Disciplina: SQM0485

Prof. Dr. Andrei Leitão

Isomeria constitucional

1. Isômeros são diferentes compostos com a mesma fórmula.

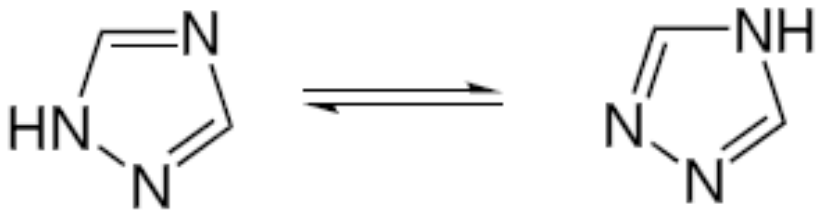
2. Isômeros constitucionais se diferem pela ordem de conexão dos átomos.

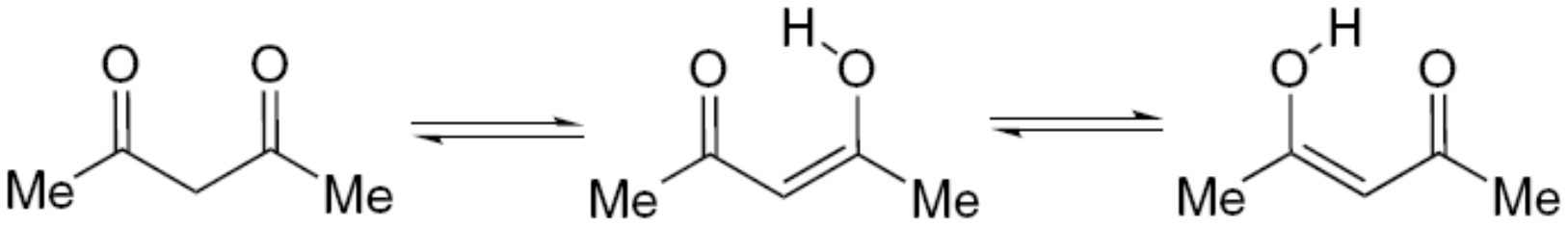
Fórmula Molecular	Número de isômeros constitucionais possíveis
C_4H_{10}	2
C_5H_{12}	3
C_6H_{14}	5
C_7H_{16}	9
C_8H_{18}	18
C_9H_{20}	35

Isomeria constitucional

Fórmula Molecular	*Isômeros Constitucionais*		
C_4H_{10}	$CH_3CH_2CH_2CH_3$ **Butano**	e	$CH_3CH(CH_3)CH_3$ **Isobutano**
C_3H_7Cl	$CH_3CH_2CH_2Cl$ **1-Cloropropano**	e	$CH_3CH(Cl)CH_3$ **2-Cloropropano**
C_2H_6O	CH_3CH_2OH **Etanol**	e	CH_3OCH_3 **Éter dimetílico**

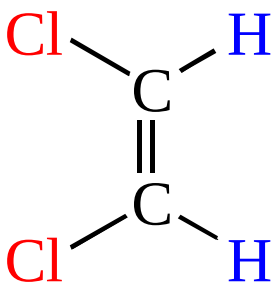
Isomeria constitucional



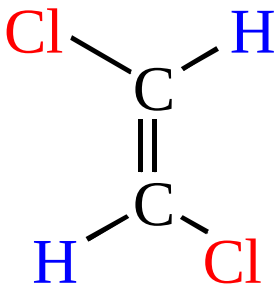


Esteroisômeros

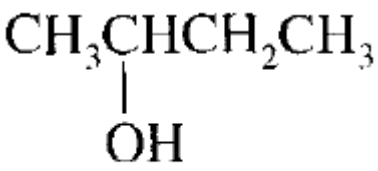
Estereoisômeros se diferem apenas pelo arranjo dos átomos no espaço. Não são isômeros constitucionais.



cis-1,2-Dichloroethene ($C_2H_2Cl_2$)
Z-1,2-Dichloroethene ($C_2H_2Cl_2$)



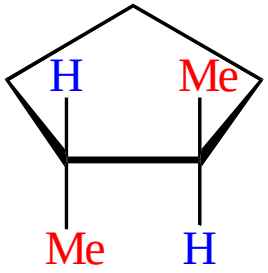
trans-1,2-Dichloroethene ($C_2H_2Cl_2$)
E-1,2-Dichloroethene ($C_2H_2Cl_2$)



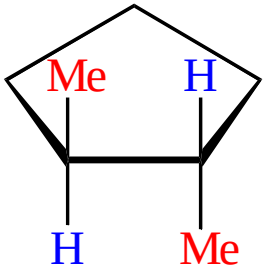
2-Butanol

Esteroisômeros (2)

Enantiômeros são imagens especulares não superponíveis.

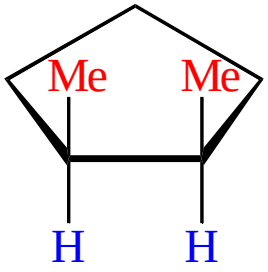


trans-1,2-Dimethylcyclopentane (C_7H_{14})

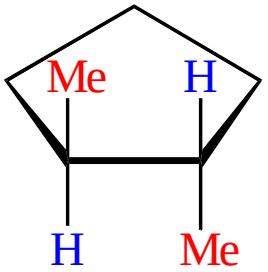


trans-1,2-Dimethylcyclopentane (C_7H_{14})

Diastereômeros não são imagens especulares.



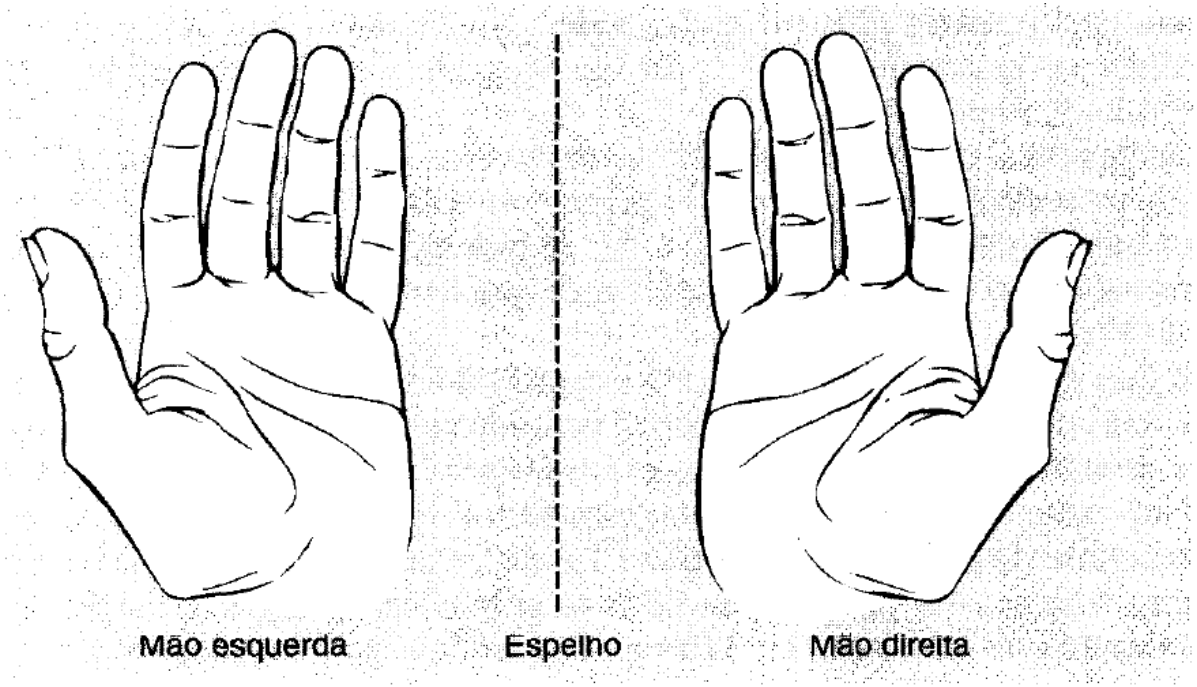
cis-1,2-Dimethylcyclopentane (C_7H_{14})

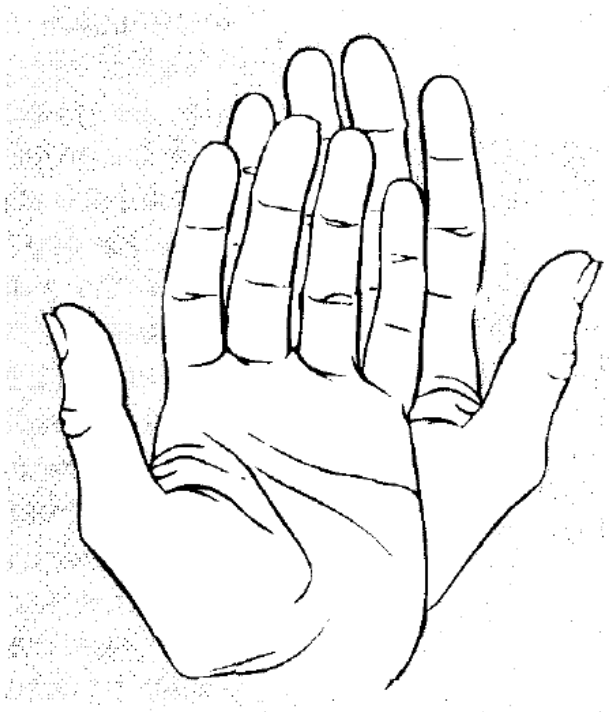


trans-1,2-Dimethylcyclopentane (C_7H_{14})

Esteroisômeros - enantiômeros

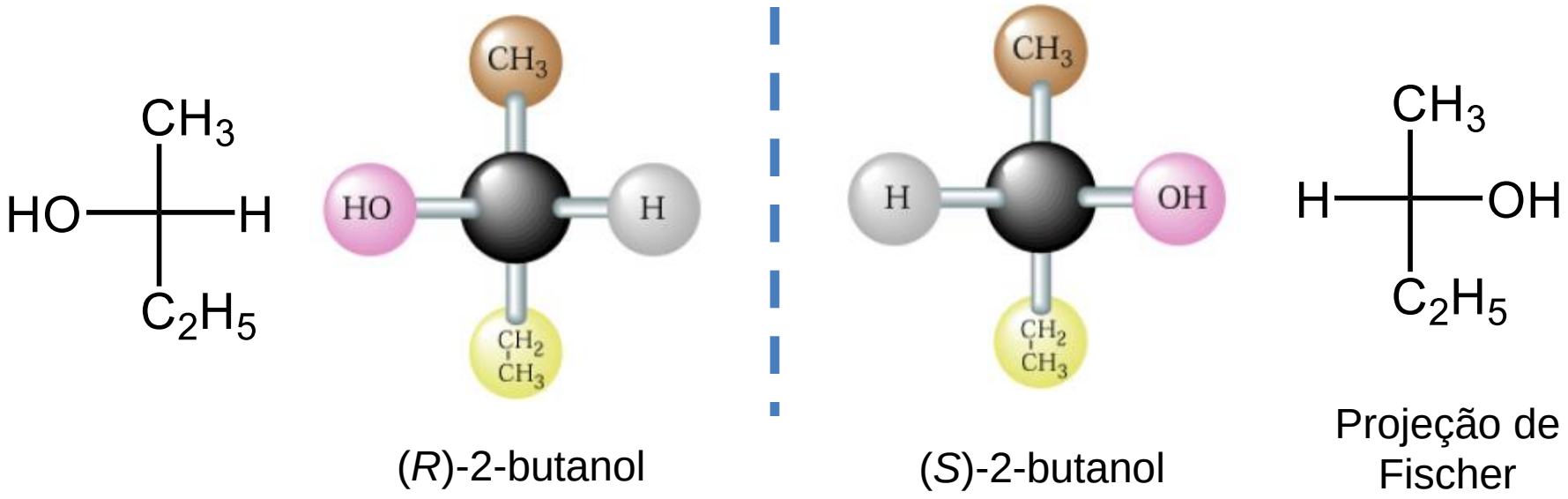
Estereoisômeros se diferem apenas pelo arranjo dos átomos no espaço. Não são isômeros constitucionais.





Estereoisomeria - Enantiômero

✓ Enantiômeros são distinguidos pela luz plano-polarizada e são a imagem especular um do outro (não se superpõem):



(*R*)-2-butanol

(*S*)-2-butanol

Projeção de Fischer

✓ O carbono assimétrico é um centro quiral

Regra de Cahn-Ingold-Prelog

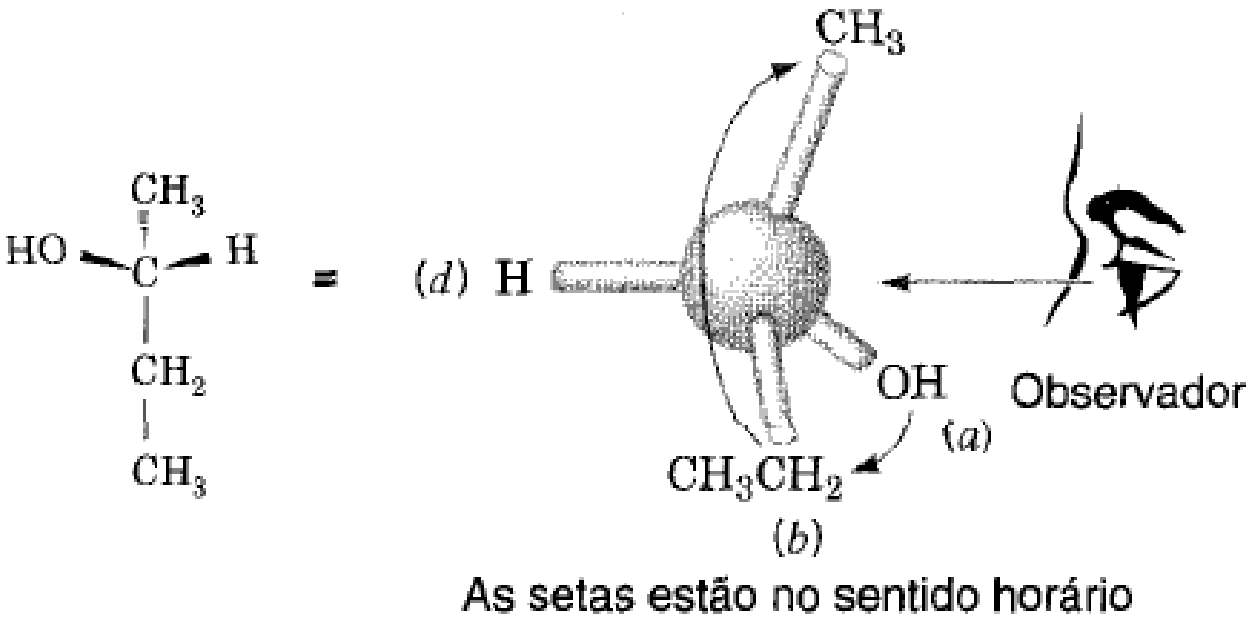
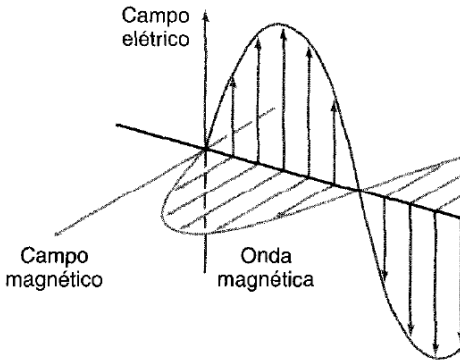
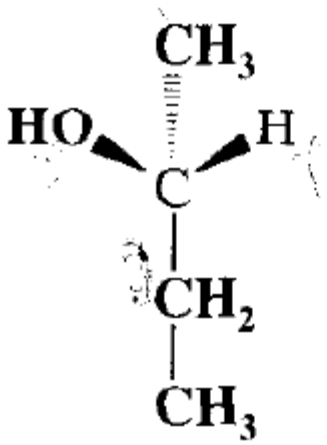


Tabela 5.1 Propriedades Físicas de (*R*)- e (*S*)-2-Butanol

Propriedade Física	(*R*)-2-Butano	(*S*)-2-Butanol
Ponto de ebulição (1 atm)	99,5°C	99,5°C
Densidade (g mL^{-1} a 20°C)	0,808	0,808
Índice de refração (20°C)	1,397	1,397

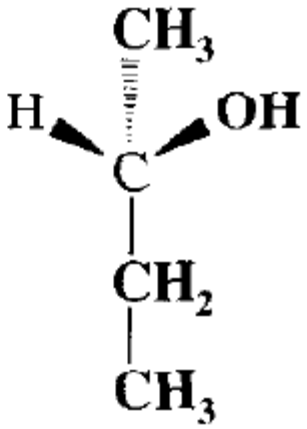
Desvio da luz plano-polarizada





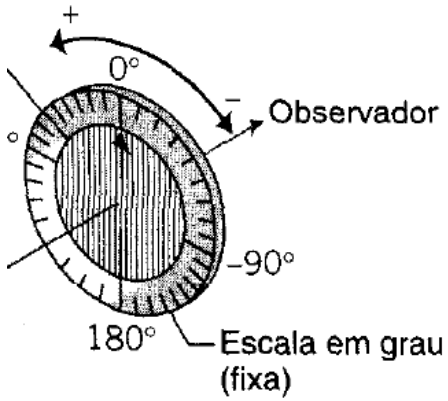
(*R*)-2-Butanol

$[\alpha]_D^{25} = -13{,}52°$



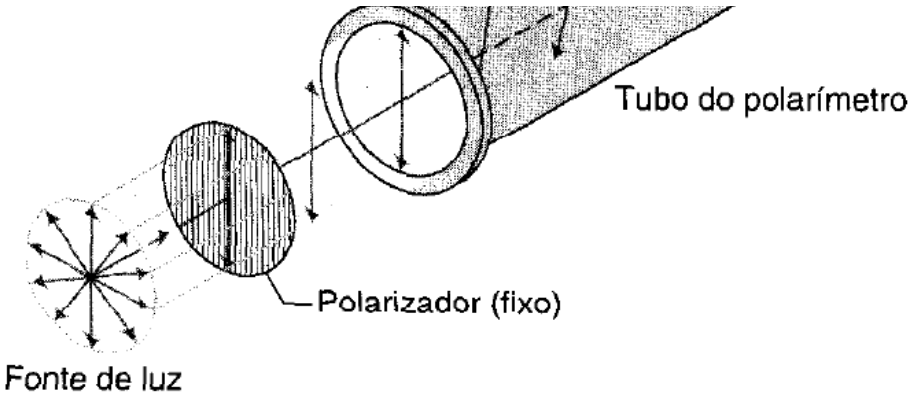
(*S*)-2-Butanol

$[\alpha]_D^{25} = +13{,}52°$



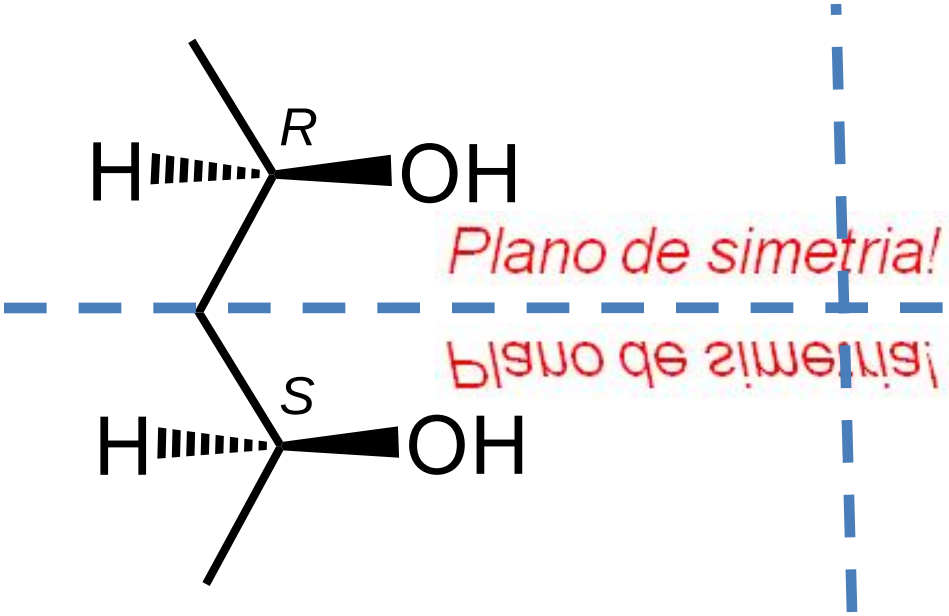
O plano de polarização da luz emergente não é o mesmo da luz polarizada de entrada.

Polarizador

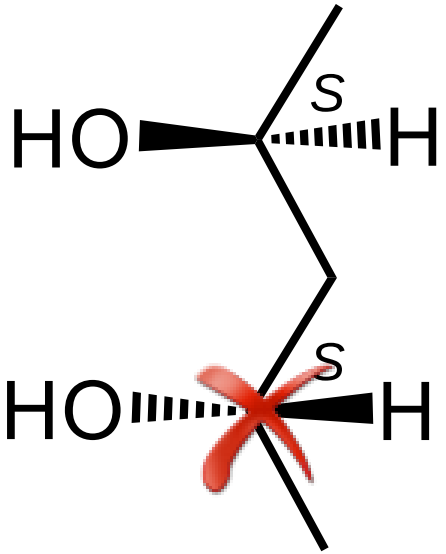


Estereoisomeria - Diastereômero

- ✓ Diastereômeros não são imagem especular um do outro:



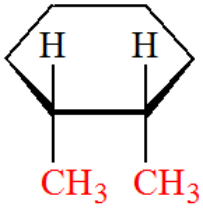
(2R,4S)-pentano-2,4-diol



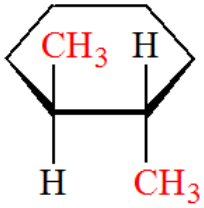
(2S,4S)-pentano-2,4-diol

Isomeria

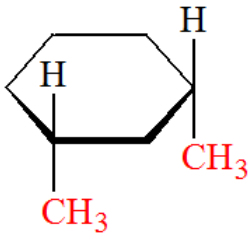
Substituinte	Isômero	PF (°C)	PE (°C)
1,2-Dimethyl-	*Z ou cis*	–50,1	130,04
1,2-Dimethyl-	*E ou trans*	–89,4	123,7
1,3-Dimethyl-	*Z ou cis*	–75,6	120,1
1,3-Dimethyl-	*E ou trans*	–90,1	123,5



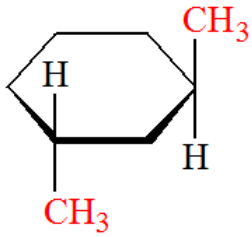
***cis*-1,2-dimetilcicloexano**



***trans*-1,2-dimetilcicloexano**

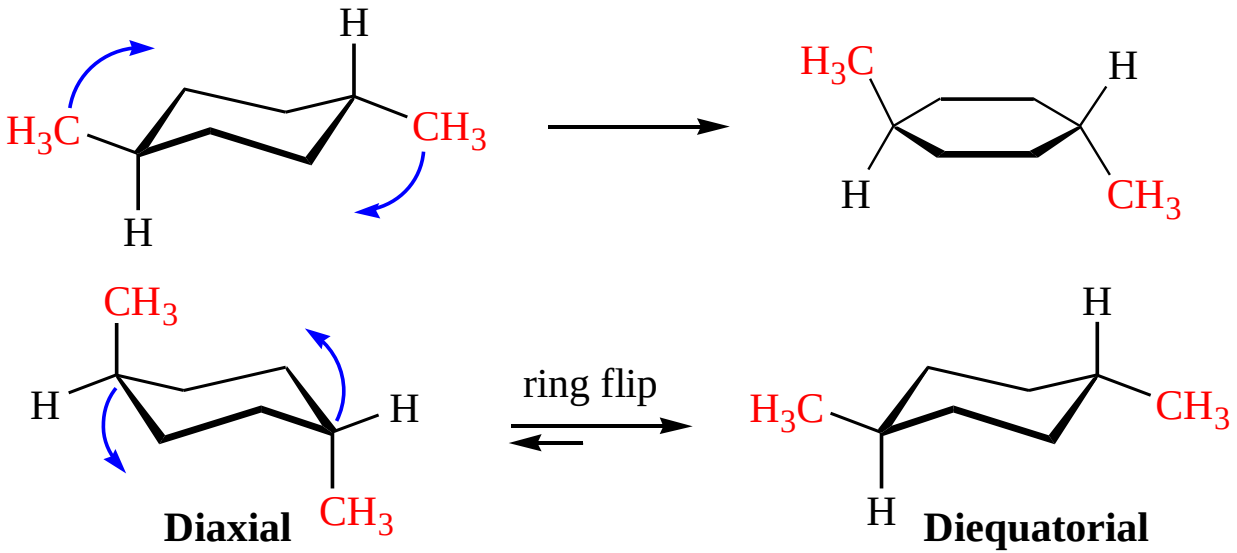


***cis*-1,3-dimetilcicloexano**



***trans*-1,3-dimetilcicloexano**

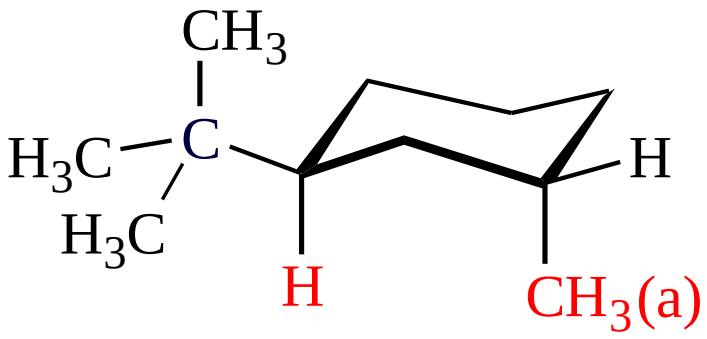
Isomeria

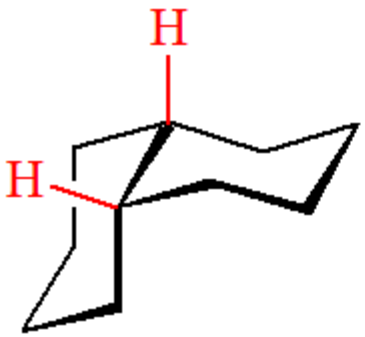


1) **Diaxial** e **diequatorial** *trans*-1,4-dimetilcicloexano.

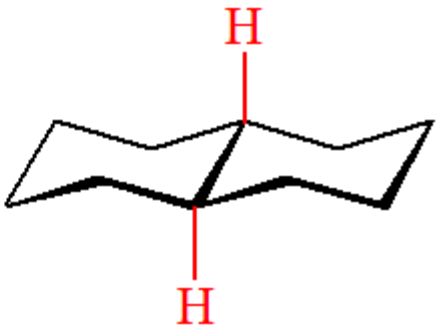
2) A conformação **diequatorial** é a **mais estável** e representa pelo menos 99% das moléculas no equilíbrio.

Isomeria





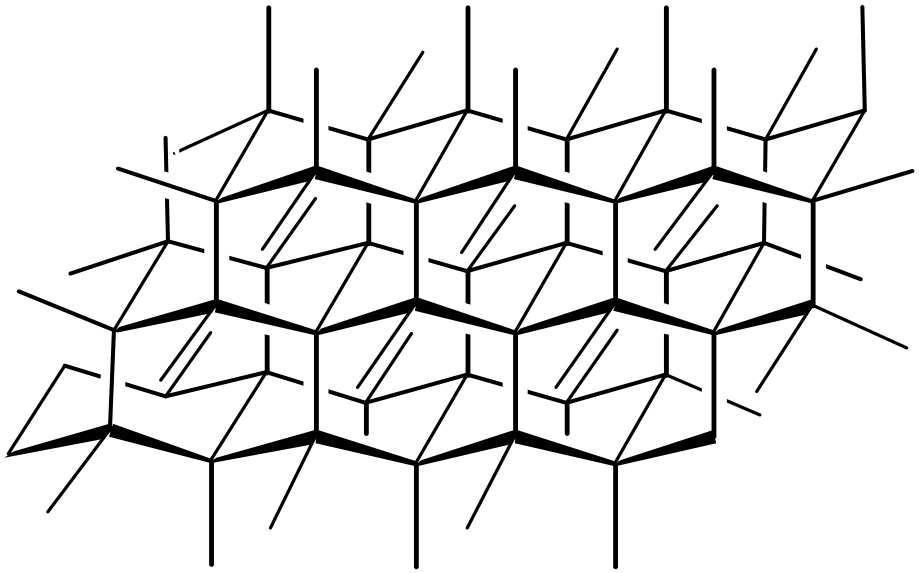
cis-Decalina



trans-Decalina

A *cis*-Decalina ferve a 195°C e a *trans*-decalina ferve a 185.5°C

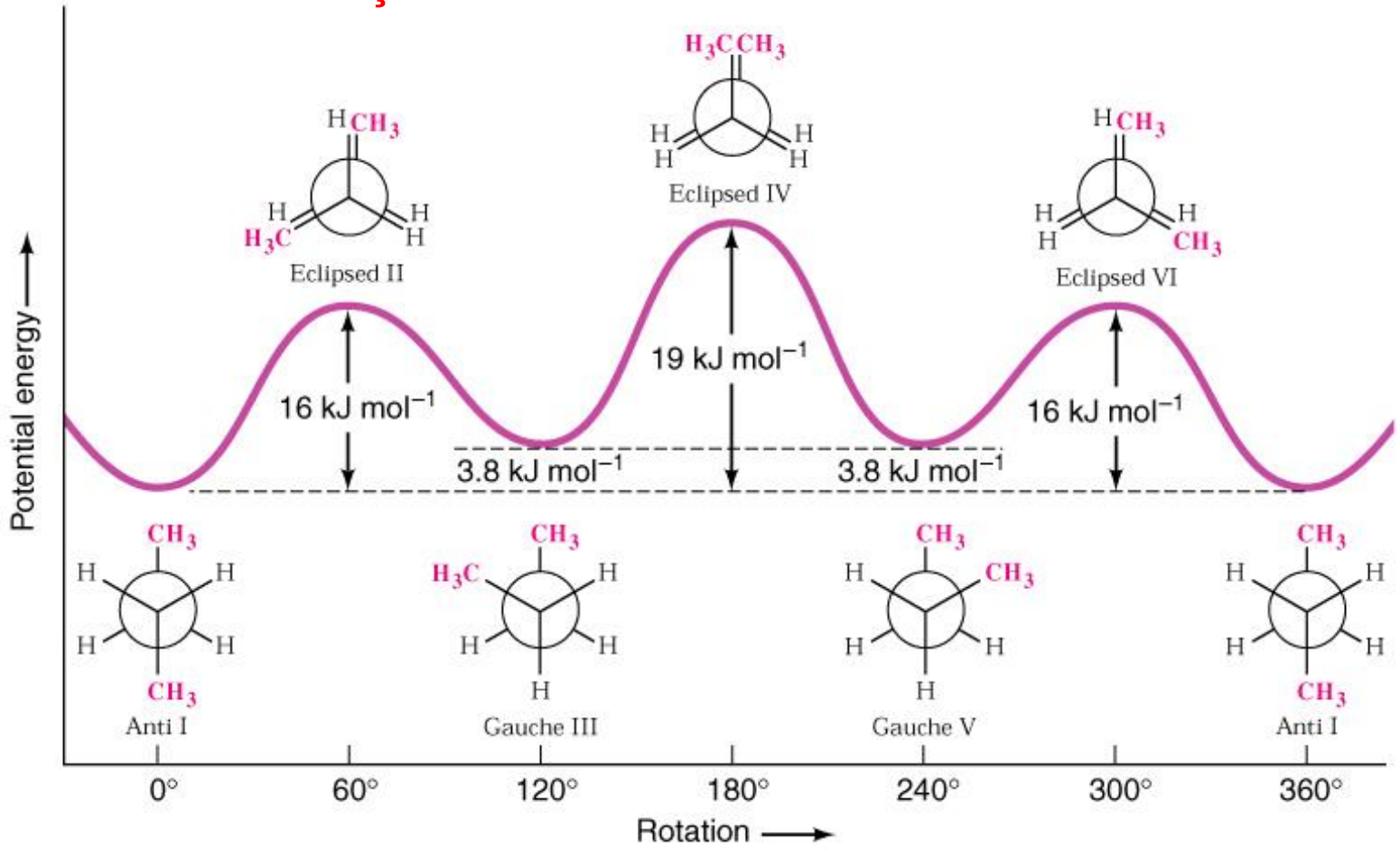
Estrutura de policiclos



Diamante

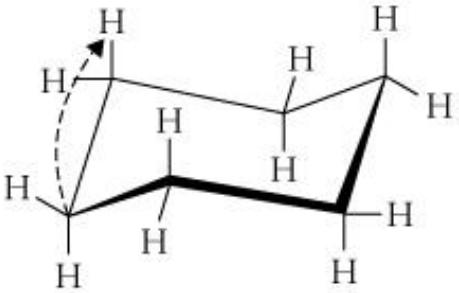
Diferença entre conformação e configuração

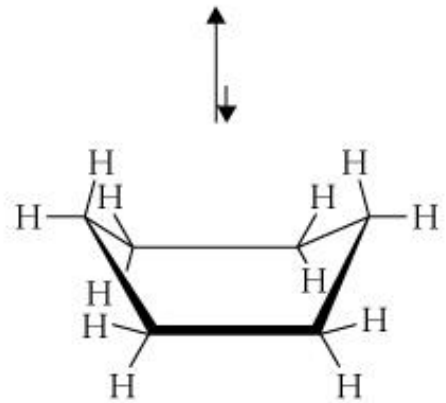
Conformação



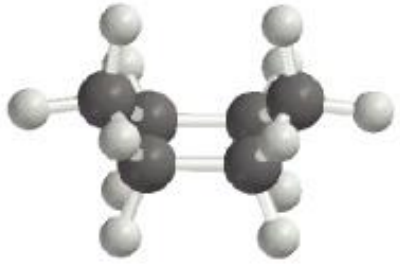
Diferença entre conformação e configuração (2)

Conformação





(a)

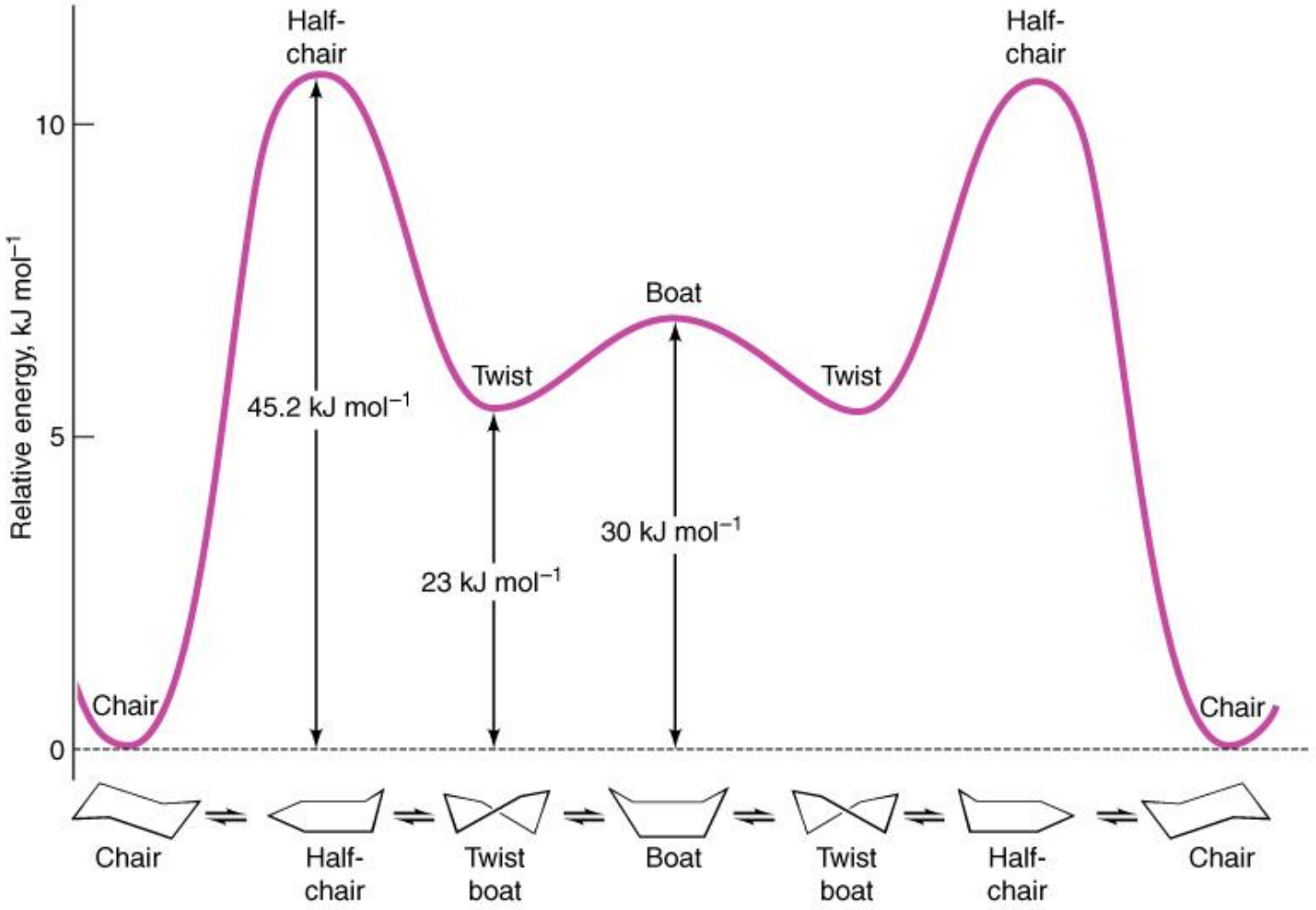


(b)

(c)

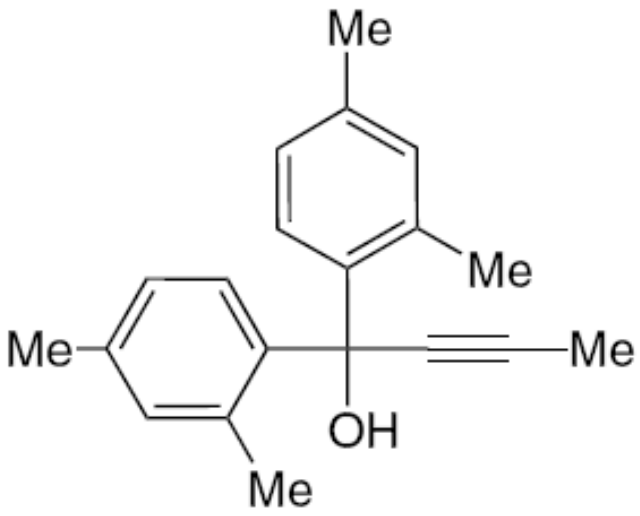
Diferença entre conformação e configuração (3)

Conformação



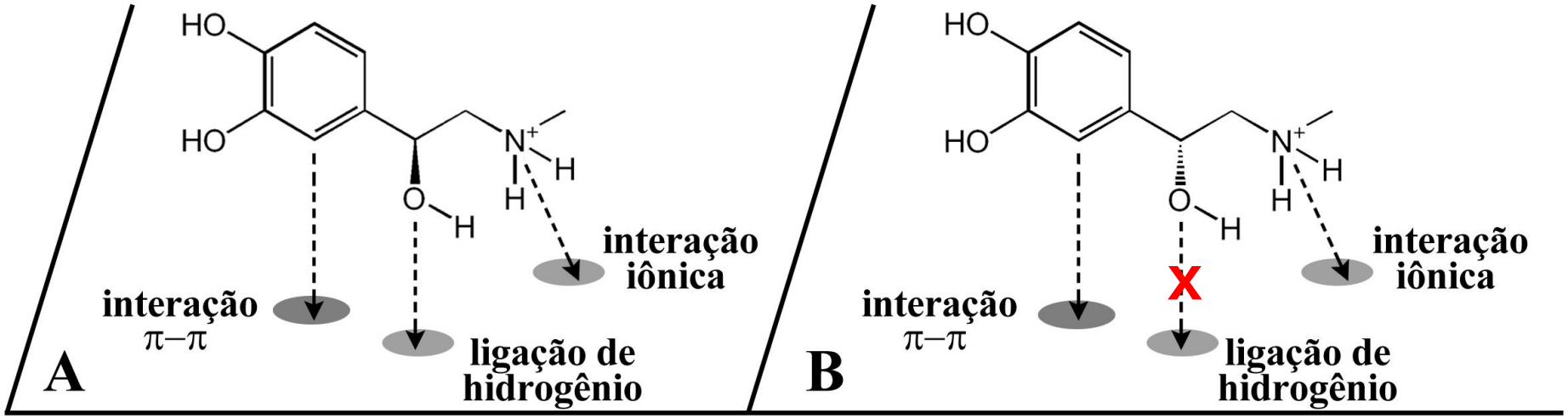
Estereoquímica

✓ **Há um centro esterogênico?**



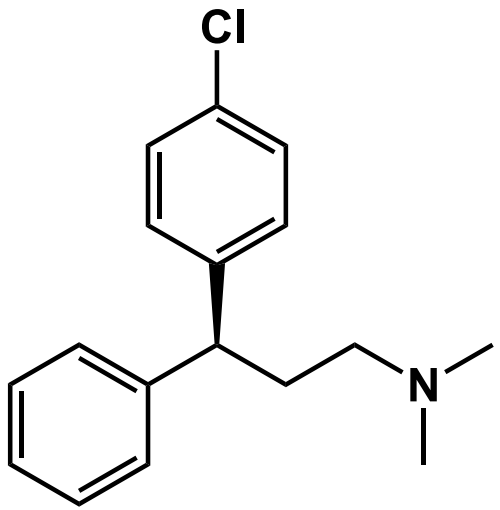
Estereoisômeros na farmacodinâmica

✓ Forma-se um co-complexo diastereoisomérico, com diferente afinidade:



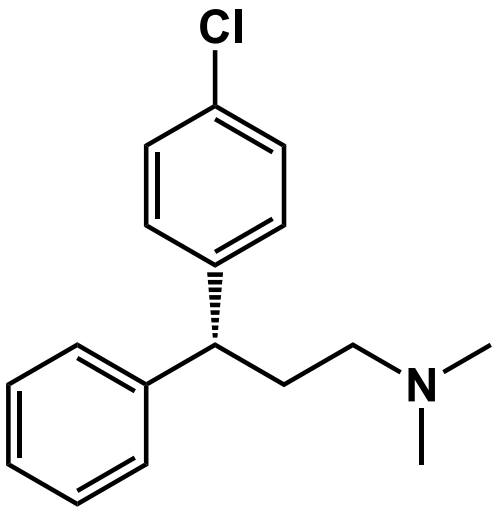
Estereoisômeros na farmacodinâmica
Exemplos:

✓ Enantiômero *S* é um inibidor 83 vezes mais potente que o *R* no receptor H1



(*S*)-clorfeniramina

Polaramine®

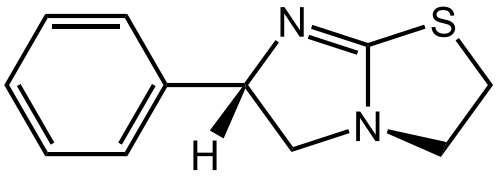


(*R*)-clorfeniramina

Estereoisômeros na farmacodinâmica
Exemplos:

- ✓ Diferentes atividades farmacológicas de enantiômeros:

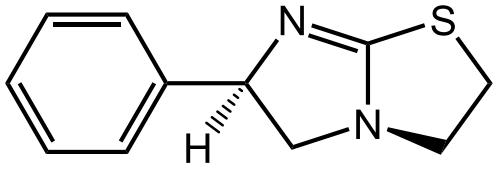
Nematocida
Imunoestimulante



Ascaridil®

(*S*) **levamisol**

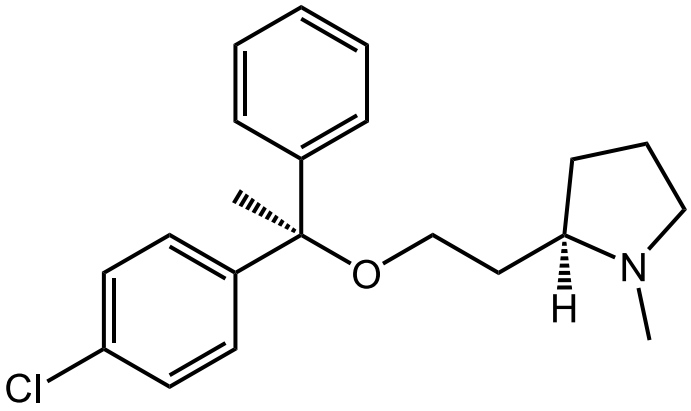
Anti-depressivo



(*R*) **dexamisol**

Estereoisômeros na farmacodinâmica
Exemplos:

✓ Atividade anti-histamínica da clemastina



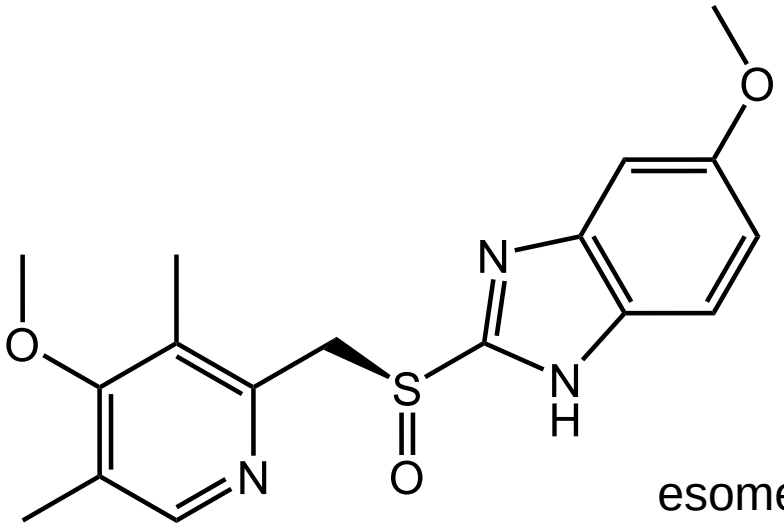
(*R*,*R*)-clemastina

Isômero	-logA_2	Prevenção da toxidez (mg kg^{-1})*
RR (clemastina)	9,45 ⇐	0,04
SS	7,99	5,1
SR	8,57	11,0
RS	9,40 ⇐	0,28

*A histamina causa espasmos no(a) alérgico(a)

Estereoisômeros na farmacocinética e toxicologia

✓ O esomeprazol é o estereoisômero *S* puro do omeprazol (disponível como racemato) lançado pela AstraZeneca

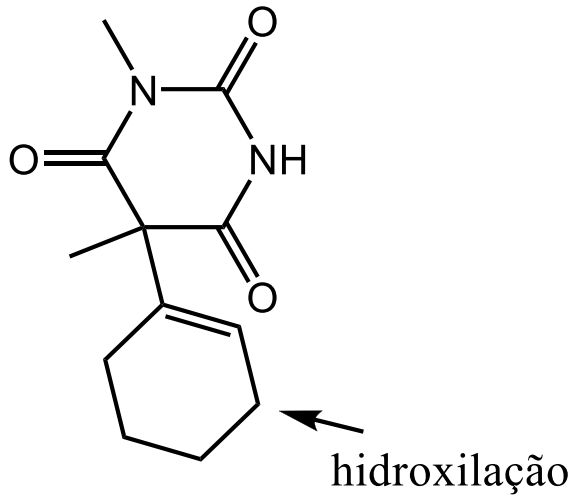


esomeprazol

Estereoisômeros na farmacocinética e toxicologia

✓ Hexobarbital

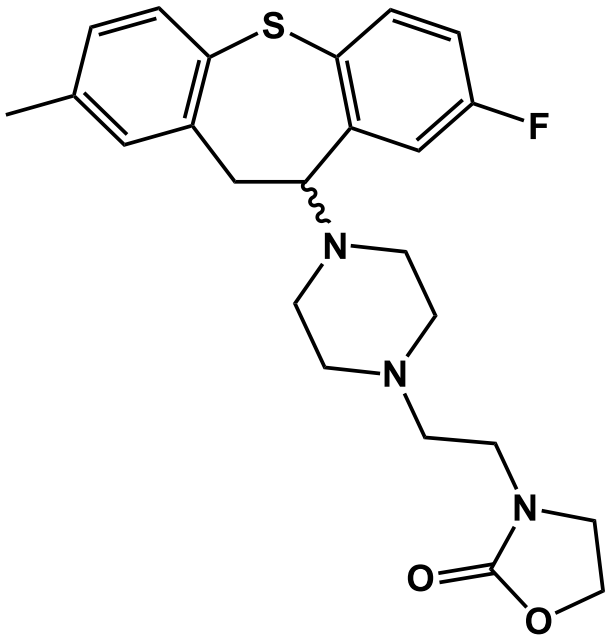
✓ Enantiômero *S* é metabolizado duas vezes mais rápido do que *R*



hexobarbital

Estereoisômeros
Estudo integrado

- ✓ Neuroléptico tricíclico clotepina

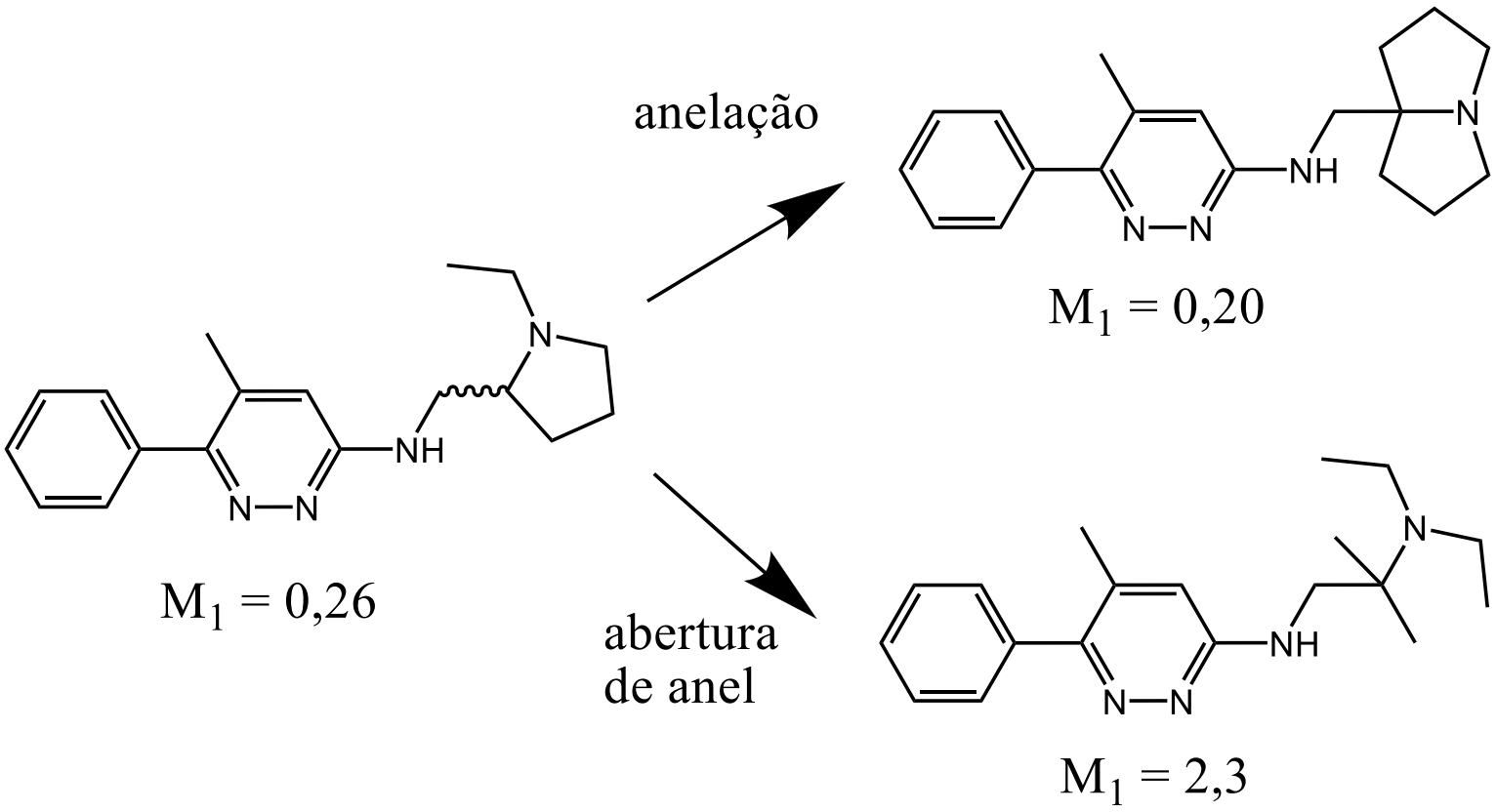


Teste	Estereoisômero		
	Rac.	***S***	***R***
% inibição da adenilato ciclase[a]	48	72	27
ED_{50} (mg kg^{-1})[b]	20	12	>30
LD_{50} (mg kg^{-1})[c]	200	515	68

[a] Concentração estudada: 1 μM
[b] Inibição do vômito em cães
[c] Toxidez aguda em camundongos
Rac. = racemato

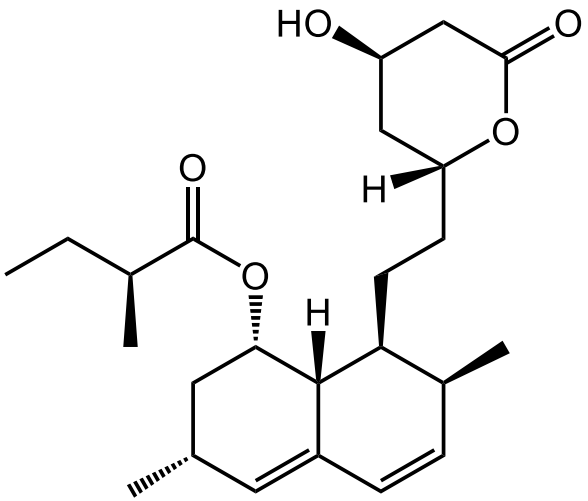
Eliminação de centros quirais
Abertura de anel ou anelação

- ✓ A introdução de simetria foi conseguida em ambos os casos



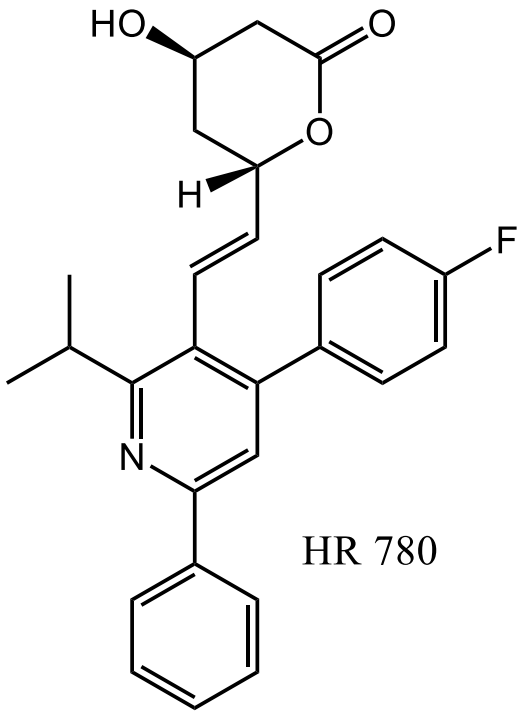
Redução de centros quirais
Simplificação molecular

- ✓ Inibidor da HMG-CoA redutase: redução do colesterol



mevinolina

8 centros quirais



HR 780

2 centros quirais

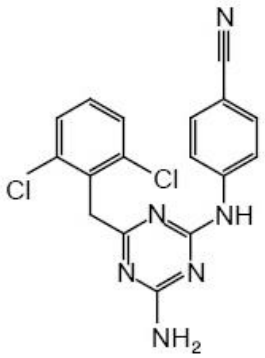
Conformação farmacofórica

✓ O que é a conformação farmacofórica?

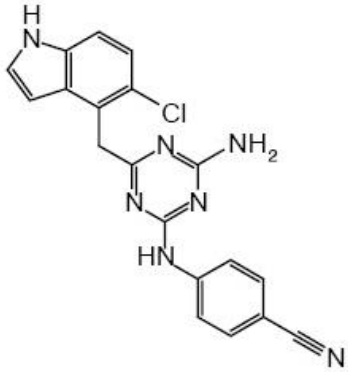
✓ É a conformação assumida pelo composto químico bioativo quando interage com o alvo macromolecular.

✓ A conformação do alvo também pode ser alterada ao interagir com o ligante

Estudo da conformação farmacofórica
Métodos biofísicos diretos

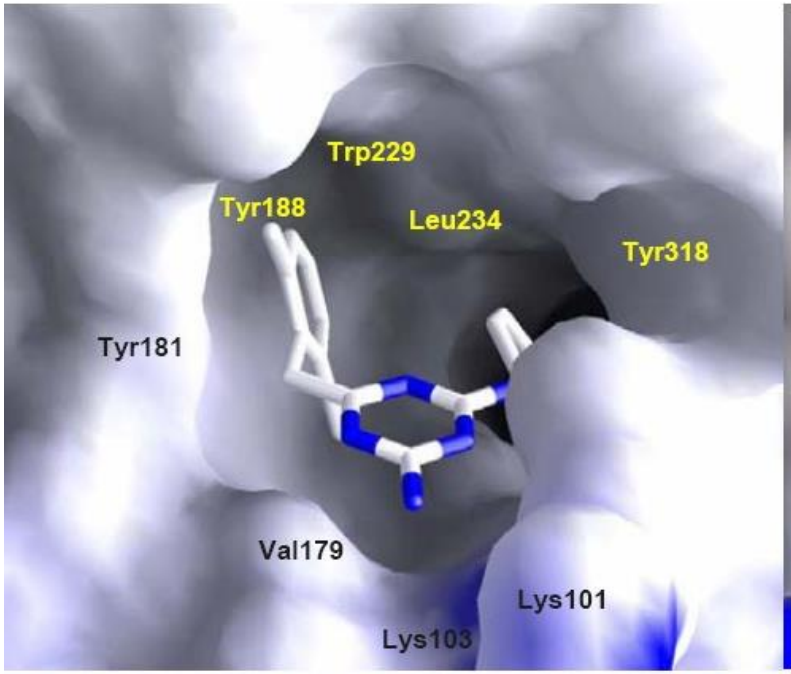


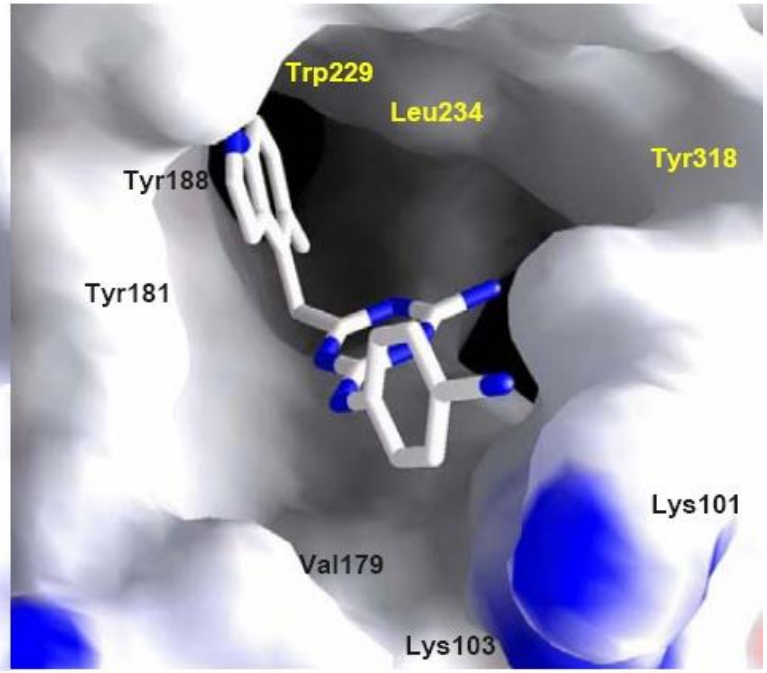
R106168



R120393

transcriptase reversa

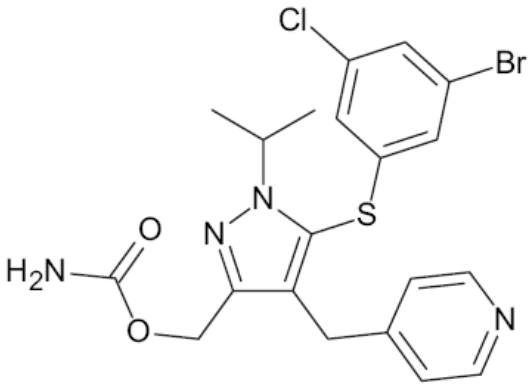




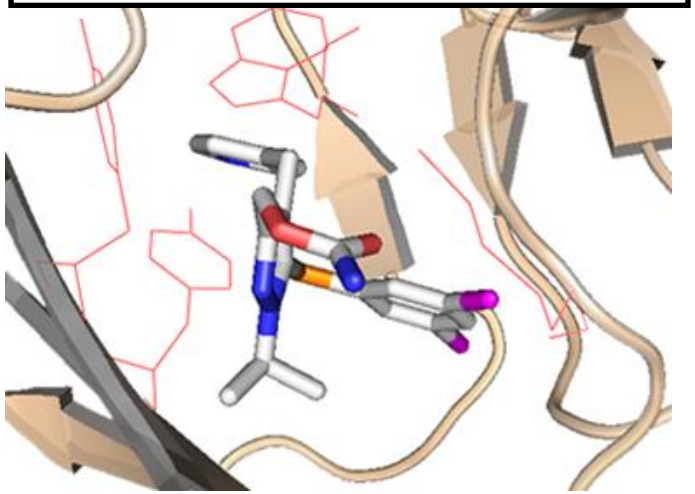
Estudo da conformação farmacofórica
Métodos indiretos

Métodos computacionais

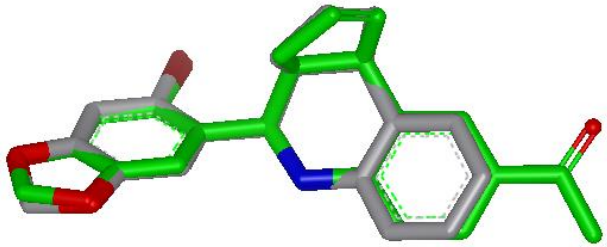
- ✓ Modelagem molecular e docagem

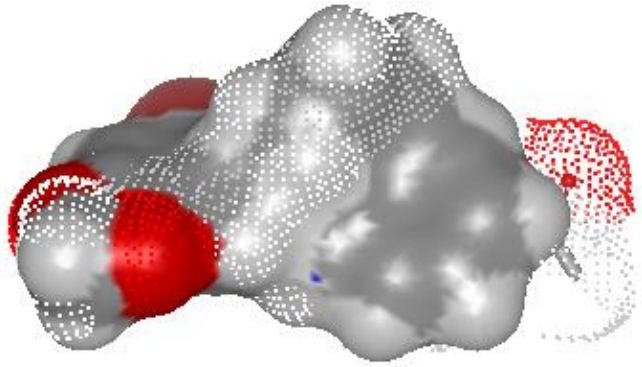


Transcriptase reversa



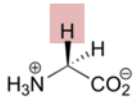
- ✓ Superposição de estruturas

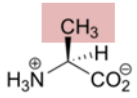


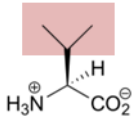


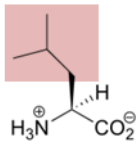
Estereoquímica em proteínas

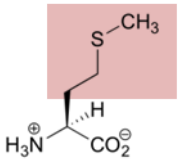
Nonpolar, aliphatic side groups

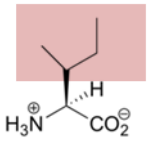

Glycine
Gly, G


Alanine
Ala, A

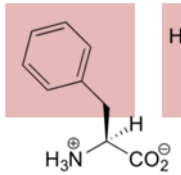

Valine
Val, V

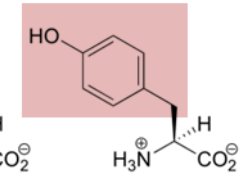

Leucine
Leu, L

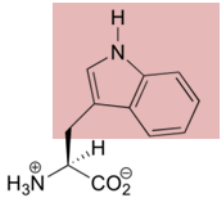

Methionine
Met, M


Isoleucine
Ile, I

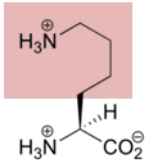
Aromatic side groups

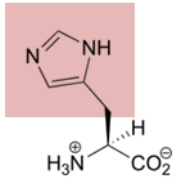

Phenylalanine
Phe, F

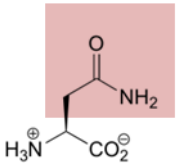

Tyrosine
Tyr, Y


Tryptophan
Trp, W

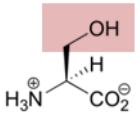
Positively charged side groups

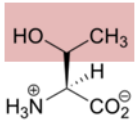

Lysine
Lys, K

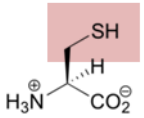

Histidine
His, H

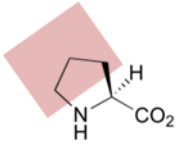

Asparagine
Asn, N

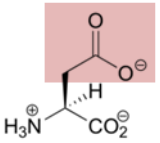
Polar, uncharged side groups

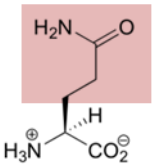

Serine
Ser, S


Threonine
Thr, T

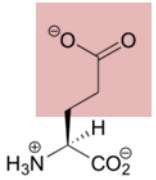

Cysteine
Cys, C

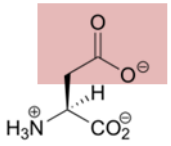

Proline
Pro, P


Aspartate
Asp, D

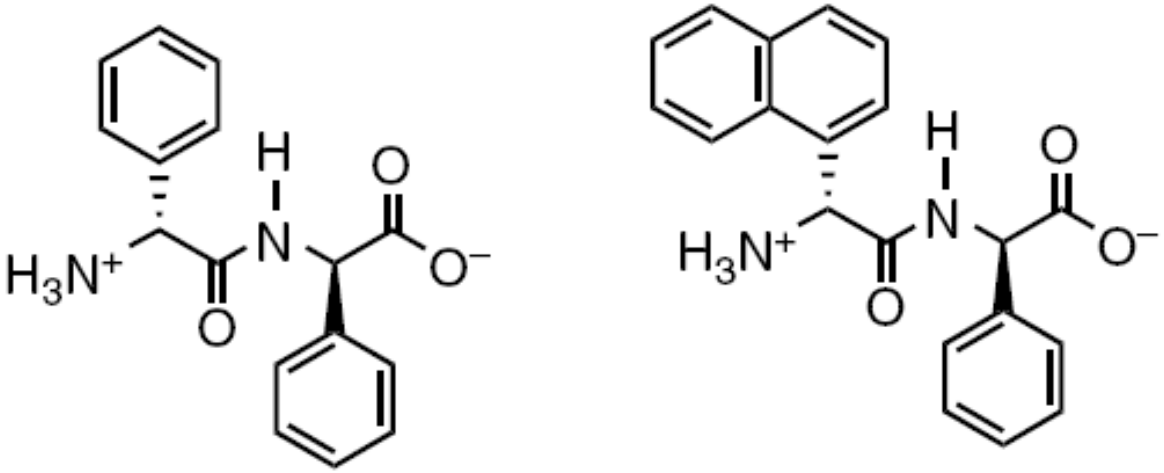

Glutamine
Gln, Q

Negatively charged side groups


Glutamate
Glu, E

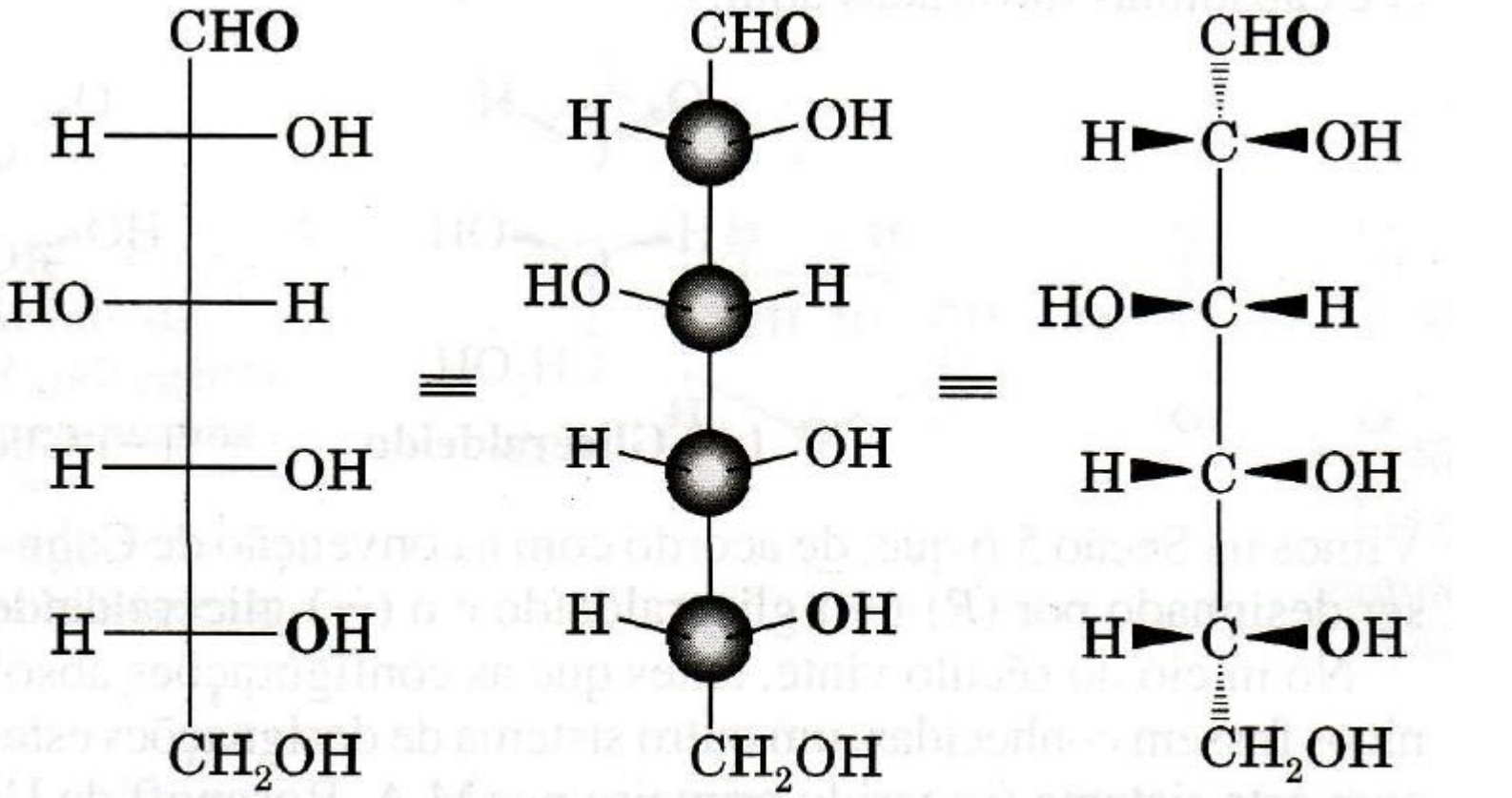

Aspartate
Asp, D

Exemplos



Dipeptídeos

Carboidratos

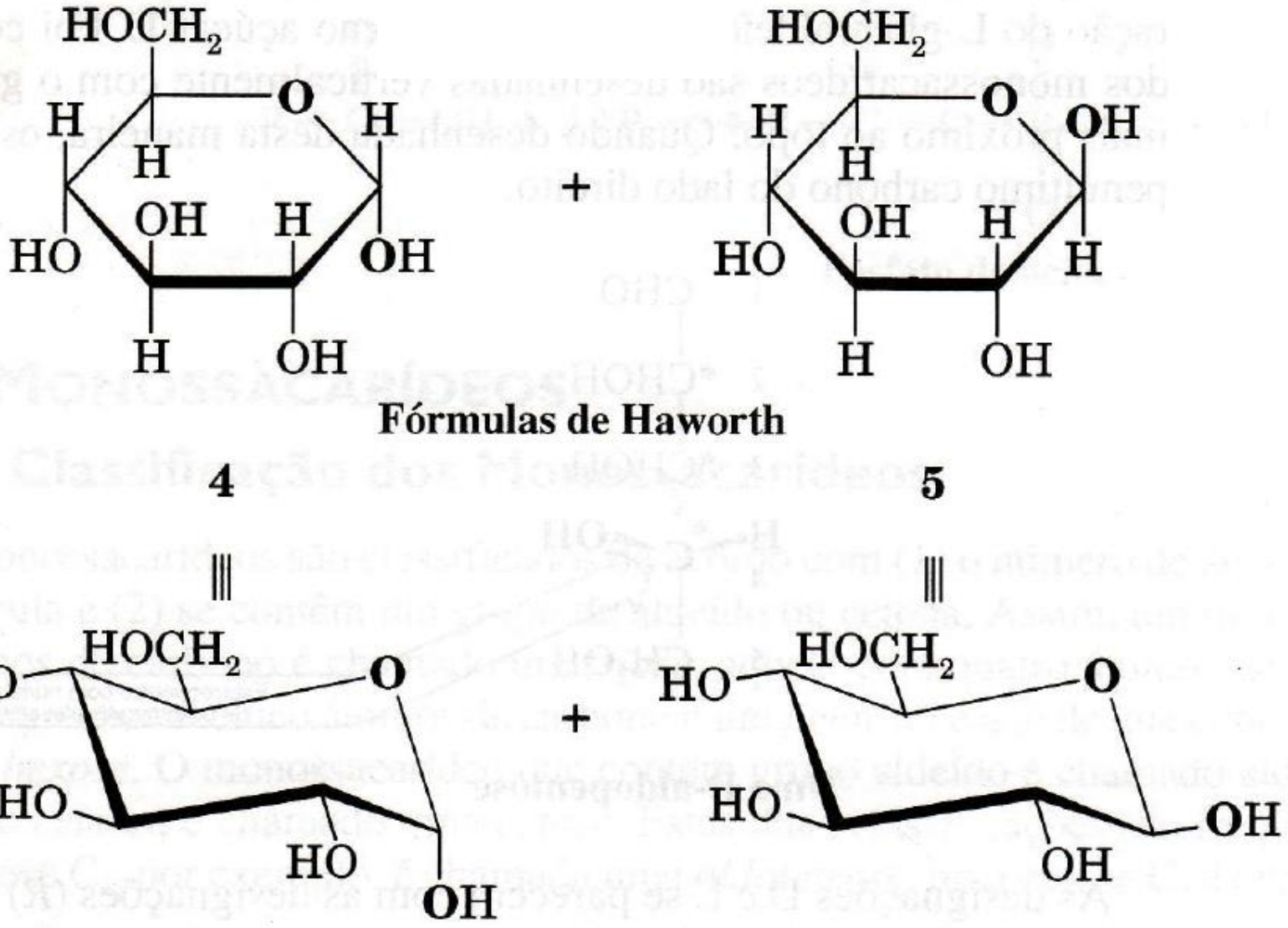


Fórmula de projeção de Fischer

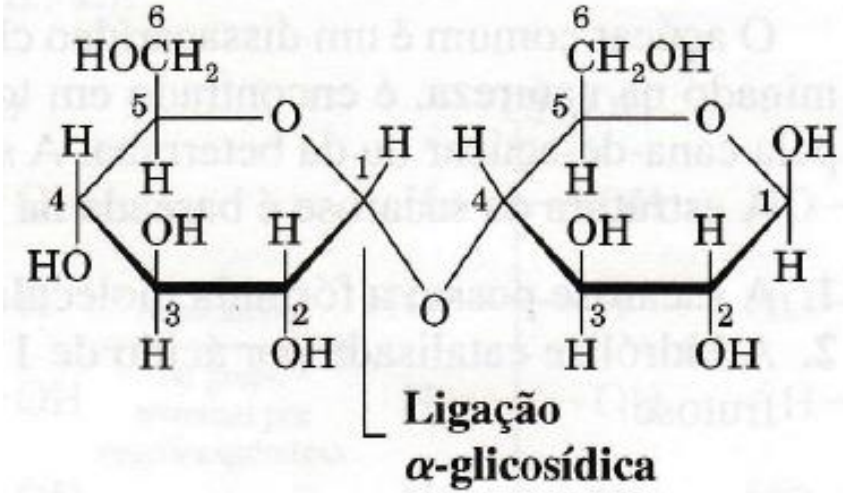
Fórmula de círculo-e-linha

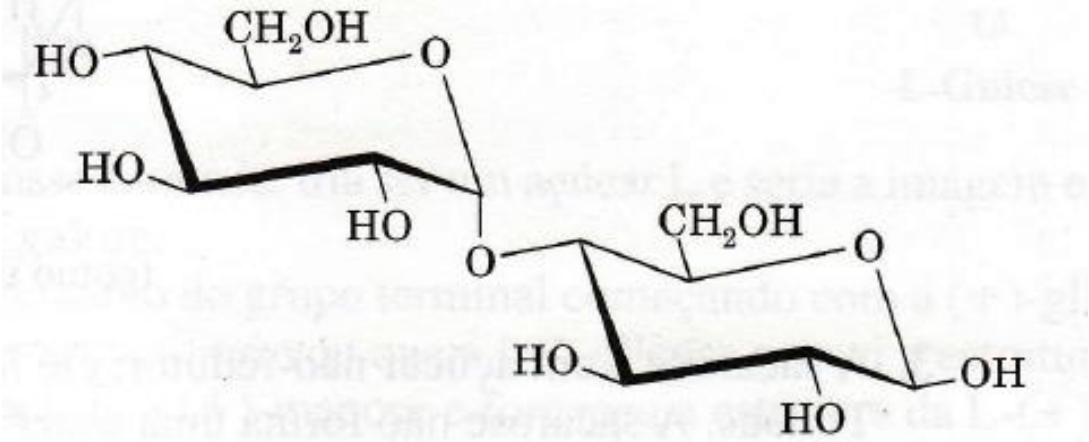
Fórmula de cunha- e-linha-e-cunha tracejada

Carboidratos

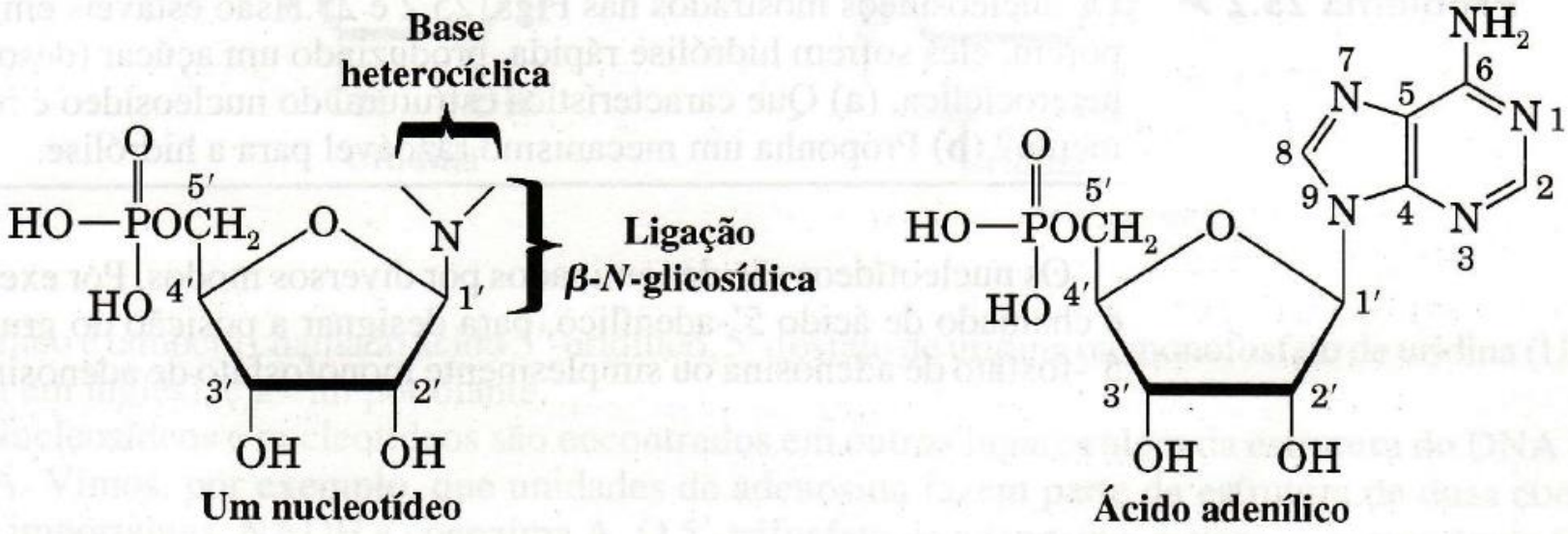


Carboidratos

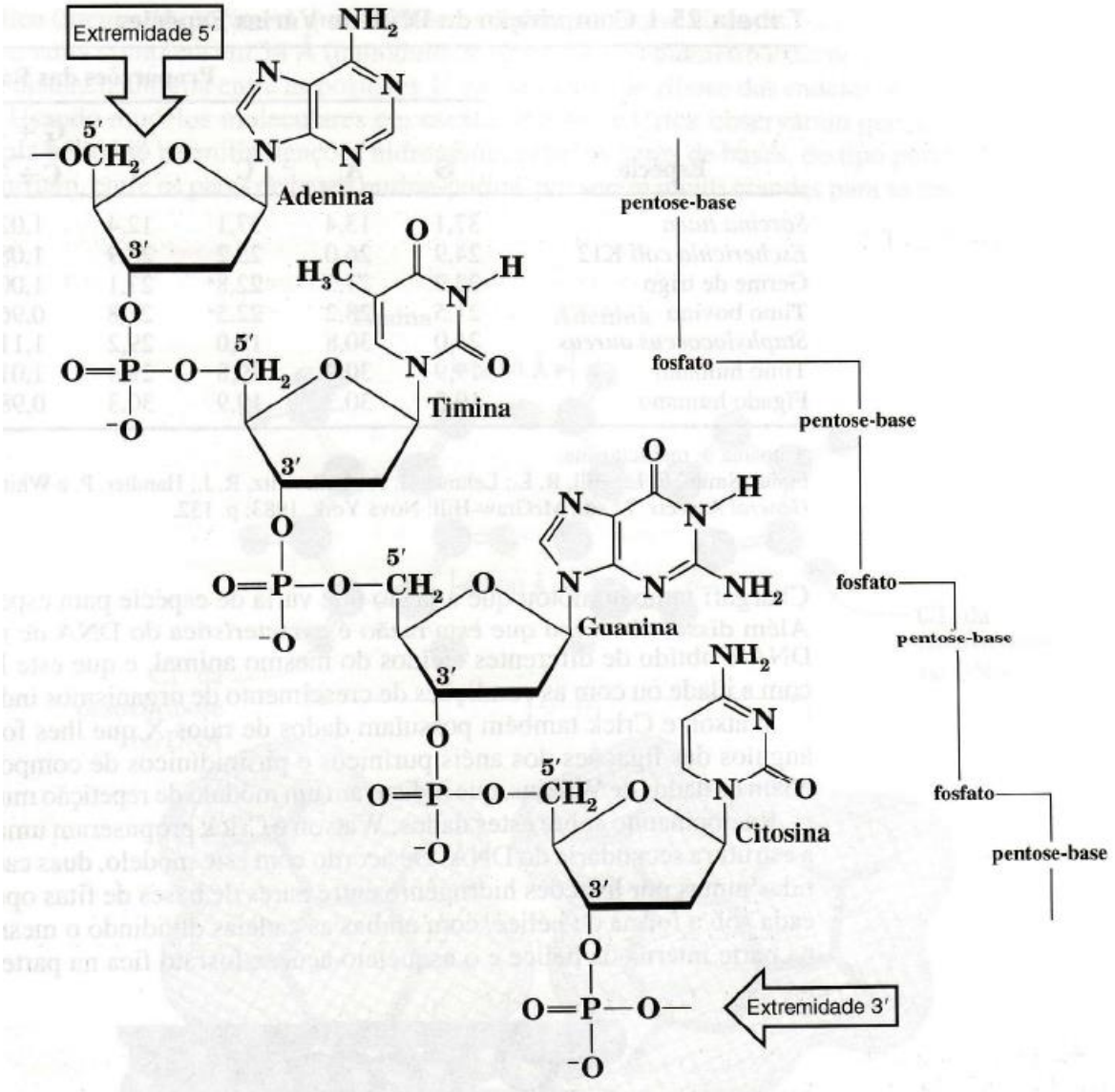




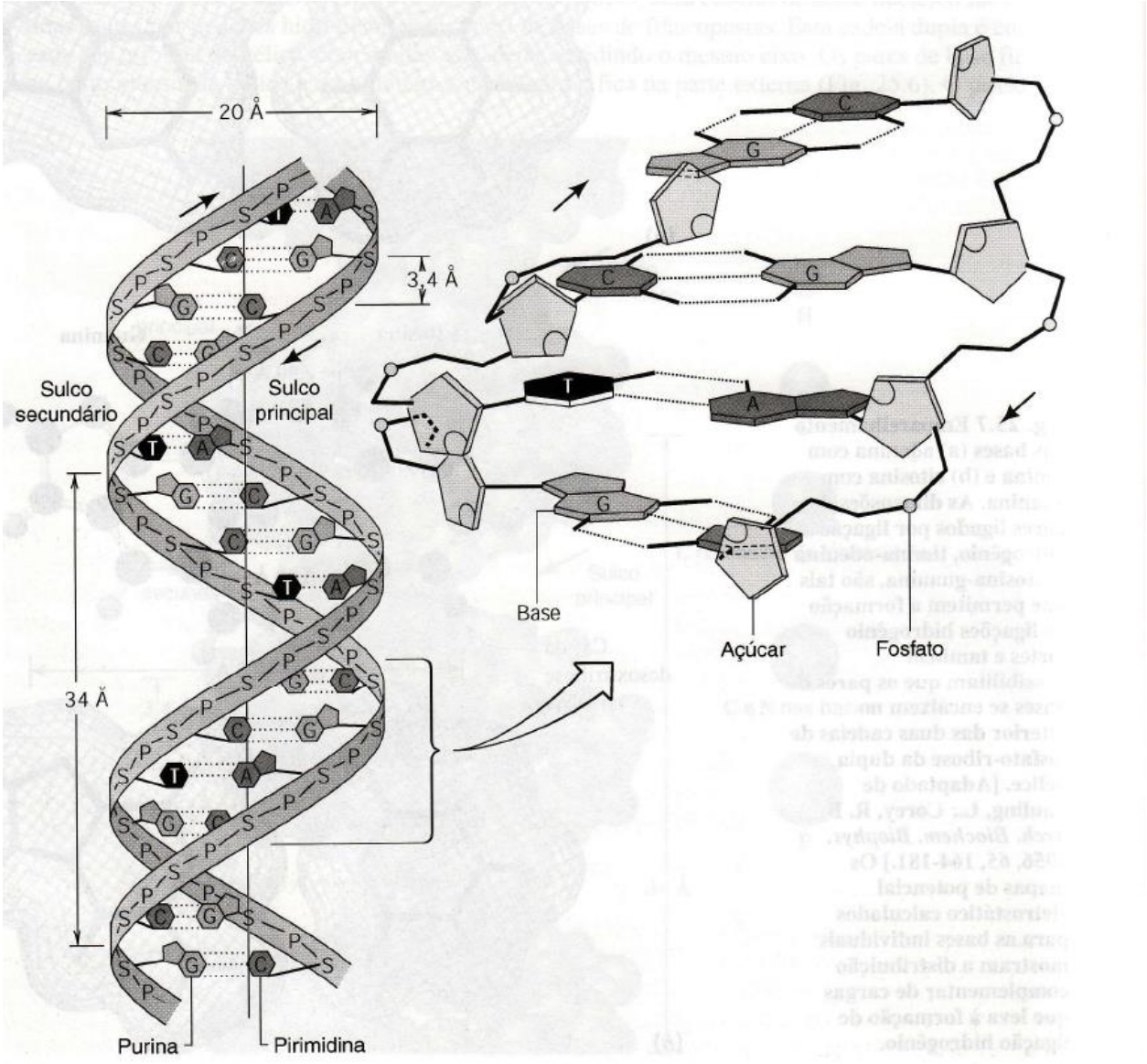
Nucleotídeo



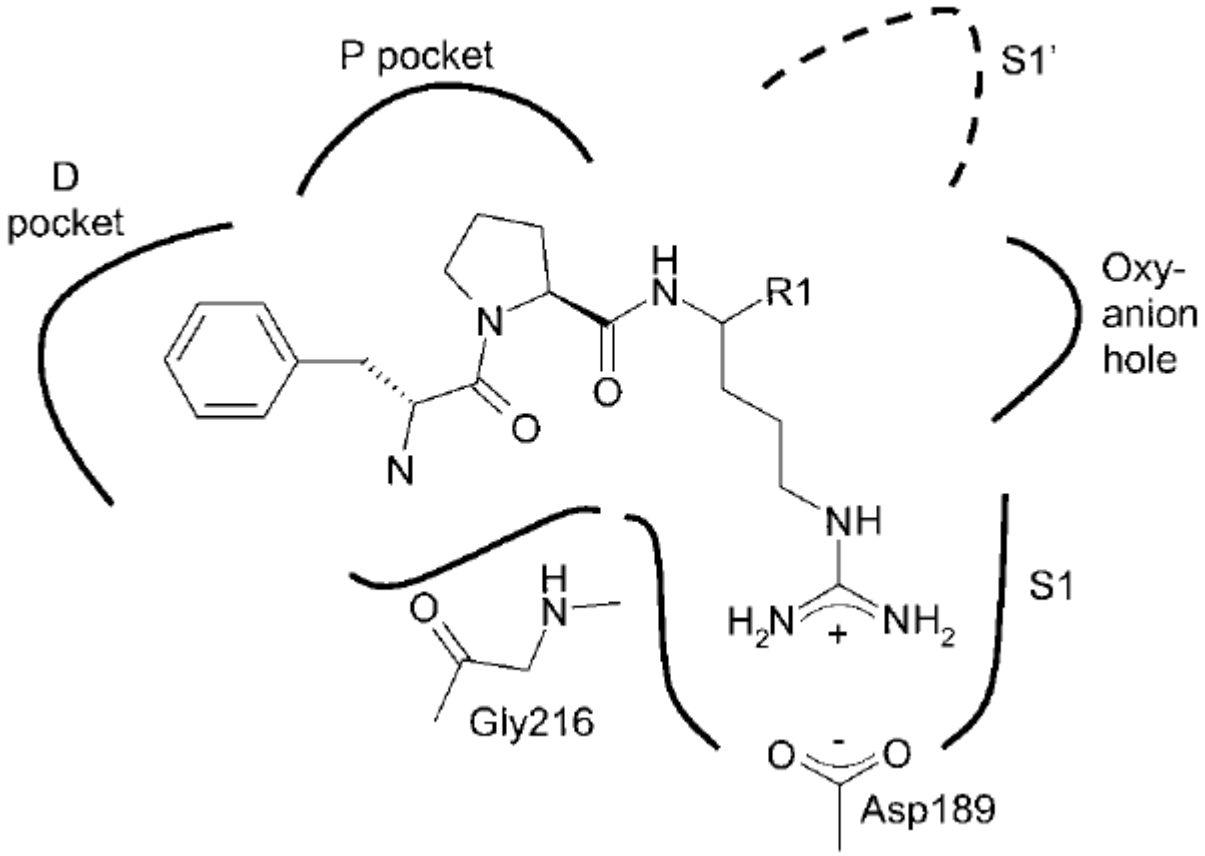
Fragmento de uma fita do DNA



Estrutura do B-DNA

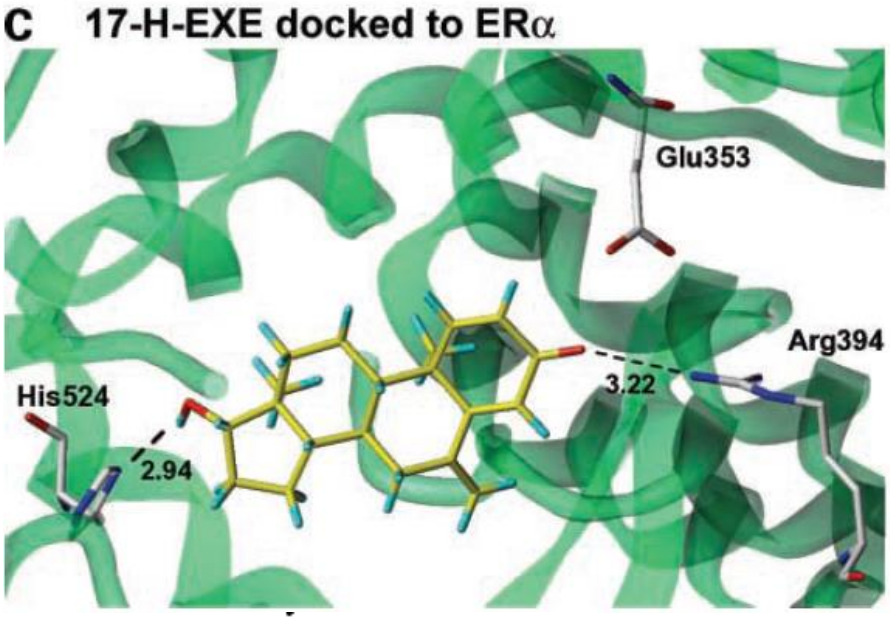


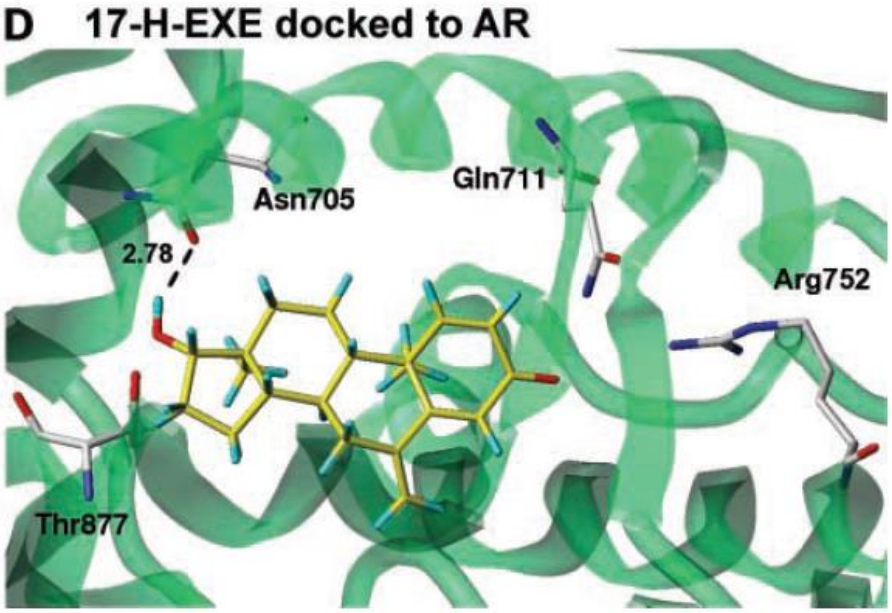
Cocomplexo: proteína-ligante

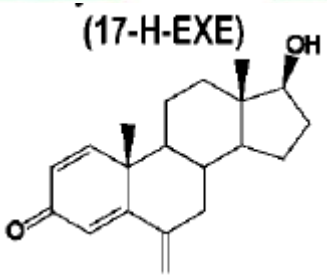


Interações intermoleculares

Interação de exemestano em diferentes receptores nucleares





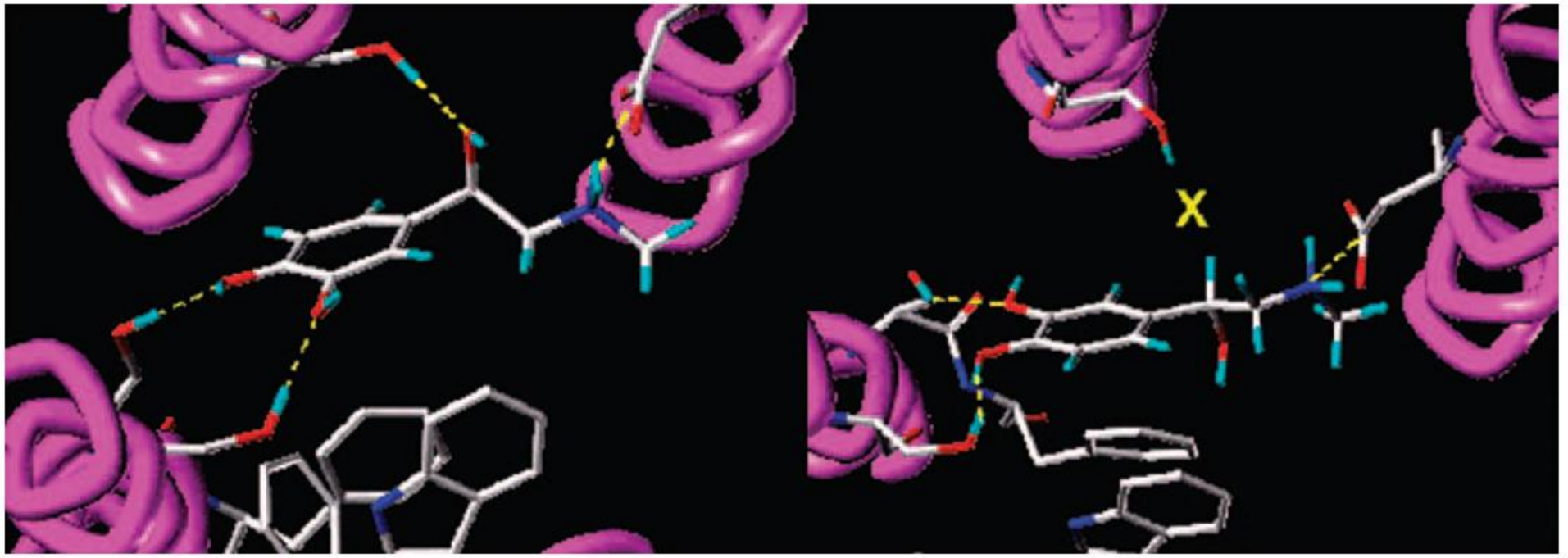


	IC_{50} (μmol L^{-1})
ERα	21,2
AR	39,6

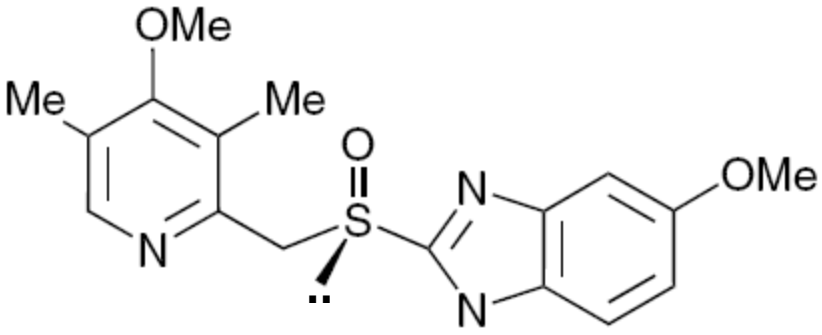
Interações intermoleculares

Epinefrina

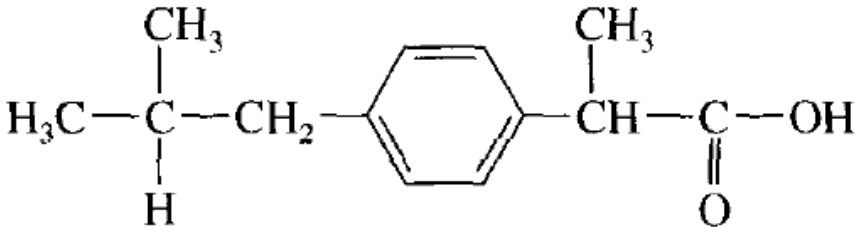
(a) (b)



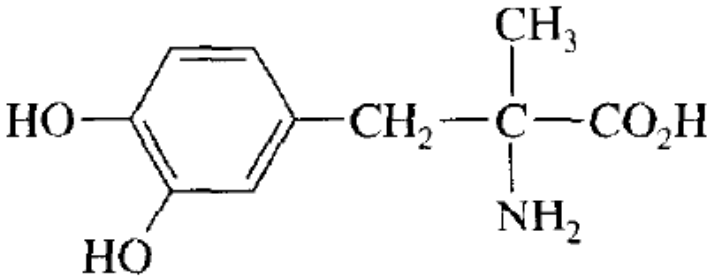
Alguns fármacos



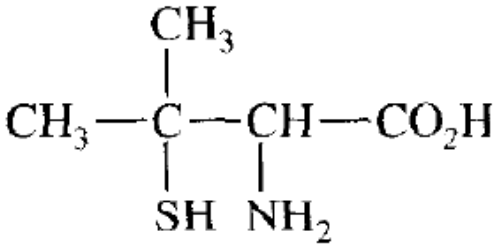
22 (*S*)-(–)-omeprazole



Ibuprofeno

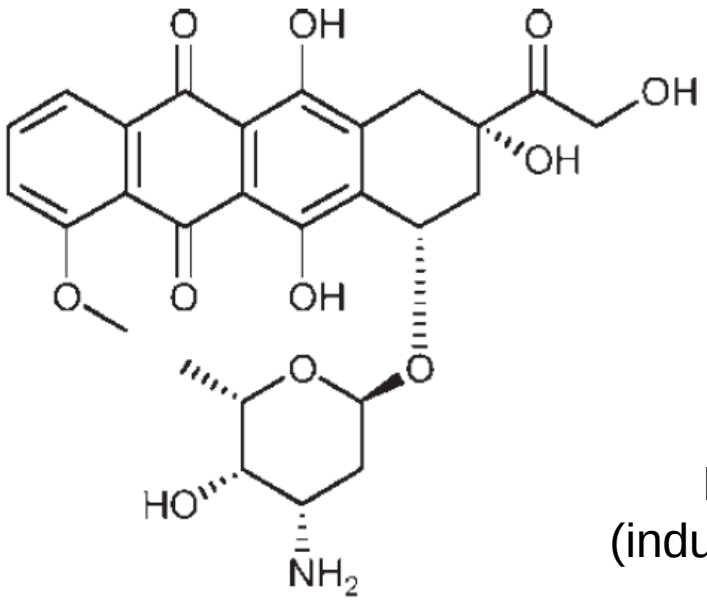


Metildopa



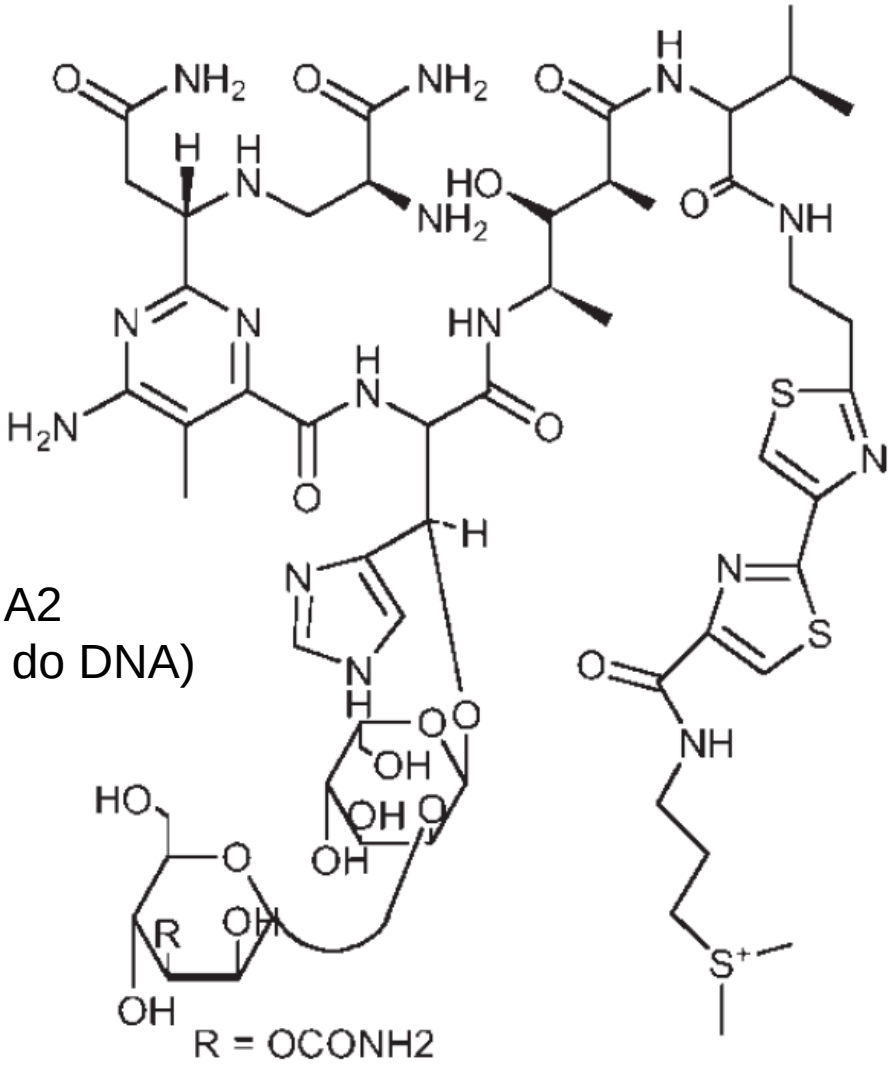
Penicilamina

Produtos naturais como antitumorais

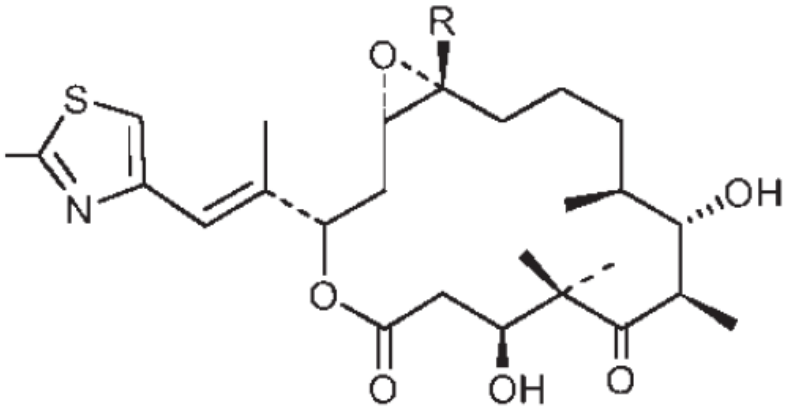


Doxorubicina
(intercalador do DNA)

Bleomicina A2
(induz clivagem do DNA)

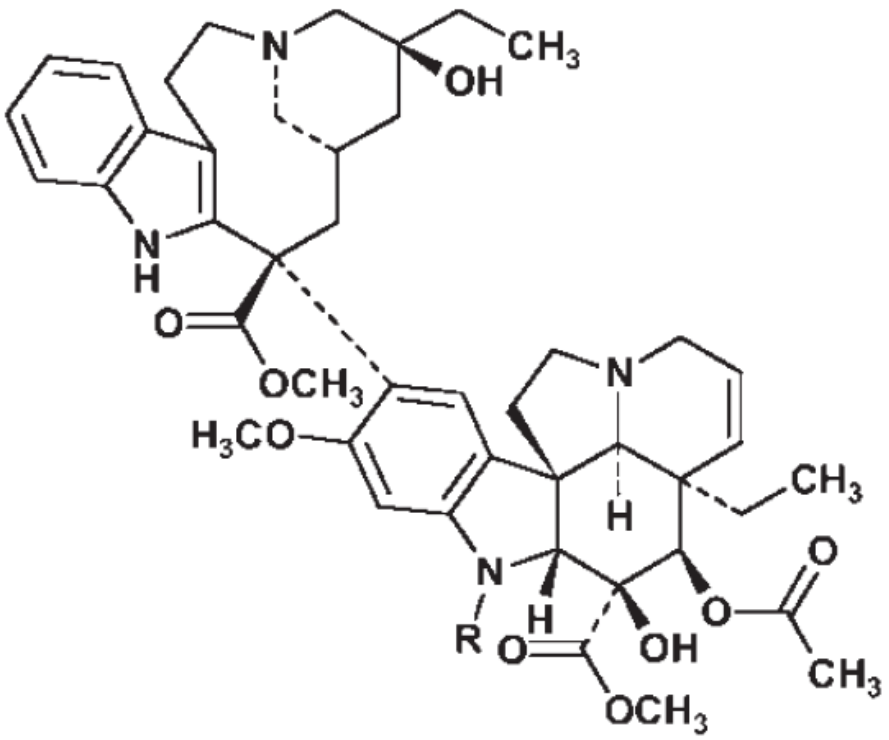


Produtos naturais como antitumorais



10a Epothilone A; R = H
10b Epothilone B; R = CH3

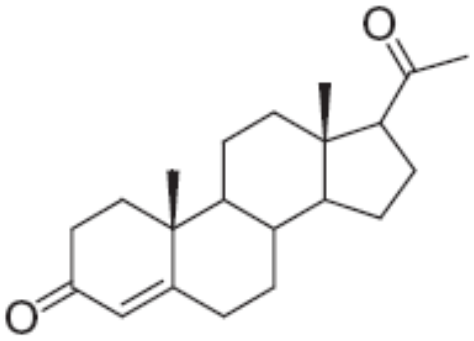
Epotilonas



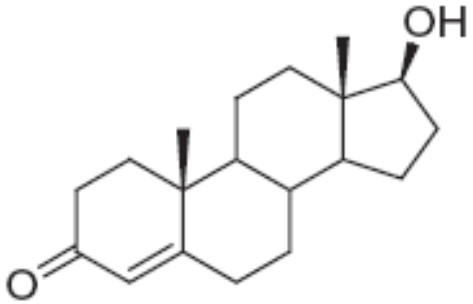
(interferem na tubulina)

21 Vinblastine R = CH_3
22 Vincristine R = CHO

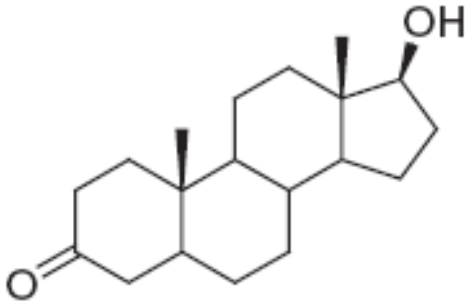
Compostos esteroidais



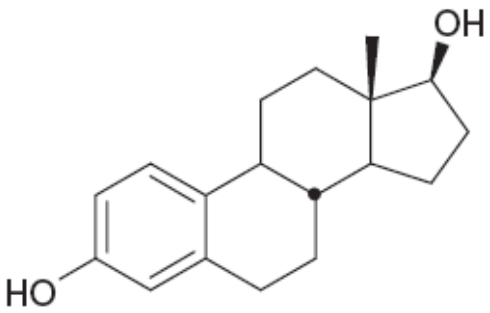
Progesterone



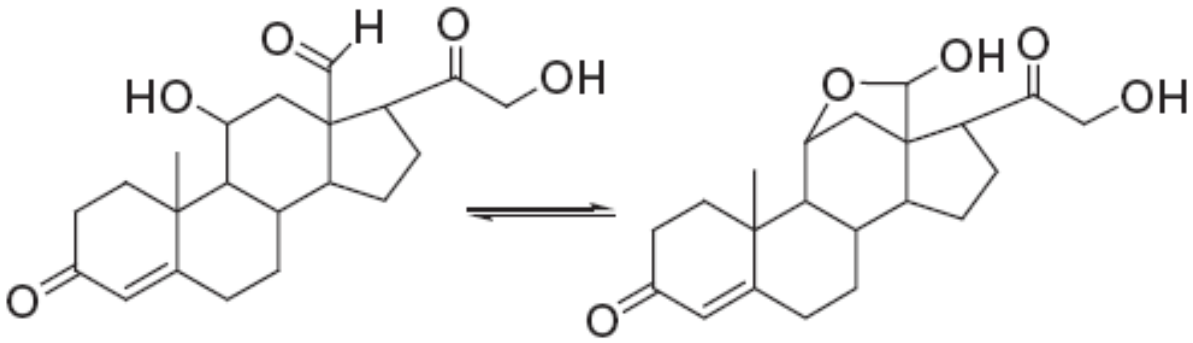
Testosterone



DHT

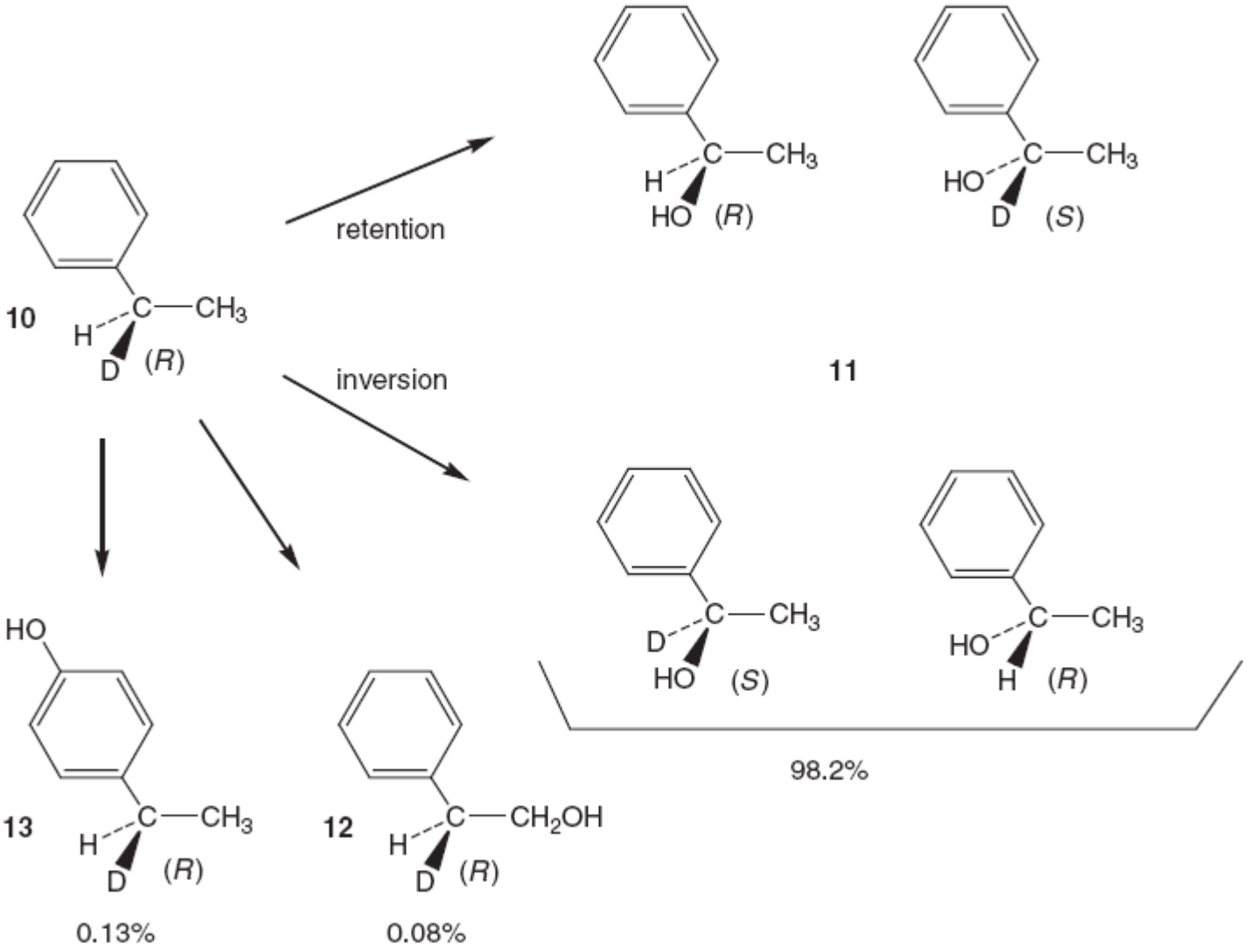


17β-estradiol

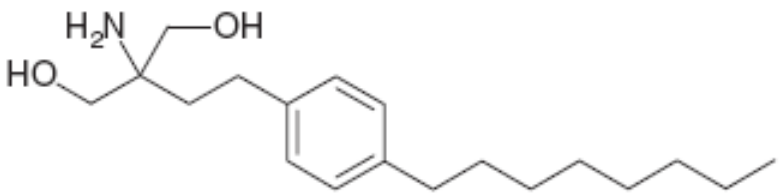


Aldosterone

Estereoquímica e metabolismo

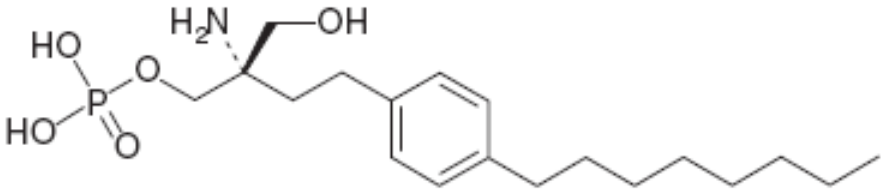


Estereoquímica e metabolismo



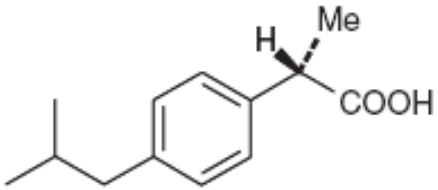
37

<= Reação de fosforilação

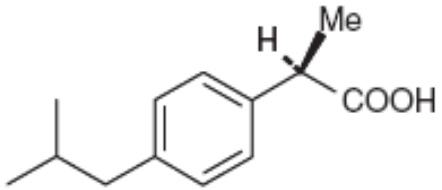


38

Conversão de ibuprofeno =>

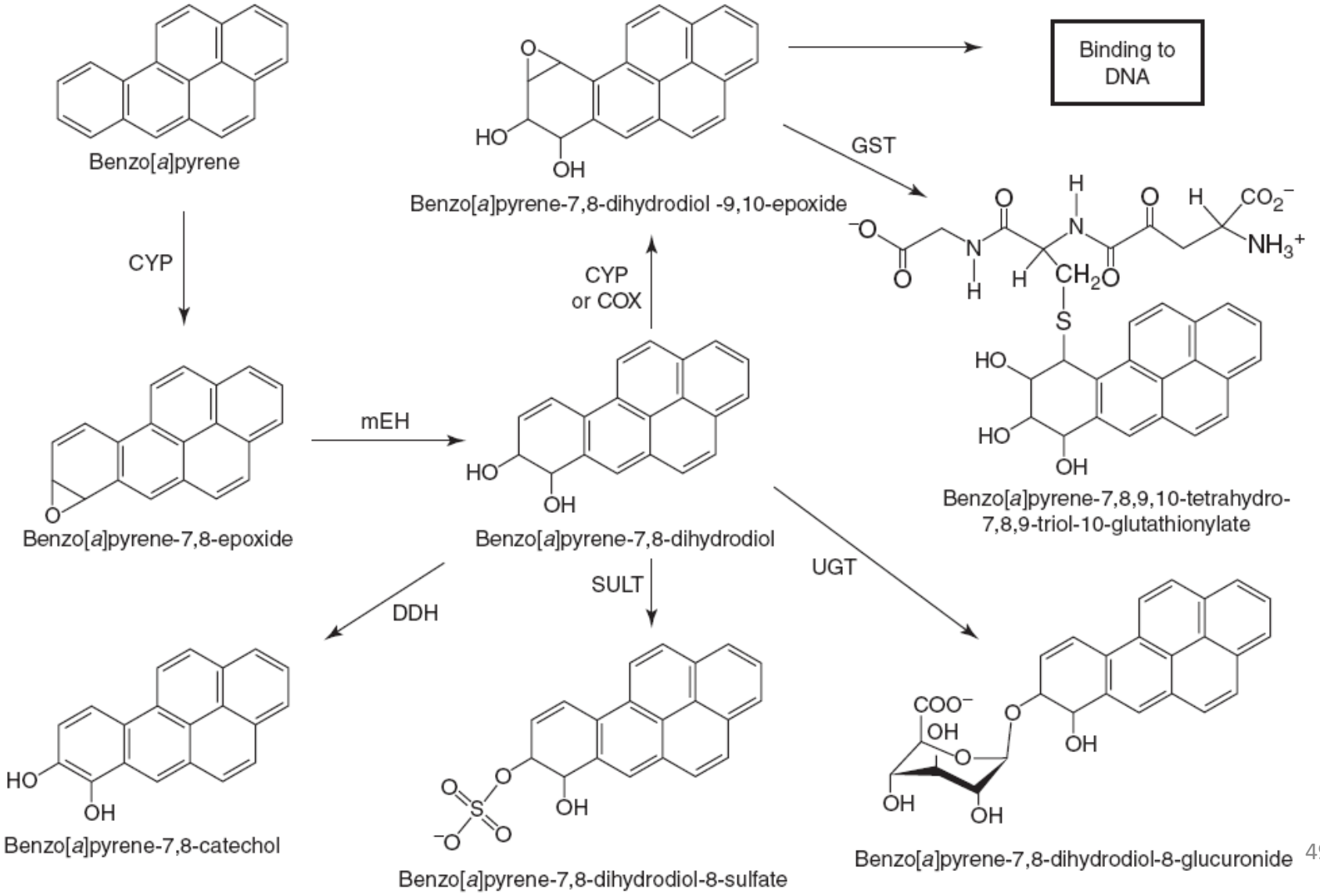


(*S*)-62

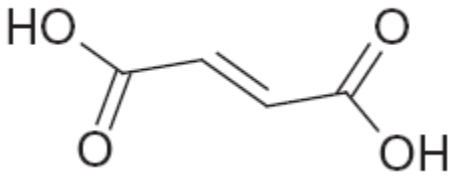


(*R*)-62

Metabolismo e efeito tóxico



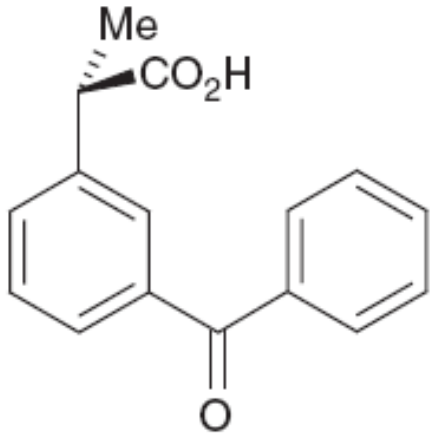
Acidez



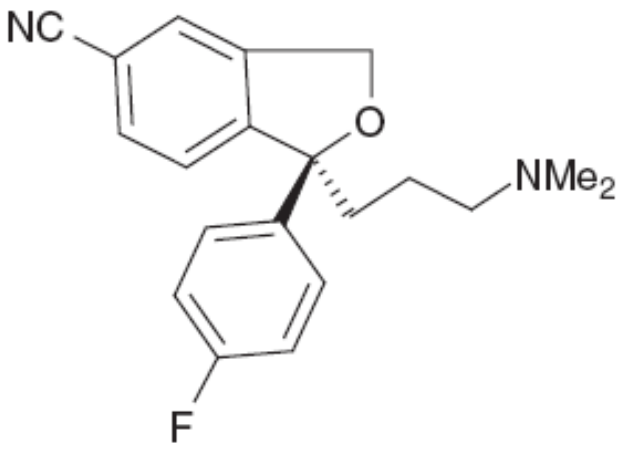
$pK_a = 3.1, 4.6$

$pK_a = 1.9, 6.3$

Outros fármacos

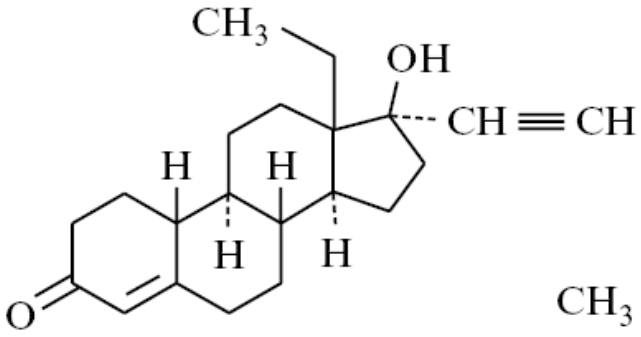


Dexketoprofen
anti-inflammatory/analgesic, 1998

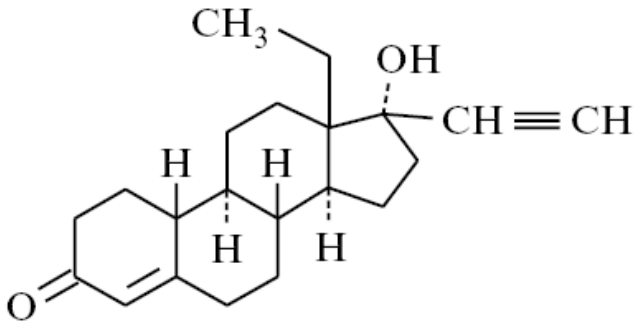


Escitalopram
antidepressant, 2001

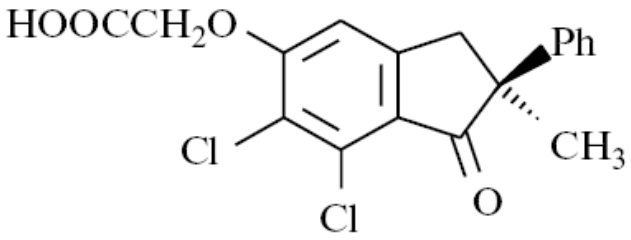
Farmacocinética



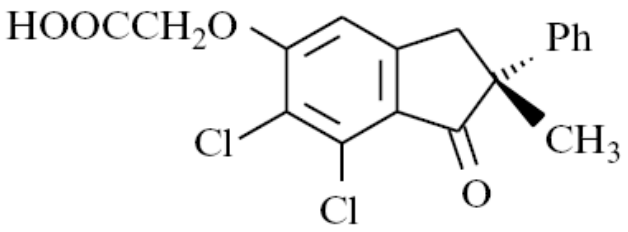
(+) Norgestrel



(–) Norgestrel



S-Indacrinone



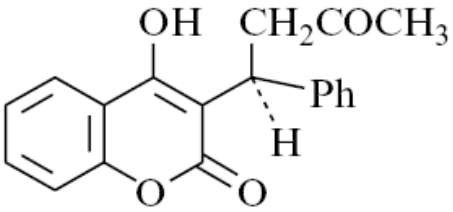
R-Indacrinone

(-) é absorvido 2 vezes mais do que (+)

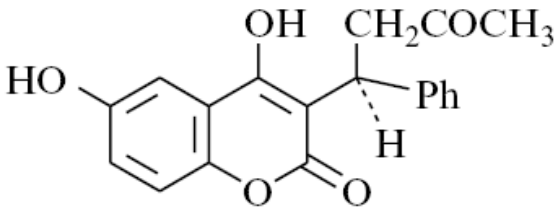
Tempo de meia-vida de *R* é 10-12 h
Tempo de meia-vida de *S* é 2-5 h

Reações regiosseletivas e estereosseletivas

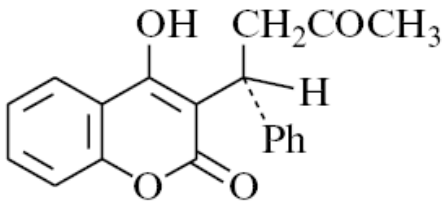
O anticoagulante warfarina (S, R) possui diferentes rotas de metabolismo



S-warfarina



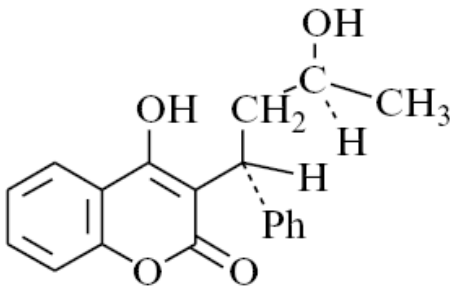
(*S*)-6-hidróxi-warfarina



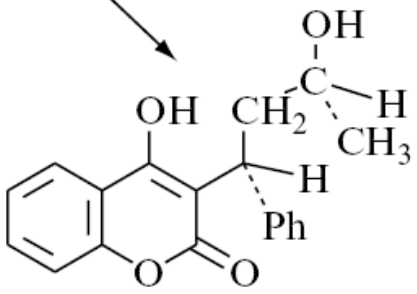
R-warfarina

Rota principal

Rota secundária



R,S-álcool



R,R-álcool