Universidade Federal do Rio de Janeiro

Química Medicinal

Parte 1

International Year of CHEMISTRY 2011

Eliezer J. Barreiro

Professor Titular

Universidade Federal do Rio de Janeiro

ejbarreiro@ccsdecania.ufrj.br

http://ejb-eliezer.blogspot.com

Laboratório de Avaliação e Síntese de Substâncias Bioativas

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

Instituto Nacional de Ciência e Tecnologia em Fármacos e Medicamentos

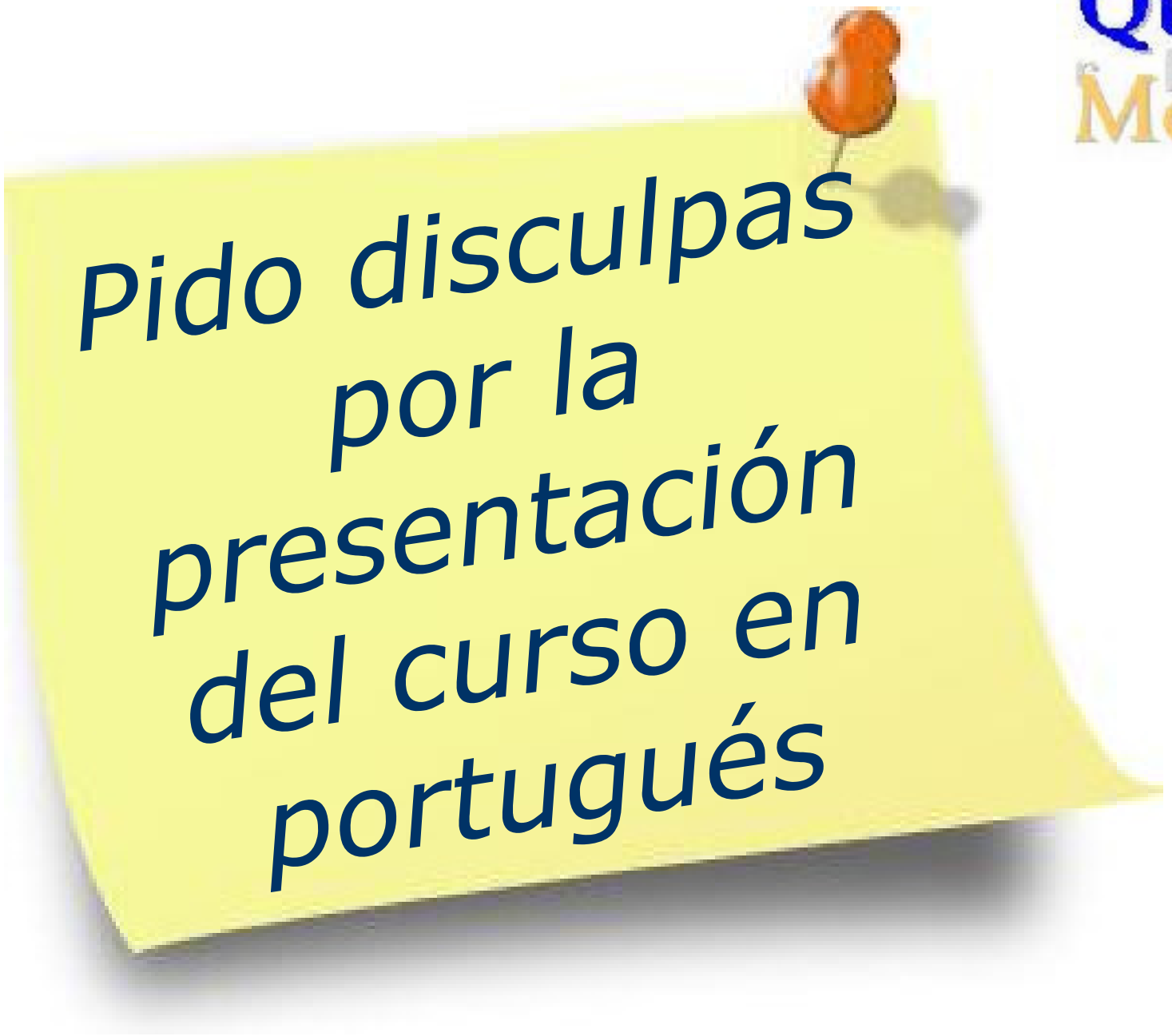
http://www.inct-inofar.ccs.ufrj.br

LASSBio®

Universidade Federal do Rio de Janeiro

UFRJ

Química Medicinal



LASSBio®

Rio de Janeiro, BR


Corcovado Hill


Sugar Loaf


Rio-Niterói bridge


Copacabana Beach


Copacabana beach view from Sugar Loaf


Sunset at Arpoador Beach


Maracanã stadium


Barra da Tijuca beach


Botanic gardem

Universidade Federal do Rio de Janeiro

Química Medicinal

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

LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas

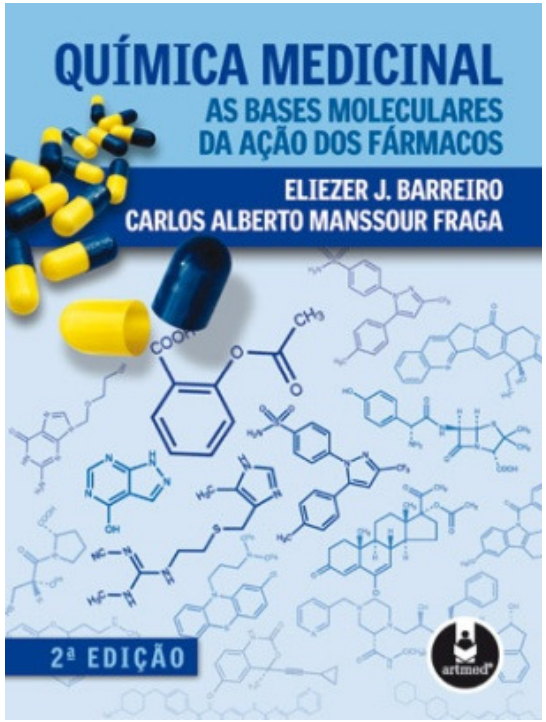
Creado em 19/04/1994 Laboratório de Avaliação e Síntese de Substâncias Bioativas

Pharmacology
Farmacologia

Molecular
Modelagem
Modeling
Molecular

Bibliografía

- Libro "Química Medicinal: As Bases Moleculares da Ação dos Fármacos“ http://www.artmed.com.br/



- Glosario de términos de Química Medicinal http://www.chem.qmw.ac.uk/iupac/medchem/

- Química Nova http://www.scielo.br/qn

Definición: Química Medicinal

estudiar los factores moleculares relacionados con el modo de acción de las drogas, incluyendo una comprensión de la relación entre la estructura química y actividad (SAR) Aparte de las propiedades que rigen su absorción, distribución, el metabolismo, la eliminación (ADME) y la toxicidad.

Química Medicinal

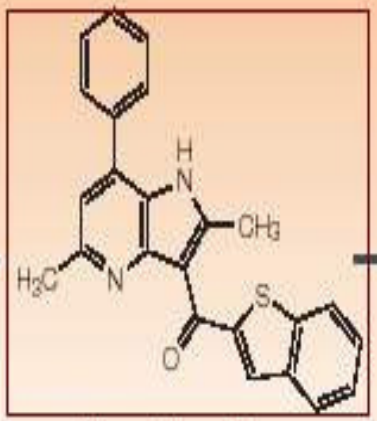
Eur. J. Med. Chem., **31**, 747 (1996)

¿Qué es un fármaco?

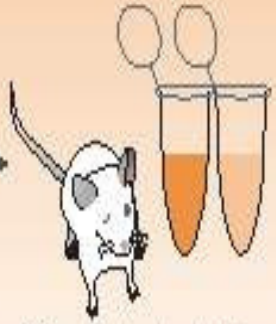
- Es una sustancia orgánica (pureza> 98%) con propiedades farmacoterapéuticas para uso médico, capaz de recuperar, promover, mantener o preservar la salud;
- Con una alta eficiencia en la diana terapéutica (PD);
- No es tóxico;
- Potente, con buena biodisponibilidad, activo en bajas dosis, por vía oral, si es posible en una sola dosis diaria;
- Metabólicamente estable y bien absorbida (PK): propiedades físico-químicas fundamentales para la actividad p.o., una buena partición pasiva en biomembrana
- Enlaces-H (donante y aceptor);
- Sintéticamente accesible en buena escala a un costo aceptable;
- Protegido por una patente para un determinado (s) indicación (s) tratamiento (s);
- ... Las propiedades moleculares de las drogas son el objeto de estudio de Química Medicinal

Preclinical studies

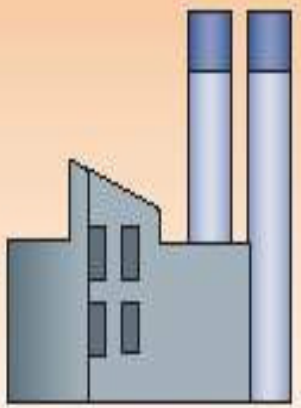
Research team formed and objectives set



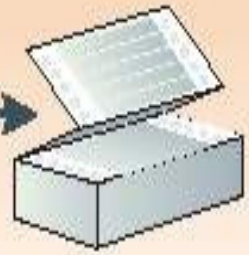
Novel chemicals synthesized



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



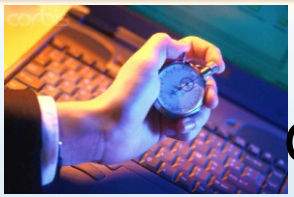
Formulation, stability scale-up synthesis, chronic safety in animals



Company files Investigational New Drug (IND) application with FDA

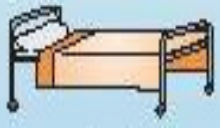
Química Medicinal

Clinical studies

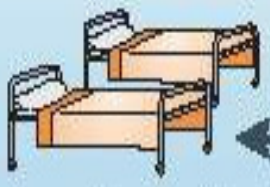


El proceso de descubrimiento/invención y desarrollo de fármacos es mui complejo ...

Phase I: studies in healthy humans (toleration)



Phase II: studies in patients (efficacy)



Phase III: large clinical trials in many patients

Company files New Drug Application (NDA)

ANVISA

FDA

FDA reviews NDA

Drug is approved for marketing

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

medicinal chemistry

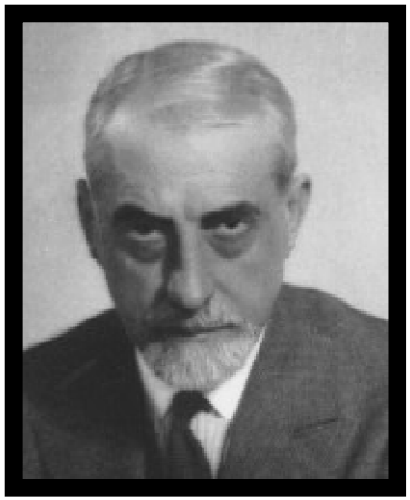
" ...medicinal chemists today live in exciting times... their work can have a beneficial effect on millions of suffering patients – surely an important motivating factor for any scientist..."

J. G. Lombardino


Joseph G. Lombardino

The Role of the Medicinal Chemist in Drug Discovery – Then and Now, *Nature Rev. Drug Disc.* **2004**, *3*, 853.

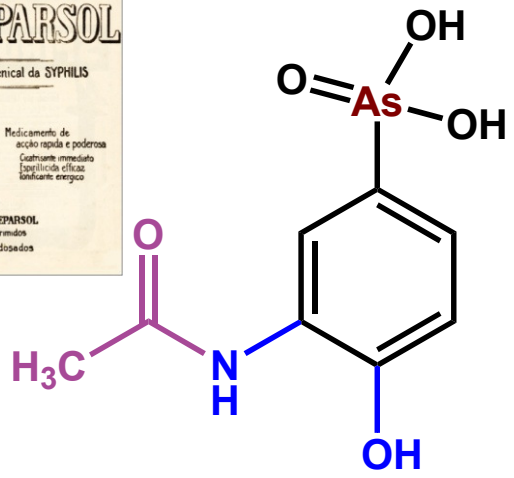
La cuna de la Química Medicinal



Ernest Fourneau
1872-1949

Stovarsol

CAS 97-44-9



Institut Pasteur (1887)
Paris, Francia

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

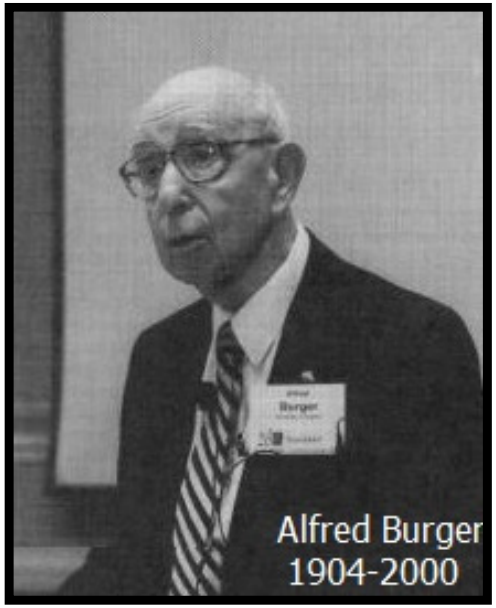
Prêmio Nobel de Fisiologia/Medicina 1957

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

Química Medicinal

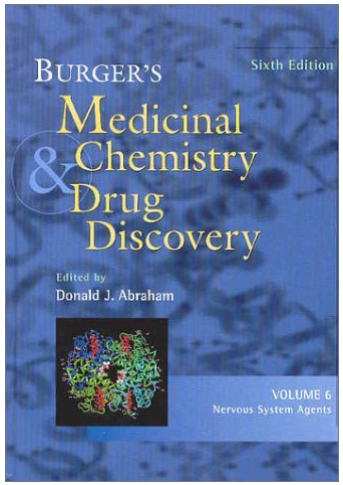
Prof. Alfred Burger

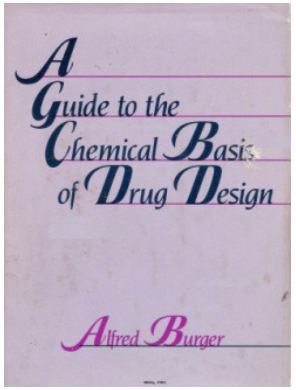


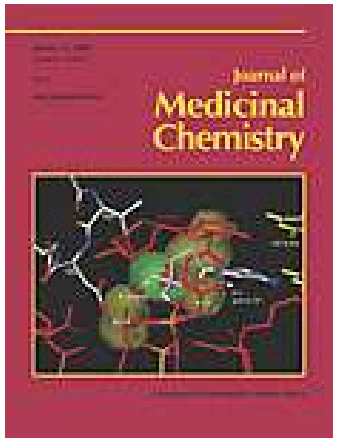
(1904-2000)

University of Virginia

EUA







1958 – creador Pharmaceutical Chemistry Journal →
después **Journal of Medicinal Chemistry**

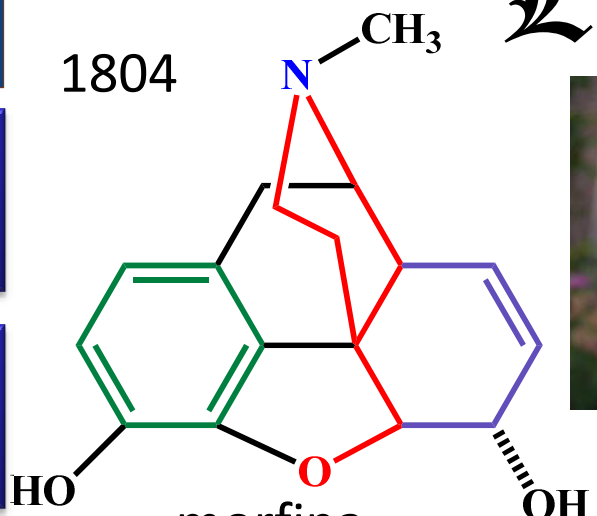
⇩

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

1978 - GlaxoSmithKline y ACS "Alfred Burger Award" in Medicinal Chemistry
T. Y. Shen - inventor de la indometacina

Las moléculas pioneras ...

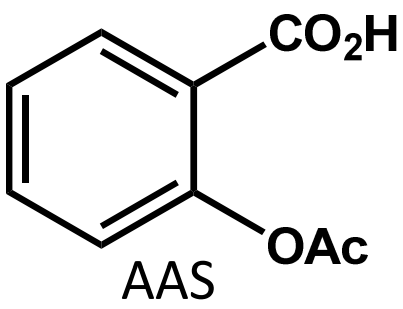
1804



morfina

$C_{17}H_{19}NO_3$

1897



AAS

$C_9H_8O_4$

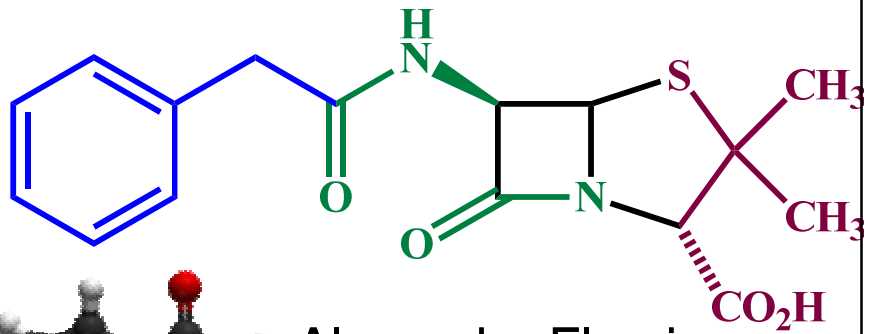
1929

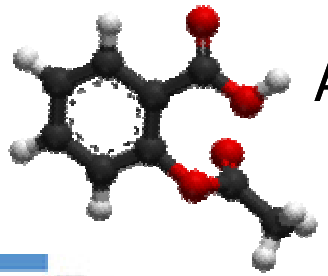
penicilina

$C_{16}H_{18}N_2O_4S$

Felix Hoffman

1868- 1946





Alexander Fleming

1881-1955

Nobel 1945

Friedrich W. A. Sertürner

1783- 1841

Sir Robert Robinson

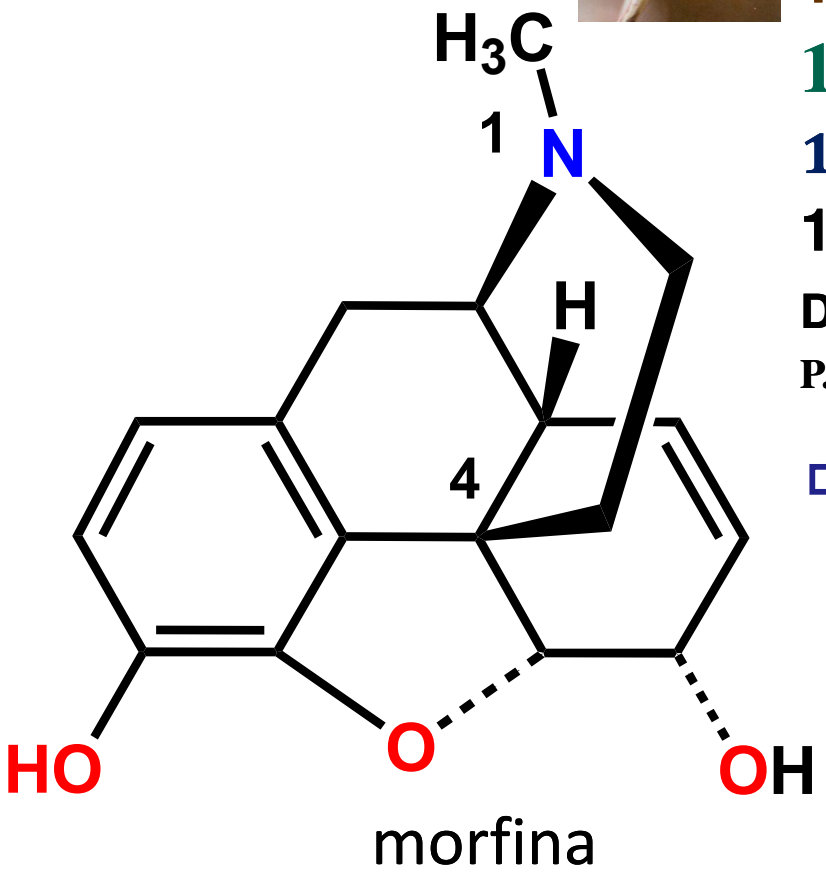
1886-1975

Nobel 1947

Productos Naturales & Fármacos: Alcalóides

Alcalóides fenantrênicos e benzilisoquinolínicos (papaverina 0,2%)

Papaver somniferum



morfina

1493-1541 Marco Polo (Veneza) ⇒ Ópio

1803 ⇒ Friedrich WA Sertürner isola a morfina ("Morpheus") ⇒ hipno-analgesia!

1815 - Setürner Co

1924 – Diidromorfinona (Dilaudid) Knoll

1925 – *Sir* Robert Robinson (estrutura)

1827 - Darmstadt , Alemanha (Merck)

1952 – M. Gates primera síntesis total

1954 - Beckett & Casey, Un. London

Descubrimiento de los receptores opióides: δ, κ, μ

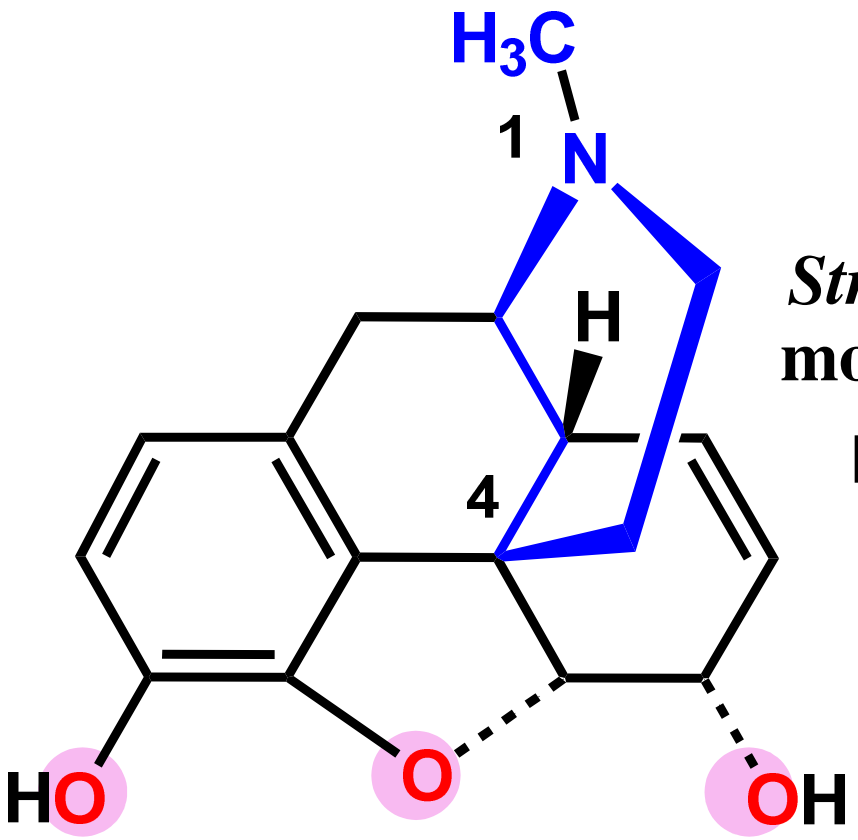
P. W. Schiller, ***Progr. Med. Chem.*** *1991*, **28,** 301

⇒

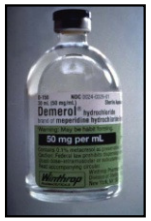
analgesia central;
tolerancia &
dependencia química;

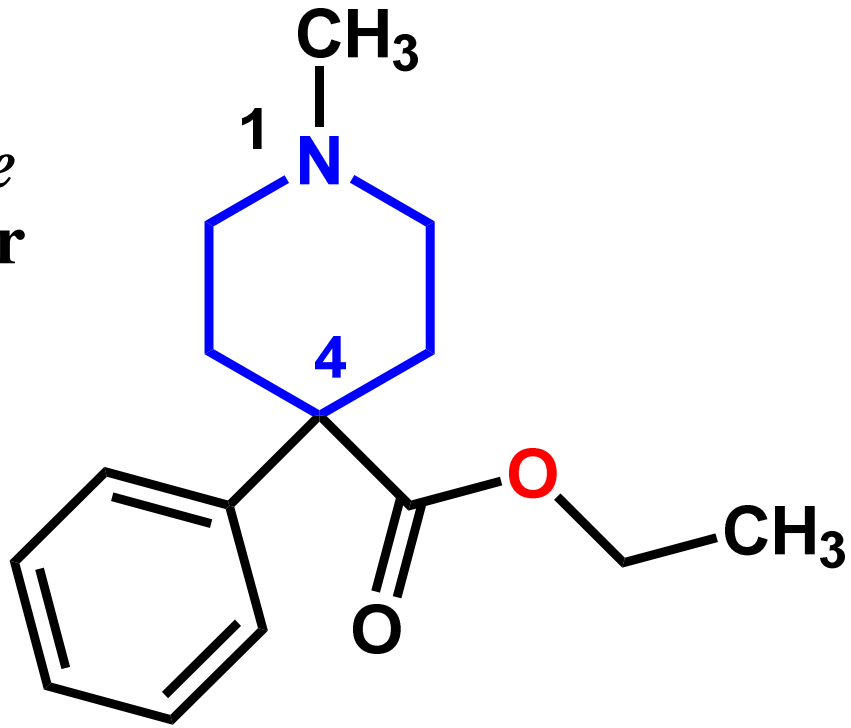
Síndrome de abstinencia;

Domando los productos naturales



Striptease molecular





morfina

PM = 285.1

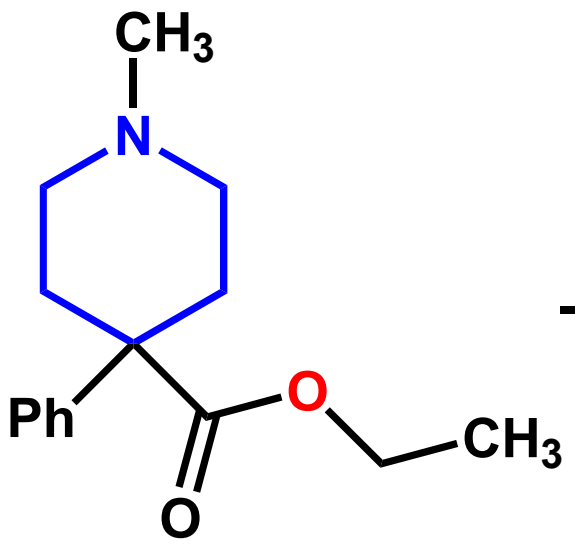
$C_{17}H_{19}NO_3$

meperidina

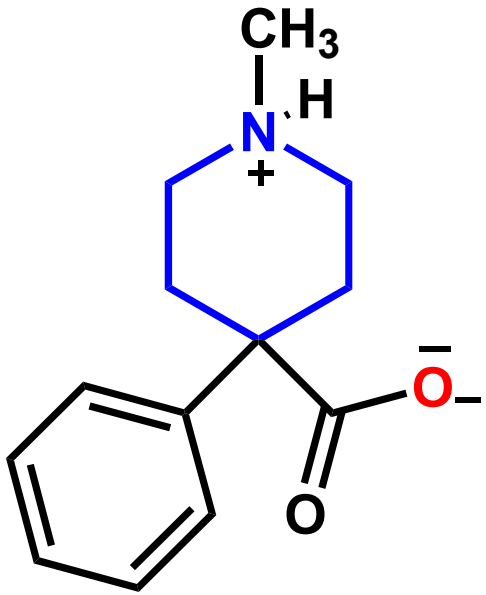
PM = 247.3

$C_{15}H_{21}NO_2$

Producto natural como protótipo

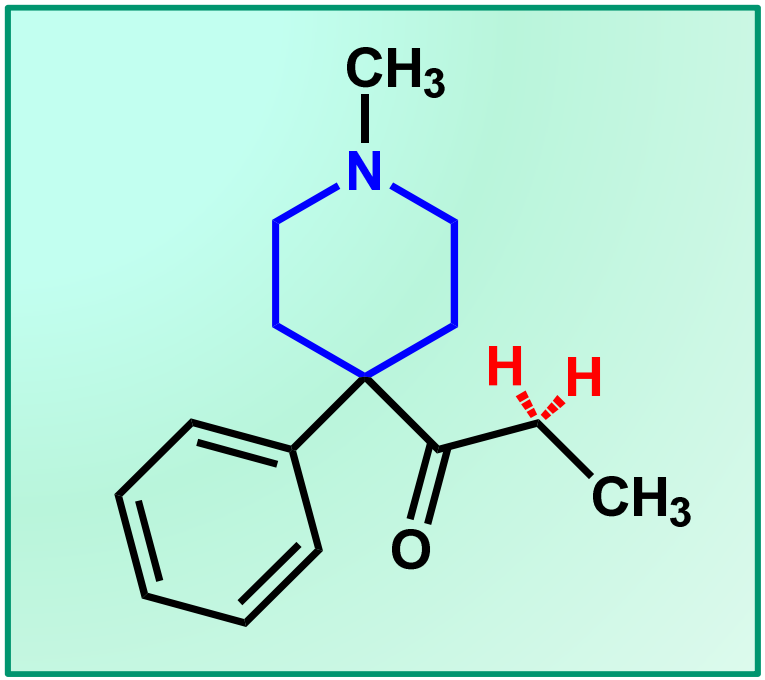


in vivo



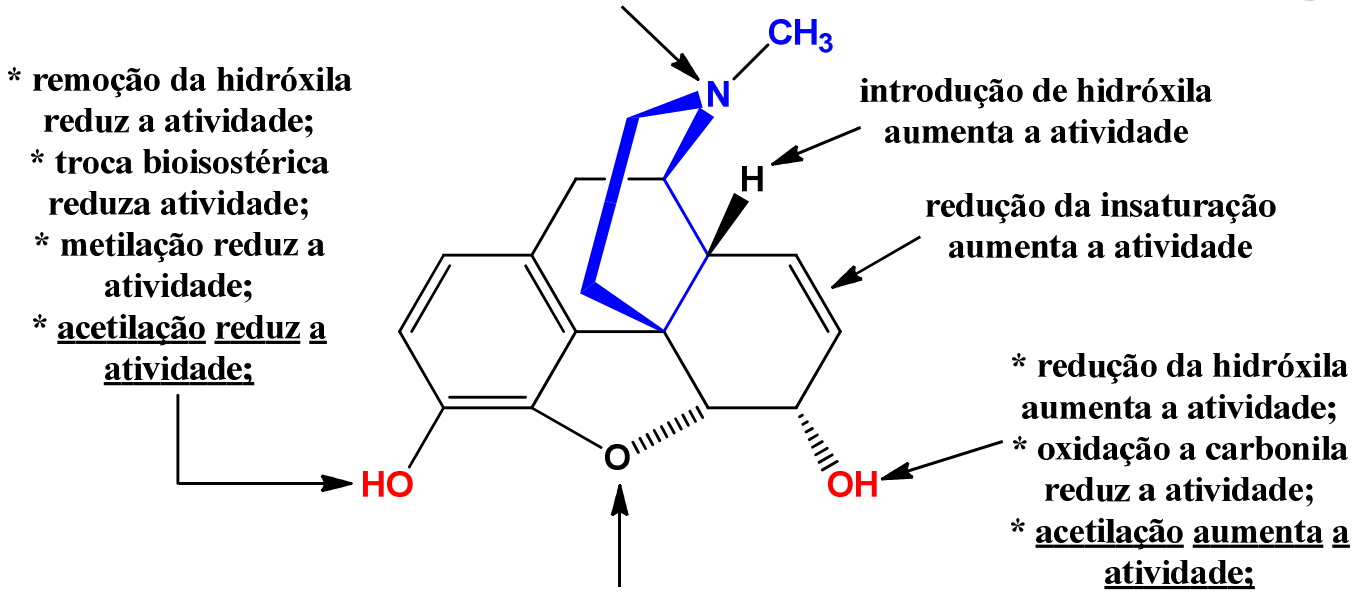
CNS

<< ClogP = 2,03 (calc.)



SAR

$N\text{-}CH_2\text{-}CH_2Ph$ aumenta a atividade
$N\text{-}CH_2\text{-}CH{=}CH_2$ produz antagonismo



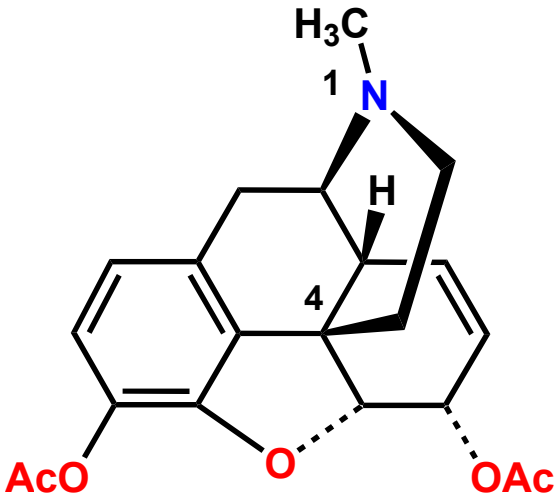
* remoção da hidróxila reduz a atividade;
* troca bioisostérica reduza atividade;
* metilação reduz a atividade;
* <u>acetilação reduz a atividade;</u>

introdução de hidróxila aumenta a atividade

redução da insaturação aumenta a atividade

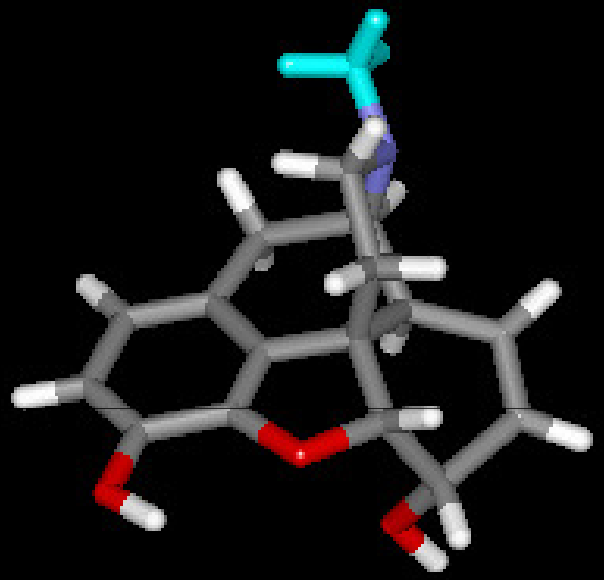
* redução da hidróxila aumenta a atividade;
* oxidação a carbonila reduz a atividade;
* <u>acetilação aumenta a atividade;</u>

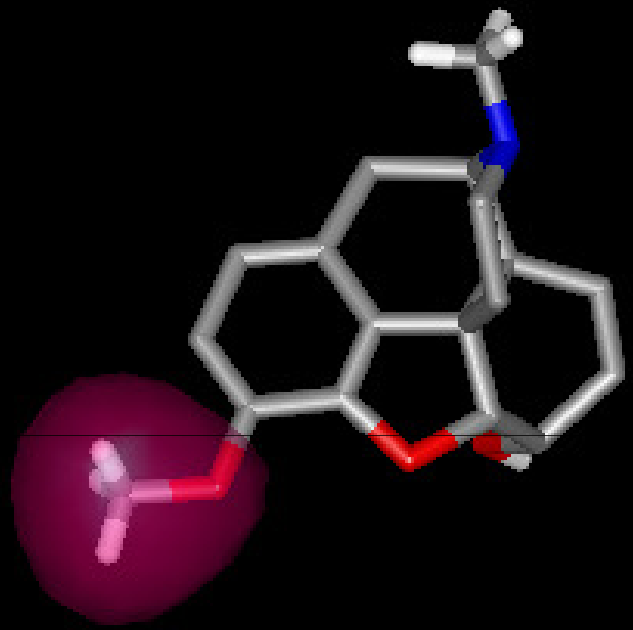
remoção aumenta a atividade

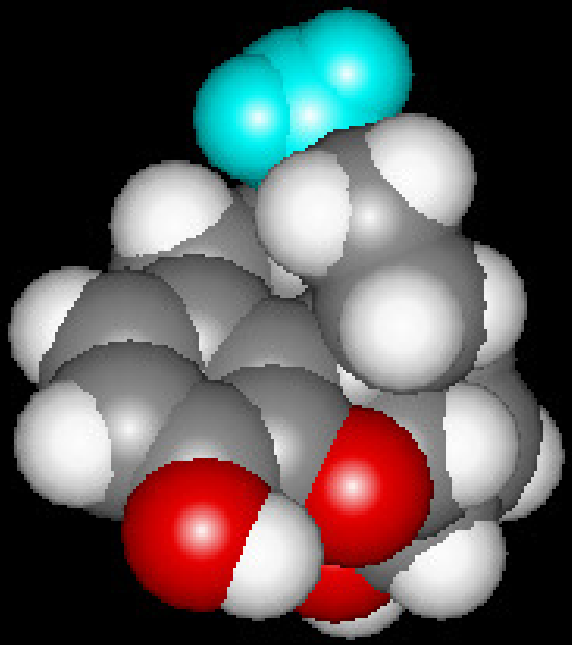


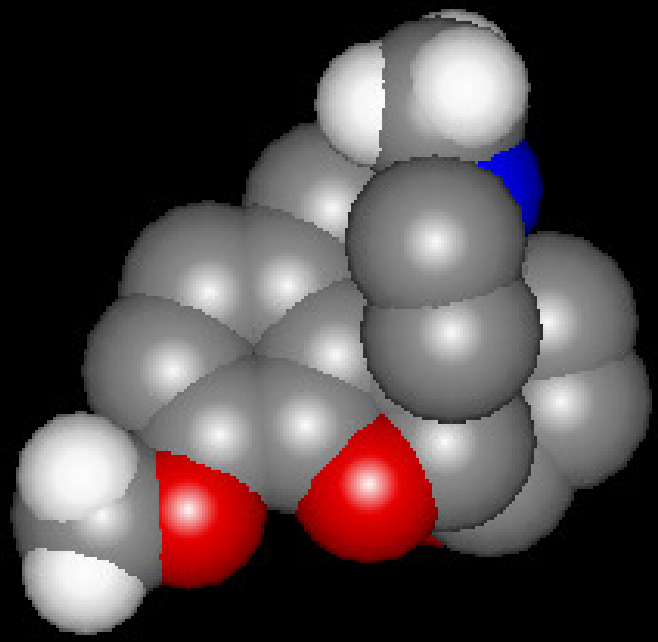
diacetilmorfina

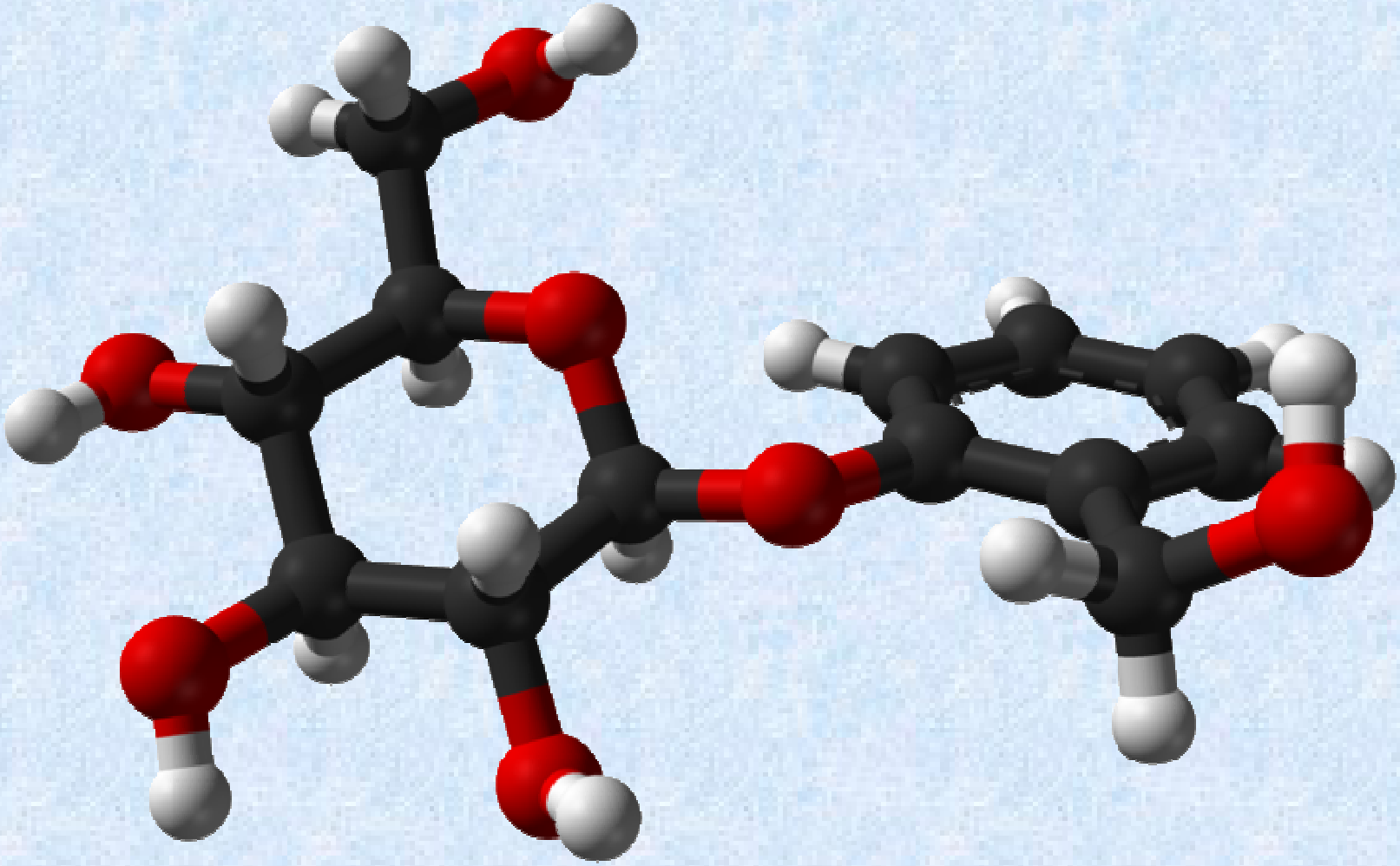
1890 a 1910 la heroína se vendía como un sustituto no adictivo de morfina



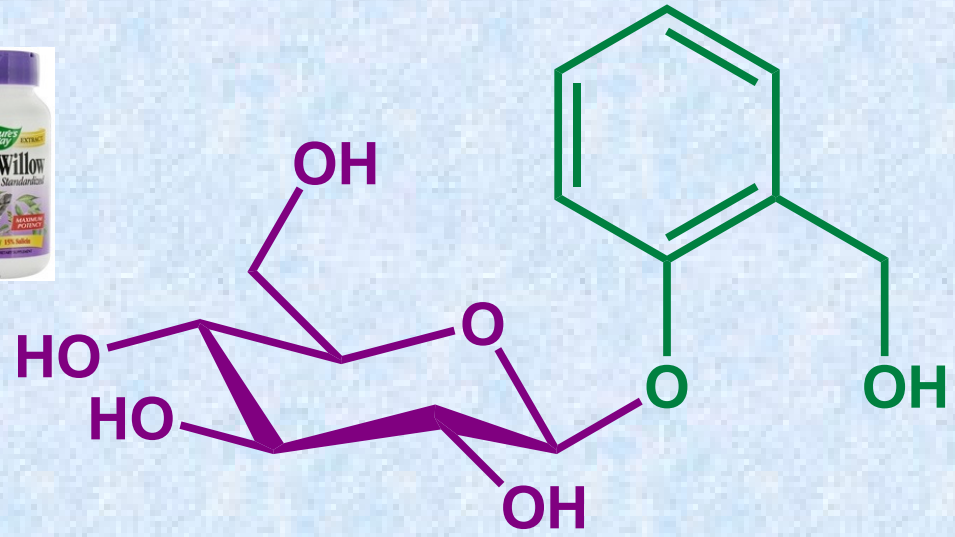








salicina



salicina

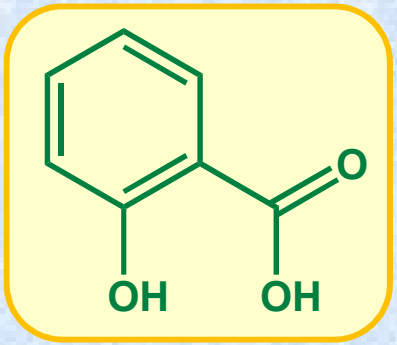
AAS

Salicina es un β-glucósido, com propiedad anti-inflamatoria obtenida de corteza de sauce (willow bark)

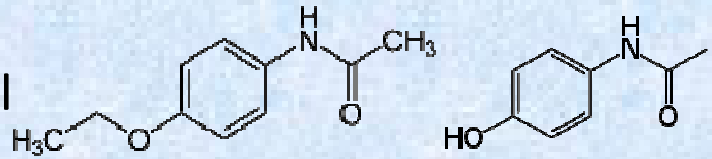
La teoría de las firmas

theory of signatures

1853 -Charles F.Gerhardt (impura)
1899 – Felix Hoffmann AAS
1886 – acetanilida (analgésico)
1887 -fenacetina
1953 - paracetamol

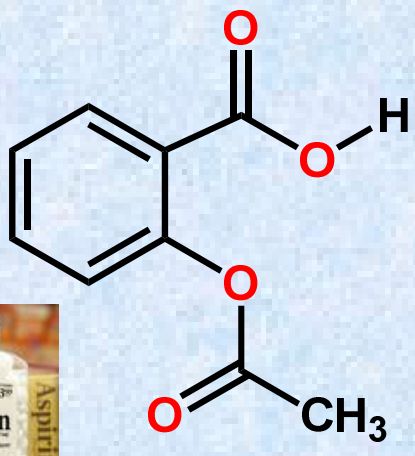


AS




Salix alba 'Vitellina-Tristis'

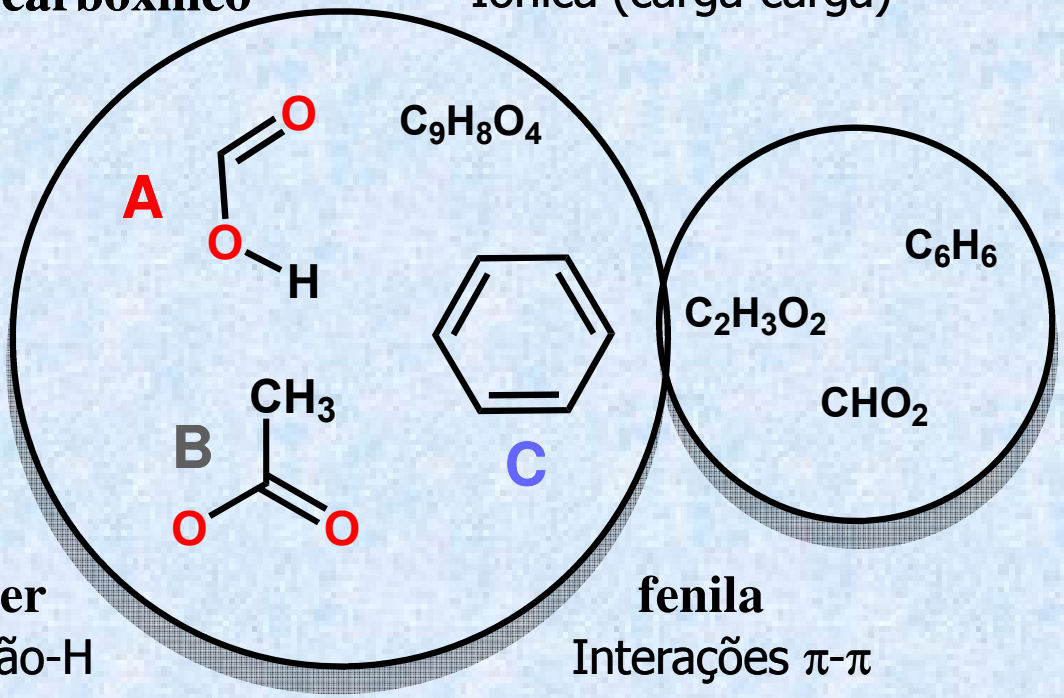
Disección Molecular



$C_9H_8O_4$

ácido carboxílico

Iônica (carga-carga)

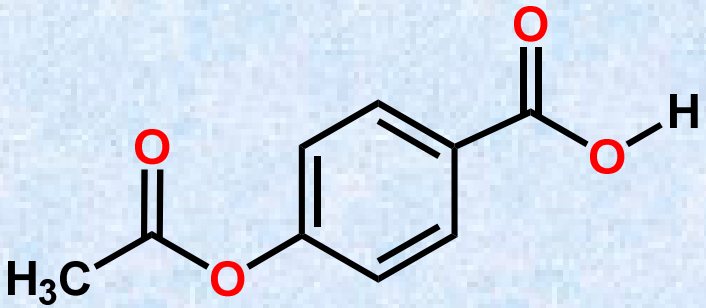


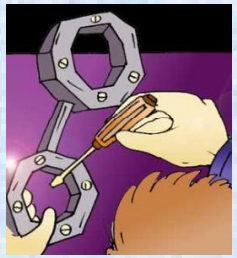
éster
Ligação-H

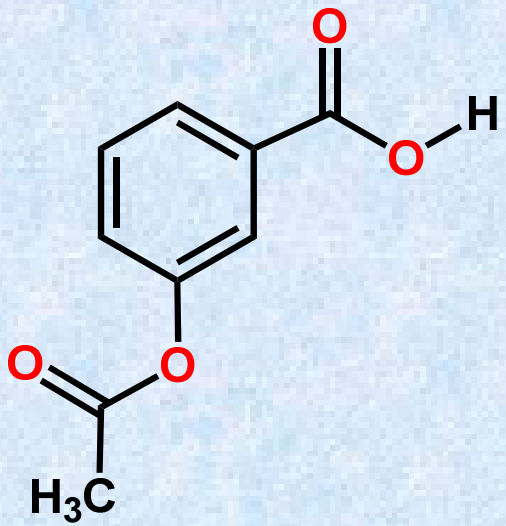
fenila
Interações π-π

Ácido acetilsalicílico

orto-**ácido acetilsalicílico**

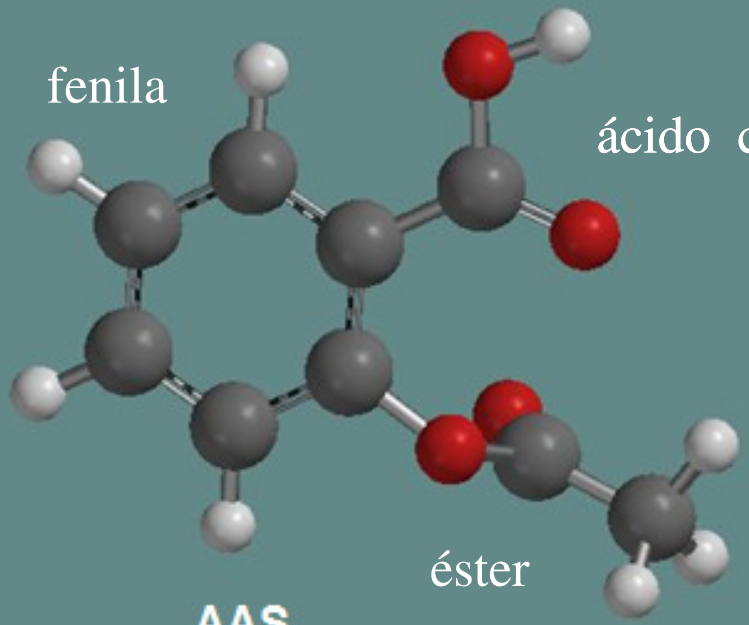


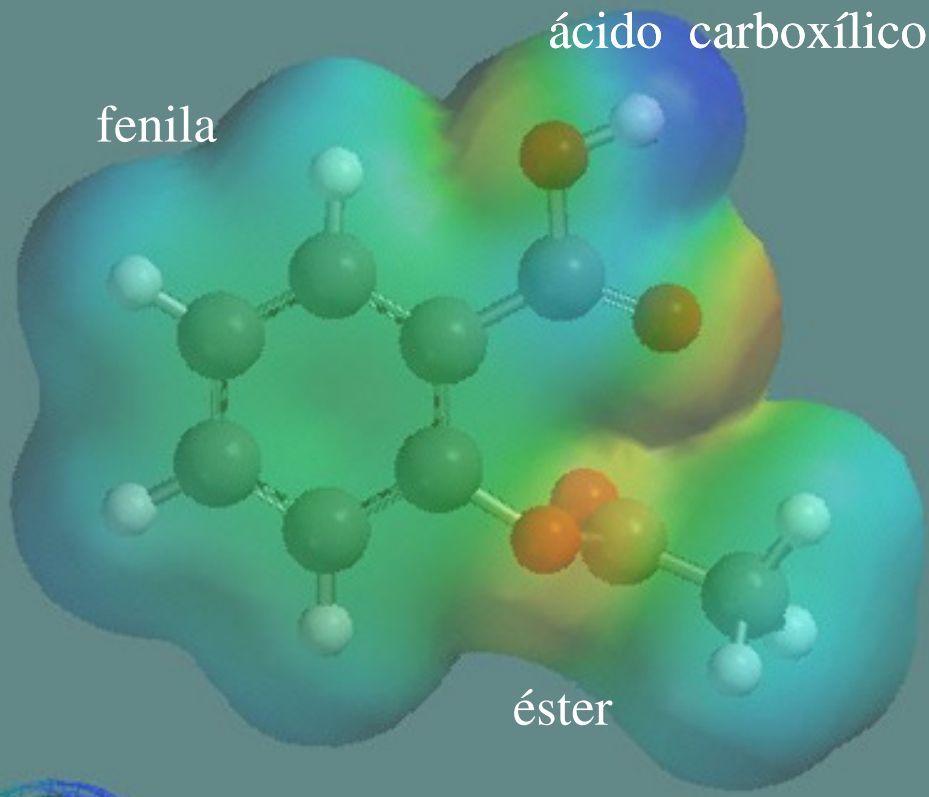


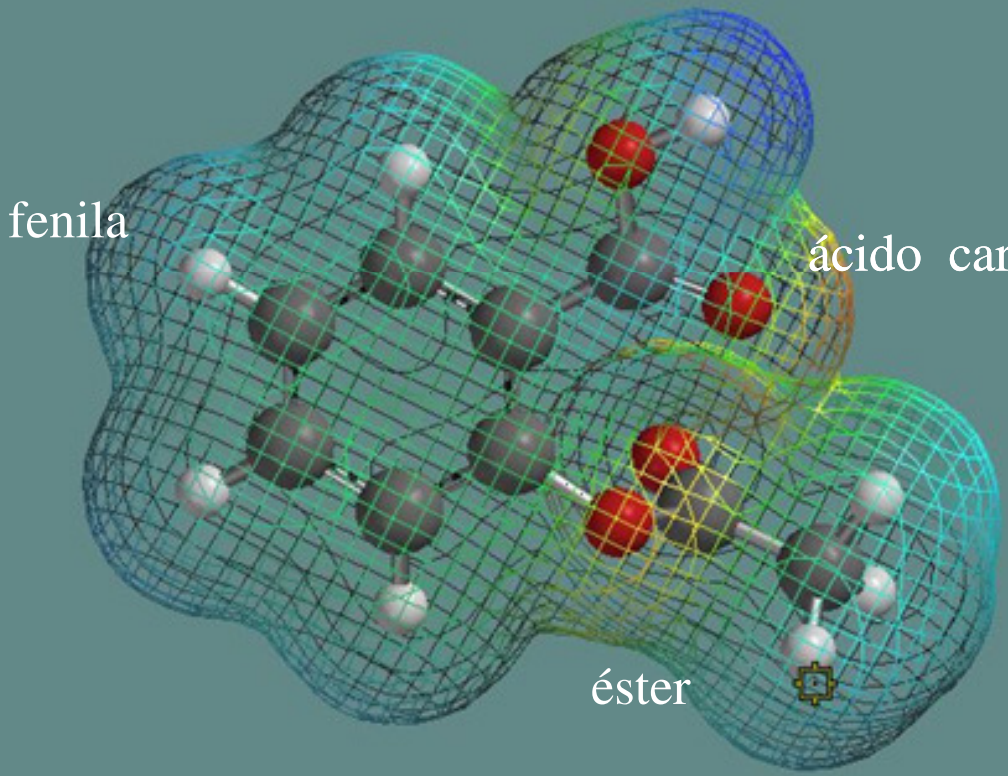


para-**ácido acetilsalicílico**

meta-**ácido acetilsalicílico**


fenila
ácido carboxílico
éster
AAS


ácido carboxílico
fenila
éster


fenila
ácido carboxílico
éster

química nova

BIODIVERSITY: POTENTIAL SOURCE FOR DRUG DISCOVERY

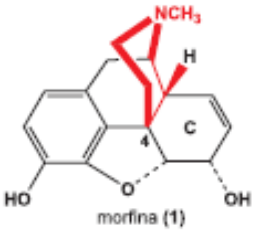
Quim. Nova, Vol. 32, No. 3, 679-688, 2009

BIODIVERSIDADE: FONTE POTENCIAL PARA A DESCOBERTA DE FÁRMACOS

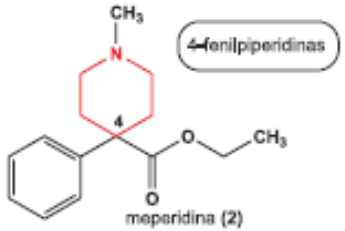
Eliezer J. Barreiro*
Departamento de Fármacos, Faculdade de Farmácia, Centro de Ciências da Saúde, Universidade Federal do Rio de Janeiro, CP 68006, 21944-910 Rio de Janeiro - RJ, Brasil
Vanderlan da Silva Bolzani*
Instituto de Química, Universidade Estadual Paulista, Rua Francisco Degni, s/n, 14800-900, Araraquara - SP, Brasil

Recebido em 16/1/09; aceito em 6/4/09; publicado na web em 9/4/09

BIODIVERSITY: POTENTIAL SOURCE FOR DRUG DISCOVERY. In economic terms, biodiversity transcends the boundaries usually given to conventional industries because it is a valuable source of biological and chemical data of great use to drug discovery. Certainly, the use of natural products has been the single most successful strategy in the discovery of novel medicines, and most of the medical breakthroughs are based on natural products. Half of the top 20 best-selling drugs are natural products, and their total sales amounted to US$ 16 billions shows the importance of natural products, which is evidenced by the new chemical entities (NCE) approved by regulatory authorities around the world in the past decade. Recently, the approval of the alkaloid galanthamine as a medicine to treat Alzheimer's disease shows that natural compounds from plants will continue to reach the market. The huge biological diversity of the Brazilian biomes, by its ability to generate new knowledge and technological innovation can be a fantastic alternative as raw material for drug discovery.



morfina (1)



meperidina (2)

Productos naturales com propriedad anti-câncer

Câncer

Fármacos Anti-câncer

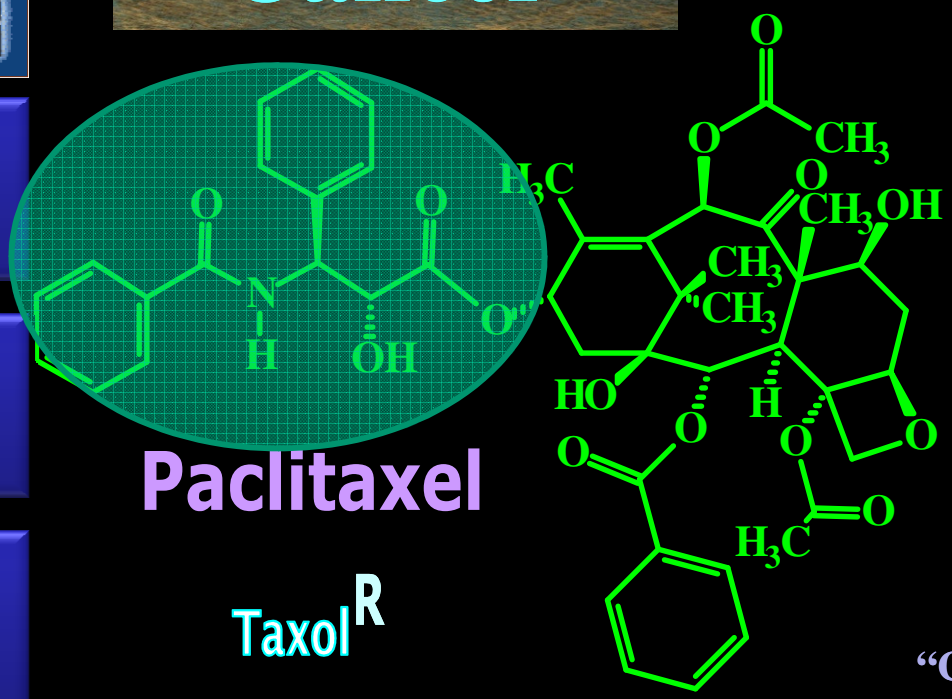
Origem

- **plantas**
  - Vincristina
    Paclitaxel
    Podofilotoxina
    Camptotecina
  - Docetaxel
    Irinotecan
    Etoposido
- **sintéticos**
- **microorganismos**
  - Doxorubicina
    Dactomicina
    Bleomicina

Alvos

- Topoisomerase I & II
- α-Tubulina
- DNA
- Tirosina quinase
- PKC
- COX

Câncer



Paclitaxel

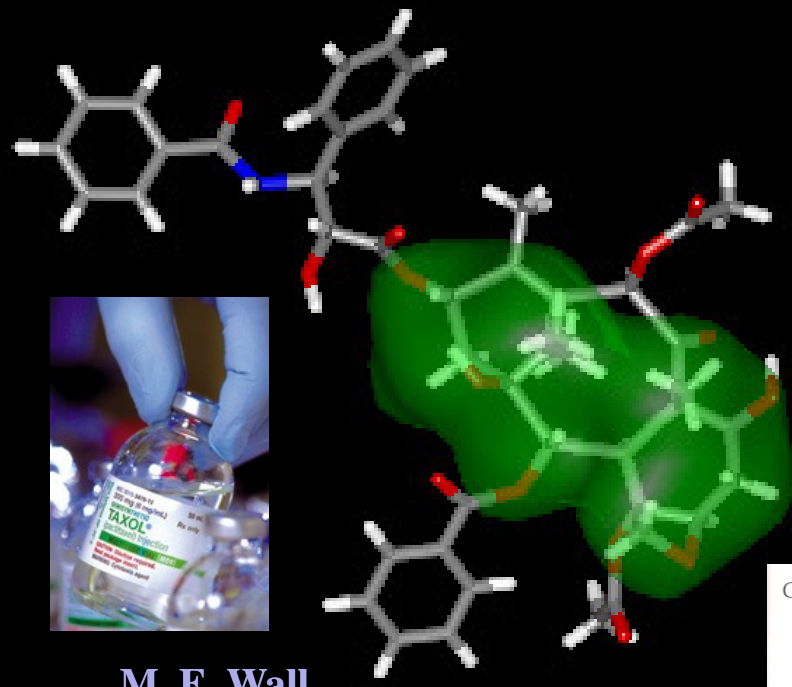
Taxol®

M. C. Wani *et al., J. Am. Chem. Soc.* 1971, *93*, 2325

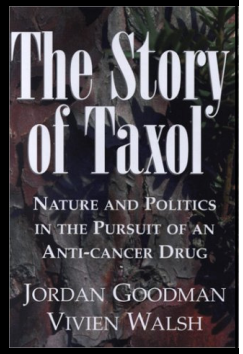
Res. Triangle Park, 1967

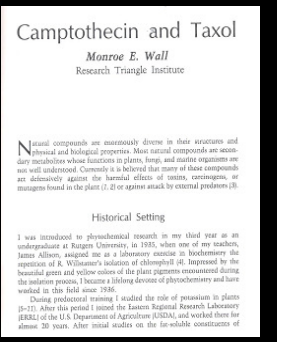
M. E. Wall & M. C. Wani

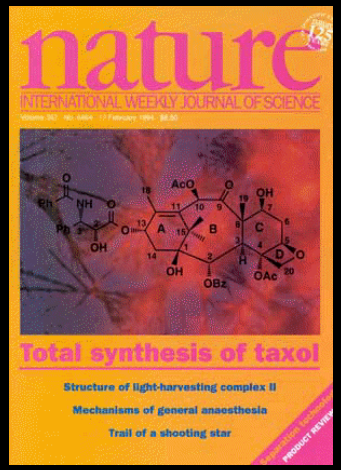
1996 - National Cancer Institute Award of Recognition

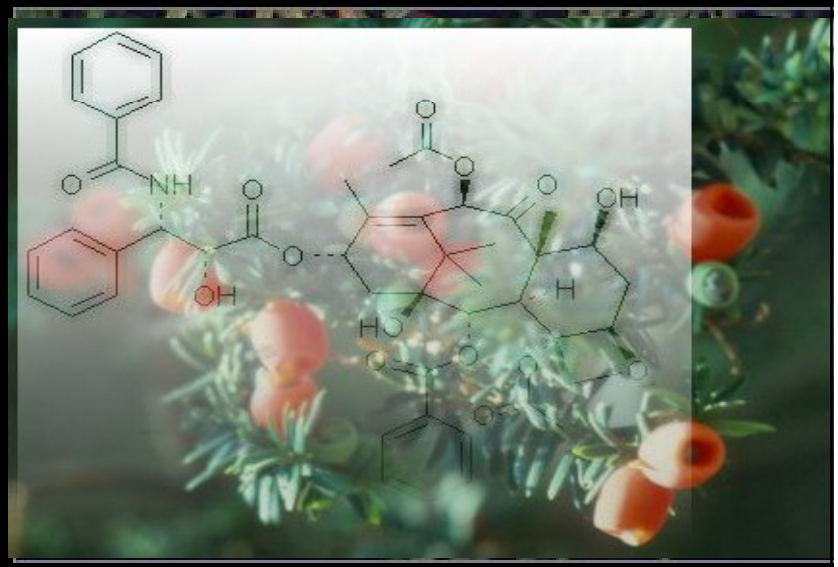


M. E. Wall,,
"Chronicles of Drug Discovery",
D. Lednicer, vol. 3, ACS, 1993,
pp. 327-348









Taxus bacatta

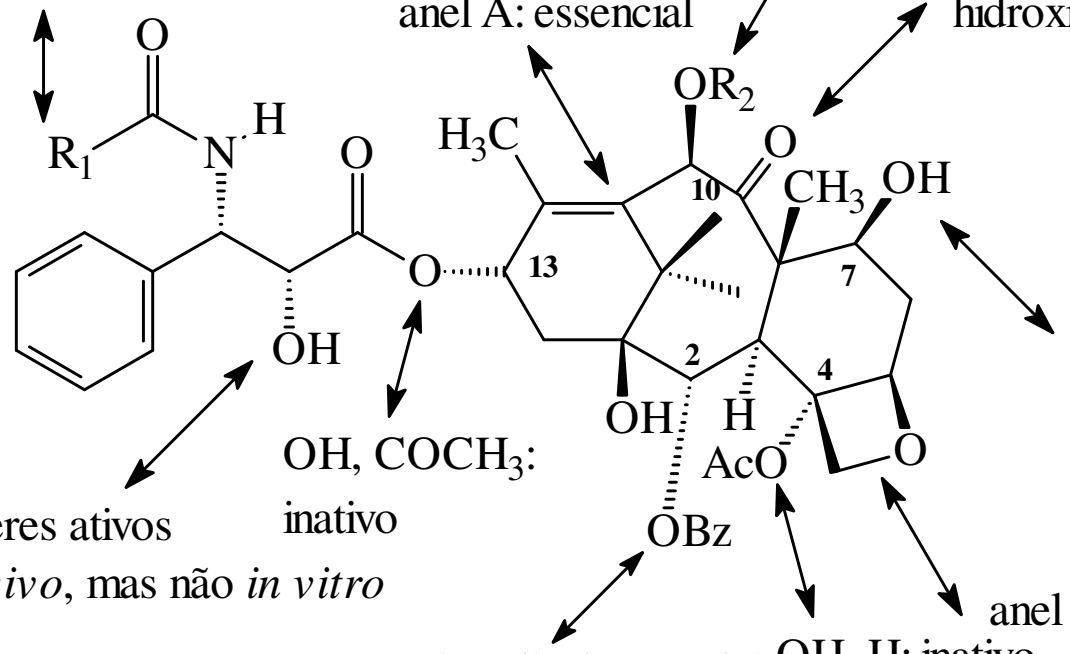
SAR dos taxóides

grupos lipofilicos e hidrofílicos: ativos

ésteres, desoxi: ativo

anel A: essencial

hidroxi em α ativo



aminoésteres,ésteres, epímero, desoxi: ativos

Câncer

Cancer de mama, Pulmão ,cérebro, garganta

ésteres ativos *in vivo*, mas não *in vitro*

OH, $COCH_3$: inativo

anel oxetano aberto: inativo

2-benziloxi essencial

OH, H: inativo

Taxotere (R_2= H, R_1= OBu)
Análogo sintético do taxol
(R_1= Ph, R_2= Ac)

Taxol (*taxus brevifolia*)

(Paclitaxel; Bristol-Myers Squibb, 1992)

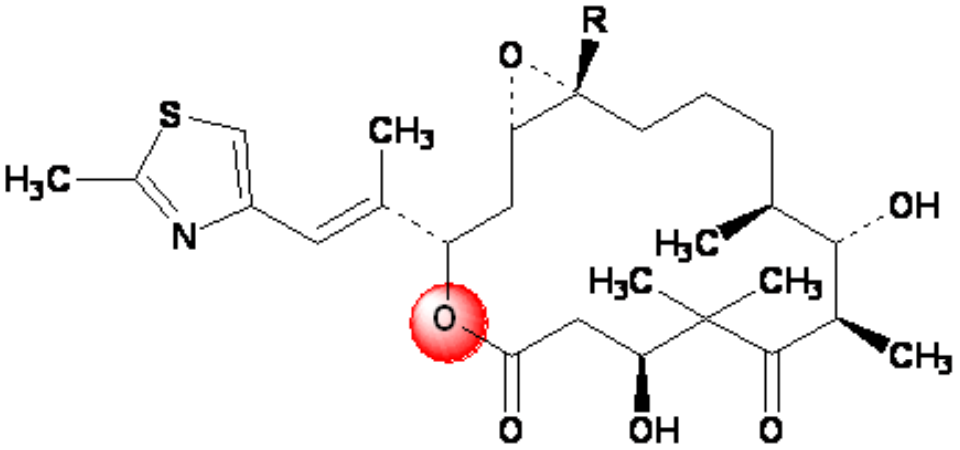
(uso: parenteral)

Toxicidad: Médula ósea
Neutropenia

Baja biodisponibilidad

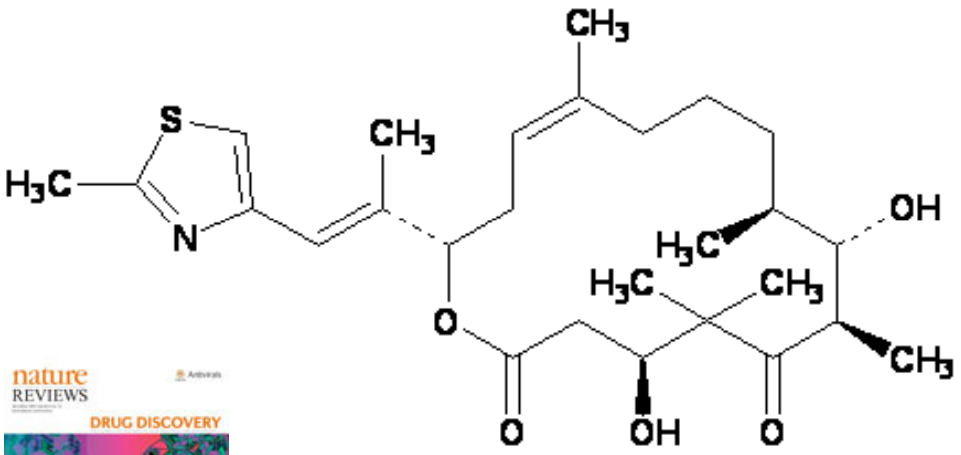
"Natural Compounds in Cancer Therapy: Promising Nontoxic Antitumor Agents from Plants and Other Natural Sources", J. Boik, Medical Press, Princeton, 2001.

Isolada de Sorangium cellulosum em 1993



Epotilona A R = H

Epotilona B R = CH_3

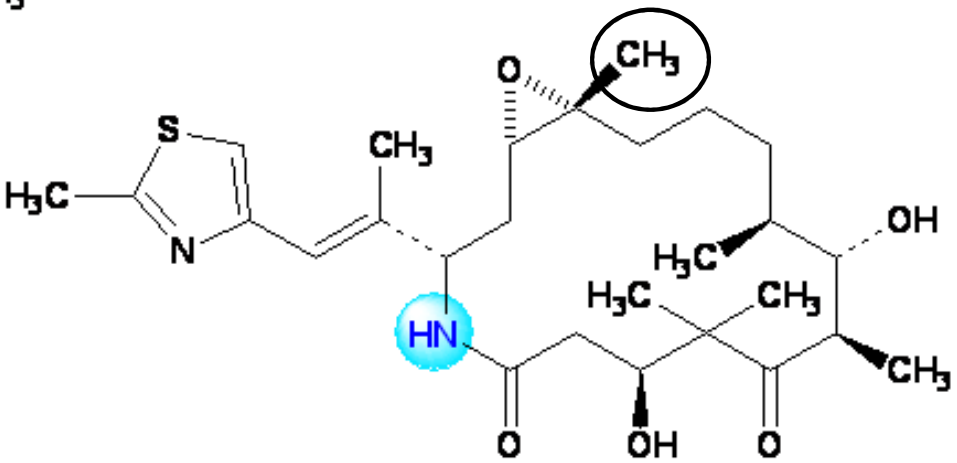


Epotilona D

A Conlin, M Fornier, C Hudiis, S Kar, P. Kirkpatrick, *Nat. Rev. Drug Discov*. **2007**, *6*, 953

2007 - Primeiro membro da classe dos macrociclos de 16 membros (epotilonas) a ser aprovado pelo FDA para tratamento do câncer metastático de mama, atuando como inibidor de microtúbulos

Análogo semi-sintético

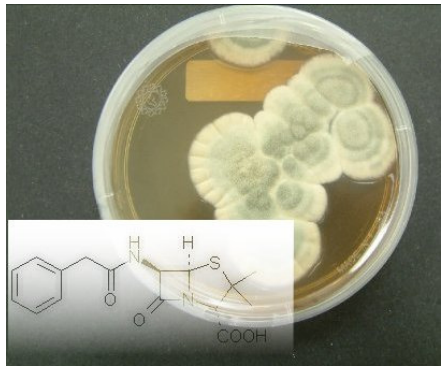


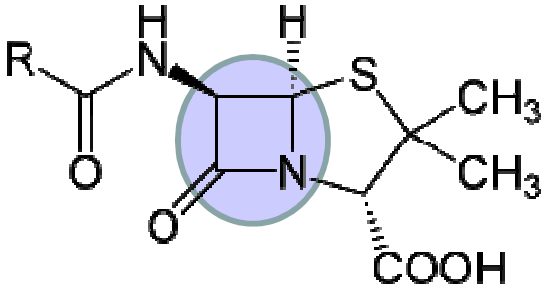
Ixabepilona

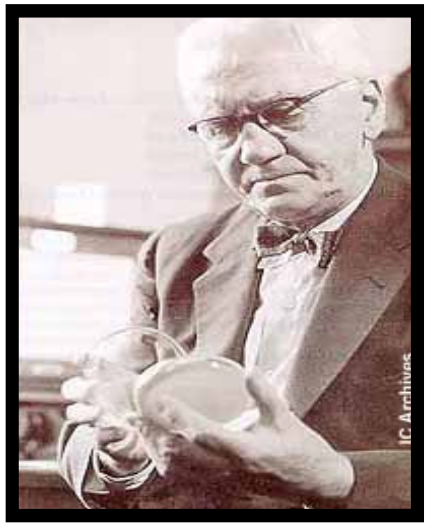
Ixempra^R

BMS, Out. 2007

Via fermentativa bacteriana, ativo em células taxano-R



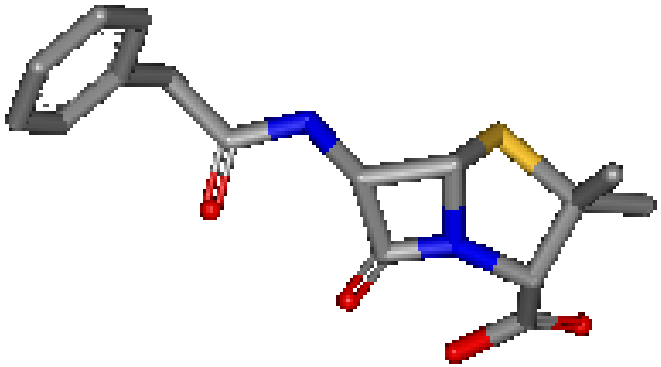




Alexander Fleming

1881-1955

http://nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-bio.html



Penicilina

1896 –Robert Duchesne

Raios X – Dorothy Hodgkin

(Prêmio Nobel, 1964)

Edward Abraham

1943 – Andrew J. Moyer

1957 – John Sheehan

http://nobelprize.org

1945

Howard W. Florey

1898-1968

http://nobelprize.org/nobel_prizes/medicine/laureates/1945/florey-bio.html

Ernst B. Chain

1906-1979

http://nobelprize.org/nobel_prizes/medicine/laureates/1945/chain-bio.html

Universidade Federal do Rio de Janeiro

Química Medicinal

Fármacos & Premio Nobel

199 Nobel laureates in Medicine
160 Nobel laureates in Chemistry
192 Nobel laureates in Physics
(from 1901 to 2011)

LASSBio®

Fármacos & el Nobel

Clave y cerradura

Lock & Key

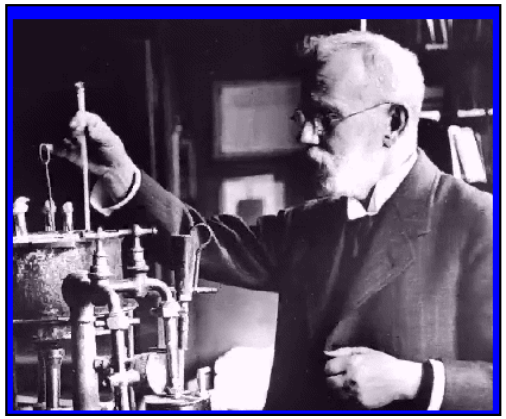
Emil Fischer

1852-1919

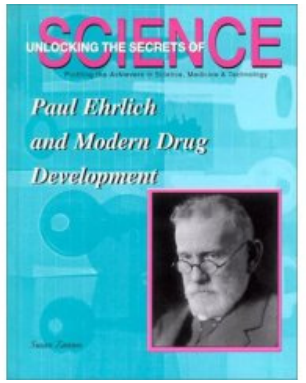
1902

http://nobelprize.org/nobel_prizes/chemistry/laureates/1902/fischer-bio.html

El paradigma de Fischer y Ehrlich



The Magic Bullet Theory



Química Medicinal

Paul Ehrlich

1854-1915

1908

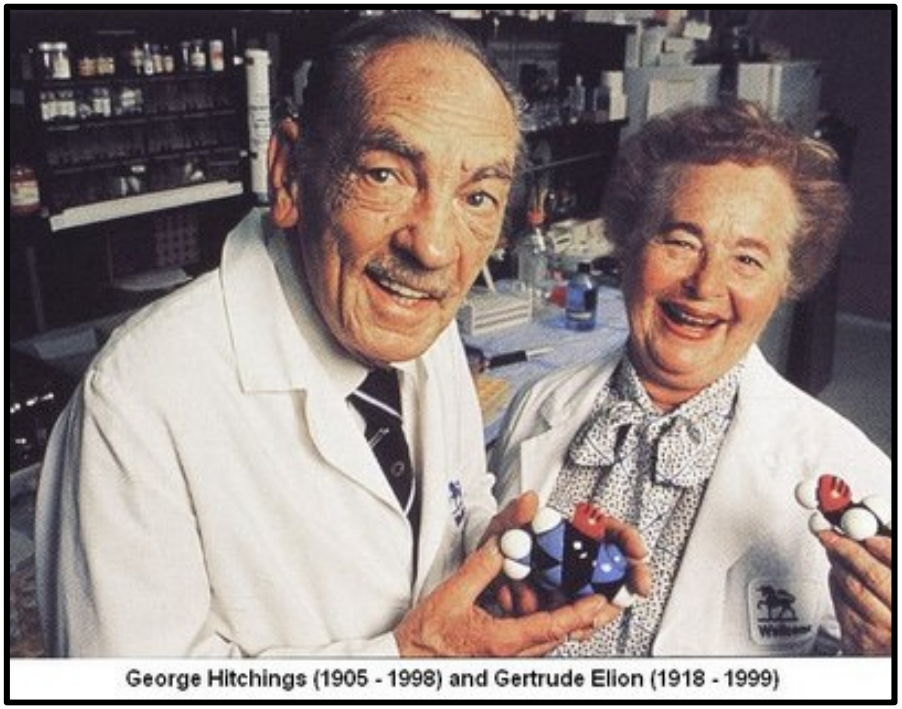
http://nobelprize.org/nobel_prizes/medicine/laureates/1908/ehrlich-bio.html

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

LASSBio®

“for their discoveries of important principles for drug treatment"

1988 – James W. Black
(1924-2009)



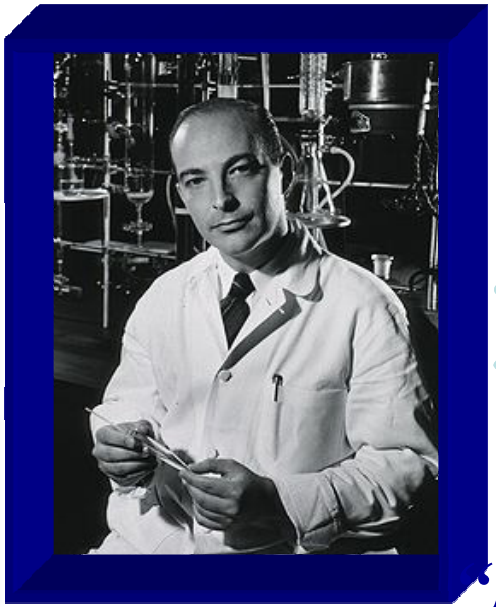
George Hitchings (1905 - 1998) and Gertrude Elion (1918 - 1999)

1988

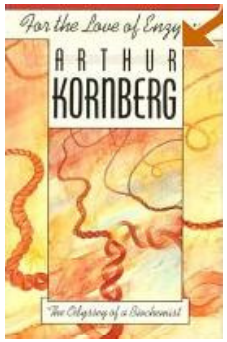
Inter-alia: **Propranolol**, cimetidina,

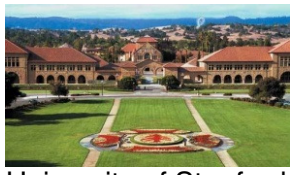
azatioprina, alopurinol, trimetoprim, **aciclovir**

Prêmio Nobel, 1959

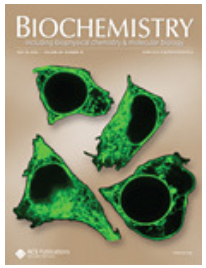


Arthur Kornberg
1918-2007





University of Stanford



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..."*

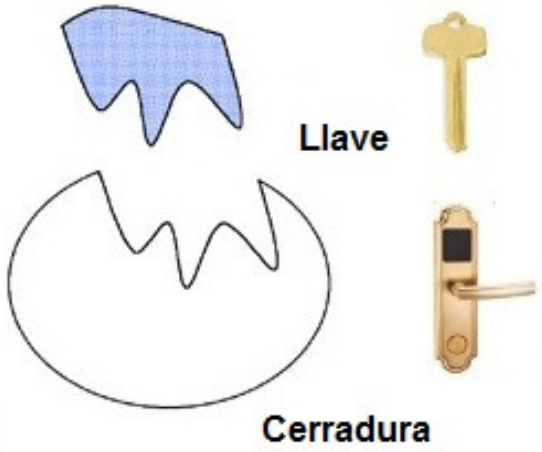
Biochemistry **1987,** *26,* 6888-6891

interdisciplinaridad

Universidade Federal do Rio de Janeiro

Química Medicinal

Clave & cerradura



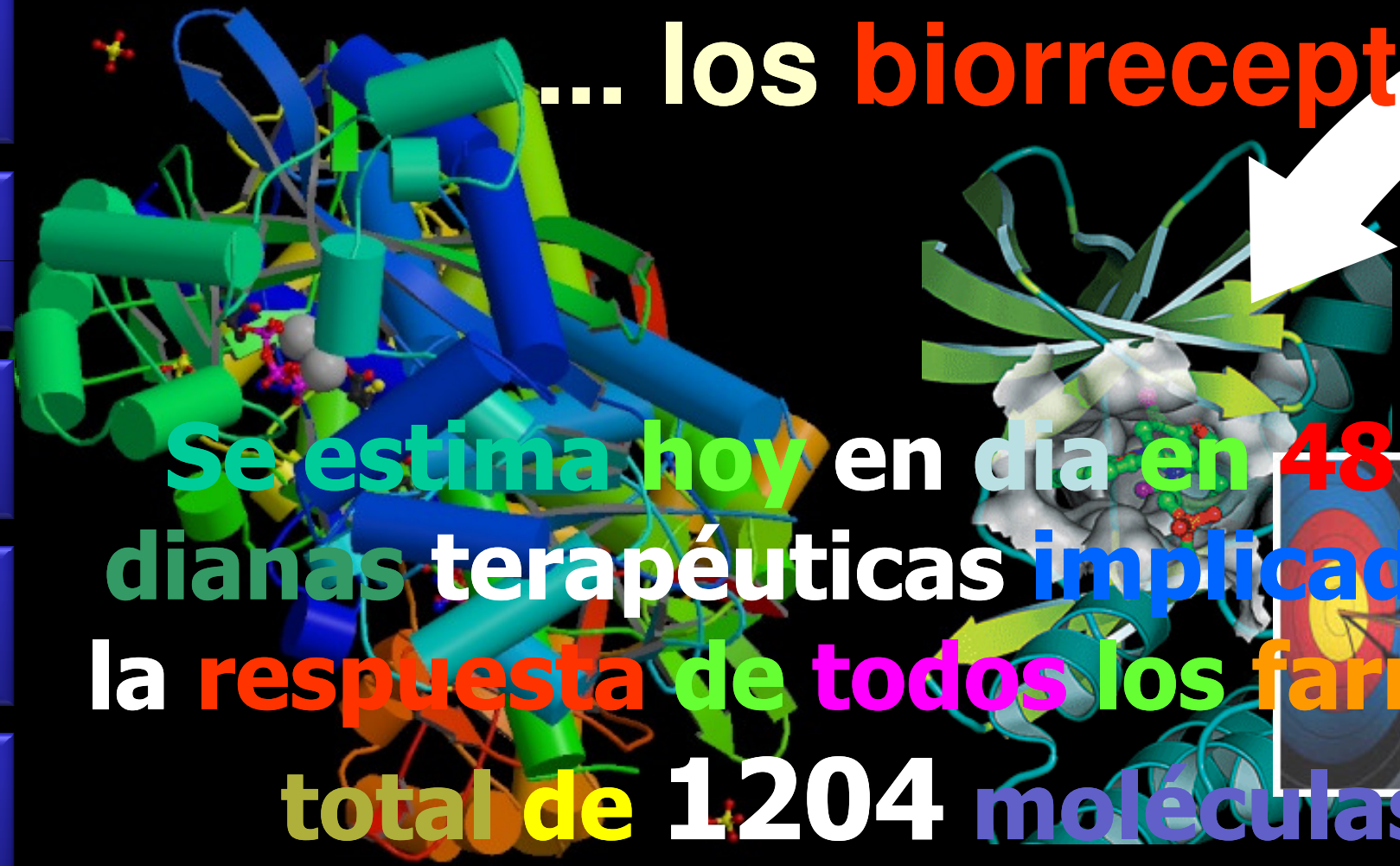
Un modelo centenario…

LASSBio®

Los fármacos actúam sobre dianas terapéuticas...

Química Medicinal

... los biorreceptores.



Se estima hoy en dia en 483* las dianas terapéuticas implicadas en la respuesta de todos los farmacos, total de 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.

La mayoría de biorreceptores de los fármacos contemporáneos son las enzimas…

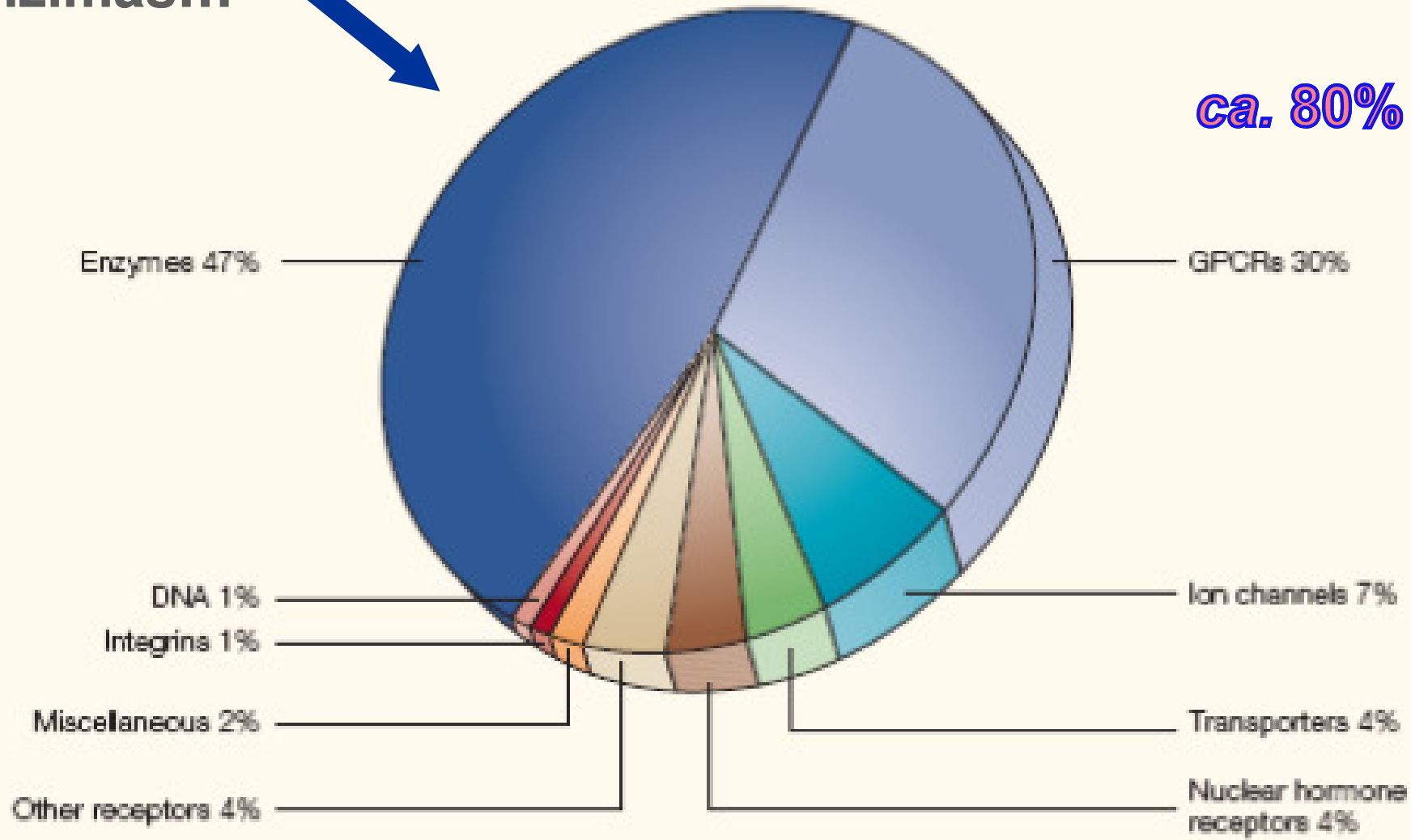


Figure 4 | **Marketed small-molecule drug targets by biochemical class.** GPCR, G-protein-coupled receptor.

www.nature.com/reviews/drugdisc

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

El "*alfabeto*" de las enzimas ...

glicina (**gly**) **ala**nina **val**ina isoleucina (**Ile**) **leu**cina

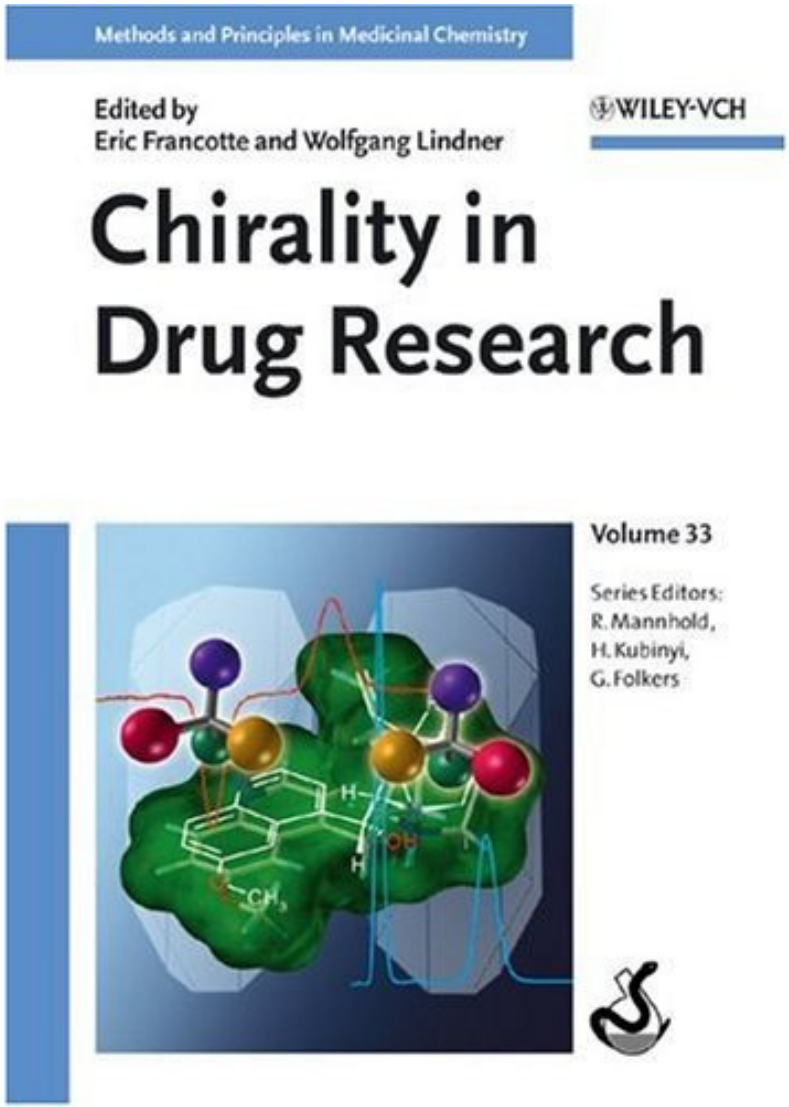
serina cisteína (**Cys**) treonina (**Thr**) **met**ionina

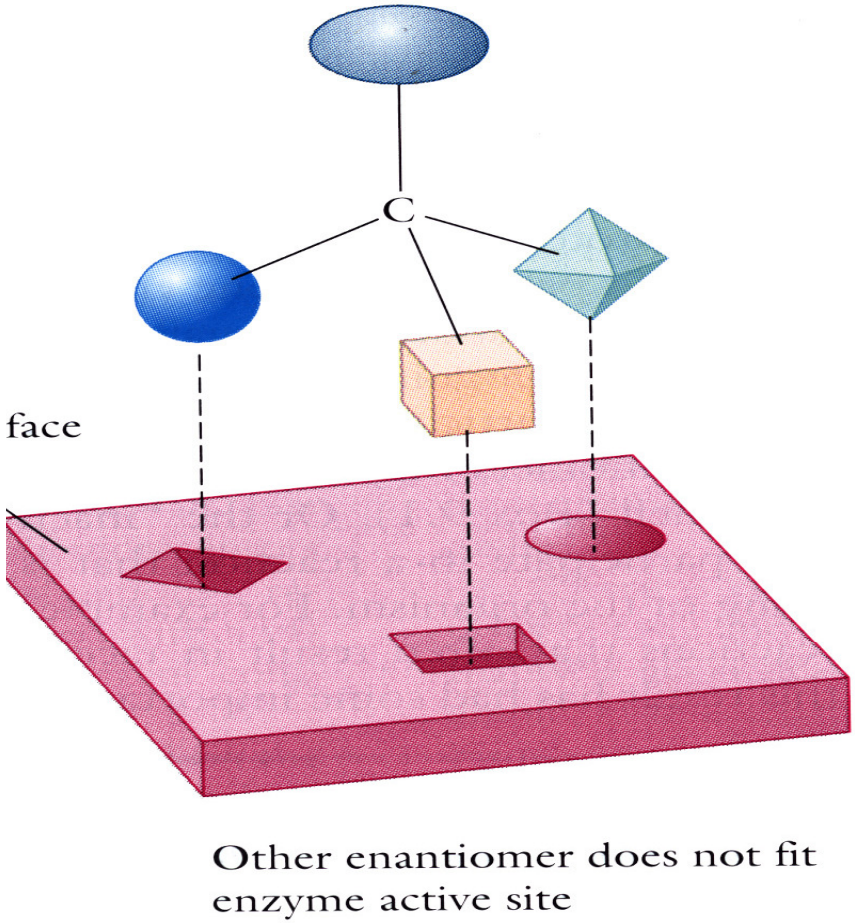
lisina (**Lys**) **arg**inina ácido **glu**tâmico ácido **asp**ártico

prolina glutamina (**Gln**) asparagina (**Asn**)

triptofano (**Trp**) fenilalanina (**Phe**) tirosina (**Tyr**) **his**tidina

La quiralidad y los fármacos





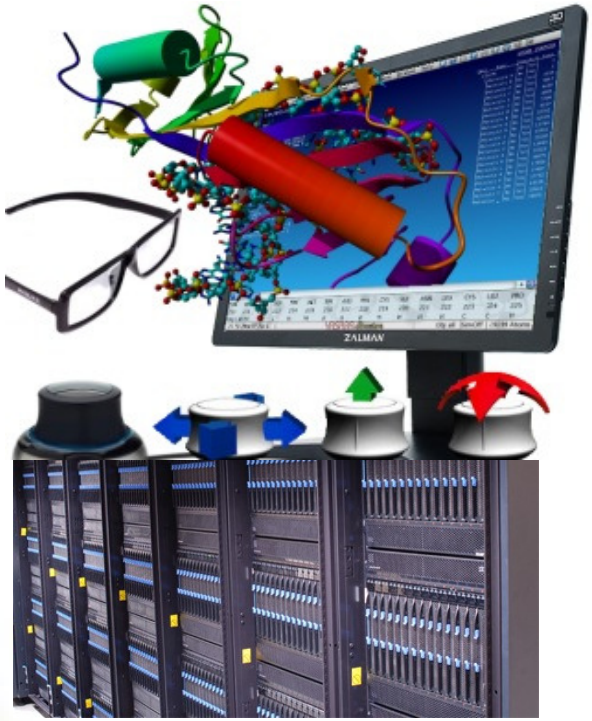
Modelo de los tres puntos

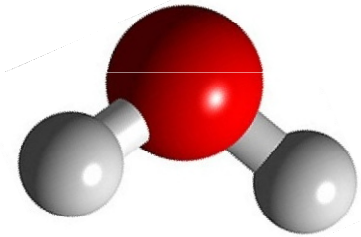
Modelo de Easson-Stedman

Universidade Federal do Rio de Janeiro

Química Medicinal

in silico





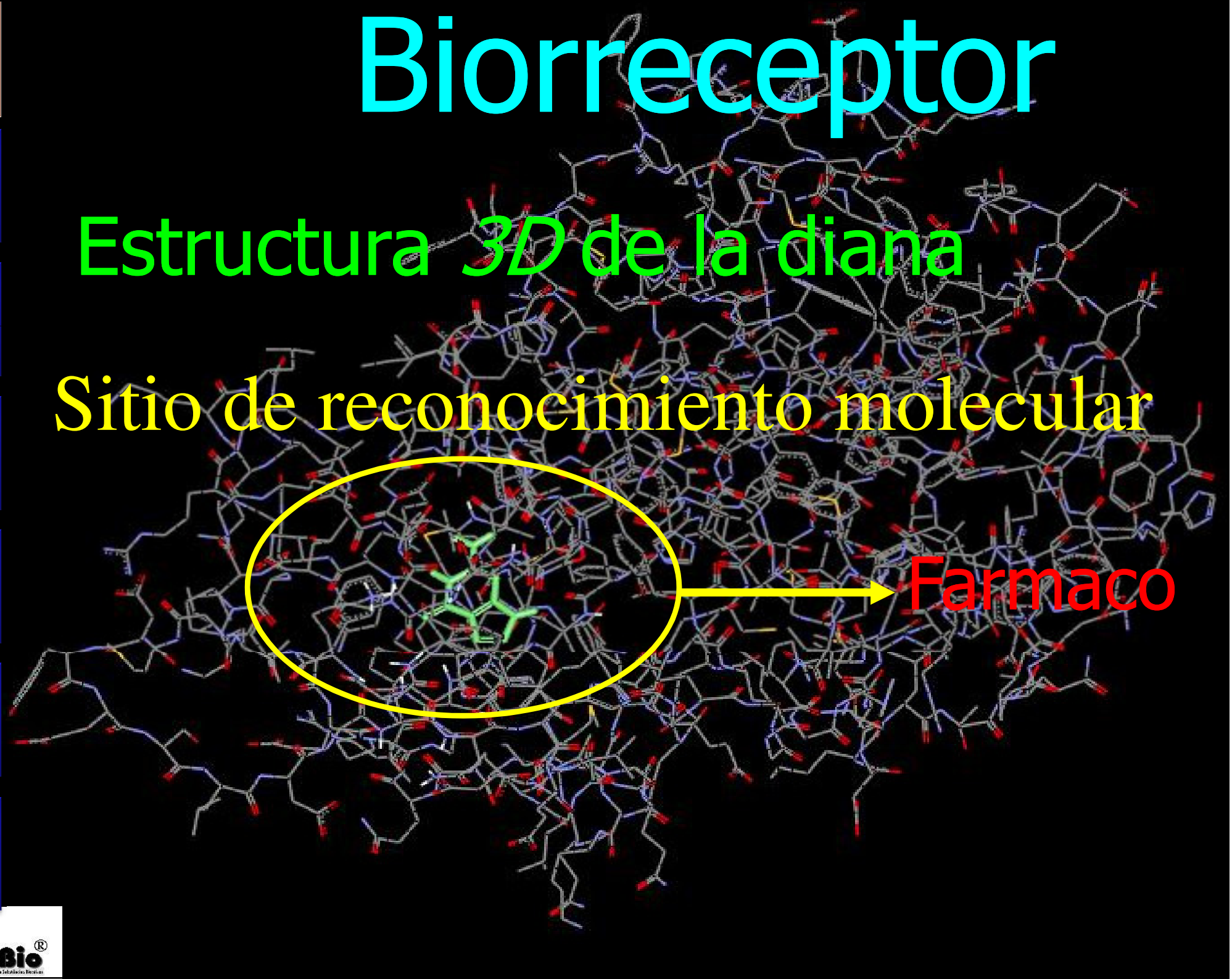
y la Quimica Computacional

LASSBio®

Biorreceptor

Estructura *3D* de la diana

Sitio de reconocimiento molecular



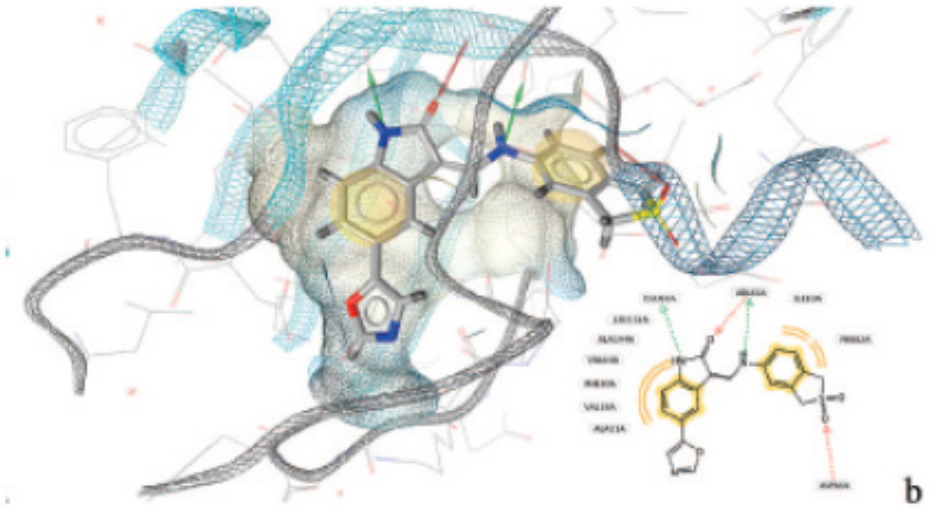
Journal of
Medicinal Chemistry

Perspective

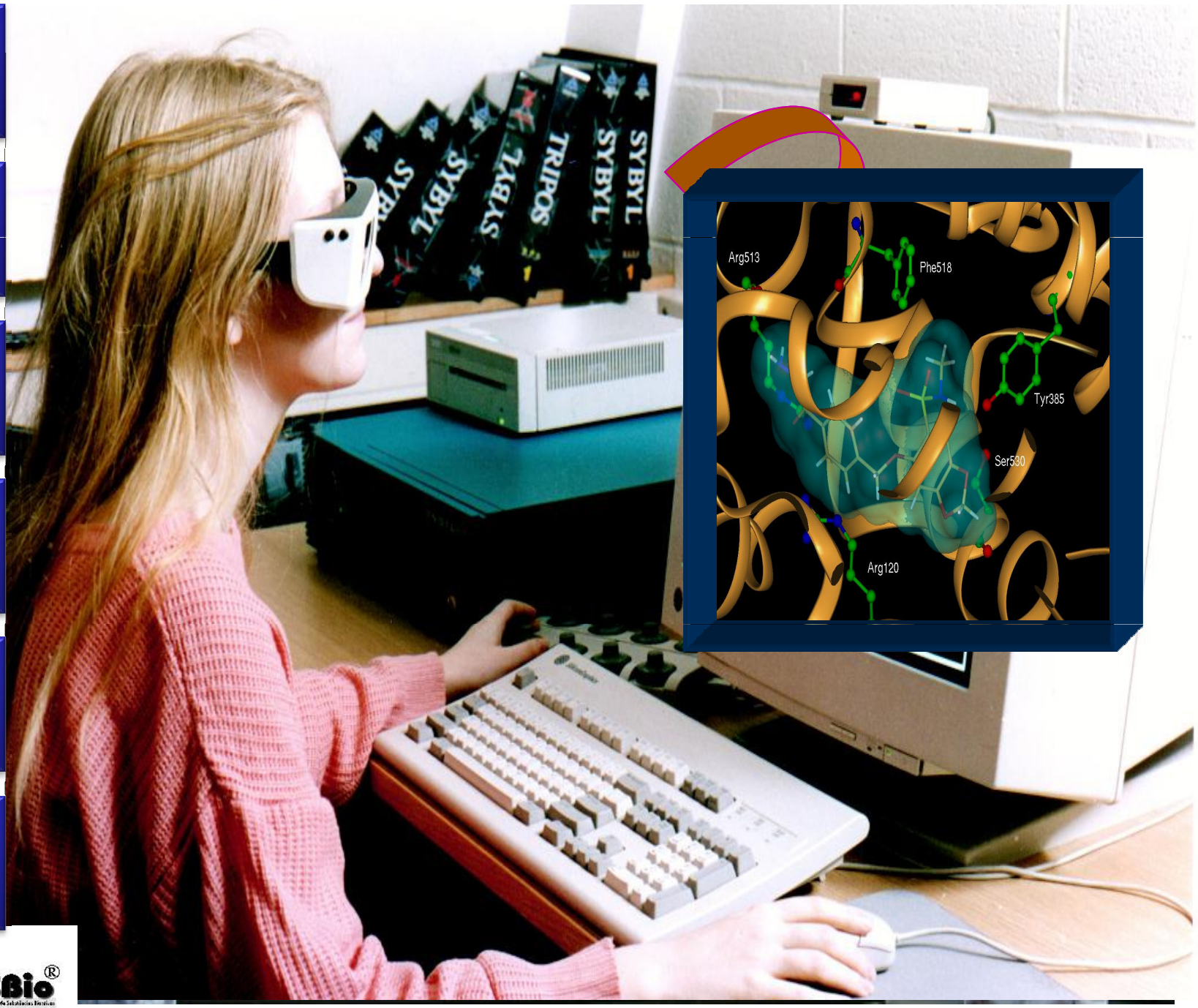
The Protein Data Bank (PDB), Its Related Services and Software Tools as Key Components for In Silico Guided Drug Discovery

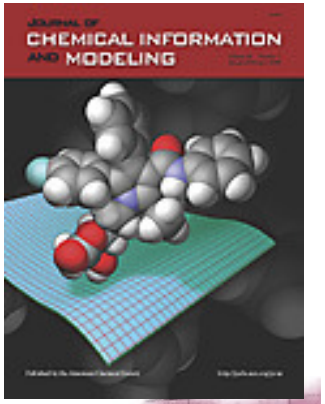
Johannes Kirchmair, Patrick Markt, Simona Distinto, Daniela Schuster, Gudrun M. Spitzer, Klaus R. Liedl, Thierry Langer, and Gerhard Wolber

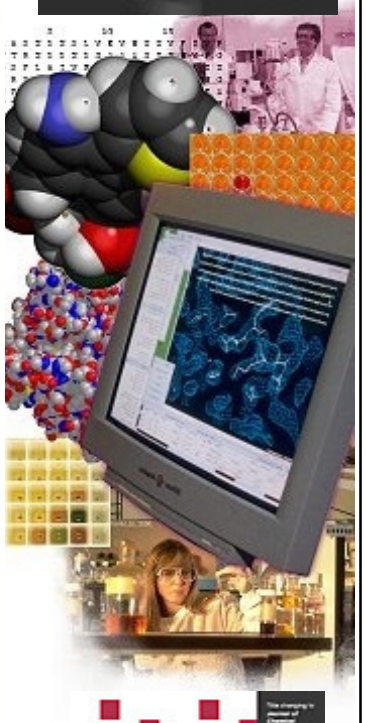
J. Med. Chem., **2008**, 51 (22), 7021-7040 • Publication Date (Web): 01 November 2008

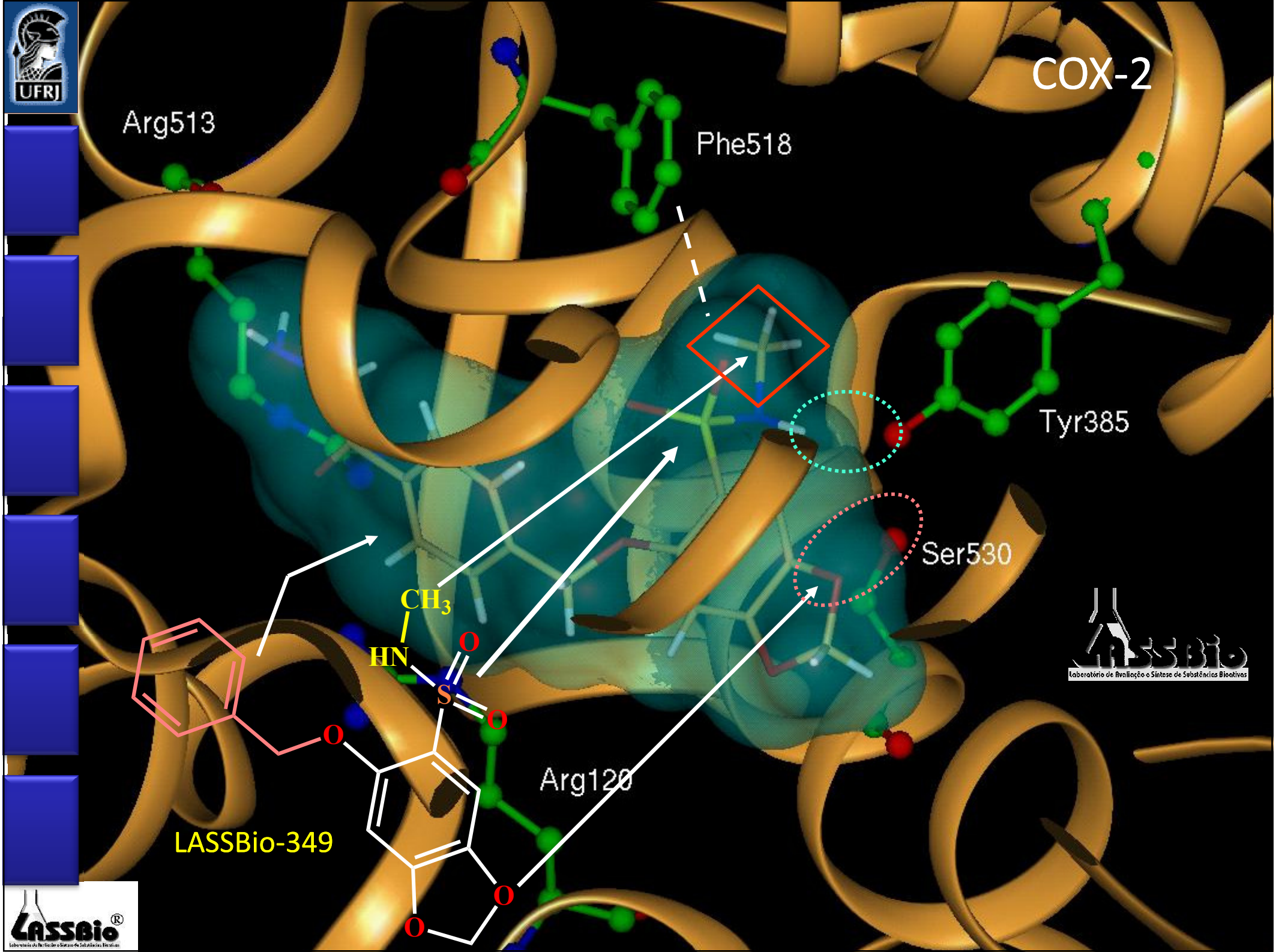


Química Computacional








COX-2
Arg513
Phe518
Tyr385
Ser530
Arg120
LASSBio-349
CH3
HN
O
S
O
O
O
O
O
LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas
LASSBio®

Universidade Federal do Rio de Janeiro

Química Medicinal

Parte 2

International Year of CHEMISTRY 2011

Eliezer J. Barreiro

Professor Titular

Universidade Federal do Rio de Janeiro

ejbarreiro@ccsdecania.ufrj.br

http://ejb-eliezer.blogspot.com

Laboratório de Avaliação e Síntese de Substâncias Bioativas

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

Instituto Nacional de Ciência e Tecnologia em Fármacos e Medicamentos

http://www.inct-inofar.ccs.ufrj.br

LASSBio®

LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas

Química Medicinal

Ejemplos caseros...

Química Medicinal

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

Eleição do alvo-terapêutico

Química Computacional

Produtos Naturais

Síntese Orgânica Medicinal

Protótipo

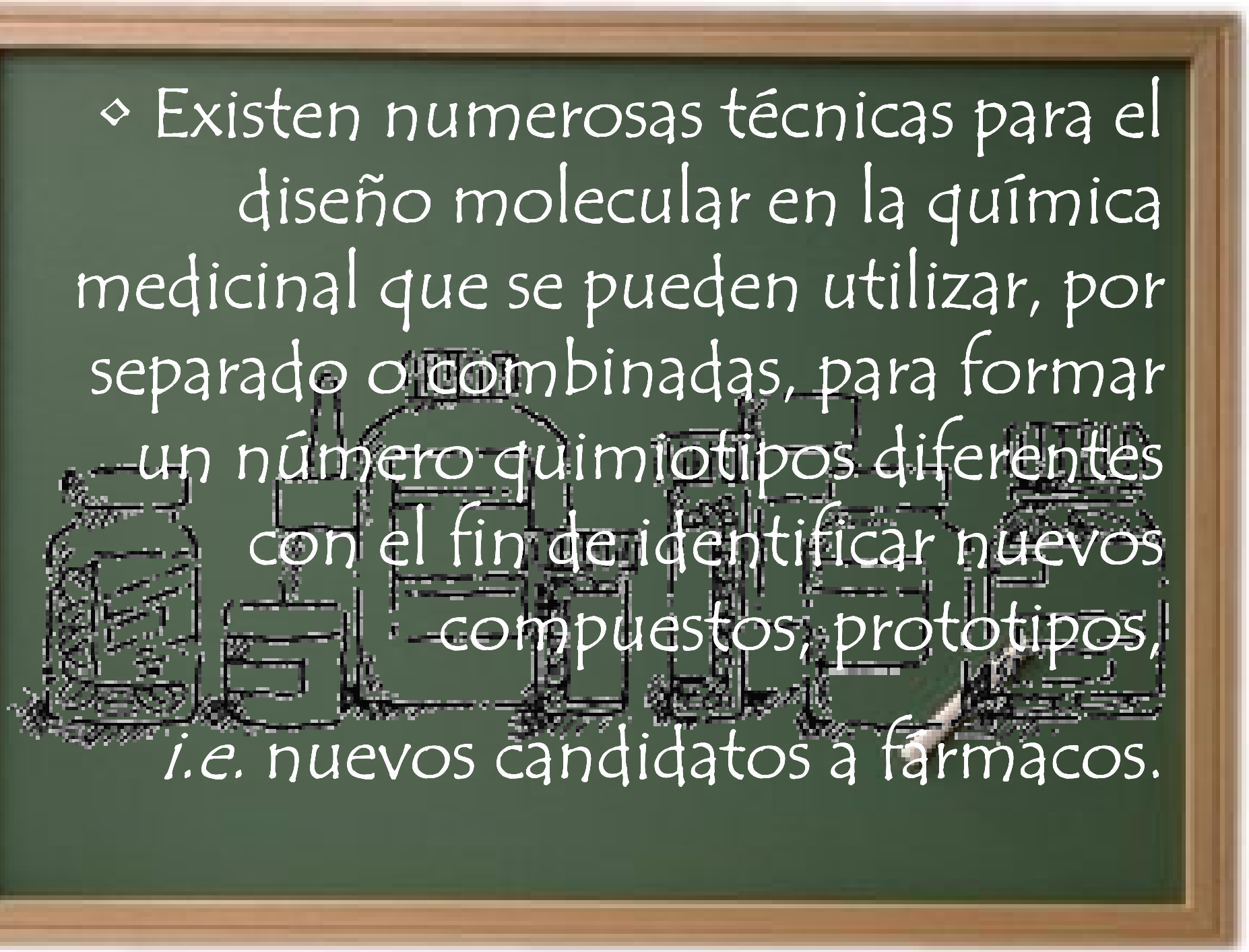
Bioensaios

Ensaios clínicos

Otimização

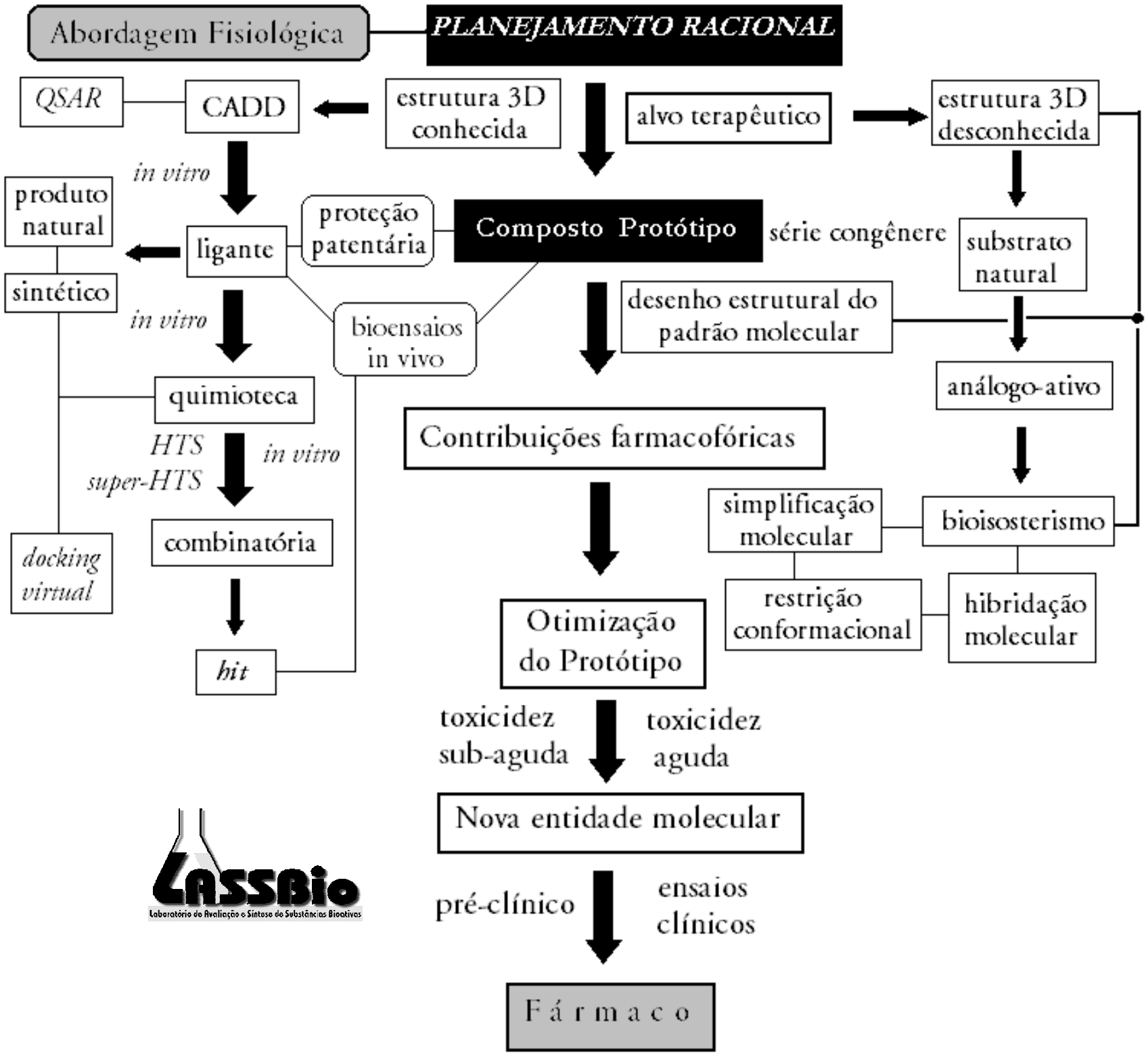
Novo fármaco

Quimioteca con 1735 compuestos activos (*in vivo*)



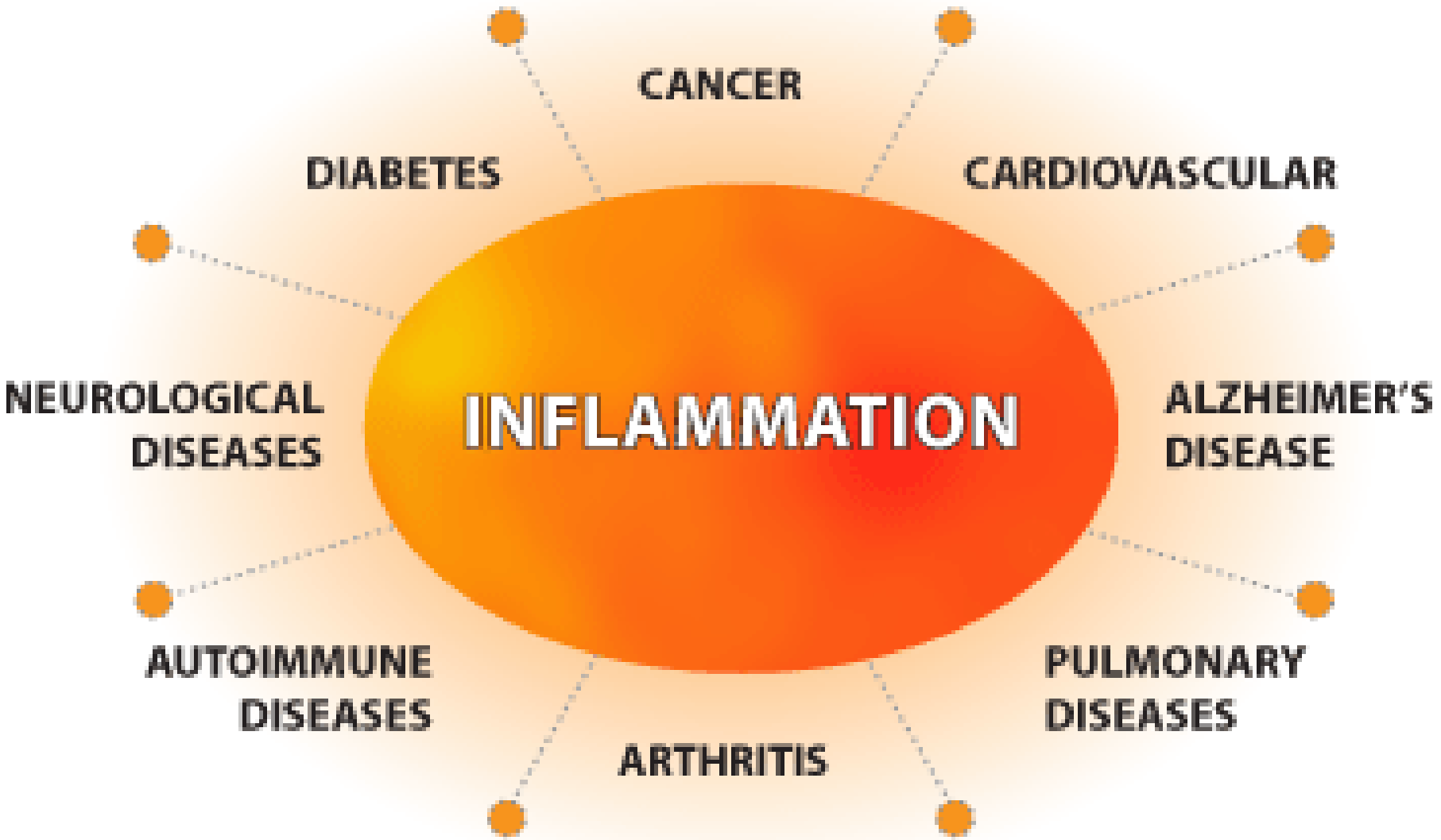
- Existen numerosas técnicas para el diseño molecular en la química medicinal que se pueden utilizar, por separado o combinadas, para formar un número quimiotipos diferentes con el fin de identificar nuevos compuestos, prototipos, *i.e.* nuevos candidatos a fármacos.

Strategies for molecular design

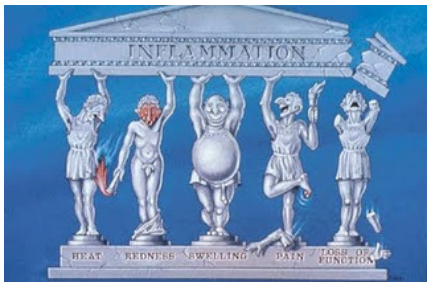


Estrategias para el diseño molecular

Enfermedades crónicas no transmisibles



La elección de la diana es un paso fundamental…



Fosfolipídios de membrana

PLA_2

CO_2H

CH_3

ácido araquidônico

anexina-1
resolvinas
NF-kB
caspases-3

⊕

resolução

⊕

apoptose

12-LOX

5-LOX

COX

LXA_4
LXB_4

LT´s &Cys-LT´s

CB´s
VR´s

dor

quimiotaxia

resolução

PPAR´s

⊕

CyPG´s

Trombina
ADP

PGD_2

⊕

⊕

PG´s

agregação
plaquetária

⊕

⊕

inflamação

dor

⊕

TNF- α

⊕

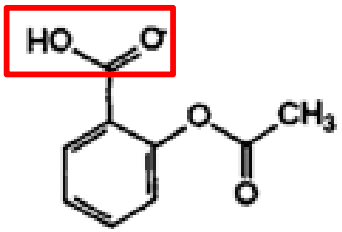
IL-1
IL-10

AMP-c

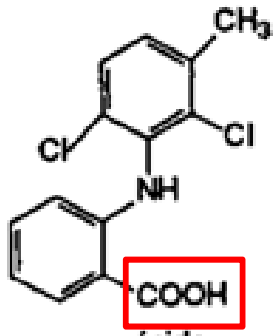
PDE-4´s

MAPK-p38

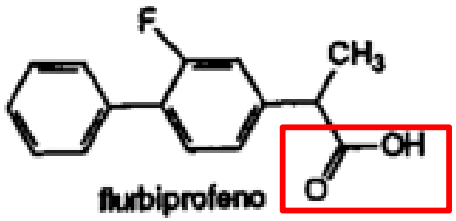
… y depende de la fisiopatologia!



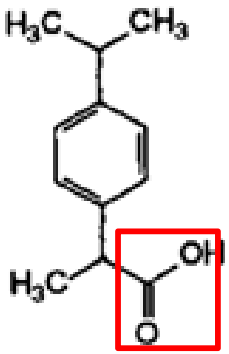
ácido acetil-salicílico (1)



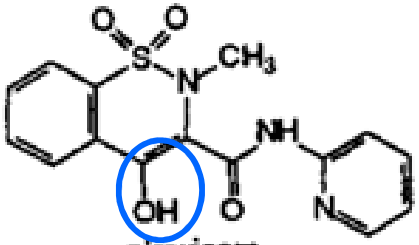
ácido meclofenâmico (2)



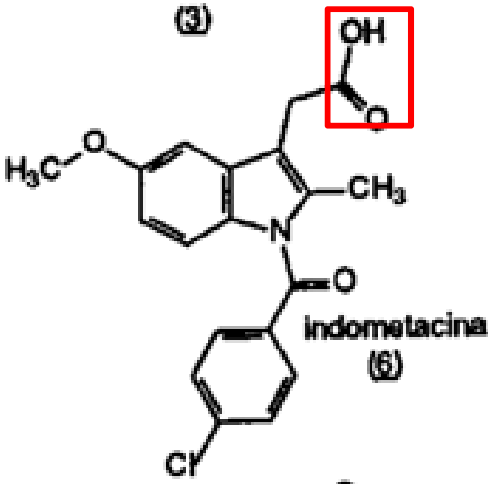
flurbiprofeno (3)



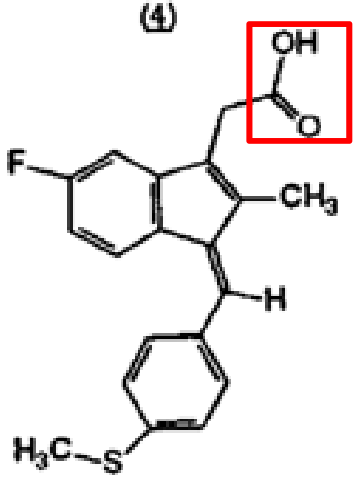
ibuprofeno (4)



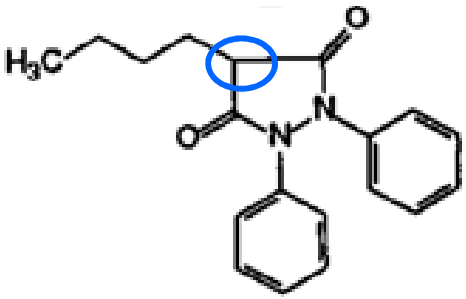
piroxicam (5)



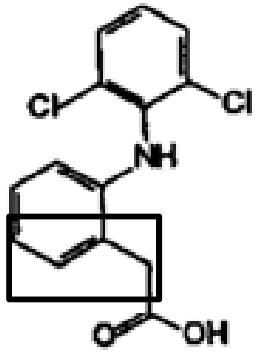
indometacina (6)



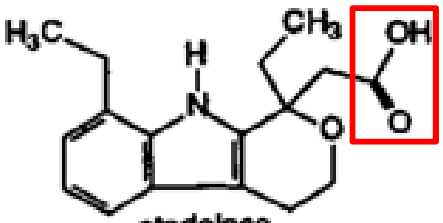
sulindaco (7)



fenilbutazona (10)

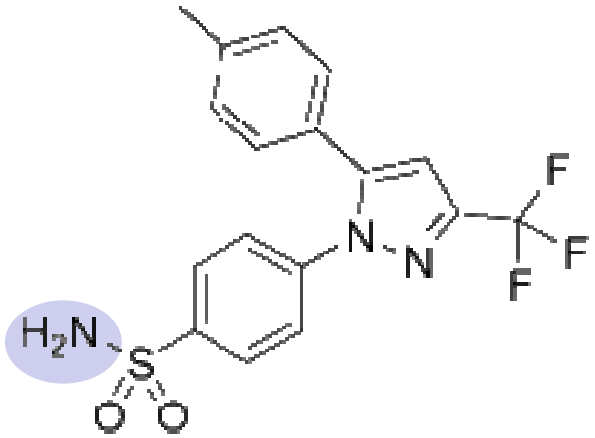


diclofenaco (9)

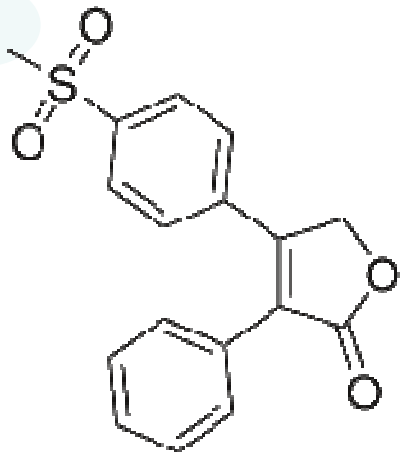


etodolaco (11)

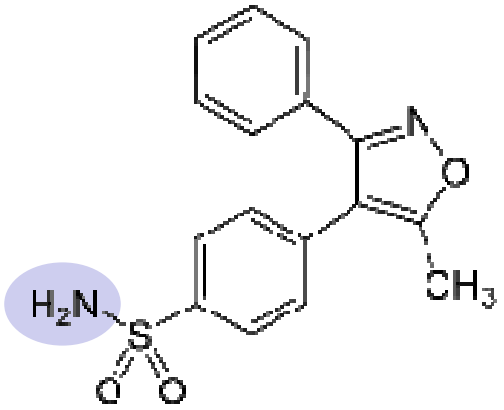
Quadro 1. NSAI'S-clássicos[21].



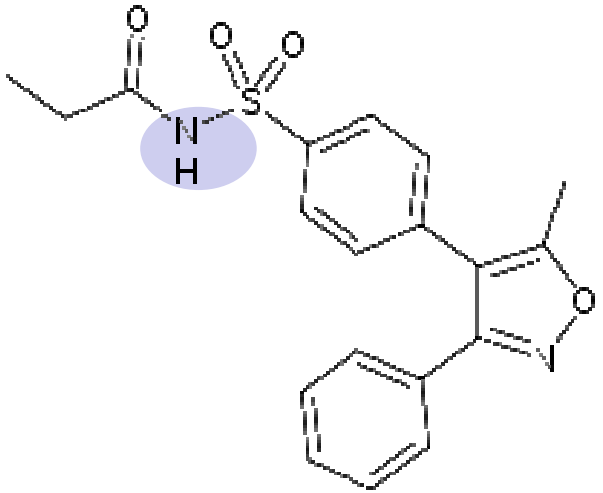
Celecoxib (**Celebra**^{R})
1999 (Pfizer US$ 30 bi)



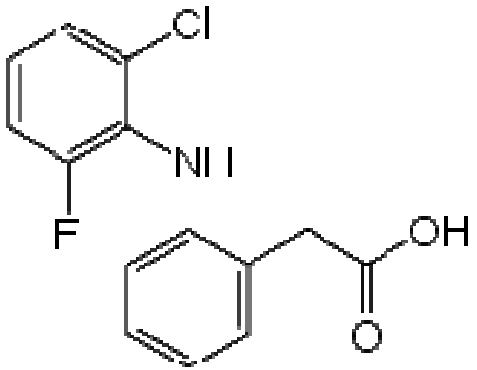
Rofecoxib (**Vioxx**^{R})
1999 - 2006



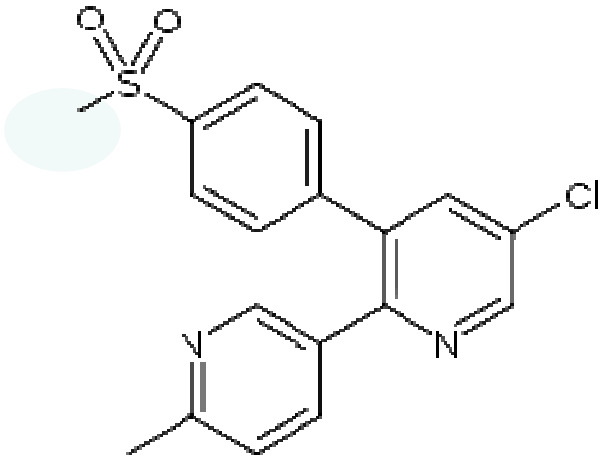
Valdecoxib (**Bextra**^{R})
2004- 2006



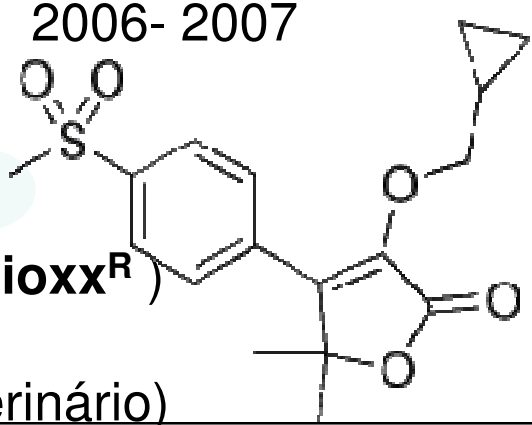
Parecoxib (**Dynastat**^{R})
2005- 2006



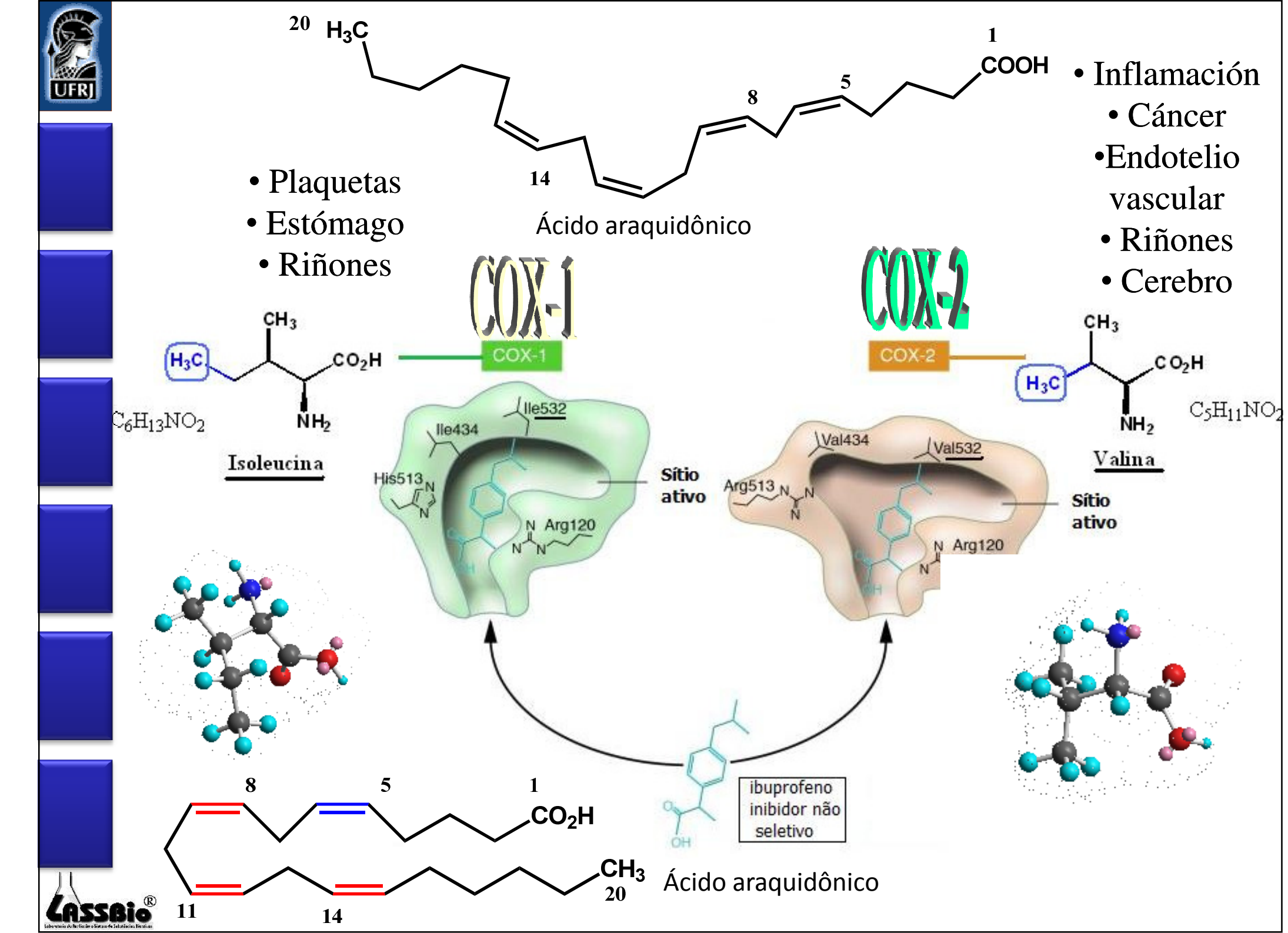
Lumiracoxib (**Prexige**^{R})
2006- 2007

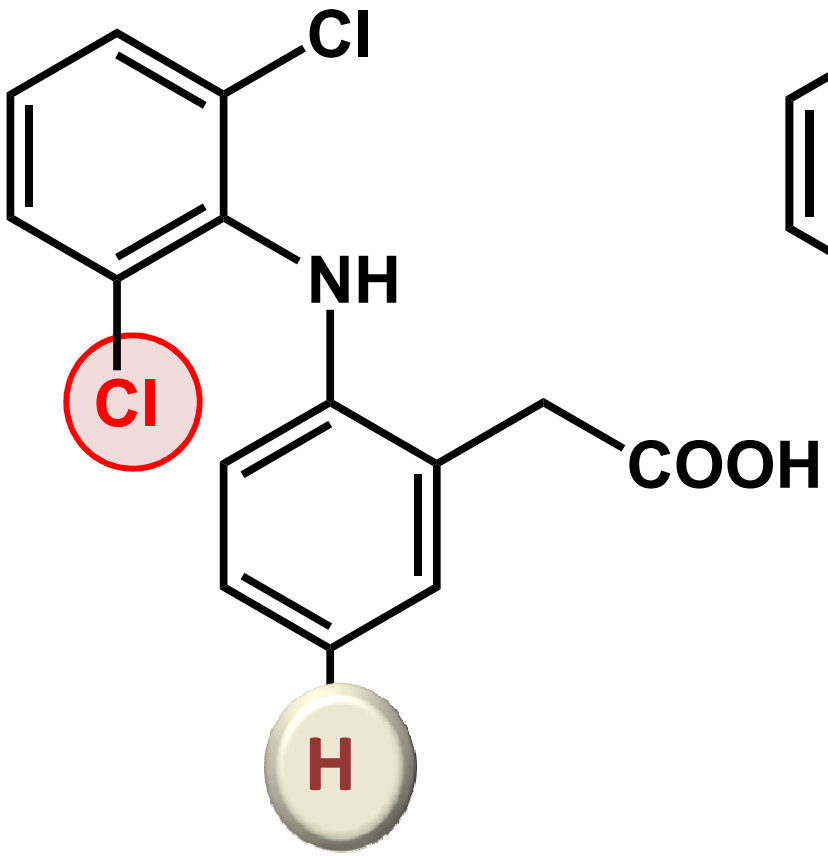


Etoricoxib (**Arcoxia**^{R})
2007- 2008

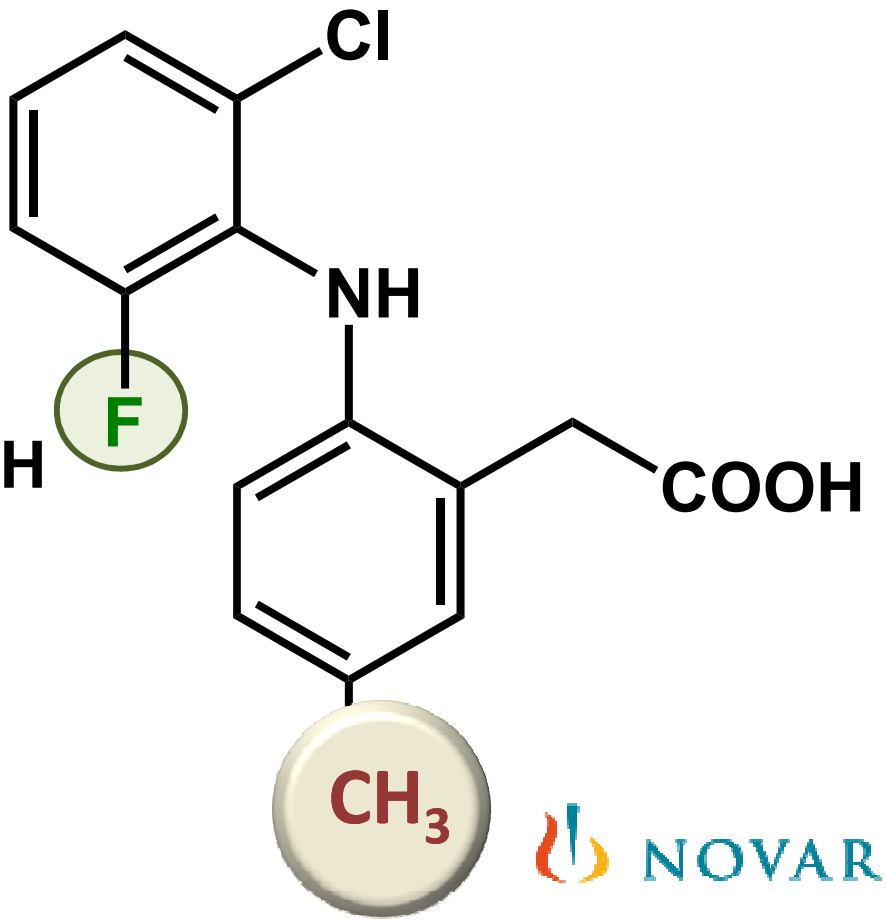


Firocoxib (**Equioxx**^{R})
2008
(FDA – uso veterinário)


20 H3C
1 COOH
8
5
14
Ácido araquidônico
• Plaquetas
• Estómago
• Riñones
• Inflamación
• Cáncer
•Endotelio vascular
• Riñones
• Cerebro
COX-1
COX-2
CH3
H3C
CO2H
NH2
C6H13NO2
Isoleucina
C5H11NO2
Valina
Ile532
Ile434
His513
Arg120
Sítio ativo
Val434
Val532
Arg513
Arg120
Sítio ativo
8
5
1
CO2H
CH3
20
11
14
Ácido araquidônico
ibuprofeno
inibidor não seletivo



Diclofenac



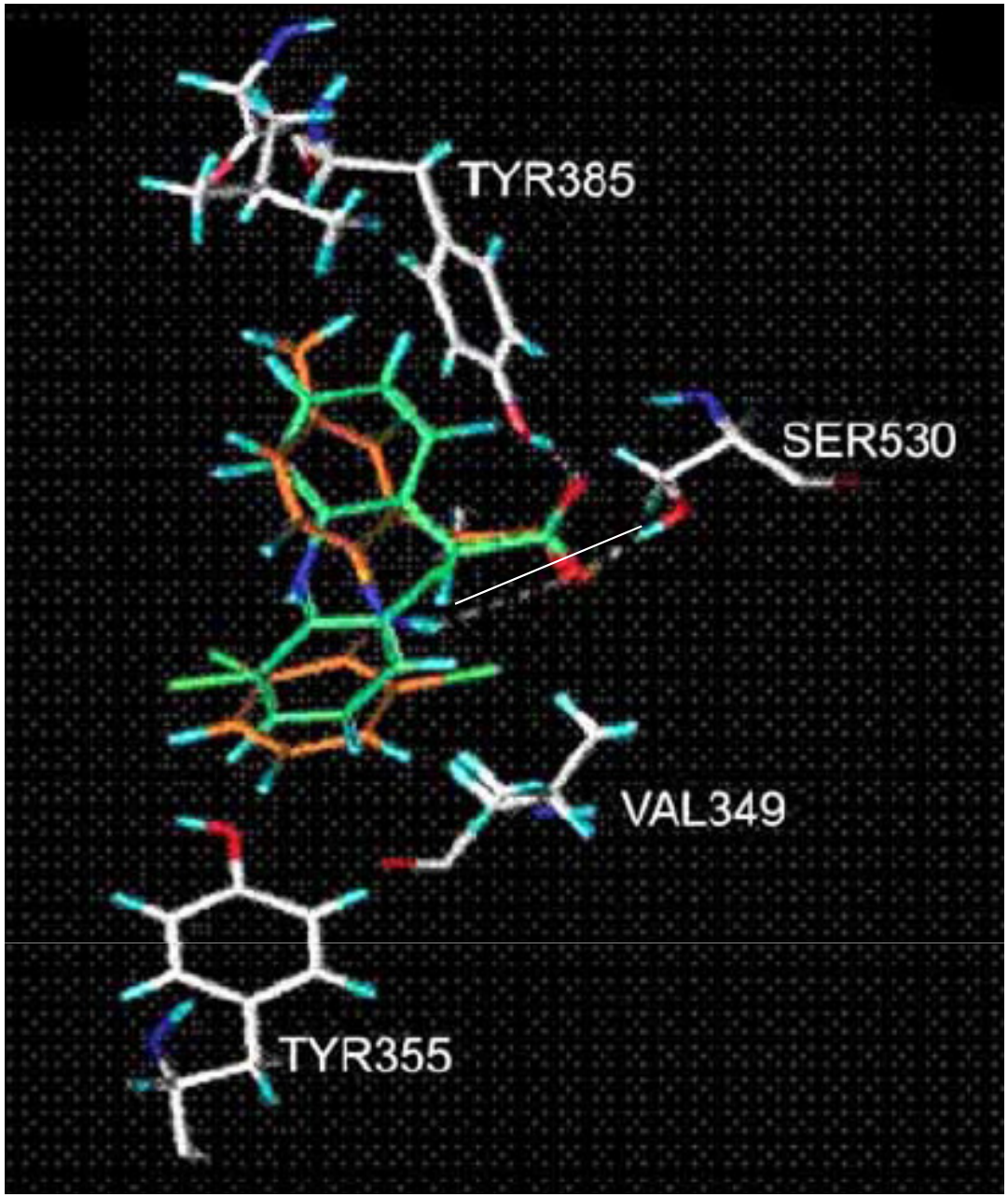
Lumiracoxib (Prexige^{R})

NOVARTIS

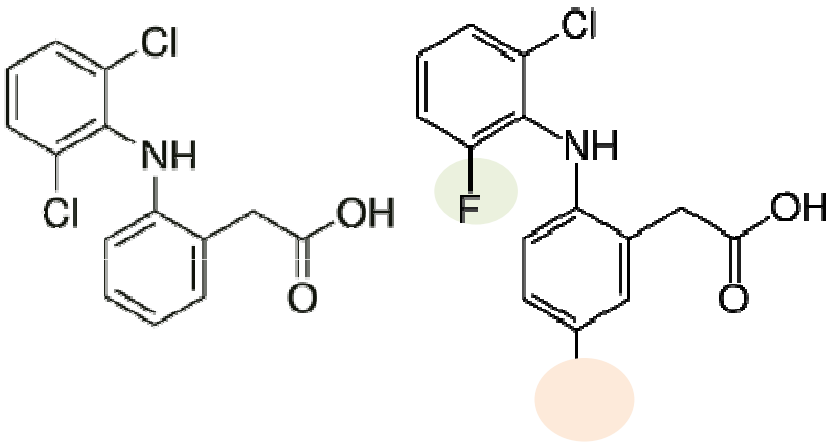
COX-1 >>>>>> COX-2

COX-2 > COX-1

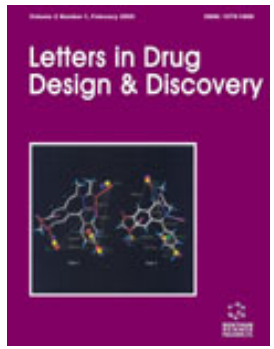
El increíble efecto de un *inteligente* grupo metilo !



COX-2 active site with lumiracoxib and diclofenac (green)



Brazilian National Health Surveillance Agency (ANVISA) ordered the withdrawal of lumiracoxib in Oct. 2008.



C. M. Corrêa, A.F. de Paula, G. M.S. da Silva, C. M.R. Sant'Anna,C.A. M. Fraga, E.J. Barreiro, Letters in Drug Design & Discovery, ***2007****, 4,* 422

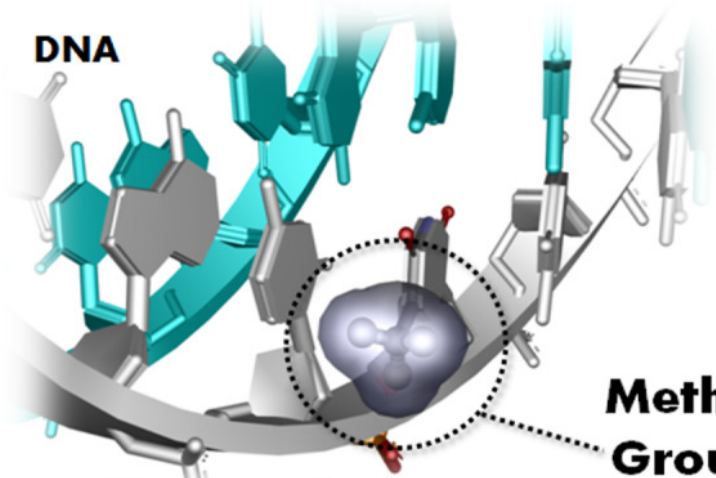
CHEMICAL REVIEWS
Chem. Rev. 2011, 111, 5215-5246
REVIEW
dx.doi.org/10.1021/cr200060g

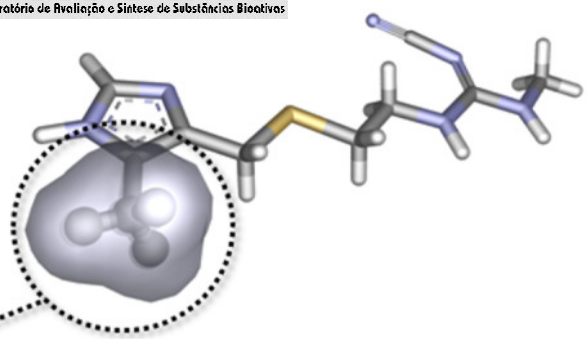
The Methylation Effect in Medicinal Chemistry

E. J. Barreiro, A. E. Kümmerle and C. A. M. Fraga

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

Química Medicinal





Methyl Group

Biomacromolecules

CH/π interactions from the methyl group of timine. Conformational changes, wich could be involved on maintenance of life.

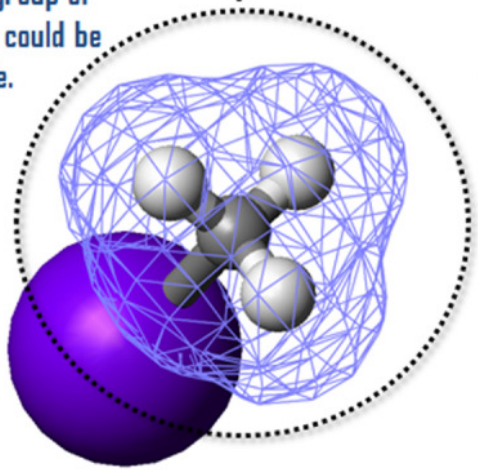
Micromolecules

The inductive eletronic effect of the methyl group is the responsible for the subtype receptors selectivity (H_2x H_1) on cimetidine

CH_3

15 Da

The stereoelectronic effects of the methyl group have great importance on biological events and are widely used by the Medicinal Chemistries in the development of new drugs.



Stereoelectronic Properties

MW = 15,03
MR = 5,65 cm³/mol
π hansch = 0,56
σ hammett = -0,17

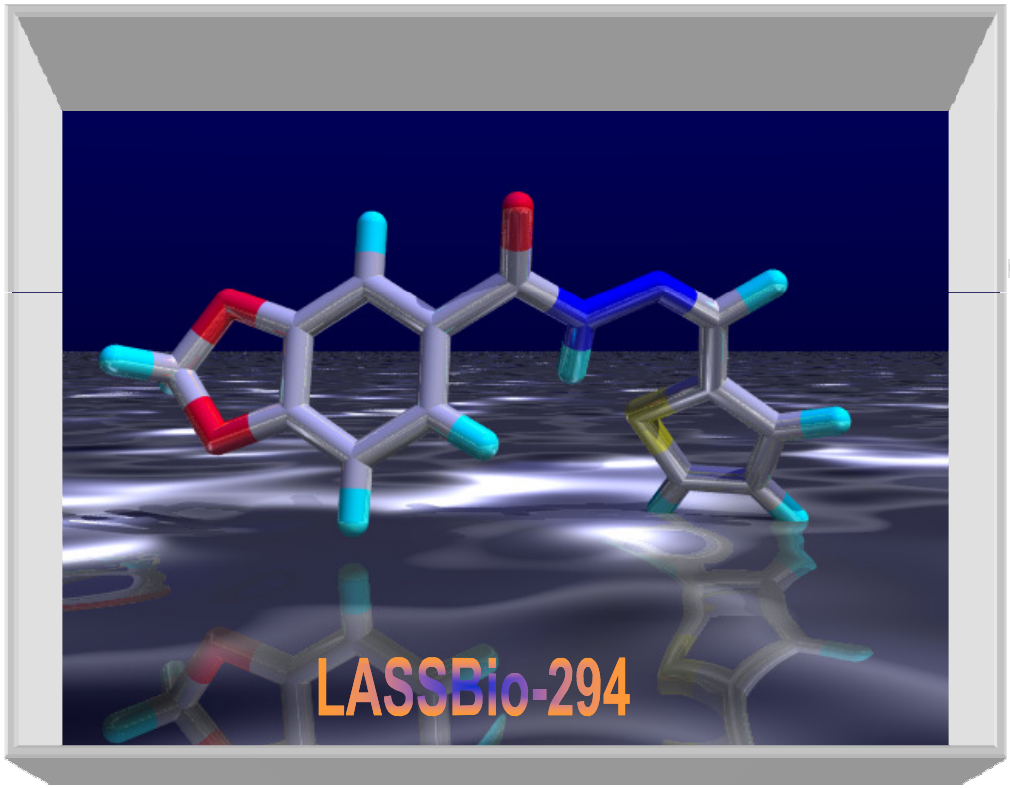
LASSBio®

Química Medicinal

La estrategia de la simplificación molecular

Comprende el uso de técnicas de cambios estructurales en un compuesto dado con el fin de reducir su complejidad estructural, que conduce a una sustancia nueva de la misma actividad que farmacológica.

Nuevo protótipo cardioactivo vasodilatador



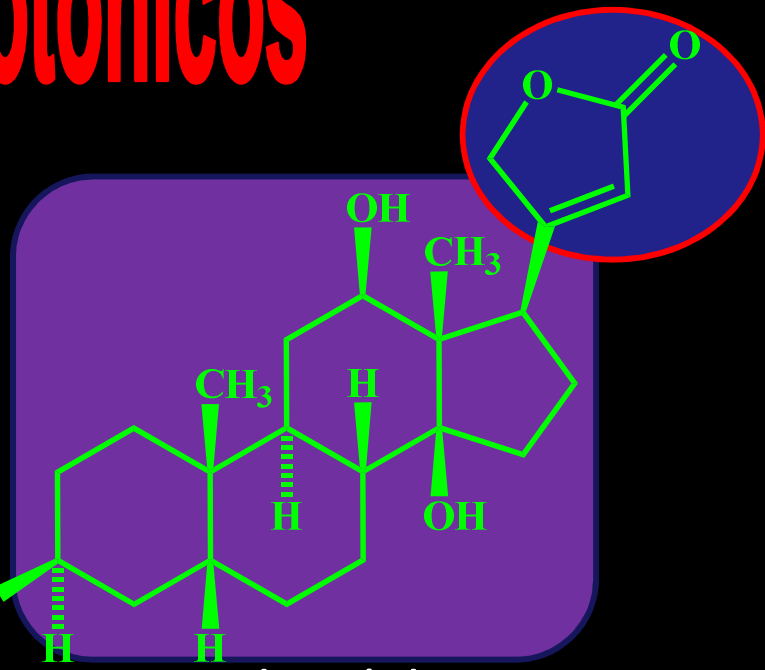
inotrópico

Uso de productos naturales abundantes como materia prima

EJ Barreiro, CAM Fraga, ALP Miranda, "Química Medicinal de Derivados *N*-Acilidrazônicos, Protótipos de Agentes Antiinflamatórios, Analgésicos e Anti-trombóticos", ***Química Nova, 25***, 129 (2002).
http://www.sbq.org.br/publicacoes/quimicanova/qnol/2002/vol25n1/21.pdf

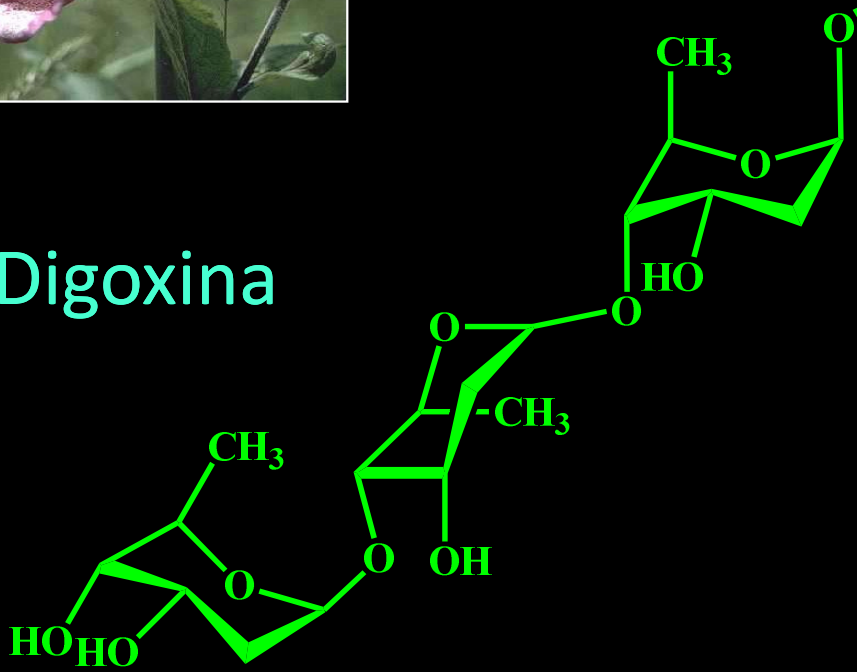
EJ Barreiro, "Estratégia de Simplificação Molecular em Química Medicinal:descoberta de Novo Agente Cardiotônico", *Química Nova*, 25, 1172 (2002).

Glucósidos cardiotónicos



cardenolidos

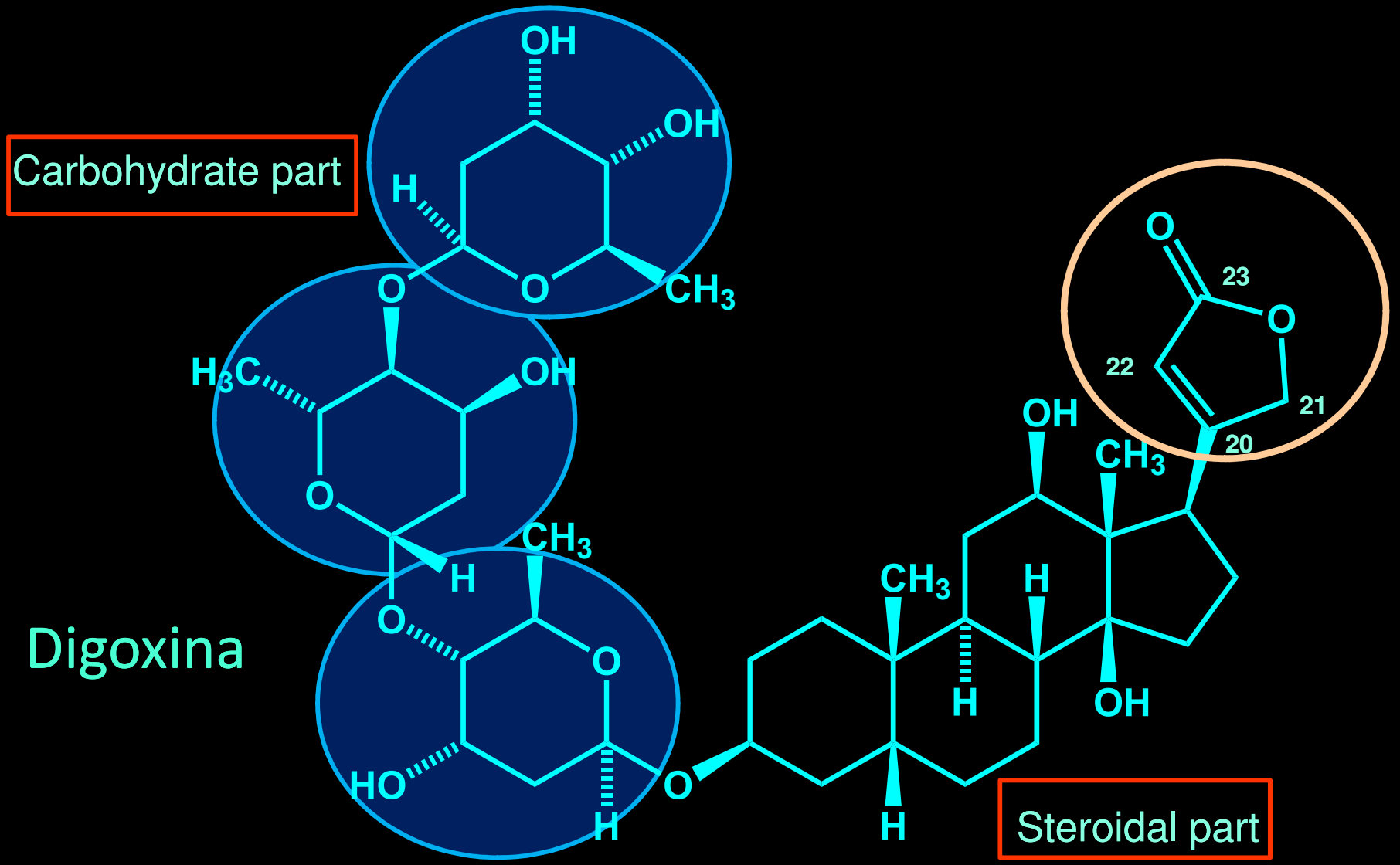
Digoxina



TI = 10

Una serie de nuevos agentes inotrópicos positivos se han desarrollado para el tratamiento de la insuficiencia cardíaca congestiva

Carbohydrate part



Digoxina

Steroidal part

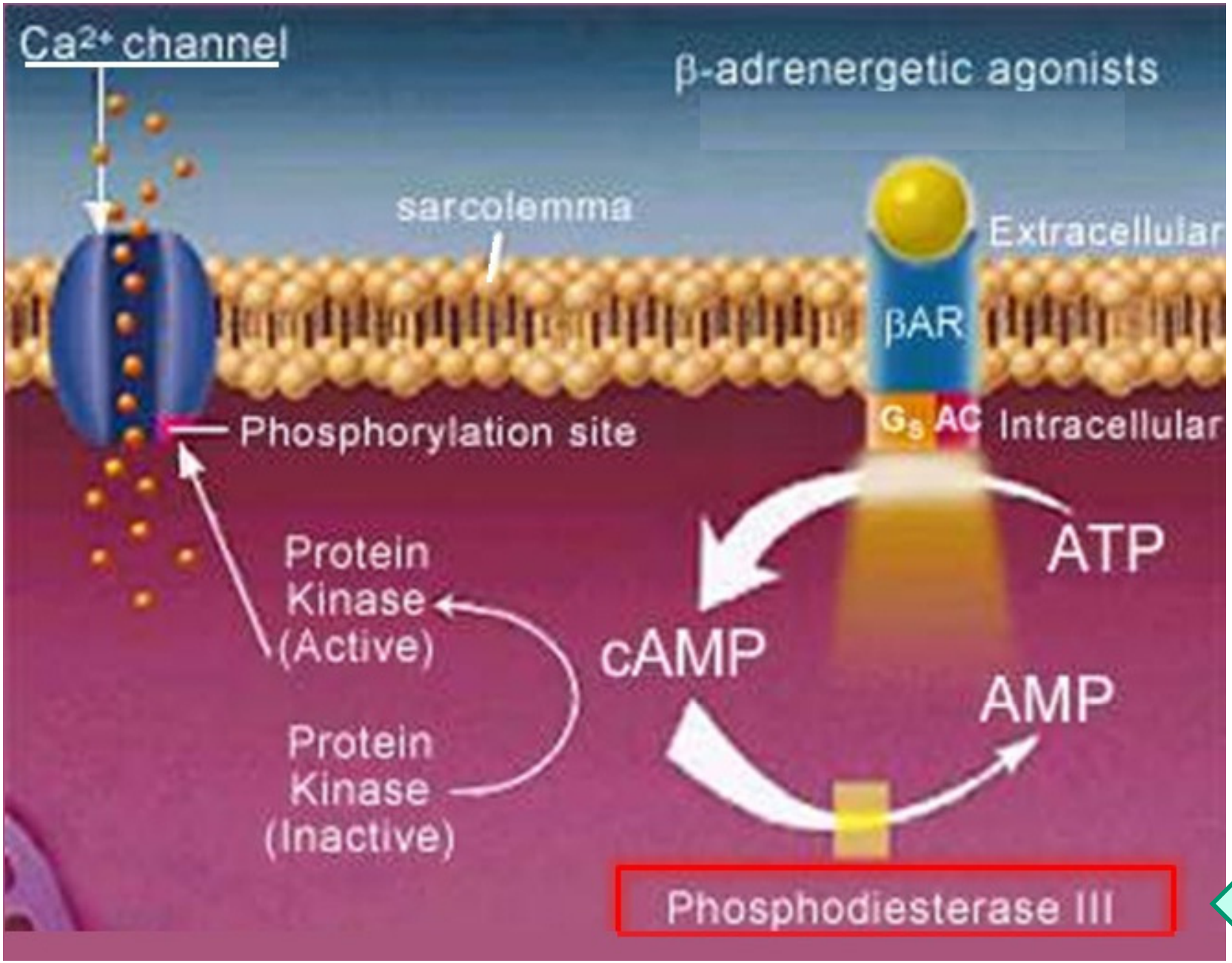
α-subunit of the Na+/K+ ATPase pump in the membranes of heart cells

Digoxin inhibit the hypoxia-inducible factor 1 (HIF-1) in 88% at 0.4 μM[&]

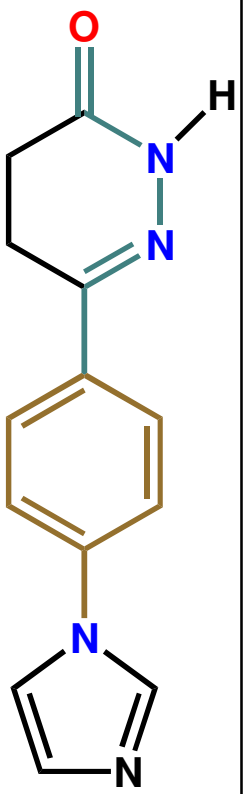
Digoxin inhibit interleukin-17*

[&] H Zhang *et al.*, Digoxin and other cardiac glycosides inhibit HIF-1α synthesis and block tumor growth, PNAS 2008

* JR Huh *et al*, Digoxin and its derivatives suppress TH17 cell differentiation by antagonizing RORγt activity, *Nature* **2011**, *472*, 486



imazodan

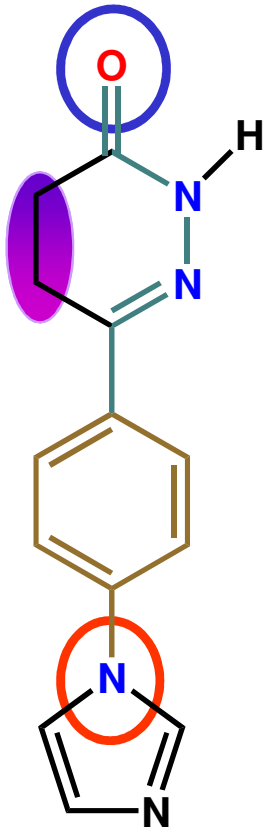


PDE-3 inhibitors enhance the left ventricular contraction acting at Ca++

Fármacos cardioactivos

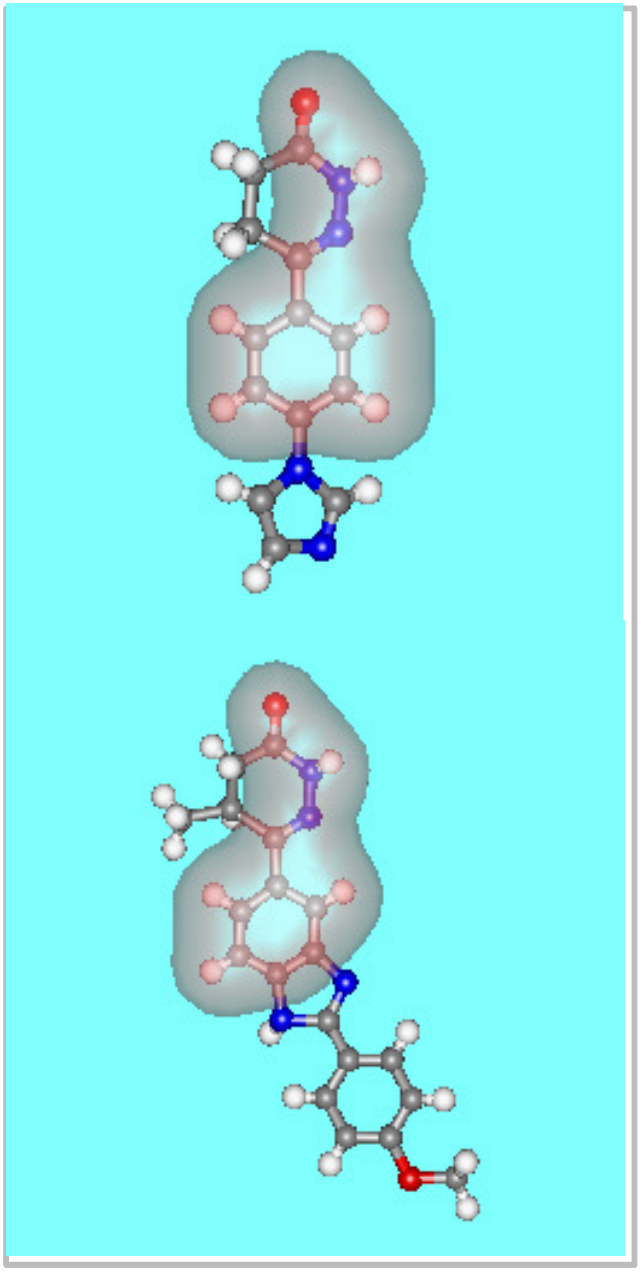
Inibidores de PDE-3 (Ca^{++})

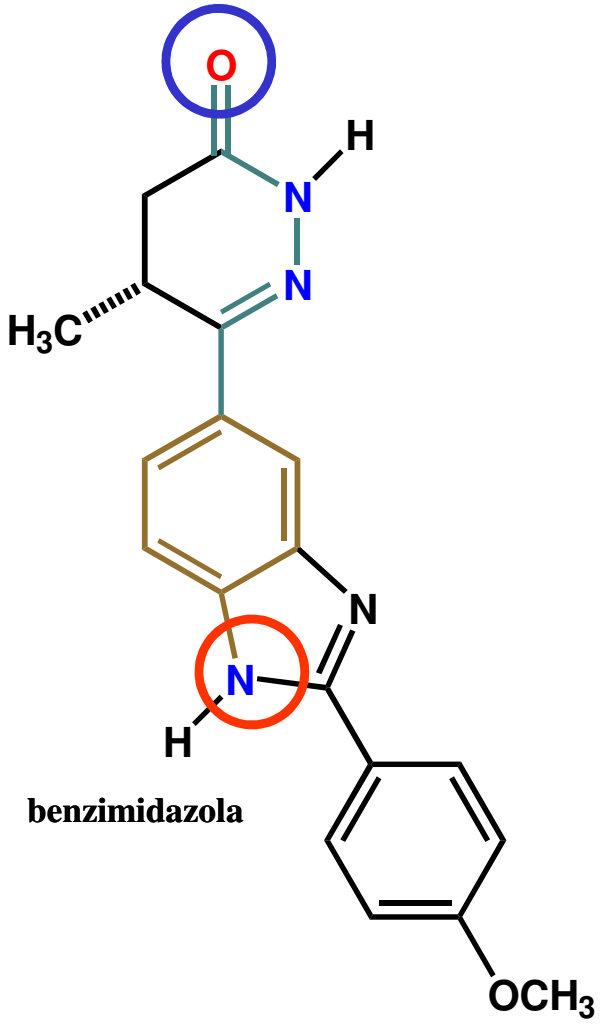
Efecto inotrópico positivo



imazodana

dihydropyridazinone





benzimidazola

pimobendana

5-metil-3(*2H*)-piridazinona

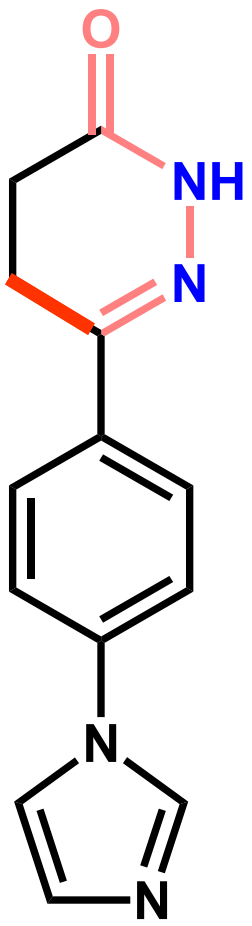
Boehringer Ingelheim

[Uso veterinário]

Diseño estructural

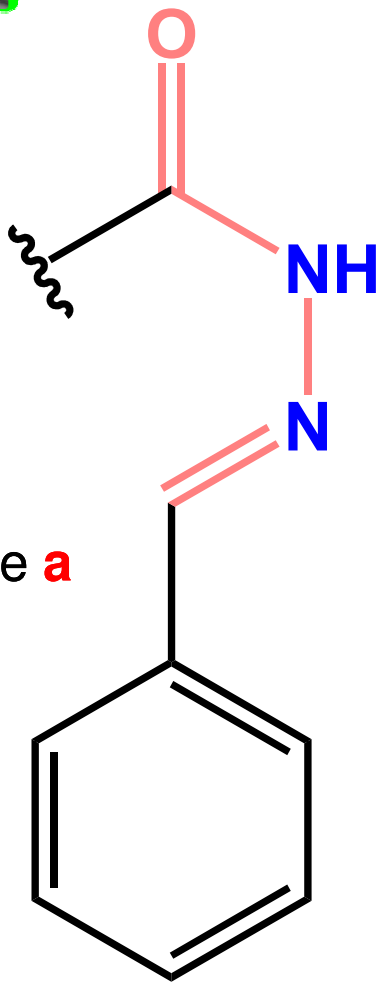
Genesis of LASSBio-294

2H-pyridazinones

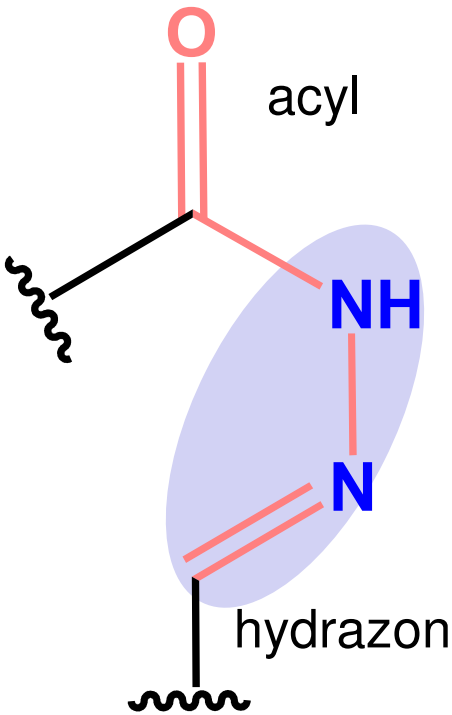


a-bond scisson

ruptura del enlace **a**



zoom



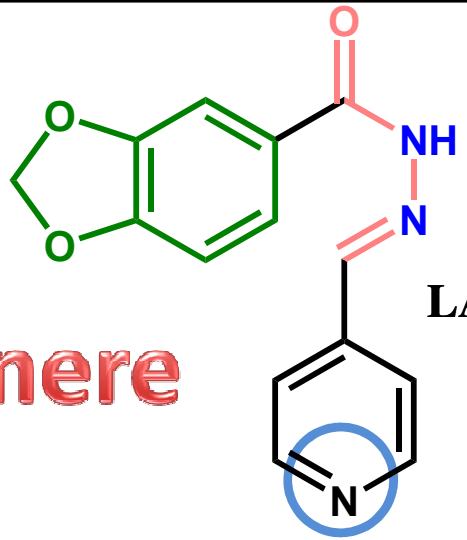
NAH

N-acylhydrazones

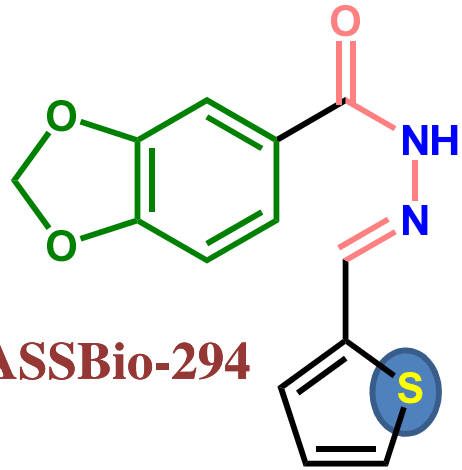
E. J. Barreiro, *et al* "Química Medicinal de Derivados *N*-Acilidrazônicos, Protótipos de Agentes Antiinflamatórios, Analgésicos e Anti-trombóticos", *Química Nova, 25*, 129-148 (2002).

http://www.sbq.org.br/publicacoes/quimicanova/qnol/2002/vol25n1/21.pdf

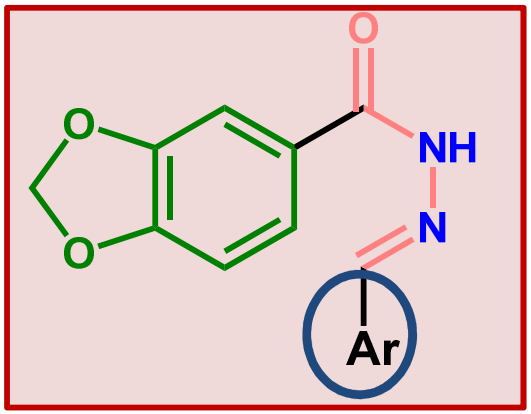
Serie congenere



LASSBio-252

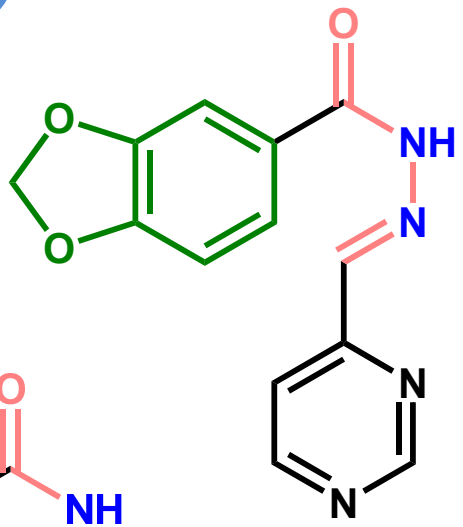


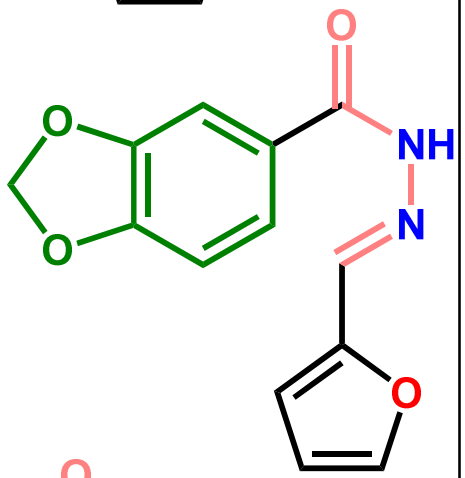
LASSBio-294



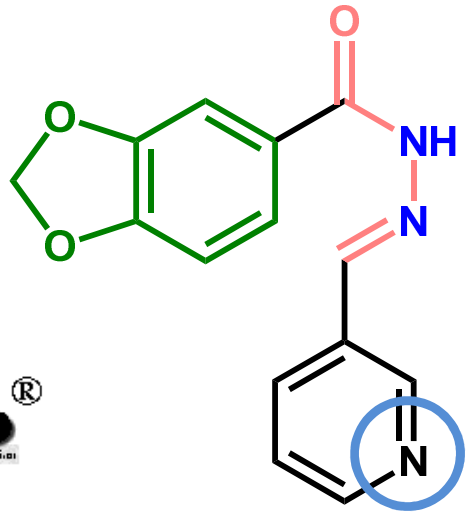
benzodioxola
(safrol)

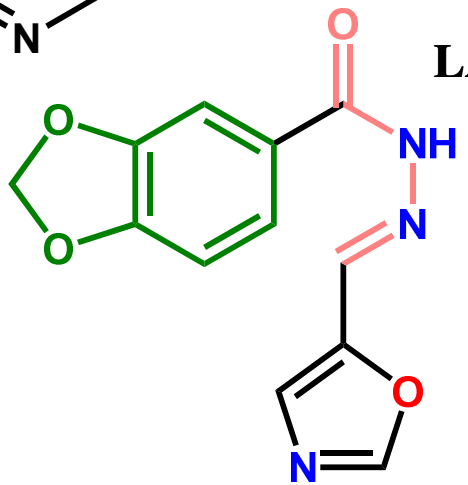
NAH





LASSBio-286

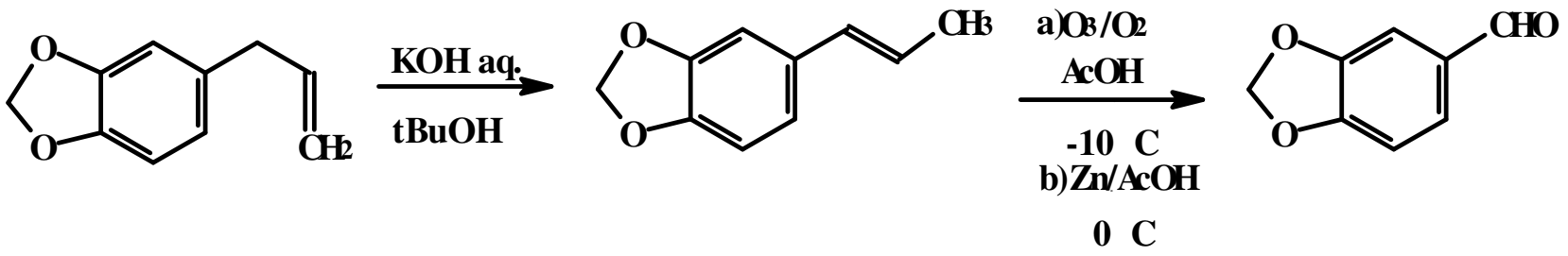




LASSBio®

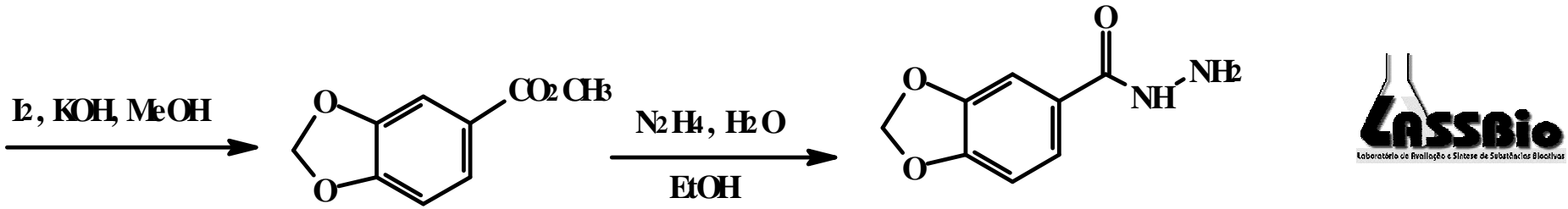
P. C. Lima, L. M. Lima, K. C. M. da Silva, P. H. O. Léda, A. L. P. Miranda, C. A. M. Fraga & E. J. Barreiro, "Synthesis and Non-addictive Analgesic Activity of Novel *N*-acylarylhydrazones and Isosters, Derived from Natural Safrole", ***Eur. J. Med. Chem.*, *35***, 187 (2000).

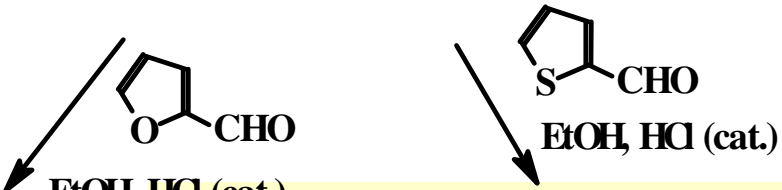
Síntesis do LASSBio-294

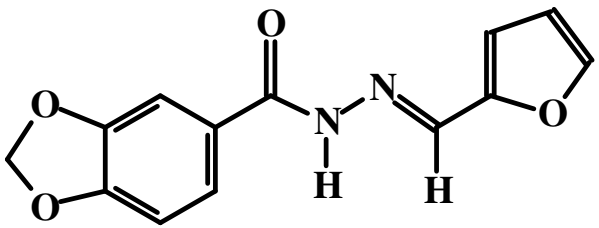


safrol

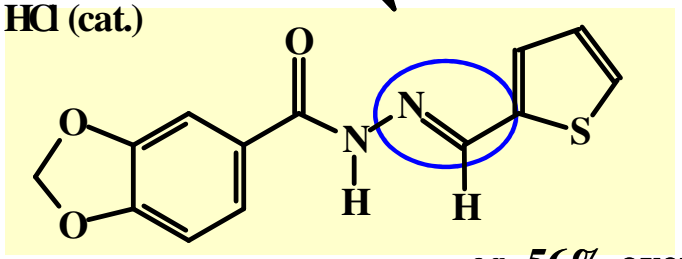
M.E.F. Lima & E. J. Barreiro, *J. Pharm. Sci.* 1992, *81*, 1219







LASSBio-286



LASSBio-294

***ca.* 56% overall yield**
2,0 M scale

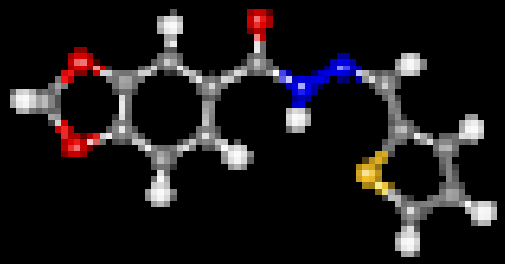
P. C. Lima, L. M. Lima, K. C. M. da Silva, P. H. O. Léda, A. L. P. Miranda, C. A. M. Fraga & E. J. Barreiro, "Synthesis and Non-addictive Analgesic Activity of Novel *N*-acylarylhydrazones and Isosters, Derived from Natural Safrole", ***Eur. J. Med. Chem.*, *35***, 187 (2000).

Propriedad estructurales

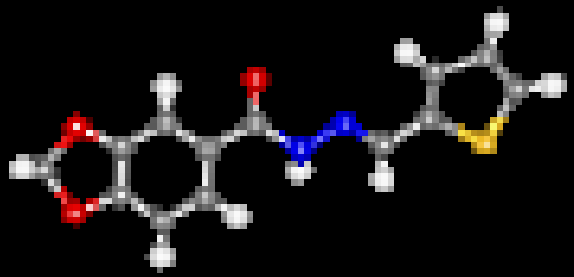
NMR ^{1}H/ ^{13}C

MS

raios-X



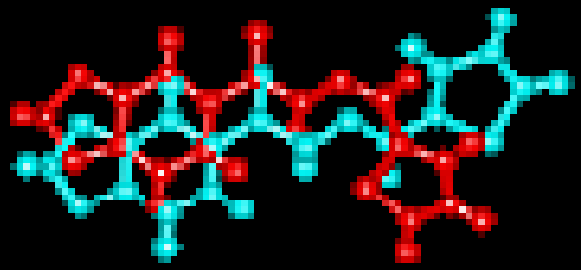
NAH



Z-isomêro

E-isomêro

LASSBio-294



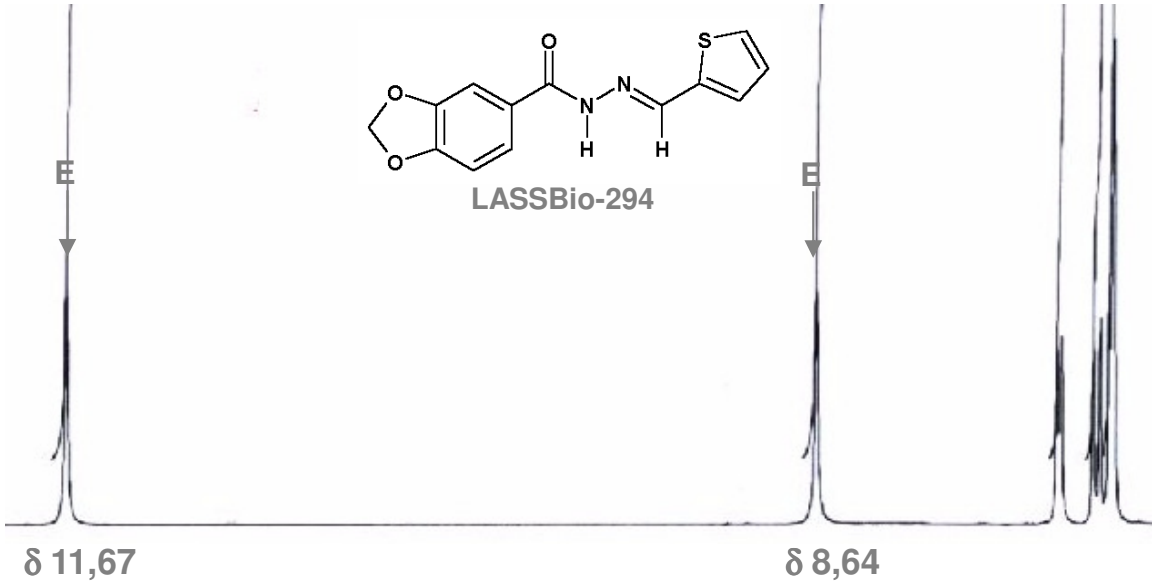
M. R. L. Santos, M. G. de Carvalho, R. Bráz-Filho, E. J. Barreiro, "^{1}H and ^{13}C of New Bioactive Isochromanylactylarylhydrazone Derivatives", ***Magn. Reson. Chem.*** **1998, 36,** 533.

L. F. C. C. Leite, E. J. Barreiro, M. N. Ramos, *et al.*, "Electron Impact Mass Spectrometry of Some 3-[3-(4-aryl)-1,2,4-oxadiazole-5-yl] acyl arylaldehyde Hydrazone derivatives", ***Spectroscopy*** 2000, **14**, 115.

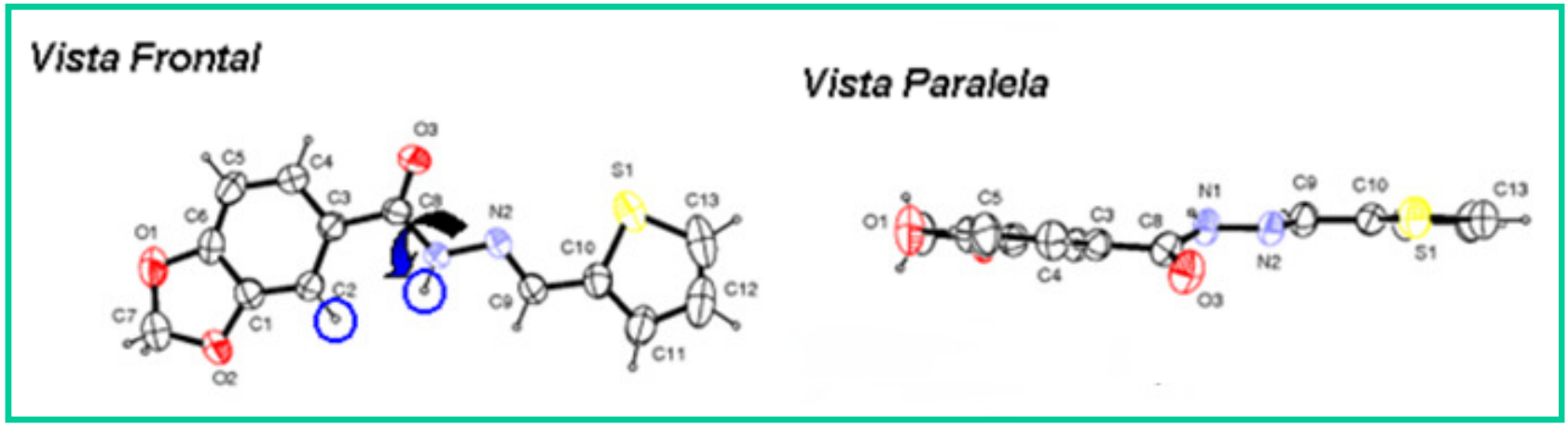
L. Pol-Fachin, C. A. M. Fraga, E. J. Barreiro, H. Verli, Characterization of the conformational ensemble from bioactive *N*-acylhydrazone derivatives, ***J. Molecular. Graphics and Modelling,*** 2010, **8**, 446

Análisis de la configuración relativa del enlace C=N (espectroscopia RNM^{1}H & Difracción de rayos X)

Composto	X	R	δ ^{1}H
LASSBio-129	O	H	8,32
LASSBio-294	S	H	8,64
LASSBio-787	S	CH_3	8,58
LASSBio-789	S	Br	8,55
LASSBio-790	S	NO_2	8,81 / 8,09
LASSBio-1028	NH	H	8,28



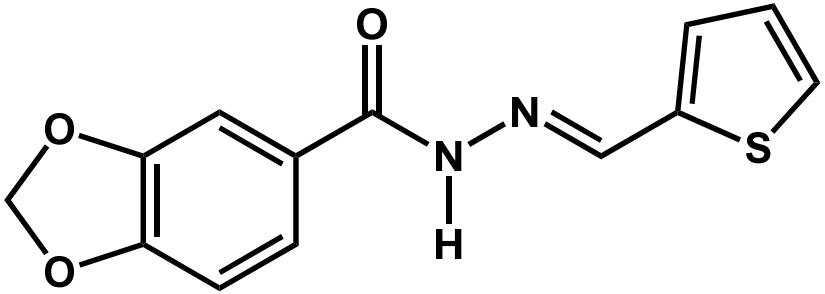
Karabatsos, G.J., *et al.* (1964) *J. Am. Chem. Soc.,* 86, 3351; Karabatsos, G.J., *et al.* (1967) *Tetrahedron*, 24, 3907; ibid (1967) *Tetrahedron*, 24, 3361.



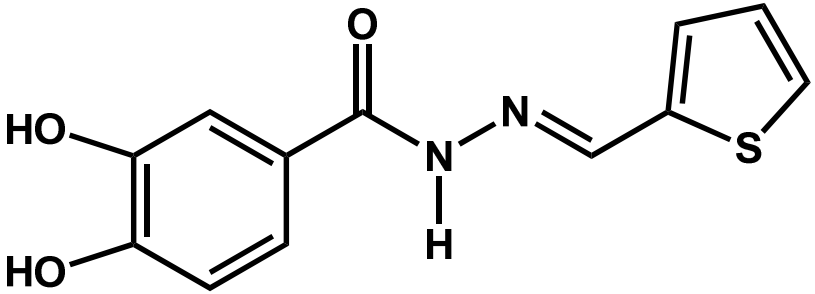
Kummerle, A. E.; Raimundo, J. M.; Leal, C. M.; Silva, G. S.; Balliano, T. A.; Pereira, M. A.; DeSimone, C. A.; Sudo, R. T.; Zapata-Sudo, G.; Fraga, C. A. M.; Barreiro, E. J. , *Eur. J. Med. Chem.* 2009, 44, 4004-4009

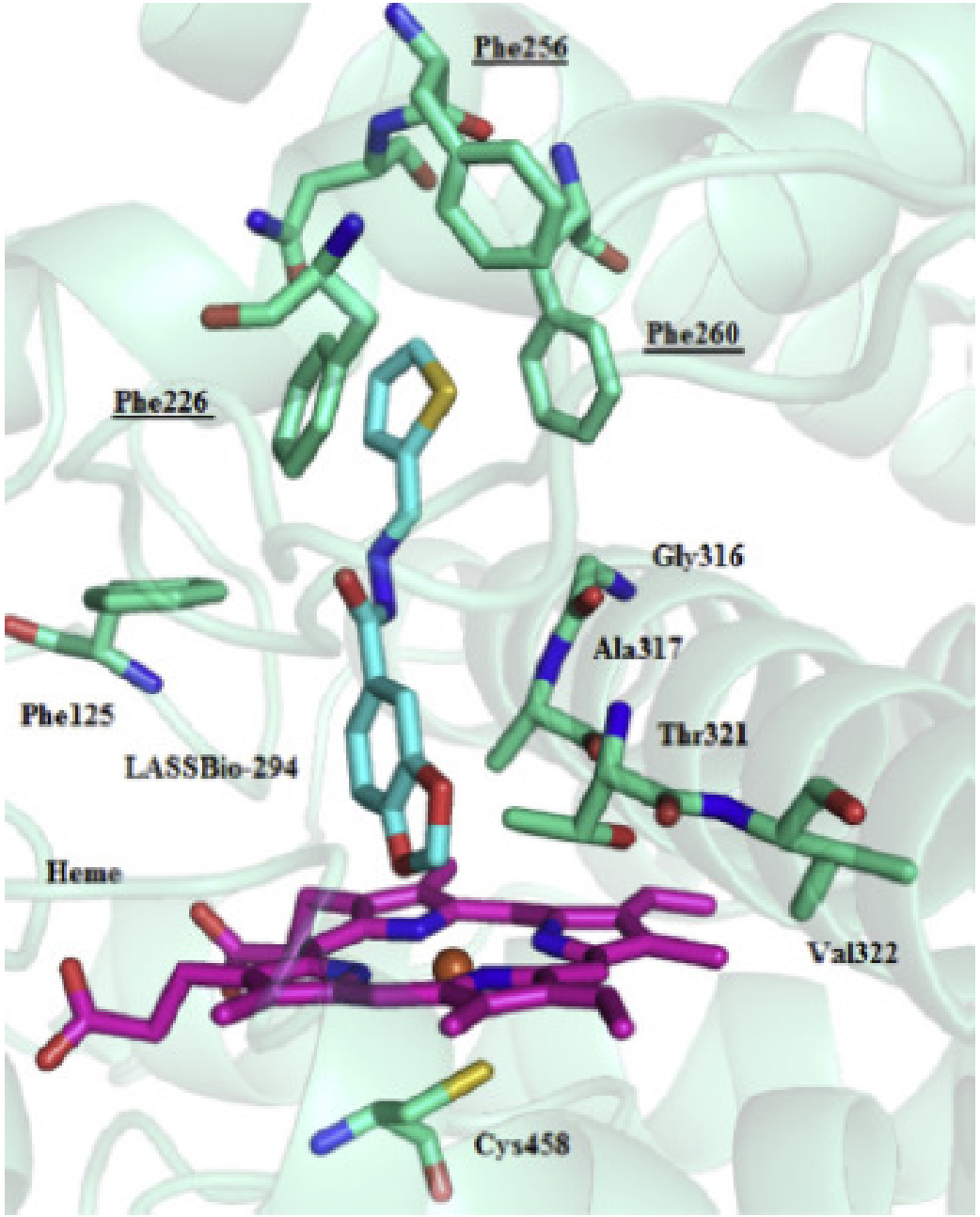
Estudios de el metabolismo

LASSBio-294



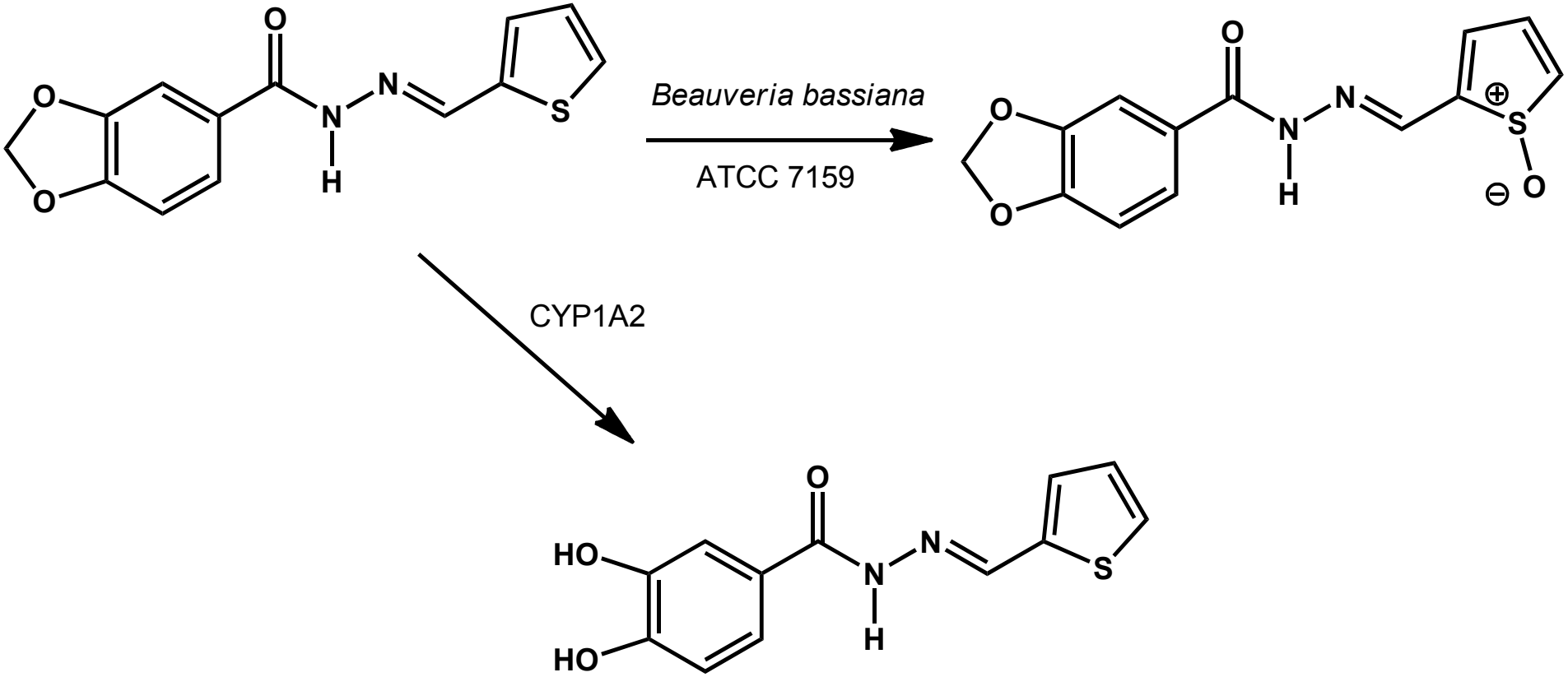
CYP1A2





A. G. M. Fraga *et al.*, "CYP1A2-mediated biotransformation of cardioactive 2-thienylidene-3,4-methylenedioxybenzoylhydrazine (LASSBio-294) by rat liver microsomes and human recombinant CYP enzymes", *Eur J. Med Chem.*, **46**, 349 (2011);

Estudios de el metabolismo en hongos



E. O. Carneiro, C. H. Andrade, R. C. Braga, *et al*., Structure-based prediction and biosynthesis of the major mammalian metabolite of the cardioactive prototype LASSBio-294, *Bioorg. Med. Chem. Lett.*, **20**, 3734 (2010).
R. C. Braga *et al*., "Determination of cardiactive prototype LASSBio-294 and its metabolites in dog plasma by LC-MS/MS: application for a pharmacokinetic studies", *J. Pharm. Biomed. Analysis*, **55**, 1024 (2011);

química nova

Quim. Nova, Vol. 25, No. 6B, 1172-1180, 2002

Divulgação

ESTRATÉGIA DE SIMPLIFICAÇÃO MOLECULAR NO PLANEJAMENTO RACIONAL DE FÁRMACOS: A DESCOBERTA DE NOVO AGENTE CARDIOATIVO

Eliezer J. Barreiro*
Departamento de Fármacos, Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Cidade Universitária, Ilha do Fundão, CP 68006, 21944-190 Rio de Janeiro - RJ

Recebido em 24/1/02; aceito em 17/4/02

STRATEGY OF MOLECULAR SIMPLIFICATION IN RATIONAL DRUG DESIGN: THE DISCOVERY OF A NEW CARDIOACTIVE AGENT. In this article are described examples of the successful use of molecular simplification strategy in the discovery of new drugs from bioactive natural products and synthetic compounds. The discovery of a new cardiotonic derivative (37, 2-thienylidene-3,4-methylenedioxybenzoylhydrazine; LASSBio-294), efficiently synthesized from Brazilian natural product and structurally designed by molecular simplification of active pyridazinone compounds reported in the literature, is described. A brief description of the pharmacological profile of this new cardiotonic lead-compound, belonging to the *N*-acylhydrazone (NAH) class, is also reported herein.

Keywords: new cardiotonic derivative; bioactive *N*-acylhydrazone compound; LASSBio-294.

Los estudios de lo mecanismo de acción

Cerep

Le Bois l'Evêque
B.P.1
86 600 Celle l'Evescault
France

STUDY NUMBER 14635
FINAL REPORT

***In Vitro* Pharmacology:**

Human Phosphodiesterase Enzyme Assays

- Study of LASSBio-294, LASSBio-785

and LASSBio-788 -

CEREP (FR)

Diversity Profile

101

Alvos Moleculares

Los estudios de lo mecanismo de acción

1929 - Szent-Györgyi

Adenosina

receptores de adenosina

G-PCR

A_1 A_{2A} A_{2B} A_3

< cAMP

> cAMP

alta baixa afinidade

< cAMP

Agonistas & antagonistas

inflamação (asma, COPD)
isquemia
artrite (doença de Crohn
sepsis

sistema cardiovascular
sistema nervoso central

epilepsia, dor,
neuroproteção
vasodilatação
isquemia cerebral (DA)

neutrófilos, linfócitos, macrofágos

produção de citocinas (TNF-alfa)

IFN-alfa, IL-12, IL-6, IL-9, IL-10
T_H1, T_H2

NKTC
NO
SO

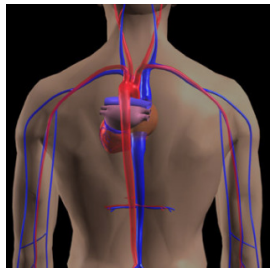
Ligando A_{2A}

IC_{50} = 9,5 µM

LASSBio-294

• *tiene una potente actividad inotrópica positiva en el músculo cardíaco, con un máximo de dos veces la fuerza de contracción de los haces musculares aislados, sin la inducción de arritmias*

• *tiene un potente efecto vasodilatador, dependiente de la dosis con IC_{50} de 74 µm en la aorta aislada de cobaya mediada a través de la guanilato ciclasa*



Tiene um mecanismo farmacológico nuevo , dual y es activo p.o.

La série congenere estudada por la optimización apresentou perfil de actividad distinto

• *bioensayos de toxicidad aguda y subcrónica no mostró ninguna reacción a la toxicidad aguda hasta 1000 µM/kg.*

Gonzalez-Serratos, H.; Chang, R.; Pereira, E. F. R.; Castro, N. G.; Aracava, Y.; Melo, P. A.; Lima, P. C.; Fraga, C. A. M.; Barreiro, E. J.; Albuquerque, E. X. *J. Pharmacol. Exp. Ther*. 299, 558-566v (**2001**); Sudo, R.T. *et al*. Brit. J. Pharm., 134, 603 (**2001**); Barreiro, E.J., Quim. Nova, 25, 129 (**2002**); Silva, C.L.M. *et al. Brit. J. Pharm*., 135, 293 (**2002**); F. C. F. Brito, A. E. Kummerle, C. Lugnier, *et al.* Novel thienylacylhydrazone derivatives inhibit platelet aggregation through cyclic nucleotides modulation and thromboxane A_2 synthesis inhibition, *Eur. J. Pharmacol*., **638**, 5 **(2010)**

Patent (USPTO) 7.091.238 (15/08/2006) ➡ *Cardiotônicos vasoativos*

Patente obtida

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,328	Aug. 15, 2006	7,091,238	22100-178943	9691

26694 7590

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

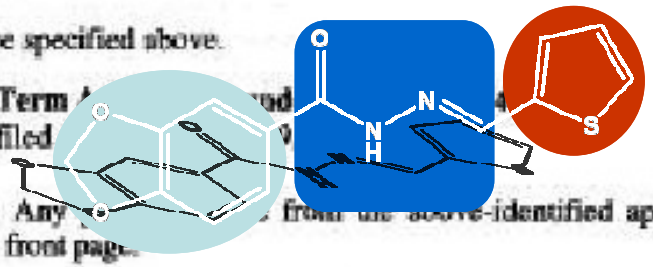
Thienylhydrazone with Digitalis-like properties (positive inotropic effects)

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term A[illegible]od
(application filed [illegible]

LASSBio-294



The Patent Term Adjustment is 109 day(s). Any [illegible] 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.

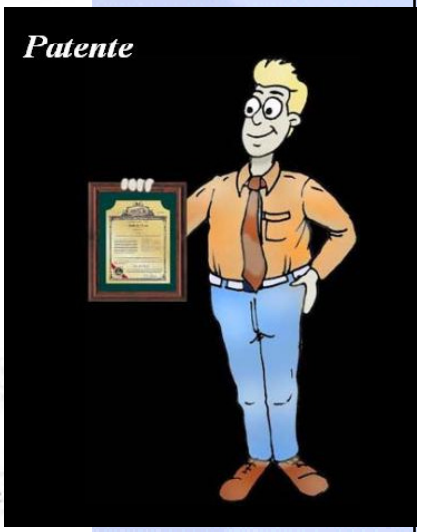
Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

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;
Ana Luisa Palhares De Miranda, Petropolis, BRAZIL;

RECEIVED
JUL 31 2006
VENABLE IP DOCKETING DEPARTMENT

PTOL-85 (Rev. 12/04)



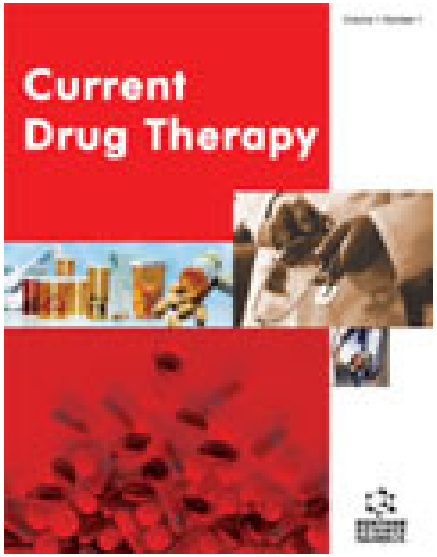
Current Drug Therapy, 2008, *3*, 000-000

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

Eliezer J. Barreiro and Carlos Alberto Manssour Fraga

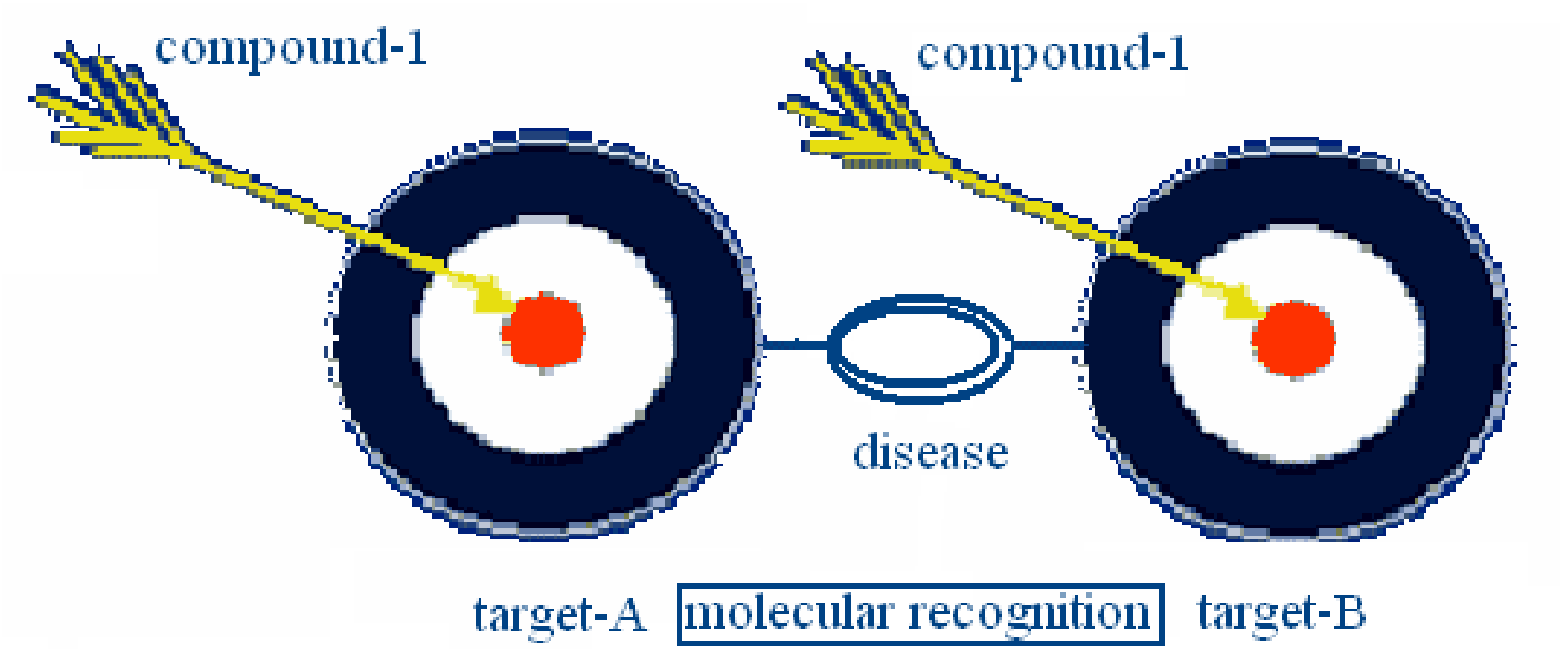
Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, P.O. Box 68023, 21944-971, Rio de Janeiro, RJ, Brazil.

Química Medicinal



El tratamiento de una fisiopatología multifactorial con una droga *mono-diana* sera siempre paliativo, especialmente en las enfermedades crónico-degenerativas que requieren medicamentos eficaces con drogas actuando sobre múltiples dianas, *i.e.* dobles, mixtos, múltiples y simbiotico.

The multiple-target lead design

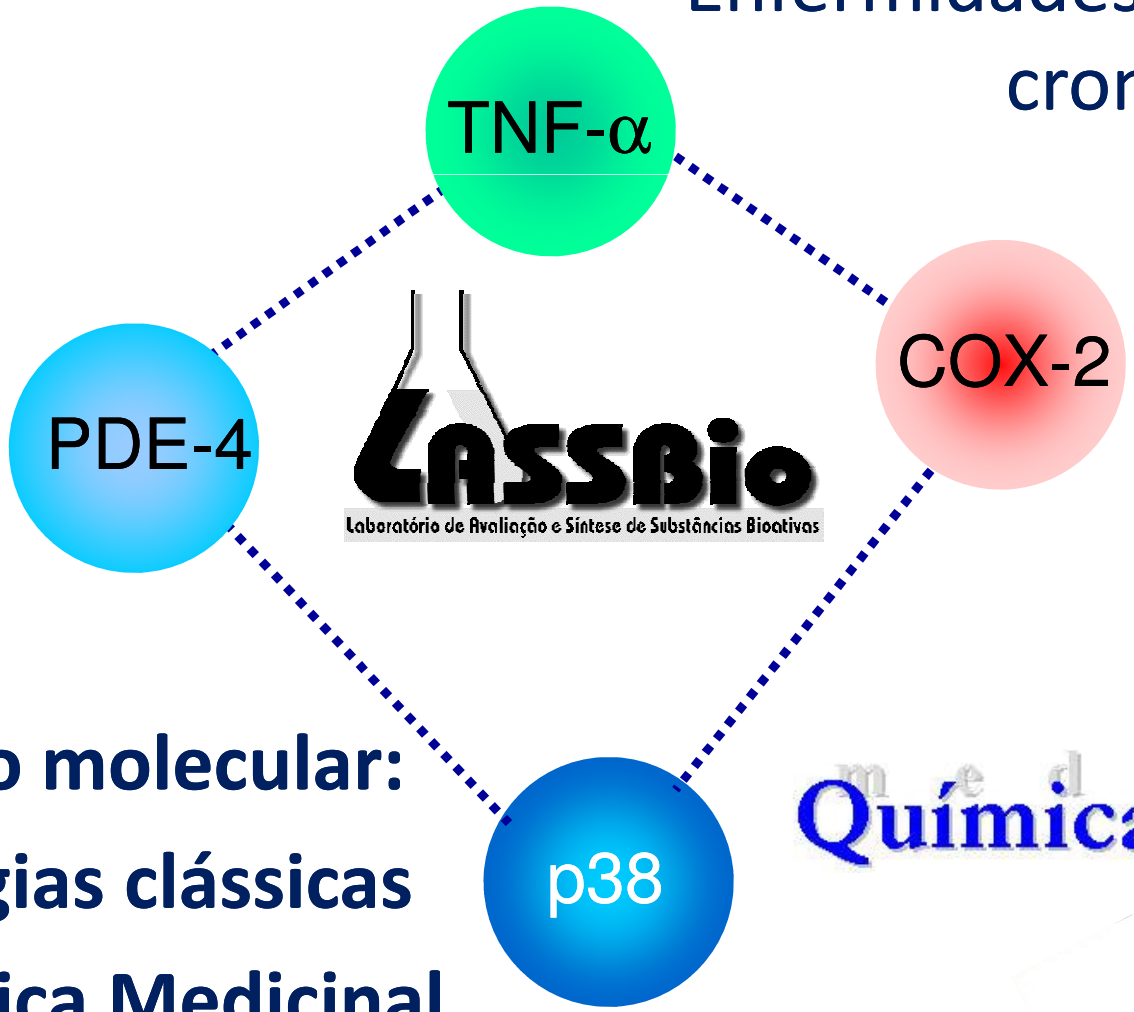


La química medicinal del siglo 21

The named symbiotic approach is a denomination that we adopt for a compound with multiple-target recognition pattern, where these receptors are connected to a same complex disease pathology but belonging to different biochemical windows.

Nuevos candidatos a fármacos simbióticos

Enfermidades inflamatorias cronicas

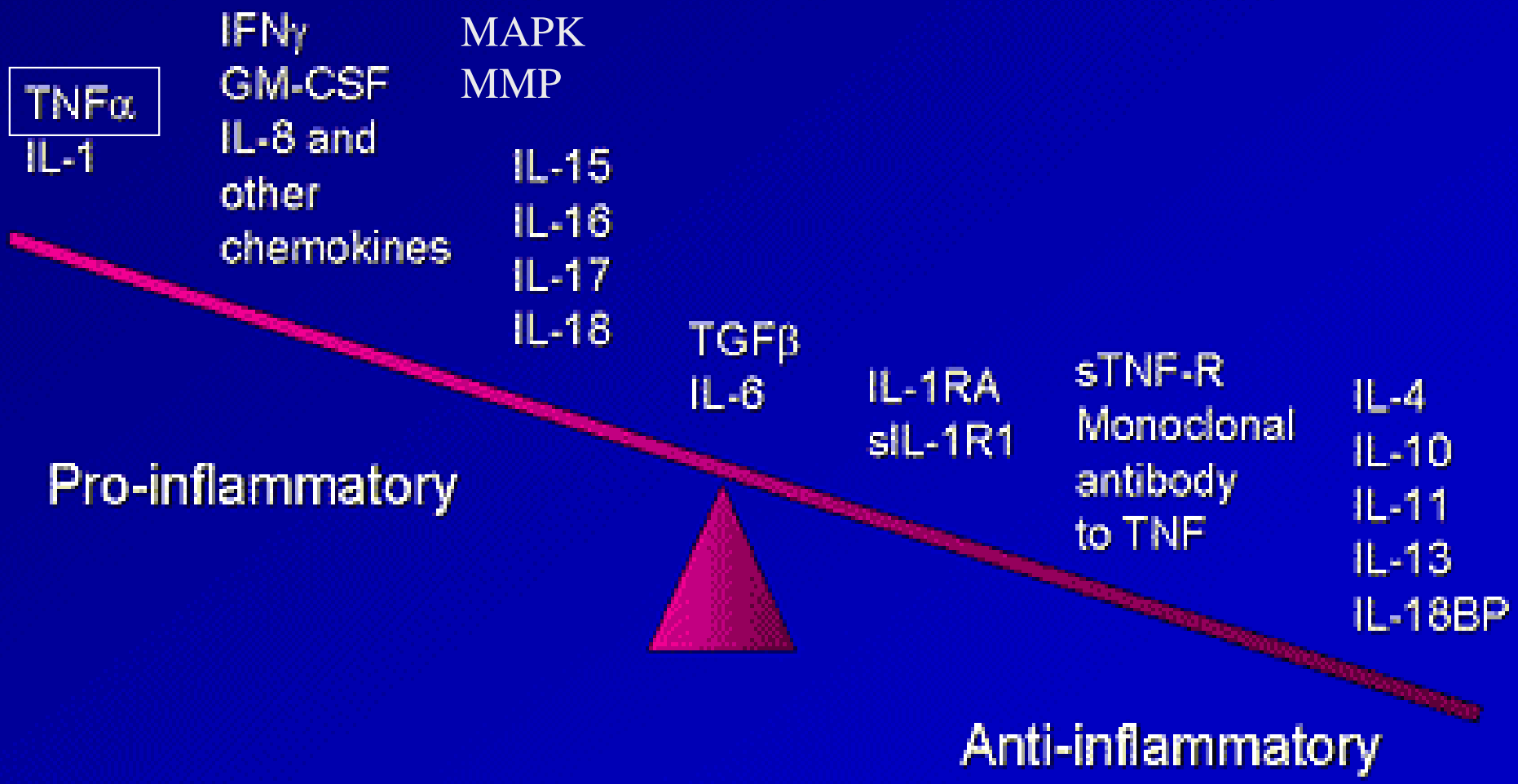


Desenho molecular: estratégias clássicas da Química Medicinal

Química Medicinal

LASSBio®

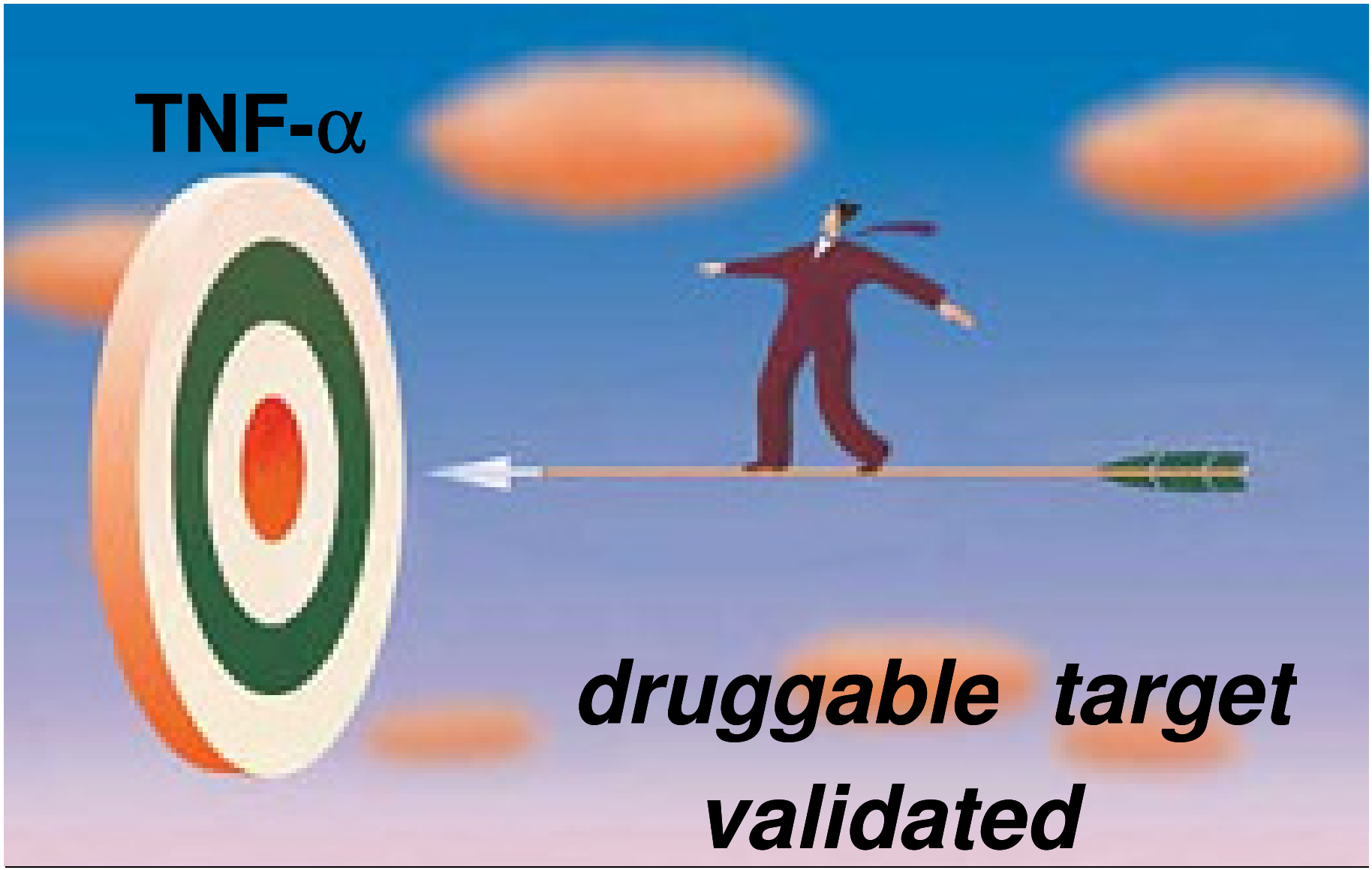
Role of Cytokines and Cytokine Inhibitors in Chronic Inflammation



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

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

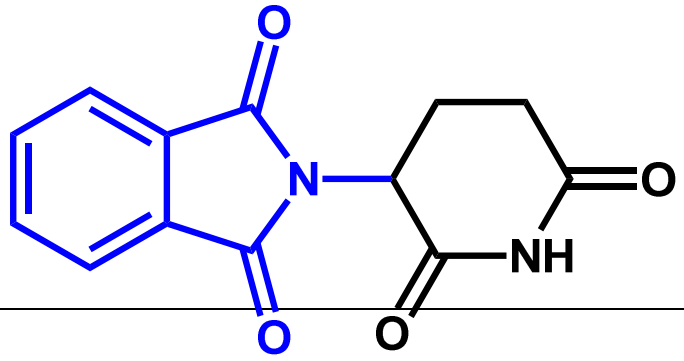
Anti-TNFα Therapies

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

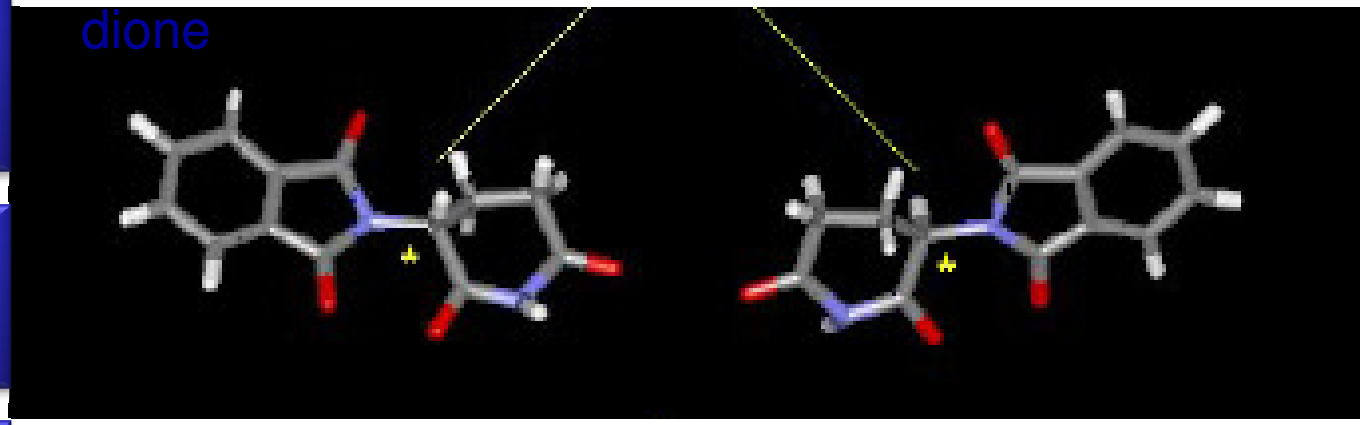
Drug	Status	Biological Form
Etanercept	approved	soluble TNFR2 coupled to Fc portion of IgG
Infliximab	approved	chimeric anti-human TNF antibodie
Adalimumab	approved	anti-human TNF antibodie
ISIS 104838	clinical	TNF anti-sense
Onercept	clinical	soluble p55 TNFR
Humicade	clinical	anti-TNF humanised IgG4

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

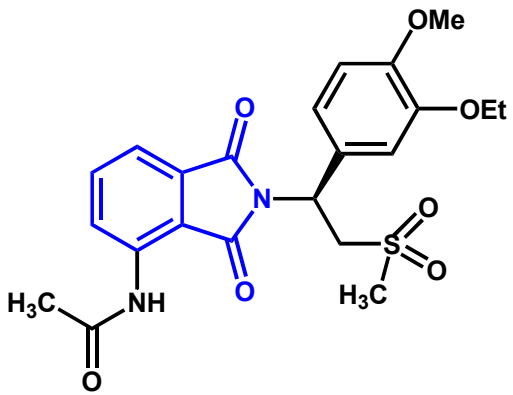


Thalidomide

Anti-TNF

TNF-α IC_{50} = 200 μM

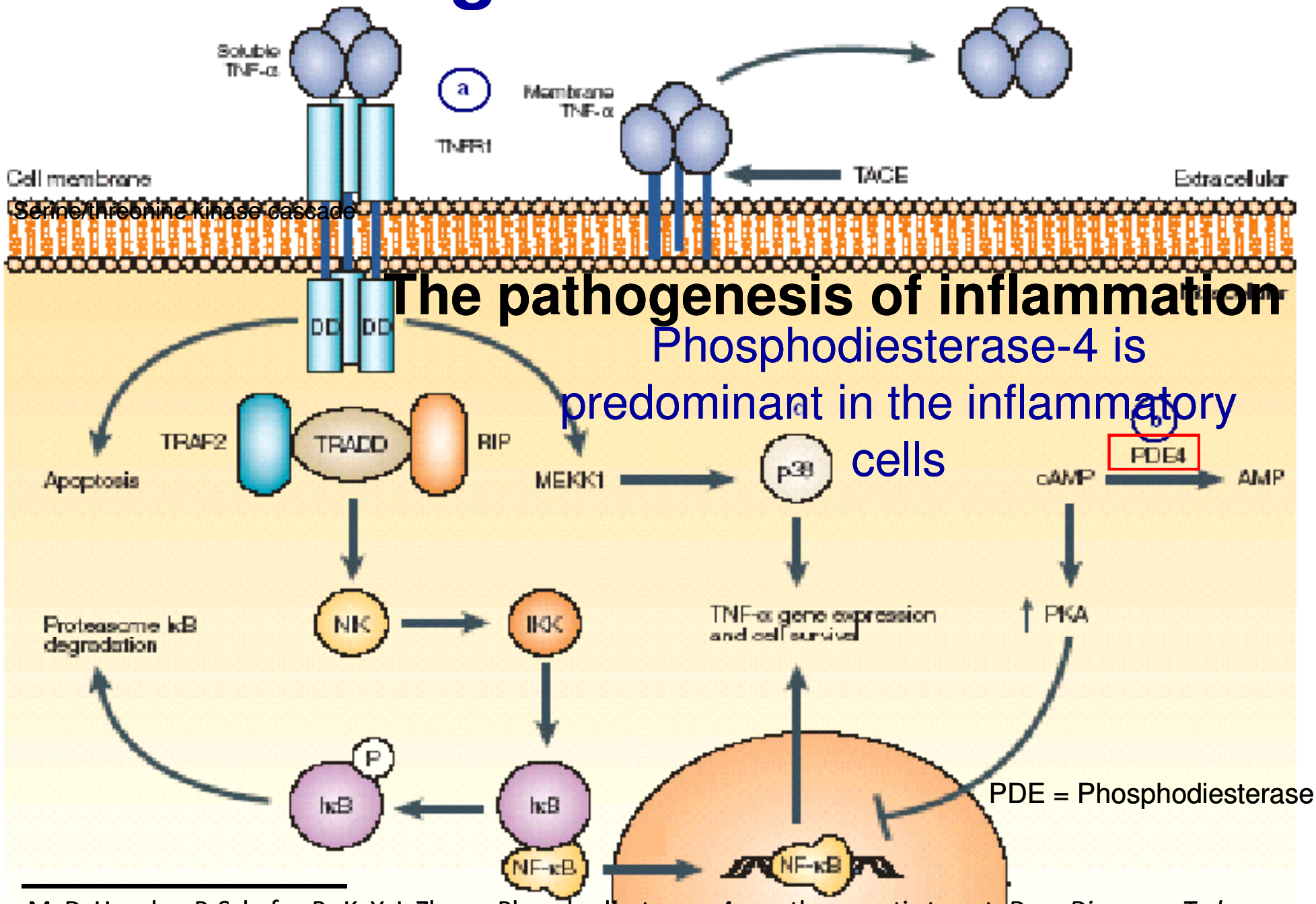
Wilhelm Kunz, 1953
Herbert Keller, 1953
CNS, 1957
Frances Kelsey, 1961
Gilla Kaplan, 1991 (TNF-α)
Elisabeth Sampaio,1997



Apremilast, Phase II, Celgene (2009)

H-W Man *et al.*, *J. Med. Chem.* **2009,** *52,* 1522

Second Target Election:PDE-4



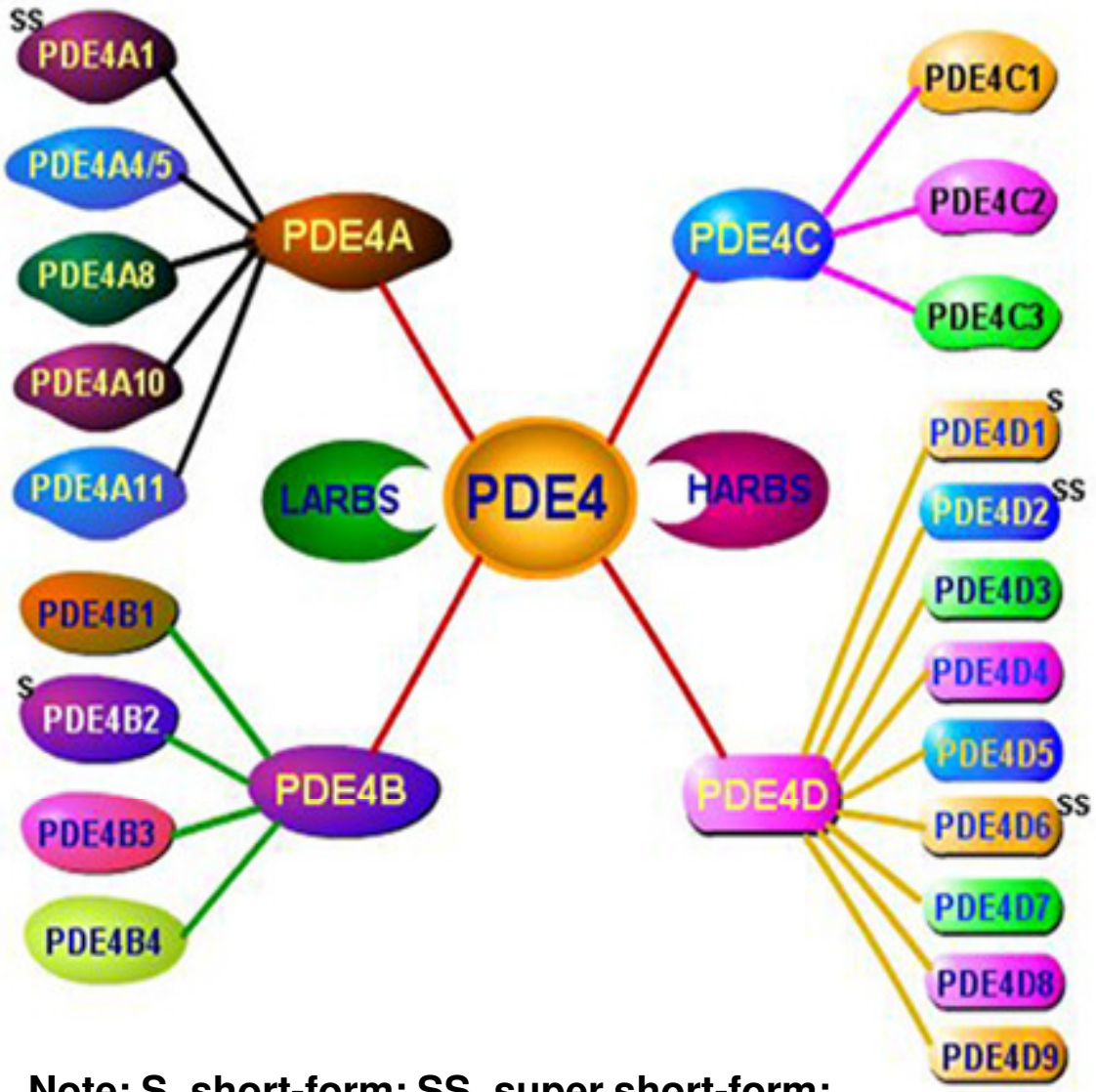
The pathogenesis of inflammation

Phosphodiesterase-4 is predominant in the inflammatory cells

PDE = Phosphodiesterase

M. D. Houslay, P. Schafer, P.; K. Y. J. Zhang, Phosphodiesterase-4 as a therapeutic target, *Drug Discovery Today* **2005**, *10,* 1503; B. J. Lipworth, Phosphodiesterase-4 inhibitors for asthma and chronic obstructive pulmonary disease, *Lancet* **2005**, *365*, 167

PDE4 subtypes and splice variants

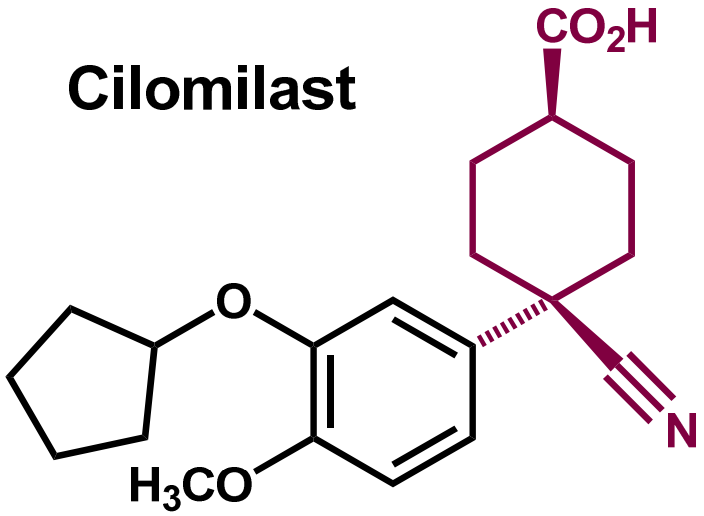


Note: S, short-form; SS, super short-form; no labels, long-form; LARBS, low-affinity rolipram binding state; HARBS, high-affinity rolipram binding state.

The phosphodiesterase 4 (PDE4) is the most important PDE family in the control of intra-cellular cAMP. PDE4 is encoded by four separate genes (PDE4A, 4B, 4C, and 4D). The PDE4 subtypes are highly distributed in inflammatory responses.

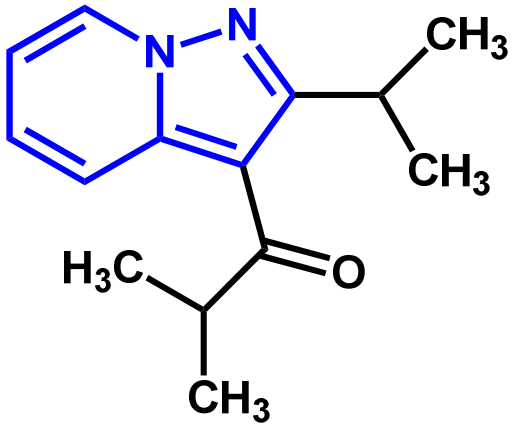
CJ Schmidt, Phosphodiesterase inhibitors as potencial cognition enhancing agents, *Curr. Topics Med. Chem.* **2010**, *10*, 222

Cilomilast



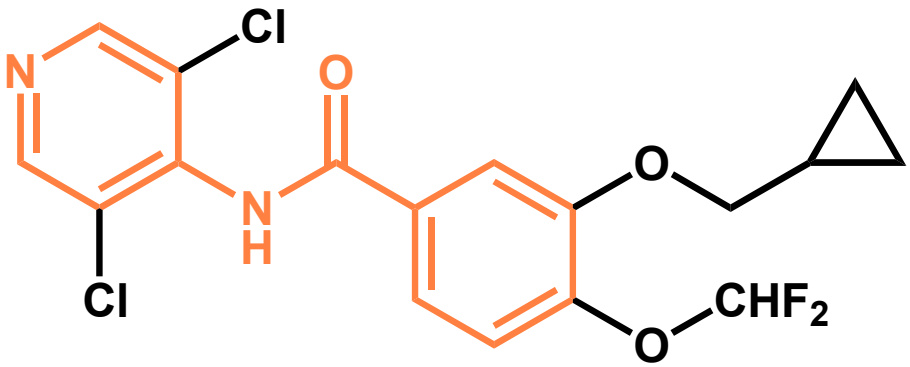
4-cyano-cyclohexyl carboxylic acid

Ibudilast



pyrazolo[1,5-*a*]pyridine

Ruflomilast

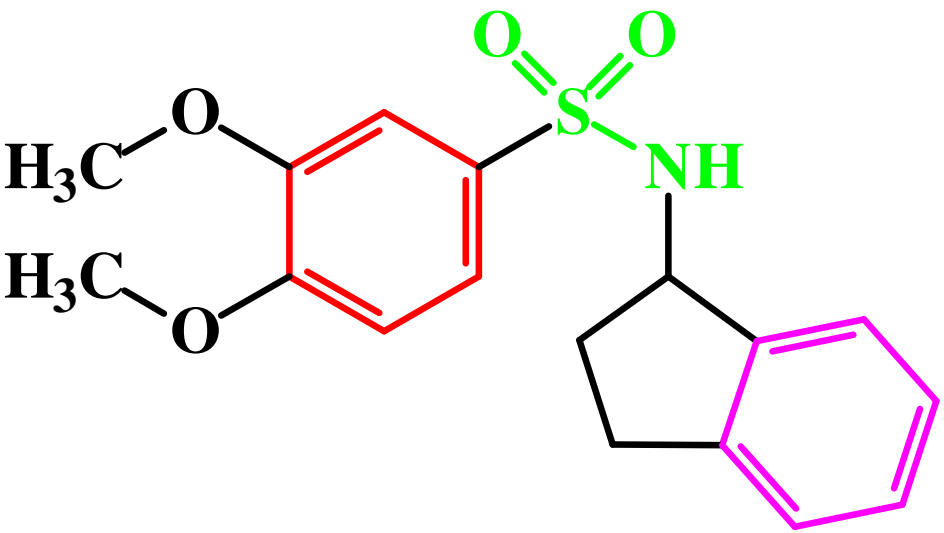


pyridine-benzamide

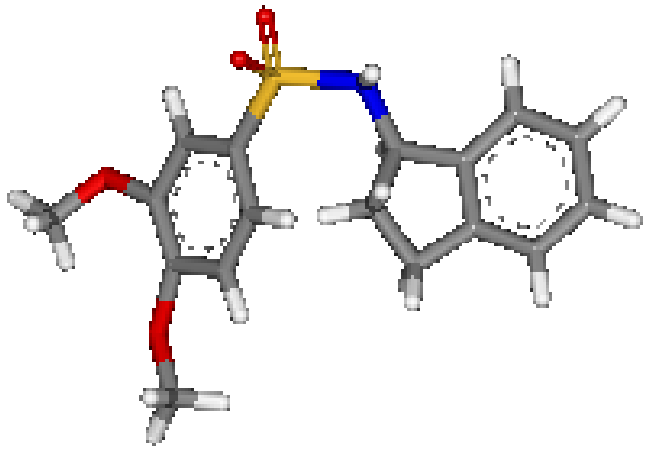
Recent advances on phosphodiesterase 4 inhibitors for the treatment of asthma and chronic obstructive pulmonary disease

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

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



Arylsulfonamide



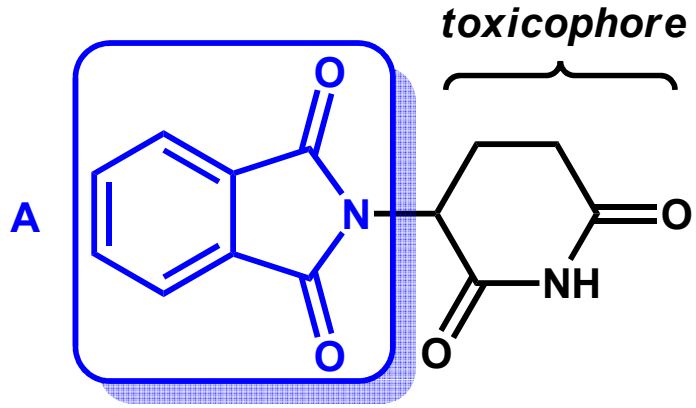
PDE-4i IC_{50} = 4.3 μM

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.

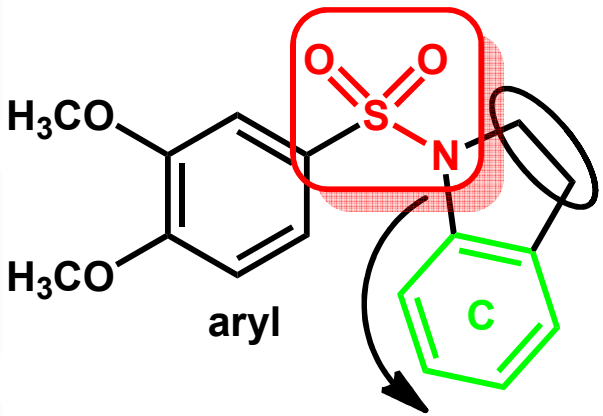
* Chiroscience Ltd, Cambridge Science Park, Cambridge, UK

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

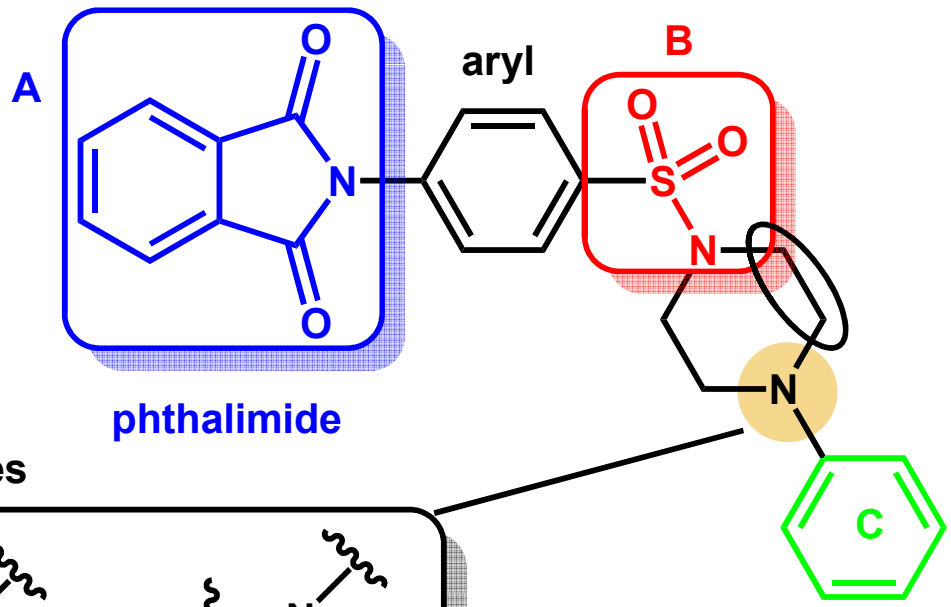


molecular hybridization

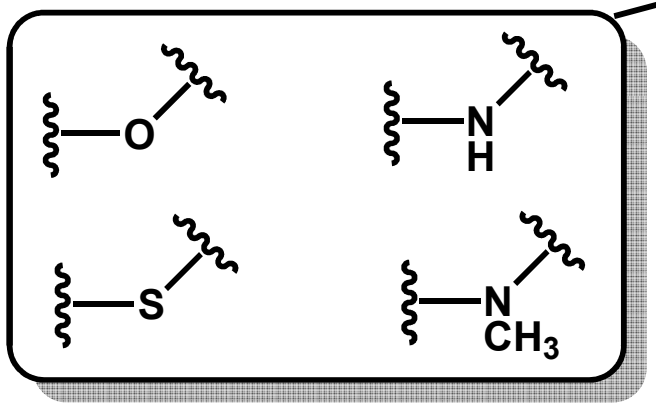
B sulfonamide



Montana *et al*., 1998



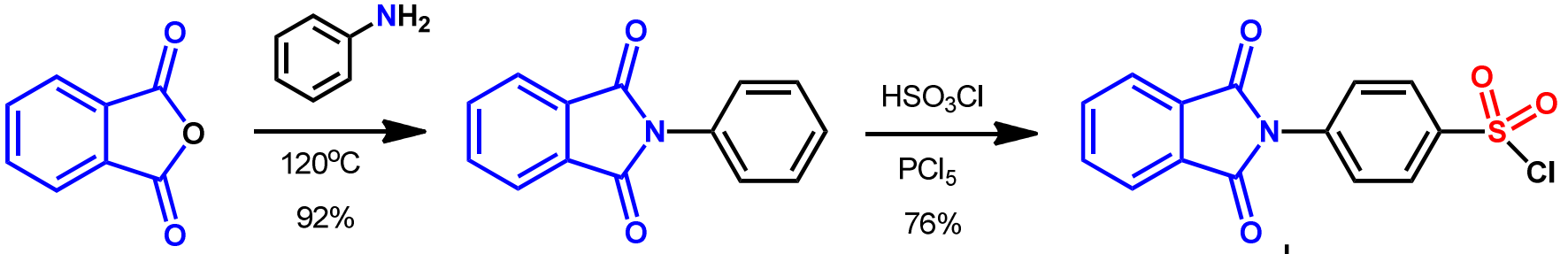
isosteres

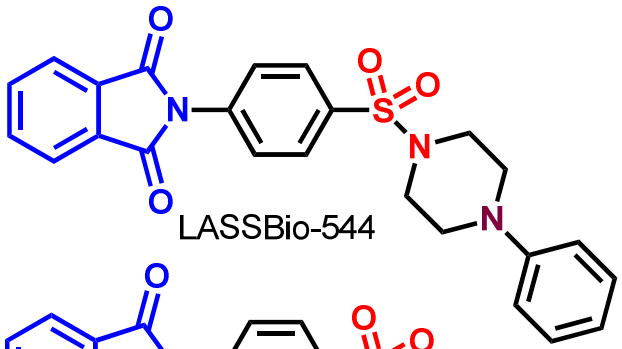


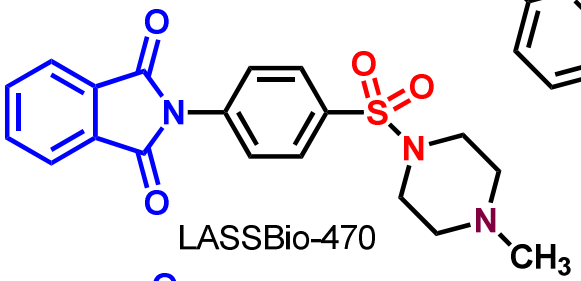
σ, π, RM

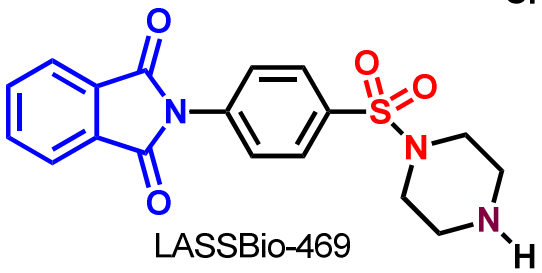
Drug Design

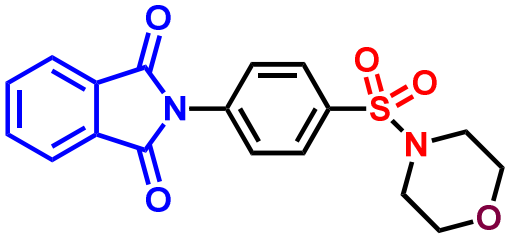
Synthesis of congeneric series

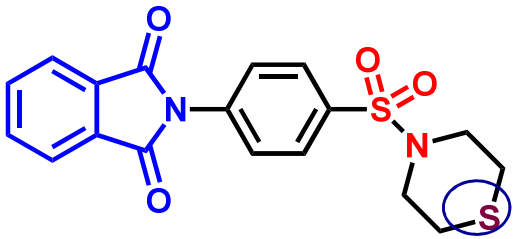



LASSBio-544


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

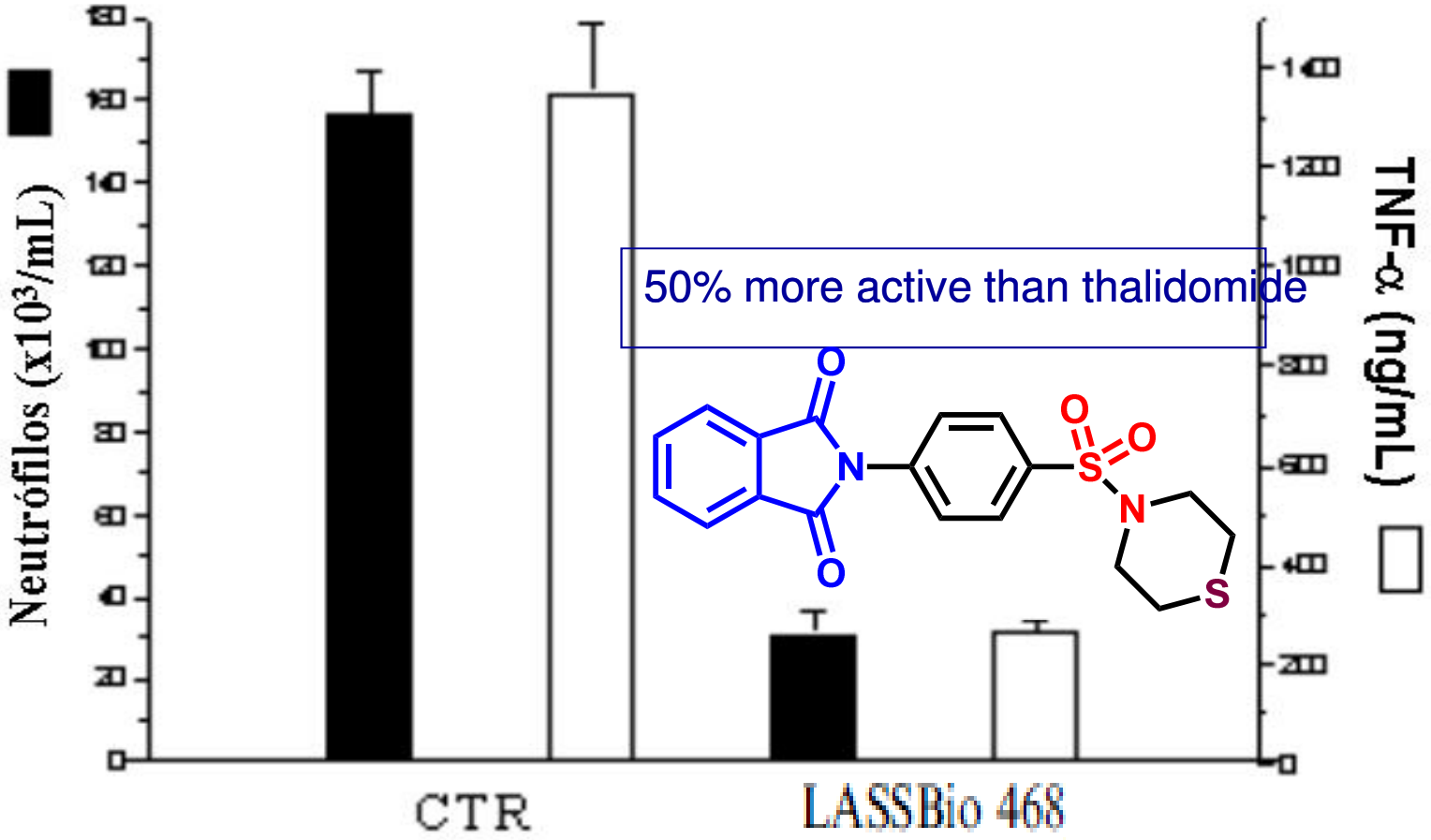
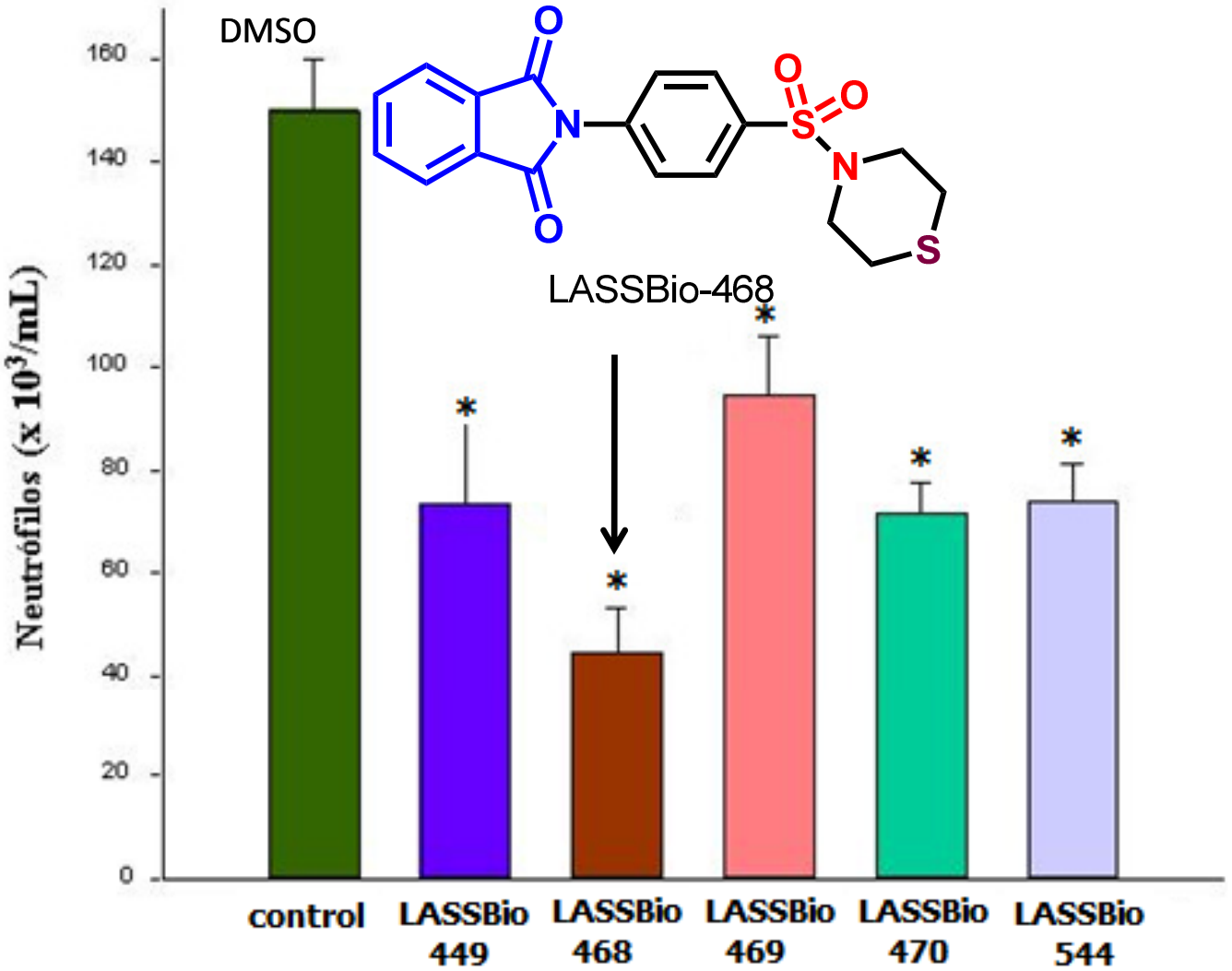


Fig. . Effect of LASSBio-468, thalidomide and pentoxifylline on survival BALB/c mice after LPS (500 µg/mice) administration.

Vera G Koatz
IBqM, Universidade Federal do Rio de Janeiro

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

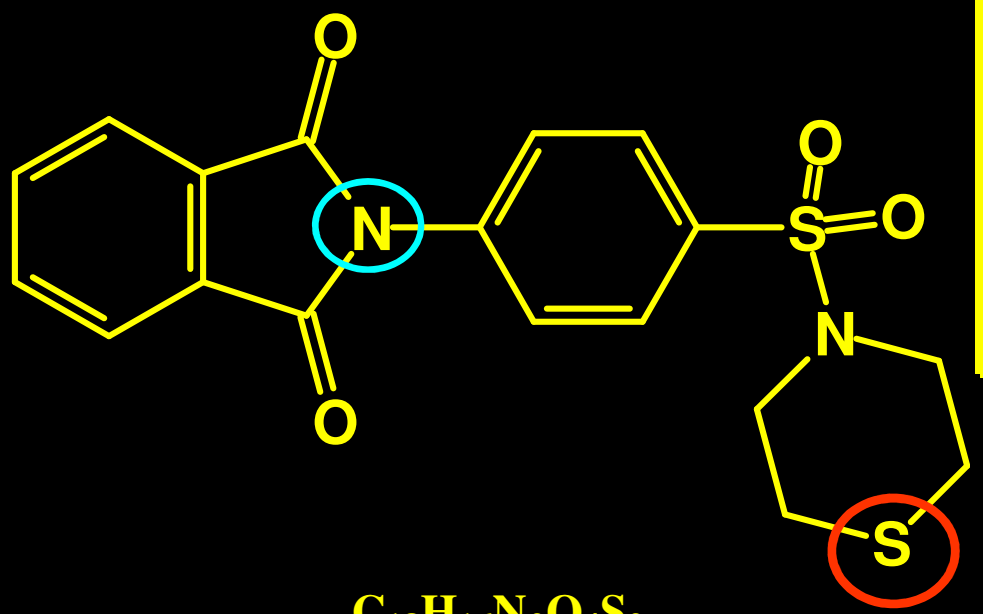
in vivo



Results are expressed as means SEM of seven animals.

Vera G Koatz
IBqM, Universidade Federal do Rio de Janeiro

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

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

IC_{50} = 13,5μM

cf. PDE-1, 2, 3, > 150 μM;

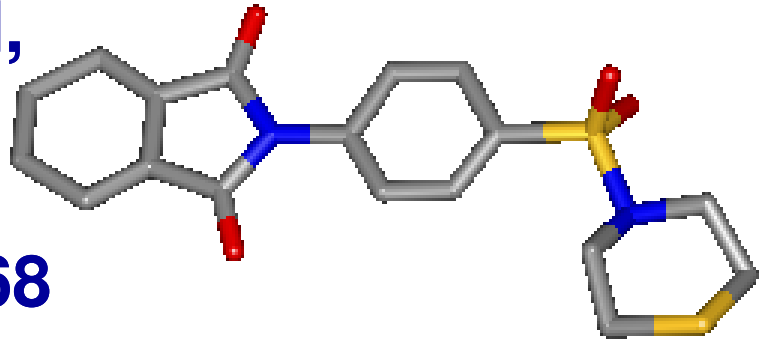
a) L. M. Lima *et al.*, "Synthesis and Anti-inflammatory Activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues", *Bioorg. Med. Chem.* 2002, 10, 3067;

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.

LASSBio-468

A new symbiotic anti-inflammatory agent

lead compound



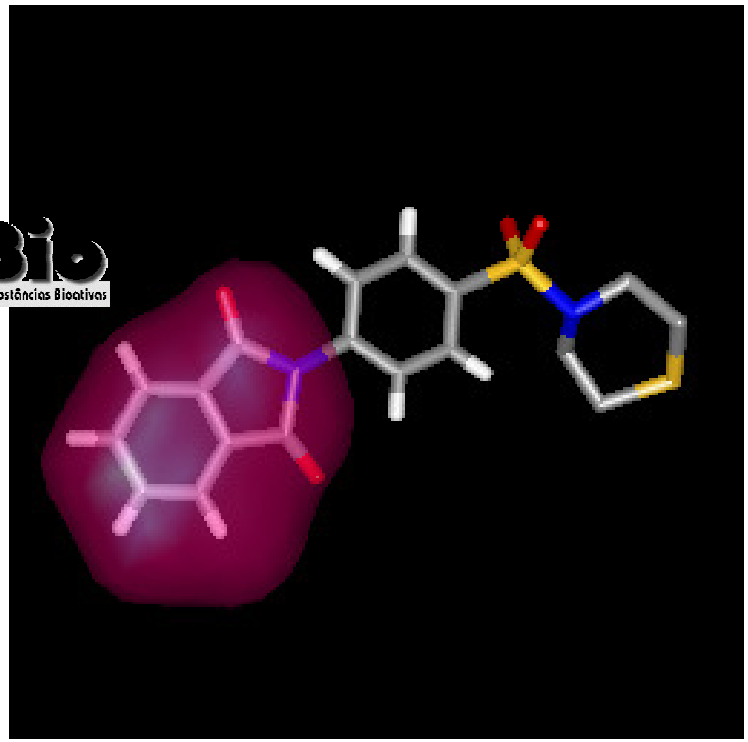
LASSBio-468 is a new dual-target anti-inflammatory lead-compound, active at TNF-α production and with inhibitory activity on PDE-4, as originally planned. LASSBio-468 is structurally simple derivative, easy to synthesized at good overall yield and 0.5 M scale. This new achiral compound presents immunomodulatory 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.

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

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

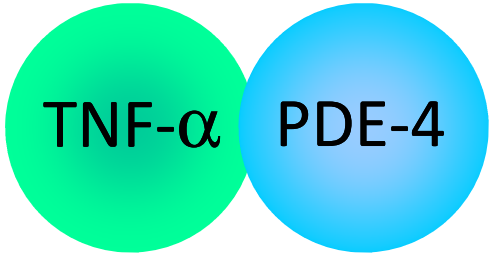
A. L. Machado *et al.*, "Design, Synthesis and anti-inflammatory activity of novel phthalimide derivatives, structurally related to thalidomide", *Bioorg. Med. Chem. Lett*. 2005, *15*, 1169

The discovery of new dual lead-compounds



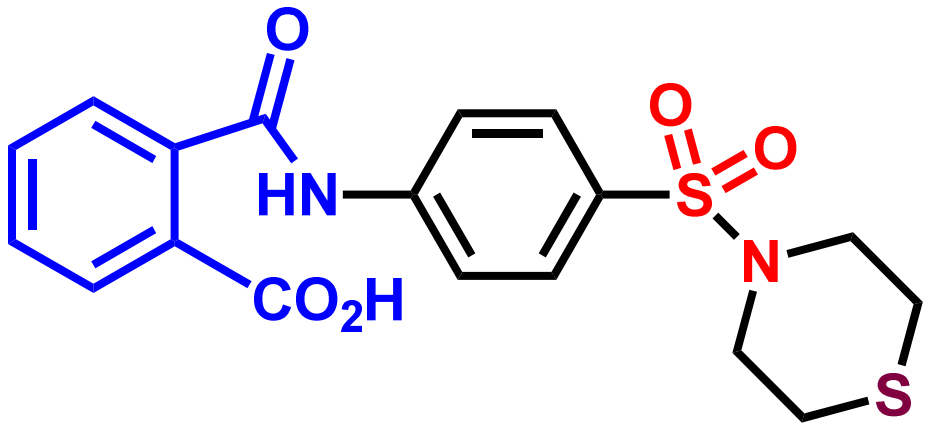
LASSBio-468

Desenhado por hibridación molecular



TNF-α ED_{50} 2,5 mg/Kg

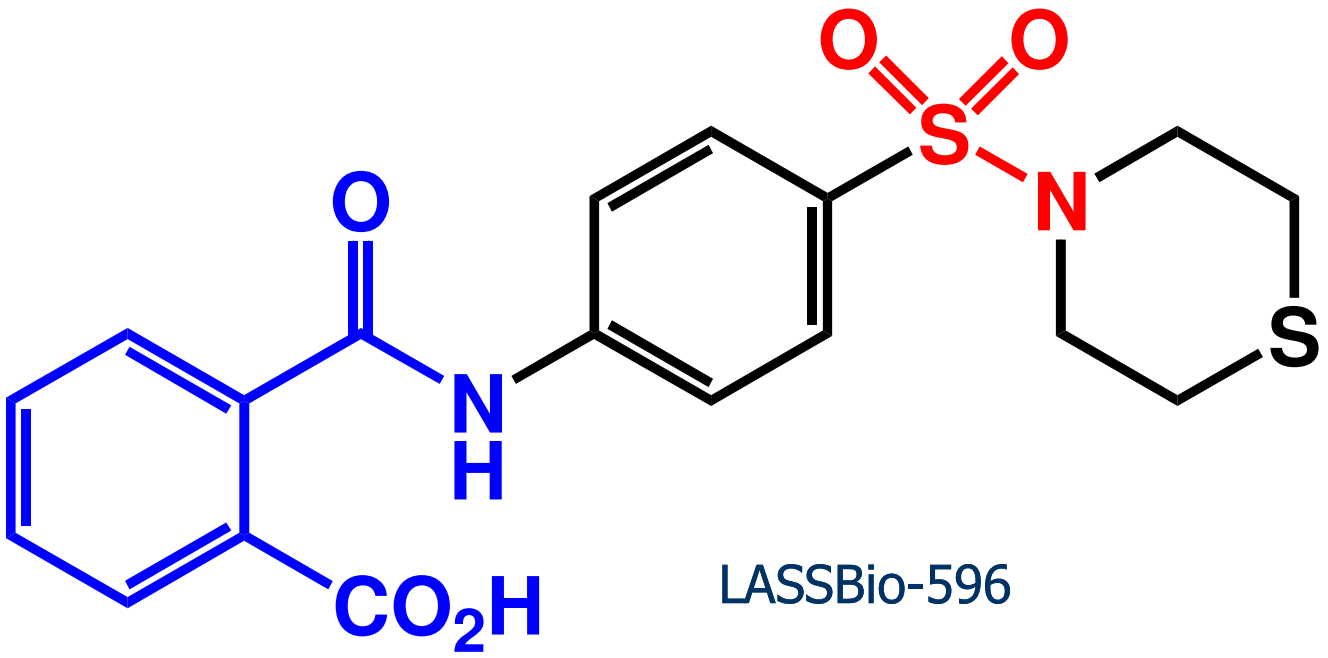
PDE-4 IC_{50} = 13,6 µM



Metabolism studies

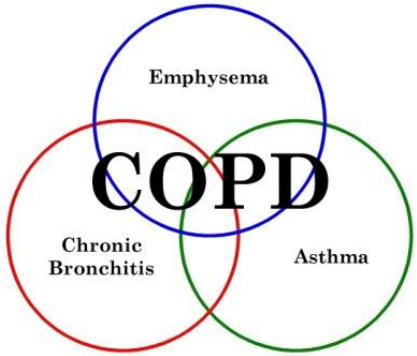
LASSBio-596

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



LASSBio-596

asthma



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

FROM THE ANALYST'S COUCH

Therapies for COPD

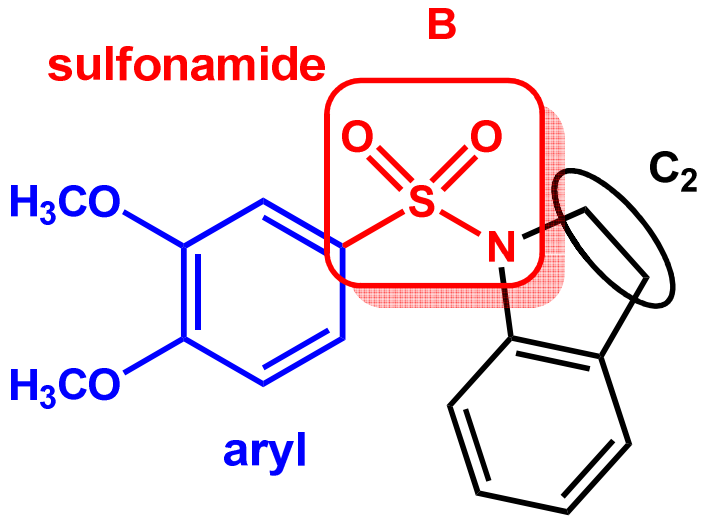
Nature Rev. Drug Discov. **2008**, *7*, 285

Uma Yasothan and Santwana Kar

Table1 | **Selected novel COPD pipeline products in development**

Drug	Developer	Target/mechanism	Status
Cilomilast	GlaxoSmithKline	PDE4 inhibitor	Phase III
Midesteine	Medea Research	Elastase inhibitor	Phase III
Roflumilast	Nycomed	PDE4 inhibitor	Phase III
Zileuton	Critical Therapeutics/ SkyePharma	LTB4 synthesis inhibitor	Phase III
681323, 856553	GlaxoSmithKline	p38 MAP kinase inhibitor	Phase II
BAYx1005	Bayer	LTB4 inhibitor	Phase II
BEA-2180-BR	Boehringer Ingelheim	Anti-inflammatory	Phase II
Infliximab	Centocor	TNF-α ligand inhibitor	Phase II
Oglemilast	Forest Laboratories/Glenmark	PDE4 inhibitor	Phase II
SCH-527123	Schering–Plough	CXCR1/CXCR2 antagonist	Phase II
Tetomilast	Otsuka Pharmaceutical	PDE4 inhibitor	Phase II
UK-432097	Pfizer	Adenosine A_{2a} receptor agonist	Phase II
656933	GlaxoSmithKline	CXCR2 antagonist	Phase I
Amelubant	Boehringer Ingelheim	LTB4 antagonist	Phase I
AZD-1236/ 9668/4818	AstraZeneca	Anti-inflammatory	Phase I
BAY-71-9678	Bayer	Elastase inhibitor	Phase I
Canakinumab	Novartis	IL1β antagonist	Phase I

A hibridación molecular



Montana *et al*., 1998

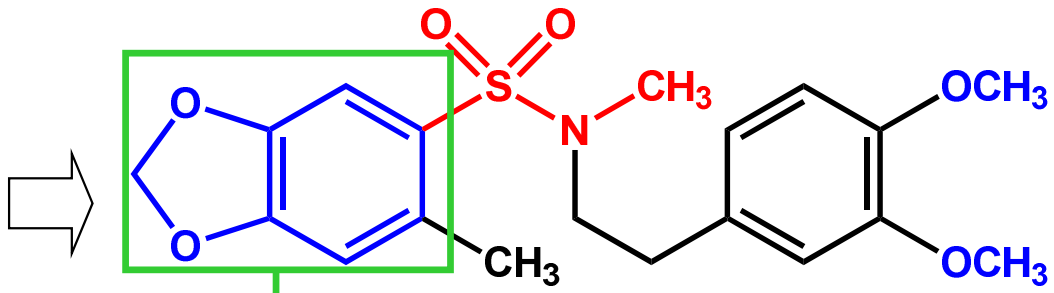
Lead -optimization

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

medicinal chemistry

LEAD COMPOUND

Lead-optimization



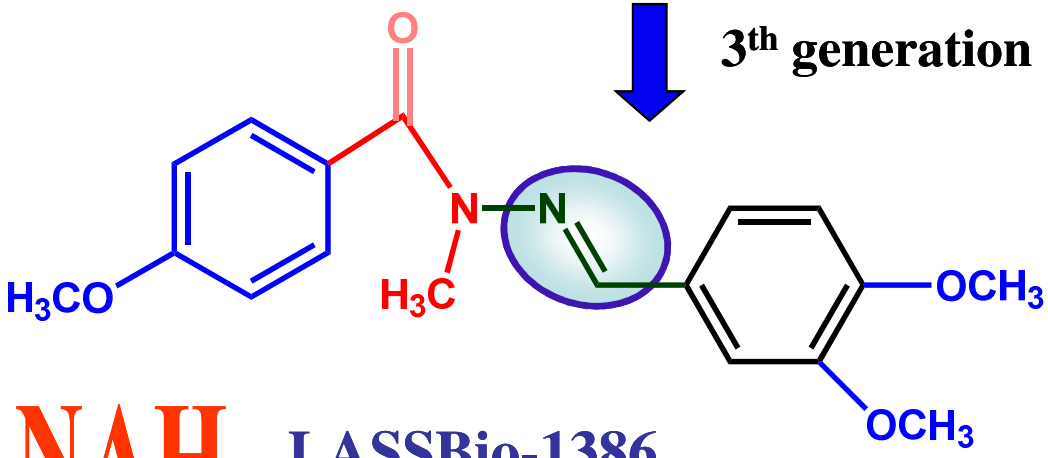
2^{nd} generation

LASSBio-959

Biophore from natural safrole

IC_{50} = **6,7** μM PDE-4

3^{th} generation

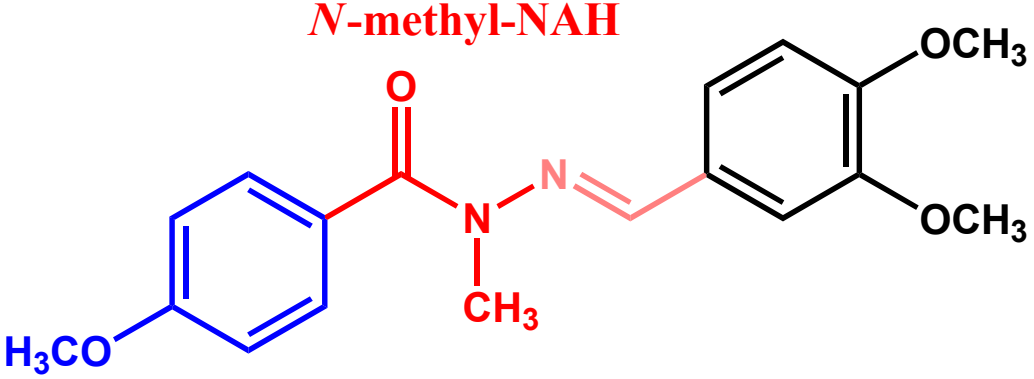


NAH

LASSBio-1386

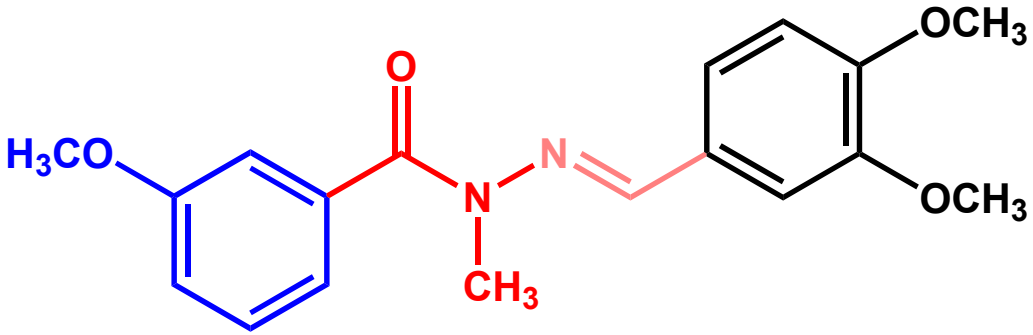
Optimización

N-methyl-NAH



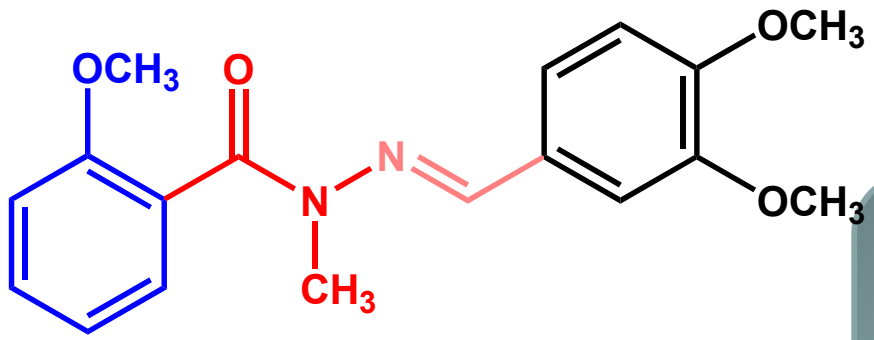
LASSBio-1386

PDE-4 IC_{50} = 105 nM



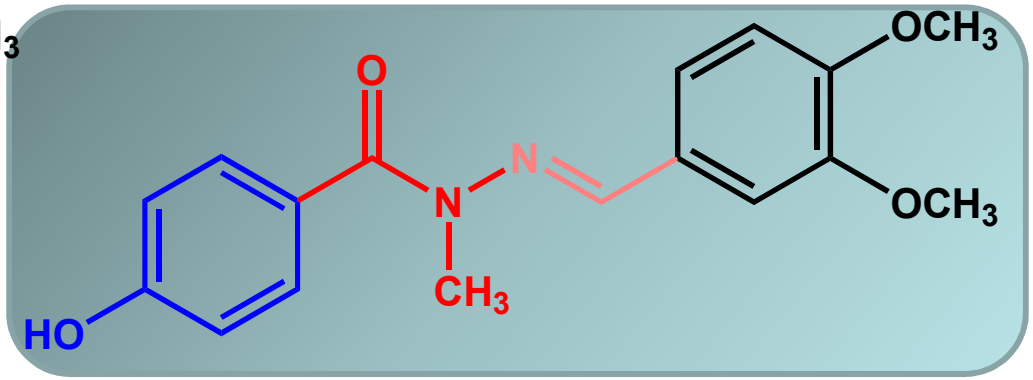
LASSBio-1407

PDE-4 IC_{50} = 200 nM



LASSBio-1406

PDE-4 IC_{50} = 220 nM



LASSBio-1393

PDE-4 IC_{50} = 50 nM

Epílogo

"For all the efforts to industrialize and automate discovery, history suggests <u>drug discovery is art as well as science</u> and relies heavily on the skill of <u>experienced drug hunters</u>..."

Charles H. Reynolds

J&J Pharmaceutical Research and Development, Spring House, Pa

em *Pharma's Road Ahead* , C&EN, Volume 84, Issue 25, June 19, 2006


Sugar Loaf montain, Rio de Janeiro city
MUCHAS
GRACIAS
ejbarreiro@ccsdecania.ufrj.br
ww.farmacia.ufrj.br/lassbio
ejb-ejbarreiro.blogspot.com