



Universidade Federal do Rio de Janeiro

A Química Medicinal e a descoberta de novos fármacos



II Escola de Inverno de Química, FURB, Blumenau, SC, 15-16 julho de 2008

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Professor Titular - UFRJ



www.farmacia.ufrj.br/lassbio



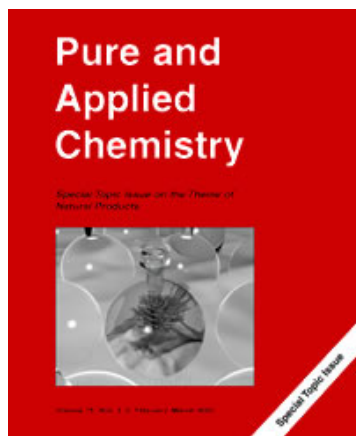


***Por favor, mantenha desligado
ou sem som.***



Obrigado !

IUPAC - Subcommittee Medicinal Chemistry & Drug Development



Medicinal chemistry is a chemistry-based discipline, also involving aspects of biological, medical and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and the construction of structure-activity relationships.

Qualidade de Vida



**Expectativa de vida ao nascer
(IBGE, BR, 2006)**

Homens ca. 68,6 anos

Mulheres ca. 76,1 anos

Média nacional: 72, 3 anos (em 2005: 71,9 anos)

Índice de Desenvolvimento Humano

IDH-ONU (saúde, educação, renda 2005)

Brasil: 0,800, i.e. 70º lugar/177 países

[1º lugar: Islândia 0,968 (81,5 anos); Noruega 0,968 (79,8 anos);

177º lugar: Serra Leoa 0,336 (41,8 anos);

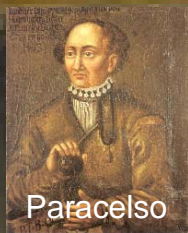
Argentina: 0,869 (74,8 anos); Uruguai: 0,852;

AL&C: 0,803; África: 0,493; Mundo: 0,749

Brasil é o 11º mais desigual do mundo com 15º lugar na economia mundial



Achilles/Chiron



Paracelso

Botica



Bayer, 1889

Felix Hoffmann

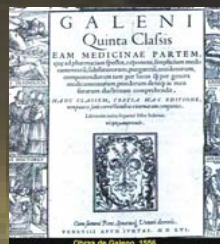
Dos tempos da botica...



Hygieia



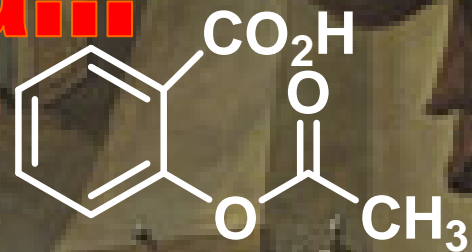
C Galeno



Óbras de Galeno, 1555



F Sertürne



Ácido acetil salicílico

O fármaco...



Saint Come et Saint Damien
Patrons des medecins chirurgiens et pharmaciens

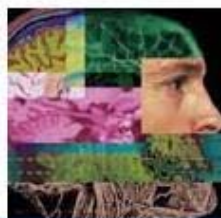


J Anchieta



J Patrocínio





the Pharmaceutical Century

TEN DECADES OF DRUG DISCOVERY

ACS PUBLICATIONS
HIGH QUALITY. HIGH IMPACT.
November 17, 2000

[Analytical Chemistry](#) | [Chemical & Engineering News](#) | [Modern Drug Discovery](#)
[Today's Chemist at Work](#) | [E-Mail Us](#) | [Electronic Readers Service](#)

1800s to 1919

Patents & Potions

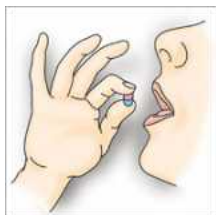


Introduction

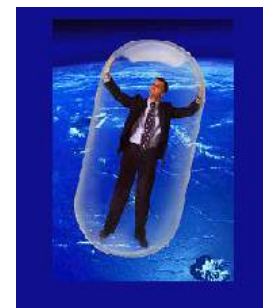
We live today in a world of drugs. Drugs for pain, drugs for disease, drugs for allergies, drugs for pleasure, and drugs for mental health. Drugs that have been rationally designed; drugs that have been synthesized in the factory or purified from nature. Drugs fermented and drugs engineered. Drugs that have been clinically tested. Drugs that, for the most part, actually do what they are supposed to. Effectively. Safely.



zoom



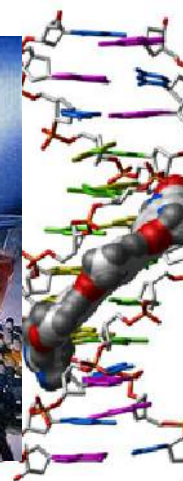
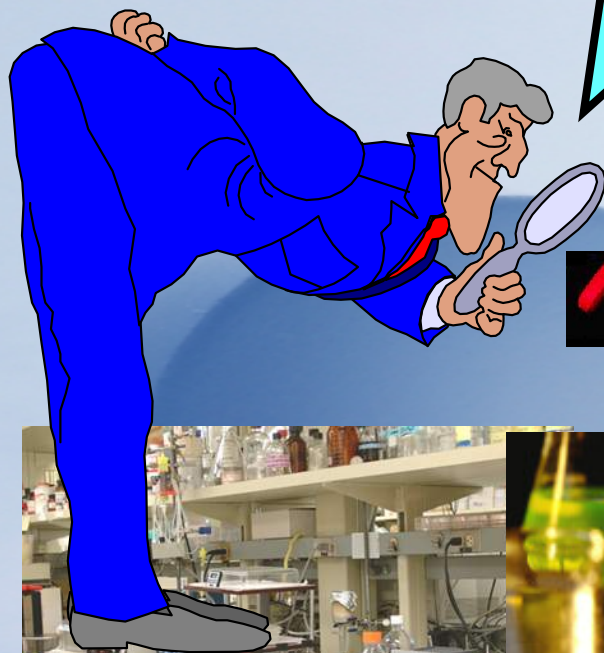
"We live today in a world of drugs. Drugs for pain, drugs for disease, drugs for allergies, drugs for pleasure, and drugs for mental health..."



... às tecnologias do futuro...!

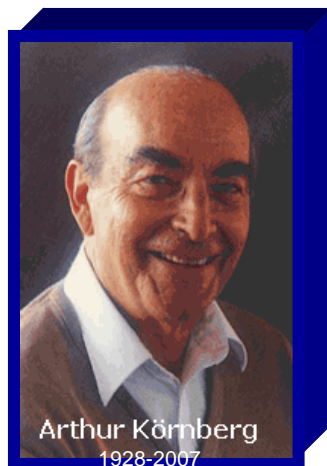


Como se descobrem
os fármacos?



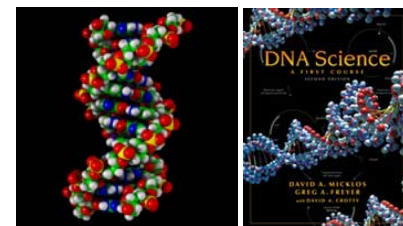
Química Medicinal

O curso



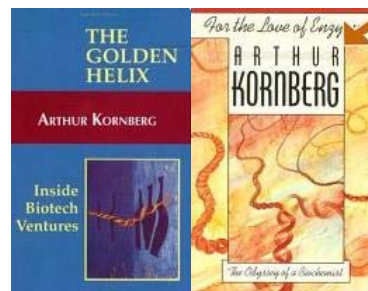
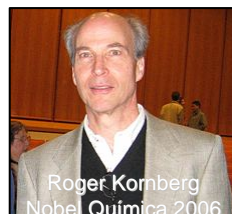
Nobel Prize, 1959

“for their discovery of the mechanisms in the biological synthesis of RNA and DNA”



“We have the paradox of the two cultures, chemistry and biology, growing further apart even as they discover more common ground. For the chemists, the chemistry of biological systems is either too mundane or too complex...”

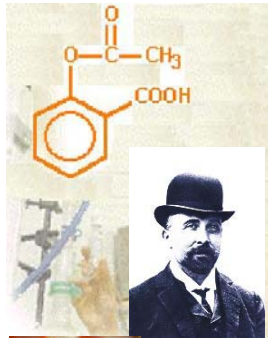
Química Medicinal



Arthur Kornberg
Annual Meeting of AAAS, 1987



Cronologia da descoberta de fármacos



AAS *	1889	1986	ciprofloxacina fluoxetina
barbitúricos	1923	1987	azidovudina lovastatina
cloroquina	1934	1988	cetirizina, enalapril
sulfonamidas	1935	1989	ozagrel mifepristona
penicilina	1942	1990	salmeterol, amlodipina
nitrofurano	1952	1991	alpidem, paroxetina
progesterona	1953	1992	paclitaxel
talidomida	1954	1993	tacrina, fanciclovir
haloperidol	1958	1994	irinotecan, pimobendan
verapamil	1962	1995	indinavir, losartan
indometacina	1963	1996	docetaxel, atorvastatina
propranolol	1964	1996	zileuton, olanzapina
salbutamol	1968	1997	zafirlukast, montelukast
prostaglandinas	1970	1998	infliximab sildenafil efavirenz
oxamniquina	1970	1999	celecoxib orlistat oseltamivir
cimetidina nifedipina	1975	2000	galantamina rofecoxib
atenolol	1976	2001	imatinib <i>rosiglitazona</i>
captopril	1977	2002	voriconazola, etoricoxib
tamoxifeno	1978	2003	gefitinibid, aripiprazola
praziquantel	1979	2004	rosuvastatina, rofecoxib
oxicams	1980	2005	pregabalin, Caduet ^R
ranitidina aciclovir	1981	2006	risperidona, garenoxacina
mefloquina misoprostol	1985	2007	maraviroc, ambrisentan



Fármacos: *o que são?*

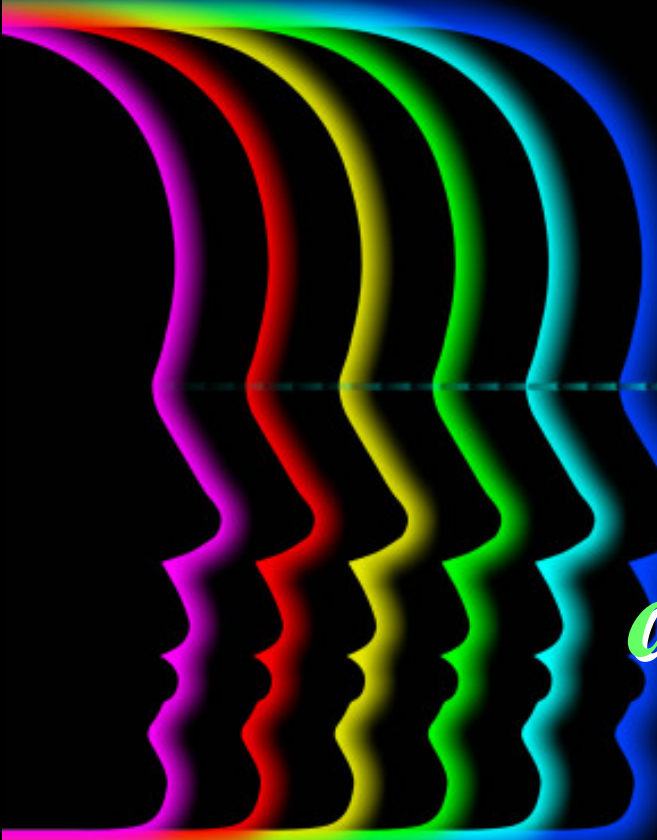




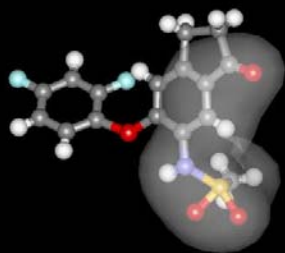
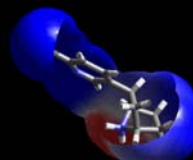

• Fármaco...

- É uma substância orgânica (> 99%) com propriedades farmacoterapêuticas para uso médico, capaz de recuperar, promover, manter ou preservar o estado de Saúde;
- Tem elevada eficácia para o alvo terapêutico (PD);
- Não tóxico;
- Potente *in vivo* com boa biodisponibilidade: ativo em doses baixas, usado por oral em dose-única ao dia;
- Bem absorvido e estável metabolicamente (PK):
 - Propriedades físico-químicas críticas para a atividade do fármaco por via oral: solubilidade, boa partição passiva membrana/água, peso molecular, ligações-H;
- Proteção intelectual (*i.e.* patenteável = conteúdo inventivo);
- Acessível sinteticamente em custos aceitáveis (*scale-up*);
- Tem aplicação médica segura & inovadora (?);

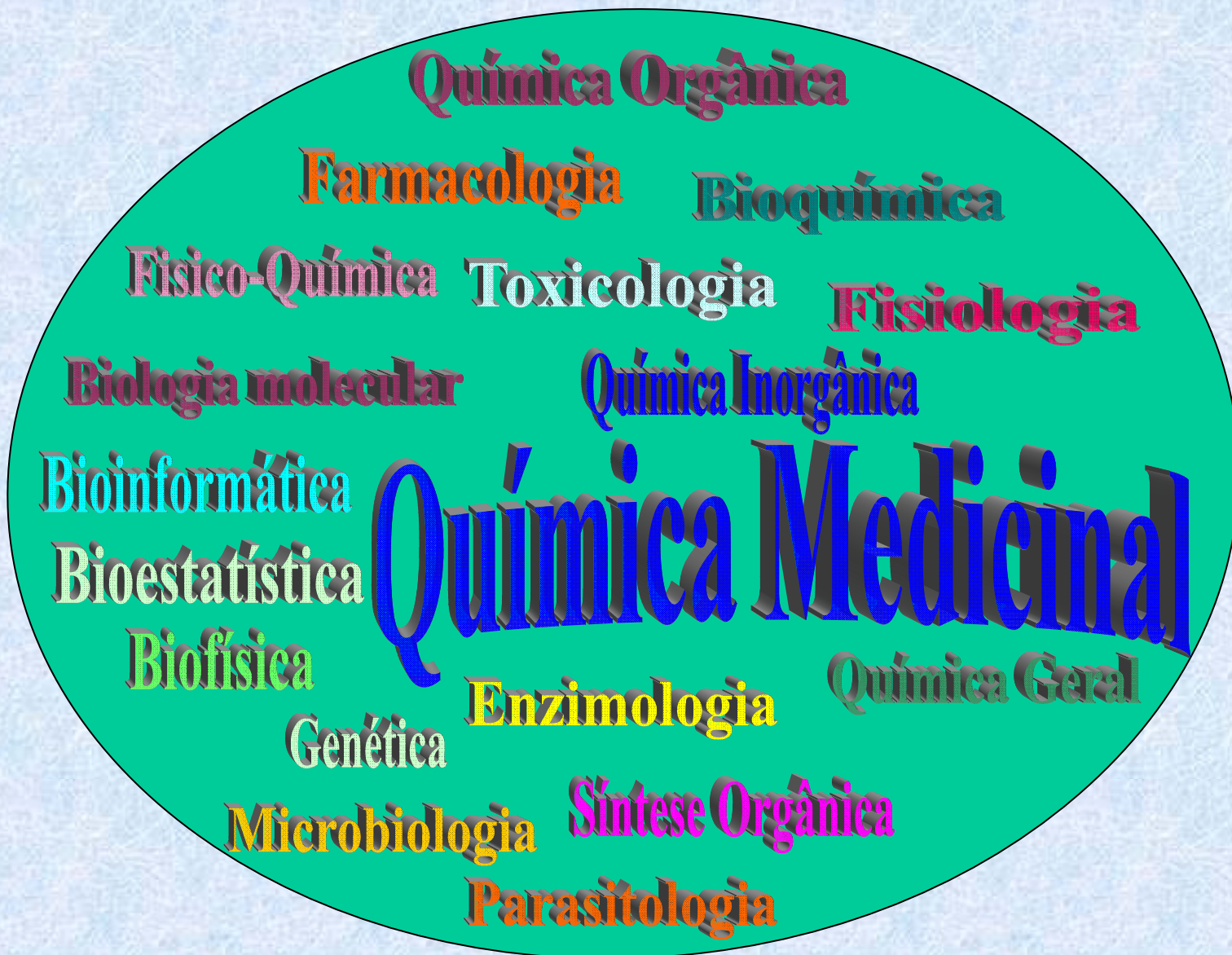
- ... as propriedades moleculares dos fármacos são objeto do estudo da **Química Medicinal**



Atualmente, os **novos**
fármacos, capazes de
atuarem em **qualquer**
alvo-terapêutico, são
descobertos/inventados
por **planejamento**
(racional).



m e d i c i n a
Química Medicinal



Interdisciplinaridade...



Os fármacos e o Nobel !

inter-alia:

**Chave-fehadura
TB**

*Paradigma da
Magic-bullet
Penicilina*



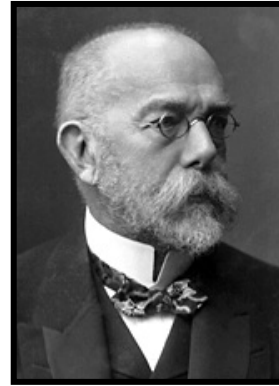
■ **189 pesquisadores
ganharam o Prêmio
Nobel de Medicina
desde 1901**



<http://nobelprize.org>



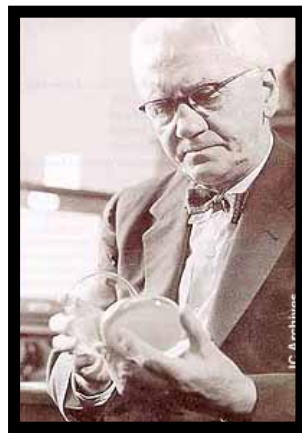
1902 - Emil H. Fisher



1905 - Robert Koch



1908 - Paul Ehrlich



1945 - Alexander Fleming



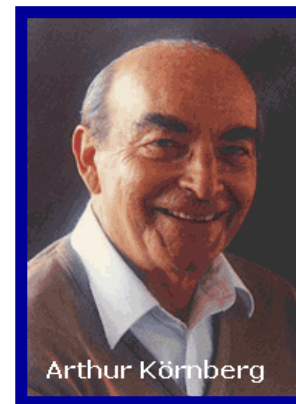
1945 - Ernest B. Chain



1945- Howard W. Florey



1937 - Albert Szent-Györgi



1959- Arthur Koenberg

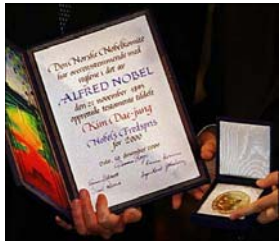




Os fármacos e o Nobel !

“for their discoveries of important principles for drug treatment”

Inter-alia:
Propranolol
Cimetidina
Aciclovir



● 150 pesquisadores
ganharam o Prêmio
Nobel de Química
desde 1901



1988 - J.W. Black



1988 -G.B. Elion



1988 -G.H. Hitchings

β -bloqueadores
antagonistas H-2
pró-fármacos antivirais



1982 –S.B.Bergström



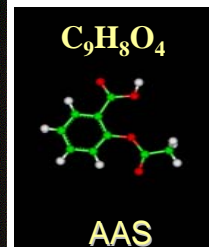
1982 –B.I.Samuelsson



1982 –J.R. Vane



1982 – AAS





Fases da ação dos fármacos

Fase farmacodinâmica

E. J. Barreiro *et al.*, Estratégias em Química Medicinal para o Planejamento de Fármacos,
Braz. J. Pharm. Sc. 2001, **37**, 269-292.



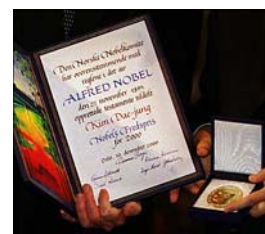
LOCK & KEY CONCEPT

(Emil Fischer, 1894)

“Um ein Bild zu gebrauchen, will ich sagen, dass Enzym und Glucosid wie **Schloss und Schlüssel** zueinander passen müssen, um eine chemische Wirkung aufeinander ausüben zu können”.



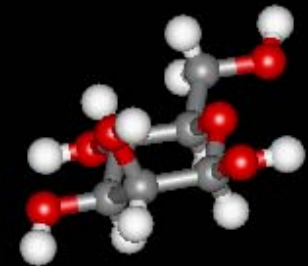
1902



medicinal chemistry

fentidrazina

“Em termos figurados, eu gostaria de dizer que enzima e glicosídeo tem que encaixar como uma chave-fechadura, de maneira a interagir quimicamente uma com a outra”.

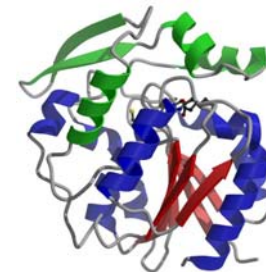
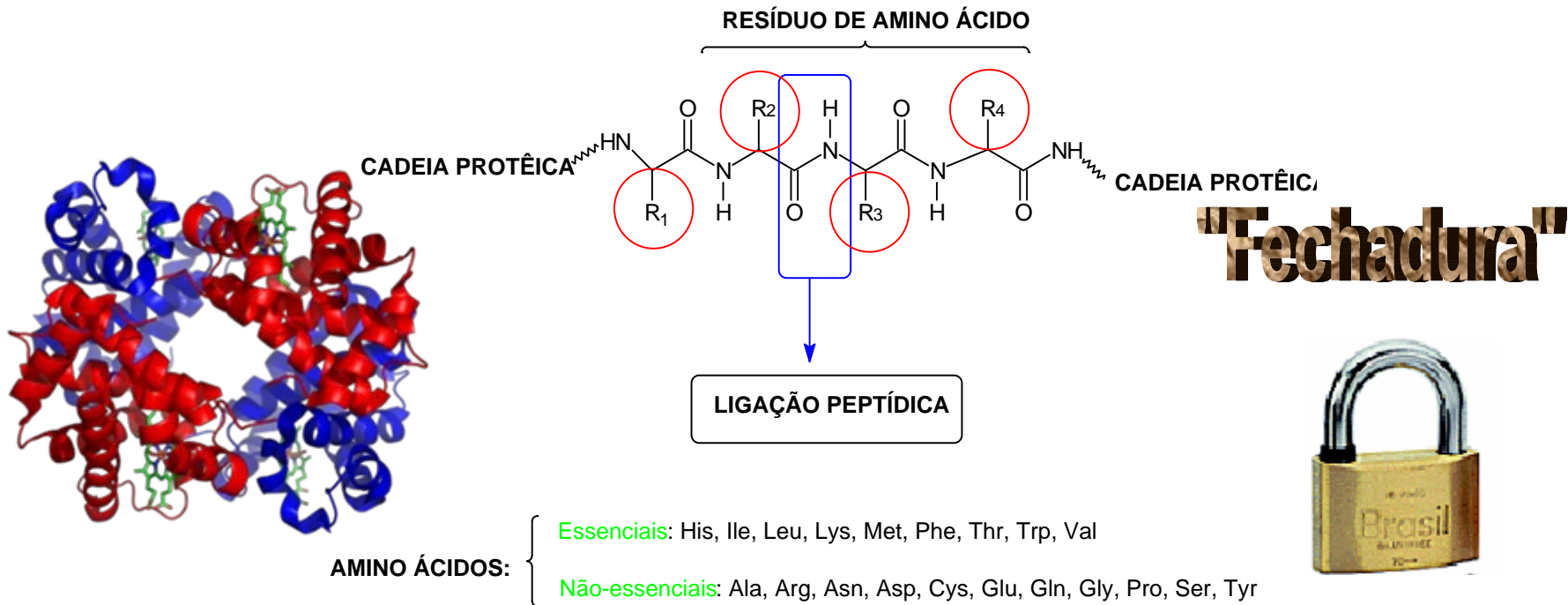


glucose

O Modelo Chave-Fechadura



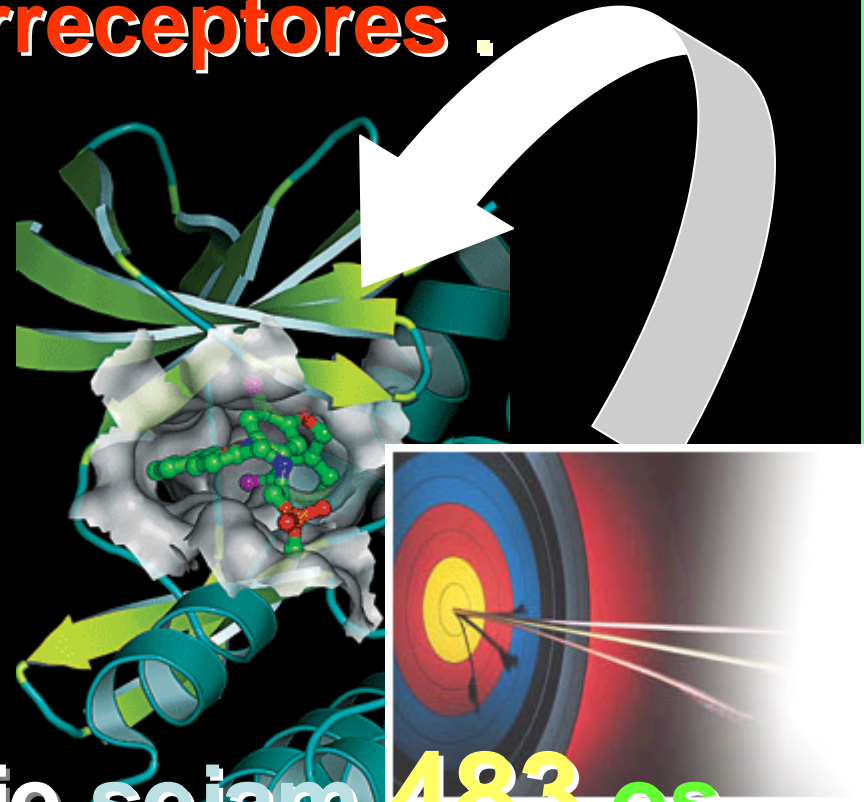
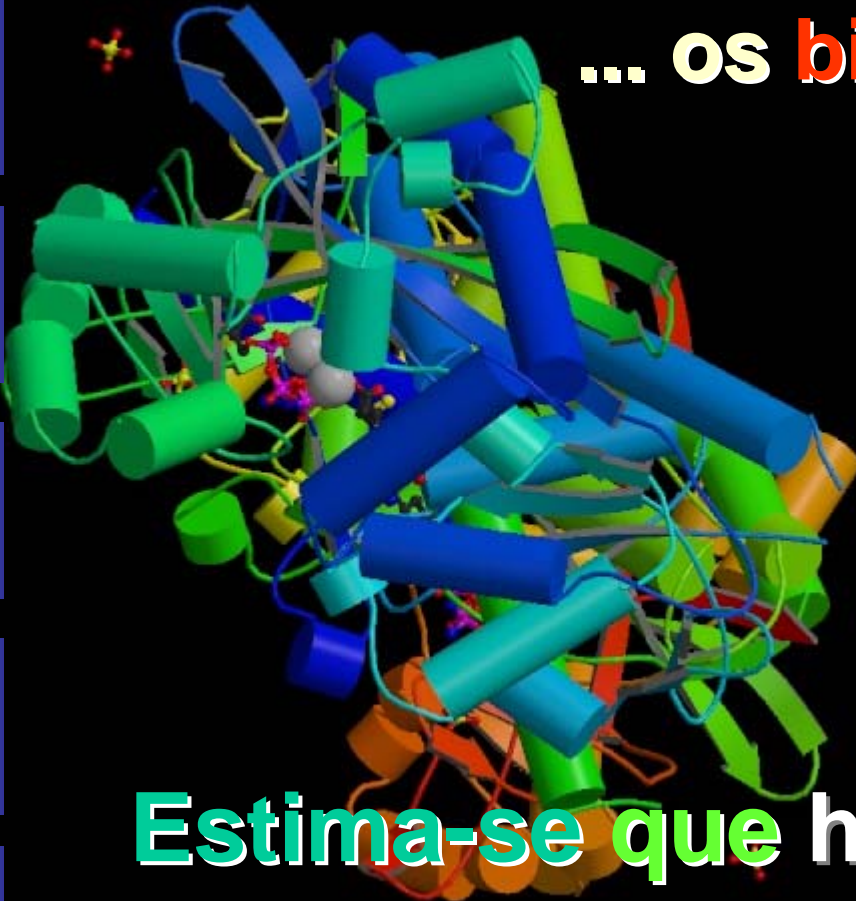
Estrutura Primária das Proteínas





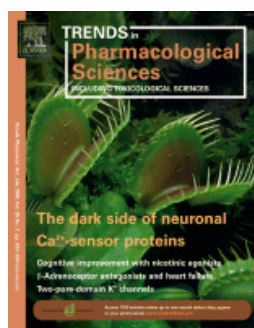
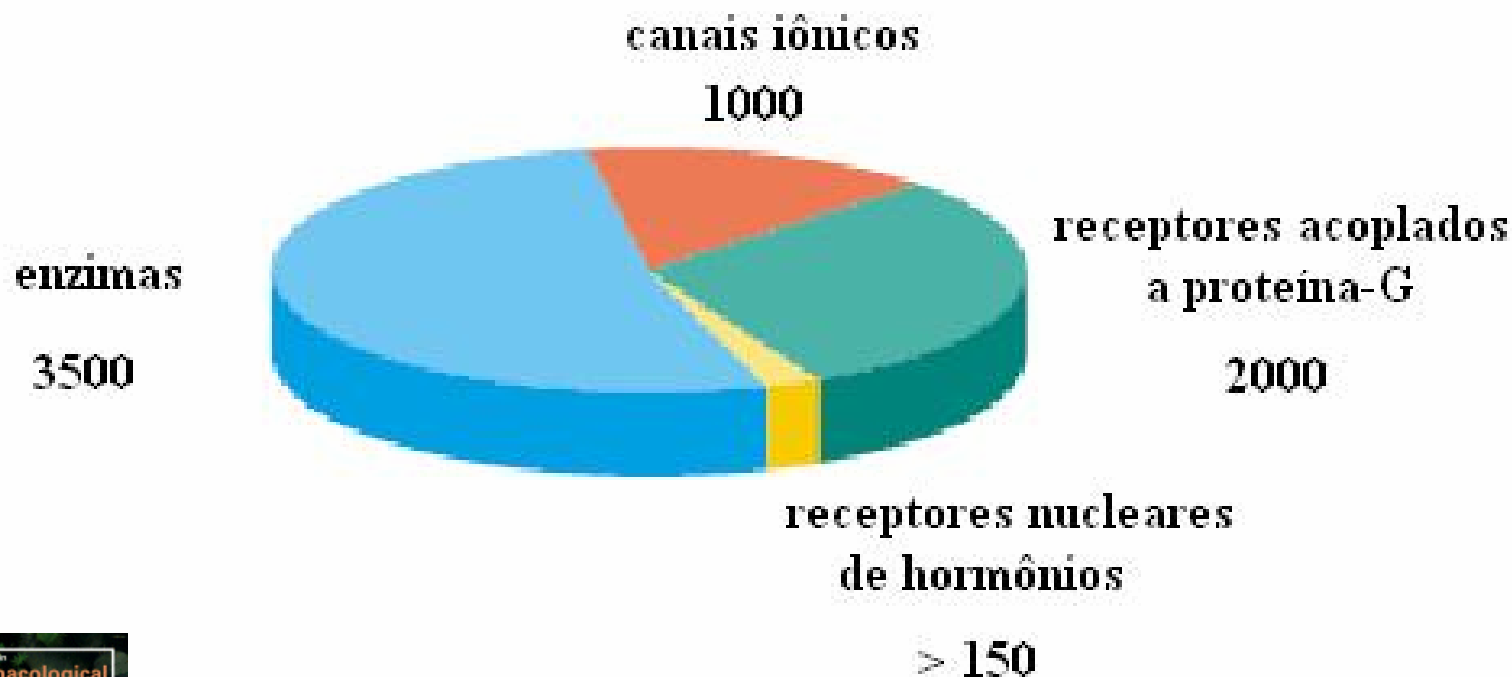
Os fármacos atuam em alvos terapêuticos...

... os **bioreceptores** .



Estima-se que hoje sejam **483** os
bioreceptores envolvidos na
resposta terapêutica de todos os
fármacos contemporâneos.

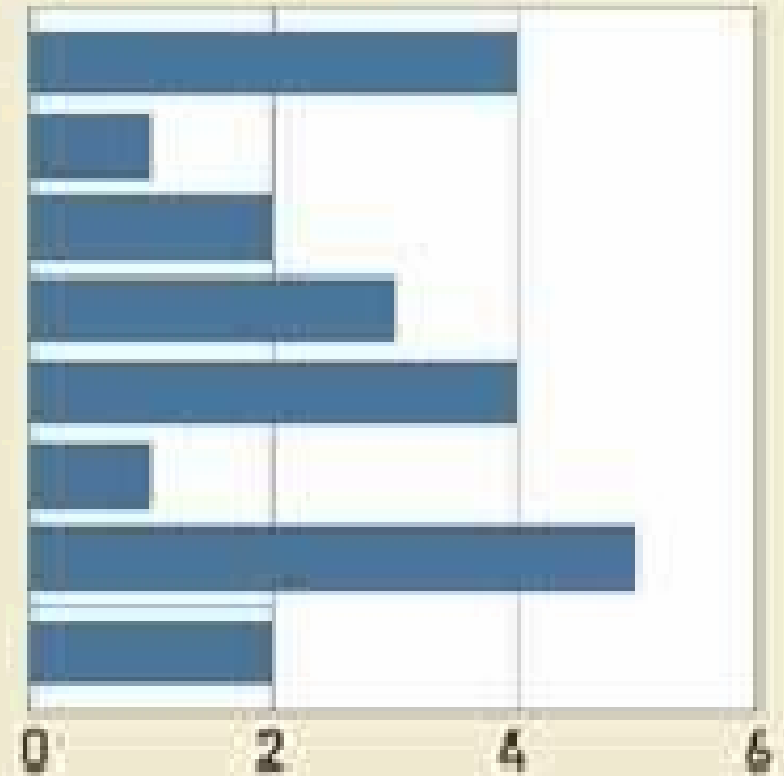
Previsão de potenciais alvos terapêuticos de distintas classes bioquímicas



GC Terstappen & A Reggiani *TRENDS in Pharmacological Sciences* Vol. 22 No. 1 January 2001

Big-Pharma e gastos com tecnologia da informação

- indústria aeroespacial
- indústria automobilística
- indústria química
- setor de embalagens
- computadores e correlatos
- indústria de petróleo
- indústria farmacêutica
- outros

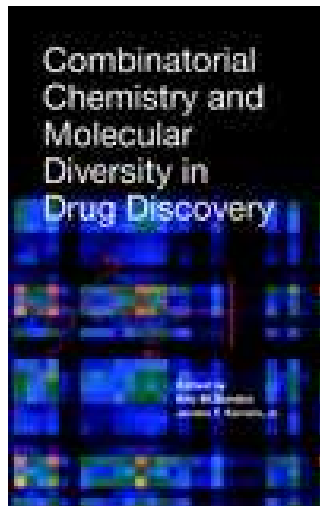


Em % do orçamento total
(2003)

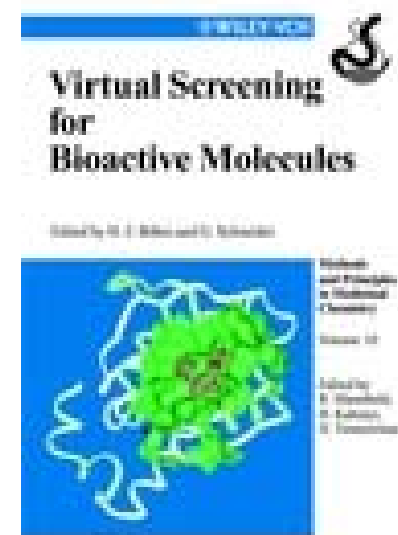
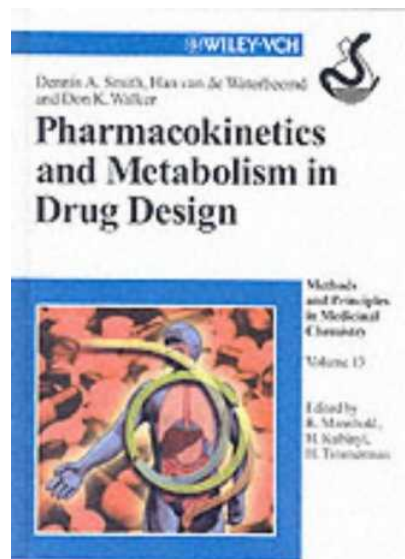
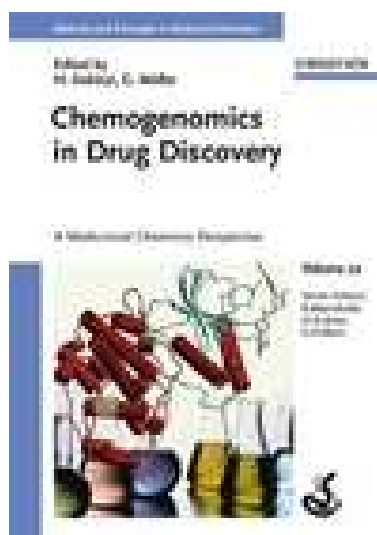
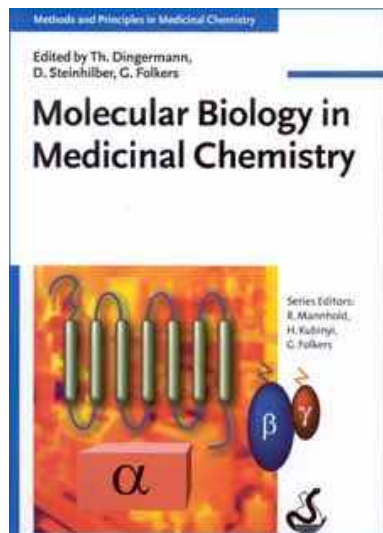




Química Combinatória



A pesquisa de novos fármacos na indústria farmacêutica tem estratégias distintas daquelas das Universidades.



James Black: *drug hunter*

IF tem tido enorme sucesso nos últimos 40 anos, baseando-se em substâncias naturais, hormônios, substratos enzimáticos como protótipos....



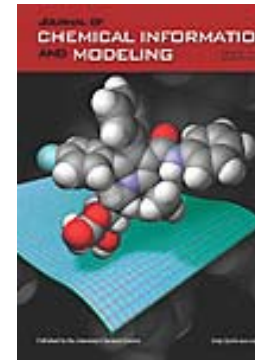
"During the last forty years I have seen the tremendous success that the pharmaceutical industry has achieved by basing its drug strategy around the naturally occurring molecules, hormone and substrates, etc. These native molecules were the leads. Close analogues and derivatives were then designed around these leads. Classical bioassays and biochemistry were able to select-in those compounds that competed with the native molecule for the same active site. Compounds with a high degree of selectivity were regularly produced. The new strategy (ie, combinatorial chemistry and HTS) may not be so lucky. Proteins are inherently 'sticky' molecules. There may well be a danger that the binding reactions used in the high-throughput screening that is used in conjunction with combinatorial chemistry will select-in nonspecific molecules. Non-selectivity may not become visible until the development stage involving intact animals is reached. Too much combinatorial chemistry might well come to be seen as a risk factor to the corporate health"¹².

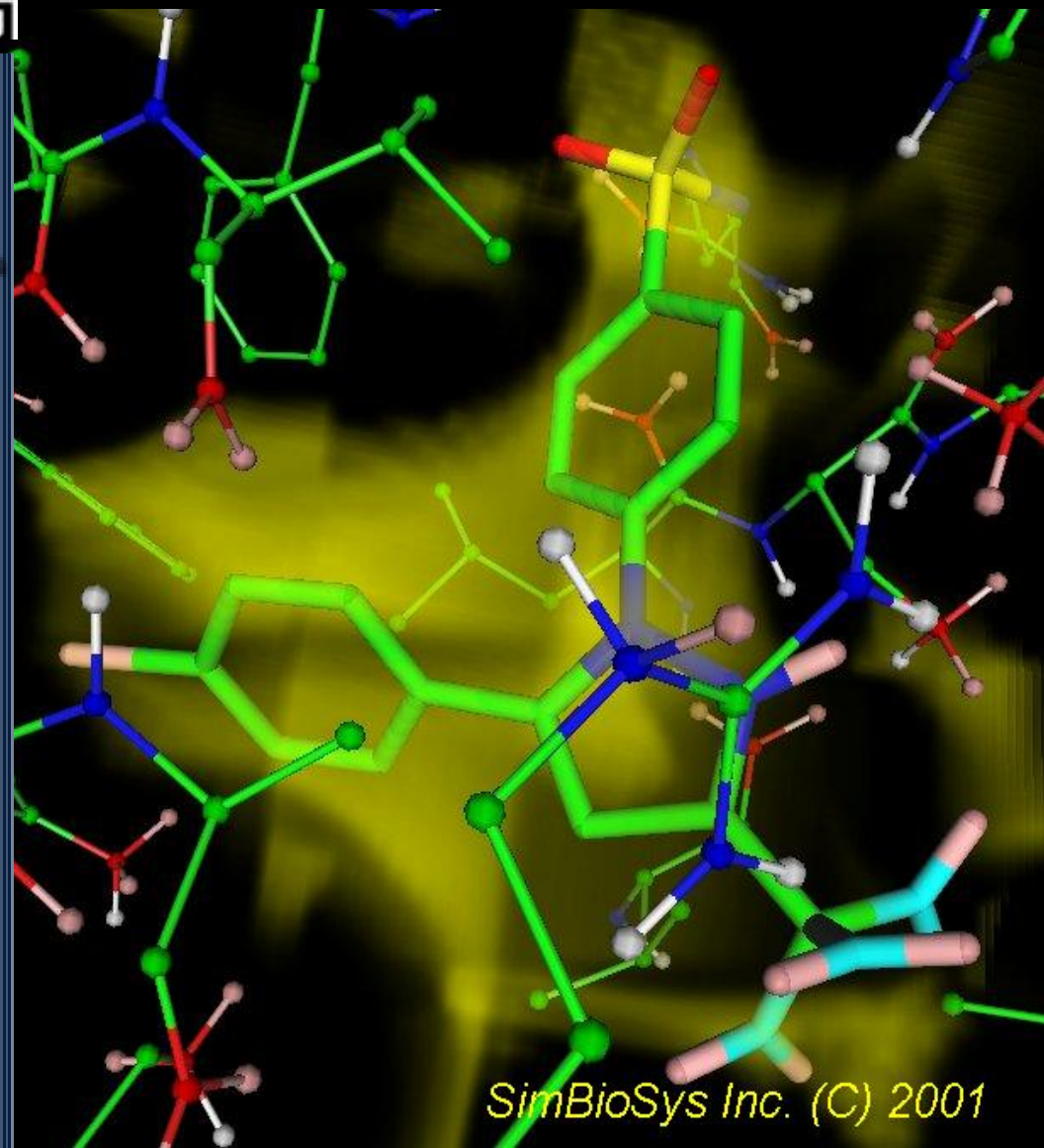
J. Black, Future perspectives in pharmaceutical research.
Pharm. Policy Law. 1, 85–92 (1999).

Modelo Chave-Fechadura



Modelagem Molecular

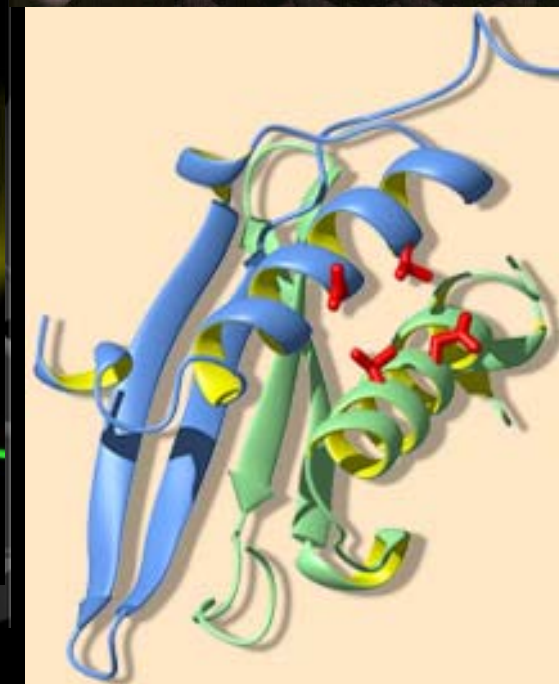




SimBioSys Inc. (C) 2001



Química
Computacional



Interação Fármaco-Receptor

Modelo “Chave-Fechadura”

“Fechadura”



?

“Chaves”



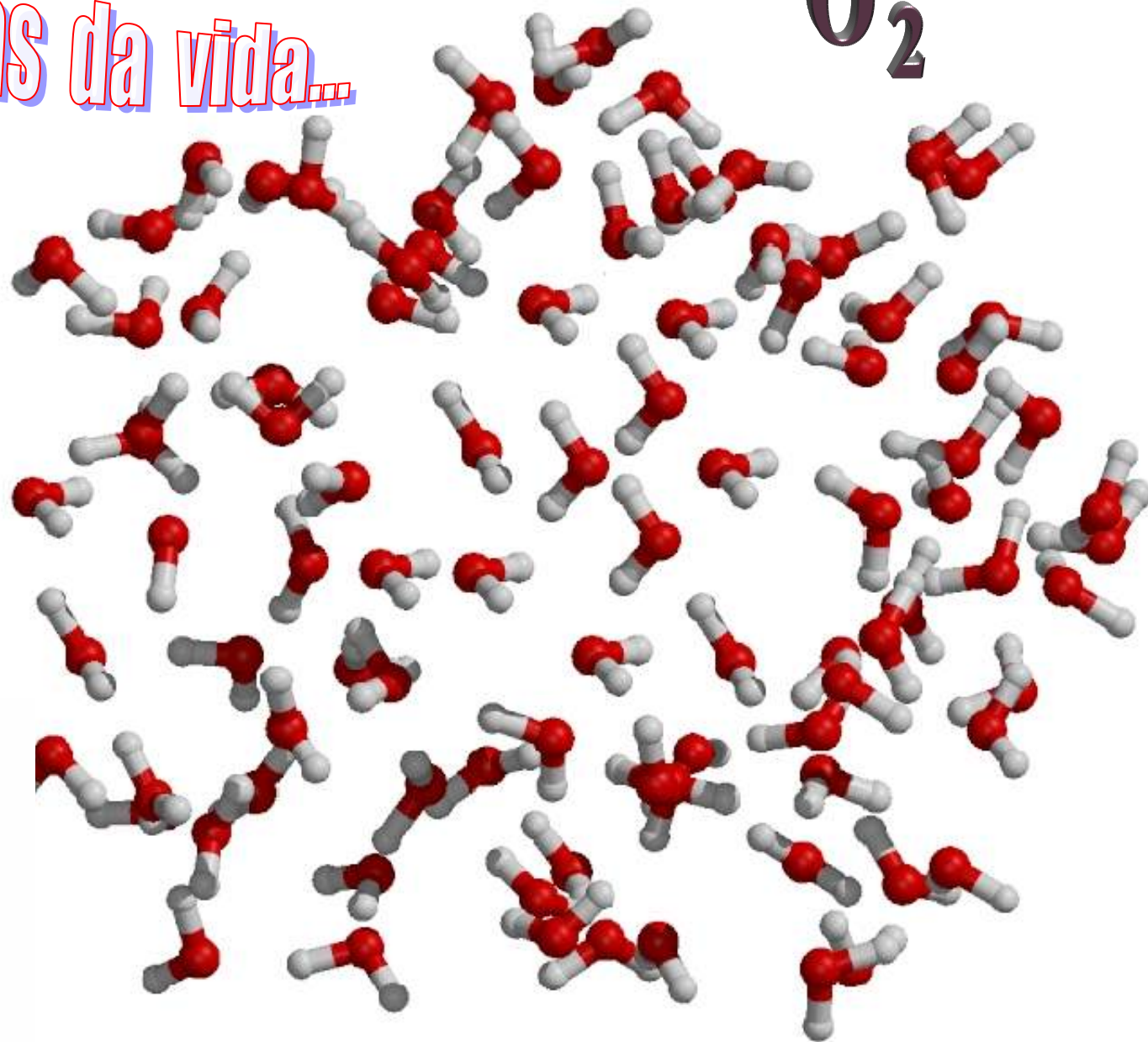
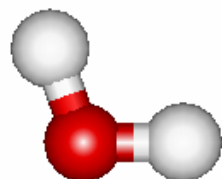
Reconhecimento
Molecular

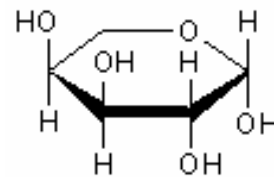
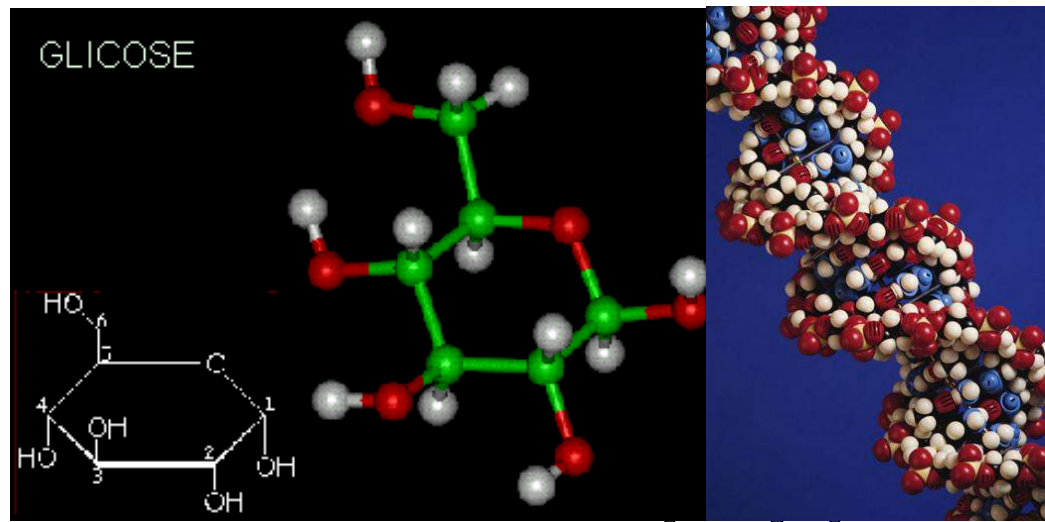
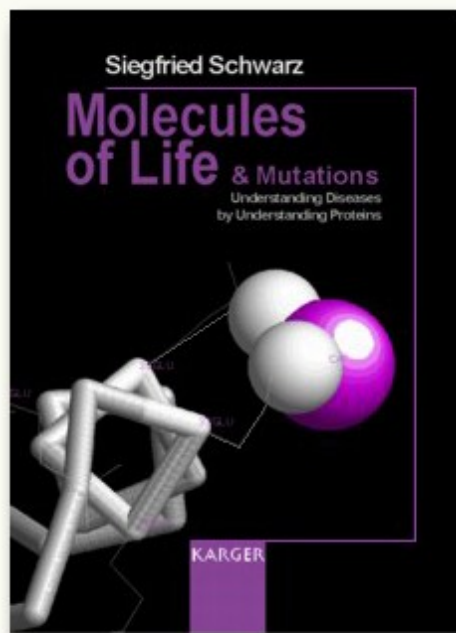
Complementaridade
Molecular

Energia aproximada de interações atômicas e moleculares

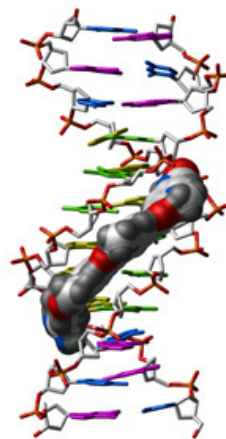
Interação	Energia (kcal/mol)
Ligação covalente	77-88 (irreversível)
Interações iônicas	~5
Ligação de hidrogênio	3-5
Atração dipolo-dipolo	1-5
Interações Hidrofóbicas	~1
Forças de dispersão de London/	0,001 – 0,2

Moléculas da vida...





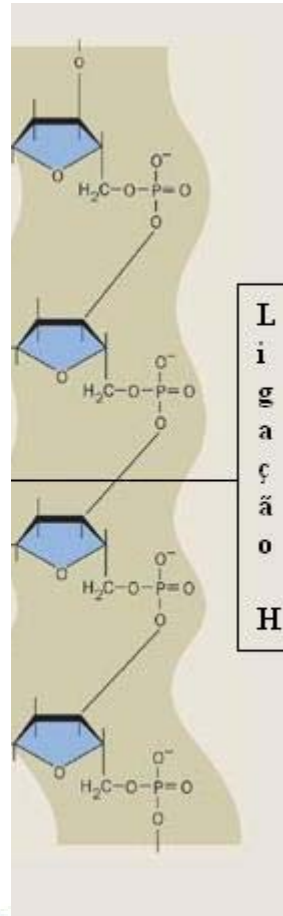
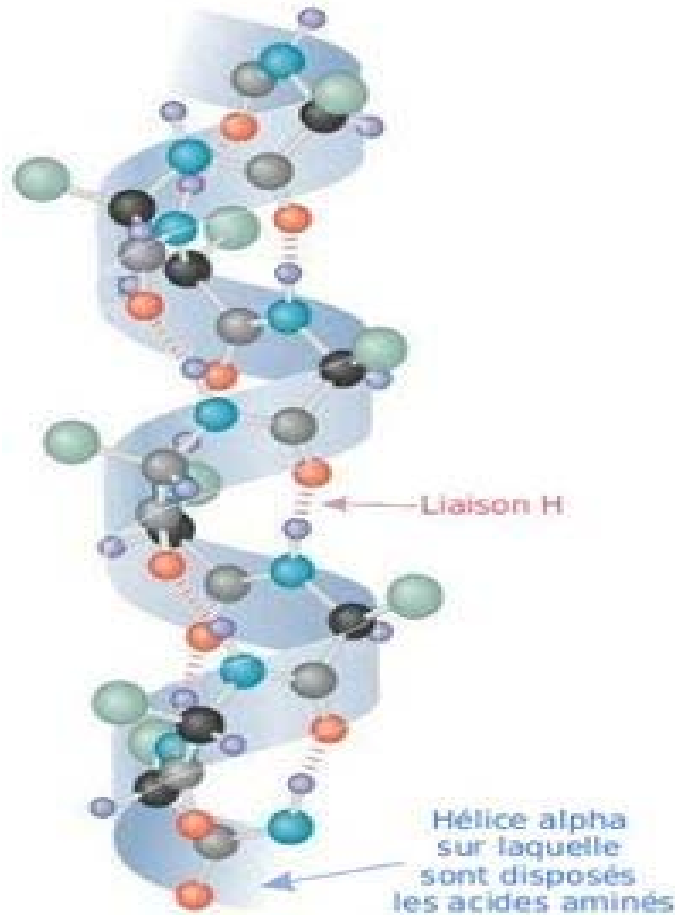
β -L-Arabinose



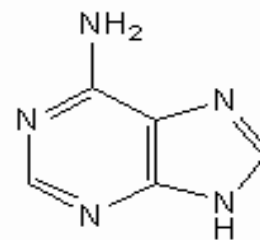
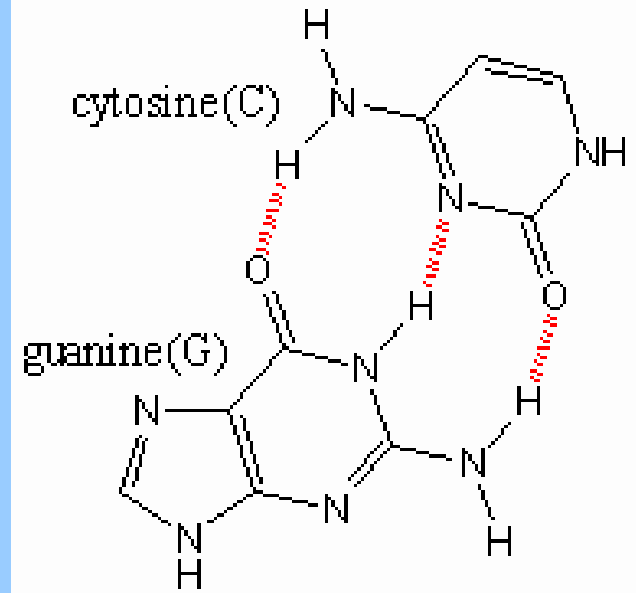
Model Compound Bound to the Minor Groove of a DNA Molecule

Carboídratos
Lipídeos
ácidos nucleicos
canais iônicos
proteínas

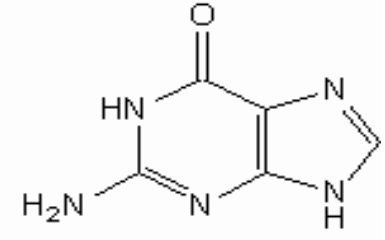
Proteínas, carboidratos, DNA, lipídeos, canais iônicos



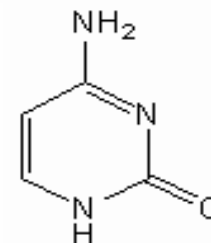
Ligação de hidrogênio = H_2O



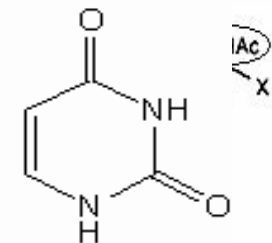
adenine (A)



guanine (G)

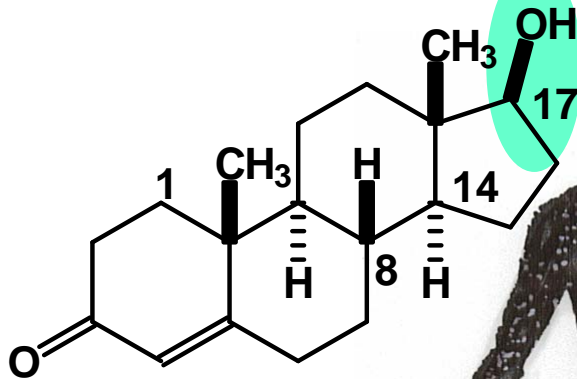


cytosine (C)



uracil (U)

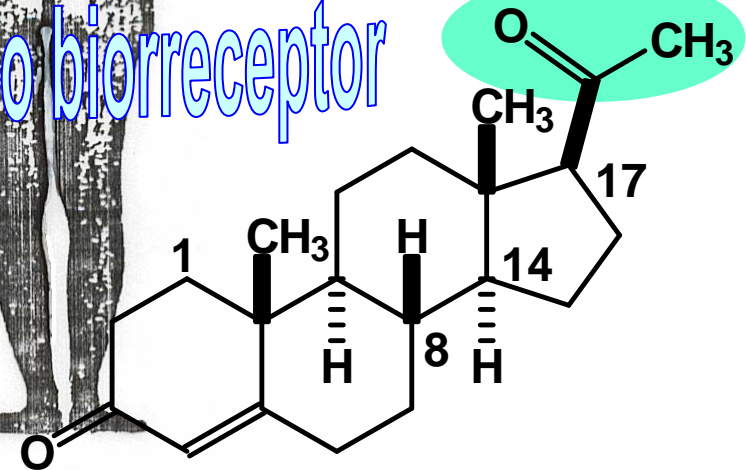
Similaridade & Dissimilaridade Molecular



testosterona



no reconhecimento molecular pelo biorreceptor

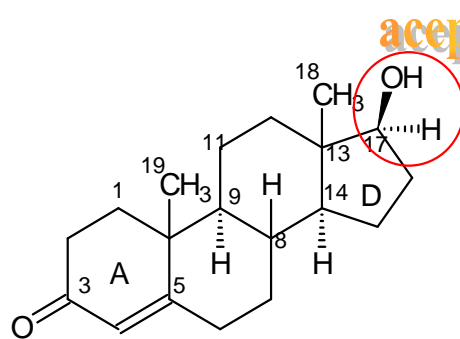


progesterona

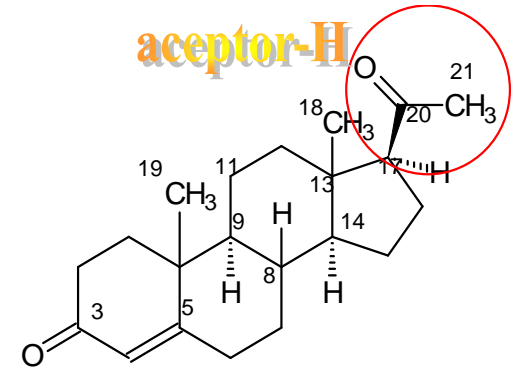
Biorreceptores

Similaridade & Dissimilaridade Molecular

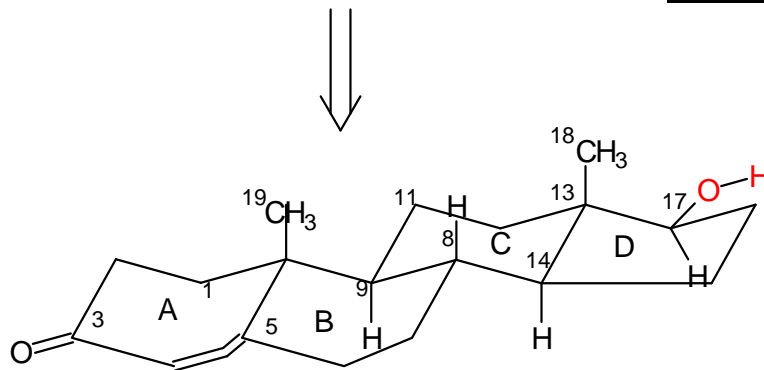
Biorreceptor



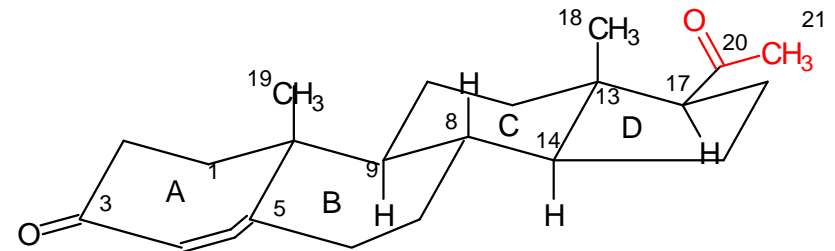
Testosterona



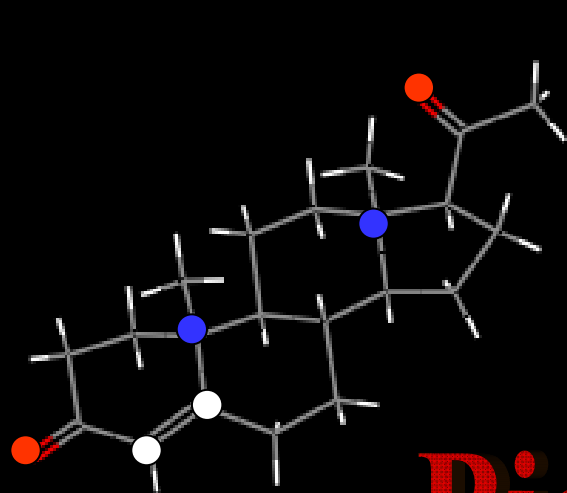
Progesterona



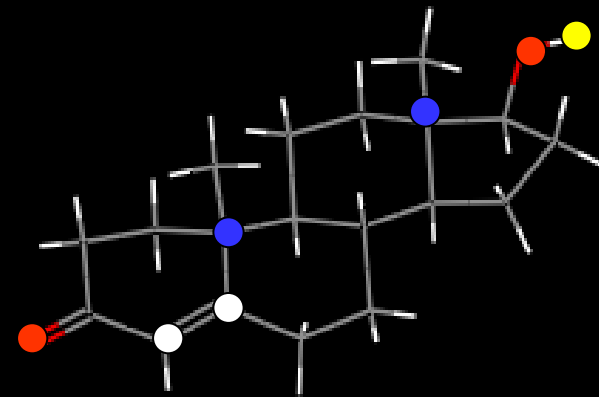
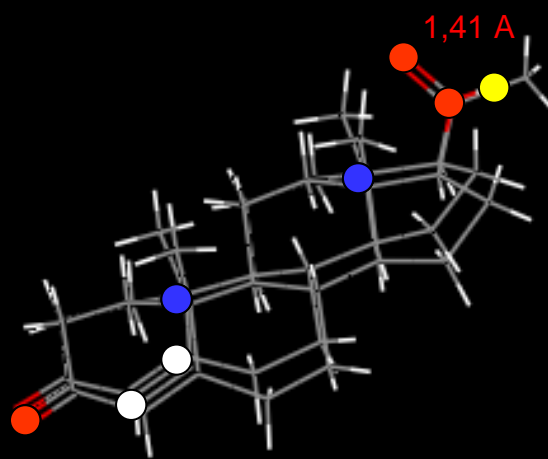
B/C C/D trans



B/C C/D trans

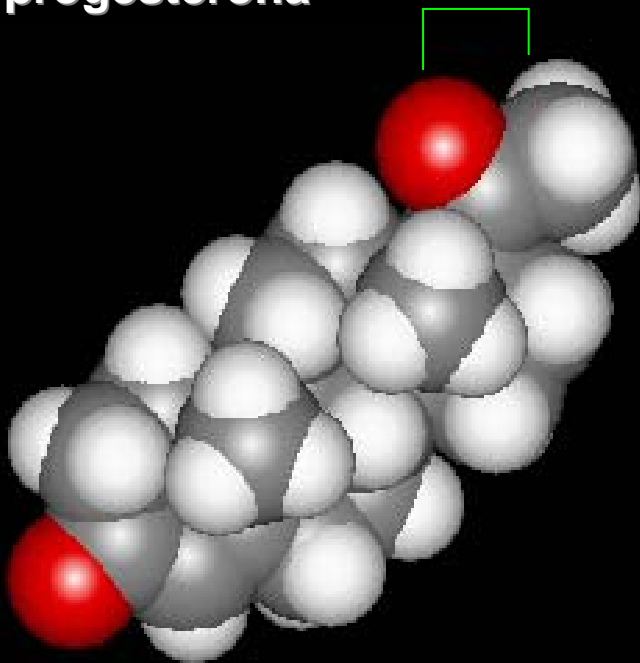


progesterona

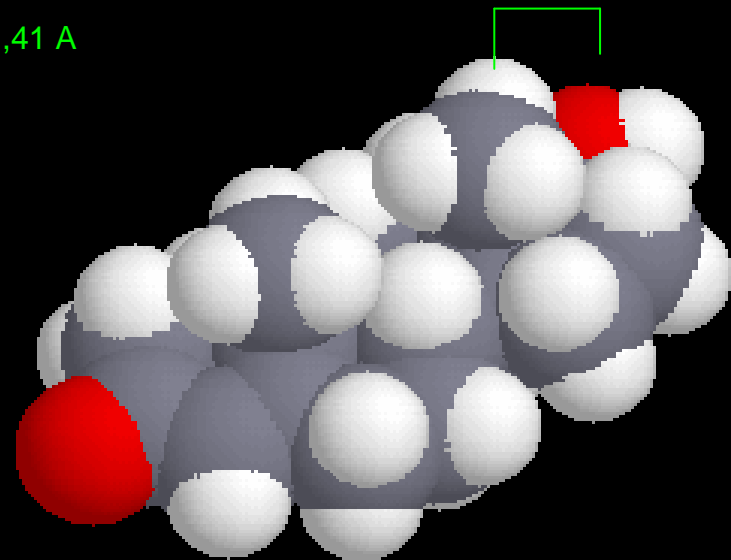


testosterona

Biorreceptores



1,41 Å





Fases da ação dos fármacos

Fase farmacocinética

E. J. Barreiro *et al.*, Estratégias em Química Medicinal para o Planejamento de Fármacos,
Braz. J. Pharm. Sc. 2001, **37**, 269-292.

Biofase

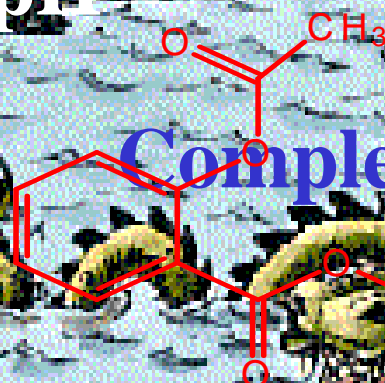
Absorção

Concentração

Meia-vida

Posologia

pH



Complexação plasmática

Deposito tissular

Metabolismo

Eliminação



Fase Farmacocinética

Predicting oral drug absorption

Predicting oral drug absorption

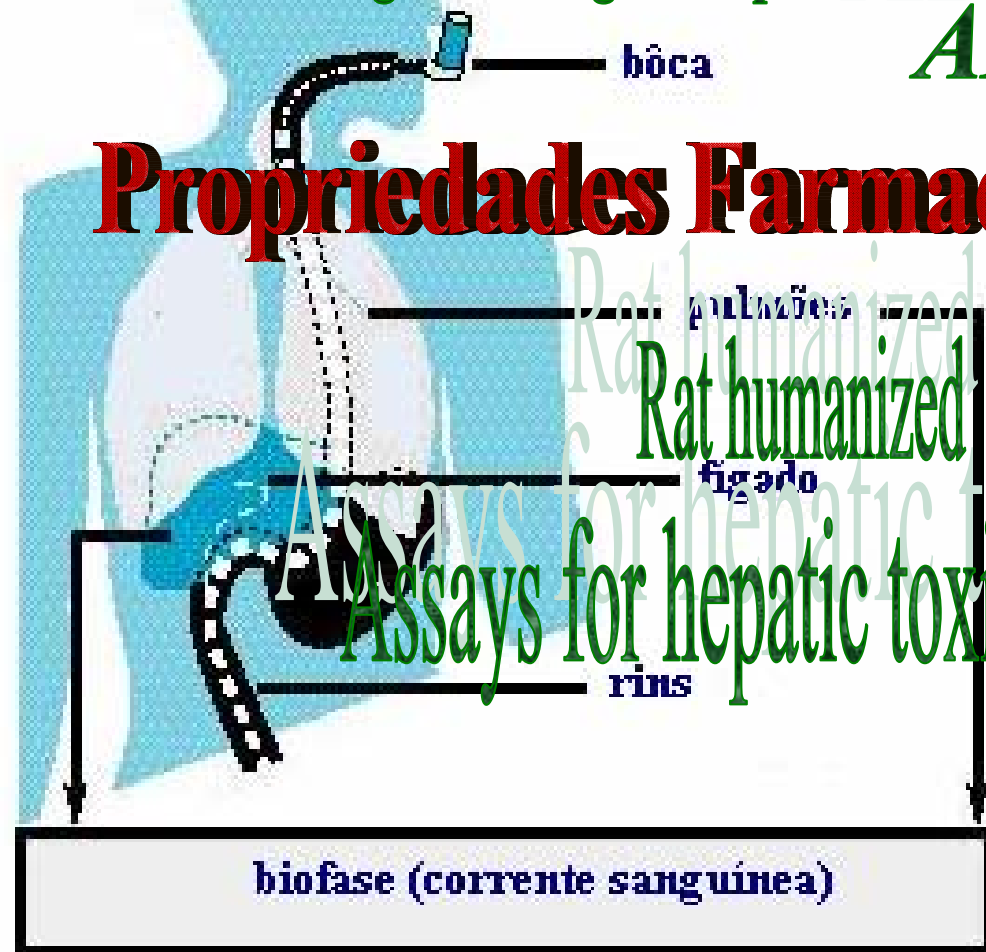
ADME*

ADMET in silico

ADMET in silico

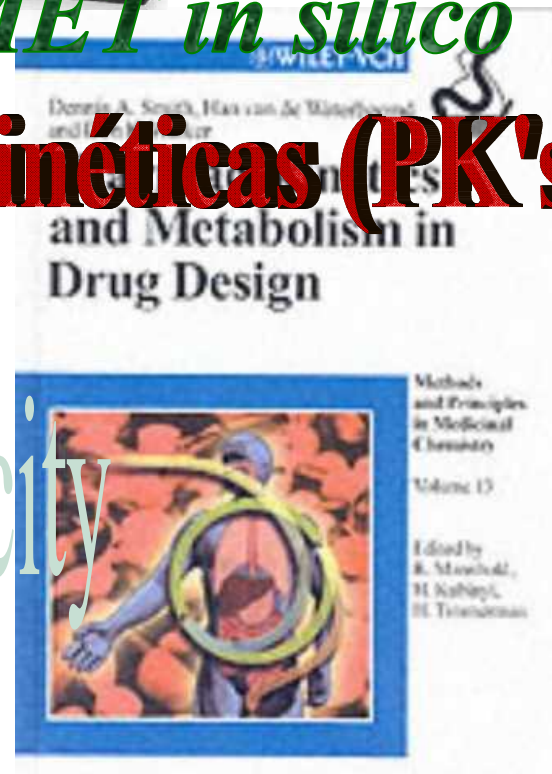


Propriedades Farmacocinéticas (PK's)



Rat humanized

Assays for hepatic toxicity



* absorção, distribuição, metabolismo & eliminação



Drug Metabolism and Disposition:

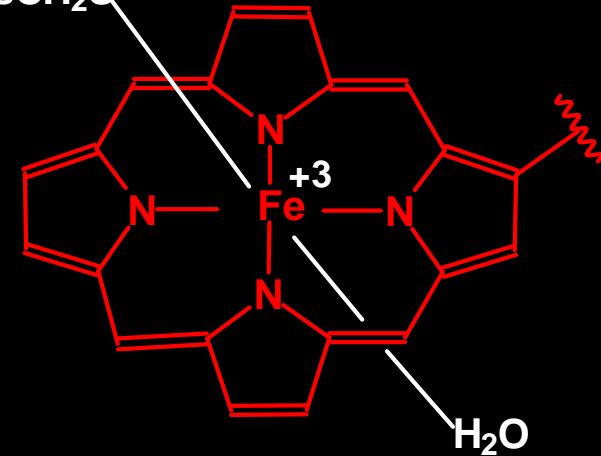
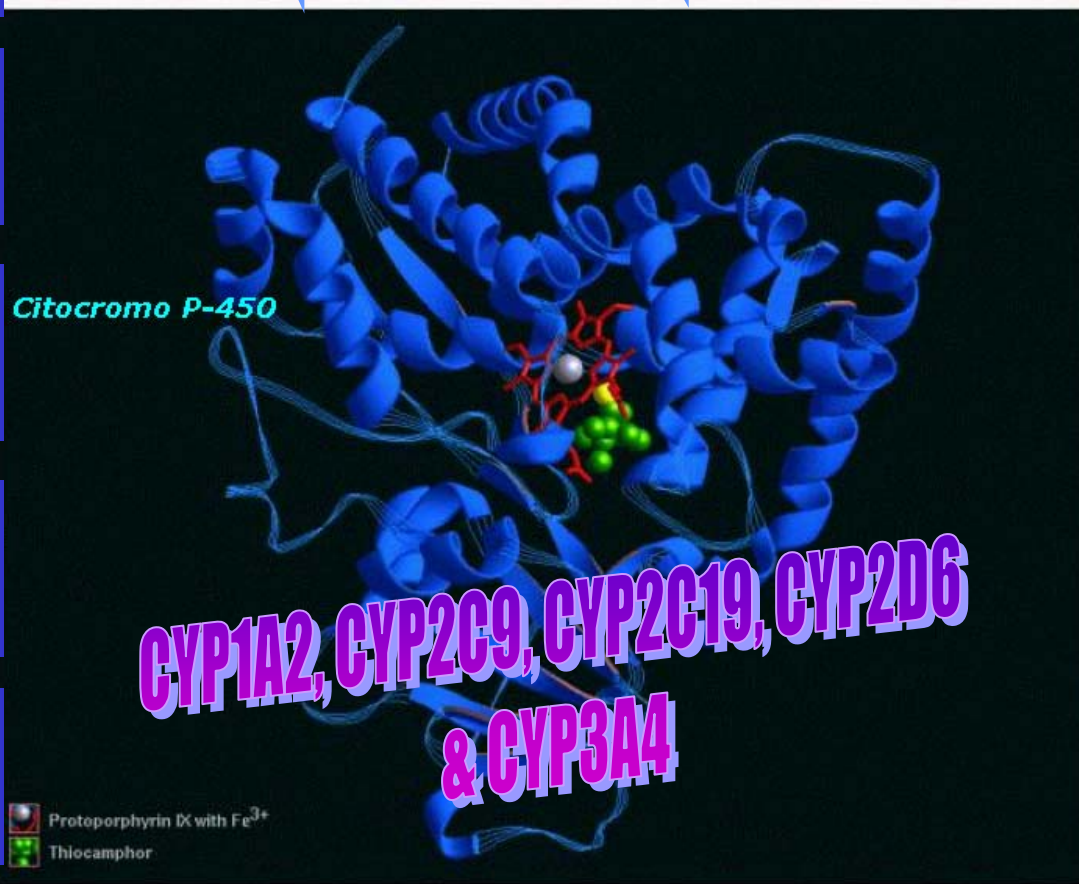
Founded in 1973 by Kenneth C. Leibman

the
biological
fate of
chemicals

**Enzimas
oxidativas**

CYP450

Citocromo P450CysCH₂S



Idade
Sexo
Raça

Polimorfismo

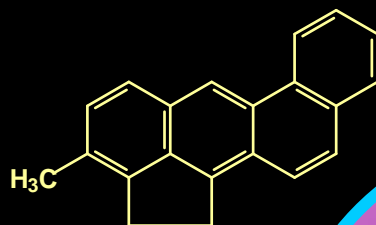
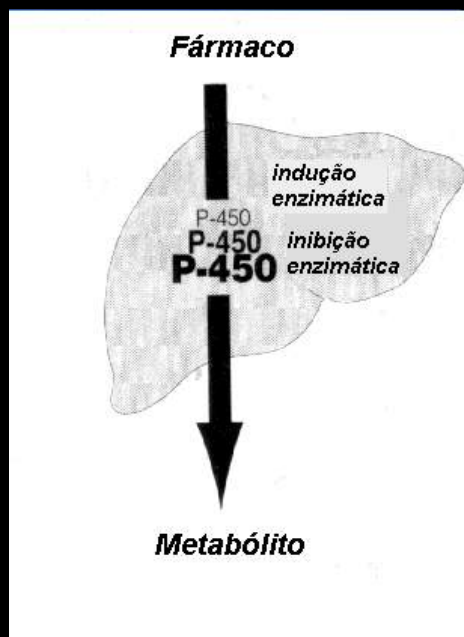
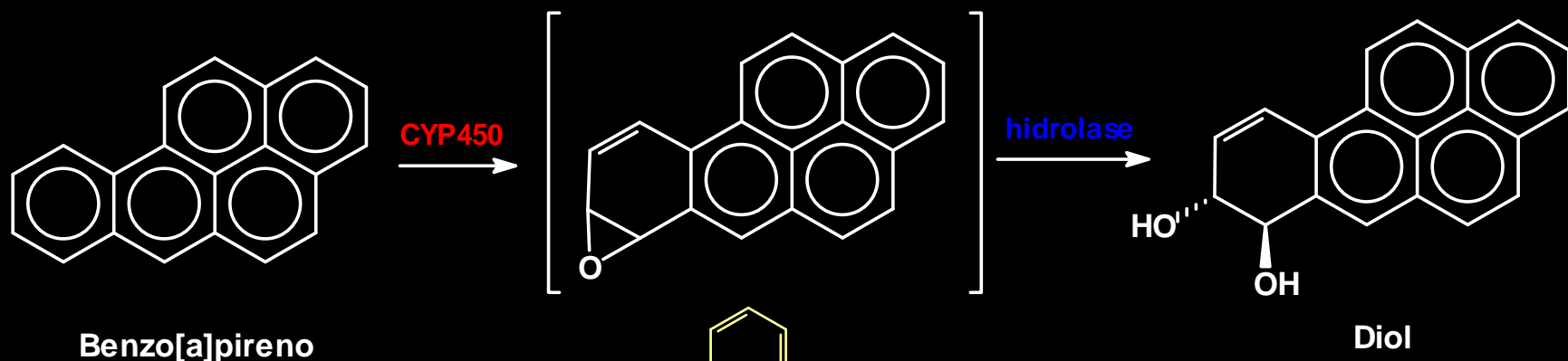
**Isoformas
(24)
CYP2C18**

Interação medicamentosa

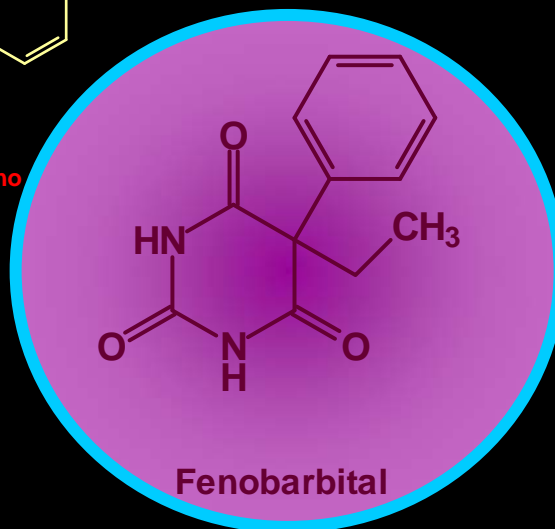
Indução / Inibição



Indutores Enzimáticos: Sistema P450



3-metilcolantreno
420, 426 nm

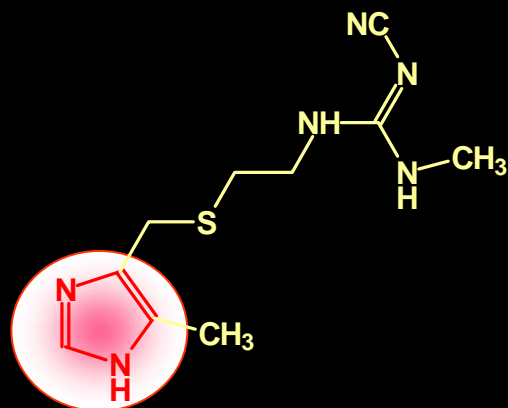
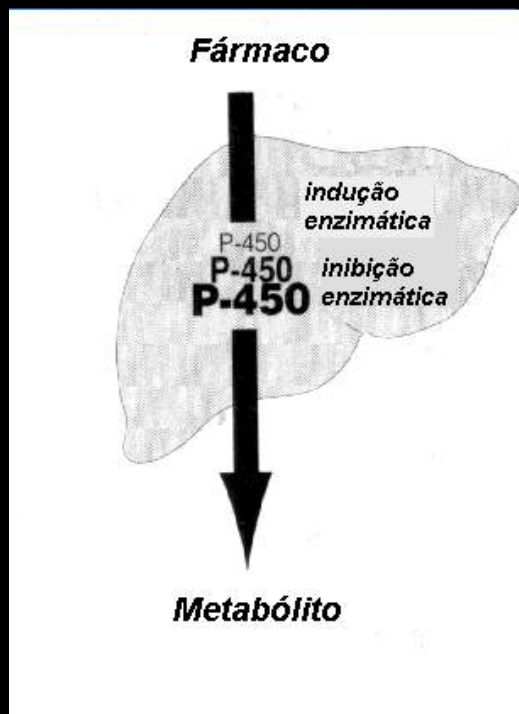


Fenobarbital

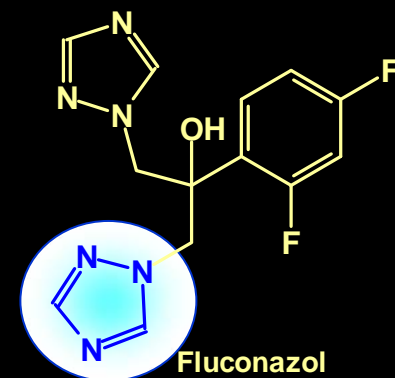
Aumentam a metabolização de fármacos
→ **reduz a meia-vida e o nível plasmático**



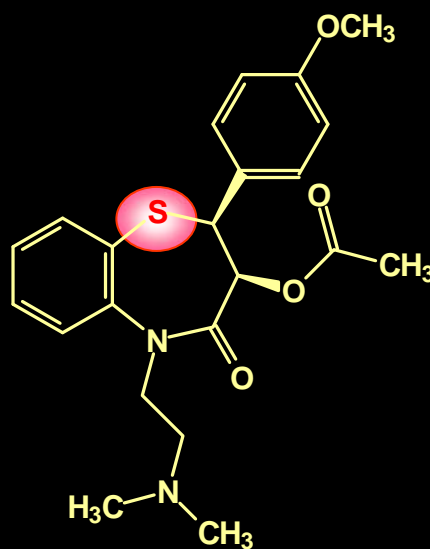
Inibidores do CYP450



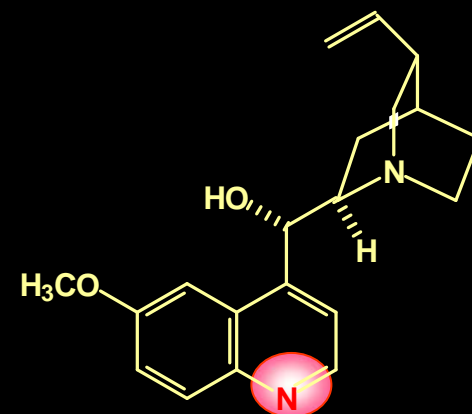
Cimetidina



Fluconazol



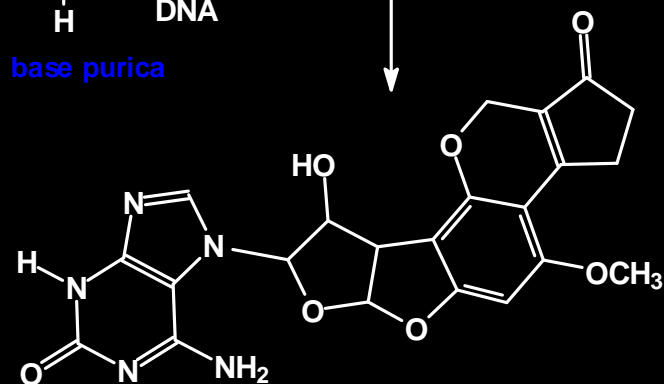
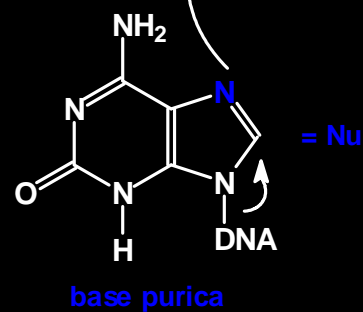
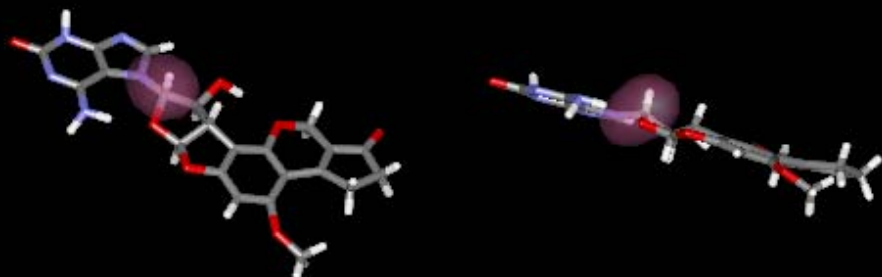
Diltiazem



Quinidina

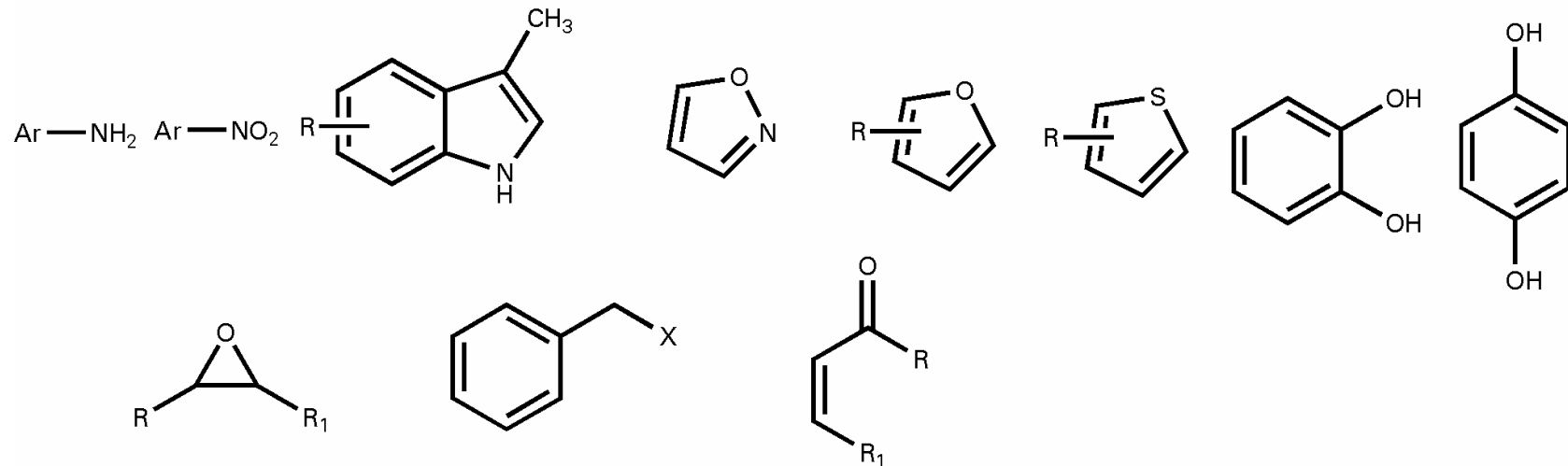
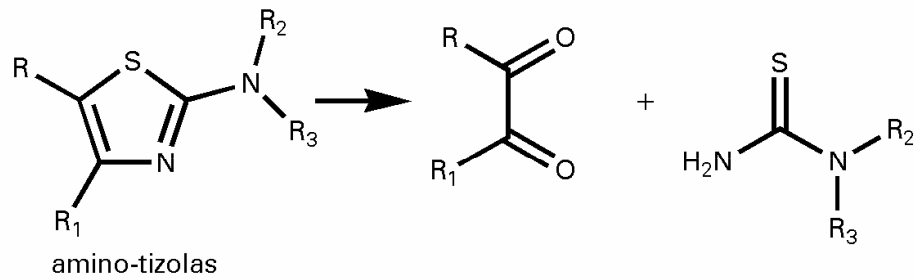
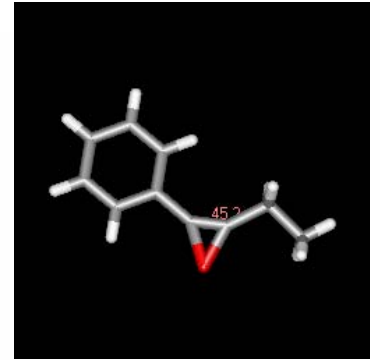
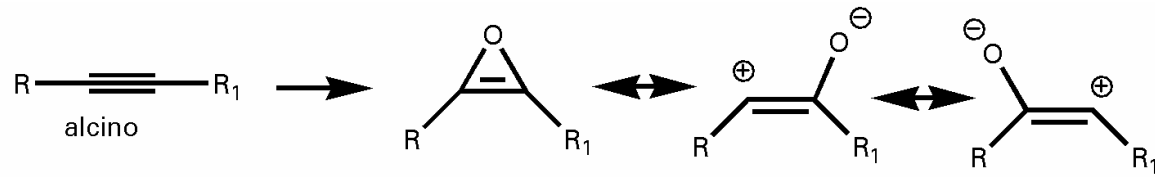


Planaridade do aduto





Grupamentos toxicofóricos



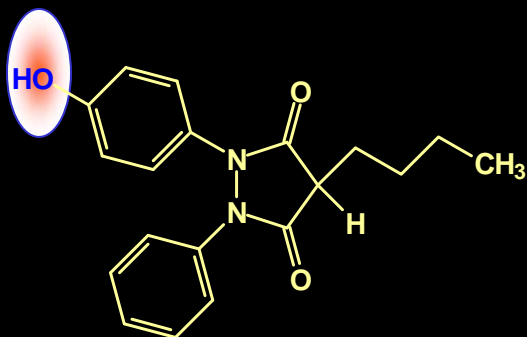
$\text{R}, \text{R}_1, \text{R}_2, \text{R}_3 = \text{H}, \text{alquila}, \text{cicloalquila}, \text{arila}, \text{heteroarila}$
 $\text{X} = \text{grupo abandonador}$



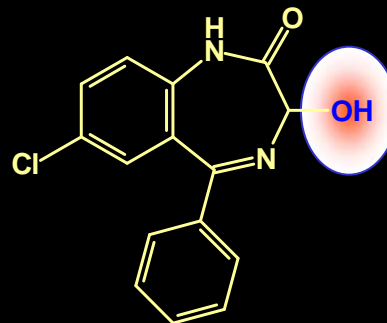
Fármacos

Descobertos pelo Estudo

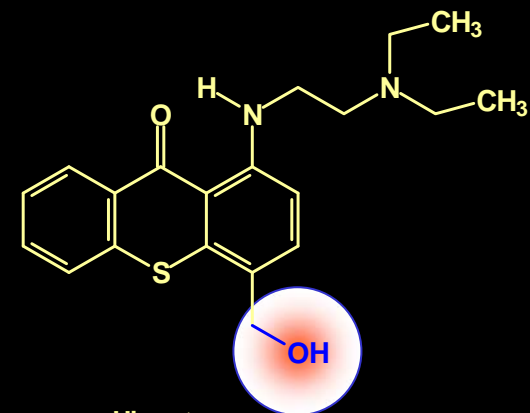
do Metabolismo



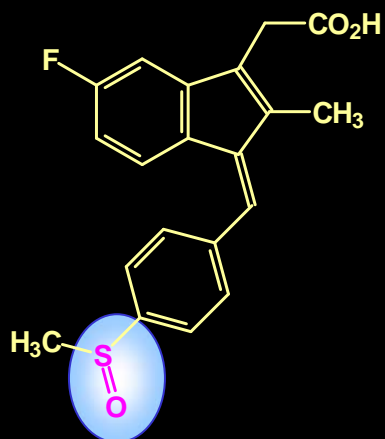
Oxifenilbutazona



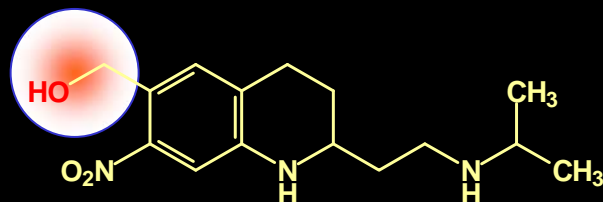
Oxazepam



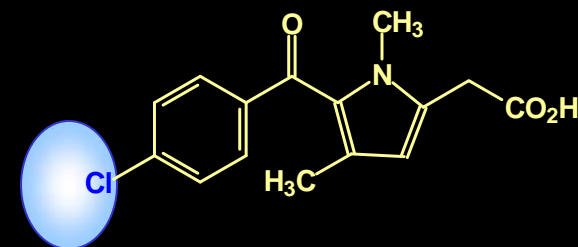
Hicantona



Sulindac

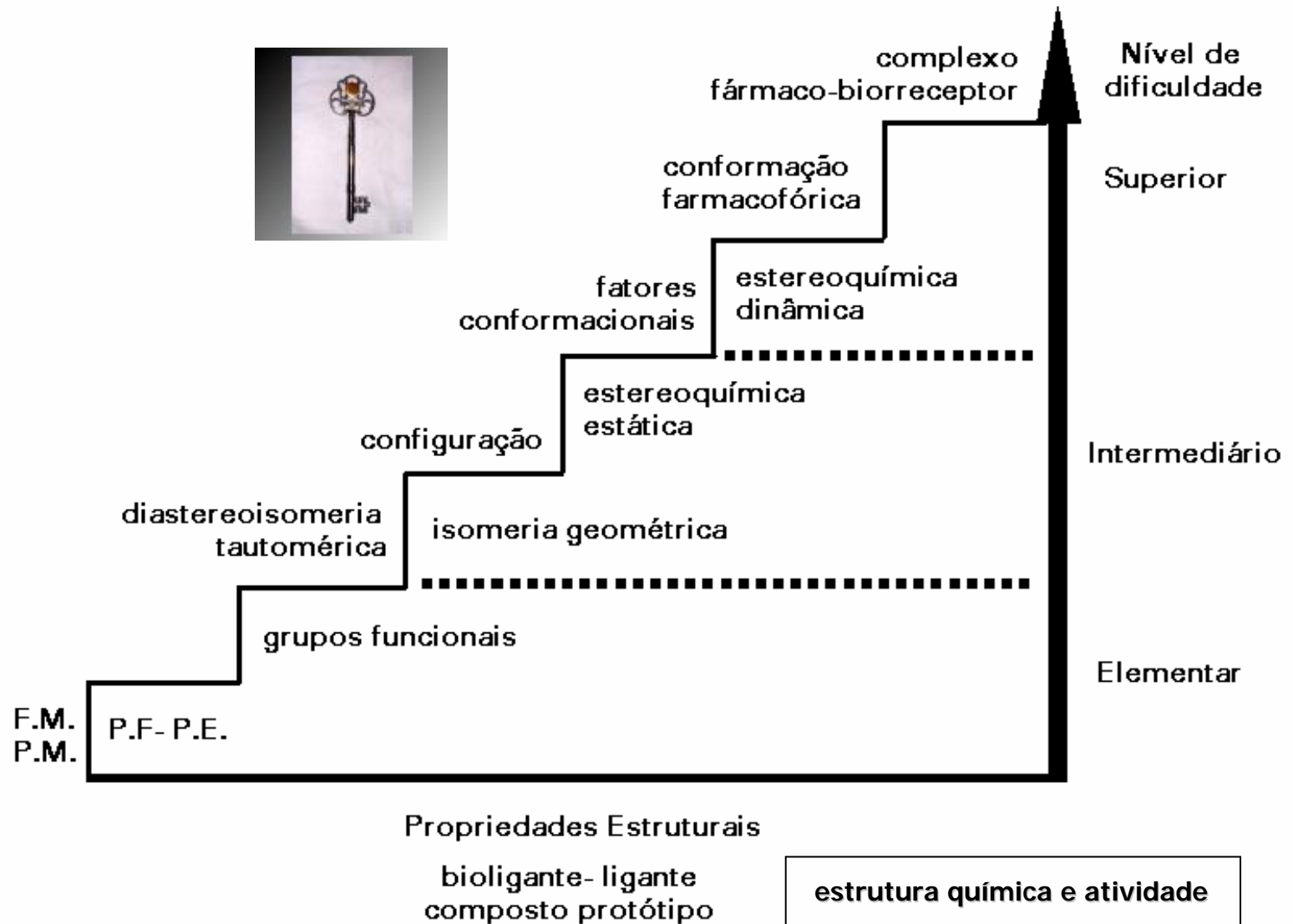


Oxaminiquina



Zomepirac

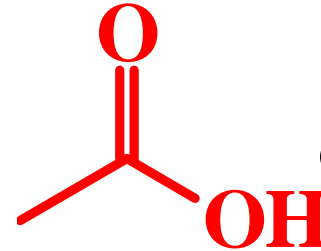
A relação entre estrutura química e propriedade



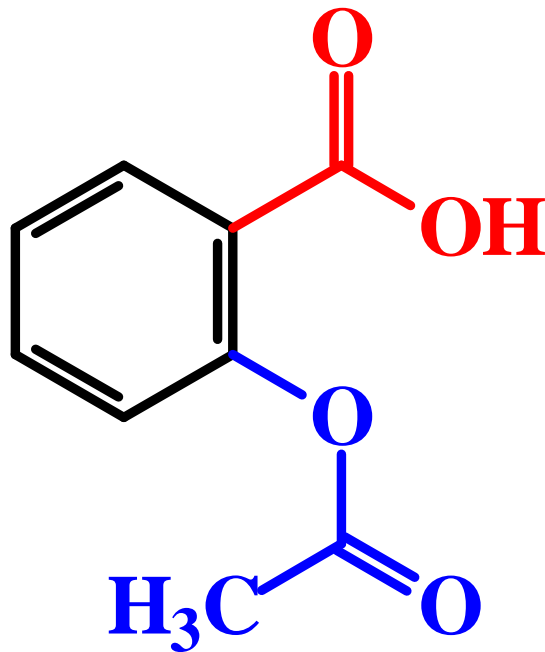


Dissecação Molecular

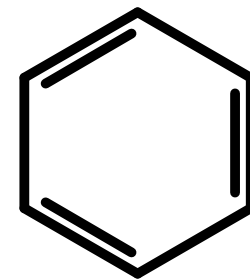
Pontos farmacofóricos



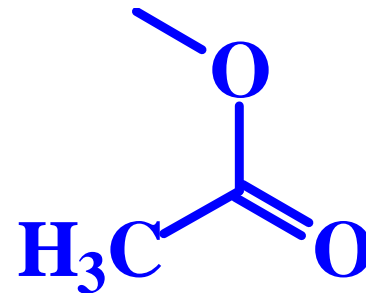
ácido carboxílico



Ácido acetil-salicílico

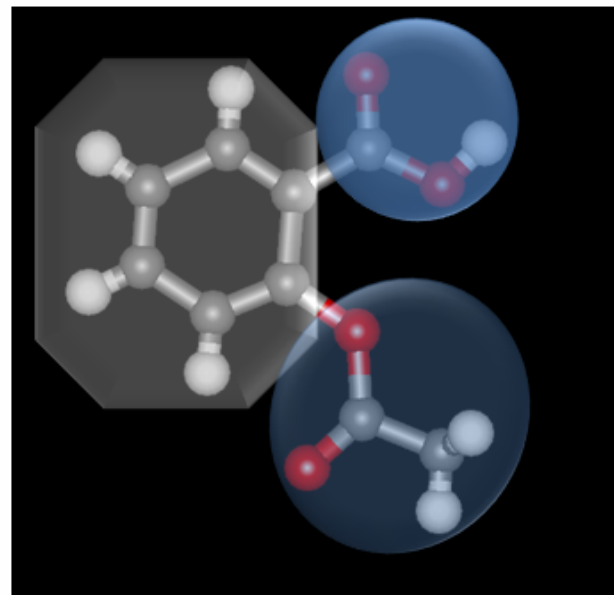
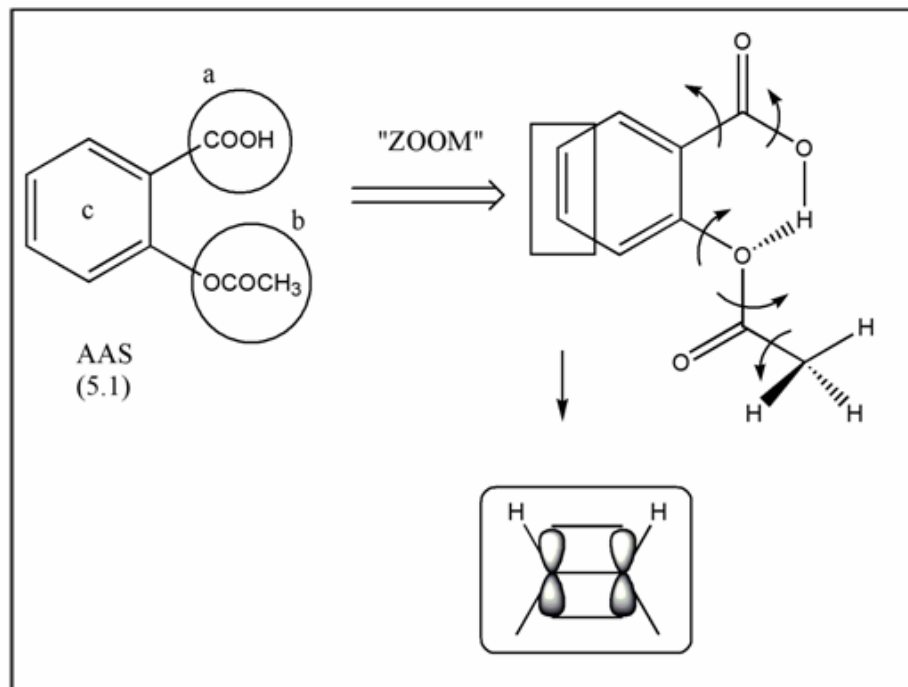


fenila

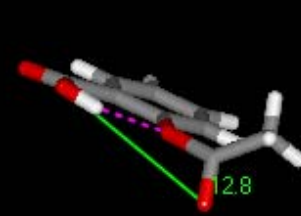
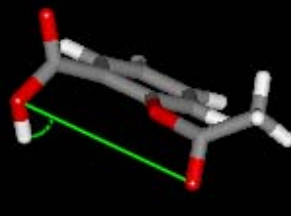
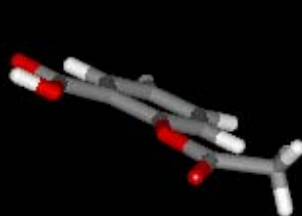
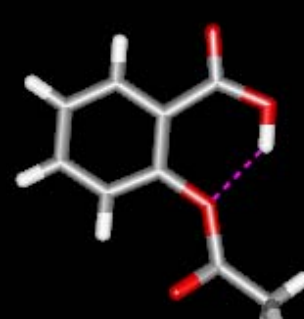
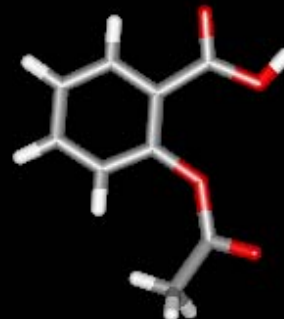
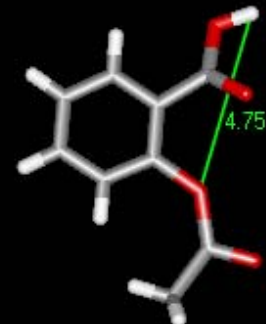
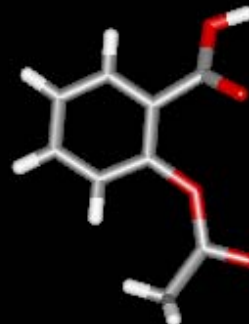
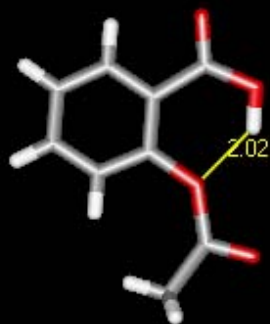
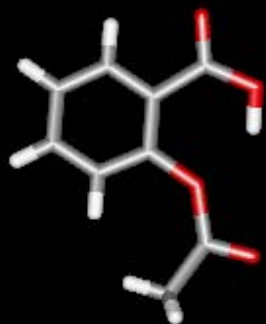


éster

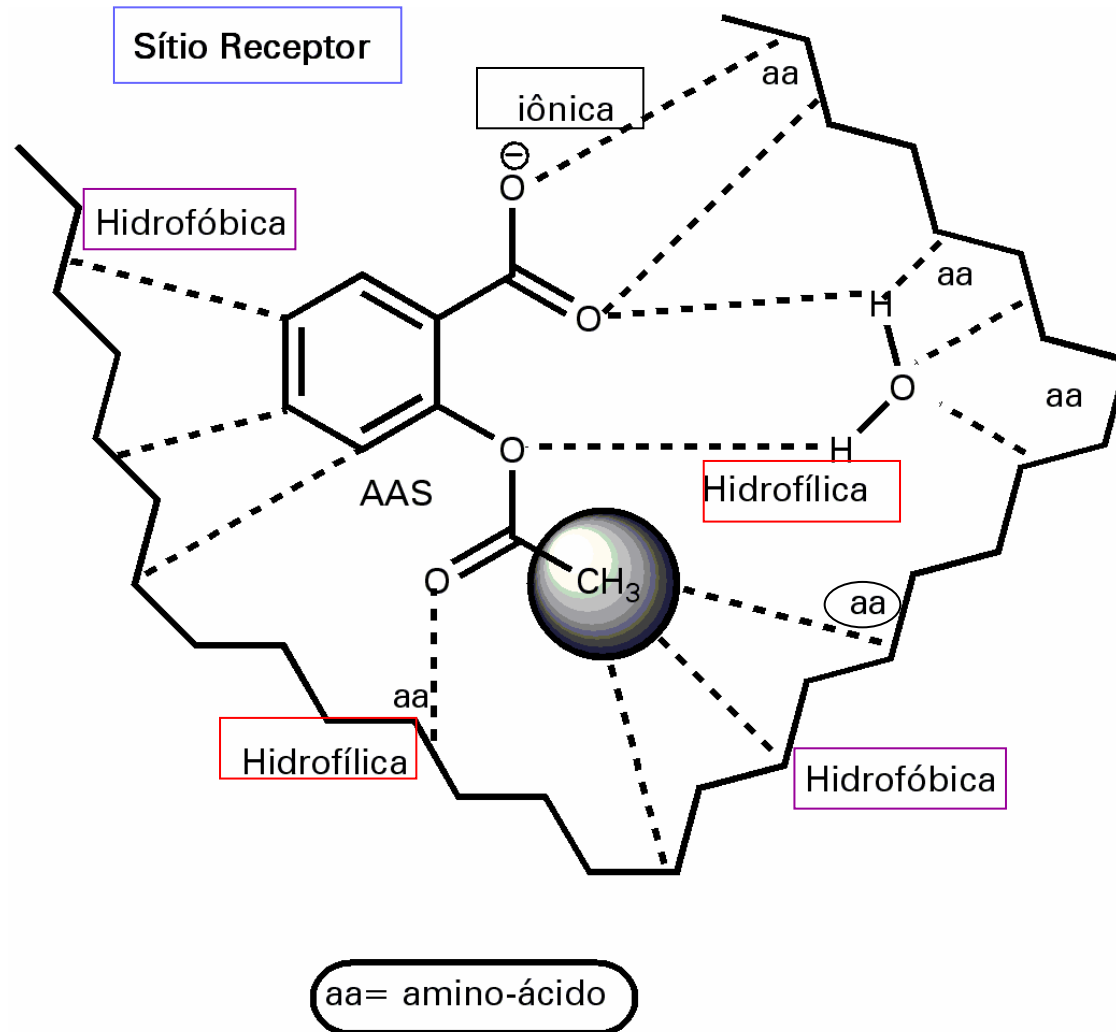
A tática de dissecação molecular: identificação de *pontos farmacofóricos*



A tática de dissecação molecular & equilíbrio conformacional



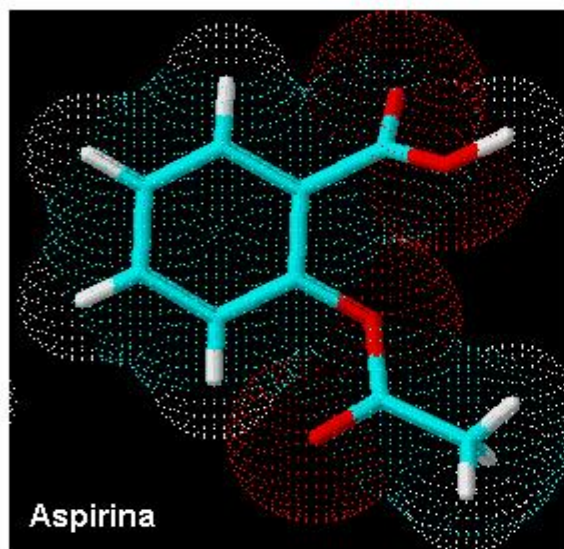
Modêlo topográfico das interações AAS-R



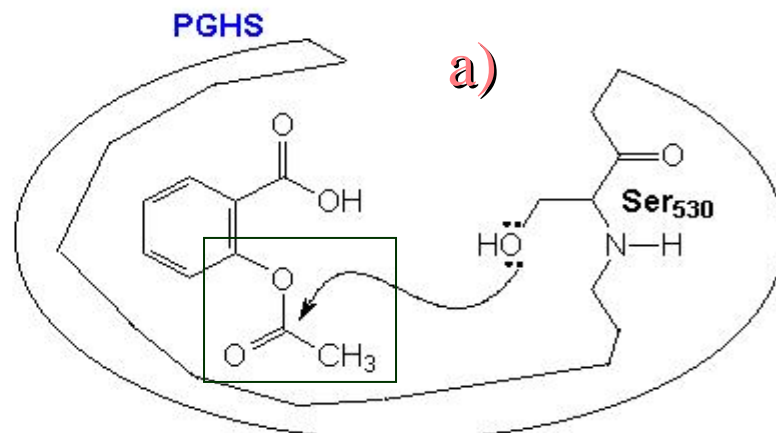
Pontos farmacofóricos e as interações com o sítio biorreceptor



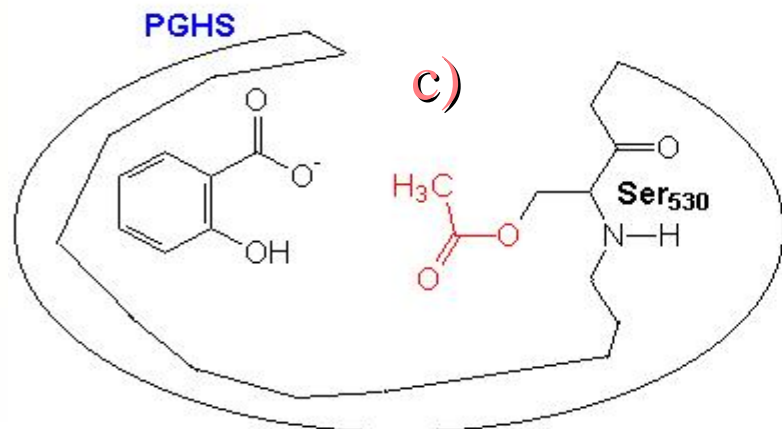
AAS



Mecanismo molecular



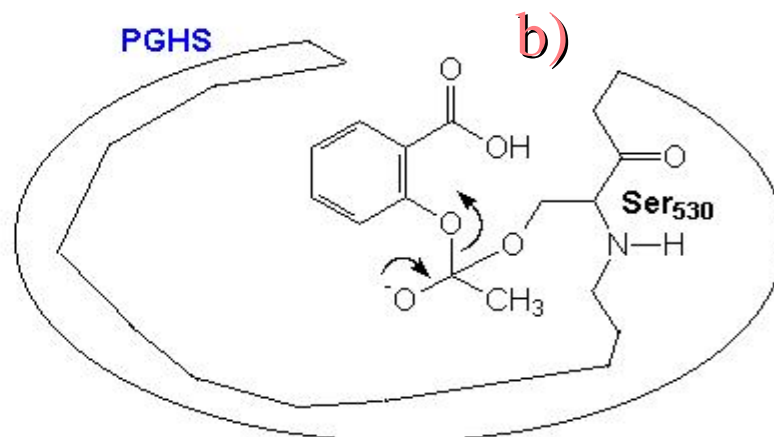
Grupo farmacofórico



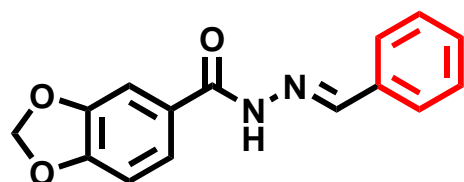
Inibição *pseudo-irreversível*



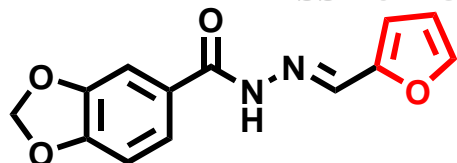
ácido araquidônico



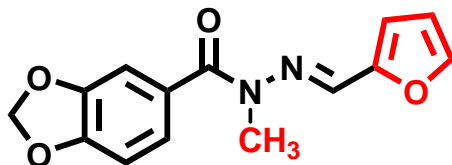
Dissecação Molecular no desenho de série congênere



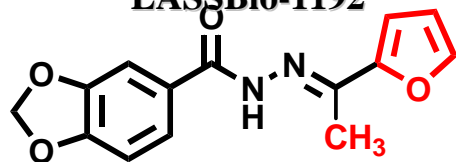
LASSBio-123



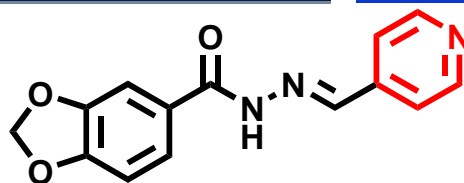
LASSBio-129



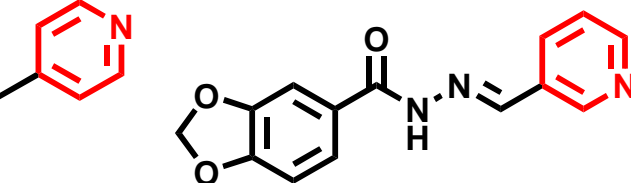
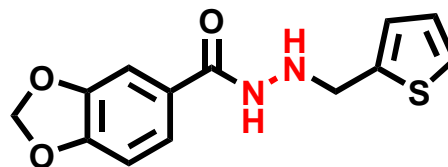
LASSBio-1192



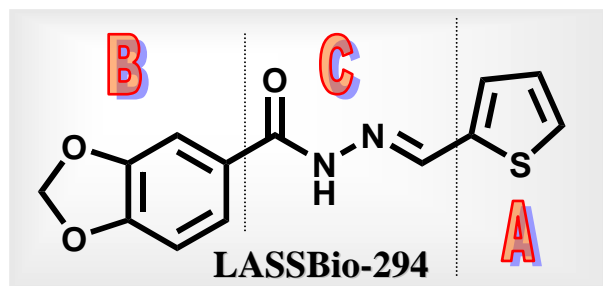
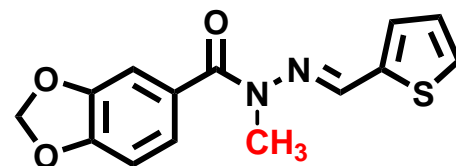
LASSBio-1099



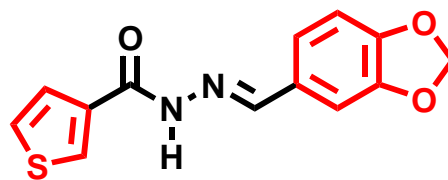
LASSBio-791



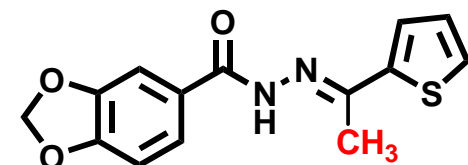
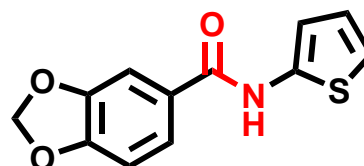
LASSBio-785
 $IC_{50} = 10,2 \mu M$



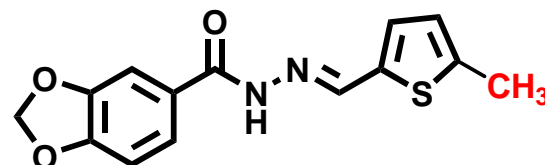
LASSBio-294
(VD) $IC_{50} = 74,0 \mu M$



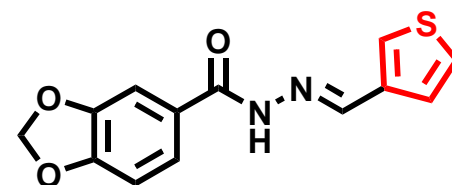
LASSBio-294



LASSBio-1029



LASSBio-787

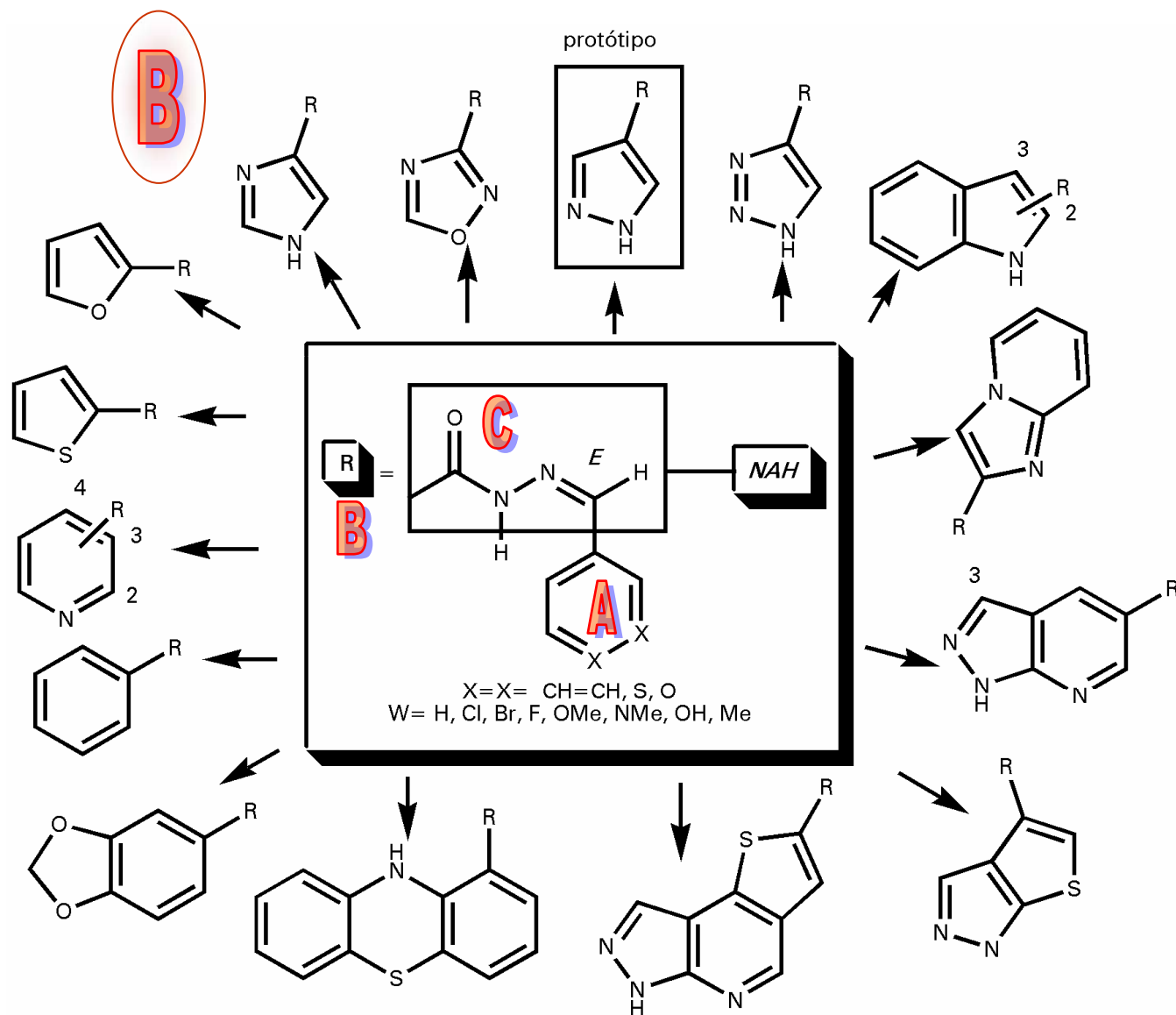


LASSBio-1027

Bioorganic Medicinal Chemistry 2005, 13, 3431

Patente BR PI0403363 9

Série
Congénère

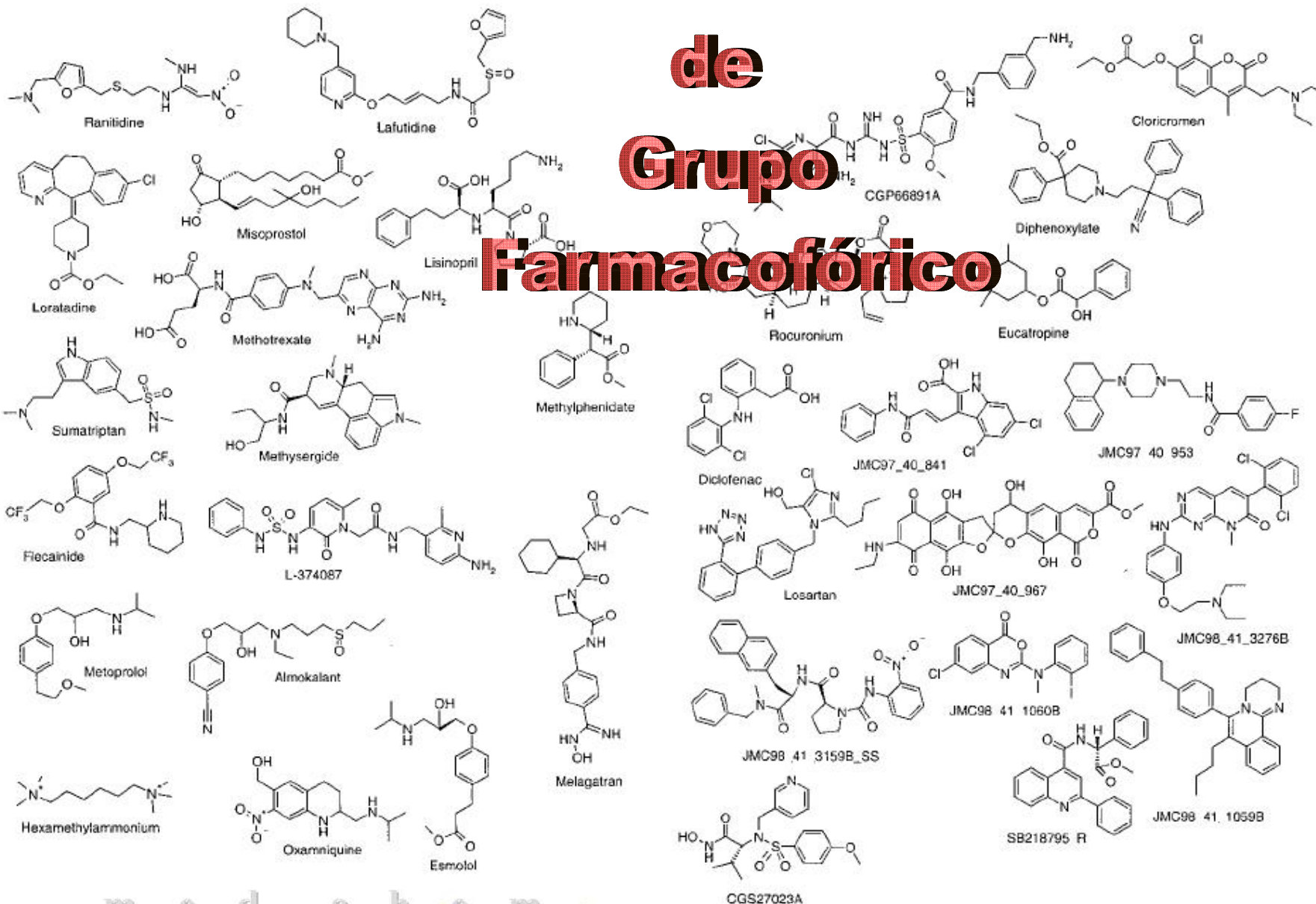


Conceito

de

Grupo

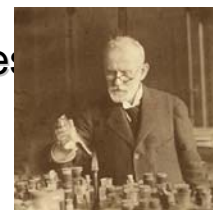
Farmacofórico





Conceito de Grupo Farmacofórico

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



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

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



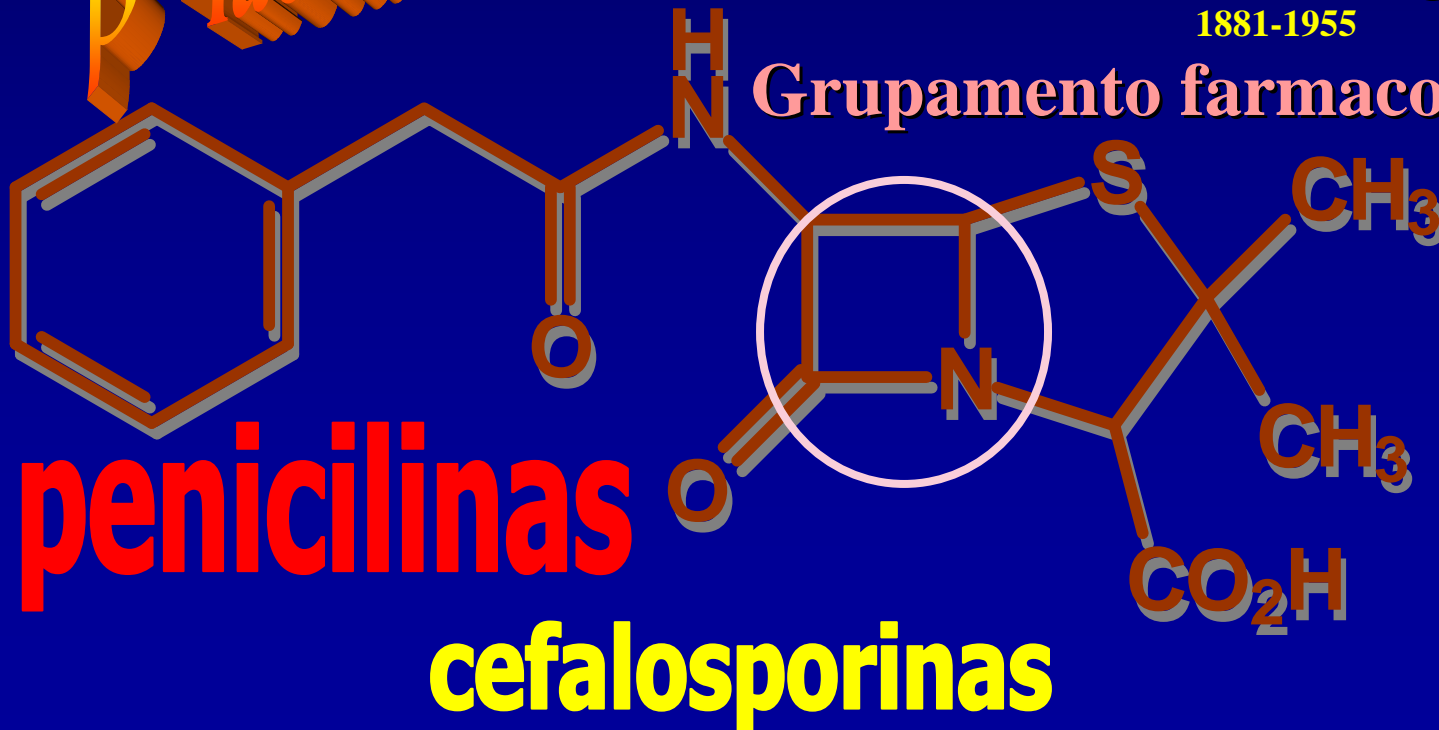
Barreiro & Fraga: É o conjunto de características eletrônicas e estéricas que caracterizam um ou mais grupos funcionais ou subunidades estruturais, necessários ao melhor reconhecimento molecular pelo receptor e, portanto, para o efeito farmacológico desejado. Farmacóforo não é uma molécula real, nem associações de grupos funcionais; ao contrário, é um conceito abstrato que representa as diferentes capacidades de interações moleculares de um grupo de compostos com o sítio receptor. O farmacóforo pode ser considerado como a "parte" molecular do fármaco essencial à atividade desejada.



Antibioticoterapia

Moléculas Salva-vidas

β -lactâmicos



E. B. Chain

1906-1979

1945 Nobel



Sir A. Fleming

1881-1955



Sir H. W. Florey

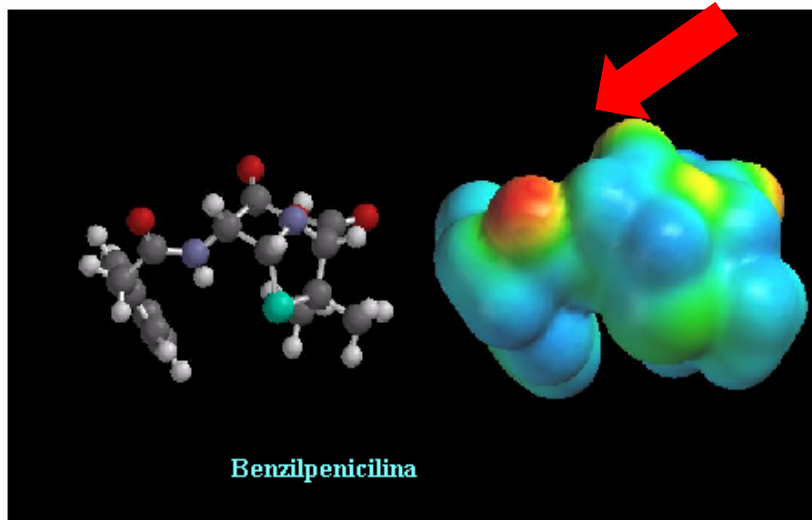
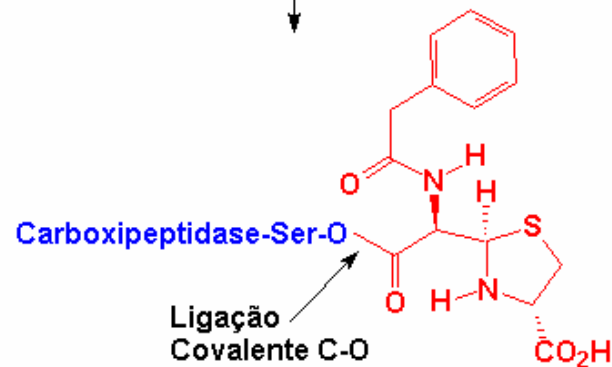
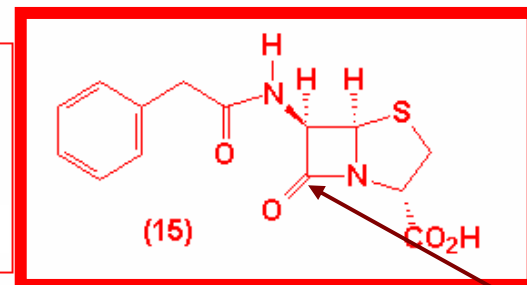
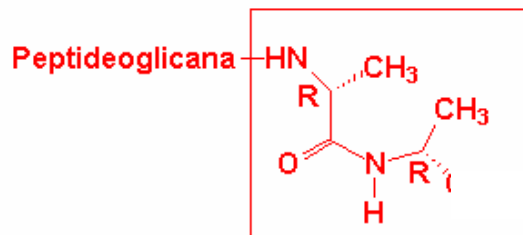
1898-1968



Grupamento farmacofórico

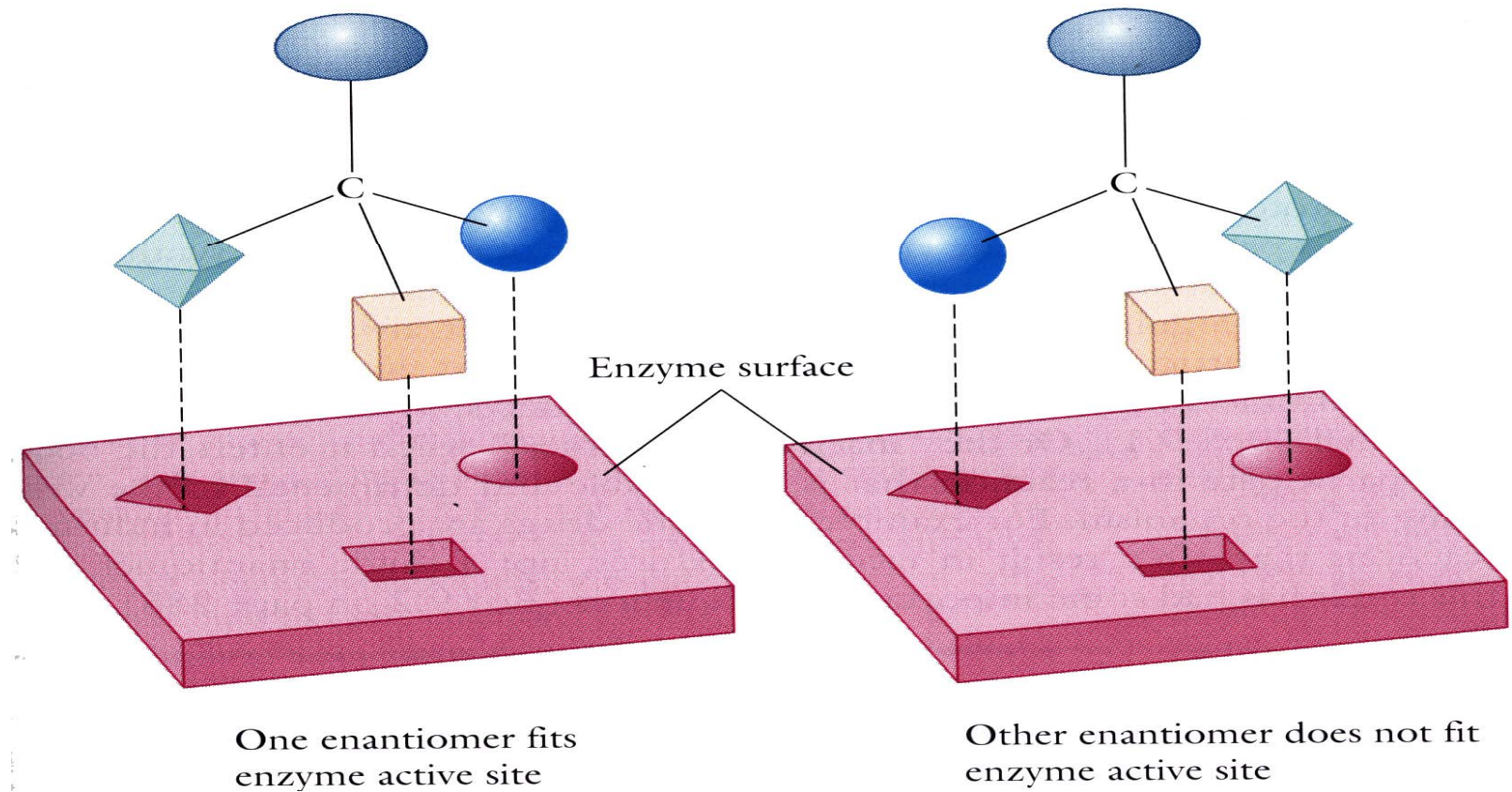


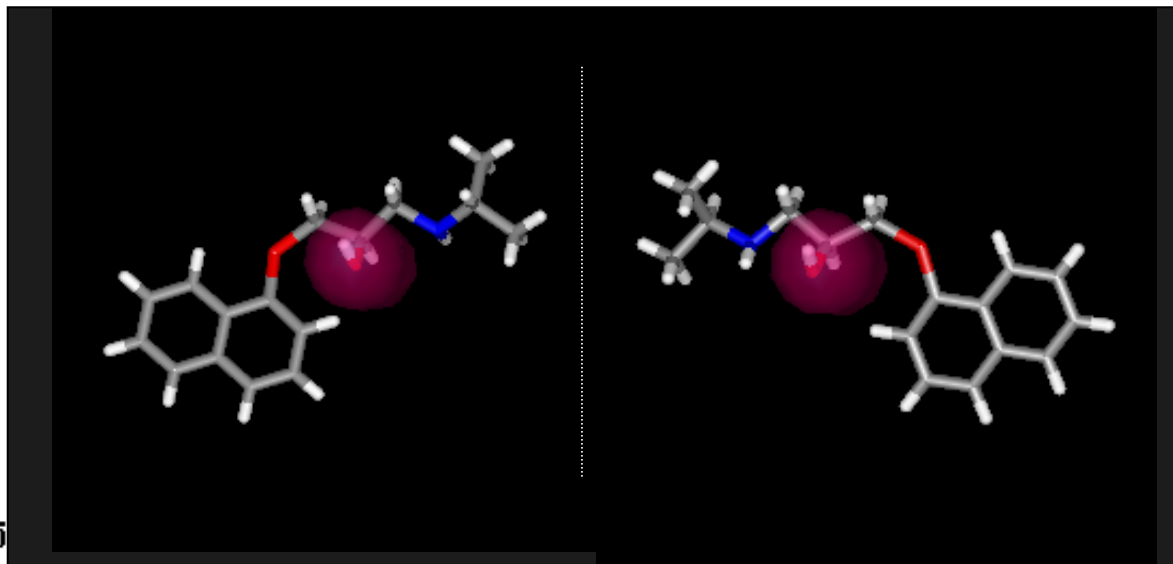
Mecanismo Molecular da Ação dos Antibióticos beta-lactâmicos



Modelo dos três pontos

Modelo de Easson-Stedman

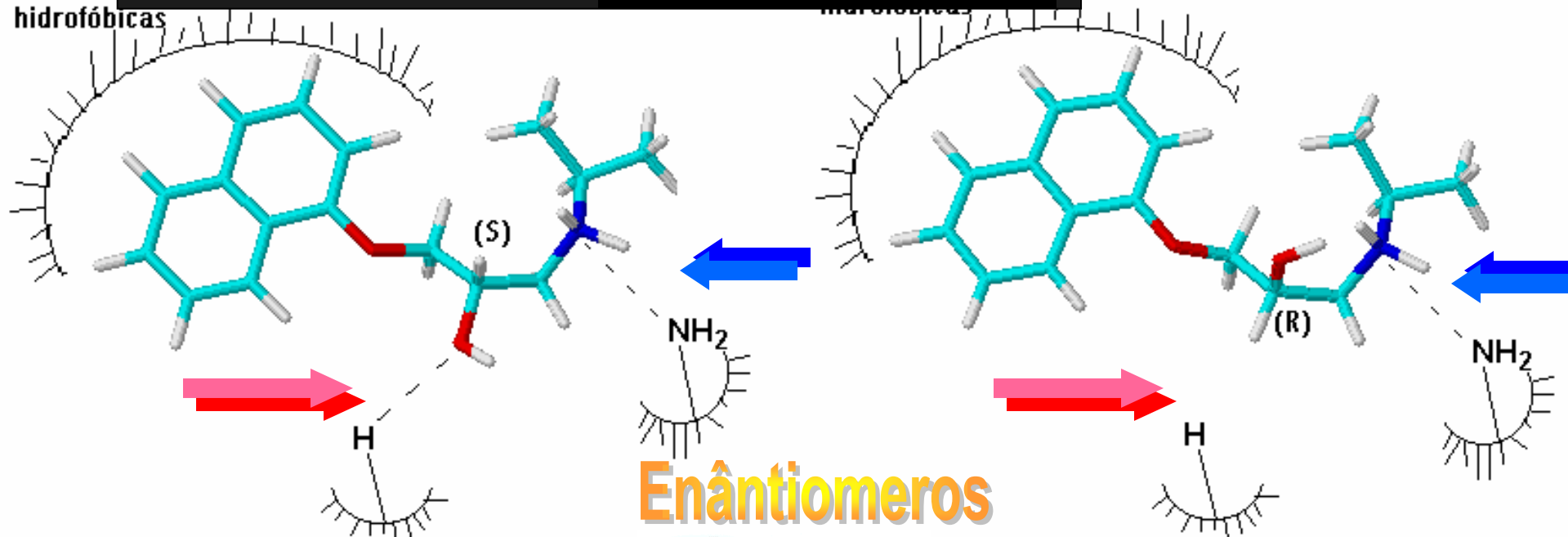




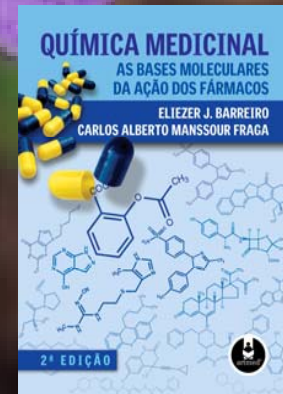
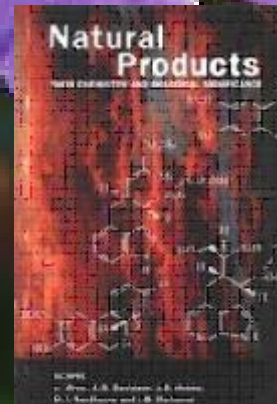
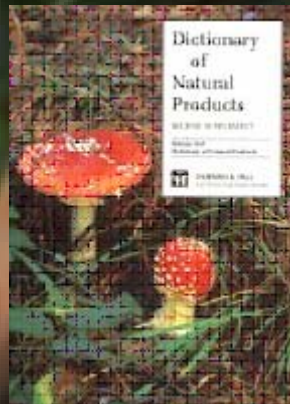
Eutômero
Distômero

Índice eudísmico

Interação
hidrofóbicas



Descoberta de Fármacos: O Papel dos Produtos Naturais



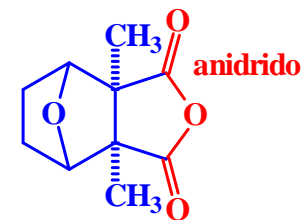
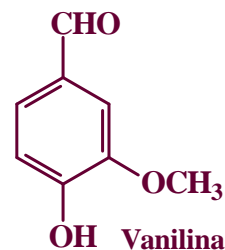


Produtos Naturais Afrodisíacos

J. Chem. Ed. 1980, 57, 341

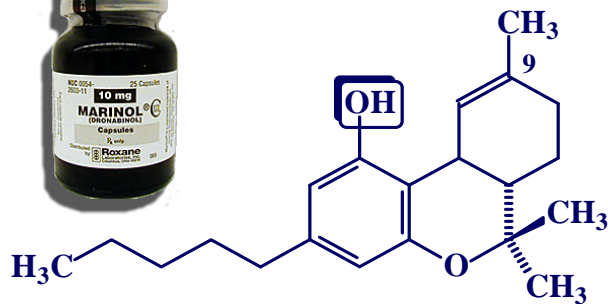
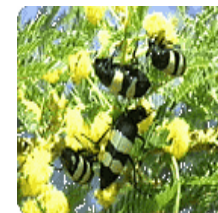
T. G. Waddell, H. Jones & A.L. Keith

“... the well known flavoring substances which has unquestionable aphrodisiac qualities...”. In: *Herbal Aphrodisiacs*, Cal., USA, 1971



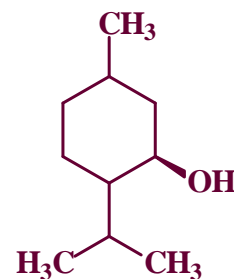
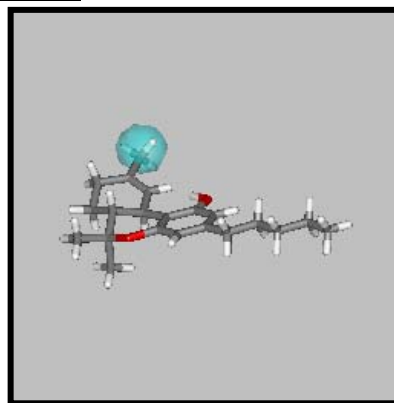
Cantaridina

Cantharis vesicatorica



THC

Canabis sativa



Mentol

Volátil



cafeína



AFRODISIACOS

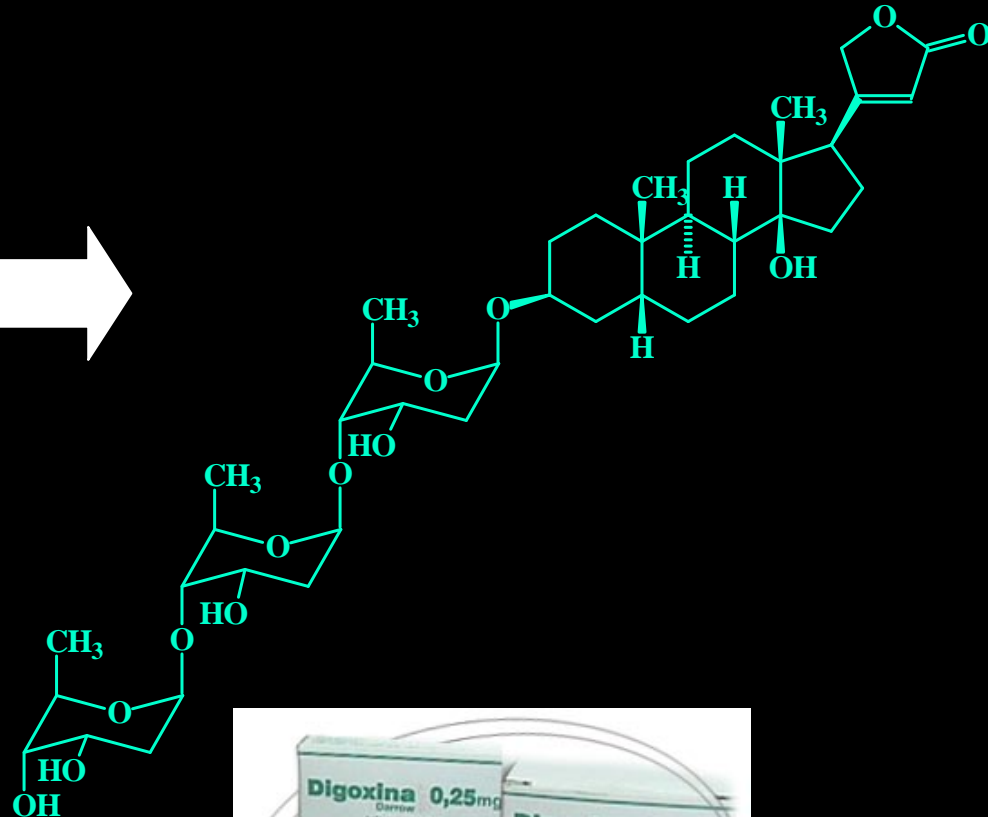
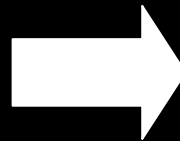
Photo Henriette Kress



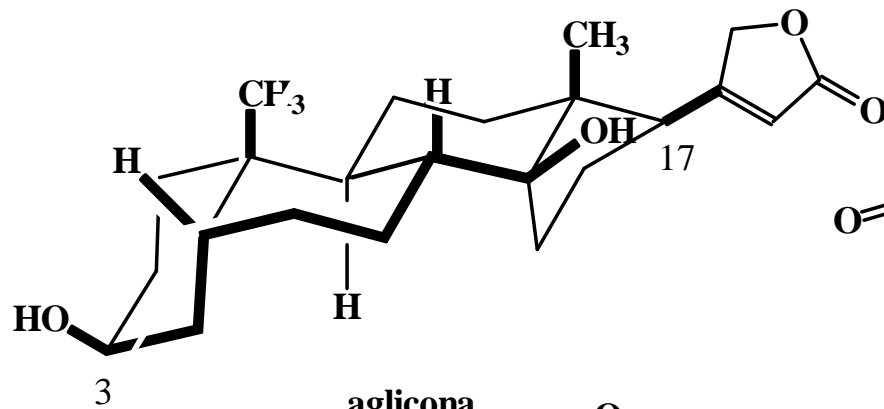
Digitalis purpurea

terpenos, alcalóides,
esteróides, flavonóides

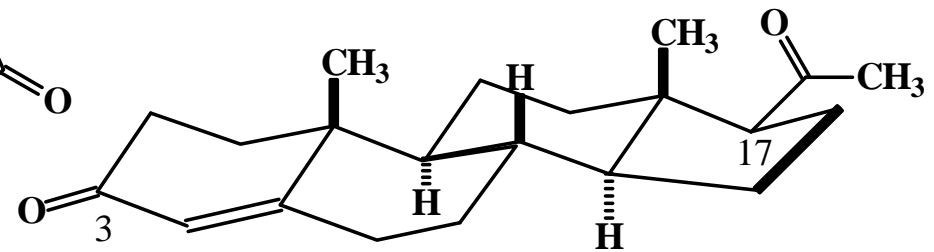
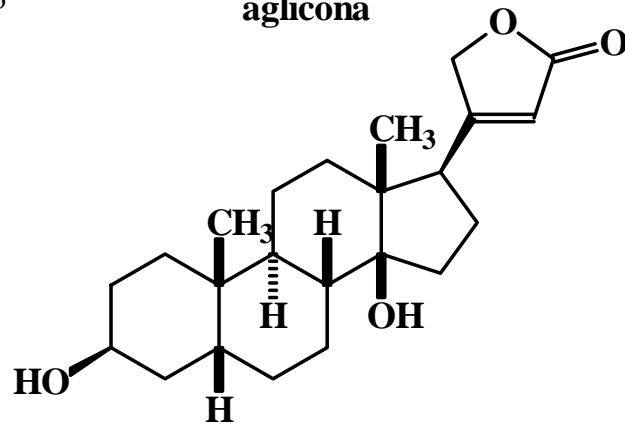
Glicosídeos Cardiotônicos



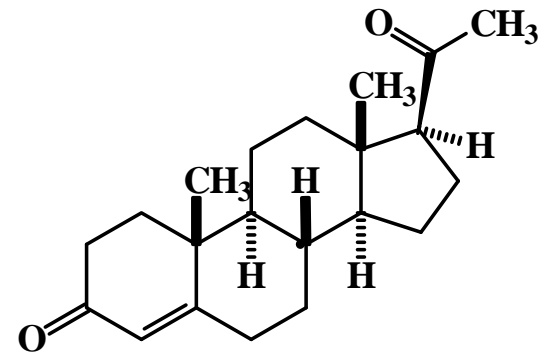
Decano dos Fármacos



aglicona



progesterona



A Importância da Conformação

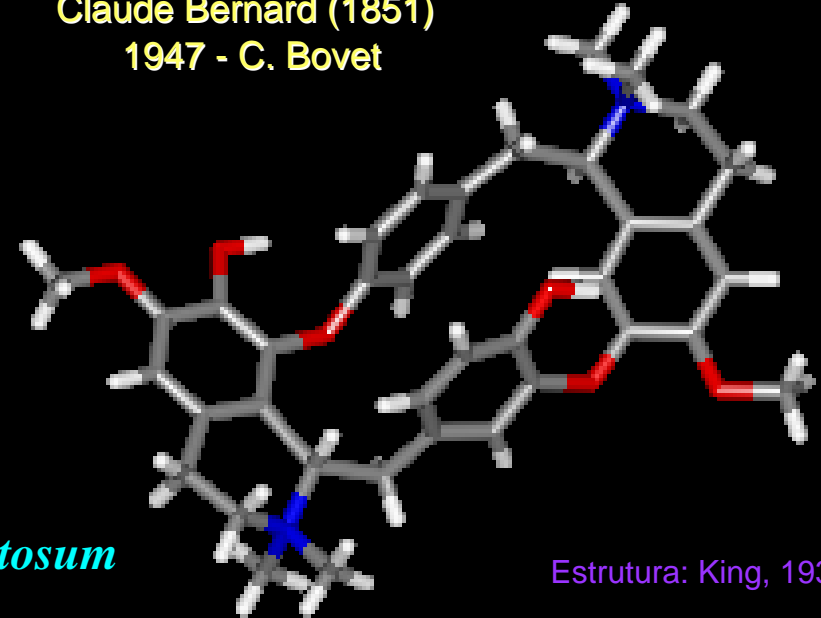


Fármaco dos Índios



Bloqueadores ganglionares

Institute Pasteur
Claude Bernard (1851)
1947 - C. Bovet



Estrutura: King, 1935

d-tubocurarina

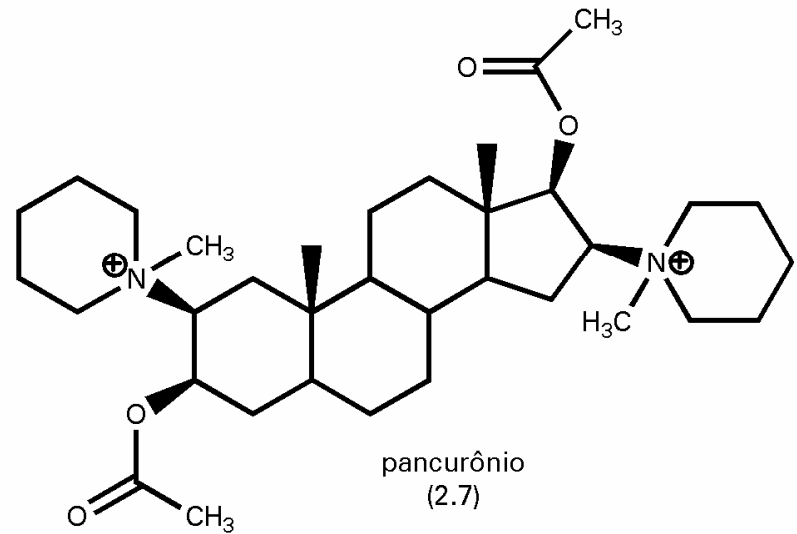
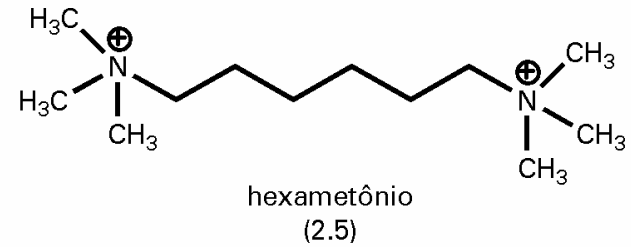
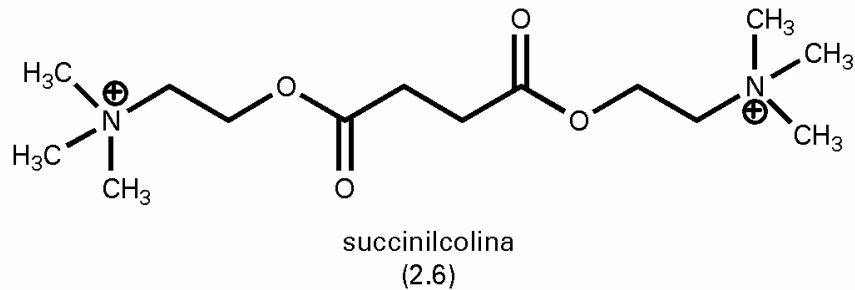
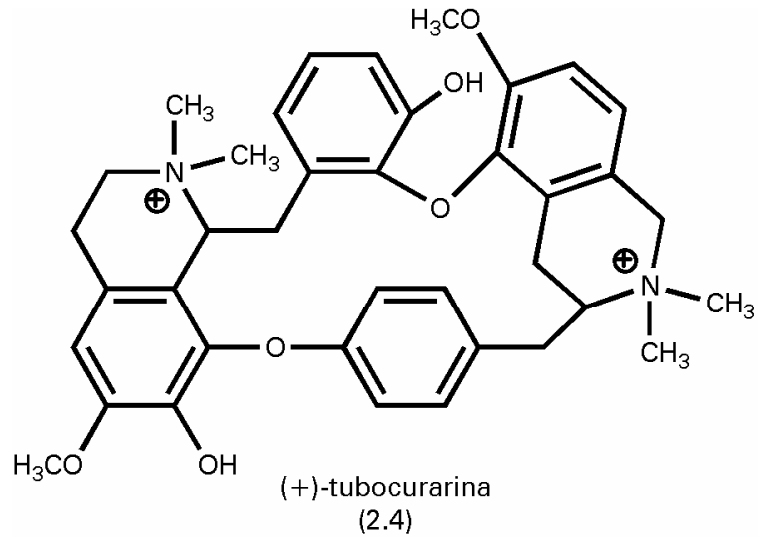


Chondrodendron_tomentosum





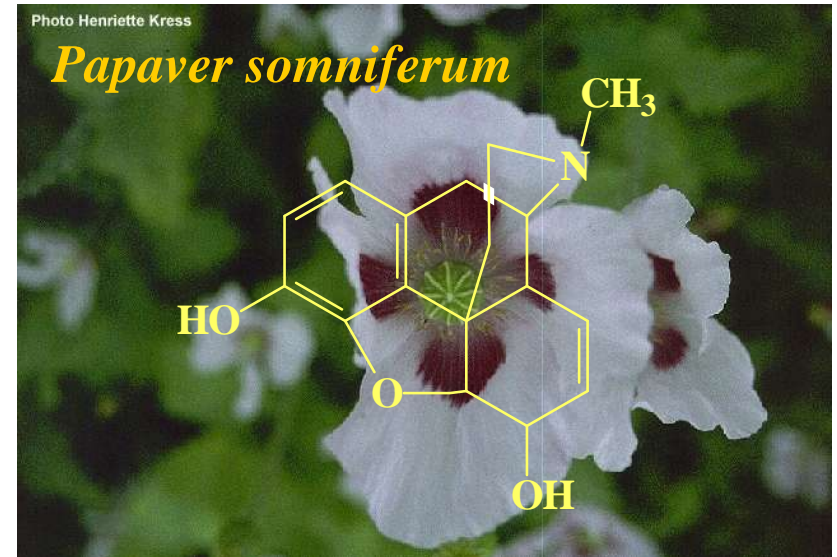
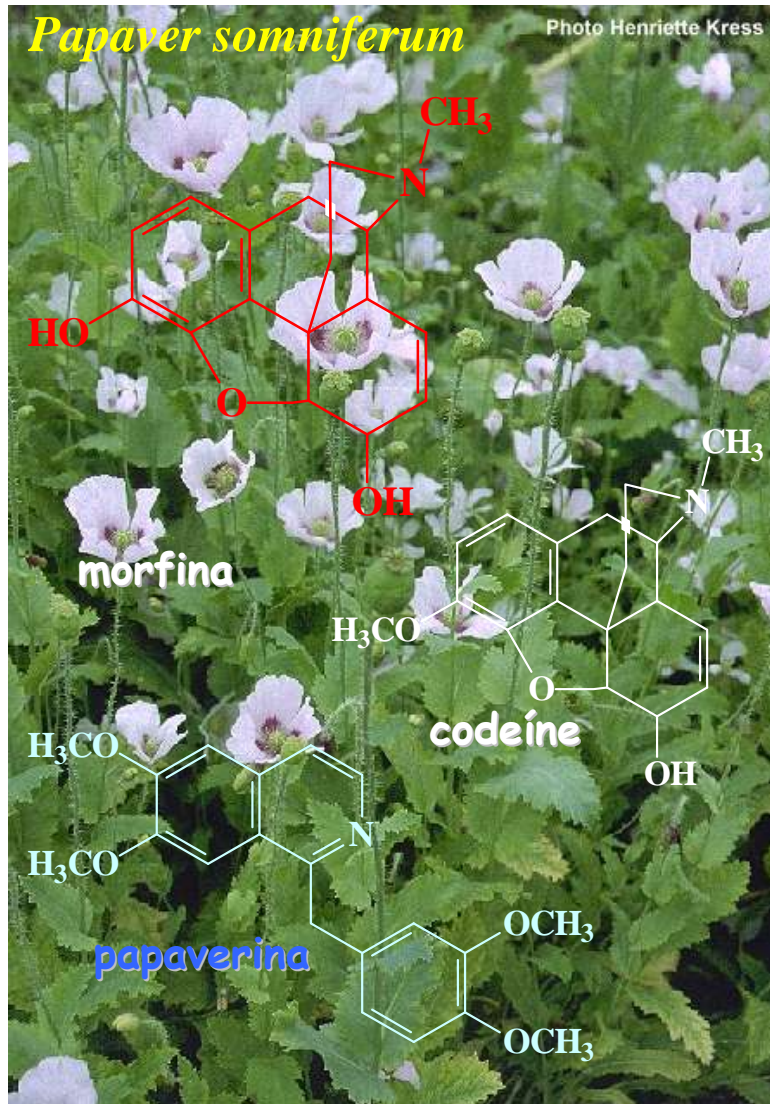
Bloqueadores ganglionares





Produtos Naturais: Morfina

Alcalóides fenantrênicos e
benzilisoquinolínicos
(papaverina 0,2%)



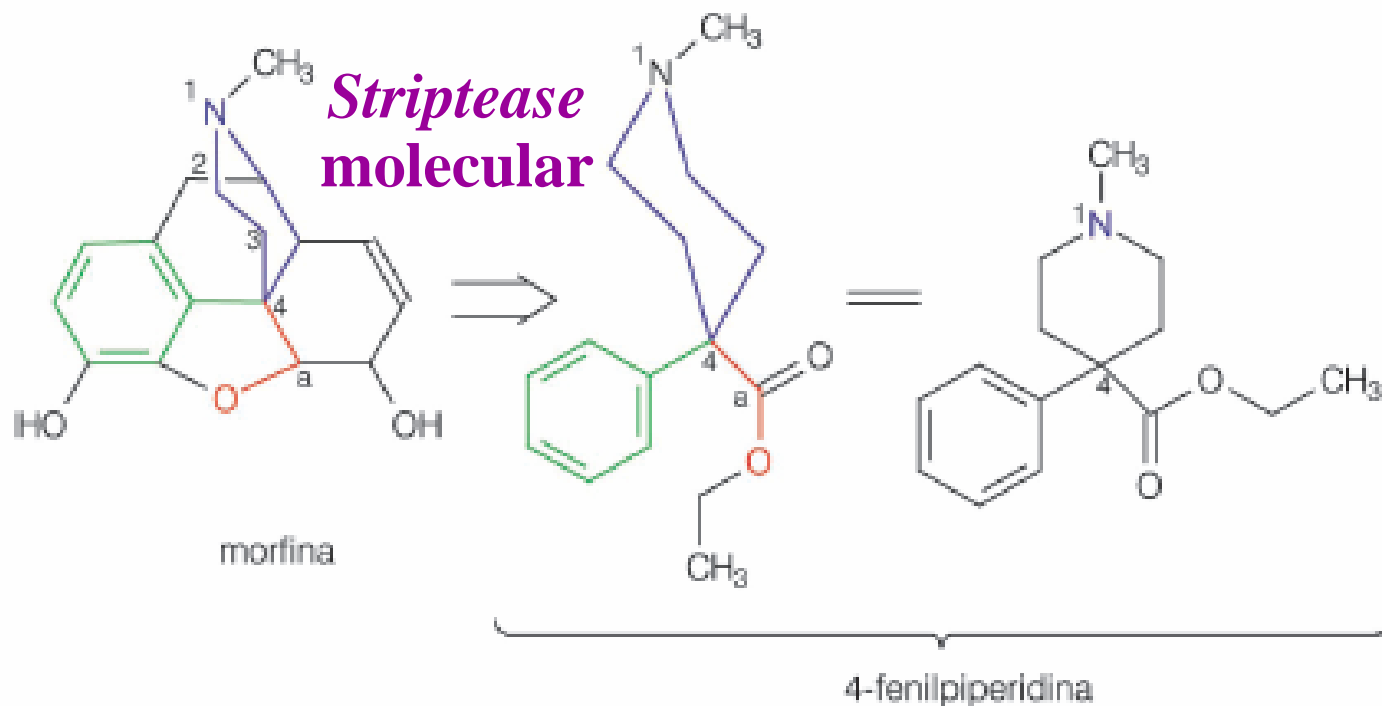
1493-1541 Marco Polo (Veneza) \Rightarrow Ópio
1806 \Rightarrow Friedrich Sertürner isola a morfina ("Morpheus") \Rightarrow hipno-analgesia

P. W. Schiller, *Progr. Med. Chem.* 1991, 28, 301

Sub-tipos de receptores centrais: δ , κ , μ

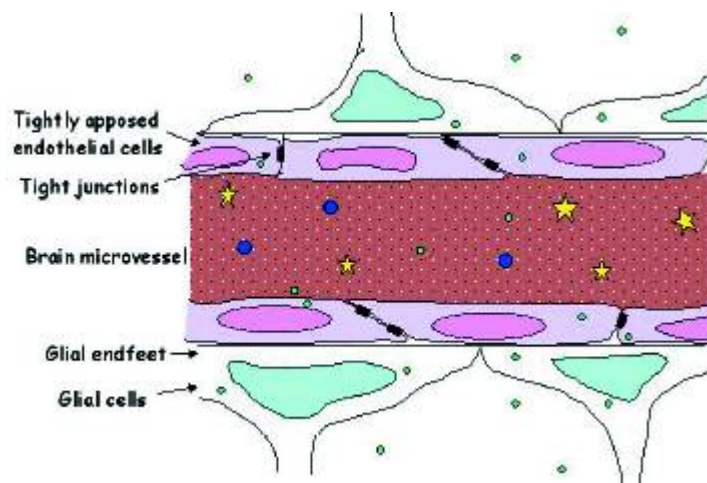
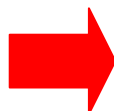
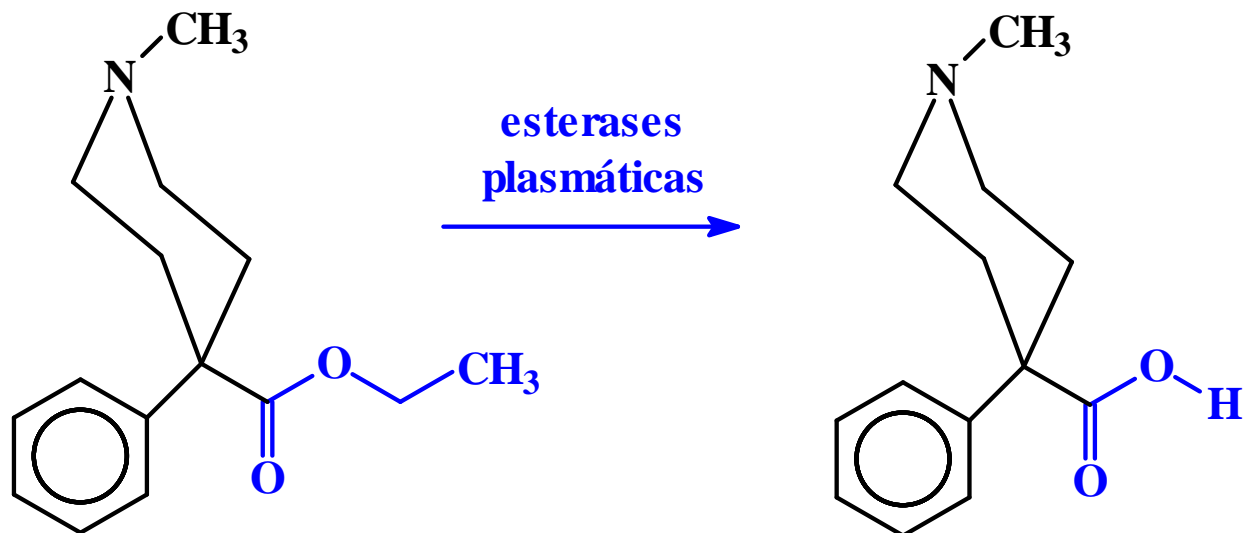
**analgesia central; tolerância;
dependência química;
síndrome de abstinência**

Primeiro exemplo de simplificação molecular



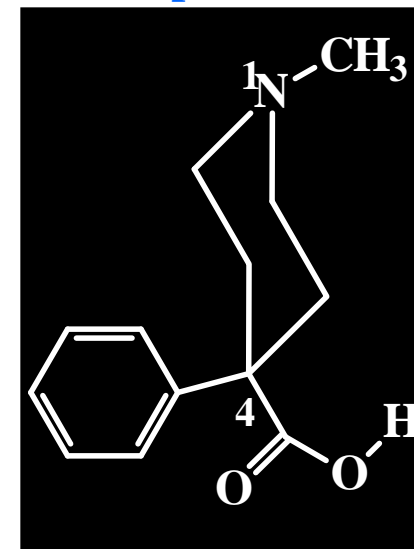
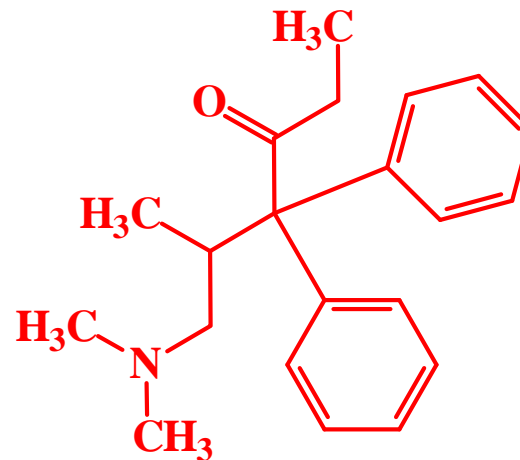
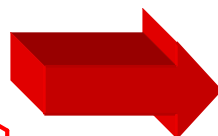
A origem dos analgésicos 4-fenilpiperidínicos a partir da estrutura da morfina: o anel piperidínico, em azul, substituído em C-4 no alcalóide por uma unidade fenila (verde) e um átomo de carbono quaternário oxigenado (a, em vermelho).

Produto natural como protótipo





Produto de hidrólise
no plasma

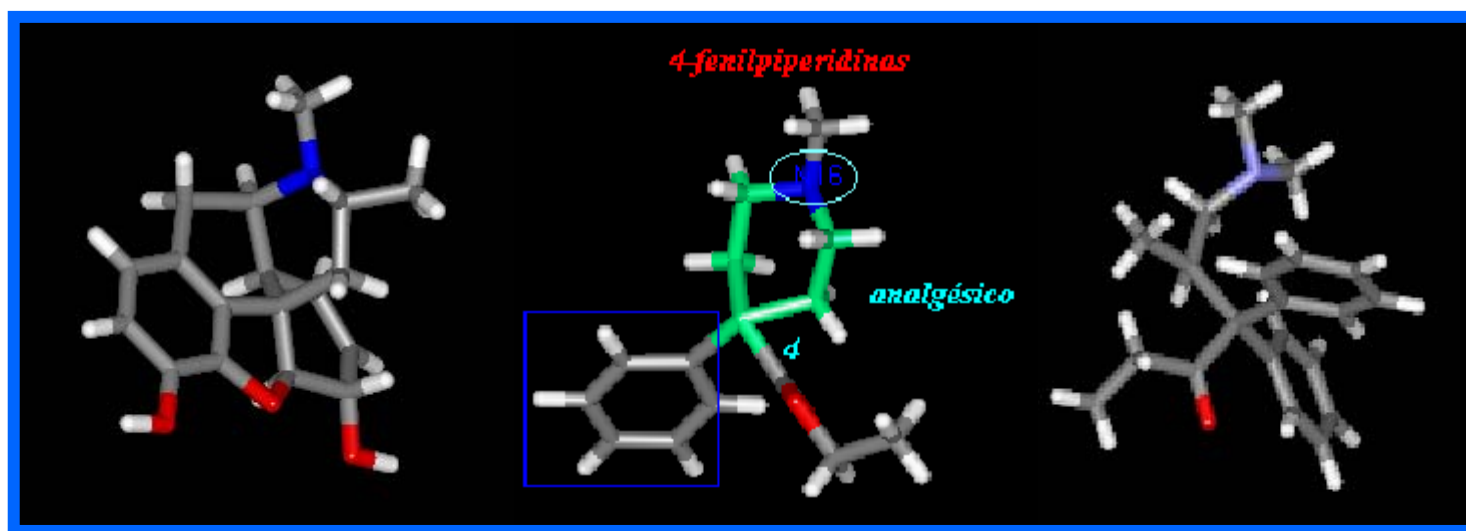


morfina

$C_{15}H_{21}NO_2$

$C_{21}H_{27}NO$

Meperidina Metadona





1ª Parte

Agentes Anti-câncer de Origem Natural



Vinca sp.



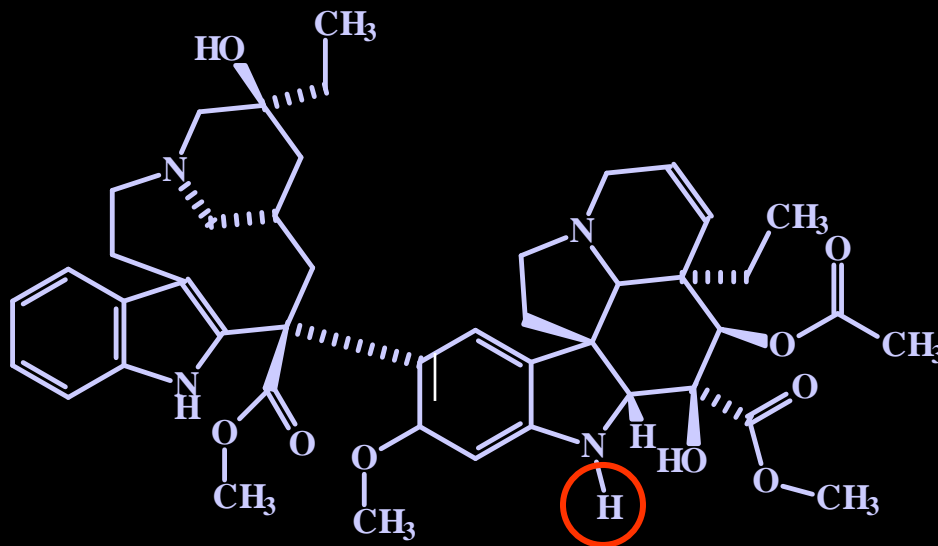
Catharanthus roseus

Câncer

Alcalóides

E. Wenkert, 1955

Inibidor mitótico (metafase)



Alcalóides bis-indólicos

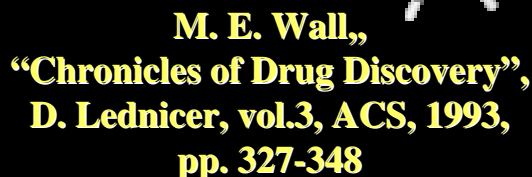
vinc ristina R= H
vim blastina R= CHO



Paclitaxel

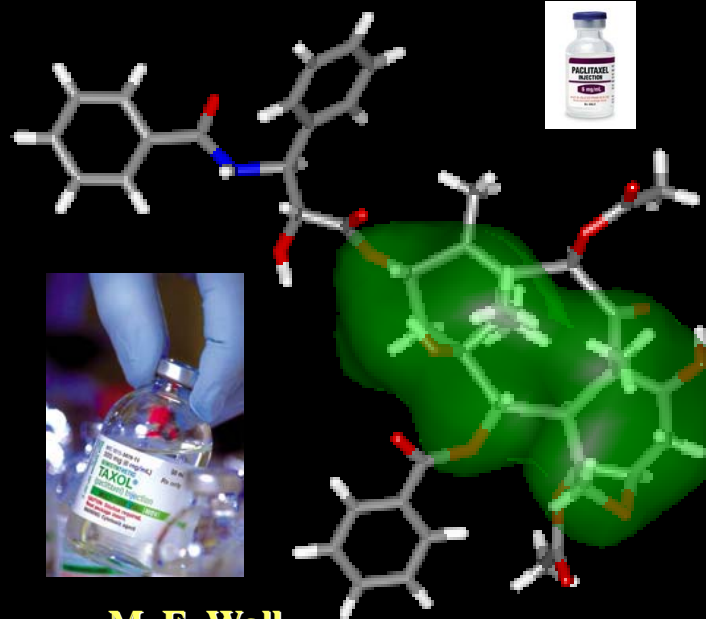
Taxol[®]

M. C. Wani *et al.*, J. Am. Chem. Soc. 1971, 93, 2325
Res. Triangle Park, 1967



M. E. Wall & M. C. Wani

1996 - National Cancer Institute Award of Recognition



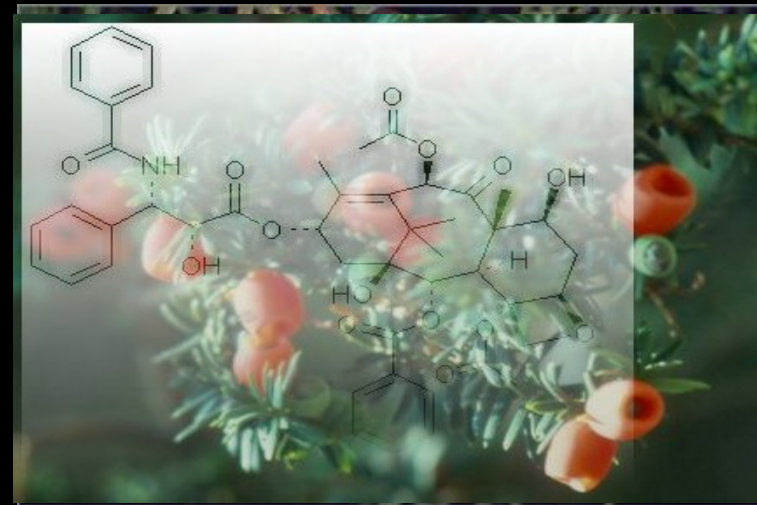
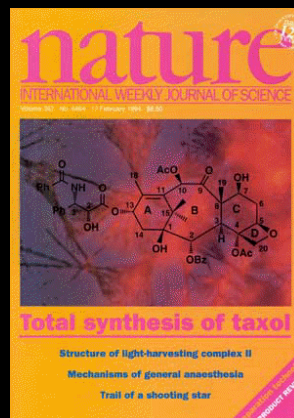
The Story of Taxol

NATURE AND POLITICS IN THE PURSUIT OF AN ANTI-CANCER DRUG

JORDAN GOODMAN
VIVIEN WALSH

TAXOL®
*Science and
Applications*

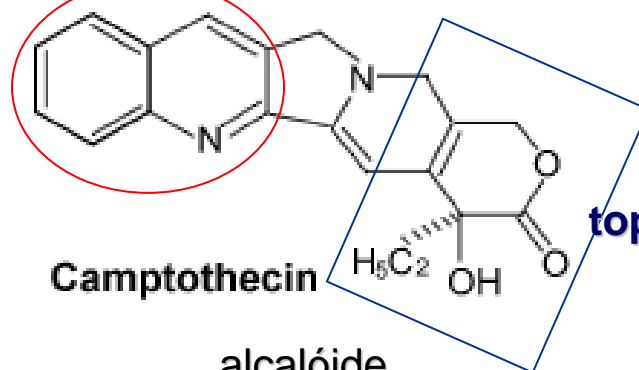
Edited by
Matthew Saffness



Taxus bacatta



Molécula “selvagem”



Camptothecin

alcalóide

quinolínico de biossíntese mista

Câncer

Inibidor de
topoisomerase-1

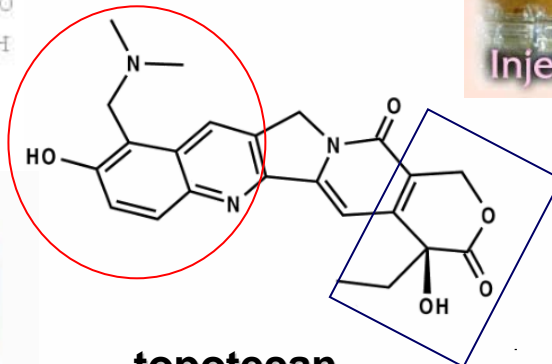


*Camptotheca
acuminata*

Wall, ME & Wani, MC “**Camptothecin: Discovery to Clinic**”
Annals of the New York Academy of Sciences 1996, 803, 1

Wall, ME, MC Wani, CE Cook, KH Palmer, AT McPhail, GA Sim, “Plant antitumor agents. 1. The isolation and structure of camptothecin, a novel alkaloidal leukemia and tumor inhibitor from *Camptotheca acuminata*” *J. Am. Chem. Soc.* 1966, 88, 3888.

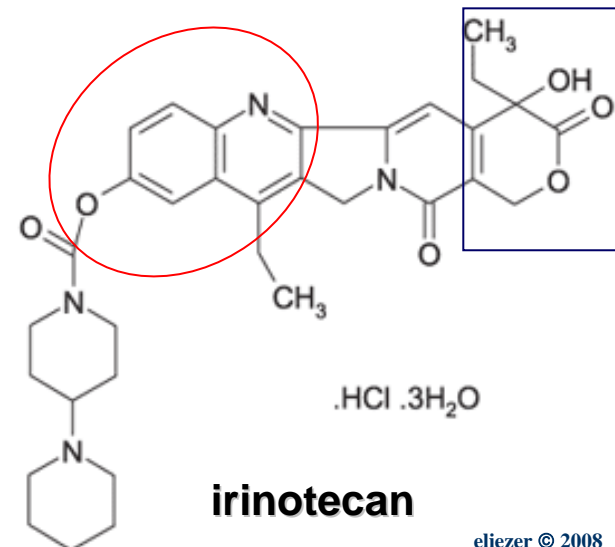
Molécula “domesticada”



topotecan



Injetável



irinotecan

.HCl .3H₂O





“Específico Pessoa”, criado pelo farmacêutico
José Torquato Pessoa, de Camocim, CE,
como preparado antiofídico.

(Francisco José de Abreu Matos)

Koji Nakanishi



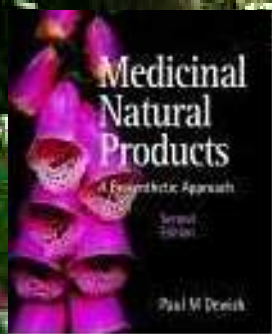
ACS, 1991

Un. Columbia EUA

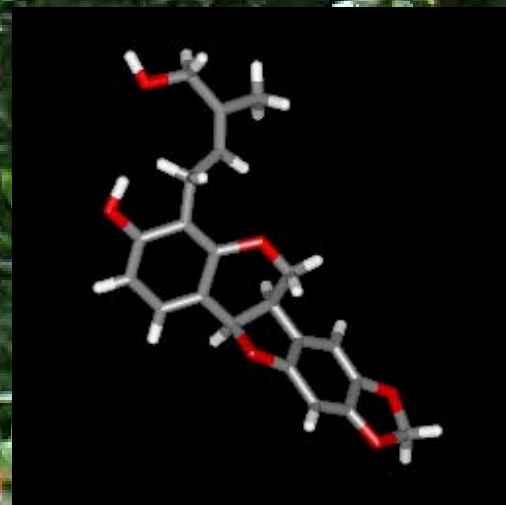
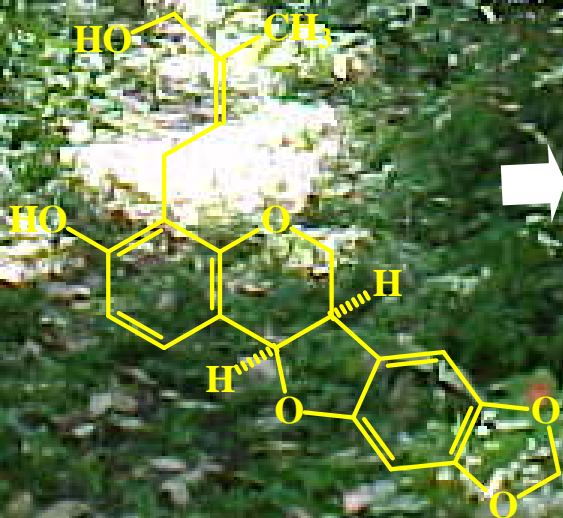
“A Wandering Natural Products Scientist “



Cabenegrina-A



Medicinal Natural Products:
A Biosynthetic Approach
Paul M. Dewick,
Wiley, 1997.



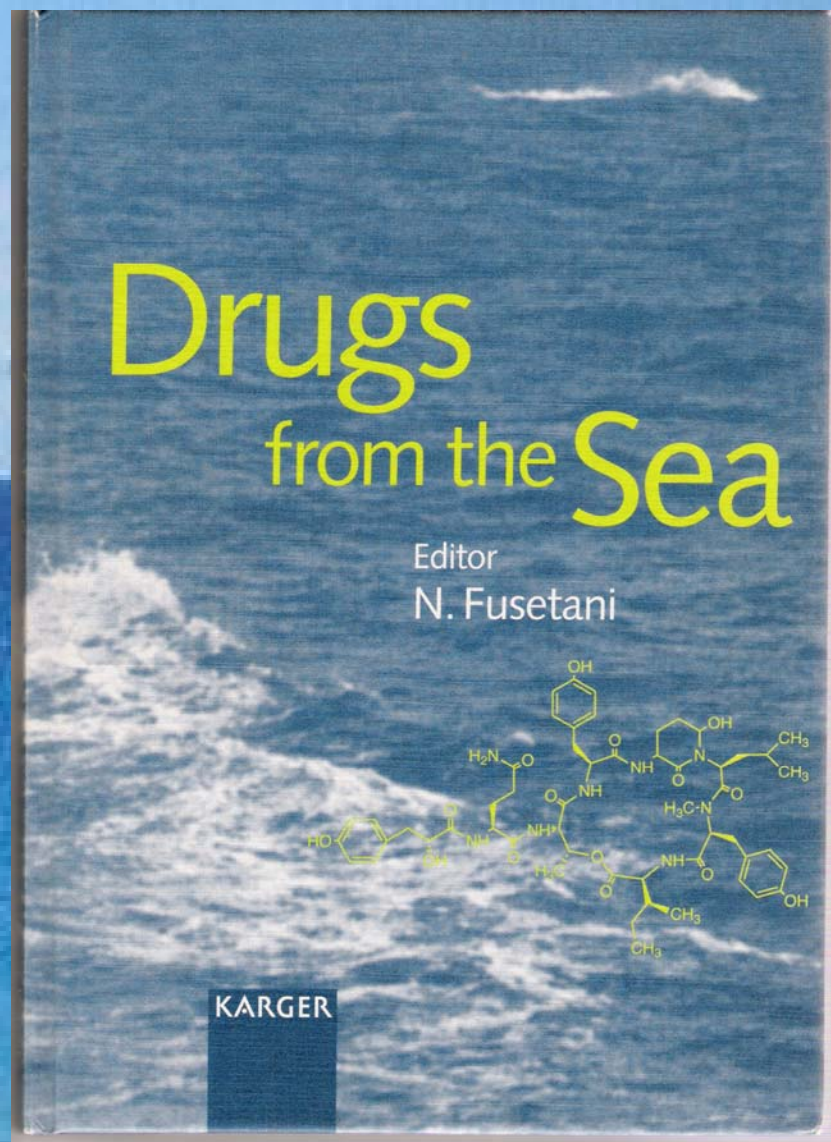
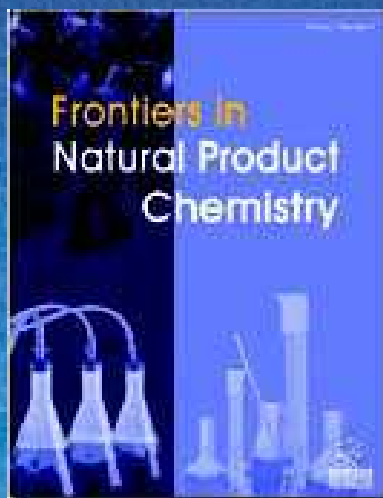
Tetrahedron Lett. 1982, 23, 3855



Produtos Naturais do Mar



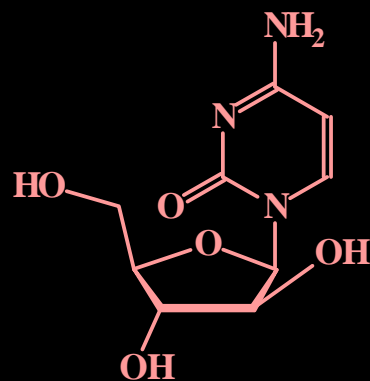
N. Fusetani



Esponjas



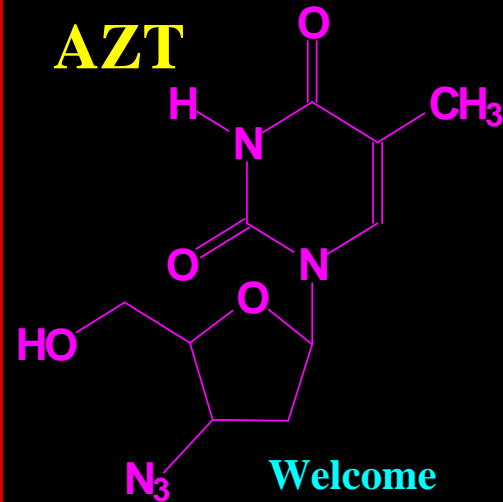
β -Citosina-arabinosido



citarabina (Ara-C)

1959

AZT



Welcome

H. Mitsuya *et al.*, 1985

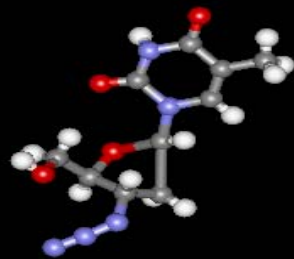
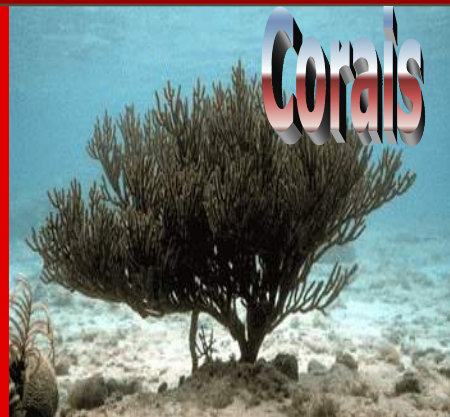
HIV-1 Reverse Transcriptase (EC: 2.7.7.49)

Residues of the active site
mutated in AZT resistance
Dipyridoxamine
Dipyridoxamine
Dipyridoxamine binding site



1988
1991

Corals



JP Horwitz *et al.*, *J. Org. Chem.* 1964, 29, 2076



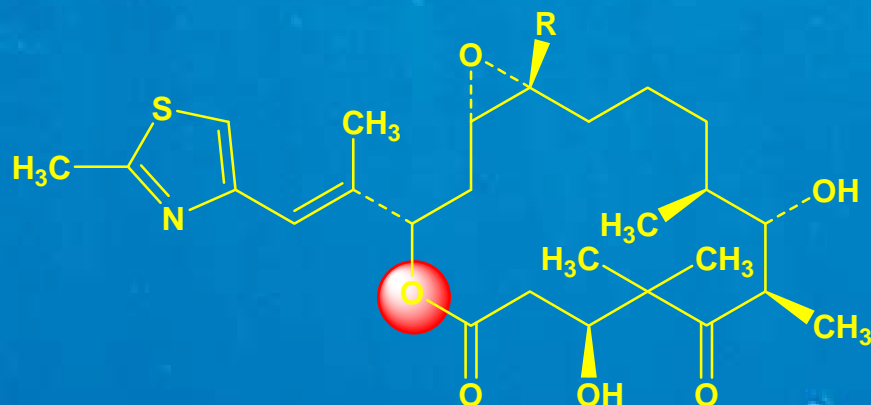
R. Gallo, 1980

Retrovir



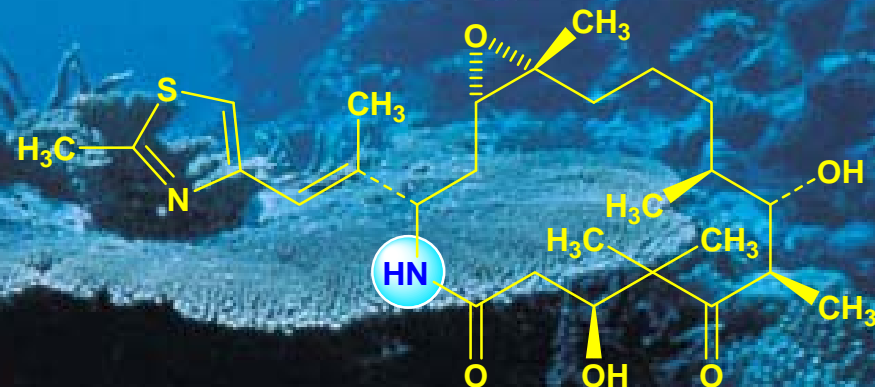
zidovudina (AZT)

1993 - Isolation from the yxobacterium *Sorangium cellulosum*

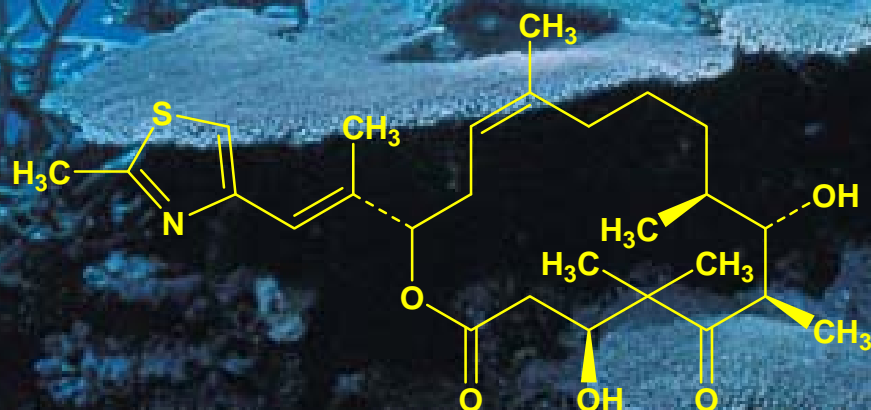


Epothilone A R = H
Epothilone B R = CH₃

2007 - The first member of eptihlone family of anticancer agents to be approved by the FDA as a cytotoxic microtubule inhibitor for the treatment of metastatic breast cancer.



Ixabepilone
(Ixempra^R)
 BMS, Out. 2007



Epothilone D

Microtubule stabilizing 16-membered macrolides



esteróides



Russell Marker



Gregory Pincus (1901-1967)

Russell E. Marker & Gregory Pincus

(J. Chem. Educ. 1973, 50, 195).

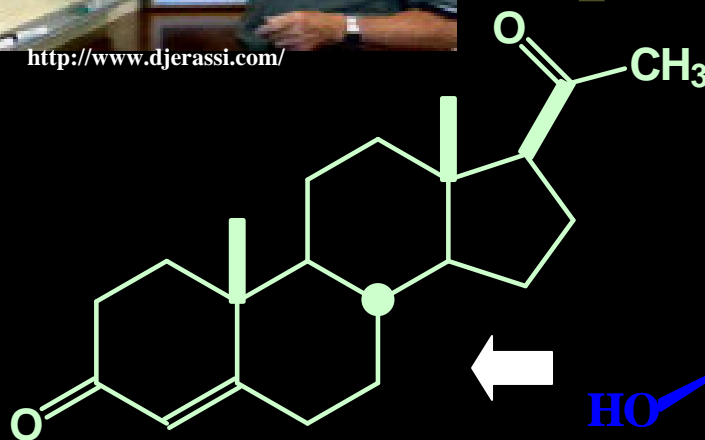
Em 1937 no "Pond Laboratory" da Universidade da Pensilvânia, EUA, Marker concluiu a primeira síntese da progesterona a partir da diosgenina

Carl Djerassi

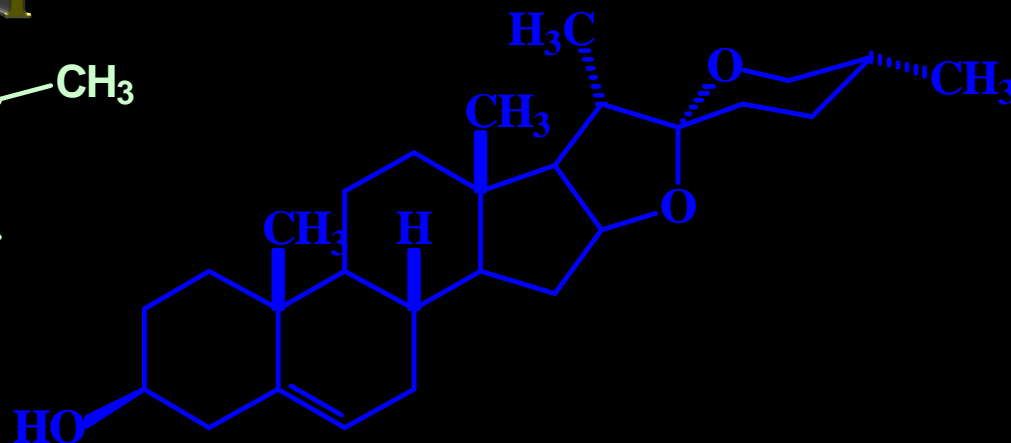


<http://www.djerassi.com/>

A Pílula Contraceptiva



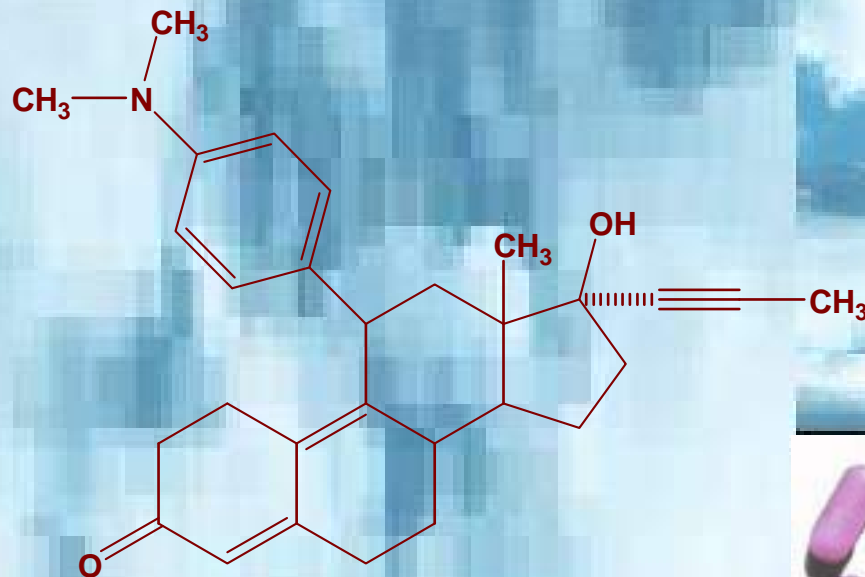
progesterona



diosgenina



mifepristona



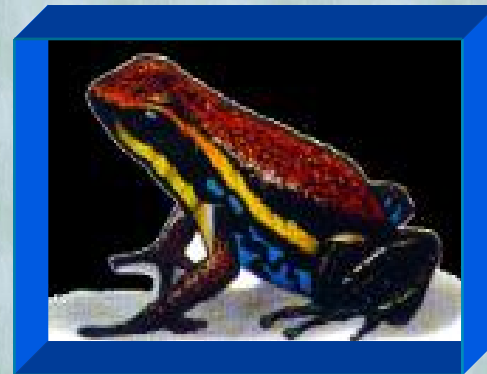
RU 486

Pílula do dia seguinte

Mifepristona



Produtos naturais de...



....cobras & sapos....

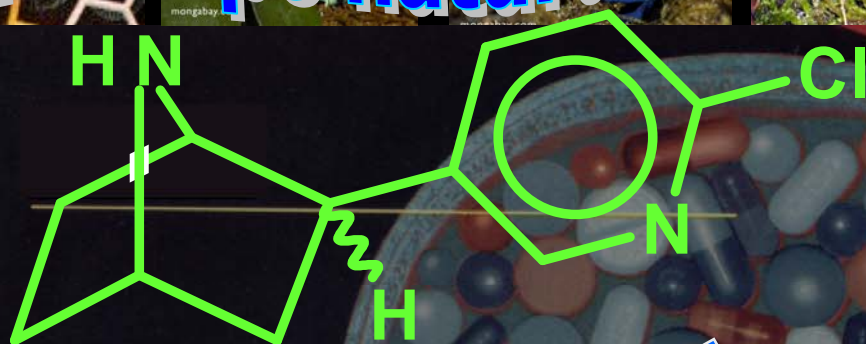


protótipo natural



John W. Daly

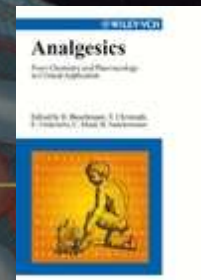
Un. Maryland, EUA



Epibatidina

200-400 vezes mais potente que a morfina

IT baixo



Primeiro PN com quimiotipo 7-azabicyclo[2.2.1]heptano

Primeiro alcalóide não-opióide, organo-clorado, analgésico.



J. W. Daly, "Ernest Guenther Award in Chemistry of Natural Products. Amphibian Skin: A Remarkable Source of Biologically Active Arthropod Alkaloids", *J. Med. Chem.* 2003, 46, 445-452

1992

J. W. Daly "Thirty Years of Discovering Arthropod Alkaloids in Amphibian Skin", *J. Nat. Prod.* 1998, 61, 162-172



Epipadobates tricolor



Inovação terapêutica



M. O. Rocha e Silva
1910-1983



jararacá

Fármacos Inteligentes

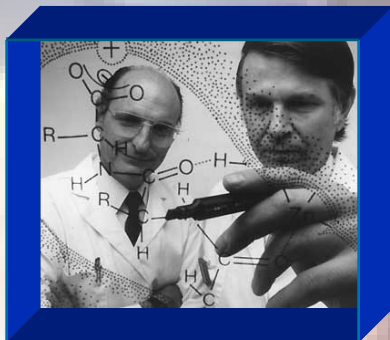


S. H. Ferreira
1934-

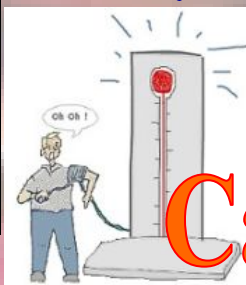
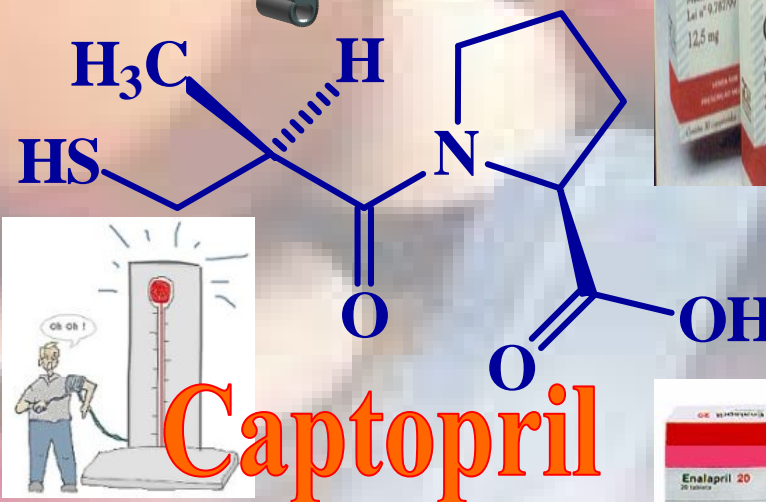
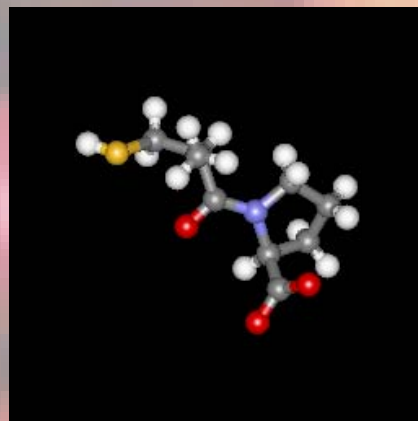
Bradicinina
(W. Beraldo, 1949)

S.H. Ferreira, A Bradykinin-potentiating factor (BFP) present in the venom of *Bothrops jararaca*, *Brit. J. Pharmacol.* 1965, 24, 163.

Inibidores da Enzima Conversora de Angiotensina

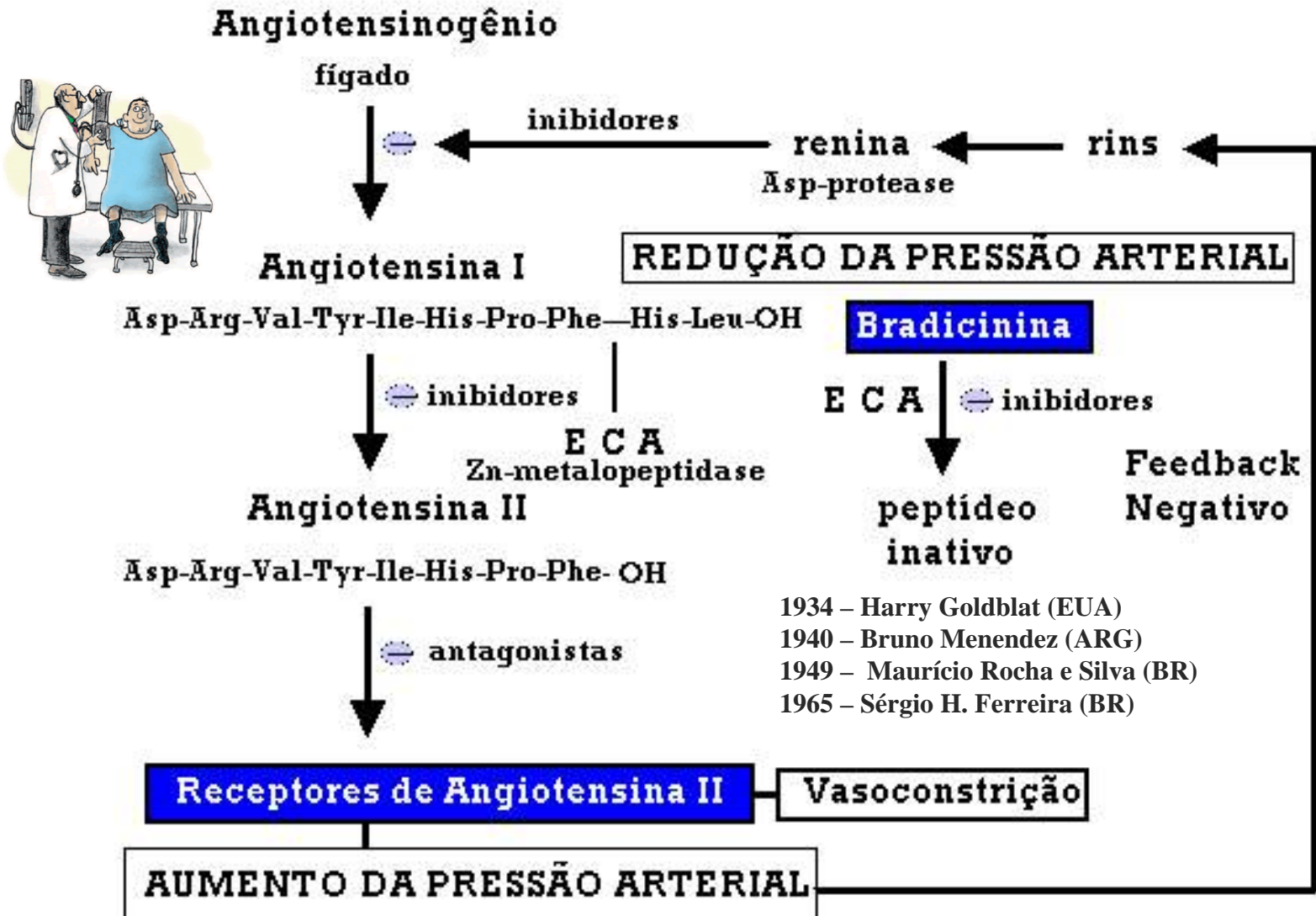


D. W. Cushman & M. A. Ondetti



M. A. Ondetti, D. W. Cushman & B. Rubin, *Chronicles of Drug Discovery*, vol. 2, J.S. Bindra & D. Lednicer, Eds., Wiley, Nova Iorque, 1983, p. 1-32

Sistema Renina-Angiotensina

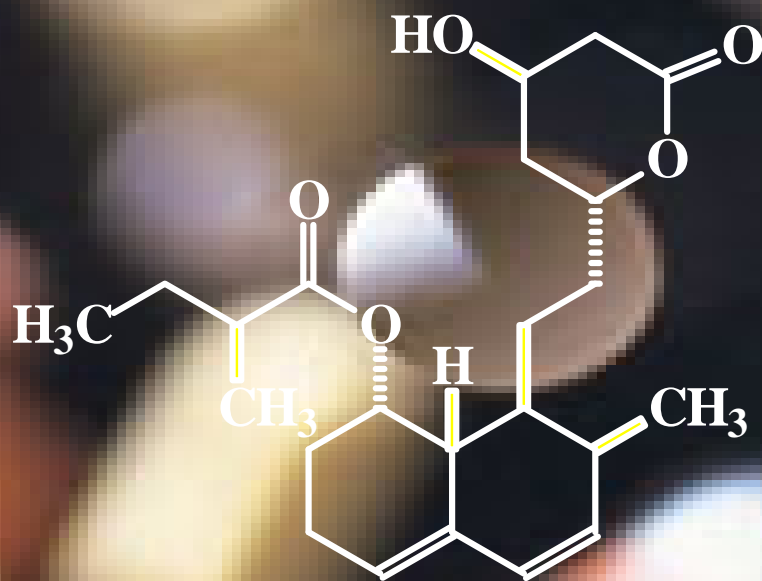




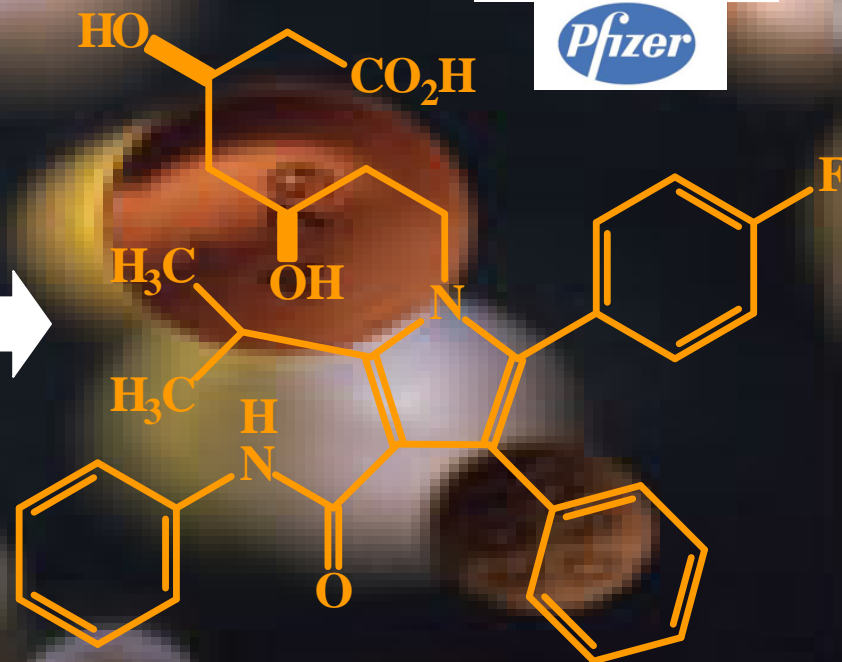
...do protótipo natural ao super-fármaco...



Pfizer



mevastatina



atorvastatina

2007: US\$ > 13,5 bi

* CE&N, Dec, 2007



Metabólito de Fungo

Protótipo natural

1975 - *Mevastatina*

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



Arthur A. Patchett

J. Med. Chem.

2002, 45, 5609.

γ -lactona

Similaridade molecular

US\$ 5,5 bi
(2007)

Pró-fármaco



IC₅₀ = 11,2 nM



Simvastatin

(*Zocor*[®])

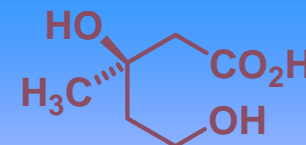
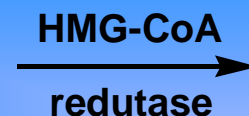
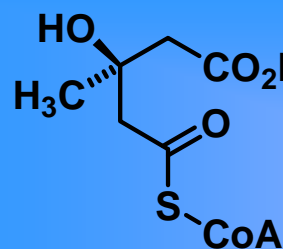
MK-733

1988

J. Med. Chem. 1986, 29, 849

Fármacos Inteligentes

Biossíntese do colesterol



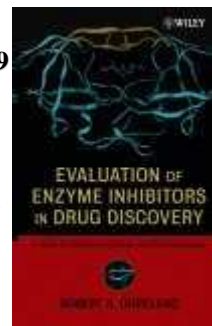
Mevilonina

Lovastatin (MK-803)

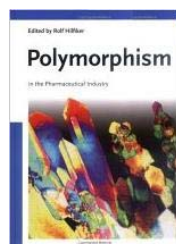
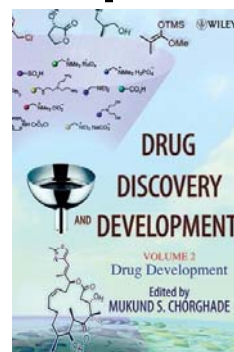
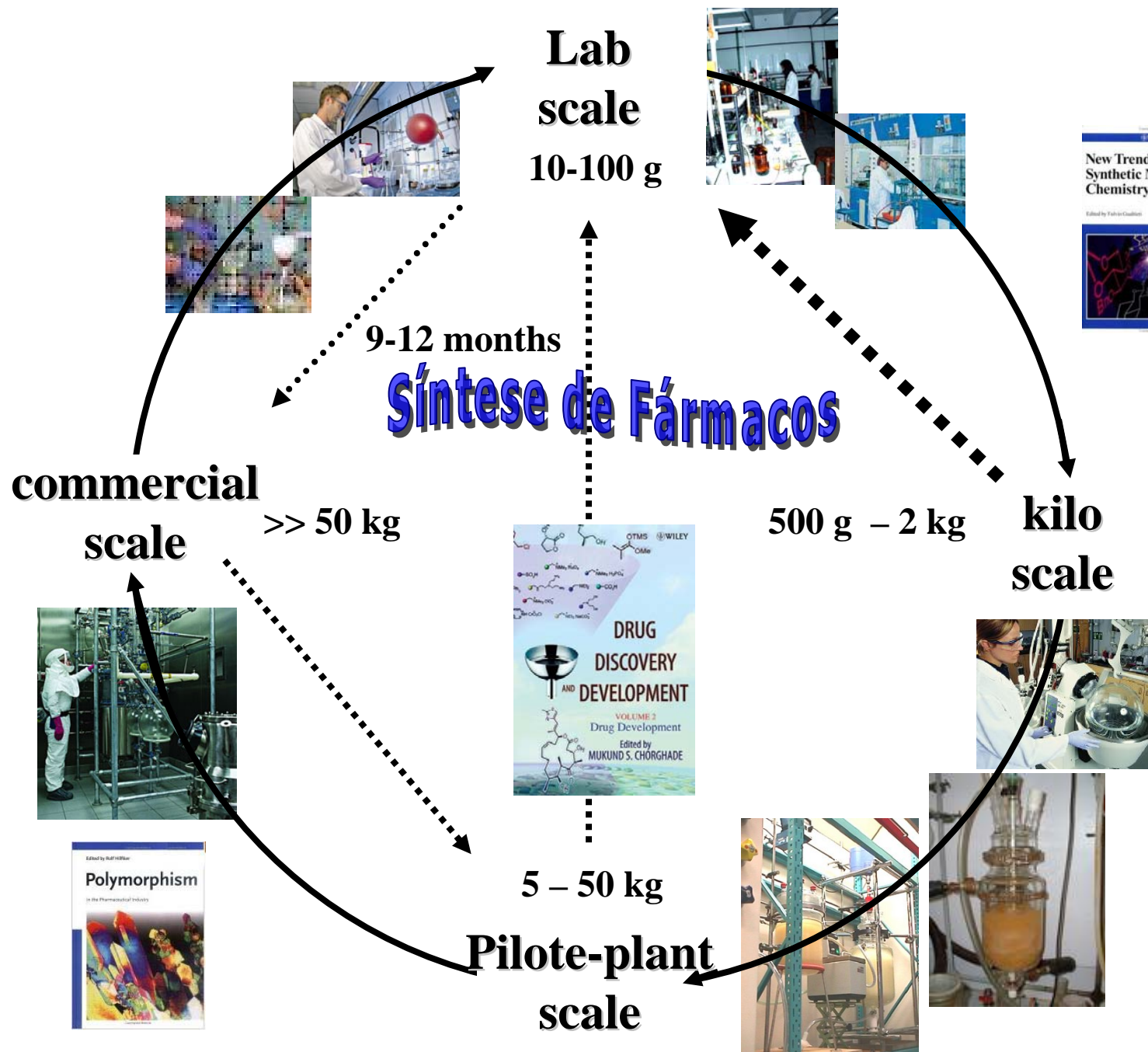
1980 - Merck & Co.

Aspergillus terreus

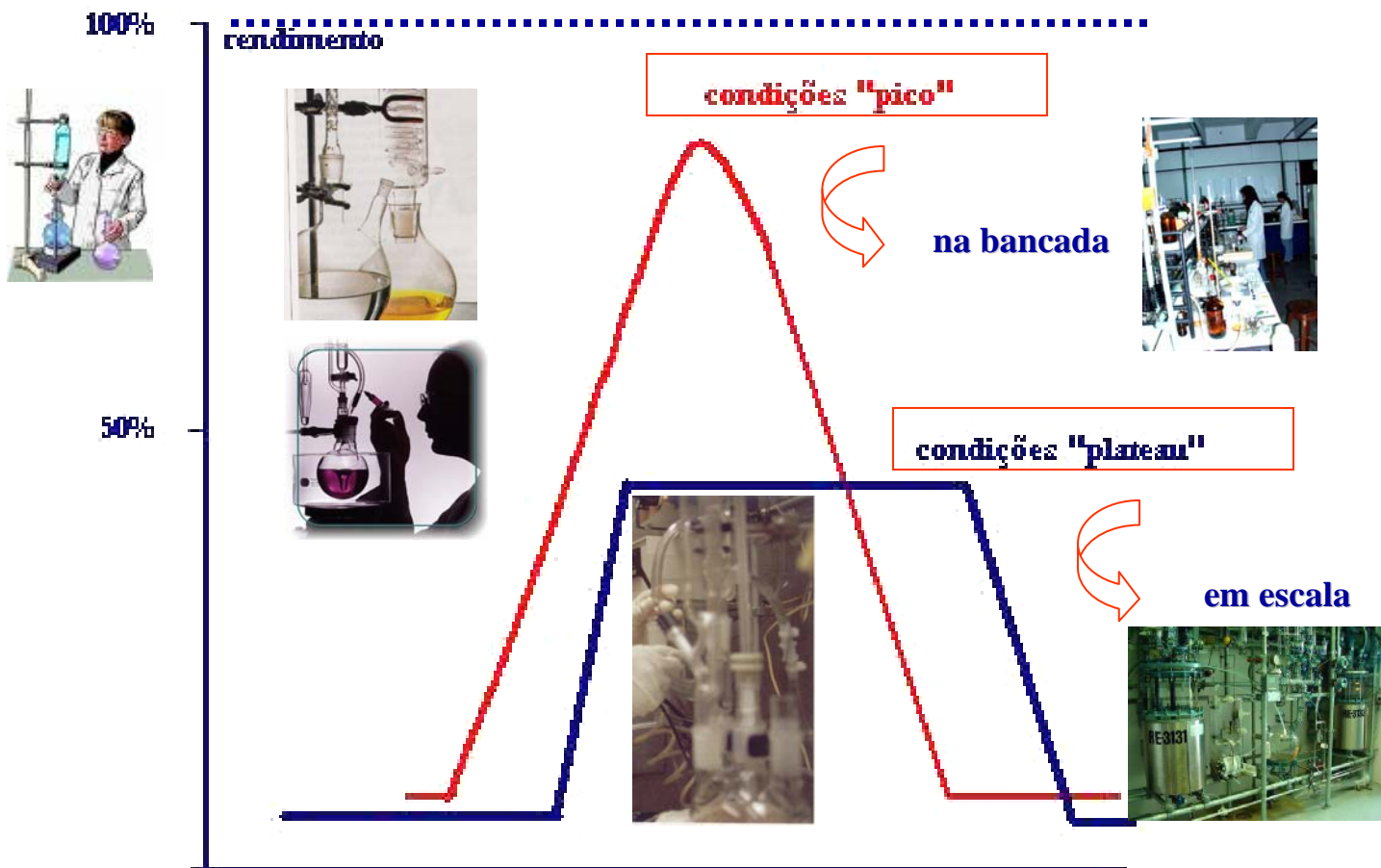
1987 - MS&D (*Mevacor*[®])







Síntese de Fármacos

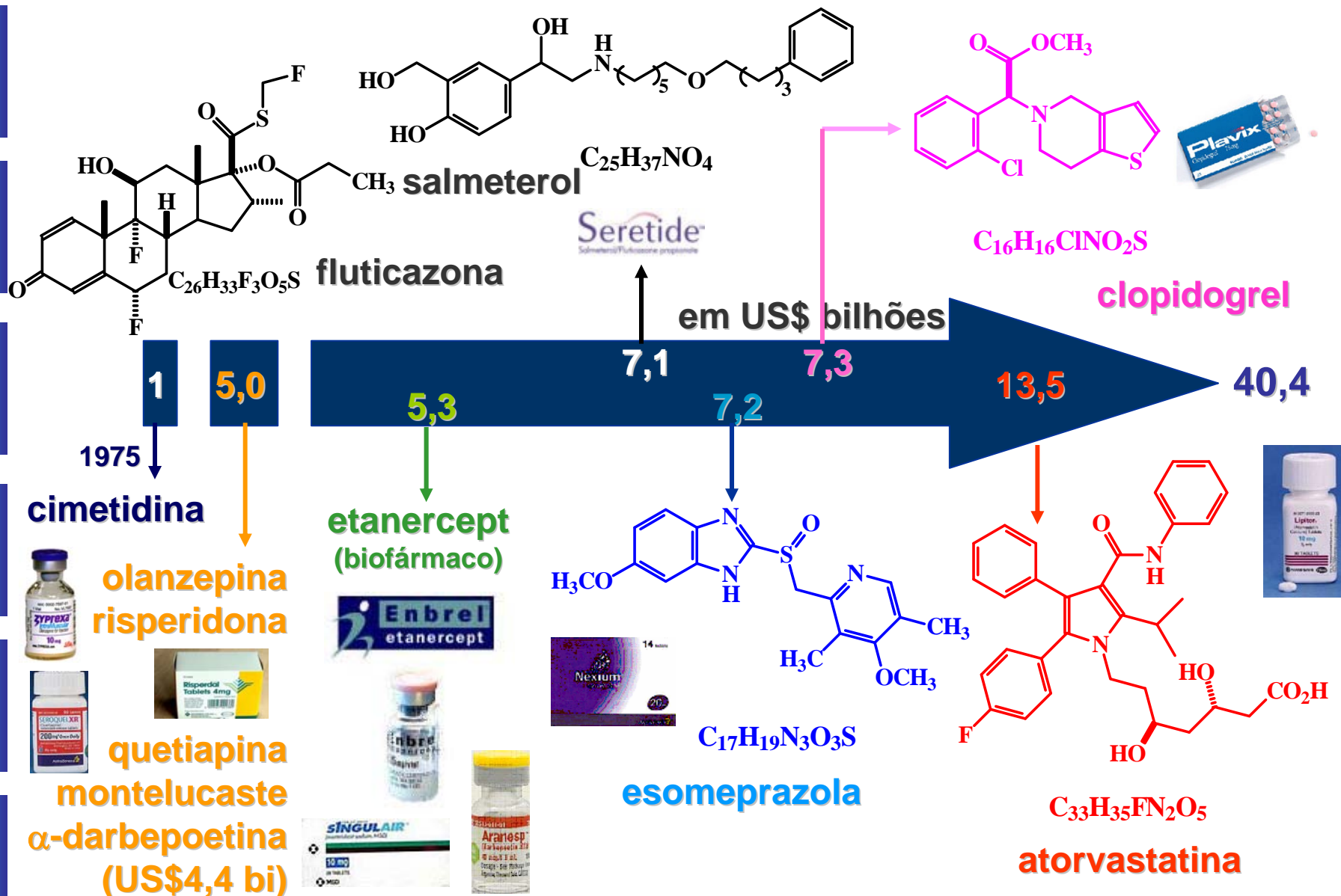


condições reacionais → dificuldade

Condições Reacionais em Escala



5-mais no mercado mundial em 2007





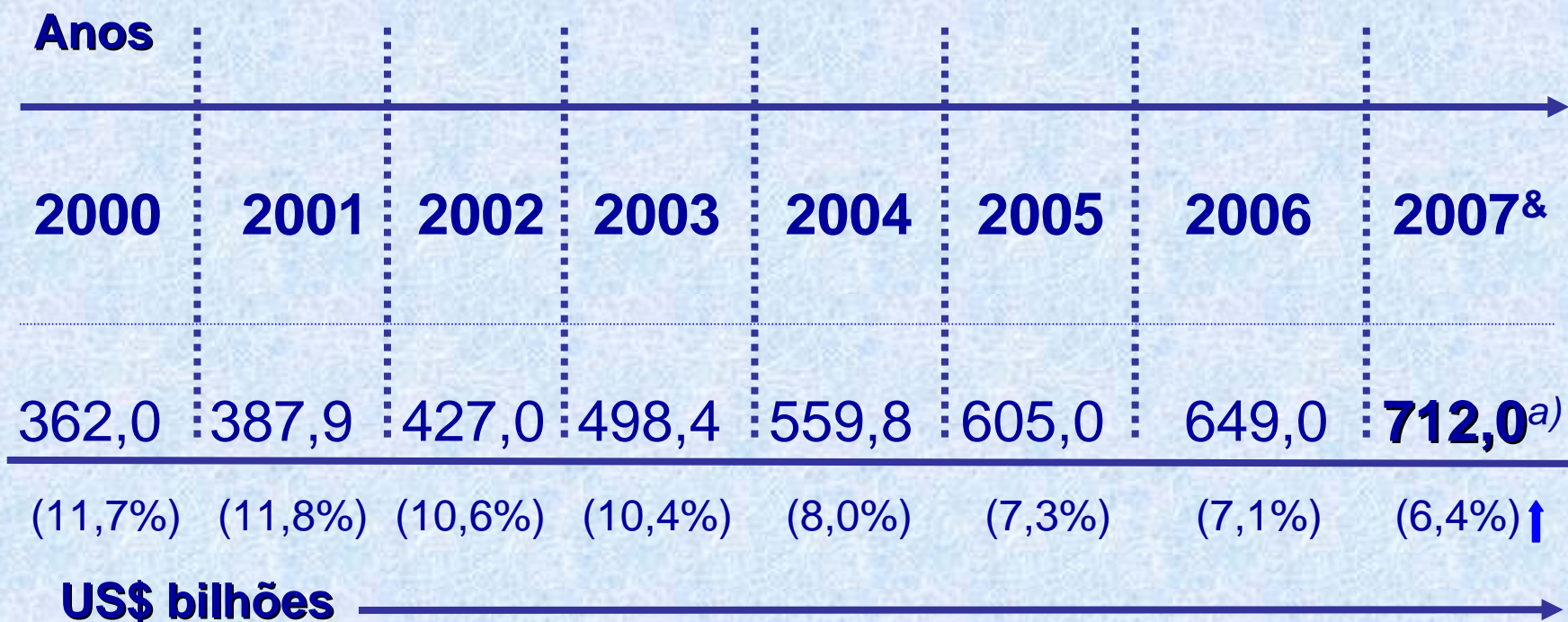
Características estruturais comuns nos cinco fármacos mais vendidos no mundo em 2007:

- Possuem apenas 7 elementos químicos: C, H, O, N, S, F, Cl;
- Todos possuem heteroátomos, 80% são heterocíclicos;
- Todos são multicíclicos (< cinco anéis);
- 80% têm unidades aromáticas;
- 02 podem ser considerados me-too;
- 01 representa uma inovação incremental;
- pertencem a apenas 03 classes terapêuticas distintas;
- são substâncias com singela diversidade química;
- Têm 11 funções químicas: areno, ácido, éster, amida, álcool, fenol, cetona, amina, éter, haleto, sulfóxido;
- são responsáveis por US\$ 38,0 bilhões em vendas;
- têm fórmula molecular: $C_{117}H_{140}ClF_4N_7O_{19}S_3$ (2153,5/5=430,7)
- cada átomo de C vale US\$ 345,3 milhões !
- Logo: Pequenas Moléculas, Grandes Negócios !





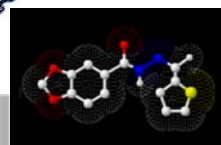
Farmacêutico Mundial



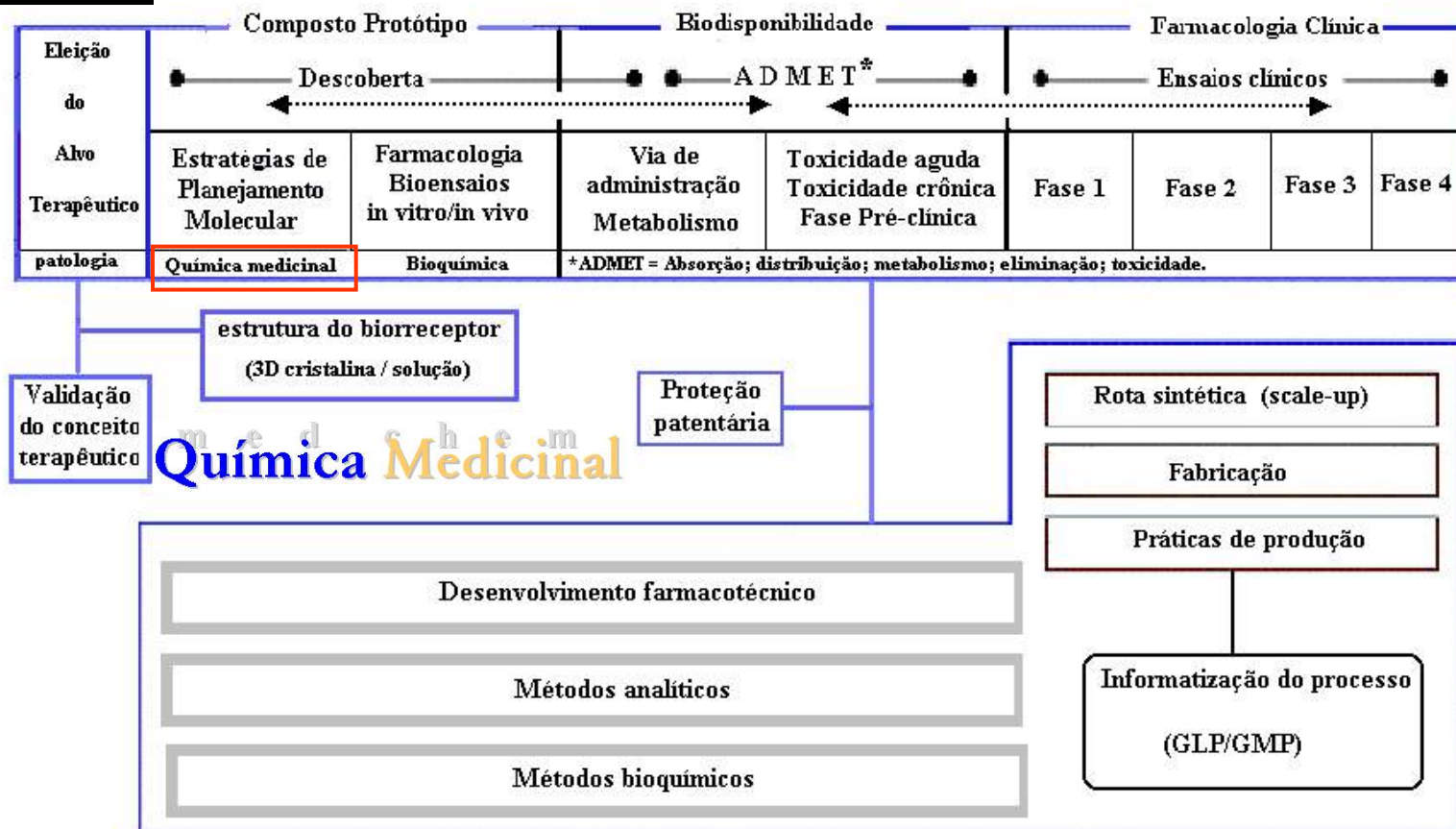
Fonte: ^{a)} <http://imshealth.com>
ims

América Latina (2007, 12%[↑]): US\$ 32 bilhões (ca. 4,8%)

& Principais classes terapêuticas (2007):
anti-câncer (6%) & anti-lipêmicos (5%)



Cadeia de inovação em fármacos



- Visão esquemática do processo de descoberta racional de fármacos, indicando, nas setas horizontais pontilhadas, os diferentes estágios consecutivos de competências multidisciplinares envolvidas, em distintos níveis hierárquicos. A figura ilustra a interação vertical necessária, em determinado estágio evolutivo do processo, entre as diversas competências biológicas, químicas e farmacêuticas, incluindo a decisão estratégica do momento apropriado à promover-se a proteção patentária das novas entidades químicas descobertas.



O processo da descoberta racional...

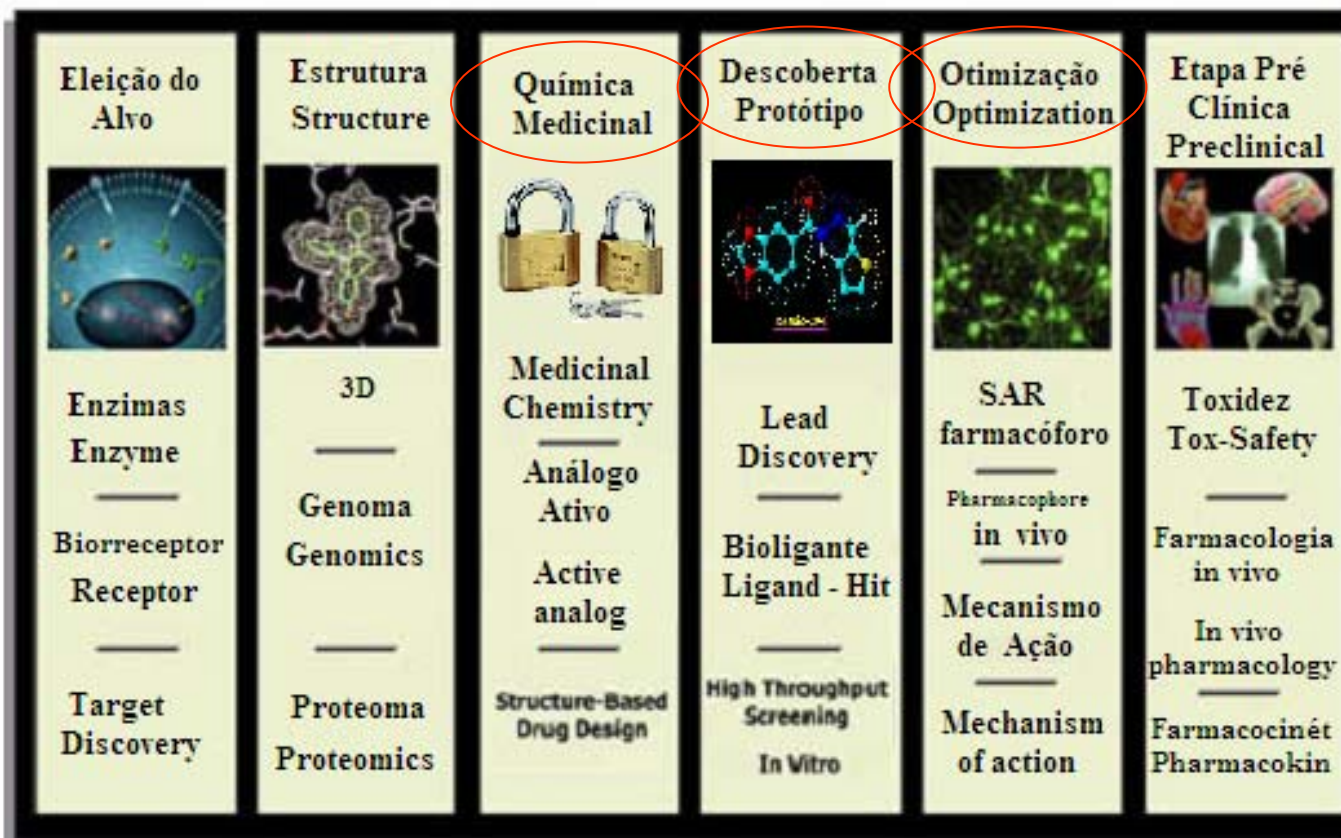
Química Medicinal



... o paradigma do composto-protótipo.



O paradigma da Química Medicinal para a descoberta de novos fármacos: *o composto-protótipo*



NOVO FÁRMACO
NEW DRUG

Química Medicinal





Physiologic approach A abordagem fisiológica



Abordagem
racional

Mechanism-based drug discovery



Descoberta do
composto-protótipo

*Estratégia do
Análogo-ativo*

*Caracterização dos
pontos & grupos
farmacofóricos
(bióforos)*

**Estrutura do
Biorreceptor
Conhecida**

DHFR
Inibidores

cimetidina

antagonistas H₂ **inibidores da ACE**
Inovações Terapêuticas

**Estrutura do
Biorreceptor
Desconhecida**

**Inibidores de
HIV Asp-proteases**
indinavir

Abordagem irracional

*Identificação
de novo hit
ou ligante*

**Alternativa
híbrida**

Abordagem irracional-racional

Imatinib
Bioinformática

Estratégias hífenadas



Physiologic approach
A abordagem fisiológica



**As estratégias de
desenho estrutural...**

**no planejamento racional
de novas moléculas candidatas
a fármacos...**



Fármaco



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 ”



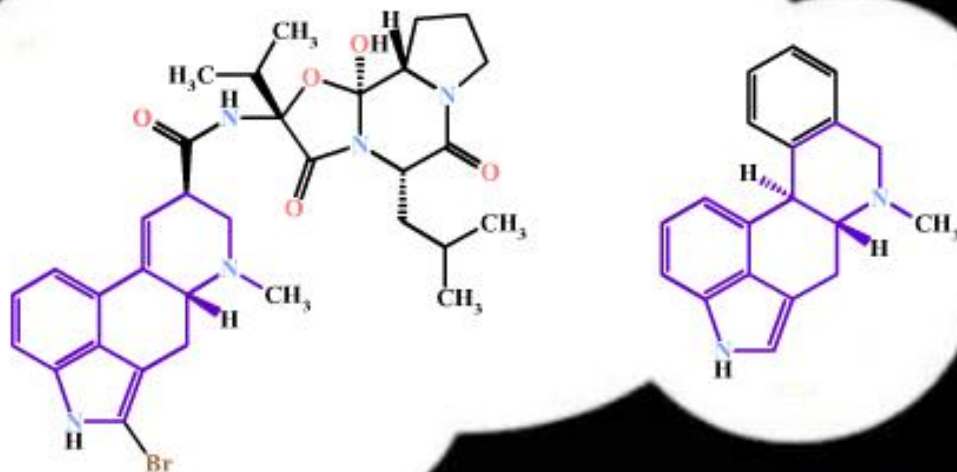
Lead
Optimization

“D-L P”





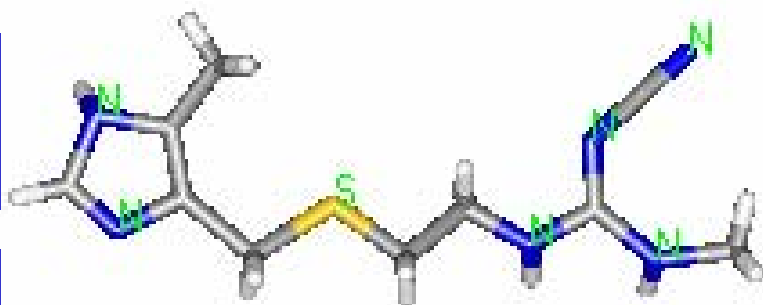
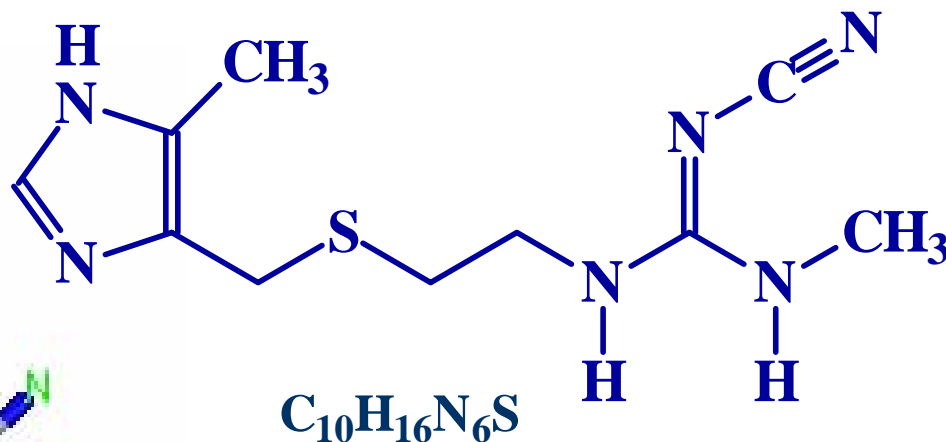
Planejamento racional



**A descoberta da
cimetidina**



Cimetidina



Inovação
terapêutica



Os descobridores da cimetidina: Ganellim, Emmet, Durant & Black, da esquerda para a direita,



National Historic Chemical Landmarks

AMERICAN CHEMICAL SOCIETY

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Cradles of
ChemistryAction!
Take Part
& Nominate

A new era of logical drug design

The research program leading to cimetidine also represented a revolution in the way pharmaceuticals are developed. Traditionally, the development of a new drug would often depend on the fortuitous discovery of a plant or microbial extract that showed some of the required biological activity. Using that first extract as a lead, many similar compounds would be made and tested for pharmacological effectiveness. In many cases, the researchers did not know how the drug worked, so finding an optimal compound was difficult.

The development of cimetidine was radically different: it was one of the first drugs to be designed logically from first principles. SK&F's multidisciplinary research team first looked at the physiological cause of acid secretion. They confirmed that a molecule found in the body called histamine triggers the release of acid when it binds to a specific receptor (now called the H_2 -receptor) in the stomach lining. Their aim was to find a molecule that successfully competed with histamine in combining with the receptor, but then blocked, rather than stimulated, acid release. Such a molecule was called a histamine H_2 -receptor antagonist and represented a new class of drugs.

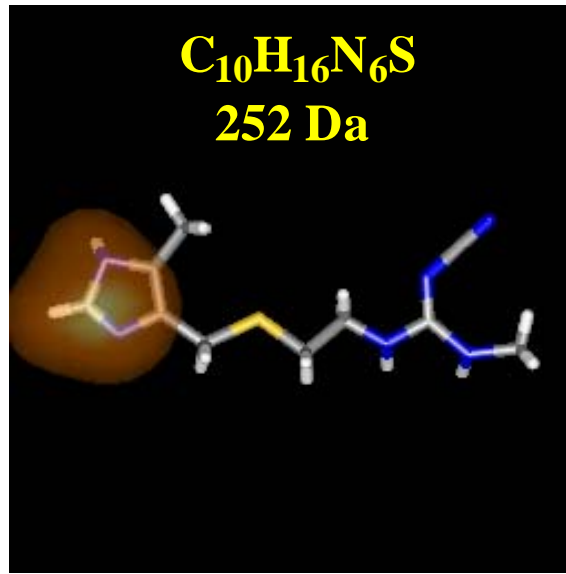
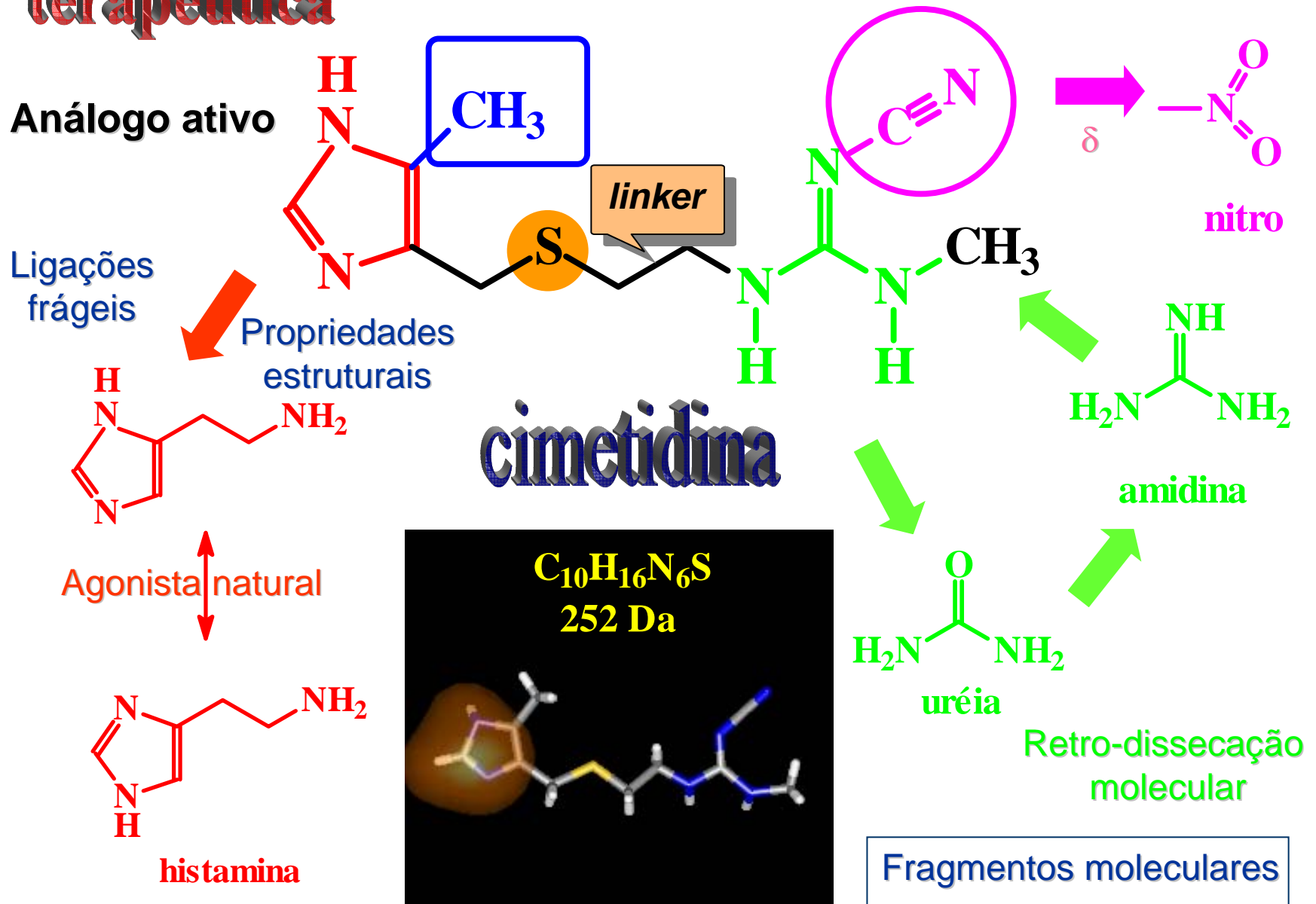
Using a step by step analysis of structural and physical properties, the team made a series of histamine-based molecules, which were then tested for antagonist activity using carefully designed pharmacological assays. Today, this approach of rational drug design underpins the discovery programs of many major pharmaceutical companies.

Abordagem Fisiológica
eleição do alvosérie congênere
identificação do protótipo
otimização do protótipo
(PD/PK & PPh)



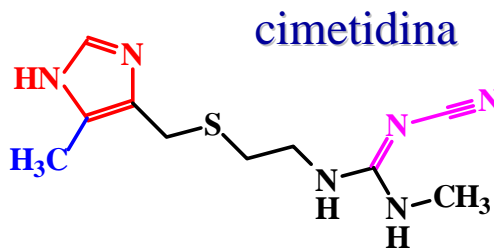
Inovação terapêutica

Abordagem Fisiológica





A gênese da cimetidina



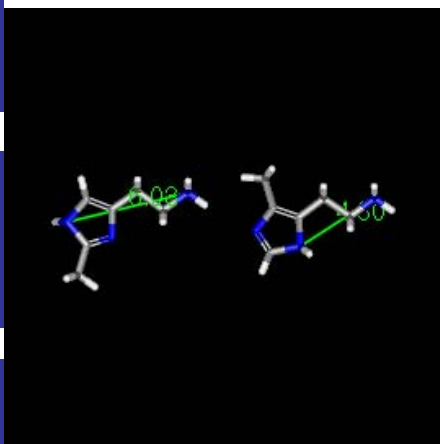
$C_{10}H_{16}N_6S$
252.33



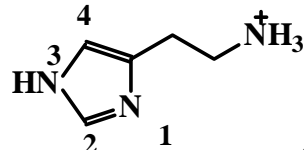
A procura do protótipo:

Tagamet= "anTAGonist" + "ciMETidine?"

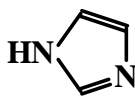
antagonista H-2



análogo-ativo

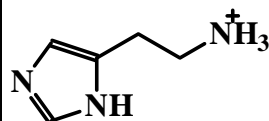


tautômeros



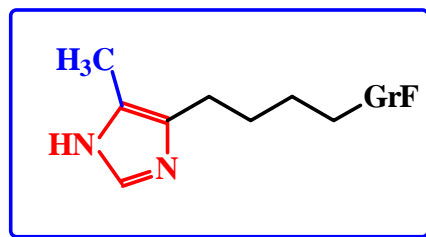
imidazola

4-Cl, 4-Br, 4-NO₂

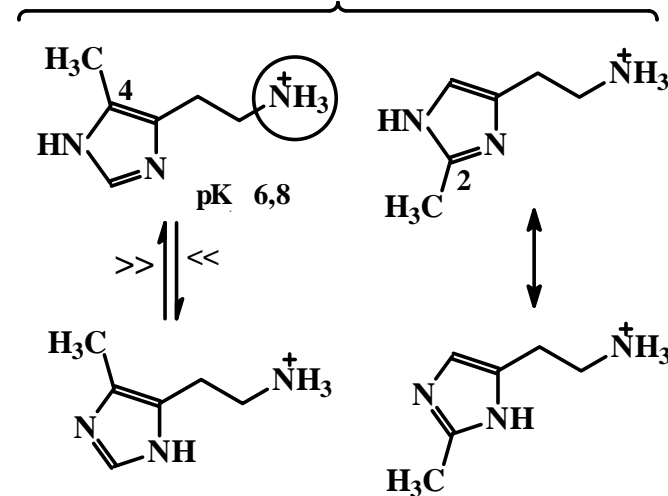


metil-alkil-imidazola

A

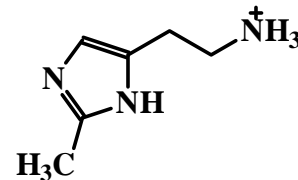
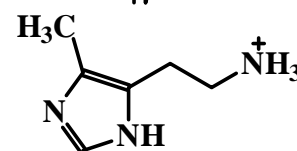


metil-histaminas



pK 6,8

>> <<

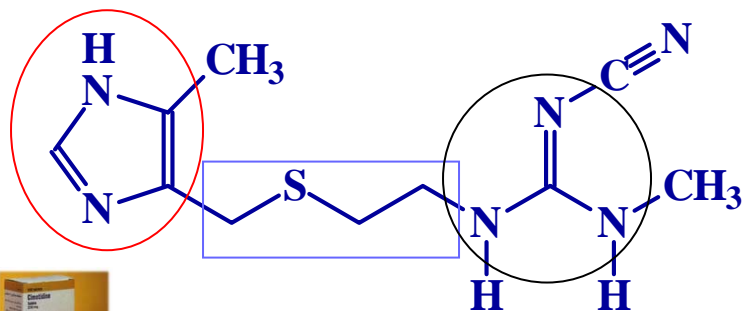


dissecação molecular



Ar = arila, heteroarila

GrF = grupo funcional



Cimetidina

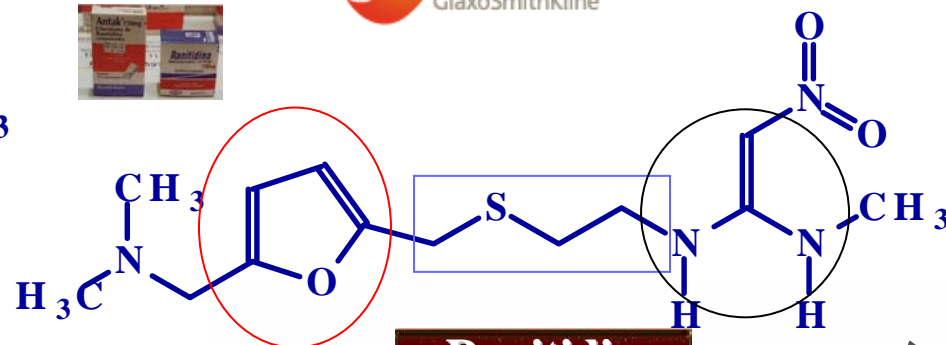
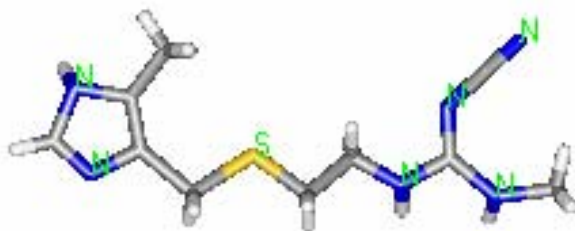
Robin Ganellin *et al.*, 1974

US 3950333 1974, 1976 - SK&F

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



*similaridade
molecular*



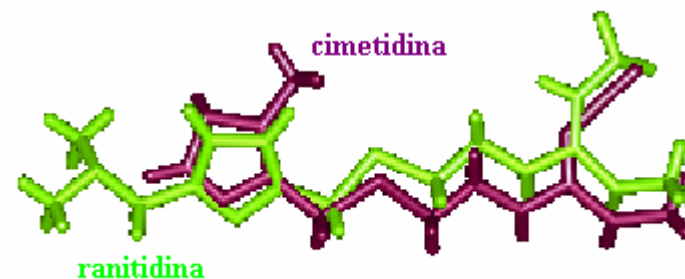
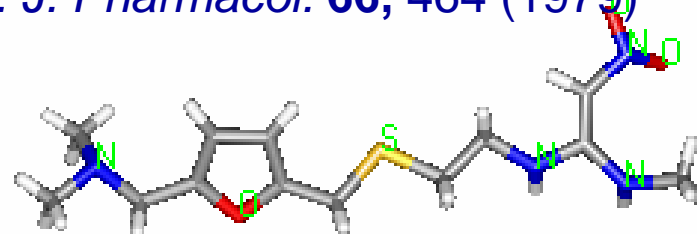
Ranitidina

Barry J. Price *et al.*, 1978

US 4128658 1978 - Allen & Hanburys

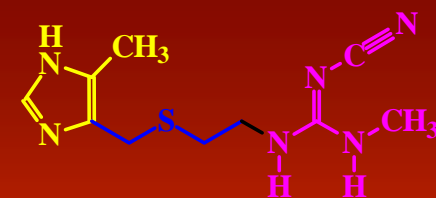
Brit. J. Pharmacol. **66**, 464 (1979)

me-too





ranetidina



cimetidina

Chifre d'affaires (2003): US\$ **35,0** bilhões

Investimentos R&D: US\$ **4,9** bilhões

Pipeline: 53 projetos em fase pré-clínica

148 projetos em desenvolvimento:

83 NCE's, 20 vacinas, 45 produtos

➤ **pequenas moléculas, grandes negócios;**



Universidade Federal do Rio de Janeiro

Laboratório de Avaliação e Síntese de Substâncias Bioativas



UFRJ campus



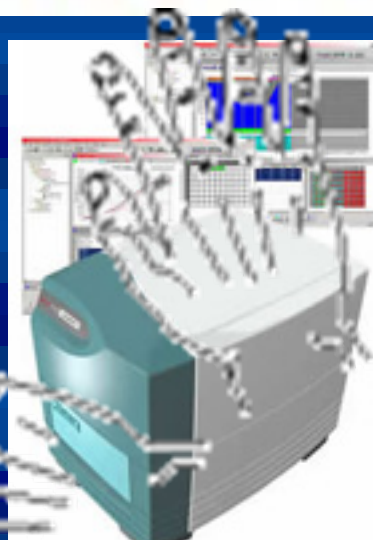
Química Medicinal



1993  2008
15 anos

Composição (03/2008)
05 doutorandos, 13 mestrandos, 13 IC's,
05 professores & 03 pós-doutores

Química Medicinal



Bioinformática

Química

Bioensaios



Biologia

Síntese Orgânica Medicinal

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LASSBIO

Pesquisar

[Pesquisa avançada](#)[Preferências](#)Pesquisar: ☒ a web ☐ páginas em português ☐ páginas do Brasil

Web

Resultados 1 - 10 de aproximadamente 13.300 para LASSBIO (0,12 segundos)

Dica: Ganhe tempo tecando Enter ao invés de clicar em "Pesquisar"

06/11/2007

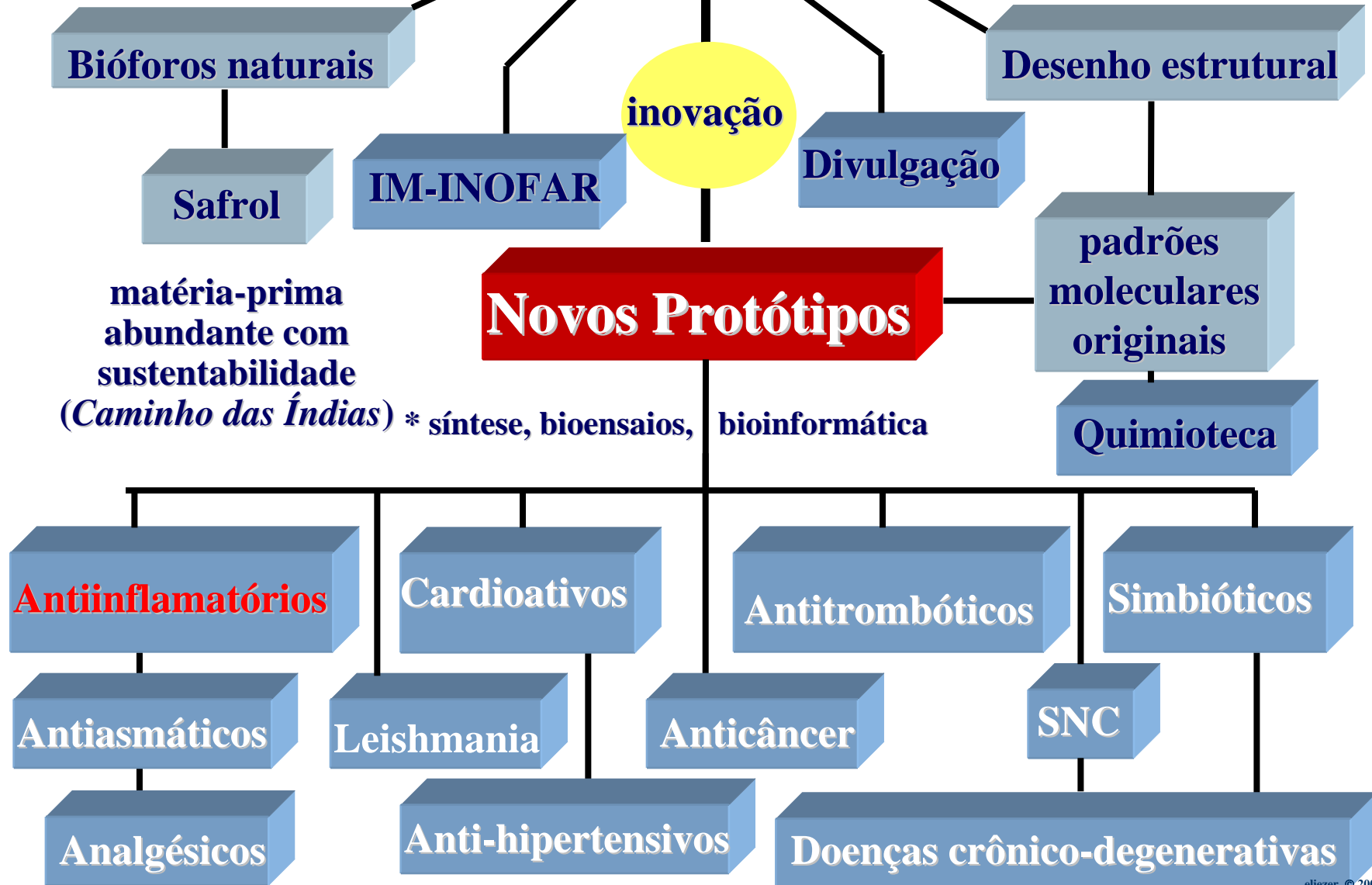
[LASSBio - Faculdade de Farmácia da UFRJ](#)Atualizada em: Desenvolvida por: Cúpula Informática · <<< **LASSBio** cadastra candidatos a Pós-Doutoramento >> · XIV EVQFM - 11 a 15 de fevereiro de 2008 ...www.farmacia.ufrj.br/lassbio/ - 2k - [Em cache](#) - [Páginas Semelhantes](#)[LASSBIO - XII EVQF-QM](#)**LASSBio** - XII Escola de Verão em Química Farmacêutica e Medicinal - Faculdade de Farmácia - UFRJ.www.farmacia.ufrj.br/lassbio/escola_veraoXI/home.html - 14k -[Em cache](#) - [Páginas Semelhantes](#)[[Mais resultados de www.farmacia.ufrj.br](#)][Amigo Oculto LASSBio 2005 - UOL Álbum de fotos](#)

Fotos da festa de confraternização em dezembro de 2005. Visualizar como: Página: 1 ...

ejb.fotos.net.br/amigo_oculto_lassbio_2005 - 23k - [Em cache](#) - [Páginas Semelhantes](#)[XI EVQFM - LASSBio,2005 - UOL Álbum de fotos](#)

Visualizar como: Página: 1 2 3 · Próxima · Fim. Página: 1 2 3 · Próxima · Fim. Visualizar como:

ejb.fotos.net.br/xievqfm - 18k - [Em cache](#) - [Páginas Semelhantes](#)[[Mais resultados de ejb.fotos.net.br](#)][Marco Fernandes - Frascos de vidro - LASSBIO - Faculdade de Farmácia](#)Marco Fernandes - Frascos de vidro - **LASSBIO** - Faculdade de Farmácia - Frascos de vidro utilizados no Laboratório de Avaliação e Síntese de Substâncias ...





LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

Química Medicinal

O Uso do Safrol



1982^{III}



E. J. Barreiro & C. A. M. Fraga, "A Utilização do Safrol, Principal Componente Químico do Óleo de Sassafrás, na Síntese de Substâncias Bioativas na Cascata do Ácido Araquidônico: Anti-inflamatórios, Analgésicos e Anti-trombóticos", *Química Nova*, 22, 744 (1999).

<http://www.scielo.br>

Mediadores da resposta inflamatória

Metabólitos dos sistemas fibrinolítico e coagulação (e.g. plasmina, fibrina)

Cininas (e.g. bradicinina)

Aminas vasoativas (e.g. histamina, serotonina)

Substância P

Produtos da cascata do complemento

Icosanóides (e.g. prostaglandinas, leucotrienos)

Fatores de adesão celular

Citoquinas, Quimicinas

NO

Espécies reativas de radicais oxigenados

Mediadores envolvidos na resolução do processo inflamatório

Lipoxinas/resolvinas

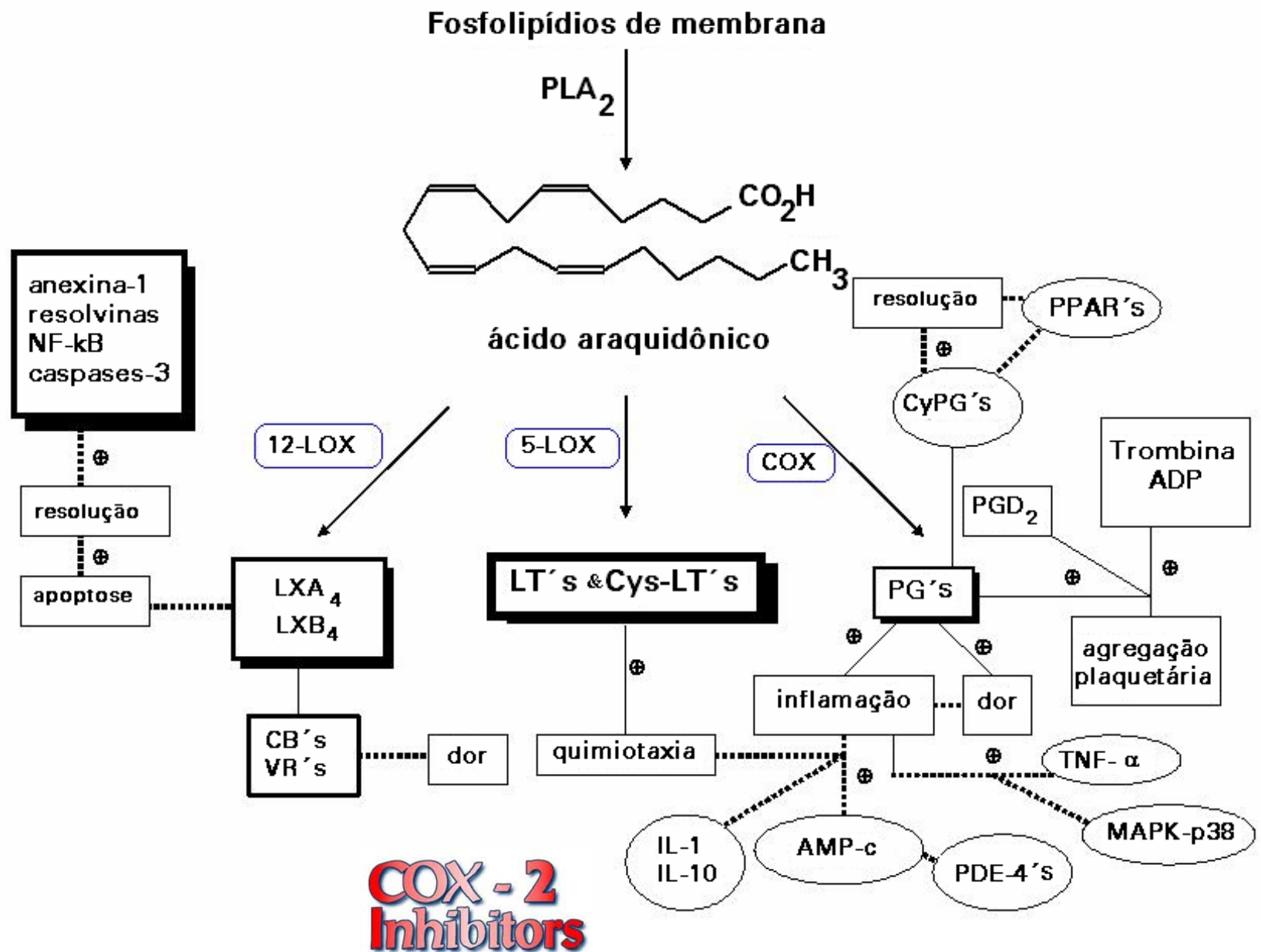
PG-ciclopentanônicas

NFκB

Anexina-1

Caspases (CD44)

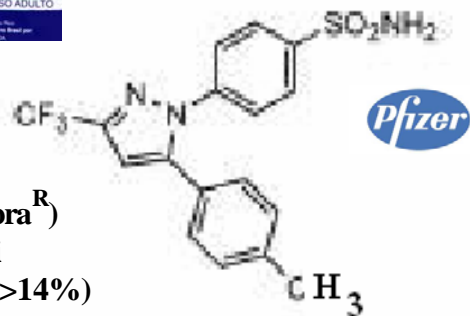
MAPK s (p38)



COX - 2 Inhibitors

CELEBRA[®] 100 mg
(CELECOXIB) USO ADULTO

SEARLE Pfizer

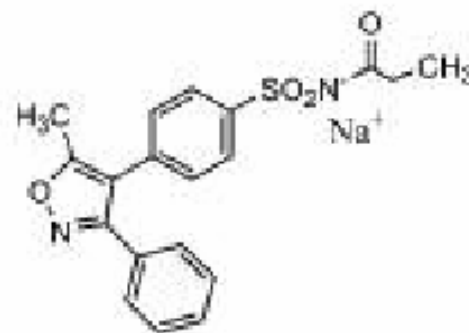


celecoxib (Celebra[®])
US\$ 797 mi
trimestre 2004 (>14%)
(Pfizer)

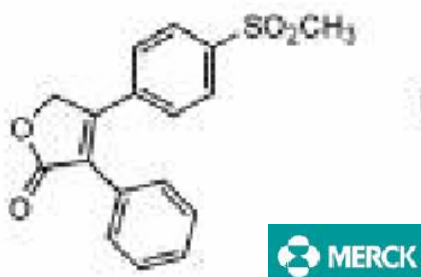
Celecoxib



Valdecoxib



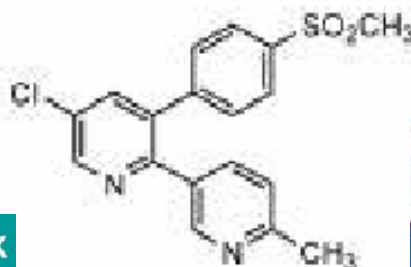
Parecoxib sodium



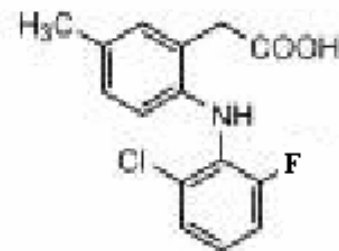
Rofecoxib



1999 – lançamento
09/2004 – retirado*
(APPROVe test)
2004 - US\$ 2.5 bilion



Etoricoxib

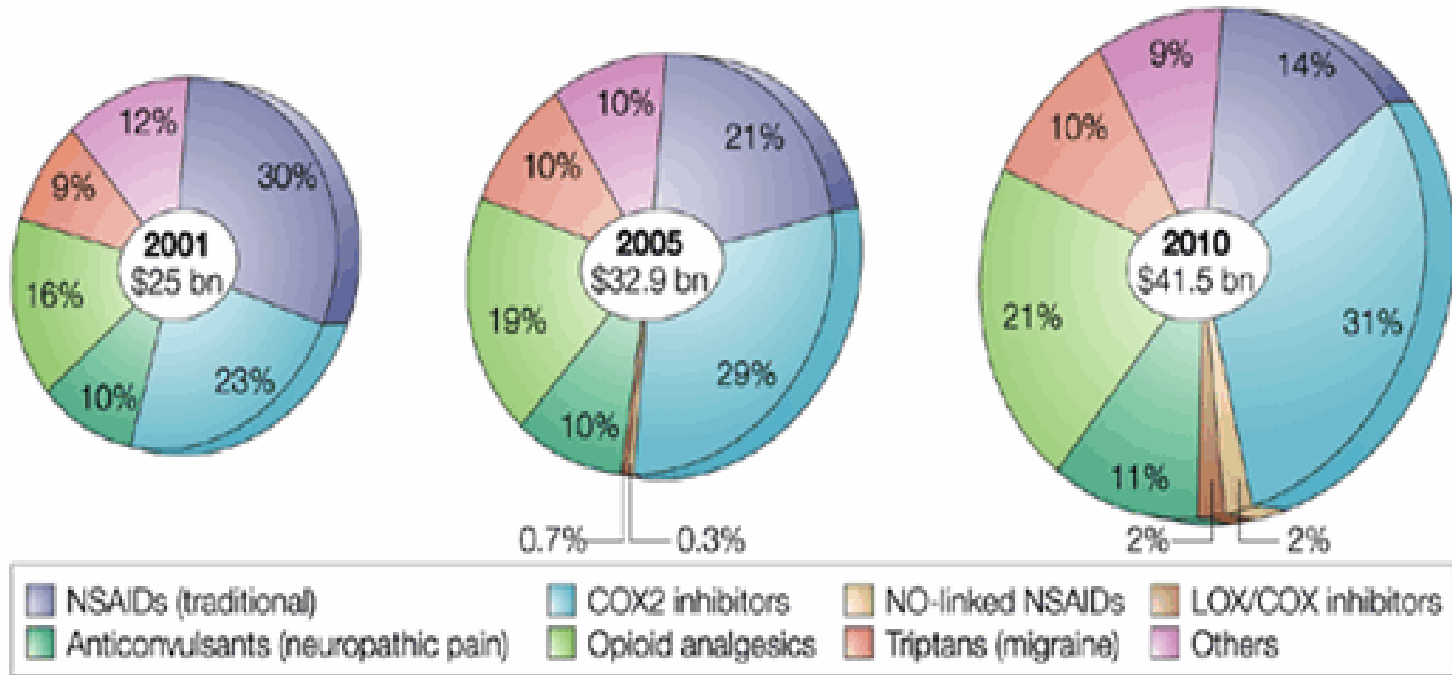


Lumiracoxib

Prexige[®]
Deracoxib* (Deramaxx[®])
Cimicoxib, Tiracoxib

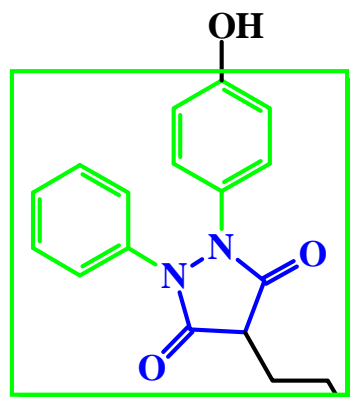
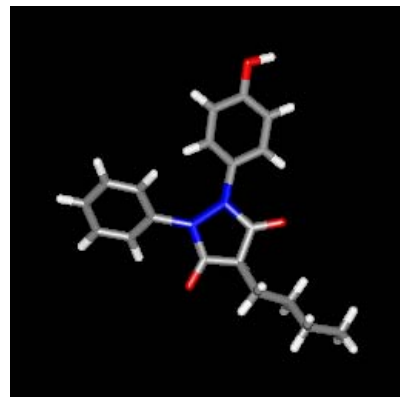
* P. Juni *et al.*, “Risk of cardiovascular events and rofecoxib:cumulative meta-analysis”, *Lancet* 2004, **364**, 2021

Mercado dos Anti-inflamatórios & Analgésicos



Nature Reviews | Drug Discovery

Gênese do Celecoxibe

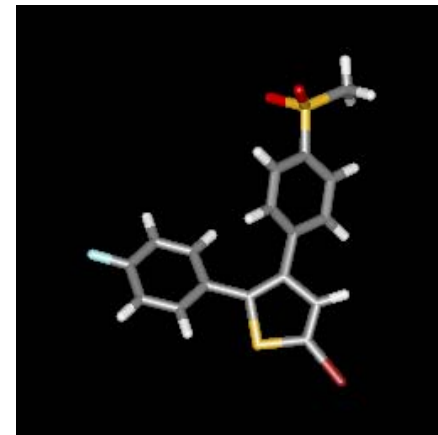
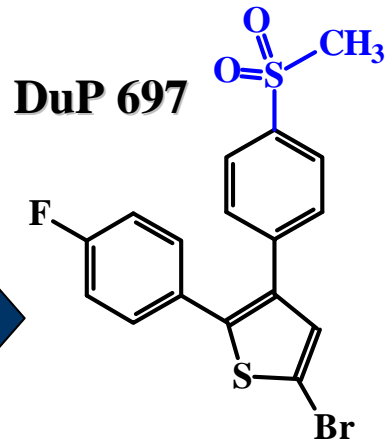


sistema terfenílico

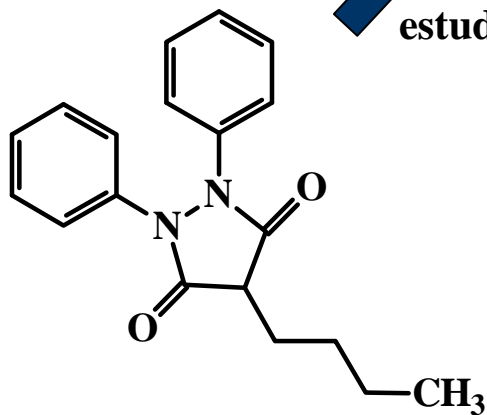
pirazolidinodiona

1956 – Oxifenbutazona (Geigy)

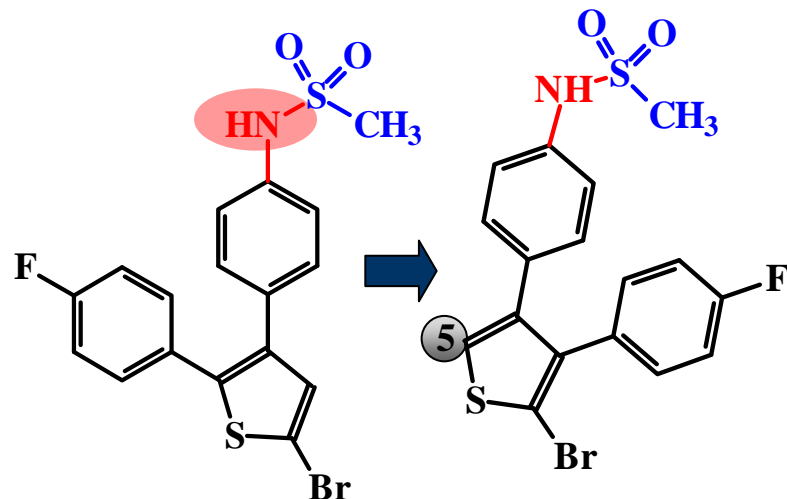
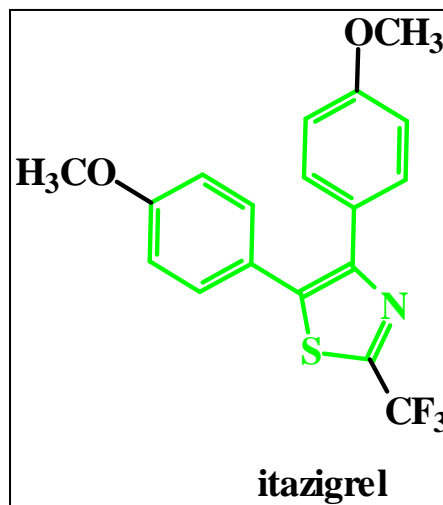
Searle



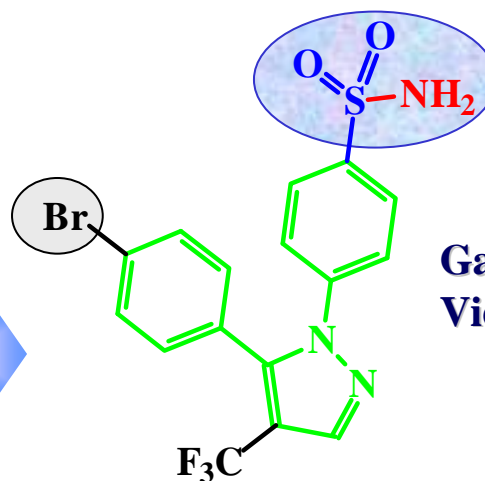
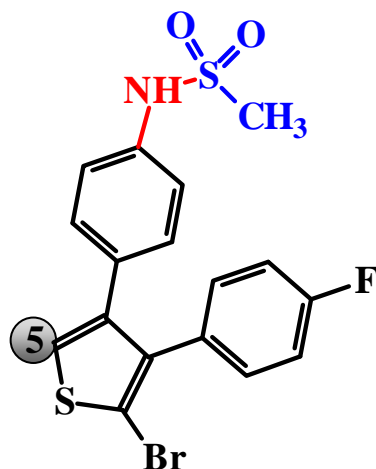
estudos de metabolismo



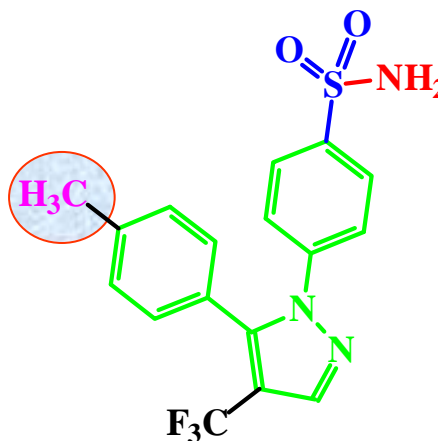
1951 – fenilbutazona (Geigy)



Gênese do Celecoxibe



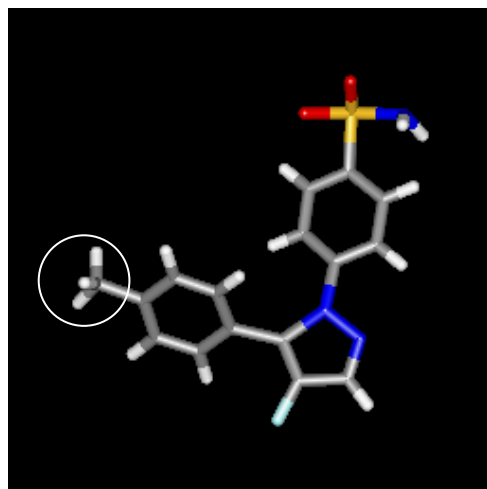
Gans (DuPont) 1990
Vida-média = 12 dias !
(ADME)



nova possível indicação:
 câncer colorretal

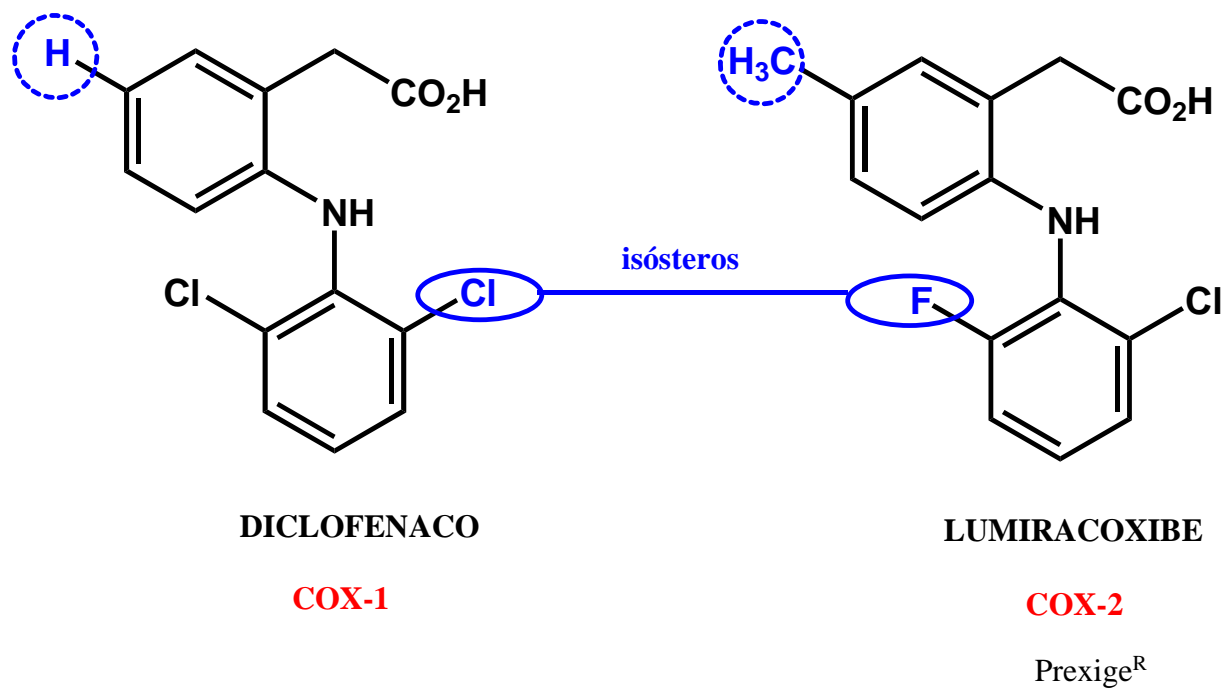


1999



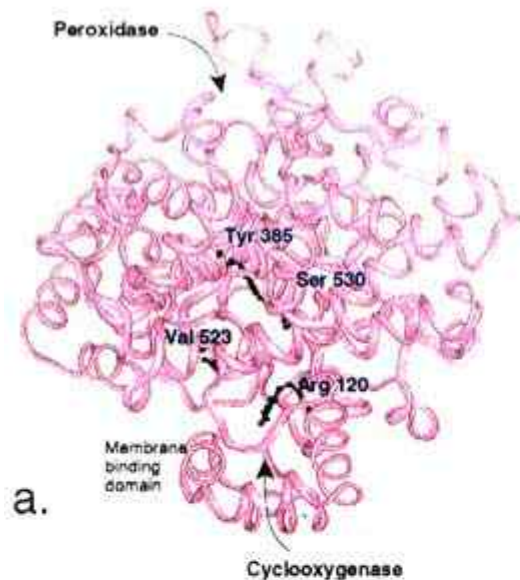
US\$ 2,4 bilhões de vendas em 2006



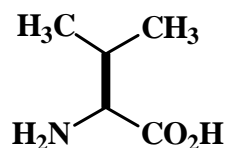


COX-2

Inflamação,
Câncer
Endotélio
vascular
Rins
Cérebro

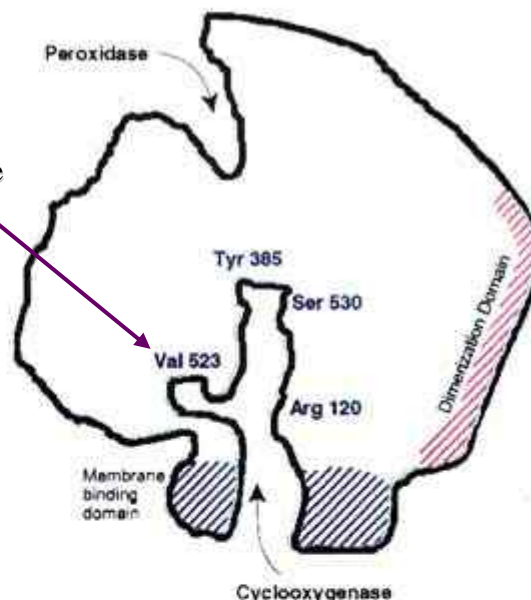


Secondary pocket site



$\text{C}_5\text{H}_{11}\text{NO}_2$
Valina

b.

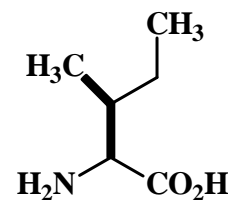
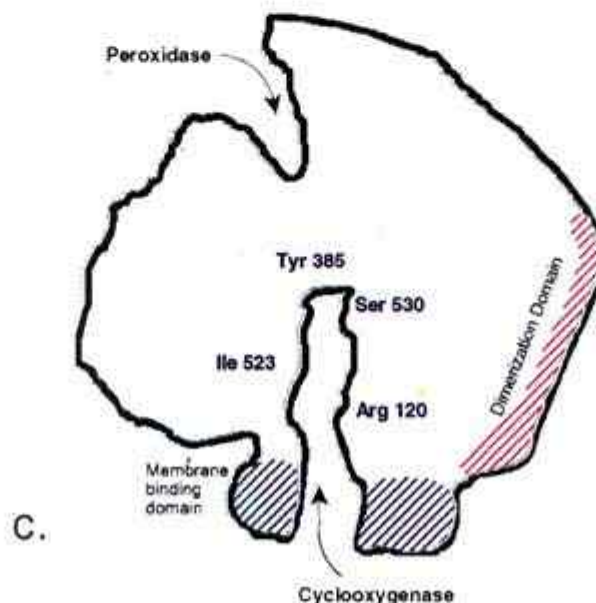


COX - 2
Inhibitors

Bad guy X good guy

COX-1

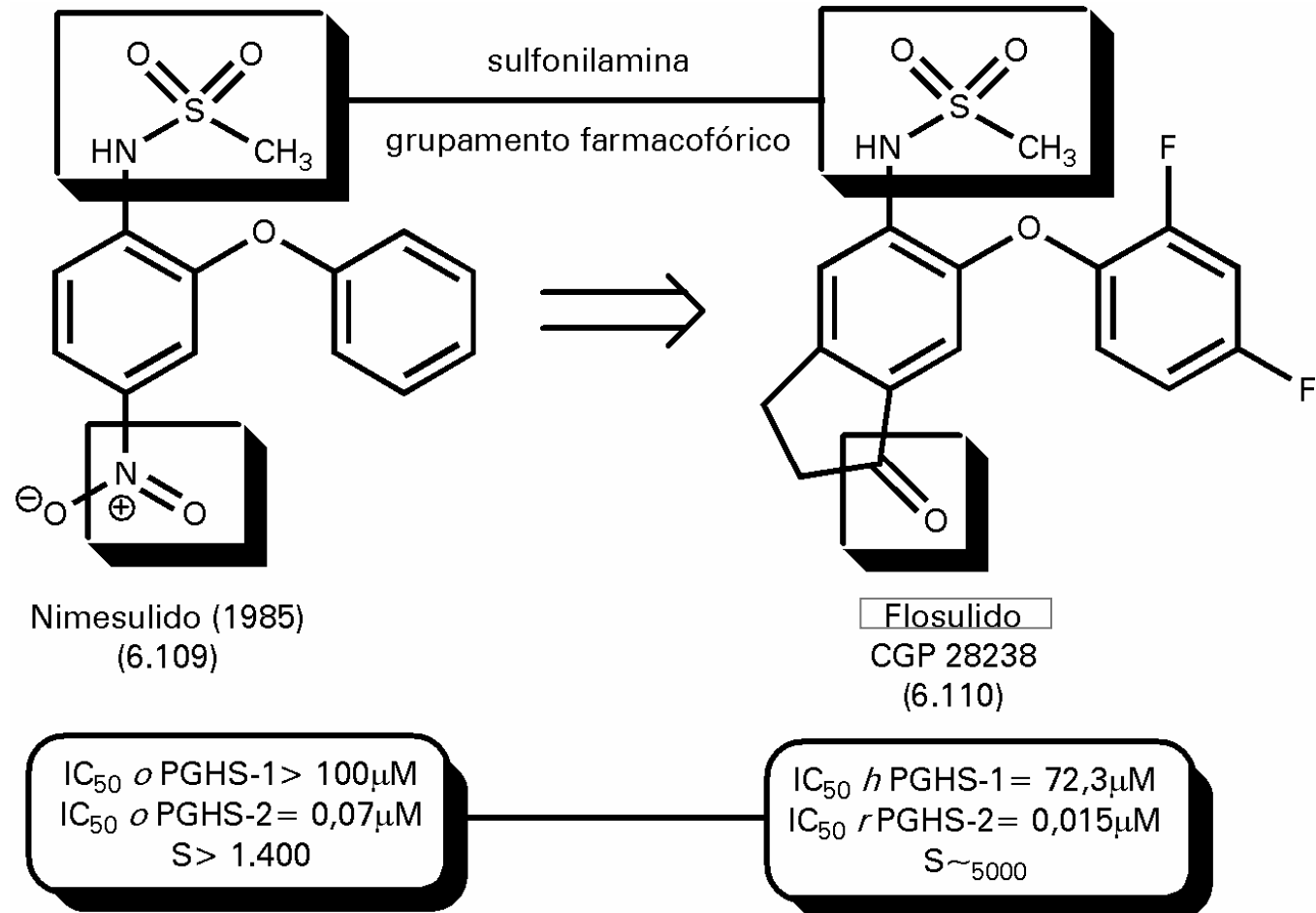
Plaquetas,
Estômago,
Rins

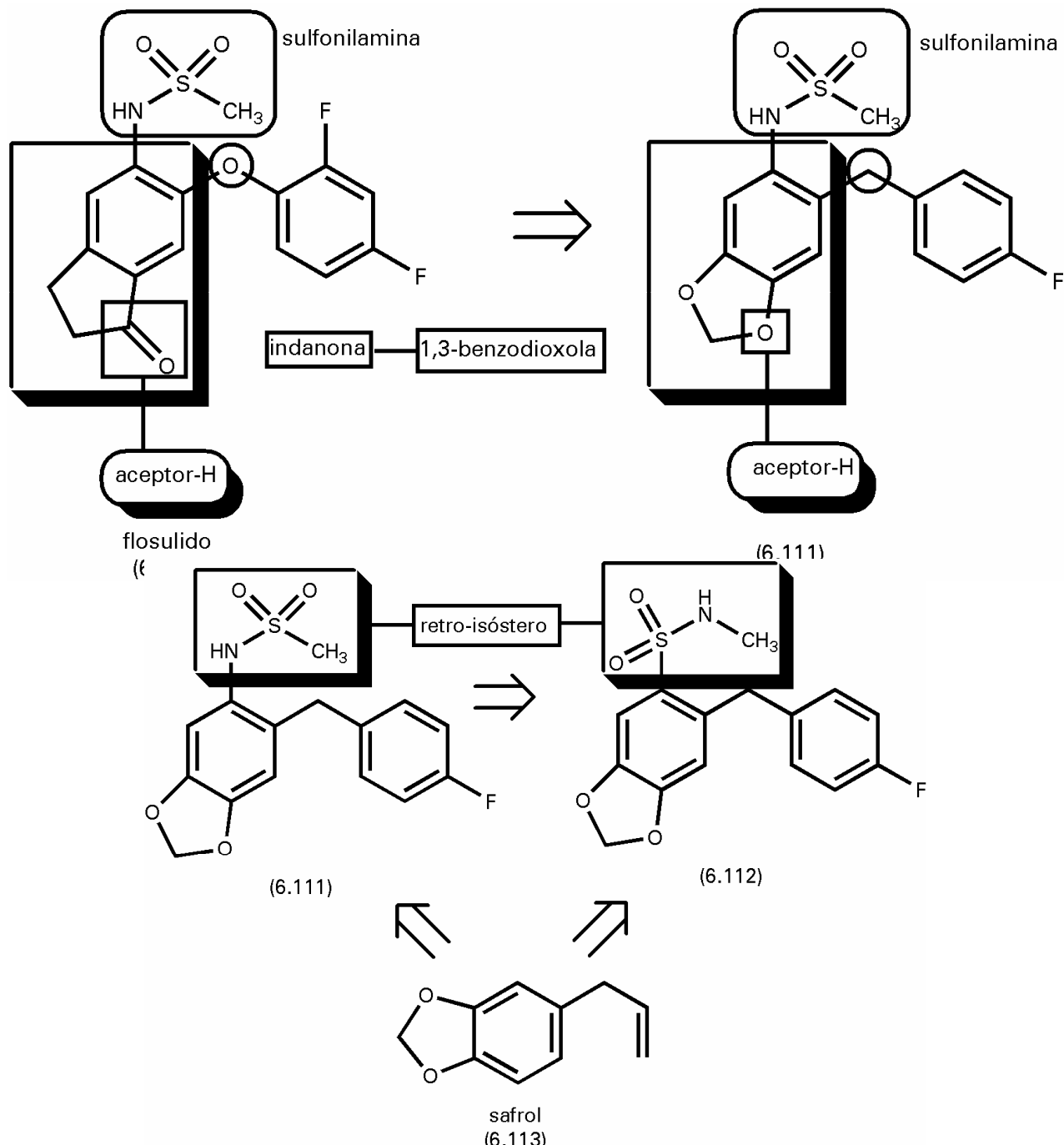


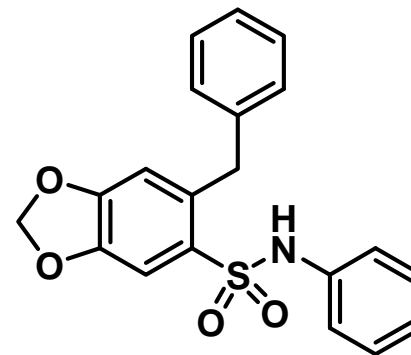
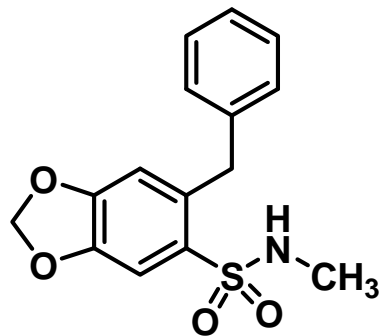
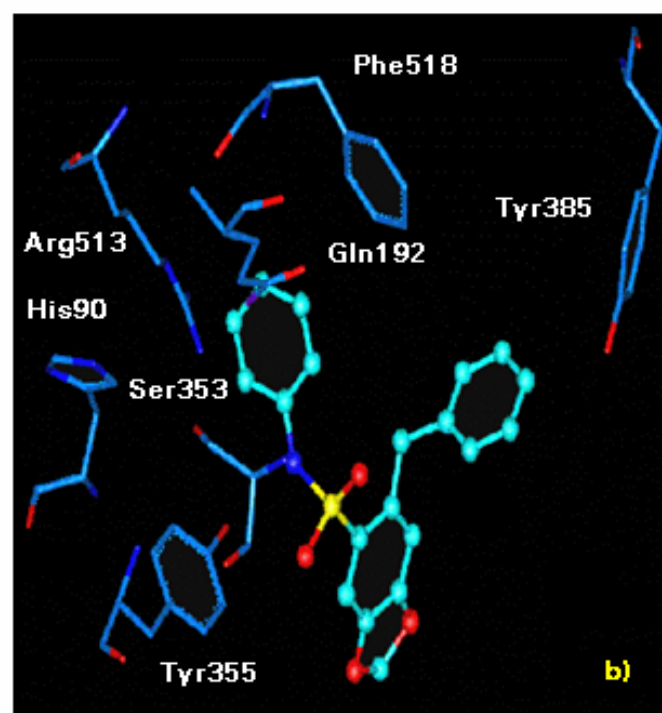
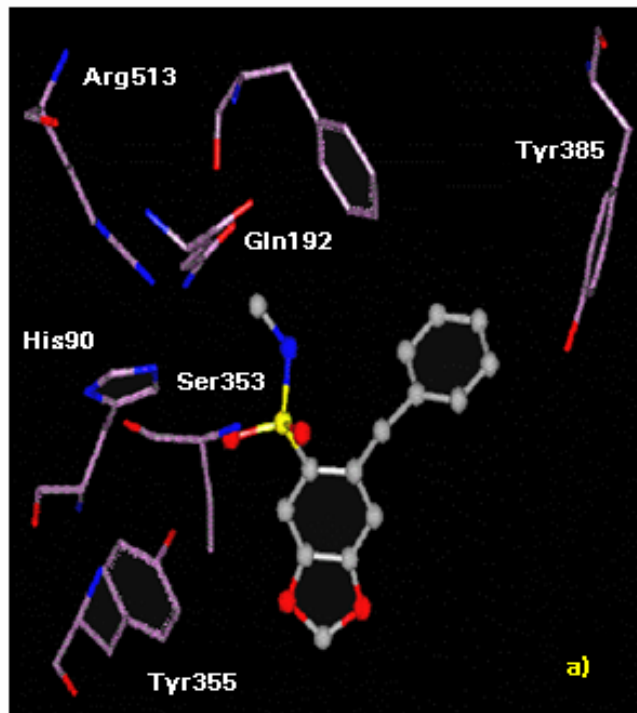
$\text{C}_6\text{H}_{13}\text{NO}_2$
Isoleucina

LASSBio-349: novo tipo de bioisosterismo

O início... lendo a literatura de patentes







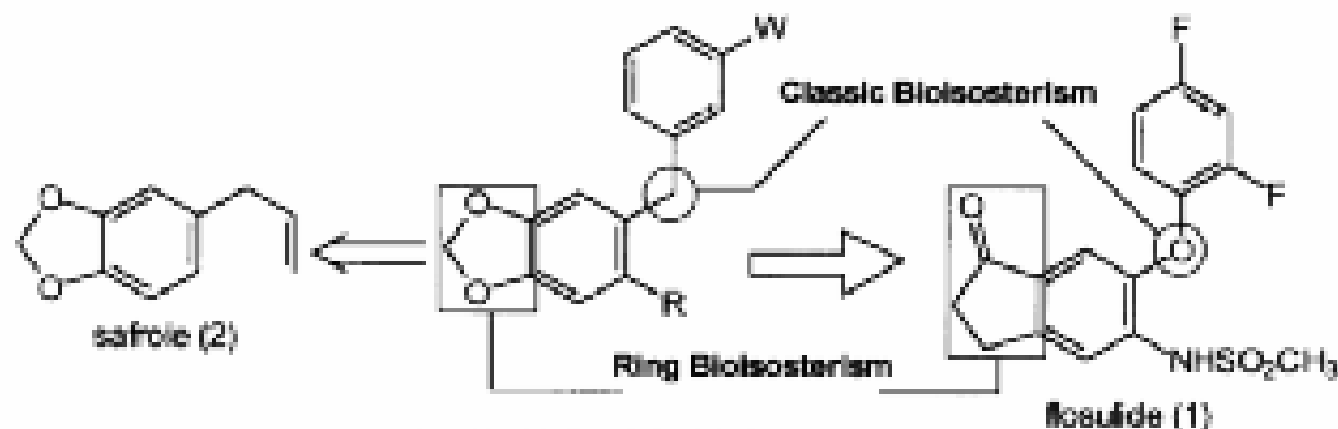
SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF NEW FLOSULIDE ANALOGUES, SYNTHESIZED FROM NATURAL SAFROLE

Adriana S. Lages,^{a,b} Kelli C. M. Silva,^a Ana L. P. Miranda,^a Carlos A. M. Fraga,^a and Eliezer J. Barreiro,^a

^a*Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, CP 68006, ZIP 21944-970, Rio de Janeiro - RJ, Brazil*

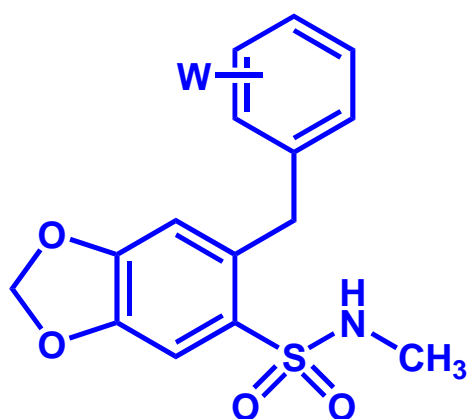
^b*Departamento de Química Orgânica, Instituto de Química, Universidade Federal do Rio de Janeiro, Rio de Janeiro - RJ, Brazil*

Received 27 October 1997; accepted 2 December 1997

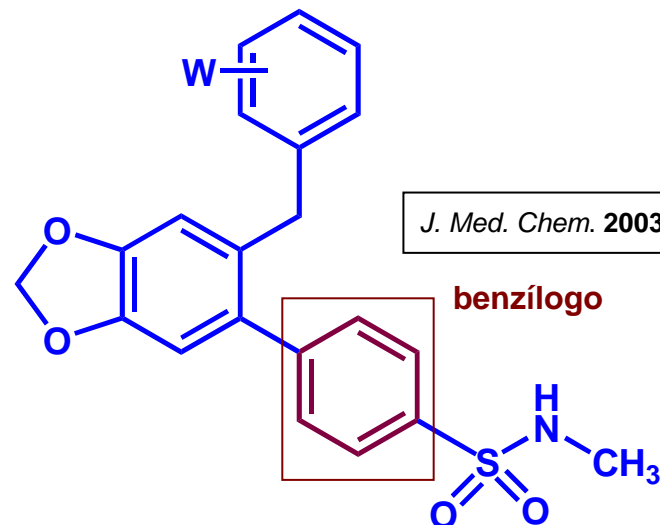


- 3a W = H; R = SO₂NHCH₃
 3b W = CF₃; R = SO₂NHCH₃
 4a W = H; R = SO₂NHPh
 4b W = CF₃; R = SO₂NHPh
 5a W = H; R = NHSO₂CH₃
 5b W = CF₃; R = NHSO₂CH₃

Novos análogos benzílogos do LASSBio-349



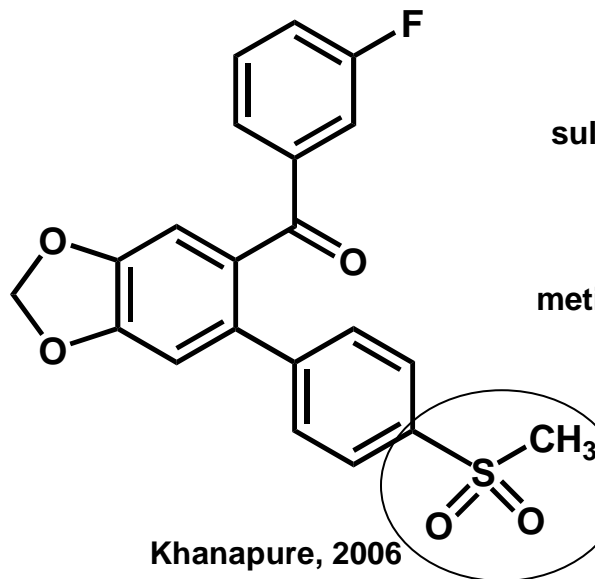
Lages, 1998



J. Med. Chem. **2003**, 46, 5484

benzílogo

Khanapure, 2003



sulfonamida



metilsulfona

J. Med. Chem. **2005**, 48, 3930

Khanapure, 2006

Nova Classe de Candidatos a Fármacos NSAID de Segunda Geração

LEAD COMPOUND
Lead-optimization

CgIRPE*

1999

LASSBio
Laboratório de Análise e Síntese de Substâncias Bioativas

	DI ₅₀	Max. Eff.
CELECOXIB 	87,7 $\mu\text{mol/kg}$	35%
LASSBio 715	44,3 $\mu\text{mol/kg}$	39%
LASSBio 445	54,6 $\mu\text{mol/kg}$	37%

Química Medicinal

Patent: PI 9902960-0 (29/04/99)

E. J. Barreiro *et al.*, Selective PGHS-2 Inhibitors: A Rational Approach for Treatment of the Inflammation, *Current Medicinal Chemistry* 2002, 9, 849



Drug Data Report

Prous Science Ed. (ES)

Vol. 23, No. 10, 2001

ASTHMA THERAPY

PROUS SCIENCE
JOURNALS



New Lead-compounds

12611 (Boehringer Ingelheim)

312652 (Bayer)

313027 (GlaxoSmithKline)

KCO-912 (Novartis)

LASSBIO-341



LASSBio
Laboratório de Pesquisa e Síntese de Substâncias Bioativas





Patentes depositadas



PI-0403363-9 20/08/2004 → ***Relaxantes musculares seletivos***

PI 0500727-5 (03/03/2005) → ***Novos candidatos neuroativos***

PI-0502016-6 03/06/2005 → ***Inibidores de p38MAPK como AI***

PI 0601885-8 (15/05/2006) → ***Novos analgésicos/AI***

PI 0303465-8 em 05/09/2003 → ***N-fenilpiperazínicos***

Moléculas que falam português...

PI-0401660-2(09 /04/2004) → ***LASSBio-596 como anti-asmáticos***

PI-0403105-9 20/05/2004 → ***LASSBio-693 como anti-trombóticos***



“...**discovery** *consists* of seeing
what everybody else has seen
and thinking what
nobody else
has not thought...”



Albert Szent-Györgi (1893-1986)

Novos Compostos-Protótipos Descobertos no LASSBio

Biochem. Eng. J., 21, 103 (2004)

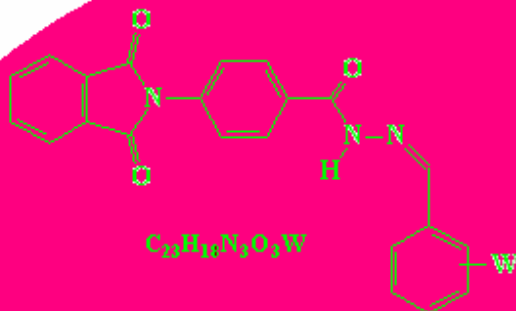
Bioorg. Med. Chem. Lett, 15, 1169 (2005)

Applied Biochem. Biotechnol., 121, 117 (2005)

Eur. J. Pharmacol., 511, 219 (2005)

INPI # 0401660-2 de 09/04/2004

LASSBio-552



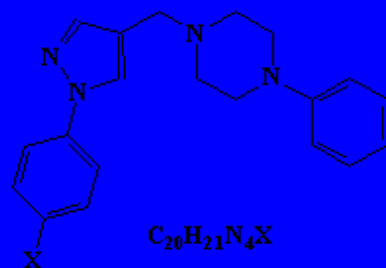
LASSBio-753

INPI # 38201866 de 29/04/1999

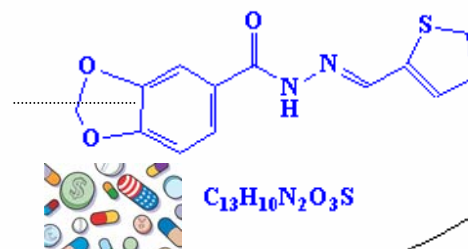
LASSBio-715



LASSBio-581



LASSBio-294



USPTO Patent # 7.091.238
August 15, 2006

INPI # 0303465-8 de 05/09/2003

Braz. J. Biol. Med. Res., 36, 625 (2003)

Bioorg. Med. Chem., 11, 4807 (2003)

J. Pharm. Biomed. Anal., 33, 1127 (2003)

Quim. Nova, 27, 949 (2004)

J. Mass Spectrometry, 40, 815-820, (2005)



J. Pharmacol. Exper. Therap., 299, 558 (2001)

Br. J. Pharmacol., 134, 603 (2001)

Br. J. Pharmacol., 135, 293 (2002)

Quim. Nova, 25, 1172 (2002)

Eur. J. Pharmacol., 470, 79 (2003)

INPI # 0403363-9 de 20/08/2004



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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
07091238	08/15/2006	7091238	33390-178943	9691

26894 1991
VENABLE LLP
P.O. BOX 34385
WASHINGTON, DC 20045-9998

**Thienylhydrazon with digitalis-like properties
(positive inotropic effects)**

7.091.238

August 15, 2006

ISSUE NOTIFICATION

Publication Number: 07091238

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)

(application filed on or after May 29, 2000)



The Patent Term Adjustment is 109 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571) 272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

APPLICANT(s) (up to 18 names are included below, see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

Roberto Takashi Sudo, Rio de Janeiro, BRAZIL;

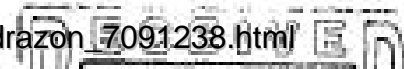
Edson X. Albuquerque, Baltimore, MD;

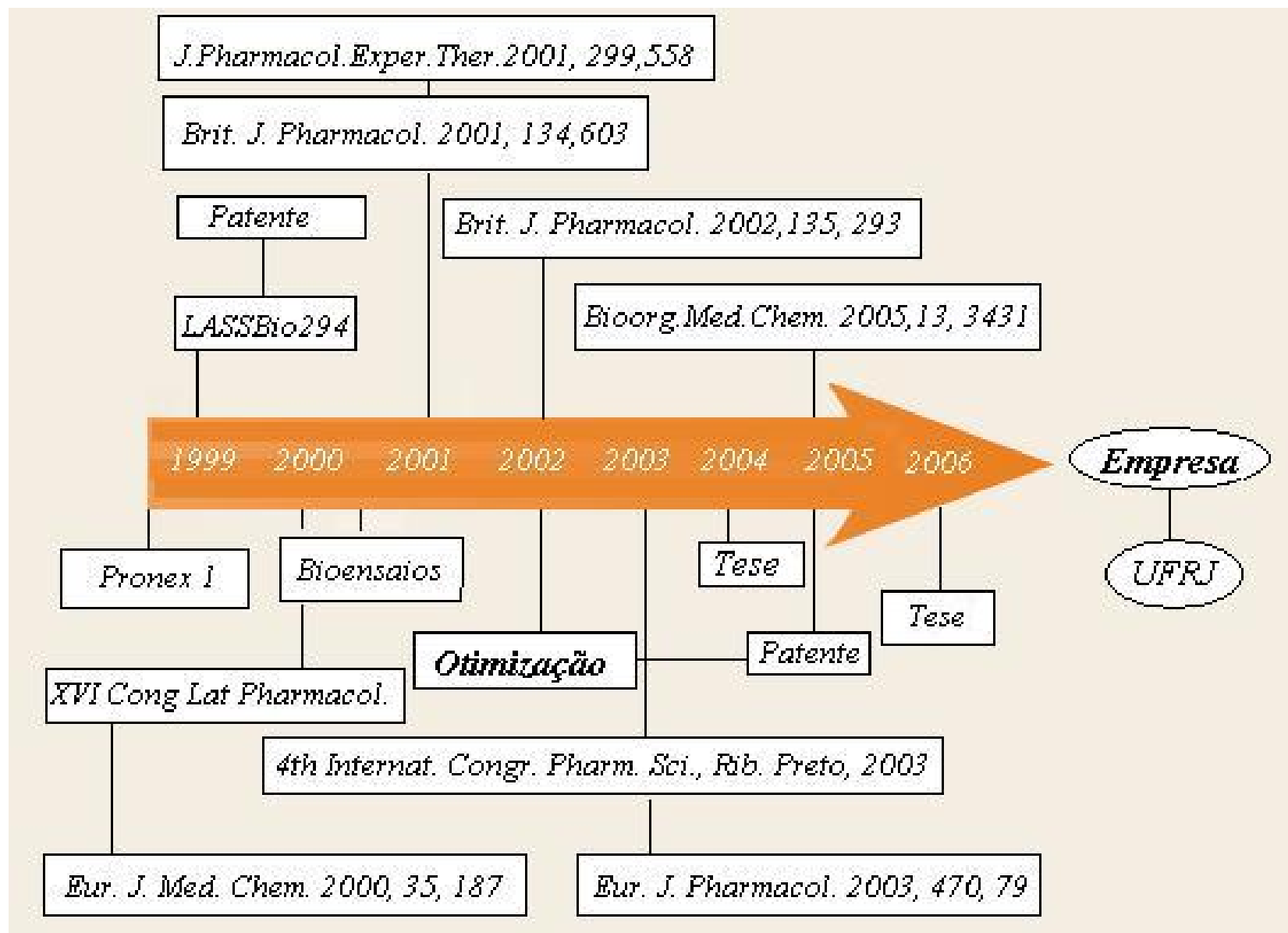
Eliezer J. De Barroiro, Rio de Janeiro, MD;

Yasuo Amcava, Rio de Janeiro, BRAZIL;

Wagner Monteiro, Curitiba, Rio de Janeiro, BRAZIL;

http://www.linkfinder.com/Patents/Thienylhydrazon_7091238.html







Catalog Name: ChemDiv, Inc. Product Library



Publication Date: 25 Apr 2003

Order Number: 2358-0022

Chemical Name: 1,3-Benzodioxole-5-carboxylic acid-2-thienylmethylenehydrazide

Registry Number: 314021-07-3

Pricing: Quantity : milligram quantities, **Price:** contact supplier

Company Info: ChemDiv, Inc.

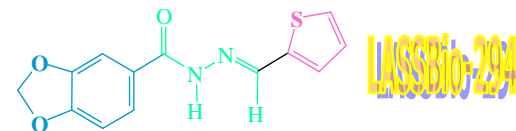
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Suite 210 San Diego, CA, 92121 **USA**

Phone: +1-858-794-4860 Fax: +1-858-794-4931

Email: info@chemdiv.com

Web: <http://www.chemdiv.com>



Catalog Name: Scientific Exchange Product List

Publication Date: 18 Feb 2005

Order Number: X-026756

Chemical Name: 1,3-Benzodioxole-5-carboxylic acid (2-thienylmethylen)hydrazide

Registry Number: 314021-07-3

Pricing: Quantity : milligram quantities, **Price:** contact supplier

Company Info: Scientific Exchange, Inc.

105 Pine River Road P O Box 918 Center Ossipee, NH, 03814 **USA**

Phone: (603) 539-7436 Fax: (603) 539-7438

Email: sales@htscompounds.com

Scientific Exchange, Inc.
Supplier of HTS compounds



Web: <http://www.htscompounds.com>

Protótipos em estudo 1



FMRP-USP



● Antinociceptivo

(analgésico para dor neuropática)



LASSBio-753: novo mecanismo de ação

**IM-INO FAR: Prof. Sérgio H. Ferreira,
Prof. Fernando Queiroz Cunha**



Instituto do Milênio

Inovação e Desenvolvimento de Fármacos e Medicamentos



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- O Instituto do Milênio - Inovação e Desenvolvimento de Fármacos e Medicamentos é um Projeto apoiado pelo [CNPq](#) e coordenado pelo Prof. Eliezer J. Barreiro.
- [O Im-Inofar disponibilizou alguns links interessantes na área de fármacos e medicamentos.](#)



Apoio:



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Cúpula Informática

Contatos:
ibelza@ccsdecania.ufri.br e naccor@ccsdecania.ufri.br

Atualizada em
Terça, 31 de Janeiro de 2006

Projeto apoiado pelo CNPq, sob nº de Pr

Protótipos em estudo 2



- Neuroativo, anti-Alzheimer

- AChEi



- LASSBio-785: PN-domesticado & otimizado

- IM-INO FAR: Profa Vanderlan Bolzani

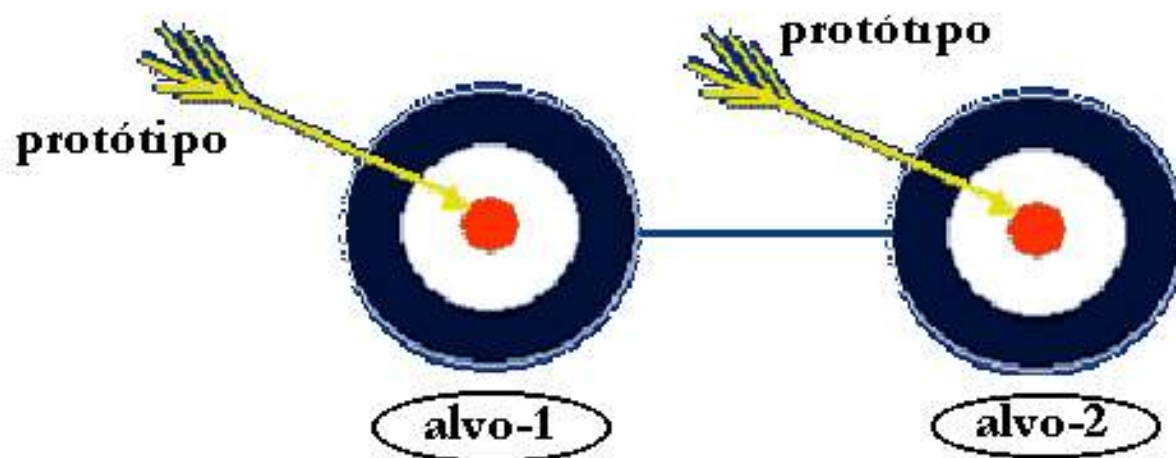


(ah...) Final ...



Fármacos Simbióticos

O desenho estrutural do novo candidato a protótipo é planejado de maneira a permitir seu reconhecimento molecular por dois distintos sítios receptores, simultaneamente, envolvidos na mesma fisiopatologia



New Insights for Multifactorial Disease Therapy: The Challenge of the Symbiotic Drugs

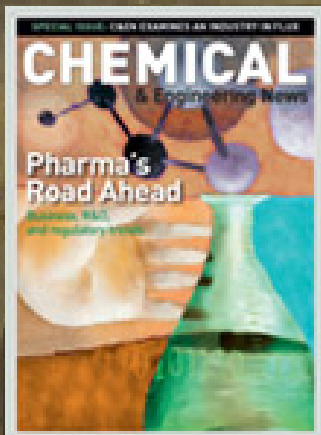
Eliezer J. Barreiro and Carlos Alberto Manssour Fraga

Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, P.O. Box 68023, 21944-971, Rio de Janeiro, RJ, Brazil.

Abstract: Some physiopathological processes involved in the genesis of diseases could suggest the necessity of designing bioligands or prototypes that aggregate, in only one molecule, dual pharmacodynamical properties, becoming able to be recognized by two elected bioreceptors. This approach can have distinct aspects and, when a novel ligand or a prototype acts in two elected targets belonging to the same biochemical pathway, *e.g.* arachidonic acid cascade, it receives the denomination of dual or mix agent. On the other hand, if these two targets belong to distinct biochemical routes and both are related to the same disease, we can characterize the agents able to modulate it as symbiotic ligands or prototypes. In the present work, we provide some examples and applications of the molecular hybridization concept for the structural design of new symbiotic ligands and prototypes, especially those applied in the treatment of chronic-degenerative disorders.

Key Words: Symbiotic drugs; molecular hybridization; multifactorial diseases; therapeutic innovation; drug design; dual compounds.





*“...history suggests drug
discovery
is art as well as science
and relies heavily on the skill
of experienced drug hunters...”*

(C&EN, June 19, 2006)



Obrigado

Corcovado, Cristo Redentor, uma das sete novas maravilhas do mundo !



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