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Aspectos da Química Farmacêutica Medicinal

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Faculdade de Farmácia**



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



Faculdade de Farmácia
Universidade Federal da Bahia
22-25 de setembro de 2008

DRS '91

Aspectos da Química Farmacêutica Medicinal

Sumário

1. Os fármacos & a Química Medicinal
2. Como se descobrem os fármacos? *Os fármacos e os prêmios Nobéis*; Como atuam os fármacos?
3. A *dissecação* molecular : grupo farmacofórico
4. Moléculas *inteligentes*: os alfabetos moleculares
5. *Domesticando* moléculas naturais
6. O paradigma do composto-protótipo
7. Fármacos *simbióticos*: exemplos *de casa*
8. Epílogo

O Curso trata do fármaco...





O que é o fármaco ?

- **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 (?);

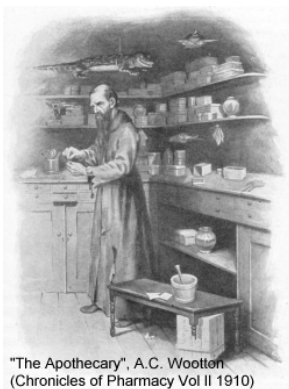
- ... as propriedades moleculares dos fármacos são objeto do estudo da **Química Medicinal**



Química Medicinal

O que é ?

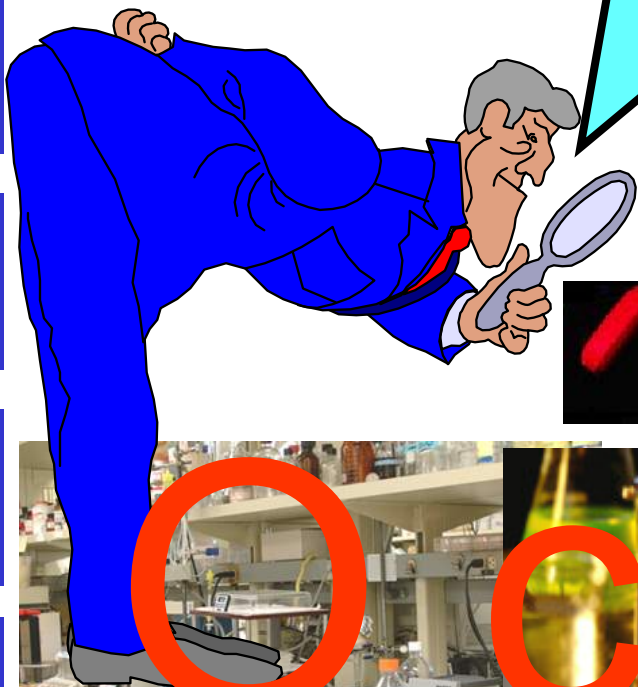
Prá que serve ?



"The Apothecary", A.C. Wootton.
(Chronicles of Pharmacy Vol II 1910)

Como **se** descobrem
os fármacos ?

Química Medicinal



curso



Química Medicinal





O processo da descoberta é complexo...

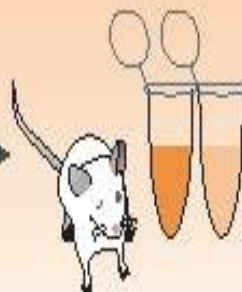


Research team formed
and objectives set

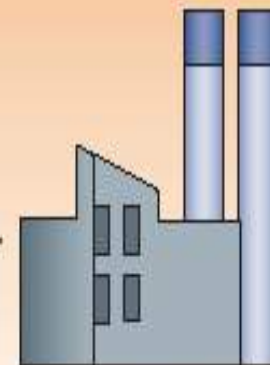


Química Medicinal

Lead compound
Composto-protótipo



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



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



Company files
Investigational New
Drug (IND) application
with FDA

Química Medicinal



Clinical studies



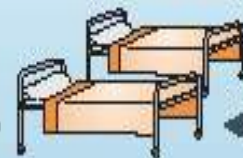
Drug is approved
for marketing

ANVISA
ANVISA
FDA

FDA reviews NDA



Company files New
Drug Application (NDA)



Phase III: large clinical
trials in many patients



Phase II: studies
in patients (efficacy)



Phase I: studies
in healthy humans
(toleration)

Adaptado de Joseph Lombardino



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

eliezer © 2008



Química Medicinal

Prof. Alfred Burger

(1904-2000)

University of Virginia

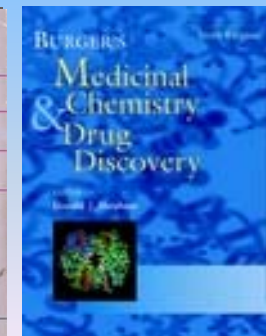
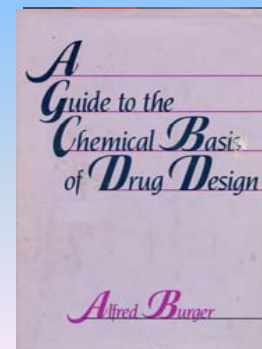
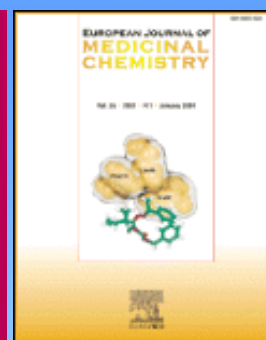
EUA

Pioneiro na Química Medicinal

Criou as bases do planejamento racional para a descoberta de novos fármacos

“Tries to be based on the ever increasing hope that biochemical rationales for drug discovery may be found”

J. Med. Chem. (ACS) vol. 34, 1991





Subcommittee Medicinal Chemistry and Drug Development



Meeting of the SC in Rio de Janeiro, Feb.13, 2005:
standing, from the left: Jörg Senn-Bilfinger, John Proudfoot, Janos Fischer, Mukund Chorghade, Eliezer J. Barreiro, Antonio Monge and Eli Breuer;
sitting: Paul W. Erhardt and Robin Ganellin

Química Medicinal

*estuda os aspectos relacionados à descoberta,
invenção de substâncias bioativas
de interesse terapêutico, i.e. fármacos.*

*Estuda os fatores moleculares do seu modo de ação,
incluindo a compreensão da relação entre a estrutura química
e a atividade (SAR), a absorção, distribuição,
metabolismo, eliminação e toxicidade.*

Eur. J. Med. Chem. 1996, 31, 747; C. R. Ganellin et al., Eur. J. Med. Chem. 2000, 35, 163

IUPAC

<http://www.iupac.org>



IUPAC

Chemistry and Human Health Division (VII)
Subcommittee on Medicinal Chemistry
and Drug Development.

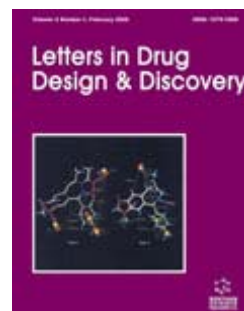
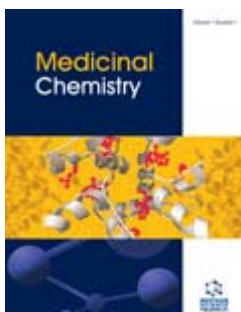


A interdisciplinaridade ...





Química Medicinal



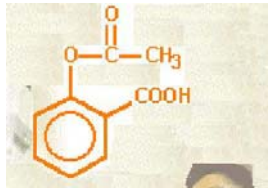
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(Universidade Federal do Rio de Janeiro, RJ, Brazil)

<http://bentham.org/open/>

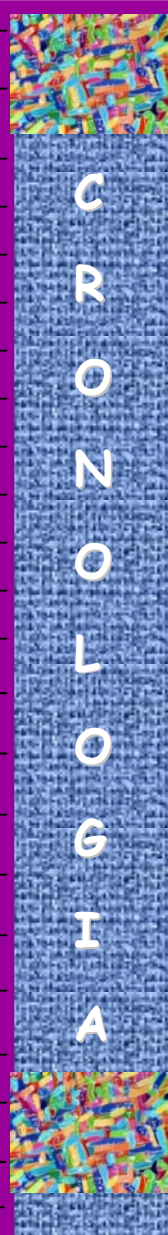




Cronologia da descoberta de fármacos

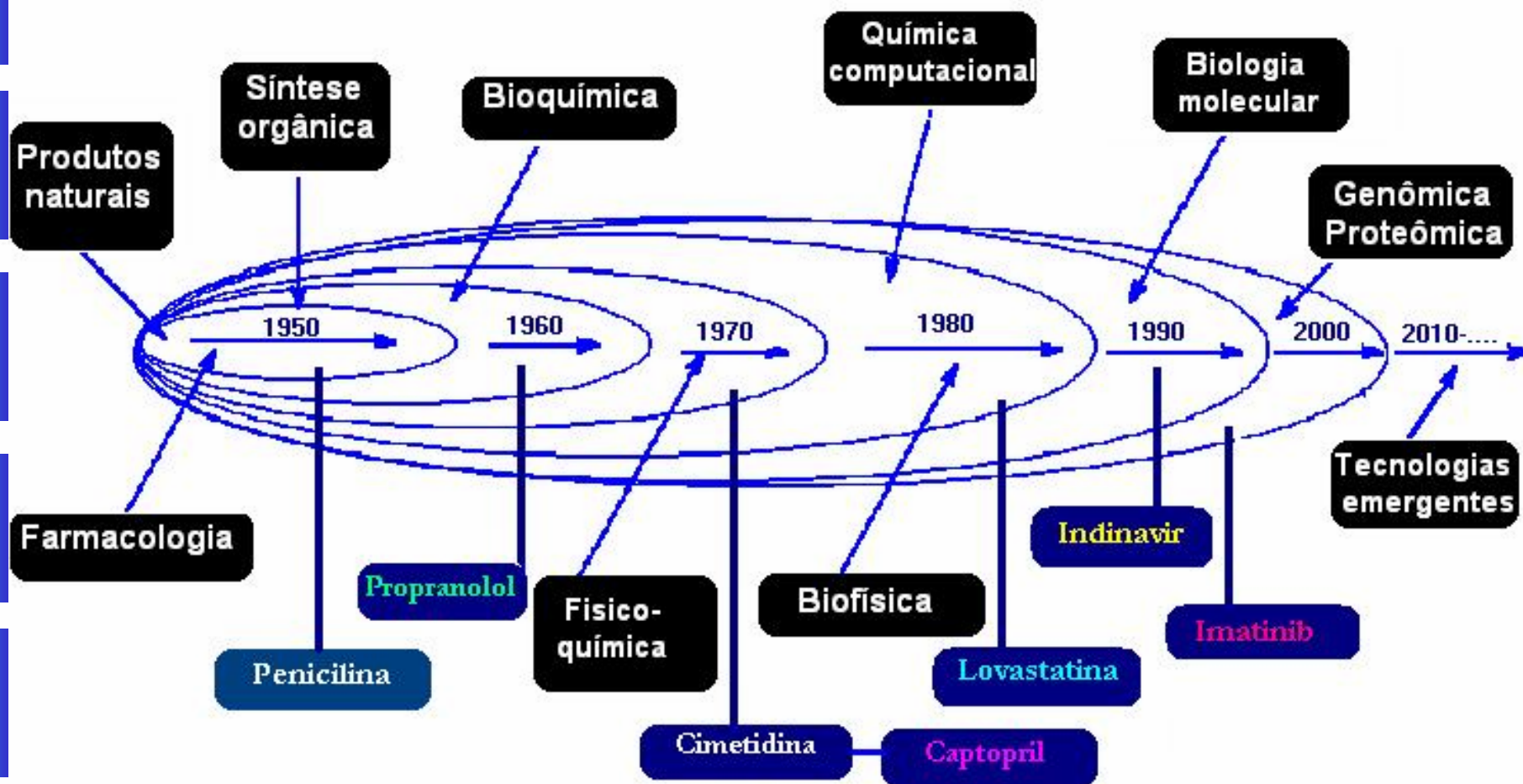


AAS *	1889		1986	ciprofloxacina fluoxetina
barbitúricos	1923		1987	zidovudina lovastatina
cloroquina	1934		1988	cetirizina, enalapril
sulfonamidas	1935		1989	ozagrel mifepristona
penicilina	1942		1990	salmeterol, amlodipina
nitrofurano	1952		1991	alpidem, paroxetina
progesterona	1953		1992	paclitaxel
talidomida	1954		1993	tacrina, fanciclovir
haloperidol	1958		1994	irinotecan, pimobendano
verapamil	1962		1995	indinavir, losartano
indometacina	1963		1996	docetaxel, atorvastatina
propranolol	1964		1996	zileuton, olanzapina
salbutamol	1968		1997	zafirlukast, montelukast
prostaglandinas	1970		1998	infliximabe sildenafil efavirenz
oxamniquina	1970		1999	celecoxibe orlistate oseltamivir
cimetidina nifedipina	1975		2000	galantamina rofecoxibe
atenolol	1976		2001	imatinibe rosiglitazona
captopril	1977		2002	voriconazola, etoricoxibe
tamoxifeno	1978		2003	gefitinibe, aripiprazola
praziquantel	1979		2004	rosuvastatina, rofecoxibe
oxicams	1980		2005	pregabalina, Caduet ^R
ranitidina aciclovir	1981		2006	risperidona, erlotinibe
mefloquina misoprostol	1985		2007	ambrisentam, maraviroc *
			2008	etravirina





A evolução da Química Medicinal



Química Medicinal

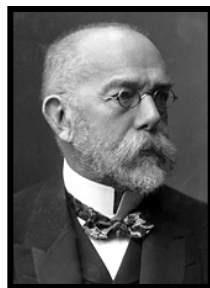


“for their discoveries of important principles for drug treatment”

<http://nobelprize.org>



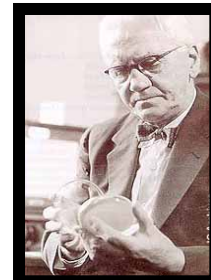
1902– EH Fisher



1905-R Koch



1908- P Ehrlich



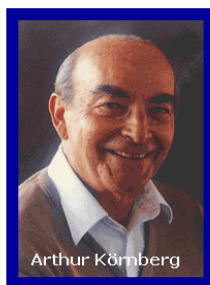
1945– A Fleming



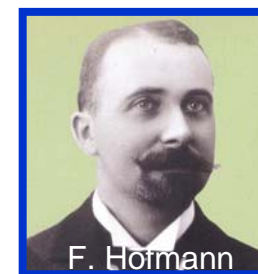
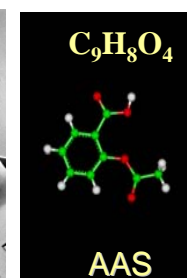
EB Chain



HW Florey



1959- A.Körnberg 1982 –SB Bergstöm BI Samuelsson JR Vane



Inter-alia:
Propranolol
Cimetidina
Aciclovir



1988 - J.W. Black G.B. Elion G.H. Hitchings

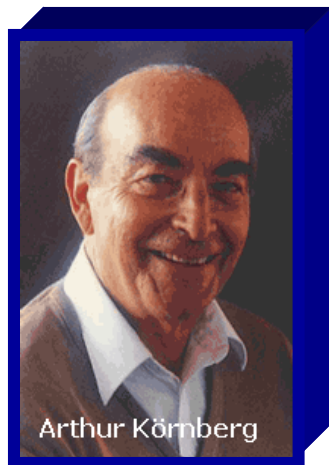
Inter-alia:

AAS

Aciclovir

Propranolol

🏆 189 pesquisadores ganharam o Prêmio Nobel de Medicina desde 1901

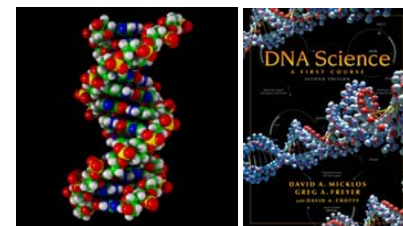


Arthur Kornberg



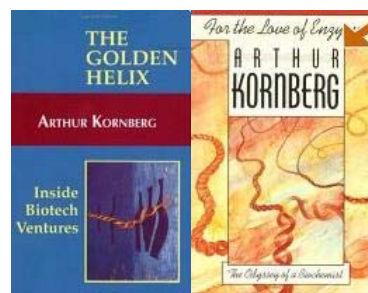
Nobel Prize, 1959

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



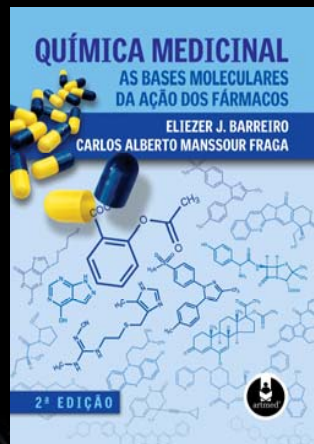
*“We have the paradox of the two cultures,
chemistry and biology,
growing further apart even as they
discover more common ground. For the chemists,
the chemistry of biological systems is either too
mundane or too complex...”*

Química Medicinal



Arthur Kornberg
Annual Meeting of AAAS, 1987

As bases moleculares



*da ação
dos
fármacos.*

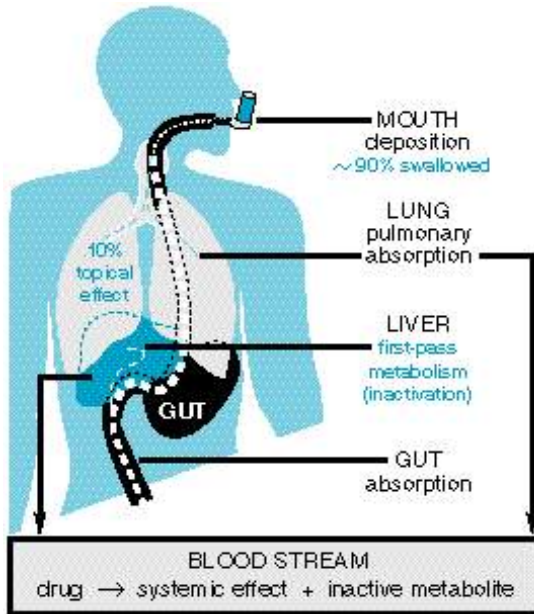
As *fases* da ação dos fármacos....

Fase farmacocinética

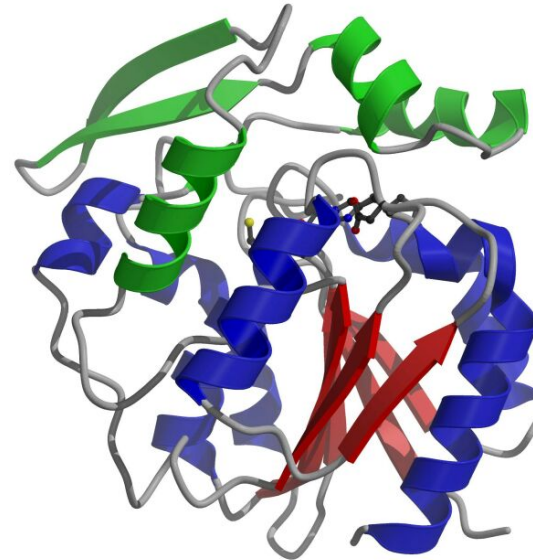
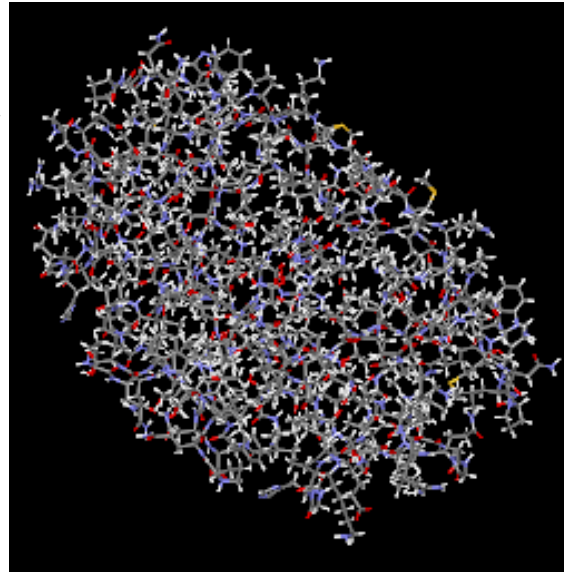
(PK)



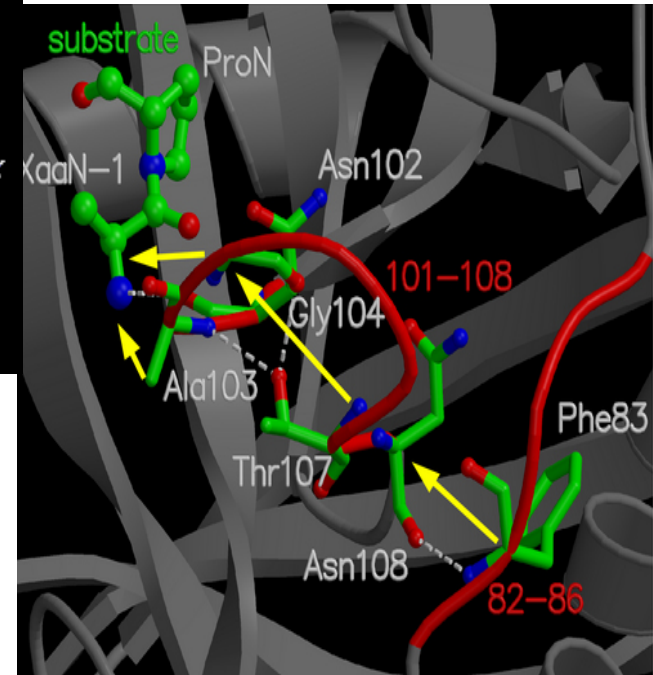
Posologia



Biofase



Biorreceptor



Efeito terapêutico



Fase farmacodinâmica

(PD)



Louis Pasteur

1822-1895

“La vie empeche
la vie”

Química
Medicinal



Emil Fisher

1852-1919

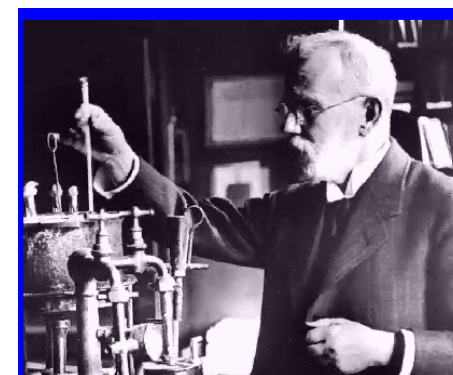
1902



Robert Koch

1843-1910

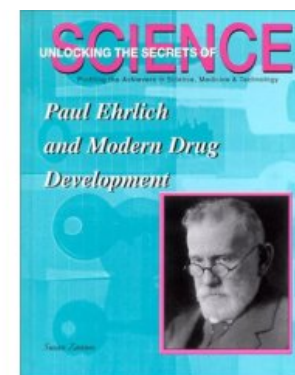
1905



Paul Ehrlich

1854-1915

1908



P. Ehrlich, *Chemotherapeutics: scientific principles, methods and results. Lancet* 1913, 2, 445₈



Paul Ehrlich
1854-1915
Nobel 1908



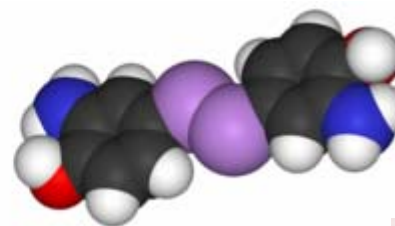
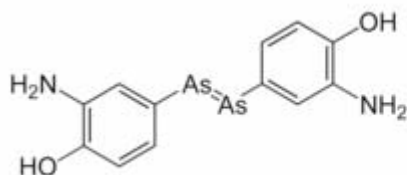
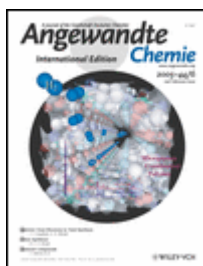
Dr. Ehrlich's Magic Bullet

SCIENCE IN THE CINEMA

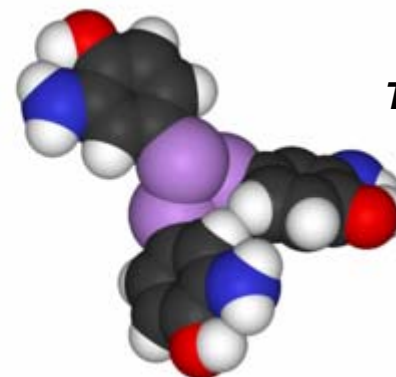
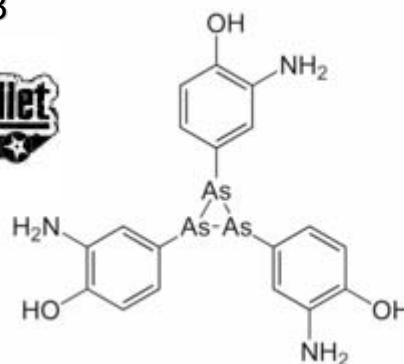
Dr. Ehrlich's Magic Bullet

Thursday ■ July 31 ■ 7:00 p.m.

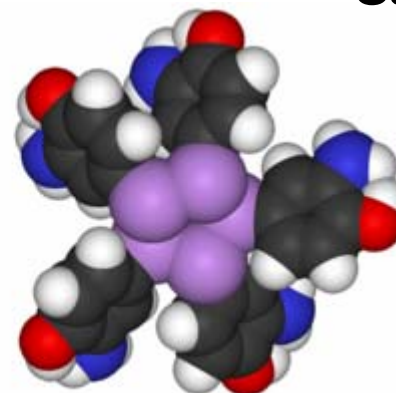
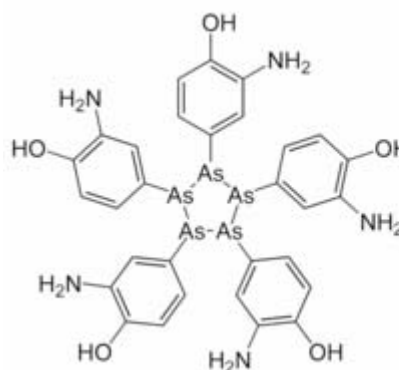
Starring
EDWARD G. ROBINSON (Dr. Paul Ehrlich)
RUTH GORDON (Mrs. Ehrlich)
OTTO KRUGER (Dr. Emil Von Behring)
DONALD CRISP (Minister Althoff)
MARIA OUSPENSKAYA (Franziska Speyer)
MONTAGU LOVE (Prof. Hartmann)
Directed by WILLIAM DIETERLE
Written by JOHN HUSTON, HEINZ
HERALD, and NORMAN BURNSIDE



Arsfenamina



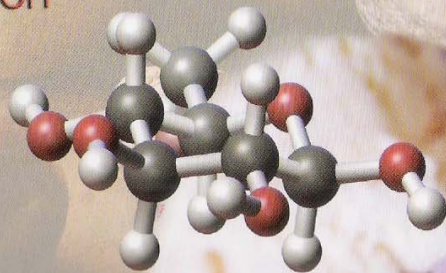
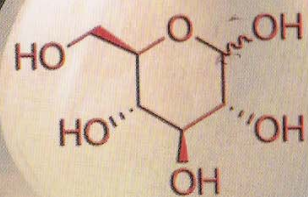
Trimêro



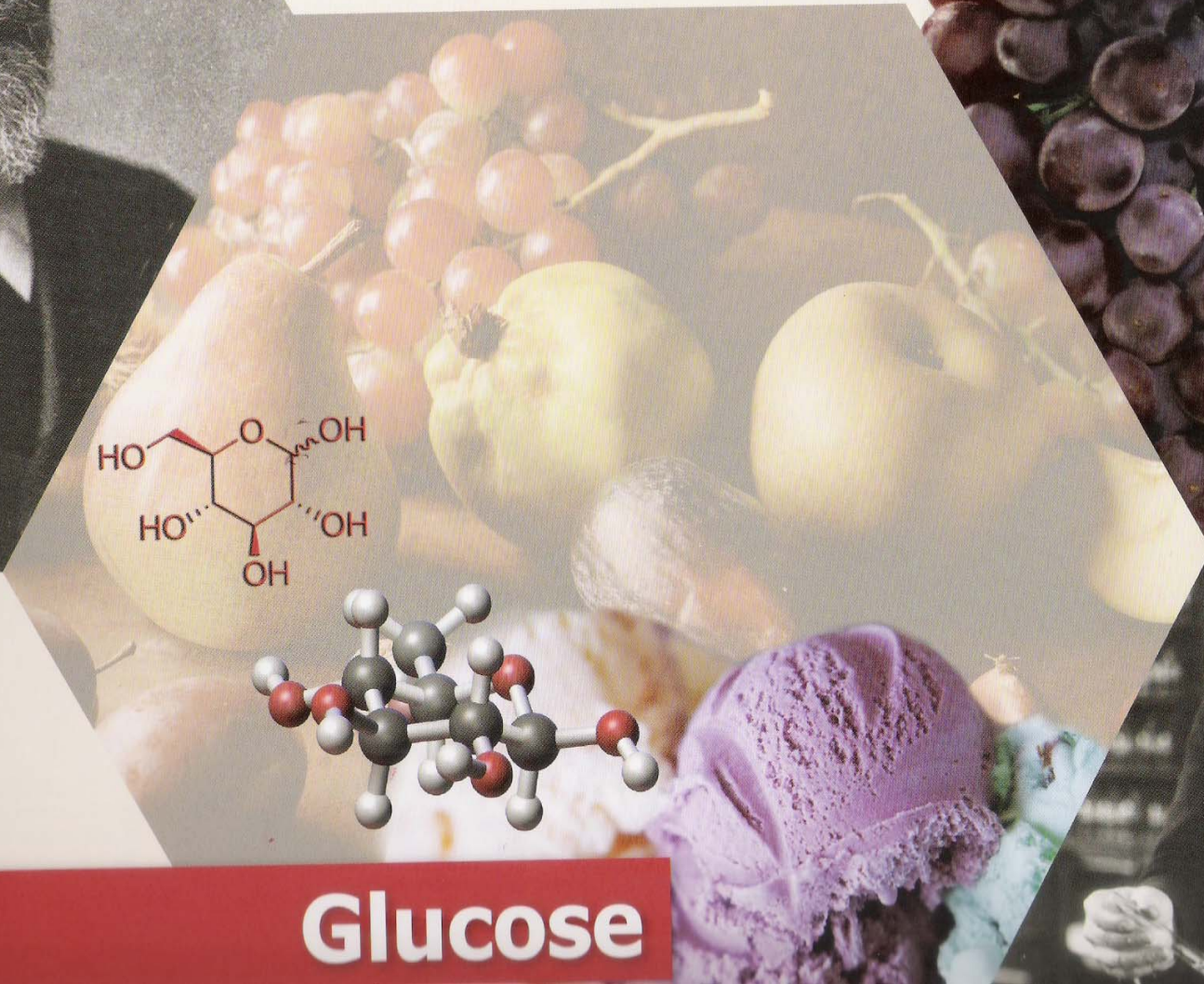
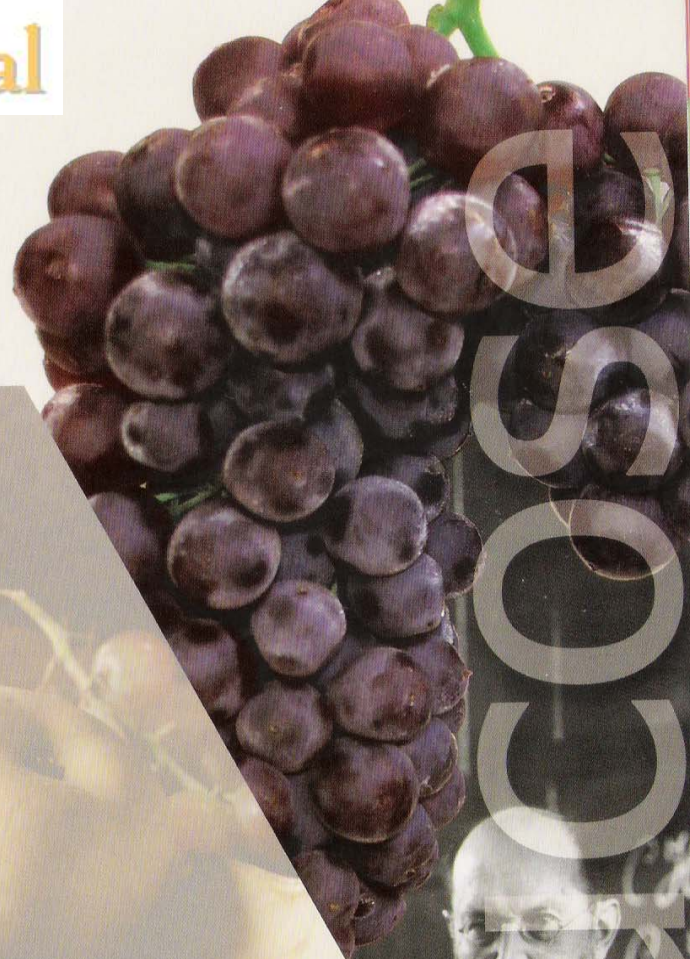
Salvarsan^R

Pentâmero

Lloyd NC, Morgan HW, Nicholson BK, Ronimus RS "The composition of Ehrlich's salvarsan: resolution of a century-old debate". *Angew. Chem. Int. Ed. Engl.* 2005, 44, 941.



Glucose





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”.

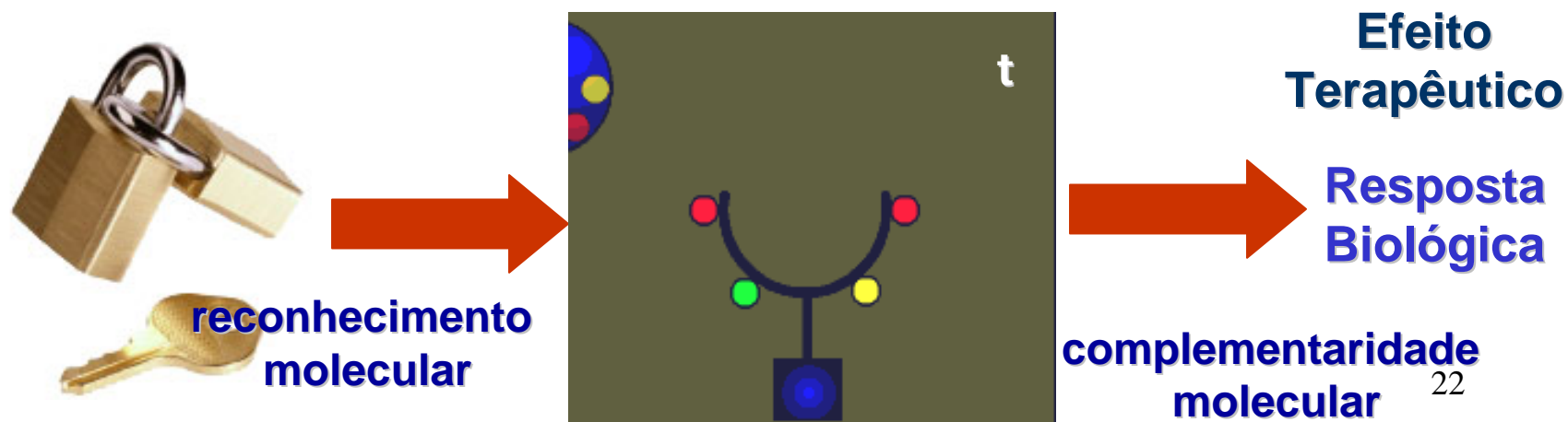
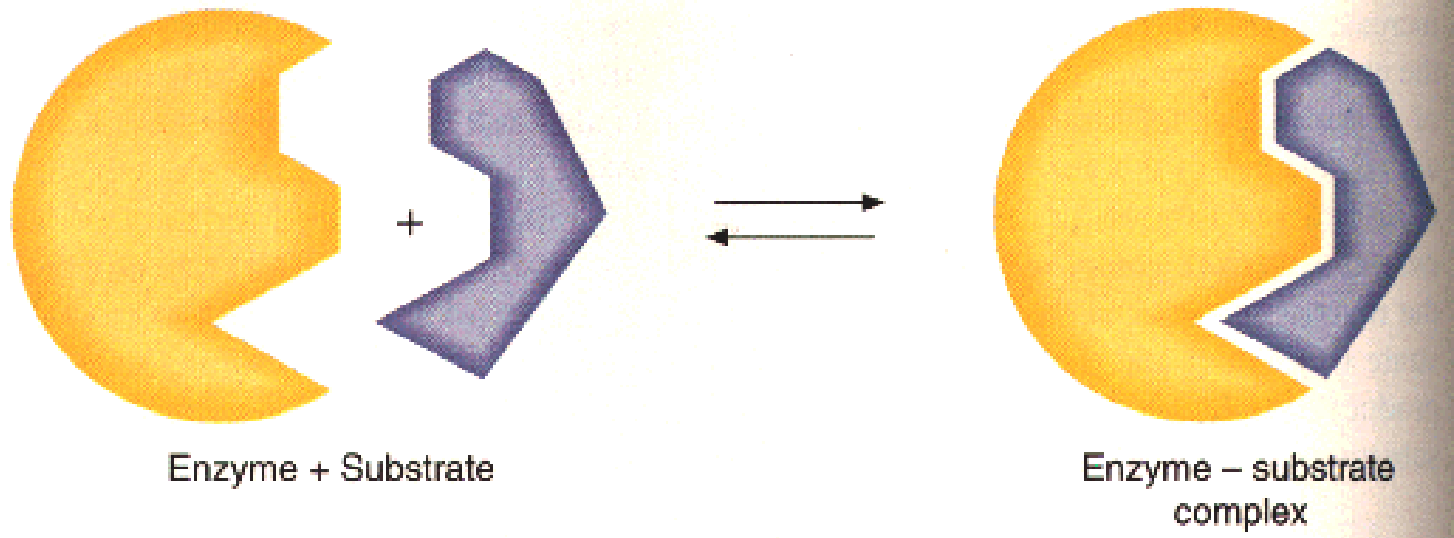


glucose

O Modelo Chave-Fechadura

Modelo Chave-Fechadura

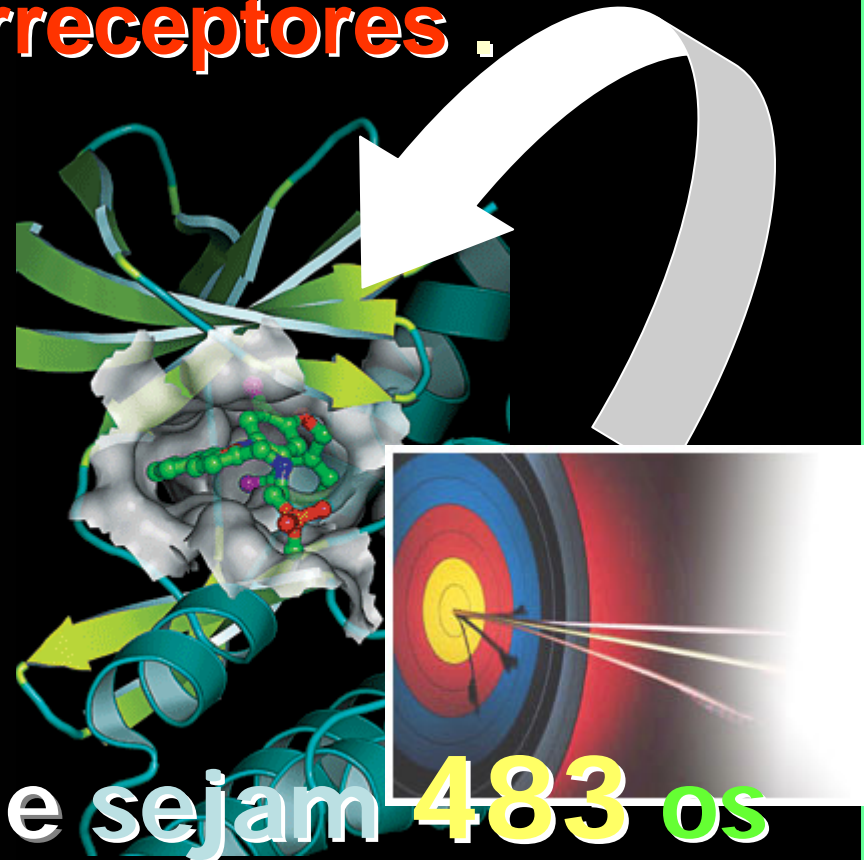
Enzima = alvo





Os fármacos atuam em alvos terapêuticos...

... os **biorreceptores** .



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



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

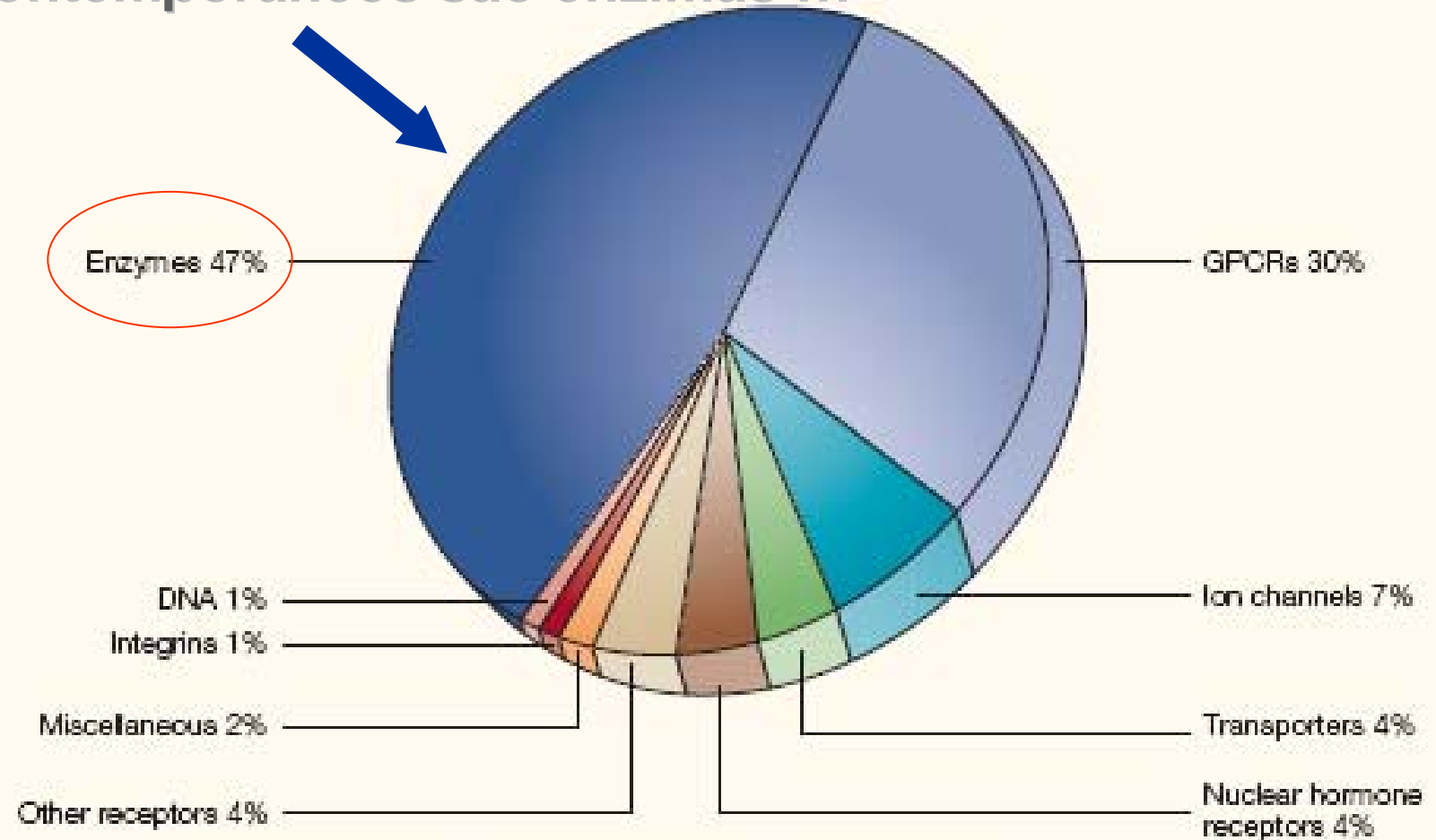


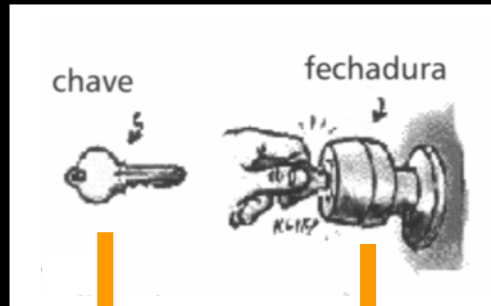
Figure 4 | Marketed small-molecule drug targets by biochemical class.
GPCR, G-protein-coupled receptor.

...de apenas 130 famílias distintas de proteínas !



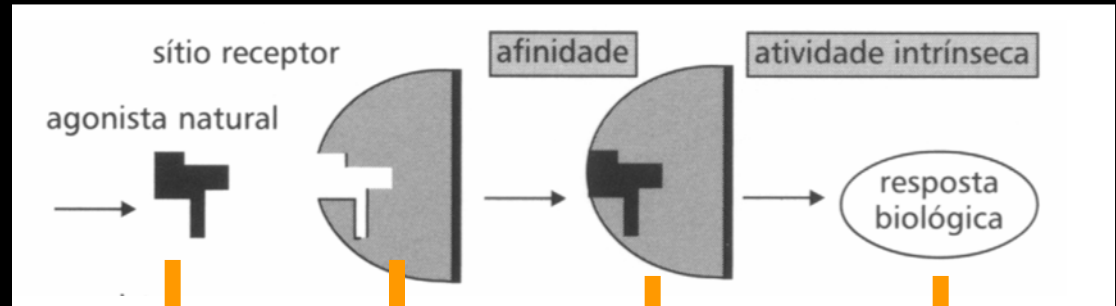


O Centenário Modelo “Chave-Fechadura”



Fármaco
Substrato
natural

Enzima
= Alvo
terapêutico

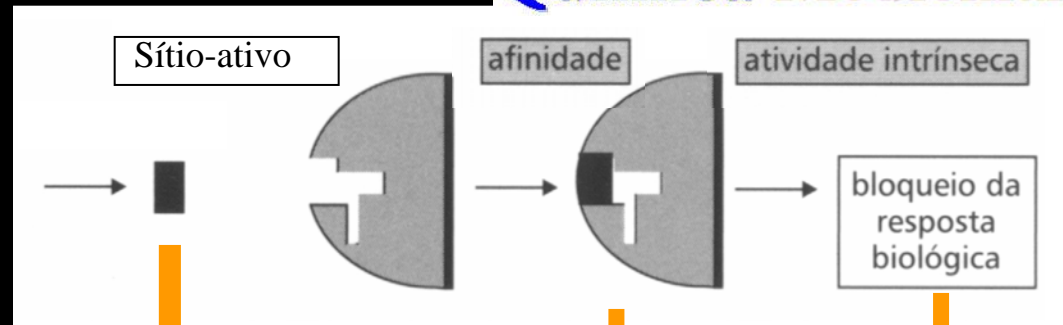
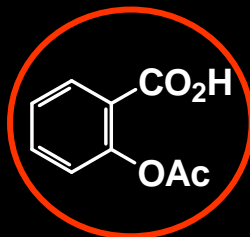


Ácido
araquidônico

PGHS-1
PGHS-2
icosanóide

PGE₂

inflamação



Inibidor: AAS

PGHS-2
PGHS-1

NSAI
AINE

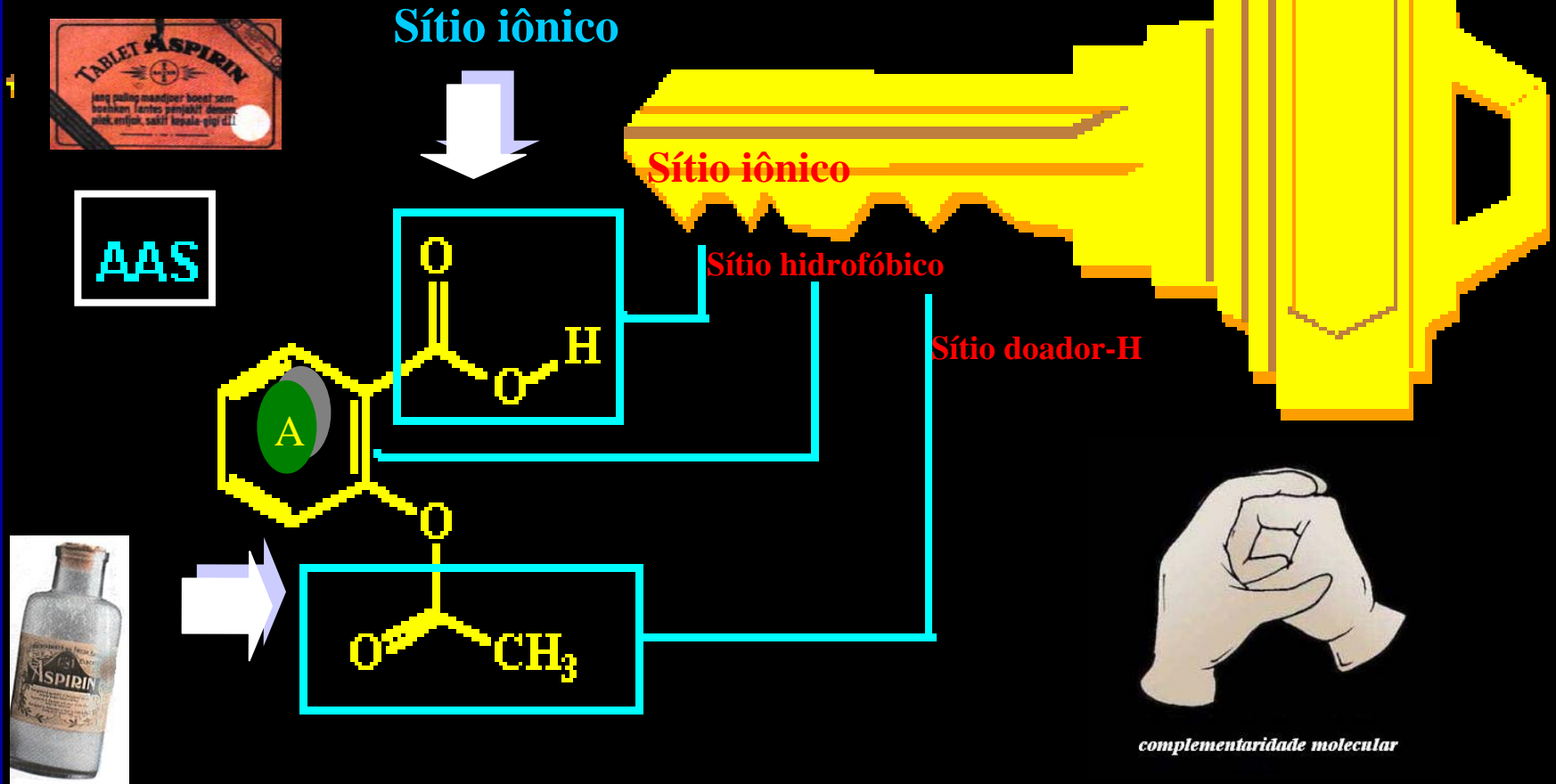
NSAI = antiinflamatórios não-esteróides

Química Medicinal



O Centenário Modelo “Chave-Fechadura”

Complementaridade do modelo Chave-fechadura



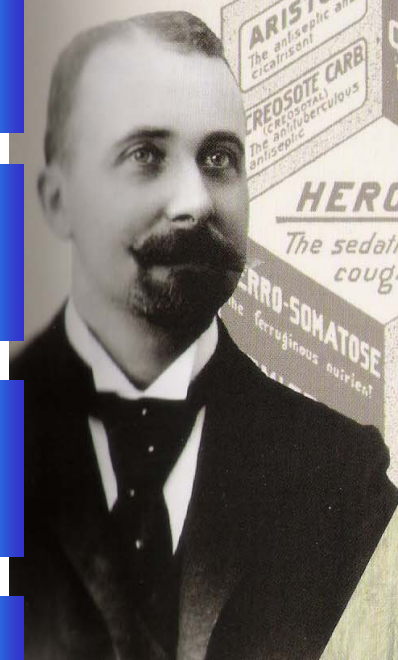


BAYER
HARMACEUTICAL
PRODUCTS.

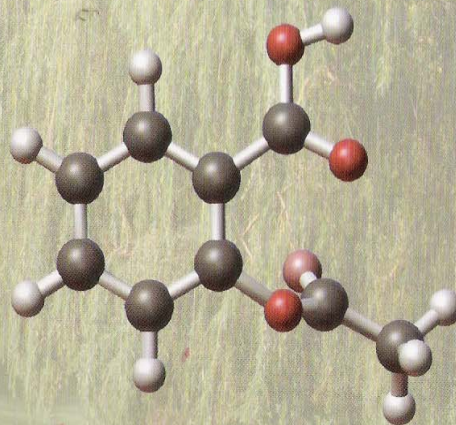
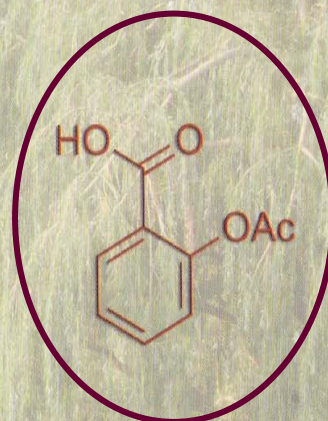


Química Medicinal

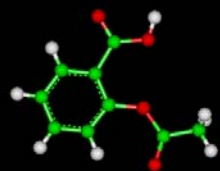
ácido acetilsalicílico



1899



- 1876 – TJ McLogan extrai a salicina
- 1853 – AAS sintetizado por CF Gerhardt
- 1897 – Felix Hoffmann & Heinrich Dreser
- 1899 – Aspirina^R
- 1980 – mecanismo de ação
- 1982 – Prêmio Nobel
- 1990 – D Simmons & WL Xie
- 1999 – Coxibes
- 2002 – COX-2i & câncer



Aspirin[®]

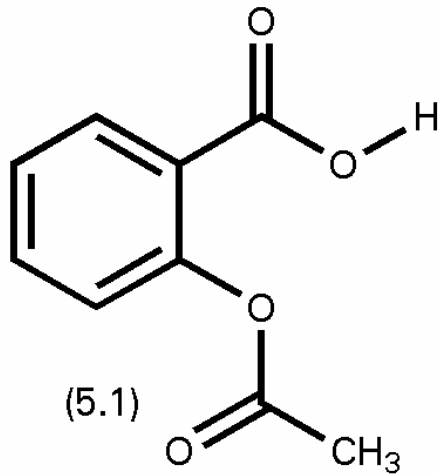


Spirea sp



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

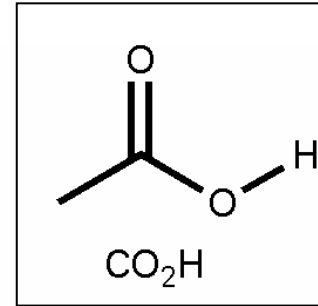
AAS



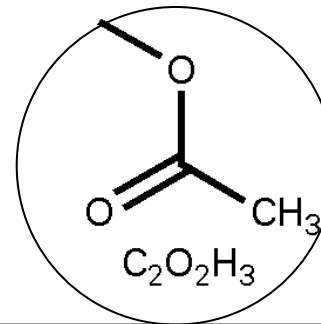
$C_9H_8O_4$

Dissecação

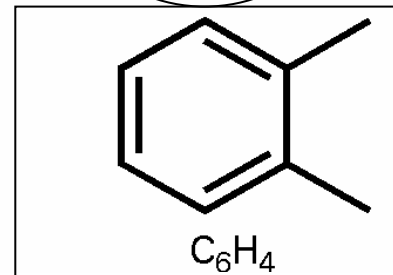
molecular



a



b

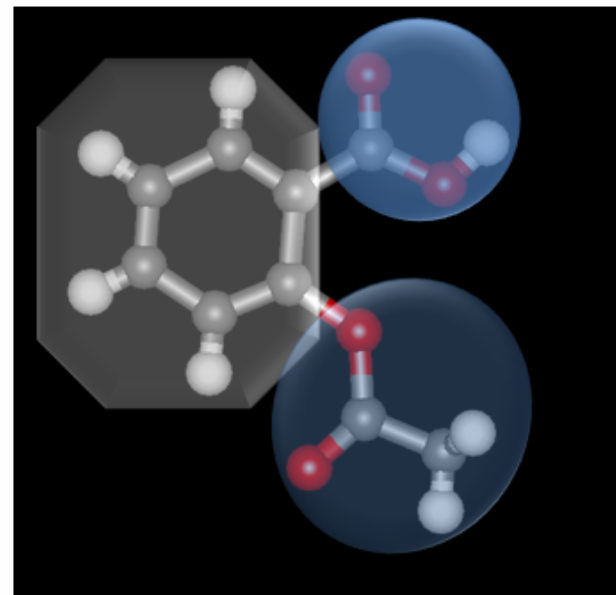
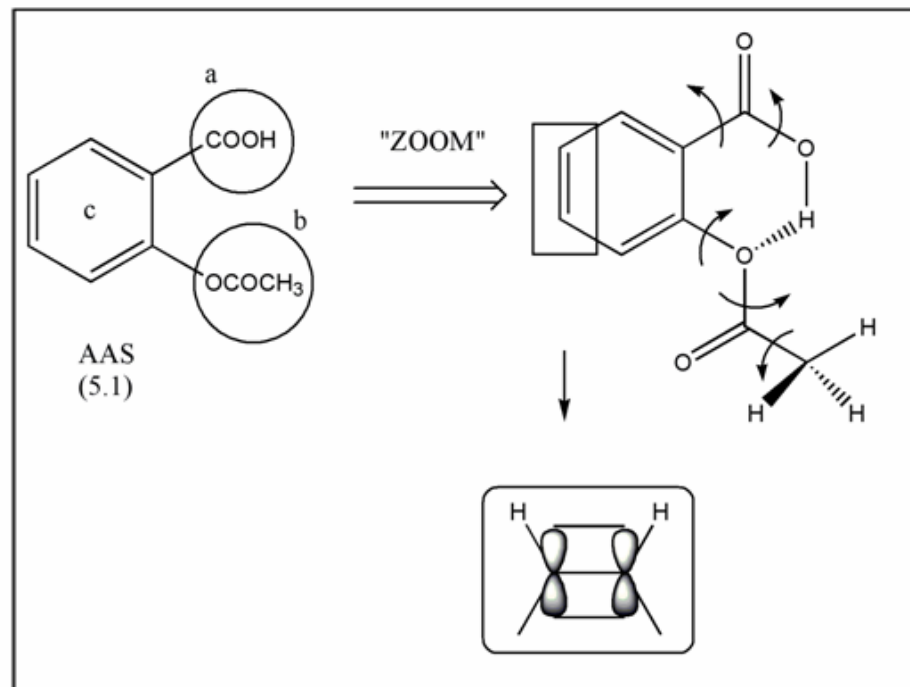


c

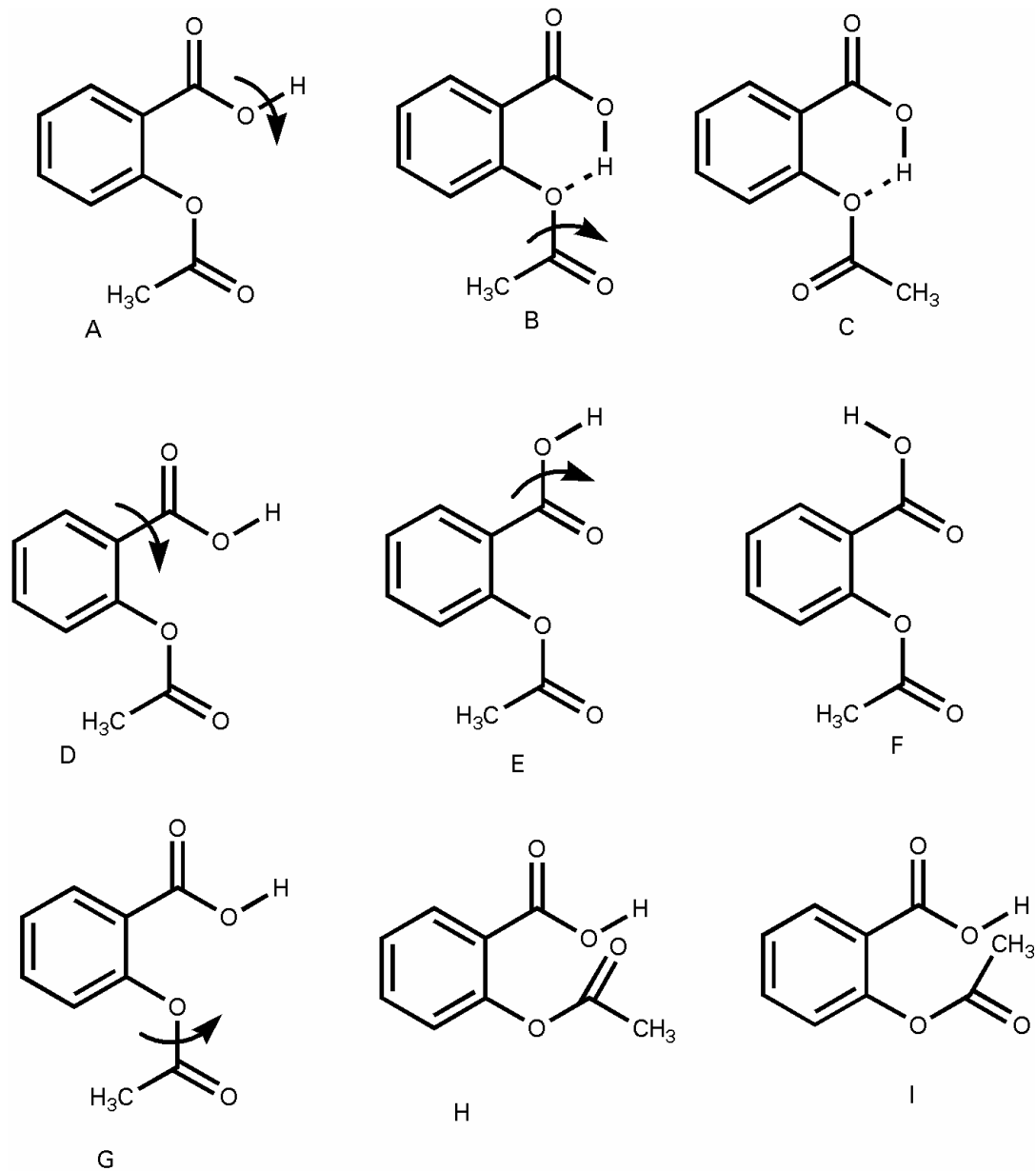


Química Medicinal

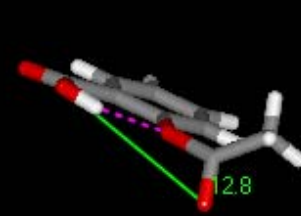
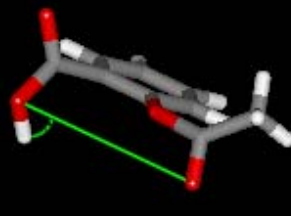
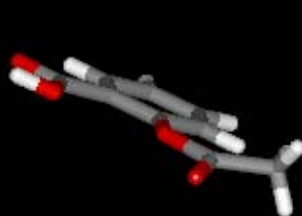
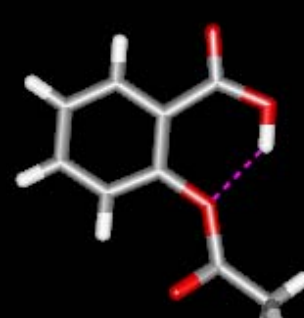
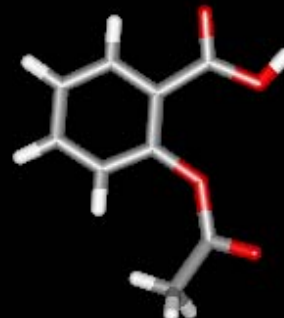
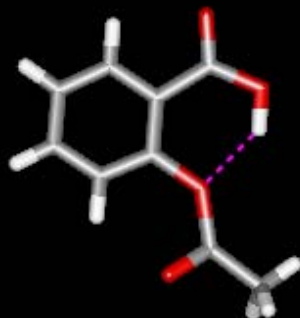
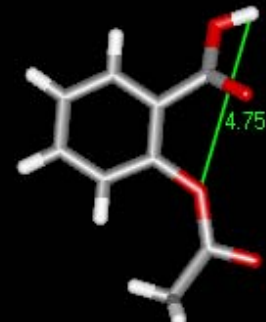
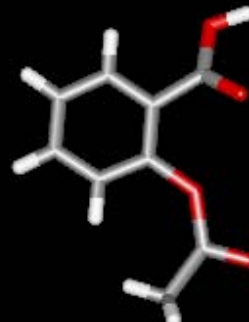
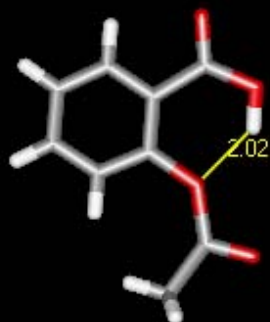
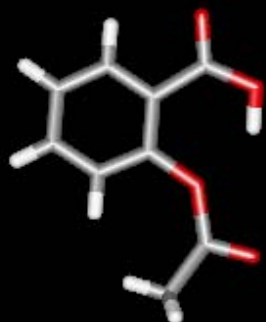
A tática de dissecação molecular: identificação de *pontos farmacofóricos*



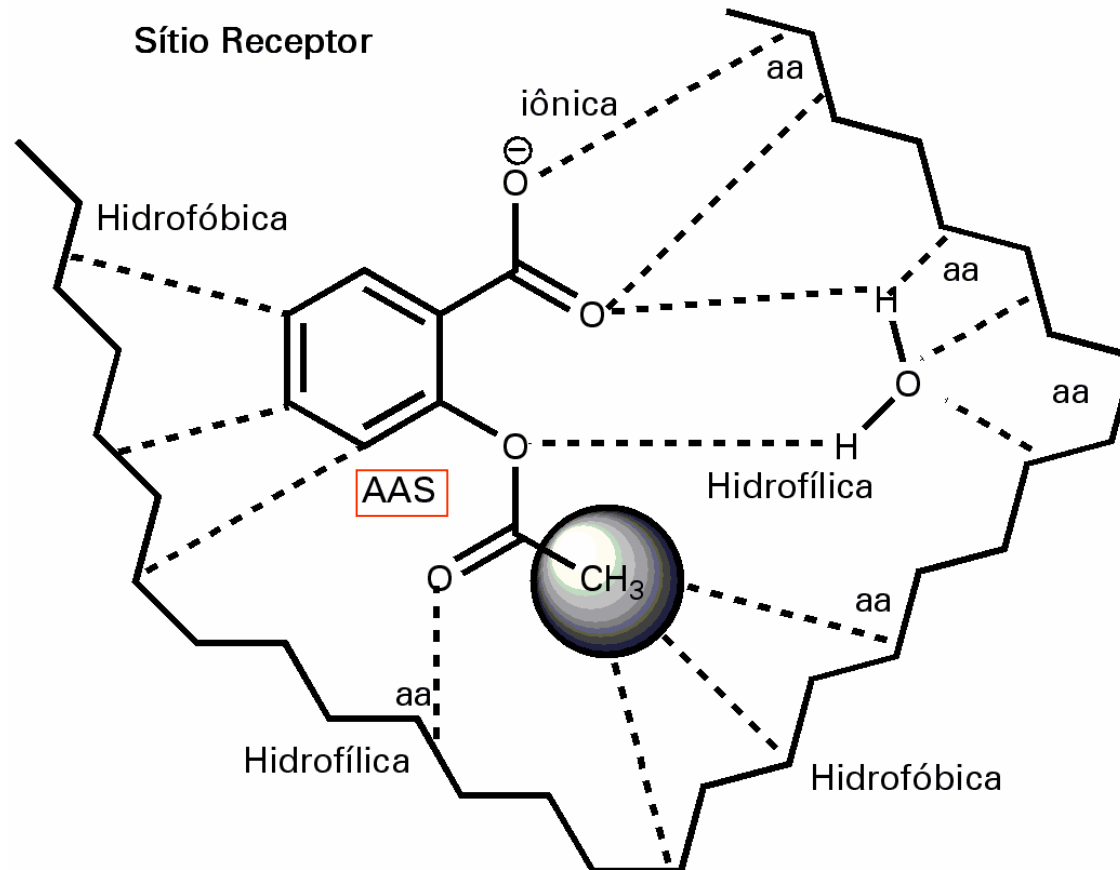
A tática de dissecação molecular & equilíbrio conformacional



A tática de dissecação molecular & equilíbrio conformacional



Pontos farmacofóricos e as interações do com o biorreceptor



aa= amino-ácido

Aspectos da Química Farmacêutica Medicinal

Sumário

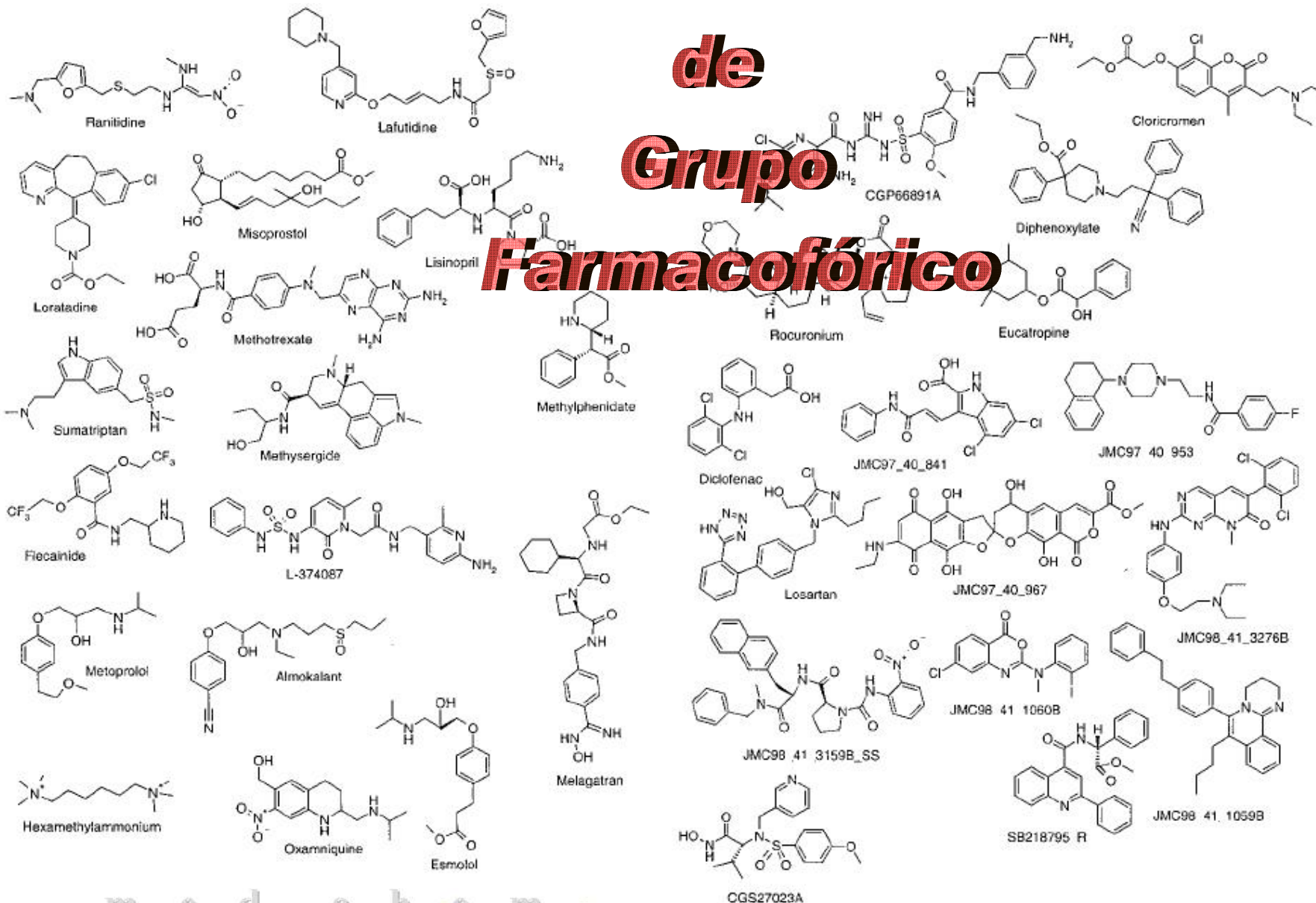
1. Os fármacos & a Química Medicinal
2. Como se descobrem os fármacos? *Os fármacos e os prêmios Nobéis*; Como atuam os fármacos?
3. A *dissecação* molecular : grupo farmacofórico
4. Moléculas *inteligentes*: os alfabetos moleculares
5. *Domesticando* moléculas naturais
6. O paradigma do composto-protótipo
7. Fármacos *simbióticos*: exemplos *de casa*
8. Epílogo

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).



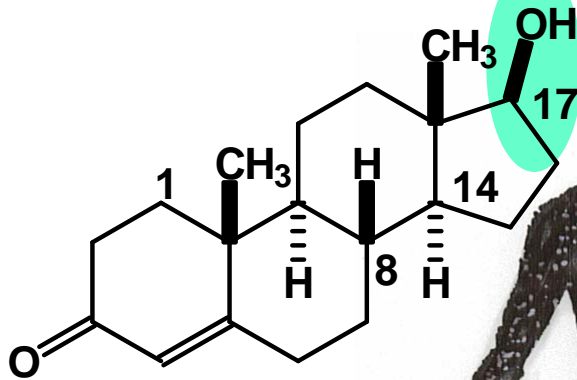
Em 1977, **Peter Gund** atualizou a definição: "a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity" (Gund. *Prog. Mol. Subcell. Biol.* 1977, 5: pp 117–143).

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.

Similaridade & Dissimilaridade Molecular



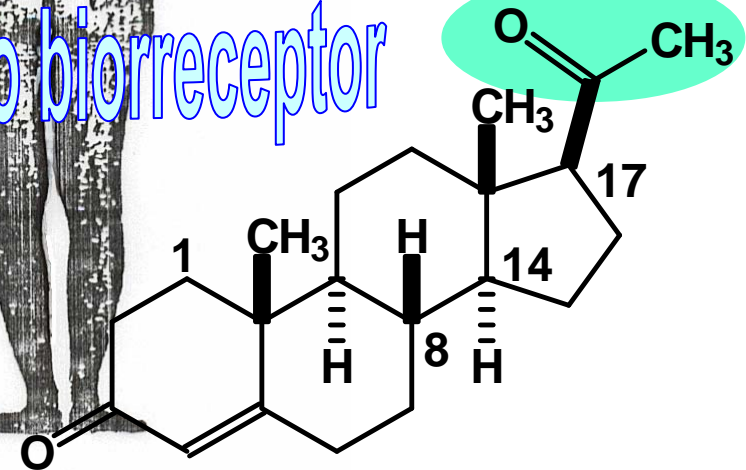
testosterona



no reconhecimento molecular do biorreceptor



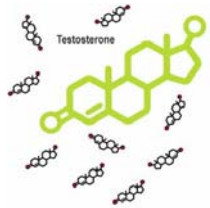
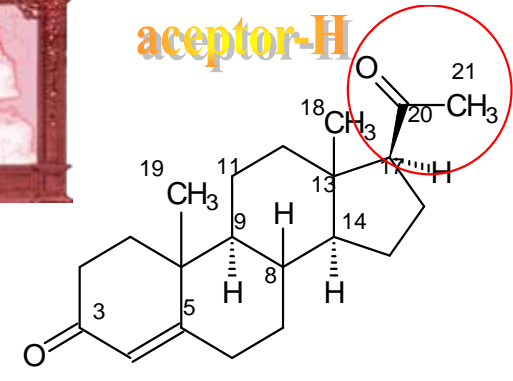
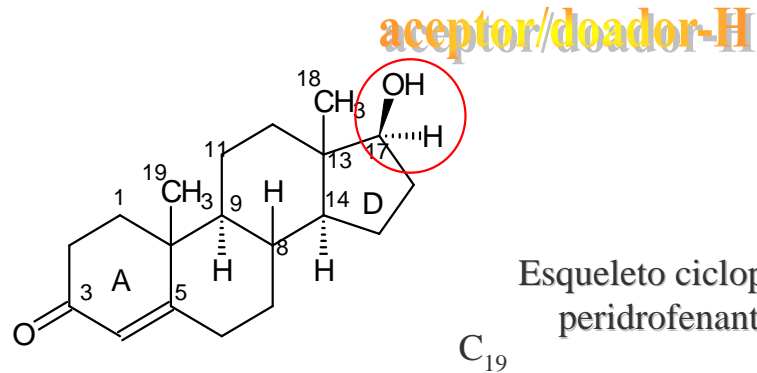
similaridade molecular



progesterona

Similaridade & Dissimilaridade Molecular

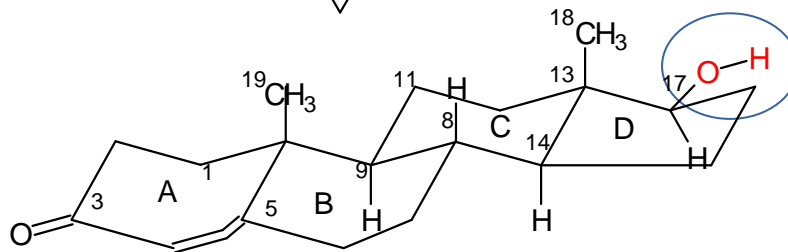
Biorreceptor



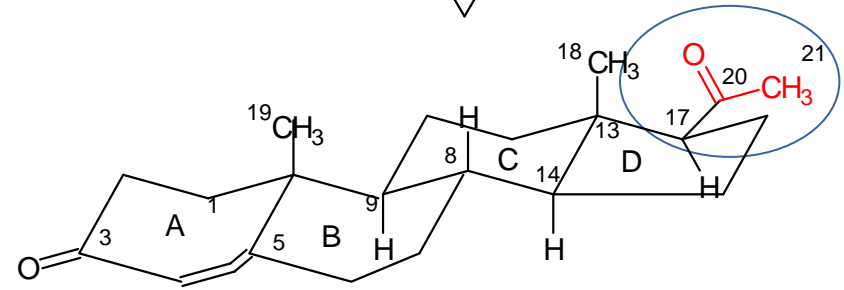
Testosterona

similaridade molecular

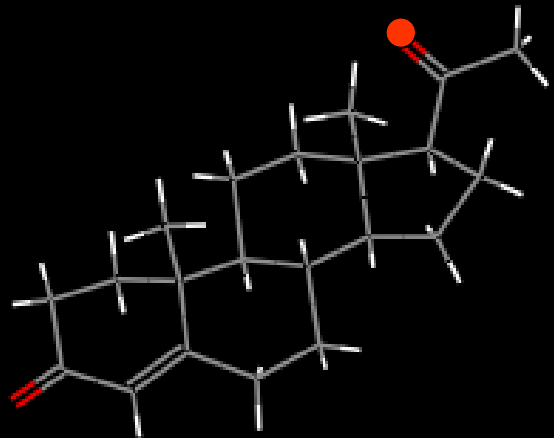
Progesterona



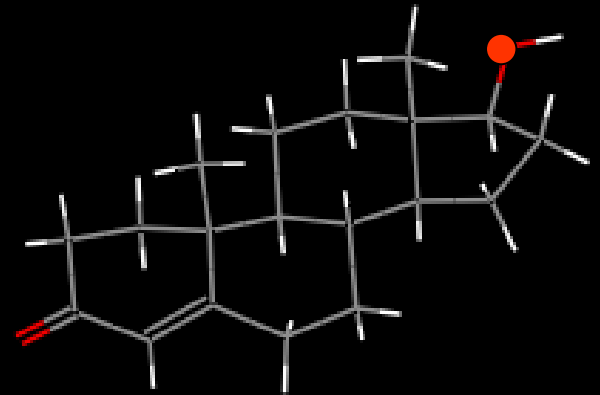
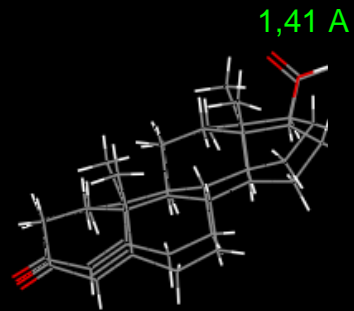
B/C C/D trans



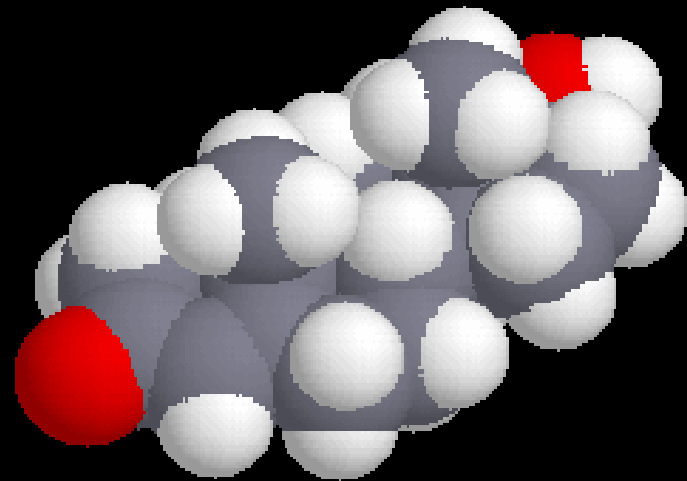
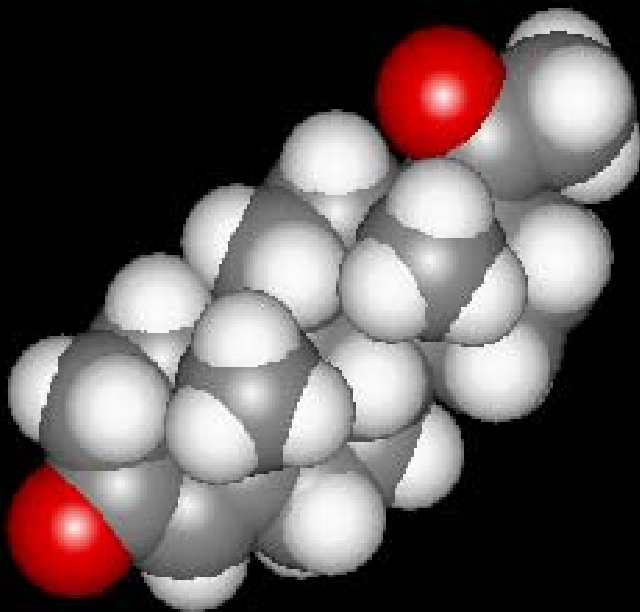
B/C C/D trans



progesterona

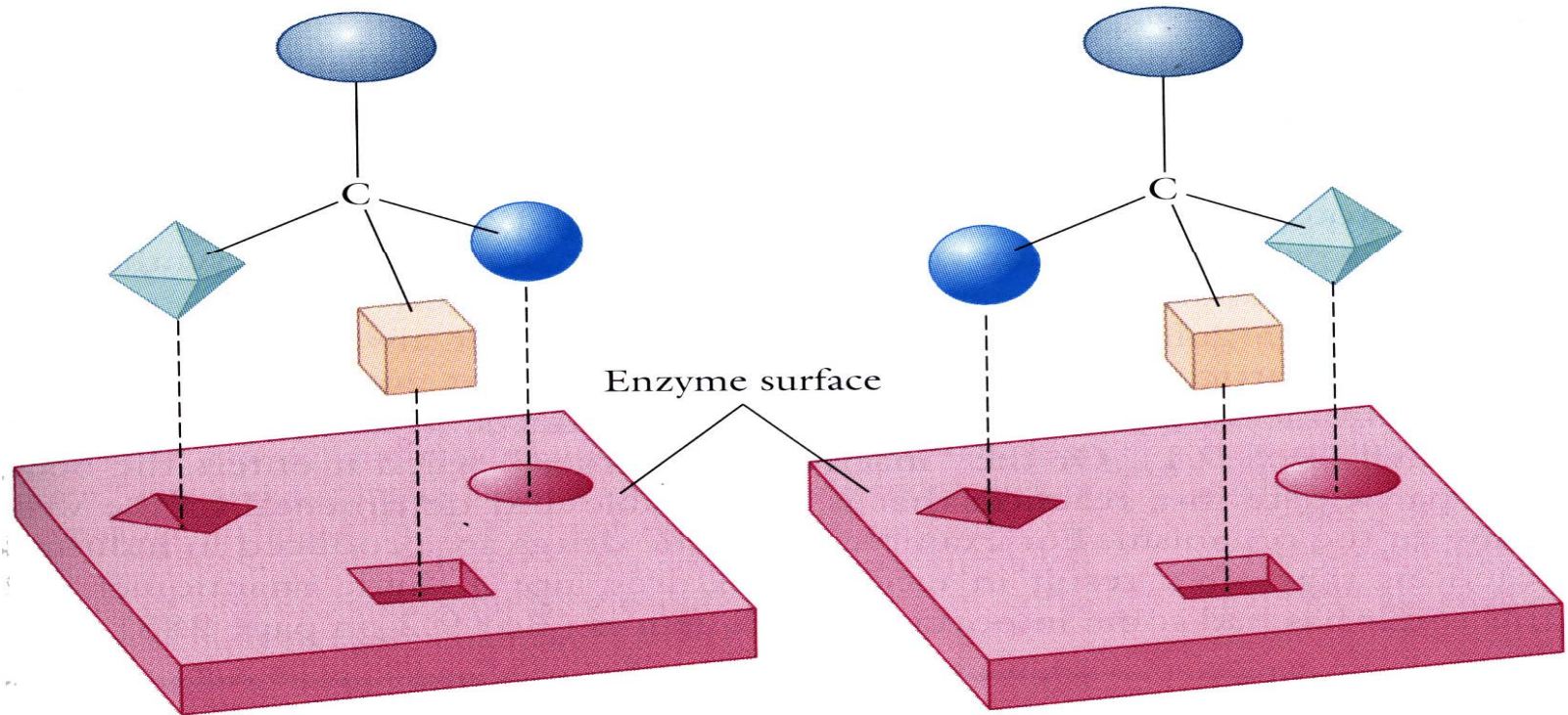


testosterona



Modelo dos três pontos

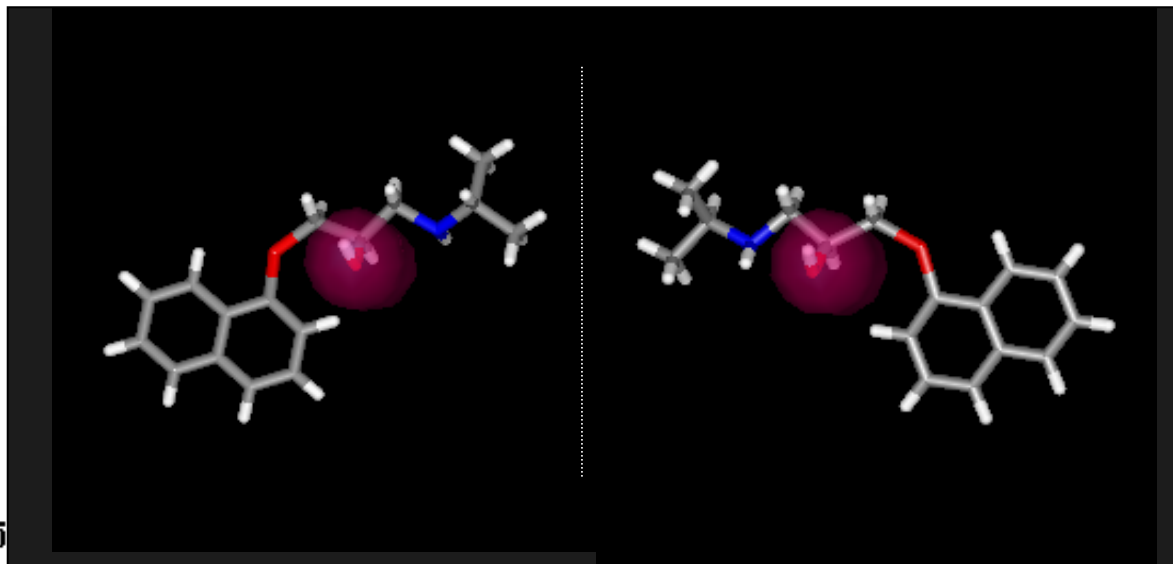
Modelo de Easson-Stedman



One enantiomer fits
enzyme active site

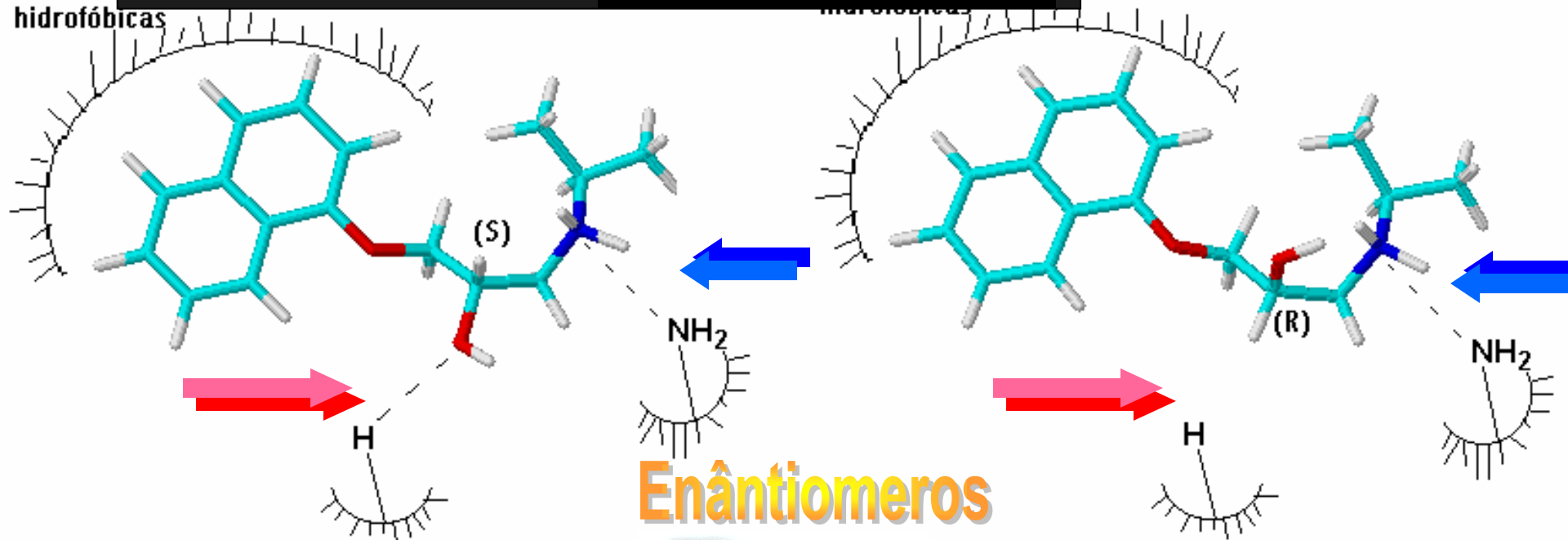
Other enantiomer does not fit
enzyme active site





Eutômero
Distômero

Interação
hidrofóbicas



A quiralidade da vida e os fármacos...



Interação Fármaco-Receptor

Modelo “Chave-Fechadura”

“Fechadura”



?

“Chaves”



Reconhecimento
Molecular

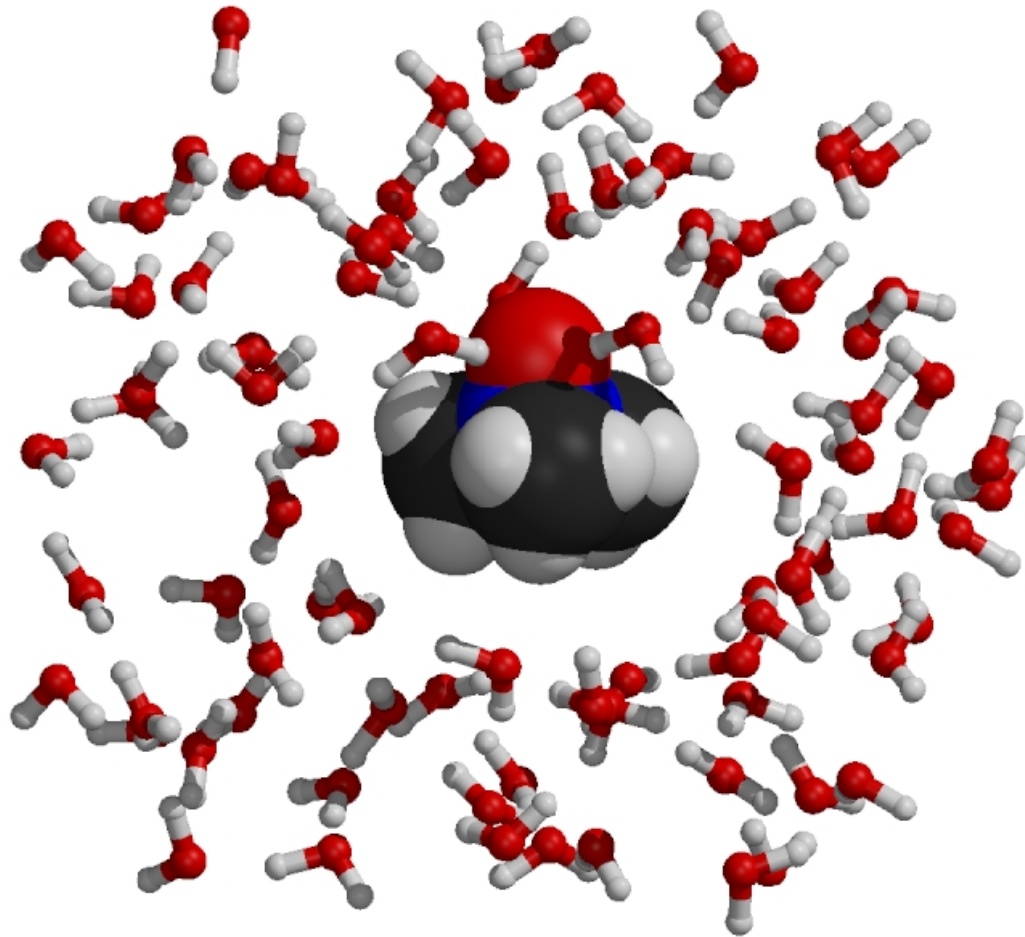
Complementaridade
Molecular

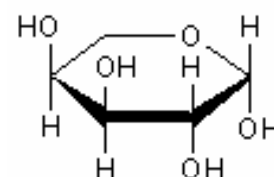
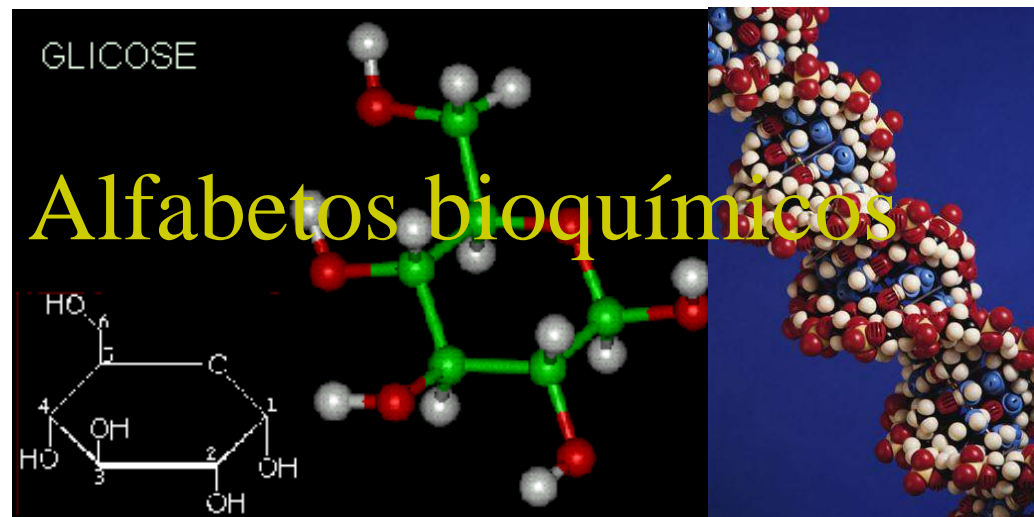
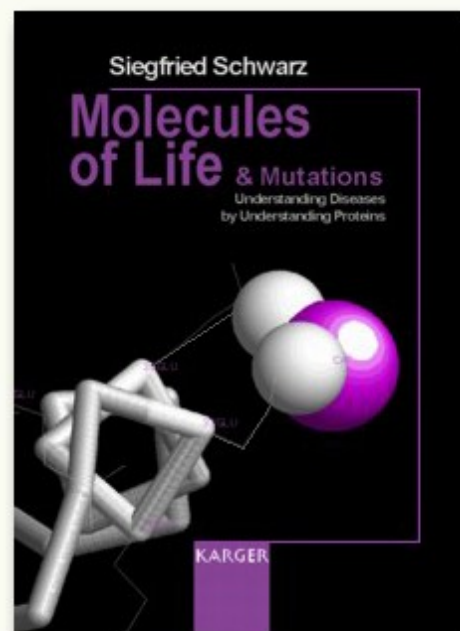
Energia aproximada de interações atômicas e moleculares

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

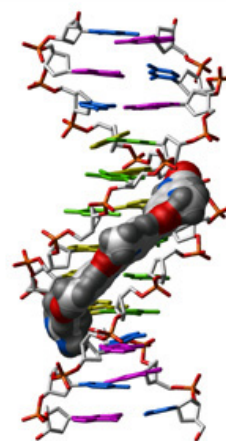
A importância das “*ligações*” frágeis...

“*ligações*” de hidrogênio ...





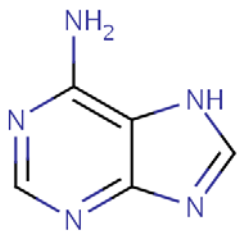
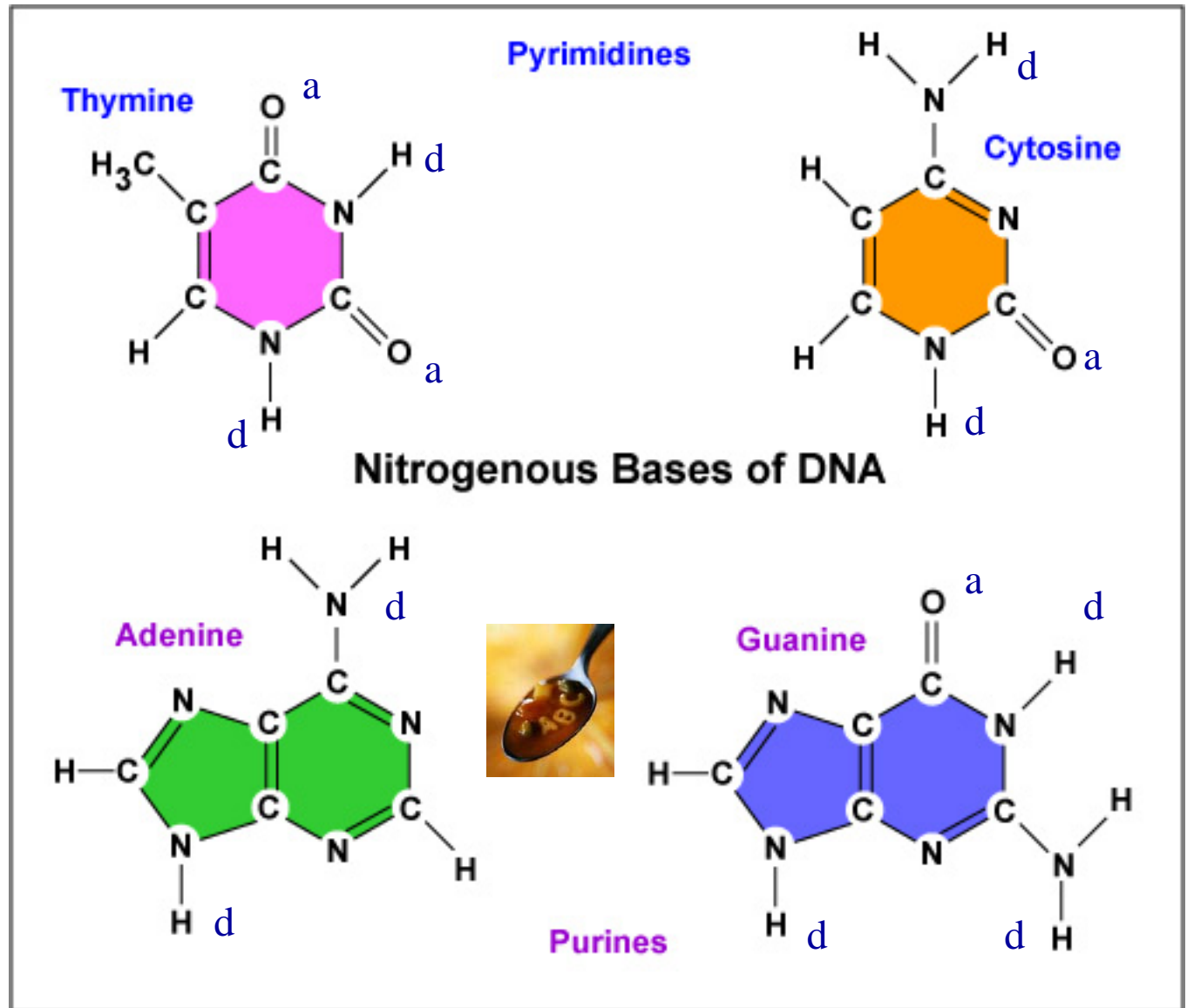
β -L-Arabinose



Model Compound Bound to the Minor Groove of a DNA Molecule

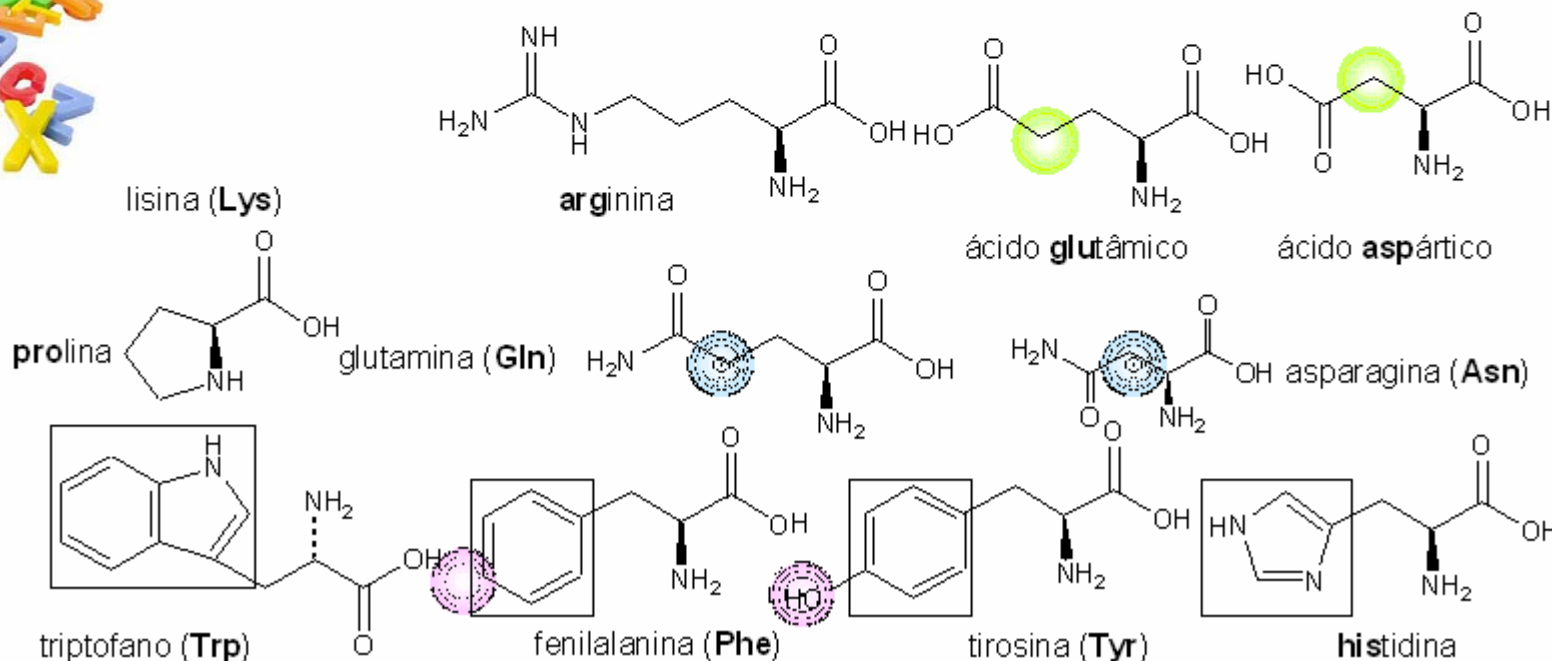
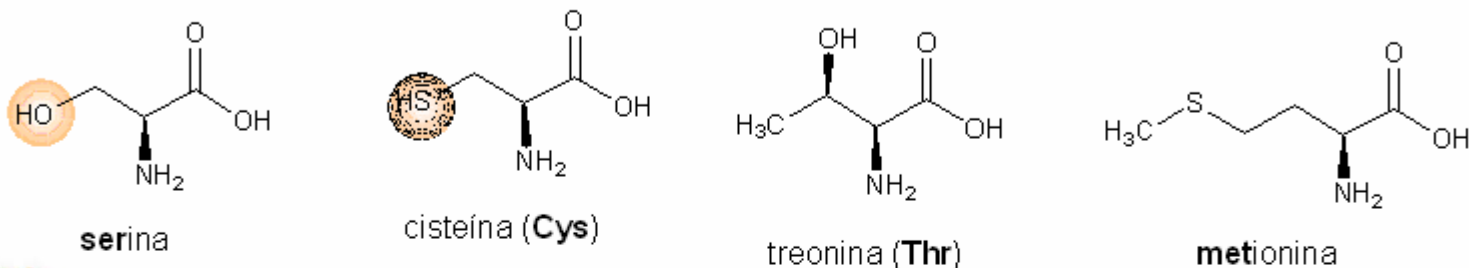
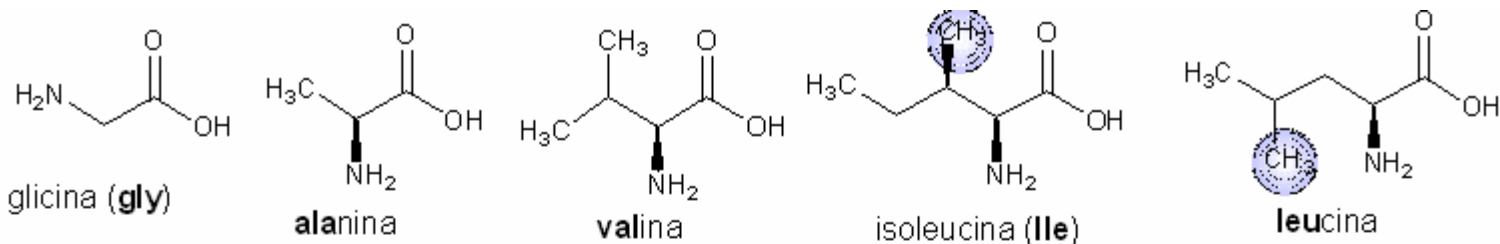
Carboídratos
Lipídeos
ácidos nucleícos
proteínas

“ligações” de hidrogênio ...

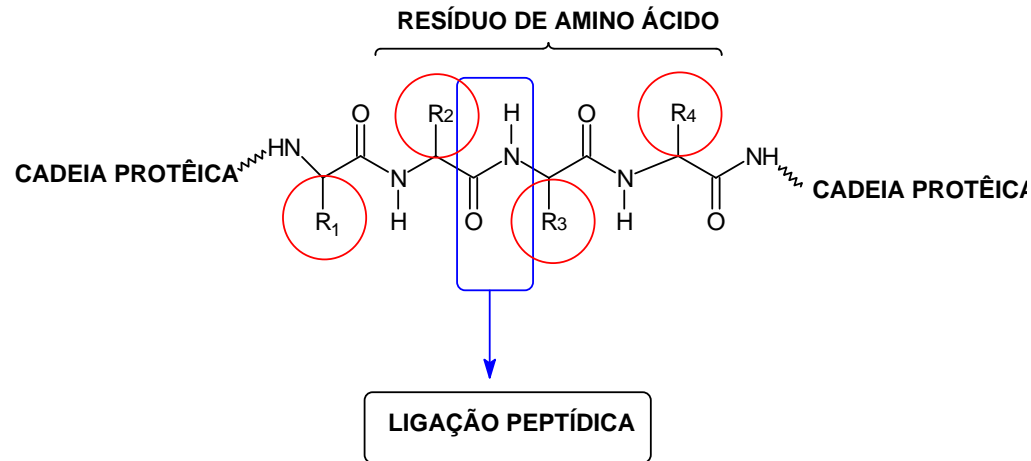
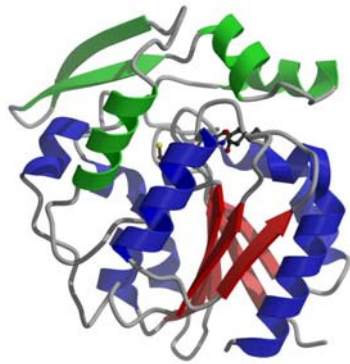




“ligações” de hidrogênio ...



Estrutura Primária das Proteínas



AMINO ÁCIDOS: {

- Essenciais: His, Ile, Leu, Lys, Met, Phe, Thr, Trp, Val
- Não-essenciais: Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, Pro, Ser, Tyr

"Fechadura"

Força das Ligações Droga-Bioreceptor:

{

- Covalente: >200kJ/mol
- Iônica: 20kJ/mol
- Hidrogênio: 7-40kJ/mol
- Van der Waals: 1.9kJ/mol



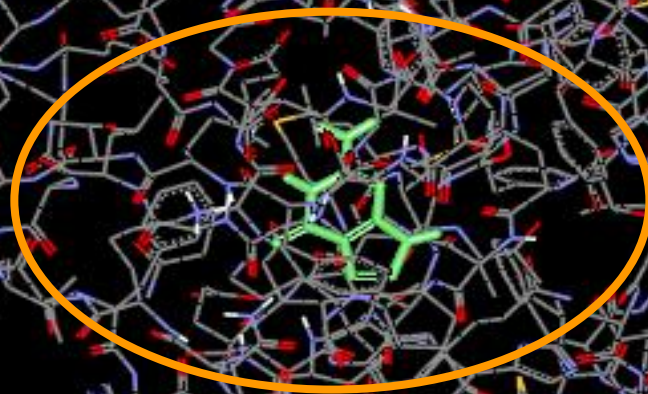


Agora...

Biorreceptor

Estrutura 3D do alvo terapêutico

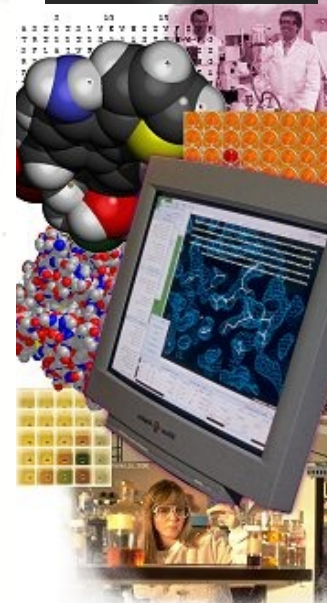
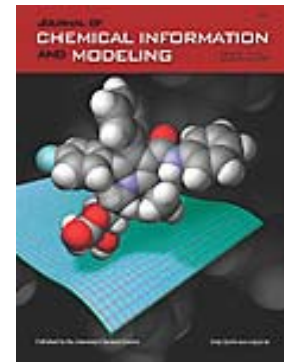
Sítio de reconhecimento molecular



Fármaco



Modelagem Molecular





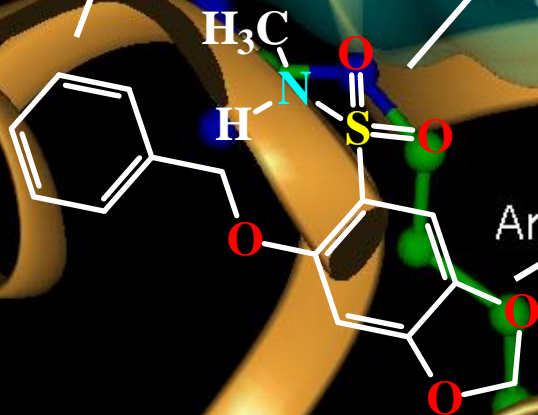
Arg513

Phe518

Tyr385

Ser530

Arg120



PK

Biofase

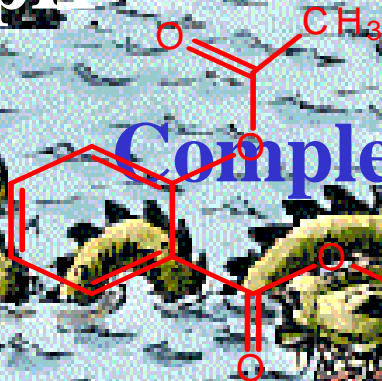
Absorção

Concentração

Meia-vida

Posologia

pH



Complexação plasmática

Depósito tissular

Metabolismo

Eliminação



Drug Metabolism and Disposition:

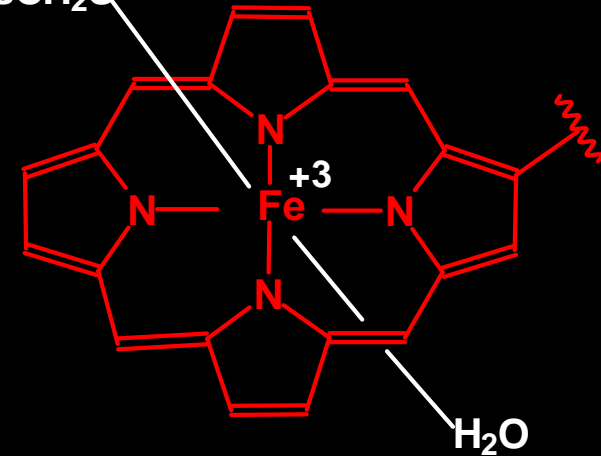
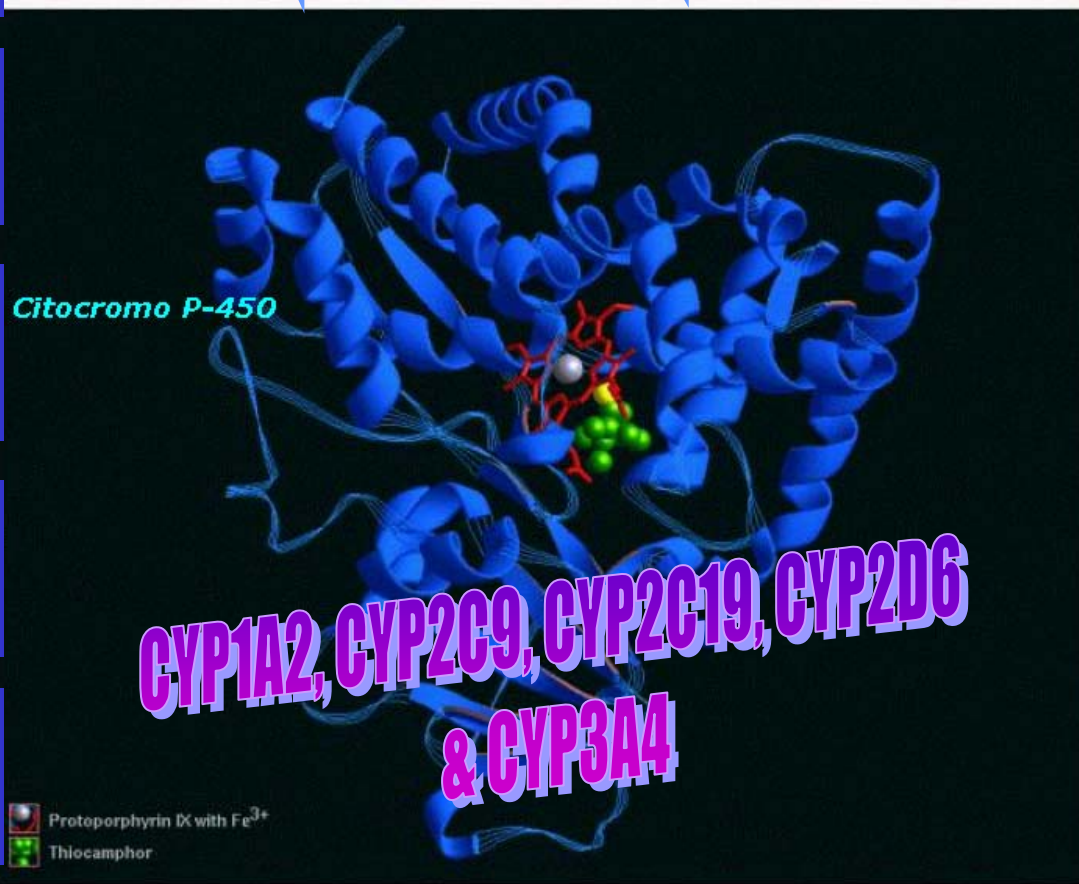
Founded in 1973 by Kenneth C. Leibman

the
biological
fate of
chemicals

**Enzimas
oxidativas**

CYP450

Citocromo P450CysCH₂S



Idade
Sexo
Raça

Polimorfismo

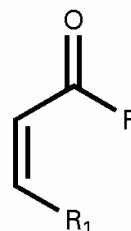
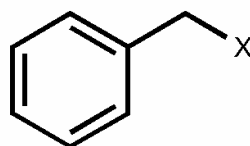
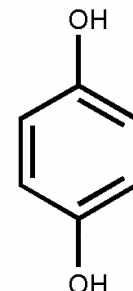
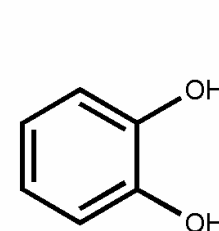
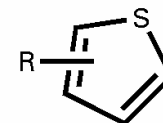
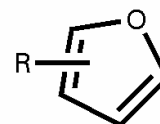
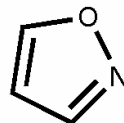
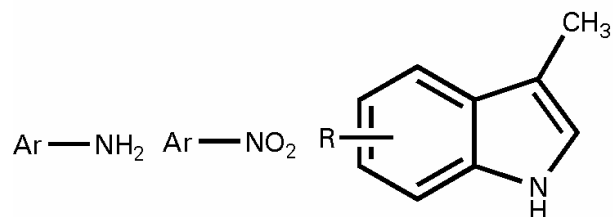
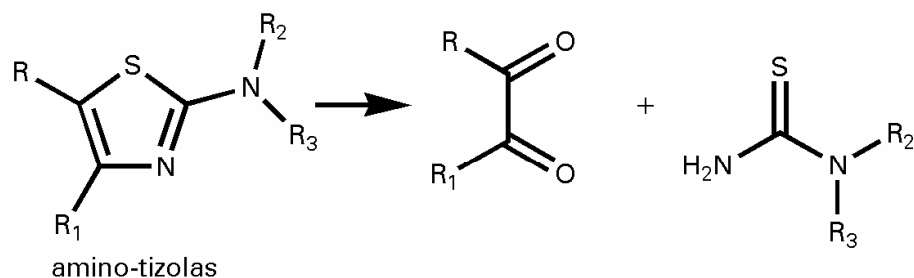
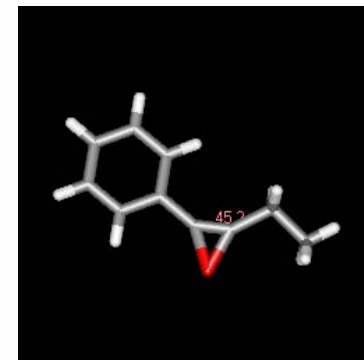
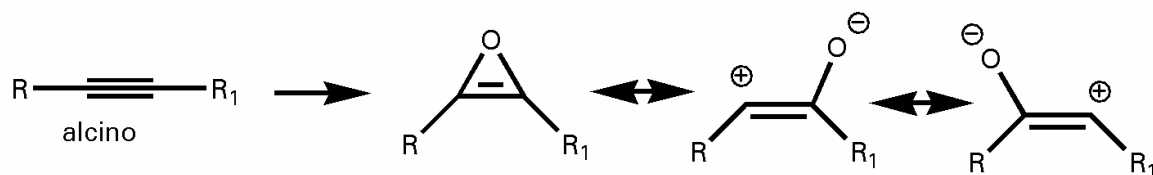
**Isoformas
(24)
CYP2C18**

Interação medicamentosa

Indução / Inibição



Grupamentos toxicofóricos



$R, R_1, R_2, R_3 = \text{H, alquila, cicloalquila, arila, heteroarila}$
 $X = \text{grupo abandonador}$

No processo oxidativo de metabolização podem se formar espécies reativas transientes, geralmente nucleofílicas, que são extremamente tóxicas.



Medicamento

Química Medicinal

F
Á
R
M
A
C
O

P
A
+
V
+
C

Fase farmacêutica

F
O
R
M
U
L
A
Ç
Ã
O

Fármaco

Biofase

Agente de depósito

Complexo tissular

Distribuição

Absorção

Metabolismo

Bioinativação

Bioativação

Hepática, plasmática, entérica

F-R

tóxico

E.T

Polimorfismo, idade, raça, sexo

PQF

P
pKa
D

Complexo plasmático

Agente de deslocamento

Indução /
inibição
enzimática

Vida-média

Agente de co-solubilidade

Afinidade
Potência
Eficácia
Sinergismo

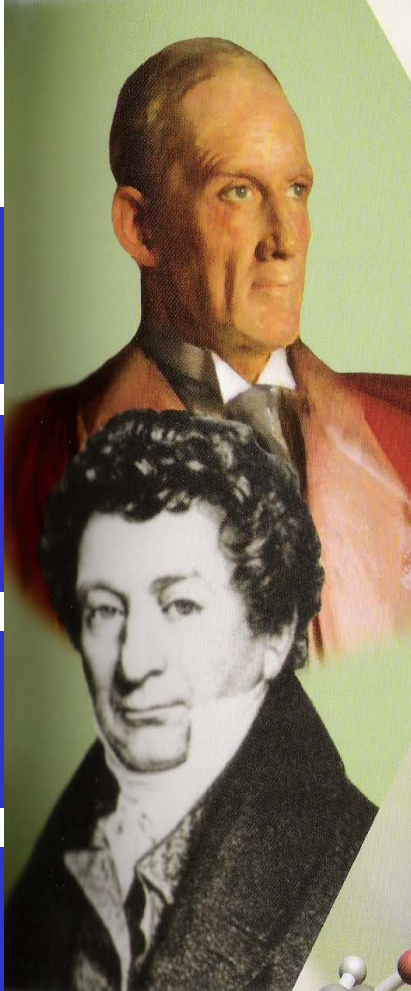
Eliminação renal

Bile, fezes, pulmão

Excreção

Fase farmacocinética
(ADME)

Fase farmacodinâmica



Marco Polo, praça de San Marco

Ópio: *Papaver somniferum*

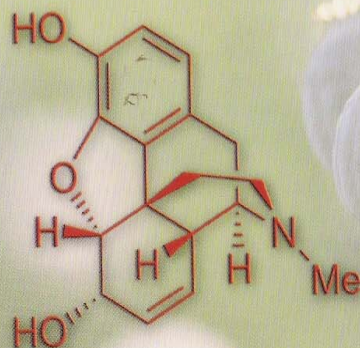
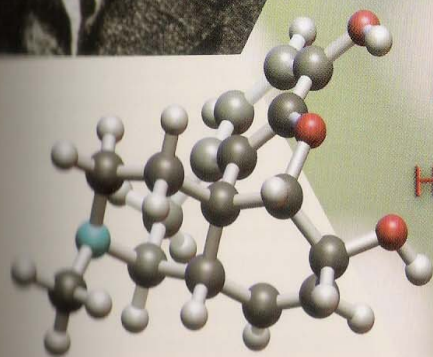
Quinine, papaverina, heroína

Hipno-analgésico

Tolerância

Dependência química

OMS



Morphine



Gênese dos Analgésicos Centrais



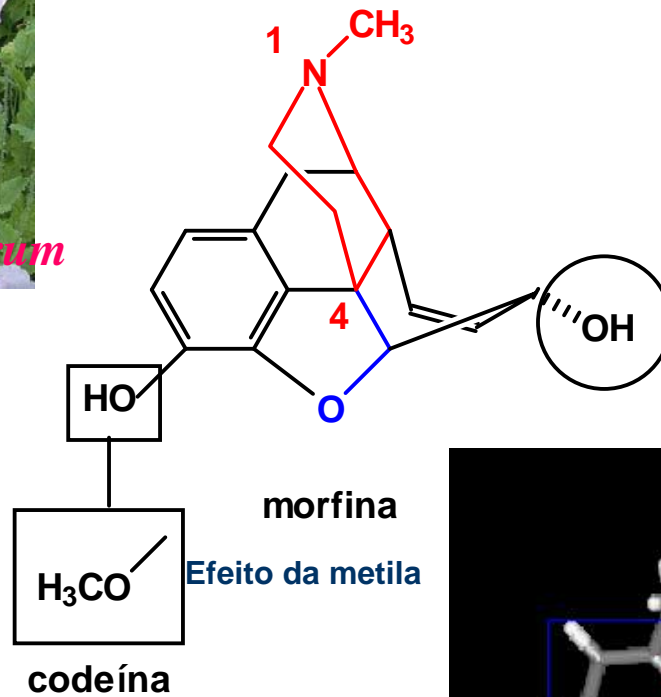
Papaver somniferum



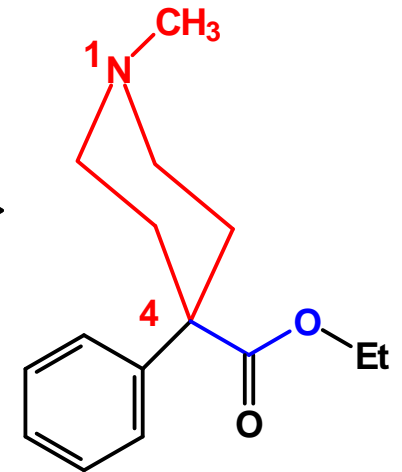
Papaver somniferum
Opium Poppy



DOR



"strip-tease"
molecular
simplificação
molecular



4-fenilpiperidinas

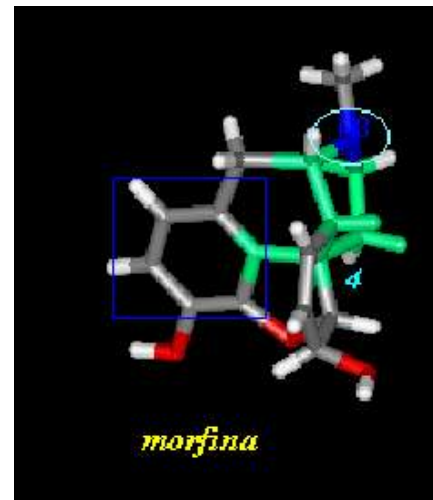
meperidina
Dolantina^R



metadona
Fenadona^R



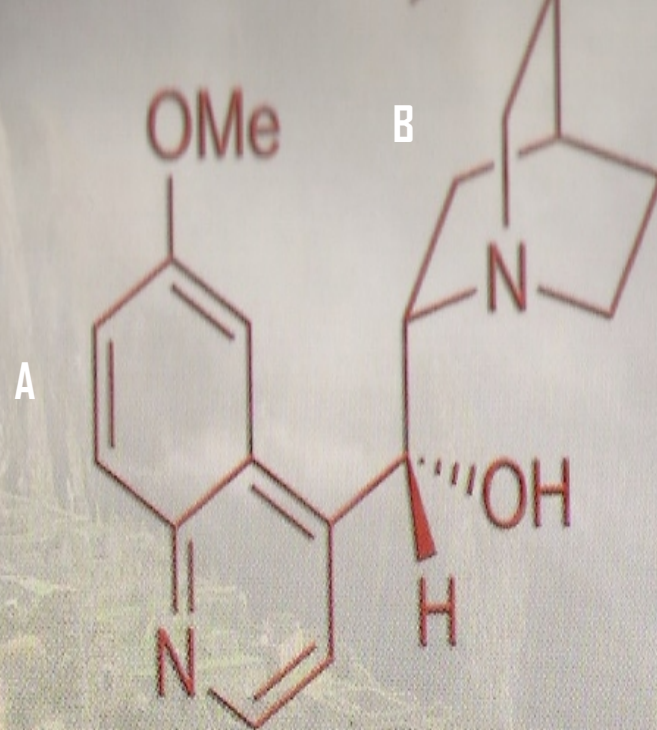
Schultz et al., 1947



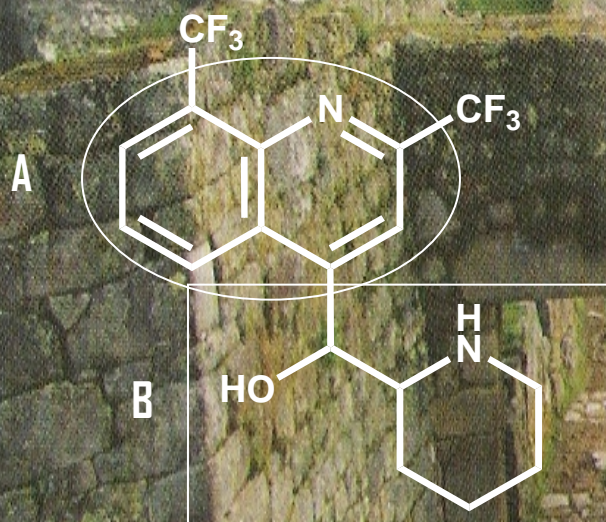
morfina

**Morfina: protótipo
natural para classe dos
hipno-analgésicos**

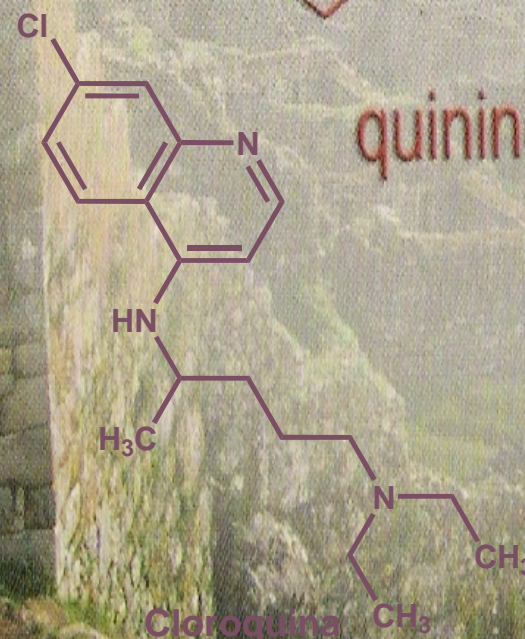
Cinchona officinalis



quinine



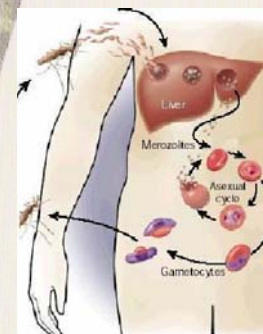
Mefloquina



Cloroquina

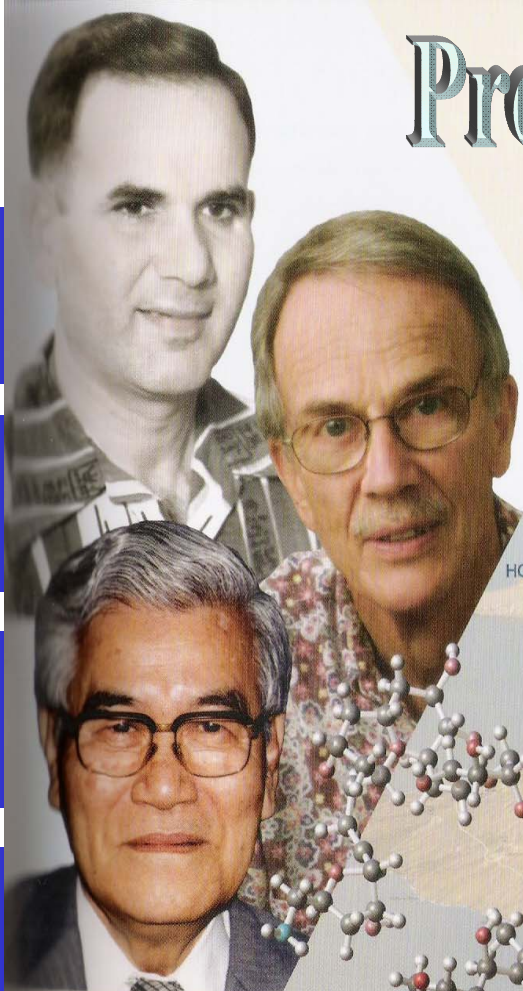
Ruins of Machu Picchu, Peru

Malária

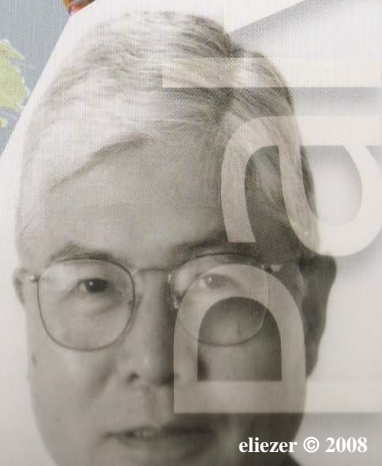
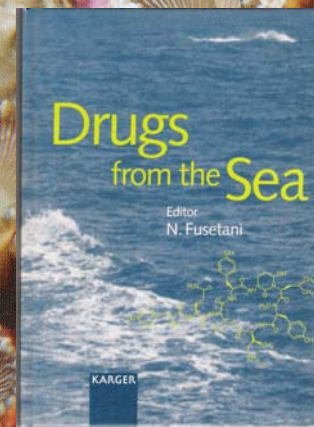
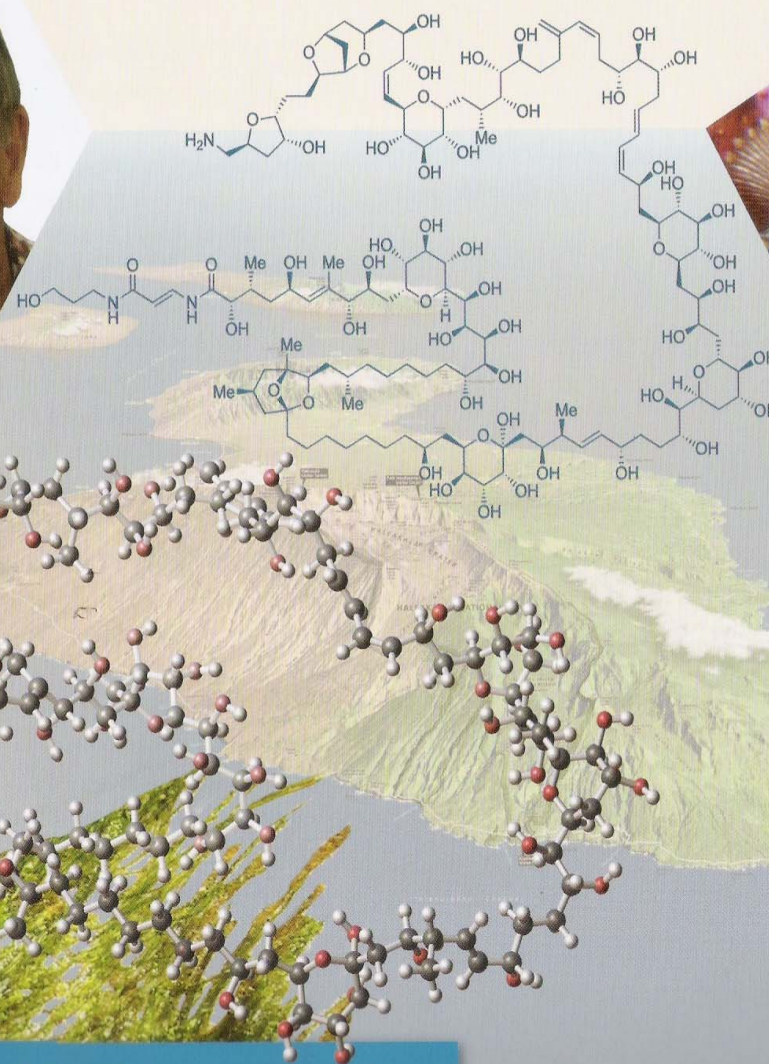




Produtos Naturais do Mar

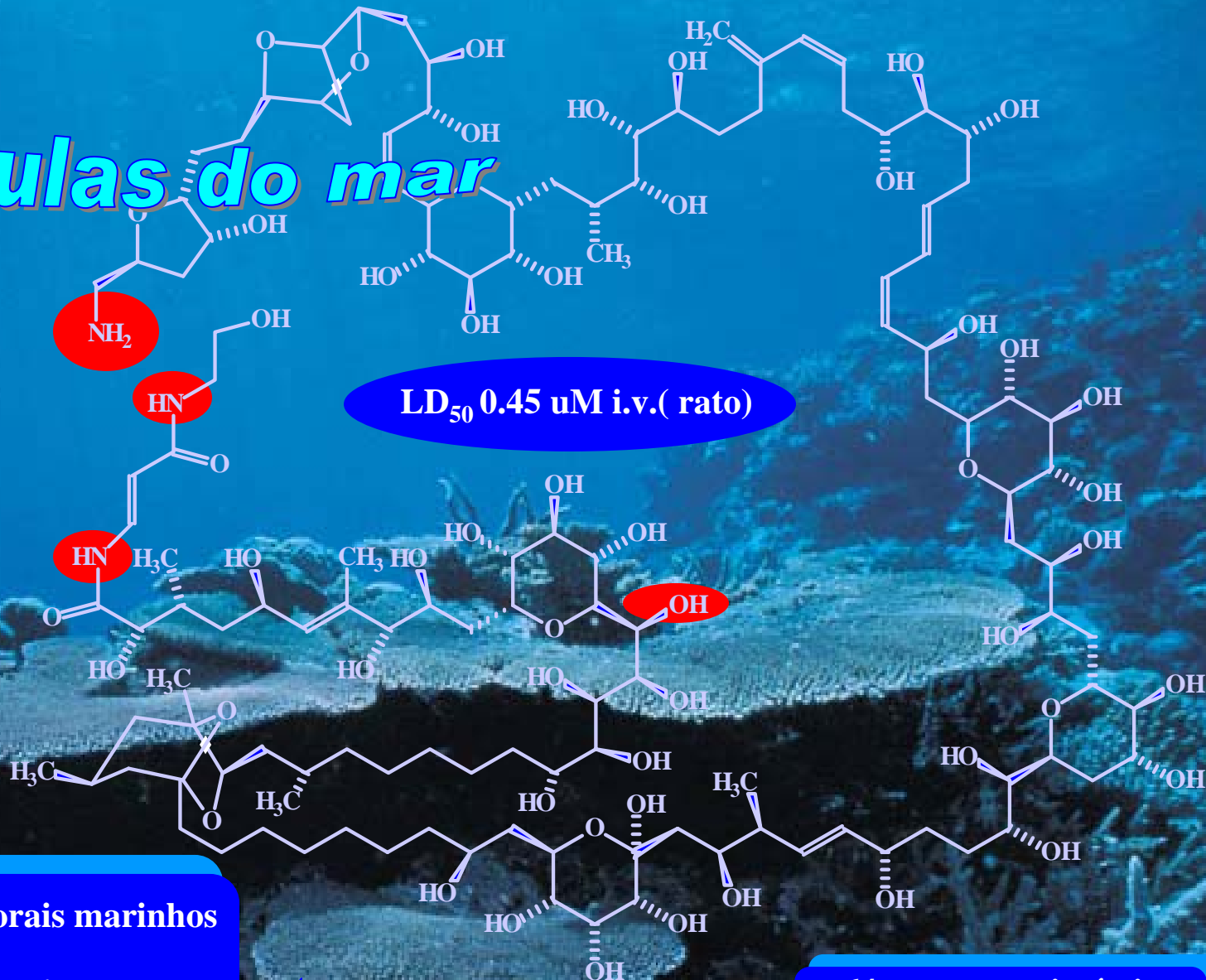


N. Fusetani



Palytoxin

Moléculas do mar



LD₅₀ 0.45 uM i.v.(rato)

1971 - Isolada de corais marinhos do gen. *Palythoa*

1982 - vasoconstrição intensa

1983 -estrutura elucidada

1989 -síntese total estereosseletiva

Y. Kishi *et al.*, 1989

Palitoxina

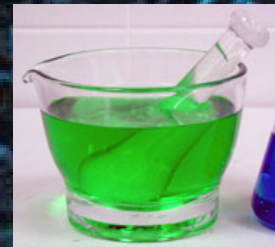
C₁₂₉H₂₂₇N₃O₅₄
PM 2684.20

64 centros assimétricos
8 ligações duplas
42 grupos hidroxilas

2⁶⁴ isômeros

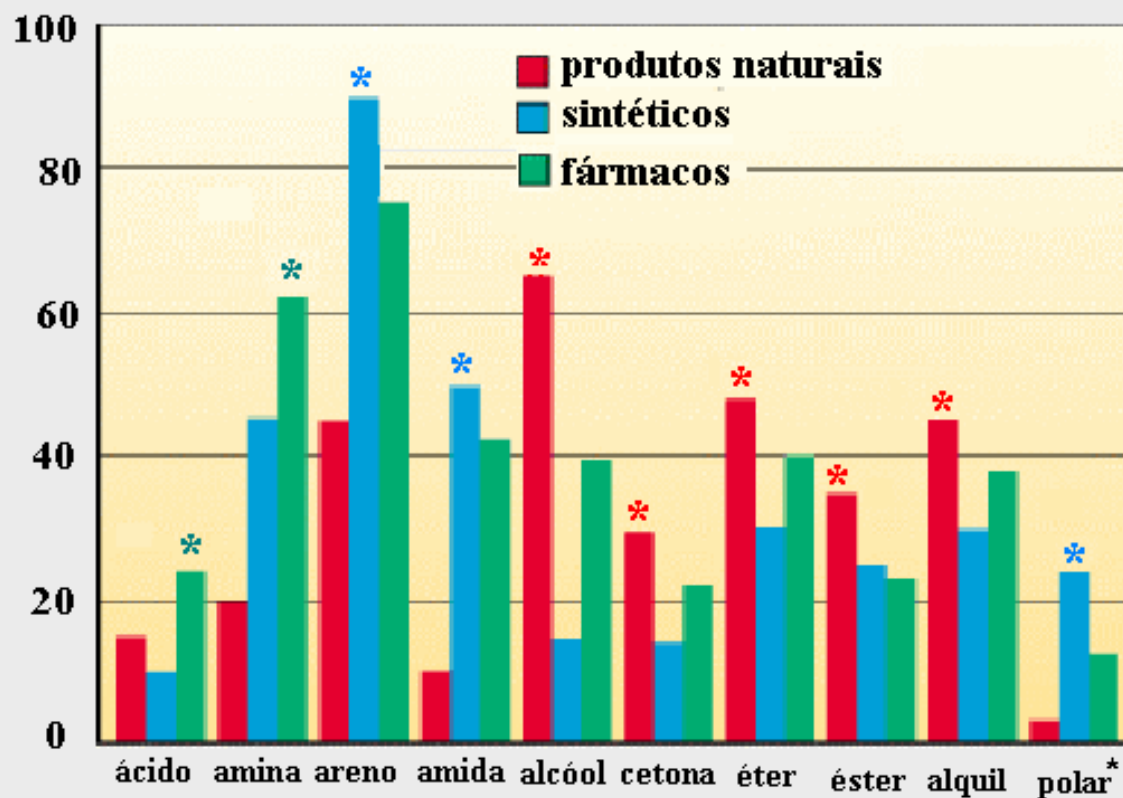
Produtos Naturais na Descoberta de Fármacos

- **Nova entidade química** (NECs; *New chemical entity*)
- **Inovação terapêutica**: mecanismo de ação **inovador**
- **Fármacos anti-câncer**, antibióticos, anti-fúngicos:
ausência de resistência cruzada
- **Elevado índice terapêutico** (IT)
- **Acessibilidade sustentável**
- **Abundância natural adequada**: ensaios pré-clínicos & clínicos
- **Proteção patentária**



DD Baker, M Chu, U Oza, V Rajgarhia, The value of natural products to future pharmaceutical discovery, *Nat Prod Rep* 2007, 24, 1225-1244.

Frequência dos Grupos Funcionais Clássicos em Diferentes Compostos



* grupos polares: F, CN, NO₂

Fonte: *Angewandte Chemie*

Aspectos da Química Farmacêutica Medicinal

Sumário

1. Os fármacos & a Química Medicinal
2. Como se descobrem os fármacos? *Os fármacos e os prêmios Nobéis*; Como atuam os fármacos?
3. A dissecação molecular : grupo farmacofórico
4. Moléculas *inteligentes*: os alfabetos moleculares
5. *Domesticando* moléculas naturais
6. O paradigma do composto-protótipo
7. Fármacos *simbióticos*: exemplos *de casa*
8. Epílogo



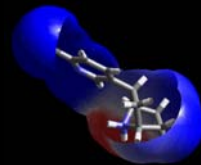
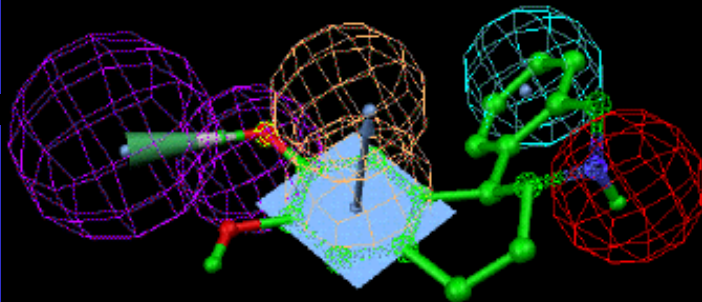
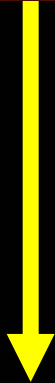
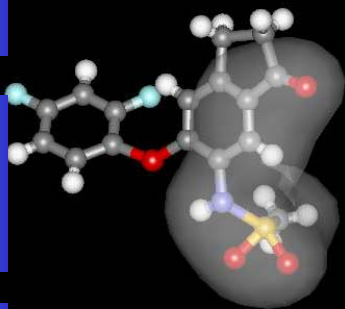
O processo da descoberta racional...



... o paradigma do composto-protótipo.



Agora...



Química Medicinal

Atualmente, os fármacos, **capazes de atuarem em qualquer alvo-terapêutico**, são descobertos **por planejamento racional**.



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 ”



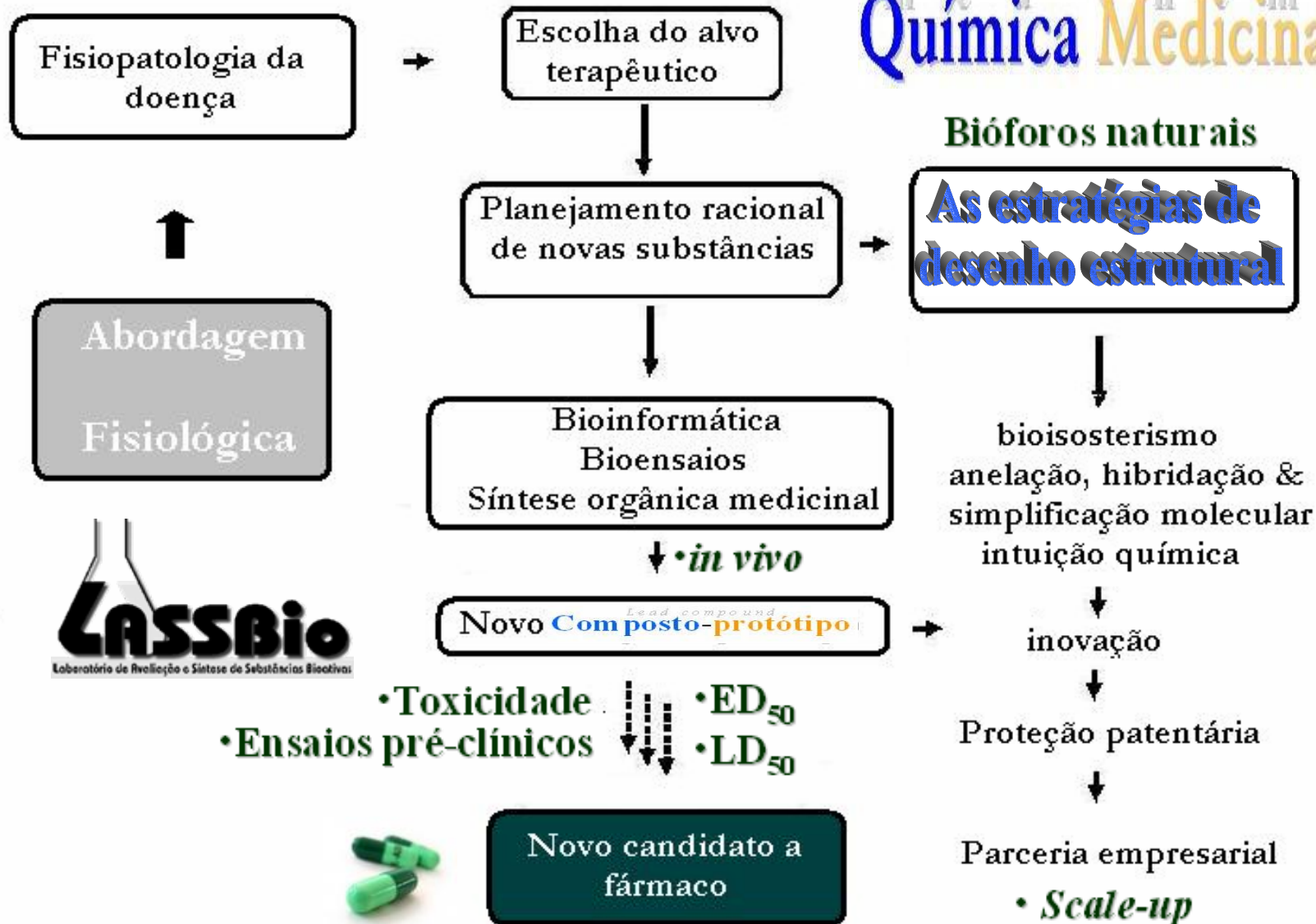
Otimização
do
Protótipo





Physiologic approach A abordagem fisiológica

med chem Química Medicinal



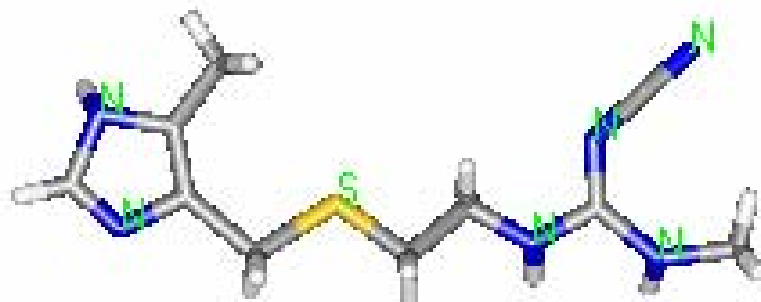


H₂-receptor
antagonists



Cimetidina

Inovação terapêutica



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

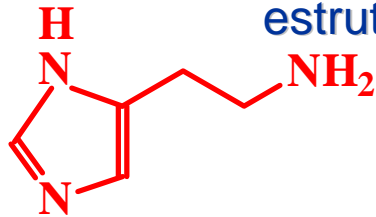


Abordagem Fisiológica

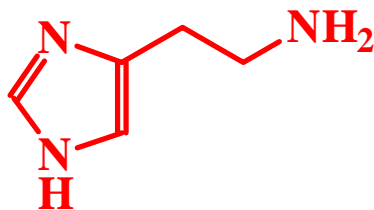
Análogo ativo

Ligações frágeis

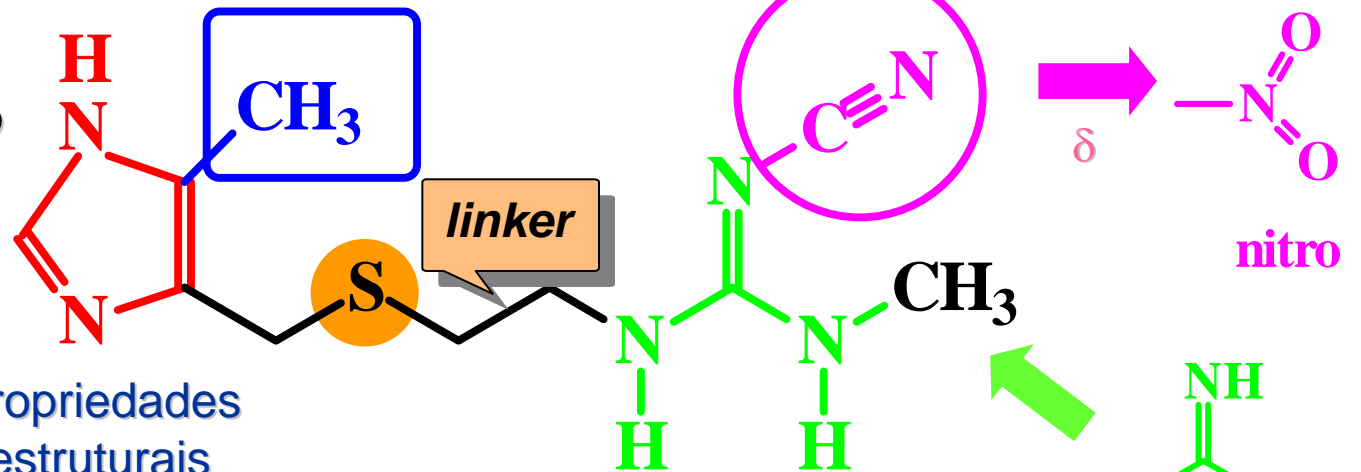
Propriedades estruturais



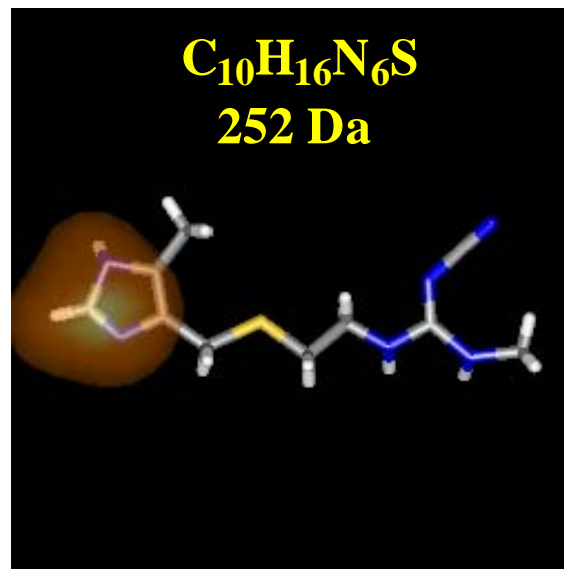
Agonista natural



histamina



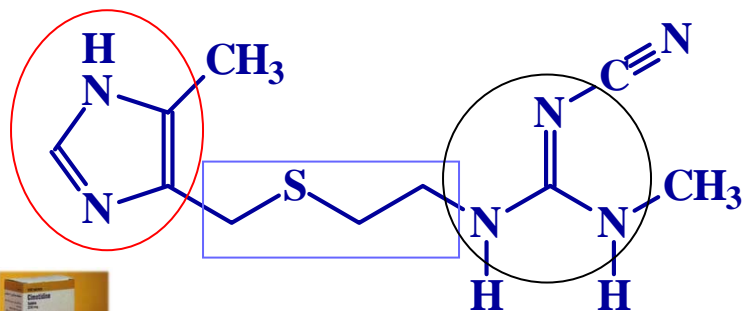
cimetidina

NC(=O)N
uréia

amidina

Retro-dissecação molecular

Fragmentos moleculares



Cimetidina

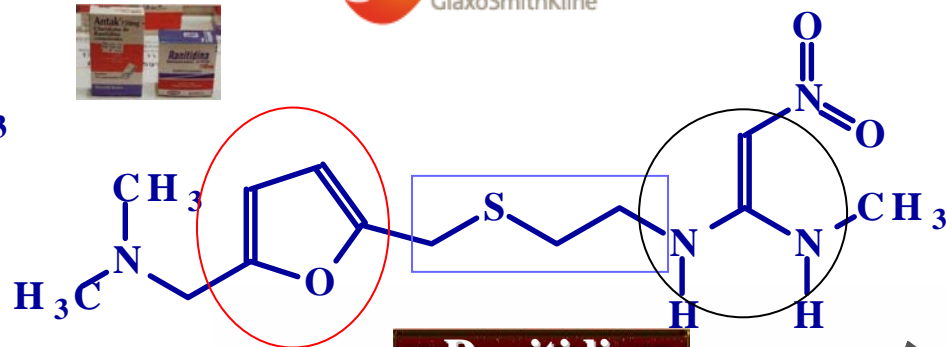
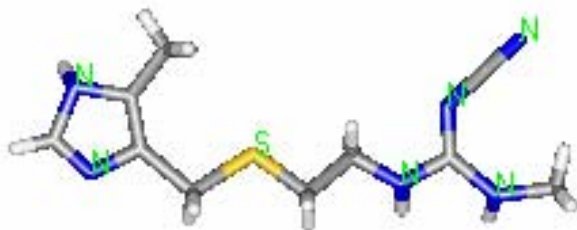
Robin Ganellin *et al.*, 1974

US 3950333 1974, 1976 - SK&F

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



*similaridade
molecular*

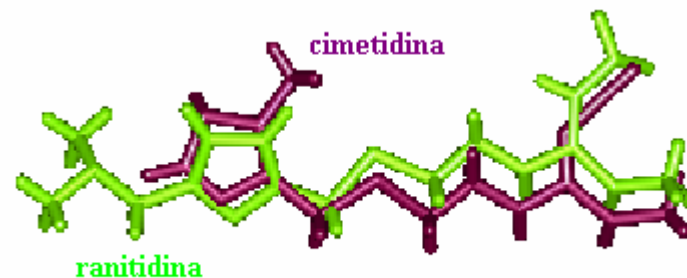
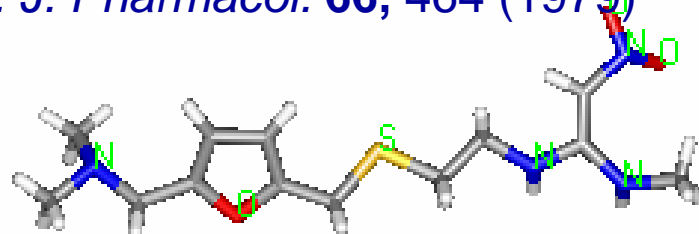


Ranitidina

Barry J. Price *et al.*, 1978

US 4128658 1978 - Allen & Hanburys

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





me-too \$

Fármacos descobertos/inventados cronologicamente após o cabeça-de-série atuando pelo mesmo mecanismo farmacológico de ação.

inter-alia: antagonistas de H-2R; β -bloqueadores; inibidores da ECA, de PDE-5;



Estatinas

1959 – F. Lynen (Al.)

1971- Akira Endo (Jpn)

Penicillium citrinum

Mevastatina (compactina)

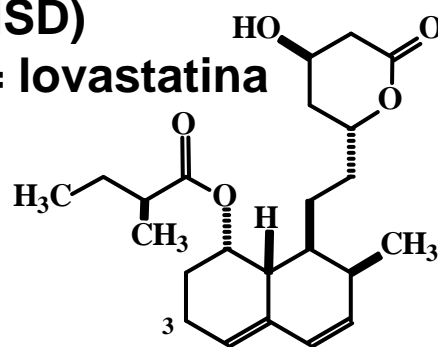
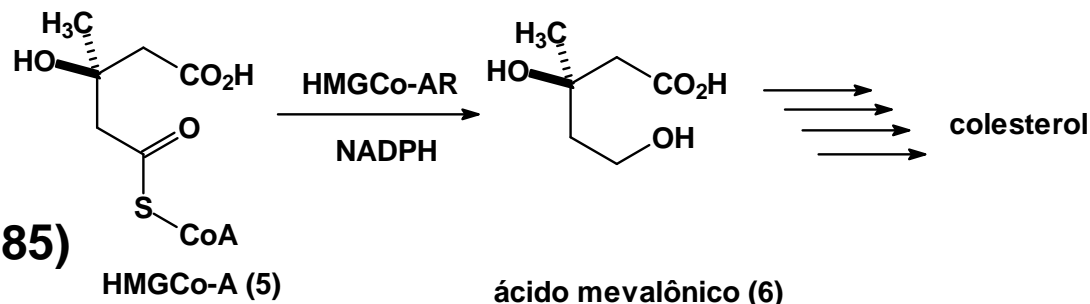
1974 – Michael Brown &
Joseph Goldstein (Nobel, 1985)

demonstram < LDL

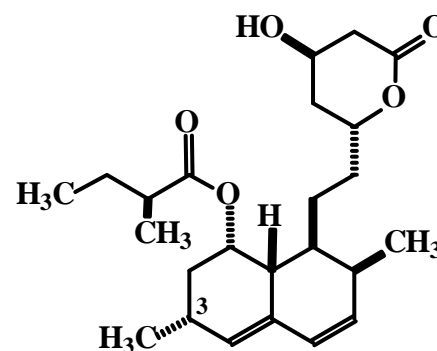
1976 – AA Patchet &

Carl Hoffman (MSD)

Aspergillus sp = lovastatina



compactina (7)



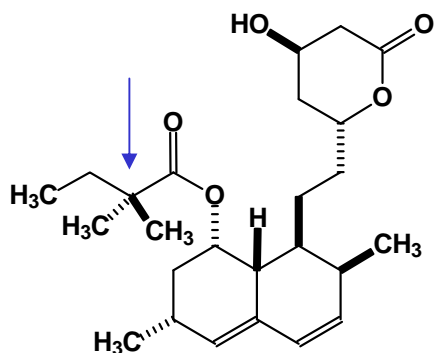
mevilonina ou lovastatina (8)

Medicamentos anti-lipêmicos representam a classe terapêutica de maior Importância, em vendas, no mercado farmacêutico.

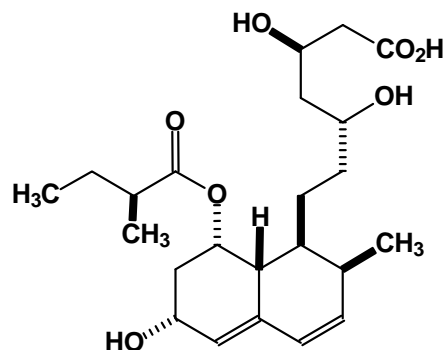
- a) Verkman, A. S. "Drug discovery in academia", Am. J. Physiol. Cell. Physiol. 2004, 286, C465-C474;
- b) Crossley, R. "From hits to leads: Focusing the eyes of medicinal chemistry", Modern Drug Discov. 2002, Dezembro, 18-22,
- c) Oprea, T. I.; Davis, A. M.; Teague, S. J.; Leeson, P. D. "Is there a difference between leads and drugs? A historical perspective" J. Chem. Inf. Comput. Sci. 2001, 41, 1308-1315



1987



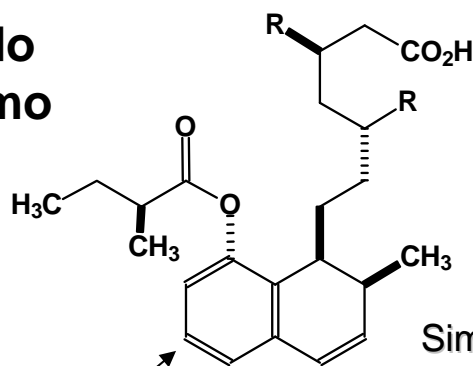
simvastatina (9)



pravastatina (10)

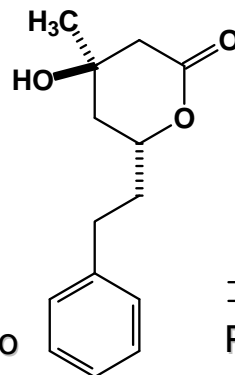
← Segunda geração

Estudos do metabolismo



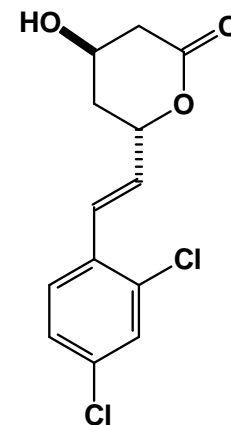
(12)

⇒
Simplificação
molecular



(11)

⇒
Padrão
aromático
aquiral

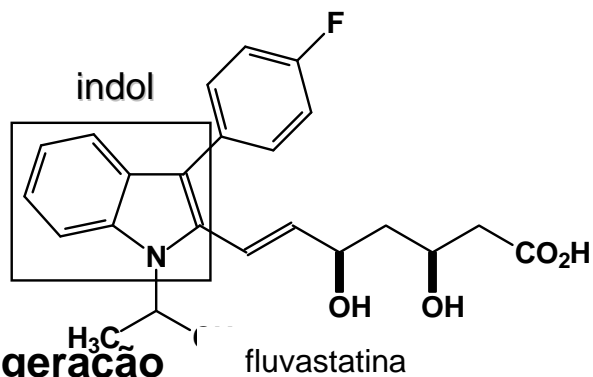


(13)

Desidratação
Desidrogenação

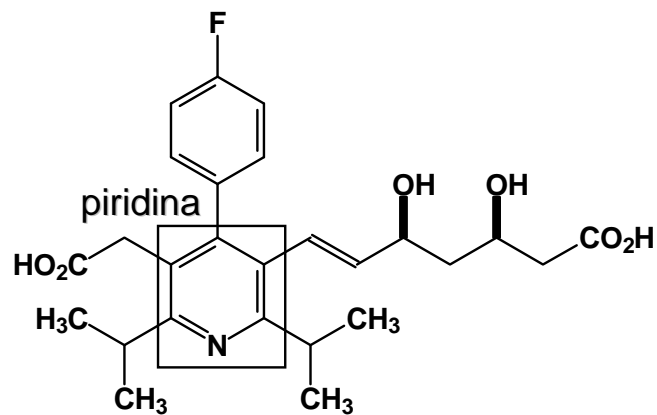


A classe das estatinas ilustra a eficiência do processo de *domesticar* produtos naturais

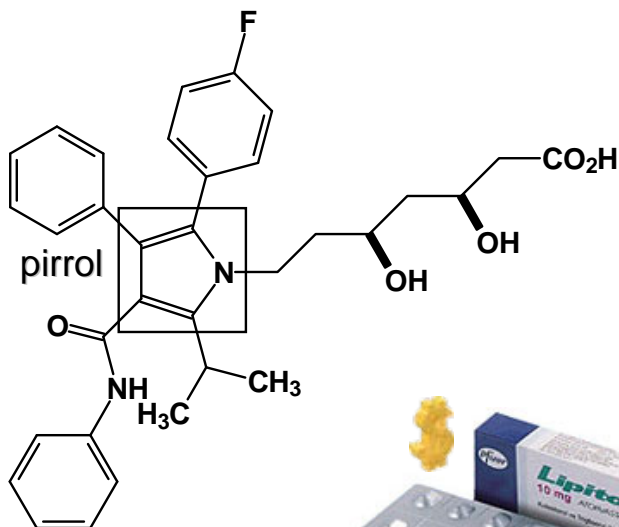


Terceira geração

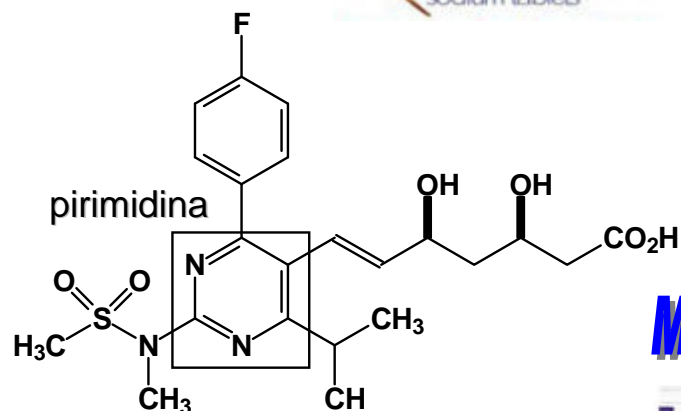
fluvastatina (14)



cerivastatina



atorvastatina



rosuvastatina



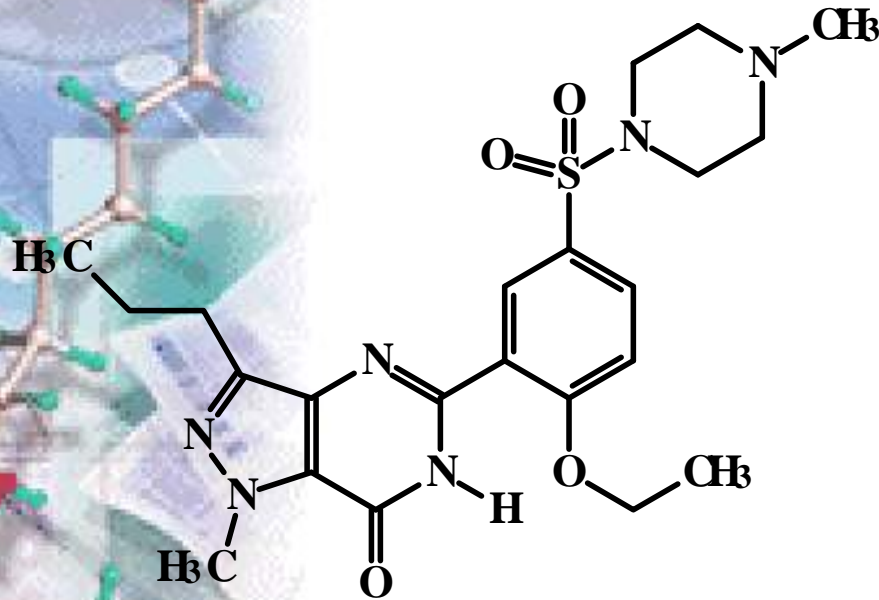
Me-too



É a classe terapêutica líder em vendas no mundo: US\$ 33 bi (2007)

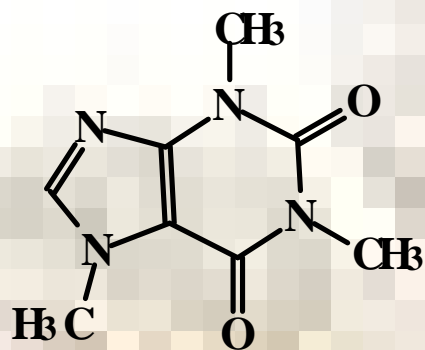


A descoberta do sildenafil

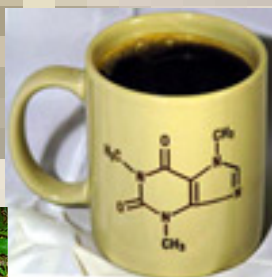




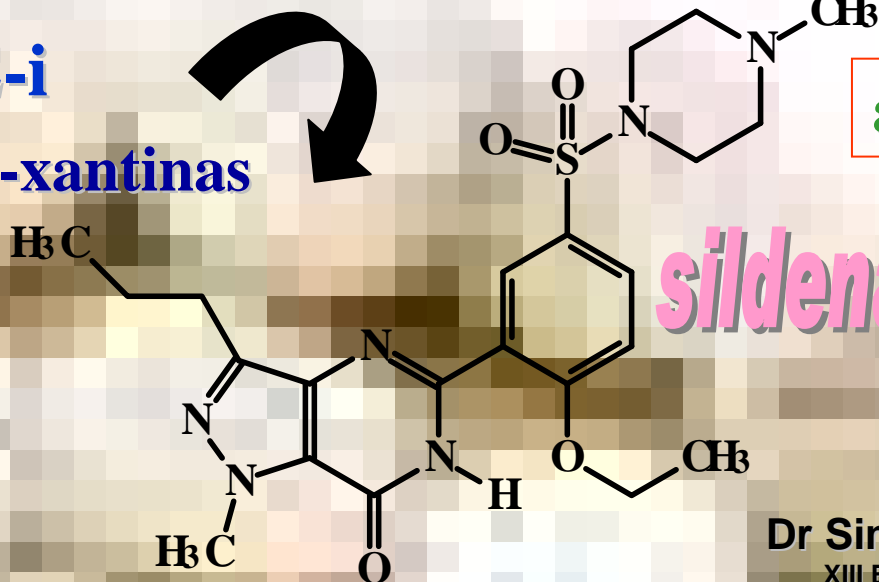
Disfunção erétil



Cafeína/teofilina



PDE-i
Metil-xantinas



sildenafil

angina

PDE -V i

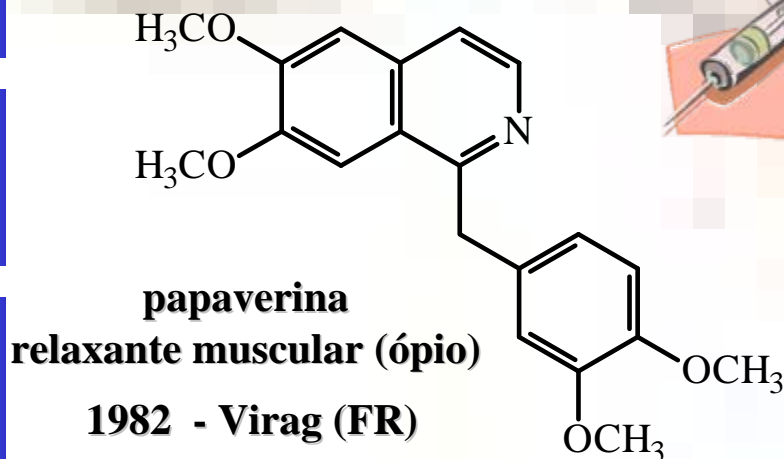
Dr Simon Campbell
XIII EVQFM, LASSBio,
UFRJ, 2005



serendipidade

**alprostadil
injetável**

Caverject[®]



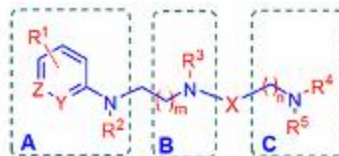
papaverina

relaxante muscular (ópio)

1982 - Virag (FR)

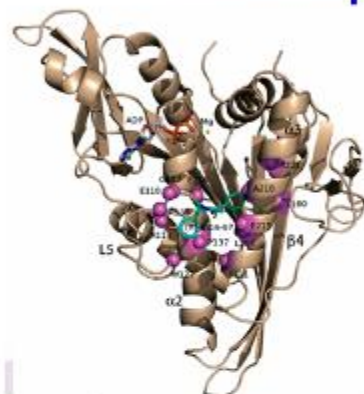
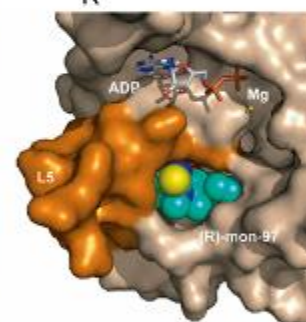
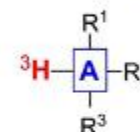
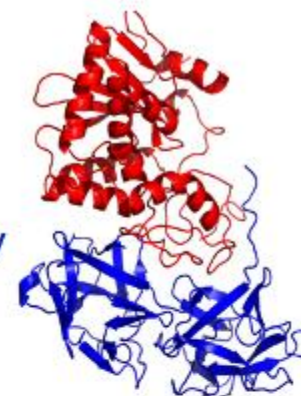


Estratégias modernas industriais de descoberta de fármacos



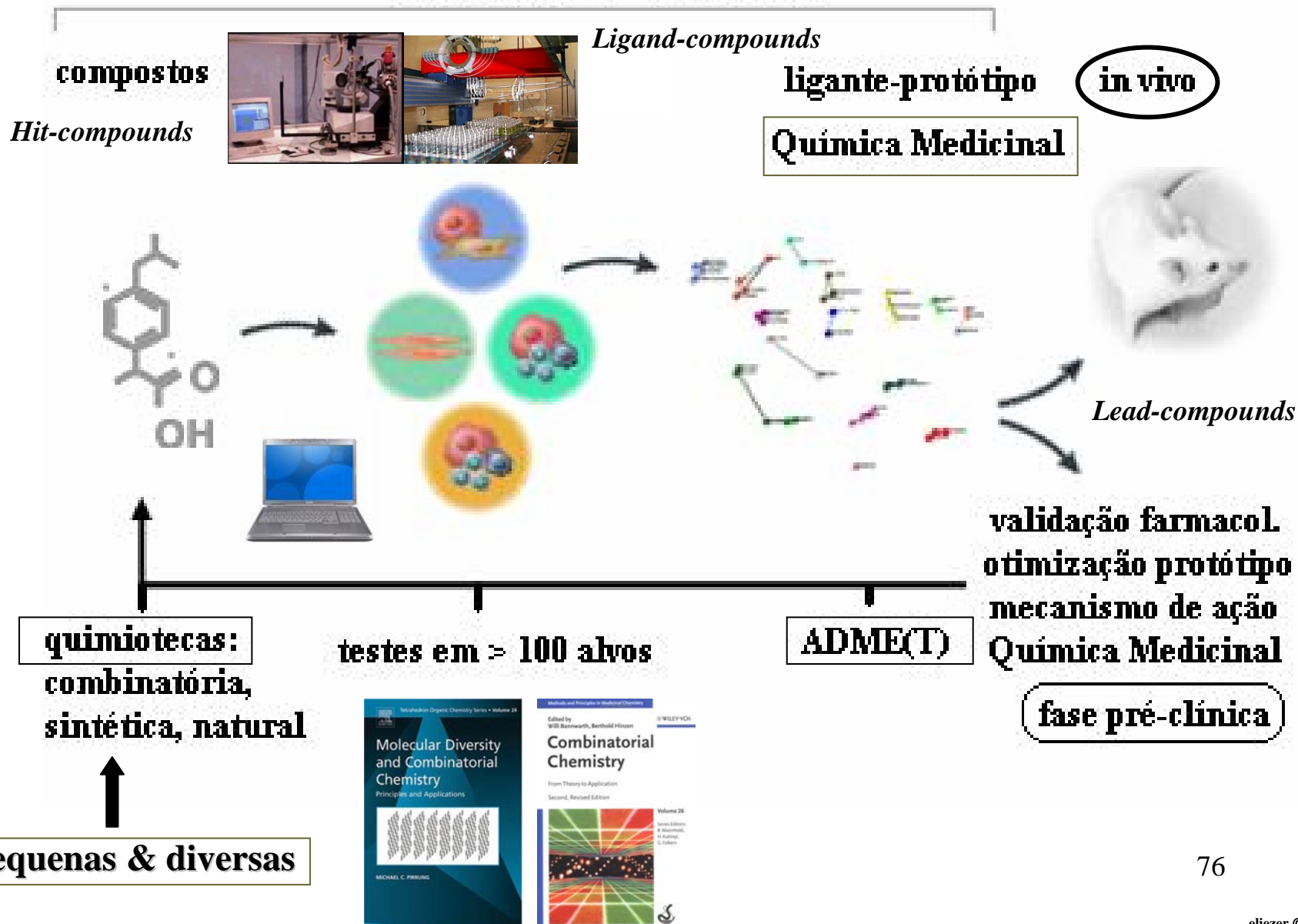
High Throughput Screening & Combinatorial Chemistry

Técnicas hifenadas: CombChem-HTS



C. Eggeling *et al.*, Highly sensitive fluorescence detection technology current available for HTS, DDT 2003, 8, 623;
P. Gribbon & A. Sewing, High-throughput drug discovery: what can we expect from HTS?, DDT 2005, 10, 17

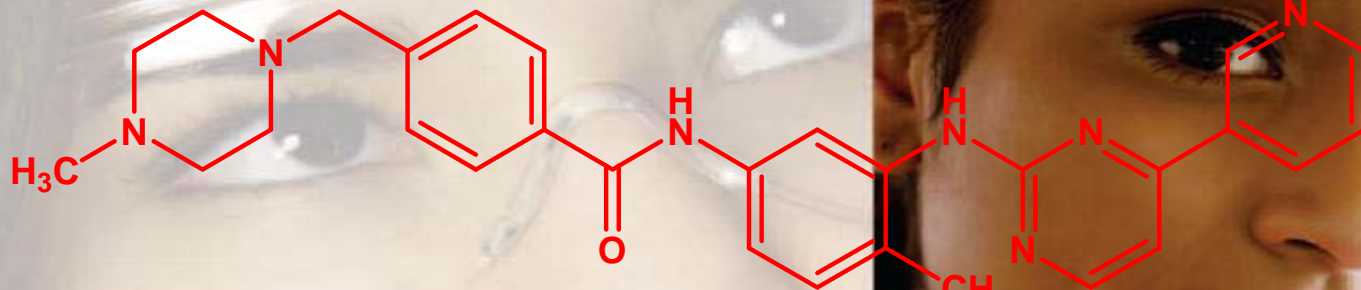
Abordagem "irracional"



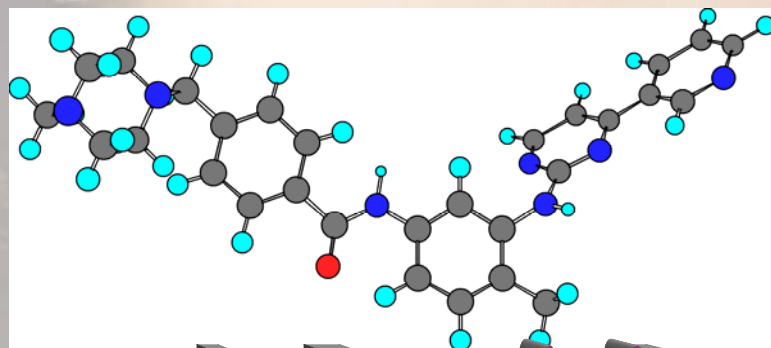


Um caso de sucesso
na abordagem “irracional”:

A DECADE OF
Innovation

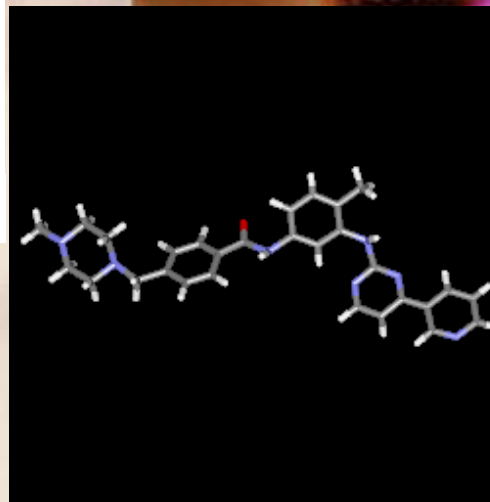


Imatinibe



PHARMACEUTICAL
INNOVATION

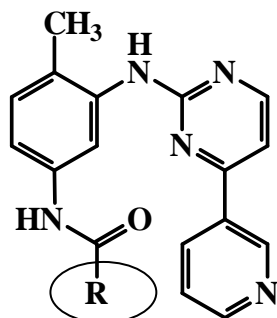
Revolutionizing Human Health



Edited by Ralph Landau, Basil Achilladelis, and Alexander Scriabine

Gênese do Imatinibe

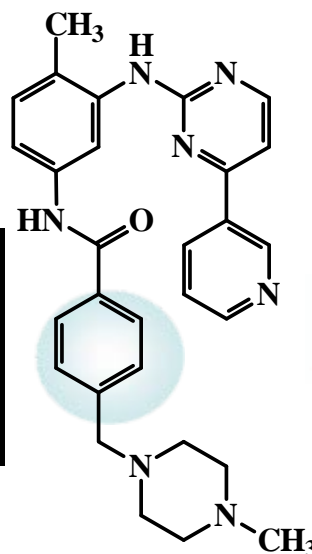
Protótipo



bcr-K inibidor

$C_{17}H_{14}N_5OR$

otimização



$C_{29}H_{31}N_7O$

imatinib

2002

NOVARTIS



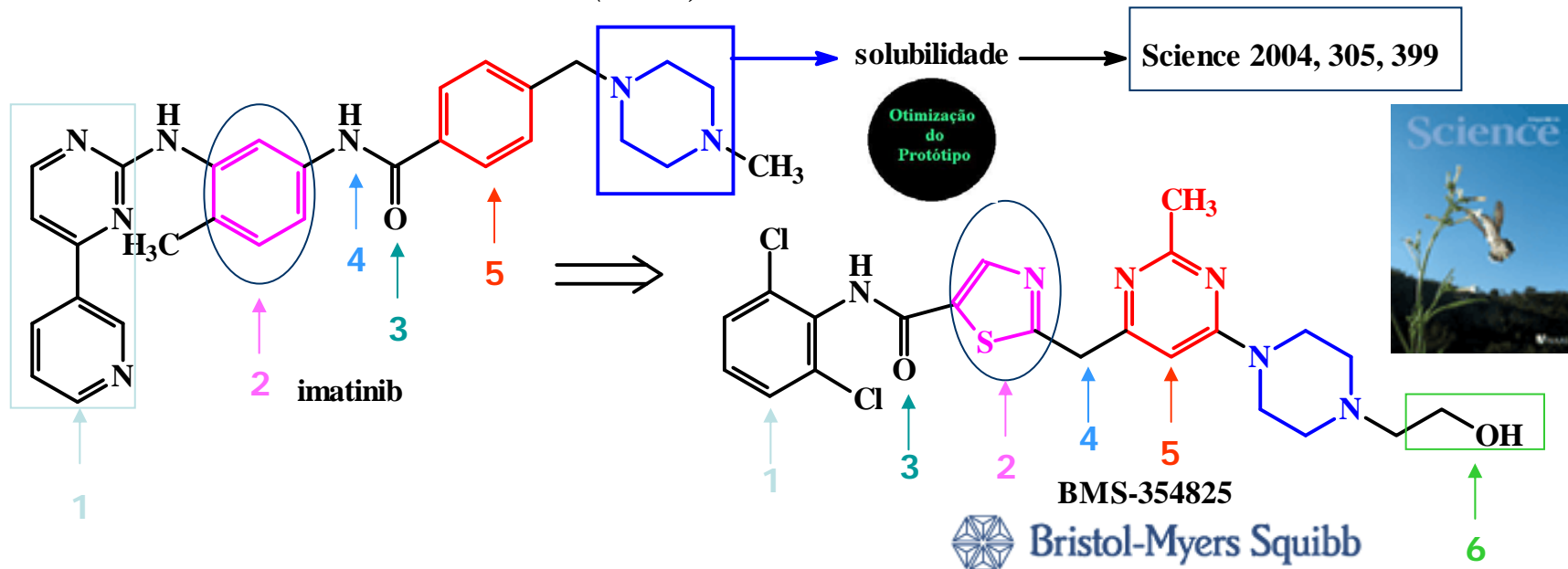
GLIVEC (STI571, IMATINIB)

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

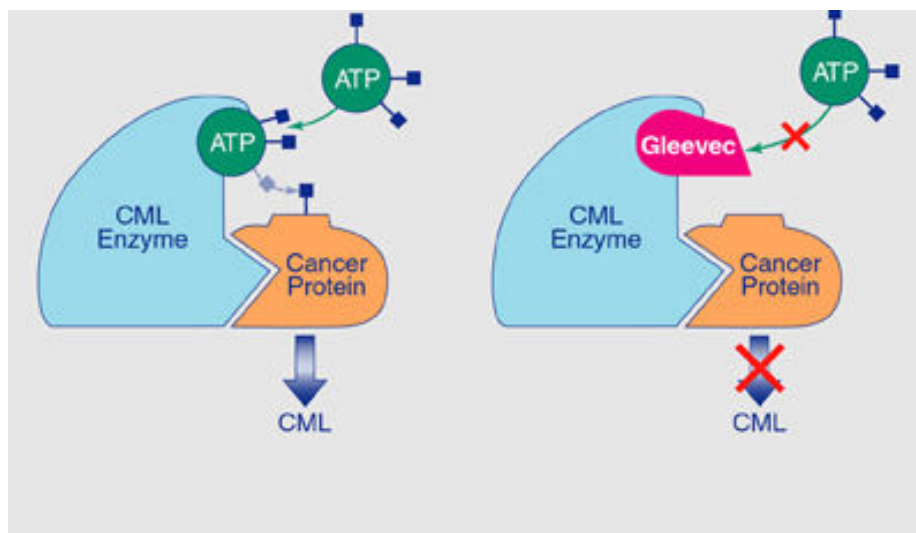
Maio de 2001 o FDA aprova imatinib (Glivec[®]) para leucemia mielóide crônica; preço: R\$ 10.000,00/30 comp. [400mg]

Desenho molecular baseado na estrutura (SBDD)

Otimização

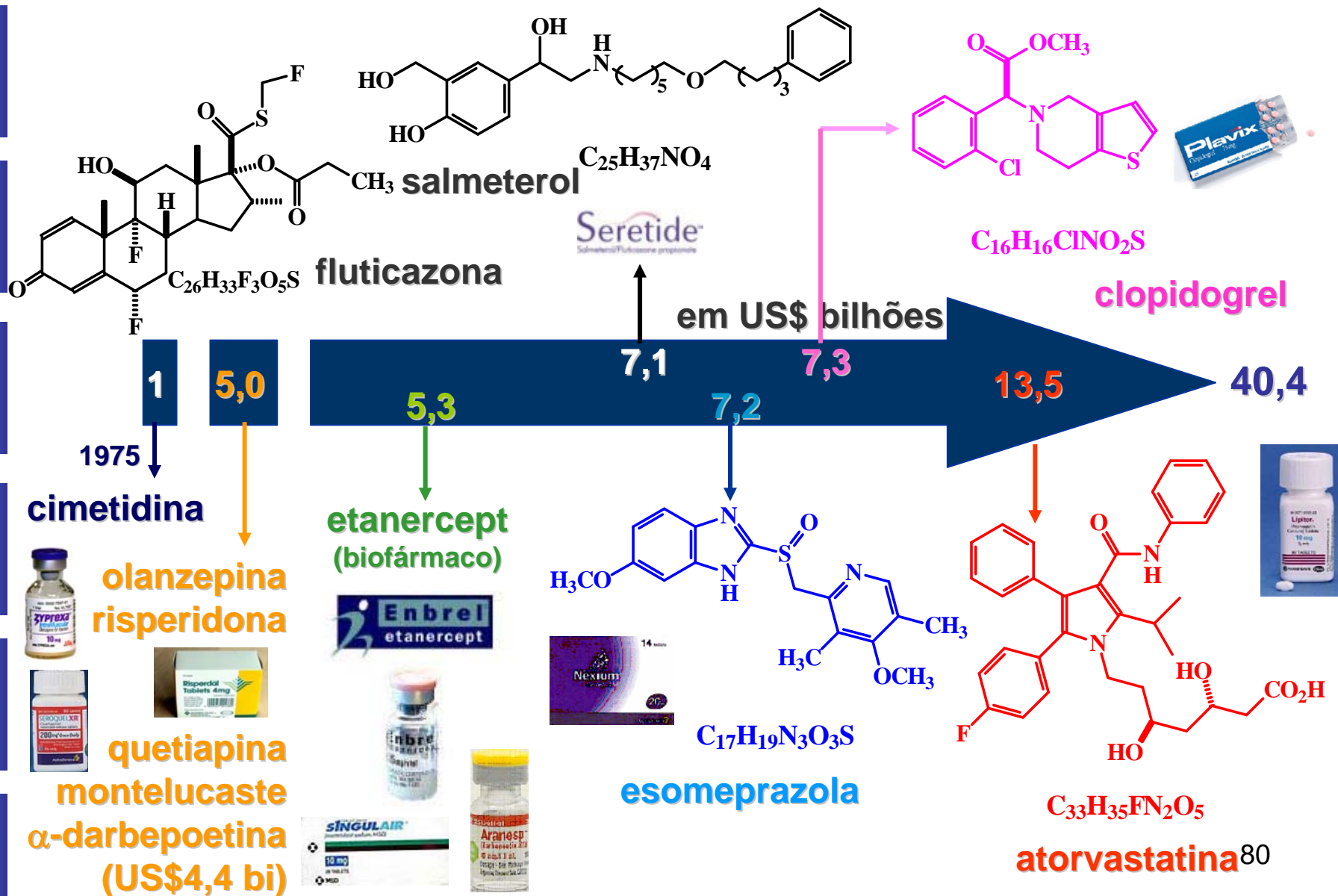


S. Ghosh, X. P. Liu, Y. Zheng, F.M. Uckun, Rational design of potent and selective EGFR tyrosine kinase inhibitors as anticancer agents, *Curr. Cancer Drugs Target*, **2001**, 1, 129-140





5-mais no mercado mundial em 2007



Fonte IMS MIDAS®, Dec 2007



Big Pharma marketing expenses

- One blockbuster drug was hyped more than Pepsi and Bud: Merck spent \$160 million in 2000 advertising Vioxx. That's more than PepsiCo spent advertising Pepsi or Anheuser-Busch spent advertising Budweiser. (National Institute for Health Care Management, "Prescription Drugs and Mass Media Advertising: 1999-2000," November 2001)



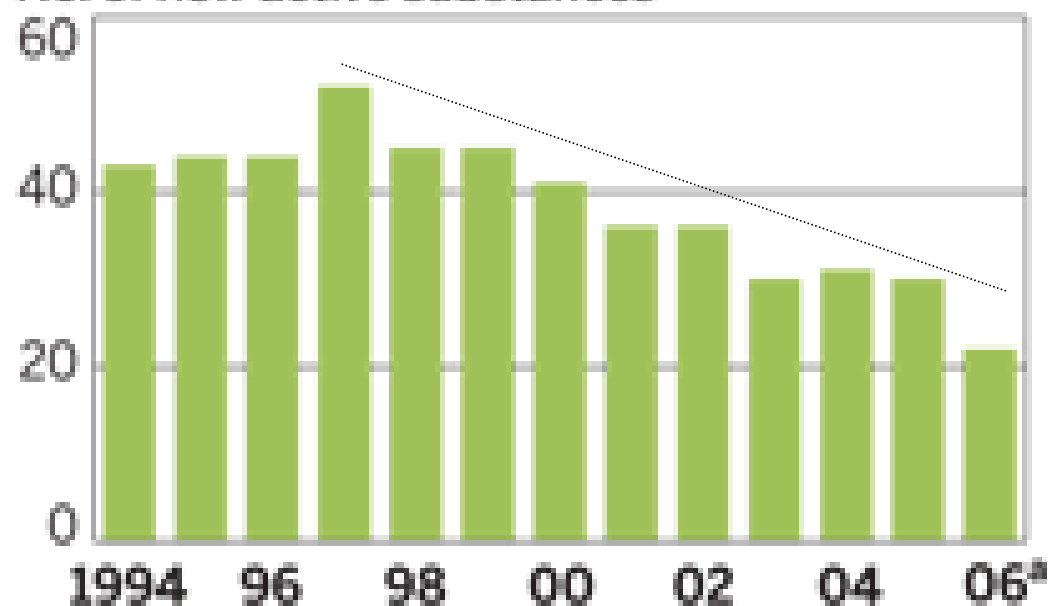
Declínio da criatividade nas Big Pharmas



J. Grimley (IMS), C&EN 2006, Dec. 04, **84**, 49
<http://pubs.acs.org/cen/coverstory/84/8449.html>

PLATEAU Number of new substances approved as drugs has leveled off

No. of new active substances



NOTE: Includes new chemical entities and biotechnology products. ^a January through August.

SOURCE: IMS Lifecycle New Product Focus



Endereço: <http://www.centerwatch.com/patient/drugs/dru847.html>

Google caduet Search 3 blocked Check AutoLink AutoFill Options caduet Web assistant

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Trial Listings Notification Services Patient's Bookstore About Research Drug Directories Additional Resources

Drugs Approved by the FDA

Drug Name: Caduet (amlodipine/atorvastatin)

The following information is obtained from various newswires, published medical journal articles, and medical conference presentations.

Description of Medical Areas

About the FDA Approved Listings

Company: Pfizer
Approval Status: Approved January 2004
Treatment for: Hypertension/Angina

General Information

Caduet combines the drugs amlodipine (Norvasc, Lotrel) and atorvastatin (Lipitor), two widely prescribed cardiovascular medications. It's the first medicine to treat two different conditions, high blood pressure and high cholesterol.

It is indicated for the treatment of hypertension, chronic stable angina and vasospastic angina (Prinzmetal's or variant angina). It is also indicated for primary hypercholesterolemia, elevated serum TG levels.

Back to Drug Listing

two component tablet

Amlodipina **Norvasc^R**

atorvastatina **Lipitor^R**

CADUETTM
amlodipine/atorvastatin tablets
5mg/10mg
USO ORAL
COMPRIMIDOS
VENDA SOB PRESCRIÇÃO MÉDICA
Contém 10 comprimidos

CHEMICAL & Engineering News
TOP Pharmaceuticals
These companies are shaping the future of medicine

(18 item(s) restante(s)) Abrindo página <http://www.centerwatch.com/patient/drugs/dru847.html>...

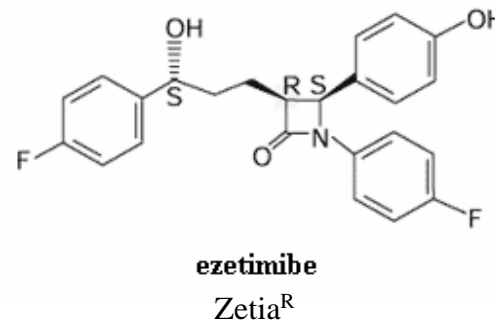
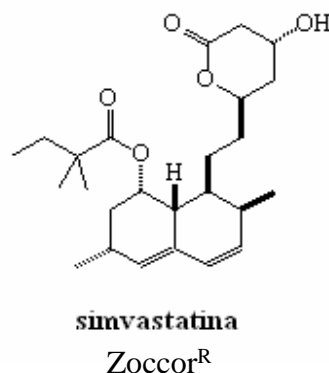
W. H. Frishman & A. L. Zuckerman, *Expert Rev. Cardio*

O setor de medicamentos cardiovasculares movimentou em 2005 *ca.* US\$ 72 bilhões

VYTORINTM
(ezetimibe/simvastatin)

Merck/Schering-Plough

two component tablet

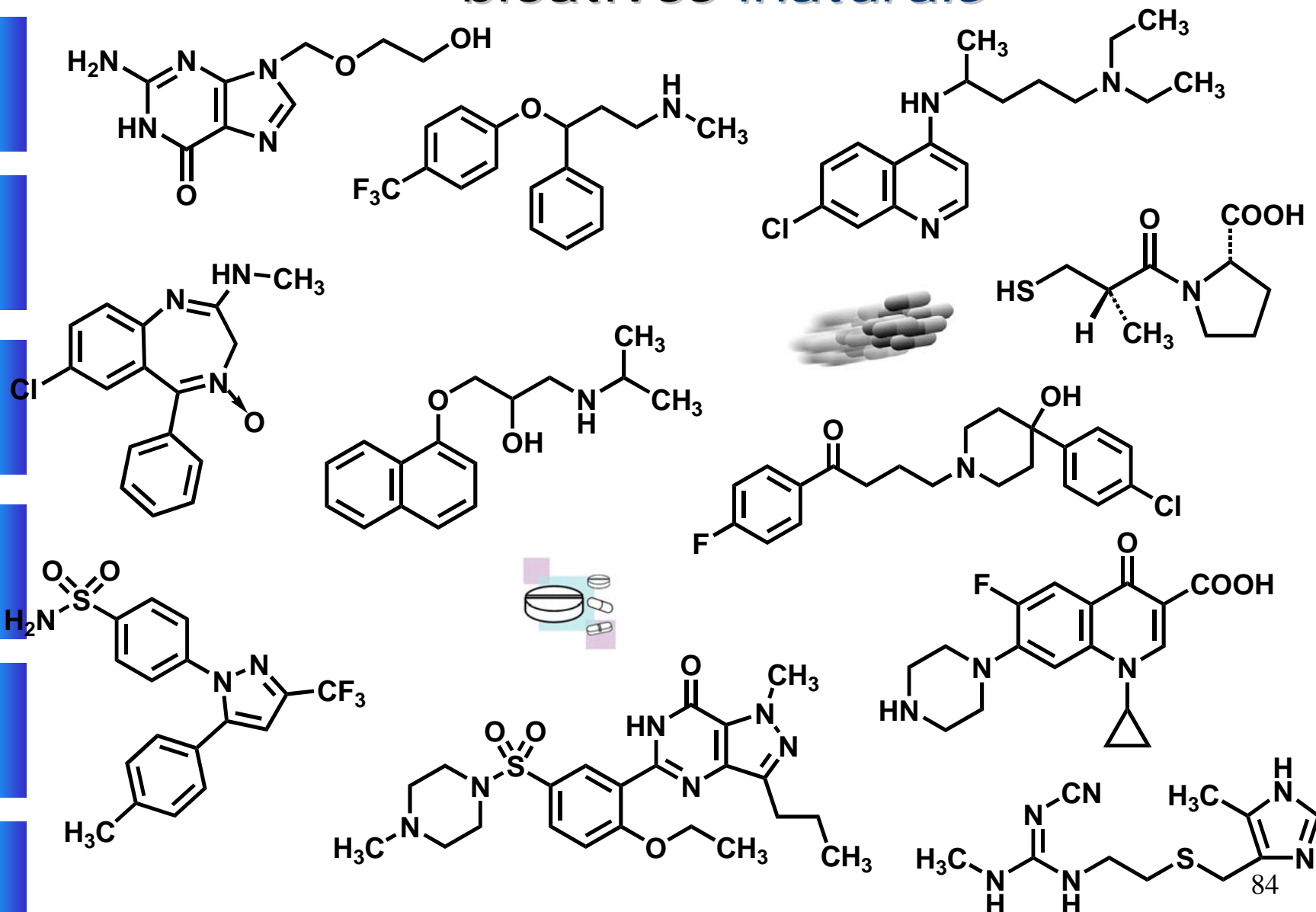


N. A. Flores, *Curr. Opin. Invest. Drugs* **2004**, 5, 984
Vytorin^R sales 2006-third-quarter = US\$527 million
Lisa M. Jarvis, "Big Pharma Regroups", *CE&N* 2006, 84, 49 (November 20)





A quimiodiversidade dos compostos bioativos *inaturais*



A quimiodiversidade dos fármacos é singela!

Características estruturais comuns nos onze fármacos :

- Representam inovações terapêuticas importantes: aciclovir, fluoxetina, cloroquina, clordiazepóxido, propranolol, captopril, haloperidol, celecoxibe, sildenafil, ciprofloxacina, cimetidina;
- pertencem a **08** classes terapêuticas distintas: > SNC;
- Possuem apenas **7** elementos químicos: C, H, O, N, S, F, Cl;
- **10/11** possuem heteroátomos, **10/11** têm heterocíclios;
- **11/11** são multicíclicos (< cinco anéis);
- **10/11** possuem sub-unidades aromáticas;
- Têm **15** funções químicas: alcano, areno, álcool, tiol, haleto, éter, tio-éter, amina, cetona, amida, ácido carboxílico, N-óxido, amidina, sulfonamida, nitrila;
- **11/11** são de origem sintética, como > 88% dos fármacos;
- são moléculas pequenas, valiosas & inteligentes !



Aspectos da Química Farmacêutica Medicinal

Sumário

1. Os fármacos & a Química Medicinal
2. Como se descobrem os fármacos? *Os fármacos e os prêmios Nobéis*; Como atuam os fármacos?
3. A dissecação molecular : grupo farmacofórico
4. Moléculas *inteligentes*: os alfabetos moleculares
5. *Domesticando* moléculas naturais
6. O paradigma do composto-protótipo
7. Fármacos *simbióticos*: exemplos *de casa*
8. Epílogo



Novos fármacos, do futuro...

•Fármacos simbióticos



novos compostos-protótipos com afinidade (SAfiR) relativa próxima capazes de serem reconhecidos molecularmente por dois alvos-terapêuticos distintos de diferentes cascatas bioquímicas, envolvidos na mesma fisiopatologia.



Symbiotic approach to new lead-candidates

(Multi-target-based new lead-candidates discovery)

*a new compound able to be effective in **two** different target, both relevant to disease but belonging to distinct biochemical pathway;*

A terapêutica do século 21, especialmente para doenças degenerativas (e.g. câncer), privilegiará fármacos que atuem em mais de um alvo terapêutico.



• Ligantes duplos/duais/mistos/bivalentes para dois alvos

(Dual, binary, dimeric, bivalent, mixed ligands)

novos compostos-protótipos com afinidade (SAfiR) relativa semelhantes, capazes de serem reconhecidos molecularmente por dois alvos-terapêuticos distintos da mesma cadeia bioquímica, envolvidos na mesma fisiopatologia.



PS Porthoguese *J. Med. Chem.* **2001**, 44, 2259

COX-LOX / TXS-TPant

Bioorg.Med.Chem.Lett. **2005**, 15, 4842

Il Farmaco **2005**, 60, 7–13; 327

Curr. Med. Chem. **2002**, 9, 941

Biochem.Pharmacol. **2001**, 62, 1433

Bioorg.Med.Chem.Lett. **2001**, 11, 1019

Trombina-fibrinogênioR's-ant.

J. Med. Chem. **2005**, 48, 3110

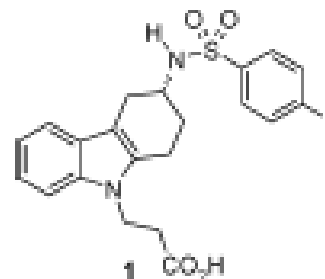
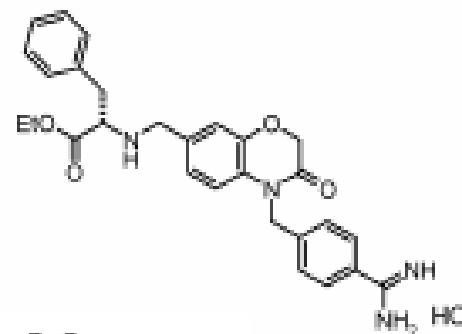
TPant./CRTH2

J. Med. Chem. **2005**, 48, 897

FGFR-1/VEGFR-2

J. Med. Chem. **2005**, 48, 4628

Benzoxazina scaffold



ramatroban



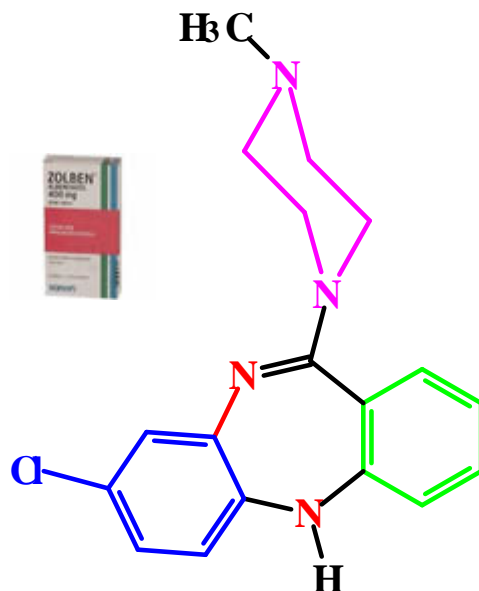
• Ligantes múltiplos

multi-ligands

Compostos com afinidade (SAfiR) por vários alvos-terapêuticos distintos, não obrigatoriamente envolvidos com a mesma fisiopatologia.

Clozapina

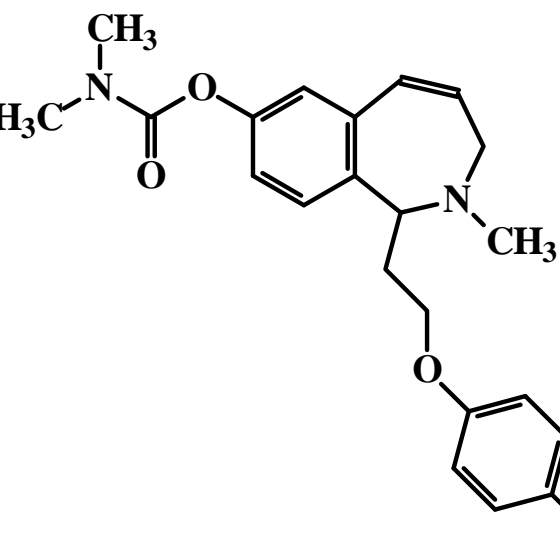
ligante promíscuo



K_i (nM)

	K_i (nM)
D ₁	53
D ₂	190
D ₃ ^b	280
D ₄ ^b	40
5-HT _{1A}	710
5-HT _{2A}	4.0
5-HT _{2C}	5.0
α ₁	3.7
α ₂	51
M ₁	0.98
H ₁	17

J. Med. Chem. **2001**, 44, 477



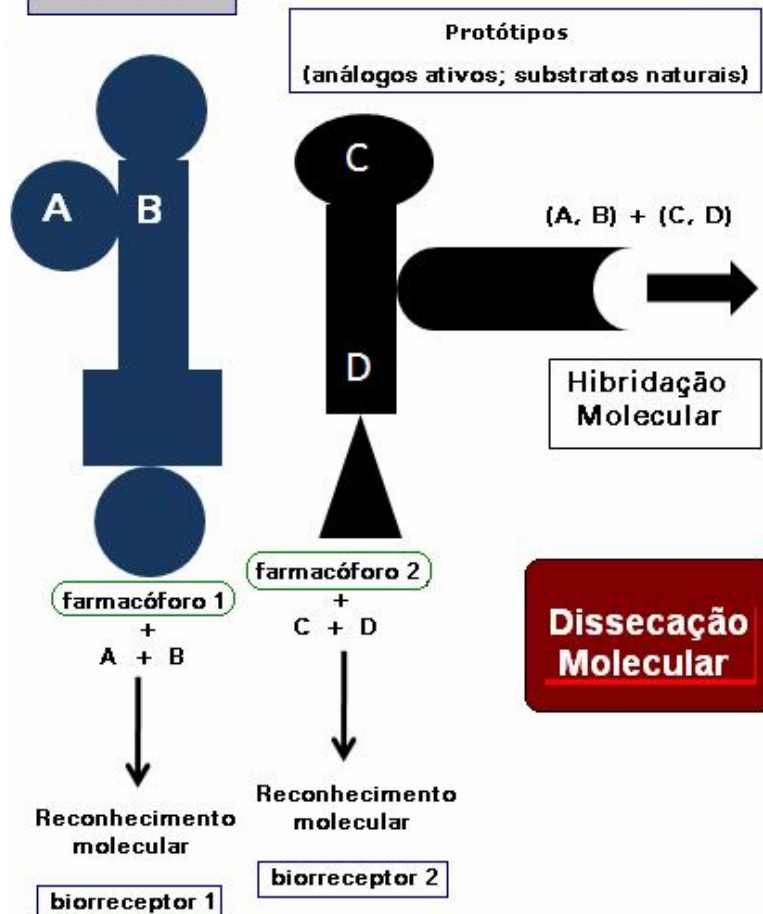
AChE / SERTⁱ

IC₅₀ = 60 / 63 nM

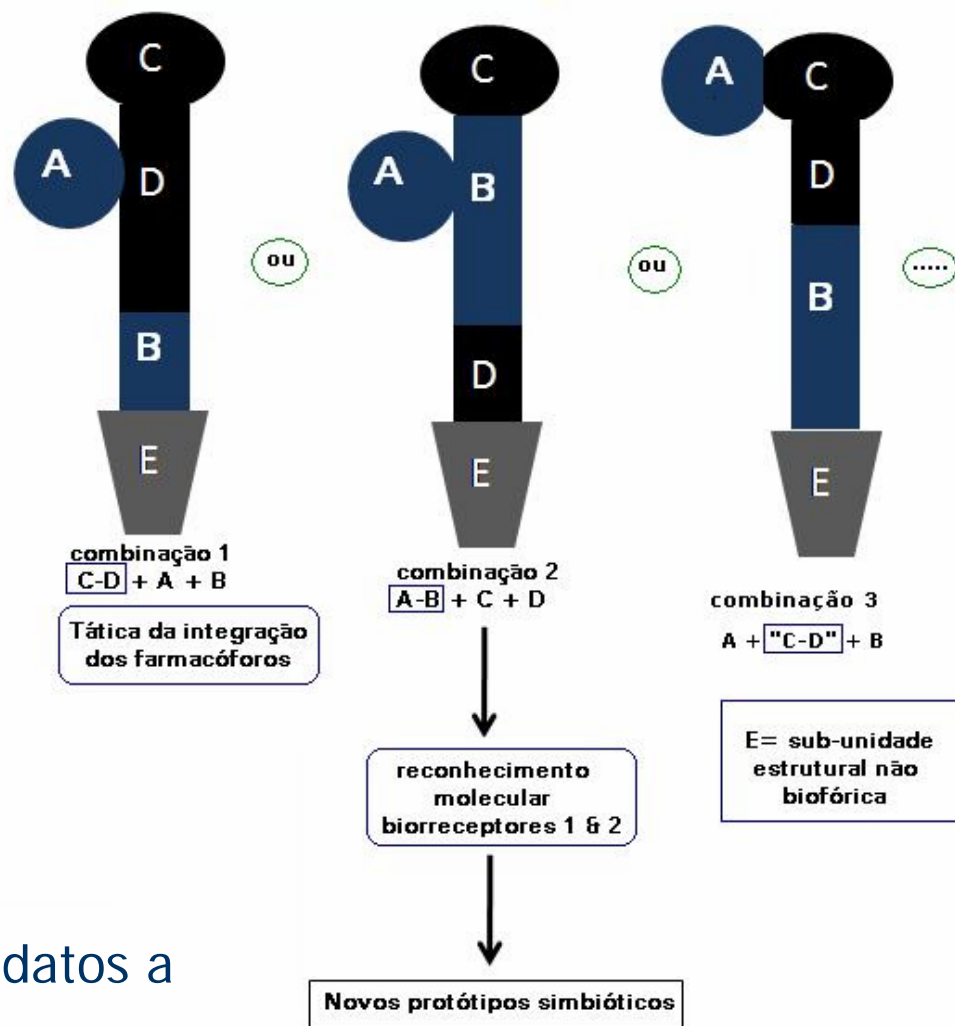
H. Kogen *et al.*, *Bioorg. Med. Chem.* **2003**, 11, 4389.



Abordagem Simbiótica



Novos padrões moleculares híbridos



O desenho molecular de candidatos a fármacos simbióticos

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.



Terapia combinada

Abordagem simbiótica

A	B	C
		
drug cocktail	multicomponent drug	multiple ligand
2 tablets 2 agents	1 tablet 2 agents	1 tablet 1 active agent

Principais cenários para a terapia multi-alvo terapêutico

B: “...there are significant risks involved in the development of multicomponent drugs...”

C: “... there has been growing interest in the (..) **rational design of ligands acting specifically on multiple targets...**” *Morphy & Rankovic, J. Med. Chem. 2005, 48, 6523*

Inter-alia: G. Glass, “Cardiovascular combinations” *Nat. Rev. Drug Discovery* **2004**, 3, 731; R. Morphy, Z. Rankovic, “From magic bullets to designed multiple ligands” *Drug Discovery Today* **2004**, 9, 641.

INFLAMMATORY RESOLUTION: NEW OPPORTUNITIES FOR DRUG DISCOVERY

Derek W. Gilroy^{}, Toby Lawrence[‡], Mauro Perretti^{*} and Adriano G. Rossi[§]*

Treatment of inflammatory diseases today is largely based on interrupting the synthesis or action of mediators that drive the host's response to injury. Non-steroidal anti-inflammatories, steroids and antihistamines, for instance, were developed on this basis. Although such small-molecule inhibitors have provided the main treatment for inflammatory arthropathies and asthma, they are not without their shortcomings. This review offers an alternative approach to the development of novel therapeutics based on the endogenous mediators and mechanisms that switch off acute inflammation and bring about its resolution. It is thought that this strategy will open up new avenues for the future management of inflammation-based diseases.

Nature Rev Drug Discov. 2004, 3, 401





Phosphodiesterase-4 as a therapeutic target

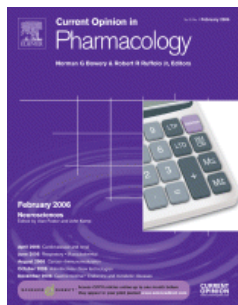
Miles D Houslay, Peter Schafer & Kam Y J Zhang

Drug Discov Today 2005, 10, 1503,

What next for rheumatoid arthritis therapy?

Simon M Blake* and Barbara A Swift

Curr Op Pharmacol. 2004, 4, 276



The p38 MAP kinase pathway as a therapeutic target in inflammatory disease

Jeremy Saklatvala

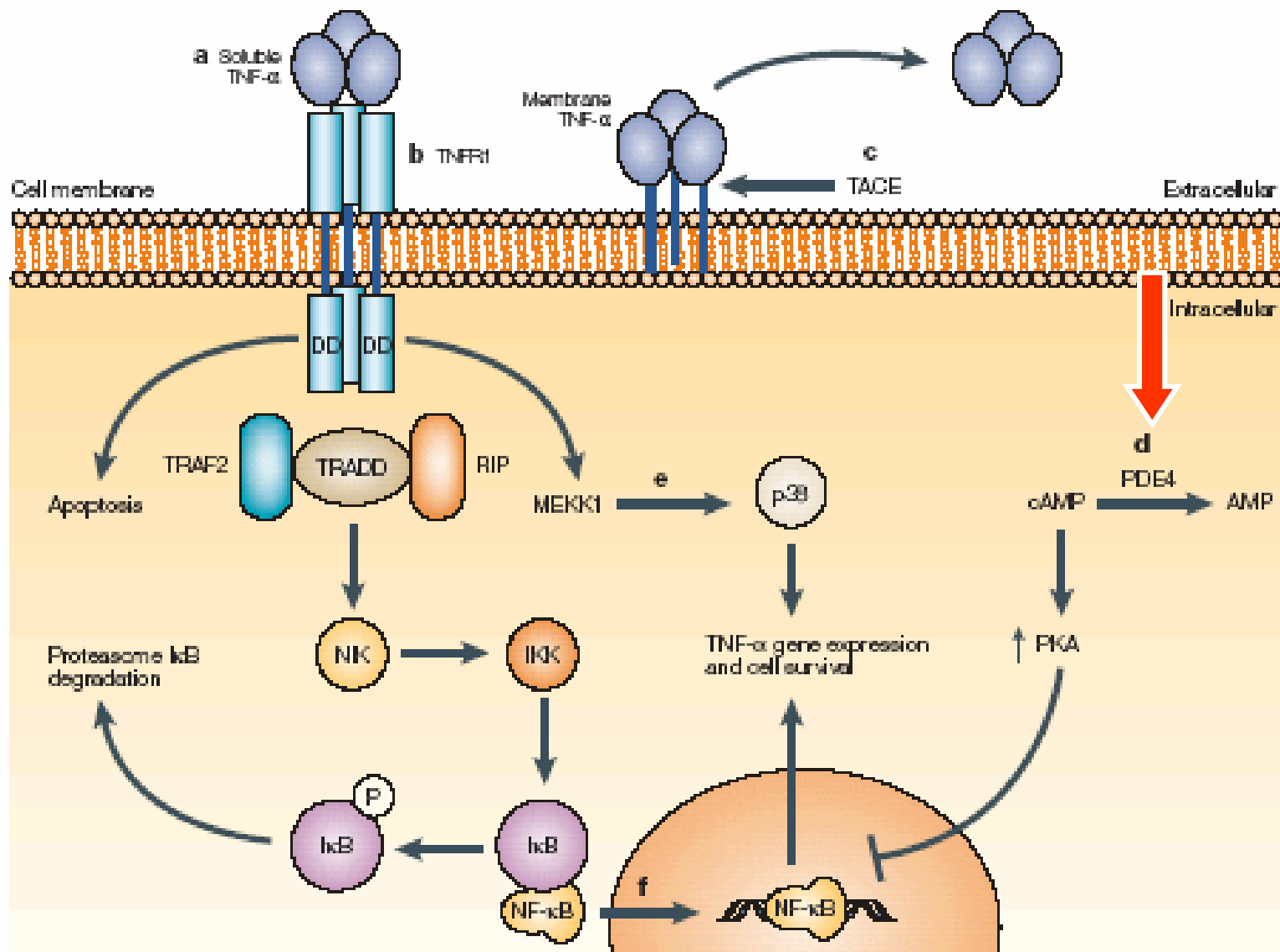
Curr Op Pharmacol. 2004, 4, 372

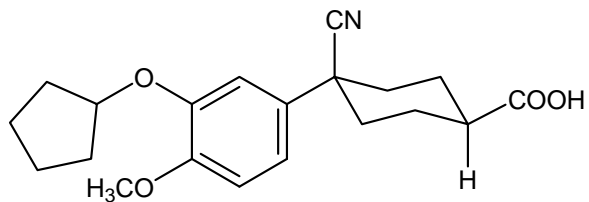
Matrix metalloproteinases in asthma and COPD

Ingel K Demedts, Guy G Brusselle, Ken R Bracke, Karim Y Vermaelen and Romain A Pauwels

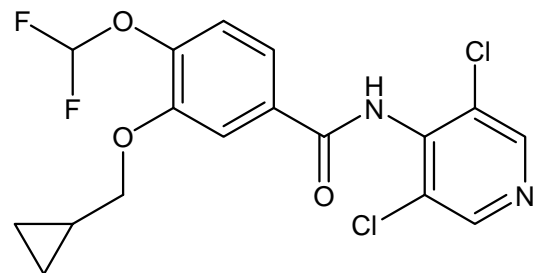
Curr Op Pharmacol. 2005, 5, 257

O primeiro alvo:





cilomilaste
GSK

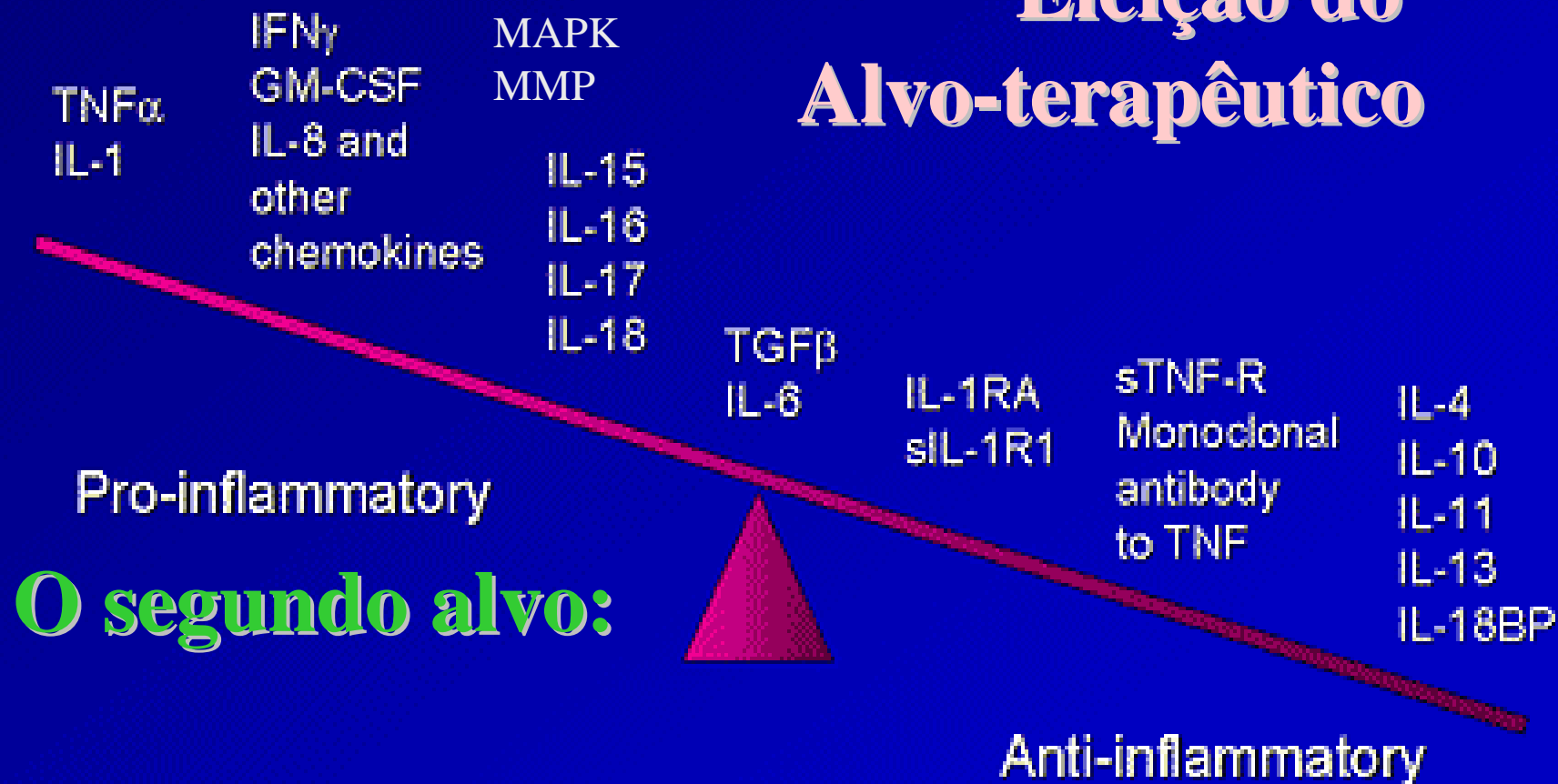


roflumilaste
Altana

**Antiinflamatórios atuando como
Inibidores de PDE-4**




Role of Cytokines and Cytokine Inhibitors in Chronic Inflammation

Eleição do Alvo-terapêutico



Arend. *Arthritis Rheum* 2001.

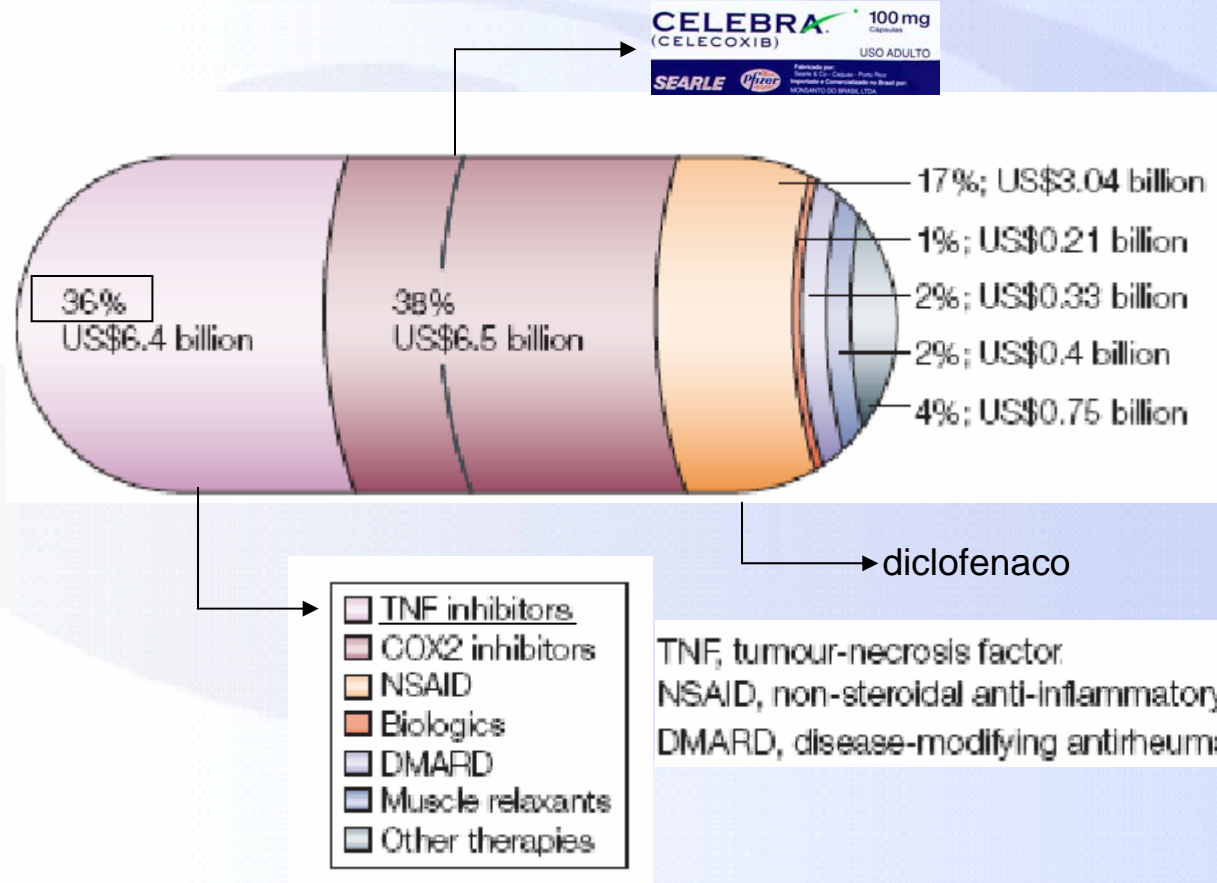
Fármacos Anti-TNF- α *

Drug	Status	Biological Form
 Etanercept Enbrel [®] 50mg R\$ 7.057,77	approved	soluble TNFR2 coupled to Fc portion of IgG
 Infliximab Remicade [®] 10mg R\$ 3.668,79	approved	chimeric anti-human TNF antibody
 Adalimumab Humira [®] 40X0,8mg R\$ 7.082,39	approved	anti-human TNF antibody
ISIS 104838	clinical	TNF anti-sense
Onercept	clinical	soluble p55 TNFR
Humicade	clinical	anti-TNF humanised IgG4

JD Gale, KF McClure, N Pullen, *Annu.Rept. Med. Chem.* 2003, **38**, 141;
B Bain, M Brazil, *Nature Rev. Drug Disc.* 2003, **2**, 693;

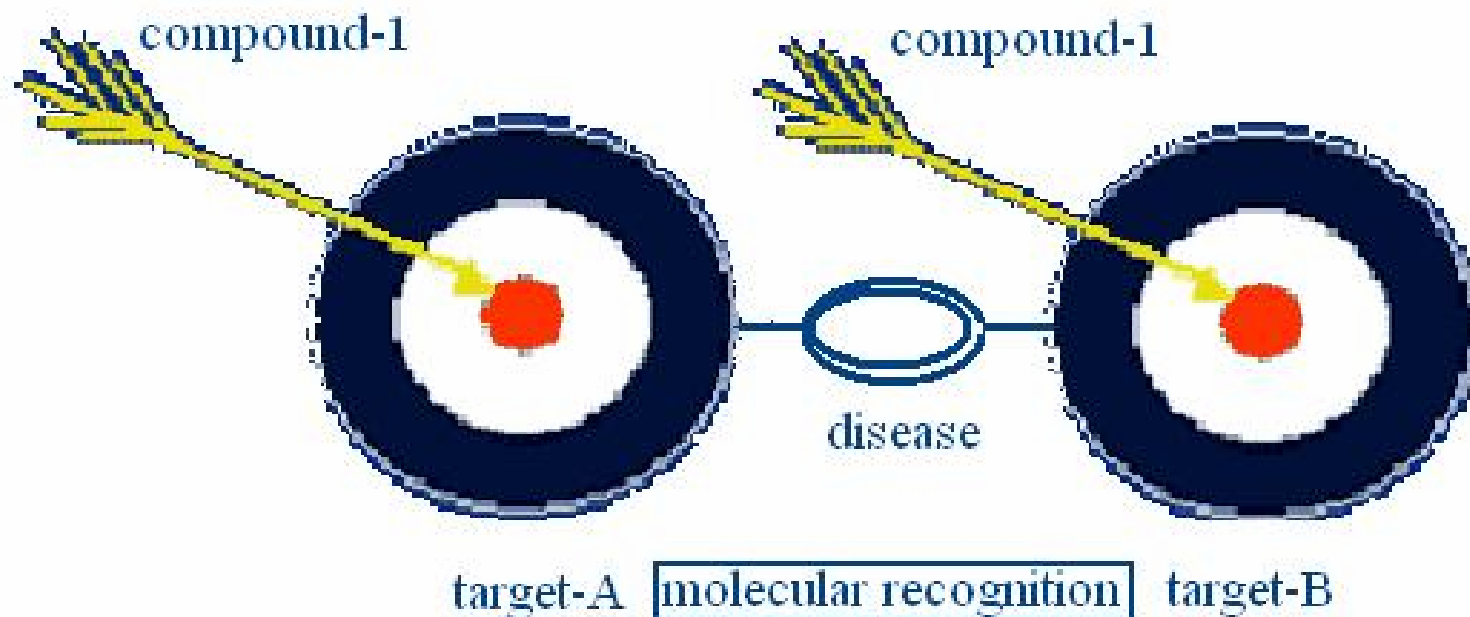
* Terapias com fármacos de origem biotecnológica (injetáveis)

2004 Worldwide sales of arthritis drugs



Adaptado de I. Melnikova, *Nature Rev. Drug Discov.* 2005, 4, 453.

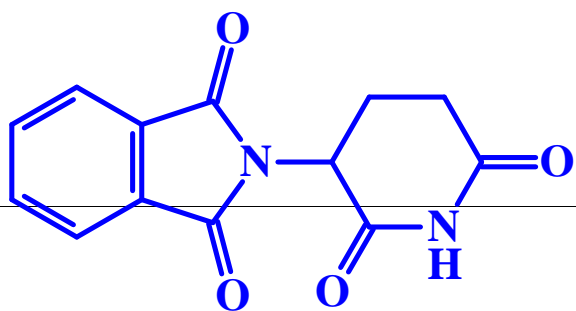
The symbiotic lead-candidate design



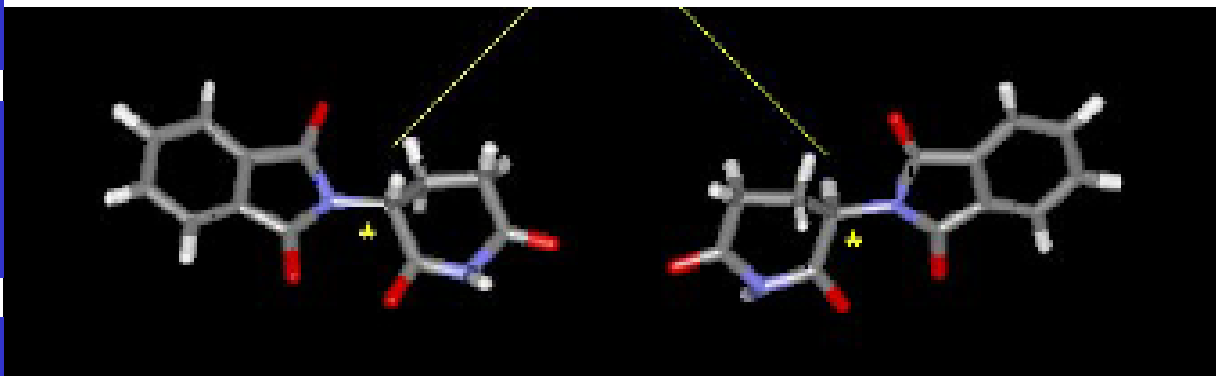
O desenho estrutural de novos candidatos a fármacos simbióticos representa uma inovação na abordagem terapêutica do tratamento de doenças crônicas que resultem, no mecanismo de sua fisiopatologia, do envolvimento de diversos e distintos biomedadores pertencentes a diferentes caminhos bioquímicos.



Talidomida



2-(2,6-Dioxo-3-piperidiny)-1*H*-isoindole-1,3(2*H*)-dione



THALIDOMIDE

TNF- α IC₅₀ = 200 μ M

Thalomid[®], Phase III, Celgene

Wilhelm Kunz, 1953

Herbert Keller, 1953

CNS, 1957

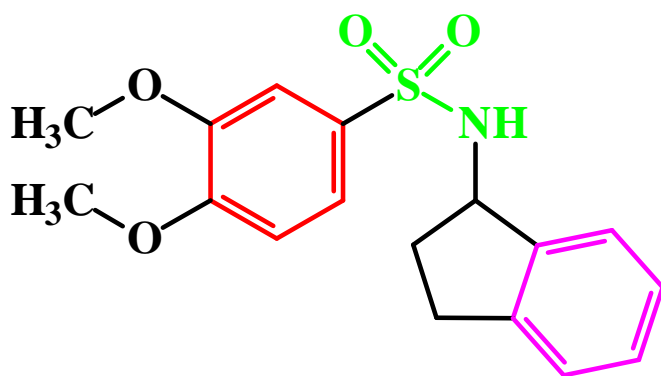
Frances Kelsey, 1961

Gilla Kaplan, 1991 (TNF- α)

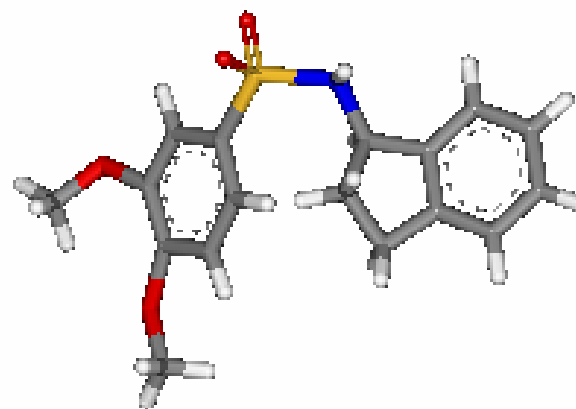
* Elisabeth P. Sampaio, 1997

L.M. Lima et al., O Renascimento de um Fármaco: Talidomida, Quim. Nova 2001, 24, 683; (www.scielo.br); E.P. Sampaio, D.S. Carvalho, J.A.C. Nery, U.G. Lopes, E.N. Sarno, "Thalidomide: An Overview of its Pharmacological Mechanisms of Action" Anti-inflammatory & &anti-alergy Agents in Medicinal Chemistry 2006, 5, 71; L.M. Lima, C.A.M. Fraga, V.L.G. Koatz, E.J. Barreiro, "Thalidomide and Analogs as Anti-inflammatory and Immunomodulator Drug Candidates", Anti-inflammatory & &anti-alergy Agents in Medicinal Chemistry 2006, 5, 79.

Chiroscience Ltd, Cambridge Science Park, Milton Road, Cambridge, UK
(Celltech Chiroscience Ltd)



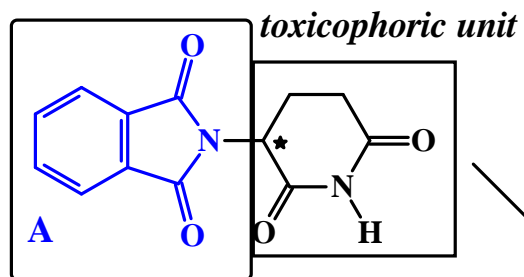
Aryl-sulfonamida



$$\text{PDE-4i IC}_{50} = 4.3 \mu\text{M}$$

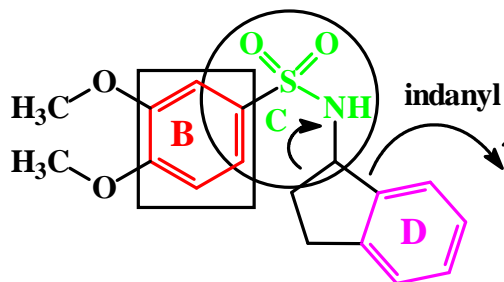
J. G. Montana, G. M. Buckley, N. Cooper, H. J. Dyke, L. Gowers,
J. P. Gregory, P. G. Hellewell, H. J. Kendall, C. Lowe, R. Maxey,
L. Miotla, R. J. Naylor, K. A. Runcie, B. Tuladhar, J. B. H. Warneck,
“Aryl sulfonamides as selective PDE-4 inhibitors” , *Bioorg. Med. Chem.*
Lett. 1998, **8**, 2635.

Gênese do LASSBio-468, Novo Agente Simbiótico



TNF- α IC₅₀ = 200 μ M

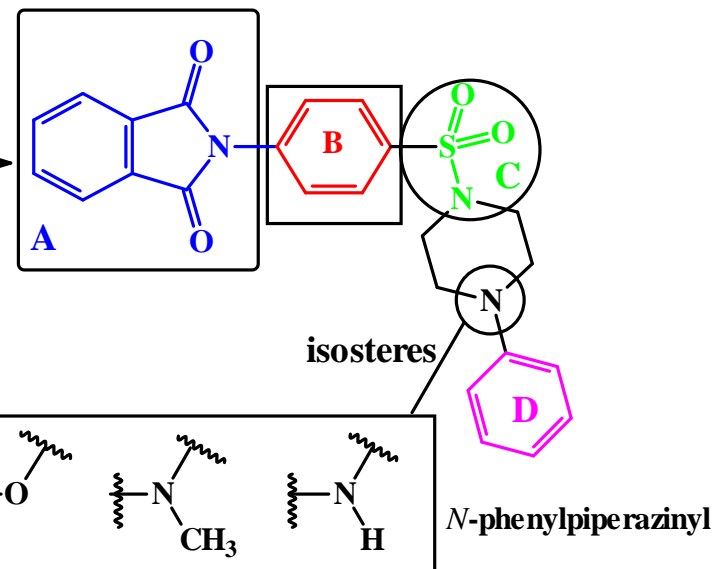
Quim. Nova 2001, **24**, 583



PDE-4i IC₅₀ = 4.3 μ M

JG Montana et al., Bioorg. Med. Chem. Lett. 1998, **8**, 2635

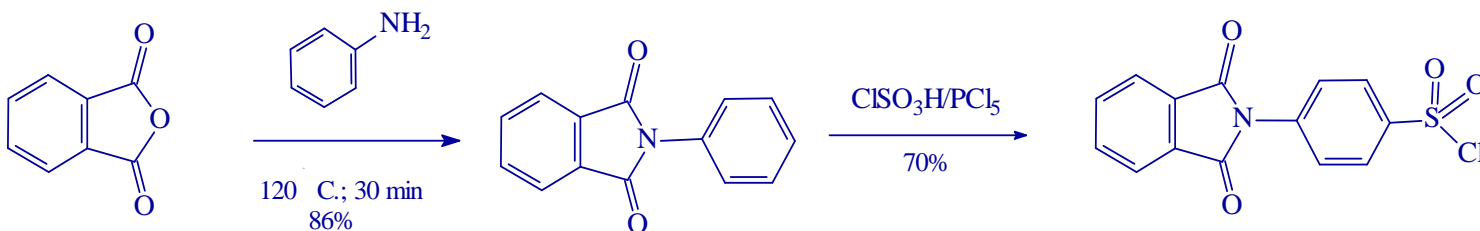
molecular
hybridization



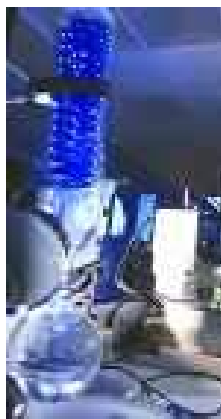
**Novo agente simbiótico com
propriedades anti-TNF- α &
inibidor de PDE-4**

isosteres
 σ , π , MR

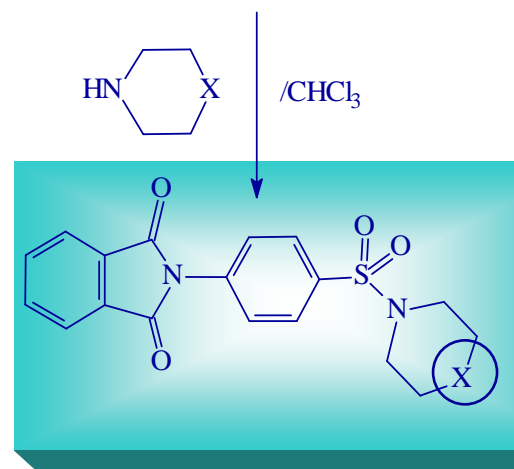
Síntese do LASSBio-468



anidrido ftálico

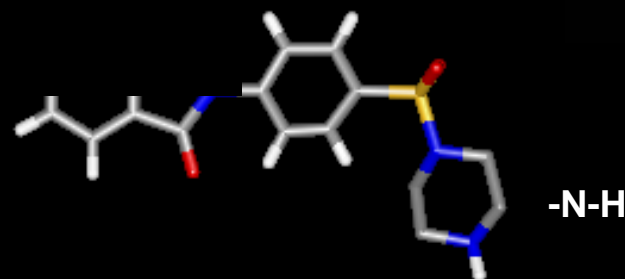
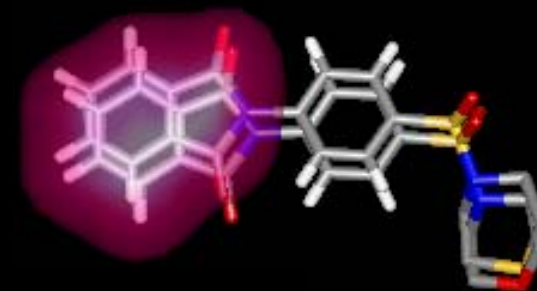
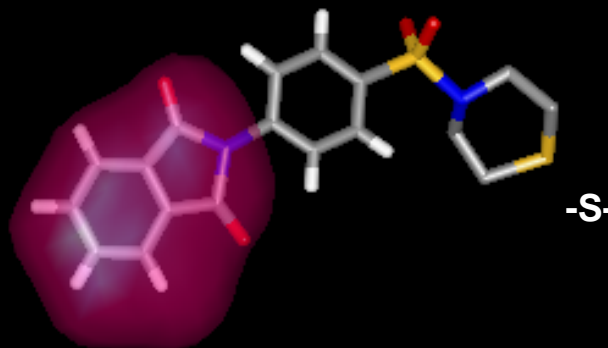
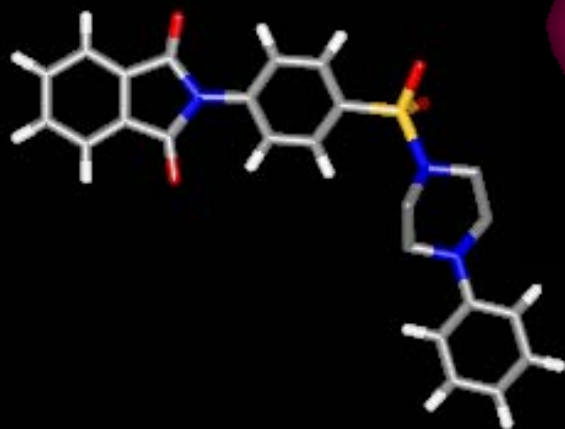
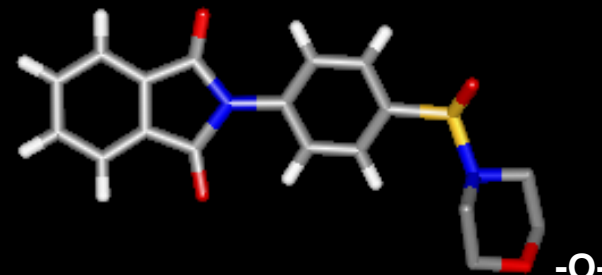


- | | |
|---------|-----|
| X = NMe | 65% |
| X = NPh | 67% |
| X = NH | 58% |
| X = O | 63% |
| X = S | 67% |

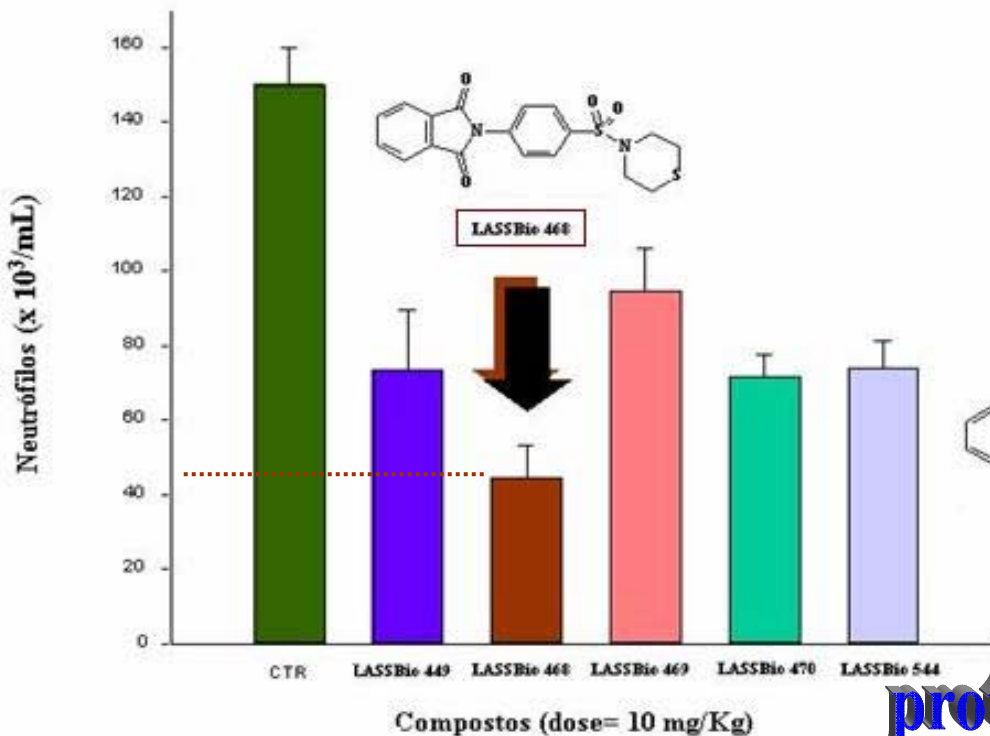


Rendimento global médio: *ca.* 20%
(escala 0.10 M *ca.* 40g)

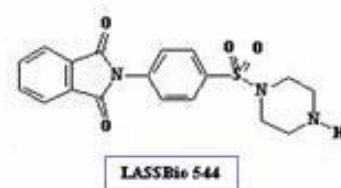
Construção da série congenérica



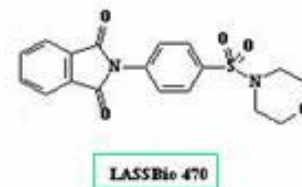
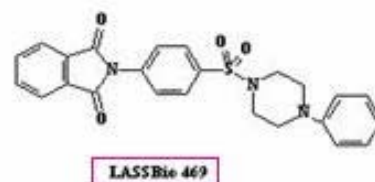
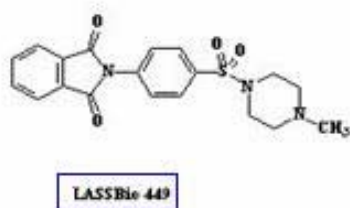
Effect of new compounds and thalidomide on neutrophil influx induced by LPS into BALB/c of mice lungs (10 mg/kg, DMSO; i.p.)



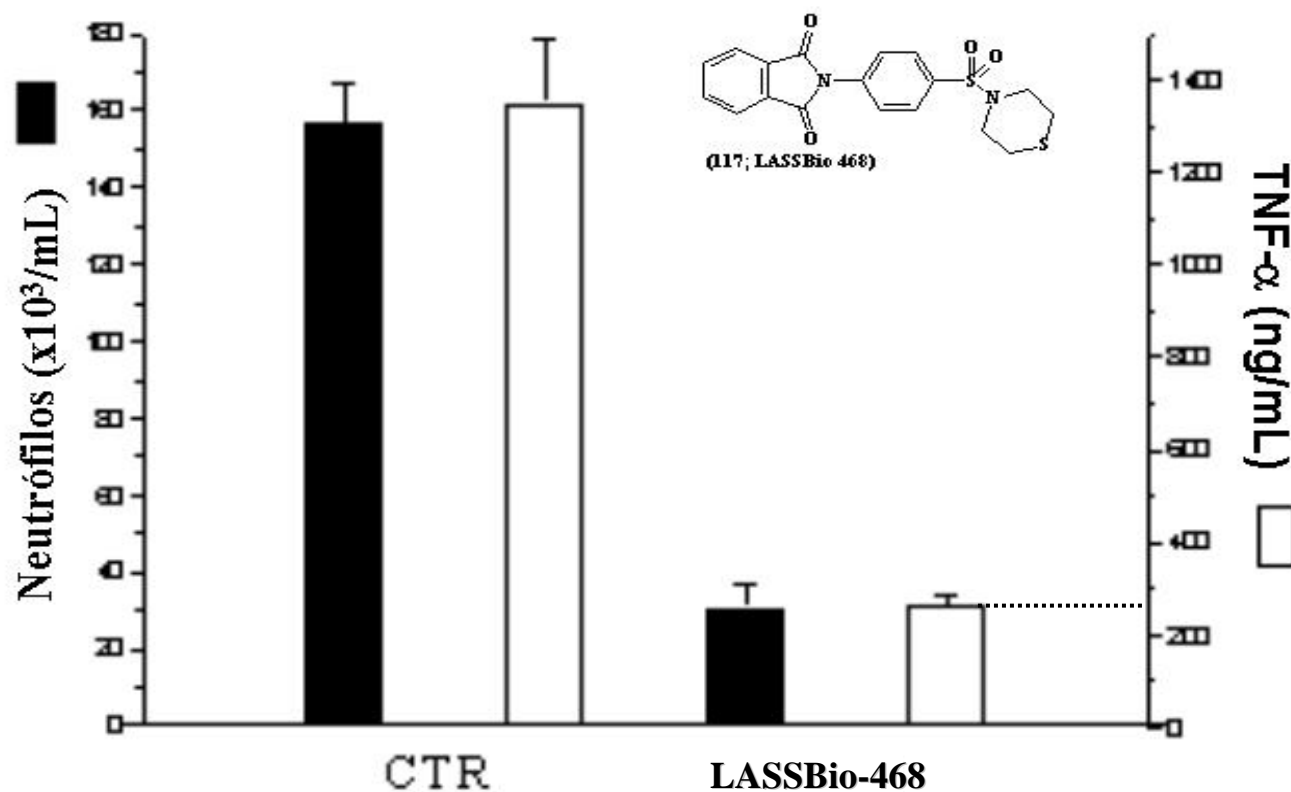
in vivo



protótipo > ligante

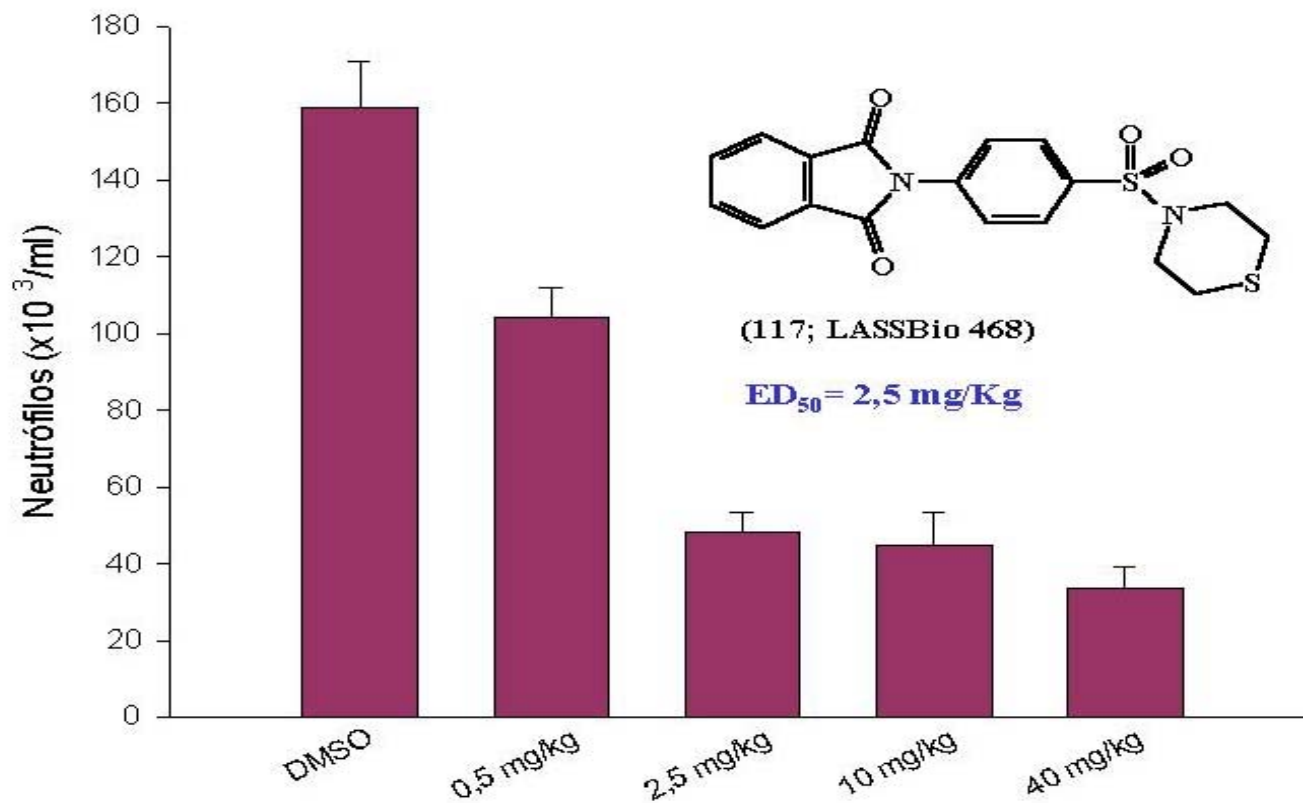


Effect of compound LASSBio 468 on TNF- α levels and neutrophil influx into the BALB/c of mice lungs

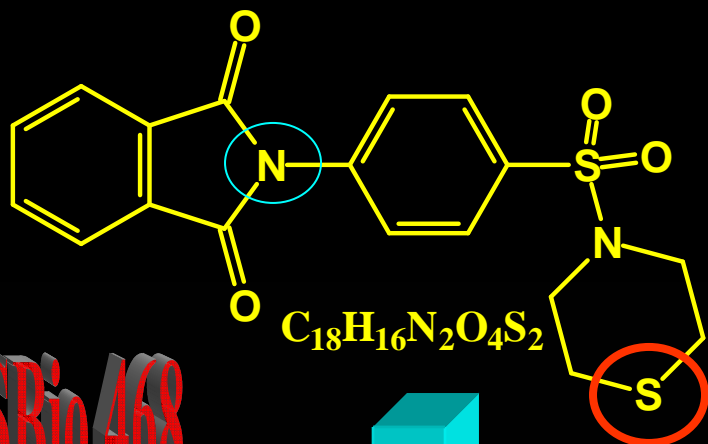


50% more active than thalidomide

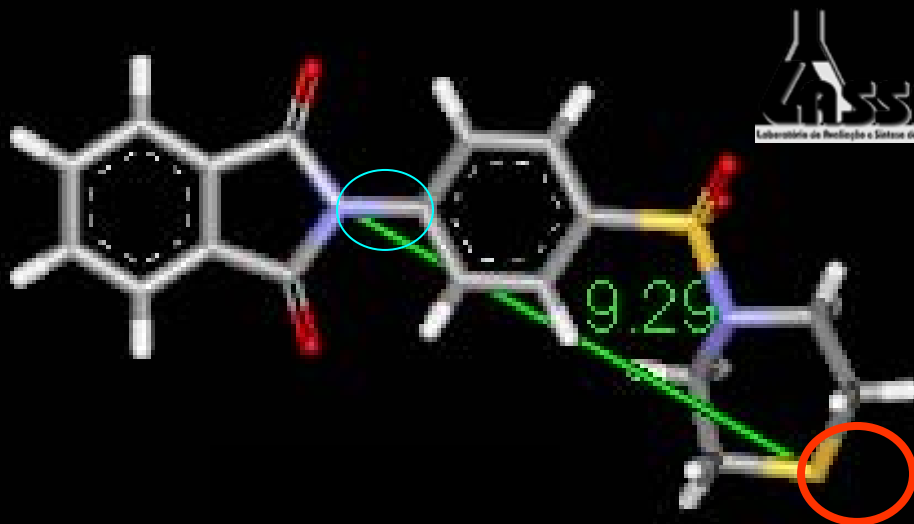
ED₅₀ of LASSBio-468 measured on neutrophil influx induced by LPS into BALB/c of mice lungs (DMSO; *i.p.*).



Novo Protótipo de Agente Anti-inflamatório Simbiótico



LASSBio 468



TNF- α ED₅₀ 2,5 mg/Kg

PDE-4 inibidor

Atividade PDE-4 de foi medida em aorta bovina:

IC₅₀ = 52 μ M

(cf. PDE-1, 2, 3, 5 > 420 μ M)

Dr Claire Lugnier
 Université Louis Pasteur de Strasbourg
 Laboratoire de Pharmacologie et de Physicochimie des Interactions
 Cellulaires et Moléculaires.

L. M. Lima, P. Castro, A. L. Machado, C. A. M. Fraga, C. Lugnier, V. L. G. Moraes, E. J. Barreiro, *Synthesis and Anti-inflammatory activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues, Bioorg. Med. Chem.* 2002, 10, 3067.



LASSBio-468

Lead compound
Composto-**protótipo**

Novo agente anti-inflamatório simbiótico

LASSBio-468, é um novo candidato a protótipo de fármaco **AI**, **DMARD**, desenhado por hibridação mol de estrutura química original, simples e aquiral, planejado como candidato a **fármaco simbiótico**, útil para o tratamento da **artrite reumatóide** e da **doença de Crohn**, com atividade protetora no **choque séptico** e na resposta granulomatosa em modelo de artrite reumatóide em camundongos, **sem efeito imunossupressor**. Possui **novo mecanismo de ação**, original, inibindo a resposta ao **TNF- α** e a atividade **PDE-4**, como desejado quando de seu planejamento estrutural.

Representa uma autêntica inovação terapêutica.



L. M. Lima *et al.*, "Synthesis and Anti-inflammatory Activity of Phthalimide

Derivatives, Designed as New Thalidomide Analogues", *Bioorg. Med. Chem.* 2002, **10**, 3067

M. S. Alexandre-Moreira *et al.*, "LASSBio-468: a New achiral Thalidomide Analogue which Modulates TNF- α and NO Production and Inhibit Endotoxic Shock and Arthritis in Animal Model", *International*

Immunopharmacology 2005, **5**, 485.



Drug Data Report

Prous Science Ed. (ES.)

Vol. 24, No. 2, 2002

Asthma Therapy

New Lead-compounds:

12611 (Boehringer Ingelheim)

312652 (Bayer)

313027 (GlaxoSmithKline)

KCO-912 (Novartis)

LASSBIO-468



Protótipos que falem português...



Web [Imagens](#) [Mapas](#) [Notícias](#) [Orkut](#) [Gmail](#) [mais ▼](#)

[Efetuar login](#)



LASSBio-468

Pesquisar

[Pesquisa avançada](#)

[Preferências](#)

Pesquisar: ☒ a web ☐ páginas em português ☐ páginas do Brasil

Web

Resultados **1 - 10** de aproximadamente **156** para **LASSBio-468** (0,52 segundos)

[International Immunopharmacology](#): **LASSBio-468**: a new achiral ... - [[Traduzir esta página](#)]

LASSBio-468: a new achiral thalidomide analogue which modulates TNF- α and NO production and inhibits endotoxic shock and arthritis in an animal model ...

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de MS Alexandre-Moreira - 2005 - [Citado por 8](#) - [Artigos relacionados](#) - [Todas as 4 versões](#)

[LASSBio-468](#): a new achiral thalidomide analogue wh...[Int ...] - [[Traduzir esta página](#)]

LASSBio-468 was recently demonstrated to inhibit the TNF-alpha production ... Treatment with **LASSBio-468** before a lethal dose injection of LPS in animals ...

[www.ncbi.nlm.nih.gov/pubmed/15683845](#) - [Páginas Semelhantes](#)

de MS Alexandre-Moreira - 2005 - [Citado por 8](#) - [Artigos relacionados](#) - [Todas as 4 versões](#)

CTD: **LASSBio-468** - [[Traduzir esta página](#)]

LASSBio-468. Equivalent Term help, 2-(4-(1,4-thiazinan-4-ylsulfonyl)phenyl)-1,3-isoindolindione. MeSH® ID help · C503834. Usage Note, This information is ...

[ctd.mdibl.org/detail.go?type=chem&acc=C503834](#) - 14k - [Em cache](#) - [Páginas Semelhantes](#)

[LASSBio-468 Summary Report | CureHunter](#) - [[Traduzir esta página](#)]

LASSBio-468: structure in first source. ... 03/01/2005 - "Treatment with **LASSBio-468** before a lethal dose injection of LPS in animals greatly inhibited ...

[www.curehunter.com/public/keywordSummaryC503834-LASSBio-468.do](#) - 27k -

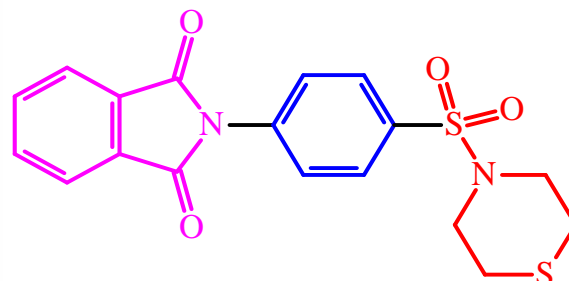
[Em cache](#) - [Páginas Semelhantes](#)

[PDF] [Imunofarmacologia](#)

Formato do arquivo: PDF/Adobe Acrobat - [Ver em HTML](#)

o protótipo **LASSBio 468**. 1. Objetivos: Este traba-. lho visa avaliar o efeito imunomodulador de LAS-. SBio 591, 651 e 468 em modelos de inflamação ...

[asp.sbftc.org.br/pub/media/Setor05.pdf](#) - [Páginas Semelhantes](#)



Concluído

Internet

112

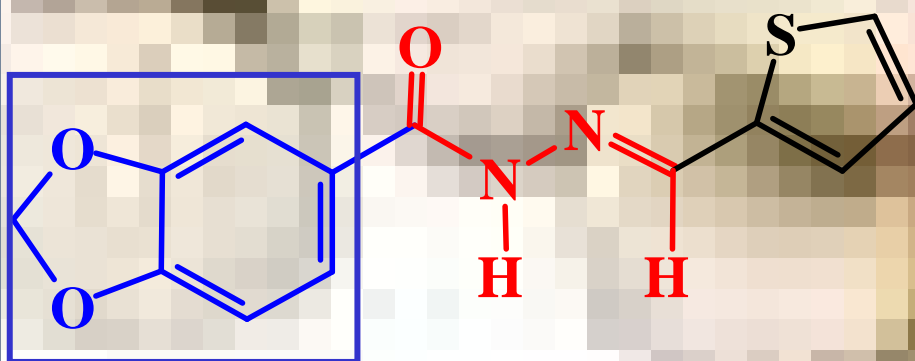
Aspectos da Química Farmacêutica Medicinal

Sumário

1. Os fármacos & a Química Medicinal
2. Como se descobrem os fármacos? *Os fármacos e os prêmios Nobéis*; Como atuam os fármacos?
3. A *dissecação* molecular : grupo farmacofórico
4. Moléculas *inteligentes*: os alfabetos moleculares
5. *Domesticando* moléculas naturais
6. O paradigma do composto-protótipo
7. Fármacos *simbióticos*: exemplos *de casa*
8. Epílogo

Novo Protótipo de Fármaco Cardioativo

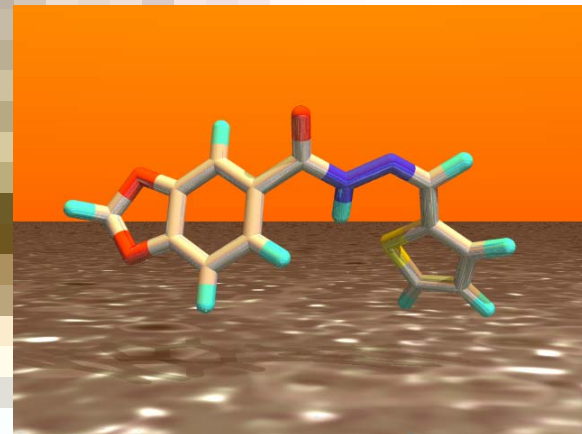
LASSBio-294



$C_{13}H_{10}N_2O_3S$

MW 274

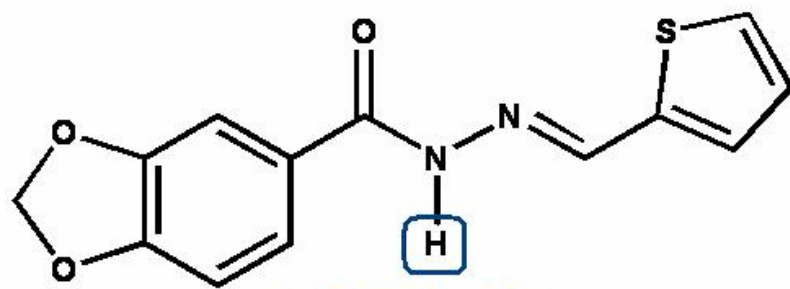
Química
Medicinal



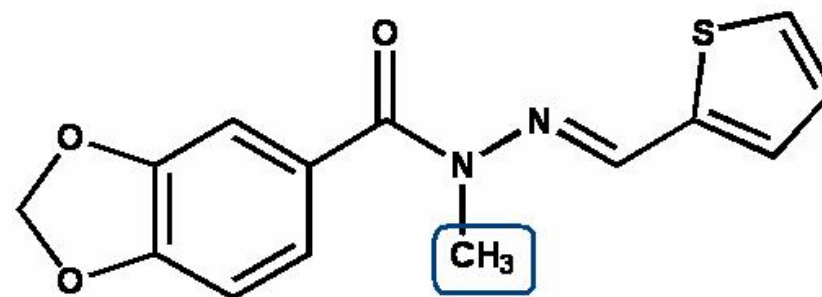
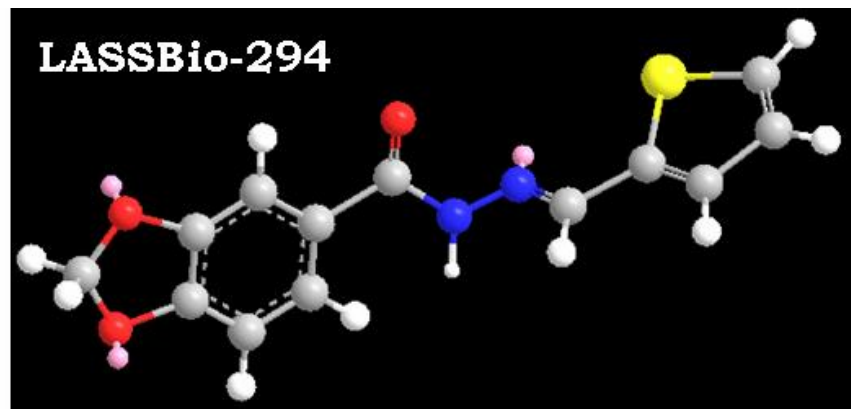
LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

O início...

Eleição do alvo.¹¹⁴



LASSBio-294
Protótipo Inotrópico e
Vasodilatador
(WO 00/78754 A1)



LASSBio-785
Protótipo Vasodilatador
(PI 0403363-9)



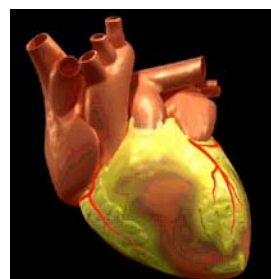
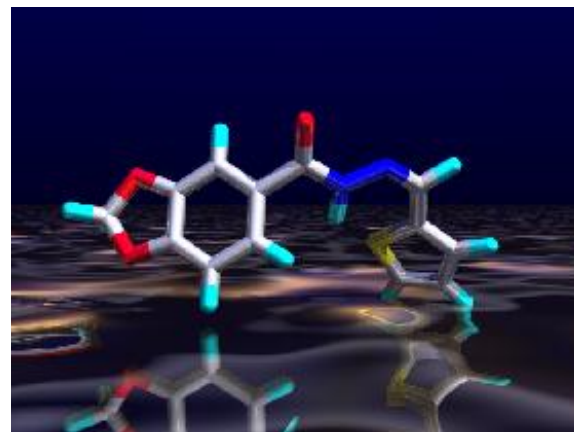


Estruturalmente simples;
Sinteticamente acessível
em ótimos rendimentos,
em escala M;

Matéria-prima disponível
(produto natural abundante).

Estudos de PK in-silico

Método analítico desenvolvido



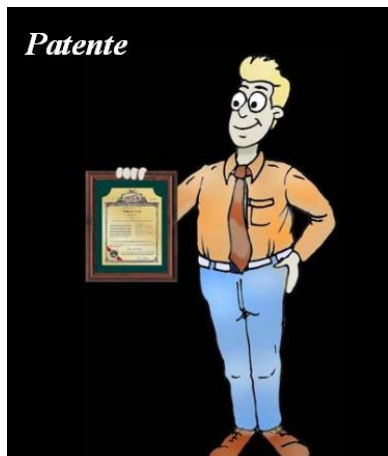
LASSBio-294

**Protótipo cardioativo,
não-digitalico, não-adrenérgico,
com propriedades
inotrópicas, vasodilatadoras
& neuroprotetoras;**

**Ativo p.o. com novo mecanismo de ação;
Sem cito-, geno- ou toxicidade**

Possíveis indicações terapêuticas:

**Cardiopatias; Alzheimer;
distrofia muscular neuropática.**



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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
104701238	06/15/2006	7091238	32390-178943	9691

26694 7390 03/26/2006
VENABLE LLP
P.O. BOX 34385
WASHINGTON, DC 20045-9998

ISSUE NOTIFICATION

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)

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

**Patente concedida US Patent # 7.091.238
(August 15, 2006)**

Roberto Takashi Sudo, Rio de Janeiro, BRAZIL;
Edson X. Albuquerque, Baltimore, MD;
Eliezer J. De Barreiro, Rio de Janeiro, MD;





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LASSBio-294

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Web

Resultados **1 - 10** de aproximadamente **682** para **LASSBio-294** (0,08 segundos)

[LASSBio-294](#)

Estamos falando do **LASSBio-294**, um fármaco desenvolvido pelo Laboratório de Avaliação de Substâncias Bioativas (LASSBio) da Universidade Federal do Rio de ...

www.inova.unicamp.br/inventabrasil/barreiro.htm - 9k - [Em cache](#) - [Páginas Semelhantes](#)

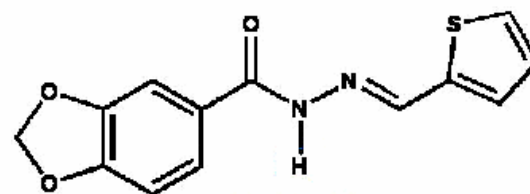
[Química Nova - Strategy of molecular simplification in rational ...](#)

Os resultados farmacológicos obtidos 70-73 indicaram que **LASSBio-294** (37) foi capaz de induzir intenso relaxamento, concentração-dependente, ...

www.scielo.br/scielo.php?pid=S0100-40422002000700018&script=sci_arttext - 103k -

[Em cache](#) - [Páginas Semelhantes](#)

de EJ Barreiro - 2002 - [Citado por 3](#) - [Artigos relacionados](#)



[Cyclic GMP-dependent vasodilatory properties of LASSBio 294 in rat ...](#) - [[Traduzir esta página](#)]

1 The effects of **LASSBio 294**, a new 3,4-methylenedioxybenzoyl-2-thienylhydrazone, on vascular tonus were investigated in isolated rat aortic rings. ...

cat.inist.fr/?aModele=afficheN&cpsid=13845348 - [Páginas Semelhantes](#)

de CLM SILVA - 2002 - [Citado por 5](#) - [Artigos relacionados](#) - [Todas as 4 versões](#)

[British Journal of Pharmacology - Cyclic GMP-dependent ...](#) - [[Traduzir esta página](#)]

Cyclic GMP-dependent vasodilatory properties of **LASSBio 294** in rat aorta ... **LASSBio 294** induced a concentration-dependent relaxation of intact rat aortic ...

www.nature.com/bjp/journal/v135/n1/full/0704473a.html - [Páginas Semelhantes](#)

de CLM Silva - 2002 - [Citado por 5](#) - [Artigos relacionados](#) - [Todas as 4 versões](#)

[British Journal of Pharmacology - Abstract of article: The new ...](#) - [[Traduzir esta página](#)]

The new compound, **LASSBio 294**, increases the contractility of intact and ... CHF, congestive heart failure; L-294, **LASSBio 294**; SR, sarcoplasmic reticulum ...

www.nature.com/bjp/journal/v134/n3/abs/0704291a.html - [Páginas Semelhantes](#)

de BT Costa - 2001 - [Citado por 4](#) - [Artigos relacionados](#) - [Todas as 4 versões](#)




Concluído

Internet

Protótipos em estudo 6

CgIRPE*

1999

	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%

LASSBio
Laboratório de Pesquisa e Síntese de Substâncias Bioativas

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



Protótipos em estudo 6

MCT/MS/FINEP – Ação Transversal – Cooperação ICTs - Empresas - INOVAÇÃO EM PRODUTOS TERAPÊUTICOS E DIAGNÓSTICOS – 08/2006

PROJETOS APROVADOS

Prot. Elet.	Ref.	INTERVENIENTE CO-FINANCIADOR	Proponente/ Executor/ Projeto	Executor	
				Nome	UF Executor
1	2318/06	Laboratório Farmacotécnico Americano S/A	Pontifícia Universidade Católica do RS - PUCRS	Tecnopuc/BFR	RS
3	2303/06	Eurofarma Laboratórios S/A	FUJB	Faculdade de Farmácia	RJ

LASSBio-715



PI 9902960-0 (1999)



*NSAI de segunda geração**

Licenciada com exclusividade pela UFRJ: DOU # 113, 14/06/2006, seção 3, p.37.



LASSBio

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19 de setembro de 2008

Web

Resultados 1 - 10 de aproximadamente 7.410 para LASSBio (0,30 segundos)

[LASSBio - Faculdade de Farmácia da UFRJ](#)

Lab Piloto de Desenvolvimento Tecnológico - **LASSBio**/UFRJ, Laboratório Piloto de Desenvolvimento Tecnológico encurta a distância entre universidade e ...

www.farmacia.ufrj.br/lassbio/ - 2k - [Em cache](#) - [Páginas Semelhantes](#)

[XIV EVQF/LASSBio](#)

LASSBio - XIV Escola de Verão em Química Farmacêutica e Medicinal - Faculdade de Farmácia - UFRJ.

www.farmacia.ufrj.br/lassbio/XIV_evqf/ - 19k - [Em cache](#) - [Páginas Semelhantes](#)

[Mais resultados de www.farmacia.ufrj.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 ...

www.imagem.ufrj.br/index.php?acao=detalhar_imagem&id_img=1626 - 23k -

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[LASSBio-294](#)

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www.inova.unicamp.br/inventabrasil/barreiro.htm - 9k - [Em cache](#) - [Páginas Semelhantes](#)

[LASSBio na RASBQ maio 2005 - UOL Álbum de fotos](#)

LASSBio na RASBQ maio 200...Fotos da 28ª RASBQ, Poços de Caldas, MG, 30 de maio - 02 junho de 2005XI EVQFM - LA...EuropeAmigo Oculto L...Imagem_009.j. ...

ejb.fotos.net.br/rasbq2005 - 18k - [Em cache](#) - [Páginas Semelhantes](#)

[\[PDF\] Preparação de metabólitos fase I e II do derivado N ...](#)

Exemplo de exercício: PDF de laboratório de síntese de substâncias bioativas





e-mail of Eliezer J. Barreiro

De: Kyle Kuhn - Paramount BioCapital Investments, LLC

Para: eliezer@pharma.ufrj.br

Cc: eliezer@ufrj.br

Data: 06/08/2007 11:01

Assunto: Phthalimide derivative LASSBio-552



Dr. Barreiro,

My name is Kyle Kuhn, I represent a **biopharmaceutical investment firm called Paramount BioCapital Investments, LLC**. My job here at Paramount is to identify promising therapeutic technologies, and explore potential investment and/or licensing opportunities.

I recently saw a summary of some information you presented at the recent International Symposium on Nitric Oxide, Cytokines and Inflammation, in Malbourne, and I would like to learn more about compound LASSBio-552.

I would like to know the development status of this compound, as well as any plans for its continued development. **I would also like to know the IP status for this technology**. Any additional information you can provide would be very helpful.

It may be more convenient to speak over the phone. If you would like to provide a number, and suggest a convenient time, I would be happy to give you a call. Alternatively, my contact information is provided below, please feel free to contact me at your convenience. I look forward to hearing from you.

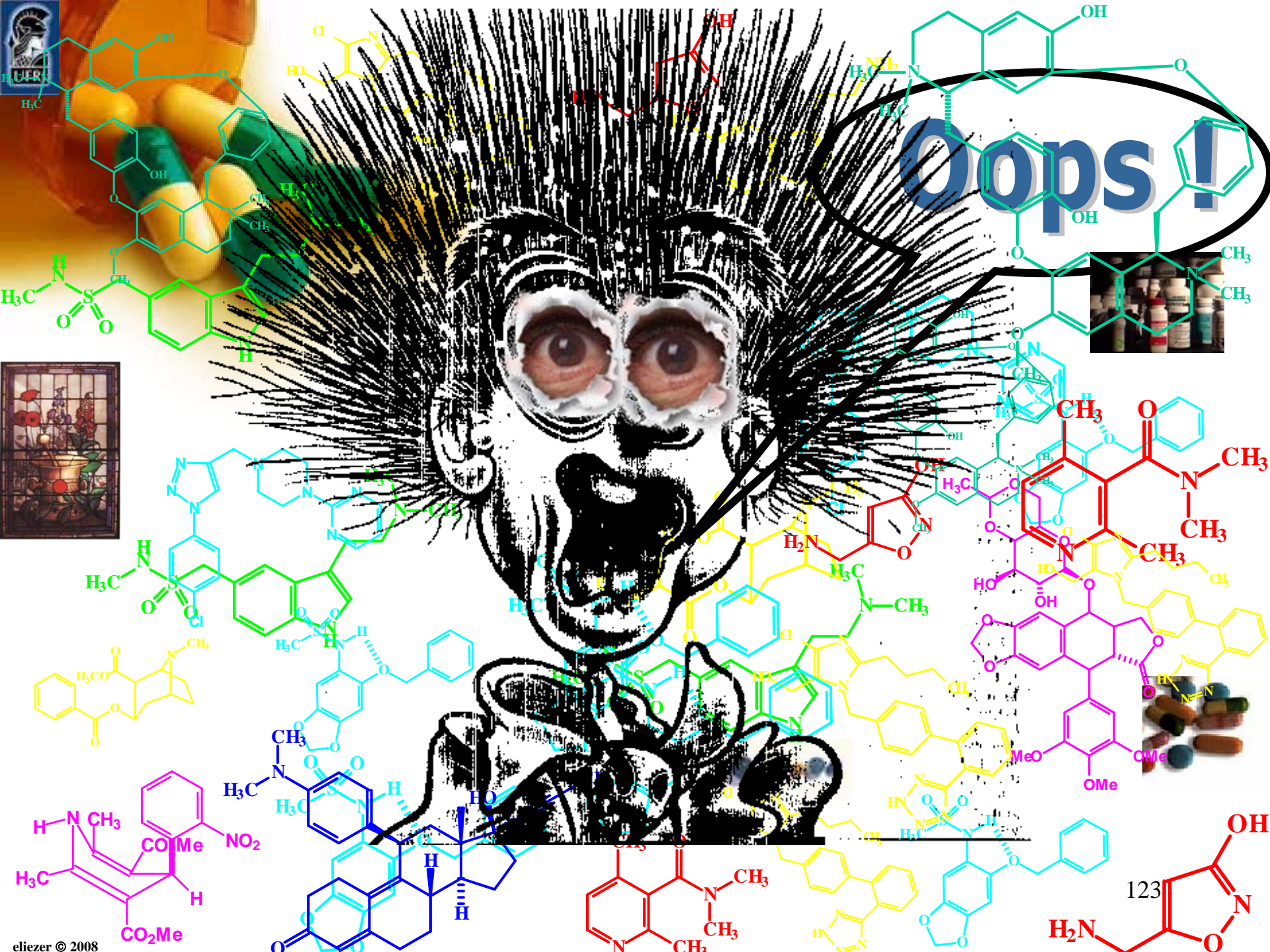
Best regards,
Kyle Kuhn

Biotechnology Venture Capital Analyst
Paramount BioCapital Investments, LLC

787 Seventh Avenue - New York, NY 10019 -Tel: 212.554.4315 -Fax: 212.554.4490

e-mail: KKuhn@Paramountbio.com





Epílogo





www.farmacia.ufrj.br/lassbio

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 - » 2004

<<< LASSBio cadastra candidatos a Pós-Doutoramento >>>



Convite:



**XIV ESCOLA DE VERÃO EM QUÍMICA
FARMACÊUTICA & MEDICINAL**

11/15 DE FEVEREIRO DE 2008

INSCRIÇÕES JÁ ABERTAS

INSTITUTOS do MILÊNIO

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Obrigado.

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