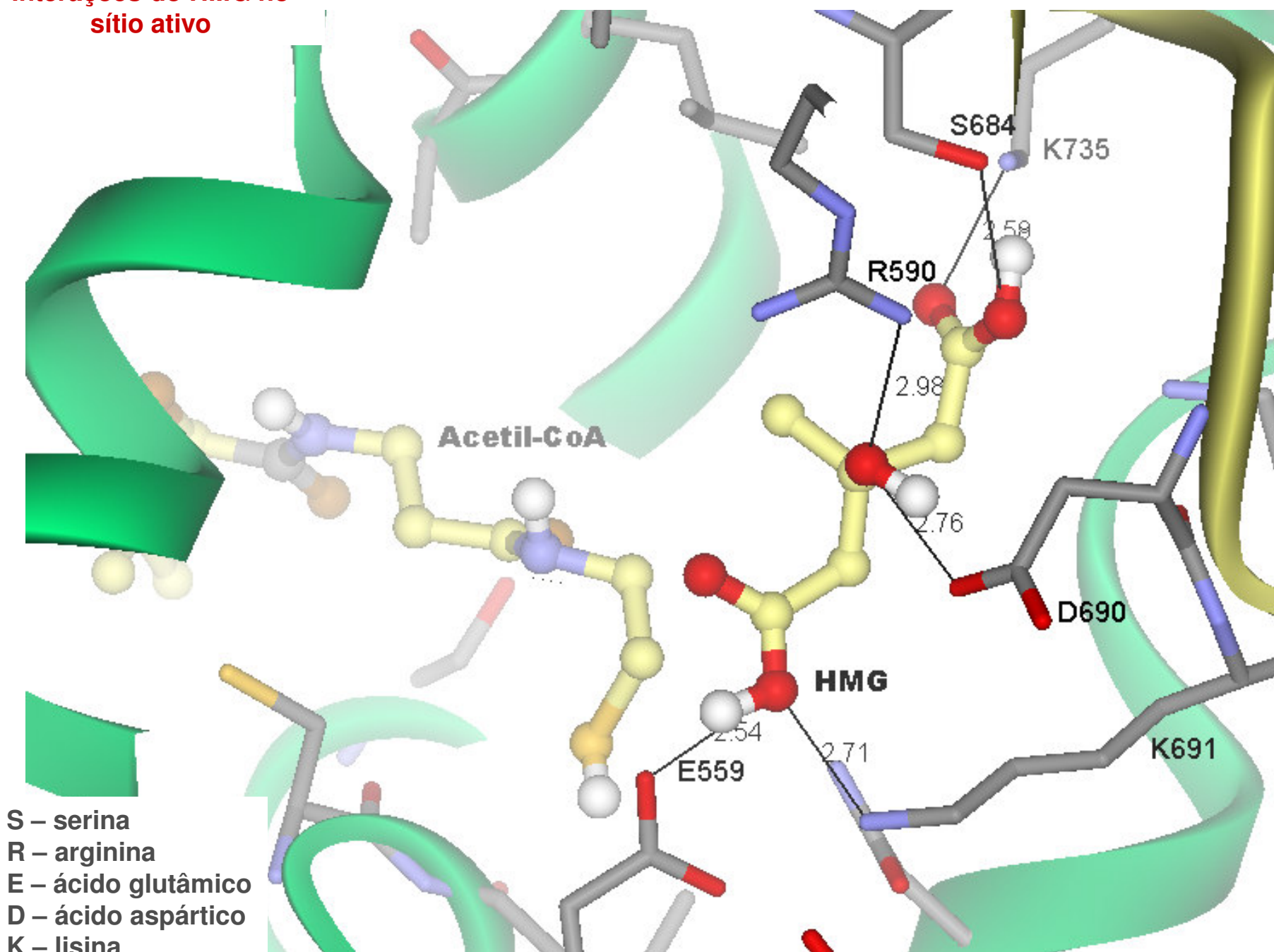




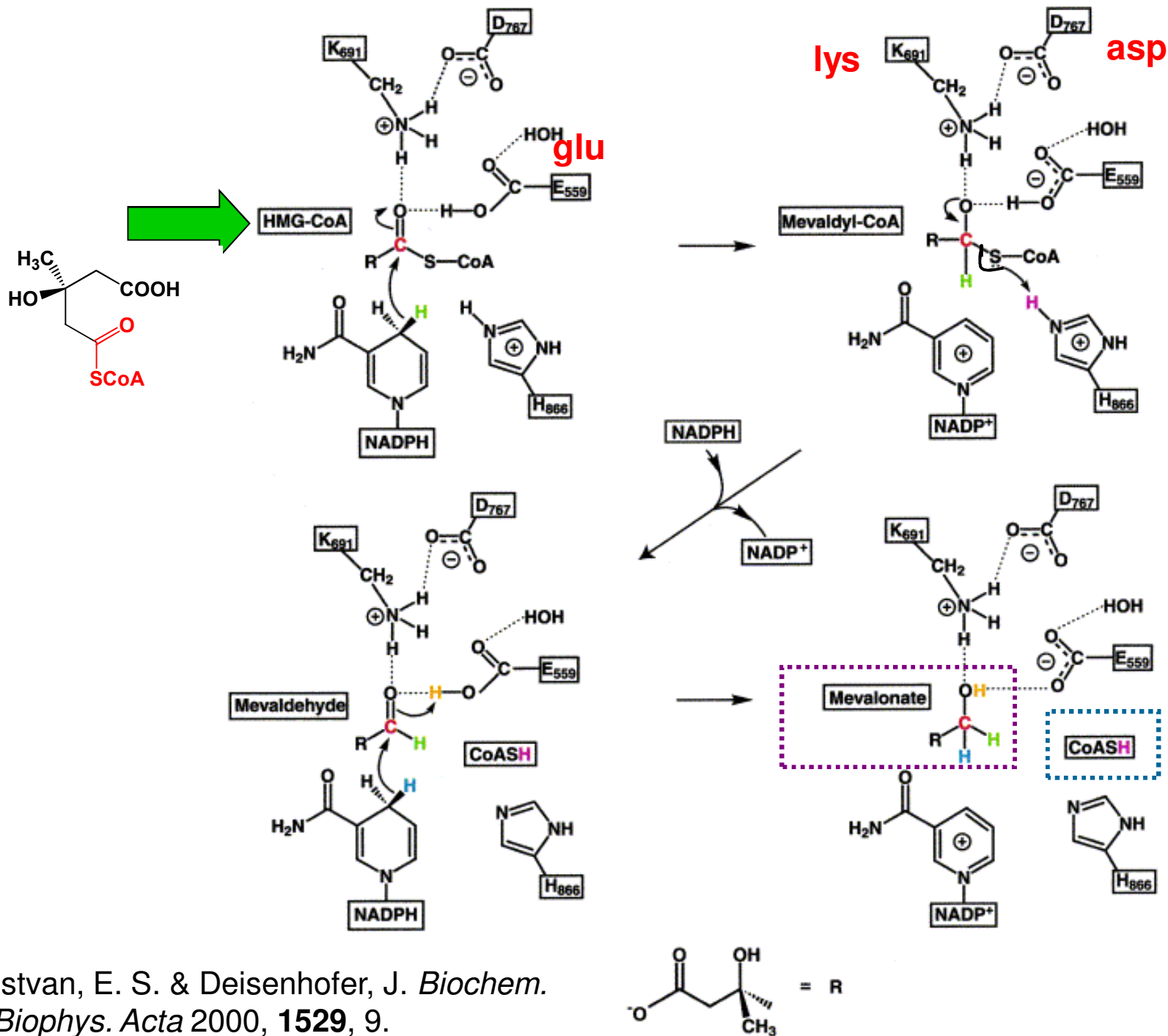
Tabernero et al.

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

**Interações do HMG no
sítio ativo**

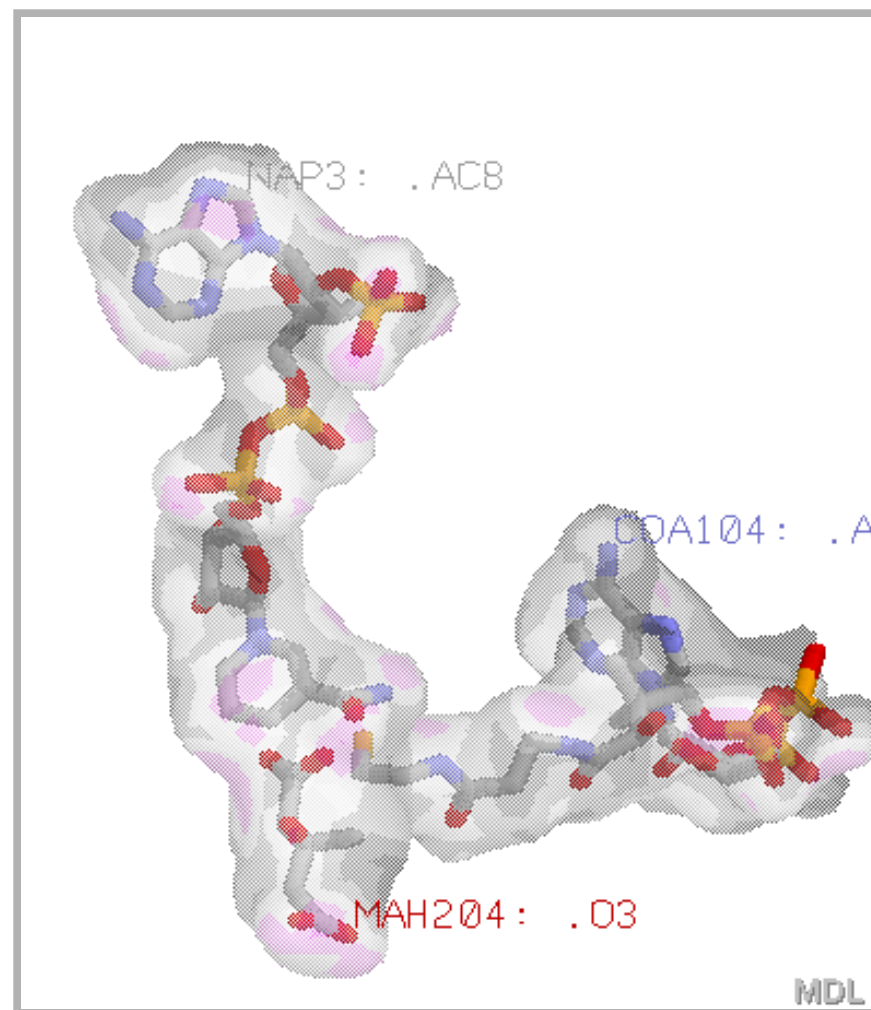
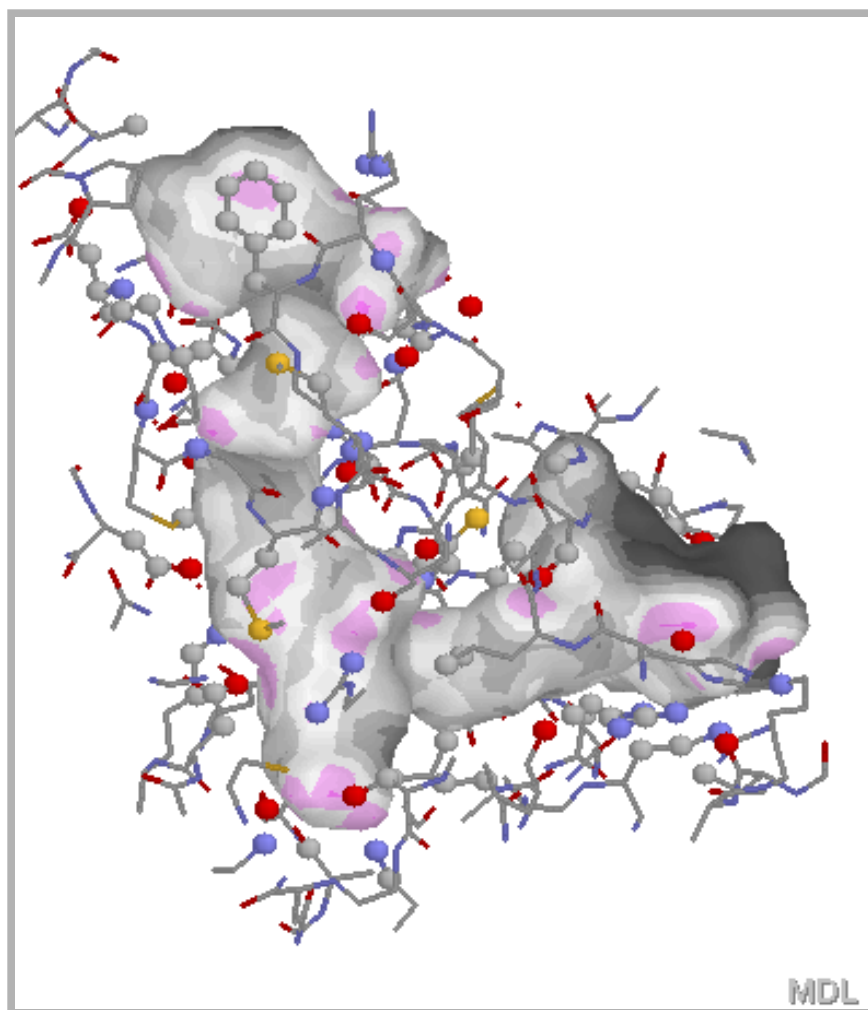


Grupo funcional do substrato	Resíduo que realiza interação	Força de Interação	Comentários
1-C=O	Glu559, Lys691*	ligação de hidrogênio	Promovem a polarização da carbonila para subsequente transferência de hidreto
3-C-OH	Asp690, Arg590	Ligação de hidrogênio	
3-C-CH ₃	Leu853	Van der Waals	
5-C-OH	Lys735	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

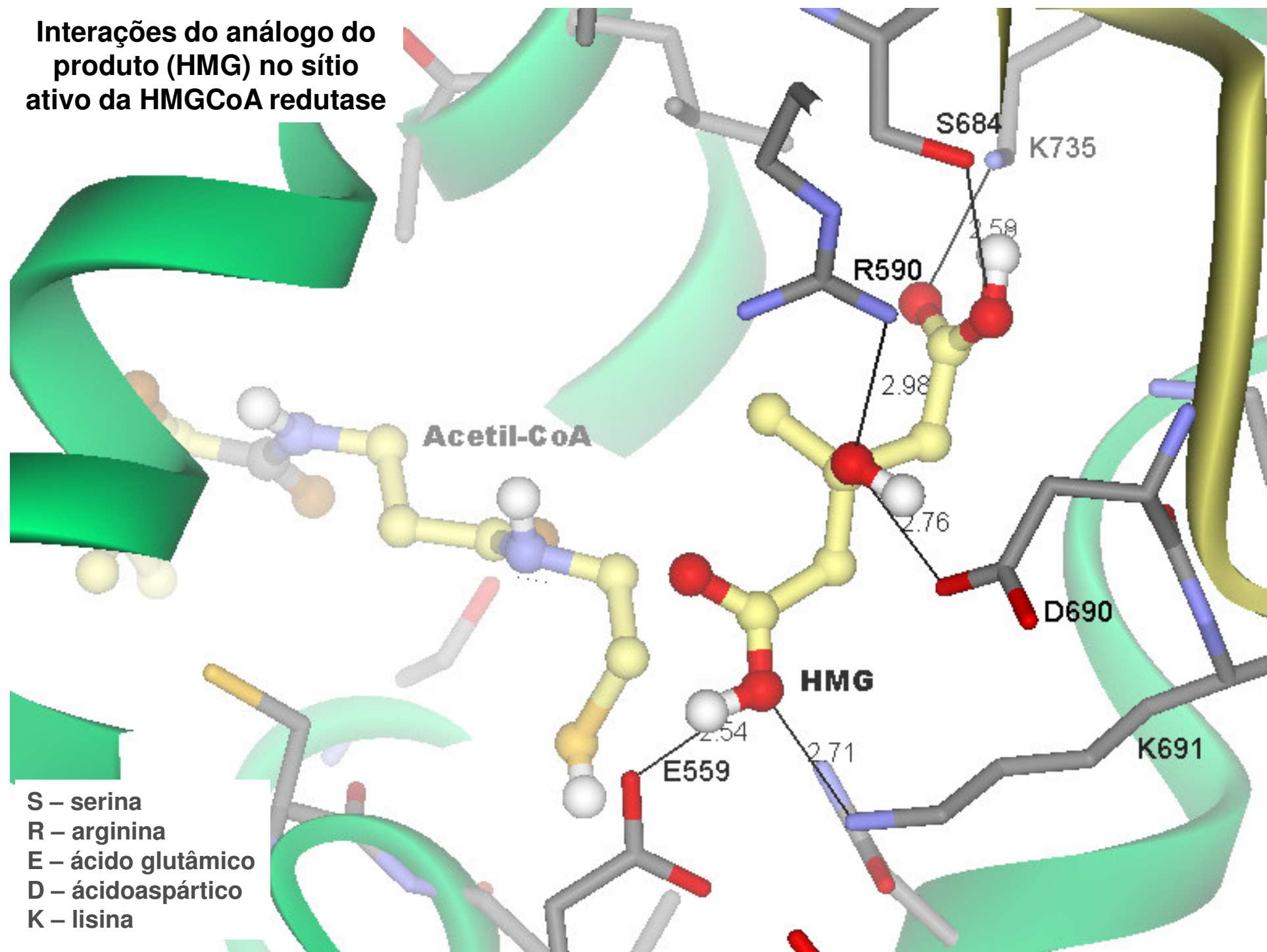


Istvan, E. S. & Deisenhofer, J. *Biochem. Biophys. Acta* 2000, **1529**, 9.

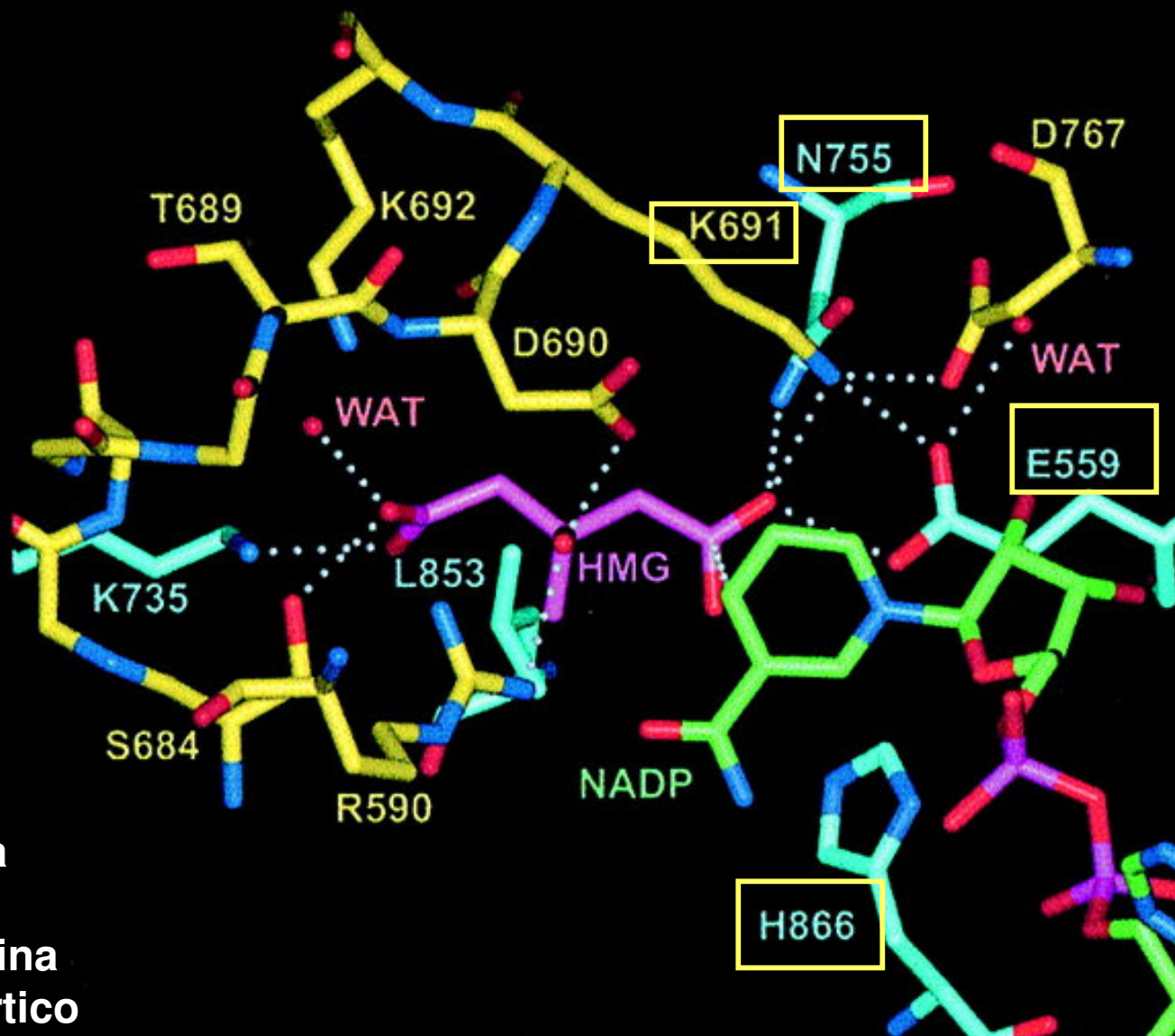
ligantes ác hidroxi-metilglutárico (análogo do produto), Acetil-CoA e NADPH



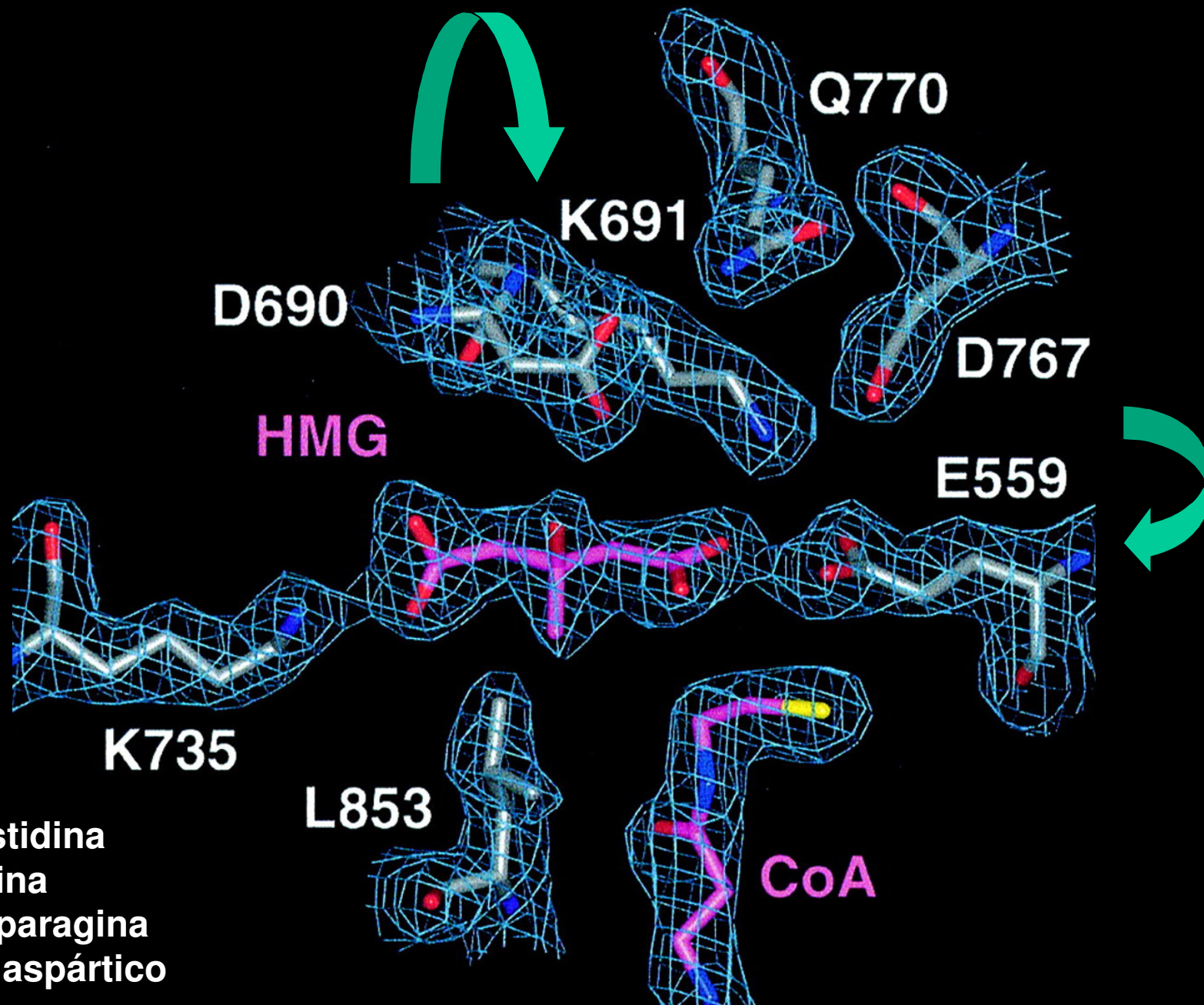
**Interações do análogo do
produto (HMG) no sítio
ativo da HMGCoA redutase**



INTERAÇÃO DOS LIGANTES NO SÍTIO CATALÍTICO



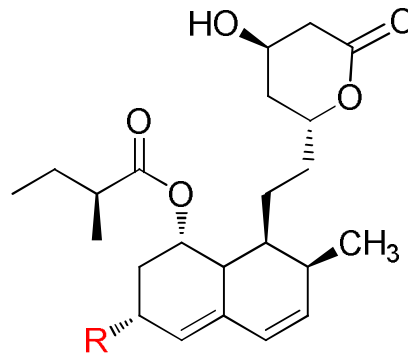
H histidina
K lisina
N asparagina
E ác aspártico





Mevastatina
Penicillium citrinum
(Sankyo
Pharmaceuticals)

Lovastatina / Mevastatina



R = CH₃ lovastatina (Mevacor)
R = H mevastatina (Compactin)

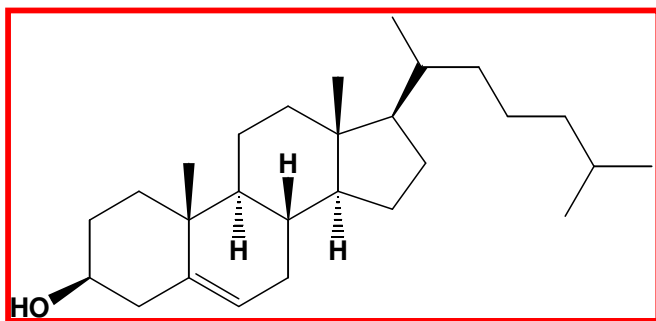


Lovastatina
Aspergillus terreus
(Merck)

Estatinas

**Novo e único mecanismo
de ação**

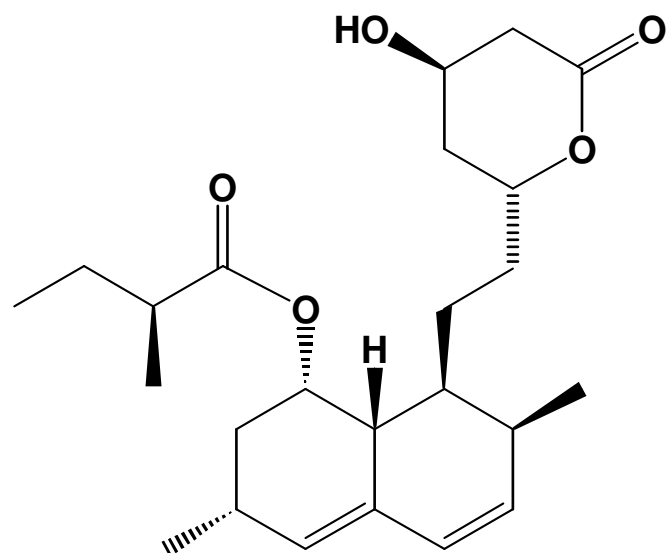
1987: introduzida no mercado



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

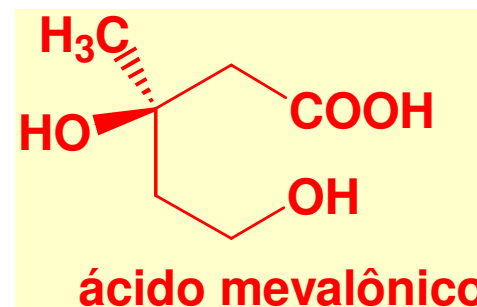
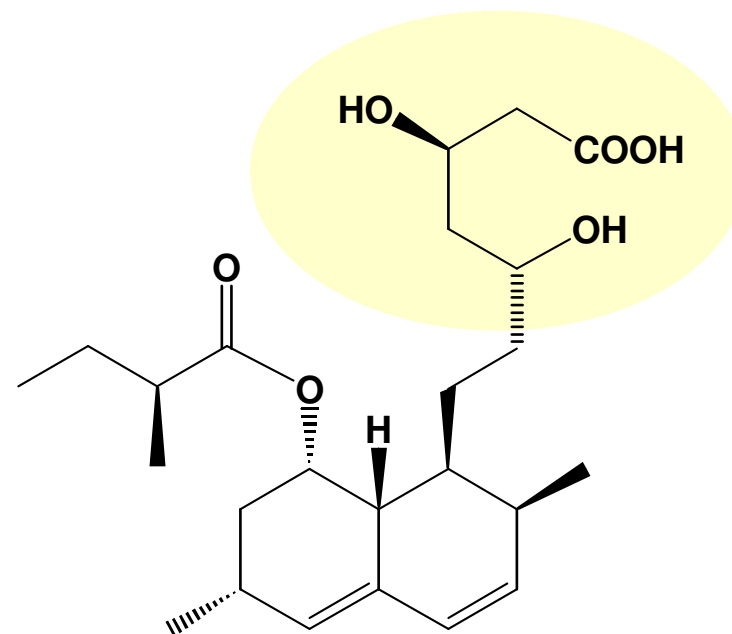




Lovastatina



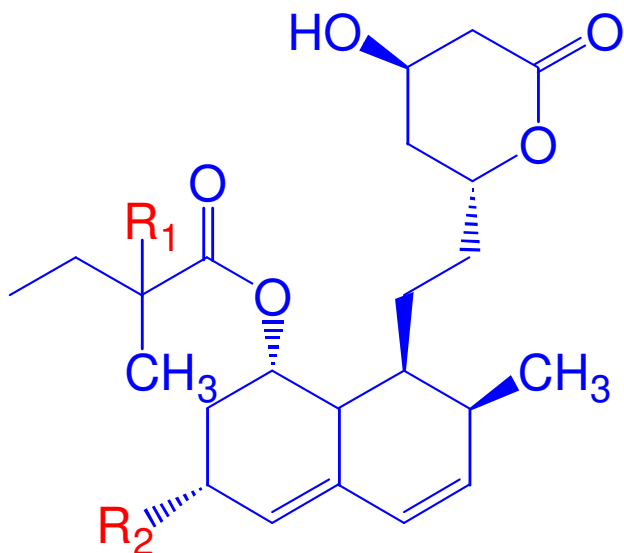
Pró-fármaco



ESTATINAS

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

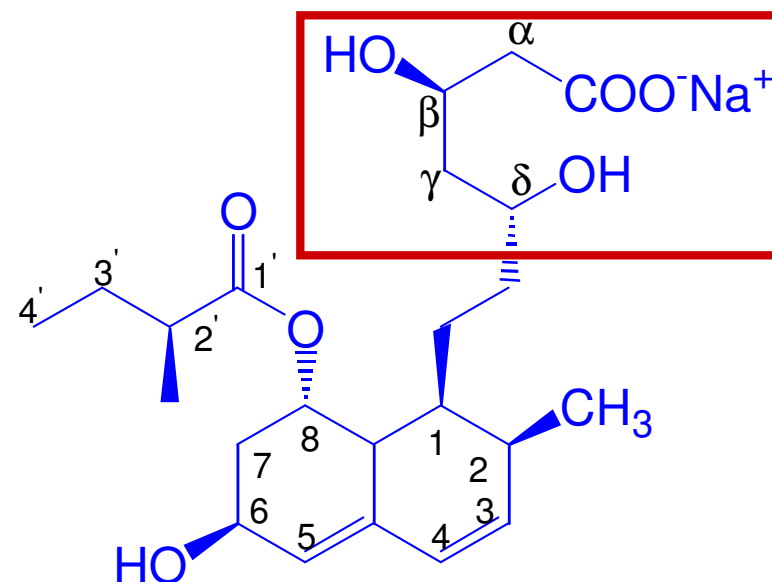
Primeira geração de fármacos:



Mevastatina $R_1=R_2=H$

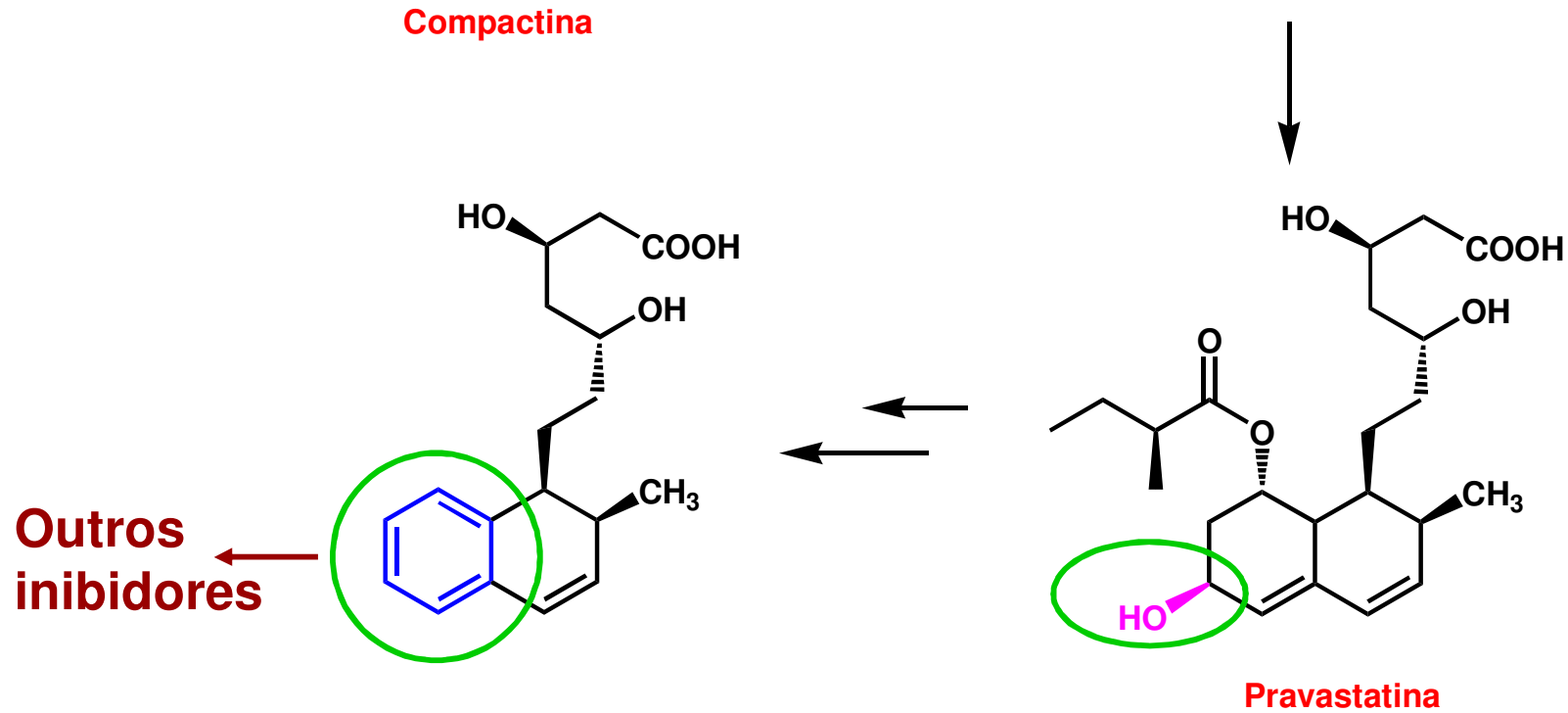
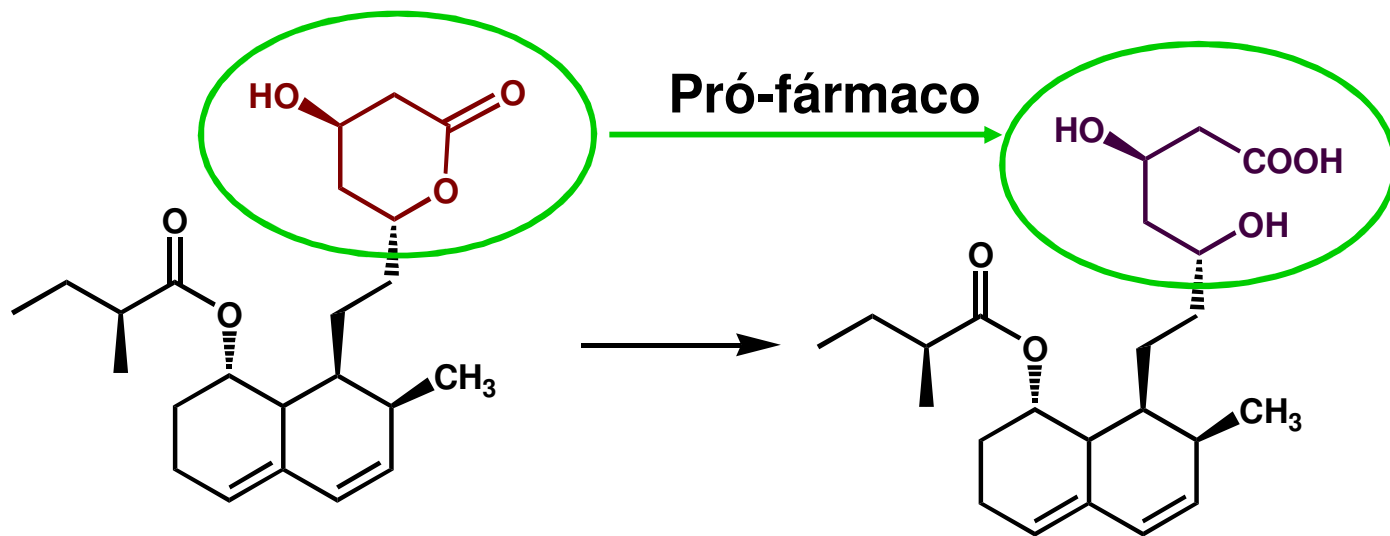
Lovastatina $R_1=H$; $R_2=CH_3$

Sinvastatina $R_1=R_2=CH_3$

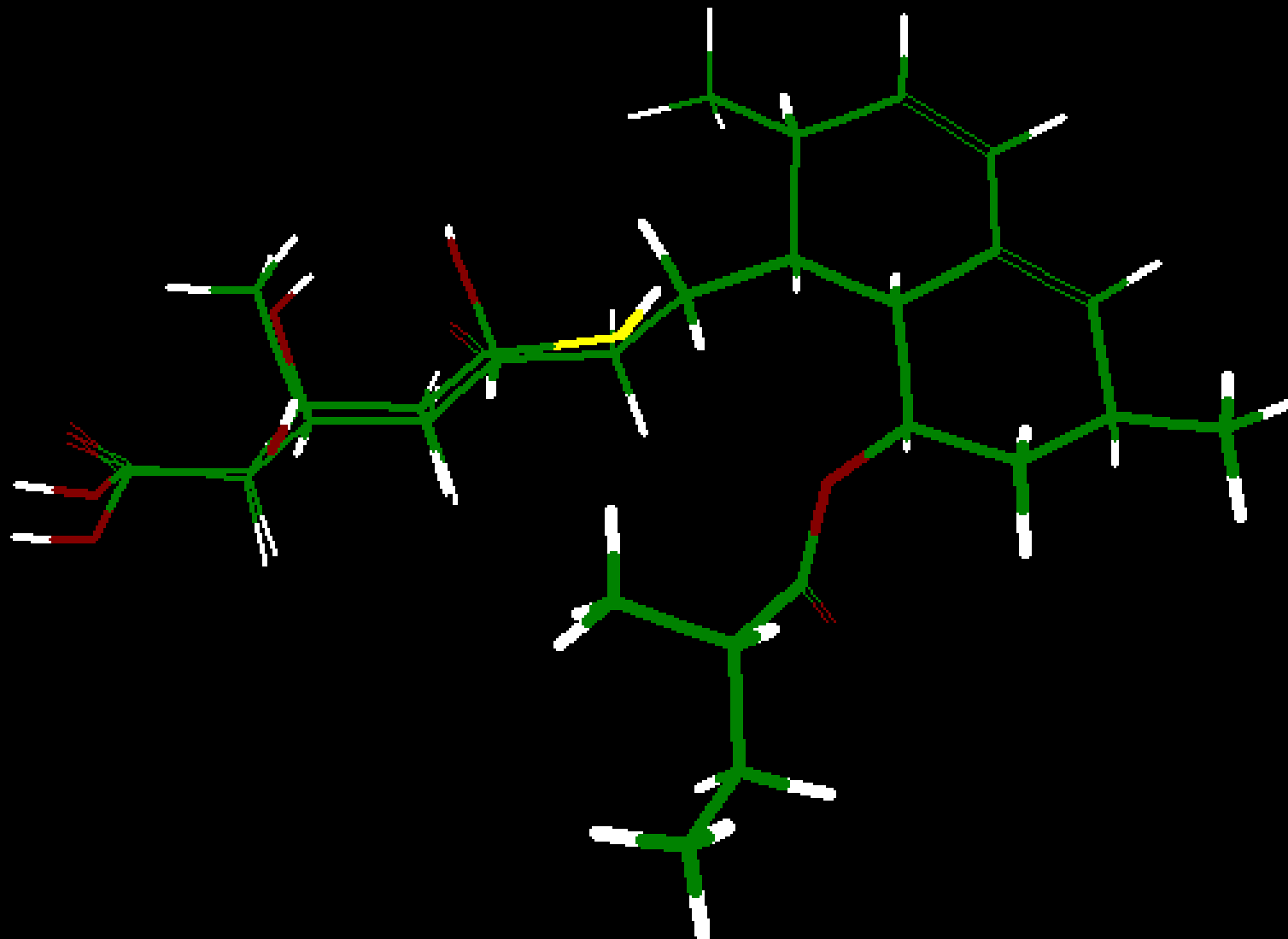


Pravastatina

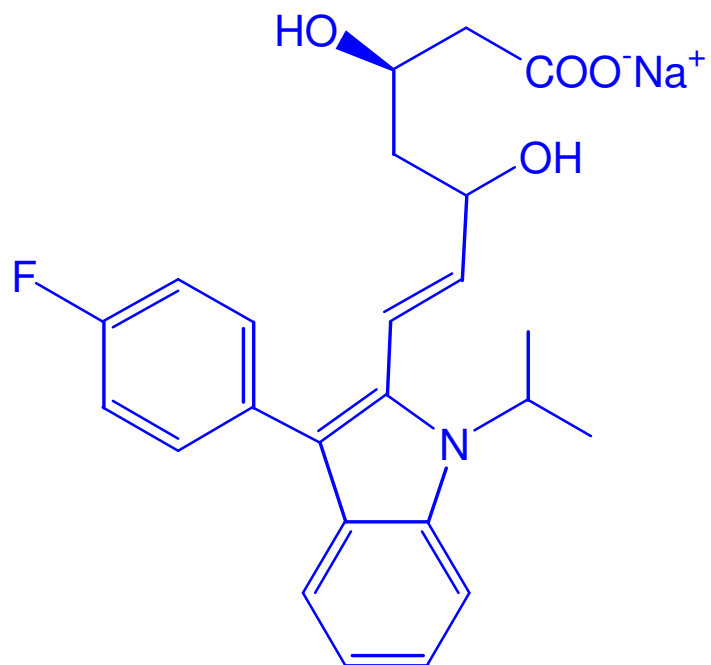
Mevastatina, lovastatina, pravastatina
Sinvastatina:



Sobreposição HMG CoA e Lovastatina

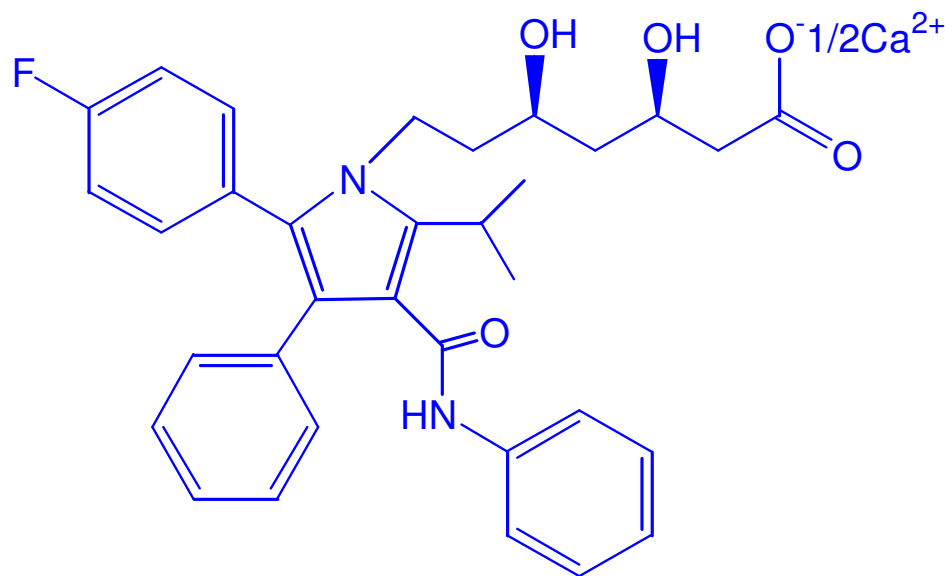


Segunda geração:



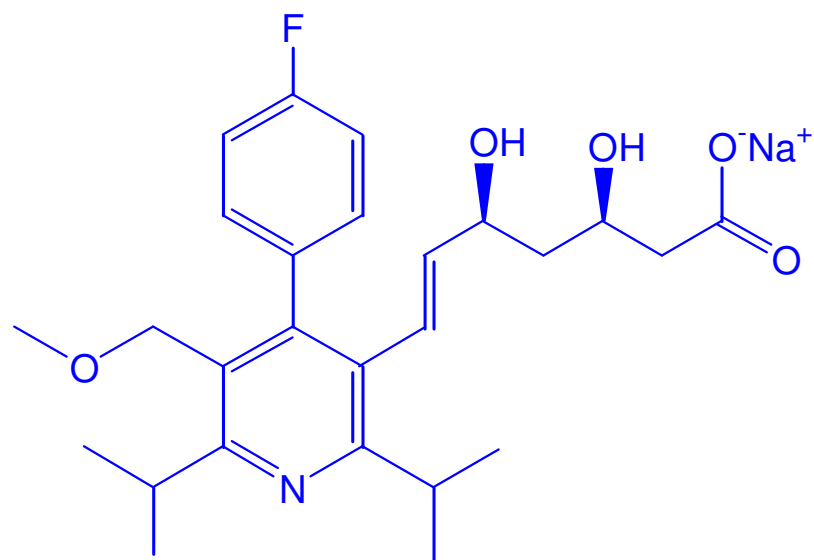
Fluvastatina

Terceira Geração:



Atorvastatina

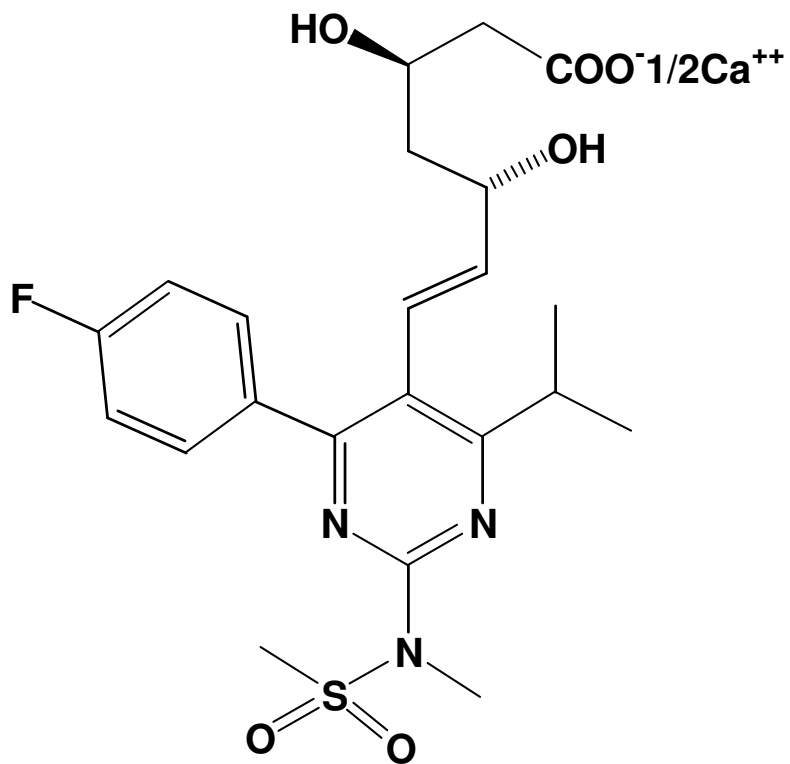
Sintéticos –
enantiomericamente puros



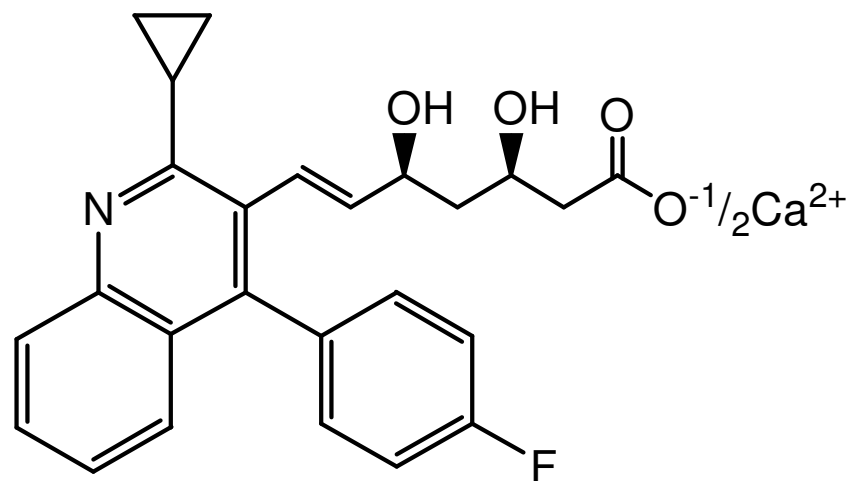
Cerivastatina

Cerivastatina

Terceira Geração:

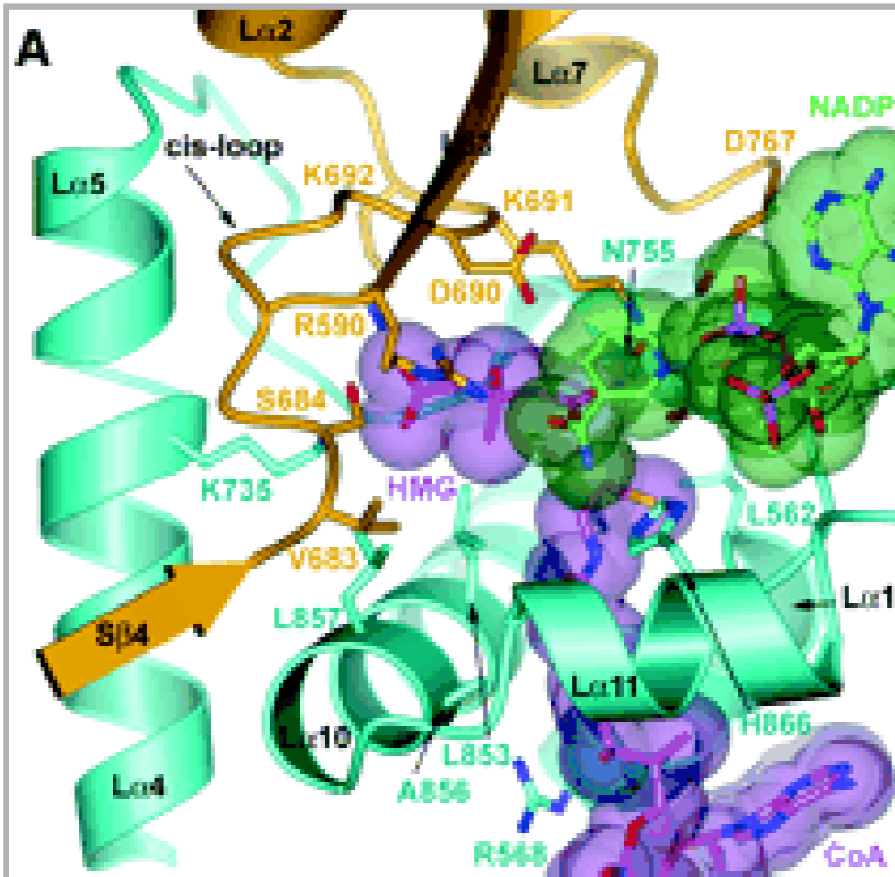


ROSUVASTATINA

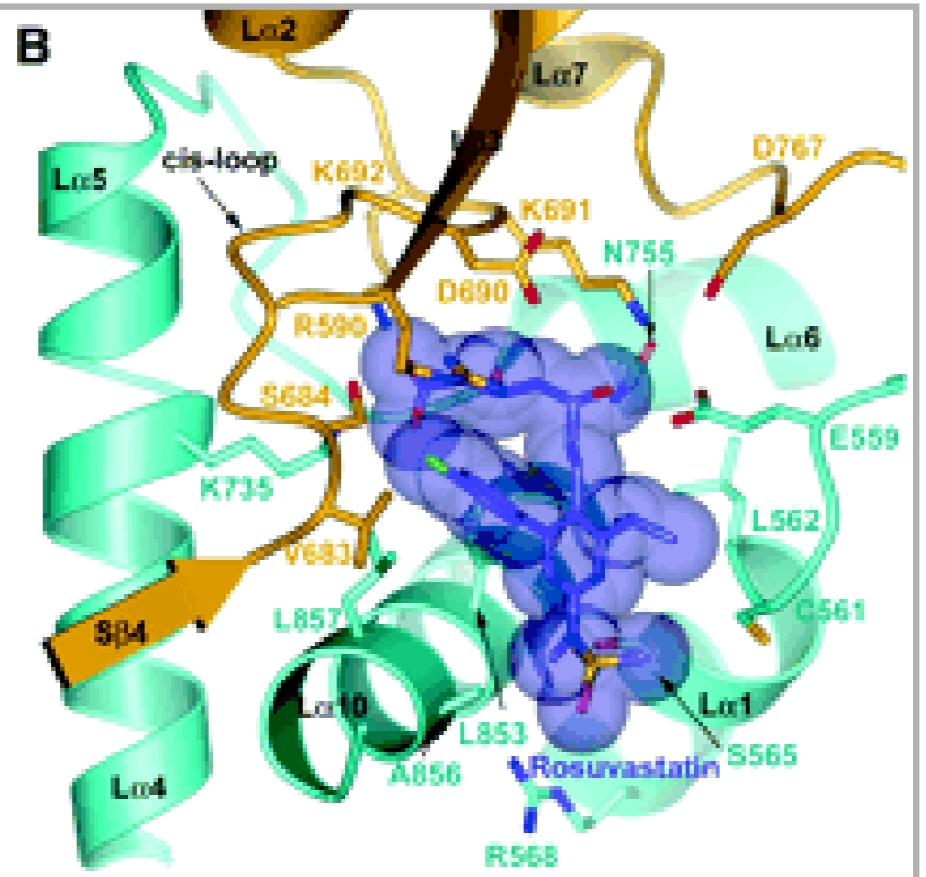


PITAVASTATINA

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

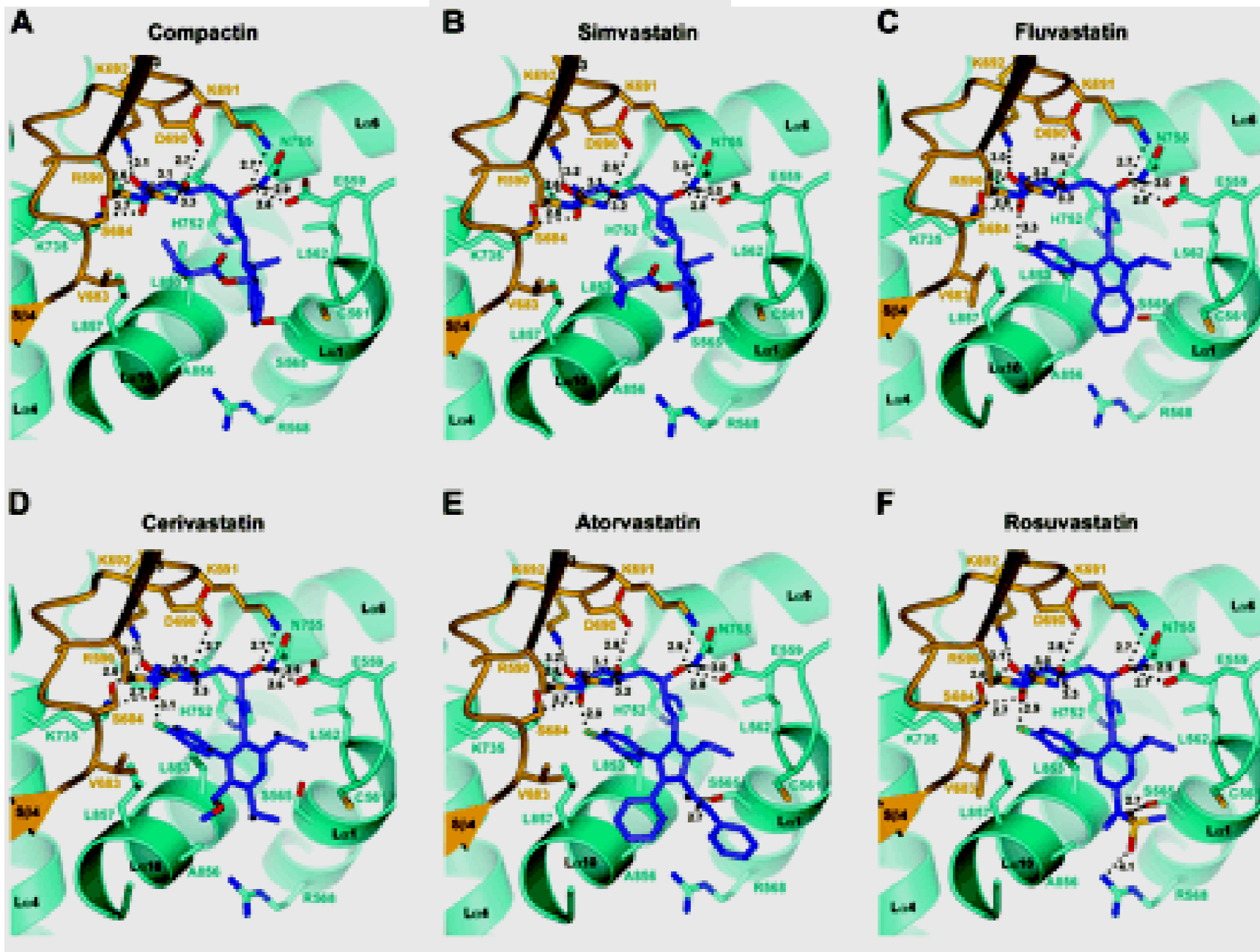


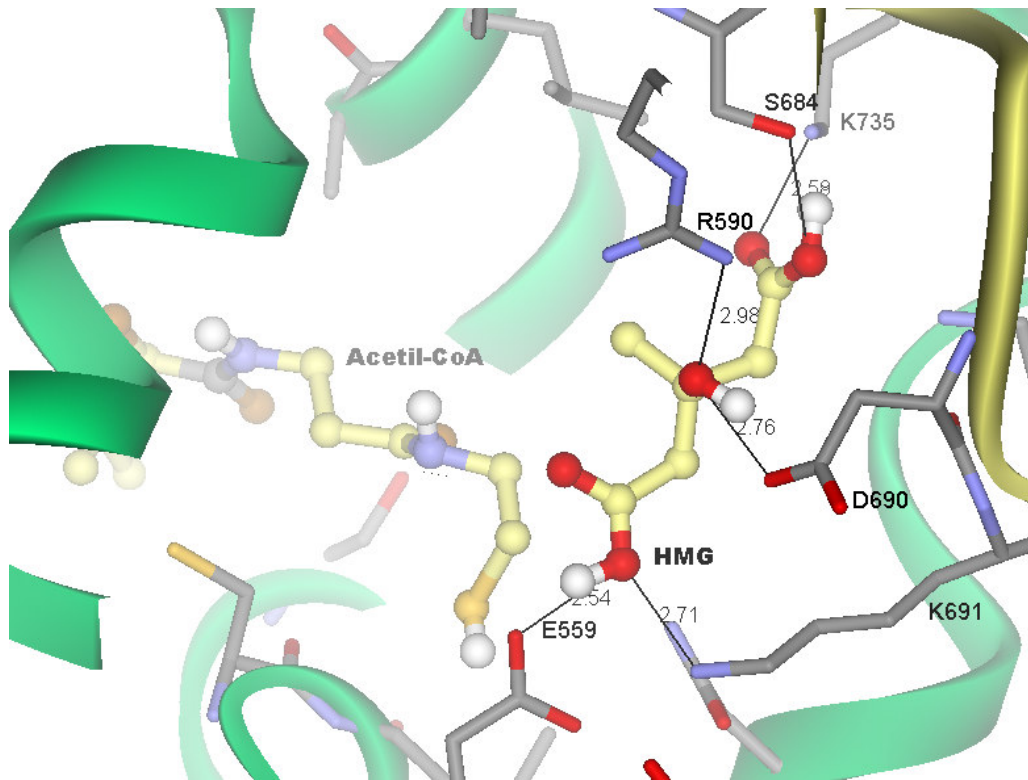
Sítio ativo da HMGR complexada com rosuvastatina

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

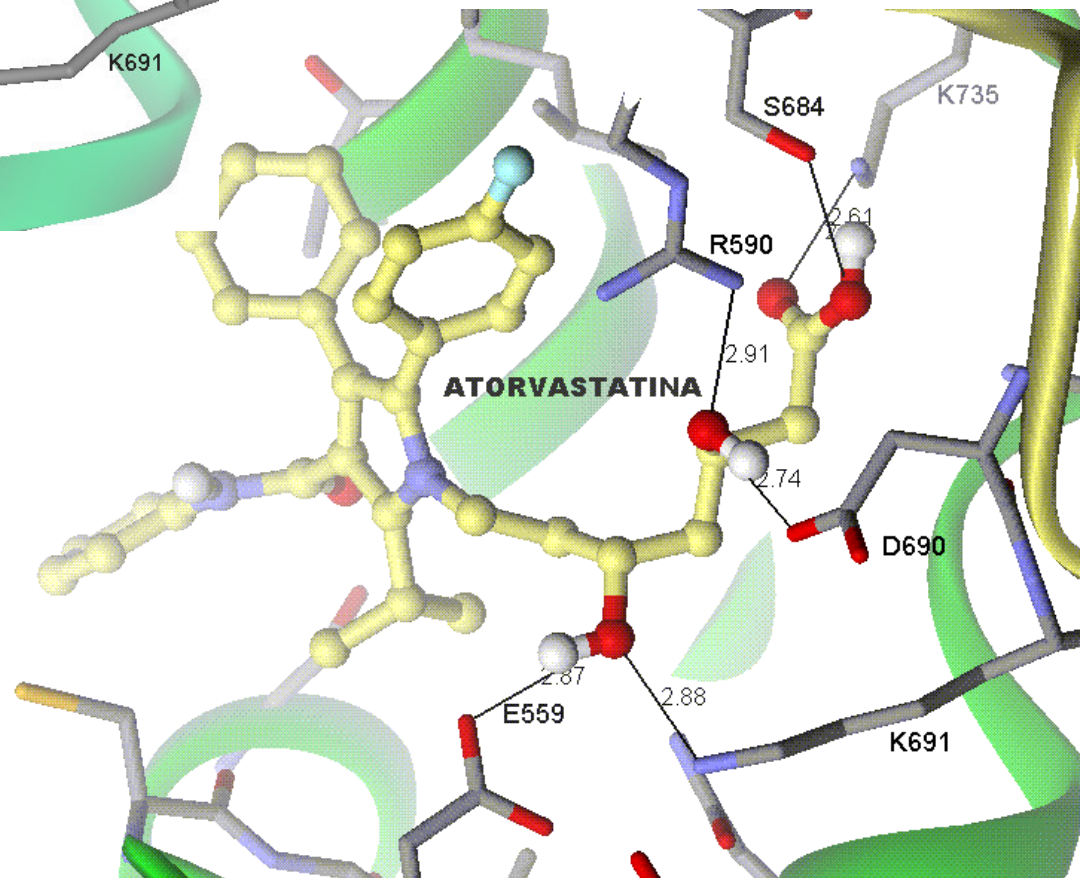


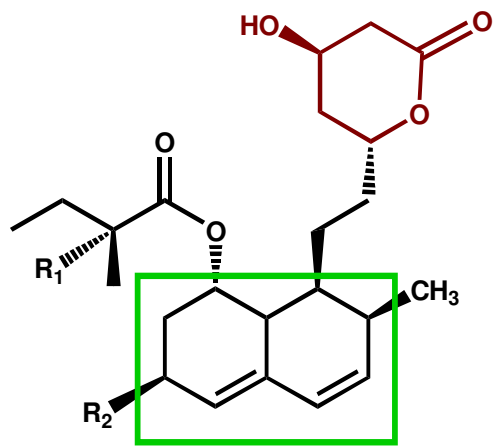


Interações do análogo do produto (HMG) no sítio ativo da HMGCoA redutase

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

Interações da Atorvastatina no sítio ativo da HMGCoA redutase

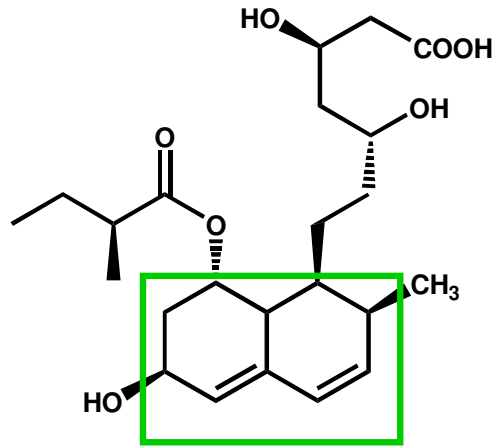




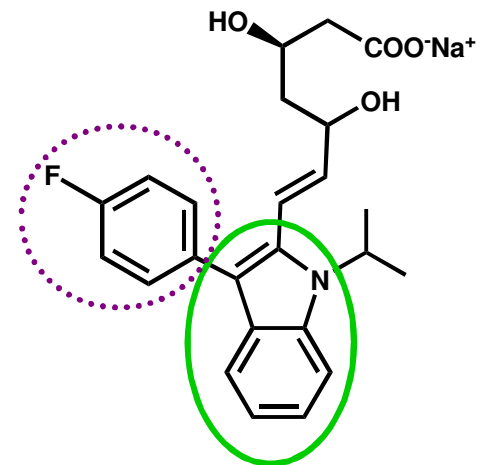
Lovastatina
(Mevacor)
Sinvastatina
(Zocor)

$R_1=H; R_2=CH_3$

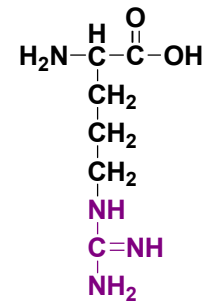
$R_1=R_2=CH_3$



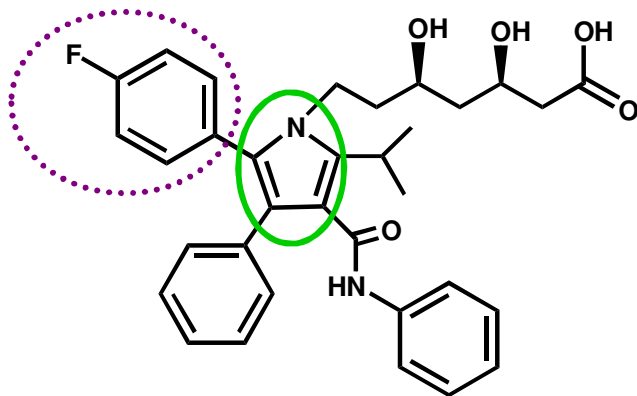
Pravastatina
(Pravachol, Mevalotin)



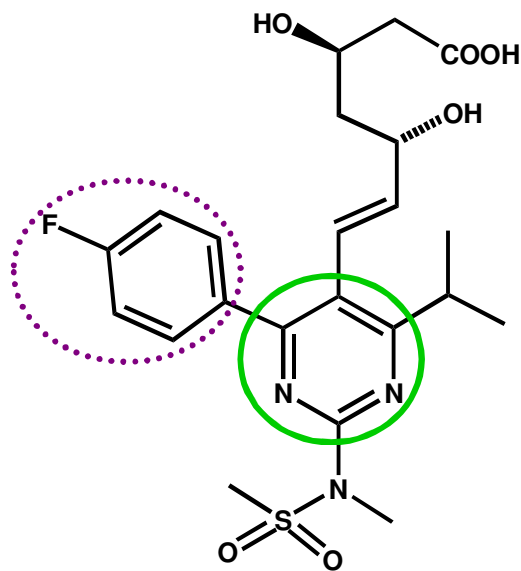
Fluvastatina
(Lescol)



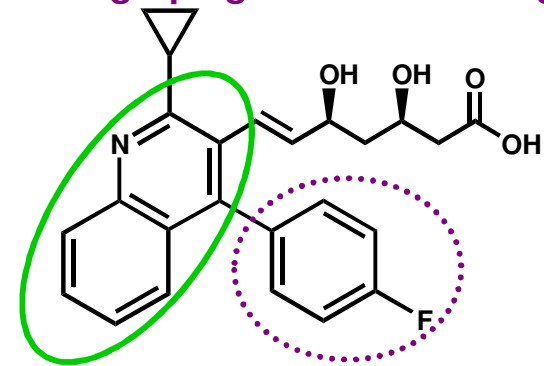
Grupo 4-fluorfenil nas
estatinas sintéticas estabelece
interações adicionais com o
grupo guanidínico da Arg590



Atorvastatina
(Lipitor)



Rosuvastatina
(Crestor)



Pitavastatina
(Livalo)

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

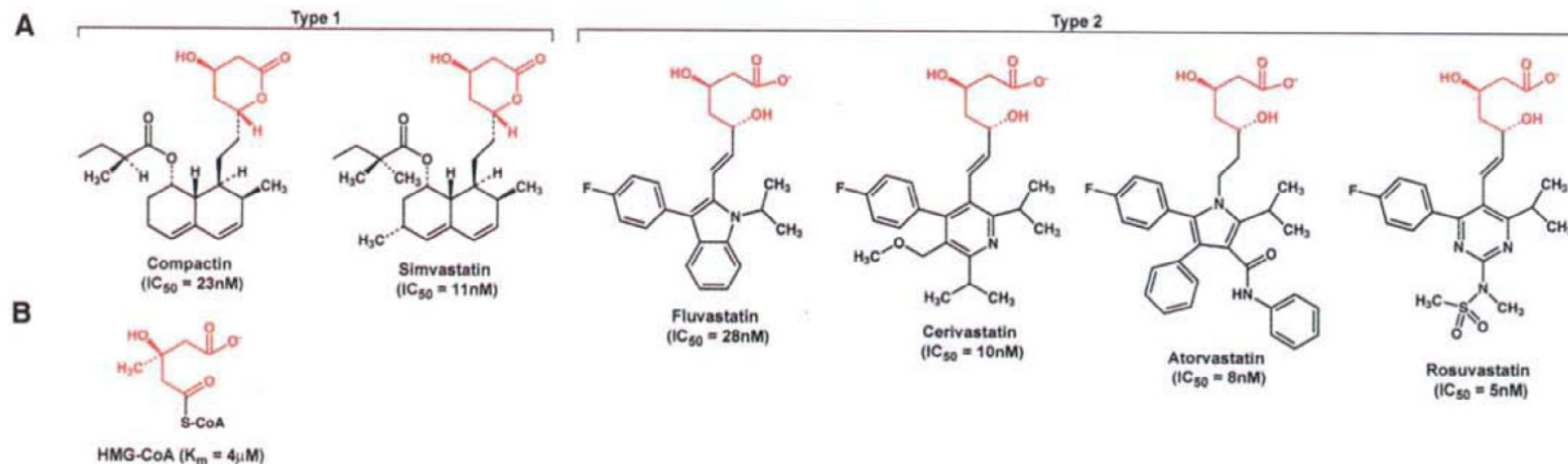
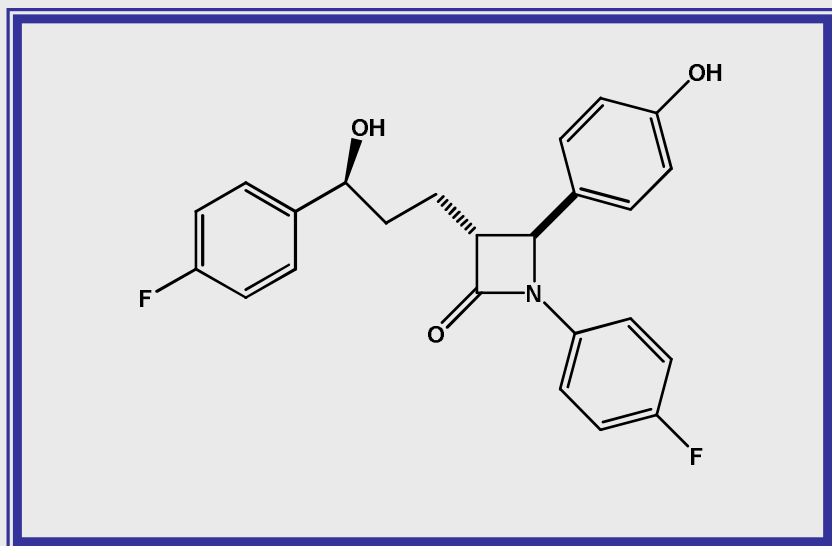


Fig. 1. Structural formulas of statin inhibitors and the enzyme substrate HMG-CoA. **(A)** Structure of several statin inhibitors. Compactin and simvastatin are examples of type 1 statins; not shown are the other type 1 statins, lovastatin and pravastatin. Fluvastatin, cerivastatin, atorvastatin, and

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).



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

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*.

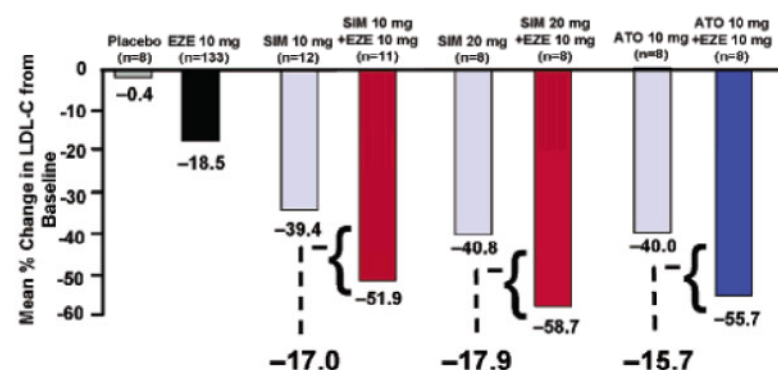


Figure 10. Ezetimibe coadministered with simvastatin or atorvastatin.

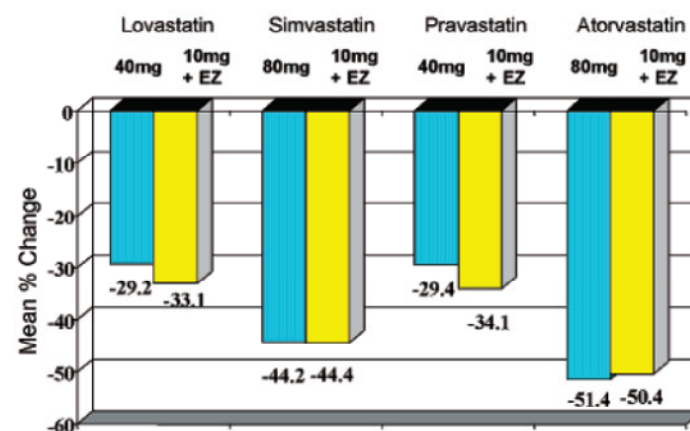


Figure 11. Effect of high- and low-dose statin coadministered with ezetimibe.

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

Usos de classes fármacos para controle de dislipidemias

