XXVIII Escola de Verão em Química Farmacêutica Medicinal Professor Eliezer Barreiro

Introdução à Química Medicinal

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Janeiro de 2022

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Sumário

→ Definição e Princípios da Química Medicinal e a Inovação Farmacêutica; Reconhecimento Molecular Fármaco-Receptor; Grupamento Farmacofórico;

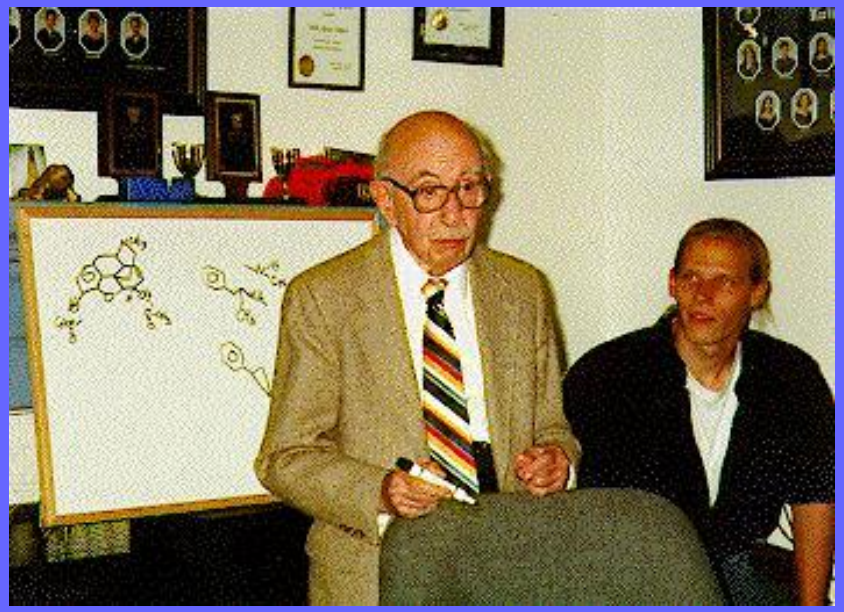
→ Propriedades Estruturais e Atividade Biológica: ADMET;

→ A importância dos Produtos Naturais e Sintéticos na Descoberta de Fármacos; Exemplos Históricos;

→ Bioisosterismo e outras Estratégias de Modificação Molecular;

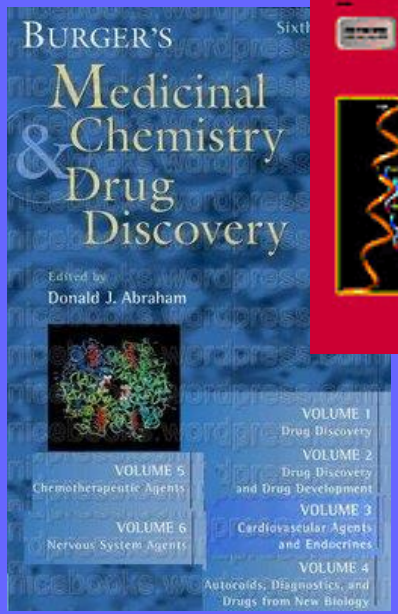
→ Fármacos de Ação Múltipla: Híbridos vs Simbióticos

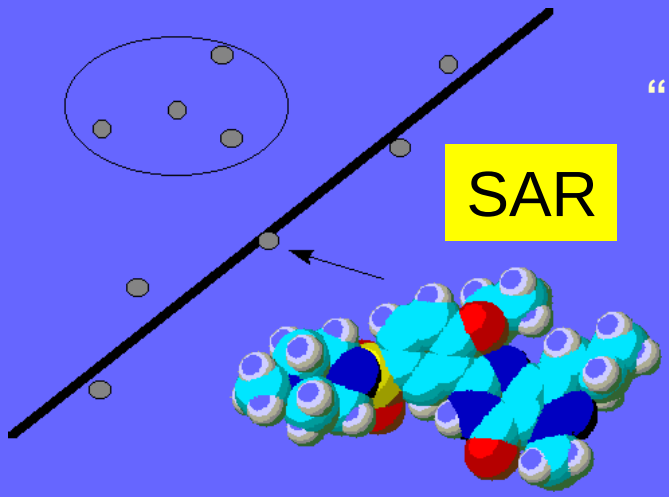
O Paradigma da Química Medicinal



"Medicinal Chemistry remains a challenging science, which provides profound satisfaction to its practitioners. It intrigues those of us who like to solve problems posed by nature. It verges increasingly on biochemistry and all the physical, genetic and chemical riddles in animal physiology which bear on medicine. Medicinal Chemists have a chance to participate in the fundamentals of prevention, therapy and understanding of diseases and thereby to contribute to a healthier and happier life."

(Alfred Burger, 1990)





"...Nobody in the world is condemned to work with as many variables as the medicinal chemist..."

(Corwin Hansch, 1993)

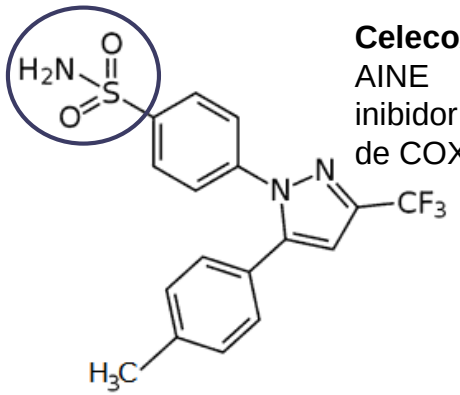
Burger's Medicinal Chemistry and Drug Discovery, Vol.1, Wolff, M. E., Ed., 5th Ed., 1994.

A Química Medicinal e o Paradigma da Invenção dos Fármacos

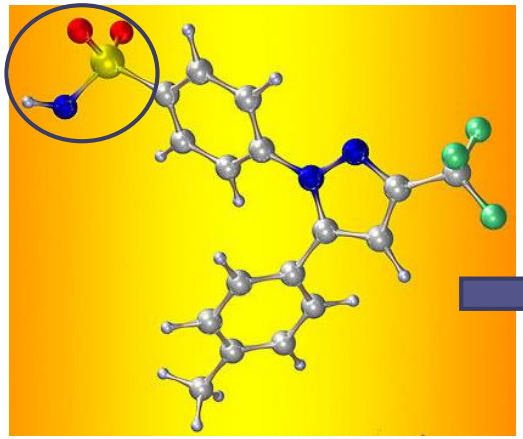
- **"Medicinal Chemistry is a chemistry-based discipline, also involving aspects of biological, medical and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and the construction of structure-activity relationships."**

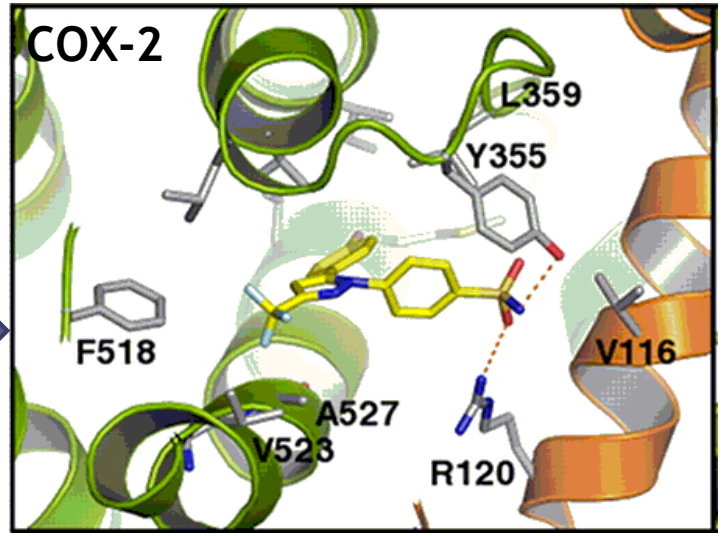
  C.G. Wermuth, C.R. Ganellin, P. Lindberg and L.A. Mitscher (1998) Glossary of Terms Used in Medicinal Chemistry, IUPAC.

- "A **pharmacophore** is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or to block) its biological response."



Celecoxibe
AINE
inibidor seletivo de COX-2





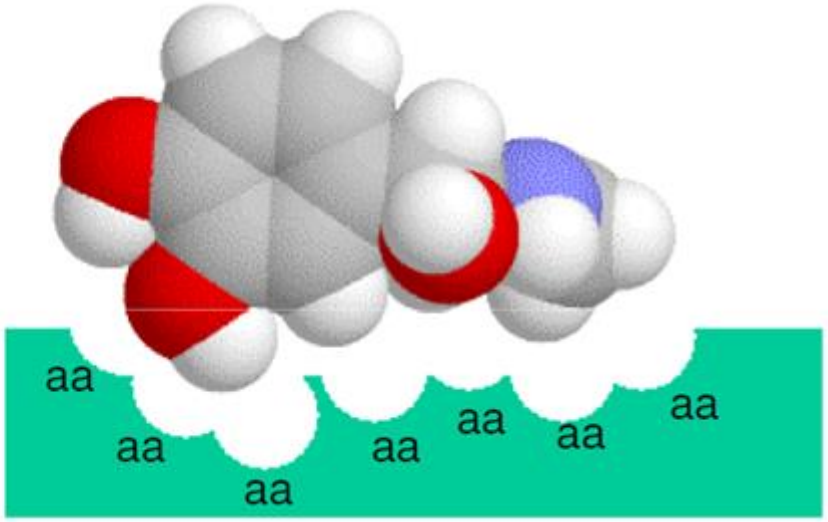
Limongelli V. *et al.* (2010) *PNAS* 107, 5411.

Interação Fármaco-Receptor

Fármaco: Eficácia depende da estabilidade do complexo fármaco-biorreceptor e do número de sítios ocupados pelo mesmo. Fármaco com baixa eficácia nunca produzem efeito máximo, mesmo se todos os receptores estiverem ocupados.

$$[F] + [R] \underset{K_{-1}}{\overset{K_1}{\rightleftharpoons}} [FR] \rightarrow \text{EFEITO FARMACOLÓGICO}$$

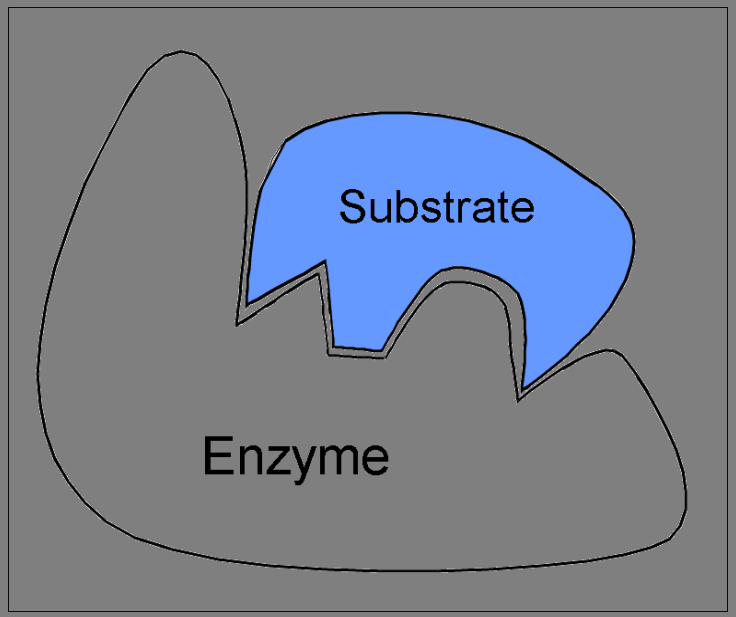
Afinidade= k1/k-1 **Eficácia (ativ intrínseca)**

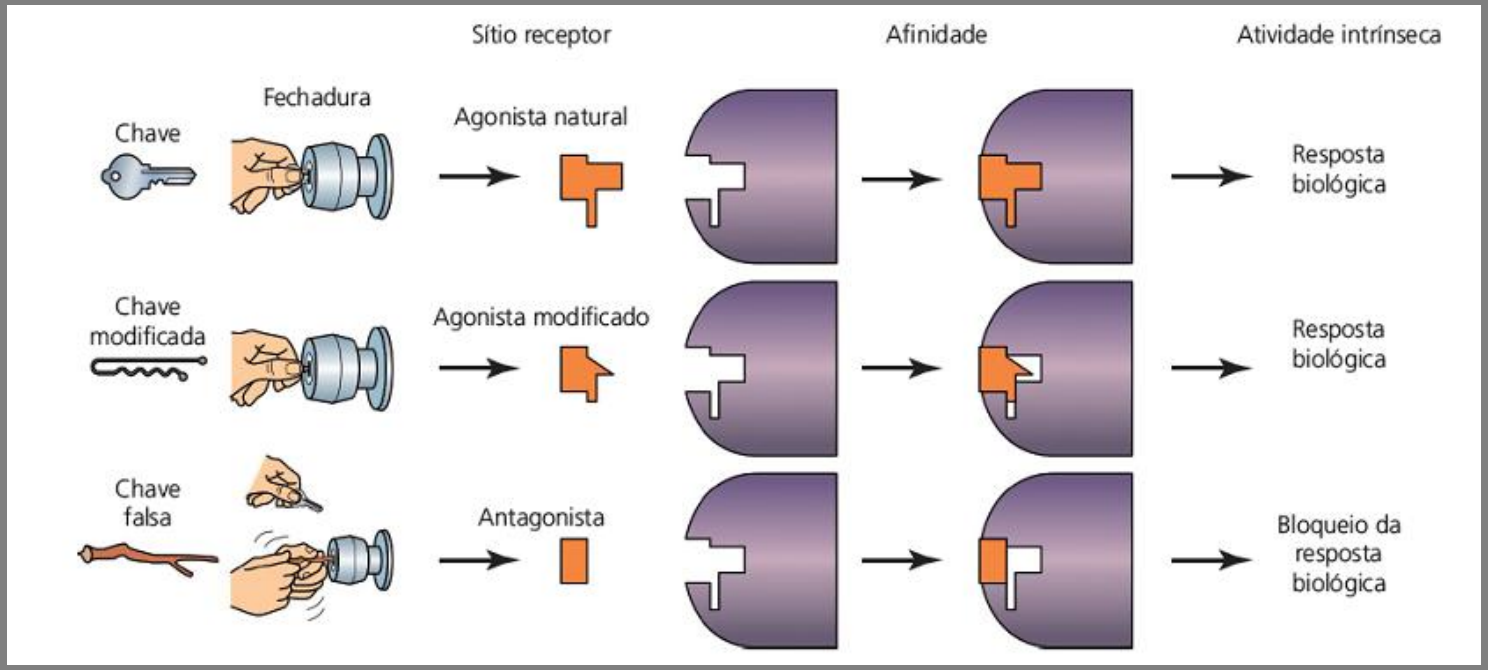


Modelo-Chave Fechadura (115 anos)

Emil Fischer
(1852-1919)
(Prêmio Nobel, 1902)

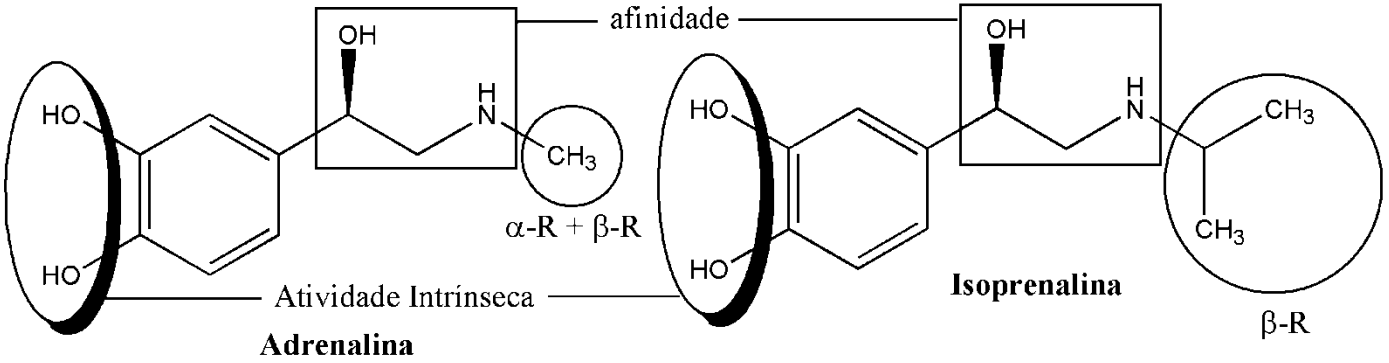
Fischer, E. H. "Dictionary of Scientific Biography", Charles Scribner's Sons: 1970-1990; Vol. 5, pp. 1-5.





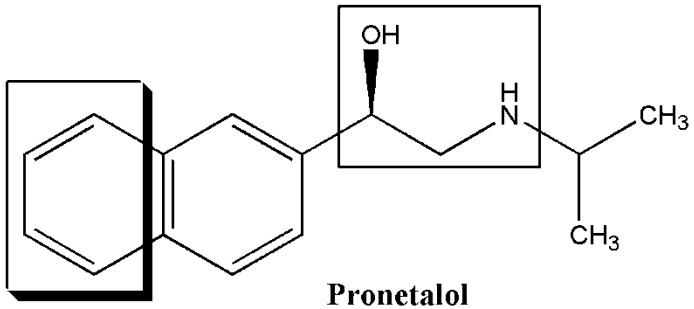
Fraga, C. A. M. & Barreiro, E. J. (2015) Química Medicinal, 3ª Edição, ArtMed, Porto Alegre.

Afinidade *versus* Atividade Intrínseca

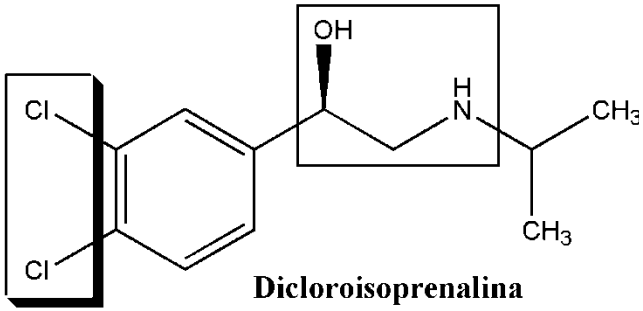


Adrenalina

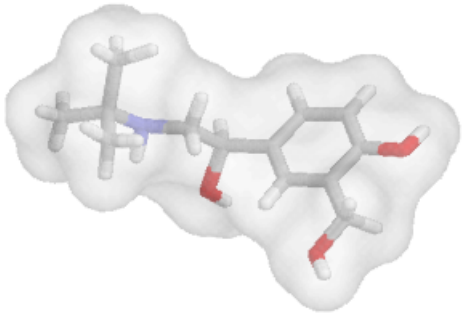
Isoprenalina

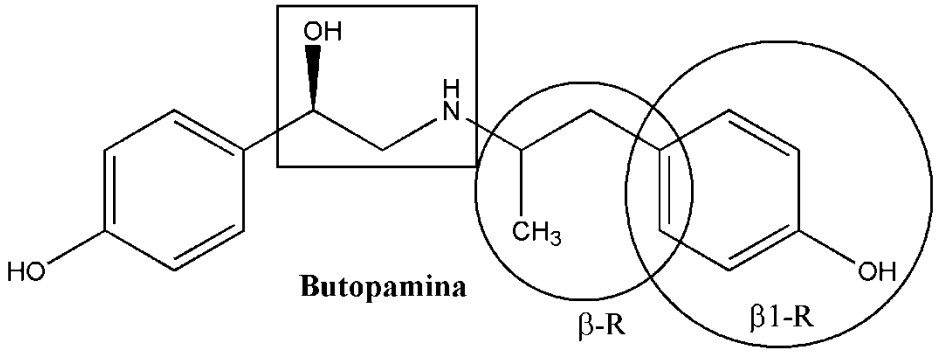


Pronetalol
Antagonista β-R

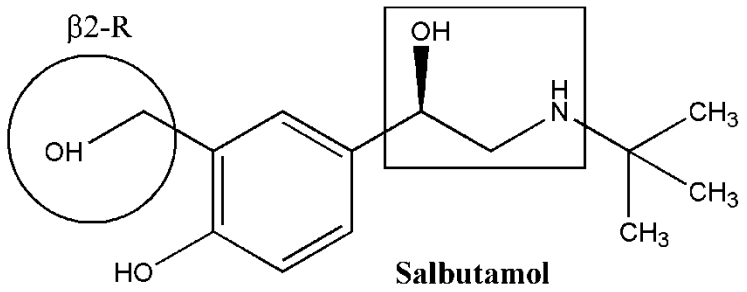


Dicloroisoprenalina
Agonista Parcial β-R





Butopamina

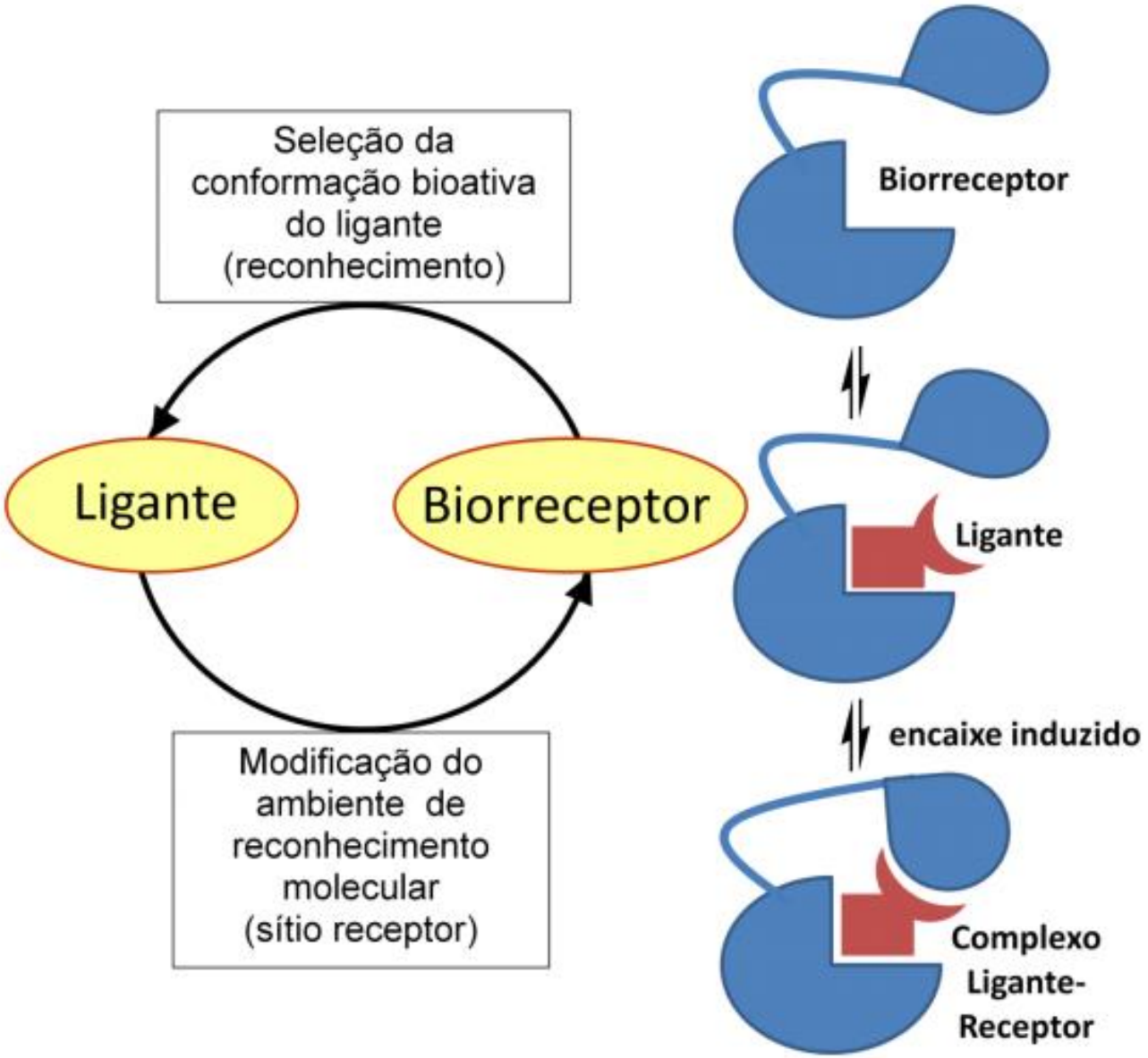


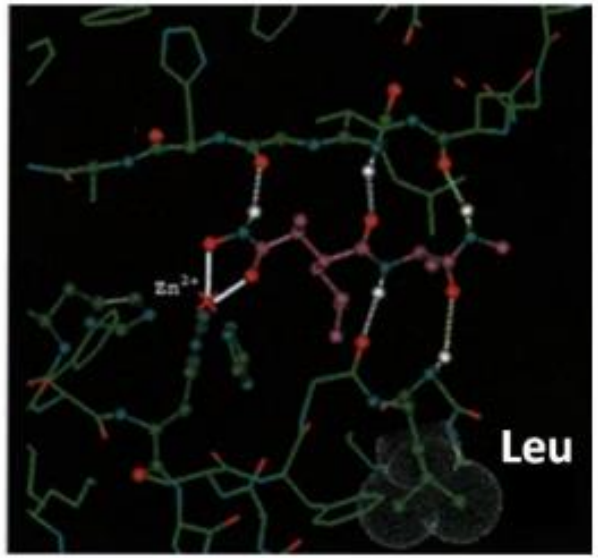
Salbutamol

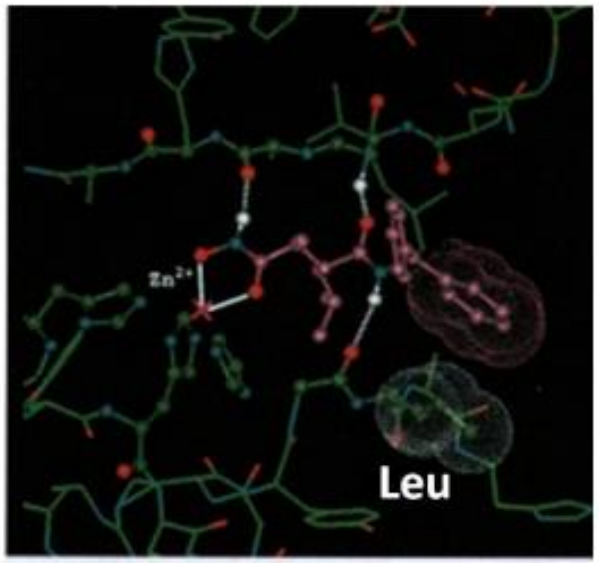
Barreiro, E. J.; Fraga, C. A. M. (2008) Química Medicinal: As Bases Moleculares da Ação dos Fármacos, 2ª Edição, Artmed, Porto Alegre.

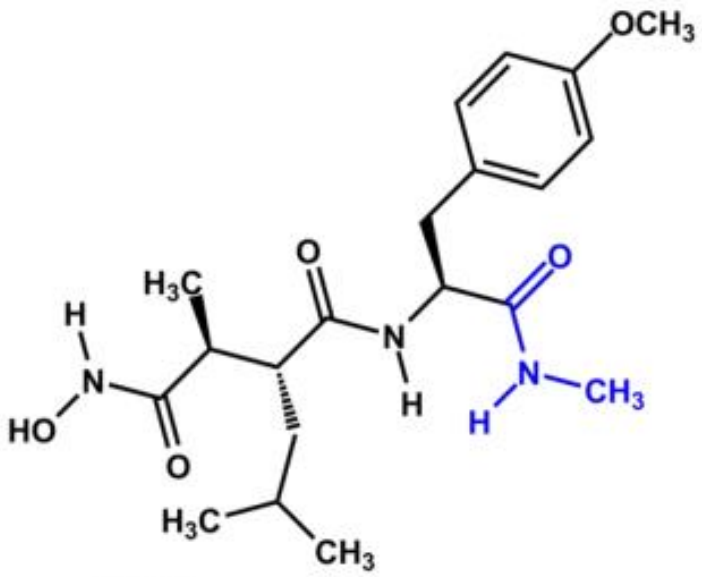
Teoria do Encaixe Induzido

Koshland Jr., D. E.; Neméthy, G.; Filmer, D.(1966) *Biochemistry 5*, 365.

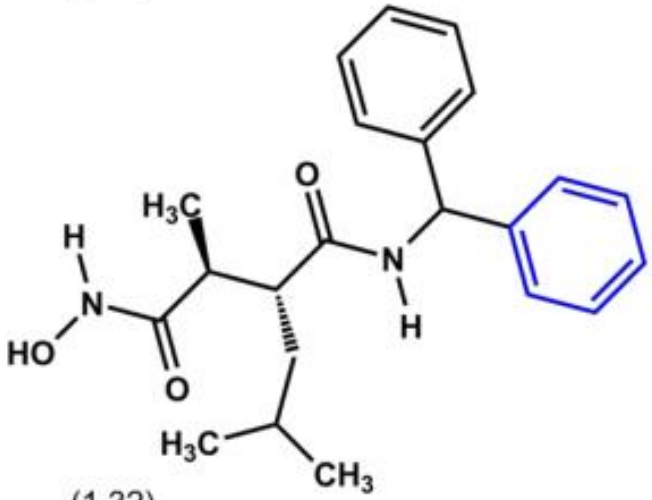








(1.31)



(1.32)

Rockwell, A.; Melden, M.; Copeland, R. A.; Hardman, K.; Decicco, C. P.; DeGrado, W. F.; *J. Am. Chem. Soc.* 1996, *118*, 10337

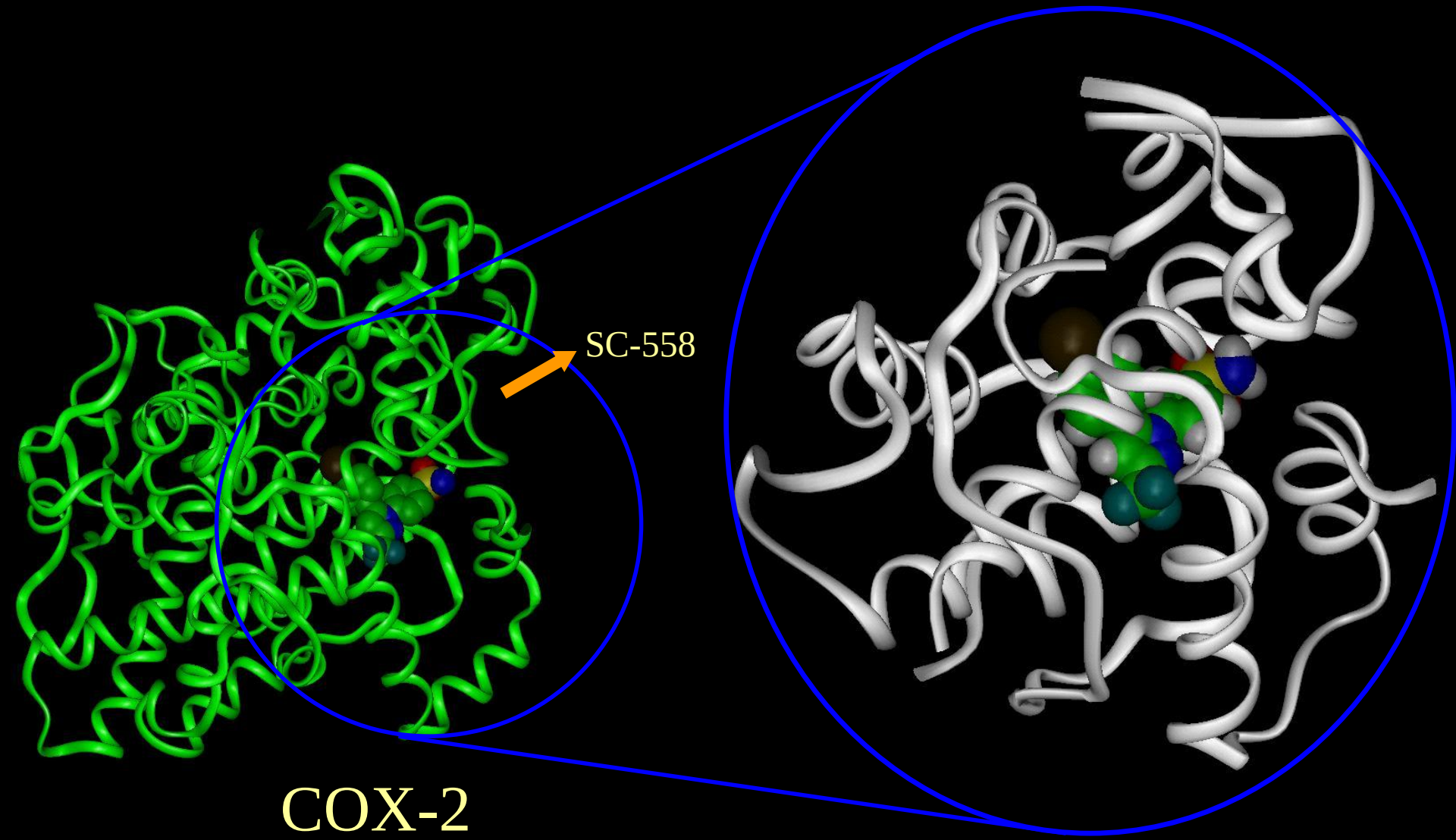
“O sucesso prático da **Química Medicinal** depende crucialmente de uma compreensão dos princípios do reconhecimento molecular (Davis & Teague, 1999).”

A determinação da estrutura 3D de receptores, assim como da manipulação destes auxiliado por computador tornou uma realidade o conceito de

Planejamento Racional de Fármacos.

Davis, A. M. & Teague, S. J., Angew. Chem. Int. Ed., **1999**, 38, 736-749

A Enzima Ciclooxigenase-2 (COX-2) e seu Sítio Ativo



Forças Envolvidas no Reconhecimento Molecular: Micro- / Biomacromolécula

- Ligações Covalentes;
- Interações Eletrostáticas:
  - Iônica;
  - Íon-Dipolo;
  - Dipolo-Dipolo;
  - Ligação de Halogênio
- Forças de Dispersão: Interação de Van der Walls;
- Interações Hidrofóbicas;
- Interações de Hidrogênio.

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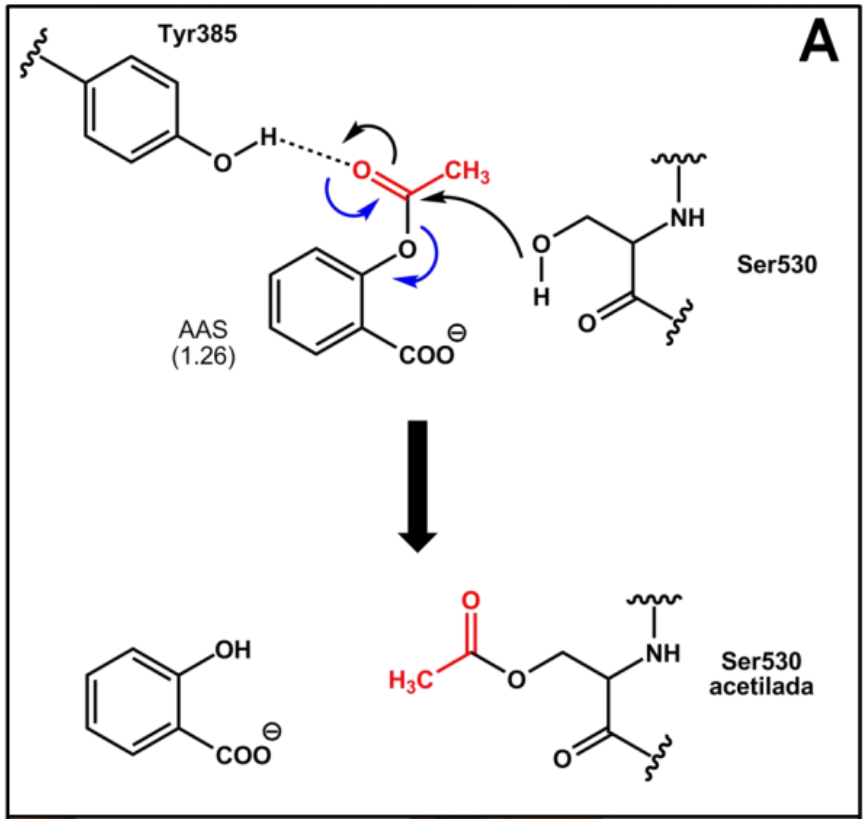
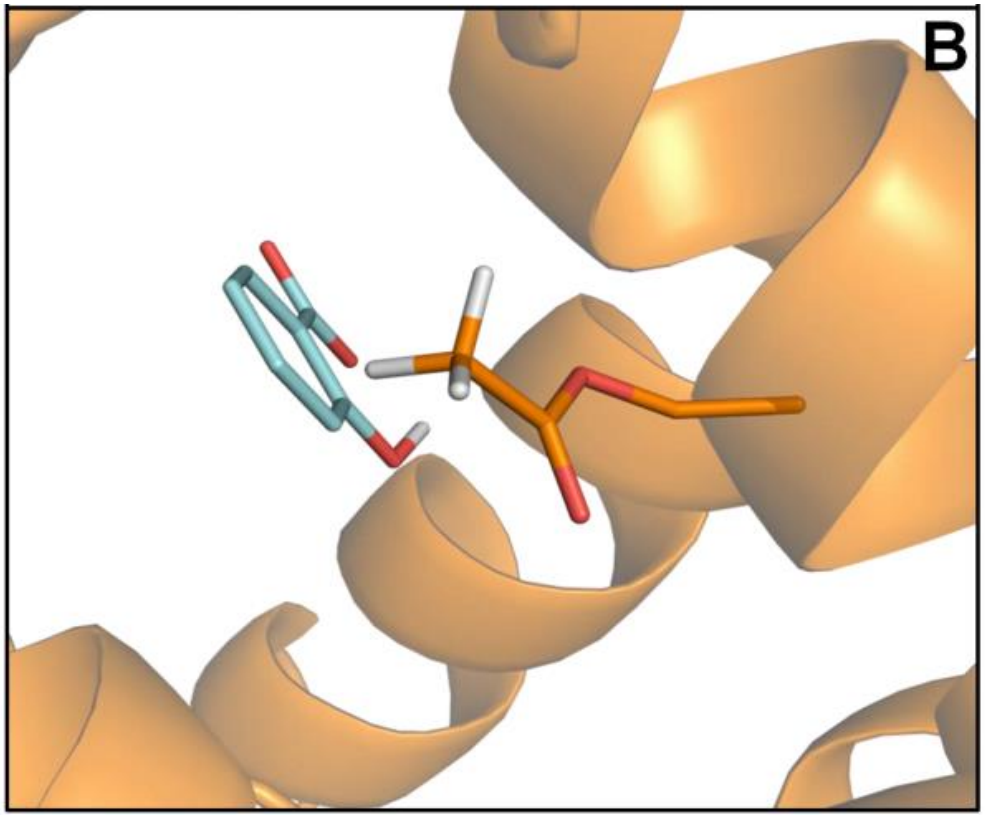
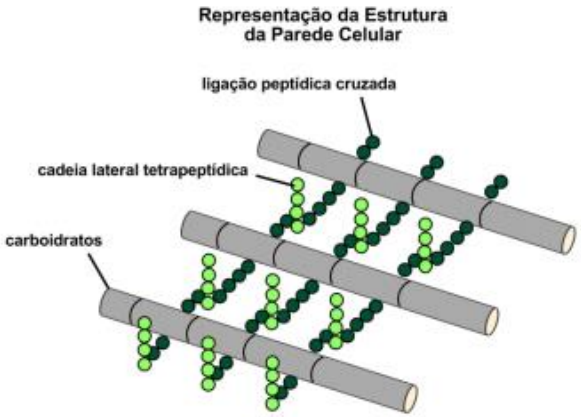
Ligações Covalentes: Reconhecimento Molecular do AAS pela PGHS (COX)

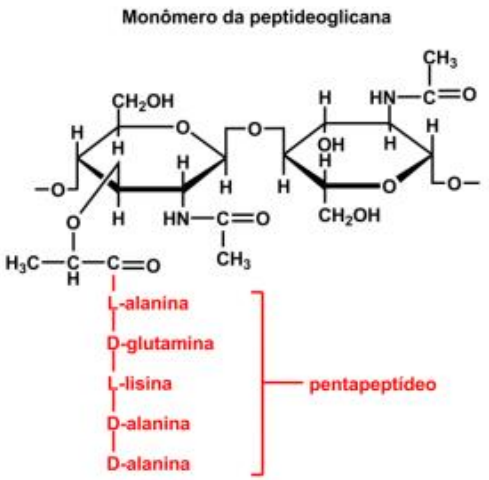


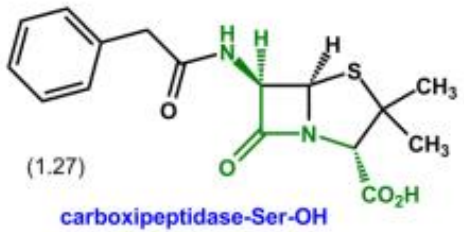


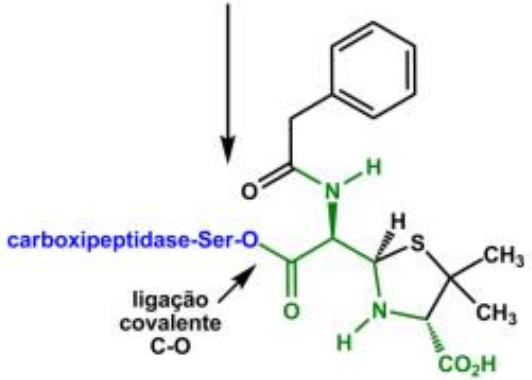
Barreiro, E. J.; Fraga, C. A. M. (2015) Química Medicinal: As Bases Moleculares da Ação dos Fármacos, 3ª Edição, Artmed, Porto Alegre.

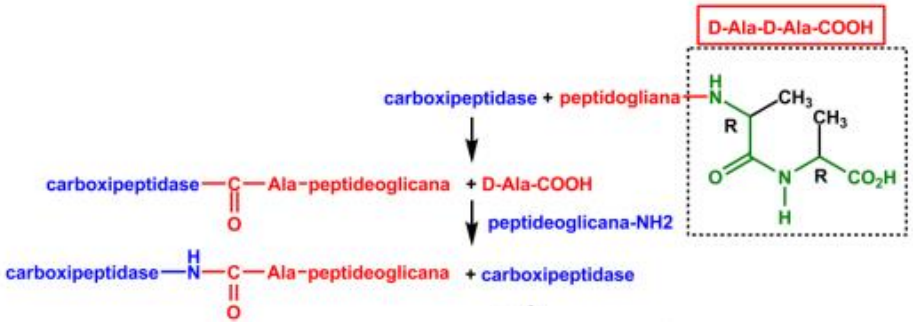
Ligações Covalentes: Mecanismo de Ação das Penicilinas

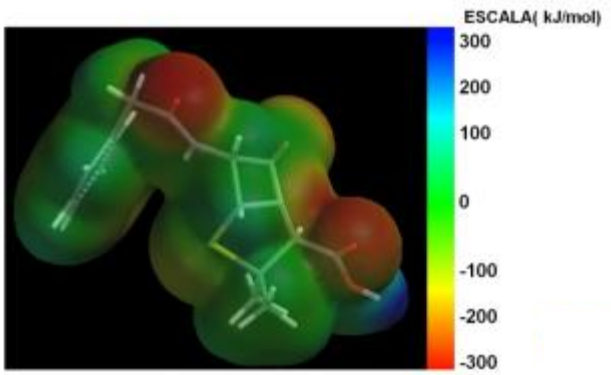












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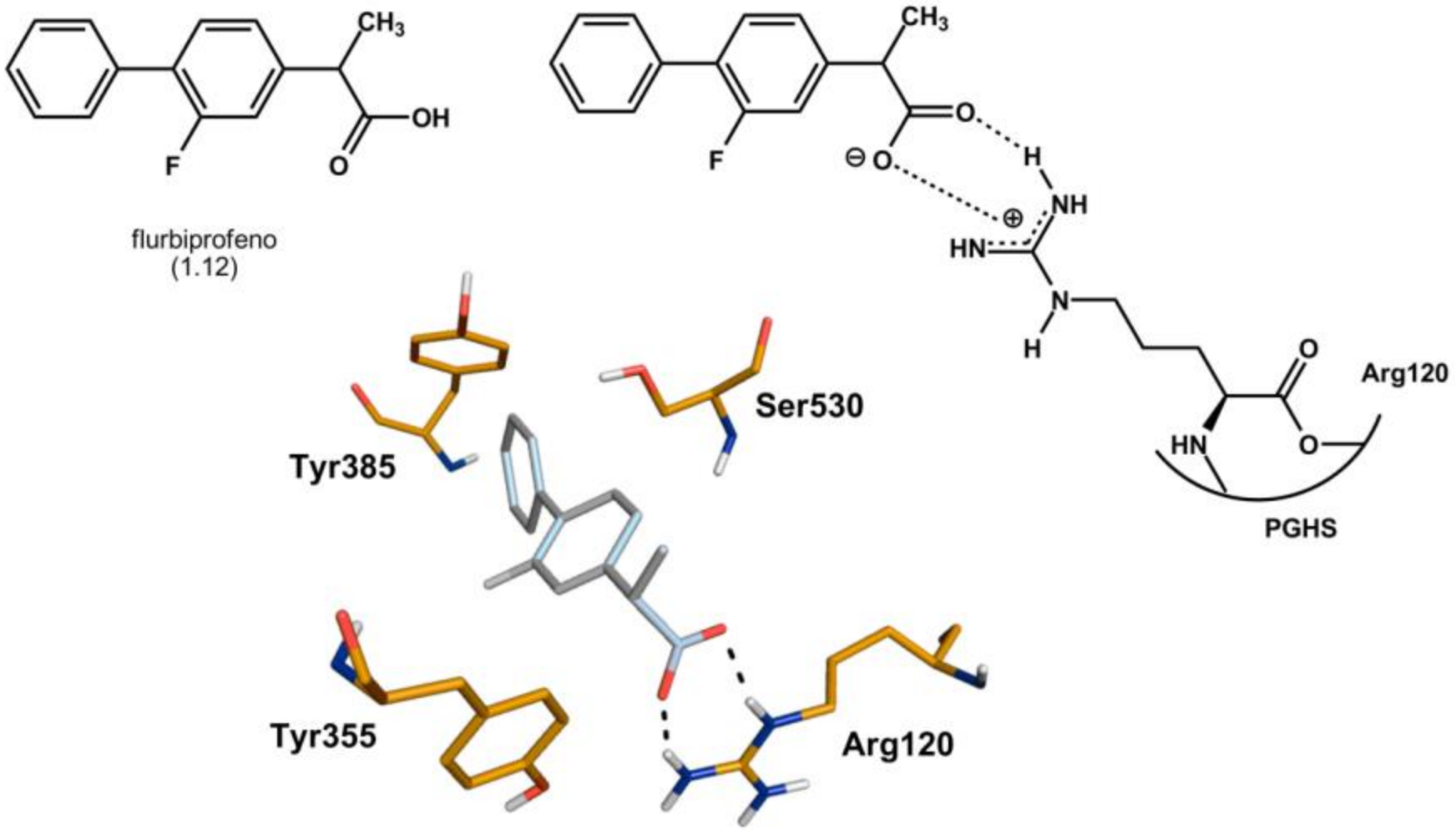
Interações Eletrostáticas: Ligação Iônica e o Reconhecimento Molecular do Flurbiprofeno



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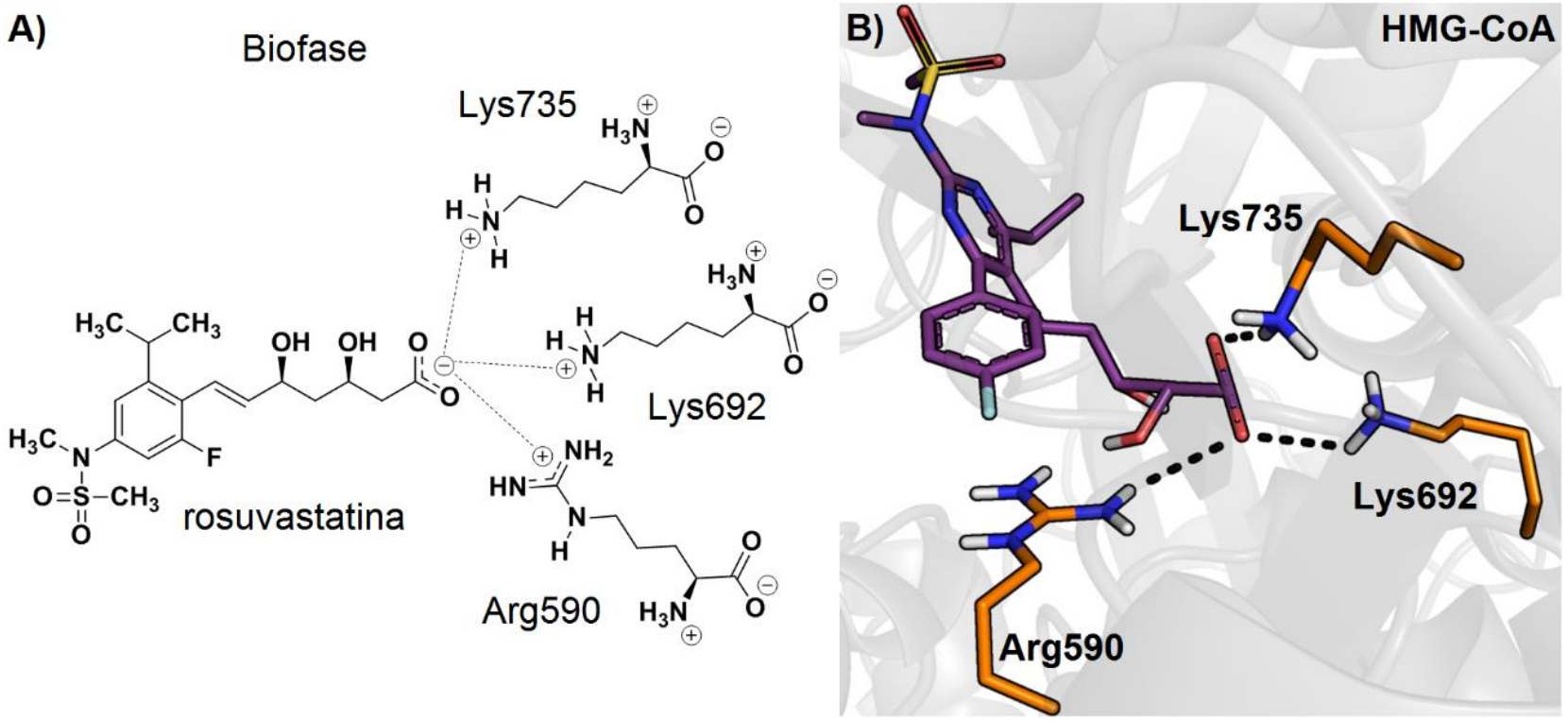
Interações Eletrostáticas: Ligação Iônica e o Reconhecimento Molecular da Rosuvastatina pela enzima HMG-CoA Redutase



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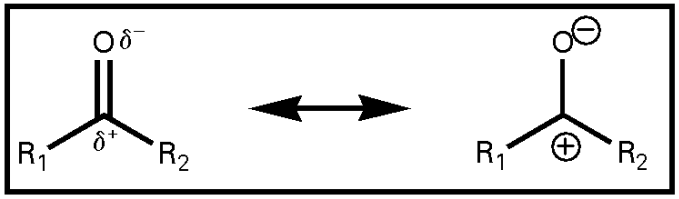
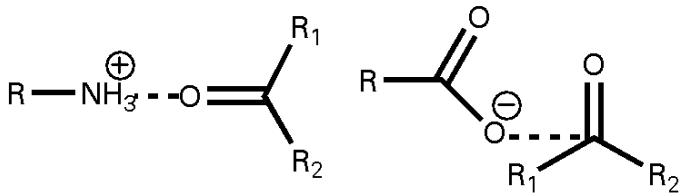
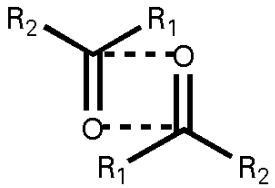
Interações Eletrostáticas: Íon-Dipolo / Dipolo-Dipolo





interações íon-dipolo



interações dipolo-dipolo

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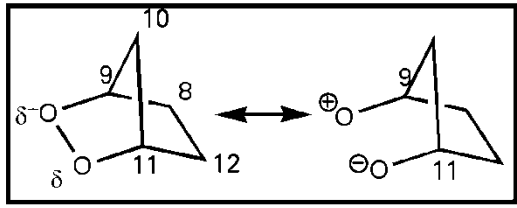

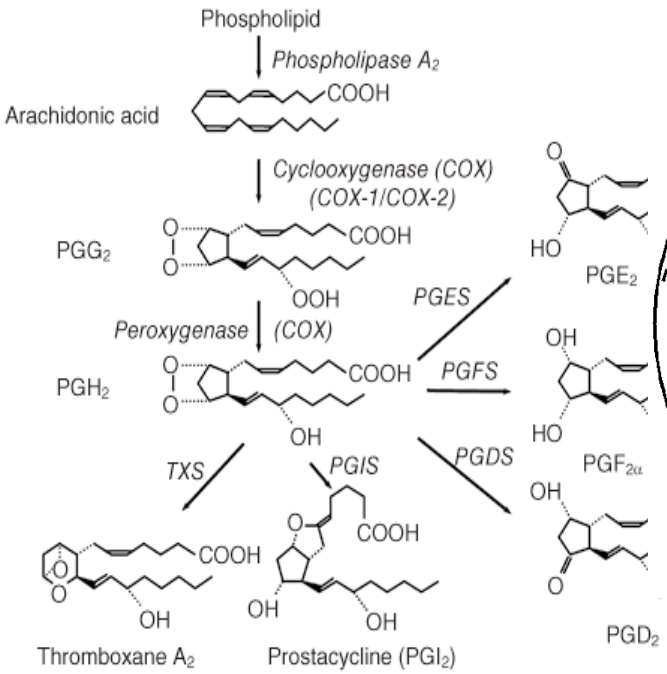

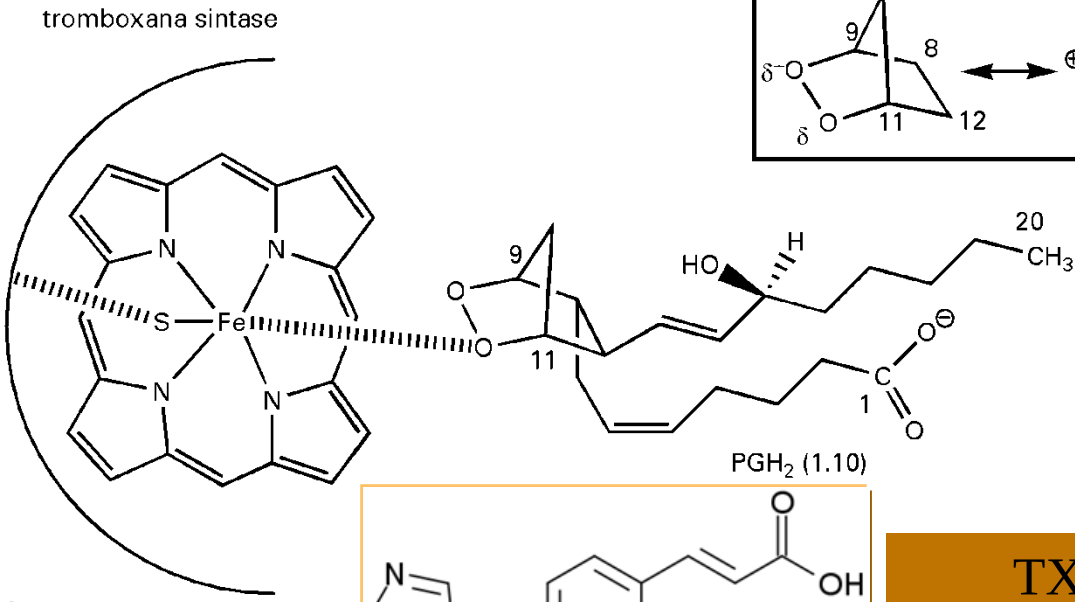

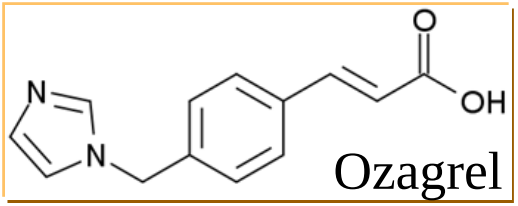

Ozagrel

TXSi
Antitrombótico

Interações Eletrostáticas: Fluconazol com a CYP51

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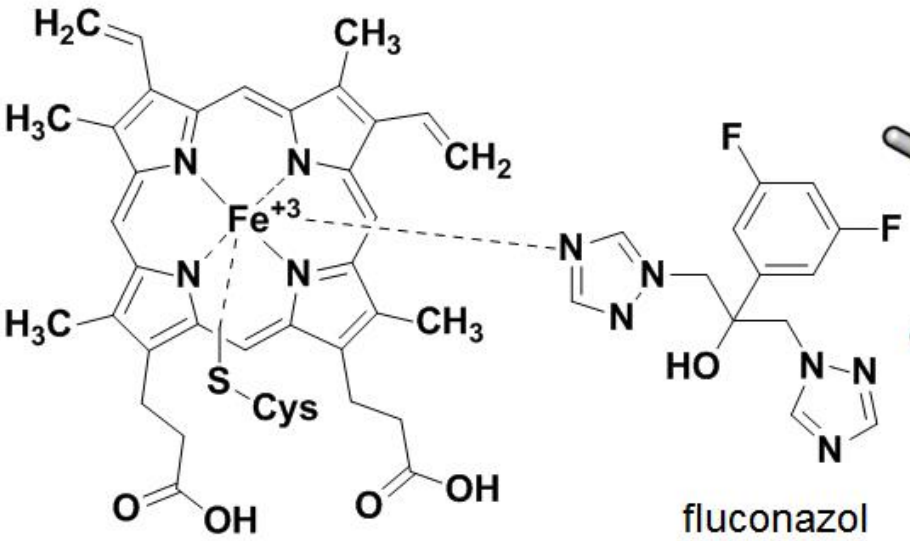
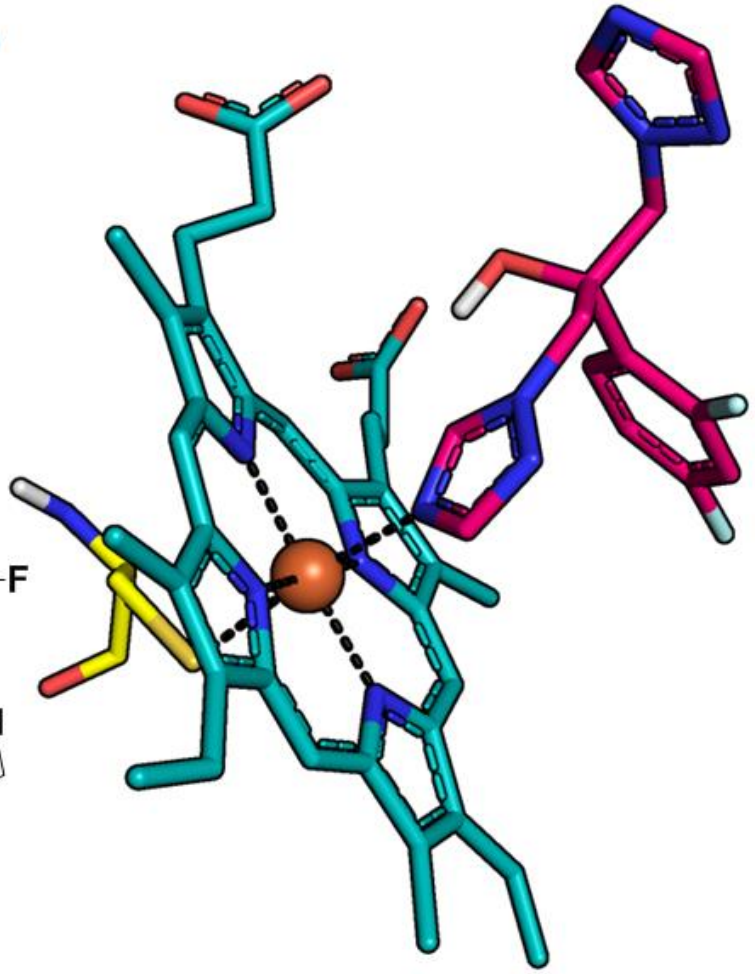
A)

Grupamento heme da CYP51

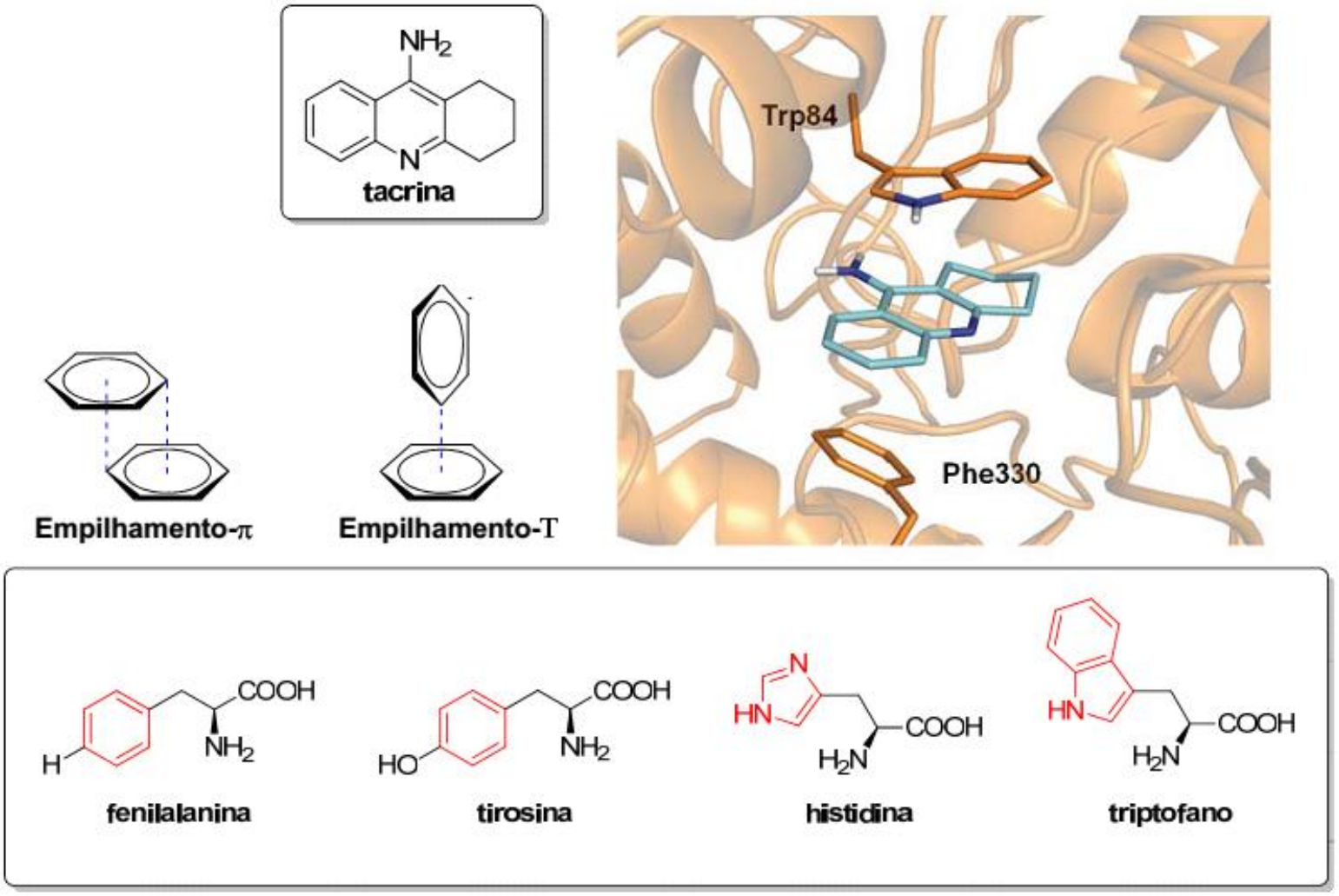


fluconazol

B)



Interações Dipolo-Dipolo: Empilhamento π



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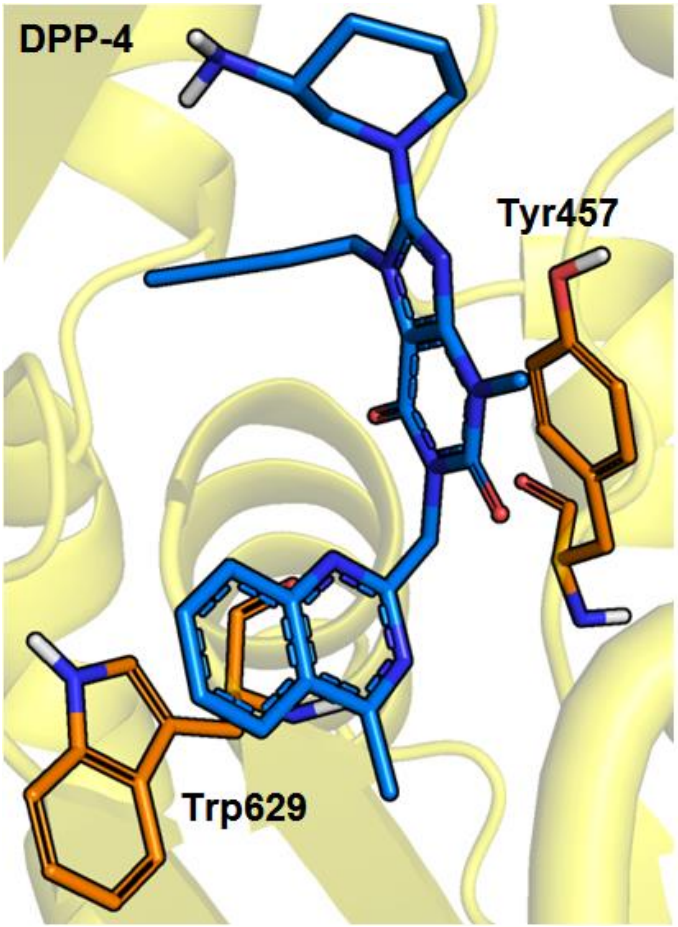
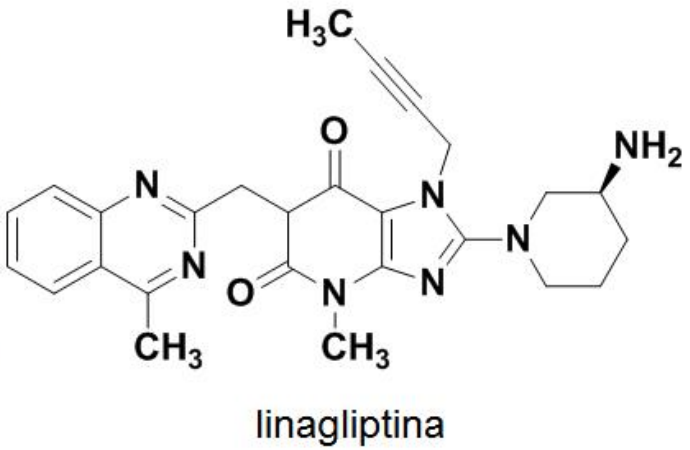
Interações de empilhamento-pi envolvidos no reconhecimento molecular do fármaco linagliptina (azul) no sítio ativo da enzima Dipeptidil-peptidase IV (DPP-4)





linagliptina

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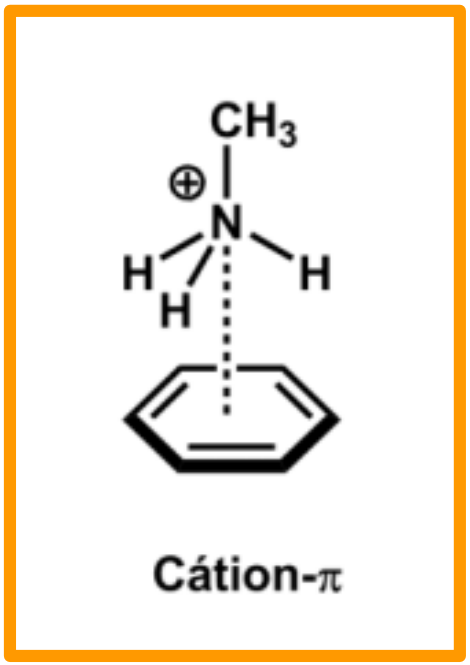
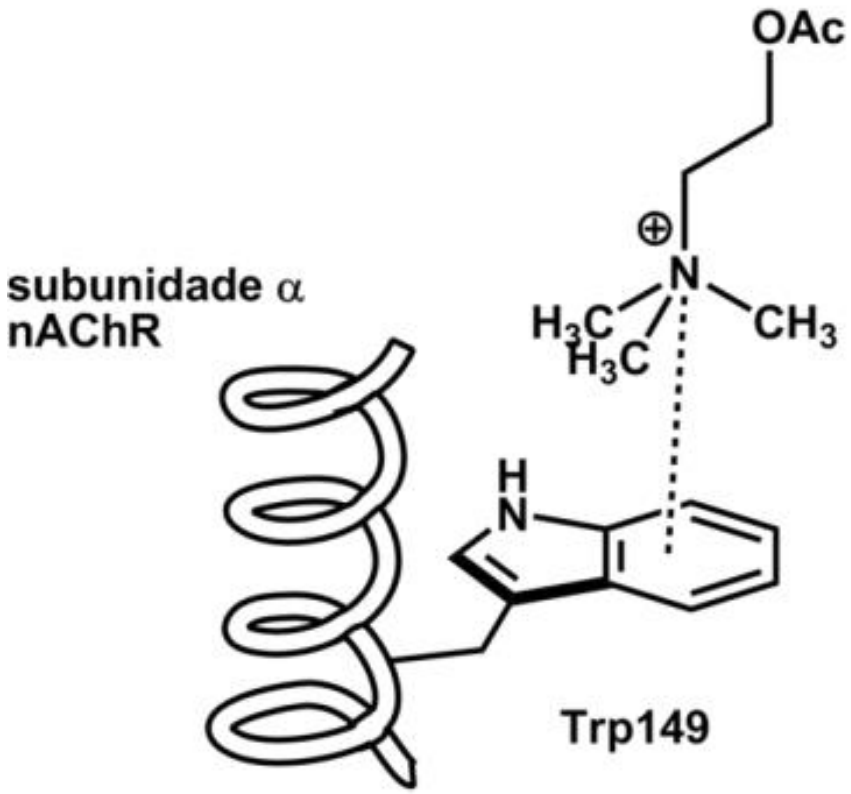
Interações Dipolo-Dipolo: Cátion π





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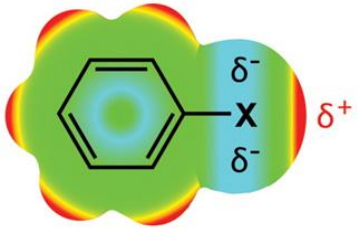
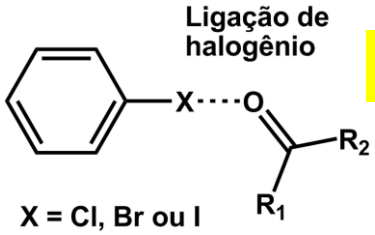
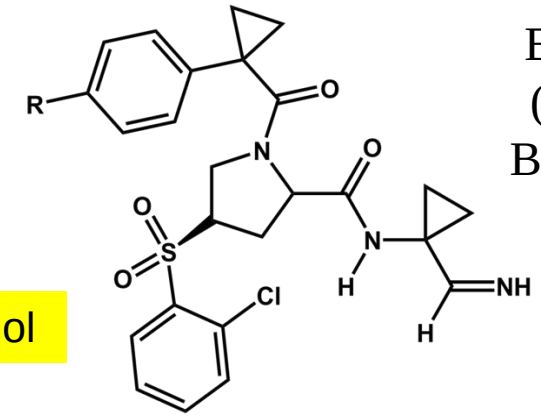
Interações Eletrostáticas: Ligações de Halogênio





1-5 kcal/mol



$R = CH_3$ (1.21)
R = I (1.22)

Afinidade 20 x maior

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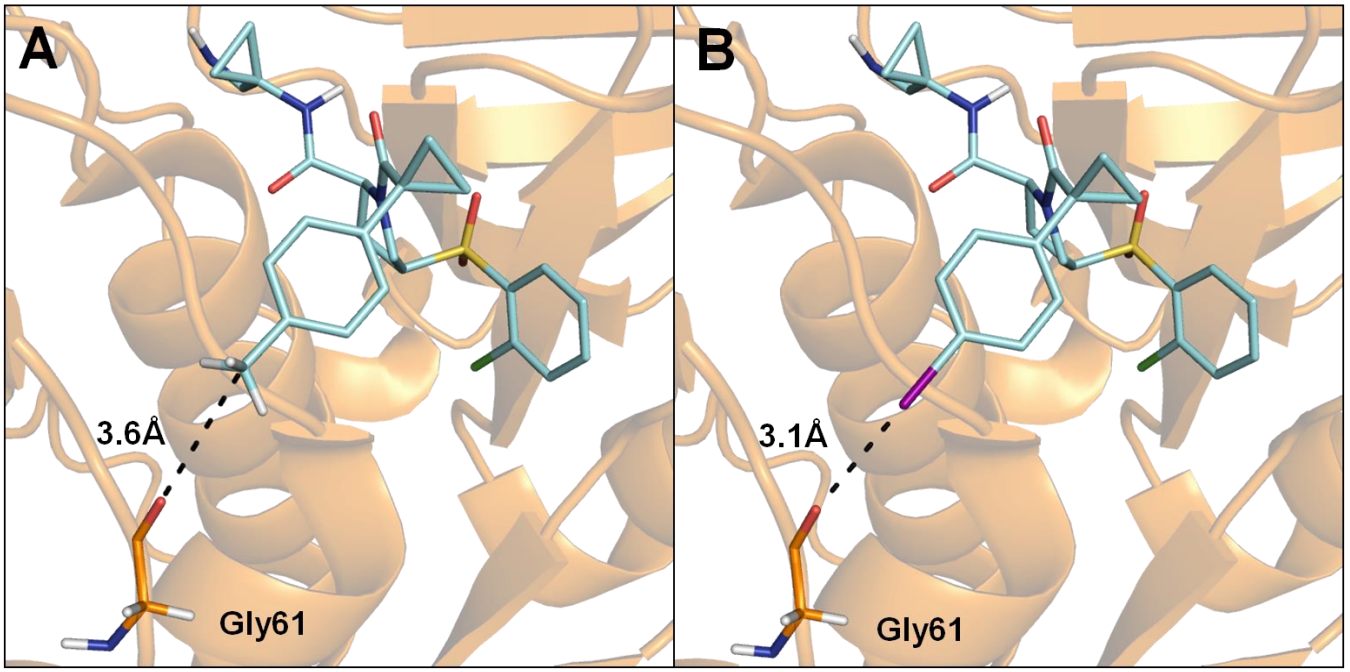
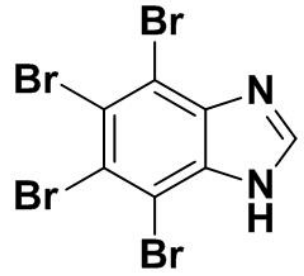
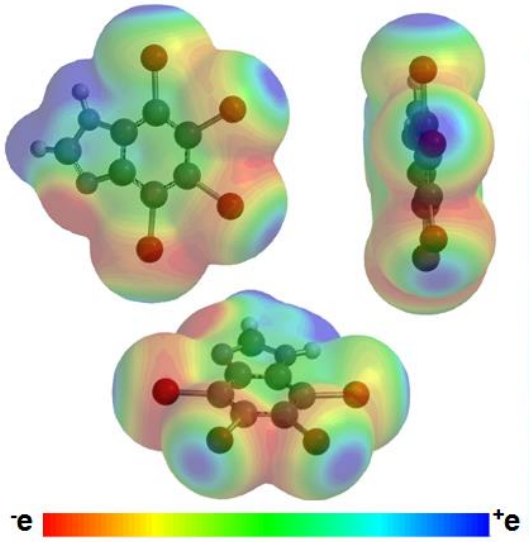
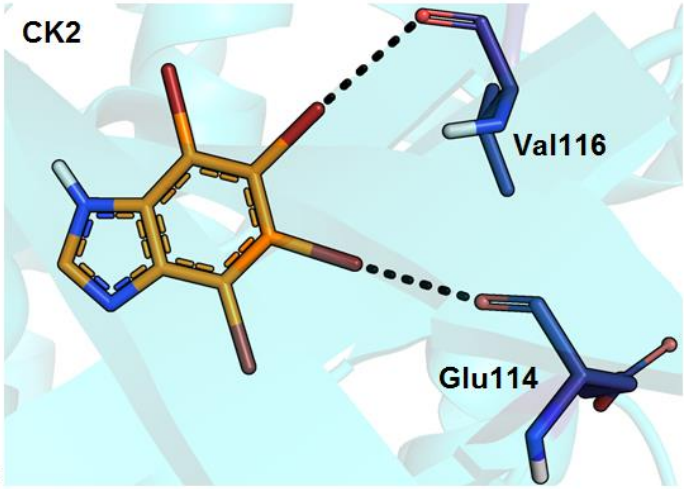


Mapa do potencial eletrostático do inibidor TBI, e as interações de halogênio realizadas na inibição da Caseína Cinase 2 (CK2)



TBI





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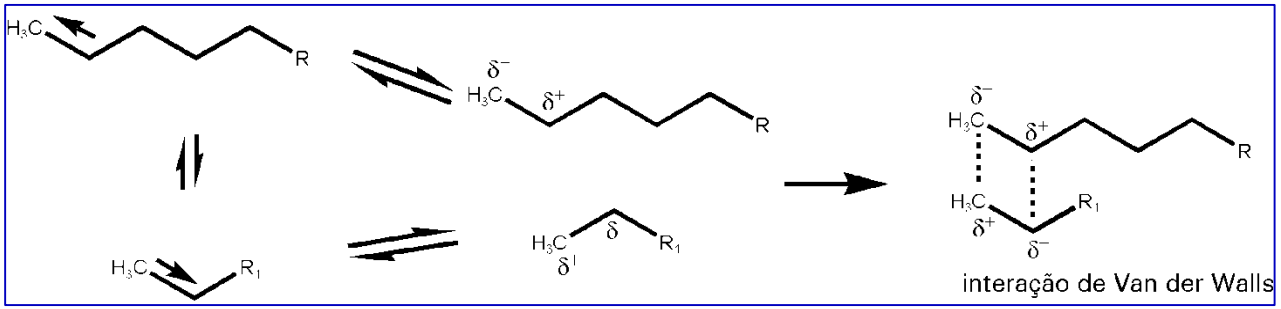
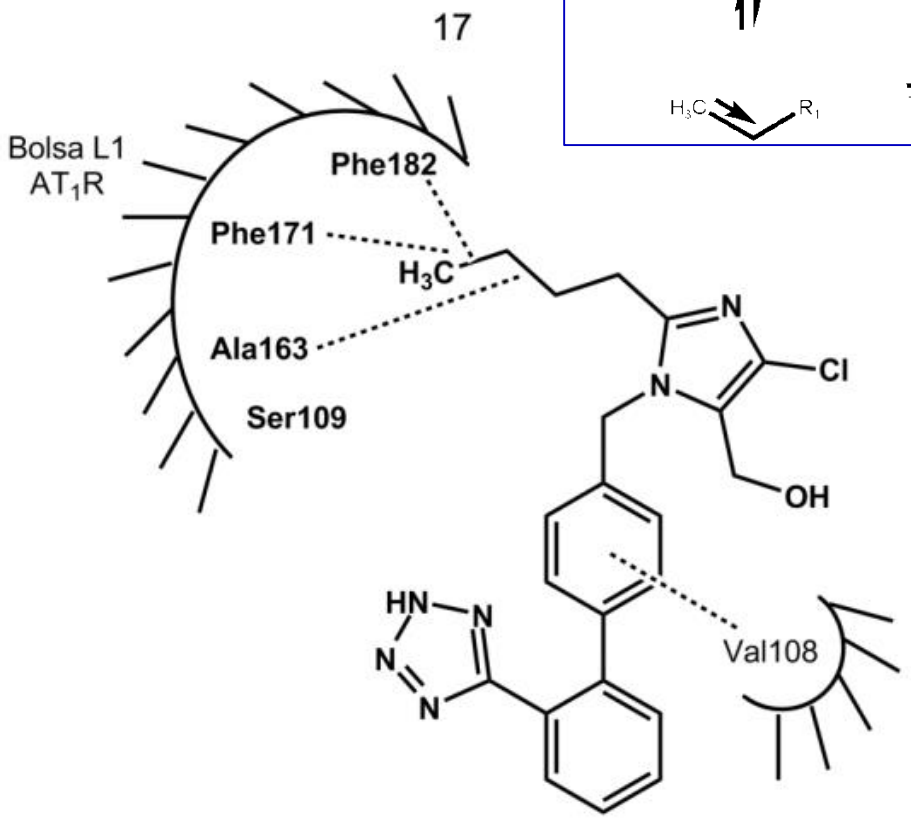
Forças de Dispersão: Interações de Van der Walls





LOSARTANA

Antagonista de Receptores AT_1

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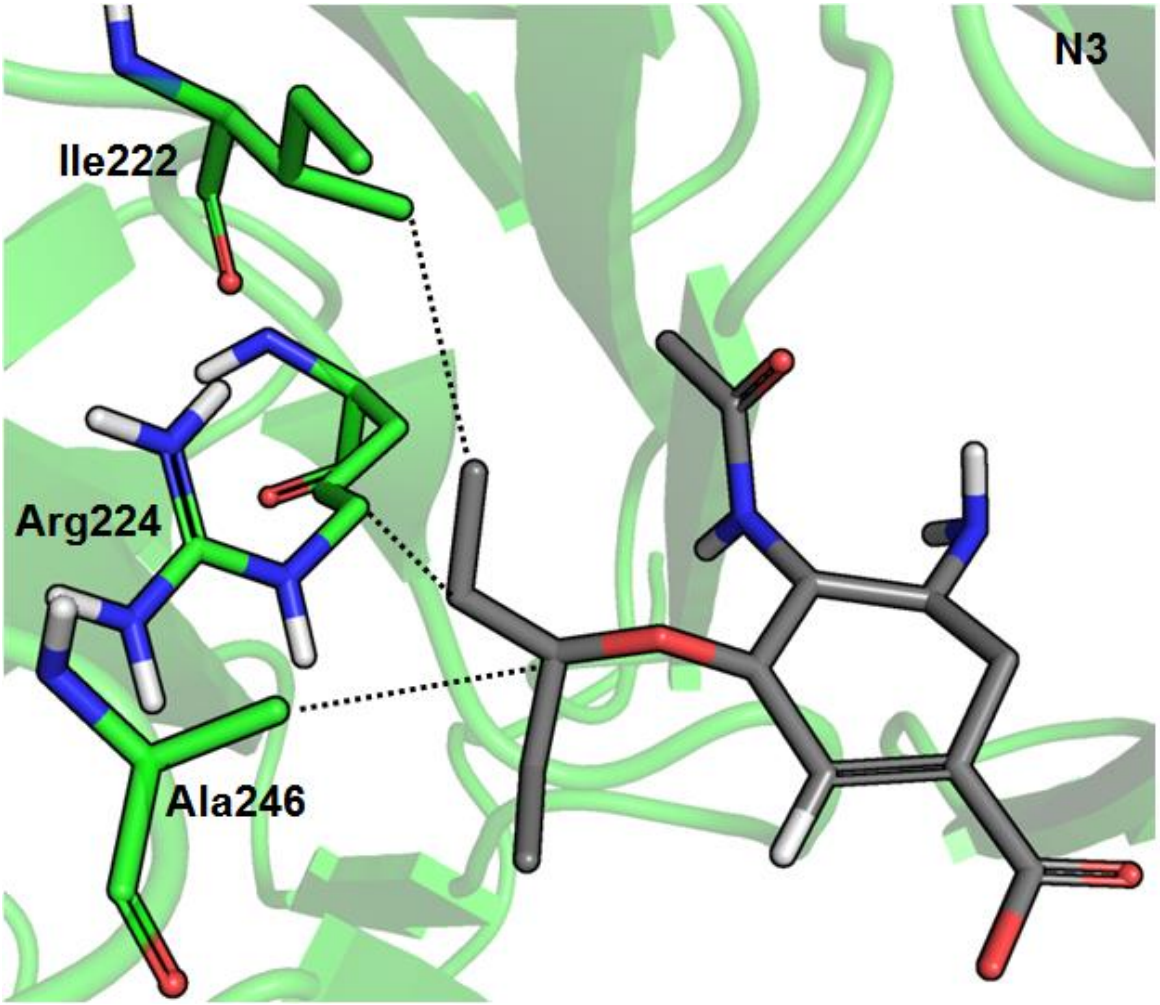
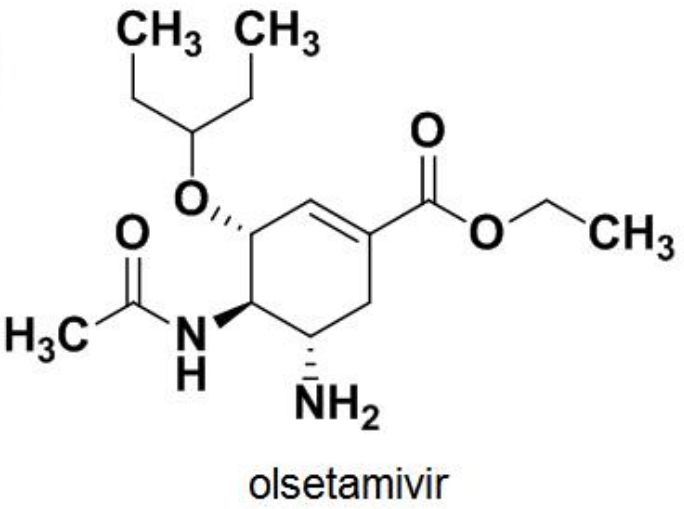
Interações de Van der Waals participantes do reconhecimento molecular do oseltamivir (cinza) no sítio ativo da enzima neuramidase 3 (N3) (PDB ID 4HZX).





olsetamivir

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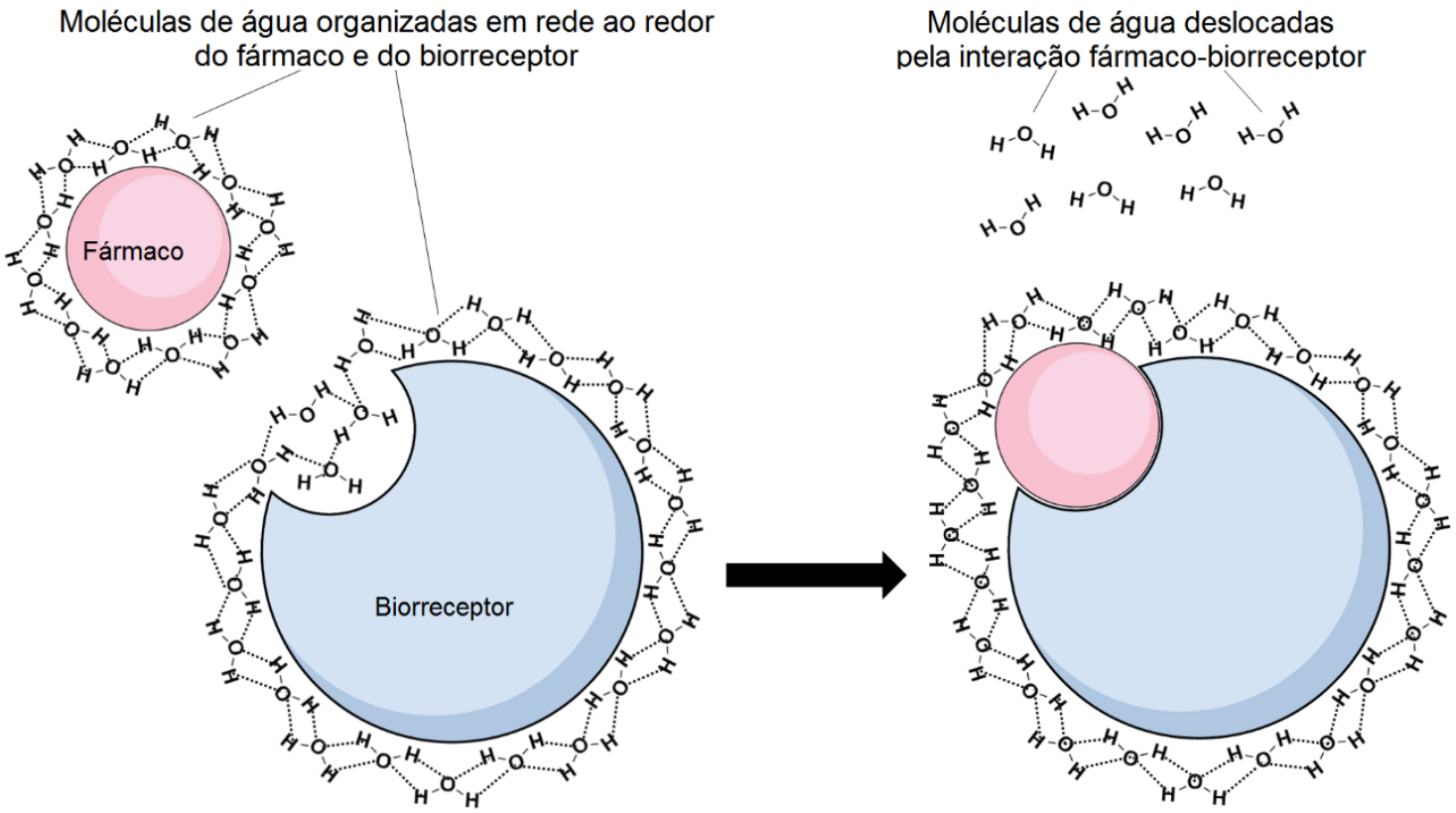
Interações Hidrofóbicas



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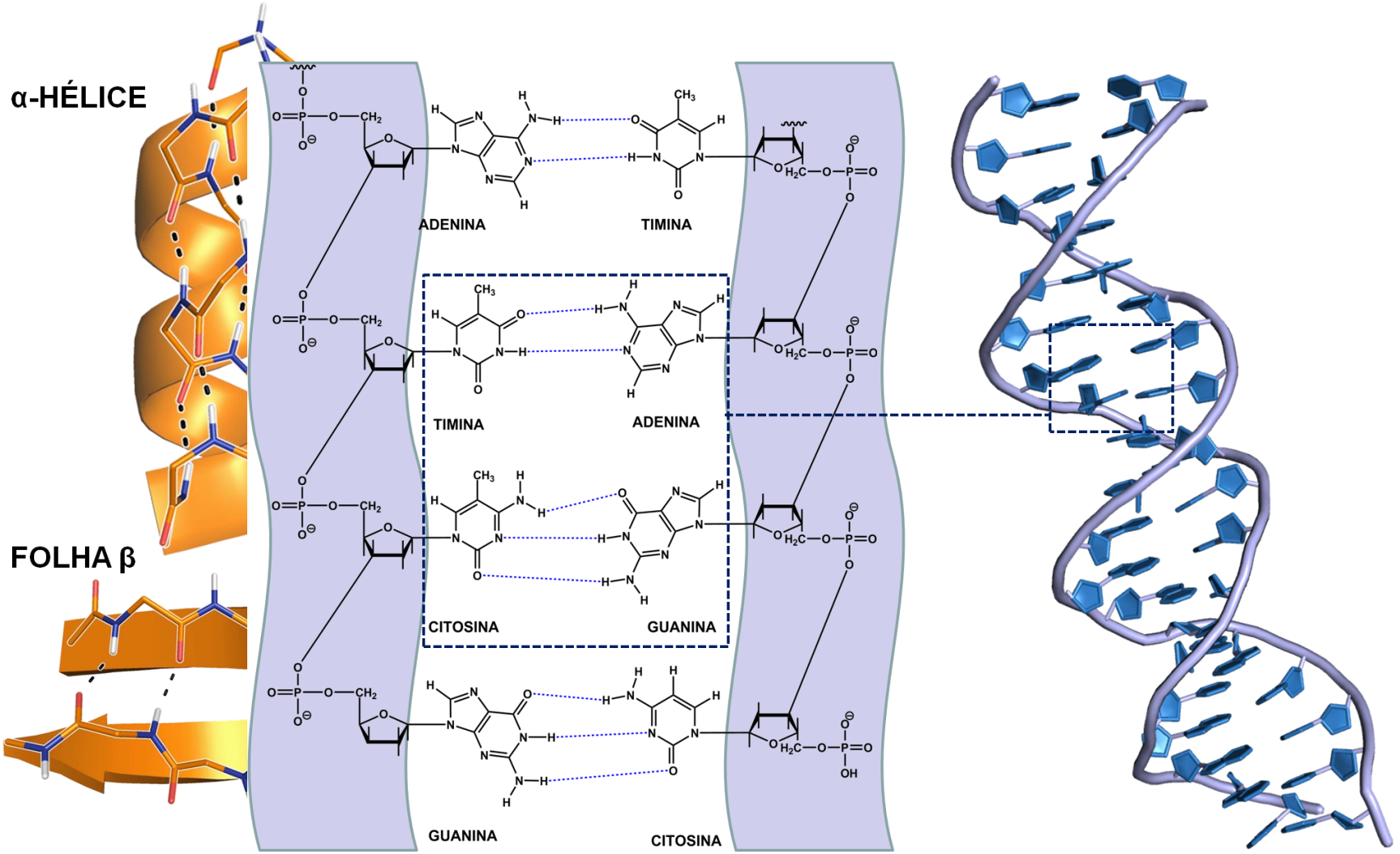
Interações de Hidrogênio



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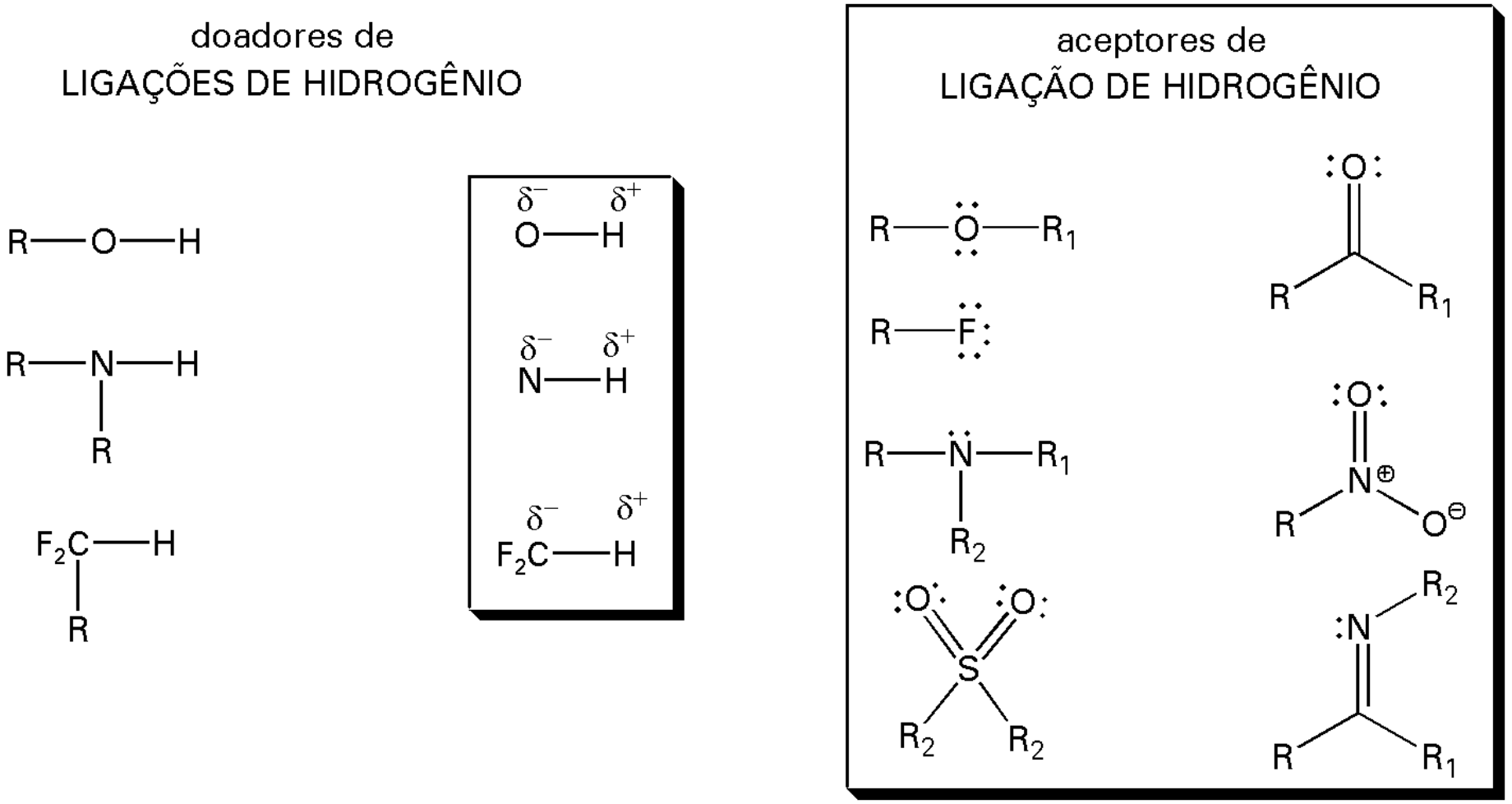
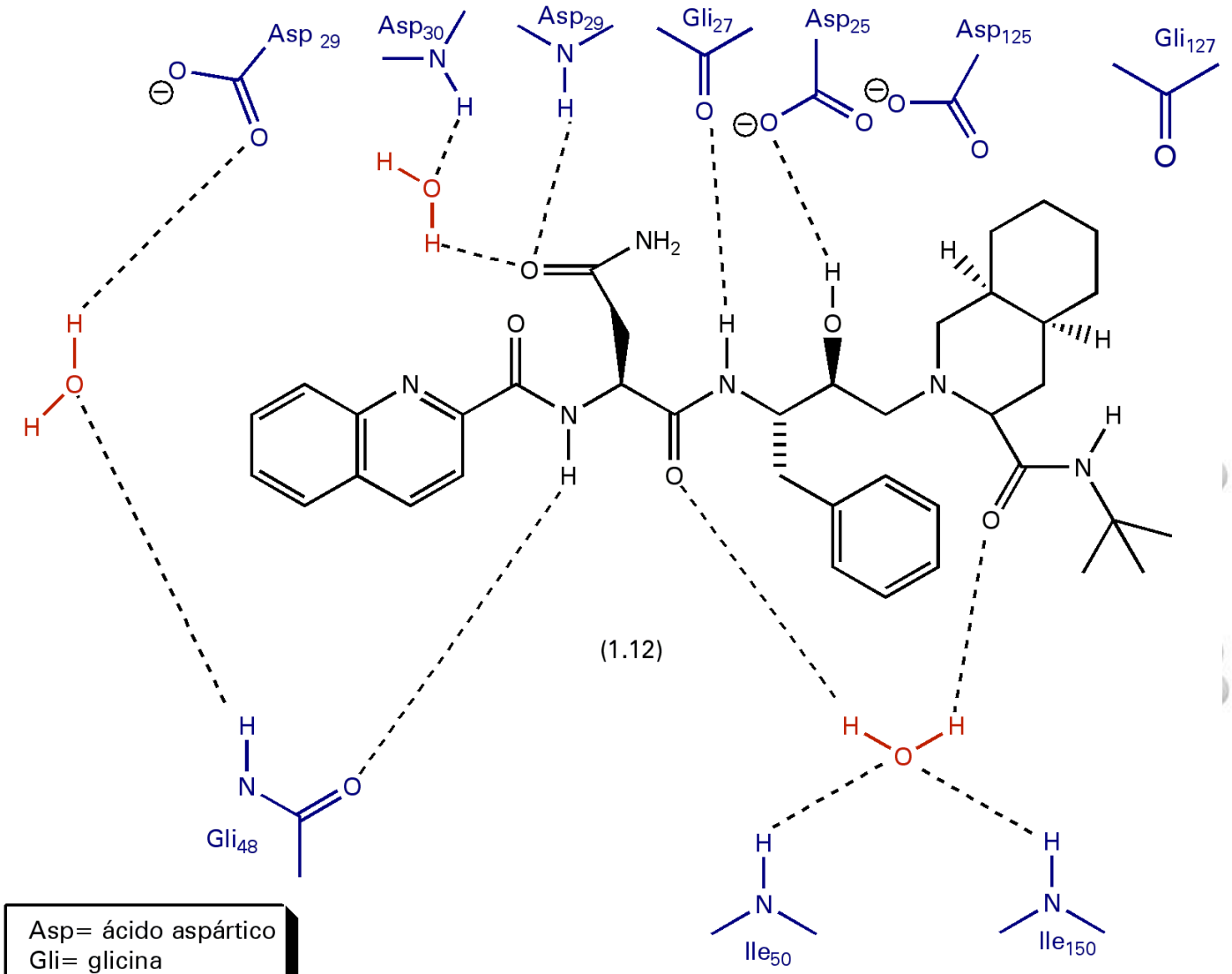
Grupos Doadores e Aceptores de Ligações de Hidrogênio



Barreiro, E. J.; Fraga, C. A. M. (2008) Química Medicinal: As Bases Moleculares da Ação dos Fármacos, 2ª Edição, Artmed, Porto Alegre.

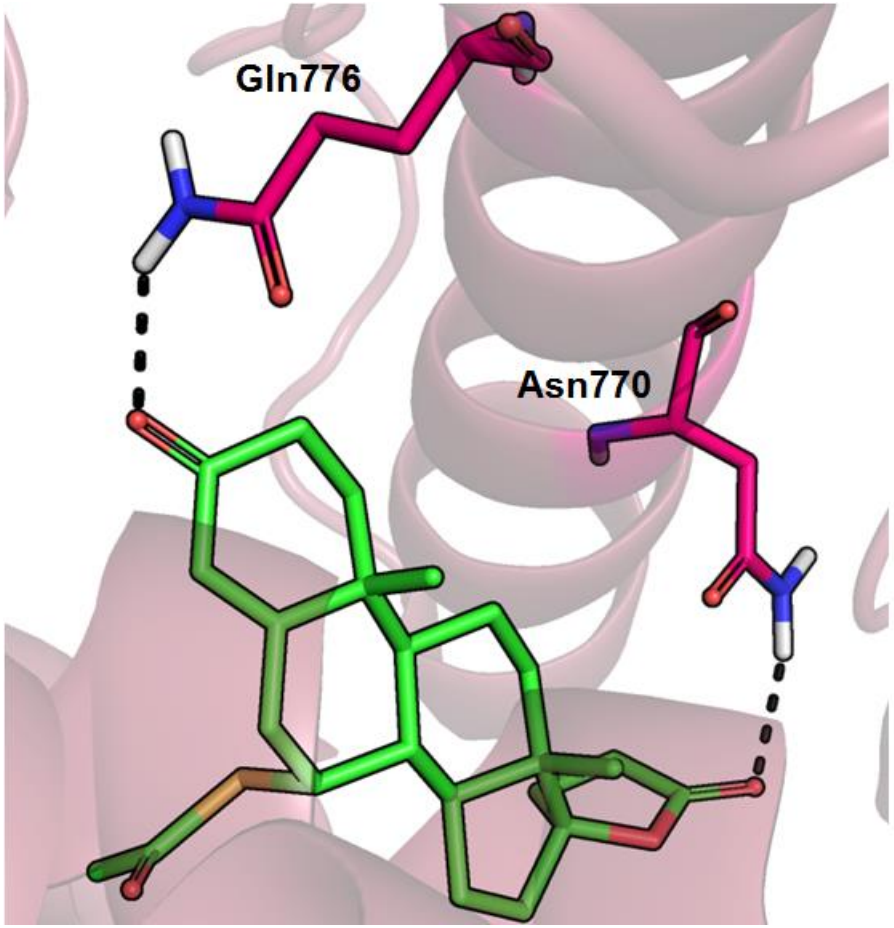
Ligações de Hidrogênio e o Reconhecimento Molecular do antiviral saquinavir pelo sítio ativo da protease do HIV-1

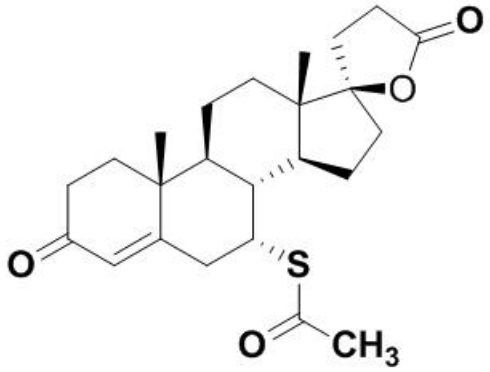


Asp= ácido aspártico
Gli= glicina
Ile= isoleucina

Barreiro, E. J.; Fraga, C. A. M. (2008) Química Medicinal: As Bases Moleculares da Ação dos Fármacos, 2ª Edição, Artmed, Porto Alegre.

Ligações de Hidrogênio e o reconhecimento molecular da espirolactona pelo sítio ativo do receptor mineralocorticoide





espironolactona

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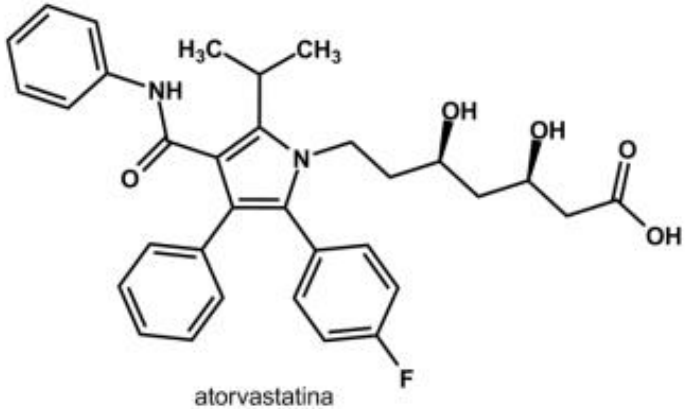
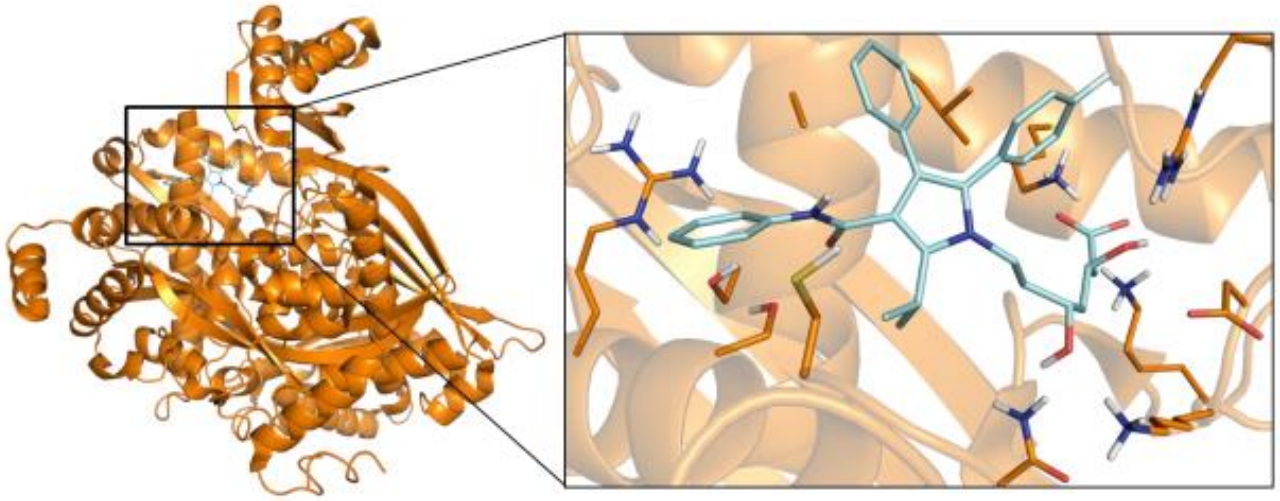
Importância dos Fatores Estereoquímicos na Interação Fármaco-Receptor



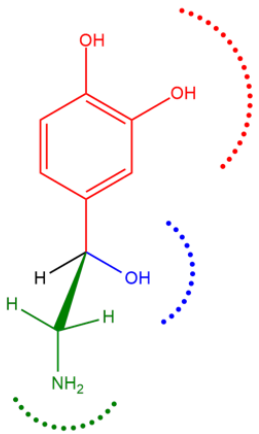
atorvastatina
(1.28)



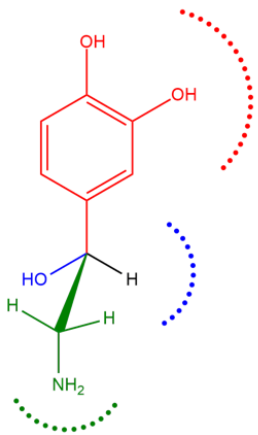
Barreiro, E. J.; Fraga, C. A. M. (2015) Química Medicinal: As Bases Moleculares da Ação dos Fármacos, 3ª Edição, Artmed, Porto Alegre.

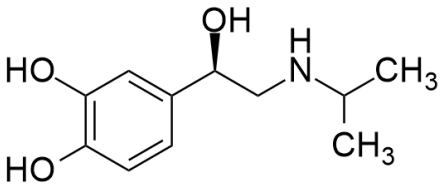
Estereoquímica em Ligantes de Receptores β-adrenérgicos

(-)-noradrenalina

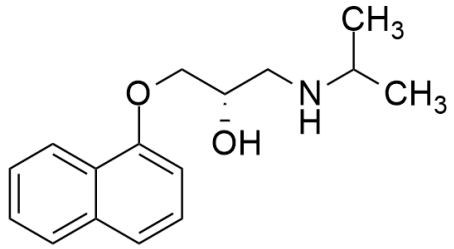


(+)-noradrenalina

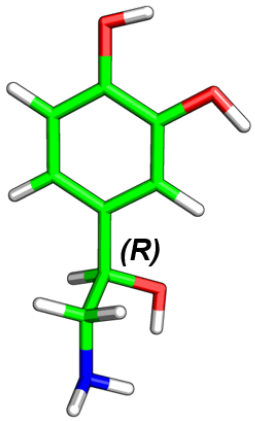


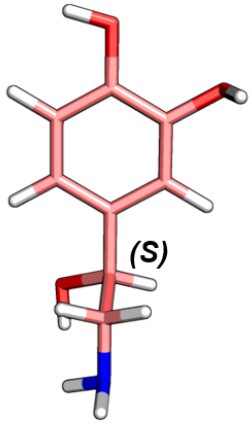


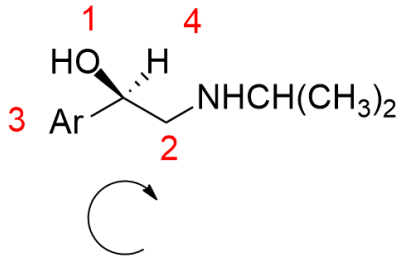
Isoproterenol
(agonista β adrenérgico)



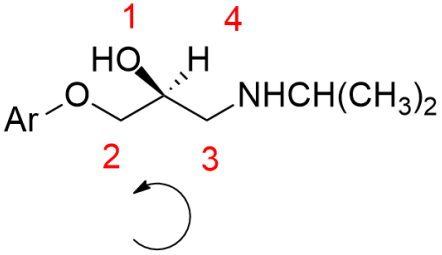
Propranolol
(antagonista β adrenérgico)





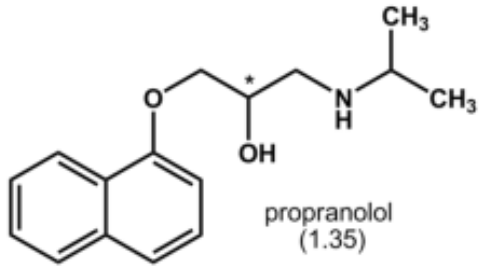


Configuração absoluta *R*

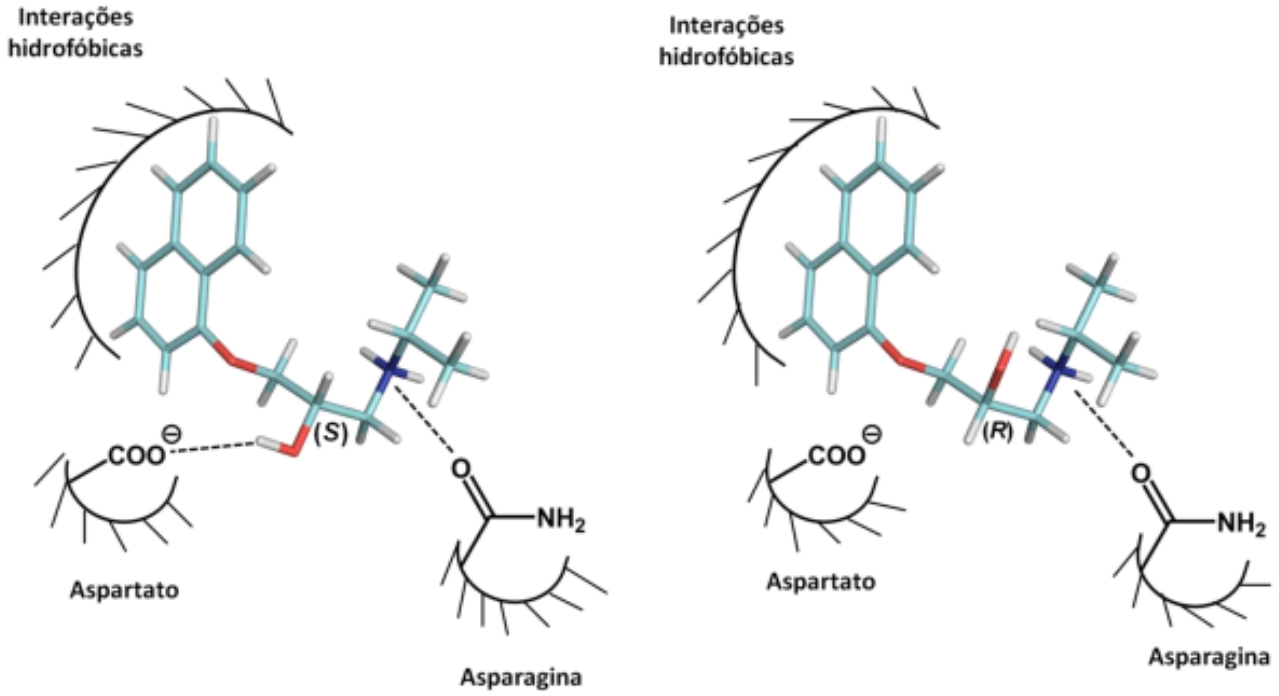


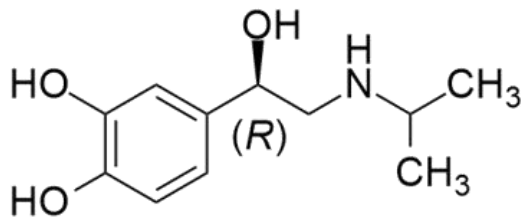
Configuração absoluta *S*

Estereoquímica em Ligantes de Receptores β-adrenérgicos

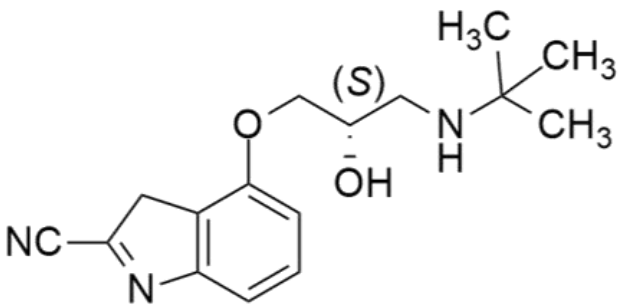


propranolol
(1.35)

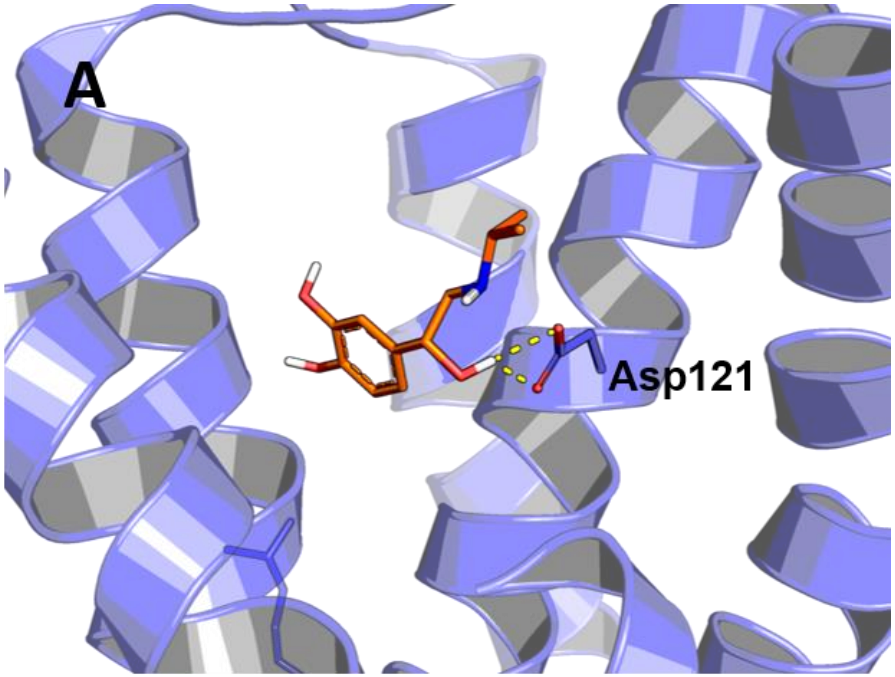


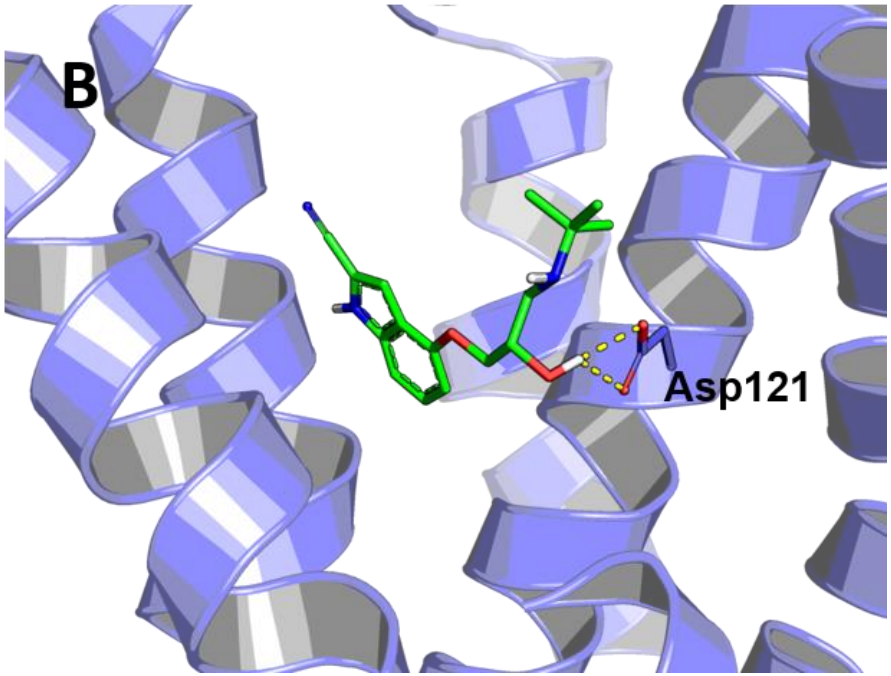


Isoproterenol
(agonista β adrenérgico)

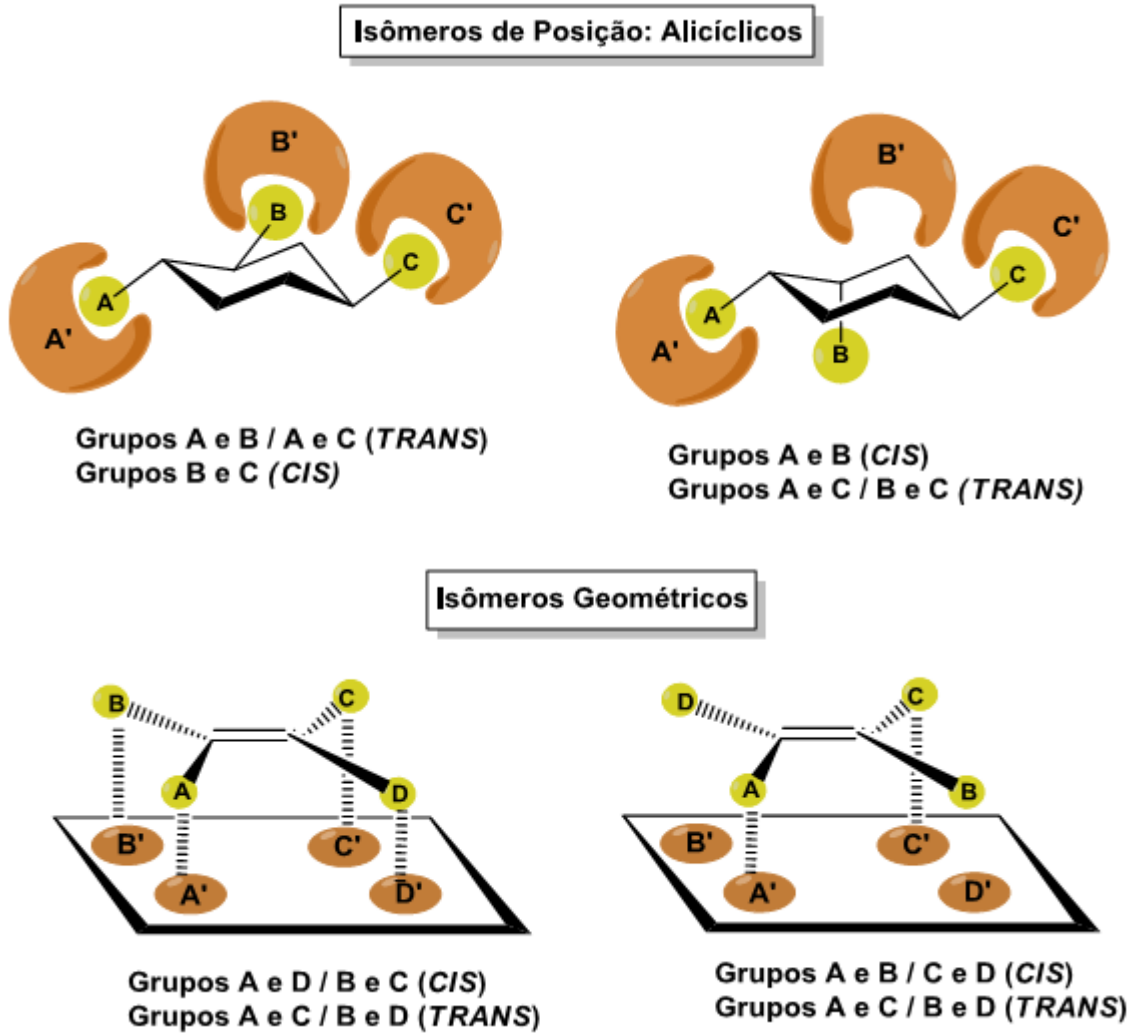


Cianopindolol
(antagonista β adrenérgico)

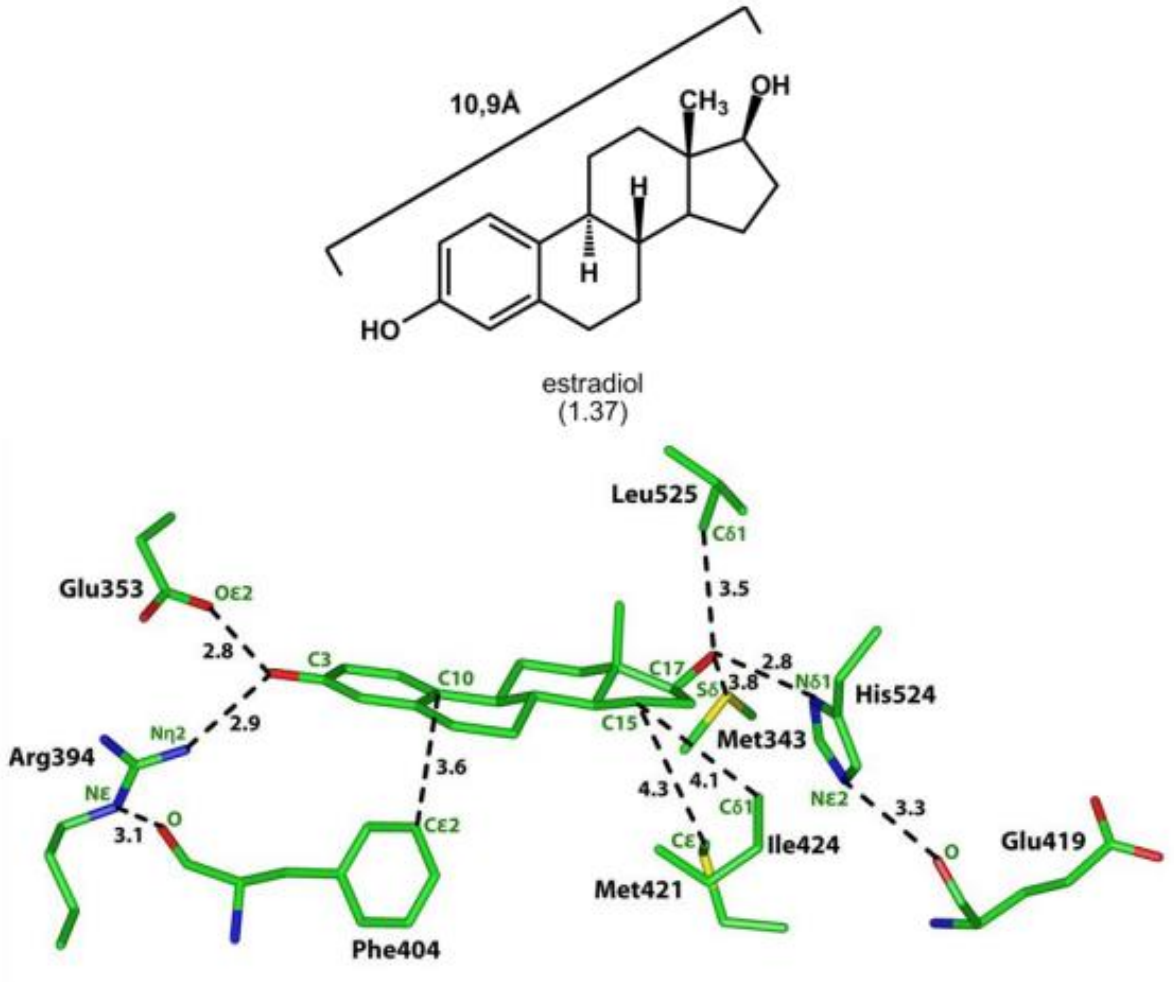




Configuração Relativa e o Reconhecimento Molecular Ligante Receptor



Interação do Estradiol com Receptores de Estrogênio Humanos



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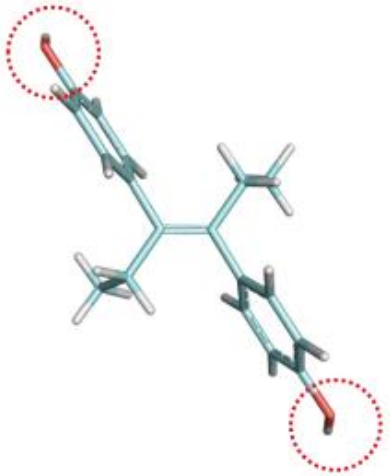
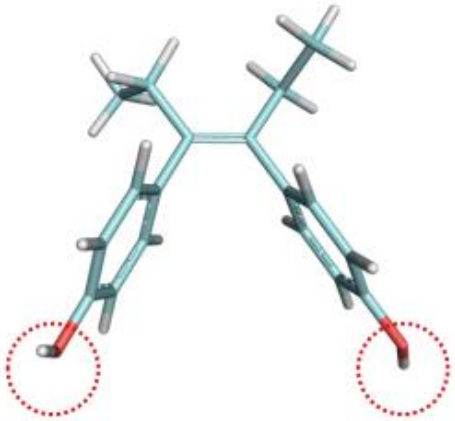
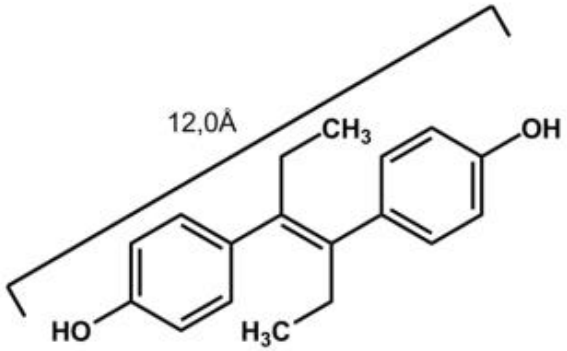
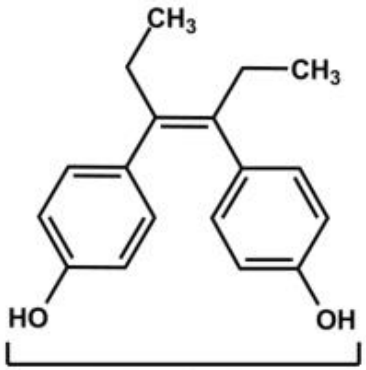
Gênese do (*E)*-Dietilestilbestrol





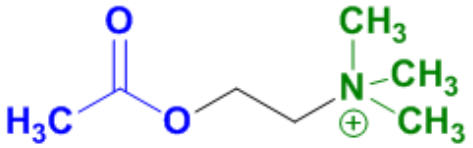


E-dietilestilbestrol
(1.36)

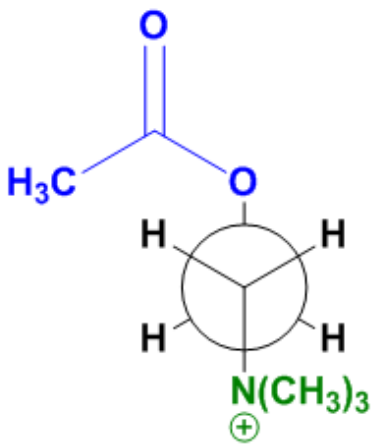


Z-dietilestilbestrol
(1.38)

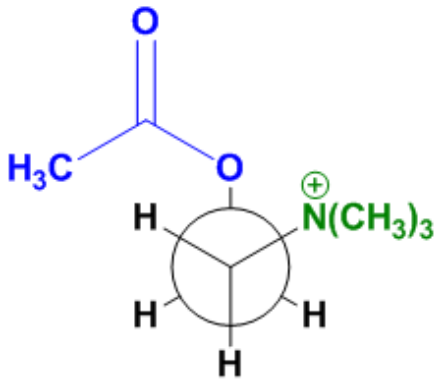
Conformação e o Reconhecimento Molecular Seletivo: Agonistas de Receptores Colinérgicos



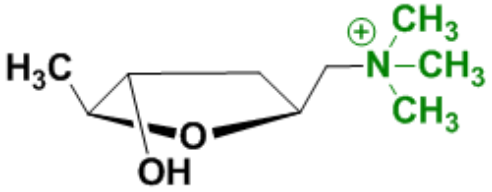
Acetilcolina



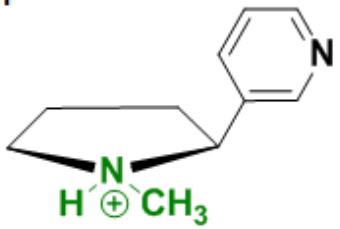
Conformação *antiperiplanar*
Receptores muscarínicos



Conformação *sinclinal*
Receptores nicotínicos

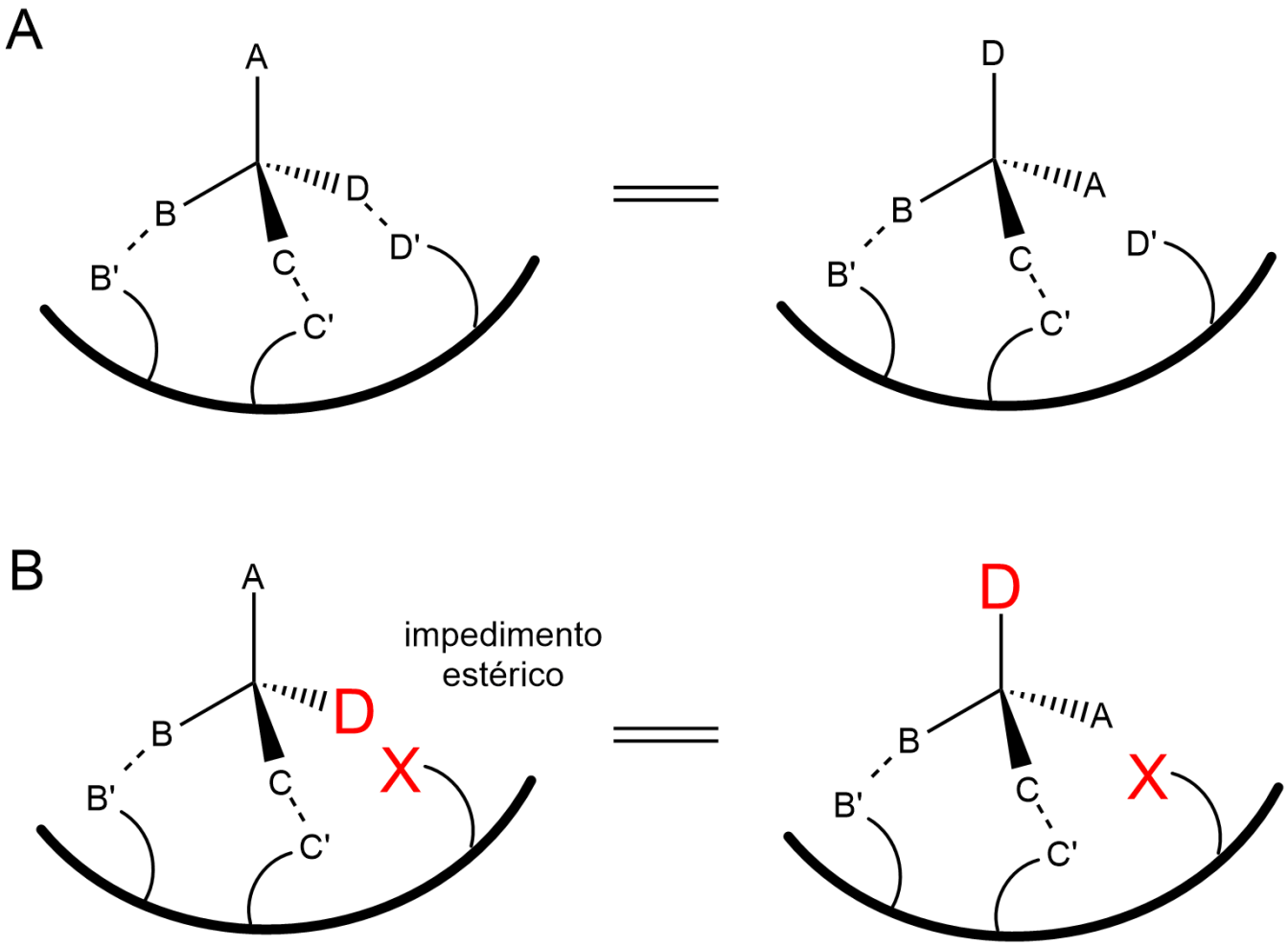


muscarina

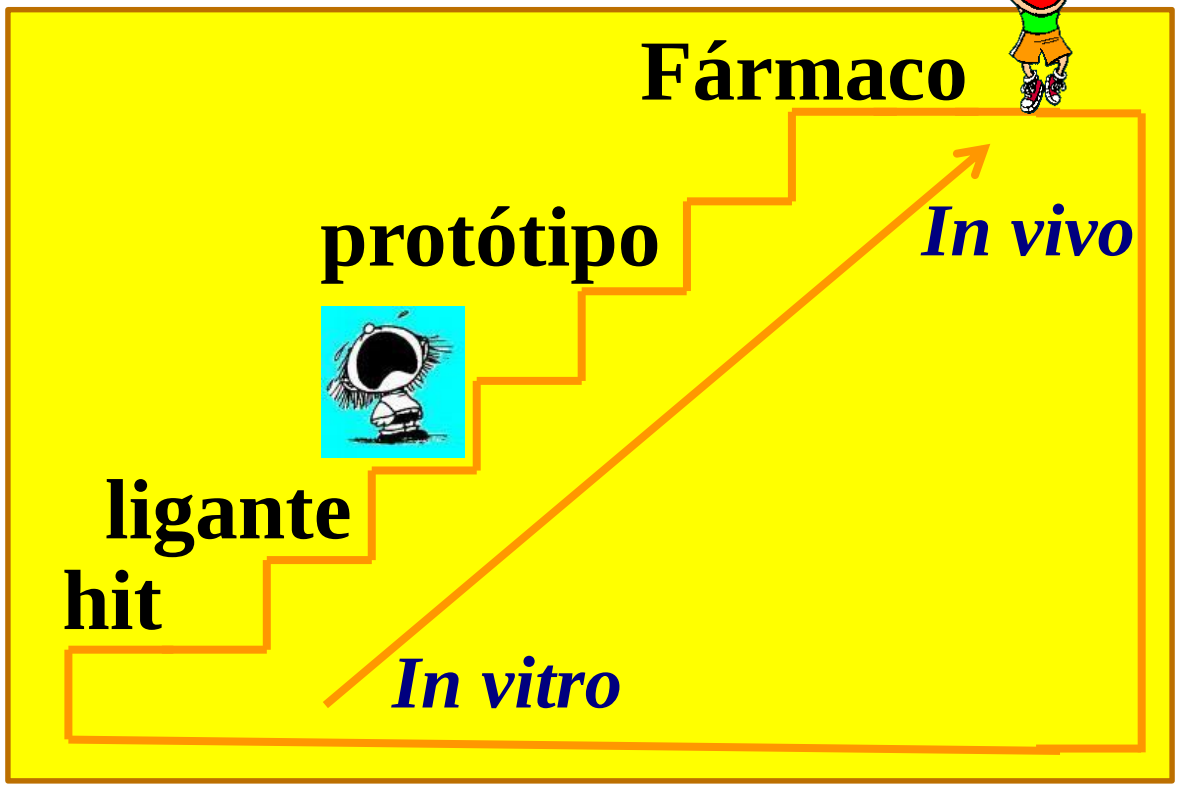


nicotina

(A) Representação esquemática do modelo de três pontos. Somente um enantiômero é reconhecido completamente pelo sítio do biorreceptor. (B) Contribuição de interações estéricas para a estereosseletividade.

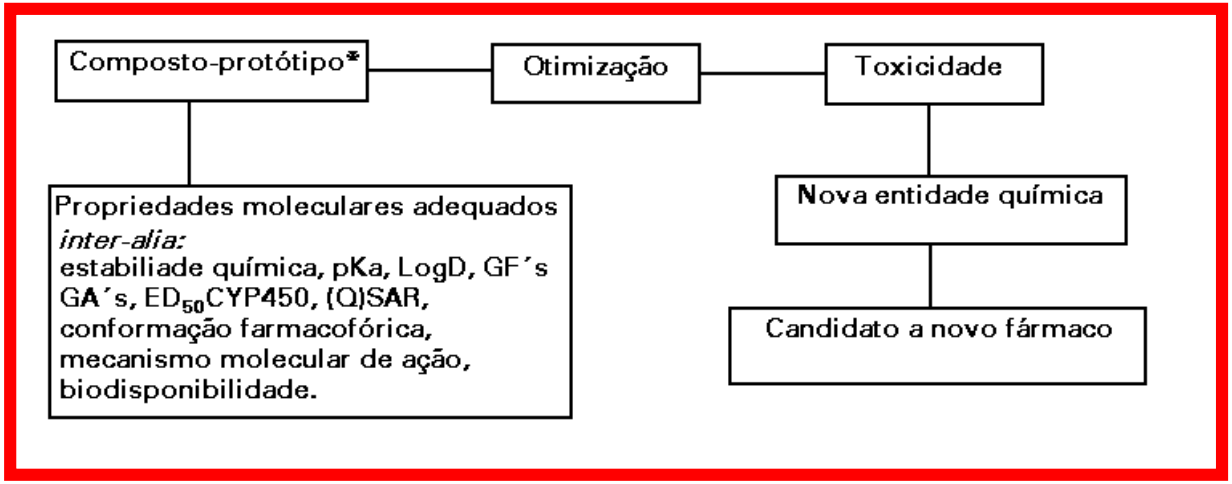


O Paradigma do Composto-Protótipo



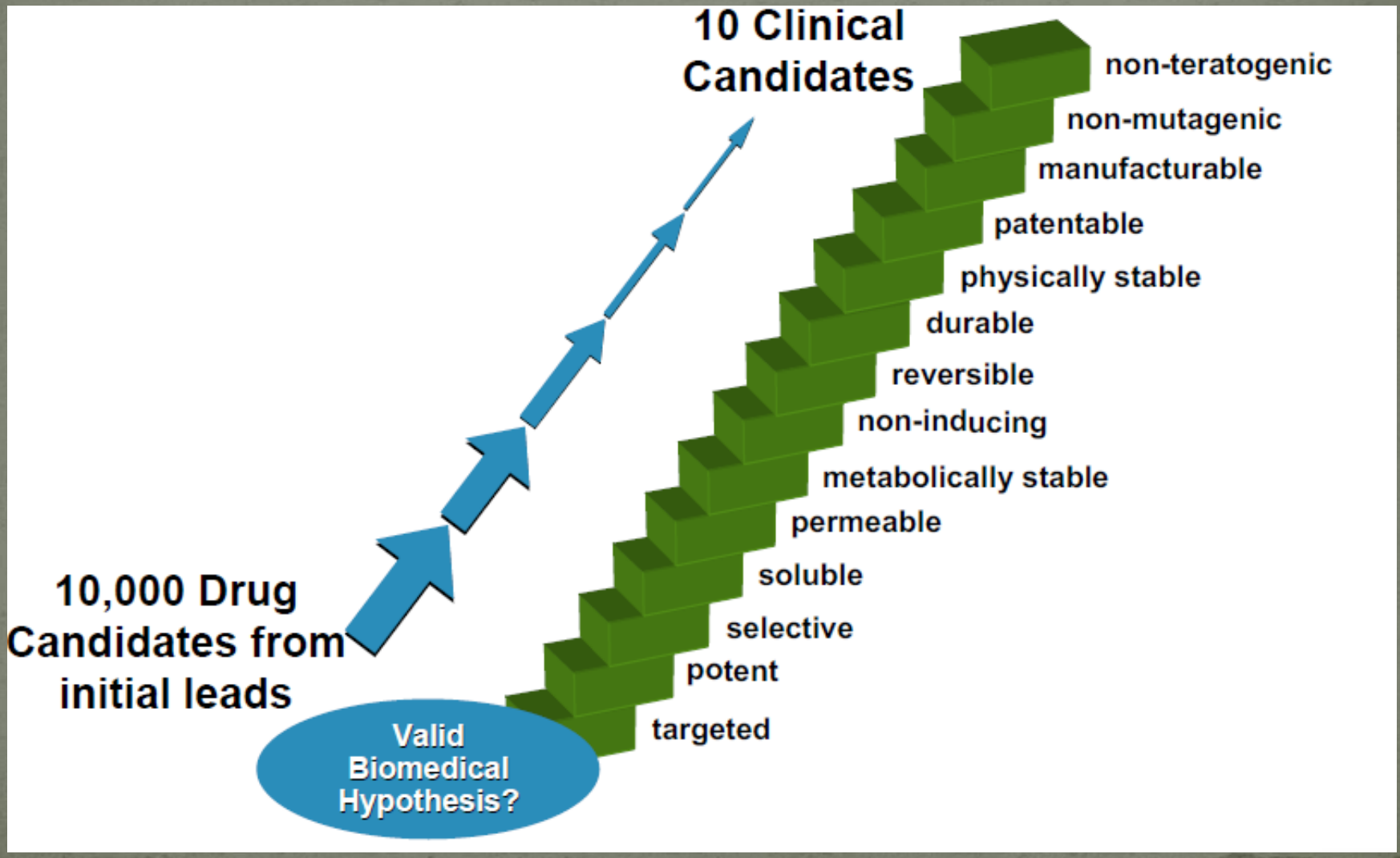
Química Medicinal

"A drug prototype is considered to be the first pure compound to have been discovered in any series of chemically or developmentally related therapeutic agents" Sneader, W. Drug Prototypes and Their Exploitation, John Wiley-Sons, 1996.

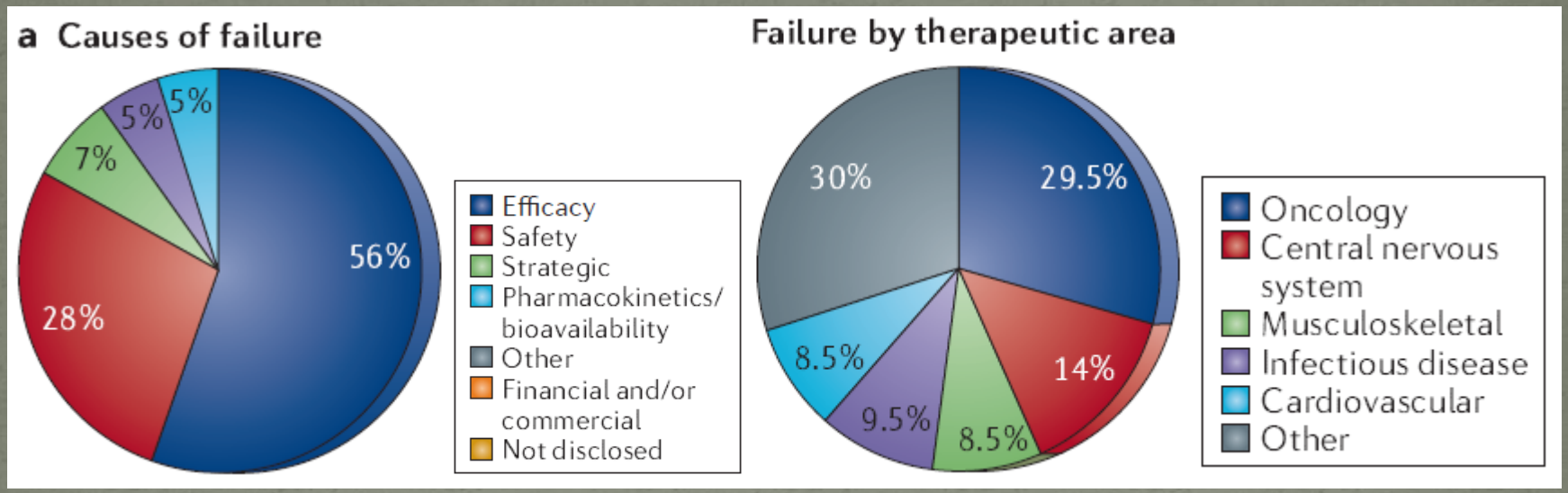


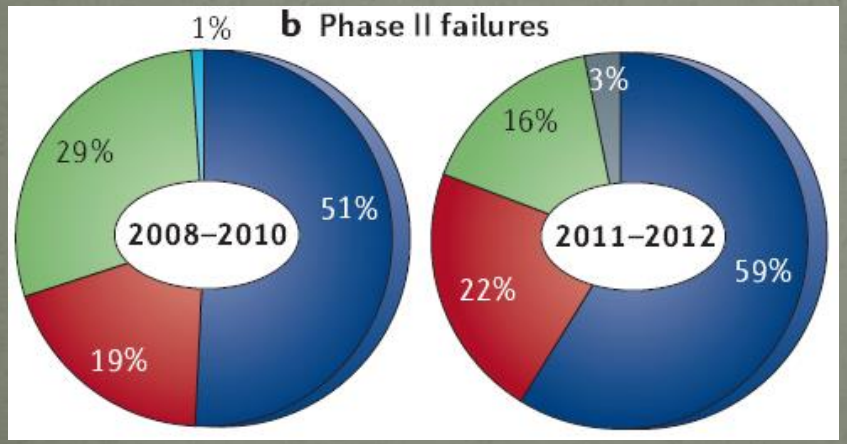
Fraga, C. A. M. & Barreiro, E. J. (2005) Química Nova 28 (Supl.), S56-S63.

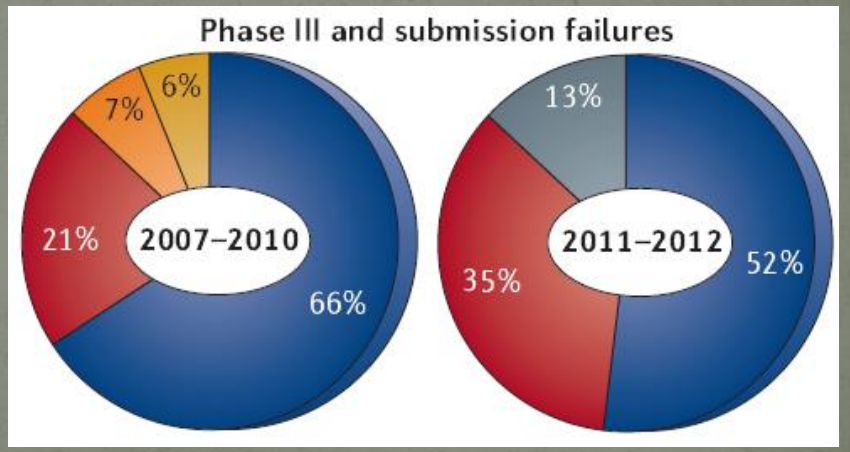
Principais características necessárias à um novo candidato as Fases de Triagem Clínica



Principais Razões para Falhas no Desenvolvimento de Fármacos

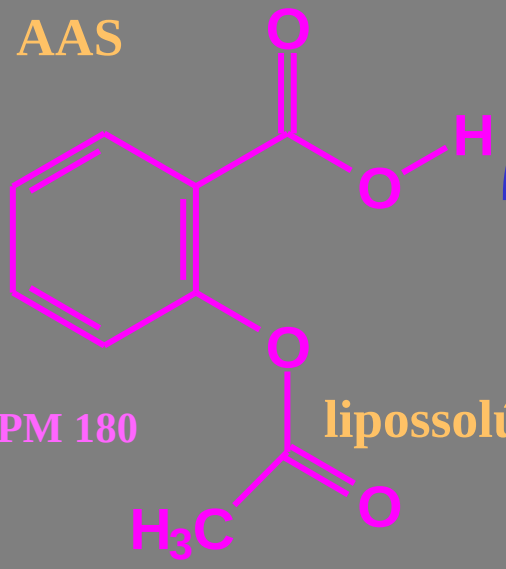






Arrowsmith & Miller (2013) Nature Rev. Drug Discovery *12*, 569;

AAS



PM 180

xenobiótico

p.o.

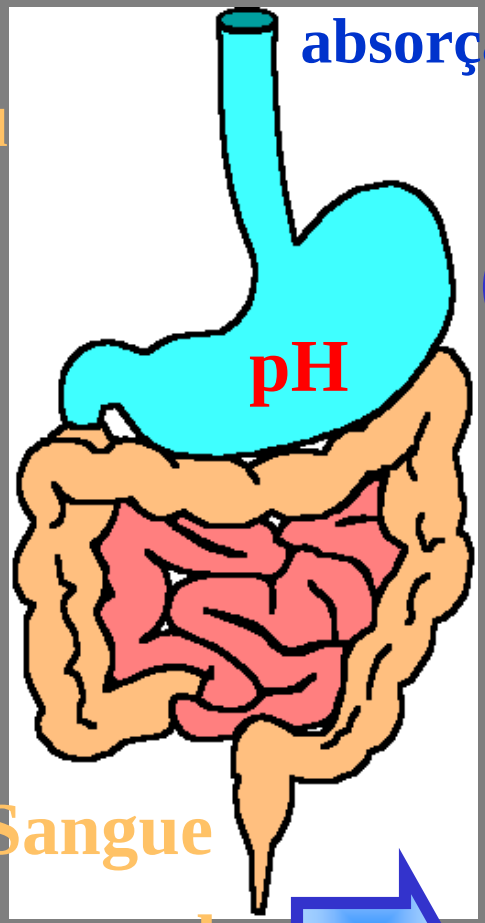
lipossolúvel

Coeficiente de partição

Posologia: concentração
tempo de meia-vida
metabólito ativo (?)
metabólito tóxico (?)
outras atividades (?)

absorção

Fatores Farmacocinéticos



BIOFASE

ADME

Fármaco:
ativo
inativo

Fígado

Rins

URINA

eliminação

hidrossolúvel

Bioativação
Biotransformação

Sangue

Retículo microssomal

Enzimas oxidativas
Citocromo P-450

Ensaios preditivos de propriedades “drug-like”

Box 4 | ***In vitro* tests: ‘now’ and ‘then’**

The following is a typical battery of tests for a modern drug discovery programme ‘today’; those marked with an asterisk were also in use ‘then’.

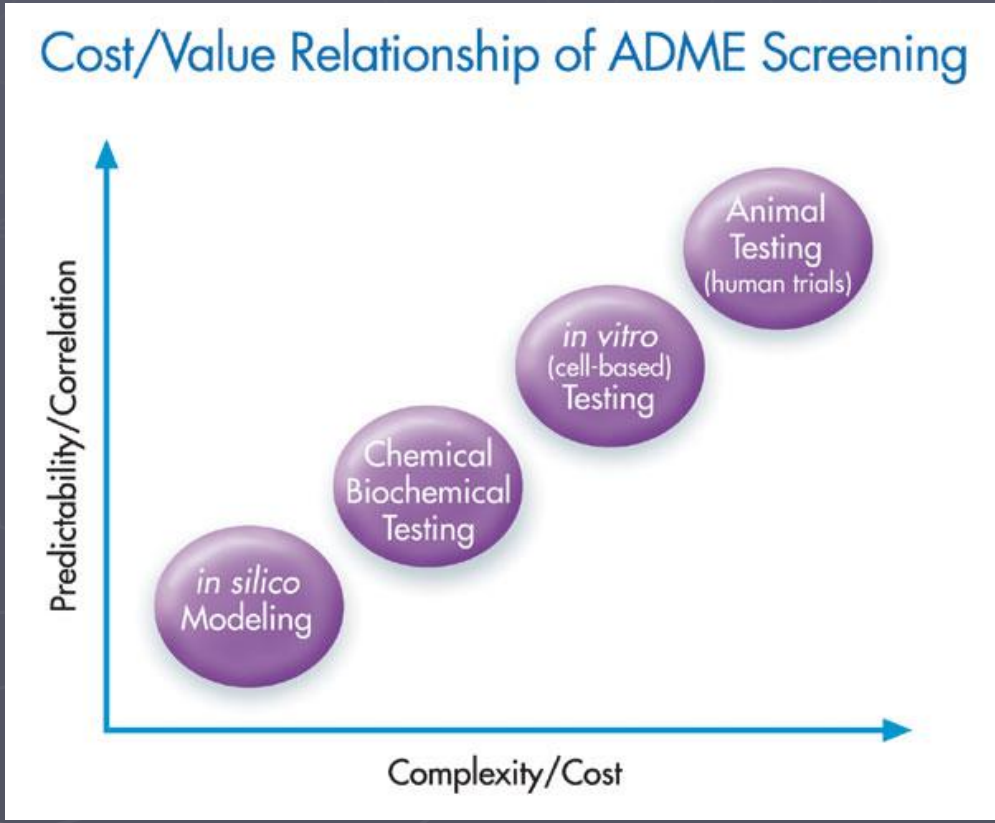
In vitro target
- Primary
- Whole cell
- Functional
- Selectivity assays

In vitro absorption, distribution, metabolism and elimination (ADME)
- Microsomal stability
- Hepatocyte stability
- P450 substrate
- P450 inhibitor
- Permeability
- Transporter efflux (for example, P-glycoprotein)
- Protein binding

Physical properties
- Rule-of-five
- *In silico* ADME

In vivo
- Functional
- *Secondary (behavioural, chronic)

Toxicity
- *Ames test
- Micronucleus test
- hERG half-maximal inhibitory concentration (IC_{50})
- P450 induction
- Broad screening
- *Others (depending on project)



Lombardino, J. G. & Lowe III, J. A. (2004) Nature Rev. Drug Discovery 3, 853-862.

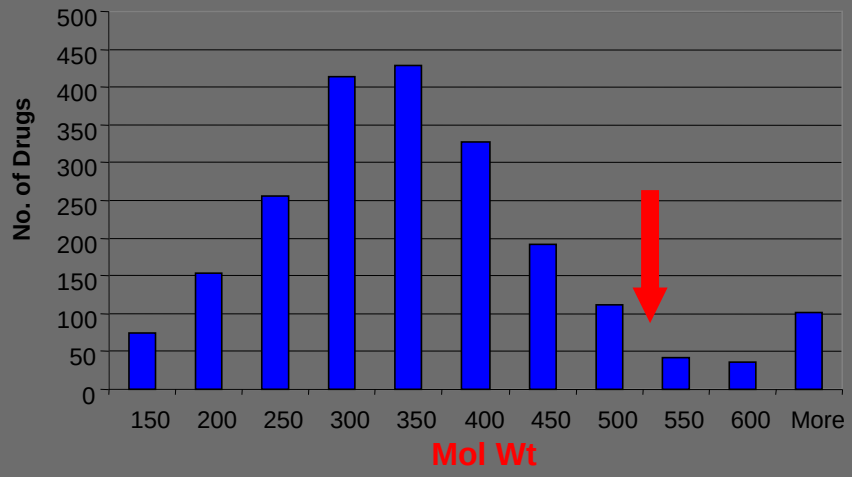
Previsão de Propriedades Fisicoquímicas 'Drug-Like' :

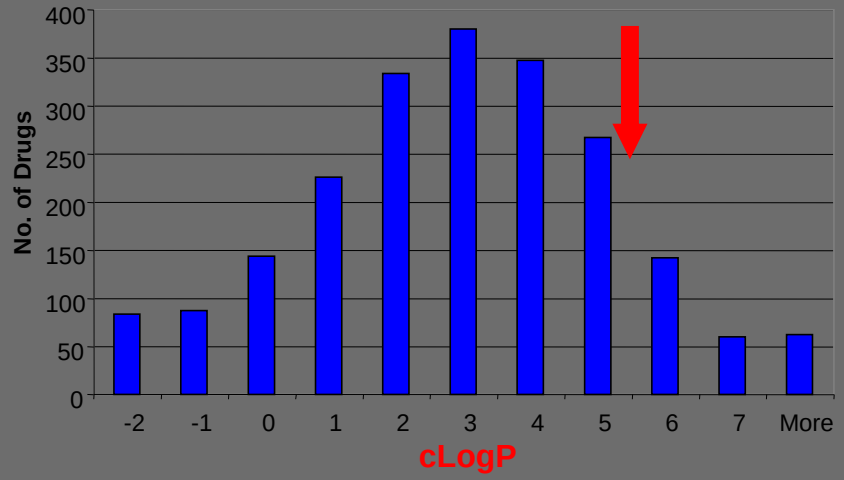
Lipinksi's 'Rule of 5' - from World Drug Index

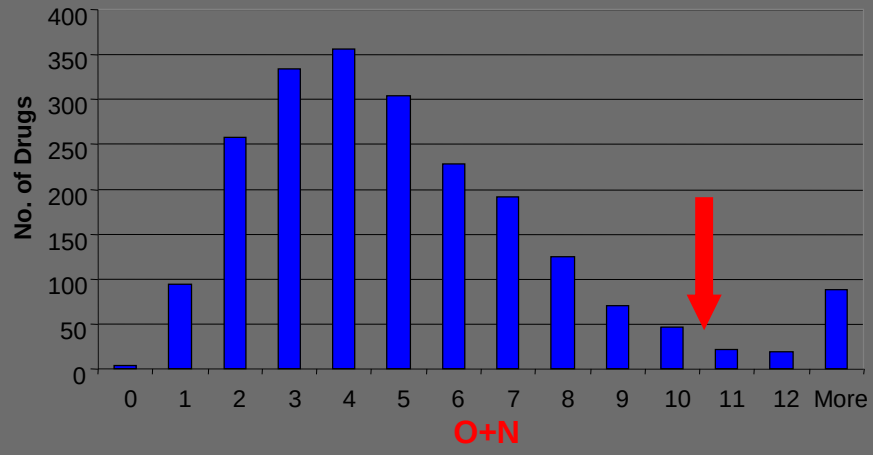
Adv. Drug. Del. Revs*.** 1997, ***23, **3**

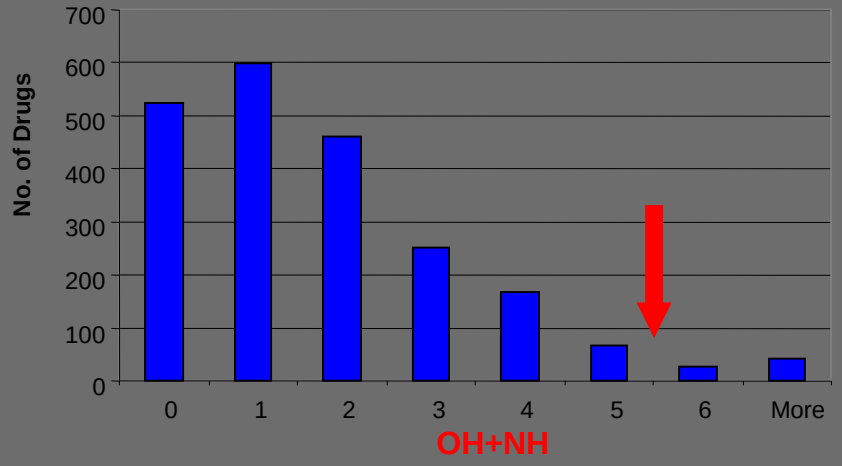
- Drug absorption is allowed when:
  - there are <5 H-bond donors (OHs & NHs)
  - there are <10 H-bond acceptors (Os & Ns)
  - the molecular weight is <500
  - the Log P (1-oct/H_2O) is <5
- Substrates for biological transporters are exceptions

Fármacos Ativos Por Via Oral (n=2137) & a Regra dos 5



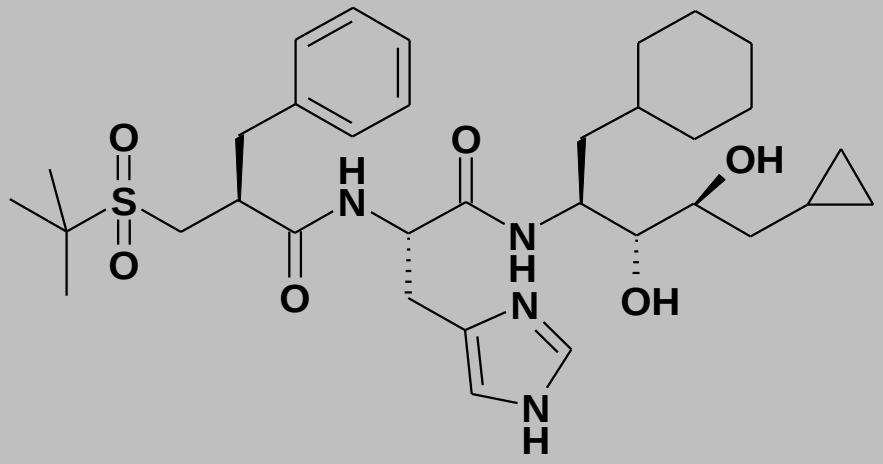






Wenlock et al, *J. Med. Chem.* **2003**, *46*,

Exemplos de Desenvolvimento de Novos Fármacos: Inibidores de Renina vs. Agonistas de Receptores de Serotonina

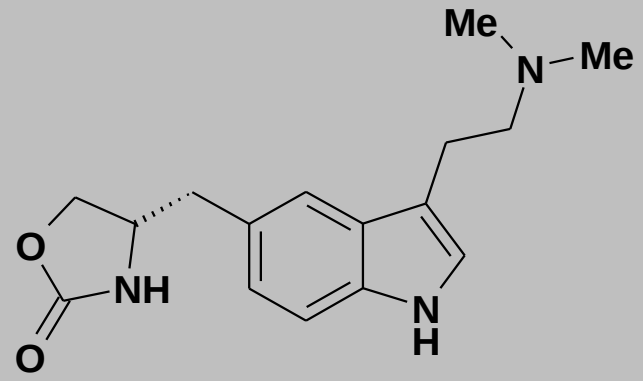


Ro 42-5892

Inibidor de Renina Típico

Falhou na Fase de Desenvolvimento

Mol Wt = 645



Zolmitriptan

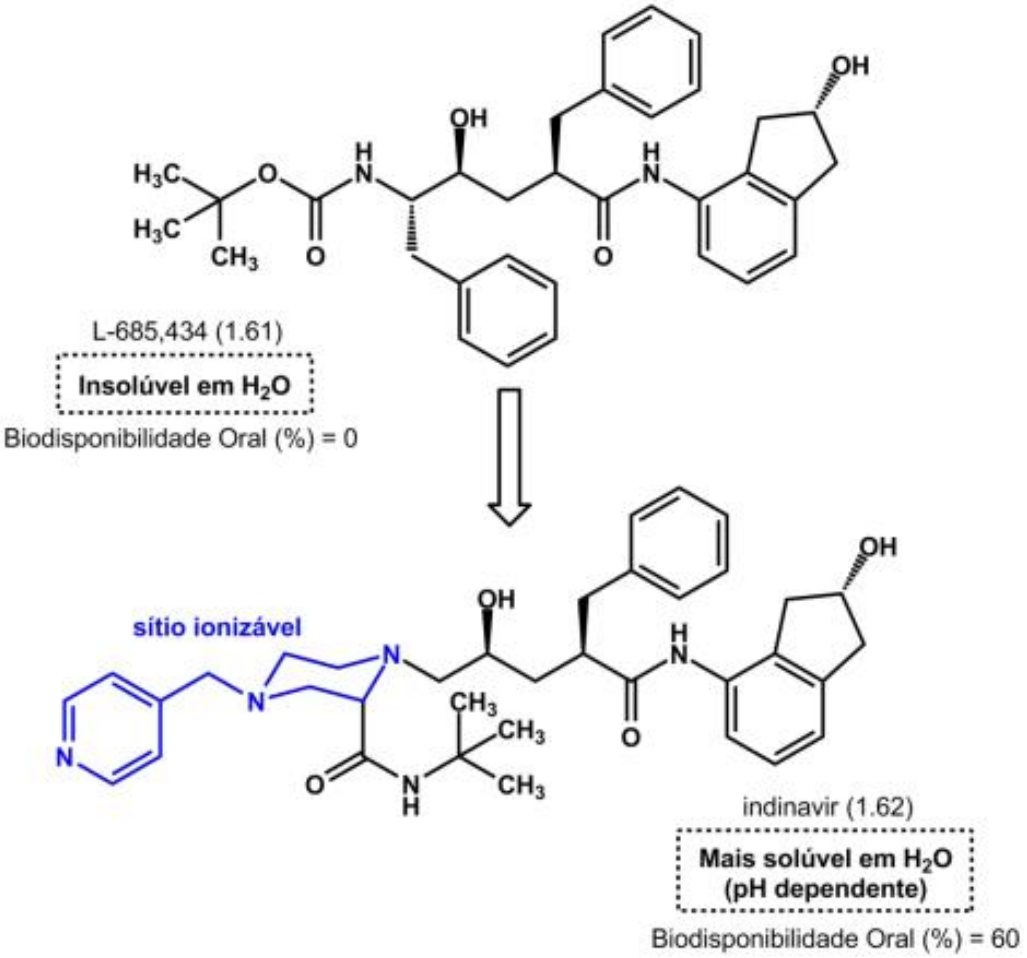
Agonista de Receptores 5-HT1D

Ativo por via oral

Comercializado para Tratamento da Enxaqueca

Mol Wt = 287

Otimização das propriedades farmacocinéticas do protótipo antiviral L-685-434



Barreiro, E. J.; Fraga, C. A. M. (2015) Química Medicinal: As Bases Moleculares da Ação dos Fármacos, 3ª Edição, Artmed, Porto Alegre.

Evolução Temporal do Processo de Descoberta de Fármacos

1800-1919
- Era das Plantas e Produtos Naturais
- Nascimento da Indústria Farmacêutica
- Quinina, Aspirina, Digitálicos, Cocaína

Anos 20 e 30
- Descoberta das Vitaminas e Vacinas
- Desenvolvimento da Química Orgânica
- Fleming descobre acidentalmente a Penicilina

Anos 40
- Era dos Antibióticos
- Desenvolvimento e Produção de Penicilina e outros antibióticos para tratar as infecções dos soldados da II Guerra Mundial
- Redução da valorização das Descobertas ao Acaso

Anos 50
- Era da Guerra Fria
- Novas Tecnologias e Instrumentação
- Compreensão da Fisiologia Humana
- Descoberta da Estrutura do DNA
- Desenvolvimento da Biotecnologia

Anos 60
- Década Farmacêutica
- Descoberta dos Contraceptivos
- Tecnologia Computacional de Elevado Desempenho
- Compreensão da Etiologia das Doenças
- Descoberta baseada em Estratégias Racionais

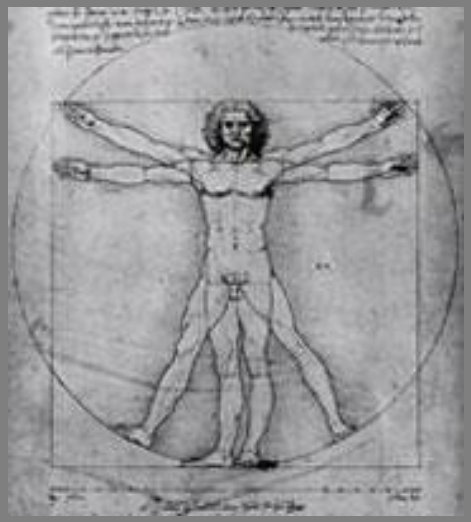
Anos 70
- Era do Combate ao Câncer
- Desenvolvimento da Engenharia Genética e da Biotecnologia
- Tecnologia Computacional de Elevado Desempenho
- Planejamento Racional auxiliado por Técnicas Computacionais

Anos 80
- Era da Descoberta do Vírus HIV e a AIDS
- Desenvolvimento da Imunologia
- Início da valorização do Mercado Farmacêutico (Blockbusters)
- Desenvolvimento da Química Combinatória

Anos 90
- Robótica e Automação na Descoberta de Fármacos
- Desenvolvimento das técnicas de HTS
- Caracterização do Genoma Humano

Século 21

* *HTS = High Throughput Screening*

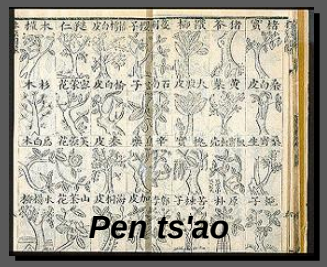


Fraga, C. A. M. & Barreiro, E. J. (2005) Química Nova 28 (Supl.), S56-S63.

A DESCOBERTA DE FÁRMACOS

A busca por substâncias terapeuticamente úteis era centrada na investigação de plantas que cresciam em jardins de instituições religiosas

Uma importante mudança de paradigma ocorreu no momento em que os alcalóides foram isolados e moléculas simples como o ácido acetil salicílico foram sintetizadas



Shen Nung

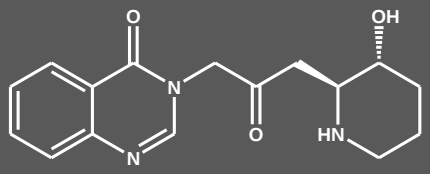
Dichroa febrífuga

Rauwolfia serpentina

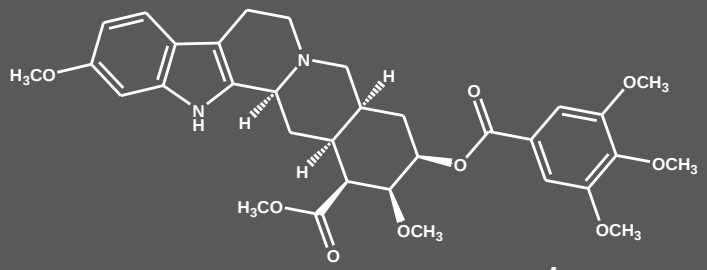
Theophrastus

5100 a.C. — **1000 a.C.** — **300 a.C.**

Gh'ang Shan — *hindus* — *opióides*



febrifugina



reserpina

papoula

Chen, K.K. (1925) J. Am. Pharm. Assoc., 14, 189.
Jang, C.S., *et al*. (1946) Science, 103, 59.
Grob, D. (1955) J. Chronic Diseases, 1, 229.
Silverman, R.B. (2004) The Organic Chemistry of Drug Design and Drug Action, Elsevier, San Diego, 10.

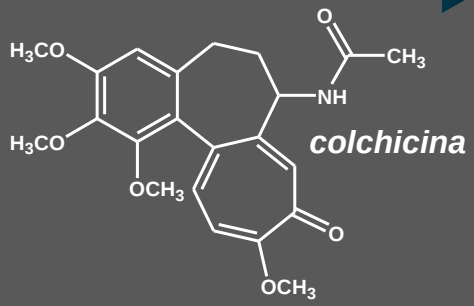
Alexander de Tralles

Colchicum autumnale

Cinchona

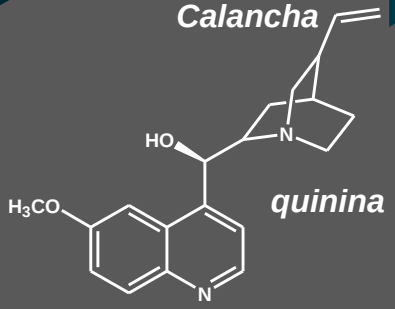
Digitalis purpurea

500 → **1633** → **1785**

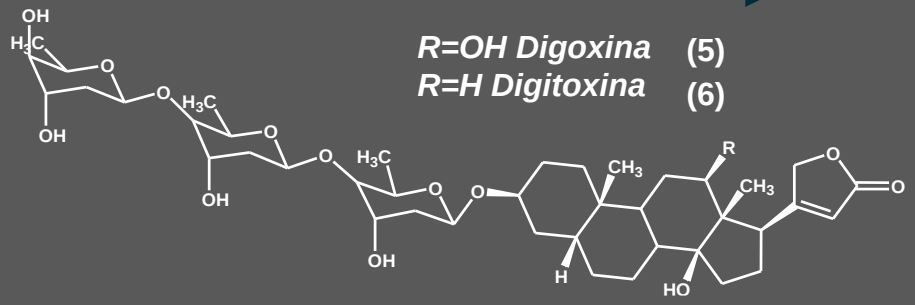


colchicina

Calancha



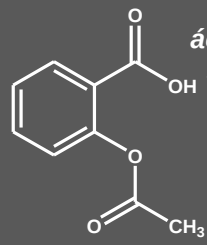
quinina



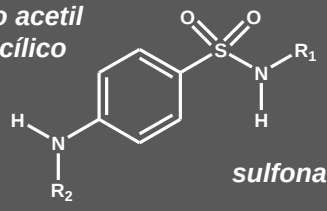
R=OH Digoxina (5)
R=H Digitoxina (6)

Início dos fármacos sintéticos e da Química Medicinal

1900 → **Futuro**



ácido acetil salicílico



sulfonamidas

Tracy, J.W. & Webster, L.T. (1993) em The Pharmacological Basis of Therapeutics, McGraw Hill, Nova Tork, 965.
Hoffman, B.F. & Bigger, T. (1991) em As Bases Farmacológicas da Terapêutica, Guanabara Kogaan, Rio de Janeiro, 536.
Newman, D.J.; Cragg, G.M.; Sneader, K.M. (2004) J. Nat. Prod., 66, 1022.
Silverman, R.B. (2004) The Organic Chemistry of Drug Design and Drug Action, Elsevier, San Diego, 10.
Burger, A. (1980) Burger's Medicinal Chemistry, Willey, Nova York, 23.

Estratégias Empregadas na Descoberta de Novos Fármacos

"SCREENING SISTEMÁTICO"

Esta estratégia consiste de um screening sistemático de um grupo de moléculas escolhidas arbitrariamente pela sua diversidade.

"MECHANISM BASED DRUG DESIGN"

(PLANEJAMENTO RACIONAL)

A melhor caracterização dos receptores, ou de métodos computacionais avançados, tem permitido um planejamento racional de novos compostos bioativos com maior base científica.

Descoberta de Fármacos

"ME-TOO"

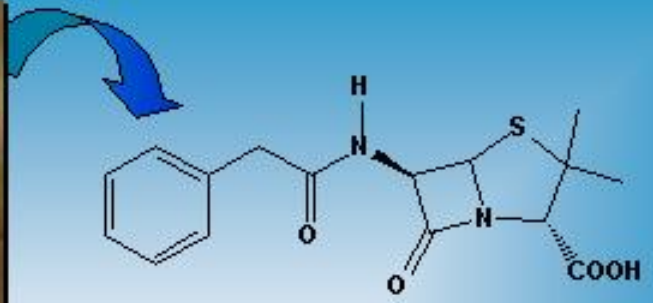
"The most fruitful basis for the discovery of a new drug is to start with na old drug." Sir James Black – Prêmio Nobel em Fisiologia e Medicina

"SERENDIPITY"

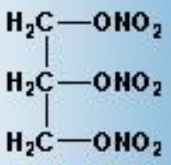
Esta estratégia envolve a utilização de informações biológicas que resultam de descobertas feitas em testes de rotina.

"... in the recent years the paradigms of drug research changed significantly..."
Kubinyi, H., 1995

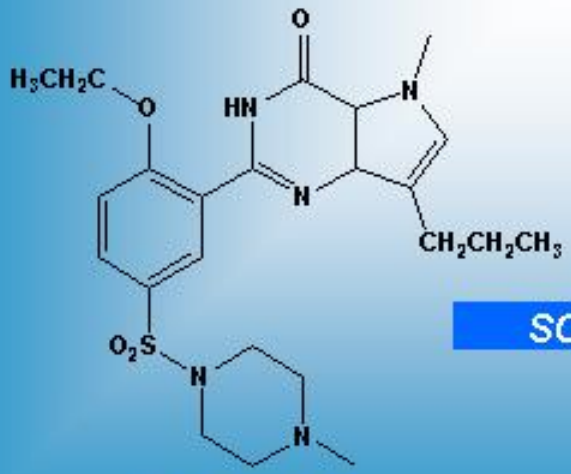
Fraga, C. A. M. & Barreiro, E. J. (2005)
Química Nova 28 (Supl.), S56-S63.



Penicilina G



trinitroglicerina



Sildenafil

SOSA

Nova classe de fármacos úteis no tratamento da disfunção erétil

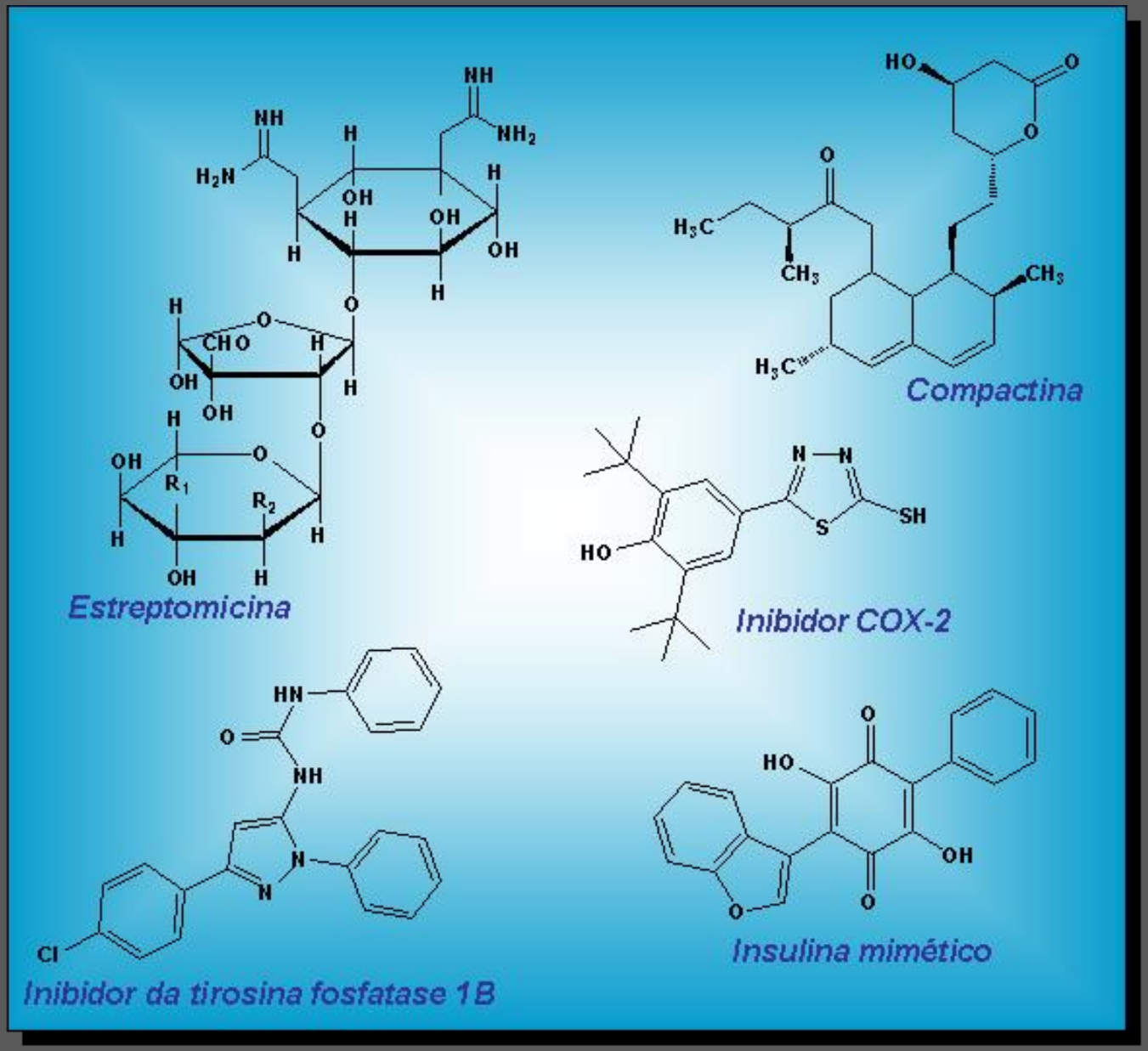
"SERENDIPITY"
A word coined by Horace Walpole, who says (Let. to Mann, 28 Jan. 1754) that he had formed it upon the title of the fairy-tale 'The Three Princes of Serendip', the heroes of which '**were always making discoveries, by accidents and sagacity**, of things they were not in quest of"

Wermuth, C.G. (2004) J. Med. Chem., 47, 1303.

Fleming, A. (1929) Br. J. Exp. Pathol., 10, 226.

Terret, N.K. (1996) Bioorg. Med. Chem. Lett., 6, 1819.

“Screening Sistemático”



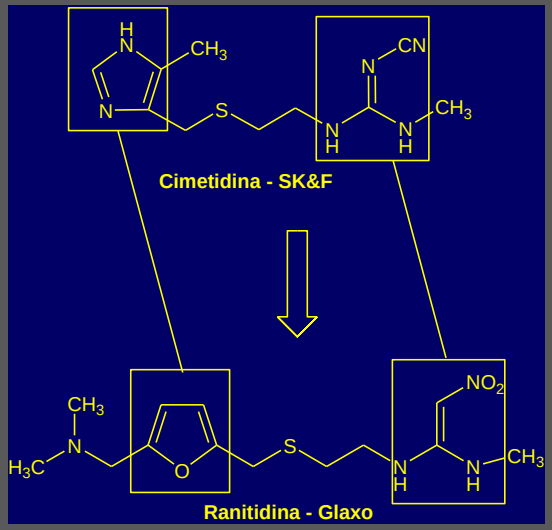
Nakamura, C.E. & Abeles, R.H. (1985) Biochemistry, 24, 1364.

Liu, K. *et al*. (2000) J. Med. Chem.,43, 3487.

Doman, T.N. *et al*. (2002) J. Med. Chem., 45, 2213.

Drews, J. (2003) Drug Disovery Today, 8, 411.

“Me-Too’s”



lovastatina

simvastatina

ramipiril
(Hoechst-Alemanha)

enalapril
(Merck-USA)

captopril

perindopril
(Servier-França)

lisinopril
(Merck-USA)

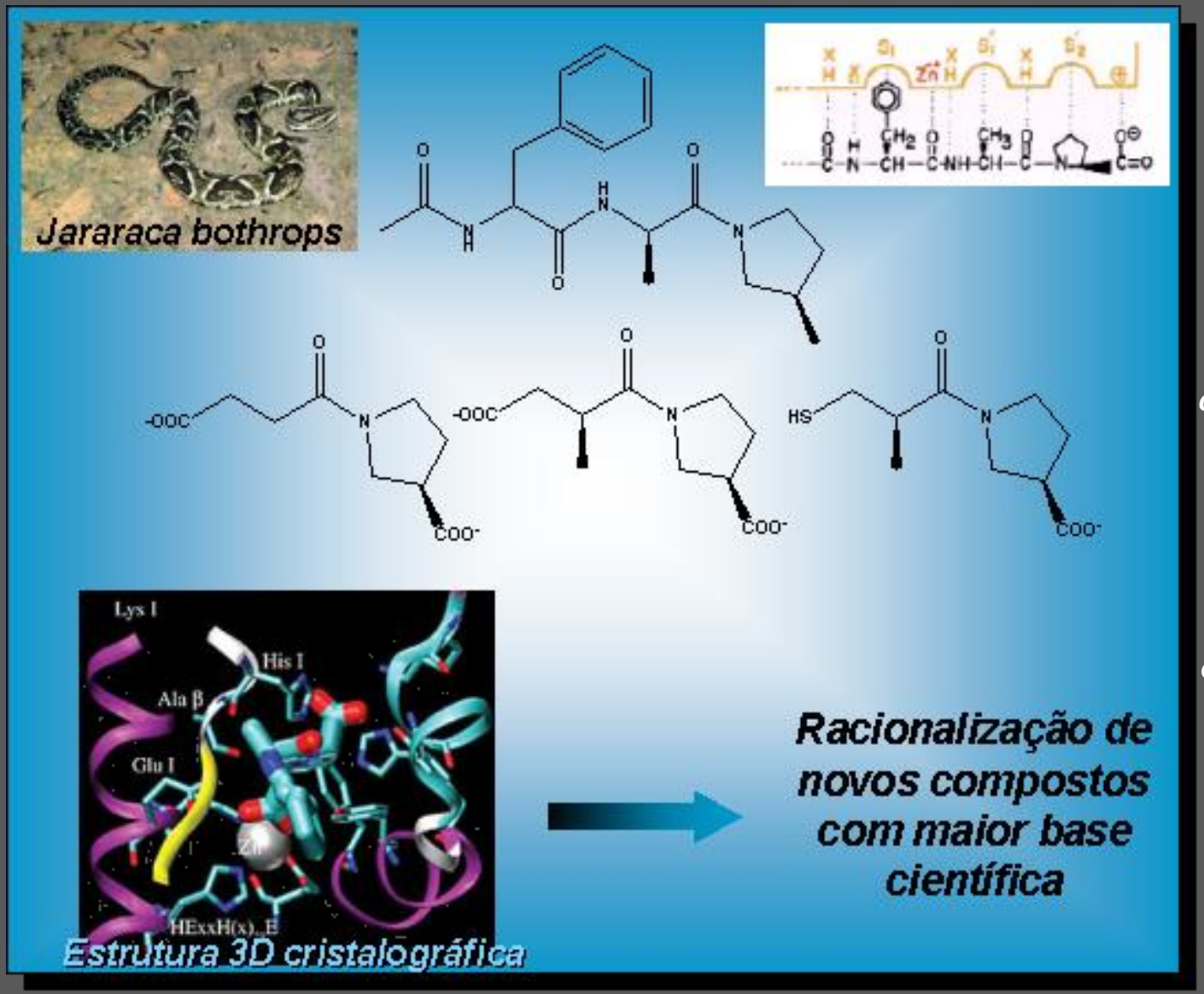
Wermuth, C.G. (2004) J. Med. Chem., 47, 1303.

Raju, T.N.K. (2000) Lancet, 355, 121.

Cushman, D.W. & Ondetti, M.A. (1991) Hypertension, 17, 589.

Tobert, J.A. (2003) Nat. Rev. Drug Disc. 2, 517.

Planejamento Baseado no Mecanismo de Ação



"O processo moderno da descoberta de fármacos, baseado no mecanismo de ação, visa a identificação de novos compostos bioativos através do desenho planejado de sua arquitetura molecular, ou a identificação de um bioligante eficiente, cuja arquitetura molecular é planejada com base na estrutura de um biorreceptor conhecido, empregando estratégias de complementaridade molecular"

Fraga, C. A. M. & Barreiro, E. J. (2001) Química Medicinal, ArtMed, Porto Alegre, p.17.

Cushman, D.W. & Ondetti, M.A. (1999) Nature, 5, 110; Ferreira, S.H. (1965) Br. J. Pharm., 24, 163; Wermuth, C.G. (1996) The Practice of Medicinal Chemistry, Academic Press, Londres.

Estratégias Racionais de Planejamento de Fármacos

Intuição Química

Bioisosterismo

Ferramentas de Modificação Estrutural

Hibridação e Simplificação Molecular

Abordagem Direta

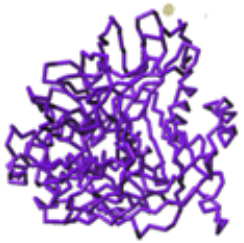
Abordagem Fisiológica

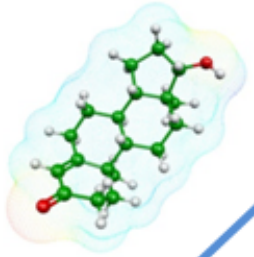
Abordagem Indireta

Eleição do Alvo Validado

Doença

Estrutura da Biomacromolécula





Estrutura do Ligante

Docking Molecular

SAFIR

SAR

SAFIR

QSAR

Dinâmica Molecular

Composto-Protótipo

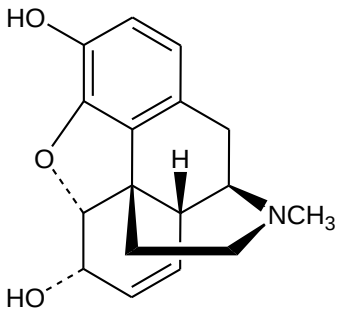
Modelagem Molecular

PK/PD

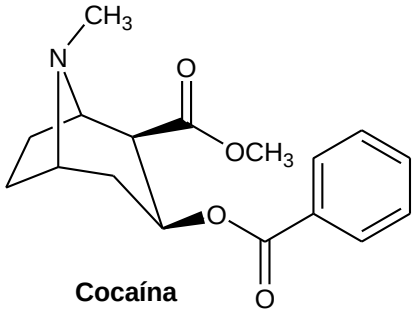
Reconhecimento Molecular

Otimização de protótipo

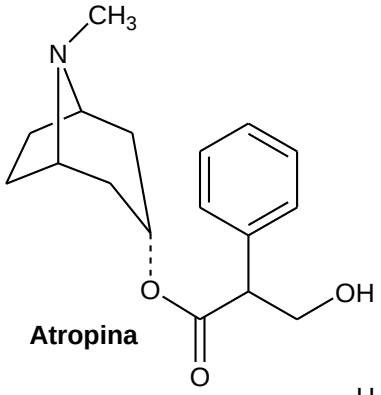
No início.....Os Produtos Naturais...



Morfina

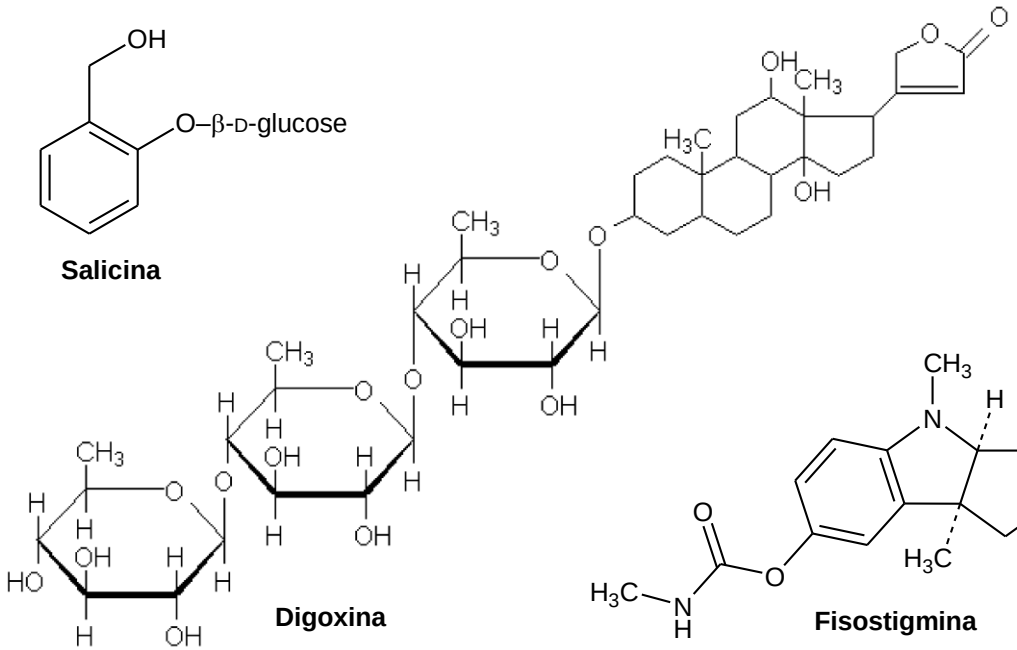


Cocaína

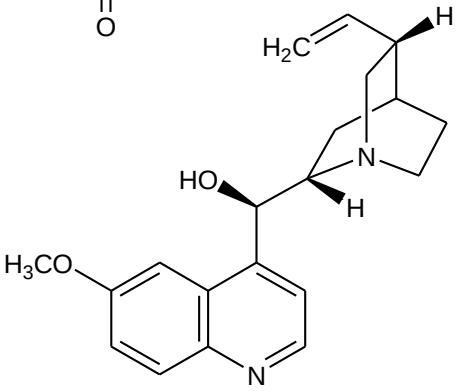


Atropina

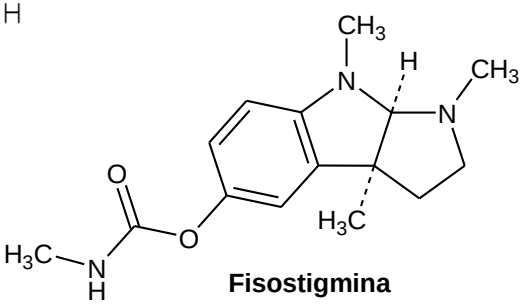
Salicina



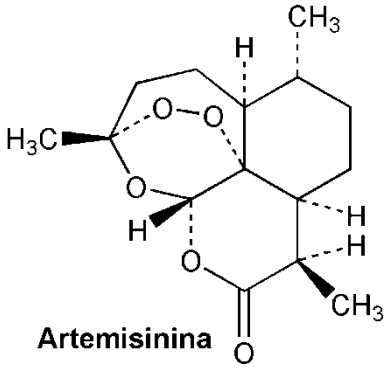
Digoxina



Quinina

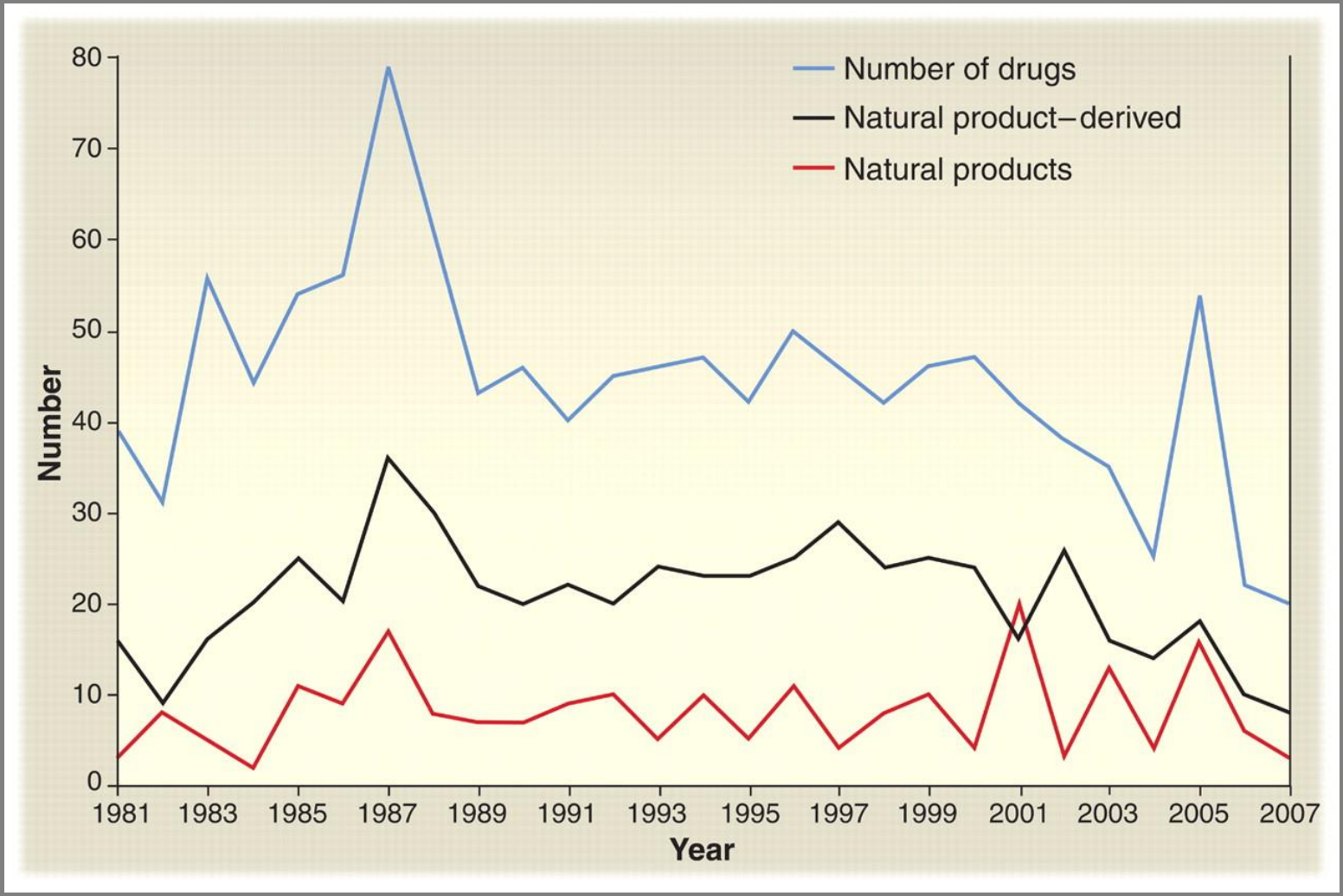


Fisostigmina



Artemisinina

Fig. 1 Number of drugs approved in the United States from 1981 to 2007.



J W Li, J C Vederas Science 2009;325:161-165

Science
AAAS

Fármacos de Origem Marinha

A

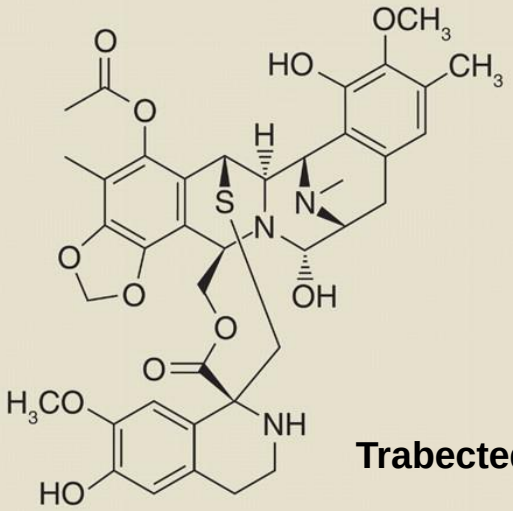
Conus magus

H_2N–CKGKGAKCSRLMYDCCTGSCRSGKC–$CONH_2$

Ziconotide

B

Ecteinascidia turbinata



Trabectedin

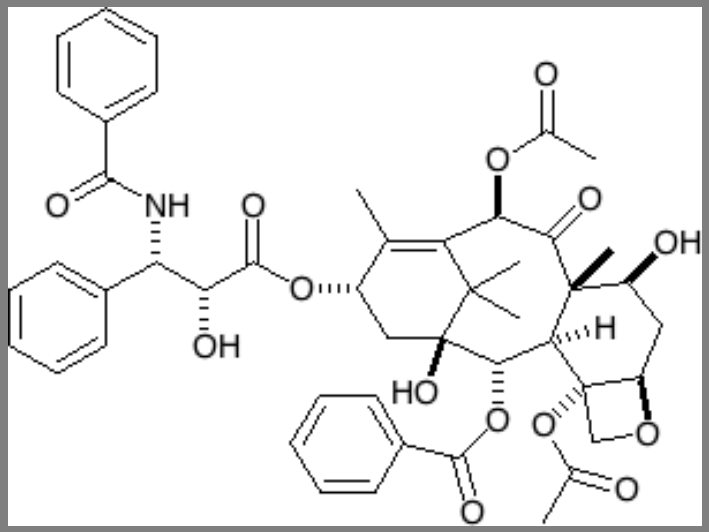
J W Li, J C Vederas Science 2009;325:161-165

Science
AAAS

Discovery of Paclitaxel

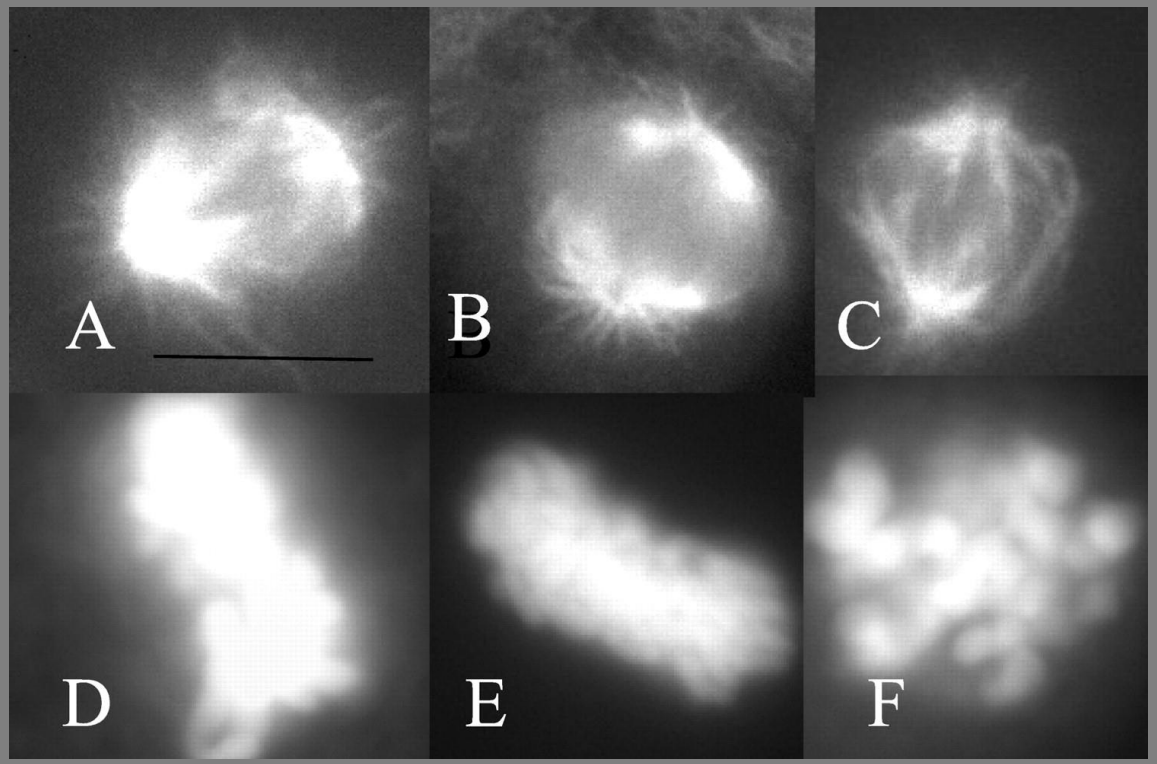
Em 1962, Arthur S. Barclay, coletou amostras de cascas do Teixo do Pacífico, *Taxus brevifolia*, em uma floresta ao Norte dos EUA, as quais apresentaram efeitos citotóxicos (1964).

Em 1965, estas amostras forma fracionadas e isoladas por Monroe E. Wall e Mansukh C. Wani (Research Triangle Institute), iniciando os trabalhos com os ingredientes ativos de *Taxus* samples. Eles denominaram o ingrediente ativo puro de 'taxol' in Junho de 1967.



Em 1969, 28 kg de extrato bruto foi isolado a partir de 1181 kg da casca de Taxus, fornecendo apenas 10 g de Taxol puro.

BMS apresentou o dossiê com os dados clínicos do Taxol ao FDA que aprovou-o para uso ao final de 1992.



Mecanismo de Ação: Taxol se liga a tubulina polimerizada promovendo a estabilização de microtúbulos e evitando sua desorganização e conseqüentemente inibindo o processo mitótico e o crescimento do cancer cancer growth (Ovariano, mama e pulmões)

Taxol é encontrado em várias espécies de Teixo (0.001 to 0.01 % do peso da casca seca).

Com base em dados do serviço florestal americano, desde 1992, 36.000 árvores foram utilizadas para produzir 327.200 kg de cascas (cerca de 9 kg/árvore) a partir das quais 24 kg de taxol foram extraídos (cerca de 0.66 g/árvore).

Aproximadamente, 1 kg é necessário para o tratamento de 480 pacientes com câncer ou 2,08 g por pessoa or 3,15 trees por pessoa. Outros estudos apontam que este número poderia chegar a 10 árvores por pacientes, dependendo do tamanho das árvores.

Síntese Total do TAXOL

-Holton, 1994 (46 etapas, linear)

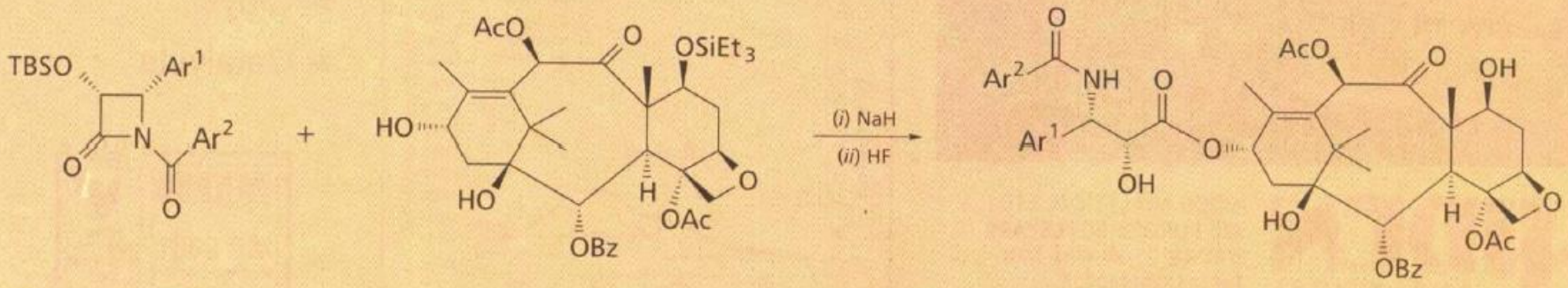
Holton R. A.; Somoza, C.; Kim, H. B. et al. First Total Synthesis of Taxol. 1. Functionalization of the B Ring, *J. Am. Chem. Soc.*, ***1994, 116, 1597-1598***

Holton R. A.; Somoza, C.; Kim, H. B. et al. First Total Synthesis of Taxol. 2. Completion of the C and D Rings, *J. Am. Chem. Soc.*, ***1994, 116, 1599-1600***

- Nicolaou, 1994 (40 etapas, 3 partes)

Nicolaou, K. C.; Yang, Z.; Lin, J. J. et al. Total Synthesis of Taxol. *Nature*, ***1994, 367, 630-634***

Scheme 1 The semi-synthesis of taxol analogues from modified side chains and protected baccatin III



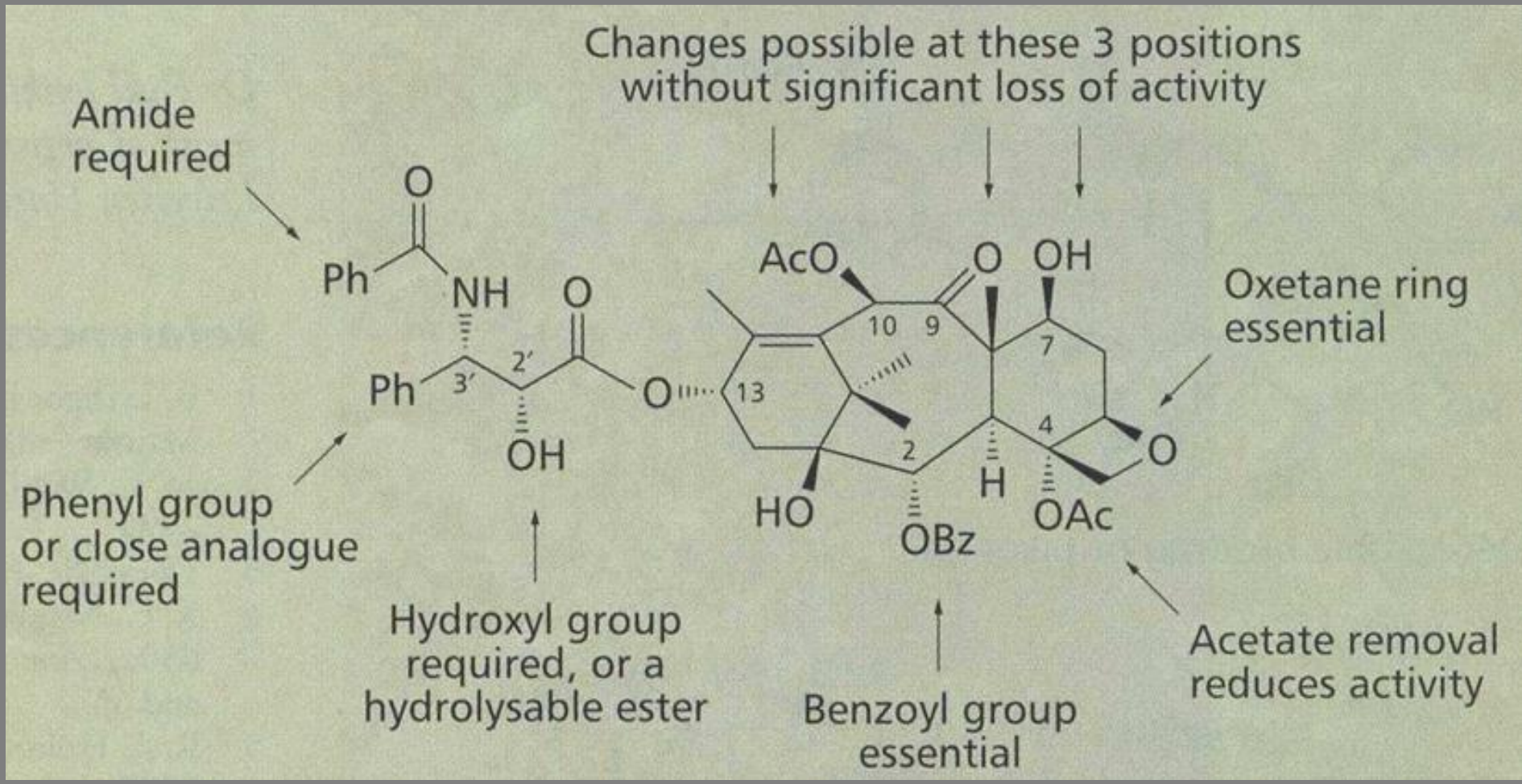
β-lactam side chain precursor (5)

7-triethylsilylbaccatin III (6)

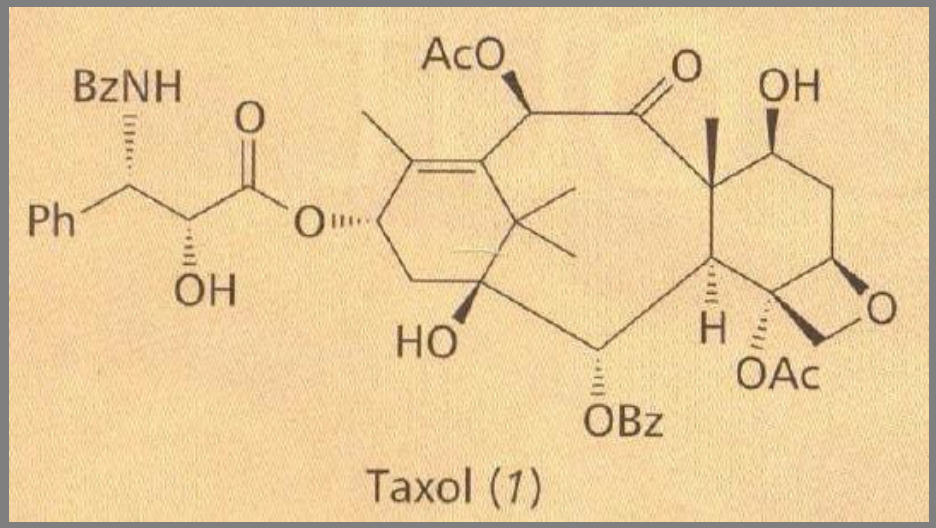
General structure of a series of taxol analogues (7)

Denis, J. N.; Greene, A. E.; Guenard, D.; Gueritte-Voegelein, F.; Mangatal, L.; Potier, P. Highly Efficient, Practical Approach To Natural Taxol, *J. Am. Chem. Soc.*, ***1988, 110, 5917***

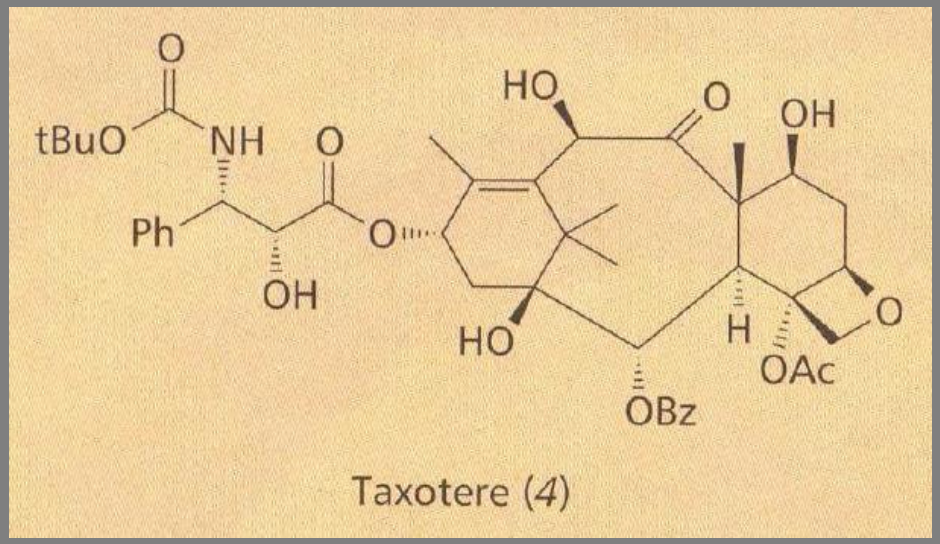
Relação Estrutra-Atividade de Análogos do TAXOL



Análogos estruturais do TAXOL

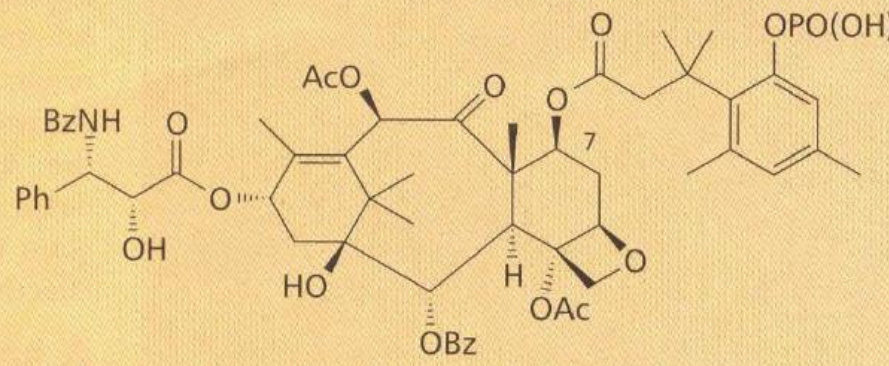


Taxol (*1*)



Taxotere (*4*)

Prodrugs of taxol



A water-soluble prodrug of taxol (*8*)

O Nascimento da Quimioterapia Moderna

- O tratamento com substâncias químicas é chamada quimioterapia. A Quinina foi uma das primeiras substâncias químicas introduzidas no tratamento de doenças (malária).
- 1796: Jenner faz experimentos com formas atenuadas do vírus da varíola (VACINAS).

Edward Jenner

- 1861: Louis Pasteur: Relação microorganismo/patologia/antimicrobianos.
- 1910: Paul Erlich descobre o salvarsan, um derivado arsenical, que foi efetivo no tratamento da sífilis.

Louis Pasteur

Quimioterapia Moderna

Prêmio Nobel Fisiologia/Medicina (1908)

P. Ehrlich, 1909

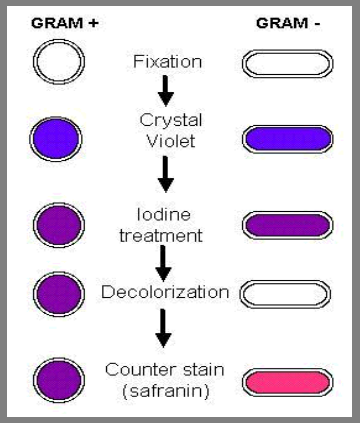
"The discoveries of those uncivilized peoples represented the sum of limitless testing of thousands of natural materials. By contrast with their selection of medicines by pure chance, we have to find first certain compounds, for example some arsenic derivatives, which show at least a low degree of therapeutic effect. Once this is done through more or less laborious tests, the purely empirical screening is replaced by preparing chemical variations, homologs and other derivatives whose efficacy has to be tested. But even at best chemical drugs are not magic bullets, and will not always hit only the center of the target, that is the disease-causing organisms. Moreover, nothing is as simple as to ascertain the lethal or the maximal well-tolerated dose, and the curative dose in a given animal species. In humans the determination of dosages is infinitely more difficult as one has to start with low doses and increase them gradually until they become therapeutically active. This is further aggravated by the occurrence of congenital or acquired idiosyncrasies from most medicines… and it cannot justly be demanded that a decision be made within a few months as to the merits or demerits of such new agents."

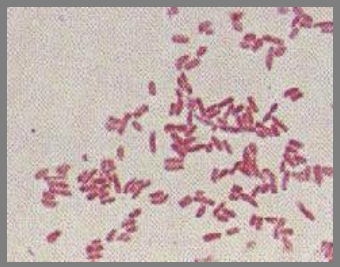
"Magic Bullets"

"Magic Bullets"

A Evolução da Quimioterapia

- Confluência da Microbiologia: Teoria da Infecção (Koch, Pasteur); Desenvolvimento da Indústria Química de Corantes na Alemanha;
- Imunologia começa a ser vista como um tipo de “quimioterapia”
- Desenvolvimento de testes diaganósticos com corantes específicos para microorganismos;
- Teste de substâncias de uso diagnóstico (corantes) como Antibióticos (Trypanosoma sp. / Febre do Sono)



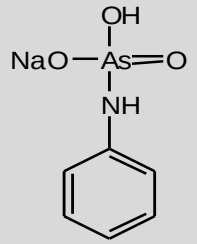


Gram

Ehrlich concebeu e reconheceu muitos dos elementos chaves da descoberta de fármacos

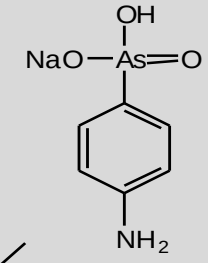
Arsenic Acid + Aniline

Atividade Antitripanossomal in Ratos



Reported Structure
Atoxyl

- Reconhecimento do uso de substâncias químicas na terapia;
- Química Sintética como ferramenta para se obter muitos derivados congêneres

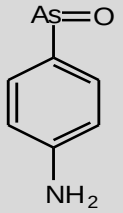


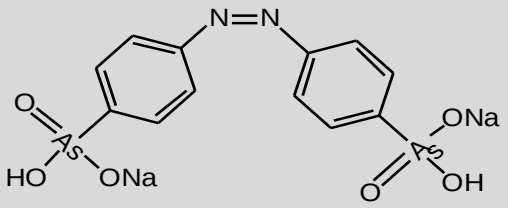
Actual Structure

Reduction

Diazotization

In Vivo Metabolism

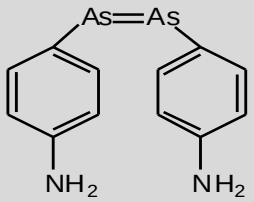




Azo-Dyes

- Metabolismo: Conceito de Metabólito Ativo;

Reduction



- Resistência dos microorganismos: Hereditariedade

Substituted Anilines and other Chemical Derivatizations

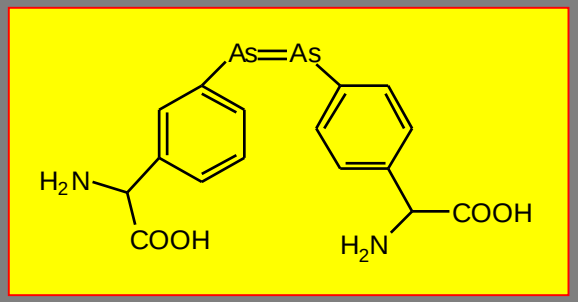
Arsephenamine (Composto 606)

◆Mais de 300 compostos foram inicialmente testados contra tripanossomas mas a cepa utilizada foi resistente a muitos deles.

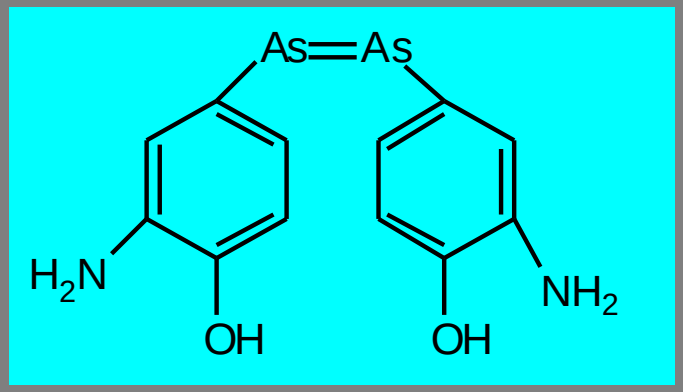
◆Então, um novo pós-doutor ingressou no grupo trazendo a expertise no modelo de espiroquetas causadoras da Sífilis em ratos. Os mesmos compostos foram re-ensaiados e o composto ¨606" mostrou uma potente atividade inibitória das espiroquetas.

◆

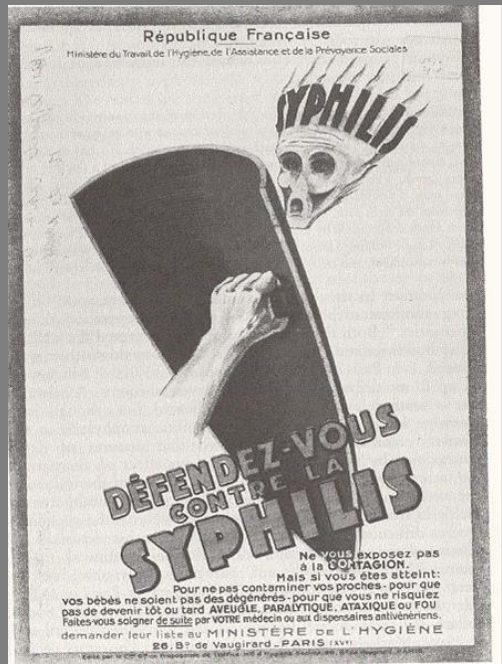
◆Este composto, chamado Salvarsan foi então empregado clinicamento no tratamento da Sífilis por muitos anos.



Composto "418" Anti-trypanosomal
Ativo em ratos mas não em humanos



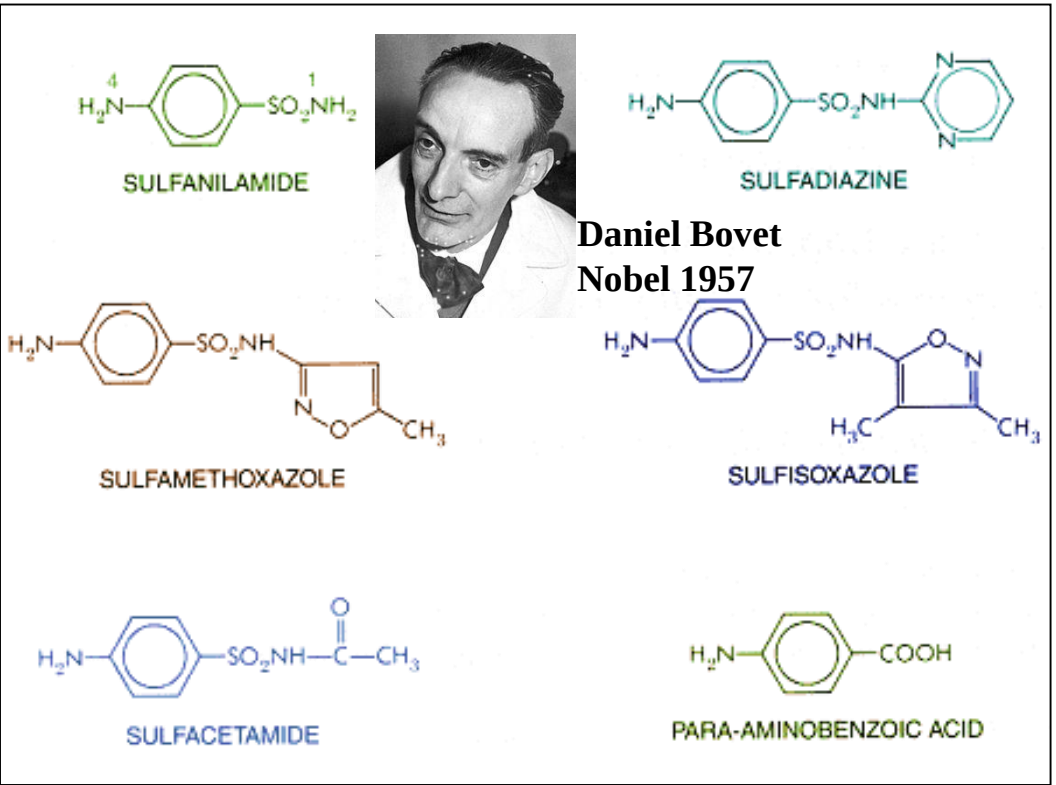
Salvarsan: Primeiro Fármaco Anti-espiroqueta empregado no tratamento da Sífilis



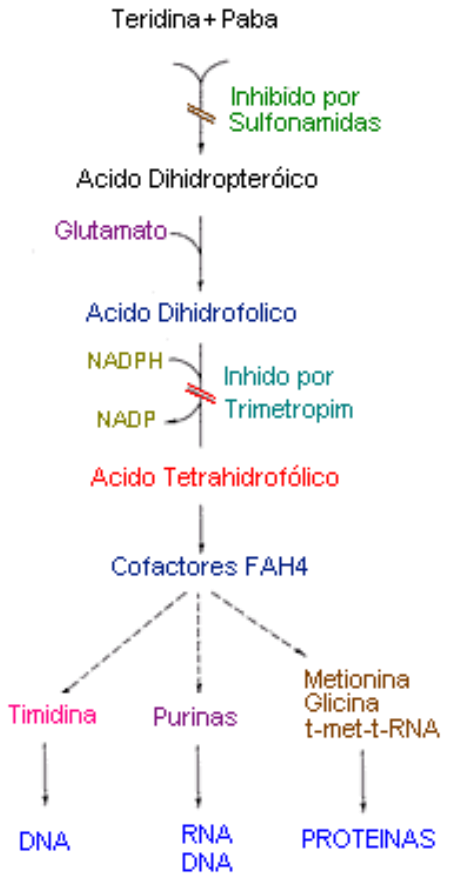
Sulfas Antibacterianas

- 1935 – Gerhard Domagk
- Nobel Fisiologia 1939
- – Prontosil
- – Sulfa Drugs

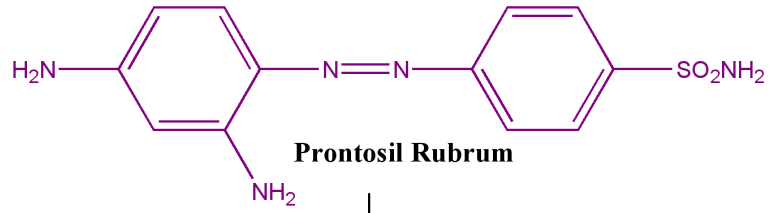
S. aureus



Daniel Bovet
Nobel 1957

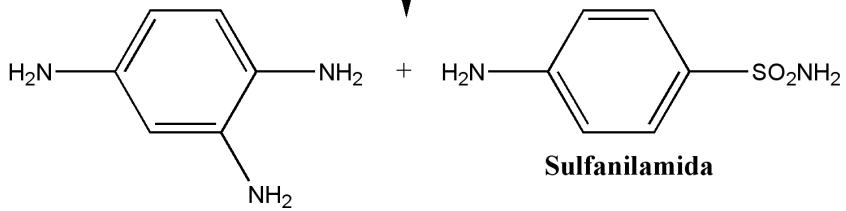


Gelmo (1908)



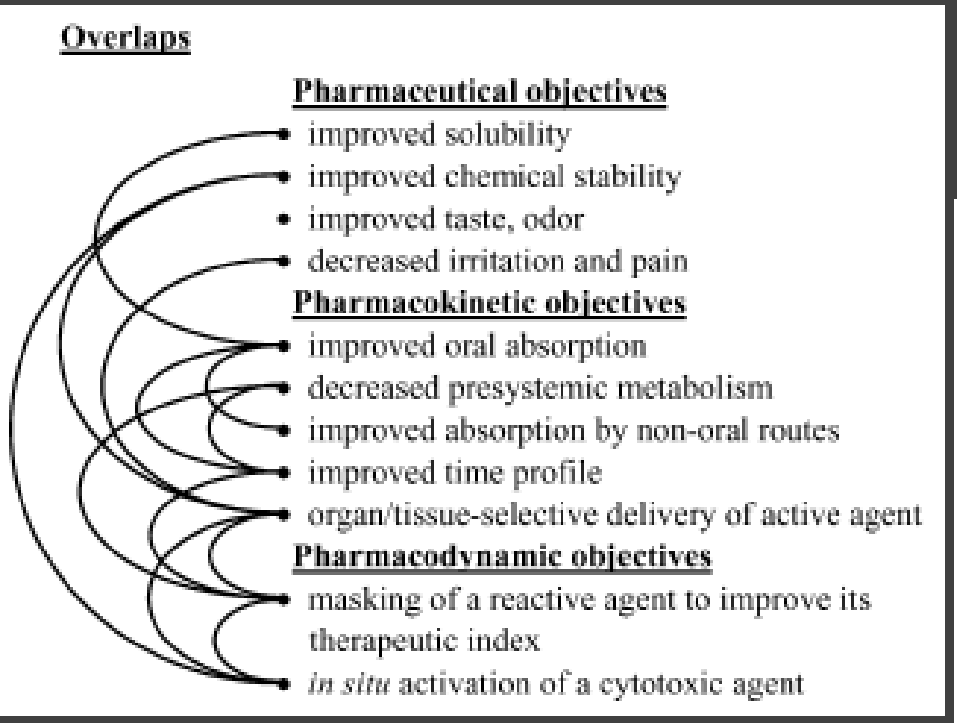
Prontosil Rubrum

NADPH Redutase



Sulfanilamida

Pró-Fármacos



- *Carrier-linked prodrugs*: where the active agent (the drug) is linked to a carrier (also known as a promoiety), and whose activation occurs by hydrolysis (esters, amides, imines. . .), oxidation or reduction (e.g. Prontosil in Fig. 1);
- *Bioprecursors*: which do not contain a promoiety yet are activated by oxidation, reduction or hydrolysis [12];
- *Macromolecular prodrugs*: where the carrier is a macromolecule such as a PEG (polyethyleneglycol) [19];
- *Drug–antibody conjugates*: where the carrier is an antibody raised against tumor cells [1,20].

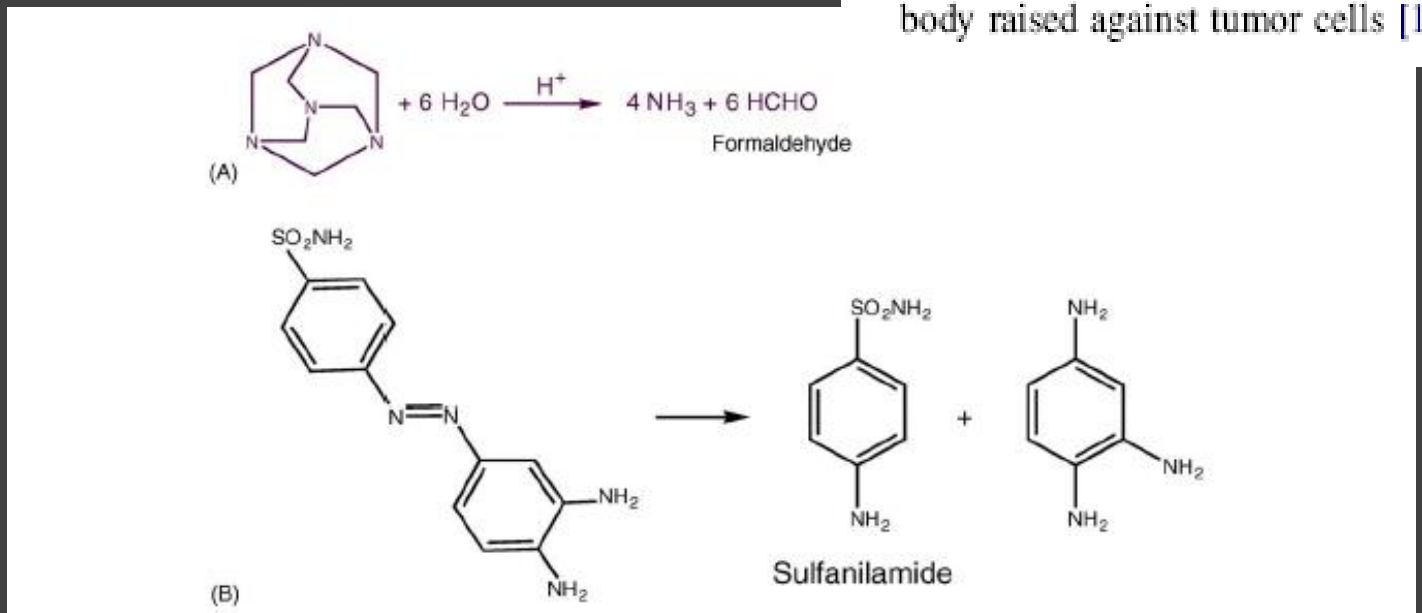


Fig. 1. Two historical examples of prodrugs. (A) Hexamine, an intentional prodrug of formaldehyde. (B) Prontosil, a fortuitous prodrug of sulfanilamide.

Contribuições do Acaso **(The Chance Discovery)**

Londres, St. Mary's Hospital, 1928

Alexander Fleming

"Serendipity"

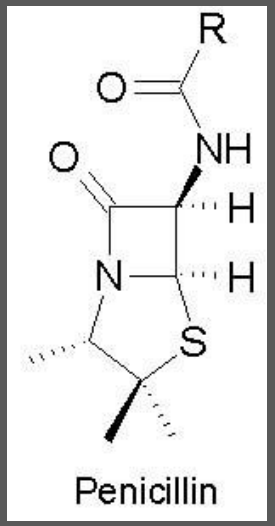
A word coined by Horace Walpole, who says (Let. to Mann, 28 Jan. 1754) that he had formed it upon the title of the fairy-tale 'The Three Princes of Serendip', the heroes of which '**were always making discoveries, by accidents and sagacity**, of things they were not in quest of"

"Chance favours the prepared mind…"

H. Florey

E. Chain

1932 - Isolation
1939 – Universidade de Oxford (Howard Florey e Ernst Chain)
1941- Primeiros ensaios em humanos
1941- Pesquisa foi tranferida para os EUA (USDA labs) em Peoria, Illinois
Summer
1943 - *Penicillium chrysogenum*
1944 - Caracterização Estrutural
1945 - Prêmio Nobel

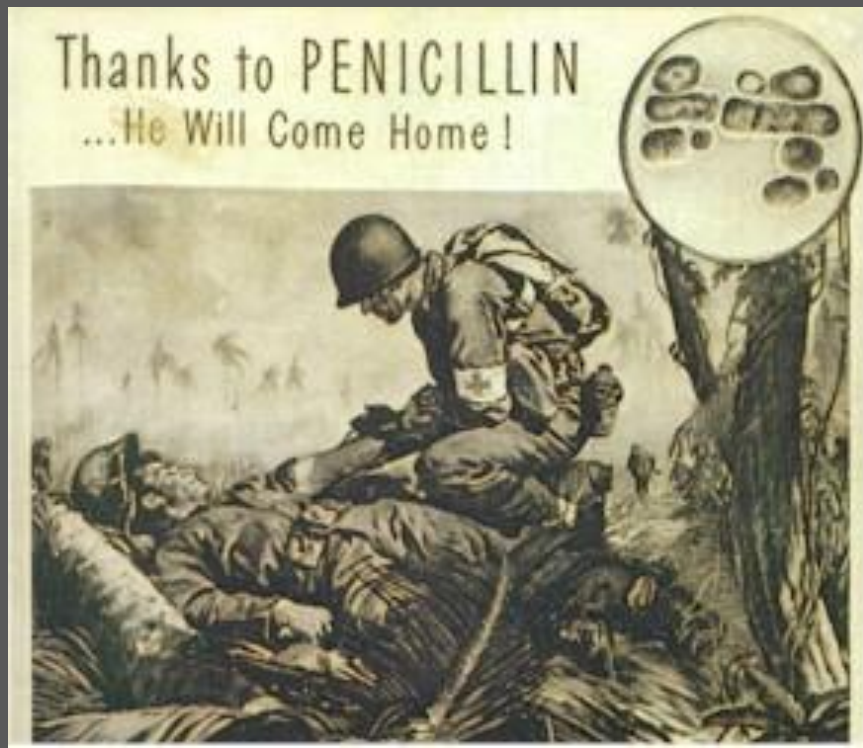


Penicillin

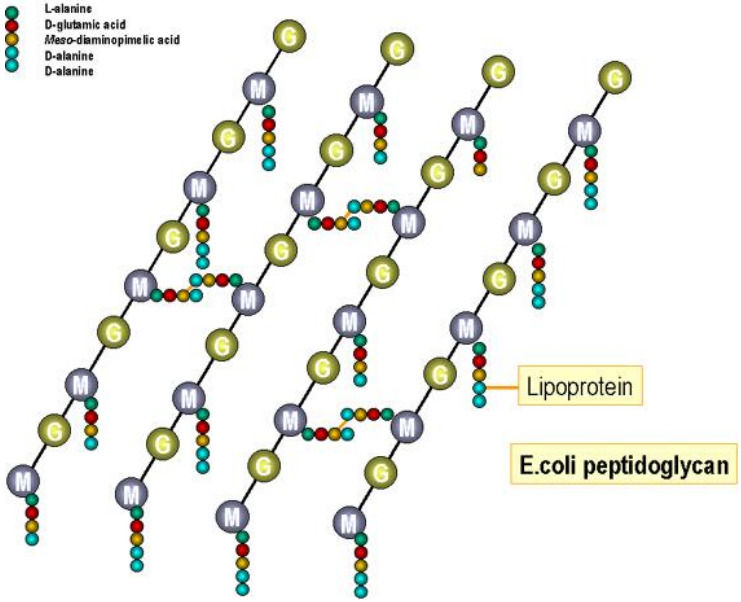
R = Benzila

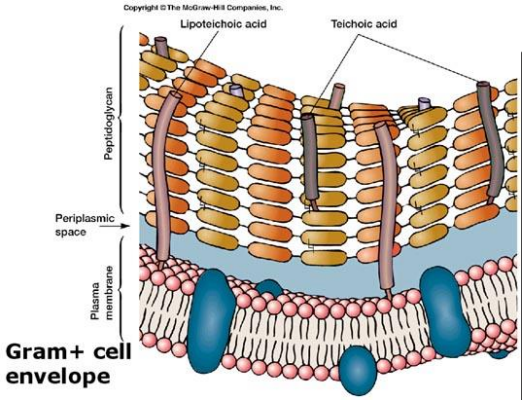
Penicilina ganha o mundo!!!

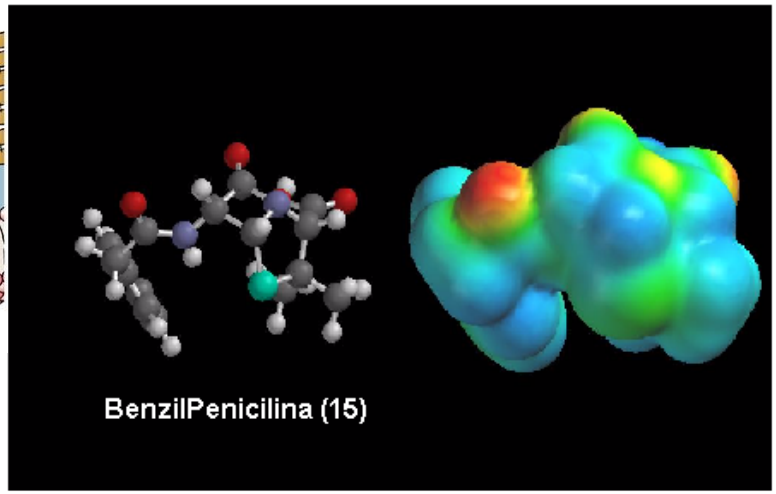
- Publicação: Florey, Chain, *et. al. Lancet*, 24 de Agosto de 1940;
- Naquele momento a 2ª Guerra Mundial avançava pela Europa, com muitos feridos e inúmeros mortos, como resultado de infecções bacterianas;
- Clamor pela descoberta de Novos Antibacterianos!
- Primeiro Ensaio de Triagem Clínica: Fevereiro de 1941 (Voluntários).

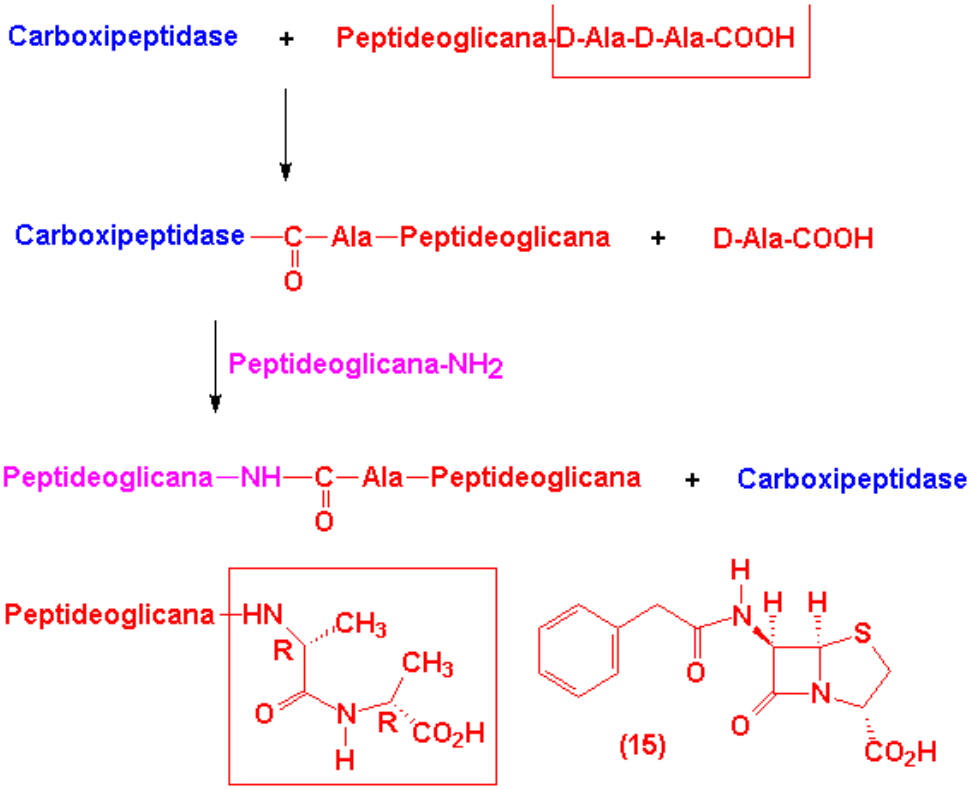


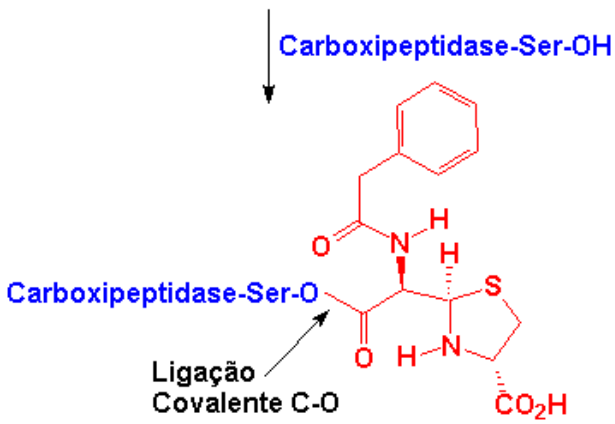
Mecanismo de Ação das Penicilinas



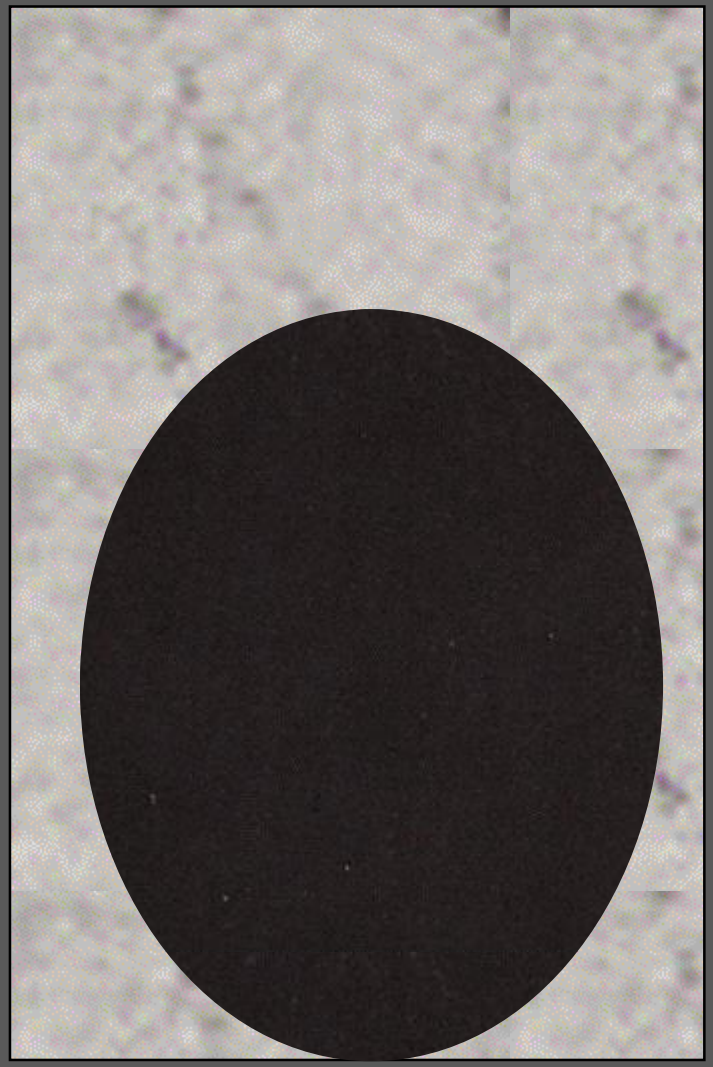




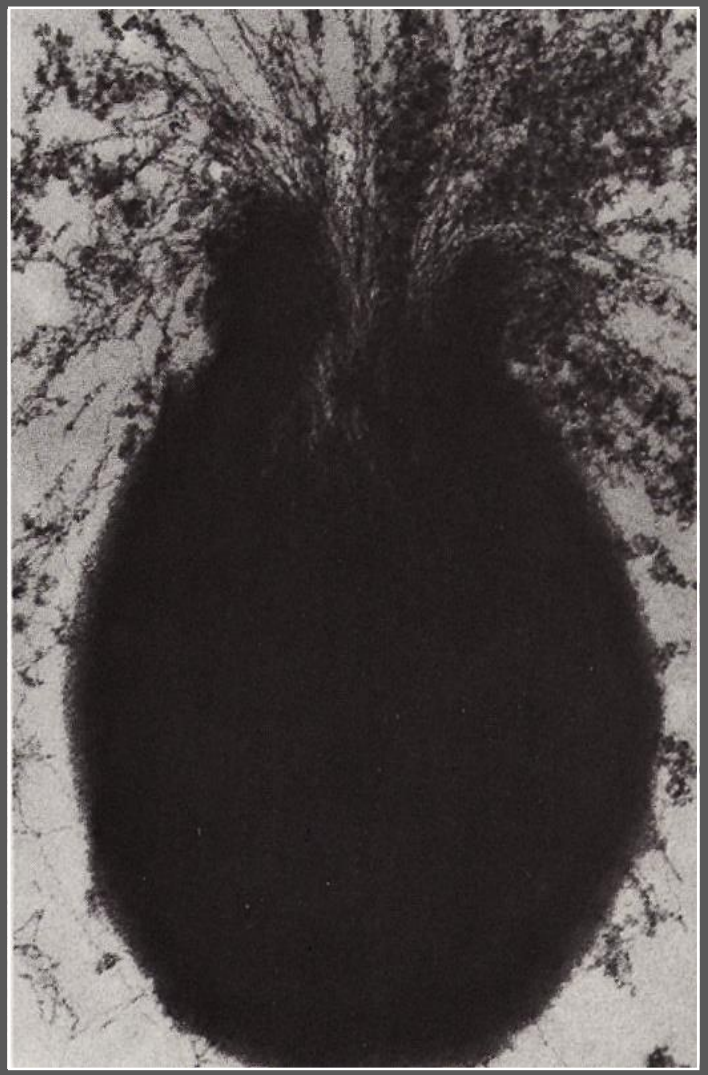




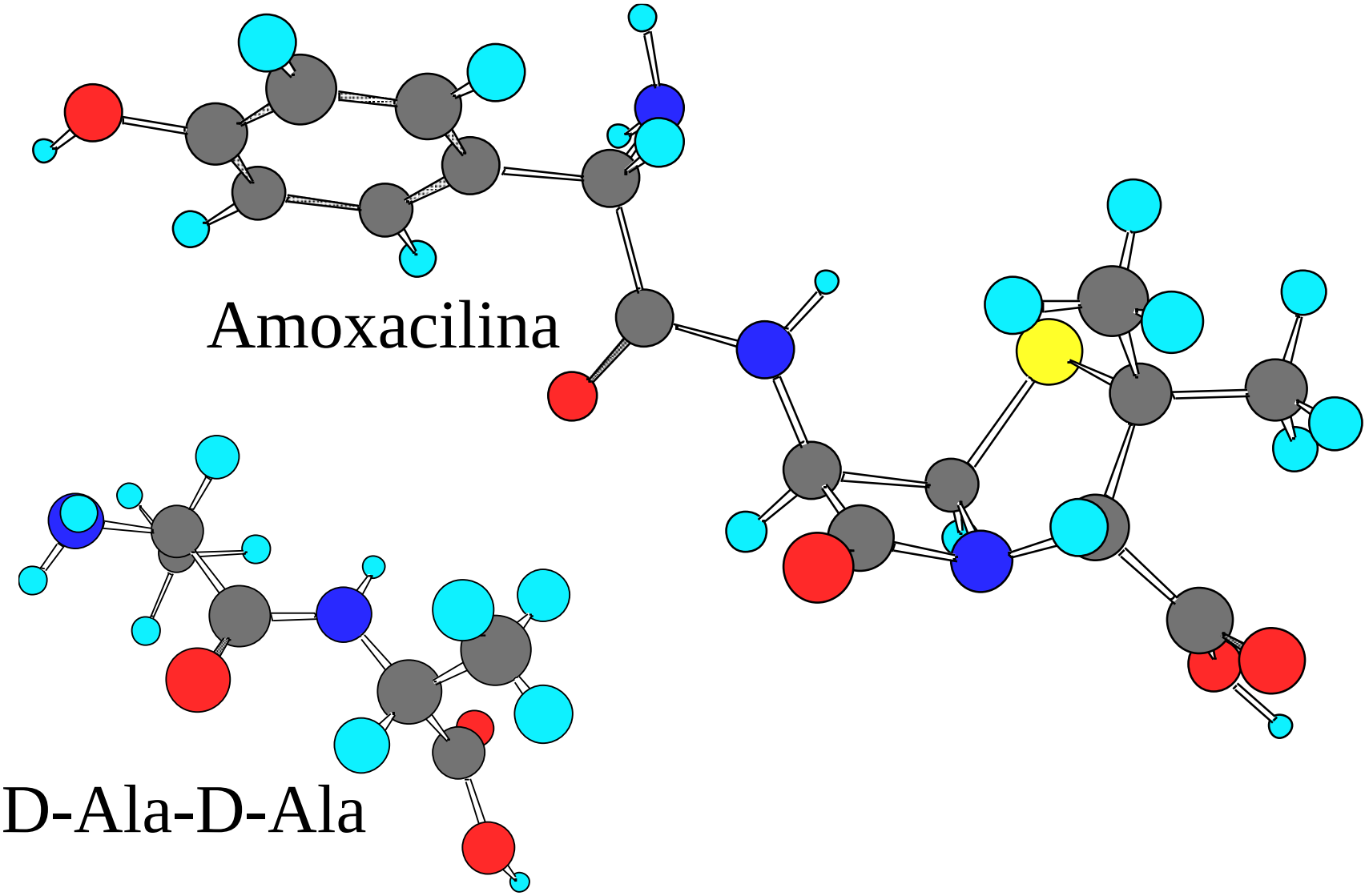
STAPHYLOCOCCUS



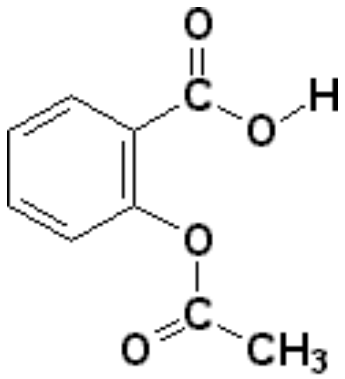
STAPHYLOCOCCUS TRATADO C/ PENICILINA



Amoxacicilina vs D-Ala-D-Ala

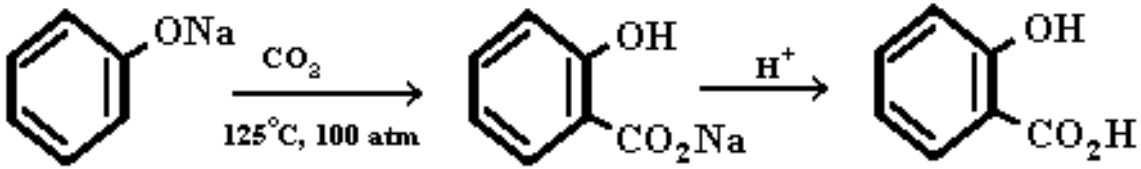


AAS



- 1853: **Charles Frederic Gerhardt first sintetiza pela primeira vez ácido acetilsalicílico, mas falha na compreensão da sua estrutura molecular e sua importância para a humanidade. Seu ácido salicílico não era puro e por isto de uso restrito.**

- 1859: **H. von Glim também descreve a preparação do ácido acetilsalicílico, também de forma impura.**
- **Enquanto isto, Herman Kolbe descobre como sintetizar o ácido salicílico a partir do alcatrão. O método que ele empregou ainda é chamado "*Síntese de Kolbe*".**
- 1869: **Karl-Johann Kraut repete os experimentos das etapas anteriores e dá as primeiras informações acuradas sobre a estrutura molecular do ácido acetilsalicílico, o éster do ácido salicílico. Como o próprio admitia, suas amostras também não estavam puras.**
- 1874: **Ácido Salicílico foi preparado industrialmente pela primeira vez usando o método de Kolbe em Dresden, Alemanha. Ele foi vendido como analgésico, mas provocava grave irritação estomacal.**



Sodium phenoxide — Sodium salicylate — Salicylic acid (79%)

The Kolbe Synthesis

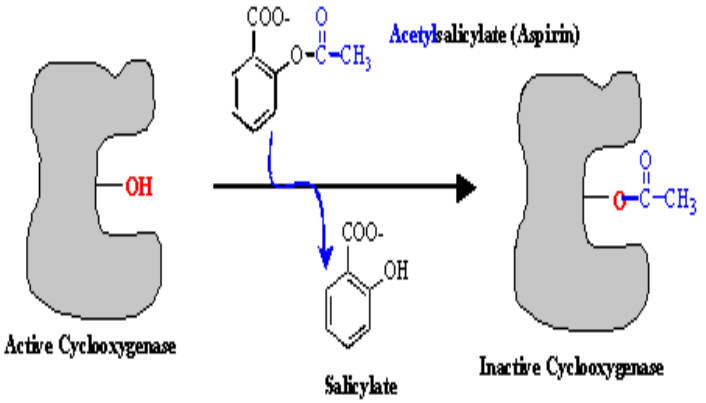
Ácido Acetilsalicílico

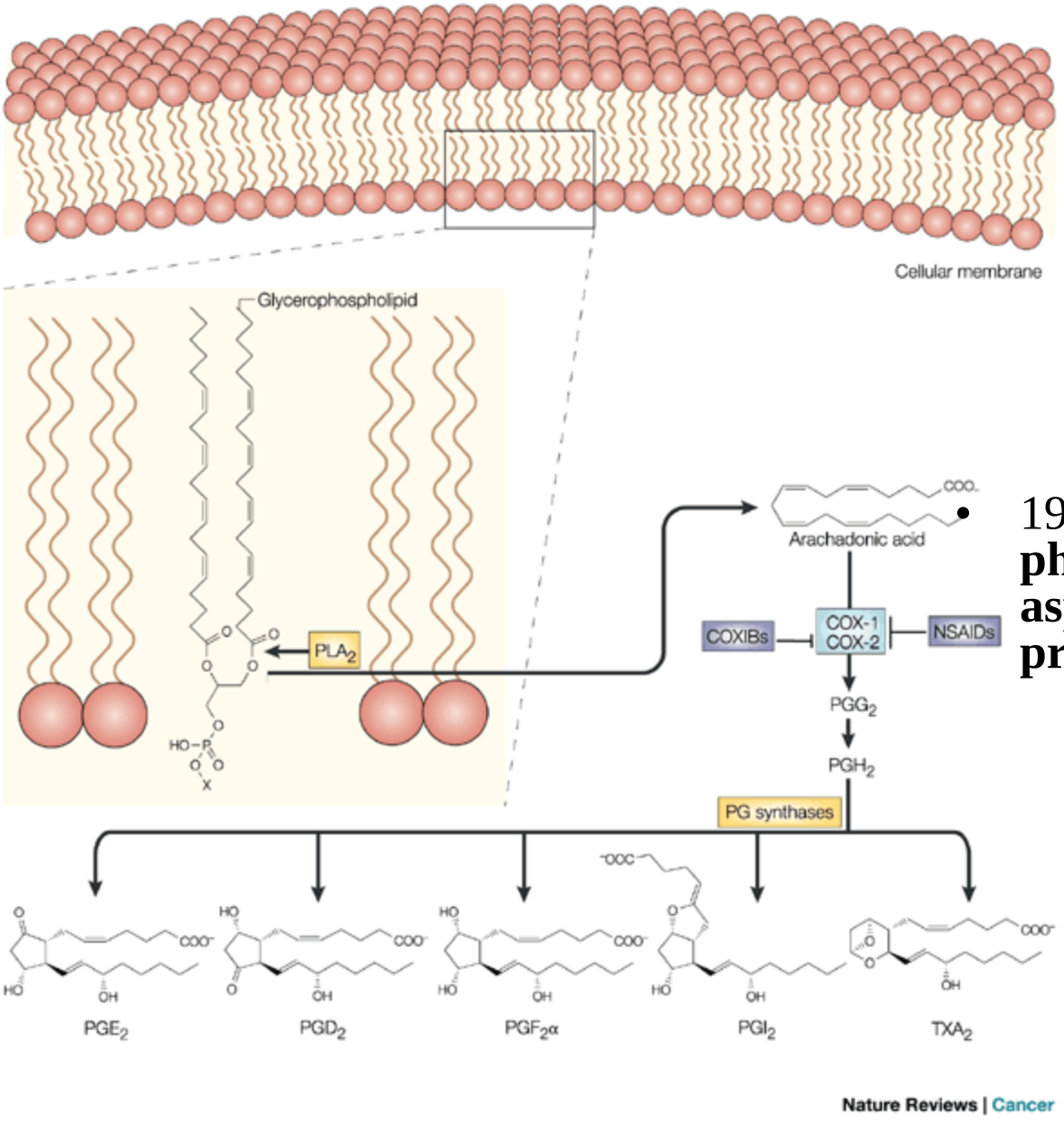
- 1897: **Felix Hoffmann, químico das indústrias Bayer na Alemanha, preparou a primeira amostra pura de AAS. Se inicia a história do AAS como conhecida até hoje.**

- 1899: **Ensaios clínicos indicam os promissores efeitos curativos do AAS. Bayer batiza o AAS de ASPIRINA e a companhia começa a distribui-la para os médicos (NA FORMA DE PÓ) administrarem em seus pacientes.**

- 1900: **Bayer introduz o primeiro comprimido de aspirina solúvel em água. Este processo reduz o custo à metade.**
- 1915: **Aspirina começa a ser utilizada sem prescrição médica.**

Mecanismo de Ação do AAS

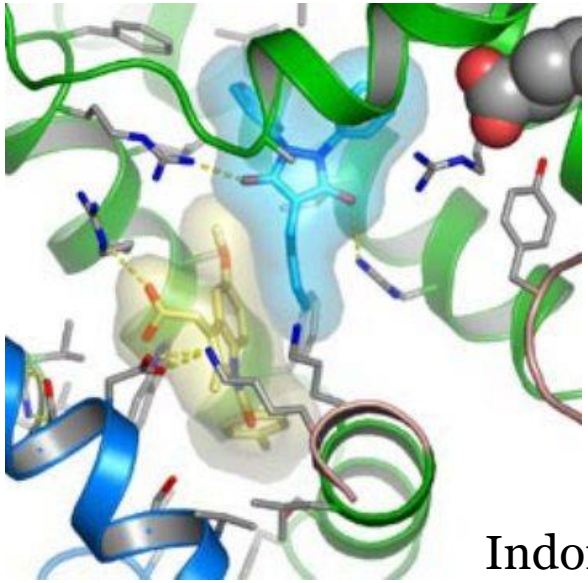


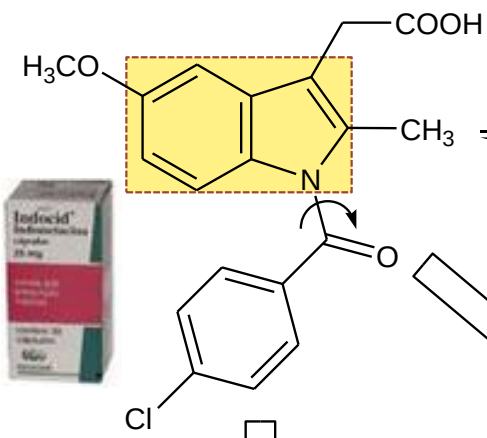


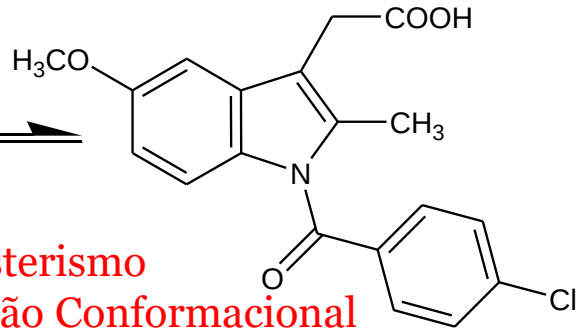
1971: **John Vane, British pharmacologist, discovers that aspirin works] by inhibiting the production of prostaglandins.**

Nobel Medicina 1982

Estratégias de Modificação Molecular na Gênese de AINE's Me-too e Me-better





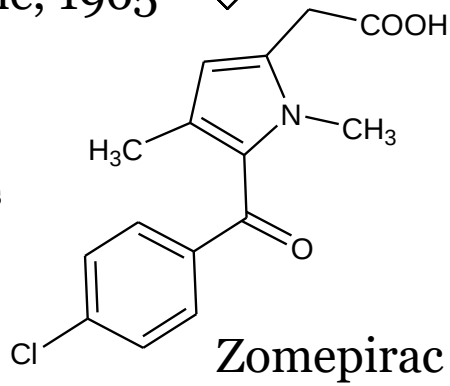


Bioisosterismo
Restrição Conformacional

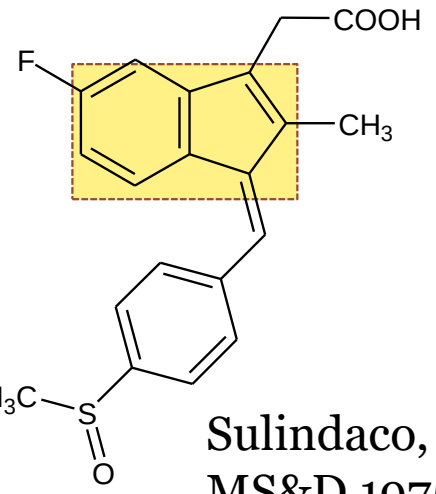
Indometacina
Merck Sharp&Dohme, 1965

Simplificação Molecular

1971: **John Vane, descobre que o mecanismo de ação da aspirina e outros AINE's envolve a Inibição da COX.**



Zomepirac
McNeil Pharma, 1980

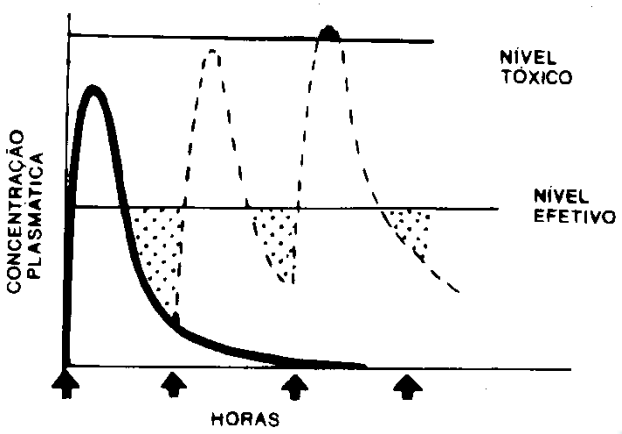


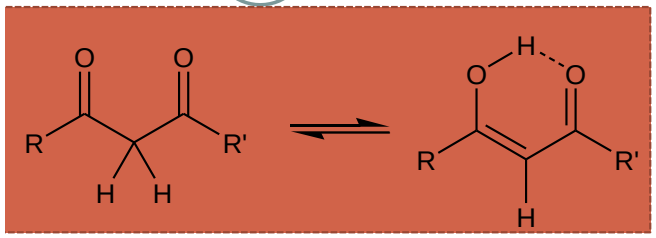
Sulindaco, Clinoril
MS&D 1975

Vane, J. R. (1971) Nature New Biol. *231*, 232.

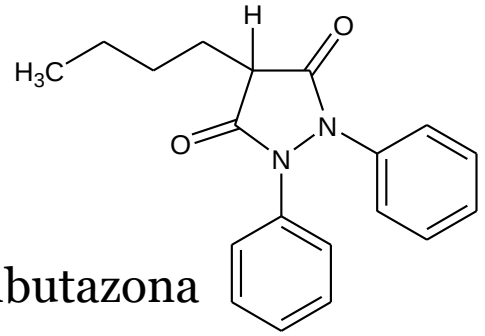
Shen, T. y. (1981) J. Med. Chem., *24*, 1-5.

Impactos sobre os AINE's de 2ª Geração

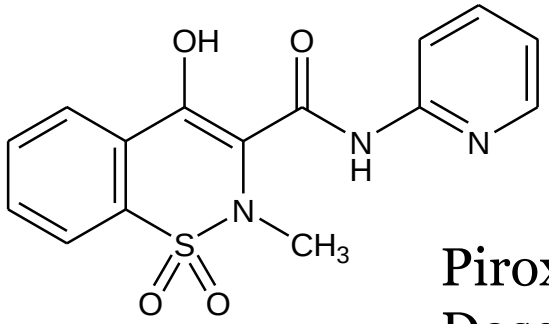




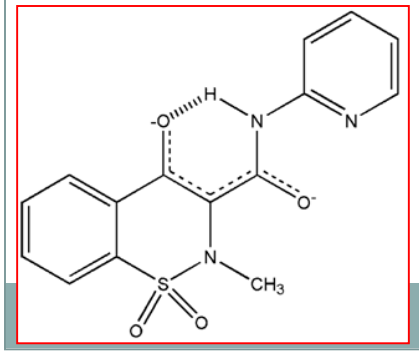
Ácidos Enólicos



Fenilbutazona



AINE	Tempo de Meia-Vida (h)		
	Rato	Macaco	Homem
Fenilbutazona	6	7	72
Indometacina	4	0,3	2
Ibuprofeno	1	---	3
Naproxeno	5	1,9	13,9
Piroxicam	16	5	45



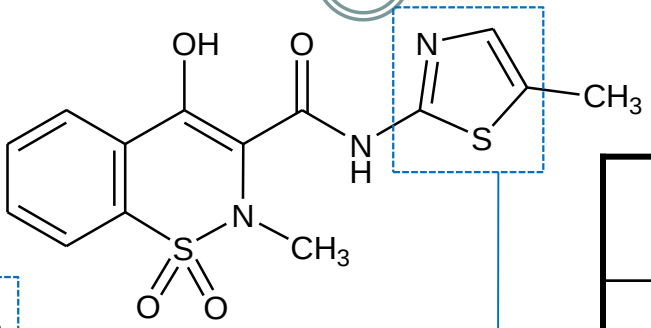
Piroxicam
Dose Única
Diária: 20 mg

J. G. Lombardino, Pfizer, 1971

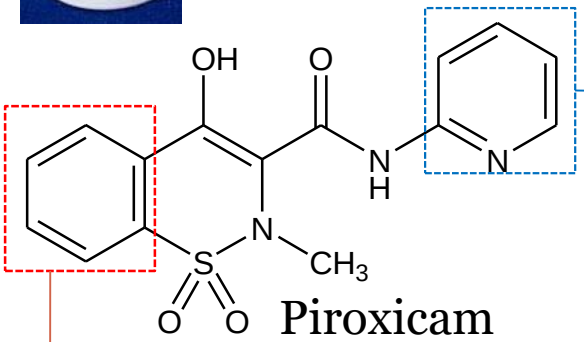
Lombardino, J. G.; Wiseman, E. (1972) *J. Med. Chem. 15, 848-849.*

Bioisosterismo Clássico: Tenoxicam e Meloxicam

Meloxicam,
Boehringer, 1996



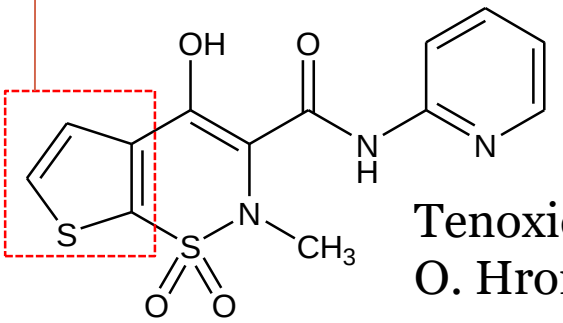
Bioisosterismo de Anéis



Piroxicam

Inibidor Seletivo
COX-2 vs COX-1

Bioisosterismo de Anéis



Tenoxicam
O. Hromatka, Roche, 1981

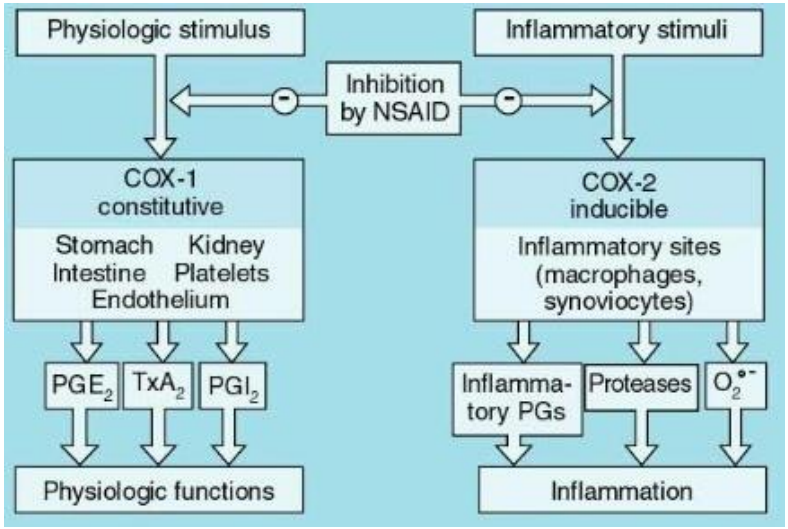
Potencial de Ulcerogeneicidade

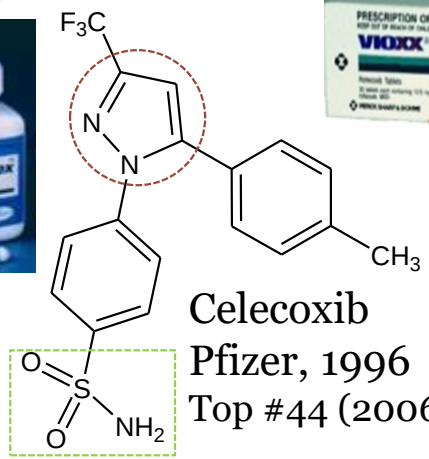
AINE	UD_{50}/ED_{50}
Aspirina	1,6
Fenilbutazona	1,8
Diclofenaco	3,1
Indometacina	9,2
Piroxicam	10,9
Tenoxicam	50,0

O. Hromatka *et al., DE 2537070 (1976)*

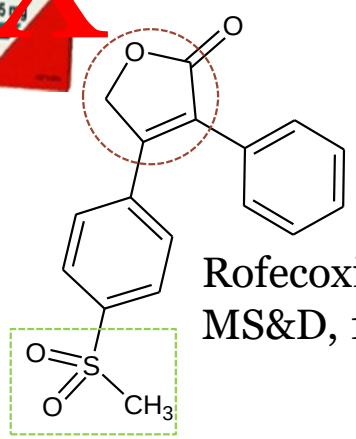
G. Trummlitz *et al., US 4233299 (1980)*

A Era dos Inibidores Seletivos de COX-2

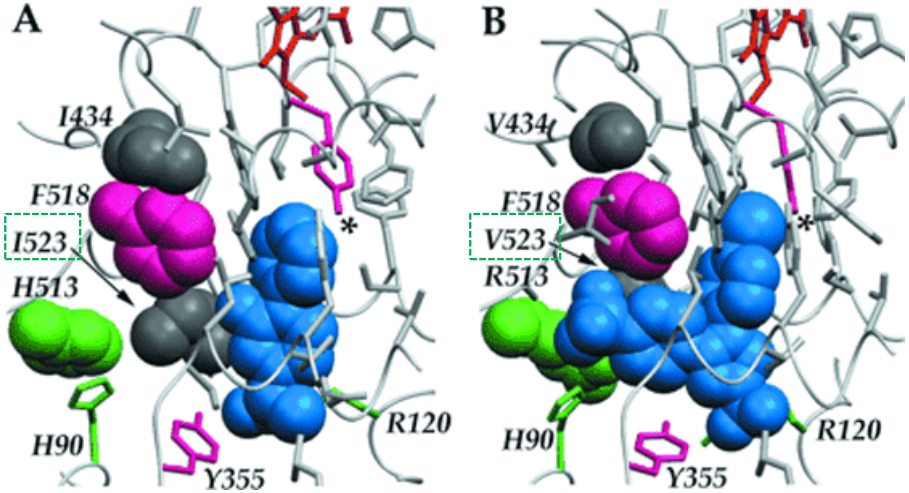


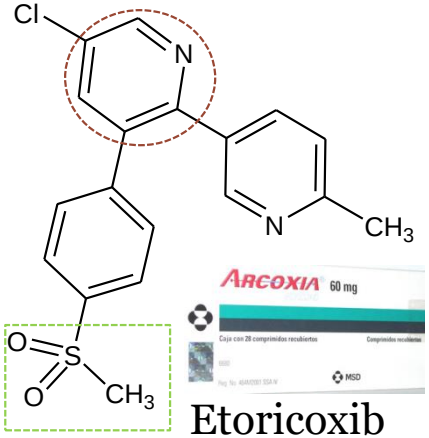


Celecoxib
Pfizer, 1996
Top #44 (2006)

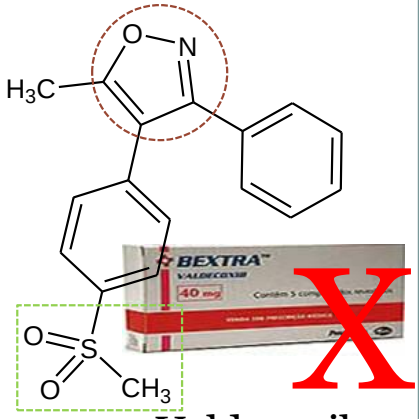


Rofecoxib
MS&D, 1999





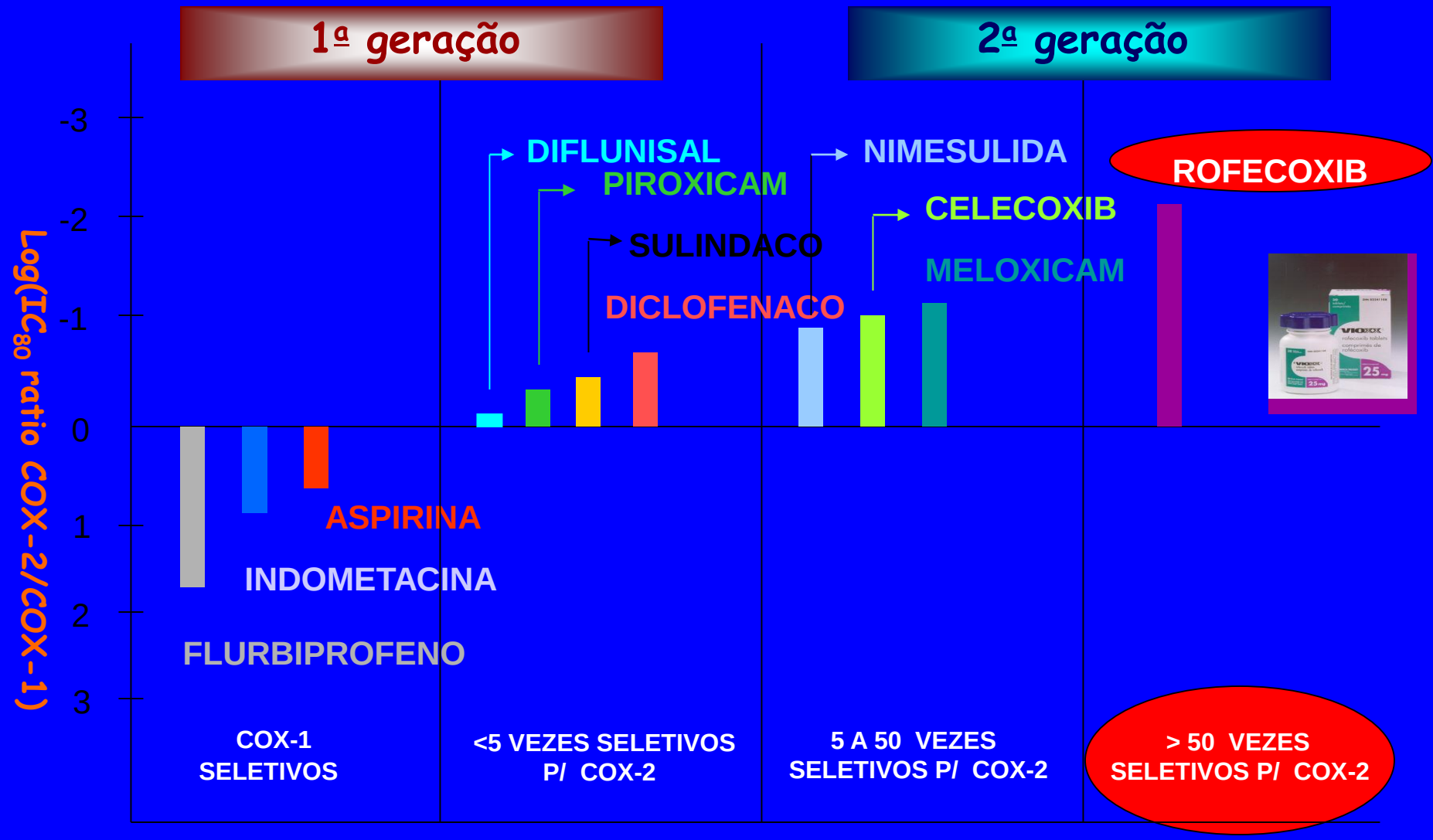
Etoricoxib
MS&D



Valdecoxib
Pfizer

Penning, T. D. *et al. (1997) J. Med. Chem. 40, 1347.*

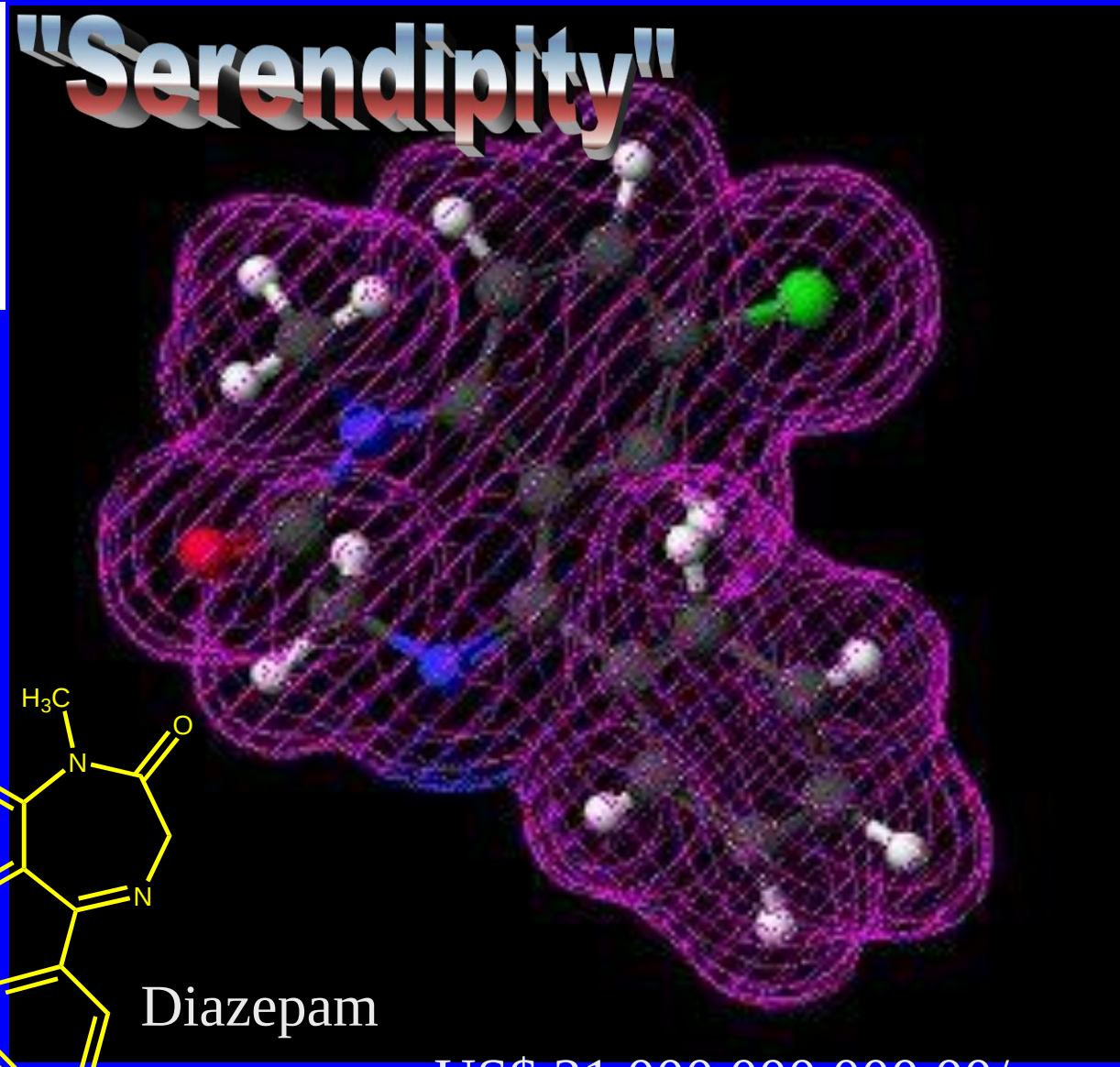
Seletividade dos Agentes Antiinflamatórios não Esteroidais

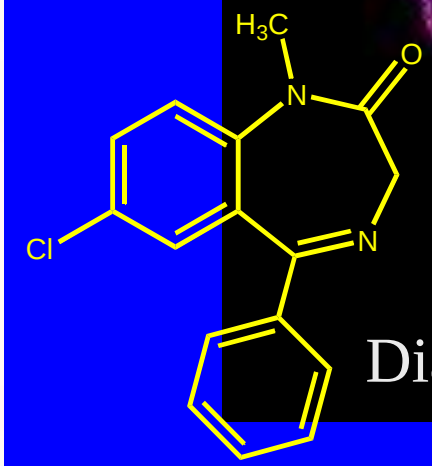


Adaptado de Warner *et al*. 1999 Proc. Natl. Acad. USA 96: 7563-7568

A História dos Fármacos Benzodiazepínicos

Leo Sternbach
Roche, 1959

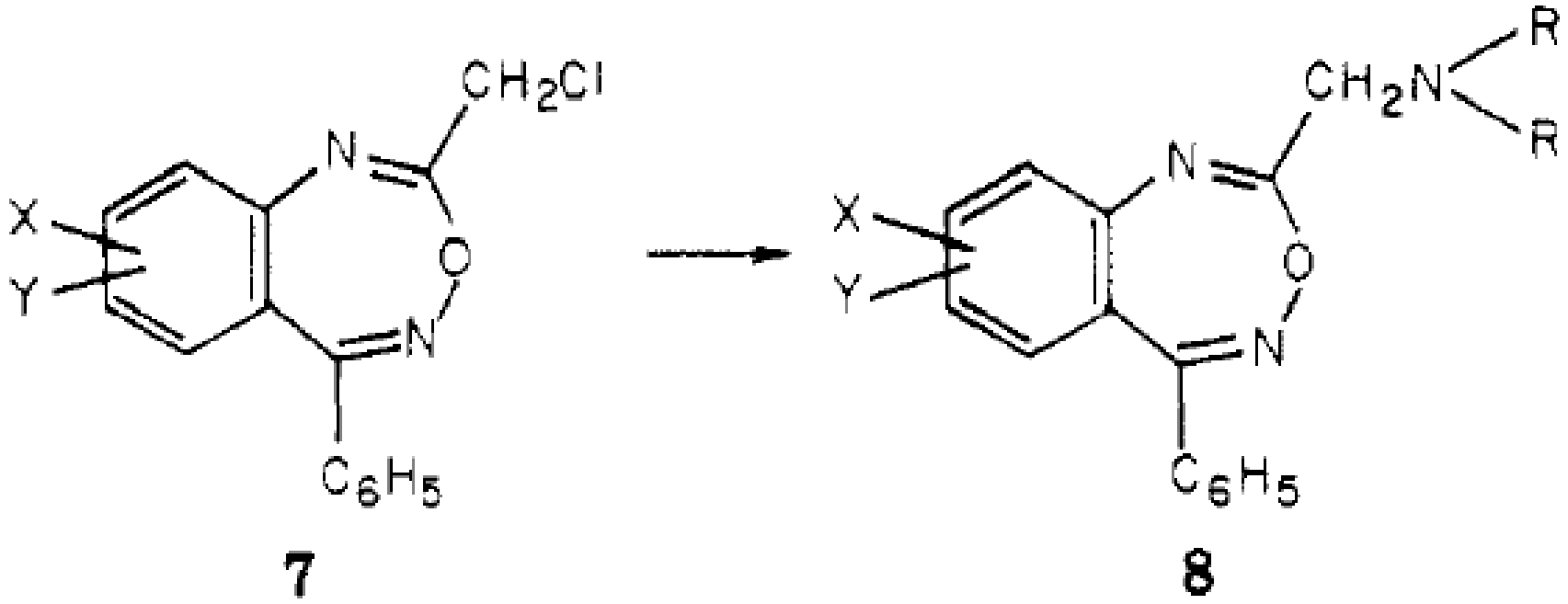




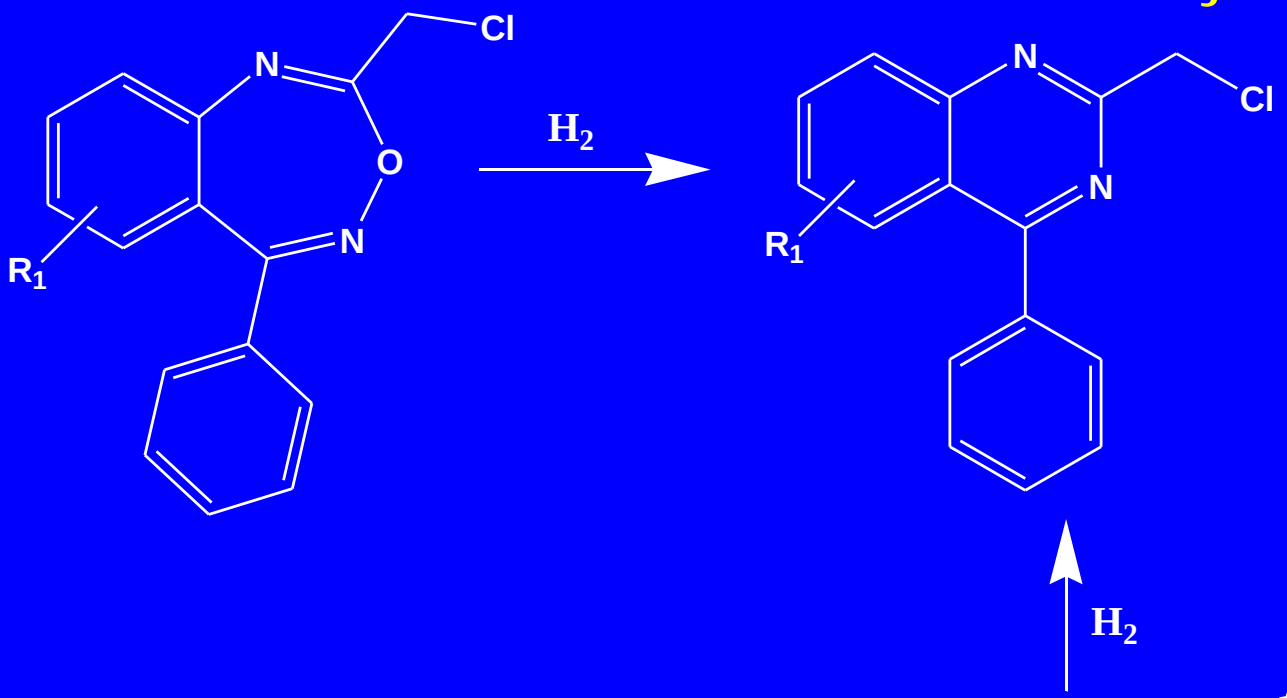
Diazepam

US$ 21.000.000.000,00/ano

Definição da Estratégia



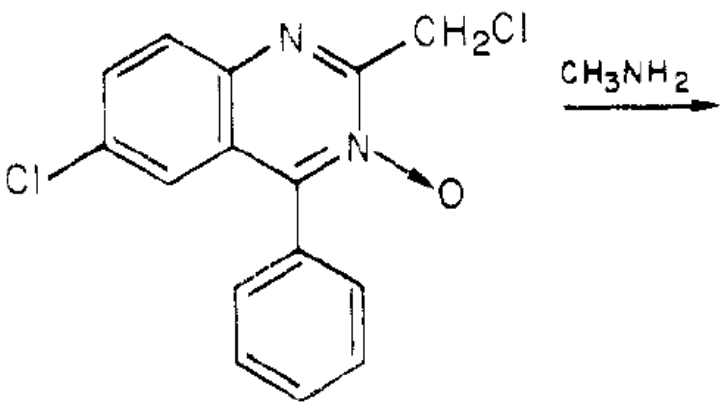
Confirmação da Estrutura das Heptoxadiazinas



Propriedades Farmacológicas: Aminas-N-óxido ou os produtos hidrogenados correspondentes foram inativos

Quinazolinas-N-Óxidos

- 1955 (Segunda Metade): Trabalho com as Quinazolinas foi interrompido.
  - Isolamento, Purificação e Degradação de Vários Antibióticos
- 1957: Limpeza do Laboratório



11

Earl Reeder (Identifica dois produtos)

- 1957 (Maio): Dr. Lowell Randall, Farmacologista

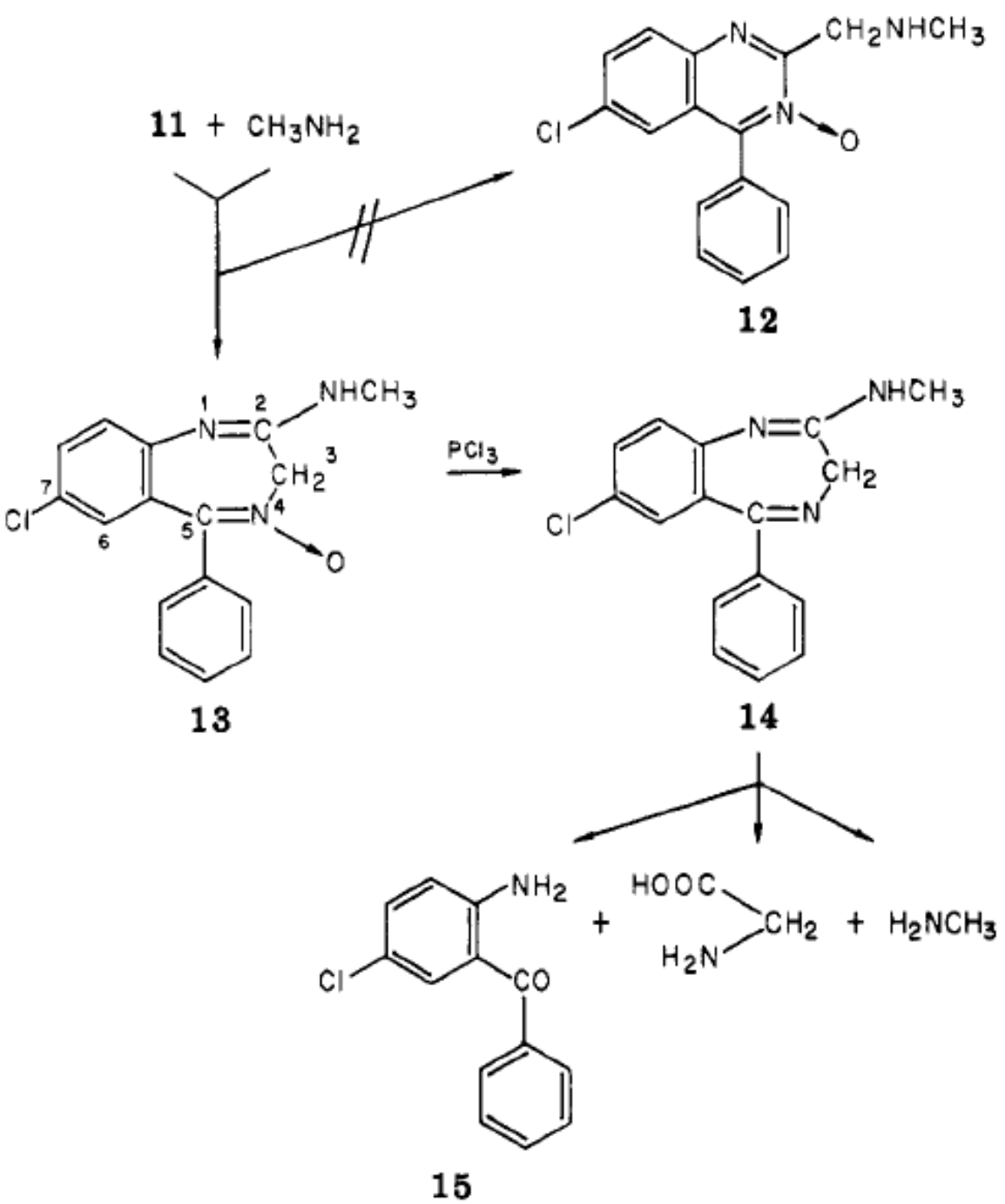
Table I. Pharmacological Properties[a] of "New Compound", Meprobamate, Chlorpromazine, and Phenobarbital

compd	inclined screen	foot shock	cat	anticonvulsant tests: pentylene-tetrazole	anticonvulsant tests: electroshock max	anticonvulsant tests: electroshock min
new compound	100	40	2	18	92	150
meprobamate	250	250	100	150	200	167
chlorpromazine	17	20	2.5	42	150	600
phenobarbital	120	80	10	75	18	90

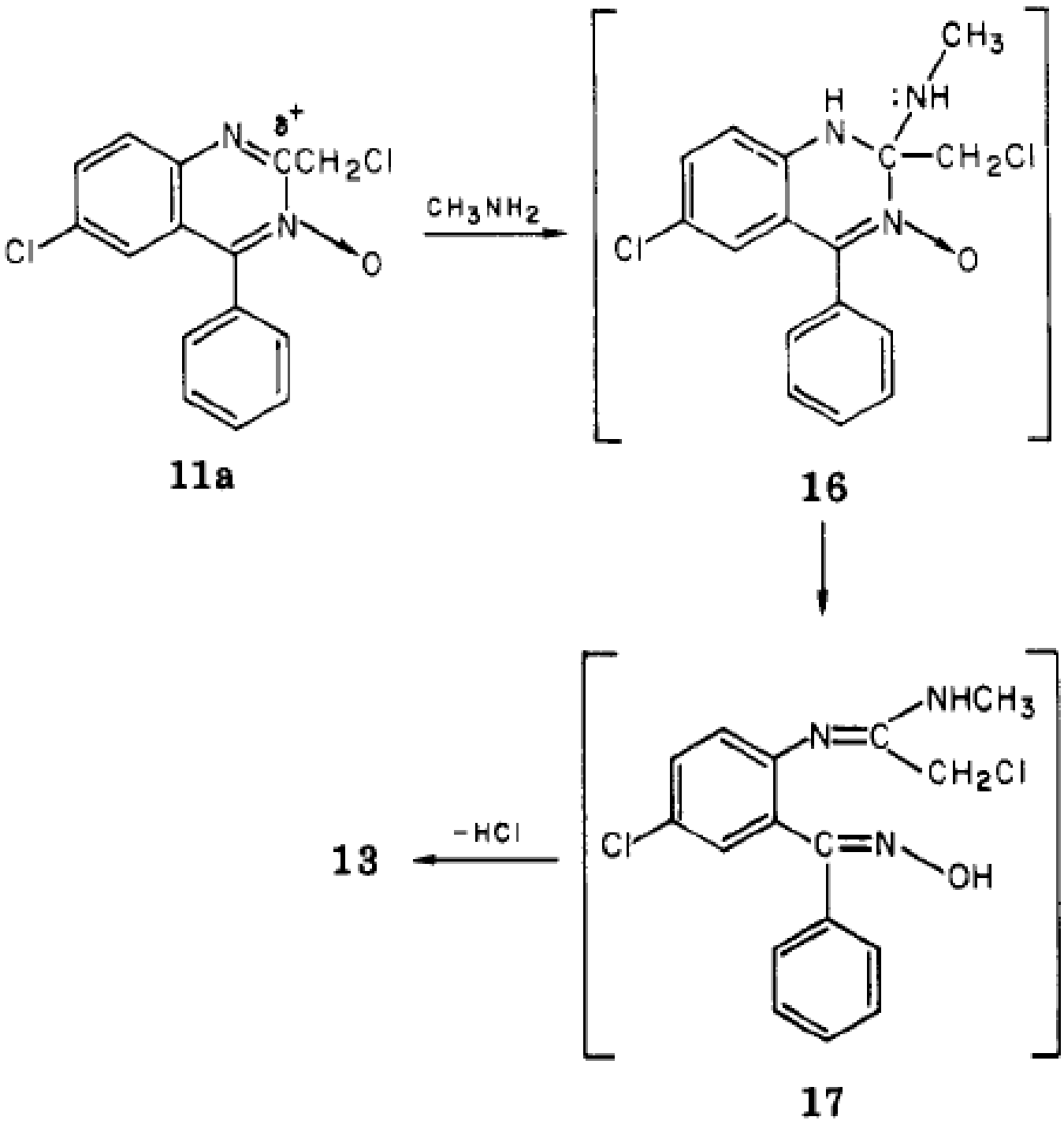
[a] Dose (mg/kg) of orally administered drug required to achieve the desired effect.

Caracterização
Estrutural
do
"Novo Composto"

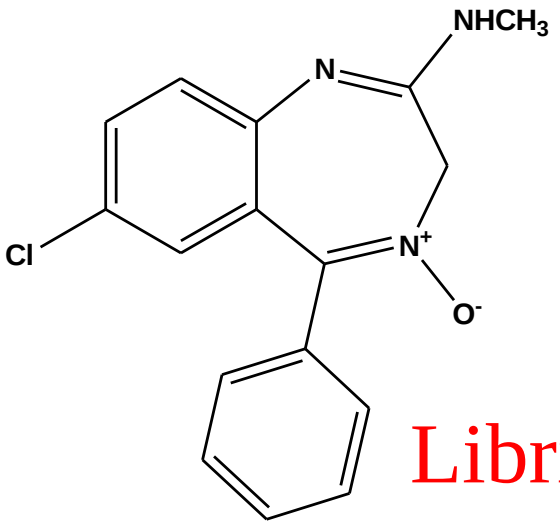
Scheme I



Mecanismo de Formação dos Derivados Benzodiazepínicos



Caracterização Farmacológica dos Produtos de Transformação do Clordiazepóxido (13)

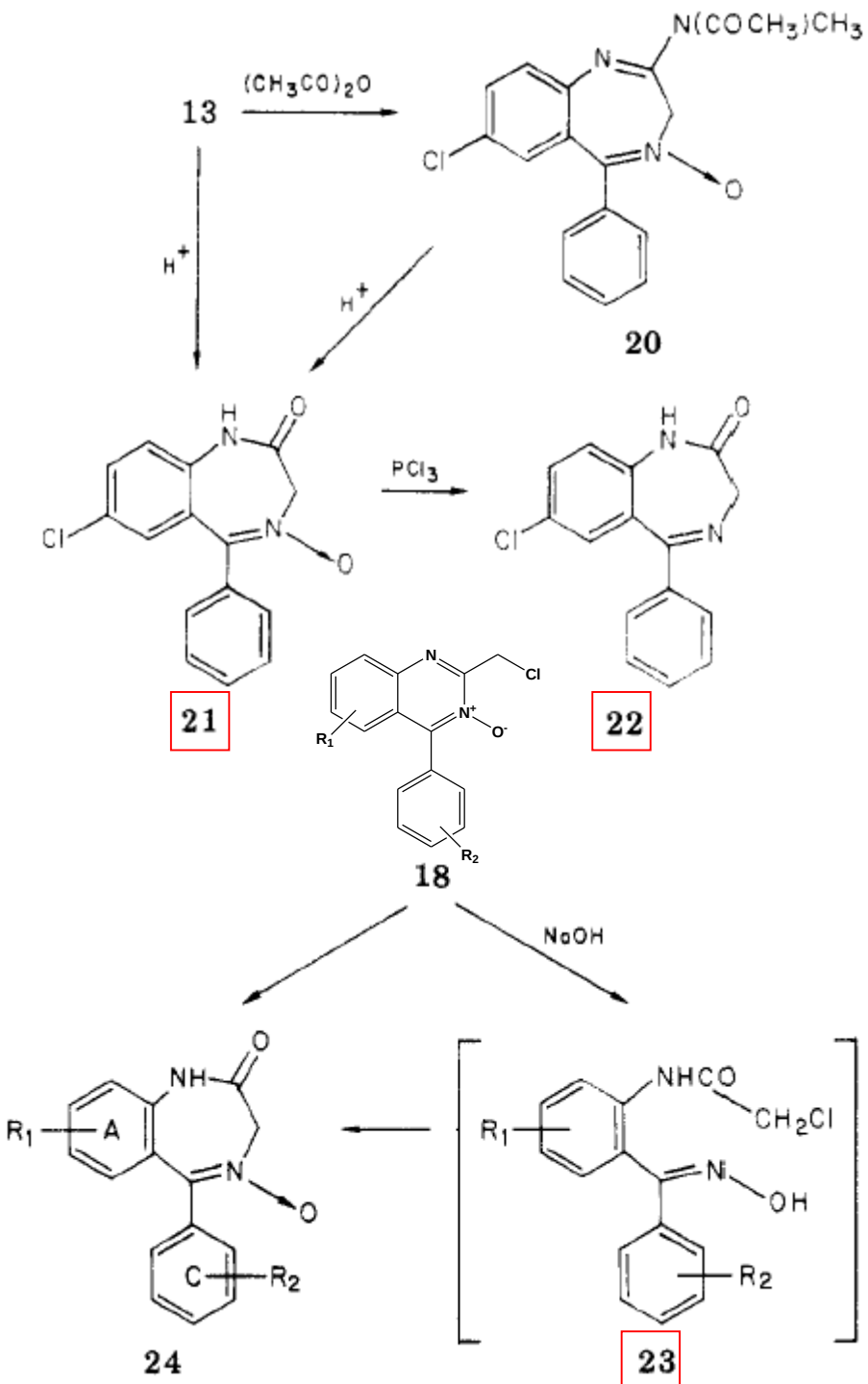


Librium[R]

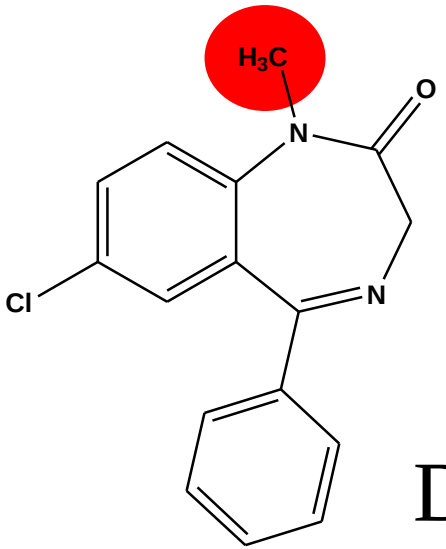
Table II. Pharmacological Activity[a] of Chlordiazepoxide and Its Transformation Products

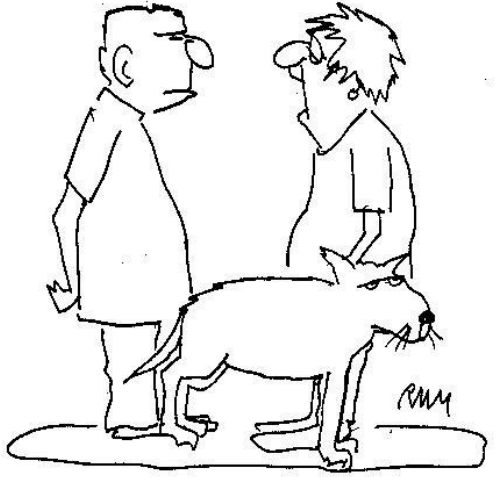
	anticonvulsant tests					
					electroshock	
compd	inclined screen	foot shock	cat	pentylene tetrazole	max	min
13	100	40	2	18	92	150
21	100	20	2	15	150	150
22	75	40	1	6	52	400
23	75	20	1	6	25	61

[a] Dose (mg/kg) of orally administered drug required to achieve the desired effect.



E assim nasceu o diazepam.....





"I was giving him his Valium, and the vial fell in the toilet, so I'm going to need a lot more!"

Diazepam (Valium^{R})

Table III. Comparison of the Pharmacological Activity[a] of Chlordiazepoxide with That of Diazepam

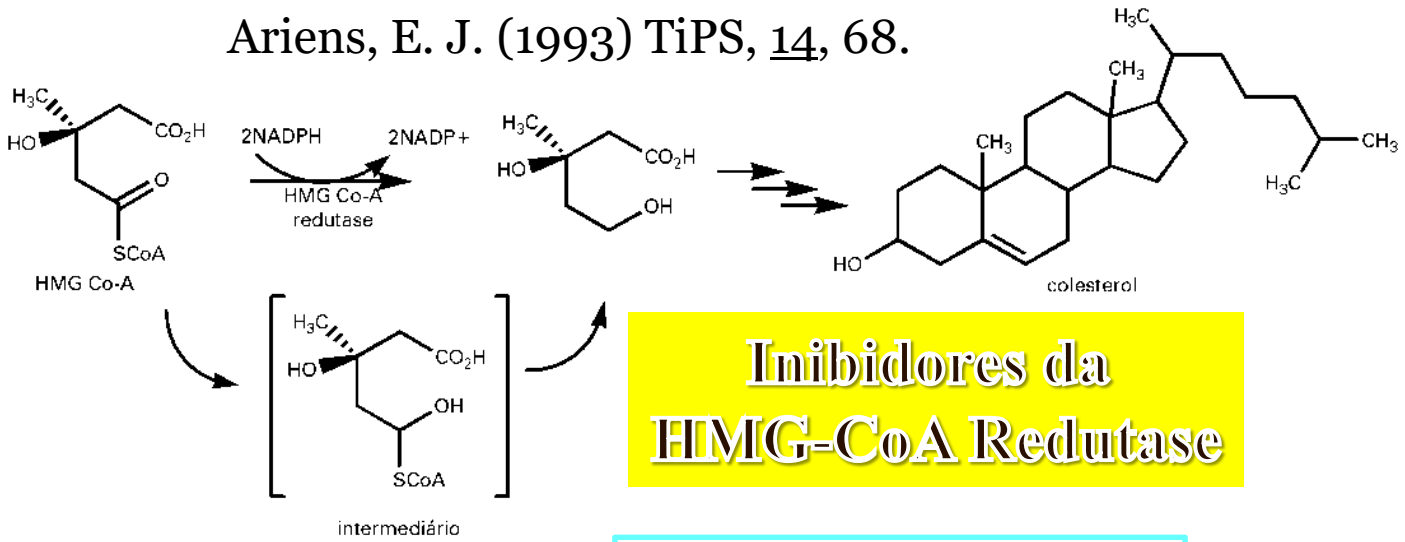
compd	inclined screen	foot shock	cat	anticonvulsant tests: pentylene-tetrazole	anticonvulsant tests: electroshock max	anticonvulsant tests: electroshock min
chlordiazepoxide	100	40	2	18	92	150
diazepam	30	10	0.2	1.4	6.4	64

[a] Dose (mg/kg) of orally administered drug required to achieve the desired effect.

- Mercado Farmacêutico:
- Librium® foi lançado em 1959
- Valium® foi lançado logo em seguida (1963)

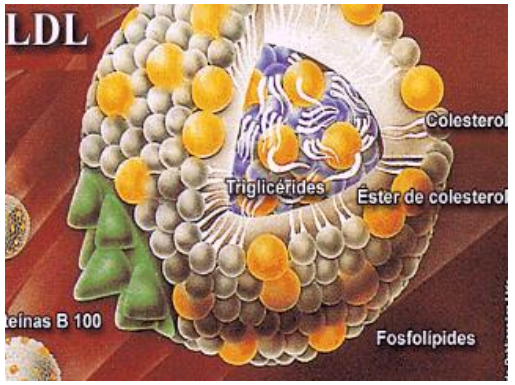
PN como inspiração na Gênese de Fármacos : Estatinas

Ariens, E. J. (1993) TiPS, 14, 68.

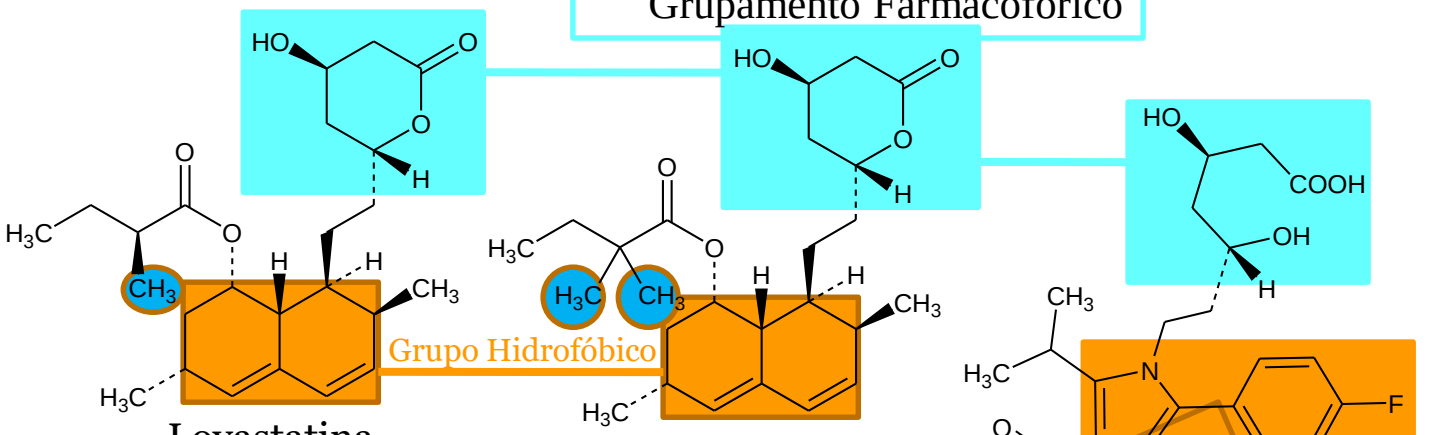


Inibidores da HMG-CoA Redutase

Biossíntese de Colesterol



Grupamento Farmacofórico



Lovastatina
Aspergillus terrens
Mevacor, Merck, 1987
IC50 = 2,2 nM
PRÓ-FÁRMACO

Simvastatina
Zocor, Merck, 1988
IC50 = 0,9 nM

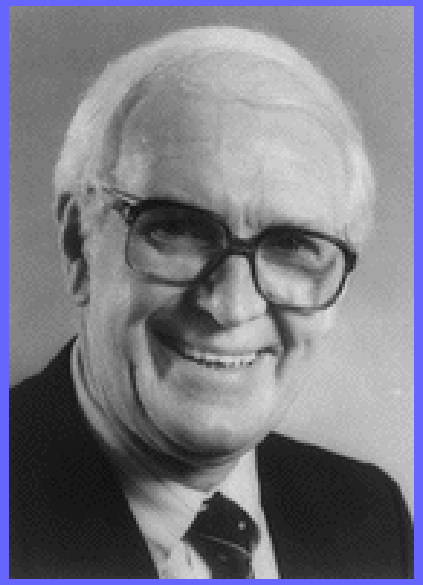
Atorvastatina
Lipitor, Pfizer
Top # 1 (2006)

Derosa G.; Salvadeo S.; Cicero, A. F. G. (2006) Curr. Op. Invest. Drugs, *7*, 826-833.

A Pesquisa por Novos Fármacos Anti-Úlceras

- Anos 60: Compreensão da fisiologia da secreção gástrica de ácido;
- Programas para a descoberta de Inibidores da ação de messageiros químicos;
- Reino Unido: ICI Pharmaceuticals, Pfizer, Smith Kline French: Antagonistas de Receptores Histaminérgicos

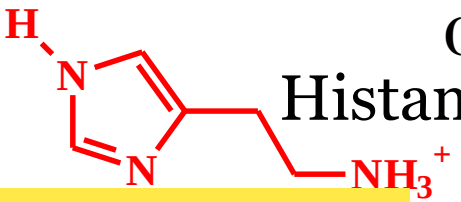
R. Ganellin
G. Durant
J. Emmett



Sir James Black
Prêmio Nobel
de Medicina, 1988

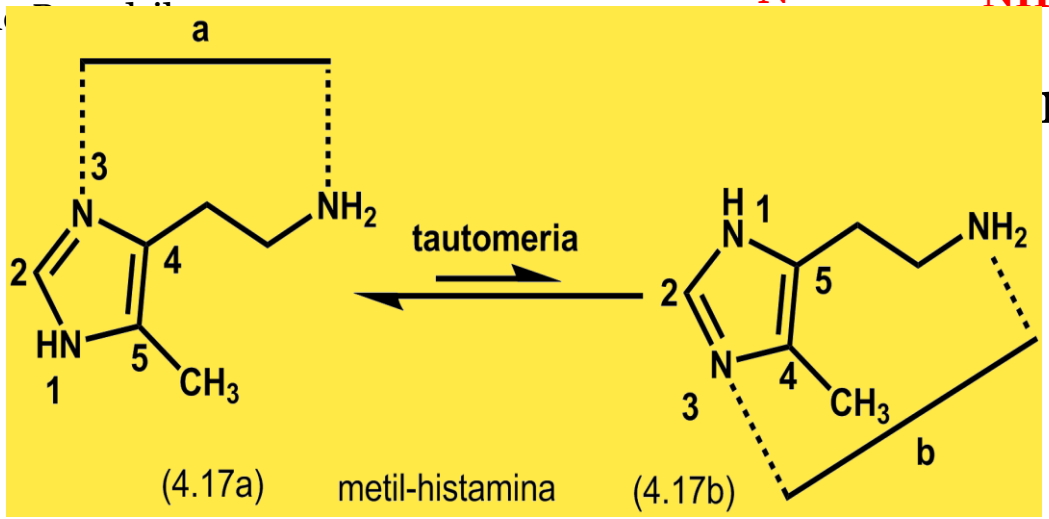
Década de 70: Programa Desenvolvimento de Antagonistas-H_2 (SK&F)

(1948) Folkow, Haeger e Kahlson: Sugerem a existência de 2 tipos de receptores sensíveis à histamina, dos quais apenas um podia ser bloqueado pel

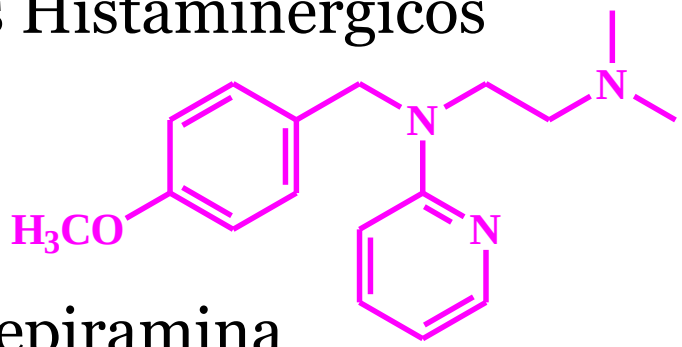


(1966) Ash e Schild: Receptor H1

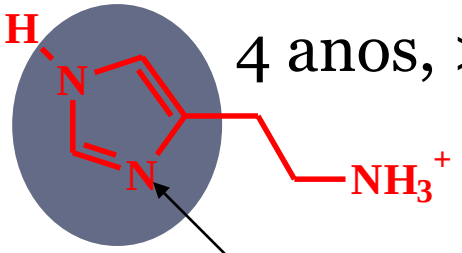
Histamina (Monocátion)



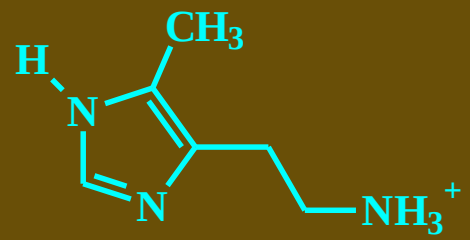
res Histaminérgicos



Mepiramina



4 anos, >200 compostos

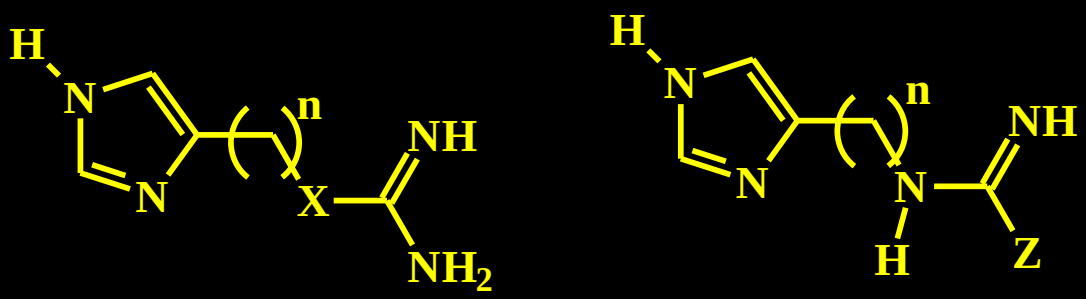


4-Metilhistamina: Agonista Seletivo
(Induz a secreção gástrica de ácido)

Idéia Original de Black: Alquilação

Lipofilicidade X Hidrofilicidade

SAR de algumas imidazolilisotiouréias, guanidinas e amidinas

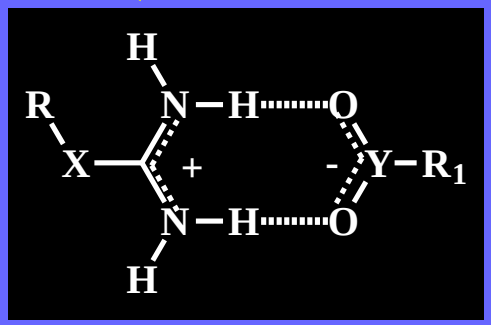


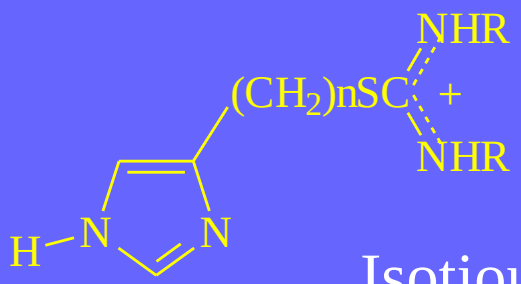
Composto	n	Substituinte	Atividade
1	2	X = NH	+
2	2	X = S	++
3	3	X = NH	+++
4	3	X = S	±
5	2	Z = SMe	±
6	2	Z = Me	±
7	3	Z = SMe	+++
8	3	Z = Me	+++

Teste de inibição da secreção gástrica de ácido, induzida por histamina; ± (detectável); + (ID_{50} > 500 μmol/Kg); ++ (ID_{50} ~ 200 μmol/Kg); +++ (ID_{50} = 100-50 μmol/Kg). ID_{50} = Dose intravenosa capaz de reduzir a secreção de ácido em 50%.

Imidazolilisotiouréias, Amidinas e Guanidinas (Monocátions)

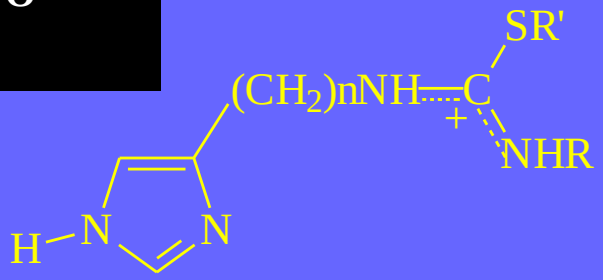
Agonismo X Antagonismo





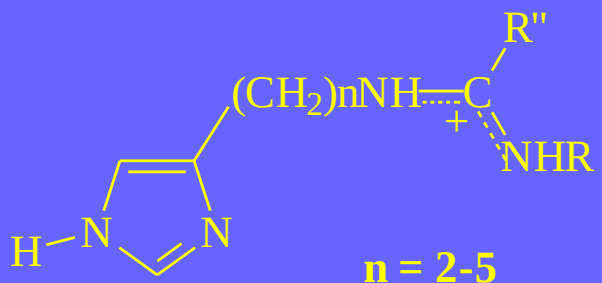
Isotiouréias

n = 2-4
R = H ou alquila



Isotiouréias Invertidas

n = 2-5
R = H ou alquila
R' = alquila



Amidinas

n = 2-5
R = H ou alquila
R'' = alquila, arila, etc.

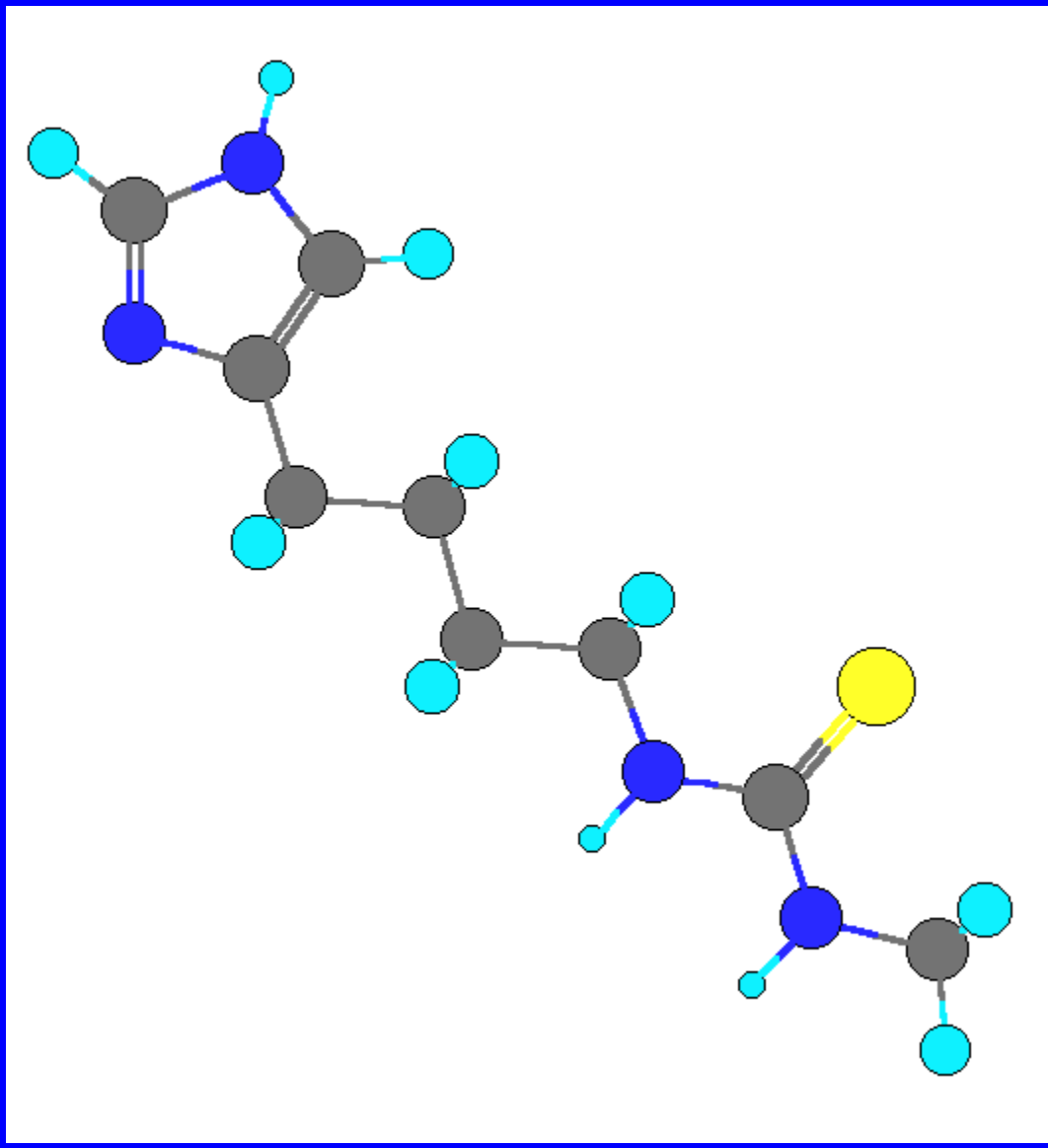
Guanidinas

Descoberta da Burimanida

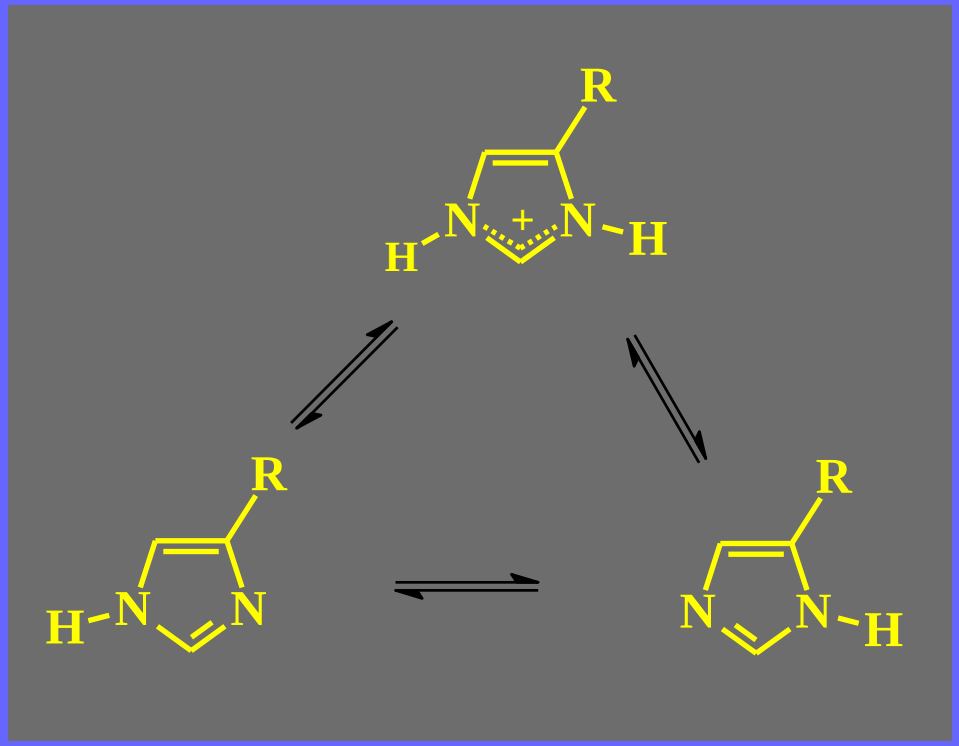
Introdução de Grupos Polares, Não Básicos

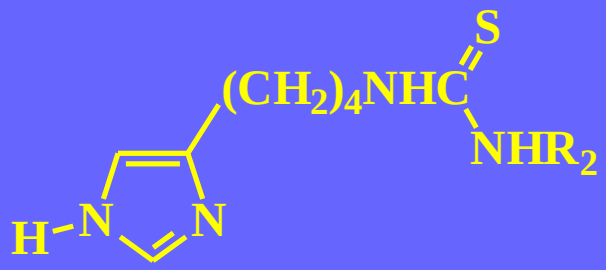
Tiouréias

(9) SK&F 91581 n = 3, R_2 = H
(10) SK&F 91863 n = 4, R_2 = H
(11) Burimamida, n = 4, R_2 = CH_3

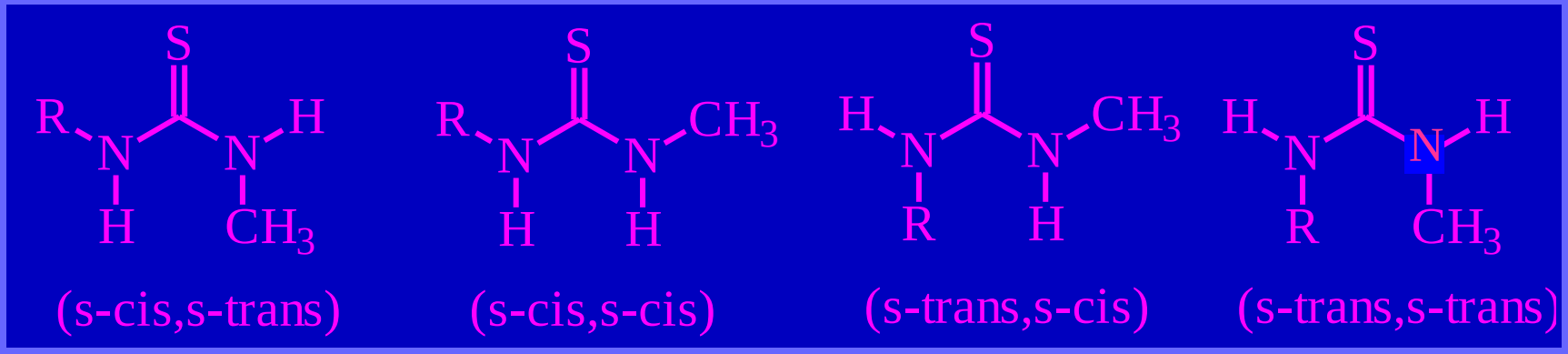


Características Estruturais da Burimamida

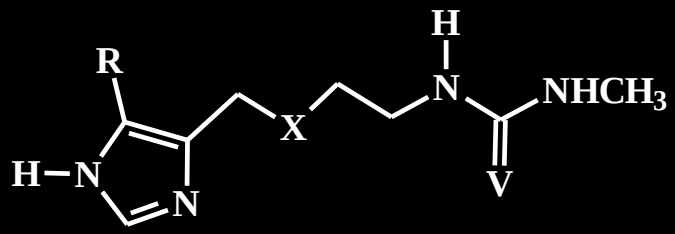




Burimamida



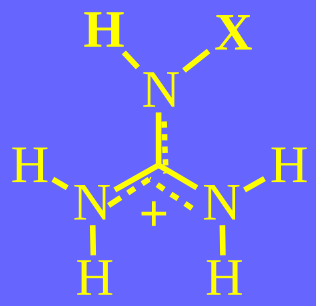
Planejamento Estrutural de Isósteros da Burimamida



Atividade em Receptores H_2

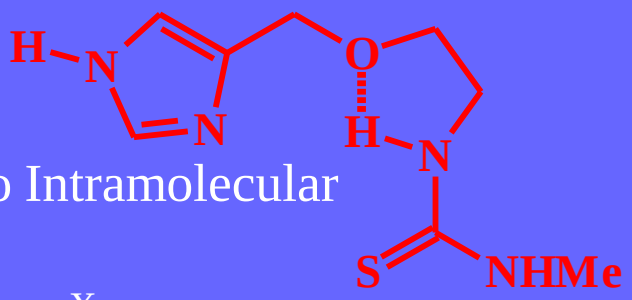
Composto	Estrutura R	Estrutura X	Estrutura V	*In Vitro* Átrio (K_B X 10^{-6} M)	*In Vitro* Útero (K_B X 10^{-6} M)	*In Vivo* Secreção de HCl ID_{50} (µg/mol)
Burimamida	H	CH_2	S	7,8	6,6	6,1
Tiaburimamida	H	S	S	3,2	3,2	5
Oxaburimamida	H	O	S	28	6,6	ND
Metiamida	CH_3	S	S	0,92	0,75	1,6
Isóstero Ureídico	CH_3	S	S	22	7,1	27
Isóstero Gunidínico	CH_3	S	NH	16	5,5	12
Isóstero Nitroguanidínico	CH_3	S	N-NO_2	1,4	1,4	2,1
Isóstero Cianoguanidínico	CH_3	S	N-CN	0,79	0,81	1,4
Isóstero Guaniluréia	CH_3	S	N-$CONH_2$	7,1	6,9	7,7

Aspectos Estruturais de Guanidinas Substituídas e Derivados

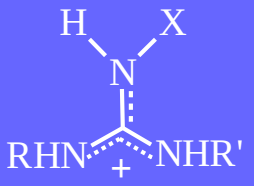


X	σ	pKa'
H	0	14,0
Ph	0,11	10,6
Ac	0,32	8,0
$CONH_2$	0,30	7,3
OMe	0,32	6,3
CN	0,59	0,4
NO_2	0,62	0,9

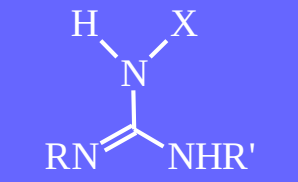
pKa = -1,2



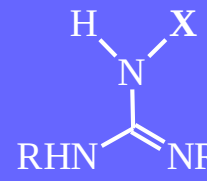
Ligação de Hidrogênio Intramolecular



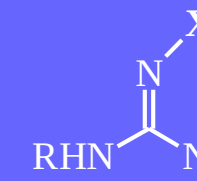
Cátion Guanidinium



Tautômero Amino



Tautômero Amino



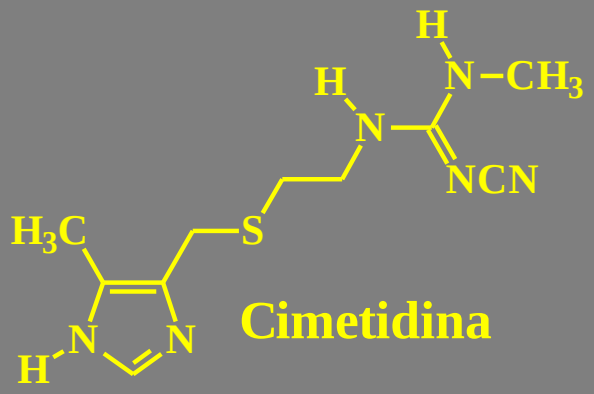
Tautômero Imino Favorecido: X = EWG

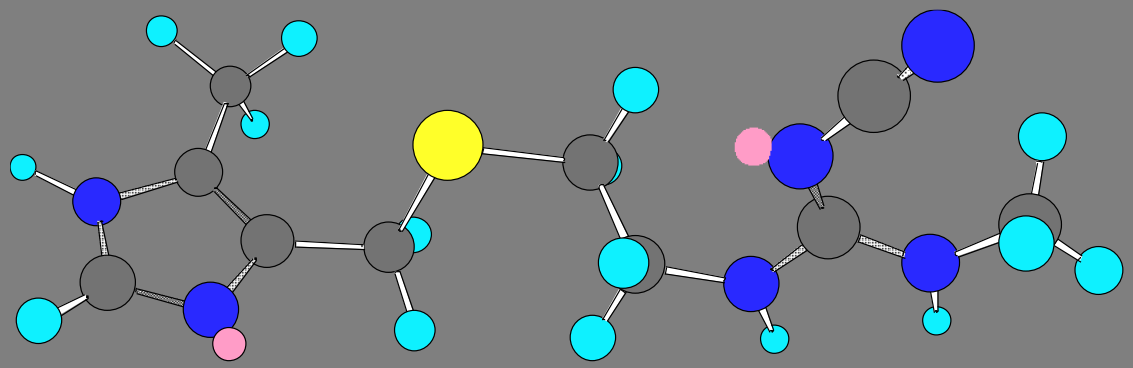
H+

H+

H+

Nasce um Novo Fármaco: Cimetidina

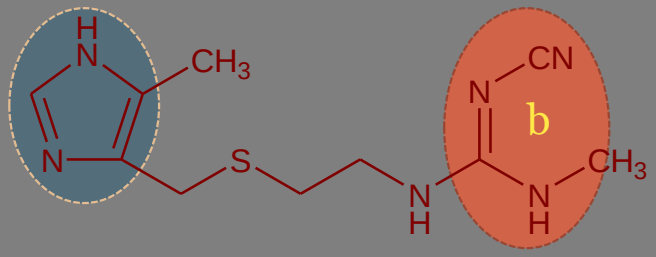




Animal	Preparação	Estimulante	ID_{50} (μmol/Kg) intravenoso
Ratos	Lúmen Estomacal Perfundido	Histamina	1,37
		Pentagastrina	1,40
Gatos	Lúmen Estomacal Perfundido	Histamina	0,85
		Pentagastrina	1,45
Cães	Lúmen Estomacal Perfundido	Histamina	1,70
		Pentagastrina	2,00

Ganellin, C. R. (1981) *J. Med. Chem.*, *24*, 913-920.

Cimetidina

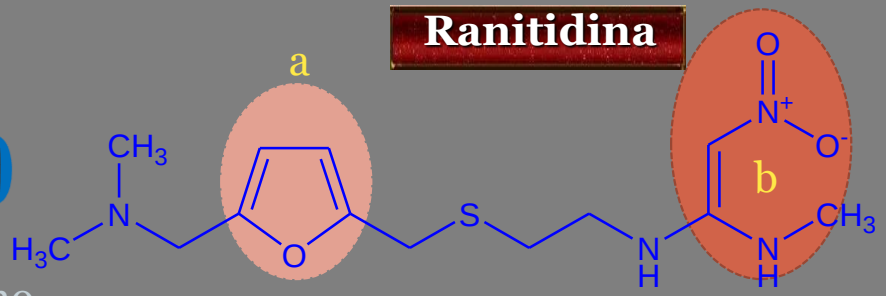


Robin Ganellin *et al.*, 1974
US 3950333 1974, 1976 - SK&F
Brit. J. Pharmacol. **53,** 435 (1975).

me-too

Bioisosterismo

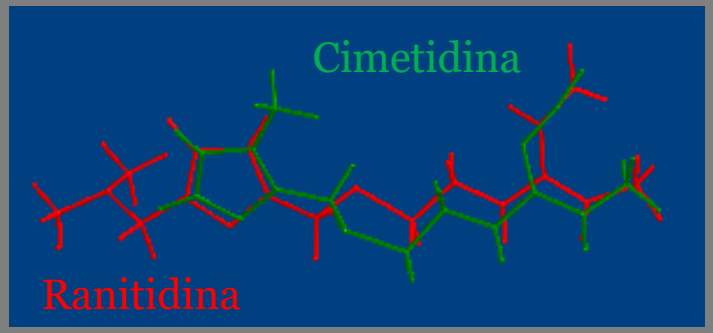
Ranitidina



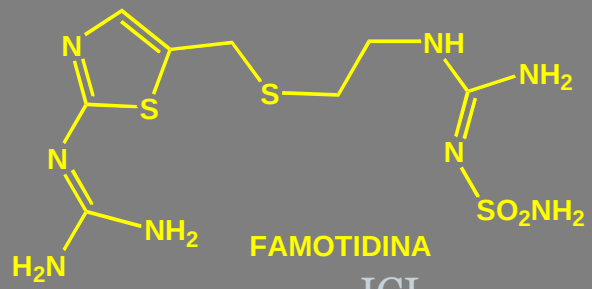
Barry J. Price *et al.*, 1978
US 4128658 1978 - Allen & Hanburys
Brit. J. Pharmacol. **66,** 464 (1979)

Glaxo

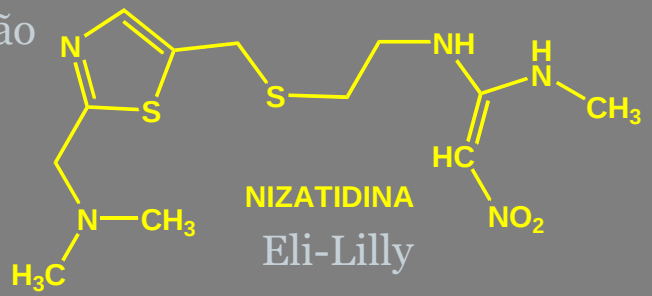
1987: Top One



Cimetidina (SK&F)
Vendas em 1976: US$ 386 milhões
Vendas em 1980: US$ 580 milhões
Top em 1983: US$ 1 bilhão



FAMOTIDINA
ICI



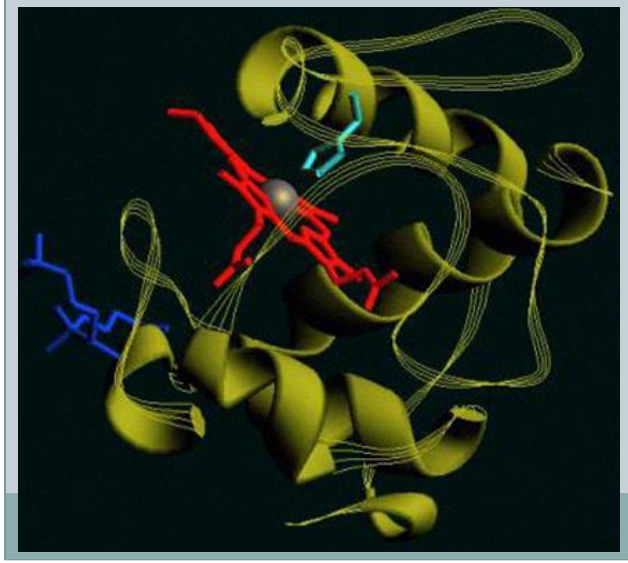
NIZATIDINA
Eli-Lilly

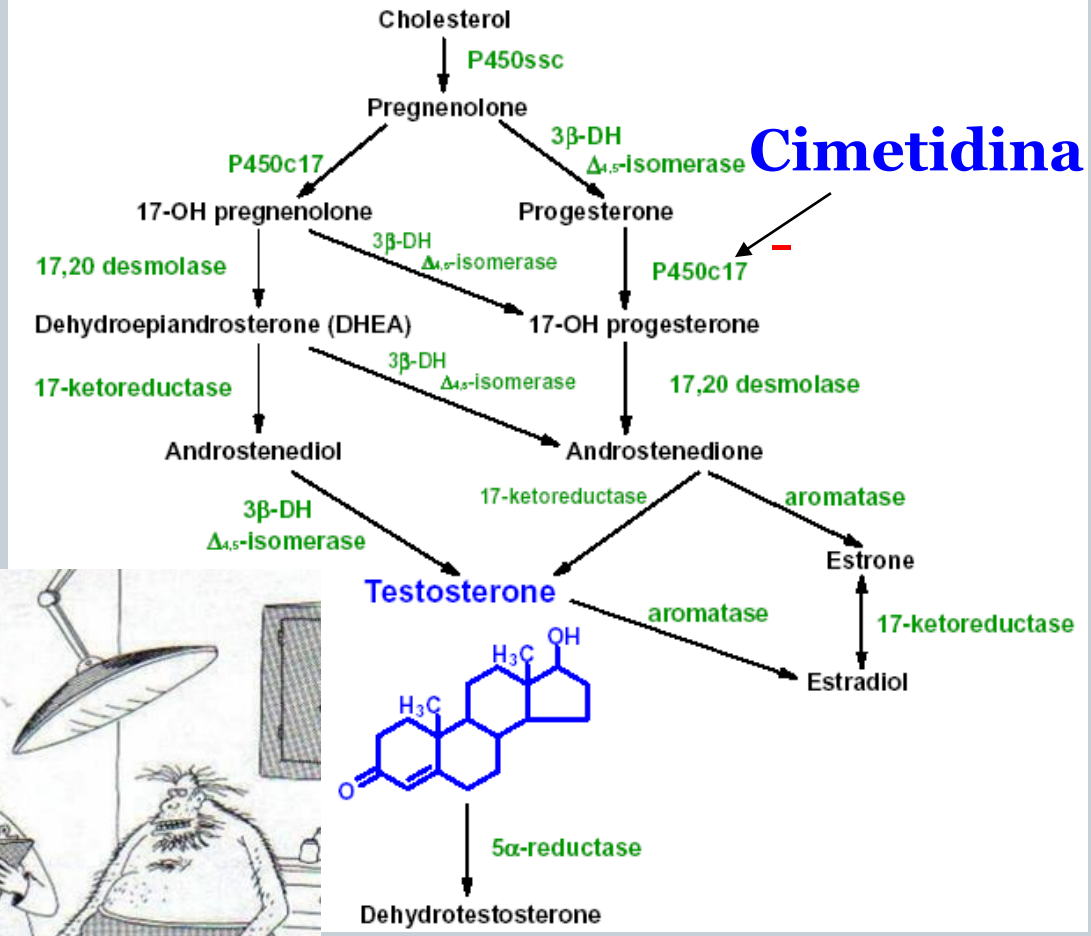
Efeitos Colaterais da Cimetidina

Principais Efeitos Colaterais Em Homens:

- Crescimento de Seios (Ginecomastia)
- Perda da Libido
- Impotência

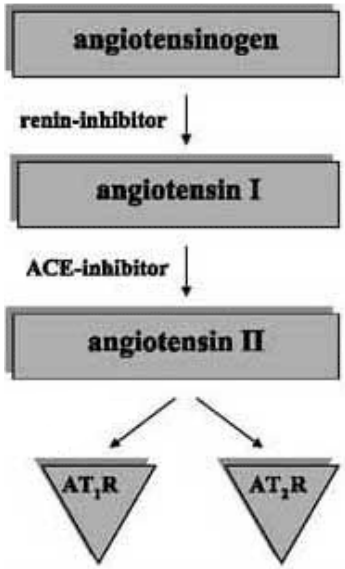
Interações Medicamentosas com vários outros fármacos metabolizados por oxidação hepática (CYP450)

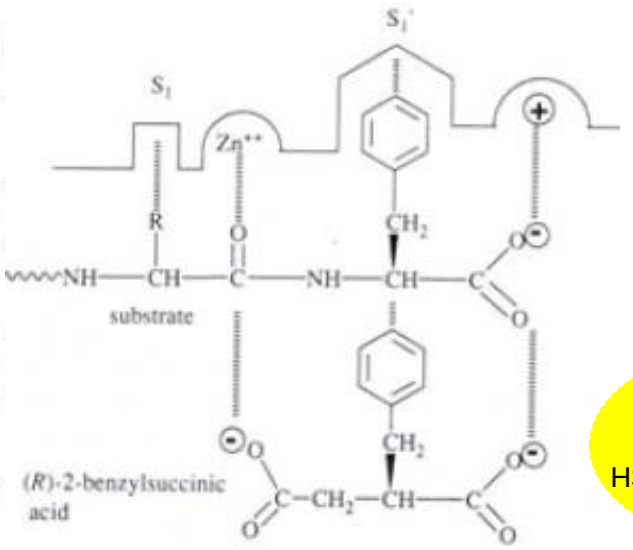


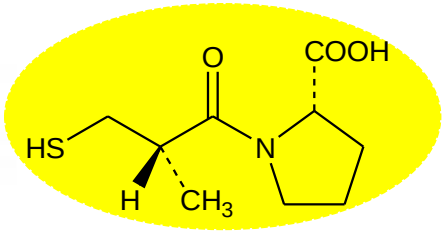


Biossíntese de Testosterona

Inibidores da Enzima Conversora de Angiotensina



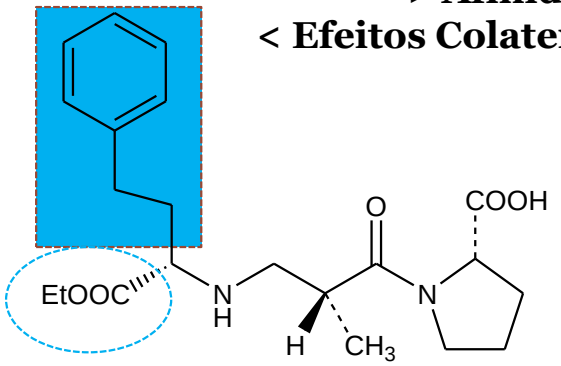




Captopril
Cushman & Ondetti, Squibb, 1997
IC_{50} = 23 nM

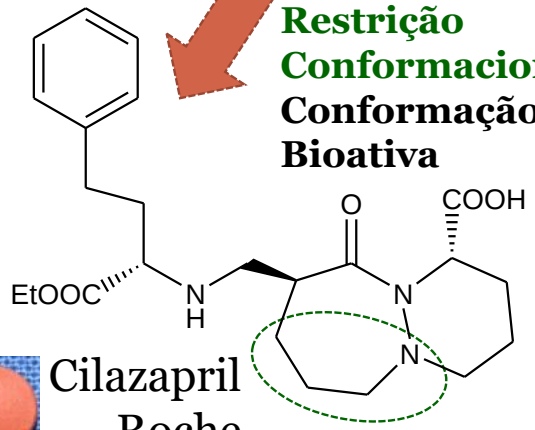
Lisinopril
Astra Zeneca

> Afinidade
< Efeitos Colaterais

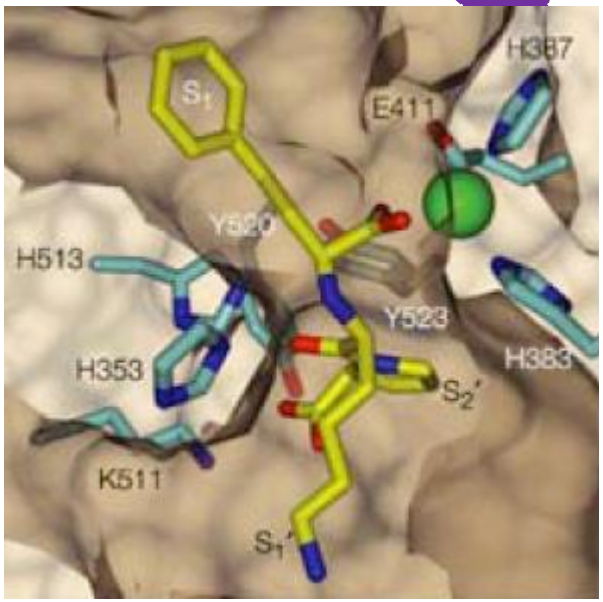


Enalapril
Merck Sharp & Dohme

Restrição Conformacional
Conformação Bioativa

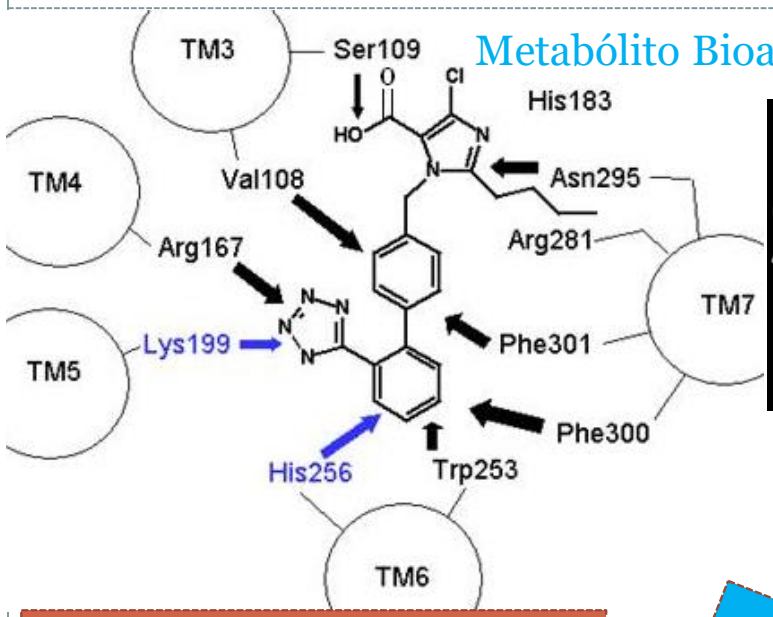


Cilazapril
Roche

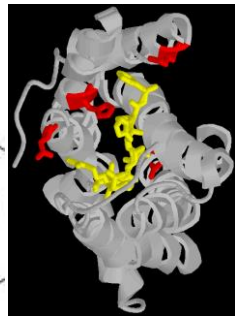


Acharya, K. R.; Sturrock, E. D.; Riordan, J. F.; Ehlers, M. R. W. (2003) Nature Rev. Drug Discov. 2, 891.

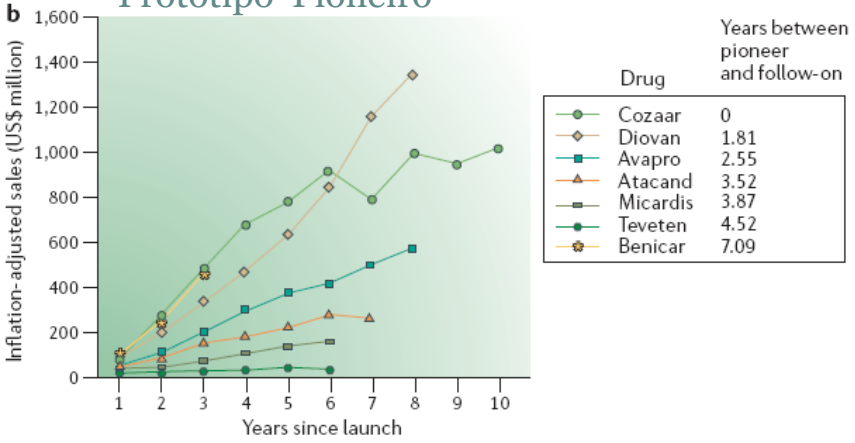
Antagonistas de Receptores AT1 de Angiotensina 2

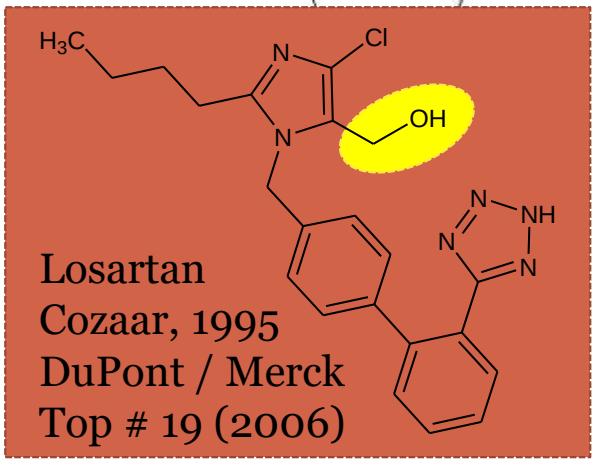


Metabólito Bioativo



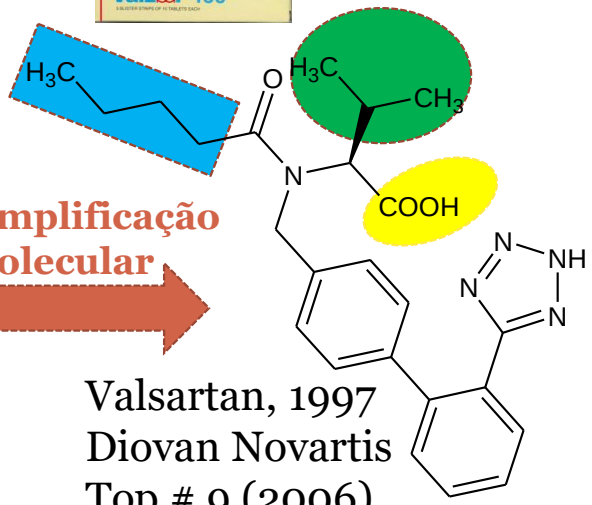
Tempo Relativo ao Lançamento do Protótipo Pioneiro



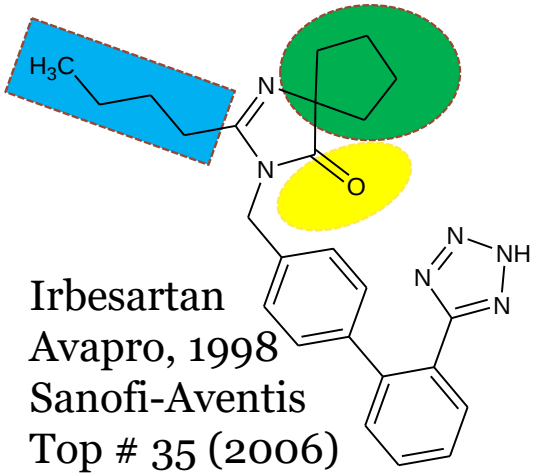


Losartan
Cozaar, 1995
DuPont / Merck
Top # 19 (2006)

Simplificação Molecular



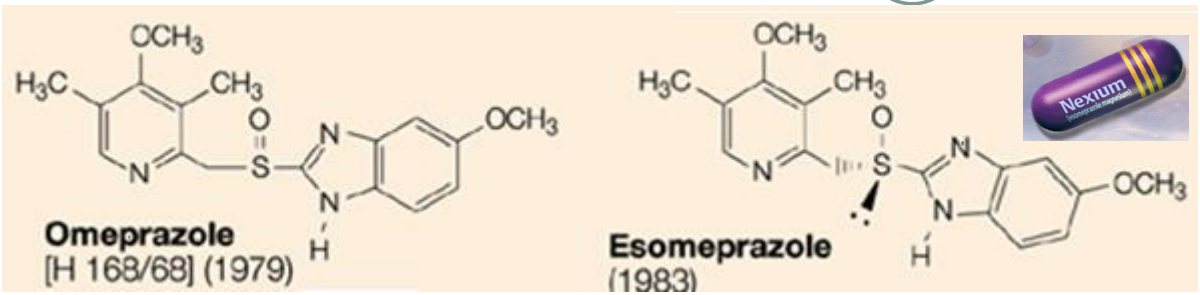
Valsartan, 1997
Diovan Novartis
Top # 9 (2006)



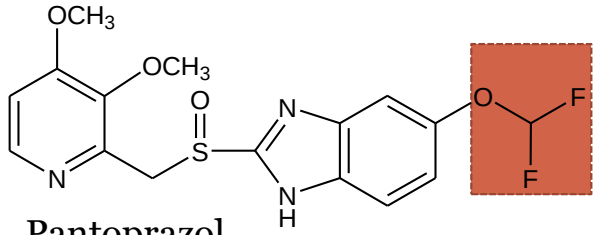
Irbesartan
Avapro, 1998
Sanofi-Aventis
Top # 35 (2006)

Cockcroft, J. R.; Sciberras, D. G.; Goldberg, M. R. and Ritter, J. M. (1993) J. Cardiovasc. Pharmacol. *22*, 584.

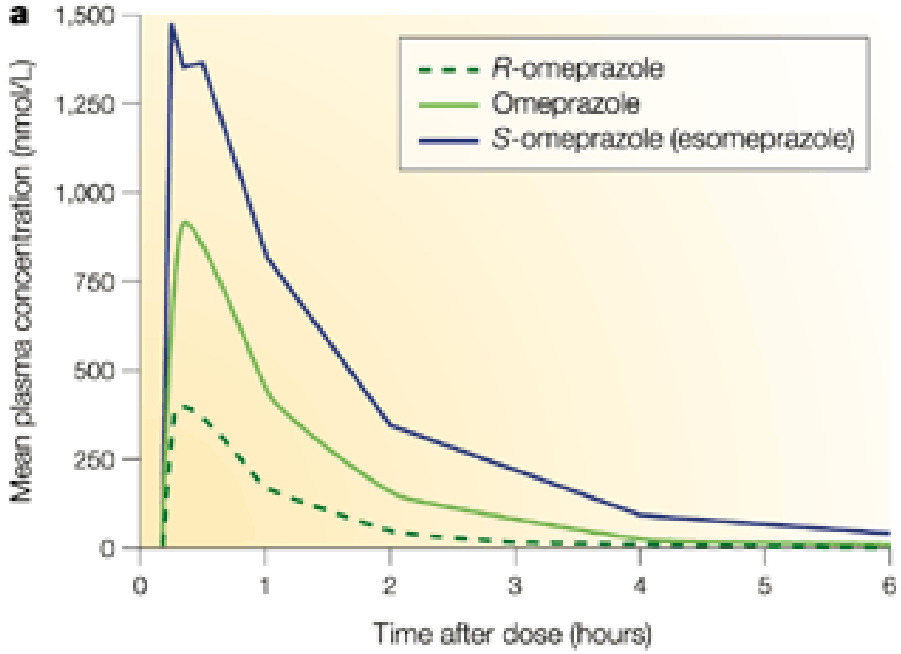
A Importância do "Switch" Quiral: Inibidores da ATPase H-K: Esomeprazola

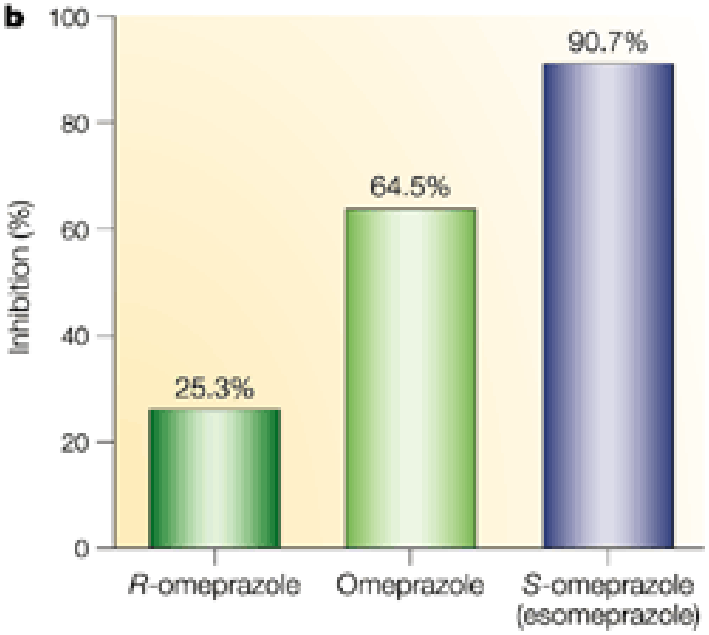


Prilosec Astra-Zeneca Top # 72 (2006) Astra-Zeneca Top # 4 (2006)



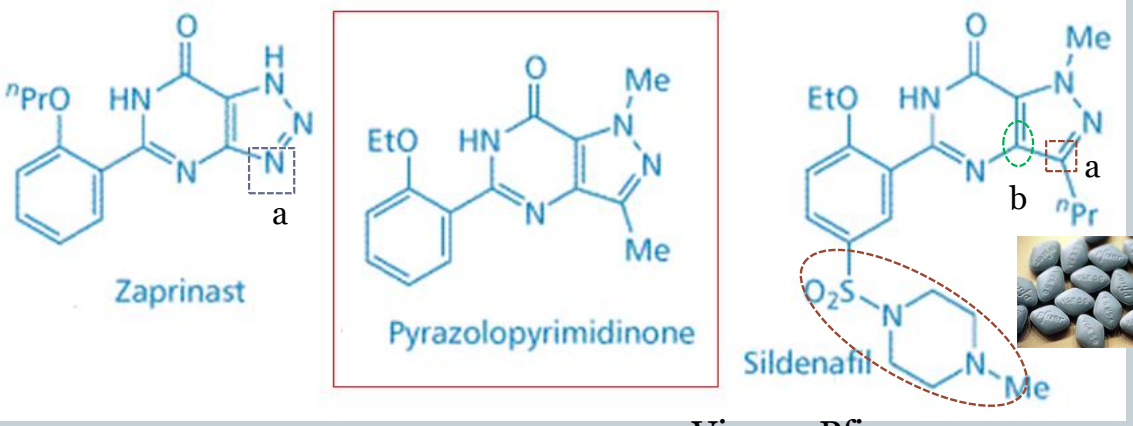
Pantoprazol
Wyeth/Altana
Astra-Zeneca Top # 14 (2006)

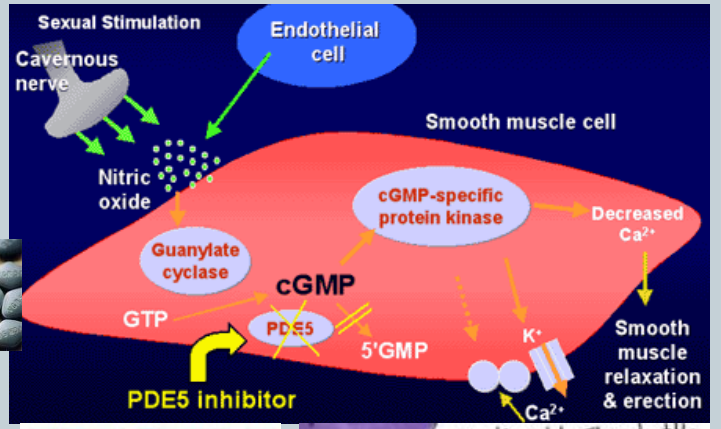




Olbe et al, *Nat Rev Drug Discovery* 2:132, 2003

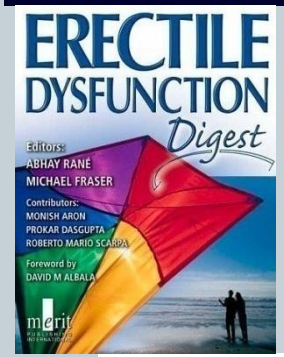
Terapia da Disfunção Erétil: Inibidores de PDE-V





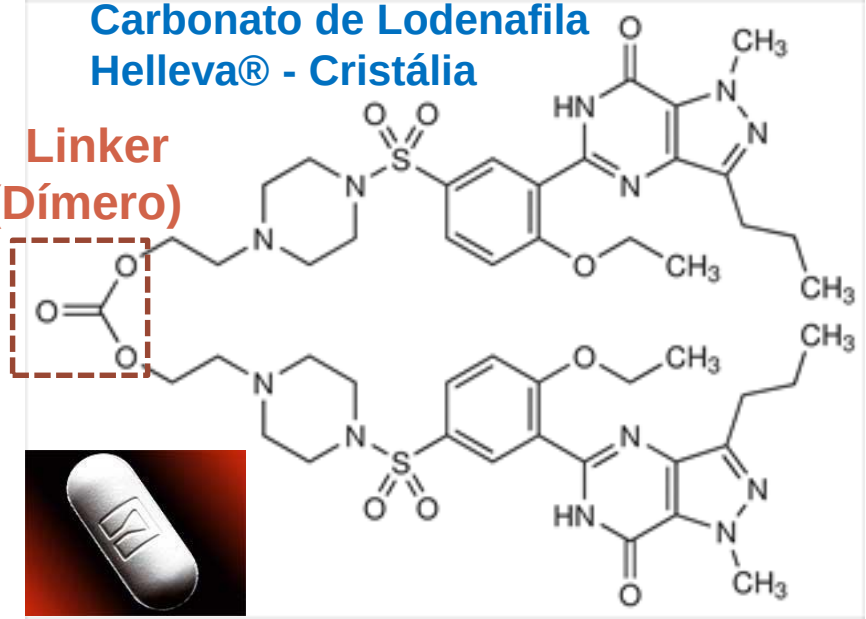
Isozyme	Zaprinast IC_{50} (nM)	Sildenafil IC_{50} (nM)

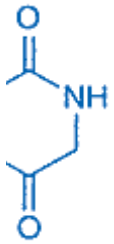
Viagra, Pfizer
Top # 57 (2006)

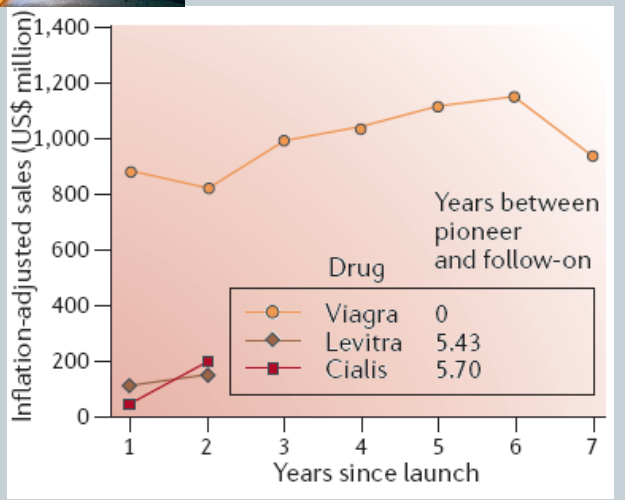


Carbonato de Lodenafila
Helleva® - Cristália

Linker (Dímero)

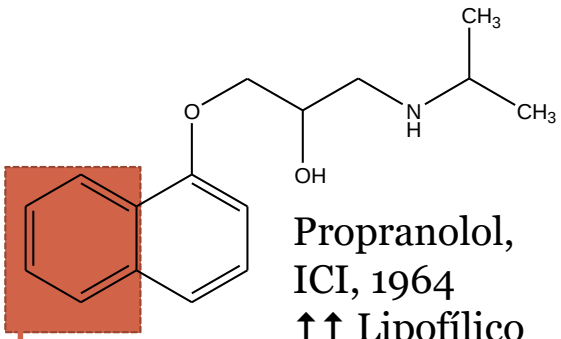






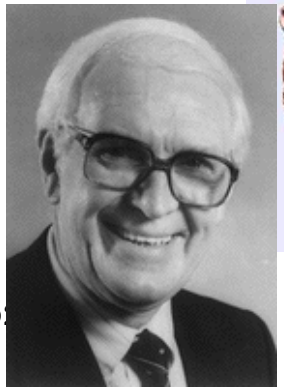
A Importância dos Me-too como Alternativas Terapêuticas

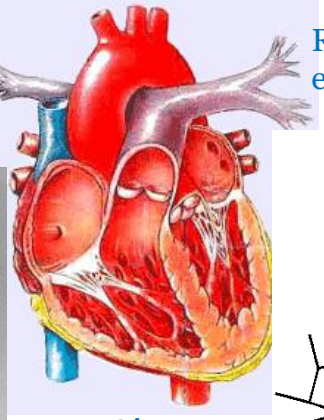
β-Bloqueadores



Propranolol,
ICI, 1964
↑↑ Lipofílico
↑Não Seletivo β1/β

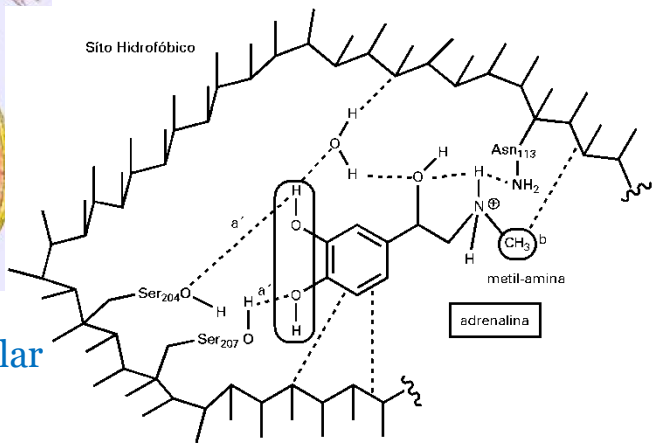
James Black

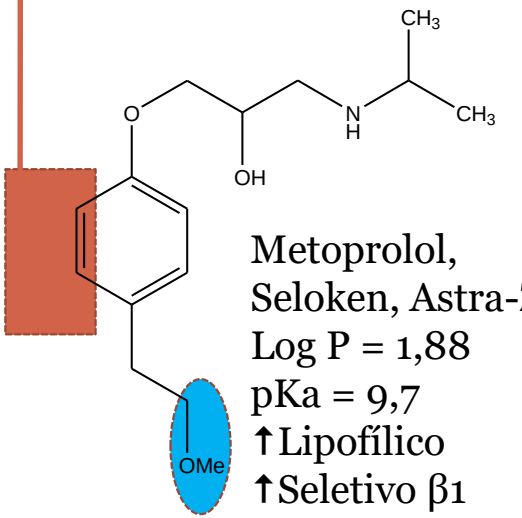




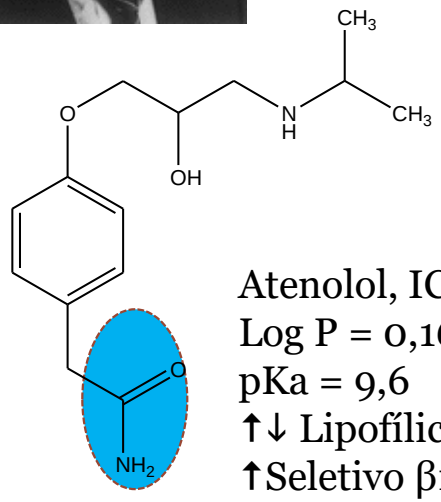
Sistema
Cardio-Vascular

Reconhecimento Molecular de Adrenalina e Propranolol em Receptores β

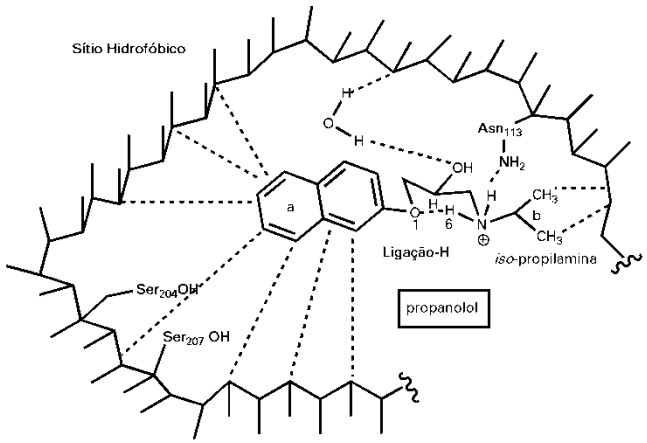




Metoprolol,
Seloken, Astra-Zeneca
Log P = 1,88
pKa = 9,7
↑Lipofílico
↑Seletivo β1



Atenolol, ICI
Log P = 0,16
pKa = 9,6
↑↓ Lipofílico
↑Seletivo β1



Shin, J.; Johnson, J. A. (2007) Pharmacotherapy, *27*, 874-887.

Descoberta e Desenvolvimento de Protótipos Candidatos a Fármacos no LASSBio-UFRJ

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

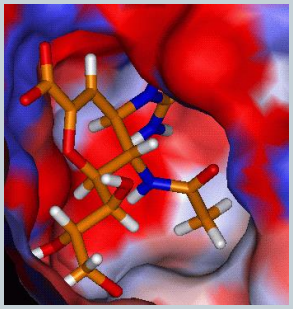
Farmacologia/
Bioquímica
PROPRIEDADES BIOLÓGICAS

Interdisciplinaridade

Avaliação do Perfil
De Bioatividade:
SAR, SAFIR
Identificação do
Composto
Protótipo

Avaliação do Perfil
De Bioatividade:
Composto-Protótipo;
Otimização Estrutural

Química Medicinal



Química Computacional
RECONHECIMENTO MOLECULAR

Planejamento e
Otimização Estrutural (Afinidade)

Química Orgânica
(Síntese Orgânica Medicinal)
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THE ROLE OF THE MEDICINAL CHEMIST IN DRUG DISCOVERY — THEN AND NOW

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Bertil B. Fredholm, William W. Fleming, Paul M. Vanhoutte and Théophile Godfraind

"It is obvious that pharmacology is one of the most important scientific disciplines that underpin research in drug discovery."

Agradecimentos

À Comissão Organizadora da
28ª Escola de Verão em Química Farmacêutica e Medicinal

Obrigado!