

Fundamentos da Química Medicinal

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UNIVERSIDADE FEDERAL DO RIO DE JANEIRO

Janeiro de 2017



LASSBio[®]

Laboratório de Avaliação e Síntese de Substâncias Bioativas

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

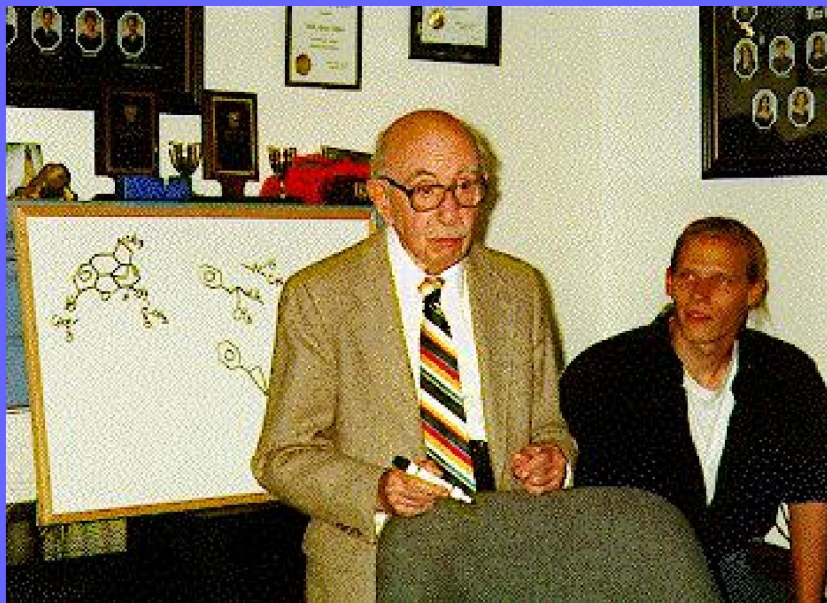
→ *Propriedades Estruturais e Atividade Biológica: ADMET;*

→ *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

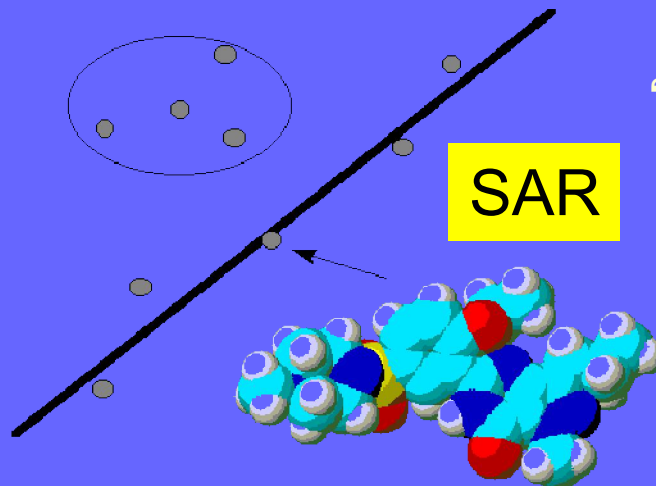


“Medicinal Chemistry remains a challenging science, which provides profound satisfaction to its practitioners. It intrigues those of us who like to solve problems posed by nature. It verges increasingly on biochemistry and all the physical, genetic and chemical riddles in animal physiology which bear 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)

BURGER'S
Sixth Edition
Medicinal
& Chemistry
Drug
Discovery

Edited by
Donald J. Abraham



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

(Corwin Hansch, 1993)

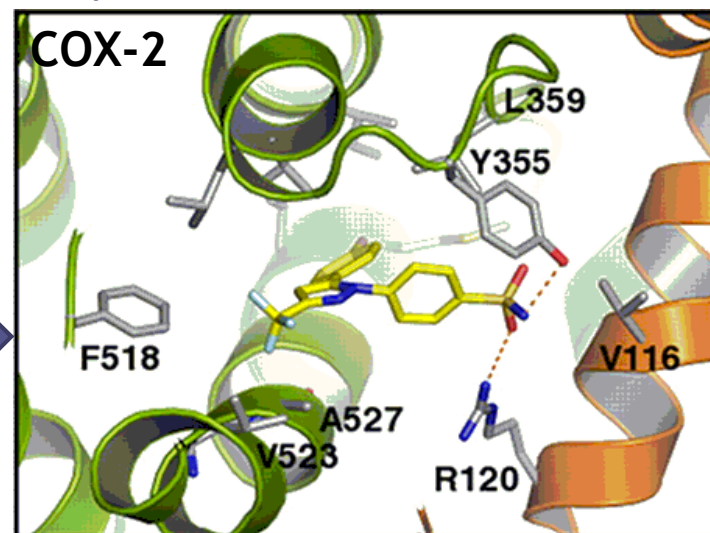
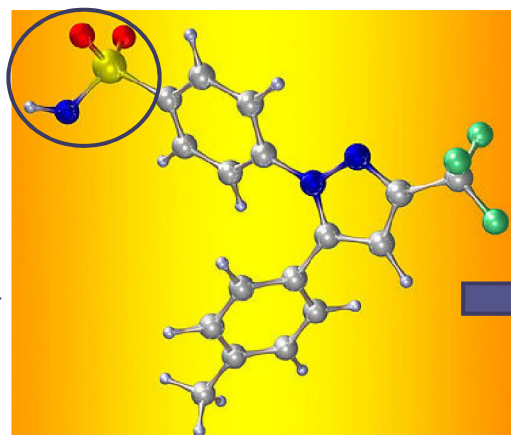
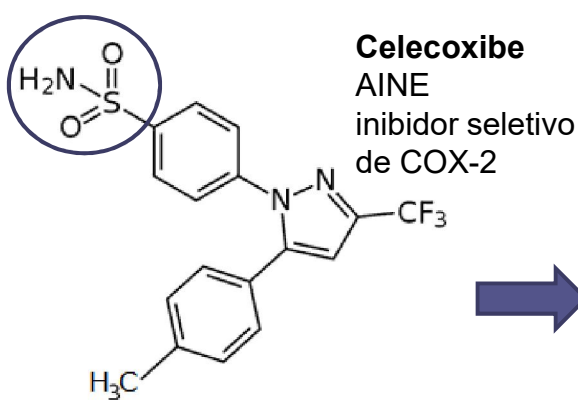
Burger's Medicinal Chemistry and Drug Discovery,
Vol. 1, Wolff, M. E., Ed., 5th Ed., 1994.

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.”

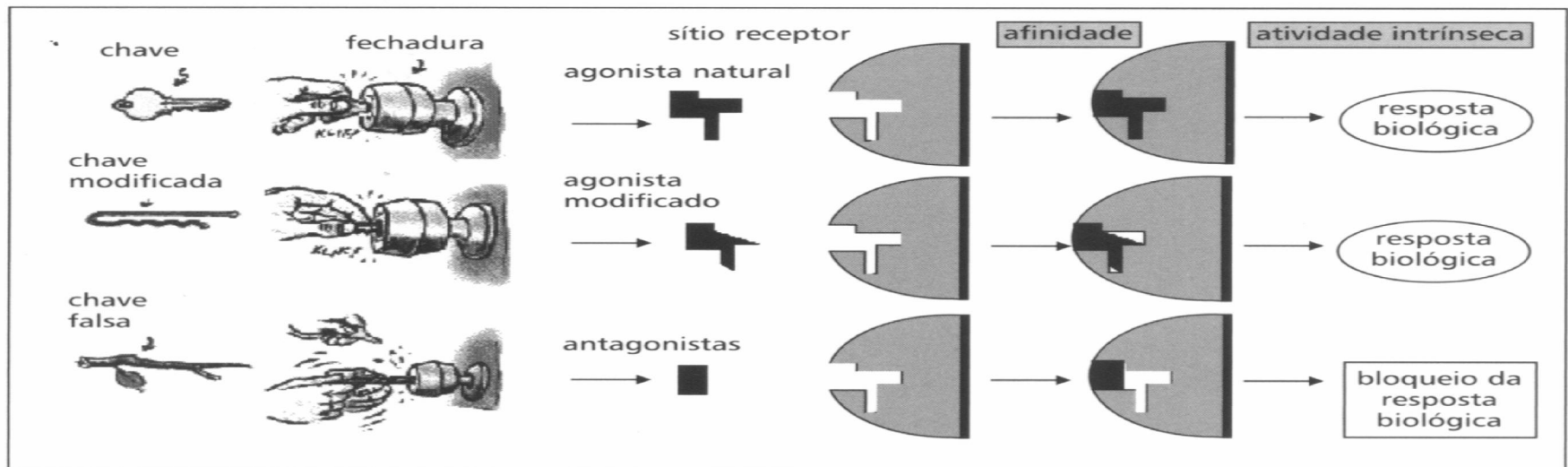
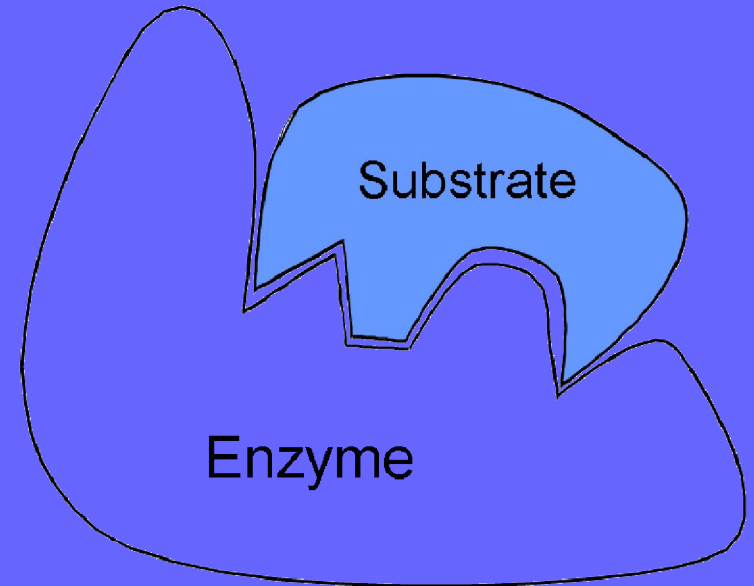


Modelo-Chave Fechadura (110 anos)

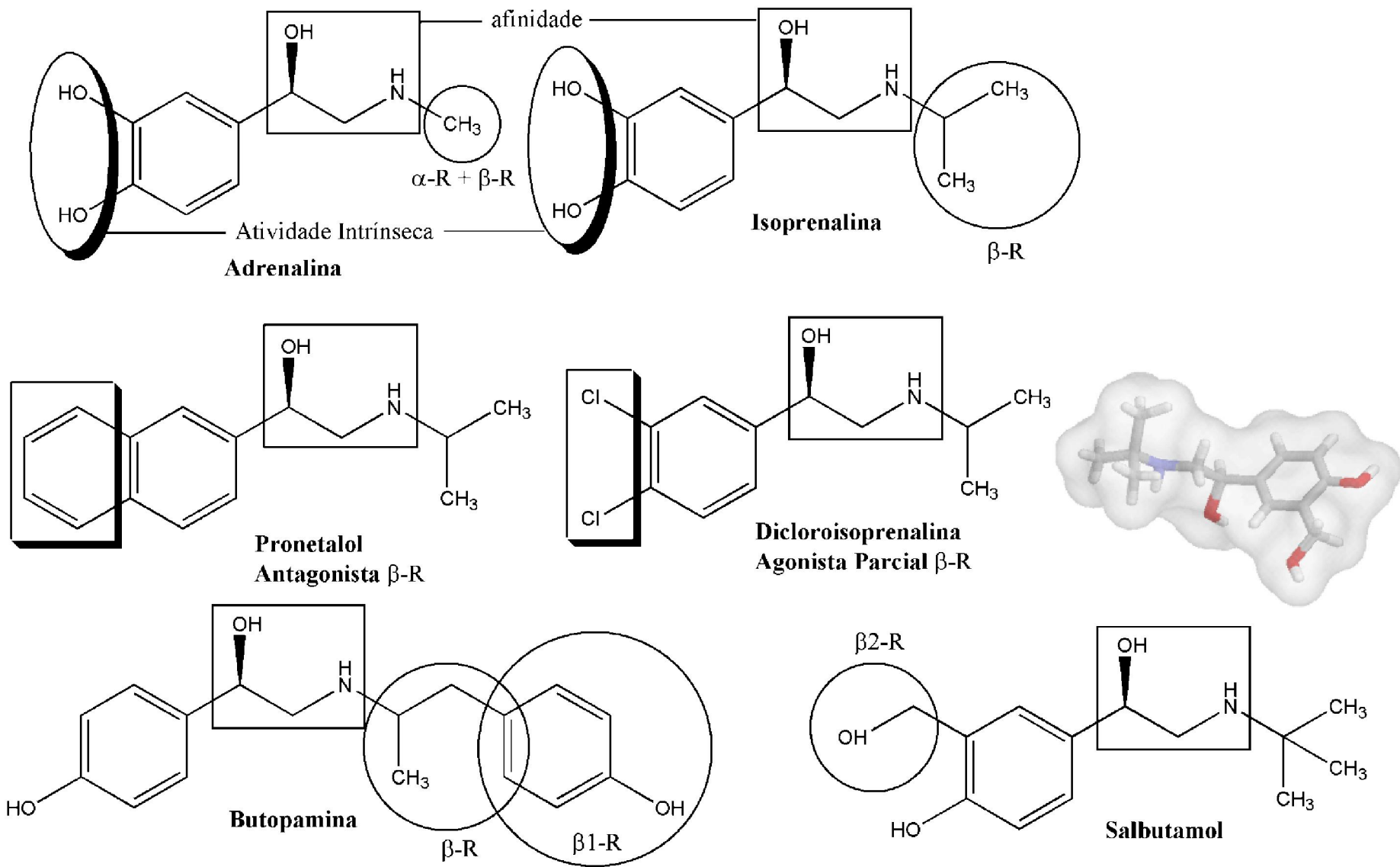


Emil Fischer
(1852-1919)
(Prêmio Nobel, 1902)

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

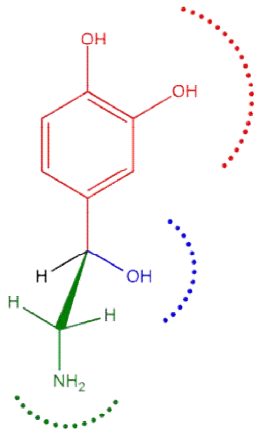


Afinidade versus Atividade Intrínseca

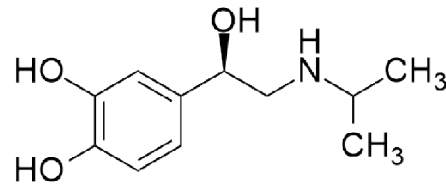
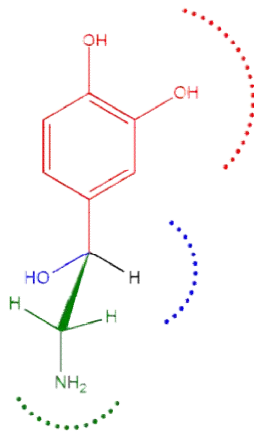


Estereoquímica em Ligantes de Receptores β -adrenérgicos

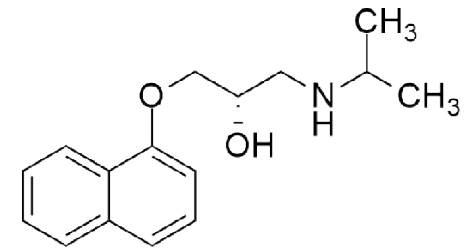
(-)-noradrenalina



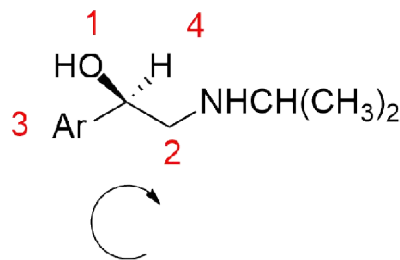
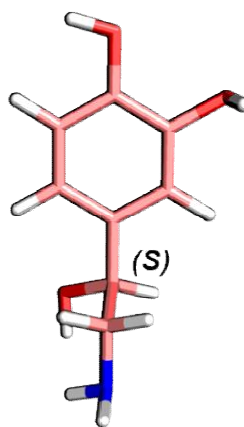
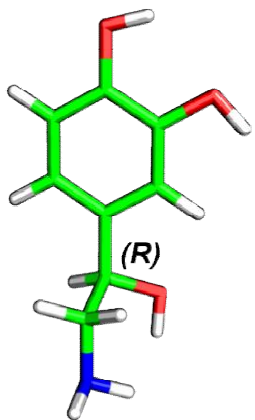
(+)-noradrenalina



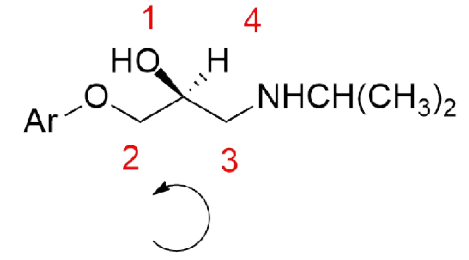
Isoproterenol
(agonista β adrenérgico)



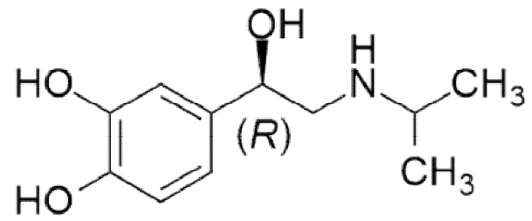
Propranolol
(antagonista β adrenérgico)



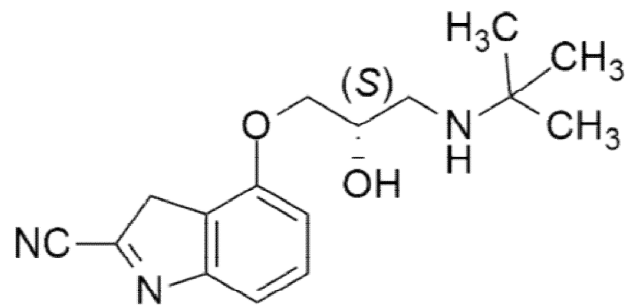
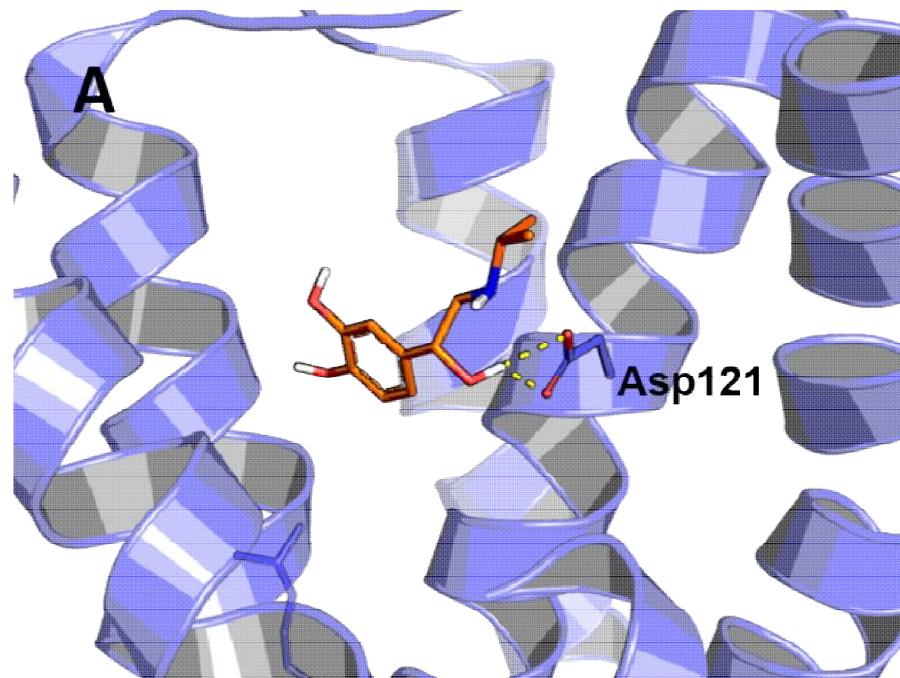
Configuração absoluta R



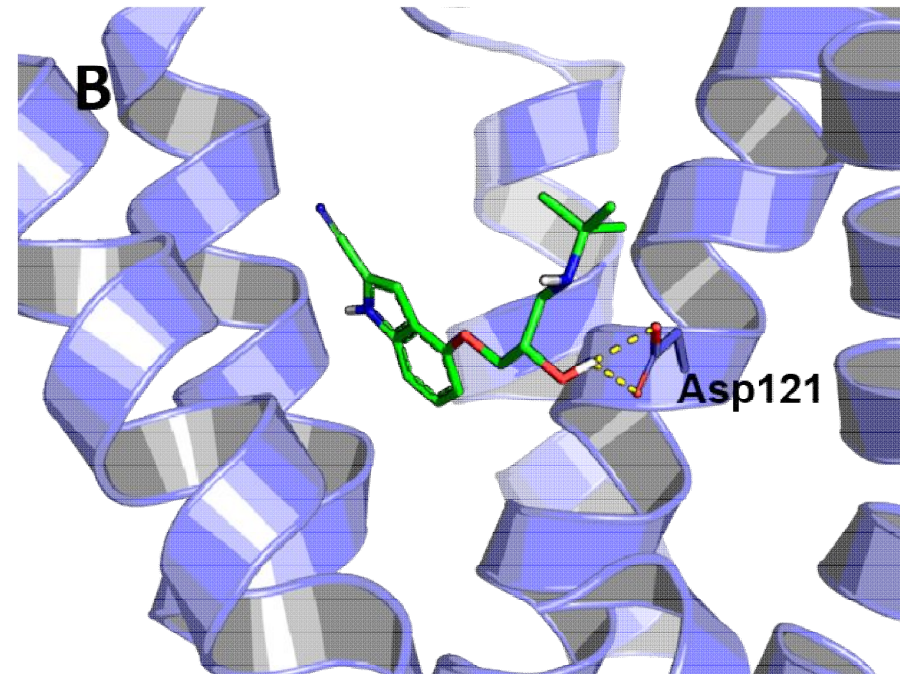
Configuração absoluta S



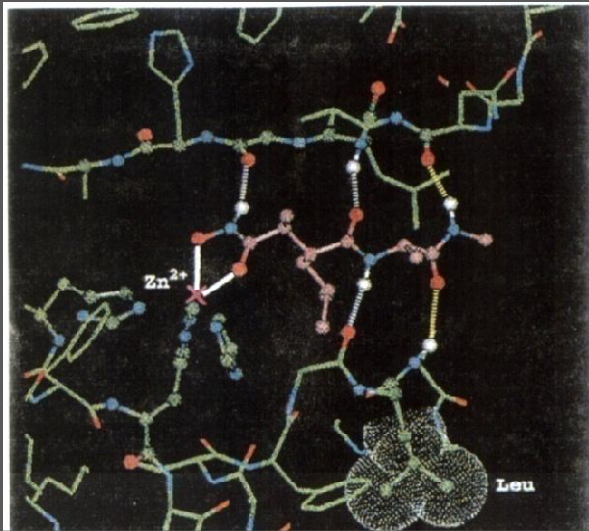
Isoproterenol
(agonista β adrenérgico)



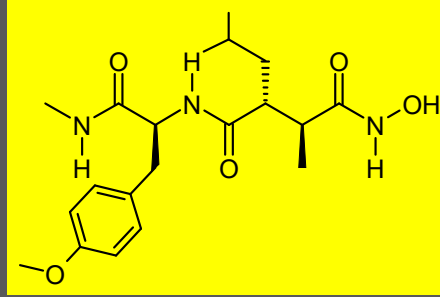
Cianopindolol
(antagonista β adrenérgico)



Teoria do Encaixe Induzido



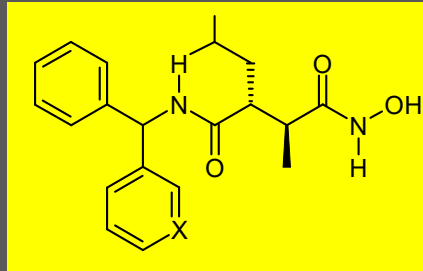
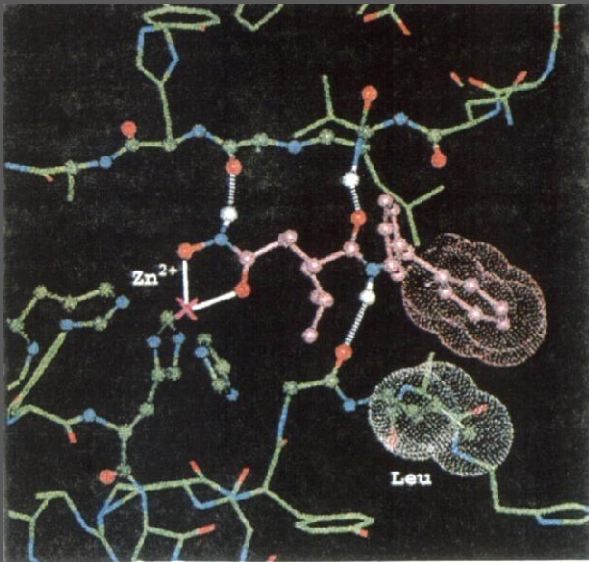
Koshland Jr., D. E.; Neméthy, G.; Filmer, D. (1966) *Biochemistry* 5, 365.



Seleção da
conformação do ligante
(reconhecimento)

Ligante

Receptor



Modificação do
ambiente molecular
(sítio receptor)

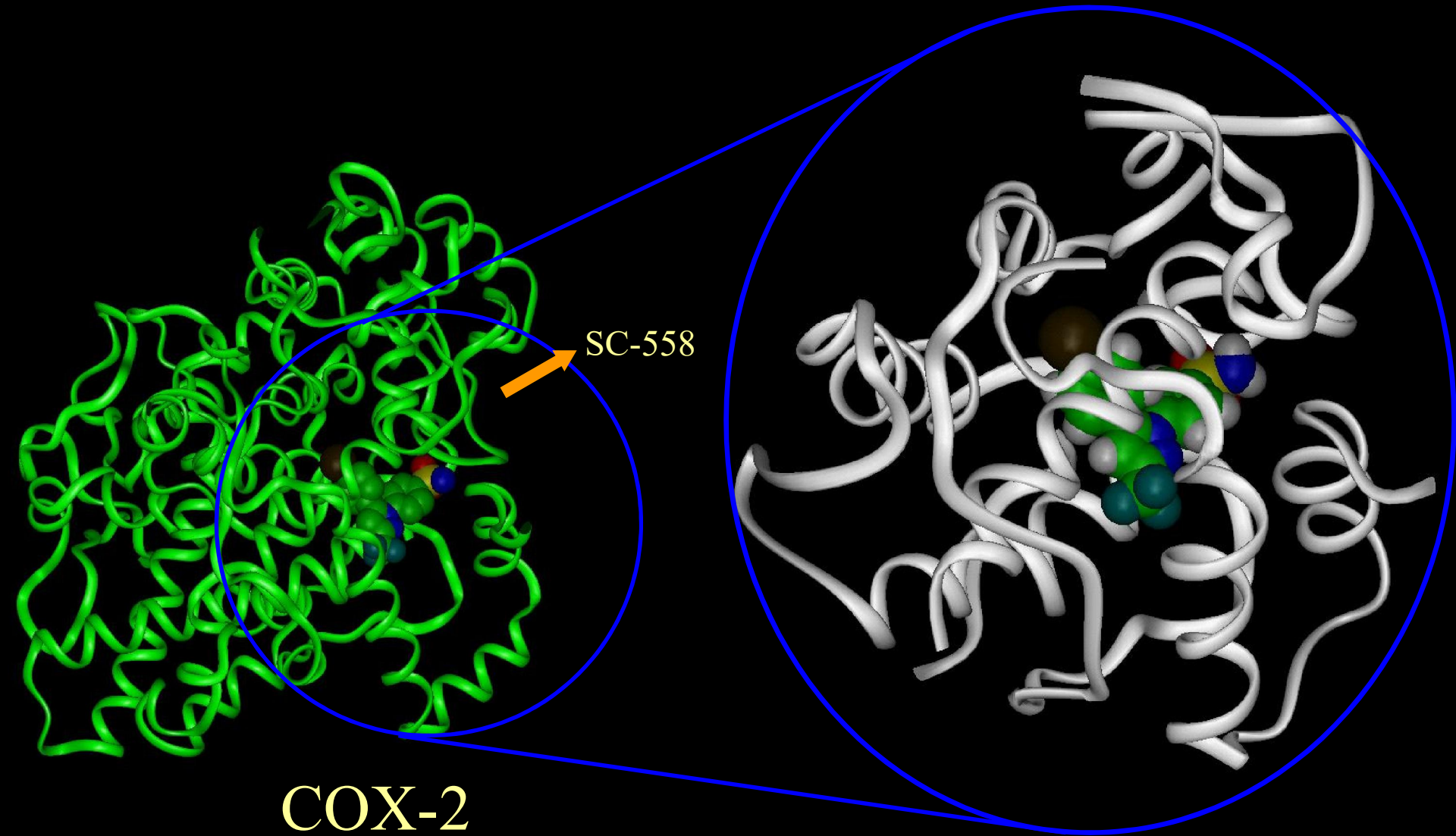
Rockwell, A.; Melden, M.; Copeland, R. A.; Hardman, K.; Decicco, C. P.; DeGrado, W. F.;
J. Am. Chem. Soc. 1996, 118, 10337

“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.**

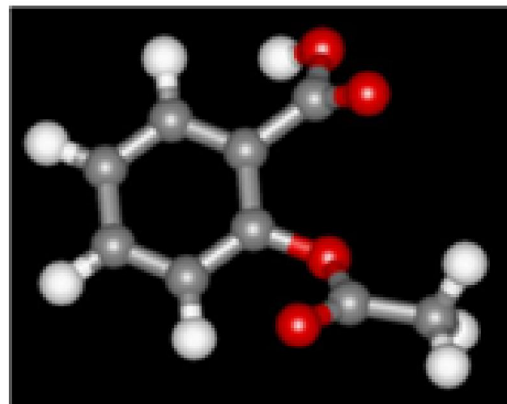
A Enzima Ciclooxygenase-2 (COX-2) e seu Sítio Ativo



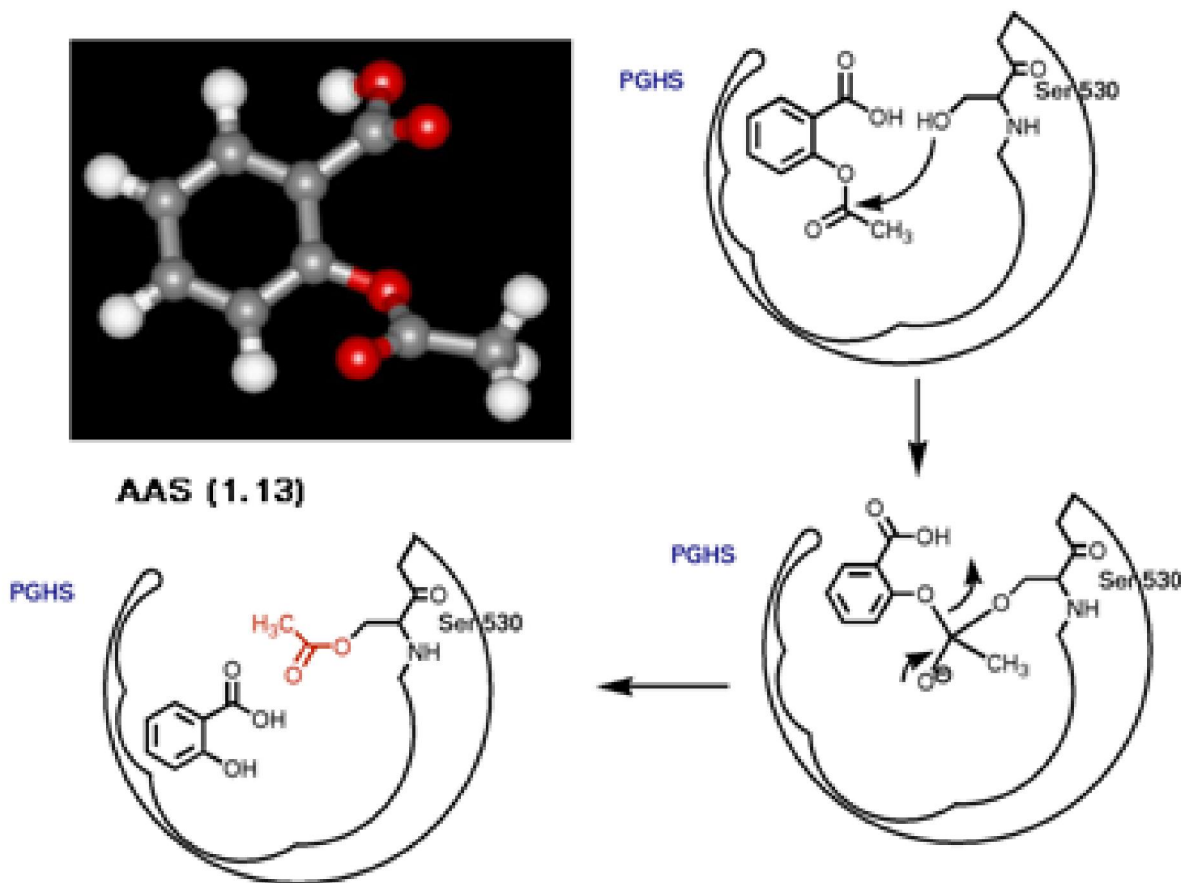
Forças Envolvidas no Reconhecimento Molecular: Micro- / Biomacromolécula

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

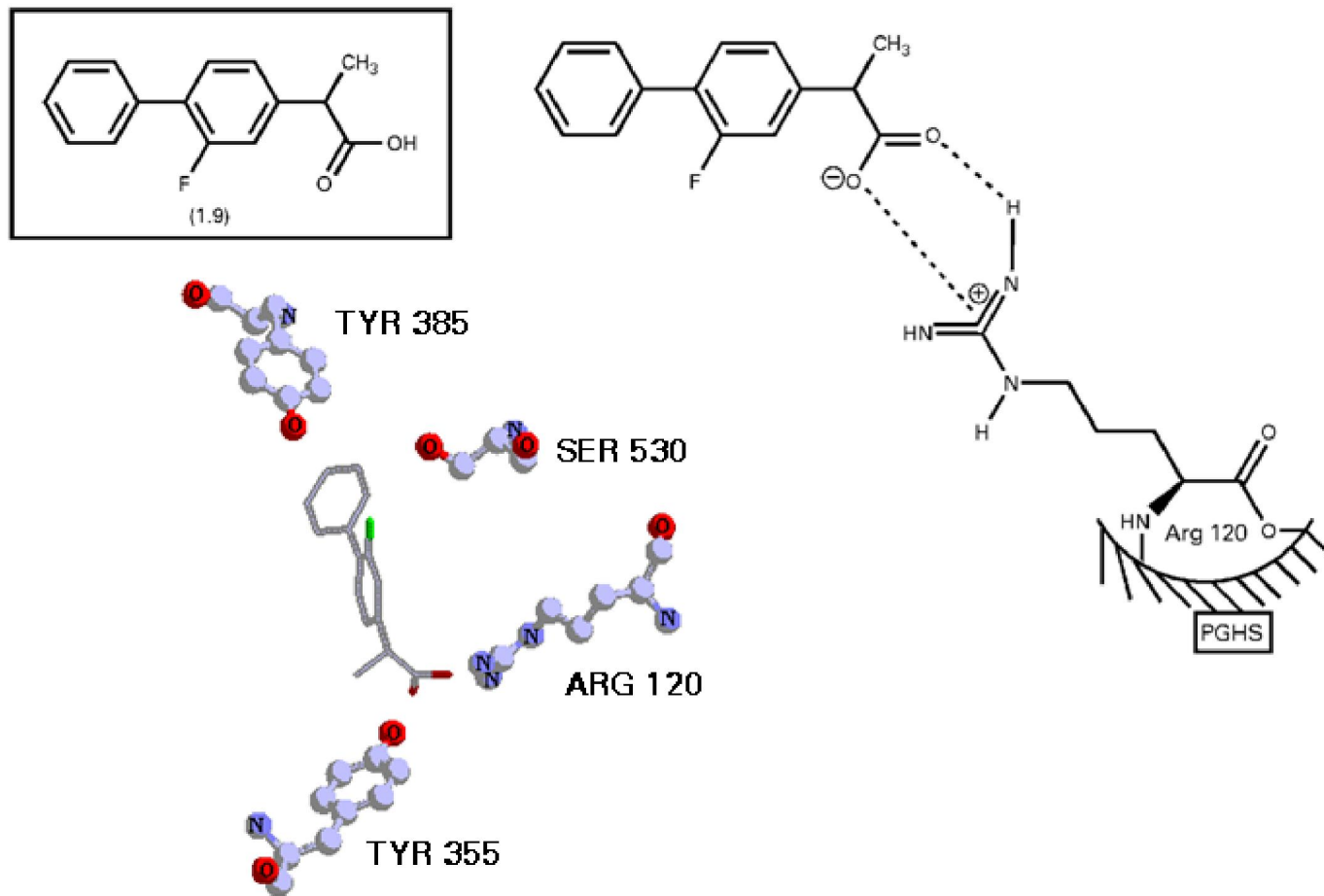
Ligações Covalentes: Reconhecimento Molecular do AAS pela PGHS (COX)



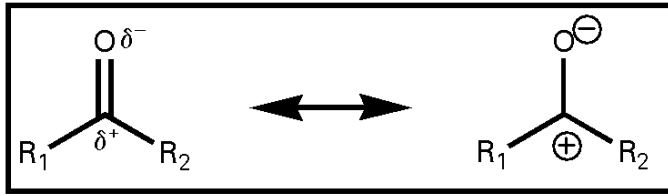
AAS (1.13)



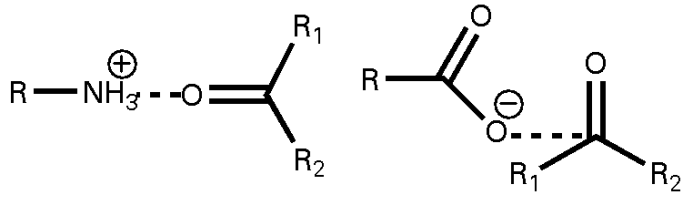
Interações Eletrostáticas: Ligação Iônica e o Reconhecimento Molecular do Flurbiprofeno pela PGHS (COX)



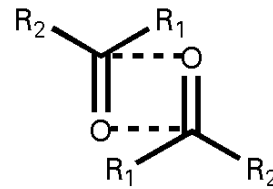
Interações Eletrostáticas: Íon-Dipolo / Dipolo-Dipolo



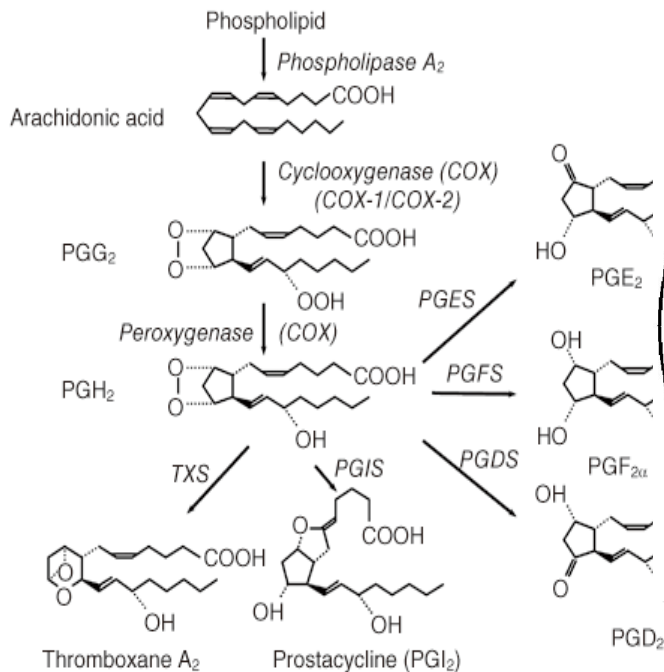
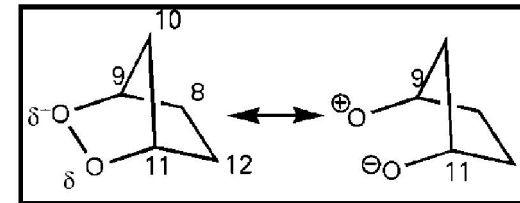
Barreiro, E. J.; Fraga, C. A. M. (2008) *Química Medicinal: As Bases Moleculares da Ação dos Fármacos*, 2ª Edição, Artmed, Porto Alegre.



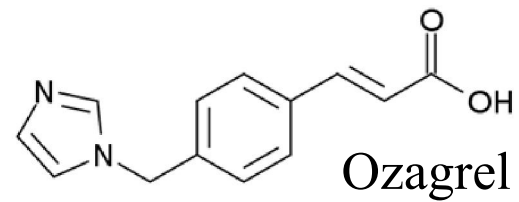
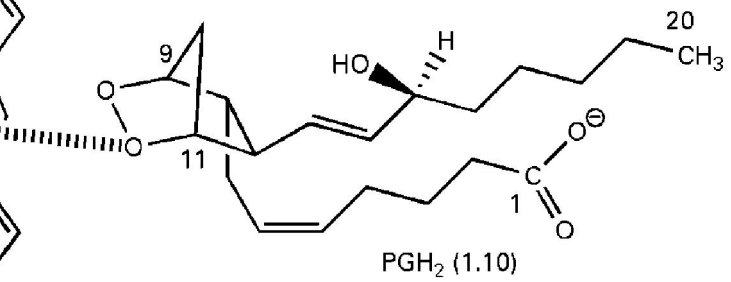
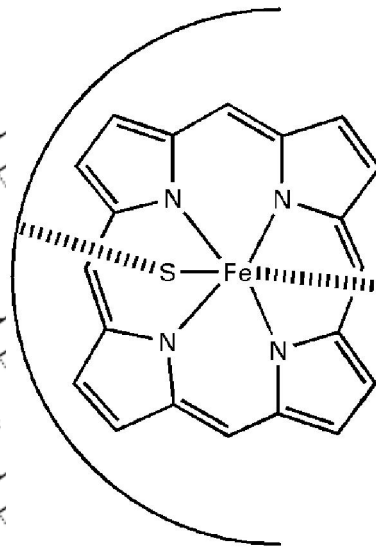
interações íon-dipolo



interações dipolo-dipolo

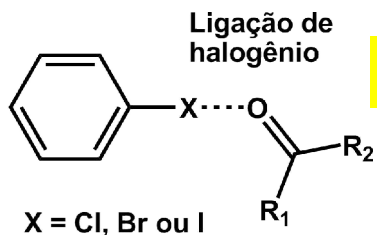
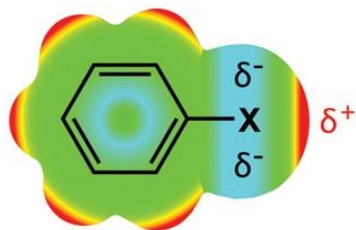


tromboxana sintase

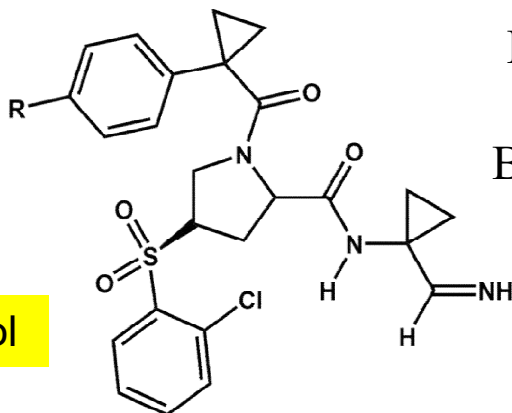


TXSi
Antitrombótico

Interações Eletrostáticas: Ligações de Halogênio



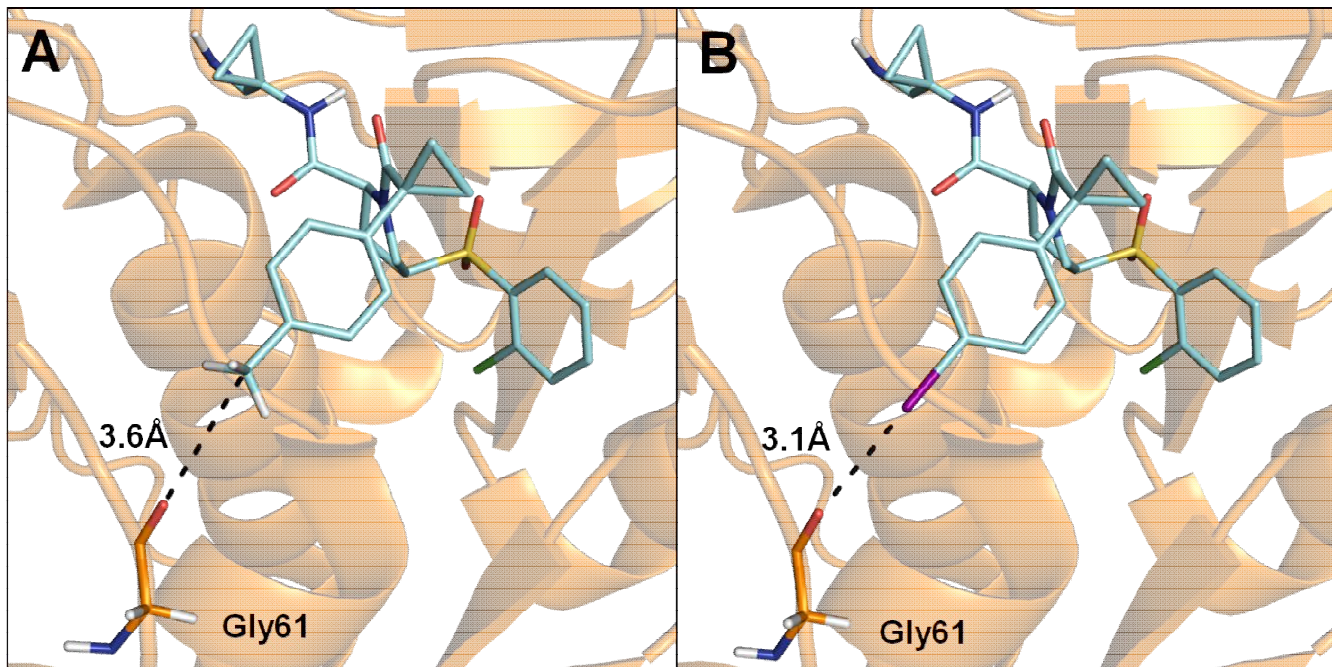
1-5 kcal/mol



R = CH₃ (1.21)
R = I (1.22)

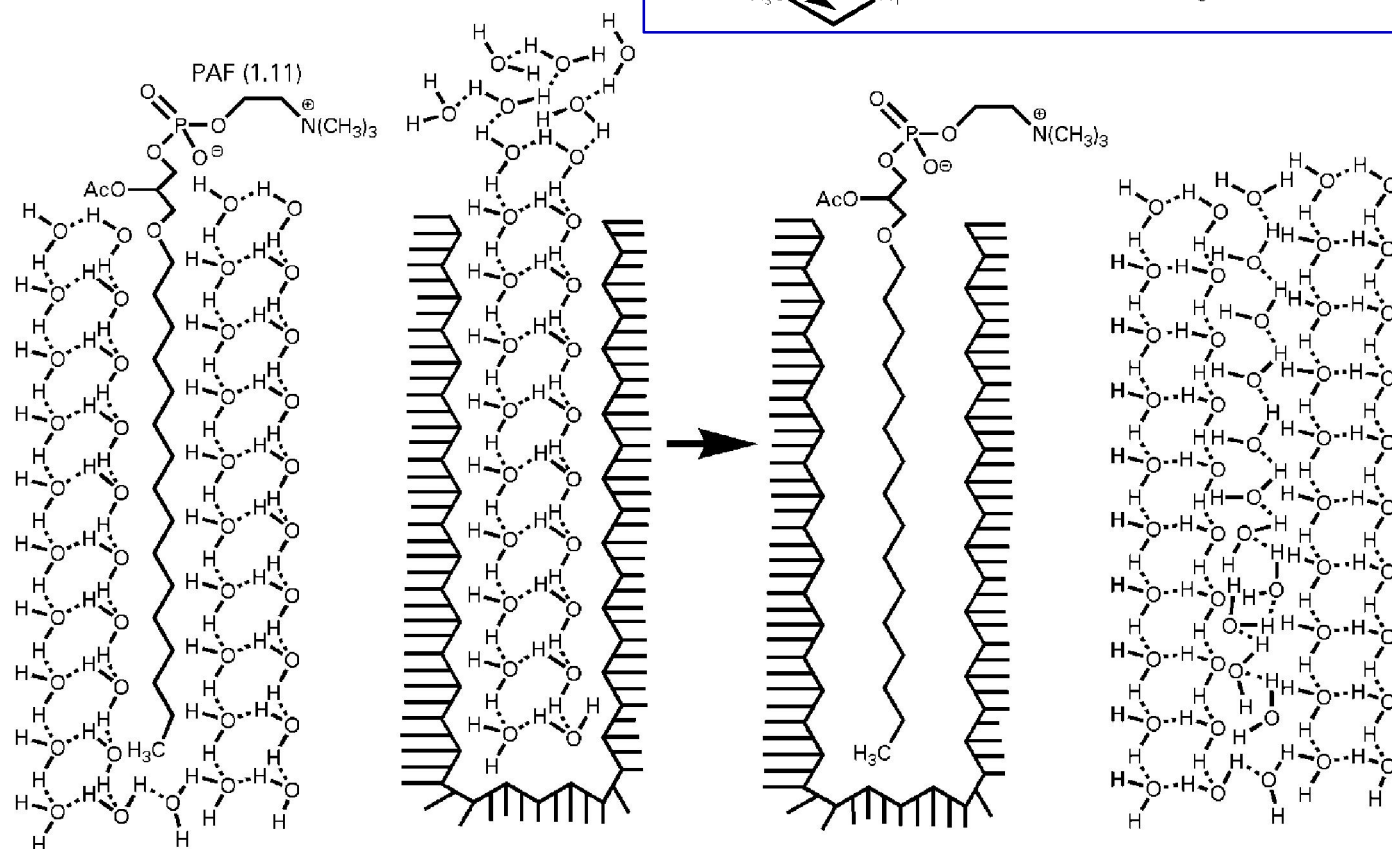
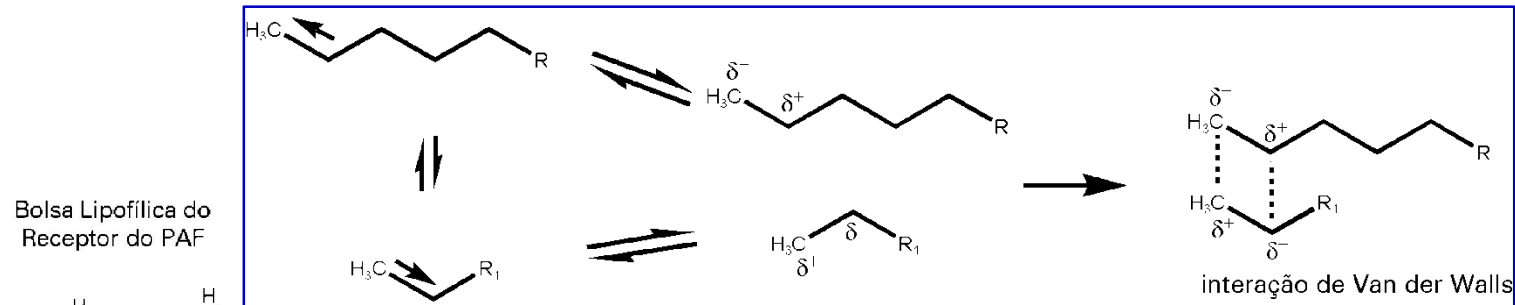
Afinidade 20 x maior

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

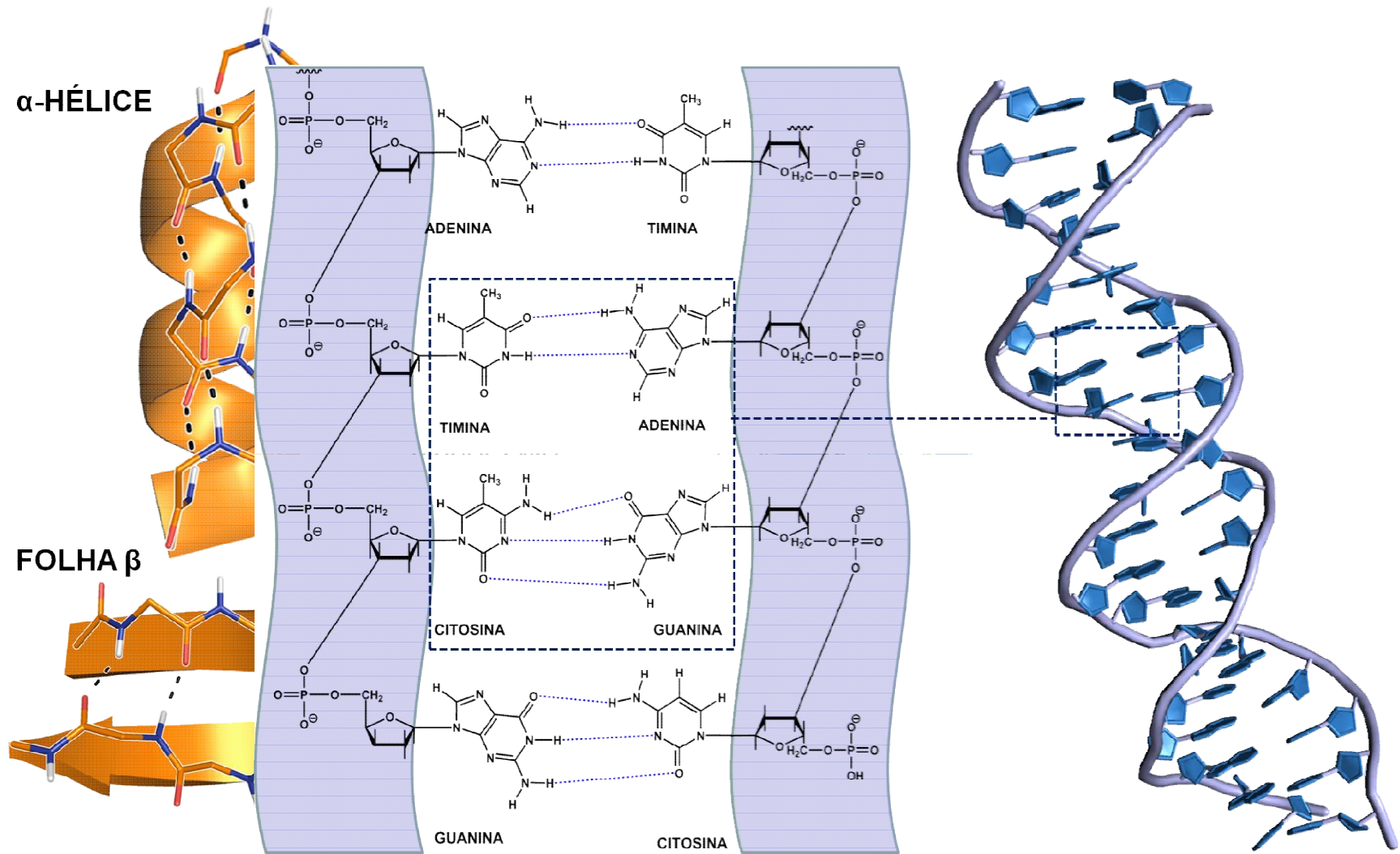


Forças de Dispersão: Interações de Van der Waals

Interações Hidrofóbicas



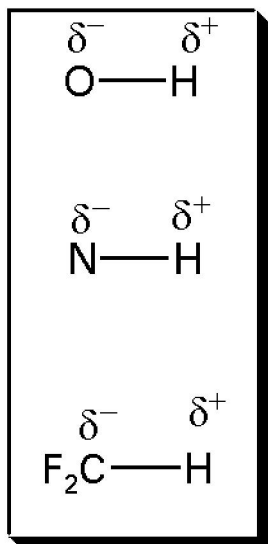
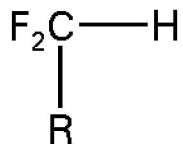
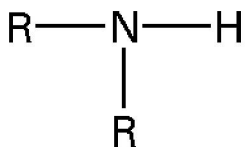
Interações de Hidrogênio



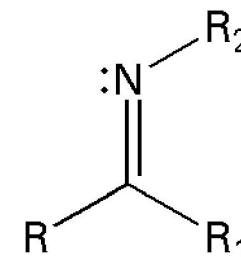
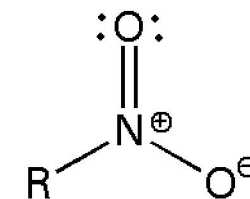
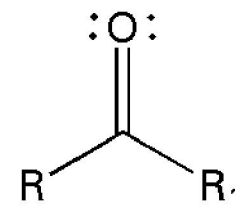
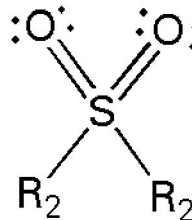
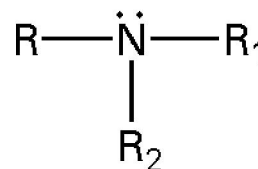
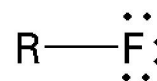
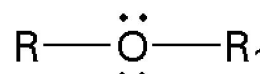
Barreiro, E. J.; Fraga, C. A. M. (2015) Química Medicinal: As Bases Moleculares da Ação dos Fármacos, 3ª Edição, Artmed, Porto Alegre.

Grupos Doadores e Aceptores de Ligações de Hidrogênio

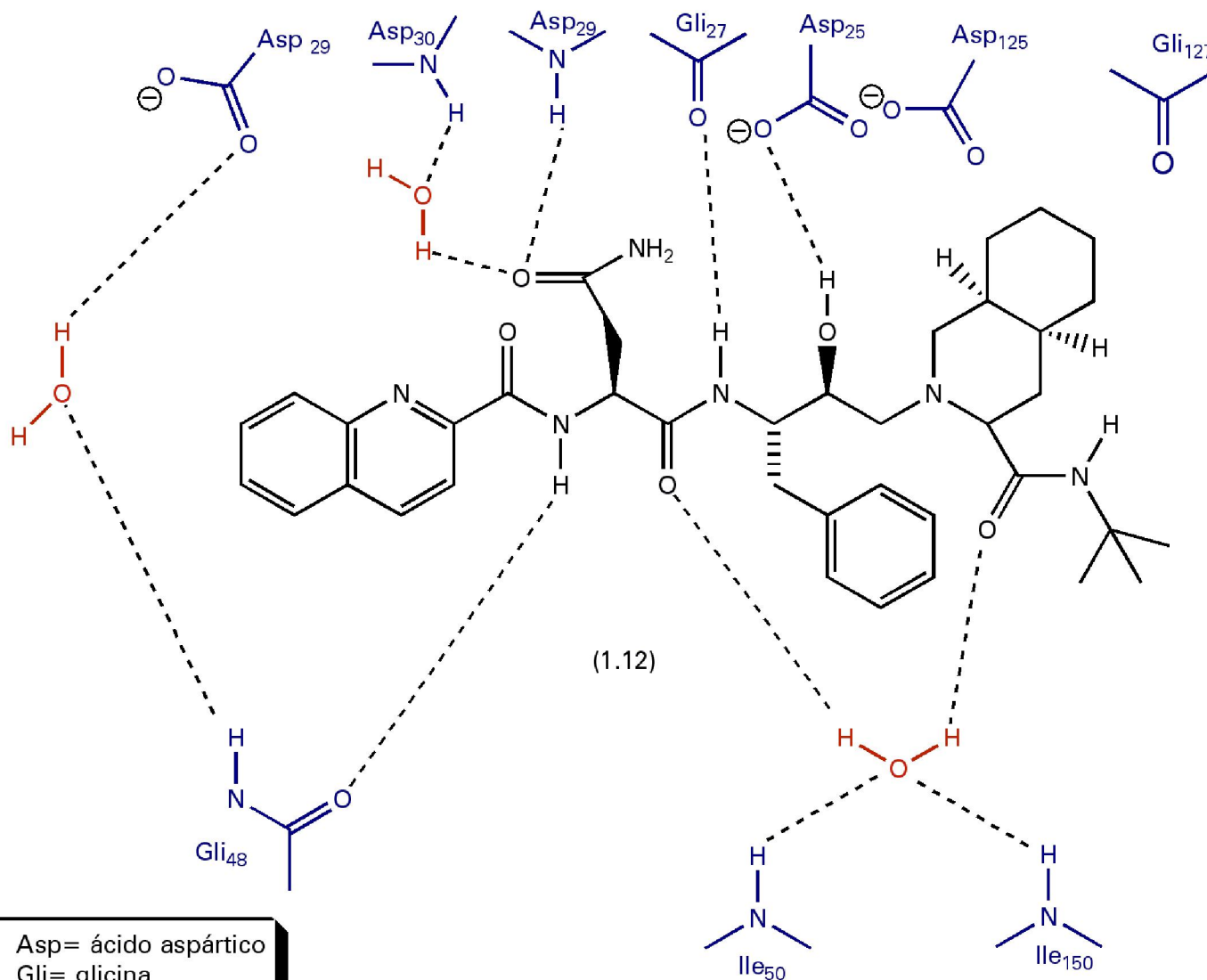
doadores de
LIGAÇÕES DE HIDROGÊNIO



aceptores de
LIGAÇÃO DE HIDROGÊNIO

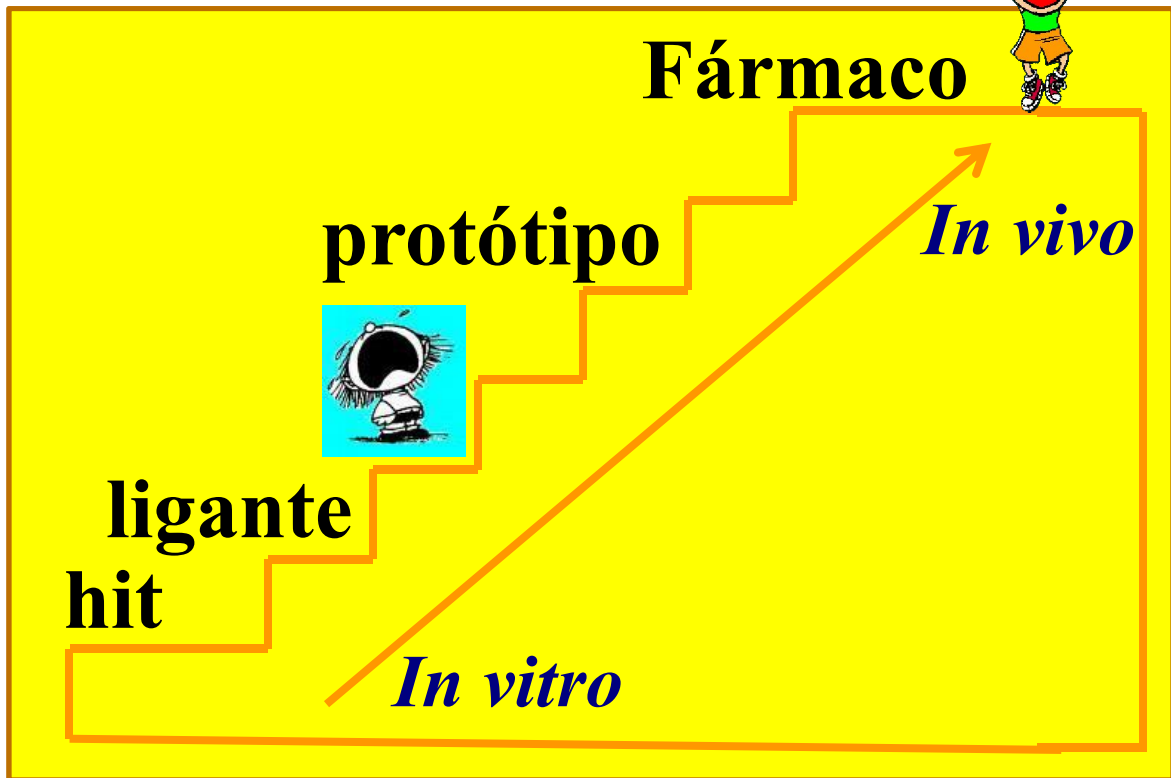


Ligações de Hidrogênio e o Reconhecimento Molecular do antiviral saquinavir pelo sítio ativo da protease do HIV-1



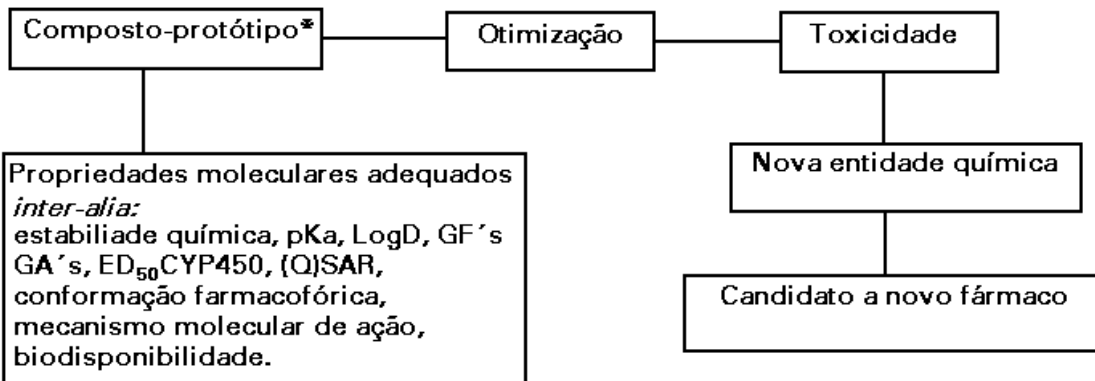
Asp= ácido aspártico
Gli= glicina
Ile= isoleucina

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



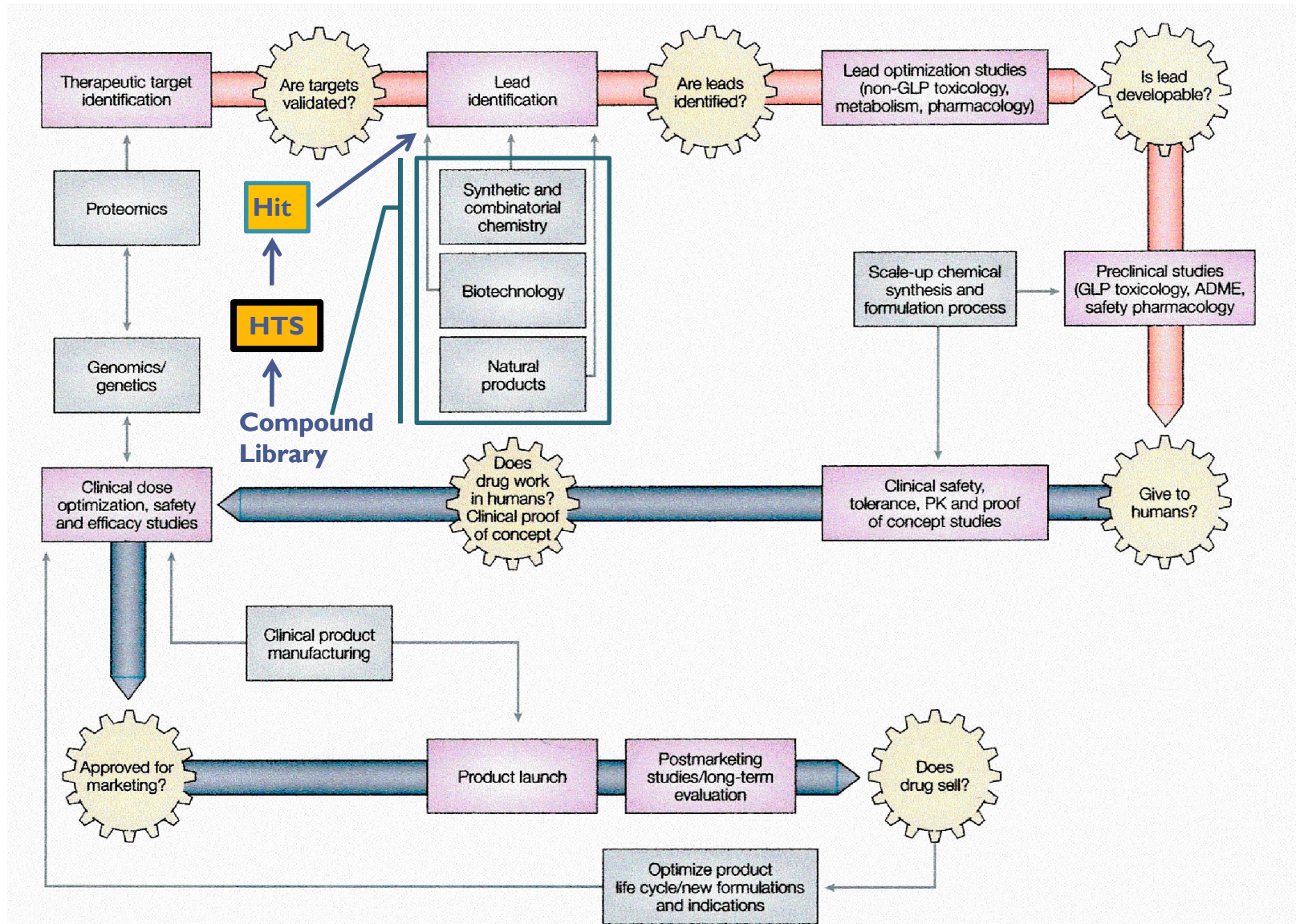
Química Medicinal

“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.

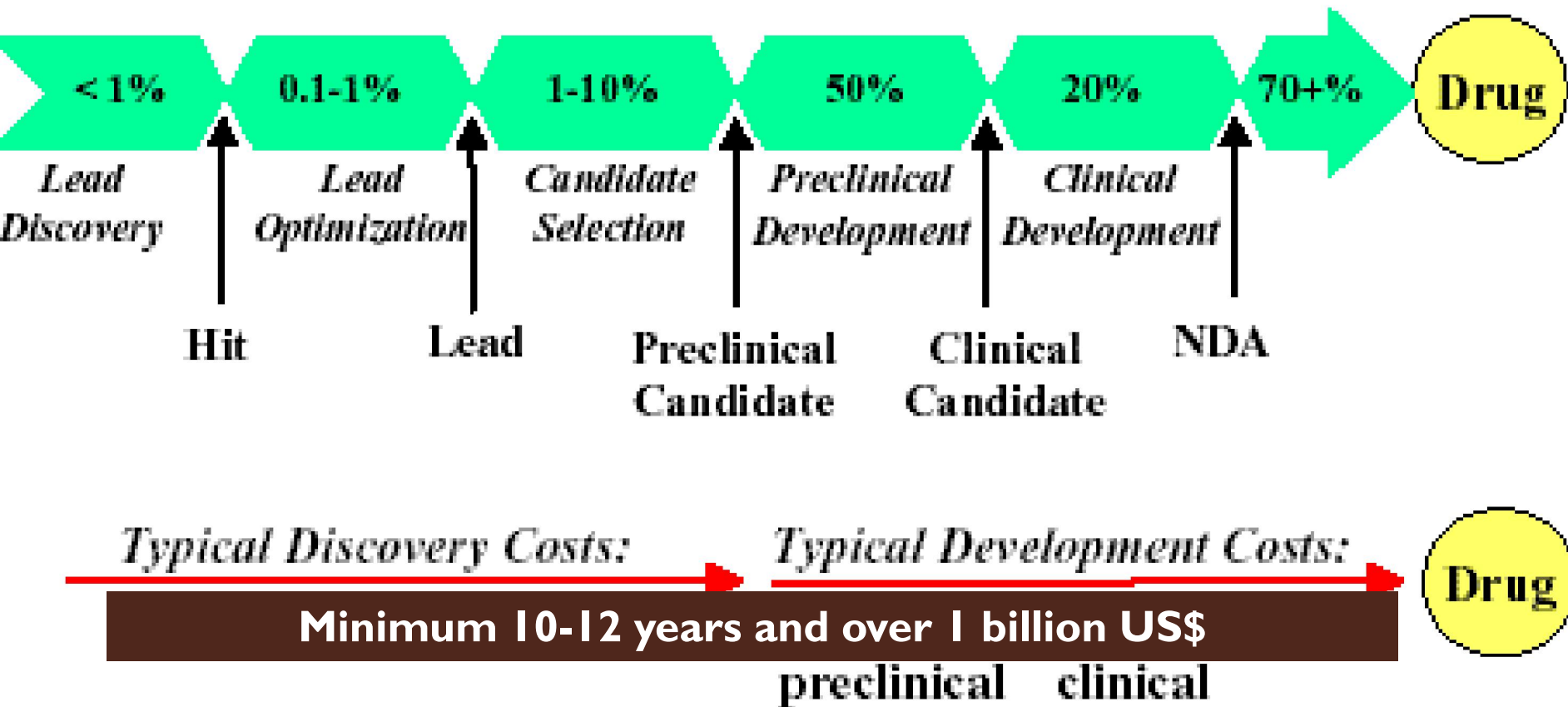
Sequência do Processo para Descoberta e Desenvolvimento de Novos Fármacos



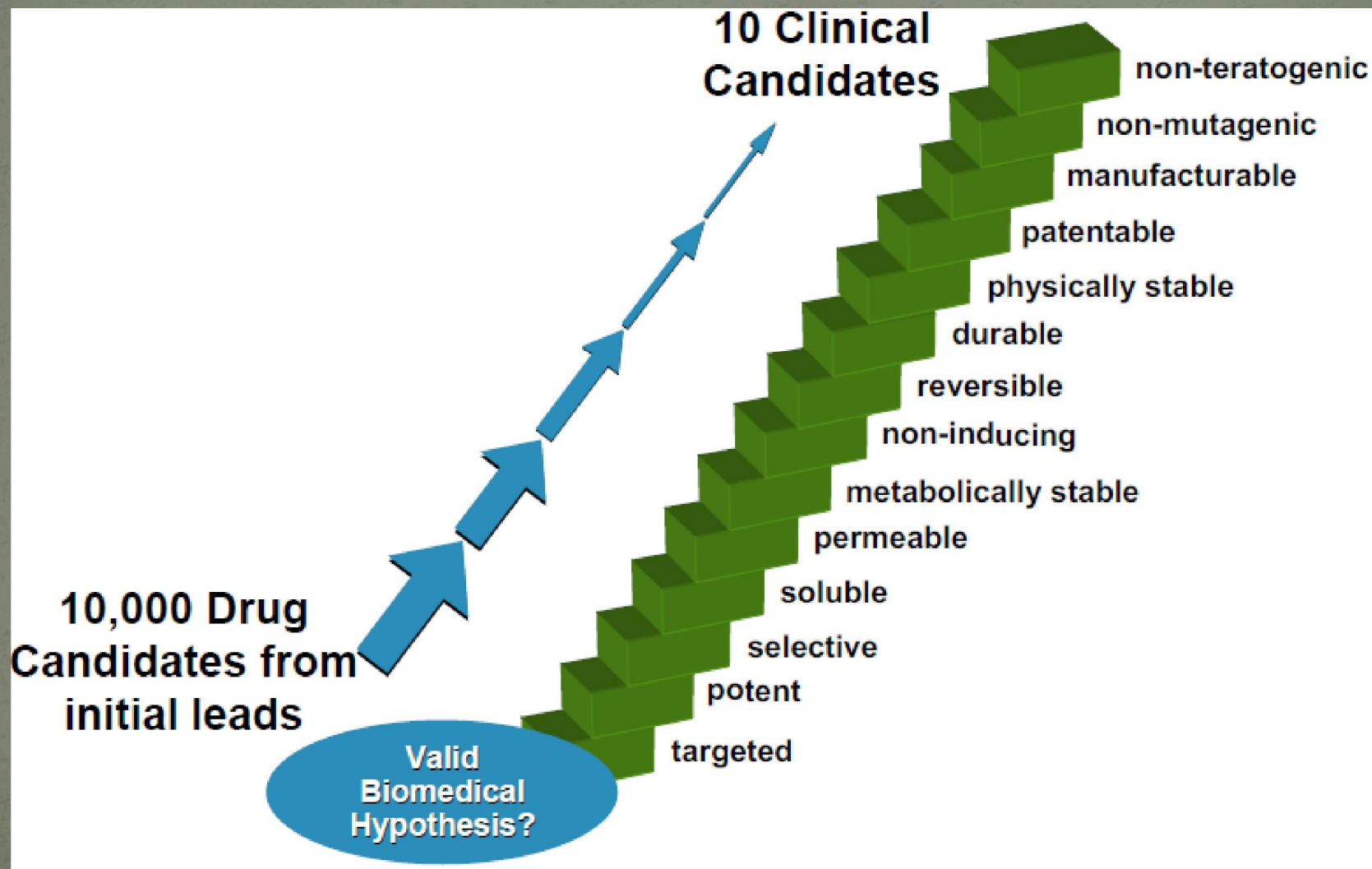
Drug Discovery and Development

A PreClinical Candidate has a 10% chance of becoming a drug

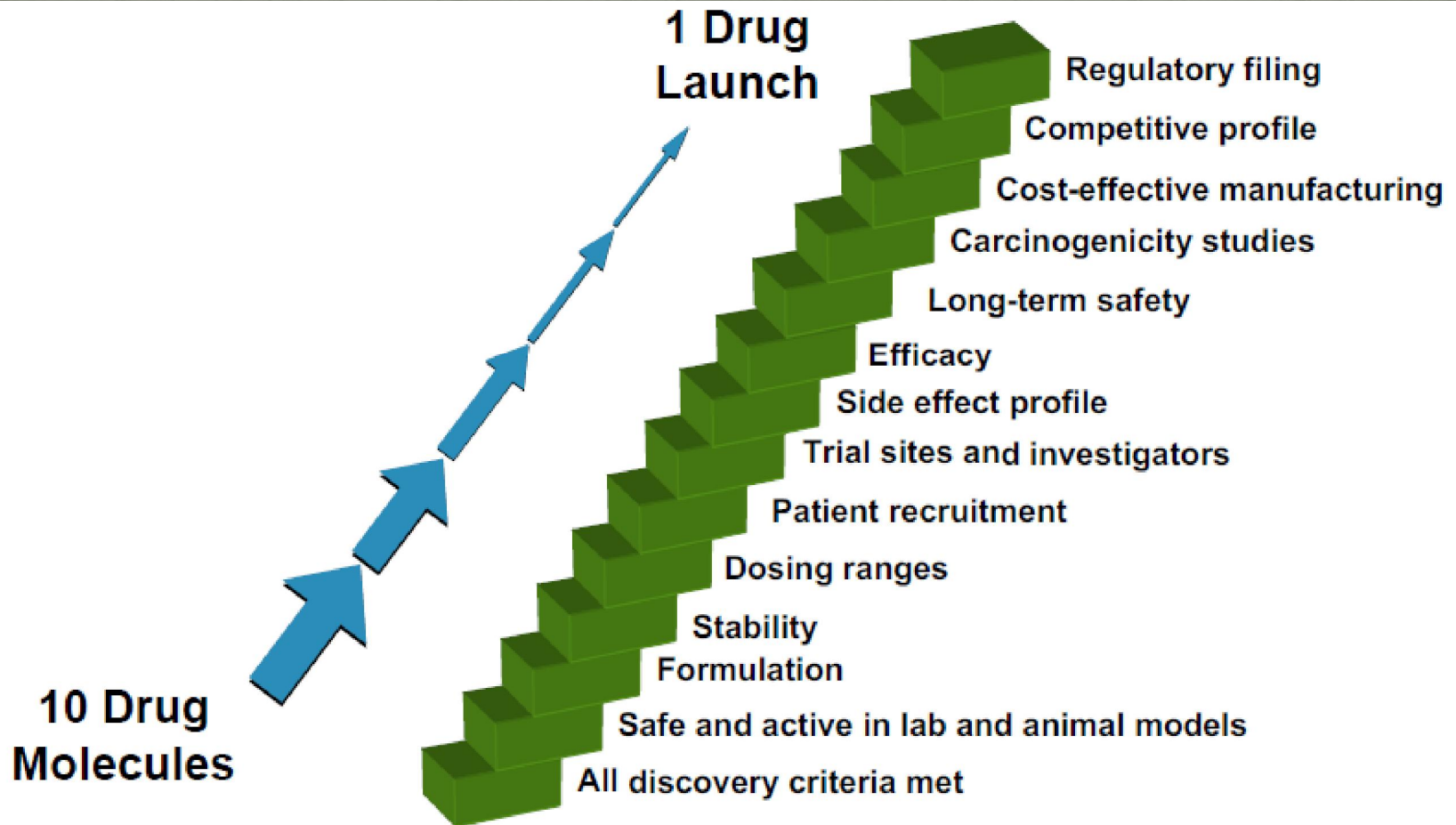
Typical Success Rates at Each Step of Drug Discovery & Development



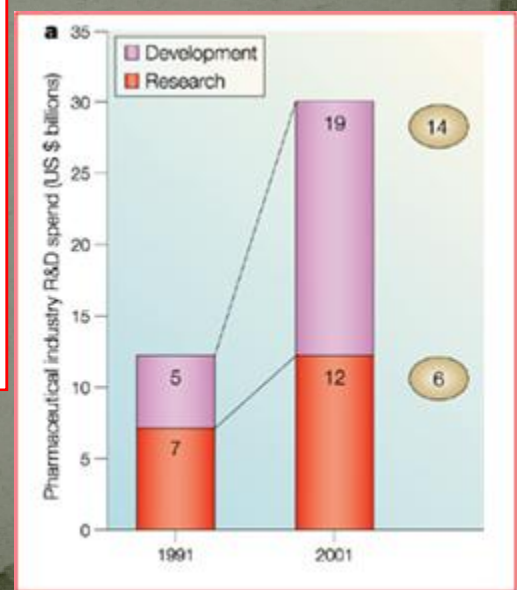
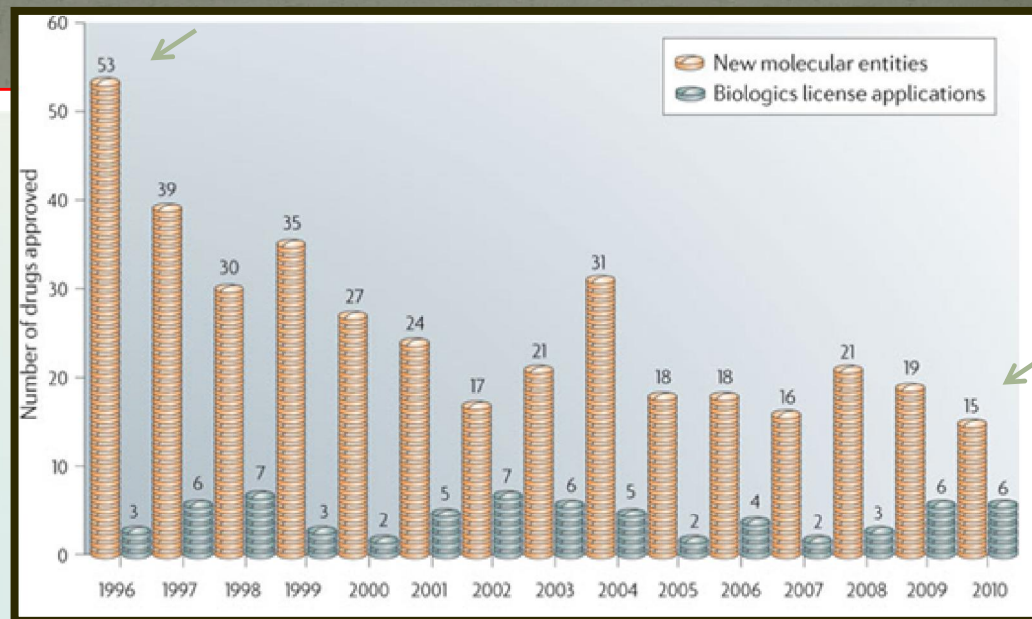
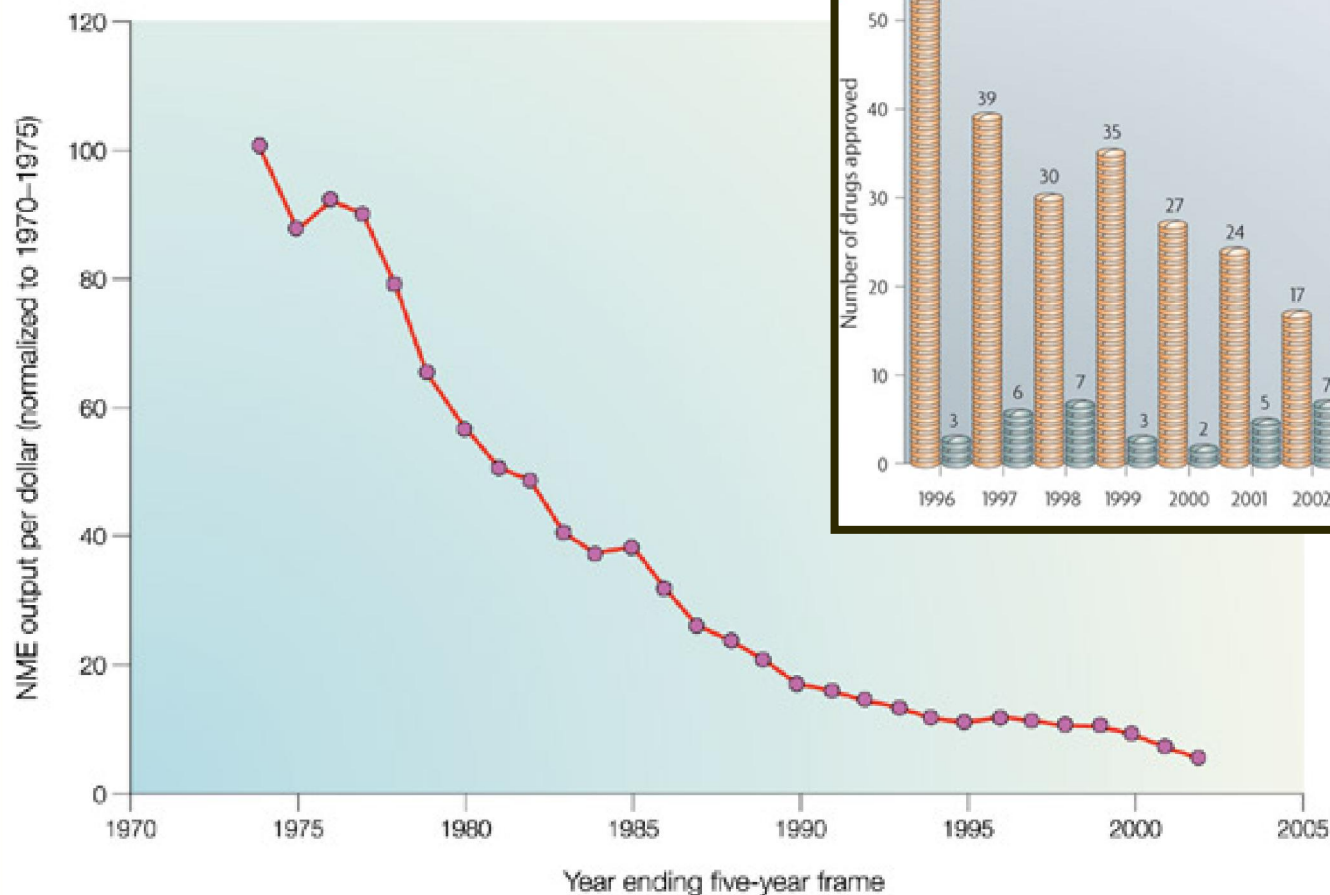
Principais características necessárias à um novo candidato as Fases de Triagem Clínica



Outras características necessárias à um novo candidato a Fármaco



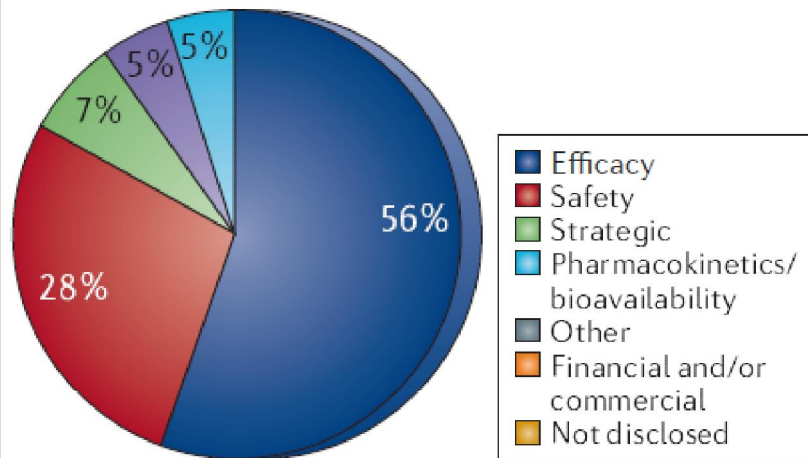
Pesquisa e Desenvolvimento de Novos Fármacos: Sinais de Declínio na Produtividade das “Big-Pharmas”



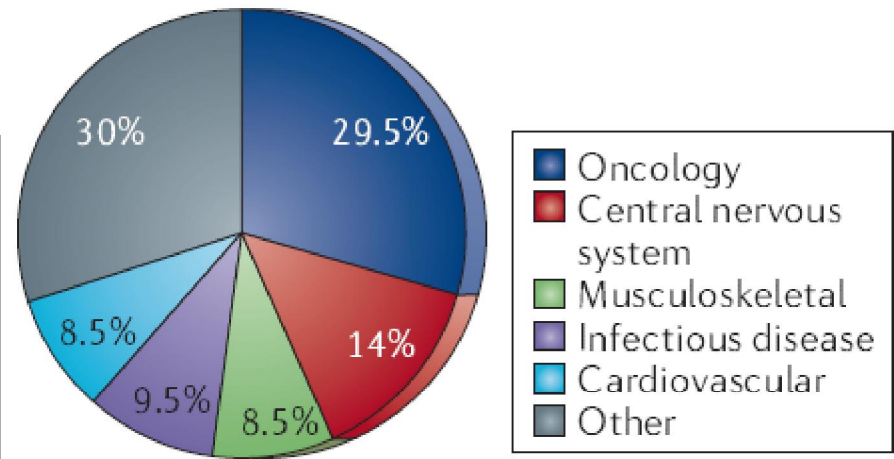
Booth & Zemmel (2004) *Nature Rev. Drug Discovery* 3, 451;
 A. Mullard (2011) *Nature Rev. Drug Discovery* 10, 82.

Principais Razões para Falhas no Desenvolvimento de Fármacos

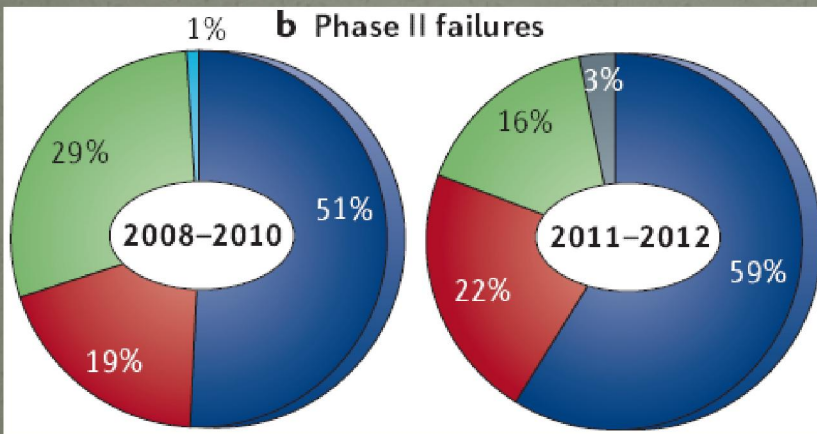
a Causes of failure



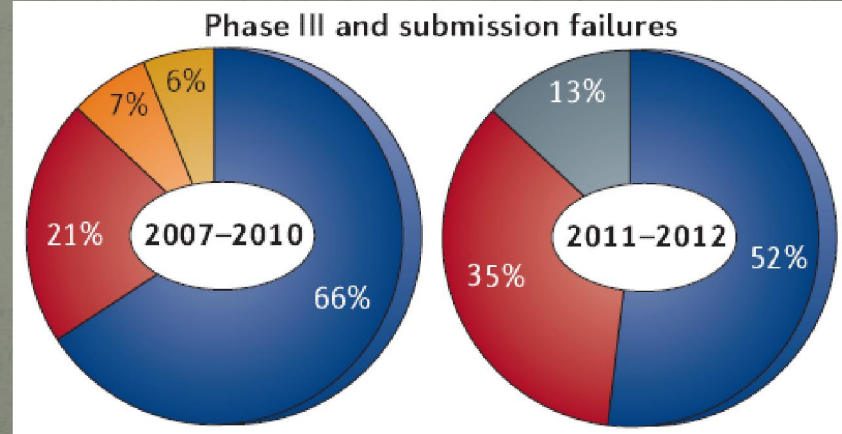
Failure by therapeutic area



b Phase II failures



Phase III and submission failures



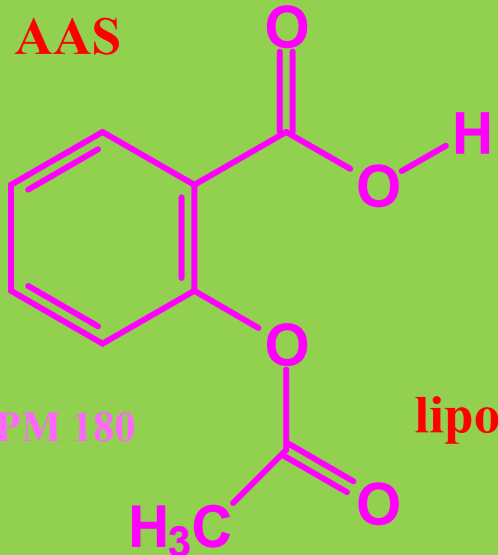
Desafios na Busca por Novos Fármacos: Acelerar o processo/reduzir custos

É como procurar uma agulha no palheiro....



xenobiótico

AAS



PM 180

H₃C

Coeficiente de partição

0,100g
0,55 mM

absorção

lipossolúvel

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

Fatores Farmacocinéticos

BIOFASE

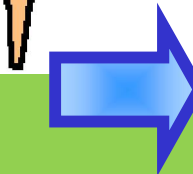
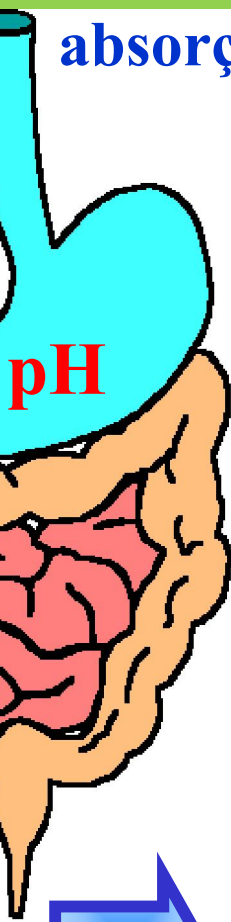
Fármaco:
ativo
inativo

Bioativação
Biotransformação

Fígado

Retículo microssomal

Sangue



ADME

Rins

URINA

eliminação

hidrossolúvel

Enzimas oxidativas
Citocromo P-450

p.o.



Farmacocinética e Metabolismo

Farmacocinética
Biodisponibilidade

Absorção
Distribuição
Metabolismo
Excreção

Metabolismo
de
Fármacos

☞ **Fase 1** Introdução de grupos Funcionais → Oxi-Red, Hidrólise, Hidroxilação, *N,O*-dealquilação.

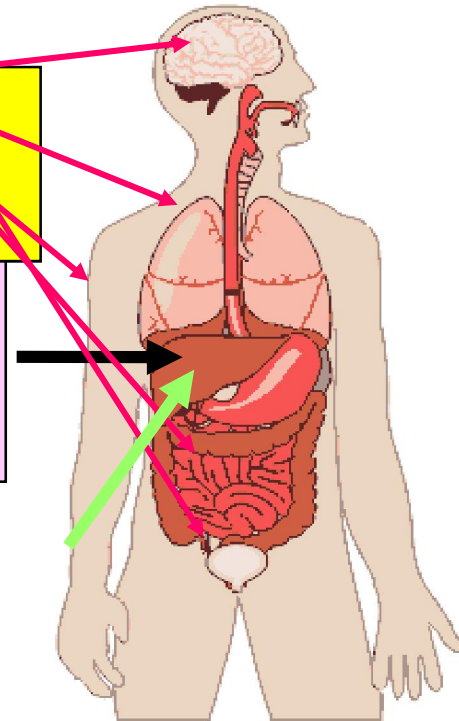
CYP450

☞ **Fase 2** Conjugação
Glucuronidação,
Sulfatação,
Glicosilação,
Acetilação, Metilação.

**Enzimas Microsossomais
Extrahepáticas
(oxidação, conjugação)**

Enzimas Microsossomais Hepáticas
(oxidação, conjugação)
Reações Oxidativas são mediadas por
Citocromo P450

Enzimas Hepáticas não-microsossomais
(acetilação, sulfatação, GSH,
álcool/ aldeído desidrogenase,
hidrólise, ox/red)



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

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

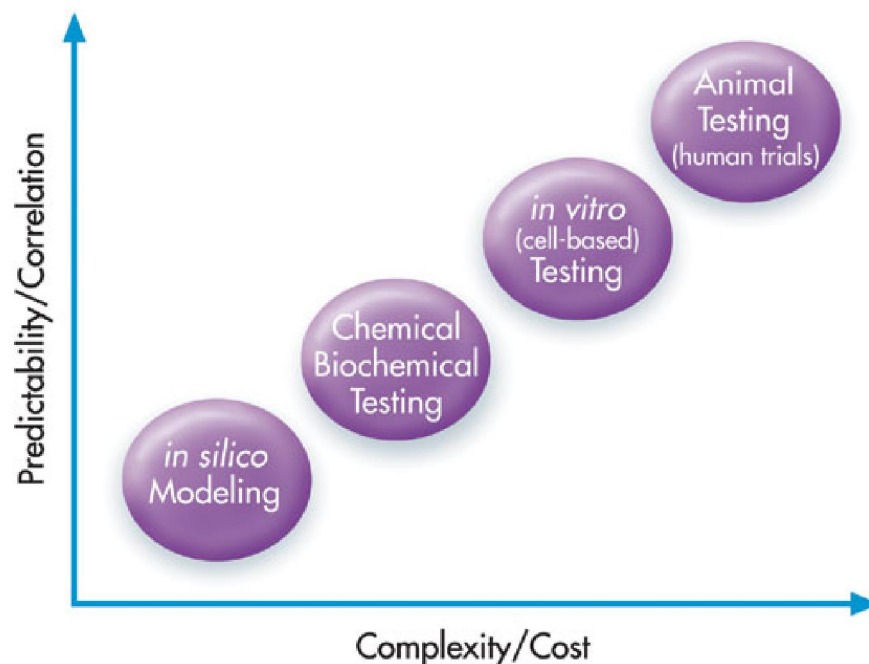
- Functional
- *Secondary (behavioural, chronic)

Toxicity

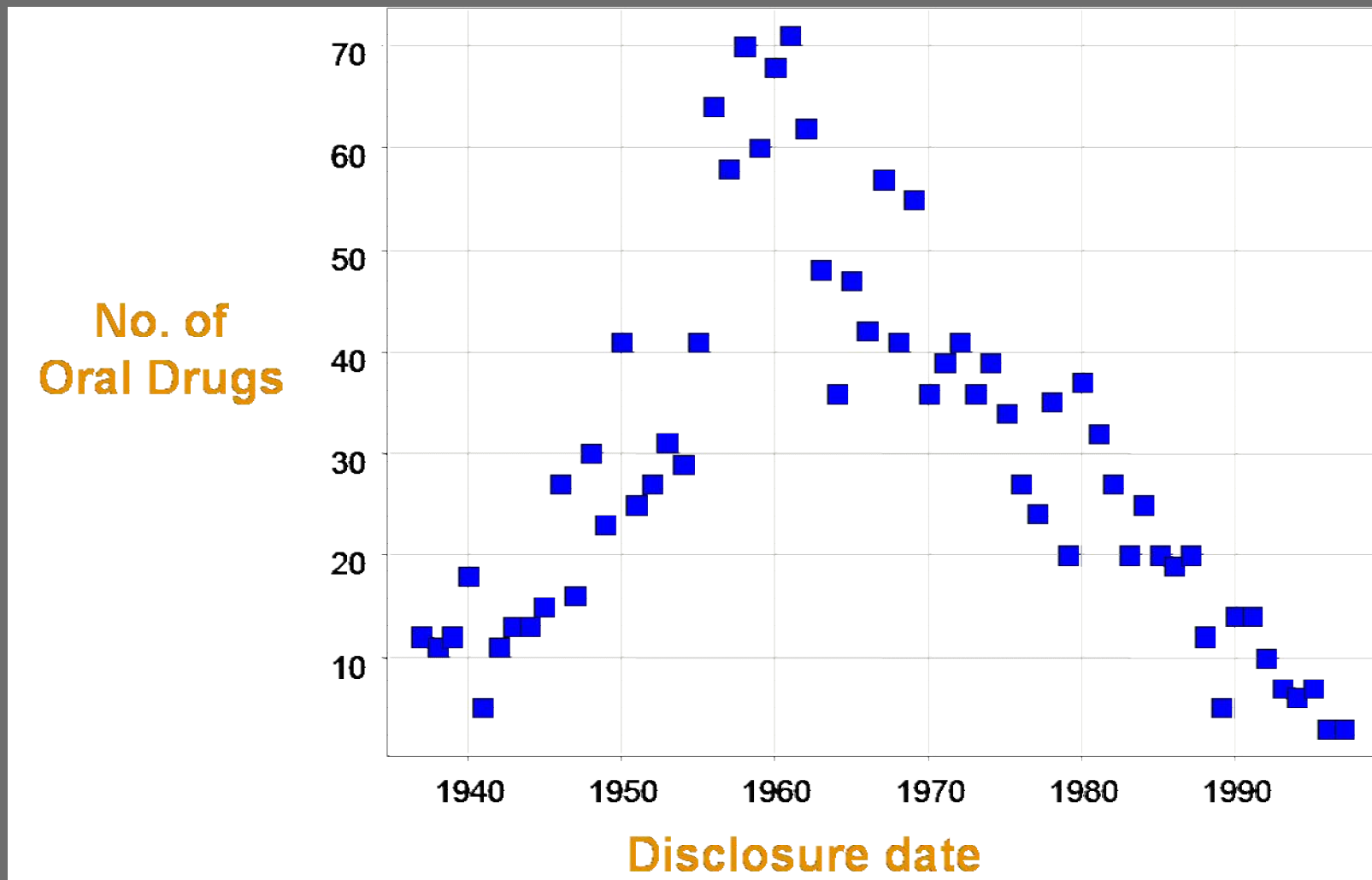
- *Ames test
- Micronucleus test
- hERG half-maximal inhibitory concentration (IC_{50})
- P450 induction
- Broad screening
- *Others (depending on project)

Ensaio preditivo de propriedades "drug-like"

Cost/Value Relationship of ADME Screening



Número de Fármacos Ativos por via Oral Lançados de 1937-1997:



Previsão de Propriedades Fisicoquímicas

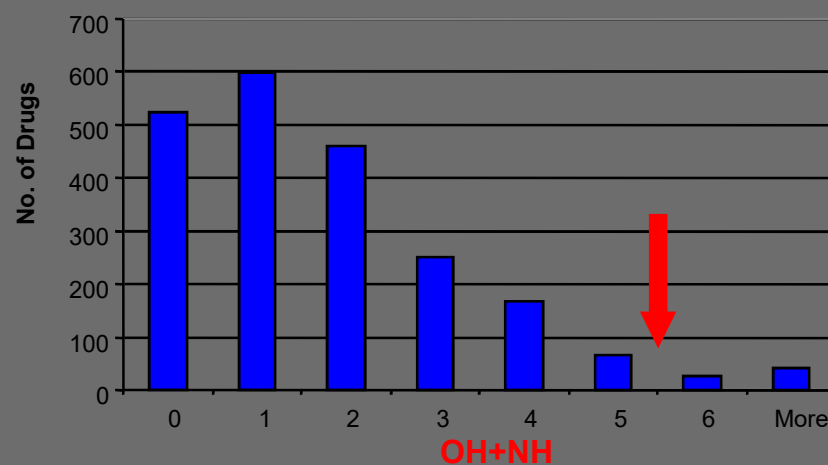
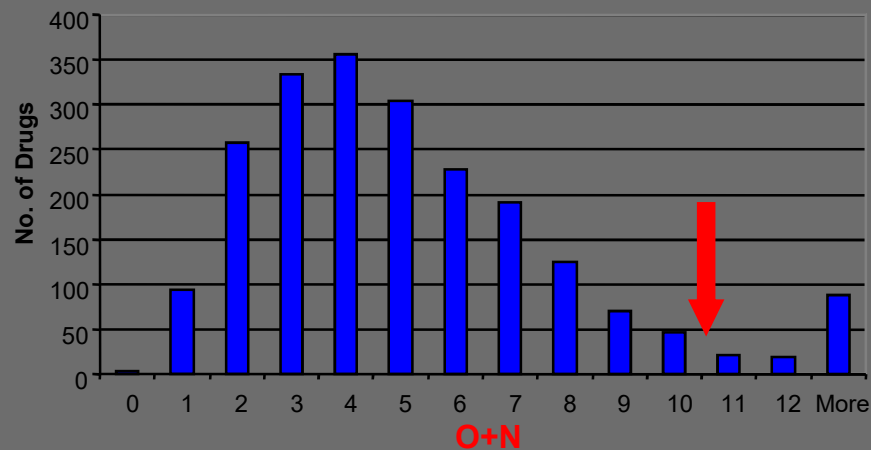
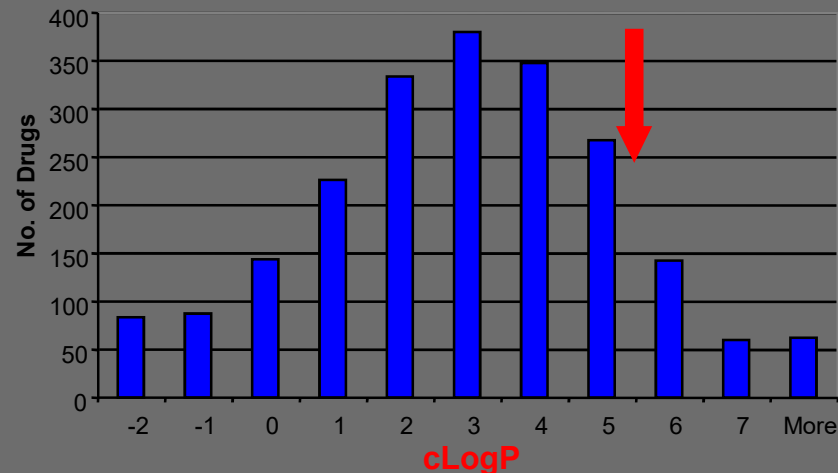
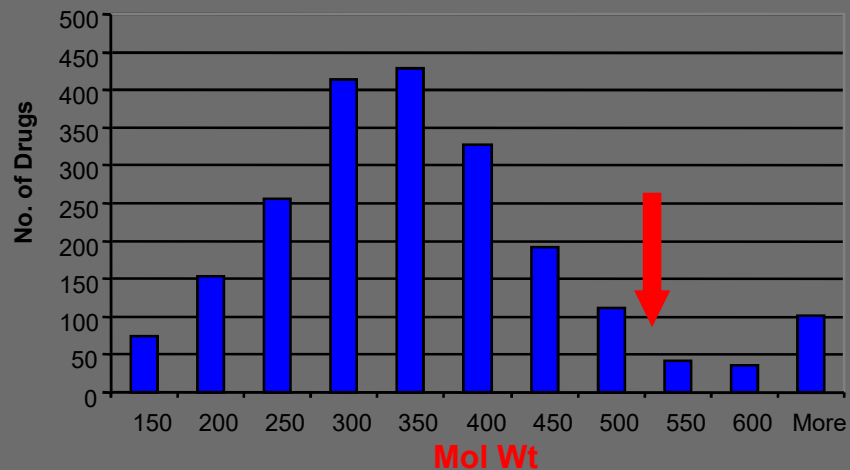
‘Drug-Like’ :

Lipinksi’s ‘Rule of 5’ - from World Drug Index

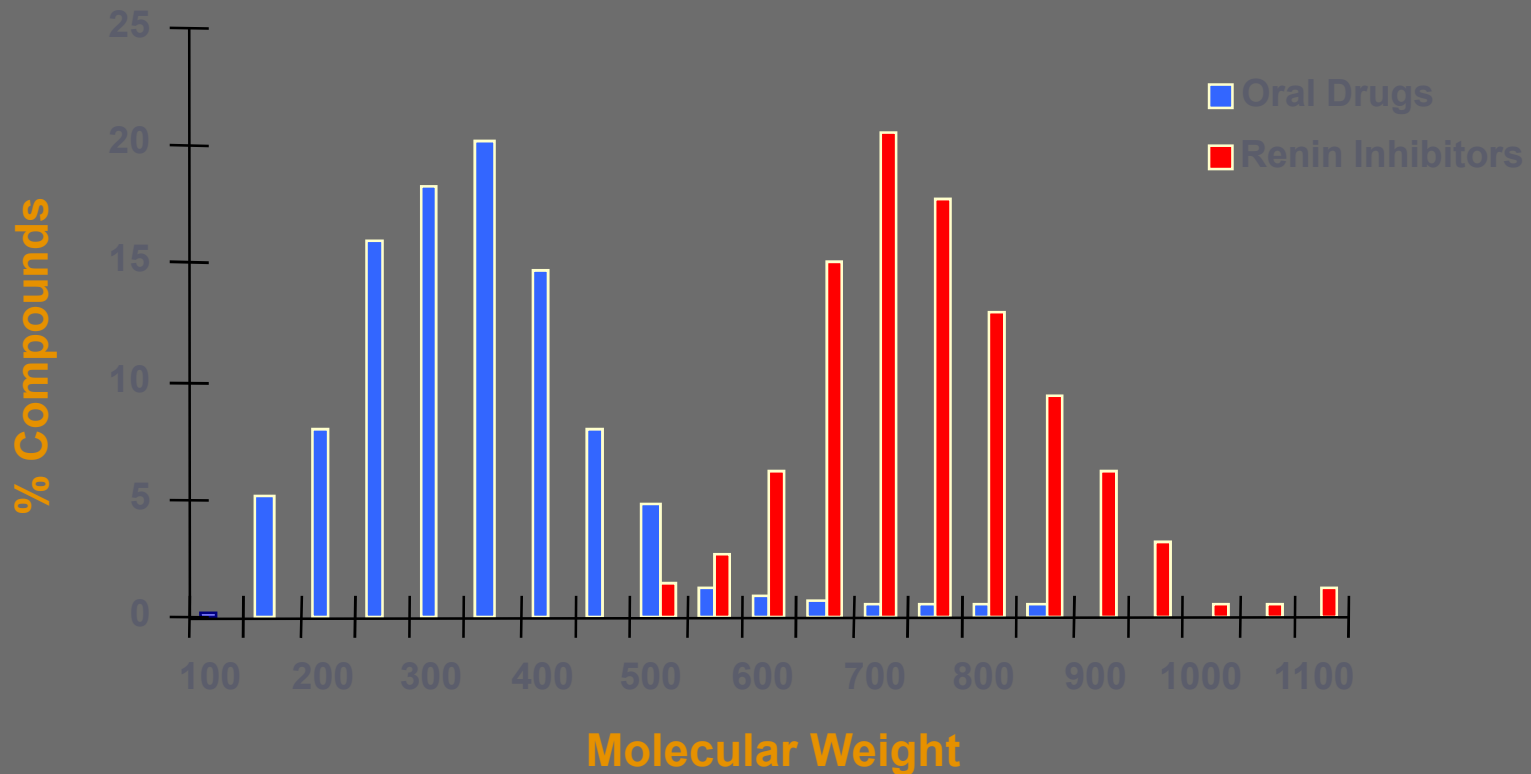
Adv. Drug. Del. Revs. 1997, 23, 3

- 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/H₂O) is <5
- Substrates for biological transporters
are exceptions

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



Exemplo Ilustrativo: Inibidores de Renina

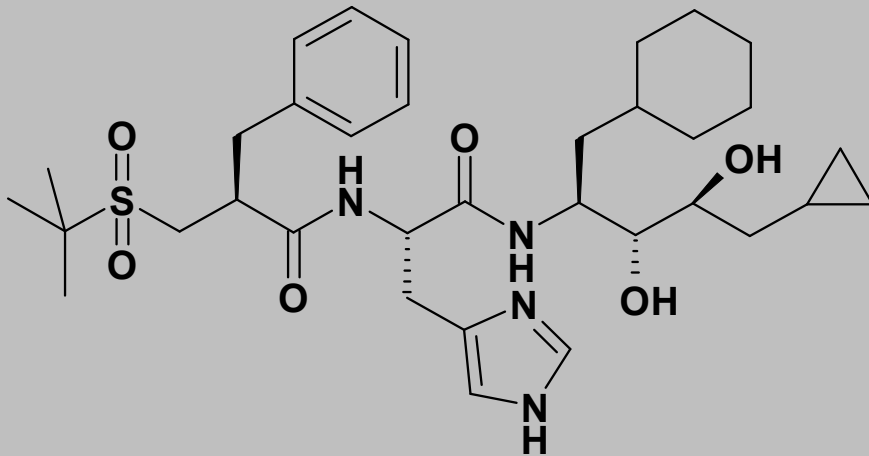


Esforço Maciço nas Principais "Big-Farmas" entre 1980s & 1990s

Nenhum inibidor de renina conseguiu entrar em Fase II

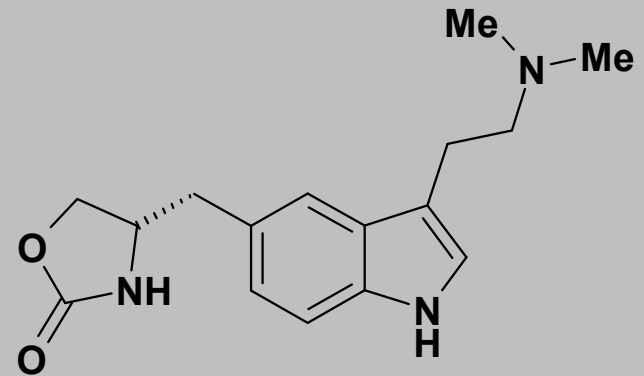
Falha devido a baixa biodisponibilidade e custo elevado (padrão peptídico)

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



Ro 42-5892

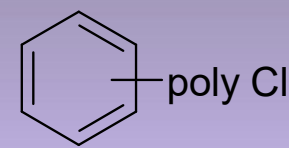
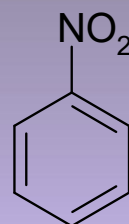
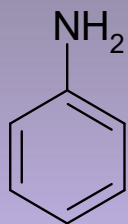
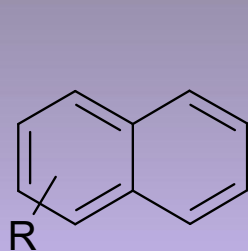
Inibidor de Renina Típico
Falhou na Fase
de DesenvolvimentoMol
Wt = 645



Zolmitriptan

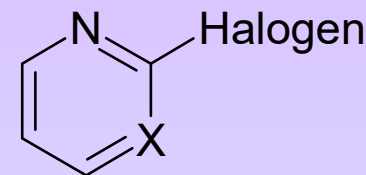
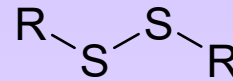
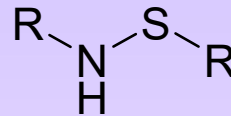
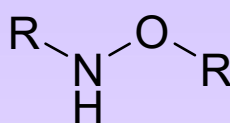
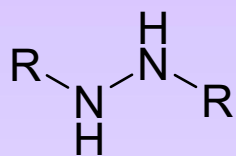
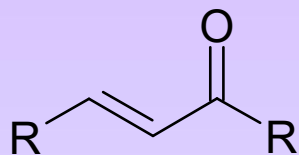
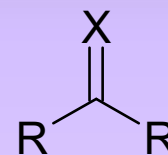
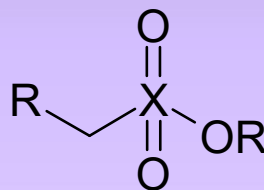
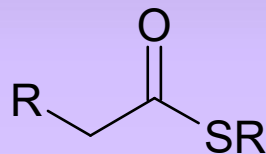
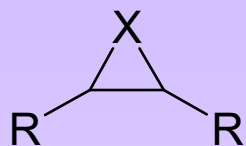
Agonista de Receptores 5-HT1D
Ativo por via oral
Comercializado para Tratamento
da Enxaqueca
Mol Wt = 287

Grupos Toxicofóricos – Exemplos a serem evitados em Compostos Protótipos



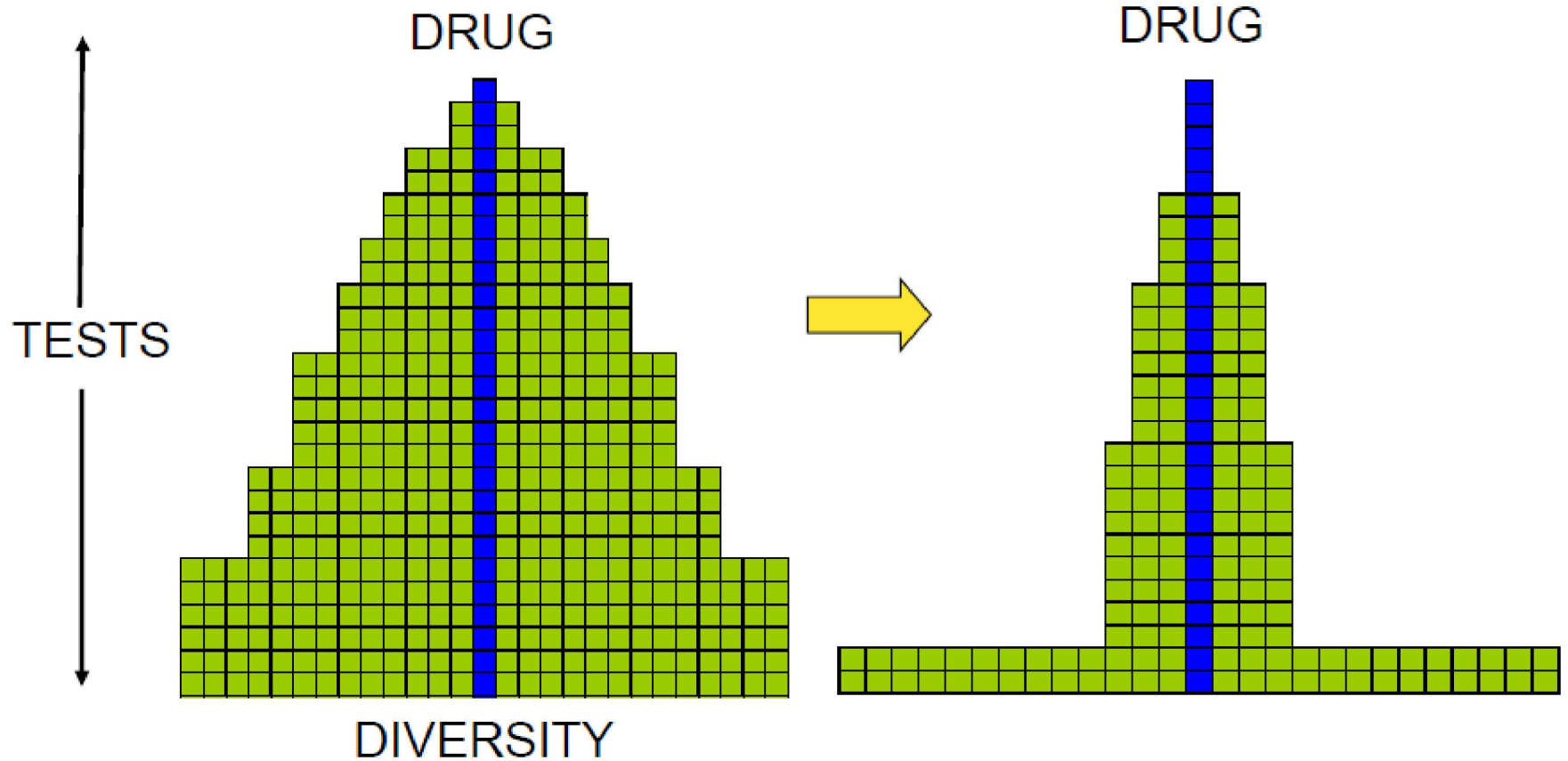
Possíveis Mutagênicos

Frequentemente tóxicos



Eletrófilos & Espécies Reativas Quimicamente

Desafios para o Processo de Descoberta de Fármacos



Inovação e o Mercado Farmacêutico Mundial

(US\$ 936 bilhões - em 2014)

Name			Sales (\$ Billion)	
Rank	Generic	Brand®	Disease	2014
1	Adalimumab	Humira	RA, CD, Ps	11.84
2	Insulin Glargine	Lantus	Diabetes	10.33
3	Sofosbuvir	Sovaldi	Hepatitis C	9.37
4	Aripiprazole	Abilify	Schizophrenia	9.28
5	Etanercept	Enbrel	RA, CD, Ps	8.70
6	Fluticasone /Salmeterol	Seretide	Asthma / COPD	8.65
7	Rosuvastatin	Crestor	Cholesterol	8.43
8	Inflimixab	Remicade	RA, CD, Ps	8.09
9	Esomeprazole	Nexium	Ulcer	7.68
10	Rituximab	Mabthera	Cancer	6.55
11	Bevacizumab	Avastin	Cancer	6.07
12	Pregabalina	Lyrica	Neuropathic Pain	6.00
13	Traztuzumab	Herceptin	Cancer	5.56
14	Tiotropium Bromide	Spiriva	COPD	5.48
15	Sitagliptin	Januvia	Diabetes	4.99
16	Acetato de Glatirâmer	Copaxone	Multiple Sclerosis	4.78
17	Insulin Aspart	Novorapid	Diabetes	4.71
18	Pegfilgrastim	Neulasta	Cancer	4.62
19	Budesonid / Formoterol	Symbicort	Asthma / COPD	4.53
20	Ranibizumab	Lucentis	Macular Degeneration	4.43

“Top-Selling Drugs” em 2014

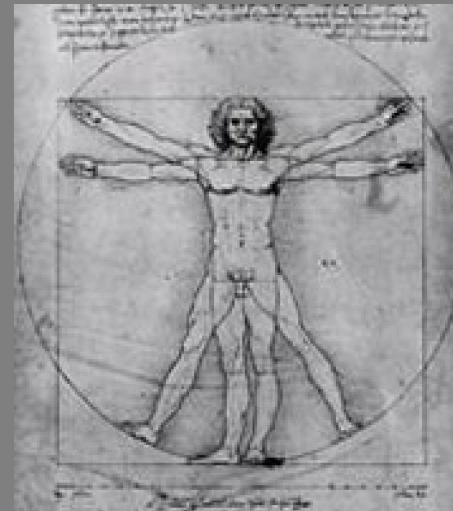
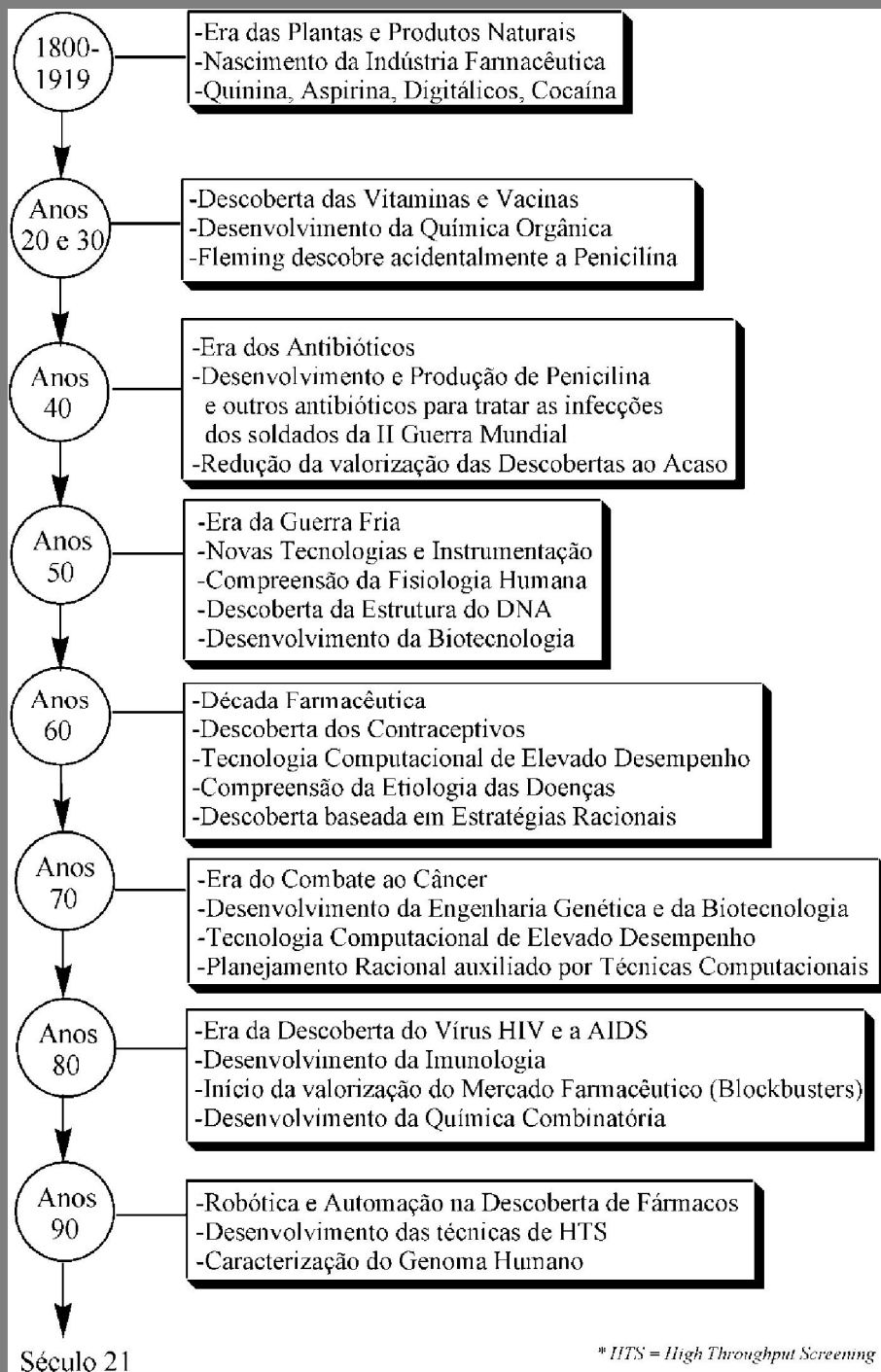


Fármacos Inovadores:
Radical ou Incremental?

Possíveis Origens para Novos Candidatos à Fármacos

- Substâncias de Baixo Peso Molecular
 - Produtos Naturais
 - Caldo Fermentativos
 - Extrato de Plantas
 - Fluidos Animais (*e.g.*, veneno de cobra)
 - Substâncias de Origem Sintética
 - Química Medicinal
 - Química Combinatorial
- Substâncias de Elevado Peso Molecular
 - Produtos Naturais
 - Produtos Recombinares
 - Produtos Quiméricos

Evolução Temporal do Processo de Descoberta de Fármacos

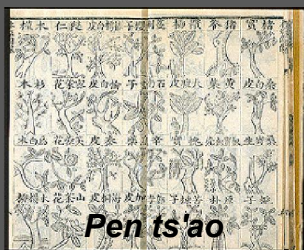


Fraga, C. A. M. & Barreiro, E. J. (2005)
Química Nova 28 (Supl.), S56-S63.

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 febrifuga



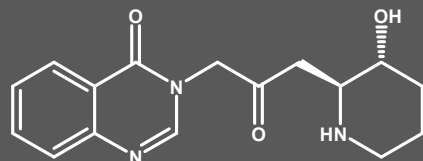
Rauwolfia serpentina



Theophrastus

5100 a.C.

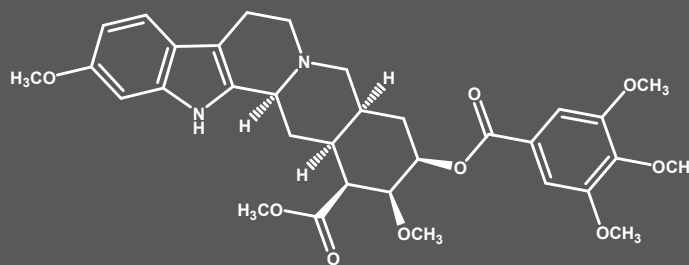
Gh'ang Shan



febrifugina

1000 a.C.

hindus



reserpina

300 a.C.

opióides



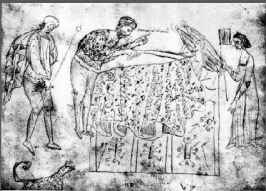
papoula

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

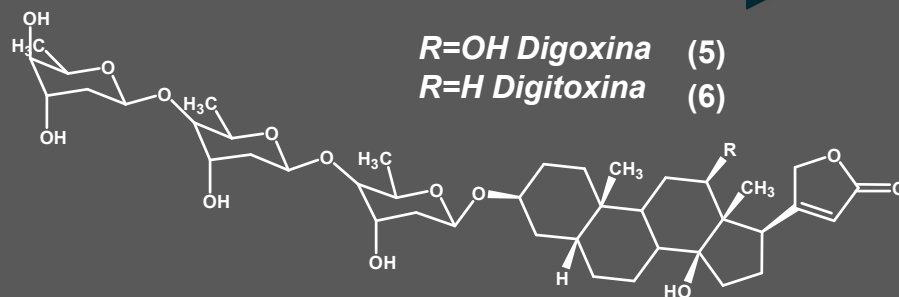
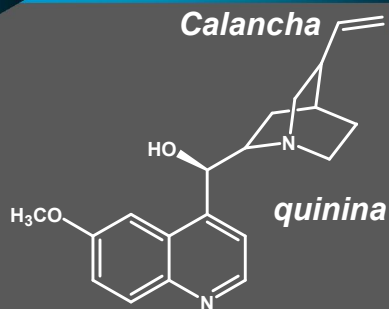
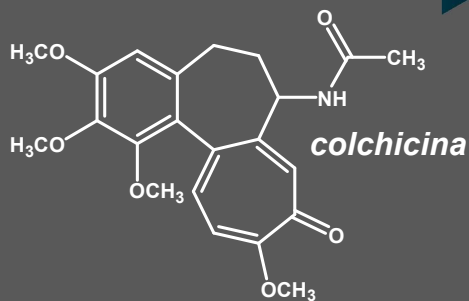
Cinchona

Digitalis purpurea

500

1633

1785



Início dos fármacos sintéticos e da Química Medicinal

1900

Futuro



Tracy, J.W. & Webster, L.T. (1993) em The Pharmacological Basis of Therapeutics, McGraw Hill, Nova York, 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.; Sneider, 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

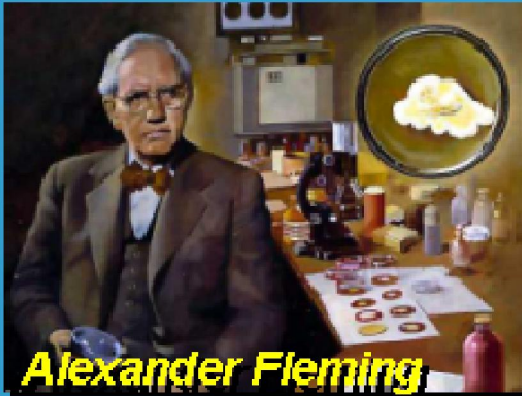
“ME-TOO”

“The most fruitful basis for the discovery of a new drug is to start with an old drug.” Sir James Black - Prêmio Nobel em Fisiologia e Medicina

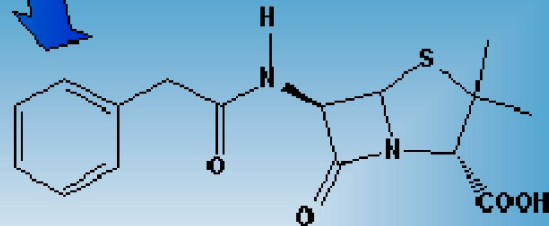
“SERENDIPITY”

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

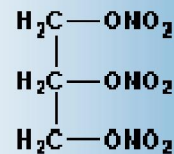
“... in the recent years the paradigms of drug research changed significantly...”
Kubinyi, H., 1995



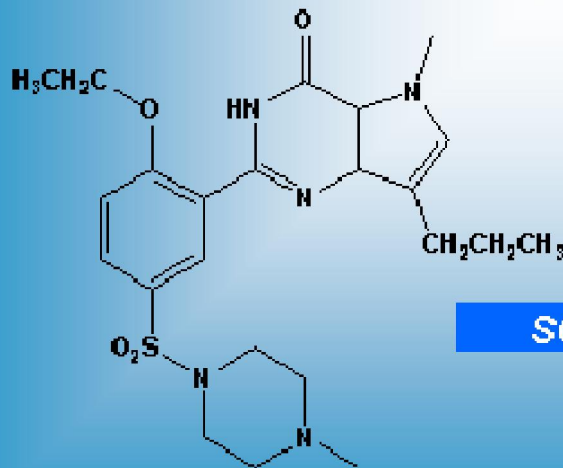
Alexander Fleming



Penicilina G



trinitroglicerina



Sildenafil

SOSA

Nova classe de fármacos úteis no tratamento da disfunção erétil

“SERENDIPITY”

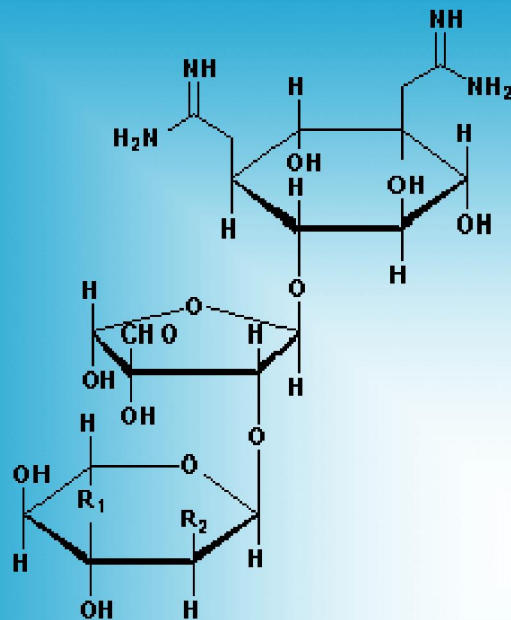
A word coined by Horace Walpole, who says (Let. to Mann, 28 Jan. 1754) that he had formed it upon the title of the fairy-tale ‘The Three Princes of Serendip’, the heroes of which ‘**were always making discoveries, by accidents and sagacity,** of things they were not in quest of”

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

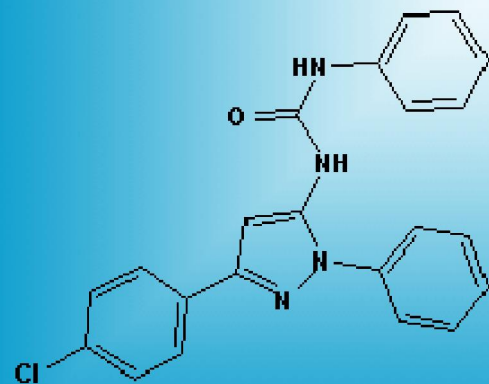
Fleming, A. (1929) Br. J. Exp. Pathol., 10, 226.

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

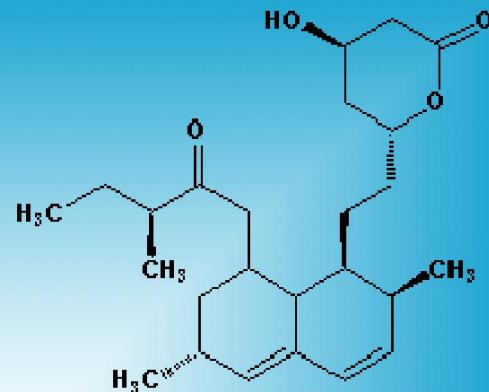
“Screening Sistemático”



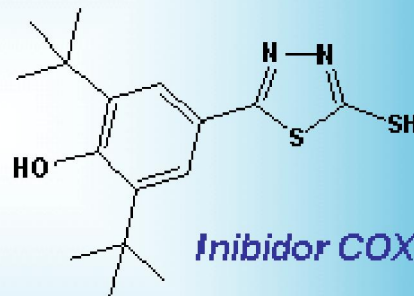
Estreptomina



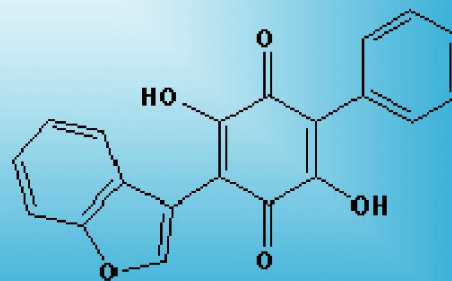
Inibidor da tirosina fosfatase 1B



Compactina



Inibidor COX-2



Insulina mimético

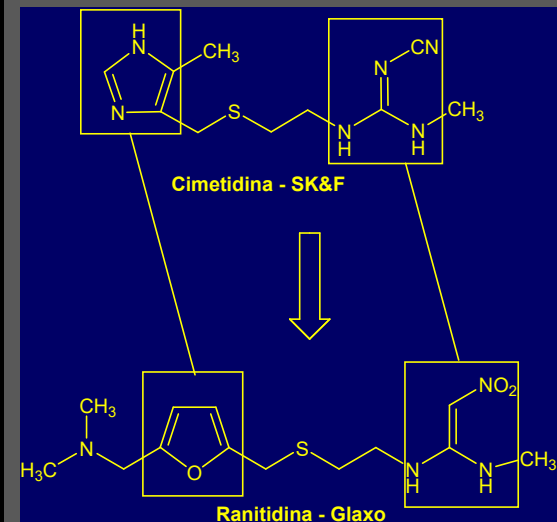
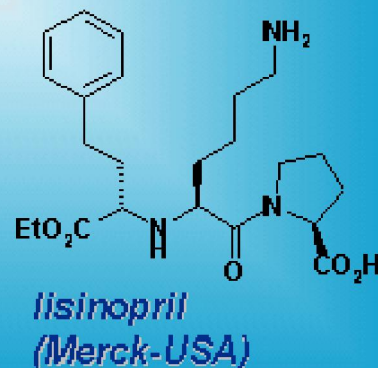
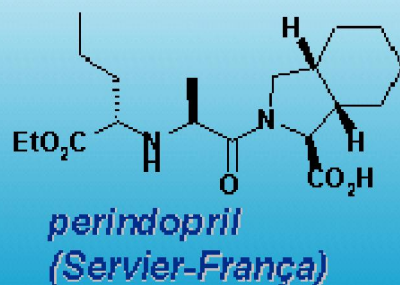
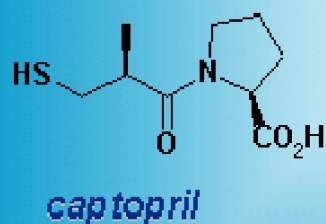
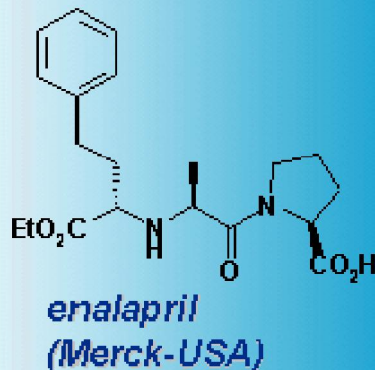
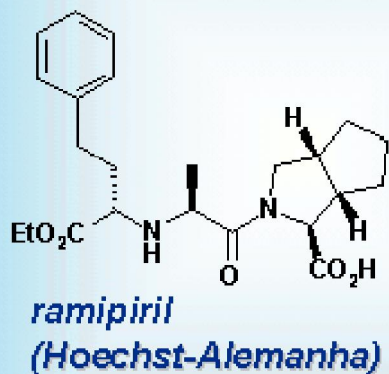
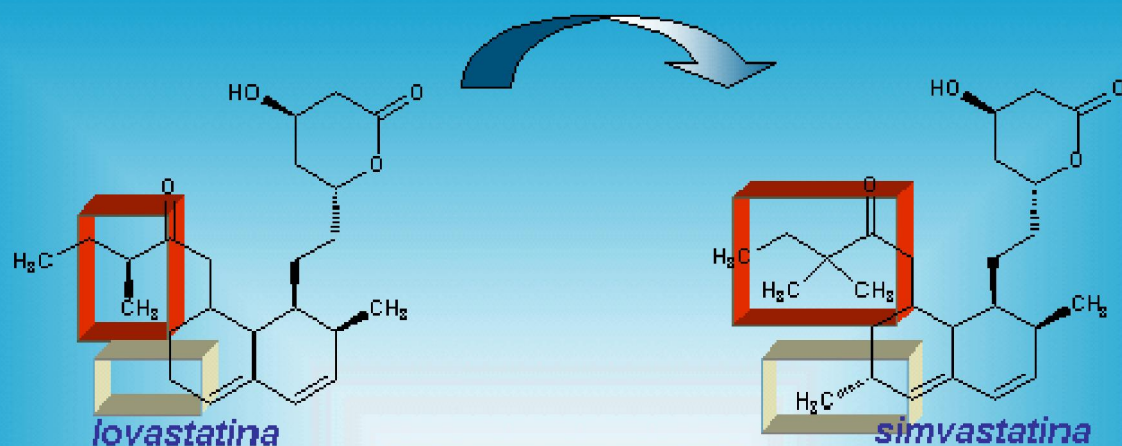
Nakamura, C.E. & Abeles, R.H. (1985) *Biochemistry*, 24, 1364.

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 Discovery Today*, 8, 411.

“Me-Too’s”



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

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

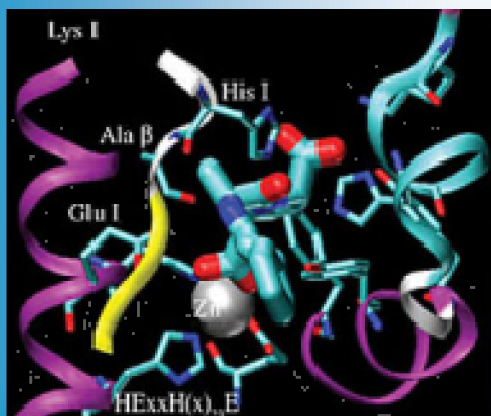
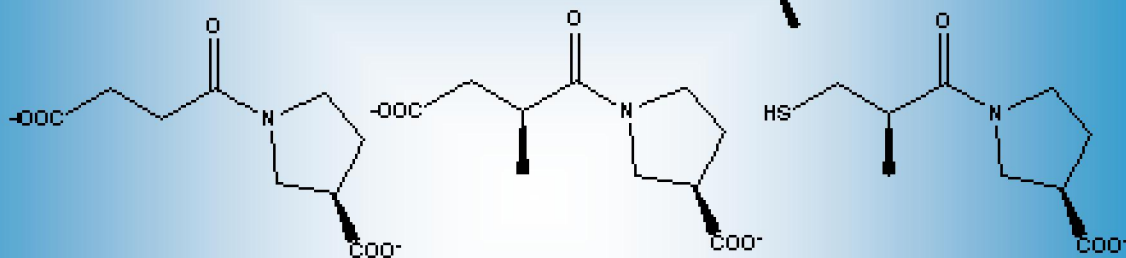
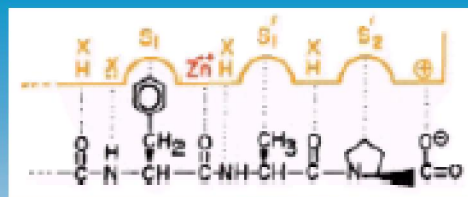
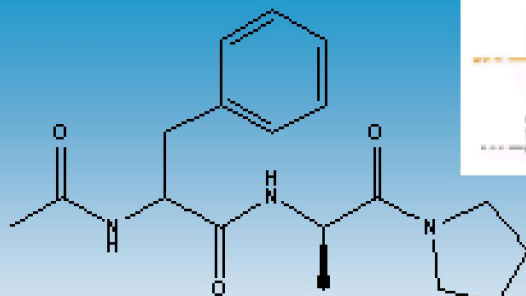
Cushman, D.W. &
Ondetti, M.A. (1991)
Hypertension, 17, 589.

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

Planejamento Baseado no Mecanismo de Ação



Jararaca bothrops



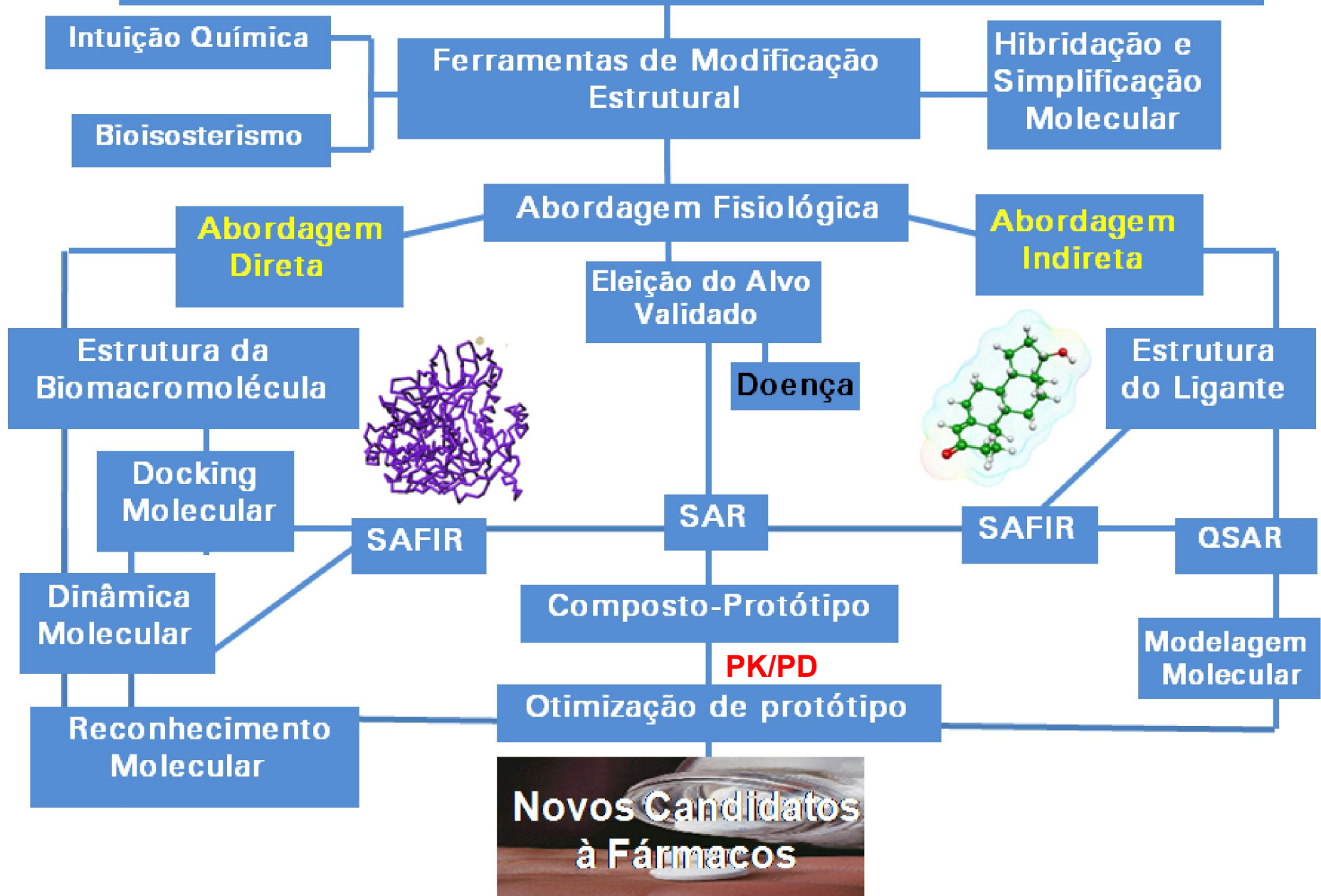
Estrutura 3D cristalográfica

**Racionalização de
novos compostos
com maior base
científica**

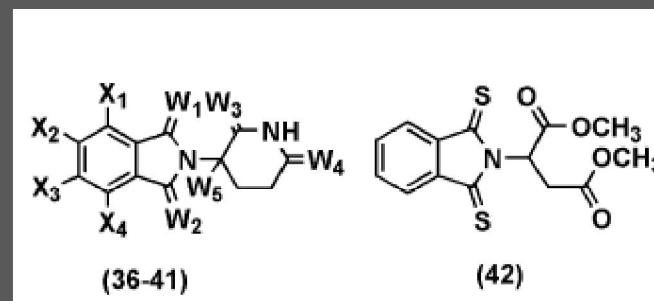
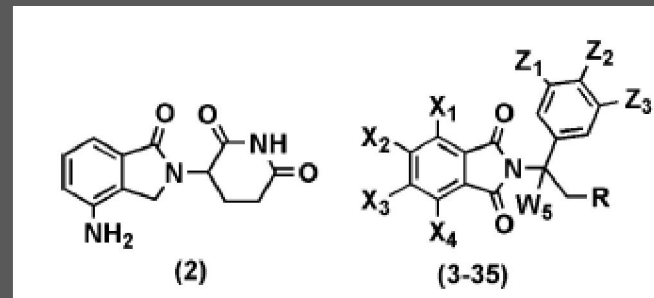
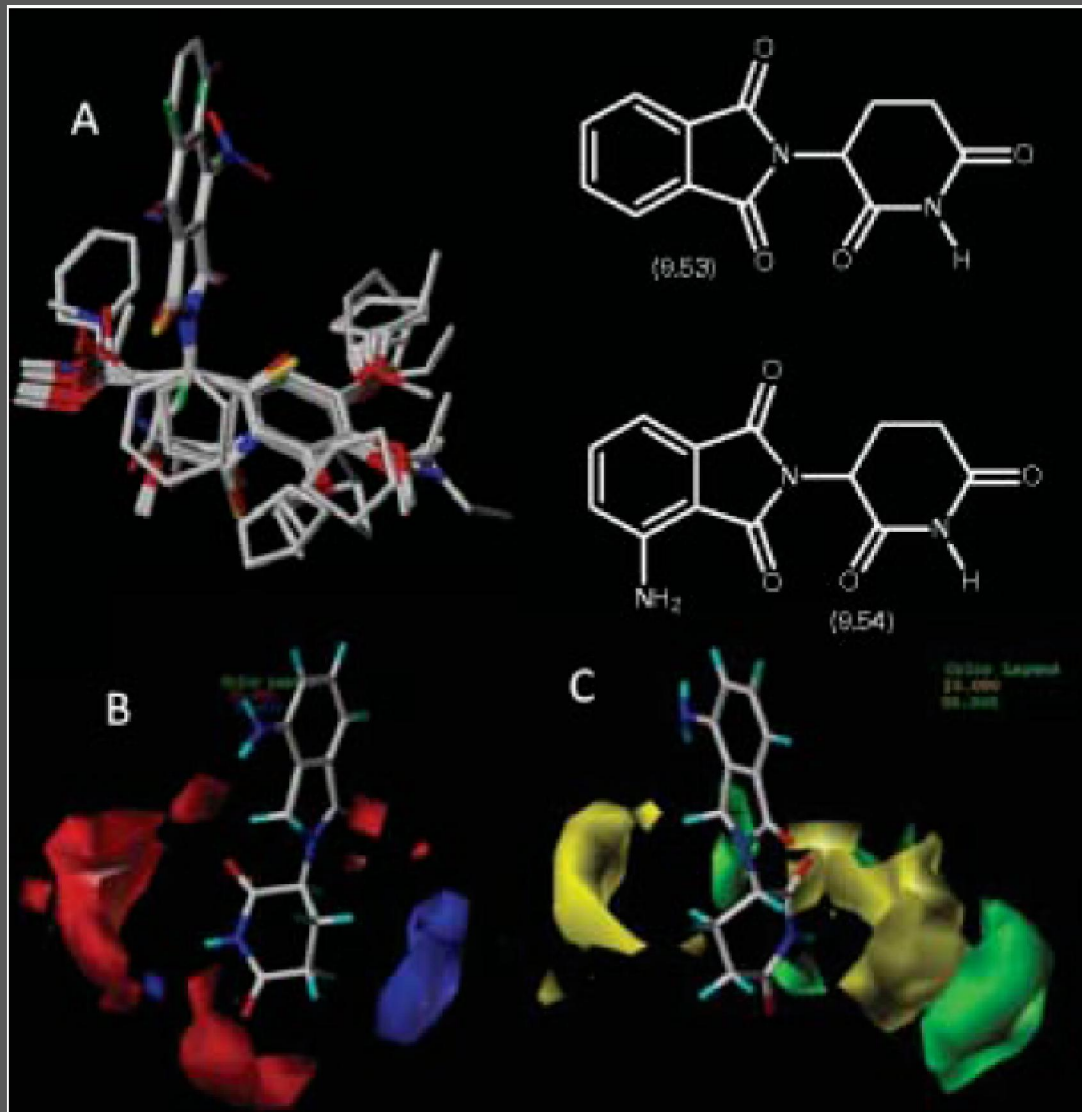
“O processo moderno da descoberta de fármacos, baseado no mecanismo de ação, visa a identificação de novos compostos bioativos através do desenho planejado de sua arquitetura molecular, ou a identificação de um bioligante eficiente, cuja arquitetura molecular é planejada com base na estrutura de um biorreceptor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

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

Estratégias Racionais de Planejamento de Fármacos

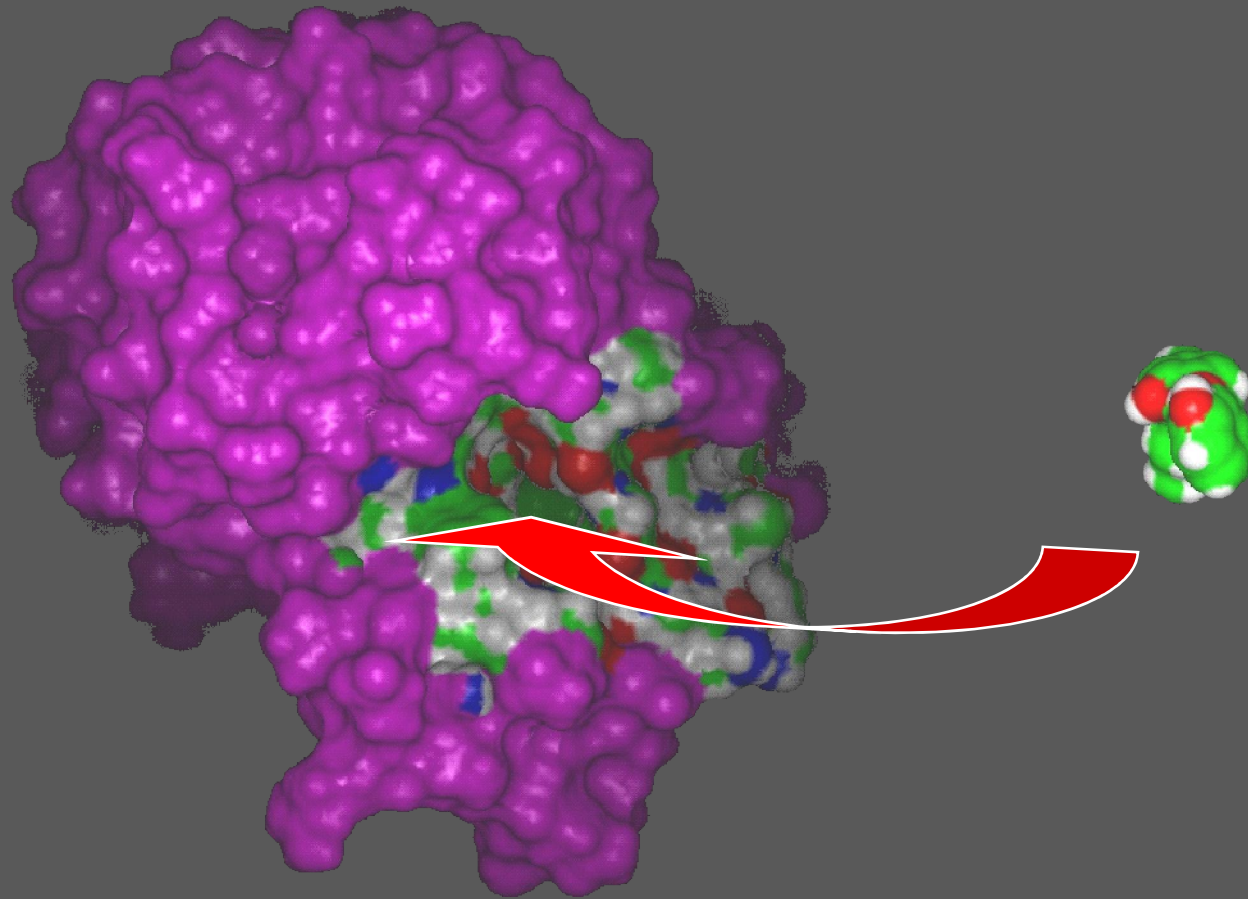


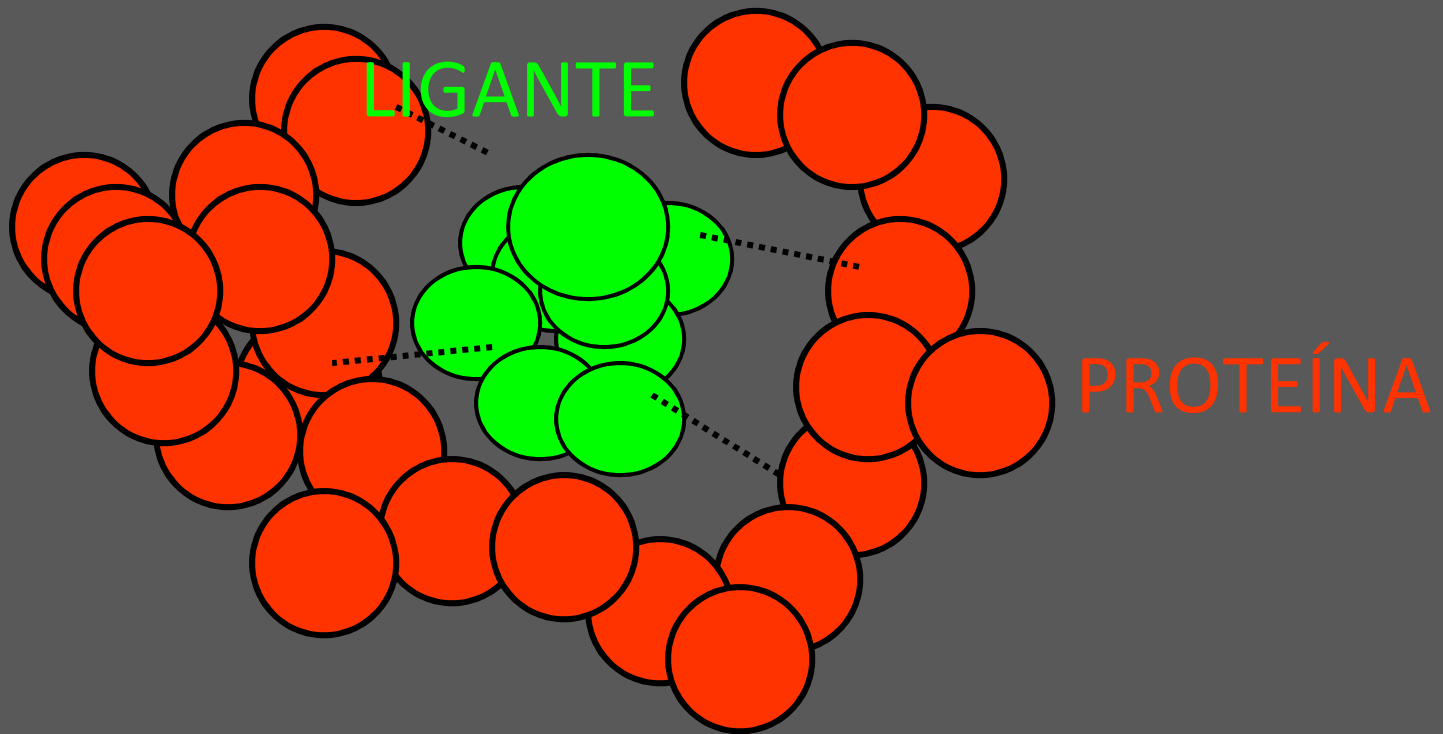
Exemplo do Uso de Métodos Indiretos de Planejamento de Fármacos: CoMFA de Análogos da Talidomida com Propriedades Anti-TNF-alfa



Avila CM, Romeiro NC, Silva GMC, Sant'Anna CMR, Barreiro EJ, Fraga CAM. Development of new CoMFA and CoMSIA 3D-QSAR models for anti-inflammatory phthalimidecontaining TNF modulators. *Bioorg. Med. Chem.* 14, 6874–85 (2006).

“Docking” de Ligantes em Proteínas





Função de Ranqueamento: Quantificação da Energia das Interações Proteína/Ligante tais como:

Interação de Hidrogênio

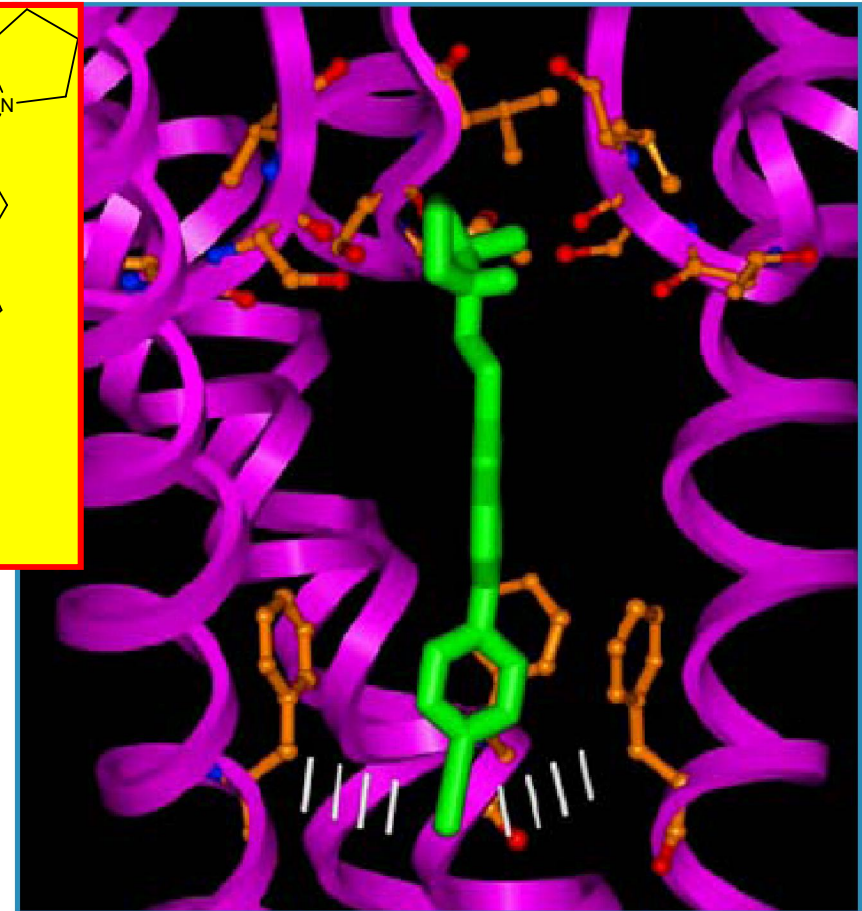
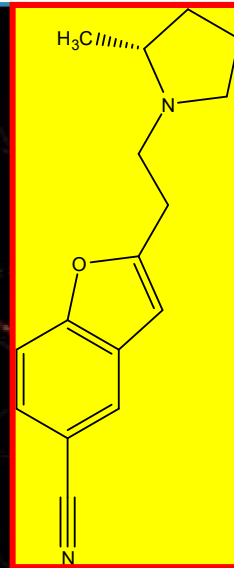
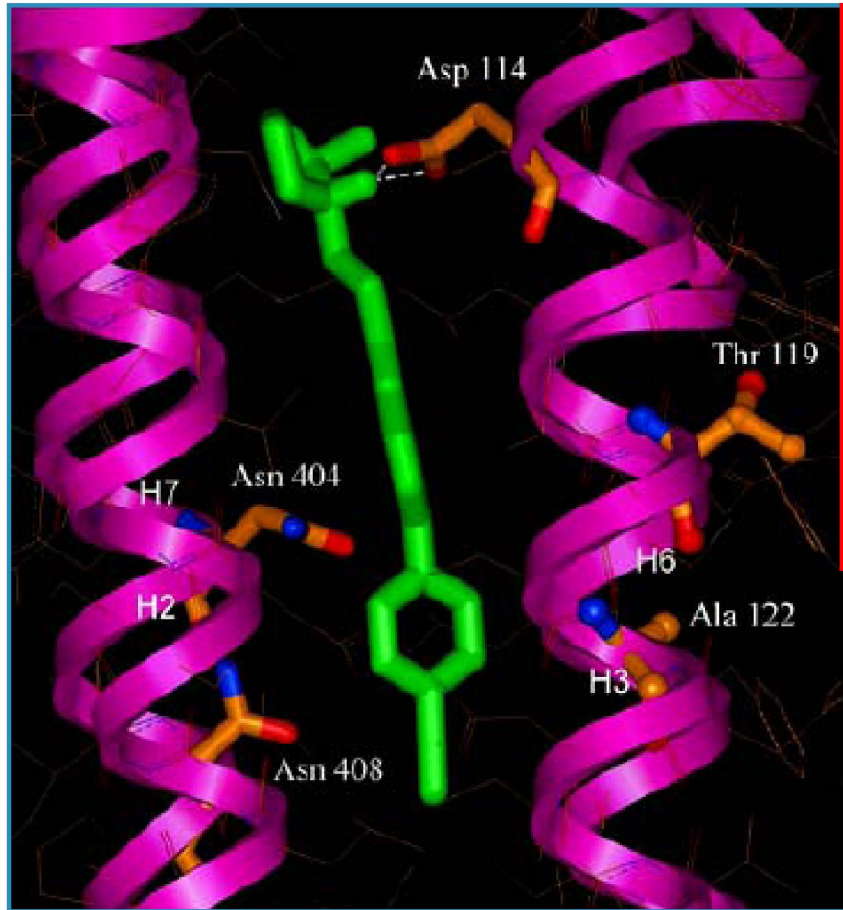
Eletrostática

Van der Waals

Hidrofóbica

π/π etc ...

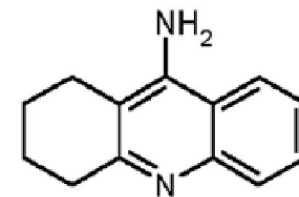
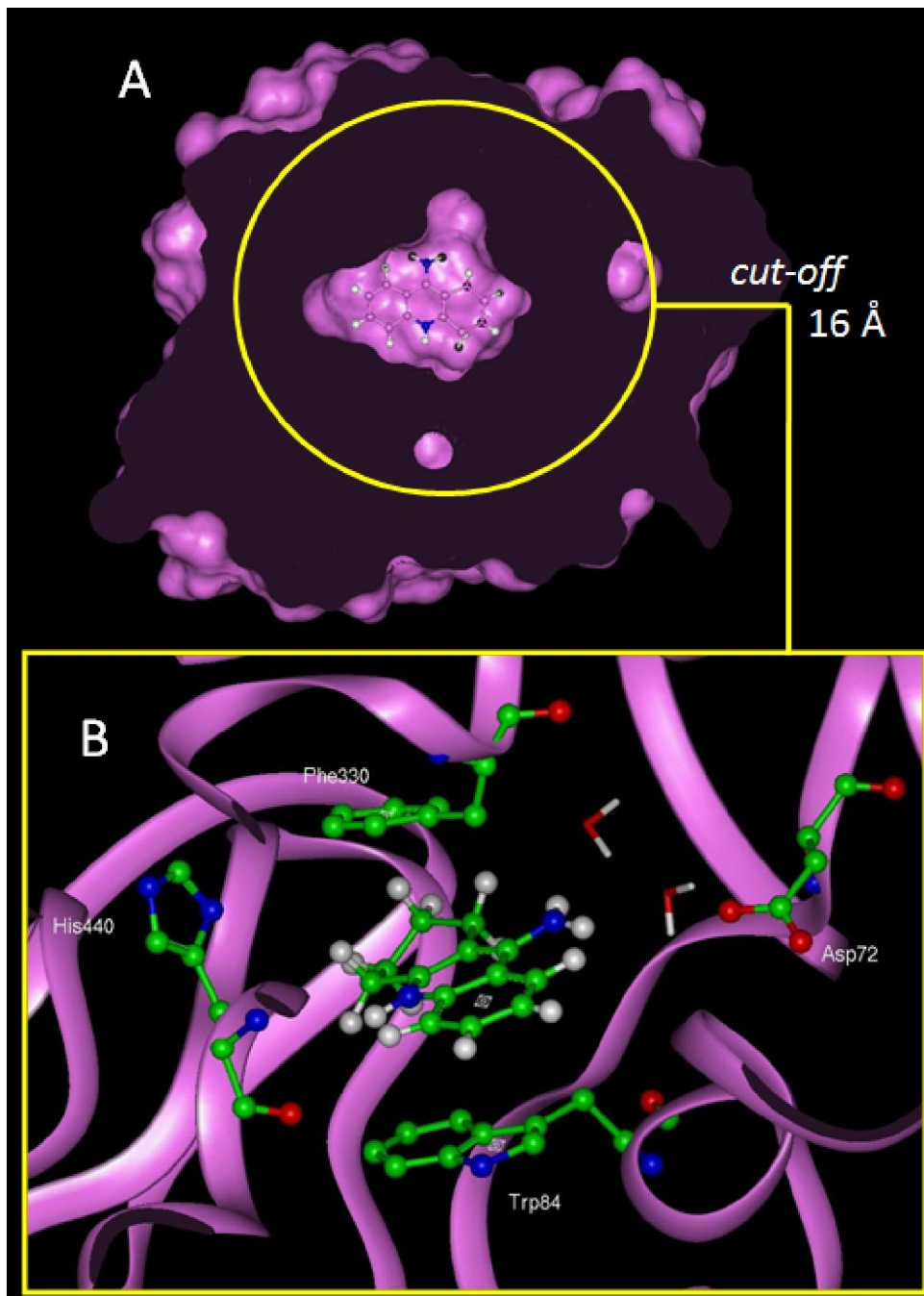
ABT-834: Um novo antagonista de receptores H3 em fase I para o tratamento de distúrbios cognitivos, identificado com o auxílio da modelagem molecular



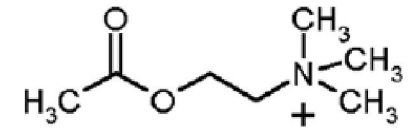
ABT-834 binds H₃ Receptor

ABT-834 repels HERG Channel (White Bars)

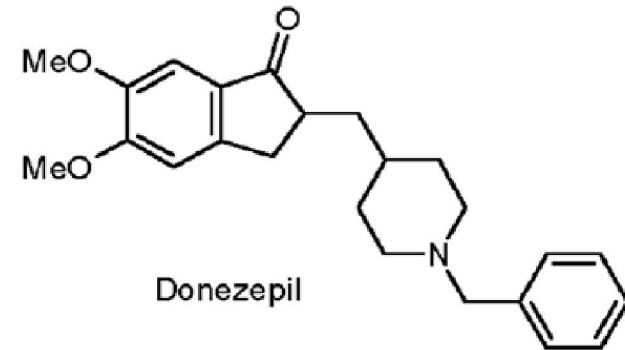
Inibidores de AChE



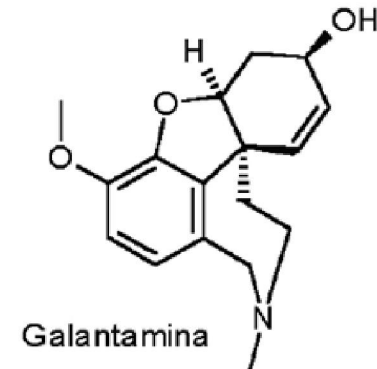
Tacrina



Acetilcolina



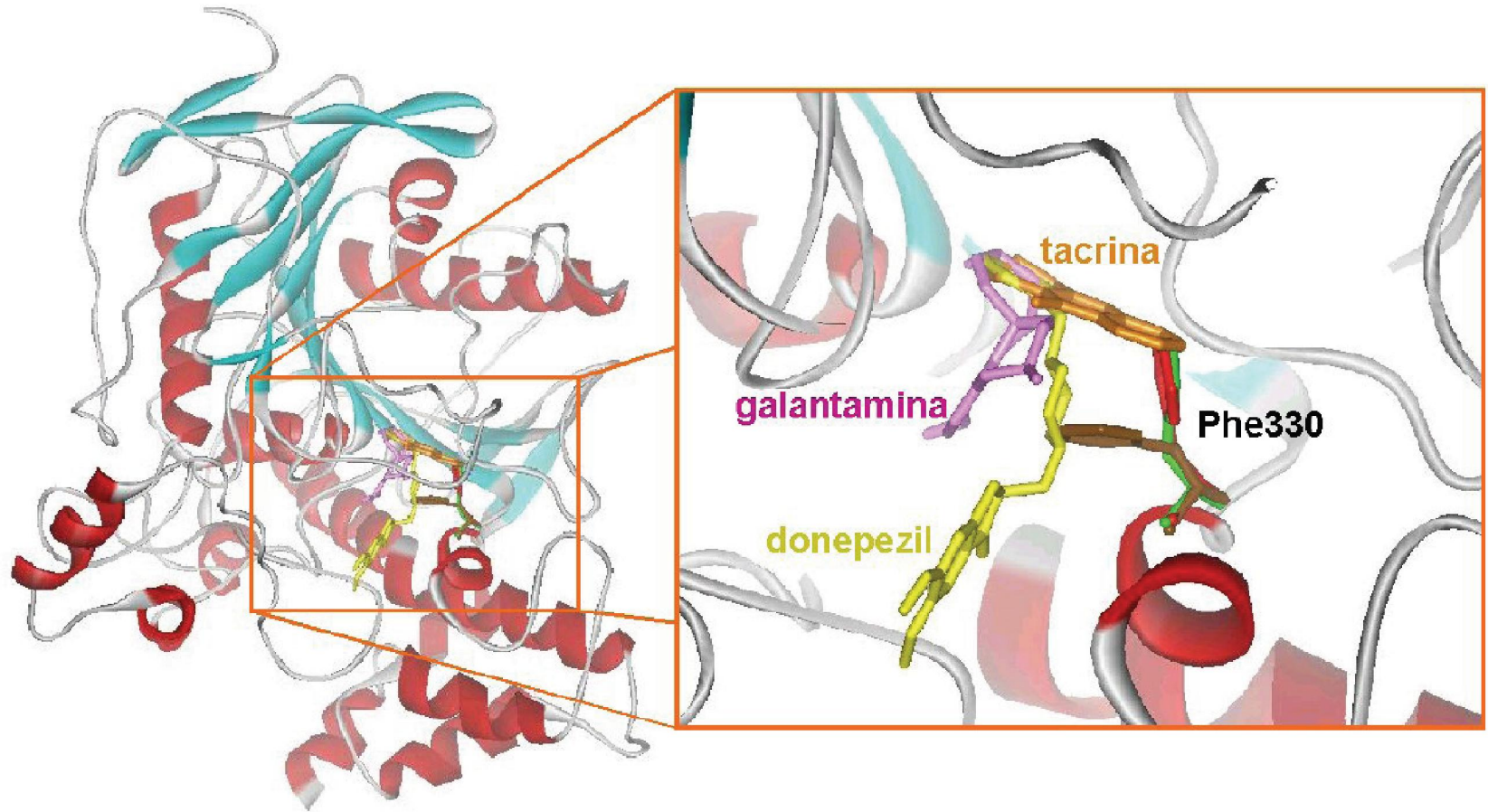
Donezepil



Galantamina

Comparação dos Modos de Interação de 3 Fármacos Inibidores de AChE

Mudanças conformacionais no sítio ativo da enzima acetilcolinesterase:



No início.....Os Produtos Naturais...

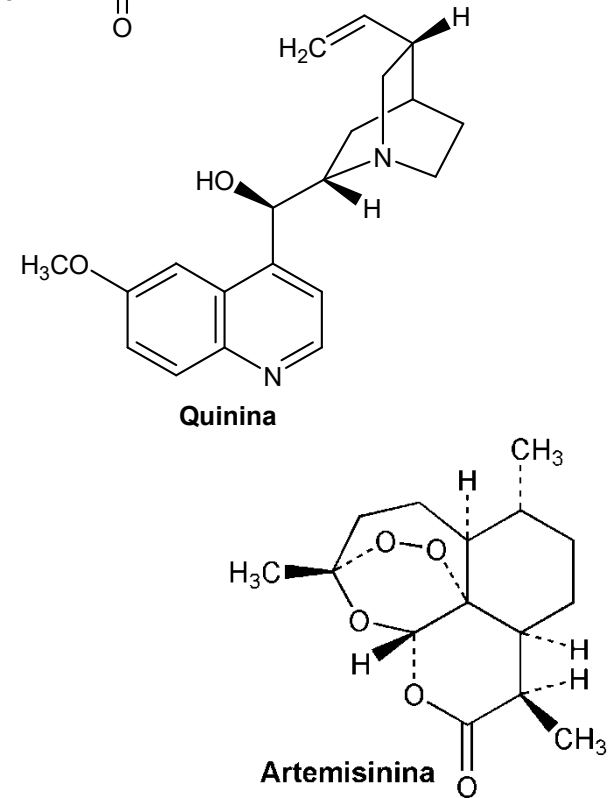
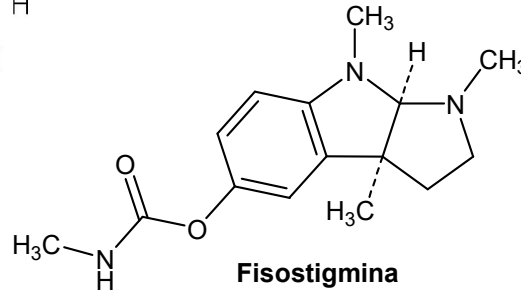
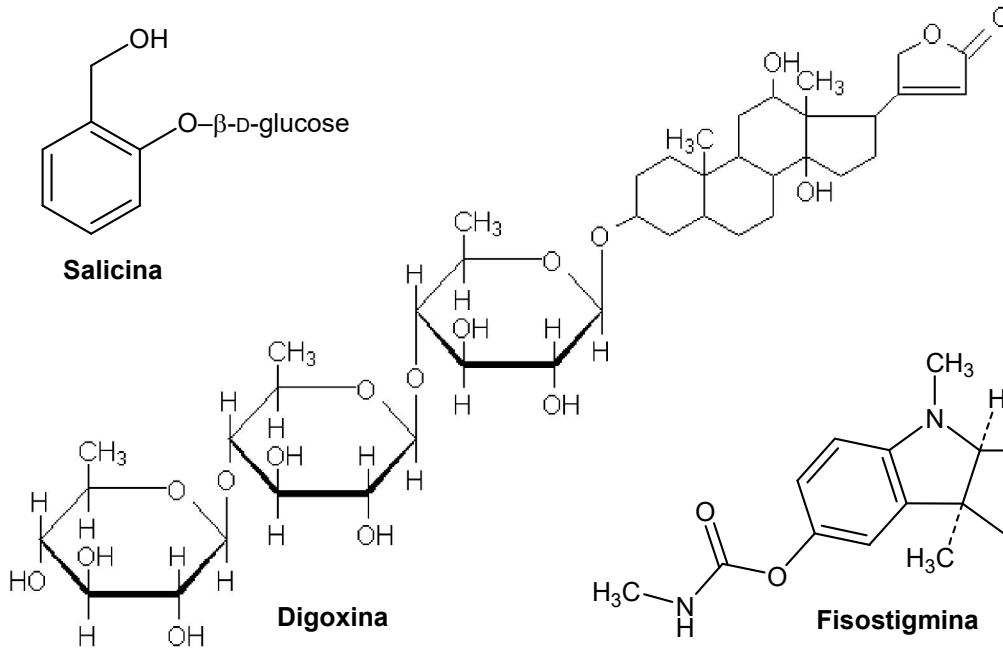
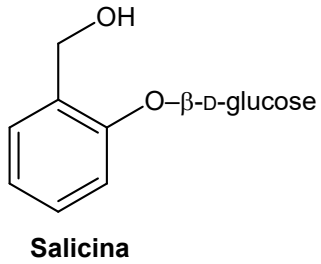
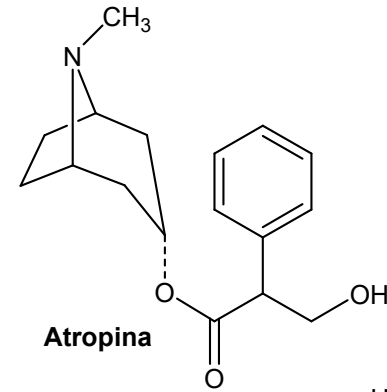
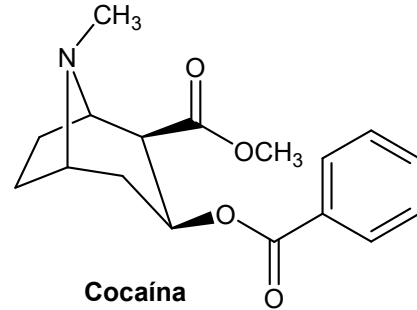
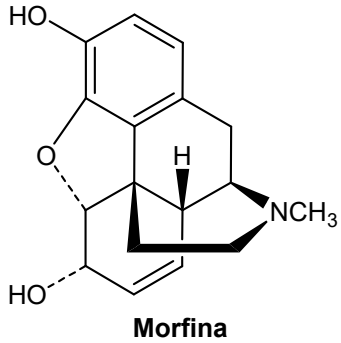
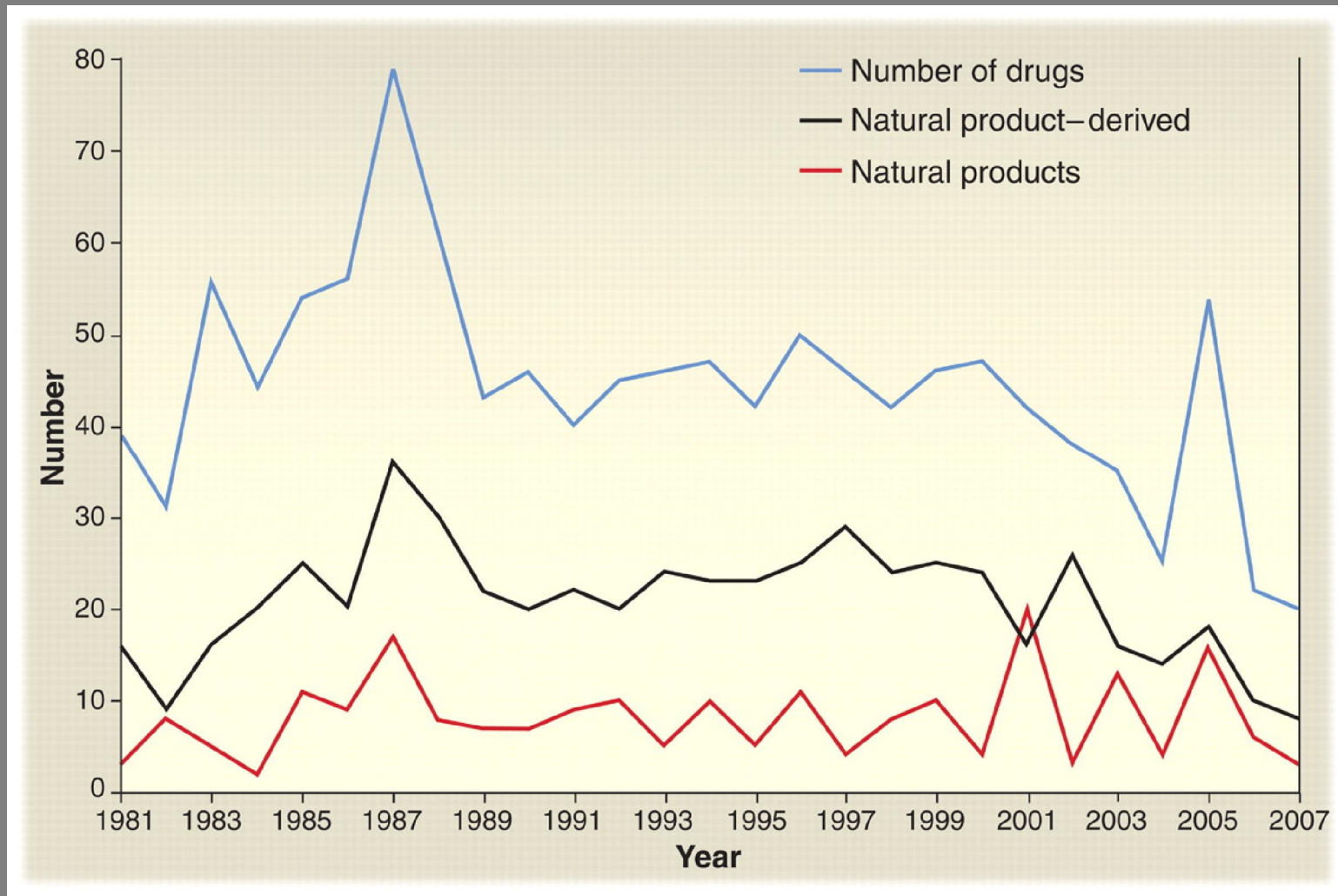


Fig. 1 Number of drugs approved in the United States from 1981 to 2007.



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



Fármacos de Origem Marinha

A

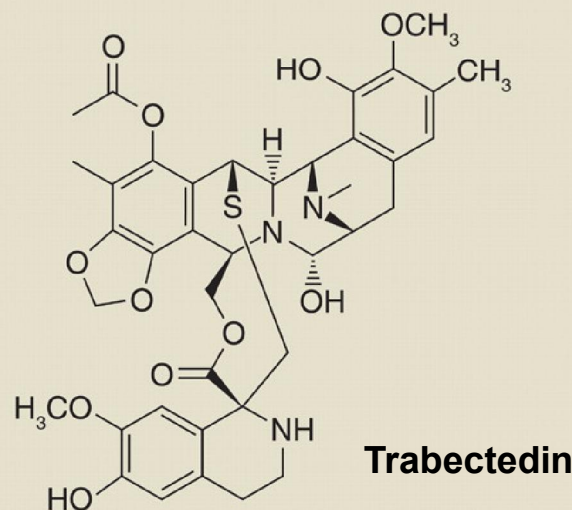
Conus magus



Ziconotide

B

Ecteinascidia turbinata



Trabectedin

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



Undisturbed Pacific Yew bark contains paclitaxel

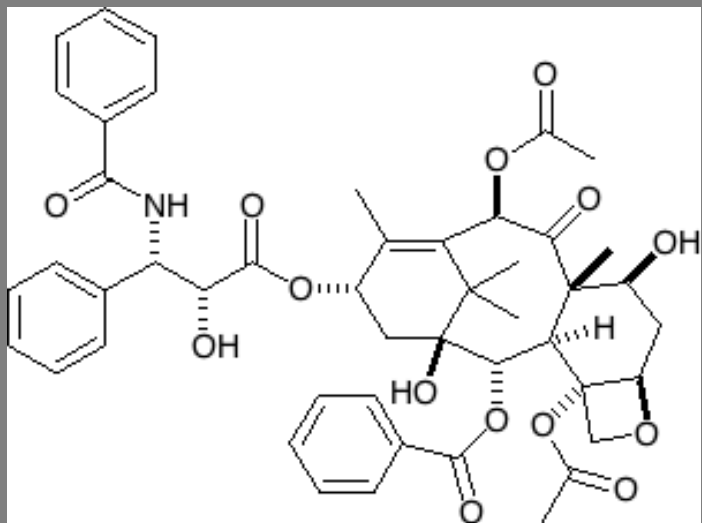


The bark is peeled and processed to provide paclitaxel

Discovery of Paclitaxel

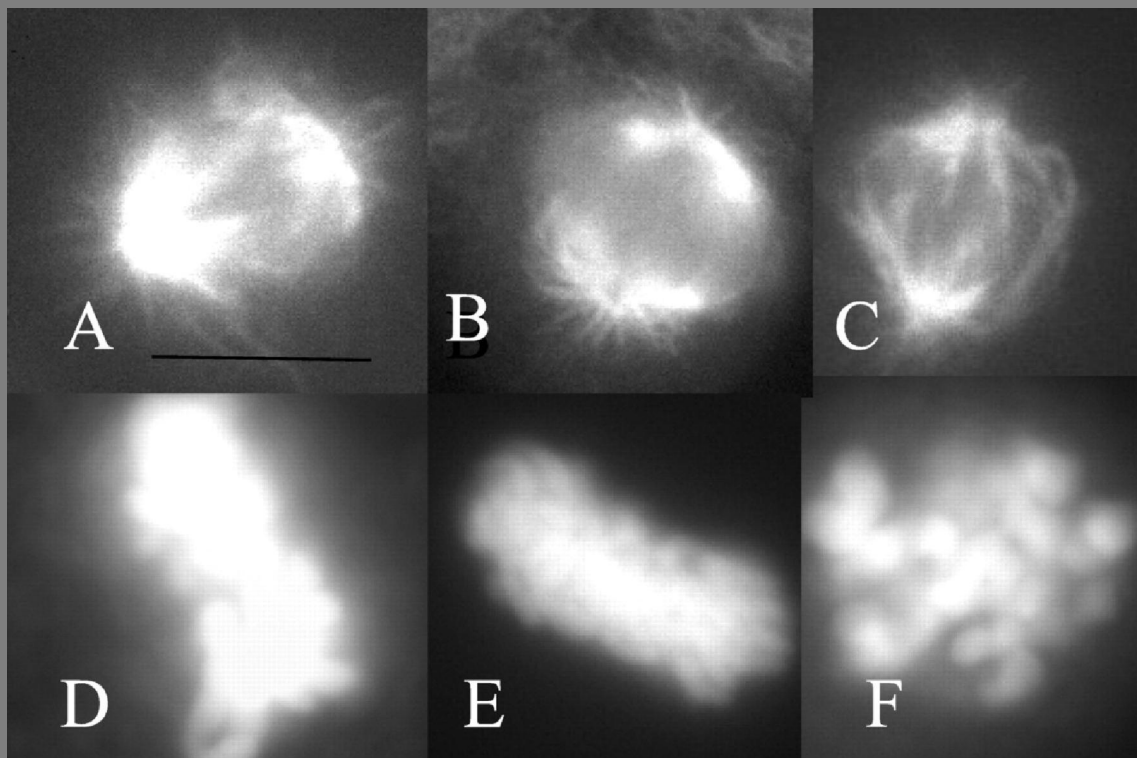
Em 1962, Arthur S. Barclay, coletou amostras de cascas do Teixo do Pacífico, *Taxus brevifolia*, em uma floresta ao Norte dos EUA, as quais apresentaram efeitos citotóxicos (1964).

Em 1965, estas amostras foram 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' em 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)

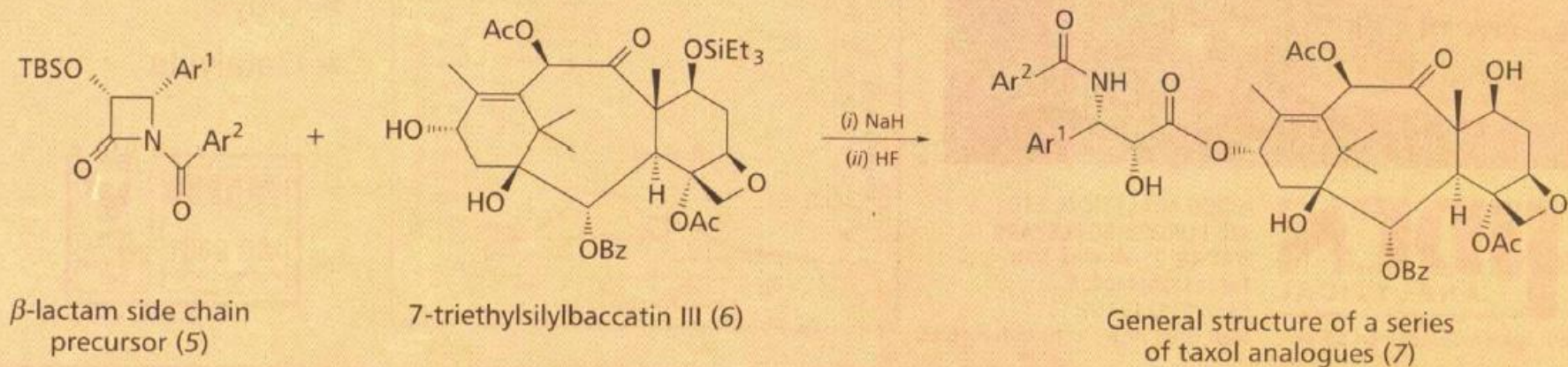
Holton R. A.; Somoza, C.; Kim, H. B. et al. First Total Synthesis of Taxol. 1. Functionalization of the B Ring, *J. Am. Chem. Soc.*, **1994**, **116**, **1597-1598**

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)

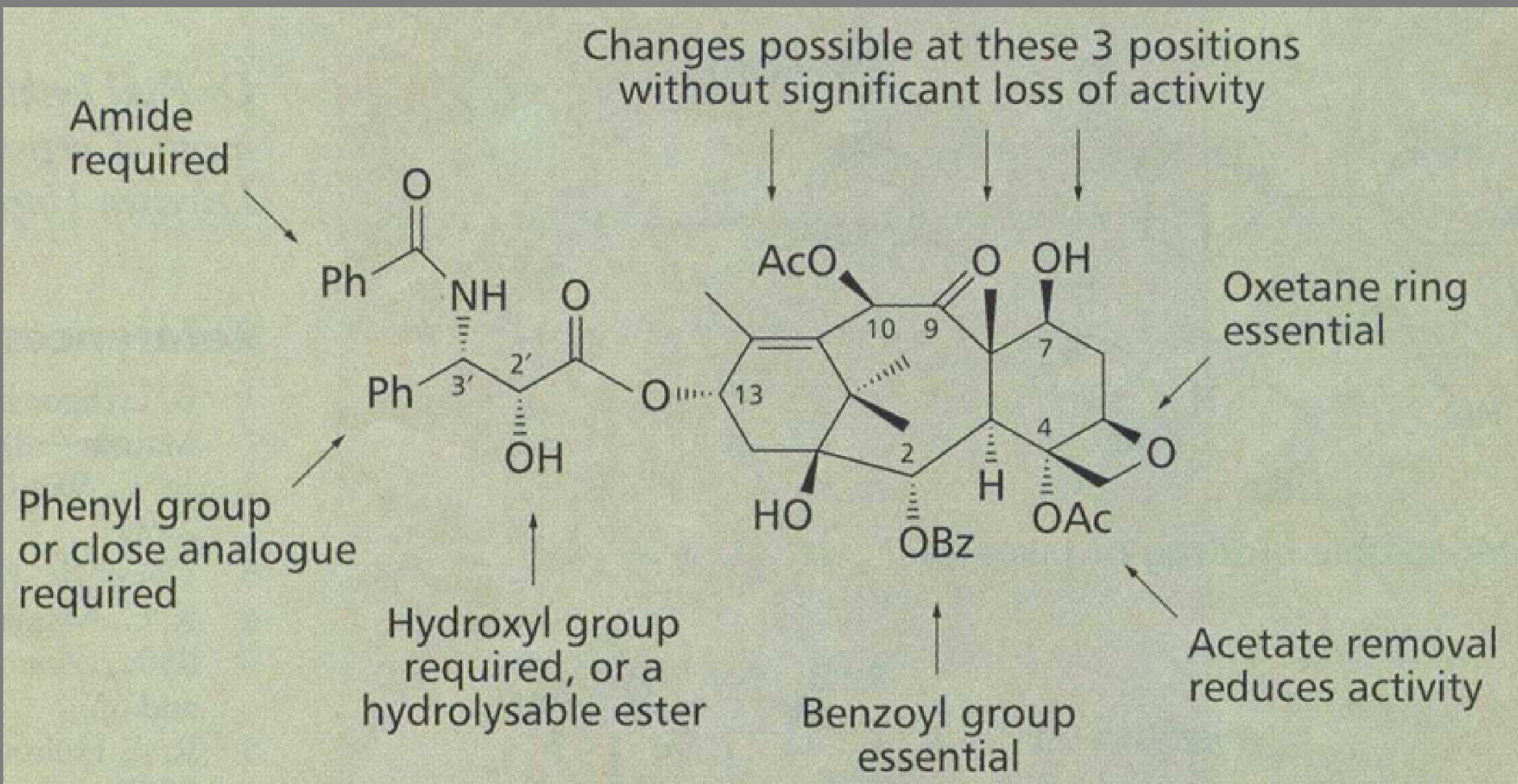
Nicolaou, K. C.; Yang, Z.; Lin, J. J. et al. Total Synthesis of Taxol. *Nature*, **1994**, **367**, **630-634**

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

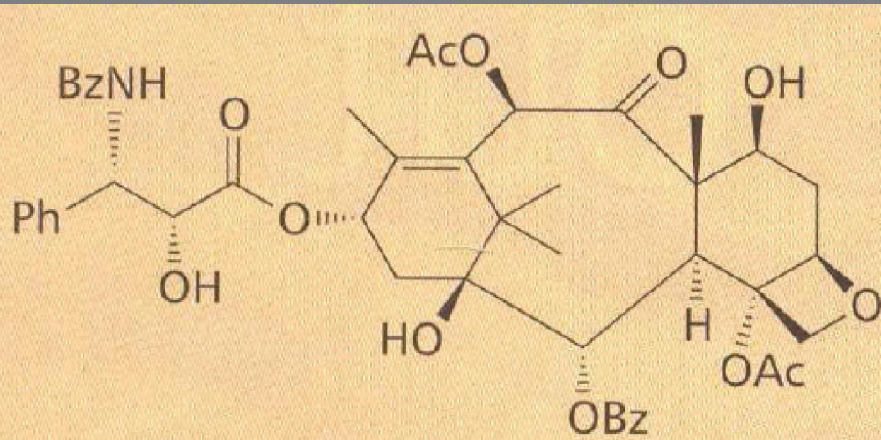


Denis, J. N.; Greene, A. E.; Guenard, D.; Gueritte-Voegelien, F.; Mangatal, L.; Potier, P. Highly Efficient, Practical Approach To Natural Taxol, *J. Am. Chem. Soc.*, **1988**, **110**, **5917**

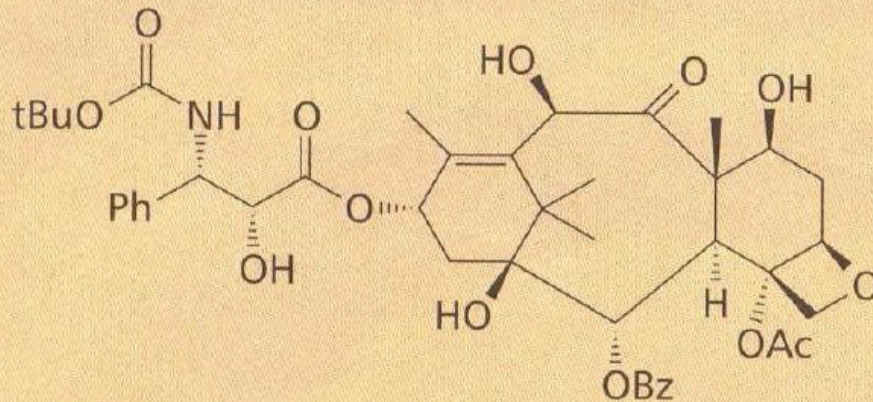
Relação Estrutura-Atividade de Análogos do TAXOL



Análogos estruturais do TAXOL

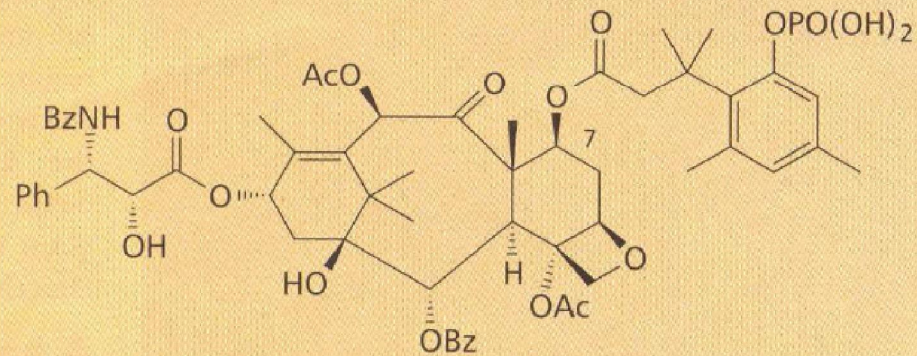


Taxol (1)



Taxotere (4)

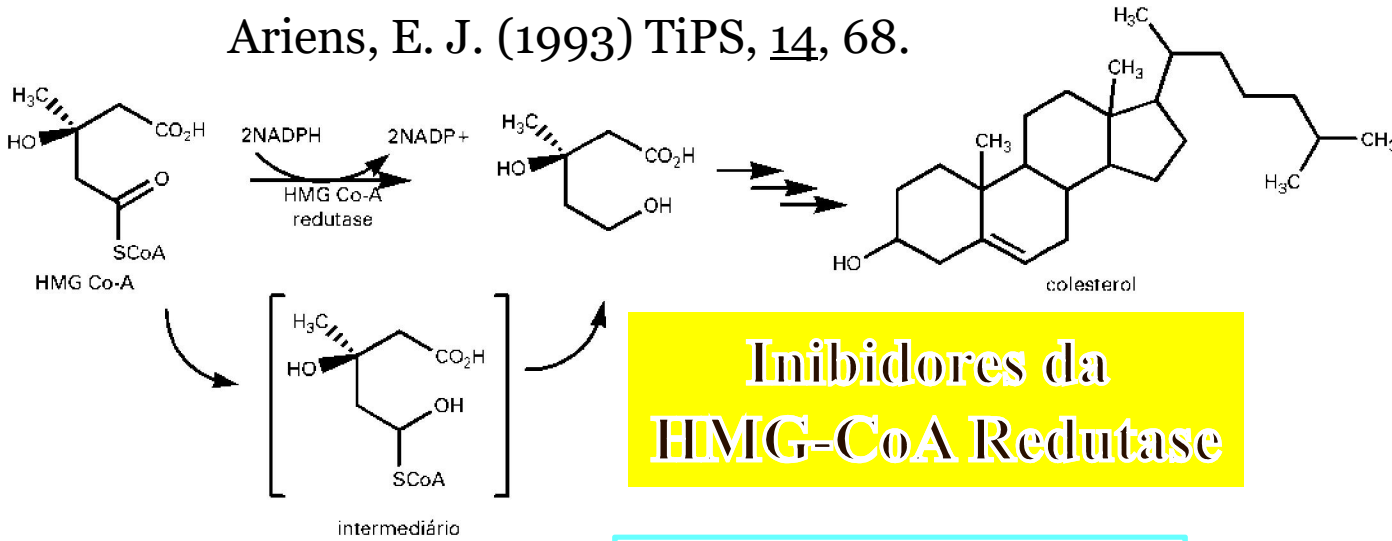
Prodrugs of taxol



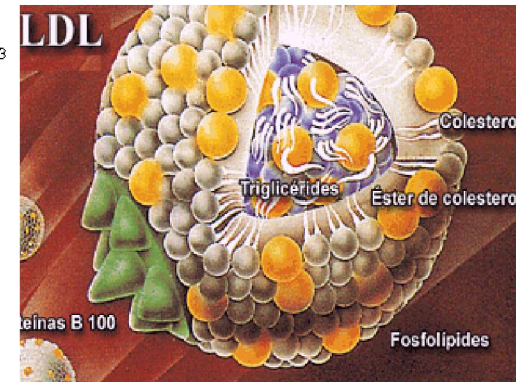
A water-soluble prodrug of taxol (8)

PN como inspiração na Gênese de Fármacos : Estatinas

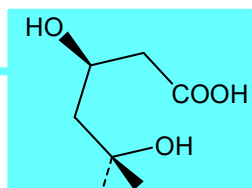
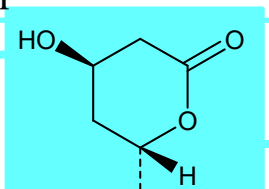
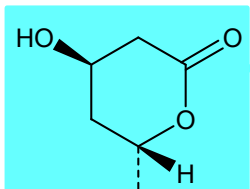
Ariens, E. J. (1993) *TiPS*, 14, 68.



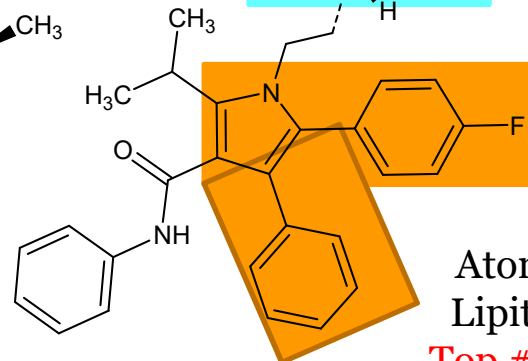
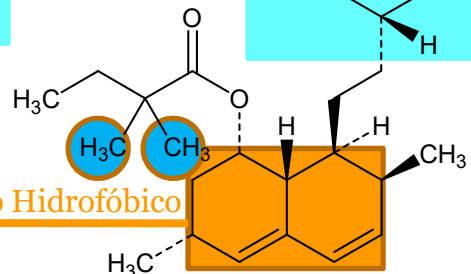
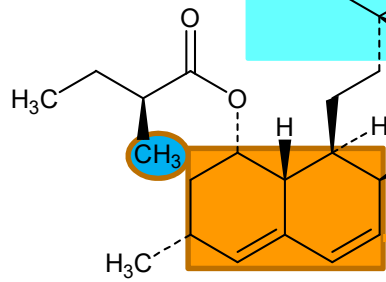
Biossíntese de Colesterol



Grupamento Farmacofórico



Grupo Hidrofóbico



Lovastatina

Aspergillus terreus

Mevacor, Merck, 1987

IC₅₀ = 2,2 nM

PRÓ-FÁRMACO

Simvastatina

Zocor, Merck, 1988

IC₅₀ = 0,9 nM

Atorvastatina

Lipitor, Pfizer

Top # 1 (2006)



Quimioterapia Moderna

P. Ehrlich, 1909



**Prêmio Nobel
Fisiologia/Medicina
(1908)**

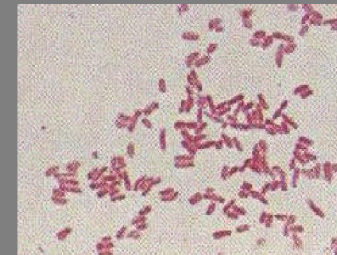
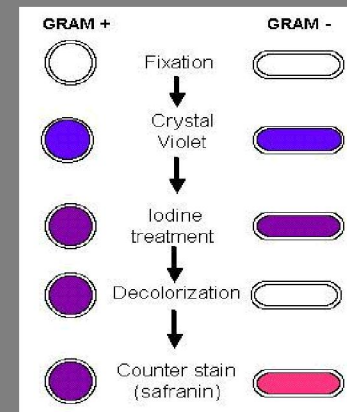
“The discoveries of those uncivilized peoples represented the sum of limitless testing of thousands of natural materials. By contrast with their selection of medicines by pure chance, we have to find first certain compounds, for example some arsenic derivatives, which show at least a low degree of therapeutic 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"

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 diagnósticos com corantes específicos para microorganismos;

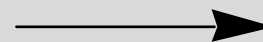
- Teste de substâncias de uso diagnóstico (corantes) como Antibióticos (Trypanosoma sp. / Febre do Sono)



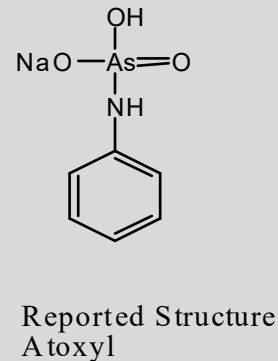
Gram

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

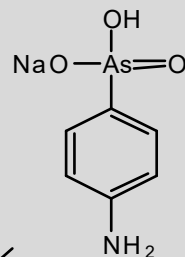
Arsenic Acid + Aniline



Atividade Antitripanossomal in Ratos



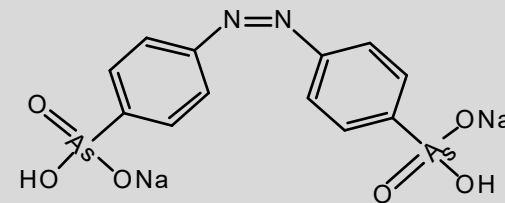
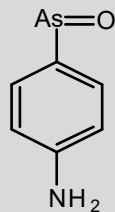
- Reconhecimento do uso de substâncias químicas na terapia;
- Química Sintética como ferramenta para se obter muitos derivados congêneres



Reduction

Diazotization

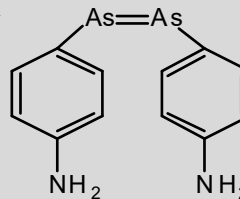
In Vivo Metabolism



Azo-Dyes

- Metabolismo: Conceito de Metabólito Ativo;
- Resistência dos microorganismos: Hereditariedade

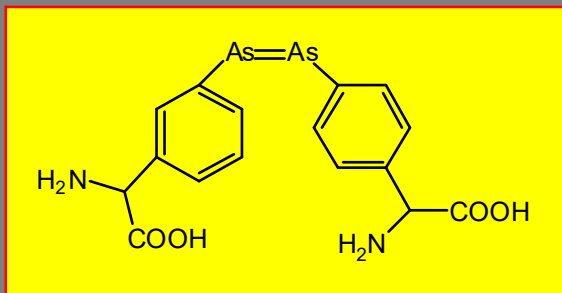
Reduction



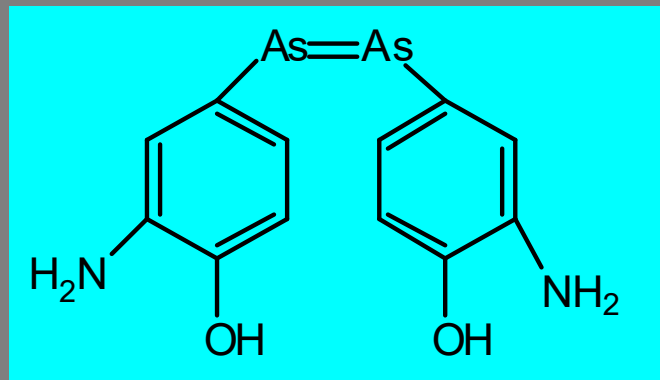
Substituted Anilines and other Chemical Derivatizations

Arsephenamine (Composto 606)

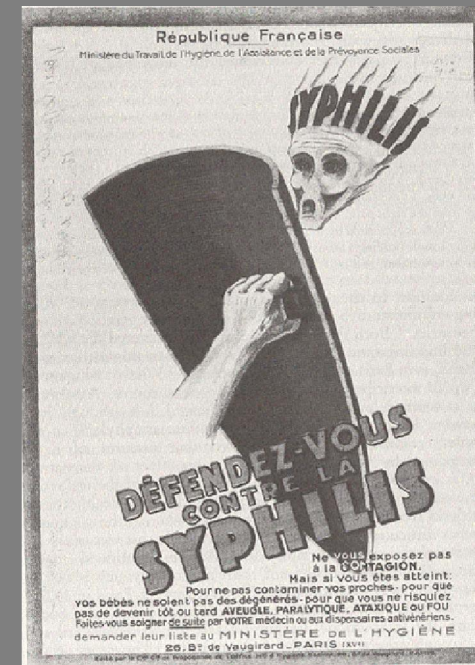
- ◆ Mais de 300 compostos foram inicialmente testados contra tripanossomas mas a cepa utilizada foi resistente a muitos deles.
- ◆ Então, um novo pós-doutor ingressou no grupo trazendo a expertise no modelo de espiroquetas causadoras da Sífilis em ratos. Os mesmos compostos foram re-ensaiados e o composto "606" mostrou uma potente atividade inibitória das espiroquetas.
- ◆
- ◆ Este composto, chamado Salvarsan foi então empregado clinicamente 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



Uso do Bioisosterismo como Ferramenta de Modificação Molecular

A bioisostere* is a compound resulting from the exchange of an atom or of a group of atoms with another, broadly similar, atom or group of atoms. The objective of a bioisosteric replacement is to create a new compound with *similar* biological properties to the parent compound. The bioisosteric replacement may be physicochemically or topologically based.

Glossary of Terms Used in Medicinal Chemistry

*** Bioisosters can exercise their biological activity on bioreceptor, whether through *agonist* or *antagonist*.**

Bioisosterismo

1919 – Langmuir

1925 - Grimm

1932 – Erlenmeyer

1951 – Friedman

1952 (1970) – A. Burger

1979 - Thornber

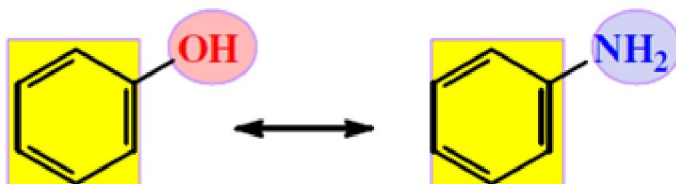
1986 – Lipinsky

1996 – Patani & LaVoie

2005 – Lima & Barreiro

2011 – Meanwell (JMC)

Similaridade molecular



Grupos funcionais

Compounds having the same number of atoms have also the same total number of electrons, the electrons may arrange themselves in the same manner. In this case the compounds or groups of atoms will be called isosteric compounds or isosteres.

Regra do Hidreto de Grimm

	Group 4A	Group 5A	Group 6A	Group 7A	Group 8A	
N° of e ⁻	6	7	8	9	10	11
	C	N	O	F	Ne	Na ⁺
	H ⁻ ↘	CH	NH	OH	FH	
		H ⁻ ↘	CH ₂	NH ₂	OH ₂	FH ₂ ⁺
			H ⁻ ↘	CH ₃	NH ₃	OH ₃ ⁺
				H ⁻ ↘	CH ₄	NH ₄ ⁺

Bioisosteres were to include all atoms and molecules which fit the broadest definition for isosteres and have a similar type of biological activity, which may even be antagonistic.

Bioisósteros Clássicos e Não-Clássicos

Table 1 – Classic bioisostere groups and atoms

<i>Monovalent</i>	<i>Divalent</i>	<i>Trivalent</i>	<i>Tetravalent</i>
, -OH, -NH ₂ , -CH ₃ , -OR -F -Cl, -Br, -I, -SH, -PH ₂ , -Si ₃ , -SR	-CH ₂ - -O- -S- -Se- -Te-	=CH- =N- =P- =As- =Sb-	=C= =Si= =N ⁺ = =P ⁺ = =As ⁺ = =Sb ⁺ =

Table 2 - Non-Classic Bioisosteres

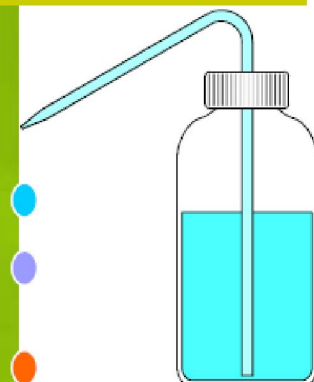
-CO- -CO ₂ - -SO ₂ - -SO ₂ NR-	-COOH -SO ₃ H -tetrazole -SO ₂ NHR -SO ₂ NH ₂	-SO ₂ NH ₂ -PO(OH)NH ₂ funcionais	-H -F clássicos -OH -CH₂OH homólogos	-CONH- -COOR- -NHCO- -ROCO- retroisósteros	-CONH ₂ -CSNH ₂ funcionais
-CON- -CH(CN)- R-S-R' (R-O-R') R-N(CN)-	-3-hydroxyisoxazole -2-hydroxychromones funcionais =N- -C(CN)=R' -halides -CF ₃ -CN -N(CN) ₂ -C(CN) ₃		-NHCONH ₂ funcionais -NH-CS-NH ₂ -NH-C(=CHNO ₂)-NH ₂ -NH-C(=CHCN)-NH ₂	-catechol -benzimidazole	-C ₄ H ₄ S -C ₅ H ₄ N aromáticos -C ₆ H ₅ -C ₄ H ₄ NH de anéis

• Bioisosterism in Molecular Modification

A chemical group can be mimicked by a similar group with similar biological activity –another example of similarity

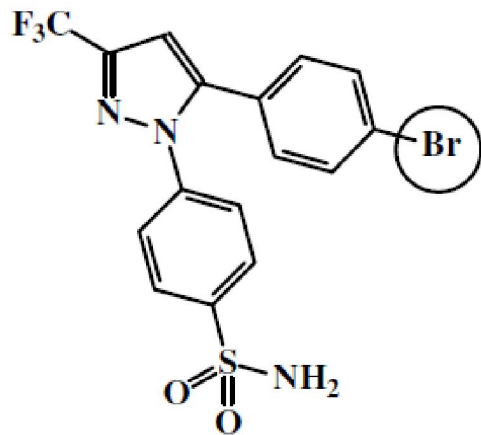
- a. Size
- b. Shape (bond angles, hybridization)
- c. Electronic distribution (Polarizability, inductive effects, charge, dipoles)
- e. Lipid solubility
- f. pK_a
- g. Chemical reactivity (including likelihood of metabolism)
- h. Hydrogen bonding capacity

Database

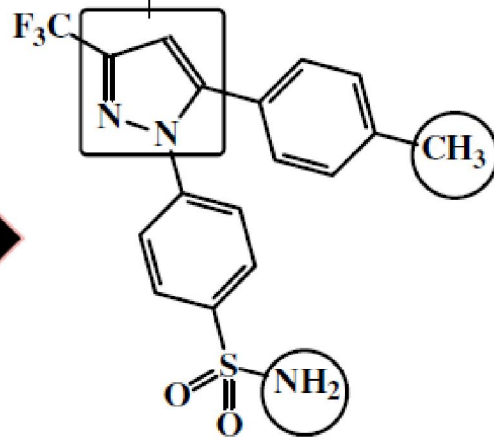


Hits

Bioisosterismo: Exemplos



SC-568

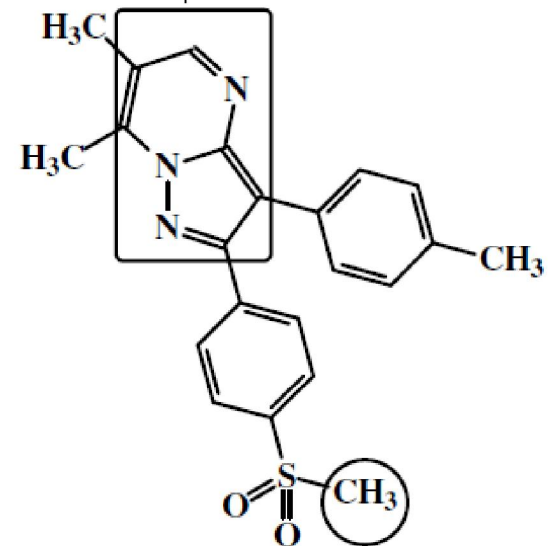


Celecoxib

$IC_{50} = 0,6 \mu M$ (COX-2)

$IC_{50} = 13,0 \mu M$ (COX-1)

IS = 21



pirazolo-pirimidina

$IC_{50} = 0,08 \mu M$ (COX-2)

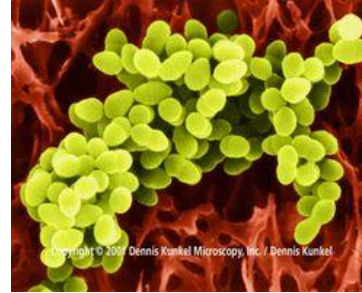
$IC_{50} > 15,0 \mu M$ (COX-1)

IS v= 125

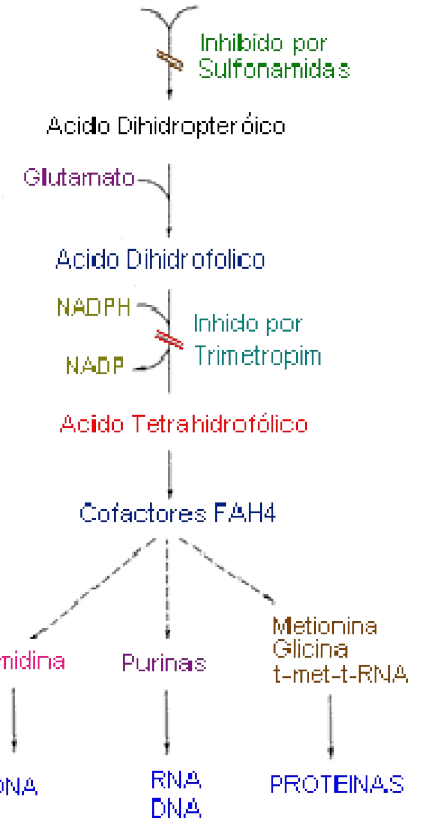


Sulfas Antibacterianas

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

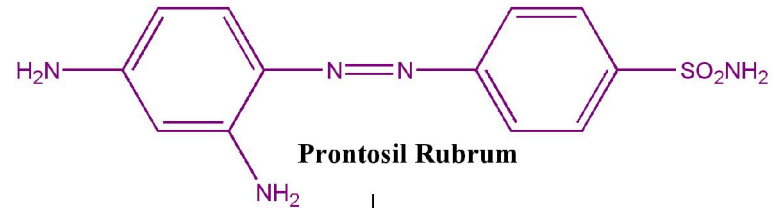


Teridina + Paba

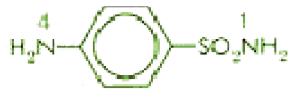
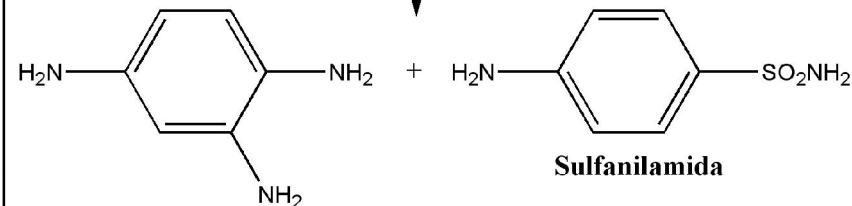


S. aureus

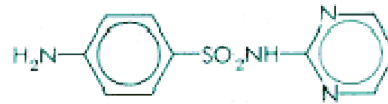
Gelmo (1908)



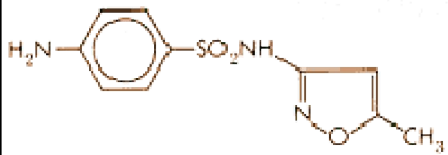
NADPH Redutase



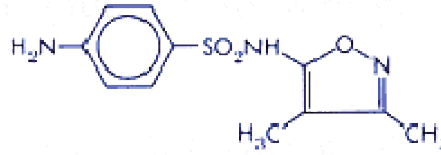
SULFANILAMIDE



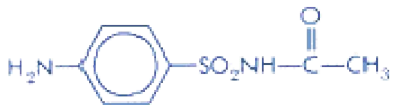
SULFADIAZINE



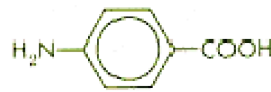
SULFAMETHOXAZOLE



SULFISOXAZOLE



SULFACETAMIDE



PARA-AMINOENZOIC ACID

Overlaps

Pharmaceutical objectives

- improved solubility
- improved chemical stability
- improved taste, odor
- decreased irritation and pain

Pharmacokinetic objectives

- improved oral absorption
- decreased presystemic metabolism
- improved absorption by non-oral routes
- improved time profile
- organ/tissue-selective delivery of active agent

Pharmacodynamic objectives

- masking of a reactive agent to improve its therapeutic index
- *in situ* activation of a cytotoxic agent

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].

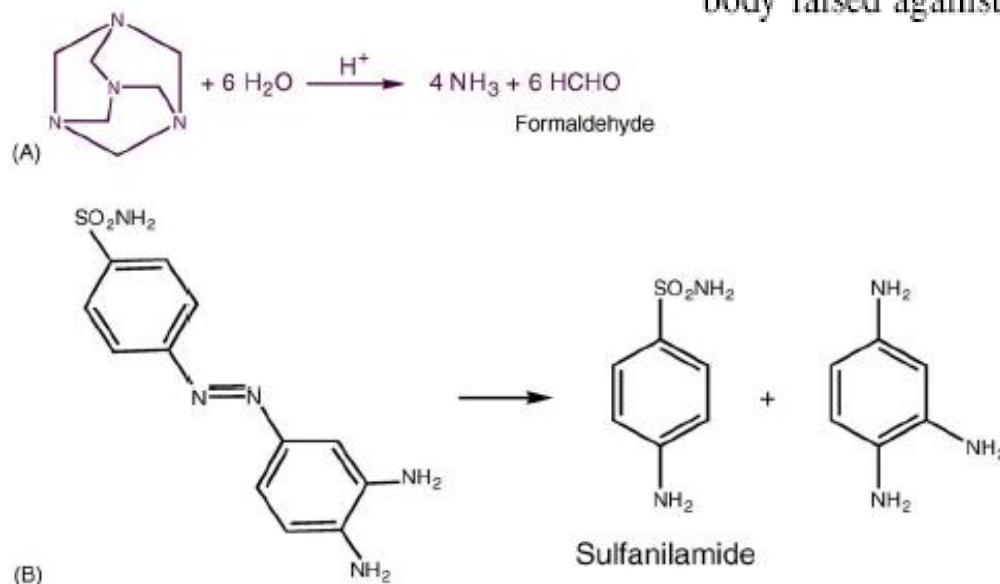
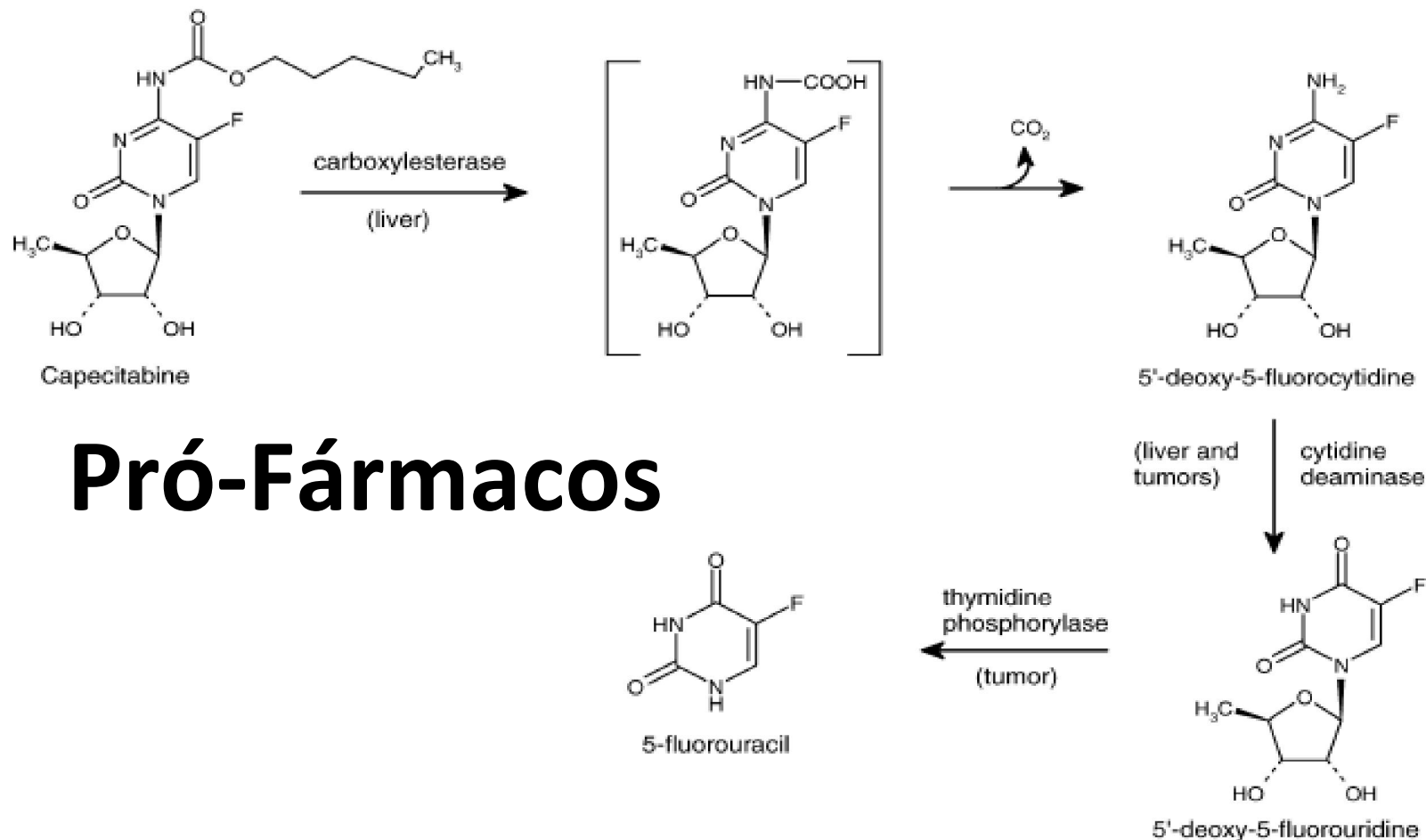


Fig. 1. Two historical examples of prodrugs. (A) Hexamine, an intentional prodrug of formaldehyde. (B) Prontosil, a fortuitous prodrug of sulfanilamide.



Pró-Fármacos

Fig. 6. The stepwise activation of capecitabine to the antitumor drug 5-fluorouracil. Note the tissue-selectivity of the last step.

Table 2

Tissue distribution of 5-fluorouracil (5-FU) following administration of 5-FU or its triple prodrug capecitabine^a

	Reported clinical dose range ($\mu\text{mol kg}^{-1}$)	AUC of 5-FU (nmol min mL^{-1}) ^b			AUC ratios ^b	
		GI tract	Blood	Tumor	Tumor/GI	Tumor/blood
Capecitabine p.o.	59–92	220–480	100–200	970–3,100	4.4–6.5	9.7–15.5
5-FU continuous i.v.	6–210	30–1,300	300–10,000	8–400	0.3–0.3	0.03–0.04
5-FU p.o.	19–41	4,400–13,000	25–100	0.9–3.4	0.002–0.003	0.03–0.03

^a The reported clinical ranges, AUCs and ratios are rounded off values taken from graphical data calculated by Tsukamoto et al. [35] using a physiologically based pharmacokinetic analysis.

^b The first and second values correspond respectively to the lower and upper limit of the reported clinical range.

Pró-Fármacos

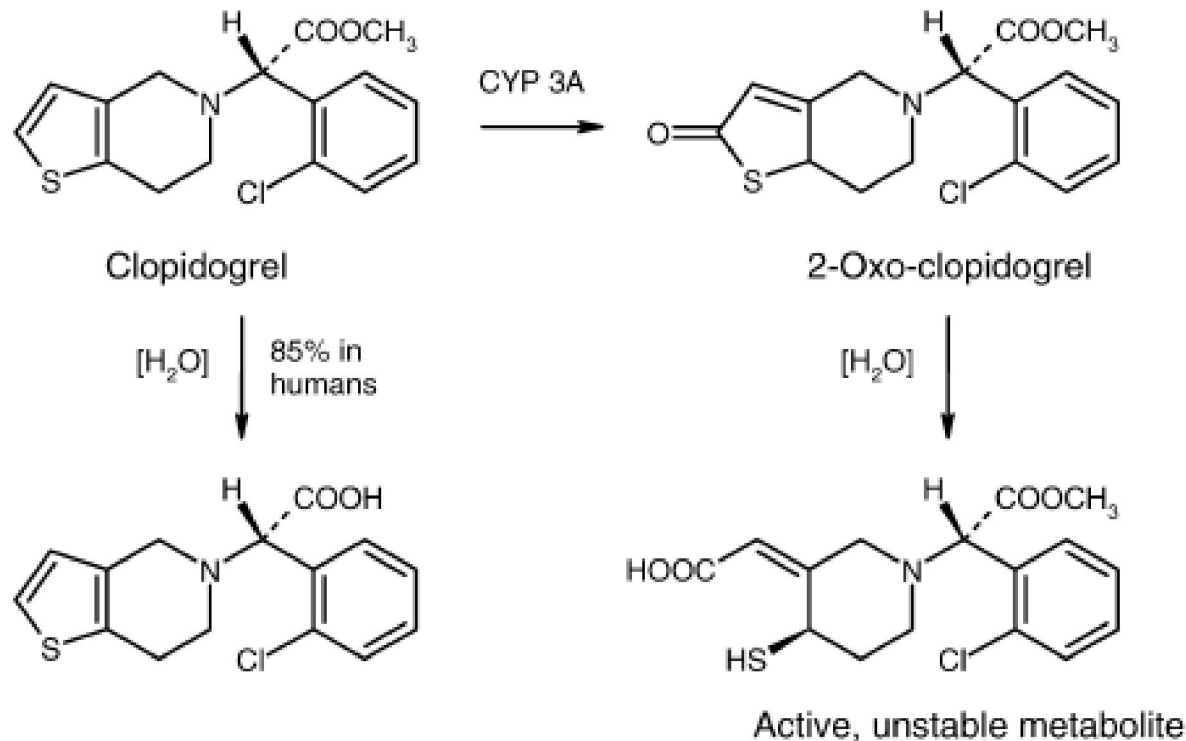
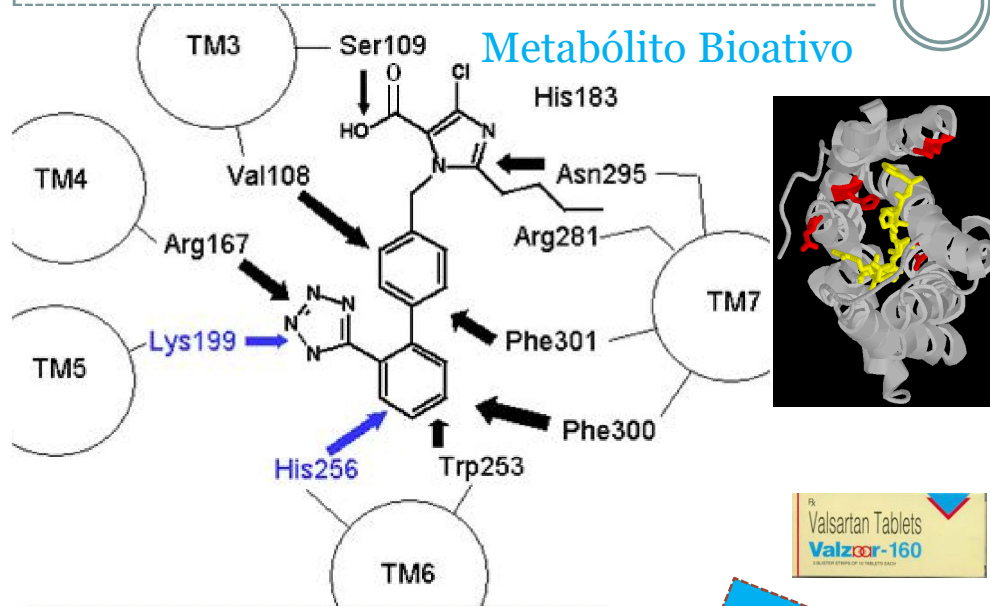
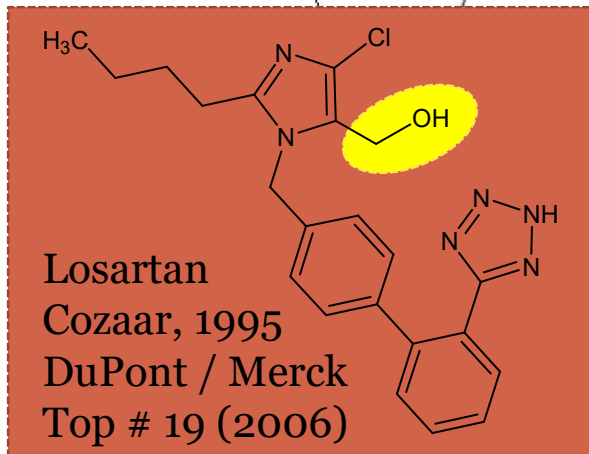
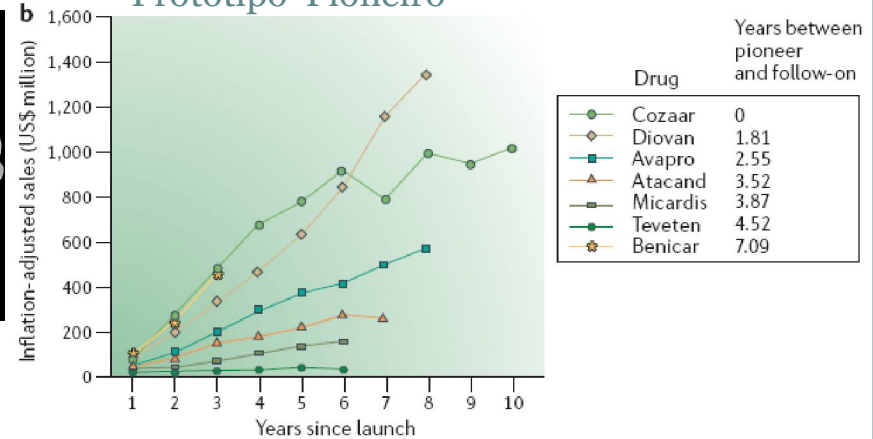


Fig. 7. Major metabolic reactions of clopidogrel in humans. Most of a dose is inactivated by hydrolysis, whereas a smaller part is activated by CYP3A to 2-oxo-clopidogrel, followed by spontaneous hydrolytic ring opening to the active agent, a highly reactive thiol metabolite which irreversibly antagonizes platelet ADP receptors via a covalent S-S bridge [37,38].

Antagonistas de Receptores AT1 de Angiotensina 2



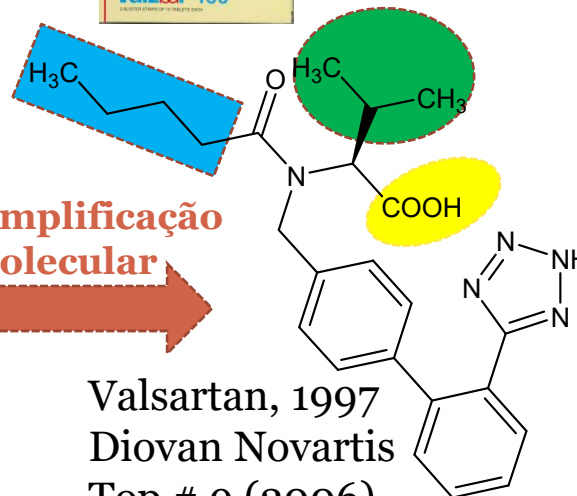
Tempo Relativo ao Lançamento do Protótipo Pioneiro



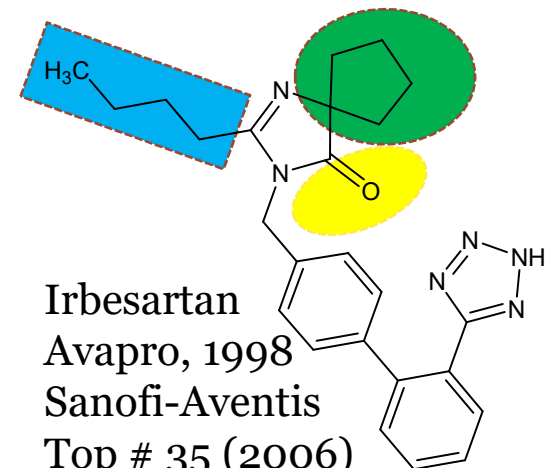
Simplificação Molecular



Valsartan, 1997
Diovan Novartis
Top # 9 (2006)



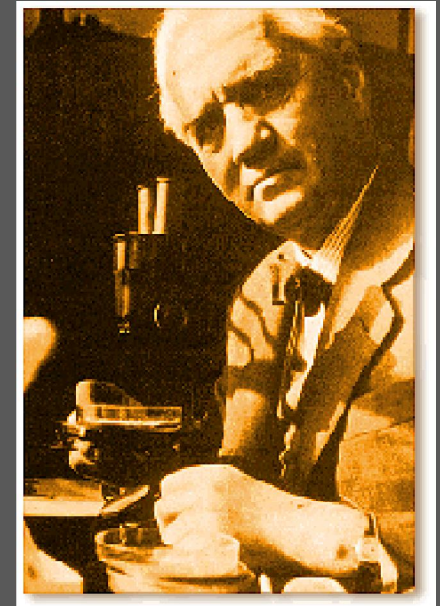
Irbesartan
Avapro, 1998
Sanofi-Aventis
Top # 35 (2006)



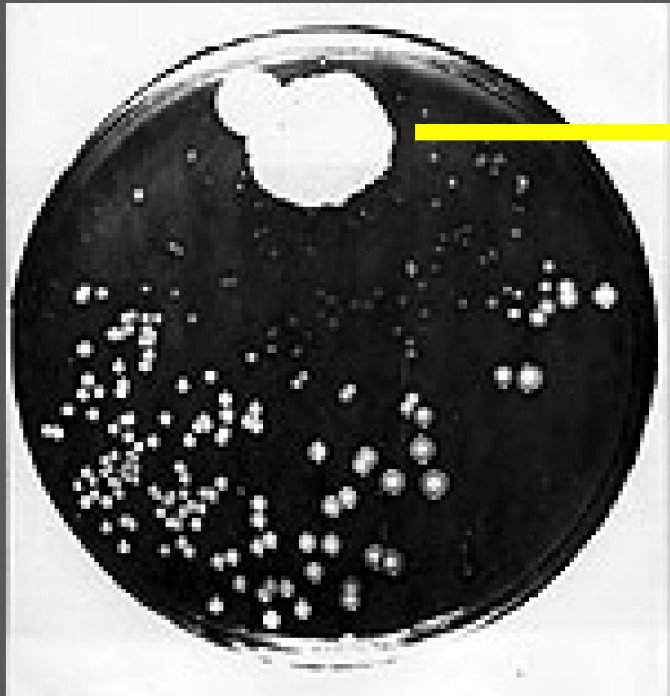
Contribuições do Acaso (**The Chance Discovery**)



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

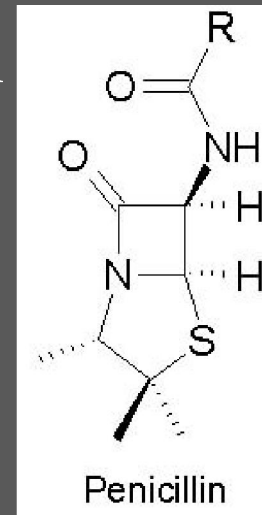
1941- Pesquisa foi transferida para os EUA
(USDA labs) em Peoria, Illinois

Summer

1943 - *Penicillium chrysogenum*

1944 - Caracterização Estrutural

1945 - Prêmio Nobel



R = Benzila

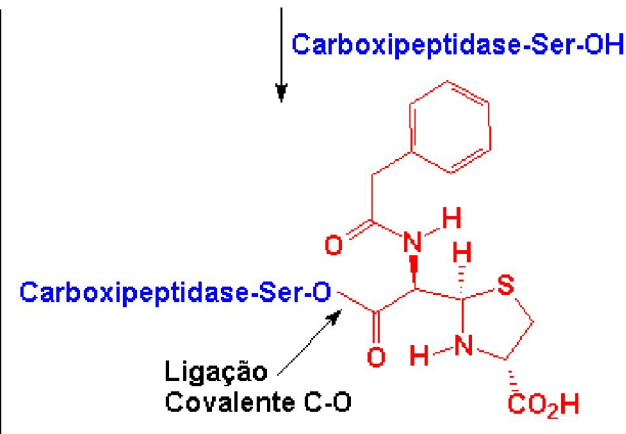
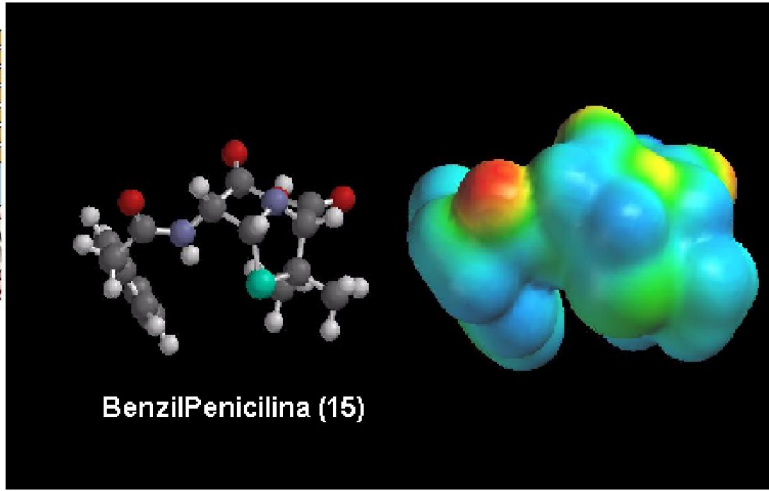
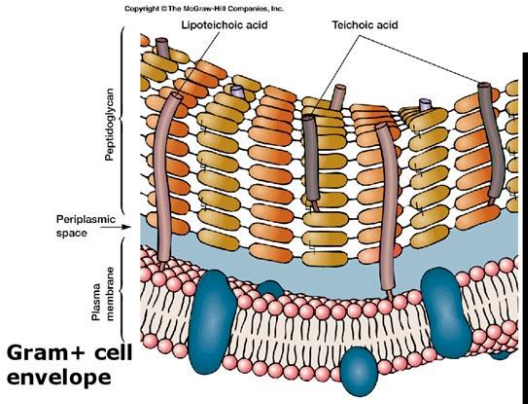
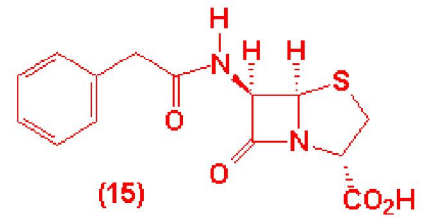
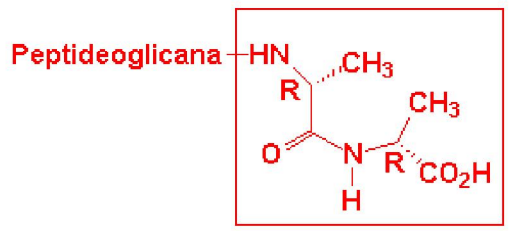
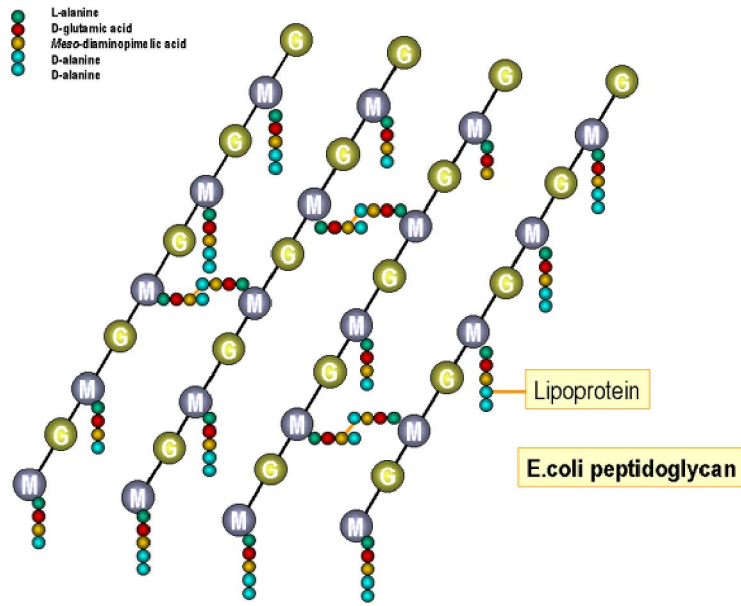


Penicilina ganha o mundo!!!

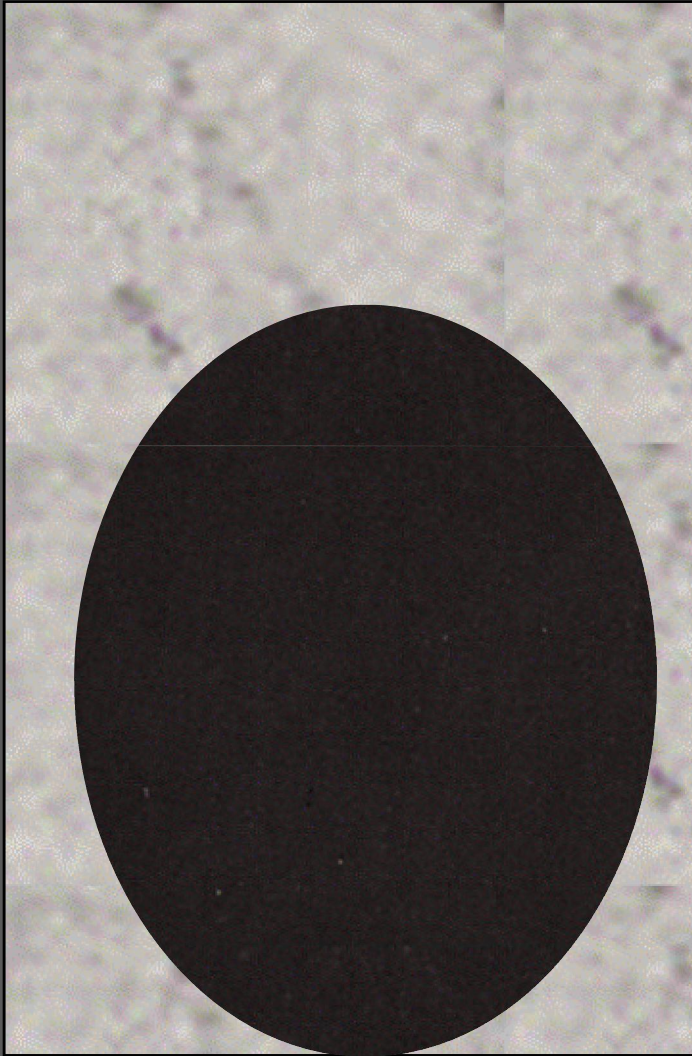
- Publicação: Florey, Chain, *et. al. Lancet*, 24 de Agosto de 1940;
- Naquele momento a 2ª Guerra Mundial avançava pela Europa, com muitos feridos e inúmeros mortos, como resultado de infecções bacterianas;
- **Clamor pela descoberta de Novos Antibacterianos!**
- **Primeiro Ensaio de Triagem Clínica: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



Mecanismo de Ação das Penicilinas



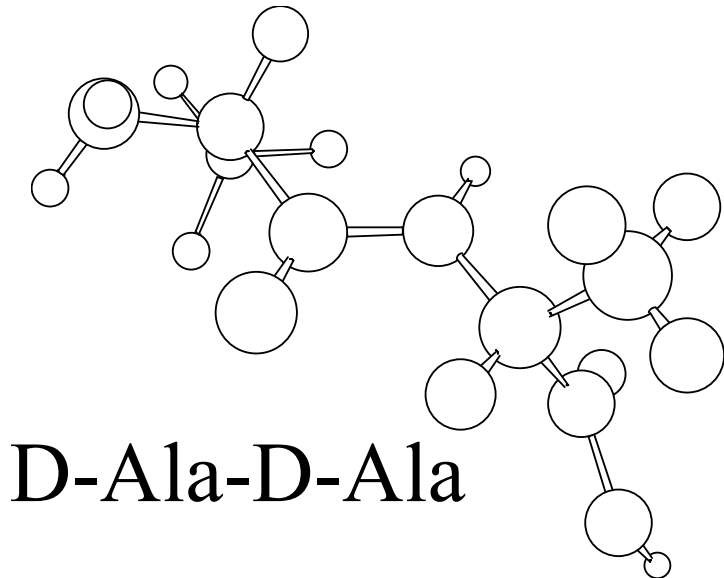
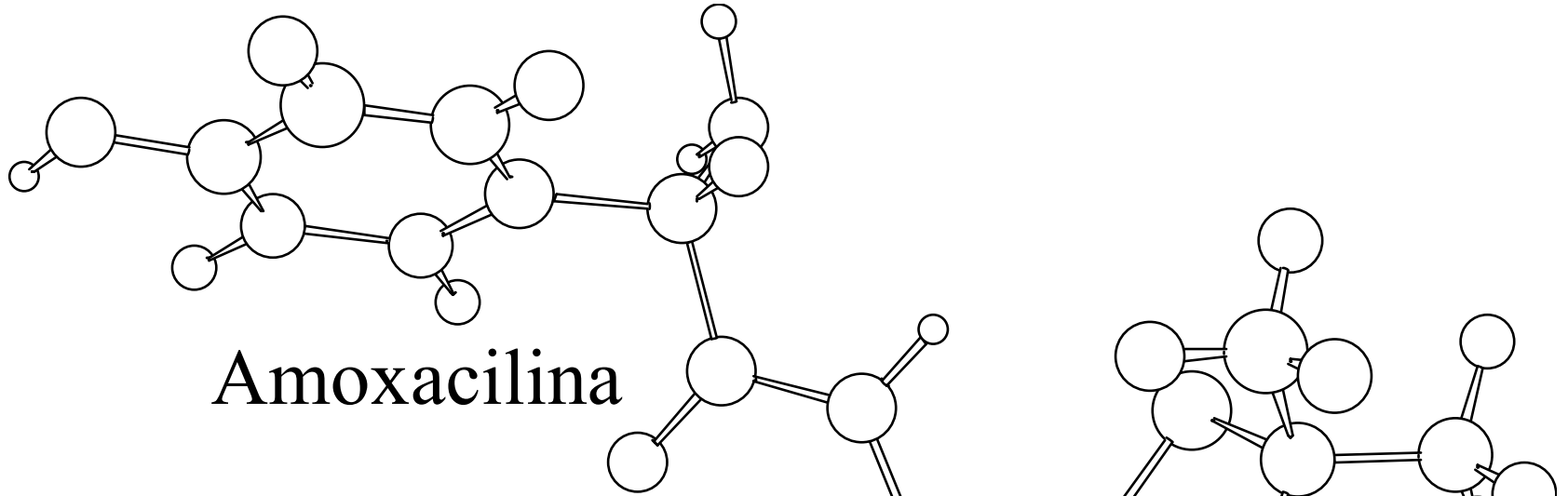
STAPHYLOCOCCUS



STAPHYLOCOCCUS TRATADO C/ PENICILINA



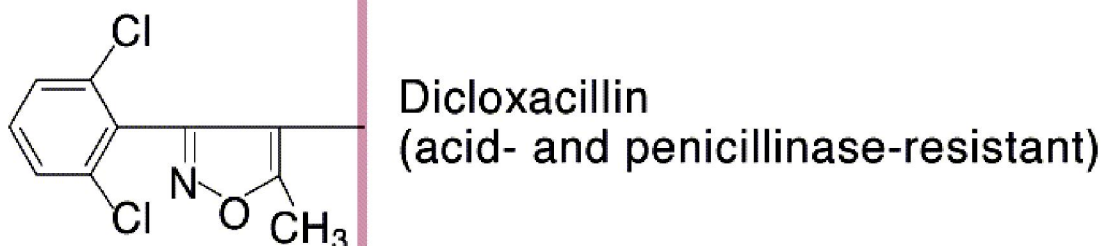
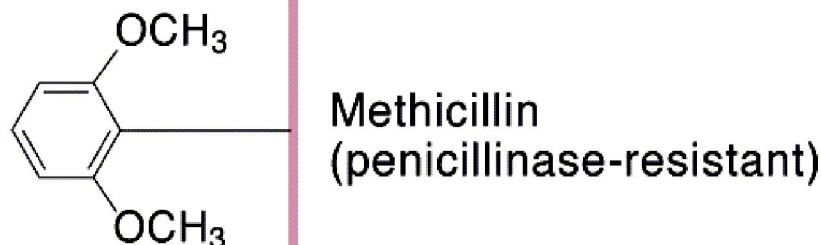
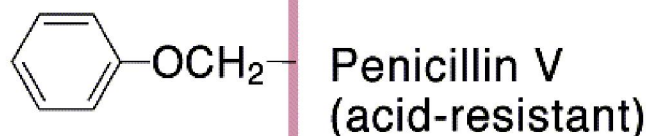
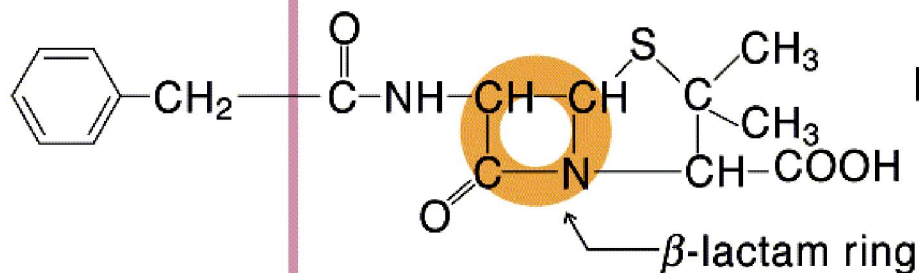
Amoxicilina vs D-Ala-D-Ala



Família de Penicilinas

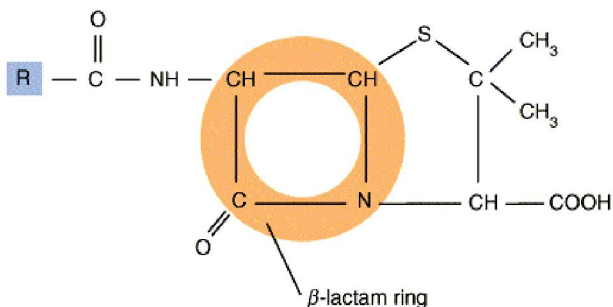
Side Chain

Basic Structure



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(a) Penicillin



(b) Cephalosporin

