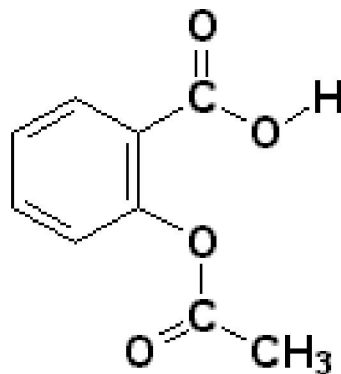
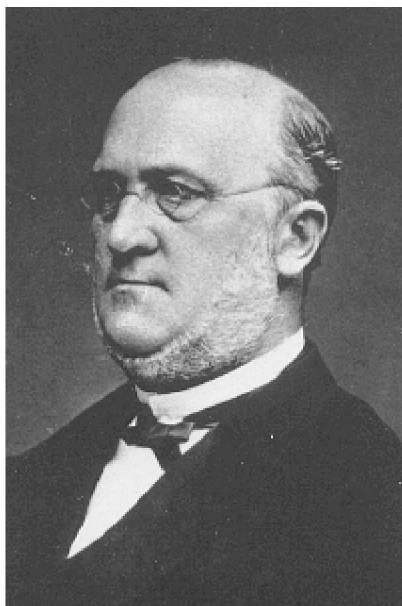


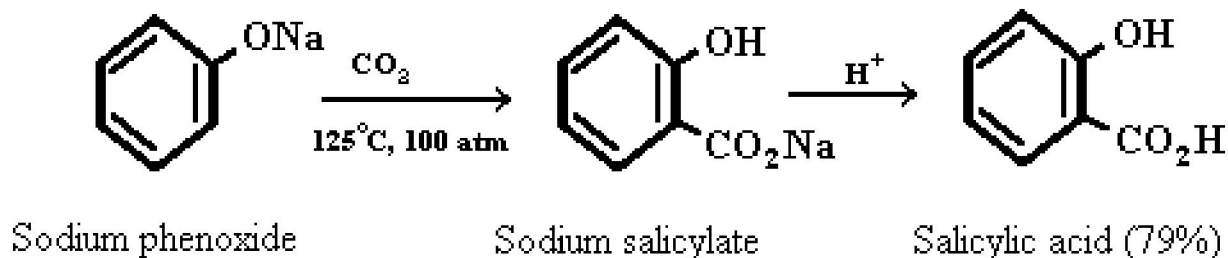
AAS



- 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.



The Kolbe Synthesis

Ácido Acetilsalicílico

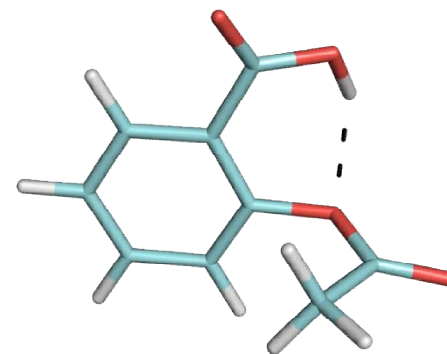
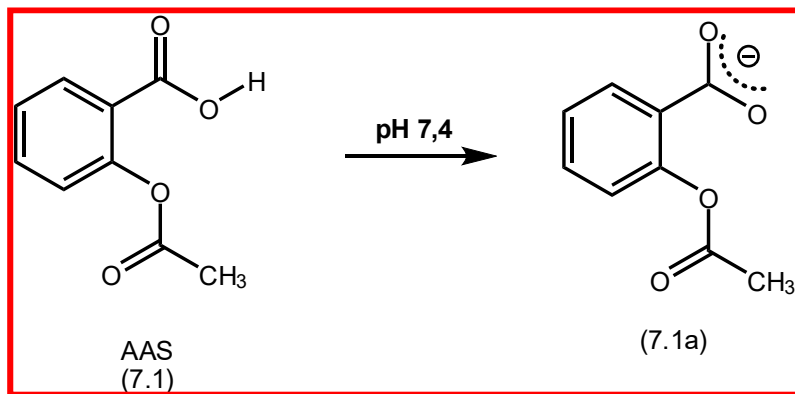
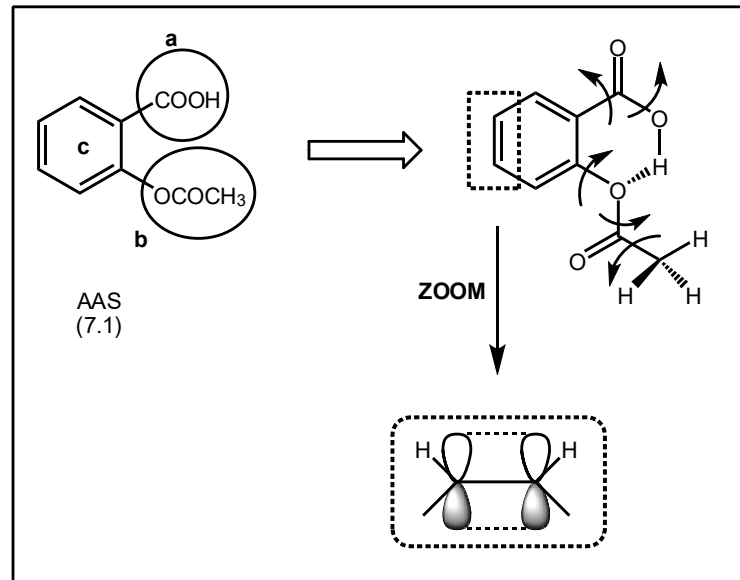
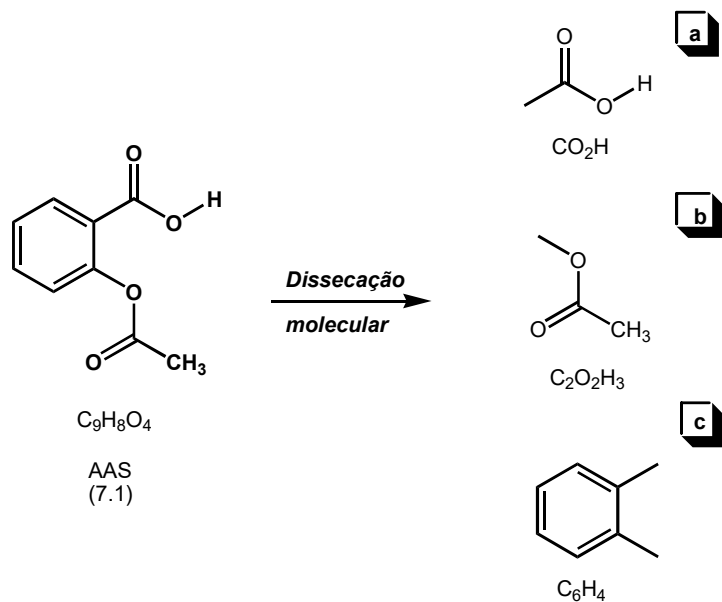
- 1897: Felix Hoffmann, químico das indústrias Bayer na Alemanha, preparou a primeira amostra pura de AAS. Se inicia a história do AAS como conhecida até hoje.
- 1899: Ensaio clínico indicam os promissores efeitos curativos do AAS. Bayer batiza o AAS de ASPIRINA e a companhia começa a distribuí-la para os médicos (NA FORMA DE PÓ) administrarem em seus pacientes.



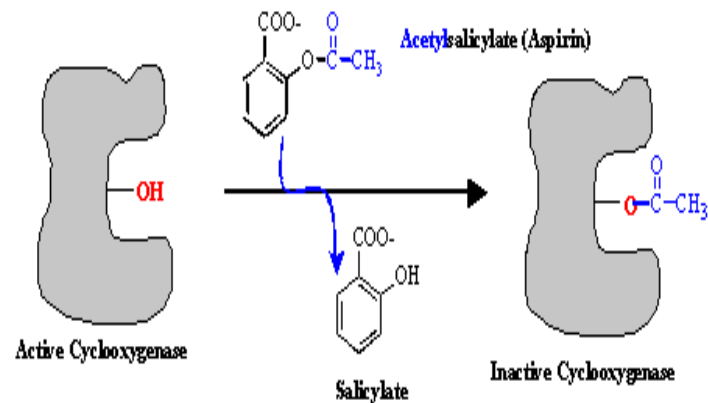
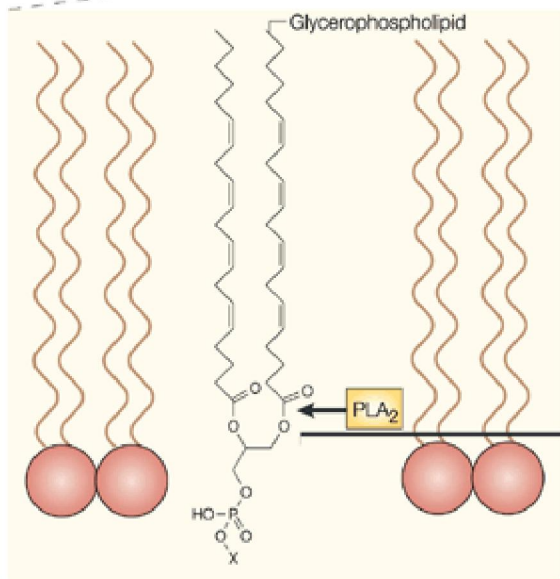
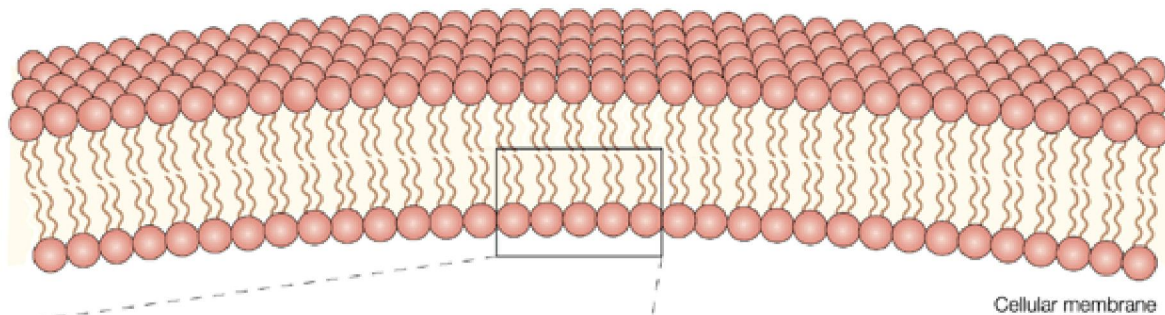
- 1900: Bayer introduz o primeiro comprimido de aspirina solúvel em água. Este processo reduz o custo à metade.
- 1915: Aspirina começa a ser utilizada sem prescrição médica.



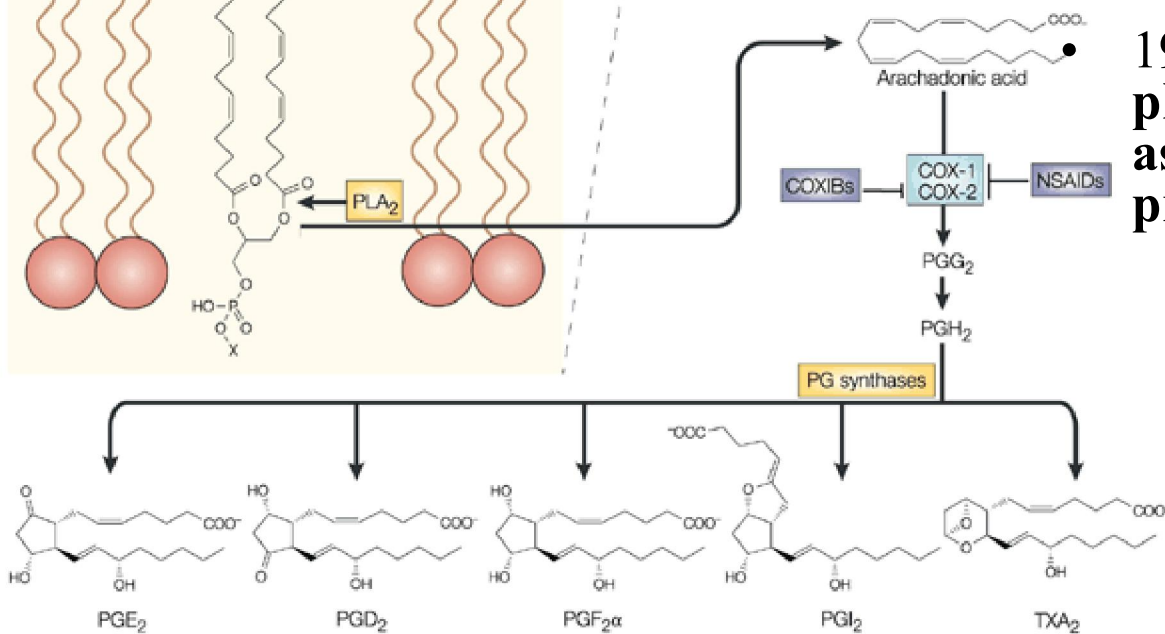
Fatores Estruturais e a Ação Farmacológica



Mecanismo de Ação do AAS



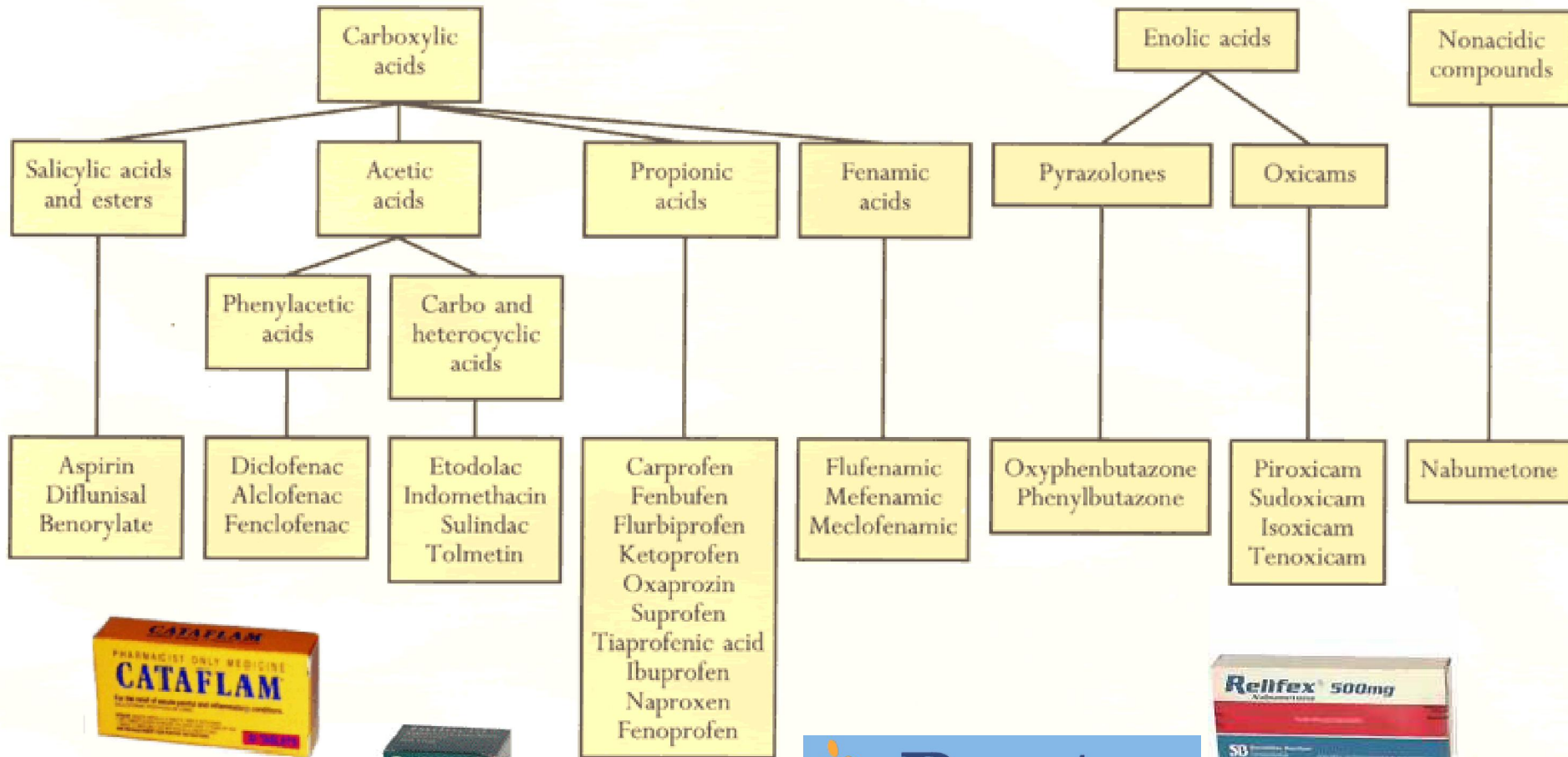
1971: John Vane, British pharmacologist, discovers that aspirin works] by inhibiting the production of prostaglandins.



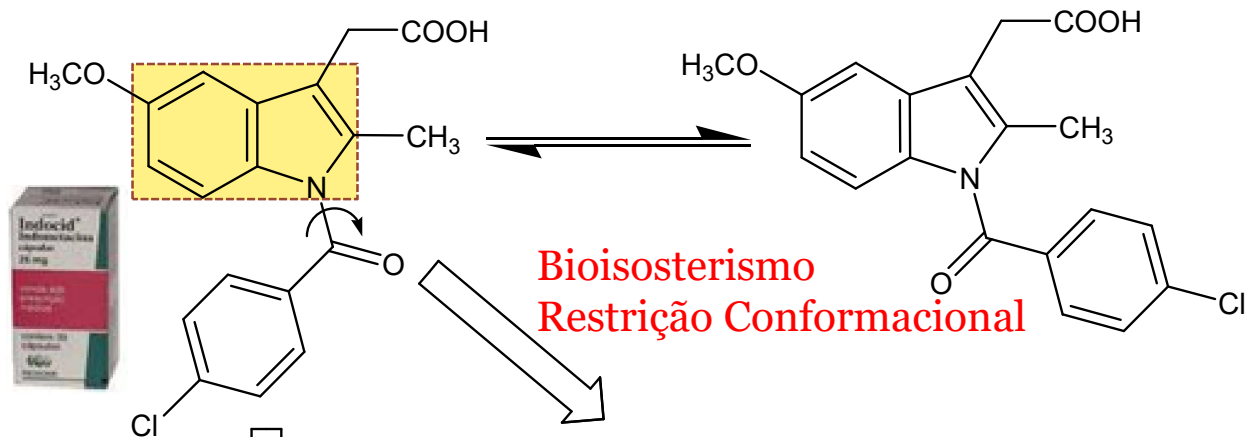
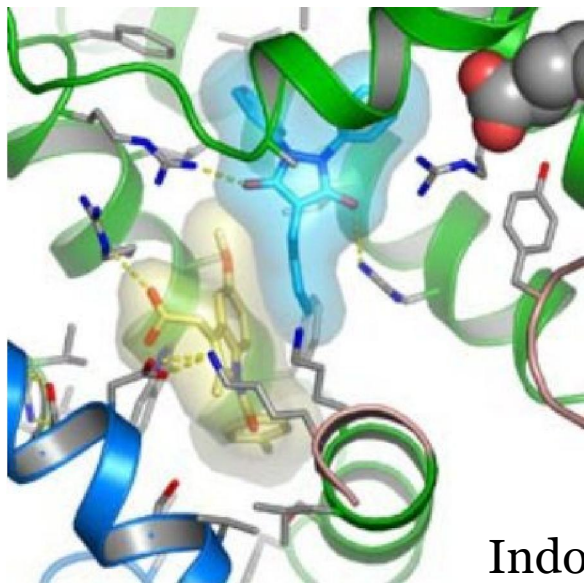
Nobel
Medicina
1982



Classificação dos AINE's

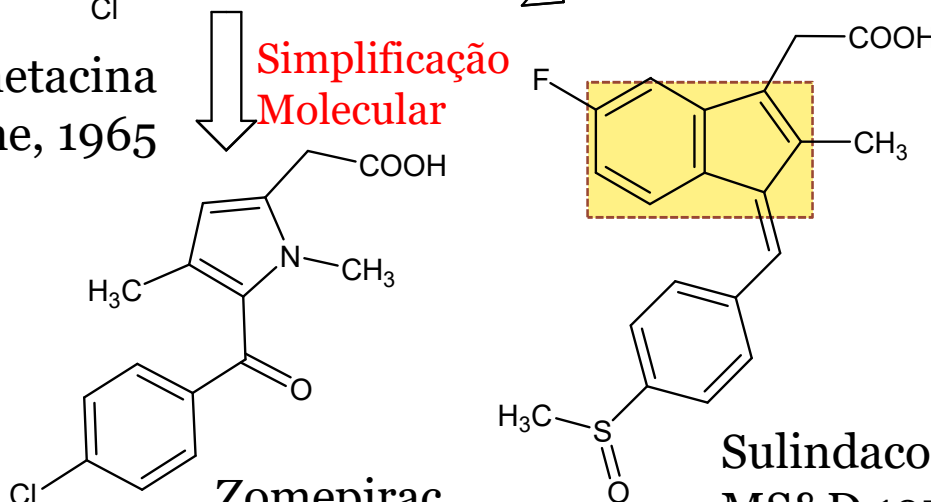


Estratégias de Modificação Molecular na Gênese de AINE's Me-too e Me-better



Indometacina
Merck Sharp&Dohme, 1965

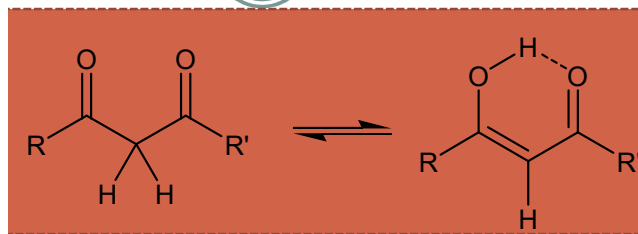
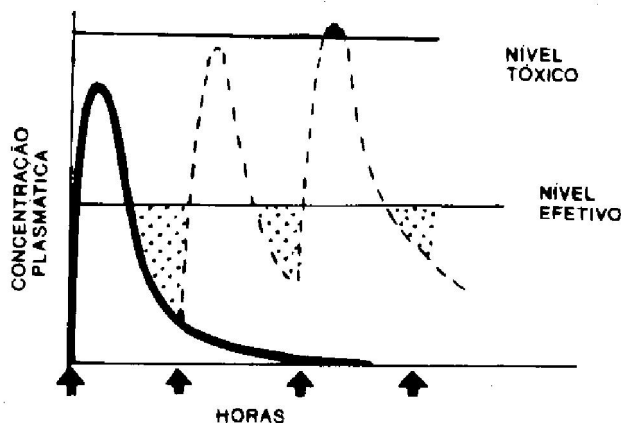
Simplificação Molecular



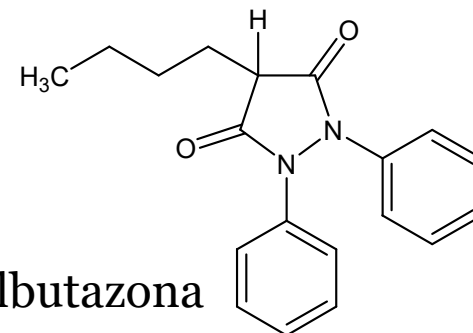
1971: **John Vane**,
descobre que o
mecanismo de ação
da aspirina e outros
AINE's envolve a
Inibição da COX.



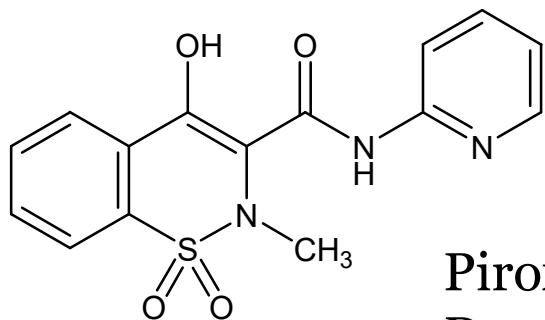
Impactos sobre os AINE's de 2ª Geração



Ácidos Enólicos



Fenilbutazona



Piroxicam
Dose Única
Diária: 20 mg

J. G. Lombardino,
Pfizer, 1971

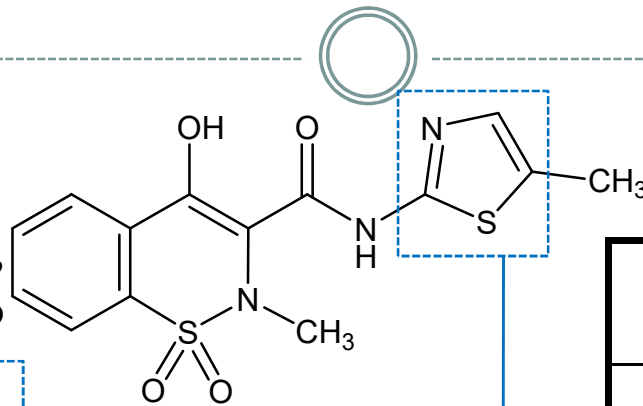


AINE	Tempo de Meia-Vida (h)		
	Rato	Macaco	Homem
Fenilbutazona	6	7	72
Indometacina	4	0,3	2
Ibuprofeno	1	---	3
Naproxeno	5	1,9	13,9
Piroxicam	16	5	45

Bioisosterismo Clássico: Tenoxicam e Meloxicam

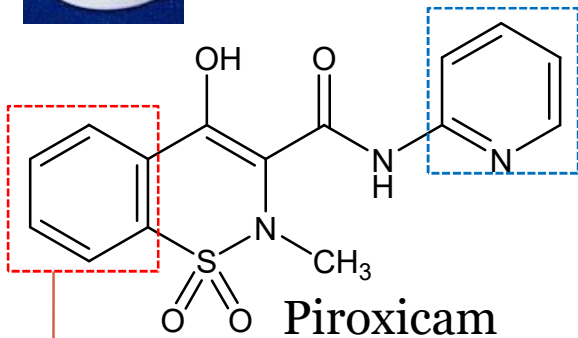


Meloxicam,
Boehringer, 1996



Potencial de Ulcerogeneidade

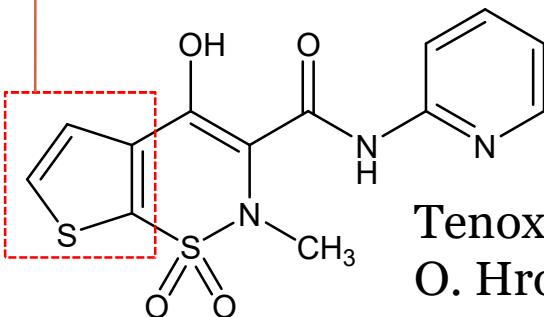
AINE	UD ₅₀ /ED ₅₀
Aspirina	1,6
Fenilbutazona	1,8
Diclofenaco	3,1
Indometacina	9,2
Piroxicam	10,9
Tenoxicam	50,0



Bioisosterismo de Anéis

Bioisosterismo de Anéis

Inibidor Seletivo
COX-2 vs COX-1



Tenoxicam
O. Hromatka, Roche, 1981

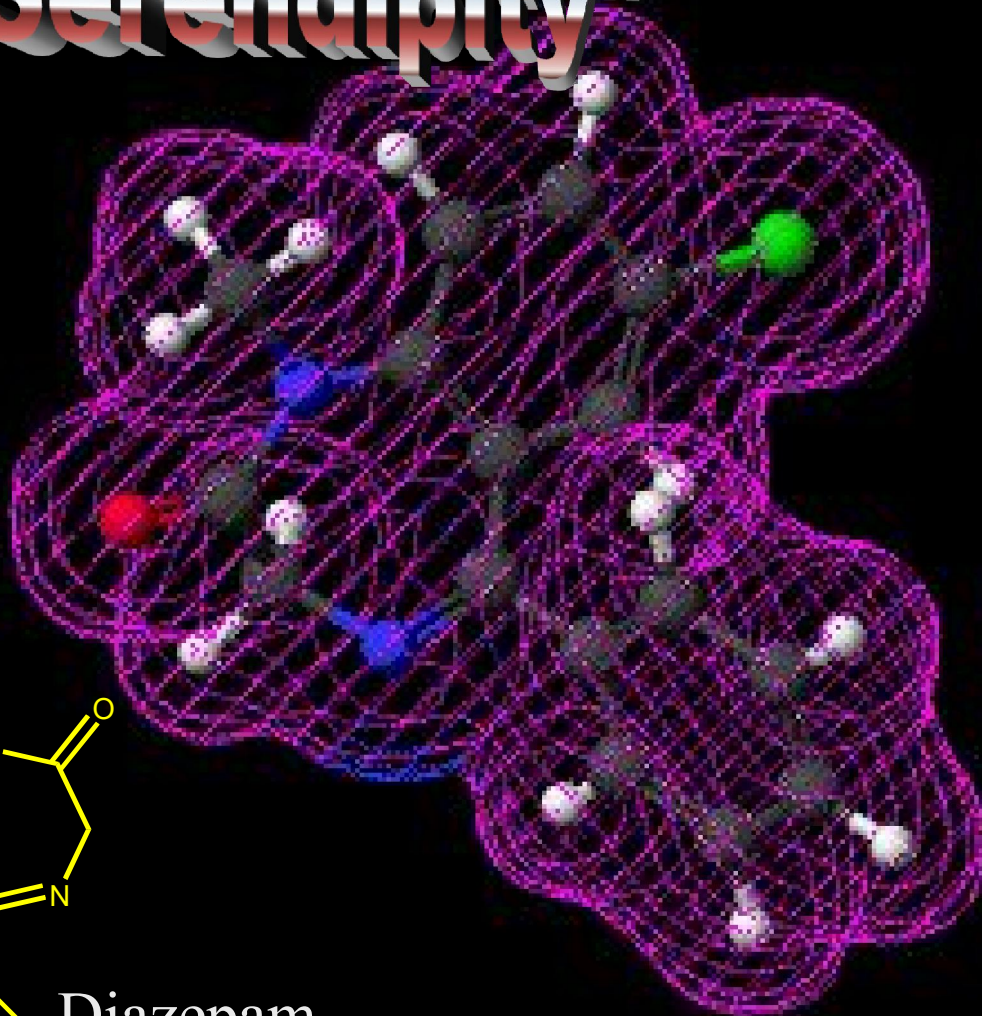


A História dos Fármacos Benzodiazepínicos



Leo Sternbach
Roche, 1959

"Serendipity"



Diazepam

US\$ 21.000.000.000,00/ano

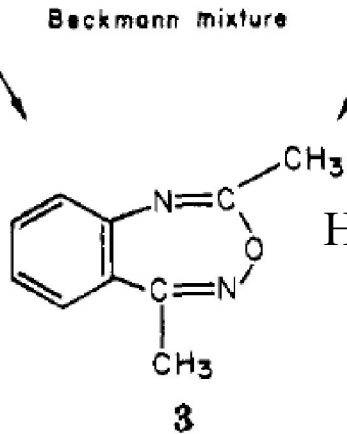
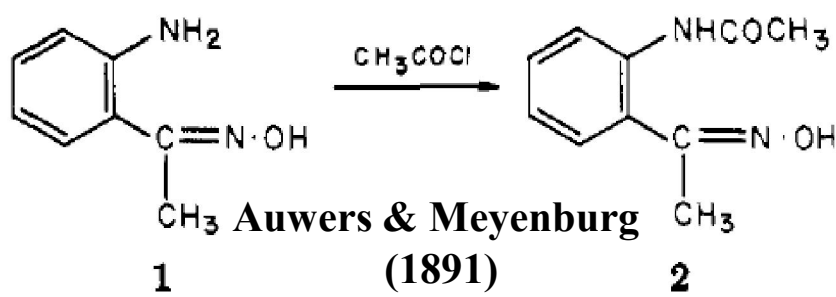


O início do problema...

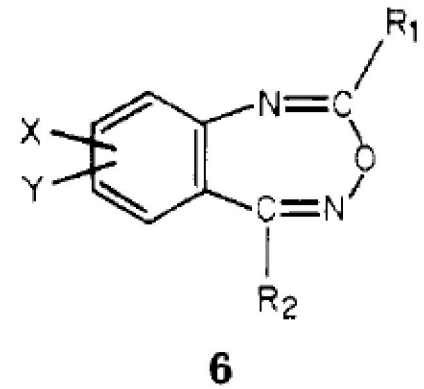
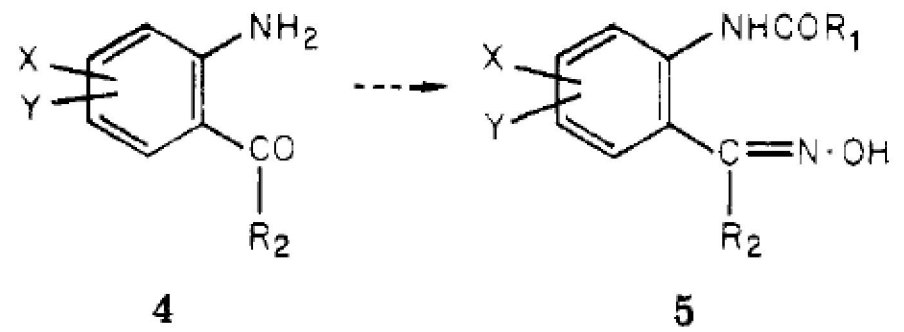
Desenvolvimento de Novos Tranquilizantes
(Roche, 1950)

Modificação de Protótipos já Existentes
x Novas Classes Químicas

Pós-Doutorado (Univ. Cracóvia, 1930) –
Corantes e Intermediários Sintéticos



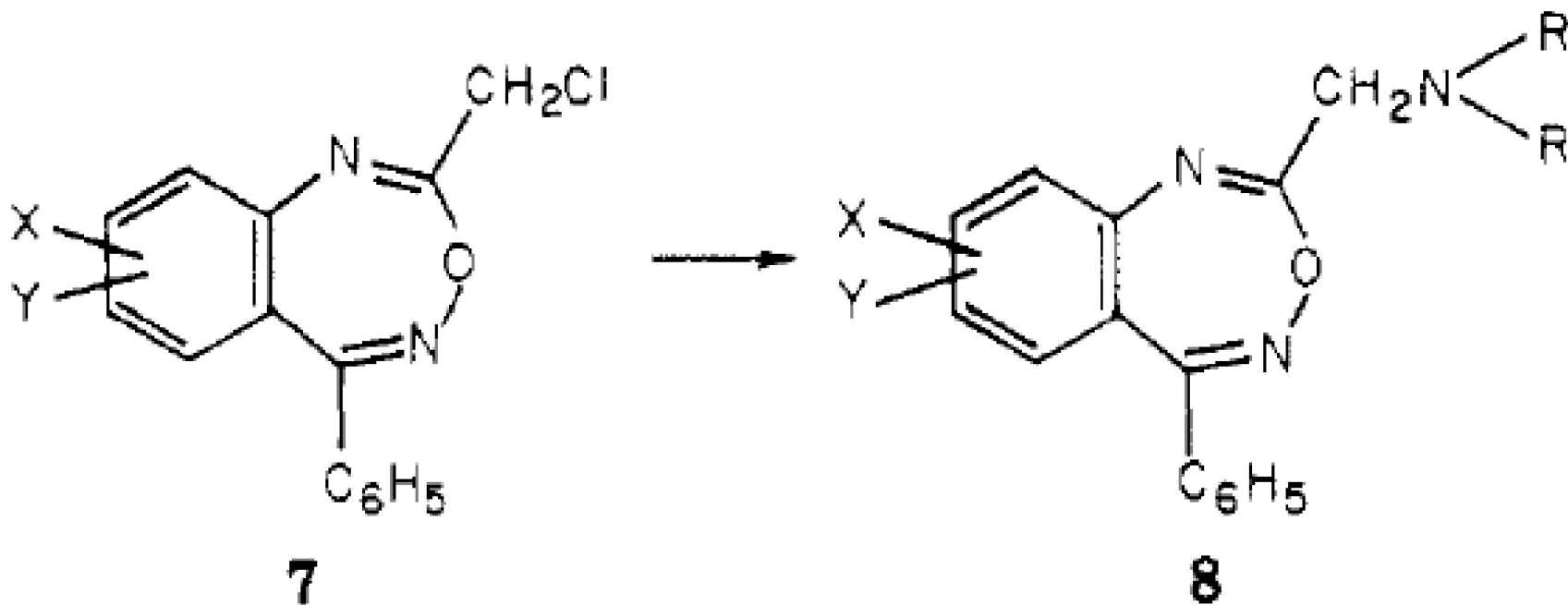
Heptoxdiazines (Estrutura química
caracterizada em 1924)



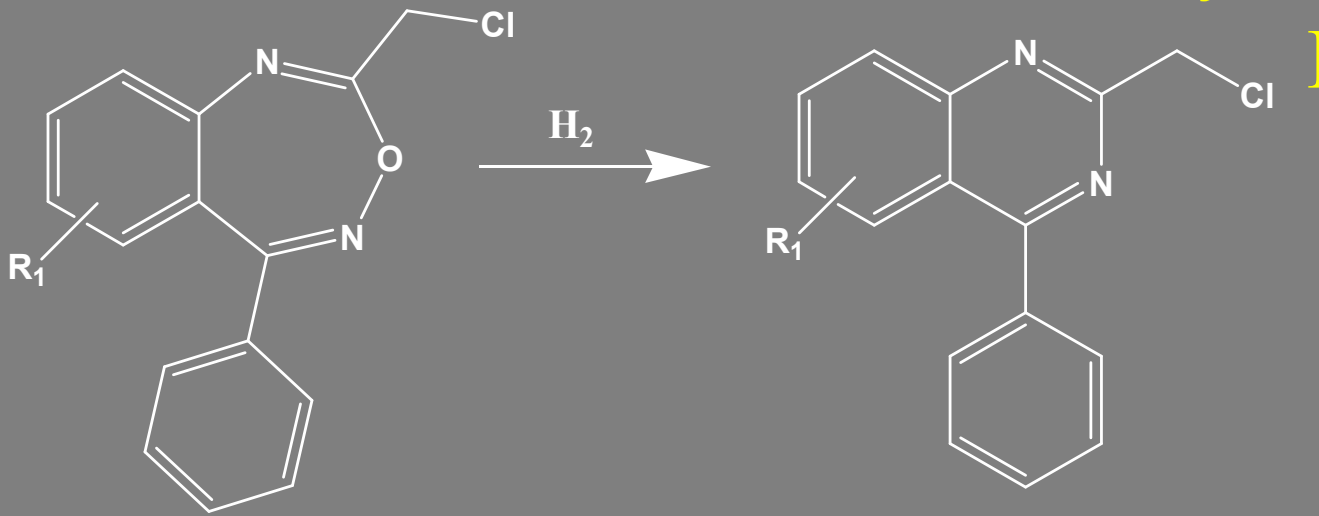
- Meprobamato (Miltown)
- Clorpromazina (SKF)
- Fenobarbital (Rhodia)

- Pouco Explorada
- Acessível
- Permitir Múltiplas Variações
- Desafio Químico
- Potencial Atividade Biológica

Definição da Estratégia

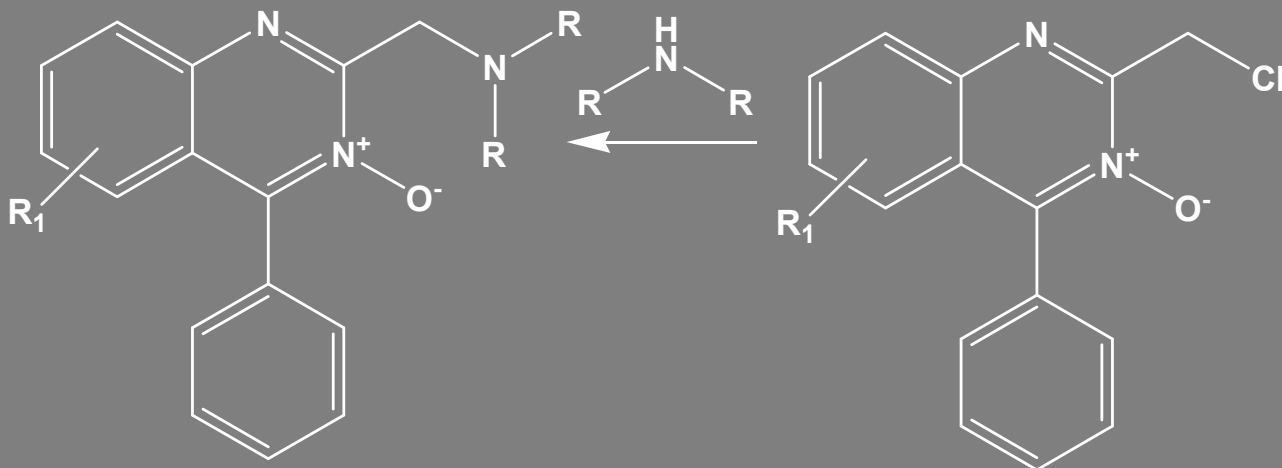


Confirmação da Estrutura das Heptoxadiazinas



Propriedades
Farmacológicas:
Aminas-N-óxido

ou os produtos
hidrogenados
correspondentes
foram inativos



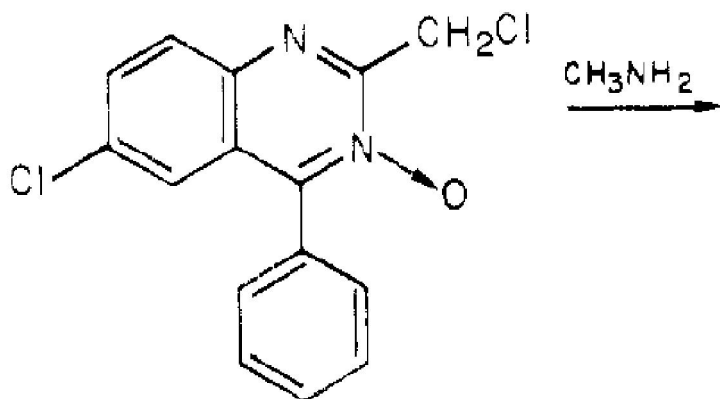
Quinazolininas-N-Óxidos

- 1955 (Segunda Metade): Trabalho com as Quinazolininas foi interrompido.

- Isolamento, Purificação e Degradação de Vários Antibióticos

- 1957: Limpeza do Laboratório

Earl Reeder (Identifica dois produtos)



11

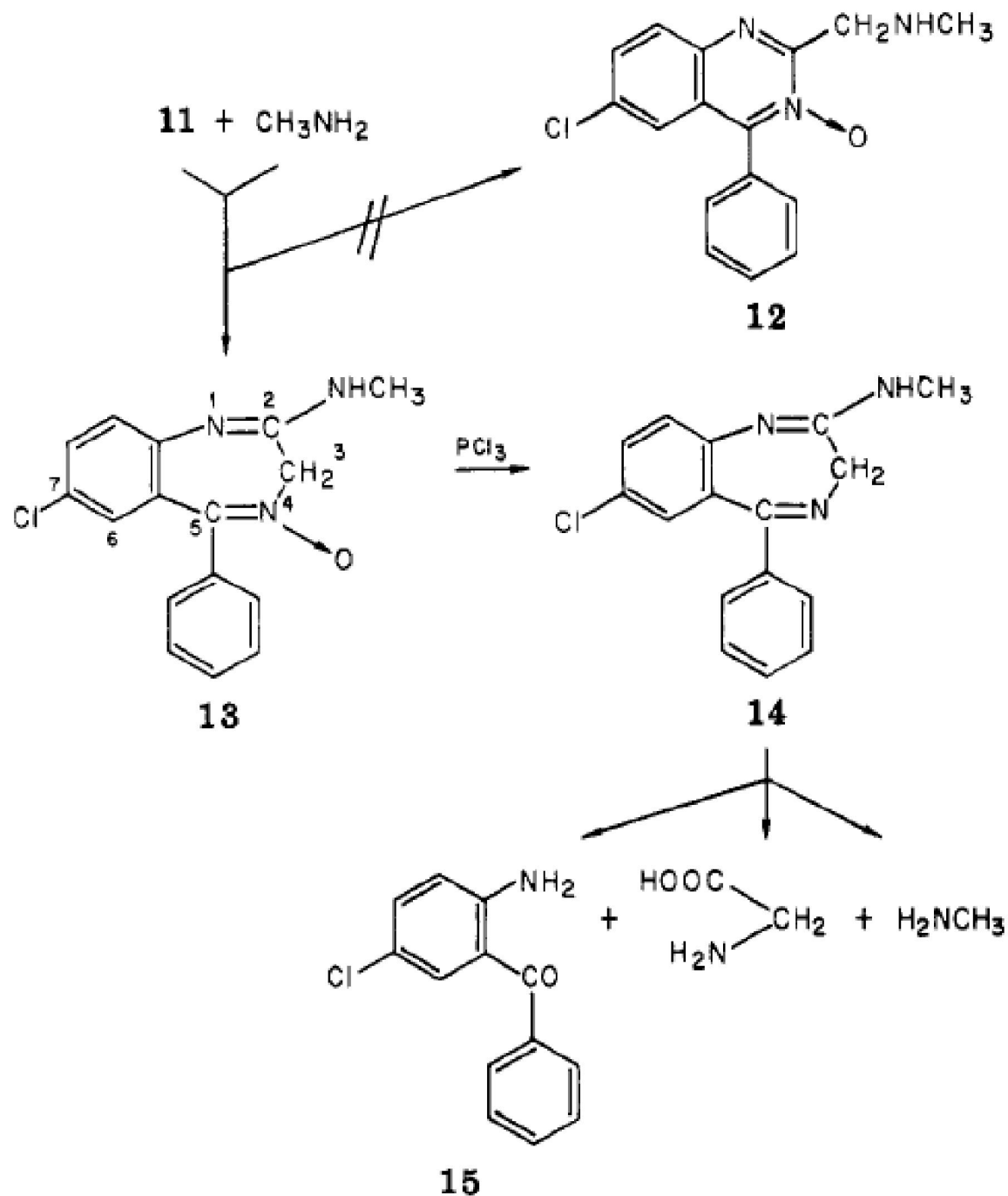
- 1957 (Maio): Dr. Lowell Randall, Farmacologista

Table I. Pharmacological Properties^a of “New Compound”, Meprobamate, Chlorpromazine, and Phenobarbital

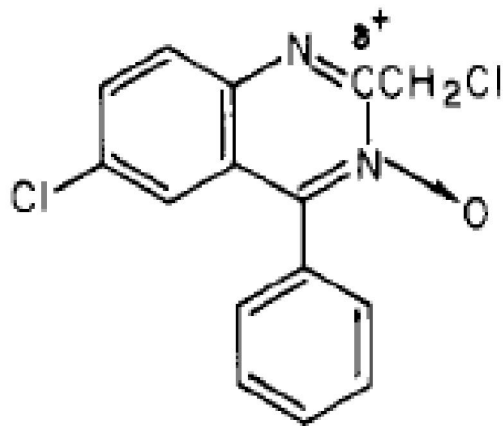
compd	inclined screen	foot shock	cat	anticonvulsant tests		
				pentylene-tetrazole	electroshock	
					max	min
new compound	100	40	2	18	92	150
meprobamate	250	250	100	150	200	167
chlorpromazine	17	20	2.5	42	150	600
phenobarbital	120	80	10	75	18	90

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

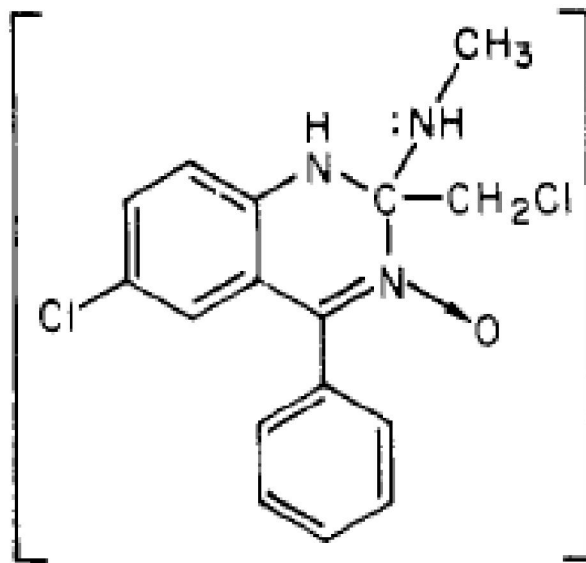
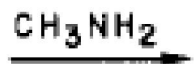
Scheme I



Caracterização
Estrutural
do
“Novo Composto”



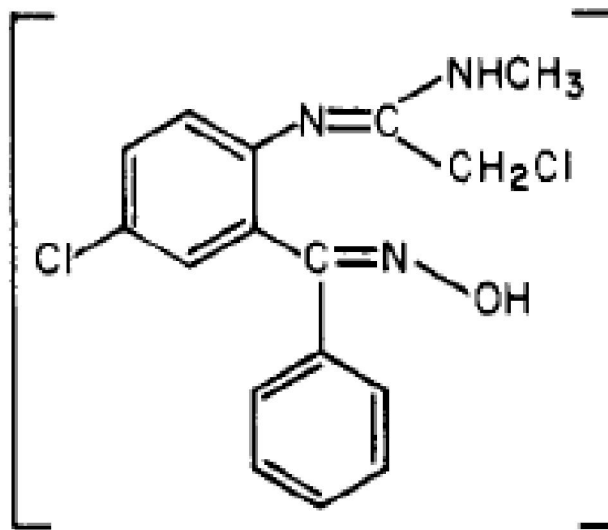
11a



16



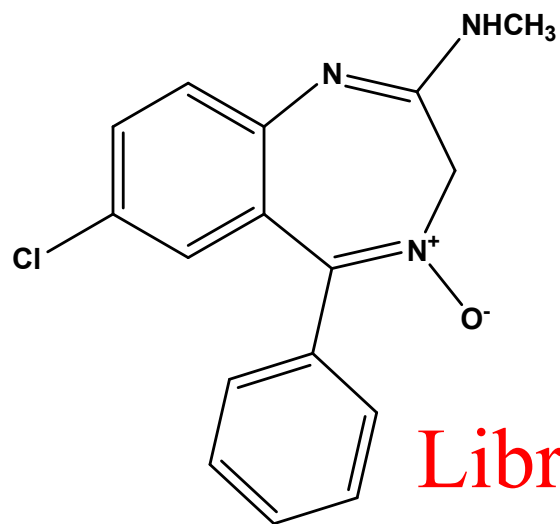
13



17

Mecanismo
de
Formação
dos
Derivados
Benzodiazepínicos

Caracterização Farmacológica dos Produtos de Transformação do Clordiazepóxido (13)



Librium^R

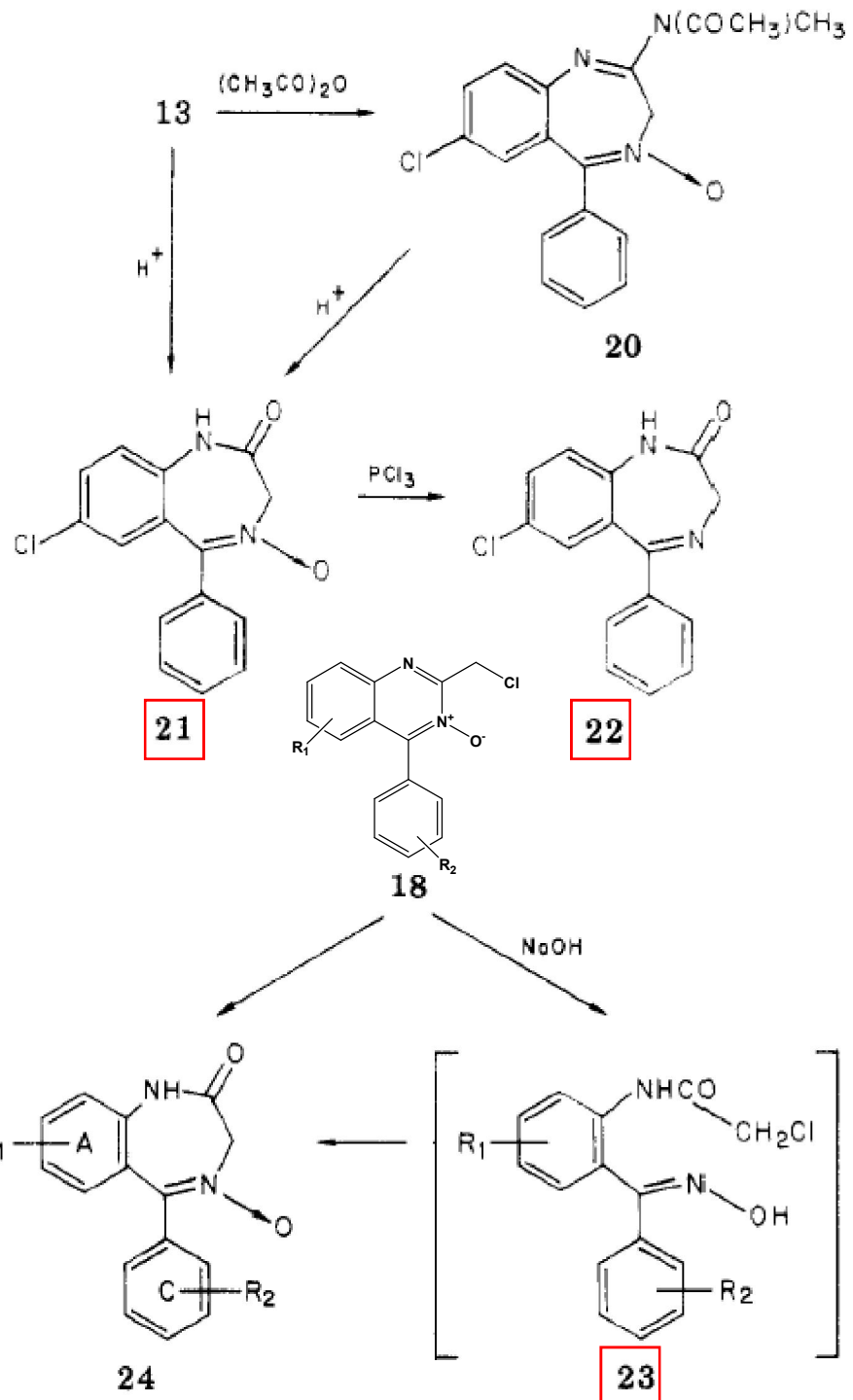
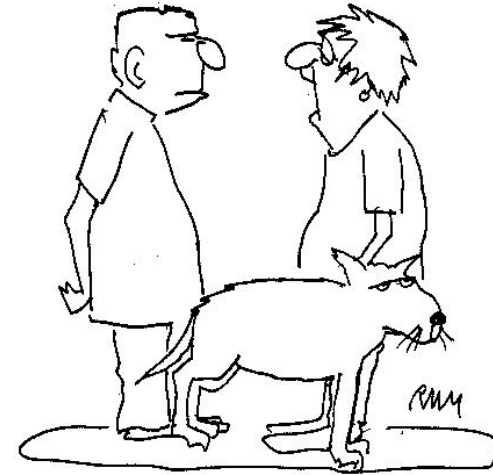
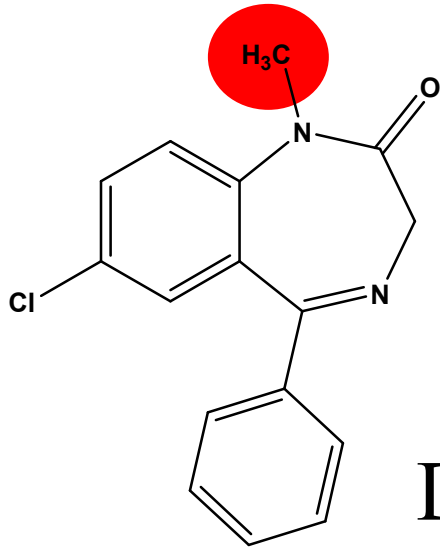


Table II. Pharmacological Activity^a of Clordiazepoxide and Its Transformation Products

compd	in- clined screen	foot shock	cat	anticonvulsant tests		
				pen- tylene tetra- zole	electroshock	
					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)

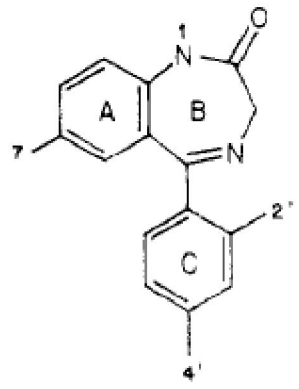
Table III. Comparison of the Pharmacological Activity^a of Chlordiazepoxide with That of Diazepam

compd	inclined screen	foot shock	cat	anticonvulsant tests		
				pentylene-tetrazole	electroshock	
					max	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.

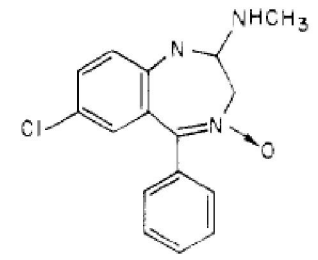
- Mercado Farmacêutico:
- Librium[®] foi lançado em 1959
- Valium[®] foi lançado logo em seguida (1963)

SAR dos Benzodiazepínicos

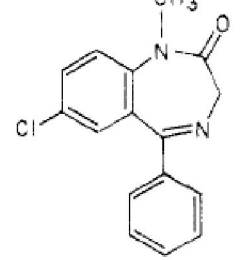


32

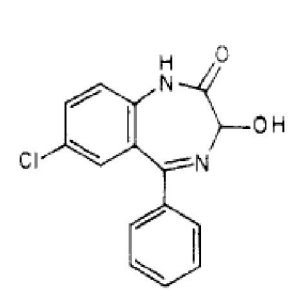
^a Ring A: (position 7) generally, increased by electron-withdrawing groups, e.g., halogens, NO₂, and CF₃, and decreased by electron-releasing groups such as CH₃ and OCH₃; decreased by any substituents in any positions other than 7. Ring B: increased by a methyl group at position 1; decreased by larger substituents; *tert*-butyl derivative is completely inactive. Ring C: increased by halogens at the 2' position (e.g., Cl and F); very strongly decreased by a substituent at the 4' position.



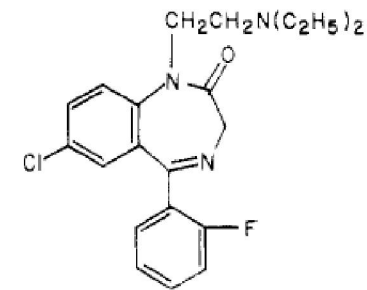
chlordiazepoxide^a
(Librium, 1960)



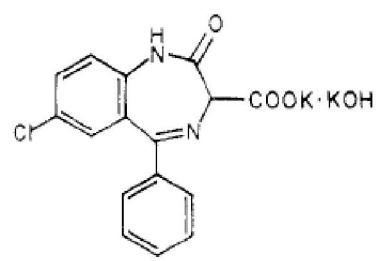
diazepam
(Valium, 1963)



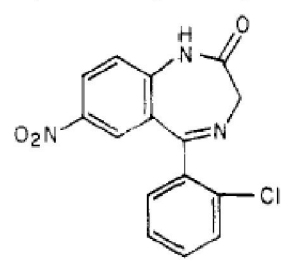
oxazepam
(Serax, 1965)



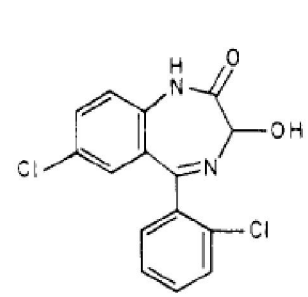
flurazepam^b
(Dalmane, 1970)



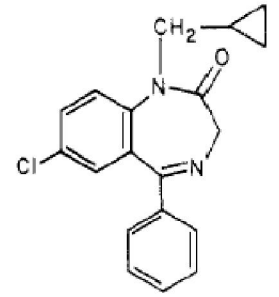
clorazepate
(Tranxene, 1972)



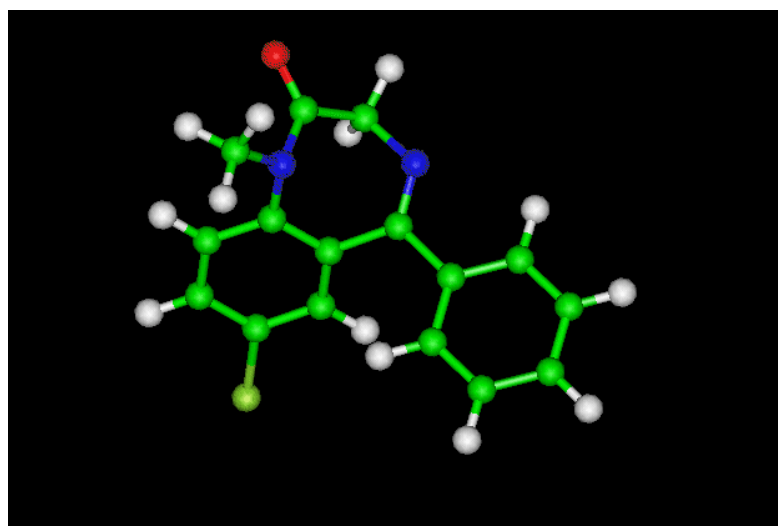
clonazepam
(Clonopin, 1975)



lorazepam
(Ativan, 1977)

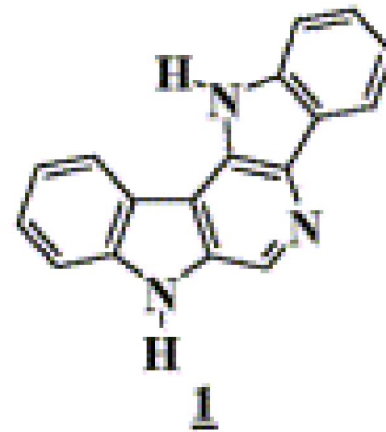
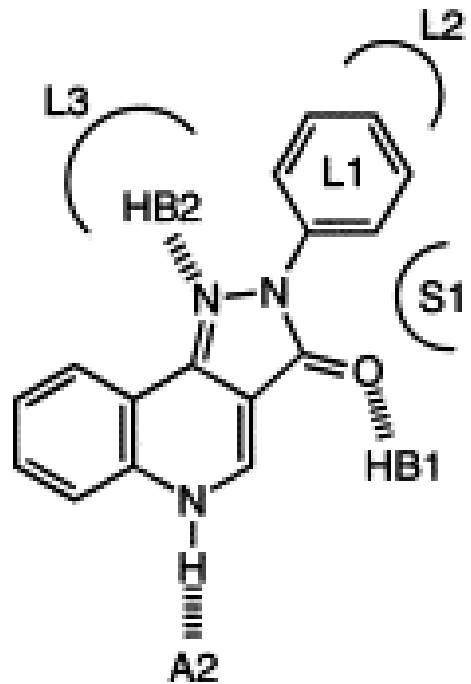
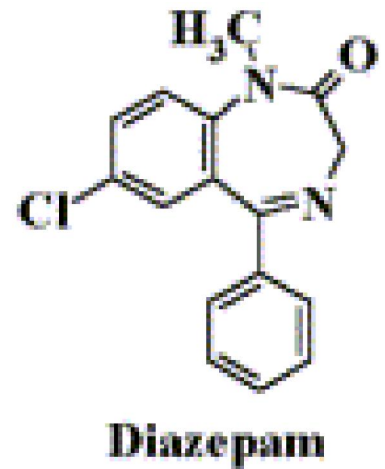
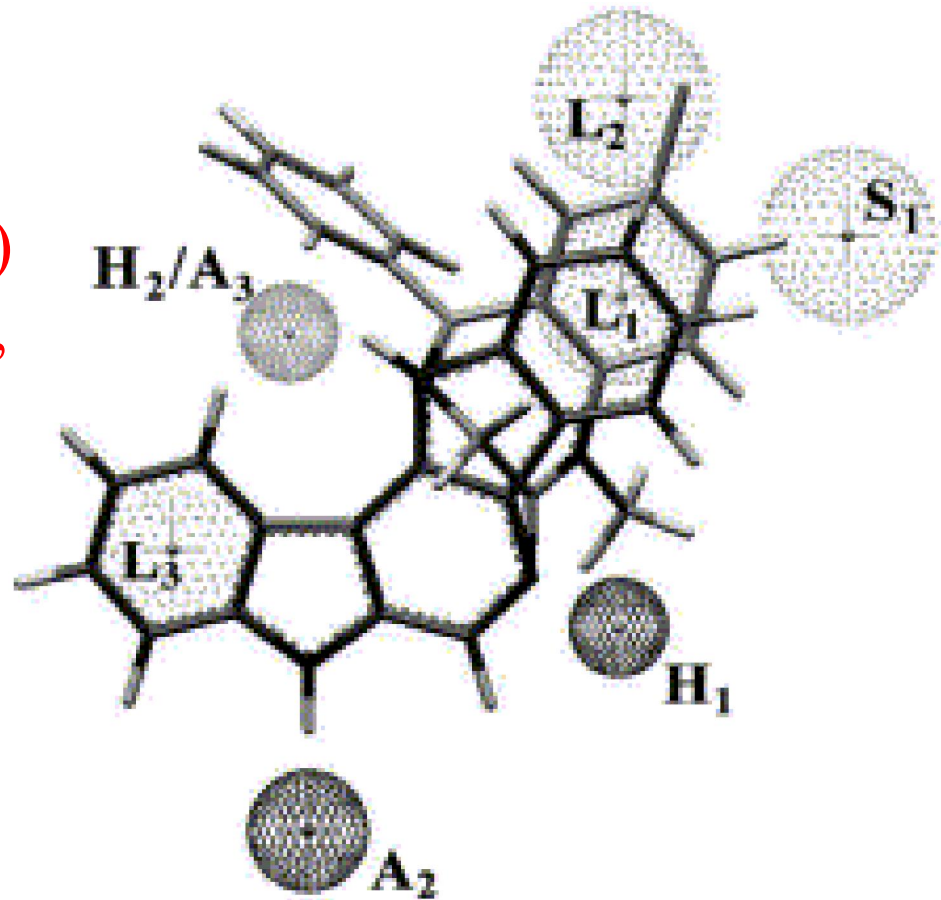


prazepam
(Verstran, 1977)



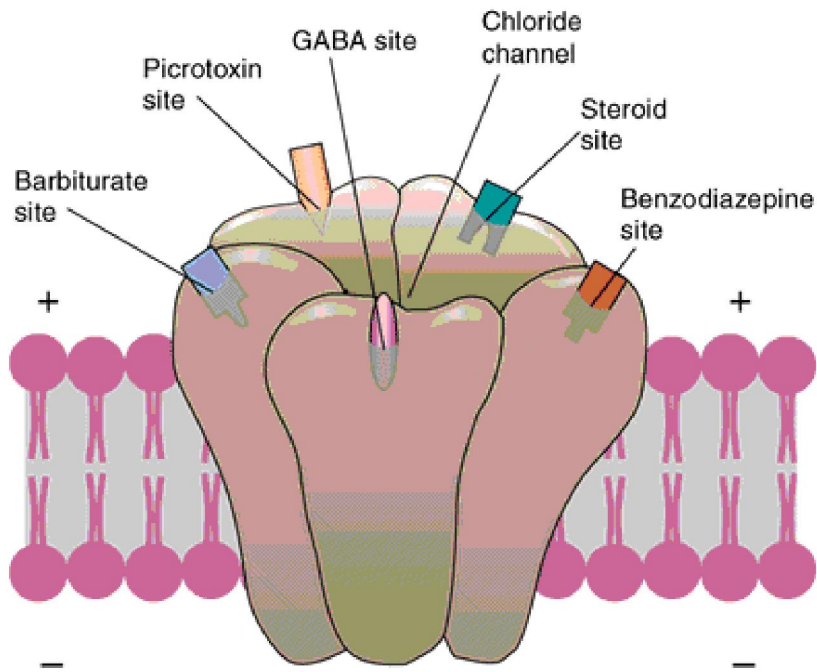
Modelos de Afinidade para o Receptor BZDP

Cook, J. M. (1998)
J. Med. Chem. **41**,
2537–2552.

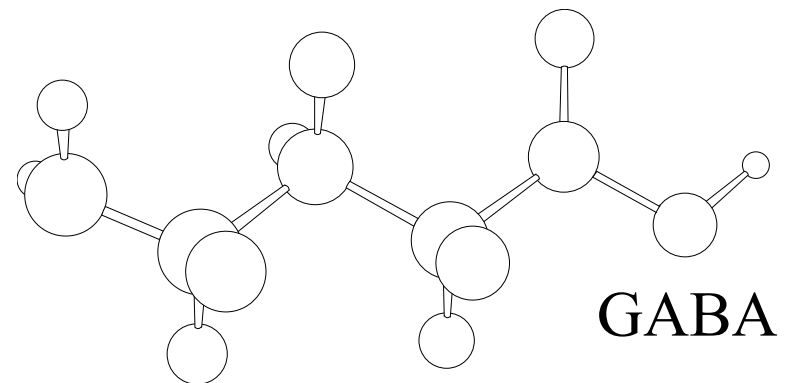
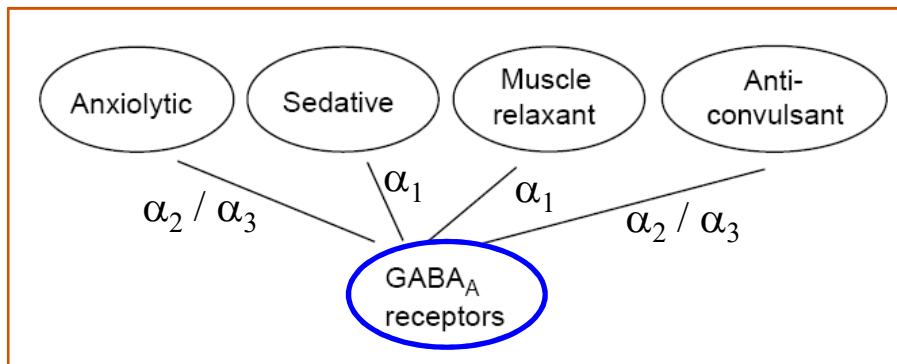
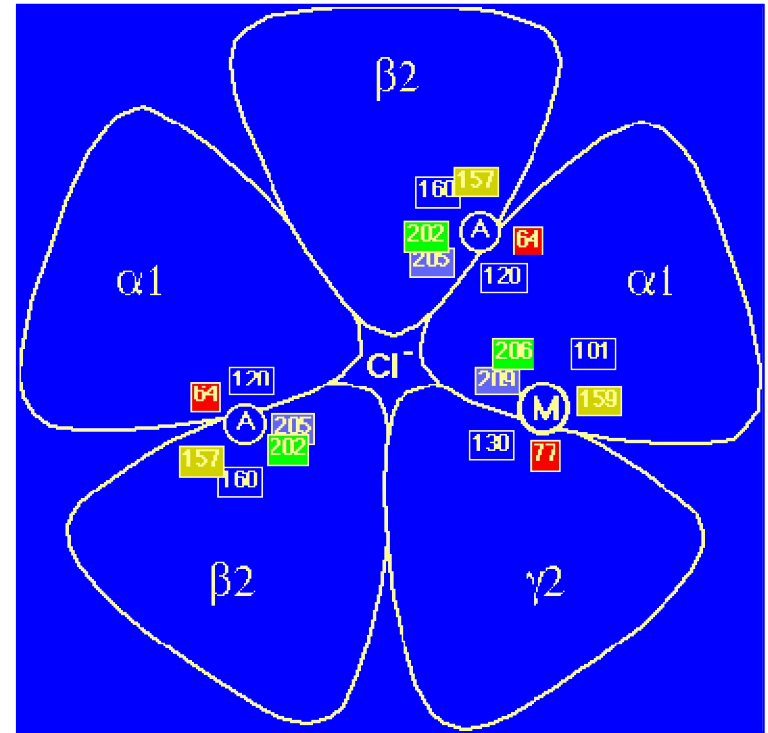


- A2 = Aceptor de Ligação Hidrogênio
- H1 = Doador de Ligação Hidrogênio
- H2/A3 = Doador/Aceptor de "H"
- L1-L-3 = Sítios Lipofílicos
- S1 = Sítio Estérico/Repulsivo

Schematic Illustration of a GABA_A Receptor, with Its Binding Sites



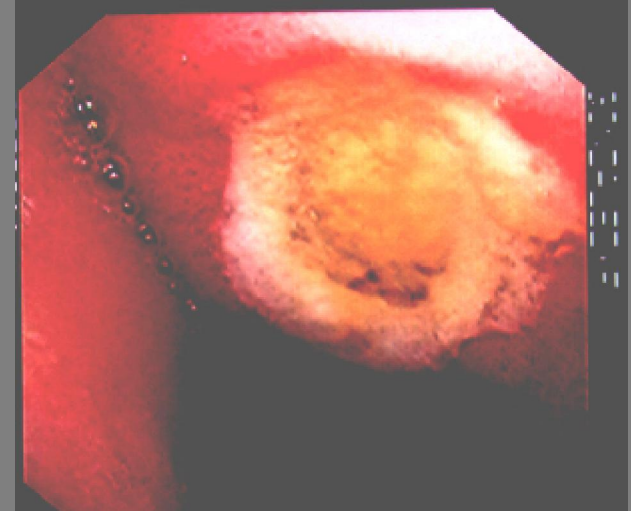
Receptor Benzodiazepínico



Definindo uma Fisiopatologia: Úlcera Péptica

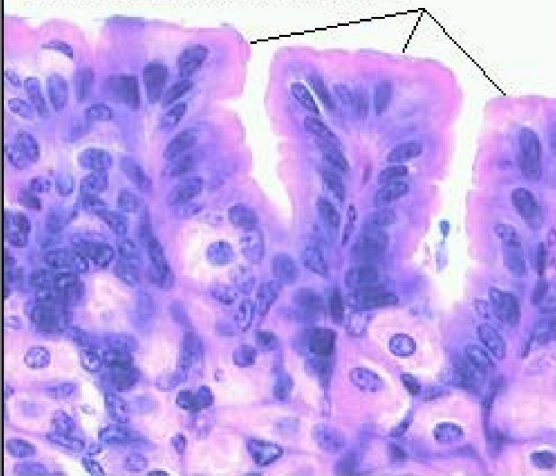


Úlceras
estomacales



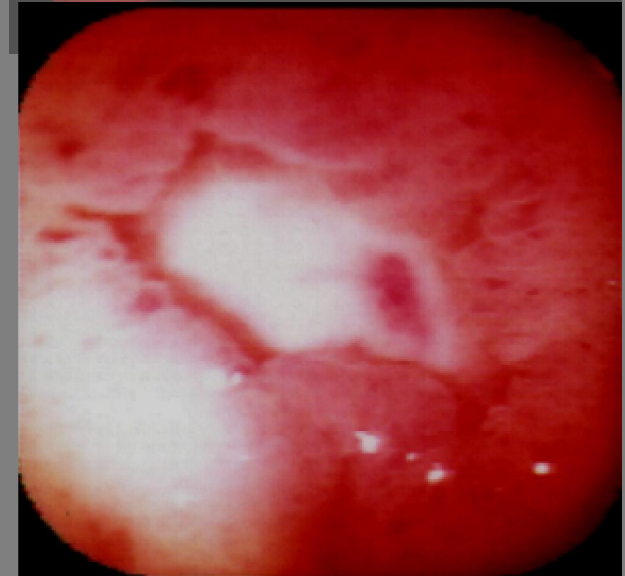
10-20% da população mundial

Mucus-secreting cells cover the surface of the stomach and extend into gastric pits

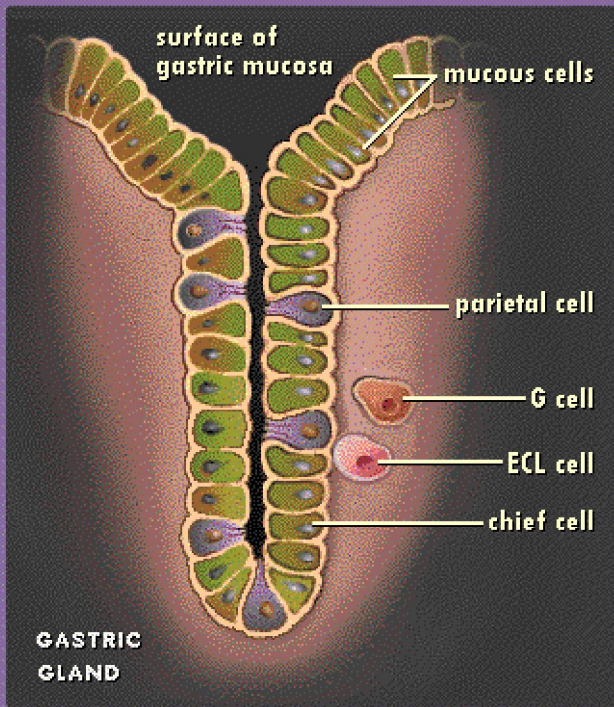


Causas:

- Produção Excessiva de Ác. Clorídrico;
- Comidas picantes e/ou condimentads;
- Tensão Emocional;
- Infecção



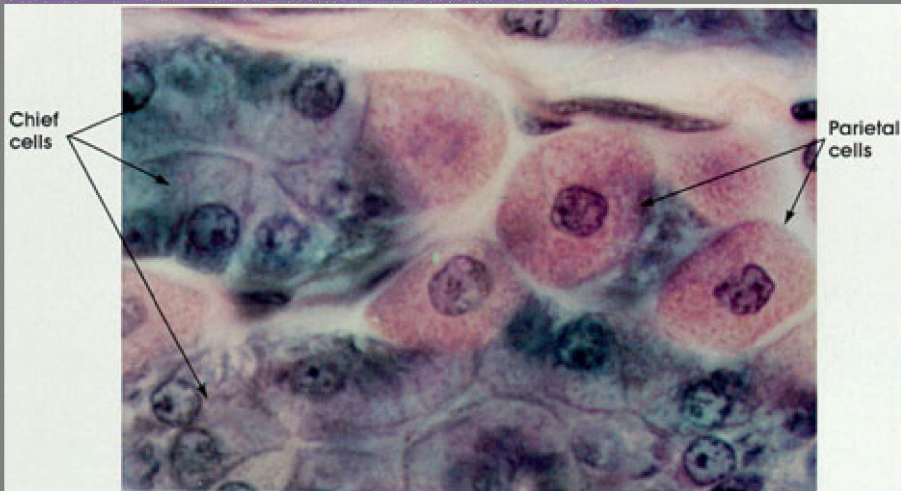
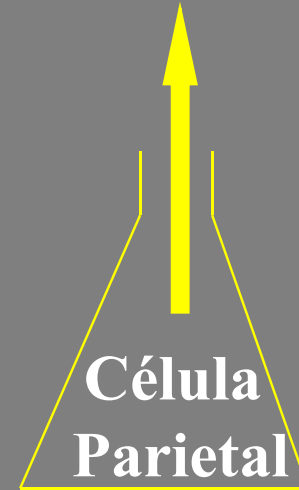
Célula Parietal



pH ~ 1-2

HCl

Pepsina
Muco

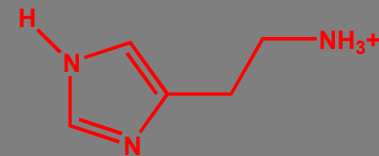


Acetilcolina

Gastrina

Histamina

Glu-Gly-Pro-Trp-Leu-
[Glu]₅-Ala-Tyr-Gly-
Trp-Met-Asp-Phe-NH₂



Tratamentos Disponíveis na Época

- Antiácidos: neutralização química do HCl liberado; trissilicato de magnésio; hidróxido de alumínio; bicarbonato de sódio; carbonato de cálcio; **Grandes quantidades / Efeito Rebote**
- Fármacos Anticolinérgicos; Ativos apenas em altas doses, levando ao bloqueio de outros receptores de acetilcolina (**Efeito tóxico**)
- Vagotomia

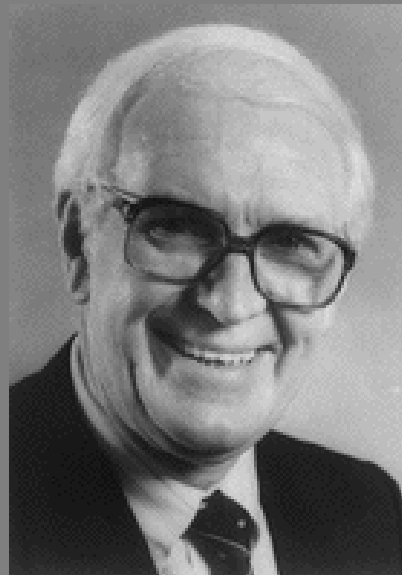


A Pesquisa de Novos Fármacos Anti-Úlceras

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



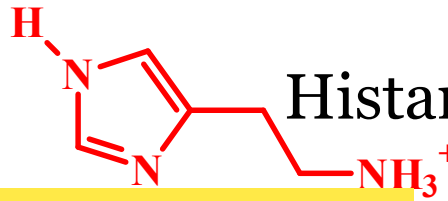
R. Ganellin
G. Durant
J. Emmett



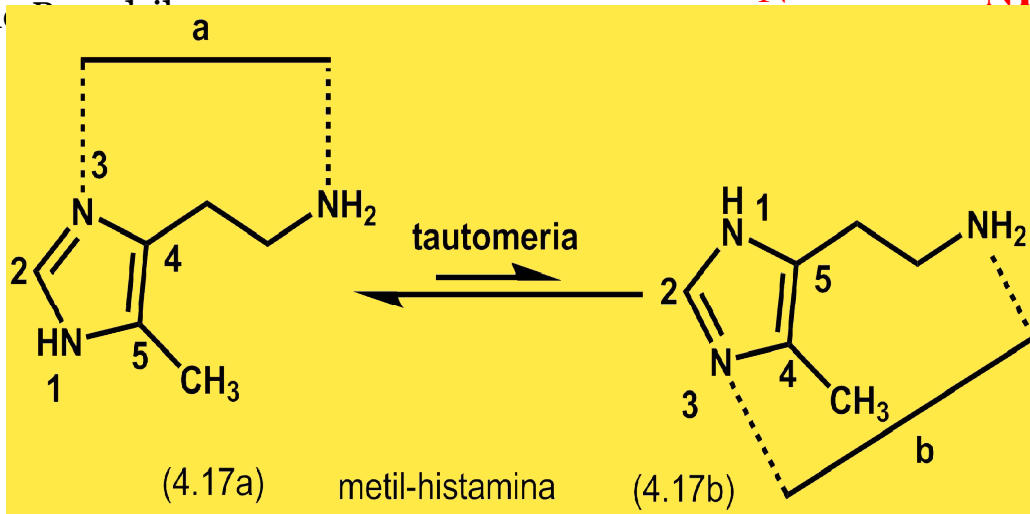
Sir James Black
Prêmio Nobel
de Medicina, 1988

Década de 70: Programa Desenvolvimento de Antagonistas- H₂ (SK&F)

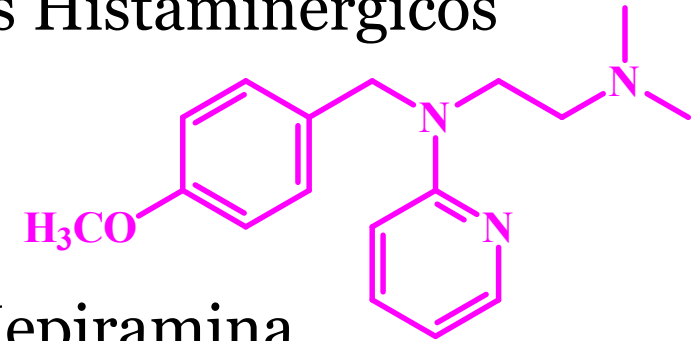
(1948) Folkow, Haeger e Kahlson: Sugerem a existência de 2 tipos de receptores sensíveis à histamina, dos quais apenas um podia ser bloqueado pelo...



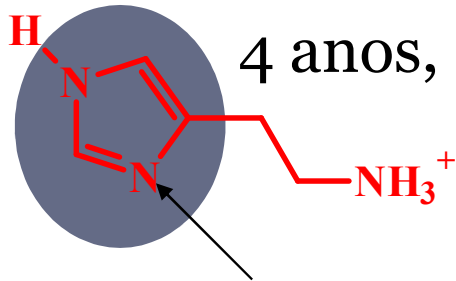
(1966) Ash e Schild: Receptor H₁
Histamina (Monocátion)



res Histaminérgicos



Mepiramina



4 anos, >200 compostos

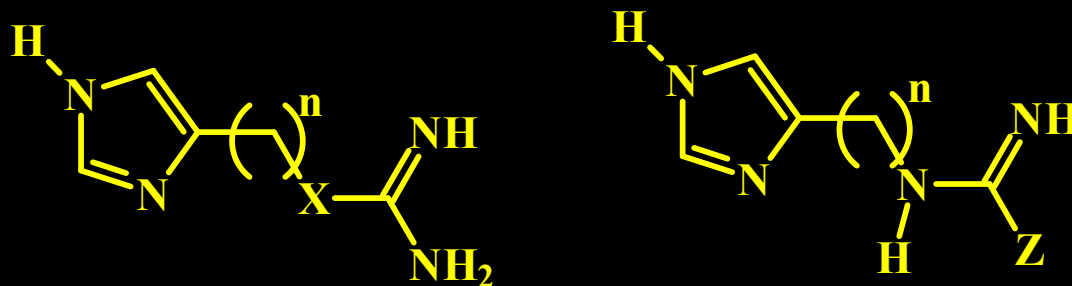
Idéia Original de Black: Alquilação

Lipofilicidade X Hidrofilicidade



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

SAR de algumas imidazolilisotiouréias, guanidinas e amidinas

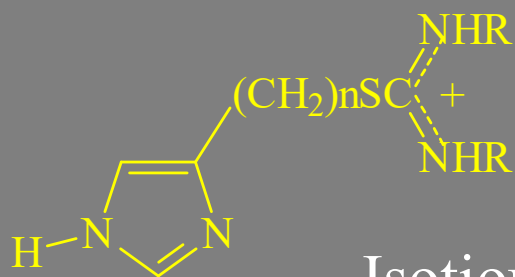
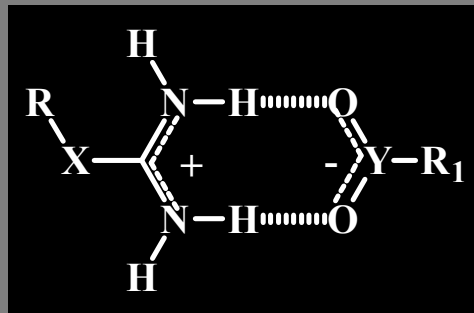


Composto	n	Substituinte	Atividade
1	2	X = NH	+
2	2	X = S	++
3	3	X = NH	+++
4	3	X = S	±
5	2	Z = SMe	±
6	2	Z = Me	±
7	3	Z = SMe	+++
8	3	Z = Me	+++

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

Imidazolilisotiouréias, Amidinas e Guanidinas (Monocátions)

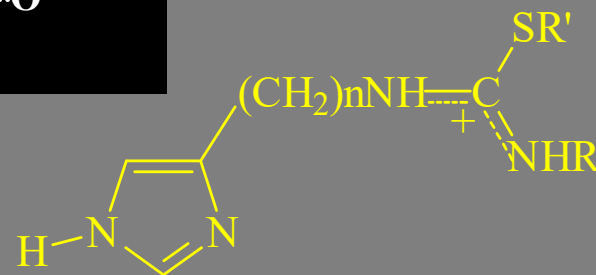
Agonismo X Antagonismo



Isotiouréias

n = 2-4

R = H ou alquila

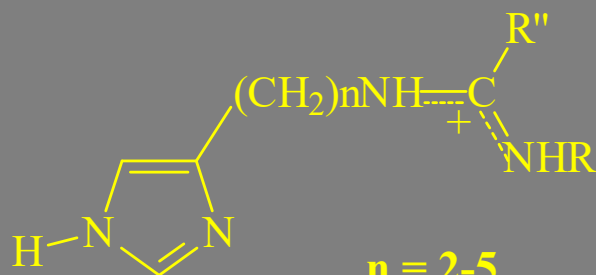


Isotiouréias
Invertidas

n = 2-5

R = H ou alquila

R' = alquila

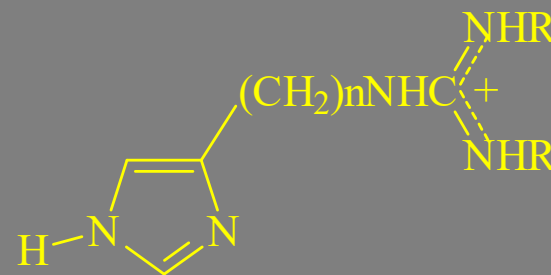


Amidinas

n = 2-5

R = H ou alquila

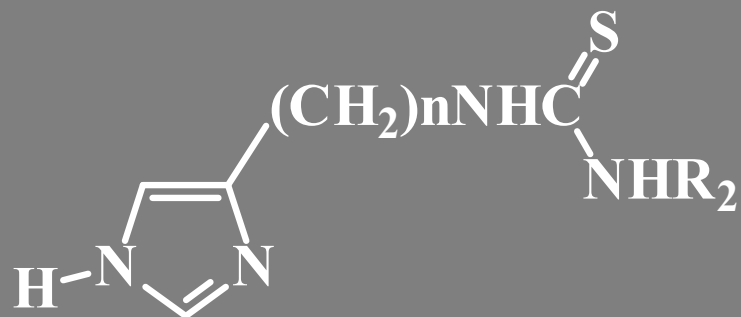
R'' = alquila, arila, etc.



Guanidinas

Descoberta da Burimamida

Introdução de Grupos Polares,
Não Básicos

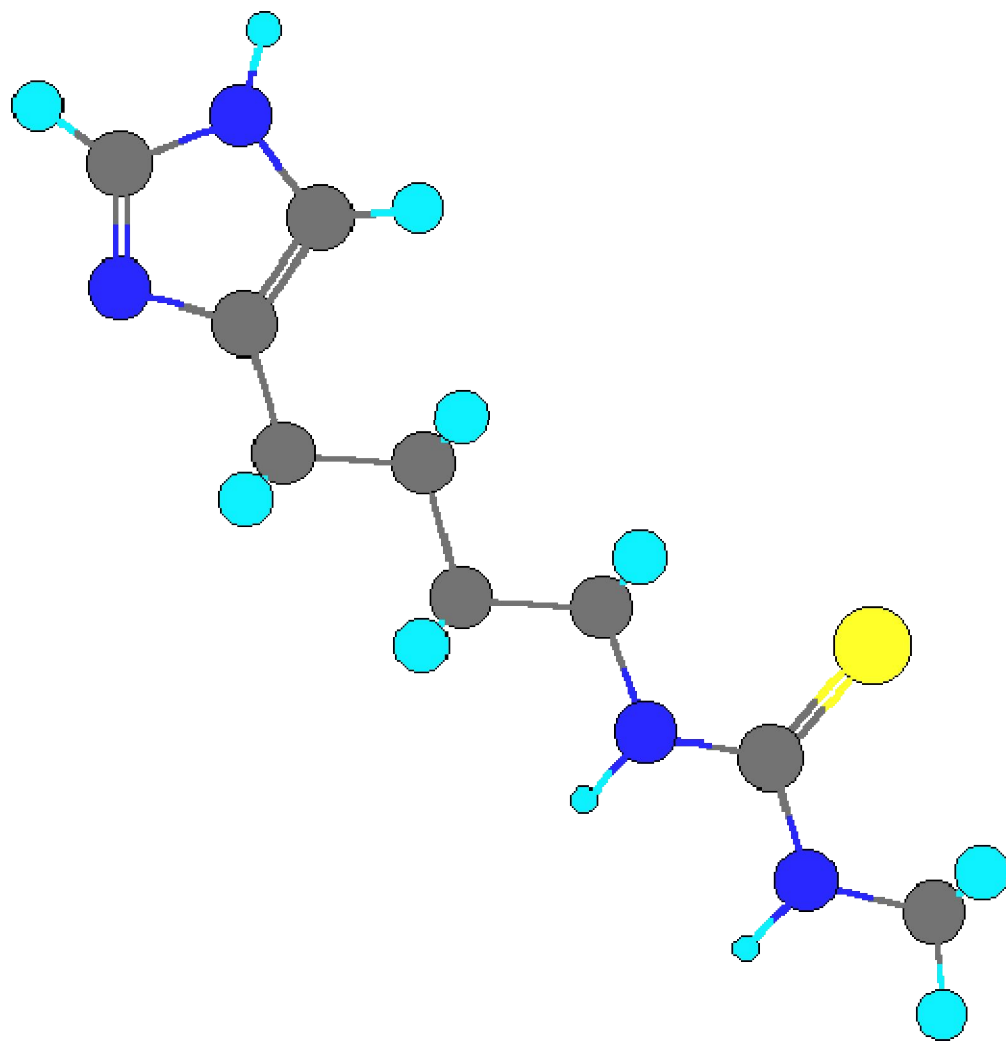


Tiouréias

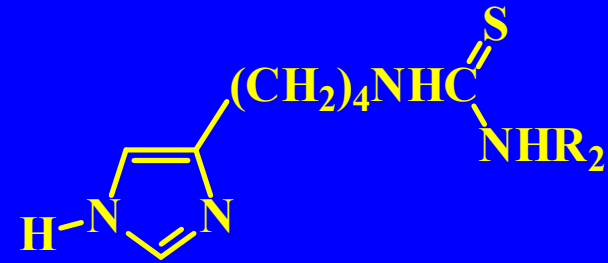
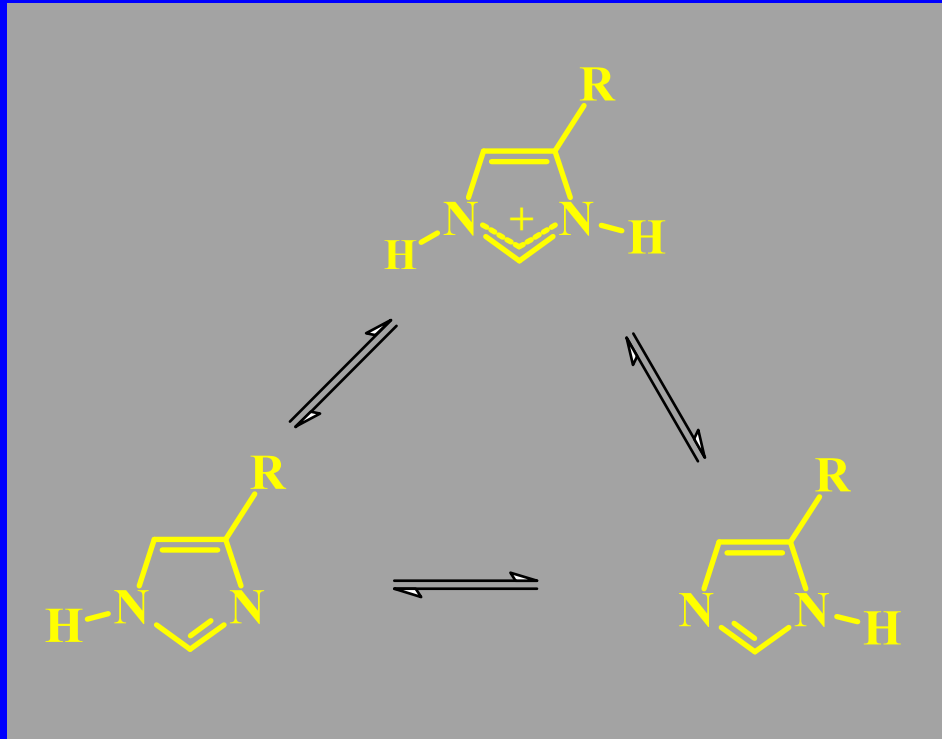
(9) SK&F 91581 $n = 3$, $\text{R}_2 = \text{H}$

(10) SK&F 91863 $n = 4$, $\text{R}_2 = \text{H}$

(11) Burimamida, $n = 4$, $\text{R}_2 = \text{CH}_3$



Características Estruturais da Burimamida



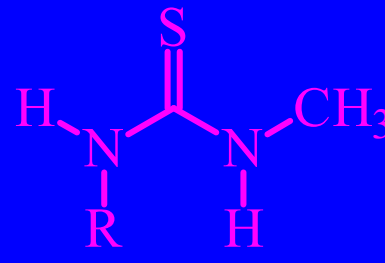
Burimamida



(s-cis,s-trans)



(s-cis,s-cis)

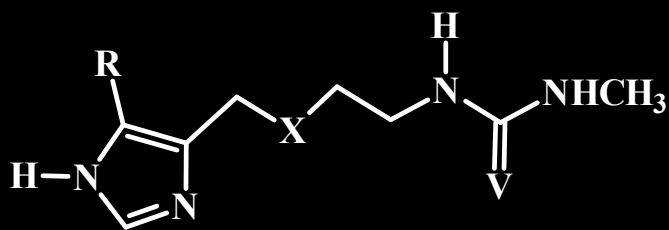


(s-trans,s-cis)



(s-trans,s-trans)

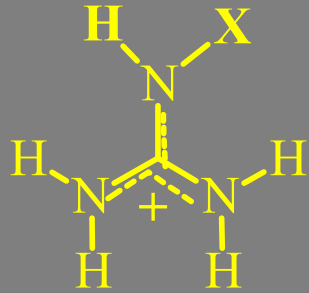
Planejamento Estrutural de Isósteros da Burimamida



Atividade em Receptores H₂

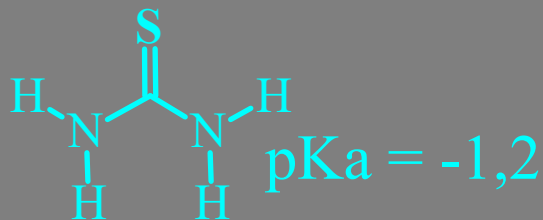
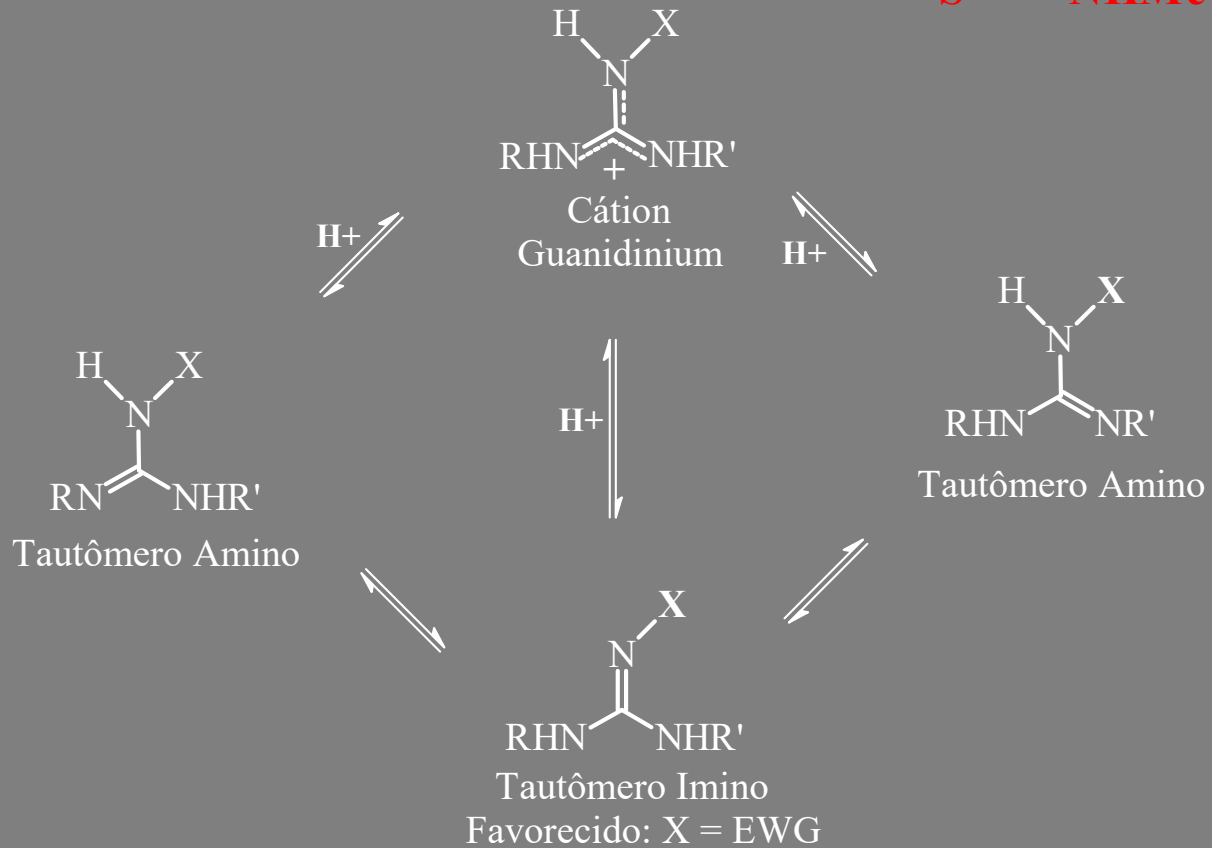
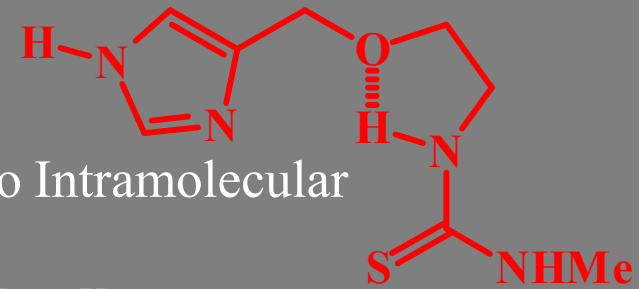
Composto	R	Estrutura		<i>In Vitro</i>		<i>In Vivo</i>
		X	V	Átrio (K _B X 10 ⁻⁶ M)	Útero (K _B X 10 ⁻⁶ M)	Secreção de HCl ID ₅₀ (μg/mol)
Burimamida	H	CH ₂	S	7,8	6,6	6,1
Tiaburimamida	H	S	S	3,2	3,2	5
Oxaburimamida	H	O	S	28	6,6	ND
Metiamida	CH ₃	S	S	0,92	0,75	1,6
Isósteros Ureídicos	CH ₃	S	S	22	7,1	27
Isósteros	CH ₃	S	NH	16	5,5	12
Gunidínico						
Isósteros	CH ₃	S	N-NO ₂	1,4	1,4	2,1
Nitroguanidínico						
Isósteros	CH ₃	S	N-CN	0,79	0,81	1,4
Cianoguanidínico						
Isósteros	CH ₃	S	N-CONH ₂	7,1	6,9	7,7
Guaniluréia						

Aspectos Estruturais de Guanidinas Substituídas e Derivados



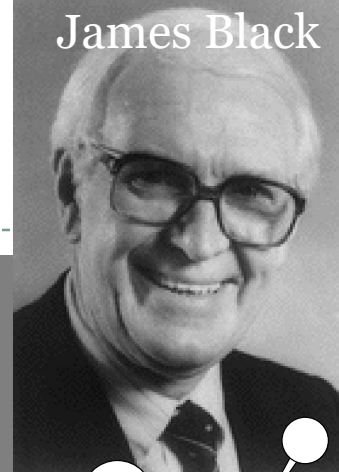
X	σ	pKa'
H	0	14,0
Ph	0,11	10,6
Ac	0,32	8,0
CONH ₂	0,30	7,3
OMe	0,32	6,3
CN	0,59	0,4
NO ₂	0,62	0,9

Ligação de Hidrogênio Intramolecular

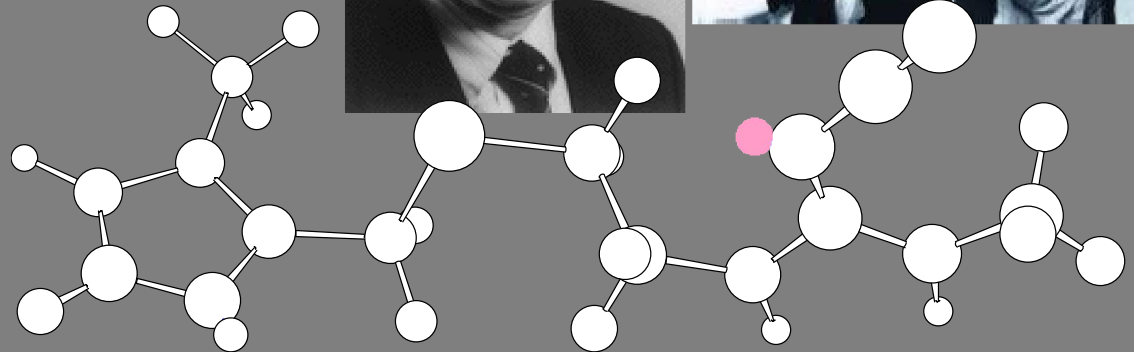
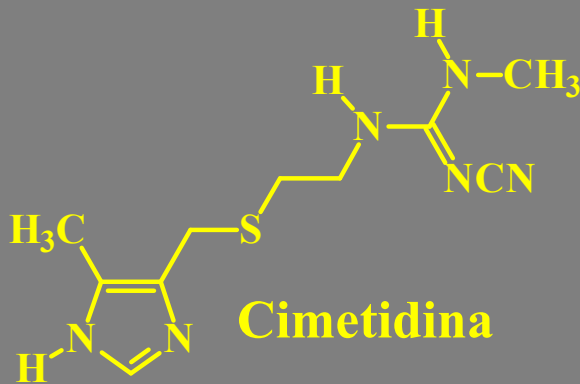
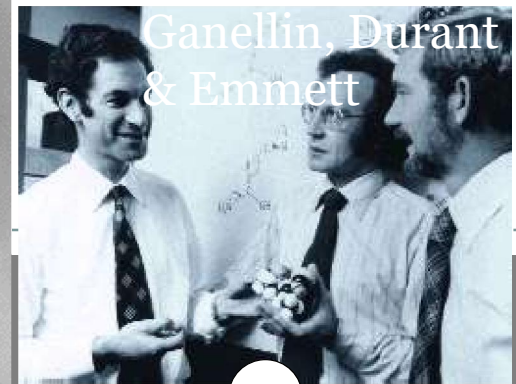


Nasce um Novo Fármaco: Cimetidina

James Black

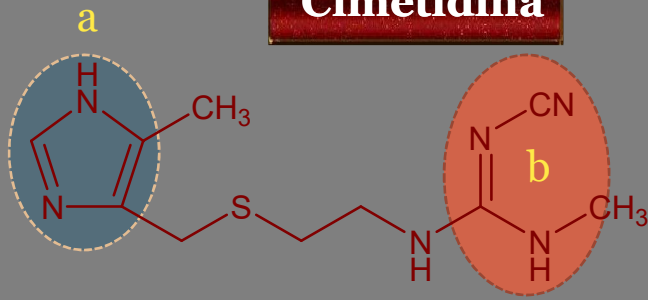


Ganellin, Durant & Emmett



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

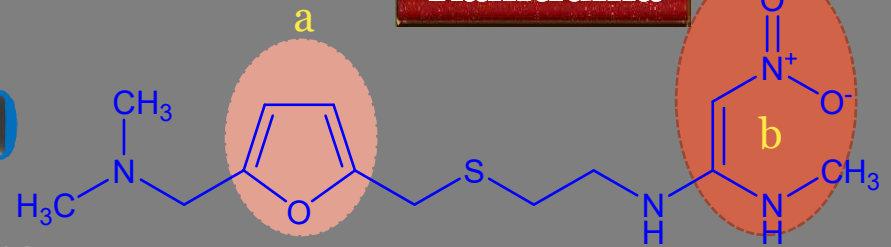
Cimetidina



me-too

Bioisosterismo

Ranitidina



Barry J. Price *et al.*, 1978

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

Robin Ganellin *et al.*, 1974

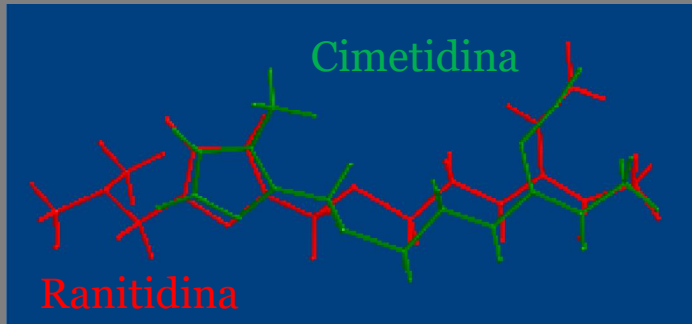
US 3950333 1974, 1976 - SK&F

Brit. J. Pharmacol. **53**, 435 (1975).



Glaxo

1987: Top One

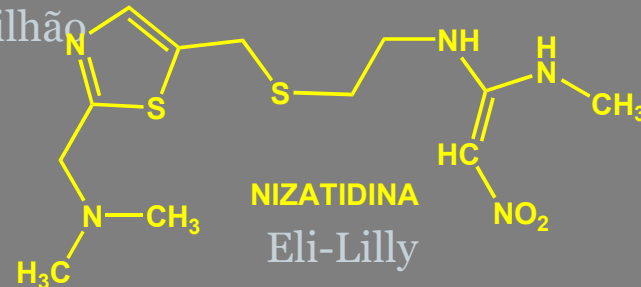
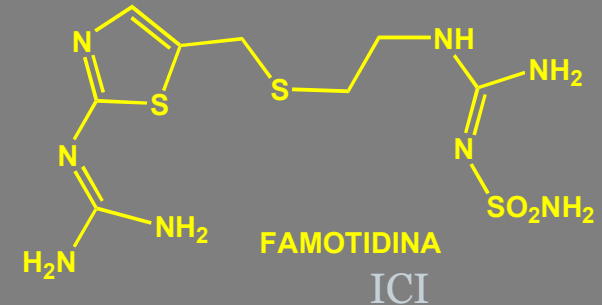


Cimetidina (SK&F)

Vendas em 1976: US\$ 386 milhões

Vendas em 1980: US\$ 580 milhões

Top em 1983: US\$ 1 bilhão

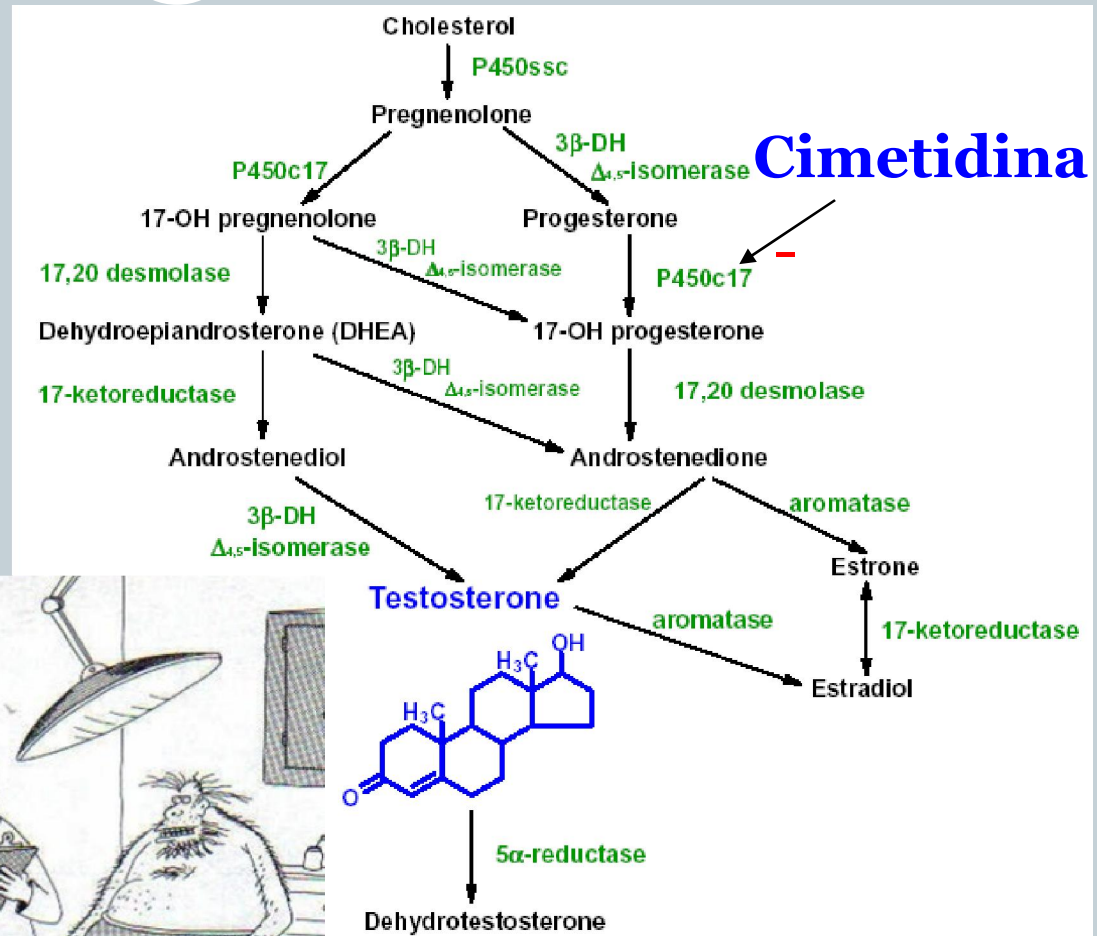
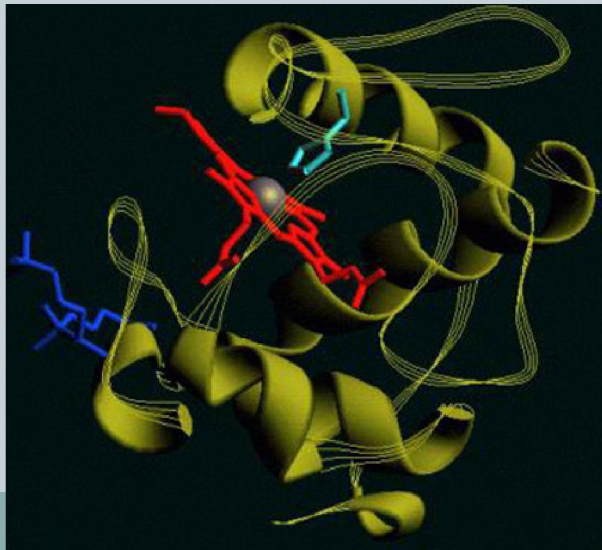


Efeitos Colaterais da Cimetidina

Principais Efeitos Colaterais Em Homens:

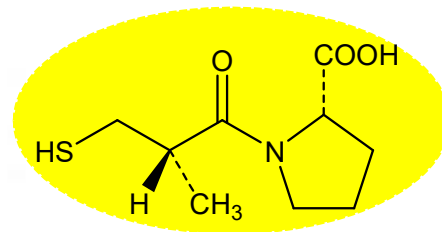
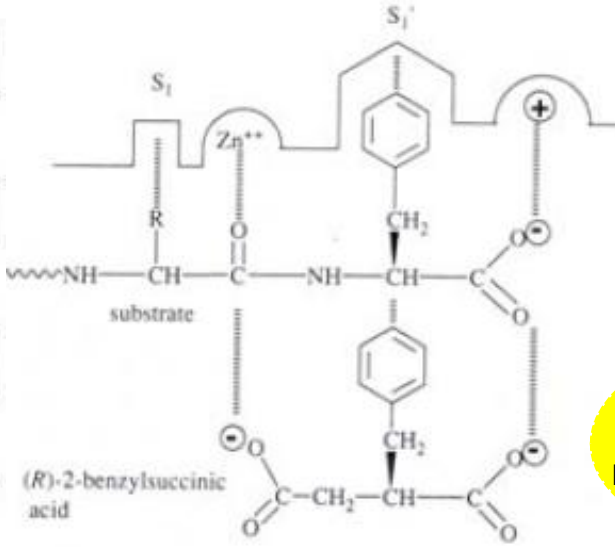
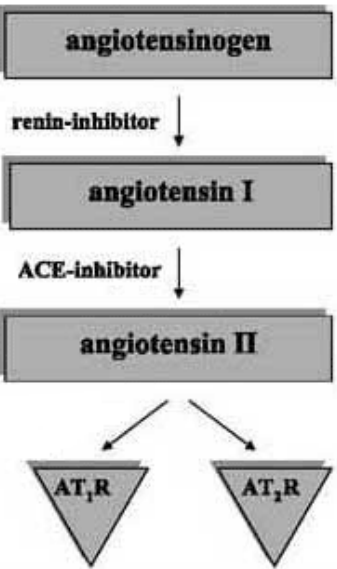
- ◆ Crescimento de Seios (Ginecomastia)
- ◆ Perda da Libido
- ◆ Impotência

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



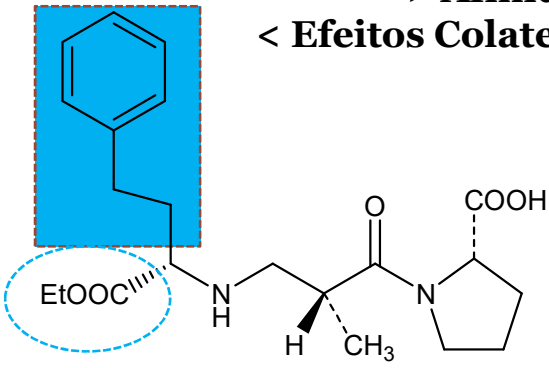
Biossíntese de Testosterona

Inibidores da Enzima Conversora de Angiotensina

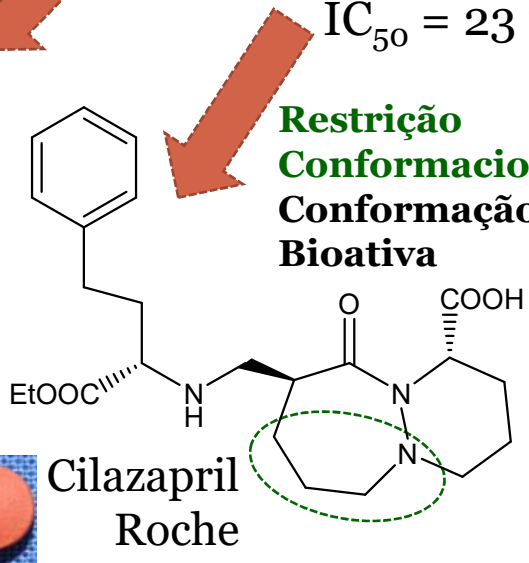


Captopril
 Cushman & Ondetti,
 Squibb, 1997
 $IC_{50} = 23 \text{ nM}$

> Afínidade
 < Efeitos Colaterais

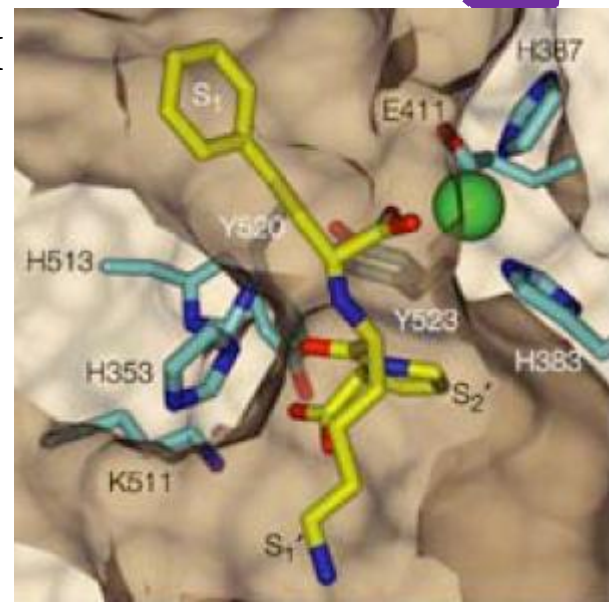


Enalapril
 Merck Sharp
 & Dohme

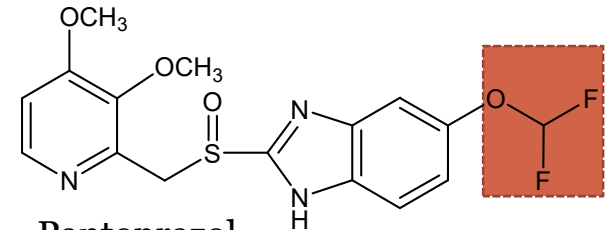
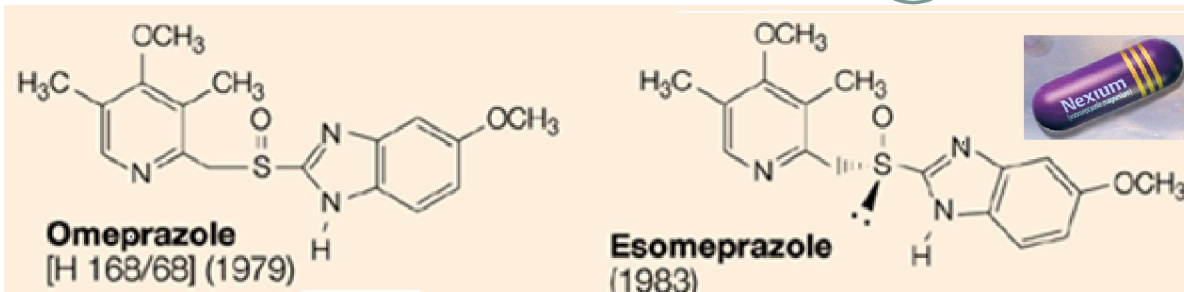


Cilazapril
 Roche

Restrição
 Conformacional
 Conformação
 Bioativa

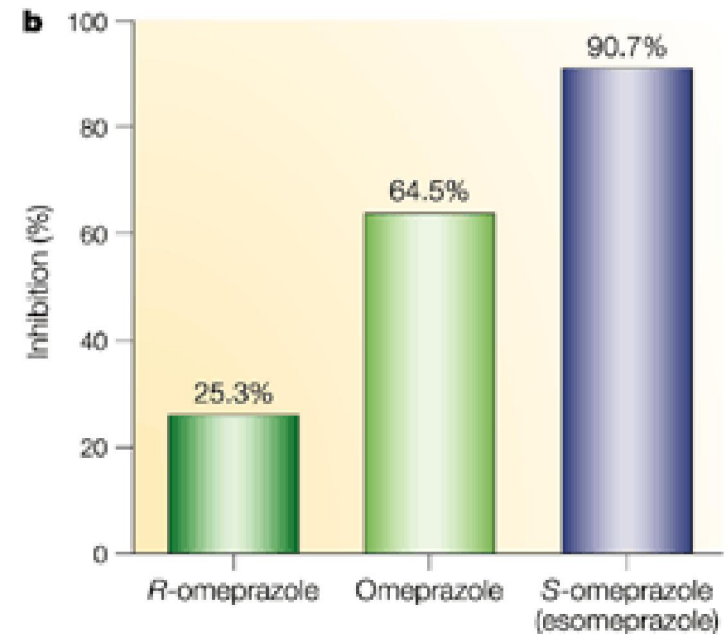
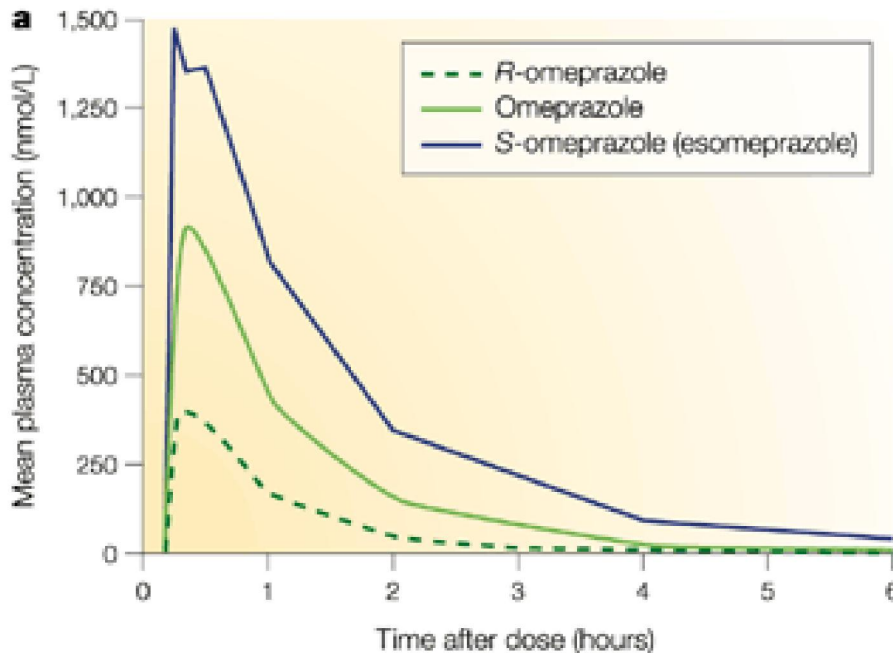


A Importância do “Switch” Quiral: Inibidores da ATPase H-K: Esomeprazola



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

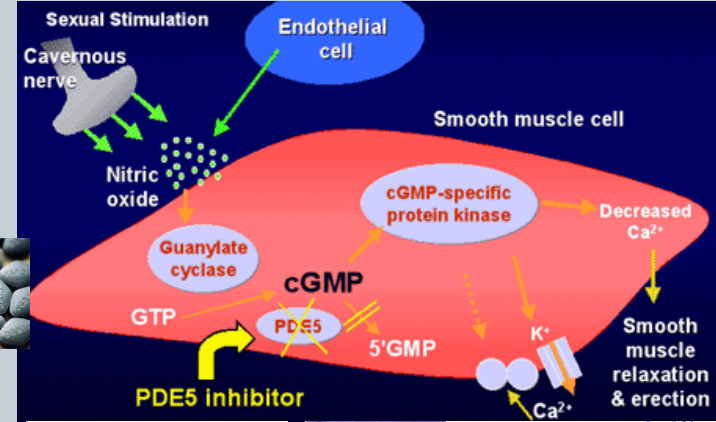
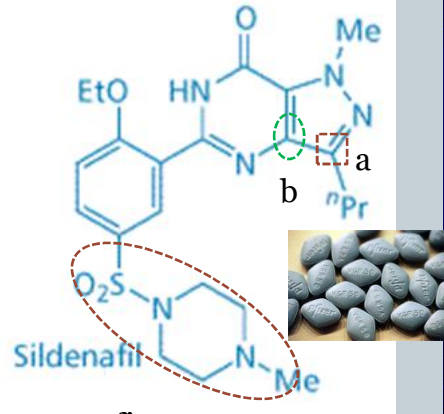
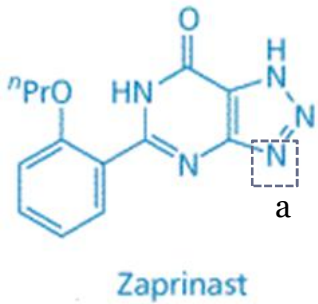
Prilosec Astra-Zeneca Top # 72 (2006) Astra-Zeneca Top # 4 (2006)



Descoberta do Sildenafil (Simon Campbell - Pfizer)

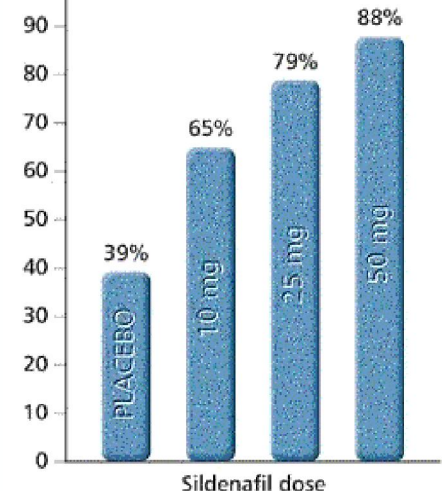
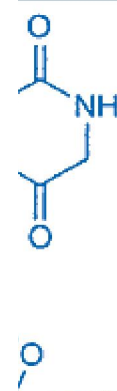
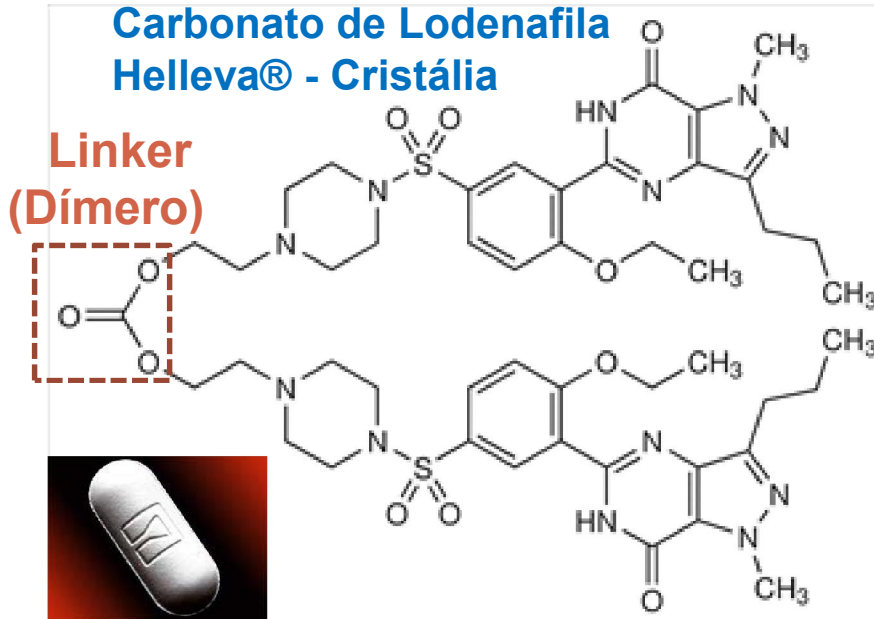
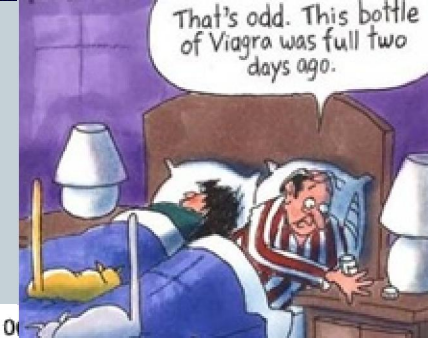
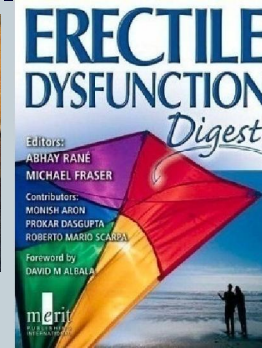
- 1985 Programa iniciado nos laboratórios Pfizer para desenvolver um tratamento para a Angina. O ponto de partida foi a modificação química do conhecido vasodilatador ZAPRINAST, o qual tinha sido desenvolvido pela Rhone Poulenc, mas que nunca alcançou o mercado.
- 1989 Aproximadamente 1600 compostos foram sintetizados no âmbito deste programa, incluindo o Sildenafil.
- 1990 Sildenafil entrou em Fase I de triagem clínica em pacientes saudáveis. Entretanto, ele não preencheu as expectativas para o tratamento de doenças coronárias. Efeito colateral em homens durante estes ensaios indicaram seu potencial para o tratamento da disfunção erétil (DE).
- 1994 Fase 2 de Triagem Clínica para o tratamento da DE.
- 1998 O FDA aprova o uso do Sildenafil (Viagra) para o tratamento da DE.

Terapia da Disfunção Erétil: Inibidores de PDE-V



Isozyme	Zaprinast	Sildenafil
	IC ₅₀ (nM)	IC ₅₀ (nM)

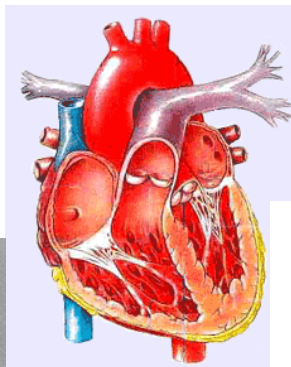
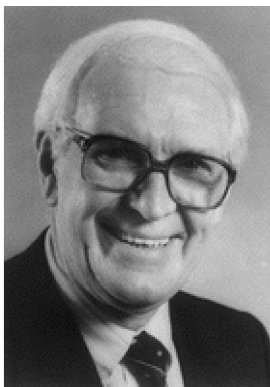
Viagra, Pfizer
Top # 57 (2006)



A Importância dos Me-too como Alternativas Terapêuticas

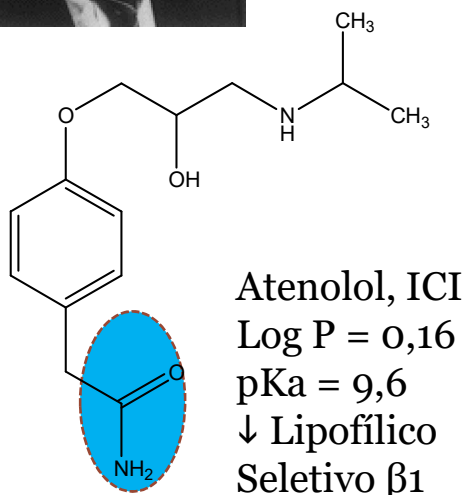
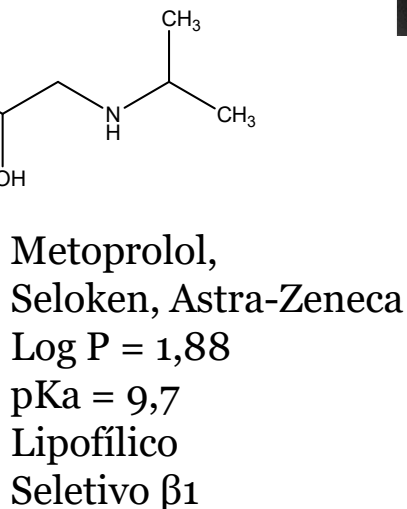
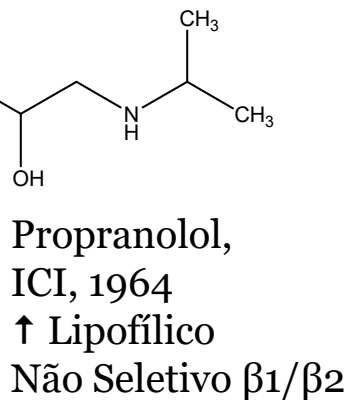
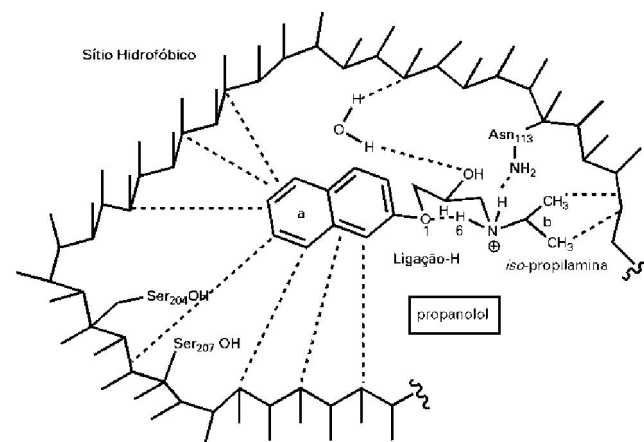
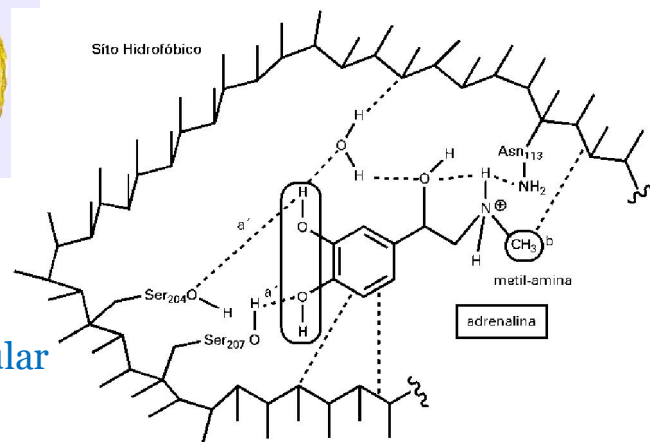
β -Bloqueadores

James Black

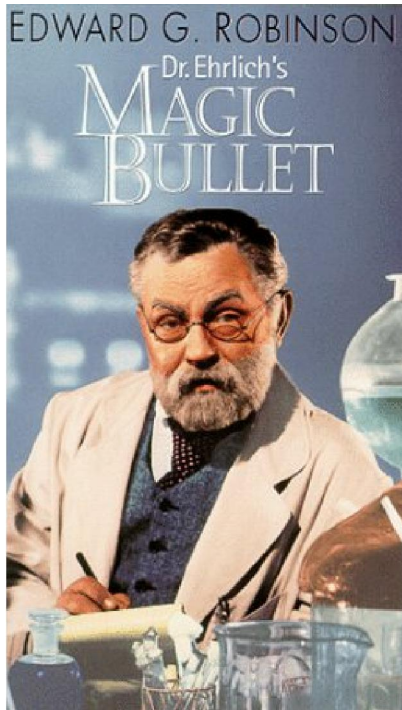


Sistema Cardio-Vascular

Reconhecimento Molecular de Adrenalina e Propranolol em Receptores β



Mudança de Paradigma: Terapia de Doenças Multifatoriais



“Single-Probe-Single-Target” = SELECTIVITY



“researchers in the drug discovery field have realized that communication mechanisms within the cell are arranged as robust, highly cooperative networks, which consist of complex nodes that interact through weak and strong links.” Espinoza-Fonseca, L. M. (2008) *Bioorg. Med. Chem.* 16, 9546.

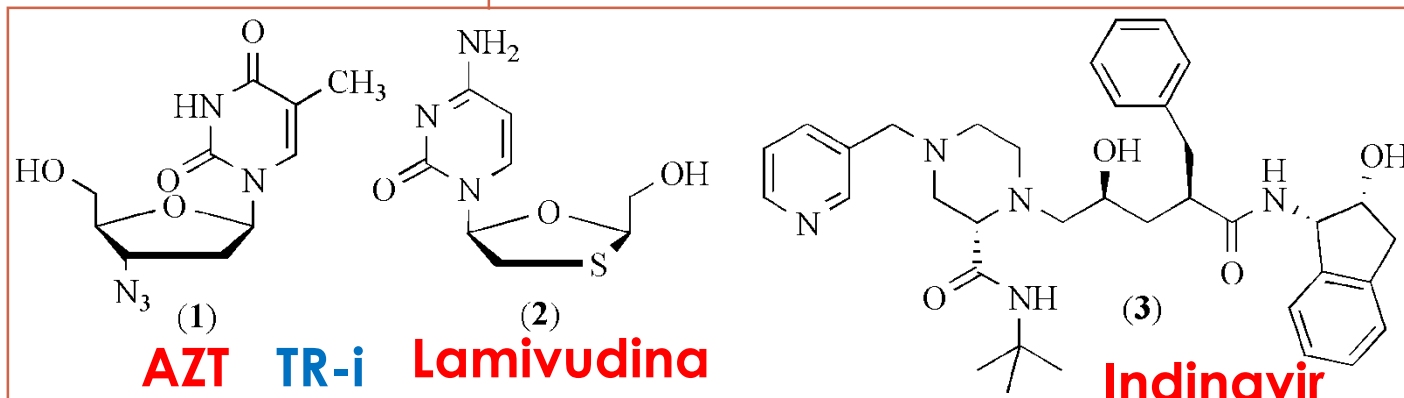
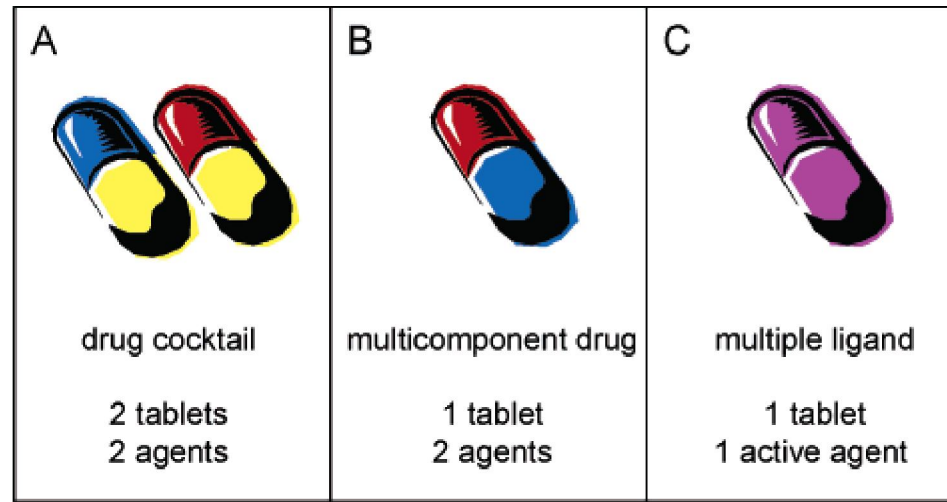
“cellular networks often possess buffering mechanisms that prevent major perturbations despite single drug-induced significant changes in one of their constituents.”

Csermely, P. (2004) *Trends Biochem. Sci.* 29, 331.

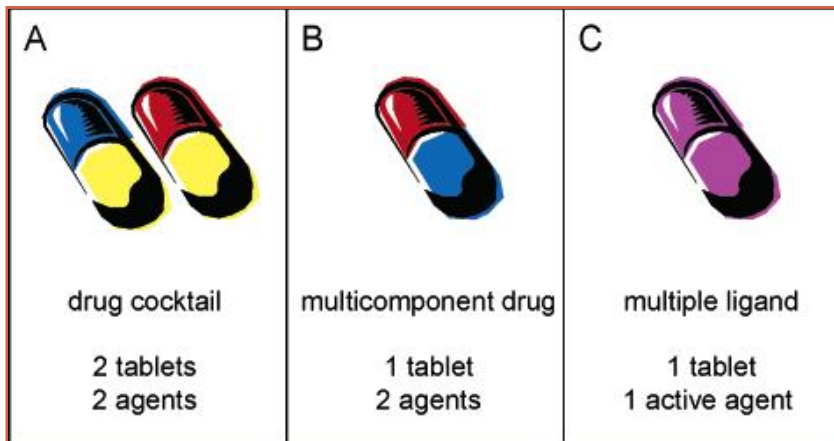
Korcsmaros, T. et al. (2007) *Exp. Opin. Drug Discovery* 2, 799.

Csermely, P. et al. (2005) *Trends Pharmacol. Sci.* 26, 178.

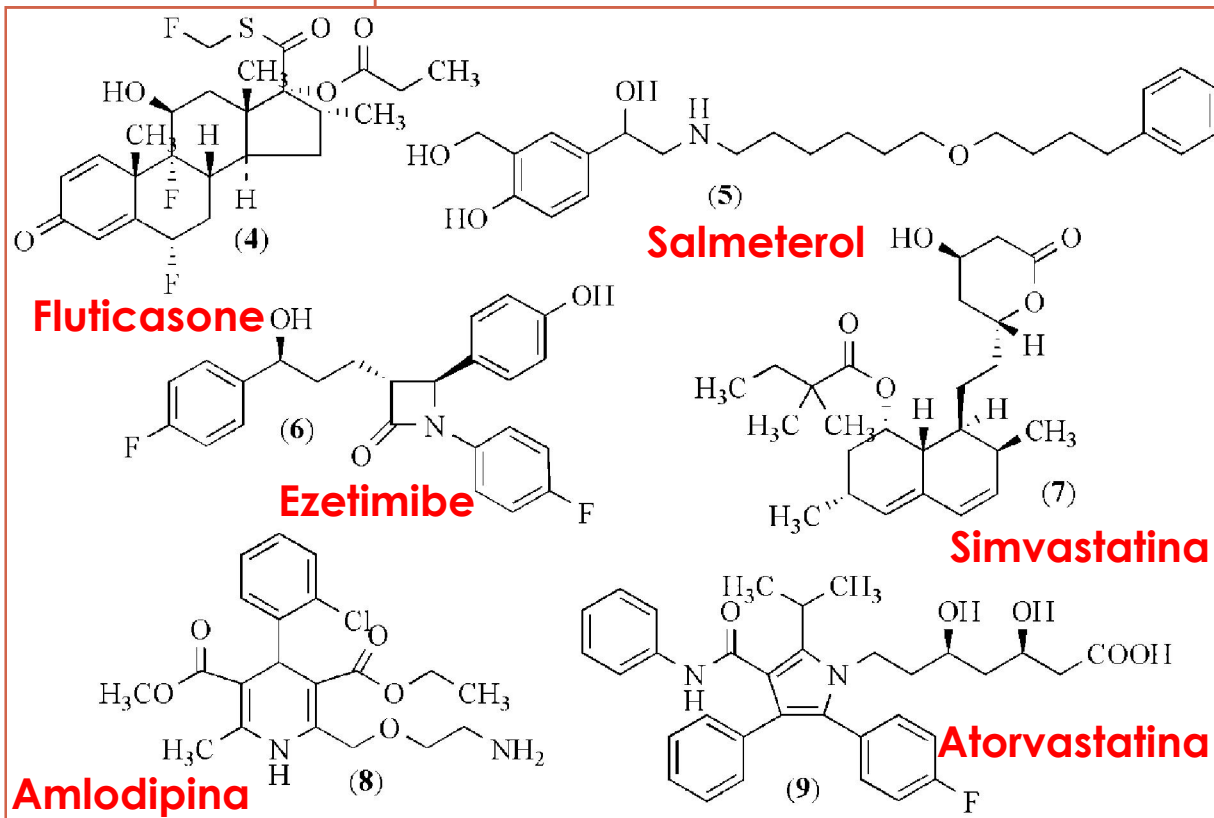
Terapia de Patologias Multifatoriais: HIV

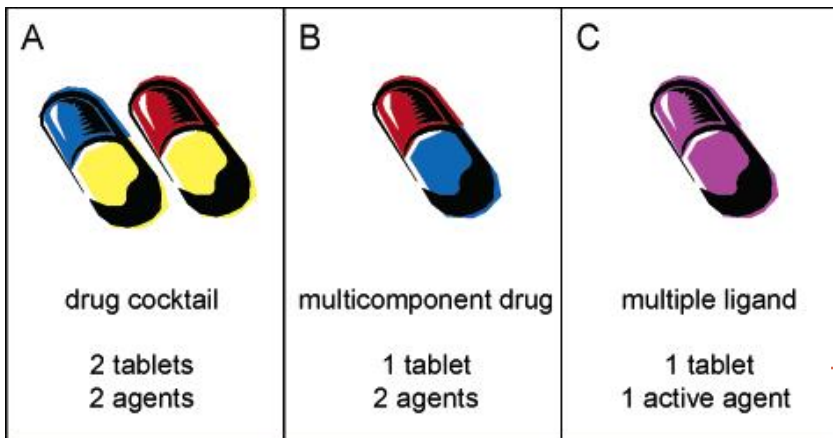


HIV
protease-i



Exemplos de Fármacos Multicomponentes Comercialmente Disponíveis



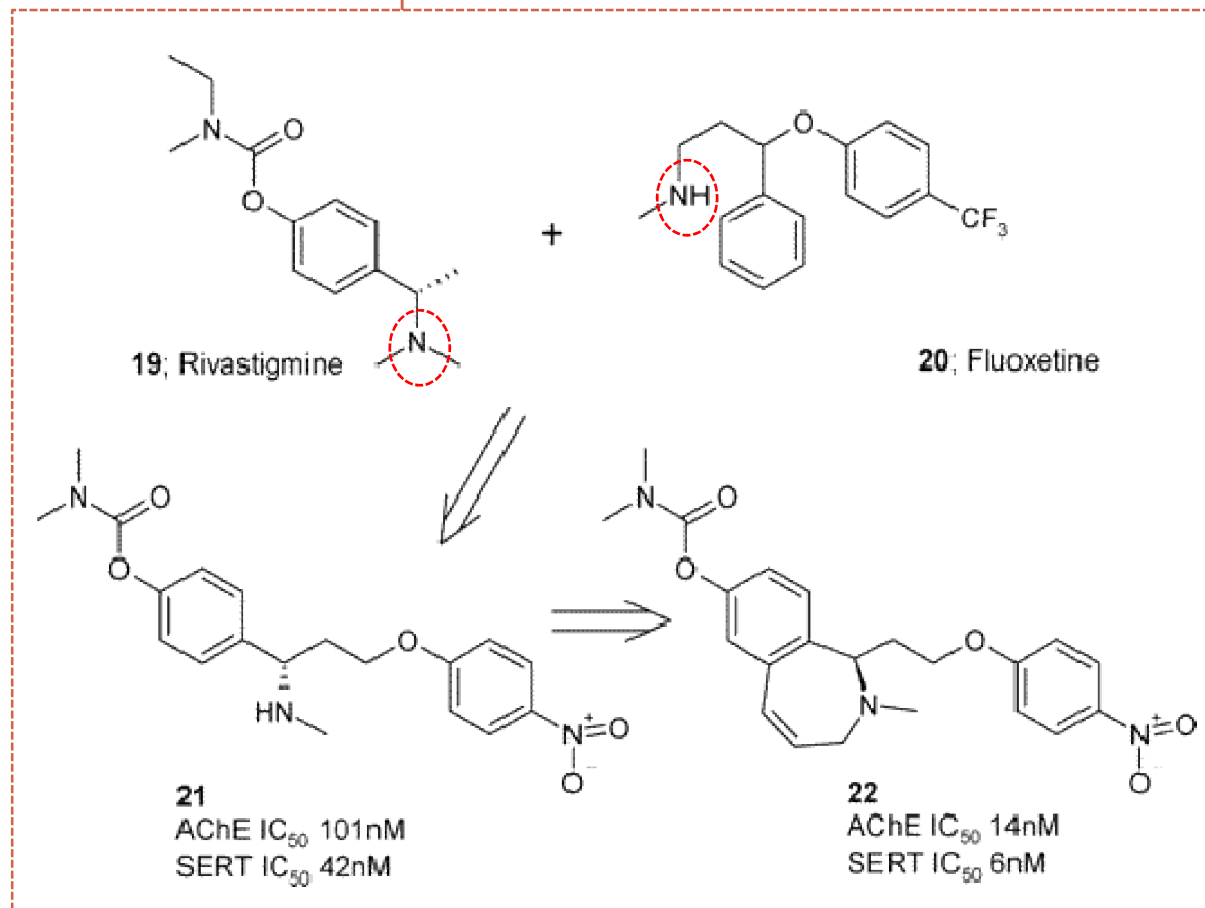


Descoberta de Ligantes Multirreptores Candidatos a Fármacos Anti-Alzheimer

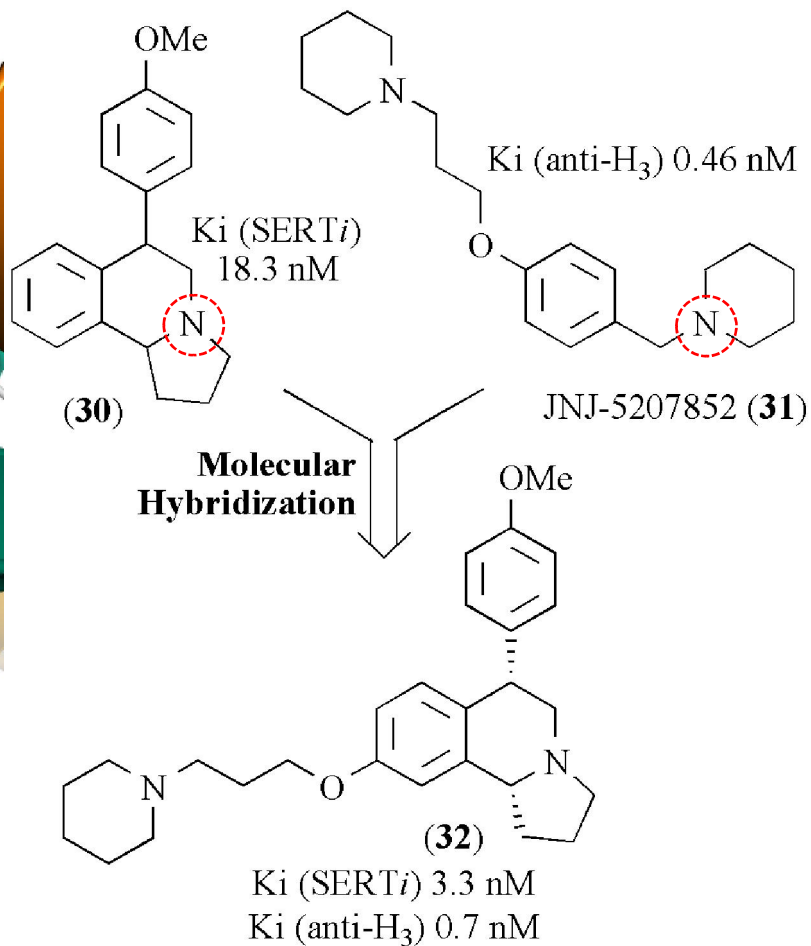
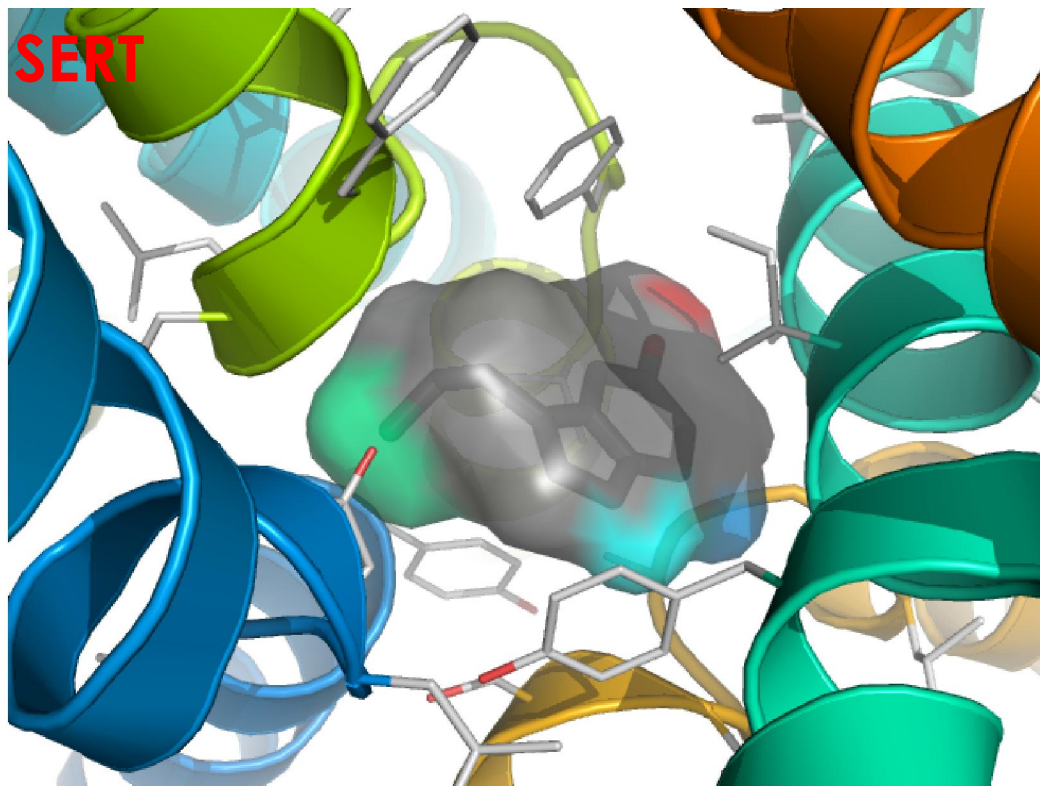


“Hibridação Molecular”

Toda, N. et al. (2003) Bioorg. Med. Chem. 11, 1935.
 Toda, N. et al. (2003) Bioorg. Med. Chem. 11, 438.

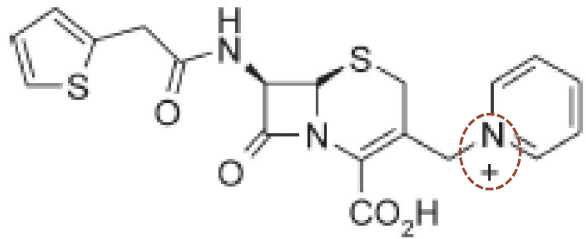
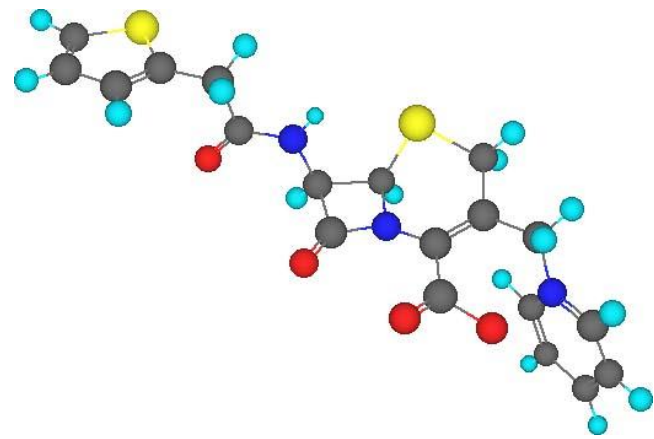


Ligantes Híbridos na Terapia da Depressão: SERTi / anti-H₃

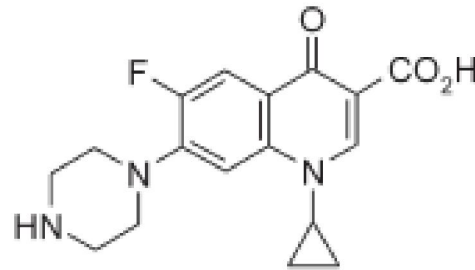


Keith, J. M. et al. (2007) *Bioorg. Med. Chem. Lett.* 17, 702.
Keith, J. M. et al. (2007) *Bioorg. Med. Chem. Lett.* 17, 2603.

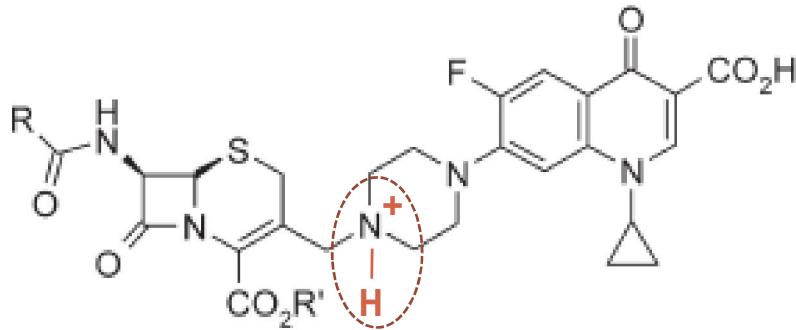
Descoberta de Híbridos Cefalosporina-quinolona com Amplo Espectro de Ação Antibacteriana



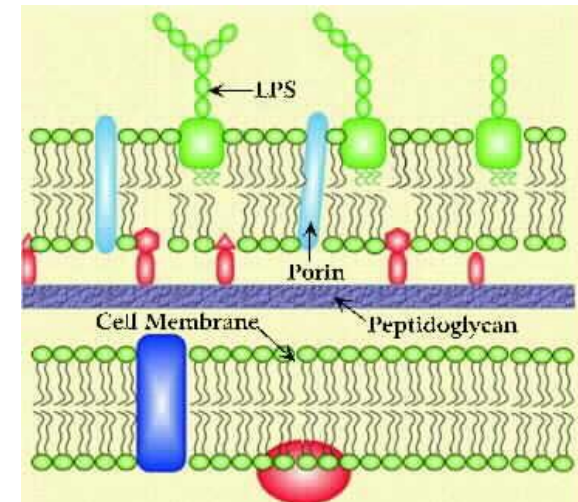
cephaloridine (antibacterial)



ciprofloxacin (antibacterial)

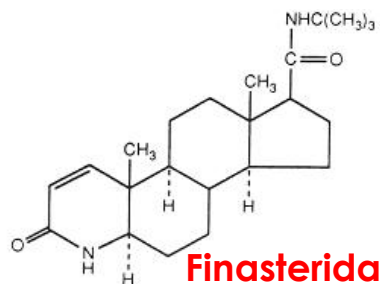


cephalosporin-quinolone hybrid derivatives
(broad spectrum antibacterial)

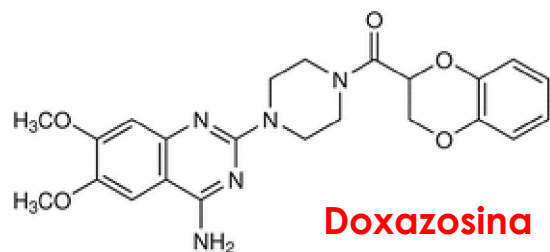


Albrecht, H. A. et al. (1994) J. Med. Chem. 37, 400.

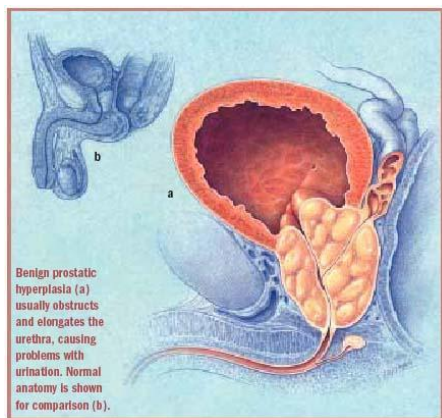
Agentes Anti-hiperplásicos Híbridos: α_1 Antagonistas / Inibidores de 5 α -redutase



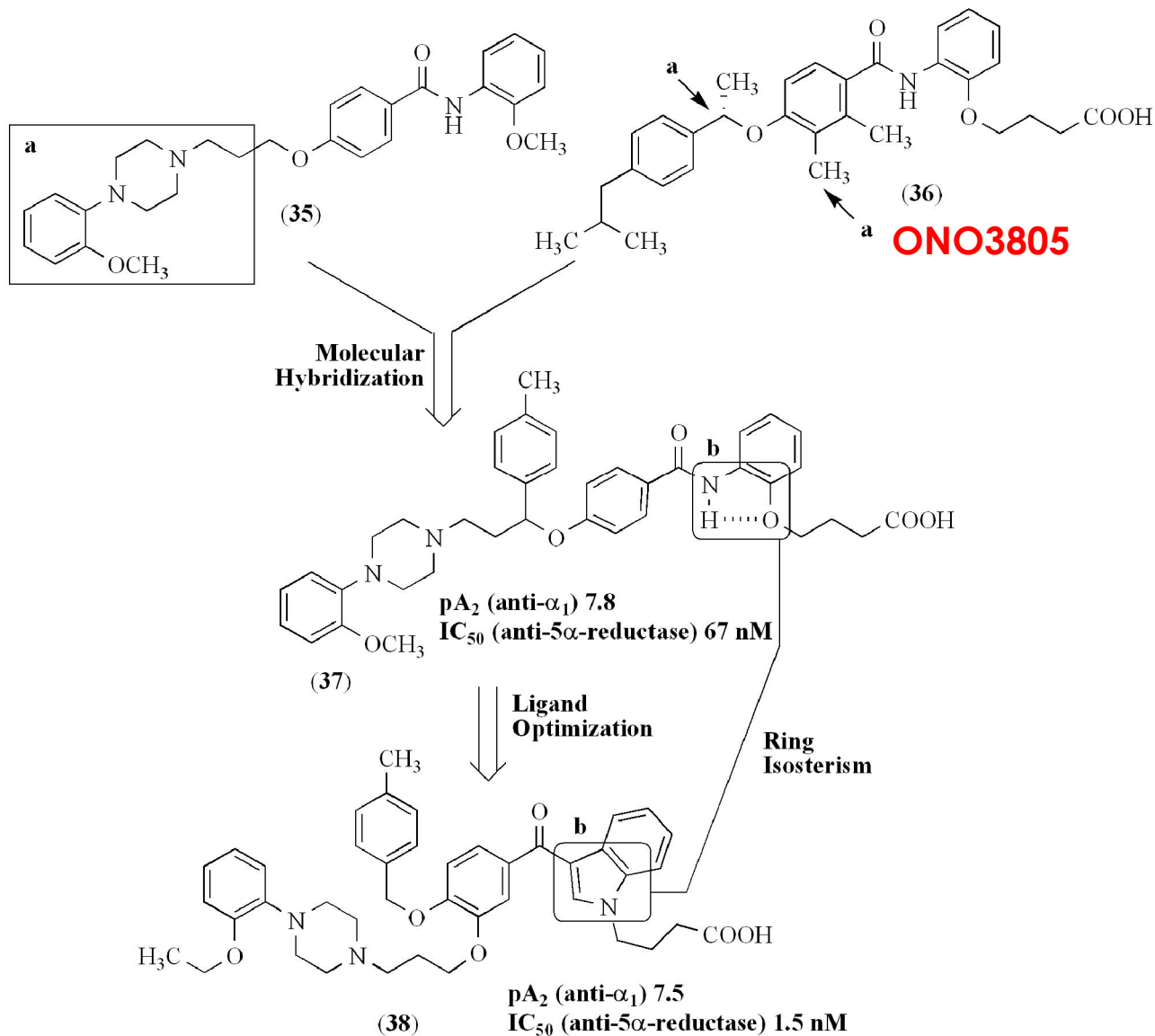
+



||

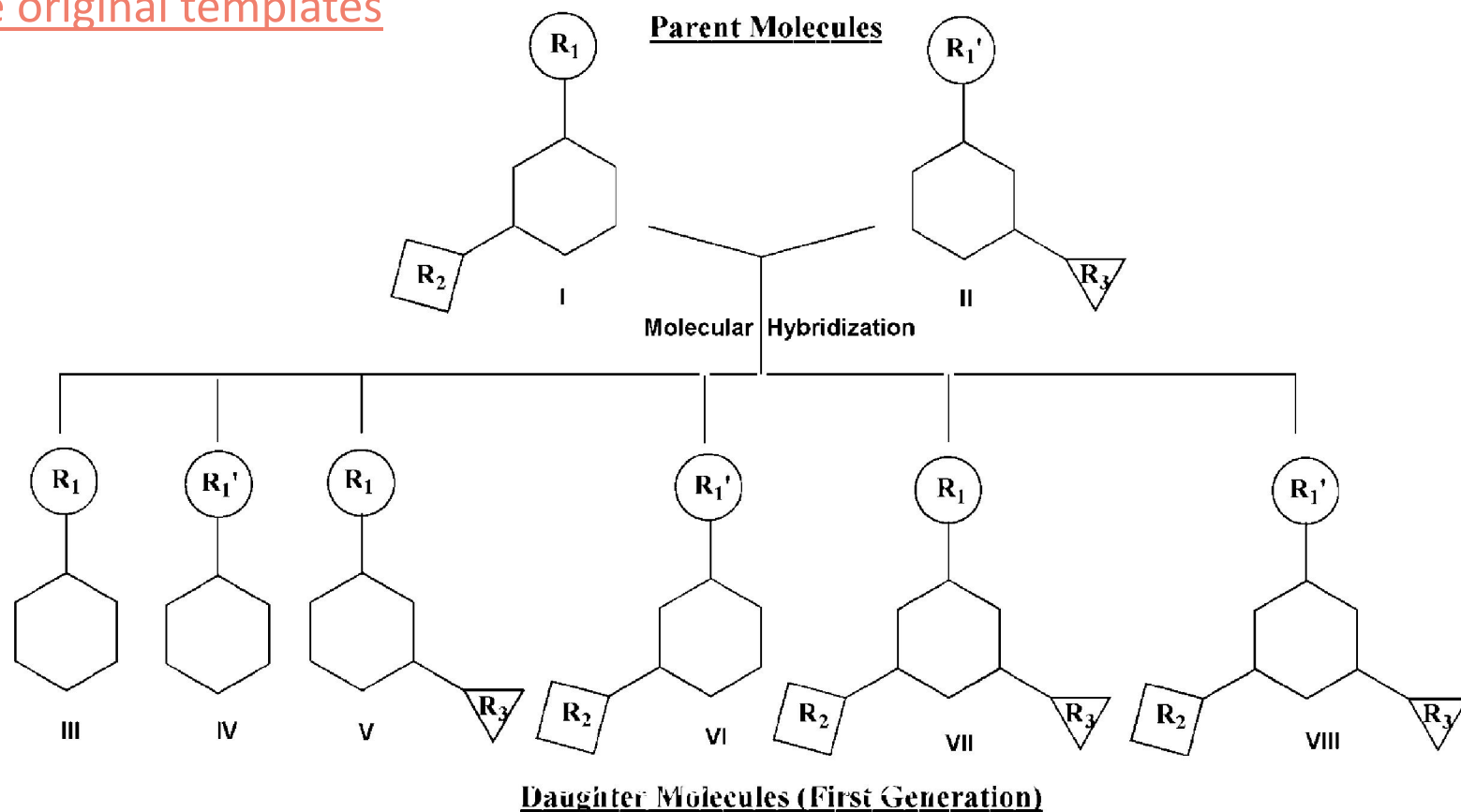


Terapia BPH

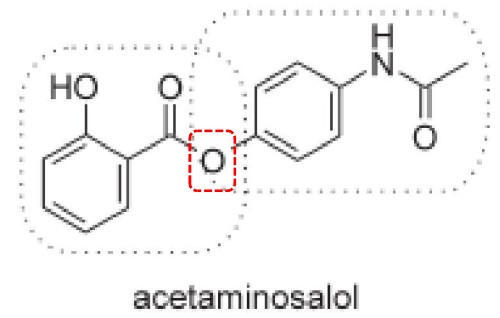
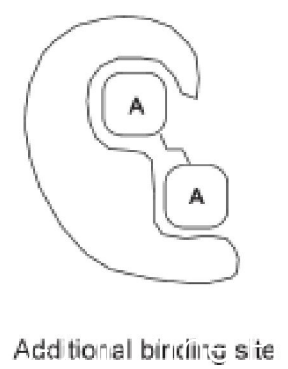
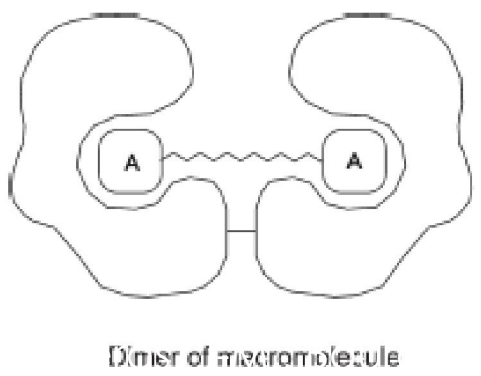
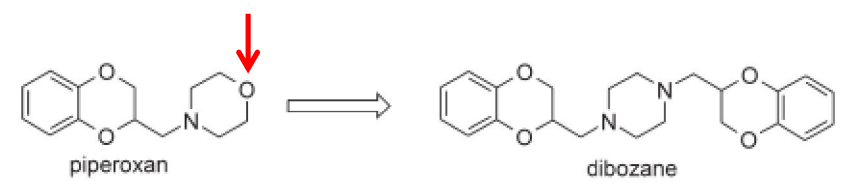
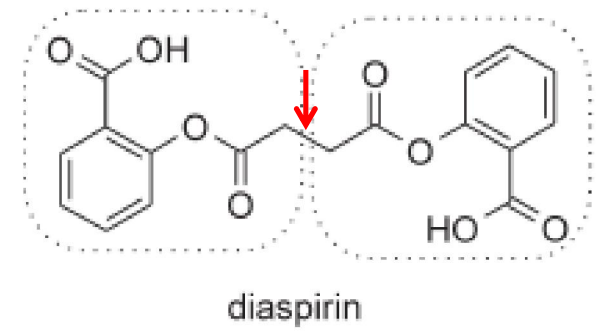
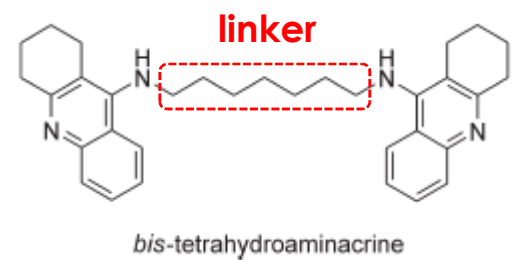
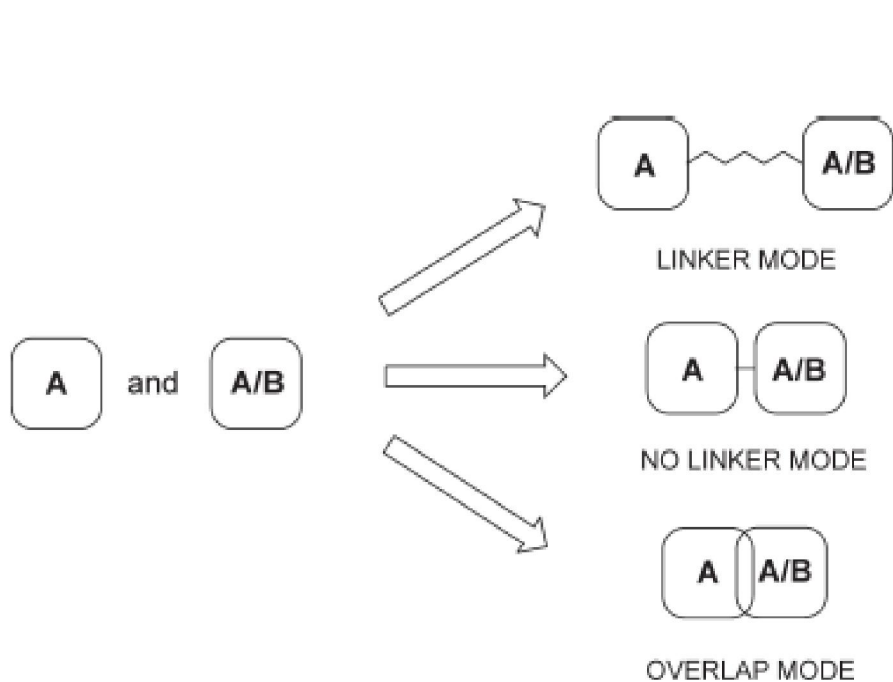


Yoshida, K. *et al.* (1998) *Bioorg. Med. Chem. Lett.*, 8, 2967.

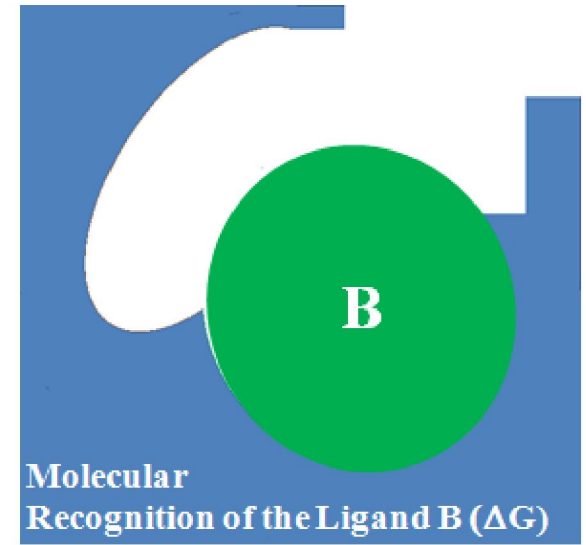
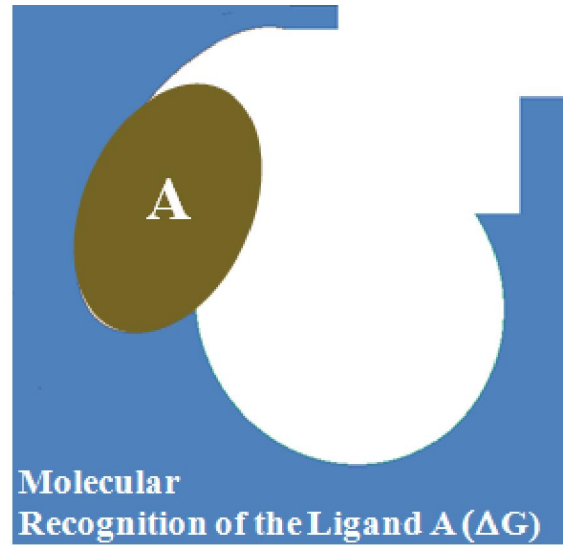
“Molecular hybridization approach emerges as a modern strategy to discover more efficient ligands or prototypes designed on the basis of the structure of two or more known bioactive substances. The initial step of this process consists of the identification of the molecular recognition pattern of pharmacophoric subunits present in these two or more template substances, already evaluated concerning the pharmacological features, followed by the fusion of these subunits in the molecular architecture of hybrid compounds combining pre-selected characteristics of the original templates”



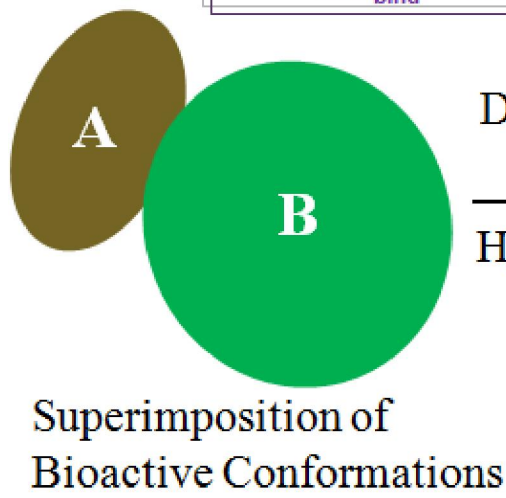
Possíveis estratégias de Hibridação Molecular



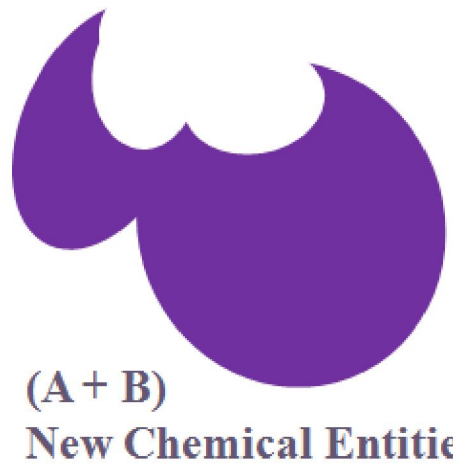
Representação ilustrativa do planejamento de um novo ligante híbrido através da sobreposição do modo de ligação de dois ligantes conhecidos com o biorreceptor alvo.



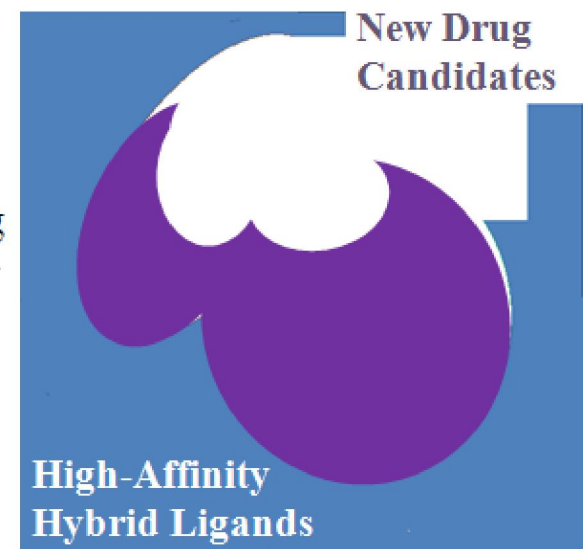
$$\Delta G_{\text{bind}} = \Delta G_{\text{match}} + \Delta G_{\text{lipo}} + \Delta G_{\text{ambig}} + \Delta G_{\text{clash}} + \Delta G_{\text{rot}}$$



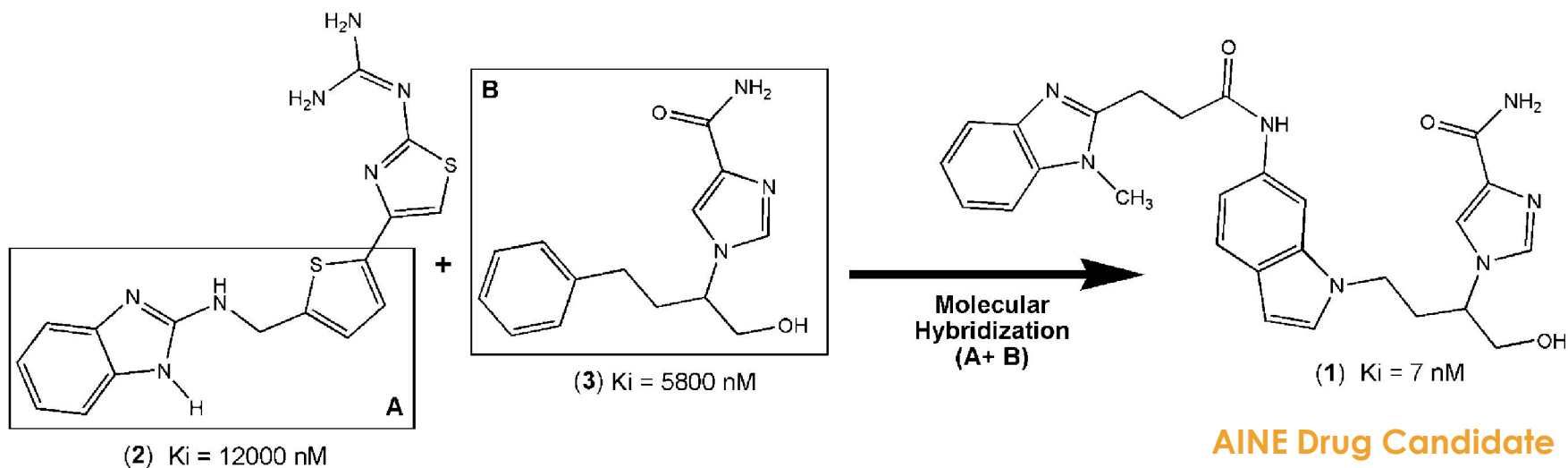
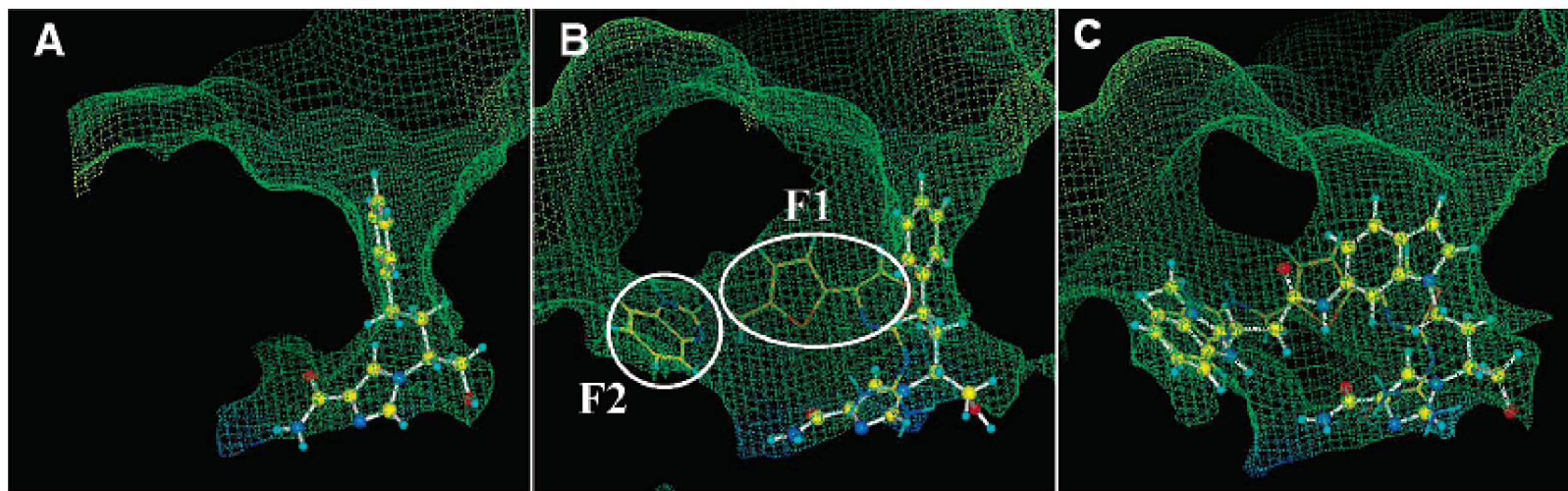
Design
of
Hybrids



Docking



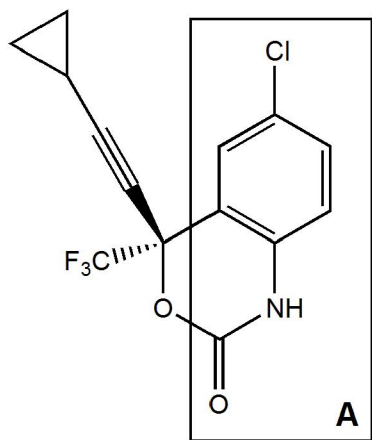
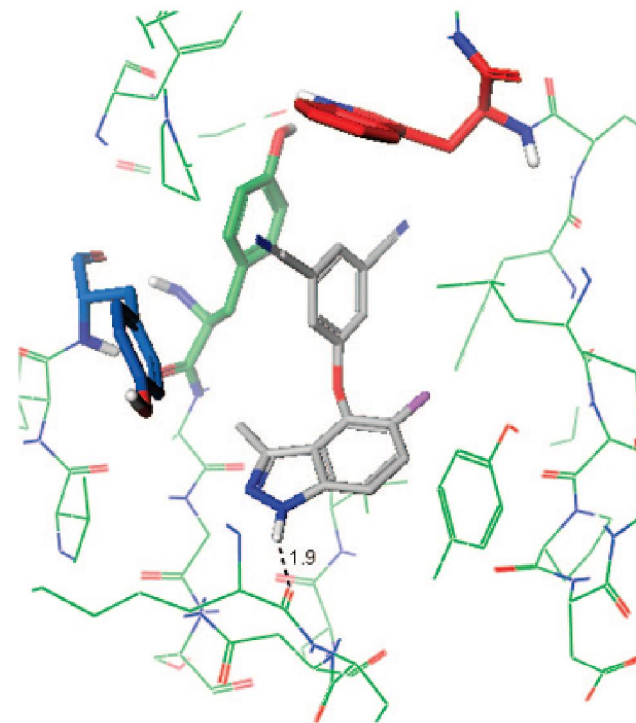
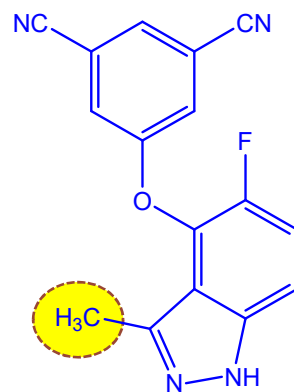
Planejamento de inibidores híbridos de adenosina deaminase.



Planejamento de inibidores híbridos de Transcriptase Reversa

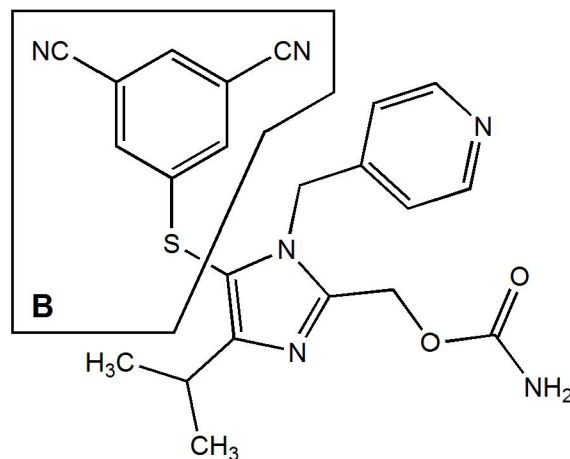


Crystallographic overlay of efavirenz (gold) and capravirine (pink) with RT



Efavirenz (**5**)
 $IC_{50} = 14 \text{ nM (wt)}$

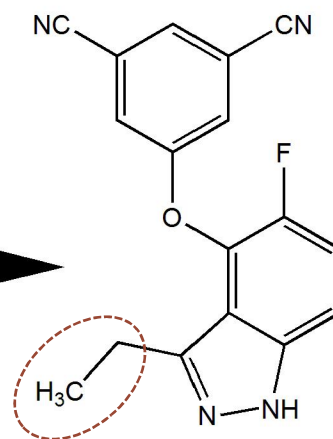
+



Capravirine (**6**)
 $IC_{50} = 47 \text{ nM (wt)}$

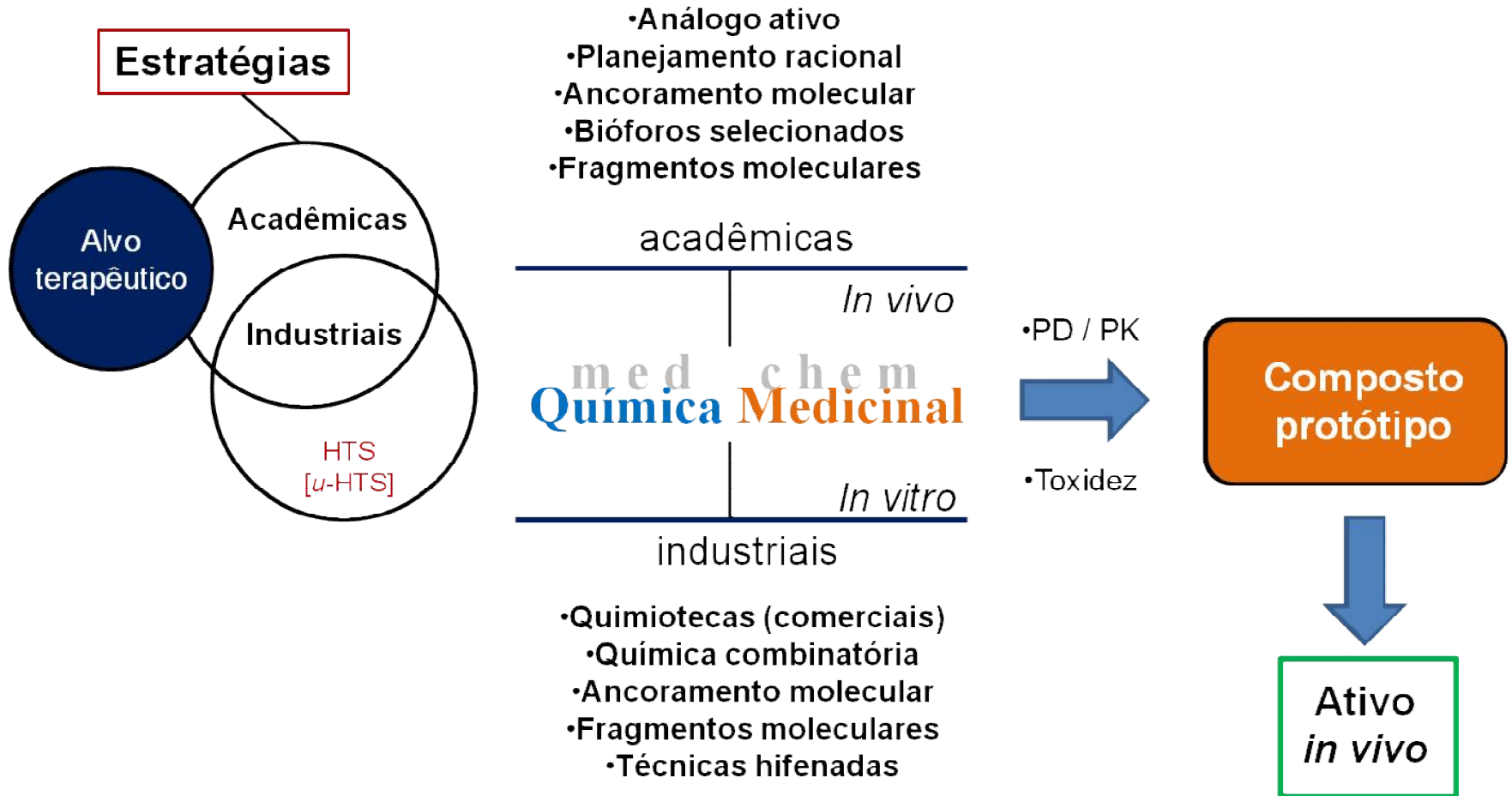


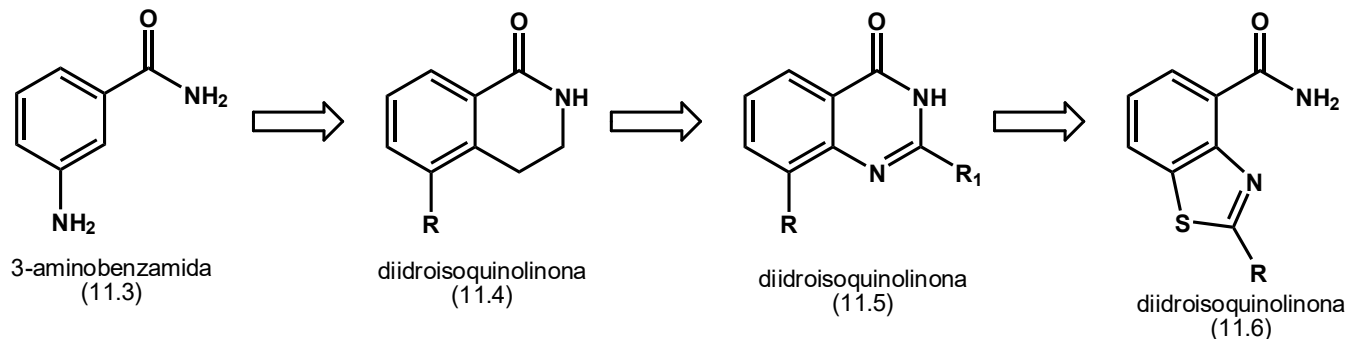
Molecular
Hybridization
(A+ B)



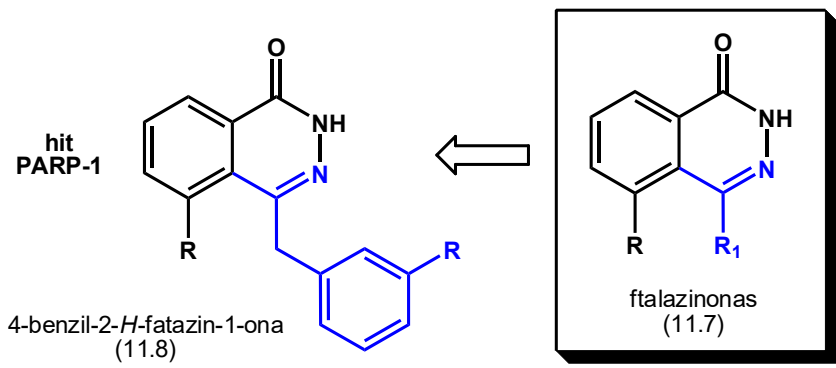
(**4**) $IC_{50} = 25 \text{ nM (wt)}$
Anti-HIV Drug Candidate

Estratégias modernas na obtenção de novos compostos-protótipos nos laboratórios de pesquisa acadêmicos e industriais

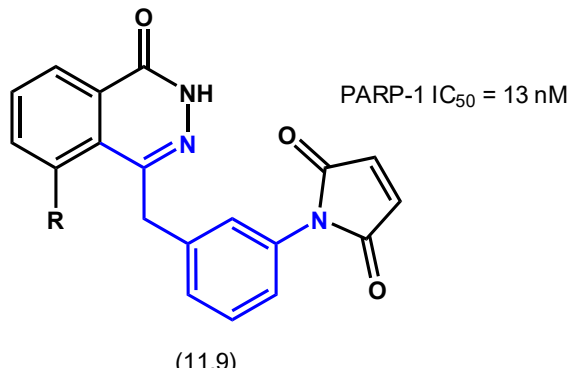




HTS screening



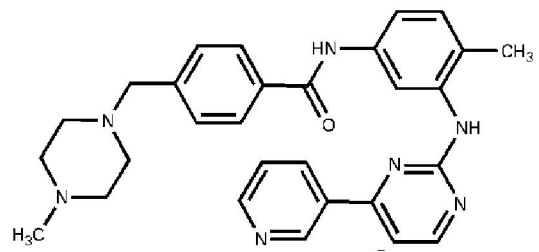
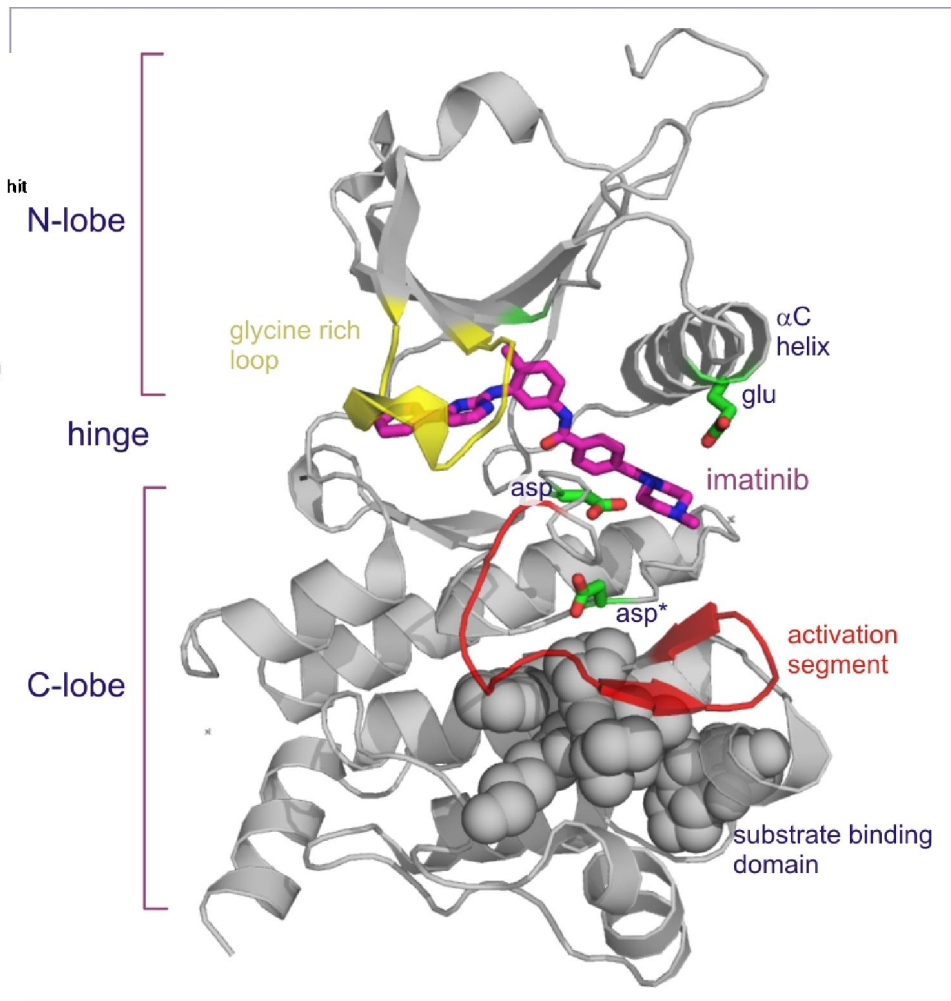
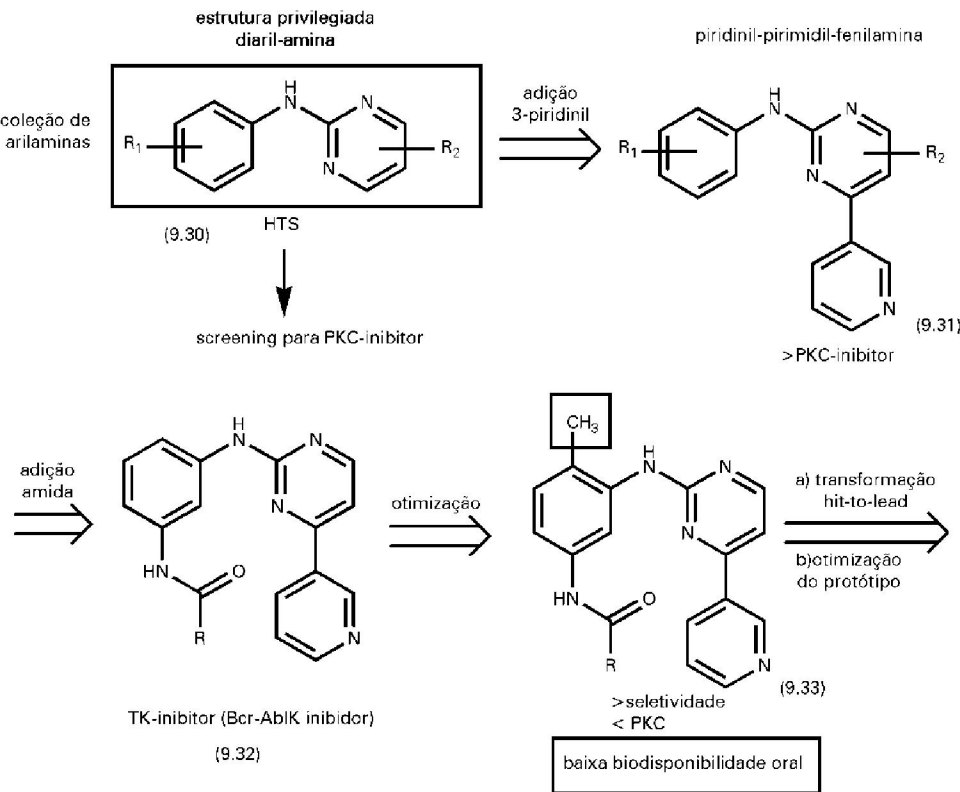
otimização



Técnicas hifenadas: HTS

Identificação do derivado ftalazinônico-imínico inibidor da poli(ADP-ribose) polimerase (PARP-1) por HTS de quimioteca selecionada.

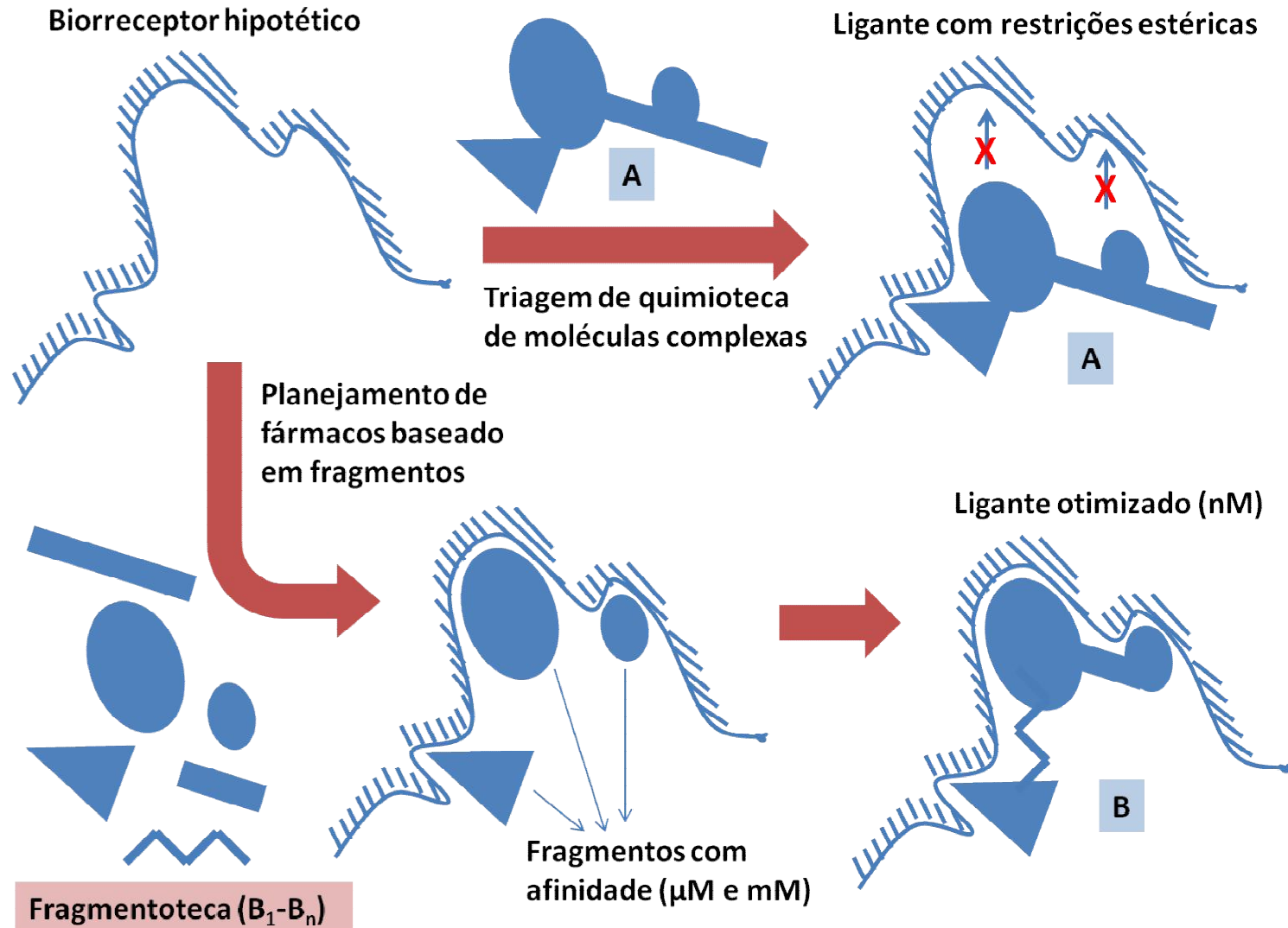
A Descoberta do Imatinibe (Gleevec)



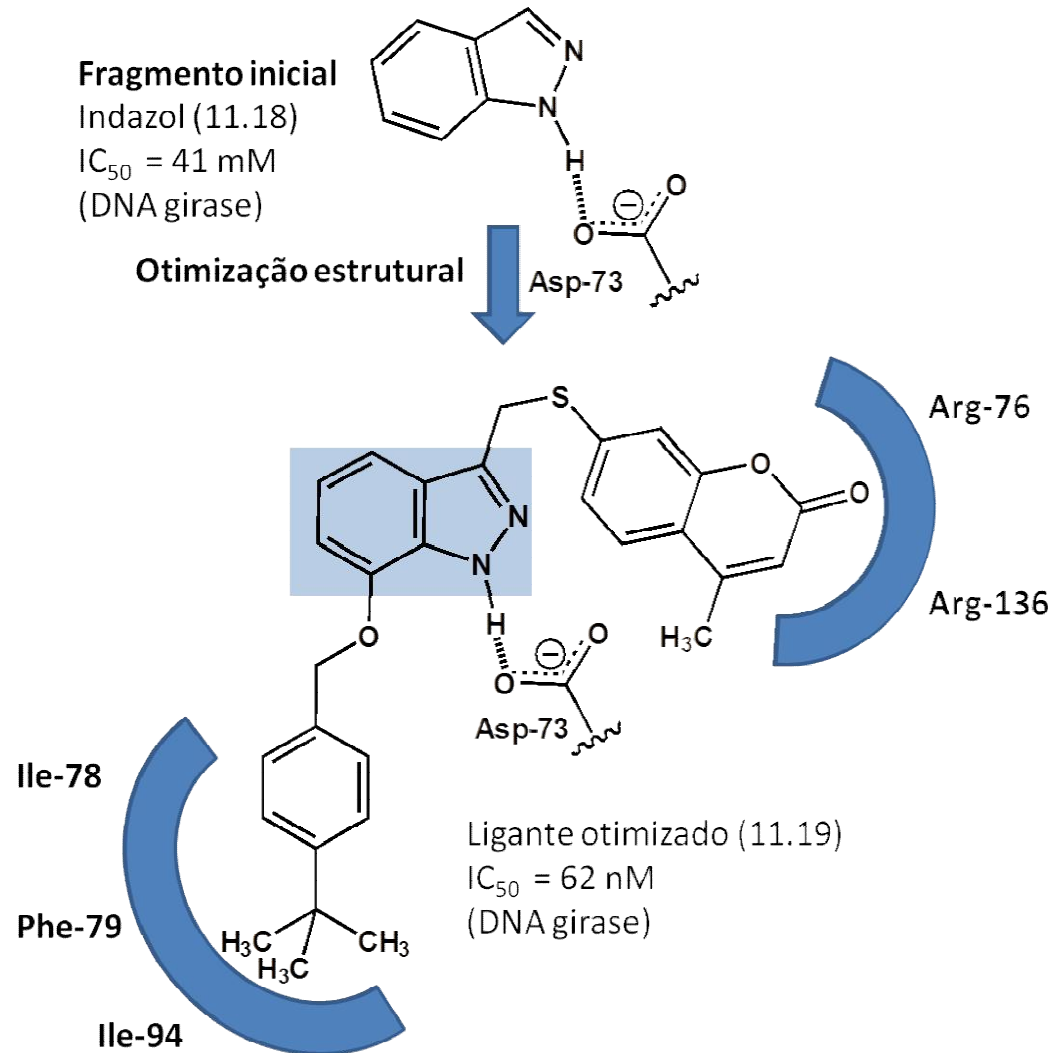
Imatinibe
Gleevec®-Novatis

Binding of Imatinib to the TK Abl. Only the catalytic domain of the tyrosine protein kinase Abl is shown. Imatinib binds the ATP binding pocket of the kinase in its inactive conformation (PDB 1OPJ). Foremen, J.; Johansen, T.; Gibb, A., Textbook of Receptor Pharmacology, 3rd Ed., CRC Press, 2010.

Representação esquemática do processo de planejamento de fármacos baseado em fragmentos moleculares.

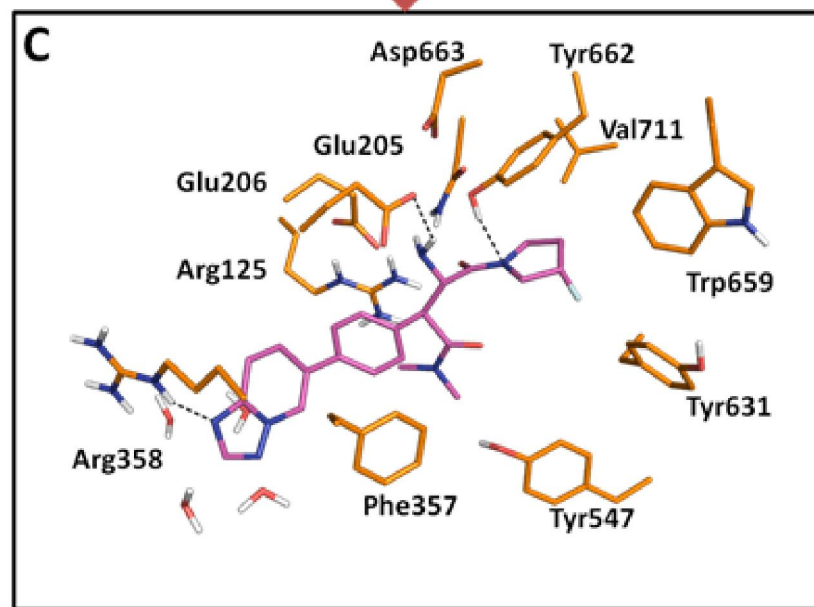
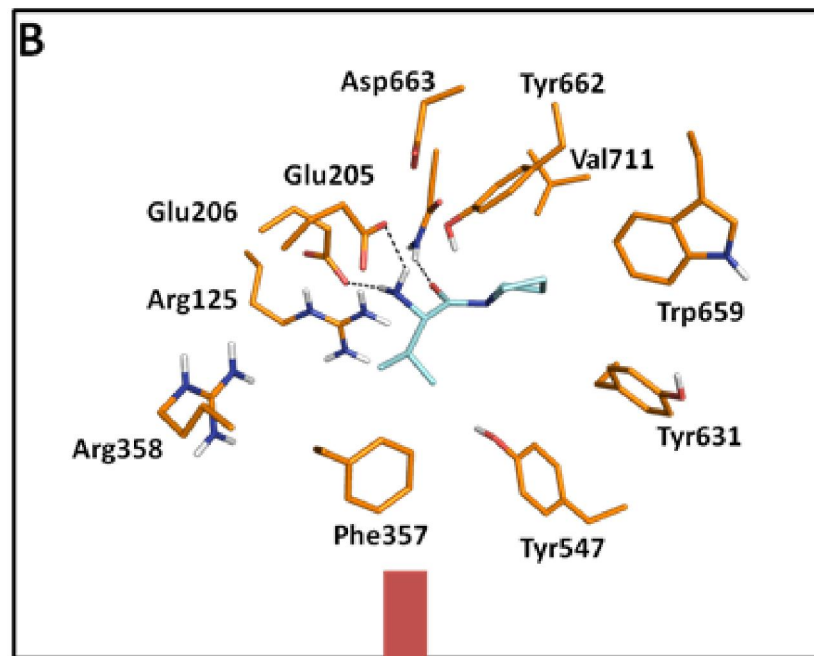
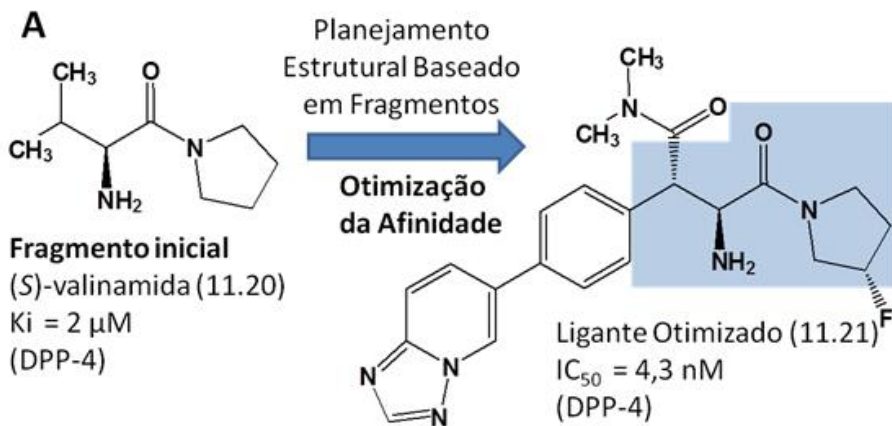


Identificação do inibidor de DNA girase a partir do fragmento molecular azaheterocíclico indazol.



Planejamento estrutural do inibidor de DPP-4 a partir do fragmento inicial valinamida

(A). Reconhecimento molecular da valinamida (B) e do protótipo azaheterocíclico (C) com sítio ativo da DPP-4 (PDB ID 1N1M e 2FJP, respectivamente).



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



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

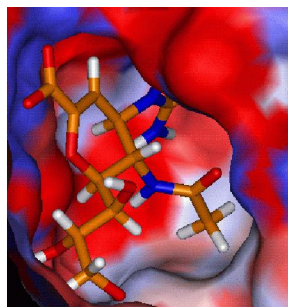


Farmacologia/
Bioquímica
PROPRIEDADES BIOLÓGICAS



Interdisciplinaridade

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



Química Computacional
RECONHECIMENTO MOLECULAR

Química Medicinal



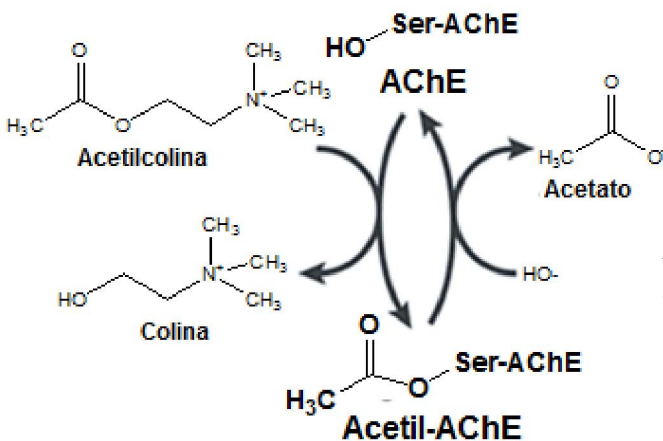
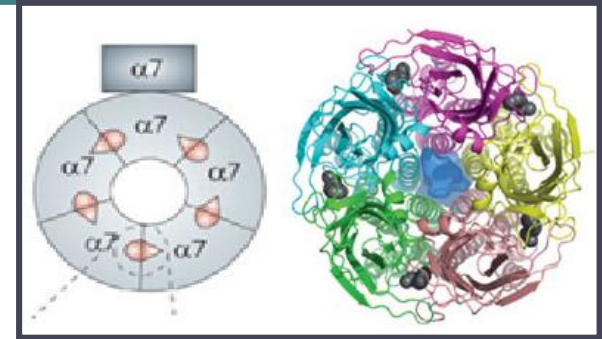
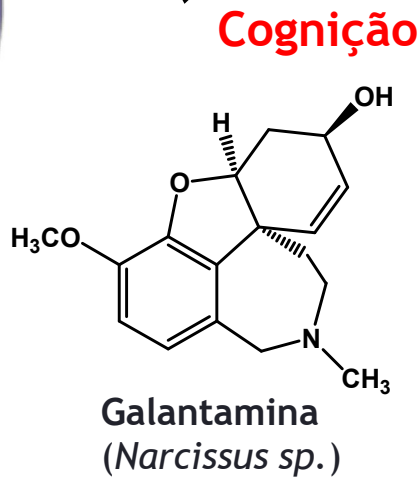
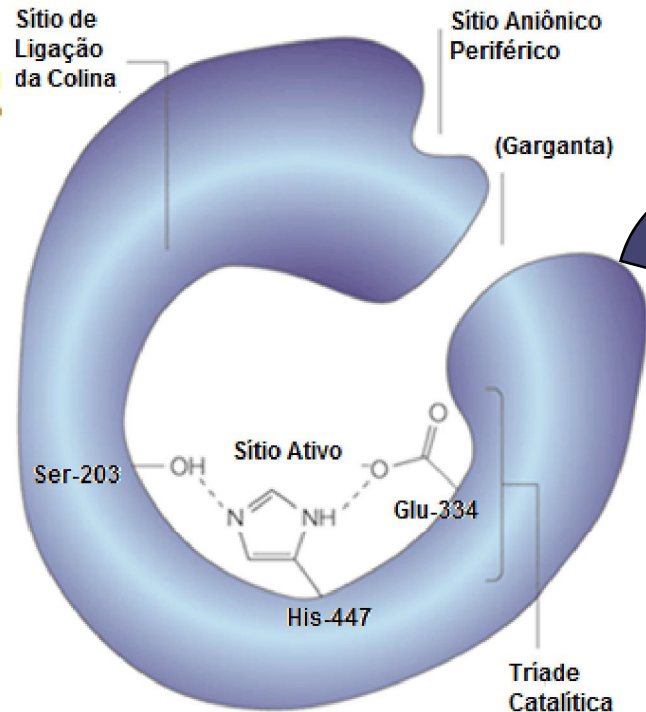
Química Orgânica
(Síntese Orgânica Medicinal)
REATIVIDADE QUÍMICA

Planejamento e Otimização Estrutural (Afinidade)

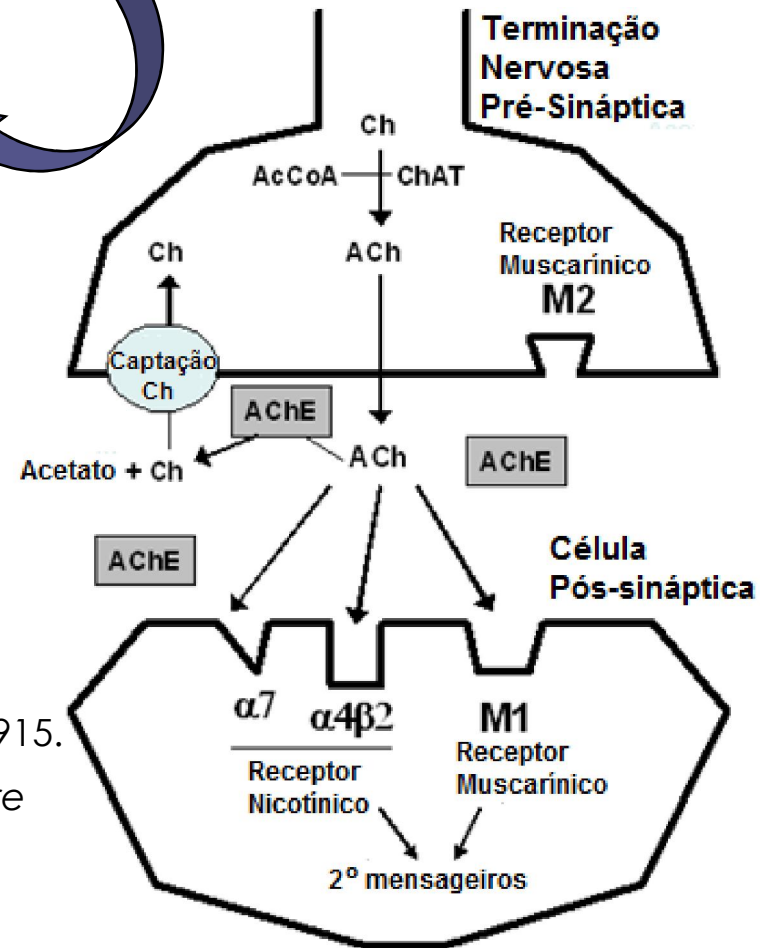
Novas Entidades Químicas



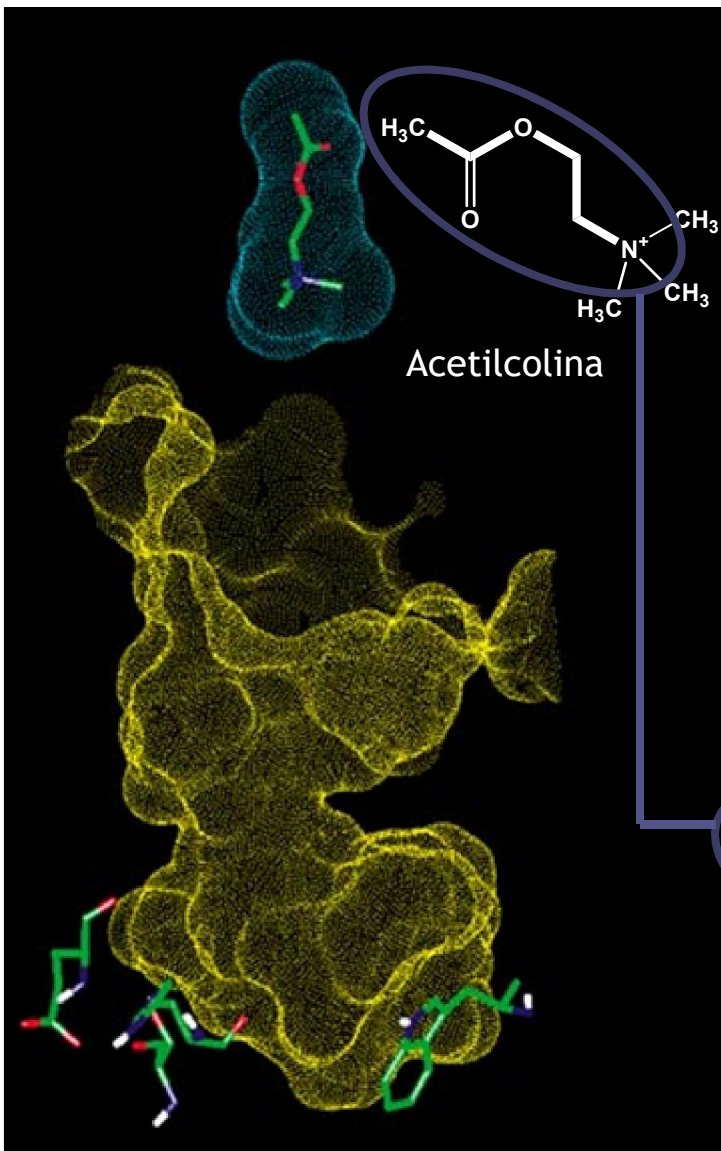
Doença de Alzheimer: Hipótese Colinérgica



Viegas-Jr, C. et al. (2005) *Mini Rev. Med. Chem.* 5, 915.
 Taly, A. et al. (2009) *Nature Rev. Drug Discov.* 8, 733.
 Bartus, R. T. et al. (1982) *Science* 217, 408



Identificação de Novos Protótipos Anticolinesterásicos por Otimização Estrutural de Produtos Naturais



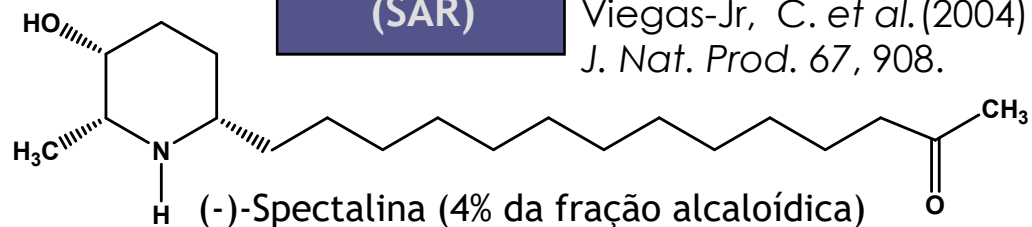
Cassia spectabilis

- Analgesia: Contorções Abdominais induzidas por AcOH / Acetilcolina

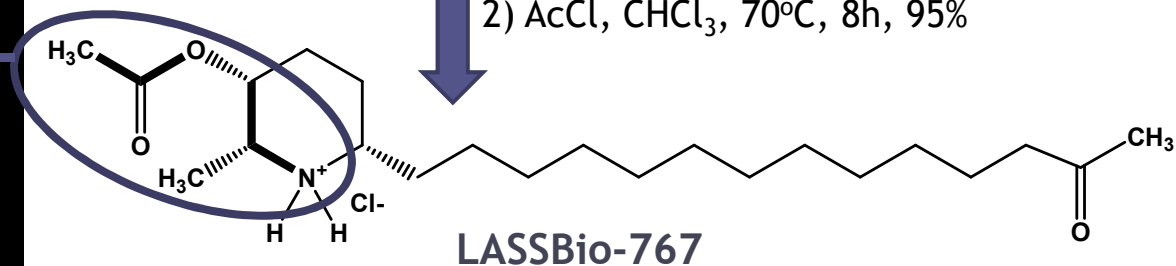


Alexandre-Moreira, M. S.; (2003) *Planta Médica* 69, 795;

Viegas-Jr, C. et al. (2004) *J. Nat. Prod.* 67, 908.

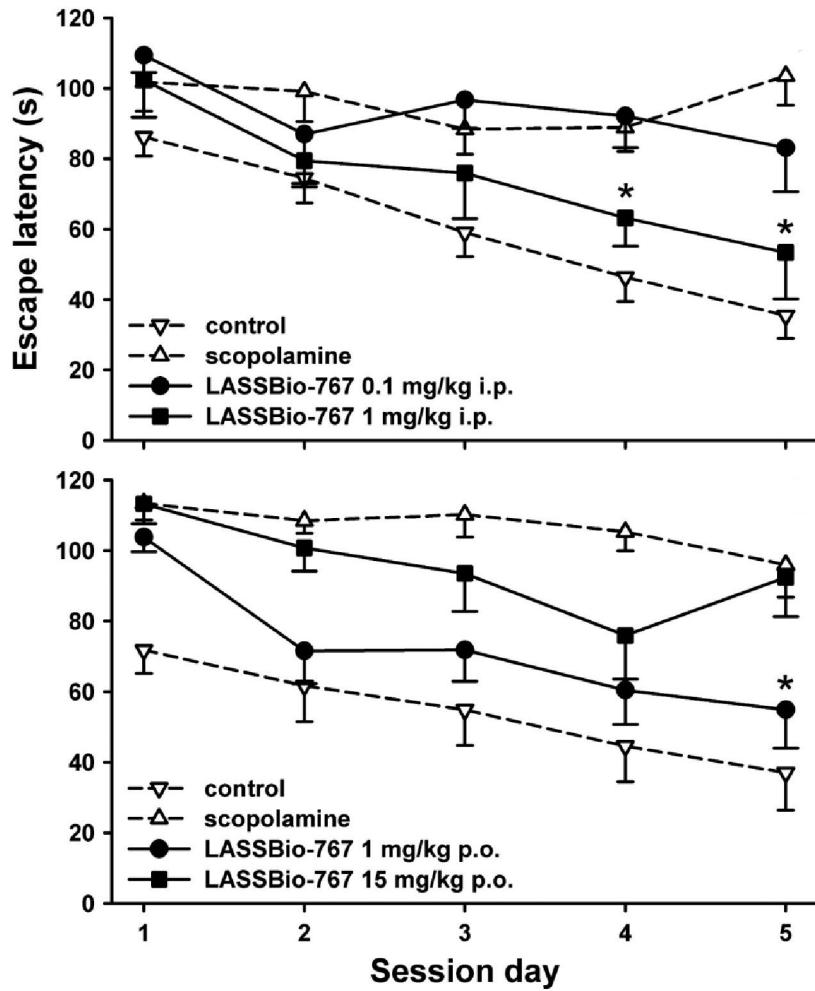


- 1) HCl, CH₂Cl₂, ta, 0.5-1 h, 100%;
- 2) AcCl, CHCl₃, 70°C, 8h, 95%

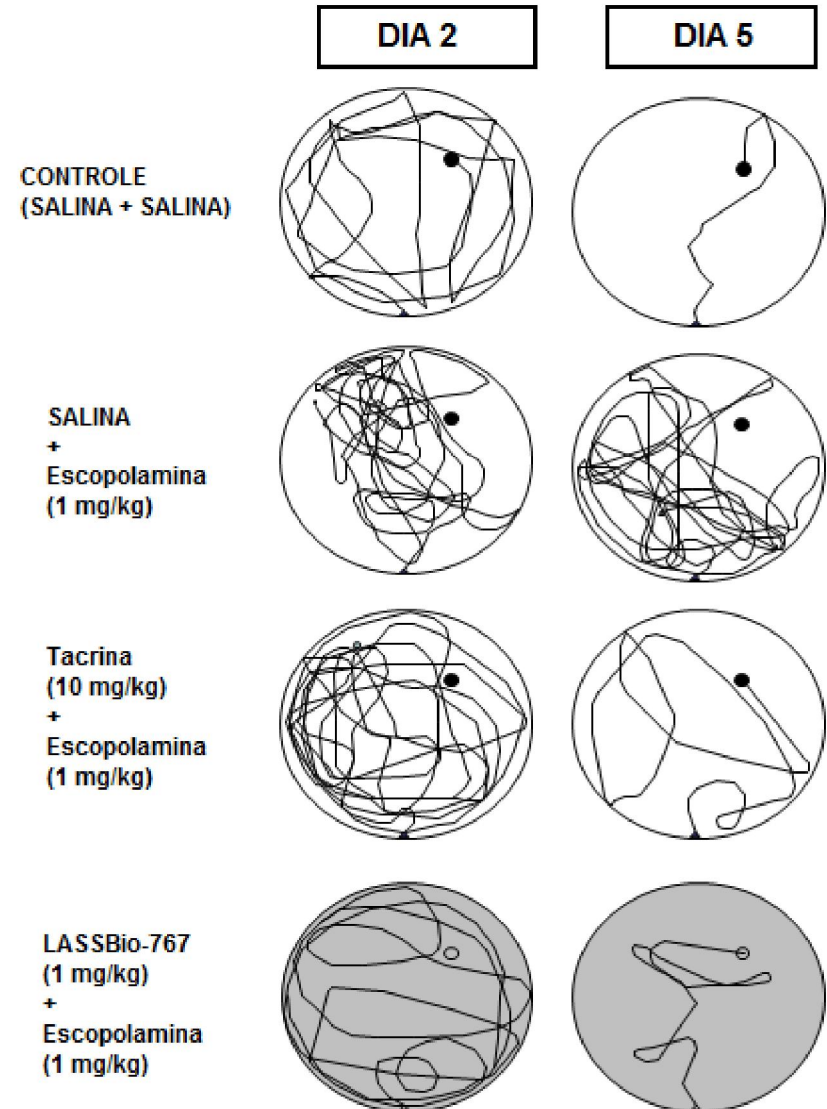


Viegas-Jr., C. et al. (2005) *Bioorg. Med. Chem.* 13, 4184.

Avaliação do efeito pró-cognitivo de LASSBio-767: Amnésia induzida por escopolomina em camundongos (labirinto aquático)



*Significativamente diferente quando comparado ao valor controle ($P < 0.05$).



DRUG DISCOVERY
REVIEW

Drug Discovery: A Historical Perspective

Jürgen Drews

*“Driven by **chemistry** but increasingly guided by **pharmacology** and the clinical sciences, drug research has contributed more to the progress of medicine during the past century than any other scientific factor.”*

Science **287**, 1960 (2000)

THE ROLE OF THE MEDICINAL CHEMIST IN DRUG DISCOVERY — THEN AND NOW

NATURE REVIEWS | **DRUG DISCOVERY** VOLUME 3 | OCTOBER 2004 | 853

Joseph G. Lombardino and John A. Lowe III†*

*“As a scientist involved at the **very earliest stages of drug discovery**, the medicinal chemist.....*



**INTERDISCIPLINARY
TEAMS**

The role of pharmacology in drug discovery

NATURE REVIEWS | **DRUG DISCOVERY** VOLUME 1 | MARCH 2002 | 237

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
23ª Escola de Verão em Química Farmacêutica e Medicinal

Obrigado!

