



Bioisosterismo

Current Medicinal Chemistry, 2005, 12, 23-49

23

Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design

Lídia Moreira Lima and Eliezer J. Barreiro*

Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro. CCS, Cidade Universitária, CP 68.006, 21944-190, Rio de Janeiro, R.J., Brazil

Abstract: This review aim to demonstrate the role of bioisosterism in rational drug design as well as in the molecular modification and optimization process aiming to improve pharmacodynamic and pharmacokinetic properties of lead compounds.



Impact Factor: 4.94

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

Glossary of Terms Used in Medicinal Chemistry

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

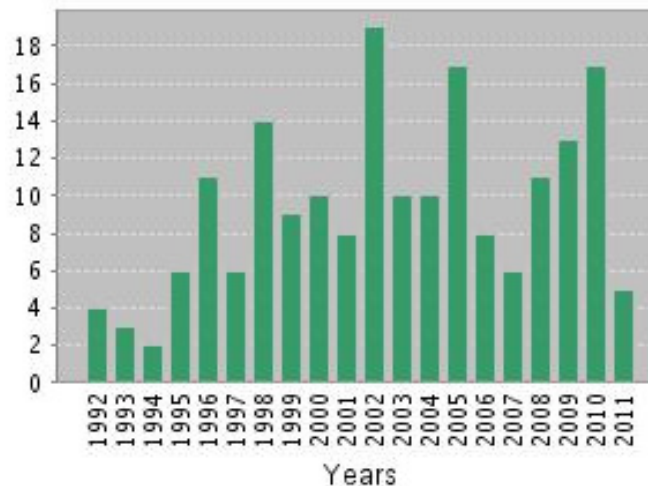


Citation Report Author=(Barreiro E J)

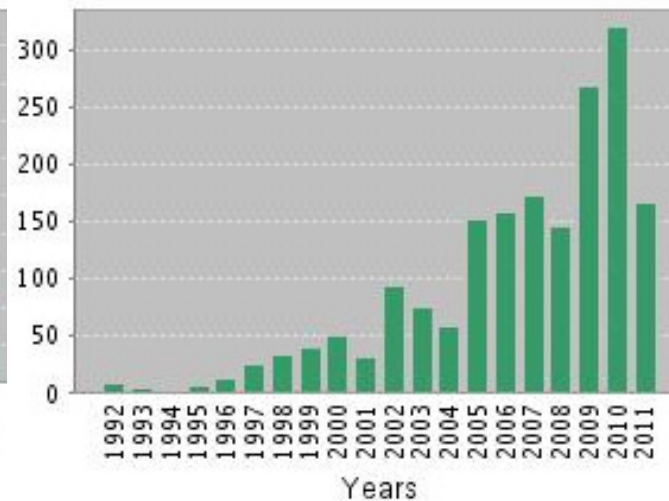
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<input checked="" type="checkbox"/> 1. Title: Bioisosterism: A useful strategy for molecular modification and drug design Author(s): Lima LMA, Barreiro EJ Source: CURRENT MEDICINAL CHEMISTRY Volume: 12 Issue: 1 Pages: 23-49 Published	19	16	37	27	19	127	18.14





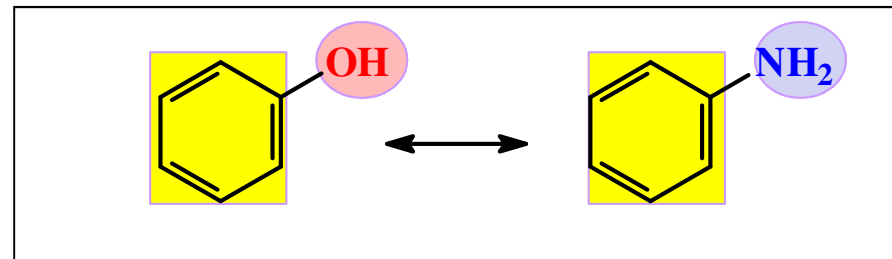
Bioisosterismo

- 1919 – Langmuir
- 1925 - Grimm
- 1932 – Erlenmeyer
- 1951 – Friedman
- 1952 (1970) – A. Burger
- 1979 - Thornber
- 1986 – Lipinsky
- 1996 – Patani & LaVoie
- 2005 – Lima & Barreiro (127 citações)
- 2011 – Meanwell (JMC)

17/06/2011

Similaridade
molecular

Grupos
funcionais



Pontos
farmacofóricos



Bioisosterismo

Table 1 – Classic bioisostere groups and atoms

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

Table 2 - Non-Classic Bioisosteres

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



Bioisosterismo

The Hydride Displacement Law

	Grupo 4A	Grupo 5A	Grupo 6A	Grupo 7A	Gases Nobres	
n° de e ⁻	6	7	8	9	10	11
	C	N	O	F	Ne	Na ⁺
	H →	CH	NH	OH	FH	
		H →	CH ₂	NH ₂	OH ₂	FH ₂ ⁺
			H →	CH ₃	NH ₃	OH ₃ ⁺
				H →	CH ₄	NH ₄ ⁺

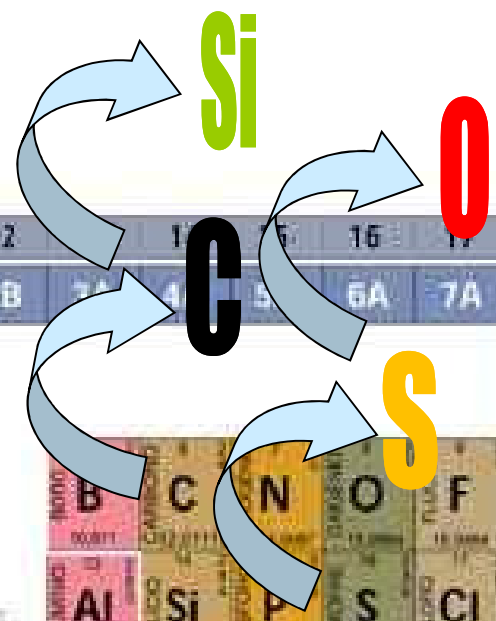
Grimm, 1925.



Tabela Periódica

Bioisosterismo

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	*	
1A	2A	3B	4B	5B	6B	7B	8B			9B	10B	2B	3A	4A	5A	6A	7A	0	
H	He																		
Li	Be	Elementos de transição										B	C	N	O	F	Ne		
Na	Mg	Elementos de transição										Al	Si	P	S	Cl	Ar		
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr		
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe		
Cs	Ba		Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn		
Fr	Ra		Dh	Ji	Rf	Bh	Hn	Mt											



Number atomic: 6

Number of protons: 6

Number of neutrons: 6

Number of electrons: 6

Symbol: C

Mass atomic: 12,01115

Element: CARBÔNIO

Lantanídeos

La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
----	----	----	----	----	----	----	----	----	----	----	----	----	----	----

Actínidos

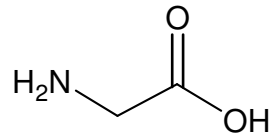
Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr
----	----	----	---	----	----	----	----	----	----	----	----	----	----	----



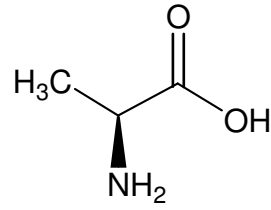
Bioisosterismo

na

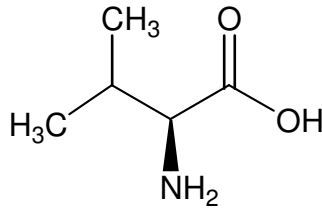
natureza



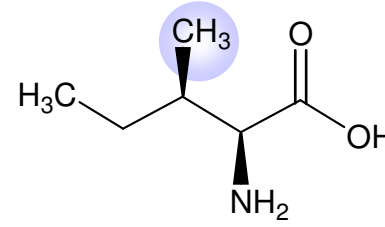
glicina (**gly**)



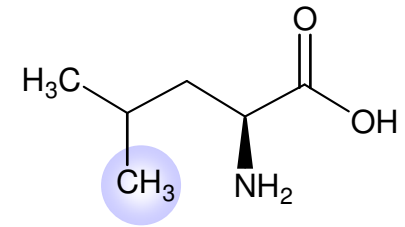
alanina



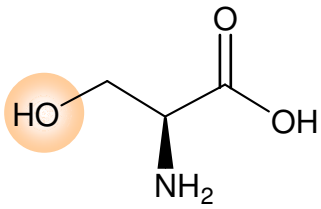
valina



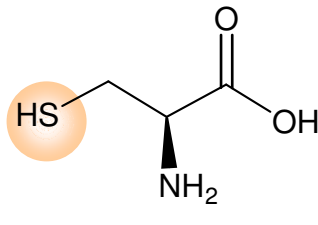
isoleucina (Ile)



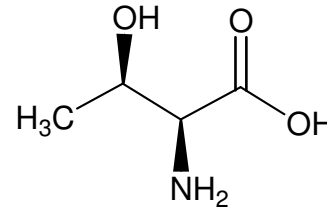
leucina



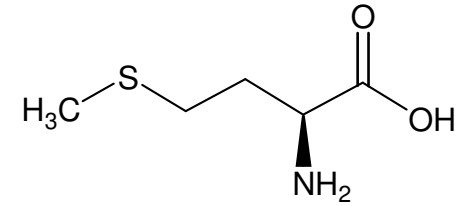
serina



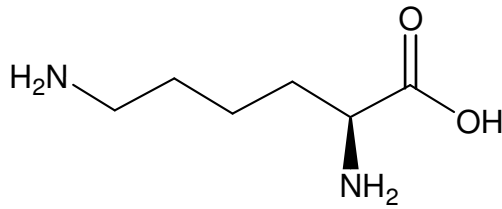
cisteína (Cys)



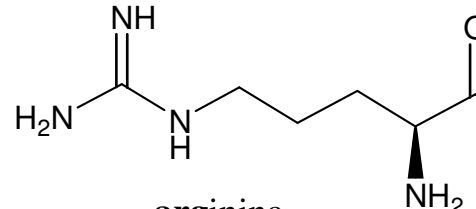
treonina (Thr)



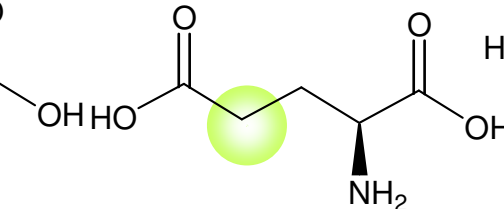
metionina



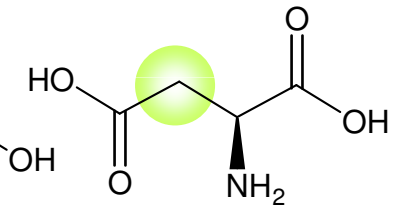
lisina (Lys)



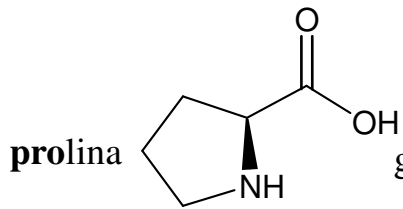
arginina



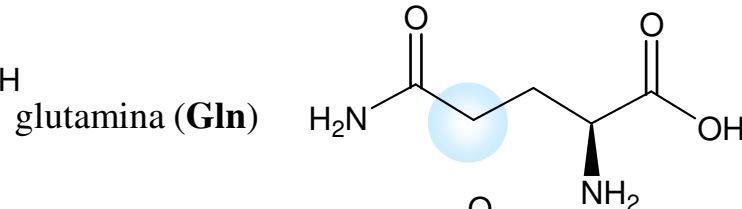
ácido glutâmico



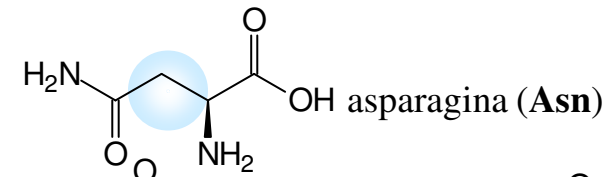
ácido aspártico



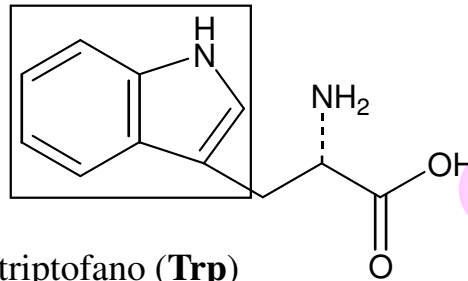
prolina



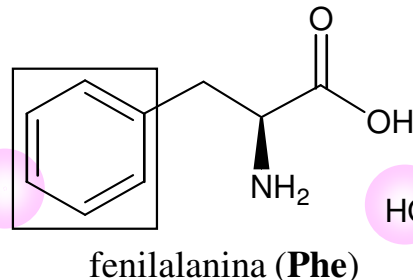
glutamina (Gln)



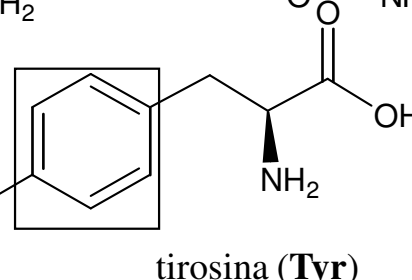
asparagina (Asn)



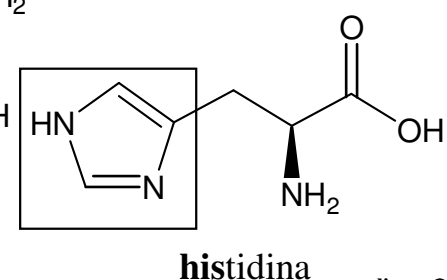
triptofano (Trp)



fenilalanina (Phe)



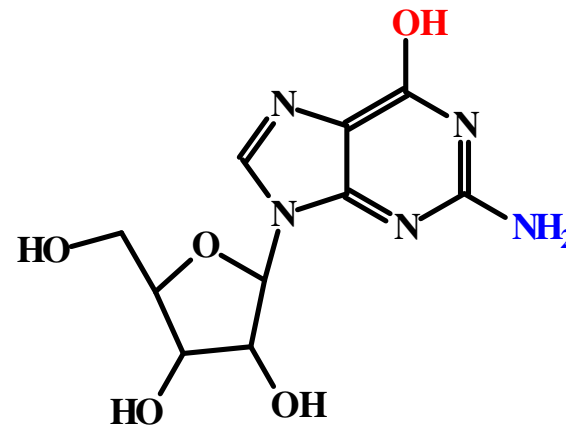
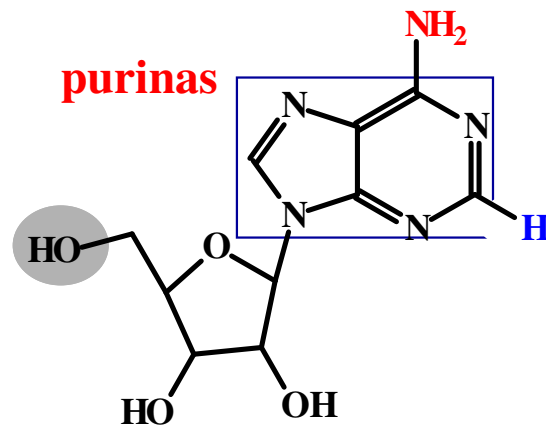
tirosina (Tyr)



histidina

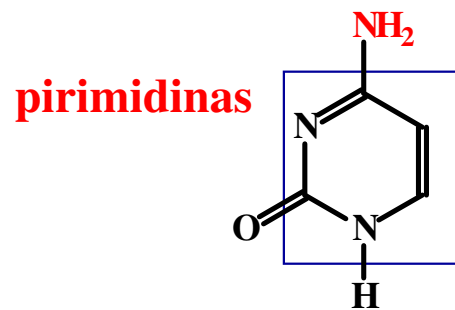


Bioisosterismo na Natureza

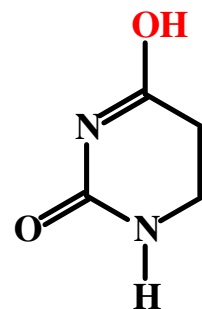


adenosina ← adenina

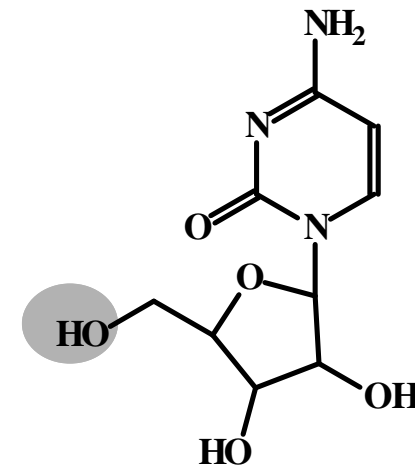
guanina → guanosina



citosina



"uracilo"



nucleosídeo



Bioisosterismo

Modulação de propriedades moleculares

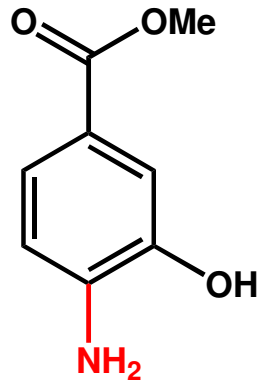
- Volume molecular (PD)
- Polarizabilidade (PD)
- Estéreo-eletrônicas (PD/PK)
- Solubilidade (PK)
- Reatividade química (PK)
- Ligação-H (PD>PK)
- pKa (PD/PK)

Modulação do bioperfil molecular

- propriedades farmacocinéticas (PK);
- propriedades farmacodinâmicas (PD; GF);
- propriedades toxicofóricas (GT);



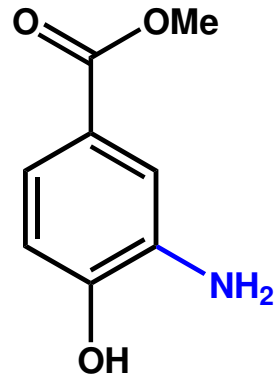
Regioisomêros



neo-ortocaína



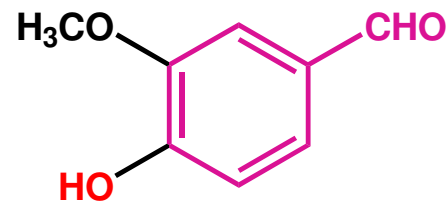
para-amino = tóxico



ortocaína

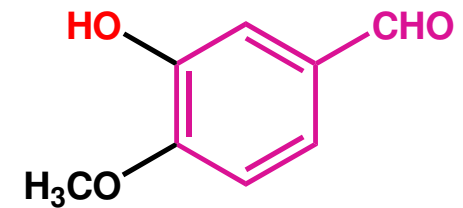


meta-amino não-tóxico



vanilina

odor característico



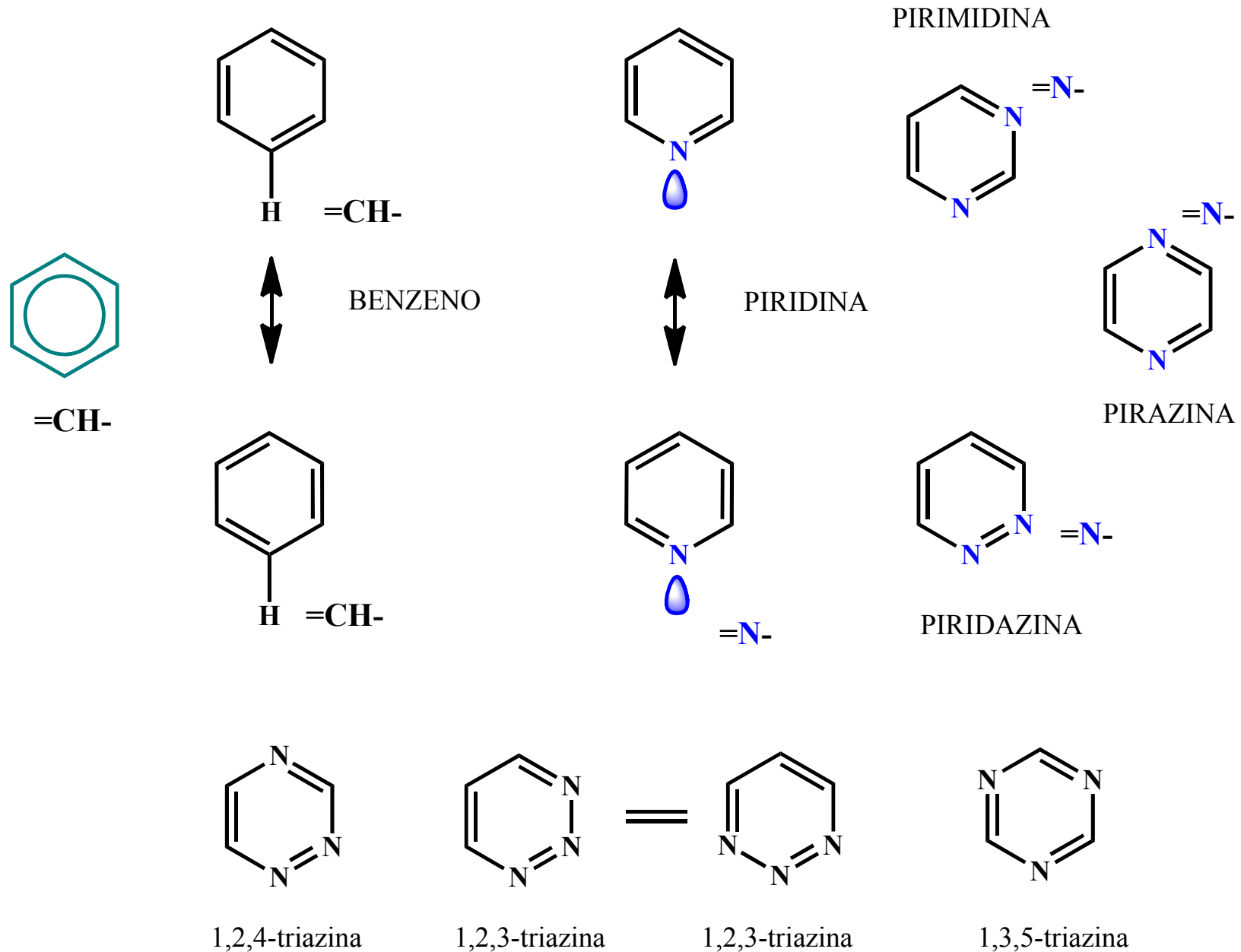
iso-vanilina

inodoro

Caso sejam bioativos, podem ser *retro-isósteros* não clássicos!

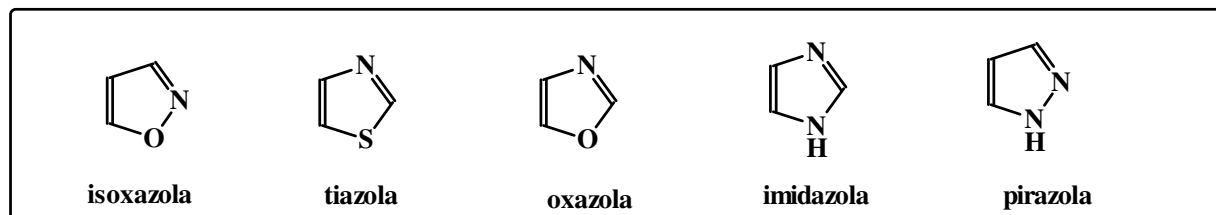
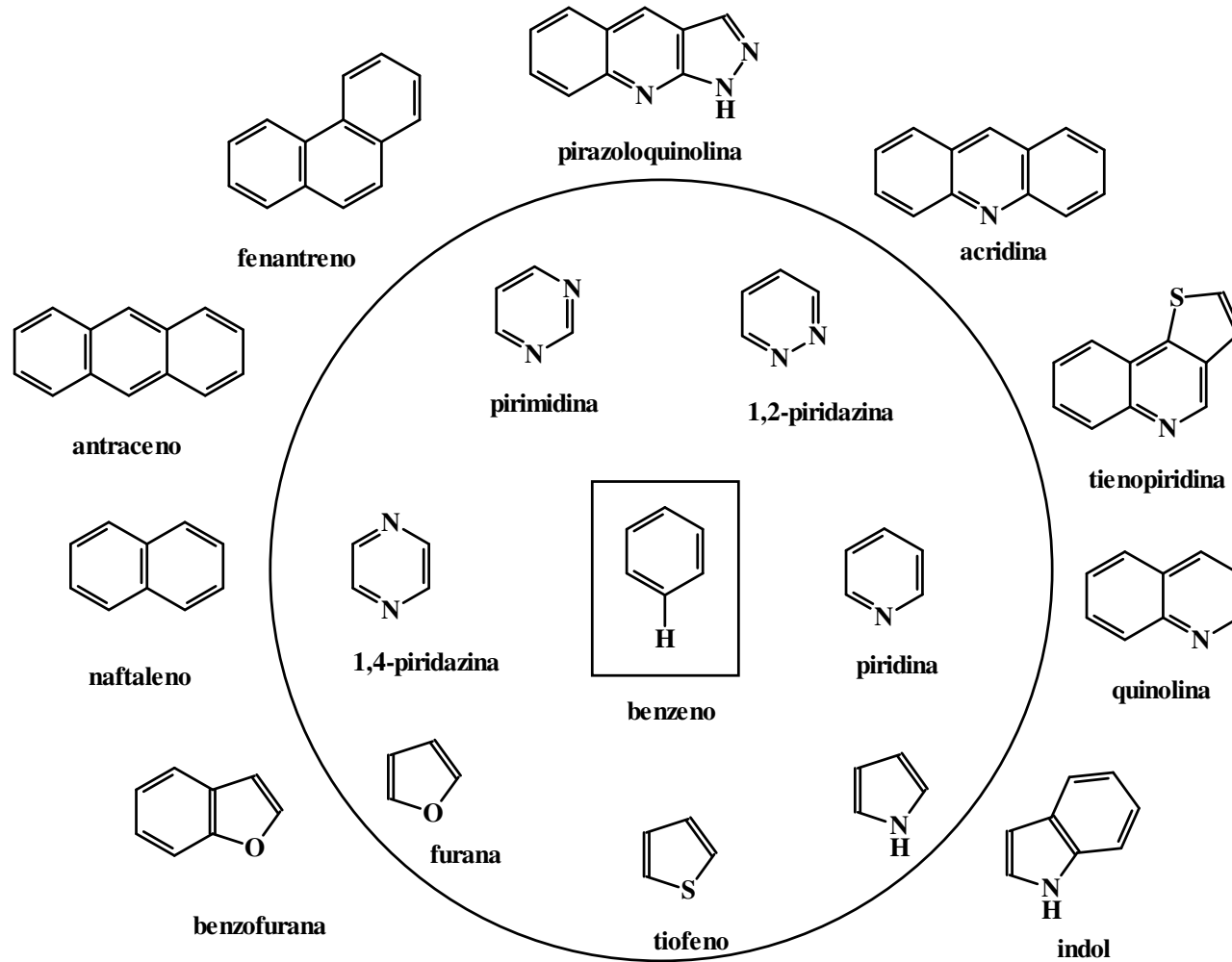


Bioisosterismo de anéis aromáticos





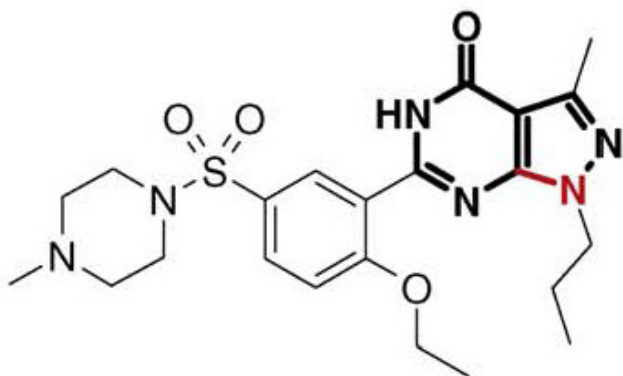
Bioisosterismo de anéis aromáticos



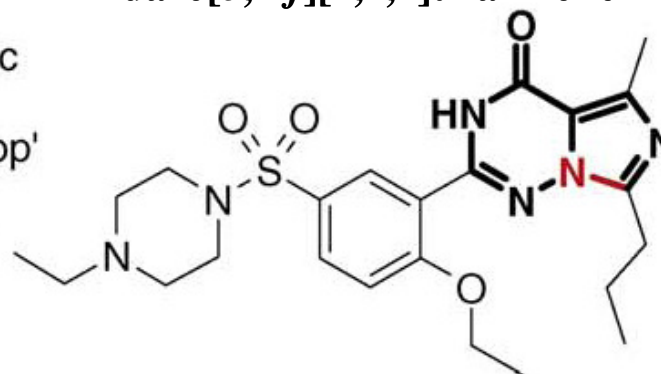


Exemplo de bioisosterismo de anéis

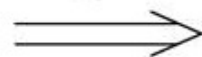
7-1*H*-pirazolo[4,3-*d*]pirimidinona



4-imidazo[5,1-*f*][1,2,4]triazinona



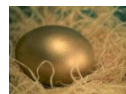
Heterocyclic
core
'Template hop'



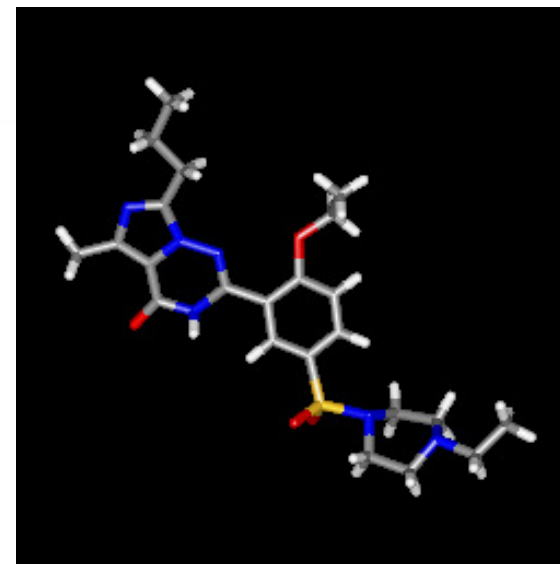
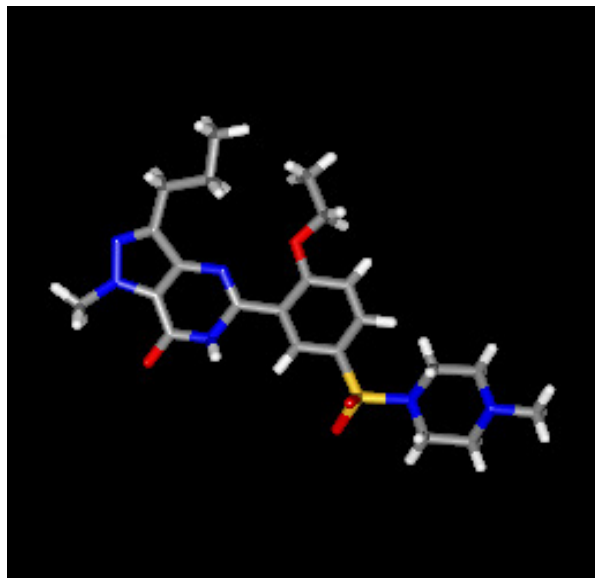
Sildenafil
Viagra®
Pfizer
March 1998

2003 – *ca.* US\$ 2 bilhões

2013 – *ca.* US\$ 3,5 bilhões

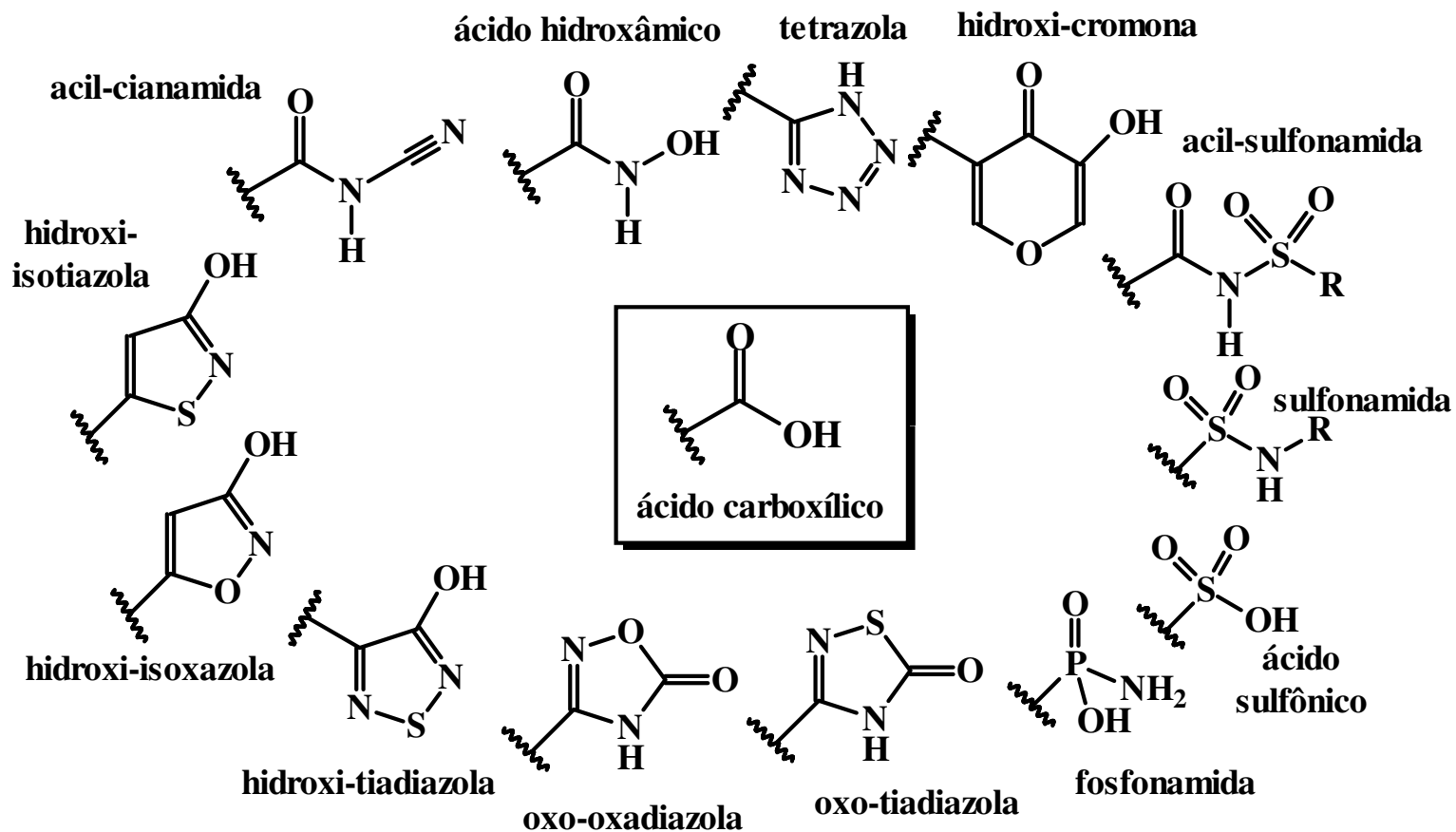


Vardenafil
Levitra®
Bayer
August 2003





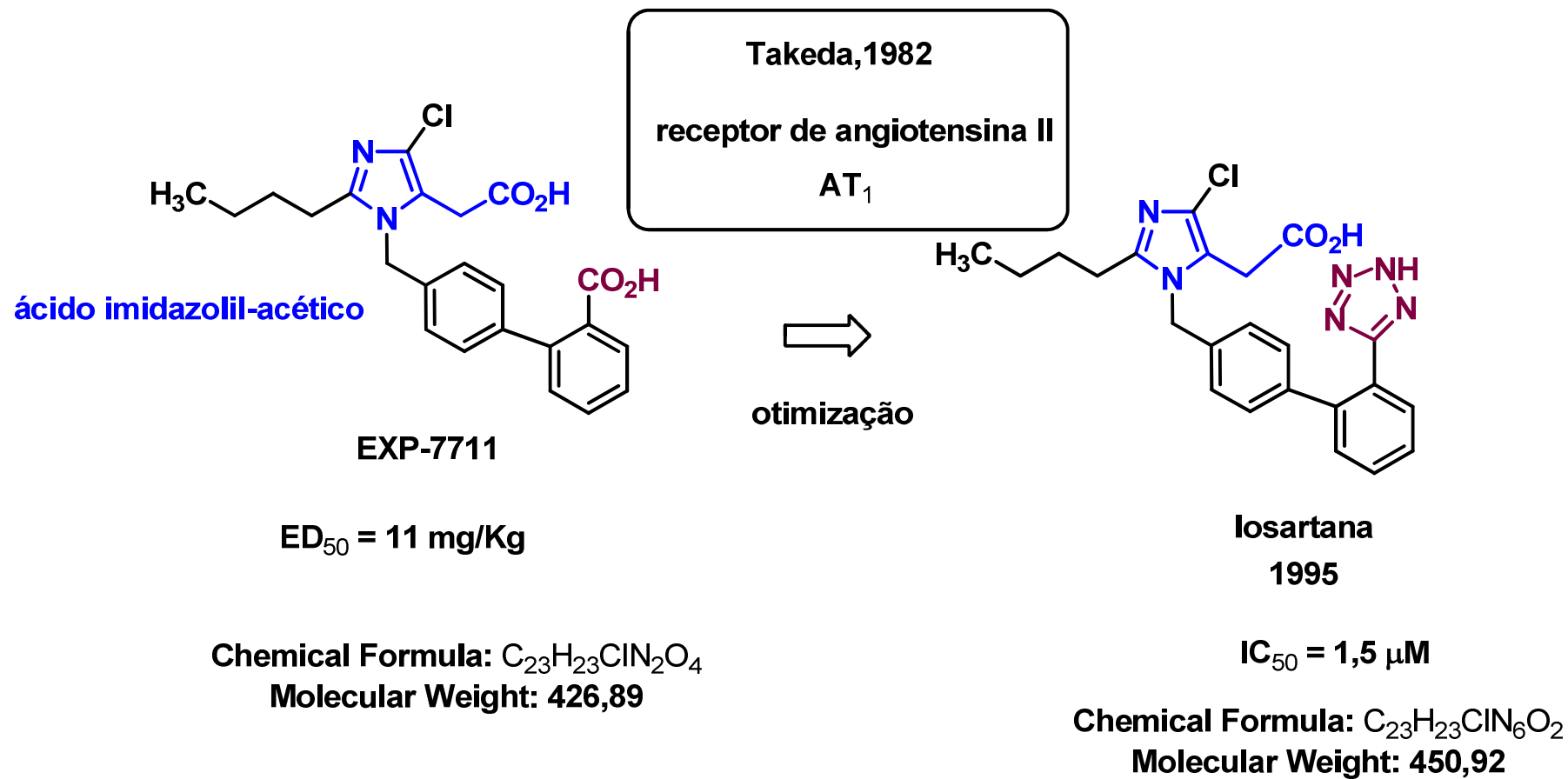
Bioisosterismo funcional



Todas as *funções orgânicas* têm a mesma diversidade de isósteros ?



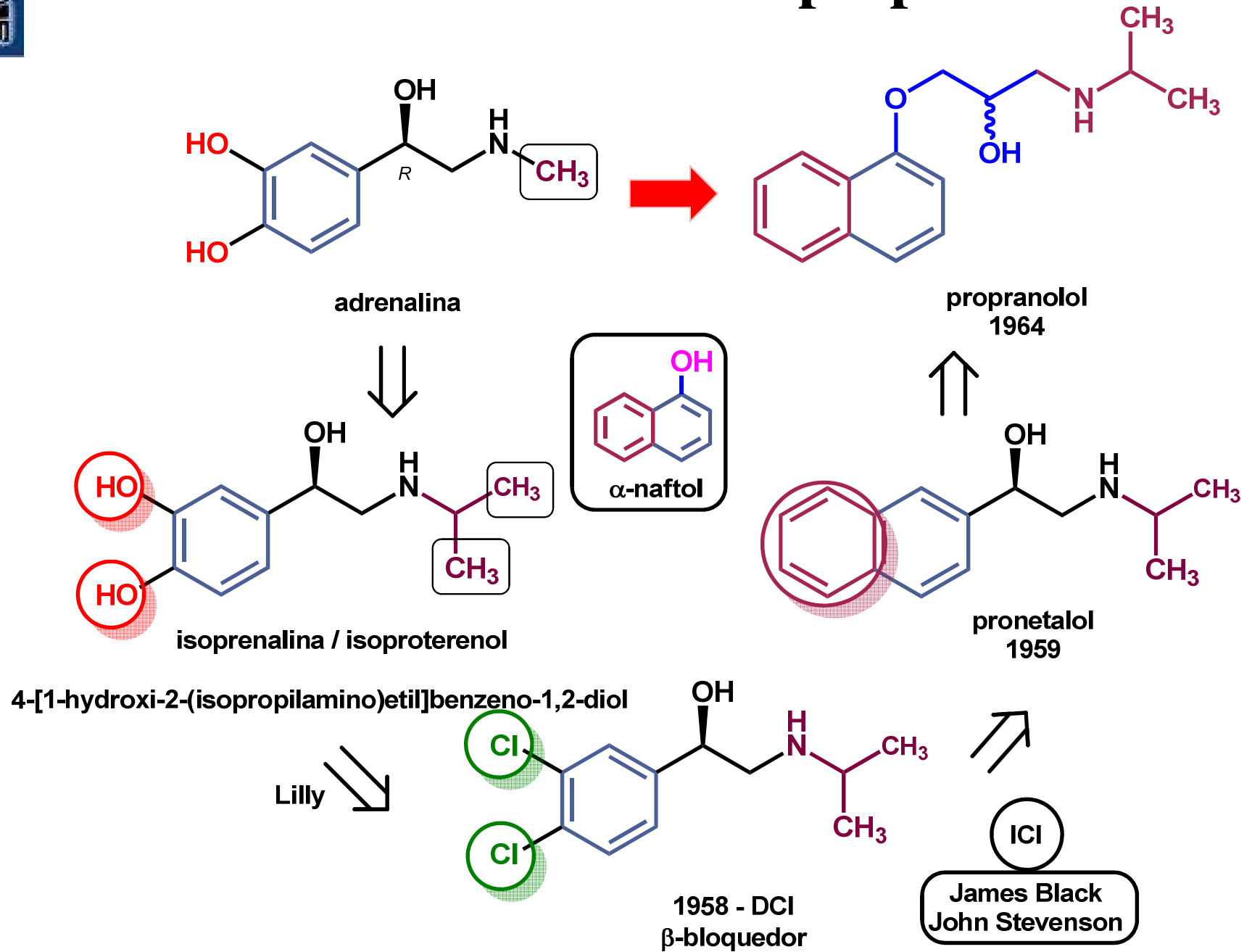
Exemplo de bioisosterismo funcional

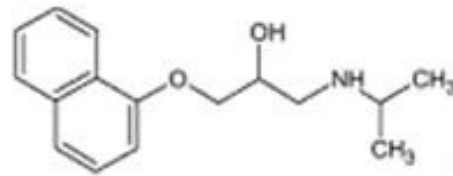


D. J. Carini *et al.*, *J. Med. Chem.* **34**, 2525 (1991)

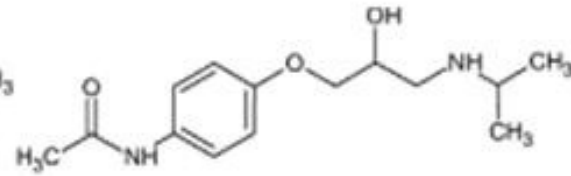


Bioisosterismo clássico: propranolol

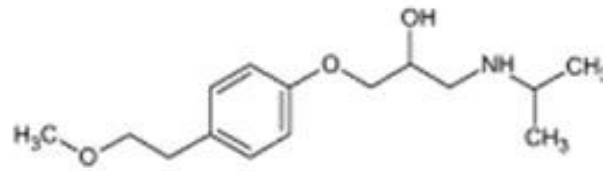




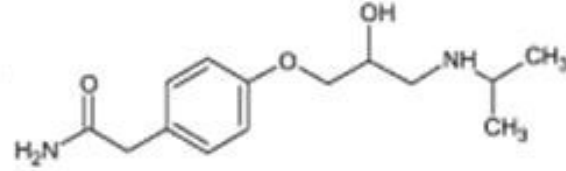
propranolol



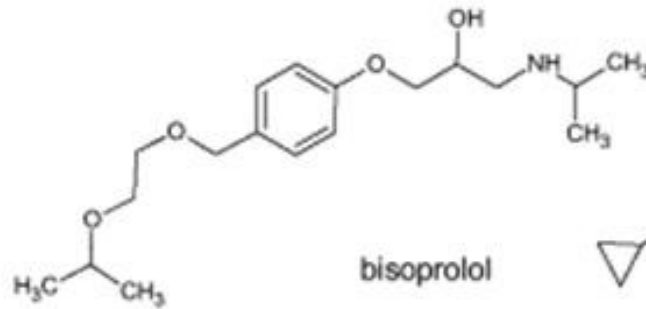
practolol



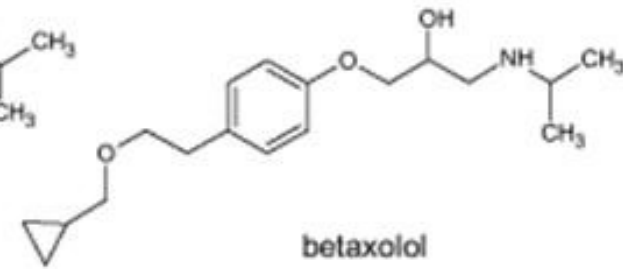
metoprolol



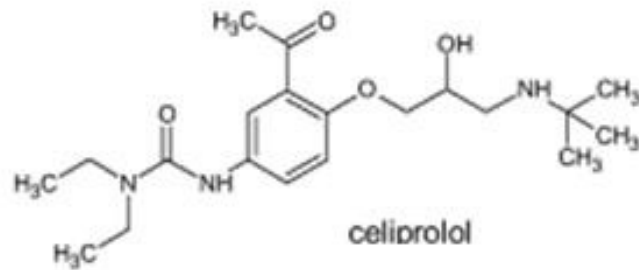
atenolol



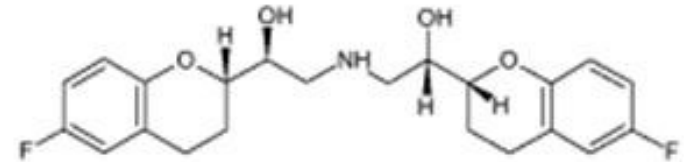
bisoprolol



betaxolol



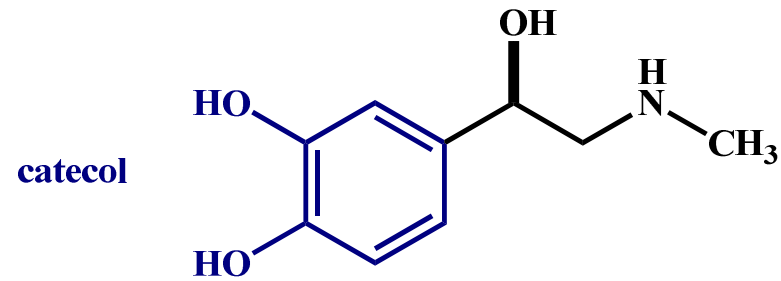
celiprolol



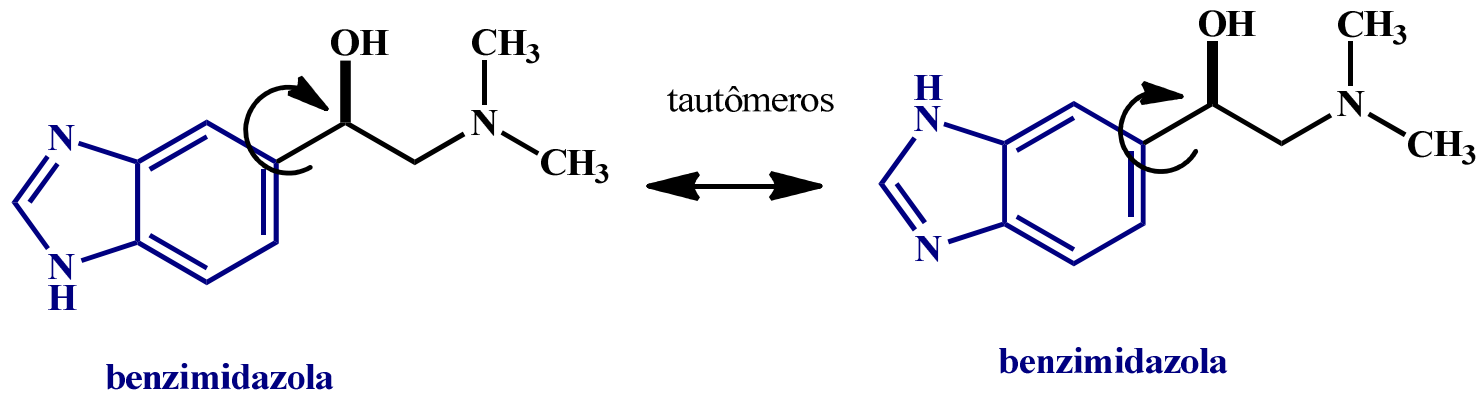
nebivolol



Bioisosterismo funcional não-clássico



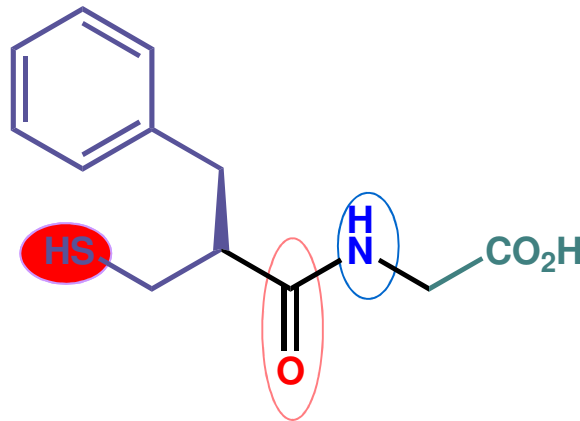
ADRENALINA





Bioisosterismo funcional

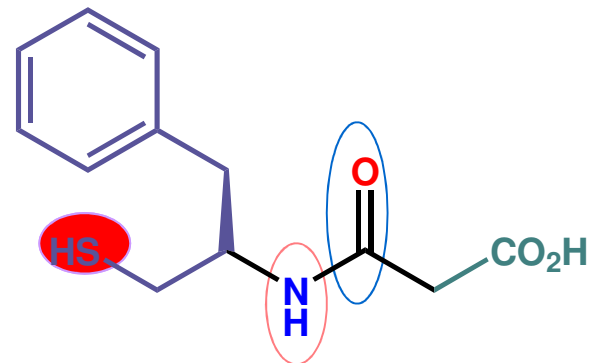
retroisosterismo



Tiorfana

ACE $K_i = 0,14 \mu\text{M}$

NEP $K_i = 0,0019 \mu\text{M}$



***retro*-Tiorfana**

ACE $K_i = > 10,0 \mu\text{M}$

NEP $K_i = 0,0023 \mu\text{M}$

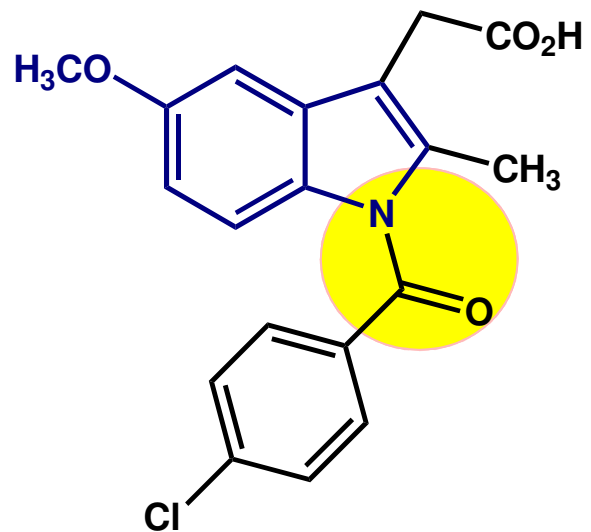
ACE = enzima conversora de angiotensina

NEP = endopeptidase neutra

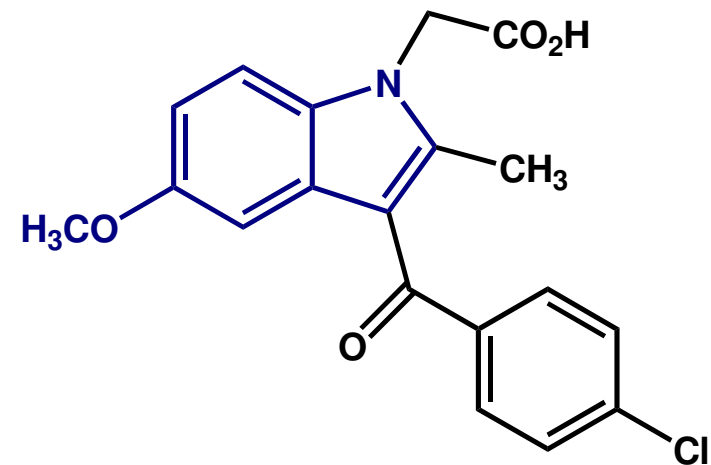


Retroisosterismo

regioisomêros



indometacina

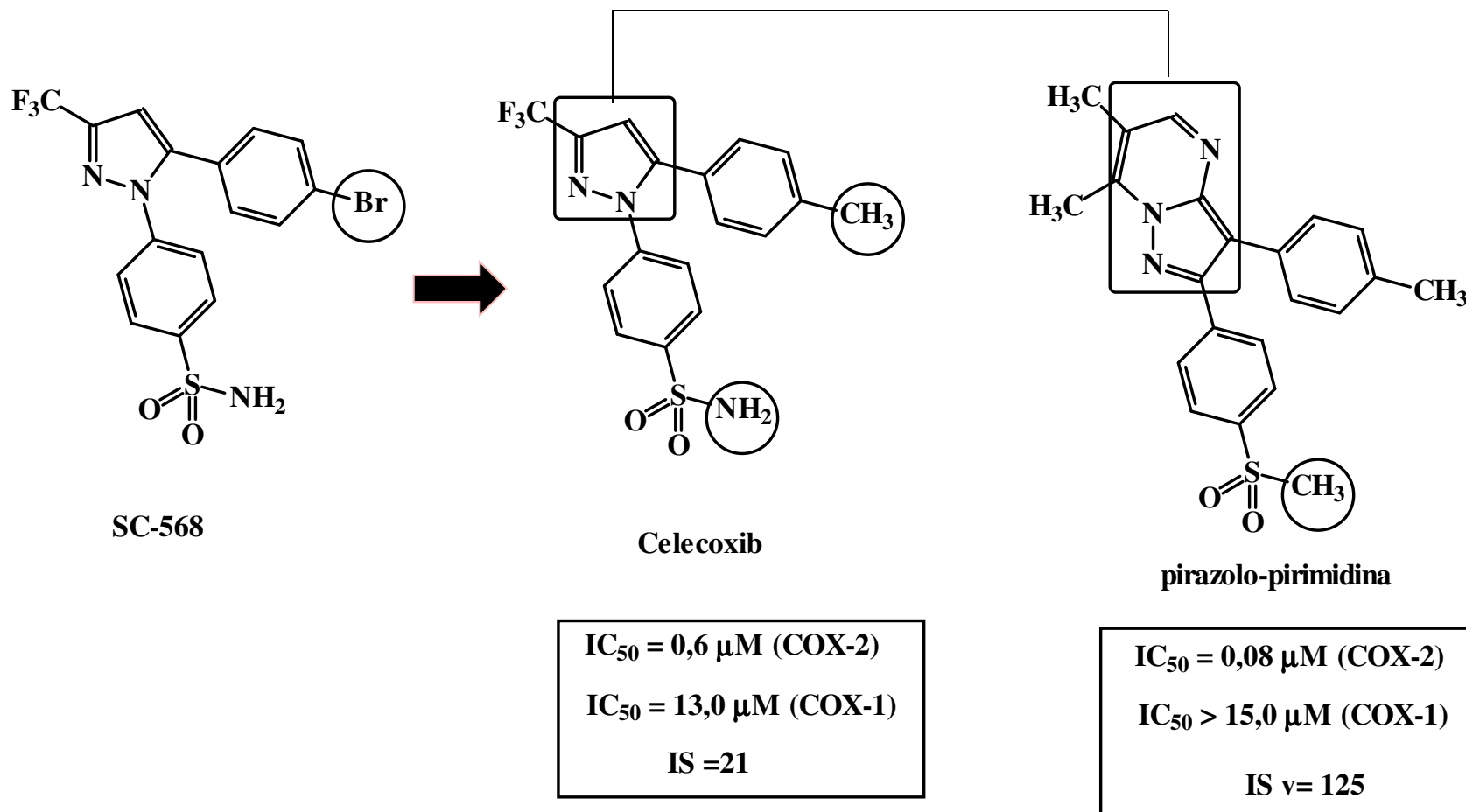


clometacina

retroisósteros

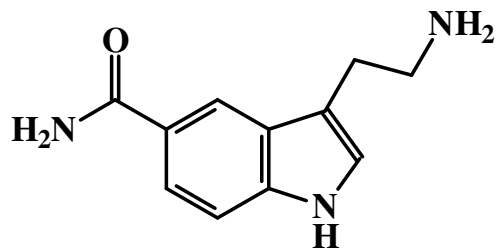


Bioisosterismo clássico e de anéis

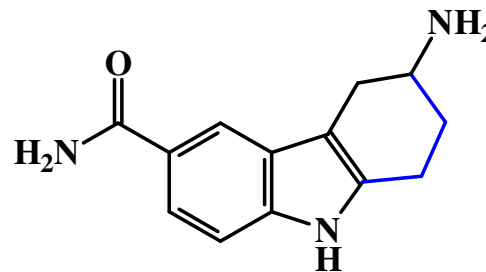




Bioisosterismo por homologia (anelação)



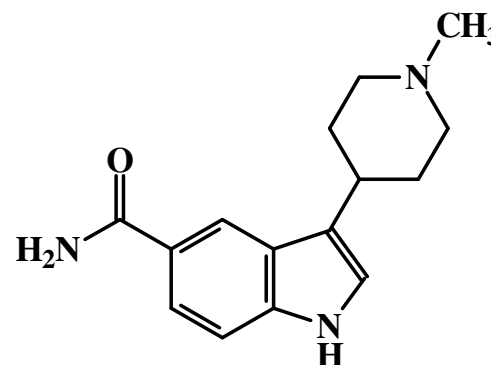
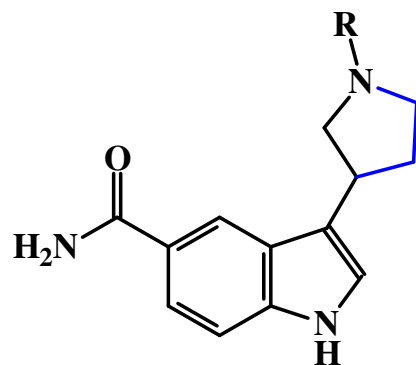
5-HT_{1D} ⊕



BRL-56905

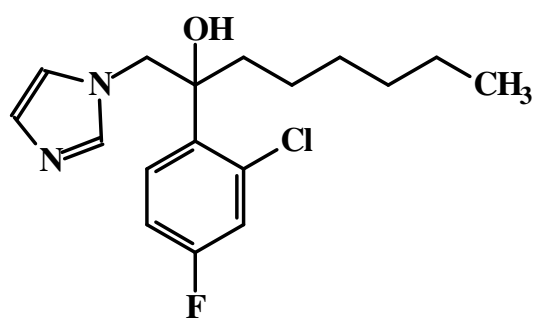
5-HT₁ ⊕

⇓ anelção

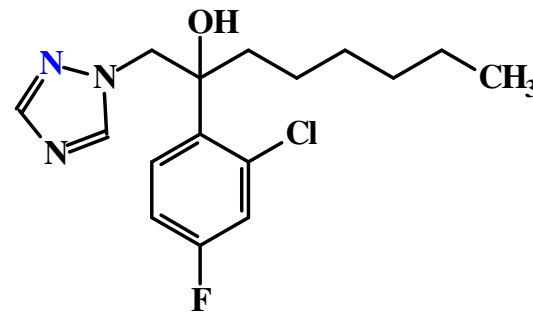




Bioisosterismo de anéis



UK46021

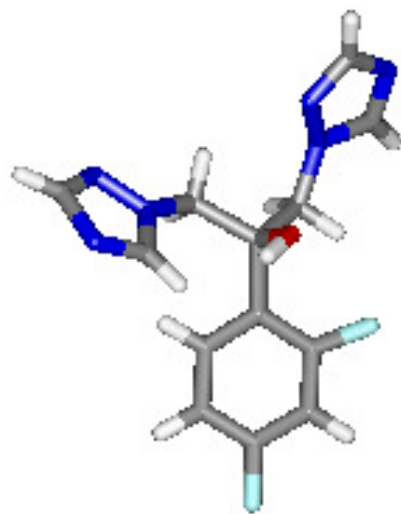


UK46245

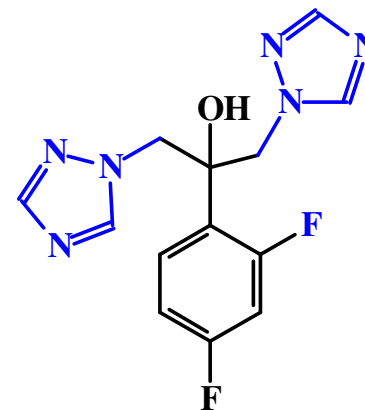
Gênese do Fluconazol



Simplificação
molecular



fluconazol

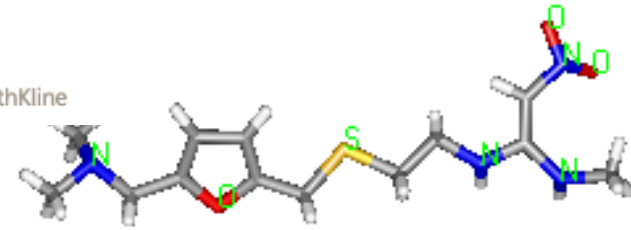
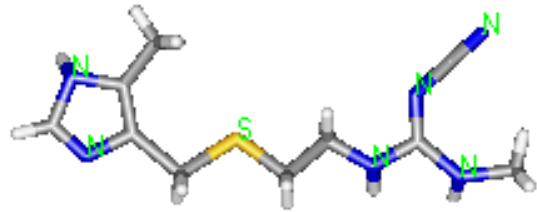


fluconazol

UK49858



Bioisosterismo & fármacos *me-too*



Cimetidina

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

me-too

Ranitidina

Barry J. Price *et al.*, 1978
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