Planejamento de Fármacos

2ª Semana de Química
Instituto de Química – UFU
21 e 22 de julho de 2014

Curso 1

Eliezer J. Barreiro

Professor Titular

http://lattes.cnpq.br/5942068988379022

Universidade Federal do Rio de Janeiro

Laboratório de Avaliação e Síntese de Substâncias Bioativas

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

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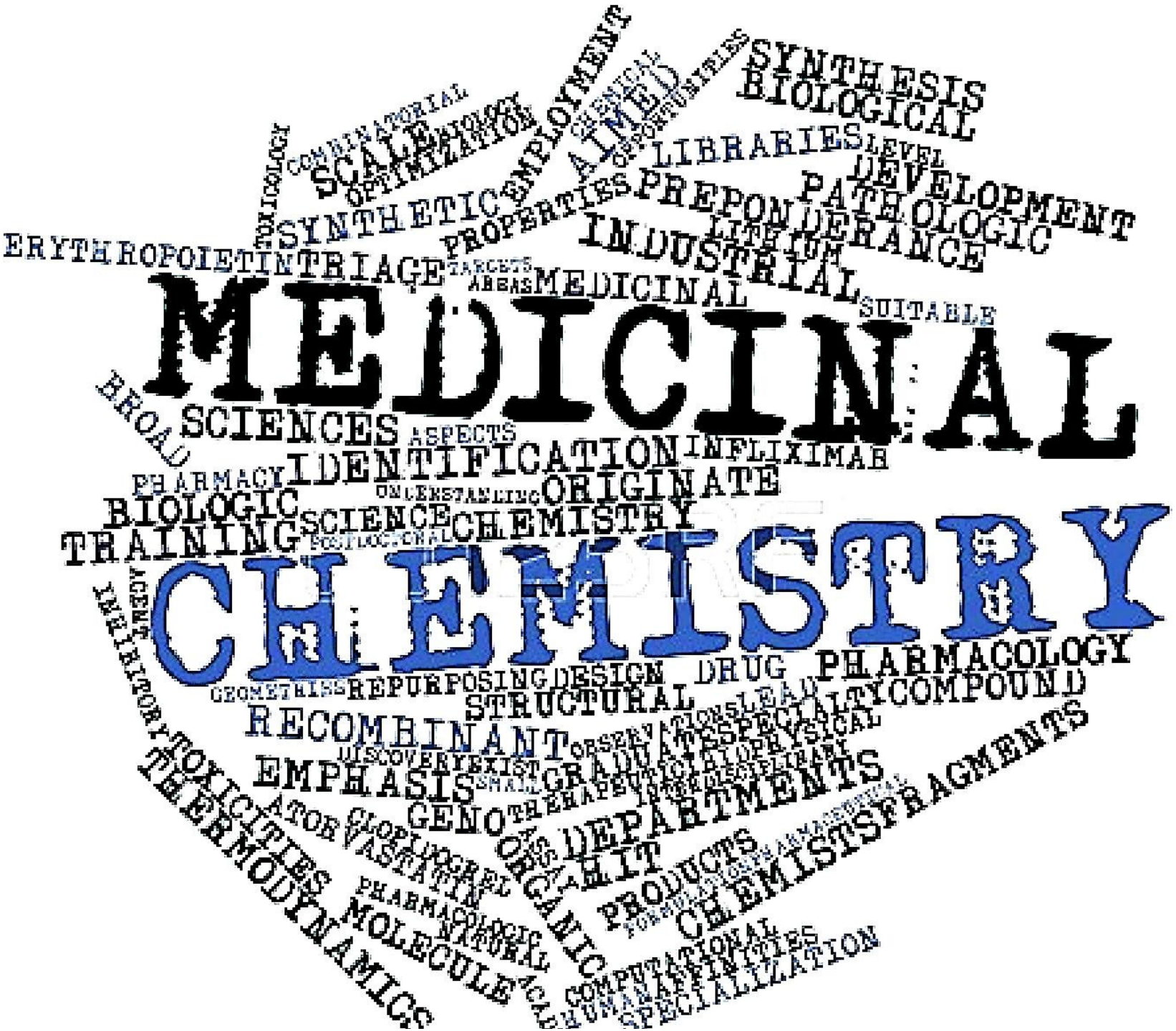


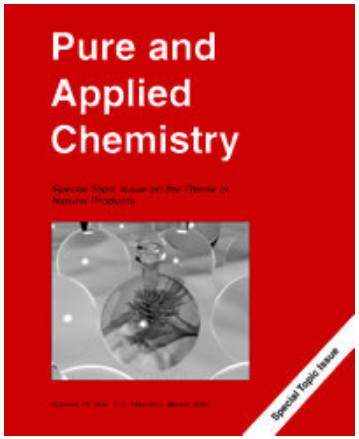
“ ...medicinal chemists today live in exciting times... their work can have a beneficial effect on millions of suffering patients – surely an important motivating factor for any scientist...”

Joseph G. Lombardino

The Role of the Medicinal Chemist in Drug Discovery – Then and Now,

Nature Rev. Drug Disc. 2004, **3**, 853.

IUPAC - Subcommittee Medicinal Chemistry & Drug Development



Definição: **Química Medicinal** é a *disciplina* que estuda os aspectos relacionados à *descoberta* ou *invenção* dos fármacos, os aspectos moleculares envolvidos em seu mecanismo de ação e aqueles que governam a *absorção*, *distribuição*, *metabolismo*, *eliminação* *toxicidade* (ADMET), incluindo a compreensão da relação entre a estrutura química e a atividade terapêutica (REA ou SAR).

Química Medicinal

IUPAC

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

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

International Union of Pure and Applied Chemistry
Chemistry and Human Health Division
Medicinal Chemistry Section

GLOSSARY OF TERMS USED IN MEDICINAL CHEMISTRY

(IUPAC Recommendations 1998)

Prepared for publication by C.G. Wermuth[1] (Chairman), C.R. Ganellin[2], P. Lindberg[3] and L.A. Mitscher[4]

[1]Faculté de Pharmacie, Université Louis Pasteur, Strasbourg (France),
[2]University College London, London (U.K.)
[3]Astra Hässle AB, Mölndal (Sweden)
[4]School of Pharmacy, University of Kansas, Lawrence (Kansas, USA)

http://www.chem.qmul.ac.uk/iupac/medchem/
World Wide Web version prepared by Gerard P. Moss
Department of Chemistry, Queen Mary University of London,
Mile End Road, London, E1 4NS, UK

Pure Appl. Chem., Vol. 85, No. 8, pp. 1725–1758, 2013.
http://dx.doi.org/10.1351/PAC-REC-12-11-23

Glossary of terms used in medicinal chemistry. Part II (IUPAC Recommendations 2013)*

Derek R. Buckle[1,‡], Paul W. Erhardt[2], C. Robin Ganellin[3], Toshi Kobayashi[4], Thomas J. Perun[5], John Proudfoot[6], and Joerg Senn-Bilfinger[7]

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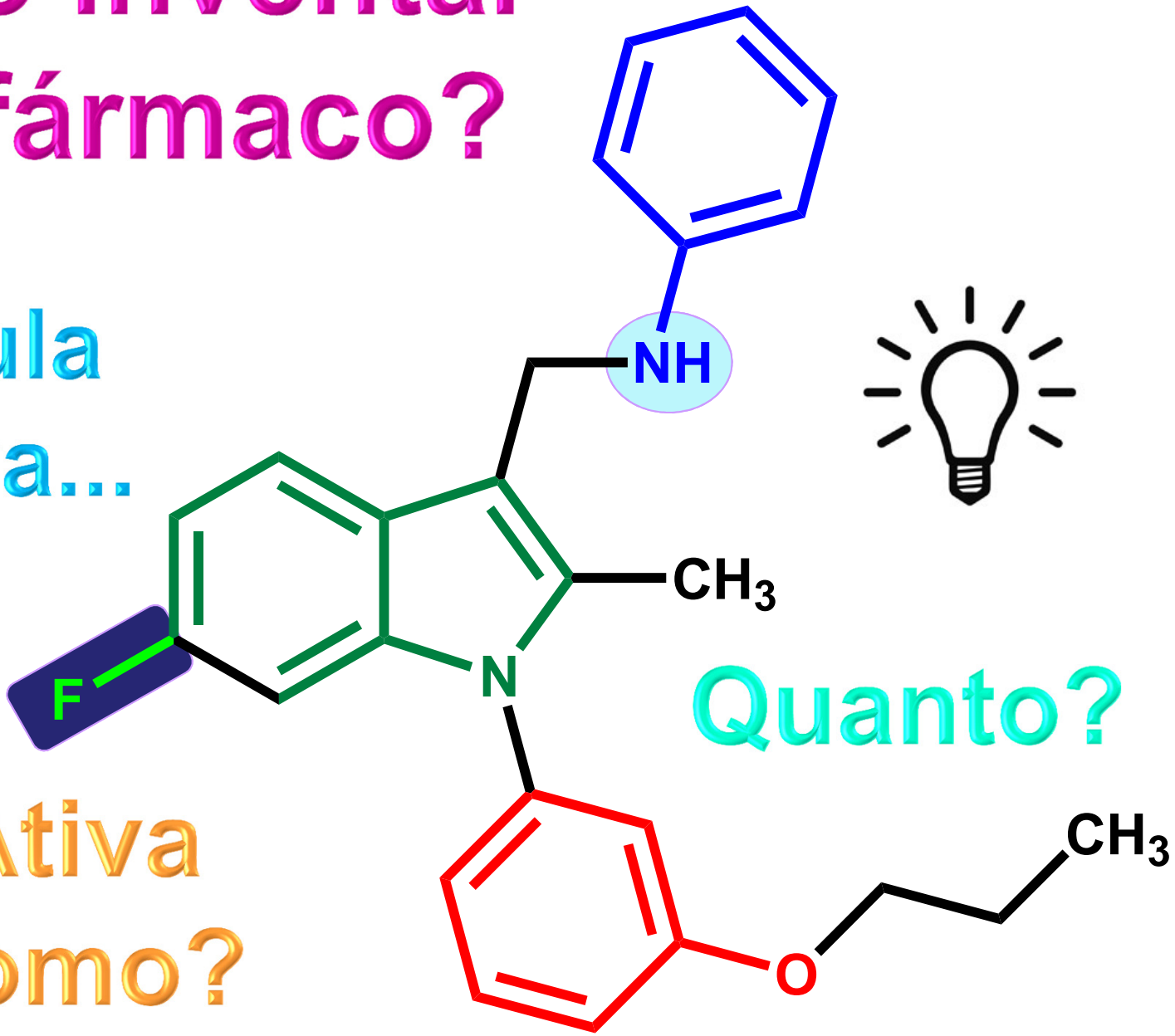
Como inventar um fármaco?

Molécula bioativa...



Quanto?

Ativa como?

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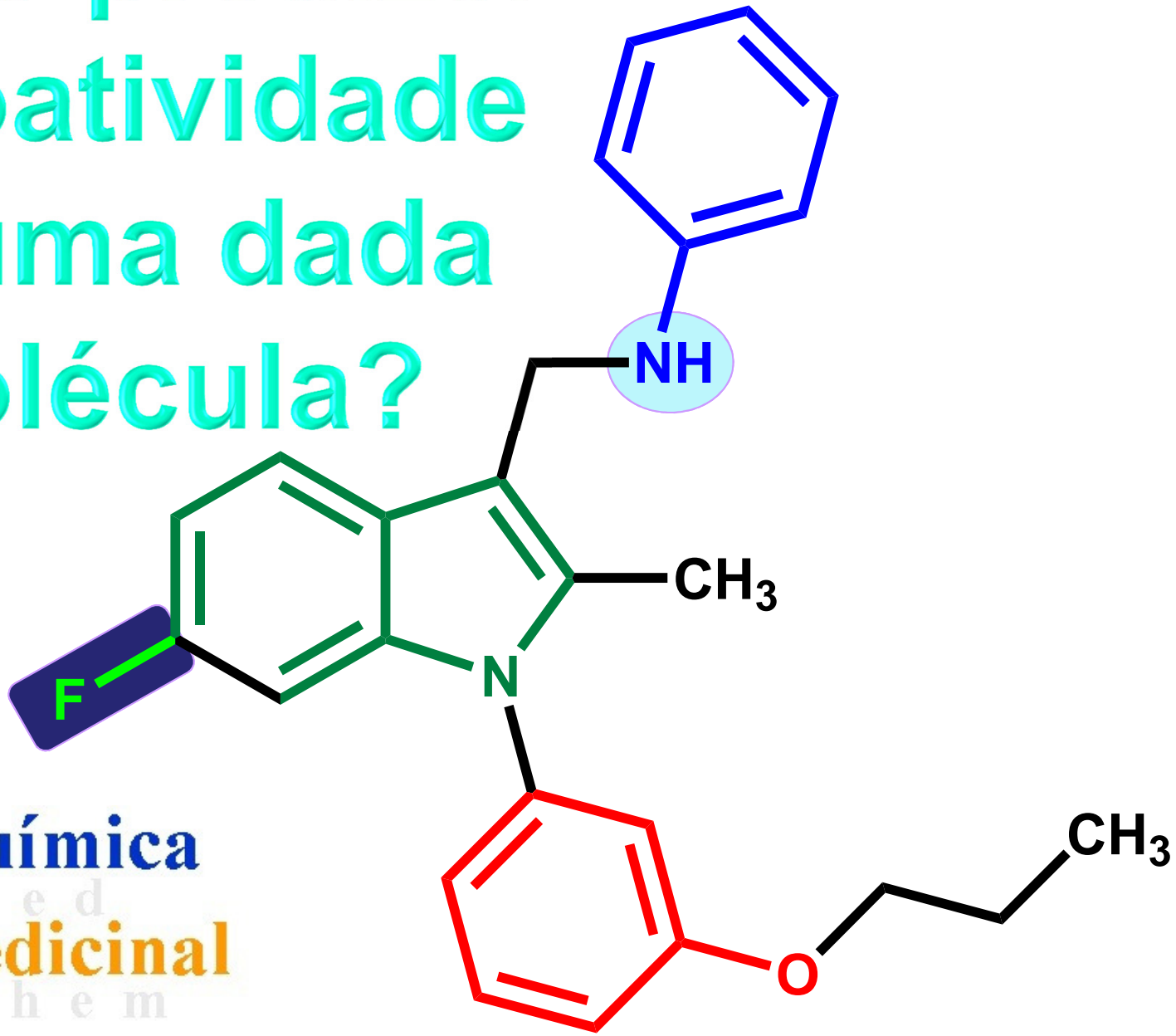
Como predizer a bioatividade de uma dada molécula?



Química
med
Medicinal
chem

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"A ciência é feita de fatos,
assim como as casas são feitas de pedras;
mas uma mera coleção de fatos não é
ciência, assim como uma pilha
de pedras, não é uma casa."

Jules Henri Poincaré

(1854-1912)

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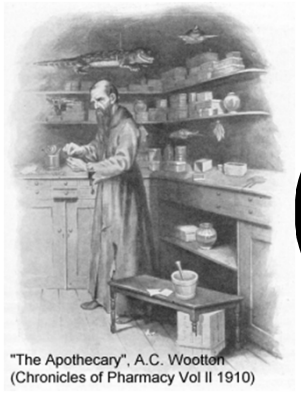
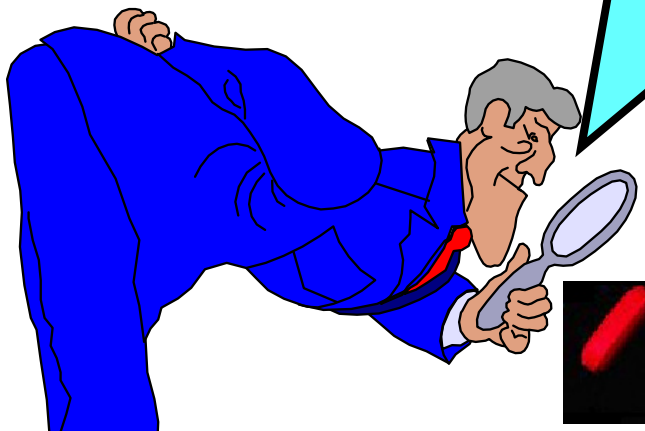
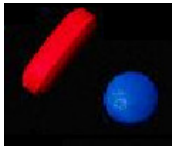
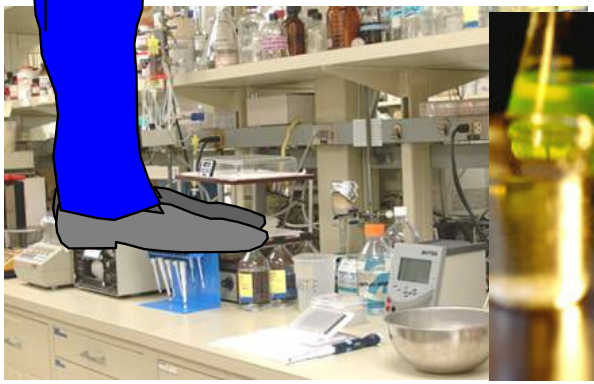
Química Medicinal

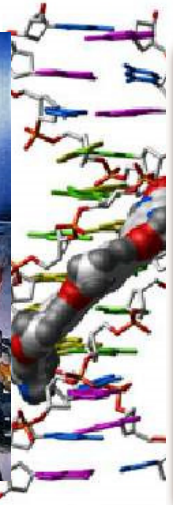

"The Apothecary", A.C. Wootton
(Chronicles of Pharmacy Vol II 1910)

Como nascem os fármacos?









Química Medicinal

O que é um 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 fisíco-químicas críticas para a atividade do fármaco por via oral: solubilidade, boa partição passiva membrana/água, pêso 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

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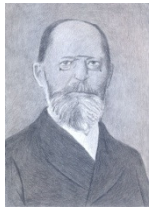
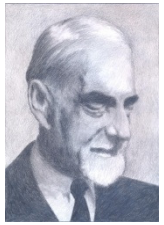
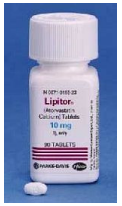
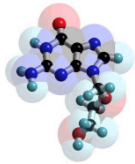
Química Medicinal

med chem









Fischer

Salvarsan^{R}

Dale

Fourneau

penicilina

Fleming

Vinca

indometacina

Valium^{R}

cimetidina

lovastatina

aciclovir

Elion

Black

imatinibe

1902 1907 1910 1911 1941 1945 1955 1962 1963 1975 1980 1981 1988 2000

1960

1889 1908 1935 1948 1949 1959 1964 1977 1982 1999

AAS

Ehrlich

Domagk

Ahlquist

cortisona

Kornberg

talidomida

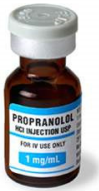
Librium^{R}

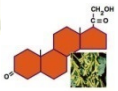
propranolol

captopril

Vane

celecoxibe





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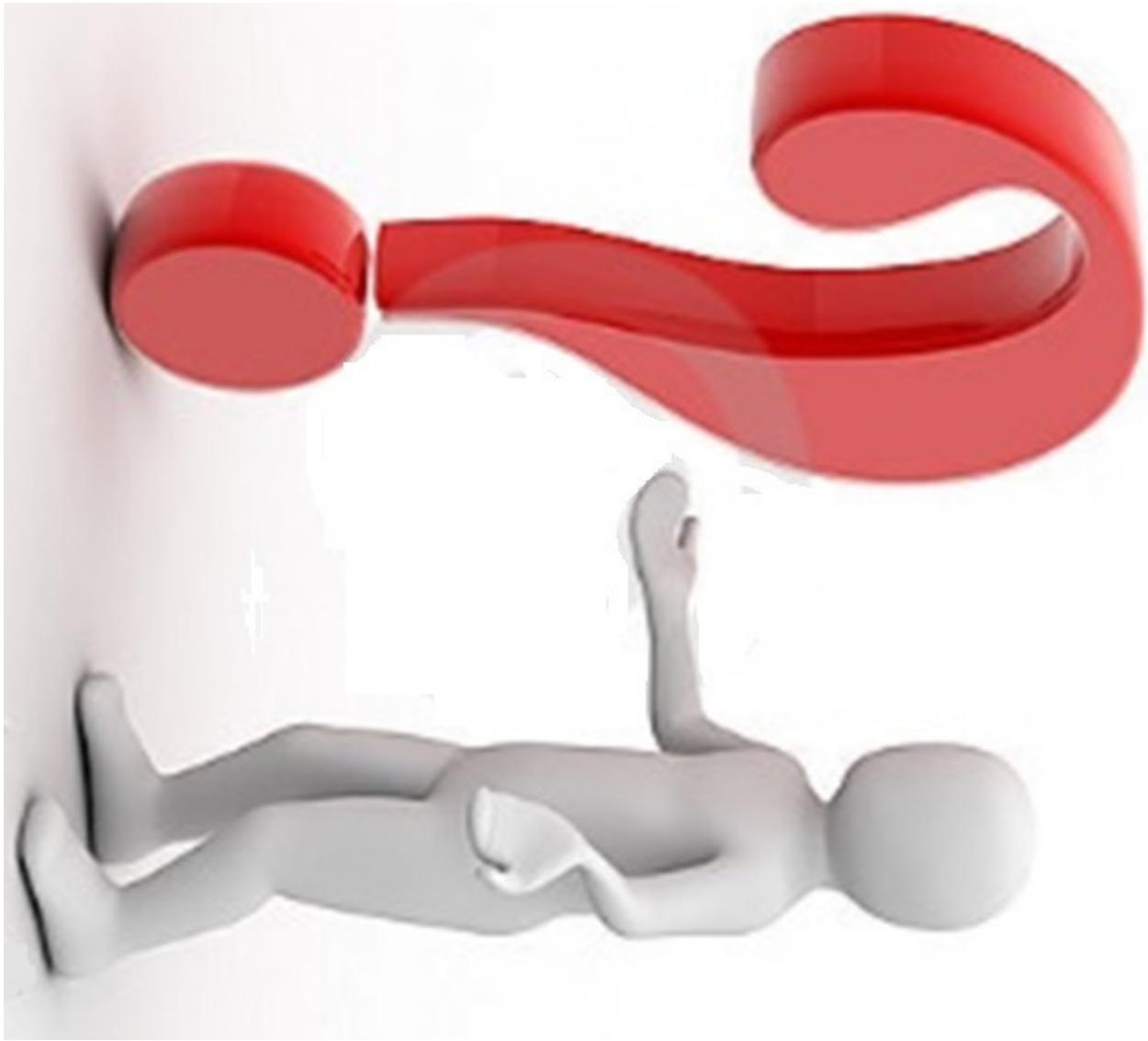

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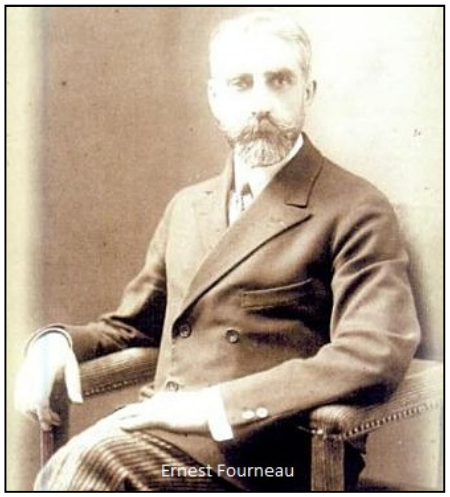
Os pioneiros

Química Medicinal

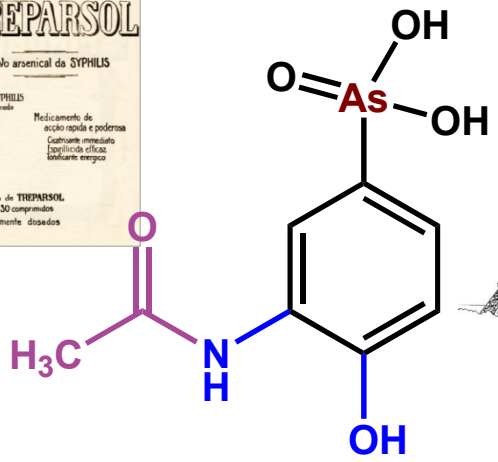
O *berço* da Química Medicinal



Ernest Fourneau
1872-1949

Stovarsol

CAS 97-44-9



Institut Pasteur (1887)

1911- Laboratoire de Chimie Thérapeutique

Institut Pasteur (Emile Roux)

1911-1944 – Jacques Tréfouël (1897-1977)
Théreze Tréfouël (1892-1978)
Germaine Benoit (1901-1983)
Federico Nitti (1903-1947)

Daniel Bovet
1907-1992 *

*Farmacêutico suiço
Doutor *h.c.* UFRJ

Prêmio Nobel de Fisiologia/Medicina 1957

Sulfonamidas, anti-histamínicos. Curare: SAR

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

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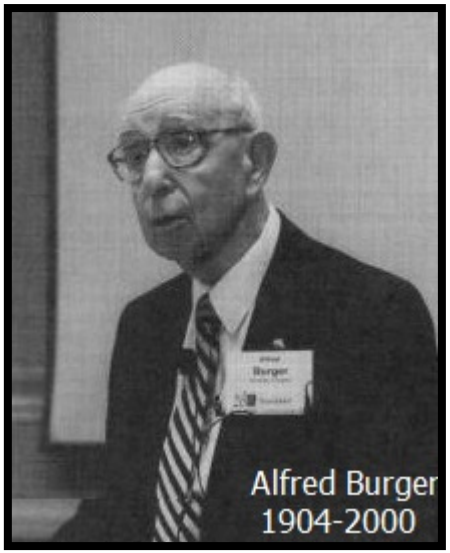


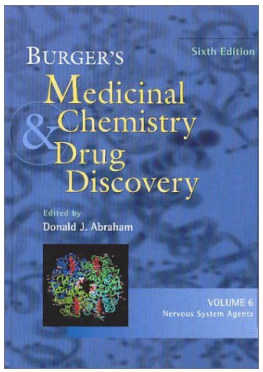
Química Medicinal

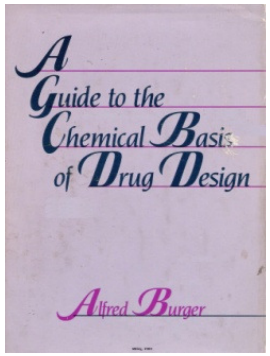
Prof. Alfred Burger

(1904-2000)

University of Virginia

EUA





II = 5,207

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 (1962)

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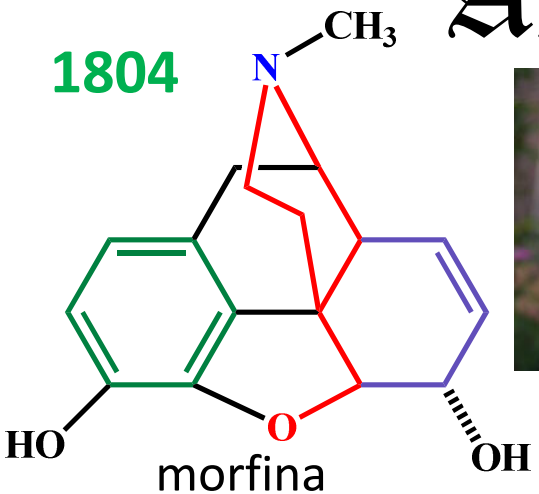
As moléculas pioneiras...

Química Medicinal

As moléculas pioneiras...

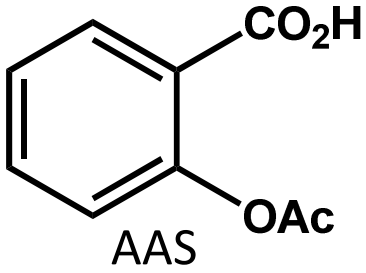
1804



morfina

$C_{17}H_{19}NO_3$

1897



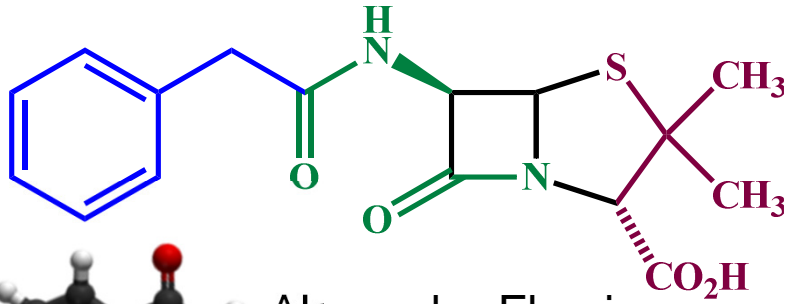
AAS

$C_9H_8O_4$

1929

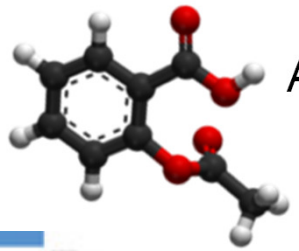
penicilina

$C_{16}H_{18}N_2O_4S$



Felix Hoffman

1868- 1946



Alexander Fleming

1881-1955

Nobel 1945

Library of Congress

Friedrich W. A. Sertürner

1783- 1841

Sir Robert Robinson

1886-1975

Nobel 1947

Produtos Naturais Vegetais: **Alcalóides**

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Alcalóides fenantrênicos e benzilisoquinolínicos (papaverina 0,2%)

Papaver somniferum

1493-1541 - Marco Polo (Oriente) ⇒ Ópio

1805 (1817) ⇒ Friedrich W A Sertürner

farmacêutico, isola a morfina

1853 – Henry How, Un Glasgow ⇒ sal 4ario

1924 – Diidromorfinona ⇒ Dilaudid^{R} (Knoll)

1925 – *Sir* Robert Robinson  **1947)**

1827 - Merck (Darmstadt, Alemanha)

1952 – M D Gates - primeira síntese total

1954 - Beckett & Casey, Un. London

1973 – C Pert & S Snyder, Un John Hopkins ⇒ receptores δ, κ, μ SNC (F. Chast, The Practice of Medicinal Chemistry, CG Wermuth Ed.)

morfina

tolerância & dependência química;

Derivados 4-fenilpiperidinícos

morfina

PM = 285.1

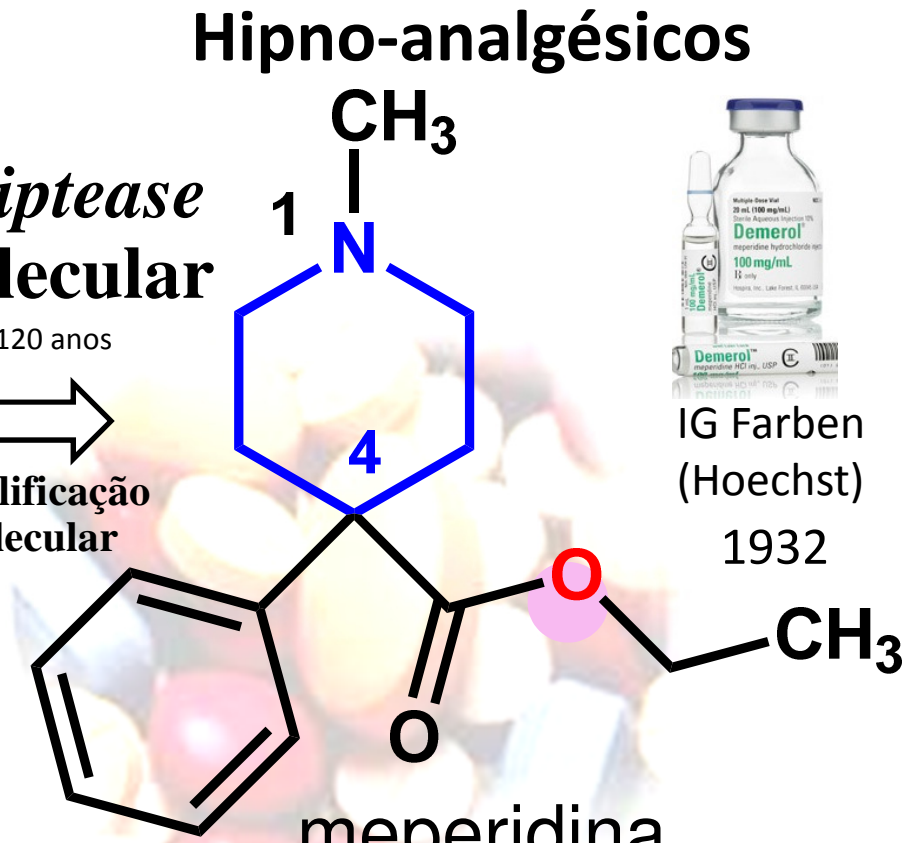
$C_{17}H_{19}NO_3$

Striptease molecular

ca. 120 anos

Simplificação molecular

Hipno-analgésicos



meperidina

μ-receptor

PM = 247.3

$C_{15}H_{21}NO_2$

IG Farben (Hoechst)

1932

petidina Dolantina^R

Metadona (Dolophine^R)

1947

Domesticando produtos naturais

EJ Barreiro, *Quim. Nova* **1990**, *13*, 29

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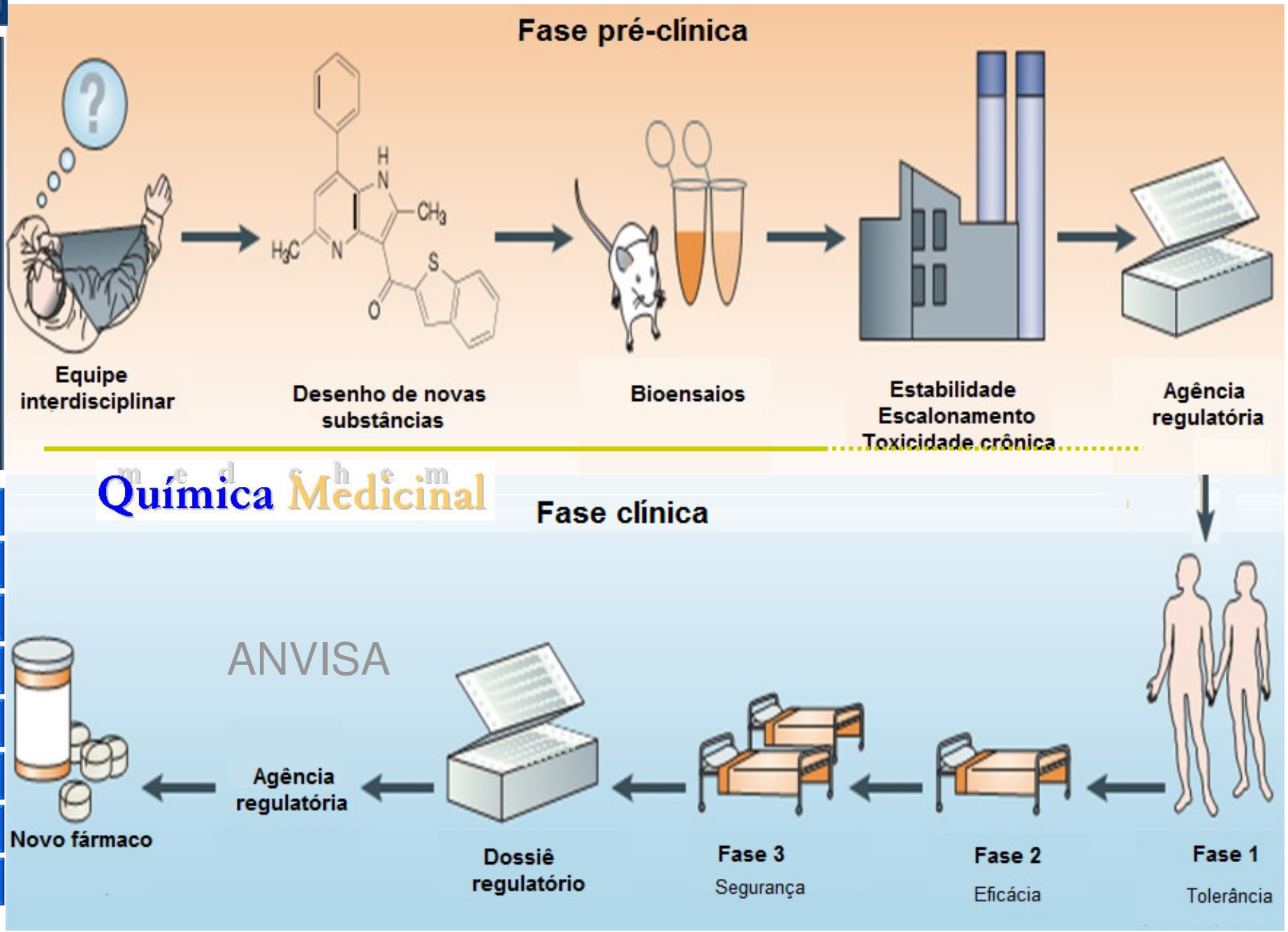
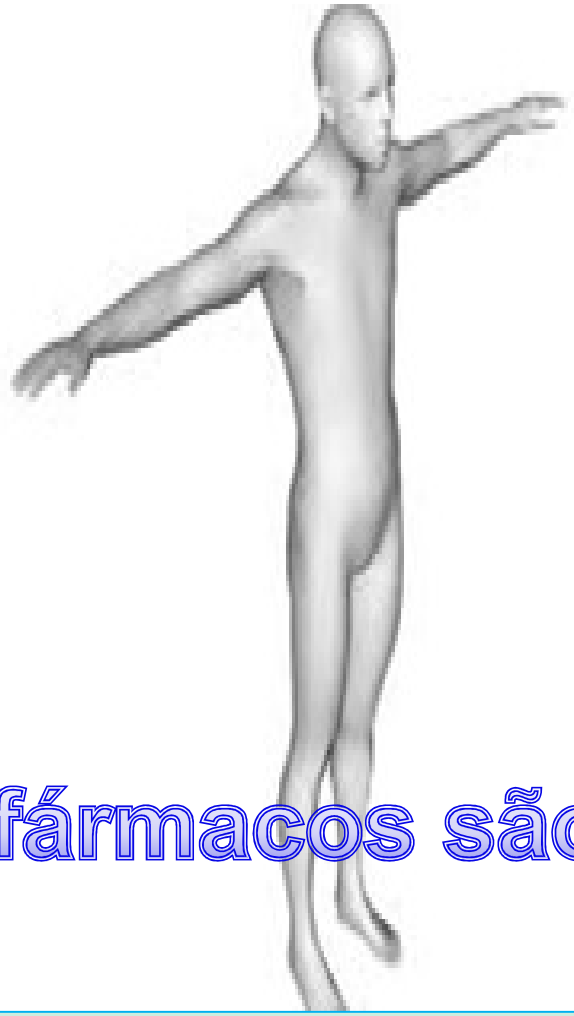
O processo de invenção de fármacos

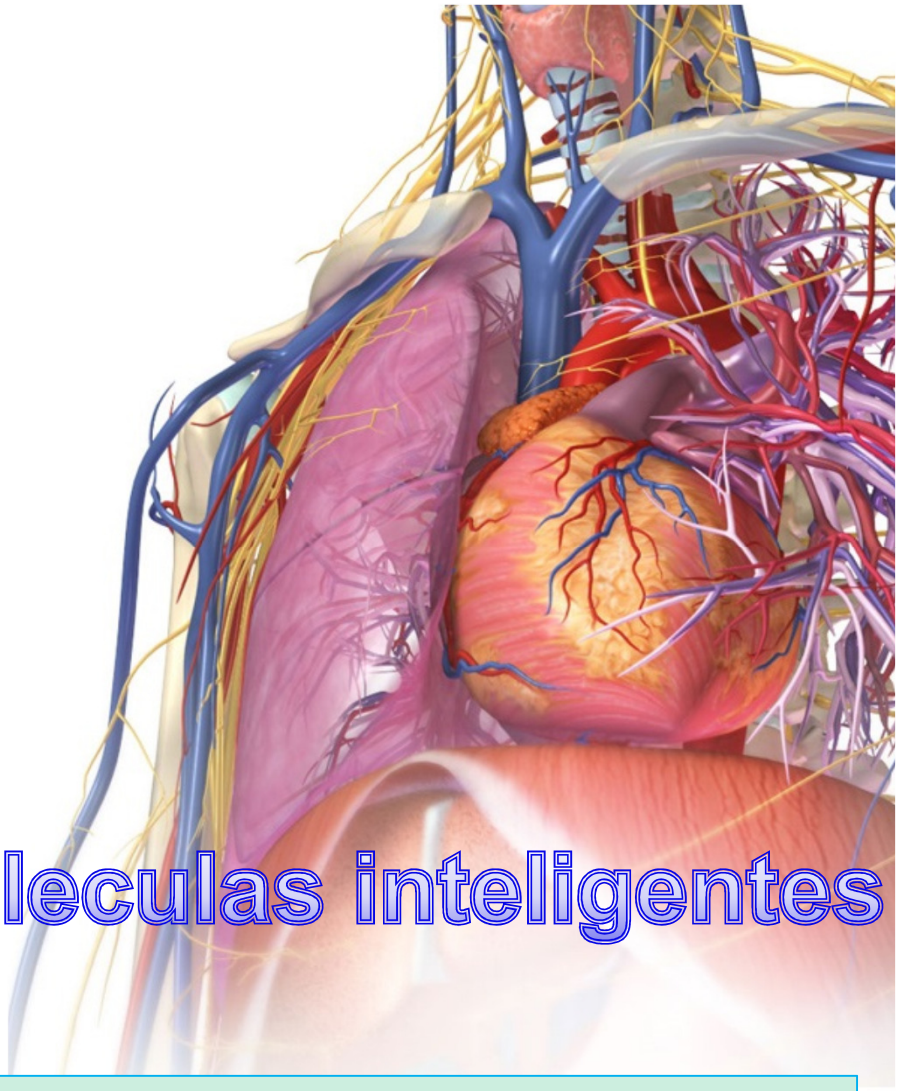
Química Medicinal

O processo da descoberta de novo fármaco



A complexidade da fisiologia...





Os fármacos são moleculas inteligentes

Os medicamentos foram uma das maiores invenções do século 20

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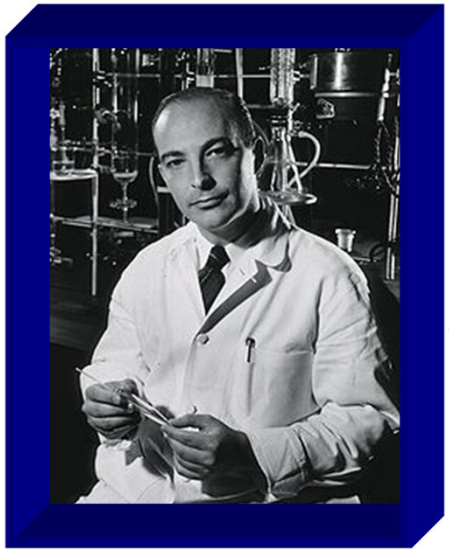


Arthur Kornberg
1918-2007

Prêmio Nobel, 1959

1987

The Two Cultures: Chemistry and Biology[1]

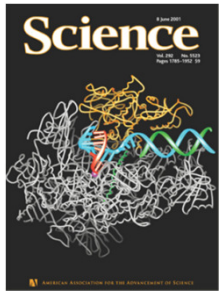
Arthur Kornberg

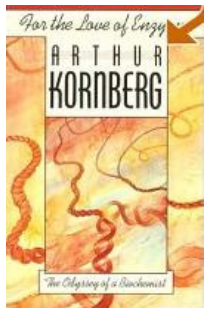
Department of Biochemistry, Stanford University, Stanford, California 94305

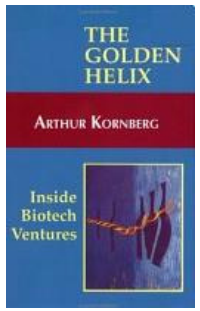
Received July 14, 1987

"Much of life can be understood in rational terms if expressed in the language of chemistry... the historical roots of chemistry and biology are intertwined in many places…

Pharmaceutical chemistry was until recently the bastion of organic chemistry… in the search for alternative or superior drugs for the treatment of various diseases..."







Química Medicinal

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

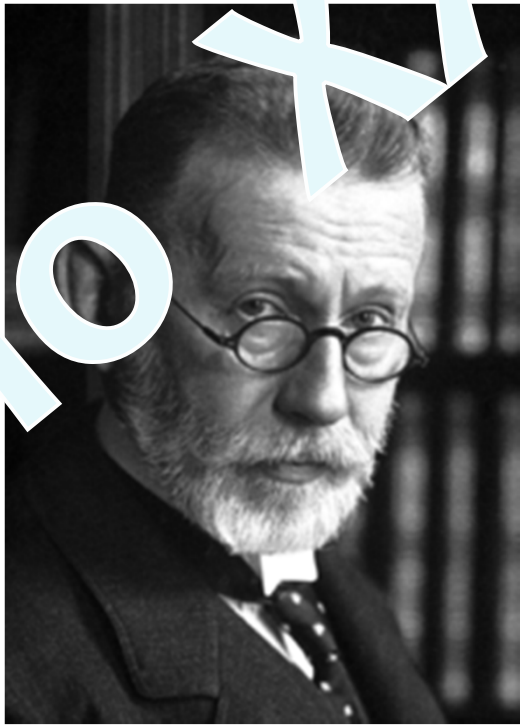
O Paradigma de Ehrlich-Fischer

Emil Fischer
1852-1919

The Nobel Prize in Chemistry 1902

LOCK & KEY CONCEPT

The Nobel Prize in Physiology or Medicine 1908



The Magic Bullet Theory

Paul Ehrlich
1854-1915

Blog com histórias & fofocas sobre fármacos

De fármacos e suas descobertas

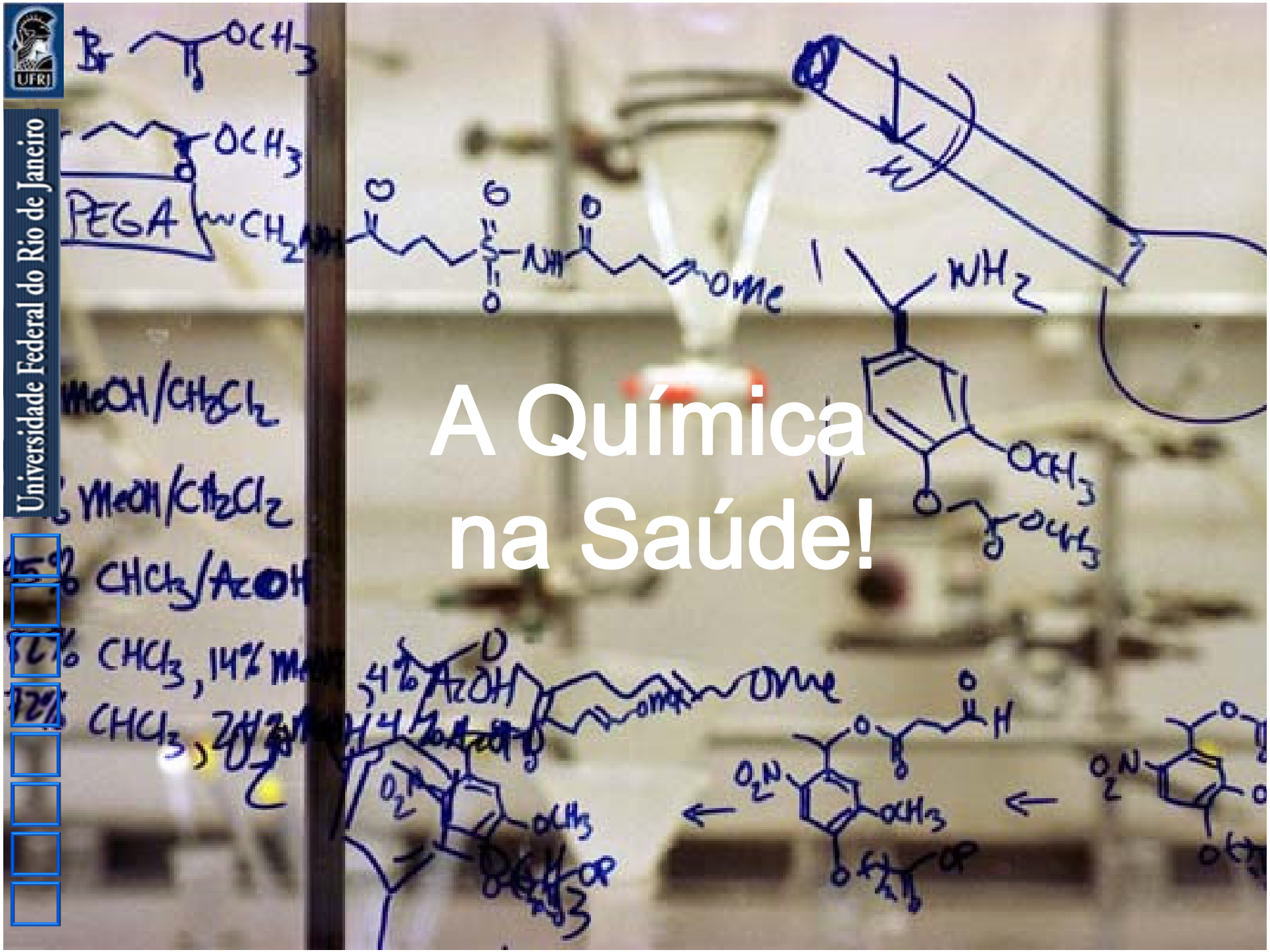
Pretende-se tratar de temas, opiniões, comentários sobre a Ciência dos Fármacos, seu uso seguro e benefícios. História da descoberta/invenção de fármacos e aspectos da formação qualificada de universitários e pós-graduandos nas Ciências dos Fármacos também são de interesse.

segunda-feira, 16 de junho de 2014

O Paradigma de Fischer-Ehrlich ou os fármacos e o prêmio Nobel

Por exemplo, dos 555 prêmios Nobel concedidos até hoje, muitos da área da Química, foram agraciados por trabalhos que viabilizaram a descoberta/invenção de fármacos inovadores, seja na área da química orgânica propriamente dita ou da síntese orgânica, como Adolf O. R. Windaus (1928), Robert Robinson (1947), Linus Pauling (1954), Dorothy Hodgkin (1964), Robert B. Woodward (1965), Donald J. Cram, Jean-Marie Lehn e Charles J. Pedersen (1987), Elias J. Corey (1990), William S. Knowles, Ryōji Noyori e K. Barry Sharpless (2001), Richard F. Heck, Ei-ichi Negishi e Akira Suzuki (2010) ou da química computacional Martin Karplus, Michael Levitt e Arieh Warshel (2013).

www.ejb-eliezer.blogspot.com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UFRJ
PEGA
A Química
na Saúde!

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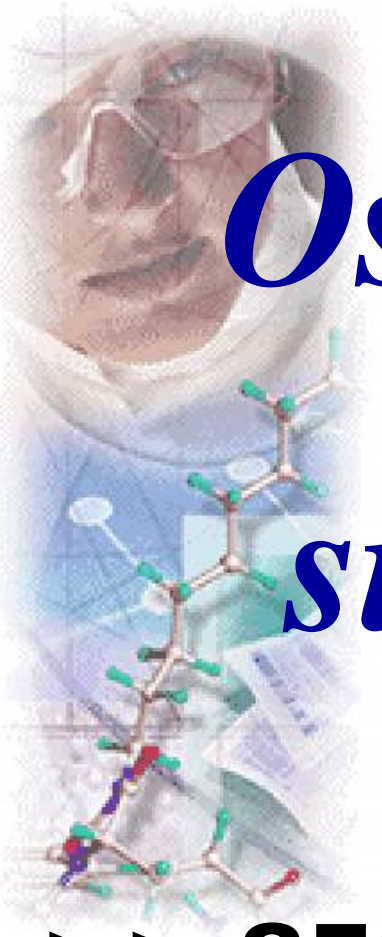
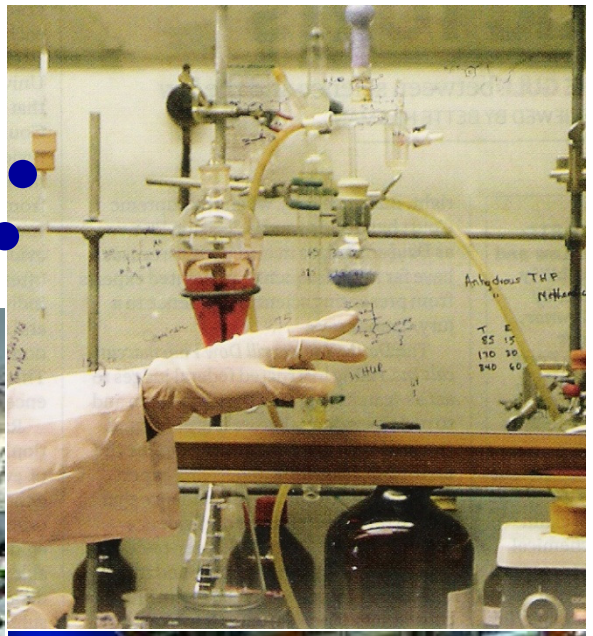
Os fármacos: sintéticos ...





>> 85% do arsenal terapêutico são de fármacos sintéticos ...

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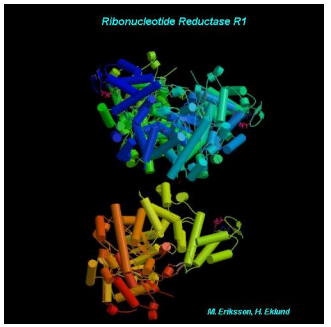
Química Medicinal

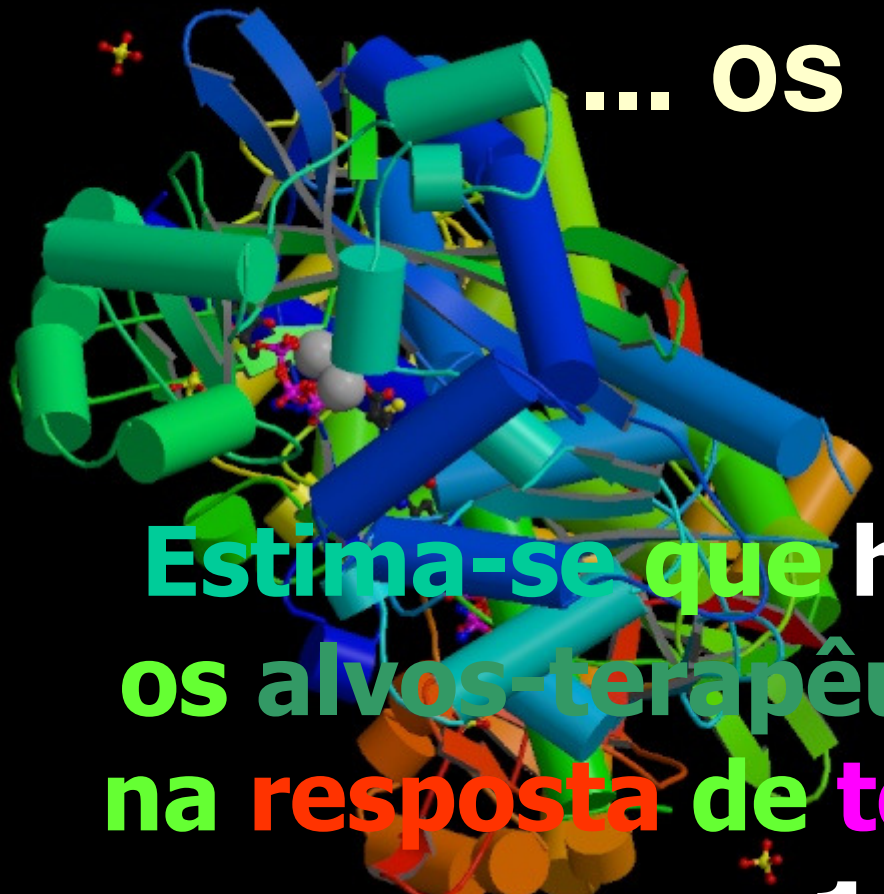
Os fármacos e os biorreceptores



Os fármacos atuam em alvos terapêuticos...

Química Medicinal

... os biorreceptores.



Estima-se que hoje sejam 483* os alvos-terapêuticos envolvidos na resposta de todos os fármacos que totalizam 1204 moléculas.&

* J. Drews, "Editorial: What's in a number?", *Nature Rev. Drug Discov.* **2006**, *5*, 975;
J. Drews & S. Ryser, Classic drug targets, *Nature Biotechnol.* **1997**, *15*, 1318;
& J.P. Overington, A-L Bissan & A.L. Hopkins, *Nature Rev. Drug Discov.* **2006**, *5*, 993;
Estes autores estimam em 324 os biorreceptores de todos os fármacos contemporâneos.

A maioria dos biorreceptores dos fármacos contemporâneos são enzimas …

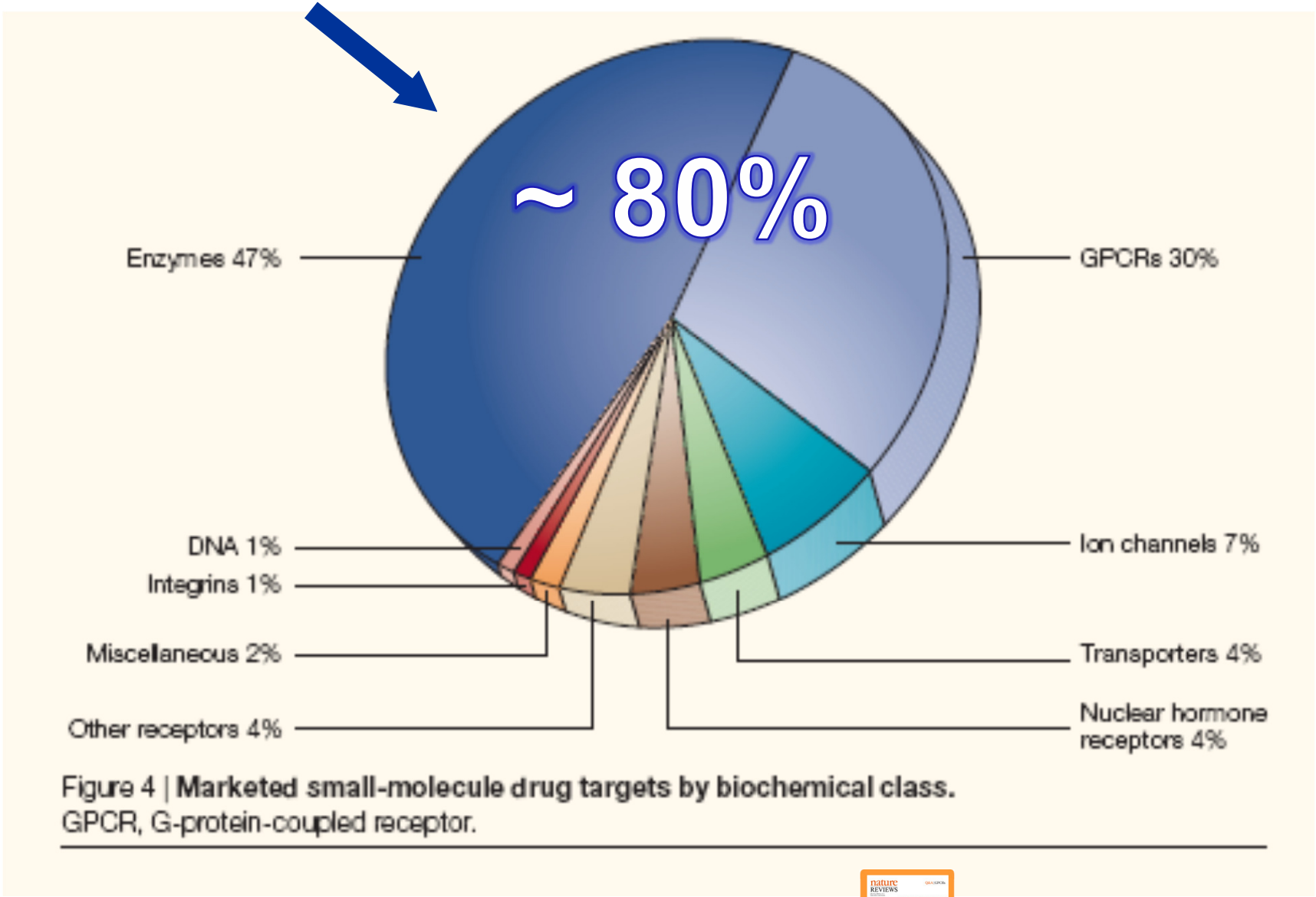


Figure 4 | **Marketed small-molecule drug targets by biochemical class.** GPCR, G-protein-coupled receptor.

www.nature.com/reviews/drugdisc

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

The Nobel Prize in Chemistry 2012

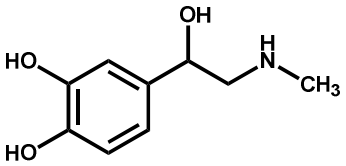


Photo: U. Montan

Robert J. Lefkowitz

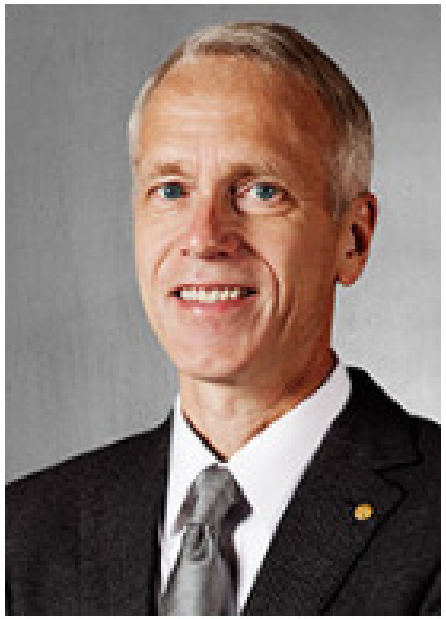


Photo: U. Montan

Brian K. Kobilka

[a] Howard Hughes Medical Institute and Duke University Medical Center, Durham, NC, USA

[b] Stanford University School of Medicine, Stanford, CA, USA

"for studies of G-protein-coupled receptors"

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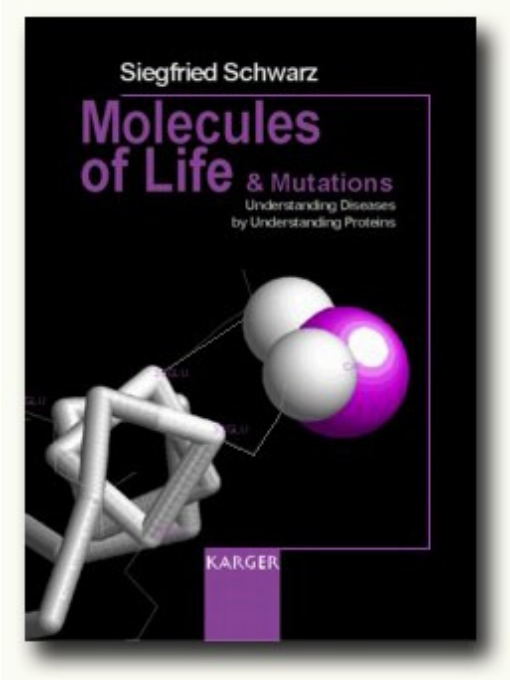
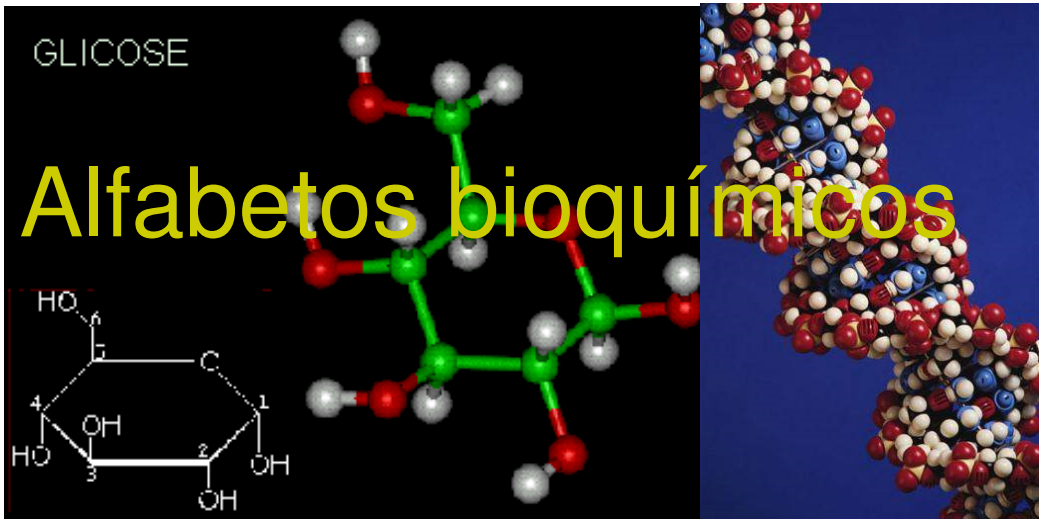
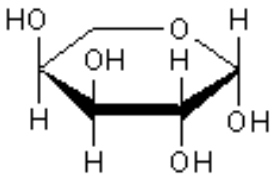
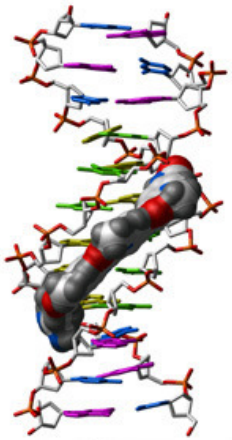




Alfabetos bioquímicos



β-L-Arabinose



Model Compound Bound to the Minor Groove of a DNA Molecule

Carboidratos

Lipídeos

ácidos nucléicos

proteínas

O "alfabeto" protêico ...

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**)

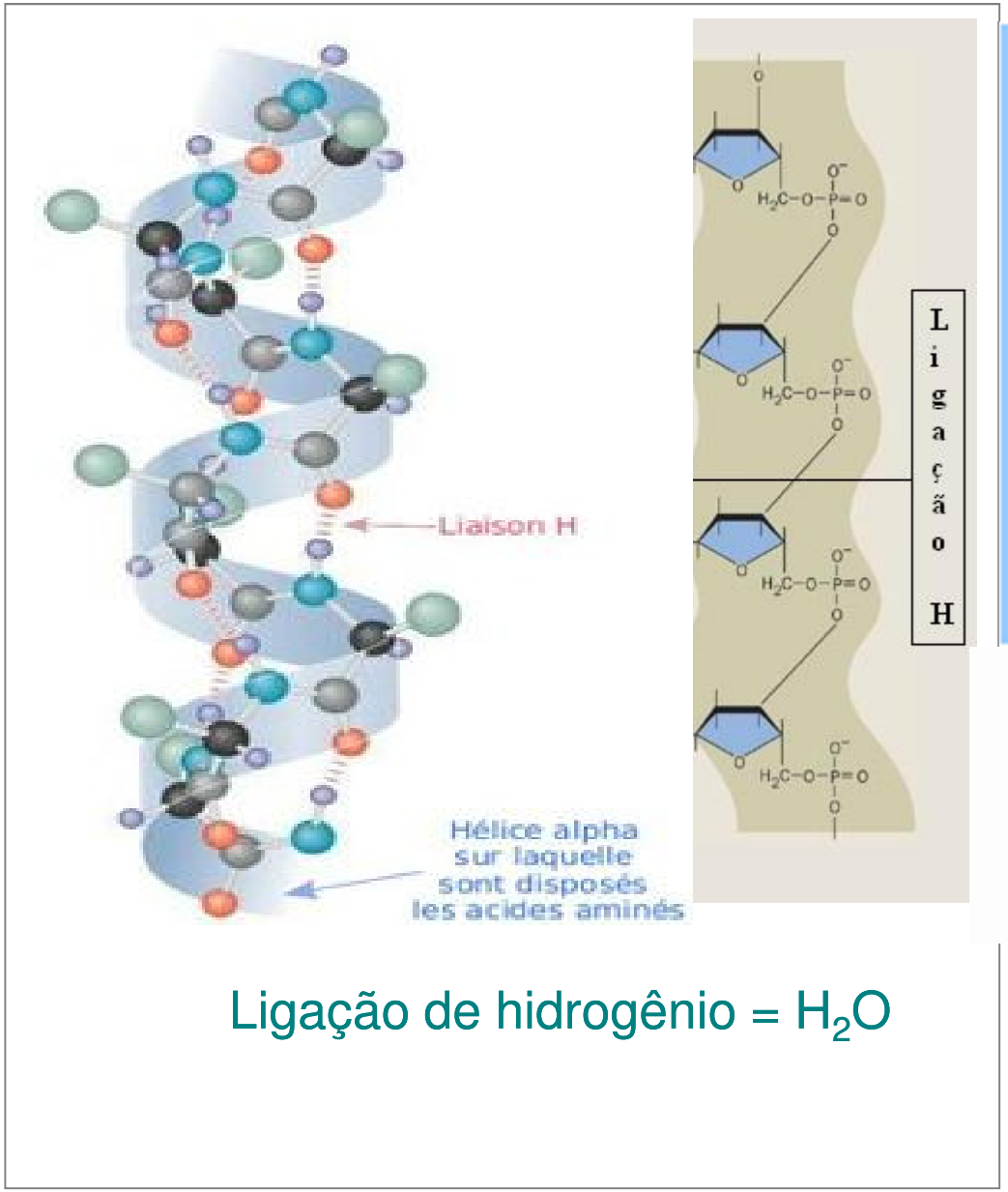
triptofano (**Trp**)

fenilalanina (**Phe**)

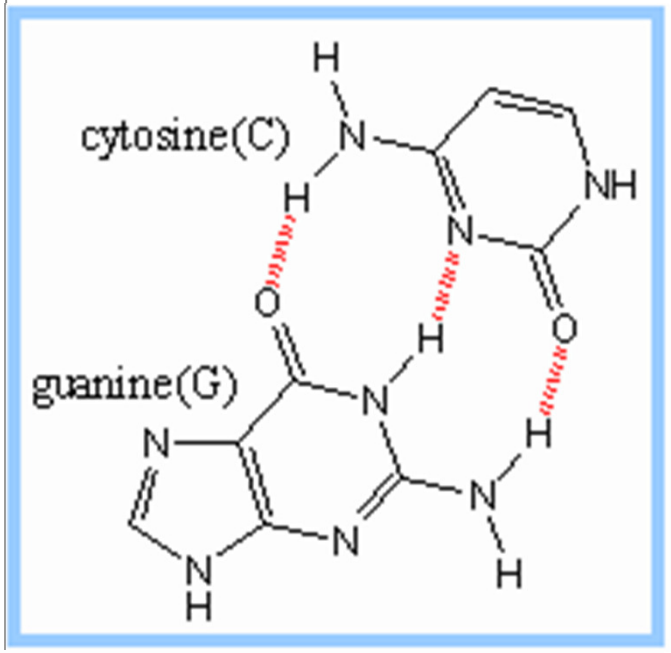
tirosina (**Tyr**)

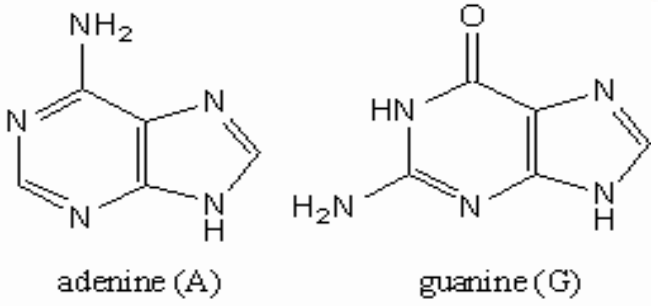
histidina

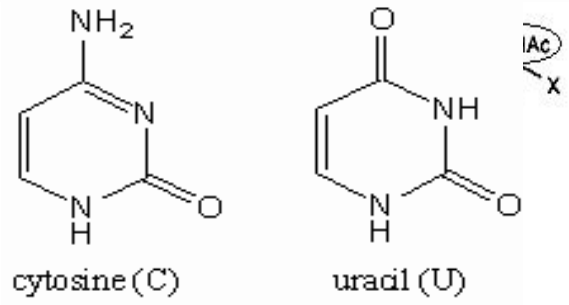
Proteínas, carboidratos, DNA, lipídeos, canais iônicos



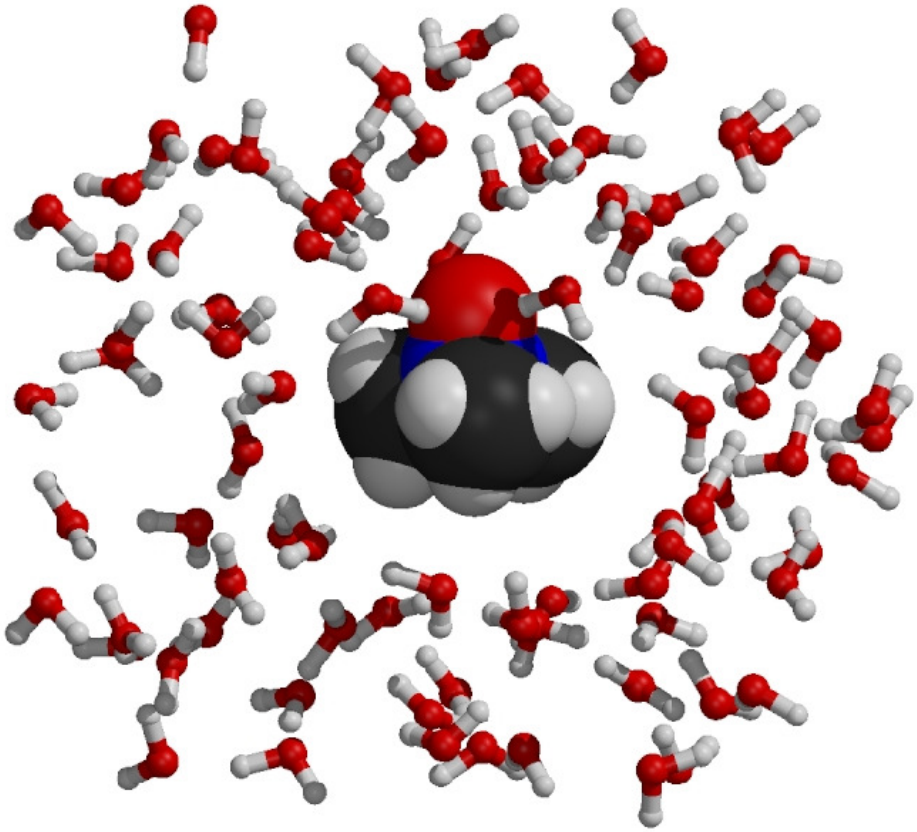
Ligação de hidrogênio = H_2O

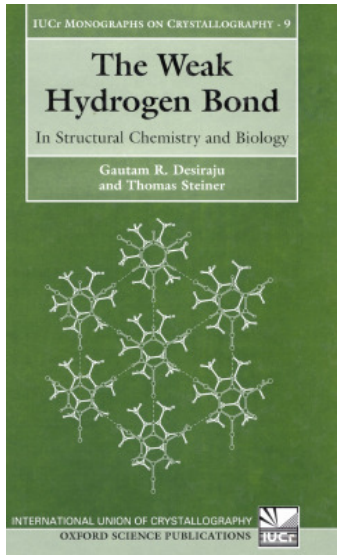






A importância das "*ligações*" frágeis...





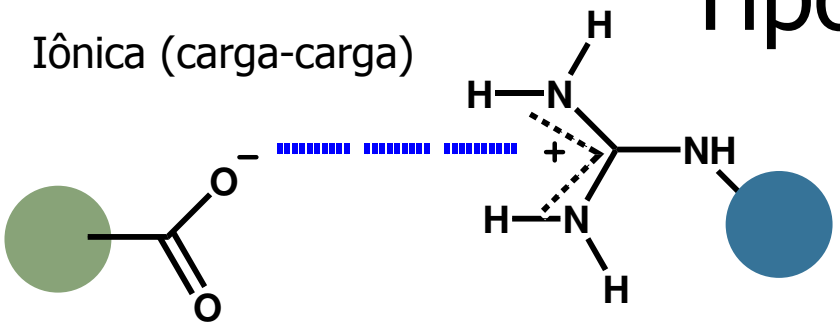
"*ligações*" de hidrogênio ...

D—H.....A

Linus Pauling, 1939

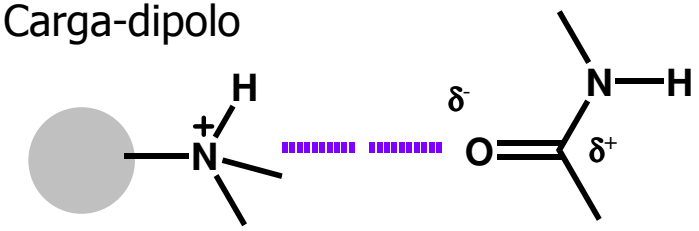
Tipos de interações F-R

Iônica (carga-carga)



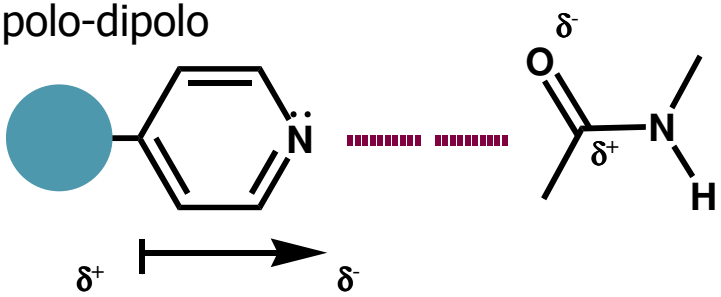
ΔG = 20-40kJ/mol

Carga-dipolo



ΔG = 12-20kJ/mol

Dipolo-dipolo

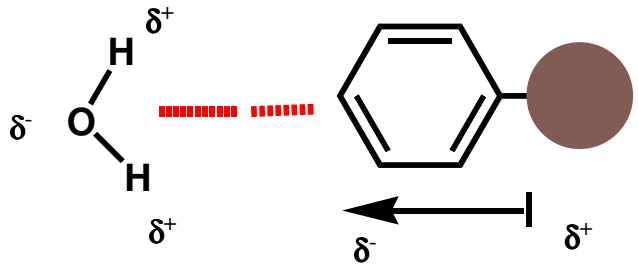


ΔG = 4-12 kJ/mol

Carga-dipolo induzido

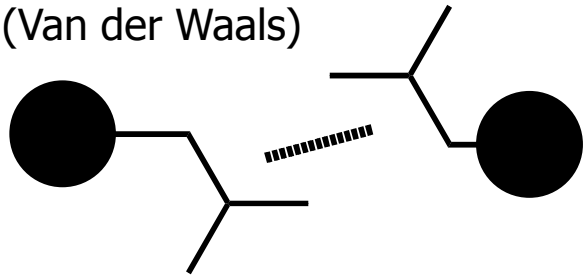
ΔG = 2-10 kJ/mol

Dipolo induzido-dipolo



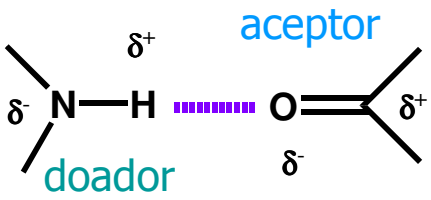
ΔG = 2 kJ/mol

Dispersão (Van der Waals)



ΔG = 2-4 kJ/mol

Ligação-H

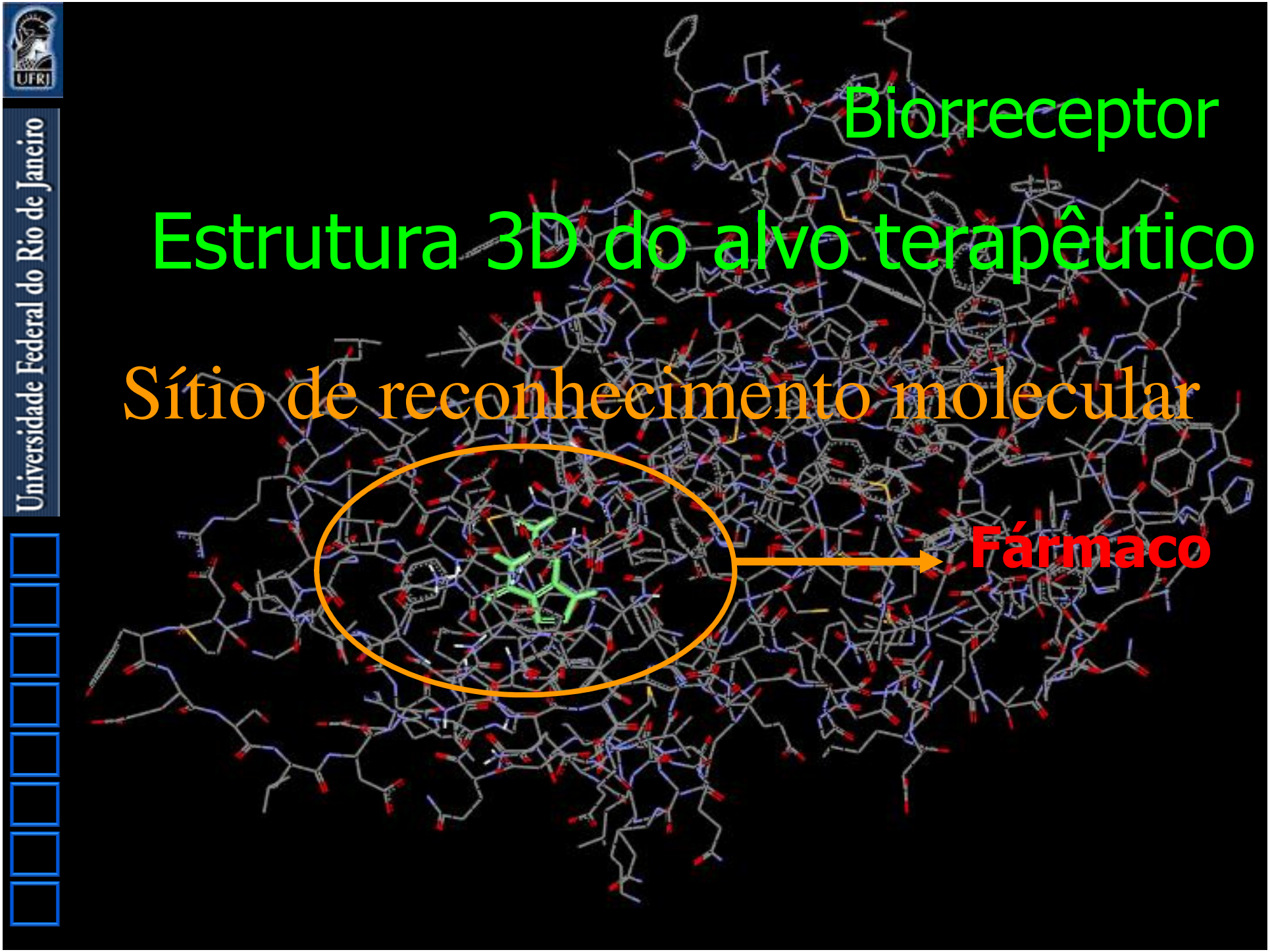


ΔG = 4-30 kJ/mol

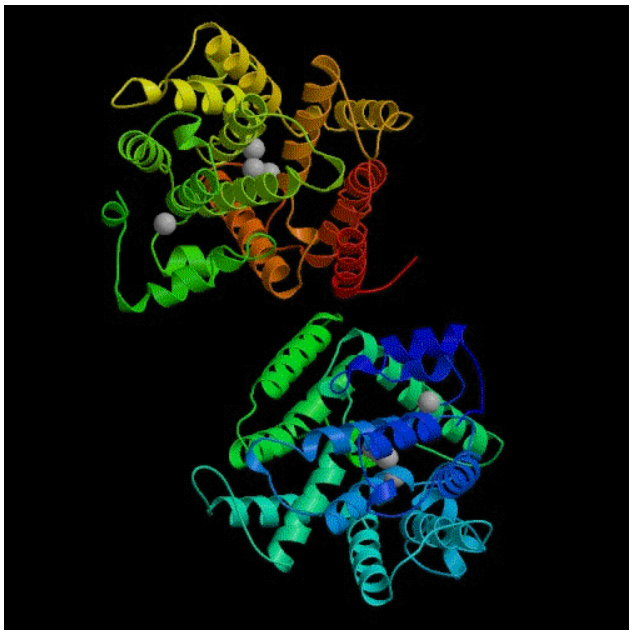
Nível hierárquico da descrição da complementaridade F-R

Complicadores:

- Encaixe-induzido
- Conformação bioativa
- Inibição alostérica/ortostérica


Universidade Federal do Rio de Janeiro
UFRJ
Biorreceptor
Estrutura 3D do alvo terapêutico
Sítio de reconhecimento molecular
Fármaco

Estruturas cristalográficas disponíveis no PDB

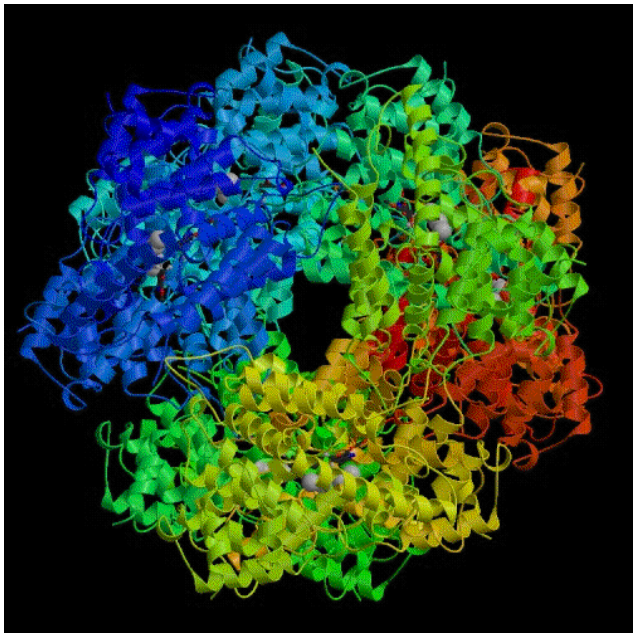


PDE4B - 1F0J

351 resíduos

Metodo: Difração de Raio-X

Resolução: **1.77 Å**



PDE4D - 1MKD

328 resíduos

Metodo: **Difraçao de Raio-X**

Resolução: **2.90 Å**

R Wang, X Fang, Y Lu, S Wang, The PDBbind Database: Collection of Binding Affinities for Protein−Ligand Complexes with Known Three-Dimensional Structures, *J. Med. Chem*. **2004**, *47*, 2977

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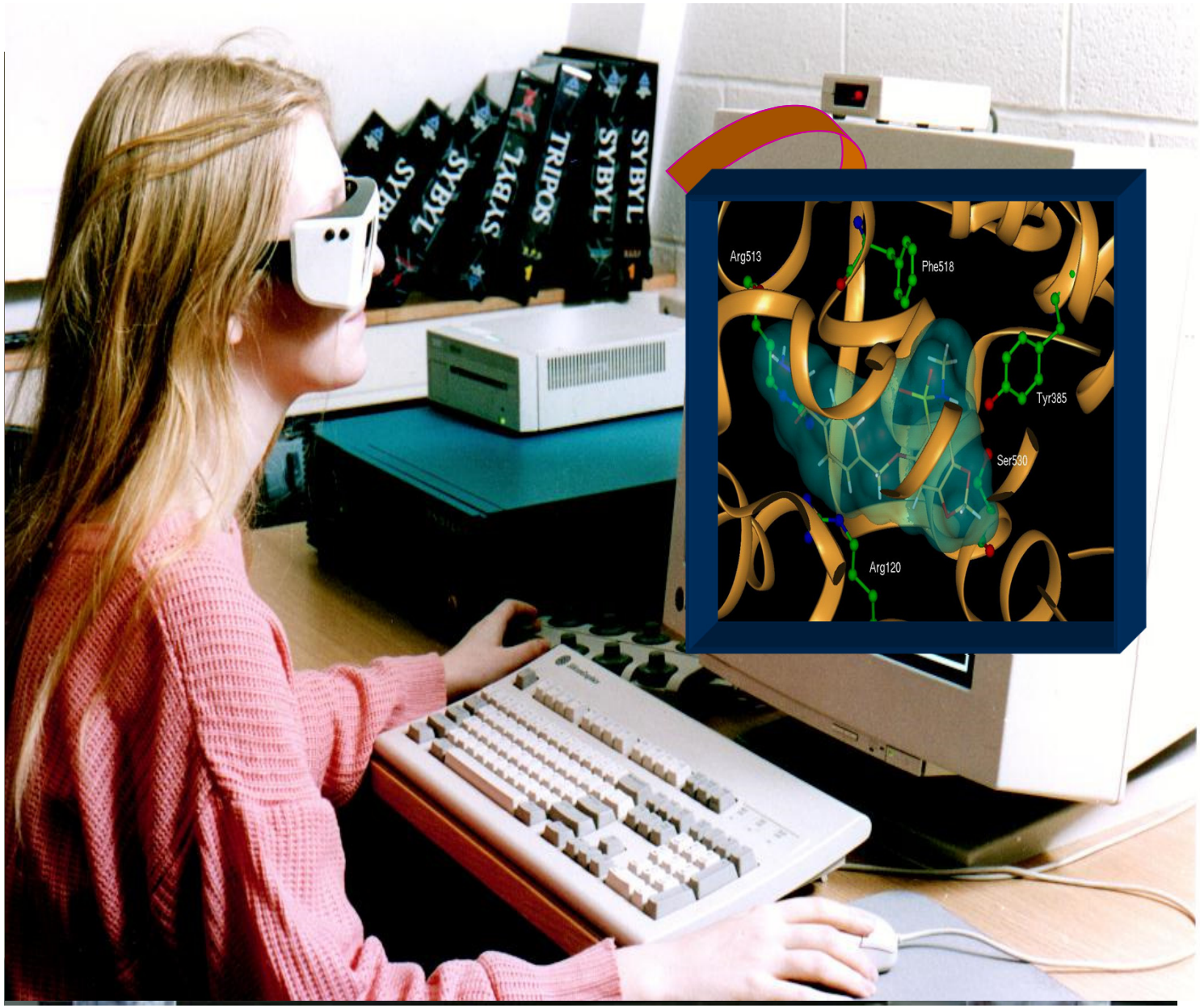

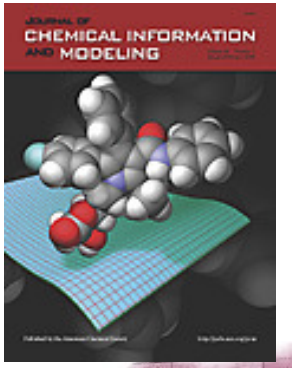

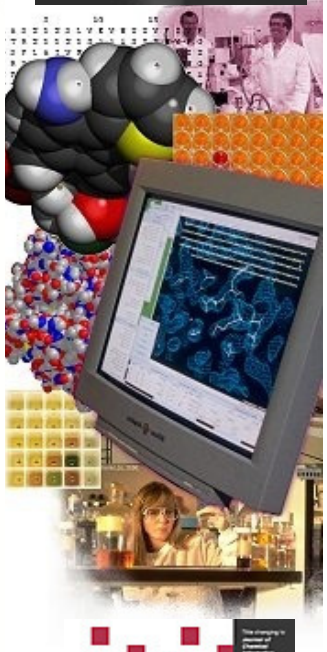

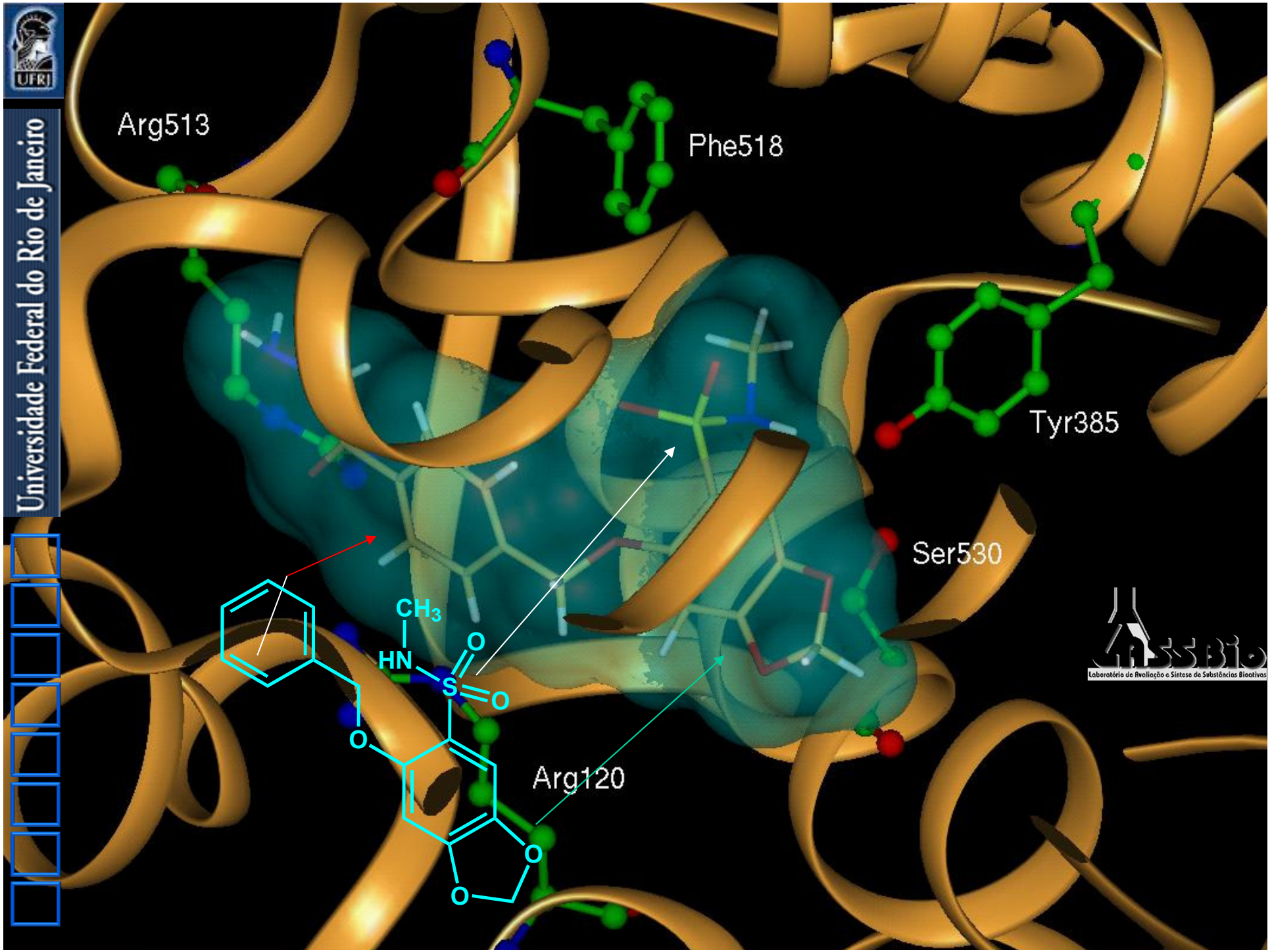
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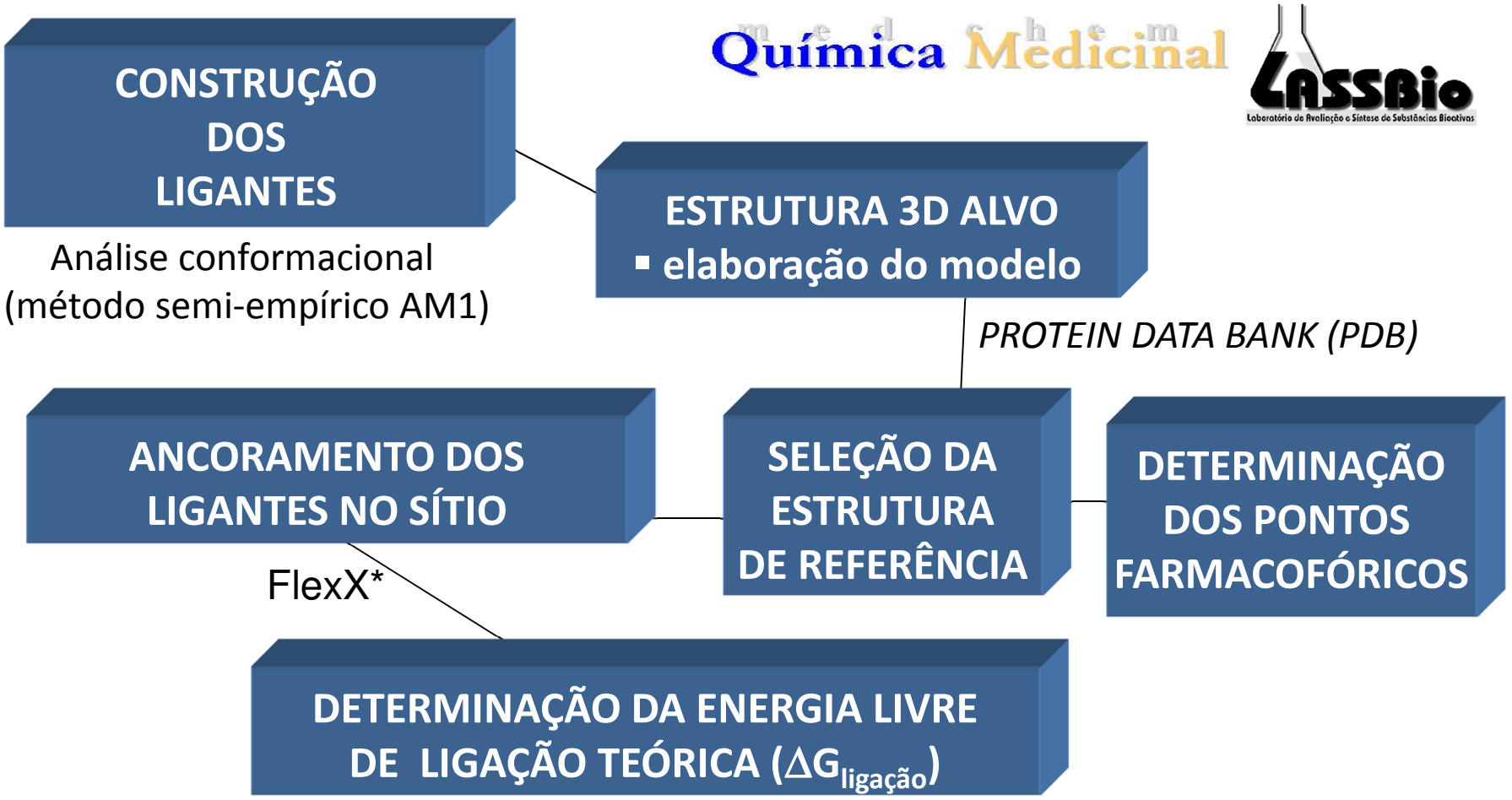
UFRJ
Arg513
Phe518
Tyr385
Ser530
Arg120
CH3
HN
S
O
O
O
O
O
LASSBIO
Laboratório de Avaliação e Síntese de Substâncias Bioativas

Metodologia: Estudos de *docking*



* FlexX one of the most cited commercial docking software

Sybyl, Version 8.0, Tripos Associates: St. Louis, MO, 2007 (**Licença # 7512**)
Spartan Pro; Wavefunction, Inc. 18401 Von Karman Avenue, Suite 370. Irvine, California 92612, USA (**Licença # 1-001259**)
FlexiDock; GLIDE; Gold; AutoDock (GNU) General Public License;

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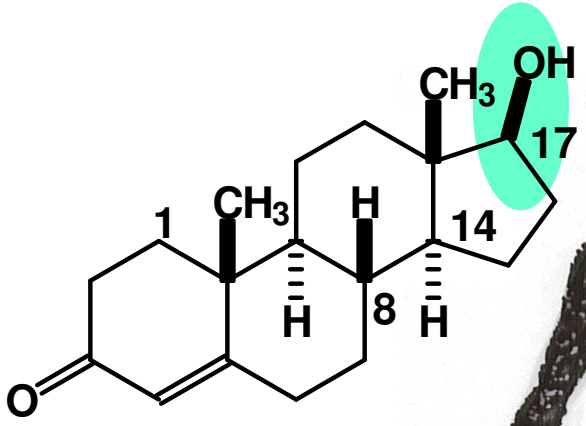
Química Medicinal

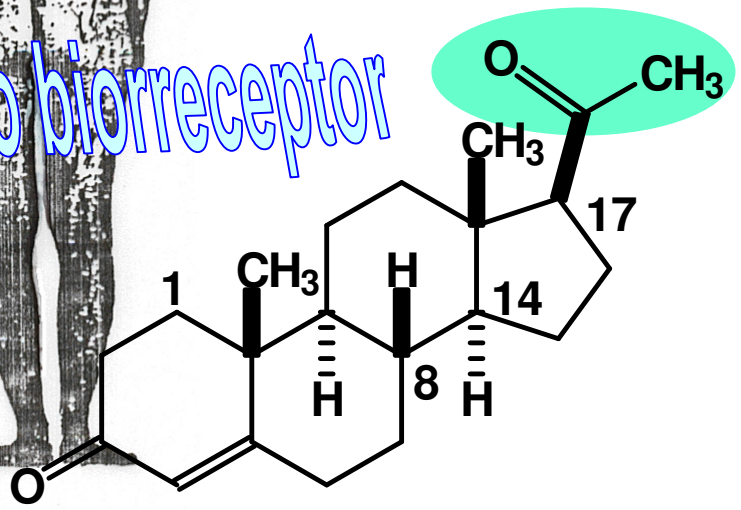
Especificidade dos biorreceptores

Similaridade & Dissimilaridade Molecular

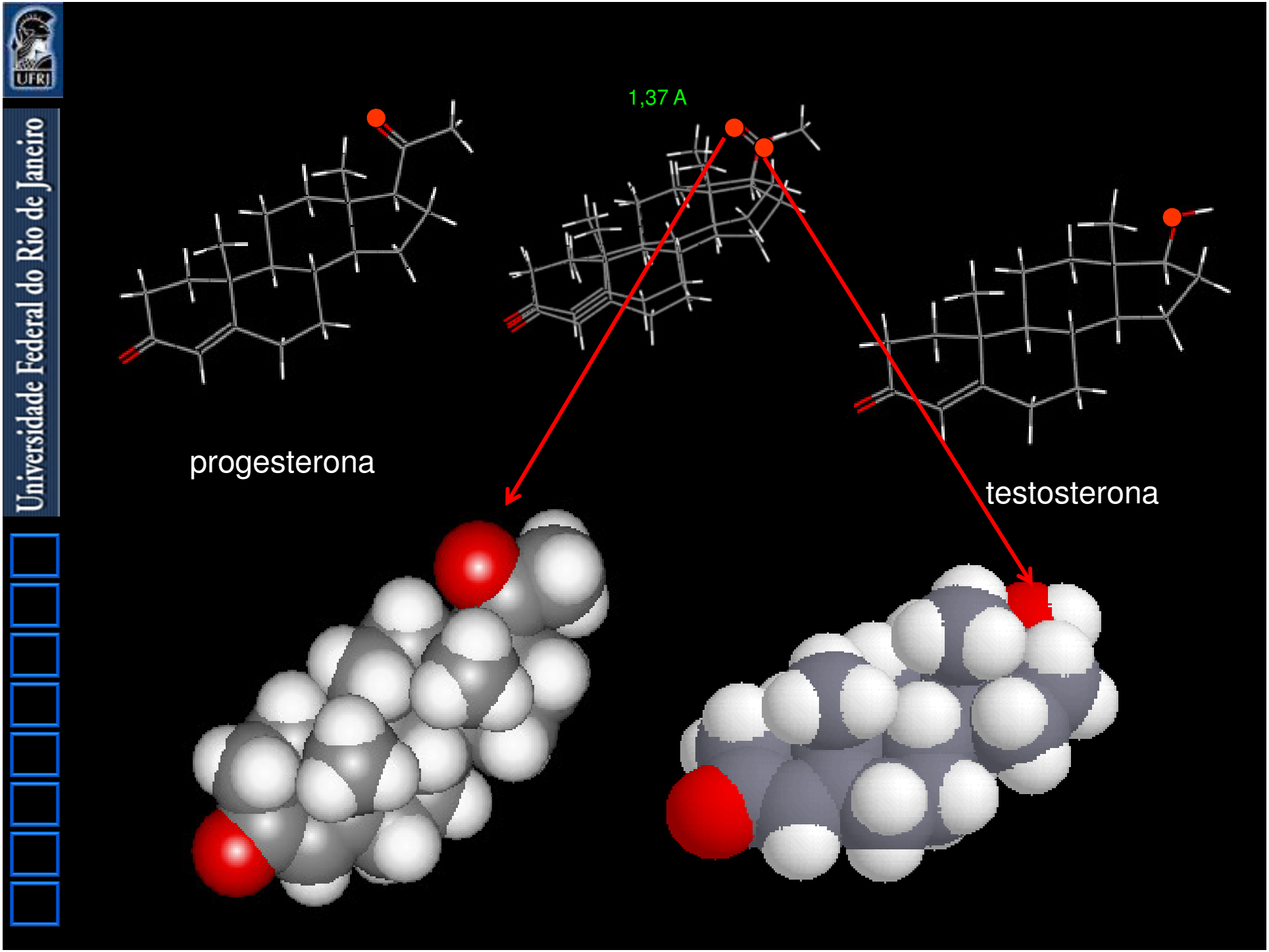


testosterona

no reconhecimento molecular do biorreceptor



progesterona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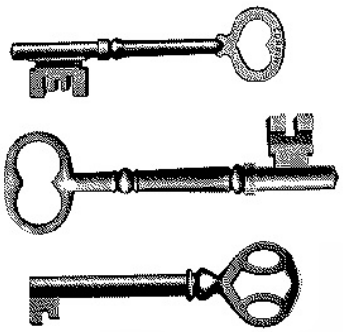
UFRJ
1,37 A
progesterona
testosterona

Universidade Federal do Rio de Janeiro

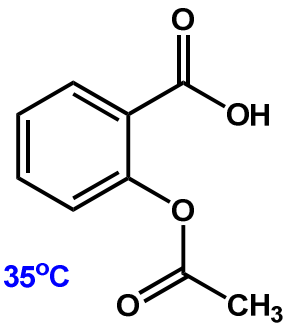
Química Medicinal

Estrutura & propriedades



Estrutura & Propriedades

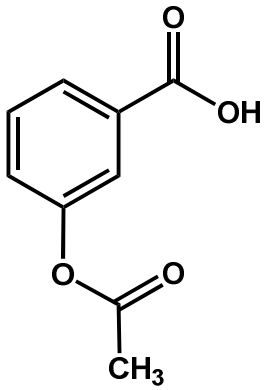
Ácido acetil salicílico (AAS)



PF = 135°C

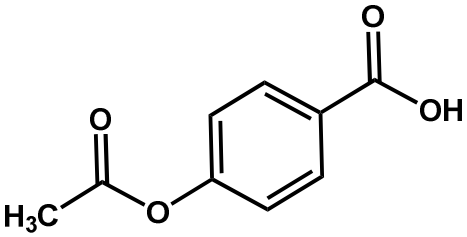
Log P: 1,21

CLogP: 1.0235



Log P: 1,18

CLogP: 1.4535

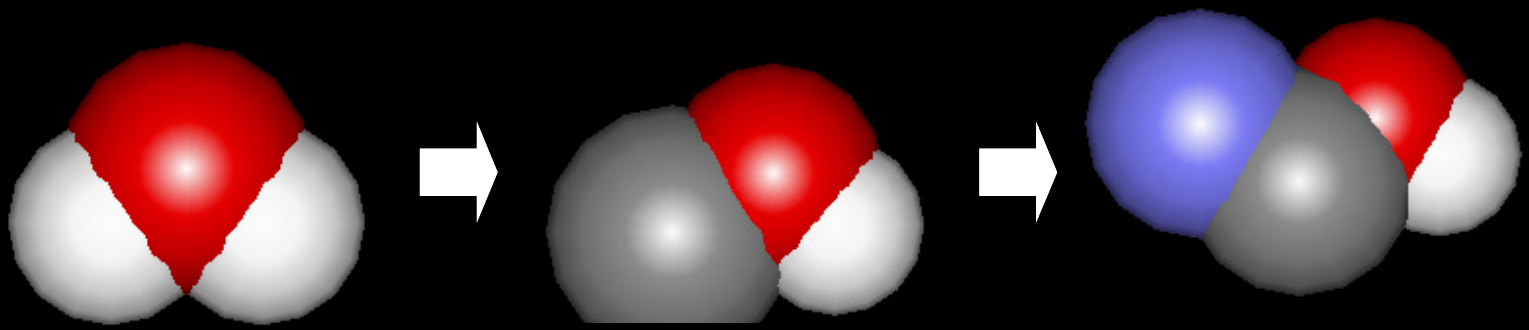


Log P: 1,18

CLogP: 1.4535

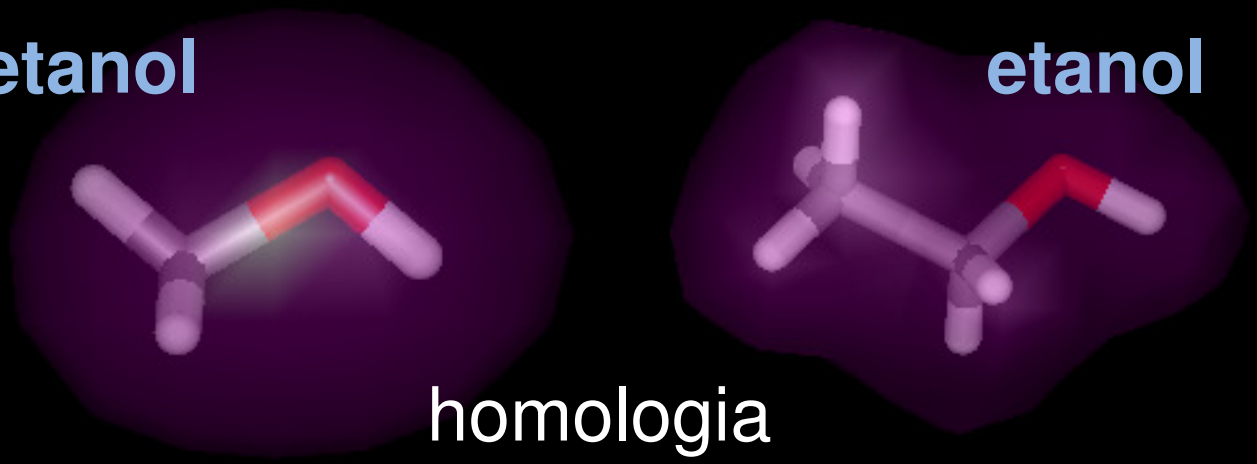
Regioisômeros = diastereoisômeros

Efeitos estruturais



H-O-H H-H_2C-O-H H_3C-CH_2-O-H

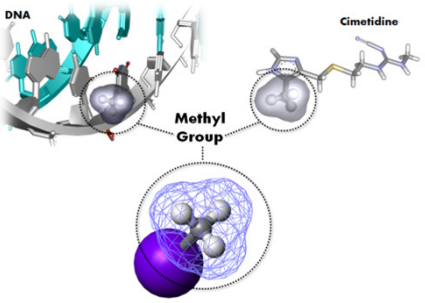
***m*etanol** **etanol**



homologia

Série homológa

água +CH_3 = metanol; +CH_3 = etanol



Chem. Rev. 2011, 111, 5215–5246

IF (2011) = 40,19

REVIEW

pubs.acs.org/CR

The Methylation Effect in Medicinal Chemistry

Eliezer J. Barreiro,*[,†,‡,§] Arthur E. Kümmerle,[||,†,§] and Carlos A. M. Fraga[†,‡,§]

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[§]Programa de Pós-Graduação em Química, Instituto de Química, Universidade Federal do Rio de Janeiro, Cidade Universitária, Ilha do Fundão, Rio de Janeiro, RJ, Brazil

dx.doi.org/10.1021/cr200060g

www.uff.br/rvq

AS de Miranda, *Rev. Virtual Quim*. **2011**, *3*, 228

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Química Medicinal

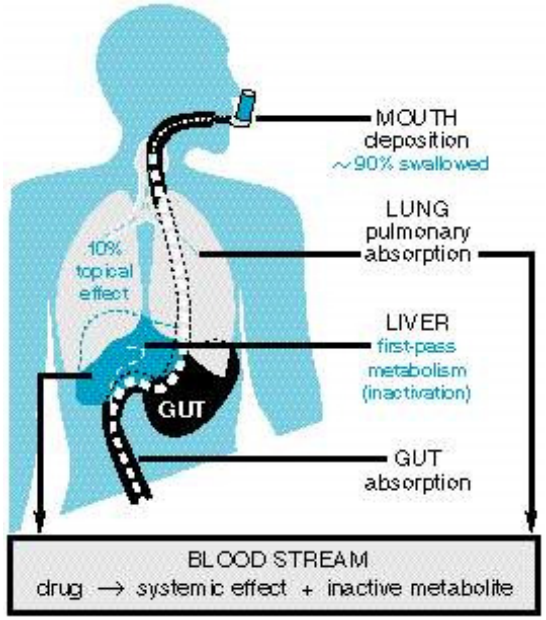
A biofase...

As *fases* da ação dos fármacos....

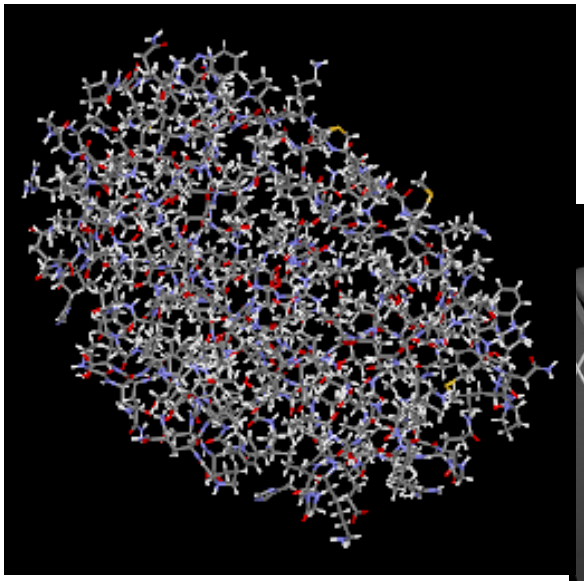
Fase farmacocinética

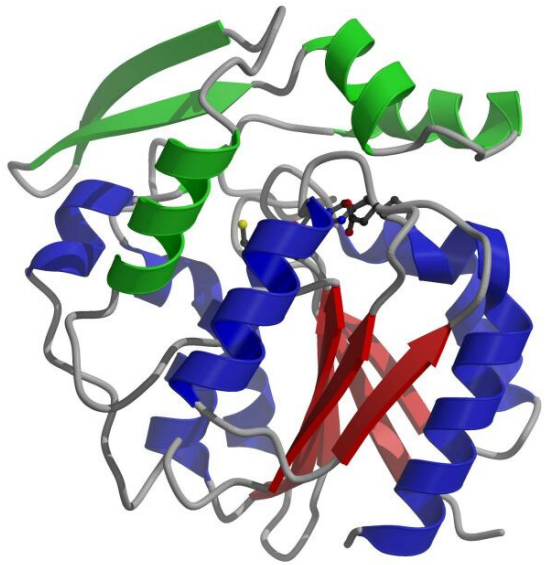
(PK)

Posologia

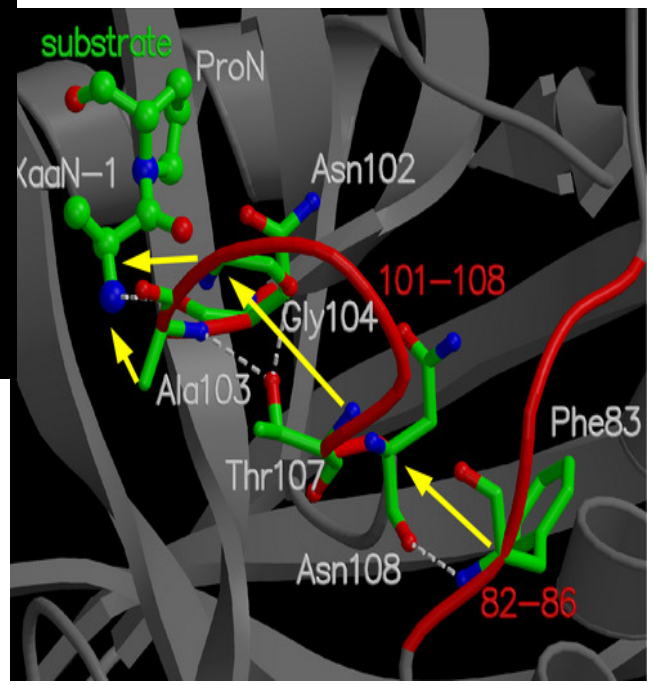


Biofase





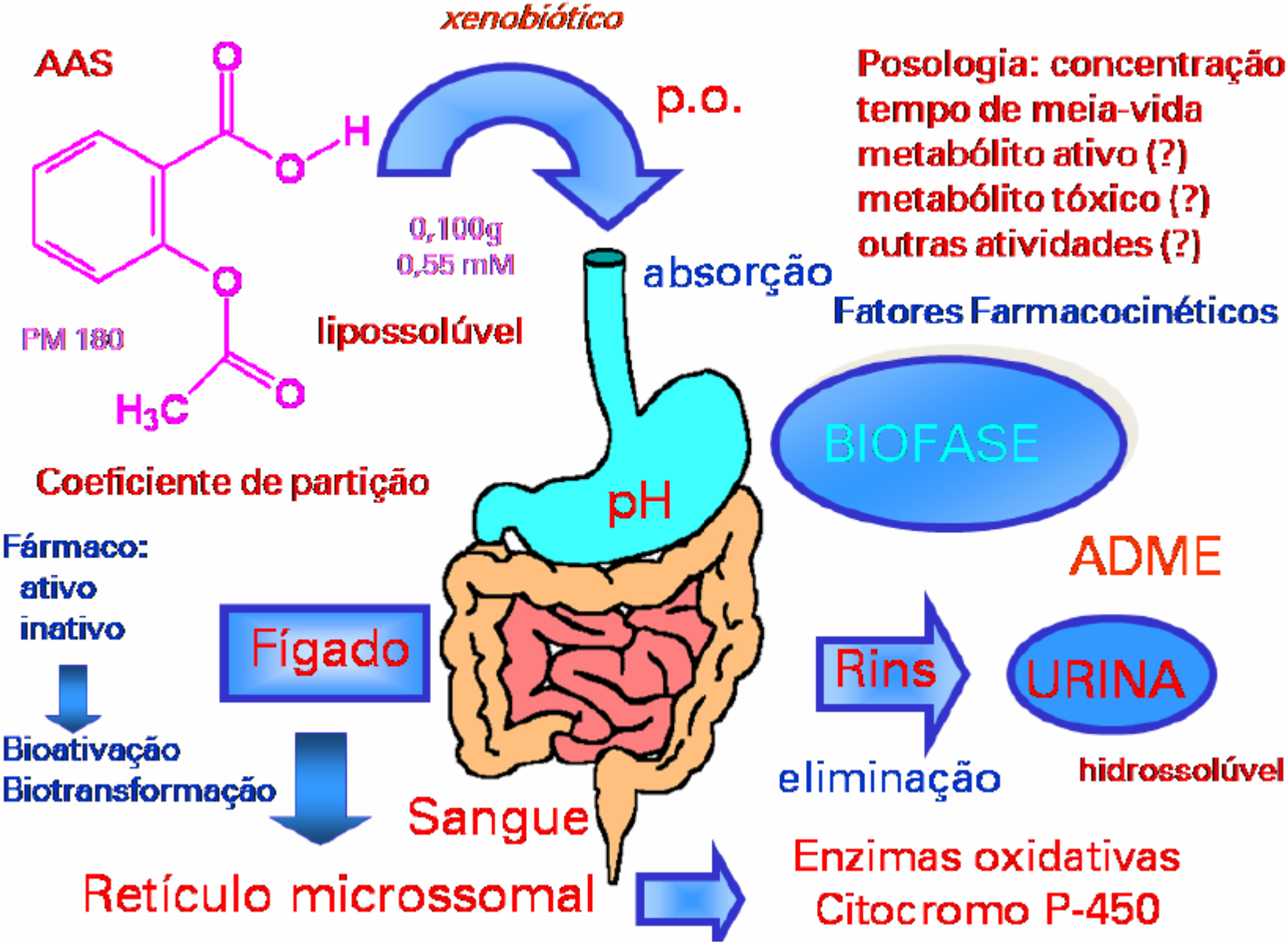
Biorreceptor

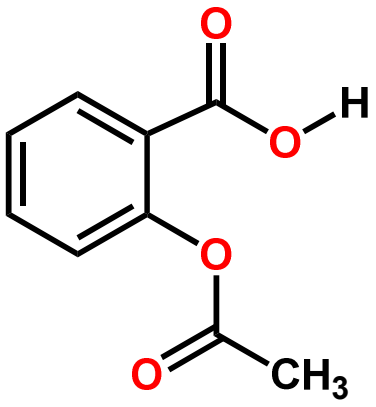


Efeito terapêutico

Fase farmacodinâmica

(PD)



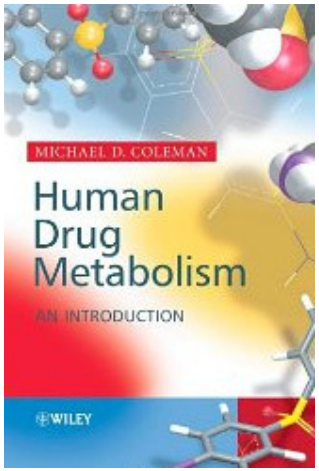


$C_9H_8O_4$

PM = 180 g

0,100 g ~ 0,5 M

70 kg



0,100 g

Fármaco

Substância ativa — M — Substância inativa

Substância atóxica — M — Substância tóxica

?? g

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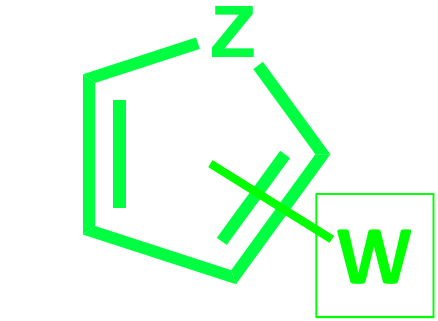
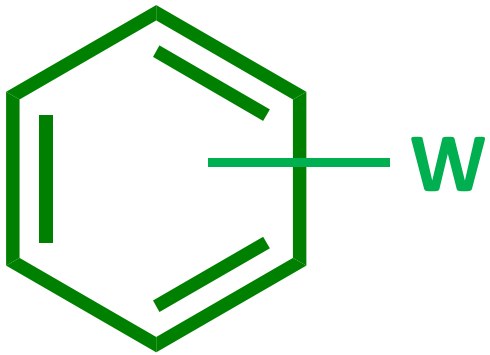
Química Medicinal

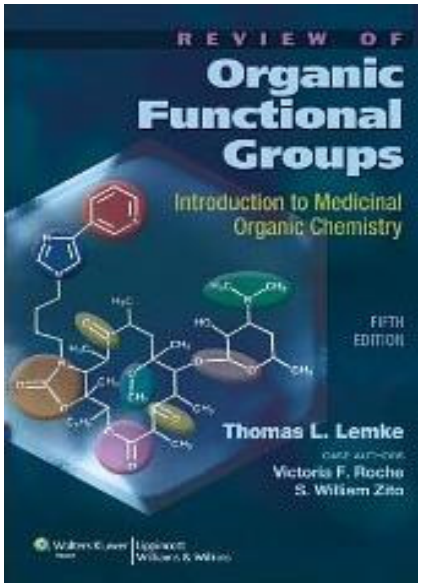
A estrutura química e os fármacos ...

Os grupos funcionais mais frequentes nos fármacos



Z = NH, O, S

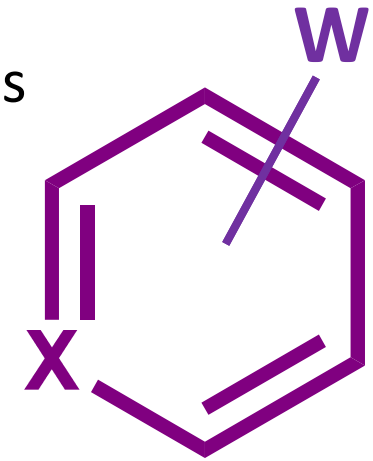




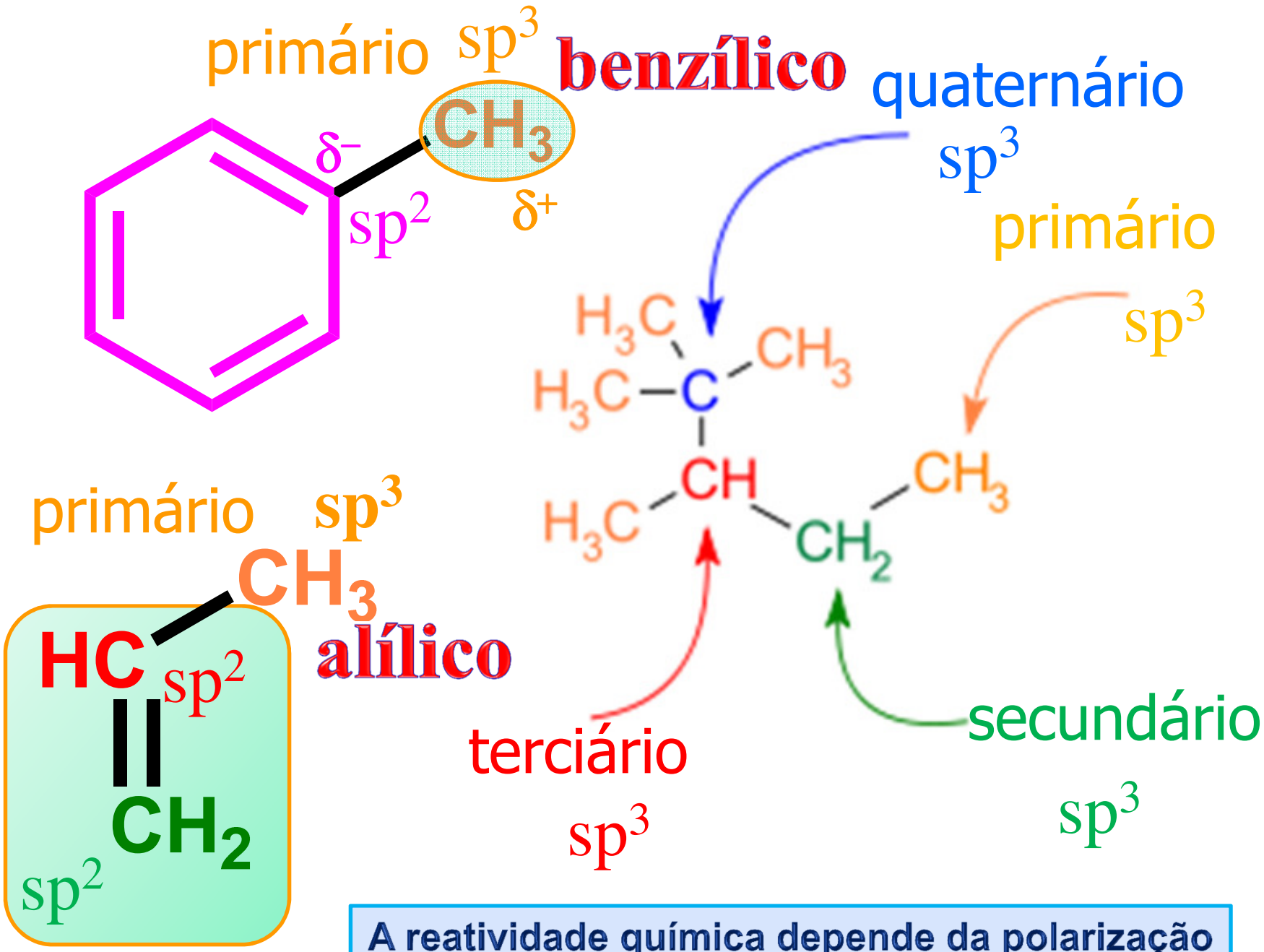
Propriedades eletrônicas

X = N

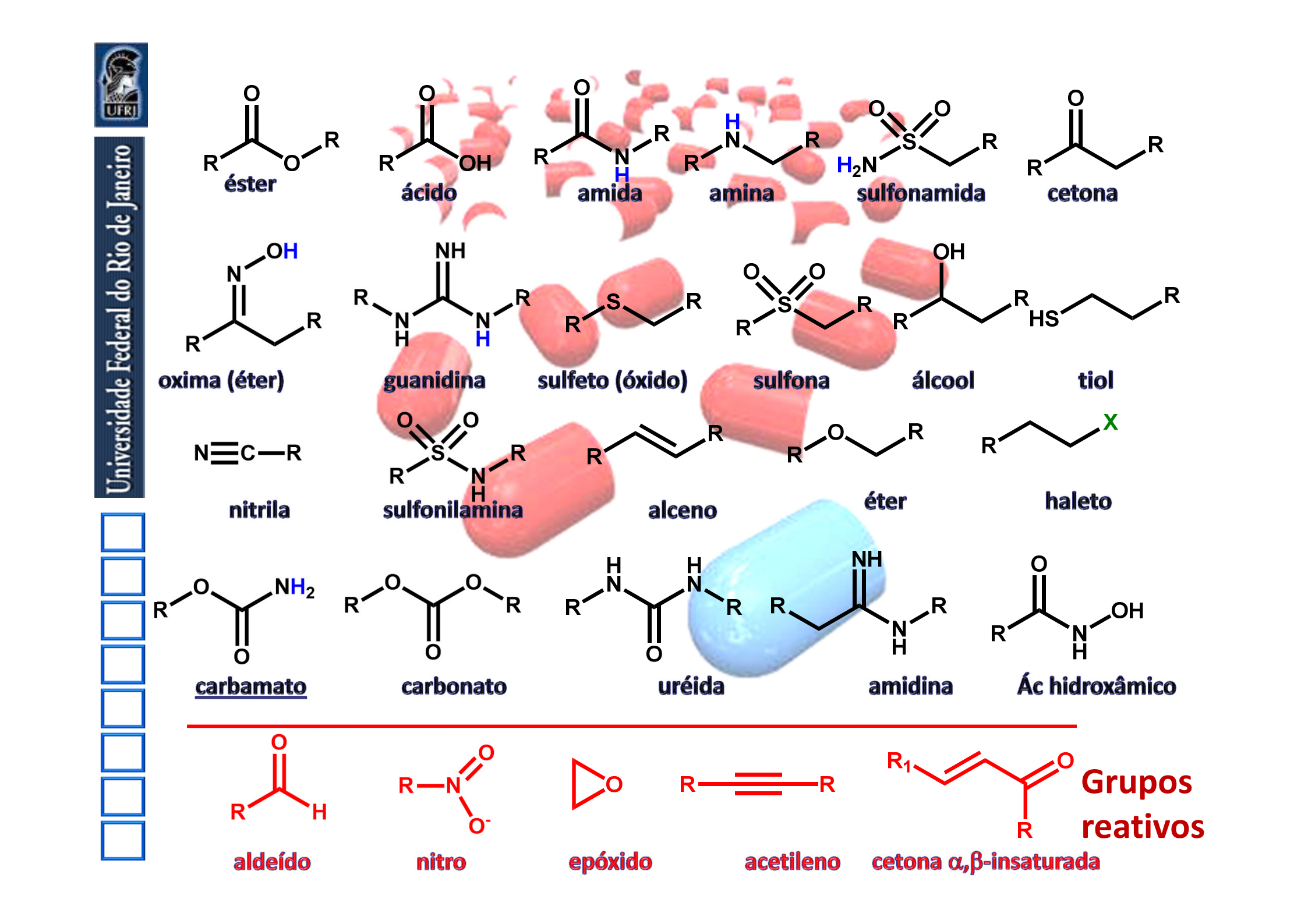
6, 10, 14, 18 π



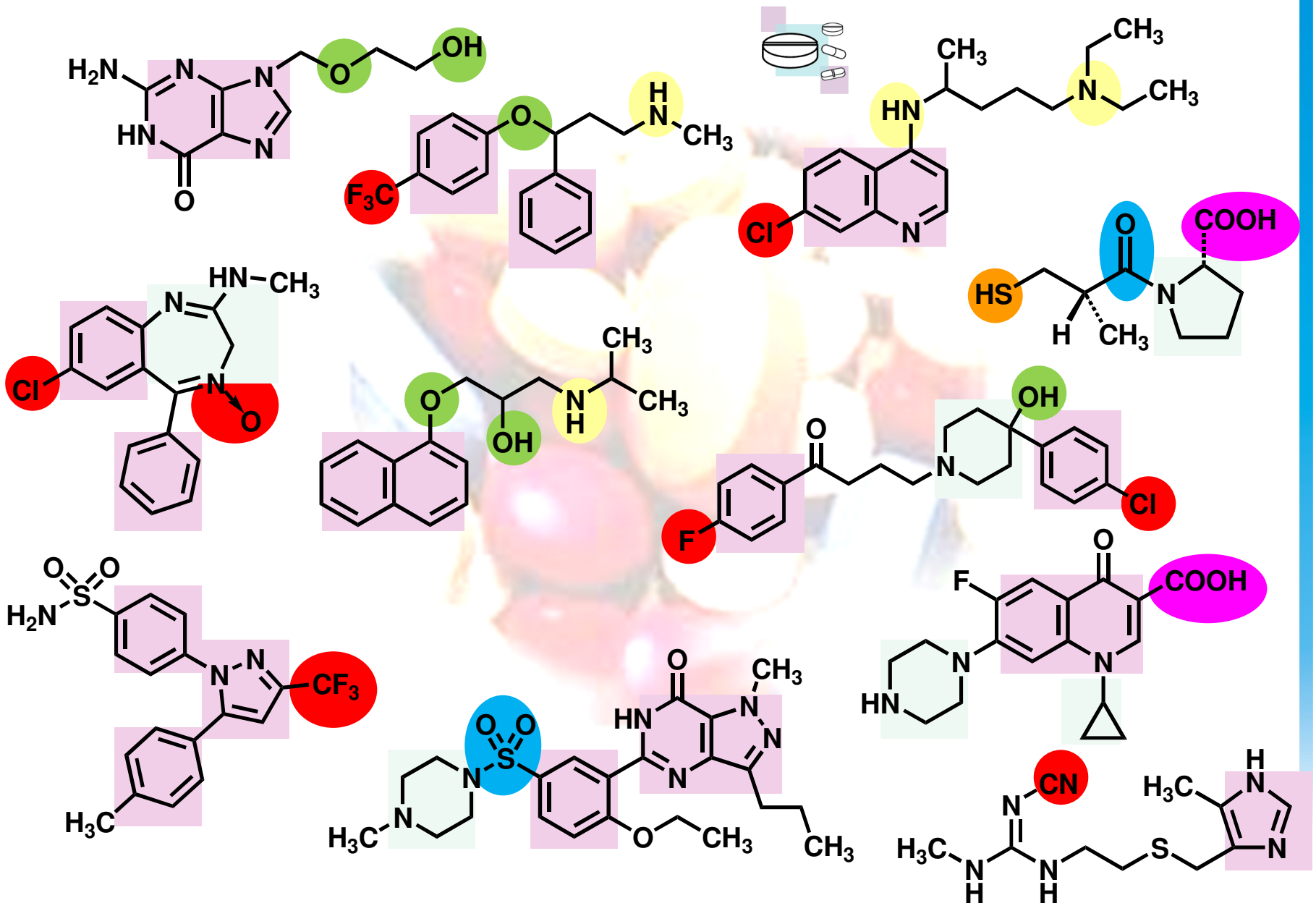
50% do fármacos atuais contêm pelo menos um *anel aromático*, capaz de poder sofrer substituições!



A reatividade química depende da polarização


Universidade Federal do Rio de Janeiro
éster
ácido
amida
amina
sulfonamida
cetona
oxima (éter)
guanidina
sulfeto (óxido)
sulfona
álcool
tiol
nitrila
sulfonilamina
alceno
éter
haleto
carbamato
carbonato
uréida
amidina
Ác hidroxâmico
aldeído
nitro
epóxido
acetileno
cetona α,β-insaturada
Grupos reativos

A quimiodiversidade dos fármacos... é singela!



Características estruturais comuns nos onze fármacos :

- Representam inovações terapêuticas importantes: aciclovir, fluoxetina, cloroquina, clordiazepóxido, propranolol, captopril, haloperidol, celecoxibe, sildenafila, ciprofloxacina, cimetidina;
- pertencem a 08 classes terapêuticas distintas: > SNC;
- São substâncias com singela diversidade química;
- Possuem apenas 7 elementos químicos: C,H,O,N,S,F,Cl;
- 10/11 possuem heteroátomos, 10/11 têm heterocíclos;
- 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;*

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Química Medicinal

Assim nascem os fármacos ...

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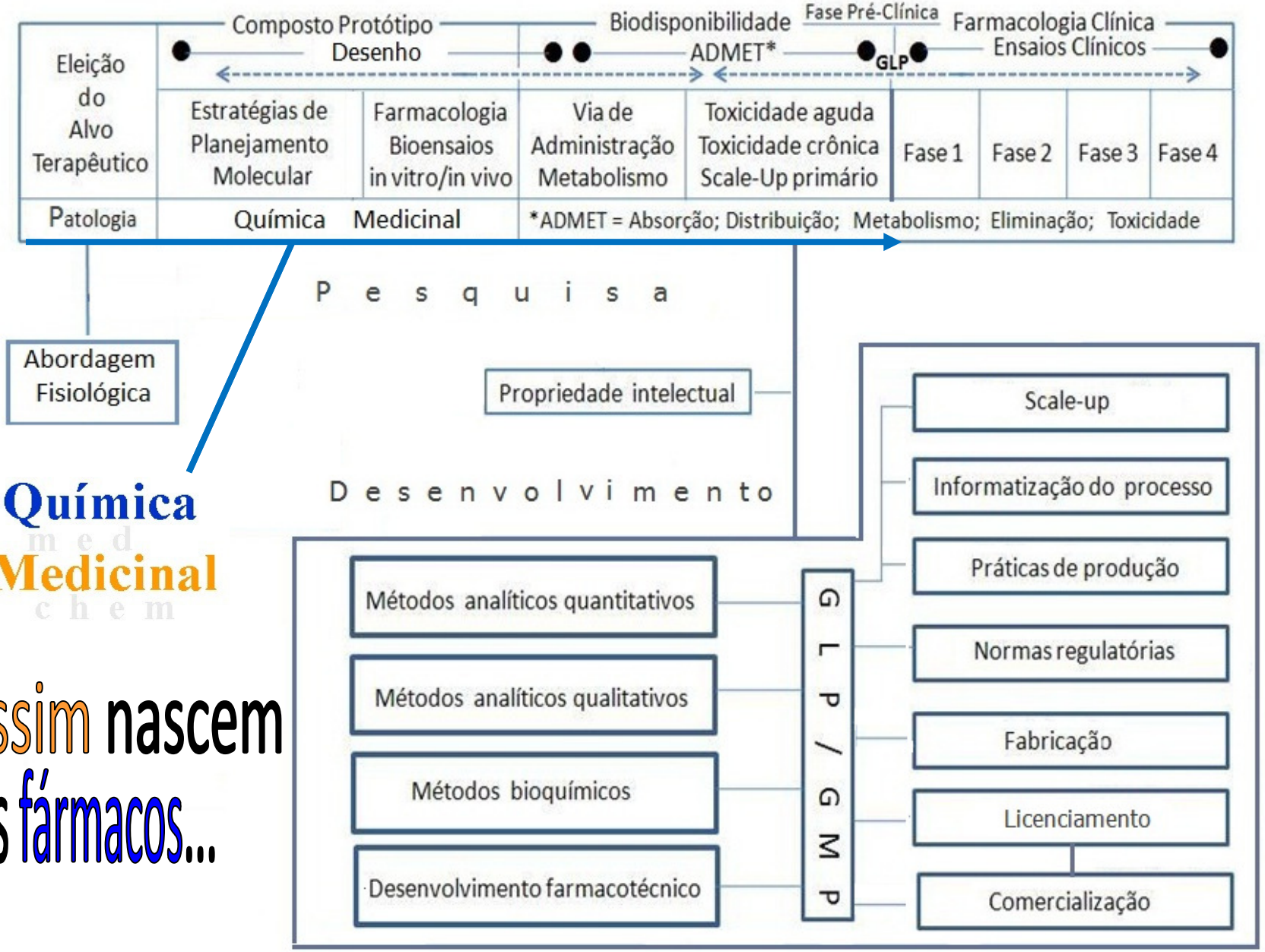
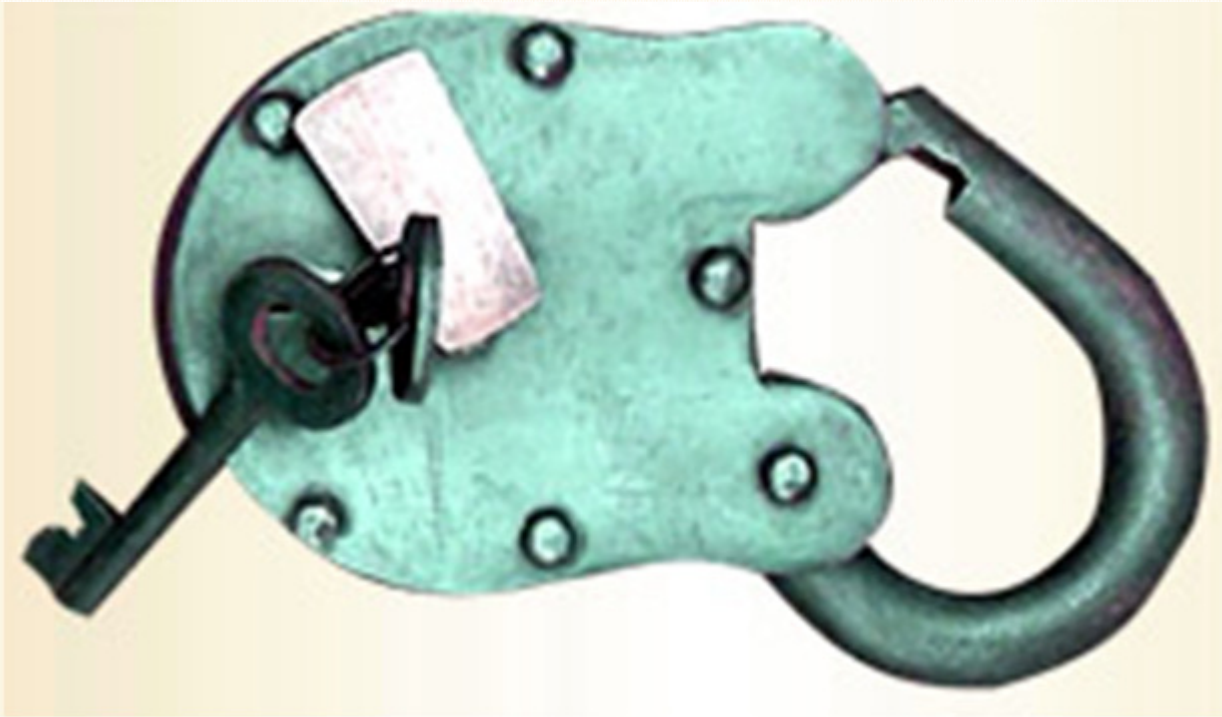


Assim nascem os fármacos...



Physiologic approach

A abordagem fisiológica

Mechanism-based drug discovery

Abordagem racional

Descoberta do composto-protótipo

Estratégia do Análogo-ativo

Caracterização dos pontos & grupos farmacofóricos (bióforos)

captopril

cimetidina

antagonistas H2

inibidores da ACE

Estrutura do Biorreceptor Conhecida

DHFR Inibidores

Alternativa híbrida

Inovações Terapêuticas

Inibidores de HIV Asp-proteases

indinavir

Identificação de novo hit ou ligante

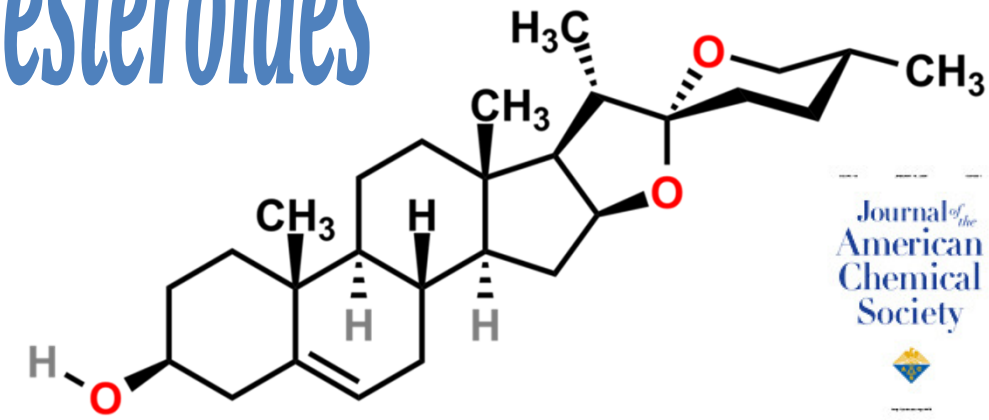
Abordagem irracional-racional

Imatinibe

Estratégias hifenadas

Estrutura do Biorreceptor Desconhecida

esteróides

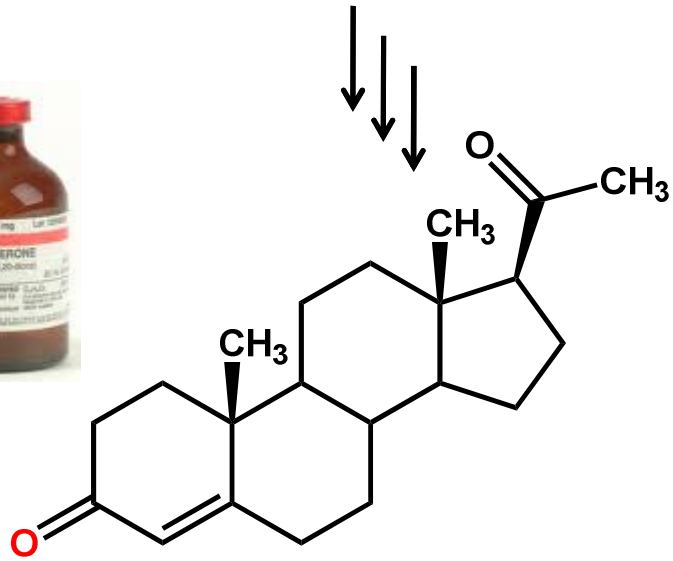


diosgenina

Laboratorios Syntex SA

Dioscorea mexicana Scheidw

RE Marker, Sterols. CXIII. Sapogenins. XLII. The conversion of the sapogenins to pregnenolones". *J. Am. Chem. Soc.*, **62** 3350–3352 (1940); P Lehmann, A Bolivar, R Quintero, Russell E. Marker - Pioneer of the Mexican steroid industry, *J. Chem. Ed.*, **50**, 195–9 (1973).

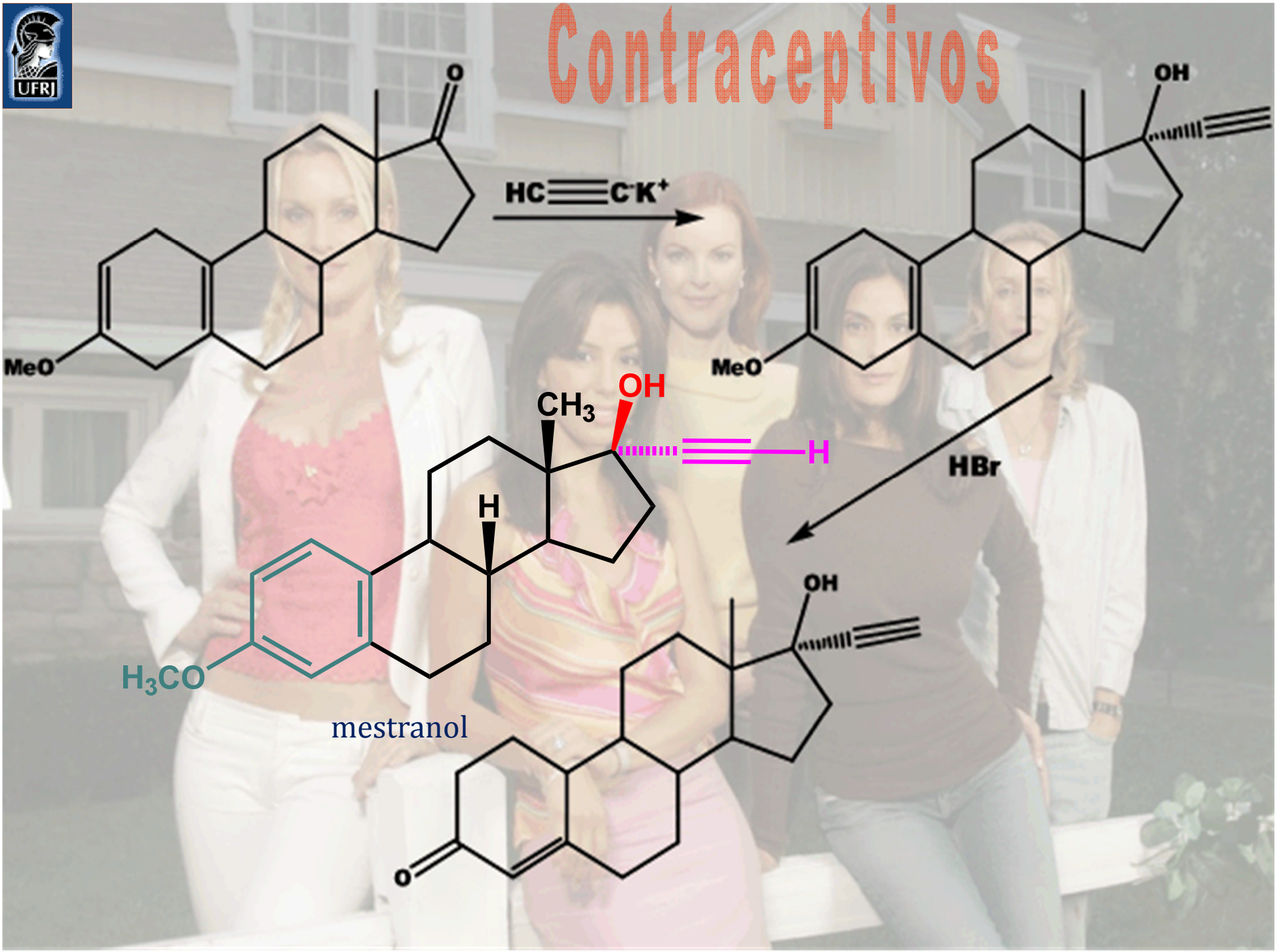


progesterona

A Pílula Contraceptiva

Carl Djerassi

Contraceptivos



mestranol

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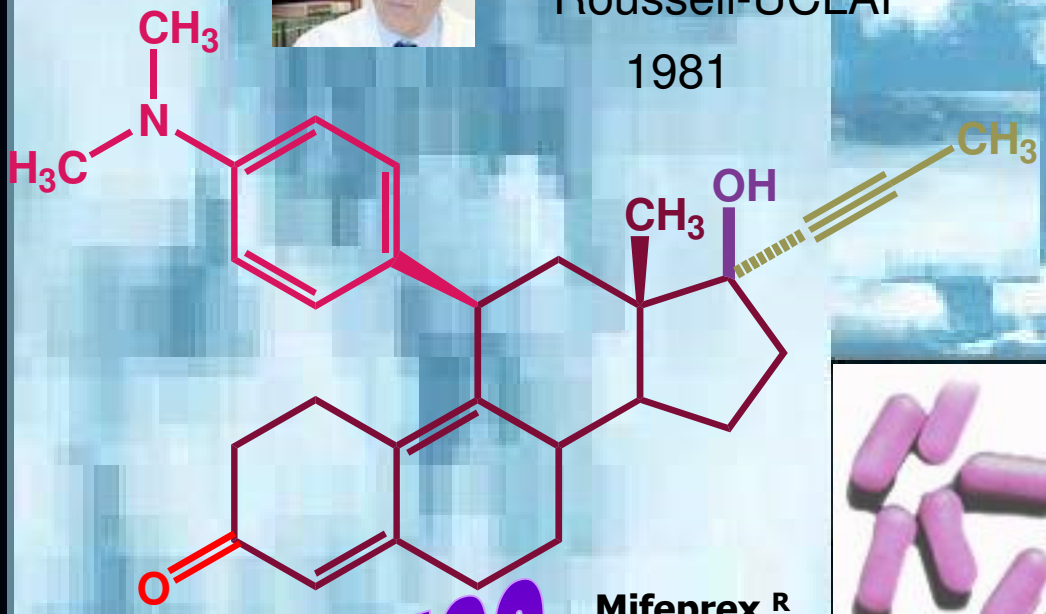
mifepristona

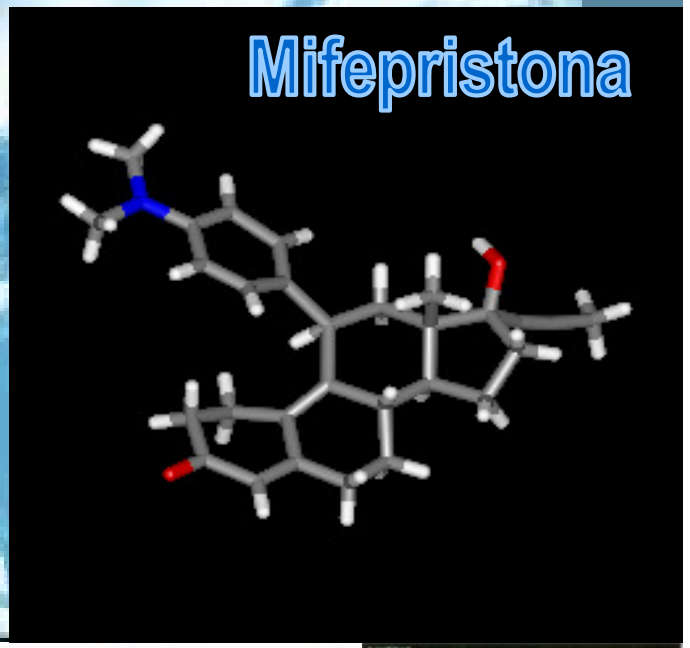
Etienne-Emile Beaulieu
Roussell-UCLAF

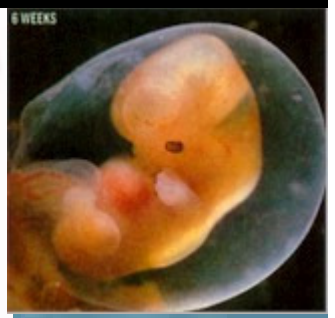
1981

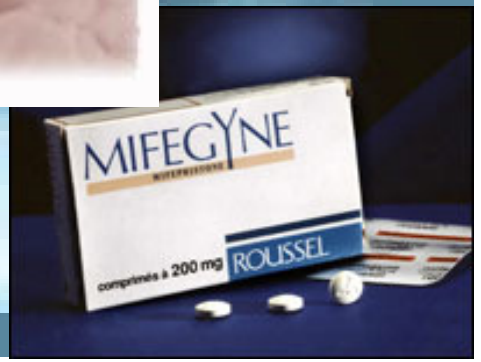


RU 486

Mifeprex R







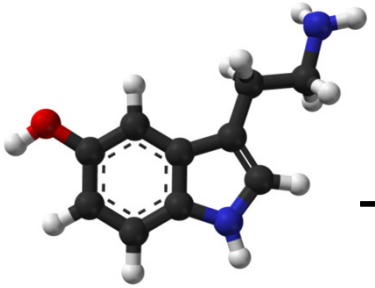
Pílula do dia seguinte

Gênese da indometacina

Tsung Y Shen

(1924 -)

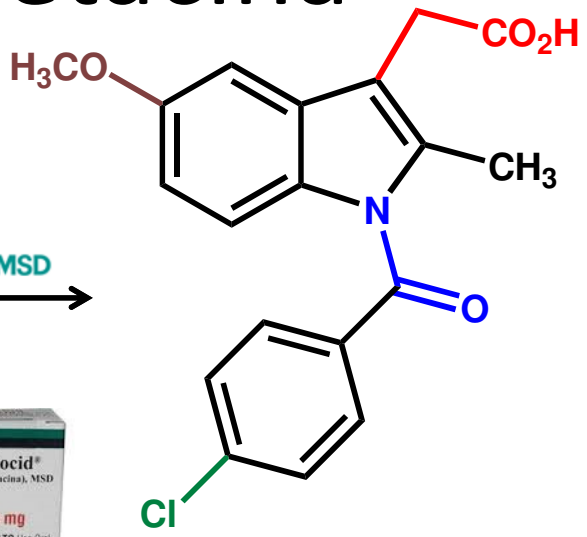
Charles Allen Winter
(1903 – 1999)



serotonina

1958

MSD



indometacina

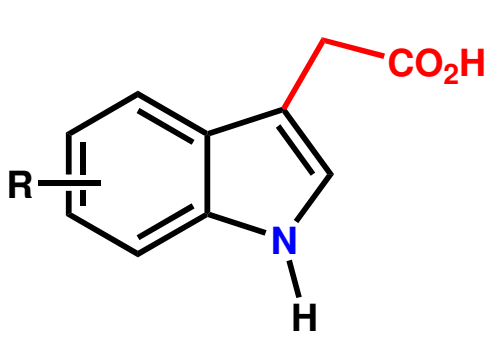
T. Y. Shen et al., *J. Am. Chem. Soc.* **1963**, *85*, 488
T. Y. Shen, Toward more selective antiarthritic therapy, *J. Med. Chem.*, **1981**, *24*, 1

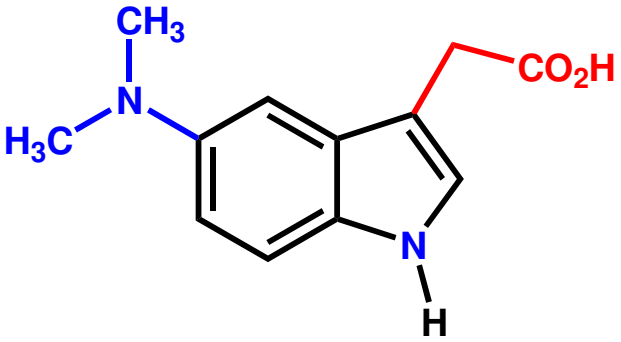
- American Chemical Society Division of Medicinal Chemistry Hall of Fame
- First winner of the GlaxoSmithKline Alfred Burger Award

American Chemical Society
Division of Medicinal Chemistry
Hall of Fame

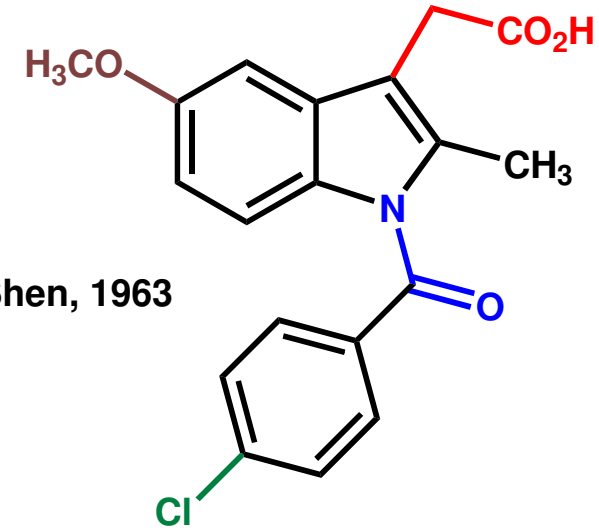
ACS Hall of Fame

Gênese da indometacina





ácidos indolil-acéticos

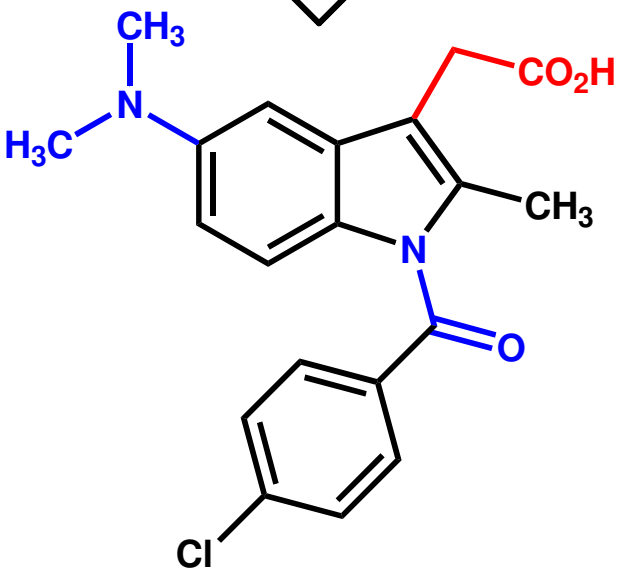


TY Shen, 1963

indometacina

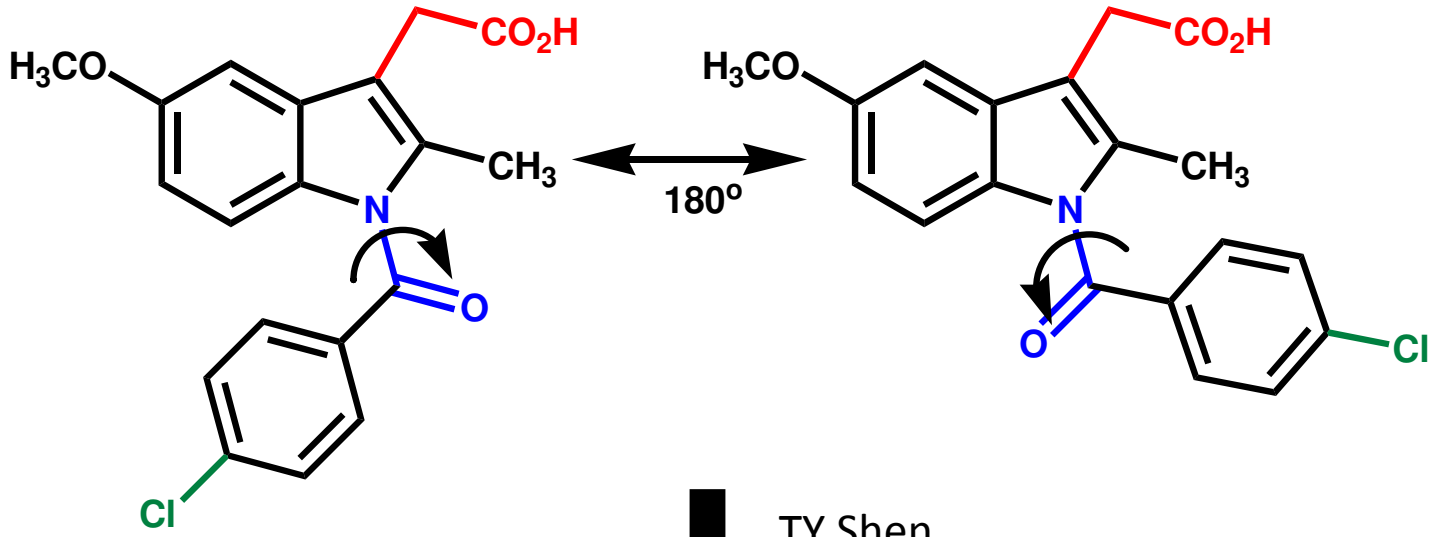
ca. 300 compostos

Charles A Winter
Cg ind r.p.e.
MSD

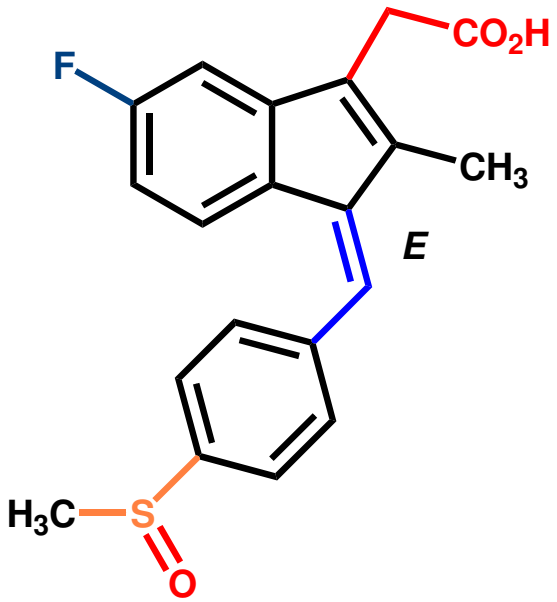


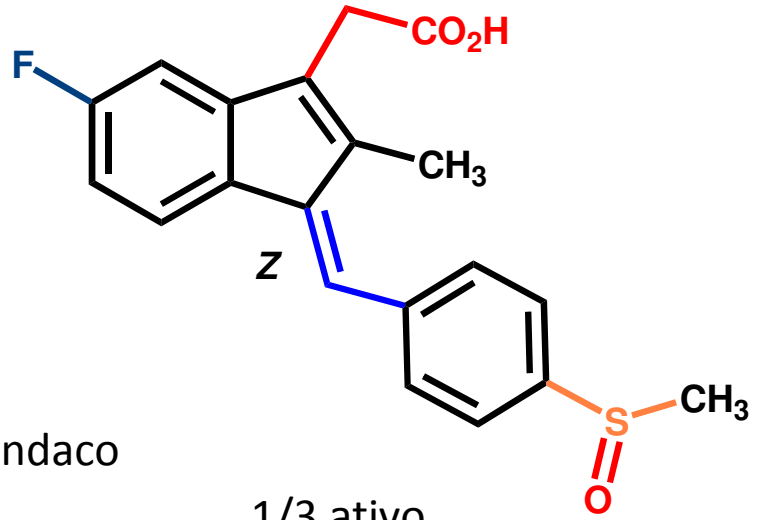
MT-587

Conformação Bioativa



TY Shen

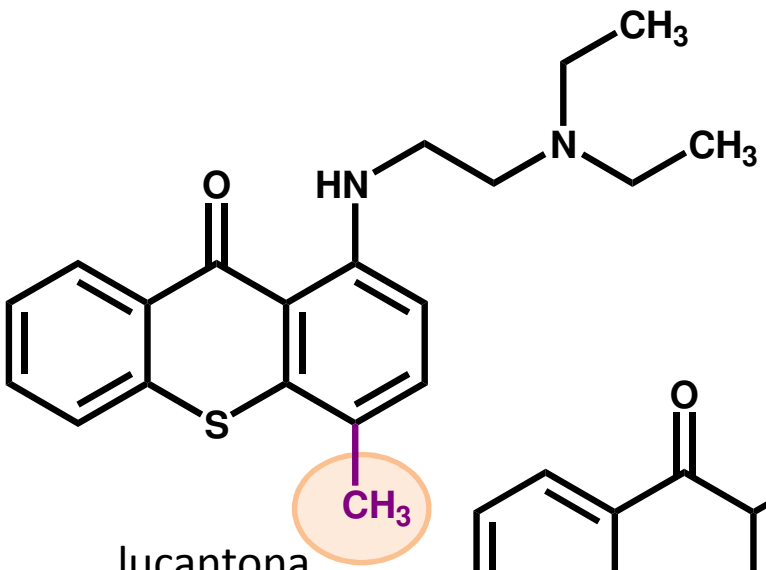




sulindaco

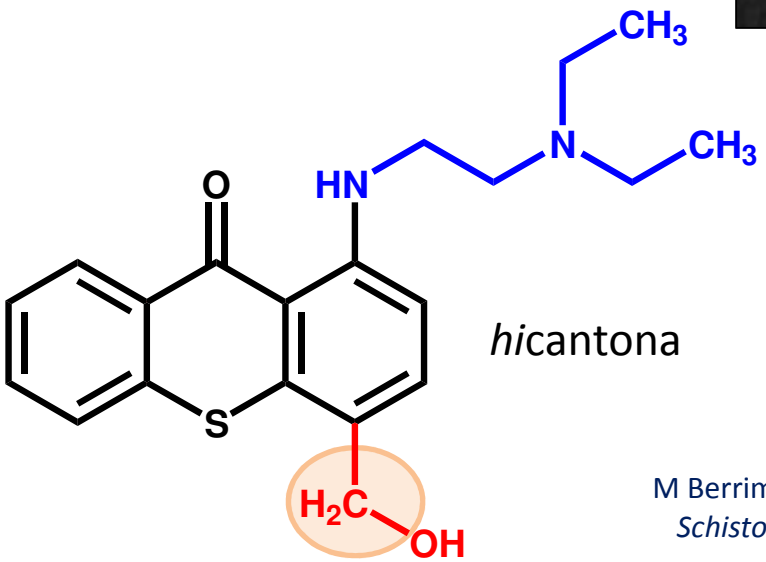
1/3 ativo

Gênese da oxamniquina



lucantona

Miracil B



*hi*cantona

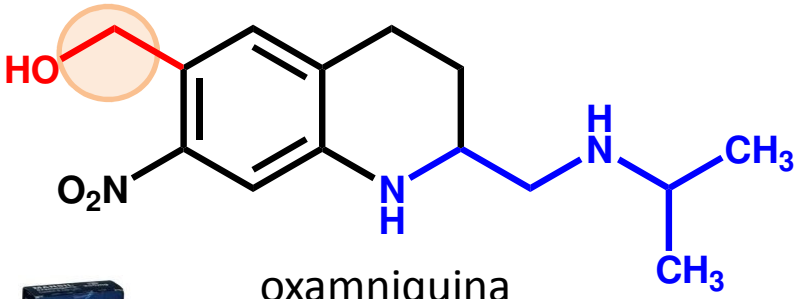
Schistosoma mansoni

140 - 60 µm

nature

M Berriman et al., The genome of the blood fluke *Schistosoma mansoni*, *Nature* **2009**, *460*, 352.

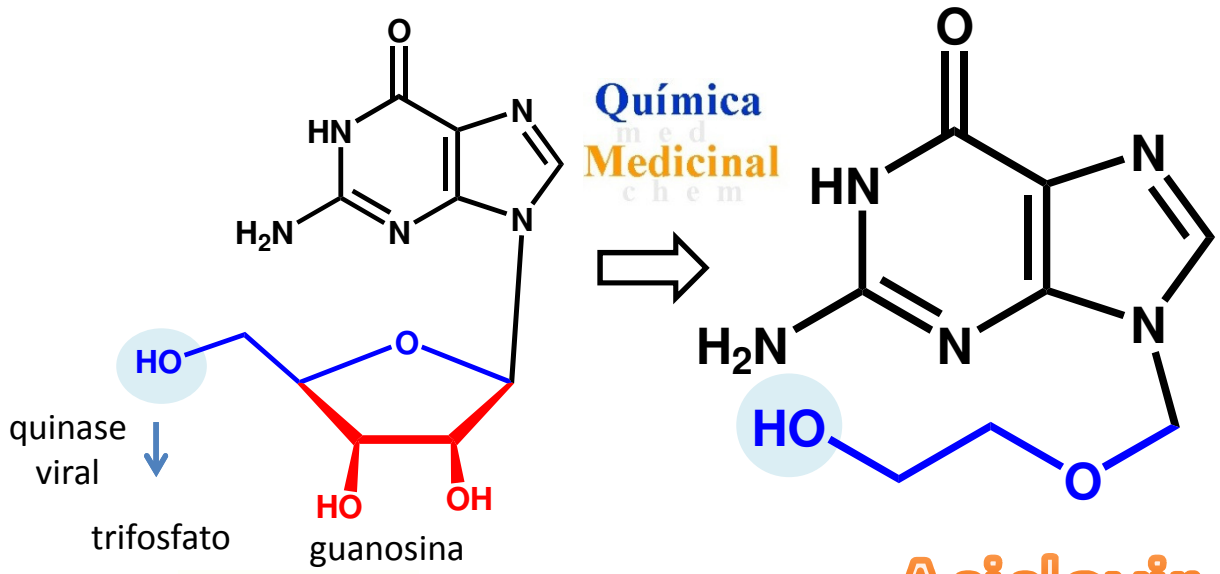
Química med Medicinal chem



oxamniquina

Kaye & Woolhouse, 1972
Pfizer, Sandwich, UK

Gênese do aciclovir



M E Avery, Gertrude Belle Elion, 23 January 1918 - 21 February 1999, *Biographical Memoirs of Fellows of the Royal Society* **2008**, *54*, 161–168.

Burroughs Wellcome (atual GSK)

1988

Gertrude B Elion
(1918-1999)

posologia

6-mercaptopurina, azatioprina, alopurinol, trimetoprim, nelarabina

E de Clercq, H Field, Antiviral prodrugs – the development of successful prodrug strategies for antiviral chemotherapy, *Br J Pharmacol* **2006**, *147*, 1

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A invenção do propranolol

Raymond Ahlquist (1914

Am J Physiol 1948, 153, 586

A STUDY OF THE ADRENOTROPIC RECEPTORS

RAYMOND P. AHLQUIST

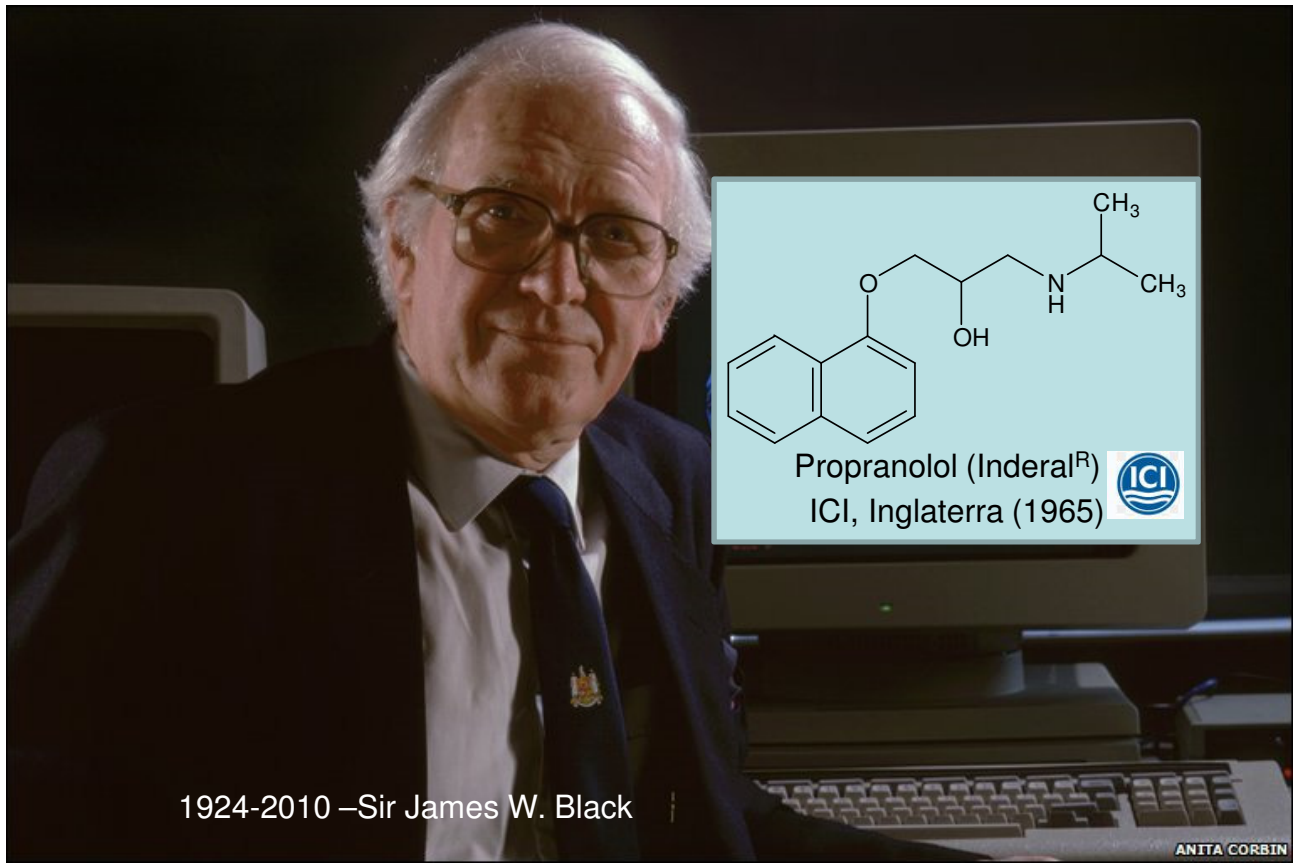
From the Department of Pharmacology, University of Georgia School of Medicine

AUGUSTA, GEORGIA

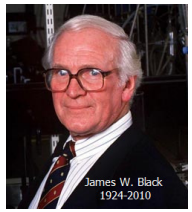
Premio Nobel
1988

Química Medicinal

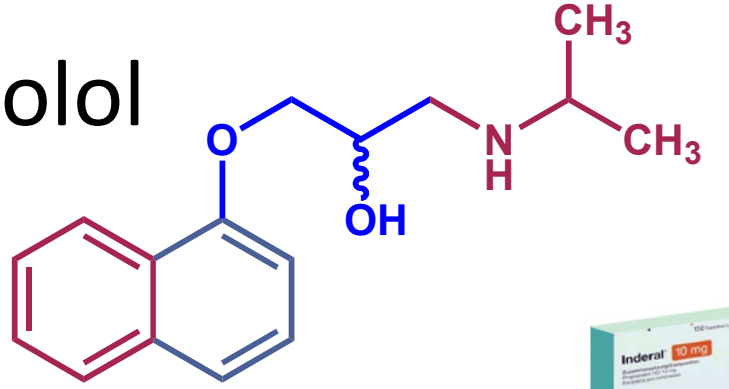
Pharmacology
Farmacologia



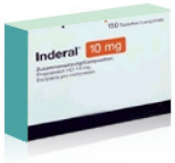
A invenção do propranolol



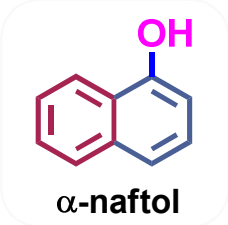
James W. Black, 1988 - "Pronethalol always seemed to us to be a prototype drug, good enough to answer questions of principle, but not good enough to be marketable"



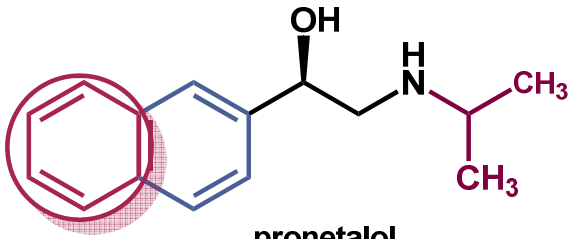
propranolol
1964



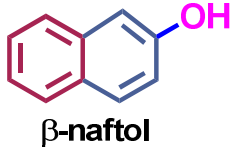
J. Black *et al.*, *Br. J. Pharmacol. Chmother.* **1965**, *25*, 577



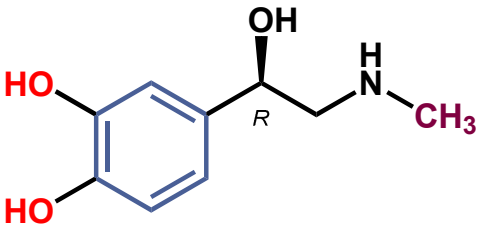
α-naftol



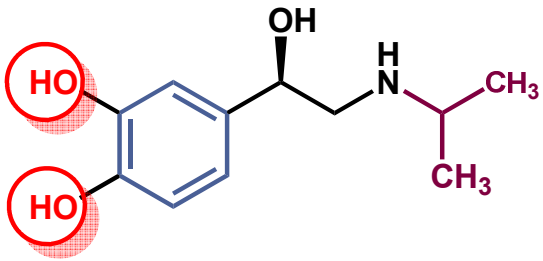
pronetalol
1959



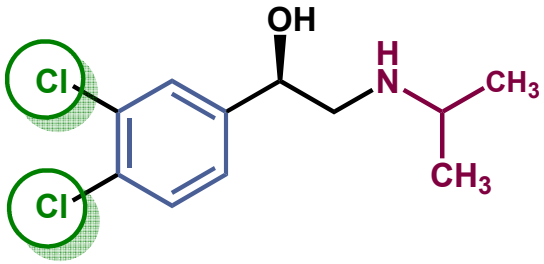
β-naftol



adrenalina

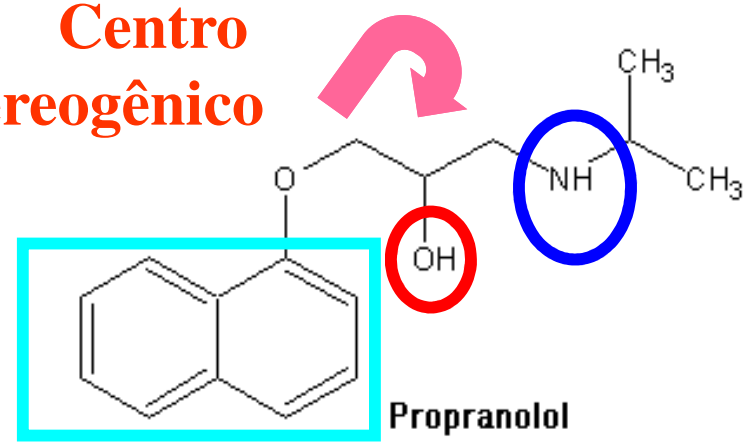


isoprenalina / isoproterenol



1958 - DCI
β-bloqueador

Centro estereogênico

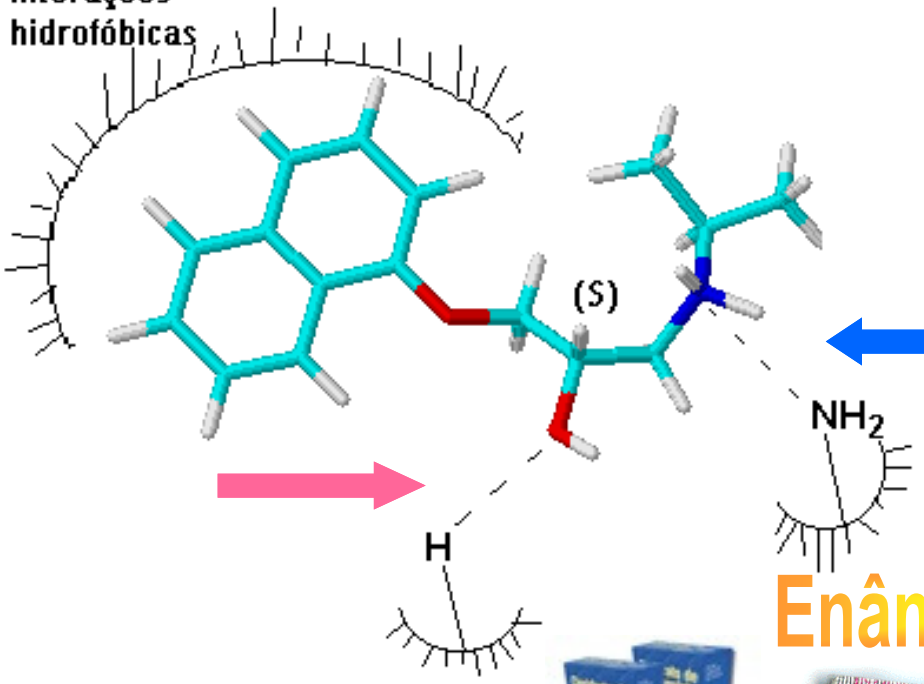


Propranolol

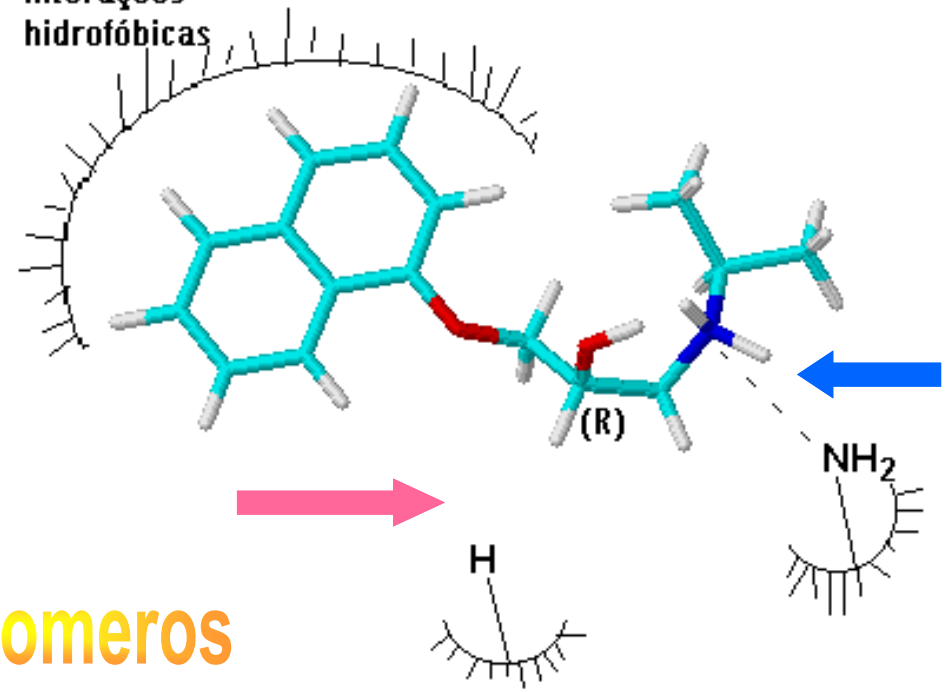
Eutômero

Distômero

Interações hidrofóbicas



Interações hidrofóbicas



Enântiomeros

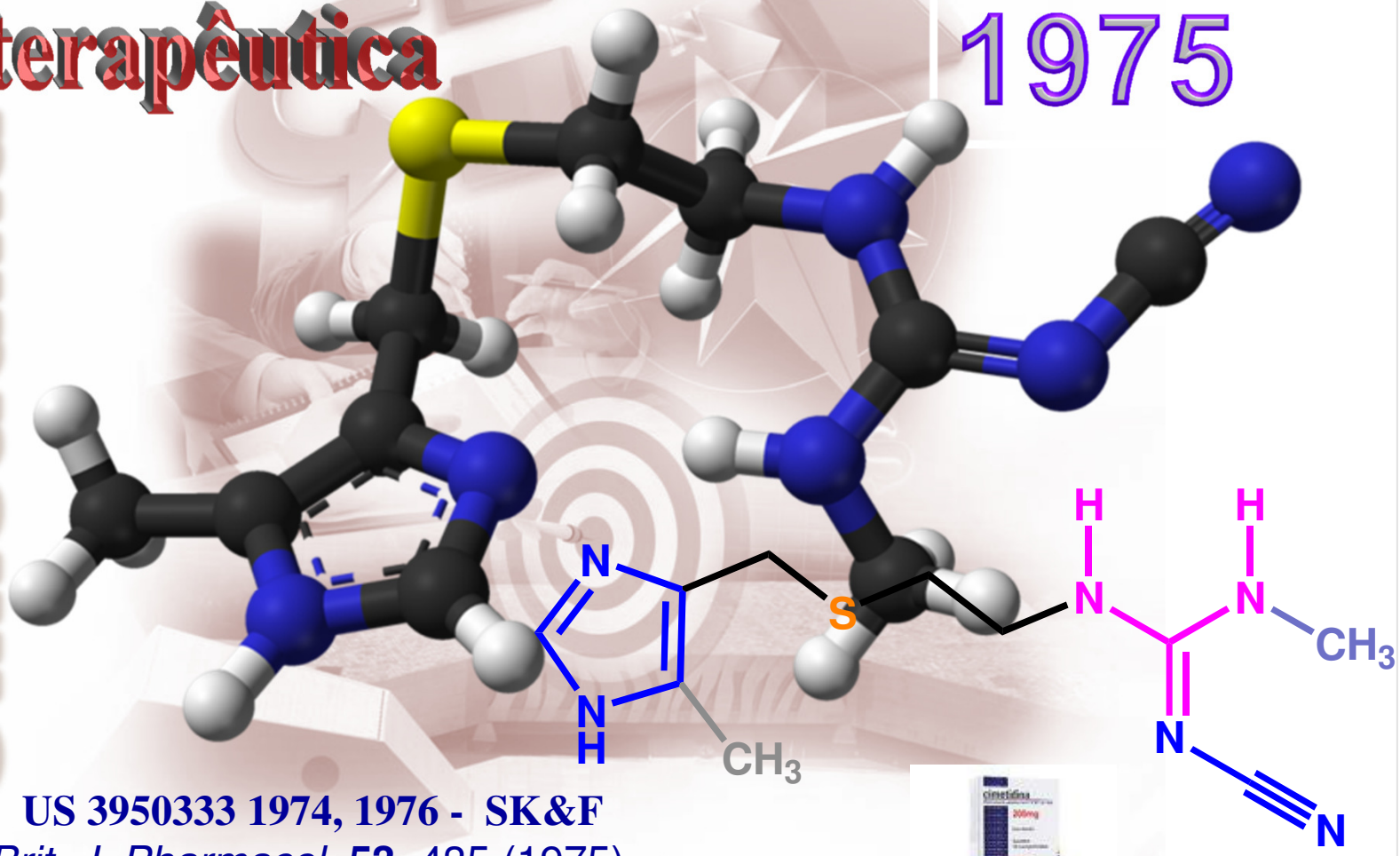
Universidade Federal do Rio de Janeiro

O desenvolvimento racional

Inovação terapêutica

1975

Cimetidina



US 3950333 1974, 1976 - SK&F

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

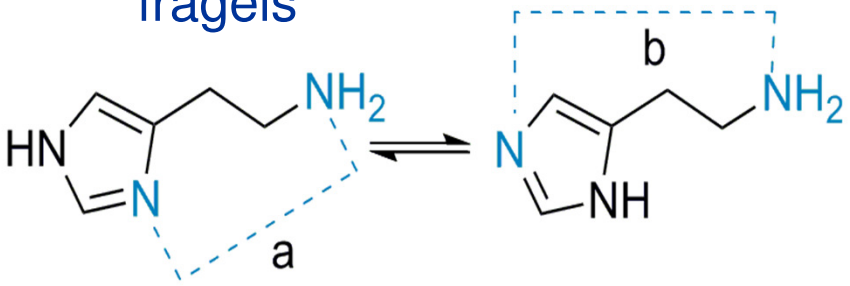
James Black, Robin Ganellin, Emmett, Durant

$C_{10}H_{16}N_6S$

Abordagem Fisiológica

Química Medicinal

Interações frágeis



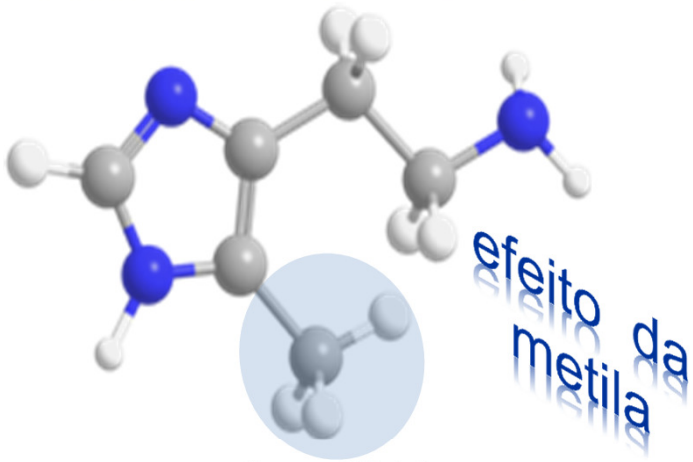
Forma A

a = 4,83 Å
b = 5,52 Å

Forma B

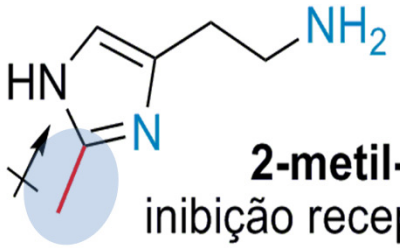
tautomêros

Propriedades estruturais



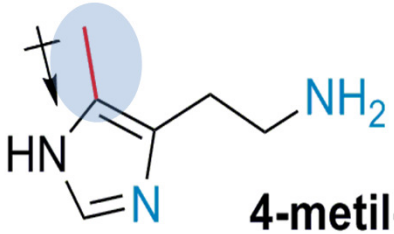
4-metil-histamina

Análogo ativo



2-metil-histamina

inibição receptores H_1 = 17%
inibição receptores H_2 = < 2%



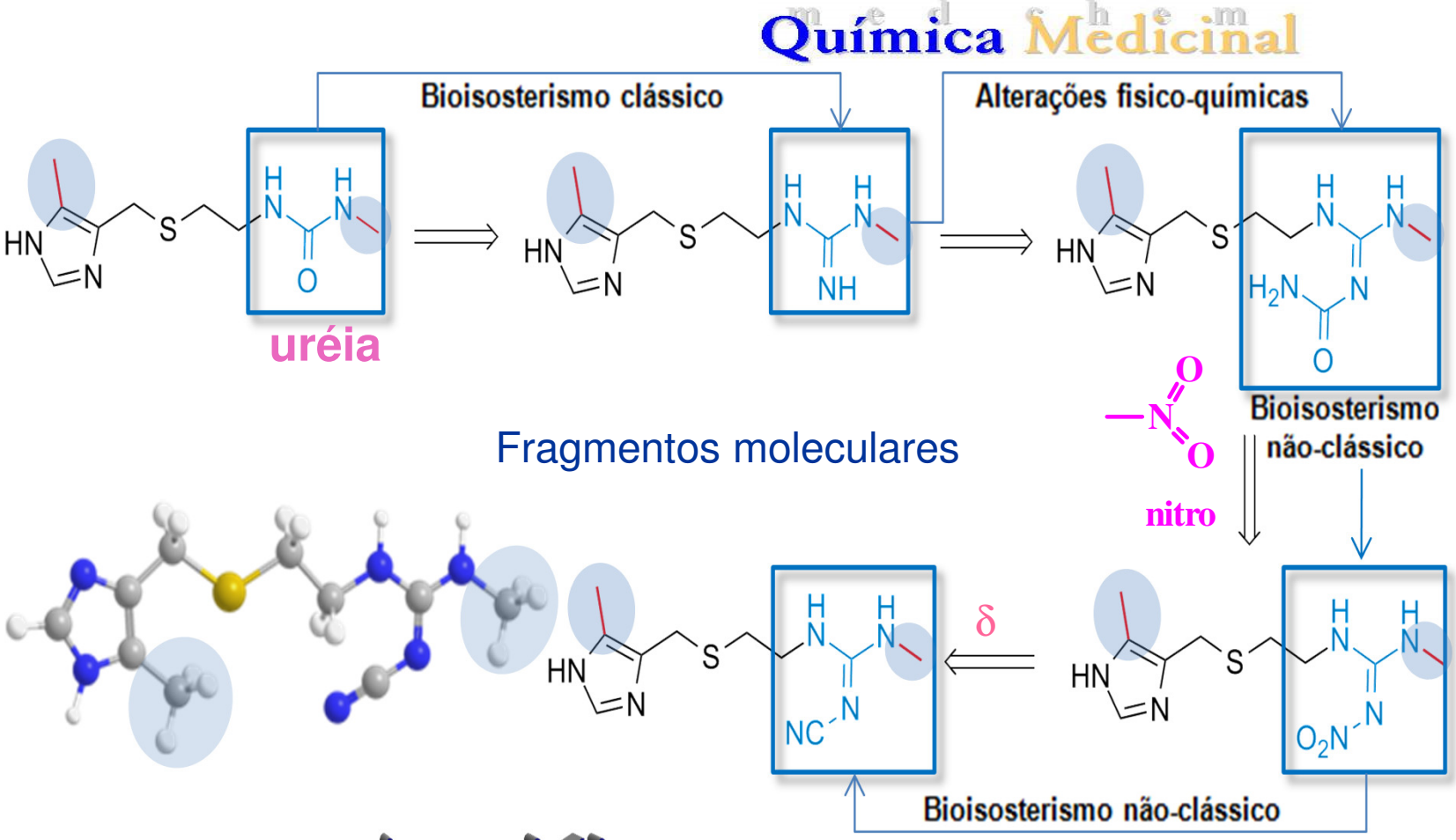
4-metil-histamina

inibição receptores H_1 = 0,2%
inibição receptores H_2 = 50%

Dois sub-tipos de H_R

Desenho estrutural baseado no substrato

Gênese da cimetidina



$C_{10}H_{16}N_6S$
PM: 252,1

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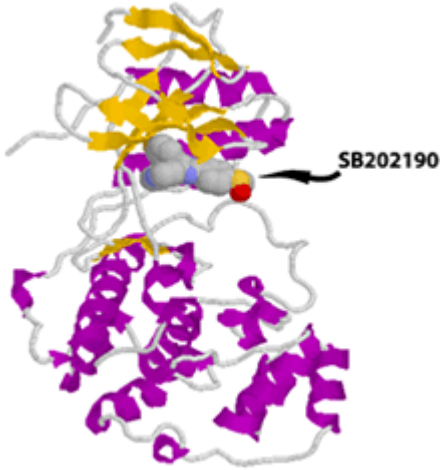
Química Medicinal

O século 21

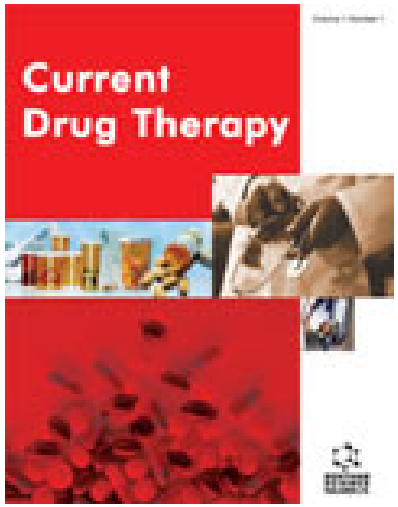


New Insights for Multifactorial Disease Therapy: The Challenge of the Symbiotic Drugs

Eliezer J. Barreiro and Carlos Alberto Manssour Fraga

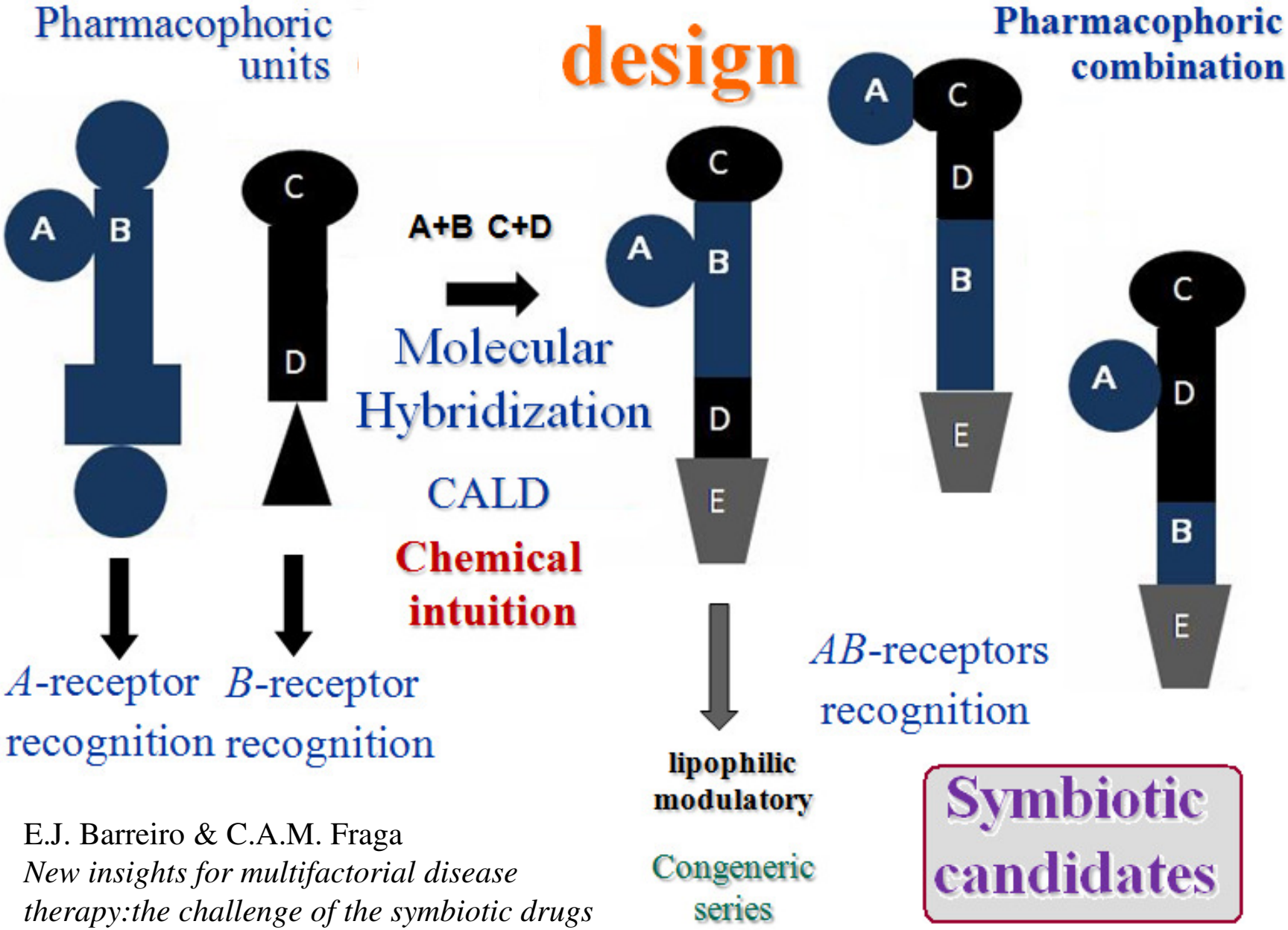
Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, P.O. Box 68023, 21944-971, Rio de Janeiro, RJ, Brazil.

Química Medicinal



O tratamento de fisiopatologias multifatoriais com fármacos mono-alvos, será sempre paliativo, especialmente em quadros crônicos-degenerativos que para tratamento eficaz exigirão fármacos multi-alvos, *i.e.* duais, duplos, mistos, múltiplos ou simbióticos.

Rational basis to symbiotic ligand design



E.J. Barreiro & C.A.M. Fraga
New insights for multifactorial disease therapy:the challenge of the symbiotic drugs
Current Drug Therapy **2008**, *3*, 1-13

UFRJ

Universidade Federal do Rio de Janeiro

Química Medicinal

Cidade Universitária, ilha do Fundão,
Rio de Janeiro, RJ

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Laboratório de Avaliação e Síntese de Substâncias Bioativas

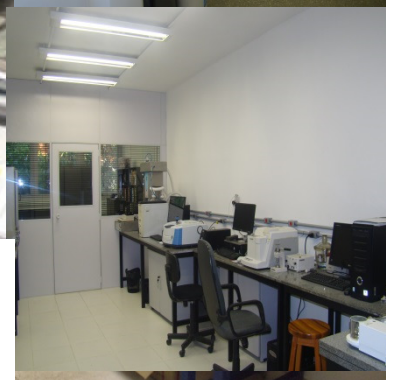
Bioensaios

Bioensaios

Criado em 19/04/1994 Laboratório de Avaliação e Síntese de Substâncias Bioativas

Molecular

Modelagem



Universidade Federal do Rio de Janeiro

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

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Laboratório de Avaliação e Síntese de Substâncias Bioativas
Universidade Federal do Rio de Janeiro

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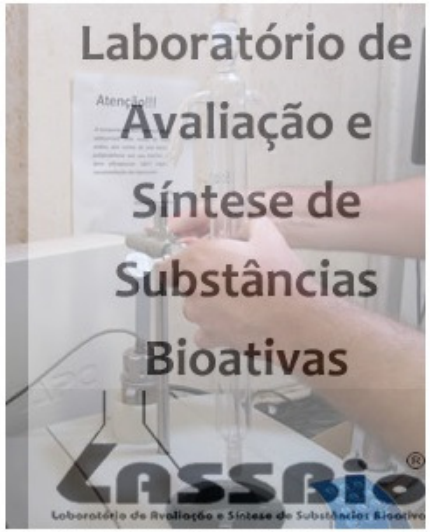
- » Inscrições abertas para a XX EVQFM
- » Fármacos na íntegra



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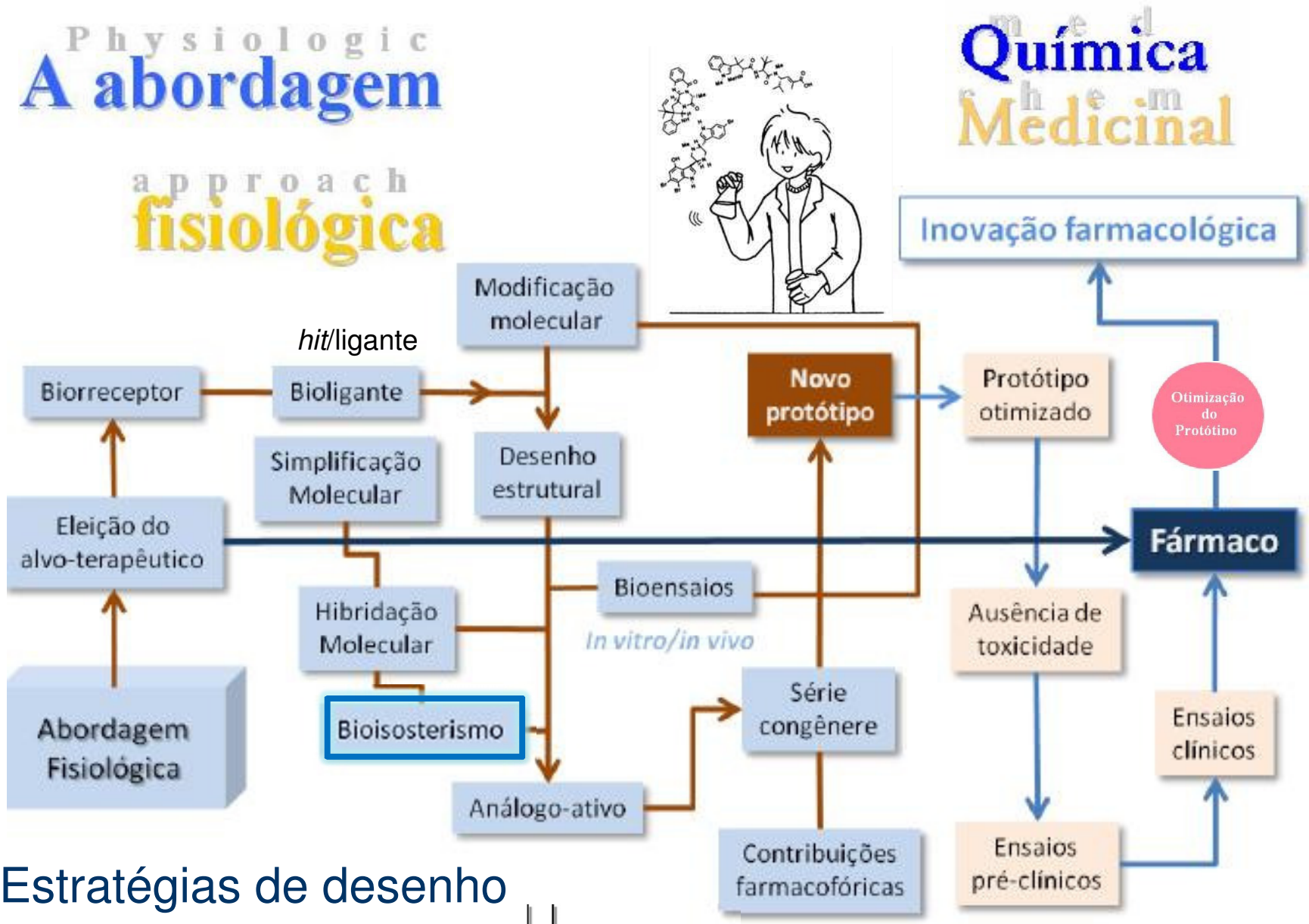
Estratégias de desenho molecular



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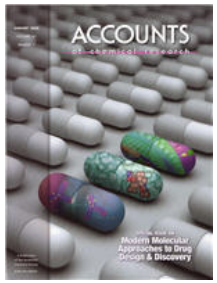
Volume 41, Number 1 ACCOUNTS OF CHEMICAL RESEARCH January, 2008

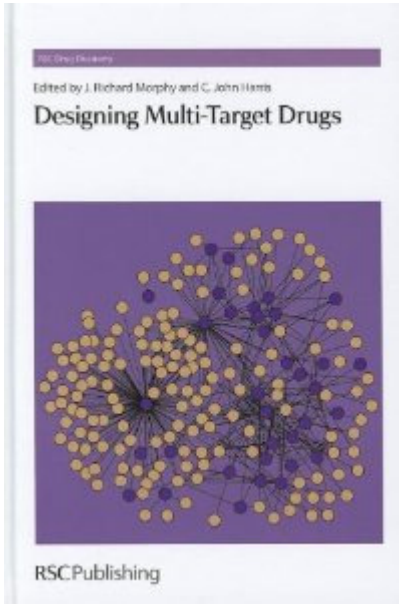
Hybrid Molecules with a Dual Mode of Action: Dream or Reality?

BERNARD MEUNIER

Palumed, rue Pierre et Marie Curie, BP 28262, 31262 Labège Cedex, France

RECEIVED ON APRIL 4, 2007





Curr Med Chem. 2011;18(32):4949-75.

Multi-target-directed ligands in Alzheimer's disease treatment.

Bajda M, Guzior N, Ignasik M, Malawska B.

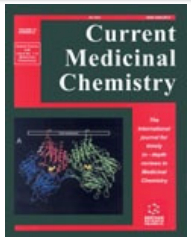
Curr Med Chem. 2011;18(31):4722-37.

Designed multiple ligands for cancer therapy.

O'Boyle NM, Meegan MJ.

⇨ Designing Multi-Target Drugs

R. Morphy & C. J. Harris, Editors
Royal Society of Chemistry,
2012

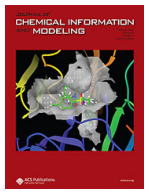


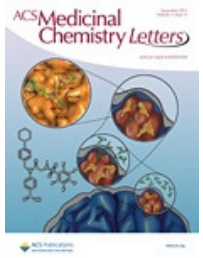
ACS Medicinal Chemistry Letters

ACS Med Chem Lett **2013**, 000

ACS Publications

pubs.acs.org/acsmedchemlett





Exploring the Chemical Space of Multitarget Ligands Using Aligned Self-Organizing Maps

Janosch Achenbach,[†] Franca-Maria Klingler,[†] René Blöcher,[†] Daniel Moser,[†] Ann-Kathrin Häfner,[†] Carmen B. Rödl,[†] Simon Kretschmer,[†] Björn Krüger,[‡] Frank Löhr,[§] Holger Stark,[†] Bettina Hofmann,[†] Dieter Steinhilber,[†] and Ewgenij Proschak*[,†]

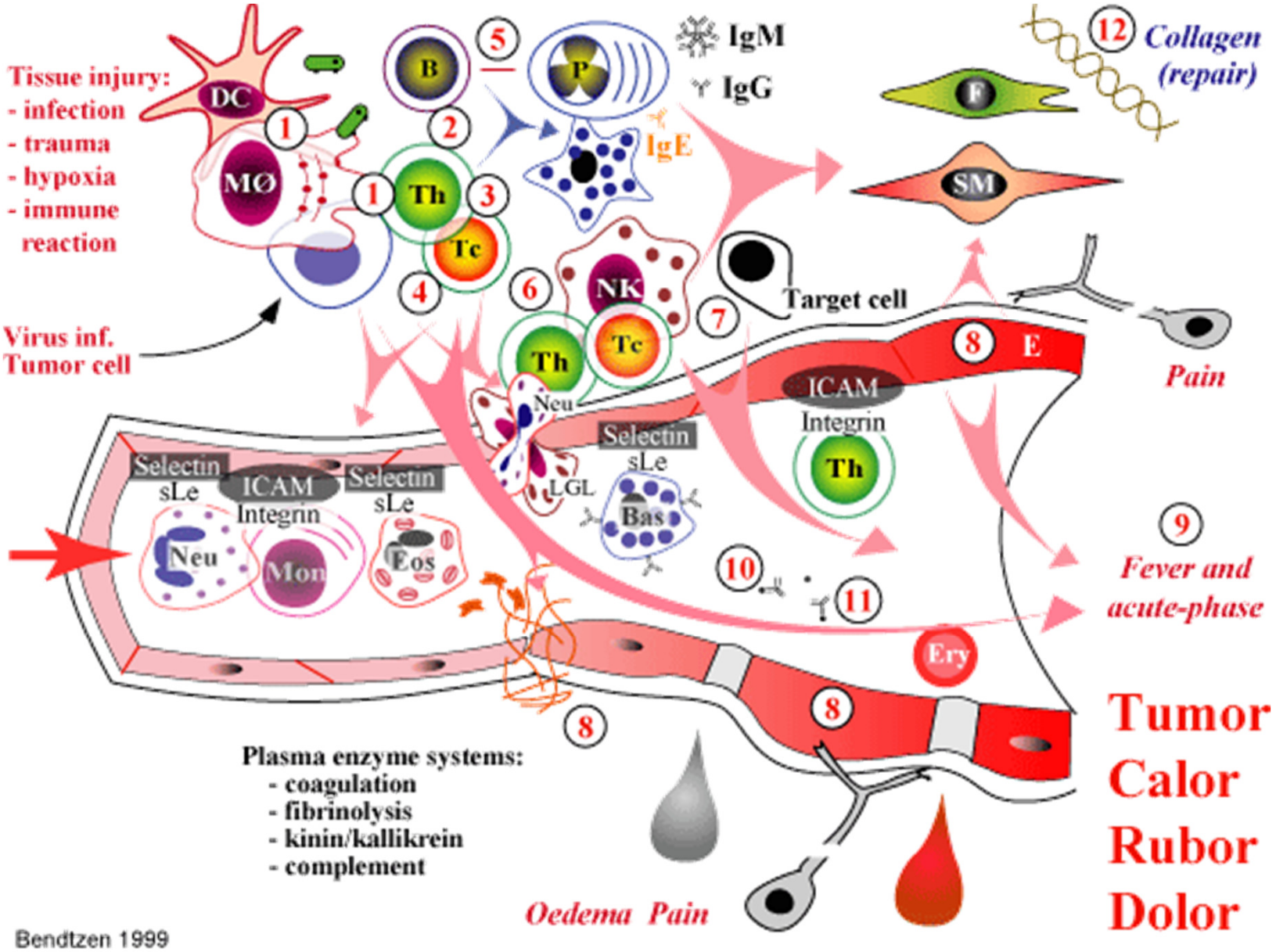
[†]Institute of Pharmaceutical Chemistry, ZAFES/OSF, Goethe University, Max-von-Laue-Strasse 9, D-60438 Frankfurt am Main, Germany

[‡]Chemical R&D—Drug Design, Merz Pharmaceuticals GmbH, Eckenheimer Landstrasse 100, D-60318 Frankfurt, Germany

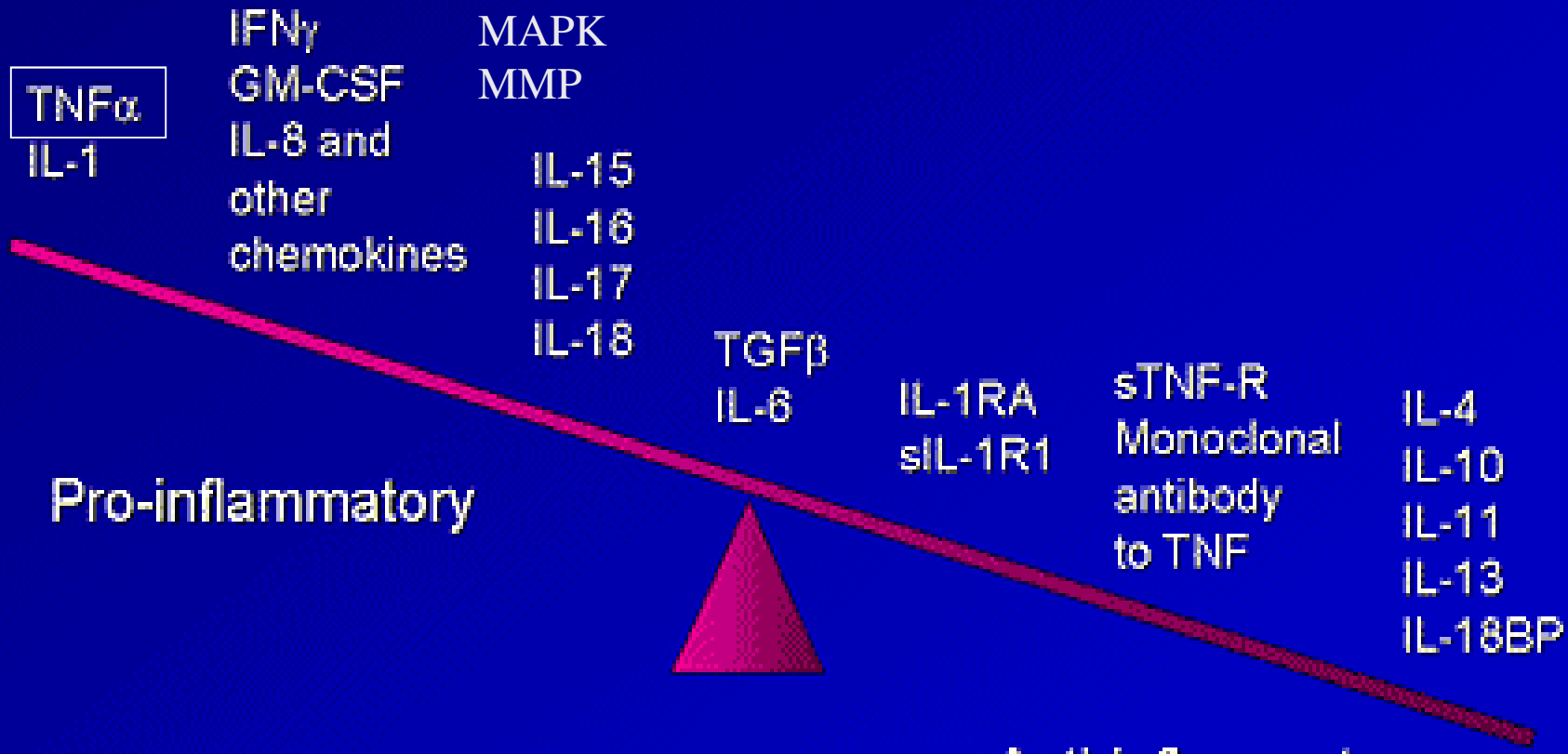
[§]Institute of Biophysical Chemistry, Goethe University, Max-von-Laue Strasse 9, D-60438 Frankfurt am Main, Germany

JL Medina-Franco et al., Shifting from the single to the multitarget paradigm in drug discovery, *Drug Discov. Today* **2013**, *18*, 495; JL Medina-Franco et al., Multitarget structure-activity relationships characterized by activity-difference maps and consensus similarity measure, *J Chem Inf Model* **2011**, *51*, 2427

Inflamação: Doença crônica não transmissível



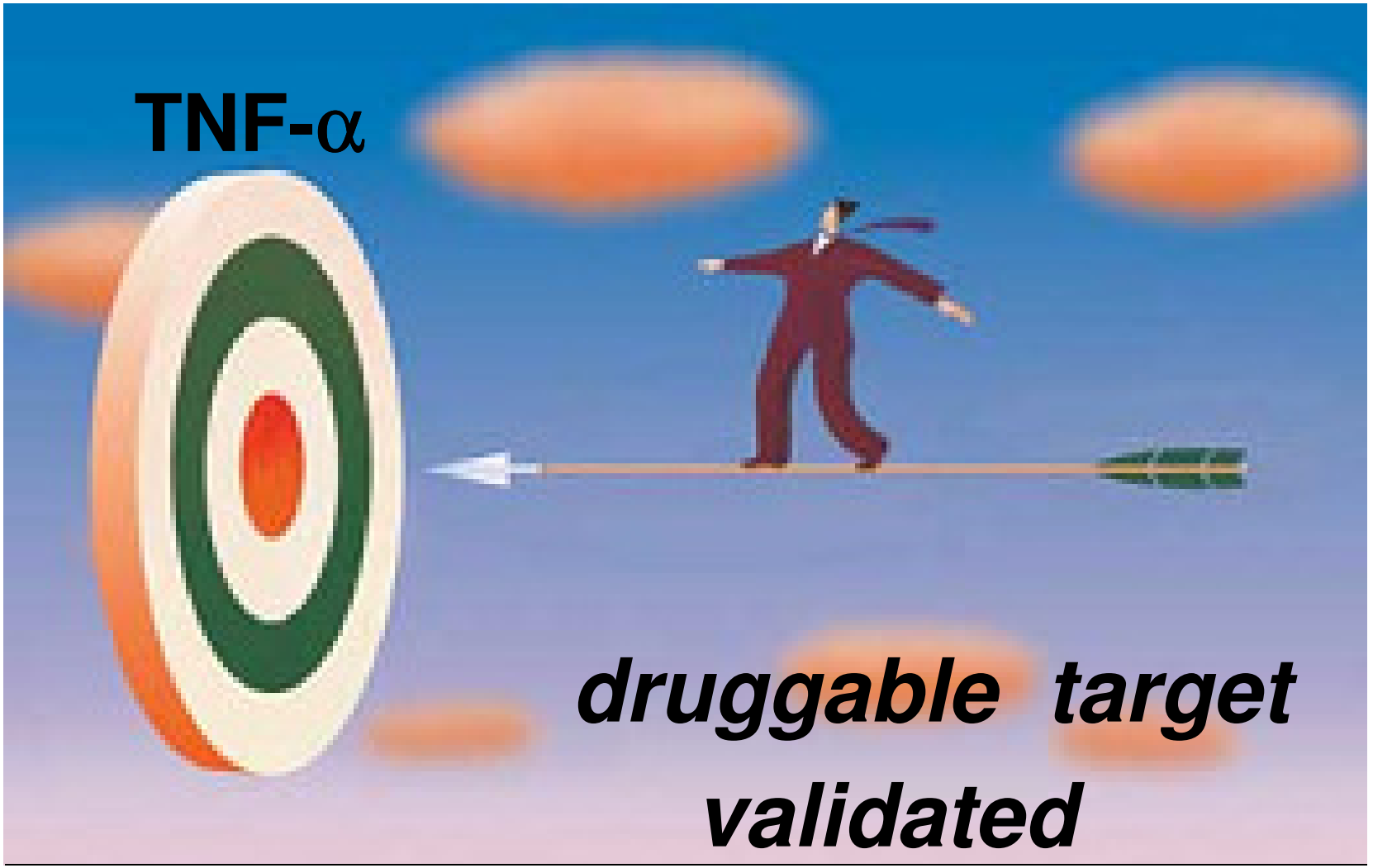
Role of Cytokines and Cytokine Inhibitors in Chronic Inflammation



Arend. *Arthritis Rheum* 2001.

* TNF-α = Tumor necrosis factor-alpha

The Target Election: TNF-α



TNF-α is a cytokine that appears rapidly in response to inflammatory injury

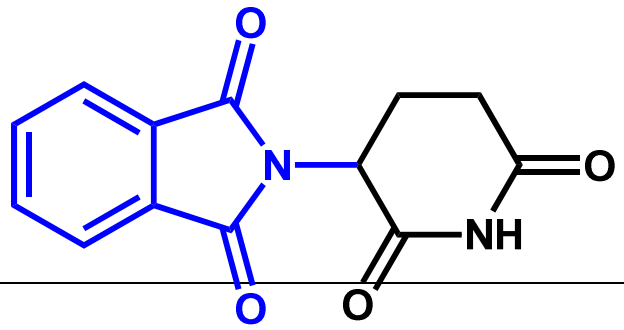
Anti-TNFα Therapies

*Protein-based anti-TNF-alpha Therapies in Clinical Use**

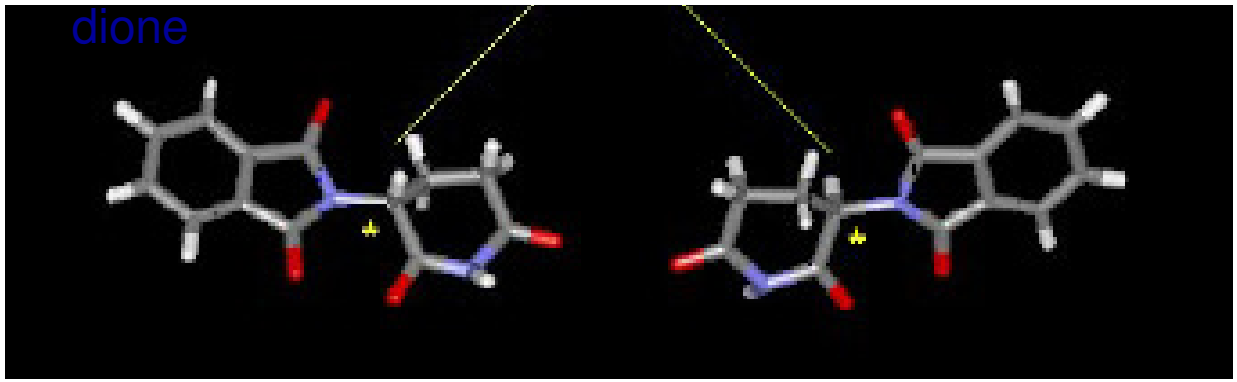
Drug	Status	Biological Form
Etanercept	approved	soluble TNFR2 coupled to Fc portion of IgG
Infliximab	approved	chimeric anti-human TNF antibodie
Adalimumab	approved	anti-human TNF antibodie
ISIS 104838	clinical	TNF anti-sense
Onercept	clinical	soluble p55 TNFR
Humicade	clinical	anti-TNF humanised IgG4

PC Taylor, Pharmacology of TNF blockade in rheumatoid arthritis and other chronic inflammatory diseases, *Curr. Op. Pharmacol*. **2010**, *10*, 308

* protein-based injectable anti-TNFα therapies



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



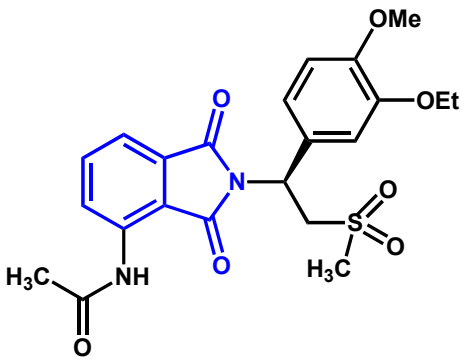
Thalidomide

Anti-TNF

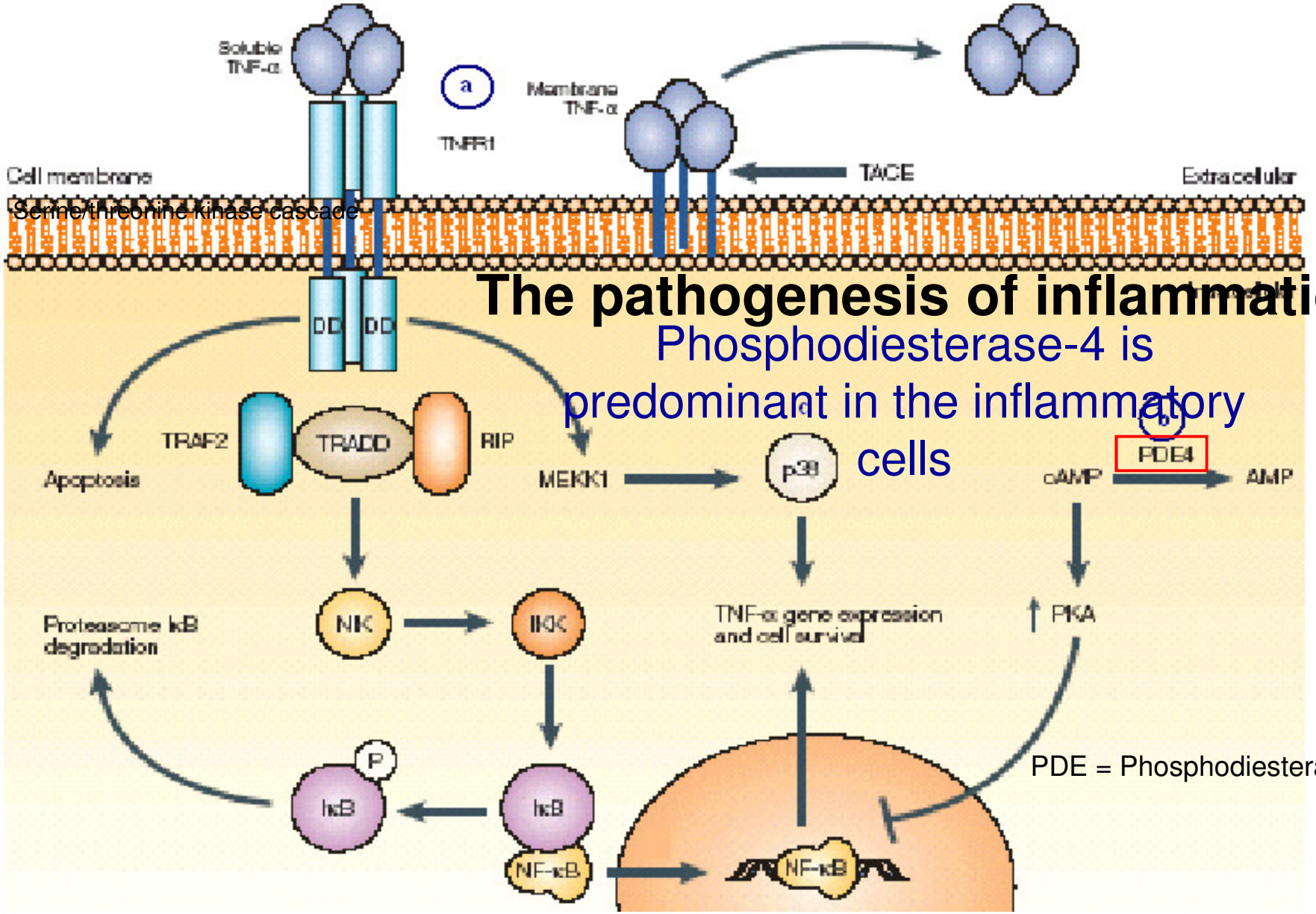
TNF-α IC_{50} = 200 μM

Wilhelm Kunz, 1953
Herbert Keller, 1953
CNS, 1957
Frances Kelsey, 1961
Gilla Kaplan, 1991 (TNF-α)
Elisabeth Sampaio,1997

Apremilast, Phase II, Celgene (2009)



Second Target Election:PDE



The pathogenesis of inflammatic

Phosphodiesterase-4 is predominant in the inflammatory cells

PDE = Phosphodiesteras

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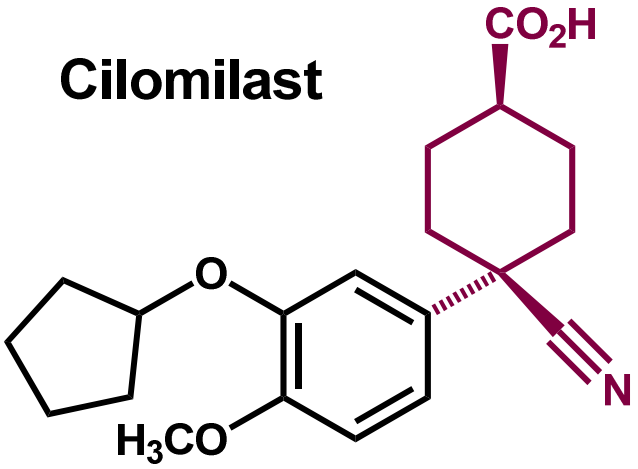
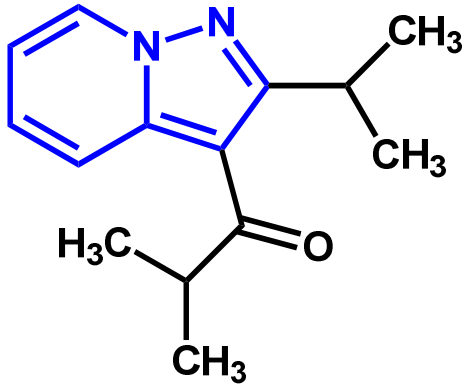
Cilomilast



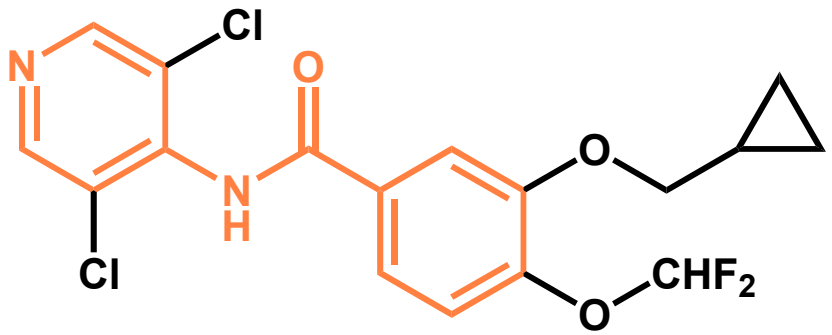
4-cyano-cyclohexyl carboxylic acid

Ibudilast



pyrazolo[1,5-*a*]pyridine

Ruflomilast

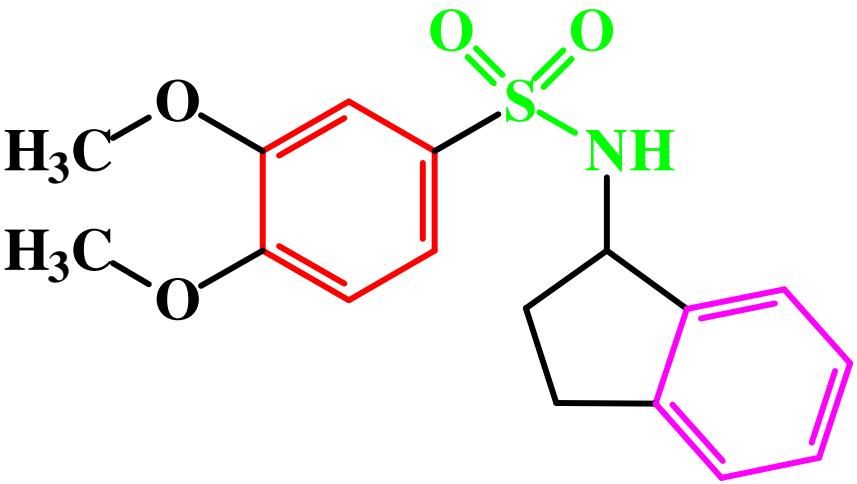


pyridine-benzamide

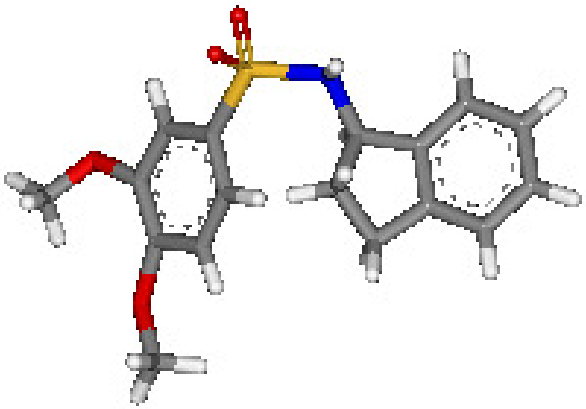
Recent advances on phosphodiesterase 4 inhibitors for the treatment of asthma and chronic obstructive pulmonary disease

A. Kodimuthali, S. S. L. Jabaris, M. Pal

J. Med. Chem. **2008**, *51*, 5471



Arylsulfonamide



PDE-4i IC_{50} = 4.3 μM

Patent US 5728712 , Application Number US/08/650672; 20 May, 1996.

J. G. Montana *et al.**, “Arylsulfonamides as selective PDE-4 inhibitors”, *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2635.

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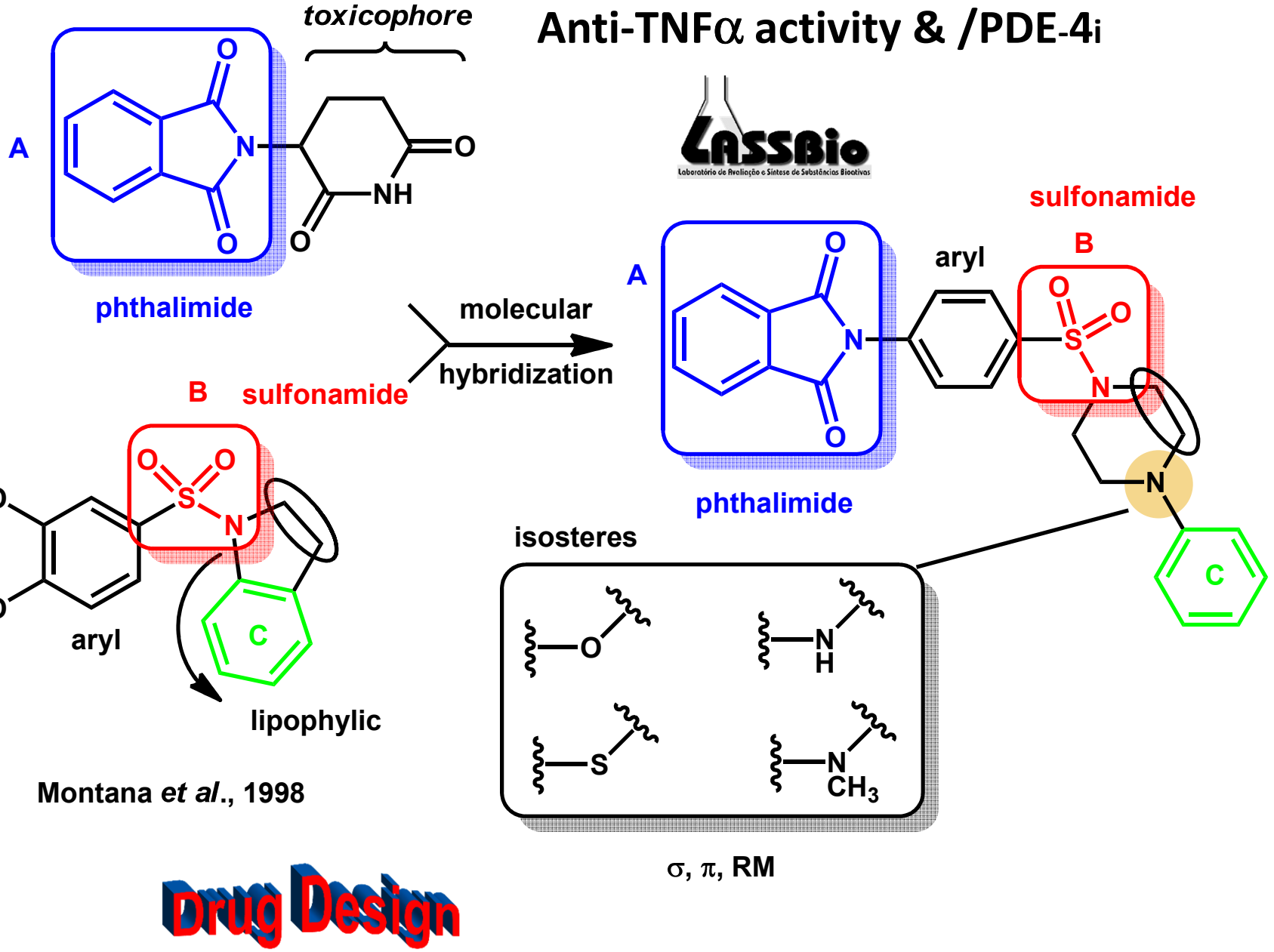
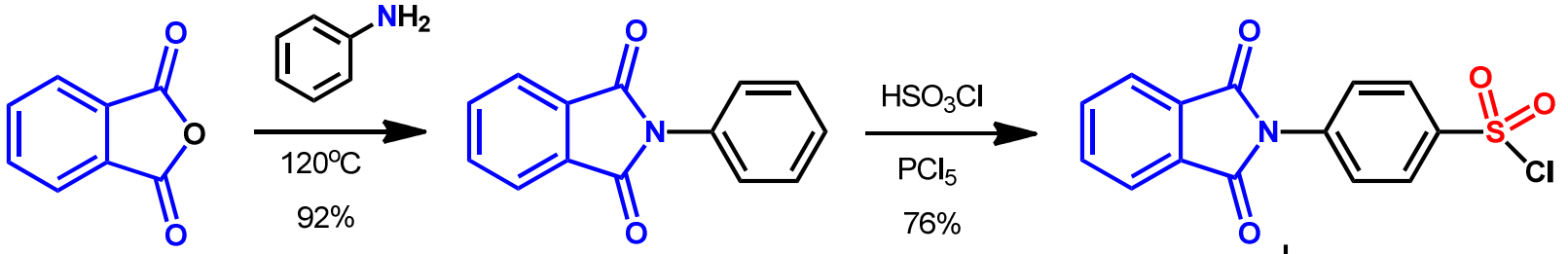
* Chiroscience Ltd, Cambridge Science Park, Cambridge, UK

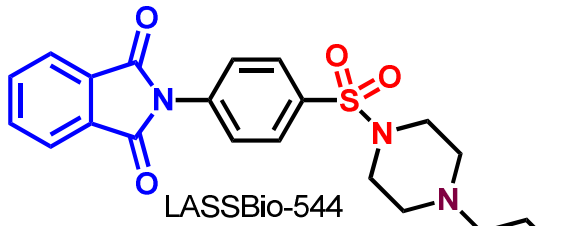
The design of new symbiotic agent with Anti-TNFα activity & /PDE-4i

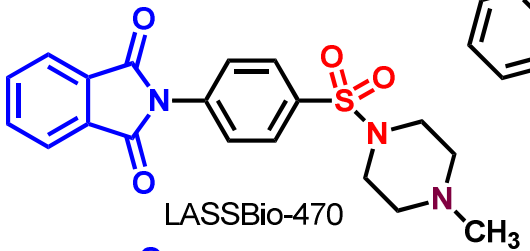


Synthesis of congeneric series

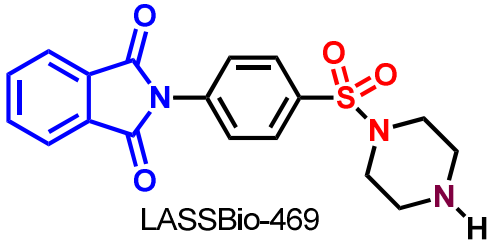


X= NPh 69%
X= NMe 67%
X= NH 58%
X= O 65%
X=S 72%

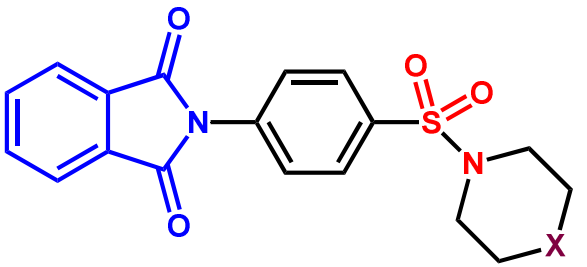

LASSBio-544

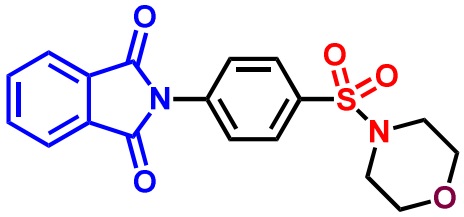


LASSBio-470

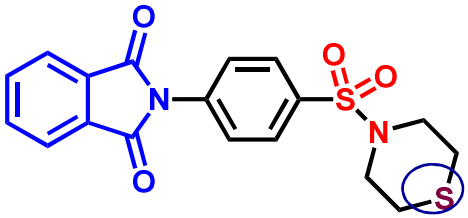


LASSBio-469





LASSBio-449



LASSBio-468

$C_{18}H_{16}N_2O_4S_2$
M.W. = 388.45

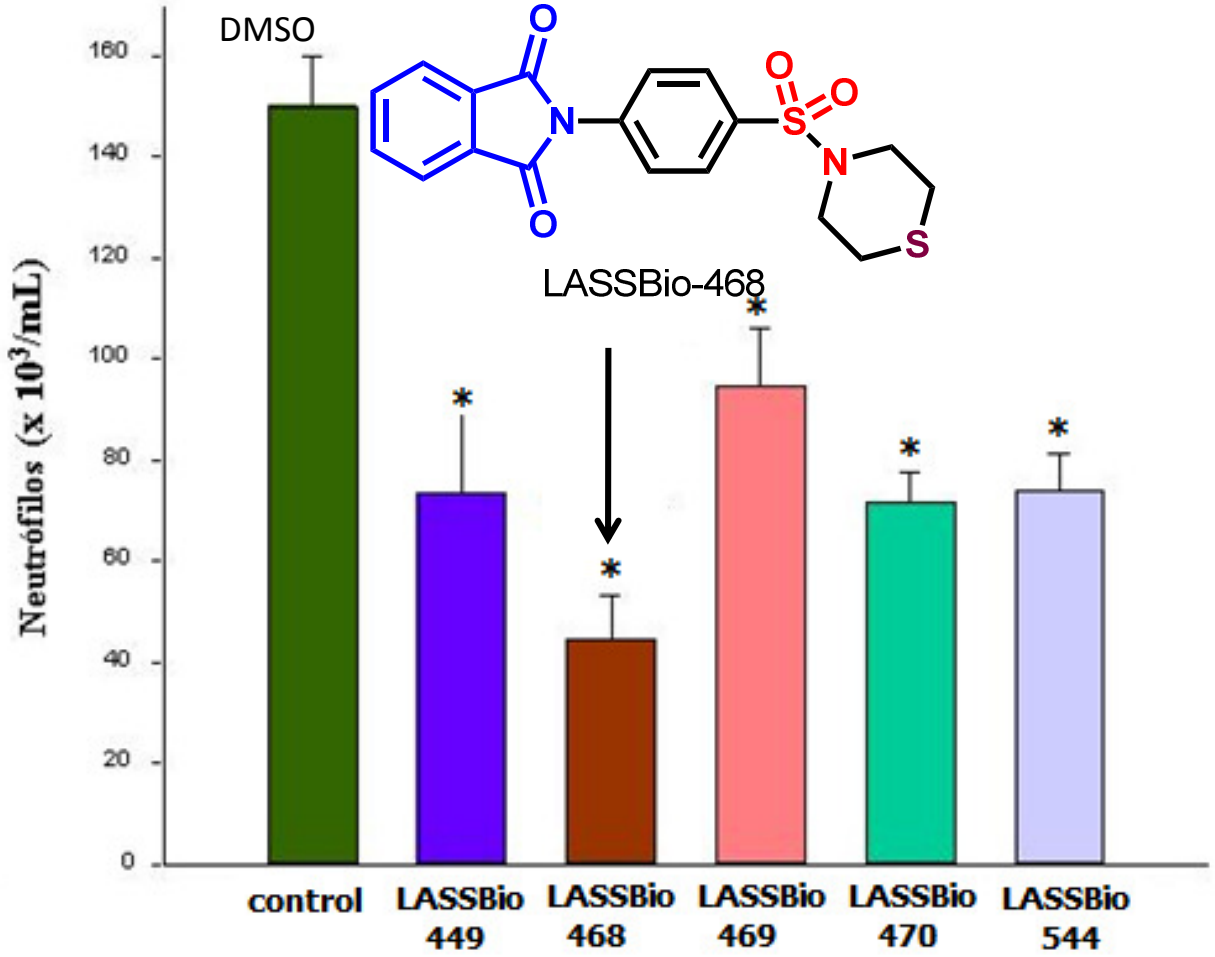
Overall yield: *ca.* 20%

(~ 0.5 M, 200 g)

Lidia M. Lima (LASSBio), PhD Thesis, IQ-UFRJ, Br., 2001

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

in vivo



Results are expressed as means SEM of seven animals.

Vera G Koatz
IBqM, Universidade Federal do Rio de Janeiro

Effect of compound LASSBio 468 (50 mg/kg, i.p.) on TNF-α levels and neutrophils influx (BALB/c of mice lungs)

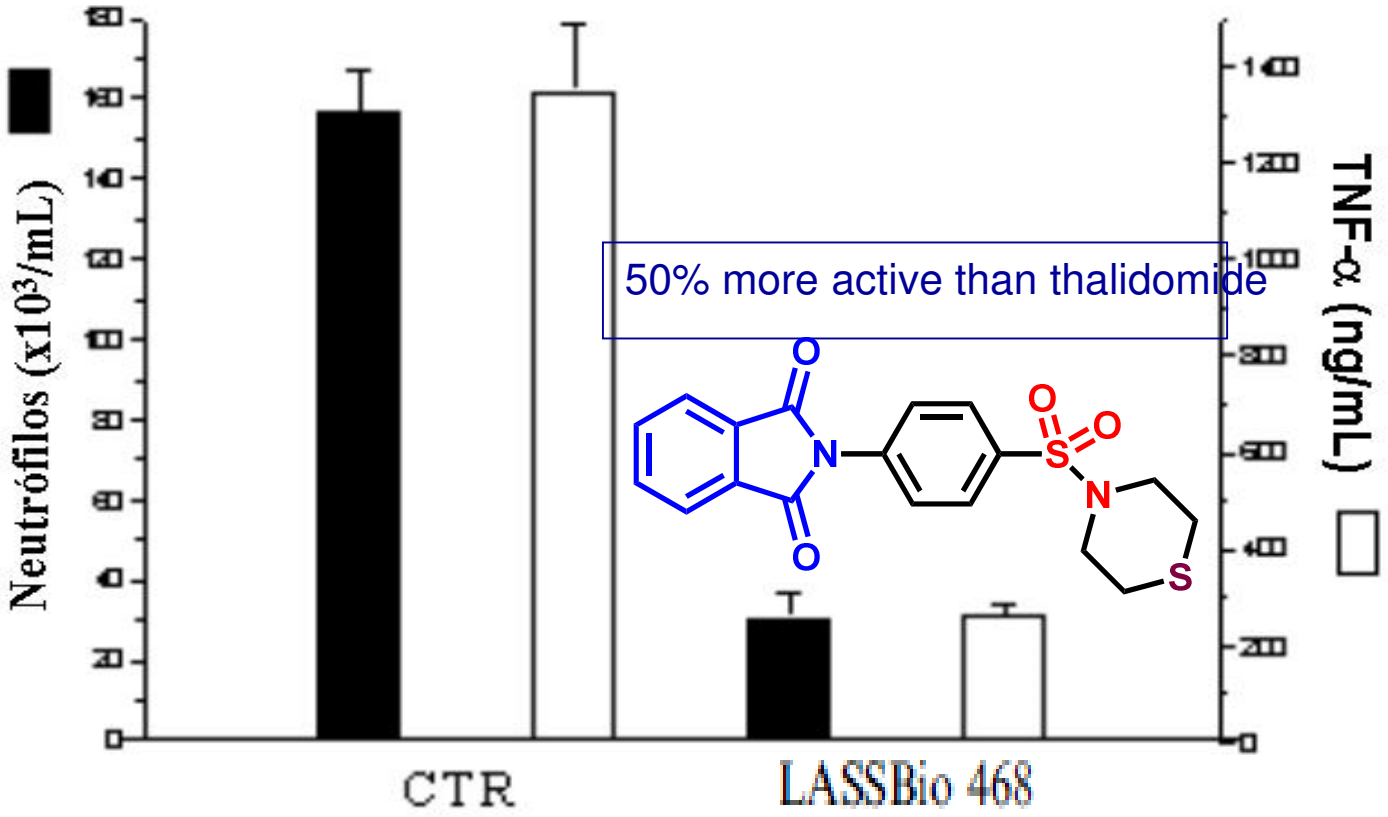
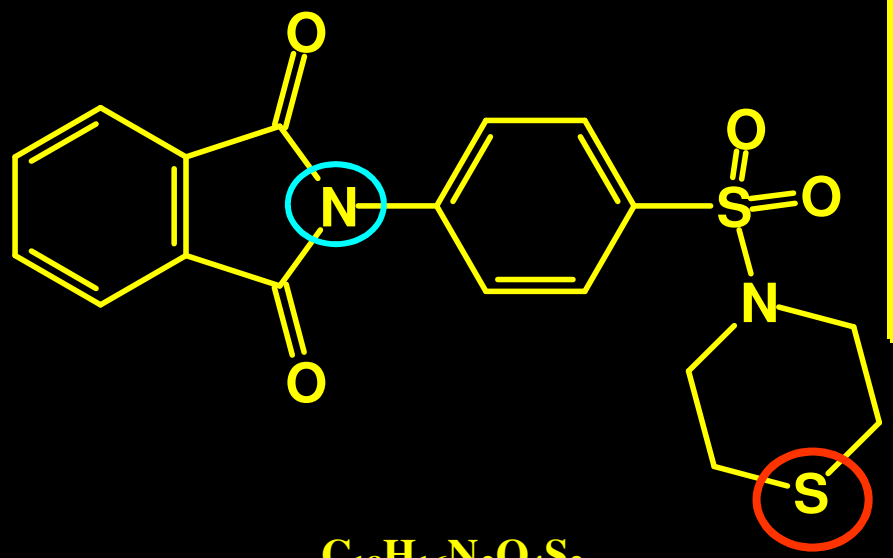


Fig. . Effect of LASSBio-468, thalidomide and pentoxifylline on survival BALB/c mice after LPS (500 µg/mice) administration.

Vera G Koatz
IBqM, Universidade Federal do Rio de Janeiro



$C_{18}H_{16}N_2O_4S_2$

LASSBio 468

TNF-α ED_{50} 2,5 mg/Kg

lead compound

PDE-4 inhibitor

IC_{50} = 13,5μM

cf. PDE-1, 2, 3, > 150 μM;

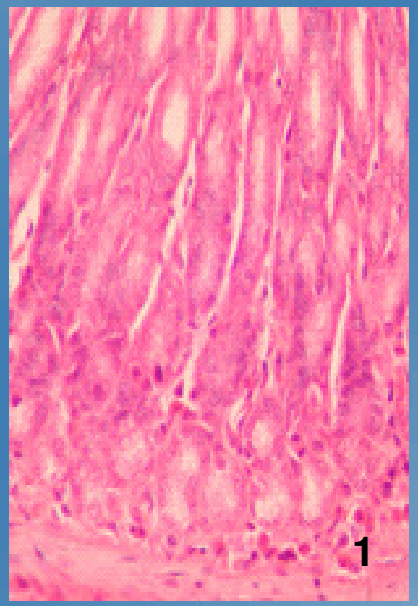
Dr Claire Lugnier (CAPES-COFECUB; LASSBio-Strasbourg)
Université Louis Pasteur, Strasbourg, FR.
Laboratoire de Pharmacologie et de Physicochimie des Interactions Cellulaires et Moléculaires.

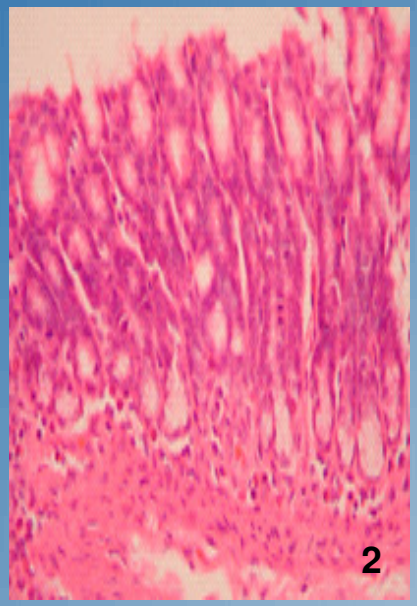
a) L. M. Lima *et al.*, "Synthesis and Anti-inflammatory Activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues", *Bioorg. Med. Chem.* 2002, 10, 3067;

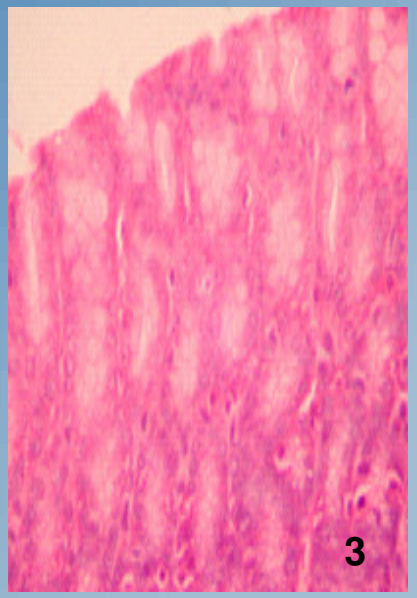
b) M. S. Alexandre-Moreira *et al.*, "LASSBio-468: a New achiral Thalidomide Analogue which Modulates TNF-α and NO Production and Inhibit Endotoxic Shock and Arthritis in Animal Model", *International Immunopharmacology* 2005, 5, 485.

Estudos de toxicidade

Histologia do estômago







(1) Fotomicrografia do estomago dos animais controle (HE – 100X);

(2) Animal tratado com talidomida. Mucosa apresentando características quase semelhantes a mucosa normal (HE – 100X);

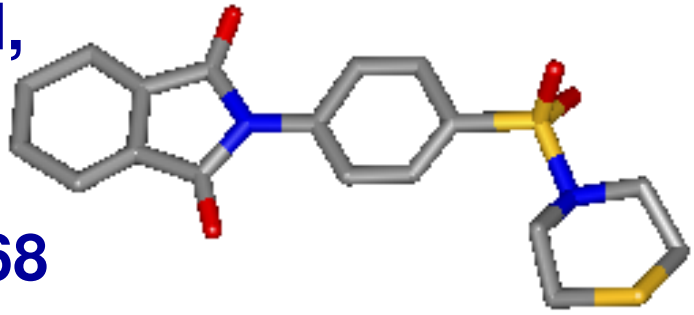
(3) Animal tratado com LASSBio 468. Mucosa apresentando características semelhantes a mucosa dos animais controle (HE – 200X);

Christina Tahkyia, IBCFF, UFRJ
Magna Suzana Alexandre-Moreira
LASSBio, Universidade Federal do Rio de Janeiro

LASSBio-468

A new symbiotic anti-inflammatory agent

LASSBio-468 is a new dual-target anti-inflammatory lead-compound, active at TNF-α production and with inhibitory activity on PDE-4, as originally planned. LASSBio-468 is structurally simple derivative, easy to synthesized at good overall yield and 0.5 M scale. This new achiral compound presents immunomodulatory activity without anti-proliferative effect, in contrast to THLD. LASSBio-468 is an useful lead-compound to treatment of chronicle inflammatory disorders as rheumatoid arthritis and shock septic syndrome.



L. M. Lima *et al.*, "Synthesis and Anti-inflammatory Activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues", *Bioorg. Med. Chem.* 2002, *10,* 3067

A. L. Machado *et al.*, "Design, Synthesis and anti-inflammatory activity of novel phthalimide derivatives, structurally related to thalidomide", *Bioorg. Med. Chem. Lett.* 2005, *15*, 1169

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Drug Data Report

Prous Science Ed. (ES.)

Vol. 24, No. 2, 2002

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

New Lead-compounds:

12611 (Boehringer Ingelheim)

312652 (Bayer)

313027 (GlaxoSmithKline)

KCO-912 (Novartis)

Asthma Therapy

LASSBIO-468

PI-0401660-2(09 /04/2004) ➡ **Novos candidatos a fármacos anti-inflamatórios**

Drug Data Report

Volume 23, Issue 10, 2001, Pages 949-1034

ANALGESIC AND ANESTHETIC DRUGS

Full Text: PDF (72 Kb)

ANALGESIC DRUGS

306339 (Euroceltique)
306344 (Euroceltique)
306935 (Ono)
307215 (Meiji Seika)
307485 (AstraZeneca)
307488 (AstraZeneca)
GRT-1539R (Grünenthal)
REN-1869 (Novo Nordisk; ReNeuron)

RESPIRATORY DRUGS

Full Text: PDF (147 Kb)

ASTHMA THERAPY

305505 (Merck KGaA)
305527 (Boehringer Ingelheim)
305570 (Euroceltique)
306350 (Advanced Medicine)
307151 (Protherics)
307296 (Nikken Chemicals)
307455 (Ube)
307490 (Icos)
307517 (Byk Gulden)
307521 (Byk Gulden)
307617 (Merck Frosst)
307627 (Celgene)
307629 (Celgene)
307841 (Bayer)
307866 (Celltech Group)
307964 (Pfizer)
308145 (Pfizer)
308151 (Pfizer)
308641 (Teijin)
308677 (Bayer)
CALP2 (University of Alabama at Birmingham; Janssen; Utrecht University)
LASSBio-468 (Universidade Federal do Rio de Janeiro)

AGENTS FOR RESPIRATORY DISTRESS SYNDROME

305451 (Shionogi)

TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES (COPD)

308751 (Bristol-Myers Squibb)

DERMATOLOGIC DRUGS

Full Text: PDF (35 Kb)

ANTIPSORIATICS

305669 (Fournier)

WOUND-HEALING AGENTS

307736 (Pfizer)

CARDIOVASCULAR DRUGS

Full Text: PDF (100 Kb)

ANTIHYPERTENSIVE DRUGS

307618 (Actelion)
308603 (Kirin Brewery)
Bay-41-8543 (Bayer)

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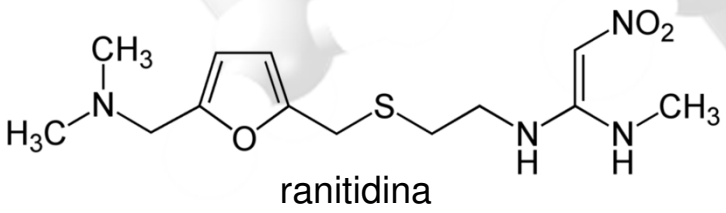
Laboratório de Avaliação e Síntese de Substâncias Bioativas

"... when it comes to drug discovery you're not trying to make complicated molecules, but make molecules that will be effective ... "



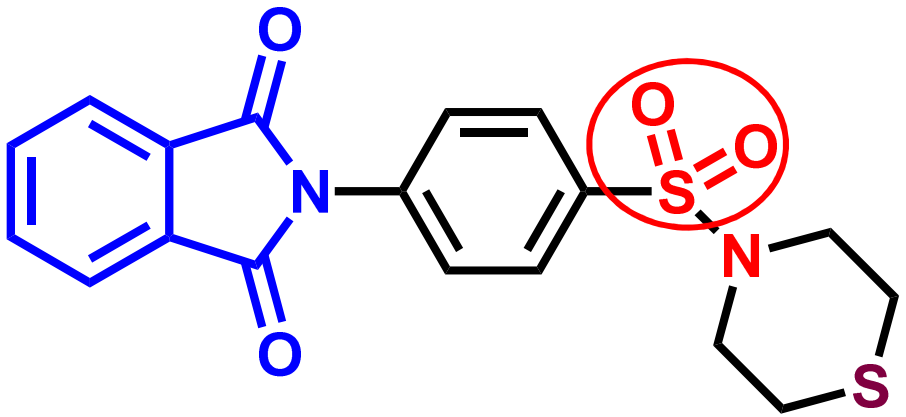
ranitidina

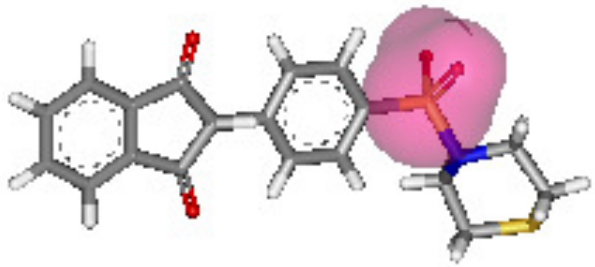
Barry J. Price

Research Director Glaxo (1967-1995)

Universidade Federal do Rio de Janeiro

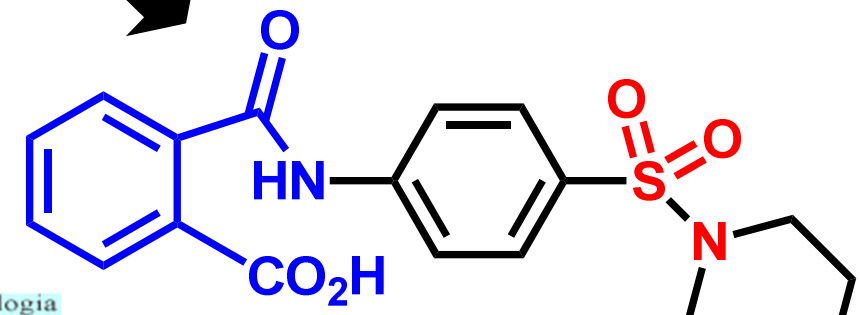
LEAD COMPOUND
Lead-optimization





LASSBio-468

Metabolism studies



LASSBio-596

Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos

www.inct-inofar.ccs.ufrj.br

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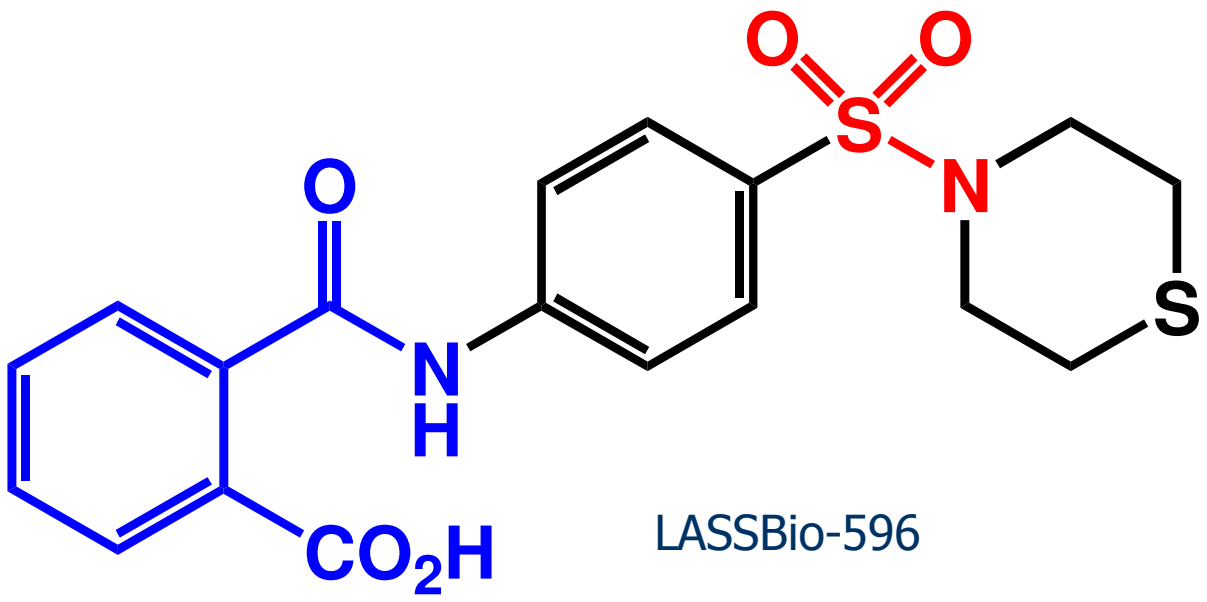
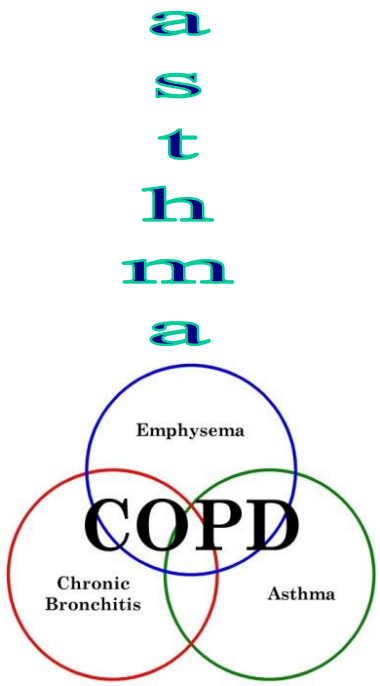
* L. M. Lima & E. J. Barreiro, "Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design", *Curr. Med.Chem.* 2005, **13,** 230



LASSBio-596



anti-fibrogenic

RVq Revista Virtual de Química

ISSN 1984-6835

Artigo

LASSBio-596: da descoberta aos ensaios pré-clínicos

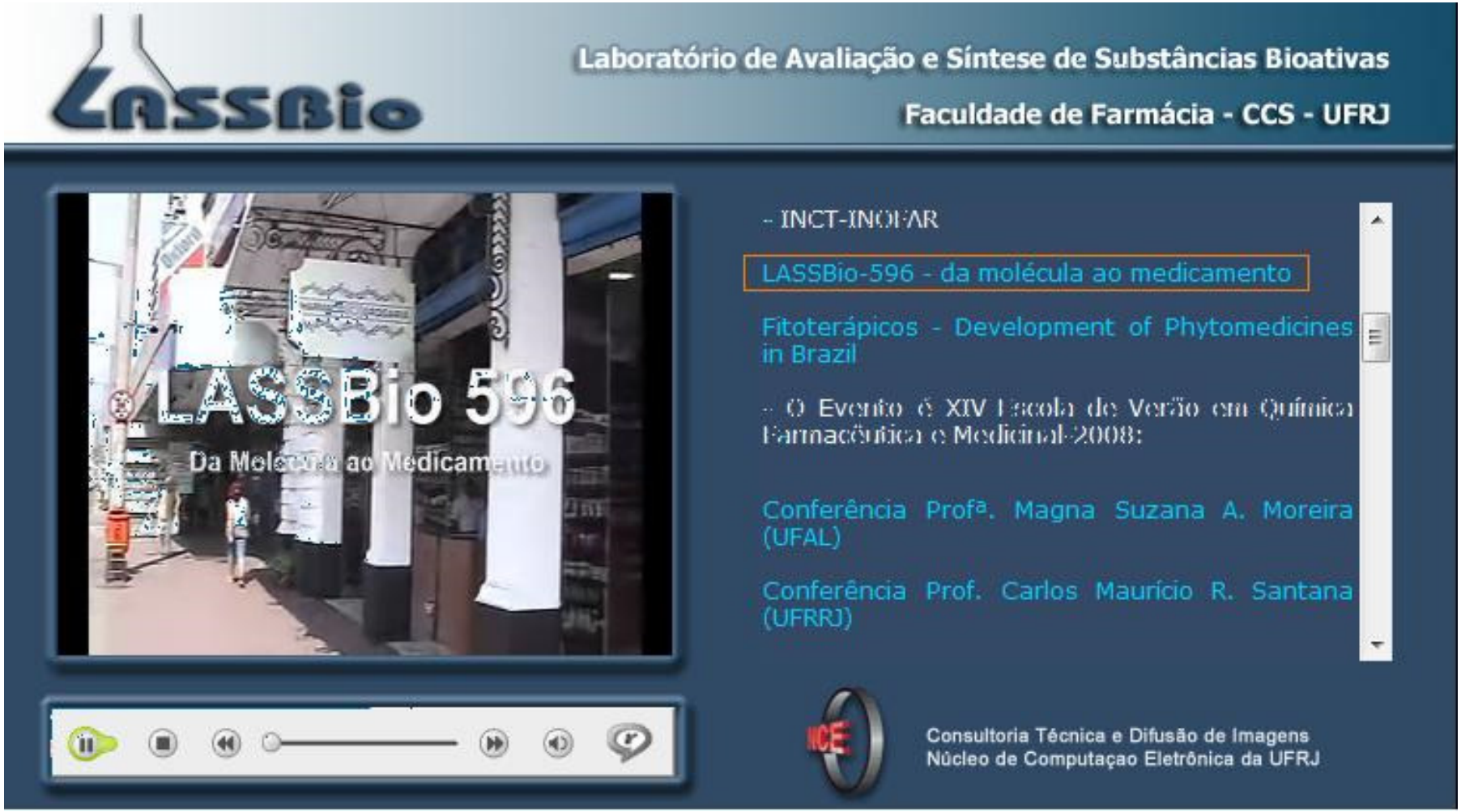
Rocco, Patricia R. M.;[a] Xisto, Debora G.;[a] Silva, J. D.;[a] Diniz, Magareth F. F. M.;[b] Almeida, Reinaldo N.;[b] Luciano, Melissa N.;[b] Medeiros, Isac A.;[b] Cavalcanti, Bruno C.;[c] Ferreira, José R. O.;[c] de Moraes, Manoel O.;[c] Costa-Lotufo, Letícia V.;[c] Pessoa, Claudia do Ó;[c] Dalla-Costa, T.;[d]* Cattani, Vitória B.;[d] Barreiro, Eliezer J.[e], Lima, Lidia M.[e]

Rev. Virtual Quim., **2010**, *2* (1), 10-27. Data de publicação na Web: 30 de agosto de 2010

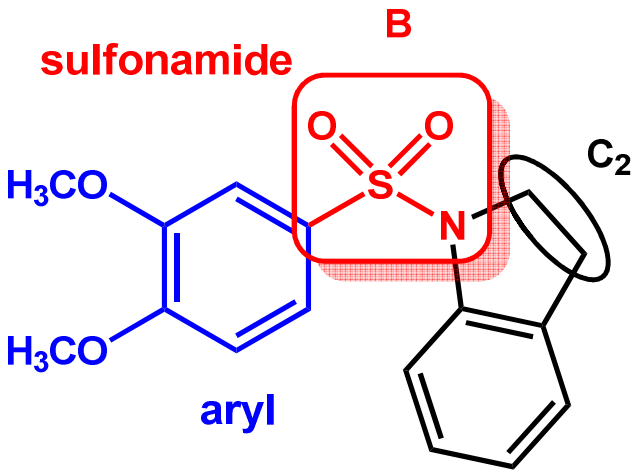
http://www.uff.br/rvq

INCT inofar — Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos — www.inct-inofar.ccs.ufrj.br

LASSBio 596 - YouTube



Mais do mesmo…

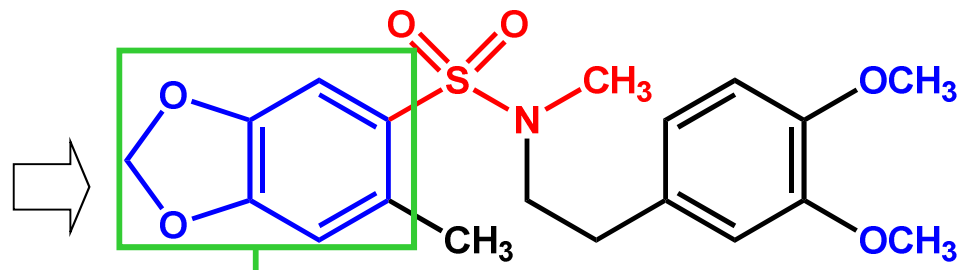


Montana *et al*., 1998

Lead -optimization

IC_{50} = **105 nM** PDE-4

medicinal chemistry



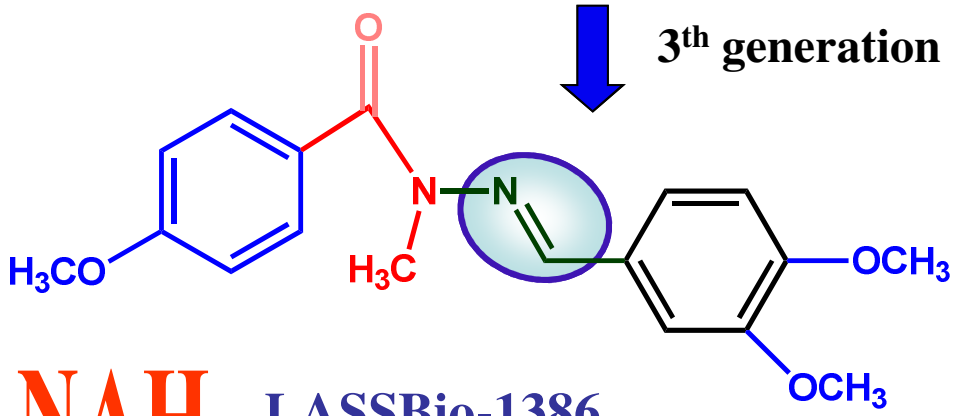
2nd generation

LASSBio-959

Biophore from natural safrole

IC_{50} = **6,7** µM PDE-4

3th generation



NAH **LASSBio-1386**

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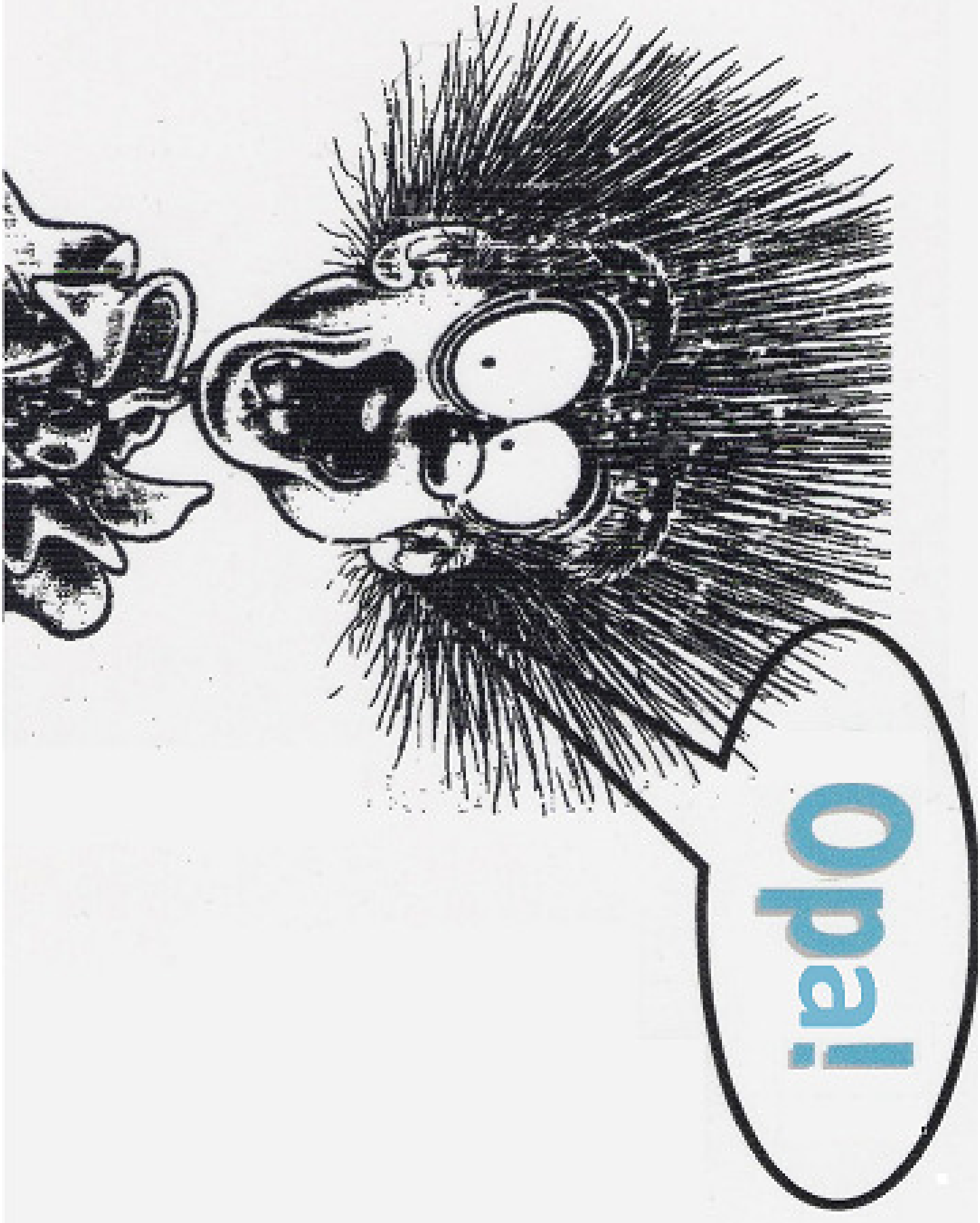

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"...discovery *consists* of seeing what everybody else has seen *and* thinking what nobody else has not thought..."

1937

Albert Szent-Györgiy (1893-1986)

INPI
Instituto Nacional da Propriedade Industrial

Consulta à Base de Dados do INPI

» Consultar por: Base Patentes | Finalizar Sessão

RESULTADO DA PESQUISA (18/05/2013)
Pesquisa por:
Todas as palavras: 'ELIEZER JESUS DE LACERDA BARREIRO no inventor' \ Foram encontrados **15** processos que satisfazem à pesquisa.

Processo	Depósito	Título
PI0806985-9	16/10/2008	DERIVADOS N-ACILIDRAZÔNICOS, PROCESSO DE PRODUÇÃO DE COMPOSTOS N-ACILIDRAZÔNICOS, COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS, USOS E MÉTODOS DE TRATAMENTO
PI0711519-9	20/09/2007	DERIVADOS IMIDAZO [1,2-a] PIRIDÍNICOS, COMPOSIÇÕES FARMACÊUTICAS COMPREENDENDO OS MESMOS E PROCESSOS PARA SUA PREPARAÇÃO
PI0705051-8	31/05/2007	USO DE COMPOSTOS QUINOXALÍNICOS ACILIDRAZÔNICOS, E COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS, NO TRATAMENTO DE QUADROS INFLAMATÓRIOS, DOR AGUDA E CRÔNICA
PI0601885-8	15/05/2006	COMPOSIÇÃO FARMACÊUTICA ANTIINFLAMATÓRIA E ANALGÉSICA CONTENDO DERIVADOS N-ACILIDRAZÔNICOS DO SAFROL, USO, E PROCESSO PARA SUA PREPARAÇÃO
PI0502016-6	03/06/2005	COMPOSTO UREÍDICOS, COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS E SEU USO NO TRATAMENTO DE DOENÇAS INFLAMATÓRIAS
PI0500727-5	03/03/2005	DERIVADOS 1-METIL-3,6,7,8 - TETRAHIDROPIRAZOLO [3,4,-B] PIRROLO [4,3-D] PIRIDINA-6,8-DIONA, PROCESSO DE PREPARAÇÃO, COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS E USOS RELACIONADOS
PI0405418-0	02/09/2004	USO DE DERIVADOS N-FENILPERAZÍNICOS E COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS
PI0403363-9	20/08/2004	RELAXANTES MUSCULARES SELETIVOS E COMPOSIÇÕES FARMACÊUTICAS
PI0401797-8	20/05/2004	USO DE ANTAGONISTAS A-ADRENÉRGETICOS N-FENILPIPERAZÍNICOS, COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS E PROCESSOS PARA SUA PREPARAÇÃO
PI0401660-2	27/04/2004	DERIVADOS N-FENILFTALIMÍDICOS E CARBAMOILBENZÓICOS FUNCIONALIZADOS, PROCESSOS PARA SUA PREPARAÇÃO E COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS
PI0305690-2	08/10/2003	NOVOS DERIVADOS PIPERIDÍNICOS, COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS E PROCESSOS PARA SUA PREPARAÇÃO
PI0303465-8	05/09/2003	NOVOS DERIVADOS N-FENILPIPERAZÍNICOS E COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS
PI0202025-4	20/05/2002	- ADRENÉRGICOS N-FENILPIPERAZÍNICOS DERIVADOS DO SAFROL, COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS E PROCESSOS PARA SUA PREPARAÇÃO
PI9902960-0	29/04/1999	NOVOS COMPOSTOS BI-PIRAZÓLICOS FUNCIONALIZADOS, NOVA CLASSE DE AGENTES ANTI-INFLAMATÓRIOS NÃO-ESTERÓIDES SINTÉTICOS
PI8201868-5	31/03/1982	SÍNTESE DE PROSTAGLANDINAS DA SÉRIE DESOXI-11-PGE

Número	Prioridade		Marca		Situação	Titular	Classe
829676309	02/05/2008	M	IVF INSTITUTO VIRTUAL DE FÁRMACOS	®	Registro	ELIEZER DE JESUS DE LACERDA BARREIRO	NCL(9) 44
827111940	20/10/2004	M	LASSBIO LABORATORIO DE AVALIAÇAO E SINTESE DE SUBSTANCIAS BIOATIVAS	®	Registro	UNIVERSIDADE FEDERAL DO RIO DE JANEIRO	NCL(8) 41

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Patente obtida

Patent (USPTO) 7.091.238 (15/08/2006)

UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/020,328	Aug. 15, 2006	7.091.238	32360-178943	9681

VENABLE LLP
P.O. BOX 34385
WASHINGTON, DC 20043-9998

Thienylhydrazone with Digitalis-like properties (positive inotropic effects)

LASSBio-294

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term (application filed

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

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

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

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

Roberto Takashi Sudo, Rio de Janeiro, BRAZIL;
Edson X. Albuquerque, Baltimore, MD;
Eliezer J. Barreiro, Rio de Janeiro, MD;
Carlos Alberto Manssour Fraga, Rio de Janeiro, BRAZIL;
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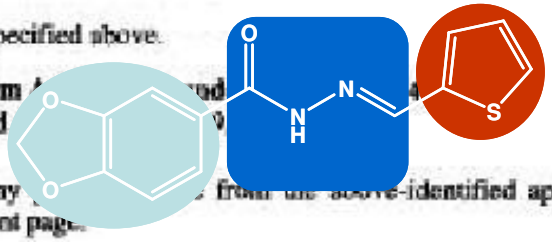
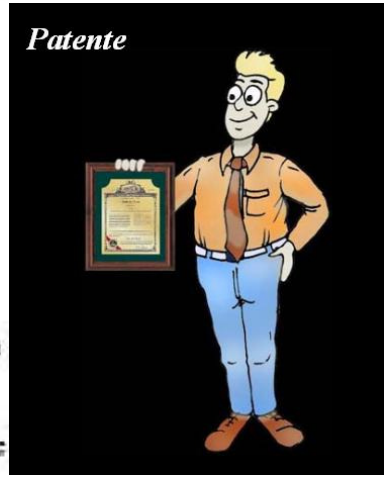
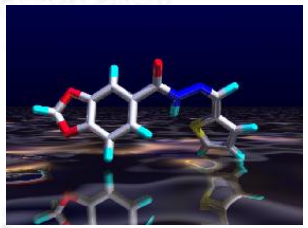




Thienylhydrazone with Digitalis-like properties (positive inotropic effects)

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26-30 de janeiro de 2015

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