Universidade Federal do Rio de Janeiro

A Química Medicinal na descobeta de fármacos

Parte 2

I SEMANA DE INTEGRAÇÃO FARMACÊUTICA DO MÉDIO ARAGUAIA - SEMEFAR

06-08 de outubro de 2010

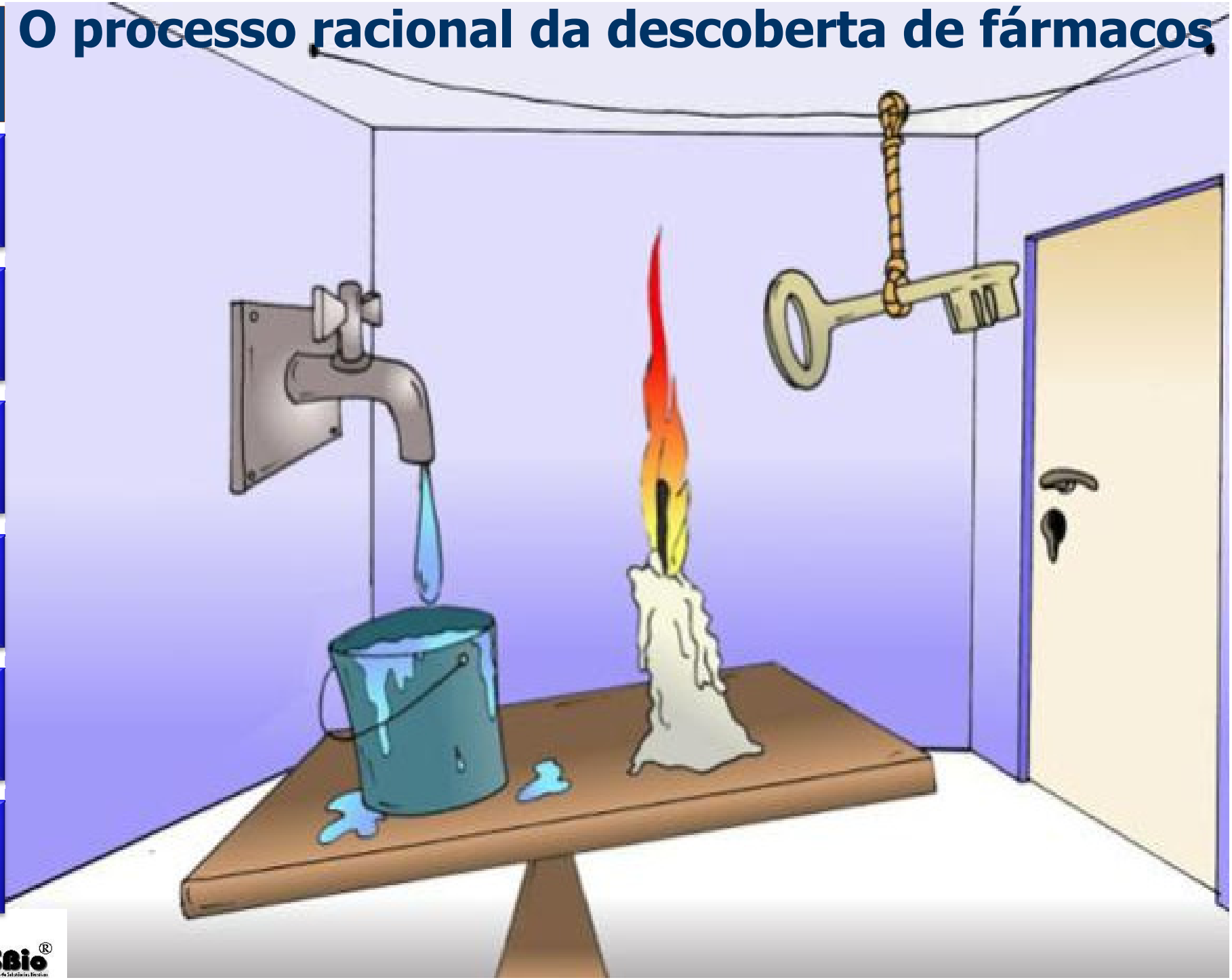
UFMT, Barra do Garças, MT

Eliezer J. Barreiro

Professor Titular

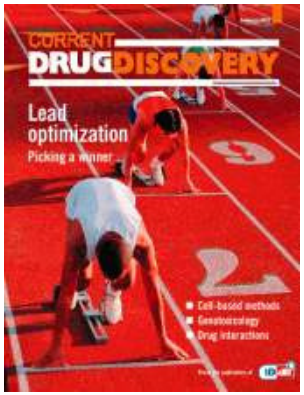
UFRJ

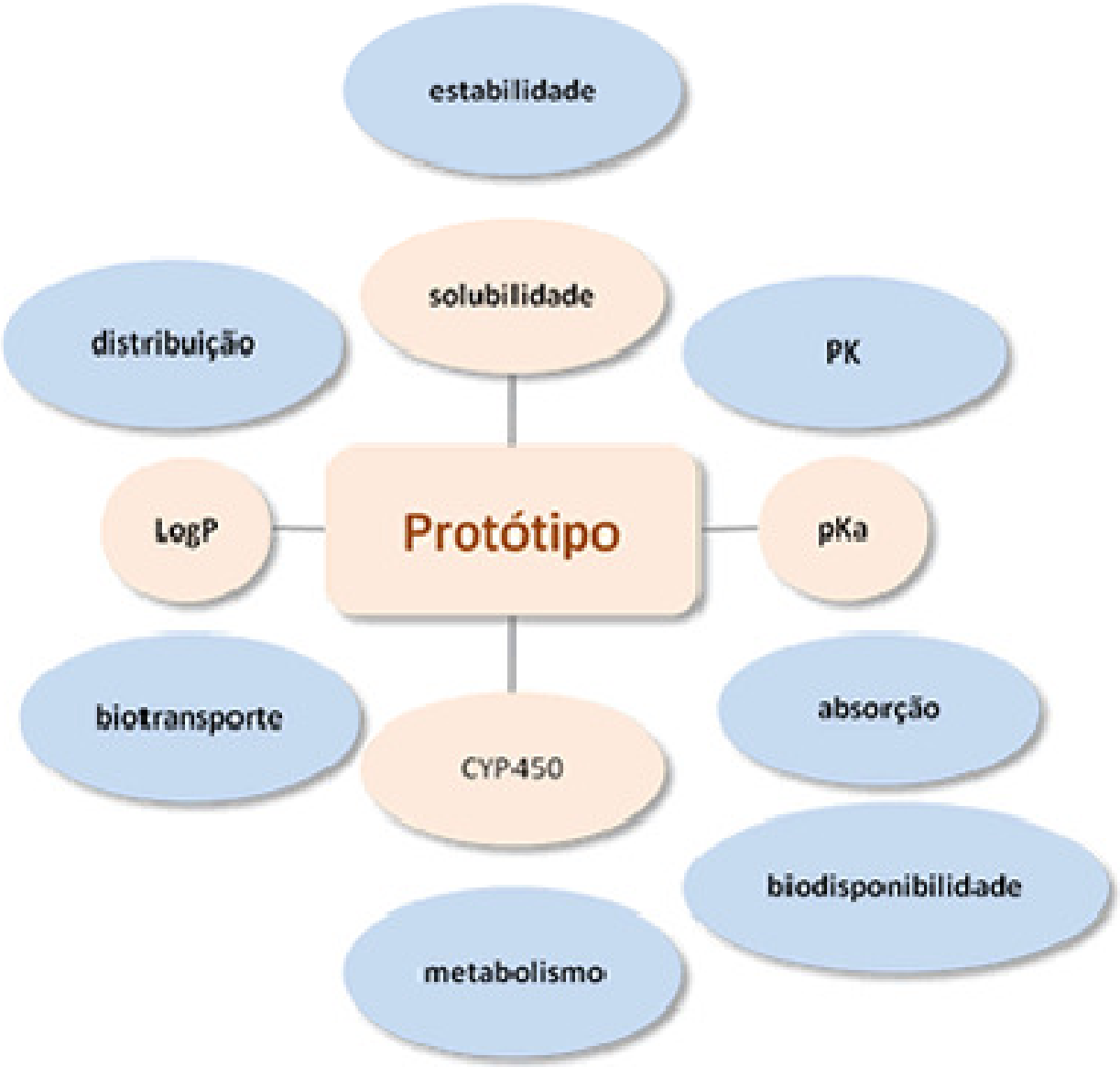
O processo racional da descoberta de fármacos



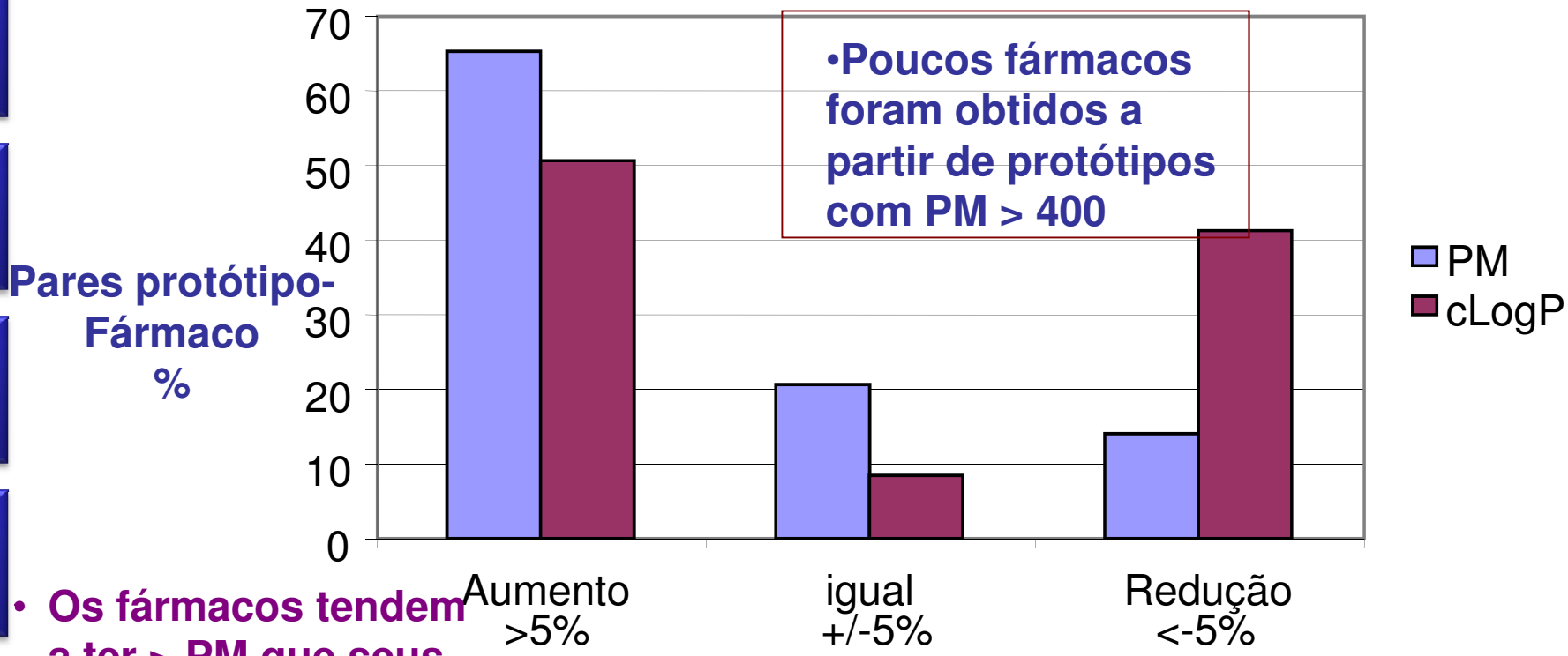
Composto-protótipo

“ O composto-protótipo é o primeiro derivado puro, identificado em uma série congênere de novas substâncias, bioensaiadas em modelos animais padronizados, relacionados à patologia a ser tratada ”





Peso molecular & lipofilicidade



- **Os fármacos tendem a ter > PM que seus protótipos: *ca.* +42 u.m.a.**

- PM aumenta em 2/3 dos casos
- Lipofilicidade aumenta em ½ dos casos

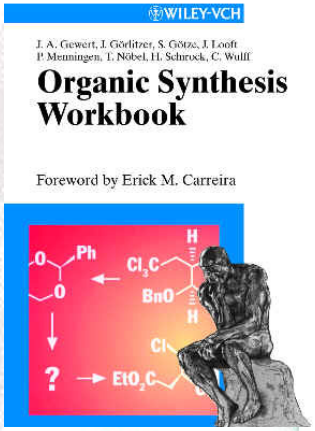
Freqüência de modificações observadas em
469 pares de compostos protótipos & fármacos

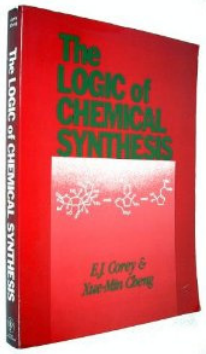
W. Sneader, *Drug Prototypes & Their Exploitation*, Wiley, 1995

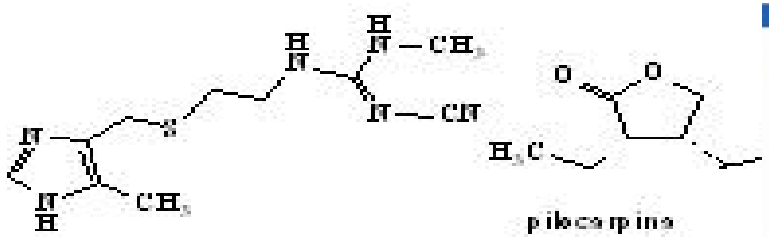
T. I. Oprea *et al., J. Chem. Inf. Comp. Sci.* **2001**, *41*, 1308

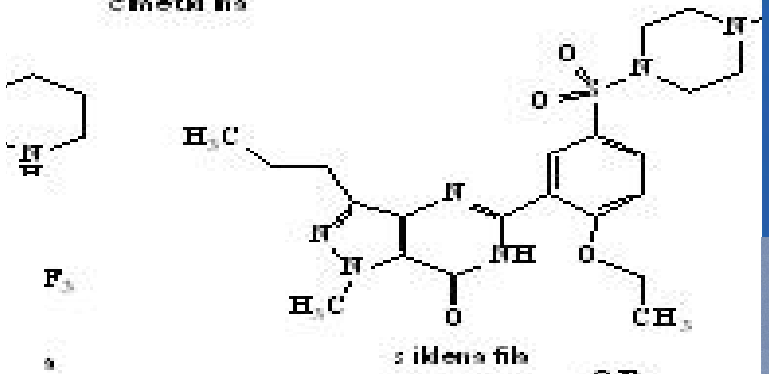
Moléculas inteligentes

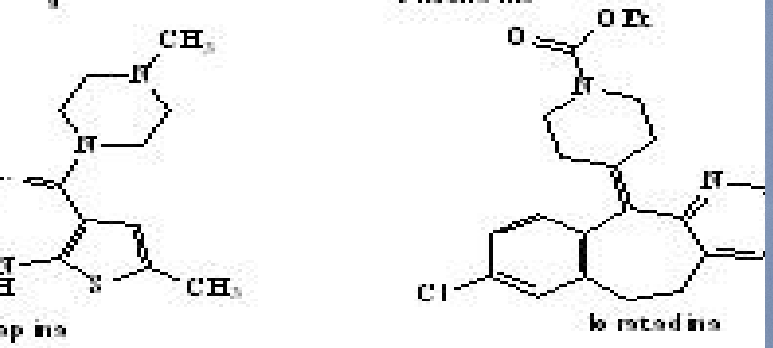
Química Medicinal

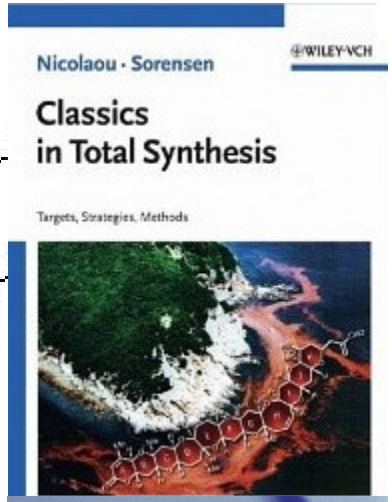


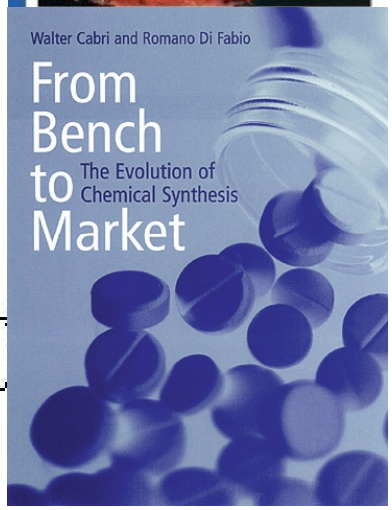


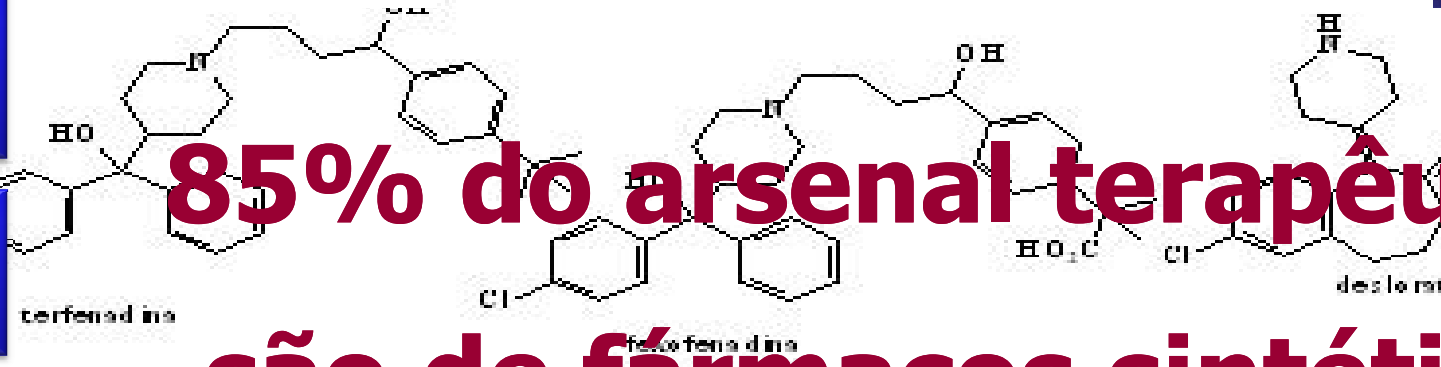












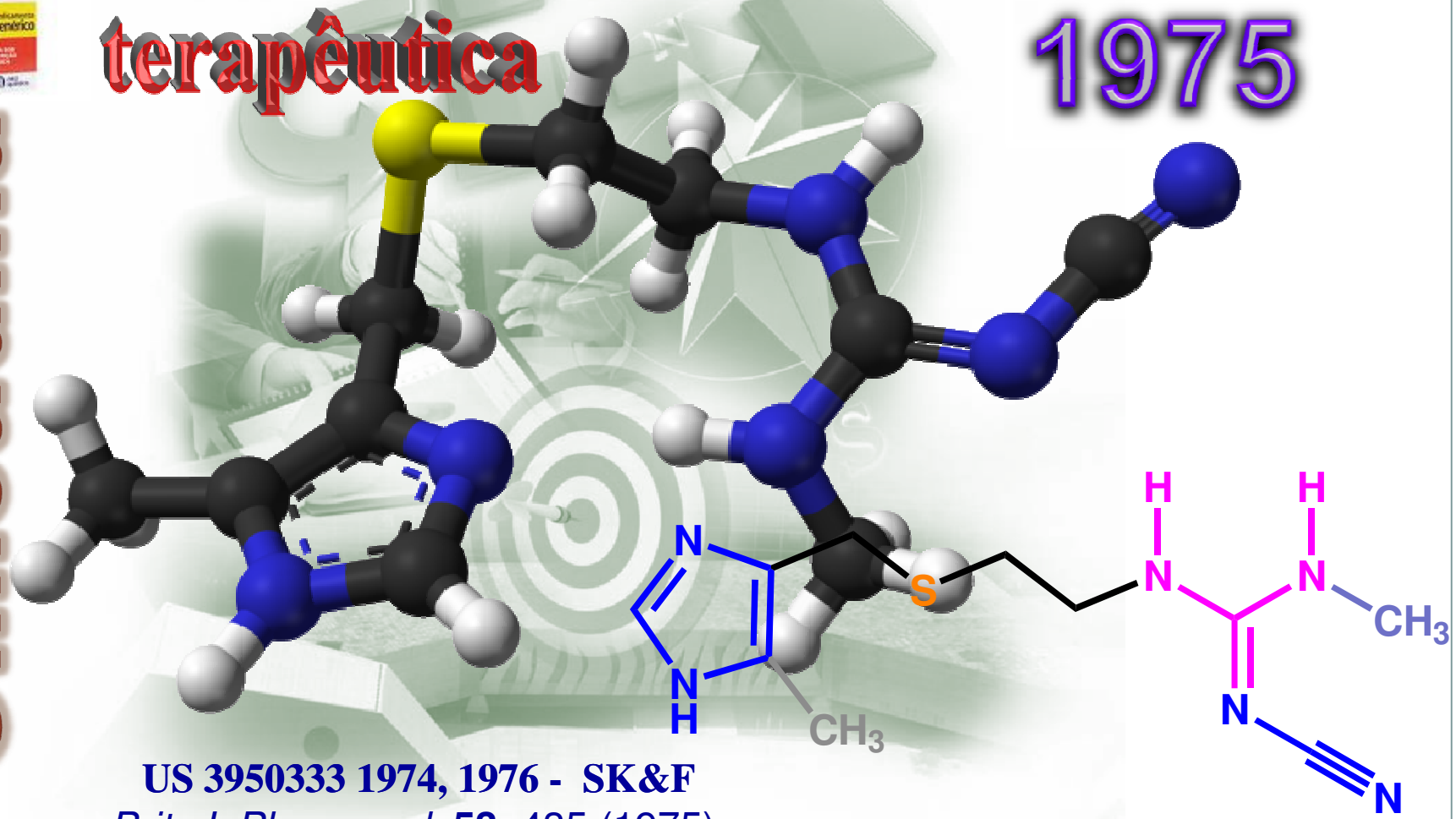
85% do arsenal terapêutico são de fármacos sintéticos

O desenvolvimento racional

Inovação terapêutica

1975

Cimetidina



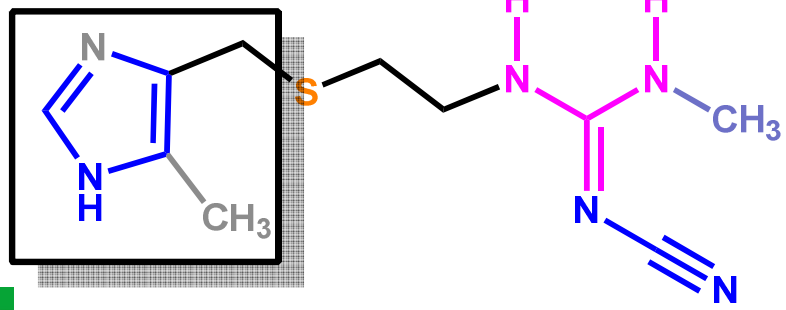
US 3950333 1974, 1976 - SK&F

Brit. J. Pharmacol. **53,** 435 (1975).

James Black, Robin Ganellin, Emmett, Durant

$C_{10}H_{16}N_6S$

metil-imidazola



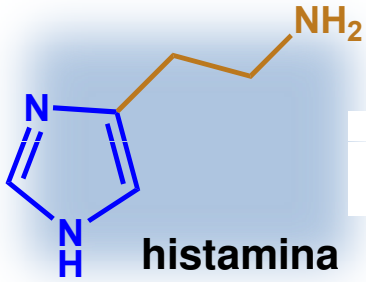
cimetidina
1976

US 3950333 1974, 1976 - SK&F
Brit. J. Pharmacol. **53**, 435 (1975).

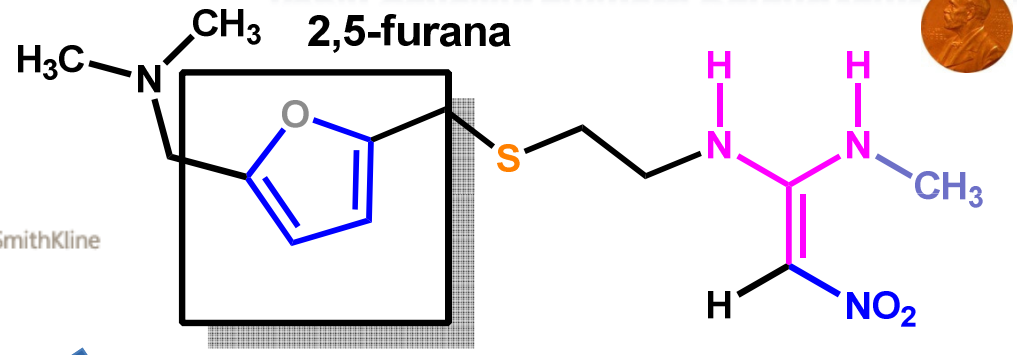
Robin Ganellin, Emmett, Durant, James Black

Mannich

2,5-furana



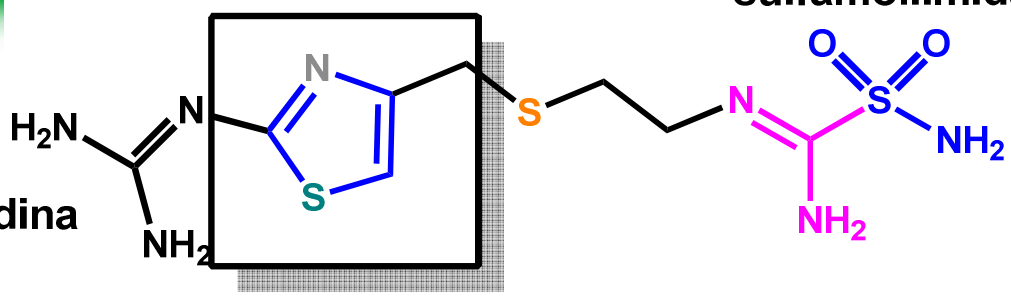
histamina



nitro-etenodiamina

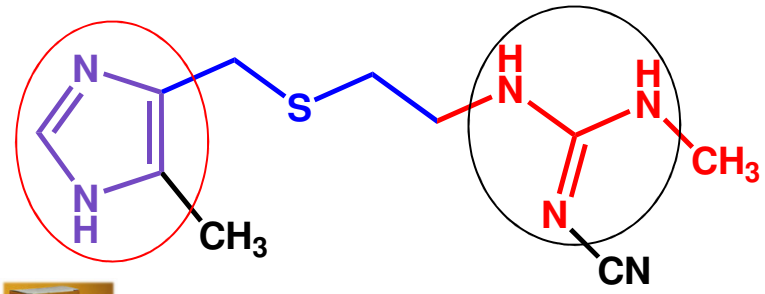
ranitidina
1981
sulfamoilimidamida

tiazola



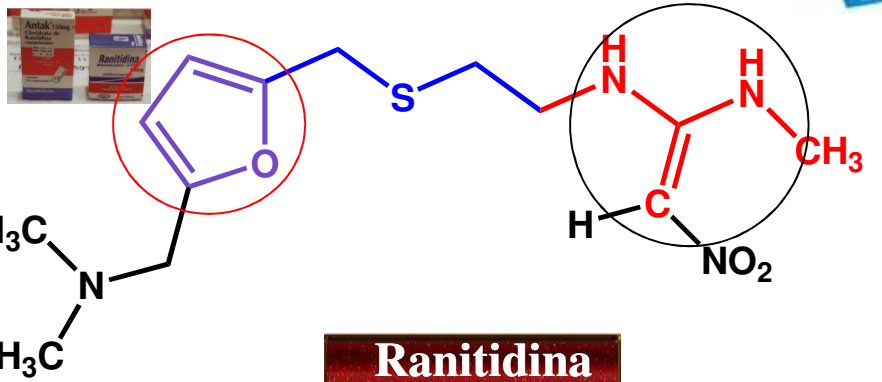
amidina

famotidina
1982



Cimetidina

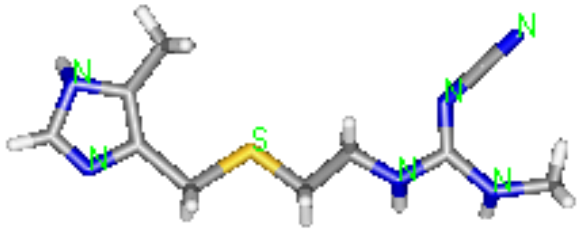
Robin Ganellin *et al.*, 1974
US 3950333 1974, 1976 - SK&F
Brit. J. Pharmacol. **53,** 435 (1975).

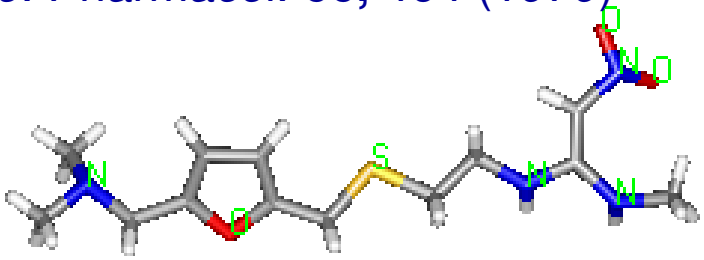


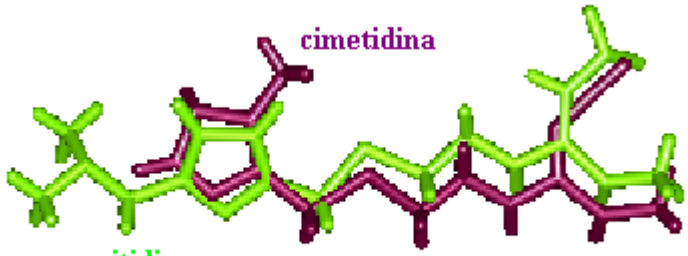
Ranitidina

Barry J. Price *et al.*, 1978
US 4128658 1978 - Allen & Hanburys
Brit. J. Pharmacol. **66,** 464 (1979)

similaridade molecular







me-too

A invenção do propranolol

Raymond Ahlquist (1914

Am J Physiol 1948, 153, 586

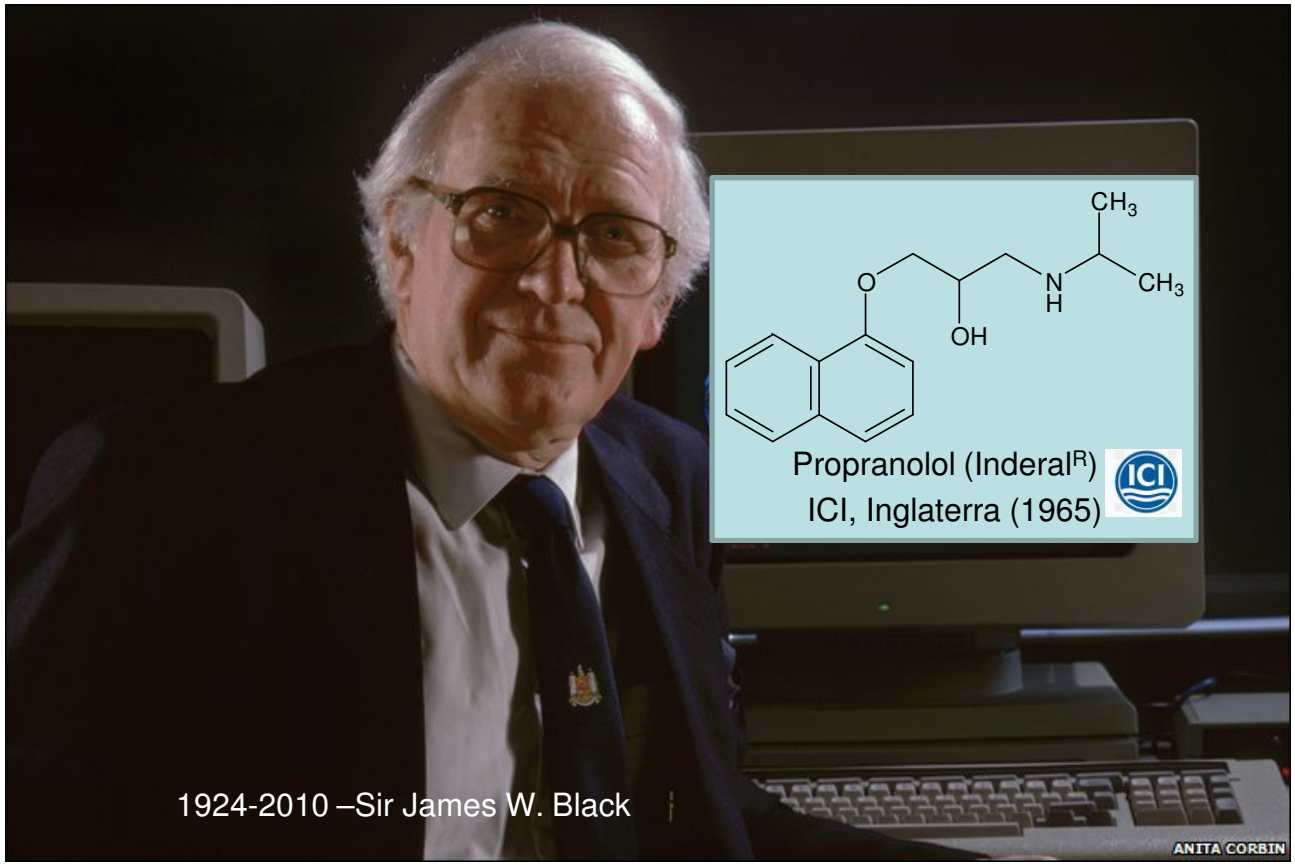
A STUDY OF THE ADRENOTROPIC RECEPTORS

RAYMOND P. AHLQUIST

From the Department of Pharmacology, University of Georgia School of Medicine

AUGUSTA, GEORGIA

Premio Nobel
1988



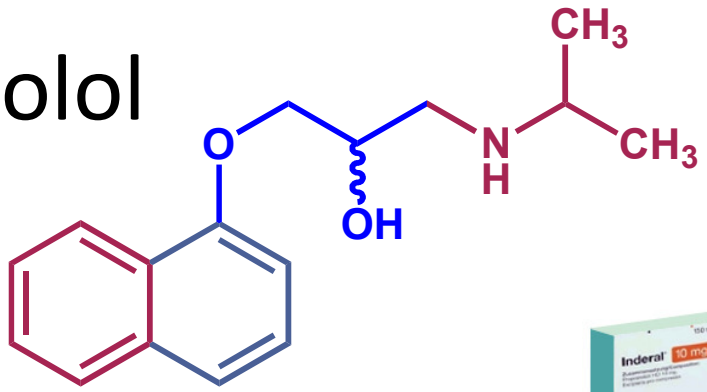
Química Medicinal

Pharmacology
Farmacologia

LASSBio®

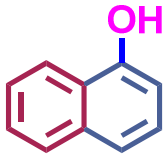
A invenção do propranolol

med Química Farmacêutica chem Medicinal

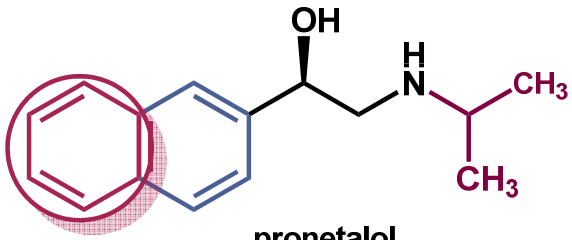


propranolol
1964

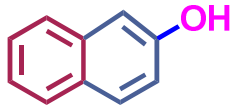
J. Black *et al.*, *Br. J. Pharmacol. Chmother.* **1965**, *25*, 577



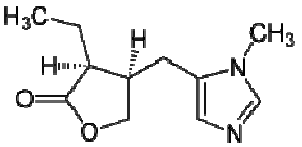
α-naftol



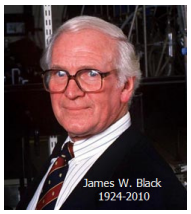
pronetalol
1959



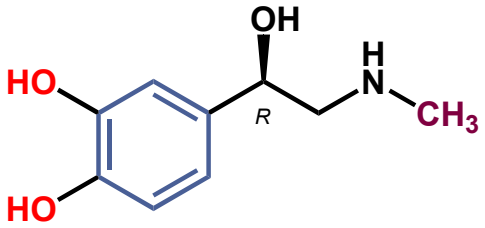
β-naftol



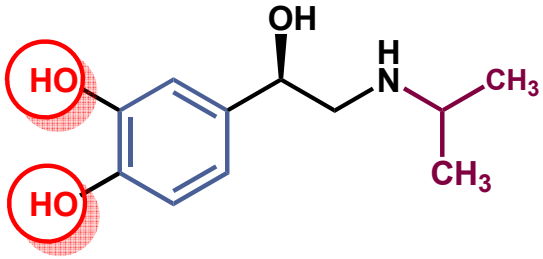
pilocarpina



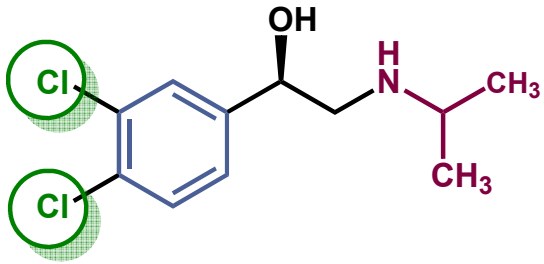
James W. Black, 1988 - "Pronethalol always seemed to us to be a prototype drug, good enough to answer questions of principle, but not good enough to be marketable"



adrenalina

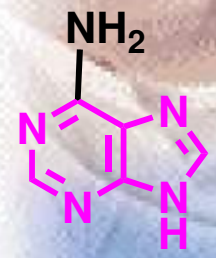


isoprenalina / isoproterenol

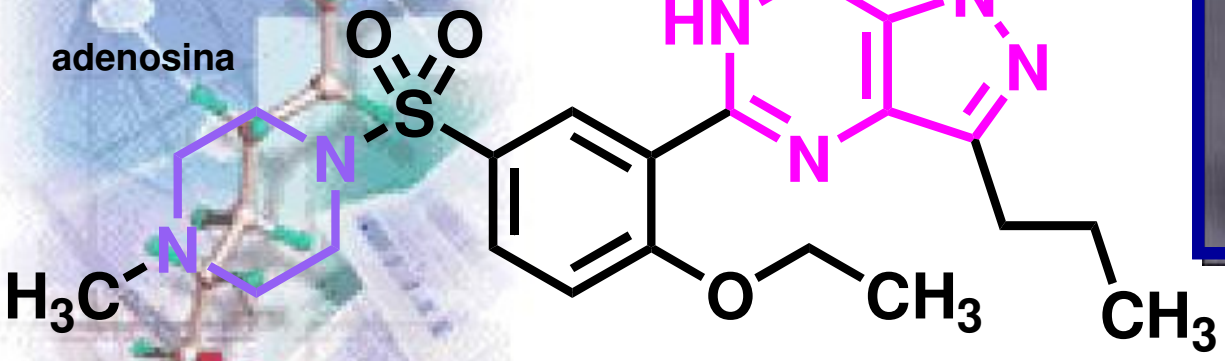


1958 - DCI
β-bloqueador

A descoberta do sildenafila



adenosina



sildenafila

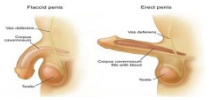
Disfunção erétil

angina

Corpus cavernosum

NO

Cafeína/teofilina



alprostadil injetável

Caverject^{R}

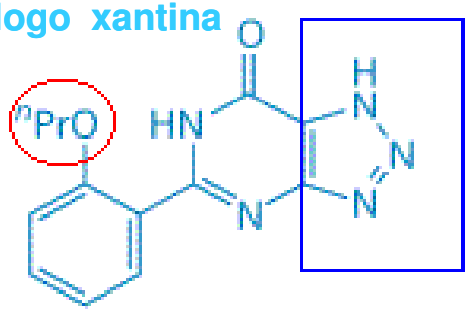
Erection

Cell membrane

Similaridade Molecular

Guanylate cyclase

análogo xantina



GTP

cGMP

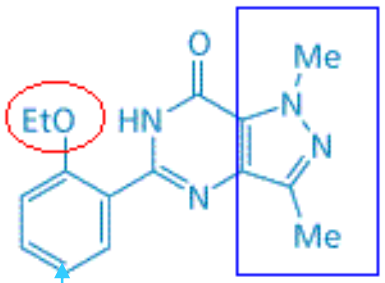
GMP

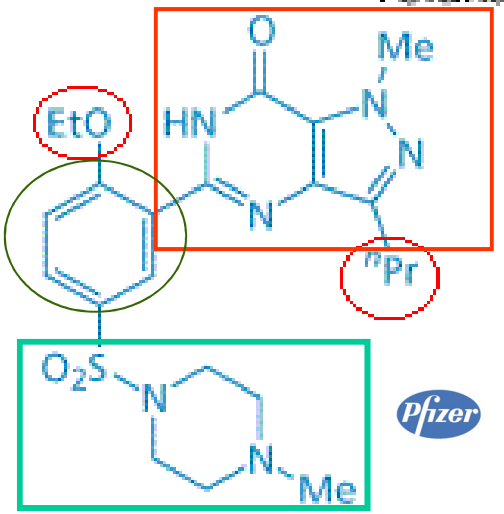
Smooth muscle relaxation

bioisosterismo

Phosphodiesterase

PDE-5 >> 6, 4





Simon Campbell

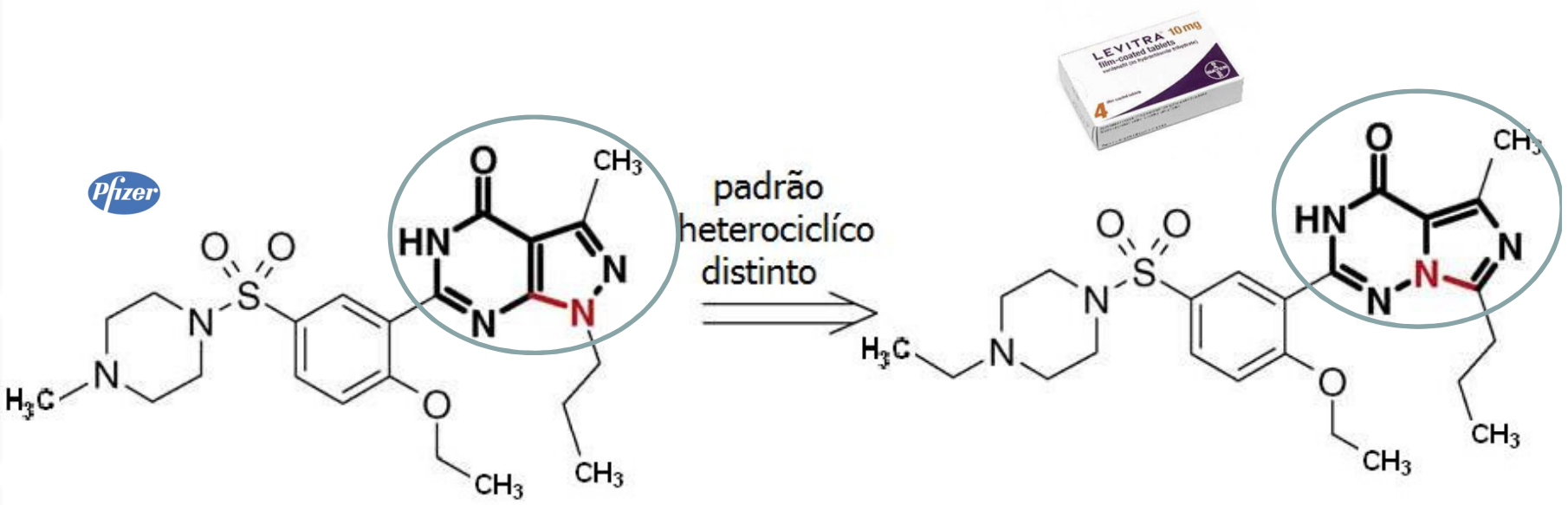
sildenafila

PDE-Vi

Pirazolopirimidona

NK Terret *et al.*, *Bioorg. Med. Chem. Lett* 1996, 6, 1819

Fármacos análogos para DE



Sildenafila
Viagra®
Pfizer

Bioisosterismo*

Vardenafila
Levitra®
Bayer

março 1998

agosto 2003

LM Lima & EJ Barreiro, Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design, *Current Medicinal Chemistry*, 2005, **12**, 23-49

European Journal of Pharmacology 591 (2008) 189–195

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Pharmacological characterization of a novel phosphodiesterase type 5 (PDE5) inhibitor lodenafil carbonate on human and rabbit corpus cavernosum

Haroldo A. Toque, Cleber E. Teixeira, Raquel Lorenzetti, Cristina E. Okuyama, Edson Antunes, Gilberto De Nucci *

Department of Pharmacology, Faculty of Medical Sciences, UNICAMP, Campinas, SP, 13081-970, Brazil

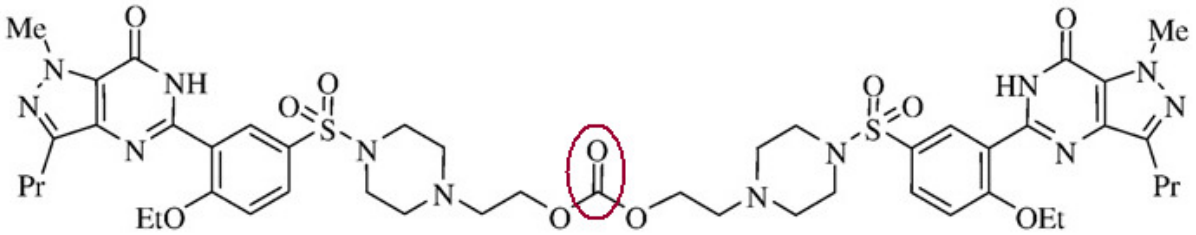
ARTICLE INFO

Article history:
Received 2 May 2008
Received in revised form 10 June 2008
Accepted 15 June 2008
Available online 19 June 2008

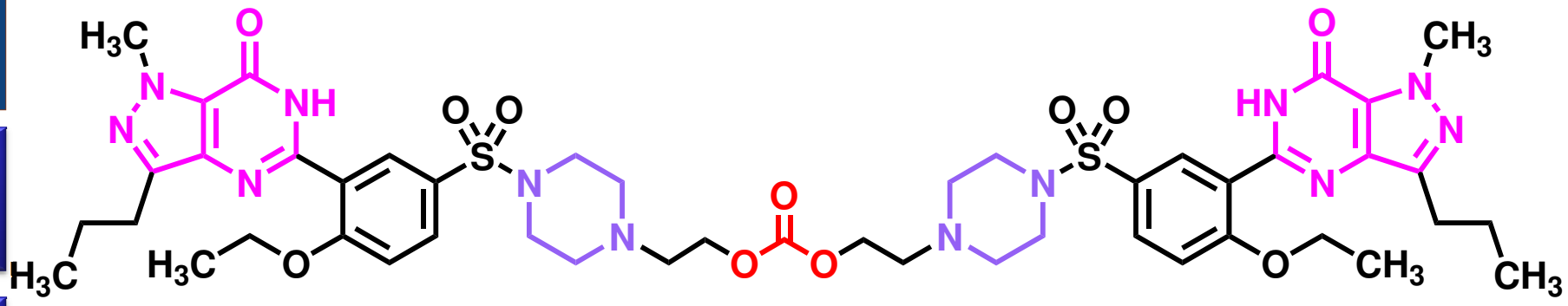
Keywords:
Erectile dysfunction
Sildenafil
Nitric oxide
Cyclic GMP
Pro-drug
Dimerization

ABSTRACT

Nitrergic nerves and endothelial cells release nitric oxide (NO) in the corpus cavernosum, a key mediator that stimulates soluble guanylyl cyclase to increase cGMP levels causing penile erection. Phosphodiesterase 5 (PDE5) inhibitors, such as sildenafil, prolong the NO effects by inhibiting cGMP breakdown. Here, we report a novel PDE5 inhibitor, lodenafil carbonate, (Bis-(2-[4-[4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-benzenesulfonyl]piperazin-1-yl}-ethyl)carbonate) that is a dimer of lodenafil. We therefore aimed to compare the effects of sildenafil, lodenafil and lodenafil carbonate on in vitro human and rabbit cavernosal relaxations, activity of crude PDE extracts from human platelets, as well as stability and metabolic studies in rat, dog and human plasma. Pharmacokinetic evaluations after intravenous and oral administration were performed in male beagles. Functional experiments were conducted using organ bath techniques. Pharmacokinetics was studied in beagles by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS), following oral or intravascular administration. All PDE5 inhibitors tested concentration-dependently relaxed (0.001–100 μM) phenylephrine-precontracted rabbit and human corpus cavernosum. The cavernosal relaxations evoked by either acetylcholine (0.01–100 μM) or electrical field stimulation (EFS, 1–20 Hz) were markedly potentiated by sildenafil, lodenafil and lodenafil carbonate. Lodenafil carbonate was more potent to inhibit the cGMP hydrolysis in PDE extracts compared with lodenafil and sildenafil. Following intravascular and single oral administration of lodenafil carbonate, only lodenafil and norlodenafil were detected in vivo. These results indicate that lodenafil carbonate works as a prodrug, being lodenafil the active moiety of lodenafil carbonate.

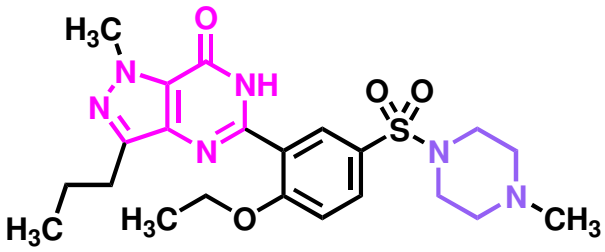


Lodenafil carbonate

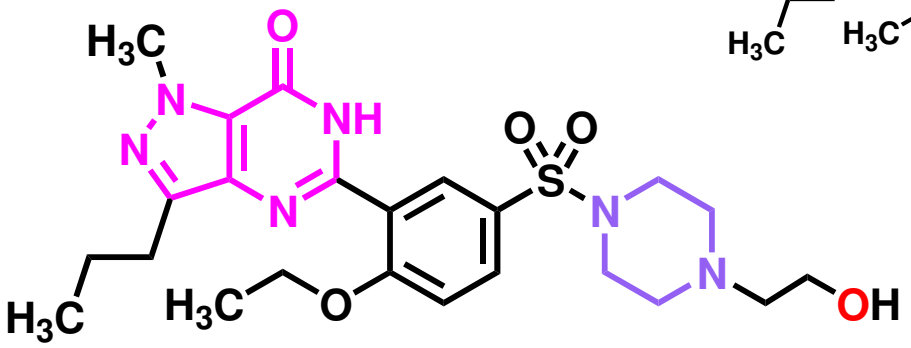


carbonato de lodenafila

in vivo



sildenafila



lodenafila

HA Toque, CE Teixeira, R Lorenzetti, CE Okuyama, E Antunes, G De Nucci, "Pharmacological characterization of a novel phosphodiesterase type 5 (PDE5) inhibitor lodenafil carbonate on human and rabbit corpus cavernosum", *European Journal of Pharmacology* **2008,** *591*, 189–95.

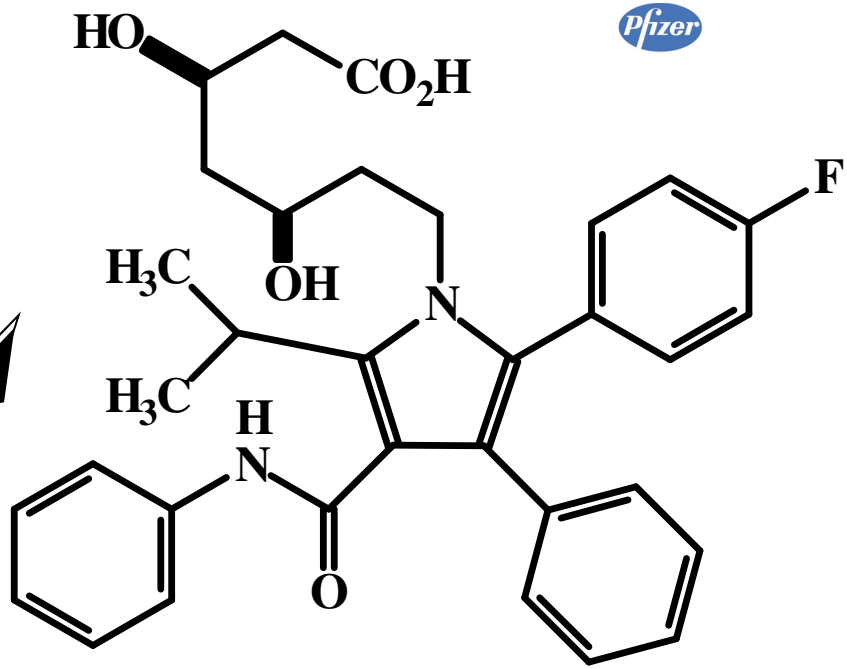
A descoberta das estatinas

Química Medicinal

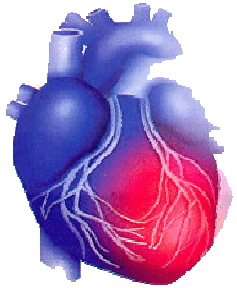
Estatinas: do protótipo natural ao super-fármaco

LDL = LIPOPROTEÍNA DE BAIXA DENSIDADE, COLESTEROL RUIM

mevastatina

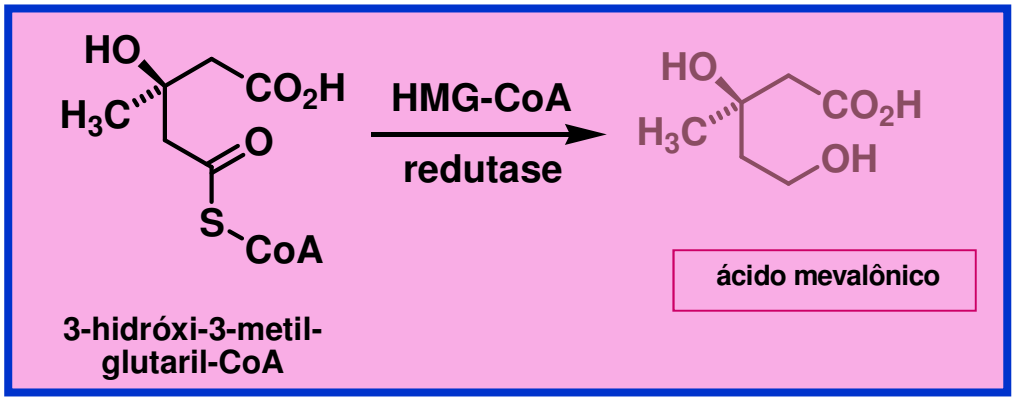


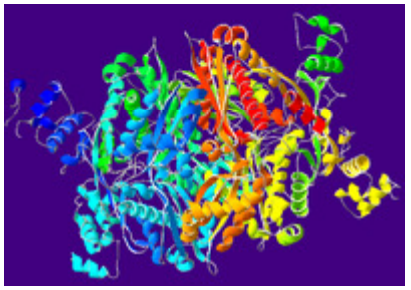
atorvastatina

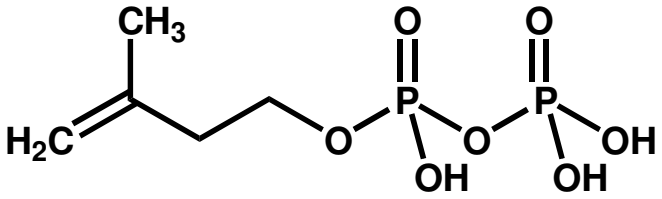


2009: US$ > 13,5 bi

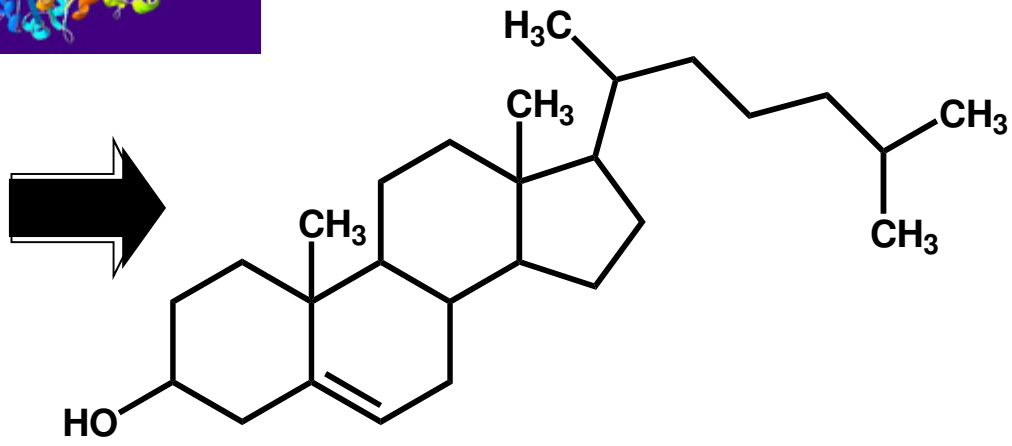
Biossíntese do colesterol







pirofosfato de isopentenila



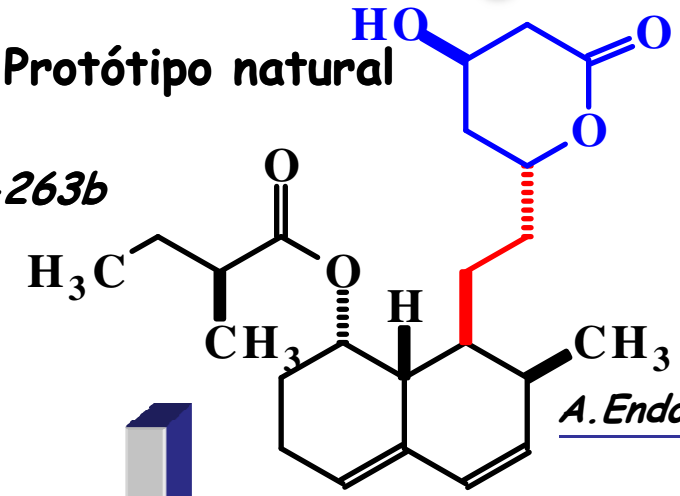
colesterol

Metabólito de Fungo

Akira Endo, Sankyo Co

1975 - Mevastatina (ML-263b

Protótipo natural



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

A.Endo, J. Med. Chem. 1985, 28, 01

Similaridade molecular

Arthur A. Patchett

J.Med.Chem. 2002,45, 5609.

γ-lactona

Mevilonina

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

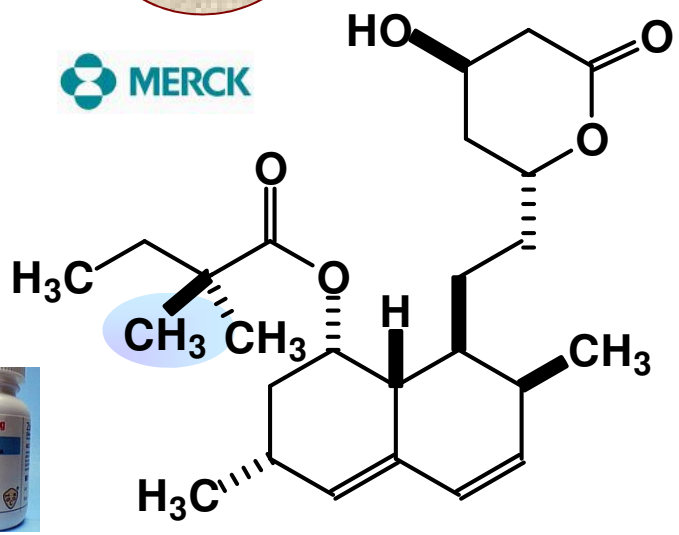
1987 - MS&D (Mevacor^{R})

US$ 5,5 bi (2007)

Pró-fármaco

MERCK

*Sim*vastatin
(Zocor^{R})
MK-733
1988

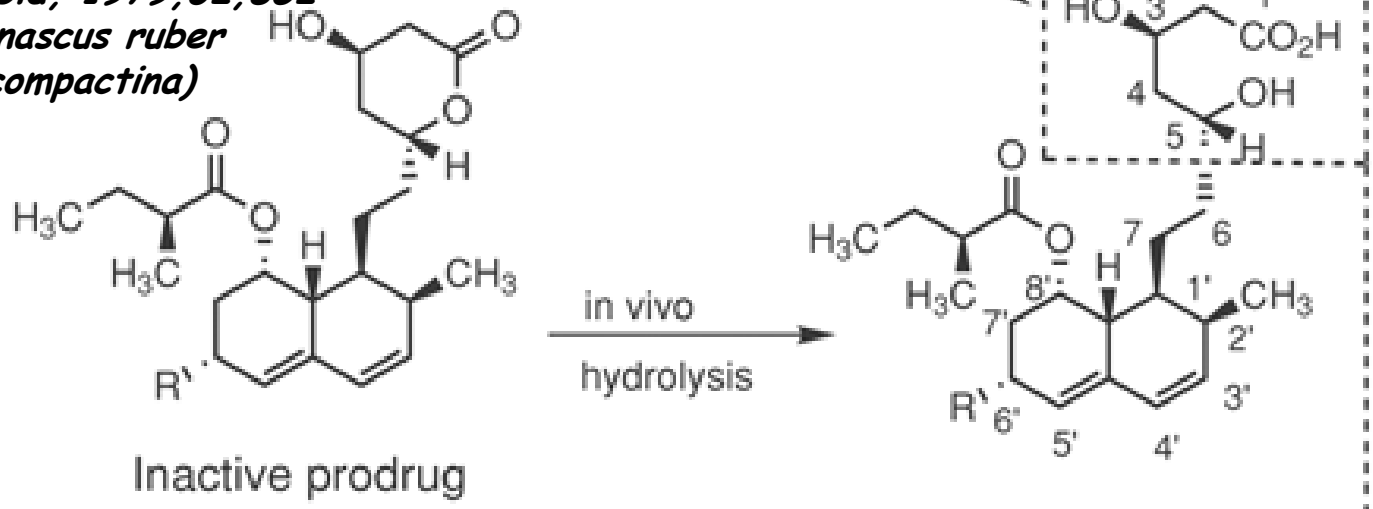


J. Med. Chem. 1986, *29*, 849

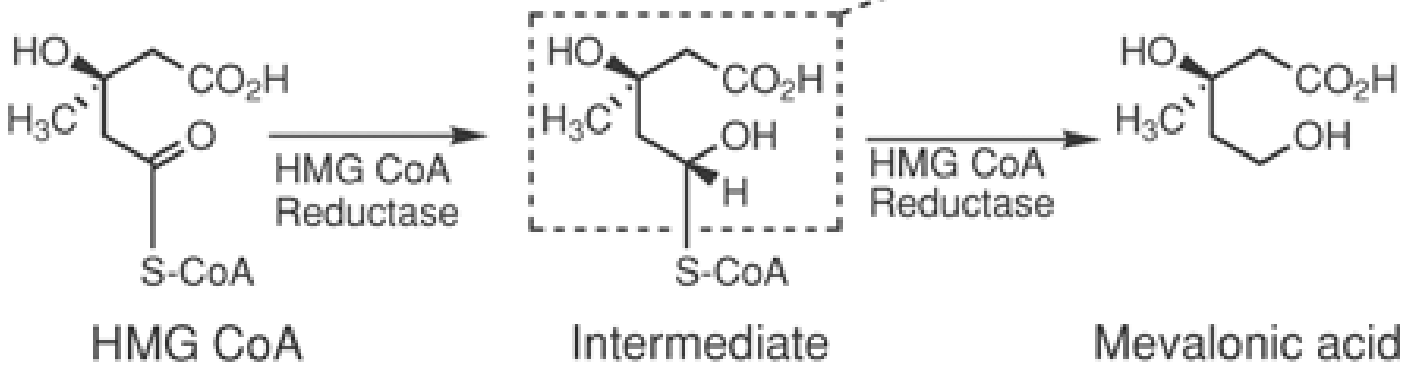
IC_{50} = 11,2 nM

Ideologia do Trabalho

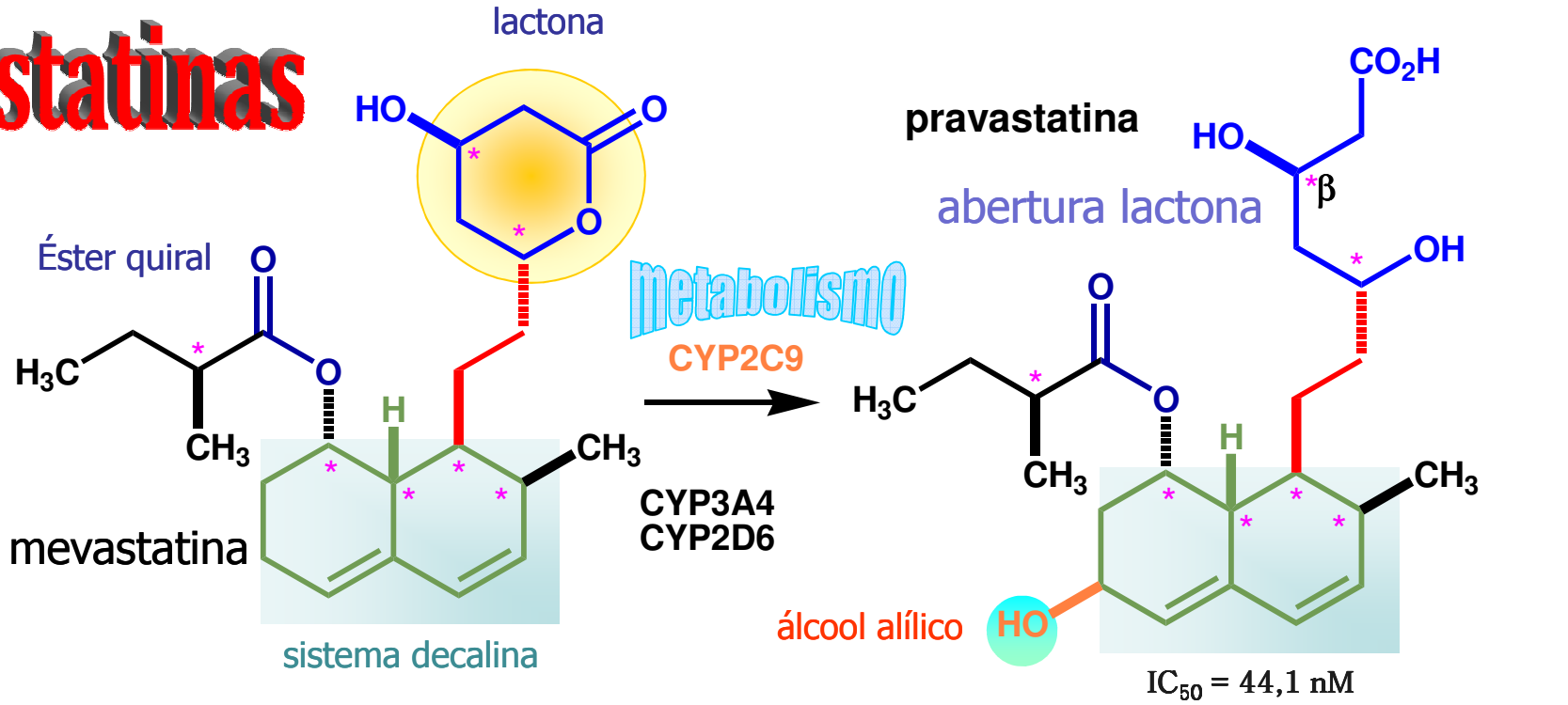
1971 – Sankyo Inc.
A.Endo, J. Antibiot.
1976, 29, 1346
Penicillium citrinum
Idem, Ibid, 1979,32,852
Monascus ruber
(compactina)

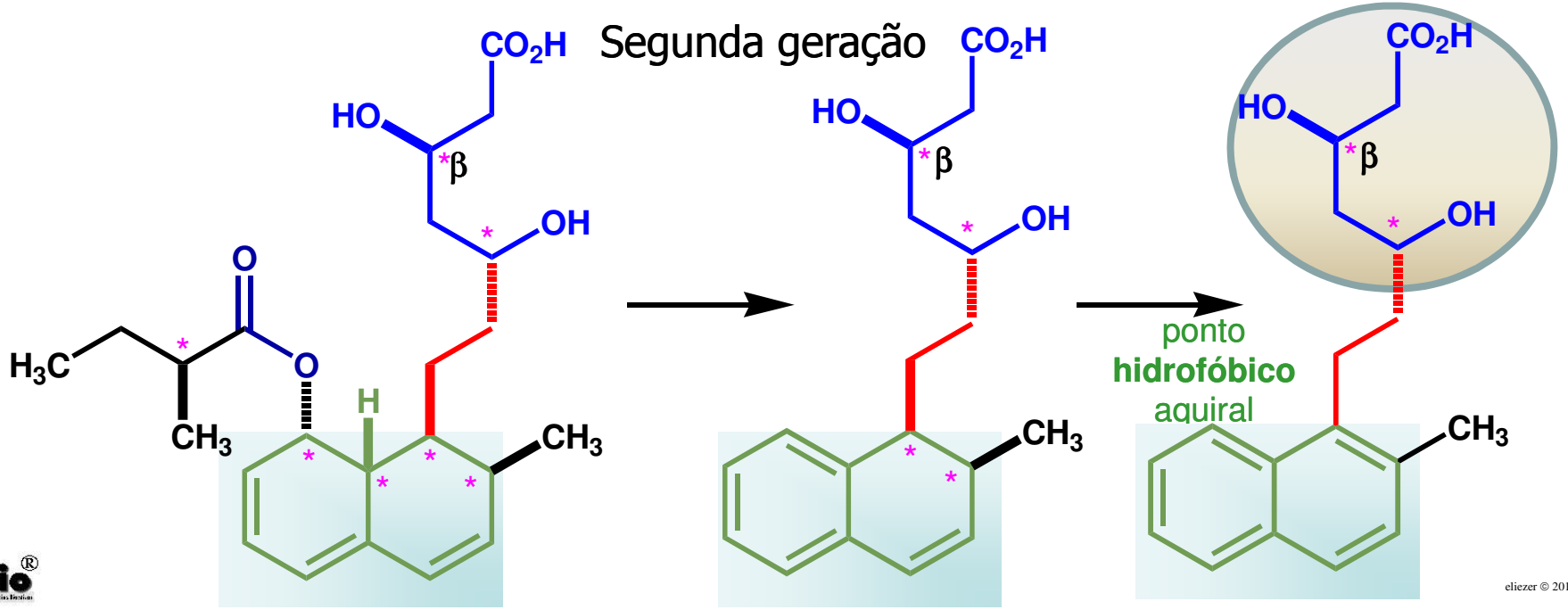


Protótipo natural ⟶ Mevastatin (R = H)
Lovastatin (R = CH_3)

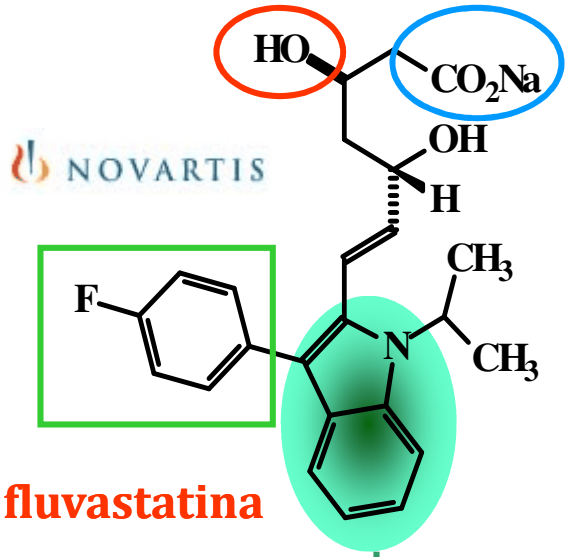


Estatinas





Gênese das estatinas de segunda geração (sm)

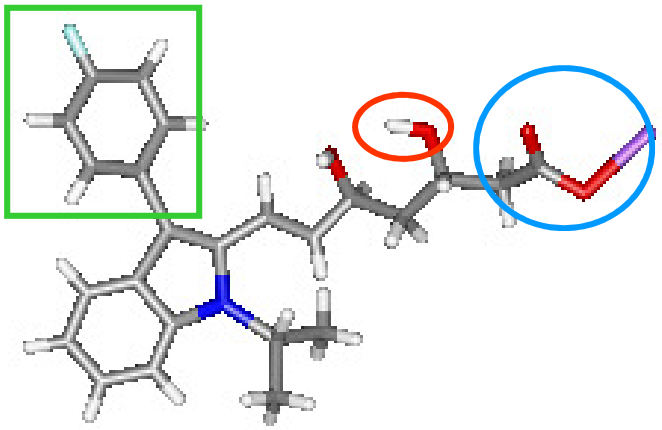


NOVARTIS

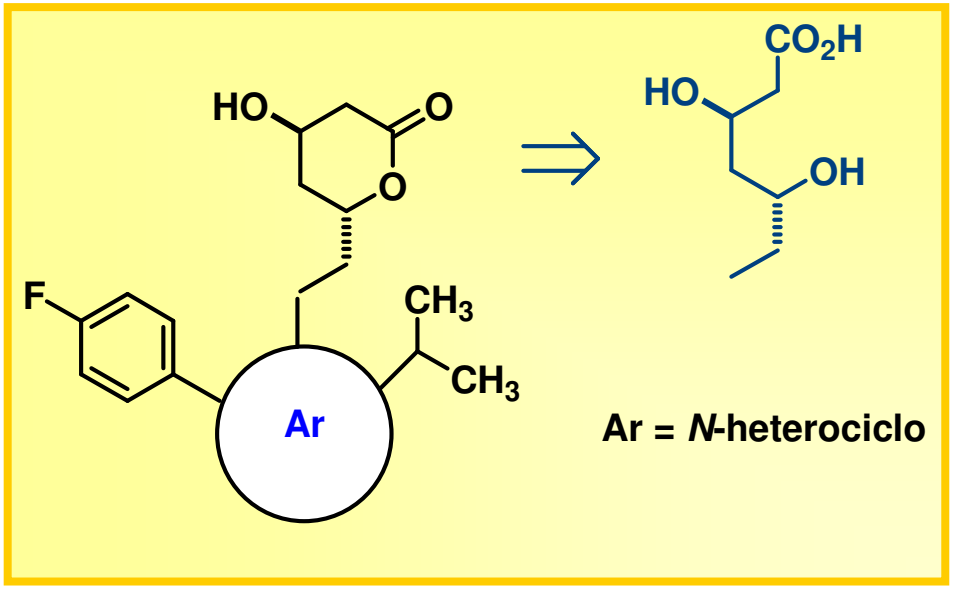
fluvastatina

IC_{50} = 27,6 nM

Sub-unidade hidrofóbica (aromática)

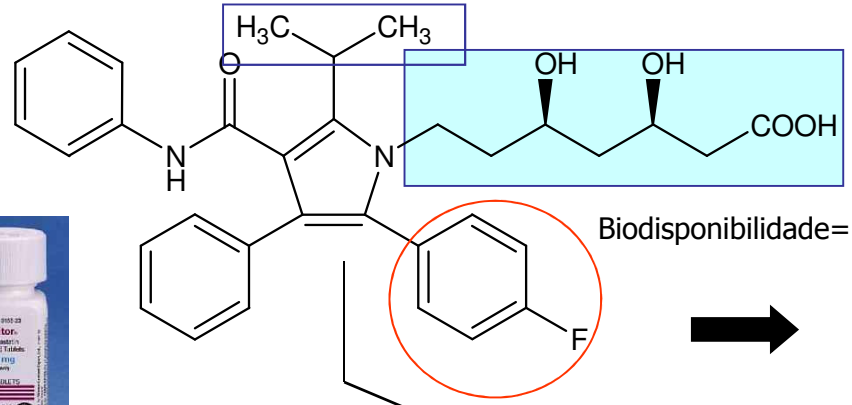


Qumiotipo das estatinas

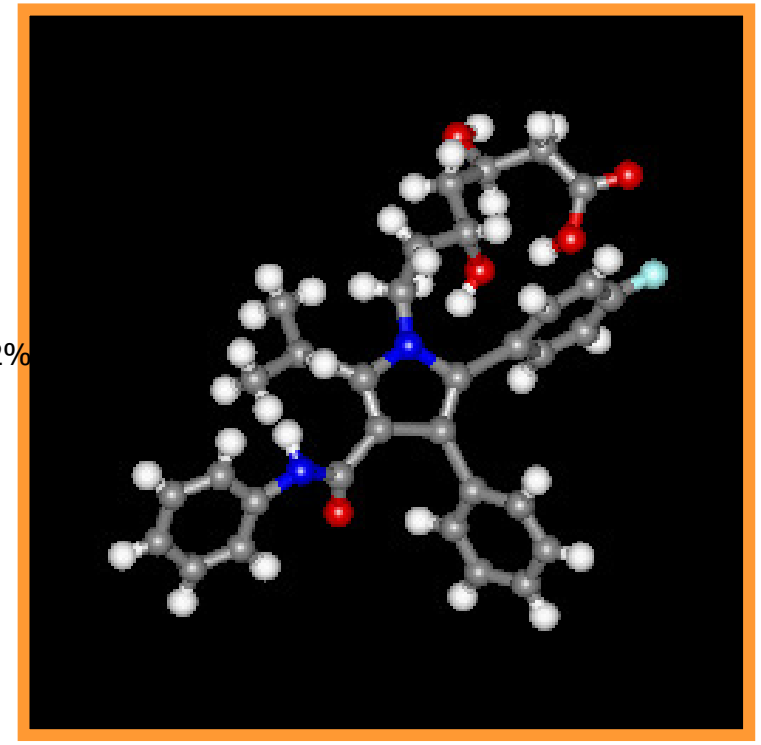


Estatinas

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



Biodisponibilidade=12%

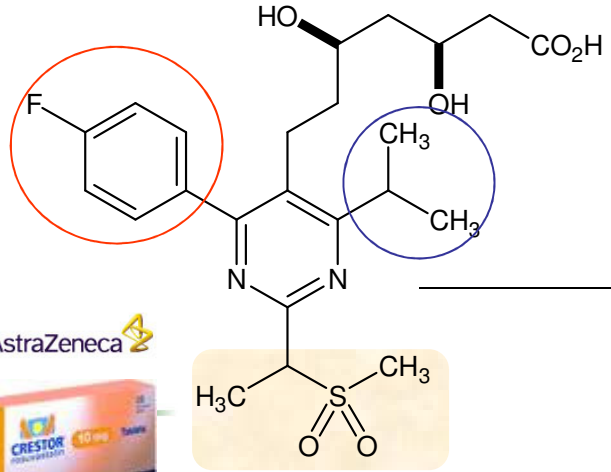


Pfizer

atorvastatina

IC_{50} = 8,2 nM

Ar

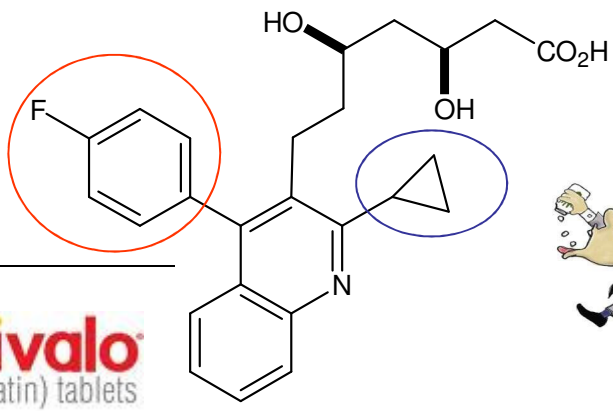


AstraZeneca

isponibilidade = 20%

rosuvastatina

IC_{50} = 5,4 nM



Livalo (pitavastatin) tablets

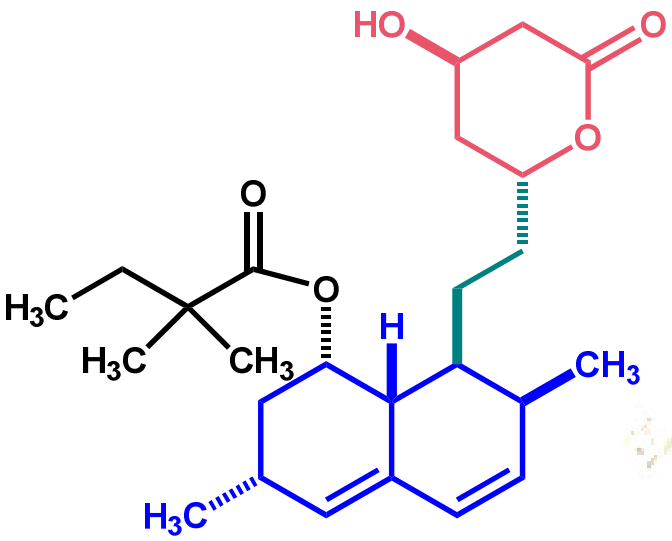
Kowa Pharmaceuticals

Biodisponibilidade=60%

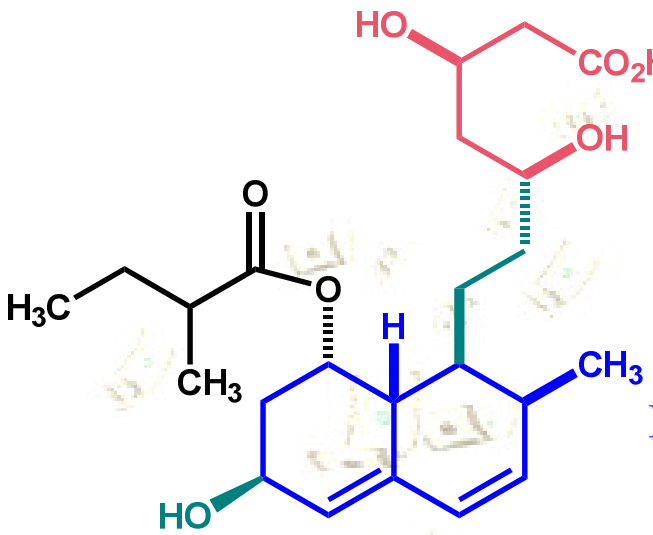
pitavastatina

IC_{50} = 3,4 nM

LASSBio®



simvastatina
1986

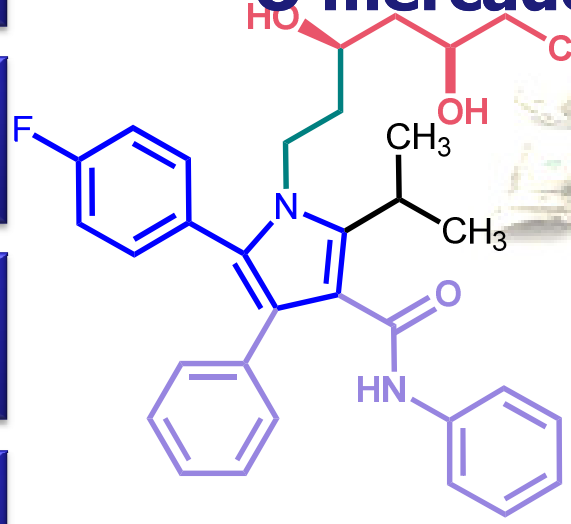


pravastatina
1988

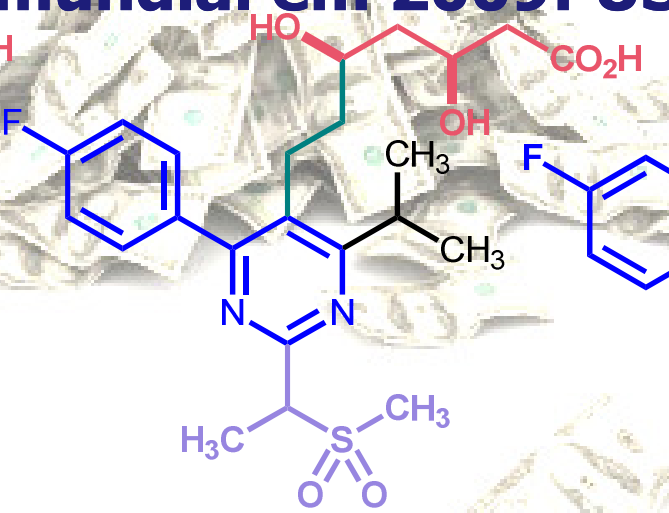
Chronicles in Drug Discovery

med Química Farmacêutica chem Medicinal

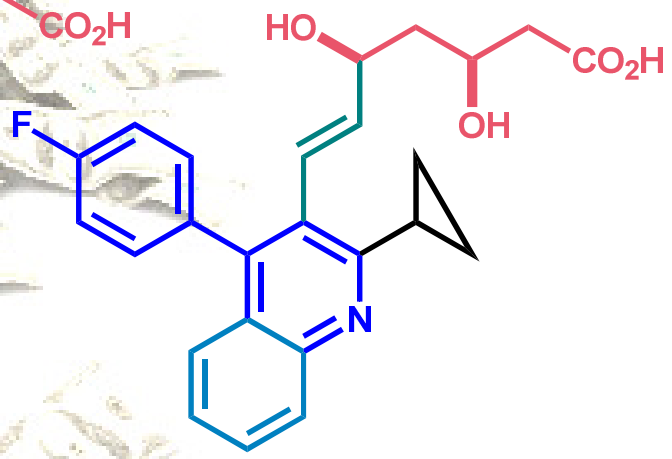
O mercado mundial em 2009: US$ 26 bi



atorvastatina
1991



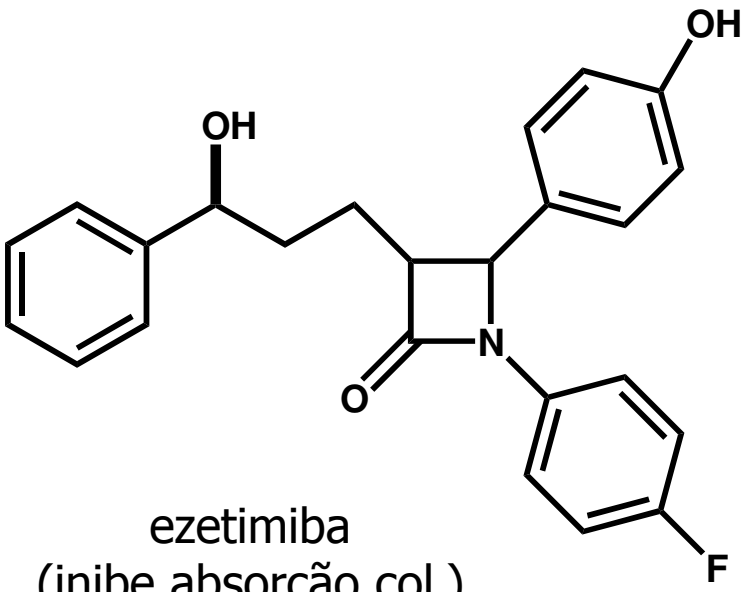
rosuvastatina
2004



pitavastatina
2009

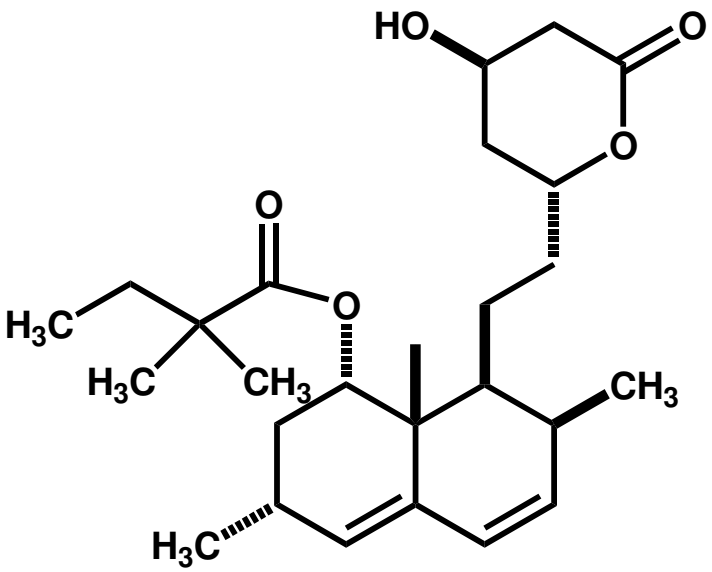
As estatinas movimentaram *ca.* R$ 290 milhões por ano no Brasil em 2008

Schering-Plough



ezetimiba
(inibe absorção col.)

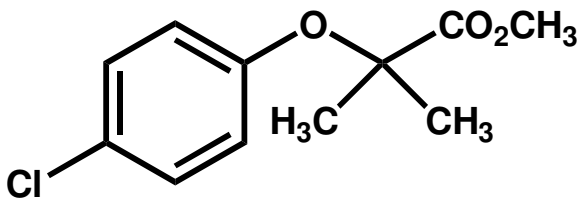
MERCK
Be well



Simvastatina
(HMGCoARi)

VYTORIN
(ezetimibe/simvastatin) tablets

American Academy of Cardiology's
57th Annual Scientific Session (2008)
Dislepidemia = hipercolesterolemia, LDL &
hipertrigliceridemia



Considerações finais

Química Medicinal

LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas

19/04/1994

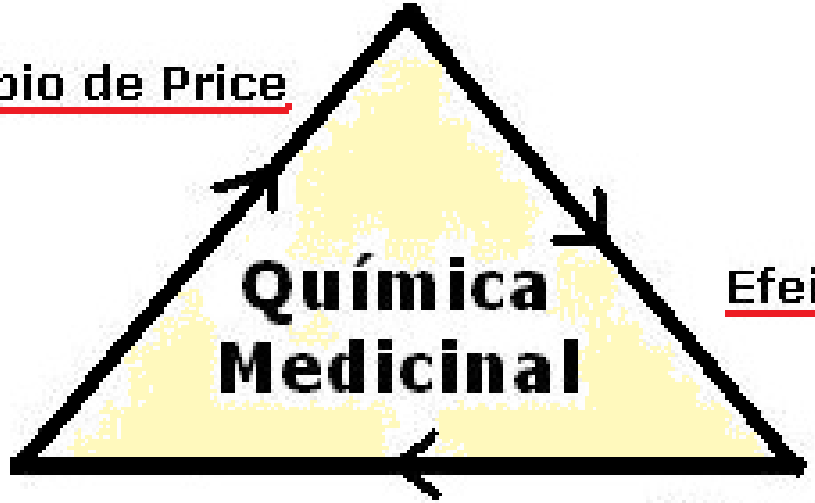
Laboratório de Avaliação e Síntese de Substâncias Bioativas

LASSBio

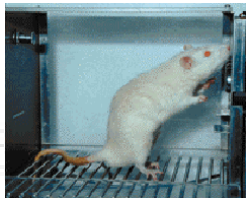
Abordagem Fisiológica

Síntese orgânica medicinal

Princípio de Price



Efeito porta-ao-lado



Bioensaios

in vivo / in vitro

Química computacional

modelagem molecular

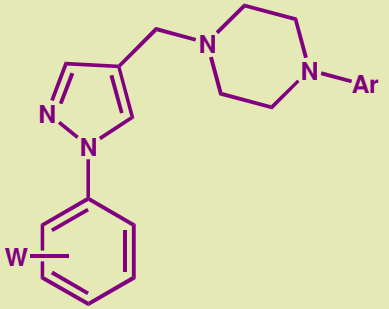
Universidade Federal do Rio de Janeiro

Novos Compostos-Protótipos Descobertos no LASSBio®

LASSBio-294

USPTO Patent # 7.091.238
August 15, 2006
2nd license agreement
ORD, UM Maryland, Baltimore, USA

LASSBio-579



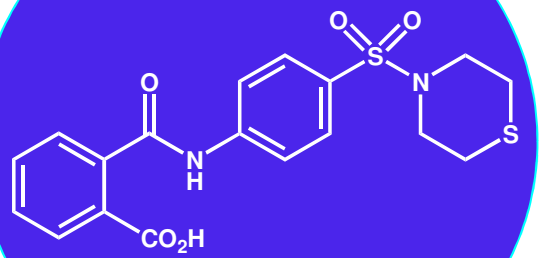
INPI # 0303465-8 de 05/09/2003

LASSBio-585

Thienylhydrazon with digitalis-like properties (positive inotropic effects)
August 15, 2006
Publication Number: 07091238

LASSBio-581

LASSBio-596



Sob contrato c/ empresa farmacêutica nacional

Otimização do protótipo

Otimização do protótipo *Otimização do protótipo*

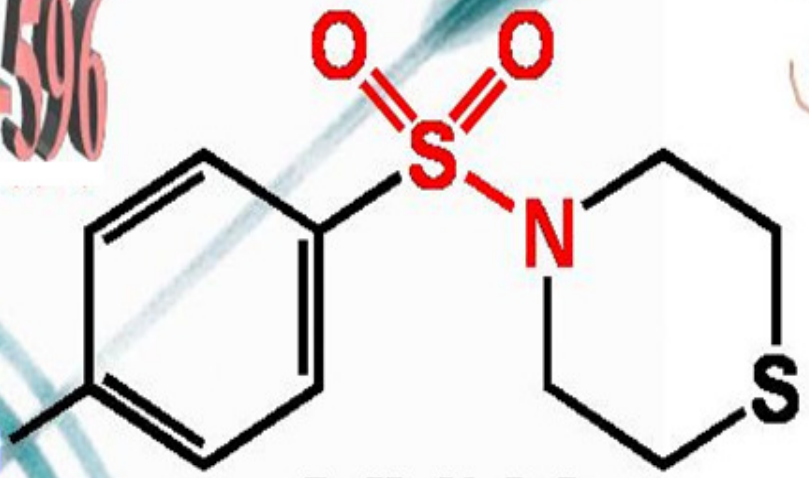
LASSBio®

Universidade Federal do Rio de Janeiro

New lead-compound for asthma

LASSBio-596

2010



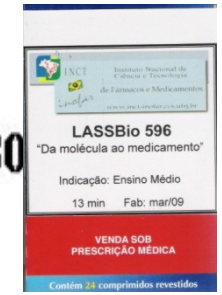
$C_{18}H_{18}N_2O_5S_2$

406,4

Log P = 2 / CLogP = 1,80

MR = 103,02

Pre-clinic studies



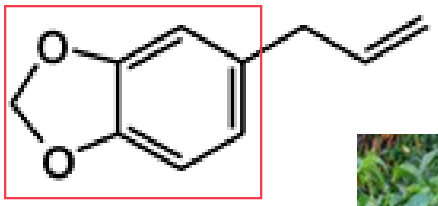
PIBR 0208767-7 - 08/11/2002
PIBR 0401660-2 - 27/04/2004

COPD

M. Lima *et al.*, *Bioorg. Med. Chem. Lett.*, **12**, 1533, 3067 (2002) ; P. R. M. Rocco *et al.*, *Eur. Respir. J.*, **22**, 20 (2003) ; M. Lima *et al.*, A*ntii-nflammatory & Anti-allergy Agents in Medicinal Chemistry*, **3**, 9 (2004) ; J. V. Bevilaqua *et al.*, *Biochem. Biotechnol.*, **121**, 117 (2005); M. S. Alexandre-Moreira *et al.*, *International Immunopharmacology*, **5**, 485 H. S. Campos *et al.*, *Braz. J. Med. Biol. Res.*, **39**, 283 (2006) ; L.M. Lima *et al.*, *Anti-inflammatory & Anti-alergy n Medicinal Chemistry*, **5**, 79 (2006)

Novo protótipo de fármaco cardioativo: LASSBio-294

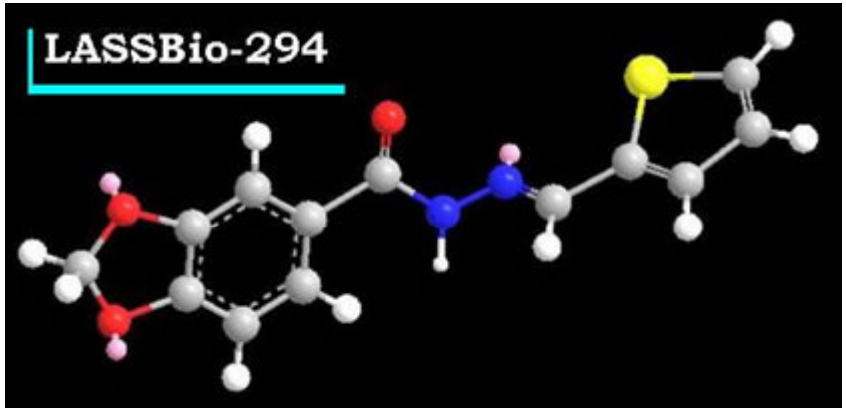
Matéria-prima abundante & sustentável



Safrol

Anel benzodioxola

Bióforo natural



Fórmula molecular $C_{10}H_{10}O_2$

Pêso molecular 162.19

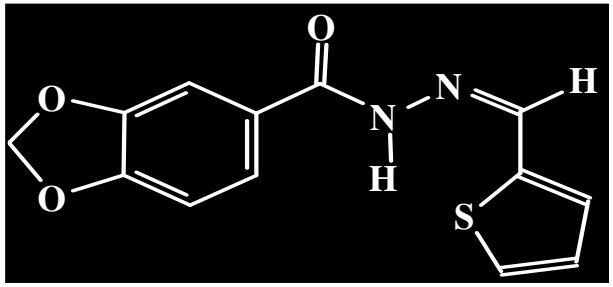
Densidade 1.096 g/cm3

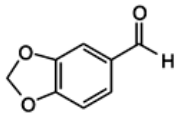
P.F. 11 °C

P.E. 232-234 °C

CAS # 94-59-7

IUPAC: 5-(2-Propenil)-1,3-benzodioxola





Piperonal

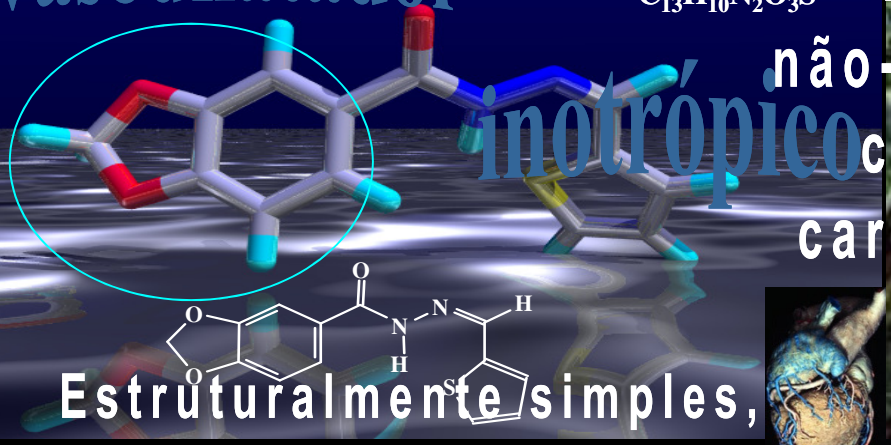
Novo Protótipo de Fármaco Cardioativo

LASSBio-294

vasodilatador

inotrópico

$C_{13}H_{10}N_2O_3S$



Estruturalmente simples, sinteticamente acessível em ótimos rendimentos, através de metodologia clássica, escalonada (1,0 M), a partir de produto natural abundante, acessível.

Safrol

Novo agente cardioativo, não-digitálico, não-adrenérgico, com potentes propriedades cardioativas & neuroprotetoras; Ativo por via oral; Sem toxicidade aguda, cito- ou genotoxicidade.

Piper longa

NAH

Patente

LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas

"Thienylhydrazon with digitalis-like properties (positive inotropic effects)" - Patente 07091238 (USPTO), 15 de agôsto de 2006; WO 2000-078754 (65 países) .

LASSBio®

Estudos de Toxicidade Aguda e Sub-aguda

✓**A toxicidade sistêmica aguda e sub-aguda foi investigada em ratos, por duas vias de administração, *p.o.* e *i.p.*, nas doses de 1000 μM/kg e 73 μM/kg, respectivamente (*i.p.*, administrando-se 2 vezes ao dia, durante 15 dias seguidos: ~ 100 vezes superior à ED_{50} *in vivo*).**

LASSBio-294

Novo protótipo de fármaco cardioativo

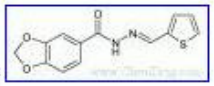
Não tem efeito letal, não provoca letargia, não reduz a motilidade, nem altera o pêso dos animais.

Não provoca alterações na contagem de células sanguíneas, hematócrito, nem altera a taxa de glicose, uréia, TGO, TGP, creatinina.

Não altera histopatologicamente orgãos vitais, tais como fígado, pulmão, SNC.

Não se observaram efeitos neurotóxicos em culturas de neurônios hipocampais de ratos, tratadas com LASSBio-294 (500 μM).
Efeito neuroprotetor foi observado em < doses.

Google lassbio-294 Pesquisar imagens Voltar aos resultados de imagens



Ver imagem em tamanho grande

242 x 92 - 2k - gif - www.chemdrug.com/.../SYNTHESIS/STR/31/311236.gif

A imagem pode ter direitos autorais.

Veja abaixo a imagem em: www.chemdrug.com/.../8_0_pgbsenqajcujdkct.html

Remover frame

药品资讯网 CHEMDRUG. COM

www.chemdrug.com 新药研发行业信息发布 首选平台!

登录 免费注册 发布信息 免费

咨询热线：028-85335741

药品资讯网--新药研发行业门户!

首 页 | 供应信息 | 求购信息 | 企业展厅 | 产品中心 | 展会信息 | 招商合作 | 人才招聘 | 专业资料 | 技术问答 | 医药搜索

请输入搜索关键字 专业期刊 找一下

热门搜索关键字: 转让 人参皂苷 吡格列酮 注射液 抗生素 维生素C 批件 fda

·如何采购？ ·如何看买家信息？

·如何增加信息的曝光度？

时政要闻 | 新药研发 | 业界动态 | 化药质量标准 | 2000版药典标准 | 其他药品标准 | 中草药数据库 | 中药方剂数据库 | 常用药物手册 | 经典有机反应 | 化学药品合成数据库 | 医药中间体数据库 | 化学物质数据库 | FDA批准药品资料 | 化学品物性数据库 | 化学品毒性数据库 | 健康论文数据库

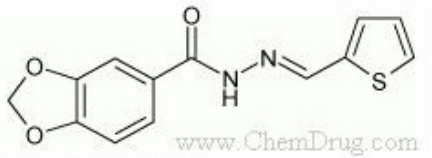
您现在的位置： >> 专业资料首页 >> 药物合成数据库 >> L-294, LASSBio-294,314021-07-3,C13-H10-N2-O3-S,(E)-N'-(Thien--药物合成数据库

【药物名称】 L-294, LASSBio-294

【化学名】 (E)-N'-(Thien-2-ylmethylene)-1,3-benzodioxole-5-carbohydrazide

【CAS登记号】 314021-07-3

【结构式】



【分子式】 C13-H10-N2-O3-S

【分子量】 274.299

【原研厂家】 LASSBio (Originator), University of Maryland (Originator)

【作用类别】 CARDIOVASCULAR DRUGS, Cerebrovascular Diseases, Treatment of, Heart Failure Therapy, NEUROLOGIC DRUGS, Positive Inotropic]ents, Phosphodiesterase III Inhibitors

AD-8717,181821-99-8,N-(2,6 DMP-802,,3-[2-[3-(4-Amidino]

Zonampanel, YM-872,21024 SB-221284,196965-14-7,5-(

推荐专业资料

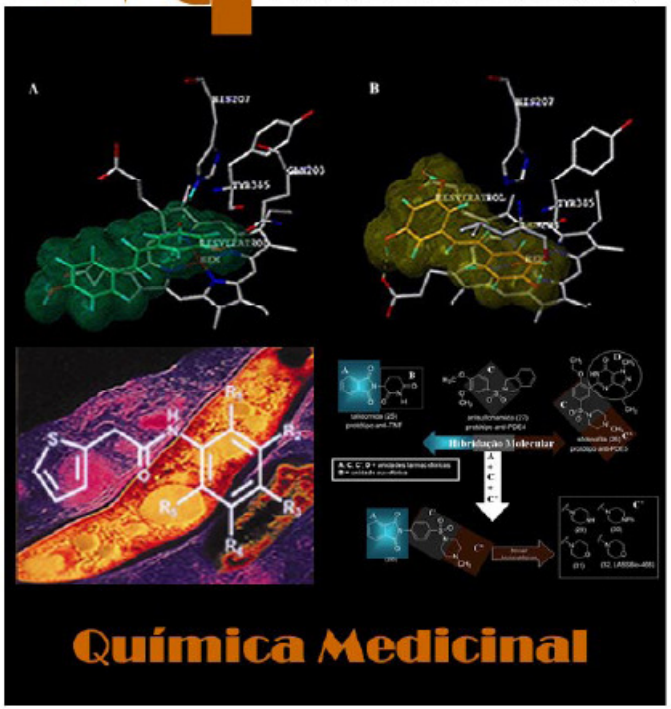
ZINC00145813,ST5197865,	Oprea1_826548,MLS000122
ZINC00151021	IUPAC Name: 3-(2-chlorophe
ZINC00257502	MLS000716050,BAS 078671
STK138182,ZINC00302421,	IUPAC Name: (3E)-3-[(4-etho
Oprea1_091018,ST031273,	ZINC00104509
ZINC00084075	IUPAC Name: (2R)-1-(4-meth
IUPAC Name: (1R,,6R)-6-[(2-	Oprea1_406105
IUPAC Name: 6-hydroxy-1-(2-	ZINC00081150
STOCK2S-20570,ZINC0026	ZINC00214910
ZINC00230690	Oprea1_042214,CBDivE_01

赞助商链接

LASSBio®

Revista Virtual de Química
www.uff.br/rvq
Volume 1, Número 1, Janeiro-Março 2009

www.uff.br/rvq



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

EJB2

Universidade Federal do Rio de Janeiro

ICB Instituto de Ciências Biomédicas

Da molécula ao corpo

Revista BIO ICB | Institucional | Programas de Graduação | Programas de Pós-Graduação | Programas de Pesquisa | Programas de Extensão | Docs ICB

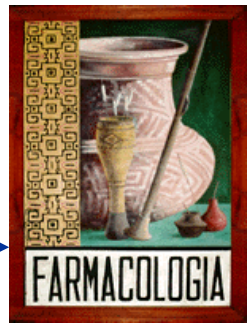
- Contato
- Cursos
- Disciplinas
- Editais de Seleção
- Informações Gerais
- Orientadores e Lir... Pesquisa

Programa de Pós Graduação em Farmacologia e Química Medicinal 2006

29 de abril de 2008

"Medicinal chemistry or pharmaceutical chemistry is a discipline at the intersection of chemistry and pharmacology involved with designing, synthesizing and developing drugs."

Interface Química-Biologia em Química Medicinal



Único programa de pós-graduação (M/D) com este perfil na América Latina

LASSBio®

Diapositivo 39

EJB2

A recente criação da PG (M&D) em Farmacologia e Química Medicinal ilustra nova perspectiva de horizonte na PG da UFRJ, pois é a primeira com o perfi desta proposta interdisciplinar na AL.l

Eliezer J. Barreiro; 04/03/2010

"Meditai se só as nações fortes podem fazer Ciência, ou se é a Ciência que as fazem fortes"

Oswaldo Cruz

Epílogo

View of the pioneer apothecary

Obrigado pela presença

Corcovado, uma das sete novas maravilhas do mundo !