

A Química Medicinal

(Planejamento Racional de Novos Fármacos)

XXXVI Semana da Química “Ciência, tecnologia e sociedade: em busca do conhecimento”

unesp Instituto de Química, UNESP – Araraquara, 25-29 de setembro de 2006

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UFRJ

Laboratório de Avaliação e Síntese de Substâncias Bioativas



Universidade Federal do Rio de Janeiro

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6. As estratégias de desenho estrutural da Química (Farmacêutica) Medicinal

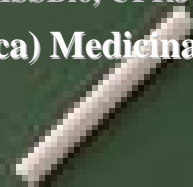
6.1 Bioisosterismo: LASSBio-346, LASSBio-501

6.3 Hibridação molecular: LASSBio-756

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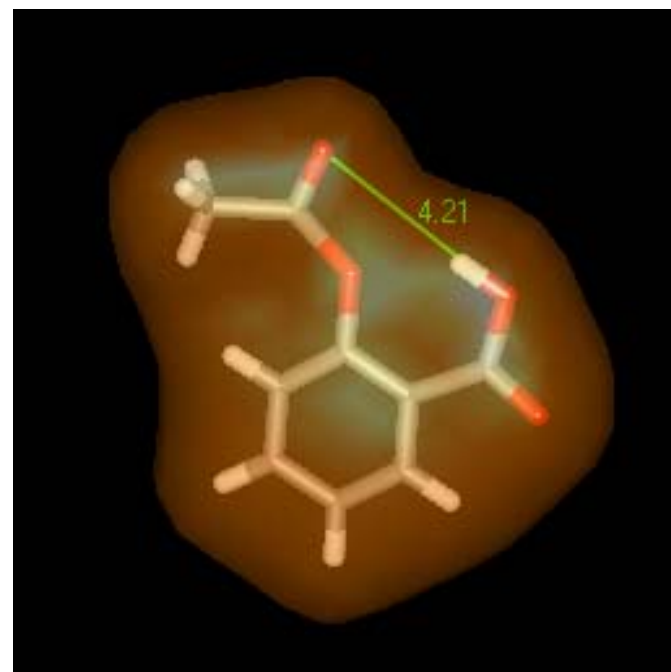
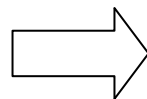
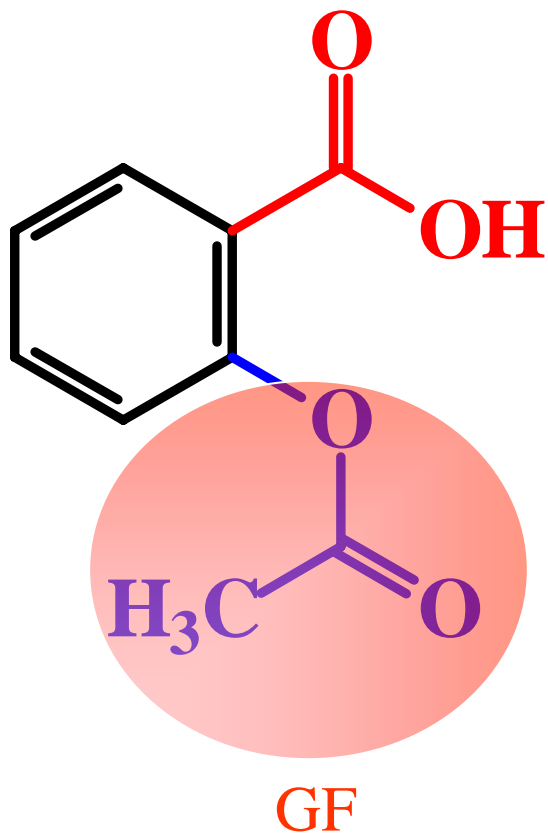
6.5 Desenho de protótipos simbióticos: LASSBio-468

7. Conclusões



Grupamento Farmacofórico do AAS

Grupamento auxofórico



Grupamento farmacofórico

arrangement of atoms (or groups of atoms) responsible for the pharmacological activity of a drug

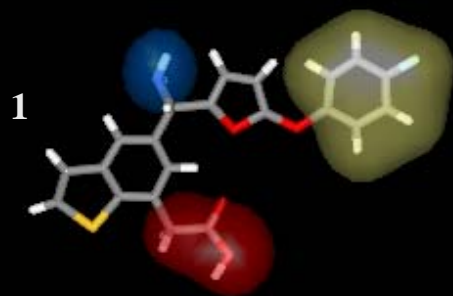
&

is a three-dimensional substructure of a molecule that carries (*phoros*) the essential features responsible for a drug's (*pharmacon*) biological activity

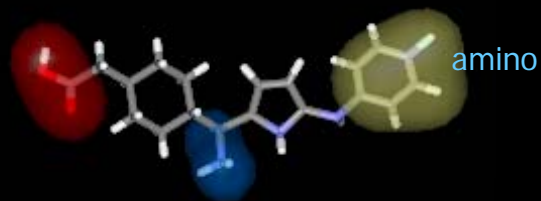
pharmacophore

fluoro-phenyl
amino group
carboxyl

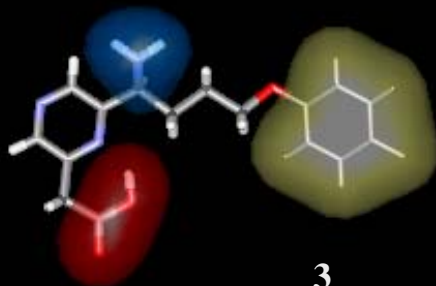
➡ pharmacophore points



carboxylic acid



amino



para-fluorophenyl

2

pharmacophore

fluoro-phenyl
amino group
carboxyl

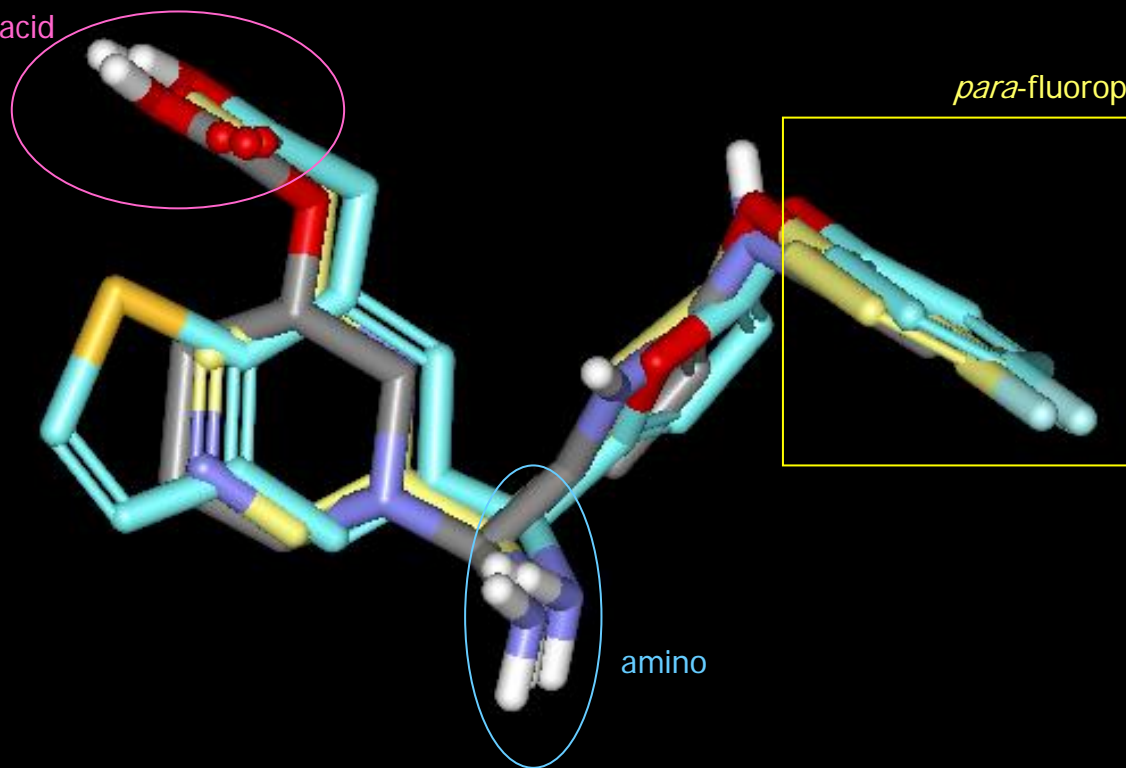
pharmacophore points

carboxylic acid

para-fluorophenyl

amino

overlap of the pharmacophoric groups ➡ molecular similarity



Grupamento farmacofórico



230

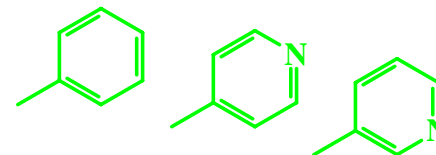
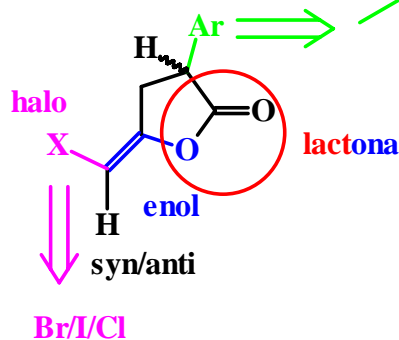
J. Med. Chem. 1986, 29, 230-238

Enol Lactone Inhibitors of Serine Proteases. The Effect of Regiochemistry on the Inactivation Behavior of Phenyl-Substituted (Halomethylene)tetra- and -dihydrofuranones and (Halomethylene)tetrahydropyranones toward α -Chymotrypsin: Stable Acyl Enzyme Intermediate

Michael J. Sofia and John A. Katzenellenbogen*



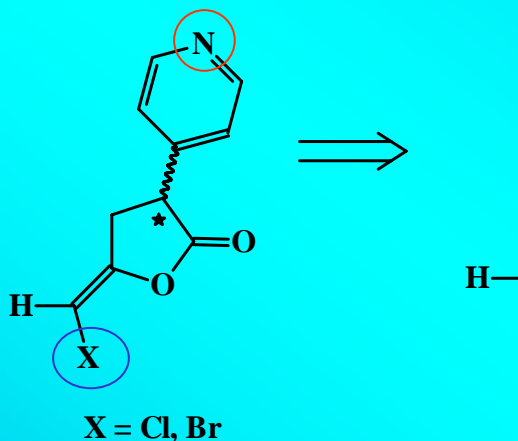
halo-enol-lactona



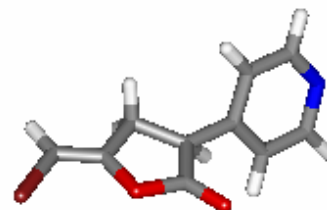
molecular diversity

Inibidor de Protease Suícida

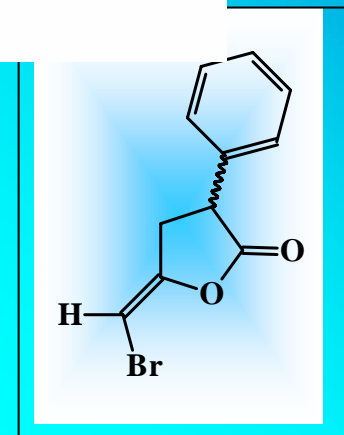
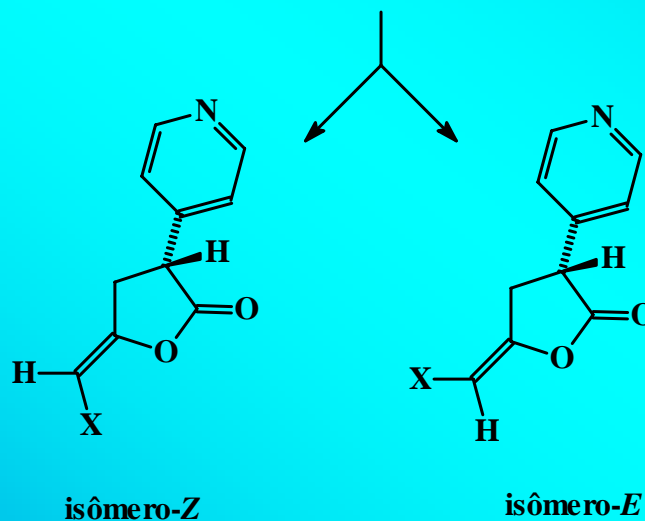
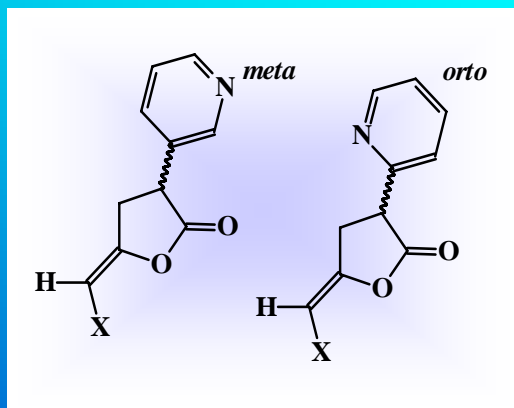
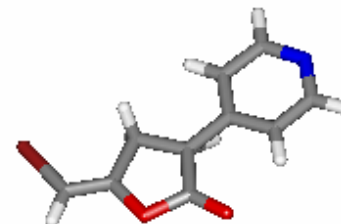
Halo-enol-lactona

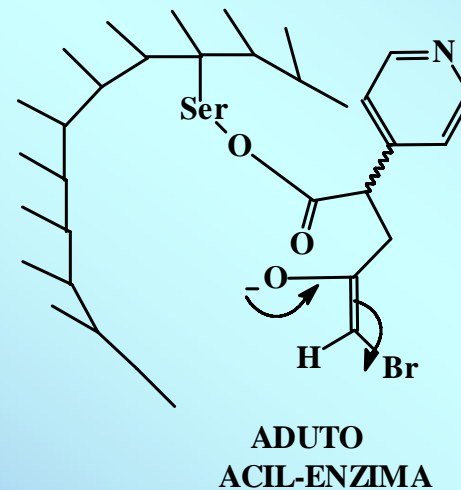
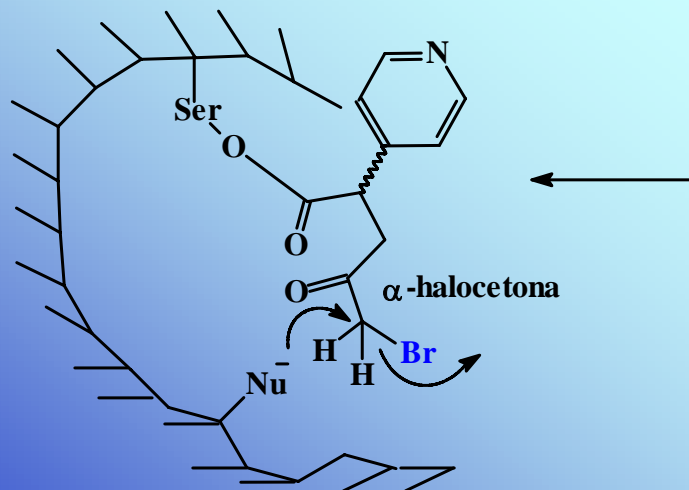
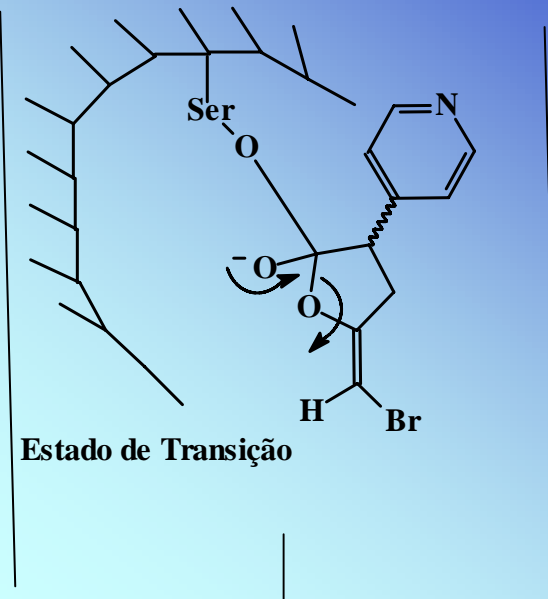
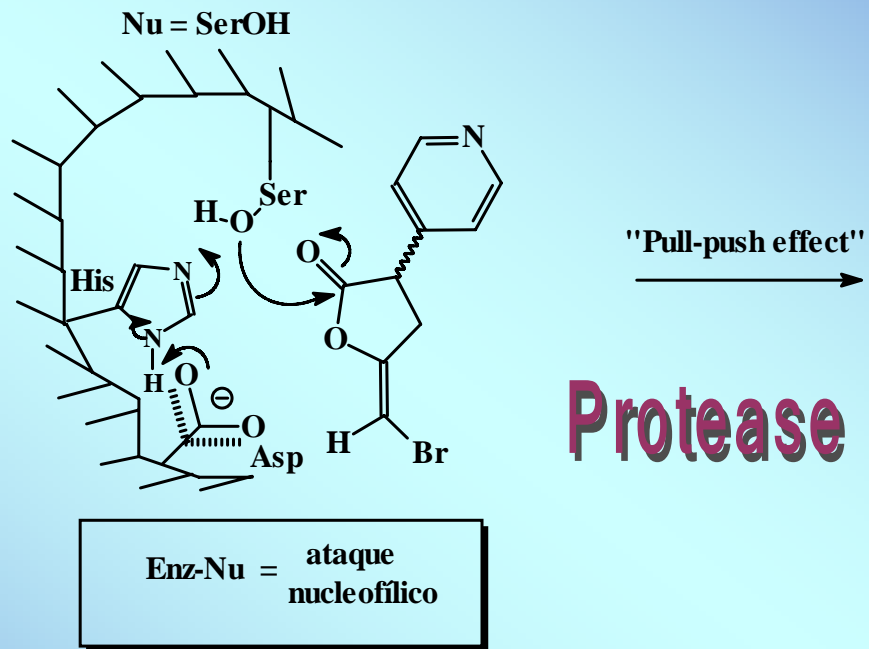


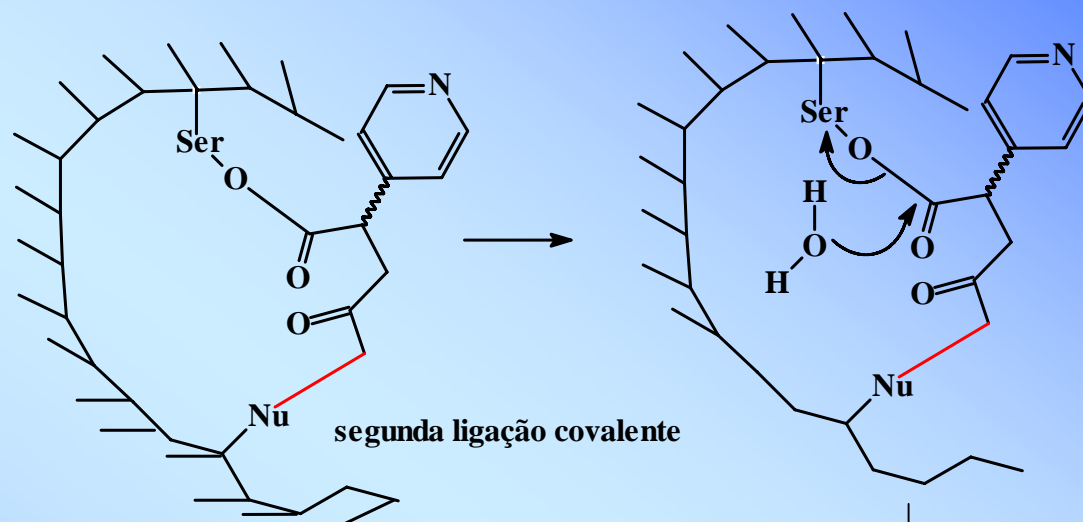
Isômero *cis*



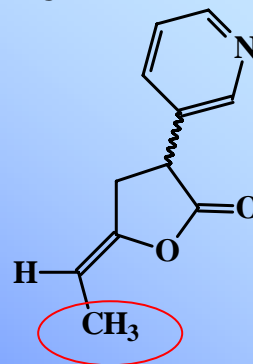
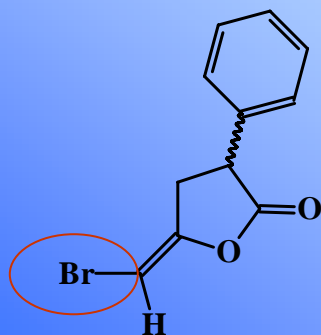
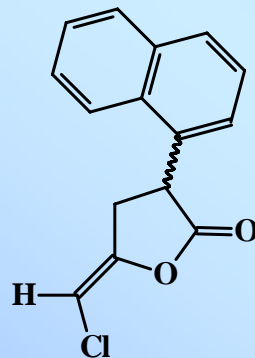
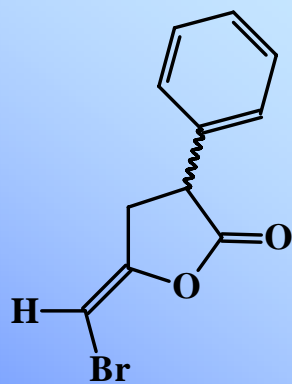
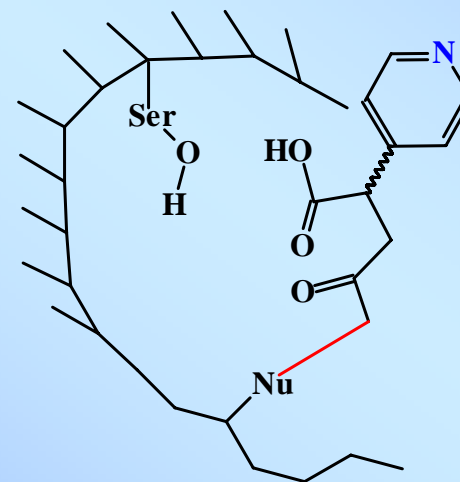
Isômero *trans*



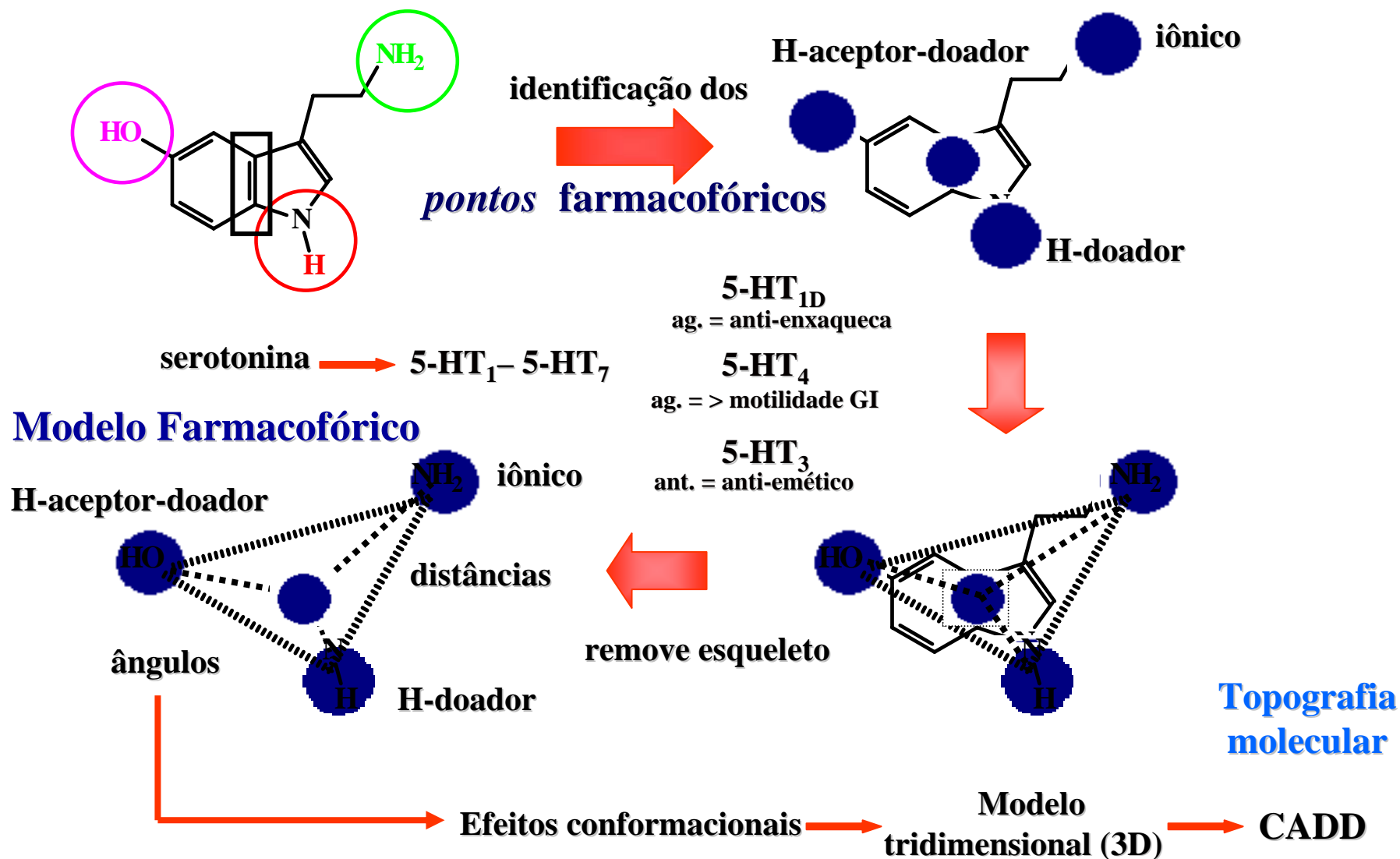




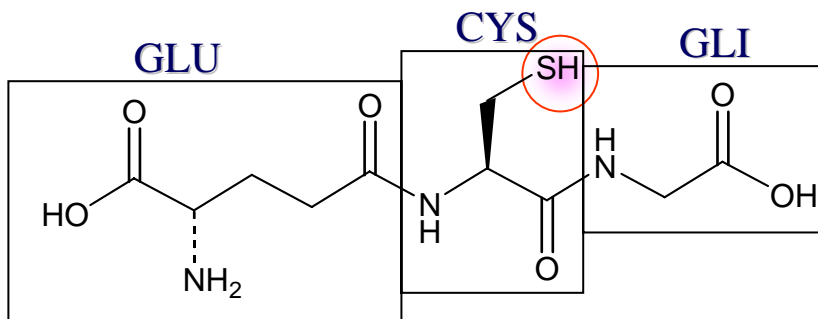
hidrólise do
acil-aducto



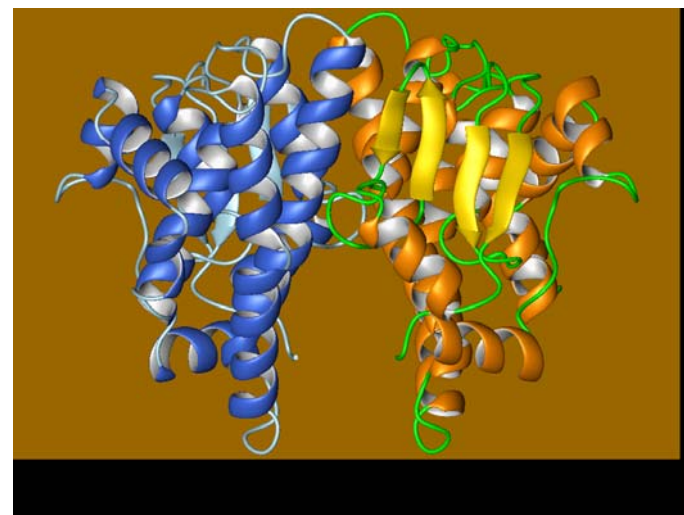
Construção de Modelo Farmacofórico 2D/3D



Grupamento toxicofórico



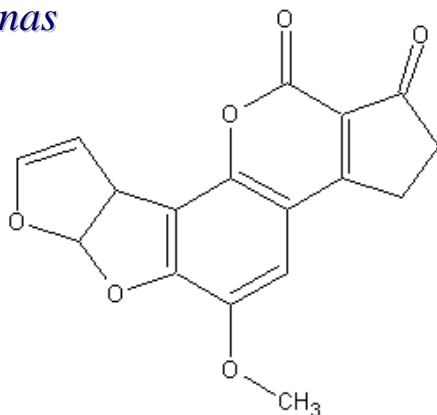
Glutatioão = (Nu⁻) bionucleófilo



Toxicofóro/toxicofórico:

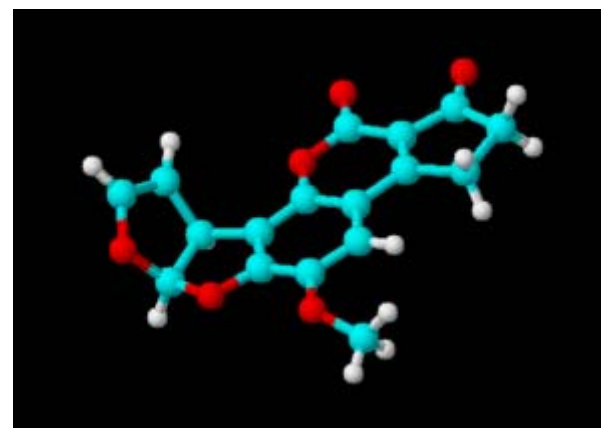
é o grupamento ou a sub-unidade estrutural de uma substância responsável pelas propriedades tóxicas.

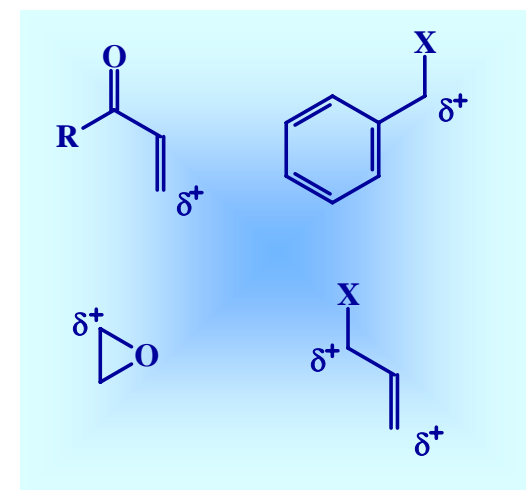
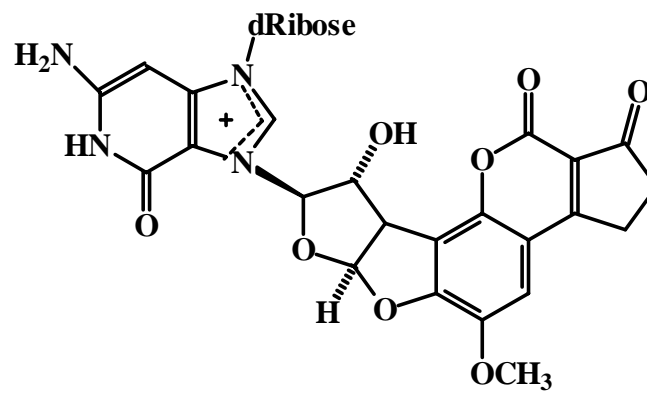
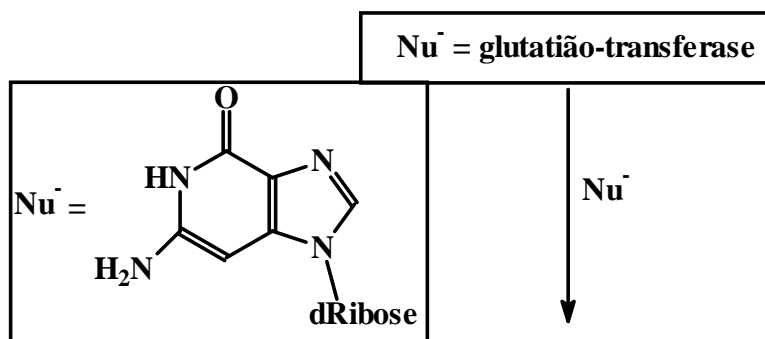
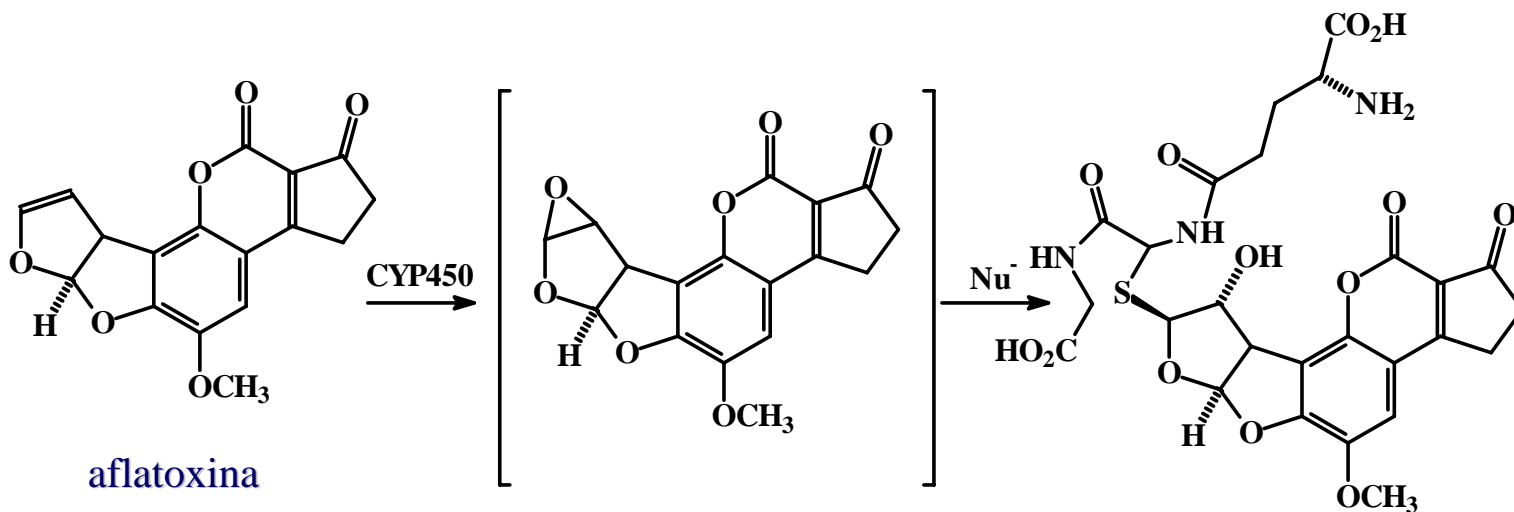
Micotoxinas



Aspergillus sp

Aflatoxina (B1/B2/G1/G2)



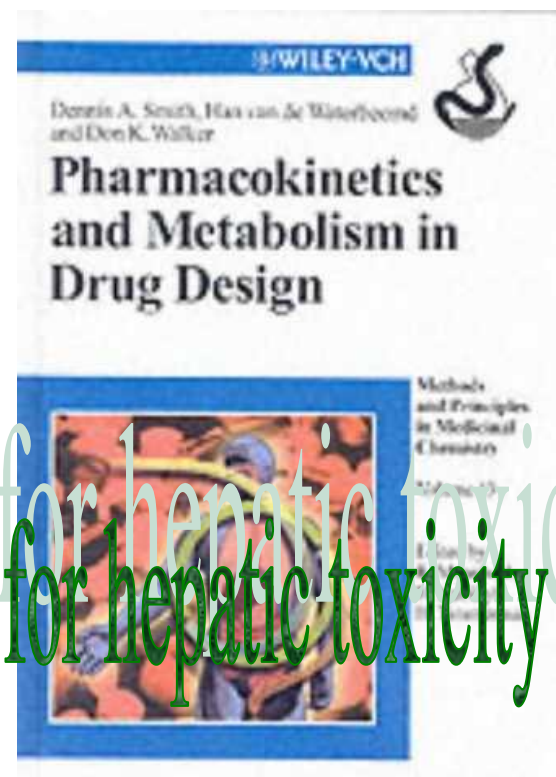


Fase Farmacocinética

Predicting oral drug absorption

Predicting oral drug absorption

ADME*



* absorção, distribuição, metabolismo & eliminação

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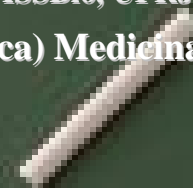
6.1 Bioisosterismo: LASSBio-346, LASSBio-501

6.3 Hibridação molecular: LASSBio-756

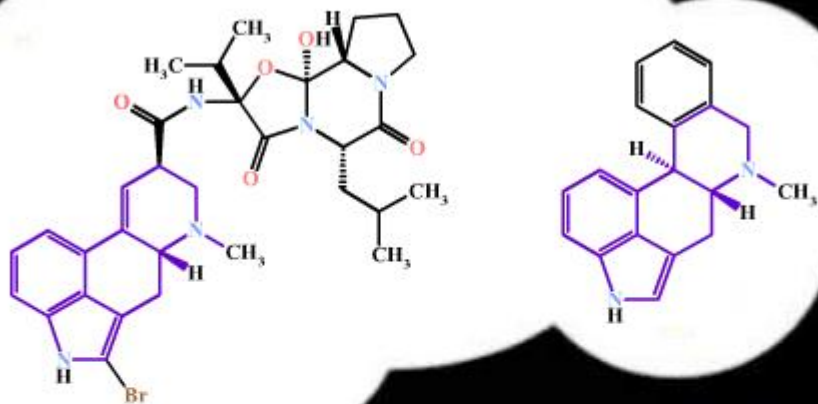
6.4 Simplificação molecular: LASSBio-294

6.5 Desenho de protótipos simbióticos: LASSBio-468

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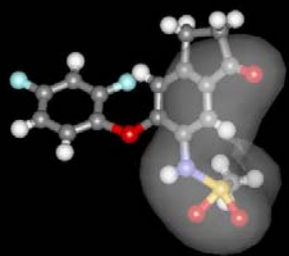


Fármacos Inteligentes



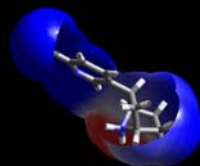
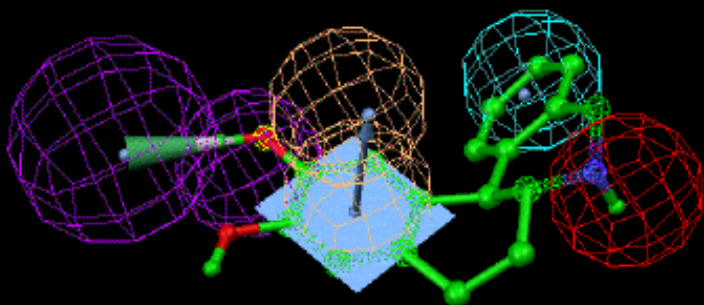
*Planejamento
racional*

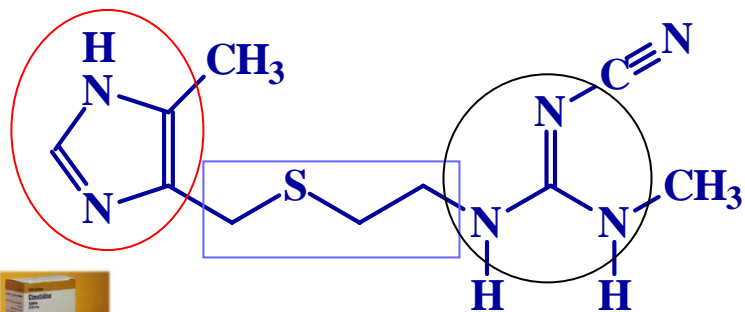




Química Medicinal

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





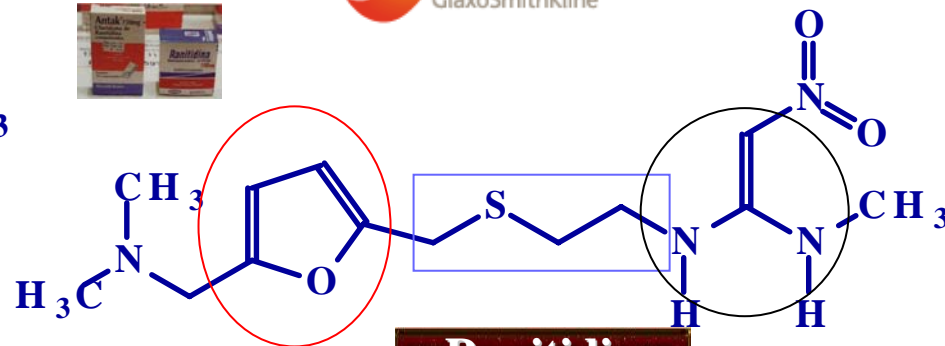
Cimetidina

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



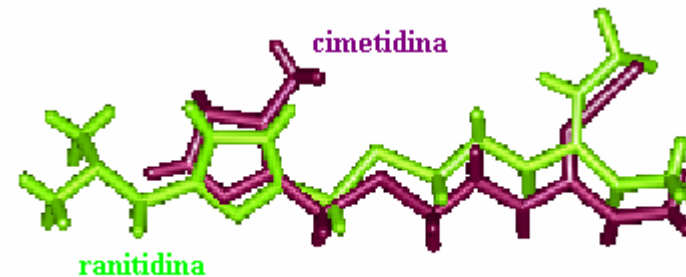
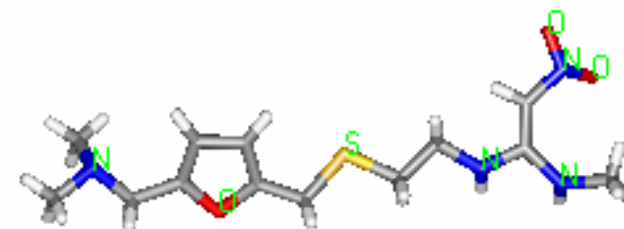
*similaridade
molecular
me-too*

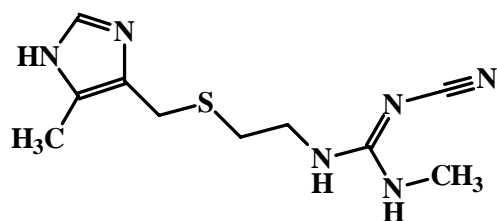
**Inovação
terapêutica**



Ranitidina

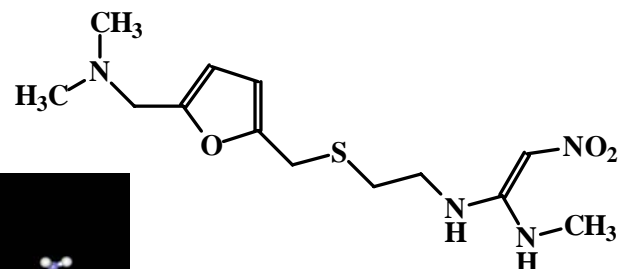
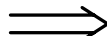
Barry J. Price *et al.*, 1978
US 4128658 1978 - Allen & Hanburys
Brit. J. Pharmacol. **66**, 464 (1979)





cimetidina

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



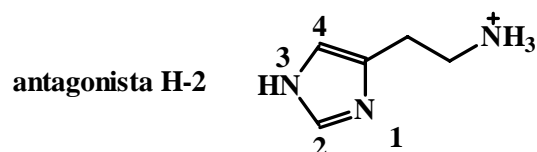
ranetidina

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

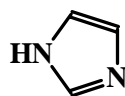
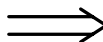
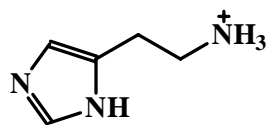


A gênese da cimetidina

A procura do protótipo:



tautômeros

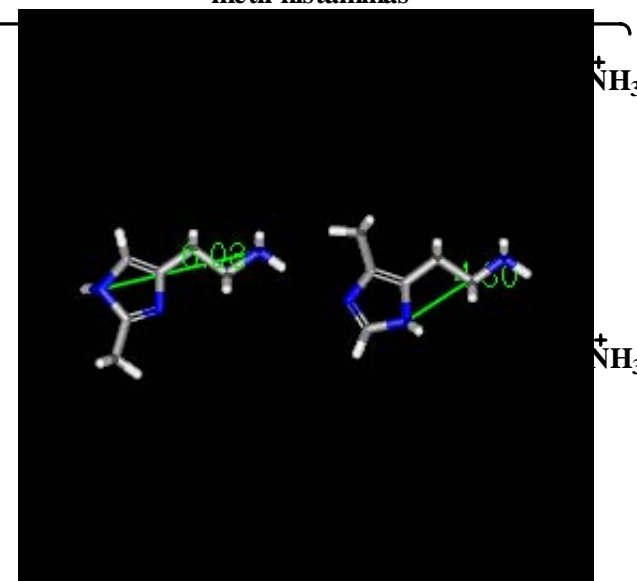


imidazola

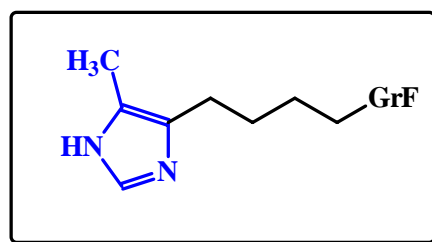


4-Cl, 4-Br, 4-NO₂

metil-histaminas



metil-alquil-imidazola



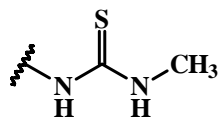
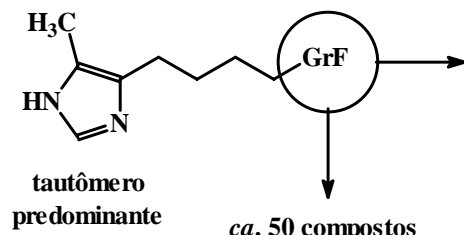
Ar

espaçador

GrF

Ar = arila, heteroarila
GrF = grupamento funcional

N-metil-tiouréia

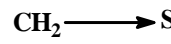


burimamida

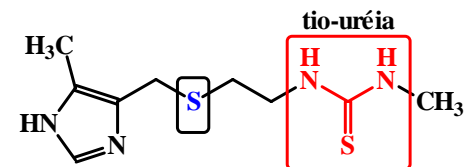
ant/agonista
& CYP450

bioisosterismo

clássico



Ensaída em 700 pacientes com
úlcera duodenal

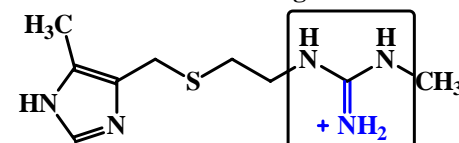


ant. seletividade H-2
& <<CYP450, p.o.

ensaios clínicos
granulocitopenia

bioisosterismo
clássico

gunidinium

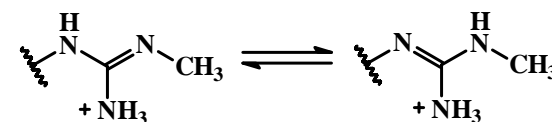


SK&F 92408

ant. seletivo H-2
ID₅₀ 12 μM/kg

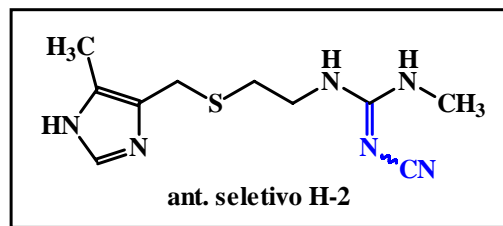
imino

amino

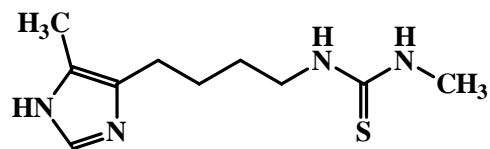


Cimetidina

ID₅₀ 1,4 μM/kg



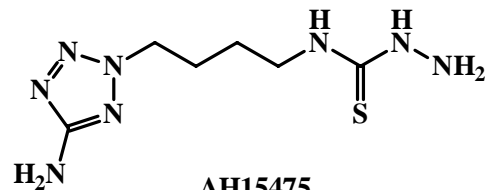
A gênese da cimetidina



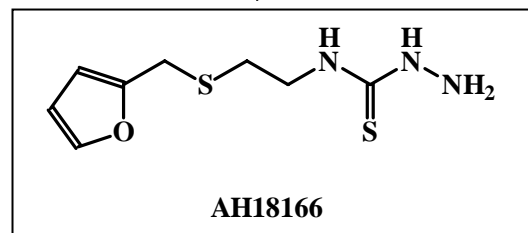
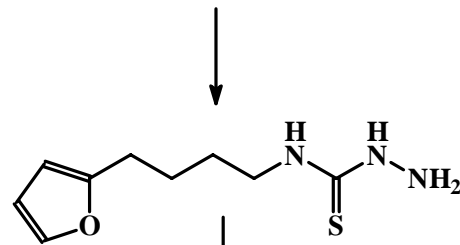
burinamida

Allen & Hanburys Ltd.

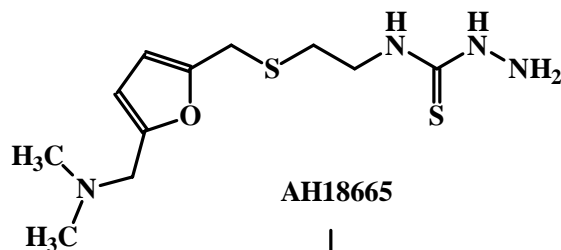
análogos da burinamida



AH15475

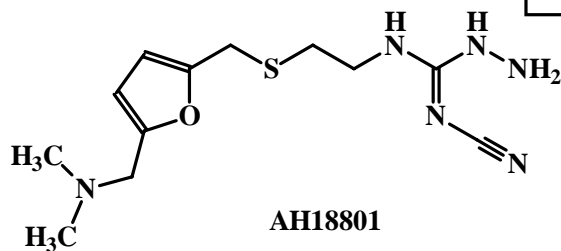


AH18166



AH18665

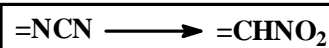
ciano-guanidila



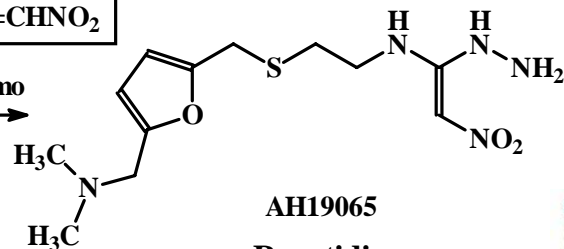
AH18801

não cristalino

mesma potência da cimetidina



bioisosterismo



AH19065

Ranetidina

nitro-vinila

cristalino



Da cimetidina à ranetidina





Endereço <http://acswebcontent.acs.org/landmarks/tagamet/newera.html>

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A new era of logical drug design

The research program leading to cimetidine also represented a revolution in the way pharmaceuticals are developed. Traditionally, the development of a new drug would often depend on the fortuitous discovery of a plant or microbial extract that showed some of the required biological activity. Using that first extract as a lead, many similar compounds would be made and tested for pharmacological effectiveness. In many cases, the researchers did not know how the drug worked, so finding an optimal compound was difficult.

The development of cimetidine was radically different: it was one of the first drugs to be designed logically from first principles. SK&F's multidisciplinary research team first looked at the physiological cause of acid secretion. They confirmed that a molecule found in the body called histamine triggers the release of acid when it binds to a specific receptor (now called the H_2 -receptor) in the stomach lining. Their aim was to find a molecule that successfully competed with histamine in combining with the receptor, but then blocked, rather than stimulated, acid release. Such a molecule was called a histamine H_2 -receptor antagonist and represented a new class of drugs.

Using a step by step analysis of structural and physical properties, the team made a series of histamine-based molecules, which were then tested for antagonist activity using carefully designed pharmacological assays. Today, this approach of rational drug design underpins the discovery programs of many major pharmaceutical companies.





National Historic Chemical Landmarks

AMERICAN CHEMICAL SOCIETY

Science That Matters



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Action!
Take Part
& Nominate

Landmark designation

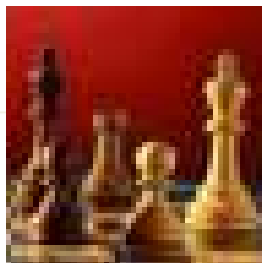
The American Chemical Society and The Royal Society of Chemistry designated the discovery of histamine H_2 -receptor antagonists, which led to the development of the anti-ulcer drug

Tagamet[®], as an International Historic Chemical Landmark in ceremonies at SmithKline Beecham's research facilities (now GlaxoSmithKline) at Harlow, United Kingdom, on November 24, 1997, and King of Prussia, Pennsylvania, on February 27, 1998. The text of the plaques at the two sites reads:

Pioneering work by scientists in the laboratories of this company led to the first clinically effective inhibitor of gastric acid secretion. The worldwide introduction of cimetidine (Tagamet) revolutionized the treatment of peptic ulcers by dramatically reducing the need for surgical intervention. The work is recognized as the classic example of the systematic modification of a natural messenger substance (histamine) to create a therapeutically useful blocking agent. Effective commercialization of this discovery was greatly facilitated by the subsequent investigation and design of novel synthetic routes, which led to the development of an efficient chemical manufacturing process.

The Royal Society of Chemistry's Historic Chemical Landmarks can be found at <http://www.rsc.org/lap/publicaf/landmarks.htm>.

Designed by [MSK Partners](#), Hunt Valley, Maryland.



Fármacos Inteligentes

Super-Super Drug

otimização de protótipo natural



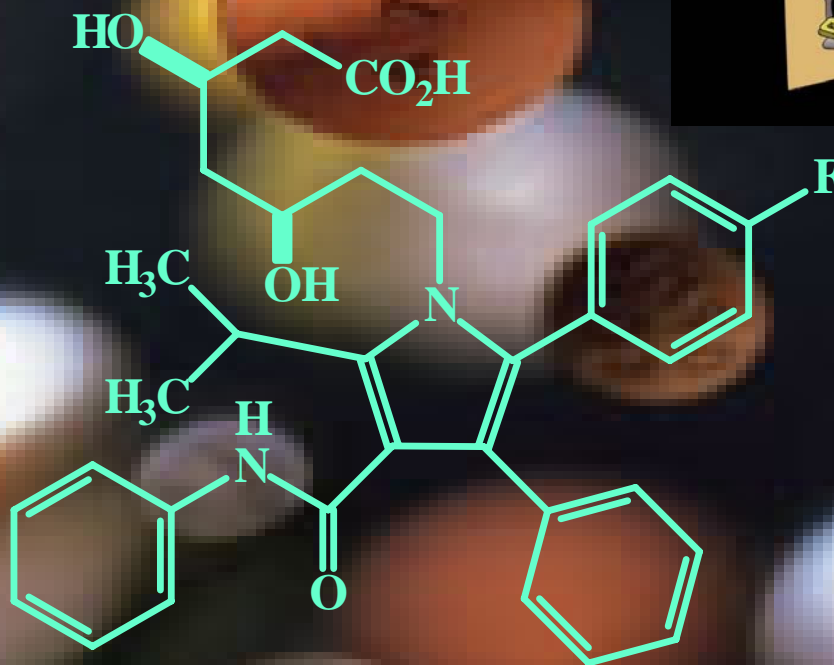
Jan., 1987: Lipitor[®]

US\$ 1 billion

2002: US\$ > 7,0 billions

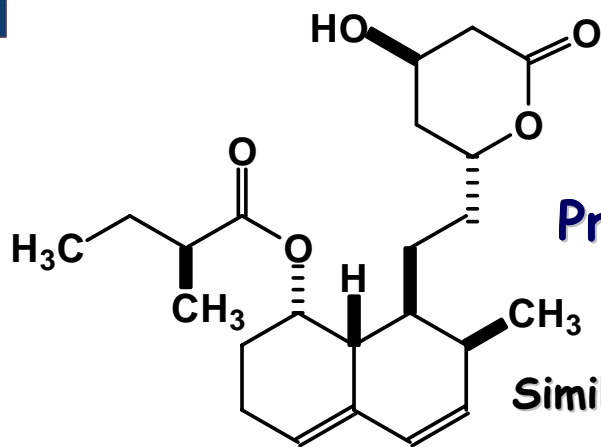
* A. M. Thayer, CE&N, Nov. 12, 2002

atorvastatina



Super-farmaco

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



Protótipo natural

Similari



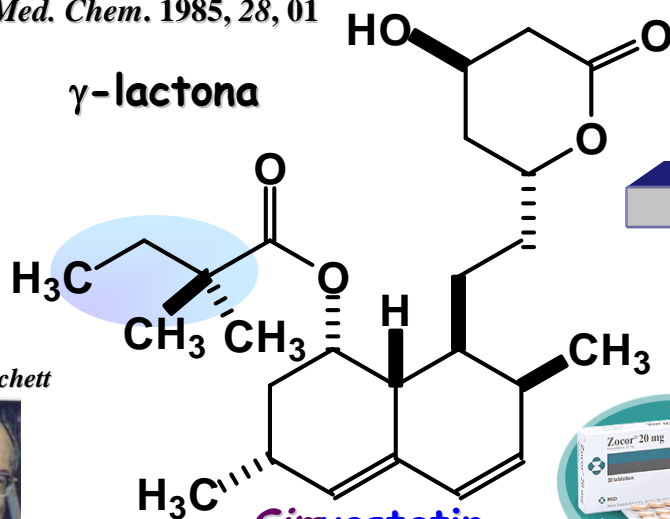
1975 - Compactina

A. Endo, J. Antibiot. 1979, 32, 806

Monascus ruber

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

γ -lactona



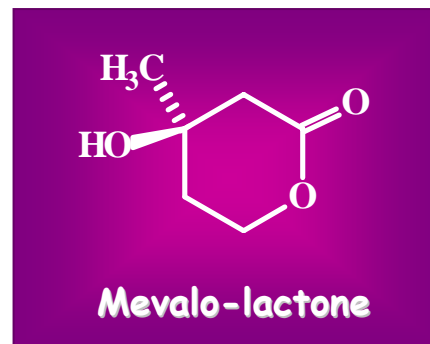
Arthur Patchett



J. Med. Chem. 1986, 29, 849

J. Med. Chem. 2002, 45, 5609

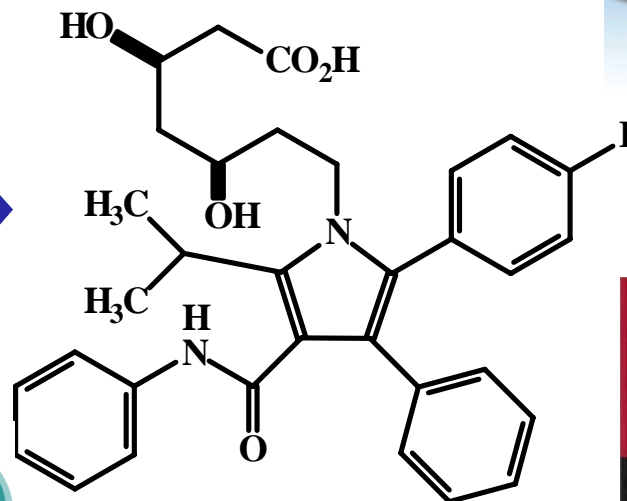
Simvastatin
(Zocor)
MK-733
1981



Mevalo-lactone

HMG-CoA reductase

ácido pirrol-heptanóico



atorvastatina

$C_{33}H_{35}FN_2O_5$



Bruce Roth

Milestones in Drug Therapy

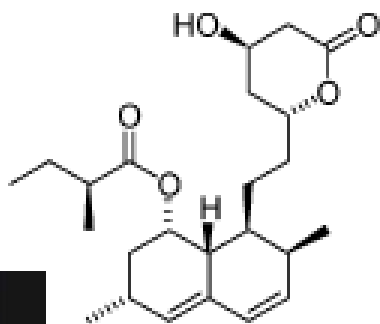
HMG-CoA Reductase Inhibitors

G. Schmitz
M. Torzavski
Editors

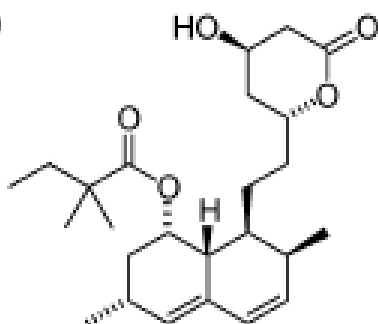




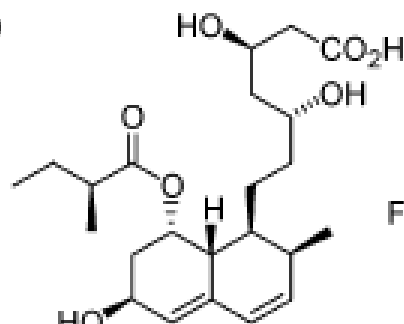
Me-too



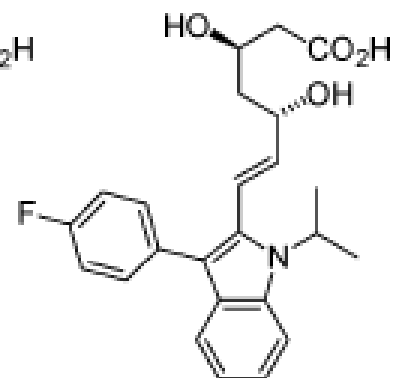
Lovastatin (15)
(Mevacor®)



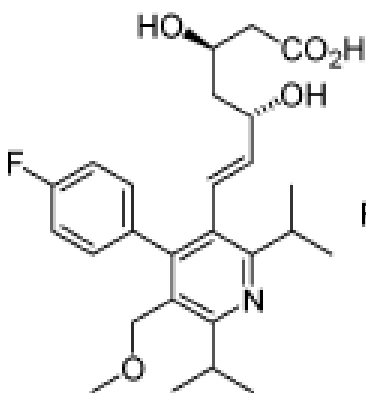
Simvastatin
(Zocor®)



Pravastatin
(Pravachol®)

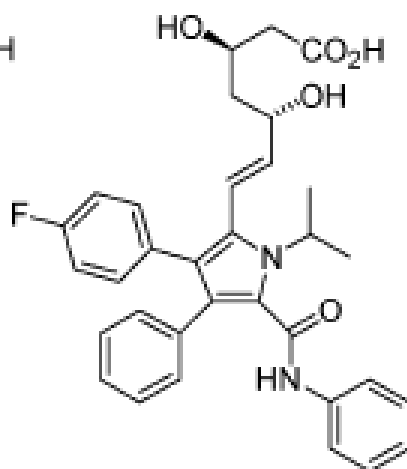


Fluvastatin
(Lescol®)

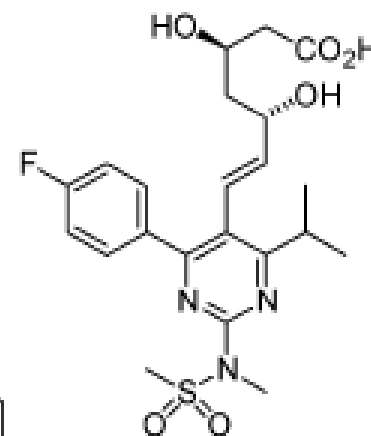


Cerivastatin
(Baycol®)

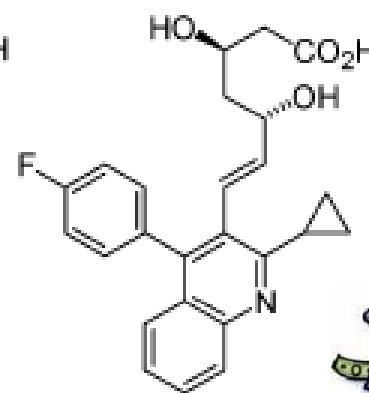
Note: removed from market



Atorvastatin
(Lipitor®)



Rosuvastatin (36)
(Crestor®)



Pitavastatin (37)
(Livalo®)



Características estruturais comuns aos cinco fármacos mais vendidos no mundo em 2004:

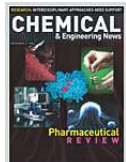
- Possuem apenas 7 elementos químicos: C,H,O,N,S,F,Cl;
- Todos possuem heteroátomos;
- Todos são multicíclicos (< cinco anéis);
- 80% têm unidades aromáticas e são heterocíclicos;
- Têm apenas 10 centros estereogênicos;

Totalizam 111 C's

1 C = US\$ 280 mi;

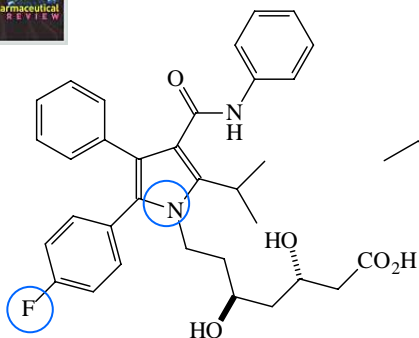
30,9%

Fonte:

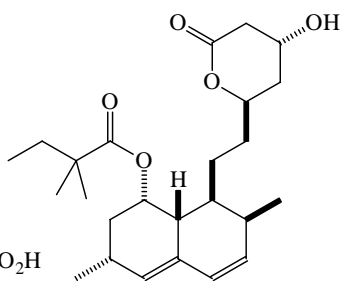


C&EN December 8, 2004
Volume 82, Number 49
S. Class pp. 18-29

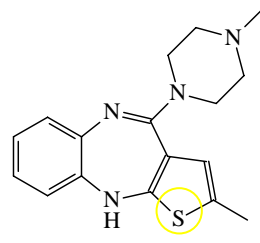
em US\$ bilhões, nos últimos 12 meses;
& estima-se que o mercado mundial, em 2004, tenha sido ca. US\$ 505 bilhões



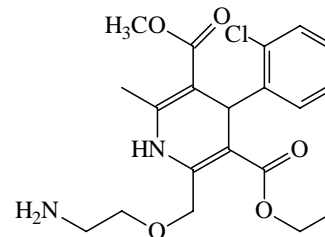
(1) $C_{33}H_{35}FN_2O_5$



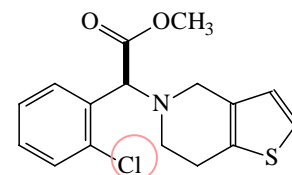
(2) $C_{25}H_{38}O_5$



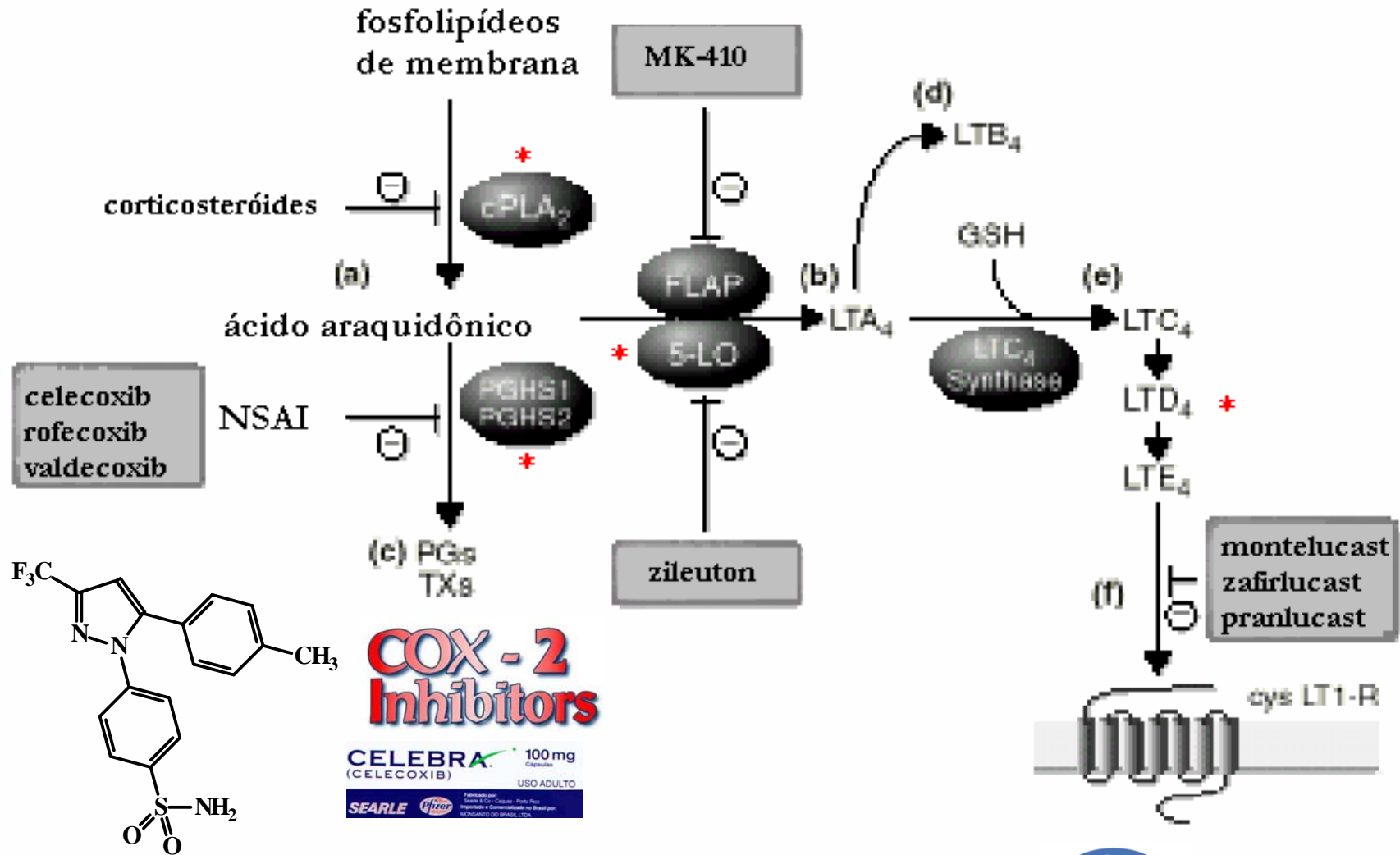
(3) $C_{17}H_{20}N_4S$



(4) $C_{20}H_{25}ClN_2O_5$



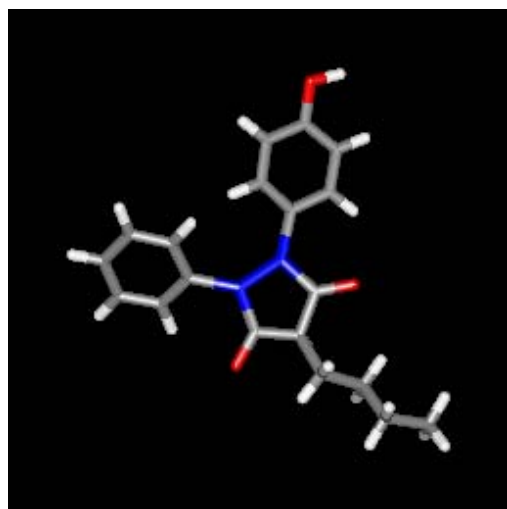
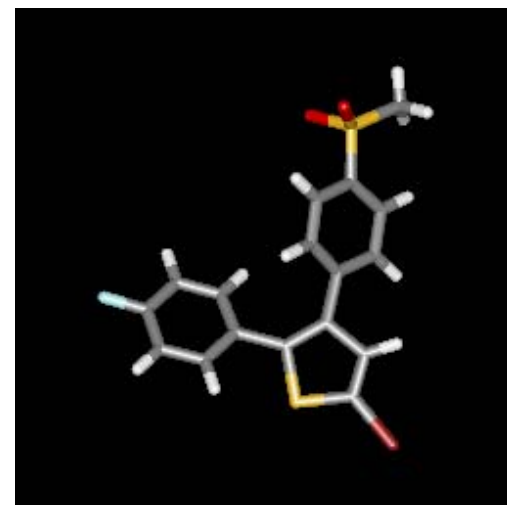
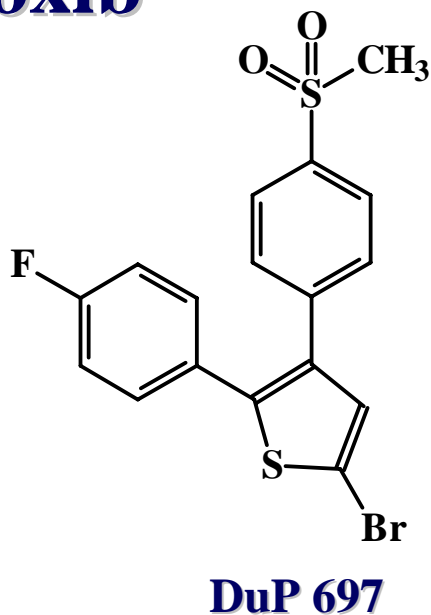
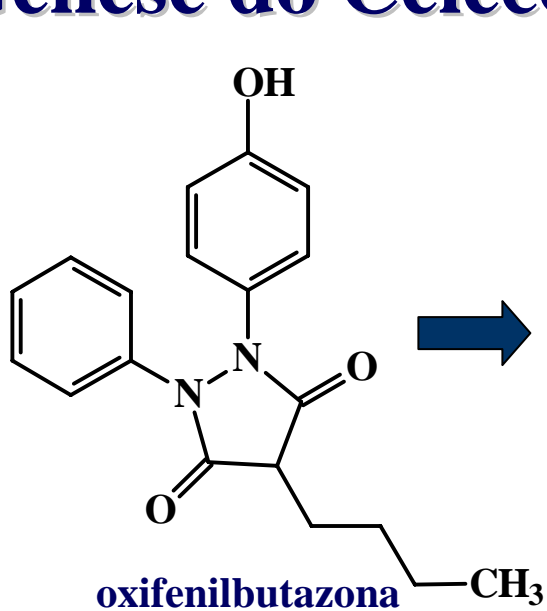
(5) $C_{16}H_{16}ClNO_2S$



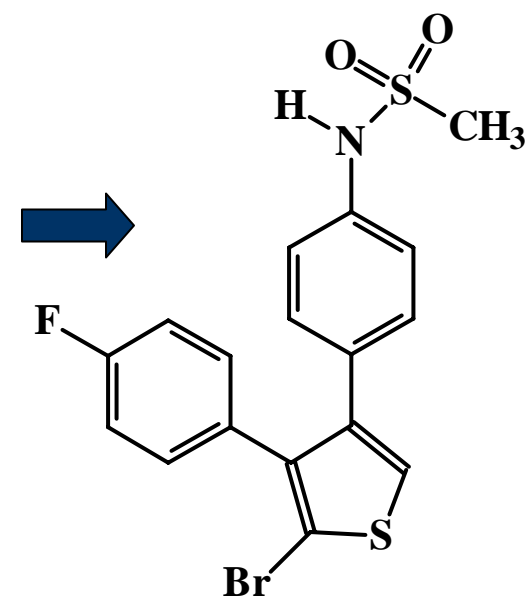
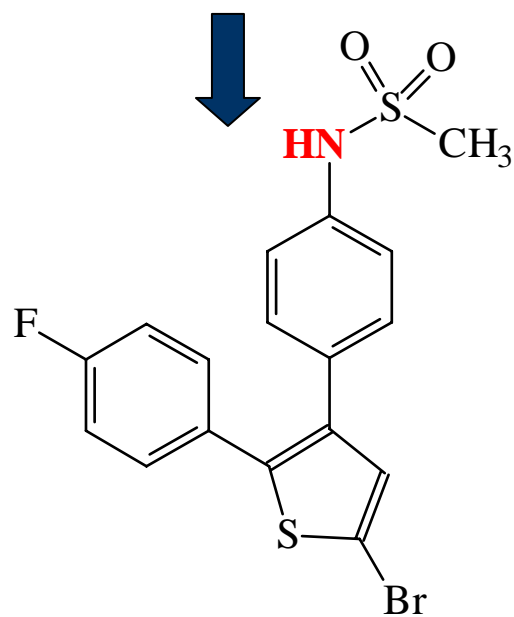
Gênese do Celecoxib



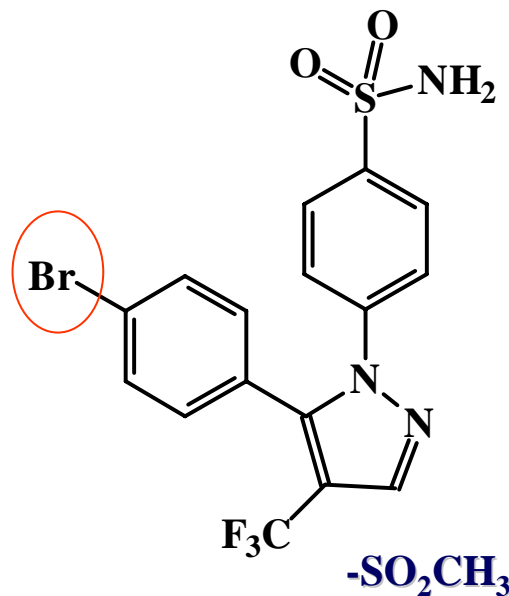
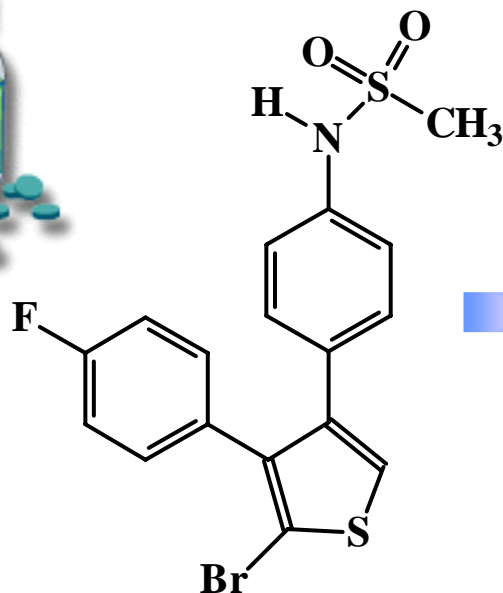
Gênese do Celecoxib



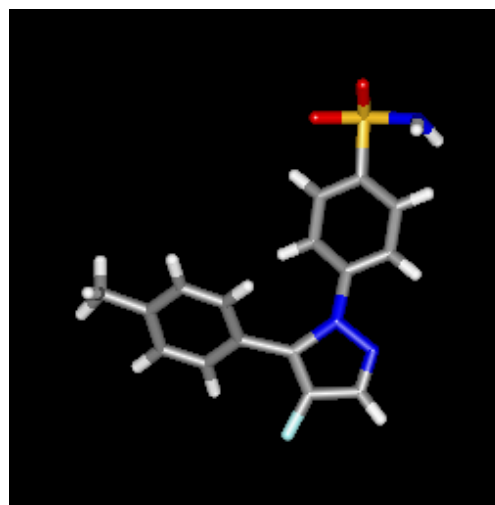
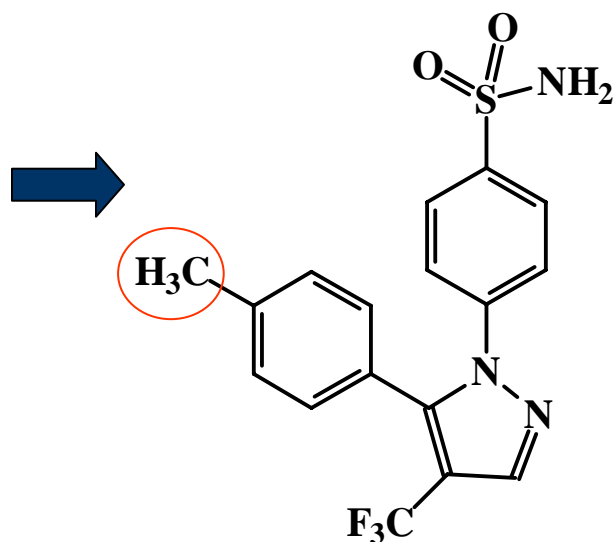
Pfizer



Gênese do Celecoxib



Gans (DuPont) 1990
Vida-média = 12 dias !
(ADME)

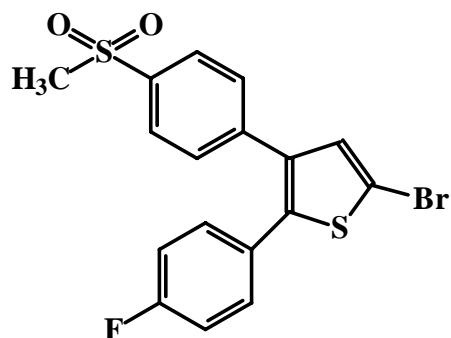


celecoxib (Celebra)

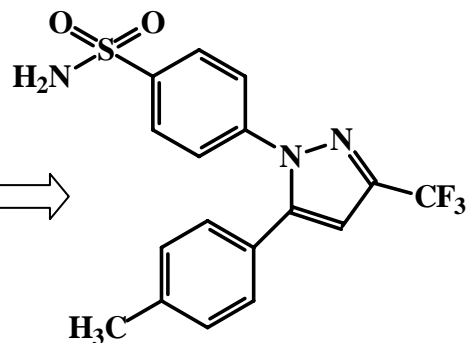
US\$ 797 milhões no
3 trimestre 2004 (>14%)



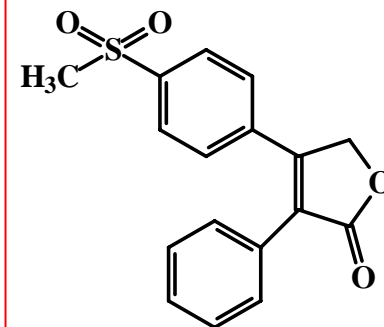
Similaridade Molecular: “*me-too*”



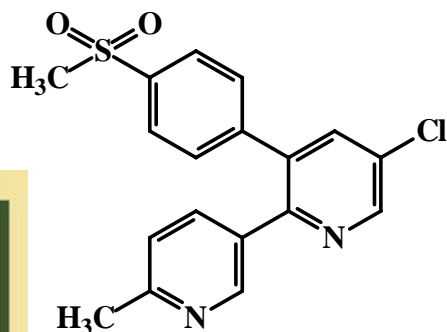
DuP 697
 $C_{17}H_{12}BrFO_2S_2$
 411.30



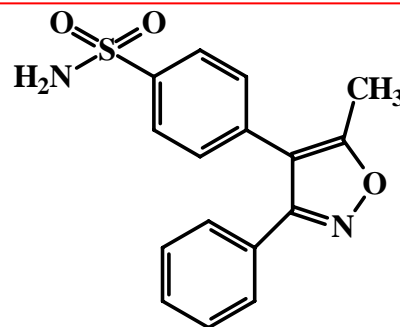
celecoxib
 1999
 $C_{17}H_{14}F_3N_3O_2S$
 381.37



rofecoxib
 1999-2004
 $C_{17}H_{14}O_4S$
 314.35



etoricoxib
 2002
 $C_{18}H_{15}ClN_2O_2S$
 358.84



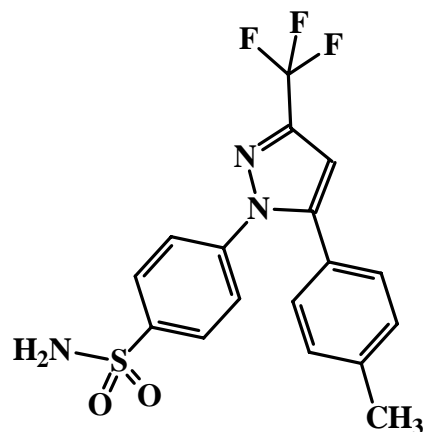
valdecoxib
 2002-2005
 $C_{16}H_{14}N_2O_3S$
 314.35

PM 314- 411 uma
 # anéis: 3
 doador-H: 0-1
 ceptor-H: 2-4

vendas US\$ 12,8 bilhões no
 3 trimestre 2004
 (agosto-outubro)

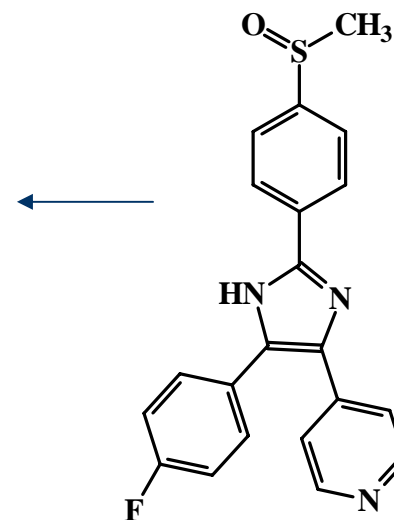
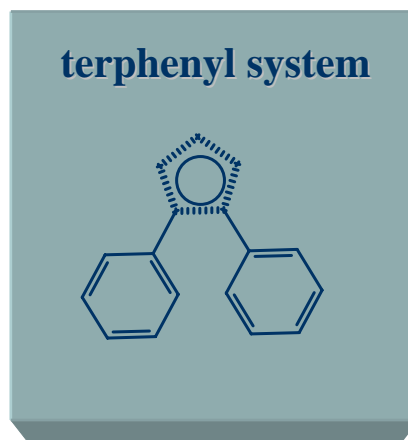


Molecular similarity recognition



C₁₇H₁₄F₃N₃O₂S
381

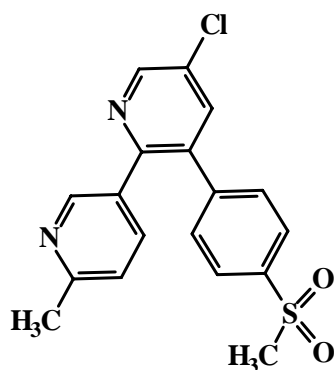
COX-2 inhibitors



C₂₁H₁₆FN₃OS
377

SB203580

P38 MAP kinase inhibitor

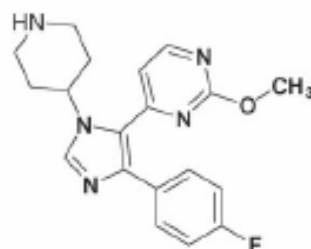


Coxib's act at p38 MAPK level?

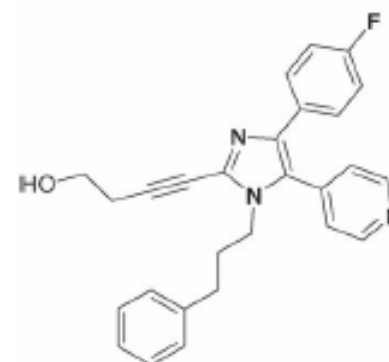
p38 MAP kinase inhibitors: A future therapy for inflammatory diseases

Ruth J. Mayer*, James F. Callahan

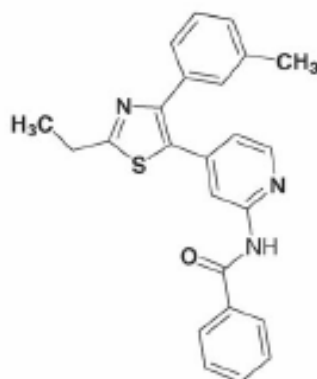
GlaxoSmithKline Pharmaceuticals, Respiratory and Inflammation CEDD, P.O. Box 1539, King of Prussia, PA 19406, USA



SB-242235
(GlaxoSmithKline)



RWJ 67657
(Johnson & Johnson)



TAK-715
(Takeda)

No Published Structures

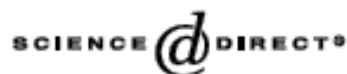
VX-702
(Vertex)

SCIO-469
(Scios)

SB-681323
(GlaxoSmithKline)



Available online at www.sciencedirect.com



Bioorganic & Medicinal Chemistry Letters 15 (2005) 3506–3509



The molecular basis for coxib inhibition of p38 α MAP kinase

Gilberto M. Sperandio da Silva,^{a,b} Lidia M. Lima,^a Carlos A. M. Fraga,^a
Carlos M. R. Sant'Anna^{a,c} and Eliezer J. Barreiro^{a,b,*}

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^b*Departamento de Farmacologia Básica e Clínica, Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, 21941-590, Brazil*

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Received 11 April 2005; revised 20 May 2005; accepted 26 May 2005

Abstract—In this work, we present the results of two combined approaches, molecular docking and comparative molecular field analysis (CoMFA), to propose how the selective cyclooxygenase-2 inhibitor celecoxib could act as a p38 mitogen-activated protein (MAP) kinase inhibitor. The docking analysis revealed why celecoxib has a less favorable binding energy ($\Delta G = -12.4$ kcal/mol) than the selective p38 MAP kinase (p38 MAPK) inhibitor, SB203580 ($\Delta G = -22.2$ kcal/mol). The CoMFA results revealed unfavorable steric effects that can be related to the predicted lower p38 MAP kinase inhibitory activity of celecoxib. Additionally, FlexX and CoMFA results also suggested that etoricoxib, another selective COX-2 inhibitor, could inhibit p38 MAP kinase.

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Binding of celecoxib & SB203580 with p38 MAPK

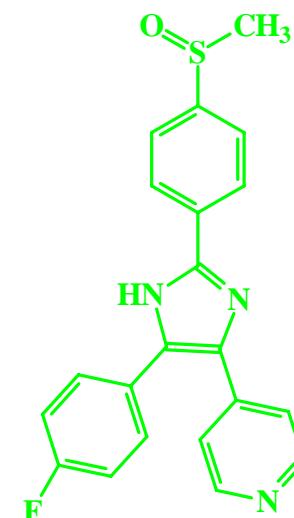
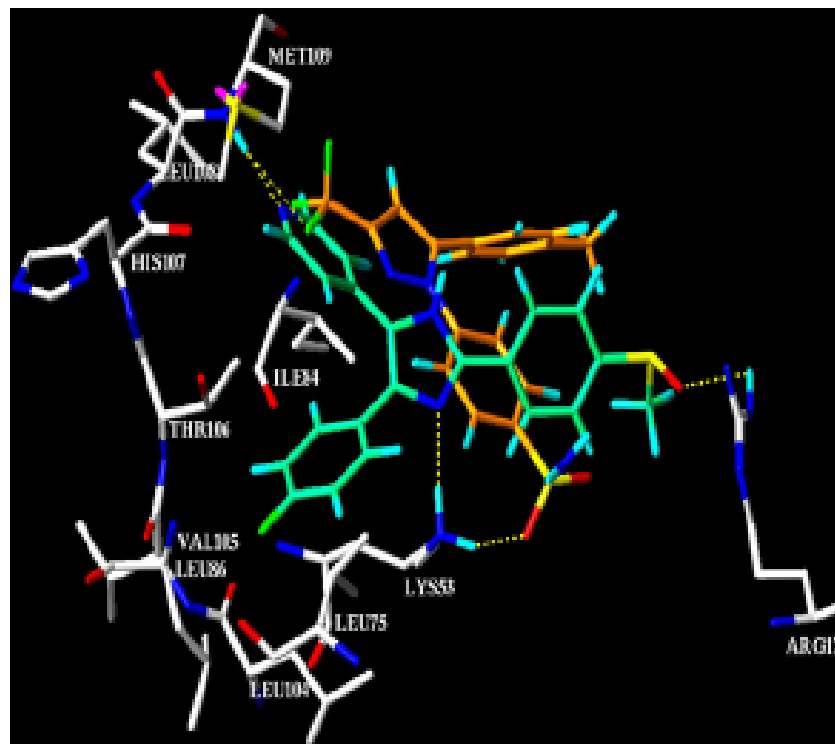
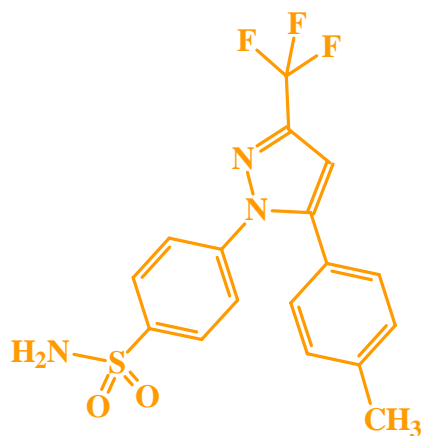


Figure 2. Probable binding conformation of celecoxib and its alignment in the binding site of p38 MAPK. FexX docking shows most important amino acid of p38 MAPK to interact with celecoxib. For celecoxib the carbon atoms are shown in orange (C), blue (N), red (O), and green (halogen). For SB203580, the carbon atoms are shown in green-blue (C), blue (N), red (O), and green (halogen).