Fármacos que atuam no SNA afetando a neurotransmissão adrenérgica

AGENTES ADRENÉRGICOS E ANTIADRENÉRGICOS

Bibliografia

G. L. Patrick. *Drugs acting on the adrenergic nervous system.* In: *An Introduction to Medicinal Chemistry*. 5th ed. Oxford University Press, Oxford, **2013**, p. 609-631 (Cap. 23).

G. L. Patrick. T*he adrenergic nervous system.* In: *An Introduction to Medicinal Chemistry*. 4th ed. Oxford University Press, Oxford, **2009**, p. 609-631 (Cap. 16).

R. K. Griffith. *Adrenergic receptors and drugs affecting adrenergic neurotransmission.* In: *Foye´s Principles of Medicinal Chemistry*, D. A. WILLIAMS, T. L. LEMKE (Eds). 6th ed. Lippincott Williams & Wilkins, Baltimore, **2008**, p. 392-416 (Cap. 13). **2013**. 7th ed. Cap. 10, p. 340-364.

Profa. Mônica Tallarico Pupo

Química Farmacêutica I

Usos Clínicos

Agonistas dos receptores β_2 ✓

Tratamento da *asma*, relaxamento da musculatura dos brônquios

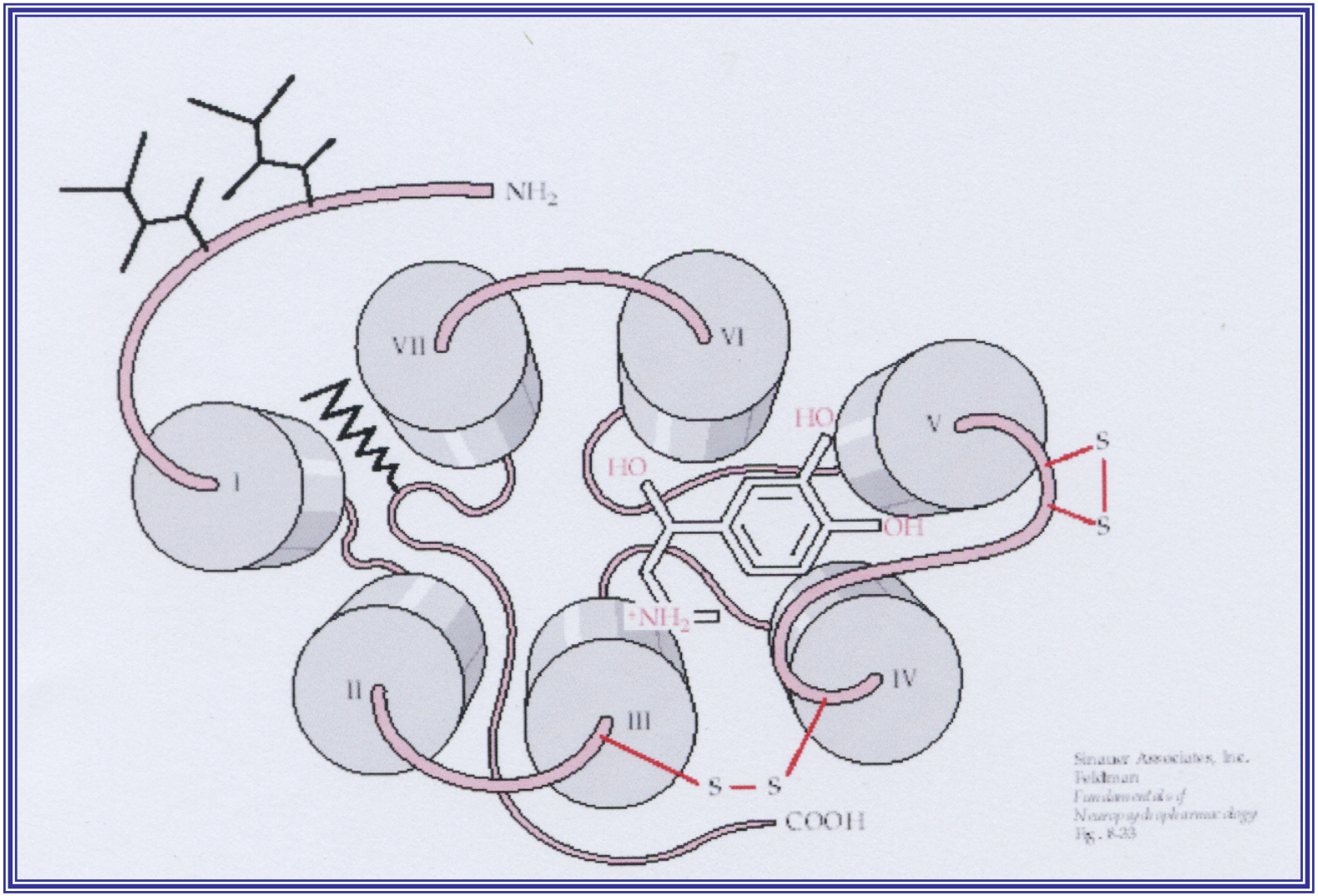
Antagonistas dos receptores α_1

Tratamento da *hipertensão*, relaxamento da musculatura dos vasos sanguíneos-dilatação

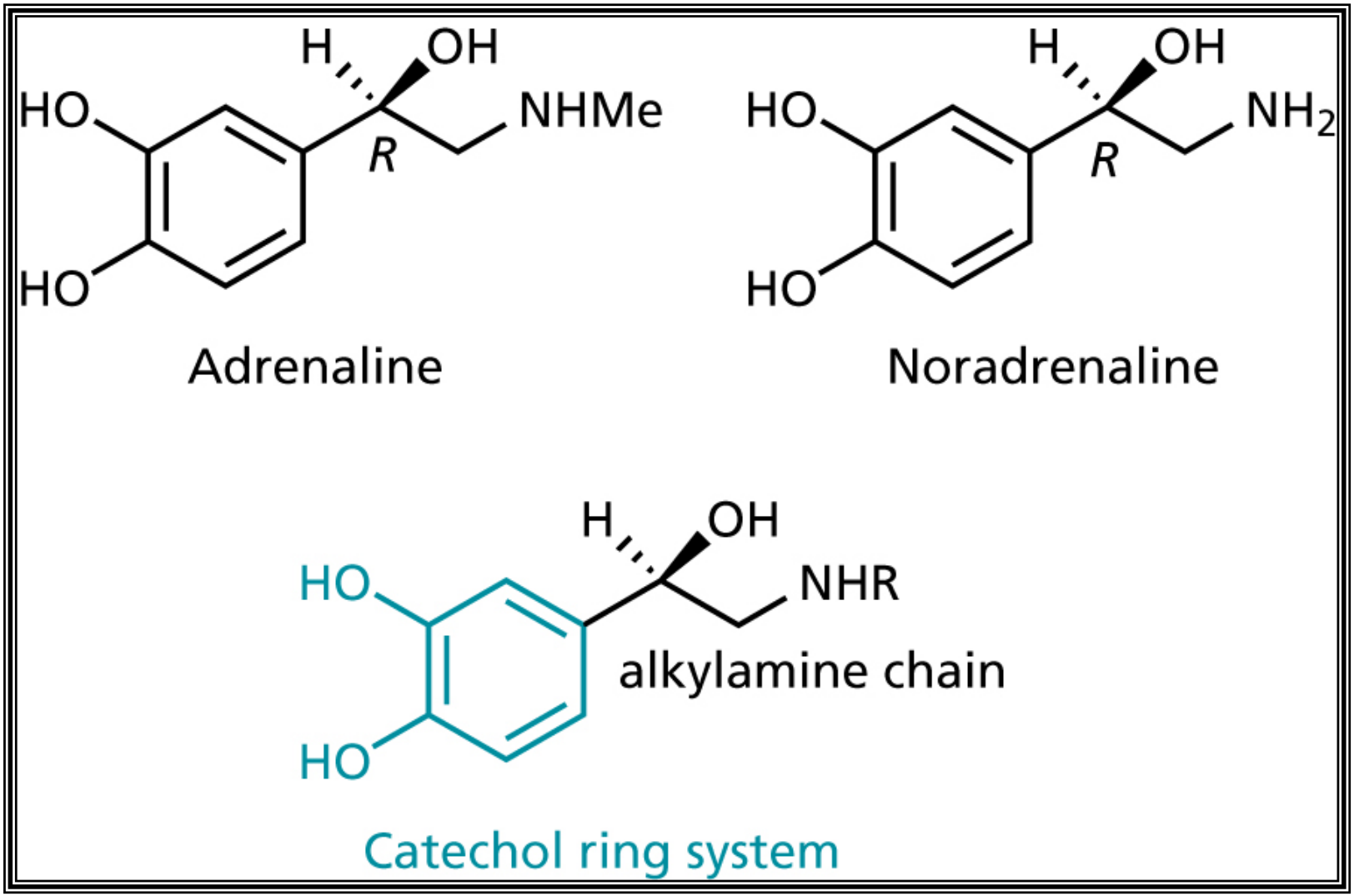
Antagonistas dos receptores β_1 ✓

Tratamento da *hipertensão*, diminuição da força de contração e batimentos cardíacos

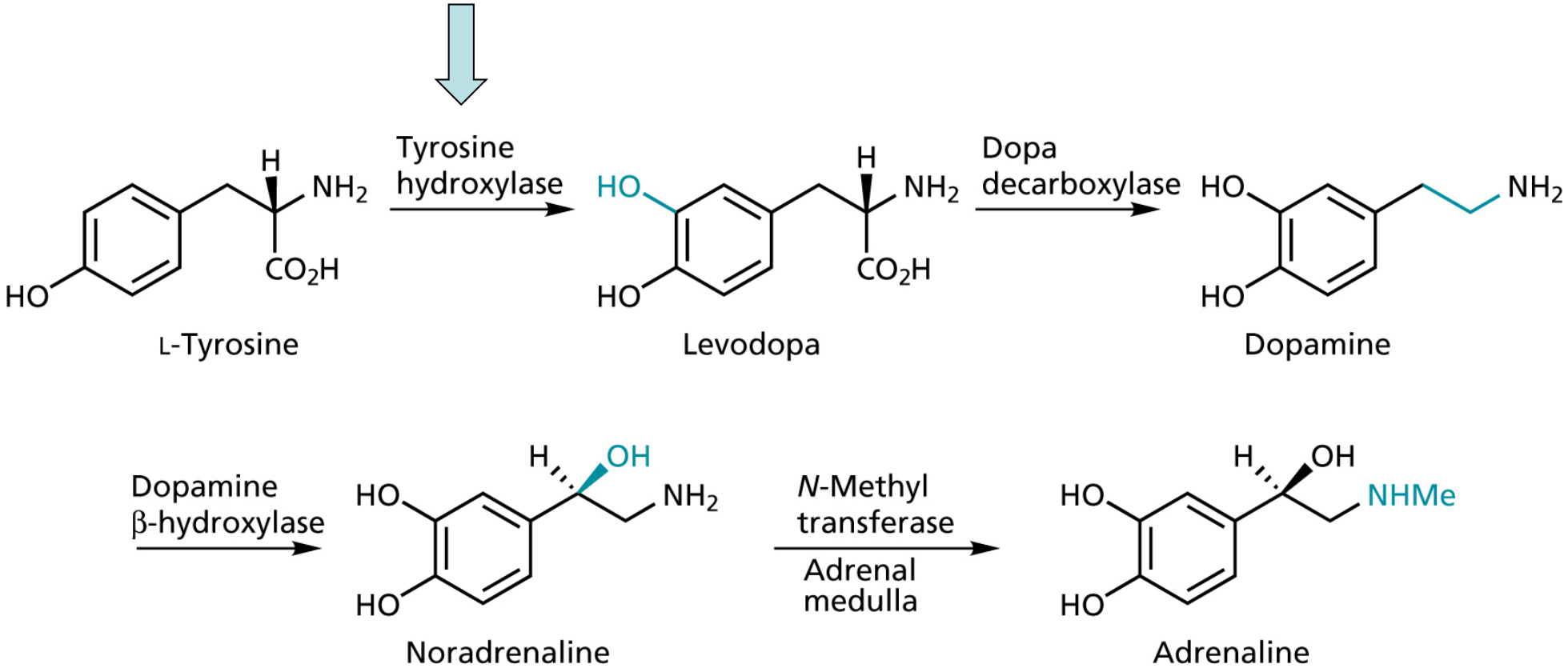
Ligação de Epinefrina no Receptor β_2Adrenérgico



Norepinefrina interage nos Domínios III, V e VI


H
OH
HO
NHMe
R
HO
Adrenaline
H
OH
HO
NH2
R
HO
Noradrenaline
H
OH
HO
NHR
alkylamine chain
HO
Catechol ring system

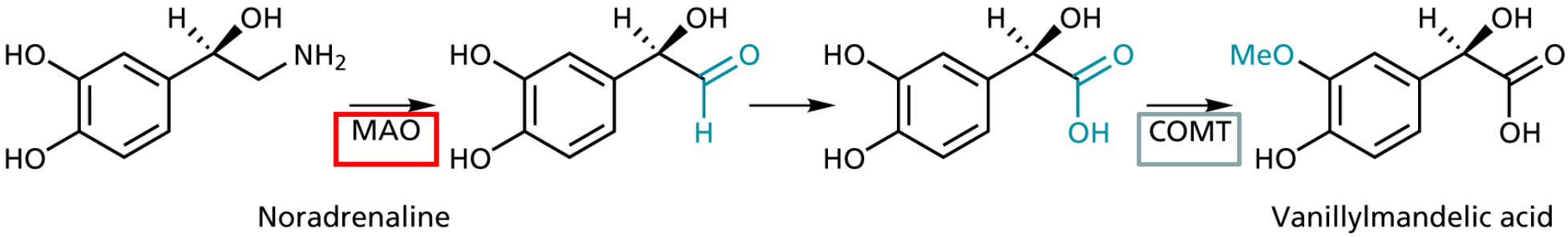
Biossíntese de Adrenalina e Noradrenalina



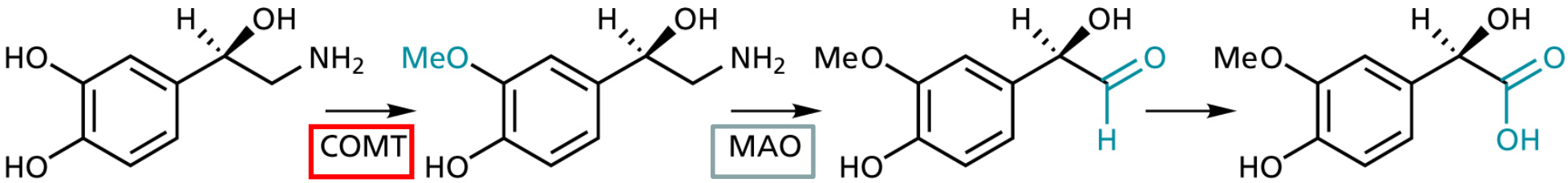
Metabolismo de Noradrenalina

MAO e COMT

Monoamino-oxidase e Catecol-*O*-metil-transferase

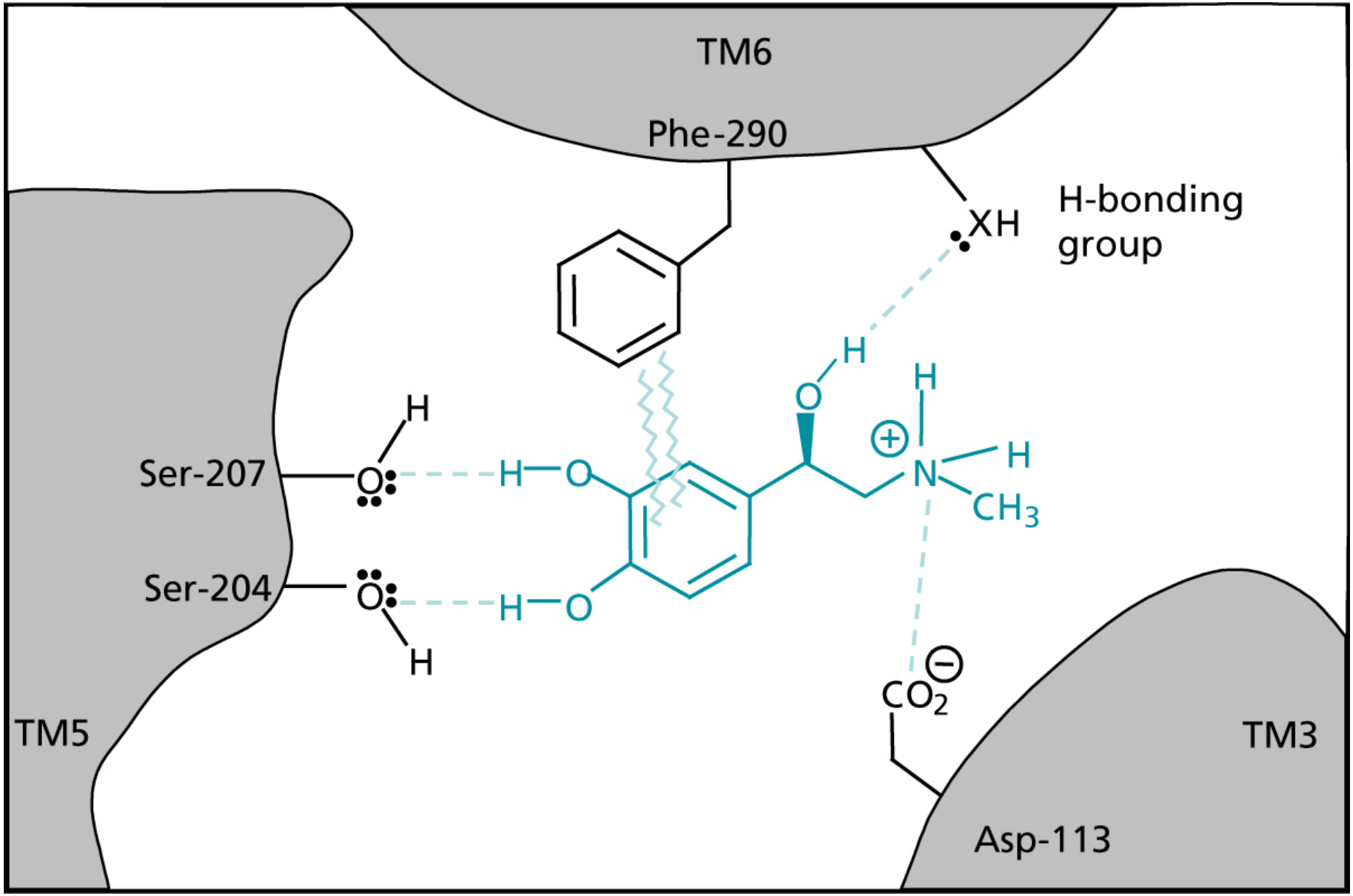


Noradrenaline — Vanillylmandelic acid

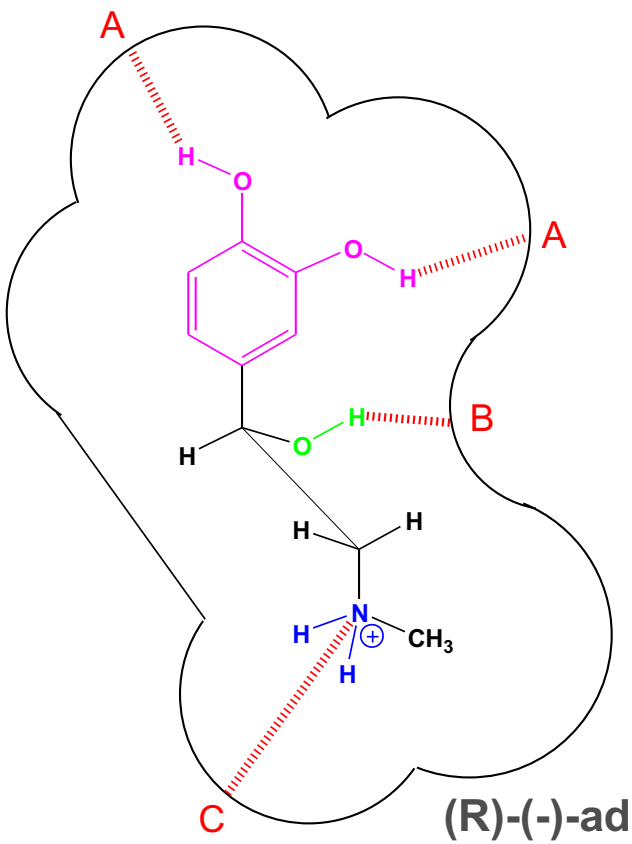


Noradrenaline — Vanillylmandelic acid

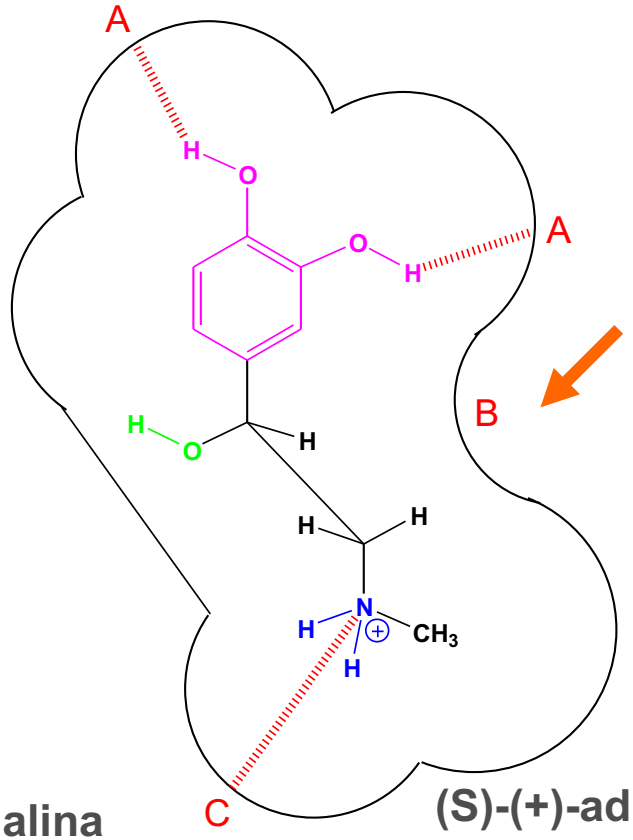
Adrenoreceptor beta



estereosseletividade



(R)-(-)-adrenalina

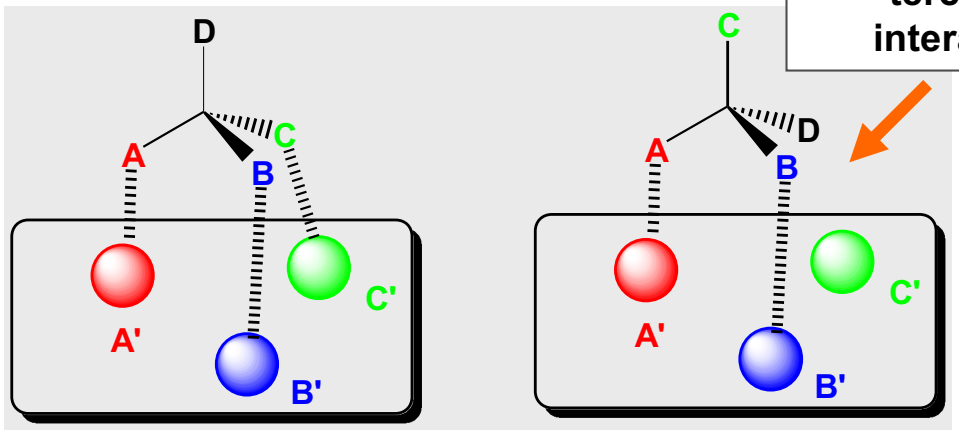


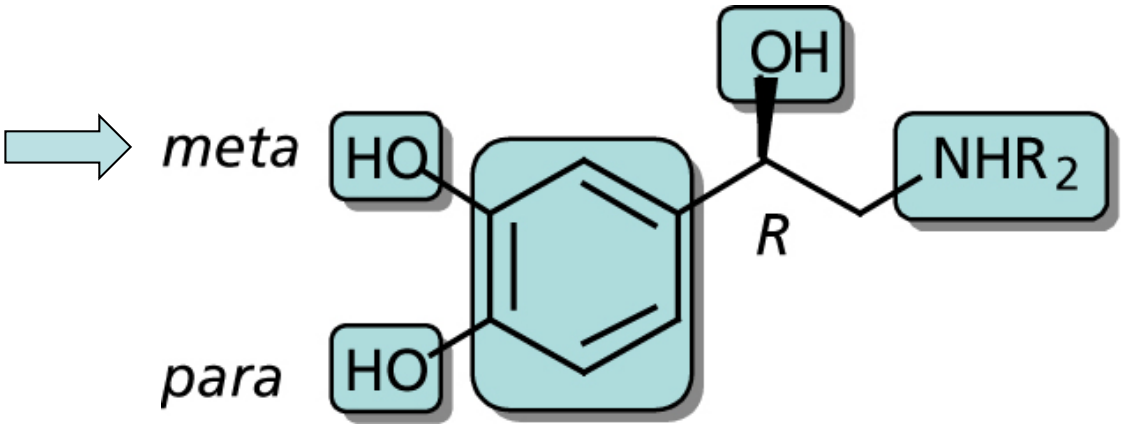
(S)-(+)-adrenalina

não ocorre a terceira interação

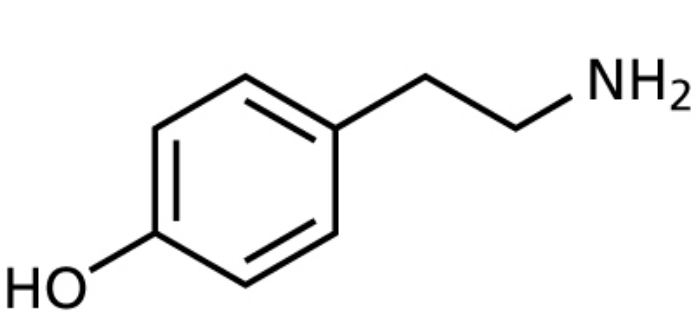
não ocorre a terceira interação

3 interações entre ligante-receptor, maior interação, maior potência

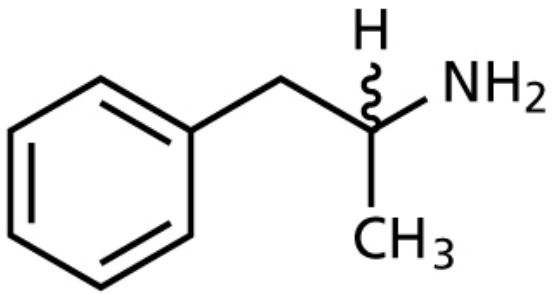




Grupos Importantes para ligação

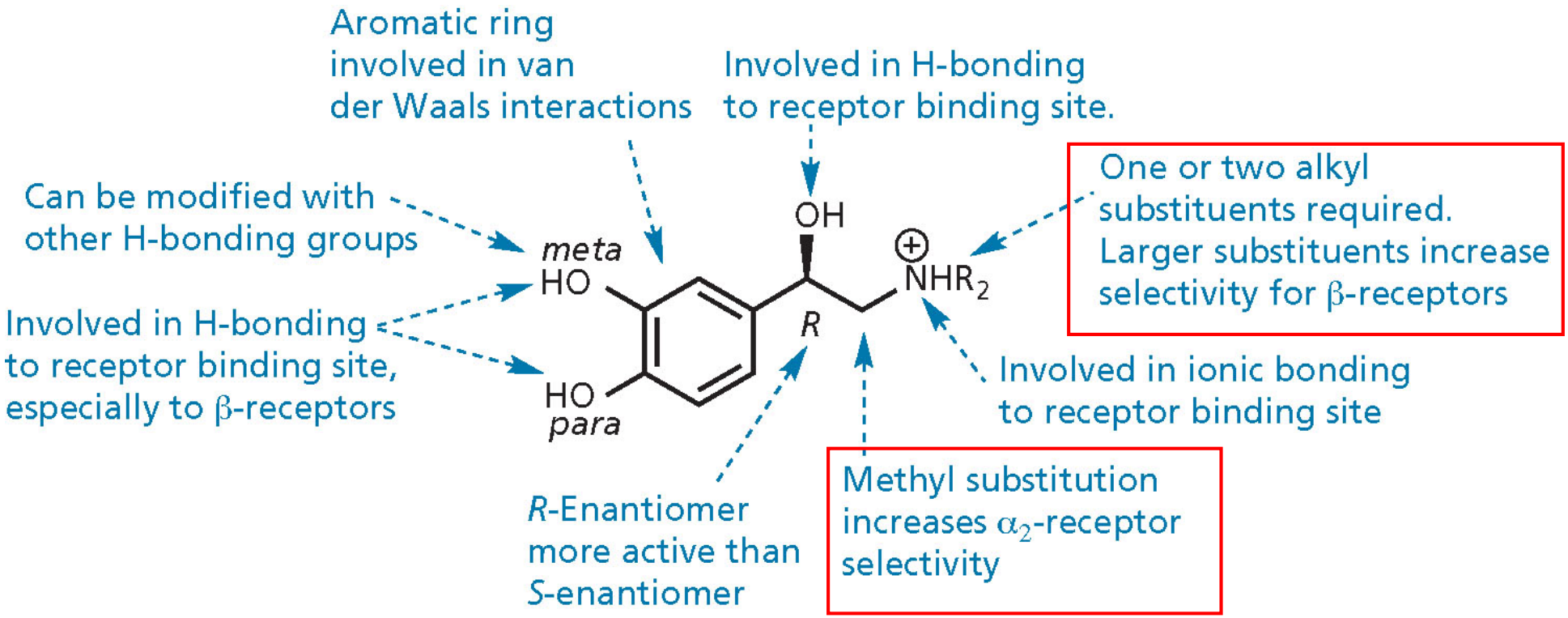


Tyramine

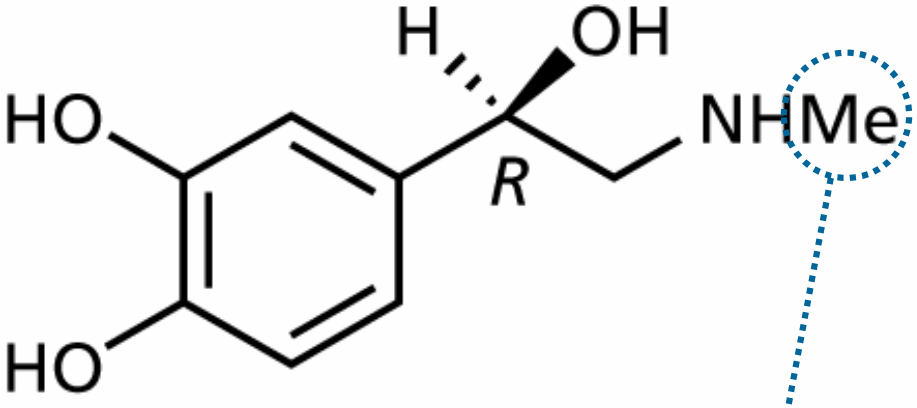


Amphetamine

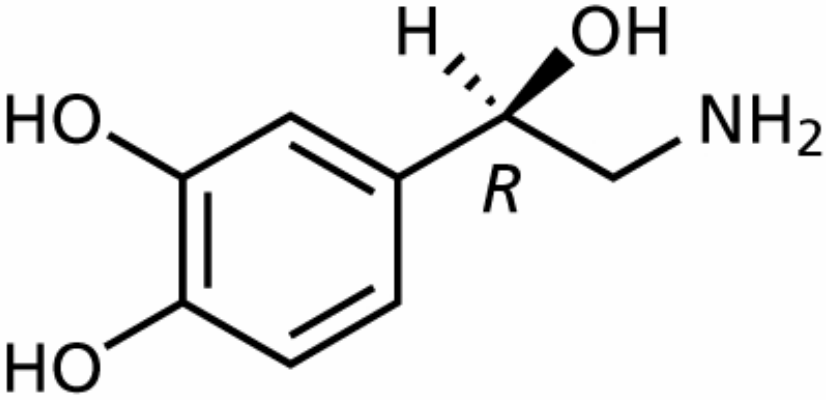
Sem afinidade pelo receptor adrenérgico


Aromatic ring involved in van der Waals interactions
Involved in H-bonding to receptor binding site.
Can be modified with other H-bonding groups
One or two alkyl substituents required. Larger substituents increase selectivity for β-receptors
meta
HO
OH
NHR2
R
Involved in H-bonding to receptor binding site, especially to β-receptors
HO
para
Involved in ionic bonding to receptor binding site
R-Enantiomer more active than S-enantiomer
Methyl substitution increases α2-receptor selectivity

Seletividade de alfa x beta



Adrenaline



Noradrenaline

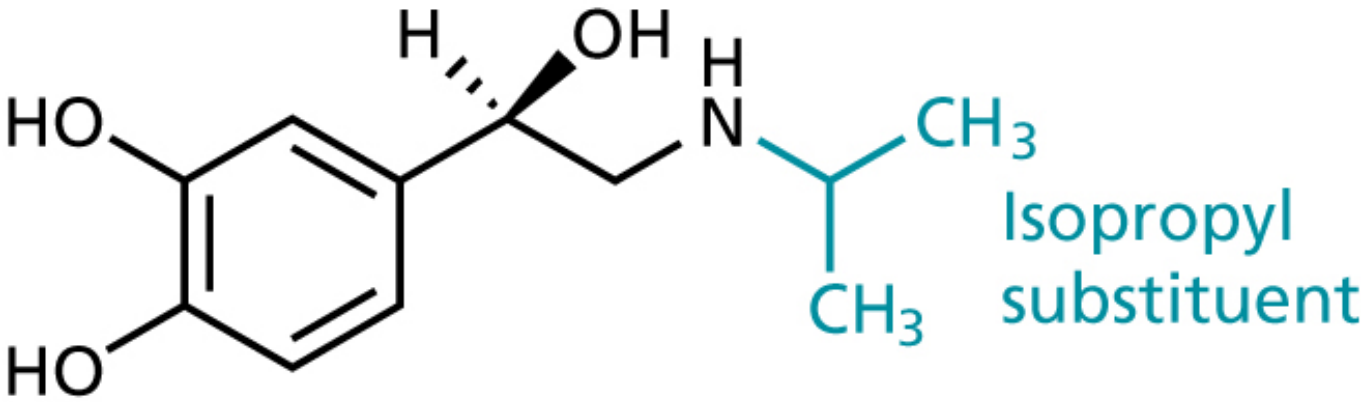
Seletividade α=β

Seletividade α>β

N-alquil tem importância na seletividade β

Seletividade alfa x beta

- **Substituintes *N*-alquílicos**
- **Aumentam atividade β**

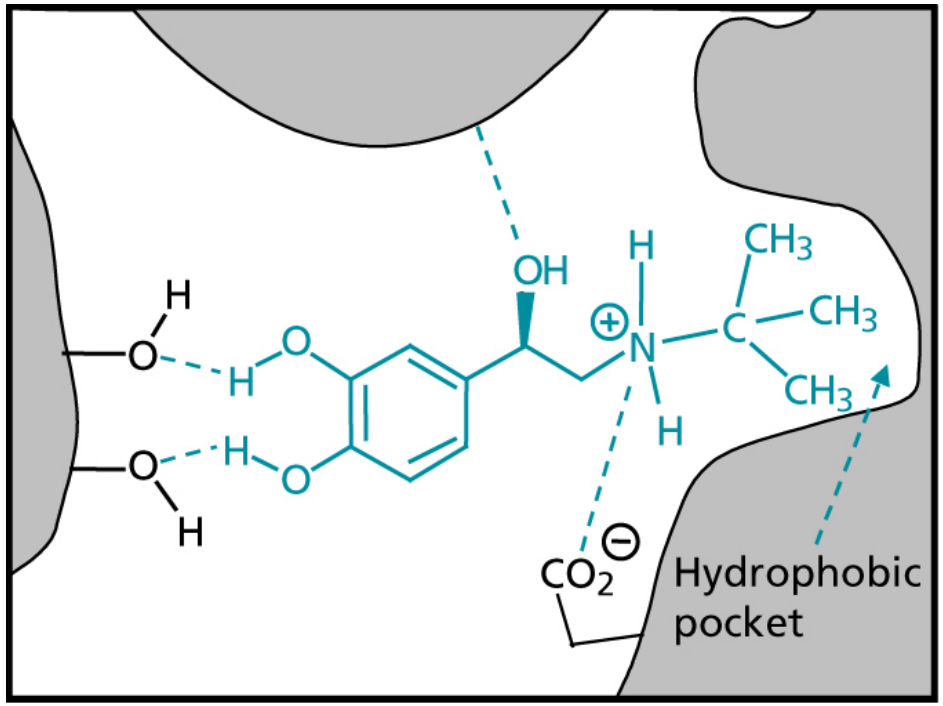


Isoprenalina – agonista β

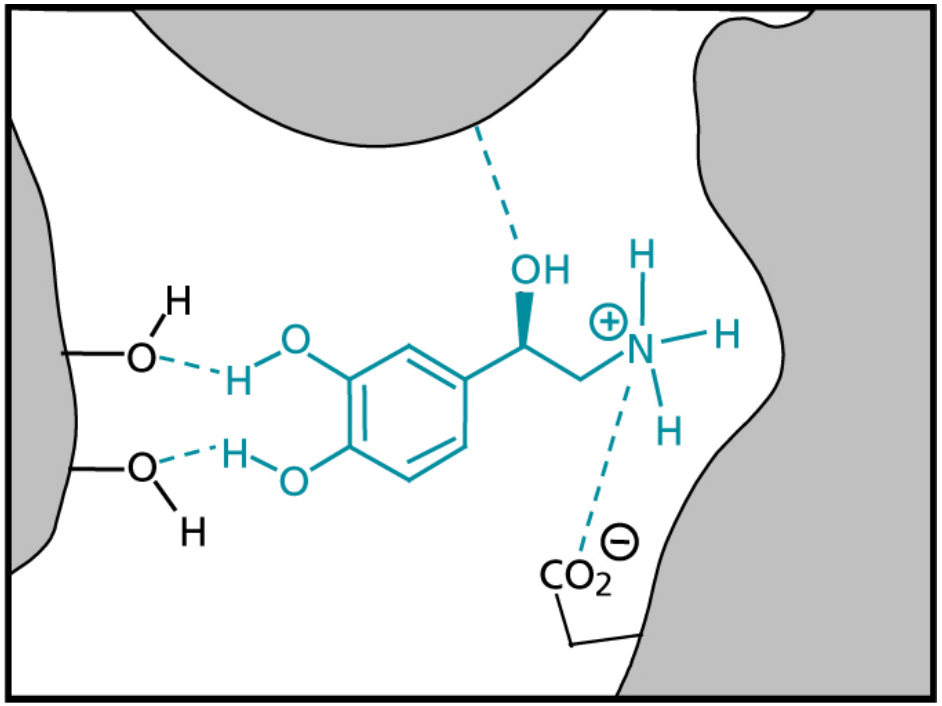
Ativa β2 nas vias aéreas (broncodilatador- ASMA)

Também ativa β1 no coração

Região hidrofóbica adicional



β-Adrenoceptor

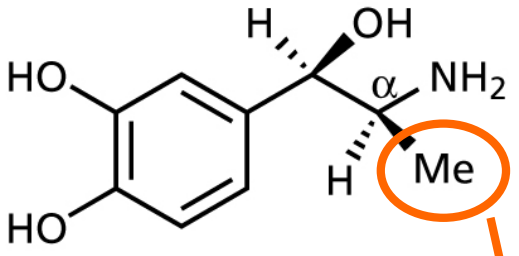


α-Adrenoceptor

Seletividade de alfa x beta

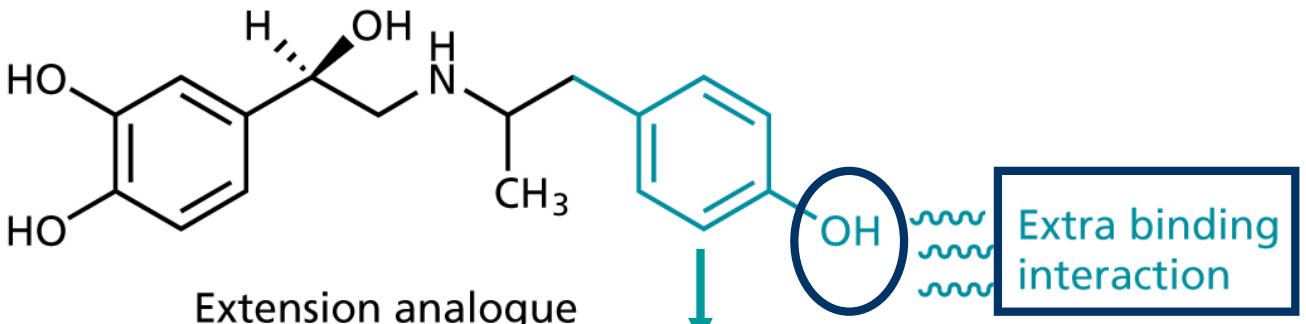
- Substituintes *N*-alquílicos
- Grupos fenílicos
- Substituinte alfa-metílico
- Extensão da cadeia

Análogos de Noradrenalina



α-Methylnoradrenaline

Aumenta seletividade α

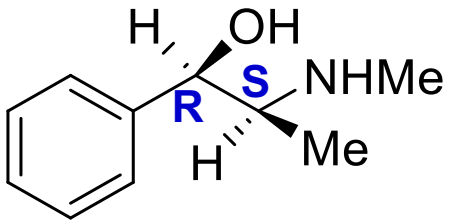


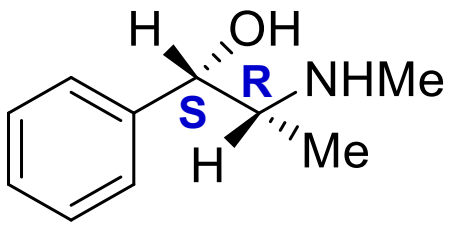
Extension analogue

Aumenta seletividade β

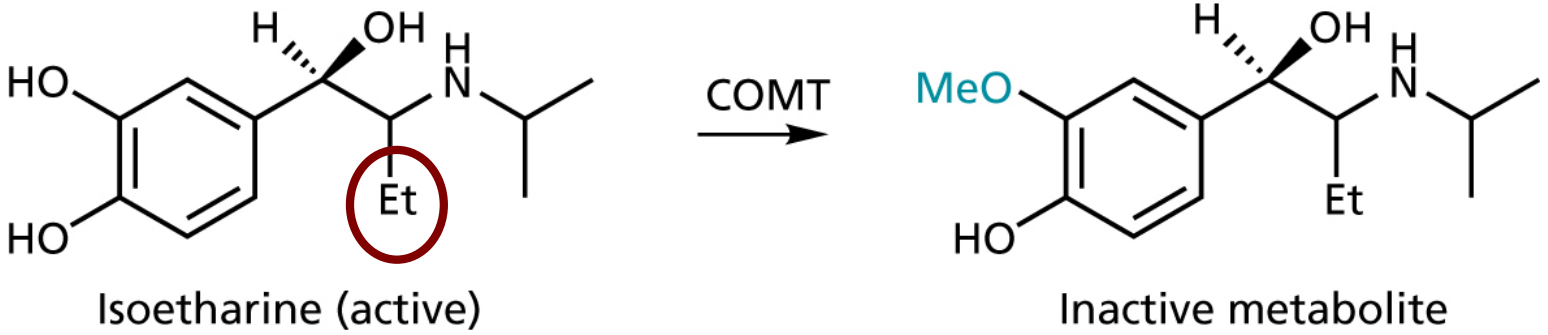
Aumenta seletividade β2

Efedrina - ativa receptores α e β: broncodilatador, vasopressor e estimulante cardíaco, ação no SNC





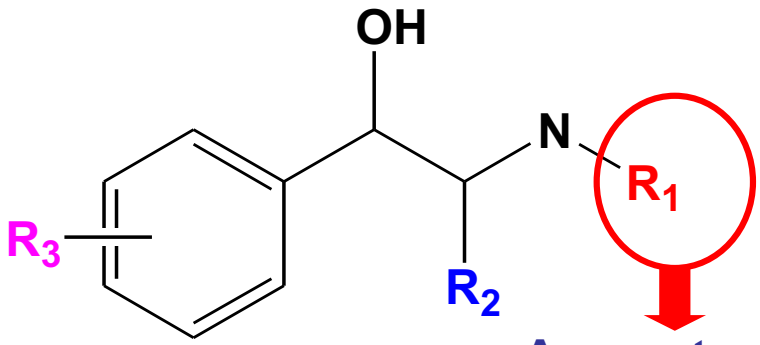
A busca por agonistas seletivos beta-2



Isoetharine (active) Inactive metabolite

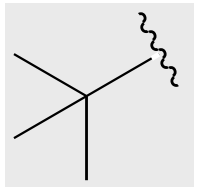
seletividade β2, com rápida duração de ação devido a metabolização pela COMT

AGONISTAS ADRENÉRGICOS

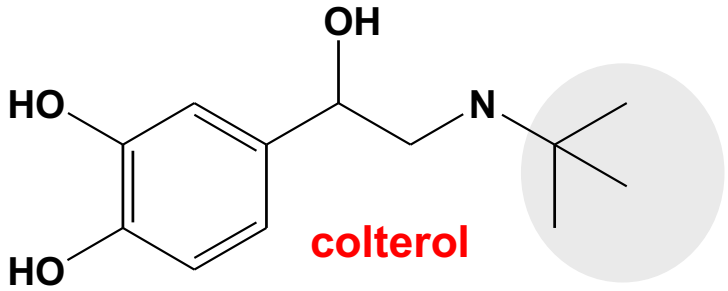


Aumenta o tamanho: ⇓ **atividade em receptores α**

(em relação a Me da epinefrina) ⇑ **atividade em receptores β**

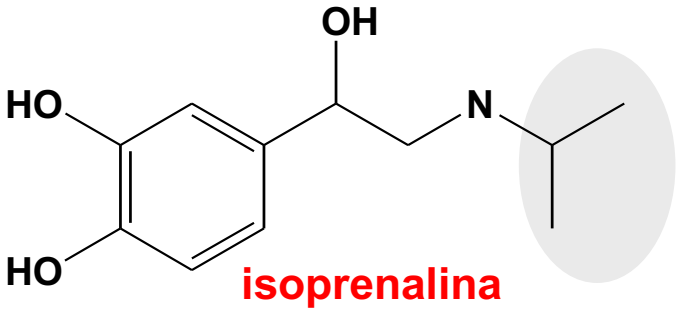


Grupo *terc*-butila: seletividade β_2



colterol

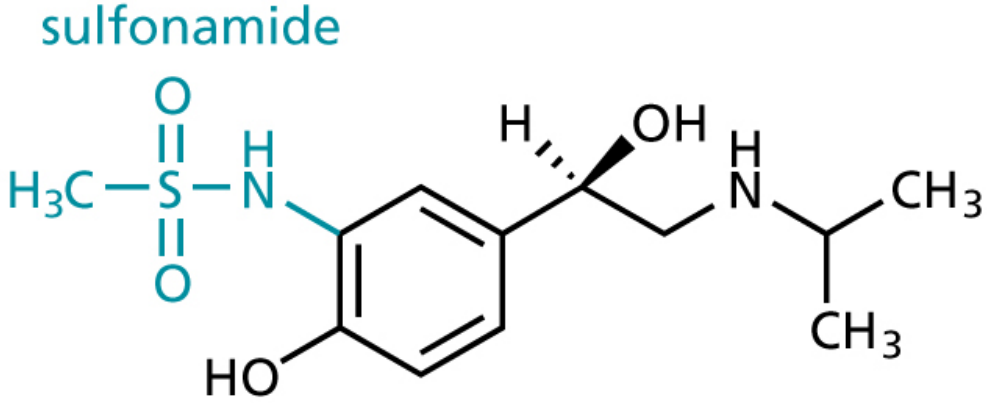
Agonista β não seletivo
(efeitos de estimulação β_1 cardíaca indesejáveis)



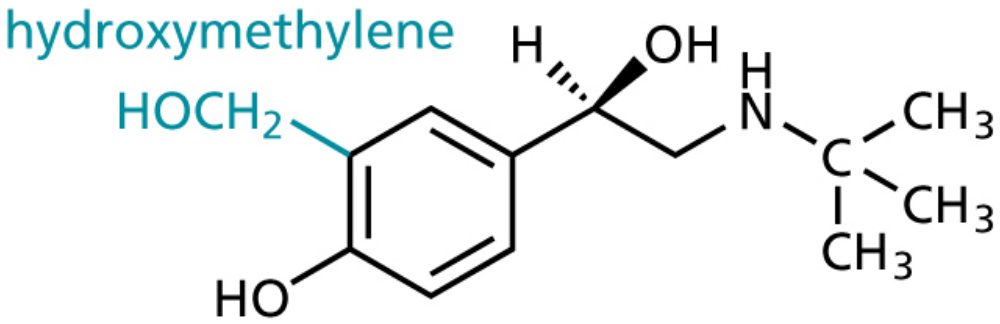
isoprenalina

Agonistas seletivos beta-2

Modificação da *m*-OH para aumentar resistência a metabolização



R-Soterenol **Agonistas β2**

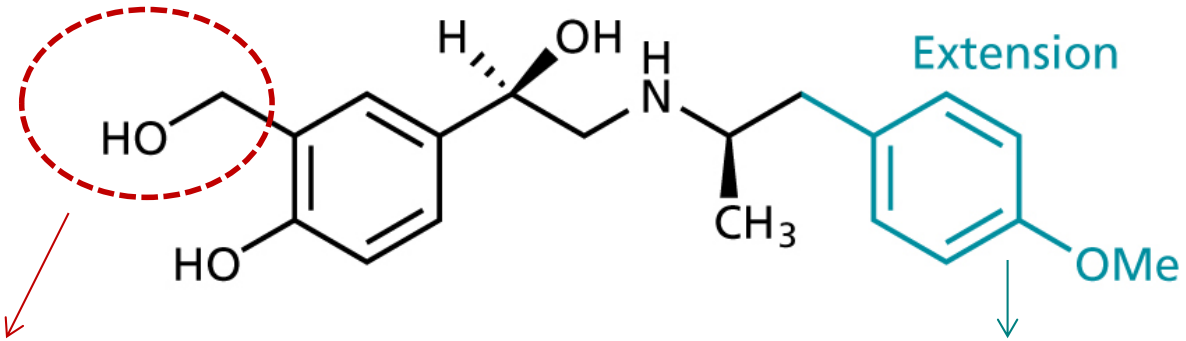


R-Salbutamol

(4 h)

2000 x menos ativo no coração

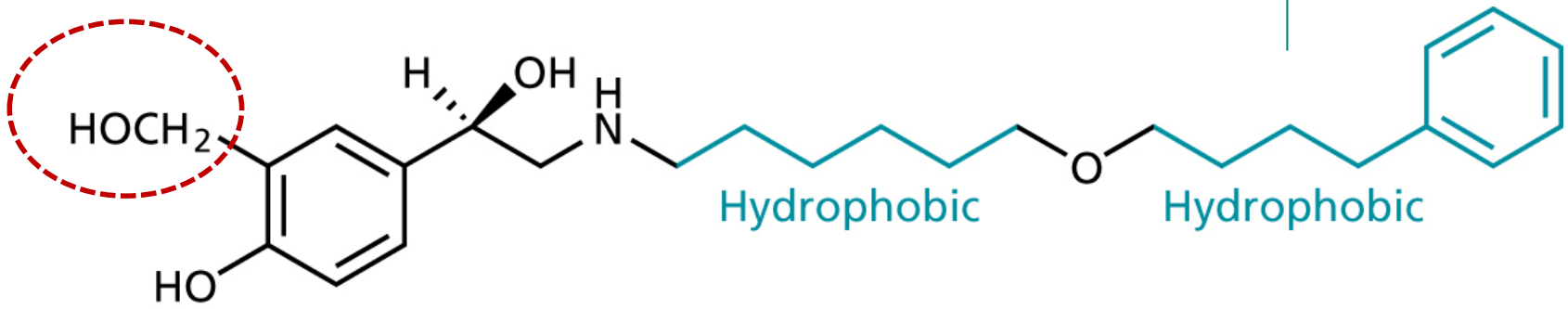
Salmefamol (6 h)



Impede metabolismo pela COMT

Maior duração de ação pela introdução de grupos com caráter lipofílico

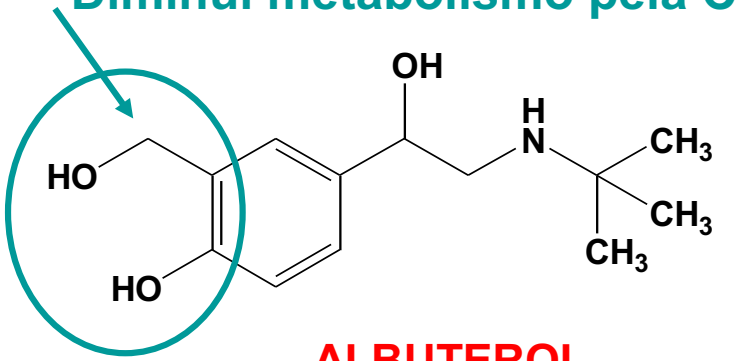
Salmeterol (12 h)



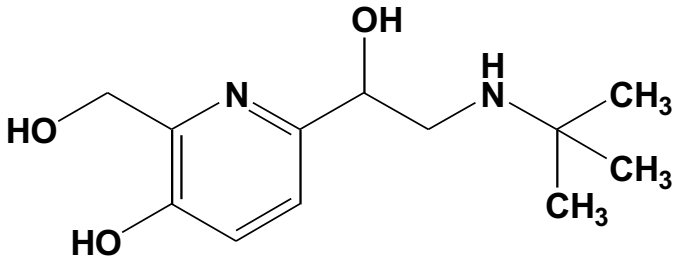
Agonistas β_2 – adrenérgicos

BRONCODILATADORES – tratamento da asma

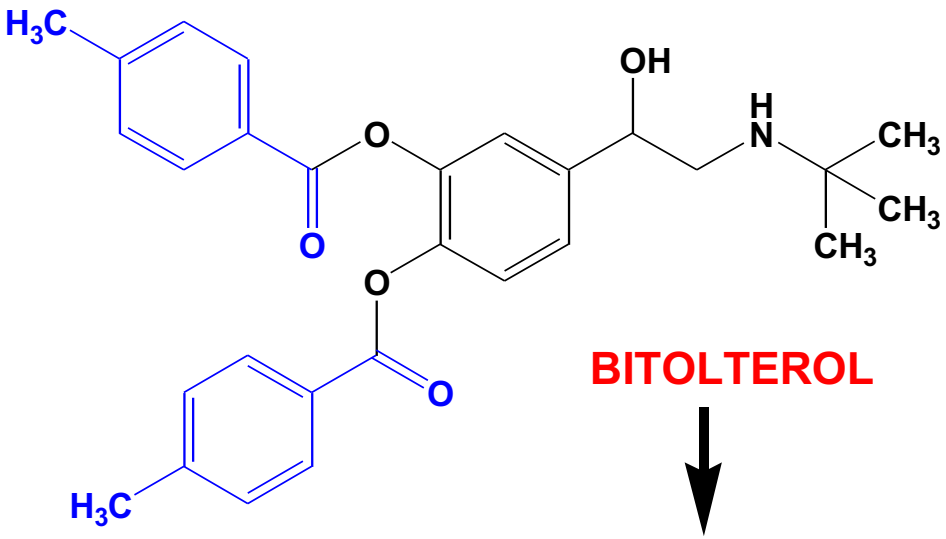
Diminui metabolismo pela COMT



ALBUTEROL
(salbutamol)

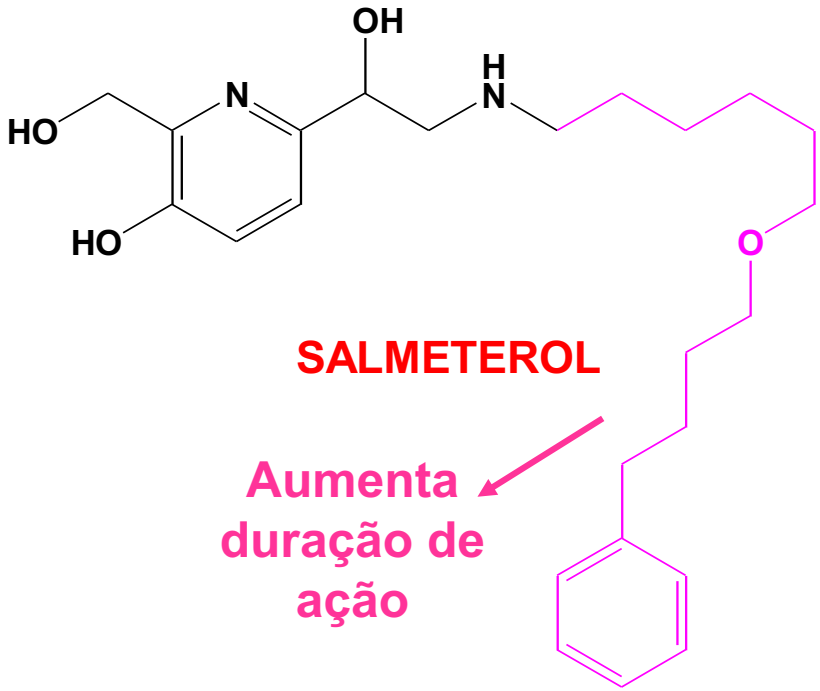


PIRBUTEROL



BITOLTEROL

COLTEROL

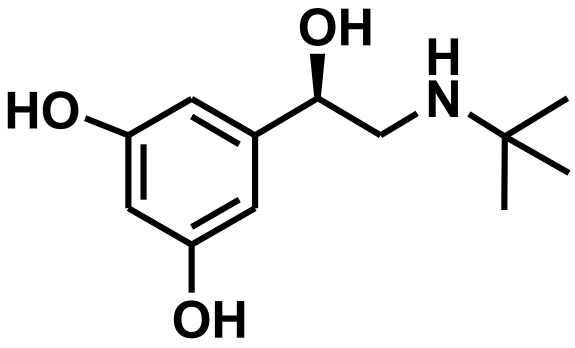


SALMETEROL

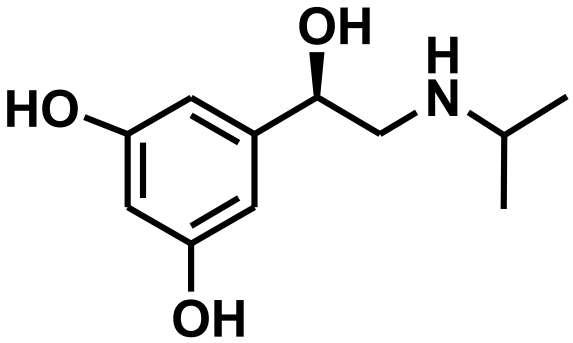
Aumenta duração de ação

Agonistas β_2 – adrenérgicos

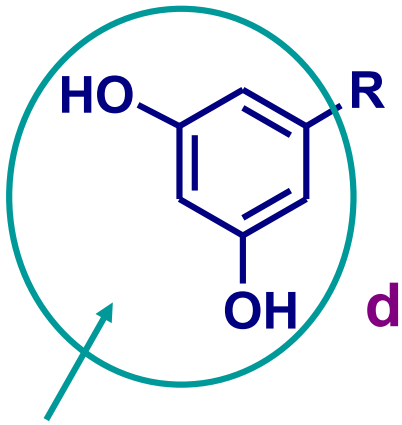
BRONCODILATADORES – tratamento da asma



terbutalina



metaproterenol

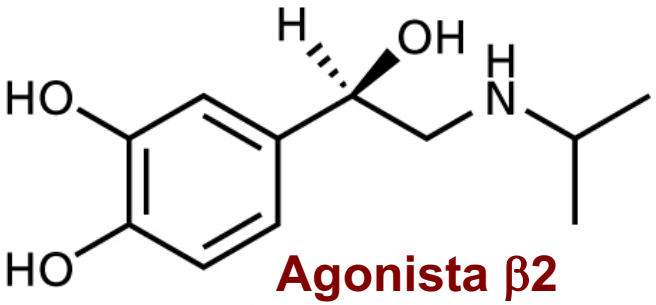


derivado 3,5-di-hidroxilado

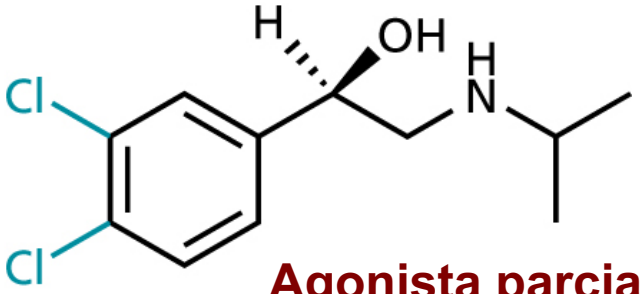
Diminui metabolismo pela COMT

Bloqueadores beta-adrenérgicos

Busca por antagonistas beta 1 do coração:
-variação no anel aromático

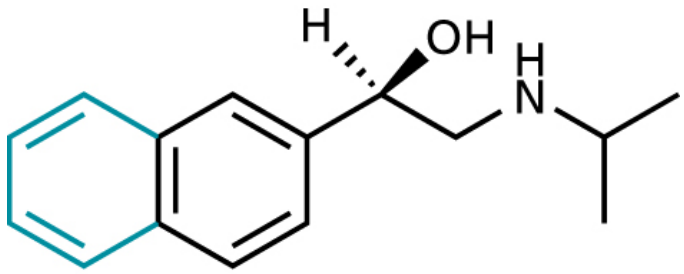


Agonista β2
Isoprenaline



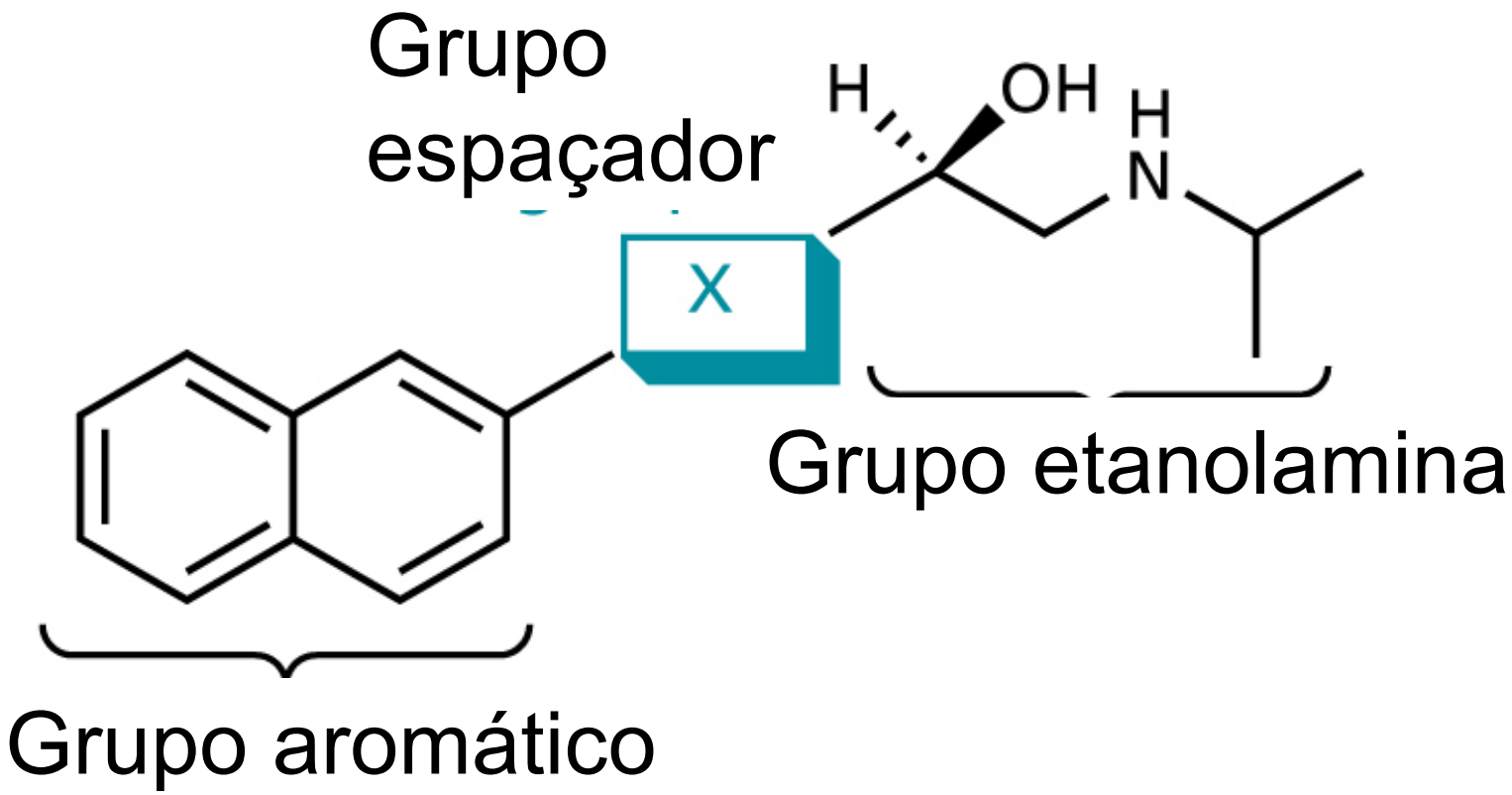
Agonista parcial
Dichloroisoprenaline

Agonista parcial, com ação antagonista
Primeiro beta-bloqueador usado clinicamente para angina, arritmias, hipertensão

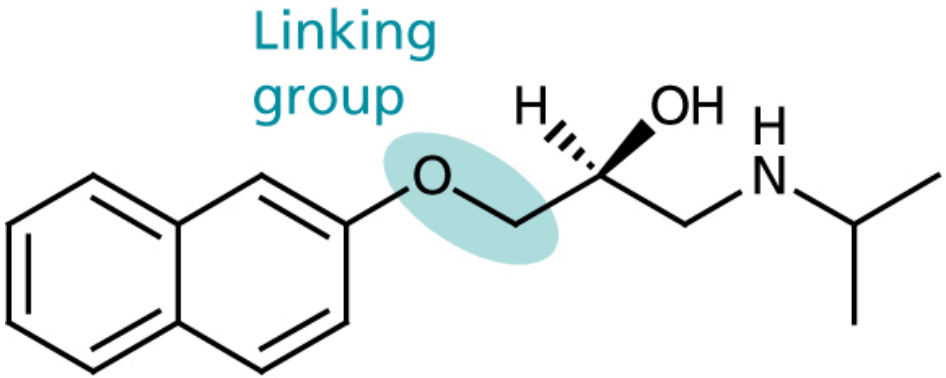


Pronethalol

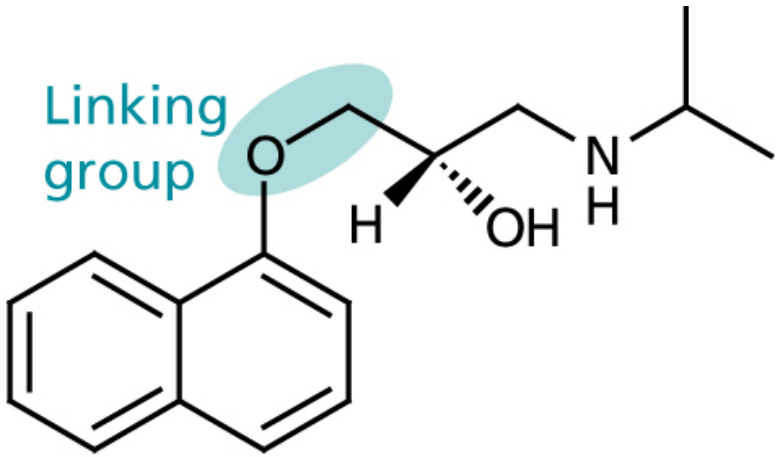
Extensão da cadeia lateral



Propranolol



Composto de interesse



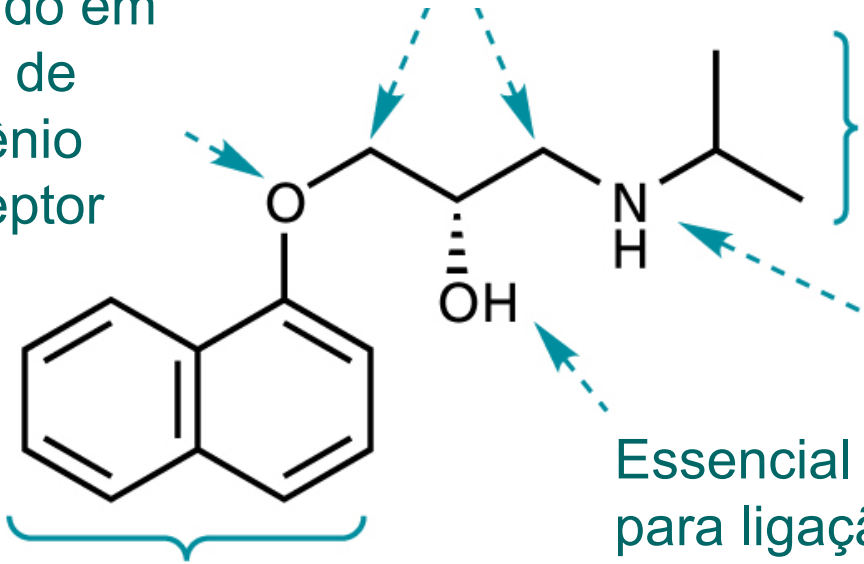
Propranolol

10-20X mais ativo que pronetalol
Introduzido para tratamento de angina
Enantiômero *S* é ativo, porém usado como racemato

Relação Estrutura-atividade

Substituição diminui a atividade

Envolvido em ligação de hidrogênio no receptor

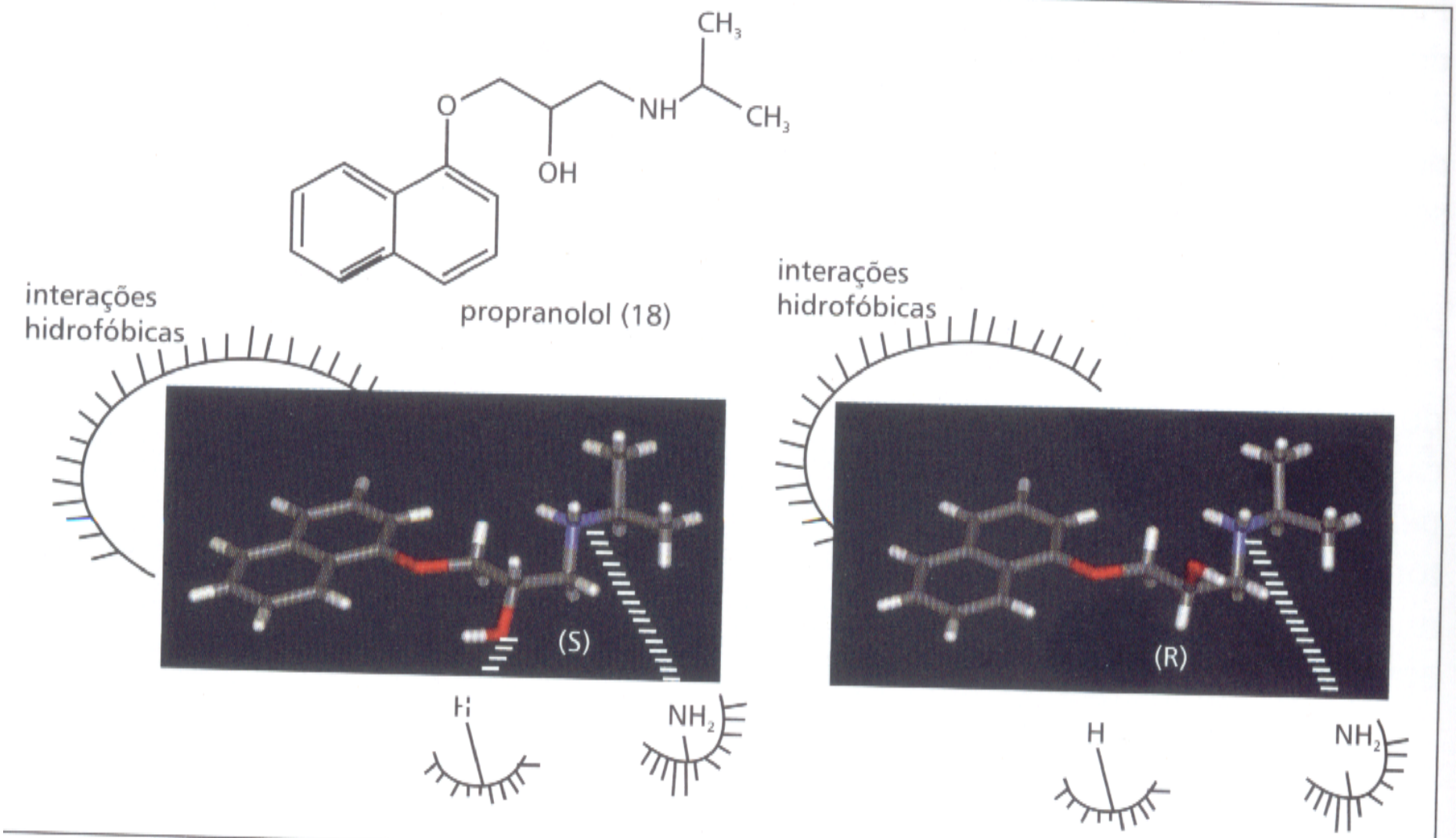


Ramificação e extensão são Desejadas para preencher o bolsão hidrofóbico (^{i}Bu, ^{t}Bu)

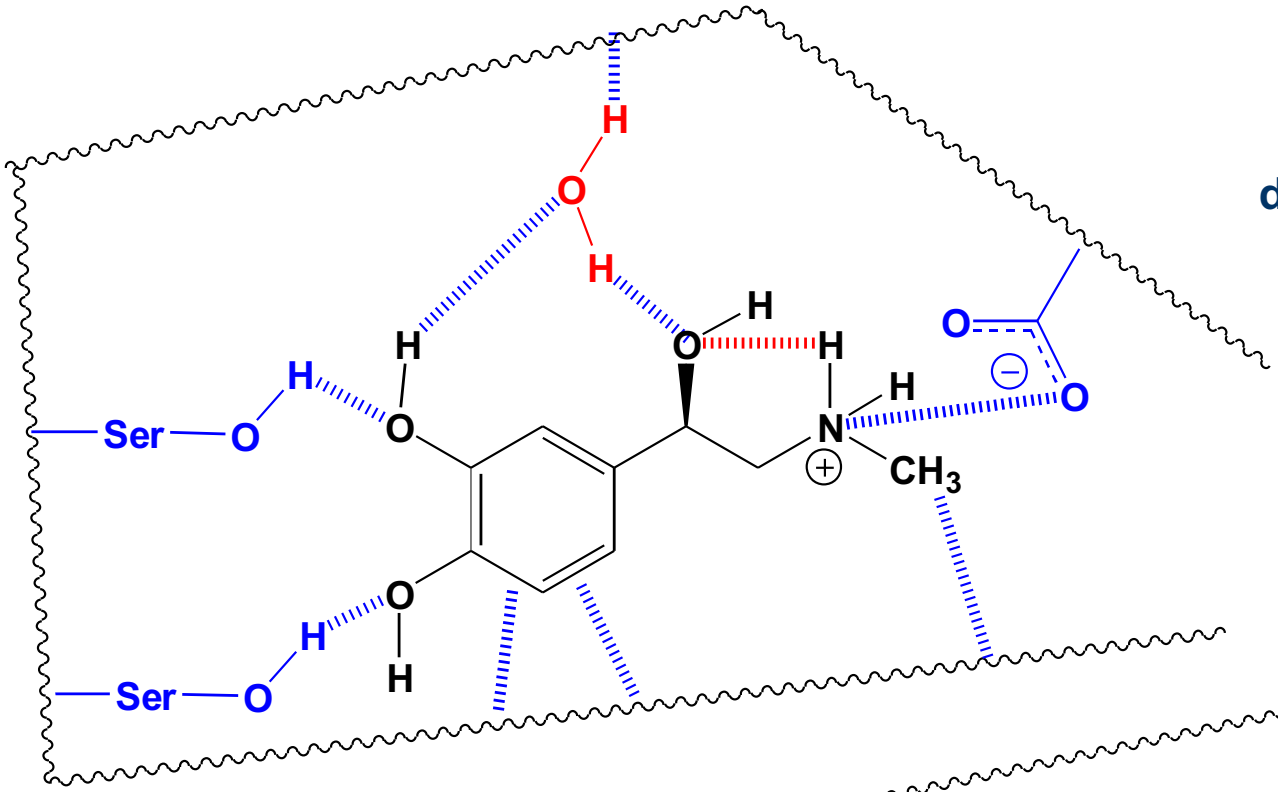
Ligação iônica essencial para interação. Deve ser Amina secundária

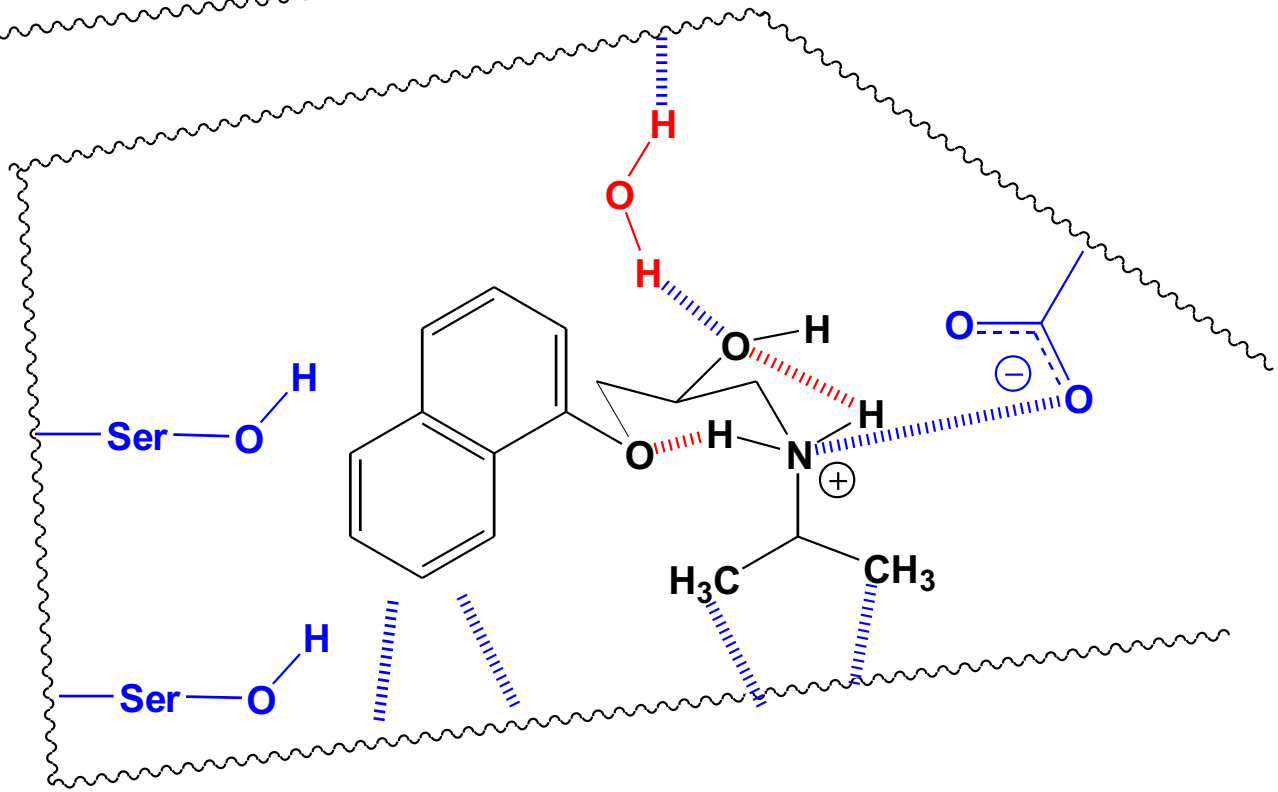
Essencial para ligação de hidrogênio

Pode ser modificado com anéis heteroaromáticos

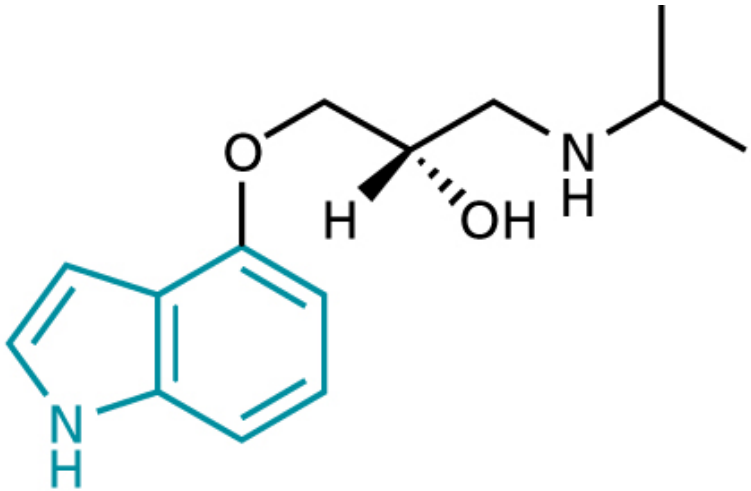

CH3
O
NH
CH3
OH
propranolol (18)
interações
hidrofóbicas
(S)
H
NH2
interações
hidrofóbicas
(R)
H
NH2

Representação esquemática da interação da adrenalina e do propranolol com o receptor β-adrenérgico

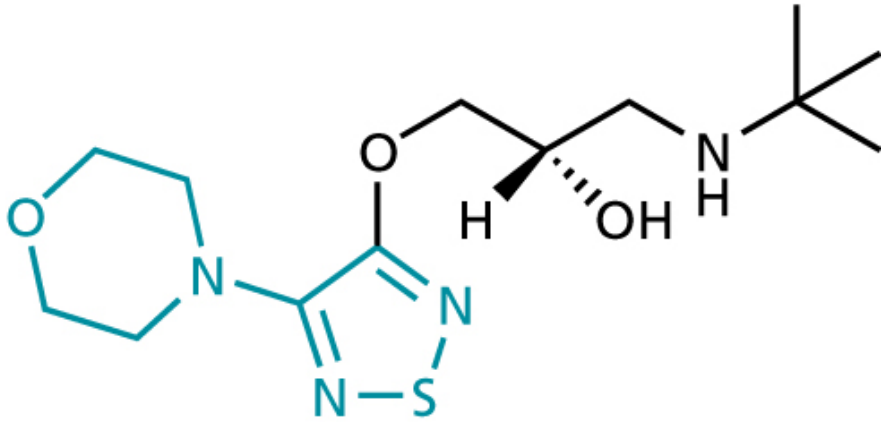




Antagonistas beta contendo anéis heterocíclicos

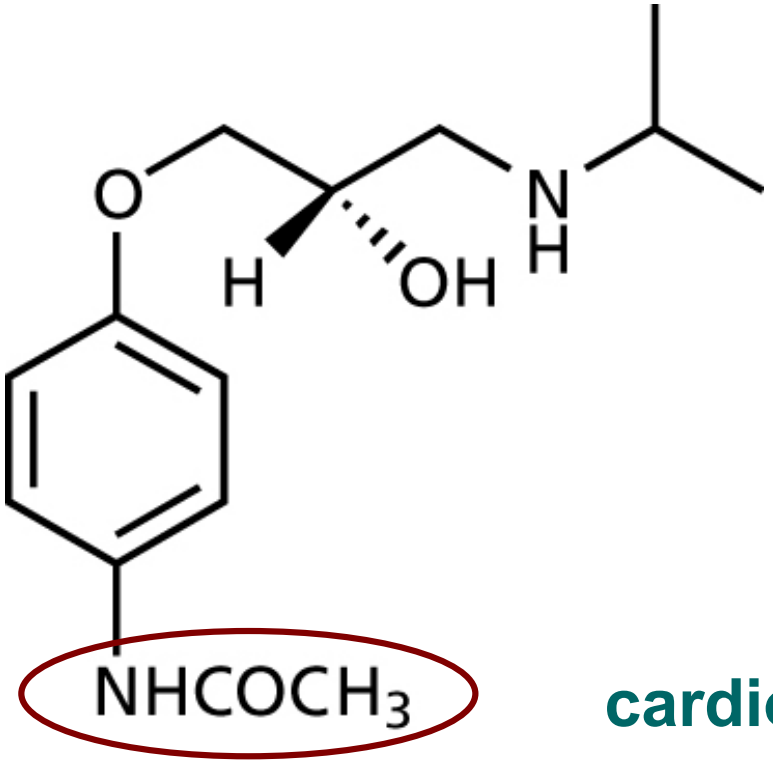


Pindolol



Timolol

Bloqueadores beta-1 seletivos (2ª geracao)

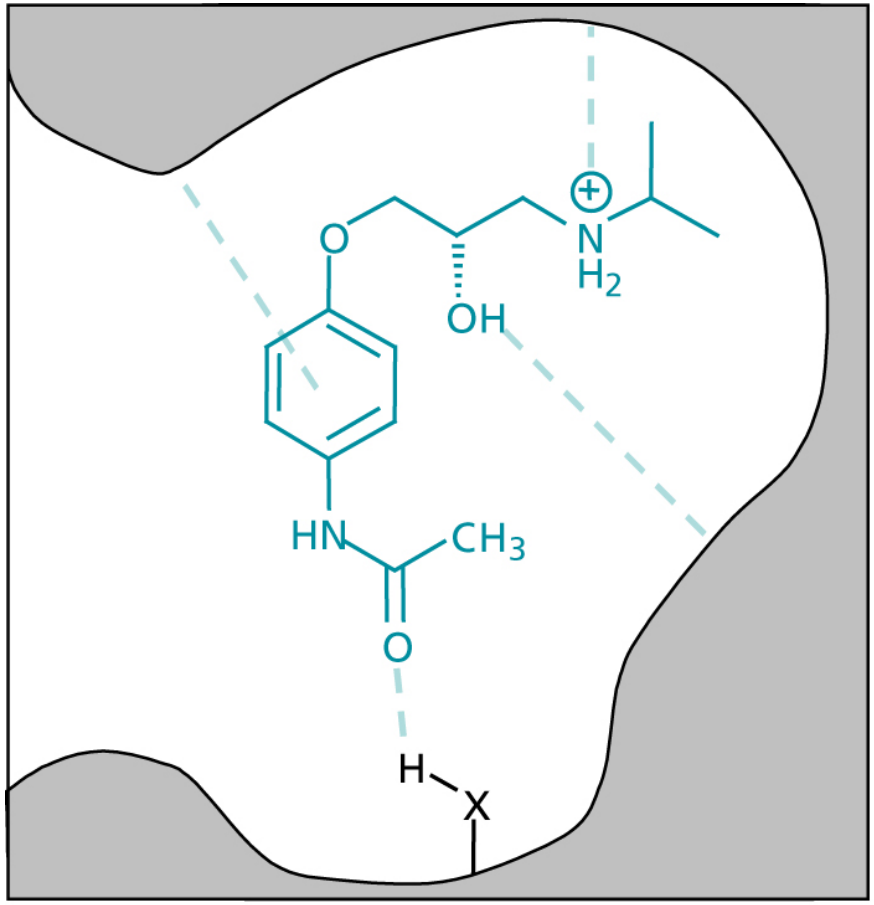


Amida em *para*
seletividade β1

cardiosseletivo

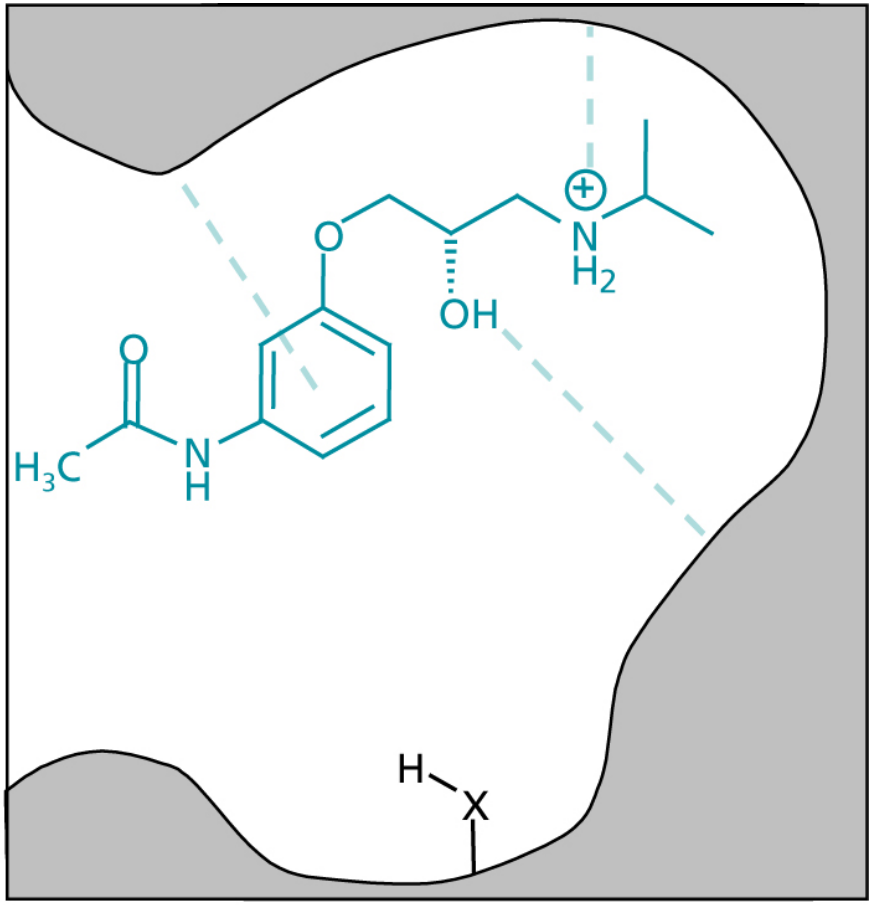
Practolol

Interações no receptor beta-1



para substitution

Interação extra por ligação de hidrogênio

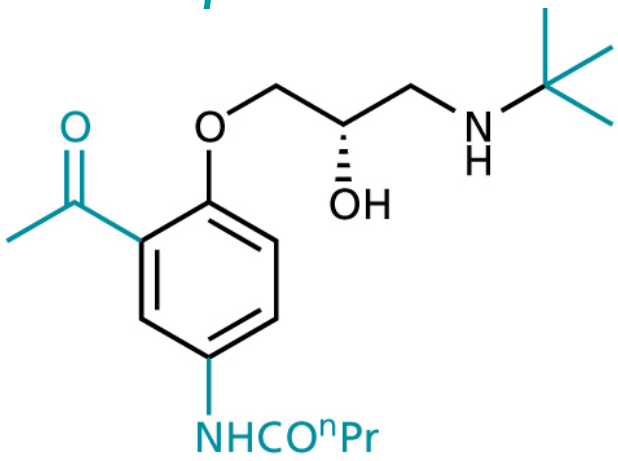


meta substitution

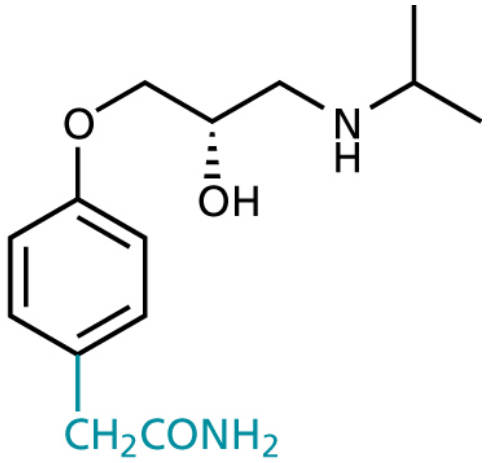
Não ocorre interação por lig. H da amida

Segunda geração de bloqueadores seletivos beta-1

Grupos em *para* capazes de estabelecer lig. de H - seletividade β1

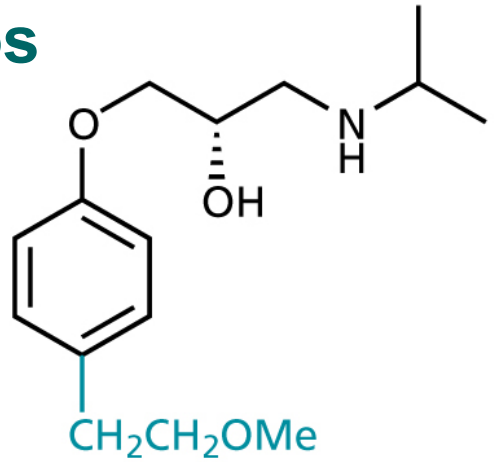


Acebutolol

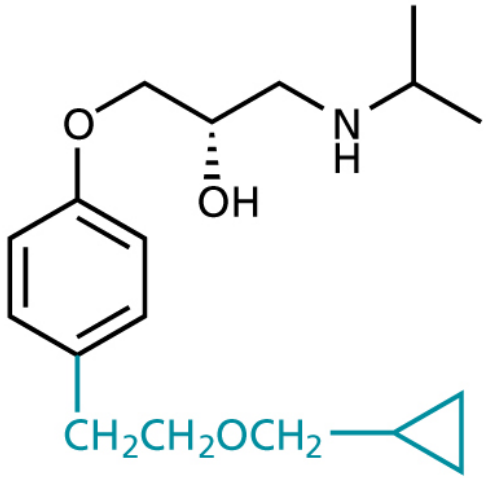


Atenolol

cardiosseletivos

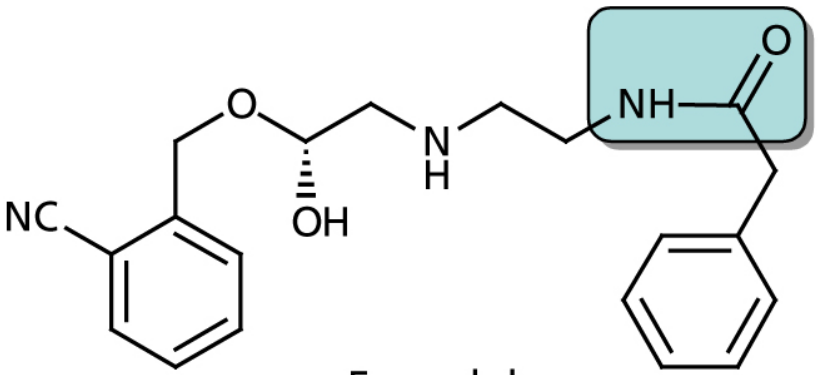


Metoprolol

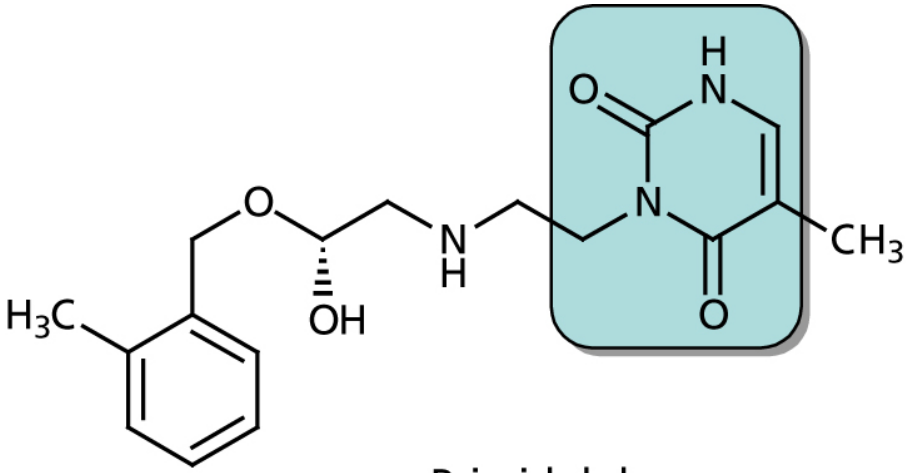


Betaxolol

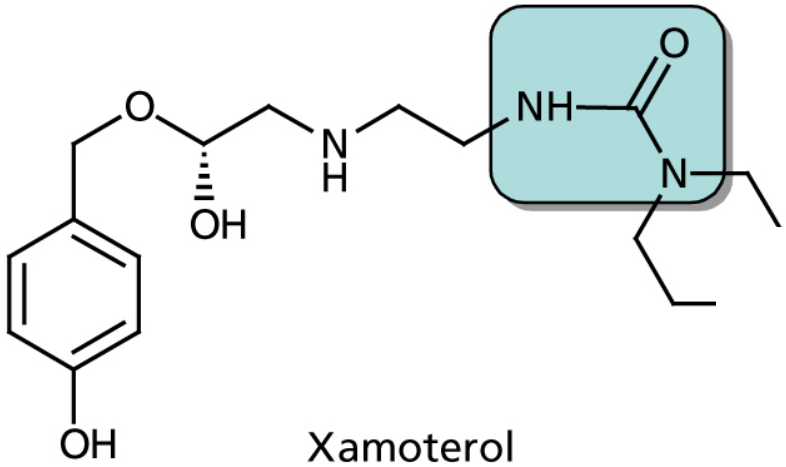
Terceira geração de bloqueadores beta-1



Epanolol



Primidolol



Xamoterol

Grupos envolvidos em ligações de hidrogênio adicionais na cadeia lateral