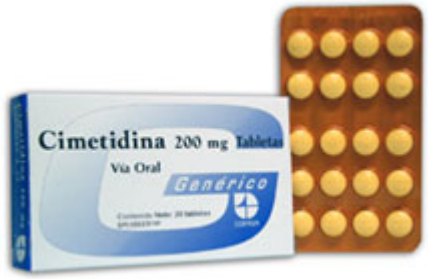
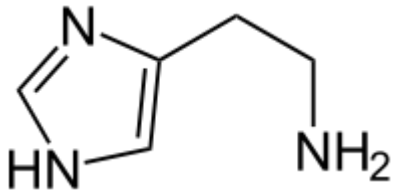
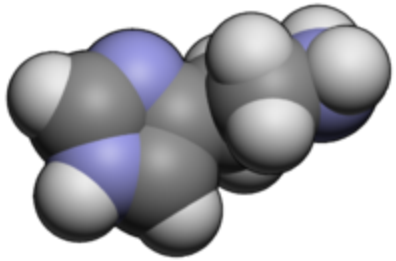
ANTI-HISTAMÍNICOS:
ANTAGONISTAS DOS RECEPTORES H1 e H2

agentes anti-alérgicos e agentes anti-úlcera

Profa. Mônica T. Pupo
Química Farmacêutica I







Bibliografia

C. R. GANELLIN, S. M. ROBBERS (eds) – Medicinal Chemistry – The role of organic chemistry in drug research, 2nd. ed., Academic Press, **1993**, p. 227-255. (Cap. 12: *Discovery of Cimetidine, Ranitidinine and other H_2-Receptor Histamine Antagonists*). **Antagonistas H2**

G. L. PATRICK – An Introduction to Medicinal Chemistry, 4th ed., Oxford University Press, **2009**, p.653-682 (Cap. 25: *Antiulcer agents*). **Antagonistas H2**

G. L. PATRICK – An Introduction to Medicinal Chemistry, 5th ed., Oxford University Press, **2013**, p.659-688 (Cap. 25: *Antiulcer agents*). **Antagonistas H2**

T. N. RILEY, J. DeRUITER *Histamine and Antihistaminic Agents*. In: J. N. DELGADO e W. A. REMERS (eds.) - Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, 10ª. ed., J. B. Lippincott, New York, 1998, p. 657-685.

A. GRINGAUZ – Introduction to Medicinal Chemistry. Drugs: How drugs act and why. VCH Pub, 1997, p. 621-653 (Cap. 13: *Histamine Antagonists and Local Anesthetics*).

D. A. WILLIAMS, T. L. LEMKE, Eds. Foye´s Principles of Medicinal Chemistry, 7th Ed., Lippincott Williams & Wilkins, **2013**, p. 1045-1072 (Cap. 32: NELSON, W.L., *Antihistamines and Related Antiallergic and Antiulcer Agents*). **Antagonistas H1 e H2**

D. A. WILLIAMS, T. L. LEMKE, Eds. Foye´s Principles of Medicinal Chemistry, 6th Ed., Lippincott Williams & Wilkins, **2008**, p. 1004-1027 (Cap. 37: NELSON, W.L., *Antihistamines and Related Antiallergic and Antiulcer Agents*).

RECEPTORES

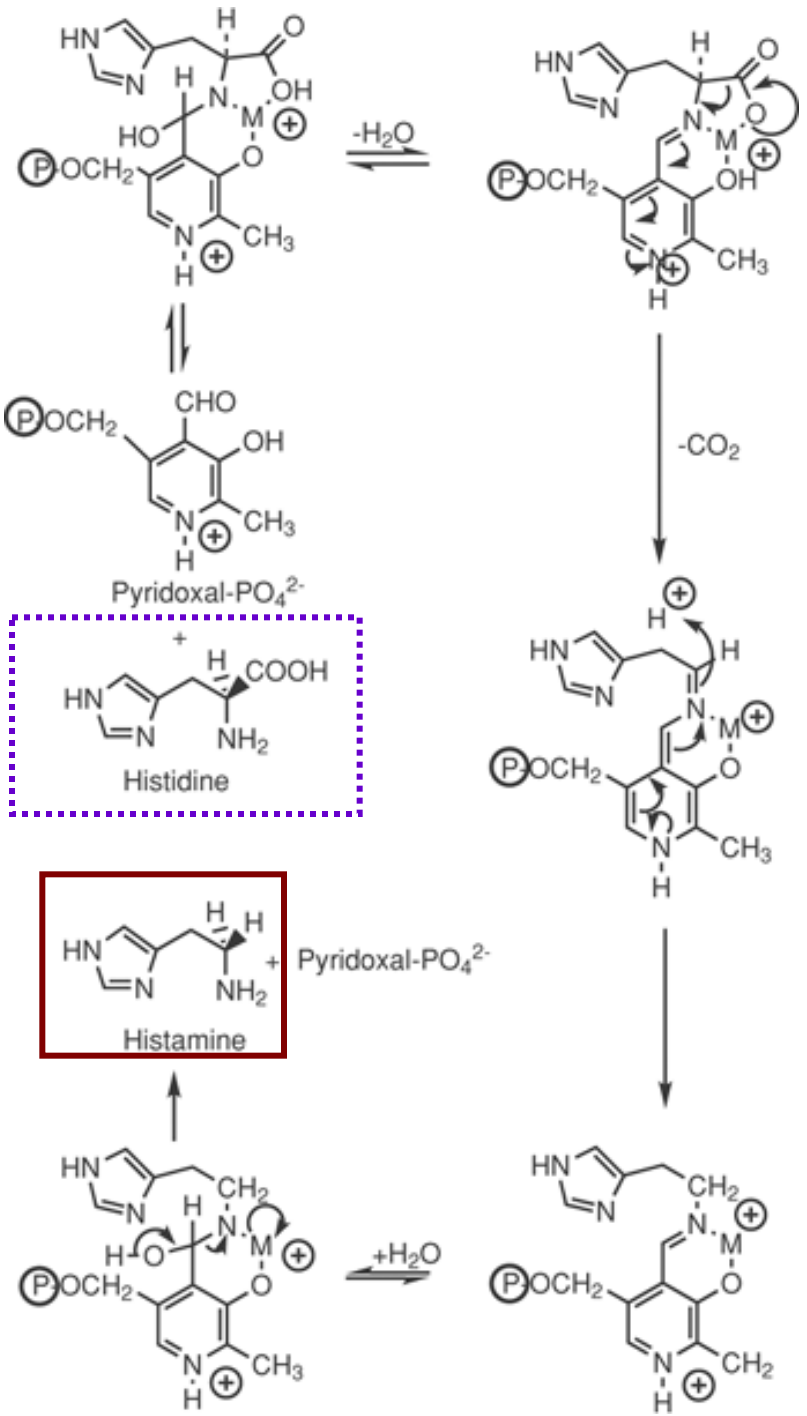
H_1	Mediação da contração da musculatura lisa, aumento da permeabilidade vascular, prurido, geração de prostaglandinas, diminuição da condução atrioventricular acompanhada de taquicardia, ativação dos reflexos vagais. Alvo para anti-alérgicos.
H_2	Mediação das ações da histamina na secreção de ácido gástrico. Alvo para fármacos anti-úlcera.
H_3	Autorreceptor pré-sináptico. Modula a síntese e liberação de histamina no SNC e tecidos periféricos Potencial alvo para fármacos contra rinite alérgica
H_4	Expresso nos mastócitos, eosinófilos e outras linhagens de células hematopoiéticas (basófilos, células T). Descoberto mais recentemente – função fisiológica ainda desconhecida. Potencial alvo para anti-inflamatórios e anti-alérgicos em desordens autoimunes (artrite reumatóide, asma, rinite alérgica)

Biossíntese de histamina

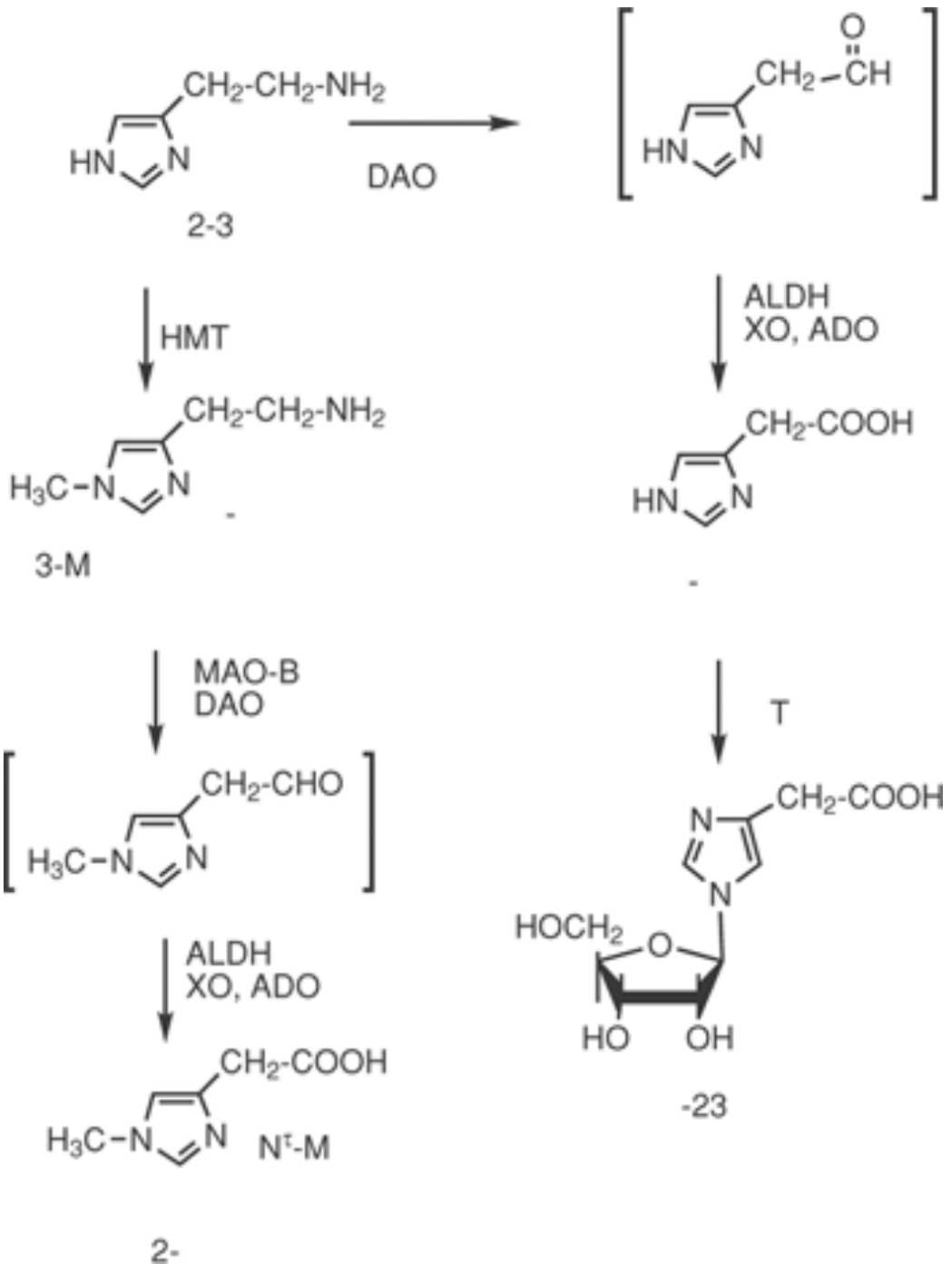
Aparelho de golgi de mastócitos e basófilos pela descarboxilação de histidina

Mecanismo molecular

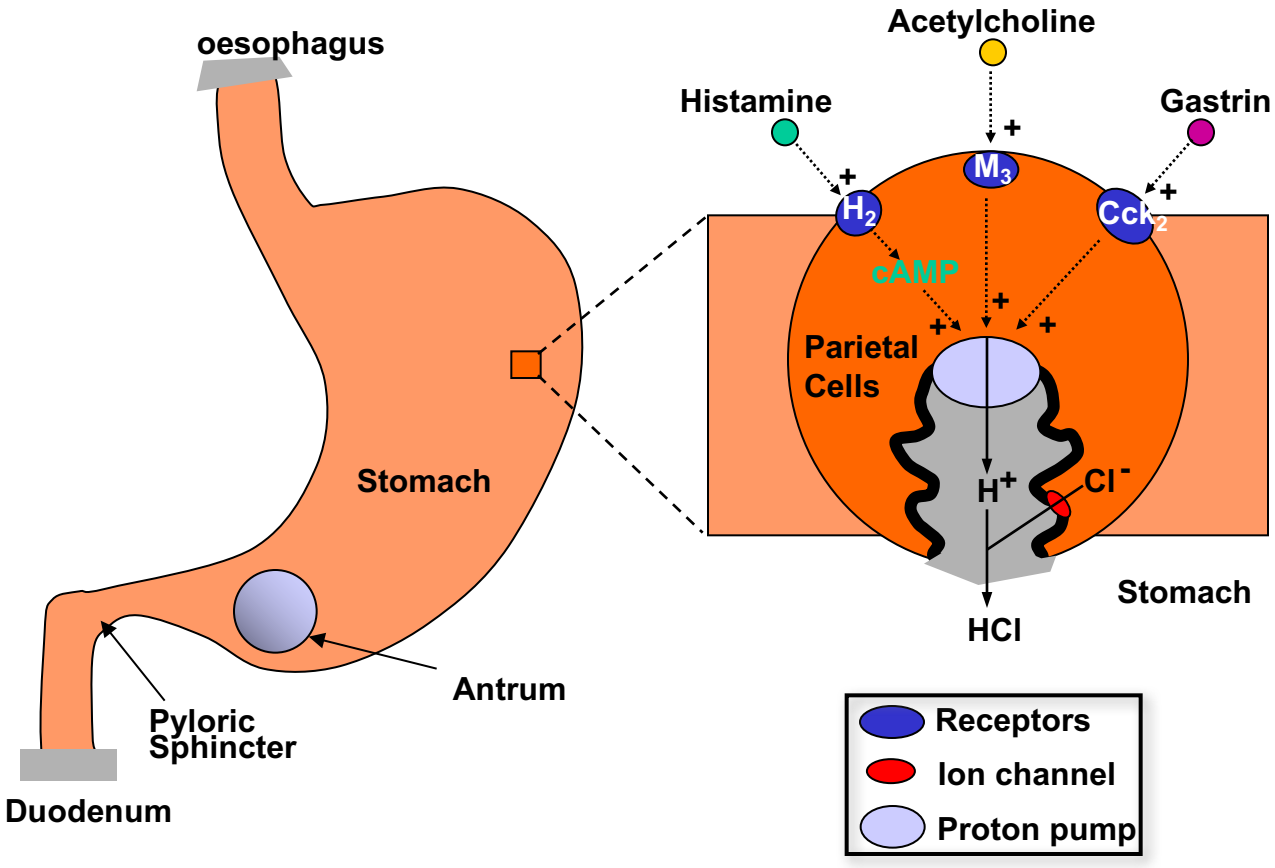
descarboxilação de histidina realizada pela enzima L-histidina-descarboxilase e piridoxal fosfato como cofator



Metabolismo de histamina: metilação e oxidação



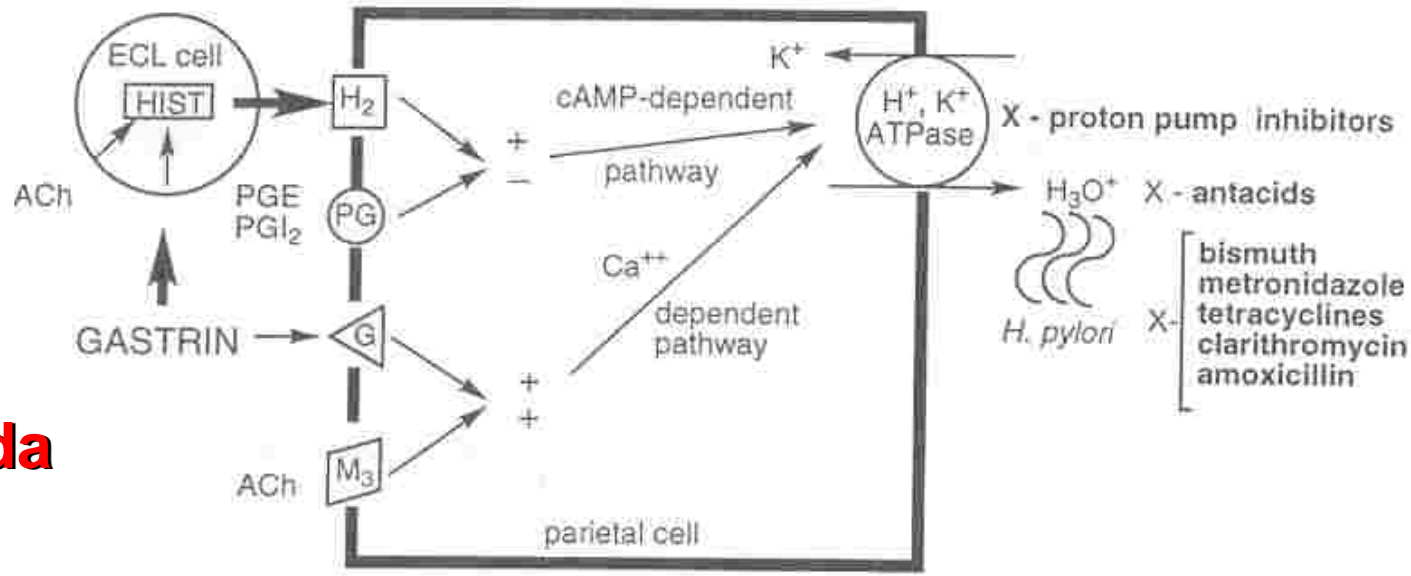
Células Parietais e liberação de ácido gástrico

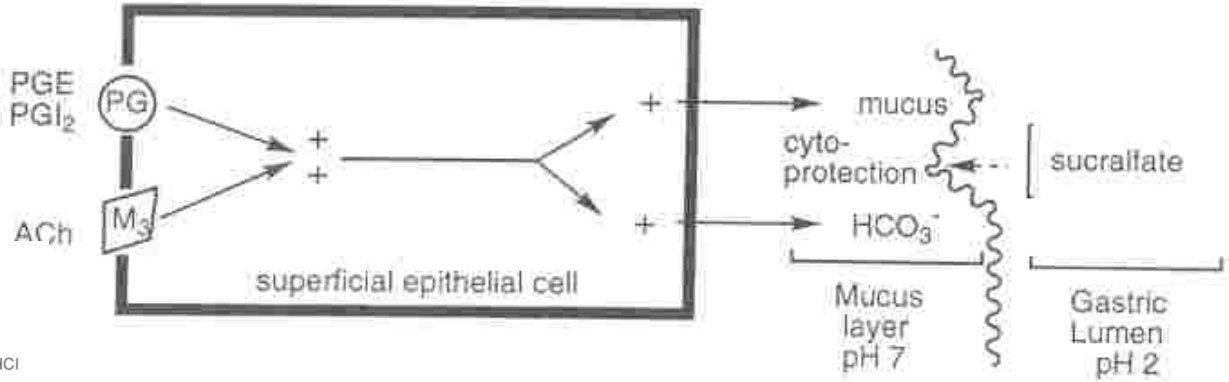


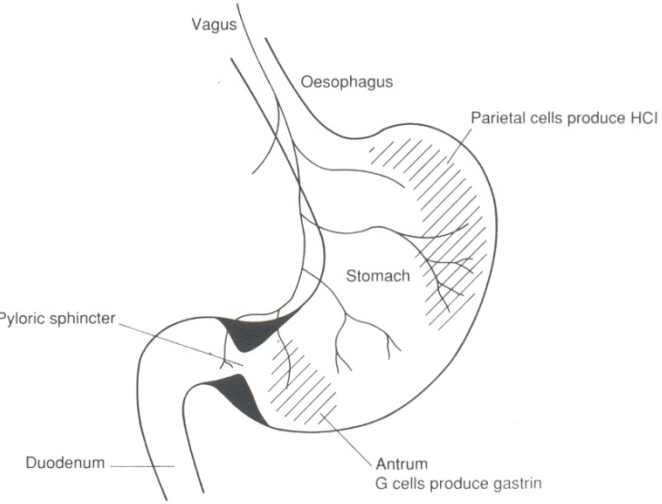
- Liberação de ácido gástrico é promovida por acetilcolina, gastrina e histamina

Liberação da secreção ácida estomacal

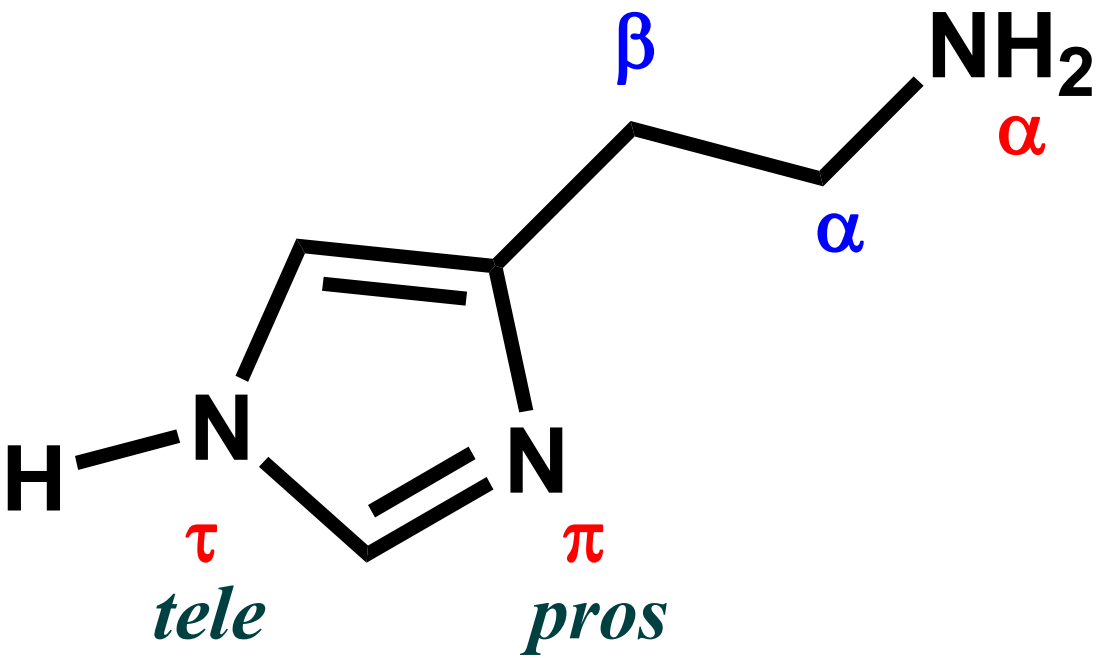
Receptores H2



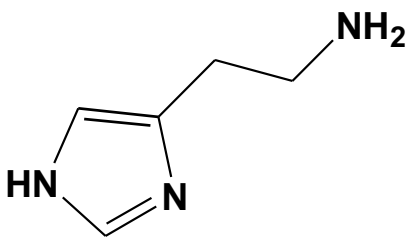


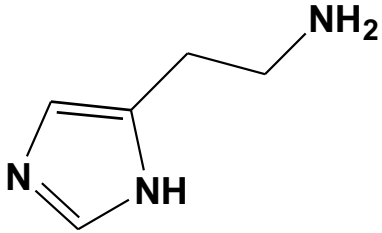


pKa = 9,8
(grupo amino terminal)



pKa = 5,74
(anel imidazólico)



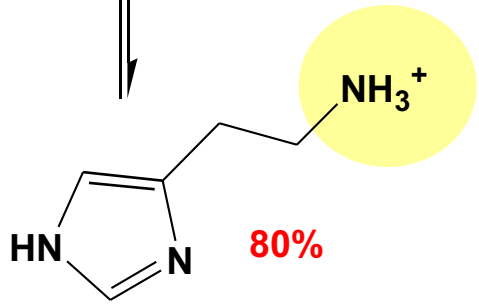


N^{τ} - tautômero

N^{π} - tautômero

Forma dominante em pH 13,0

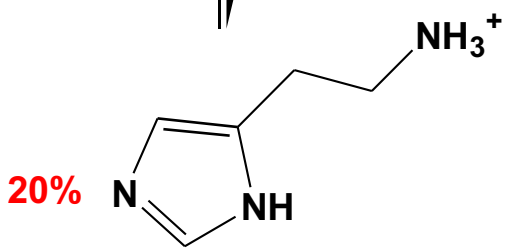
Importante para atividade biológica

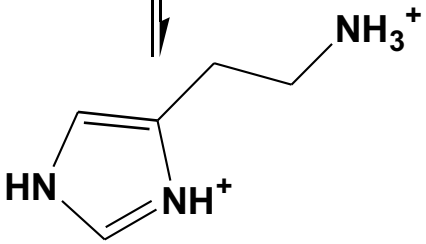


Monocátions
99,6% das formas no plasma (pH 7,4)

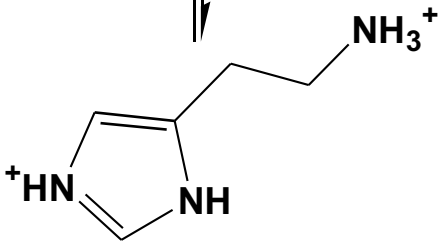
80%

20%



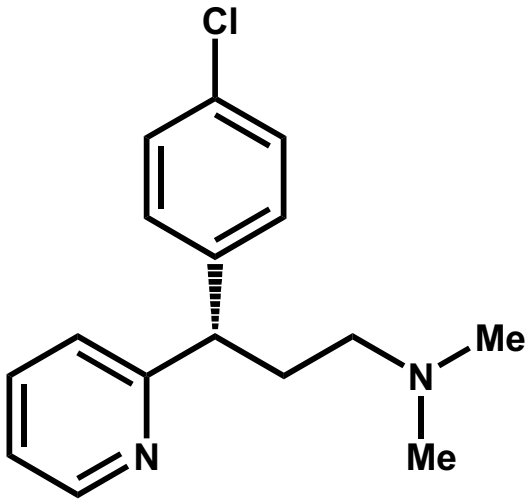


Dicátions

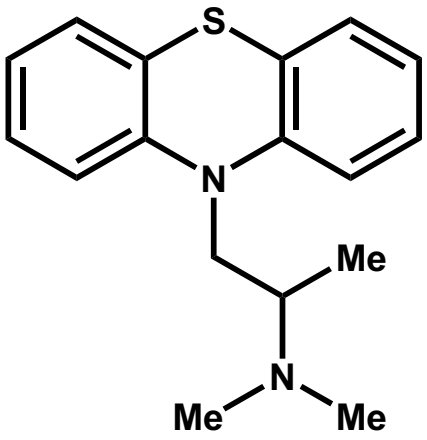


Forma dominante em pH 2,0

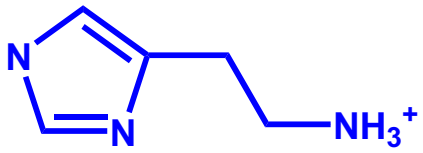
Antagonistas H1



Dexclorfeniramina
(polaramine)

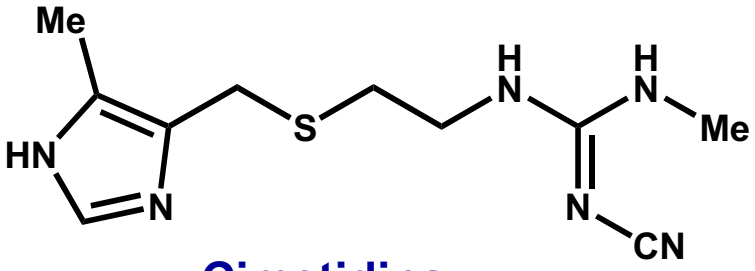


Prometazina
(fenergan)

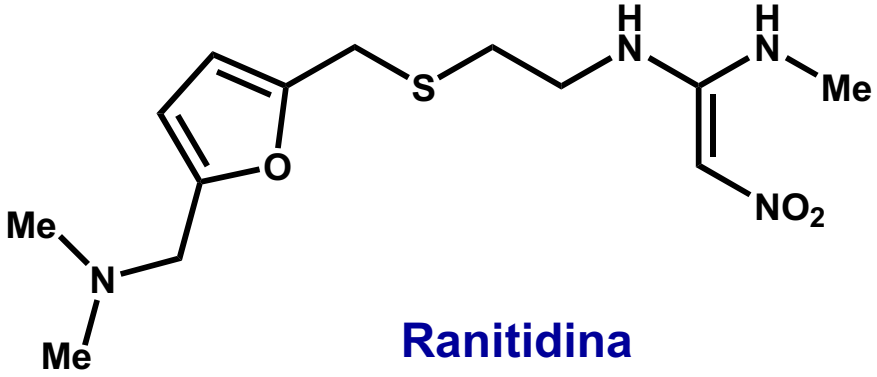


histamina

Antagonistas H2



Cimetidina
(tagamet)



Ranitidina
(antak)

Antagonistas de histamina liberada no processo alérgico

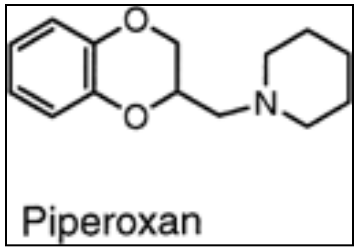
Primeira geração de anti-histamínicos H1

- ✓ etilenodiaminas
- ✓ etanolaminas
- ✓ alquilaminas
- ✓ piperazinas
- ✓ tricíclicos

Segunda geração de anti-histamínicos H1

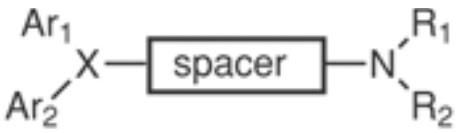
Antagonistas de histamina liberada no processo alérgico

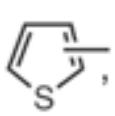
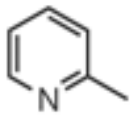
Afetam receptores colinérgicos, adrenérgicos, dopaminérgicos e serotoninérgicos



Piperoxan

Relação estrutura-atividade:

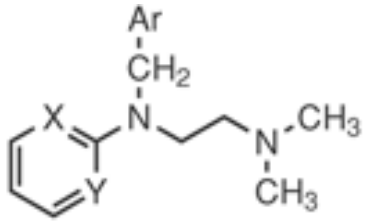


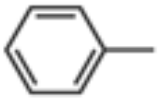
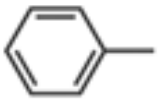
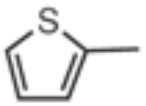
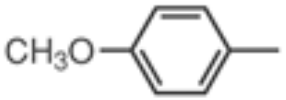
Ar_1, Ar_2 = (Y)-Ph-,  , 

Etilenodiaminas →	X = N	$R_1 = R_2 = CH_3$	Spacer = $-(CH_2)_n-$ (n = 2 or 3, usually 2)
Etanolamina →	X = CHO	$R_1 - R_2 = (CH_2)_{4-6}$	
Alquilamina →	X = CH	$R_1 = CH_3(H)$, $R_2 = CH_2Ar$	

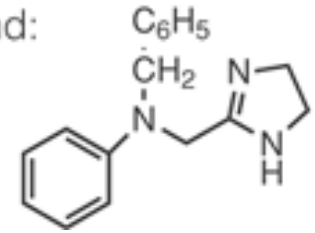
Primeira geração de anti-histamínicos H-1

Etilenodiaminas



Drugs	X	Y	Ar
Phenbenzamine	CH	CH	
Tripelennamine (pyribenzamine)	N	CH	
Methapyrilene	N	CH	
Thonzylamine	N	N	

Related compound:

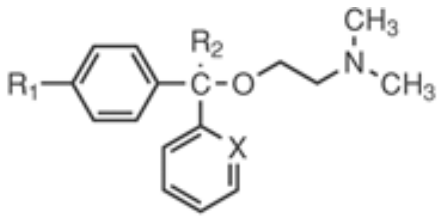


Antazoline

Primeira geração de anti-histamínicos H-1

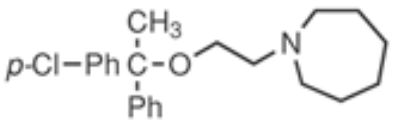
Éteres de etanolamina

Usada no tratamento de Parkinson devido à sua ação central anti-colinérgica

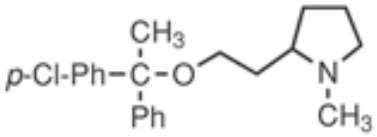


Drugs	Trade Name	R_1	R_2	X
Diphenhydramine Dimenhydrinate	Benadryl Dramamine	H	H	CH
Bromodiphenhydramine		Br	H	CH
Chlorodiphenhydramine		Cl	H	CH
Carbinoxamine	Colistin	Cl	H	N
Doxylamine	Decapryn Unisom	H	CH_3	N

Related compounds:



Setastine (Loderix)



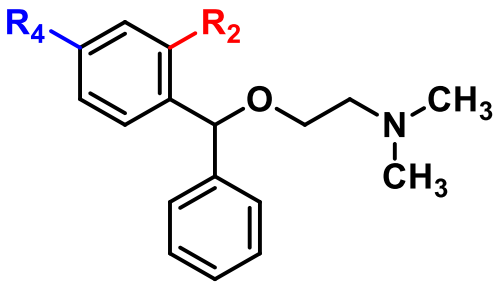
Clemastine (Tavist)

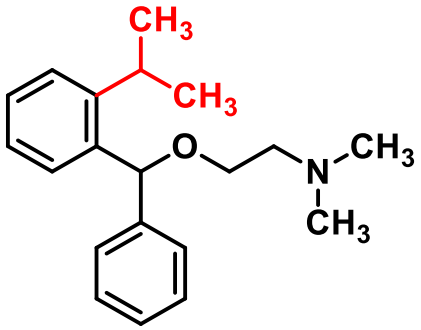
Maior seletividade para receptores H1 em relação a receptores muscarínicos

Atividade anti-histamínica x anticolinérgica

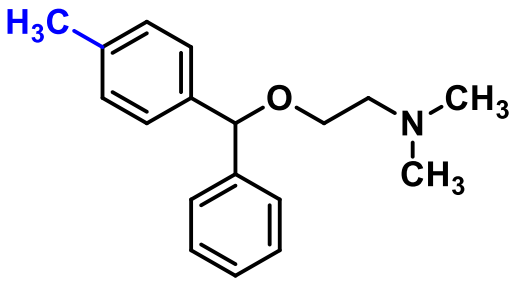
Substituintes alquílicos em R2 (Me, Et, iPr, tBu):
diminuem ação anti-histamínica e aumentam anticolinérgica

Substituintes alquílicos em R4 (Me, Et, iPr, tBu):
diminuem ação anti-colinérgica e aumentam levemente anti-histamínica





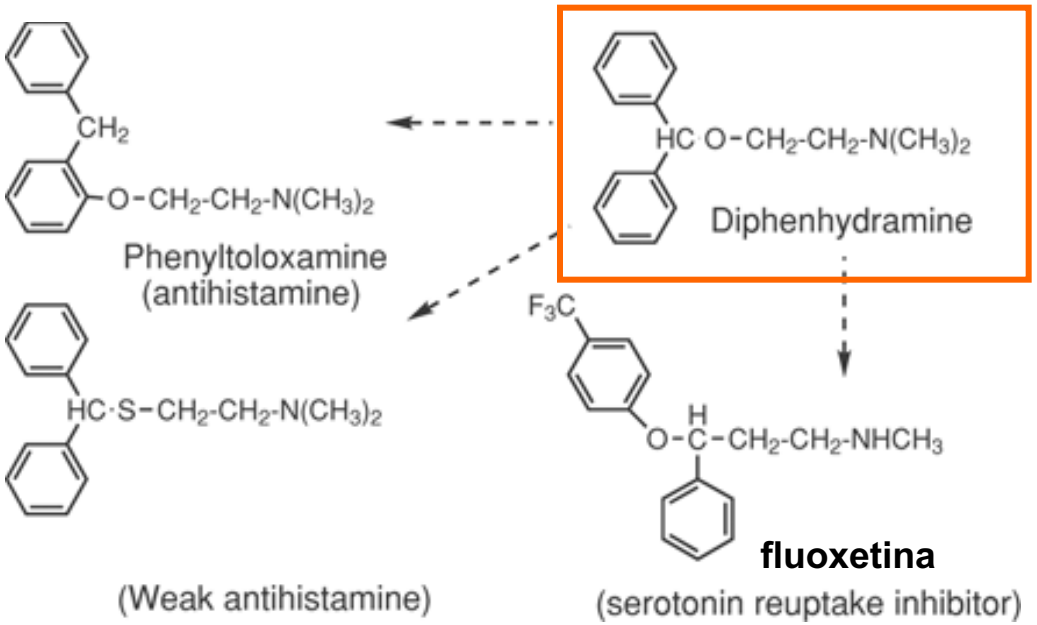
Maior ação anticolinérgica



Maior ação anti-histamínica

Enantiômeros com configuração *S* são geralmente mais potentes

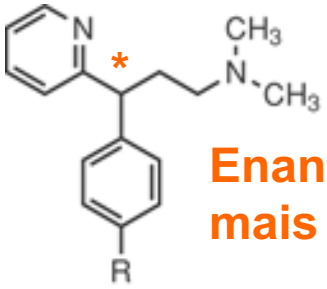
Semelhança estrutural de difenidramina com outros agentes ativos



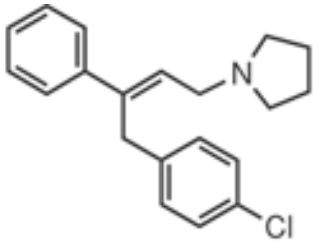
Anti-histamínico

Primeira geração de anti-histamínicos H-1

Alquilaminas



Enantiômeros S mais ativos

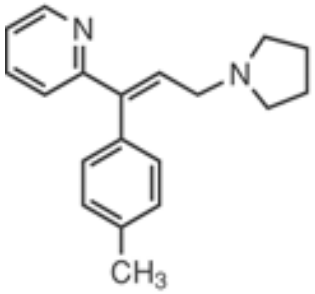


R = H; Pheniramine

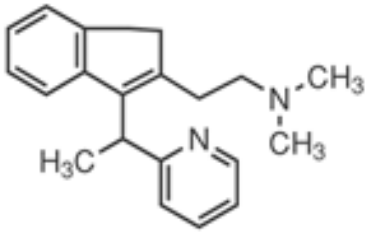
R = Cl; Chlorpheniramine (Chlortrimeton)
Dexchlorpheniramine (Polaramine)

R = Br; Brompheniramine (Dimetane)
Dexbrompheniramine (Disomer)

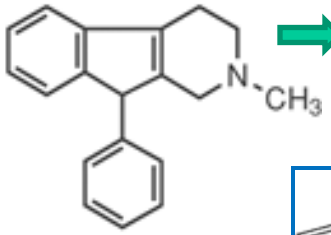
E - Pyrrobutamine
(Pyronil)



Triprolidine
(Actidil)

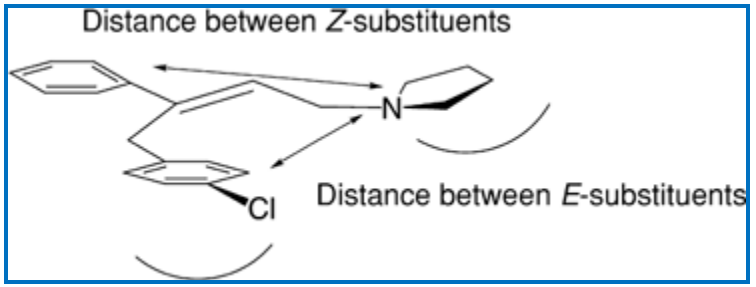


Dimethindene
(Forhistal)



Phenindamine
(Nolahist)

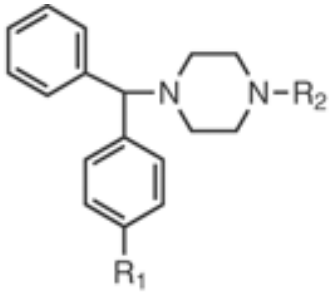
Isômeros E mais ativos que Z

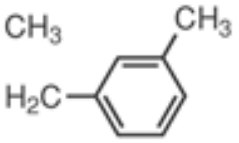
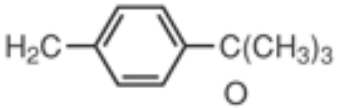
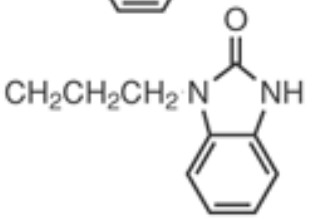


Menor efeito sedativo central comparado aos derivados de etilenodiamina e etanolamina
Maior seletividade para os receptores H1 x muscarínicos

Derivados de Piperazinas

Relacionados à série de etilenodiaminas e éteres etanolaminas

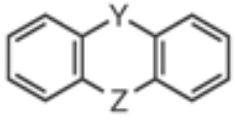


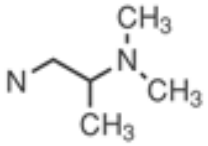
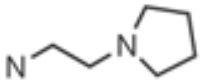
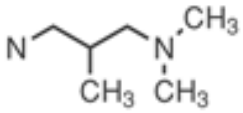
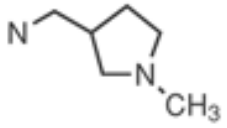
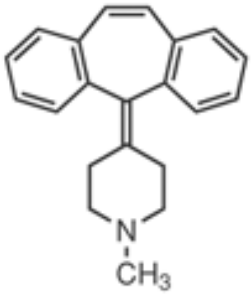
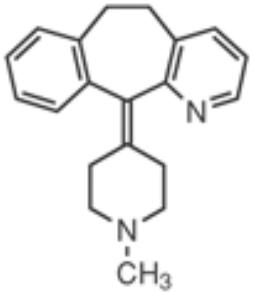
Drugs	Trade name	R_1	R_2
Cyclizine	Marezine	H	CH_3
Chlorcyclizine	Mantadil	Cl	
Meclizine	Antivert	Cl	
Buclizine	Bucladin-S	Cl	
Oxatomide	Tinset	H	
Hydroxyzine	Atarax	Cl	$CH_2CH_2OCH_2CH_2OH$
Cetirizine	Zyrtec	Cl	$CH_2CH_2OCH_2COOH$ **2ª geração**

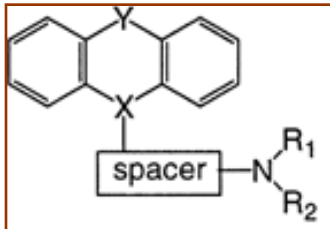
metabolismo

Alguns usados como anti-eméticos, mas possuem significante atividade anti-colinérgica

Anti-histamínico tricíclico



Drugs	Trade name	Y	Z
Promethazine	Phenergan	S	
Pyrathiazine		S	
Trimeprazine	Temaril	S	
Methdilazine	Tacaryl	S	
Cyproheptadine (Periactin)			
Azatadine (Optimine)			



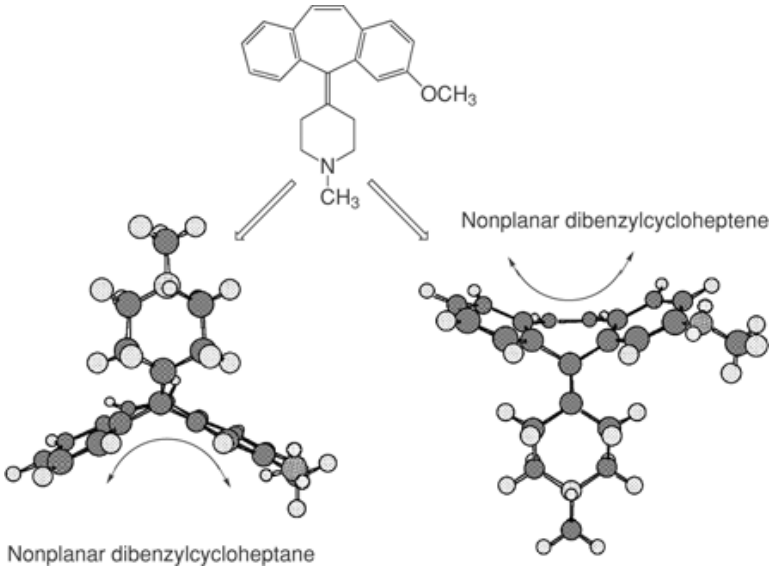
X = C, CH, N, etc.

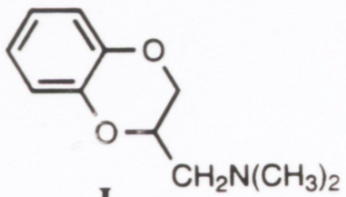
Y = CH_2, S, O, NH, CH_2O, CH_2CH_2, CH=CH, etc.

spacer = two or three carbons

R_1, R_2 = Me, or five membered ring

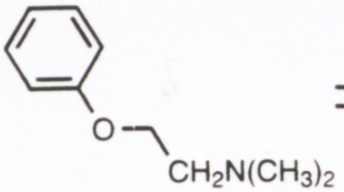
Efeito sedativo pronunciado
Também usados no tratamento da náusea e vômito





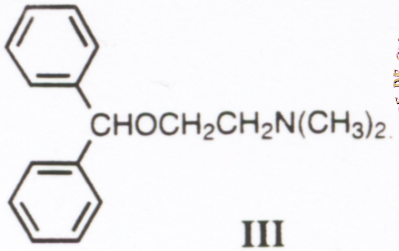
I

Benzodioxanes
(antihistaminic)



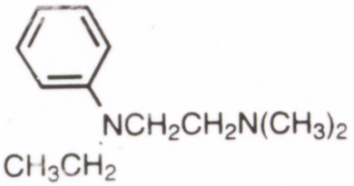
II

Ethanolamines
(antihistaminic)



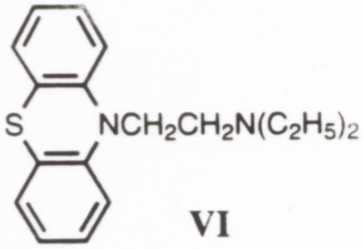
III

Diphenhydramine
(antihistaminic)



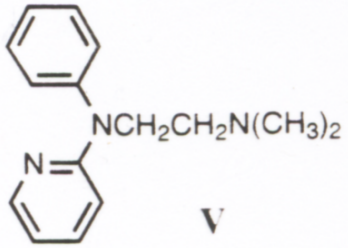
IV

Ethylenediamines
(antihistaminic)



VI

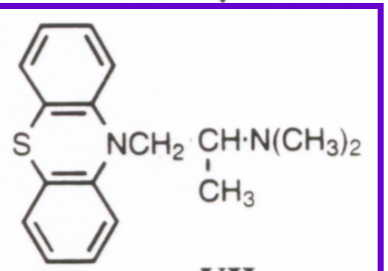
Diethazine
(anti-Parkinson)



V

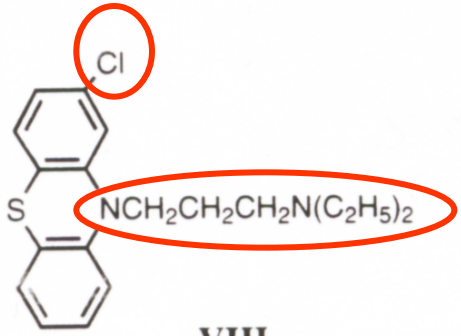
Tripelennamine
(antihistaminic)

Apresenta ação anti-histamínica, mas com forte efeito sedativo
Usado como anti-Parkinson, devido à ação anti-muscarínica



VII

Promethazine
(antihistaminic)



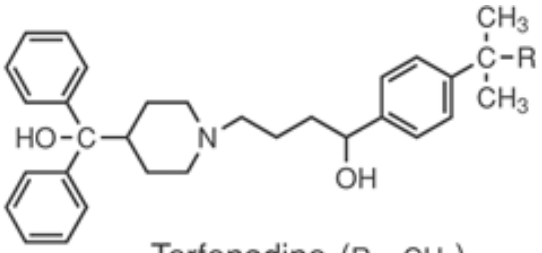
VIII

Chlorpromazine
(antipsychotic)

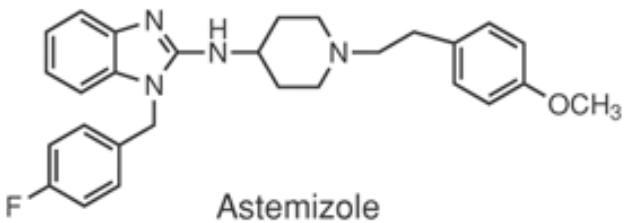
Desenvolvimento dos fármacos Fenotiazínicos

Segunda geração de anti-histamínicos H-1

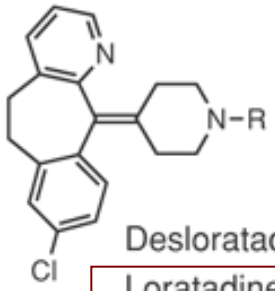
Não causam sedação e apresentam menor efeito anticolinérgico



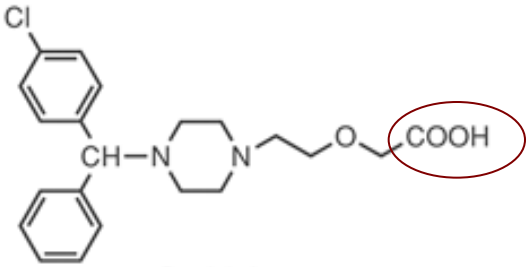
Terfenadine (R = CH_3)
Fexofenadine (R = COOH)



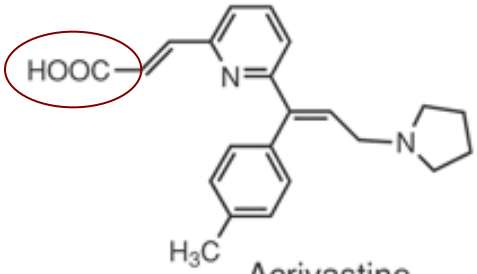
Astemizole



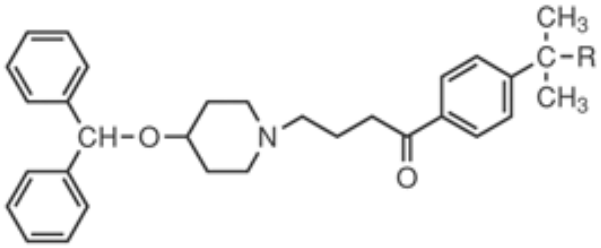
Desloratadine (R = H)
Loratadine (R = $COOCH_2CH_3$)



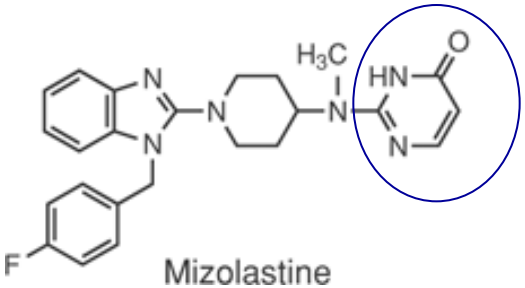
Cetirizine



Acrivastine



Ebastine (R = CH_3)
Carebastine (R = COOH)



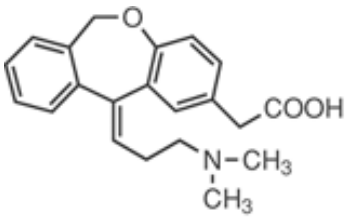
Mizolastine

- **estruturas mais hidrofílicas (*caráter anfotérico*);**
- **podem ser substratos para sistemas proteicos de efluxo de drogas;**
- **maior seletividade H1**

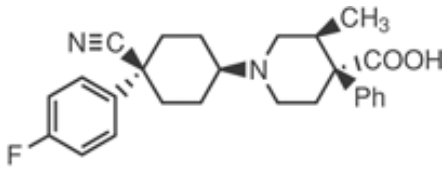
Anti-histamínicos tópicos

Usos:

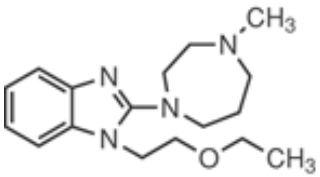
✓ **alívio de coceira nos olhos, congestão da conjuntiva e eritema**



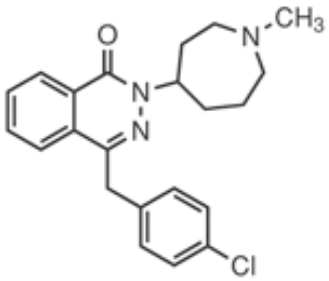
Olopatadine



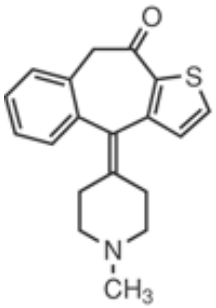
Levocabastine



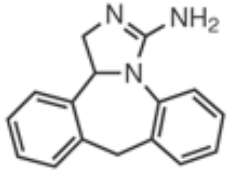
Emedastine



Azelastine



Ketotifen



Epinastine

Como introduzir na estrutura características que levariam ao antagonismo H_2 seletivo, sem o conhecimento da estrutura do receptor ???

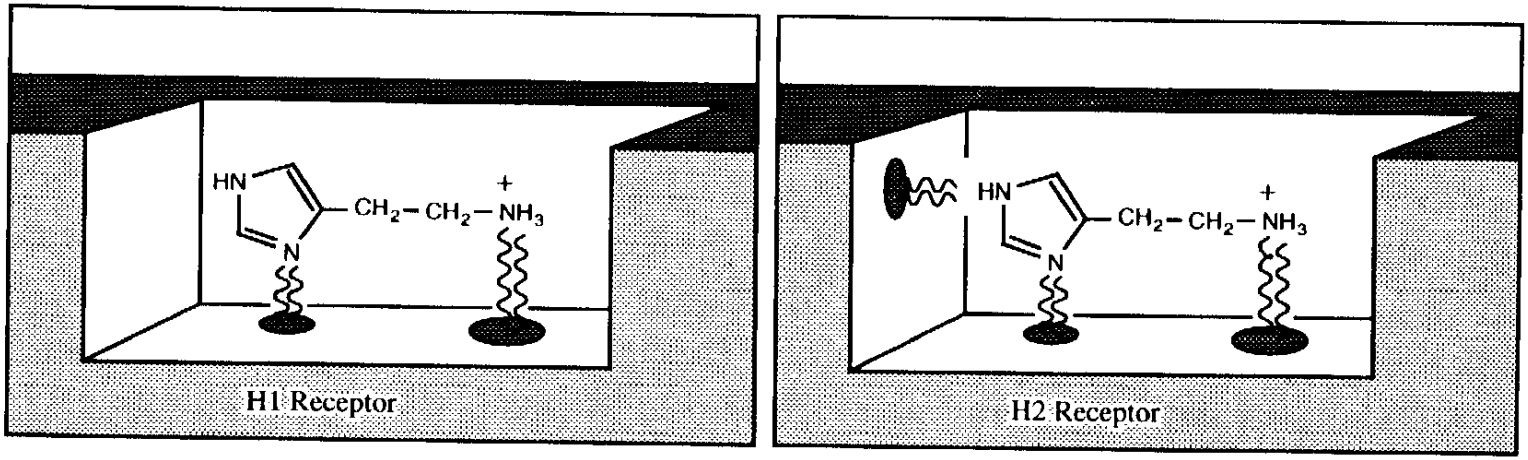
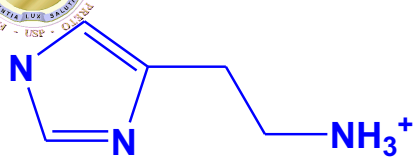
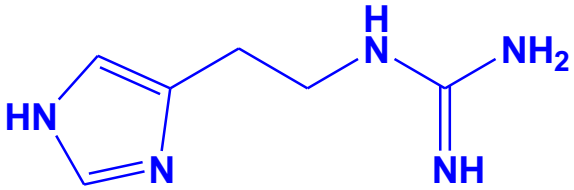


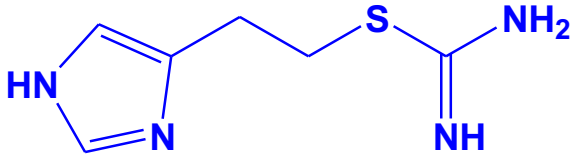
Fig. 13.8 Binding interactions for H1 and H2.

(SK&F) Após o fracasso de mais de 200 compostos...



histamina

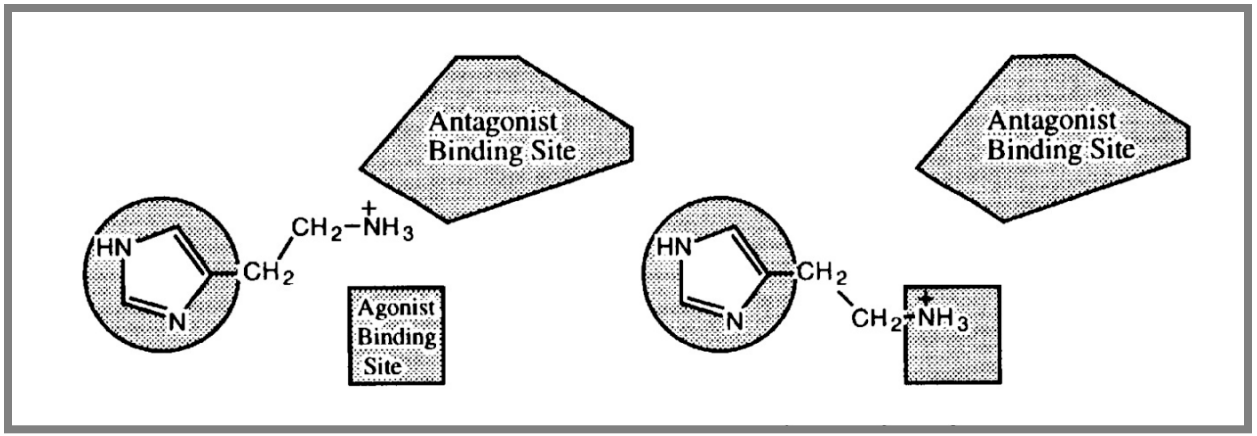


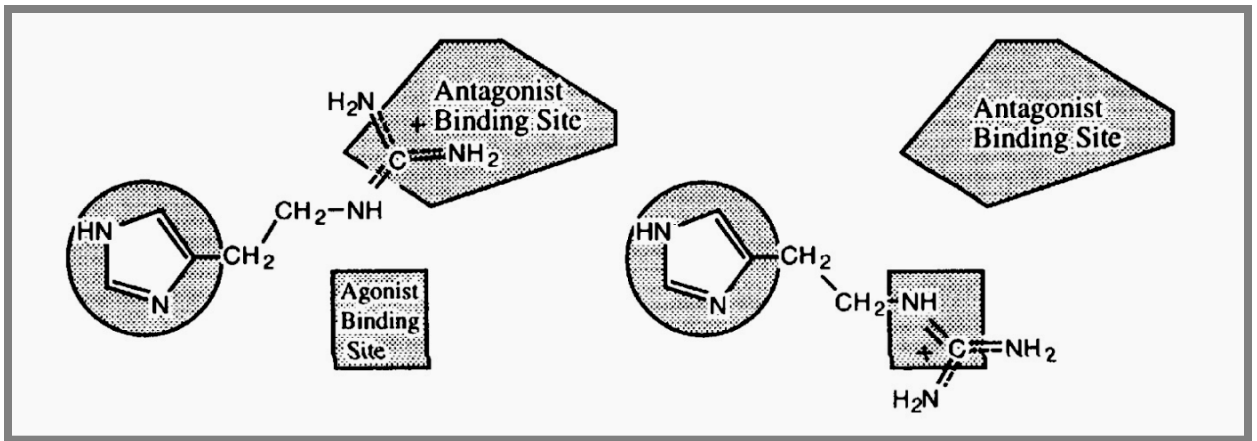


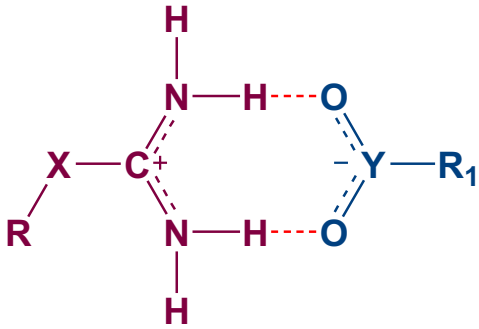
Mais ativo

Fraca ação antagonista, mas com ação agonista parcial

Hipóteses para as interações com o receptor H2







amidinas poderiam atuar como antagonistas através de ligação adicional com o receptor (Asp)

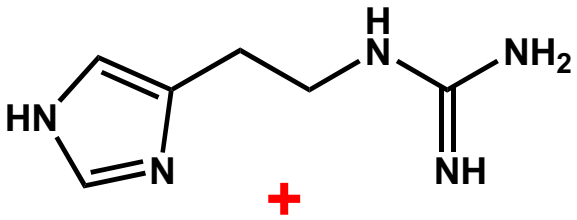
Atividade

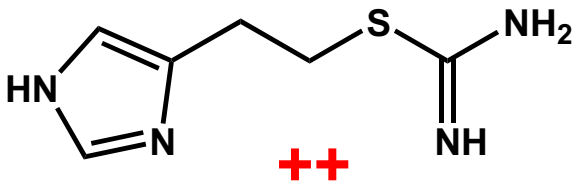
+- : detectável

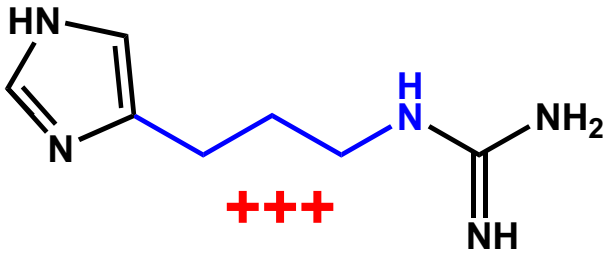
+ : ID_{50}>500μmol/kg

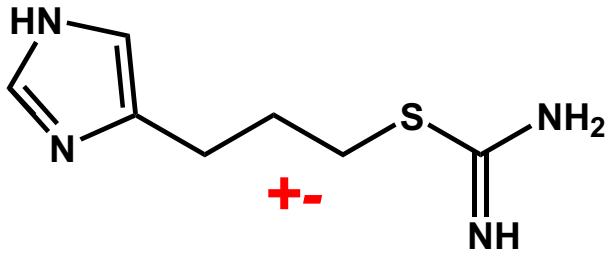
++ : ID_{50}~200μmol/kg

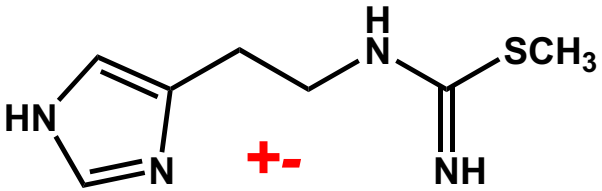
+++ : ID_{50}=50-100μmol/kg

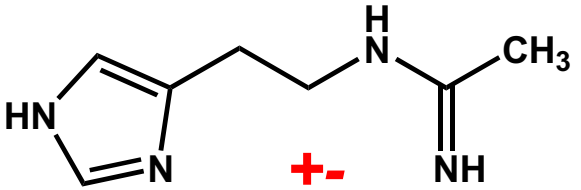


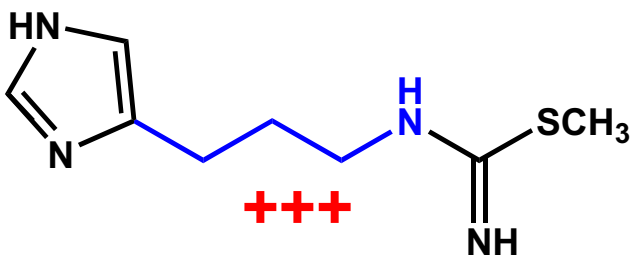


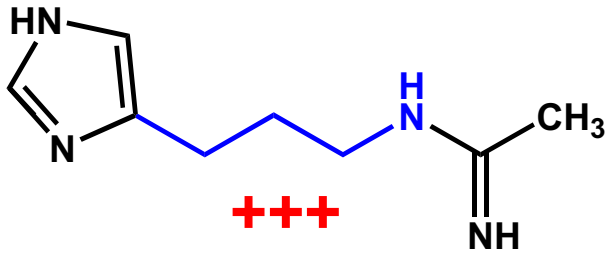






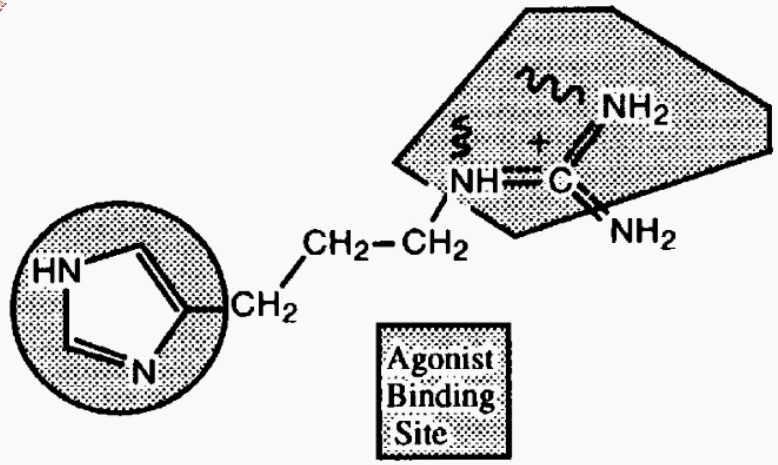




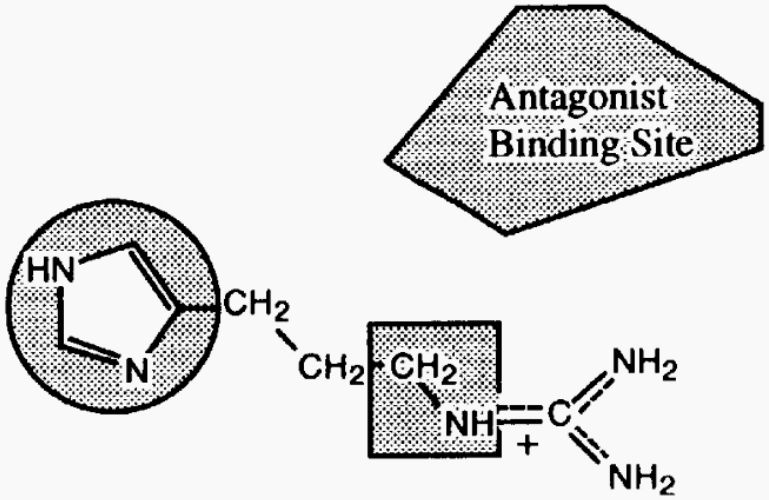


Nas isotiouréias e carboxamidinas reversas a ligação de H com o receptor deveria incluir um NH dentro da cadeia lateral e 3C entre os grupos farmacofóricos

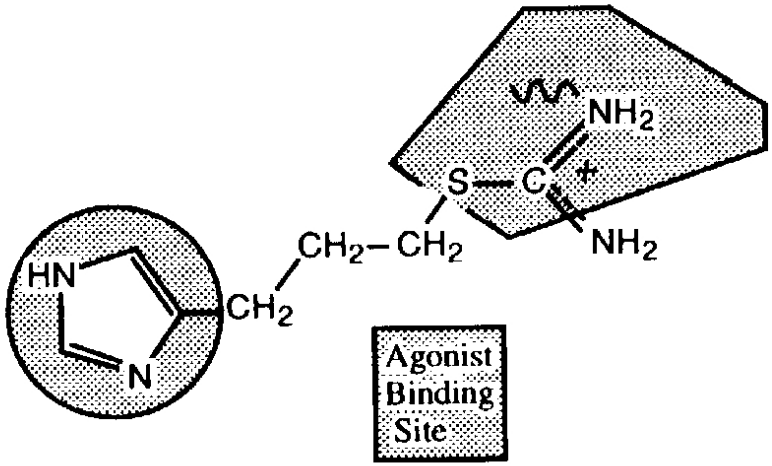
Problema: atuam como agonistas parciais



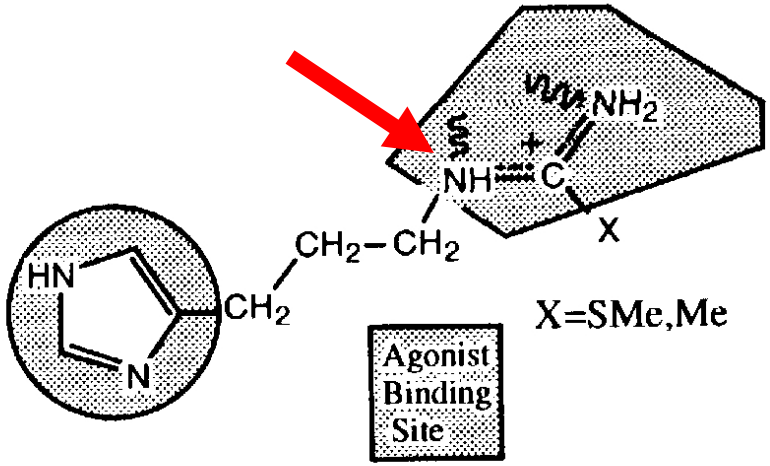
GOOD BINDING AS ANTAGONIST



BINDING AS AGONIST

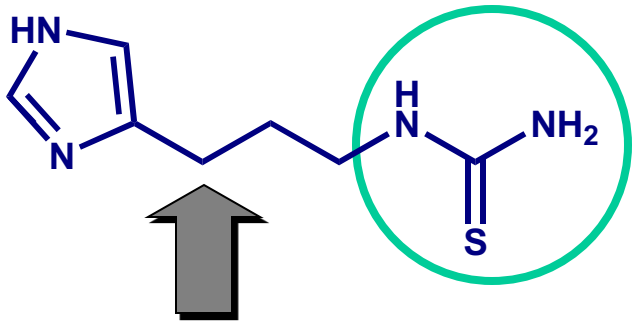


POOR BINDING AS ANTAGONIST



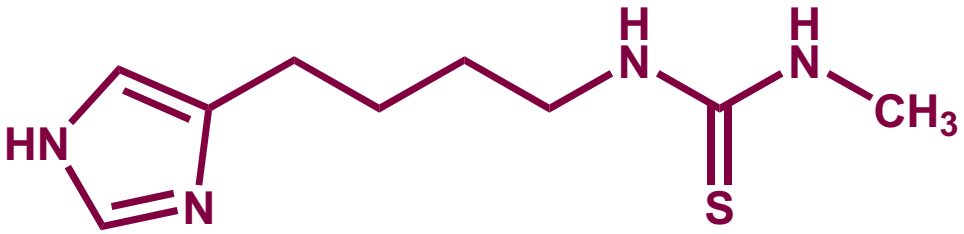
GOOD BINDING AS ANTAGONIST

Alternativa: substituição do grupo guanidina fortemente básico por grupos polares não básicos



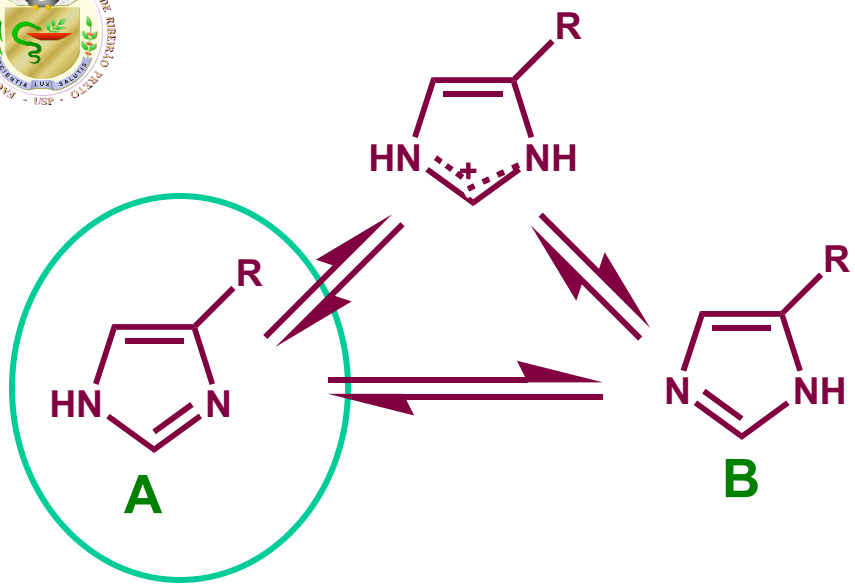
Não atua como agonista parcial
Fraca ação antagonista
Neutra em água

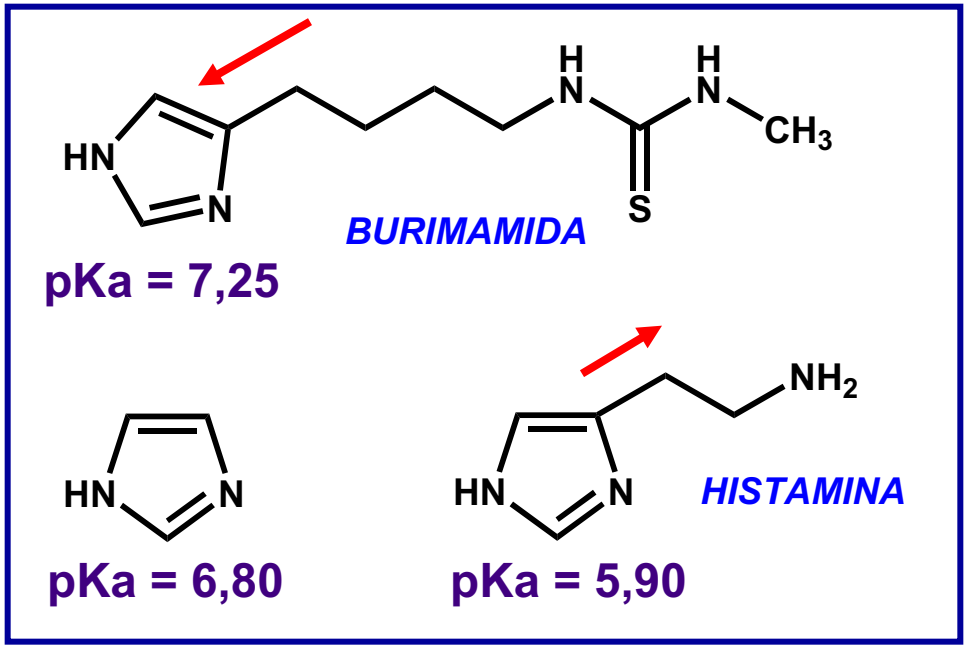
Aumento da cadeia lateral



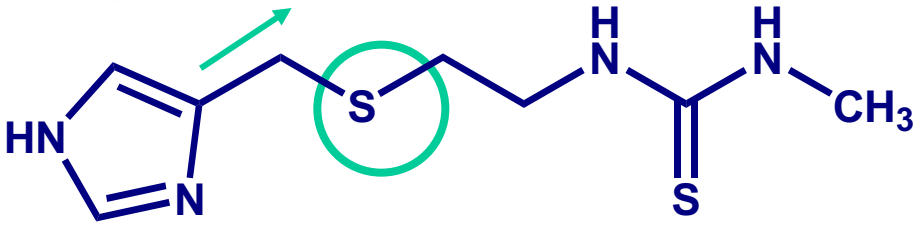
burimamida

Antagonista competitivo puro
Altamente seletivo
Não ativo por via oral





Estabilização do tautômero mais ativo e diminuição do pKa



TIABURIMAMIDA

Mais ativo

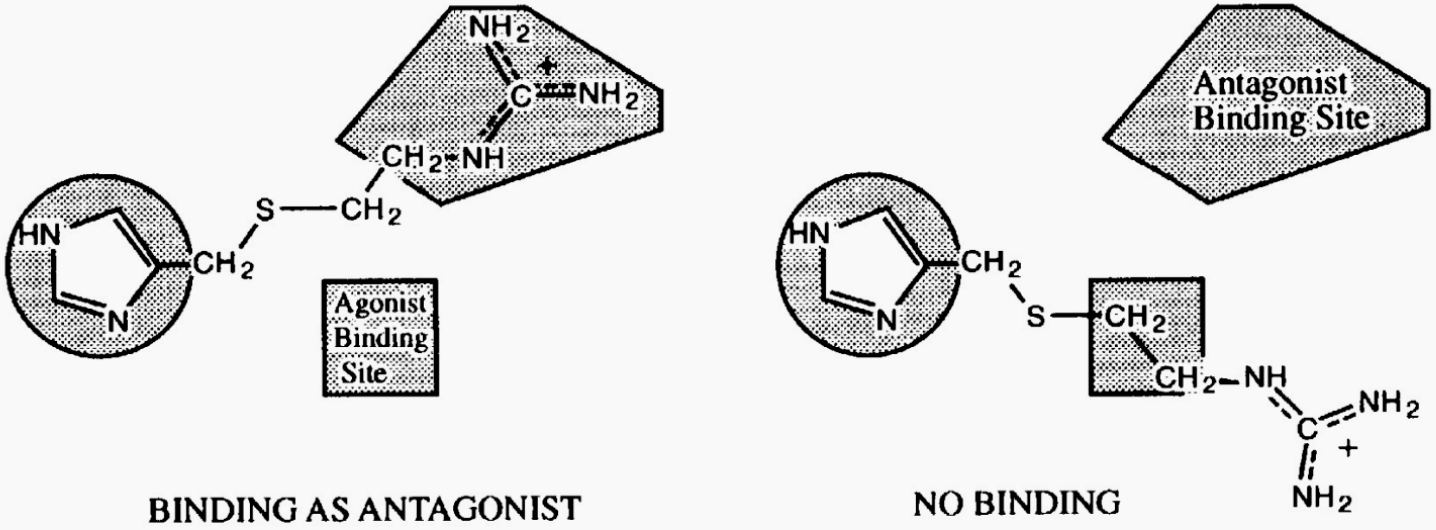


Fig. 13.33 Four-carbon unit chain.

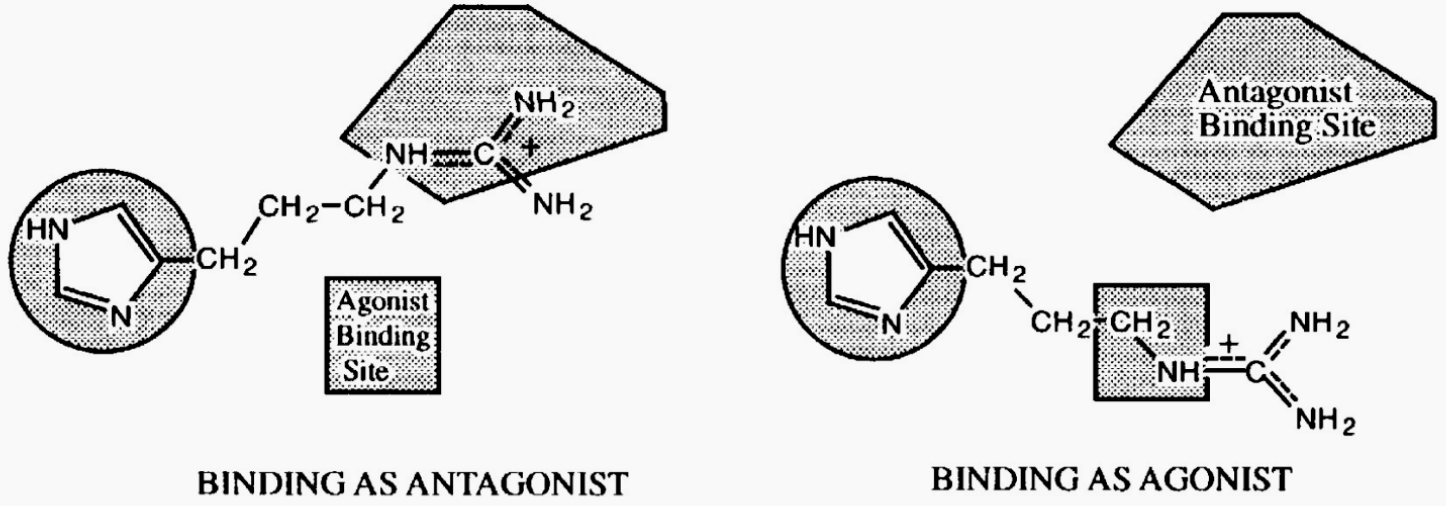
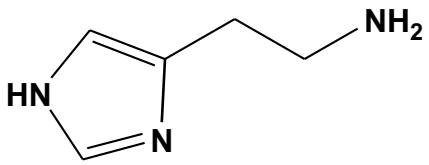
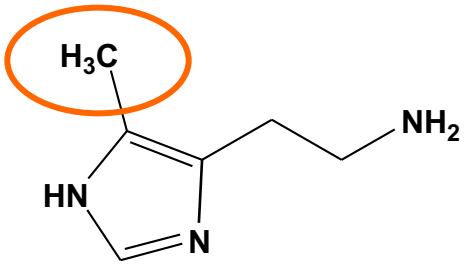
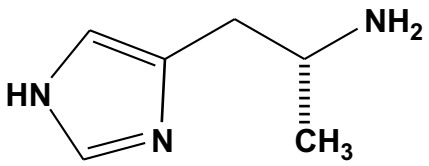
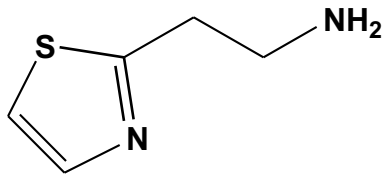
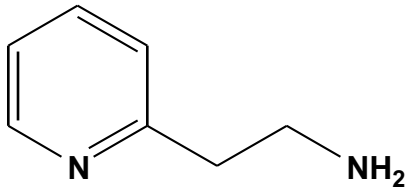
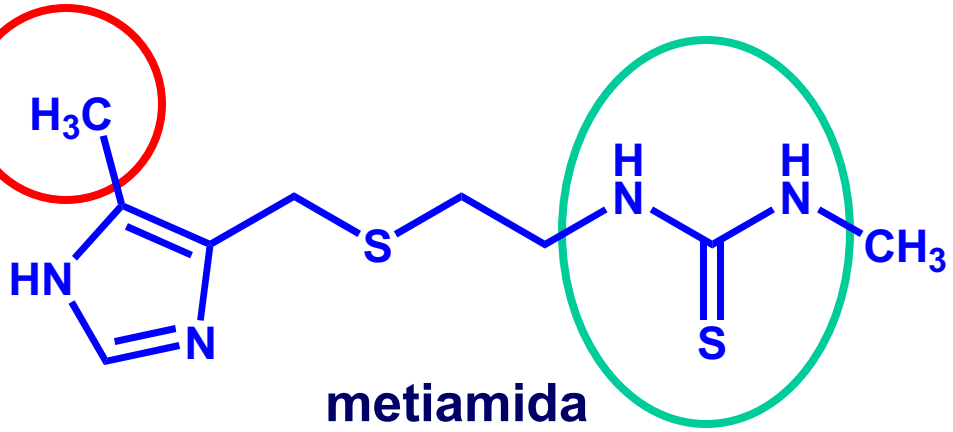


Fig. 13.34 Three-carbon unit chain.

Agonistas Histamínicos	Atividade H_1 relativa a histamina	Atividade H_2 relativa a histamina	Atividade H_3 relativa a histamina
	100,0	100,0	100,0
	0,23	39,0	<0,008
	0,49	1,0	1.550,0
	26,0	0,3	<0,008
	5,6	2,5	<0,06

Estabilização do tautômero

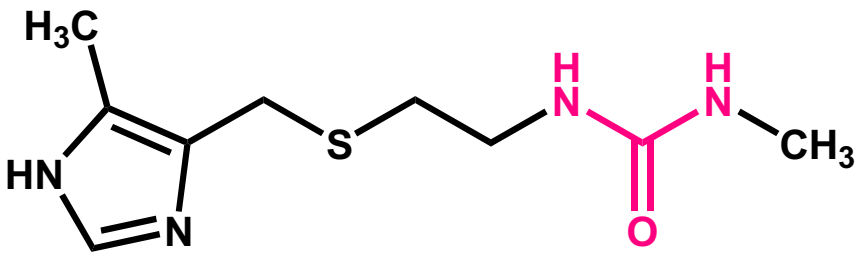
Antagonista mais potente



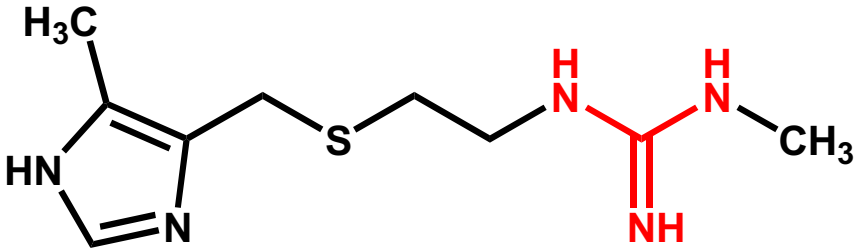
metiamida

Tiouréia

Diminuição do número de leucócitos



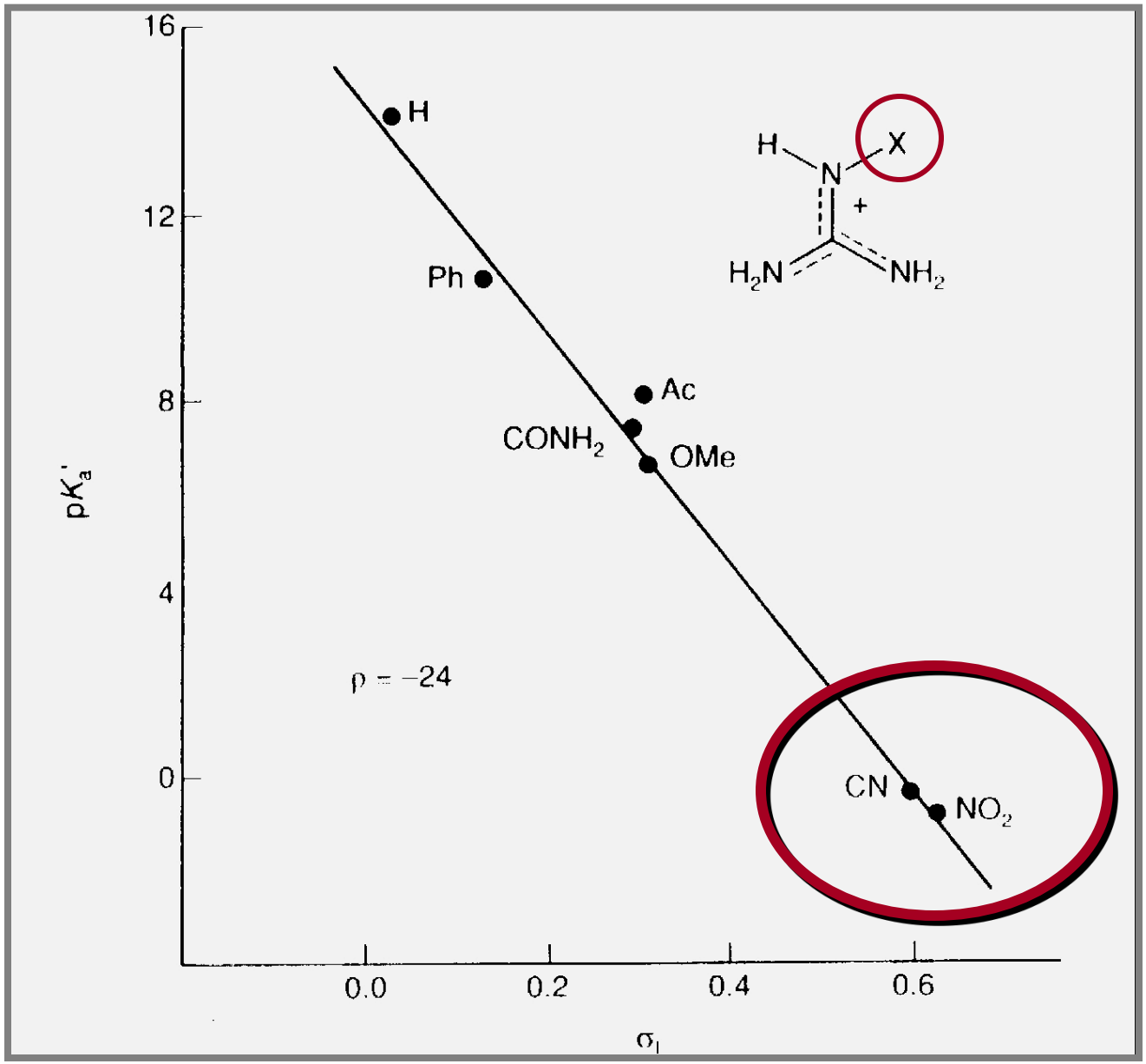
isóstero com uréia



isóstero com guanidina

Menos ativos que metiamida

Reduzir a basicidade do grupo guanidina



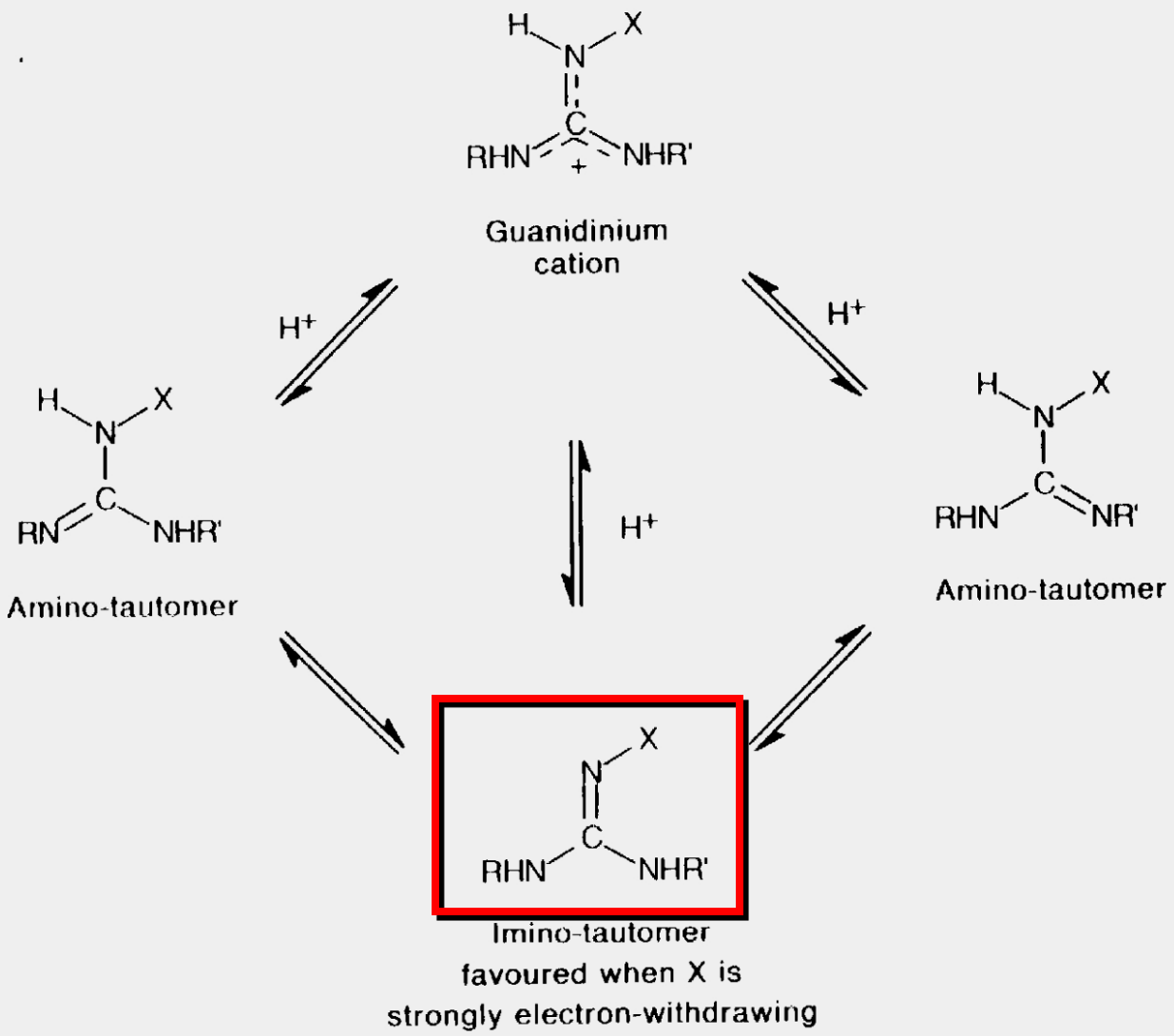
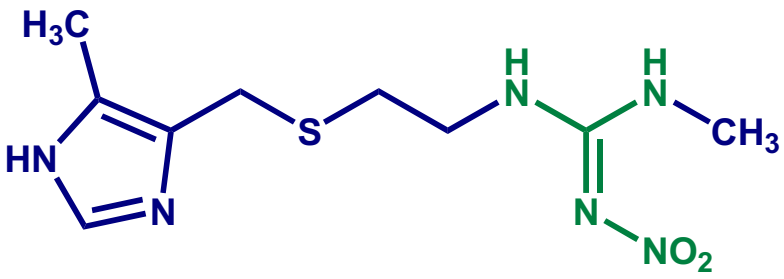
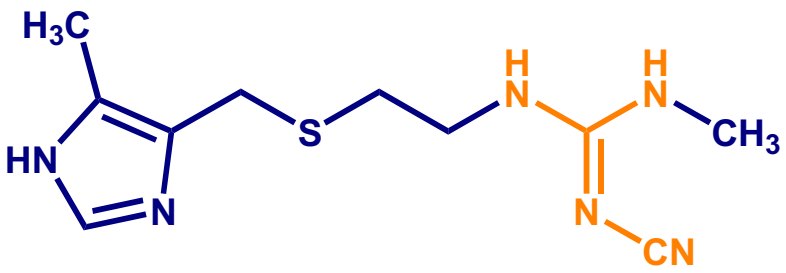


Fig. 12.8 Equilibria between the guanidinium cation and the three conjugate bases.



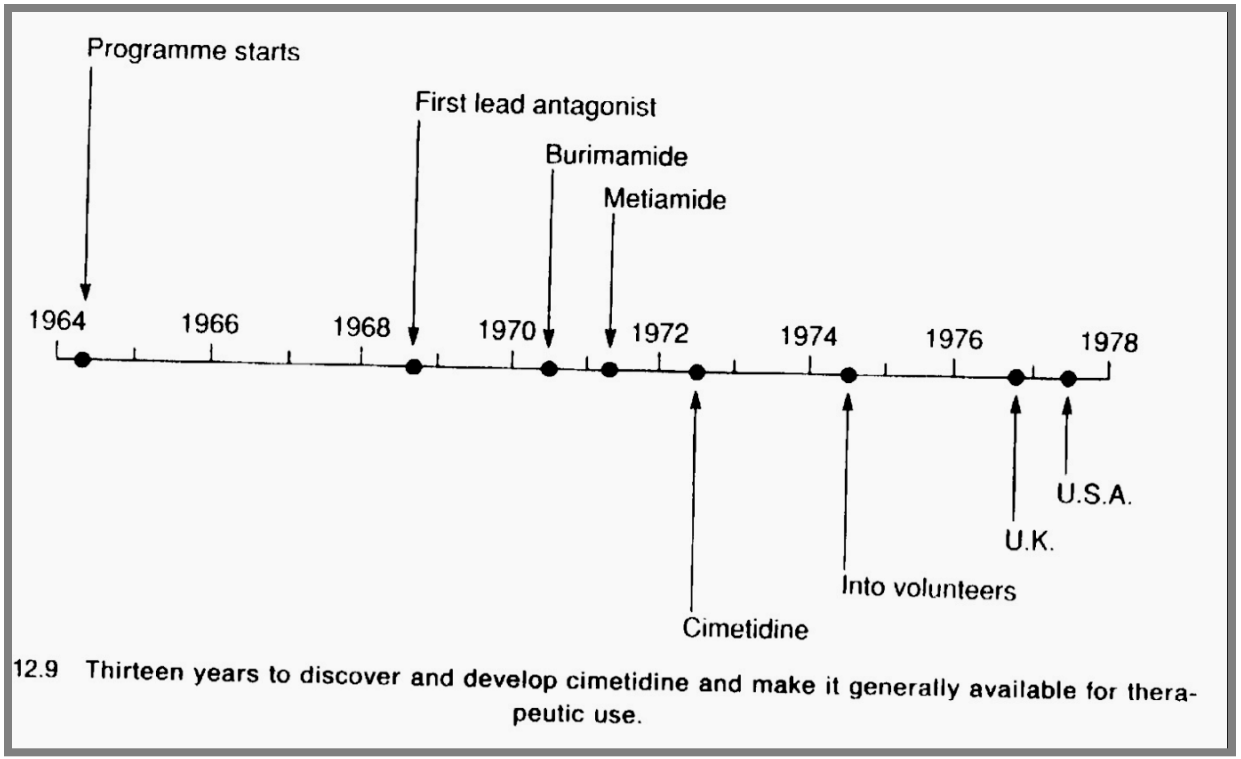


Nitroguanidina - pKa = 0,4

Cianoguanidina - pKa = 0,9

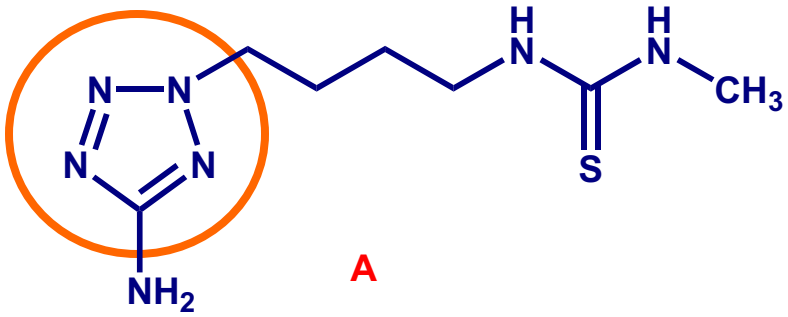
Tiouréia - pKa = -1,2

cimetidina



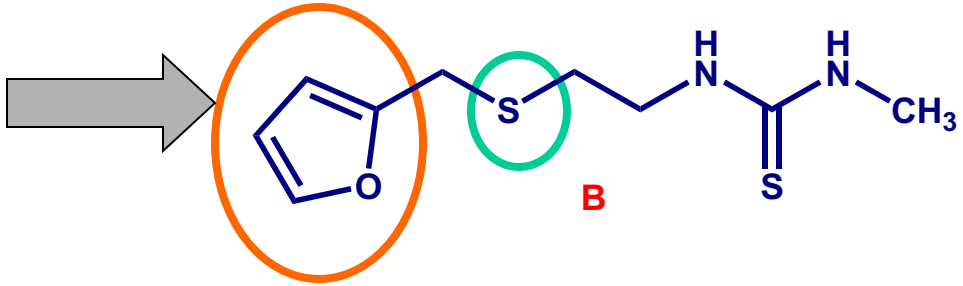
12.9 Thirteen years to discover and develop cimetidine and make it generally available for therapeutic use.

Desenvolvimento da ranitidina (Merck)



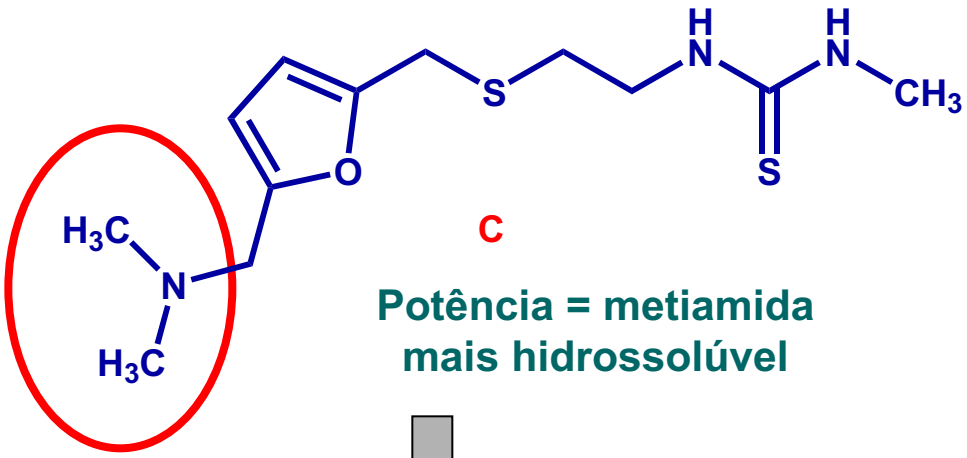
A

Potência = burimamida



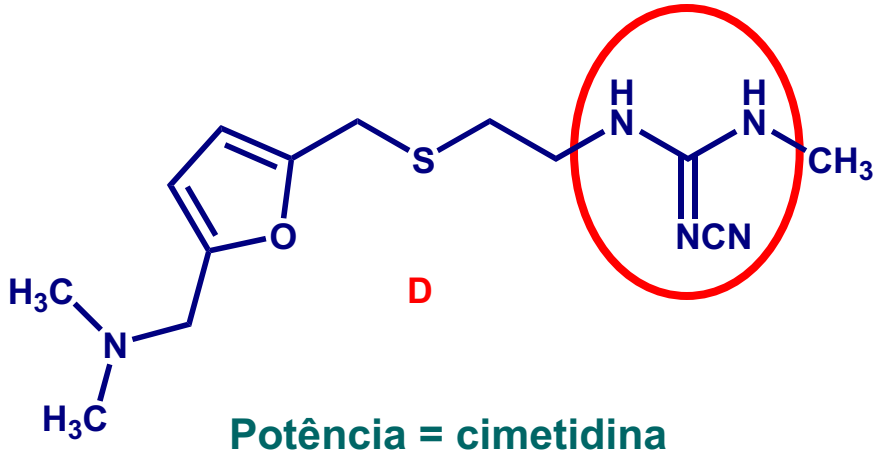
B

Ativo, mas pouco hidrossolúvel



C

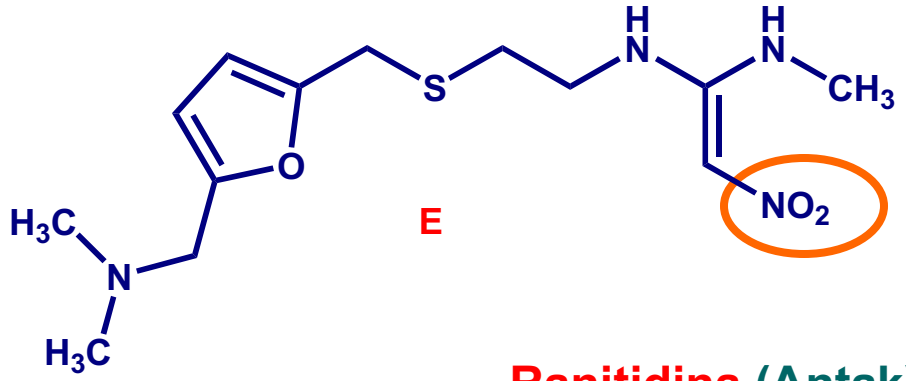
Potência = metiamida
mais hidrossolúvel



D

Potência = cimetidina

PF e baixa cristalinidade dificultaram desenvolvimento farmacêutico

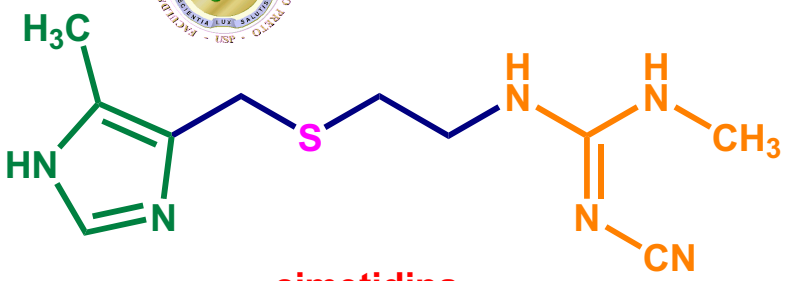


E

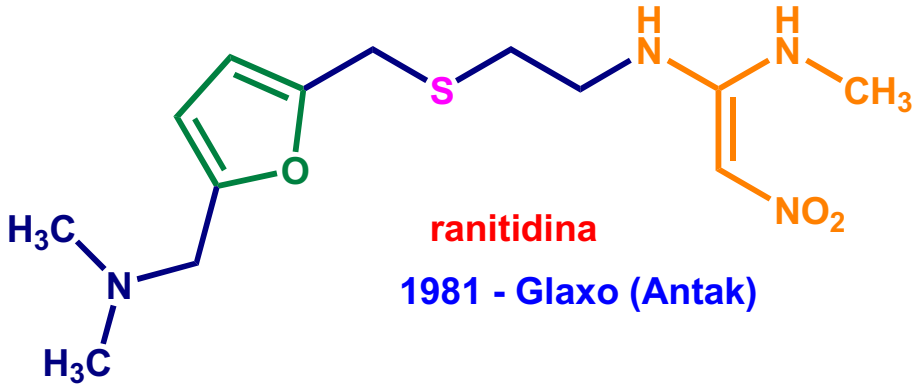
Ranitidina (Antak)

4 a 5 vezes mais potente que cimetidina

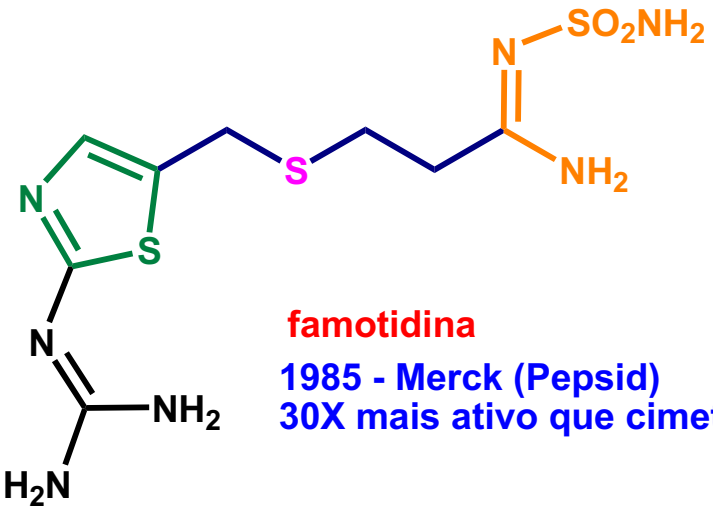
Antagonistas do receptor H2



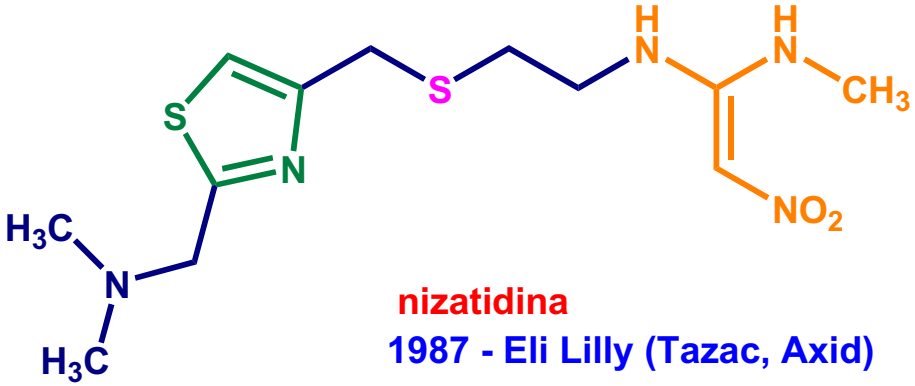
cimetidina
1977 - SK&F (Tagamet)



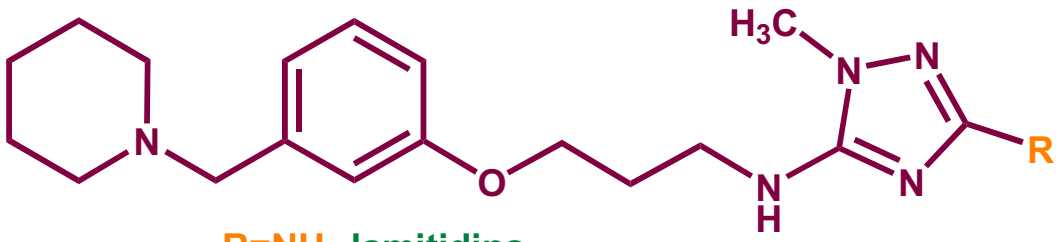
ranitidina
1981 - Glaxo (Antak)



famotidina
1985 - Merck (Pepsid)
30X mais ativo que cimetidina

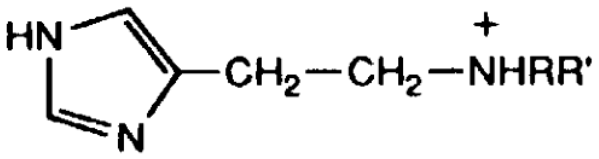


nizatidina
1987 - Eli Lilly (Tazac, Axid)

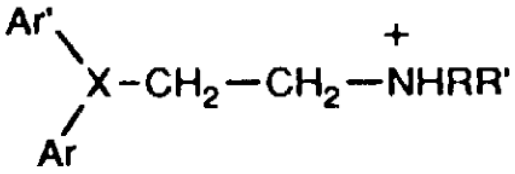


R=NH_2 lamitidina
R=CH_2OH loxtidina

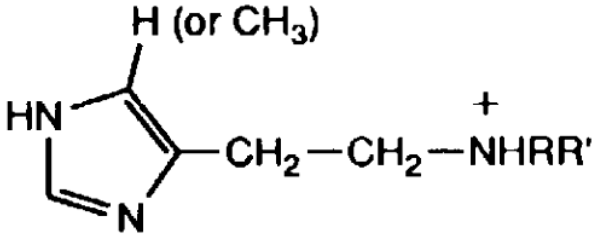
- ✓ **Agentes de ação prolongada** (5-10X mais potentes que ranitidina, e com duração 3X maior)
- ✓ Foram retirados dos estudos clinicos por apresentarem toxicidade com uso prolongado



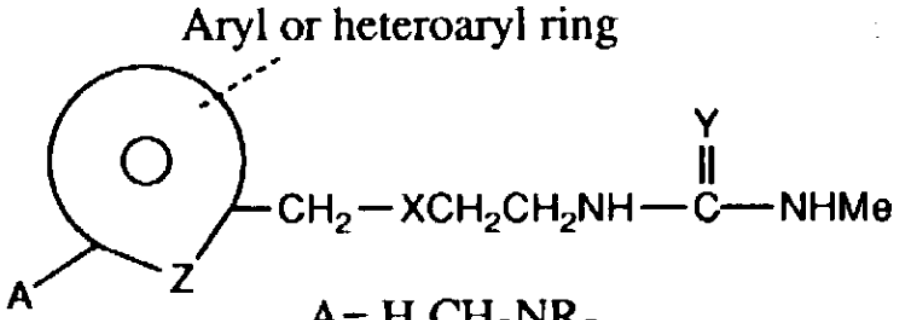
H1 Agonist



H1 Antagonist



H2 Agonist



A= H,CH_2NR_2
X= S, CH_2
Y= S, NCN,$CHNO_2$
Z= CH,N,O,S

H2 Antagonist

Fig. 13.61 Comparison between H1 and H2 agonists and antagonists.