Aula 4 – 17/06

Tópicos Especiais em Química Medicinal

Tópicos Especiais em Química Medicinal
Código: **BMF-777**
Carga Horária: 45 horas
Créditos: 3 créditos

Conceito de Grupo Farmacofórico

Paul Ehrlich (1909) – Um **farmacóforo** "carries (*phoros*) the essential features responsible for a drug's (= pharmacon's) biological activity"
(Ehrlich. *Dtsch. Chem. Ges.* 1909, 42: p.17).

Em 1977, **Peter Gund** atualizou a definição: "a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity"
(Gund. *Prog. Mol. Subcell. Biol.* 1977, 5: pp 117–143).

IUPAC: "an ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger (or block) its biological response".

⇩

Barreiro & **Fraga**: **É o conjunto de características eletrônicas e estéricas que caracterizam um ou mais grupos funcionais ou subunidades moleculares, necessários ao melhor reconhecimento pelo receptor, logo para o efeito farmacológico desejado**. **Farmacóforo** não é uma molécula real, nem associações de grupos funcionais; ao contrário, é um conceito abstrato que representa as diferentes capacidades de interações moleculares com o sítio de reconhecimento molecular de um dado bioreceptor.

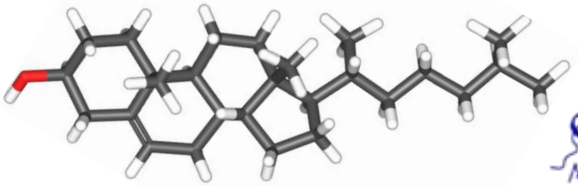
Uma inovação bilionária: as estatinas

Heinrich Wieland
1877-1957

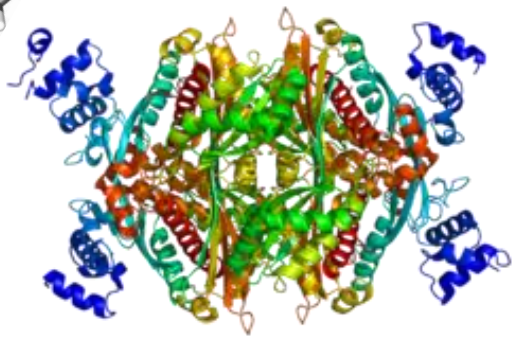
1927

Adolf Windaus
1876-1959

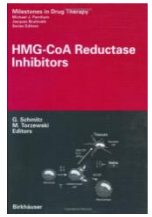
1928



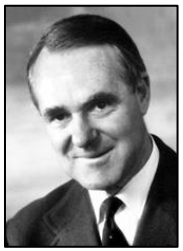
colesterol



HMGCoAR

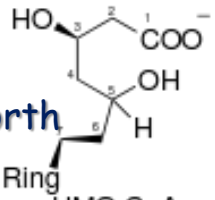


1964

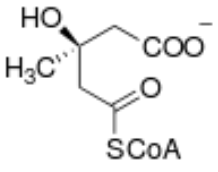


John Cornforth

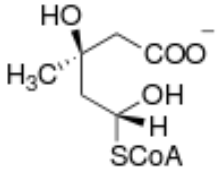
1975



HMG CoA
Reductase inhibitor



HMG CoA



Mevaldyl CoA transition state intermediate

Konrad Bloch
1912-2000

Feodor Lynen
1911-1979

1985

LDL

Joseph L Goldstein

University of Texas, Dallas

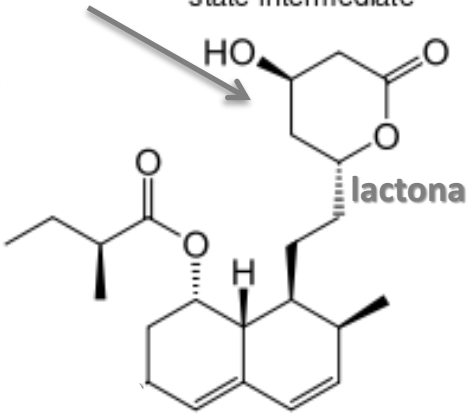
Michael S Brown

Akira Endo

Albert Lasker Award
for Clinical
Medical Research, 2008*

J Med Chem
1985, *28*, 1

Daiichi-Sankyo

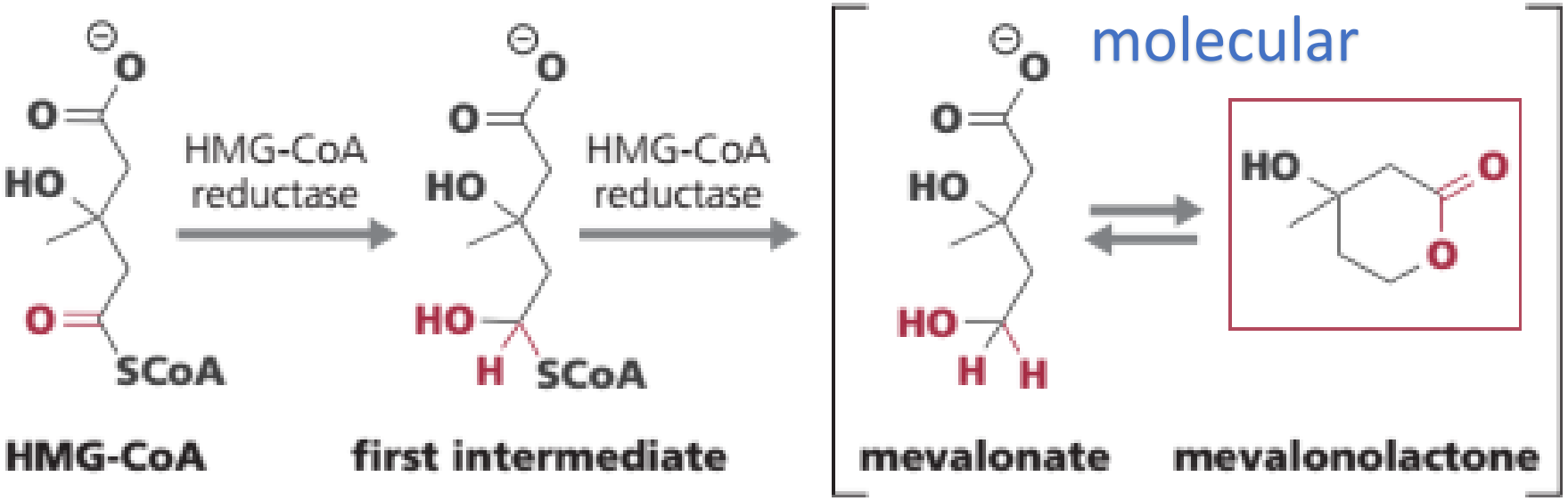


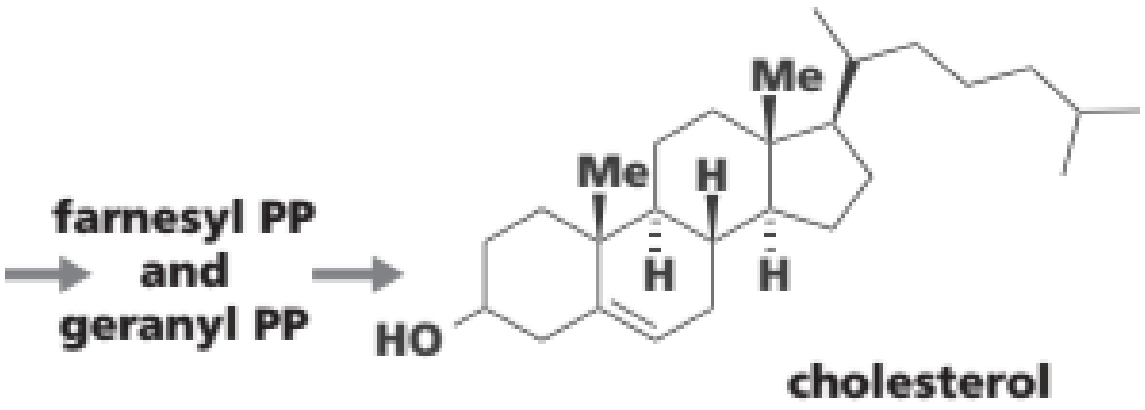
Mevilonina /compactina
Penicillium citrinum

* A Endo, A gift from nature: the birth of the statins, *Nature Medicine* **2008**, *14*, 26

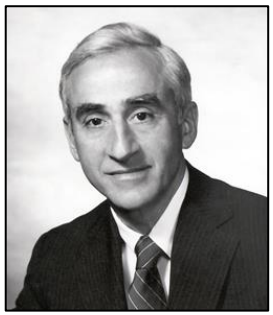
Biossíntese do Colesterol

Similaridade molecular





Uma inovação bilionária: as estatinas



Dr P. Roy Vagelos

Vice-Presidente Pesquisa Farmacêutica da Merck (Presidente & CEO)

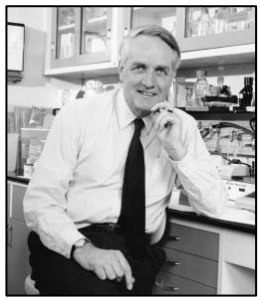
1976 - confidentiality agreement

MERCK

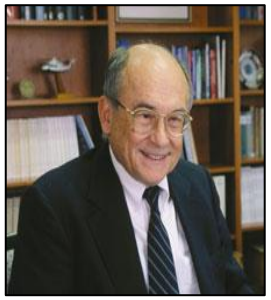
Daiichi-Sankyo

Alfred W. Alberts

Aspergillus terreus



Georg Albers-Schönberg



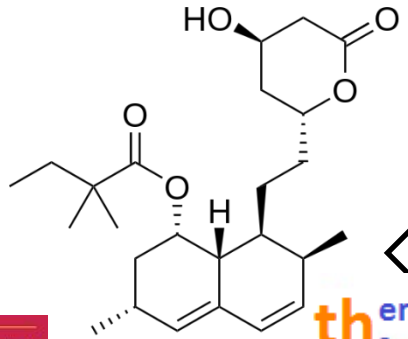
Arthur A. Patchett

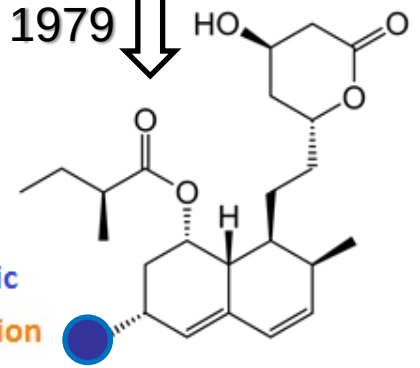
Diretor do Departamento New Lead Discovery

Alfred Burger Award 2002

Química Medicinal

1979





Aspergillus terreus

lovastatina

therapeutic innovation

simvastatina

first-in-class

1982

ZOCOR (SIMVASTATIN)

"blockbuster mentality"

1991

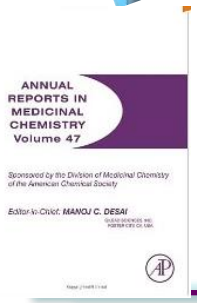
Pfizer atorvastatina

fifth-in-class

J. Med. Chem. **1986,** *29*, 849

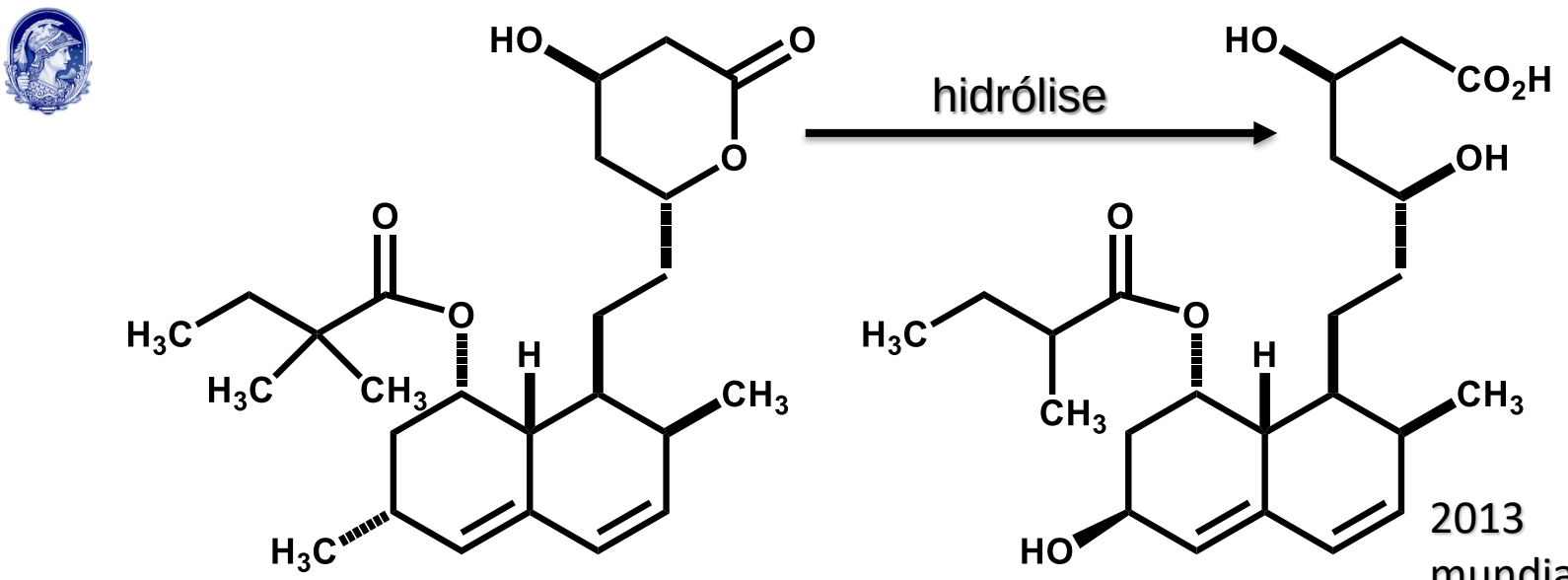
C. H. Heatcock, Un Berkeley, US

A descoberta da lovastatina



> 45 milhões de pessoas usaram estatinas (2005)

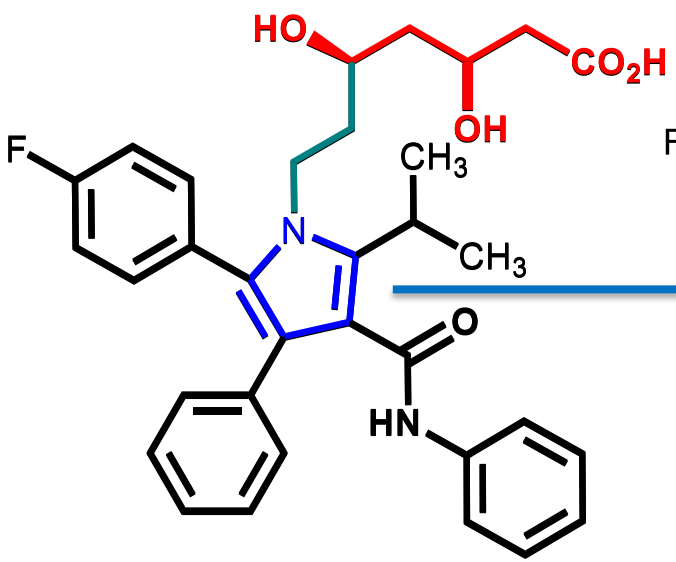
PS Anderson, Reflexions on medicinal chemistry at Merck, West Point, *Annu Rept Med Chem* **2012**, *47*, 3



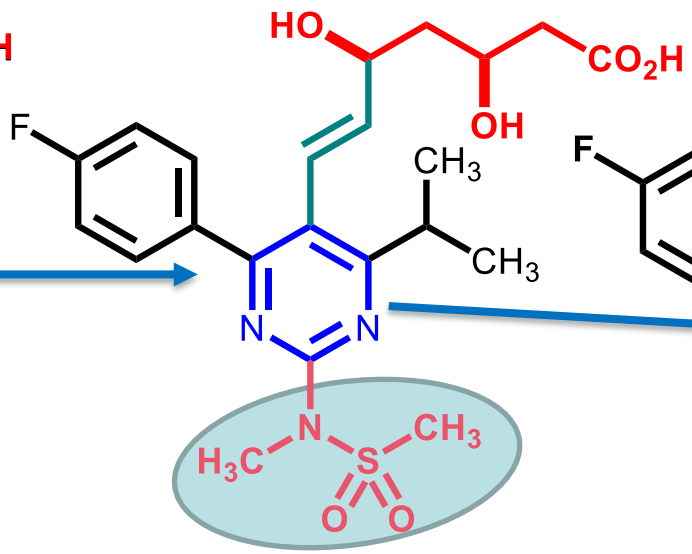
simvastatina
1986

pravastatina
1988

2013 - O mercado mundial de estatinas foi *ca.* US$ 26 bi

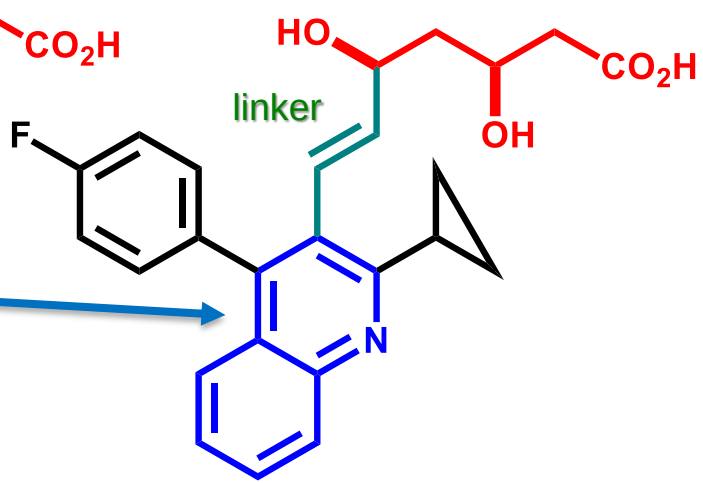


atorvastatina
1991

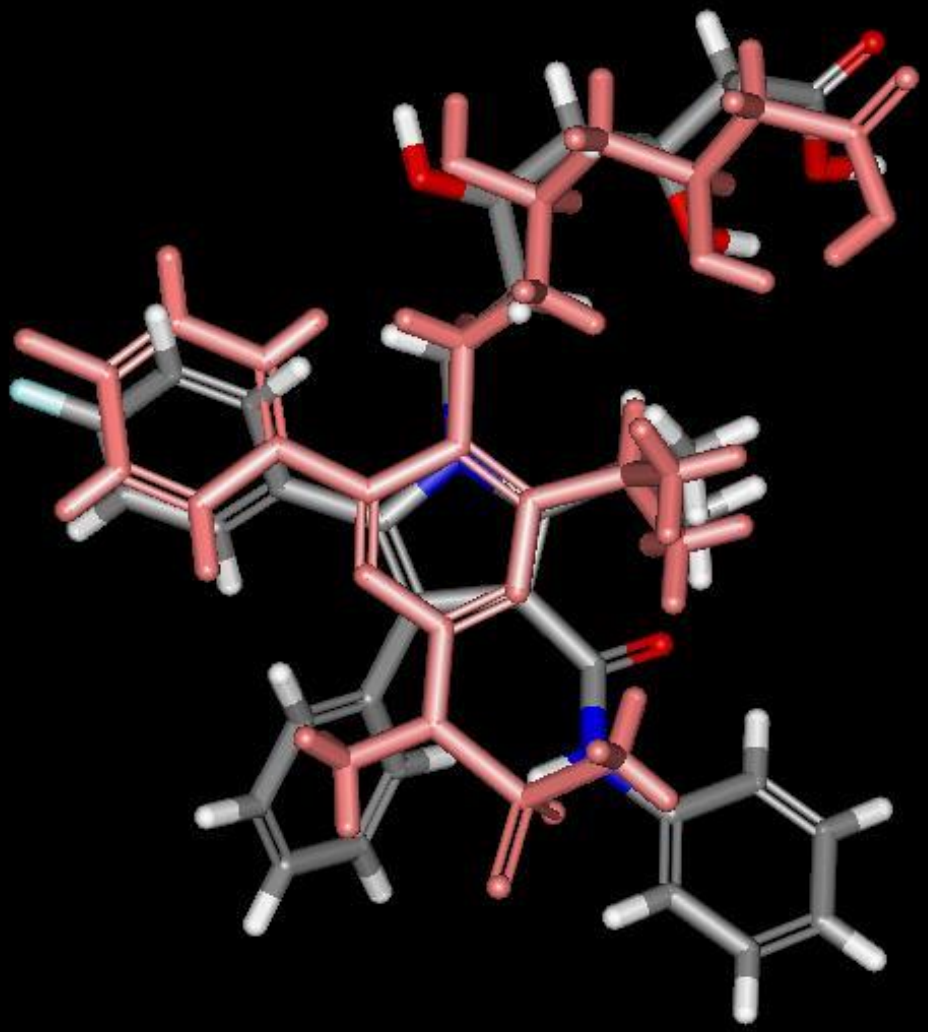


rosuvastatina
2004

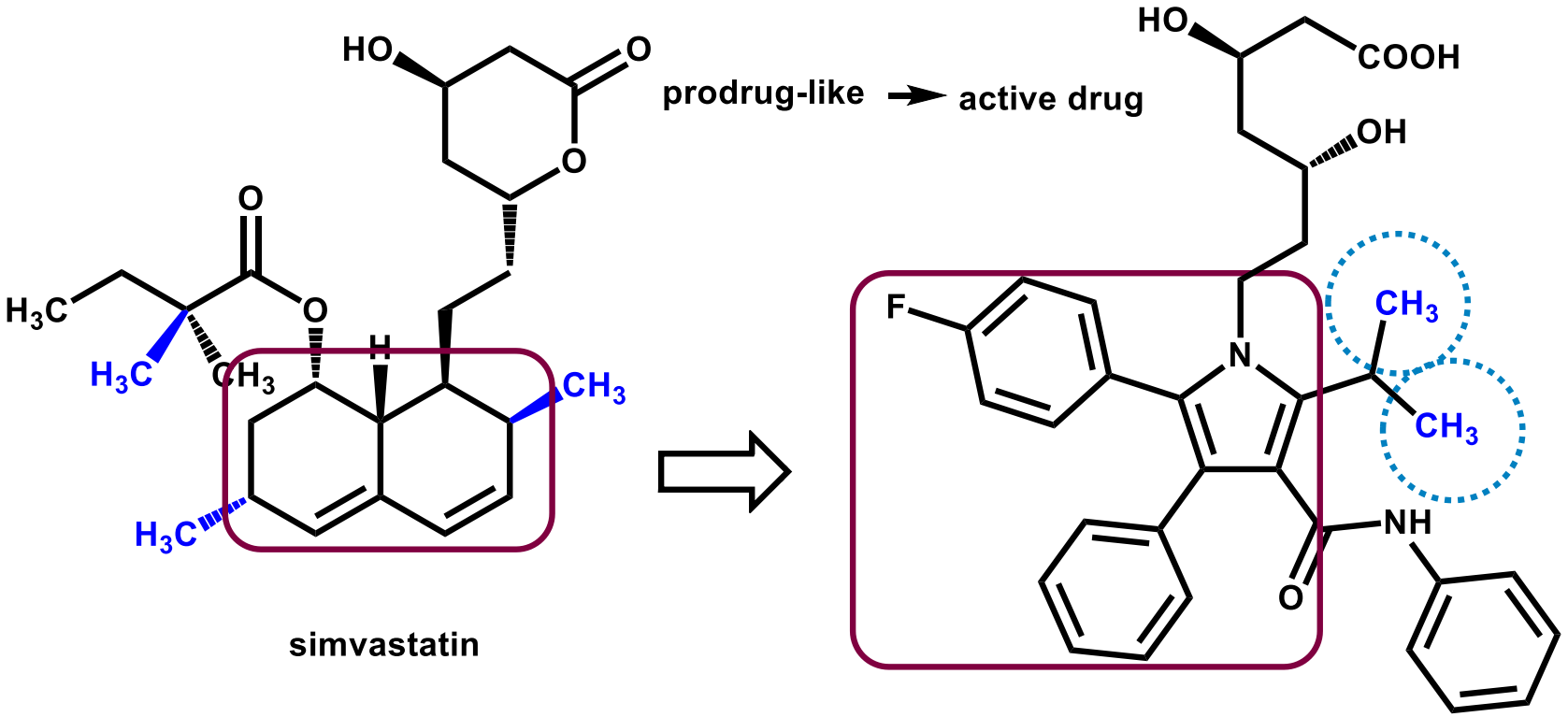
2016 - US$ 3,4 bi



pitavastatina
2009



Simvastatina & Atorvastatina



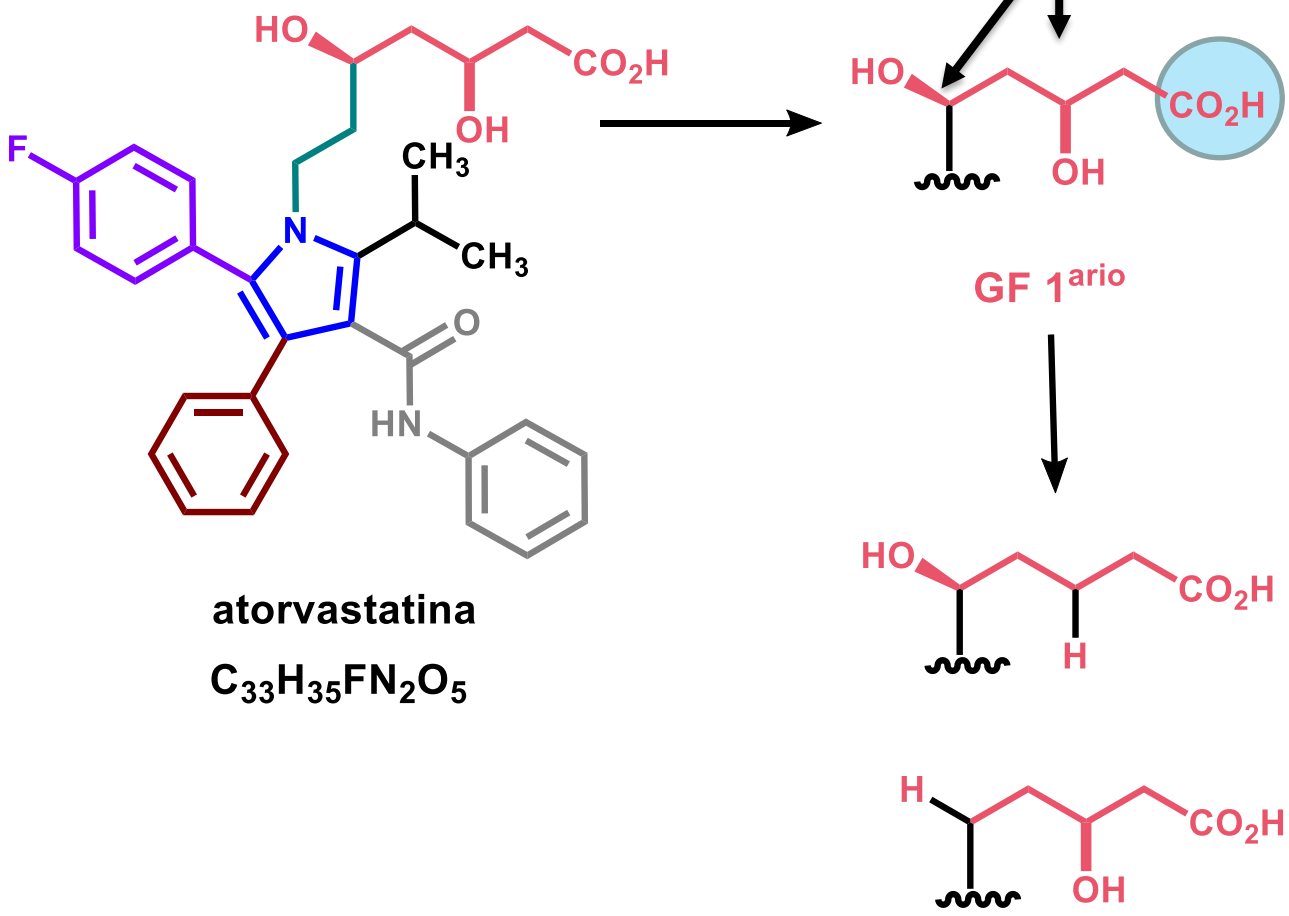
simvastatin

atorvastatin

IC_{50} HMG-CoAR = 8 nM

Grupamento farmacofórico

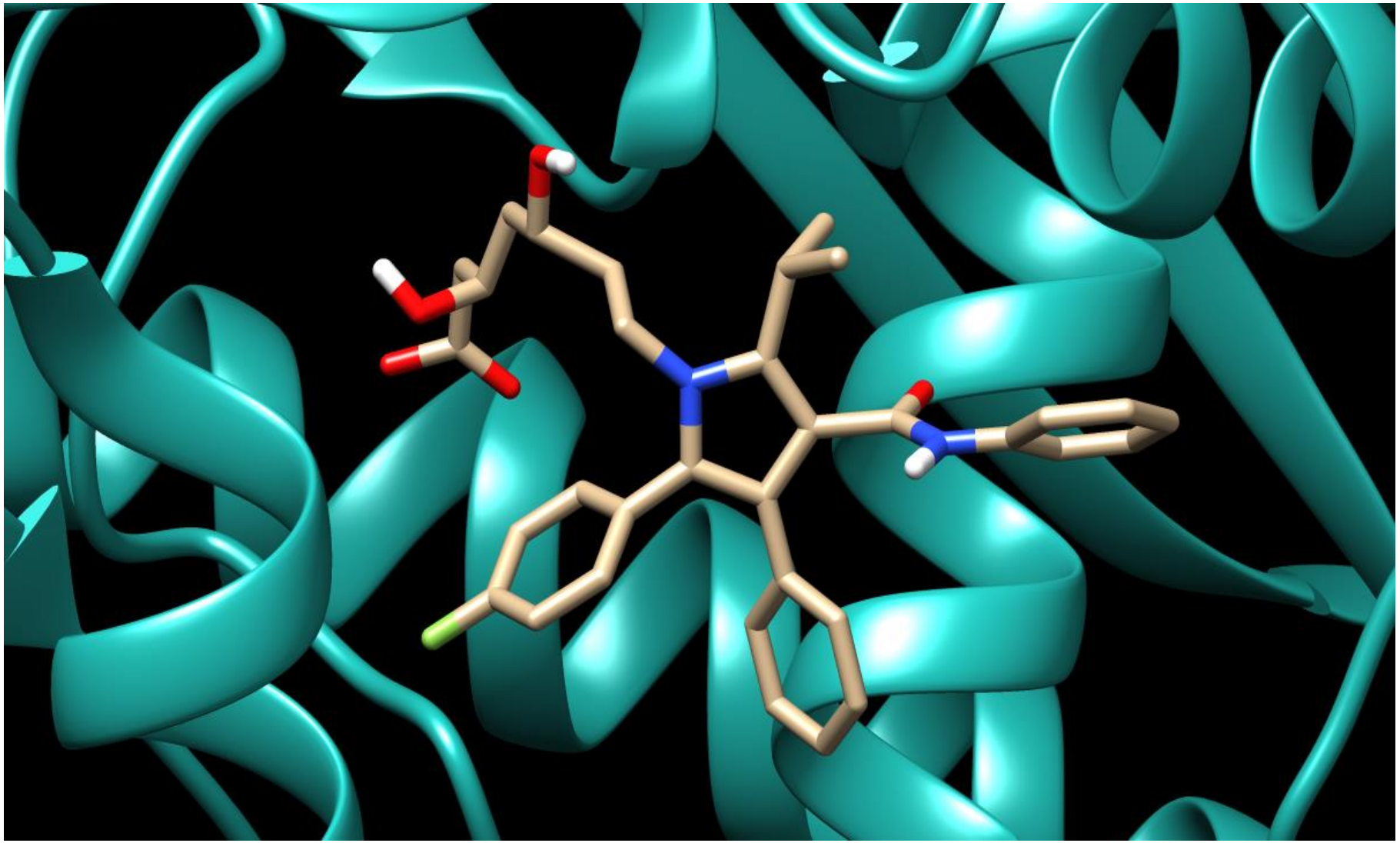
Hipótese de trabalho:



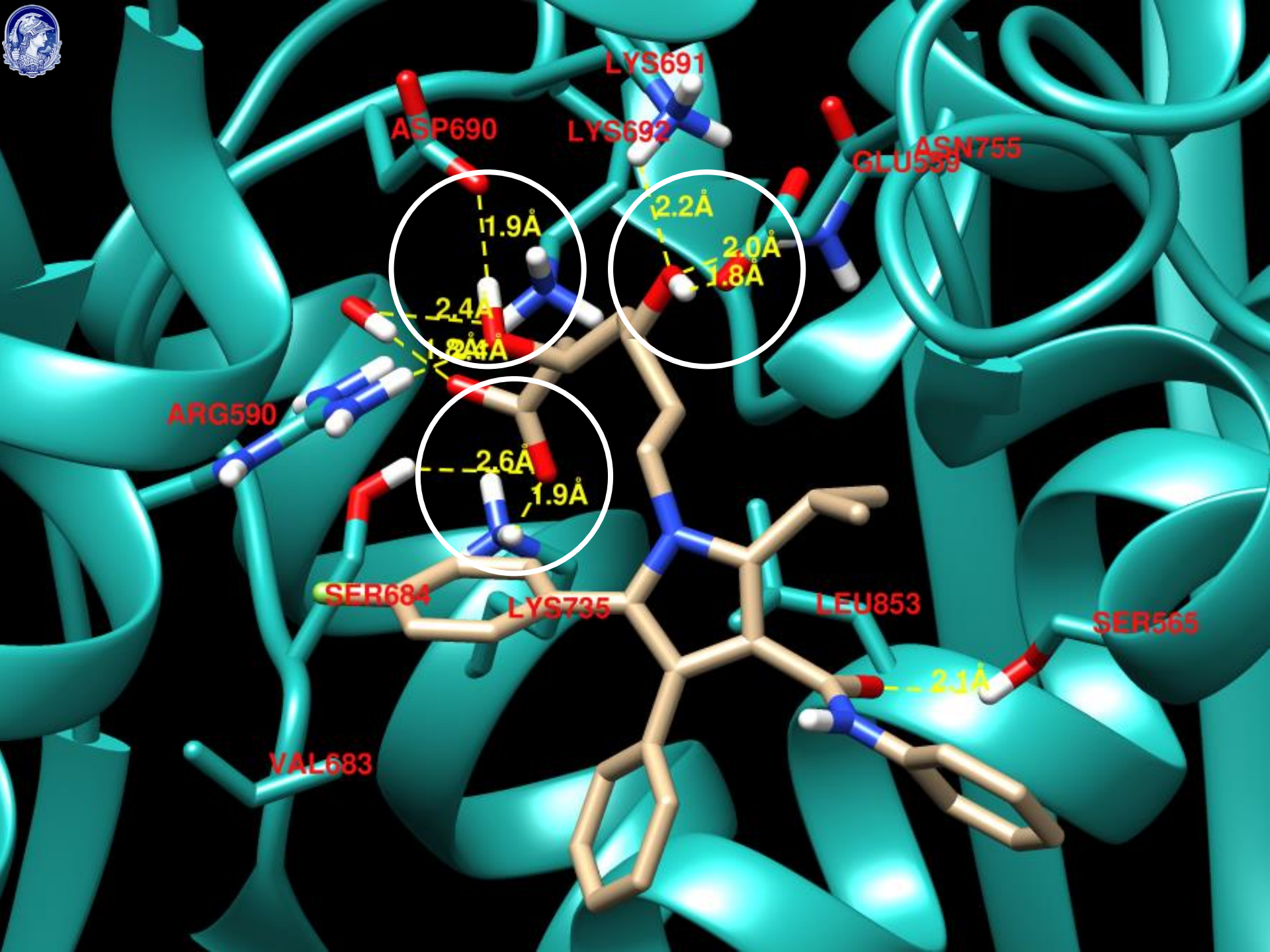
atorvastatina

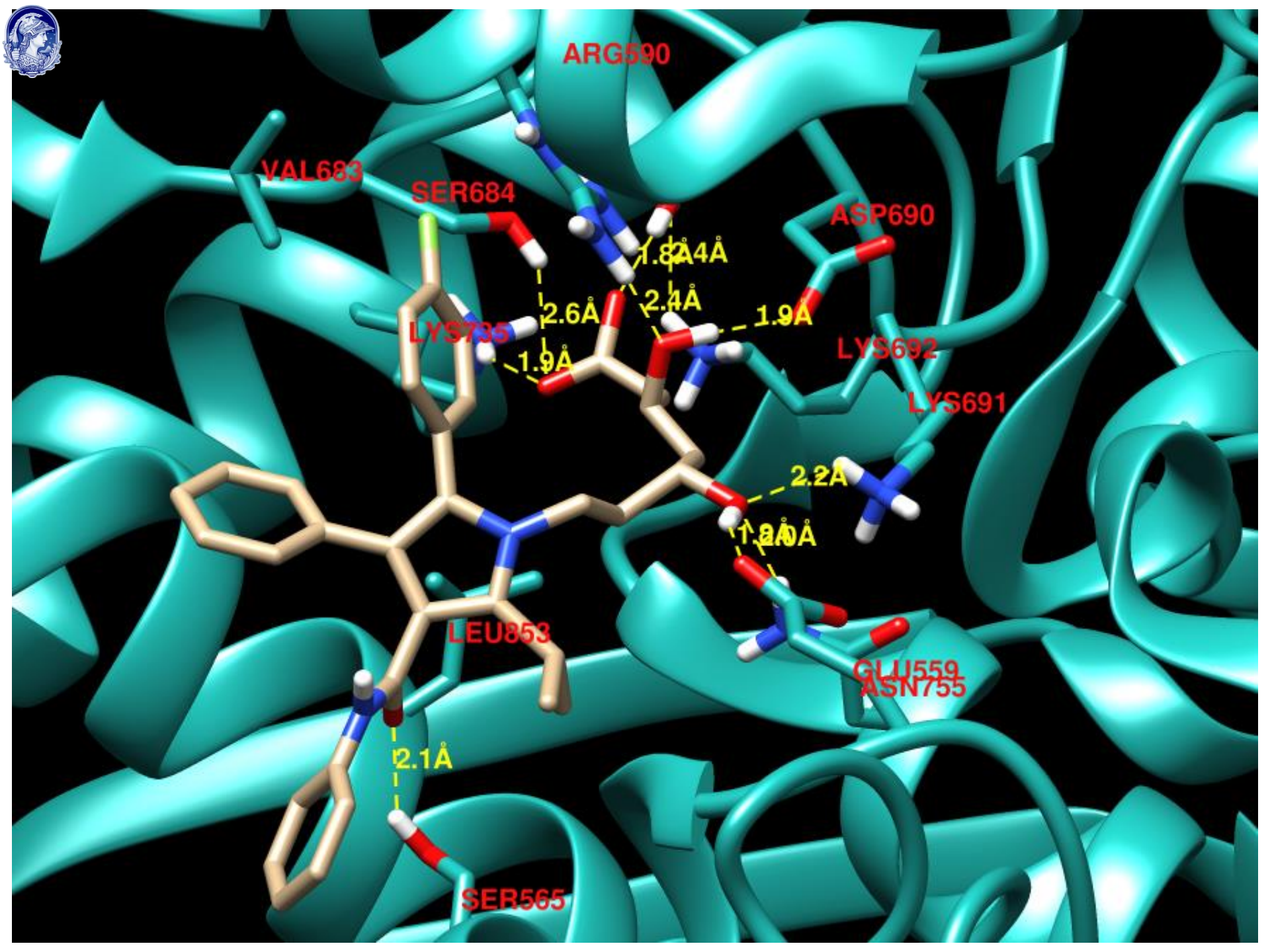
$C_{33}H_{35}FN_2O_5$

Identificando o GF



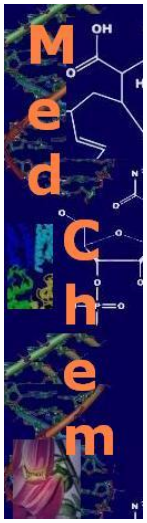
Atorvastatina no sítio de reconhecimento molecular pela HMGCoAR


LYS691
ASP690
LYS692
ASN755
GLU559
1.9Å
2.2Å
2.0Å
1.8Å
2.4Å
ARG590
2.6Å
1.9Å
SER684
LYS735
LEU853
SER565
2.1Å
VAL683


ARG590
VAL683
SER684
ASP690
1.8Å
2.4Å
2.6Å
2.4Å
1.9Å
LYS735
1.9Å
LYS692
LYS691
2.2Å
LEU853
GLU559
ASN755
2.1Å
SER565

Estatinas

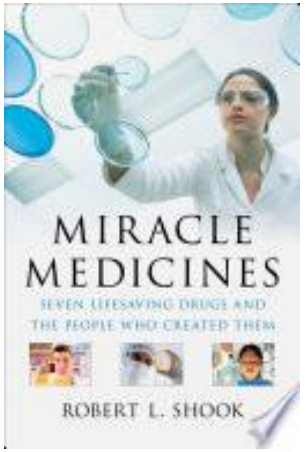
Atorvastatina



1985 - Bruce D Roth
Warner-Lambert
Pyrrole chemistry – Un . Rochester

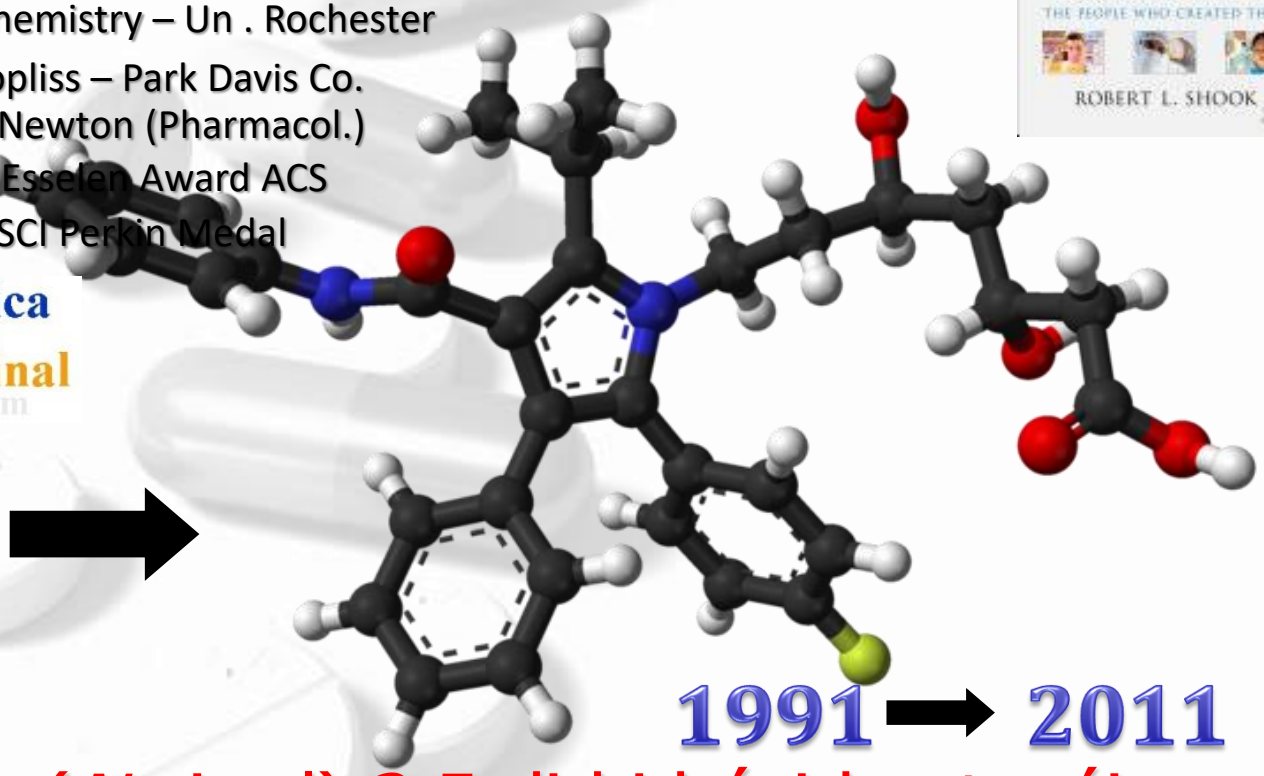
John Topliss – Park Davis Co.
Roger Newton (Pharmacol.)
2003 Esselen Award ACS
2013 SCI Perkin Medal

1991



Pfizer

Química
Medicinal



1991 → 2011

ácido (*N*-pirrol)-3,5-di-hidróxi-heptanóico

Síntese: *ca.* 200 toneladas/ano

HMGCo-AR IC_{50} = 8,2 nM

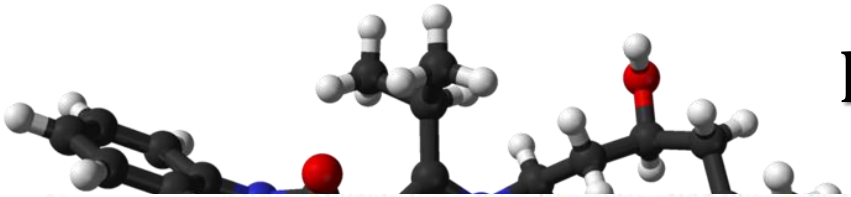
Fármaco recordista mundial em vendas: US$ 150 bilhões

B. D. Roth, *Progr. Med. Chem.* **2002**, *40*, 1-22

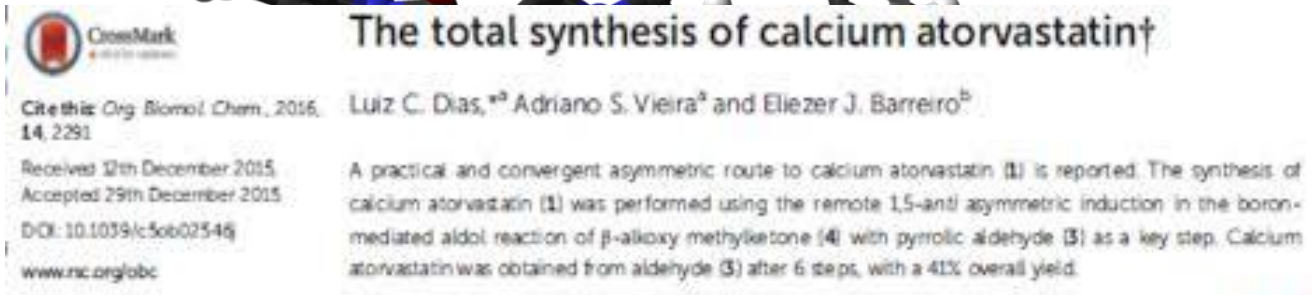
B. D. Roth, et al., *J. Med. Chem.* **1990**, *33*, 21-31

Atorvastatina

sintetizada em 1985, por Bruce D. Roth,
na Parke-Davis Warner-Lambert Co.
Patent US 5273995 Pfizer (1991)
19 etapas; 5% rendimento



Estudo de rotas de síntese, a partir de intemediários primários de menor custo, de fármacos genéricos:



The total synthesis of calcium atorvastatin†

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Accepted 29th December 2015

DOI: 10.1039/c5ob02546j

www.rsc.org/obc

Luiz C. Dias,*[a] Adriano S. Vieira[a] and Eliezer J. Barreiro[b]

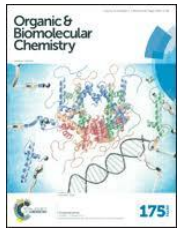
A practical and convergent asymmetric route to calcium atorvastatin (1) is reported. The synthesis of calcium atorvastatin (1) was performed using the remote 1,5-*anti* asymmetric induction in the boron-mediated aldol reaction of β-alkoxy methylketone (4) with pyrrolic aldehyde (3) as a key step. Calcium atorvastatin was obtained from aldehyde (3) after 6 steps, with a 41% overall yield.

Professor Luiz Carlos Dias
& Dr Adriano Siqueira Vieira
IQ, UNICAMP

O maior *bestseller* da história da indústria farmacêutica mundial

Vendas mundiais: US$ >150 bilhões (1991-2011)

18 etapas; 19% rendimento; 5g escala

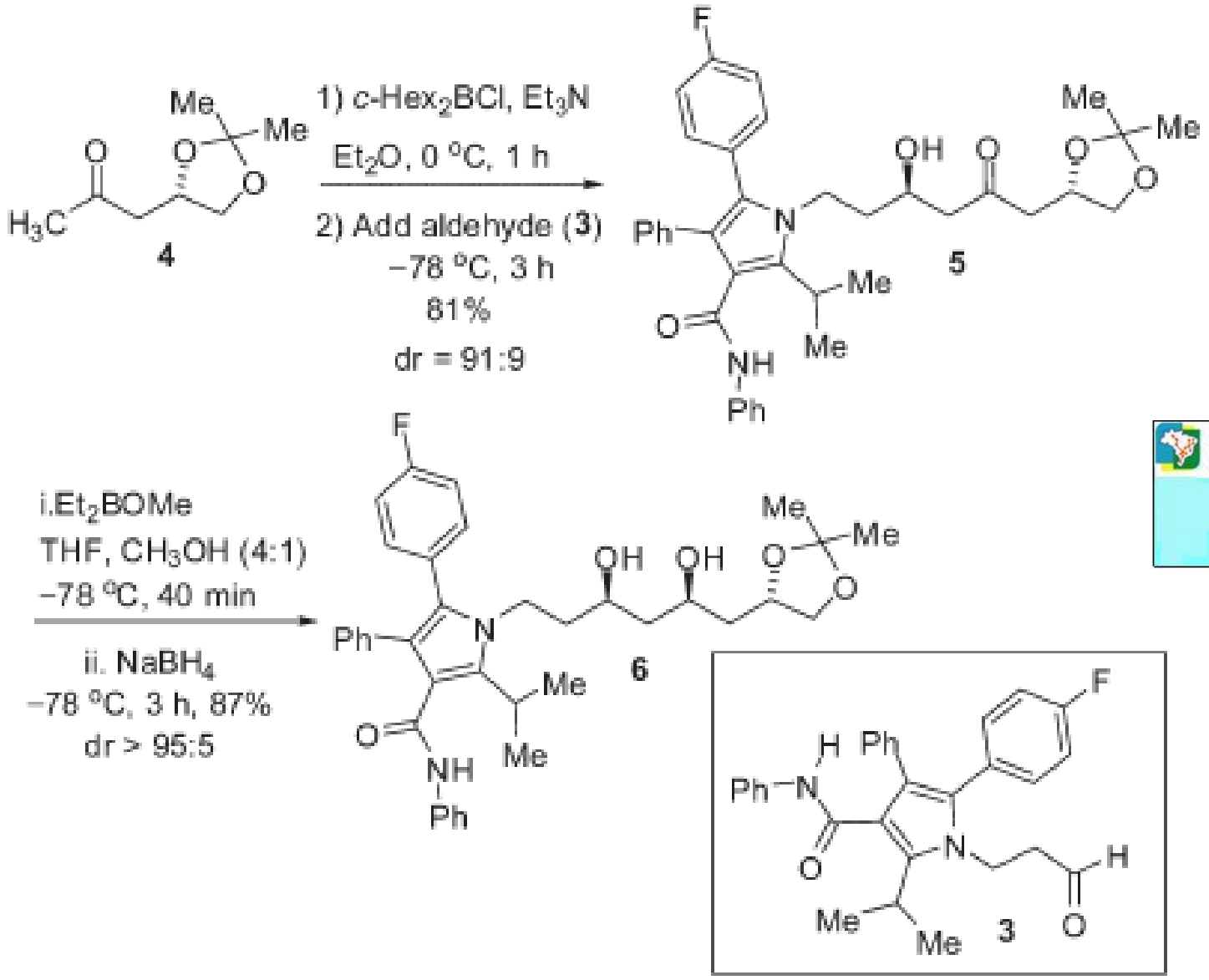


•LC Dias, AS Vieira, EJ Barreiro, Total Synthesis of Calcium Atorvastatin, *Organic & Biomolecular Chemistry,* **2016,** *14,* 2291-2296

• INPI Patente 01810015039, 2001 (BR)
Nova rota de síntese da atorvastatina cálcica usando novos intermediários.
WO2012145808A1

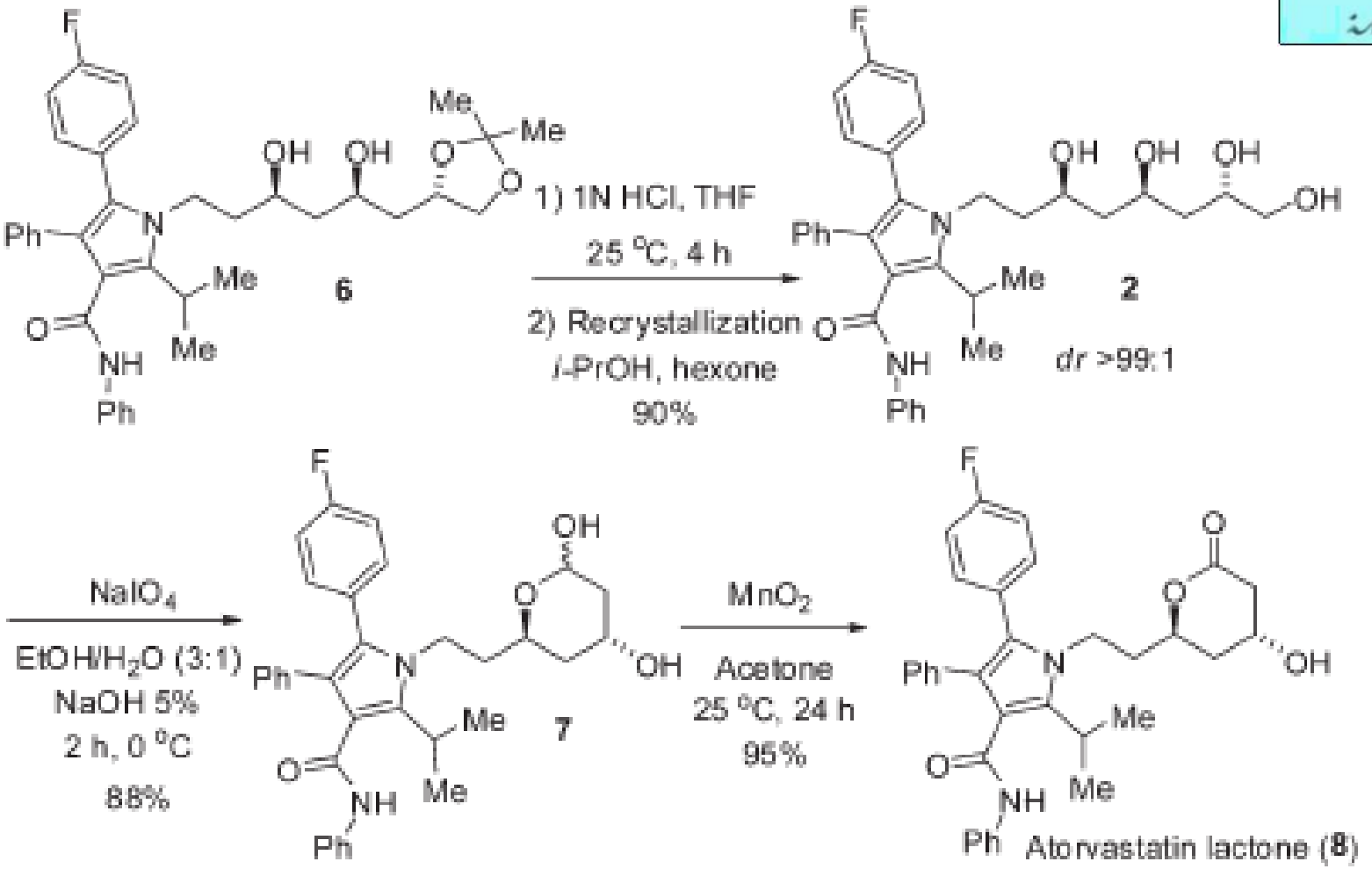
INCT-INOFAR: www.inct-inofar.ccs.ufrj.br

Síntese total



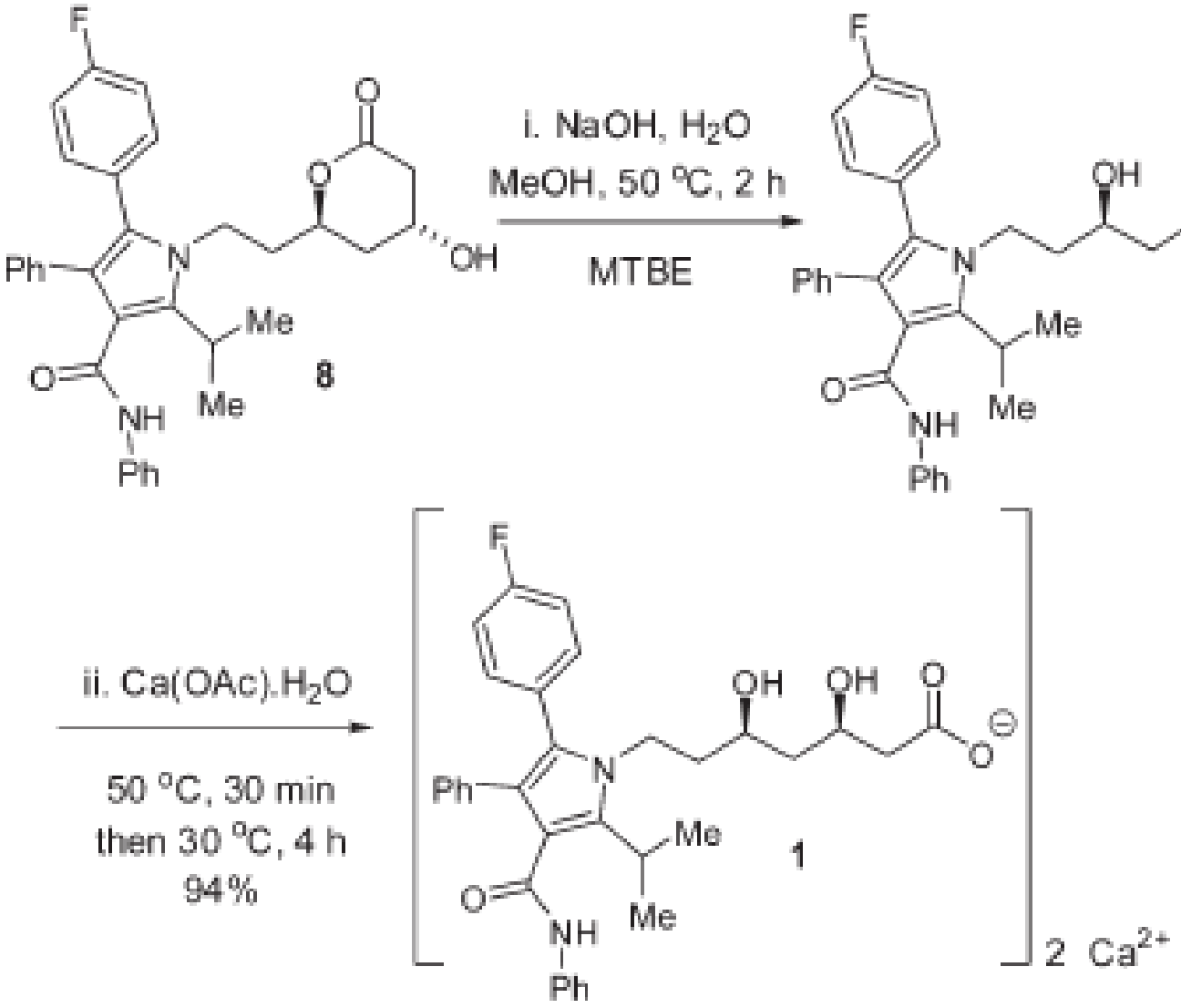
Scheme 2 Aldol reaction and diastereoselective reduction of β-hydroxyketone **5**.

Síntese total



Scheme 3 Acid hydrolysis reaction of acetonide **6** and preparation of lactone **8**.

Síntese total



Scheme 4 Synthesis of calcium atorvastatin (1).

Então?

Os grupos funcionais da molécula de um fármaco têm a mesma relevância para a atividade?

chave

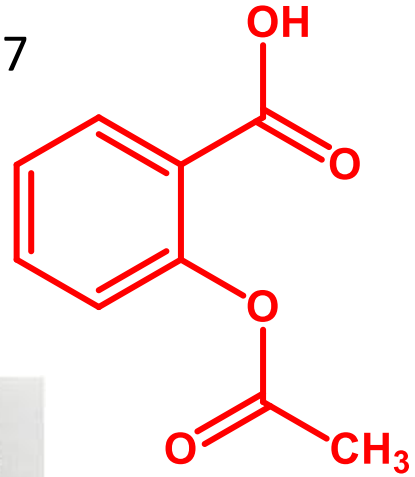
fecha*dura*

Ácido acetilsalicílico

1897

AAS

$C_9H_8O_4$



Felix Hoffman
1868- 1946

1982

Sune K. Bergström
Bengt I. Samuelsson
John R. Vane

Molécula pioneira

150 YEARS OF INVENTION

BAYER celebrates its spirit of innovation and ponders how to apply it next

ALEX SCOTT, C&EN LONDON

ASPIRIN, POLYCARBONATE, polyurethane, and the first synthetic insecticide are among the catalog of chemicals invented by scientists at Bayer. Ciba-Geigy, Hoechst, ICI, Rhône-Poulenc, and other European ... also have their place in the history ... but all have been dismantled ... by the competitors.

... by shifting with the ... selling one specialty ... the field of pharmaceuticals, ... the dark years of World War II, and more ... recently metamorphosed into a firm intent on fulfilling its mission statement "Science for a Better Life."

"Our greatest achievement is our continuous ability to innovate," Bayer Chairman Marijn E. Dekkers tells C&EN. "The company cannot exist in the long term without changing and adapting," he says, evoking Charles Darwin's theory of evolution, a thesis published just four years before Bayer was established.

"I could pick numerous examples," Dekkers says when asked to name the firm's most important invention. "The discovery of the antibacterial effects of sulfonamides, the invention of the polycarbonate Makrolon or polyurethanes, the first synthetic insecticide, various seeds, our recent pharmaceutical product addition like Xarelto," a drug for preventing ... against blood clots. "Then of course ... aspirin ...

Bayer ... at a time when Eur... taking off. Friedrich Bayer ... and master dyer Johann Friedrich Weskott started the company together, which was initially named "Friedr. Bayer et comp.," and began producing aniline dyes. It was 13 years before Alexander Graham Bell obtained a patent for the first telephone and the same year that London opened the world's first underground rail network, albeit powered by horses.

The firm was initially located in Wuppertal, Germany, less than 20 miles from its current headquarters in Leverkusen. Within just 12 years, Bayer was selling dyestuffs beyond Germany, including in the U.K. And by 1881, it had a staff of 300 and was producing a range of dyes. Although both founders died within 20 years of starting Bayer, they had created an organization capable of sustaining rapid growth.

Bayer kicked off celebrations for its 150th anniversary in February at its annual results conference in Leverkusen. Activities included the unveiling of an exhibition and the launch of a two-seat helium-filled airship constructed from many of the firm's materials. The exhibition features 21 giant letters, each representing a company innovation. Collectively, the letters spell out Science for a Better Life. The airship ... exhibition will be displayed at more ... on five continents during ... of the year.

The ... celebration focuses on a research heritage that continues to this day. In 2012, Bayer spent $8.1 billion on R&D. Of the firm's 110,900 employees, 12,900 are involved in research, and Bayer ...

1863 Company starts up
Friedrich Bayer (left), a dye salesman, and master dyer Johann Friedrich Weskott create the firm. The focus is solely on producing synthetic dyes.

1899 Invents aspirin
The medicine is still one of the firm's best-selling drugs.

1913 Workforce hits 10,000

This aerial shot of Bayer's Leverkusen, Germany, site was taken looking west from a zeppelin airship in the summer of 1913.

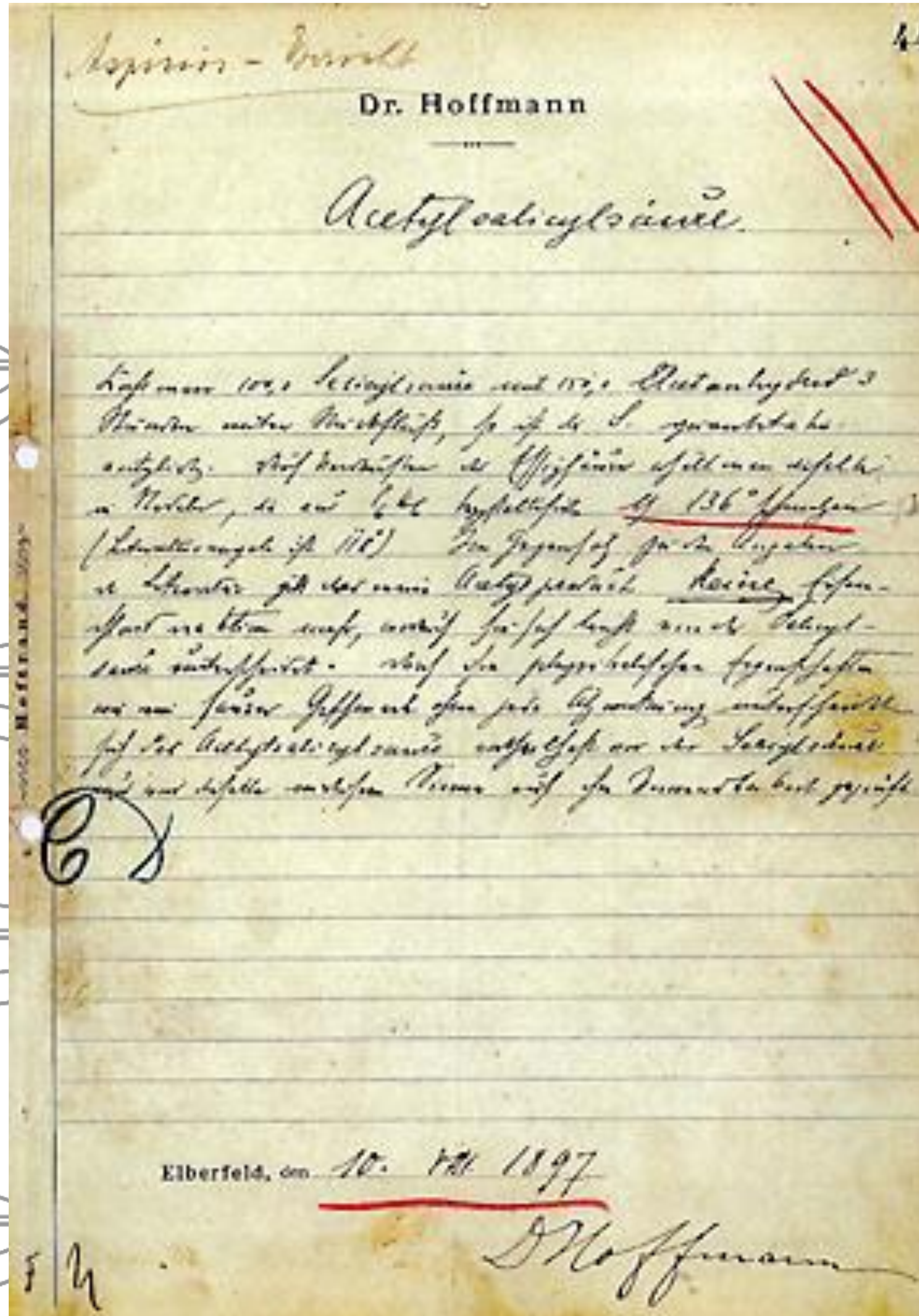
1937 Invents polyurethane
Employee Otto Bayer—no relation to the founder—divines the polymer.

Otto Bayer demonstrates a polyurethane foam experiment during a 1952 presentation.

BAYER THROUGH THE YEARS

1925 Merges into IG Farben
IG Farben is subsequently involved in war crimes during World War II, including provision of the pesticide Zyklon B, which was used in gas chambers during the Holocaust, and forced labor of—and experiments on—prisoners from the Auschwitz concentration camp.

1932 Discovers sulfonamide
Bayer scientist Gerhard Domagk discovers sulfonamide, the first family of antimicrobial drugs. In 1939, Domagk was awarded a Nobel Prize for his work.



44

Dr. Hoffmann

Acetylsalicylsäure

Elberfeld, den 10. VIII 1897

D. Hoffmann

Molécula pioneira

Ácido acetilsalicílico

AAS

1982

Sune K. Bergström

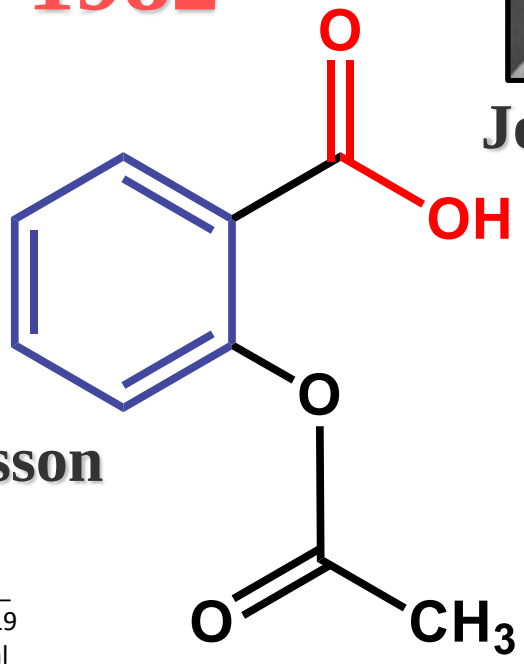
(1916-2004)

http://nobelprize.org/nobel_prizes/medicine/laureates/1982/bergstrom-autobio.html

Bengt I. Samuelsson

(1934-)

http://nobelprize.org/nobel_prizes/medicine/laureates/1982/samuelsson-autobio.html



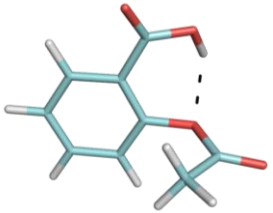
John R. Vane

(1927-2004)

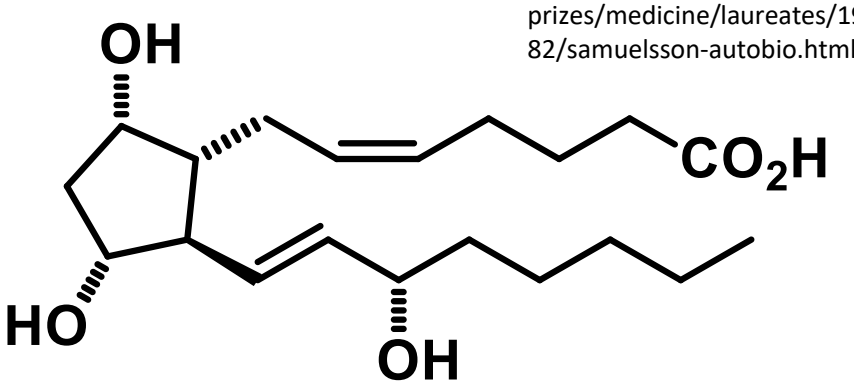
http://nobelprize.org/nobel_prizes/medicine/laureates/1982/vane-autobio.html

$C_9H_8O_4$

1889 ➡ 1982



AAS



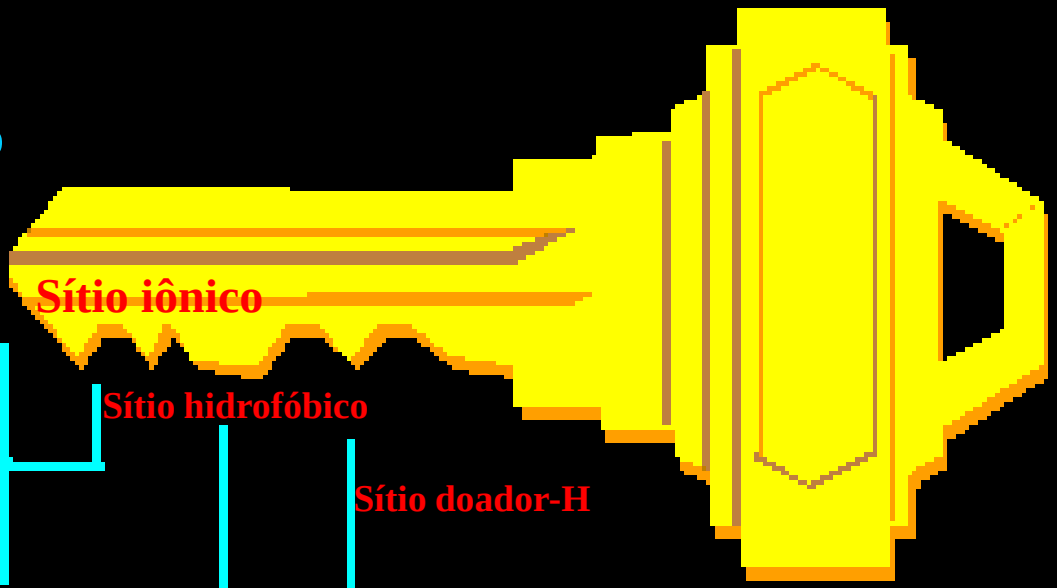
Prostaglandina $F_{2\alpha}$

O Centenário Modelo *"Chave-Fechadura"*

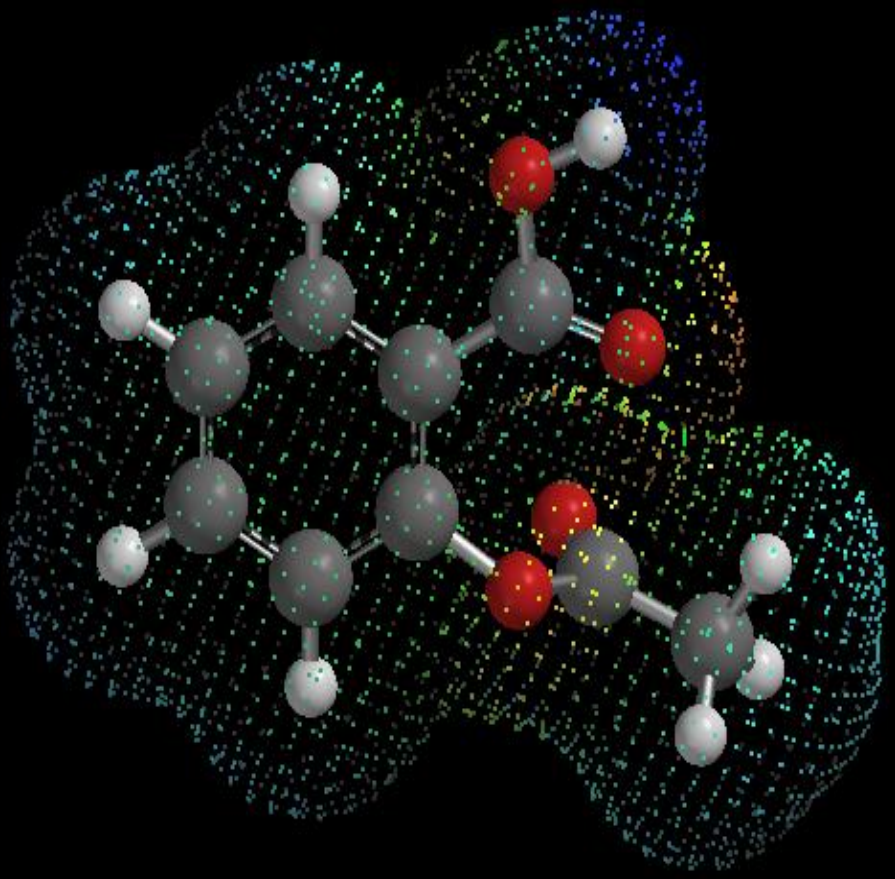
Complementaridade do modelo Chave-fechadura

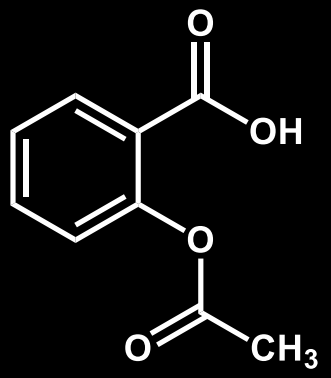
AAS

Sítio iônico

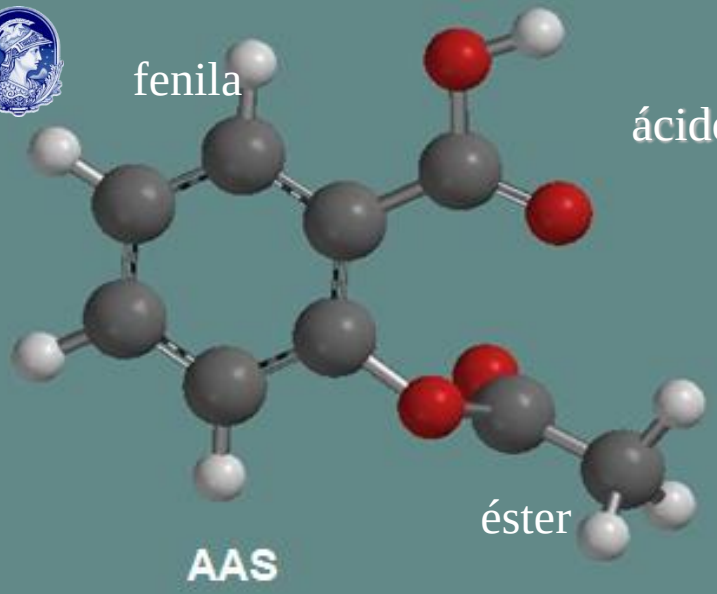


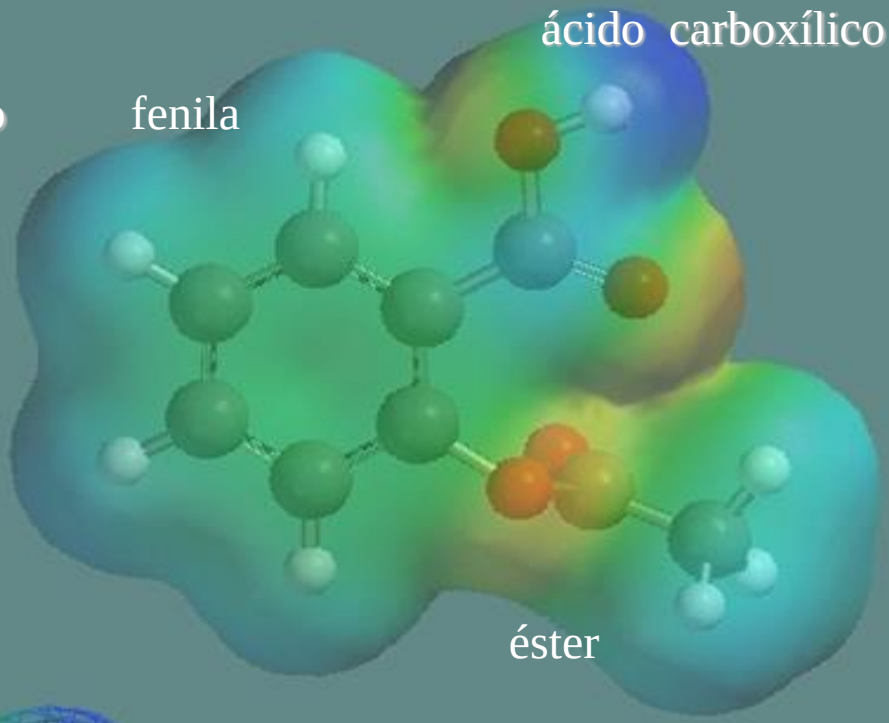
Ácido acetil salicílico





Dissecação molecular


fenila
ácido carboxílico
éster
AAS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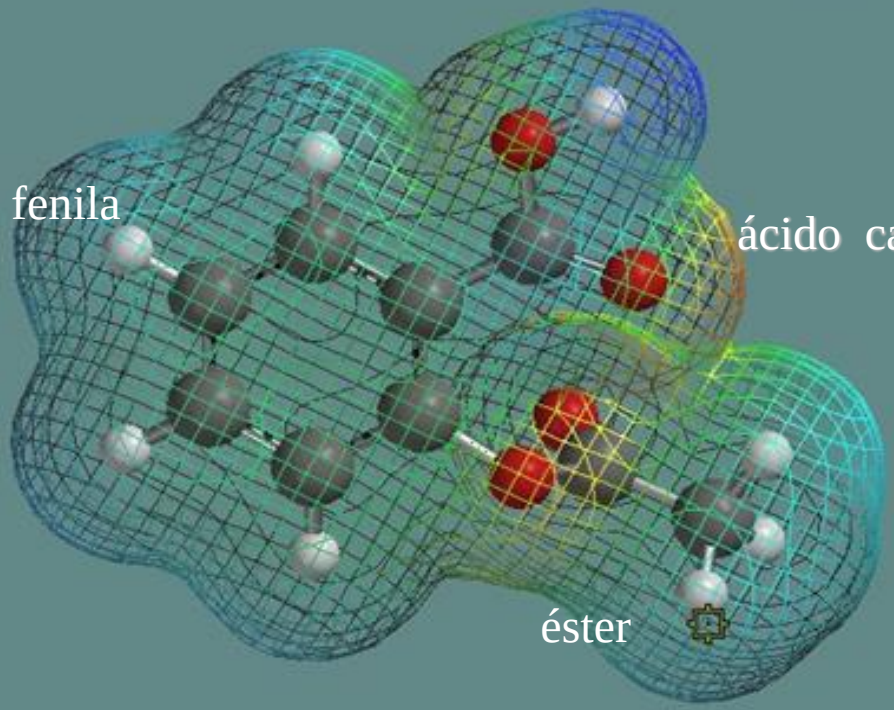
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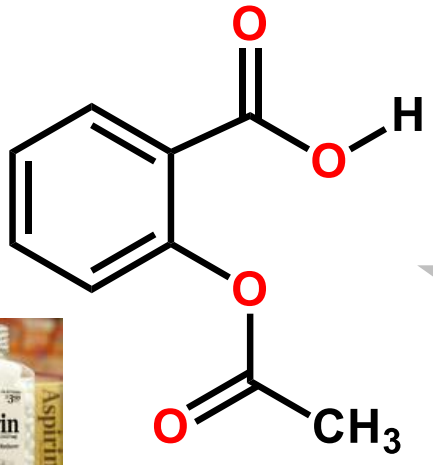
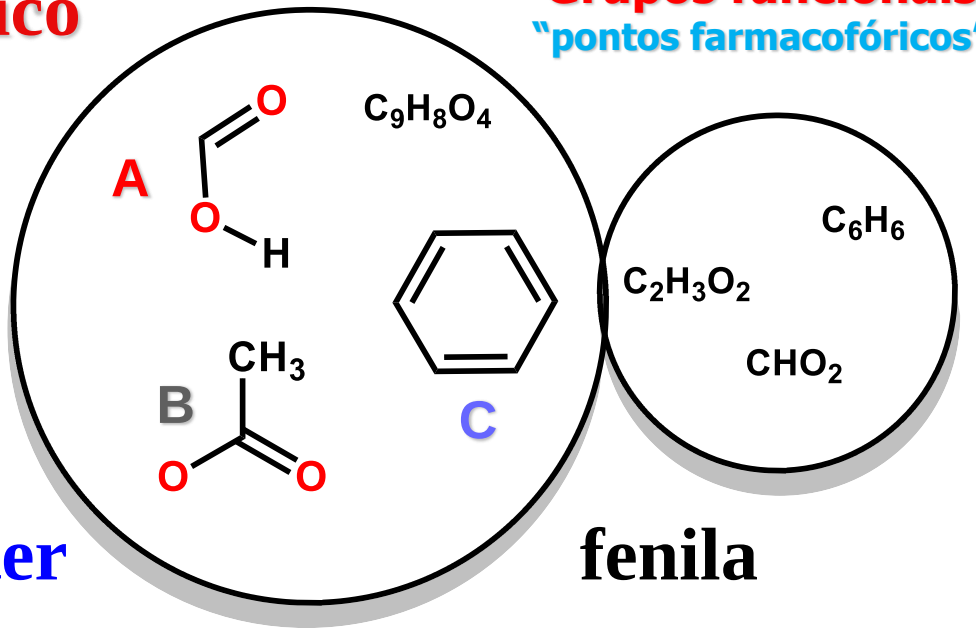
Dissecação Molecular

ácido carboxílico



$C_9H_8O_4$

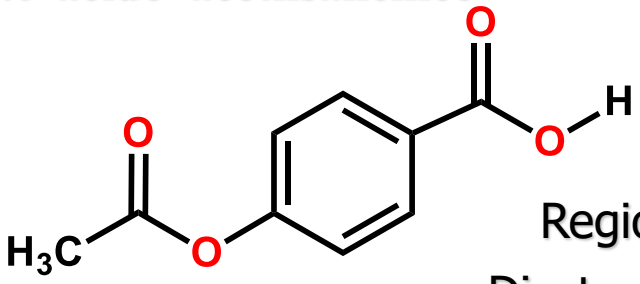
Grupos funcionais
"pontos farmacofóricos"

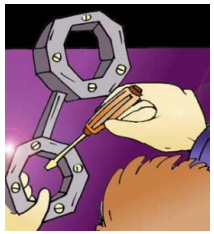


éster **fenila**

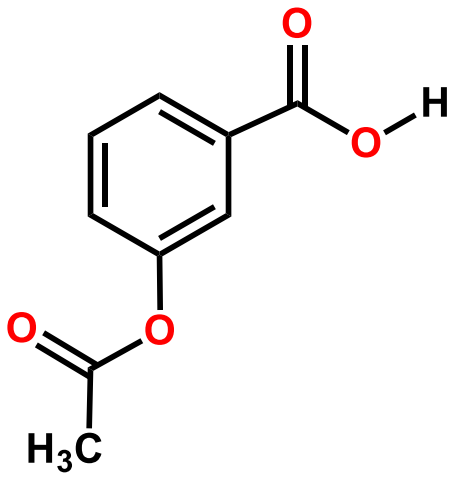
Ácido acetilsalicílico

orto-**ácido acetilsalicílico**





Regioisômeros
Diasterêoisomeros

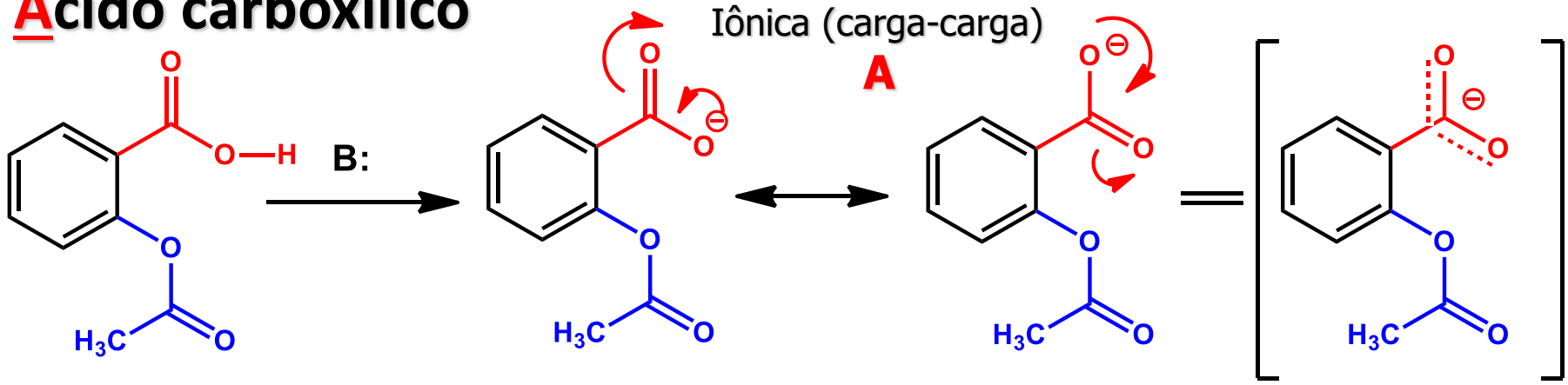


para-**ácido acetilsalicílico**

meta-**ácido acetilsalicílico**

Dissecação molecular

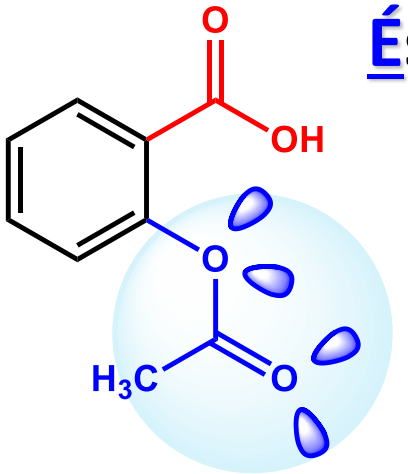
Ácido carboxílico

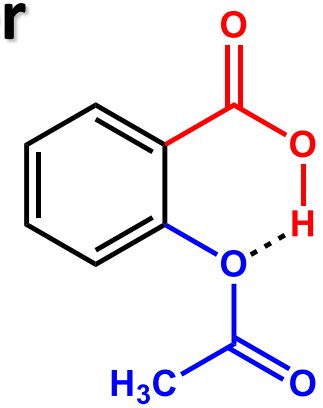


AAS

Propriedades moleculares

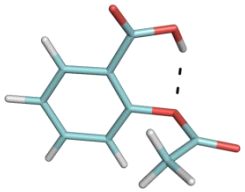
Éster





Ligação-H

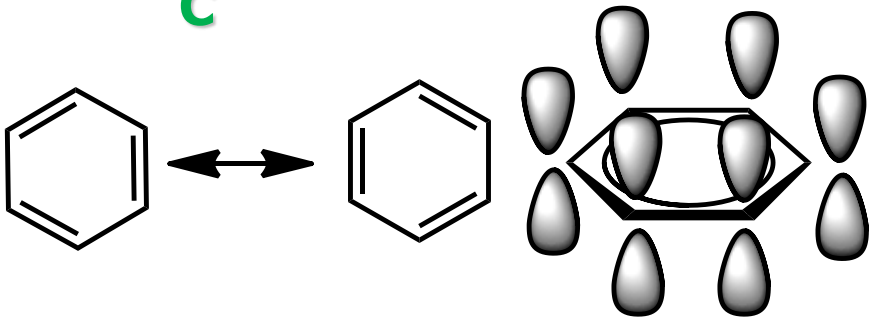
B



Fenila

Interações π-π

C



E_{int} =A >B >> C

Pontos farmacofóricos