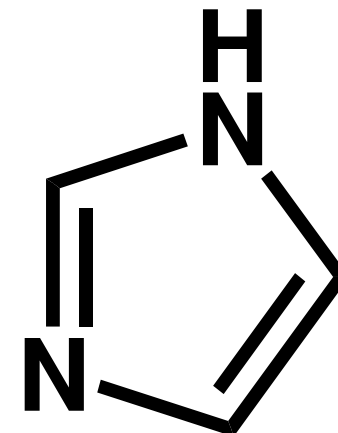




Universidade Federal do Rio de Janeiro

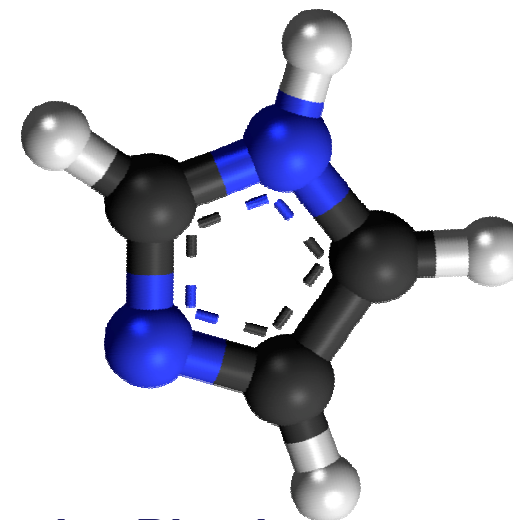
*A imidazola,  
o prêmio Nobel  
& fármacos.*



*Pretende-se identificar, a partir de uma molécula extremamente simples –  $C_3H_4N_2$ , possíveis interrelações complexas e pouco evidentes...*

*Eliezer J. Barreiro*

Professor Titular  
UFRJ



Laboratório de Avaliação e Síntese de Substâncias Bioativas

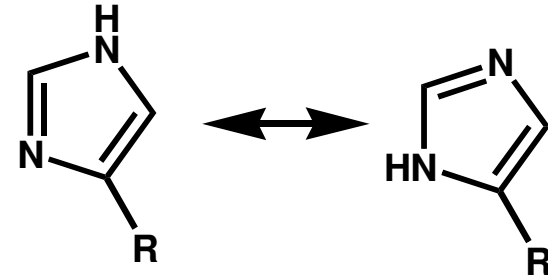
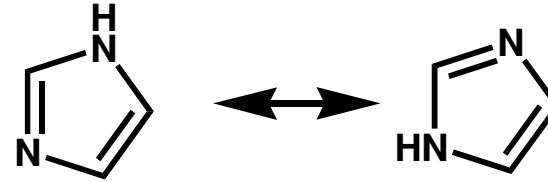
Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos  
INCT-INOVAR

# Imidazola

CAS: 288-32-4

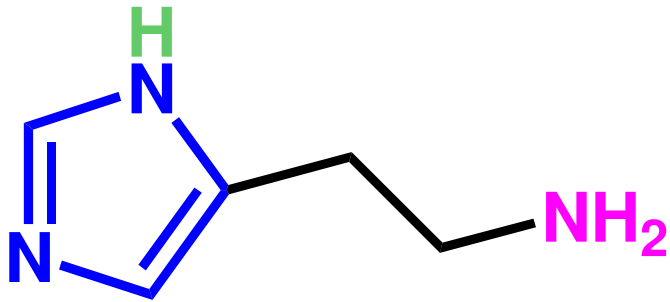
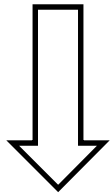
$C_3H_4N_2$   
PM= 68,08

1858



Tautômeros

Diazola

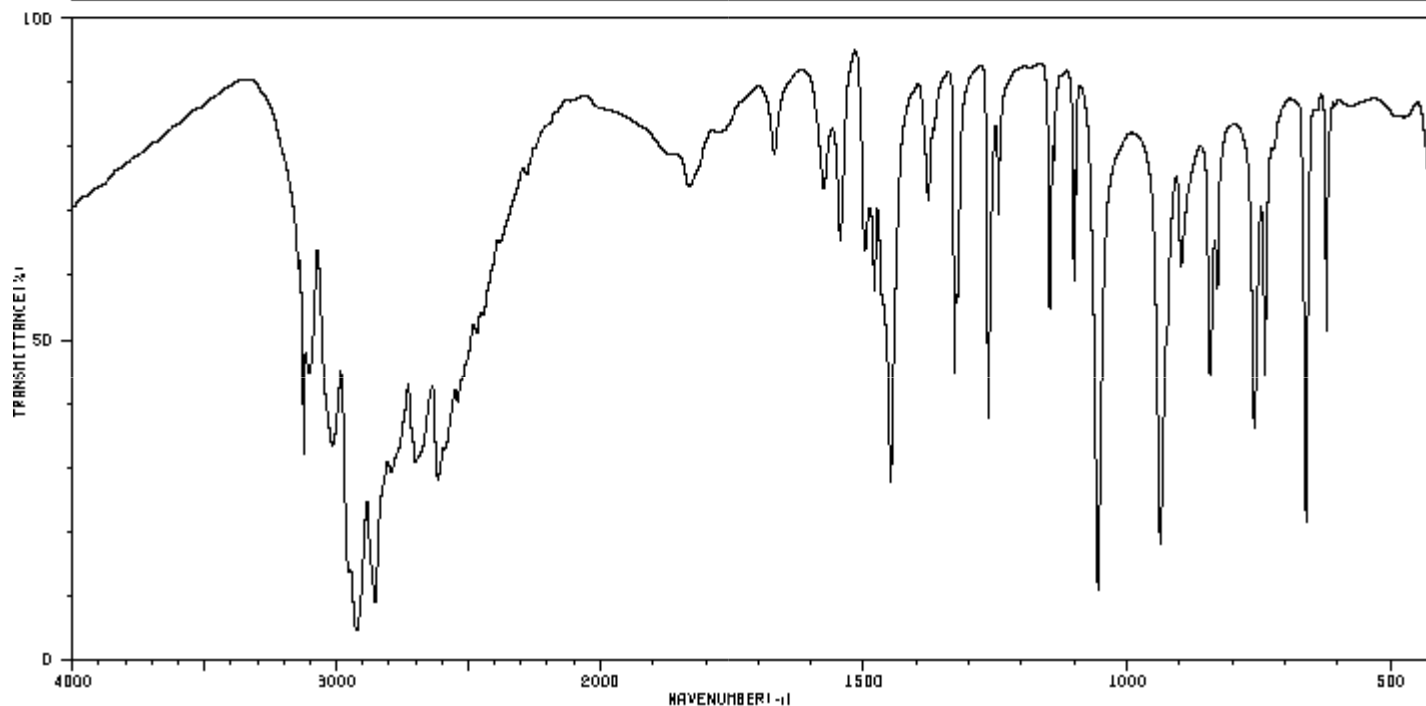


$C_5H_9N_3$   
PM=111,15

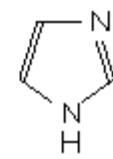
# Histamina



HIT-NO=621	SCORE= ( )	SDBS-NO=1051	IR-NIDA-62205 : NUJOL MULL
IMIDAZOLE			
C <sub>3</sub> H <sub>4</sub> N <sub>2</sub>			



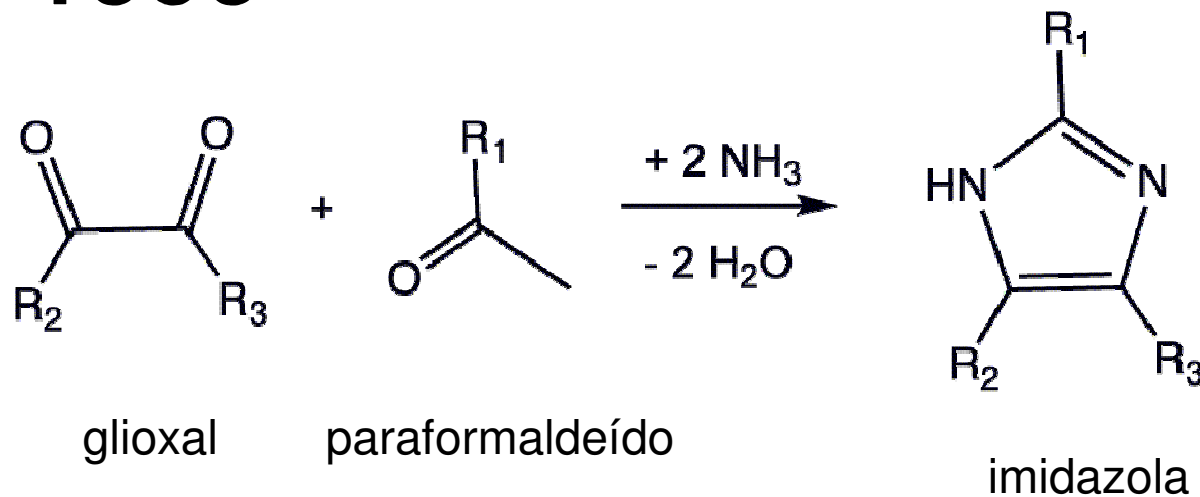
3146	60	2700	30	1644	64	1263	37	898	50
3125	31	2615	27	1497	62	1244	68	842	43
3102	44	2594	32	1480	57	1147	59	629	57
3014	33	2540	39	1449	27	1099	57	759	36
2924	4	2466	50	1378	70	1055	10	739	43
2854	9	2277	72	1326	43	937	18	660	21
2794	29	1830	72	1323	55	924	48	621	50



<http://www.chemspider.com/Chemical-Structure.773.html> (Dez 29, 2014)

# 1858

## Reação de Debus-Radziszewski



H. Debus, Ueber die Einwirkung des Ammoniaks auf Glyoxal, *Justus Liebigs Annalen der Chemie*, **107**, 199–208 (1858).

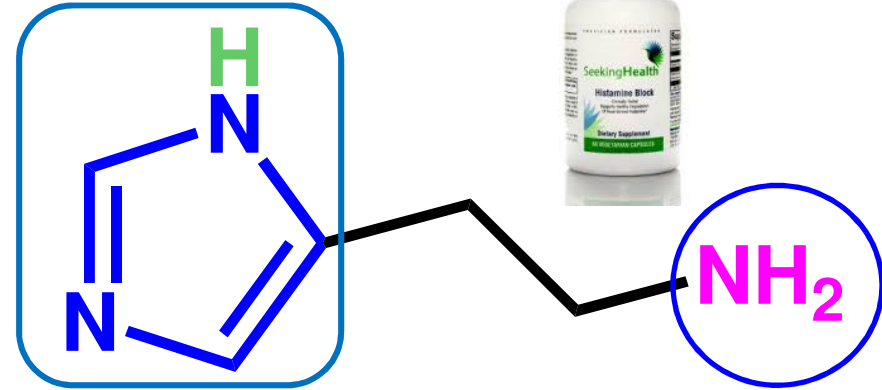
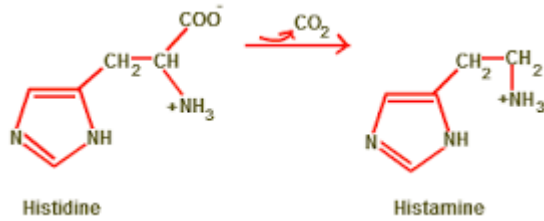
Ueber die Einwirkung des Ammoniaks auf Glyoxal;  
von *Heinrich Debus*.

(Gelesen vor der Royal Society zu London.)

Wenn Alkohol langsam durch Salpetersäure bei gewöhnlicher Temperatur oxydirt wird, entstehen neben anderen Substanzen Glyoxal  $C_2H_2O_2$  und Glyoxylsäure  $C_2H_2O_4^*$ ). Ich habe die Untersuchung dieser Körper fortgesetzt und theile hier vorläufig einige der erhaltenen Resultate mit.

# Histamina

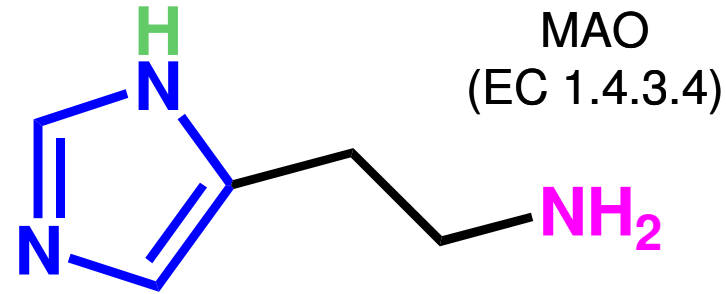
L-histidina descarboxilase  
(vitamina B6)  
EC 4.1.1.22



1907 - Adolf O. R. Windaus, aquece a histidina e descobre a histamina  
 1911 – Henry H. Dale, isola a histamina estudando a neurotransmissão  
 nos laboratórios Wellcome, Londres.

# Autacóide

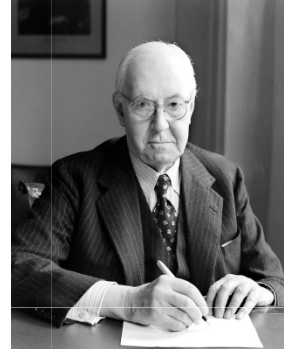
H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub> (GPCR)



1928

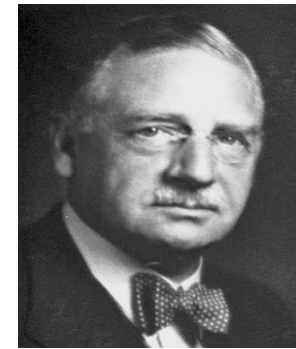


Adolf O. R. Windaus  
(1876-1959)



Henry H. Dale  
(1875-1968)

1936



Otto Loewi  
(1873-1961)

H. H. Dale, P. P. Laidlaw, The physiological action of  $\beta$ -iminazolyethylamine,  
*J. Physiol. (Lond.)* **1910**, 41, 318-44.



- Alteração da frequência cardíaca; Aumento da permeabilidade; Broncoconstrição; Participação nas reações anafiláticas e alérgicas; Secreção gástrica; Vasodilatação arteriolar;

Am J Physiol 1948, 153, 586



Raymond Ahlquist (1914)

A STUDY OF THE ADRENOTROPIC RECEPTORS

RAYMOND P. AHLQUIST

*From the Department of Pharmacology, University of Georgia School of Medicine*

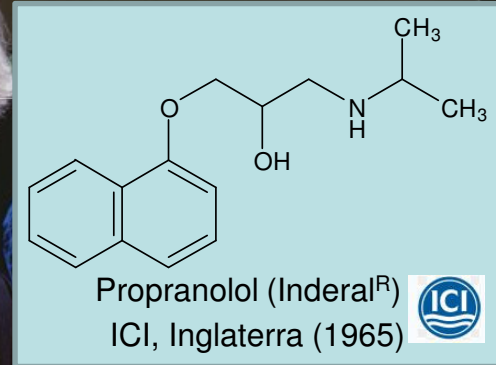
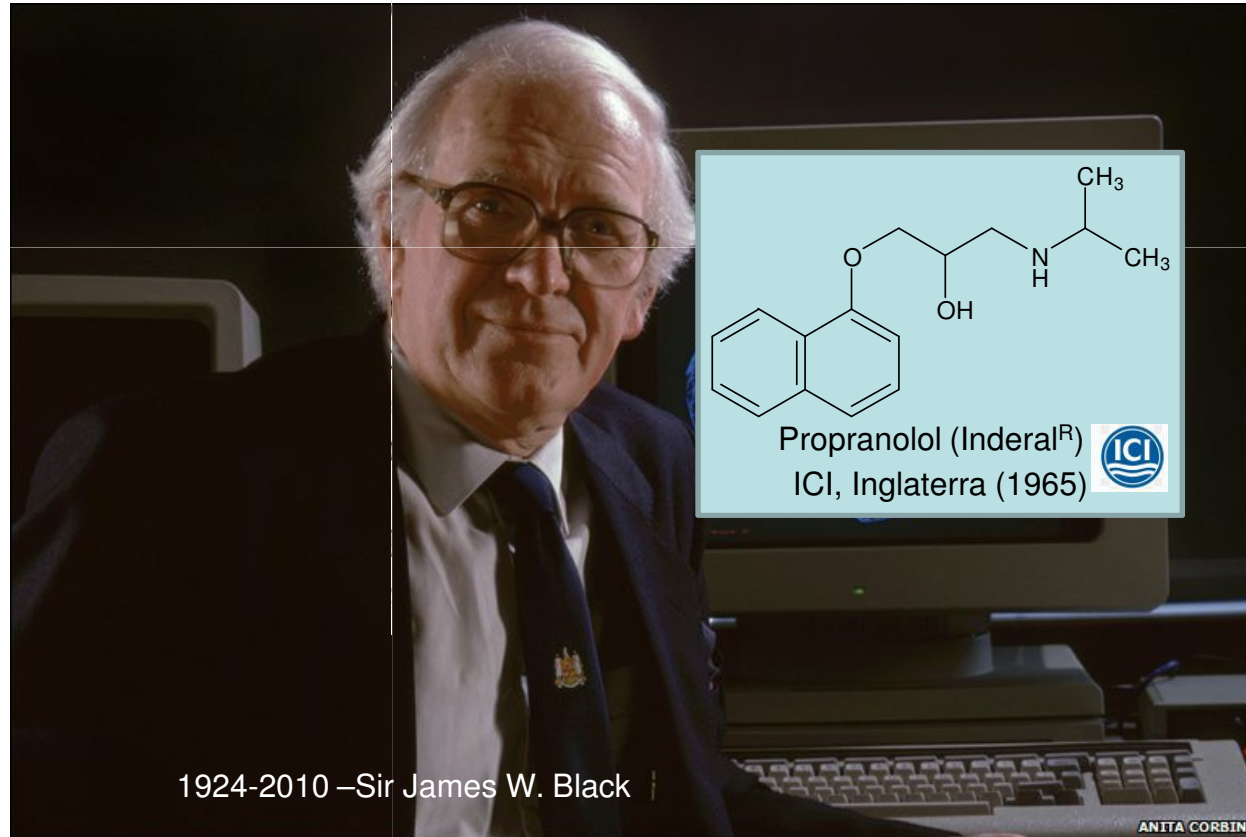
AUGUSTA, GEORGIA



1905 – Henry Dale

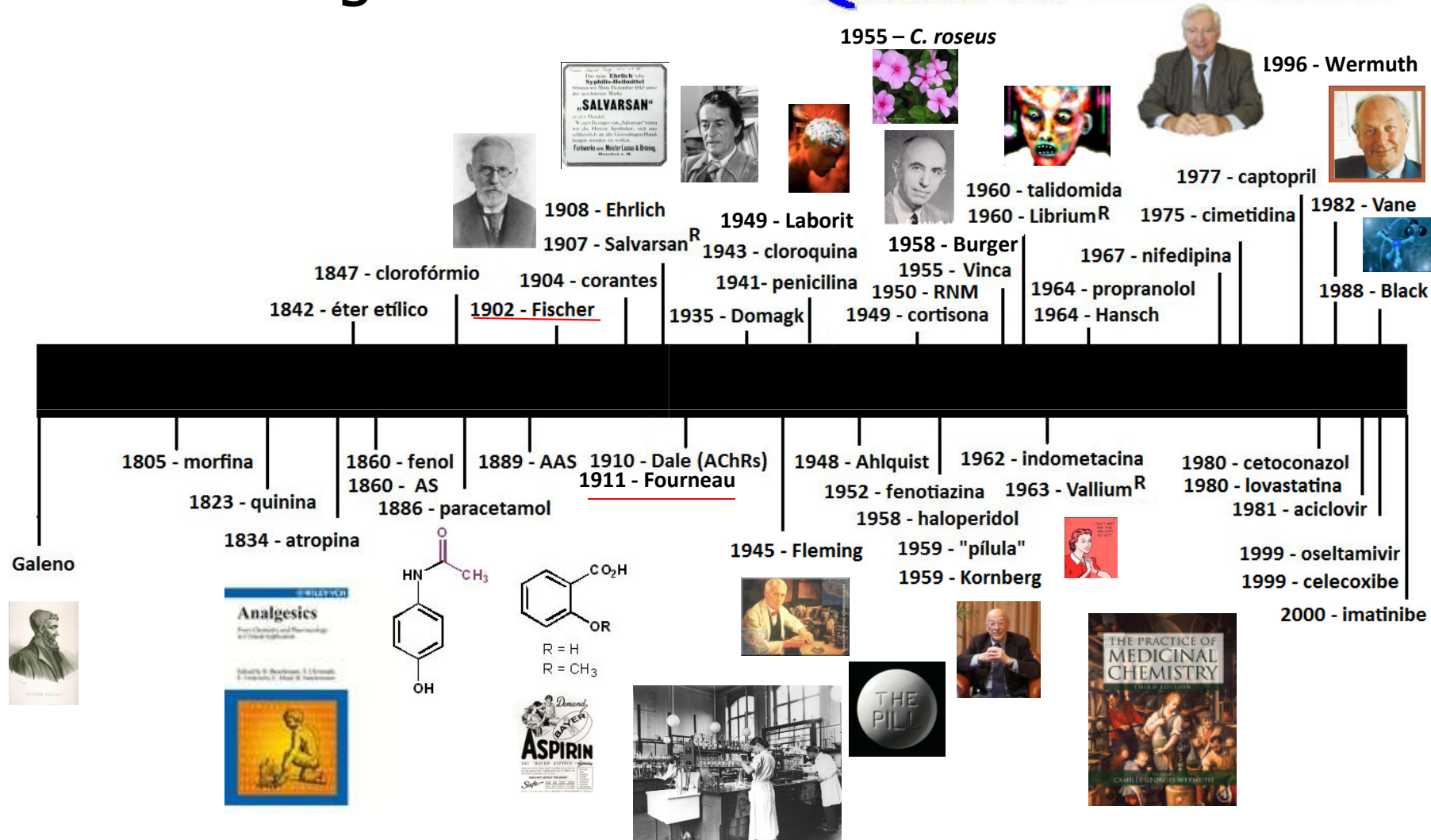


**Premio Nobel  
1988**



R Ganellin, W Duncan, Obituary James Black (1924-2010), *Nature* **2010**, 464, 1292; CPPage, J Schaffhausen, NP Shankley, The scientific legacy of Sir James W. Black, *TIPS* **2011**, 32, 181;

# Cronologia histórica da **Química Medicinal**



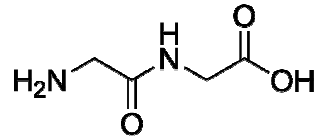
“A target is not truly validated until a drug is proven effective in human trials”

Oliver C. Steinbach, Head at Altana Pharma, Konstanz, AL

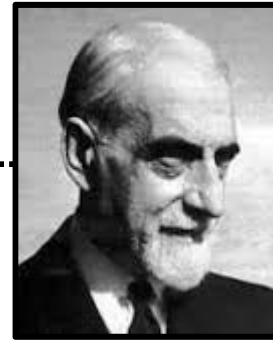




Emil Fischer  
(1852-1919)



glicilglicina  
(1901)



Ernest Fourneau  
(1872-1949)

Química  
med  
Medicinal  
chem



Daniel Bovet  
(1907-1992)

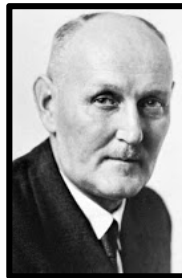
1902



1957



Adolf O. R. Windaus  
(1876-1959)



Gerhard Domagk  
(1895-1964)

1939

**Anti-histamínicos**

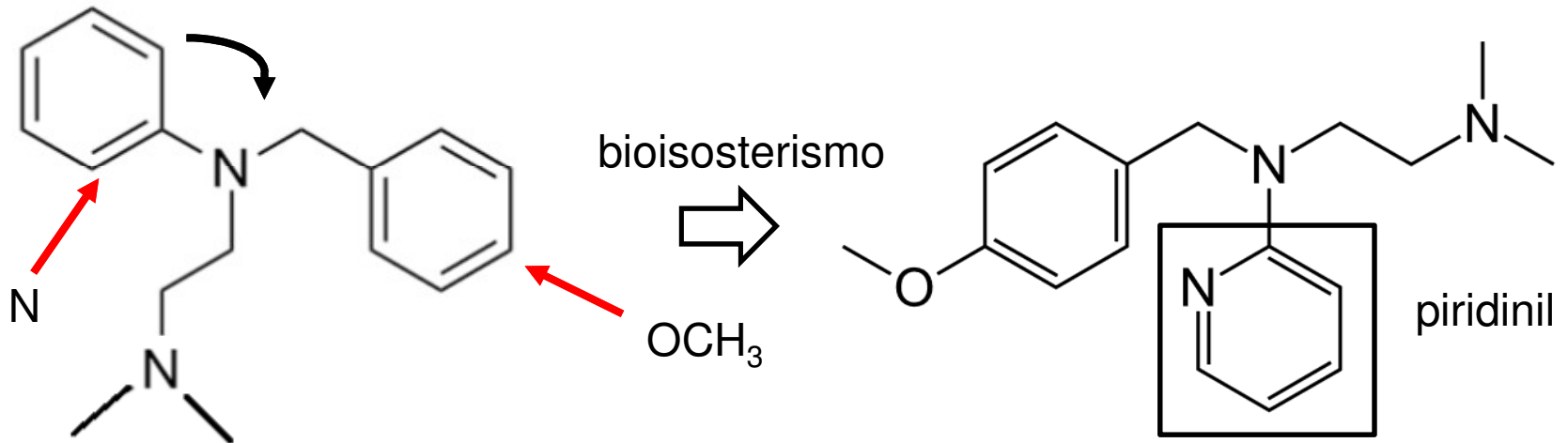
Sulfonamidas

Curare

1º *paper* sobre SAR  
(1939)

*Curare and Curare-like Agents.*

1942 -----> 1944 (Daniel Bovet)

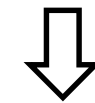
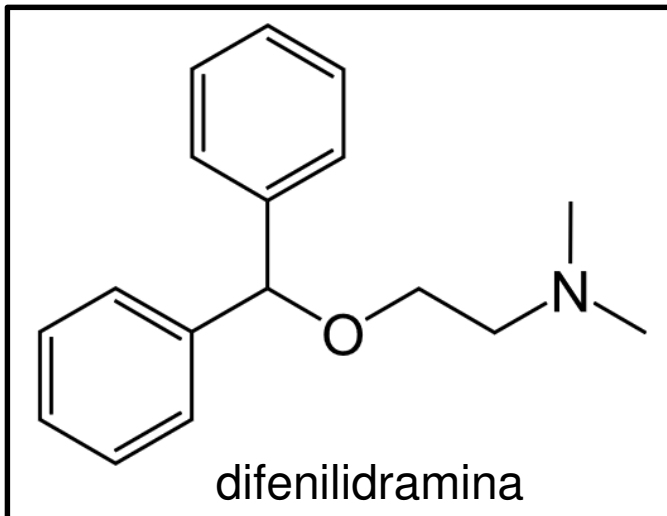


fenbenzamina  
Antergan<sup>R</sup>

mepiramina  
Neotergan<sup>R</sup>

Química  
med  
Medicinal  
chem

1943 - George Rieveschl (EUA)

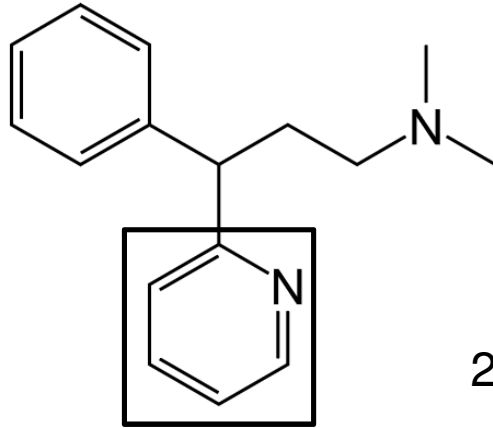


1<sup>o</sup> anti-histamínico

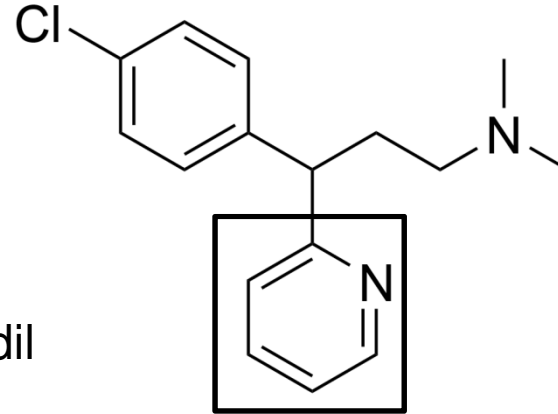
$$K_i H_1 = 0,4 \text{ nM}$$

$$K_i H_2 = 5200 \text{ nM}$$

$$K_i H_{3,4} > 10000 \text{ nM}$$

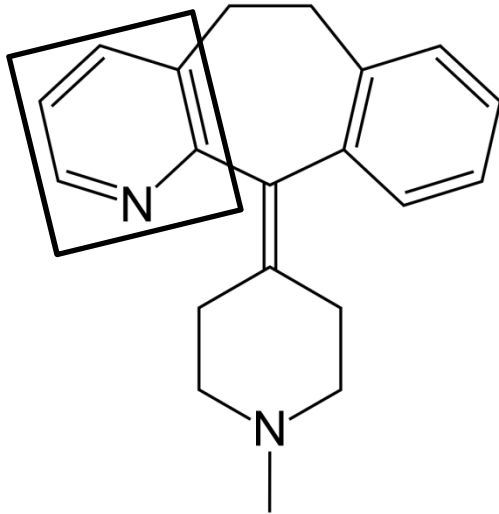


difenilidramina

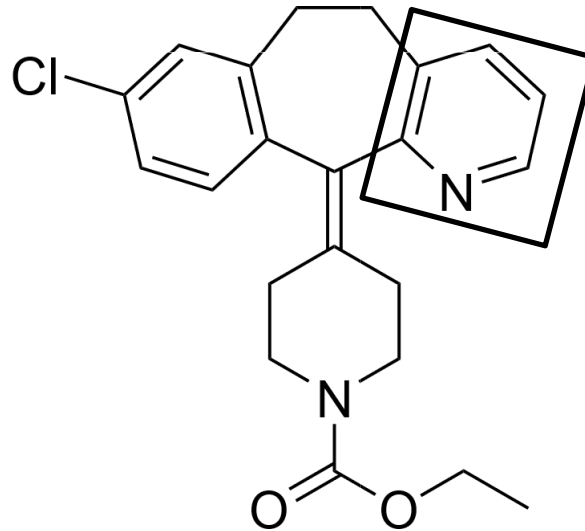


fenilramina

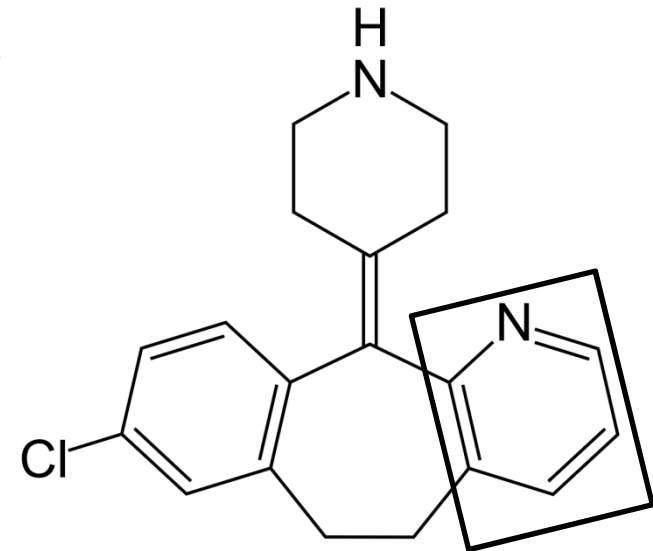
2-pirimidil



azatadina



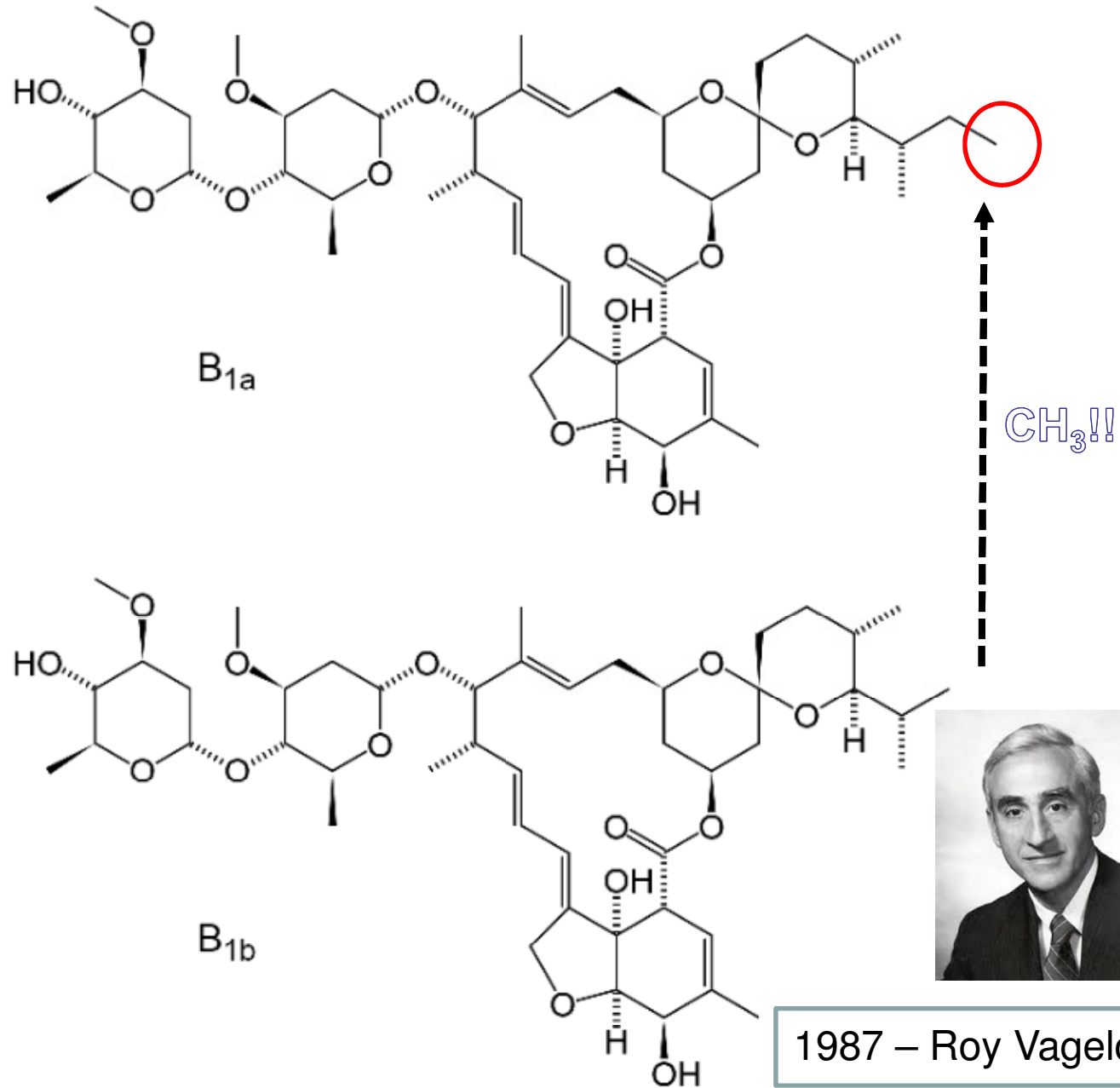
loratadina



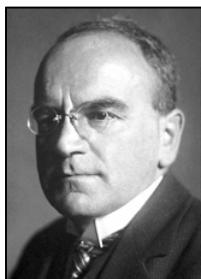
desloratadina



# Ivermectina



# Uma inovação bilionária: as estatinas



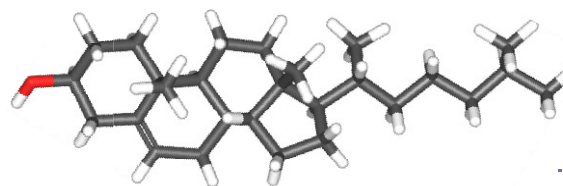
Heinrich Wieland  
1877-1957

1927

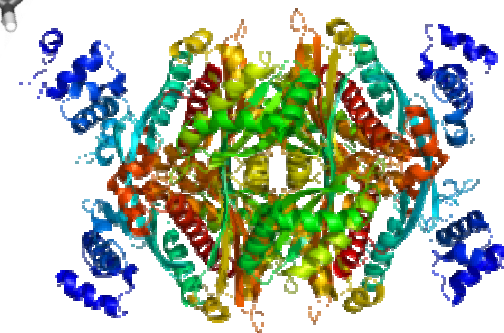


Adolf Windaus  
1876-1959

1928



colesterol



HMGCoAR



1964



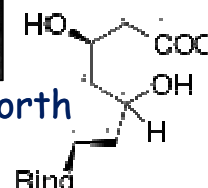
Konrad Bloch  
1912-2000



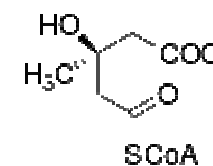
Feodor Lynen  
1911-1979



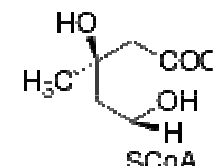
John Cornforth  
1975



HMG CoA Reductase inhibitor



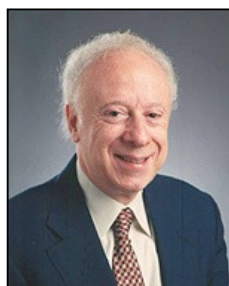
HMG CoA



Mevaldyl CoA transition state intermediate

1985

LDL

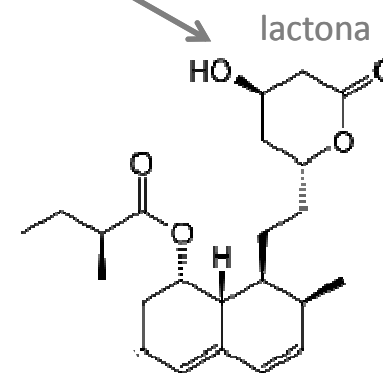


Joseph L Goldstein Michael S Brown  
University of Texas, Dallas



Akira Endo  
Albert Lasker Award  
for Clinical  
Medical Research, 2008\*

A.Endo, *J Med Chem*  
1985, 28, 1



mevilonina



\* A Endo, A gift from nature: the birth of the statins, *Nature Medicine* 2008, 14, 26

# Atorvastatina

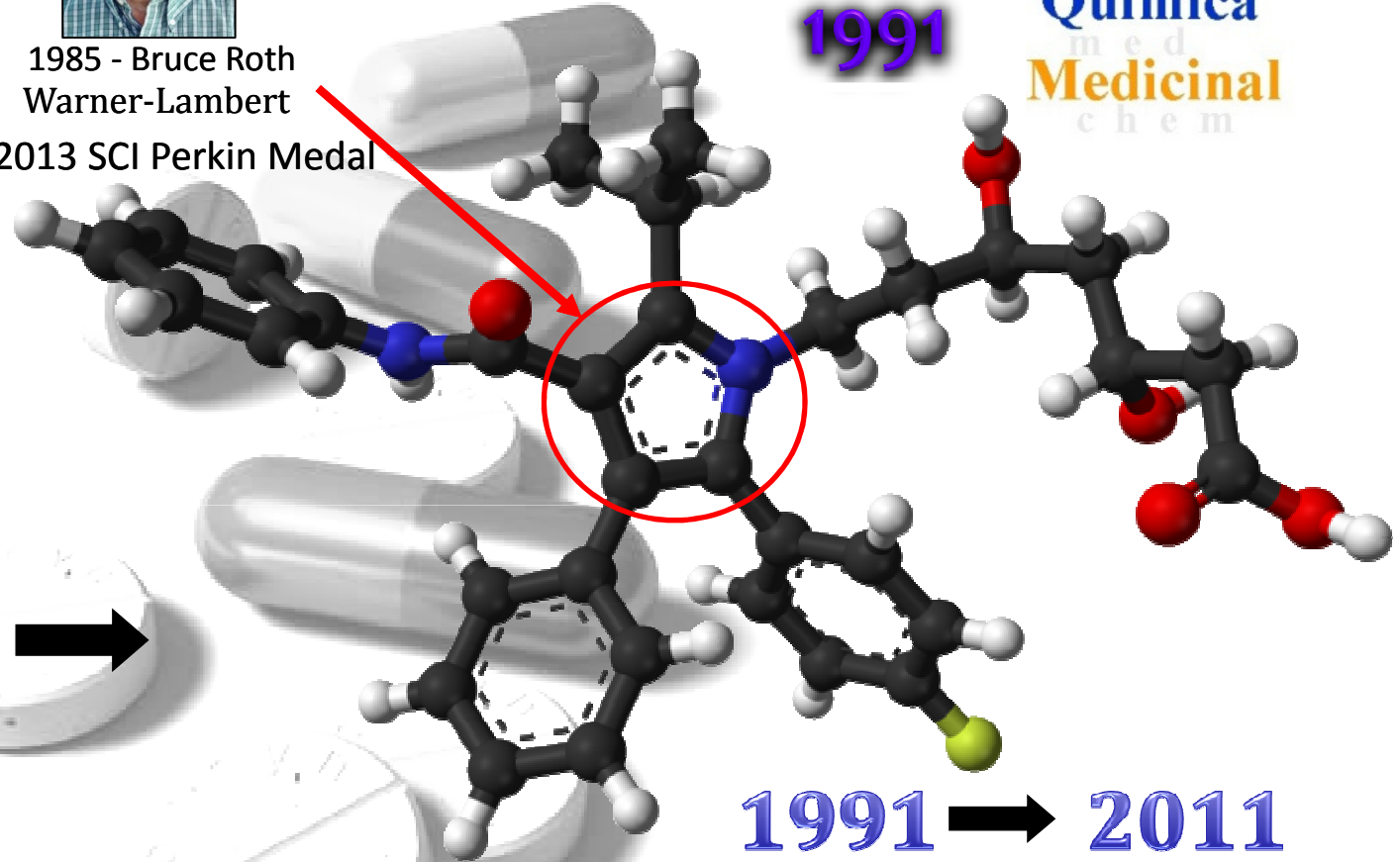


1985 - Bruce Roth  
Warner-Lambert  
2013 SCI Perkin Medal

# Estatinas

Química  
med  
Medicinal  
chem

1991



1991 → 2011

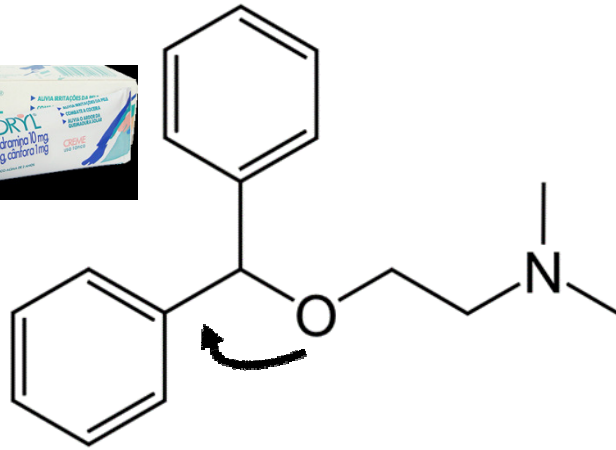
**ácido (*N*-pirrol)-3,5-di-hidróxi-heptanóico**  
 Síntese: *ca.* 200 toneladas/ano      HMGCo-AR IC<sub>50</sub> = 8,2 nM



**Fármaco recordista mundial em vendas:  
US\$ 150 bilhões**

B. D. Roth, *Progr. Med. Chem.* **2002**, *40*, 1-22

B. D. Roth, et al., *J. Med. Chem.* **1990**, *33*, 21-31

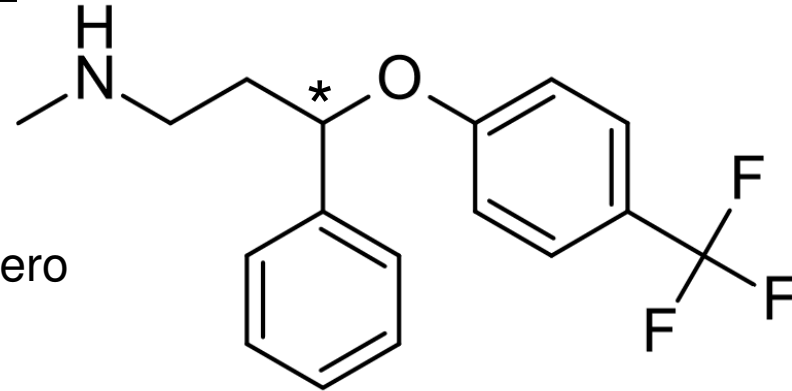


1943 - difenilidramina

retroisómero



1987 - David T. Wong

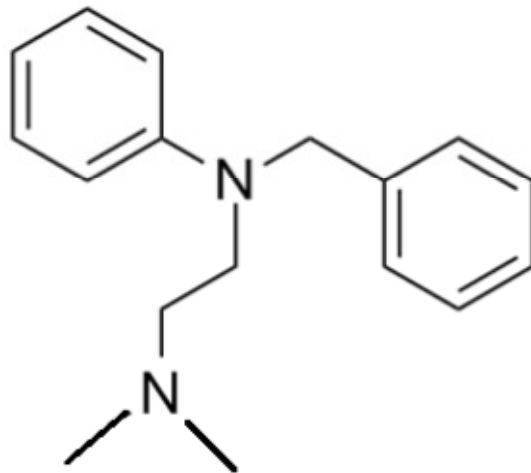


fluoxetina

Eli Lilly Co.



2010 - >> 24,4 milhões de prescrições EUA



1942 - fenbenzamina

Ki (nM) SERT= 1,0

NET= 660

DAT= 4180

5-HT<sub>2A</sub> =200

5-HT<sub>2B</sub> ≥5000

5-HT<sub>2C</sub> =260

M<sub>1</sub> =870

M<sub>2</sub> =2700

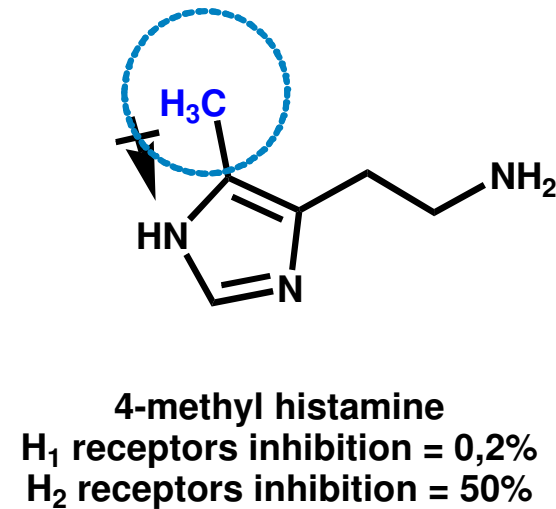
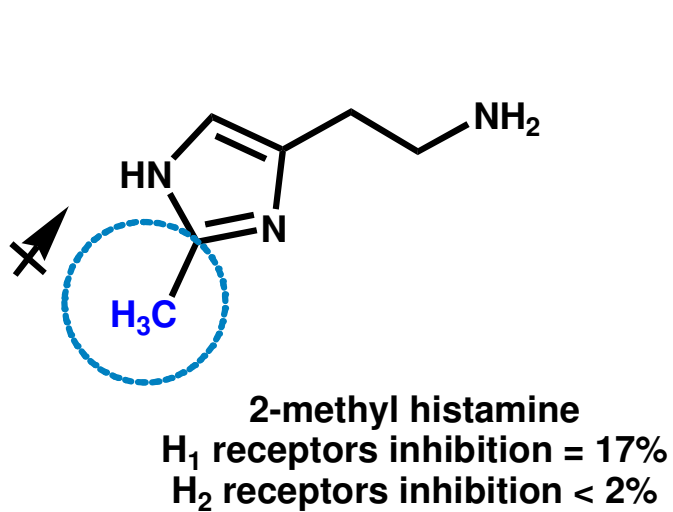
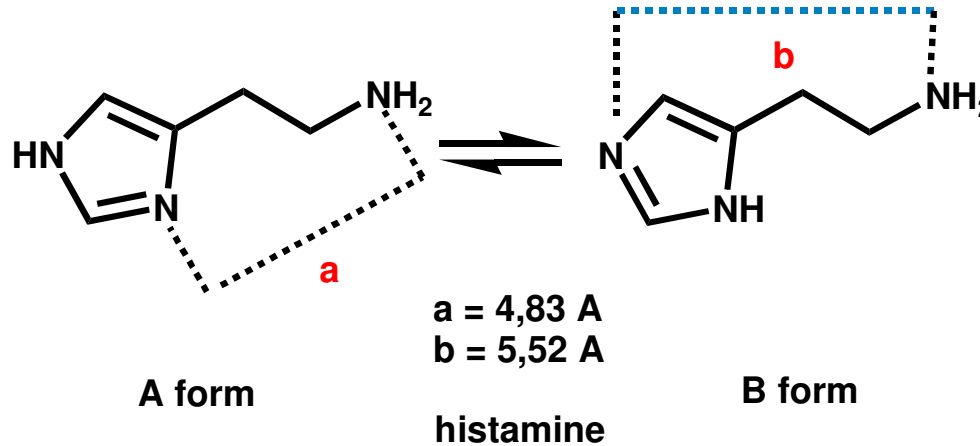
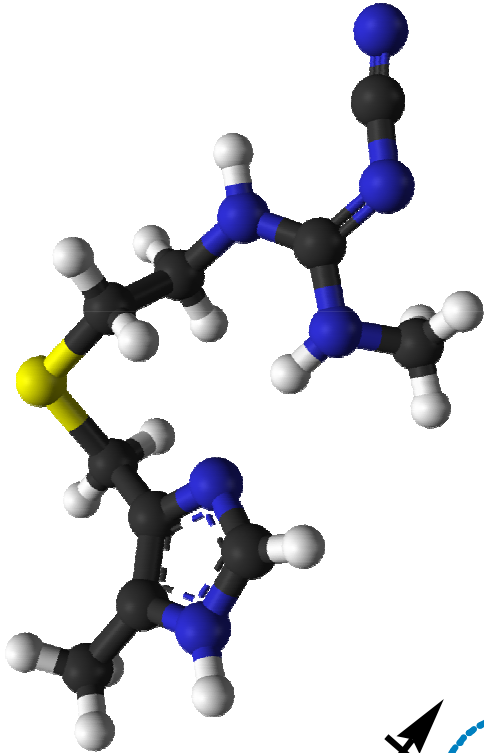
M<sub>3</sub> =1000

M<sub>4</sub> =2900

M<sub>5</sub> =2700

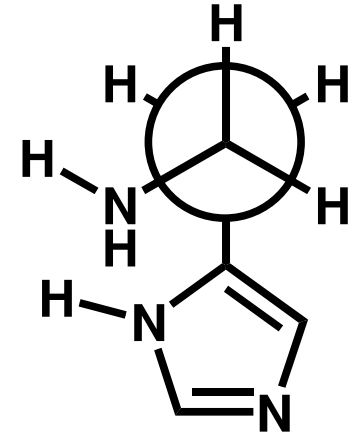
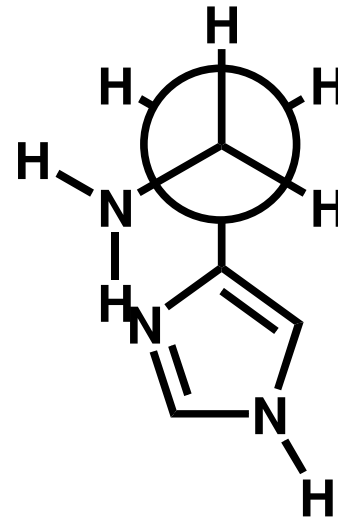
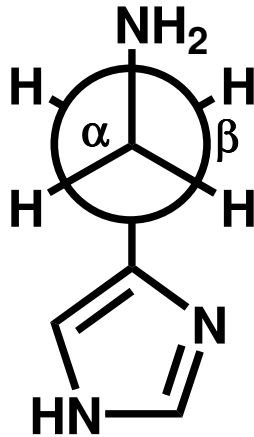
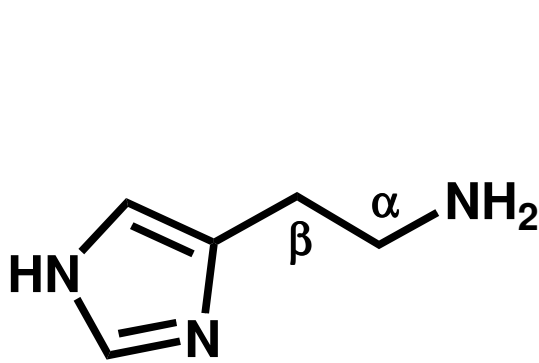
# Gênese da cimetidina: a vedete de hoje!

1964 - James W. Black & Michael Parsons, C Robin Ganellin, Graham Durant, John Emmett  
 (Smith Kline & French Res. Institute, Wilwyn, UK)

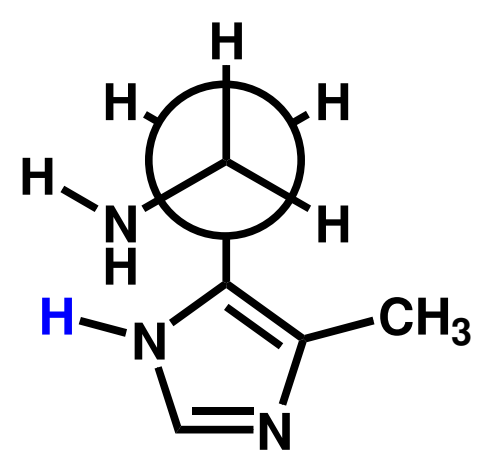
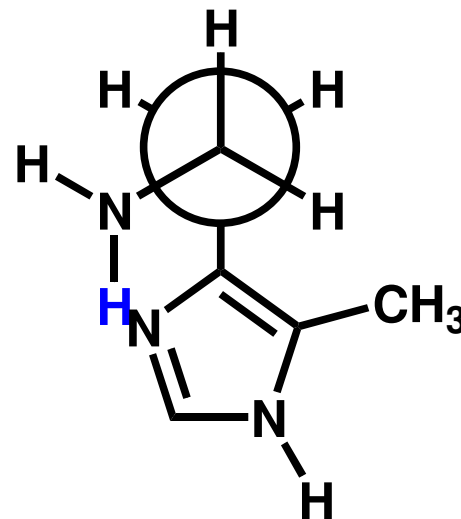
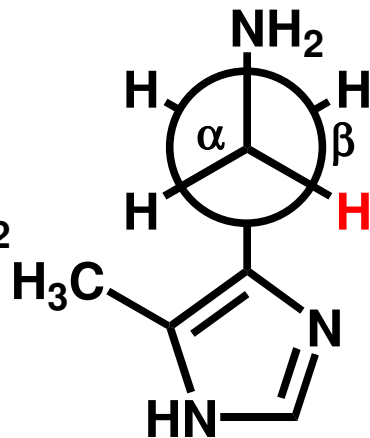
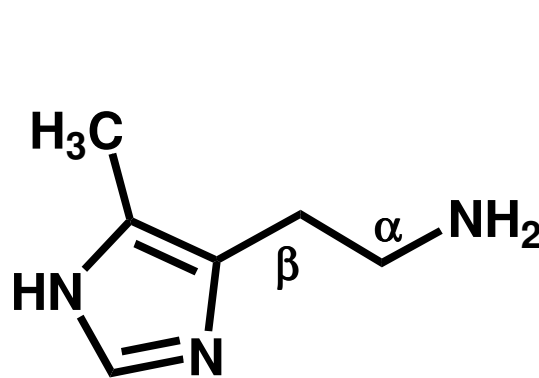




# Conformações da histamina



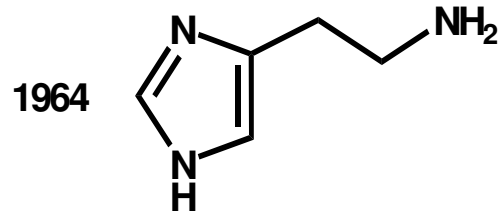
## Confôrmers



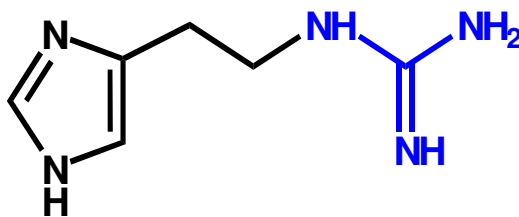
THE DISCOVERY OF  
HISTAMINE H<sub>2</sub>-RECEPTOR  
ANTAGONISTS  
SmithKline Beecham Pharmaceuticals  
Smith Kline & French Laboratories  
1972

SK&F

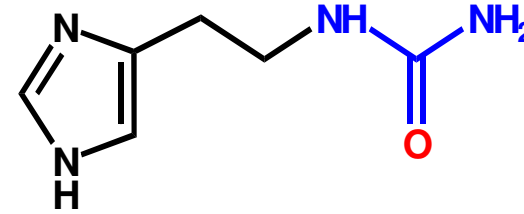
C Robin Ganellin



histamina

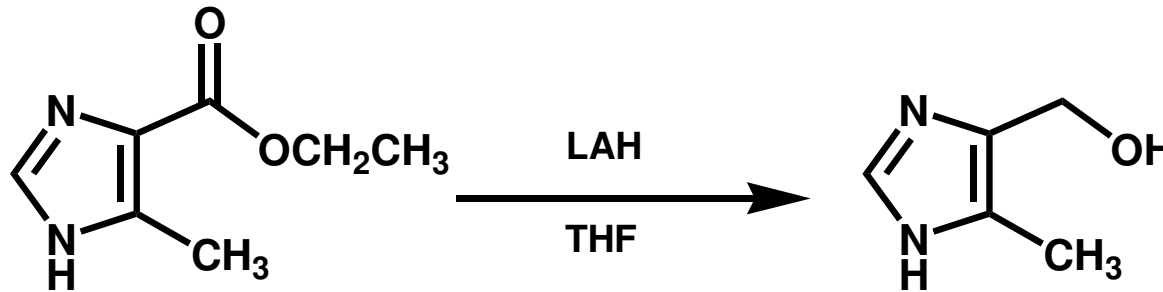


guanilistamina  
ag.

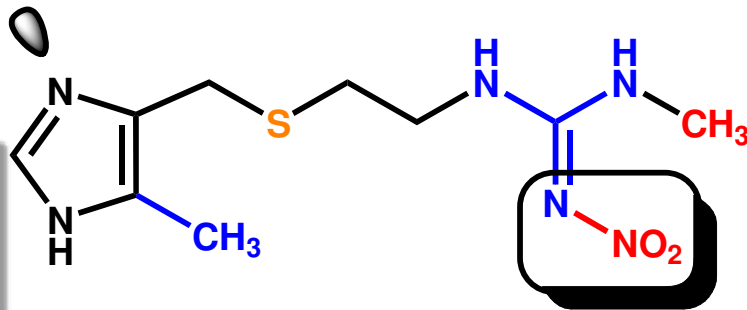
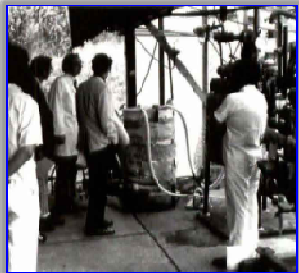


ureído-histamina

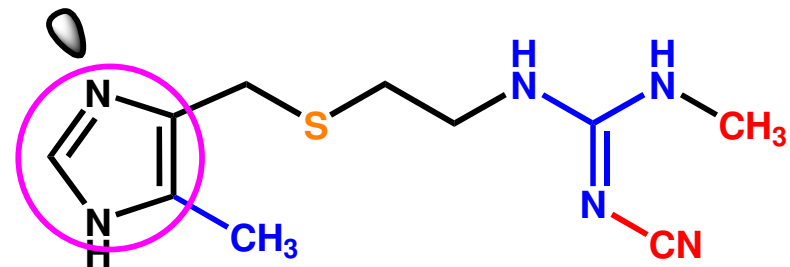
1970



1972



otimização (< ef. sang.)  
sem cristalinidade



cimetidina

“...**discovery** *consists* of seeing  
 what everybody else **has seen**  
**and thinking what**  
**nobody** else  
 has not thought...”



1937

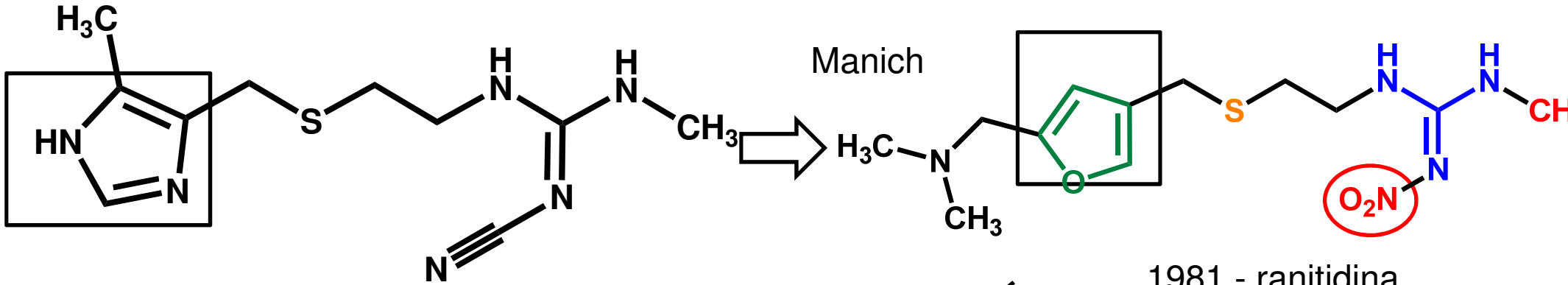


*Albert Szent-Györgyi (1893-1986)*

SK&F



1977 - John Bradshaw  
(Allen & Hanburys Ltd, Glaxo)

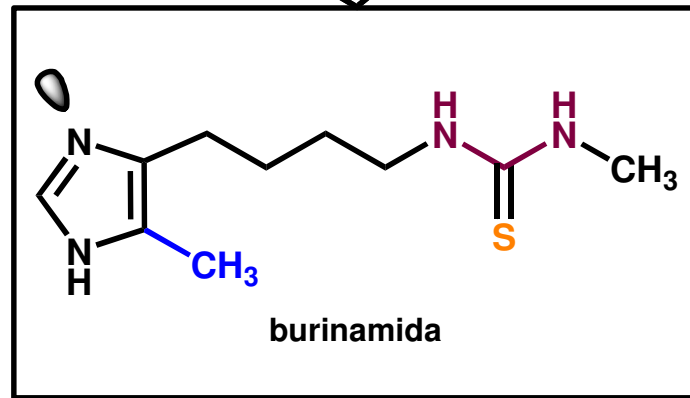


cimetidina  
CYP450

1981 - ranitidina



James W. Black



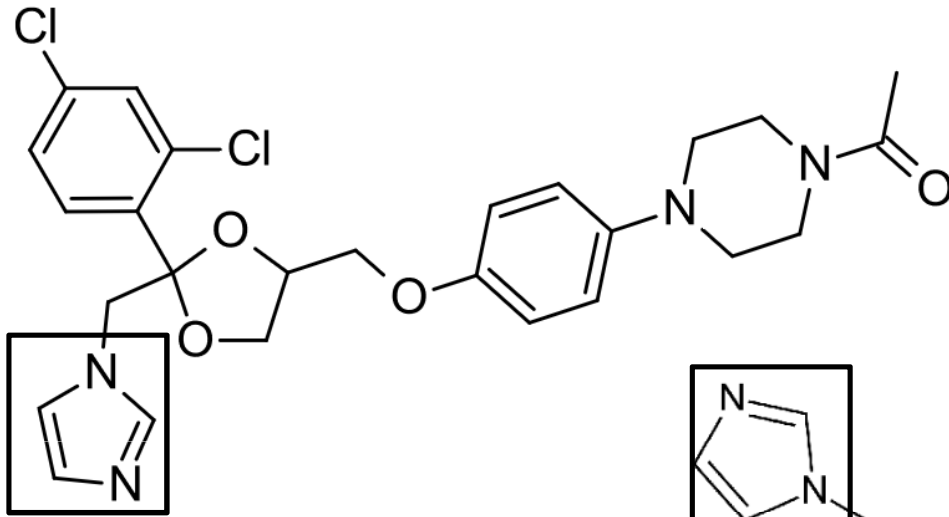
burinamida



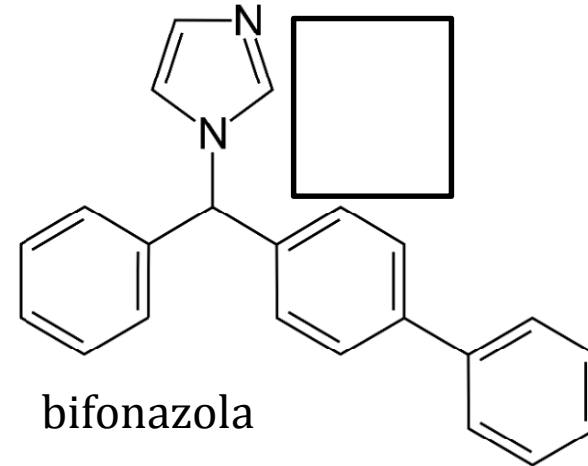
1977 - Barry Price  
(Allen & Hanburys Ltd, Glaxo)

# Imidazola: Privilegiado?

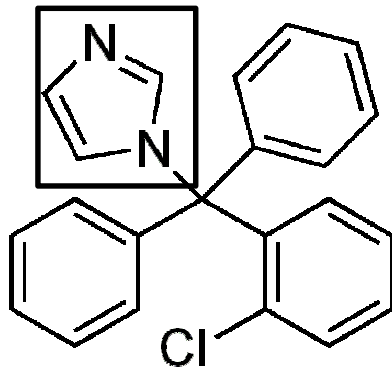
1976 - Janssen Pharma



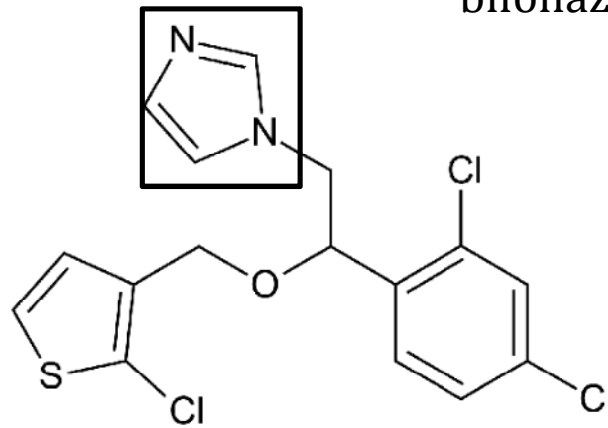
cetoconazole



bifonazole



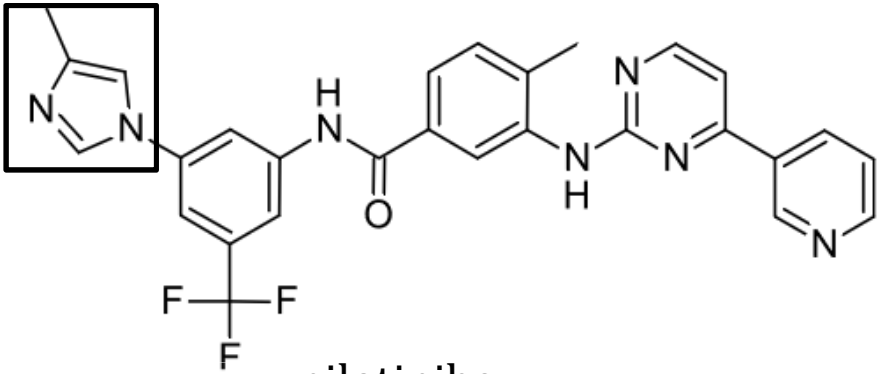
clotrimazole



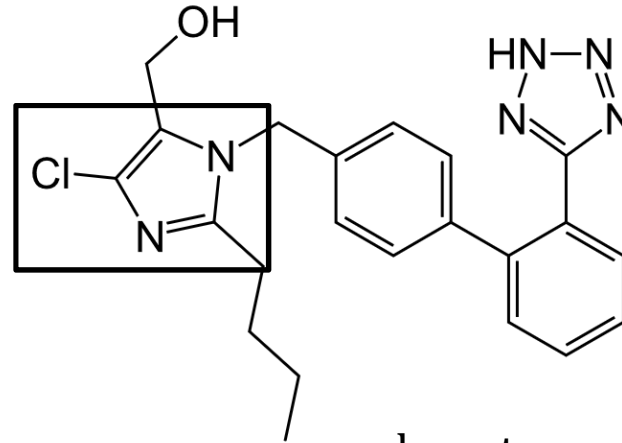
tioconazole

Fenticonazole  
Isoconazole  
Ketoconazole  
Luliconazole  
Miconazole  
Omoconazole  
Oxiconazole  
Sertaconazole  
Sulconazole  
Odansetrona  
Cilansetrona

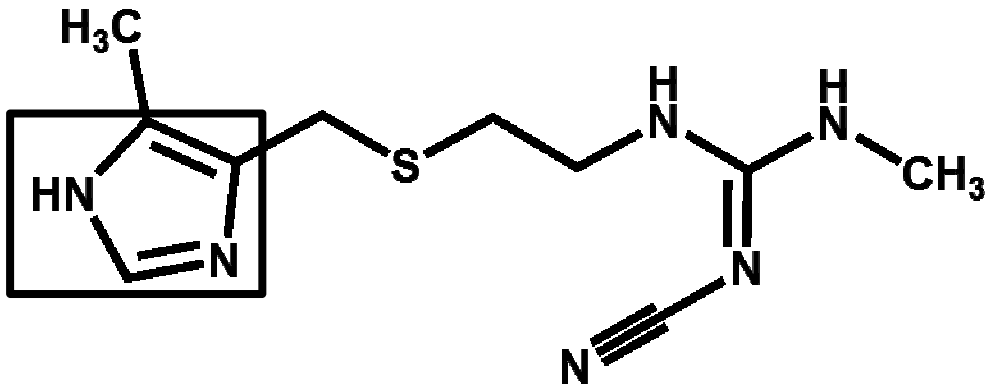
# Imidazola = Inibidor CYP



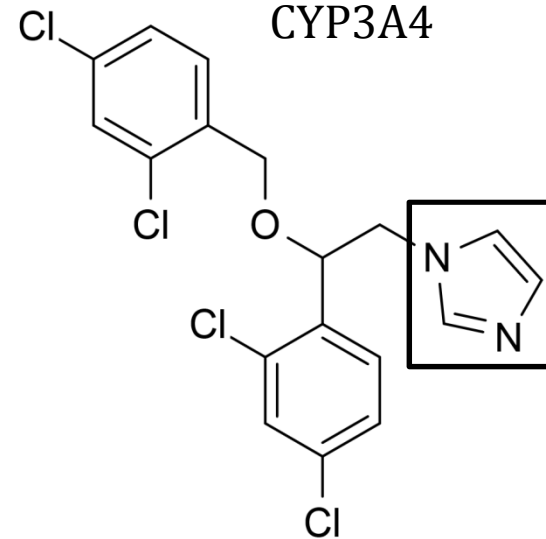
nilotinibe  
CYP3A4



losartana  
CYP3A4

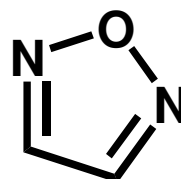
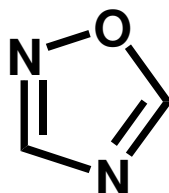
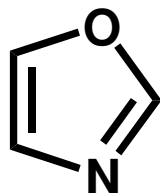
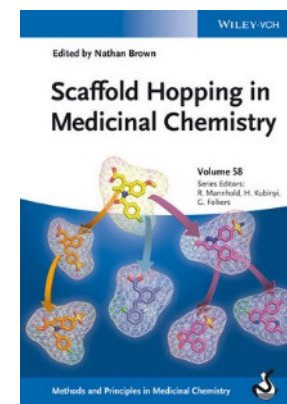
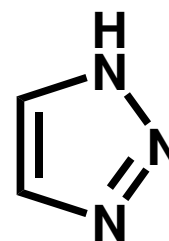
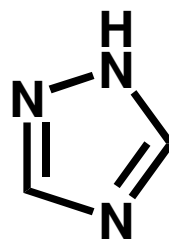
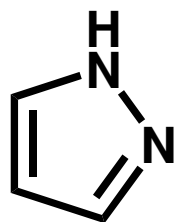
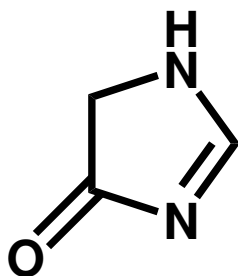
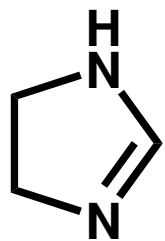


CYP1A2, CYP2C9, CYP2C19, CYP2D6

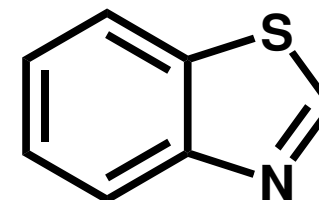
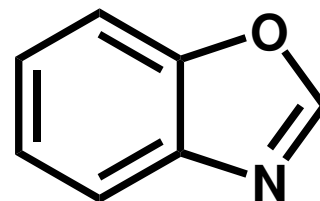
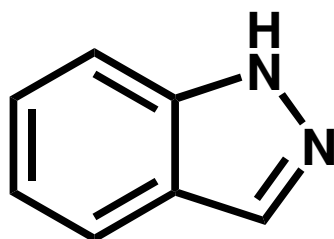
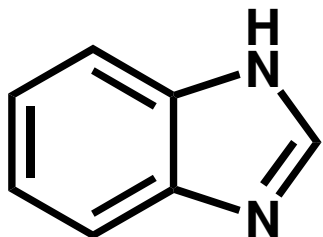


miconazola  
CYP1A2, CYP2C9, CYP2C19

# Variações no sistema imidazólico



*Privileged scaffold*



# Conclusões

**“Knowledge can be  
communicated,  
but not wisdom.”**



**Herman Hesse**

*(1877-1962)*

*(O conhecimento pode ser transmitido, mas não a sabedoria.)*



Tudo do bom e  
do melhor em 2015

*Fi m*



Sorry vegans!