

PRINCÍPIOS & FUNDAMENTOS

da Química Medicinal

PARTE 3

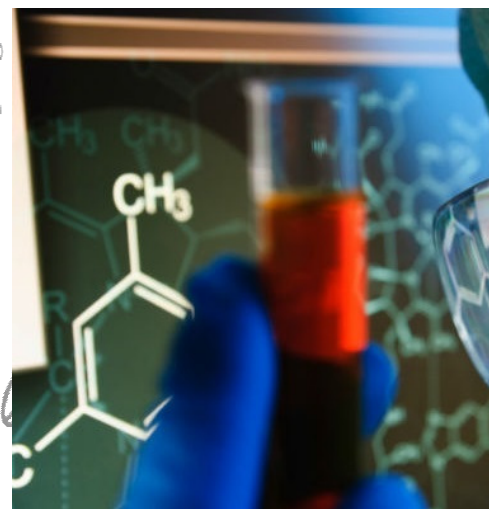
Eliezer J. Barreiro

Professor Titular

Universidade Federal do Rio de Janeiro



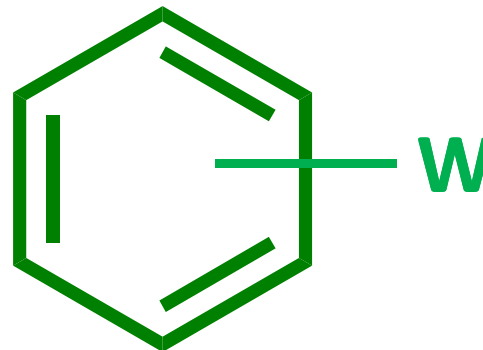
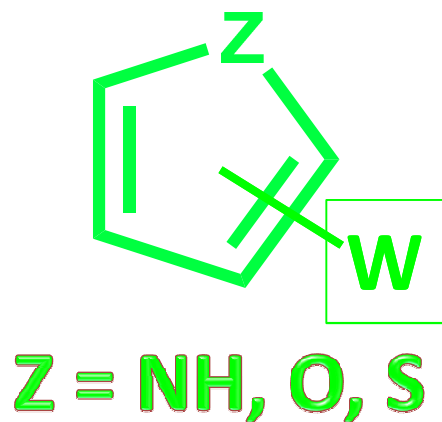
instituto de química
Universidade Federal do Rio de Janeiro



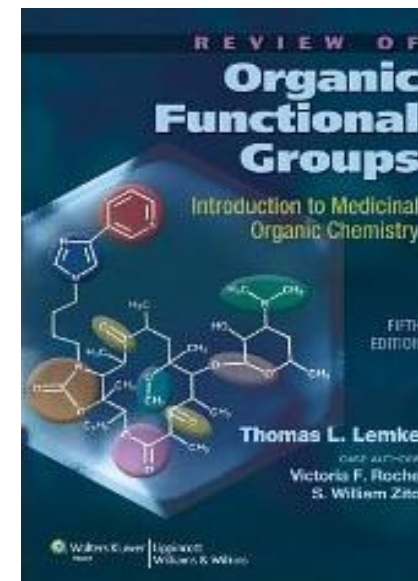
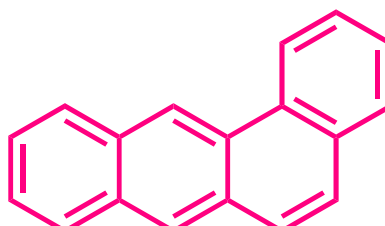
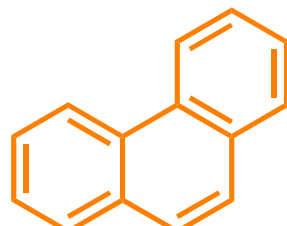
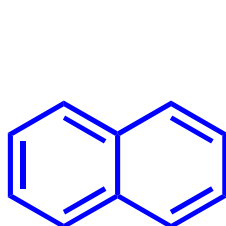
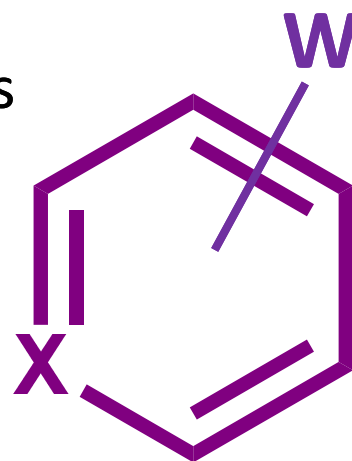
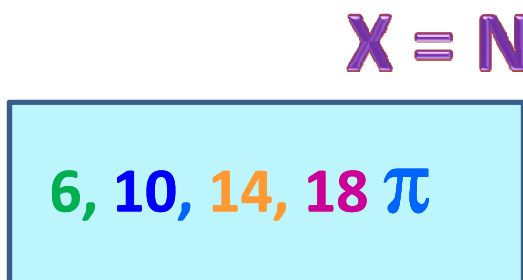


Os grupos funcionais mais frequentes nos fármacos

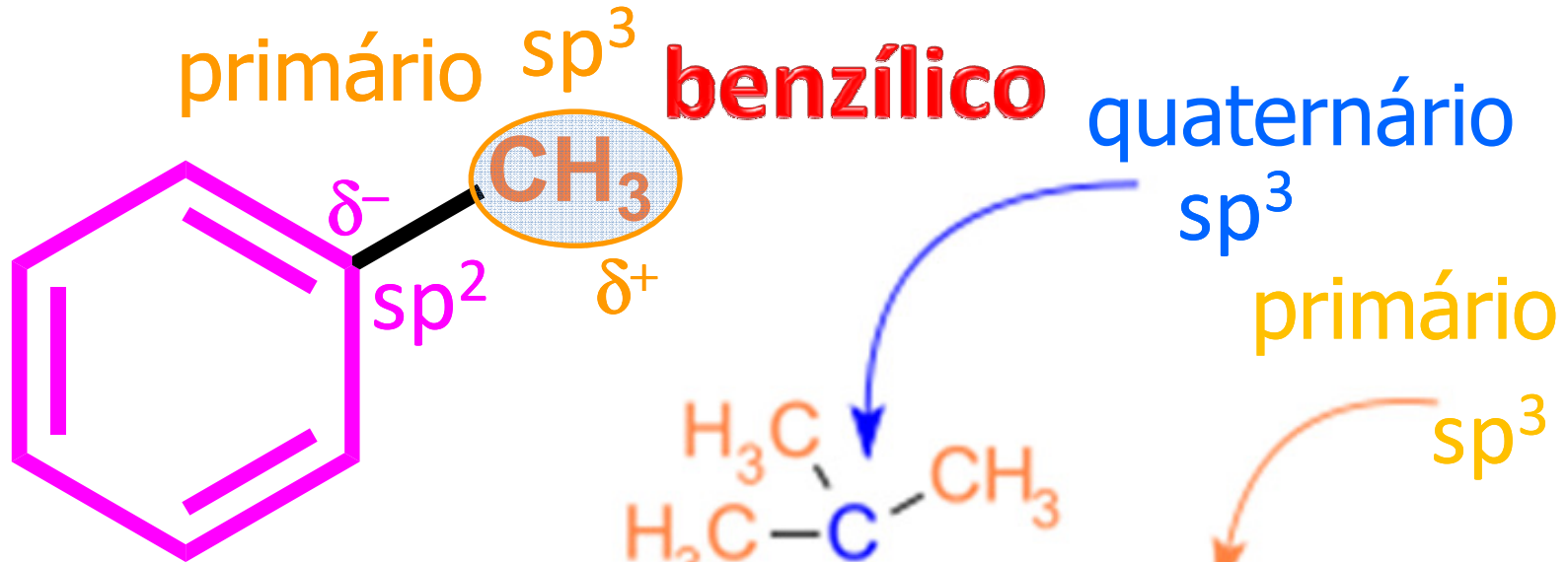
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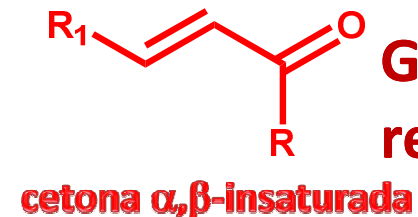
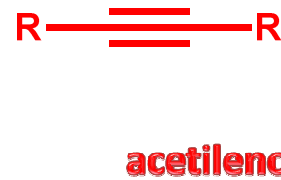
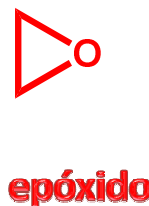
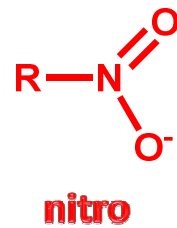
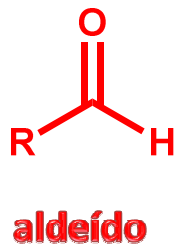
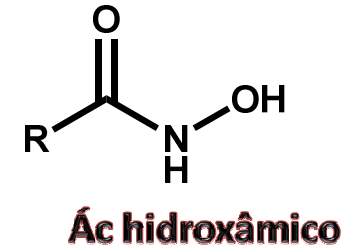
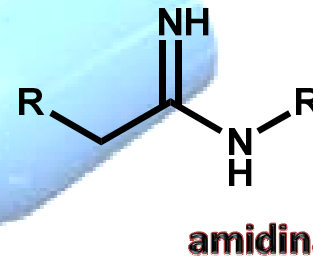
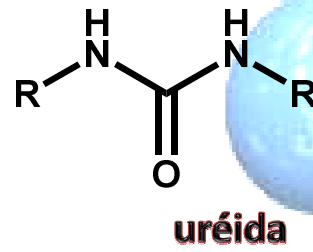
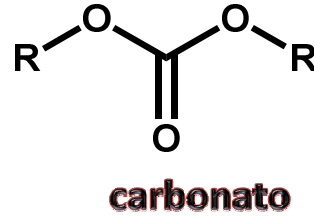
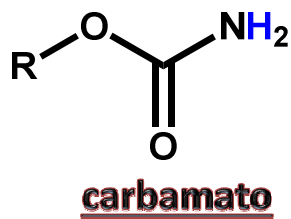
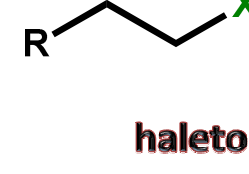
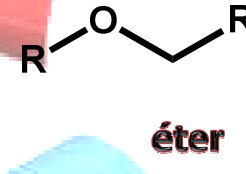
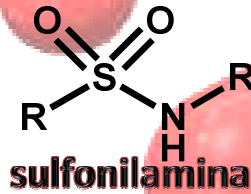
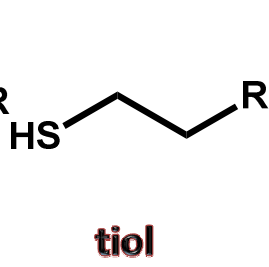
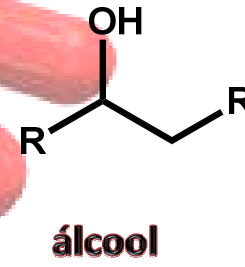
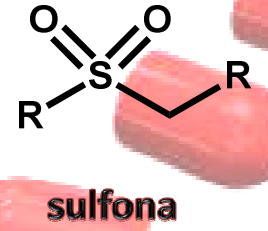
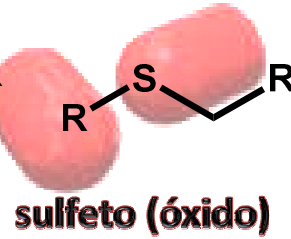
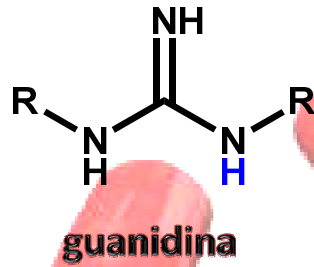
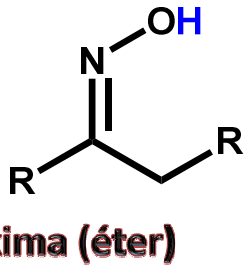
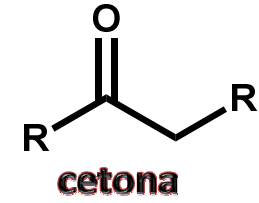
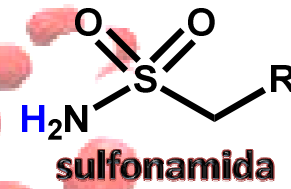
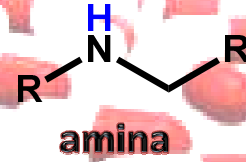
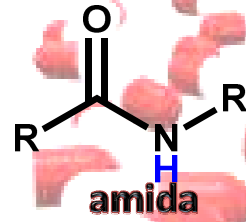
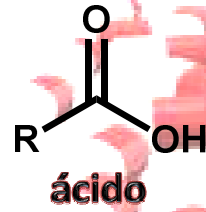
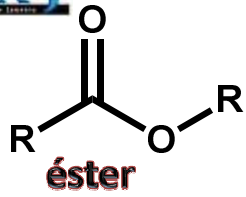
Propriedades eletrônicas



50% dos fármacos atuais
contêm pelo menos um
anel aromático, capaz de
poder sofrer substituições!



A reatividade química depende da polarização



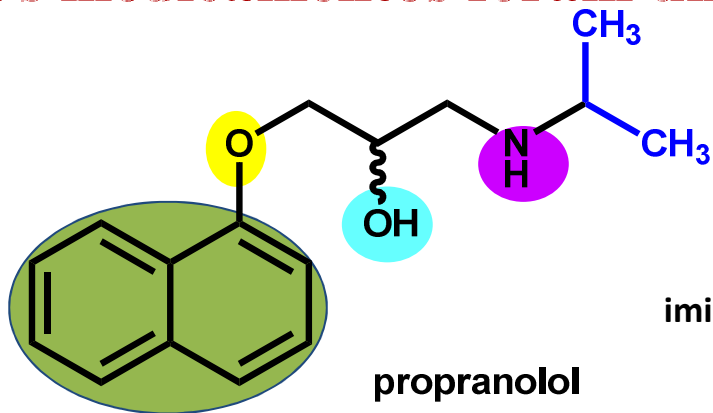
Grupos reativos



Os medicamentos foram uma das principais invenções do século 20

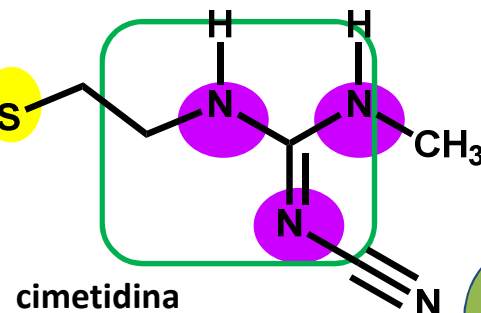
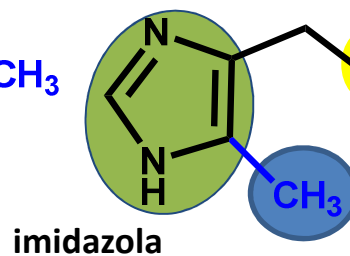
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Química
med
Medicinal
chem

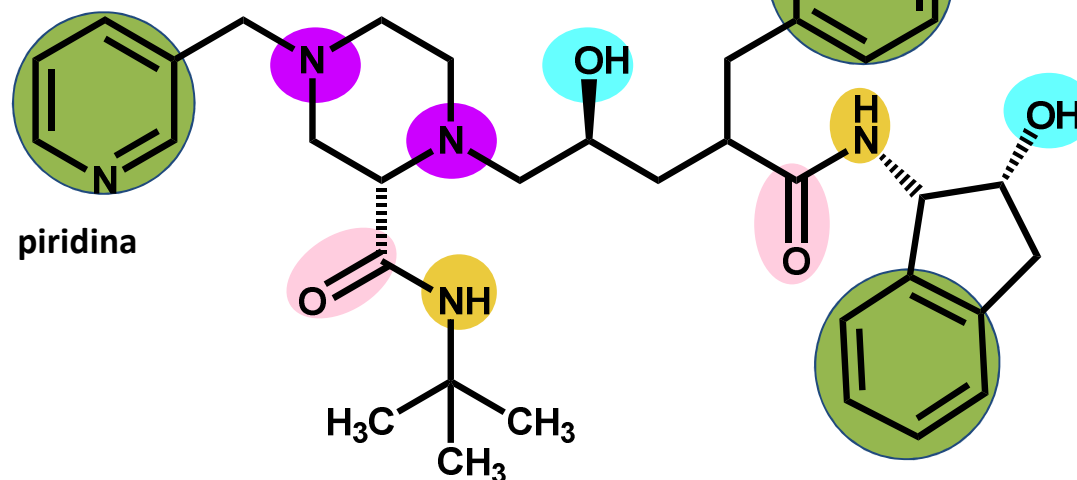


naftila

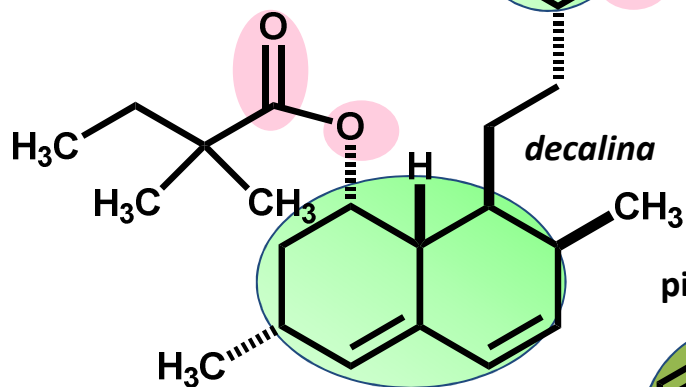
100%
cíclicos



fenila

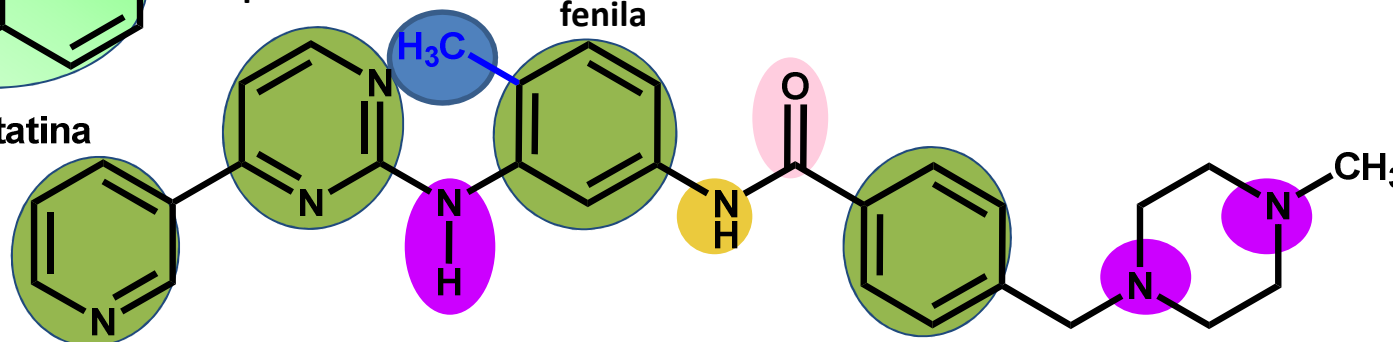


fenila



pirimidina

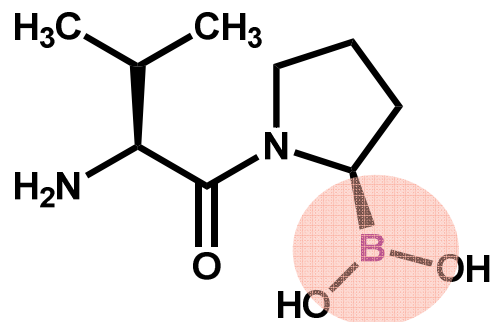
fenila



75%

possuem anel
aromático





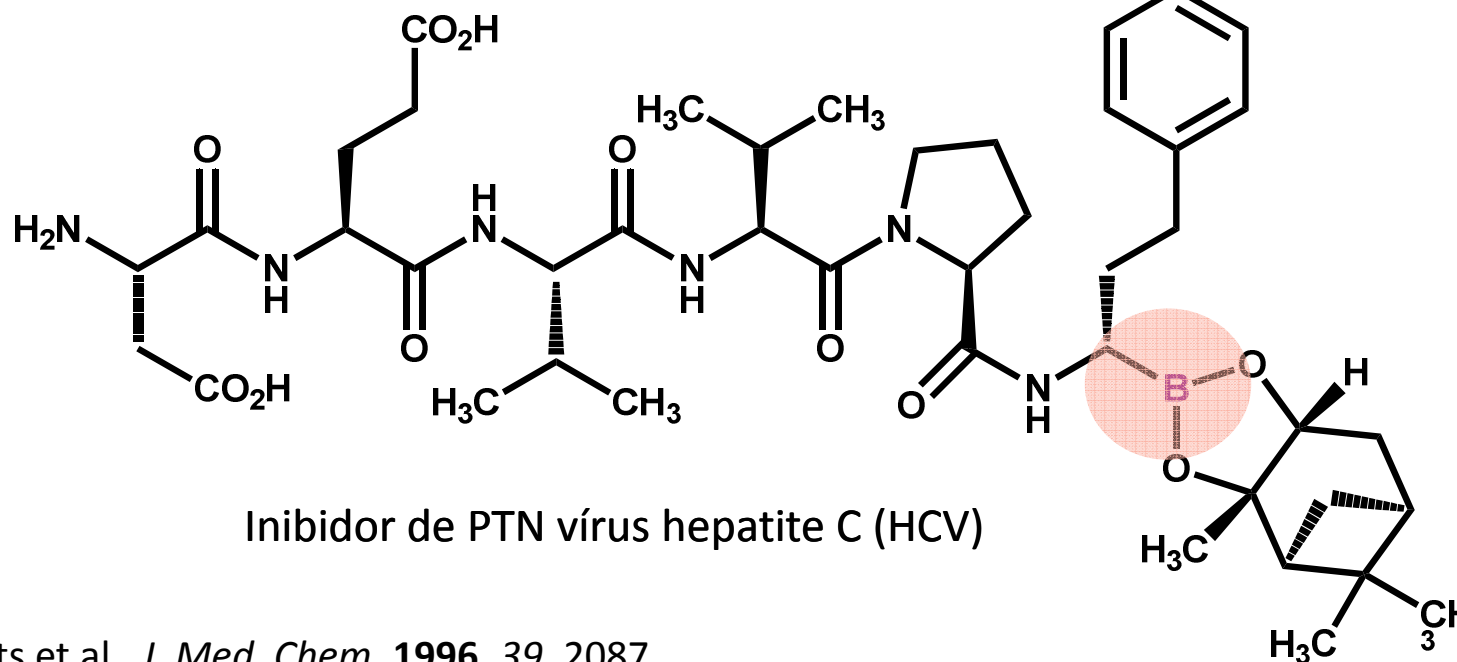
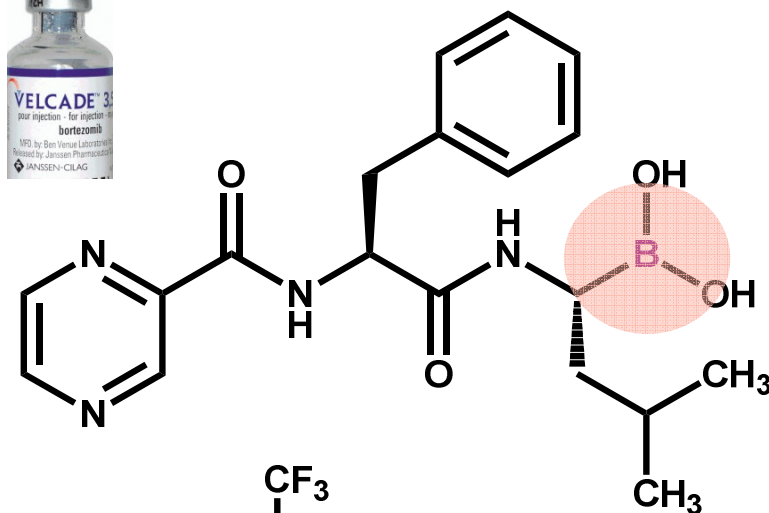
Inibidor de DPP-4
PHX-1147

Tufts Un & Boehringer Ingelheim



Bortezonibe

Janssen-Cilag
Velcade^R

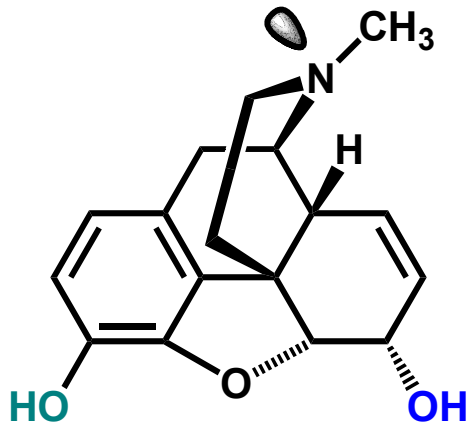


Inibidor de PTN vírus hepatite C (HCV)

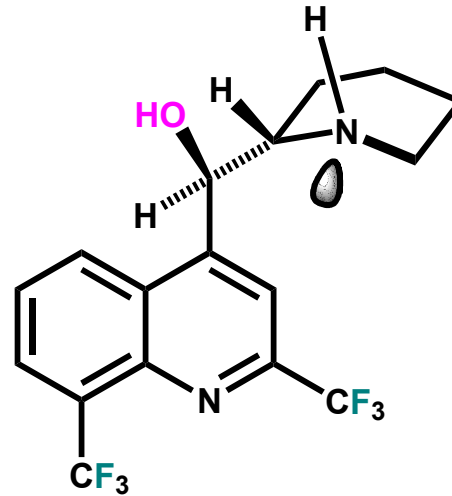
SJ Coutts et al., *J. Med. Chem.* **1996**, *39*, 2087

S J Baker et al, Therapeutic potential of boron-containing compounds, *Future Med Chem* **2009**, *1*, 1275

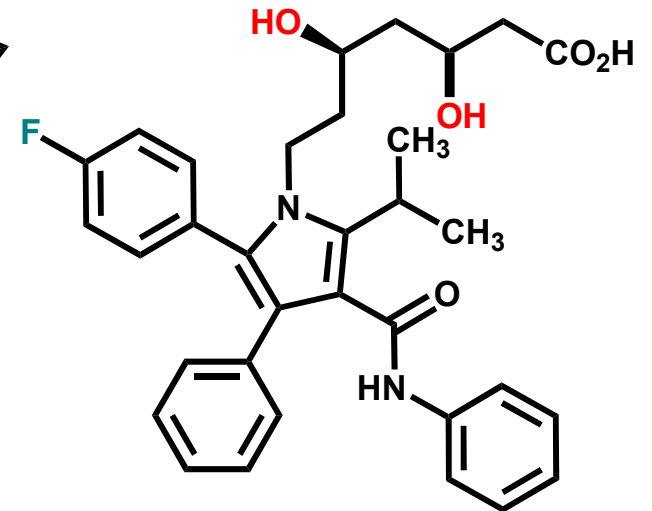
O quê têm em comum?



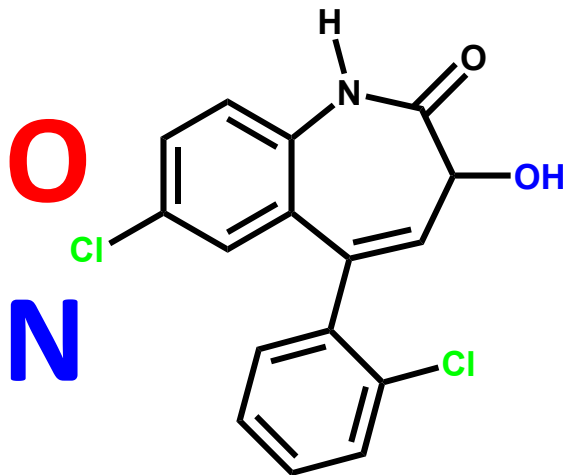
morfina
C₁₈H₂₁NO₃



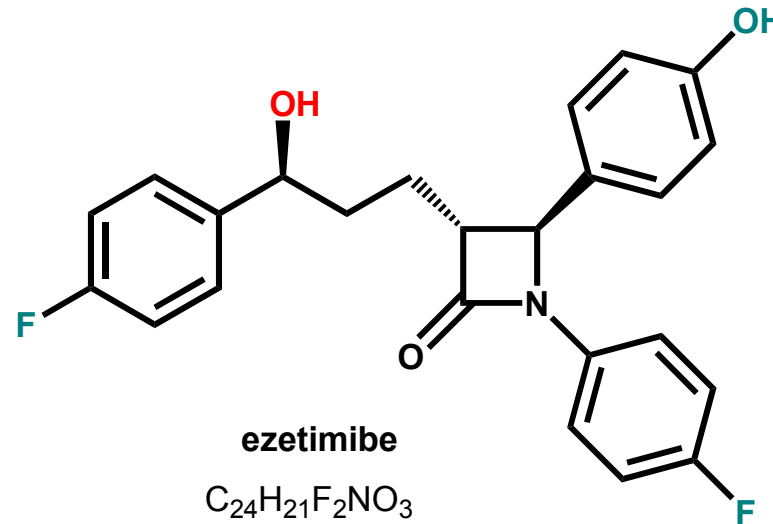
mefloquina
C₁₇H₁₆F₆N₂O



atorvastatina
C₃₃H₃₅FN₂O₅



lorazepan
C₁₆H₁₁Cl₂NO₂



ezetimibe
C₂₄H₂₁F₂NO₃

F

C

Cl

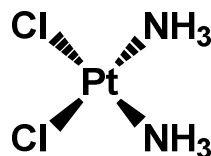
O

N

H



Para sua informação...

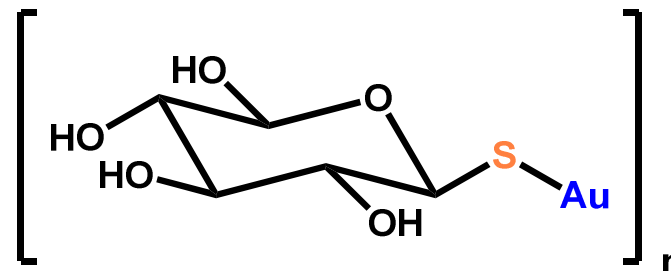


cisplatina

1978

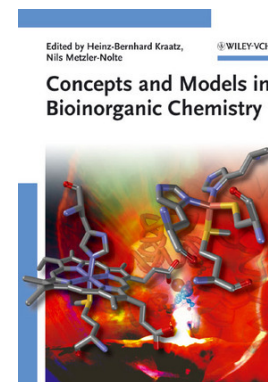
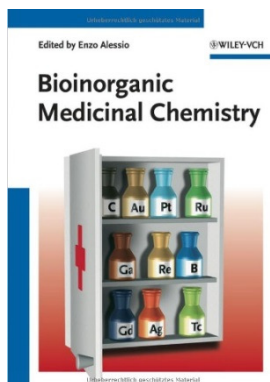
CDDP

E Wong, C M Giandomenico, Current Status of Platinum-Based Antitumor Drugs, *Chem Rev* **2009**, *99*, 2451



aurotioglucose

C. Frank Shaw III, Gold-Based Therapeutic Agents, *Chem Rev* **2009**, *99*, 2589



- E. Alessio, *Bioinorganic Medicinal Chemistry*, ed Wiley-VCH, Weinheim, 2011
- H-B Kraatz, N Metzler-Nolte, *Concepts and Models in Bioinorganic Chemistry*, Wiley-VCH, Weinheim, 2006

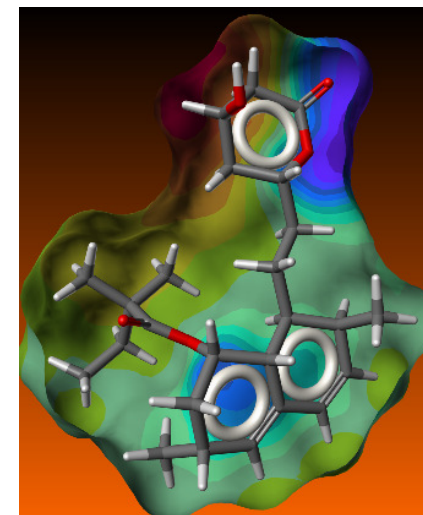
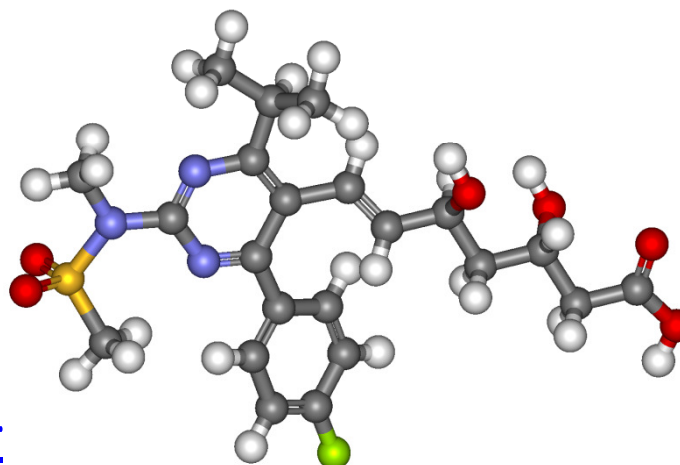
Freeware para estruturas químicas

- Isis Draw 2.5

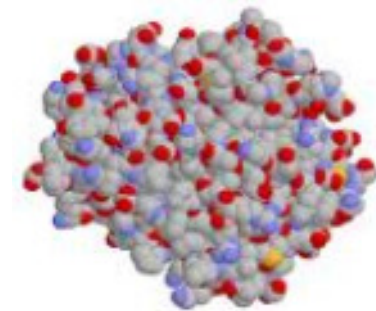
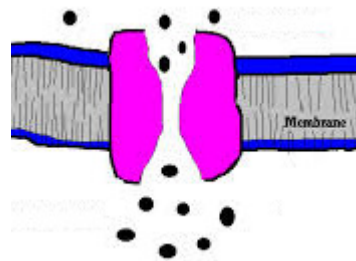
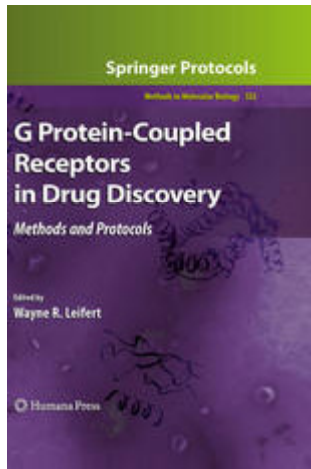
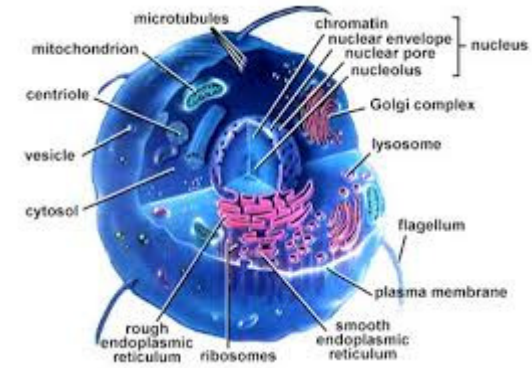
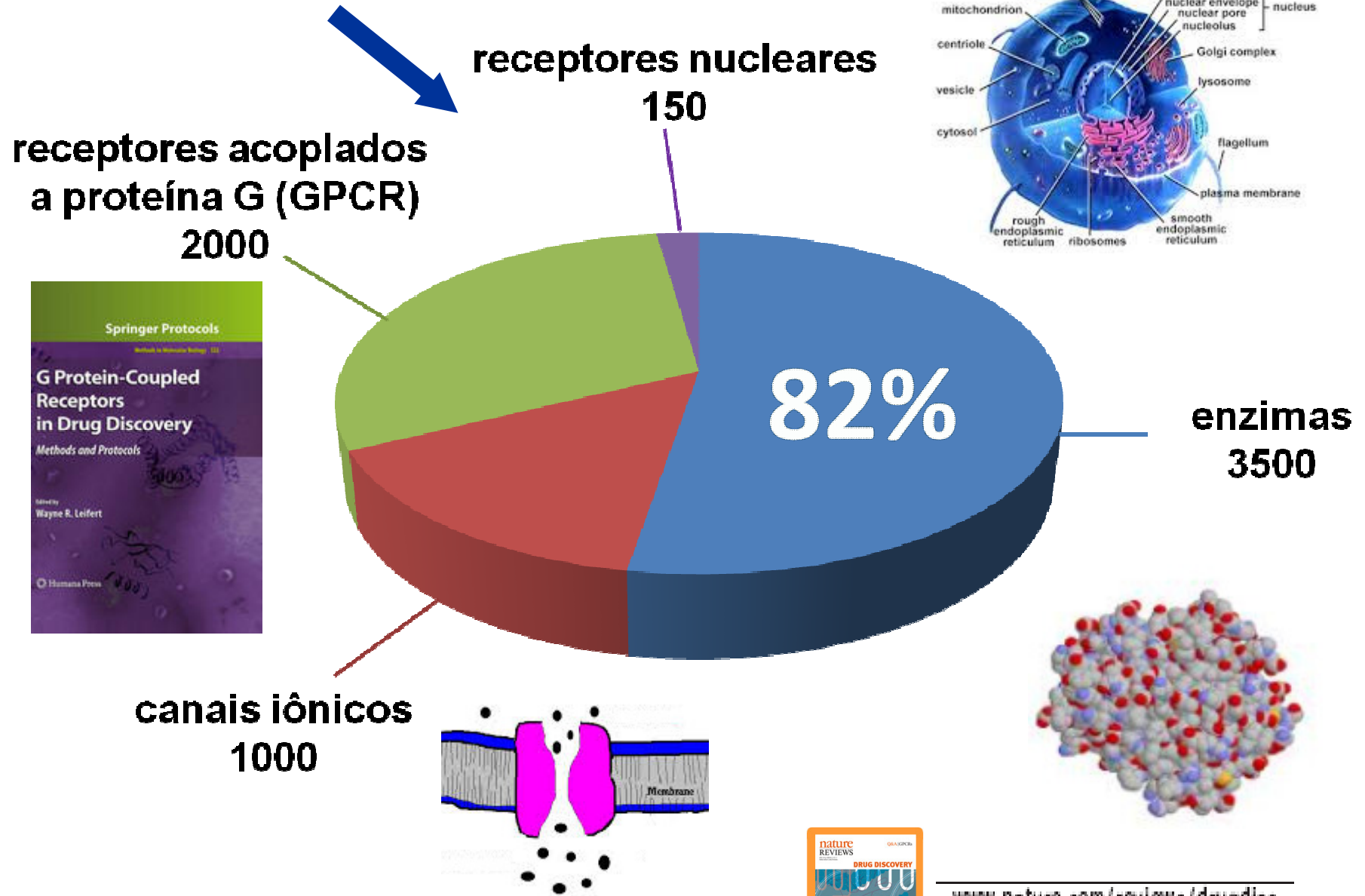
<http://www.lemon.com.br/produto.cfm?id=1956#download>

- www.pymol.org

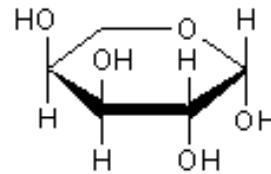
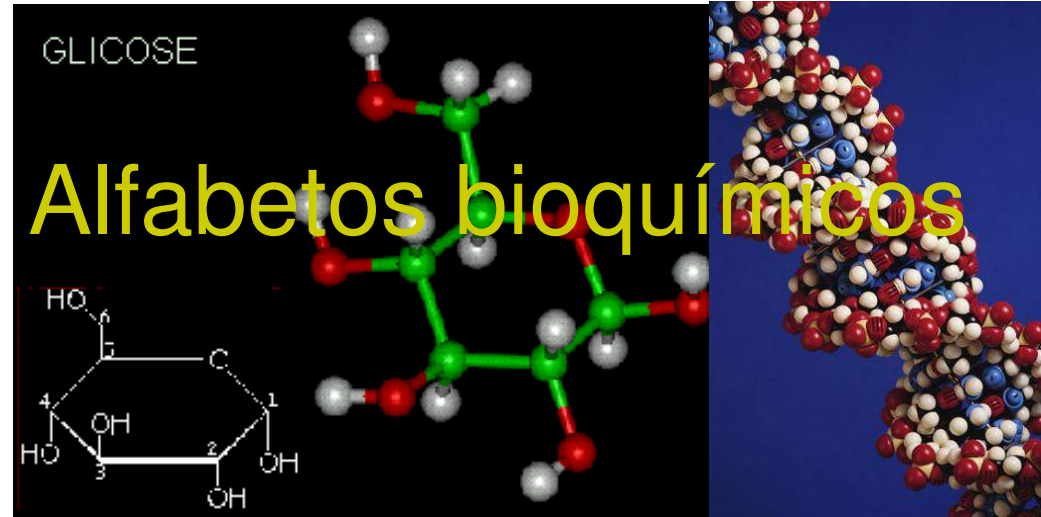
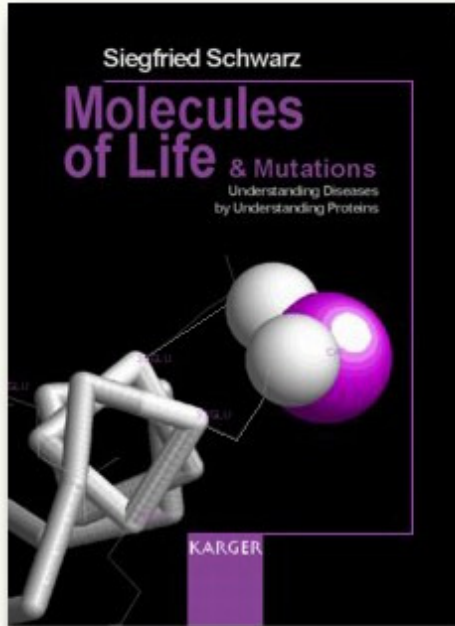
- <http://ciencia-em-si.webnode.pt/products/software-para-o-desenho-de-estruturas-quimicas/>



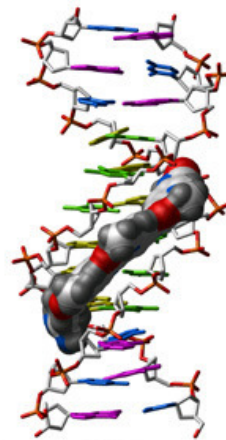
A maioria dos biorreceptores dos fármacos contemporâneos são enzimas ...



www.nature.com/reviews/drugdisc
Hopkins, A. L. & Groom, C. R. The druggable genome. *Nature Rev. Drug Discov.* 1, 727-30 (2002).



β -L-Arabinose



Model Compound Bound to the Minor Groove of a DNA Molecule

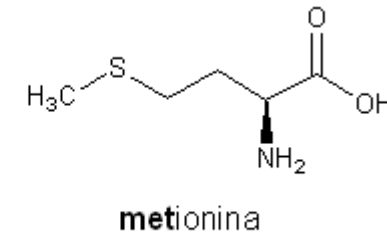
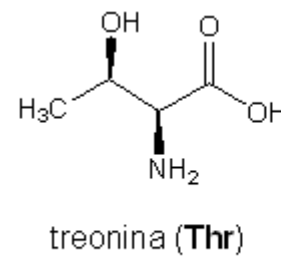
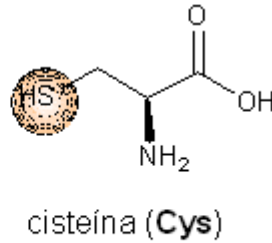
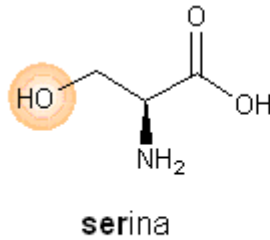
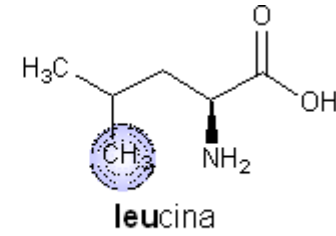
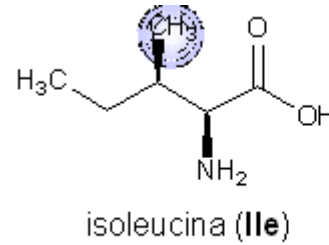
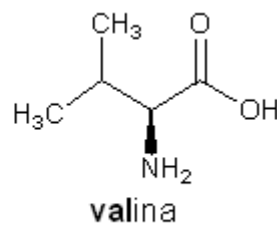
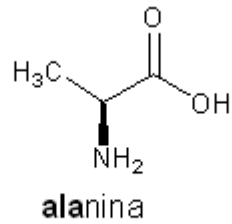
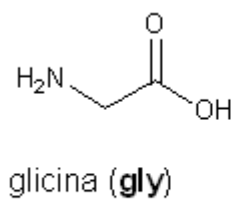
Carboídratos

Lipídeos

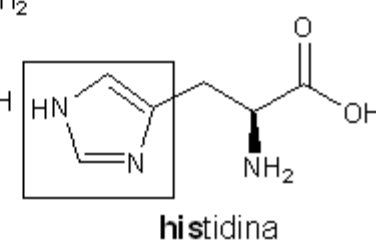
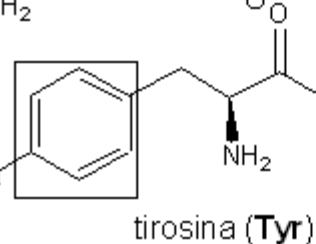
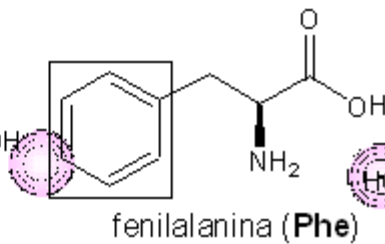
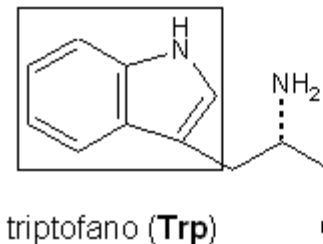
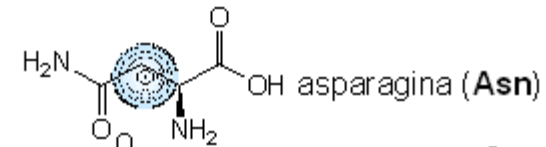
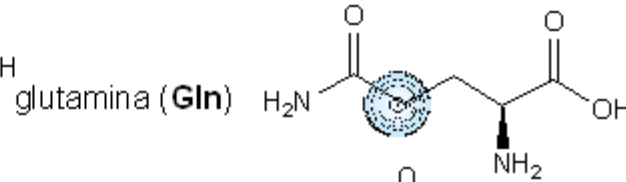
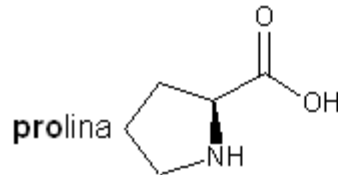
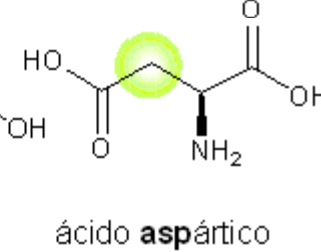
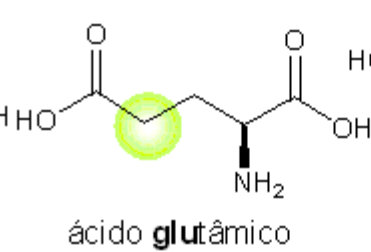
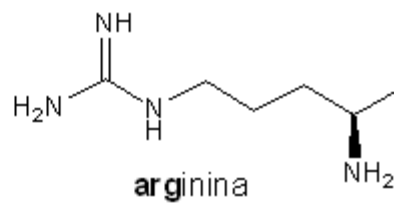
ácidos nucleícos

proteínas

O "alfabeto" protéico ...



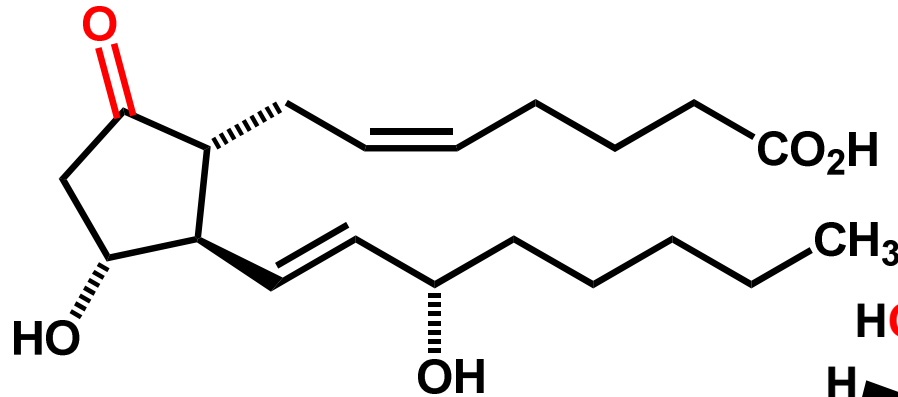
lisina (**Lys**)



Similaridade molecular

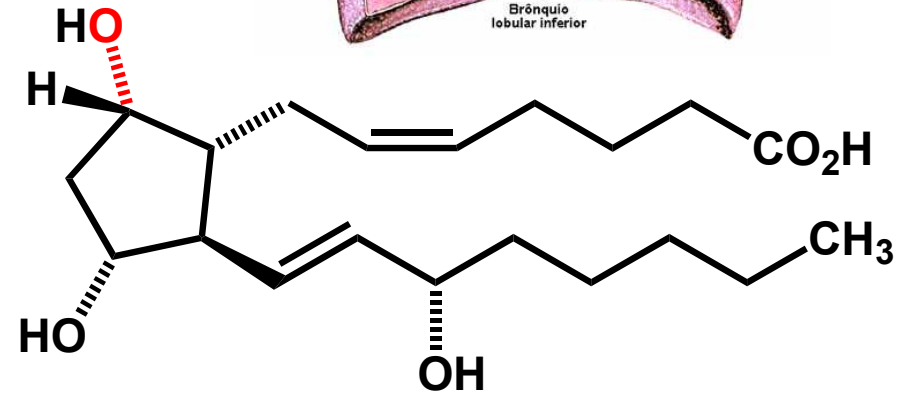
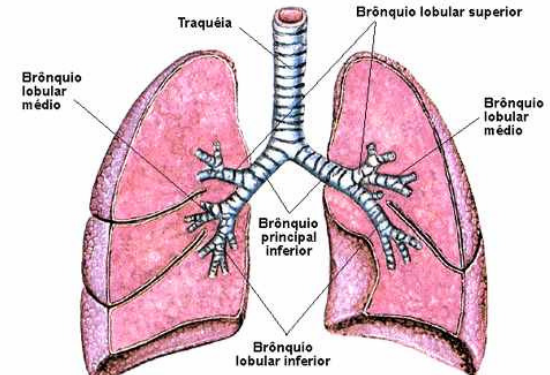


Similaridade Molecular



PGE₂

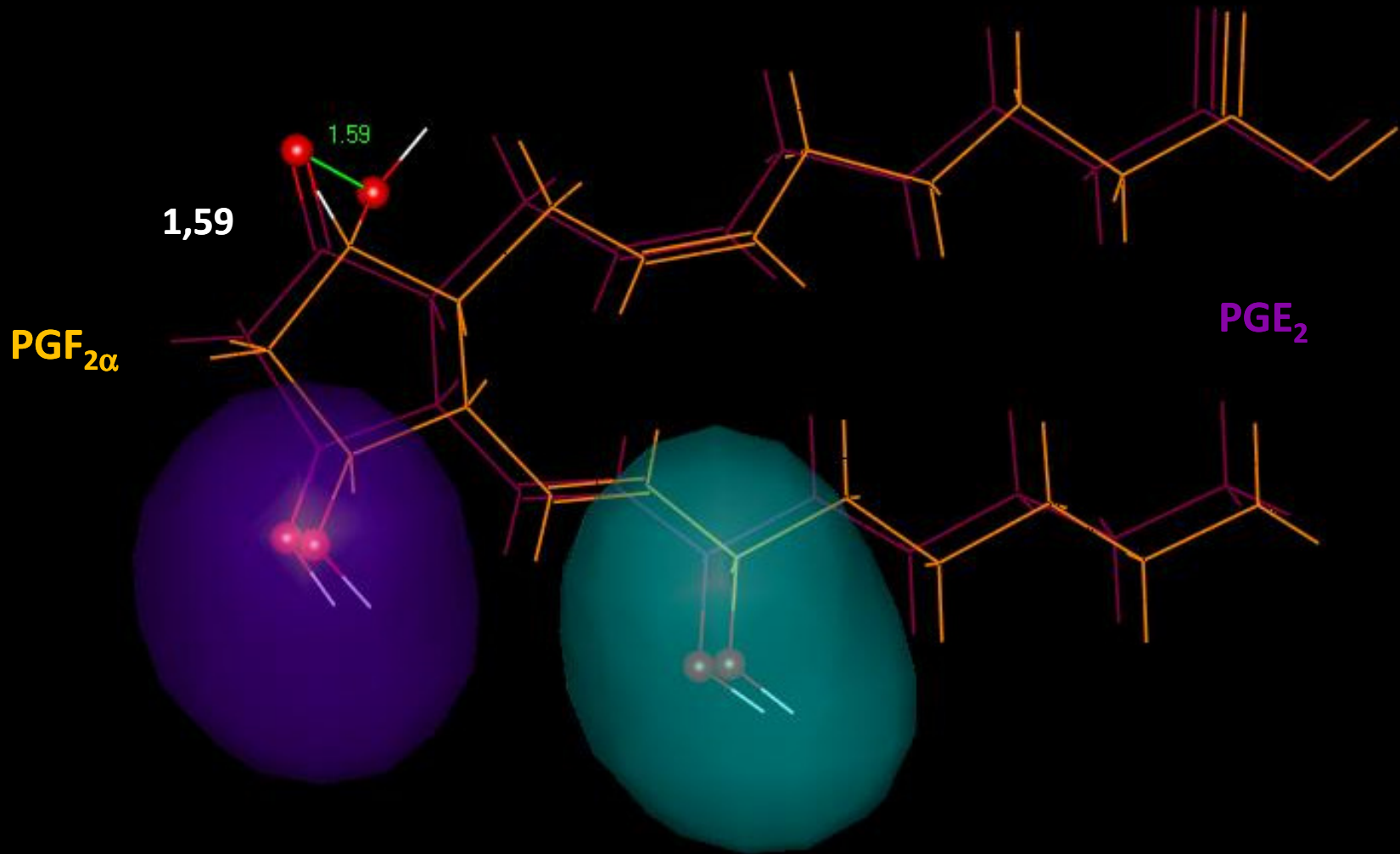
PGF_{2α} em cães provoca forte broncodilatação



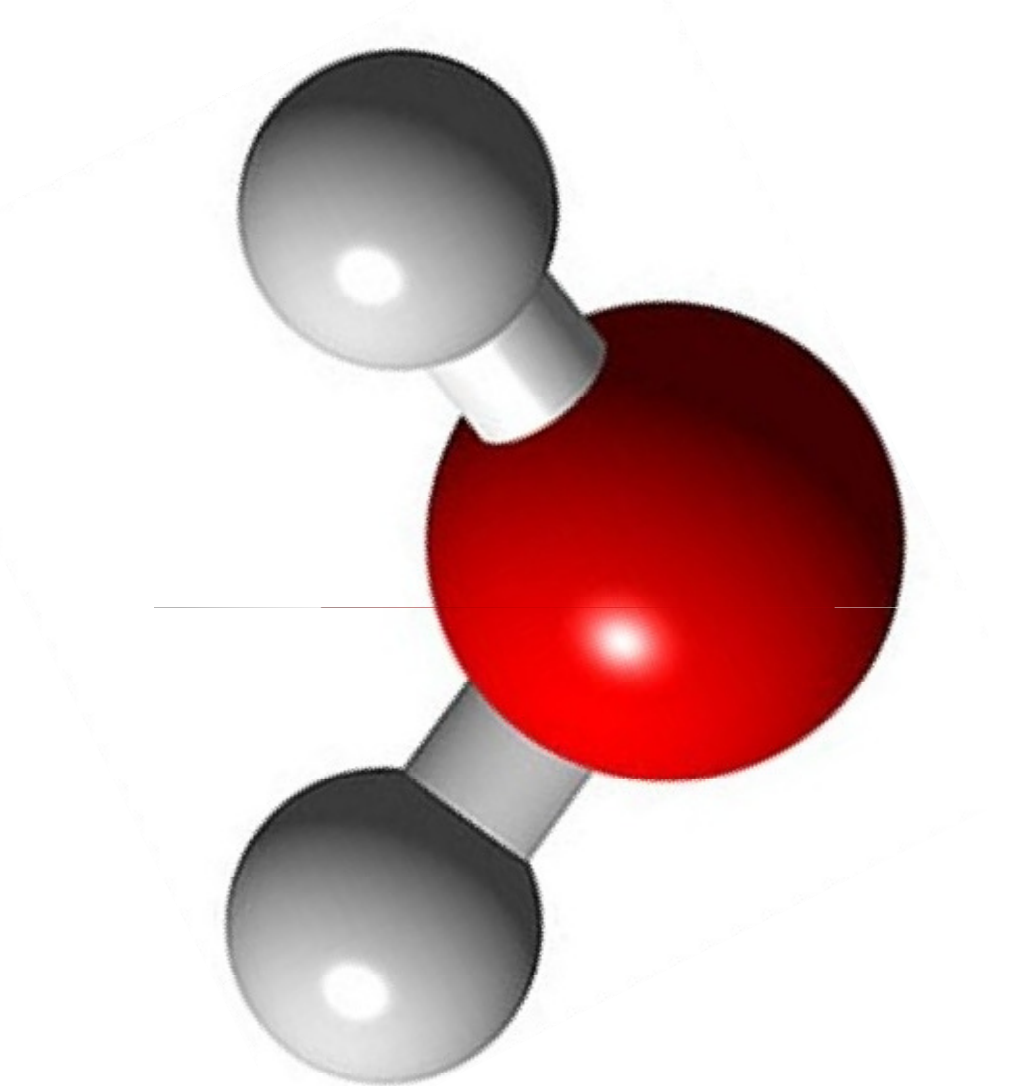
PGF_{2α}

PGF_{2α} em cães provoca severa broncoconstrição



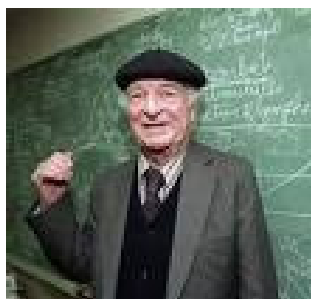
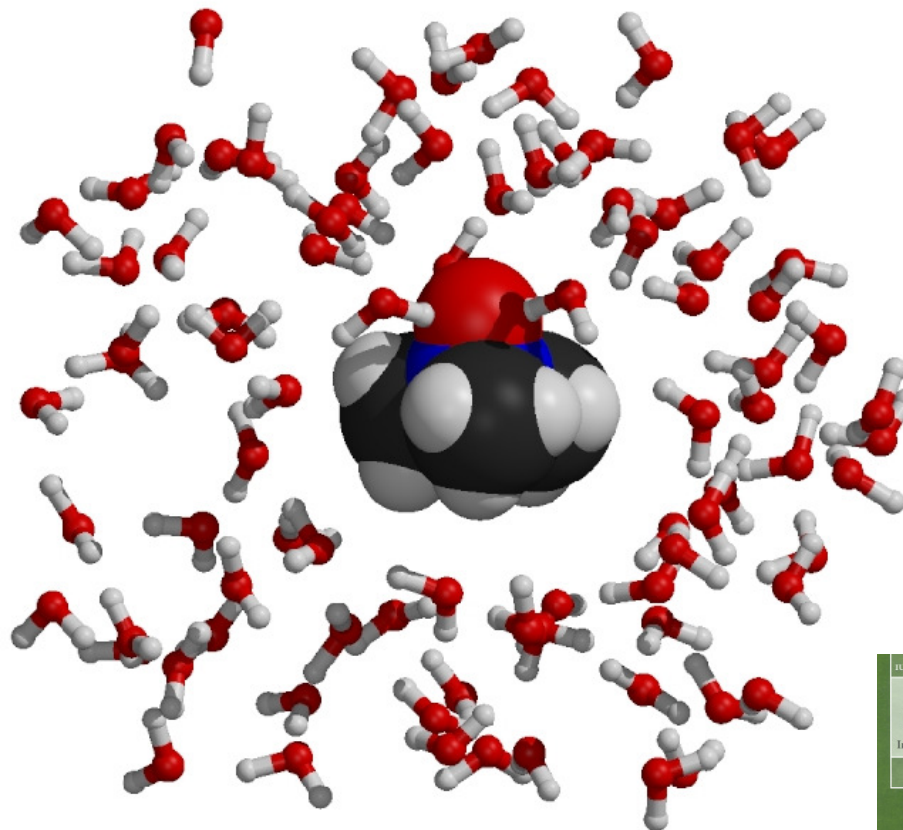
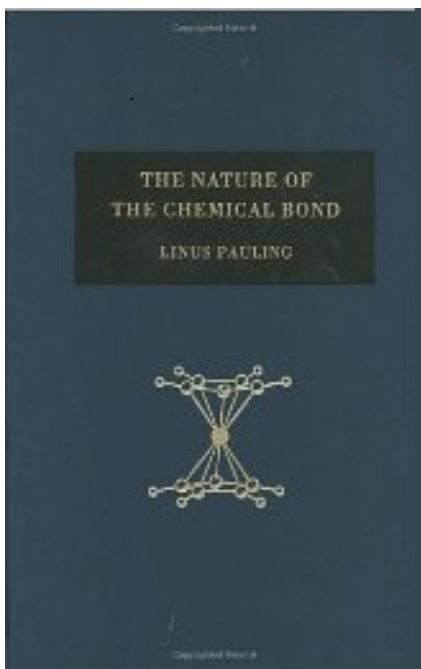


Pontos farmacofóricos



O que têm em comum?

A importância das “ligações” frágeis...

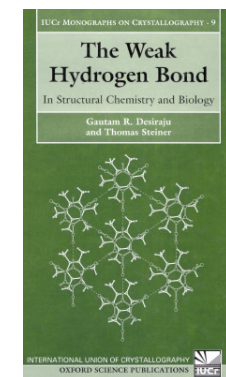


Linus C. Pauling
1901-1994

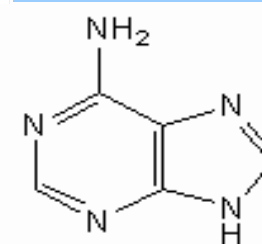
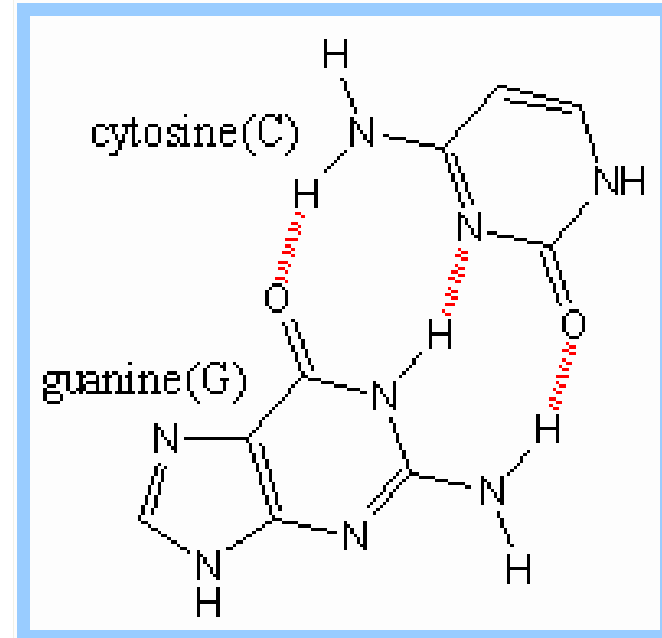
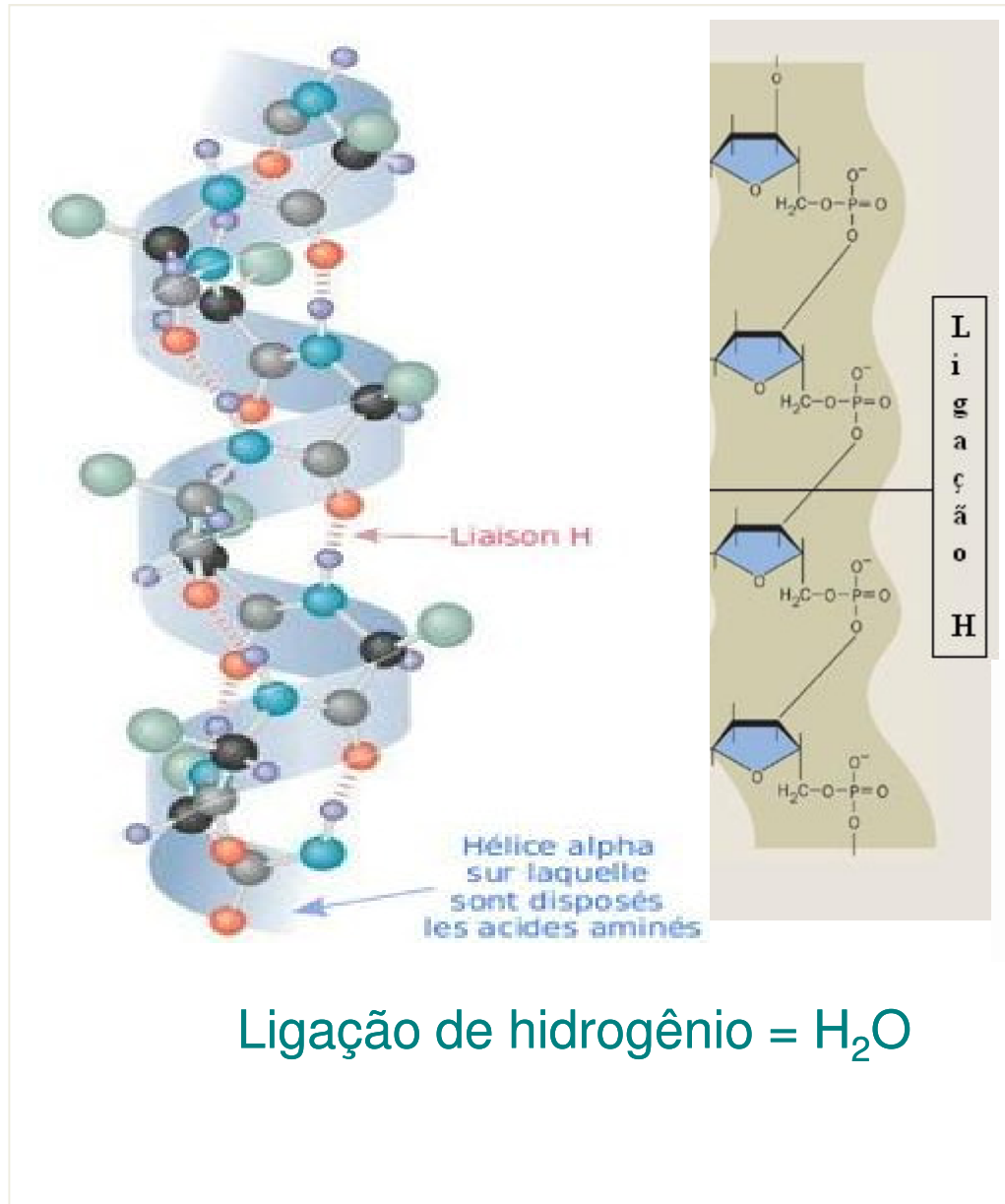


1954, 1962

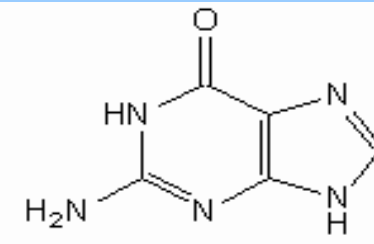
“ligações”
de hidrogênio ...



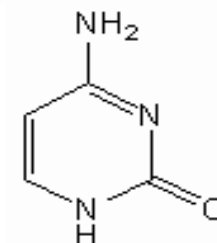
Proteínas, carboidratos, DNA, lipídeos, canais iônicos



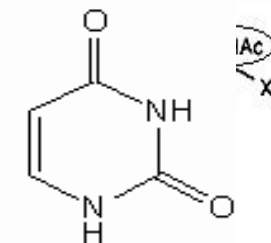
adenine (A)



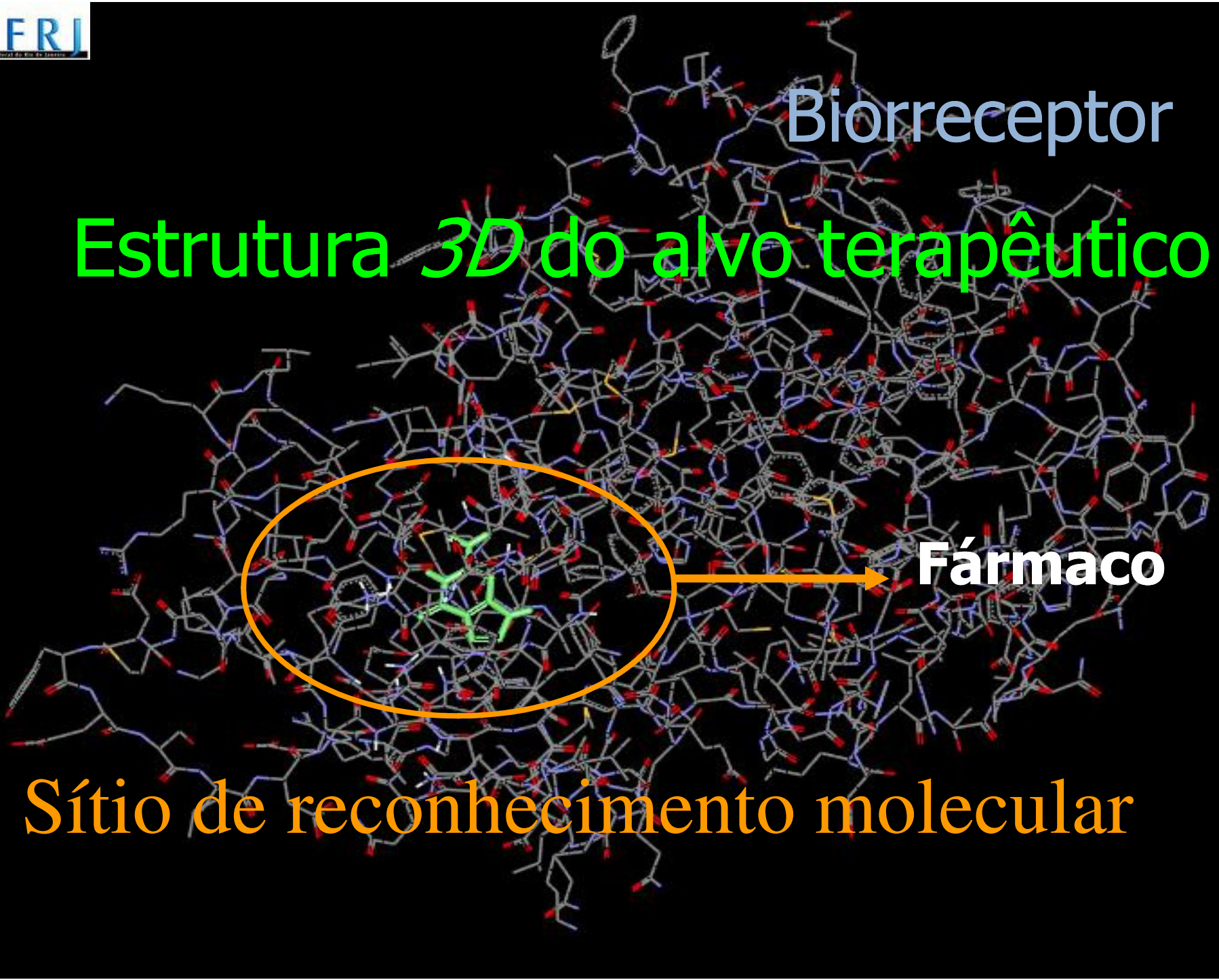
guanine (G)



cytosine (C)



uracil (U)



Biorreceptor

Estrutura 3D do alvo terapêutico

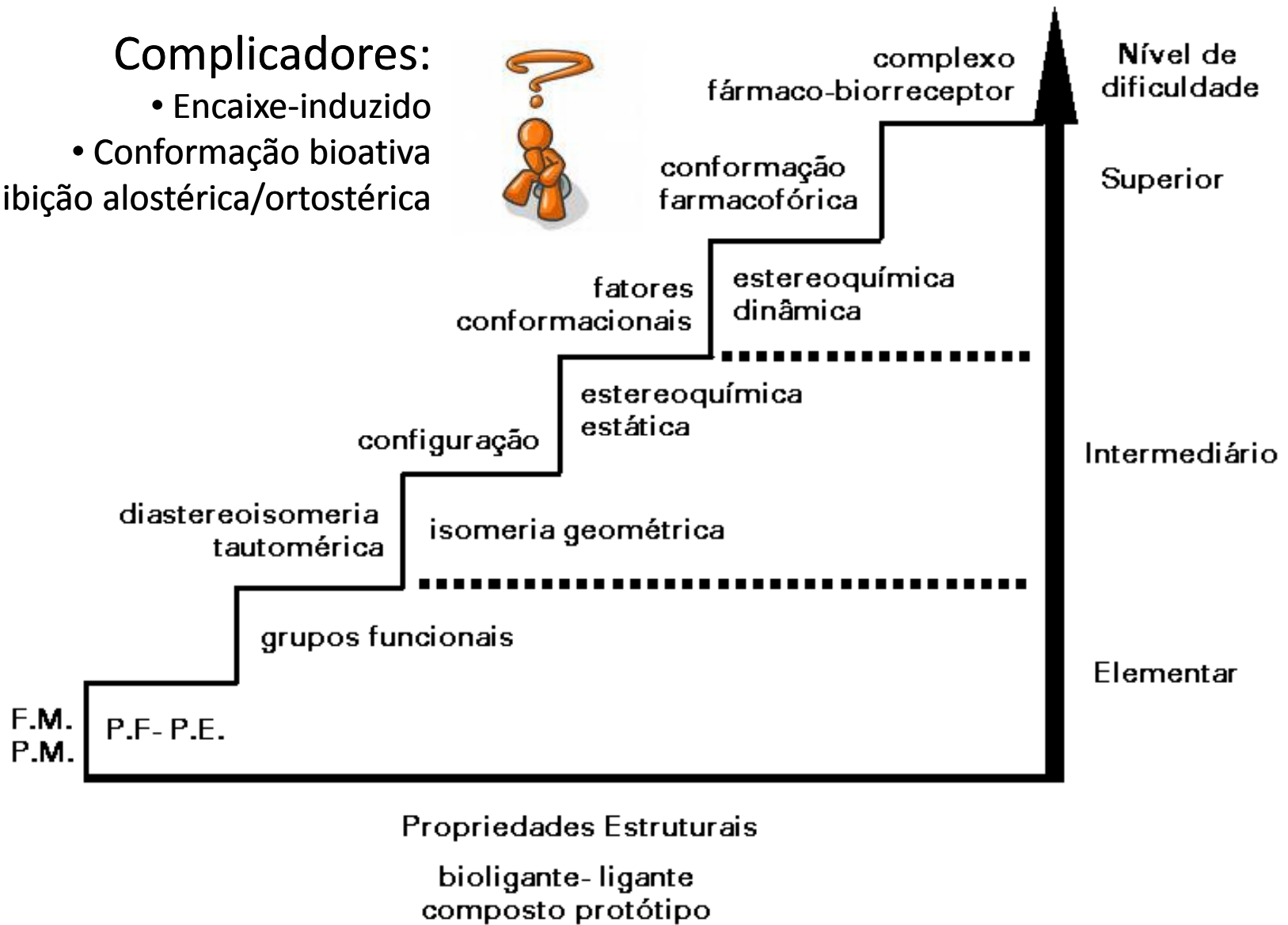
Fármaco

Sítio de reconhecimento molecular

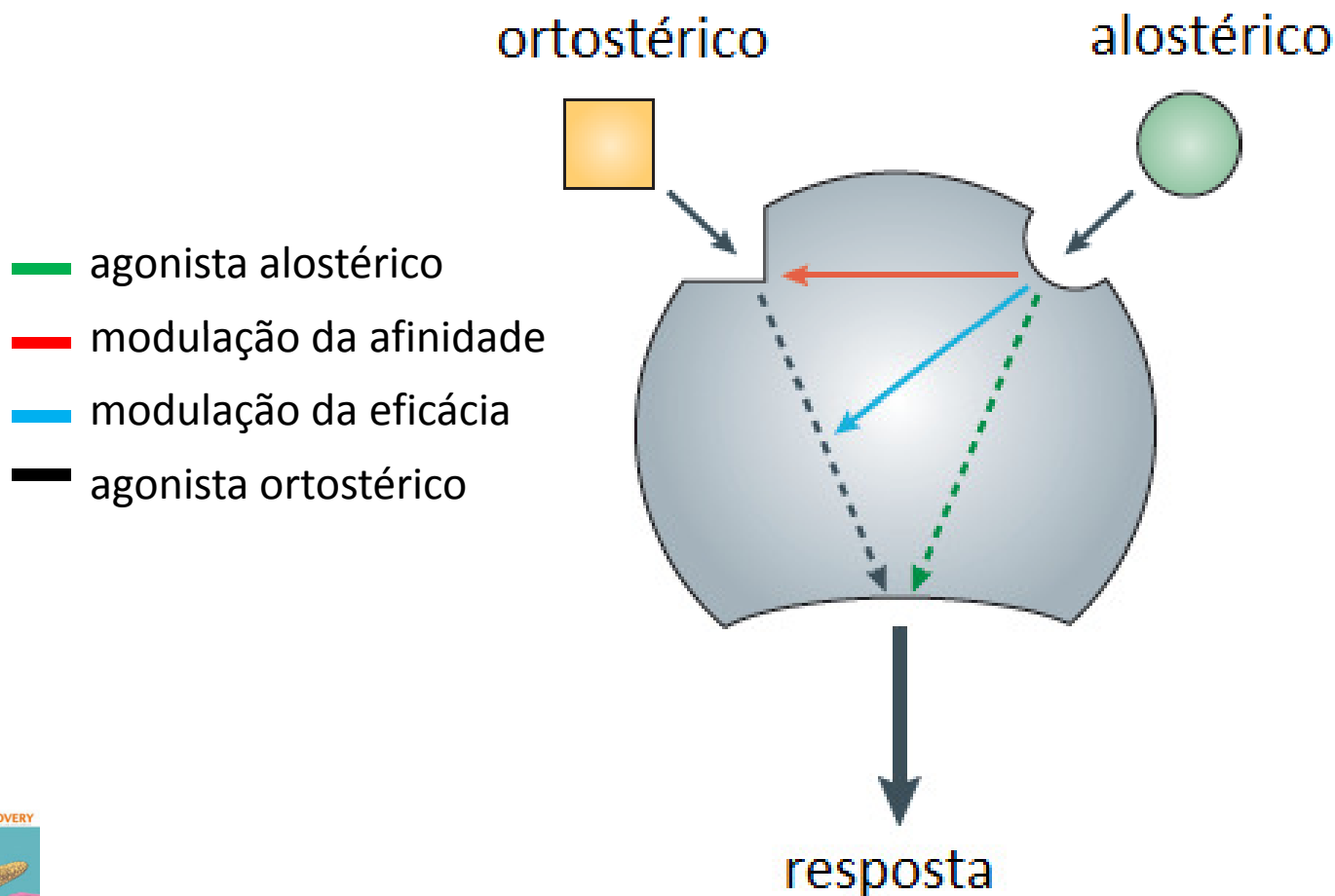


Nível hierárquico da descrição da complementaridade F-R

- Complicadores:**
- Encaixe-induzido
 - Conformação bioativa
 - Inibição alostérica/ortostérica



O desenho de novos candidatos a fármacos alostéricos é um desafio!



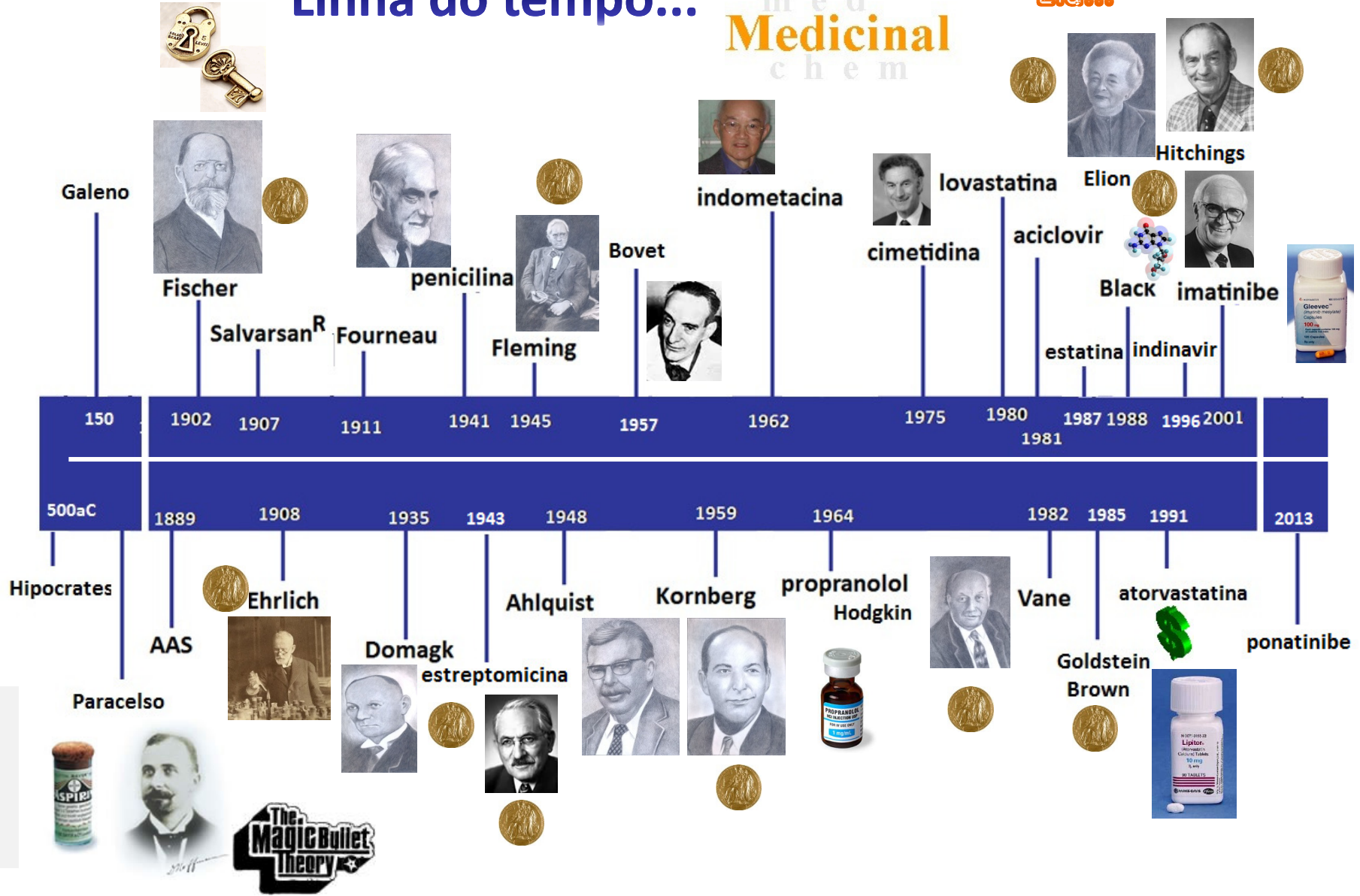


O desenho de novas
moléculas
candidatas a fármacos
é um processo
complexo !

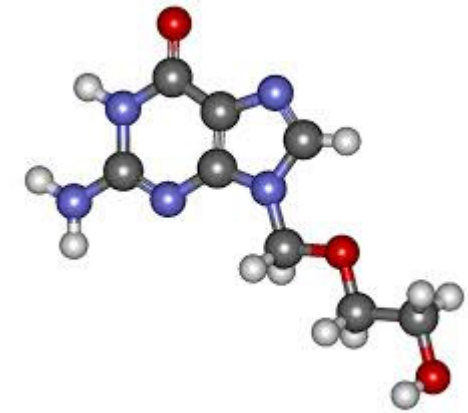
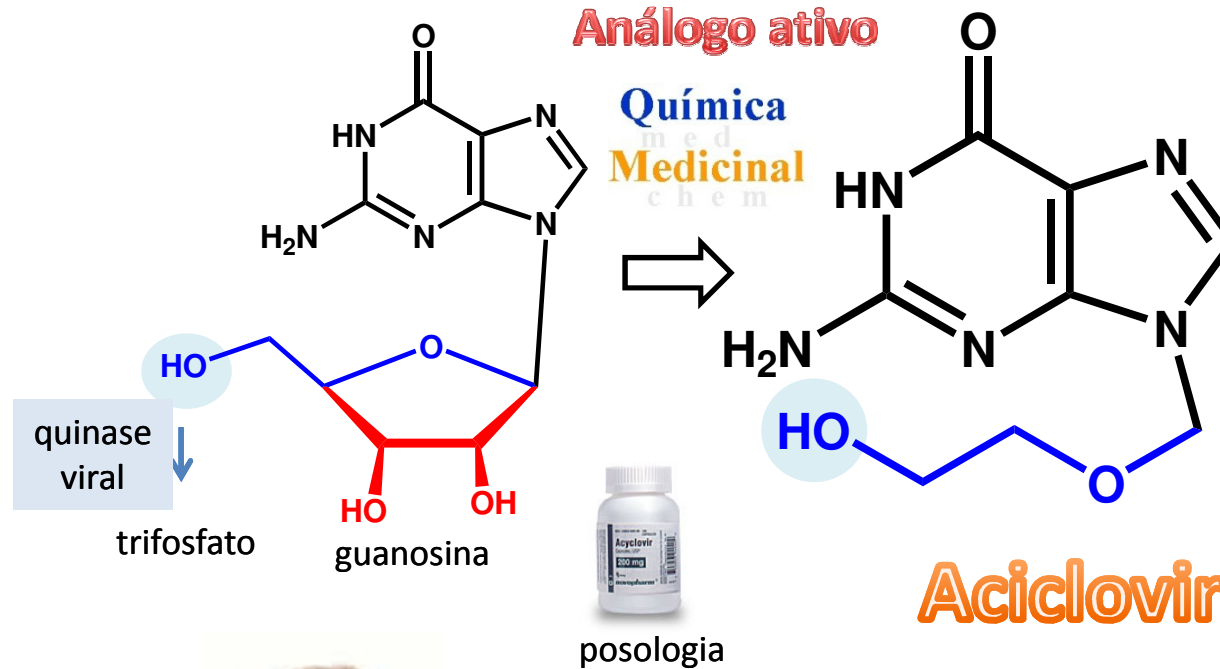
Química Medicinal

Linha do tempo...

Ela...



Gênese do aciclovir



George Hitchings (1905 - 1998) and Gertrude Elion (1918 - 1999)

Burroughs Wellcome
(atual GSK)

6-mercaptopurina,
azatioprina,
alopurinol, trimetoprim,
nelarabina



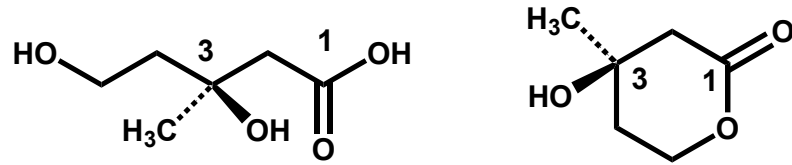
Gertrude B Elion
(1918-1999)



1988

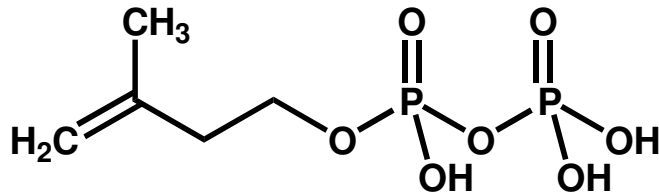
M E Avery, Gertrude Belle Elion, 23 January 1918 - 21 February 1999, *Biographical Memoirs of Fellows of the Royal Society* 2008, 54, 161-168.

Biossíntese do colesterol

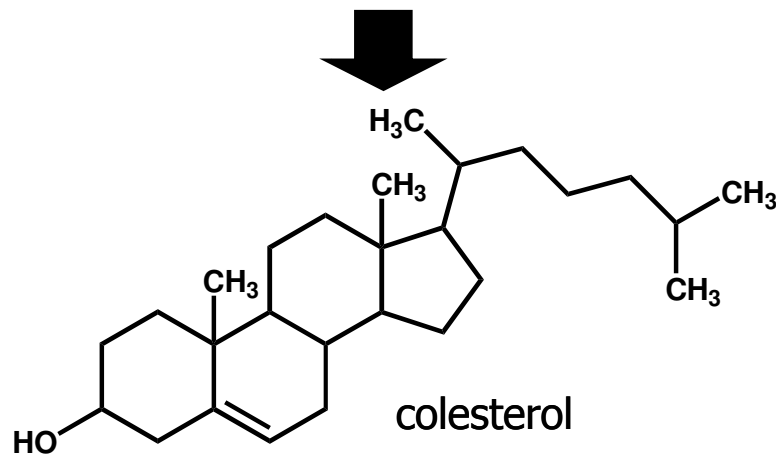


ácido mevalônico

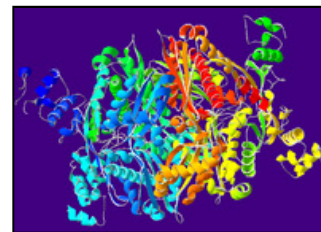
mevalolactona



pirofosfato de isopentenila



colesterol



HMG-CoA reductase



1985

LDL

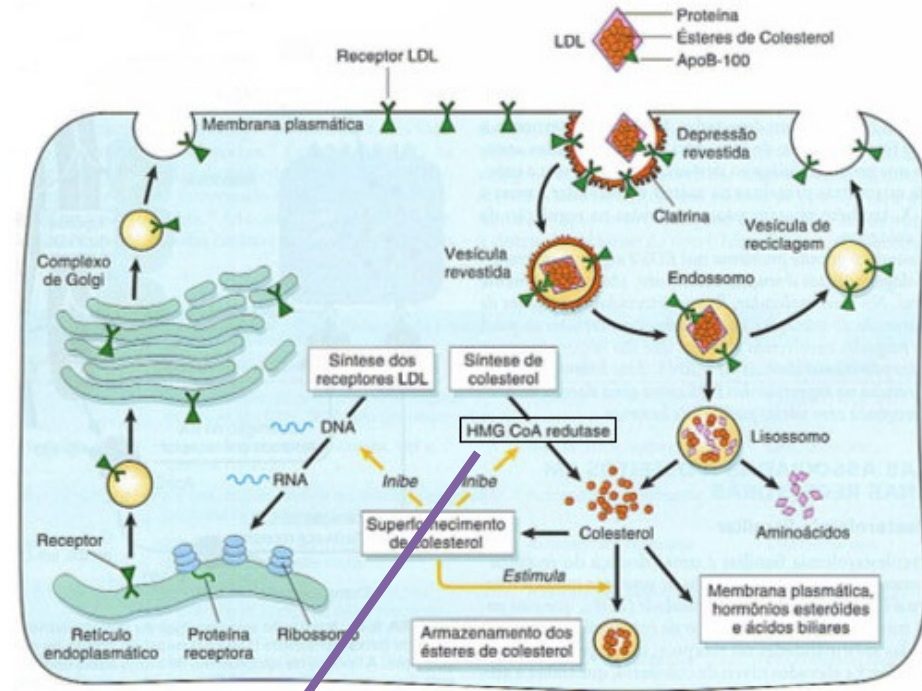


JL Goldstein



MS Brown

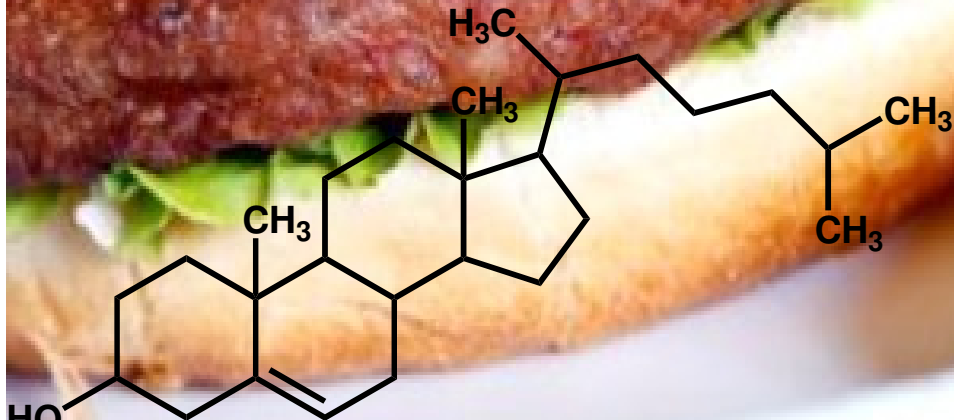
University of Texas, Dallas



JL Goldstein, MS Brown, History of Discovery: The LDL Receptor, *Arterioscler. Thromb. Vasc. Biol.* **2009**, 29, 431-438;
 MS Brown, JL Goldstein, A receptor-mediated pathway for cholesterol homeostasis, *Science* **1986**, 232, 34-47;
 JL Goldstein, MS Brown, A Golden Era of Nobel Laureates, *Science* **2012**, 338, 1033-1034



Universidade Federal do Rio de Janeiro





Akira Endo, Sankyo Co

1975 – Mevastatina (ML-263b) Protótipo natural

A.Endo, *J. Med. Chem.* **1985**, 28, 1; idem, *Proc Jpn Acad SerB* **2010**, 86, 484

Metabólito de Fungo

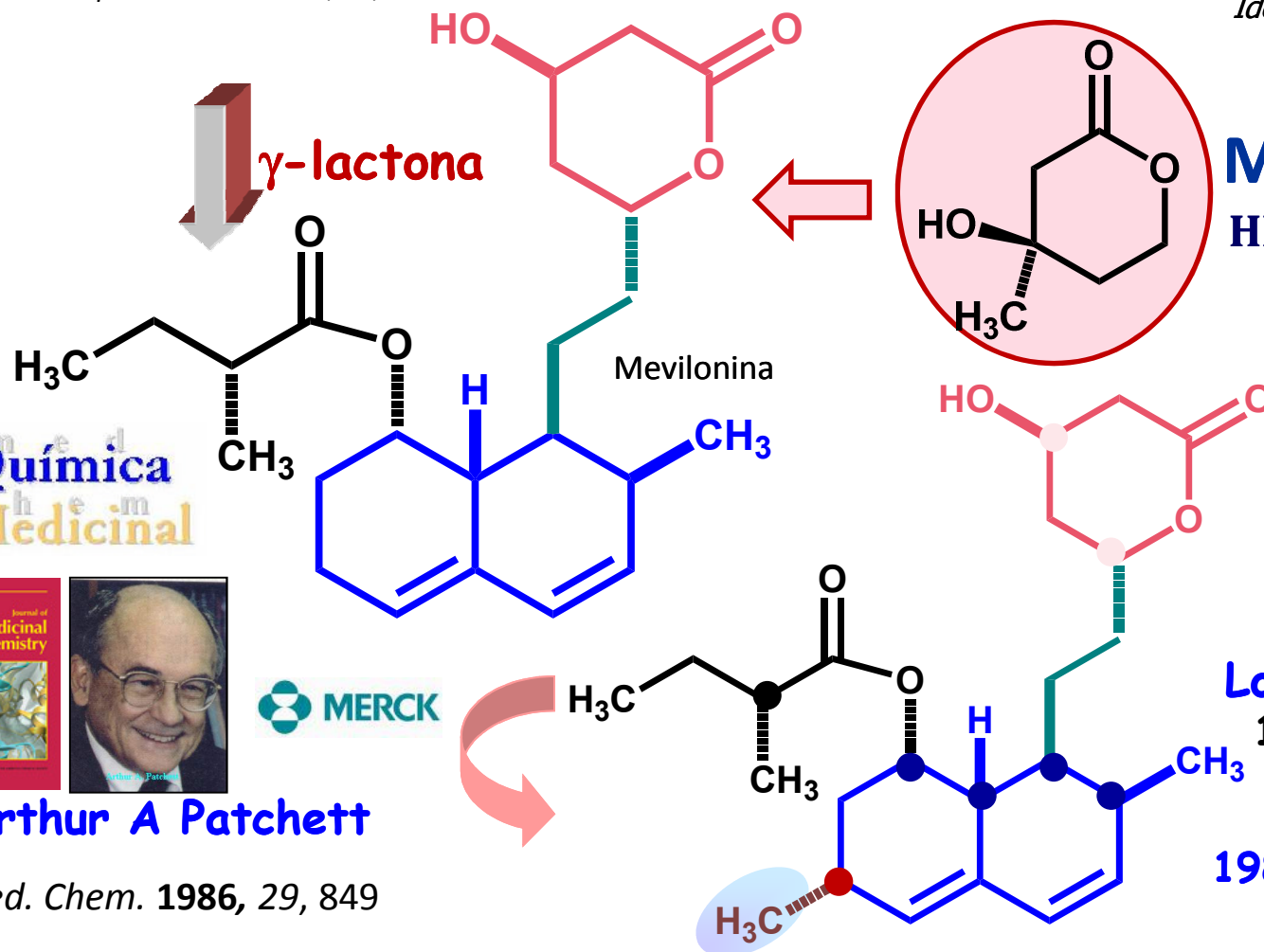
Estatinas



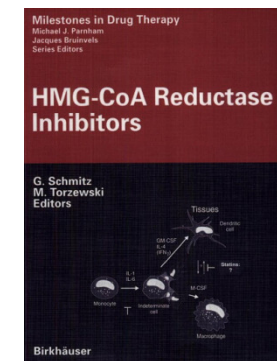
A.Endo, *J. Antibiot.* **1976**, 29, 1346
Penicillium citrinum
Idem, *Ibid*, **1979**, 32, 852
Monascus ruber
(compactina)

Similaridade molecular

Mevalolactona
HMG-CoA redutase



Química Medicinal



Lovastatin (MK-803)
1980 – Merck & Co.
Aspergillus terreus

1987 – MS&D (Mevacor[®])



Arthur A Patchett

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





3ª geração



atorvastatina
1991



AstraZeneca

rosuvastatina
2004

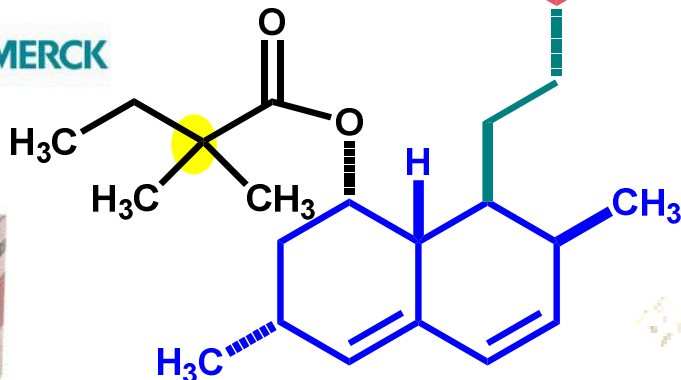
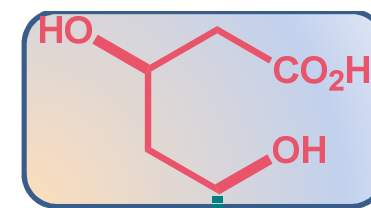


pitavastatina
2012 (BR)

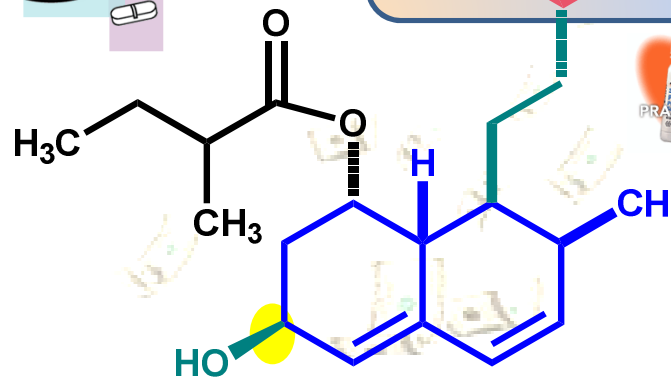
2ª geração



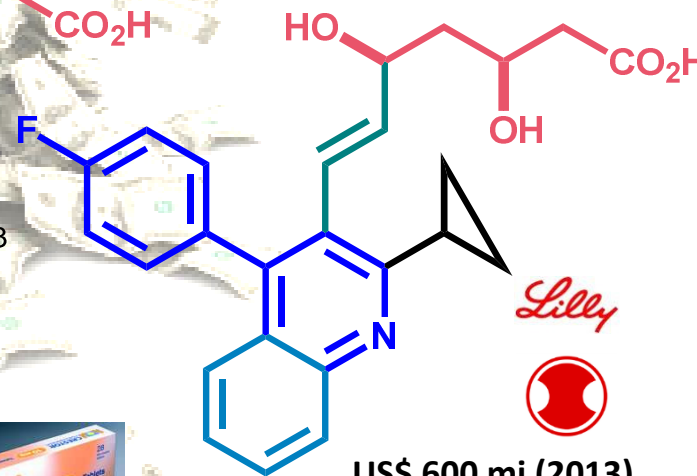
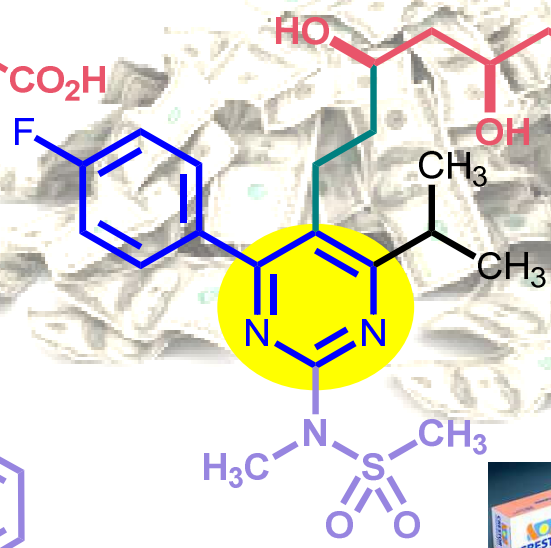
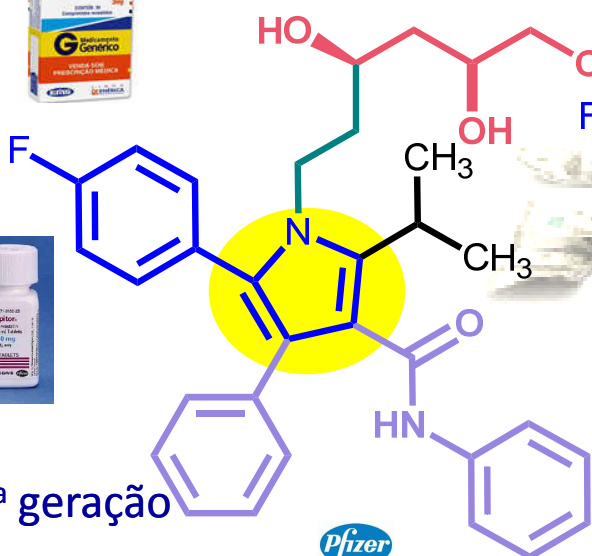
(2006)



simvastatina
1986



pravastatina
1988

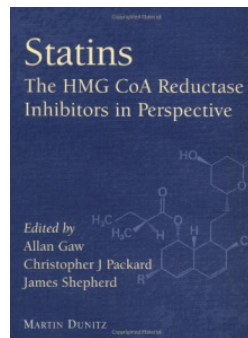


Lilly

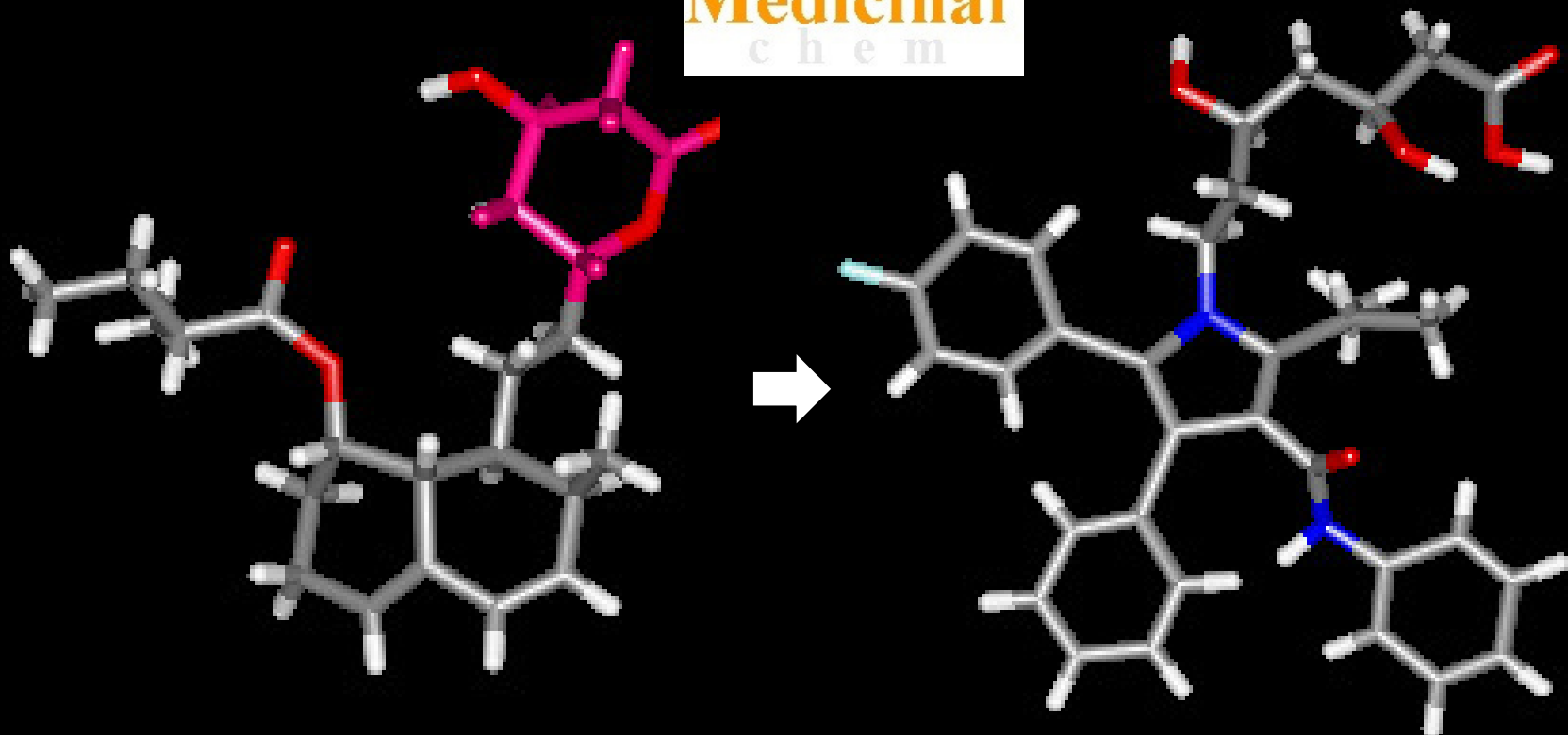


US\$ 600 mi (2013)

O mercado mundial de estatinas foi estimado em US\$ 22 bilhões (2011)



Química
m e d
Medicinal
c h e m



Estatinas

Química
med
Medicinal
chem

atorvastatina

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

1991 → 1997



Bruce D Roth

2013 SCI Perkin Medal

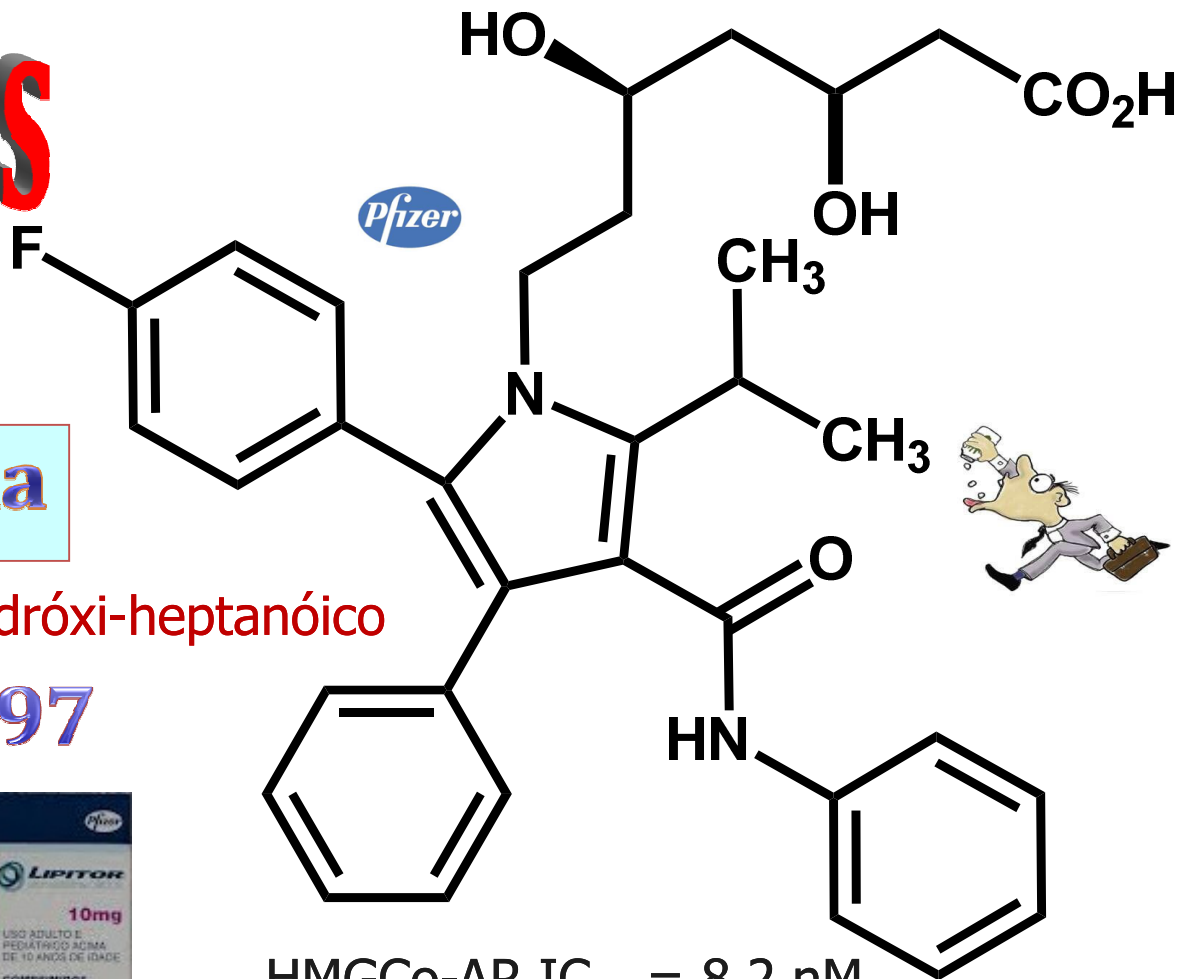
B. D. Roth, *Progr. Med. Chem.* **2002**, *40*, 1-22

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

Warner-Lambert



Pfizer

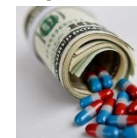


HMGC_o-AR IC₅₀ = 8,2 nM

Biodisponibilidade=12%

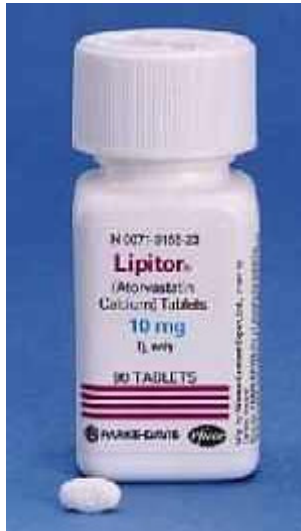
2005 – US\$ 13 bi; 2011 – US\$ 13,3 bi;

Síntese: *ca.* 200 toneladas/ano
ca. >> 45 milhões de pessoas (2005)



Total de Vendas = *ca.* US\$ 150 bilhões (1991-2011)

Total em vendas do Lipitor^R no período de 2001 a 2011



ANO DE VENDAS	EM BILHÕES (US)
2001	7,0
2002	8,6
2003	10,3
2004	12,0
2005	12,8
2006	13,0
2007	13,5
2008	13,8
2009	13,3
2010	13,3
2011	12,2
Total	119,2





1 February 2011



Pfizer to close UK research site

Drug maker Pfizer is to close its research and development (R&D) facility in Kent, which employs 2,400 people.



Universidade Federal do Rio de Janeiro



<http://www.bbc.co.uk/news/business-12335801>

Pfizer Co., Sandwich, UK

Debate sobre Big Pharma



Top-10 em faturamento (2013)

<u>Empresa</u>	Faturamento
Novartis	50,1
Pfizer	44,3
<u>Sanofi</u>	37,7
Merck	37,4
Roche	35,6
Glaxo Smith Kline	32,5
Astra Zeneca	30,2
Johnson & Johnson	28,9
<u>Teva</u>	24,4
Eli Lilly	22,4
TOTAL	343,5



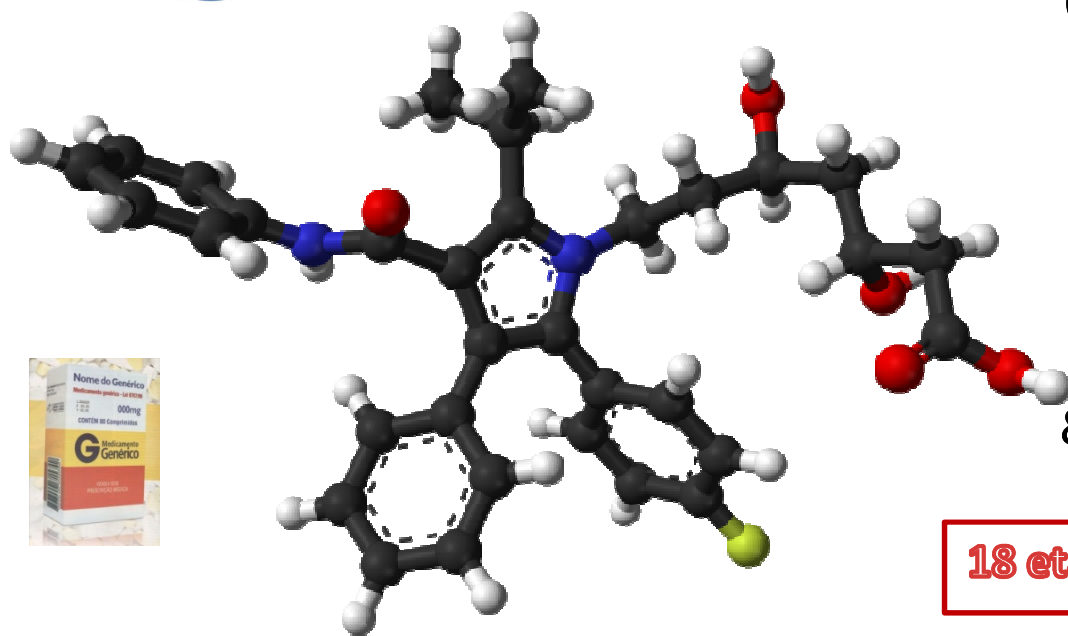
PIB US\$ 50,3 bi; < US\$ 50 bi = Uruguai, Bolívia, Paraguai, Costa Rica, Panamá,

Atorvastatina

sintetizada em 1985, por Bruce D. Roth,
na Parke-Davis Warner-Lambert Co.

Patent US 5273995 Pfizer (1991)

 **19 etapas; 5% rendimento**



O maior *bestseller* da história da indústria farmacêutica mundial

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



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



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

18 etapas; 19% rendimento; 5g escala

• LC DIAS, AS VIEIRA, EJ BARREIRO, INPI
25/04/2011, Patente de Invenção,
PI1101952-2, Processo de obtenção de
atorvastatina cálcica utilizando novos
intermediários e atorvastatina assim obtida.

Projeto CNPq nº 573.564/2008-6 «» FAPERJ nº E-26/170.020/2008

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[Equipe](#)

[Consultoria Científica](#)

[Grupos de Pesquisa](#)

[Pesquisadores](#)

[Annual Activities Report](#)

[Artigos](#)

[Publicações](#)

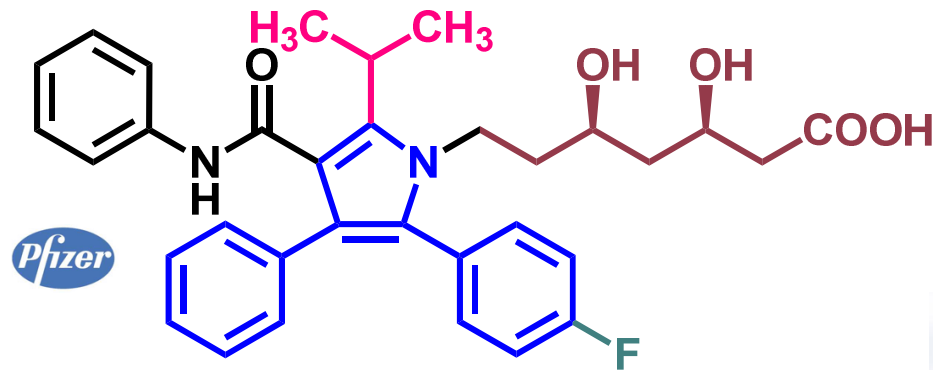
[Reuniões](#)

[Divulgação](#)

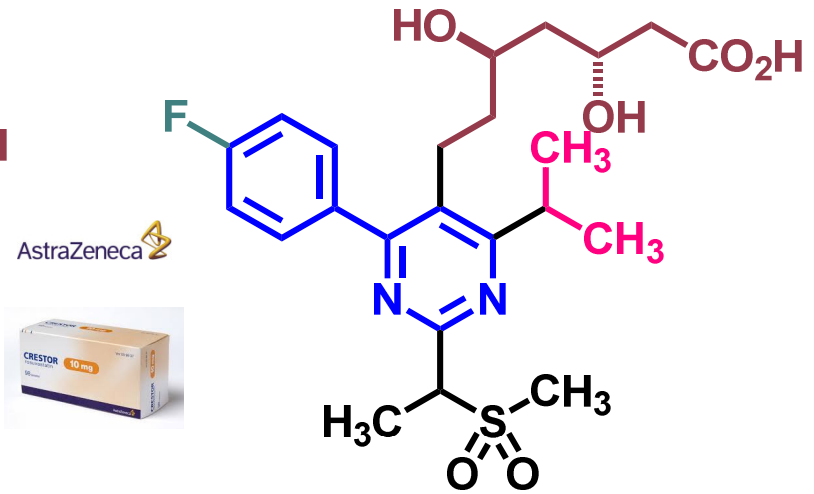


www.inct-inofar.ccs.ufrj.br

Grupamento farmacofórico



atorvastatina

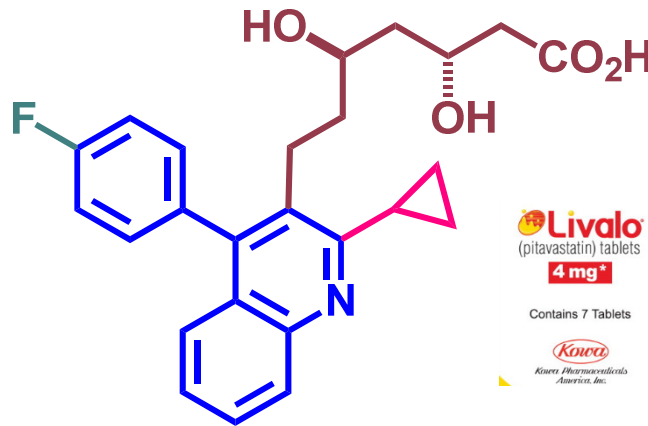


rosuvastatina

Estatinas



A classe mais valiosa de toda história dos medicamentos!



pitavastatina



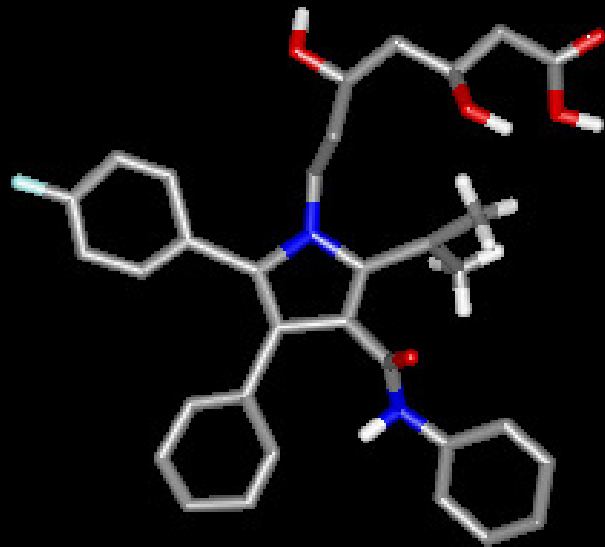
AstraZeneca

Livalo
(pitavastatin) tablets
4 mg*

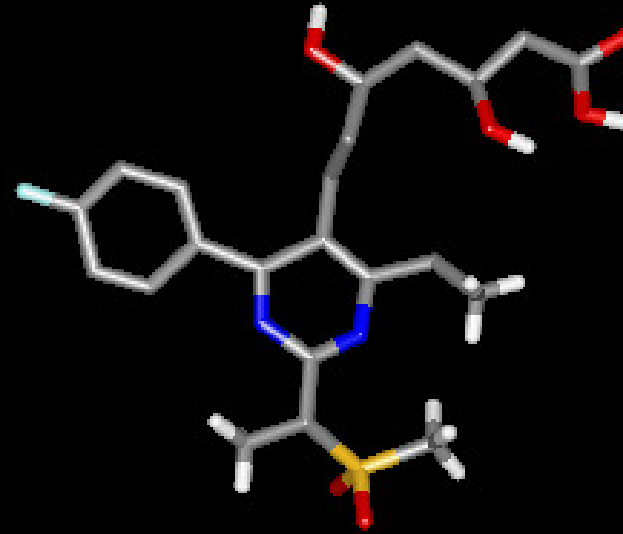
Contains 7 Tablets

Kowa
Kowa Pharmaceuticals
America, Inc.

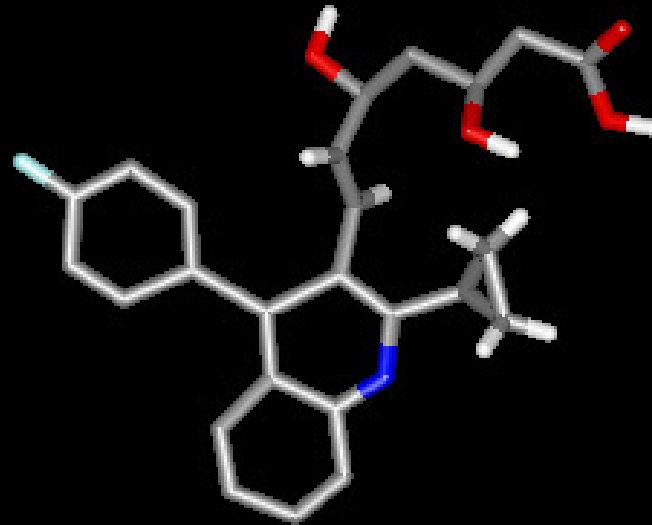
Química
med
Medicinal
chem



atorvastatina

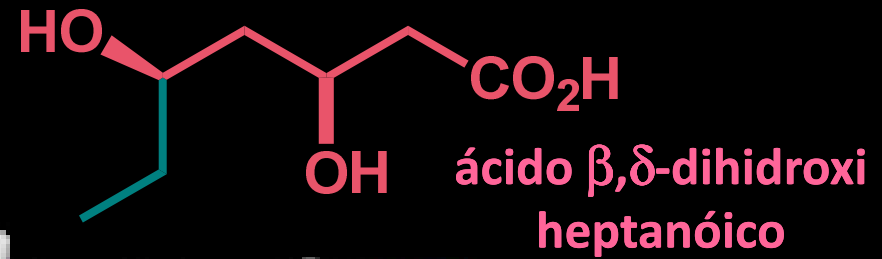


rosuvastatina

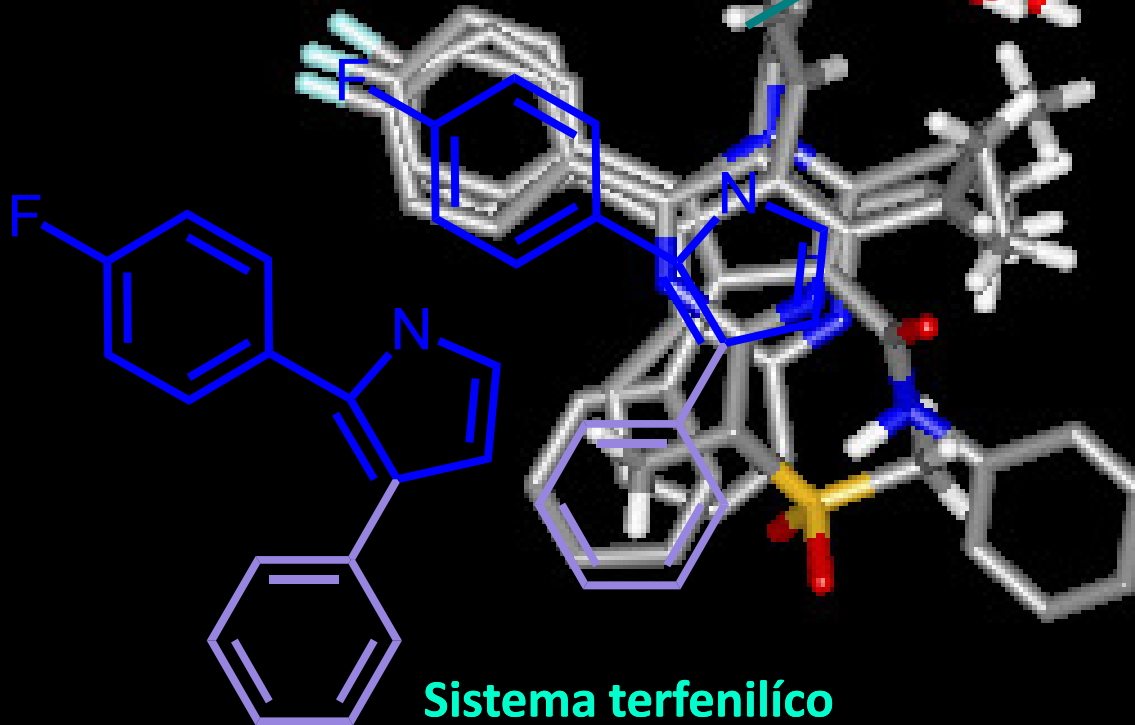


pitavastatina

Grupamento farmacofórico



Pontos farmacofóricos



Grupamento auxofórico

Bióforos



Emil Fischer
 1852-1919
1902
 E. Fischer, Ber. Dtsch.
 Chem. Ges. 1890, 23, 799



Paul Ehrlich
 1854-1915
1908

O paradigma de Ehrlich & Fischer



THE LANCET

"In patients with locally advanced or high-risk local prostate cancer, addition of local radiotherapy to endocrine treatment halved 10-year prostate-cancer-specific mortality."

Physiologic
A abordagem
 approach
fisiológica

P. Ehrlich, *Chemotherapeutics: scientific principles, methods and results*. *Lancet* 1913, 2, 445



Conceito de composto-protótipo

É a primeira *substância* de uma série *congênere* – *i.e.* estruturalmente relacionada – com atividade em modelos farmacológicos validados *in vivo* - que pode vir a ser otimizado por modificações moleculares subsequentes, planejadas.

Química
m e d
Medicinal
c h e m



A Química Medicinal e o paradigma do composto-protótipo

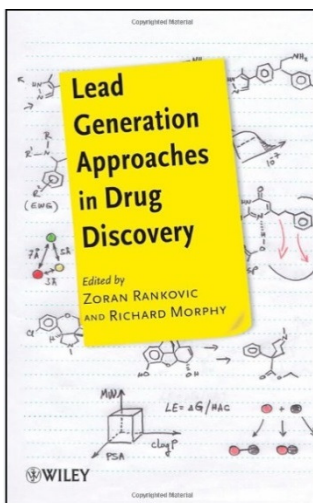
E. J. Barreiro *Rev. Virtual Quim.*, 2009, 1 (1), 18-26.

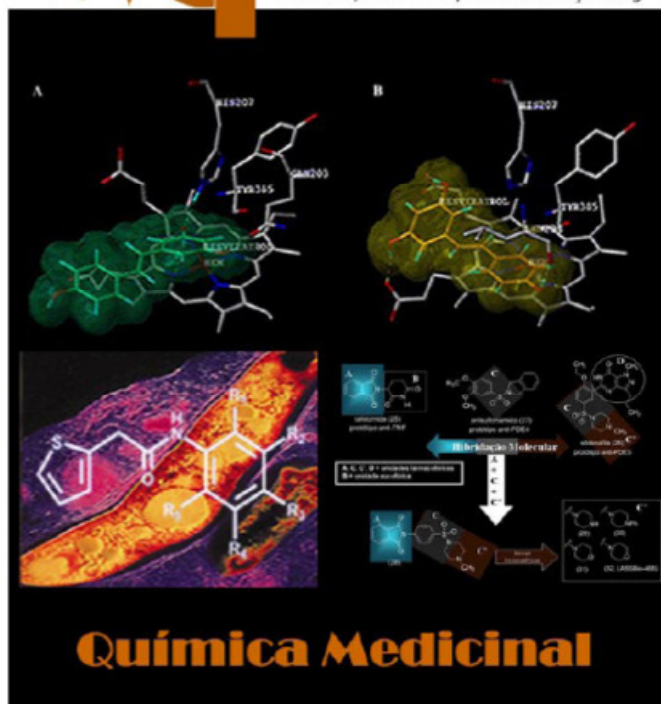
<http://www.uff.br/rvq>

Otimização do protótipo

Química
med
Medicinal
chem

Lead Optimization





O medicamento é instrumento essencial à preservação, manutenção e promoção da Saúde. O acesso ao medicamento representa um importante fator de inclusão social que depende da disponibilidade do fármaco – princípio ativo contido no medicamento e que em 85% dos casos é de origem sintética. Neste cenário, a importância do saber-fazer fármacos e medicamentos passa a representar um componente estratégico para o pleno exercício da soberania de nosso País. A universalização do acesso ao medicamento, para o cumprimento do preceito de nossa Carta Magna de 1988, quanto ao direito de todos os brasileiros e brasileiras à Saúde, depende, mais do que possa parecer, deste componente.

1. A inovação em fármacos: O processo de planejamento racional
2. O principal paradigma da química medicinal moderna: A descoberta do composto-protótipo
3. Novos compostos-protótipos descobertos no *Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio®)*

Artigo de Divulgação



A Química Medicinal e o paradigma do composto-protótipo

Barreiro, E. J.*

Rev. Virtual Quim., 2009, 1 (1), 18-26. Data de publicação na Web: 30 de Janeiro de 2009

<http://www.uff.br/rvq>



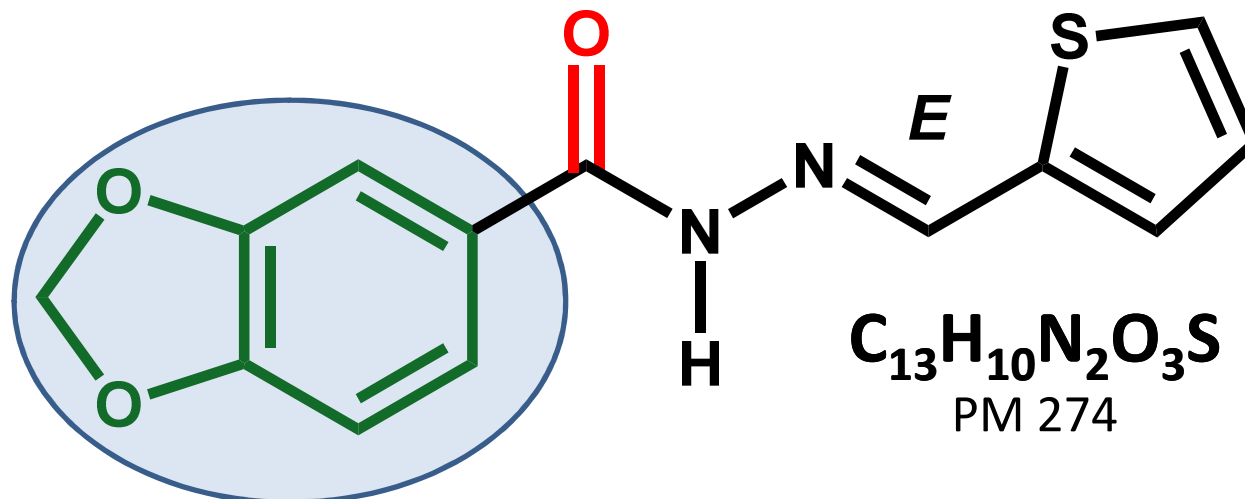
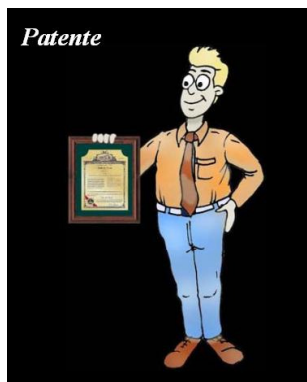
LASSBio-294

Novo protótipo de fármaco cardioativo*

*US Patent US7091238-15/08/2006

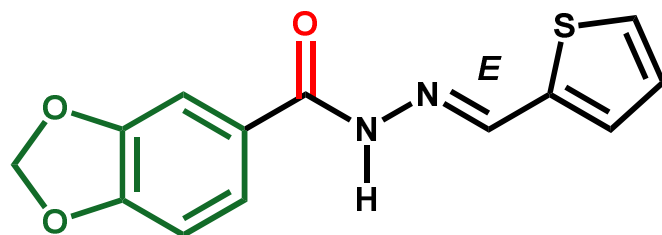
*European Patent EP1532140; WO-0078754

Thienylhydrazone with digitalis-like properties (positive inotropic effects)



- ✓ Estruturalmente simples; rota de síntese com >55% de rendimento global, empregando matéria-prima acessível; escalonável até 5,0 kg (18,2 M);
- ✓ Potentes propriedades inotrópicas positivas & vasodilatadoras; também neuroprotetoras; ativo por via oral; boa biodisponibilidade;
- ✓ Novo mecanismo farmacológico de ação: ligante de receptores adenosinérgicos;
- ✓ Sem citotoxicidade, genotoxicidade, nem toxicidade sistêmica (aguda e sub-aguda) em duas vias de administração (*p.o.* e *i.p.**) nas doses **1000 μ M/kg** e **73 μ M/kg**, respectivamente;

i.p.* = 2 vezes ao dia, durante 15 dias seguidos: ~100 vezes ED_{50} *in vivo***.



química nova



Quim. Nova, Vol. 25, No. 6B, 1172-1180, 2002

ESTRATÉGIA DE SIMPLIFICAÇÃO MOLECULAR NO PLANEJAMENTO RACIONAL DE FÁRMACOS: A DESCOBERTA DE NOVO AGENTE CARDIOATIVO

Eliezer J. Barreiro*

Departamento de Fármacos, Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Cidade Universitária, Ilha do Fundão, CP 68006, 21944-190 Rio de Janeiro - RJ

Recebido em 24/1/02; aceito em 17/4/02

STRATEGY OF MOLECULAR SIMPLIFICATION IN RATIONAL DRUG DESIGN: THE DISCOVERY OF A NEW CARDIOACTIVE AGENT. In this article are described examples of the successful use of molecular simplification strategy in the discovery of new drugs from bioactive natural products and synthetic compounds. The discovery of a new cardiotoxic derivative (37, 2-thienylidene-3,4-methylenedioxybenzoylhydrazine; LASSBio-294), efficiently synthesized from Brazilian natural product and structurally designed by molecular simplification of active pyridazinone compounds reported in the literature, is described. A brief description of the pharmacological profile of this new cardiotoxic lead-compound, belonging to the *N*-acylhydrazone (NAH) class, is also reported herein.

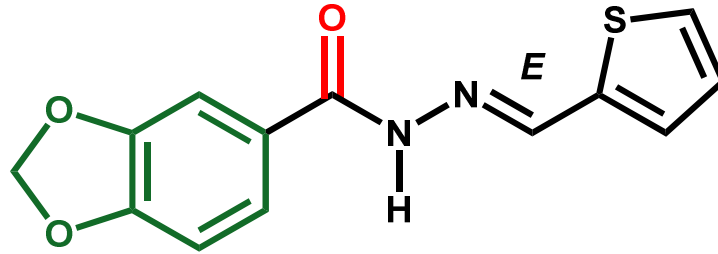
Keywords: new cardiotoxic derivative; bioactive *N*-acylhydrazone compound; LASSBio-294.



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RESULTADOS RECENTES

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N-acylhydrazone improves exercise intolerance in rats submitted to myocardial infarction by the recovery of calcium homeostasis in skeletal muscle

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LASSBio-294 na Web


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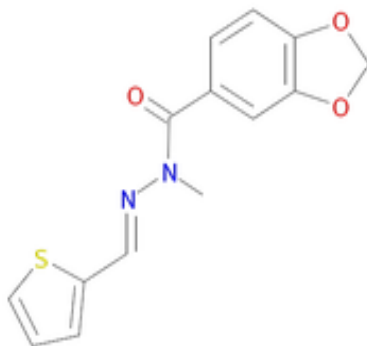
ChEMBL Statistics

- DB: ChEMBL_17
- Targets: 9,356

EBI > Databases > Small Molecules > ChEMBL Database > Compound Search > CHEMBL573324

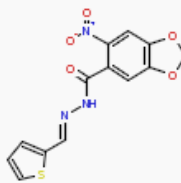
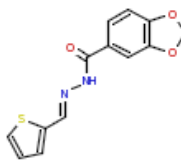
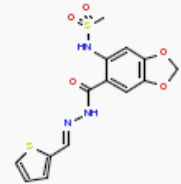
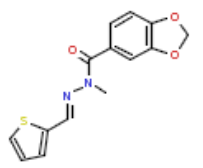
Compound Report Card

Compound Name and Classification

Compound ID	CHEMBL573324	 <p>CHEMBL573324</p>
Compound Name		
ChEMBL Synonyms	LASSBio-785	
Max Phase	0	
Trade Names		
Molecular Formula	C14H12N2O3S	

Additional synonyms for CHEMBL573324 found using [NCI Chemical Identifier Resolver](#)



Compound	Synonyms	Max Phase	Parent Mol Weight	ALogP	PSA	HBA	HBD	#RO5 Vio.	#Rotatable Bonds	Passes Rule of Three	Med Chem Friendly	QED Weighted
 CHEMBL234618	<u>LASSBio-880</u>	0	319.29	2.3	133.97	6	1	0	4	N	N	.52
 CHEMBL233194	<u>LASSBio-294</u>	0	274.3	2.4	88.16	4	1	0	3	N	Y	.69
 CHEMBL519627	<u>LASSBio-929</u>	0	367.4	1.32	142.71	6	2	0	5	N	Y	.6
 CHEMBL573324	<u>LASSBio-785</u>	0	288.32	2.61	79.37	4	0	0	3	N	Y	.64

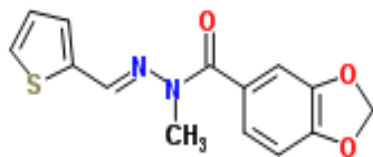
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N-Methyl-N'-[(E)-2-thienylmethylene]-1,3-benzodioxole-5-carbohydrazide



[?](#) 2D 3D Save Zoom

 - Double-bond stereo

ChemSpider ID: **9623943**

Molecular Formula: $C_{14}H_{12}N_2O_3S$

Average mass: 288.321686 Da

Monoisotopic mass: 288.056854 Da

▼ Systematic name

N-Methyl-N'-[(E)-2-thienylmethylene]-1,3-benzodioxole-5-carbohydrazide

▶ SMILES and InChIs

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Target: 1a1c Proto-oncogene tyrosine-protein kinase Src

left click rotate
right click or scroll zoom
ctrl + left click translate
ctrl + right click slab and fog

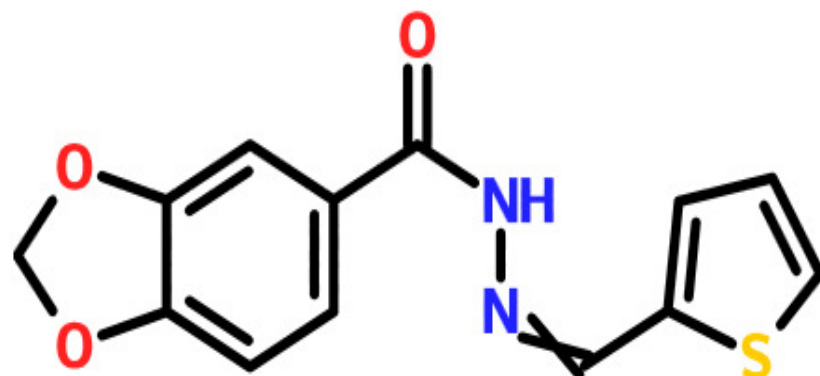
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- Label all residues
- SER1
- ILE2
- GLN3
- ALA4
- GLU5
- GLU6
- TRP7
- TYR8
- PHE9
- GLY10
- LYS11
- ILE12
- THR13
- ARG14
- ARG15
- GLU16
- SER17
- GLU18
- ARG19
- LEU20
- LEU21
- LEU22
- ASN23
- ALA24
- GLU25

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MCULE-4810413925

Compound [Show structure](#)

InChIKey: YMOJHAPRGAZUPL-UHFFFAOYSA-N

SMILES: C(=O)(NN=CC1=CC=CS1)C1=CC=C2C(OC2)=C1

Formula: C₁₃H₁₀N₂O₃S

Amount	Price [?]	Purity (%)	Delivery time [?]	
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