Universidade Federal do Rio de Janeiro

A Química Medicinal na descoberta de fármacos

Parte 1

I SEMANA DE INTEGRAÇÃO FARMACÊUTICA DO MÉDIO ARAGUAIA

06-08 de outubro de 2010

UFMT, Barra do Garças, MT

Eliezer J. Barreiro

Professor Titular

UFRJ

Conteúdo

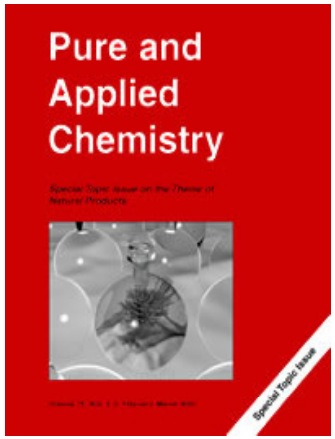
DEFINIÇÃO Química Medicinal; os Pioneiros (Ernest forneau; Alfred Burger); a EVOLUÇÃO cronológica **DA** QUÍMICA Farmacêutica Medicinal; os FÁRMACOS e o prêmio **Nobel (**Emil Fischer; Paul Ehrlich; Robert KOCH/louis Pasteur; *Alexander* Fleming; Ernest Chain; Howard FLOREY; George ***Hitchings;*** Gertrude Belle ELION; *Sir* James W. *Black*; bent *Samuelsson*; SUNE bergstron; John VANE; A. von Szent-Györgyi; W. N. Haworth; Linus C. Pauling; Arthur Kornberg); o que são os *fármacos,* suas MOLÉCULAS; as *moléculas* PIONEIRAS; cronologia da DESCOBERTA de *fármacos*; noções sobre o PAPEL dos produtos NATURAIS na *descoberta* de fármacos; a cadeia da *descoberta* dos FÁRMACOS; como nascem os FÁRMACOS; o PARADIGMA de Fischer; abordagem fisiológica;os BIORRECEPTORES & o modelo chave-fechadura; αbeto*S bioquímicos*; bioinformática & *QUÍMICA* COMPUTACIONAL; Topografia 3D dos BIORRECEPTORES; TIPOS de interações FÁRMACOS-biorreceptores; SIMILARIDADE e dissimilaridade no *reconhecimento* MOLECULAR; as *fases* DA ação dos FÁRMACOS; FASE farmacocinética; *conceito* de grupamento FARMACOFÓRICO, *auxofórico & toxicofórico*; *conceito* de COMPOSTO-protótipo; fármacos, moléculas INTELIGENTES; fármacos sintéticos; *planejamento* RACIONAL (*Cimetidina;* **SILDENAFILA;** *lodenafila*; estatinas; ORLISTAT); considerações finais: o *mercado* FARMACÊUTICO e suas MOLÉCULAS bilionárias; trabalhos realizados no **LASSBio-UFRJ** (exemplos DE *casa):* novos COXIBES; *LASSBio-294* candidato a fármaco cardioativo inovador *& LASSBio-596,* novo composto-protótipo de fármaco anti-asmático; *BIBLIOGRAFIA*; convite; Agradecimentos.

IUPAC - Subcommittee Medicinal Chemistry & Drug Development

IUPAC

http://www.iupac.org

www.chem.qmul.ac.uk/iupac/medchem/



Química Medicinal é uma disciplina baseada na química, também envolvendo aspectos e conceitos de ciências biológicas, médicas e farmacêuticas. Está voltada para a invenção, descoberta, desenho, identificação e preparação de compostos bioativos, ao estudo do seu metabolismo, a interpretação molecular de seu modo de ação e à construção de relações entre a estrutura química e a atividade biológica apresentada.

Pure & Appl. Chem., Vol. 70, No. 5, pp. 1129–1143, 1998.
Printed in Great Britain.
© 1998 IUPAC

Eur. J. Med. Chem., *31*, 747 (1996)

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SciELO

The Scientific Electronic Library Online - SciELO is an electronic library covering a selected collection of Brazilian scientific journals.

The library is an integral part of a project being developed by FAPESP - Fundação de Amparo à Pesquisa do Estado de São Paulo, in partnership with BIREME - the Latin American and Caribbean Center on Health Sciences Information. Since 2002, the Project is also supported by CNPq - Conselho Nacional de Desenvolvimento Científico e Tecnológico.

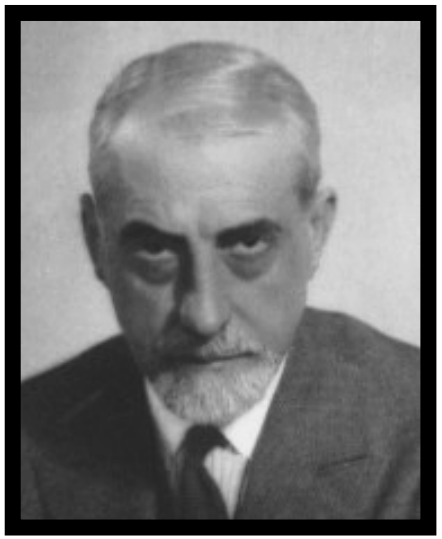
The Project envisages the development of a common methodology for the preparation, storage, dissemination and evaluation of scientific literature in electronic format.

Fatos históricos:

Os pioneiros

Química Medicinal

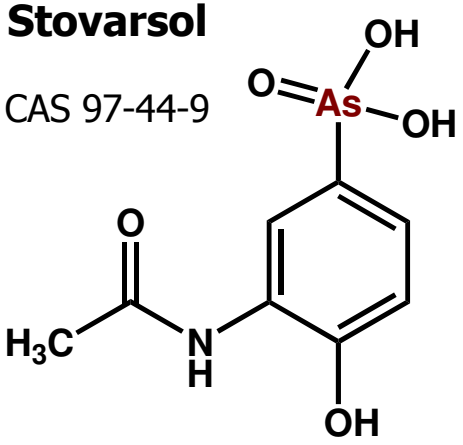
O berço da Química Medicinal



Ernest Fourneau
1872-1949

Stovarsol

CAS 97-44-9



Institut Pasteur (1887)

1911- Laboratoire de Chimie Thérapeutique

Institut Pasteur (Emile Roux)

1911-1944 – J. Tréfouël, Th. Tréfouël, G. Benoit, D. Bovet, F. Nitti

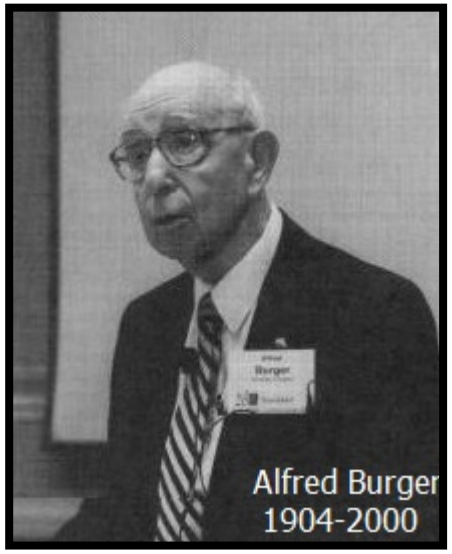
Prontosil rubrum (sulfonamidas)

Curare: SAR

Daniel Bovet
1907-1992

Prêmio Nobel de Fisiologia/Medicina 1957

J-P Fourneau, « Ernest Fourneau foundateur de la Chimie Pharmaceutique française », *Revue de l´Histoire de la Pharmacie*, t.XXXIV, nº 275, 335-355



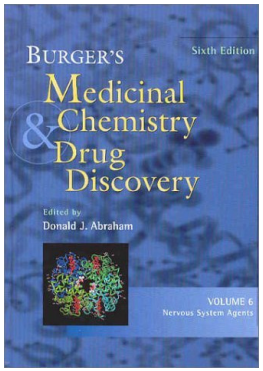
Química Medicinal

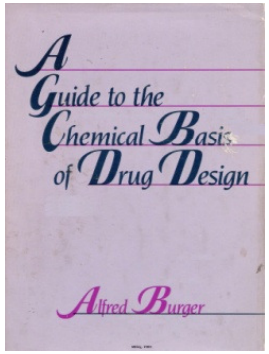
Prof. Alfred Burger

(1904-2000)

University of Virginia

EUA



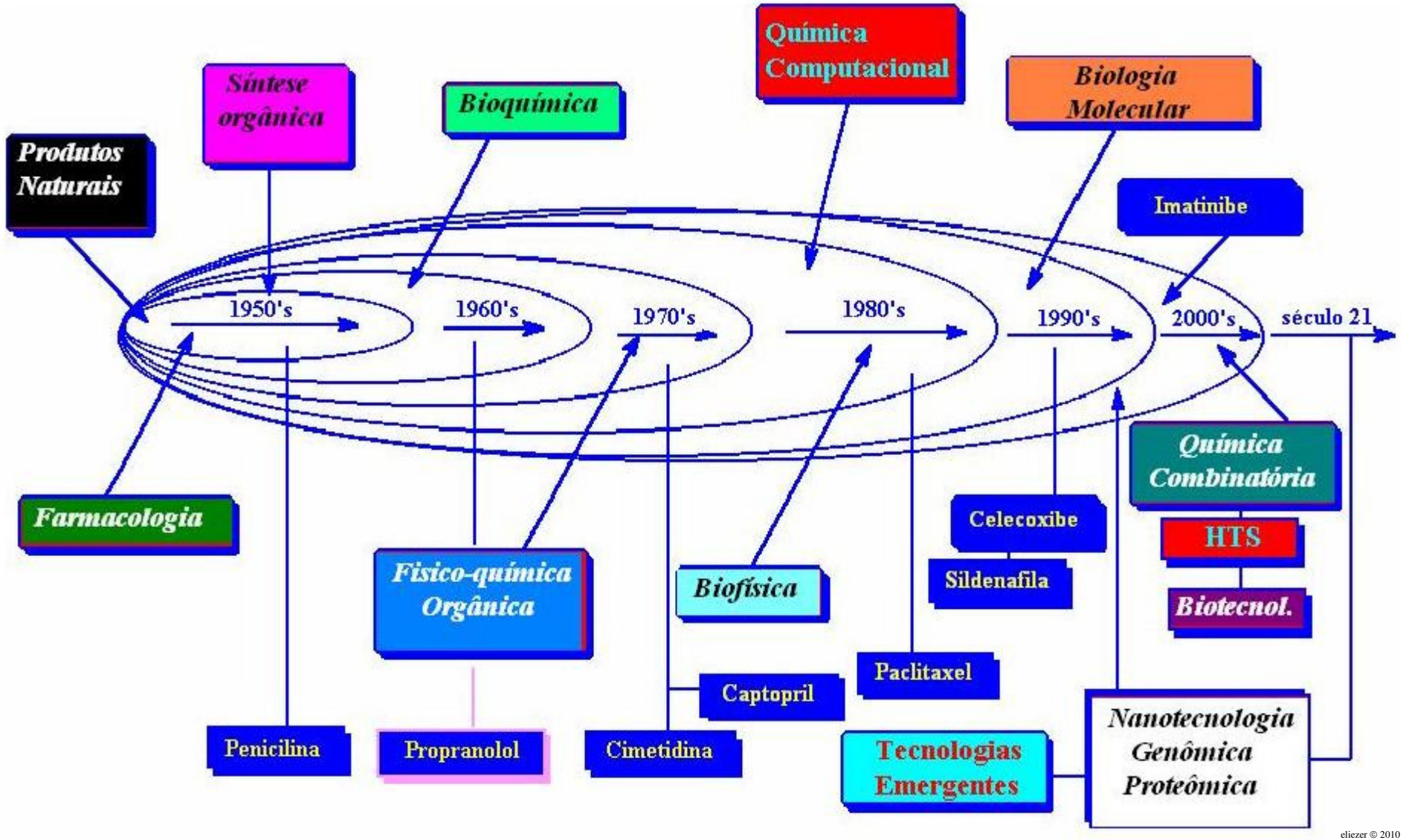


1958 – cria o Journal of the Medicinal and Pharmaceutical Chemistry → depois Journal of Medicinal Chemistry

"An Editor's Commentary on the Birth of a Journal"
J. Med. Chem. **1991**,*34*, 2-6

1978 - GlaxoSmithKline cria com ACS o "Alfred Burger Award" em Química Medicinal
T. Y. Shen - inventor da indometacina

A evolução cronológica da Química Farmacêutica Medicinal



Os Fármacos e o Prêmio Nobel

Os fármacos e o Prêmio Nobel

Louis Pasteur

1822-1895

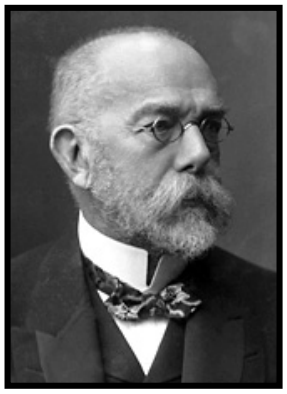
"La vie empeche la vie"

"L'hazard ne favorisée que les sprits preparées"

Emil Fischer

1852-1919

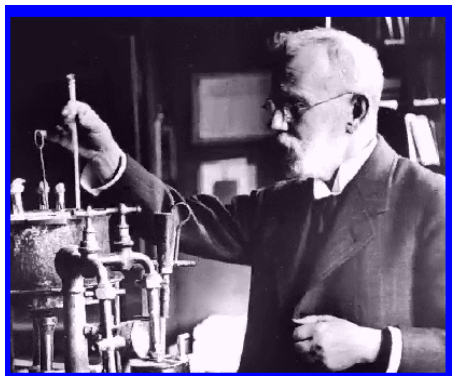
1902



Robert Koch

1843-1910

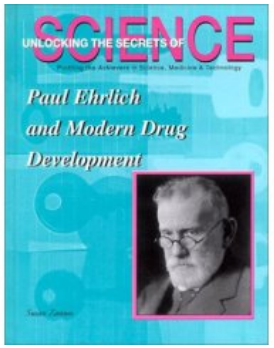
1905



Paul Ehrlich

1854-1915

1908



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

One-molecule, one-target paradigm

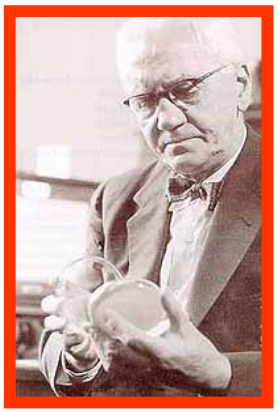
The Magic Bullet Theory

Antibioticoterapia

Penicilinas

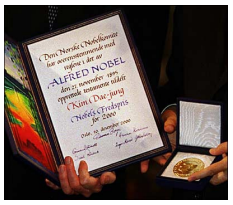
Moléculas Salva-vidas

β-lactâmicos



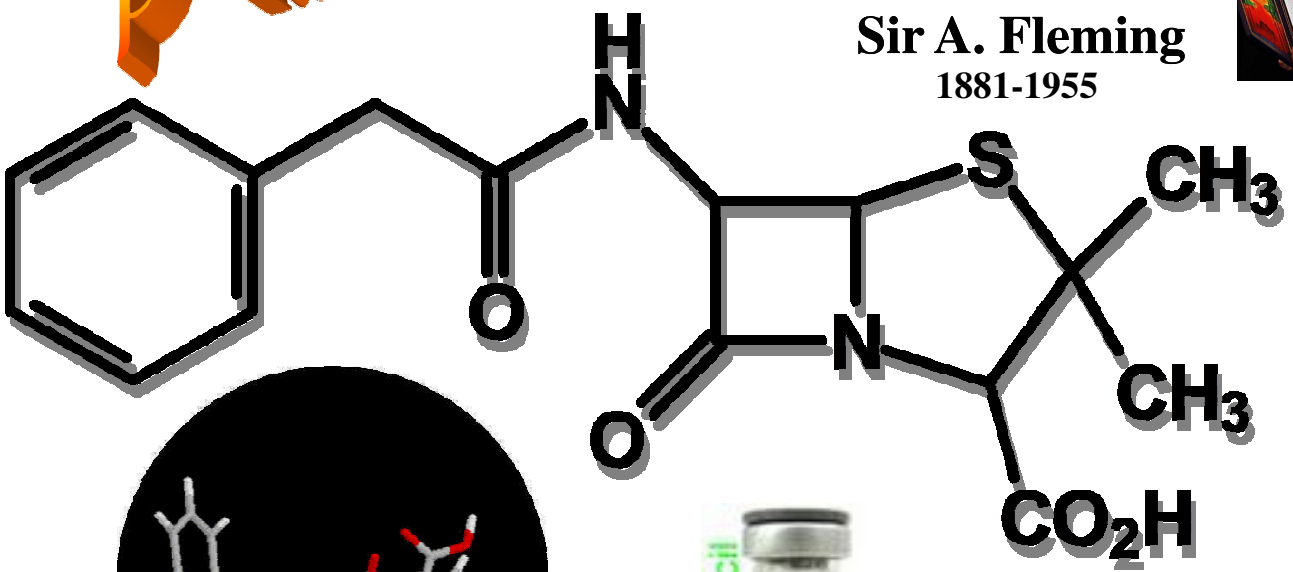
Sir A. Fleming
1881-1955

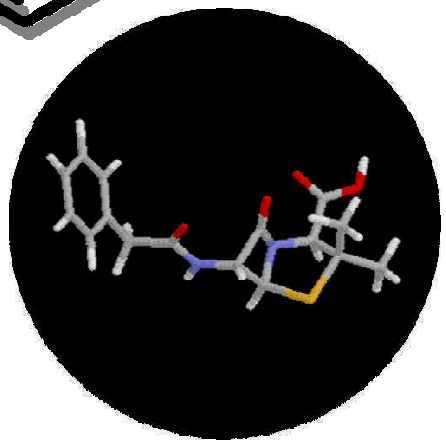
Sir H. W. Florey
1898-1968



1945

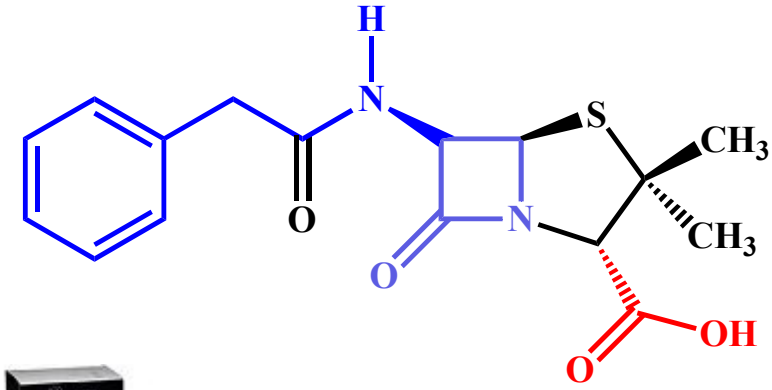
E. B. Chain
1906-1979



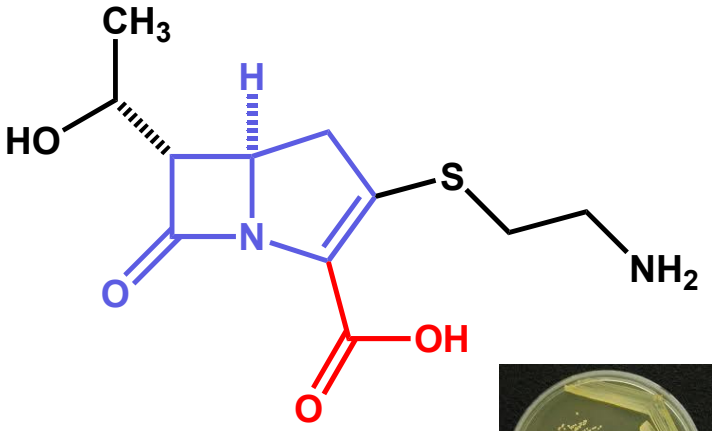


Penicillum notatum

serendipidade

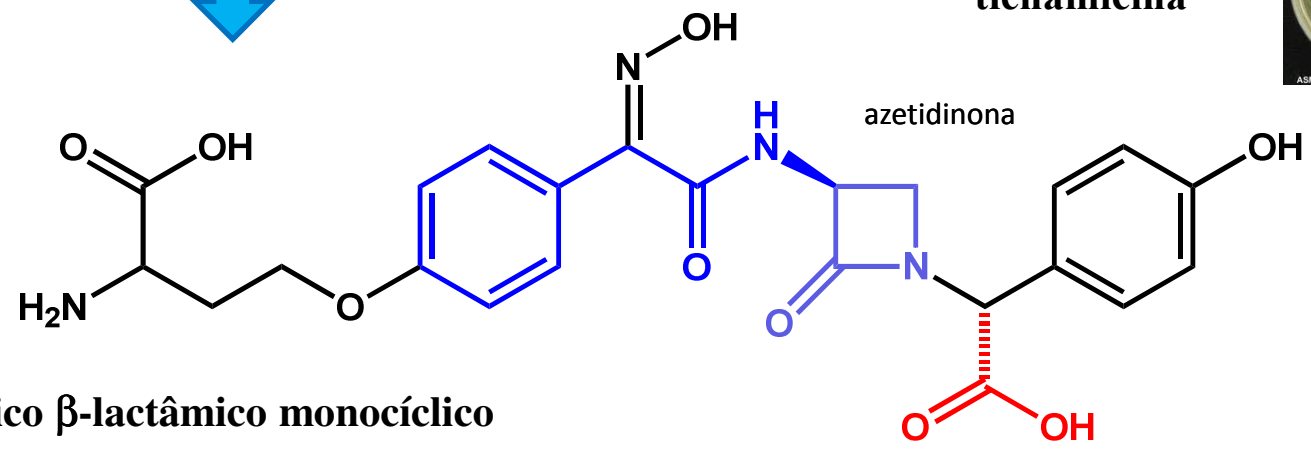


penicillin G



tienamicina

azetidinona



Antibiótico β-lactâmico monocíclico

nocardicina

Nocardia uniformis

Ativo *via* oral

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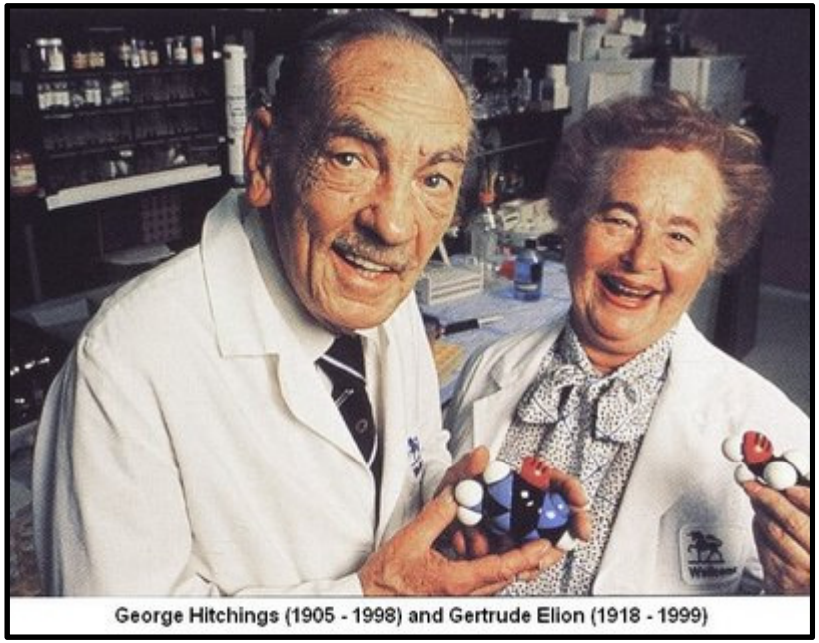
“for their discoveries of important principles for drug treatment"

1988 – James W. Black
(1924-2009)



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

1988

Inter-alia: Propranolol, cimetidina, azatioprina, alopurinol, trimetoprim, aciclovir (AZT)

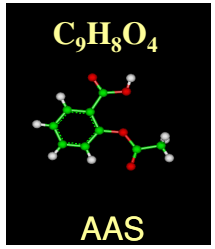
Os fármacos e o Nobel !

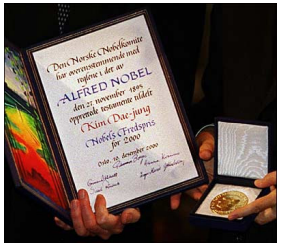
1982 –S.B.Bergstöm

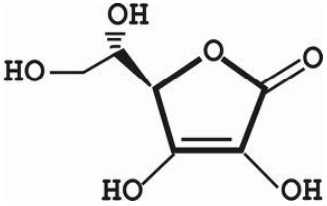
1982 –B.I.Samuelsson

1982 –J.R. Vane

1982 – AAS

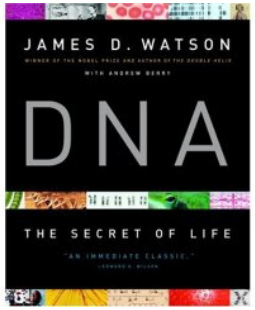






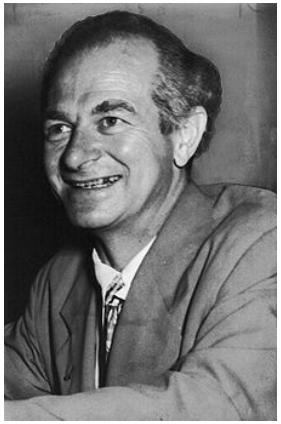
1937 – Vit C

1937 – W. N. Haworth



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

1937 –A. von Szent-Györgyi



1954 & 1962 – L. C. Pauling

EJB1

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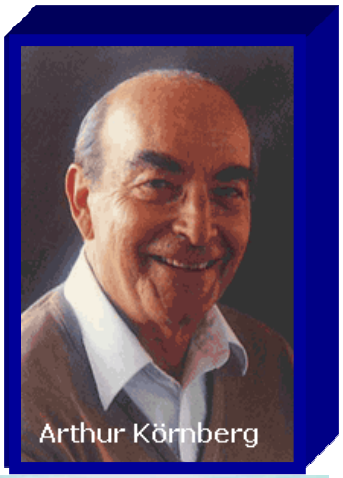
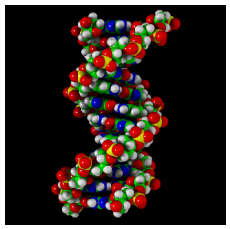
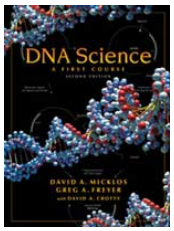
Nobel Prize, 1959



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





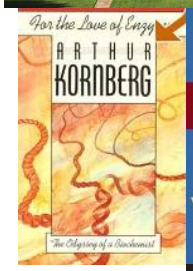
"We have the paradox of the two cultures,

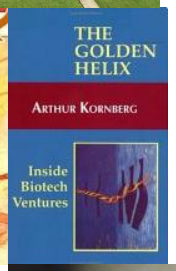
***chemistry** and **biology**,*

growing further apart even as they discover more common ground....

Pharmaceutical chemistry was until recently the bastion of organic chemistry…

in the search for alternative or superior drugs for the treatment of various diseases."





Arthur Körnberg

Biochemistry **1987**, *26*, 6888-6891

Interdisciplinaridade

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Diapositivo 15

EJB1

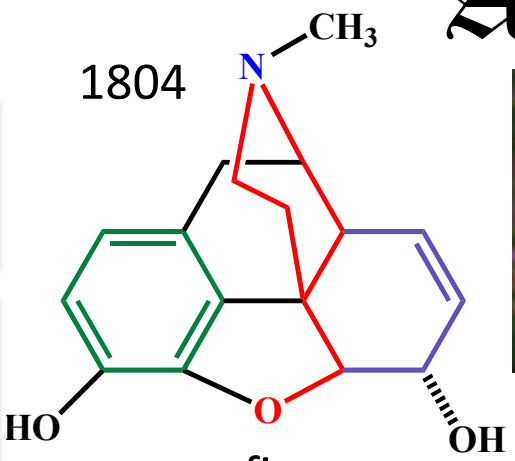
Kornberg definiu as bases da interdisciplinaridade das ciências dos fármacos quando antecipou a necessidade de aproximar-se a Química e a Biologia.

Eliezer J Barreiro; 27/08/2010

m e d Química Farmacêutica Medicinal chem

As moléculas pioneiras...

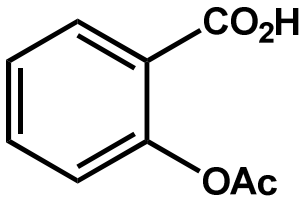
1804



morfina

$C_{17}H_{19}NO_3$

1897



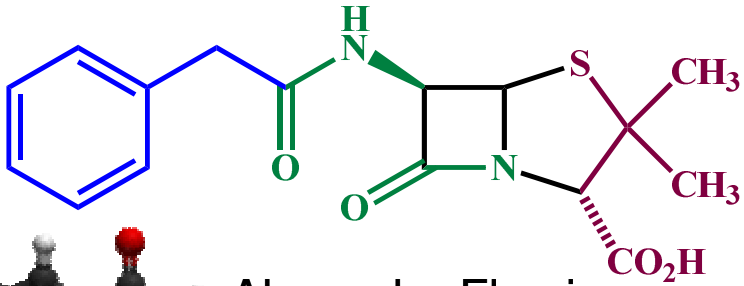
AAS

$C_9H_8O_4$

1929

penicilina

$C_{16}H_{18}N_2O_4S$

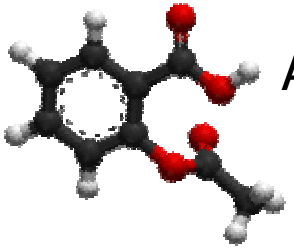


Friedrich W. A. Sertürner

1783- 1841

Felix Hoffman

1868- 1946



Alexander Fleming

1881-1955

Nobel 1945

Henry How

1853 – Un. Glasgow

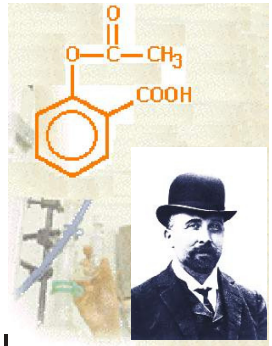
Sir Robert Robinson

1886-1975

Nobel 1947

Library of Congress

Cronologia da descoberta de fármacos



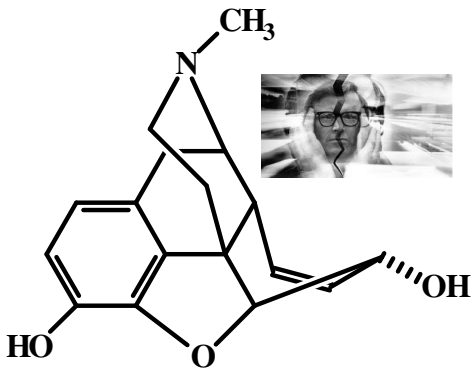
AAS *	**1889**	**1986**	**ciprofloxacina fluoxetina**
barbitúricos	**1923**	**1987**	**zidovudina lovastatina**
cloroquina	**1934**	**1988**	**cetirizina, enalapril**
sulfonamidas	**1935**	**1989**	**ozagrel mifepristona**
penicilina	**1942**	**1990**	**salmeterol, amlodipina**
nitrofurano	**1952**	**1991**	**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**	**1997**	**zafirlukast, montelukast**
salbutamol	**1968**	**1998**	**infliximabe sildenafila efavirenz**
prostaglandinas	**1970**	**1999**	**celecoxibe orlistate oseltamivir**
oxamniquina	**1970**	**2000**	**galantamina rofecoxibe**
cimetidina nifedipina	**1975**	**2001**	**imatinibe *rosiglitazona***
atenolol	**1976**	**2002**	**voriconazola, etoricoxibe**
captopril	**1977**	**2003**	**gefitinibide, aripiprazola**
tamoxifeno	**1978**	**2004**	**rosuvastatina, rofecoxibe**
praziquantel	**1979**	**2005**	**pregabalina, Caduet^{R}**
oxicams	**1980**	**2006**	**risperidona, erlotinibe**
ranitidina aciclovir	**1981**	**2007**	**maraviroc*, ambrisentam**
mefloquina misoprostol	**1985**	**2008**	**etravirina**
		2009	**pitavastatina**

CRONOLOGIA

O papel dos produtos naturais

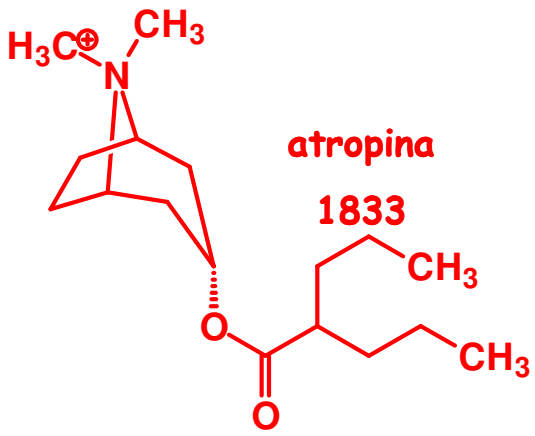
Os Produtos Naturais e a Descoberta de Novos Fármacos

Quimiodiversidade



morfina

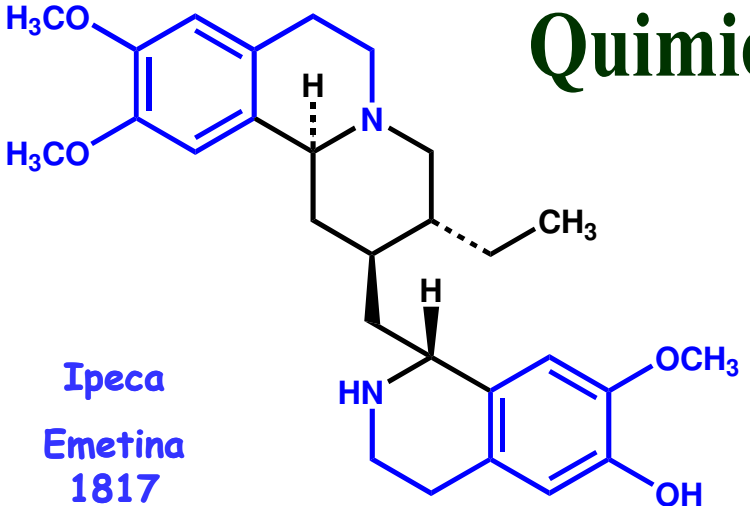
1806



atropina

1833

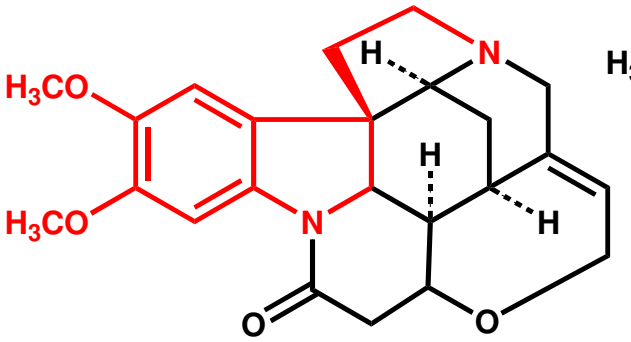
terpenos, alcalóides, esteróides, flavonóides, lignanas, ligninas, iridóides, policetídeos, quinonas, cumarinas



Ipeca

Emetina

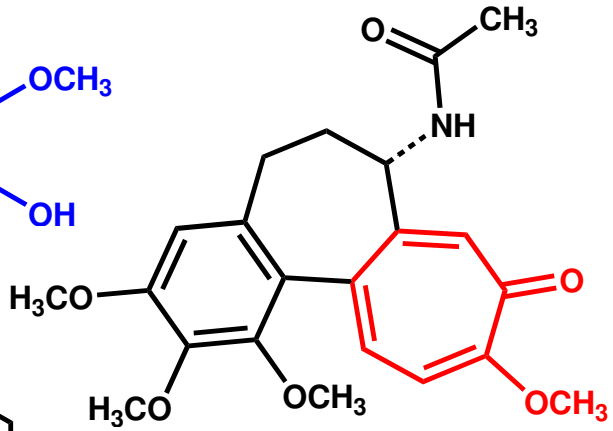
1817



Estriquinina

1817

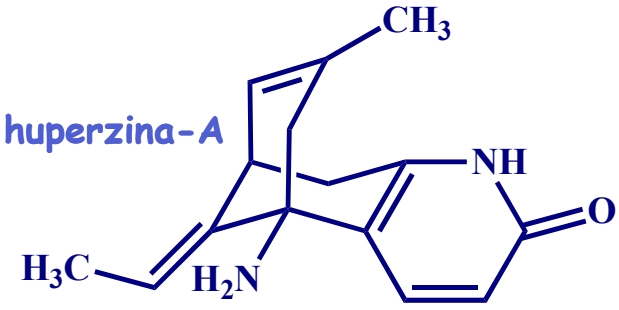
Strychnos nux vomica



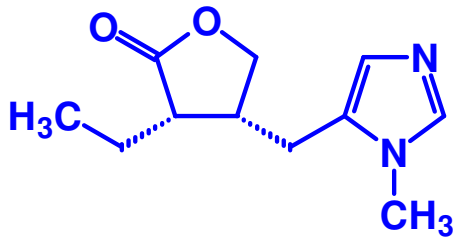
Colcichina

1820

Colchicum autumnale

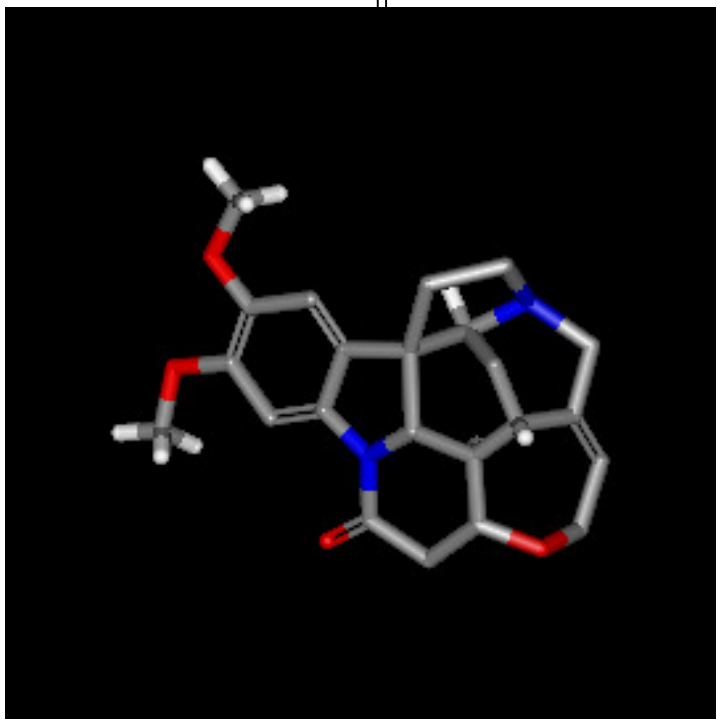


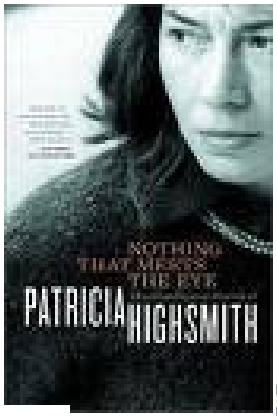
Huperzia serrata.

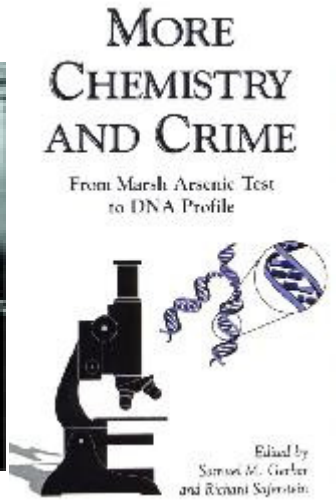


Pilocarpina

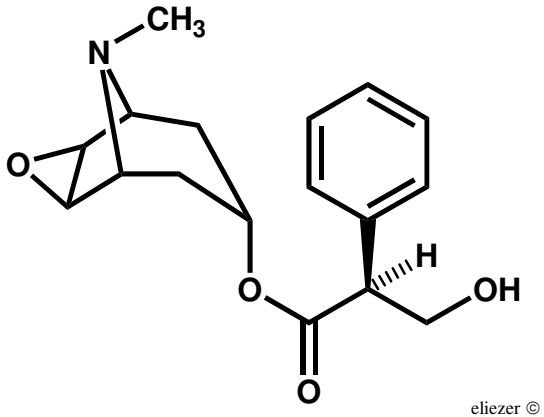
Estriquinina



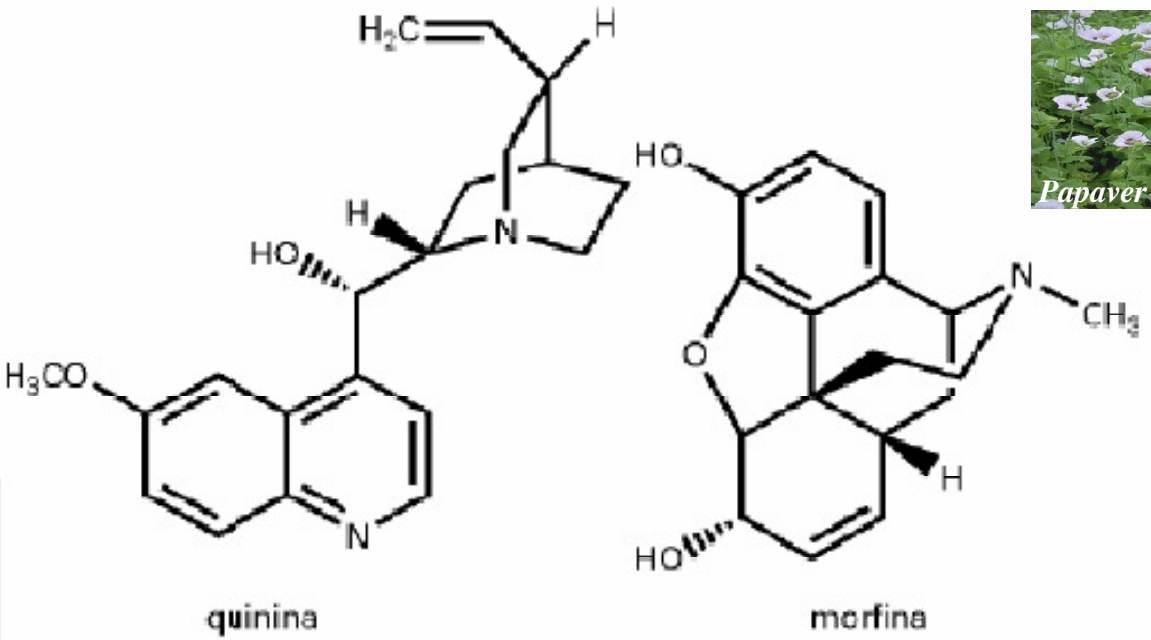




Escopolamina

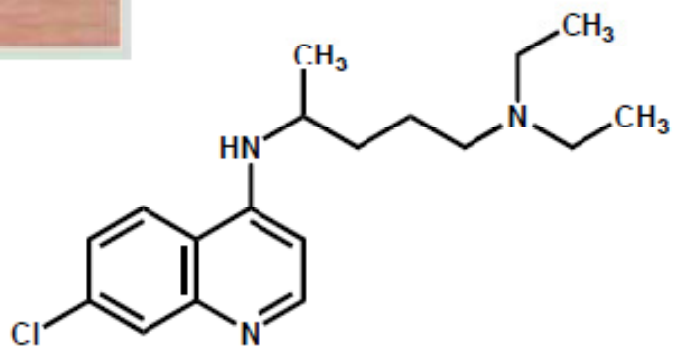


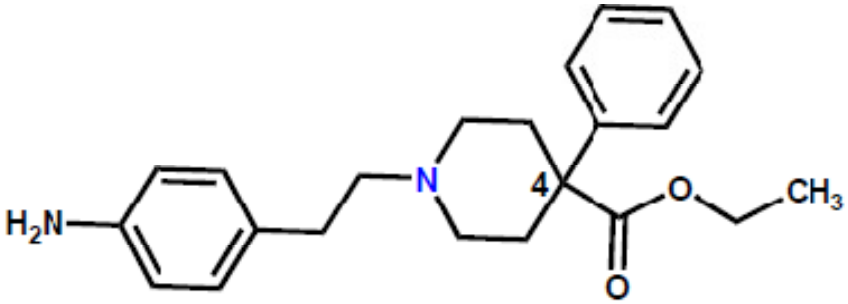
Cinchona officinalis



Papaver somniferum

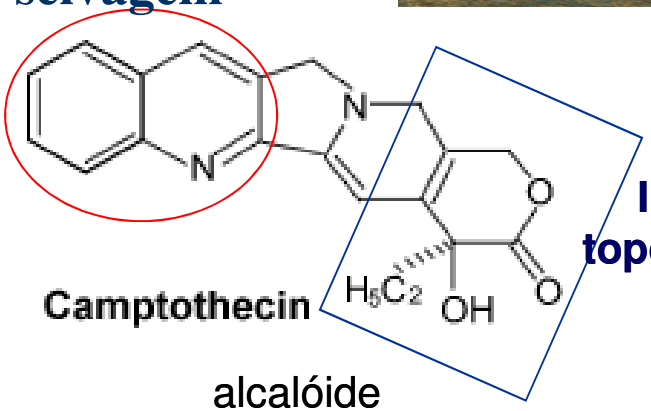
Alcalóides = alcalinos = bases nitrogenadas naturais





Câncer

Molécula "selvagem"



Camptothecin

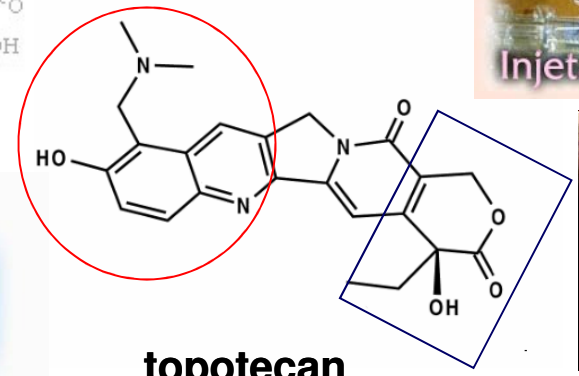
Inibidor de topoisomerase-1

alcalóide quinolínico de biossíntese mista

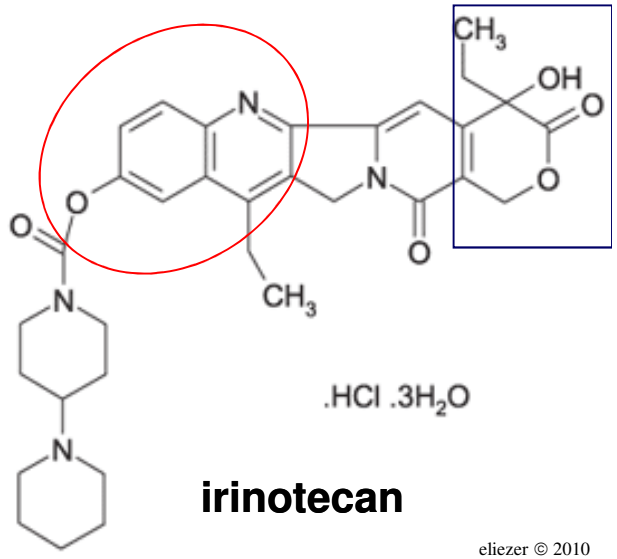
Wall, ME & Wani, MC "**Camptothecin: Discovery to Clinic**" *Annals of the New York Academy of Sciences 1996,* 803, 1

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

Molécula "domesticada"

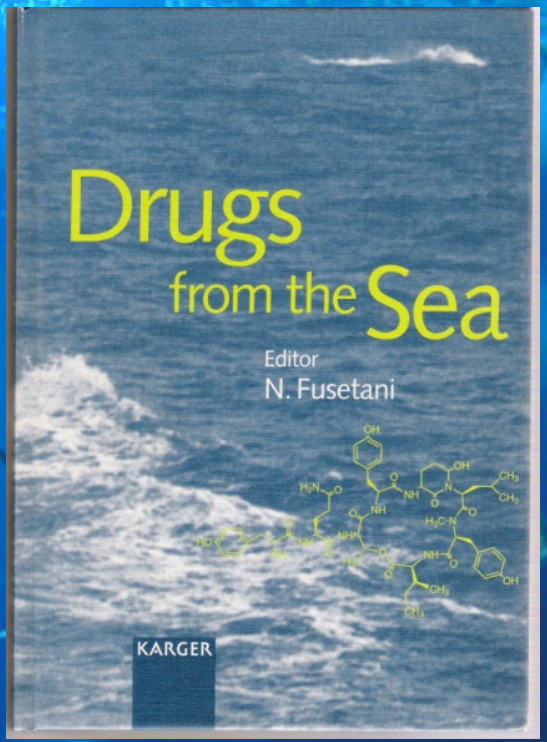


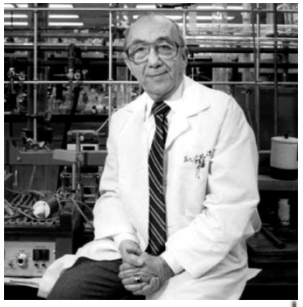
topotecan



irinotecan

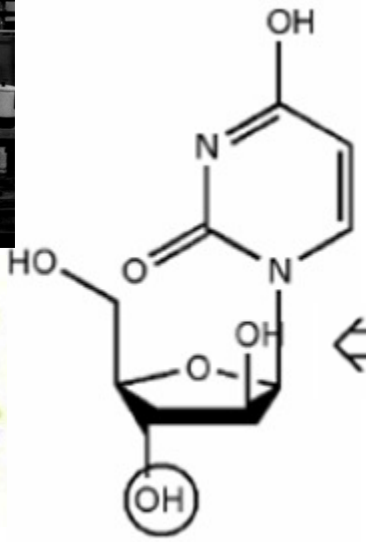
Produtos Naturais do Mar



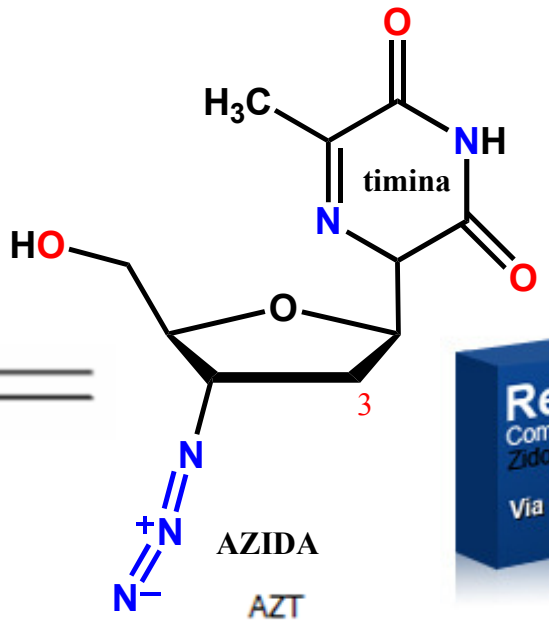


Jerome Horwitz

1964-sintetizada



Ara-C



AZIDA

AZT

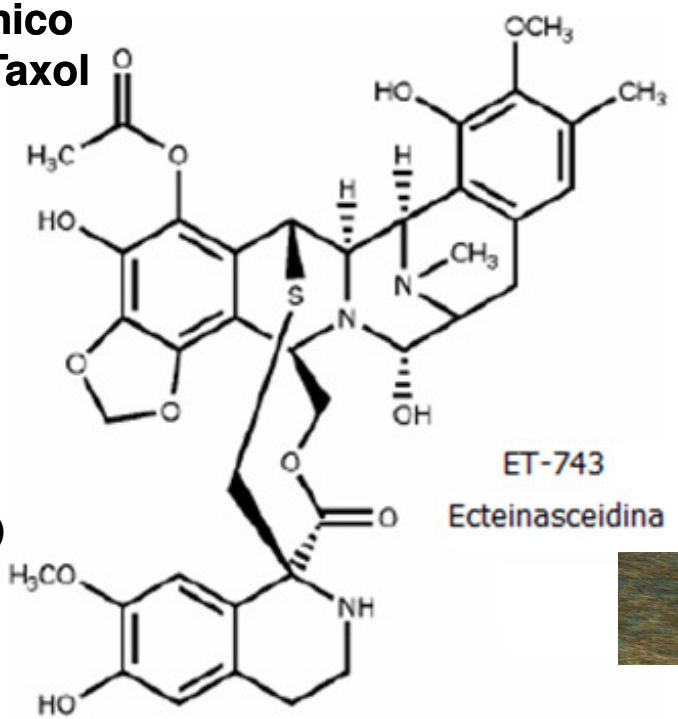
Novo Fármaco anti-câncer

Derivado tetraidroquinolínico

100 vezes mais ativo que Taxol

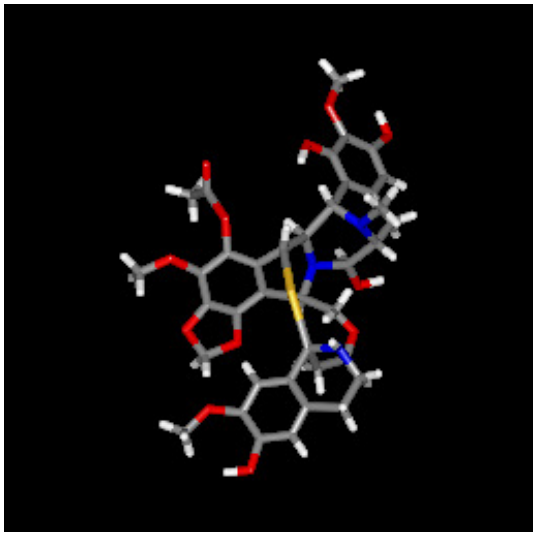
Yondelis™

(trabectedina)



ET-743

Ecteinasceidina



Câncer

Produtos Naturais Marinhos em Ensaios Clínicos

Composto	Organismo	Fase	Doença
KRN7000	Porifera	I	câncer
IPL-567	Porifera	I	inflamação
methopetrosin	Celenterata	I	inflamação
GST-21	nemertea	I	Alzheimer
Dolastatina 10	molusco	II	câncer
LU-103793	molusco	I	câncer
Ziconotido (SNX-111)*	molusco	III	dor crônica
Briostatina	Briozoa	II	câncer
Didemnina B	Urocordarta	II	câncer
Ecteinascidina (ET-743)	Urocordata	II	câncer
Esqualamina	Cordata	I	câncer

* Peptídeo-conotoxina (Prialt^{R}) aprovado pelo FDA para uso em dor neuropática por injeção intratecal em 2008

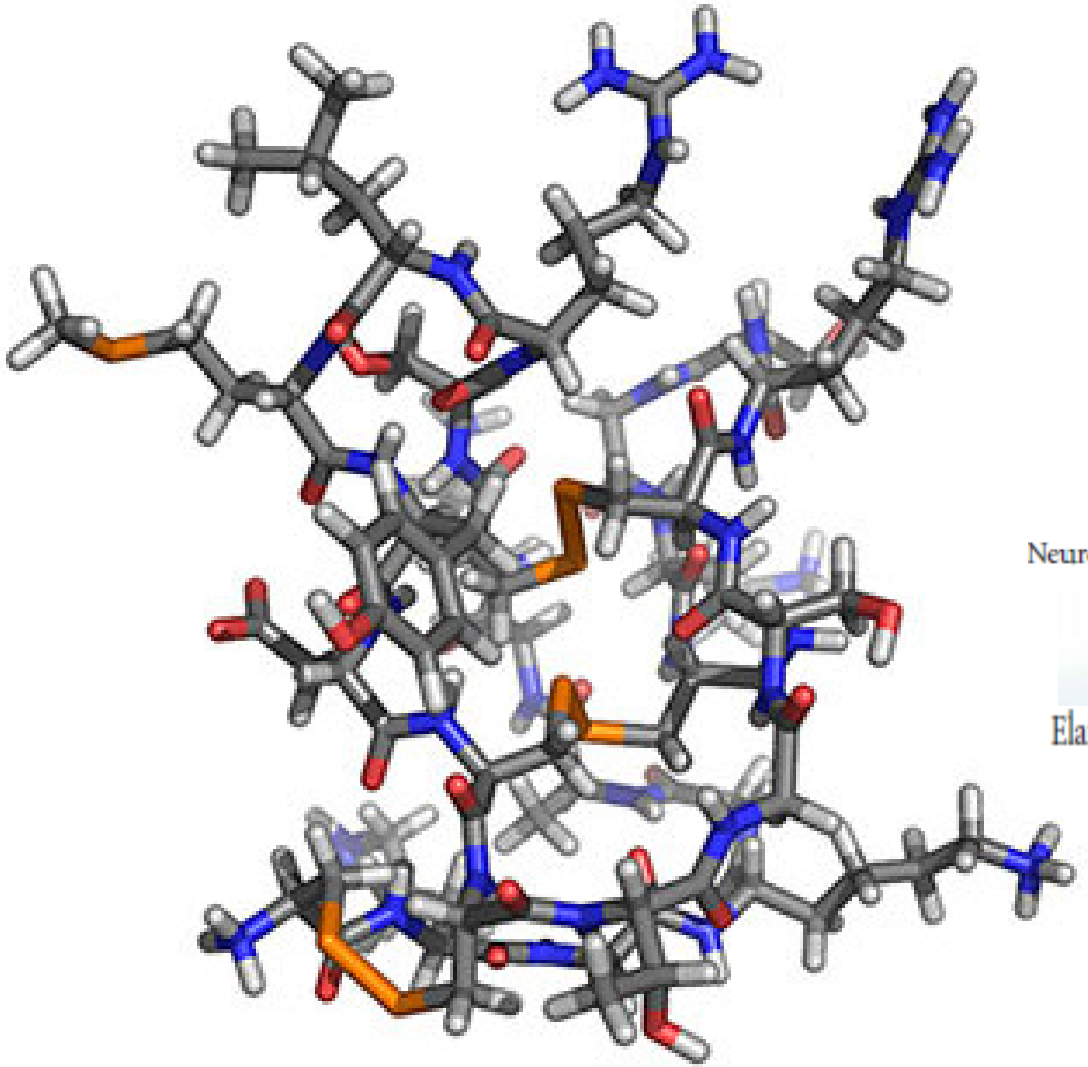
1980 - Michael McIntosh & Baldomero Olivera

Ziconotídeo

$C_{102}\ H_{172}\ N_{36}\ O_{32}\ S_7$

FDA em 28/12/2004; Eur Comm. em 22/02/2005

Uso intratecal



25 aa

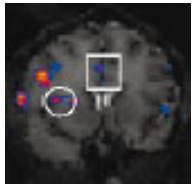
Conus magus

SNX-111

Neurex (Menlo Park, CA)

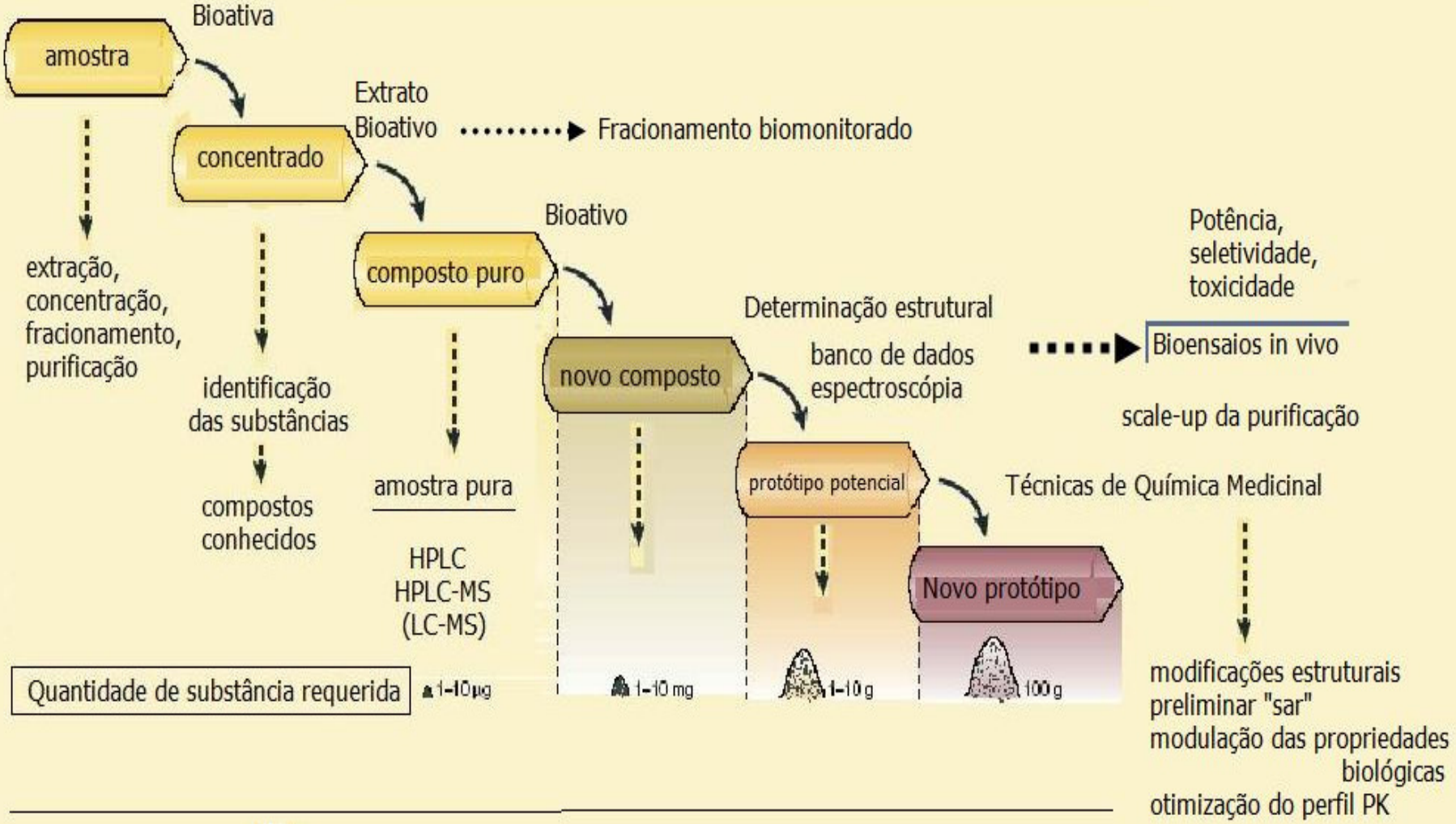
Elan Pharmaceuticals

(Dublin, Ireland



Antagonista de canais Ca^{++} voltagem dependentes tipo-N

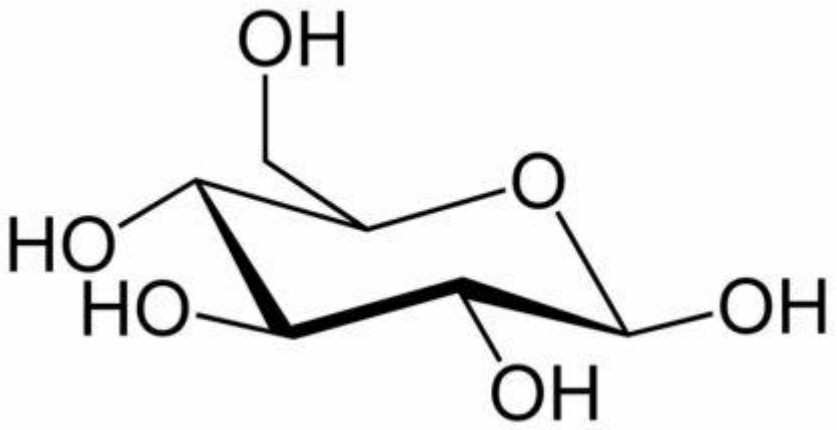
Processo de descoberta de novos hits-naturais



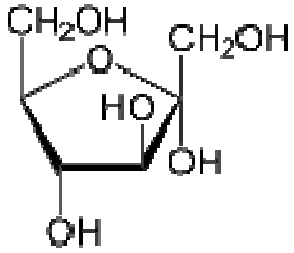
Adaptado de

F. E. Koehn & G. T. Carter, The evolving role of natural products in drug discovery, Nature Review Drug Discovery, 2005, 4, 206-220

Como nascem os fármacos



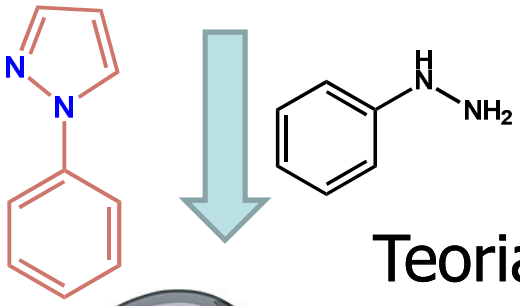
Glicose



frutose

The Nobel Prize in Chemistry 1902
Emil Fischer

Emil Fischer
1852-1919



Teoria da chave-fechadura

Complementaridade molecular

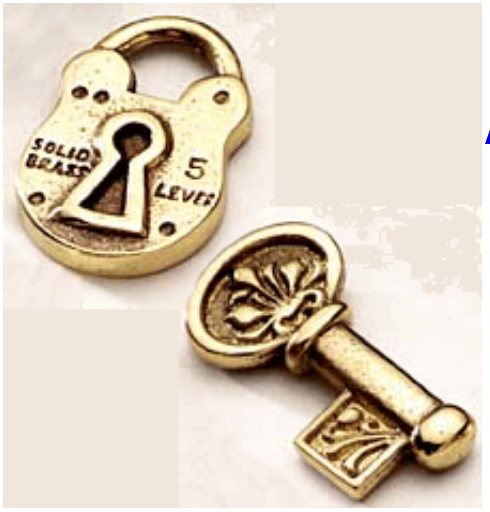
Reconhecimento molecular

Interação fármaco-receptor

O paradigma de Fischer

Emil Fischer
1852-1919
1902

LOCK & KEY
CONCEPT



Biorreceptor

macrobiomolécula

baseado no sítio de reconhecimento

Planejamento racional

Fármaco

micromolécula

baseado no ligante / análogo-ativo

Robin Ganellin gives his views on medicinal chemistry and drug discovery

Interview by Stephen L. Carney

C. Robin Ganellin, FRS, Smith Kline & French Professor Medicinal Chemistry, University College London

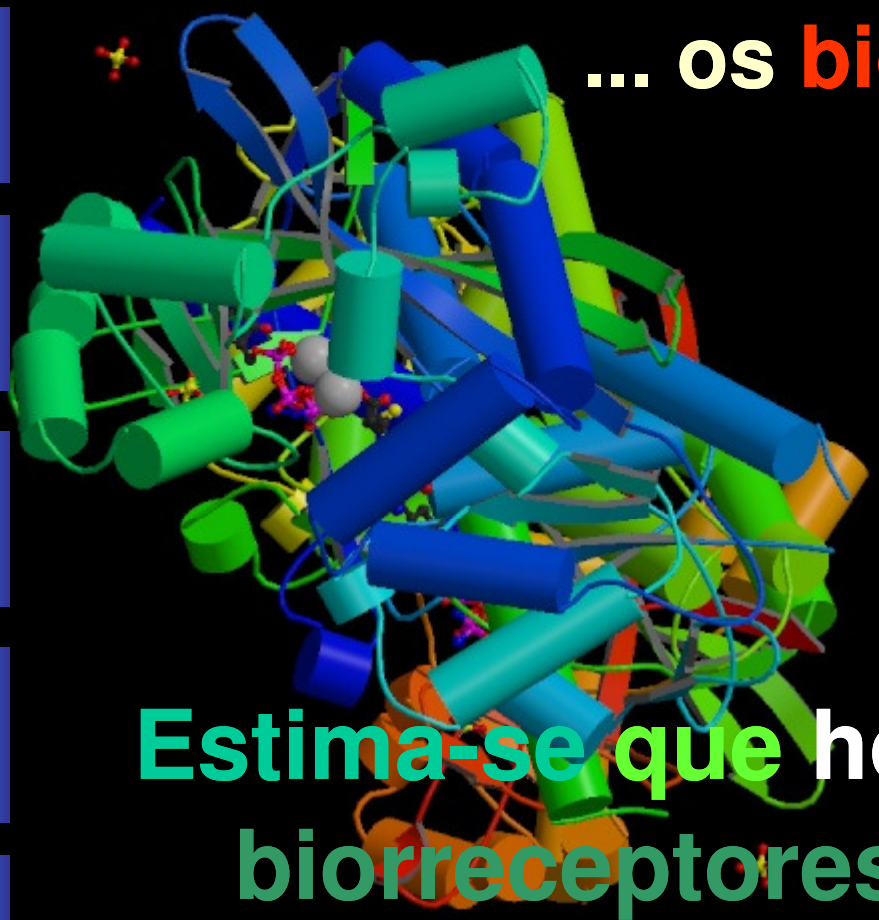
Physiologic approach
A abordagem fisiológica

C. Robin Ganellin, *Drug Discovery Today* **2004**, *9*, 158

Os biorreceptores

Os fármacos atuam em alvos terapêuticos...

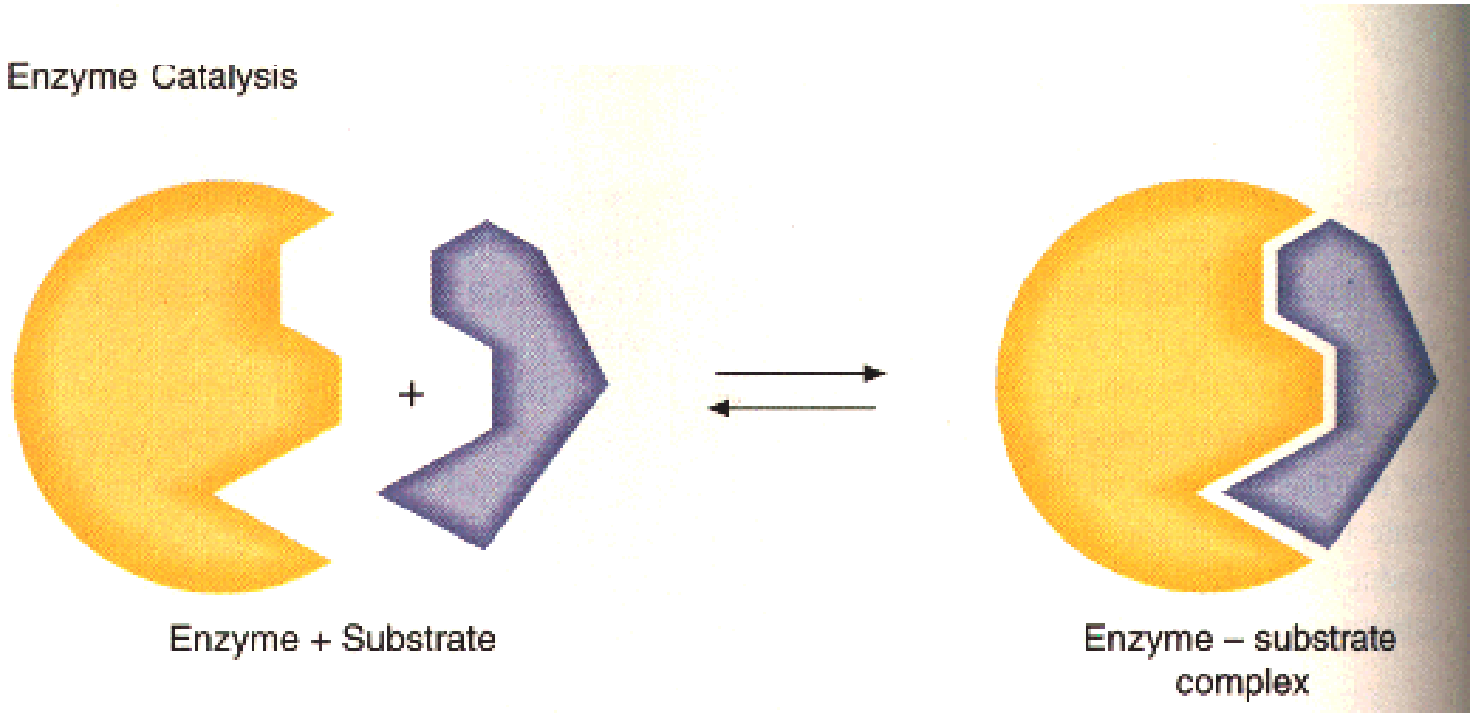
... os biorreceptores .

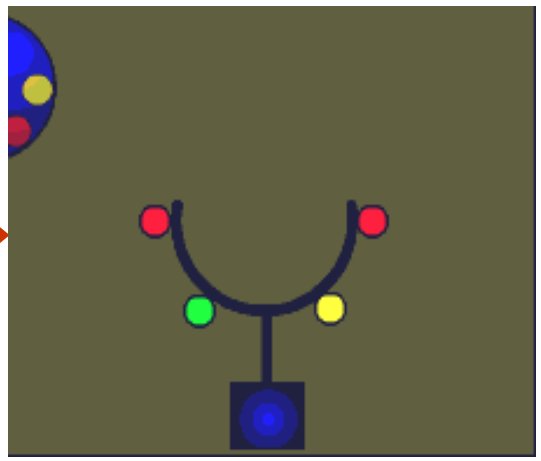


Estima-se que hoje sejam 483 os biorreceptores envolvidos na resposta terapêutica de todos os fármacos contemporâneos.

J. Drews, S. Ryser, **Classic drug targets**. *Nature Biotechnol. 1997,* 15, 1318

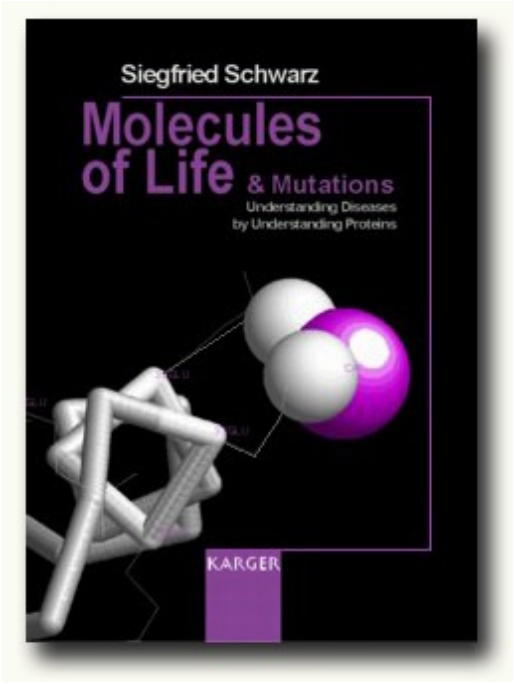
Modelo Chave-Fechadura

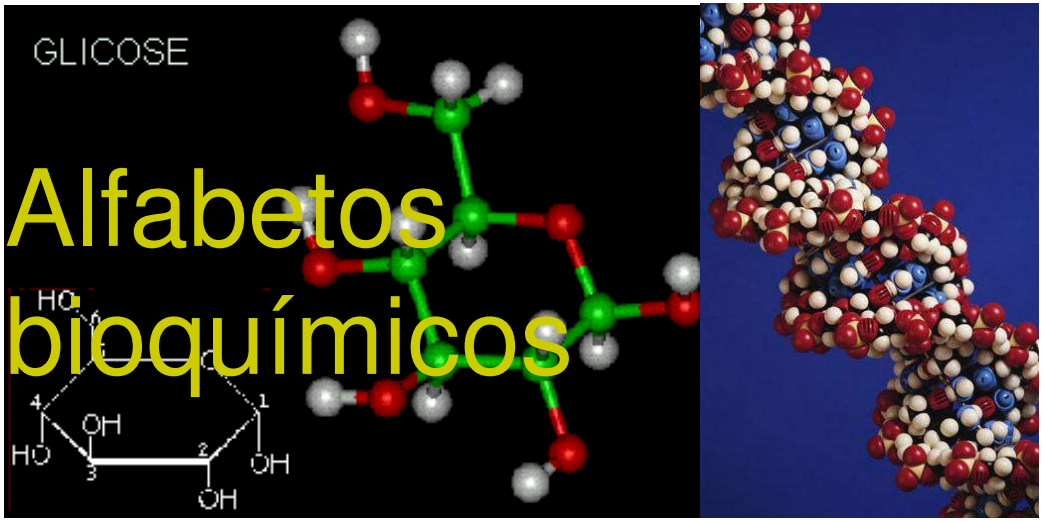




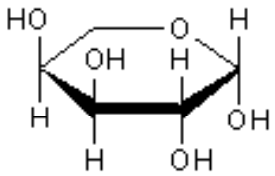
Resposta Biológica

reconhecimento molecular

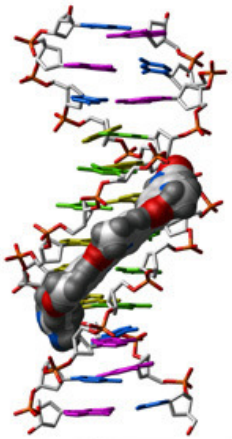




Alfabetos bioquímicos



β-L-Arabinose



Model Compound Bound to the Minor Groove of a DNA Molecule

Carboidratos
Lipídeos
ácidos nuclêicos
proteínas

Amino-ácidos essenciais

glicina (**gly**)

alanina

valina

isoleucina (**Ile**)

leucina

serina

cisteína (**Cys**)

treonina (**Thr**)

metionina

lisina (**Lys**)

arginina

ácido **glu**tâmico

ácido **asp**ártico

prolina

glutamina (**Gln**)

asparagina (**Asn**)

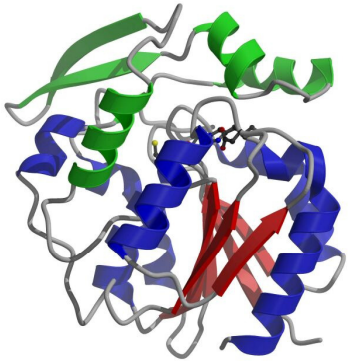
triptofano (**Trp**)

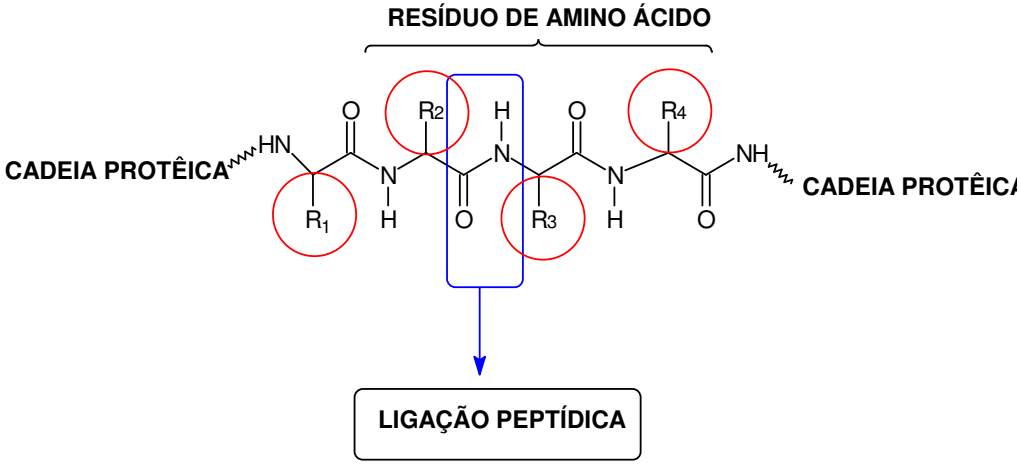
fenilalanina (**Phe**)

tirosina (**Tyr**)

histidina

Estrutura Primária das Proteínas





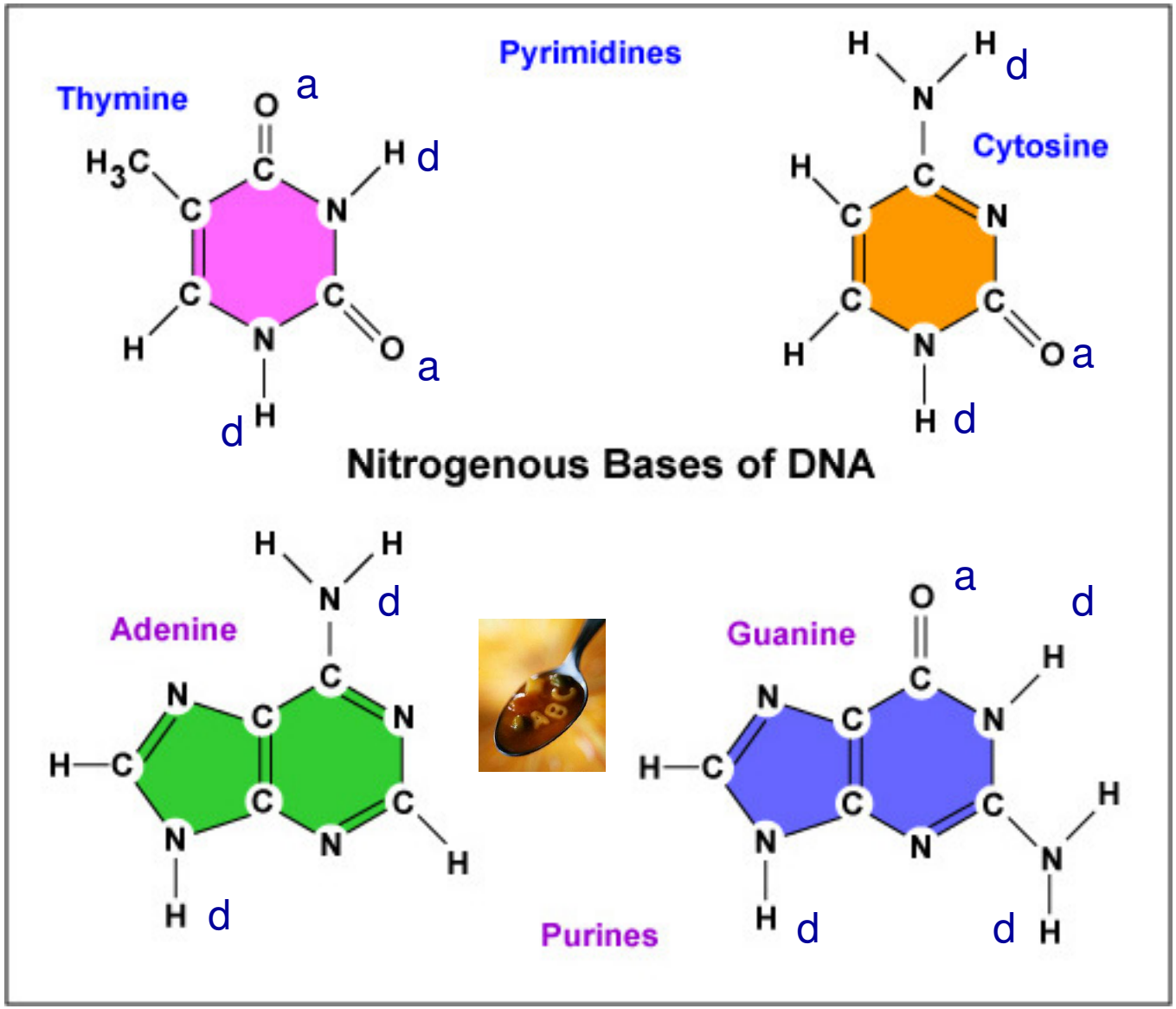
AMINO ÁCIDOS:

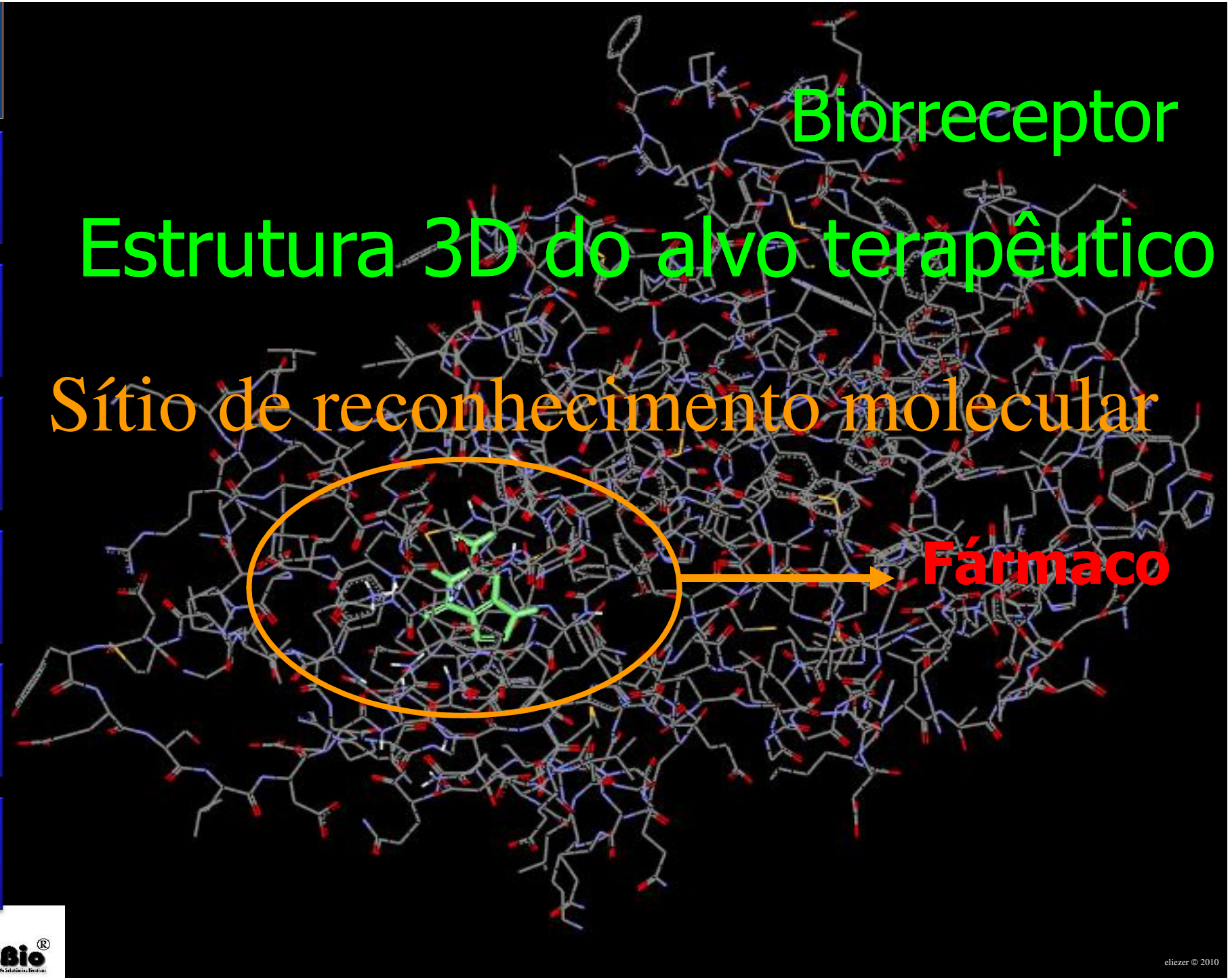
Essenciais: His, Ile, Leu, Lys, Met, Phe, Thr, Trp, Val

Não-essenciais: Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, Pro, Ser, Tyr

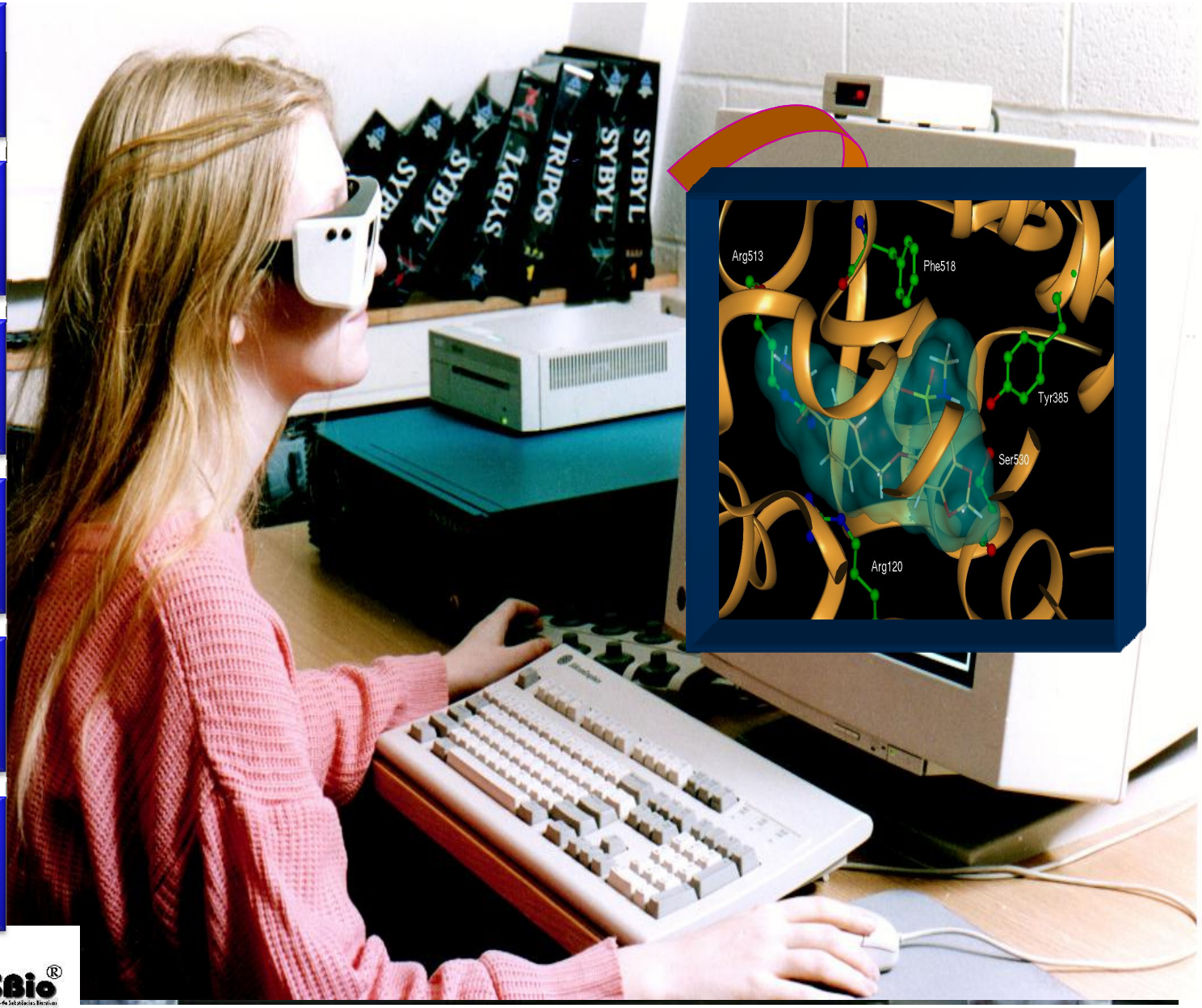
"Fechadura"

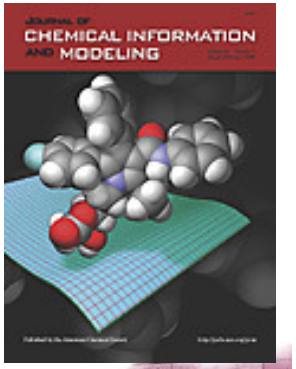
“*ácidos nuclêicos...*

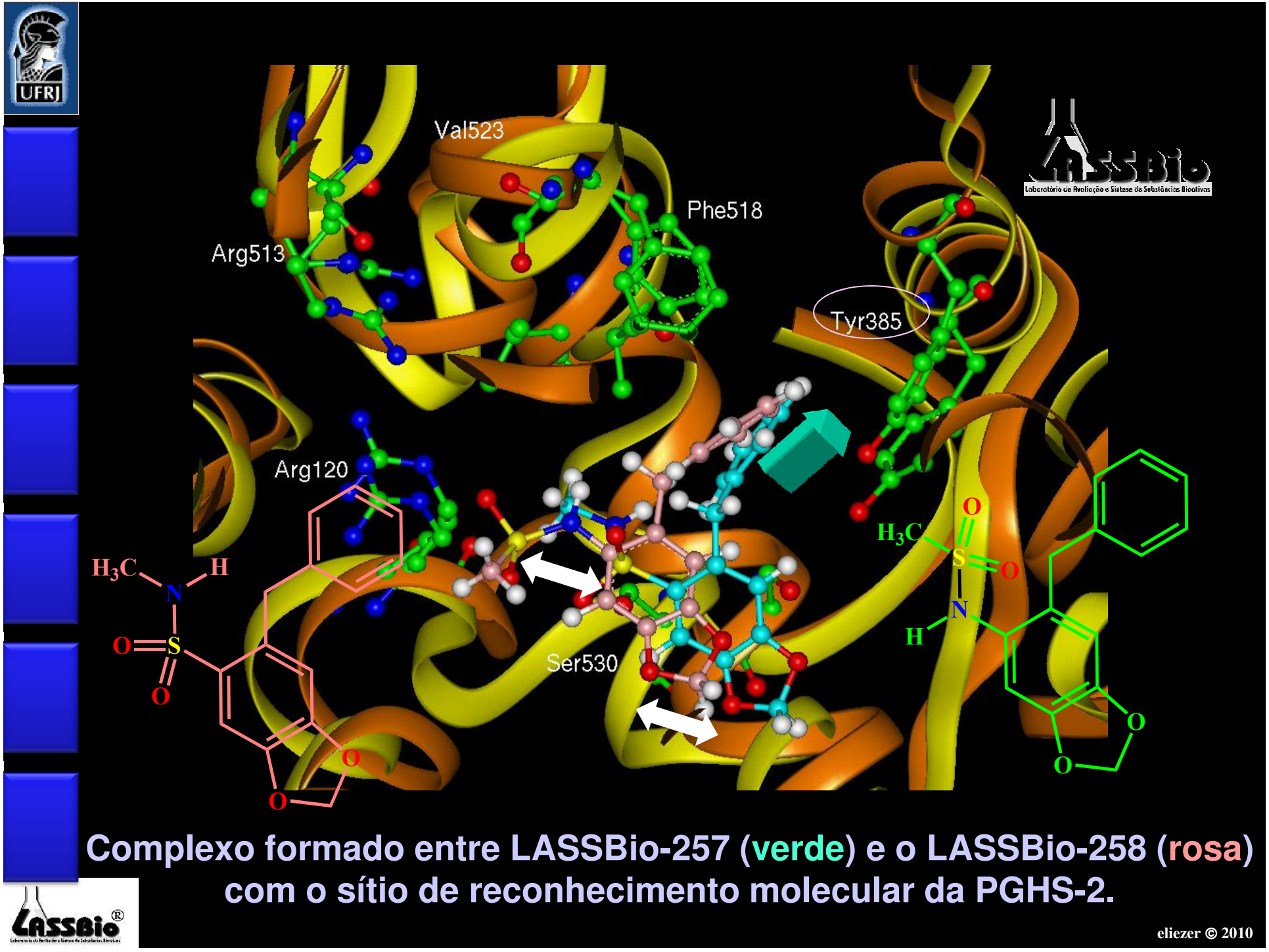



Biorreceptor
Estrutura 3D do alvo terapêutico
Sítio de reconhecimento molecular
Fármaco
eliezer © 2010

Bioformática

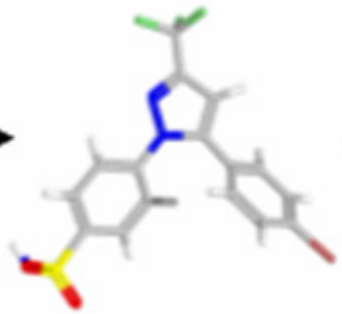




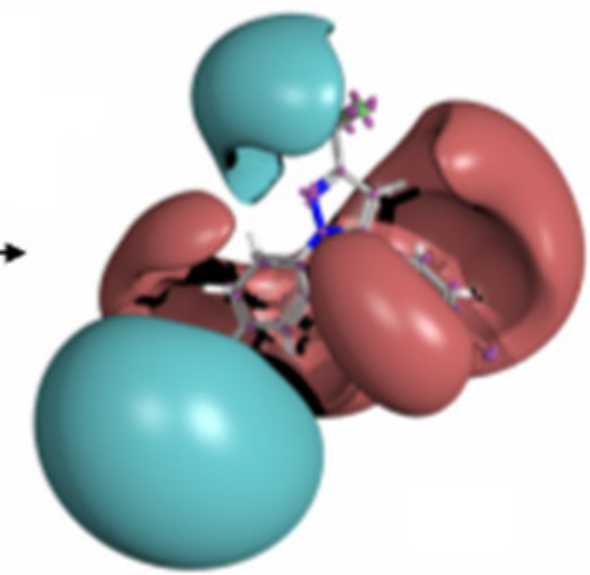


Complexo formado entre LASSBio-257 (verde) e o LASSBio-258 (rosa) com o sítio de reconhecimento molecular da PGHS-2.

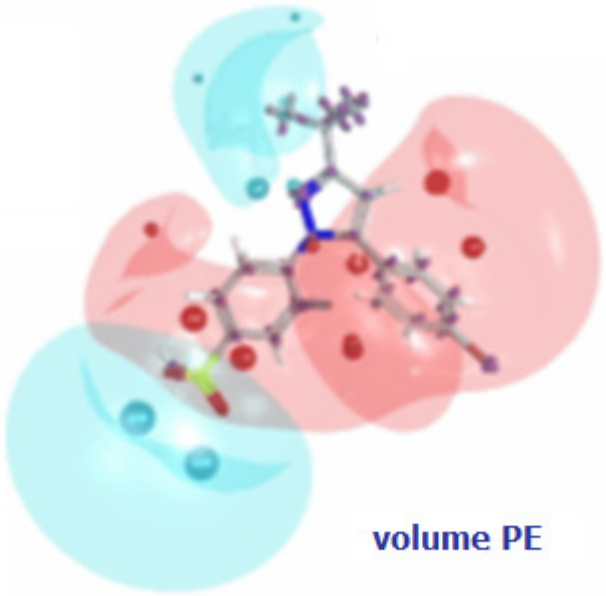
2D



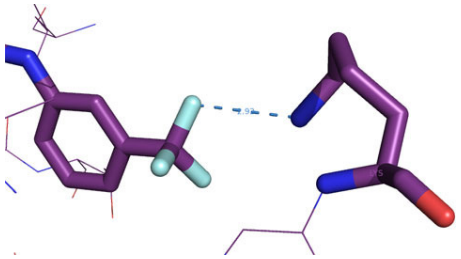
3D



MPE



volume PE



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

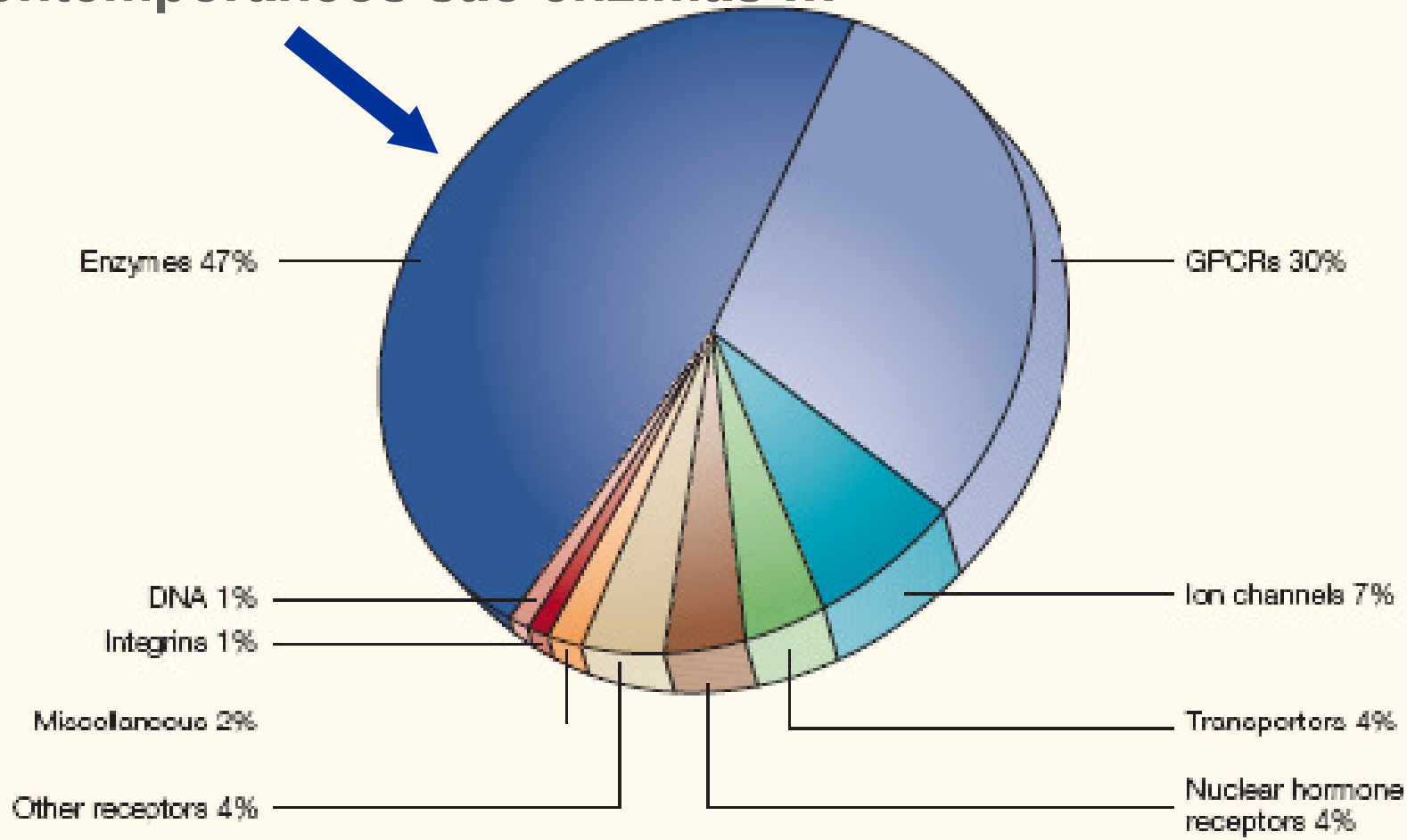
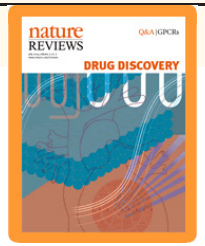


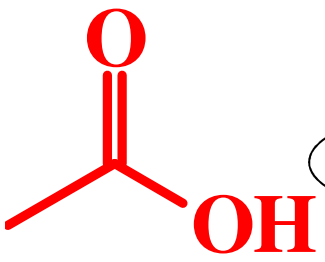
Figure 4 | **Marketed small-molecule drug targets by biochemical class.** GPCR, G-protein-coupled receptor.



www.nature.com/reviews/drugdisc

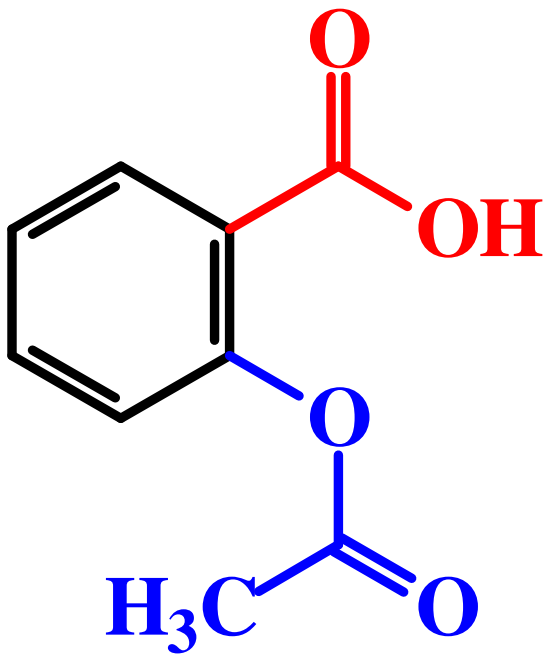
Hopkins, A. L. & Groom, C. R. The druggable genome. *Nature Rev. Drug Discov.* 1, 727–30 (2002).

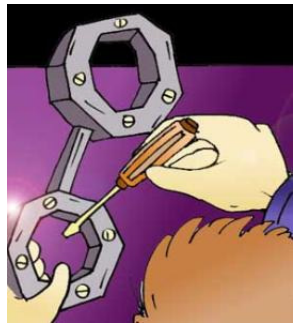
Dissecação Molecular

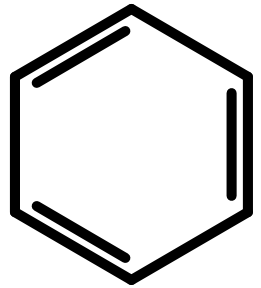


ácido carboxílico

A

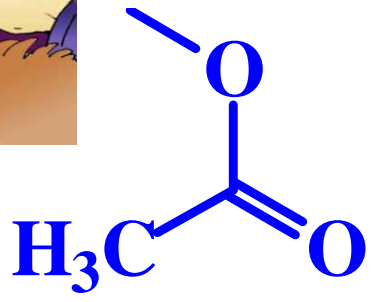






B

fenila

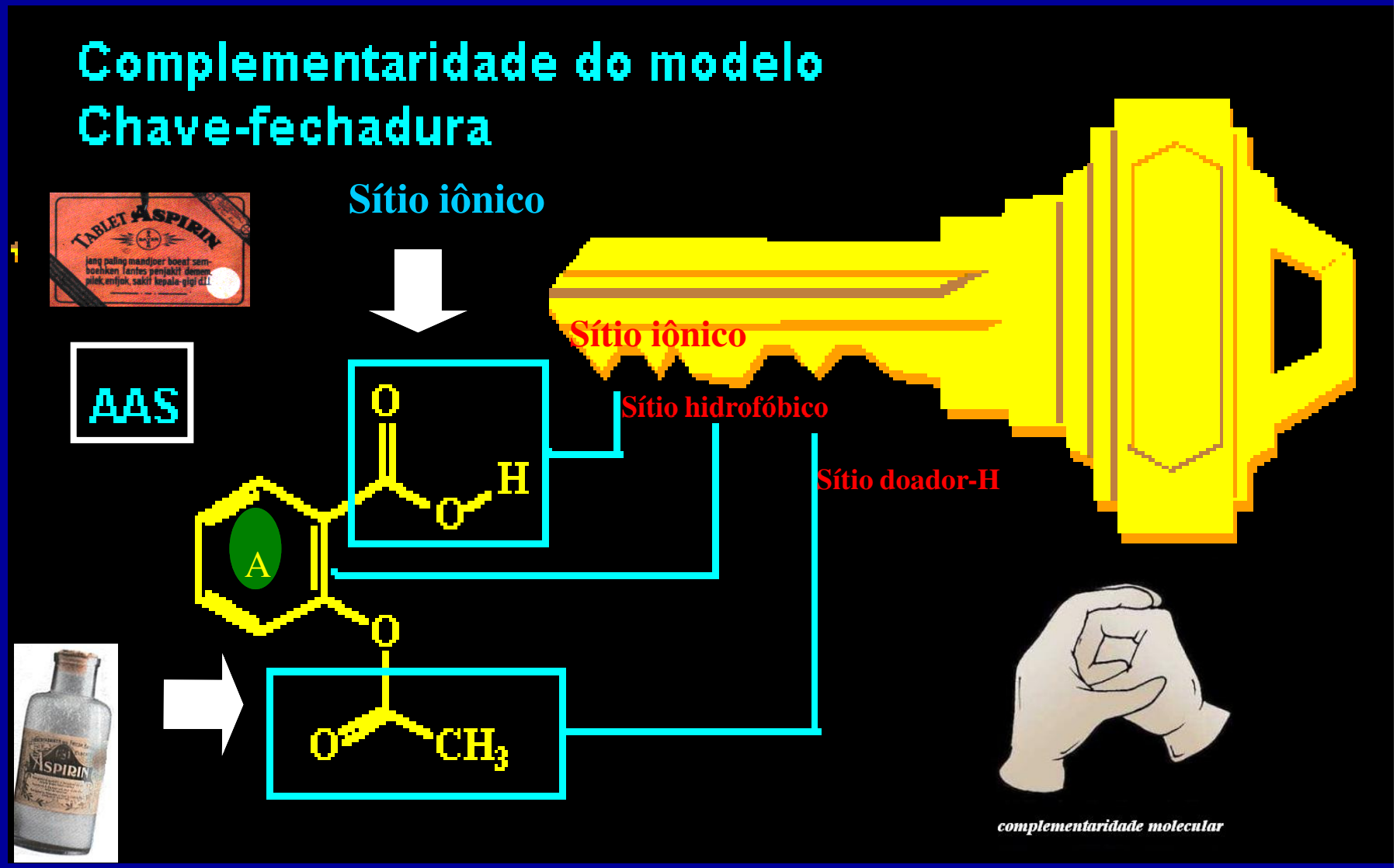


éster

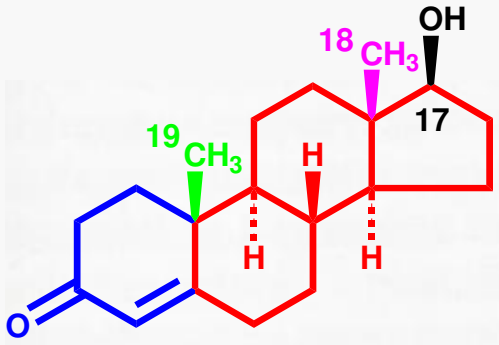
C

Ácido acetilsalicílico

O Centenário Modelo *"Chave-Fechadura"*

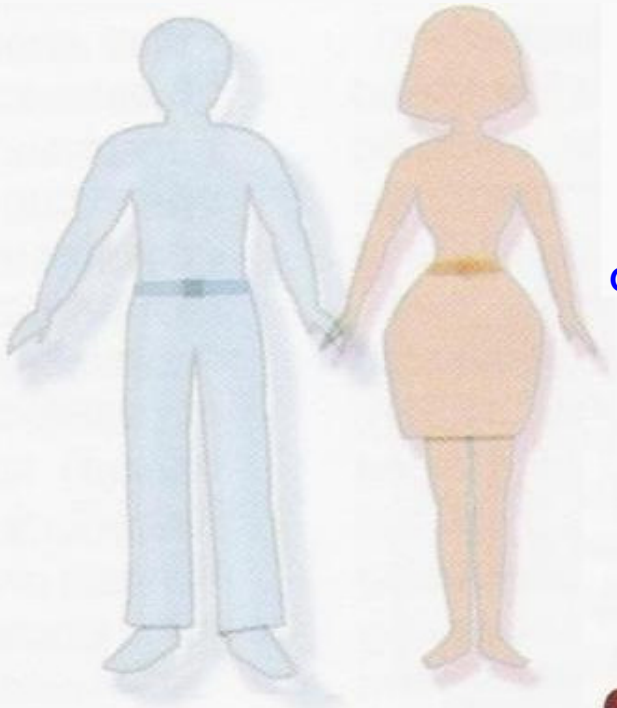


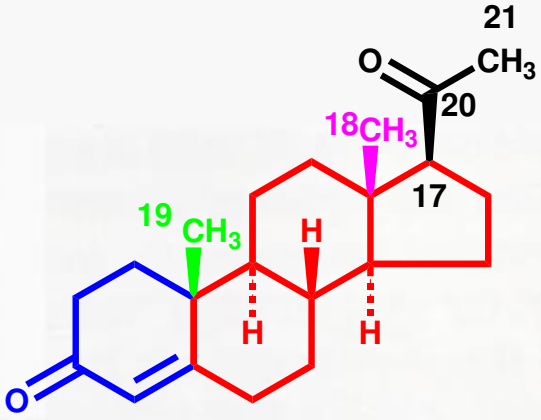
A similaridade e a dissimilaridade molecular



Testeosterone
$C_{19}H_{28}O_2$

Testosterone





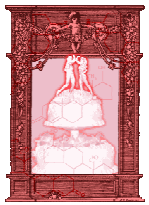
Progesterone
$C_{21}H_{30}O_2$

Progesterone

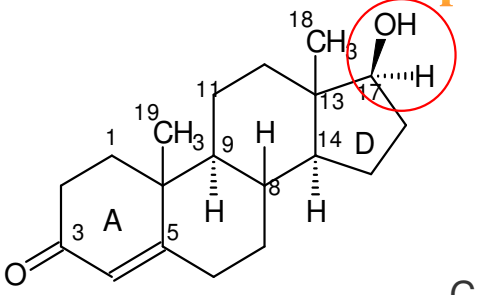
no reconhecimento molecular do biorreceptor

Similaridade & Dissimilaridade Molecular

Biorreceptor

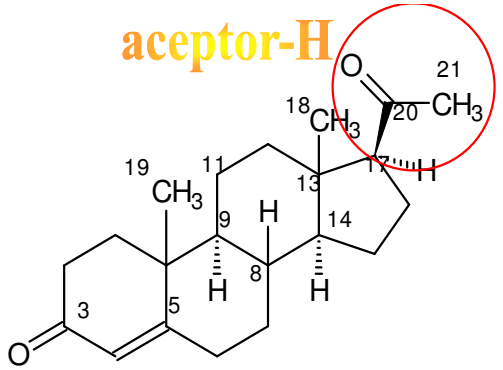


aceptor/doador-H



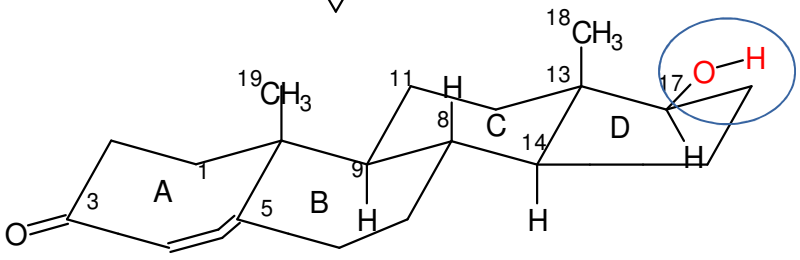
Esqueleto ciclopentano
peridrofenantreno

aceptor-H

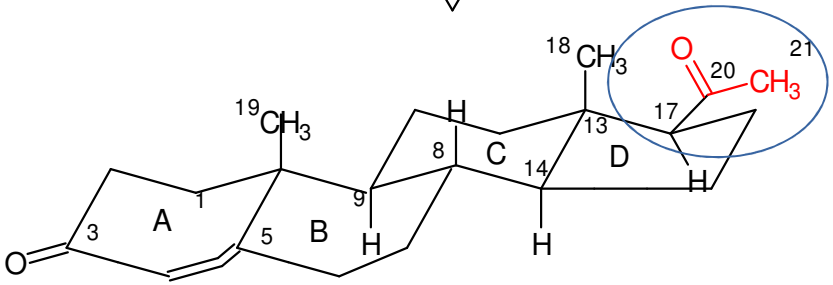


C_{19} C_{21}

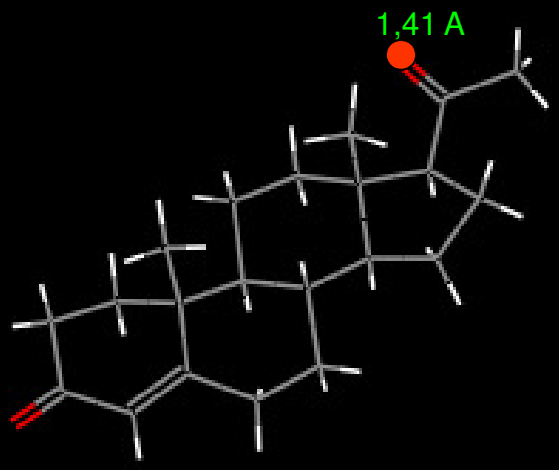
Testosterona — similaridade molecular — Progesterona

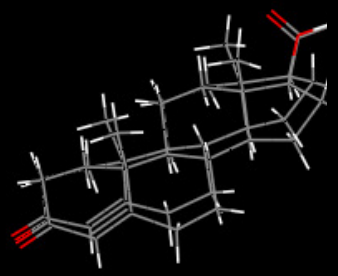


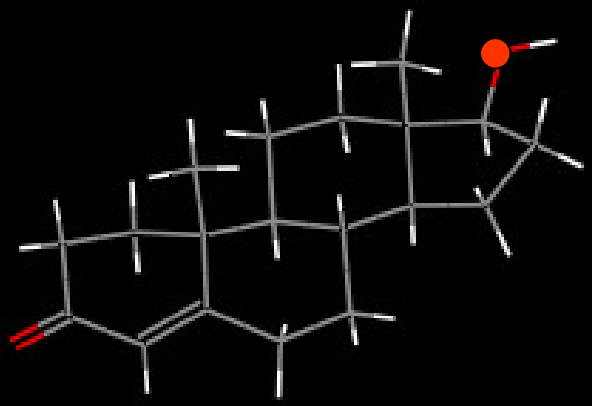
B/C C/D trans



B/C C/D trans

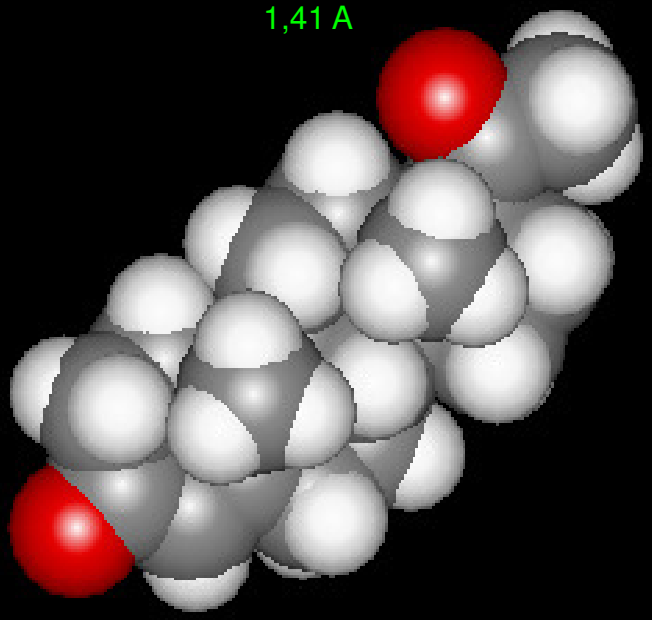


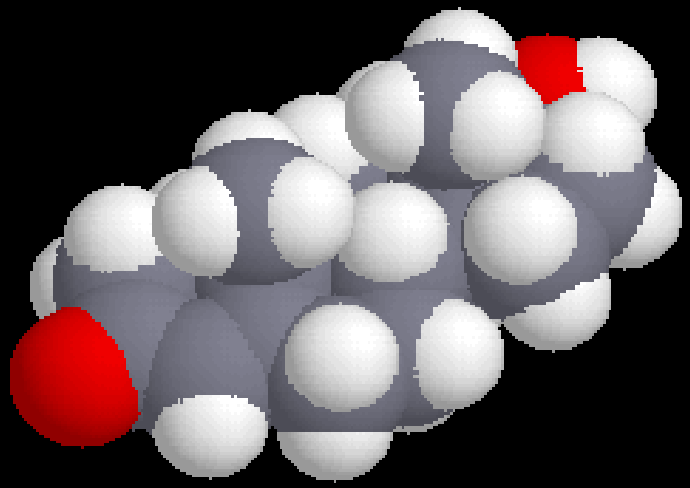




progesterona

testosterona



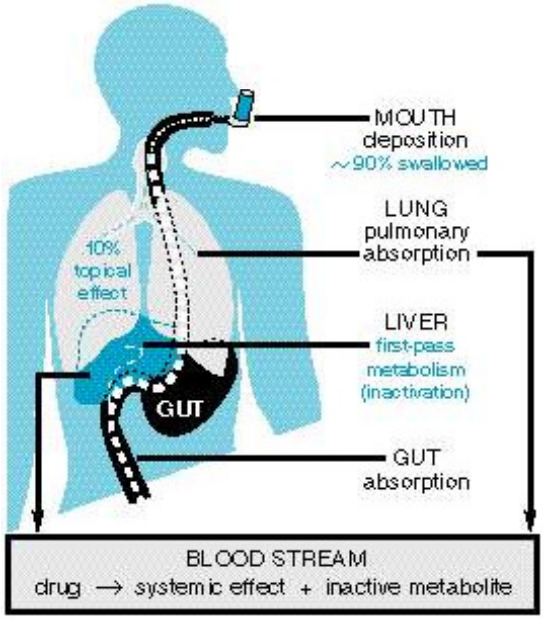


As *fases* da ação dos fármacos....

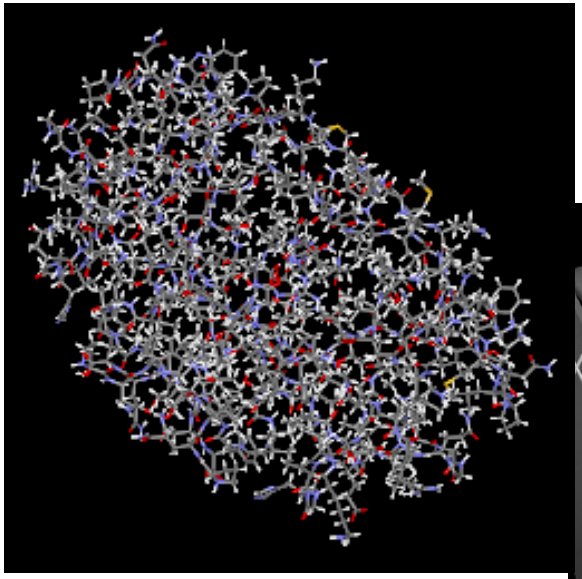
Fase farmacocinética

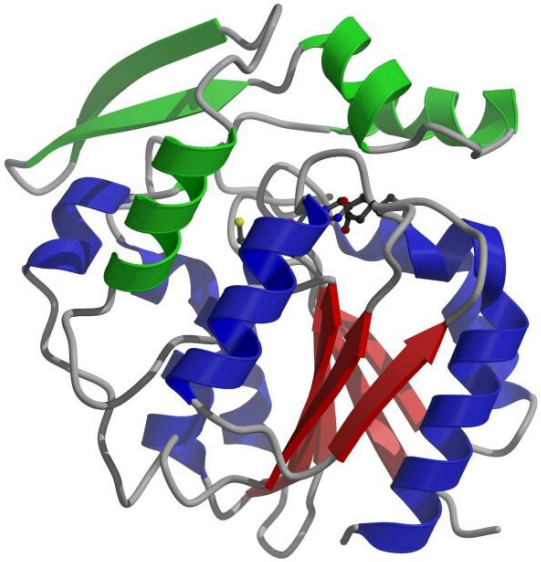
(PK)

Posologia

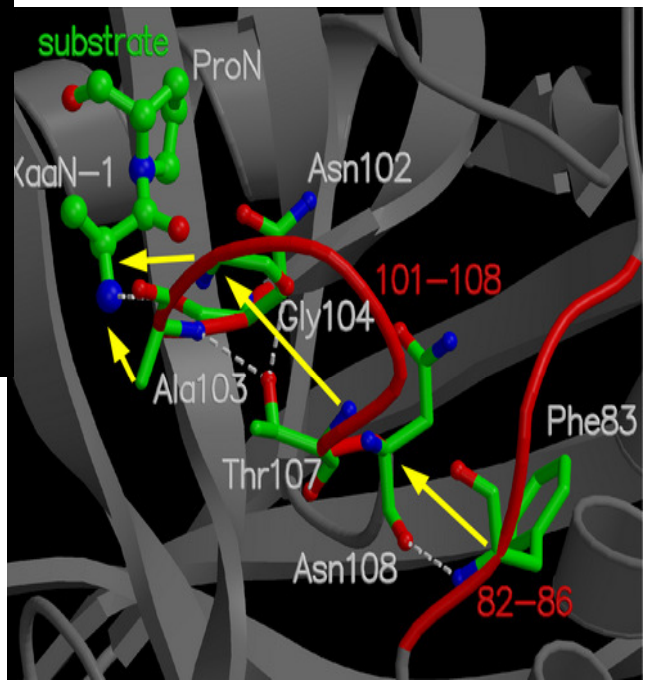


Biofase





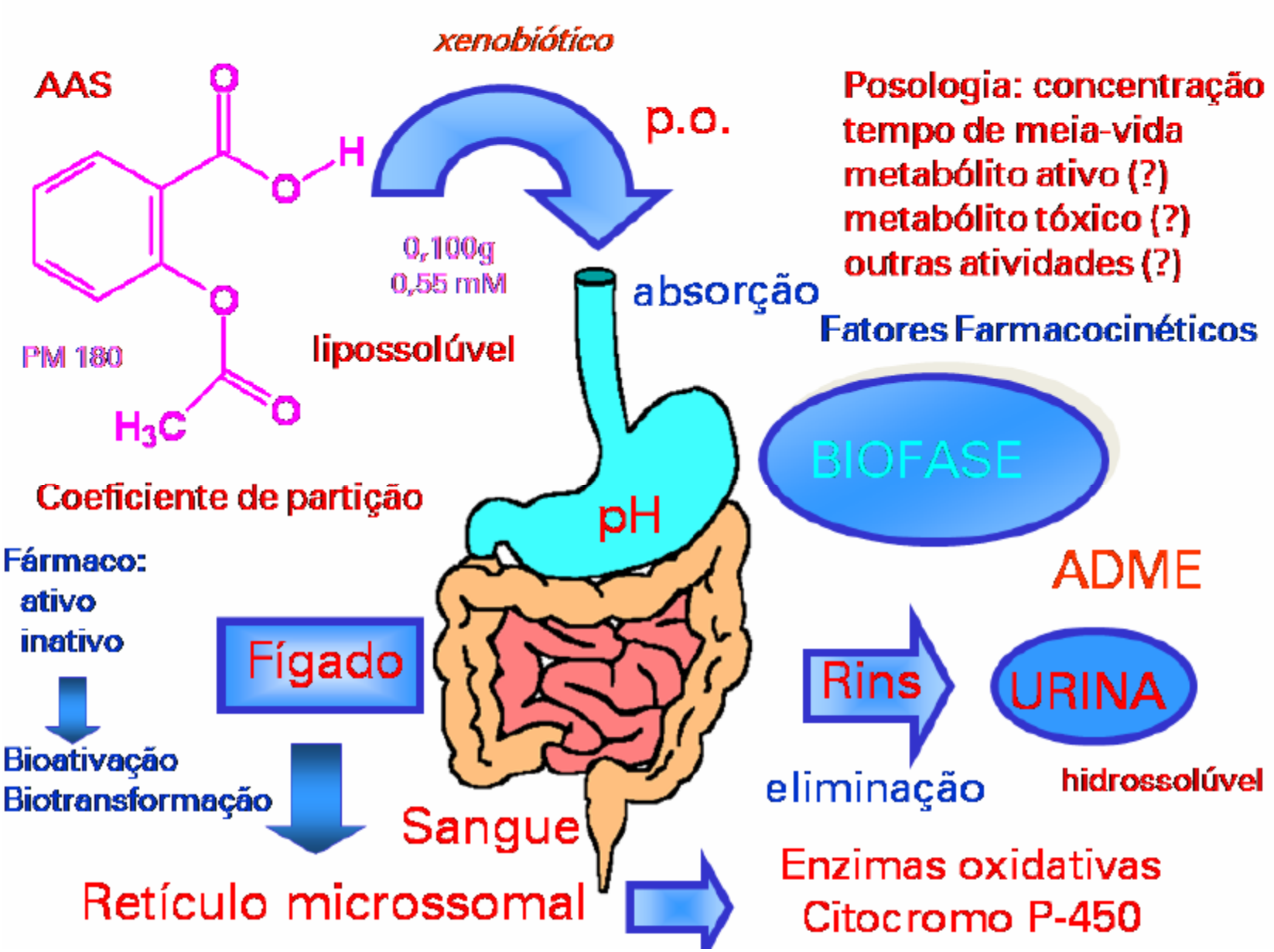
Biorreceptor

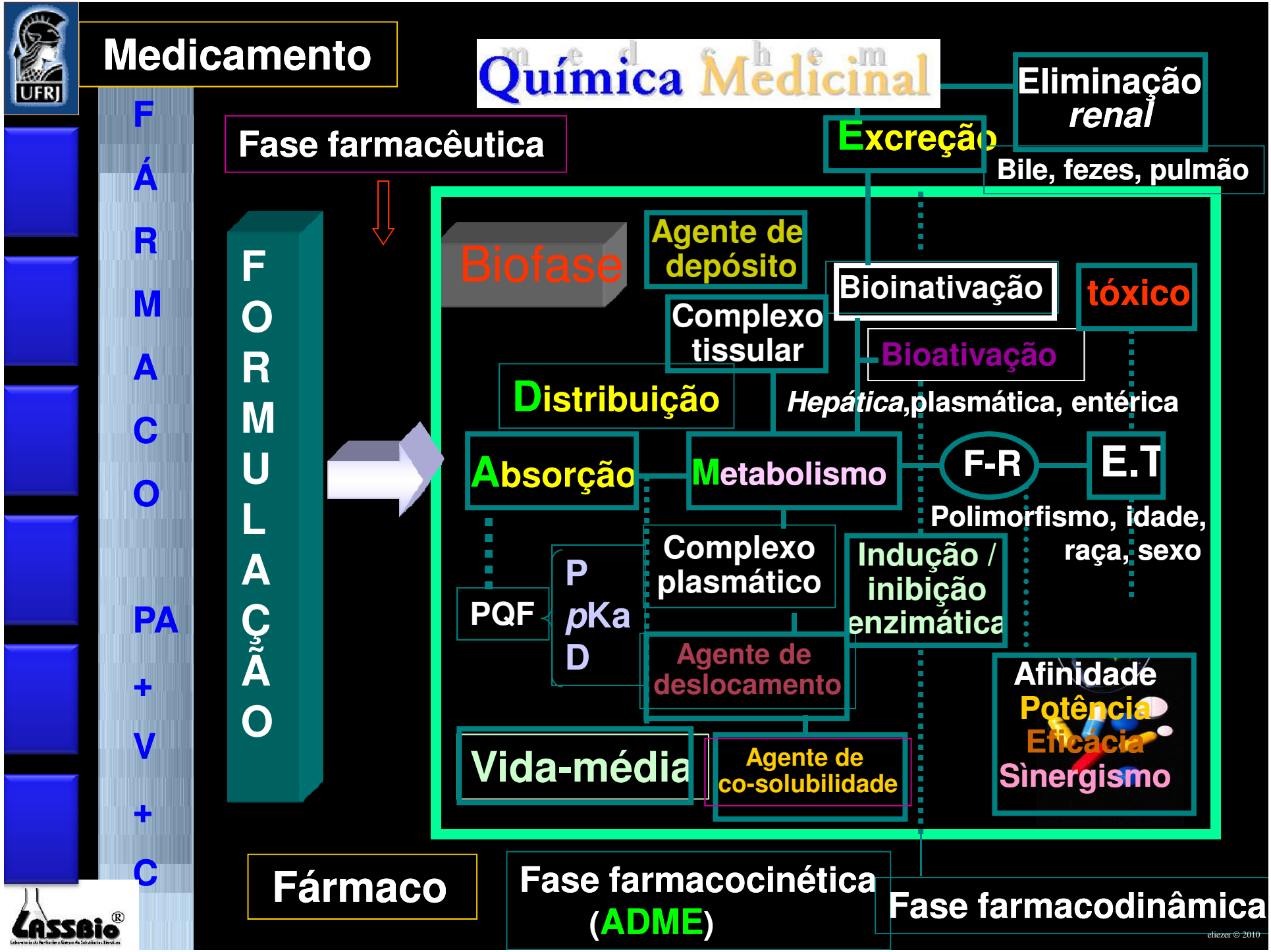


Efeito terapêutico

Fase farmacodinâmica

(PD)




Medicamento
FÁRMACO
PA + V + C
Química Medicinal
Fase farmacêutica
FORMULAÇÃO
Eliminação renal
Excreção
Bile, fezes, pulmão
Biofase
Agente de depósito
Bioinativação
tóxico
Complexo tissular
Bioativação
Distribuição
Hepática,plasmática, entérica
Absorção
Metabolismo
F-R
E.T
Polimorfismo, idade, raça, sexo
Complexo plasmático
Indução / inibição enzimática
PQF
P
pKa
D
Agente de deslocamento
Afinidade
Potência
Eficácia
Sinergismo
Vida-média
Agente de co-solubilidade
Fármaco
Fase farmacocinética (ADME)
Fase farmacodinâmica
LASSBio®
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Rato Transgênico Humanizado

Homology modeling of rat and human CYP 2D isoforms and computacional rationalization of experimental ligand-binding specifities, NPE Vermeulen *et al.*, *J. Med. Chem.* 2003, *46*, 74

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

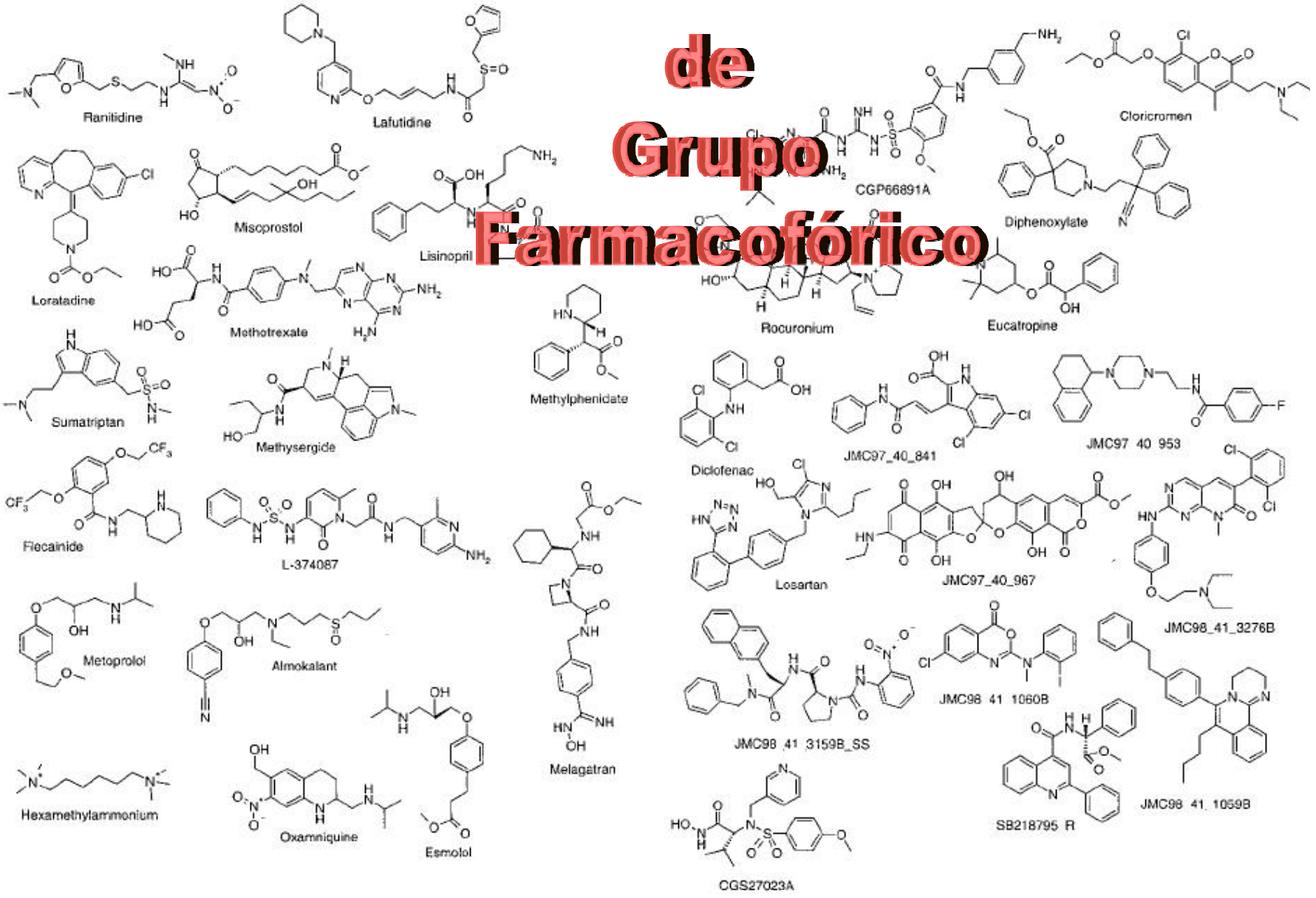
Animal transgênico com mPXR-, hPXR+ que possui mesmo perfil de resposta à ação de fármacos que humanos. Possui CYP 3A isoenzimas (xeno-sensor) que permite o estudo de interações de fármacos simulando o estudo em humanos.

(Adaptado de Hugo Kubinyi 2002)

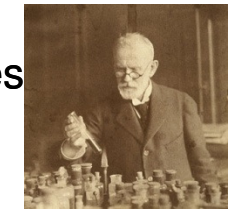
Conceito de Grupamento Farmacofórico

Química Medicinal

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).

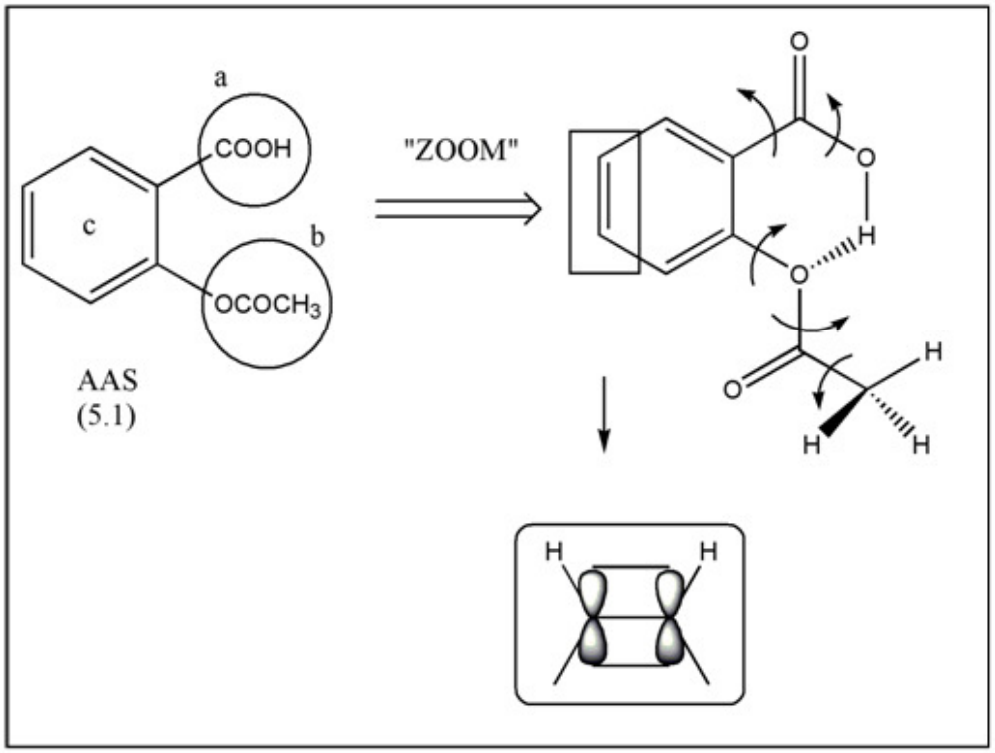
Barreiro & Fraga:

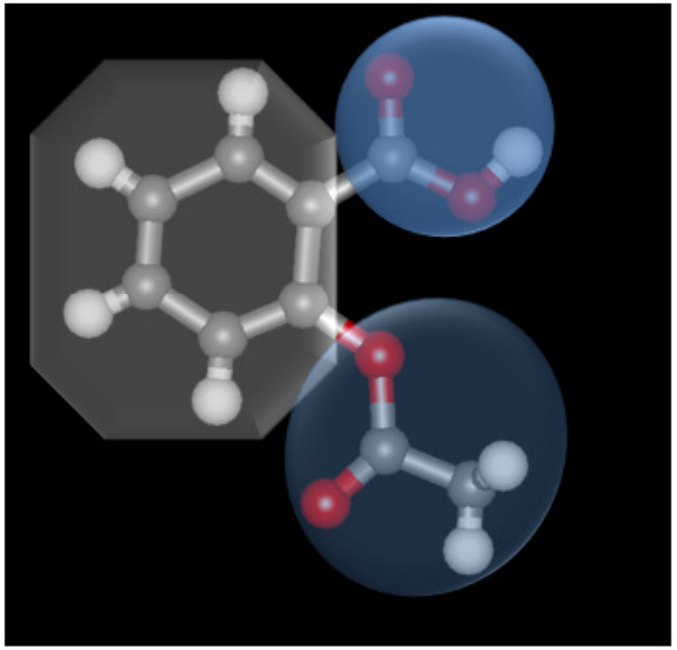
É o conjunto de características eletrônicas e estéricas que caracterizam um ou mais grupos funcionais ou subunidades estruturais, necessários ao melhor reconhecimento molecular pelo receptor e, portanto, para o efeito farmacológico desejado.

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.

A identificação do *grupo farmacofórico*

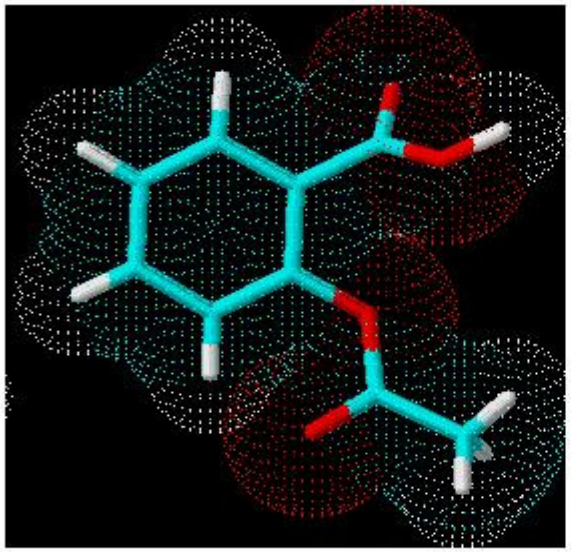


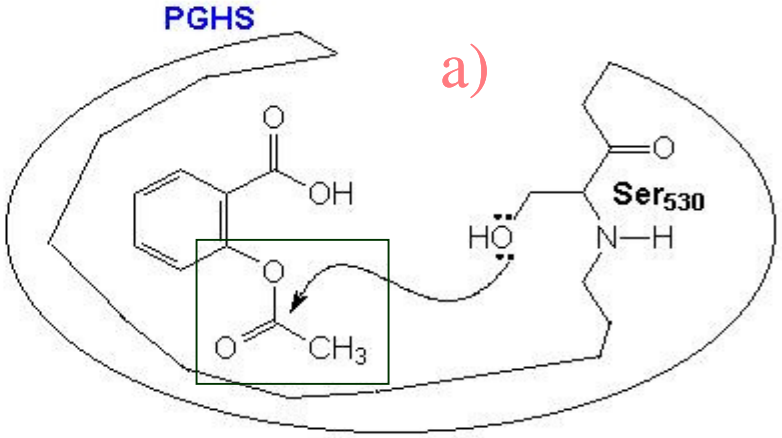


tática de dissecação molecular

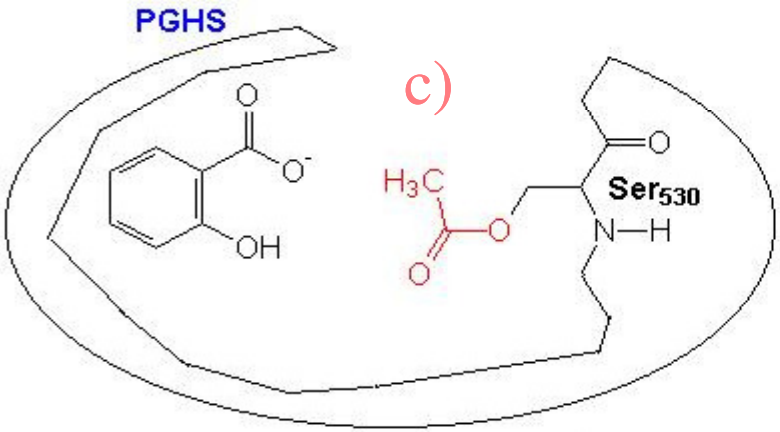
Mecanismo molecular

AAS

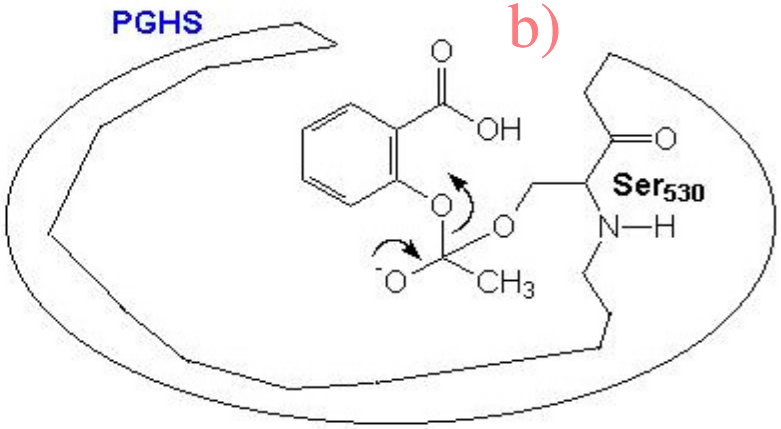


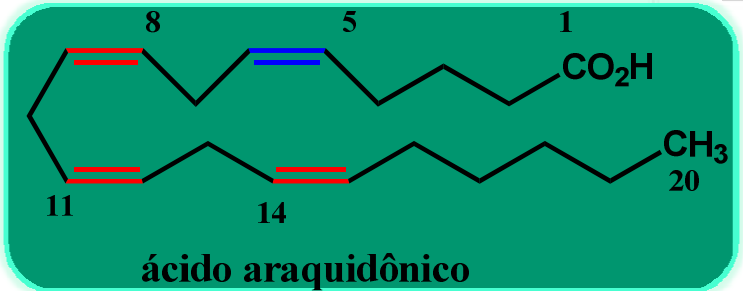


Grupamento farmacofórico



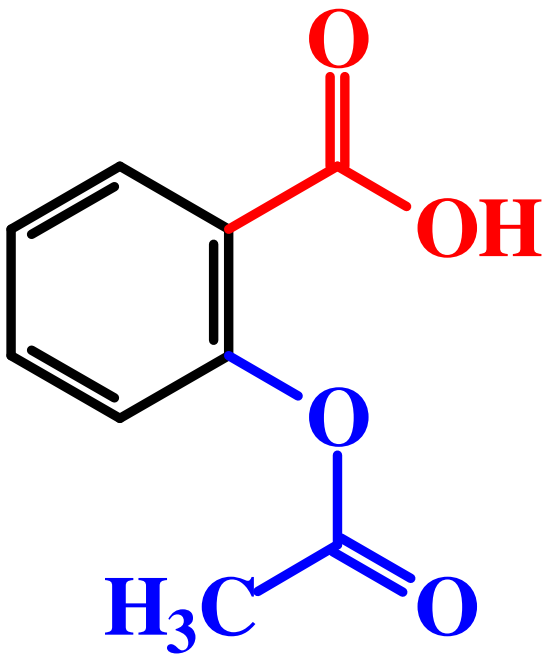
Inibição *pseudo*-irreversível





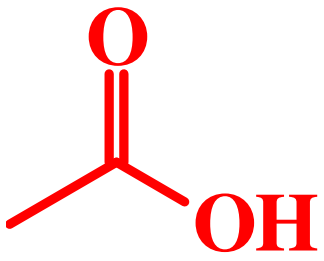
ácido araquidônico

Conceito de Grupo Auxofórico



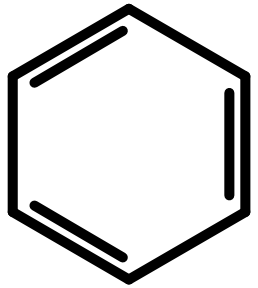
Ácido acetilsalicílico

Auxofórico



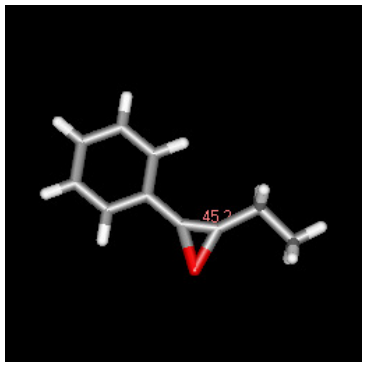
ácido carboxílico

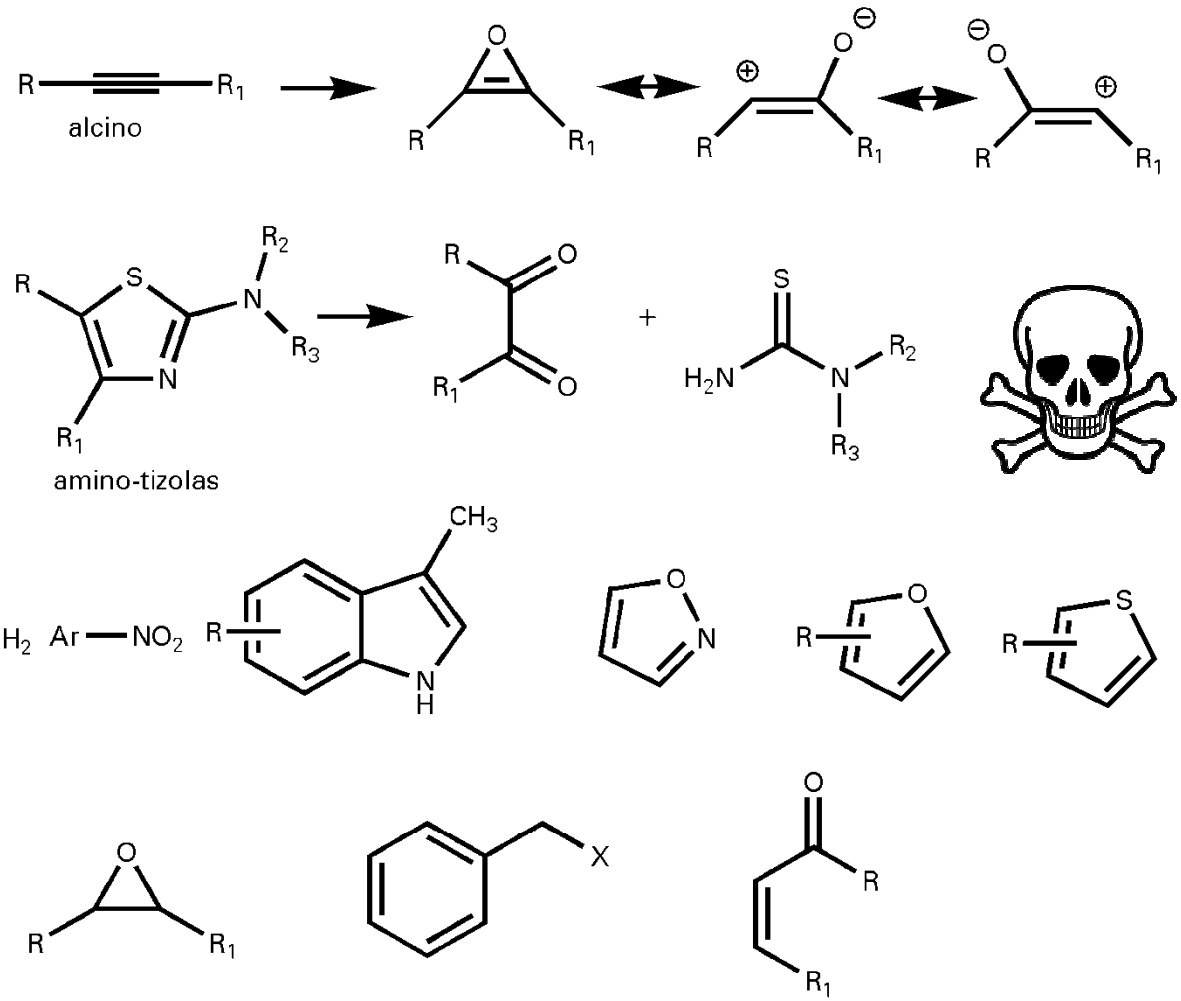
Auxofórico



fenila

Conceito de Grupo Toxicofórico





R, R_1, R_2, R_3= H, alquila, cicloalquila, arila, heteroarila
X= grupo abandonador