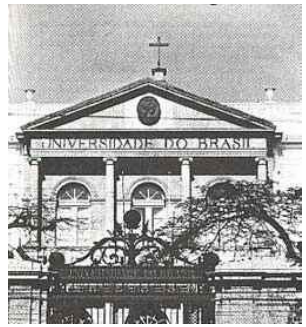
Introdução à Química Farmacêutica Medicinal
Parte 2

UFRJ XIII Escola de Verão UFRJ
em Química Farmacêutica e Medicinal



Eliezer J. Barreiro

Universidade Federal do Rio de Janeiro

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas
www.farmacia.ufrj.br/lassbio

3. A Origem dos Fármacos II

Produtos naturais de origem marinha

O acaso na descoberta de fármacos: *serendipity*

Fármacos sintéticos: AAS

4. As razões moleculares da ação dos fármacos

O centenário modelo "*chave-fechadura*" de Emil Fisher

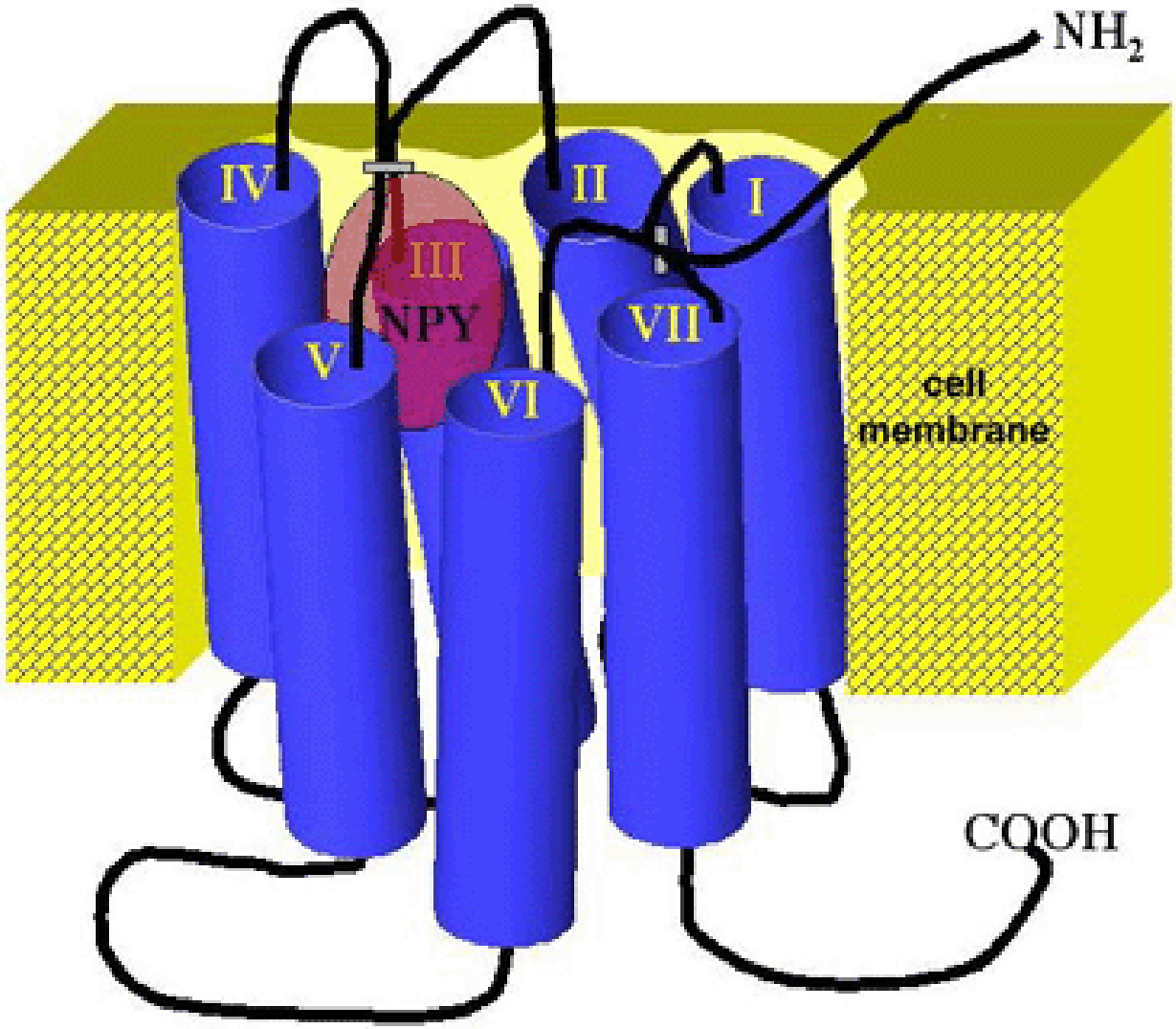
A bioinformática e a Química Medicinal

Construção de mapas topográficos de biorreceptores

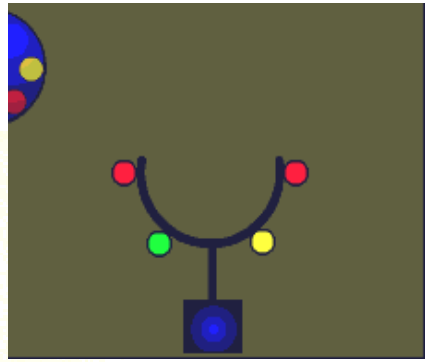
O conceito de grupamento farmacofórico

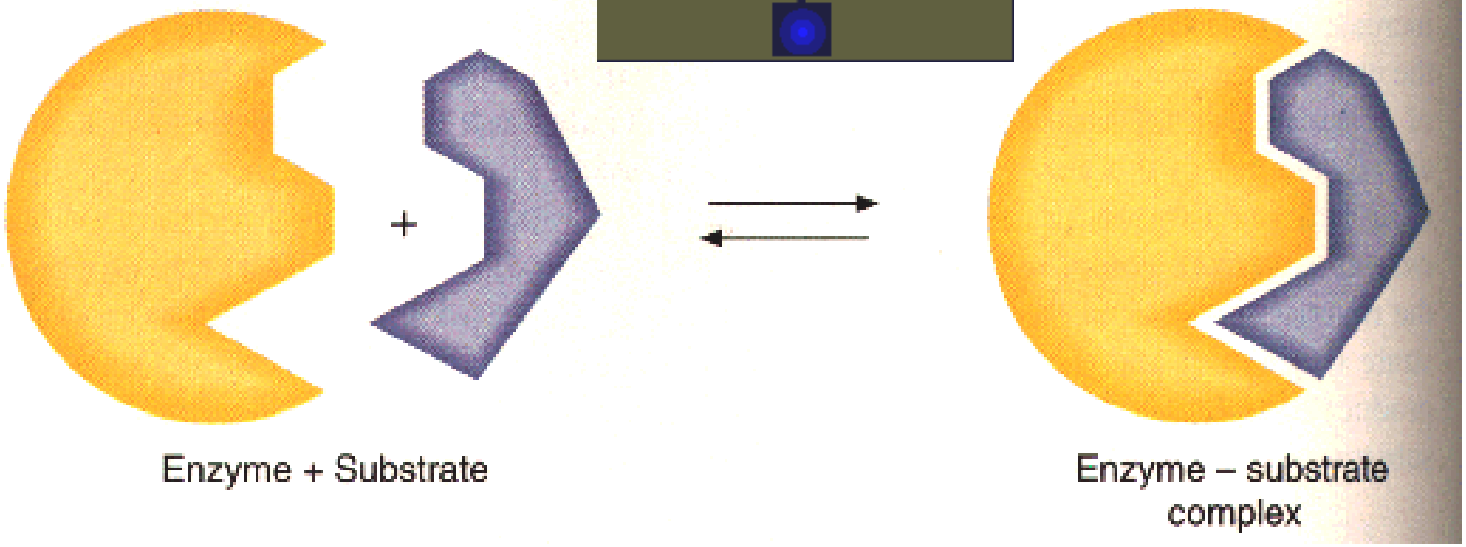
Fatores estruturais e atividade: similaridade e dissimilaridade

Localização dos biorreceptores



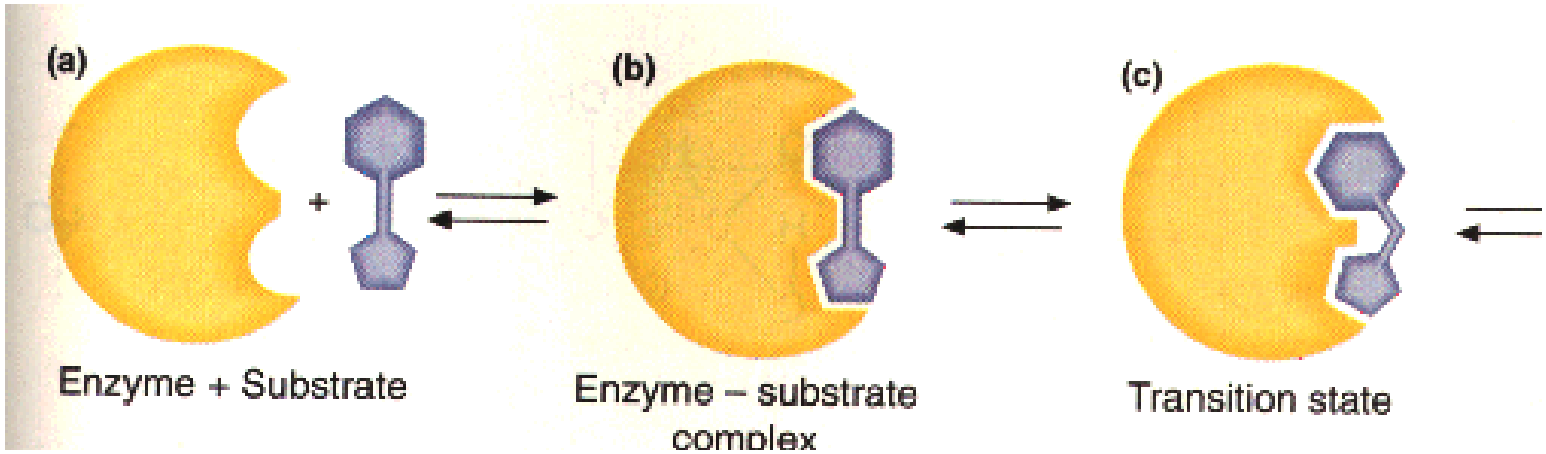
Enzyme Catalysis

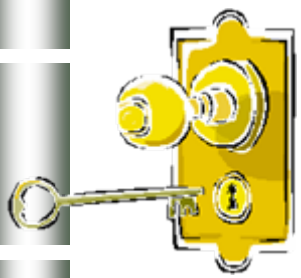


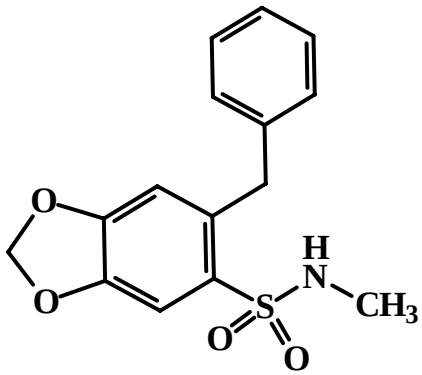


Enzyme + Substrate

Enzyme – substrate complex







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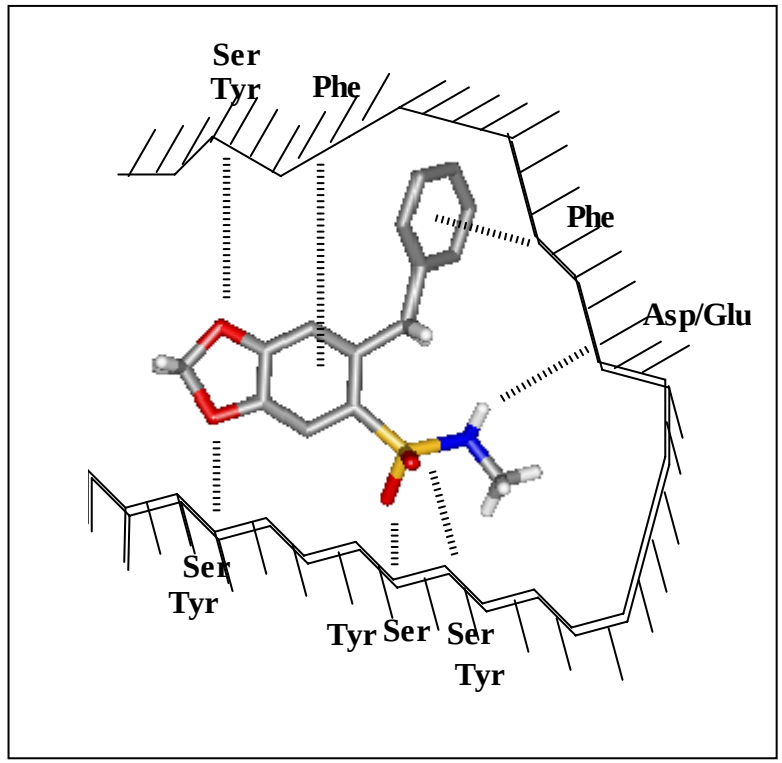
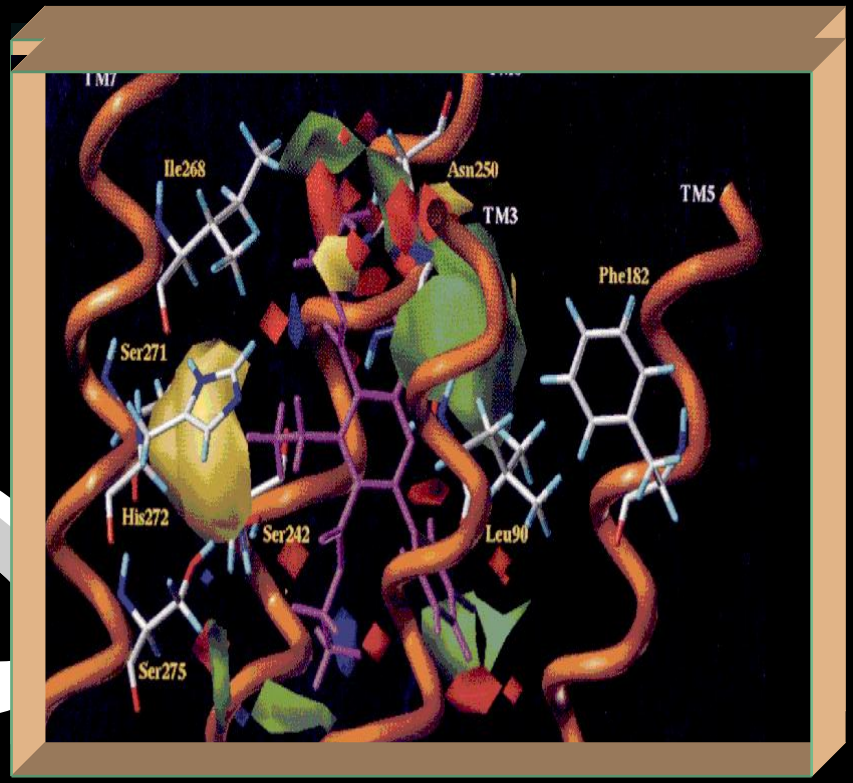
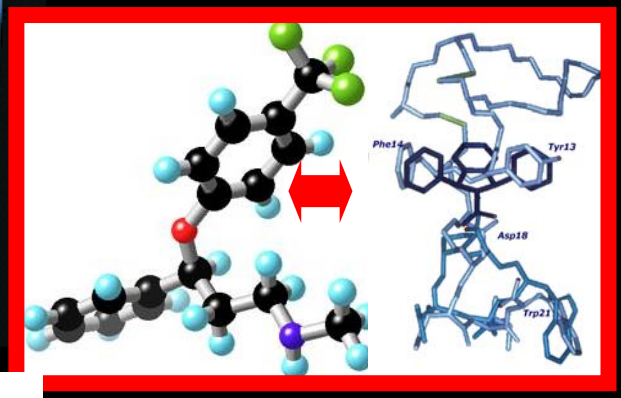


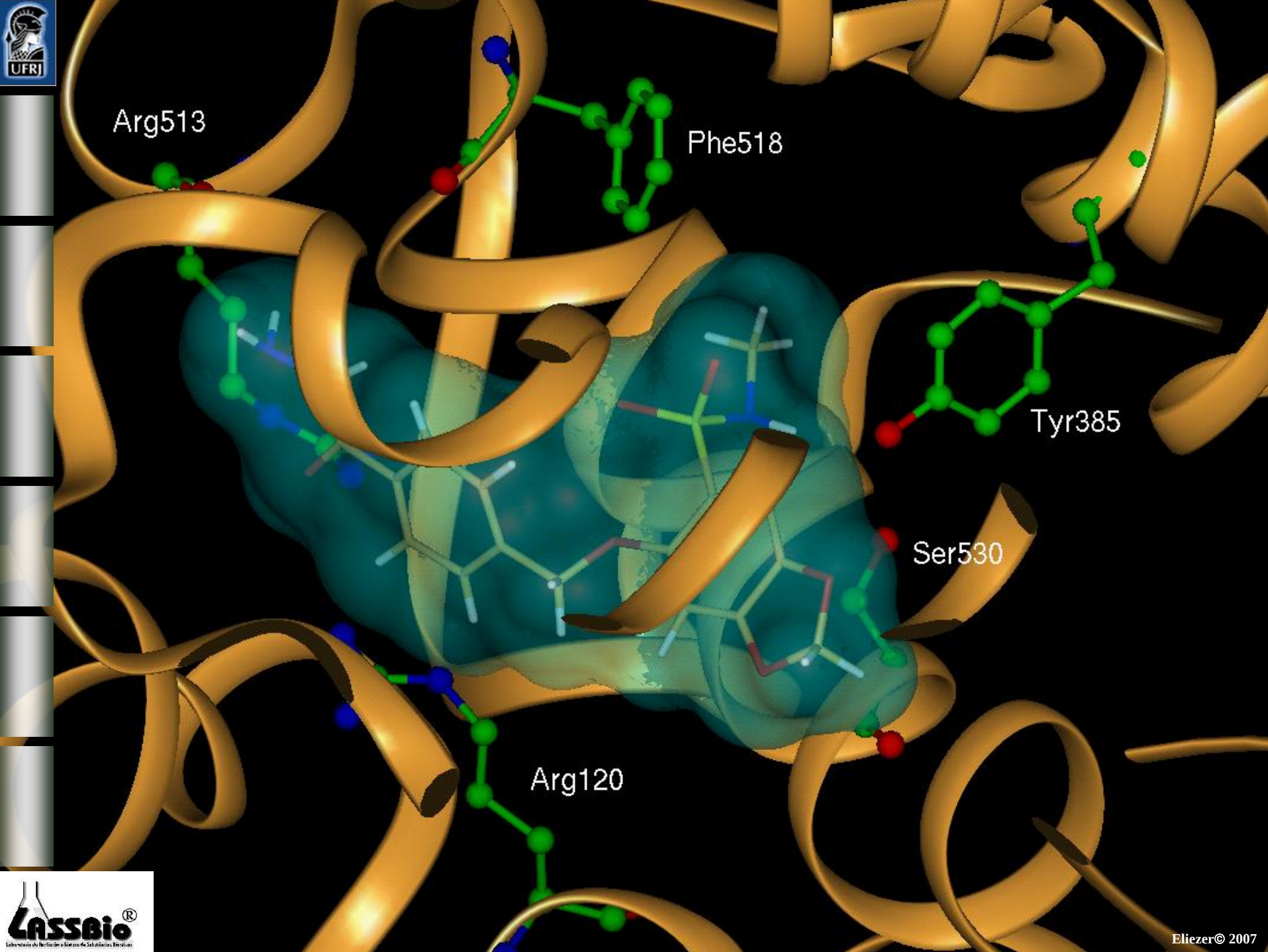
Modelagem Molecular

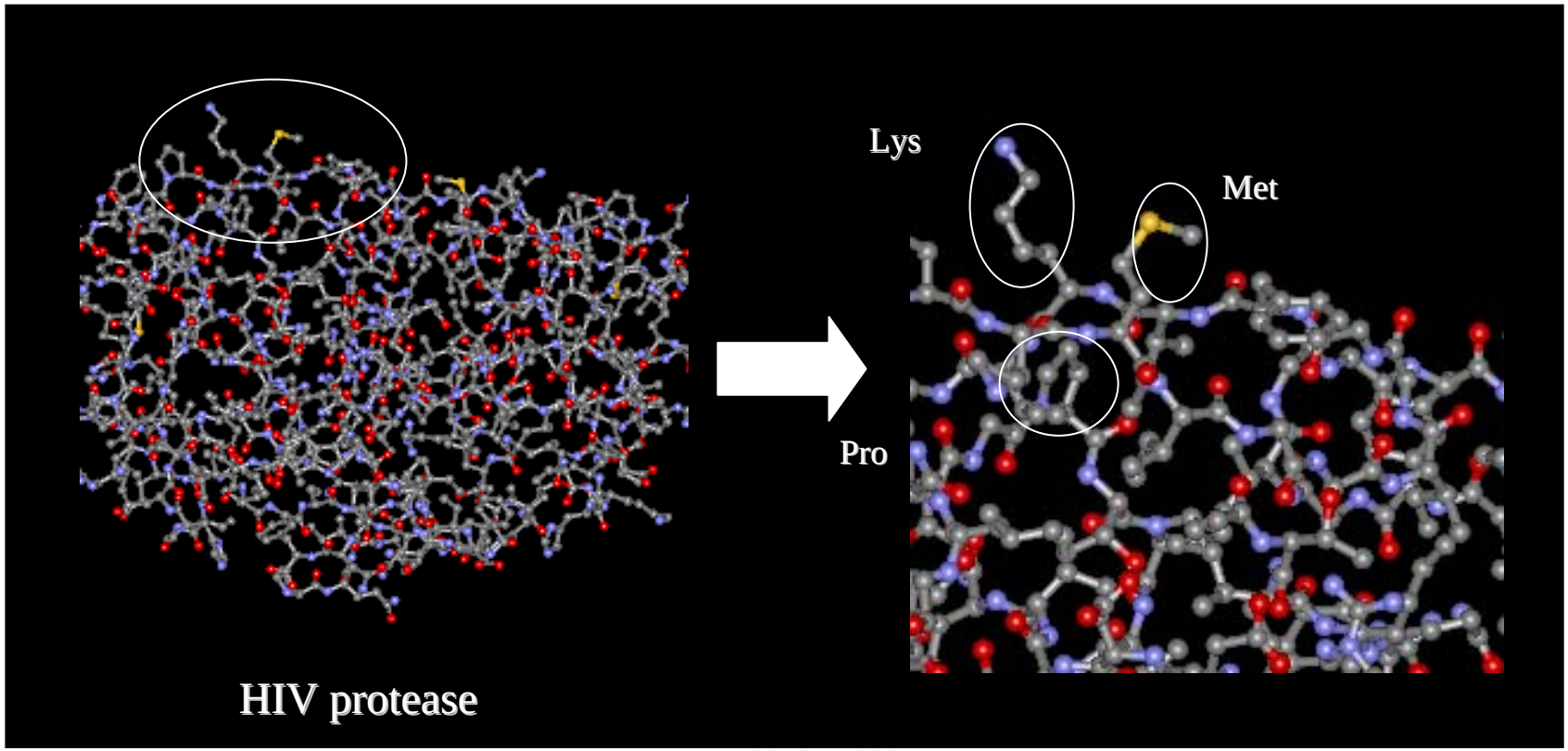
Sistema otimizado de interface gráfica

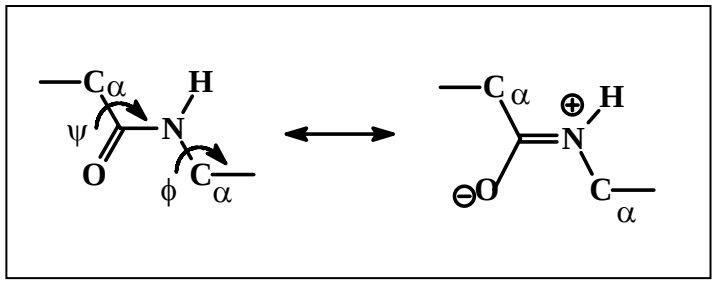


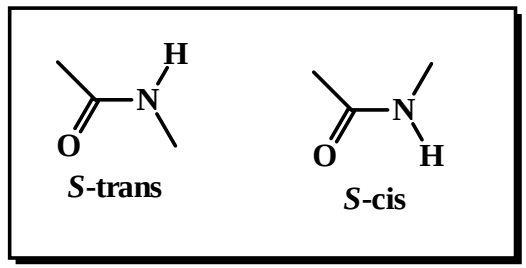


Huperzine-A in the active-site of AChE

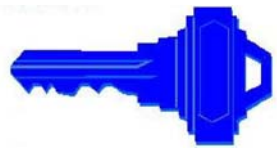


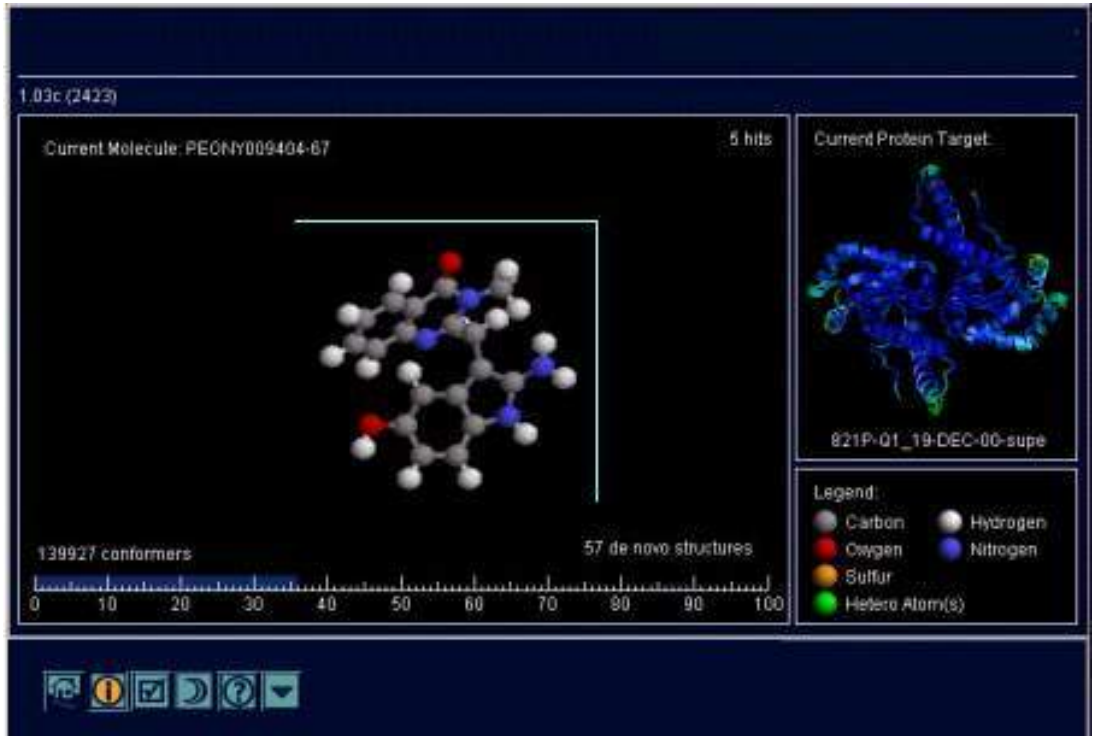


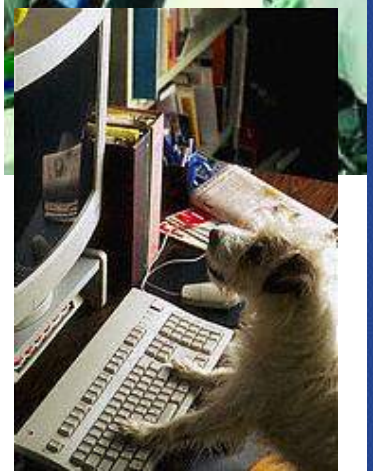


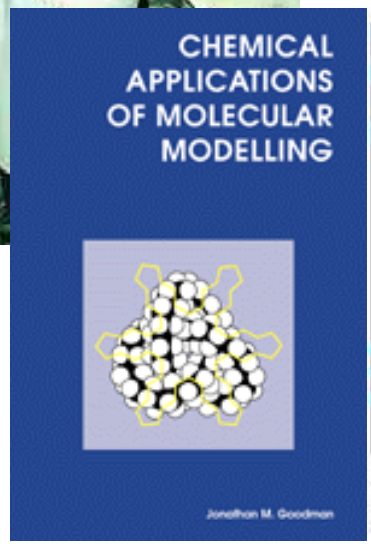


proteínas
enzimas
biorreceptores









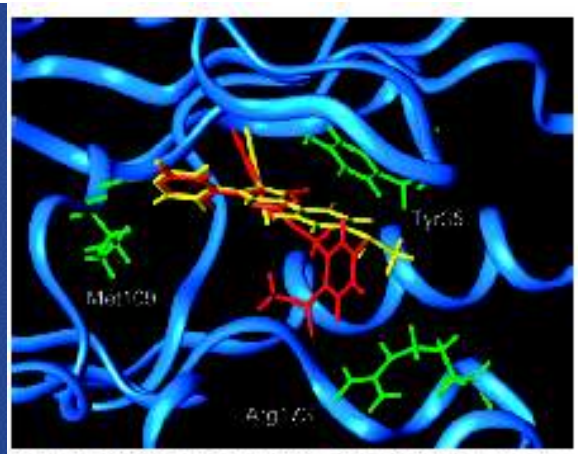
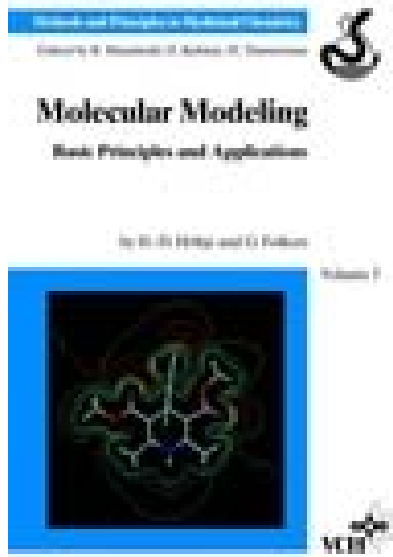
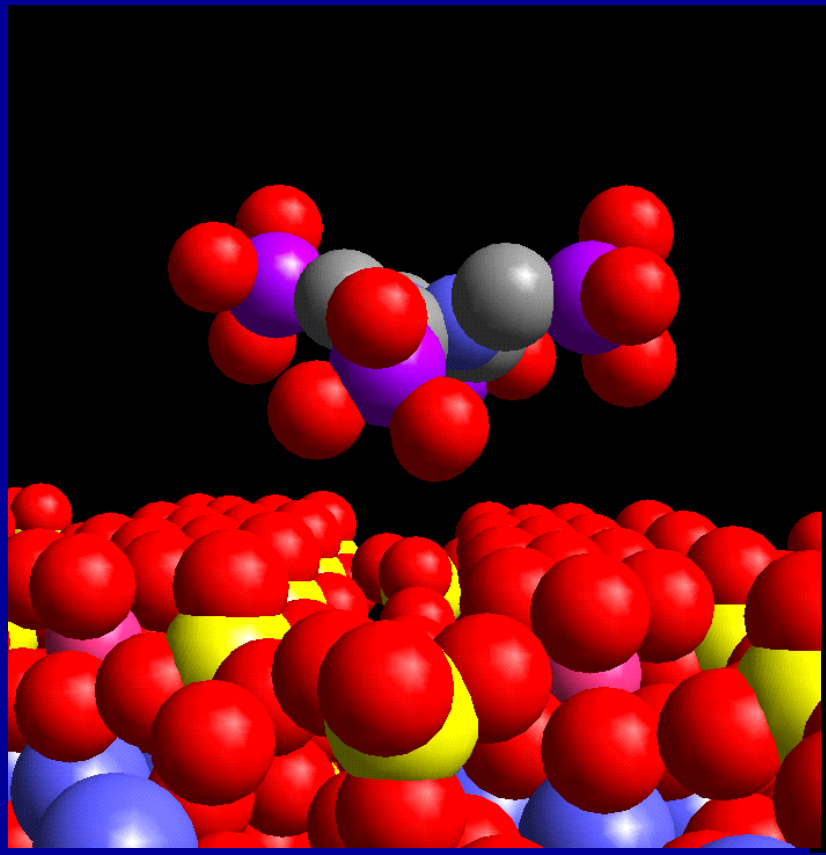
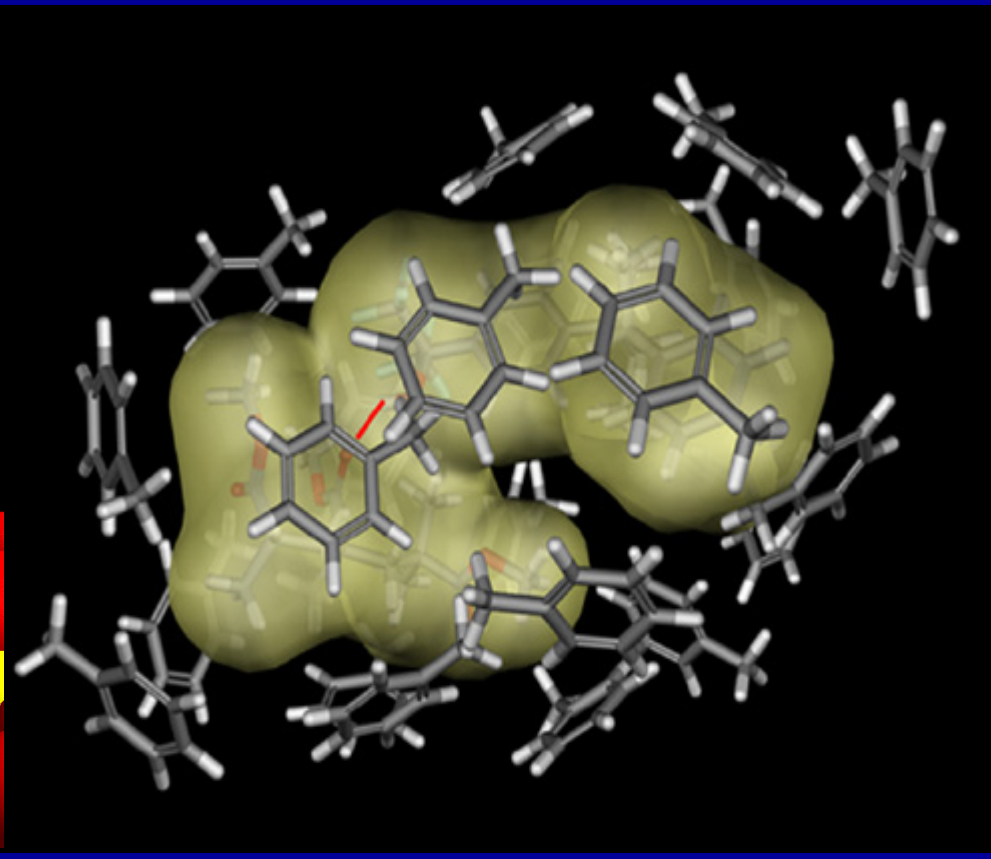


Figure 2. Superposition of SB 203580 (yellow) in complex with p38 MAP kinase[15] and compound **14** (red).[22] Thr35, Met109, and Arg173 are depicted in green.







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Apr 3 1997 09:53:33

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http://www.acdlabs.com/download/

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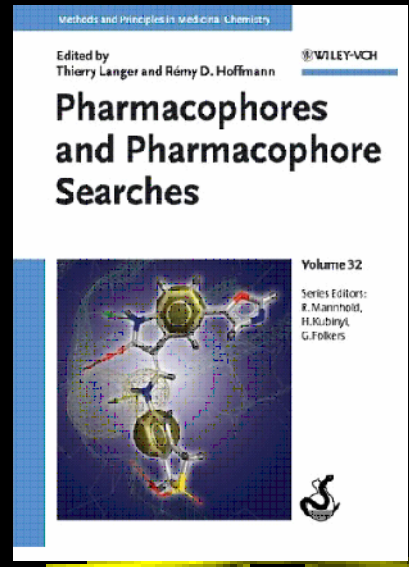
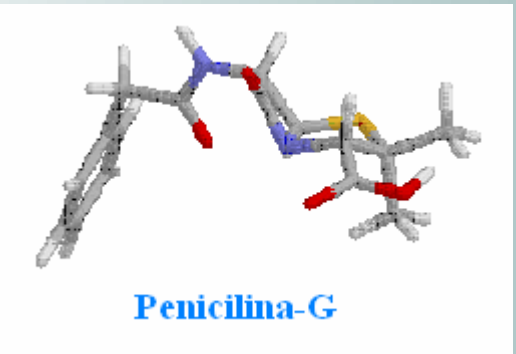
Reconhecimento Molecular: Interação Enzima-Substrato

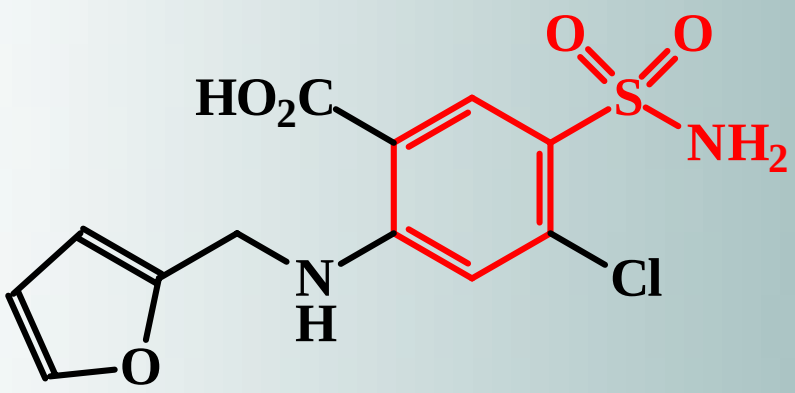


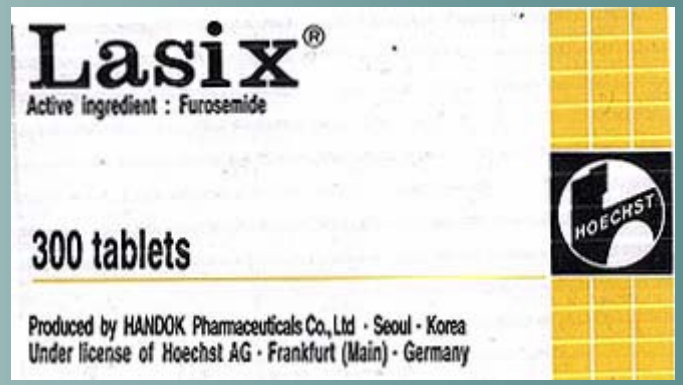
Farmacóforo

Identificação do Farmacóforo



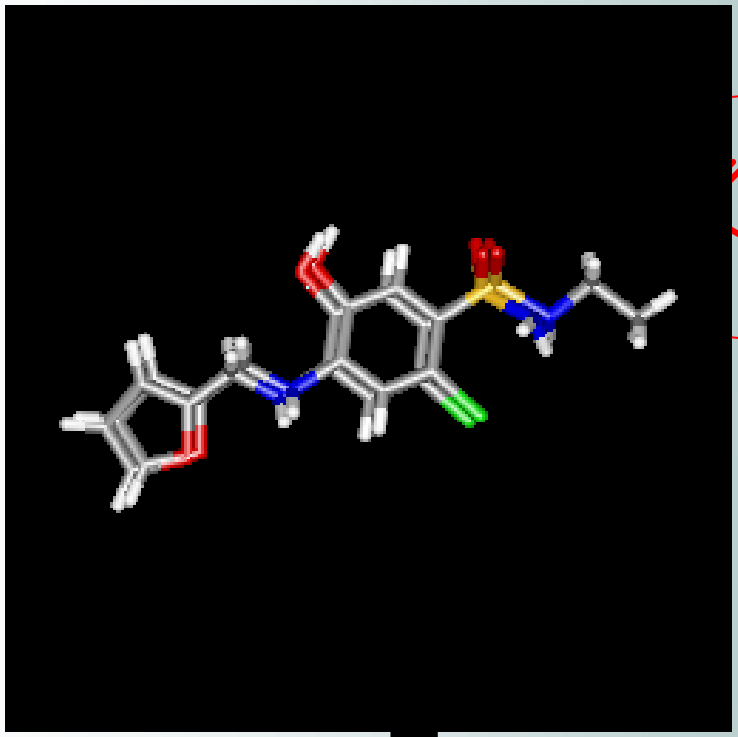
Anel β-lactâmico

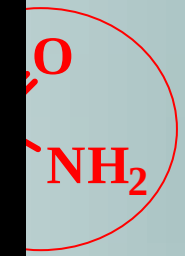




Sulfonamida diurética

Identificação do Farmacóforo

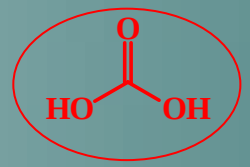


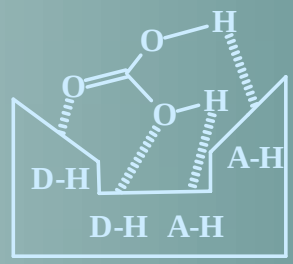


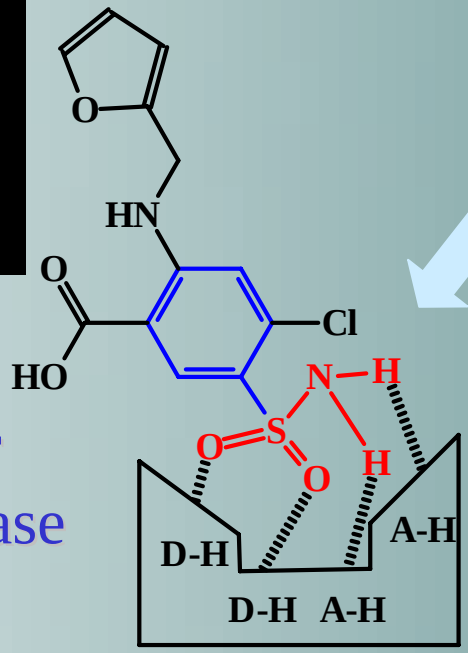
substrato natural da anidrase carbônica

H_2CO_3

ácido carbônico

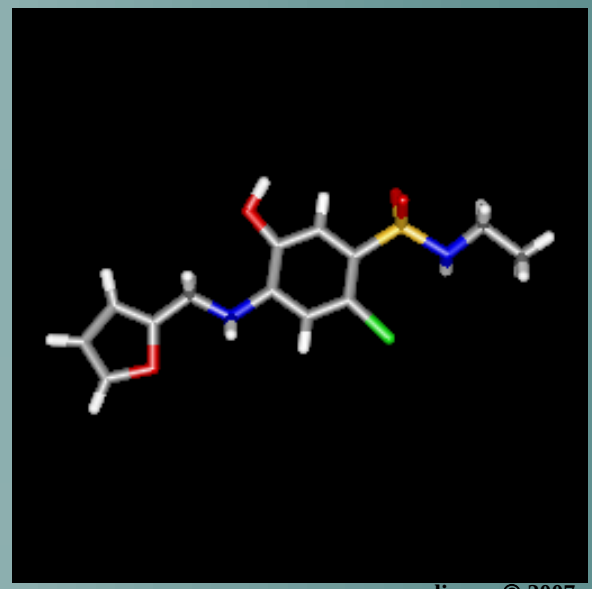




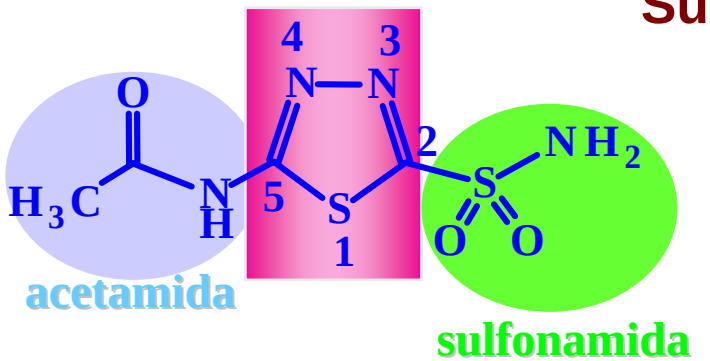


atua como inibidor competitivo da anidrase carbônica

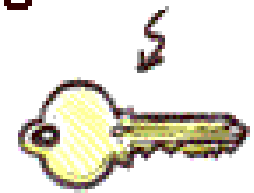
sítio ativo da anidrase carbônica

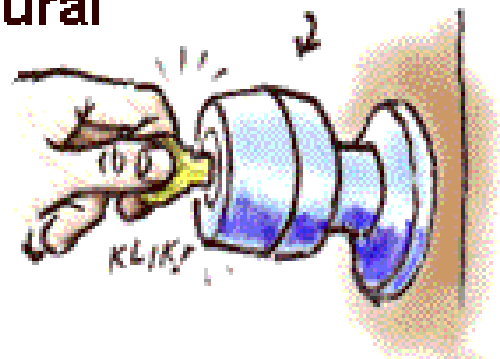


Modelo chave-fechadura



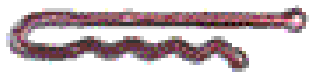
Agonista Natural

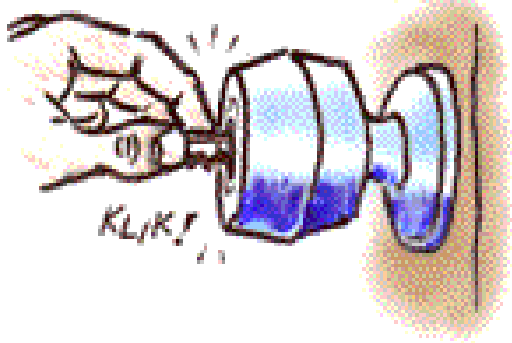




Substrato natural

Agonista

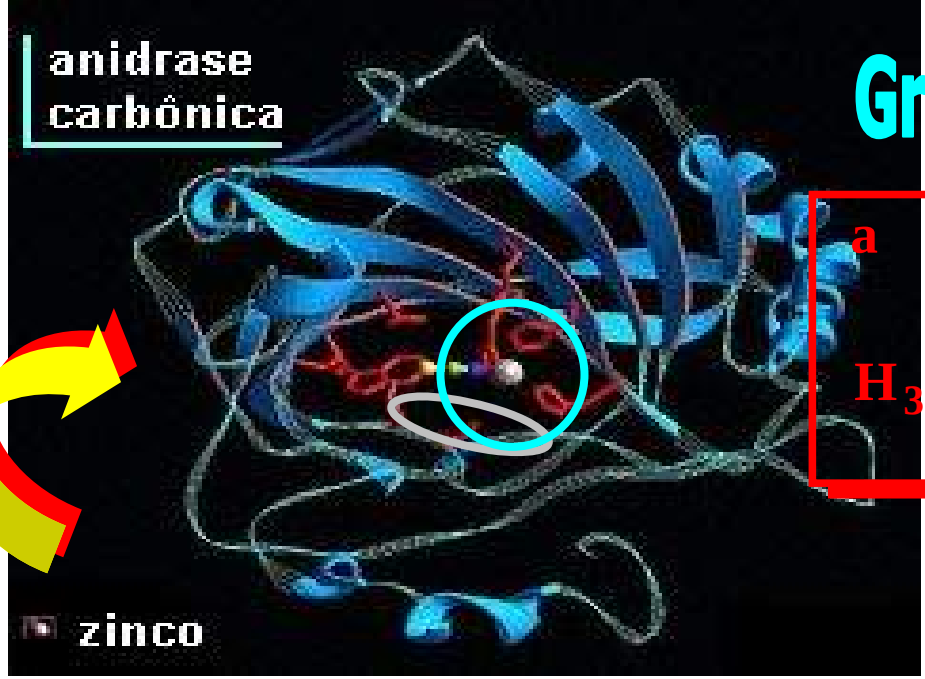




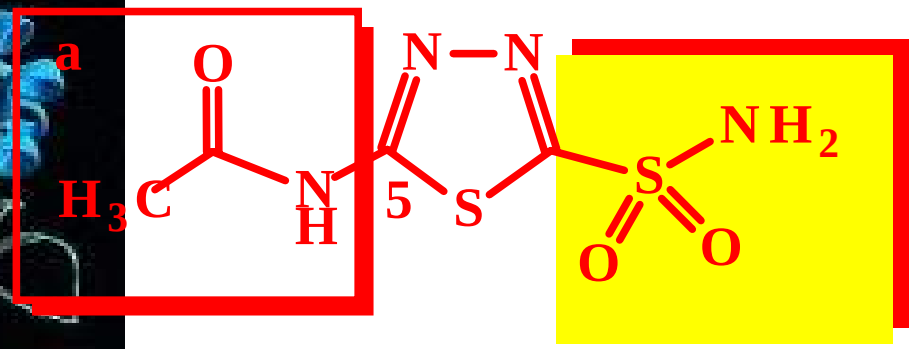
Bioreceptor

Antagonista

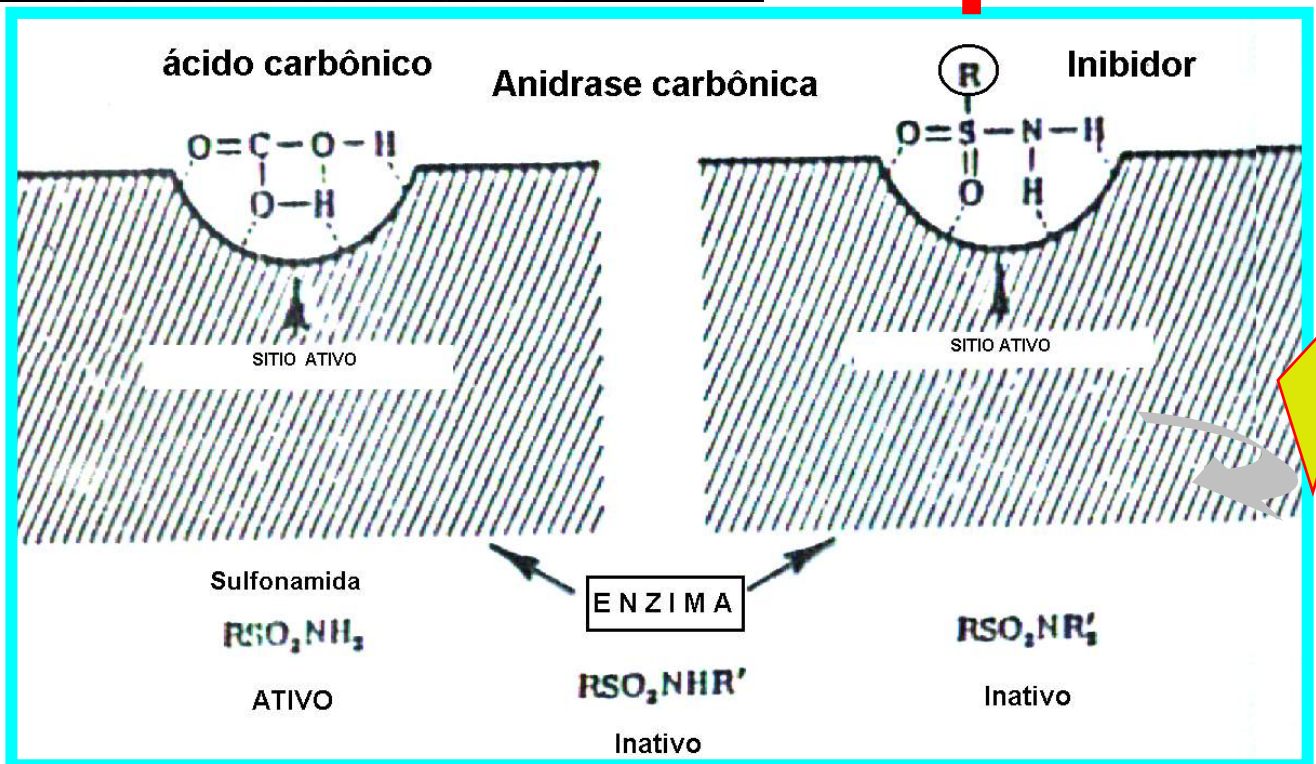
Inibidor enzimático

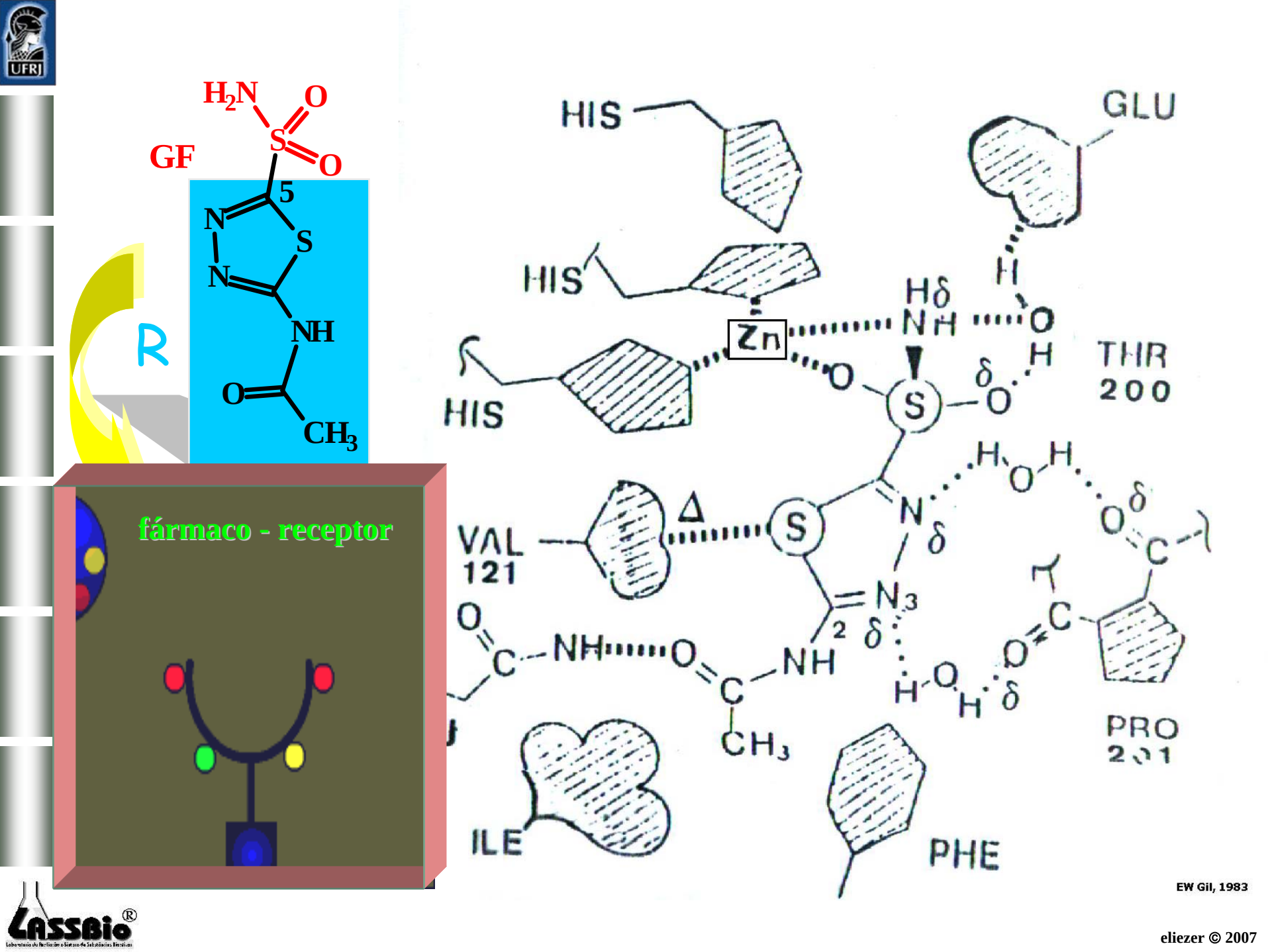


Grupamento Farmacofórico

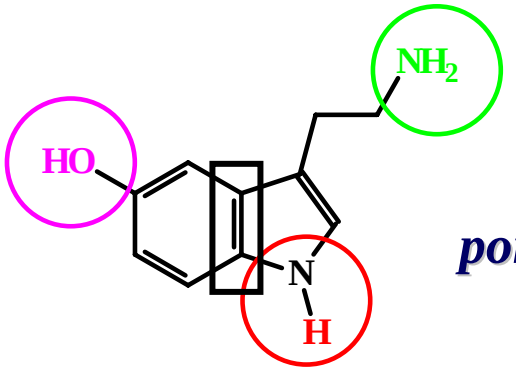


acetazolamida

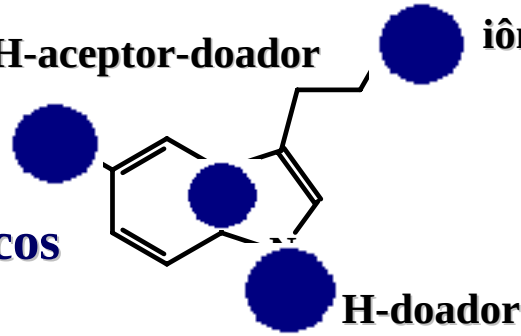




Construção de Modelo Farmacofórico 2D/3D



identificação dos *pontos* farmacofóricos



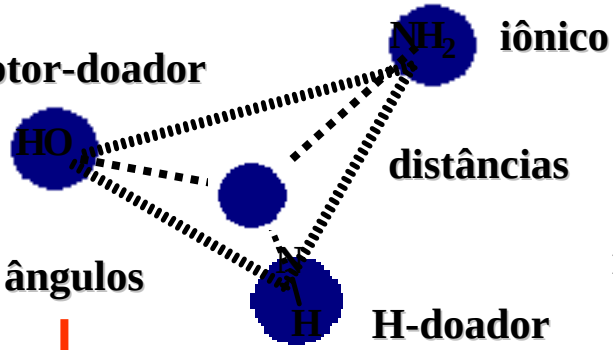
serotonina → 5-HT$_1$– 5-HT$_7$

5-HT$_{1D}$
ag. = anti-enxaqueca

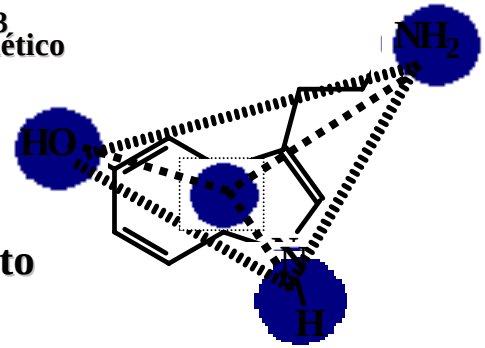
5-HT$_4$
ag. = > motilidade GI

5-HT$_3$
ant. = anti-emético

Modelo Farmacofórico



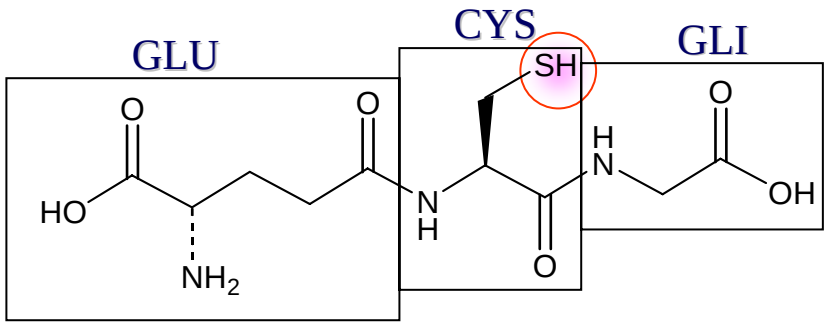
remove esqueleto

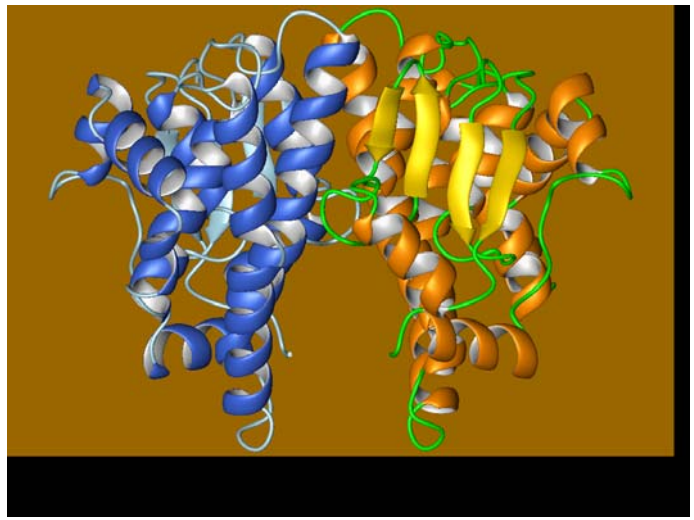


Topografia molecular

Efeitos conformacionais → Modelo tridimensional (3D) → CADD

Grupamento toxicofórico



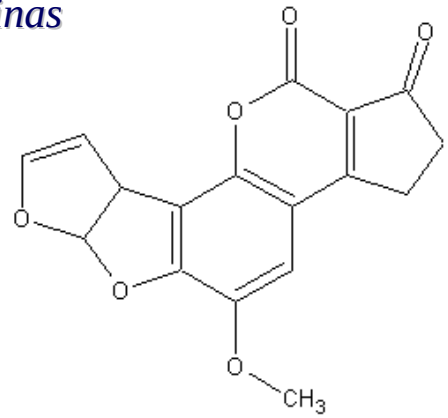


Glutatião = (Nu^-) bionucleófilo

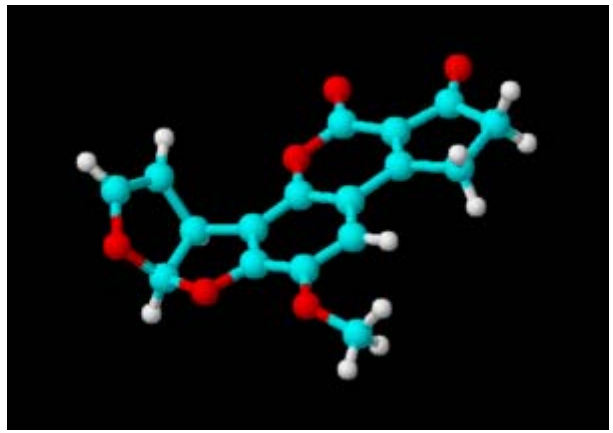
Toxicofóro/toxicofórico:

é o grupamento ou a sub-unidade estrutural de uma substância responsável pelas propriedades tóxicas.

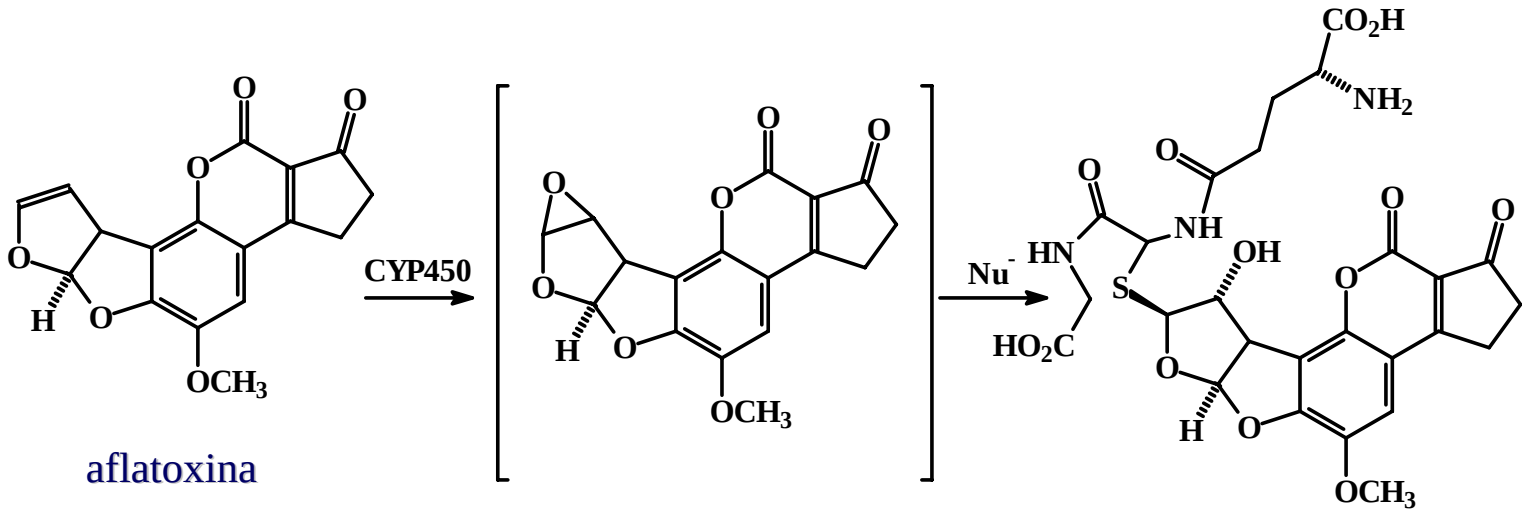
Micotoxinas

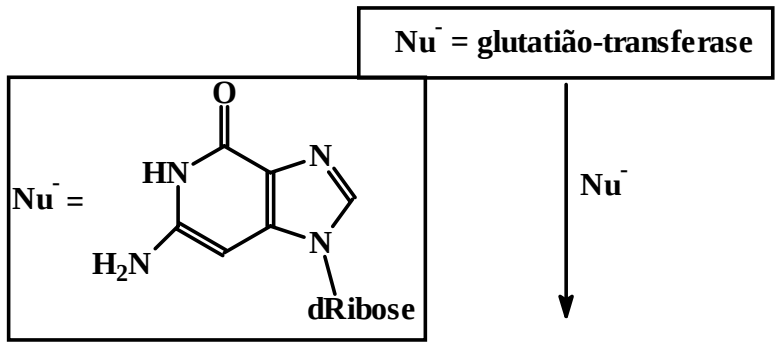


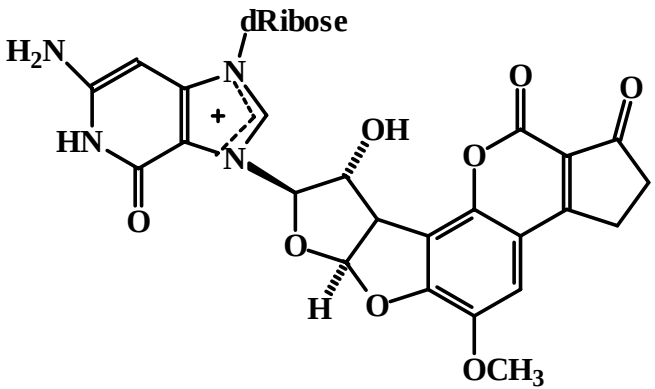
Aspergillus sp

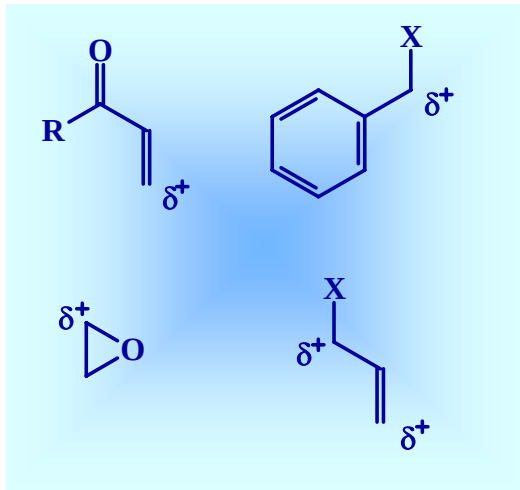


Aflatoxina (B1/B2/G1/G2)









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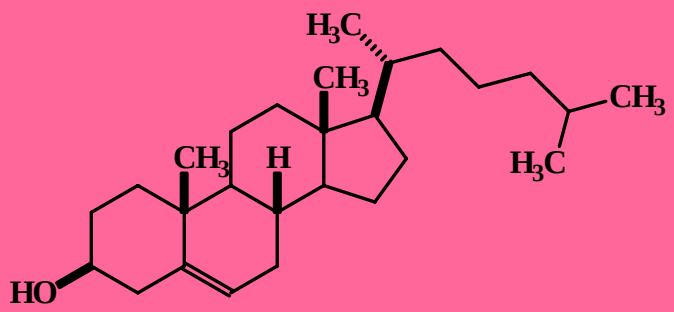
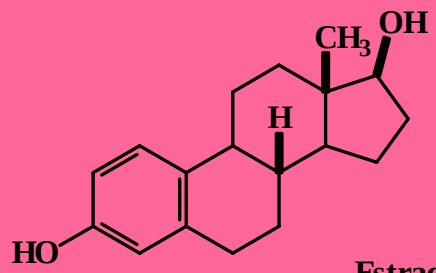
Similaridade e Dissimilaridade Molecular

H. Kubinyi, Chemical similarity and biological activities, *J. Braz. Chem. Soc.* 2002, 13, 717

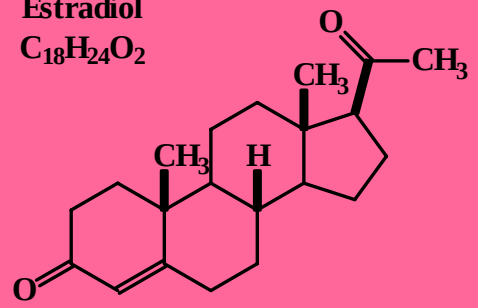
Bioformação dos Hormônios Sexuais



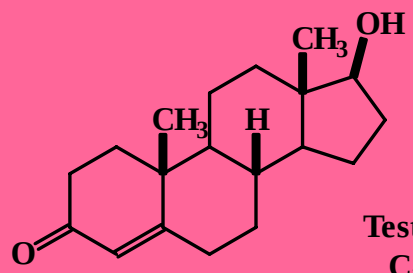
Colesterol
$C_{27}H_{46}O$



Estradiol
$C_{18}H_{24}O_2$

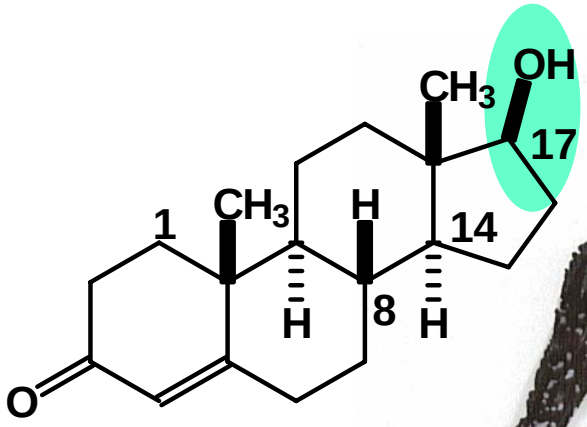


Progesterona
$C_{21}H_{30}O_2$



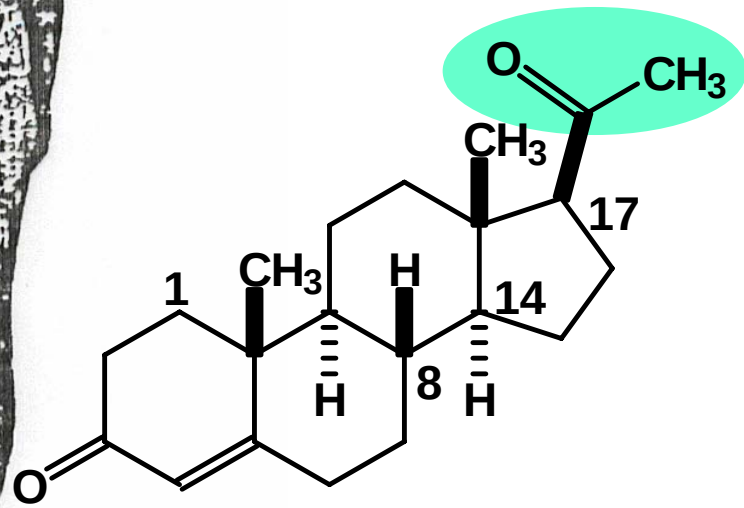
Testosterona
$C_{19}H_{28}O_2$

Similaridade & Dissimilaridade Molecular



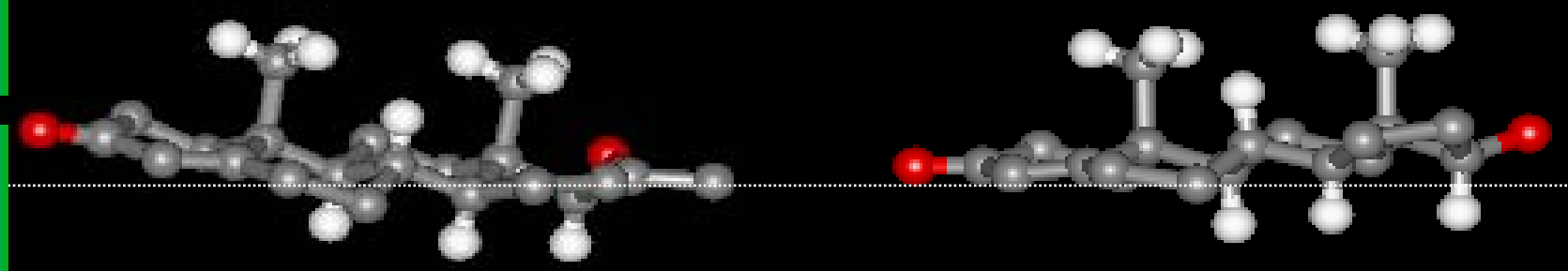
testosterona

Seletividade do Biorreceptor



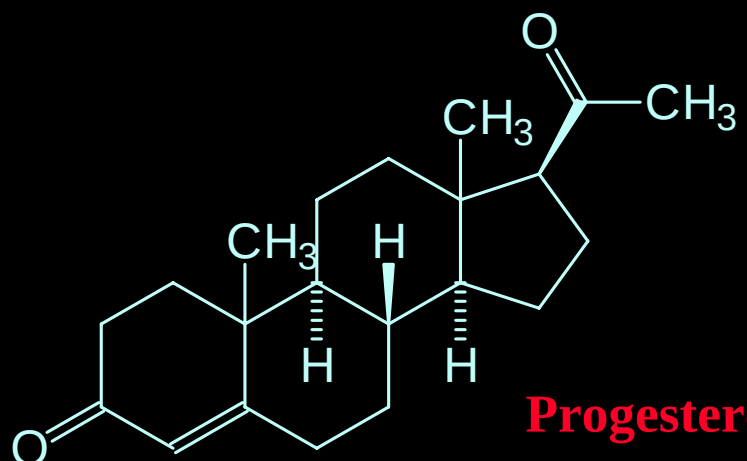
progesterona

Similaridade & Dissimilaridade Molecular



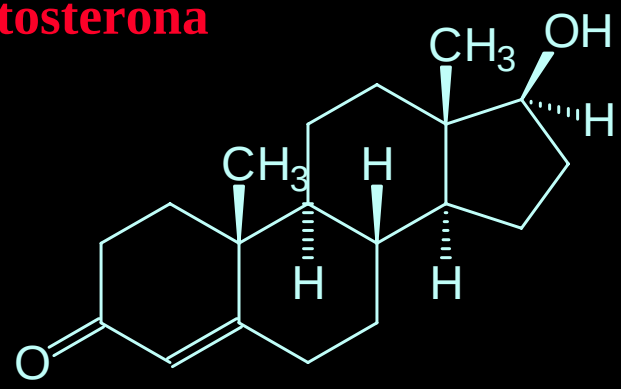
C-17

C-17



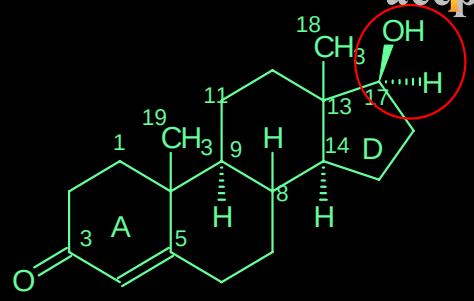
Progesterona

Testosterona

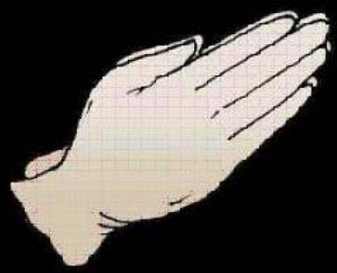


Similaridade & Dissimilaridade Molecular

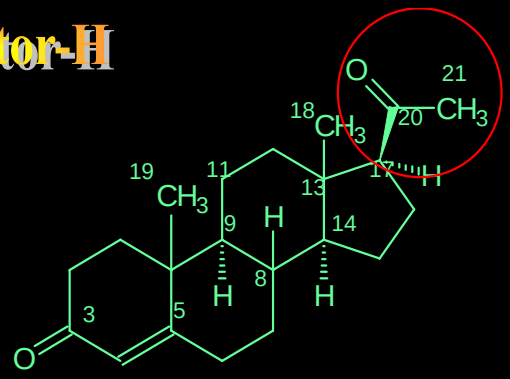
aceptor/doador-H aceptor-H



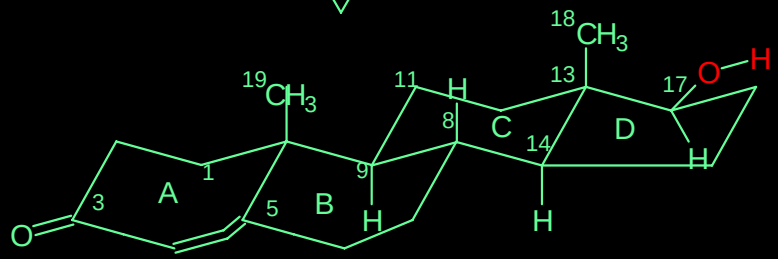
Testosterona



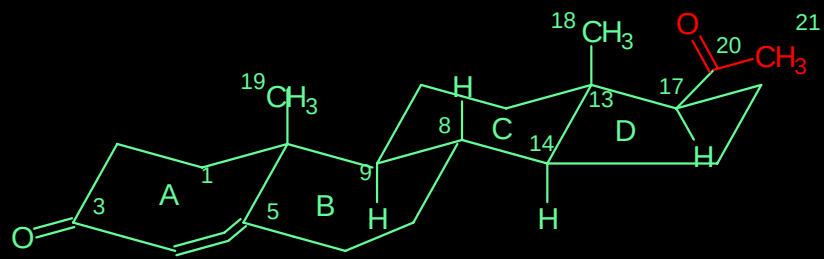
similaridade molecular



Progesterona



B/C C/D trans



B/C C/D trans

5. Planejamento racional de fármacos

O processo da descoberta

A estratégia da abordagem fisiológica

O paradigma do composto-protótipo

Novas estratégias para a descoberta de fármacos

A importância do metabolismo: ADME

Fármacos inteligentes

Estratégias de desenho estrutural:

- A importância do bioisosterismo: análogos & *me-too*
- O processo de hibridação molecular
- O processo de simplificação molecular

6. Considerações finais

O processo de descoberta...

A Estratégia da Abordagem Fisiológica

identificação, eleição do alvo-terapêutico;

comprovação do conceito terapêutico;

produtos naturais: vegetais, fungos, marinhos sintéticos, peptídeos, química combinatória

Química Medicinal

Abordagem Fisiológica

literatura, patentes, fármacos antigos me-too

screening

Ciclo interativo hierárquico

estrutura-protótipo

Principal paradigma

Composto-protótipo

original ativo p.o.

lead compound

Química Medicinal

Composto-Protótipo

Um composto que exibe propriedades farmacológicas que comprovam seu valor como ponto de partida para desenvolvimento de um fármaco.

in vivo

Lead Optimization

Otimização

Processo de modificação molecular planejada do composto-protótipo, visando maximizar suas propriedades farmacológicas.

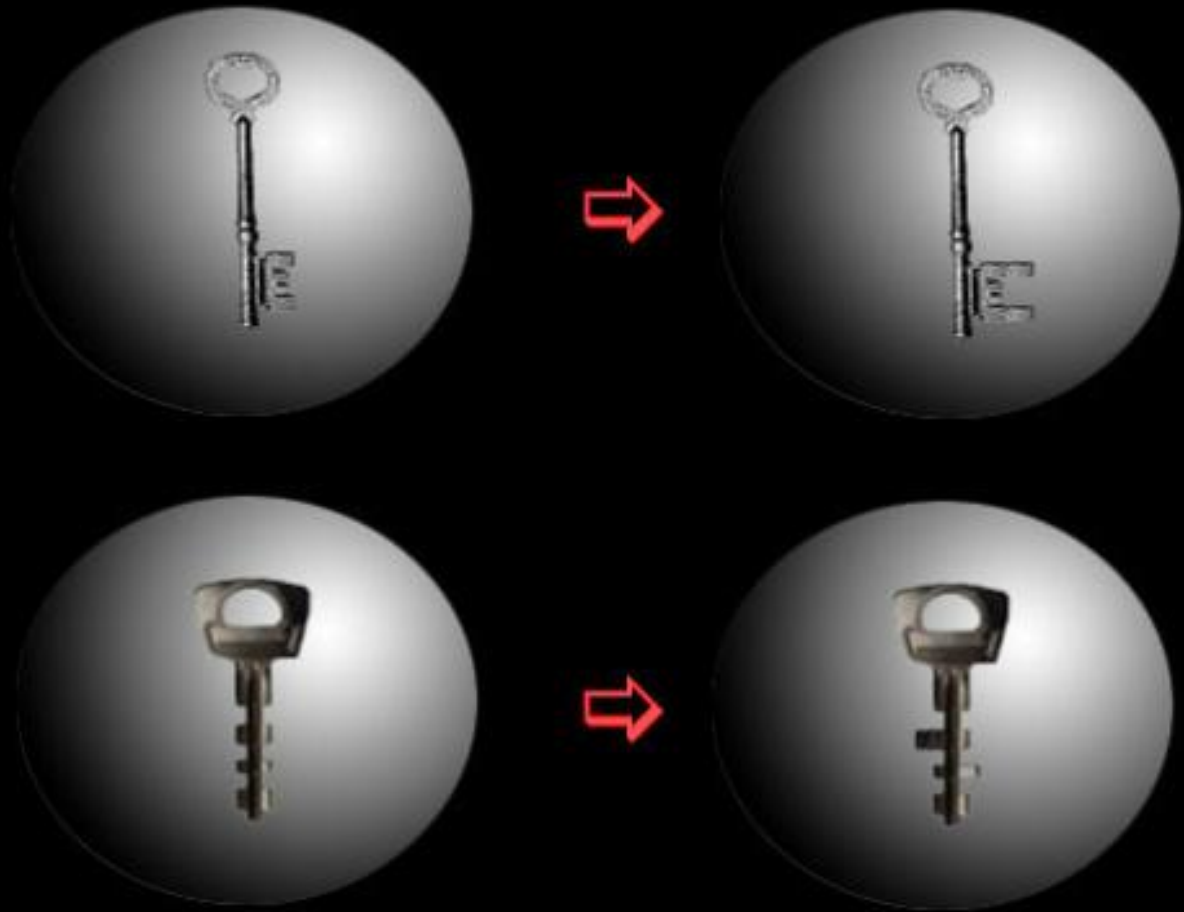
Composto-protótipo

“ O composto-protótipo é o primeiro derivado puro, identificado em uma série congênere de novas substâncias, bioensaiado em modelos animais padronizados, relacionados à patologia a ser tratada.”

Lead generation

is the term applied to strategies developed to identify compounds which possess a desired but non-optimized biological activity

Otimização do Composto-protótipo



Lead Optimization

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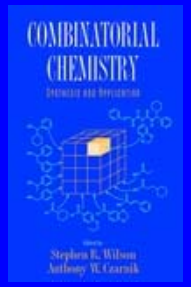
Seleção de Novos Candidatos a Fármacos

Modelo antigo



Um químico
Um robô
Um computador
Uma semana
10000 moléculas

Um químico
Uma semana
Uma molécula

Modelo moderno

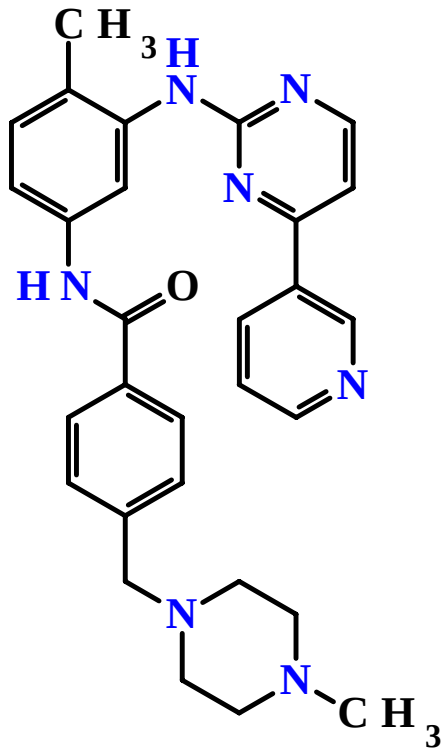
hit

bioligante

Química Combinatorial

A escolha do alvo-terapêutico

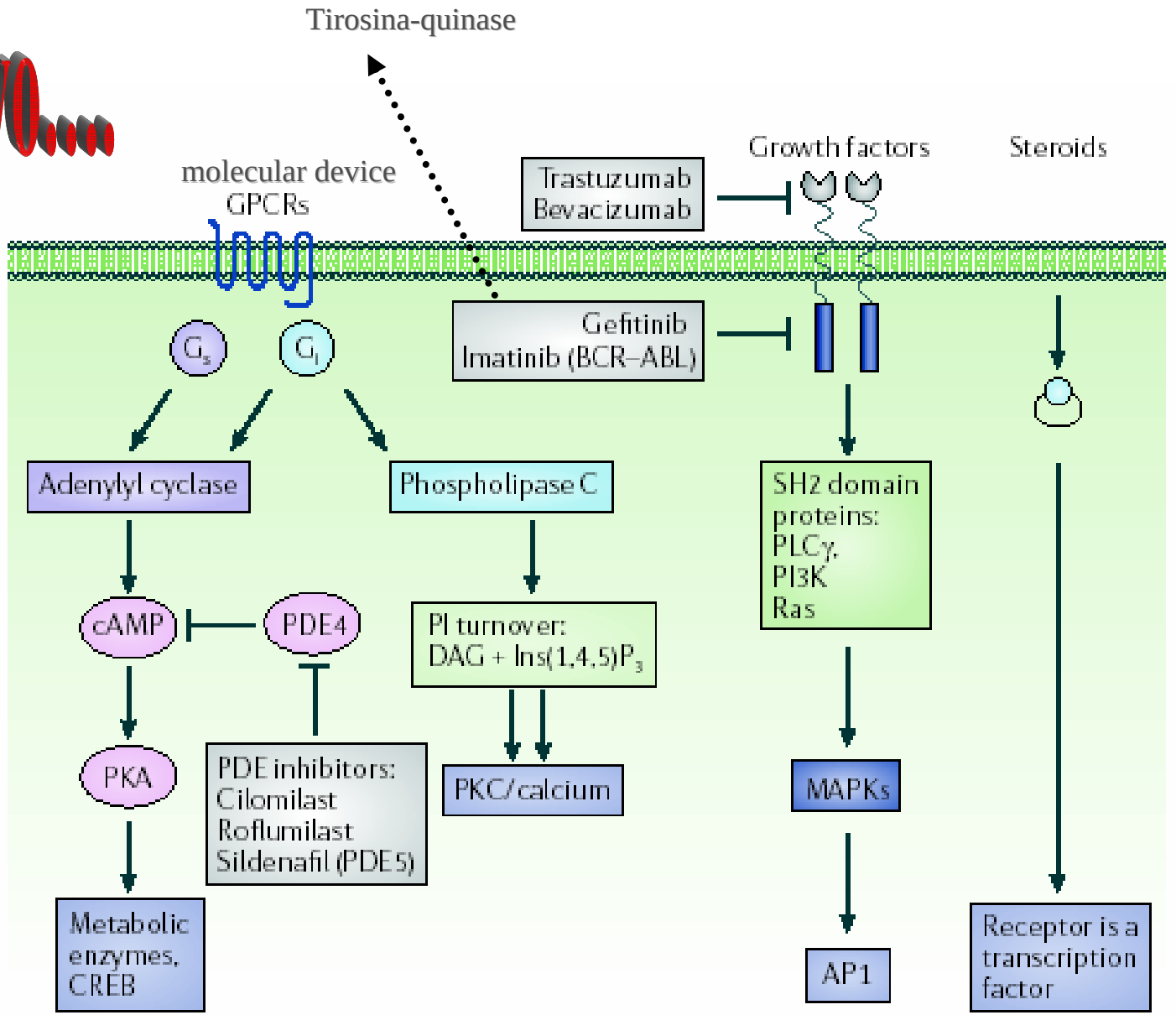
A descoberta do imatinib



$C_{29}H_{31}N_7O$

leucemia mielóide crônica:
deformação adquirida que modifica o DNA de células da medula.

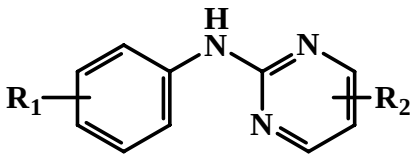
O alvo...



Contribuição do HTS: Gênese do Imatinib (Glivec^{R}, STI571)

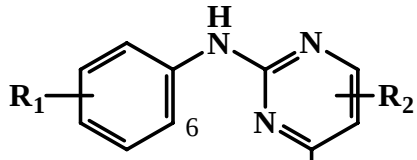
diarilaminas ⟶ *N*-pirimidilanilina → **hit**

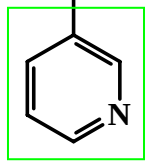
screening para inibidors de PKC
S. Teague, 1999



estrutura privilegiada

quinase-inibidor



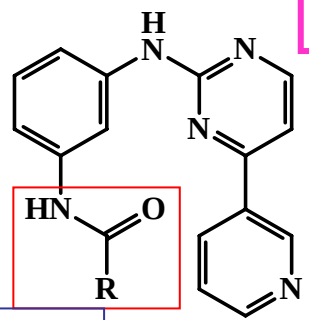


PKC-inibidor

introdução de sub-unidade 3'-pirimidil aumentava a atividade PKC-i (*in vitro*)

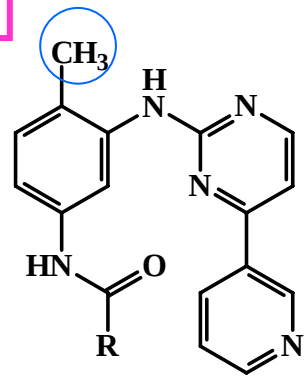
introdução de substituinte metila em C-6 reduzia a atividade PKC-i (*in vitro*)

hit ⟶ **lead**



PKC/bcr-K inibidor

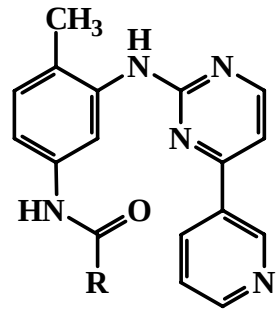
Quando R_1 = unidade alquilamida >> atividade PKC-I (*in vitro*)



bcr-K inibidor

otimização

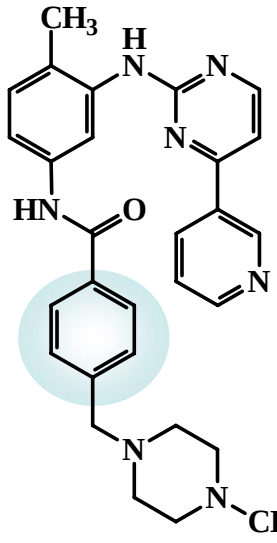
introdução grupamento *peri*-metila < atividade PKCi >> tirosina-quinase



bcr-K inibidor

$C_{17}H_{14}N_5OR$

otimização



$C_{29}H_{31}N_7O$

imatinib

2002

Gleevec

Novartis

GLIVEC (STI571, IMATINIB)

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

Maio de 2001 o FDA aprova imatinib (Glivec^R) para leucemia mielar crônica

NATURE REVIEWS | DRUG DISCOVERY VOLUME 1 | 2002 | 493

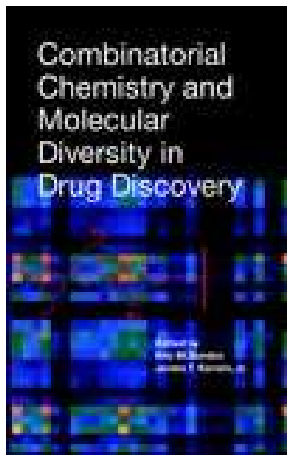
Novos Hits-Leads identificados por (S)HT-Screening*

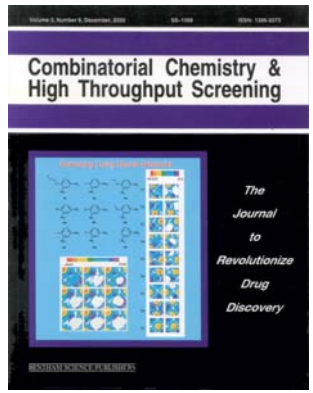
	1996	1999	2003	2004
Compostos bioensaiados	100000	430000	615000	1050000
Média da potencia (nM)	3000	400	10	10
Média de sucesso	20%	50%	58%	65%
Protótipos identificados por alvo-ensaiado	1,0	1,7	1,9	2,0

*Dados da GlaxoSmithKline

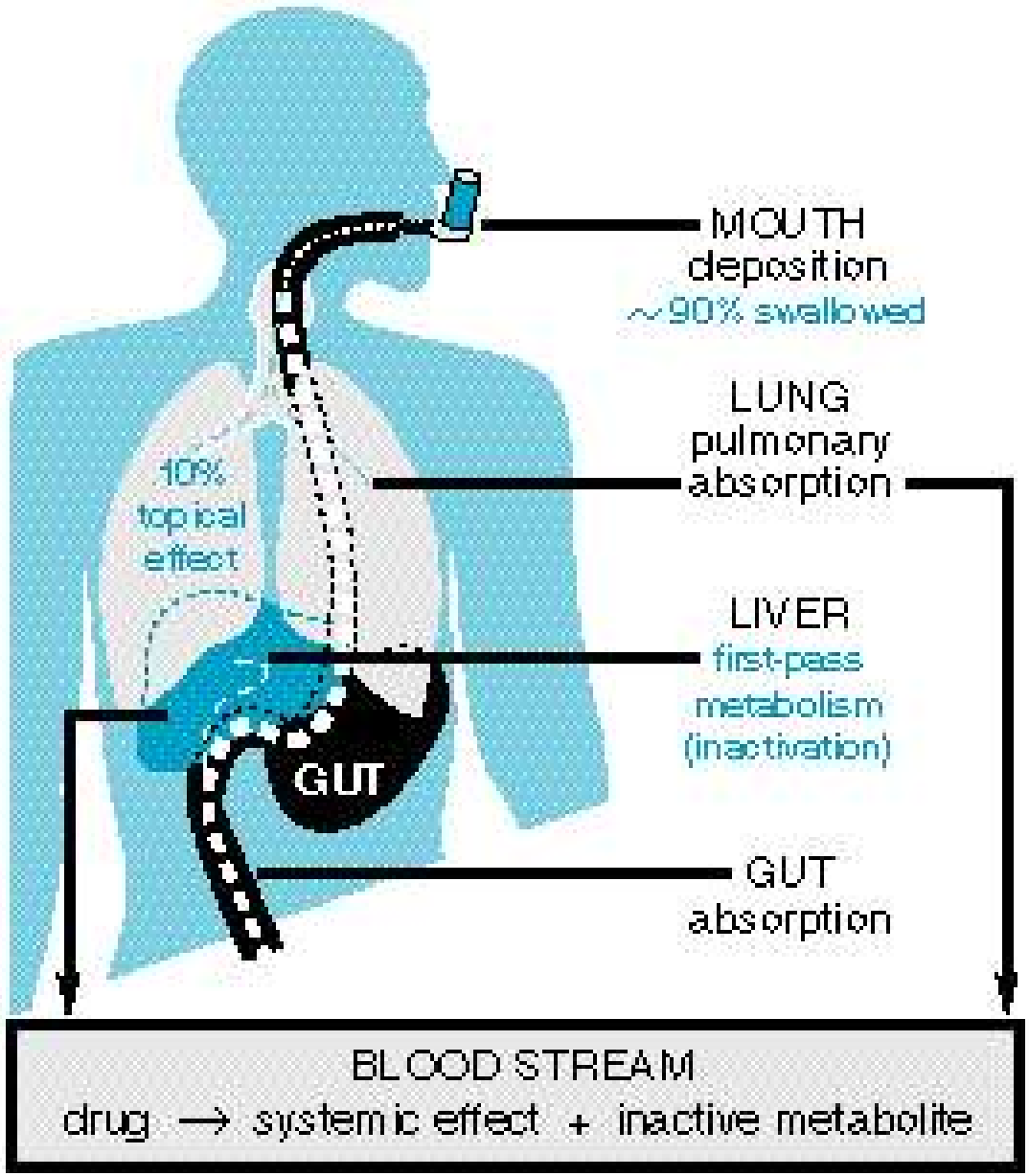
R Mullin, C&EN 2004, 82 (#30, 26 de julho) 23.

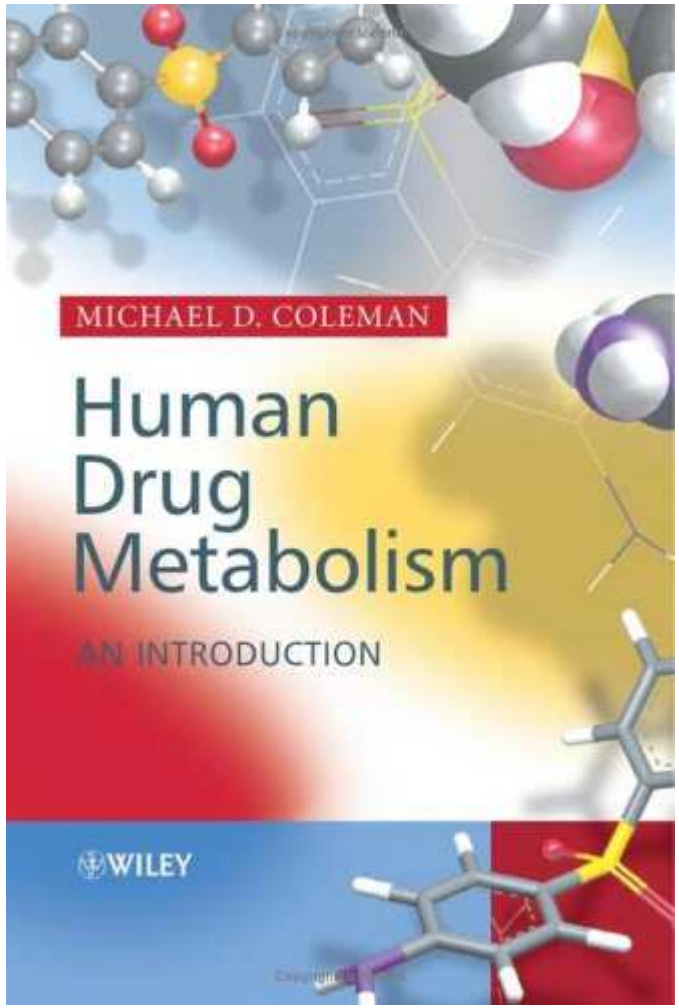
Drug Discovery & Molecular diversity





ADME





Biofase

Absorção

pH

Concentração

Meia-vida

Posologia

Complexação plasmática

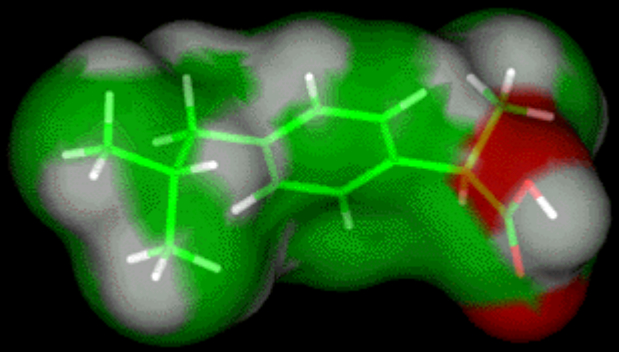
Deposito tissular

Metabolismo

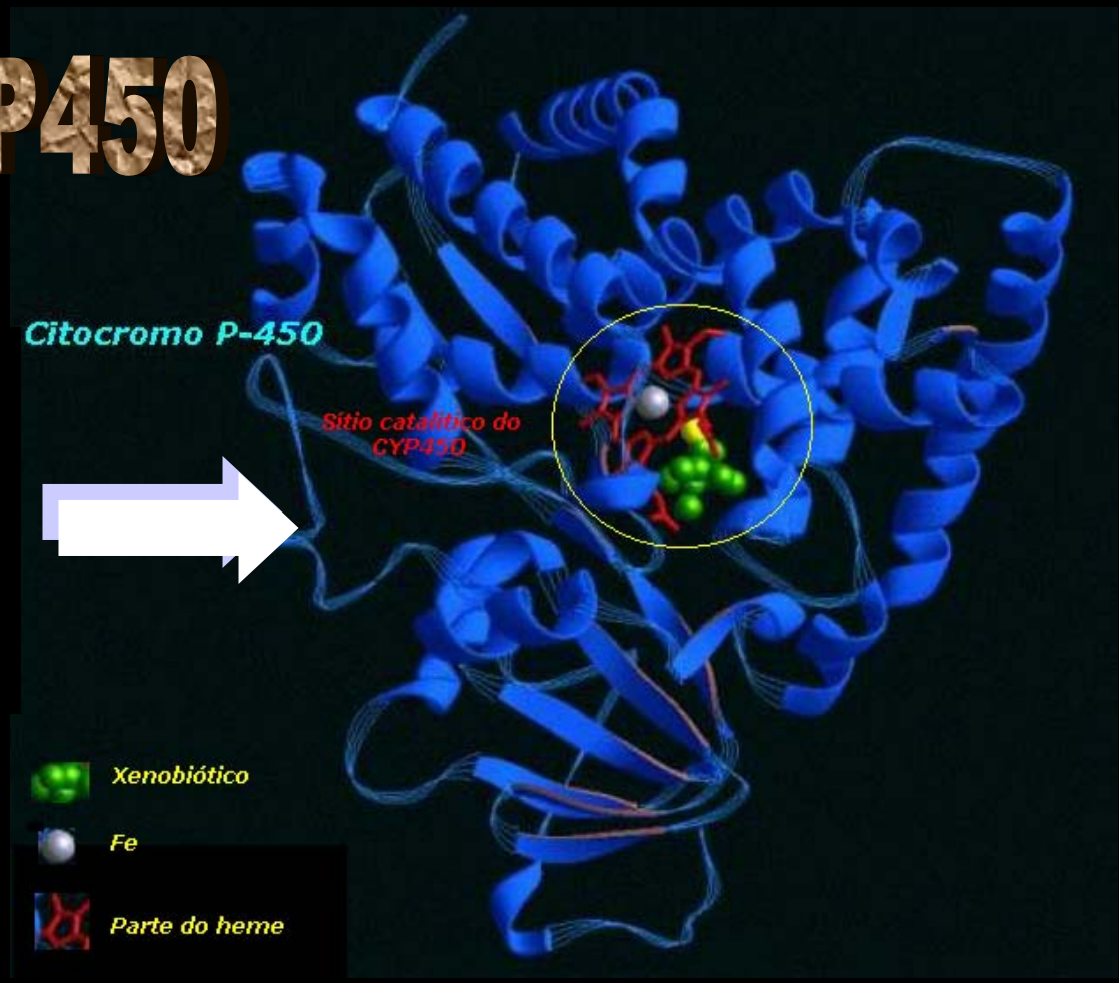
Eliminação

Enzimas oxidativas: fase 1

Citocromo P450



Fármaco



Retículo microssomal hepático

FÁRMACO PA + V + C

Fase farmacêutica

FORMULAÇÃO

Eliminação *renal*

excreção

Bile, fezes, pulmão

Biofase

Agente depositário

Bioinativação

tóxico

Complexo tissular

Bioativação

Distribuição

Hepática, plasmática, entérica

Absorção

Metabolismo

DR

ET

Polimorfismo, idade, raça

PQF

P
pKa
D

Complexo plasmático

Indução enzimática

IT

Agente de deslocamento

Afinidade
Potência
Eficácia
Sinergismo

Vida-média

Fase farmacocinética (ADME)

Fase farmacodinâmica

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6. Considerações finais

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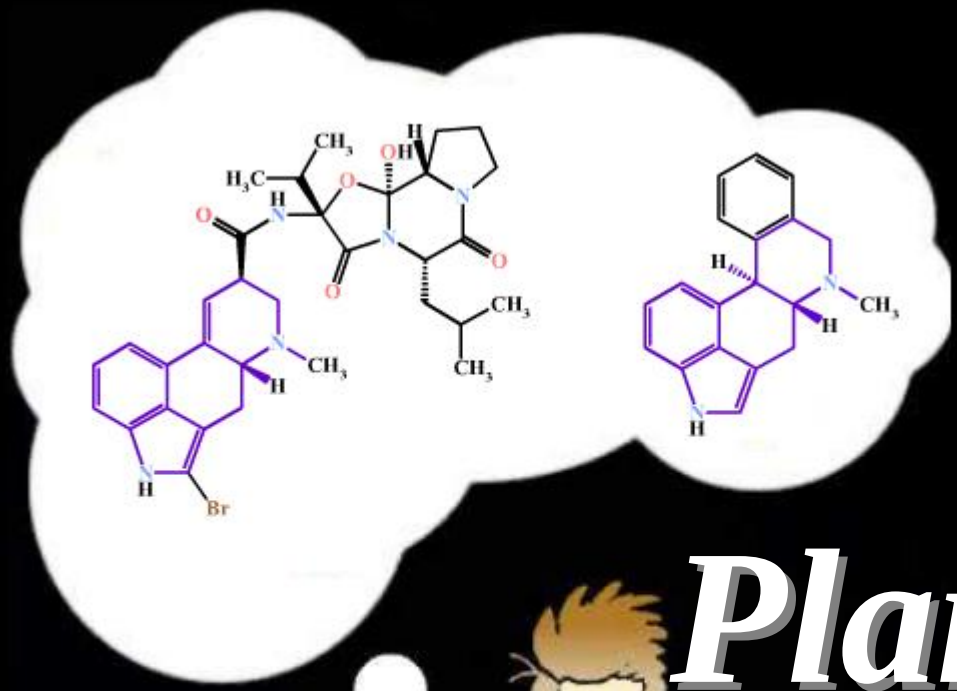
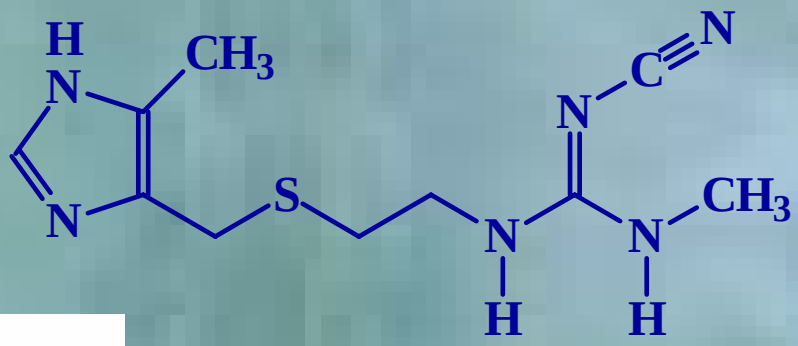
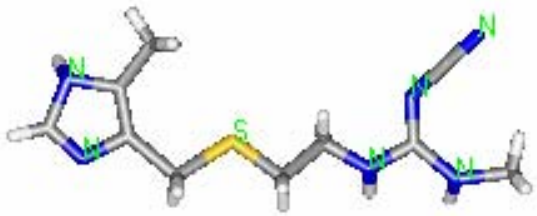


Planejamento racional

Cimetidina

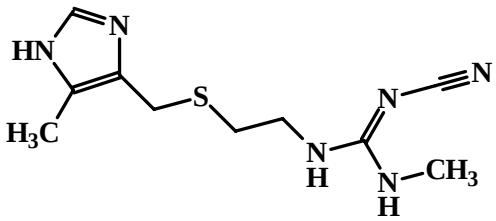
Inovação terapêutica





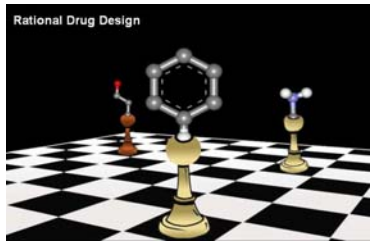
cimetidina

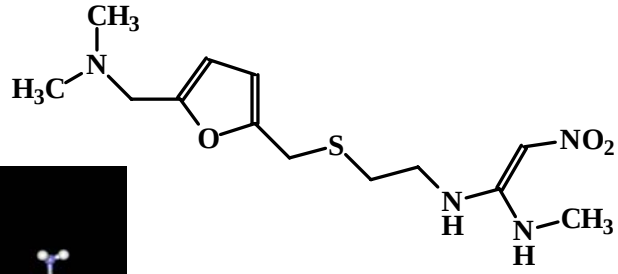
Os descobridores da cimetidina: Ganellim, Emmet, Durant & Black, da esquerda para a direita,



cimetidina

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





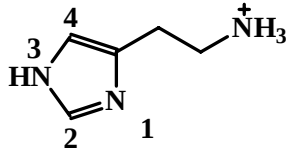
ranetidina

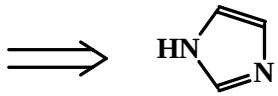
$C_{13}H_{22}N_4O_3S$
314.40

A gênese da cimetidina

A procura do protótipo:

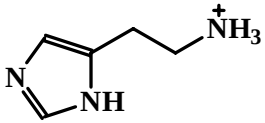
antagonista H-2





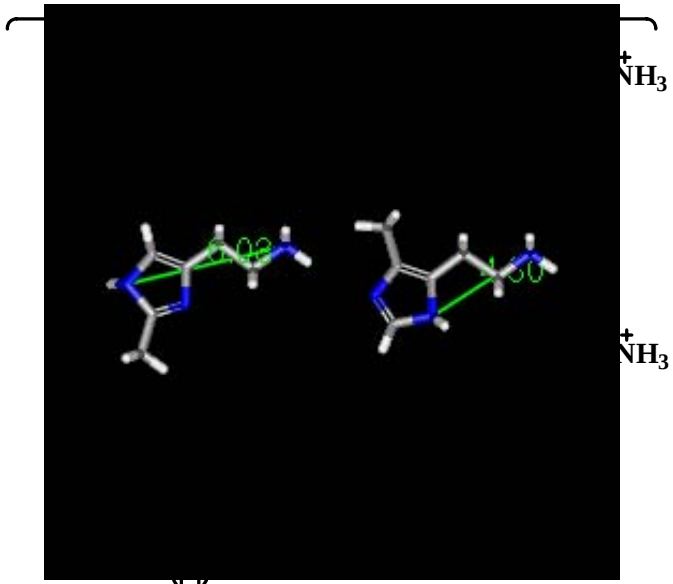
imidazola

tautômeros

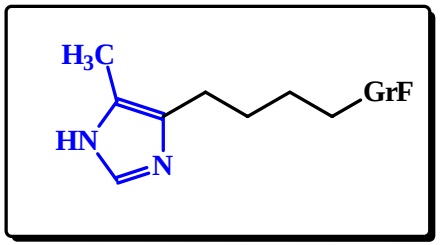


4-Cl, 4-Br, 4-NO_2

metil-histaminas

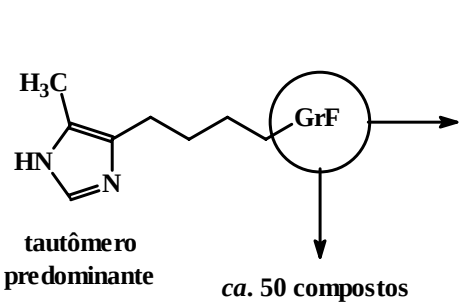


metil-alquil-imidazola



Ar = arila, heteroarila
GrF = grupamento funcional

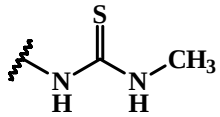
A gênese da cimetidina



tautômero predominante

ca. 50 compostos

N-metil-tiouréia

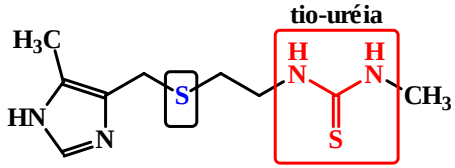


burimamida

ant/agonista & CYP450

bioisosterismo clássico

$CH_2 \rightarrow S$



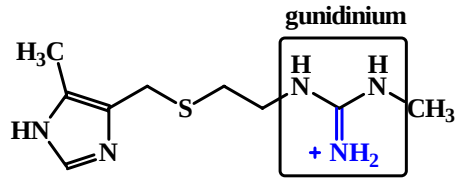
tio-uréia

metiamida

Ensaiada em 700 pacientes com úlcera duodenal

ant. seletividade H-2 & <<CYP450, p.o. ⇒ ensaios clínicos granulocitopenia

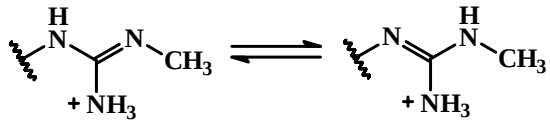
bioisosterismo clássico



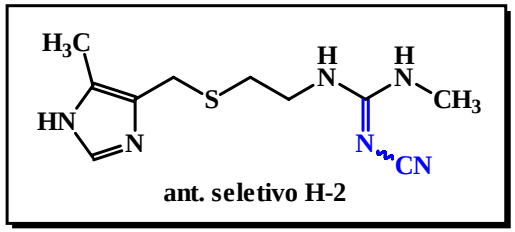
gunidinium

SK&F 92408
ant. seletivo H-2
ID_{50} 12 μM/kg

imino ⇌ amino



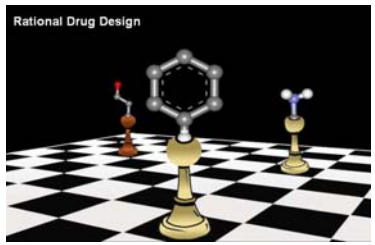
bioisosterismo



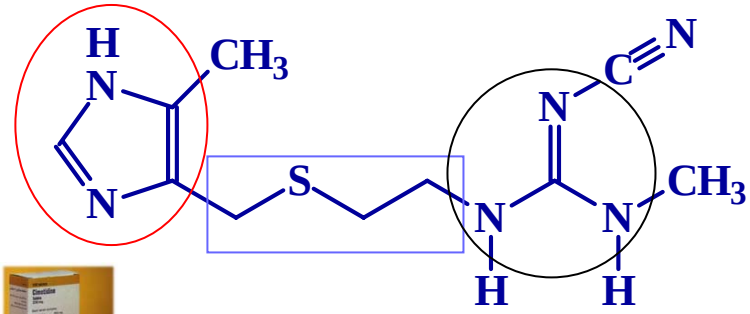
ant. seletivo H-2

Cimetidina

ID_{50} 1,4 μM/kg

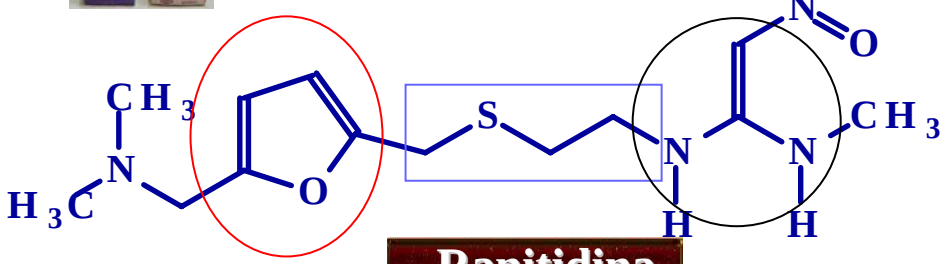


JW Black, WHM Duncan, CJ Durant, CR Ganellin & EM Parsons, Definition and Antagonism of Histamine H2-receptors, *Nature* 1972, **236**, 385; CR Ganellin, *Drug Discovery & Development* 2006 **1**, 295.



Cimetidina

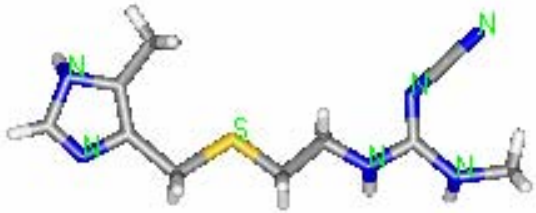
Robin Ganellin *et al.*, 1974
US 3950333 1974, 1976 - SK&F
Brit. J. Pharmacol. **53,** 435 (1975).



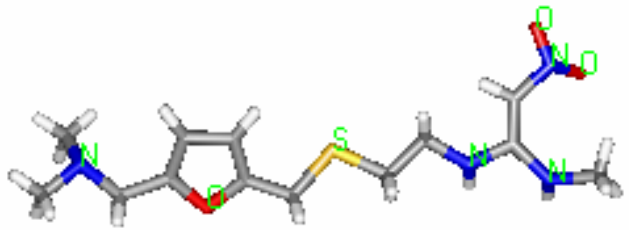
Ranitidina

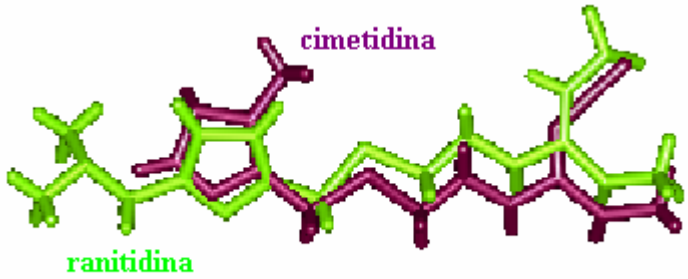
Barry J. Price *et al.*, 1978
US 4128658 1978 - Allen & Hanburys
Brit. J. Pharmacol. **66,** 464 (1979)

similaridade molecular



me-too





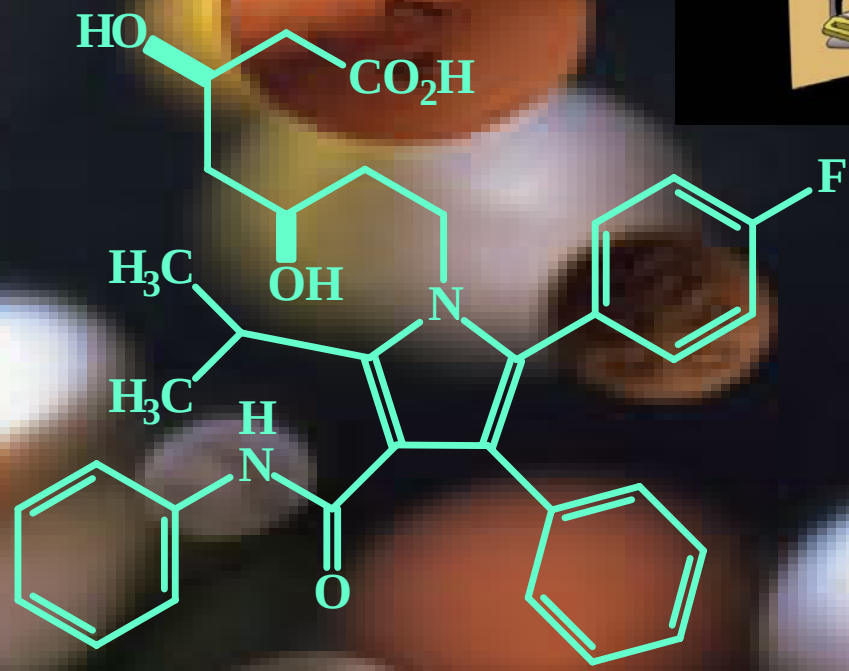
Tagamet= "anTAGonist" + "ciMETidine?"

Fármacos Inteligentes

Super -Super Drug

otimização de protótipo natural

* A. M. Thayer, CE&N, Nov. 12, 2002



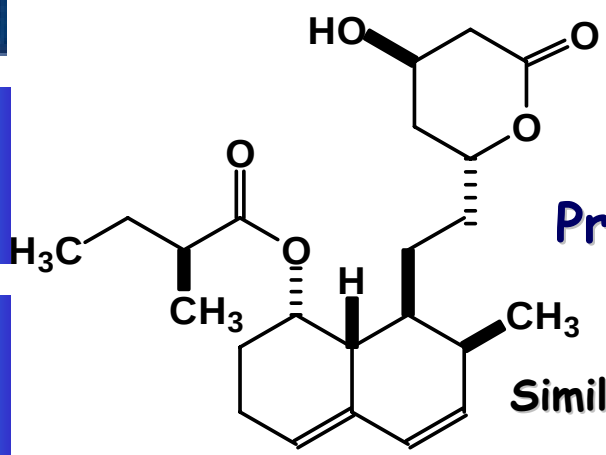
atorvastatina

Pfizer

http://pubs.acs.org/cen/coverstory/83/8325/index.html

Super-fármaco

* A. M. Thayer, CE&N, Nov. 12, 2002



Protótipo natural

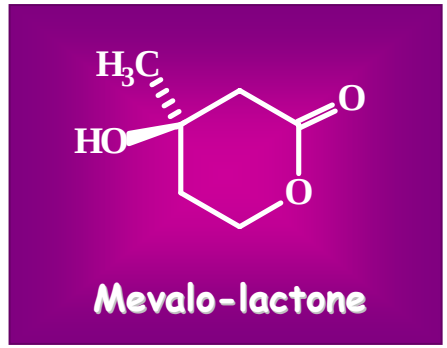
Similari r

1975 - Compactina

A. Endo, J. Antibiot. 1979, 32, 852

Monascus ruber

A.Endo, *J. Med. Chem.* 1985, *28*, 01



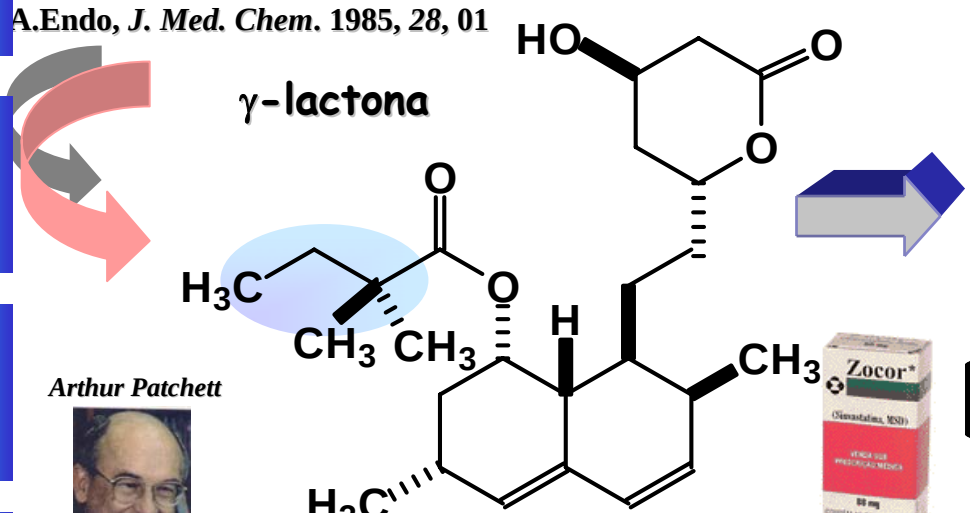
HMG-CoA reductase

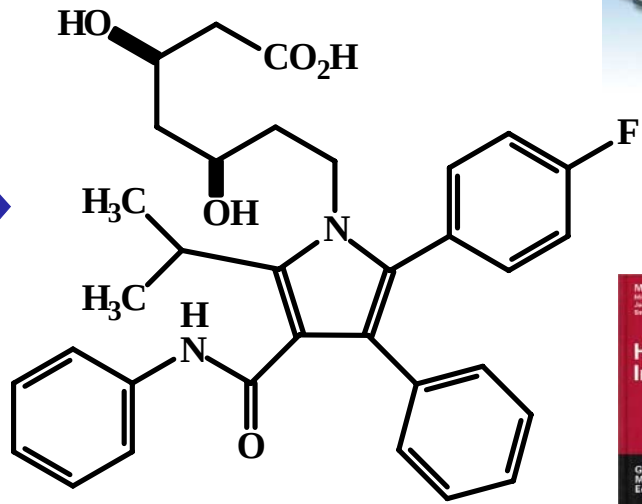
ácido pirrol-heptanóico

Pfizer

Bruce Roth

γ-lactona





Arthur Patchett

Simvastatin

(Zocor)

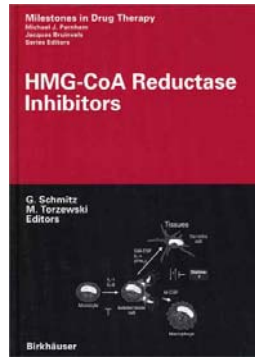
MK-733

1981

MERCK

atorvastatina

$C_{33}H_{35}FN_2O_5$

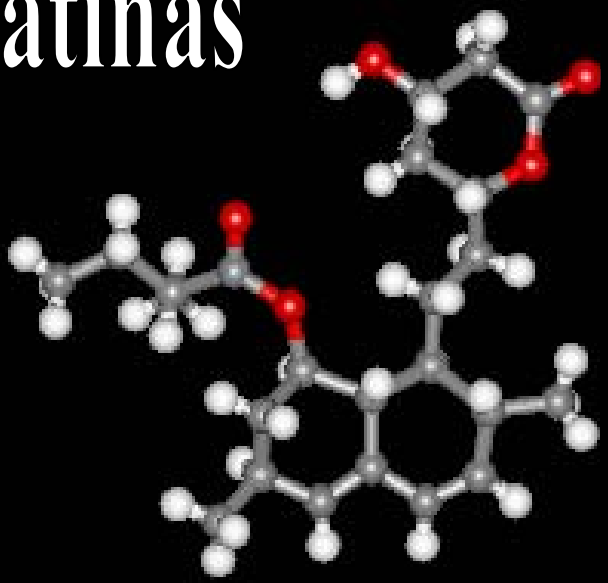


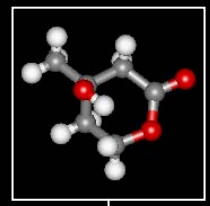
J. Med. Chem. 1986, *29*, 849

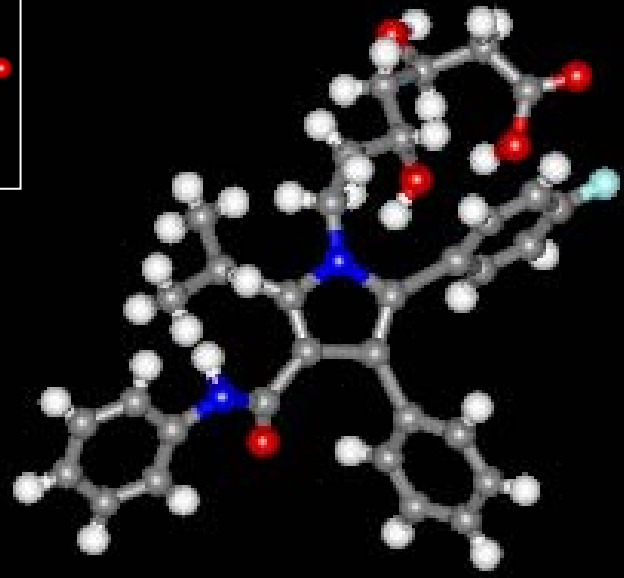
J. Med. Chem. 2002,45, 5609

Estatinas

farmacóforo

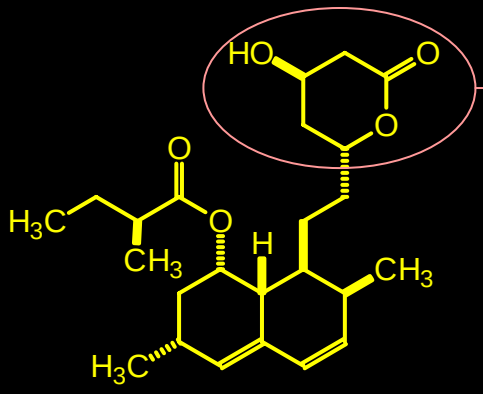


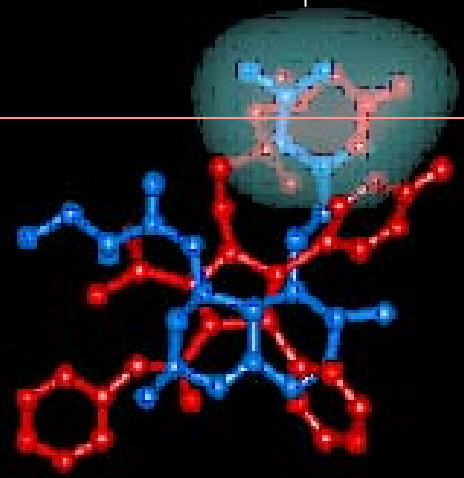




compactina

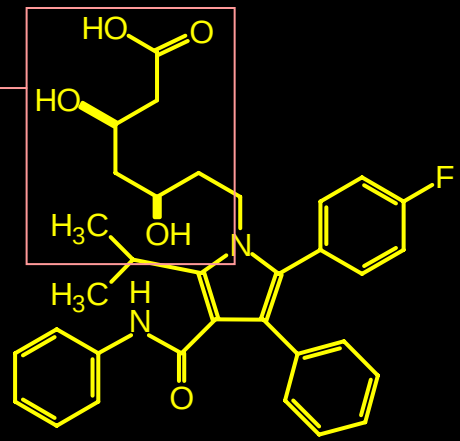
$C_{24}H_{36}O_5$





atorvastatina

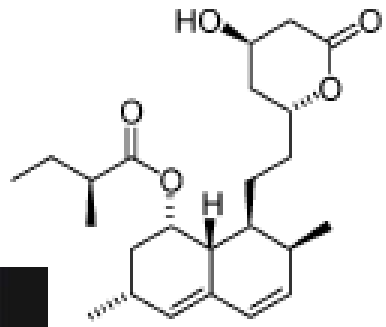
$C_{33}H_{35}FN_2O_5$



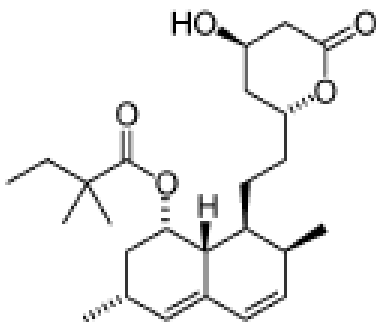
Sobreposição da compactina (azul) com a atorvastatina (vermelho)

Lipitor, king of the me-toos

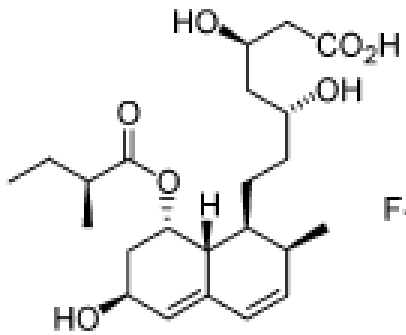
Me-too



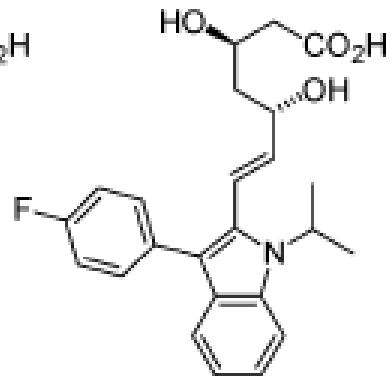
Lovastatin (15)
(Mevacor®)



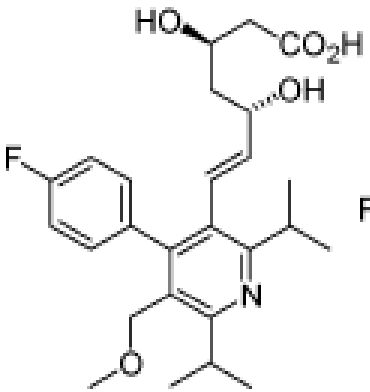
Simvastatin
(Zocor®)



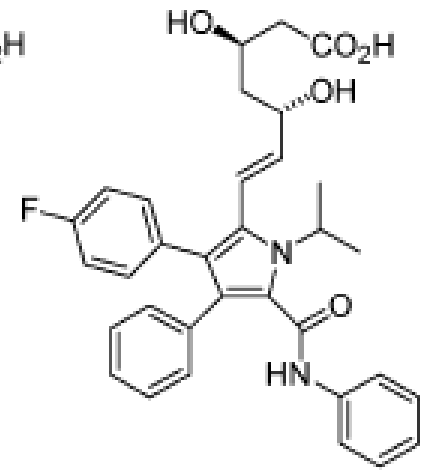
Pravastatin
(Pravachol®)



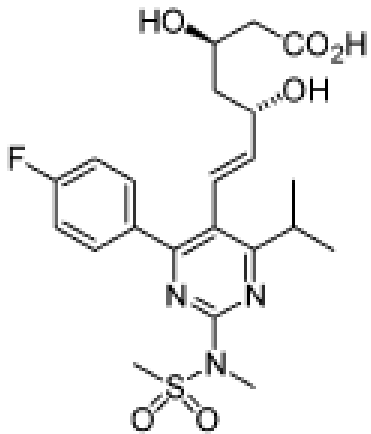
Fluvastatin
(Lescol®)



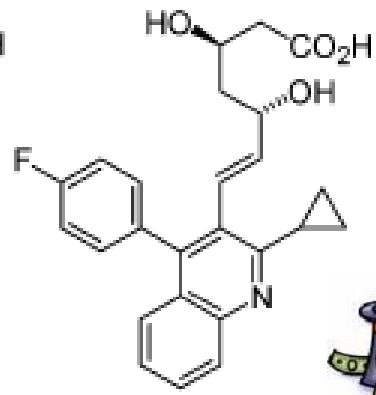
Cerivastatin
(Baycol®)
Note: removed from market



Atorvastatin
(Lipitor®)



Rosuvastatin (36)
(Crestor®)

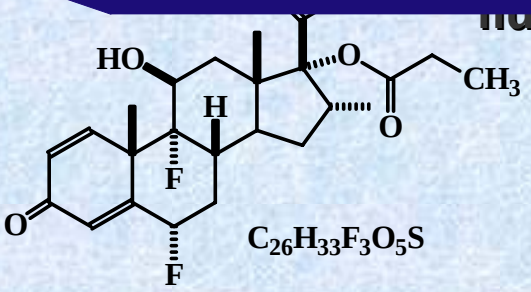


Pitavastatin (37)
(Livalo®)

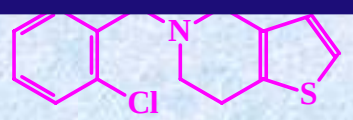
Os *top*-5 fármacos no mercado mundial

Características estruturais comuns aos cinco medicamentos mais vendidos no mundo em 2006:

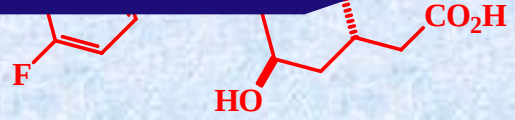
- Possuem apenas 7 elementos químicos: C,H,O,N,S,F,Cl;
- Todos possuem heteroátomos;
- Todos são multicíclicos (< cinco anéis);
- 90% têm unidades aromáticas;
- 80% são heterocíclicos;
- 03 podem ser considerados me-too;
- 01 representa uma inovação incremental;
- pertencem a 03 categorias terapêuticas;



$C_{26}H_{33}F_3O_5S$



$C_{16}H_{16}ClNO_2S$



$C_{33}H_{35}FN_2O_5$

atorvastatina

Fonte: J. Grimley (IMS), C&EN 2006, Dec. 04, **84**, 49

http://pubs.acs.org/cen/coverstory/84/8449.html

Química Medicinal

Um composto protótipo ainda não é um fármaco

Um composto protótipo é um candidato a fármaco

PROTÓTIPO

Topografia do sítio receptor

Eleição do Alvo-terapêutico

Fisiopatologia do Processo

Modelagem molecular

CALD

CADD

Abordagem Fisiológica

Análogo Ativo

Estratégias de desenho estrutural da Quimica Medicinal

Hibridação molecular

Bioisosterismo

Simplificação molecular

Estratégias de desenho molecular

Bioisosterismo

Current Medicinal Chemistry, 2005, *12*, 23-49

Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design

Lídia Moreira Lima and Eliezer J. Barreiro*

Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro. CCS, Cidade Universitária, CP 68.006, 21944-190, Rio de Janeiro, R.J., Brazil

http://www.bentham.org/cmc/samples/cmc12-1/0002C.pdf

Abstract: This review aim to demonstrate the role of bioisosterism in rational drug design as well as in the molecular modification and optimization process aiming to improve pharmacodynamic and pharmacokinetic properties of lead compounds.

Analogue

(IUPAC recommendation 1998)

„An analogue is a drug whose structure is related to that of another drug but whose chemical and biological properties may be quite different."

Me-too drug

(IUPAC recommendation 1998)

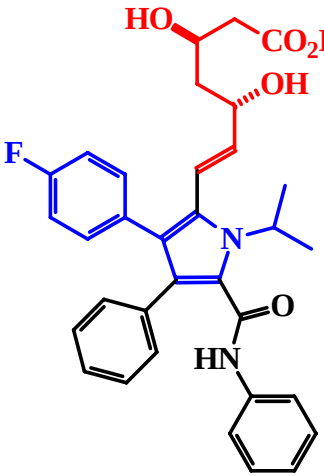
„A me-too drug is a compound that is structurally very similar to already known drugs, with only minor pharmacological differences."

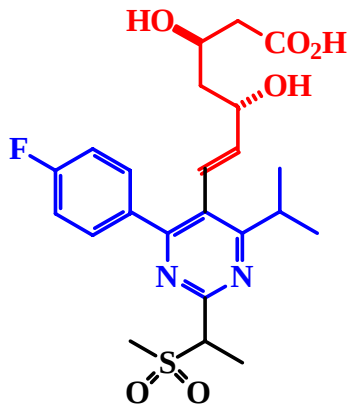
C-G Wermuth, Pure & Applied Chemistry 1998, 70, 1129-1143

A estratégia do *me – too*…

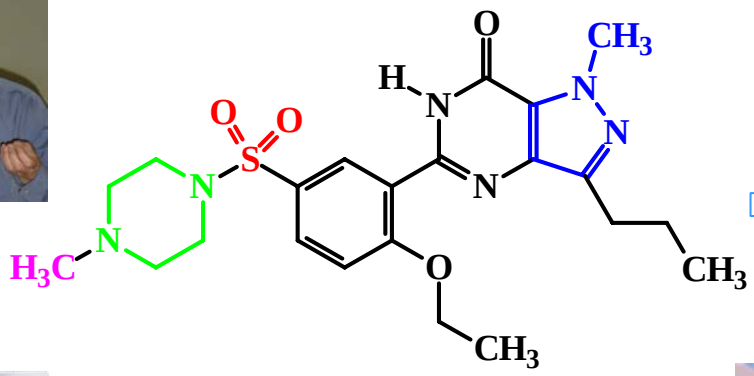
me-too

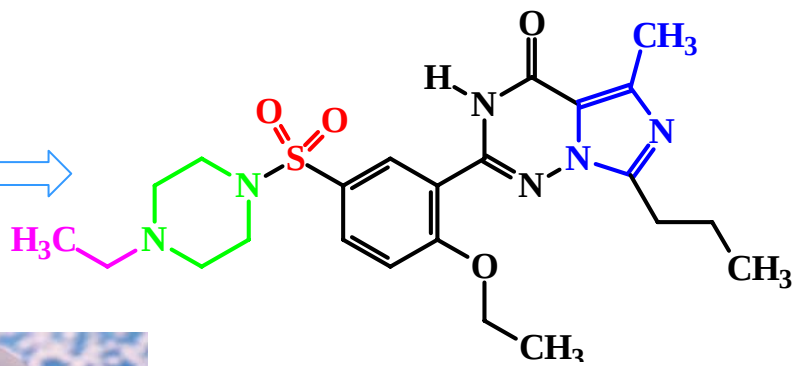
atorvastatina





rosuvastatina





sildenafil

vardenafil

Bayer HealthCare Pharmaceuticals

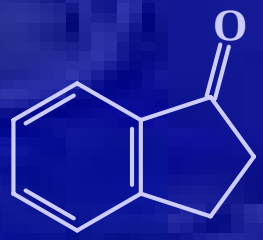
GlaxoSmithKline

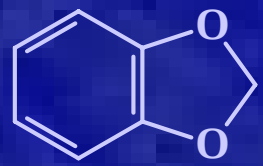
Schering-Plough

Bioisosterismo no LASSBio

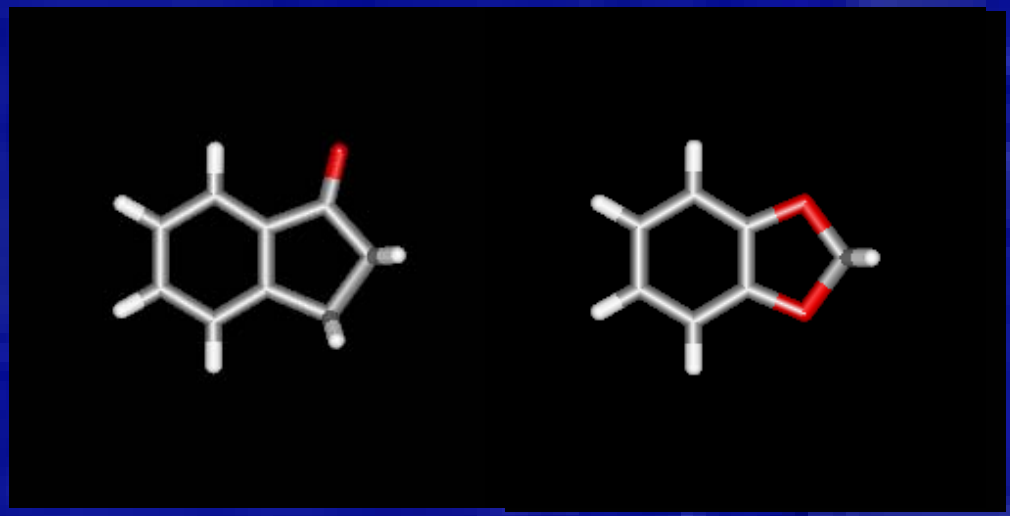
L.M. Lima & E. J. Barreiro, "Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design", *Current Medicinal Chemistry* 2005, 12, 23-49.

Nova Relação Bioisostérica



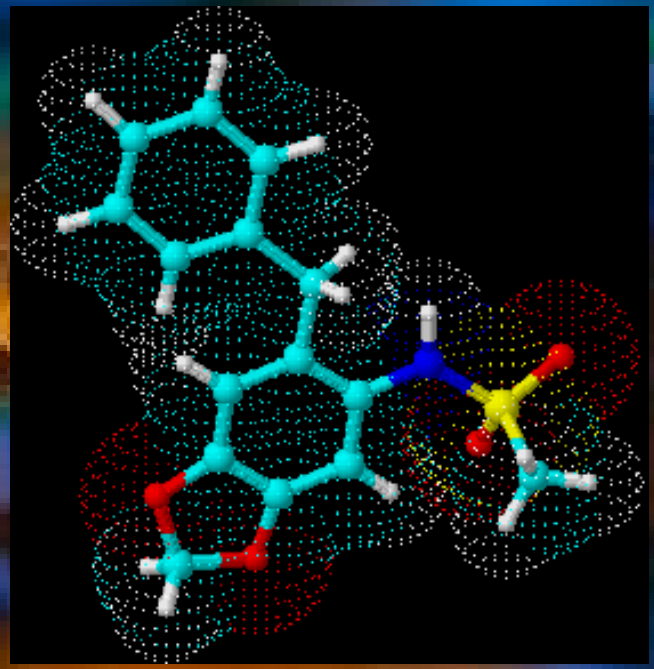


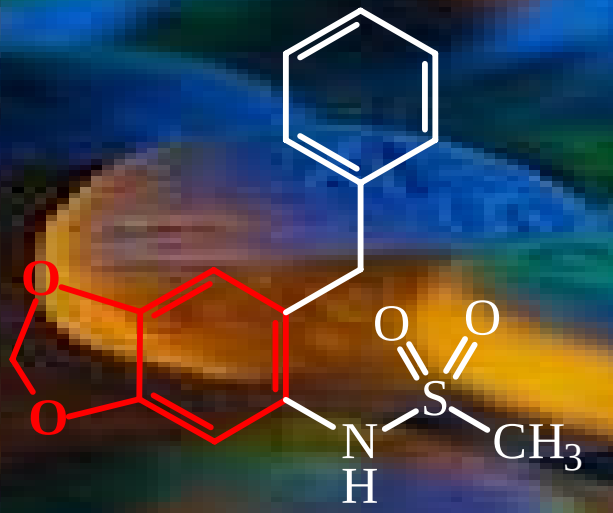
Indanona - Benzodioxola



M. E. F. LIMA & **E. J. BARREIRO**, "The Synthesis and Antiinflammatory Properties of a New Sulindac Analogue Synthesized from Natural Safrole*", J. Pharmaceutical Sciences*, 81, 1219-1222 (1992).

Novos Protótipos de Fármacos Anti-inflamatórios





LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas
medicinal chemistry
Química Medicinal

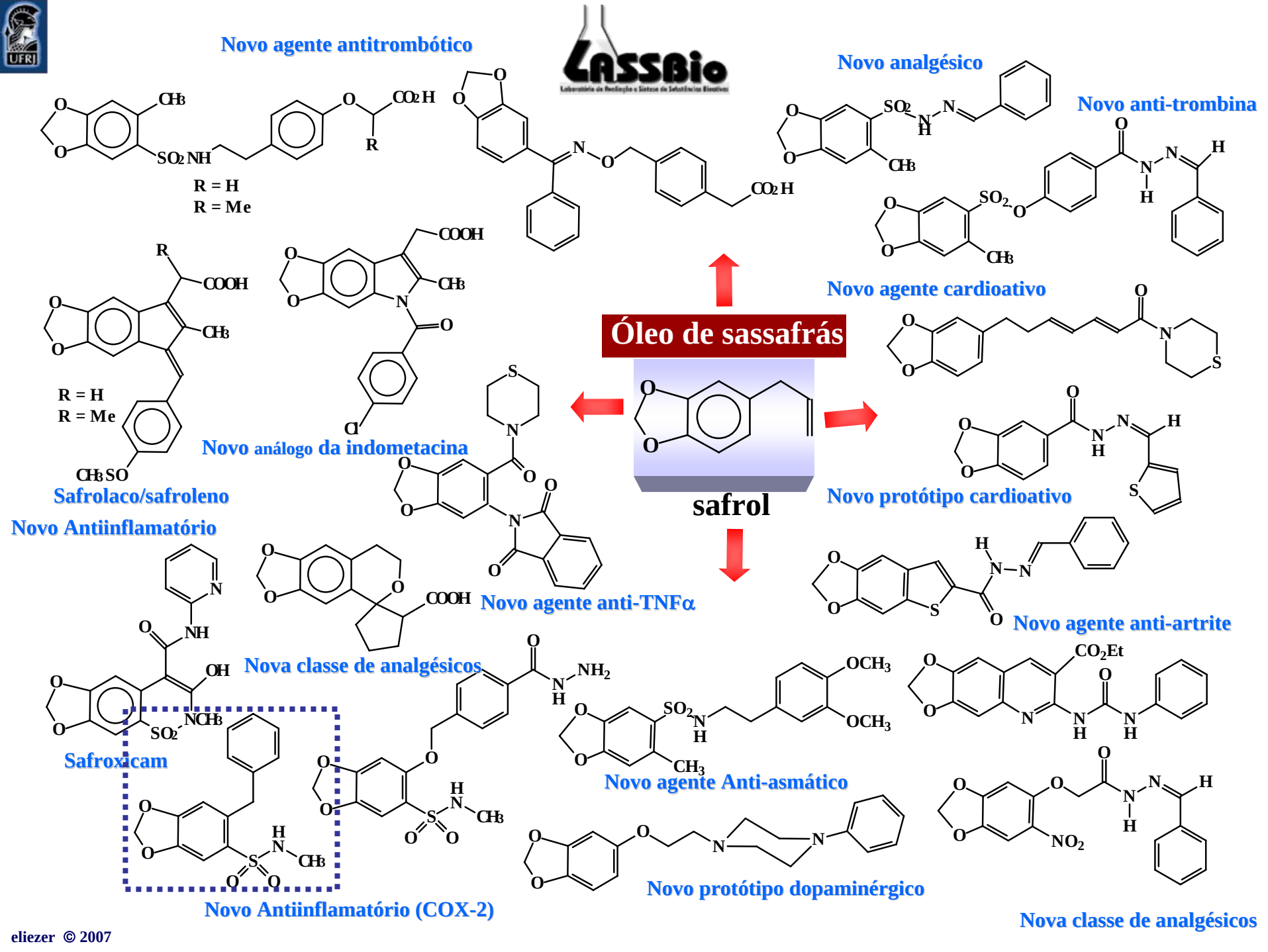
LASSBio-326

LASSBio-257

Eleição do Alvo-terapêutico

Ciclooxigenase (COX)

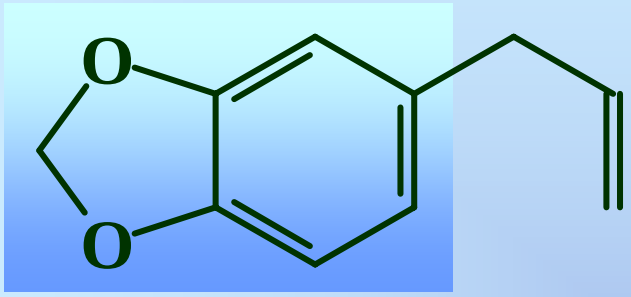
Ácido araquidônico
Icosanóides (PG, TX,)
três isoformas



Oléo de Sassafrás

Produto natural brasileiro abundante

Ocotea sp.



Alil-benzeno

$C_{10}H_{10}O_2$

LASSBio

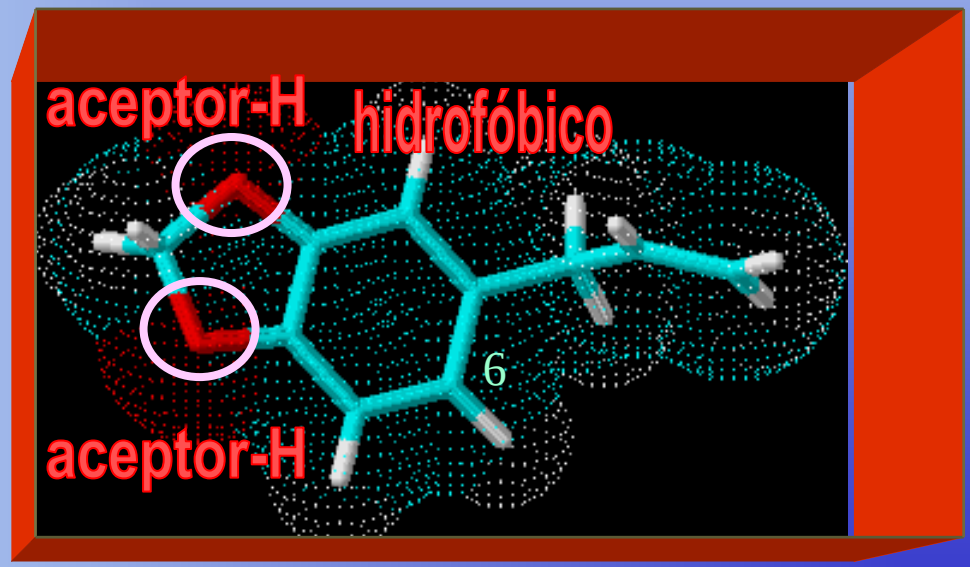
Laboratório de Realização e Síntese de Substâncias Bioativas

Canela Sassafrás

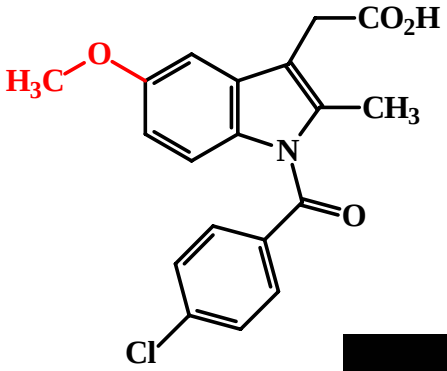
Piper sp

Ocotea pretiosa Mezz

Bióforo Natural



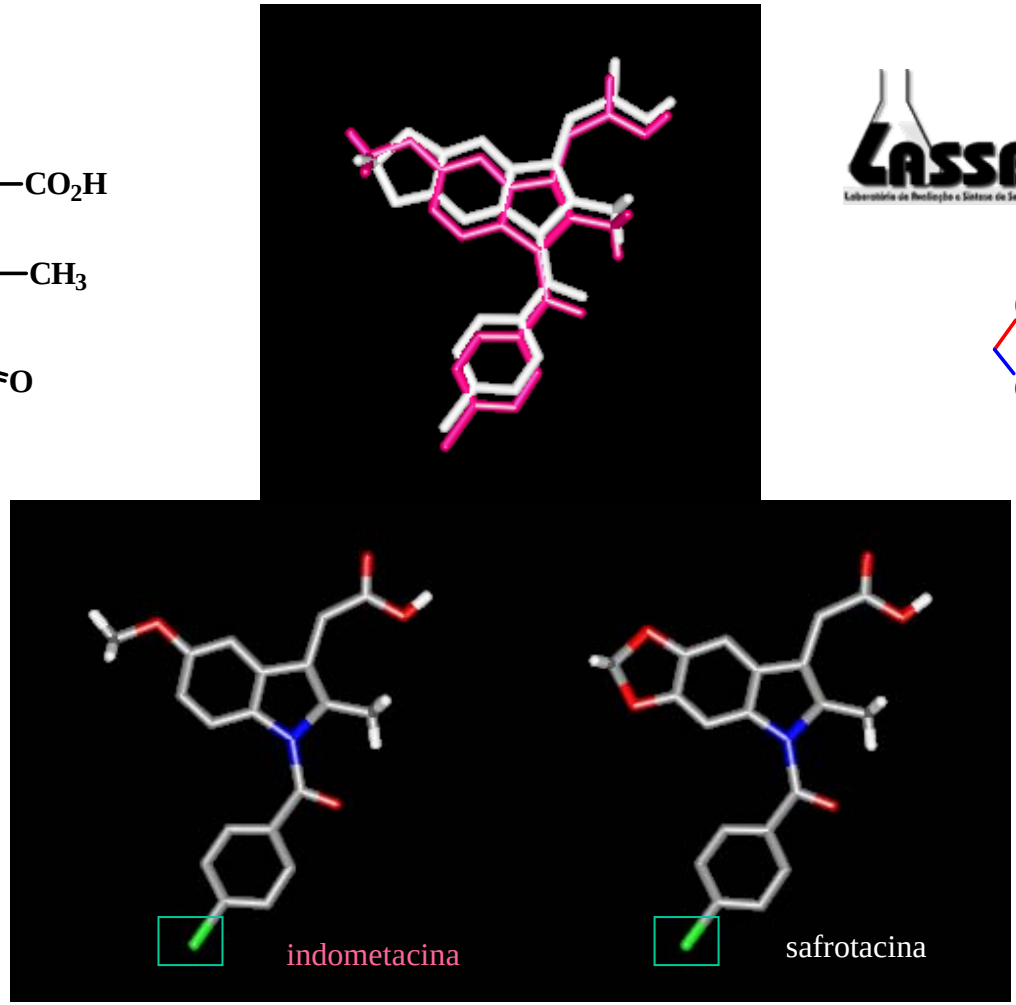
E. J. Barreiro & C. A. M. Fraga, *Química Nova, 22*, 744 (1999).

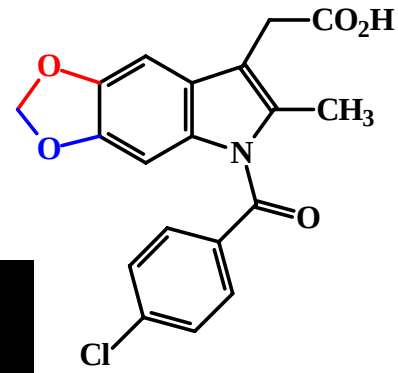


Indometacina

$C_{19}H_{16}ClNO_4$

357.79





Safrotacina

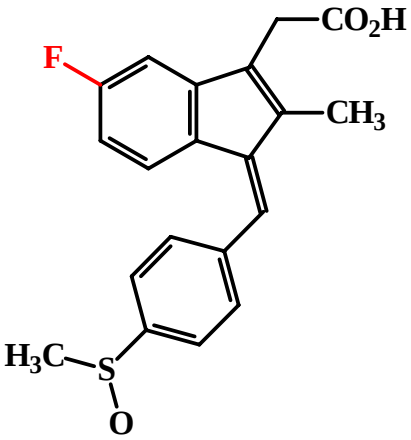
$C_{19}H_{14}ClNO_5$

371.77

T. Y. Shen *et al., J. Am. Chem. Soc.* **85,** 488 (1963);
T. Y. Shen, **US 3161654** (1964 to Merck)

E. J. Barreiro *et al.*, "An Improved Synthesis of Indole Derivatives Related to Indomethacin from Natural Safrole", Journal of Chemical Research (M) 1142-1165, (1982).

Química Nova, 22, 744 (1999)

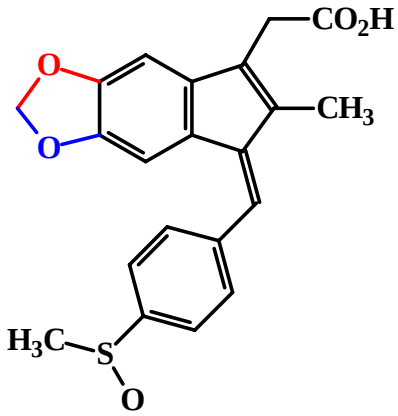


Sulindaco

$C_{20}H_{17}FO_3S$

356.41

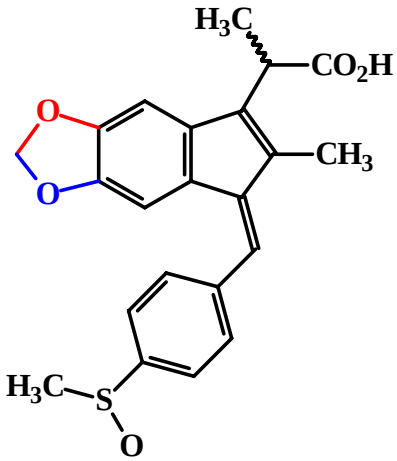
T.-Y. Shen *et al.*, **US 3654349** (1971,1972, Merck)



Safrolaco

$C_{21}H_{18}O_5S$

382.43

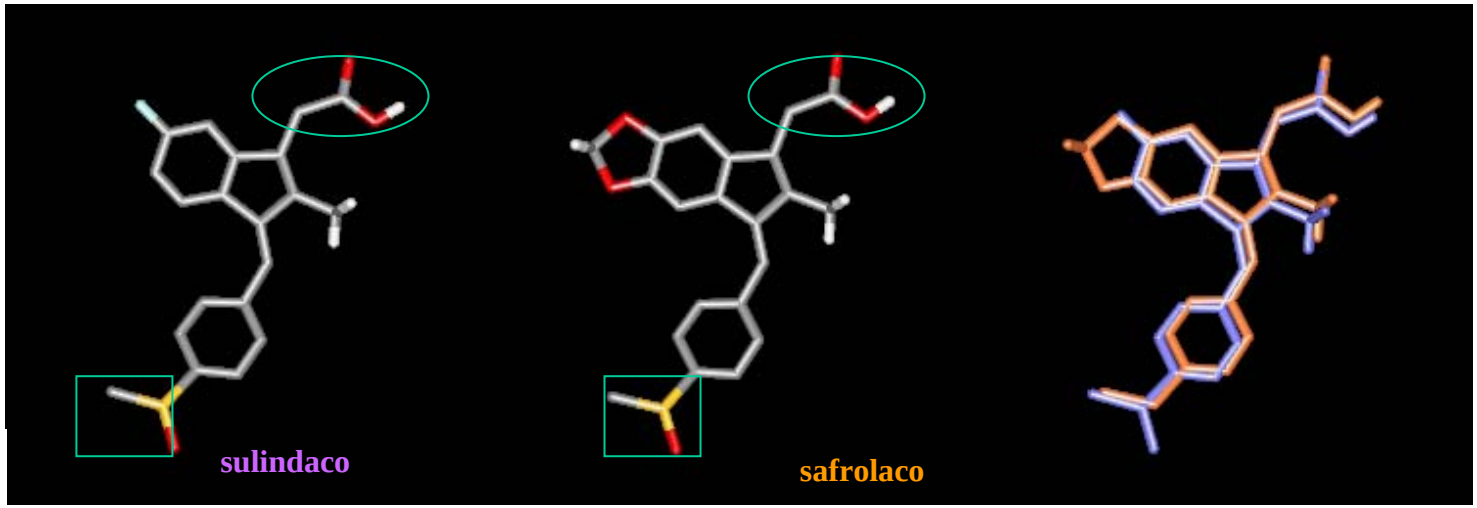


Safroleno

$C_{22}H_{20}O_5S$

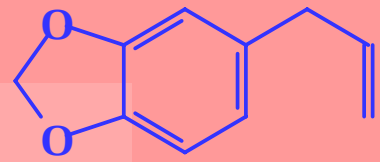
396.45

MEF Lima, EJ Barreiro, "The Synthesis and Antiinflammatory Properties of a New Sulindac Analogue Synthesized from Natural Safrole", **J. Pharmaceutical Sciences**, 81, 1219 (1992).

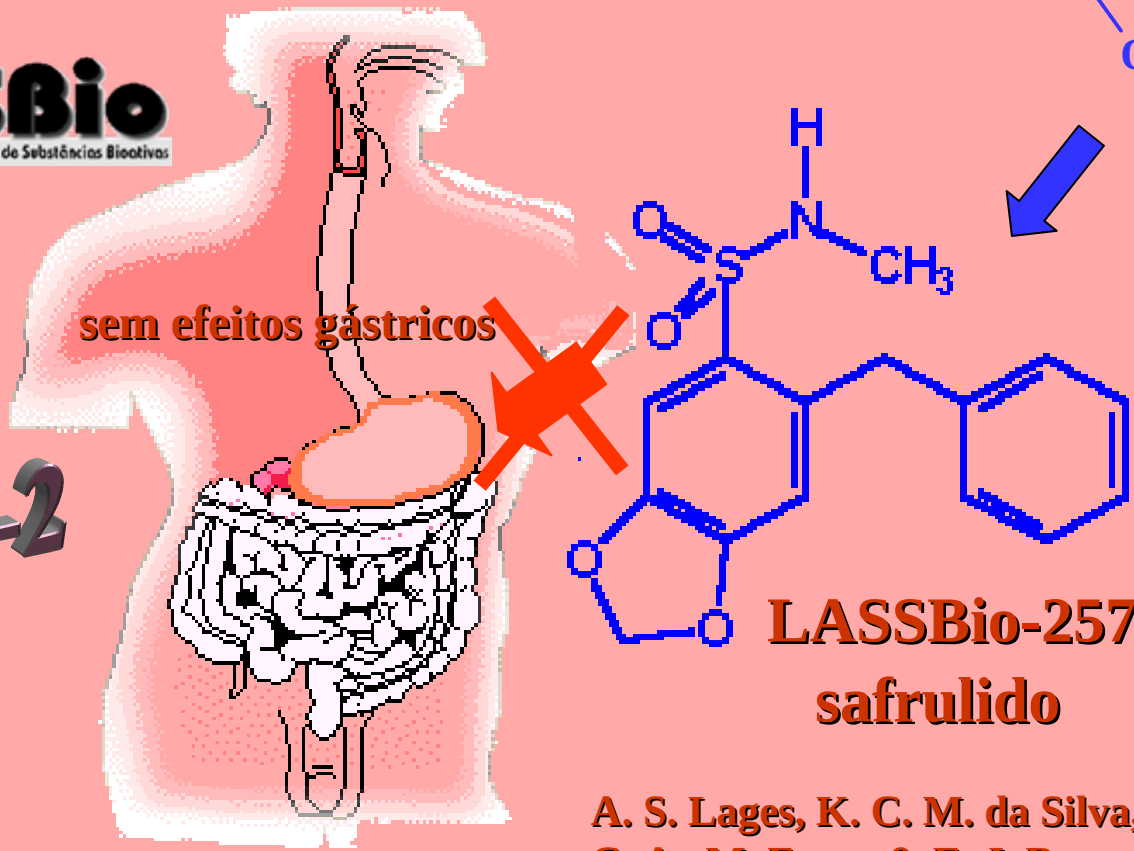


Novo Protótipo de Fármaco Antiinflamatório de Segunda Geração

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas



safrol



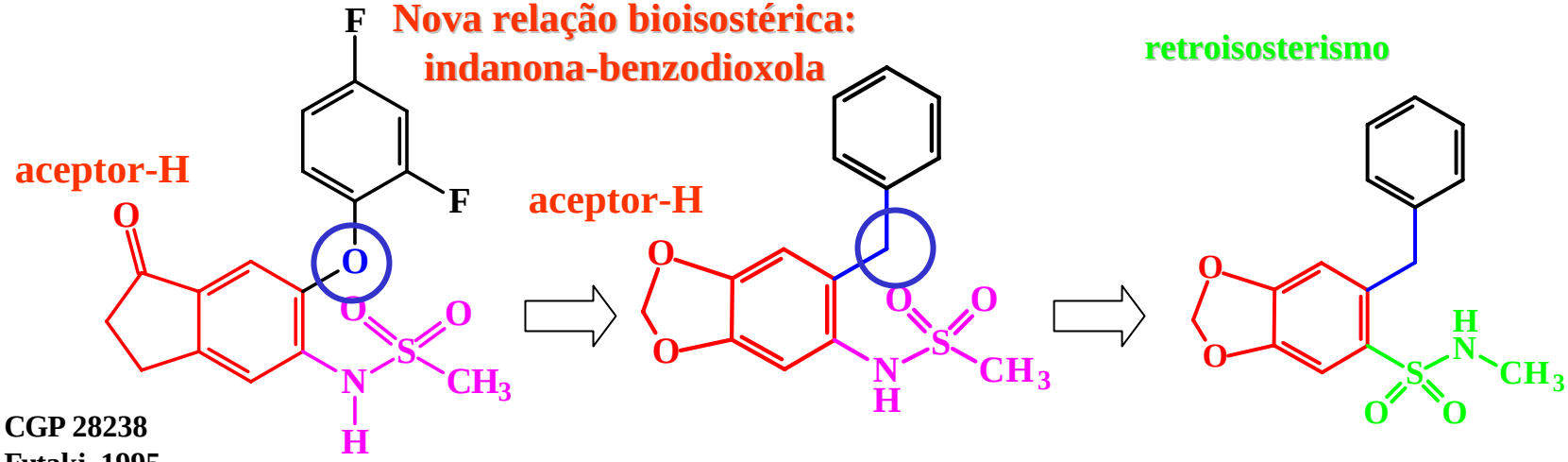
LASSBio-257
safrulido

Química Medicinal

A. S. Lages, K. C. M. da Silva, A. L. P. Miranda, C. A. M. Fraga & E. J. Barreiro, "Synthesis and Pharmacological Evaluation of New Flosulide Analogues, Synthesized from Natural Safrole", *Bioorg. Med. Chem. Lett.* 1998, 8, 183.

Nova relação bioisostérica: indanona-benzodioxola

retroisosterismo



CGP 28238
Futaki, 1995

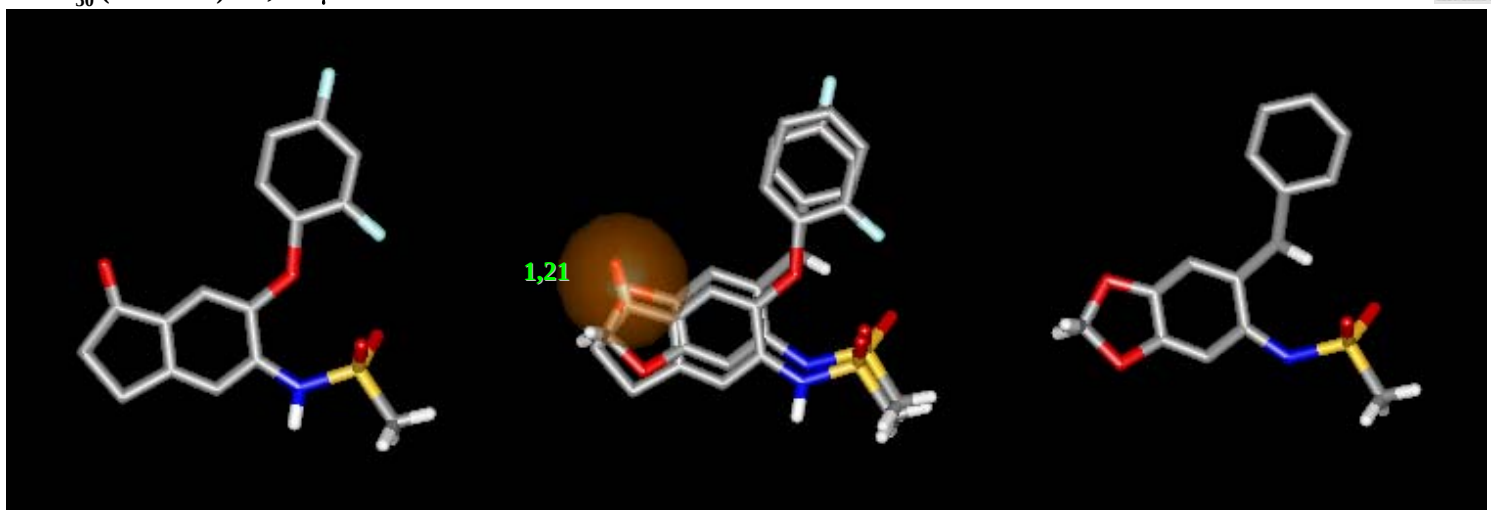
Flosulido
$C_{16}H_{13}F_2NO_4S$
353.34

IS COX-1/COX-2 = 5000
IS = índice de seletividade
IC_{50} (hPGHS-1) = 73,2 μM
IC_{50} (rPGHS-2) = 0,015 μM

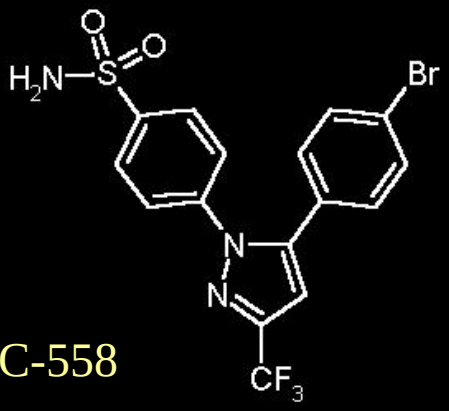
safrulido
$C_{15}H_{15}NO_4S$
305.34

safronamida
$C_{15}H_{15}NO_4S$
305.34

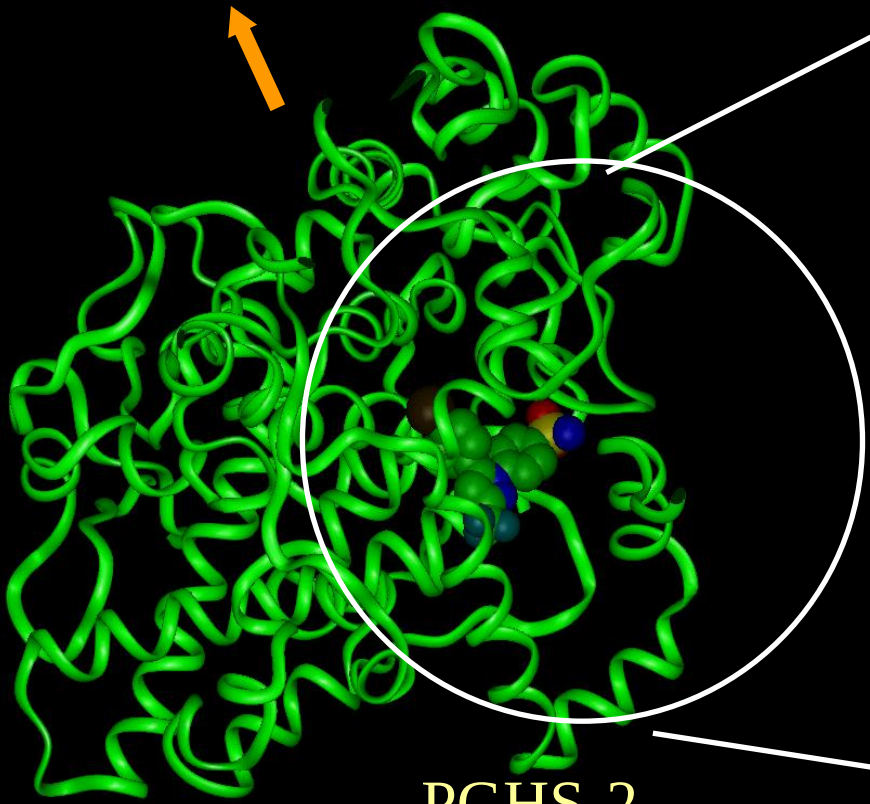
EJ Barreiro *et al*., **Bioorg.Med. Chem. Lett**., 8, 183 (1998)



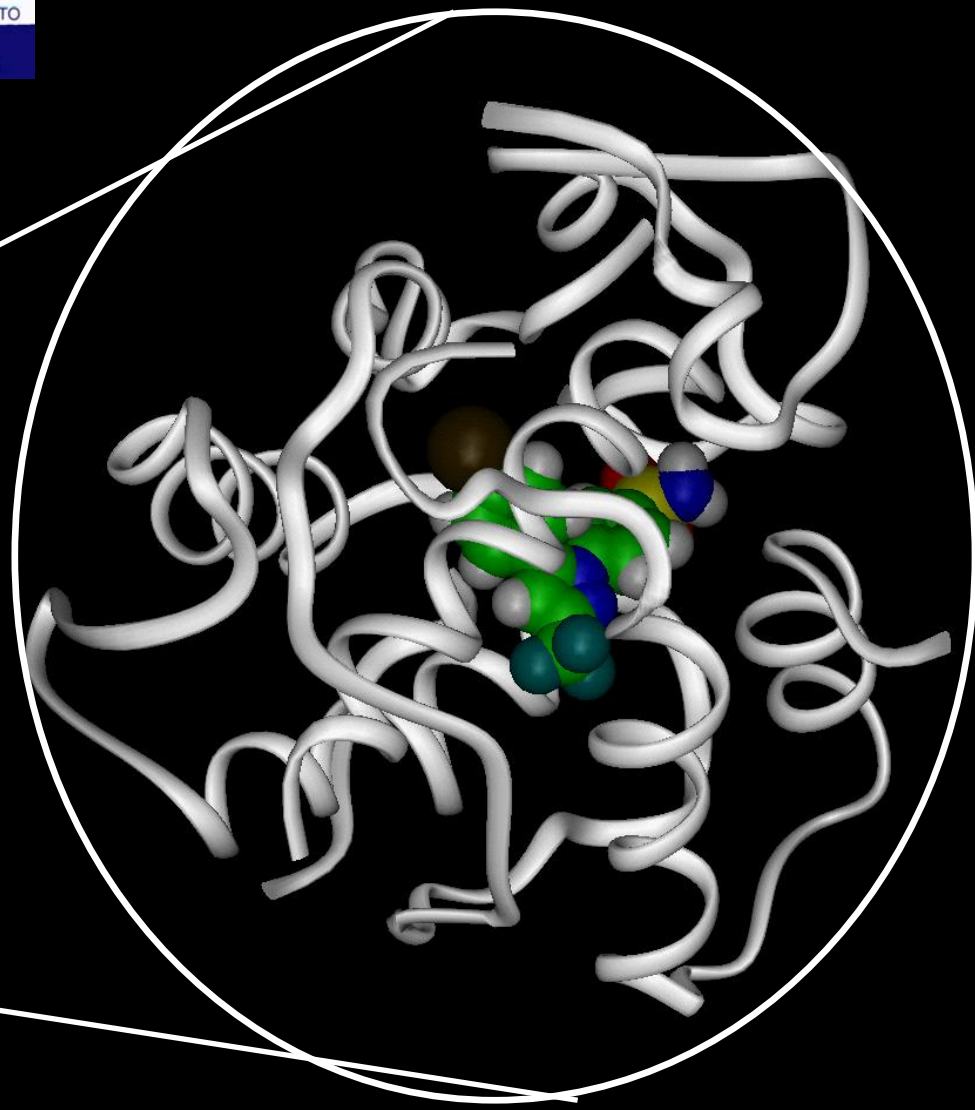
Sítio Ativo da PGHS-2



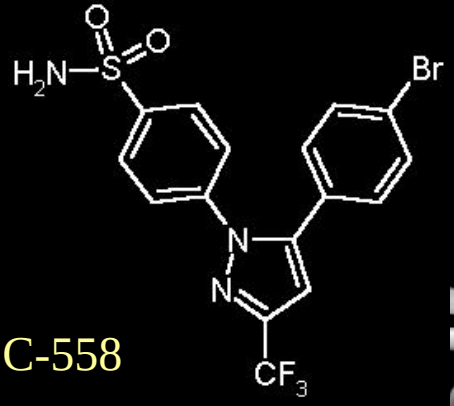
SC-558



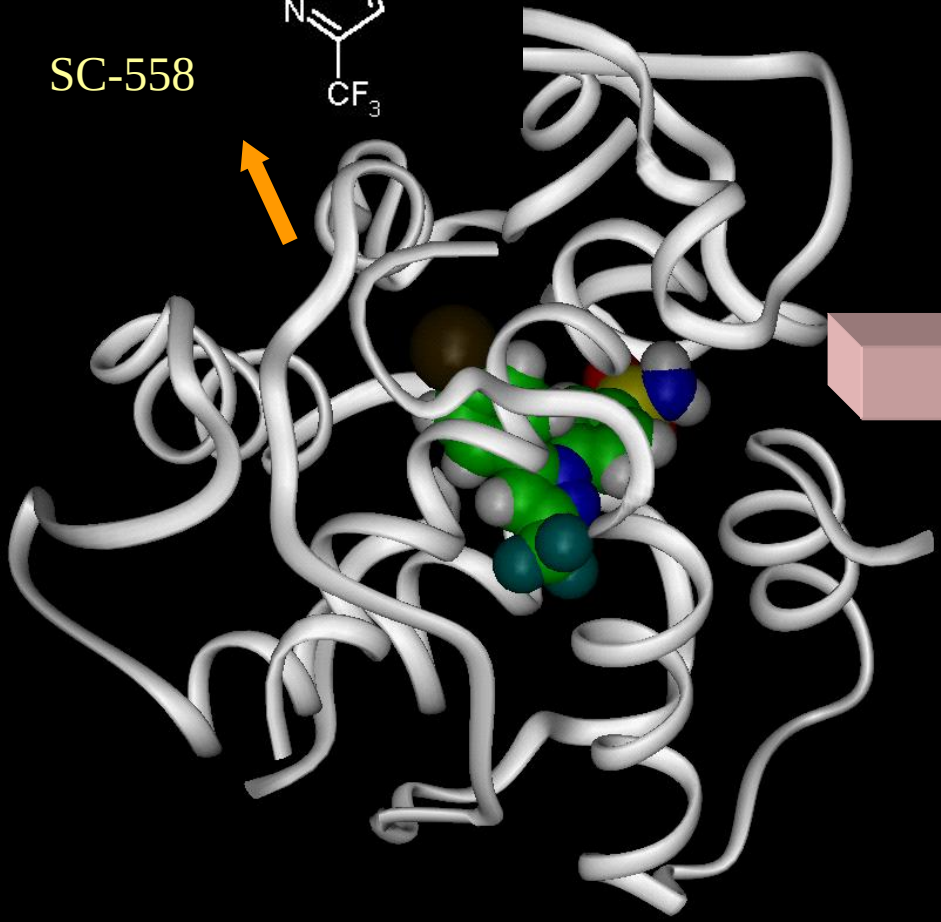
PGHS-2

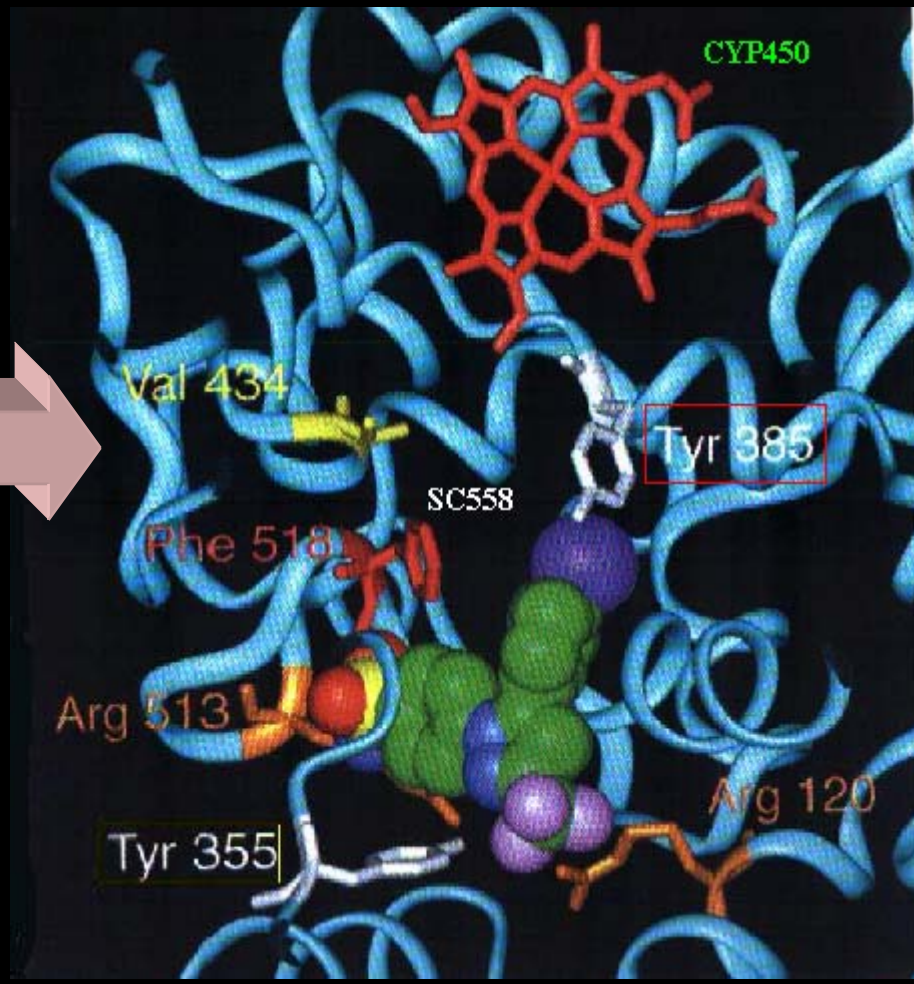


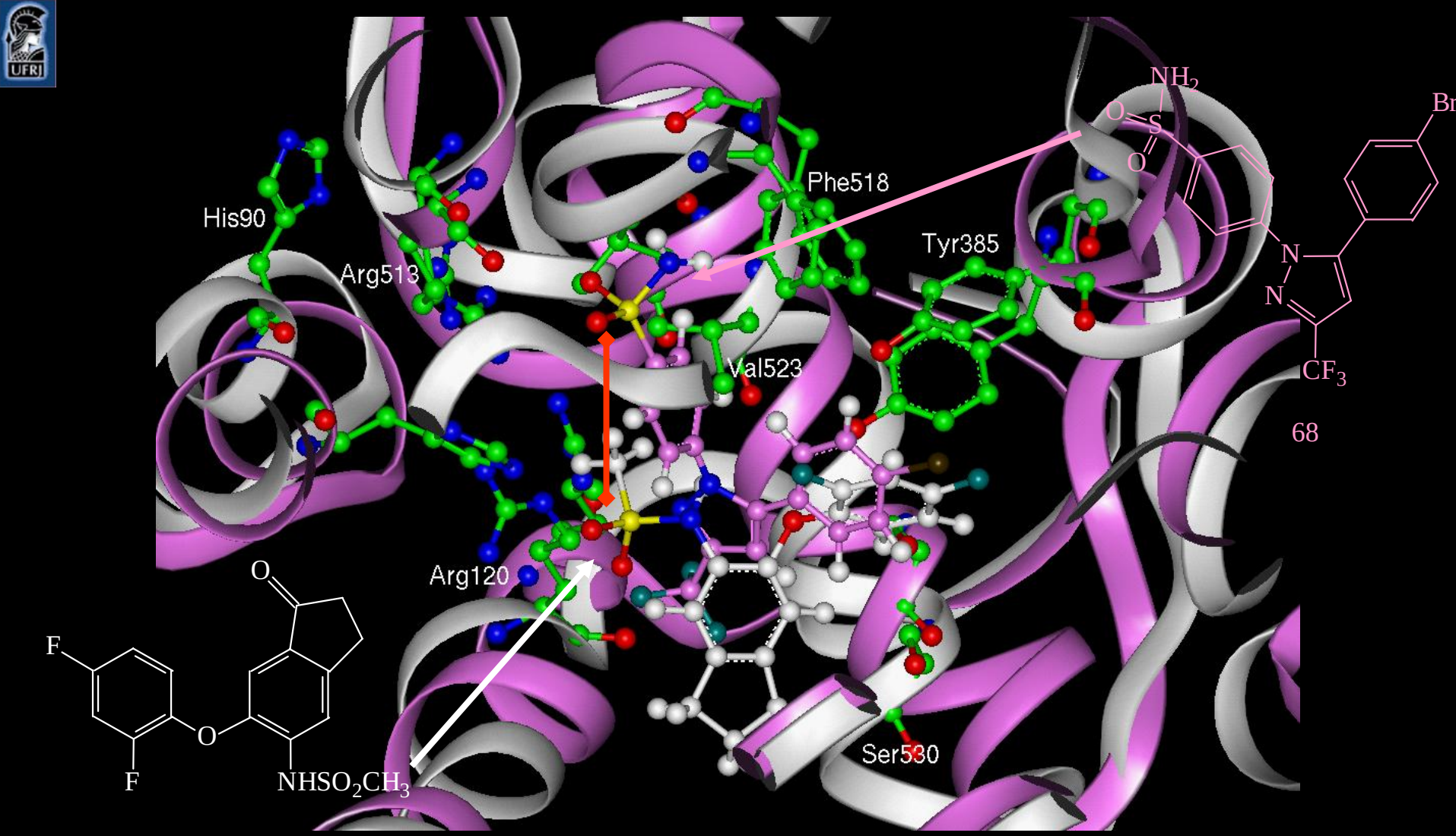
Sítio Ativo da PGHS-2



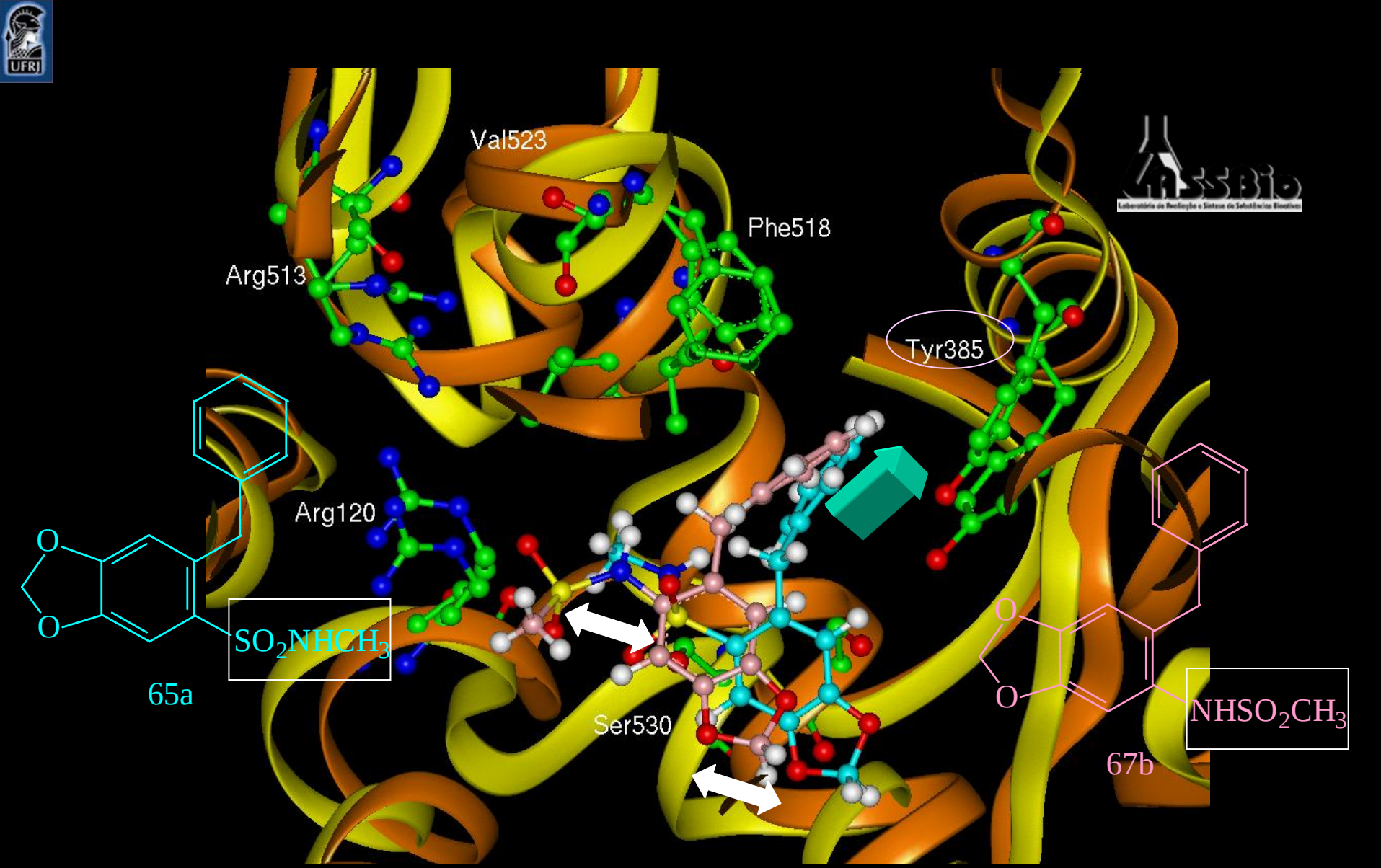
SC-558



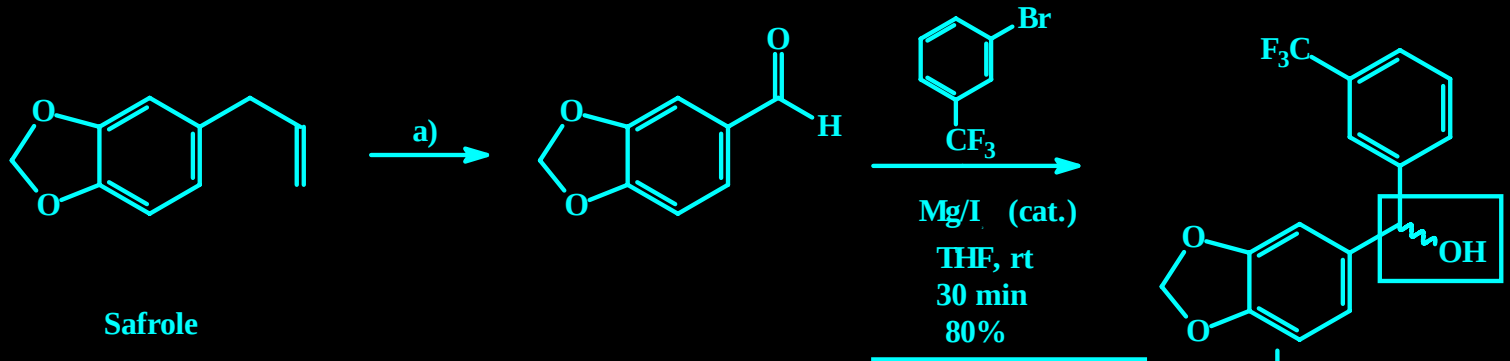




Overlap of the complex between flosulide (White) and SC-558 (Pink) on the subset of AA-residues in the binding pocket of the PGHS-2 .



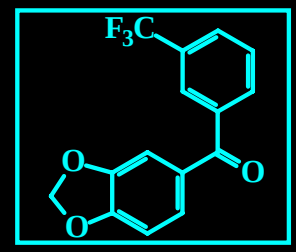
Complex between LASSBio-257 (**65a,** blue) and the new sulide LASSBio-258 (**67b**, pink) with the subset of aa-residues in the binding pocket of the PGHS-2.

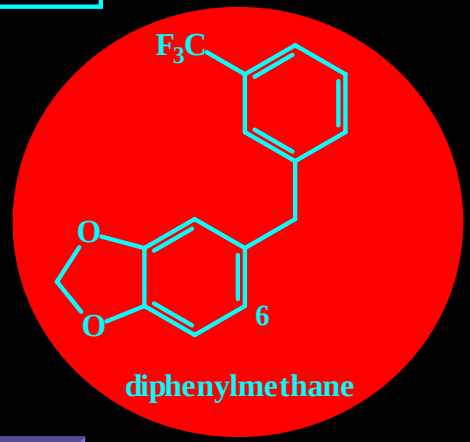


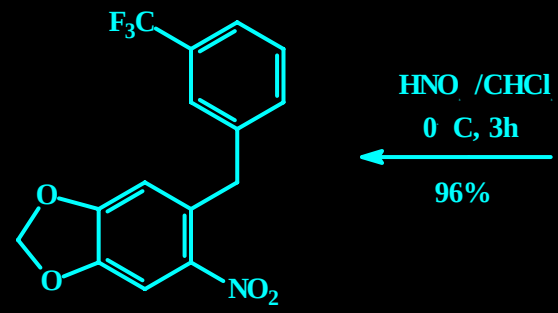
Safrole

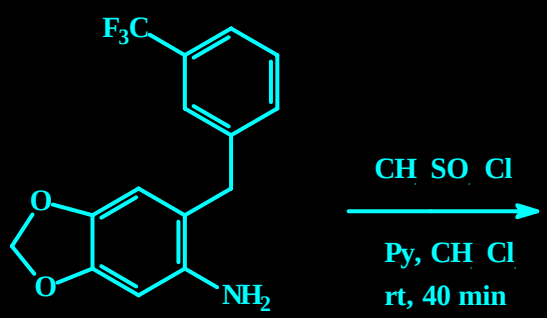
a) EJ Barreiro *et al*., 1982.

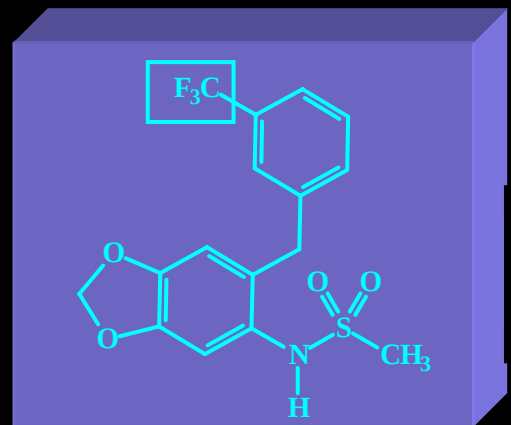
Novo Sulido obtido a partir do safrol

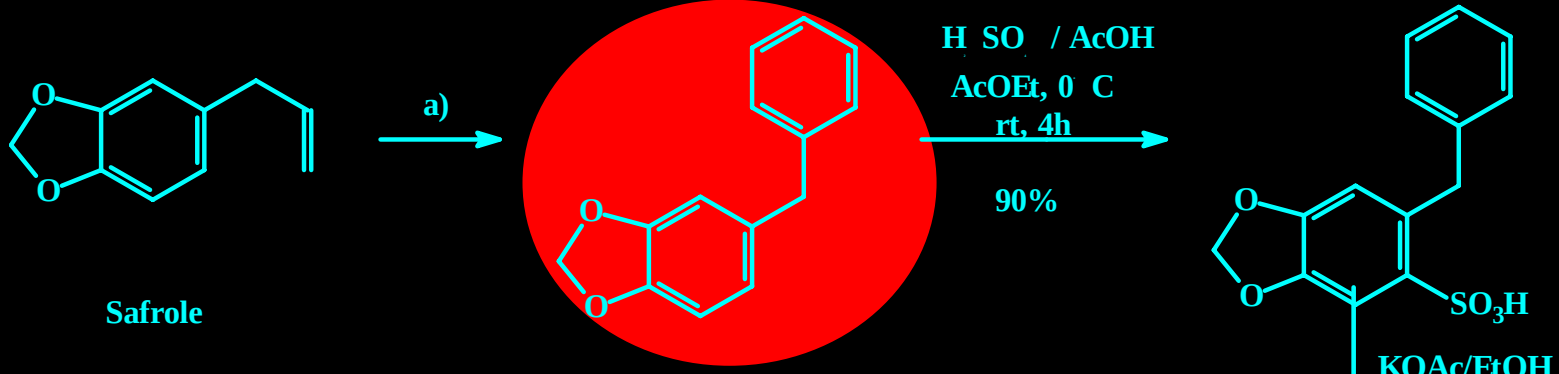








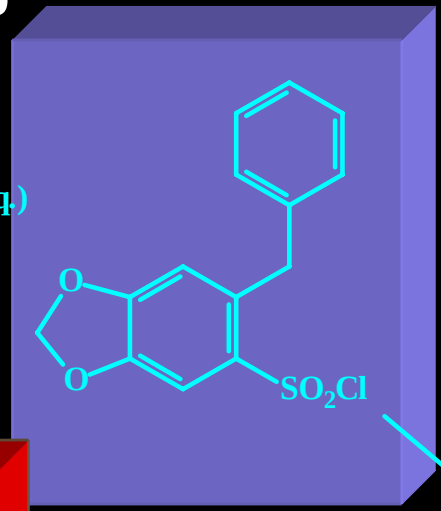


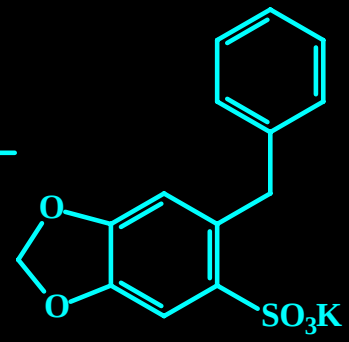


Safrole

a) AS Lages *et al.*, *Bioorg.Med.Chem.Lett.8*,183 (1998)

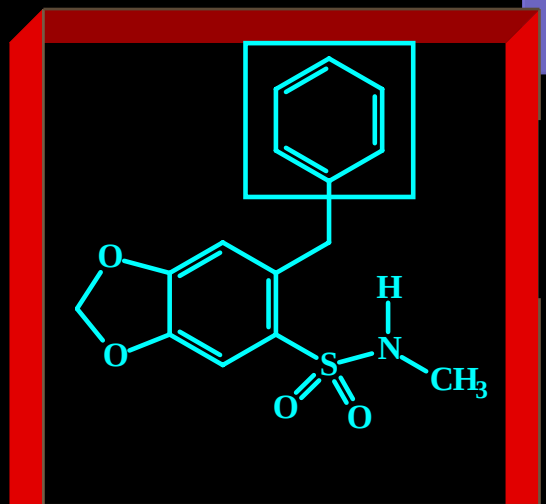
Novo retroisóstero a partir do safrol



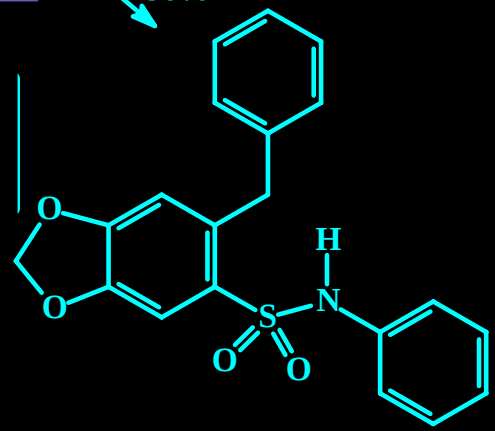


SO Cl / DMF (cat.)
60 C, 4h
57%

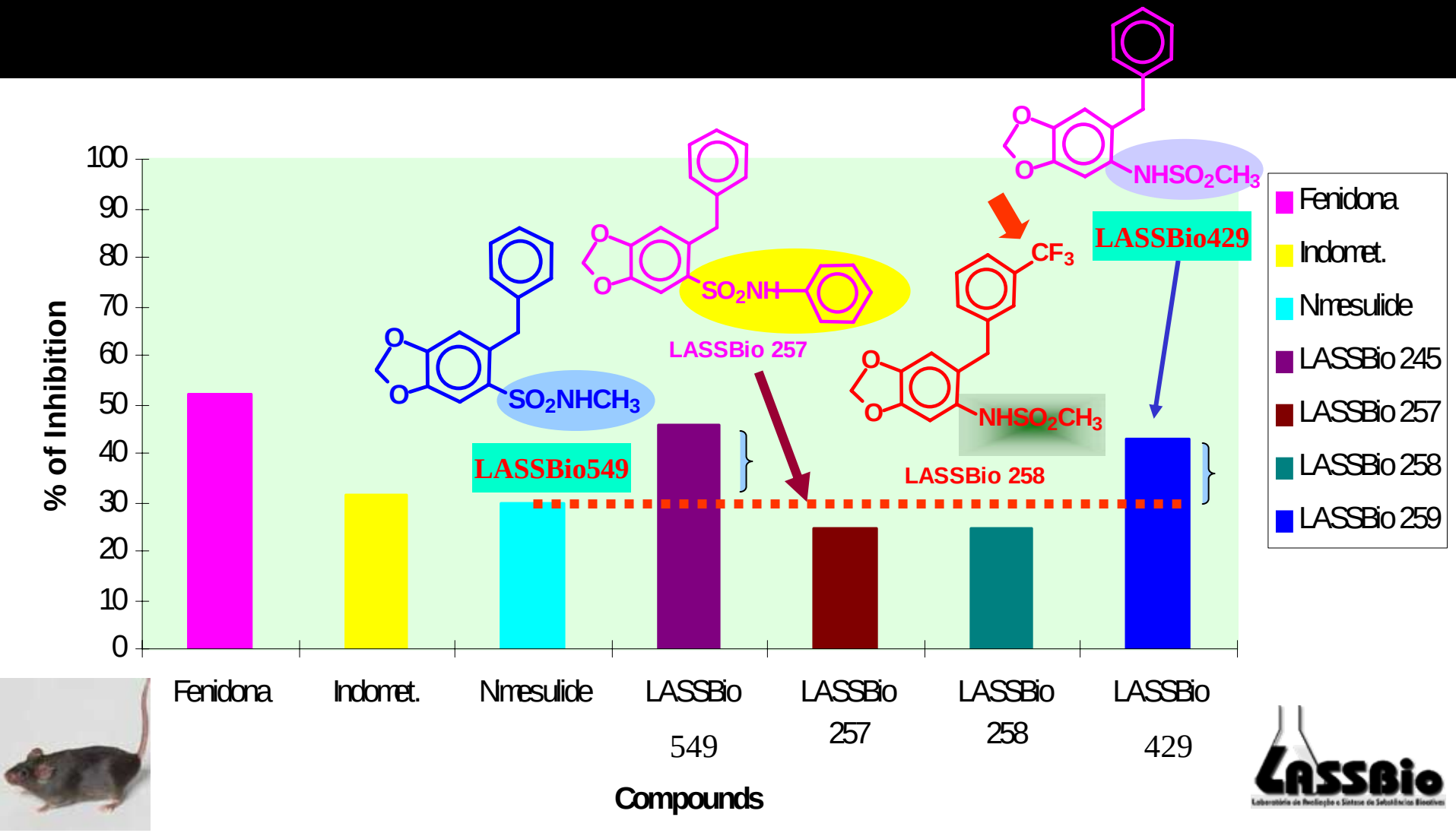
40% CH NH (aq.)
CHCl
0 C, 4h
95%



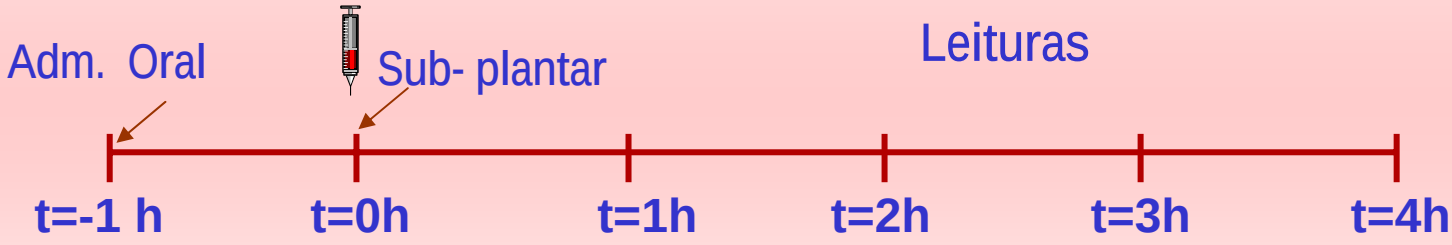
PhNH /CHCl
rt, 2h
96%



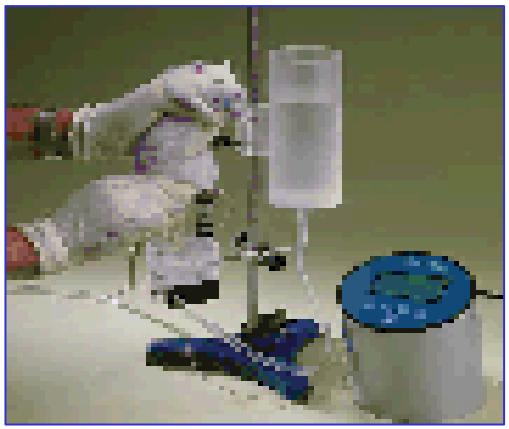
Effect of new candidates of PGHS-2 inhibitors in the carrageenan-induced rat paw edema (100 µM, *po*)



Edema de Pata de Rato Induzido por Carragenina (1%)



(FERREIRA, *et al*., 1979)



Pletismógrafo

Animais: Ratos

Massa:150-200g

Sexo: ambos

ENSAIO DE TOXICIDADE

(GAD & CHENGELIS, 1989)

A incidência de óbitos foi verificada em ratos, após administração diária, durante período de sete dias, da mesma dose efetiva (p.o.)

Sinais de letargia, convulsões, perda de peso, considerados indícios de toxicidade aguda, não foram observados.

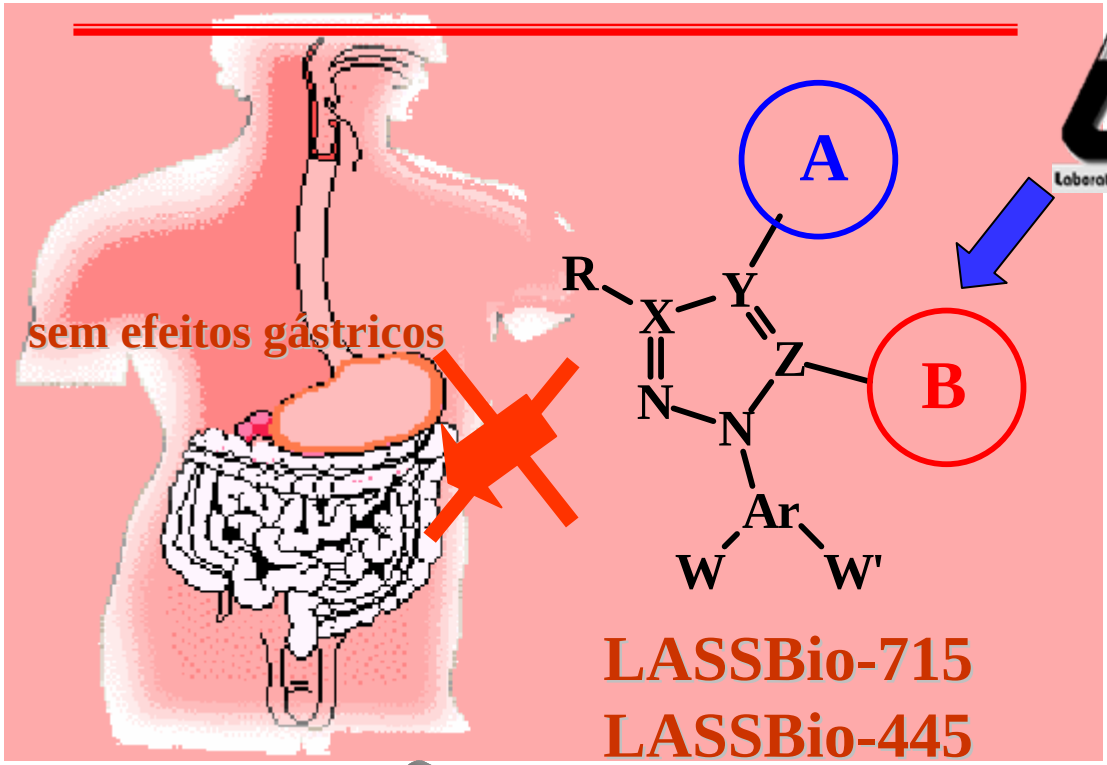
Ensaio de Toxicidade Aguda

LASSBio 715 & LASSBio 455

DOSE 600 e 1400 μg/Kg, (Via oral, dose única)

- **Sem alterações comportamentais (*e.g.* catatonia, letargia, movimentação);**
- **Registro do peso diário: sem alteração;**
- **Aspecto do pelo: normal;**
- **Consumo de ração e água: normais;**
- ***LASSBio715 e 455 não apresentaram efeitos tóxicos em 1.400 μg/Kg.***

Novo Protótipo de Fármaco Antiinflamatório de Segunda Geração



LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

COX-2

E. J. Barreiro, M. P. Veloso, A. L. P. Miranda, C. A.M. Fraga, C. R. Rodrigues, "Novos Agentes Anti-inflamatórios Pirazólicos", Pedido de privilégio de invenção depositado em 29 de abril de 1999, INPI PI-38201866

Nova Classe de Candidatos a Fármacos NSAI de Segunda Geração

LEAD COMPOUND
Lead-optimization

CgIRPE*

		DI_{50}	Max. Eff.
1999	CELECOXIB 	87,7 μmol/kg	35%
LASSBio	**LASSBio 715**	44,3 μmol/kg	39%
	LASSBio 445	54,6 μmol/kg	37%

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

Química Medicinal

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

Novo NSAI de segunda geração

ED_{50} = 75,0 μM/kg

Sem toxicidade aguda em protocolos com roedores e cães;

Sem efeitos histopatológicos (fígado, pulmão, rins, SNC);

Sem efeito ulcerogênico (*p.o.* crônico);

LD_{50}/ED_{50} > 45 vezes

Em fase de ensaios pré-clínicos finais

Primeiro candidato a ensaio clínico de Fase 1 descoberto no LASSBio

Estratégias de desenho estrutural: Simplificação & hibridação

LASSBio-294

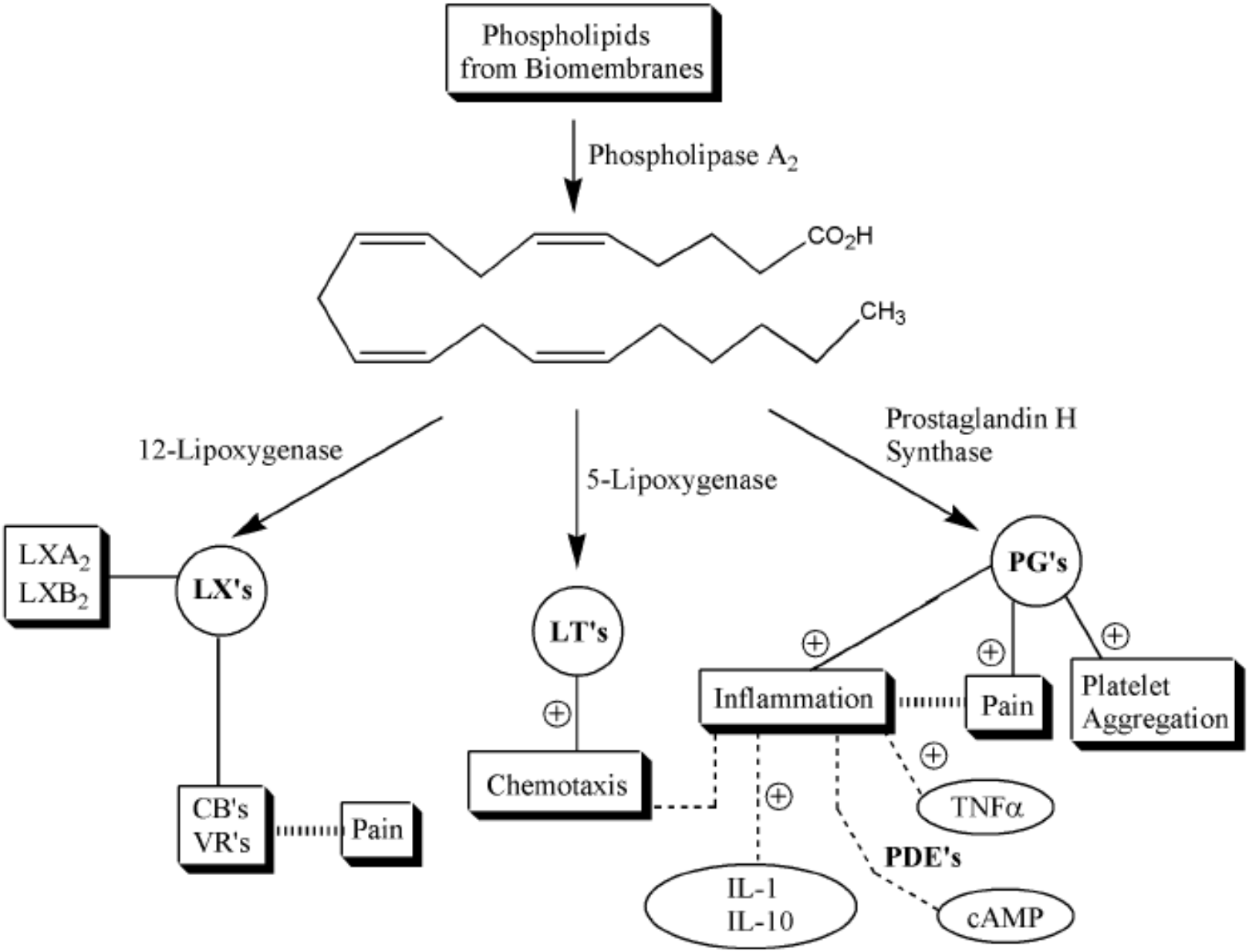


Figure 3: Some physiological mediators of inflammation, pain and thrombi formation.

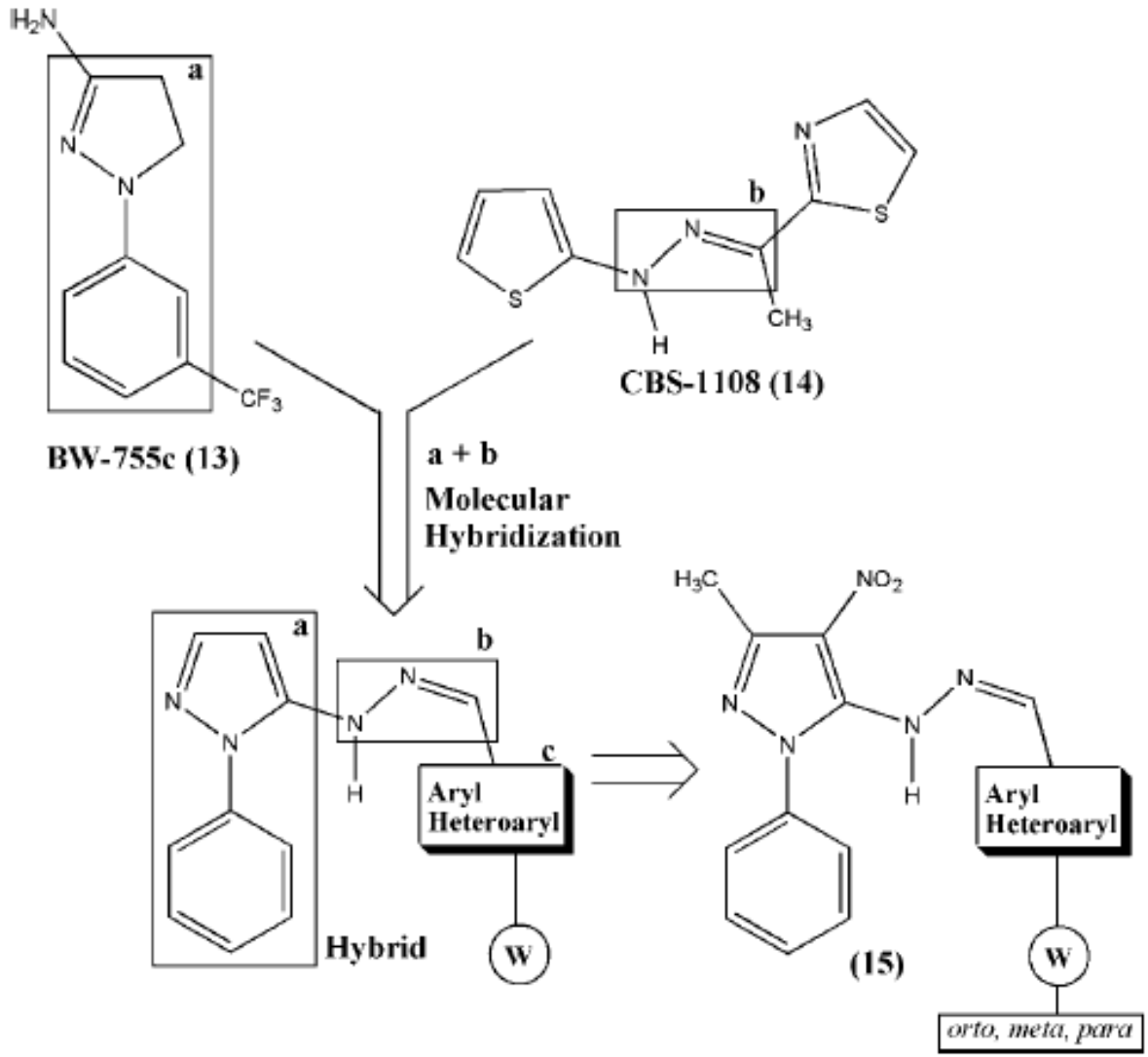
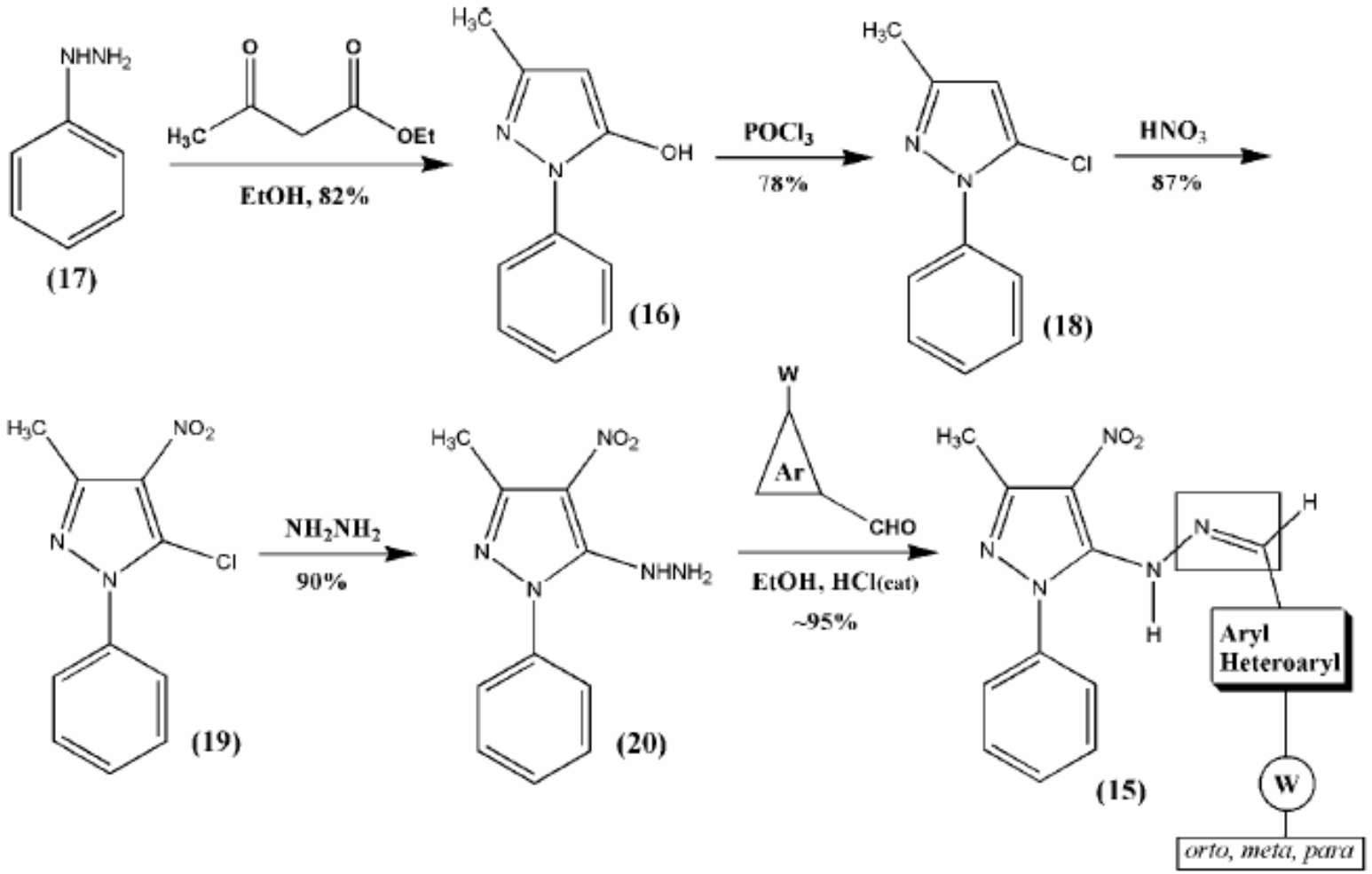
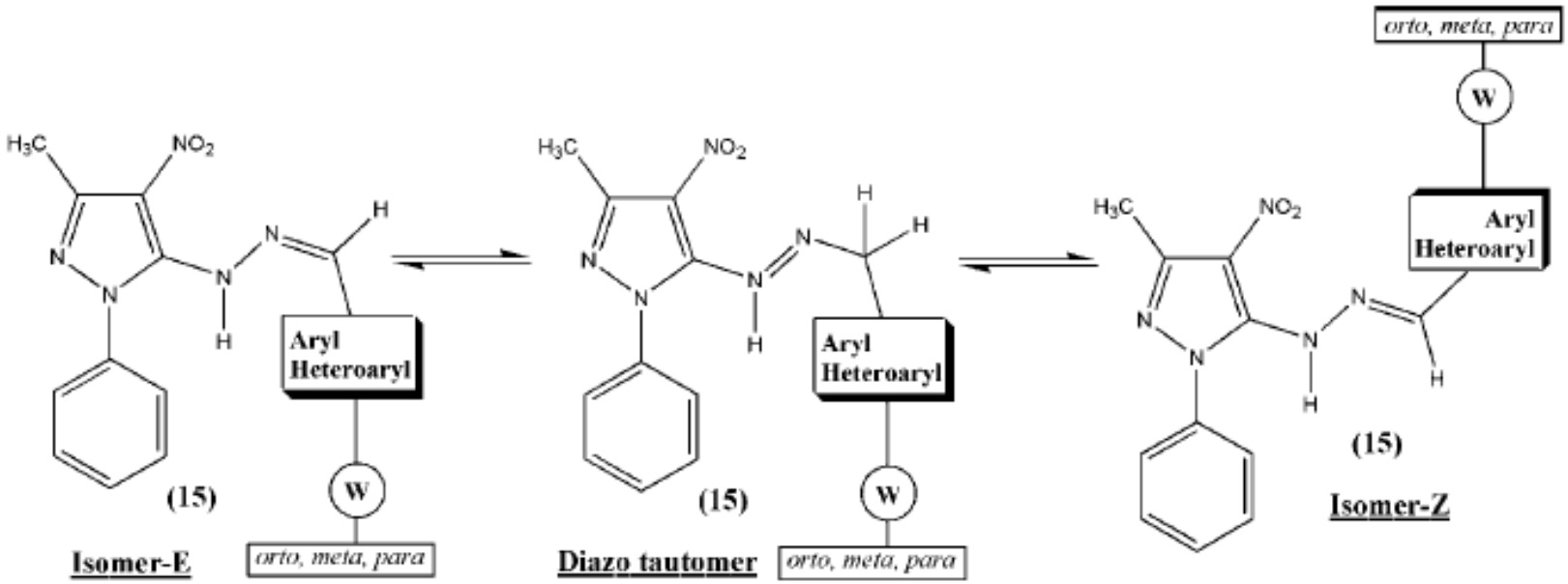


Figure 6: Design concept of*N*-phenylpyrazole-5-arylhydrazone derivatives (15).



Scheme 1: Synthetic route exploited in the construction of nitro-pyrazole NAH series (15).



Scheme 2: Possible diastereomeric and diazo-tautomeric equilibration of hydrazone derivatives from series (15).

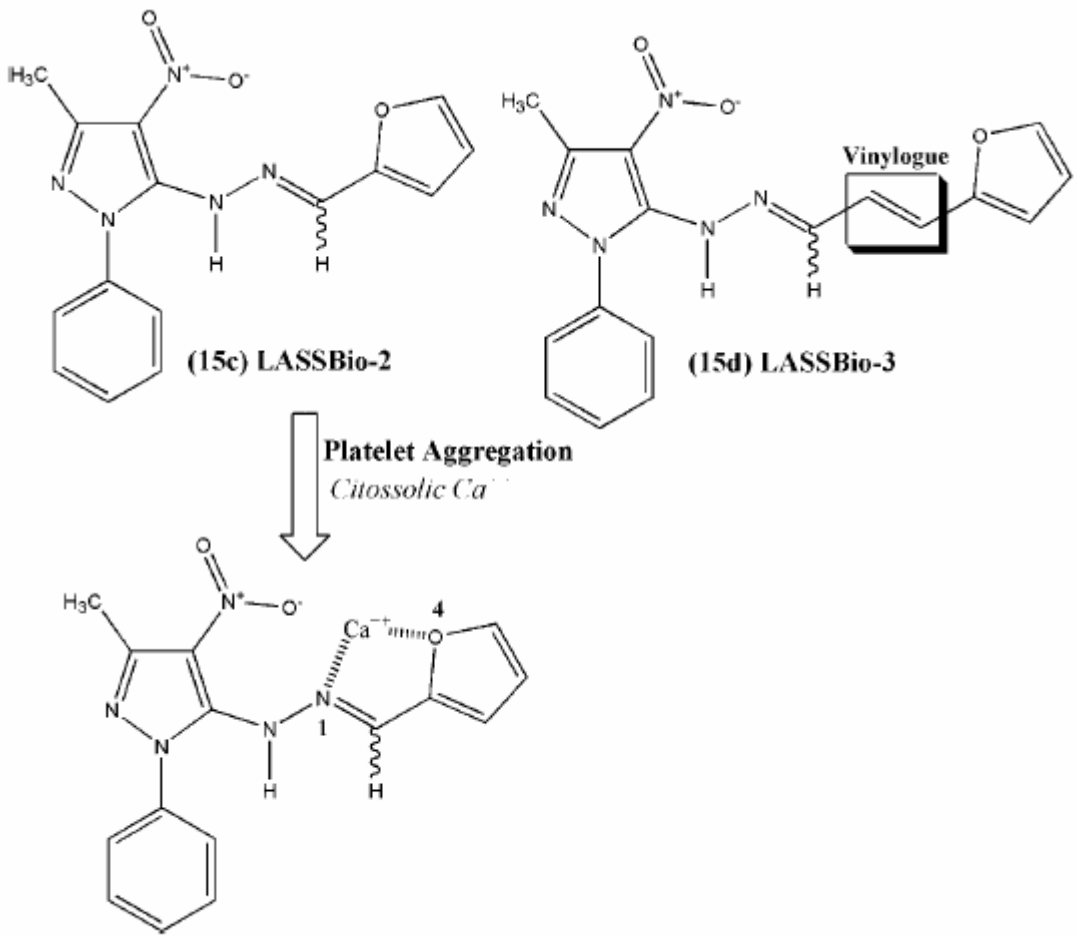


Figure 7: New bioactive hydrazone derivatives from series (15).

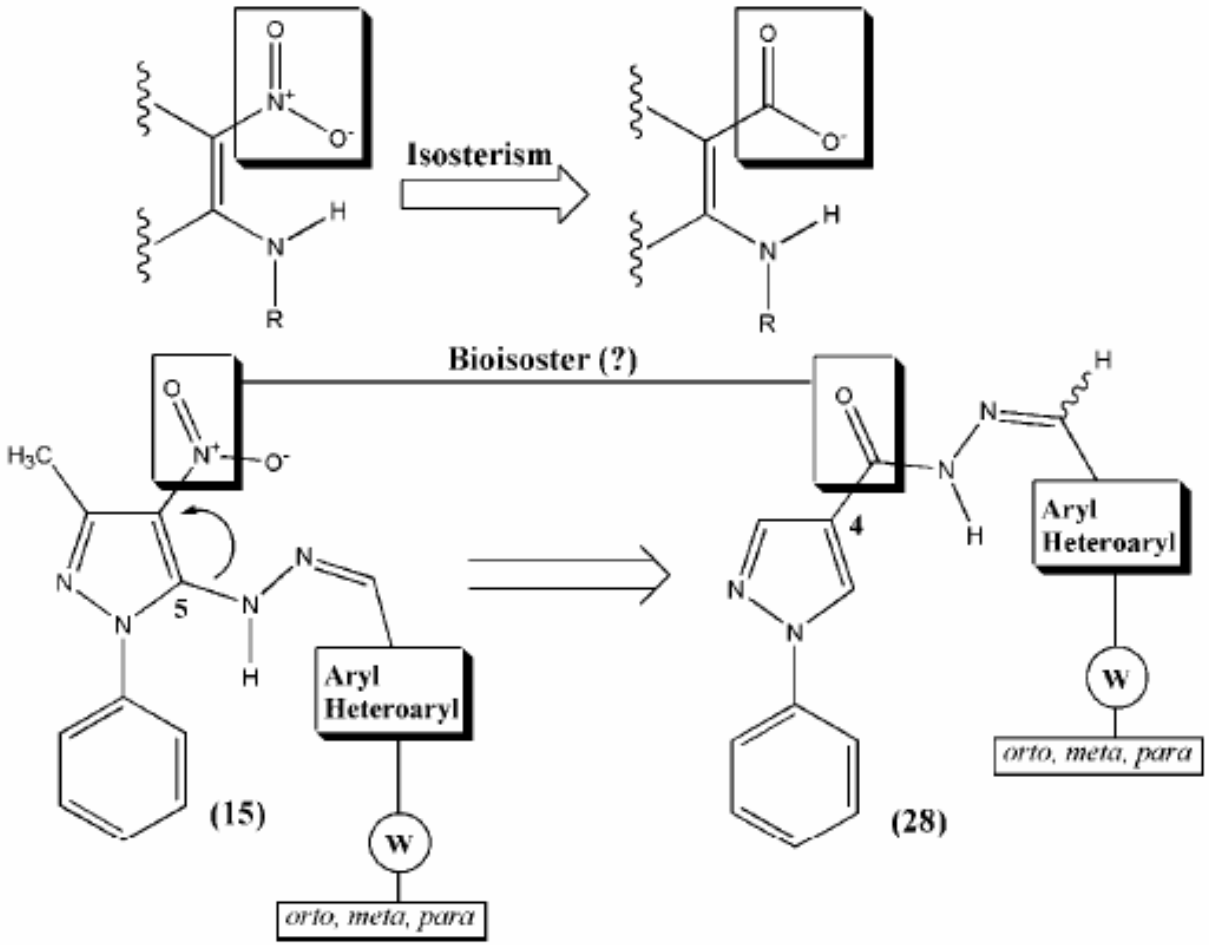
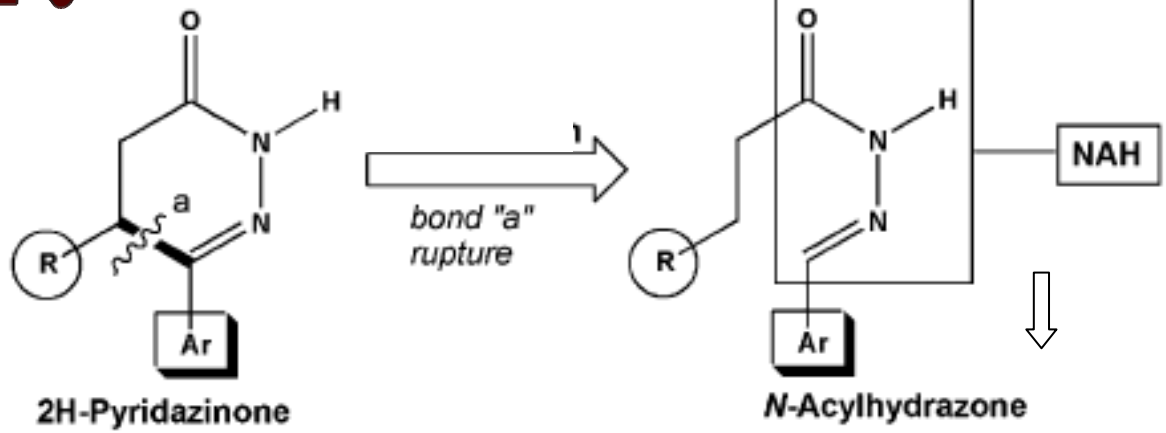


Figure 13: Structural design of isosteric pyrazole NAH series (28).

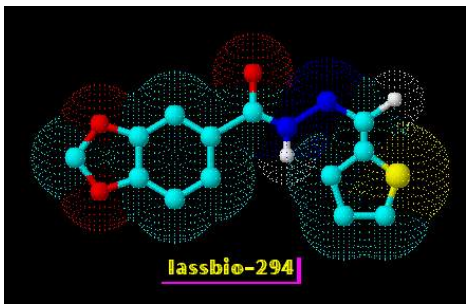
Molecular simplification

NAH-unit as isostere of pyridazinone moiety

PDE-3



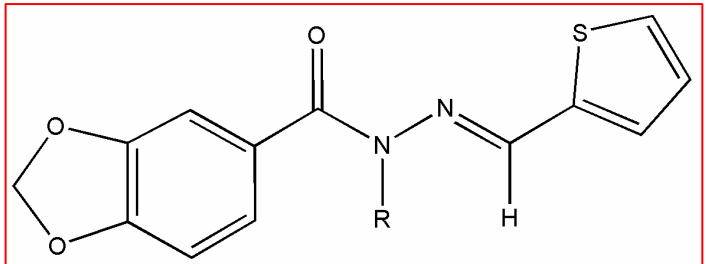
Imazodan, pimobendan



$C_{13}H_{10}N_2O_3S$

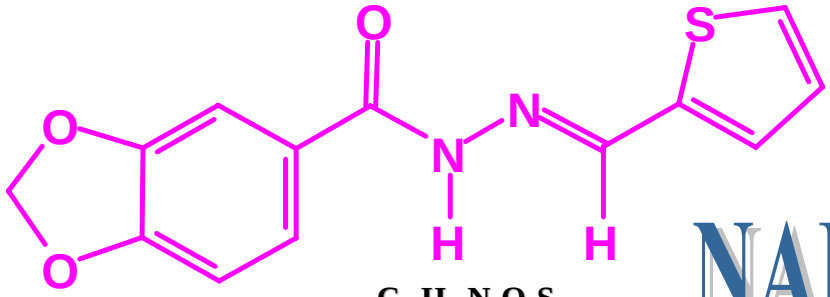
PM 274

Lima, P. C. *et al*. (2000) *Eur. J. Med. Chem.* 35, 187.



(56ae) R =H (LASSBio-294)

Novo Protótipo de Fármaco Cardioativo



$C_{13}H_{10}N_2O_3S$

NAH

LASSBio-294

Novo agente cardioativo, seletivo, não-digitálico, não-adrenérgico, com potentes propriedades inotrópicas & vasodilatadoras; Ativo por via oral; Sem toxicidade aguda.

Estruturalmente simples; Sinteticamente acessível em ótimos rendimentos; Matéria-prima disponível (produto natural abundante).

USPTO Patent 7,091,238 (08/2006)

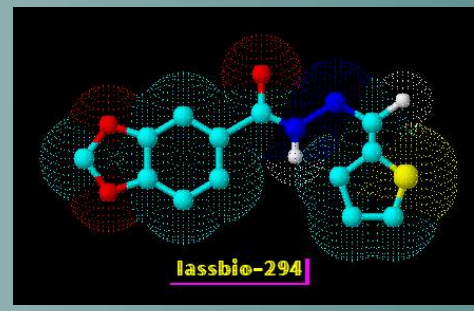
"Novel, Non-toxic Chronotropic Stimulator of Cardiac and Skeletal Muscle"

EX Albuquerque, EJ Barreiro, RT Sudo, "LASSBio 294 A Novel Digitalis-like Compound with Potential Antifadigue Activity", USPTO Provisorial Number 60-140,352 (1999); US 7091238; WO Patent 2000-878754; Eur. Patent 2000;

Estudos de Toxicidade Aguda e Sub-aguda

✓A toxicidade sistêmica aguda e sub-aguda foi investigada em ratos, por duas vias de administração, *p.o.* e *i.p.*, nas doses de **1000 μM/kg** e **73 μM/kg**, respectivamente (*i.p.*, administrando-se 2 vezes ao dia, durante 15 dias seguidos: ~ **100 vezes superior à ED_{50} *in vivo***).

LASSBio-294



Não tem efeito letal, não provoca letargia, não reduz a motilidade, nem altera o pêso dos animais.

Não provoca alterações na contagem de células sanguíneas, hematócrito, nem altera a taxa de glicose, uréia, TGO, TGP, creatinina.

Não altera histopatologicamente orgãos vitais, tais como fígado, pulmão, SNC.

Não se observaram efeitos neurotóxicos em culturas de neurônios hipocampais de ratos, tratadas com LASSBio-294 (500 μM).
Efeito neuroprotetor foi observado em < doses.

Novo protótipo de fármaco cardioativo

Office of Research & Development

515 West Lombard Street, Suite 500
Baltimore, Maryland 21201
Tel. (410) 706-1874; Fax. (410) 706-5035
http://www.orad.umaryland.edu/industry/technologies/therapeutics.php

USPTO 60-525,353 (1999) → Novo Protótipo Cardioativo*

USPTO 7,091,238 15/08/2006 → WO 2000-078754 (64 países)

LASSBio 294: a novel compound having digitalis-like cardiotonic properties and the potential to reduce muscle fatigue

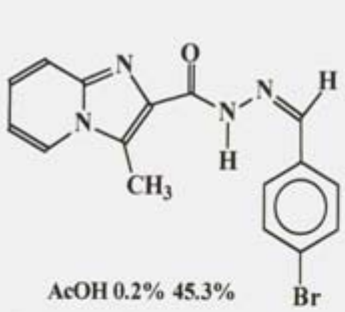
Tech ID # 1558EA

otimização

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

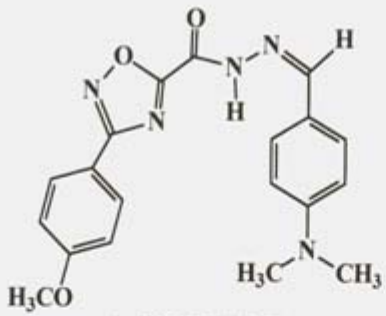
http://www.inventabrasil.hpg.ig.com.br/ytabela.htm
http://www.comciencia.br/reportagens/farmacos/farma08.htm

Novos Protótipos Descobertos no LASSBio



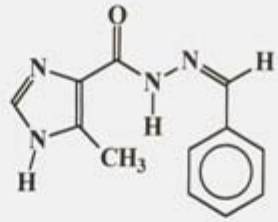
AcOH 0.2% 45.3%

Eur. J. Med. Chem., 33, 225 (1998)



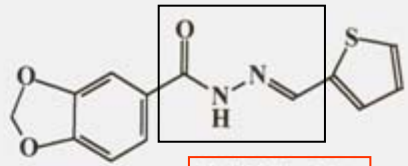
AcOH 0.2% 49.5%

Il Farmaco, 54, 747-757 (1999)



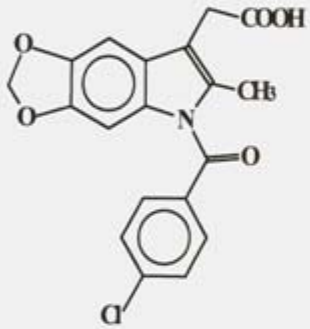
AcOH 0.2% 76.6%

Bioorg. Med. Chem., 8, 2243 (2000)
Química Nova, 25, 129 (2002)

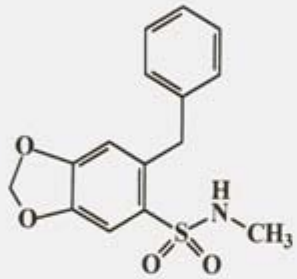


LASSBio-294

Química Nova, 25, 1172 (2002)
J. Pharmacol. Exper. Therap., 299, 558 (2001)
Br. J. Pharmacol., 134, 603 (2001)
Br. J. Pharmacol., 135, 293 (2002)
Eur. J. Pharmacol., 470, 79 (2003)

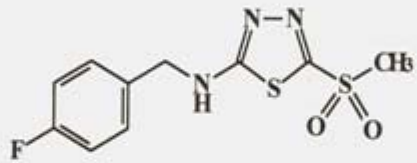


J. Chem. Res.(S), 102 (1982)
Química Nova, 22, 744 (1999)



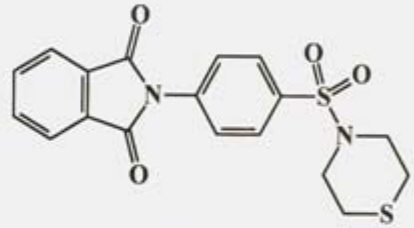
LASSBio-326

Bioorg.Med. Chem. Lett., 8, 183 (1998)



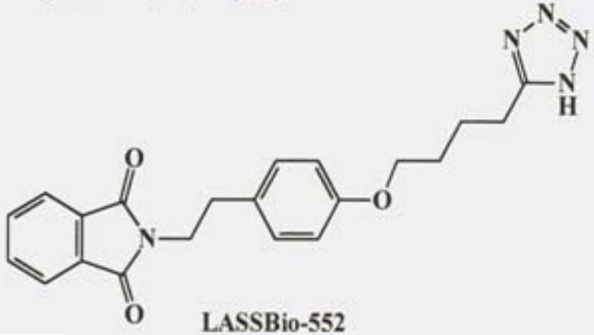
LASSBio-756

LS Varandas, MSc UFRJ, 2000



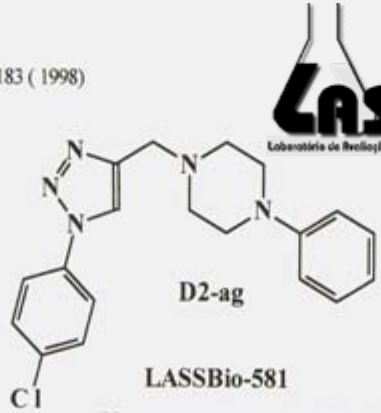
LASSBio-468

Bioorg. Med. Chem., 10, 3067 (2002)



LASSBio-552

Bioorg. Med. Chem. Lett., 12, 1533 (2002)



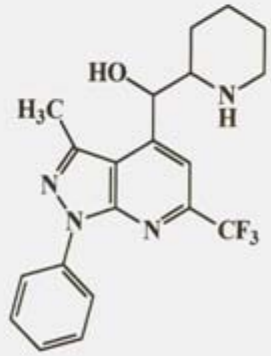
D2-ag

LASSBio-581

Bioorg. Med. Chem., 11, 4807 (2003)
Braz. J. Biol. Med. Res., 36, 625 (2003)
J. Pharm. Biomed. Anal., 33, 1127 (2003)

LASSBio-599

Eur. J. Med. Chem., 37, 163 (2002)



LASSBio-323

Boll. Chim. Farm., 139, 14 (2000)

Diversidade Molecular

Full Text

US 7,091,238 B1

Print this page

THIENYLHYDRAZON WITH DIGITALIS-LIKE PROPERTIES (POSITIVE INOTROPIC EFFECTS)

Roberto Takashi Sudo, Rio de Janeiro (Brazil); Edson X. Albuquerque, Baltimore, Md. (US); Eliezer J. De Barreiro, Rio de Janeiro (Brazil); Yasco Aracava, Rio de Janeiro (Brazil); Wagner Monteiro Cintra, Rio de Janeiro (Brazil); Paulo De Assis Melo, Niteroi (Brazil); Francois Germain Noel, Rio de Janeiro (Brazil); Gisele Zapata Sudo, Rio de Janeiro (Brazil); Claudia Lucia Martins Da Silva, Rio de Janeiro (Brazil); Newton Goncalves de Castro, Rio de Janeiro (Brazil); Patricia Dias Fernandes, Rio de Janeiro (Brazil); Carlos Alberto Manssour Fraga, Rio de Janeiro (Brazil); and Ana Luisa Palhares De Miranda, Petropolis (Brazil)

Assigned to University of Maryland, Baltimore, Md. (US)

Appl. No. 10/70,328

PCT Filed Jun. 21, 2000, PCT No. PCT/US00/17024
§ 371(c)(1), (2), (4) Date Apr. 08, 2004,

PCT Pub. No. WO00/78754, PCT Pub. Date Dec. 28, 2000.

Claims priority of provisional application 60/140352, filed on Jun. 21, 1999.

Int. Cl. ***C07D 409/12*** (2006.01); ***A61K 31/381*** (2006.01); ***C07D 317/62*** (2006.01)

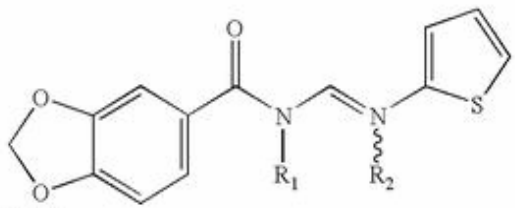
U.S. Cl. 514—444

21 Claims

15/08/2006

1. A chemical compound having the formula (I)

(I)



wherein,

R_1 is selected from the group consisting of hydrogen, allyl of 1 to 6 carbon atoms, unsubstituted phenyl, and substituted phenyl;

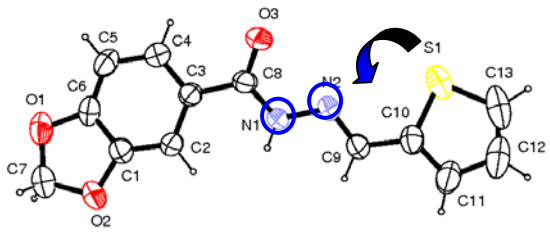
R_2 is selected from the group consisting of H, alkene, un-substituted phenyl, and substituted phenyl; or a pharmaceutically acceptable salt thereof.

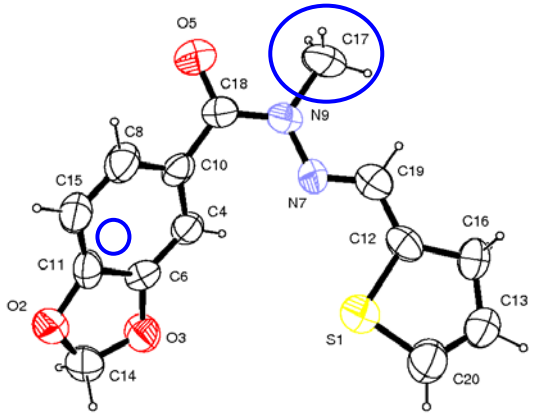
LASSBio-294

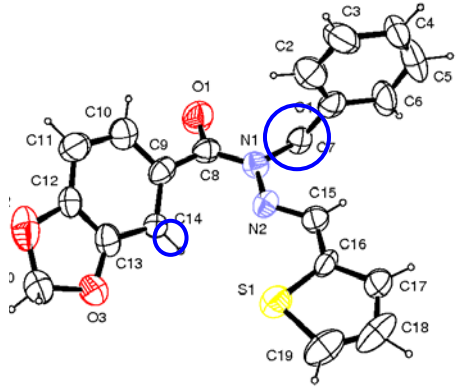
LASSBio-785

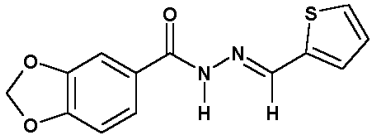
LASSBio-786

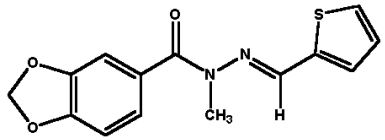
Vista Frontal

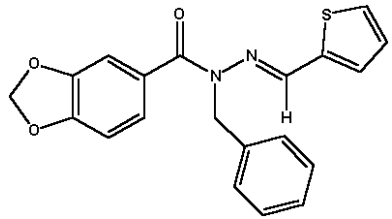




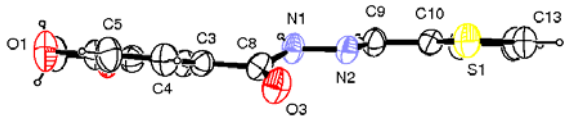


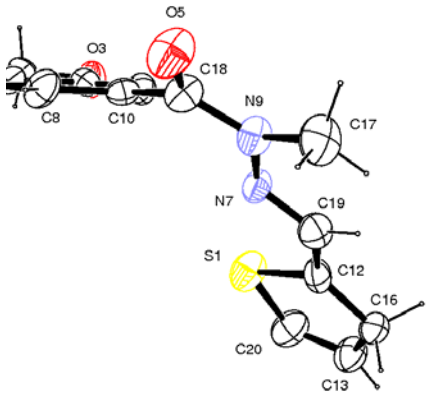


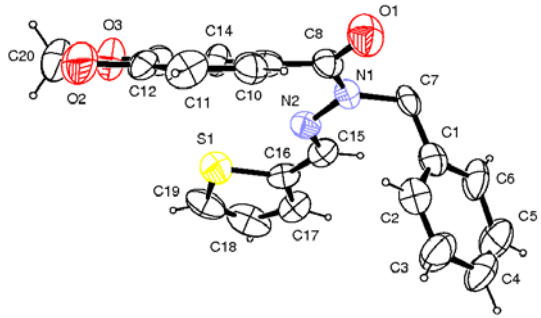




Vista Paralela







Kummerle, A. E. (2005) Tese de Mestrado, IQ-UFRJ.

Web Imagens Grupos Notícias **mais »**

Google LASSBio 294 Pesquisar Pesquisa avançada Preferências

Pesquisar: a web páginas em português páginas do Brasil

Web Resultados **1** - **10** de aproximadamente **451** para **LASSBio 294** (**0,11** segundos)

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

LASSBio-294

Estamos falando do **LASSBio-294**, um fármaco desenvolvido pelo Laboratório de Avaliação **...**
O próprio **LASSBio-294**, embora seja fruto da modelagem molecular, **...**
inventabrasilnet.t5.com.br/barreiro.htm - 9k - Em cache - Páginas Semelhantes

Inventores Brasileiros - Fármacos

O **LASSBio-294** (que atua no aumento das contrações cardíacas), foi desenvolvido a partir de modelagem molecular e teve pedido de patente solicitado no INPI **...**
inventabrasilnet.t5.com.br/yfarmac.htm - 67k - Em cache - Páginas Semelhantes

[PPT] Apresentação do PowerPoint

Formato do arquivo: Microsoft Powerpoint - Ver em HTML
Avaliar os perfis antiinflamatório e analgésico da série de derivados N-Acilidrazônicos nitrados (3) , análogos do composto **LASSBio 294**. 3. METODOLOGIAS **...**
acd.ufrj.br/~pharma/**lassbio**/download/painel1_SBFTE04.ppt - Páginas Semelhantes

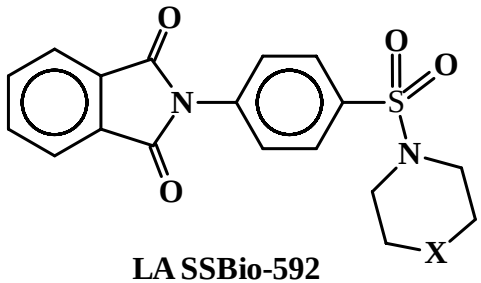
Química Nova - Strategy of molecular simplification in rational ...

Outrossim, o efeito de relaxamento observado com **LASSBio-294** (37) permaneceu inalterado quando os anéis de aorta isolados de ratos foram pré-tratados com K+ **...**
www.scielo.br/scielo.php?pid=S0100-40422002000700018&script=sci_arttext - 75k - Em cache - Páginas Semelhantes

Química Nova - <B>Estratégia de simplificação molecular no ...

A descoberta de novo protótipo cardiotônico **LASSBio-294** (37) **...** De fato, a hipótese de inibição de PDE5 e 3 no mecanismo de ação de **LASSBio-294** foi **...**
www.scielo.br/scielo.php?script=sci_arttext&pid=S0100-40422002000700018&lng=pt&nrm=iso - 66k - Em cache - Páginas Semelhantes

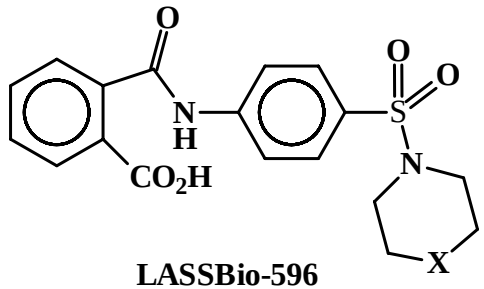
Novos Protótipos Descobertos no LASSBio



LA SSBio-592

Bioorg. Med. Chem., 10, 3067 (2002)

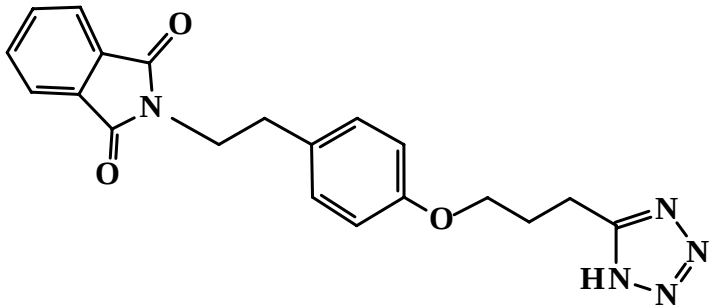
PI 061192-1 (09/11/2002)



LASSBio-596

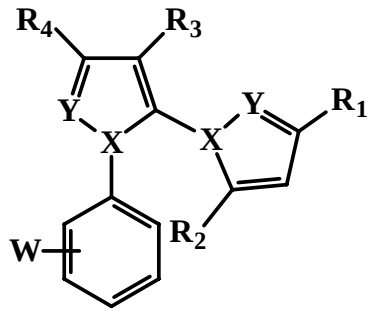
Bioorg. Med. Chem., 10, 3067 (2002)

PI-0401660-2(27 /04/2004)

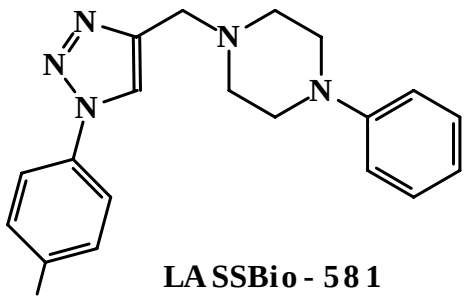


LASSBio-552

Bioorg. Med. Chem. Lett., 12, 1533 (2002)



LASSBio-715



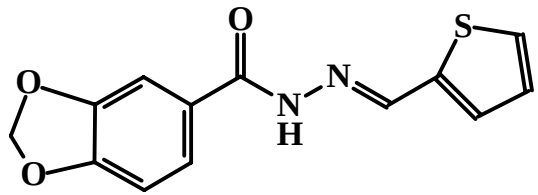
LA SSBio - 581

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

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

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

PI 0303465-8 em 05/09/2003



LASSBio-294

5. Planejamento racional de fármacos

O processo da descoberta

A estratégia da abordagem fisiológica

O paradigma do composto-protótipo

Novas estratégias para a descoberta de fármacos

A importância do metabolismo: ADME

Fármacos inteligentes

Estratégias de desenho estrutural:

- **A importância do bioisosterismo: análogos & *me-too***
- **O processo de hibridação molecular**
- **O processo de simplificação molecular**

6. Considerações finais

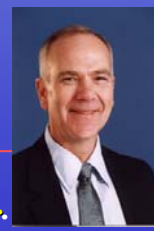
Rato Transgênico Humanizado

Humanized mouse model

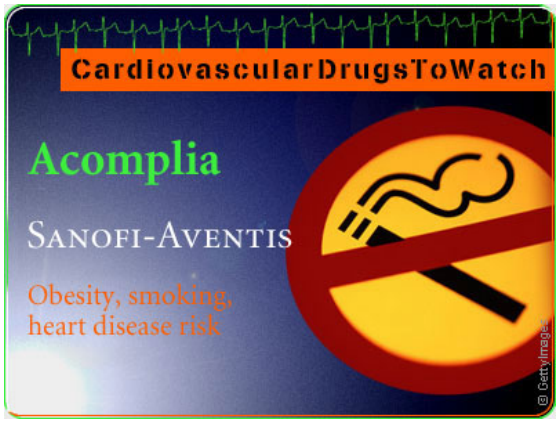
W. Xie & R. M. Evans, *Drug Discovery Today* 2002, *7*, 509-515

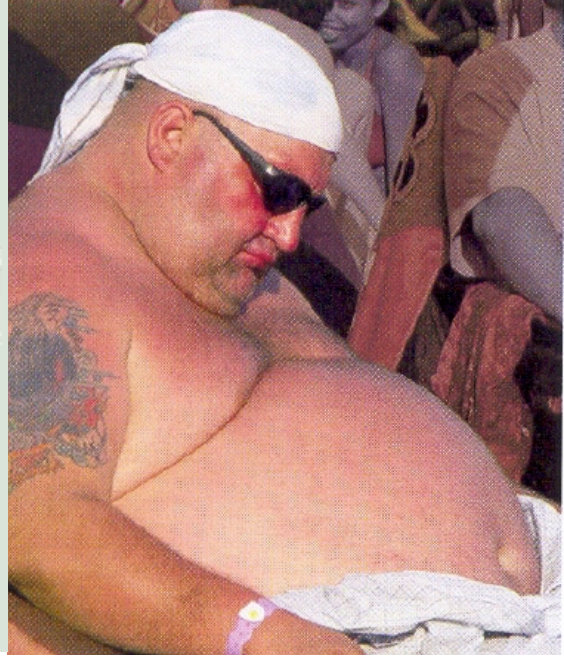
This mouse is a xeno-sensor allows the investigation of drug-drug interactions .

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



Erhardt, Medicinal Chemistry in the new Millennium. A Glance into the Future, *Pure Appl. Chem.* 2002, *74*, 703.





Animal transgênico com obesidade provocada, Representa primeiro modelo para estudo de novos fármacos anti-obsidade (anti-5HT's).

Novas formulações

Exubera[R]

Pfizer Exubera®

Insulina para inalação:

diabetes tipo 1 e 2

sanofi aventis

Pfizer