Universidade Federal do Rio de Janeiro

57ª JORNADA FARMACÊUTICA DA UNESP

Mini-curso:"SITUAÇÃO DO DESENVOLVIMENTO DE FÁRMACOS NO BRASIL"

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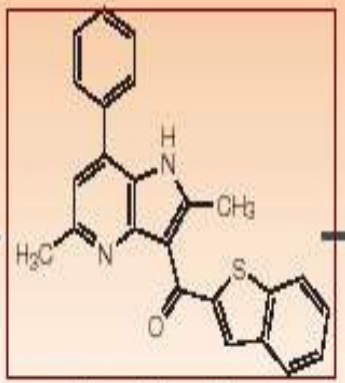
Programa de Desenvolvimento de Fármacos – ICB - UFRJ

http://www.farmacia.ufrj.br/lassbio

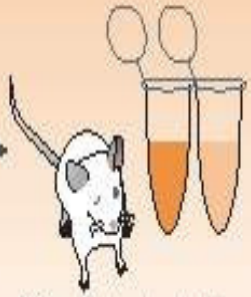
57ª JORNADA FARMACÊUTICA DA UNESP; Mini-Curso: A Situação do desenvolvimento de FÁRMACOS no Brasil; O PROCESSO DE descoberta/invenção de FÁRMACOS; definições; os FÁRMACOS e os medicamentos; a inovação; as moléculas pioneiras; o mercado farmacêutico mundial & do BRASIL; o processo de descoberta; novos fármacos; inovação e desenvolvimento de FÁRMACOS; a inovação TECNOLÓGICA farmacêutica; os FÁRMACOS e a **Pesquisa**; a produção DO conhecimento; a PRODUÇÃO científica brasileira; OS fármacos e o Prêmio NOBEL; (Louis Pasteur), Emil Fischer; Paul Ehrlich; Robert KOCH; *Alexander* Fleming; Ernest Chain; Howard FLOREY; bent *Samuelsson*; SUNE bergstron; John R. VANE; George ***Hitchings;*** Gertrude Belle ELION; Albert von Szent-Györgyi; W. N. Haworth; *L. C.* Pauling; James D. Watson; Francis H C Crick; a **INTERDISCIPLINARIDADE**; o PERFIL da pesquisa CIENTÍFICA contemporânea; o *processo de* DESENVOLVIMENTO de fármacos; A cadeia **da inovaçÃo** em *fármacos*; *inovação* TERAPÊUTICA; Planejamento RACIONAL; Cimetidina; ranetidina e o surgimento de uma *Big-Pharma*; *inovação e* patentes; *características* da INDÚSTRIA farmacêutica; moléculas BILIONÁRIAS; os fármacos sintéticos; inovação radical e INCREMENTAL; losartana; sildenafila; *carbonato de* lodenafila; IMATINIBE; me-toos; Caduet^{R}; fluoxetina; *olanzepina*; butenosida; formeterol; fluticazona; *salmeterol*; rosuvastatina; *fenofibrato*; anlodipina; **atorvastatina**; simvastatina; EZETINIBA; *animais* transgênicos; CRISE na inovação; carência de *moléculas* **inovadoras**; ZICONOTIDEO; oportunidades em genéricos; *novas tecnologias*; MOLÉCULAS inteligentes; INCT-INOFAR; considerações finais; universidade-empresa; novo composto-protótipo de fármaco cardioativo: **LASSBio-294**; *programa de pós-graduação em Farmacologia e QUÍMICA MEDICINAL (M&D)*; *PRONFAR;* convite; agradecimentos.

Preclinical studies

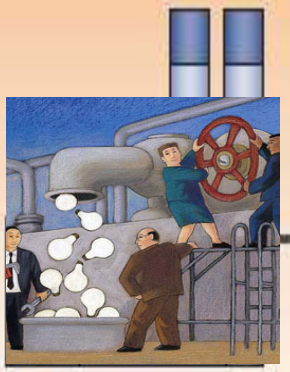
Research team formed and objectives set



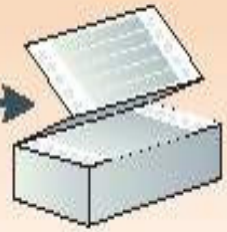
Novel chemicals synthesized



Chemicals tested for efficacy and safety in test tubes and animals. Results used to choose drug candidate.

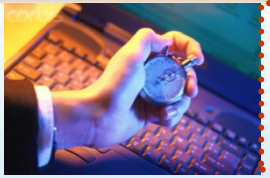


Formulation, stability scale-up synthesis, chronic safety in animals

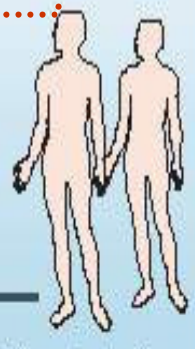


Company files Investigational New Drug (IND) application with FDA

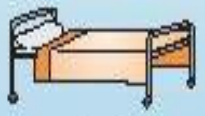
Clinical studies



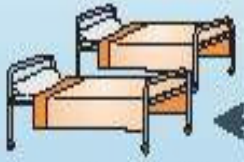
O processo de descoberta/invenção de novos fármacos é complexo…



Phase I: studies in healthy humans (toleration)



Phase II: studies in patients (efficacy)



Phase III: large clinical trials in many patients

Company files New Drug Application (NDA)

ANVISA

FDA

FDA reviews NDA

Drug is approved for marketing

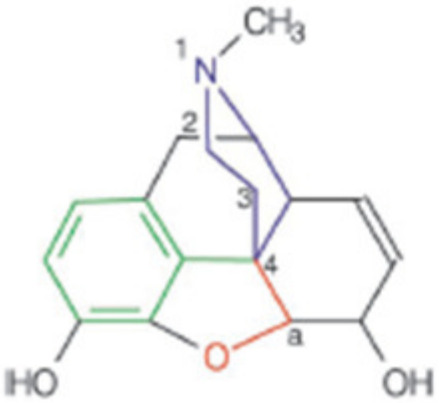
JA Lombardino & JA Lowe III, Nature Rev. Drug Disc. 2004, 3, 853

O fármaco…

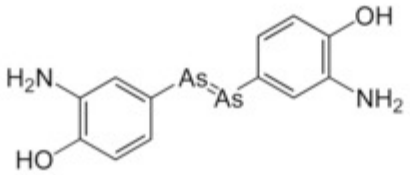
O uso de fármacos é milenar

Jacques Louis David, A morte de Sócrates, MAM, Nova Iorque, EUA

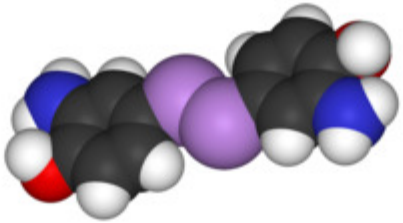
As moléculas pioneiras...

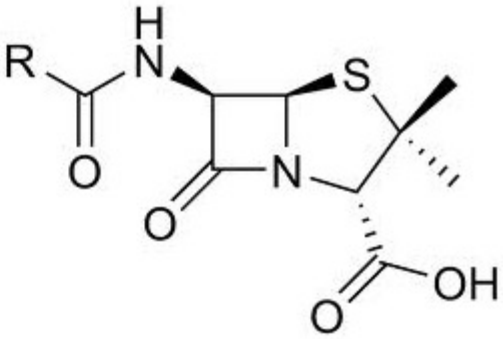


morfina



arsfenamina





penicilina

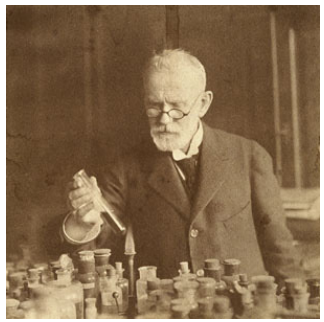
Henry How

1853 – Un. Glasgow

Paul Ehrlich

1854-1915

Nobel 1908



Alexander Fleming

1881-1955

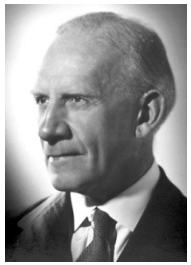
Nobel 1945

Library of Congress

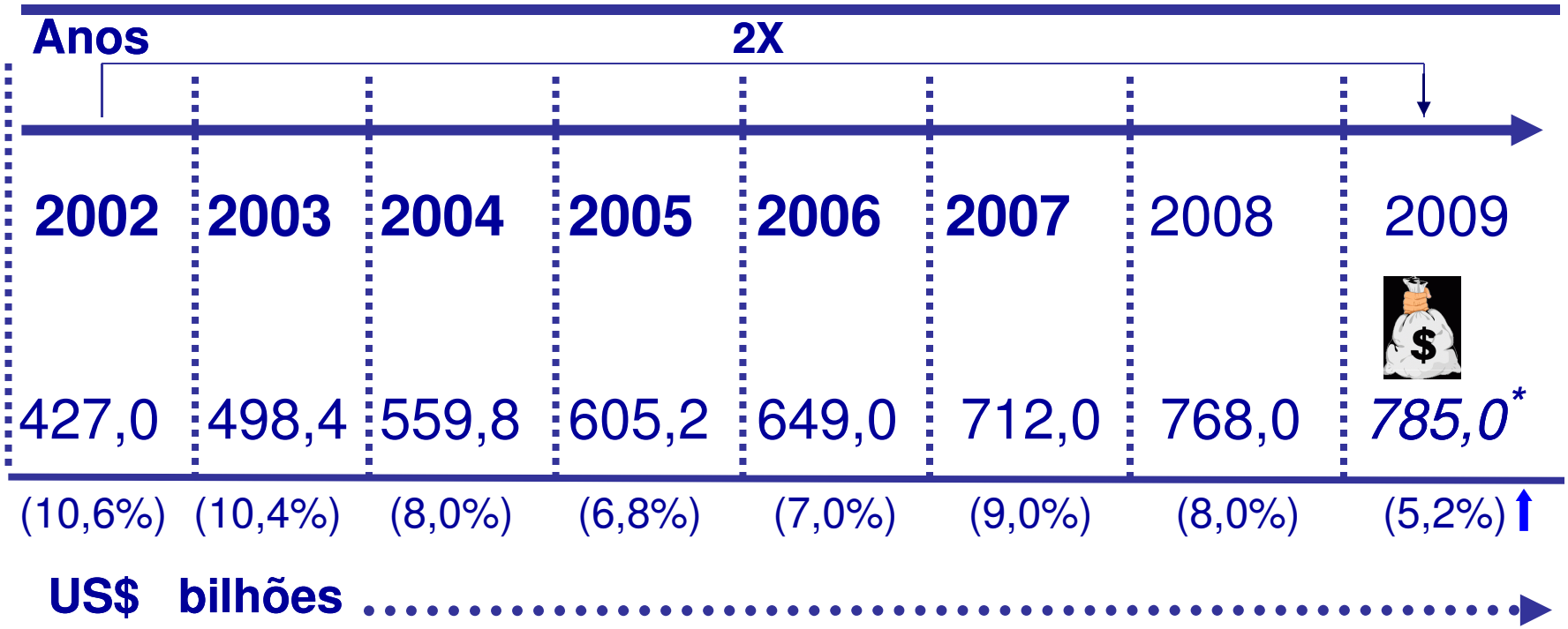
Sir Robert Robinson

1886-1975

Nobel 1947



Mercado Farmacêutico Mundial



*Fonte: SJ Ainsworth *C&EN*, Dec. 07, p.13, 2009

América Latina:

Brasil:1,6% (10º lugar) = US$ 11,6 bilhões

***Top*-10: US$ 561,9 bilhões (USA: US$ 300 bilhões = 40%; Jp, Fr, Al.)**

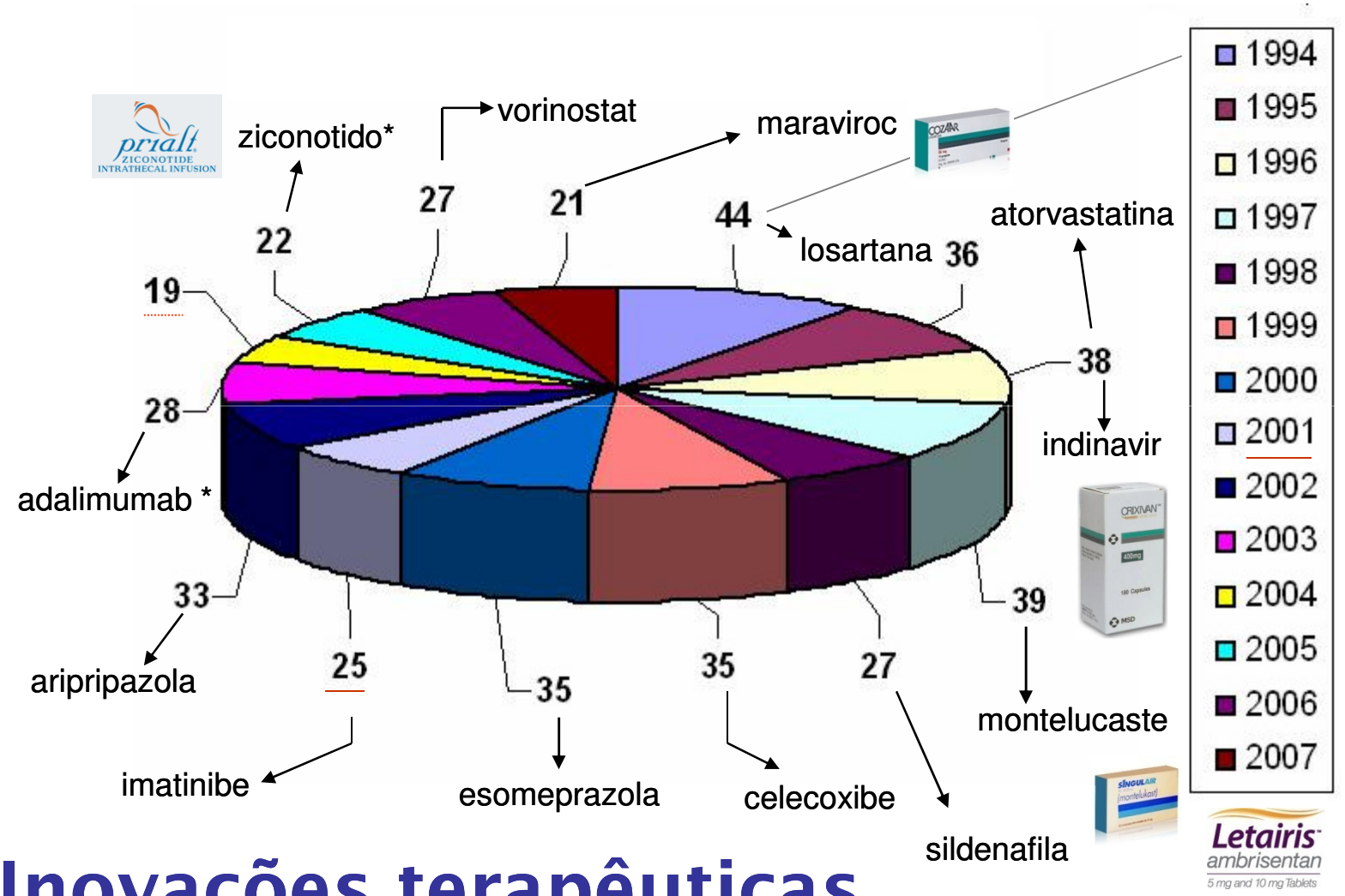
Principais classes terapêuticas:

oncológicos (6,9%)

& anti-lipêmicos (4,7%)

2010-2013: osteoporose, DRC

Novos fármacos lançados por ano / 1994 - 2007



Inovações terapêuticas

ca. 30 novos fármacos lançados / ano

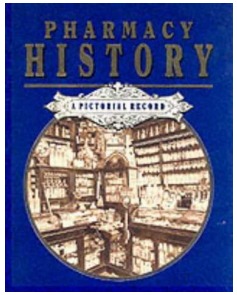
Pesquisa

Inovação

Desenvolvimento

A Inovação Farmacêutica

Dicionário Aurélio

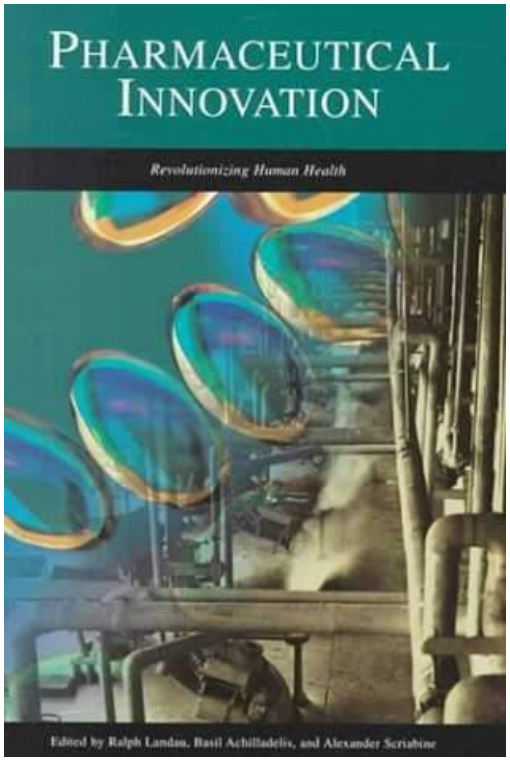


Inovação:

ato ou efeito de inovar.

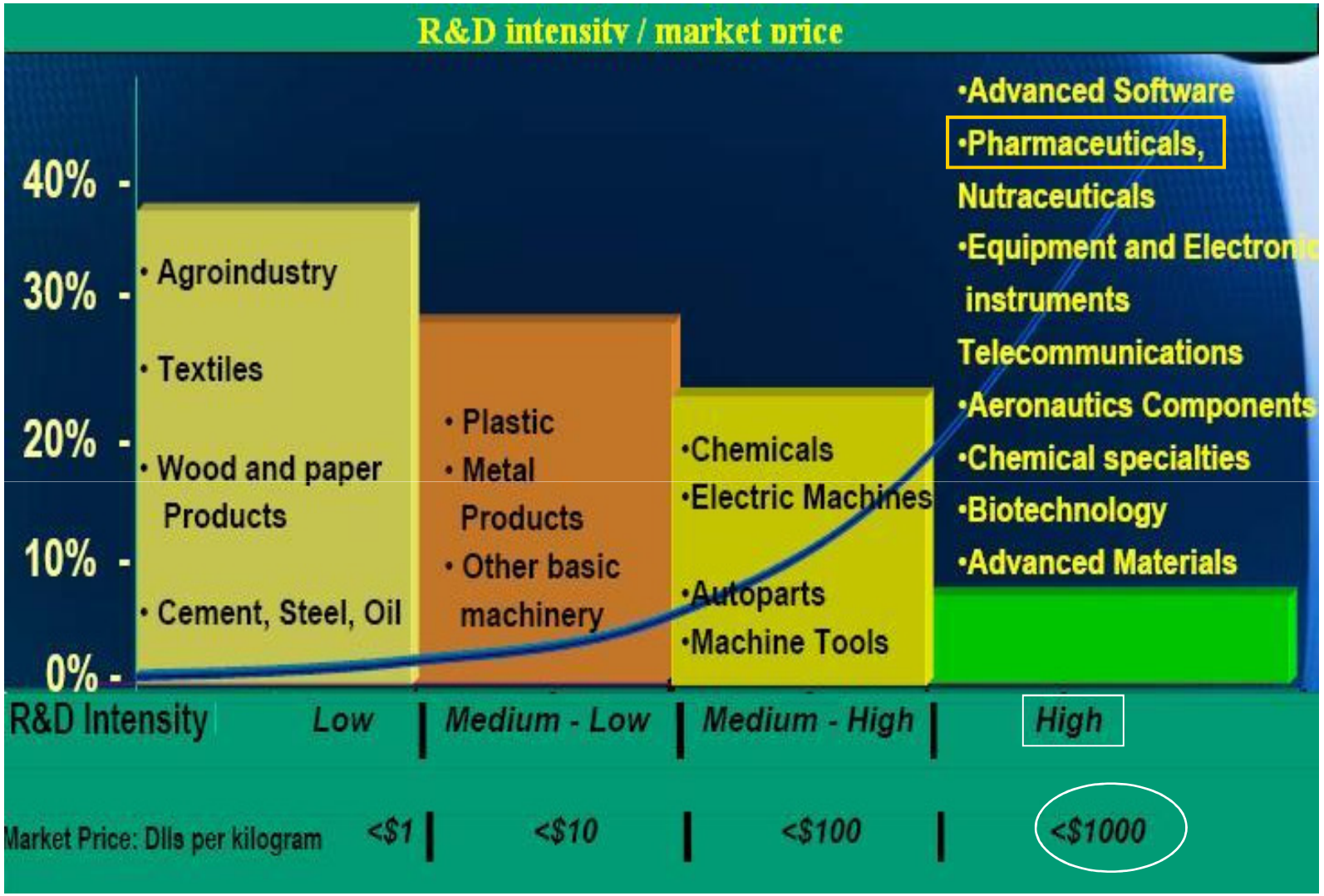
Inovação: significa novidade ou renovação. A palavra é derivada do termo latino *innovatio*, e se refere a uma idéia, método ou objeto que é criado e que pouco se parece com padrões anteriores

A inovação tecnológica é um dos processos mais dinâmicos da atividade industrial. Este dinamismo se expressa de forma acentuada na inovação tecnológica farmacêutica que, mais do que qualquer outra, depende da efetiva interação entre Ciência & Tecnologia.



A **inovação tecnológica farmacêutica** é produto da *descoberta* ou da *invenção e* o principal *driving-force* da indústria farmacêutica que *desenvolve* fármacos.

A inovação em fármacos depende da pesquisa

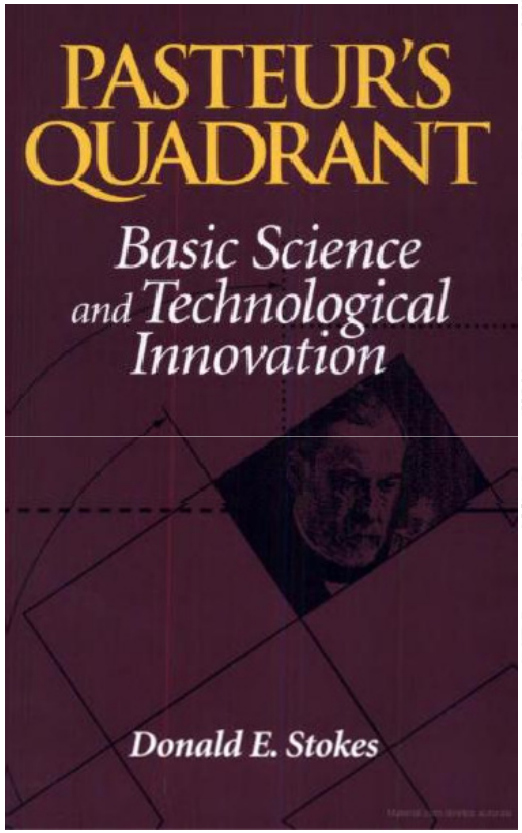


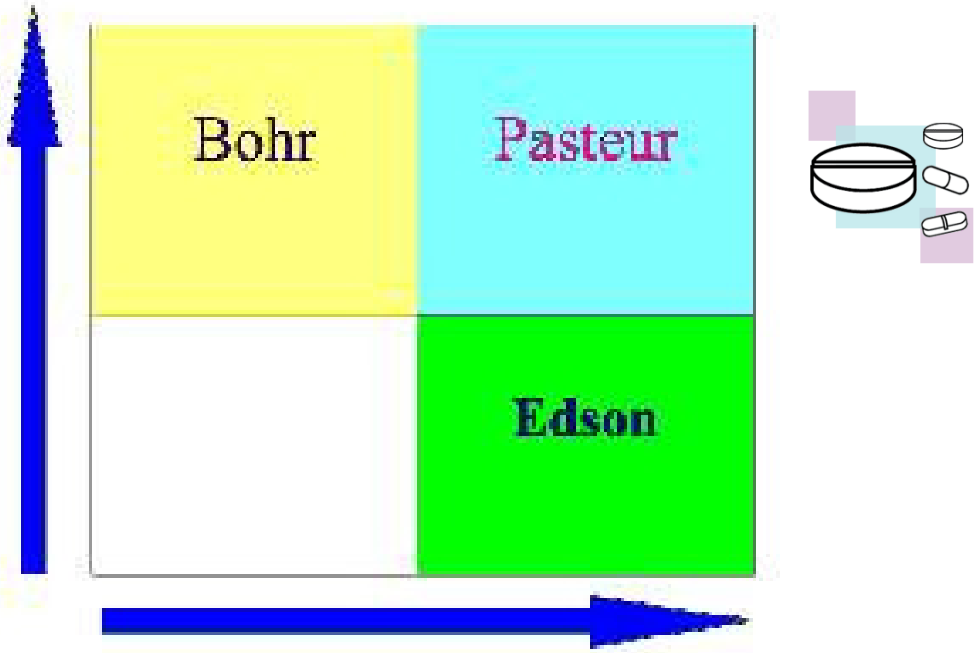
The New York Times, 15 de maio de 2007
O mercado global de patentes é de US$ 200 bi!

Em 2006, o Brasil ocupava o 48º lugar dentre os inovadores, a Rússia 37ª , o México 45ª, o Chile 47ª, a Índia 58ª e a China 59ª.

EJB12

The production of knowledge





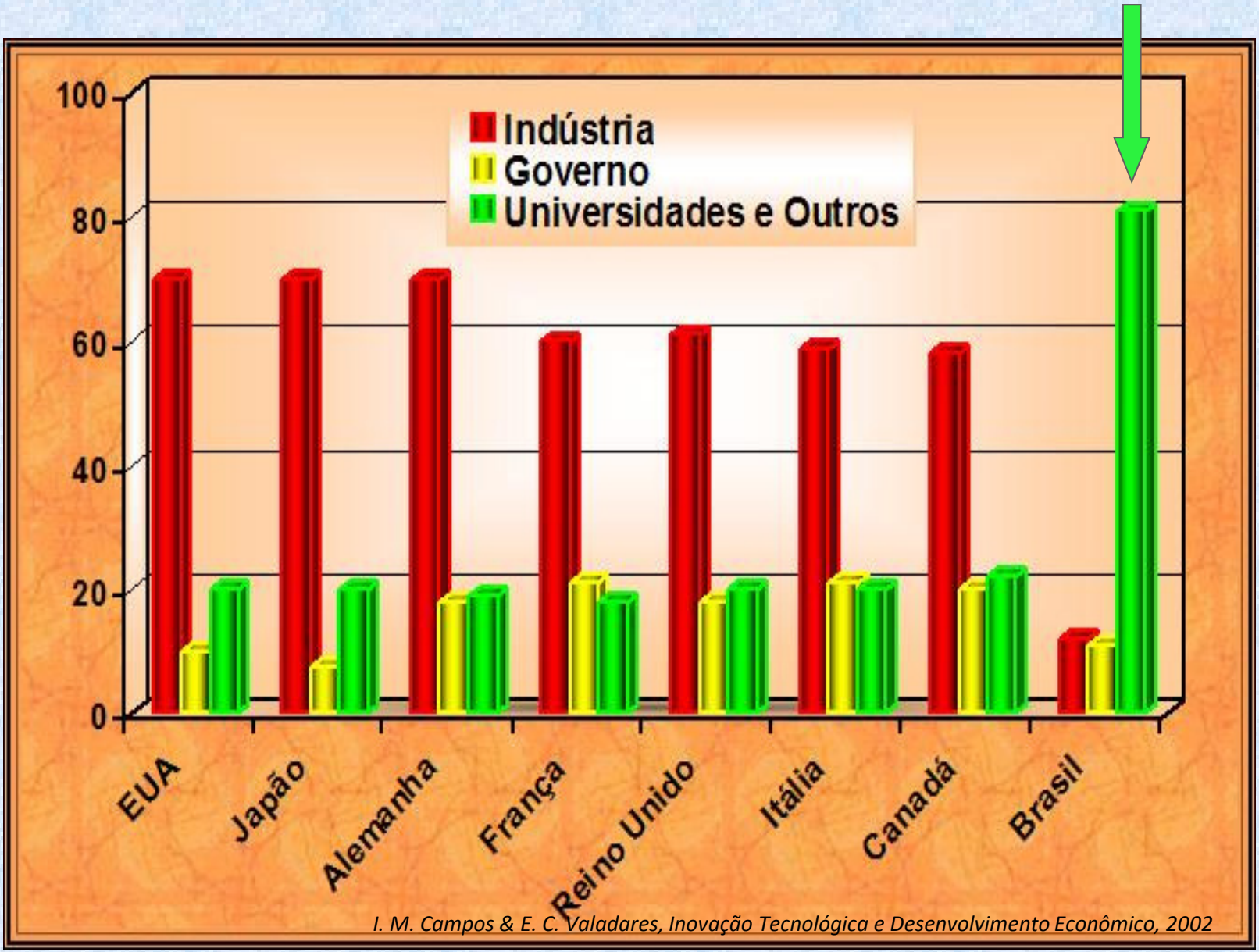
D. E. Stokes; Pasteurs Quadrant: Basic Science and Technological Innovation, Book News, Inc., Portland, EUA, 1999.

M. Gibbons *et al*., The new production of knowledge: the dynamics of science & research in contemporary societies, SAGE, London, 1994.

EJB12 The production of knowlegde

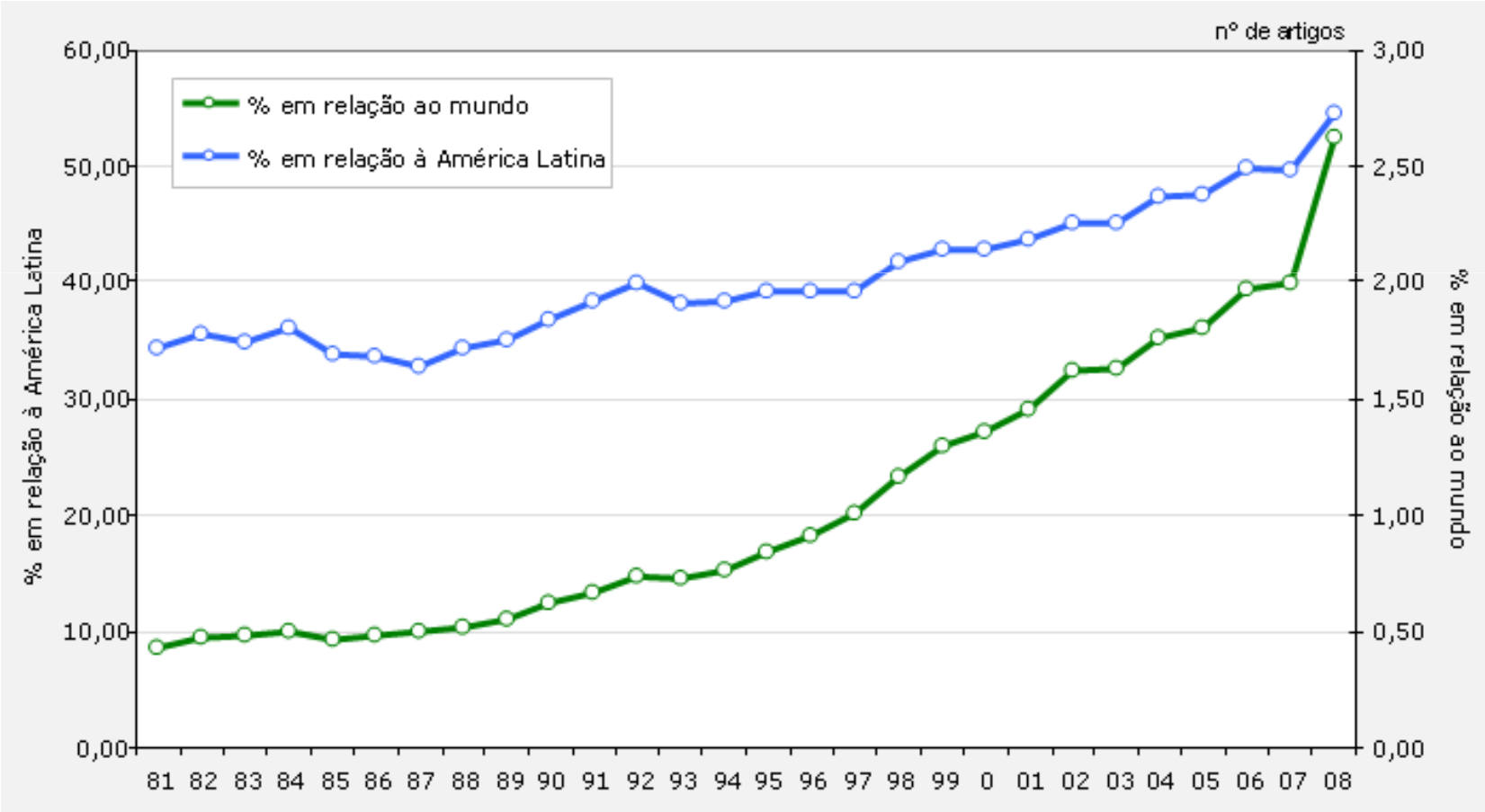
Eliezer J Barreiro; 02/05/2010

Aonde se faz a ciência no Brasil ?



I. M. Campos & E. C. Valadares, Inovação Tecnológica e Desenvolvimento Econômico, 2002

Artigos brasileiros publicados em periódicos científicos internacionais indexados na Thomson ISI, em relação à América Latina e ao Mundo, 1981-2008



Produção científica do Brasil

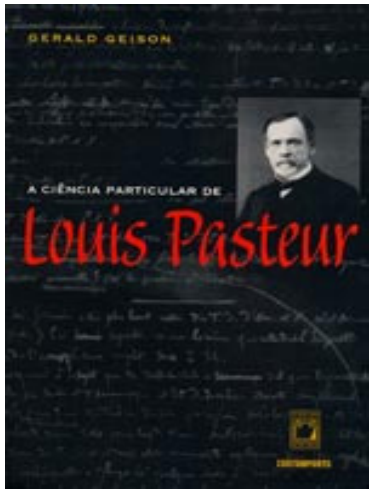
Ano	Brasil	América Latina	Mundo	% do Brasil em relação à América Latina	% do Brasil em relação ao Mundo
1981	1.949	5.687	456.306	34,27	0,43
1982	2.257	6.360	473.663	35,49	0,48
1983	2.325	6.671	484.748	34,85	0,48
1984	2.439	6.768	485.007	36,04	0,50
1985	2.409	7.119	516.901	33,84	0,47
1986	2.575	7.673	531.800	33,56	0,48
1987	2.624	8.037	528.090	32,65	0,50
1988	2.842	8.288	549.659	34,29	0,52
1989	3.160	9.025	570.774	35,01	0,55
1990	3.640	9.906	588.087	36,75	0,62
1991	4.008	10.474	604.880	38,27	0,66
1992	4.733	11.883	642.531	39,83	0,74
1993	4.663	12.203	644.539	38,21	0,72
1994	5.210	13.571	682.641	38,39	0,76
1995	6.038	15.437	716.128	39,11	0,84
1996	6.626	16.878	730.127	39,26	0,91
1997	7.331	18.677	730.557	39,25	1,00
1998	8.853	21.147	762.725	41,86	1,16
1999	10.072	23.501	777.872	42,86	1,29
2000	10.521	24.528	777.734	42,89	1,35
2001	11.581	26.478	796.755	43,74	1,45
2002	12.928	28.619	797.471	45,17	1,62
2003	14.237	31.536	875.242	45,15	1,63
2004	14.993	31.642	854.158	47,38	1,76
2005	17.711	37.236	981.781	47,56	1,80
2006	19.280	38.697	981.747	49,82	1,96
2007	19.496	39.296	977.792	49,61	1,99
2008	30.415	55.742	1.158.247	54,56	2,63

20 ANOS

59%

405%

Os fármacos e o Prêmio Nobel



Louis Pasteur

1822-1895

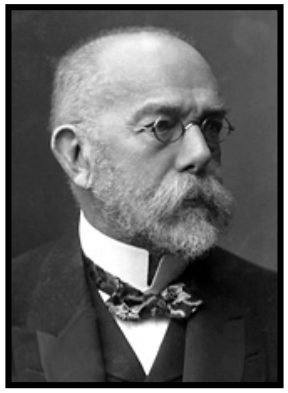
"La vie empeche la vie"

"L'hazard ne favorisée que les sprits preparées"

Emil Fischer

1852-1919

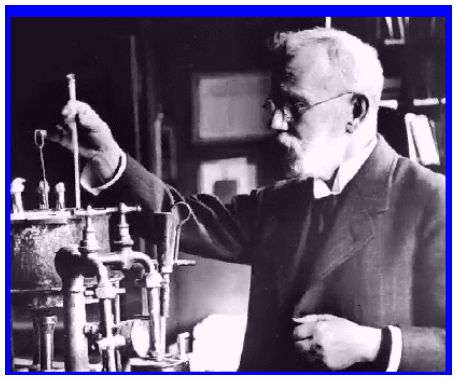
1902



Robert Koch

1843-1910

1905

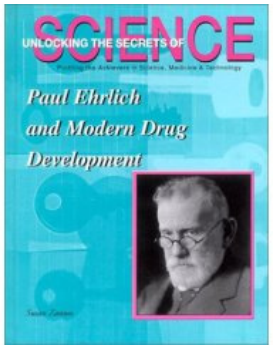


Paul Ehrlich

1854-1915

1908

Lock & Key

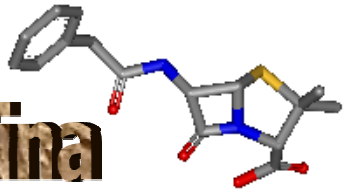


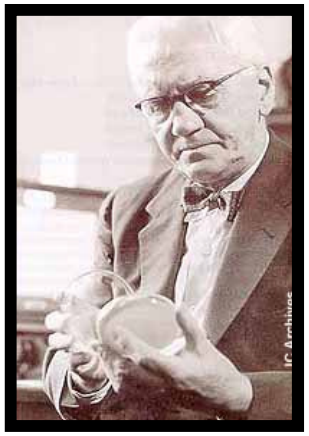
P. Ehrlich, *Chemotherapeutics: scientific principles, methods and results*. *Lancet* 1913, **2**, 445

One-molecule, one-target paradigm

The Magic Bullet Theory

Os fármacos e o Nobel !





1945 - Alexander Fleming

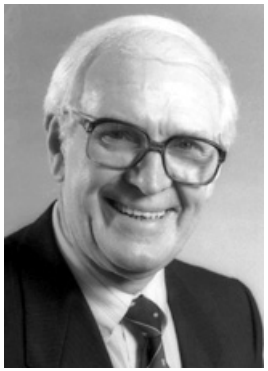
1945 - Ernest B. Chain

1945- Howard W. Florey

http://nobelprize.org

"for their discoveries of important principles for drug treatment"

- **193 pesquisadores ganharam o Prêmio Nobel de Medicina desde 1901.**



1988 - J.W. Black

1988 - G.B. Elion

1988 - G.H. Hitchings

***Inter-alia*:**
Propranolol
Cimetidina
Aciclovir

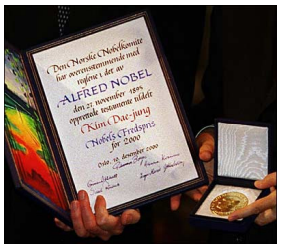
Os fármacos e o Nobel !

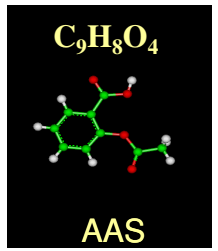
1982 –S.B.Bergstöm

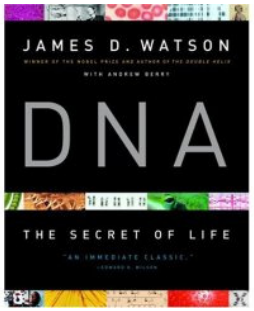
1982 –B.I.Samuelsson

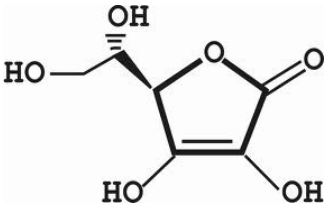
1982 –J.R. Vane

1982 – AAS







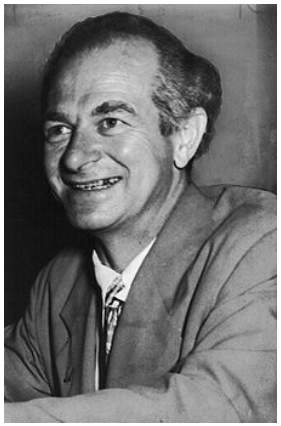


1937 – Vit C

1937 – W. N. Haworth

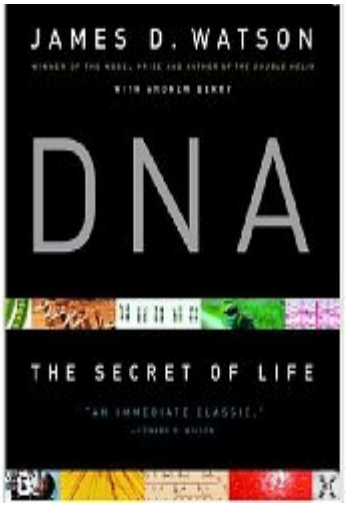
- **157 pesquisadores ganharam o Prêmio Nobel de Química desde 1901**

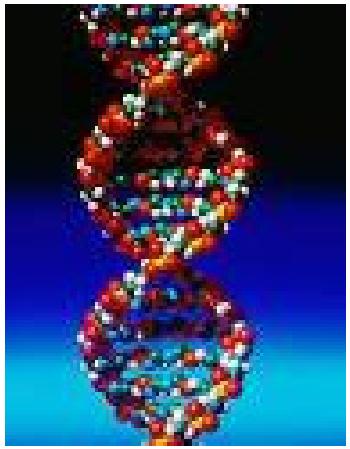
1937 –A. von Szent-Györgyi



1954 & 1962 – L. C. Pauling

EJB15





Francis Crick and James Watson in Cambridge, England, 1953
(Courtesy of the James D. Watson Special Collection. Cold Spring Harbor Laboratory Archives. From Watson J.D. 1968. *The Double Helix*. Atheneum Press. New York.)

1962

Maurice H. F. Wilkins

O físico Crick & biólogo Watson

Watson, JD & Crick, FHC Nature *1953,* **171**, 737–738

Interdisciplinaridade

Slide 20

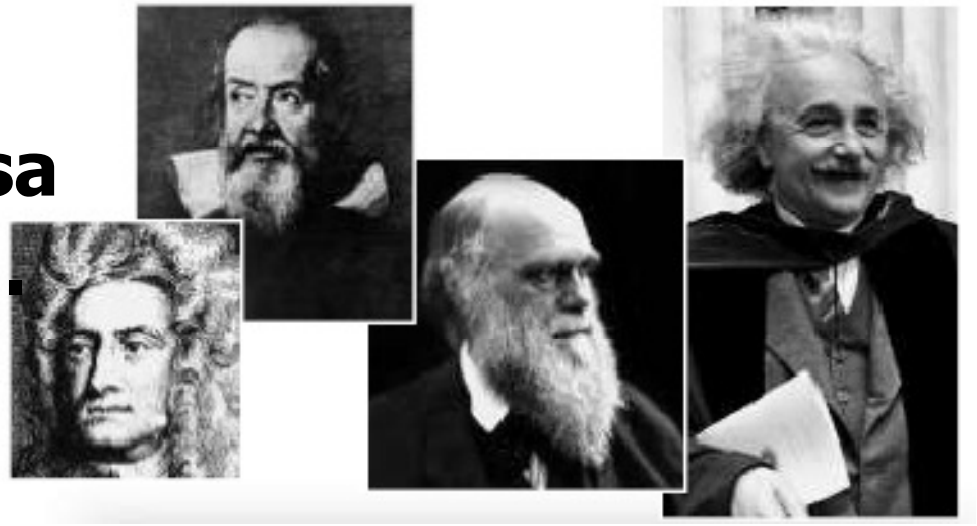
EJB15

Exemplos de extraordinárias conquistas do conhecimento humano deveram-se às associações de capacidades e competências complementares, essenciais à sua consecução: e.g. DNA em publicação de apenas 2 páginas em prestigioso periódico científico que resultou, décadas depois, na era ômica.

JD Watson & FHC Crick, Nature, 1953, 171, 737-738

Eliezer J. Barreiro; 04/03/2010

O perfil da pesquisa científica...



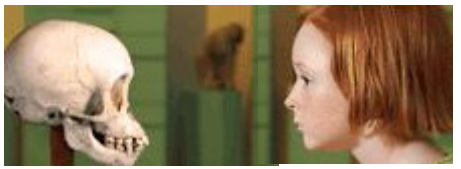
Galileo, Newton, Darwin, & Einstein

O físico Crick & biólogo Watson

Sequenciamento do genoma humano

The Sequence of the Human Genome

J. Craig Venter, Mark D. Adams, Eugene W. Myers, Peter W. Li, Richard J. Mural, Granger G. Sutton, Hamilton O. Smith, Mark Yandell, Cheryl A. Evans, Robert A. Holt, Jeannine D. Gocayne, Peter Amanatides, Richard M. Ballew, Daniel H. Huson, Jennifer Russo Wortman, Qing Zhang, Chinnappa D. Kodira, Xiangqun H. Zheng, Lin Chen, Marian Skupski, Gangadharan Subramanian, Paul D. Thomas, Jinghui Zhang, George L. Gabor Miklos, Catherine Nelson, Samuel Broder, Andrew G. Clark, Joe Nadeau, Victor A. McKusick, Norton Zinder, Arnold J. Levine, Richard J. Roberts, Mel Simon, Carolyn Slayman, Michael Hunkapiller, Randall Bolanos, Arthur Delcher, Ian Dew, Daniel Fasulo, Michael Flanigan, Liliana Florea, Aaron Halpern, Sridhar Hannenhalli, Saul Kravitz, Samuel Levy, Clark Mobarry, Knut Reinert, Karin Remington, Jane Abu-Threideh, Ellen Beasley, Kendra Biddick, Vivien Bonazzi, Rhonda Brandon, Michele Cargill, Ishwar Chandramouliswaran Rosane Charlab, Kabir Chaturvedi, Zuoming Deng, Valentina Di Francesco, Patrick Dunn, Karen Eilbeck, Carlos Evangelista, Andrei E. Gabrielian, Weiniu Gan, Wangmao Ge, Fangcheng Gong, Zhiping Gu, Ping Guan, Thomas J. Heiman, Maureen E. Higgins, Rui-Ru Ji, Zhaoxi Ke, Karen A. Ketchum, Zhongwu Lai, Yiding Lei, Zhenya Li, Jiayin Li, Yong Liang, Xiaoying Lin, Fu Lu, Gennady V. Merkulov, Natalia Milshina, Helen M. Moore, Ashwinikumar K Naik, Vaibhav A. Narayan, Beena Neelam, Deborah Nusskern, Douglas B. Rusch, Steven Salzberg, Wei Shao, Bixiong Shue, Jingtao Sun, Zhen Yuan Wang, Aihui Wang, Xin Wang, Jian Wang, Ming-Hui Wei, Ron Wides, Chunlin Xiao, Chunhua Yan, Alison Yao, Jane Ye, Ming Zhan, Weiqing Zhang, Hongyu Zhang, Qi Zhao, Liansheng Zheng, Fei Zhong, Wenyan Zhong, Shiaoping C. Zhu, Shaying Zhao, Dennis Gilbert, Suzanna Baumhueter, Gene Spier, Christine Carter, Anibal Cravchik, Trevor Woodage, Feroze Ali, Huijin An, Aderonke Awe, Danita Baldwin, Holly Baden, Mary Barnstead, Ian Barrow, Karen Beeson, Dana Busam, Amy Carver, Angela Center, Ming Lai Cheng, Liz Curry, Steve Danaher, Lionel Davenport, Raymond Desilets, Susanne Dietz, Kristina Dodson, Lisa Doup, Steven Ferriera, Neha Garg, Andres Gluecksmann, Brit Hart, Jason Haynes, Charles Haynes, Cheryl Heiner, Suzanne Hladun, Damon Hostin, Jarrett Houck, Timothy Howland, Chinyere Ibegwam, Jeffery Johnson, Francis Kalush, Lesley Kline, Shashi Koduru, Amy Love, Felecia Mann, David May, Steven McCawley, Tina McIntosh, Ivy McMullen, Mee Moy, Linda Moy, Brian Murphy, Keith Nelson, Cynthia Pfannkoch, Eric Pratts, Vinita Puri, Hina Qureshi, Matthew Reardon, Robert Rodriguez, Yu-Hui Rogers, Deanna Romblad, Bob Ruhfel, Richard Scott, Cynthia Sitter, Michelle Smallwood, Erin Stewart, Renee Strong, Ellen Suh, Reginald Thomas, Ni Ni Tint, Sukyee Tse, Claire Vech, Gary Wang, Jeremy Wetter, Sherita Williams, Monica Williams, Sandra Windsor, Emily Winn-Deen, Keriellen Wolfe, Jayshree Zaveri, Karena Zaveri, Josep F. Abril, Roderic Guigó, Michael J. Campbell, Kimmen V. Sjolander, Brian Karlak, Anish Kejariwal, Huaiyu Mi, Betty Lazareva, Thomas Hatton, Apurva Narechania, Karen Diemer, Anushya Muruganujan, Nan Guo, Shinji Sato, Vineet Bafna, Sorin Istrail, Ross Lippert, Russell Schwartz, Brian Walenz, Shibu Yooseph, David Allen, Anand Basu, James Baxendale, Louis Blick, Marcelo Caminha, John Carnes-Stine, Parris Caulk, Yen-Hui Chiang, My Coyne, Carl Dahlke, Anne Deslattes Mays, Maria Dombroski, Michael Donnelly, Dale Ely, Shiva Esparham, Carl Fosler, Harold Gire, Stephen Glanowski, Kenneth Glasser, Anna Glodek, Mark Gorokhov, Ken Graham, Barry Gropman, Michael Harris, Jeremy Heil, Scott Henderson, Jeffrey Hoover, Donald Jennings, Catherine Jordan, James Jordan, John Kasha, Leonid Kagan, Cheryl Kraft, Alexander Levitsky, Mark Lewis, Xiangjun Liu, John Lopez, Daniel Ma, William Majoros, Joe McDaniel, Sean Murphy, Matthew Newman, Trung Nguyen, Ngoc Nguyen, Marc Nodell, Sue Pan, Jim Peck, Marshall Peterson, William Rowe, Robert Sanders, John Scott, Michael Simpson, Thomas Smith, Arlan Sprague, Timothy Stockwell, Russell Turner, Eli Venter, Mei Wang, Meiyuan Wen, David Wu, Mitchell Wu, Ashley Xia, Ali Zandieh, and Xiaohong Zhu



Science **2001** *291*, 1304-1351 [DOI: 10.1126/science.1058040]

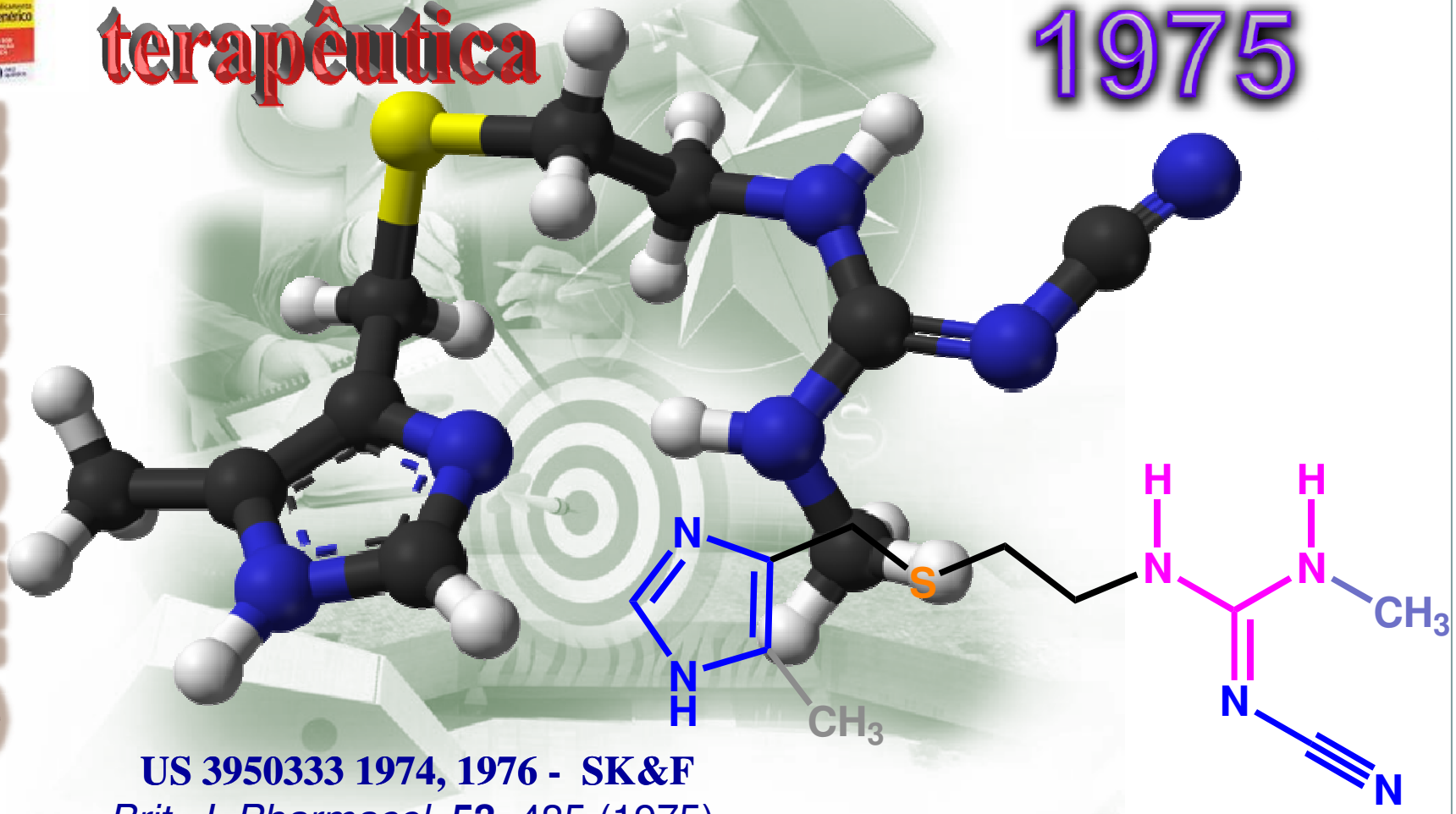
O processo de desenvolvimento de fármacos....

O desenvolvimento racional

Inovação terapêutica

1975

Cimetidina

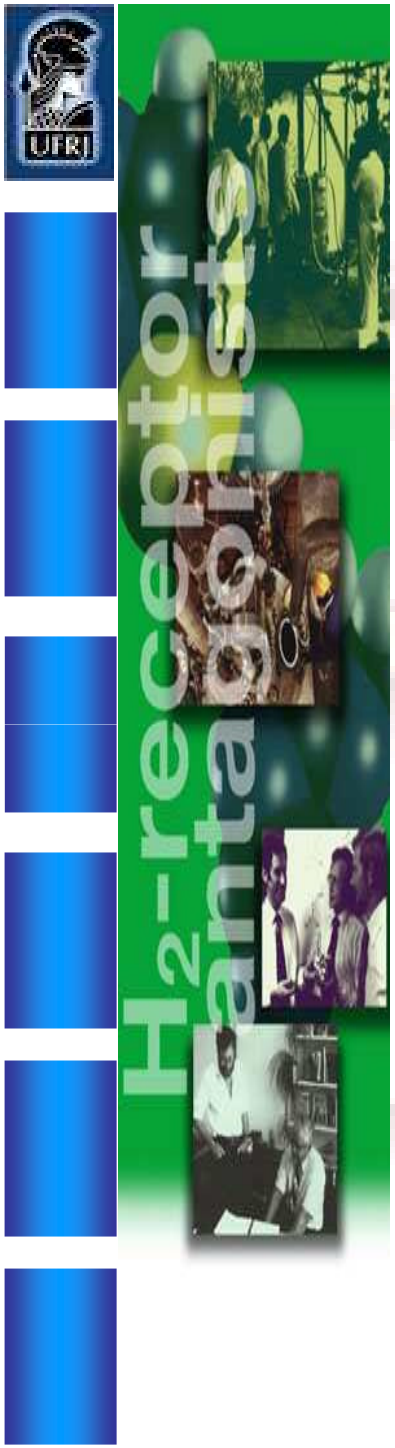


US 3950333 1974, 1976 - SK&F

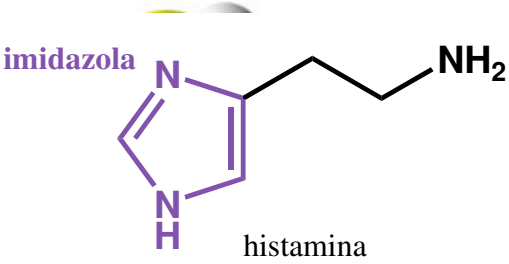
Brit. J. Pharmacol. **53,** 435 (1975).

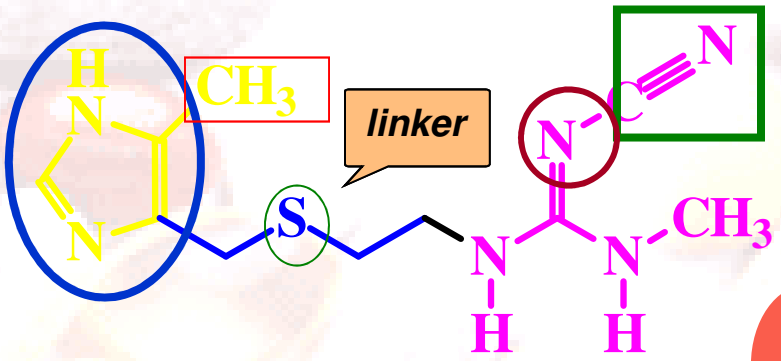
James Black, Robin Ganellin, Emmett, Durant

$C_{10}H_{16}N_6S$



Uma invenção...





1975 - SK&F (Black, Ganellin, Emmet & Durant)

US 3950333 1974, 1976

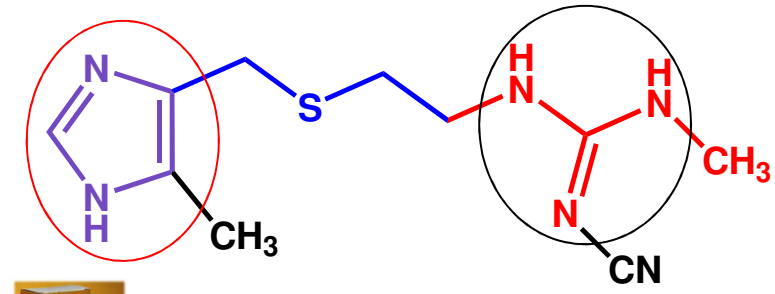
Brit. J. Pharmacol. 1975, **53,** 435

= inovação terapêutica !

Primeiro fármaco a atingir US$ 1 bilhão em vendas no ano do lançamento (1979)

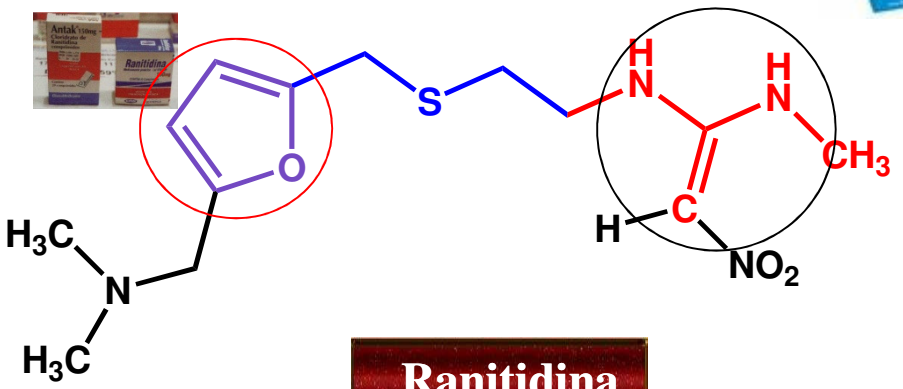
Os inventores: C. Robin Ganellin, Graham J. Durant, Michael E. Parsons, & James W. Black (Prêmio Nobel de Medicina em 1988) (foto →) + John C. Emmett, William A. M. Duncan, 1975;

JW Black, WAM Duncan, CJ Durant, CR Ganellin & EM Parsons, Definition and Antagonism of Histamine H_2-receptors, *Nature* **1972,** *236*, 385-390 (doi:10.1038/236385a0)



Cimetidina

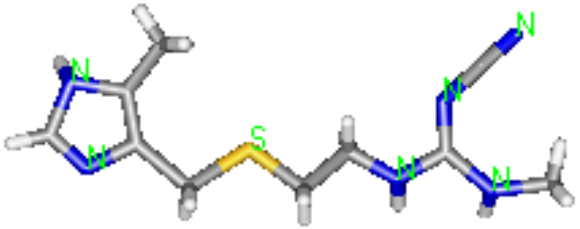
Robin Ganellin *et al.*, 1974
US 3950333 1974, 1976 - SK&F
Brit. J. Pharmacol. **53,** 435 (1975).

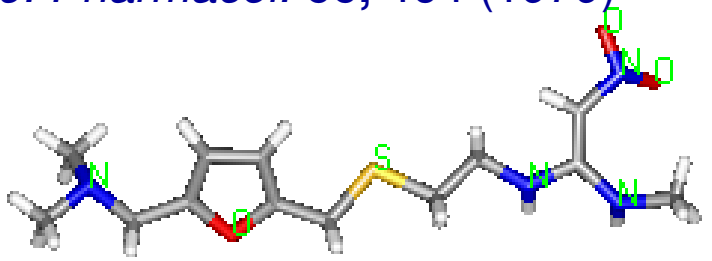


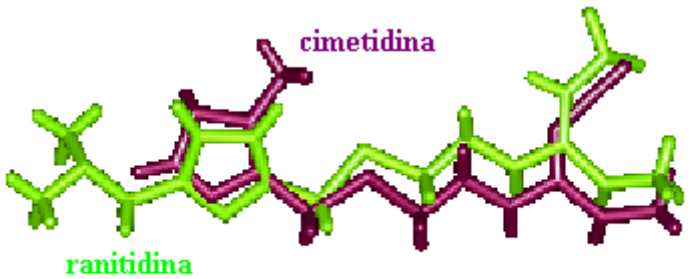
Ranitidina

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

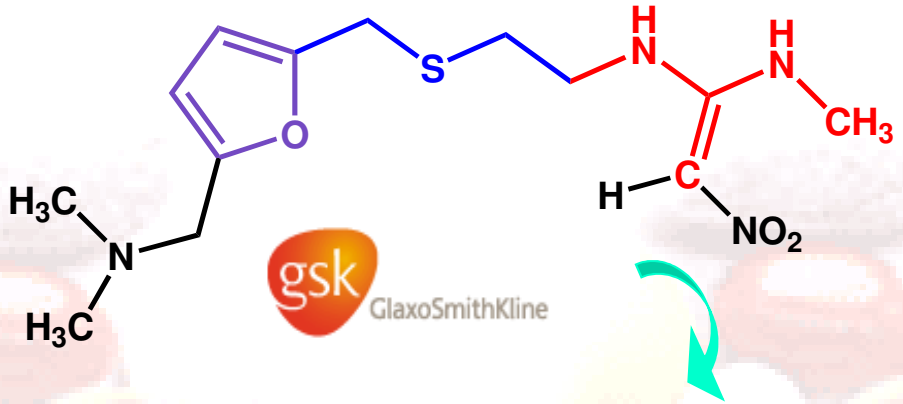
similaridade molecular







me-too



2008 annual results: **US$ 36,5 bi**
(~ > 10%/y)

***ca*. 21% do faturamento origina-se em NP's**
Investimentos RD&I: > US$ 2,04 bilhões
4 produtos com vendas > US$ 1 bi
80 fábricas em 37 países com 100.000 empregos
(*ca*. 16.500 em RD&I)
***Pipeline*: 51 projetos em fase pré-clínica**
158 projetos em desenvolvimento:
85 NCE's, 20 vacinas, 45 produtos

http://biopharm.gsk.com - Updated May 15, 2009

Top 15 Global corporations

	Empresa	Vendas (US$mi)	Sede
1	Pfizer	43,363	US
2	GlaxoSmithKline	36,506	UK
3	Novartis	36,506	Switzerland
4	Sanofi-Aventis	35,642	France
5	AstraZeneca	32,516	UK/Sweden
6	Hoffmann–La Roche	30,336	Switzerland
7	Johnson & Johnson	29,425	US
8	Merck & Co.	26,191	US
9	Abbott	19,466	US
10	Eli Lilly and Company	19,140	US
11	Amgen	15,794	US
12	Wyeth	15,682	US
13	Teva	15,274	Israel
14	Bayer	15,660	Germany
15	Takeda	13,819	Japan

IMS Health 2008

Inovação & Patentes

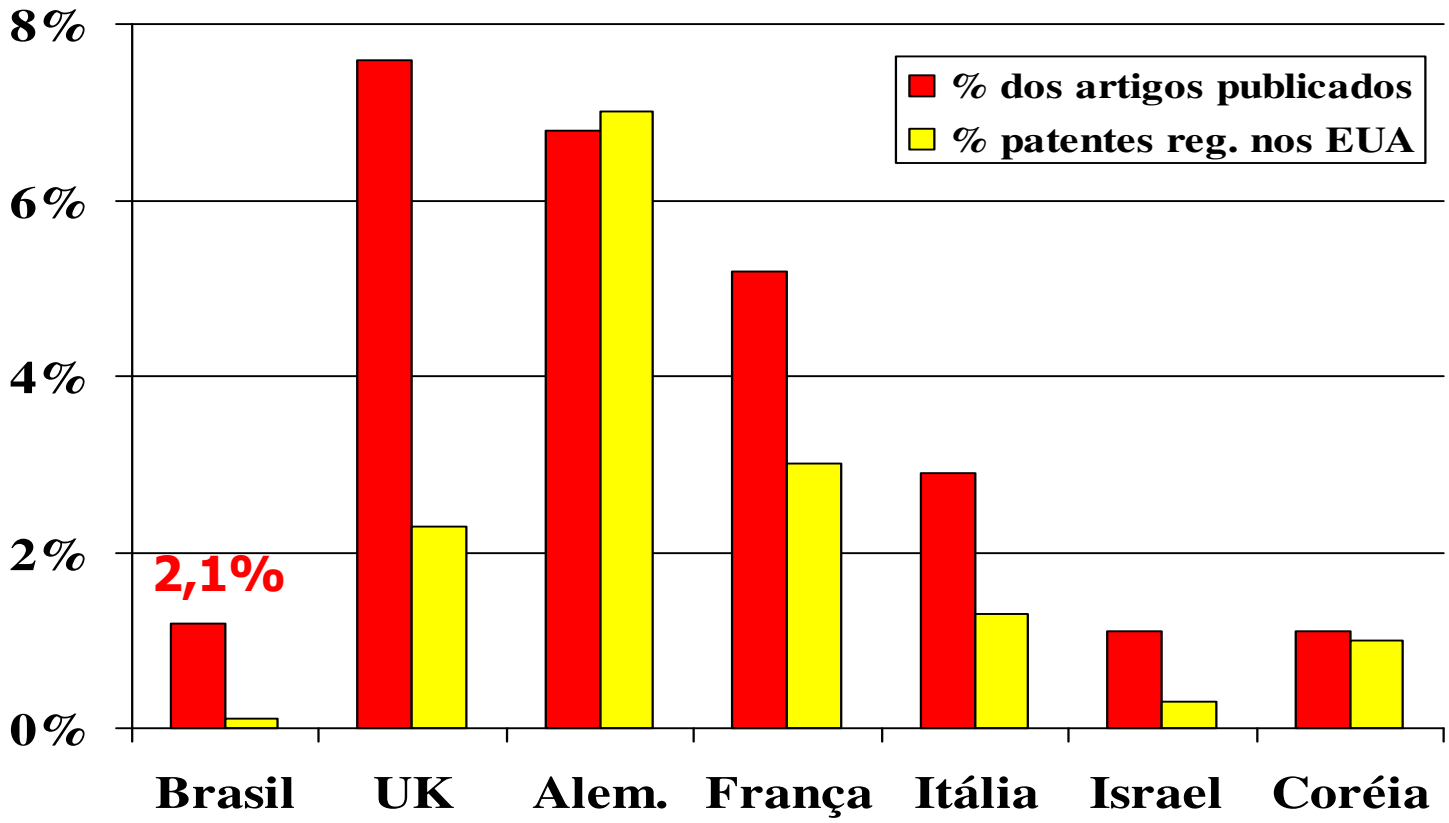
Descoberta: corresponde à ação de descobrir, de achar, de fazer conhecer o que não era conhecido.

Invenção: do latim "*inventio*" corresponde à ação ou efeito de inventar, isto é, ter espontaneamente a idéia de, criar no pensamento, etc.

Privilégio: do latim "*privilegium*", corresponde ao direito ou vantagem especial que se concede a uma ou mais pessoa, com exclusão das outras, fazendo exceção ao direito comum ou à regra geral. Diploma que contém a concessão de um Privilégio.

Privilégio de Invenção: PATENTE

Participação mundial em artigos publicados em revistas indexadas SCI e patentes registradas nos EUA

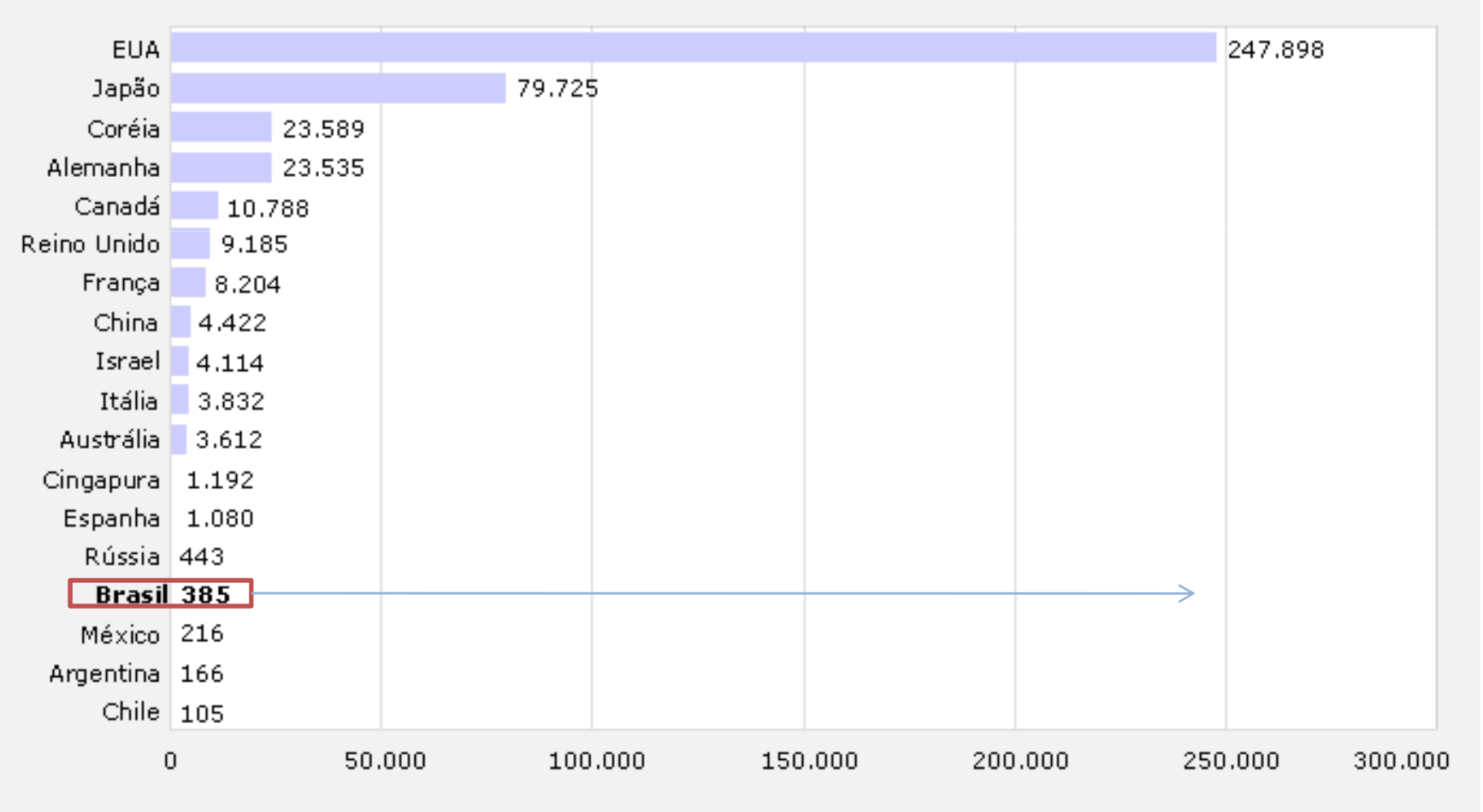


O Brasil se coloca em 28º lugar no *ranking* mundial de patentes e tecnologia. De acordo com dados divulgados pelo USPTO, o País efetuou apenas 101 registros de patentes em 2008, ficando atrás da China (1.536), e da Índia (636) A Malásia ultrapassou a colocação brasileira, pelo segundo ano consecutivo.

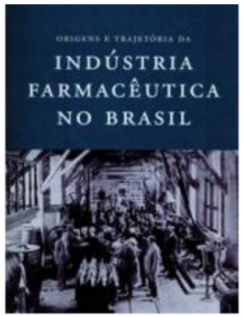
Fonte: Jornal do Commercio - Texto de Jaqueline Porto - 20/07/2009.

http://www.valormp.com.br/index.php?menu=noticia&codigo=111

Pedidos de patentes de invenção depositados no escritório de marcas e patentes dos Estados Unidos da América, alguns países, 2007

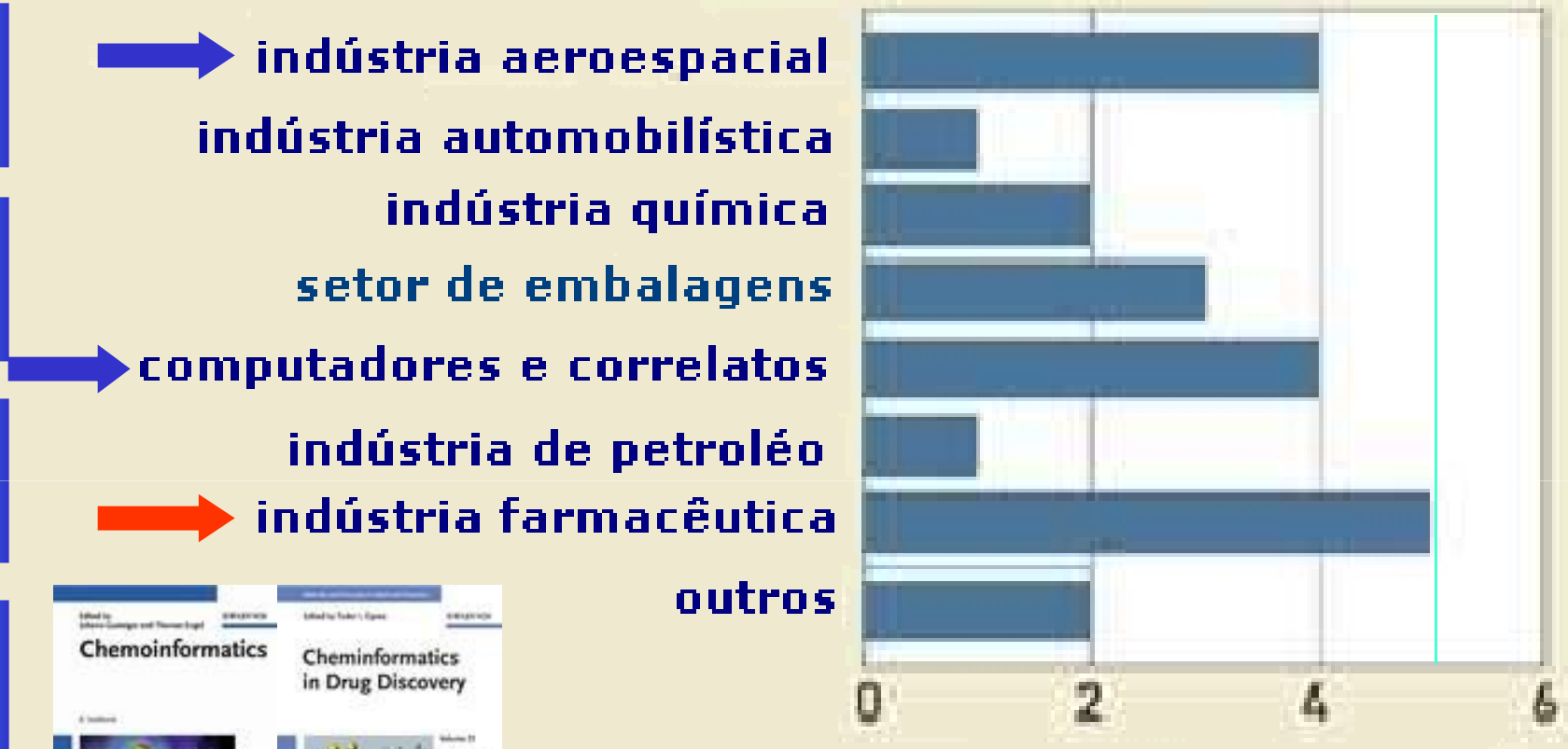


Indústria Farmacêutica



- a indústria farmacêutica é *intensiva* em pesquisa ➡ caráter estratégico;
- padrão de competição é em novos produtos;
- inovação tecnológica, com *investimentos* em pesquisa e desenvolvimento (~ 8-10%);
- intensa atividade de *propriedade* intelectual;
- expressivos gastos em marketing e propaganda (~14% faturamento) .

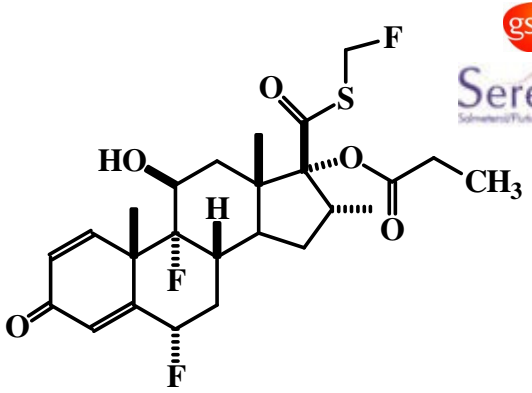
Big-Pharma e gastos com tecnolgia da informação



Bioinformática

Nota: 500 empresas de teconologia da informação foram consultadas; 23 empresas químicas e 25 indústrias farmacêuticas; Fonte: AMR Research (C&EN, ACS, 2004)

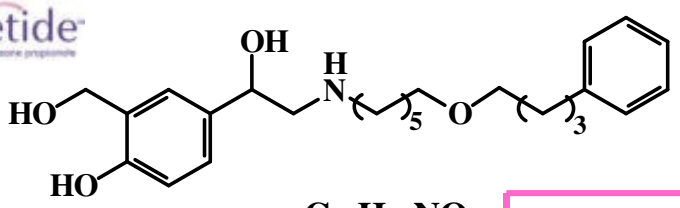
Os *top-5* fármacos no mercado mundial* 2009



$C_{26}H_{33}F_3O_5S$

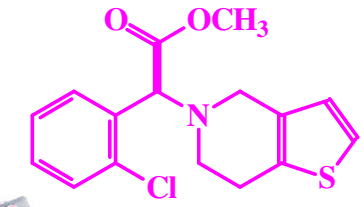
gsk Seretide

fluticazona salmeterol (GSK, 2012)



$C_{25}H_{37}NO_4$

Clopidogrel (BMS, 2011)



$C_{16}H_{16}ClNO_2S$

Bristol-Myers Squibb Company

1 | 2,0 | 4,5-5,5 | 5,6 | 7,7 | 7,9 | 8,8 | 13,4 | 43,4

em US$ bilhões

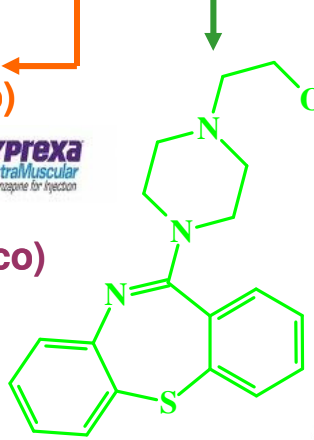
Etanercept (Enbrel^R, biofármaco)

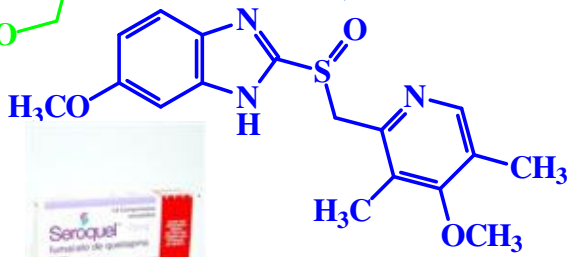
Olanzapina

Infliximabe (Remicade^R, biofármaco)

Montelukast (Singulair^R, Merck)

Rosuvastatina (Crestor^R, AZ)

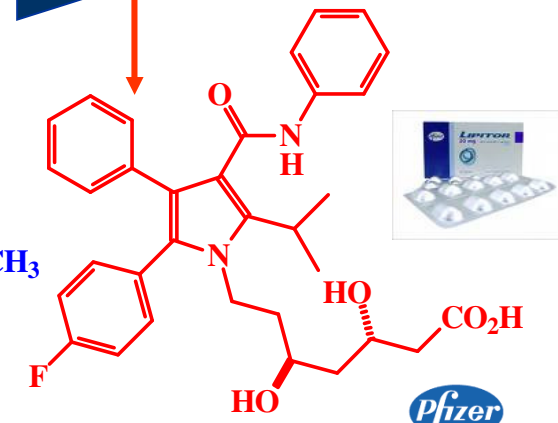




$C_{17}H_{19}N_3O_3S$

AstraZeneca

Esomeprazola (AZ)



$C_{33}H_{35}FN_2O_5$

Pfizer

Atorvastatina (Pfizer; 06/2011)

68,1 (8,2%)

CRESTOR rosuvastatin calcium

Quetiapina (AZ, 2012)

Nexium (esomeprazole magnesium)

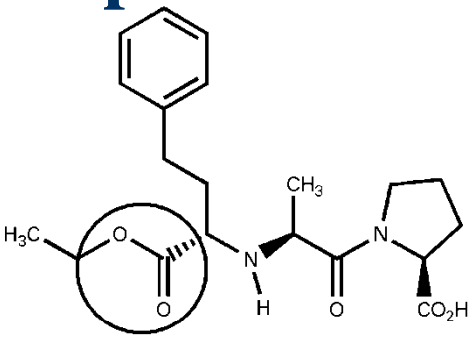
* SJ Ainsworth, *C&EN* **2009** (07/12) 13-21

Características estruturais comuns aos cinco fármacos mais vendidos no mundo em 2009:

- Possuem apenas 7 elementos químicos: C,H,O,N,S,F,Cl;
- 80% dos fármacos são heterocíclicos;
- Todos são policíclicos (< cinco anéis);
- 80% têm unidades aromáticas;
- 03 podem ser considerados *me-too*;
- 01 representa uma inovação incremental;

- pertencem a apenas 04 classes terapêuticas distintas;
- possuem uma tímida diversidade química:
- são responsáveis por US$ 43,2 bilhões em vendas;

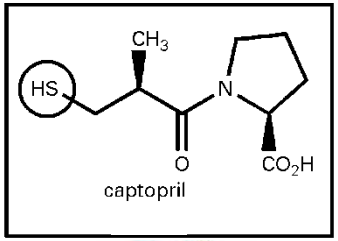
Anti-hipertensivos inibidores da enzima conversora



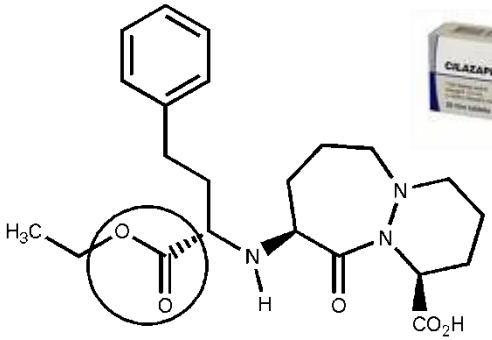
enalapril

MERCK

Bristol-Myers Squibb Company

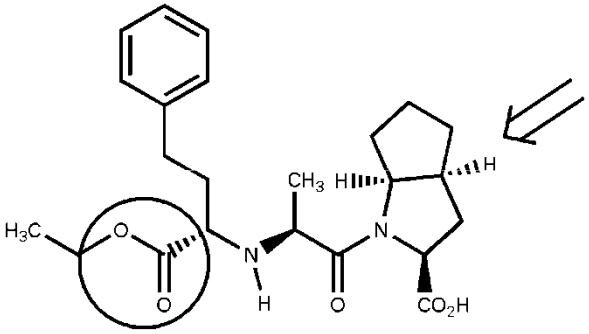


captopril



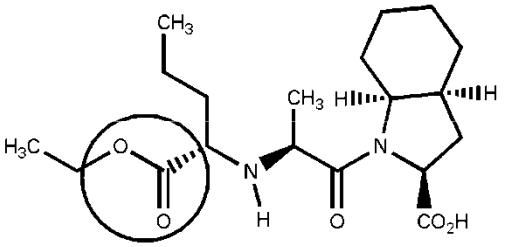
cilazapril

Roche



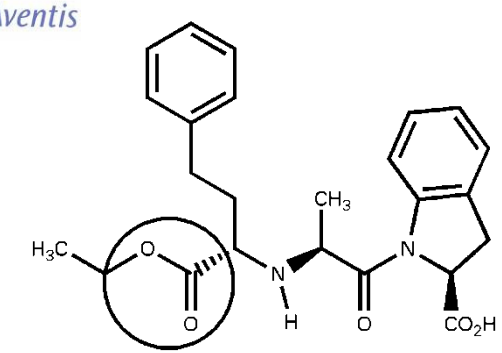
ramipril

Aventis



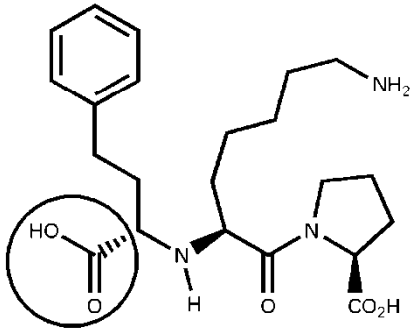
perendopril

SOLVAY



quinapril

Pfizer



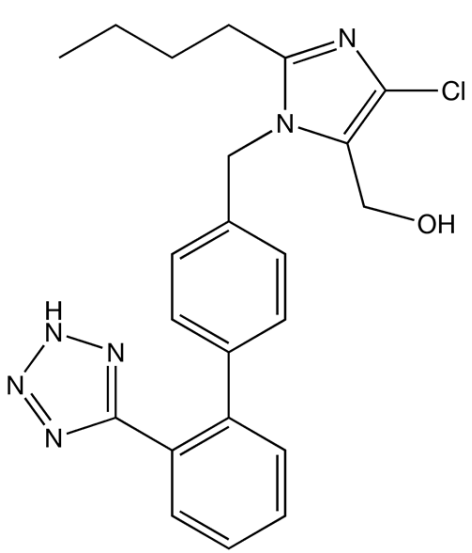
lisinopril

AstraZeneca

Os fármacos: sintéticos ...

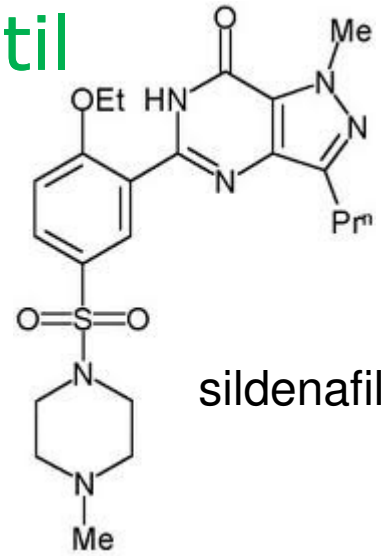
85% do arsenal terapêutico
são de fármacos sintéticos

Hipertensão arterial



losartana

Disfunção erétil



sildenafila

Inovação radical

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

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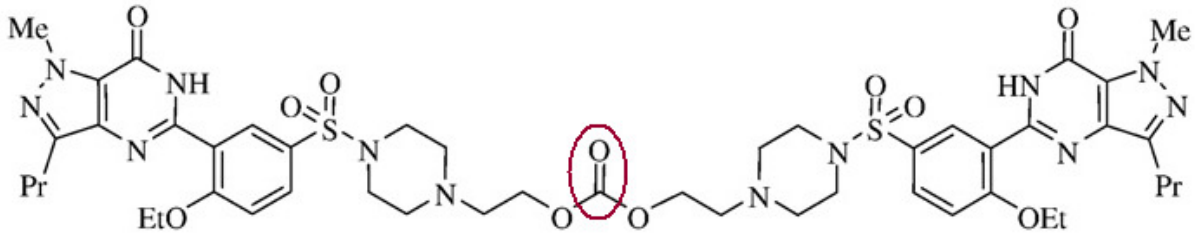
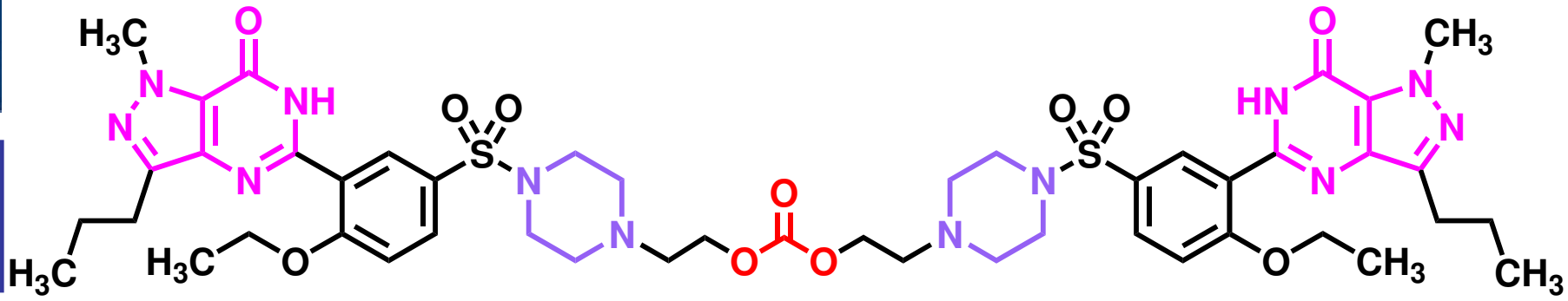
Sildenafil
Nitric oxide
Cyclic GMP
Pro-drug
Dimerization

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.

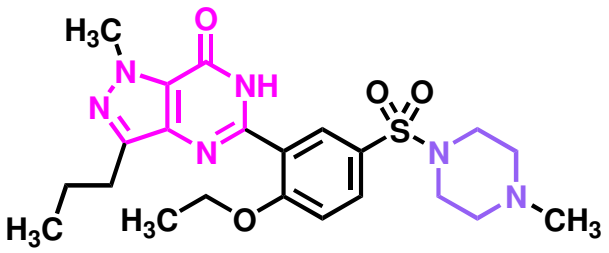


Lodenafil carbonate

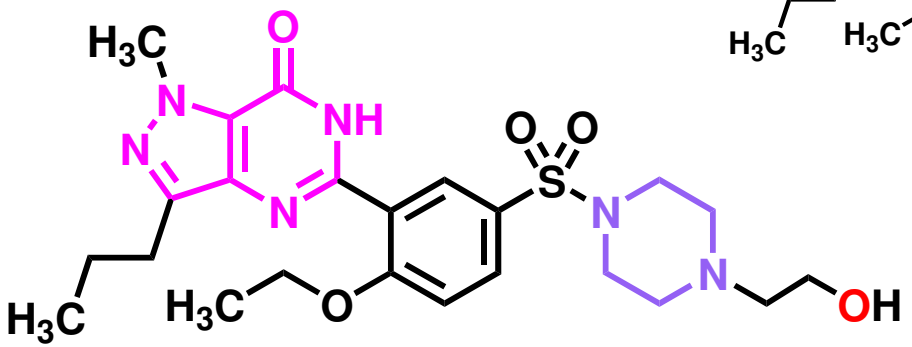


carbonato de lodenafila

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 inovação farmacêutica

...quando uma nova molécula sintética ou não, é descoberta, a primeira pergunta é: ela funciona?

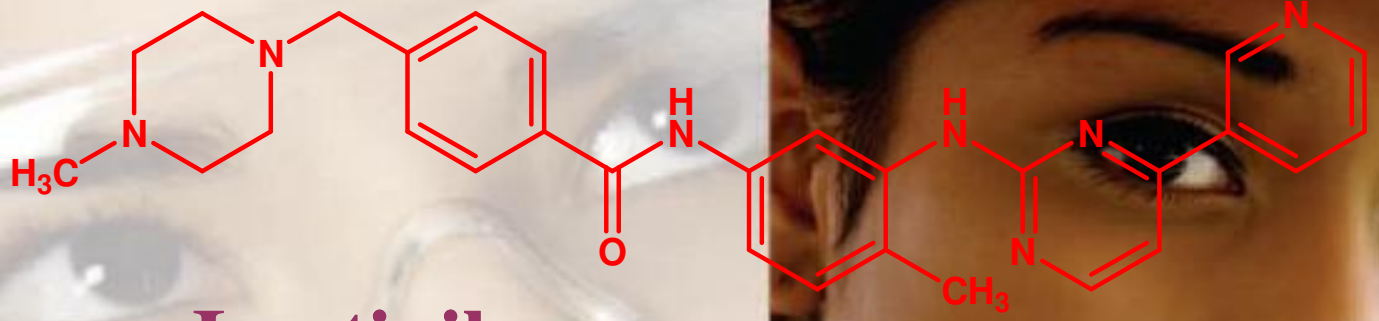
Imediatamente uma segunda pergunta surge:

Como podemos otimizá-la?

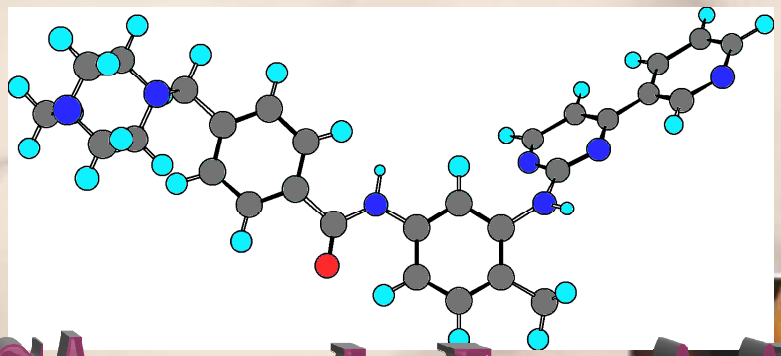
Muitas vezes pequenas modificações estruturais São suficientes...

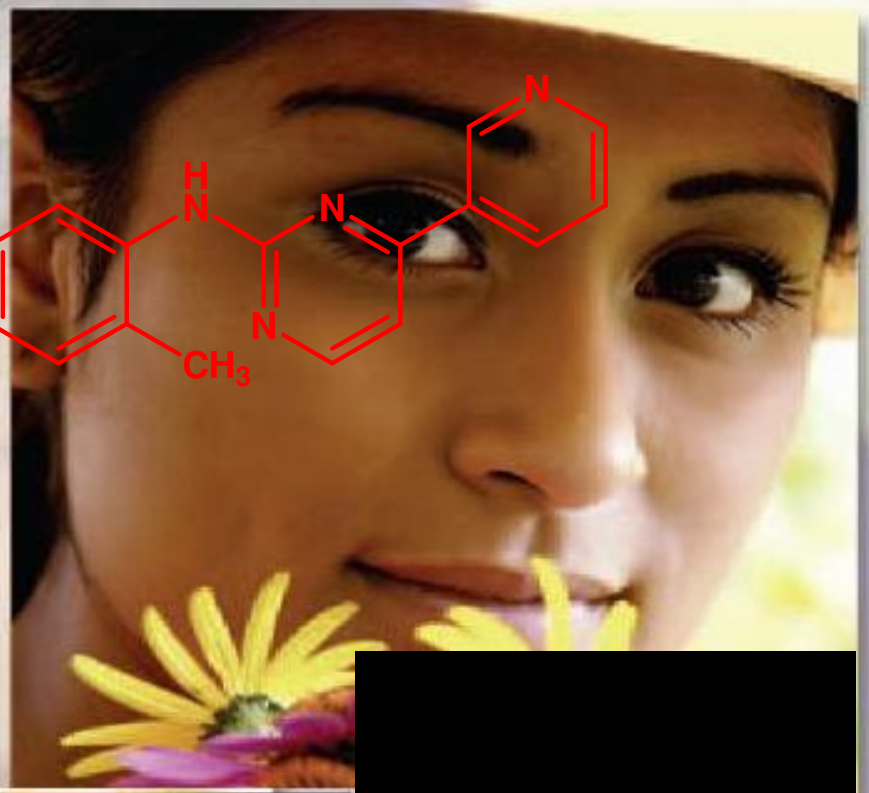
Um caso de sucesso na abordagem "irracional"

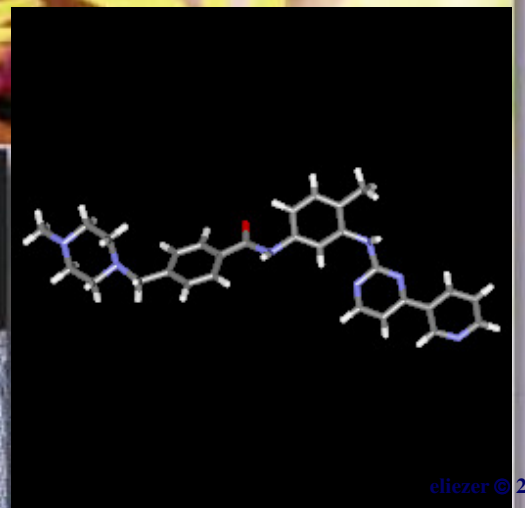
A Decade of Innovation



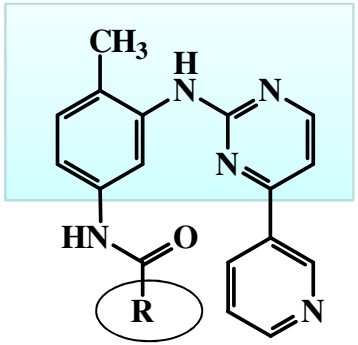
Imatinibe







Gênese do Imatinibe



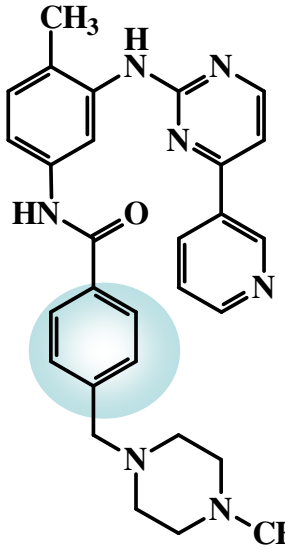
bcr-K inibidor

$C_{17}H_{14}N_5OR$

otimização

⇒

Hit-compound



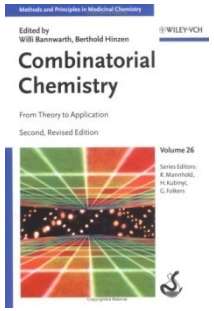
$C_{29}H_{31}N_7O$

imatinib

2002

NOVARTIS

GLIVEC (STI571, IMATINIB)



Técnicas hifenadas: CombChem-HTS

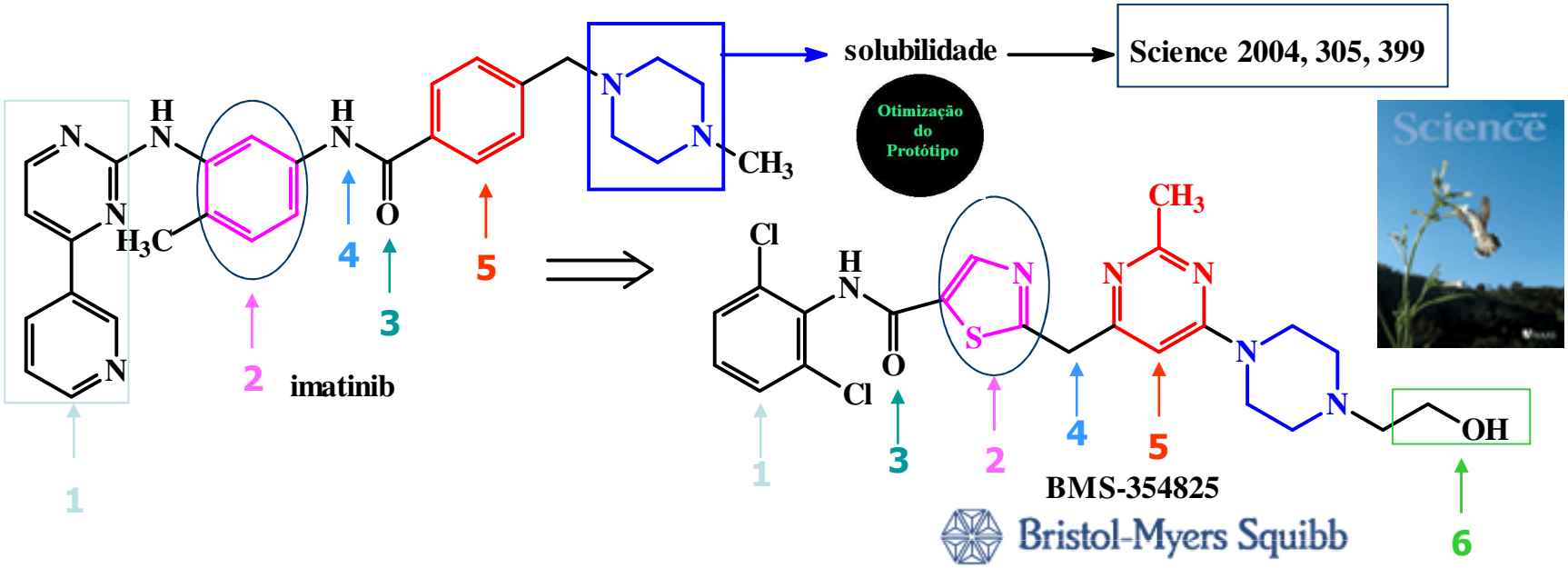
1990 – identificação do hit por HTS em quimiotecas de fenilaminopirimidinas (PAP) ativas em PKC.

Maio de 2001 o FDA aprova imatinib (Glivec^R) para leucemia mielóide crônica; preço:R$ 10.000,00/30 comp. [400mg]

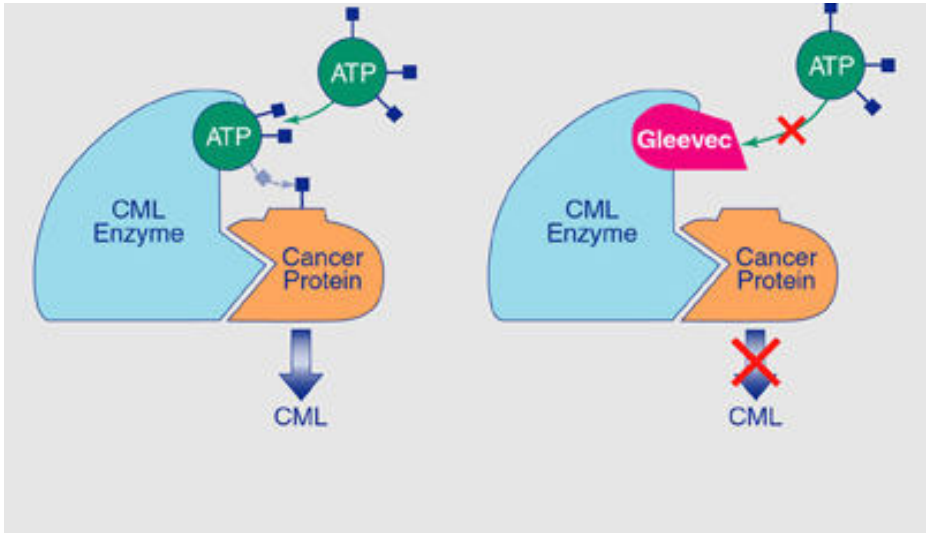
NATURE REVIEWS | DRUG DISCOVERY VOLUME 1 | 2002 | 493

Desenho molecular baseado na estrutura (SBDD)

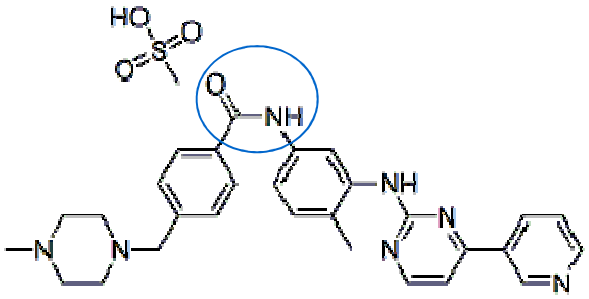
Otimização



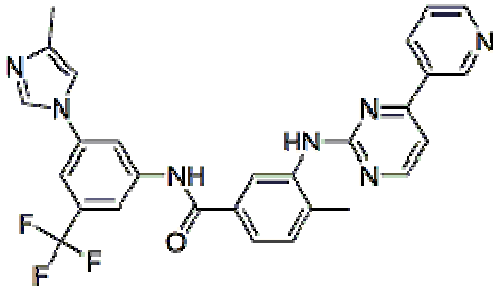
S. Ghosh, X. P. Liu, Y. Zheng, F.M. Uckun, Rational design of potent and selective EGFR tyrosine kinase inhibitors as anticancer agents, *Curr. Cancer Drugs Target*, **2001**, *1*, 129-140



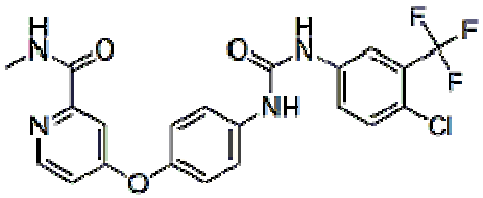
Inibidores de TyrK (tinibes)



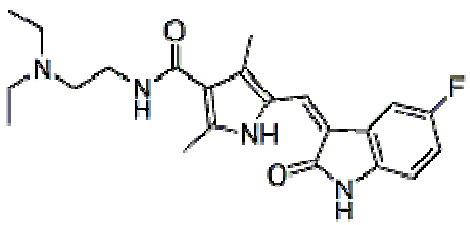
Imatinibe (bcr-abl)



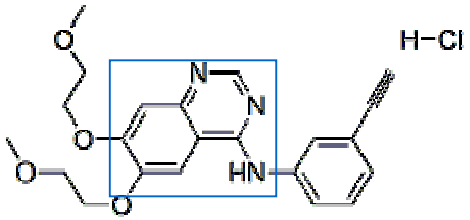
nilotinibe



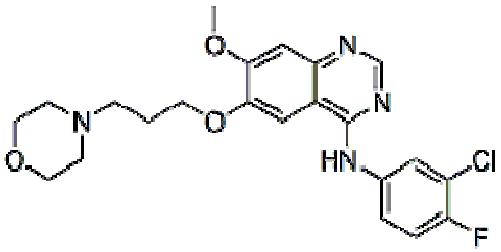
sorafenibe



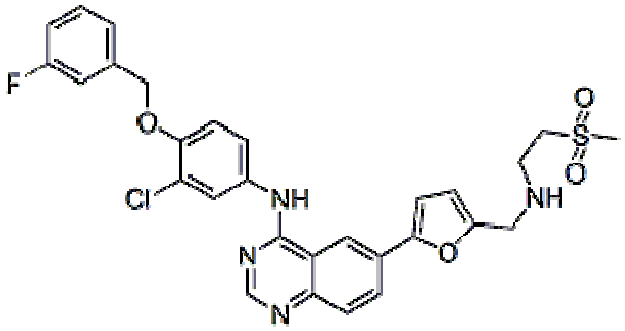
sunitinibe



erlotinibe



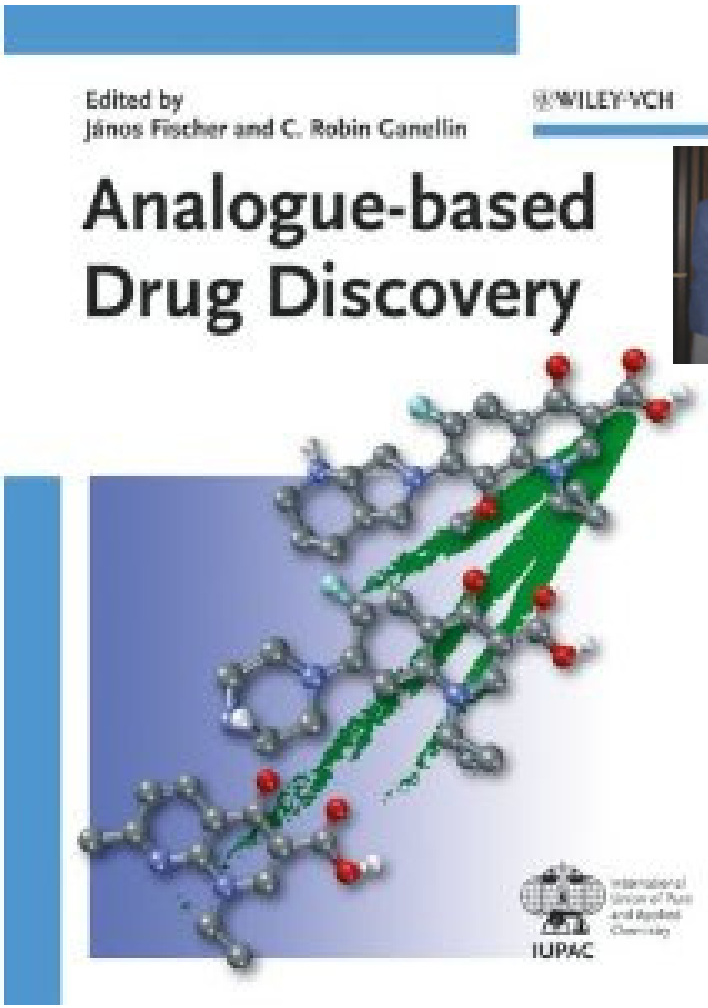
gefitinibe



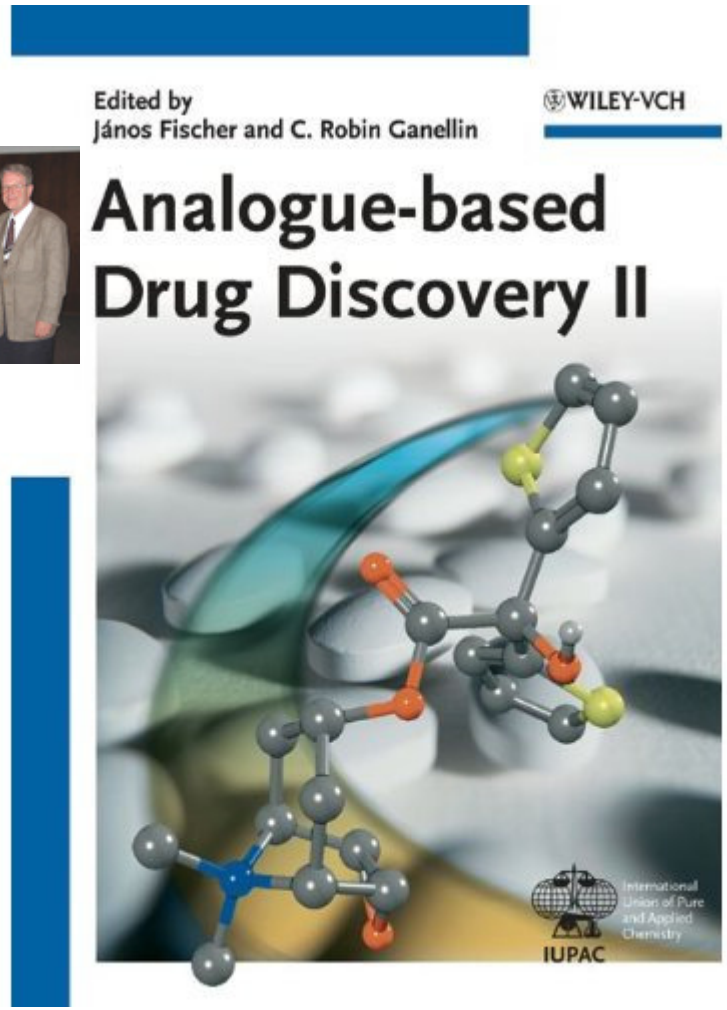
lapatinibe

Janos Fischer is research laboratory head at Richter Ltd., Budapest, Hungary.

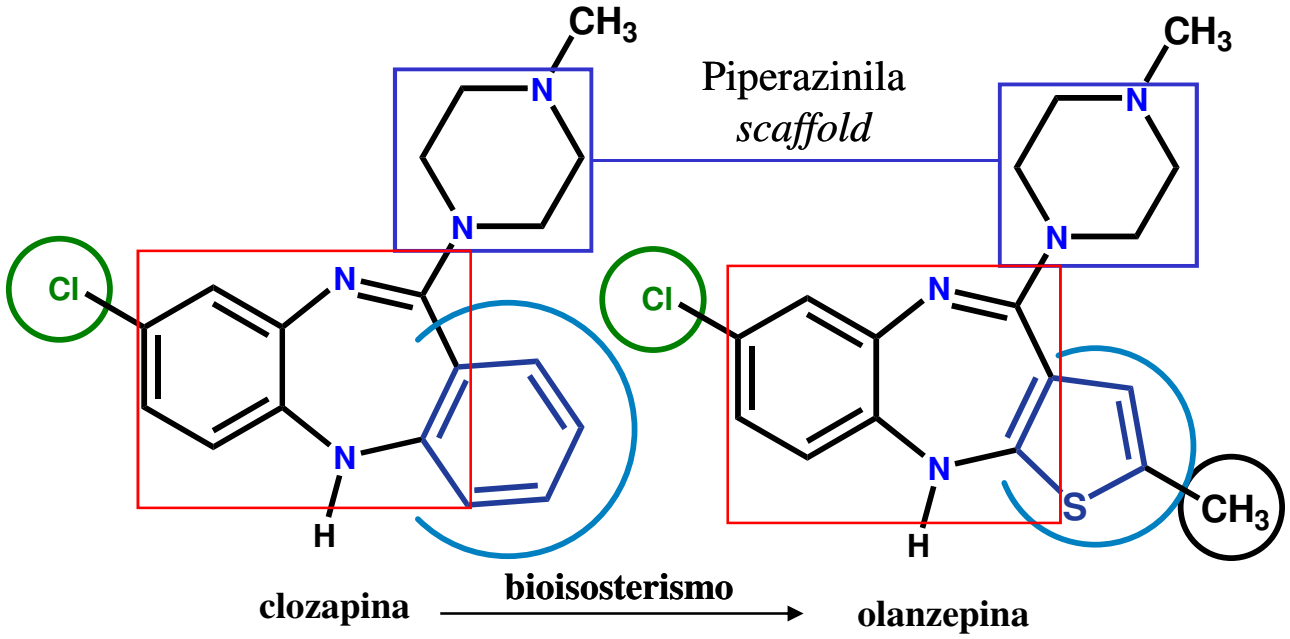
Robin Ganellin is Emeritus Professor of Medicinal Chemistry at University College London, UK.



ISBN-10 3527325492
Setembro de 2010



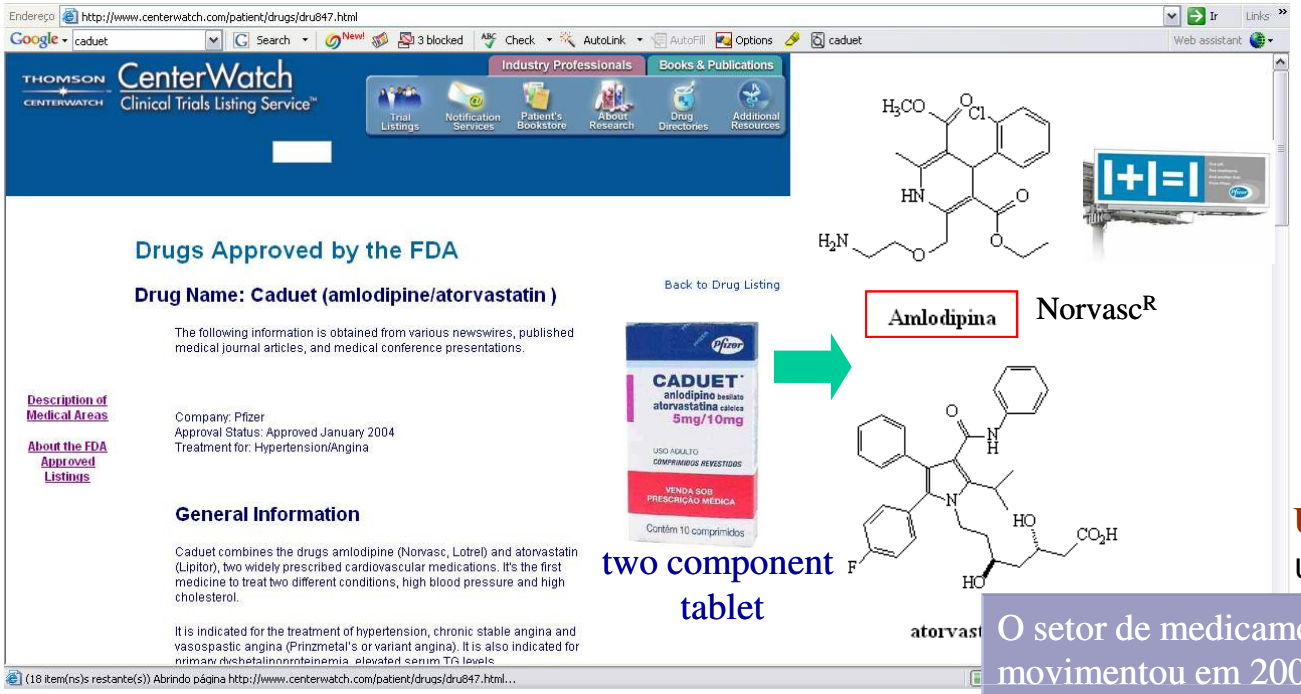
ISBN-10 3527325492
Setembro de 2010

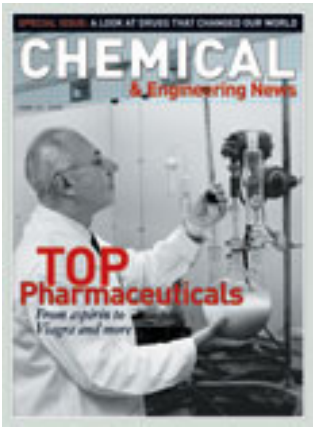


Current Medicinal Chemistry, **12**, 23-49 (2005)
http://www.bentham.org/cmc/samples/cmc12-1/0002C.pdf

	clozapina	olanzapina
D_1	53	10
D_2	190	2.1
D_3[b]	280	49
D_4[b]	40	28
5-HT_{1A}	710	7100
5-HT_{2A}	4.0	1.9
5-HT_{2C}	5.0	2.8
α_1	3.7	7.3
α_2	51	140
M_1	0.98	2.1
H_1	17	5.6

M. Rowley, L. J. Bristow, P. H. Hutson, J. Med.Chem. **2001**, *44*, 477





US$ 266 milhões em 2006

USPTO 6,455,574 / AUG 11,2018

O setor de medicamentos cardiovasculares movimentou em 2005 *ca.* US$ 72 bilhões; Estatinas superaram US$ 32 bilhões em 2006.

W. H. Frishman & A. L. Zuckerman, *Expert Rev. Cardiovas. Ther.*

VYTORIN (ezetimibe/simvastatin)

Merck/Schering-Plough

two component tablet

- *Inovação incremental*

simvastatina

Zocor®

ezetimibe

Zetia®

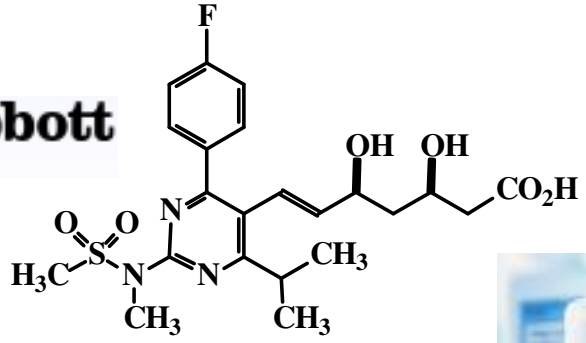
N. A. Flores, *Curr. Opin. Invest. Drugs* **2004**, *5*, 984

Vytorin® sales 2006-third-quarter = US$527 million

Lisa M. Jarvis, "Big Pharma Regroups", CE&N 2006, 84, 49 (November 20)

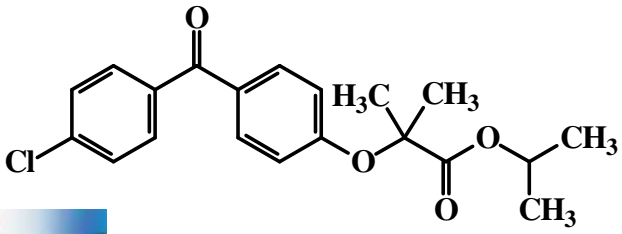
CRESTOR® (rosuvastatin calcium)/TriCor® (fenofibrate tablets)

AstraZeneca and Abbott Laboratories will jointly develop and commercialize a fixed-dose combination product that will target three blood lipids: low-density lipoprotein (*bad* cholesterol); high-density lipoprotein (HDL), so-called good cholesterol; and triglycerides.
The single-pill product will contain AstraZeneca's Crestor statin drug and Abbott's ABT-335 (Solvay) or fenofibrate.



rosuvastatina

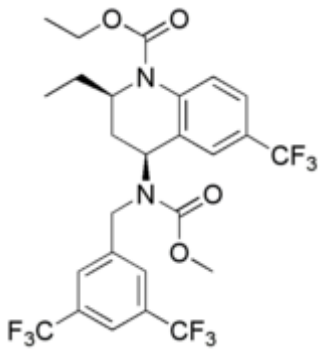
Crestor



fenofibrato

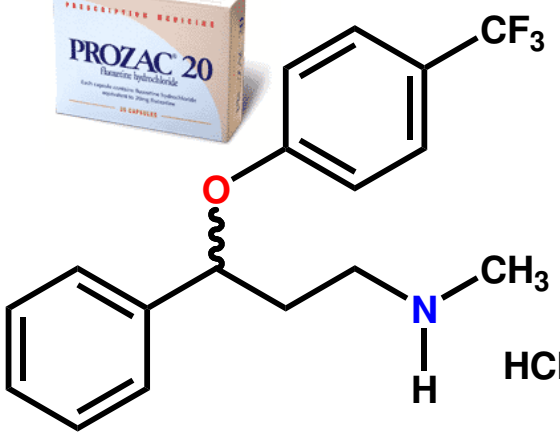
Tricor[R]

Pfizer is developing its own combination of its Lipitor[TM] statin with the HDL-raising compound torcetrapib (stoped all trials in Dec. 2006):

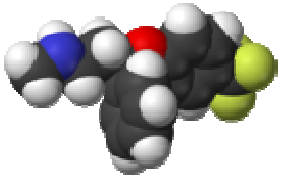


The cholesterol market is currently valued at US $17,0 billion

Symbyax®
Olanzapine and Fluoxetine HCl Capsules



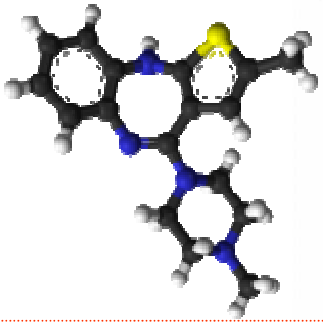
cloridrato de fluoxetina

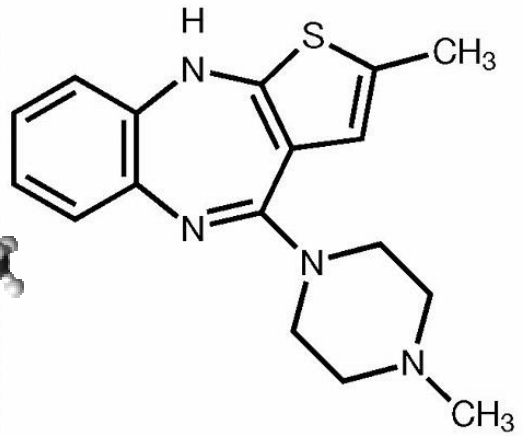


DT Wong, KW Perry, FP Bymaster,
Nat. Rev. Drug Discov. **2005**, *4,* 764

Lilly

+





olanzapine

Antipsicótico: esquizofrênia, disordem bipolar;

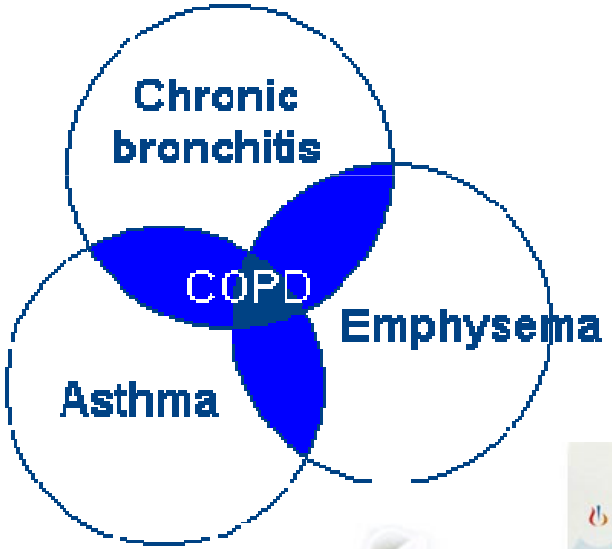
Lilly

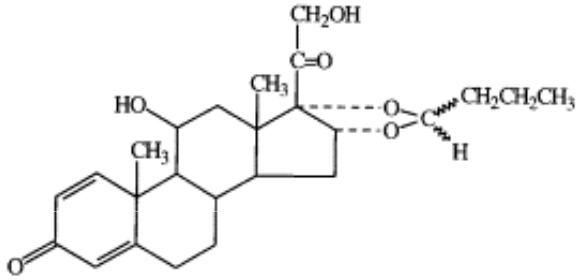
Em 2005, *Zyprexa*^{R} totalizou US$ 4,2 bilhões em vendas.

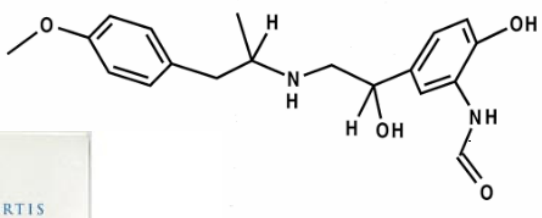
Symbicort turbo®, é um medicamento da AstraZeneca compreendendo combinação de dois fármacos antigos:

budesonida (glicocorticóide) & formoterol (**agonista-β2 adrenérgico seletivo**), **indicado *para tratamento da doença pulmonar obstrutiva crônica (DPOC)***.

AstraZeneca



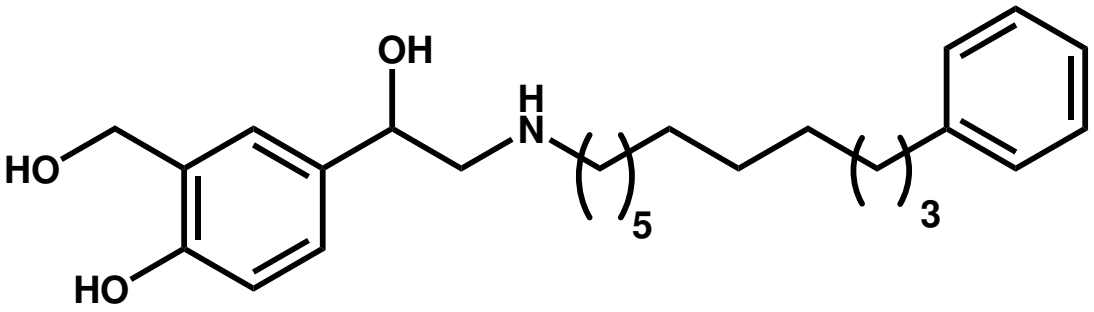




Aerocaps

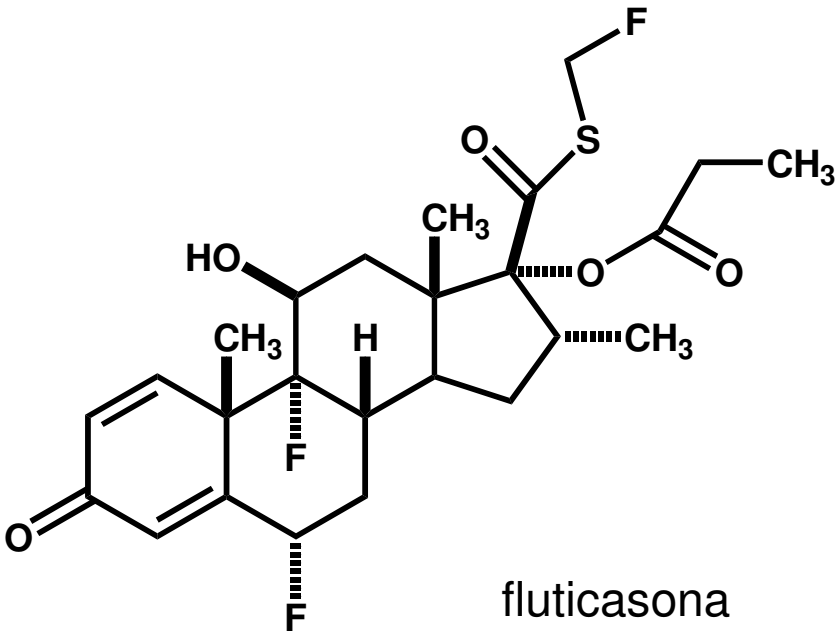
Novartis

Biossintética



salmeterol

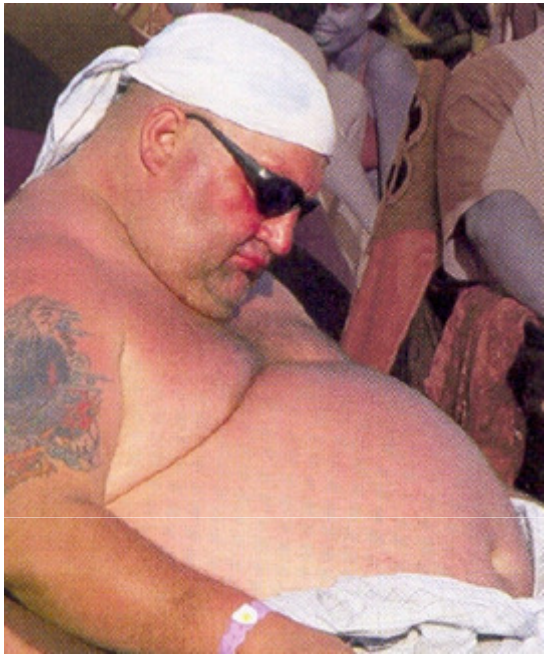
+

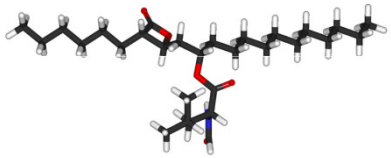


fluticasona

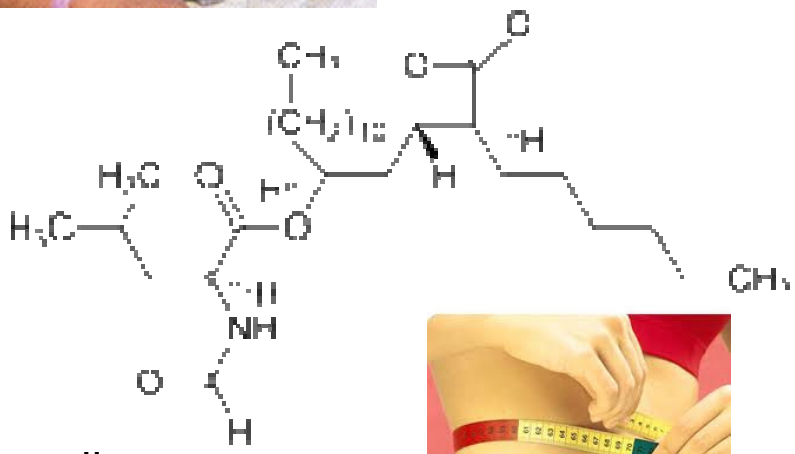
Em 2009, *Seretide*^{R} totalizou US$ 7,7 bilhões em vendas.

Inovação terapêutica: obesidade





Animal transgênico com obesidade provocada, representou primeiro modelo in vivo para estudo de novos fármacos anti-obsidade.



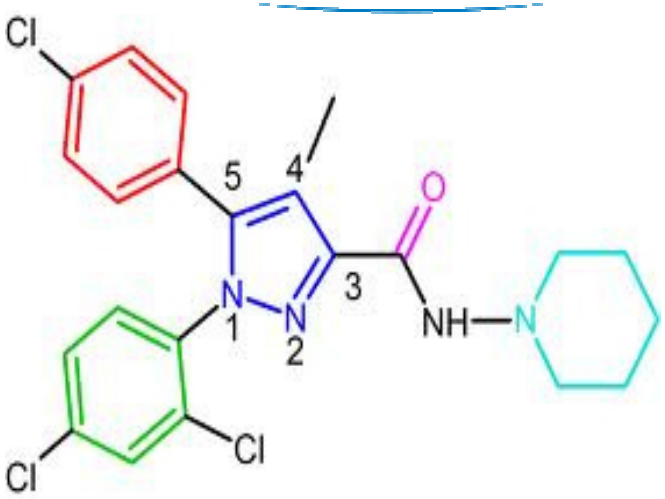
orlistat

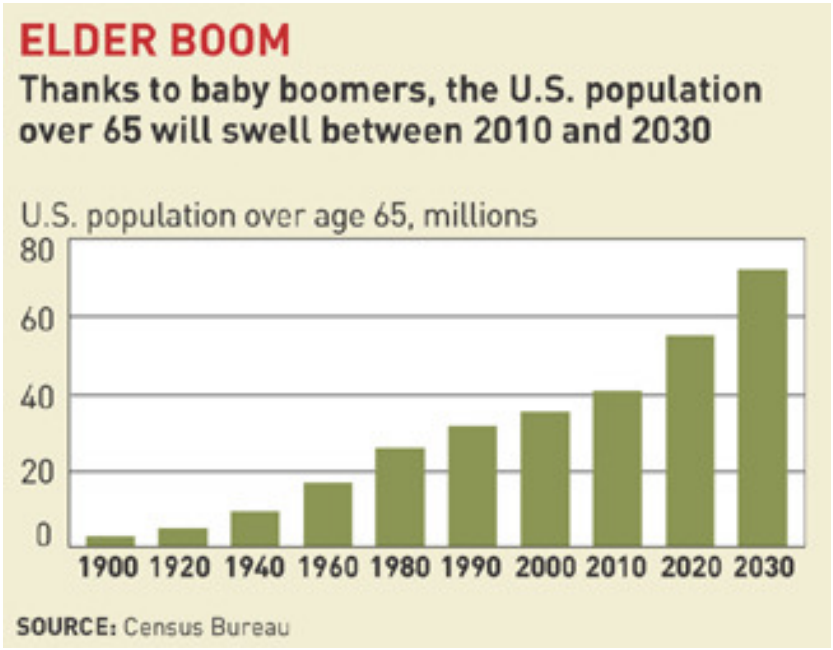
Lançado em 2006,

retirado em 2008

(RE 4.087/2008)

sanofi aventis

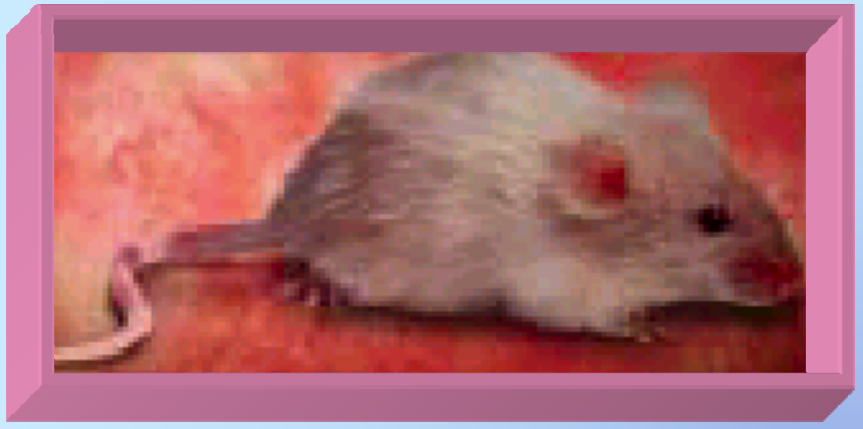




À esquerda rato transgênico "envelhecido" (equivalente a 100 anos humanos).

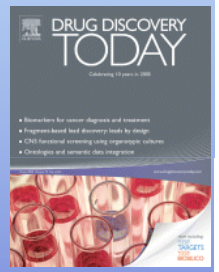
Rato Transgênico Humanizado

Humanized mouse model



W. Xie & R. M. Evans, *Drug Discovery Today* 2002, *7*, 509-515

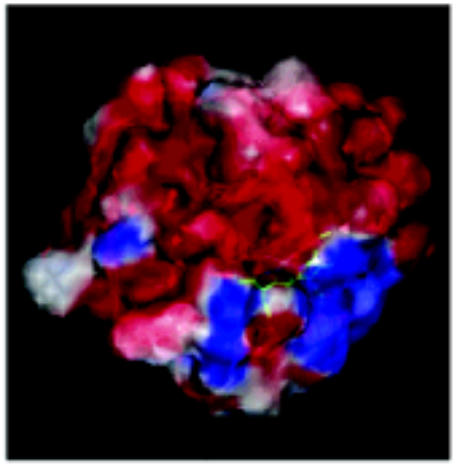
This mouse is a xeno-sensor allows the investigation of drug-drug interactions .



Animal transgênico com mesmo perfil de resposta à ação de fármacos que humanos. Possui CYP3A isoenzimas (*xeno-sensor*) que permite o estudo de interações de fármacos, simulando o estudo em humanos.

Modelagem por homologia das isoformas do CYP2D6 humano e do rato e subseqüente racionalização computadorizada das interações com ligantes permitiu esclarecer as especificidades moleculares destas interações.

a)

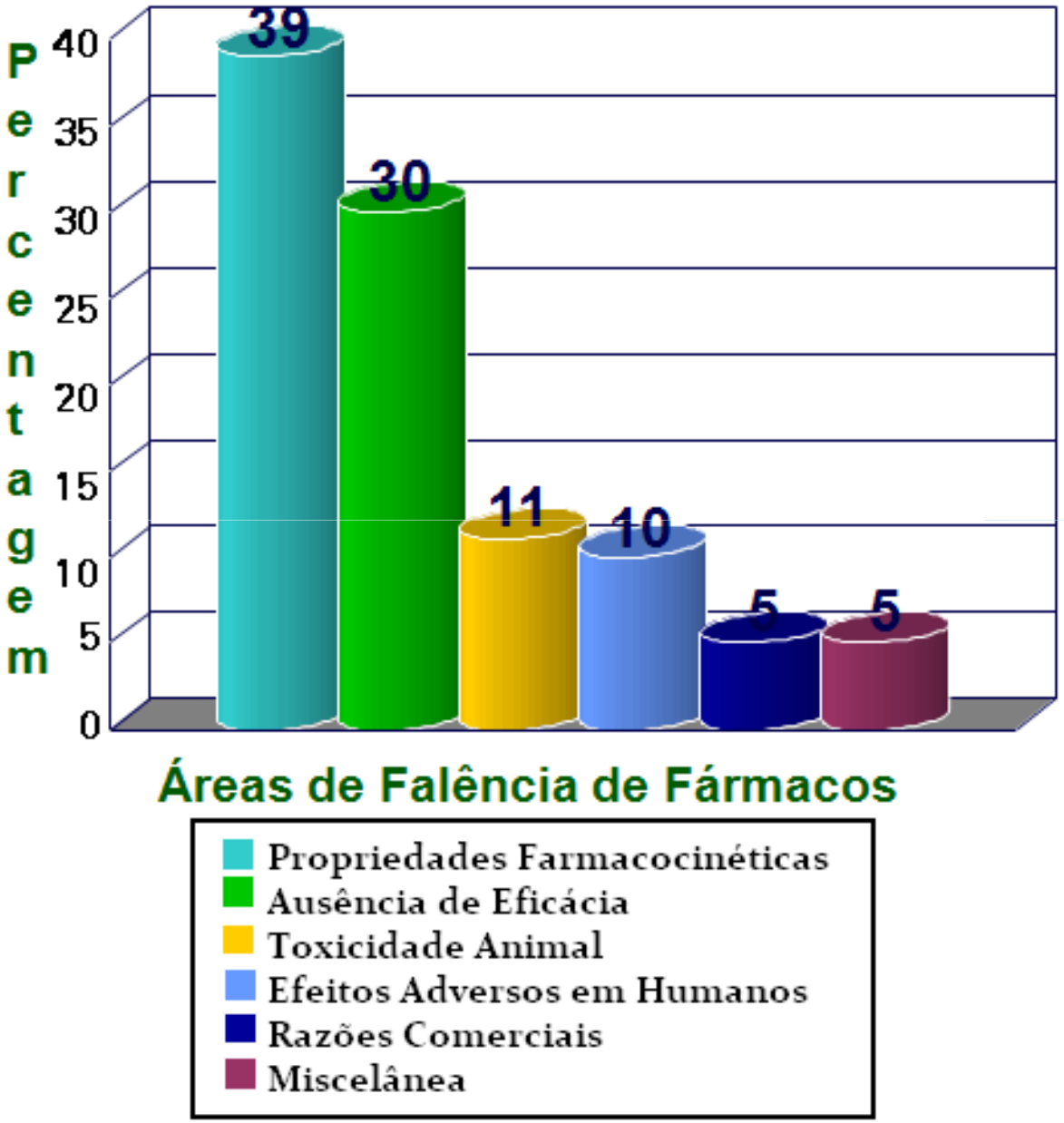


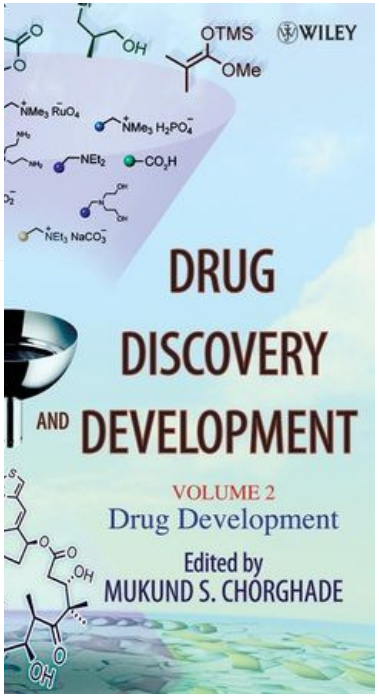
b)

a) Potencial eletrostático no sítio-ativo de CP2D6; b) sítio-ativo, contendo o grupo heme (verde) ao fundo.

NPE Vermeulen et al., J. Med. Chem. 2003, 46, 74.

Razões para Falência de Fármacos





Obrigado
pela presença
e atenção.

Corcovado, uma das sete novas maravilhas do mundo !