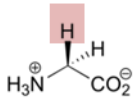
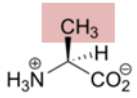
Química Medicinal

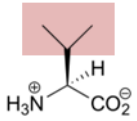
Prof. Dr. Andrei Leitão

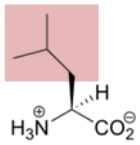
Estereoquímica em proteínas

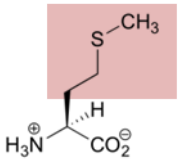
Nonpolar, aliphatic side groups

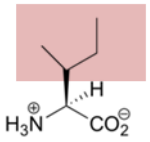

Glycine
Gly, G


Alanine
Ala, A

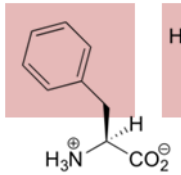

Valine
Val, V

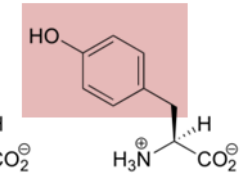

Leucine
Leu, L

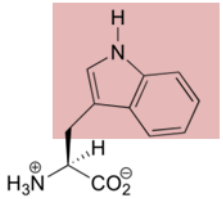

Methionine
Met, M


Isoleucine
Ile, I

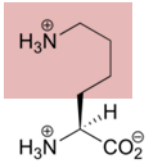
Aromatic side groups

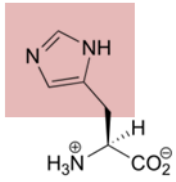

Phenylalanine
Phe, F

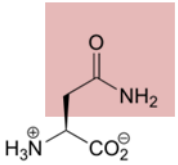

Tyrosine
Tyr, Y


Tryptophan
Trp, W

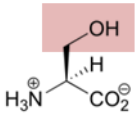
Positively charged side groups

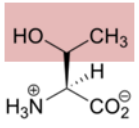

Lysine
Lys, K

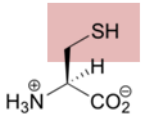

Histidine
His, H

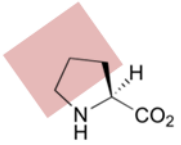

Asparagine
Asn, N

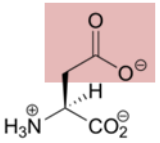
Polar, uncharged side groups

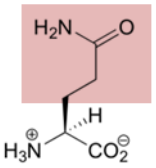

Serine
Ser, S


Threonine
Thr, T

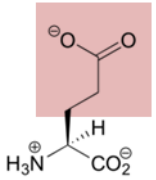

Cysteine
Cys, C

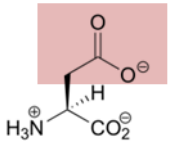

Proline
Pro, P


Aspartate
Asp, D

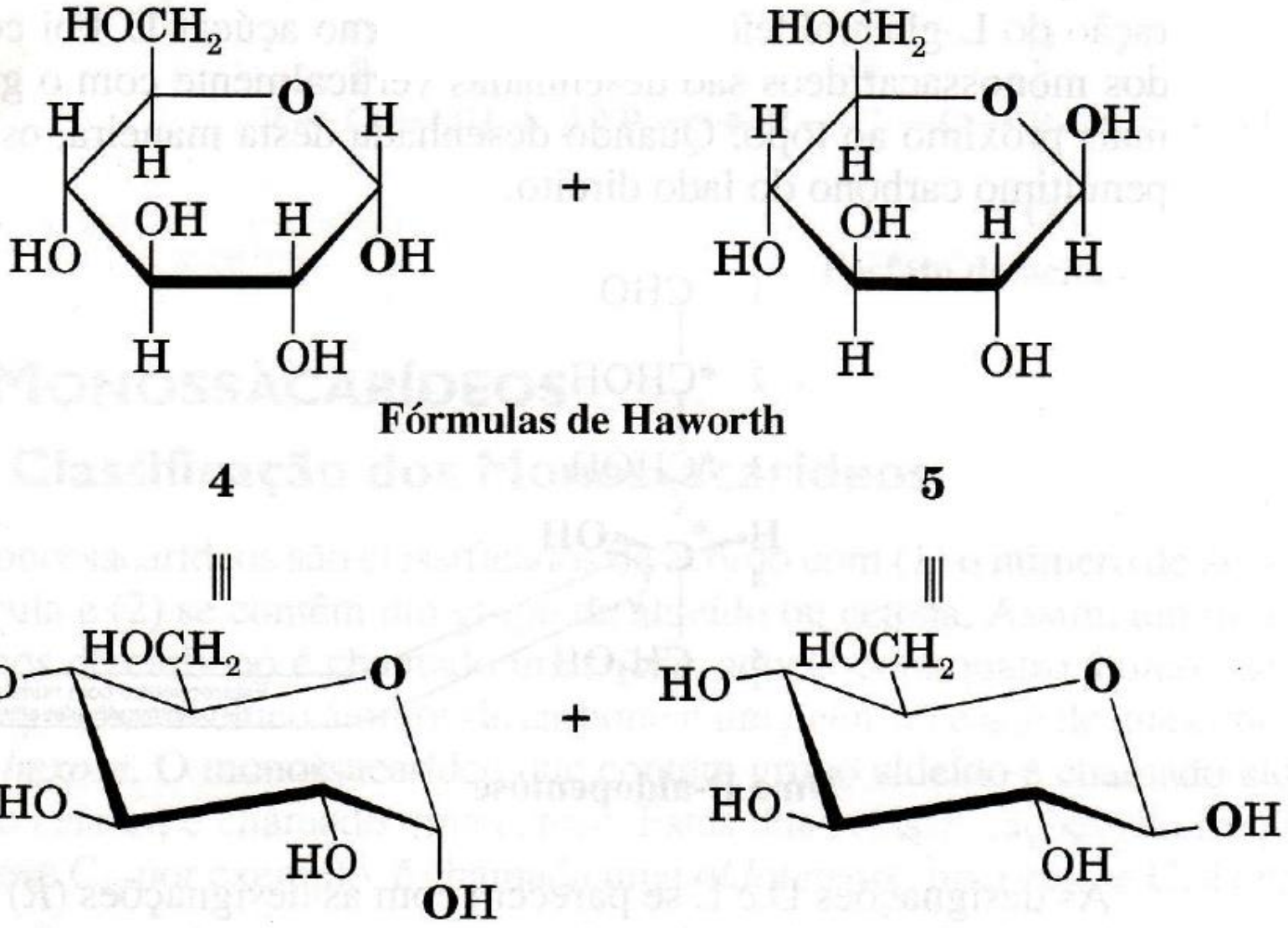

Glutamine
Gln, Q

Negatively charged side groups

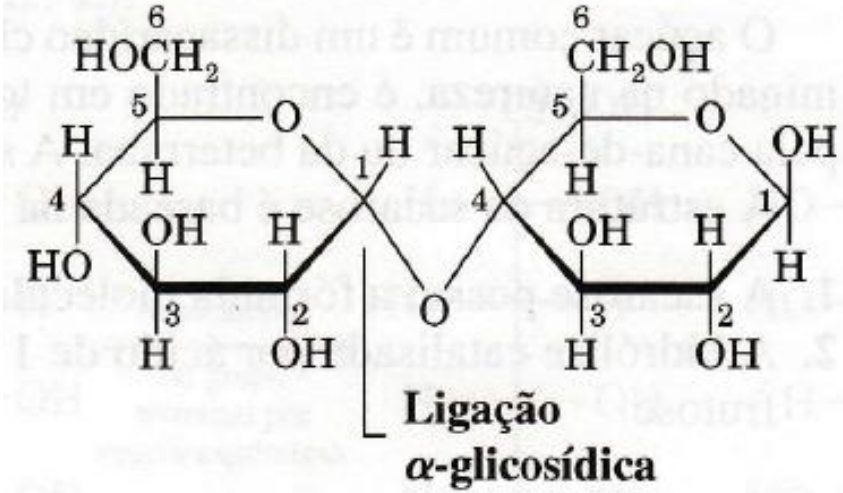

Glutamate
Glu, E

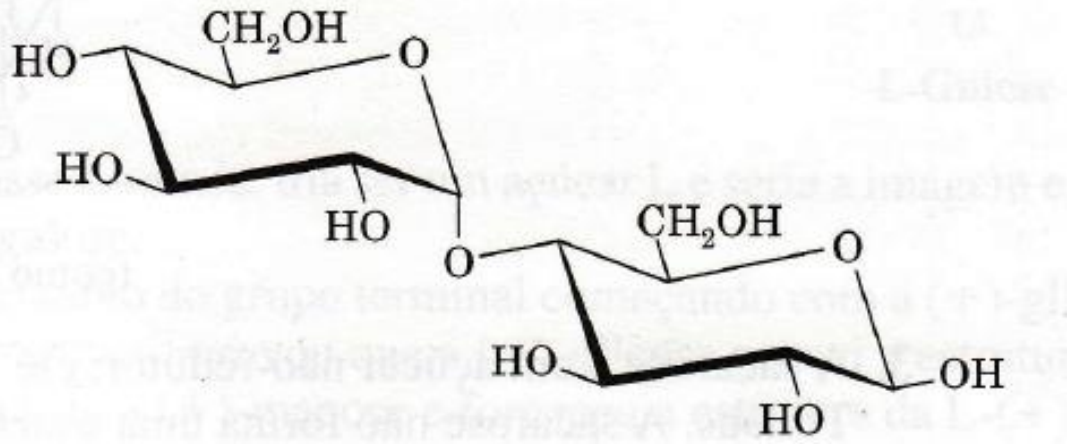

Aspartate
Asp, D

Carboidratos

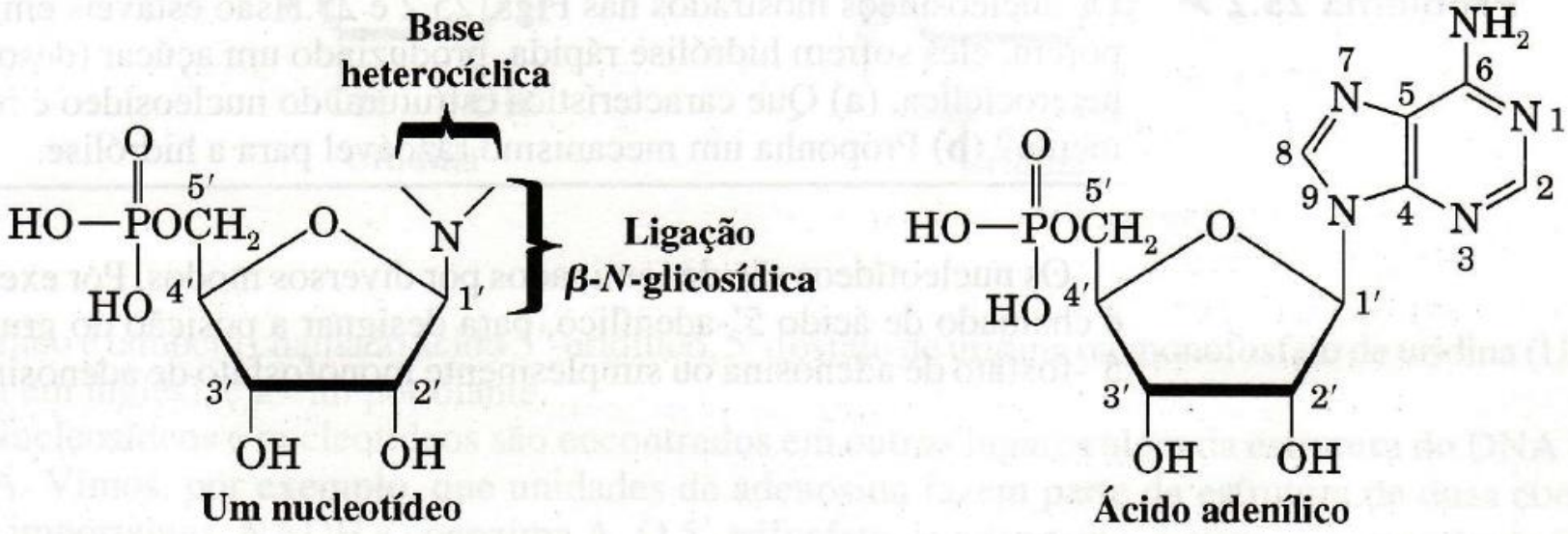


Carboidratos

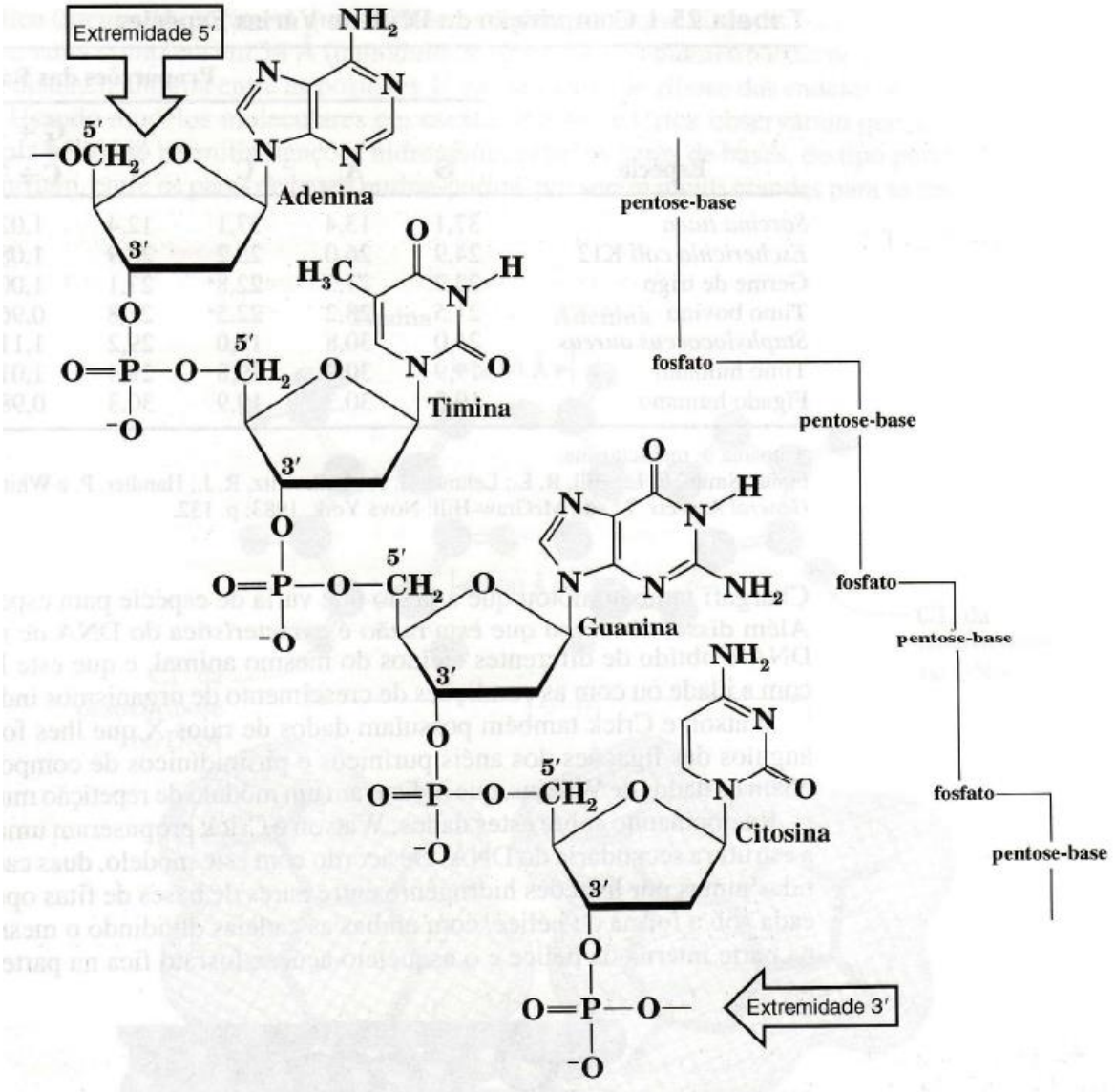




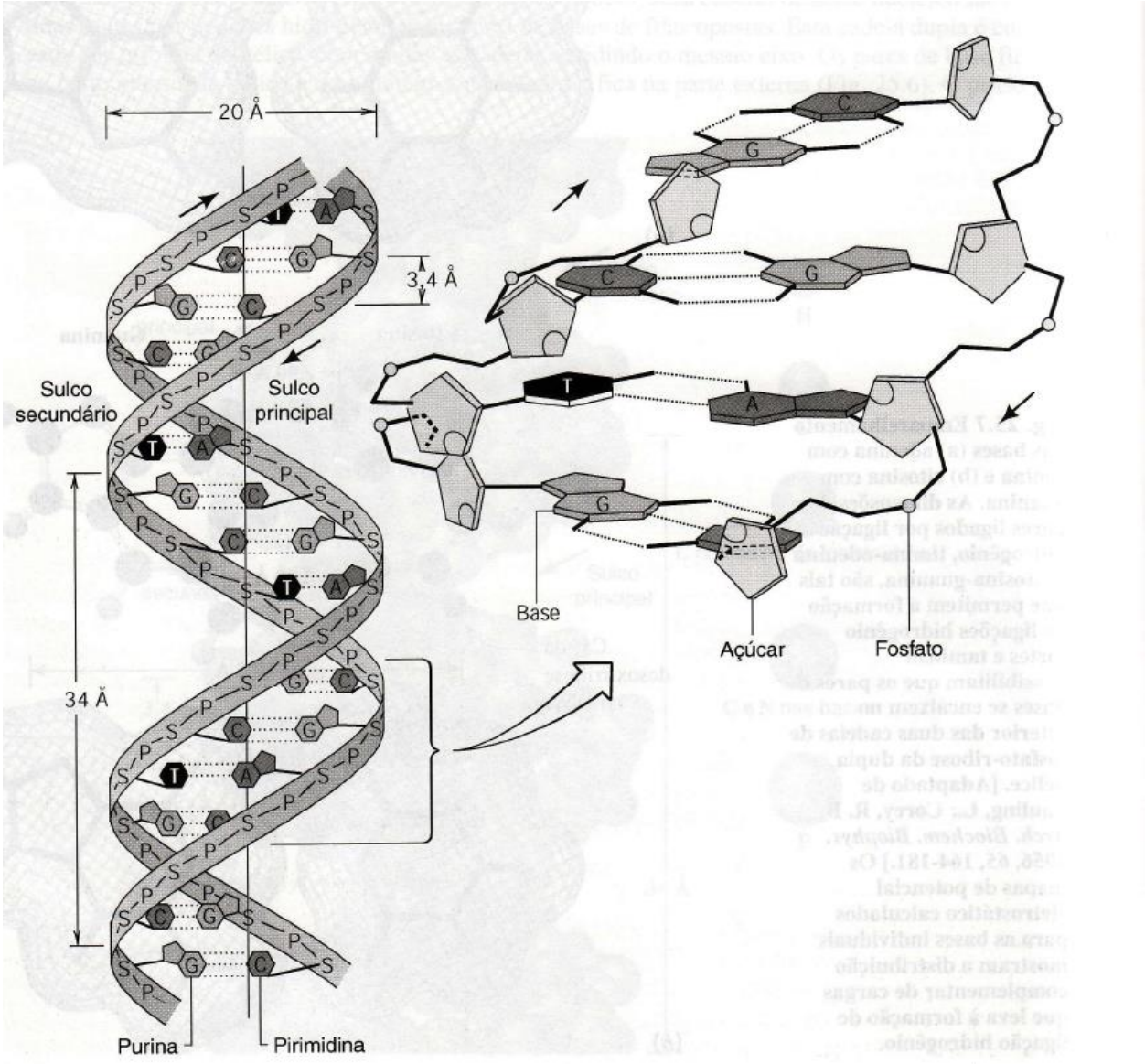
Nucleotídeo



Fragmento de uma fita do DNA



Estrutura do B-DNA



Fármacos quirais

- Racematos

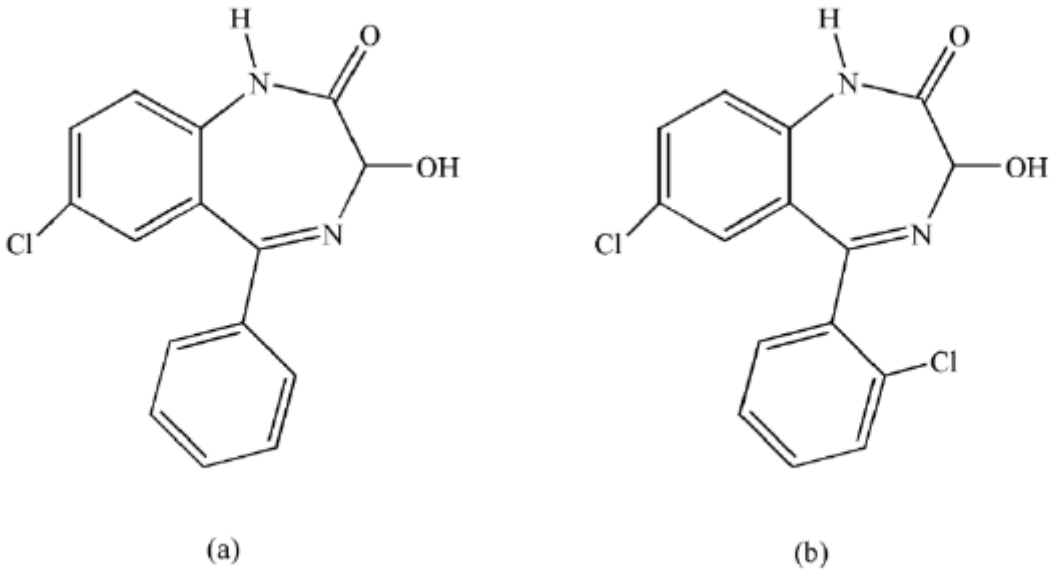


Figura 4.2 Estrutura dos benzodiazepínicos (a) oxazepam e (b) lorazepam

Fármacos quirais

- Enantiômeros puros

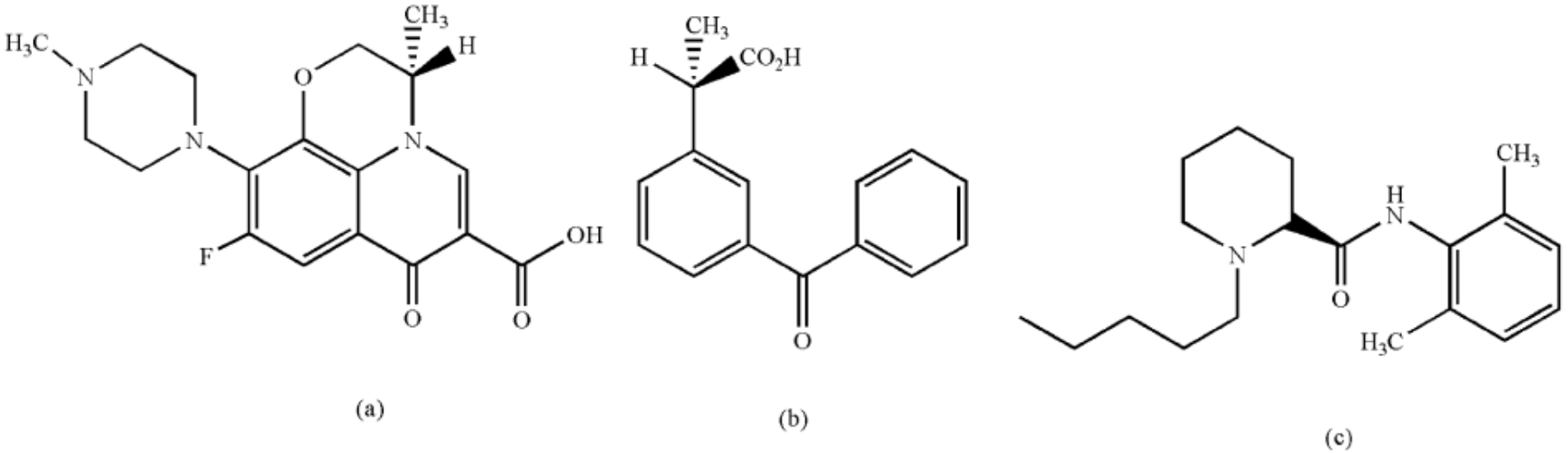


Figura 4.3 Estruturas químicas dos fármacos (a) levofloxacina, (b) dexcetoprofeno e (c) levobupivacaína

Antiúlcera

- Sulfóxidos quirais

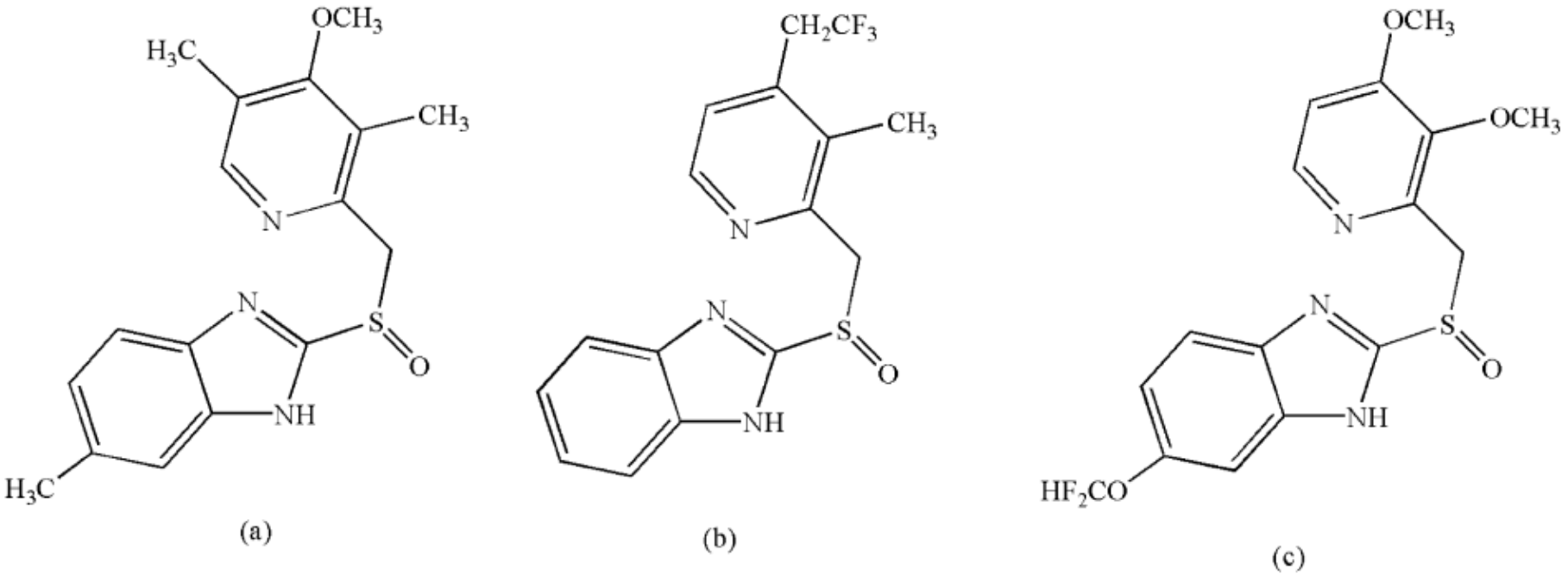


Figura 4.6 Estrutura química do (a) omeprazol, (b) lansoprazol e (c) pantoprazol

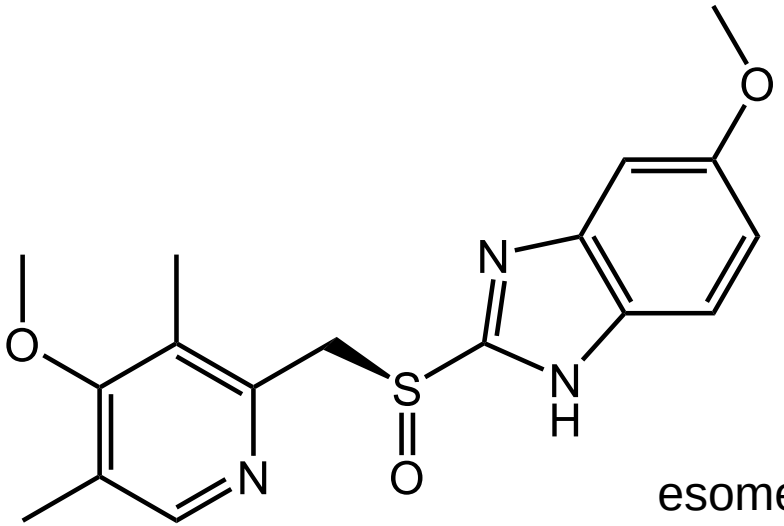
Racemato vs. Enantiômeros puros

Os enantiômeros puros podem ter:

- Atividades distintas
- Um enantiômero pode ser ativo, outro inativo
- Mesma atividade com potência diferente
- Potência igual

Estereoisômeros na farmacocinétida e toxicologia

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

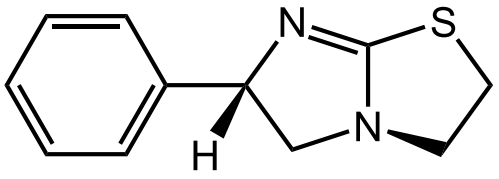


esomeprazol

Estereoisômeros na farmacodinâmica
Exemplos:

- ✓ Diferentes atividades farmacológicas de enantiômeros:

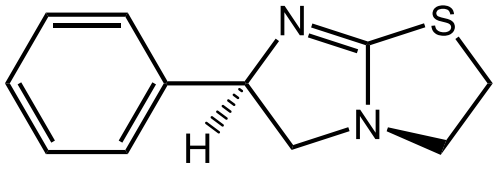
Nematocida
Imunoestimulante



Ascaridil®

(*S*) **levamisol**

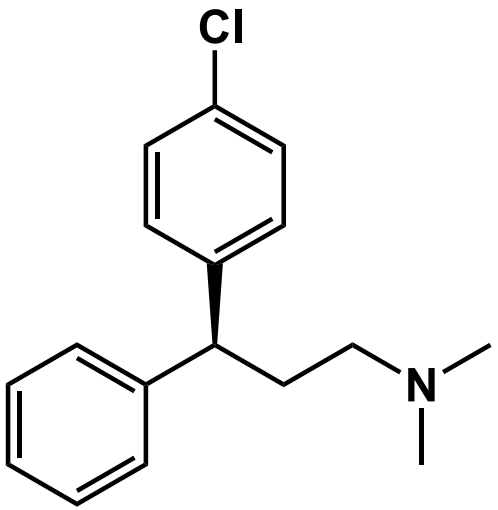
Anti-depressivo



(*R*) **dexamisol**

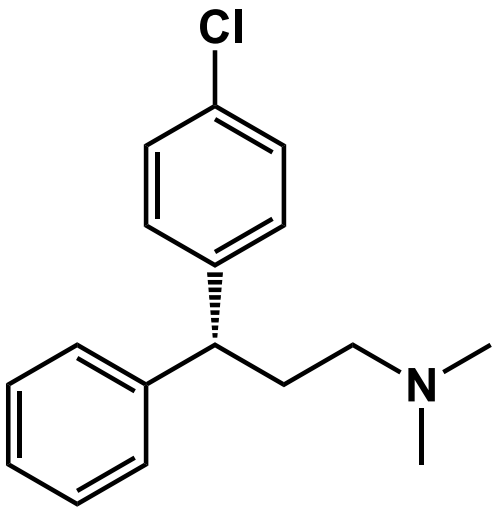
Estereoisômeros na farmacodinâmica
Exemplos:

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



(*S*)-clorfeniramina

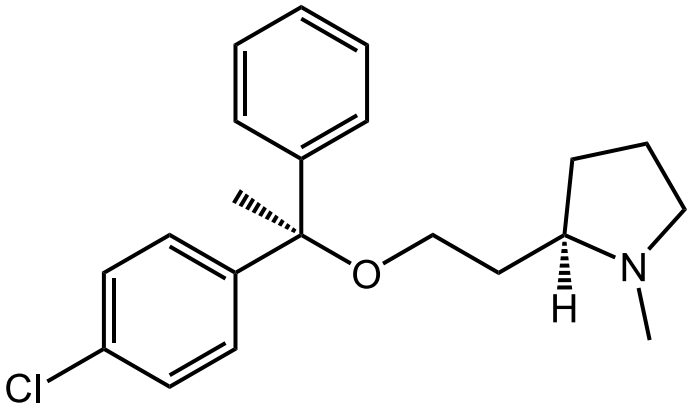
Polaramine®



(*R*)-clorfeniramina

Estereoisômeros na farmacodinâmica
Exemplos:

✓ Atividade anti-histamínica da clemastina



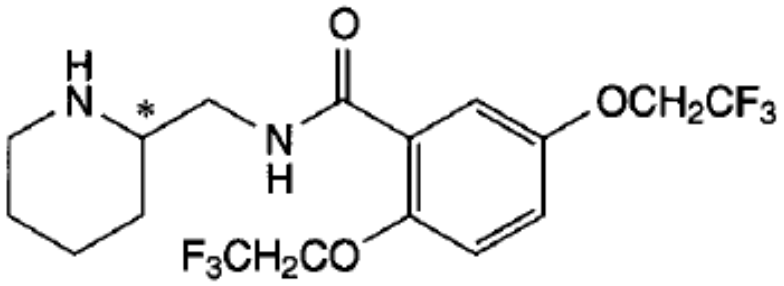
(*R*,*R*)-clemastina

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

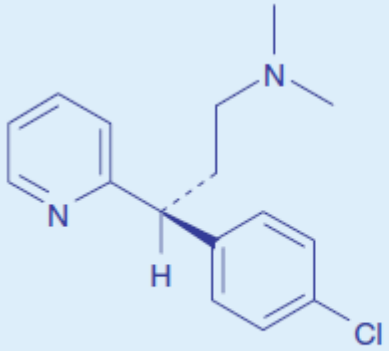
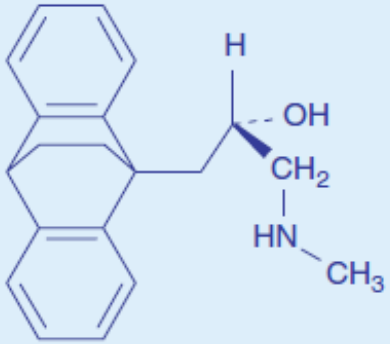
*A histamina causa espasmos no(a) alérgico(a)

Racemato vs. Enantiômeros puros

- Fecainida (antiarrítmico): enantiômeros puros têm a mesma atividade farmacológica e não têm grande distinção em termos de metabolismo



Racemato vs. Enantiômeros puros

Composto	Atividade	Razão S/R
 S(+)-Chlorpheniramine (Polaramine)	K_i values for human brain frontal lobe sites labeled by [3H]-mepyramine	S(+)/R(−) = 83
 S(+)-Oxaprotiline	IC_{50} values for noradrenaline uptake into rat brain synaptosomes	S(+)/ R(−) = 1000

Racemato vs. Enantiômeros puros

TABLE 26.6 Antagonism in Couples of Enantiomers

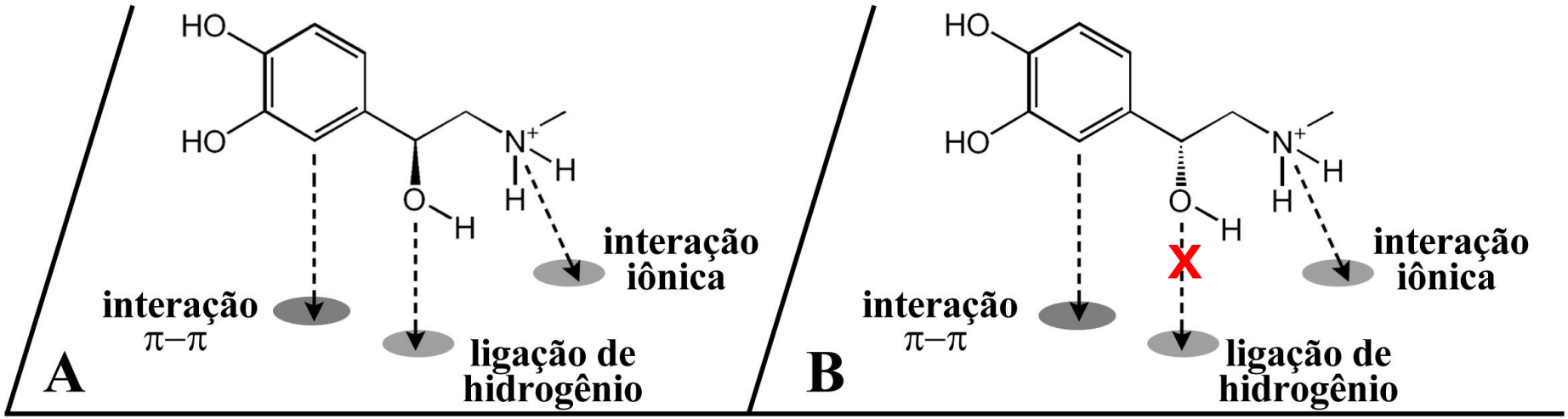
Compound	Eutomer	Distomer	Racemate
N-Isopropyl-norepinephrine	(−) α-Adrenergic agonist	(+) Inactive competitive antagonist	(±) Partial agonist
5-Ethyl-5(1,3-dimethylbutyl)barbituric acid	(+) Convulsant	(−) Depressant	(±) Convulsant
Ozolinone (metabolite of etazoline)	(−) Diuretic	(+) Inhibits low doses of (−) or of furoxemide	(±) Diuretic
Picenadol	(+) Morphinomimetic	(−) Narcotic antagonist	(±) Partial agonist
Alpha-(2,4,5)-trichloro-phenoxy-propionic acid	(+) Auxin-like plant growth regulator	(−) Decreases activity of (+)	(±) Auxin-like plant growth regulator
6-Ethyl-9-oxaergoline (EOE)	(−) Dopamine agonist	(+) Dopamine antagonist	(±) Dopamine agonist

(+)dextro (-) levo

Estereoisômeros na farmacodinâmica

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

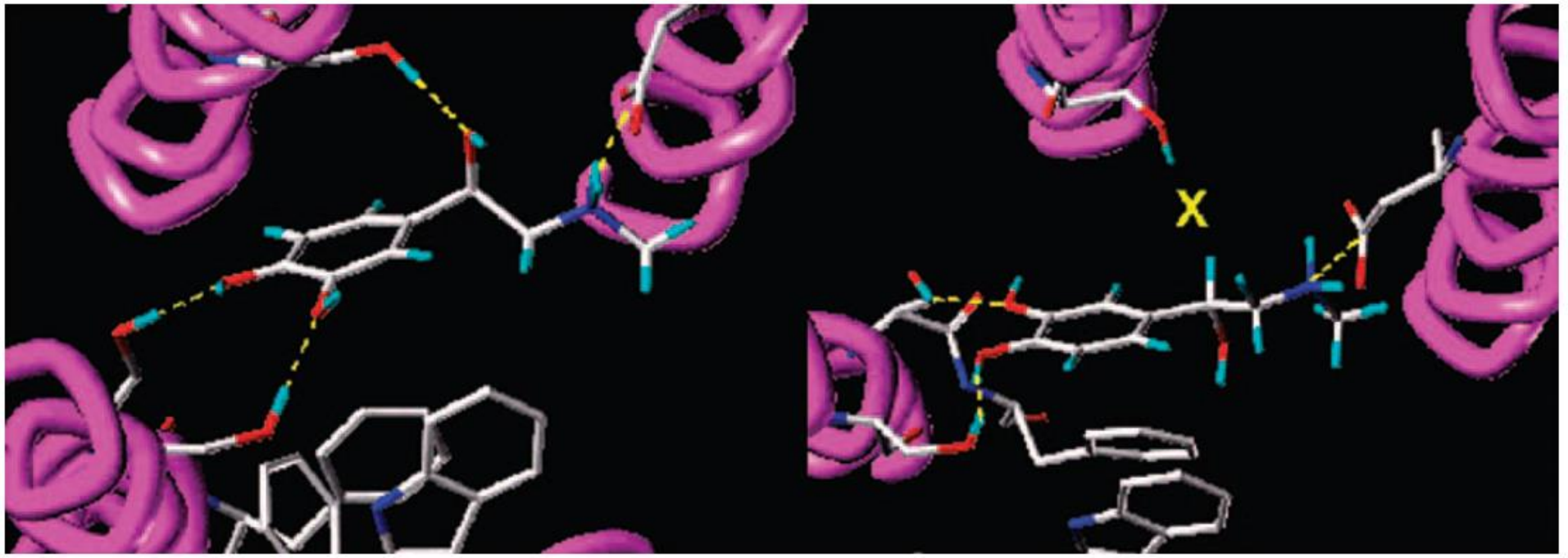
Epinefrina



Interações intermoleculares

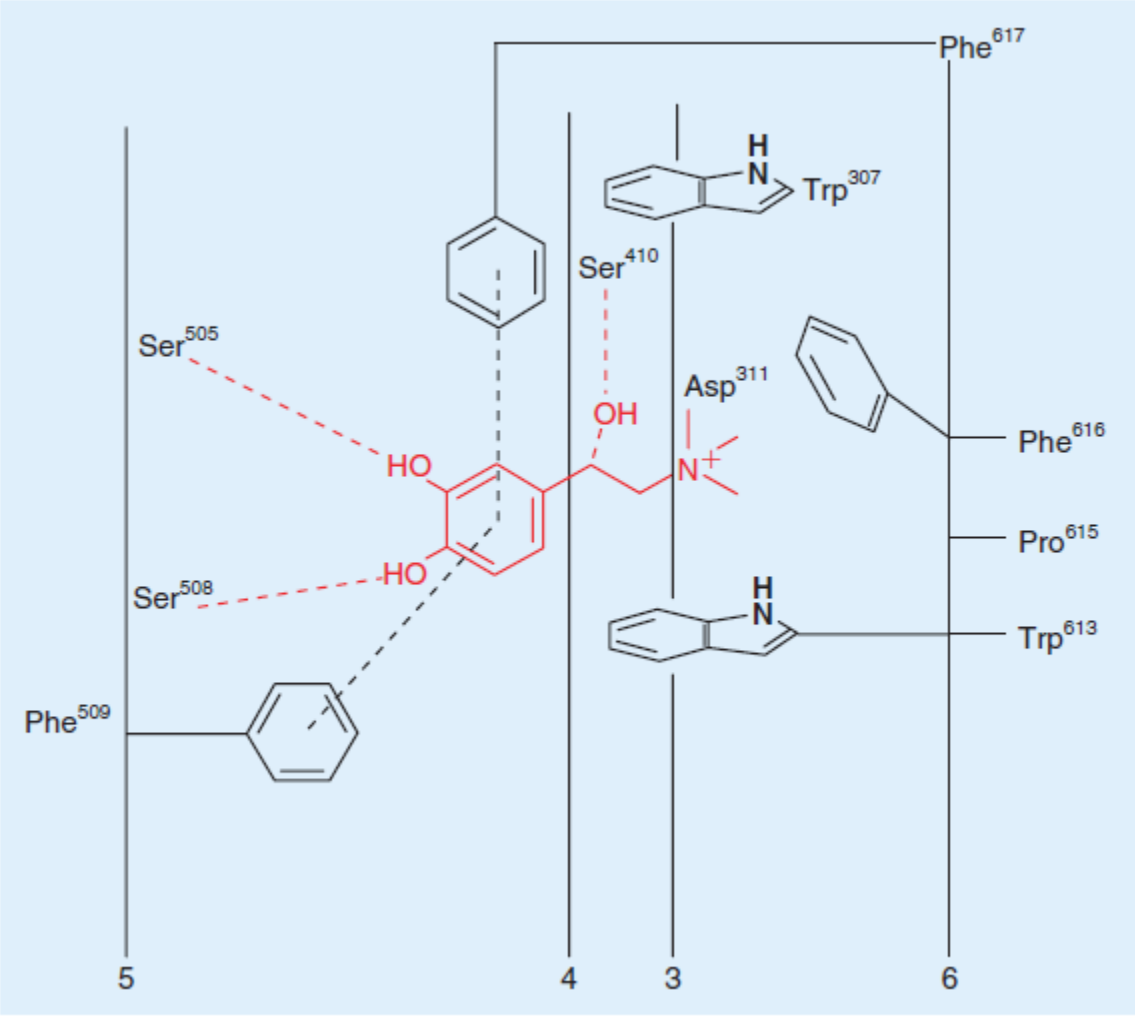
Epinefrina

(a) (b)



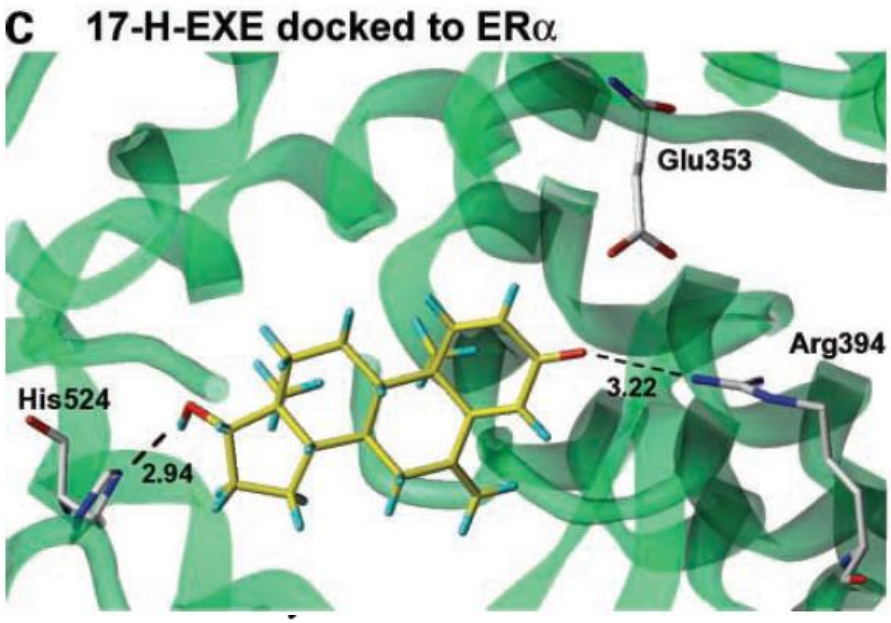
Interações intermoleculares

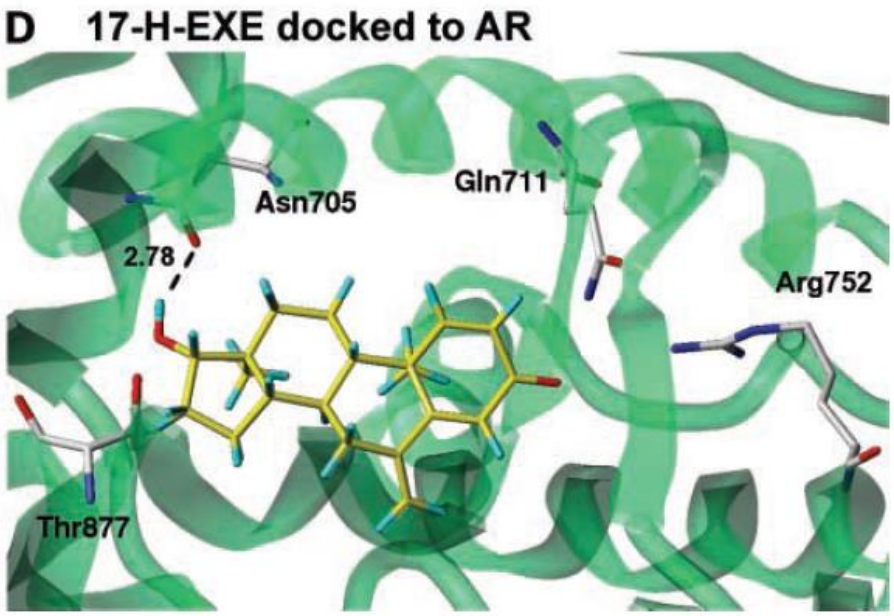
Epinefrina

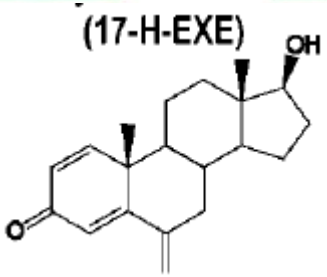


Interações intermoleculares

Interação de exemestano em diferentes receptores nucleares

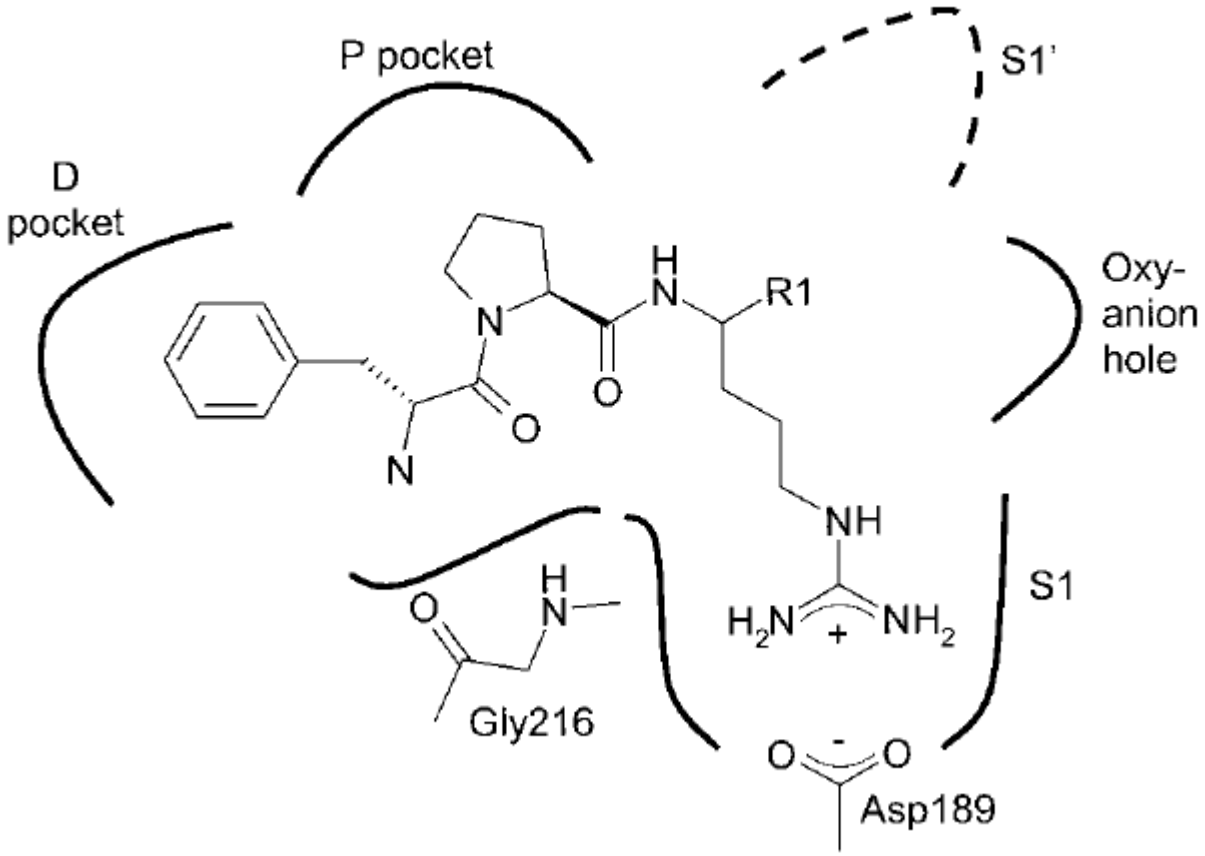






	IC_{50} (μmol L^{-1})
ERα	21,2
AR	39,6

Cocomplexo: proteína-ligante



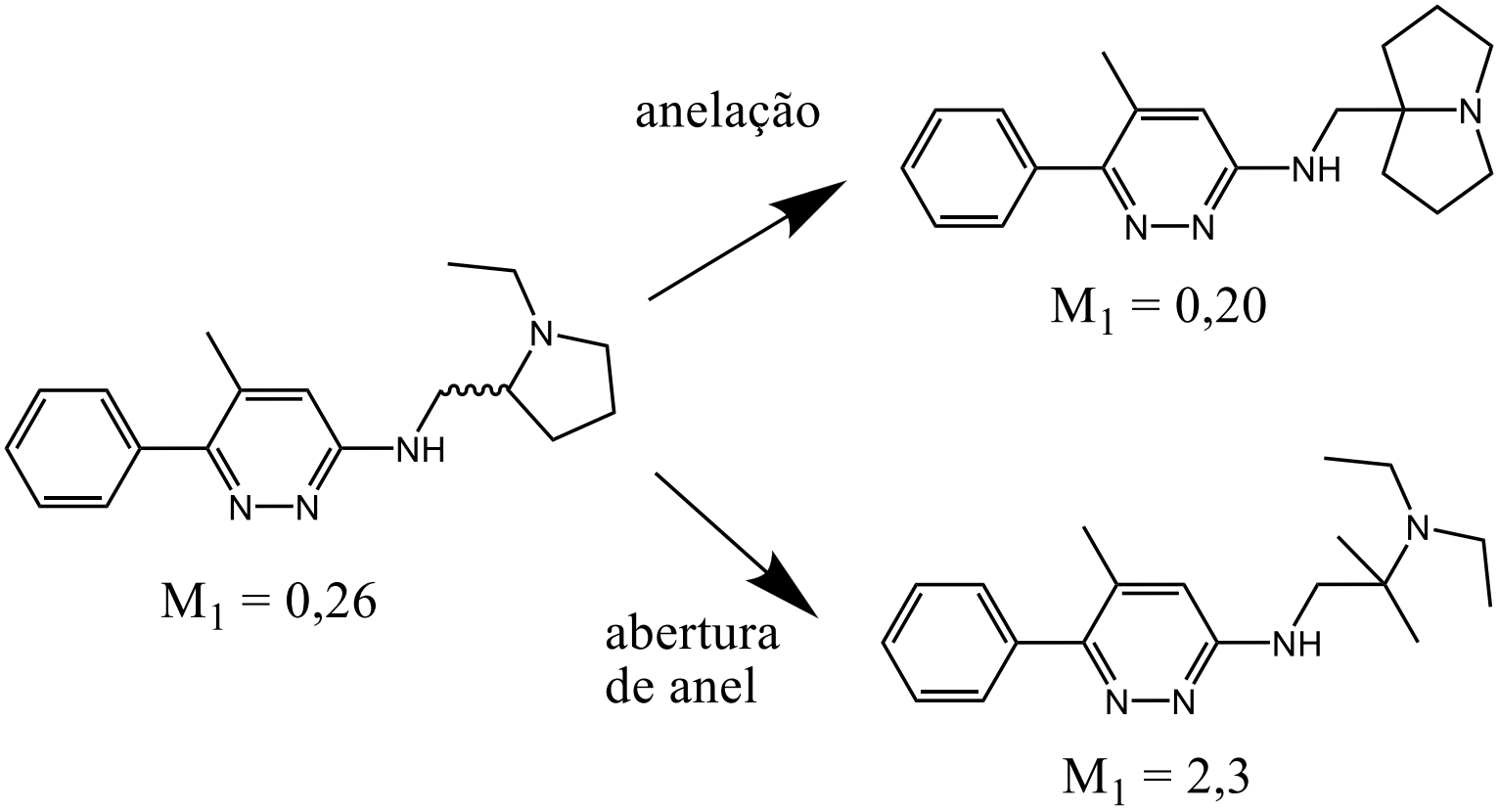
Estratégias em química medicinal

- ✓ Redução do número ou eliminação dos centros quirais
  - Abertura de anel
  - Anelação
  - Simplificação molecular

- ✓ Estudo da conformação farmacofórica
  - Métodos biofísicos diretos: RMN, raios-X
  - Métodos indiretos: síntese de análogos rígidos
    métodos computacionais

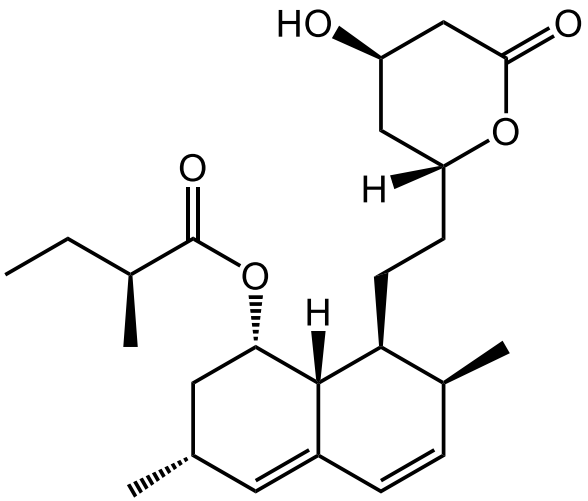
Eliminação de centros quirais
Abertura de anel ou anelação

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



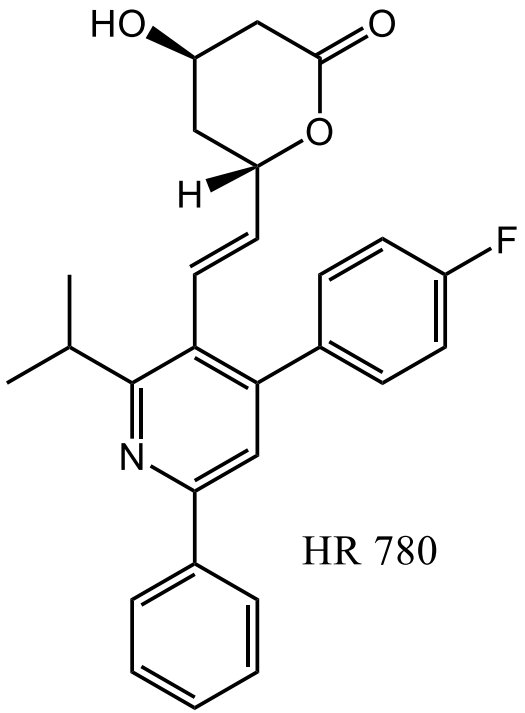
Redução de centros quirais
Simplificação molecular

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



mevinolina

8 centros quirais

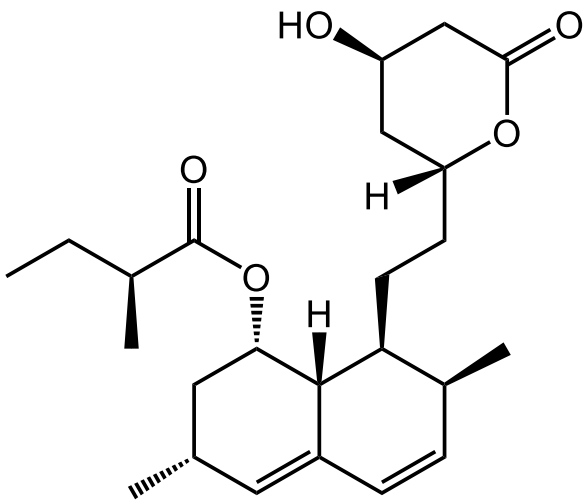


HR 780

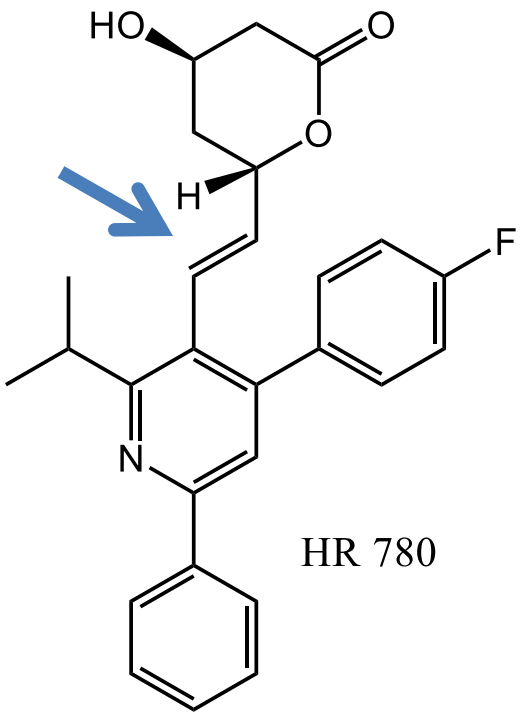
2 centros quirais

Estudo da conformação farmacofórica por método indireto

- ✓ Inibidor da HMG-CoA redutase: redução do colesterol
- ✓ Existe algo mais neste exemplo?



mevinolina

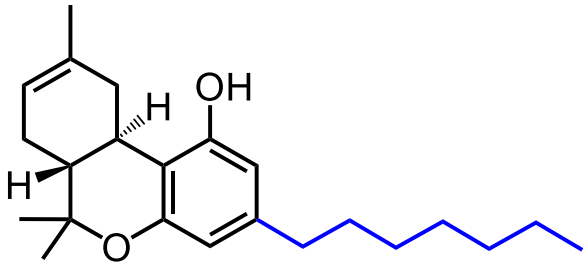


HR 780

Redução da liberdade conformacional por meio da síntese de análogo rígido

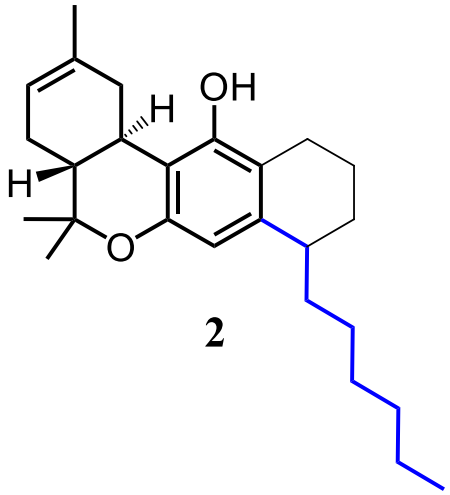
Estudo da conformação farmacofórica
Métodos indiretos

Síntese de análogos rígidos

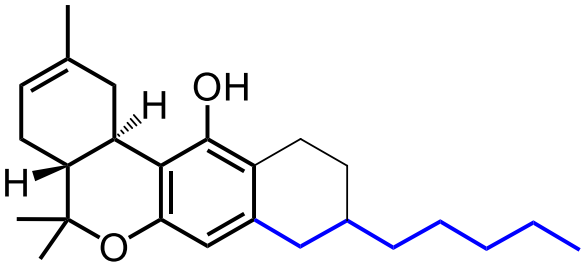


1

n-heptil-Δ^8-THC



2

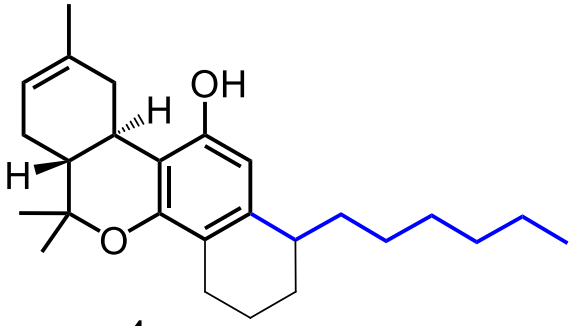


3

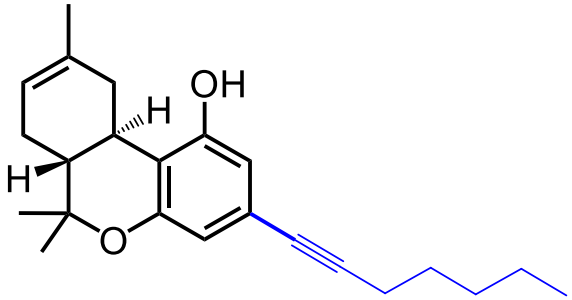
K_i (nM)			
CB1	0,43	22,3	402,4
CB2	0,39	58,6	161,5

Estudo da conformação farmacofórica
Métodos indiretos - continuação

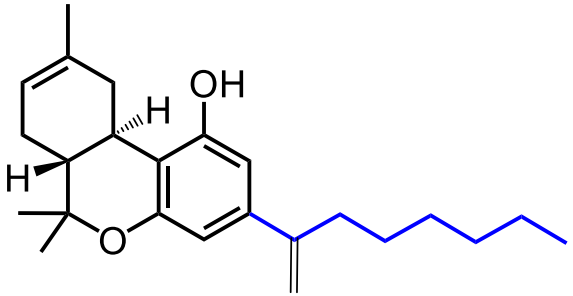
Síntese de análogos rígidos



4



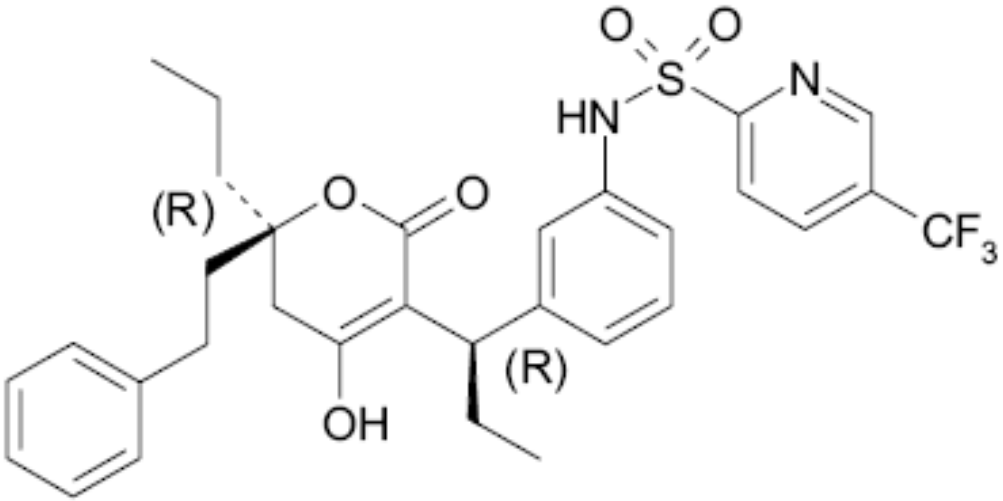
5



6

K_i (nM)			
CB1	542,1	0,65	0,32
CB2	455,6	3,1	0,52

Relações entre estrutura química e atividade biológica (SAR)



46 tipranavir Ki = 8 pM

anti-HIV
Inibidor da protease

R,S-diastereomer: Ki 18 pM
S,R-diastereomer: Ki 32 pM
S,S-diastereomer: Ki 220 pM