



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. *The 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

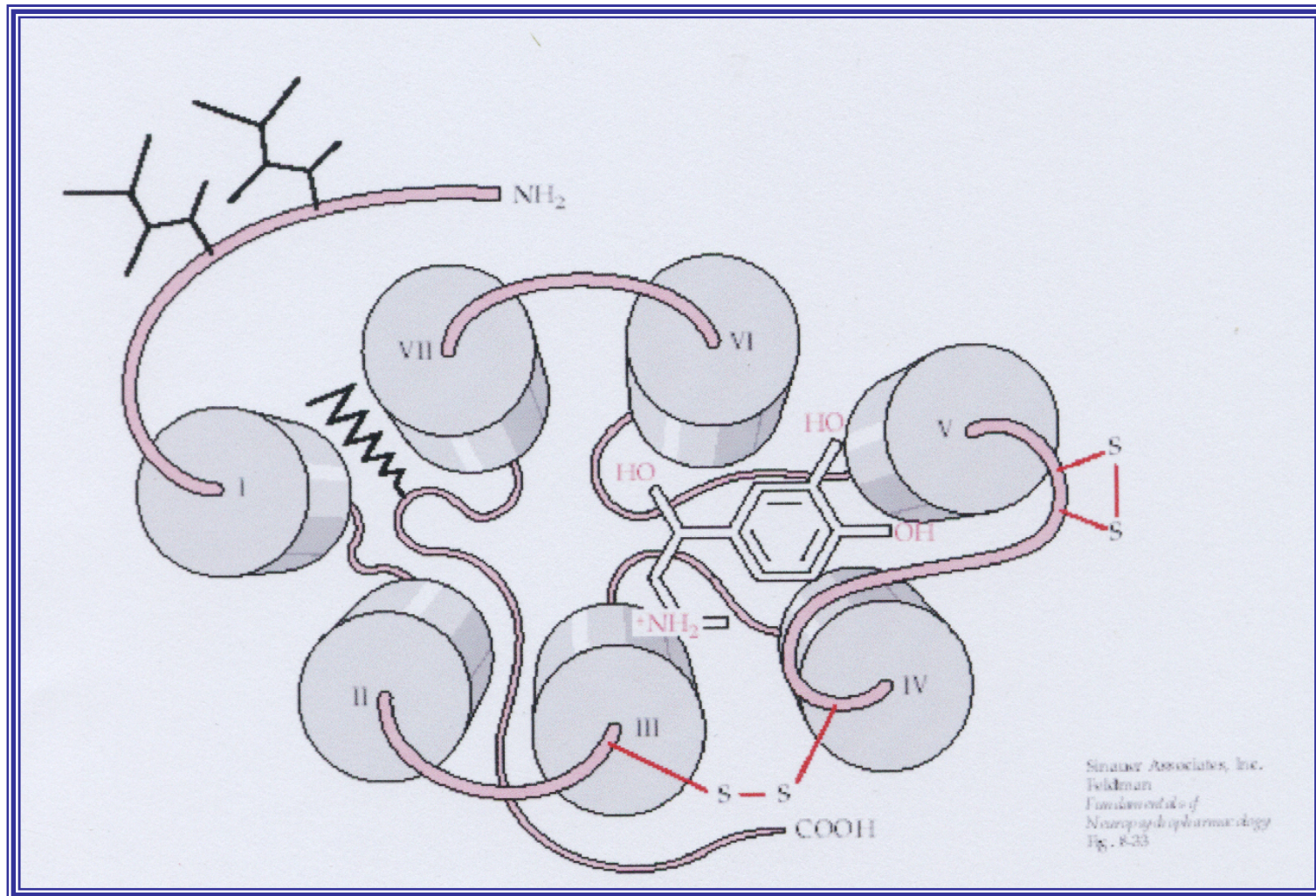
Tratamento da **hipertensão**, relaxamento da musculatura dos vasos sanguíneos-dilatação

Antagonistas dos receptores β_1 ✓

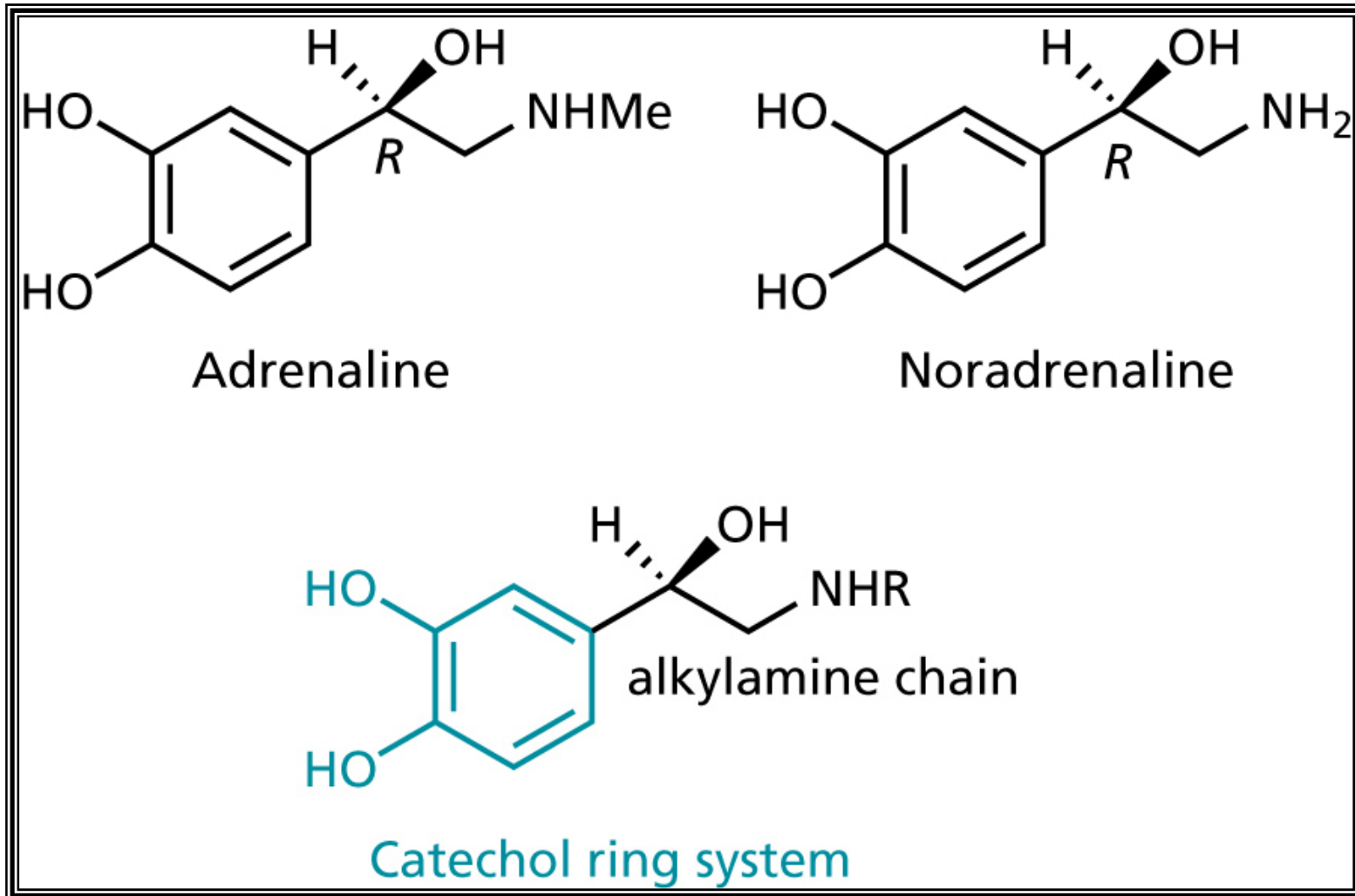
Tratamento da **hipertensão**, diminuição da força de contração e batimentos cardíacos



Ligação de Epinefrina no Receptor β_2 Adrenérgico

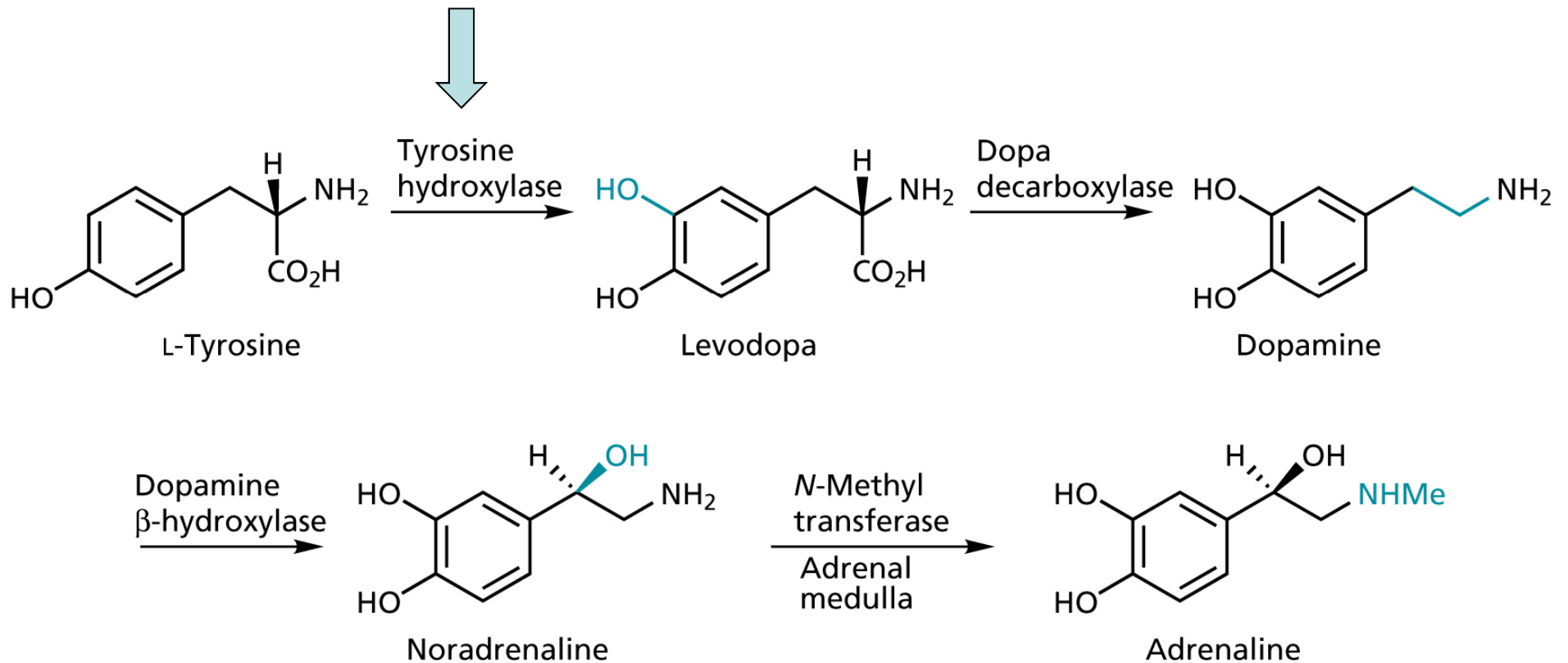


Norepinefrina interage nos Domínios III, V e VI





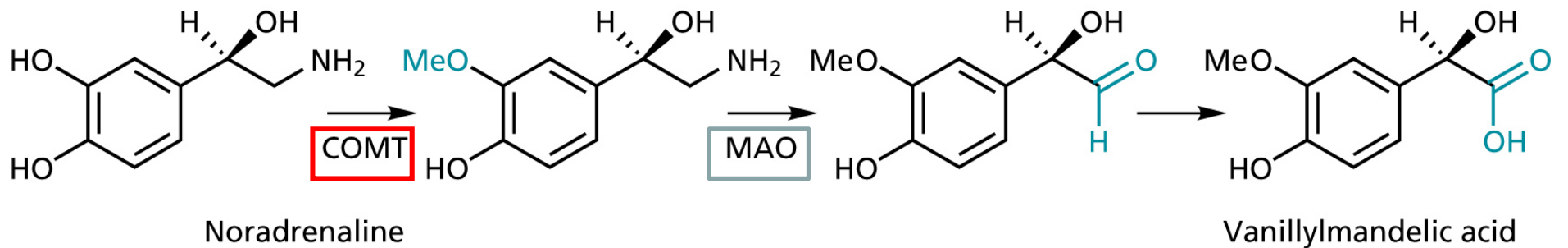
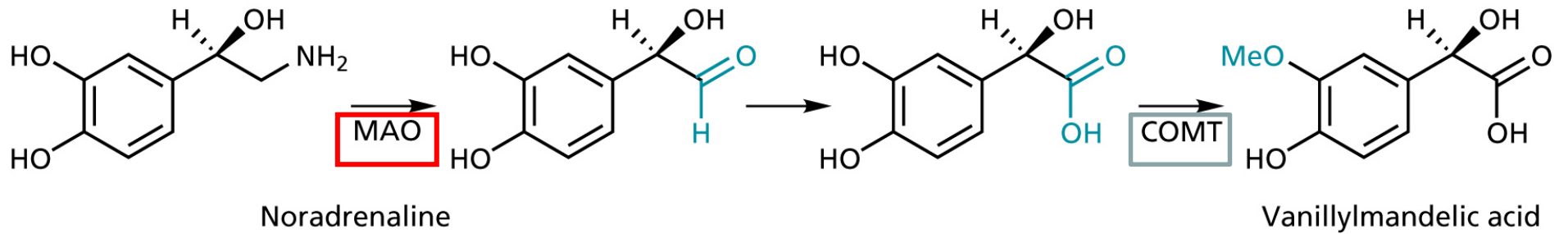
Biossíntese de Adrenalina e Noradrenalina





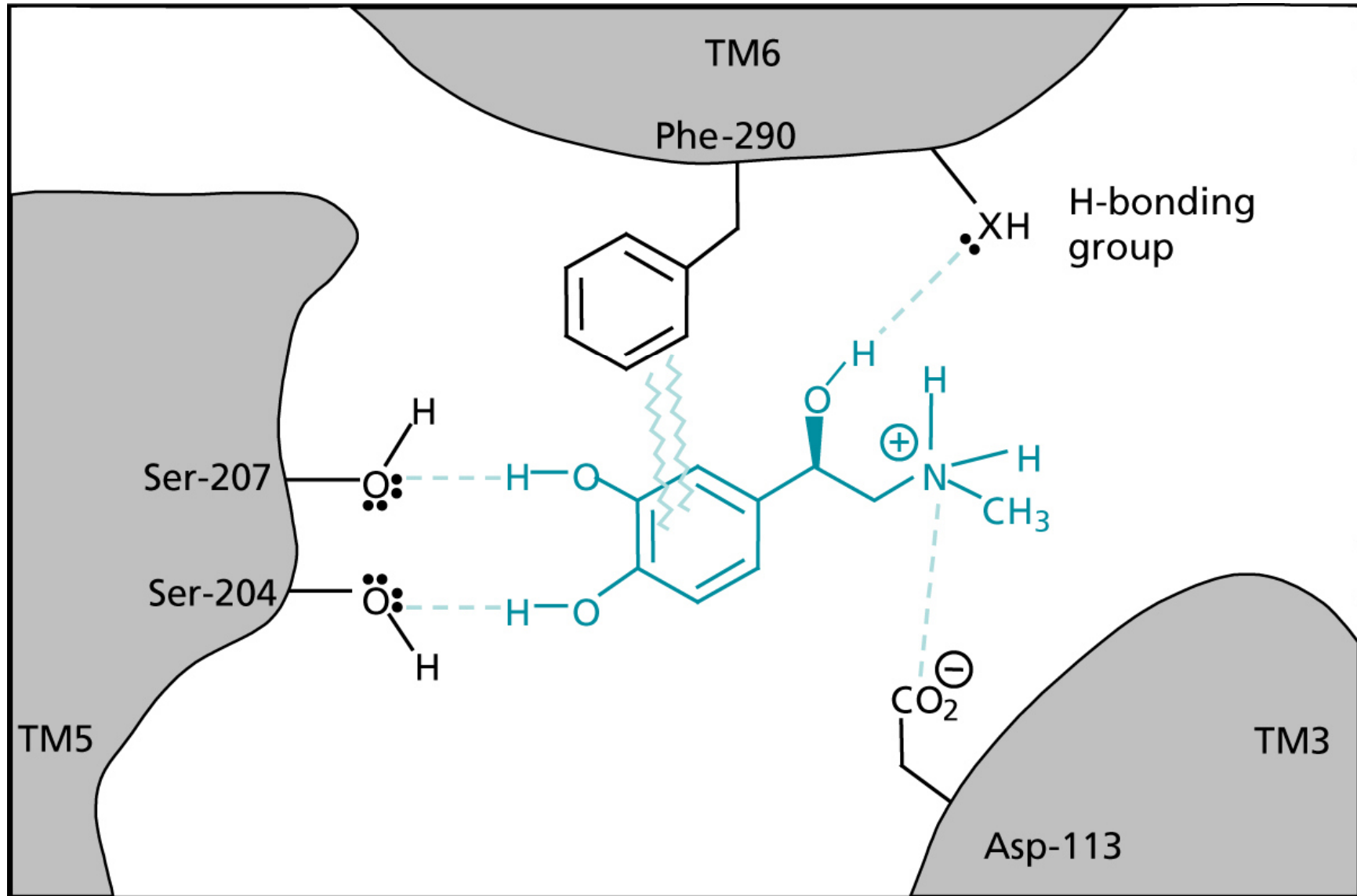
Metabolismo de Noradrenalina

MAO e COMT

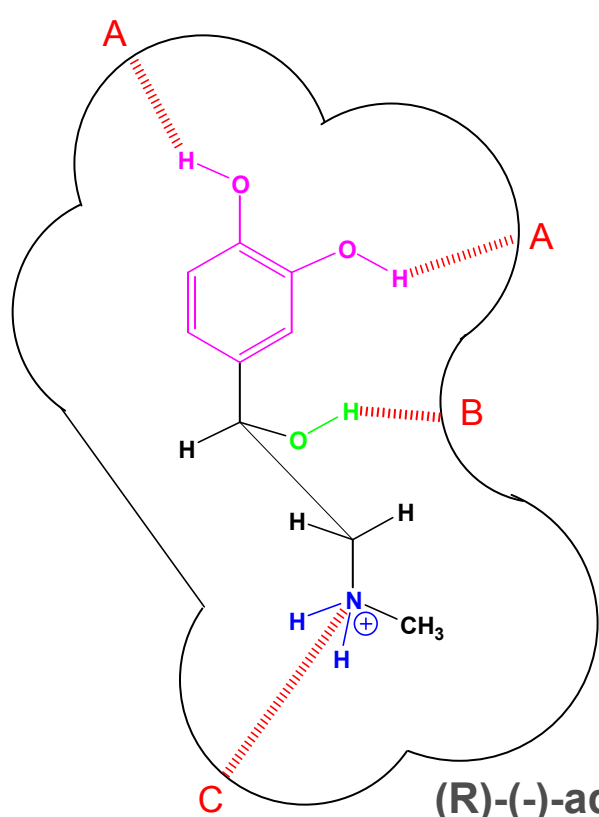




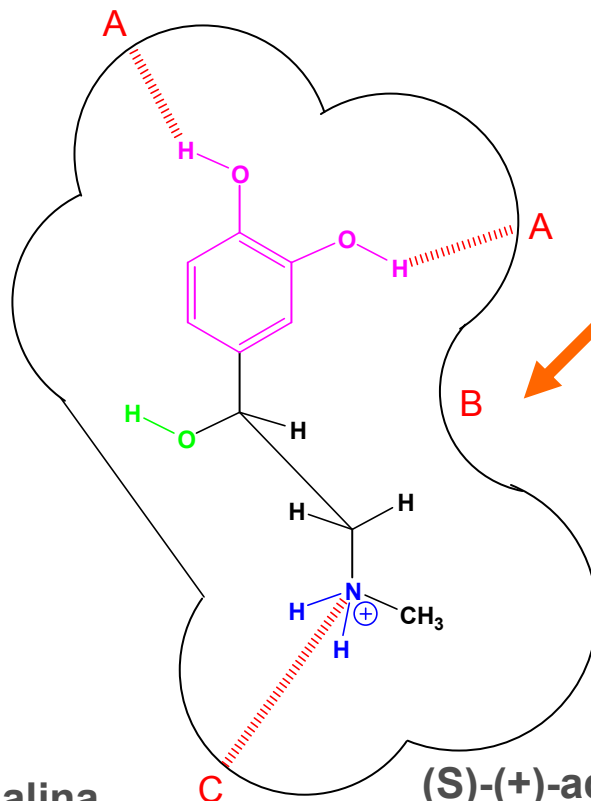
Adrenoreceptor beta



estereosseletividade



(R)-(-)-adrenalina

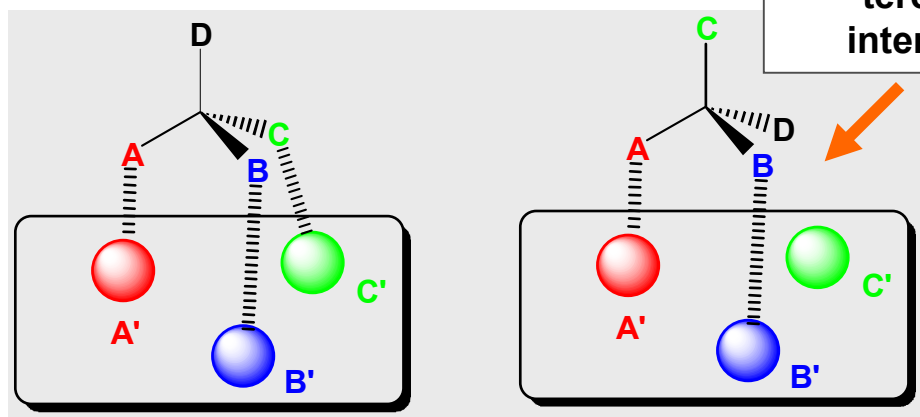


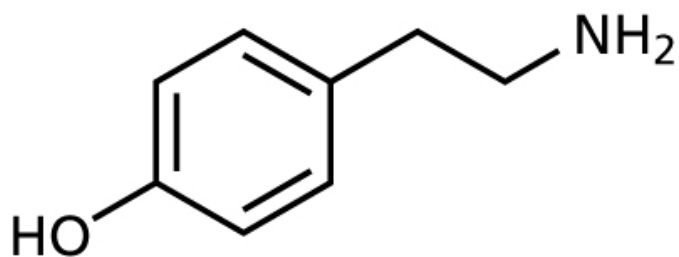
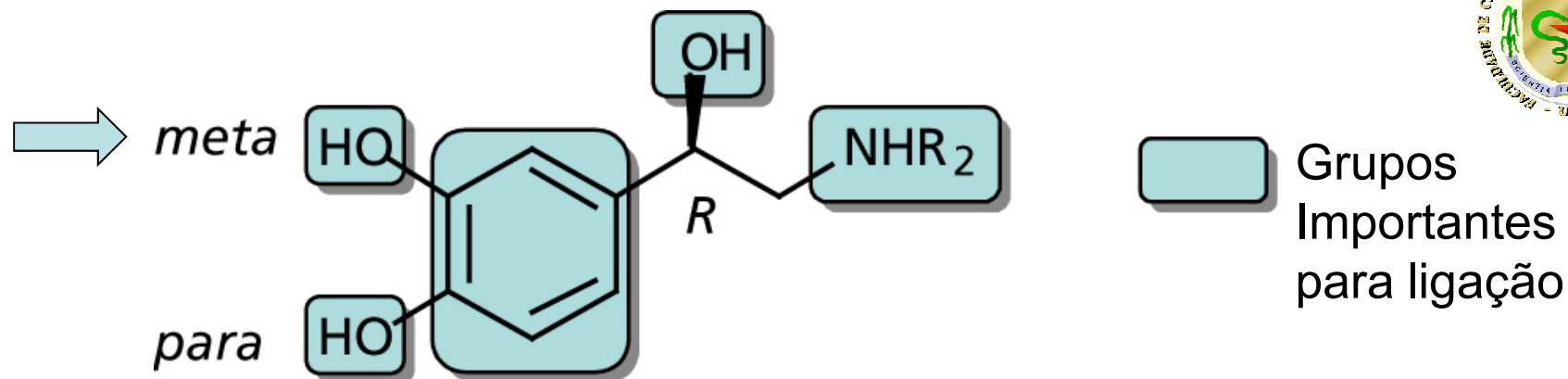
(S)-(+)-adrenalina

não ocorre a terceira interação

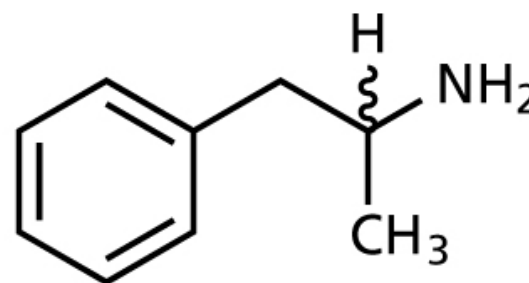
não ocorre a terceira interação

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



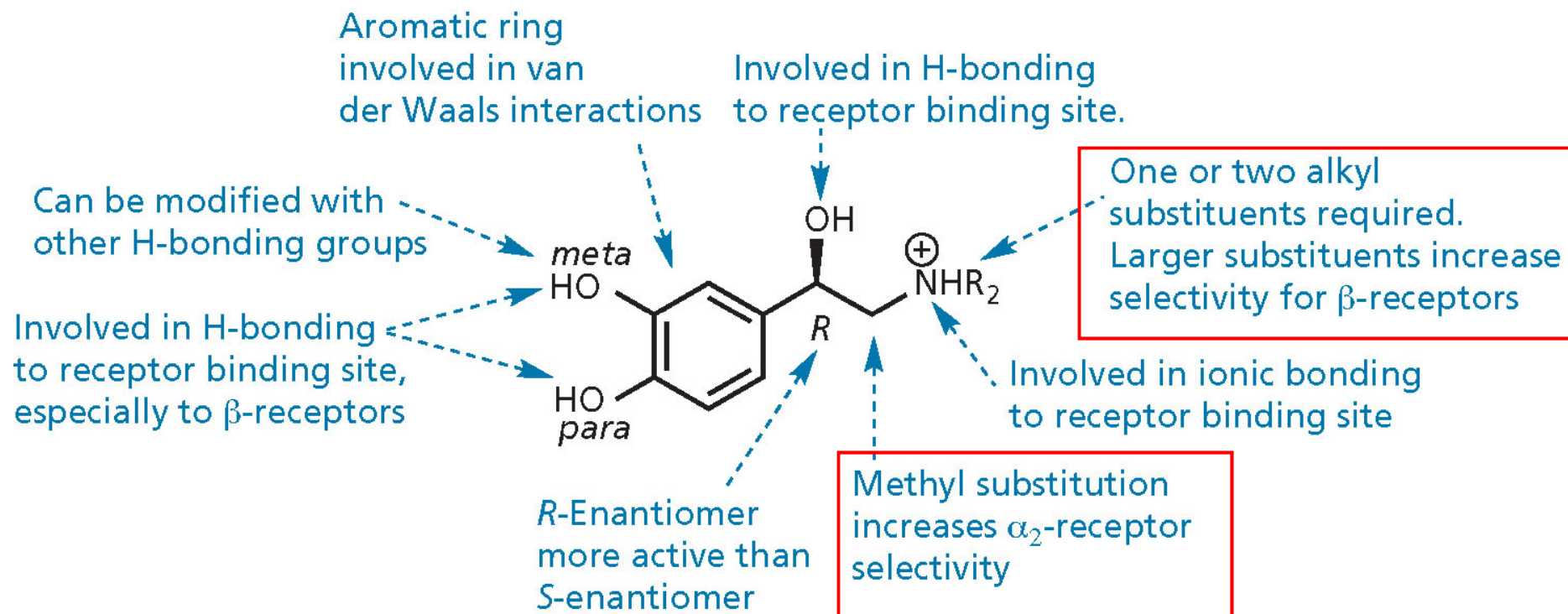


Tyramine



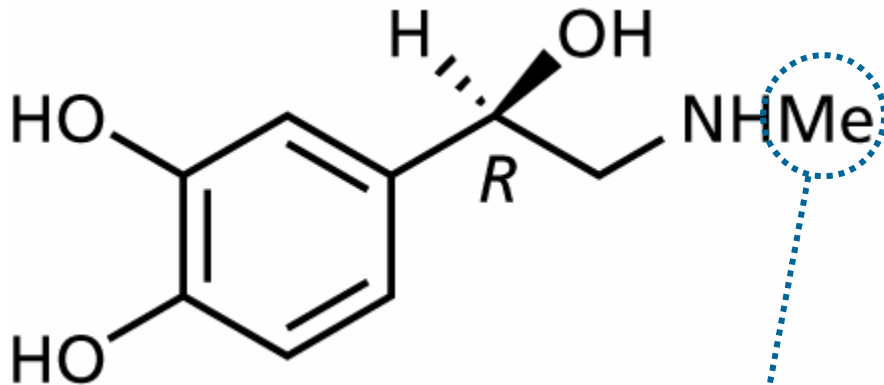
Amphetamine

Sem afinidade pelo receptor adrenérgico



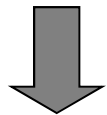


Seletividade de alfa x beta

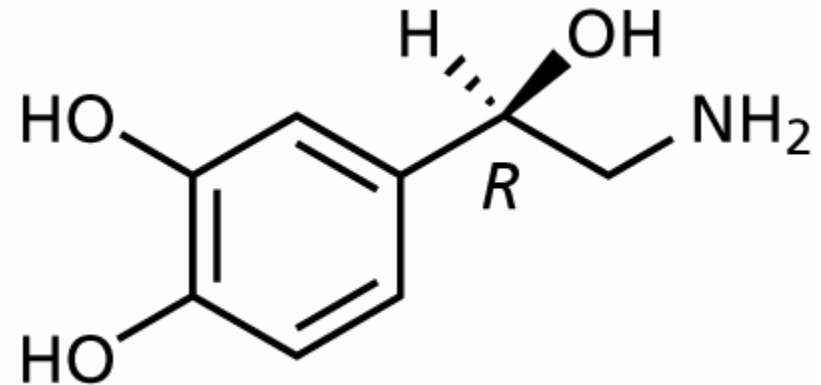


Adrenaline

Seletividade $\alpha=\beta$



N-alkil tem importância na seletividade β



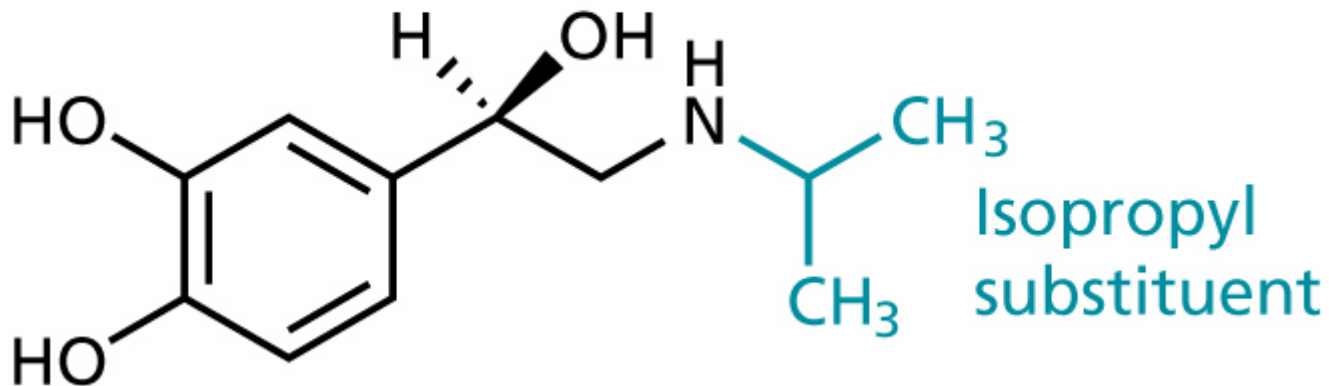
Noradrenaline

Seletividade $\alpha>\beta$



Seletividade alfa x beta

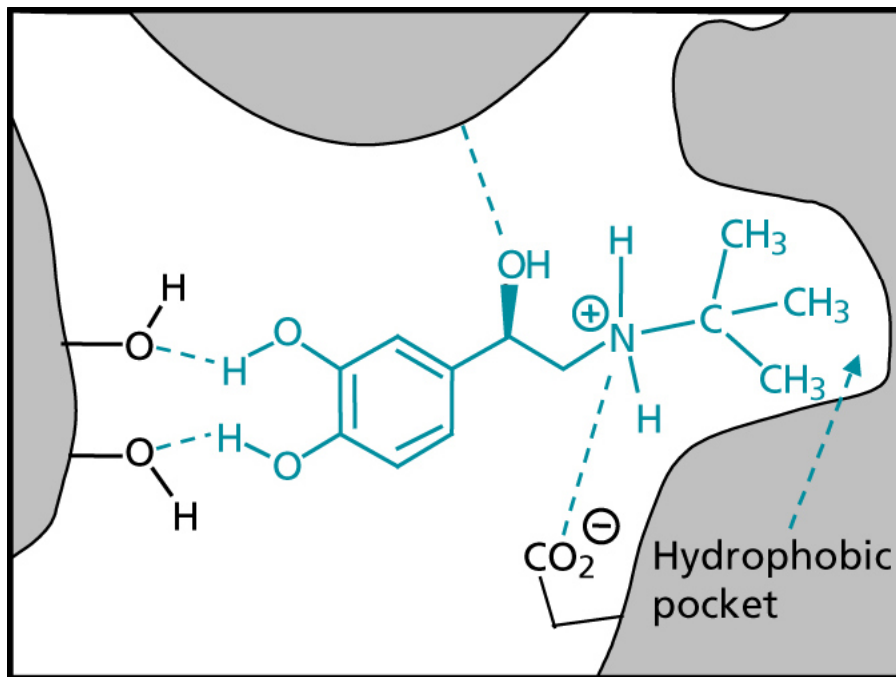
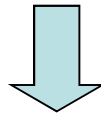
- Substituintes *N*-alquílicos
- Aumentam atividade β



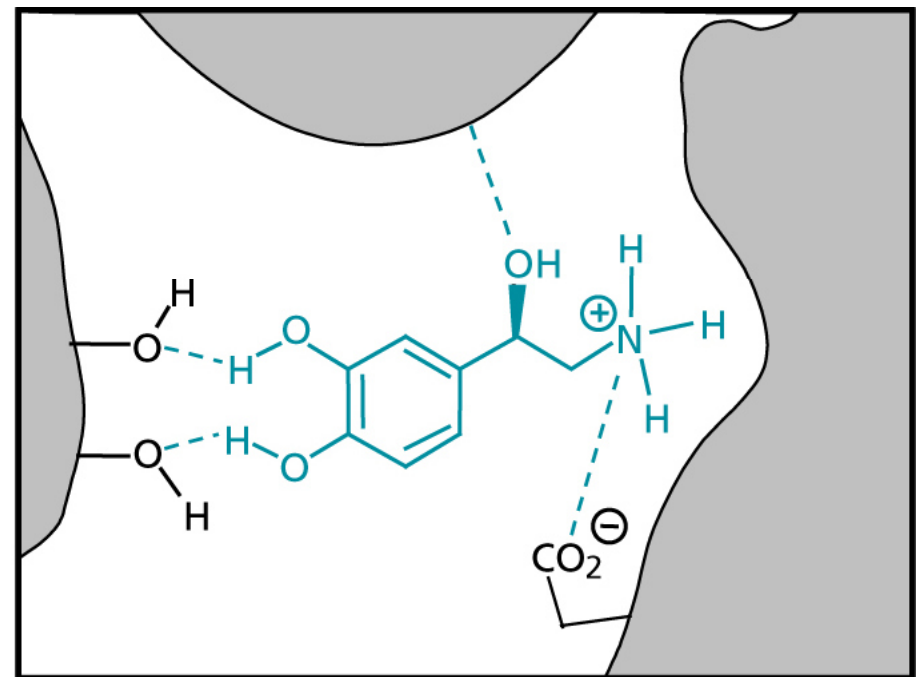
Isoprenalina – agonista β
Ativa $\beta 2$ nas vias aéreas (broncodilatador- ASMA)
Também ativa $\beta 1$ no coração



Região hidrofóbica adicional



β -Adrenoceptor



α -Adrenoceptor

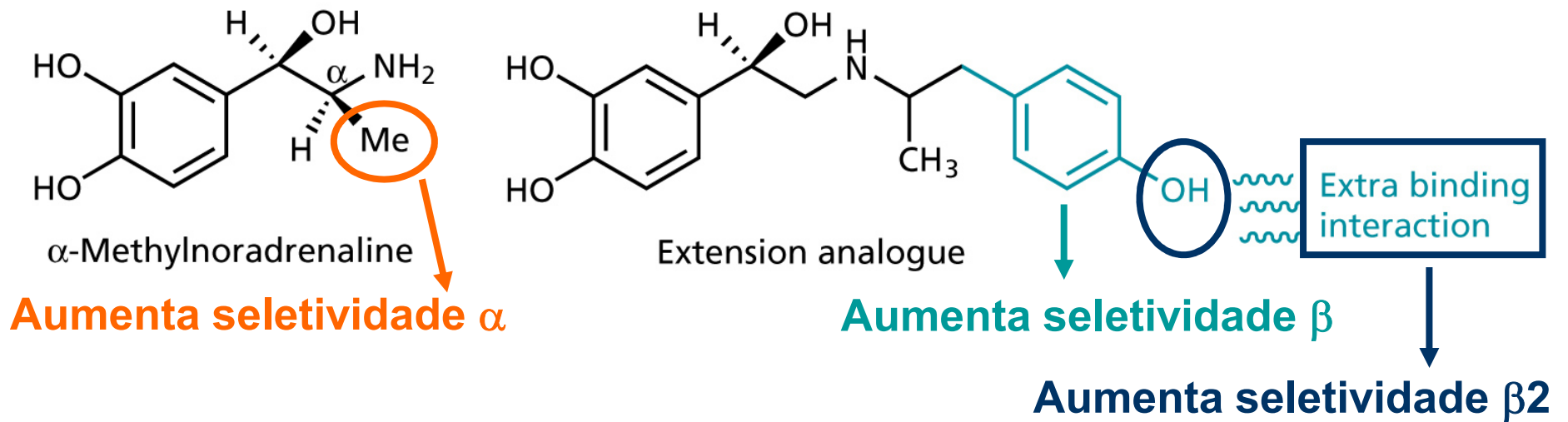


Seletividade de alfa x beta

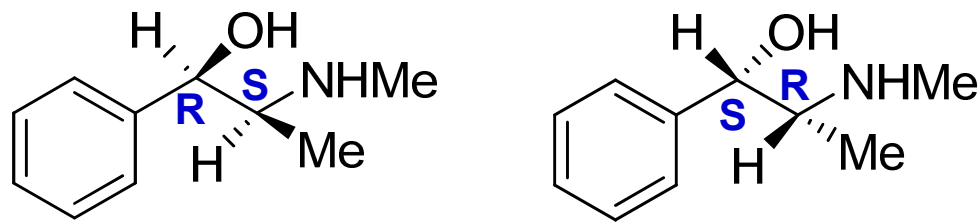
- Substituintes *N*-alquílicos
- Grupos fenílicos
- Substituinte alfa-metílico
- Extensão da cadeia



Análogos de Noradrenalina

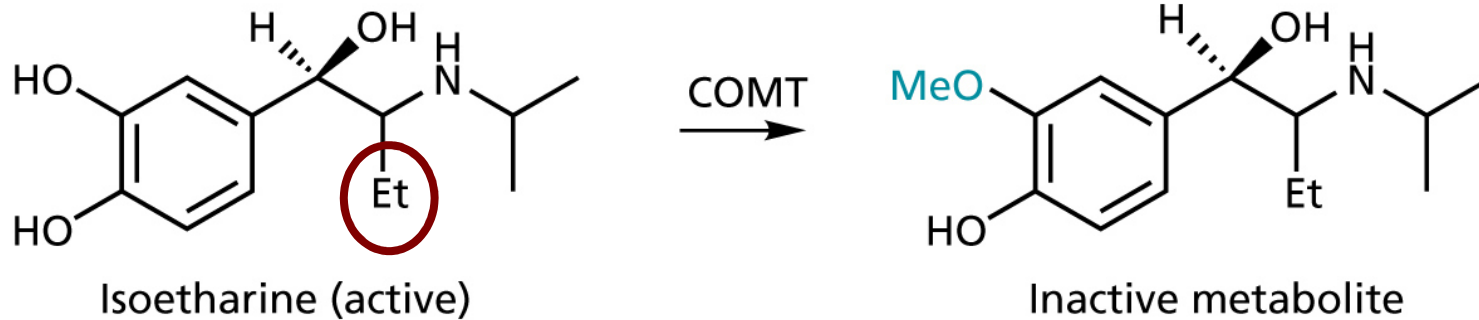


Efedrina - ativa receptores α e β : broncodilatador, vasopressor e estimulante cardíaco, ação no SNC



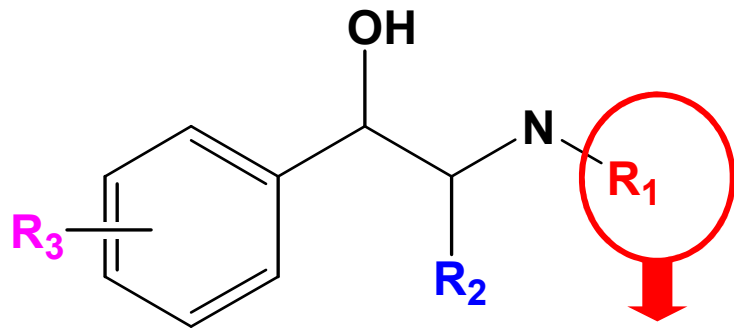


A busca por agonistas seletivos beta-2



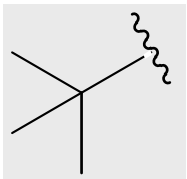
seletividade β_2 , com rápida duração de ação devido a metabolização pela COMT

AGONISTAS ADRENÉRGICOS

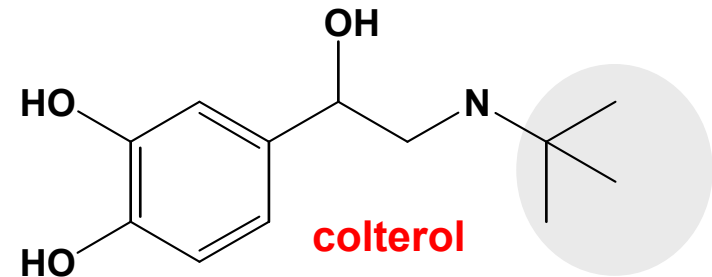


Aumenta o tamanho:
(em relação a Me da epinefrina)

↓ atividade em receptores α
↑ atividade em receptores β

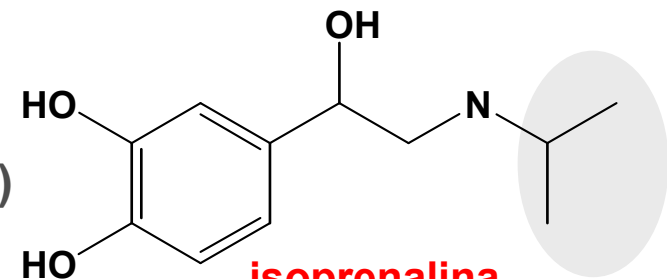


Grupo *terc*-butila: seletividade β_2



colterol

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



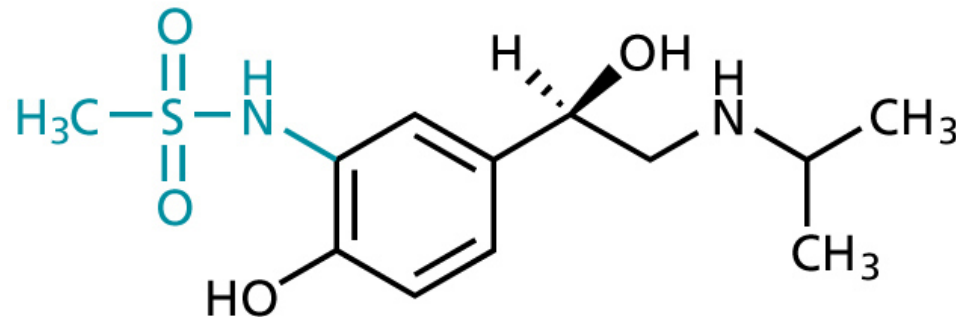
isoprenalina



Agonistas seletivos beta-2

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

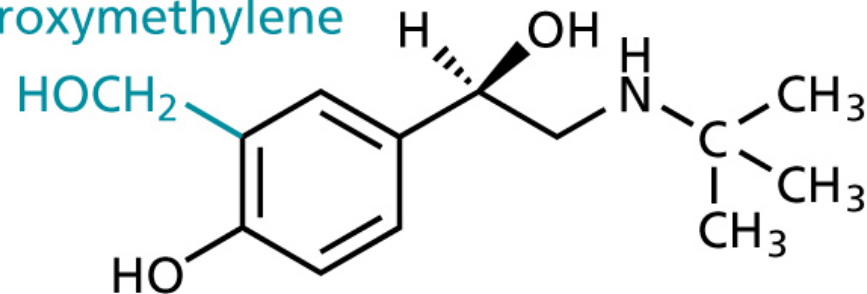
sulfonamide



R-Soterenol

Agonistas β 2

hydroxymethylene



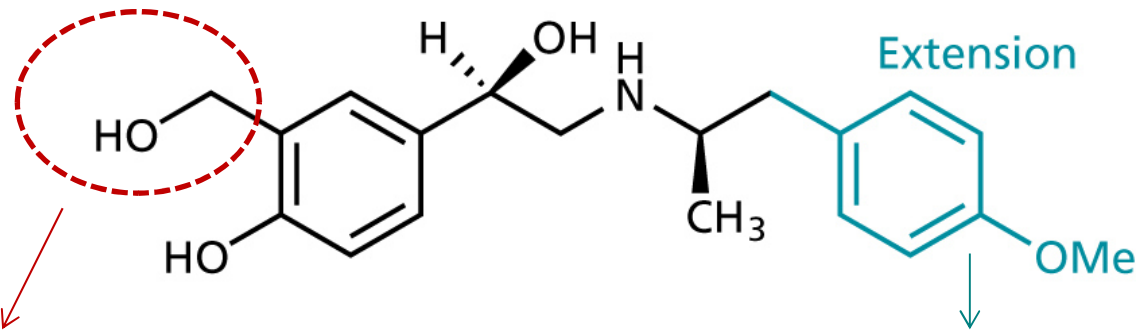
R-Salbutamol

(4 h)

2000 x menos ativo no coração



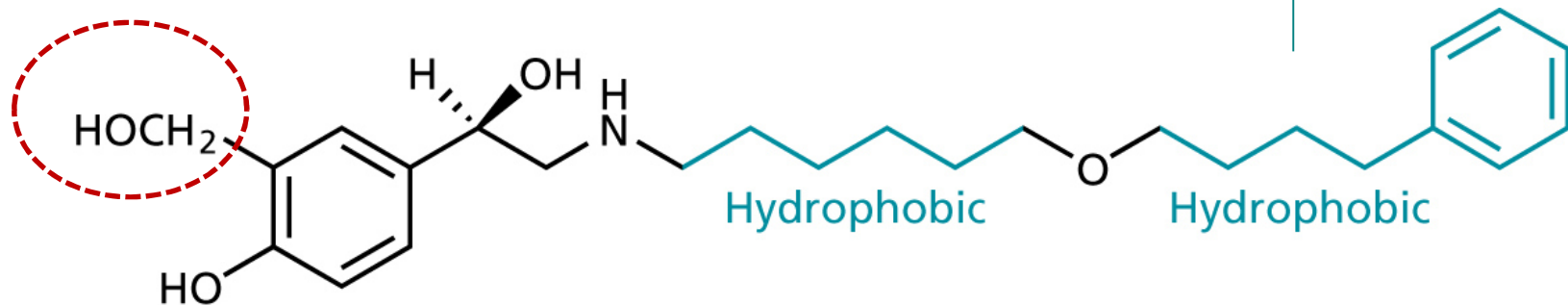
Salmefamol (6 h)



**Impede metabolismo
pela COMT**

**Maior duração de ação pela
introdução de grupos com
caráter lipofílico**

Salmeterol (12 h)

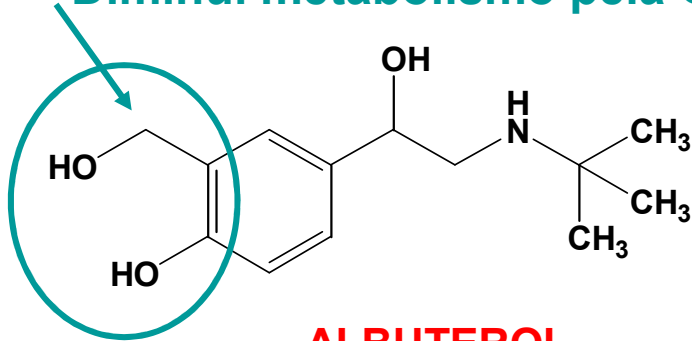




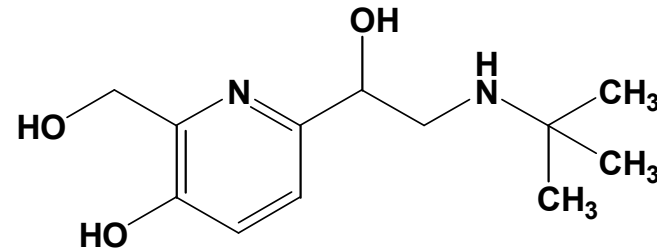
Agonistas β_2 – adrenérgicos

BRONCODILATADORES – tratamento da asma

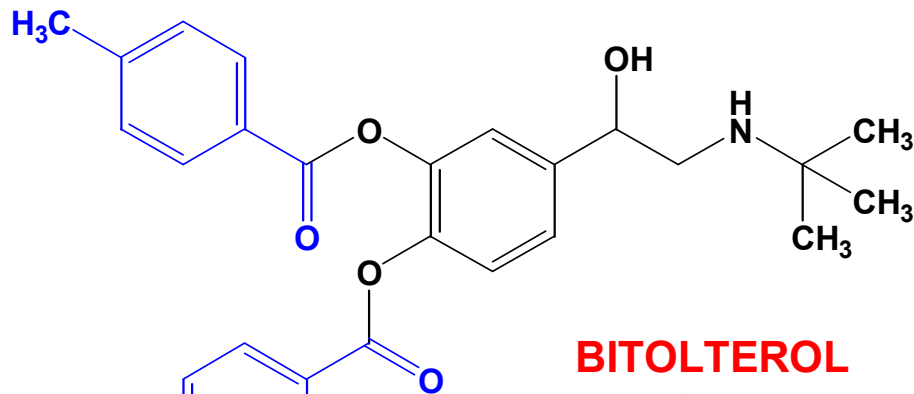
Diminui metabolismo pela COMT



ALBUTEROL
(salbutamol)



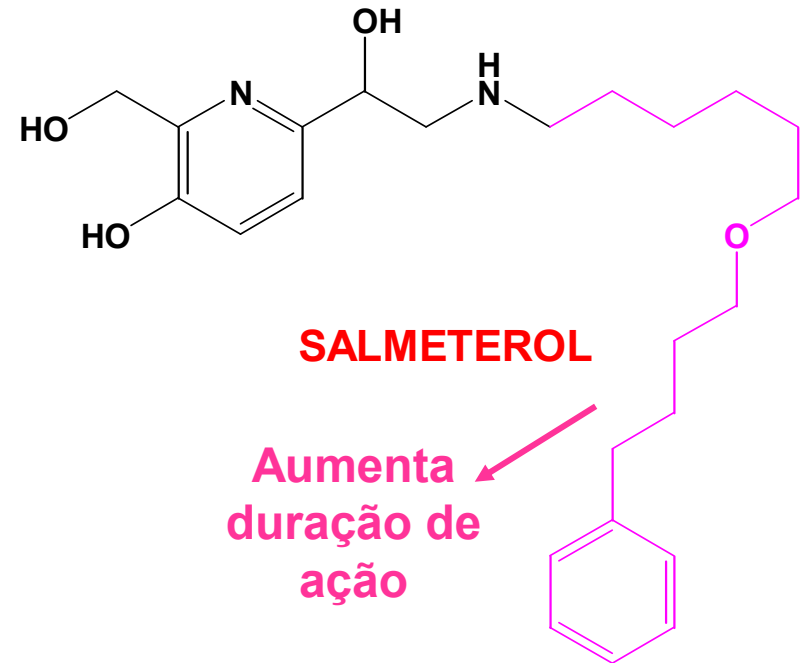
PIRBUTEROL



BITOLTEROL



COLTEROL



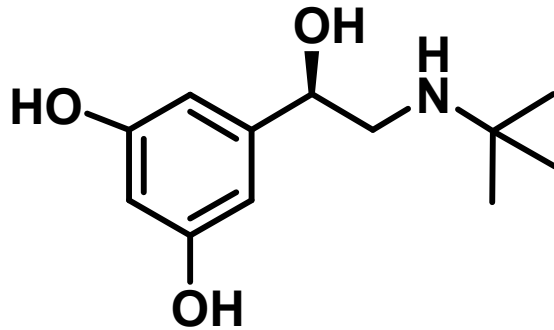
SALMETEROL

Aumenta
duração de
ação

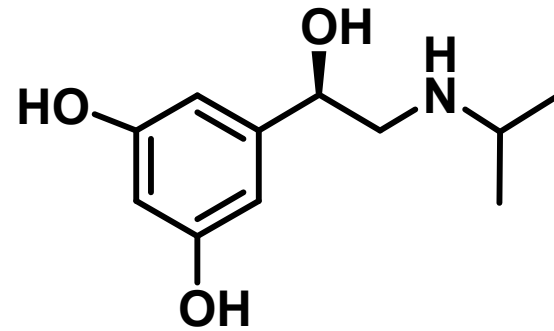


Agonistas β_2 – adrenérgicos

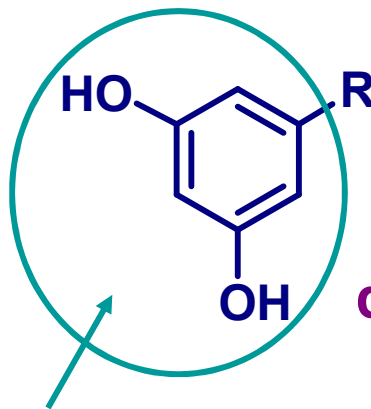
BRONCODILATADORES – tratamento da asma



terbutalina



metaproterenol



derivado 3,5-di-hidroxilado

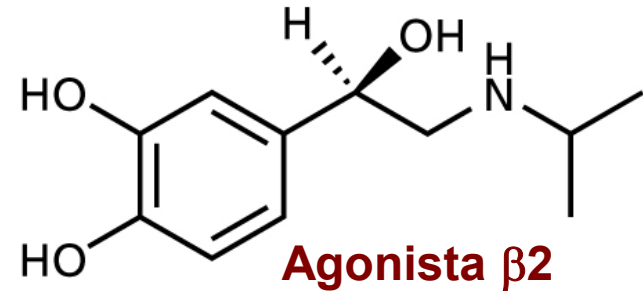
Diminui metabolismo pela COMT



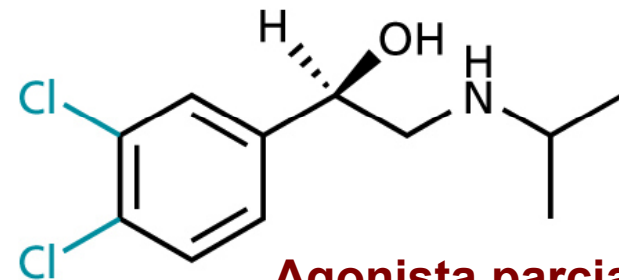
Bloqueadores beta-adrenérgicos

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

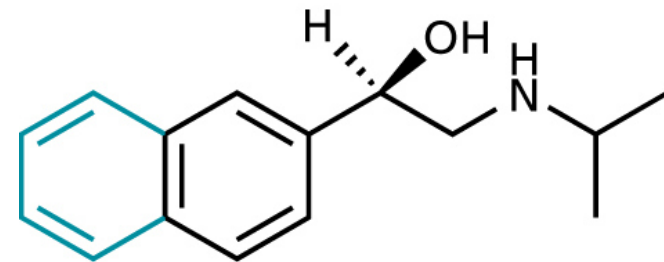
Agonista parcial, com ação antagonista
Primeiro beta-bloqueador usado clinicamente para angina, arritmias, hipertensão



Isoprenaline



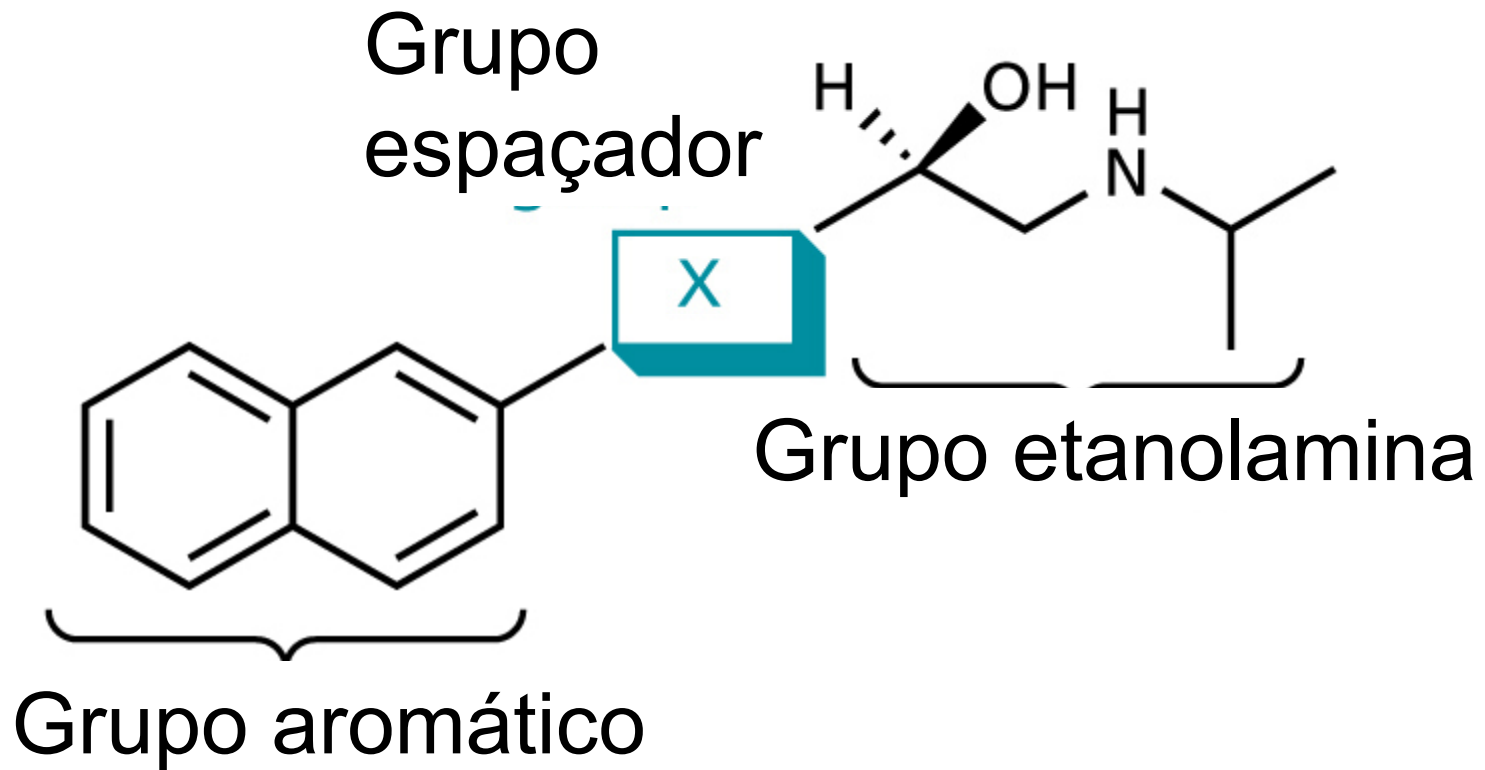
Dichloroisoprenaline



Pronethalol

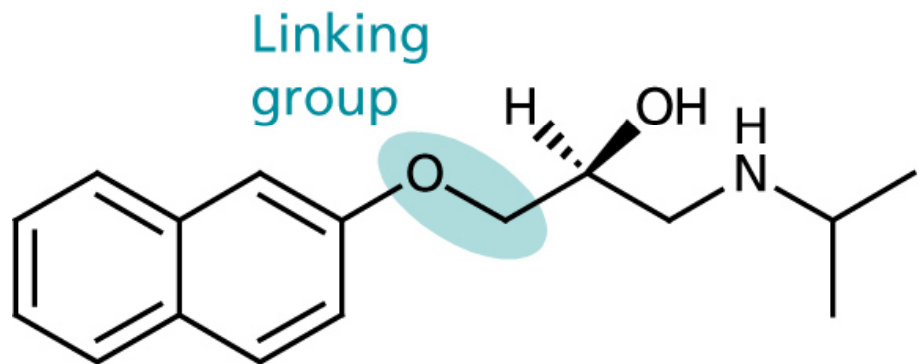


Extensão da cadeia lateral

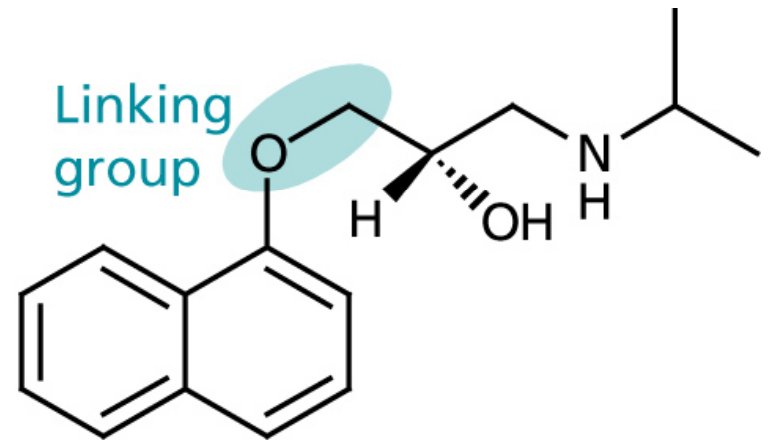




Propranolol



Composto de interesse

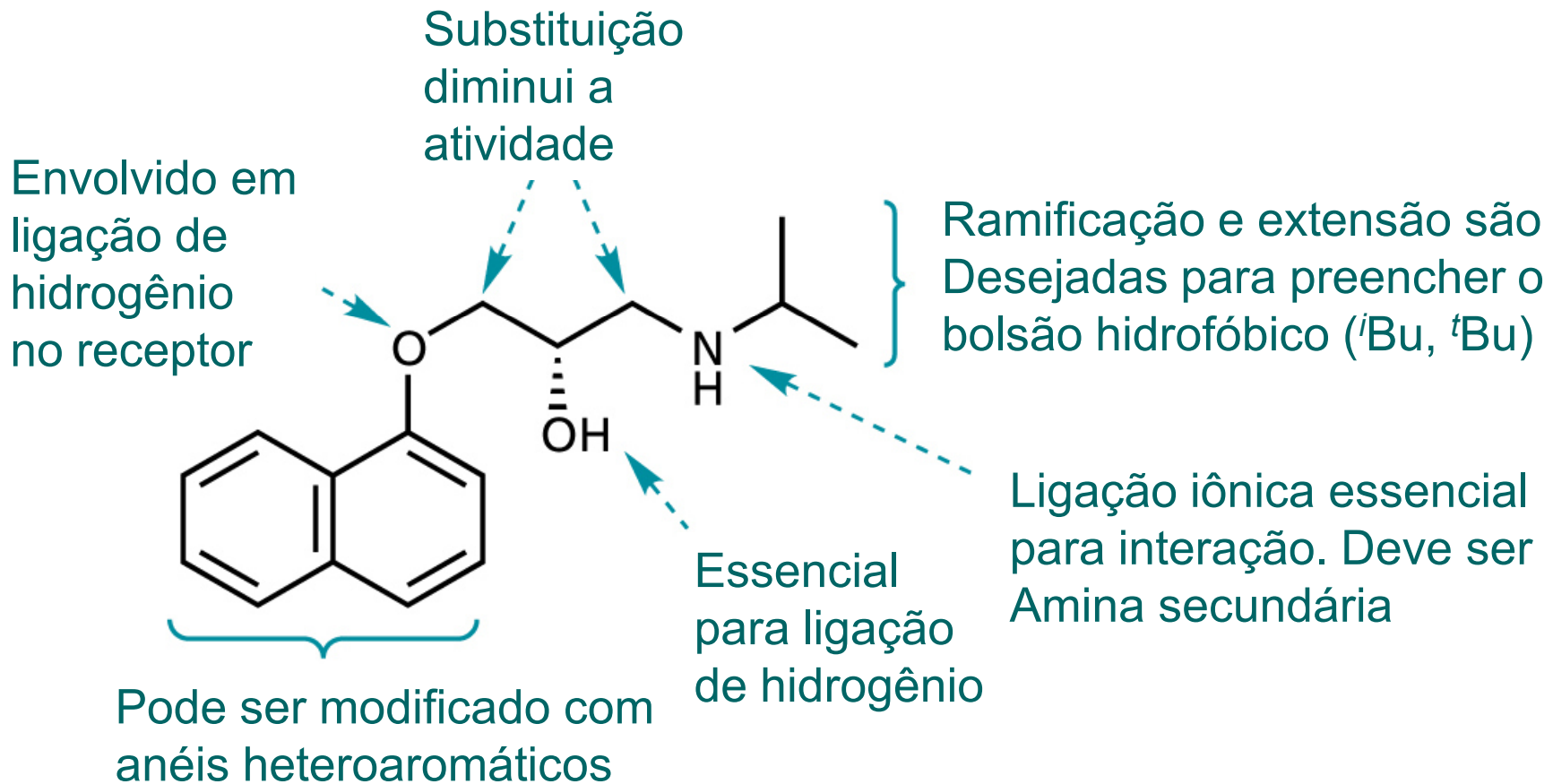


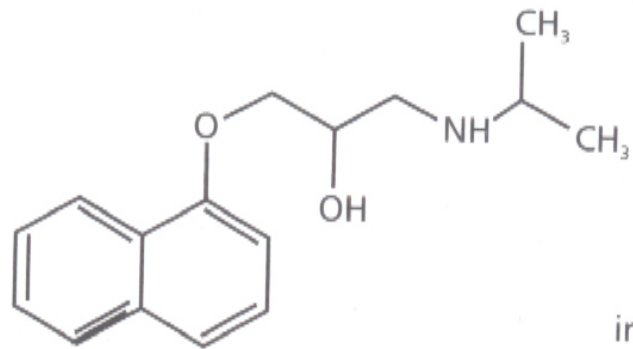
Propranolol

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



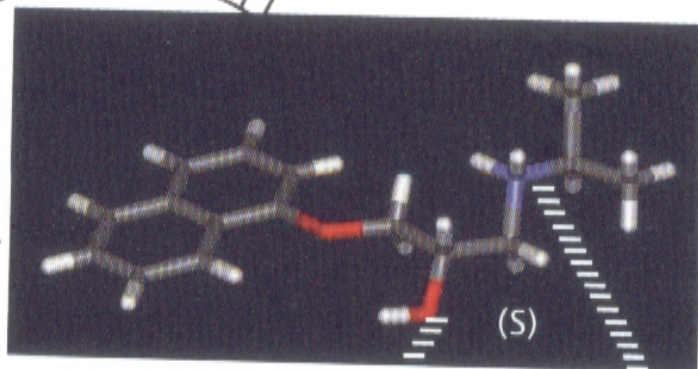
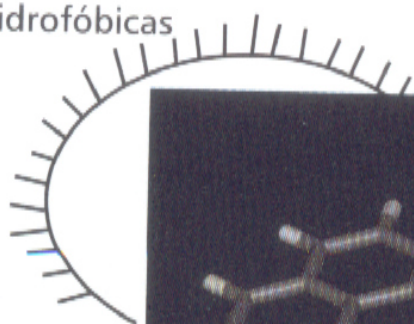
Relação Estrutura-atividade



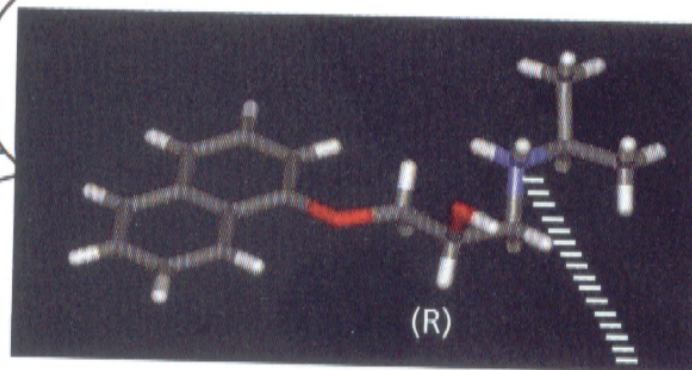
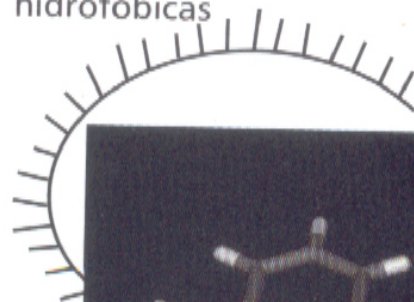


propranolol (18)

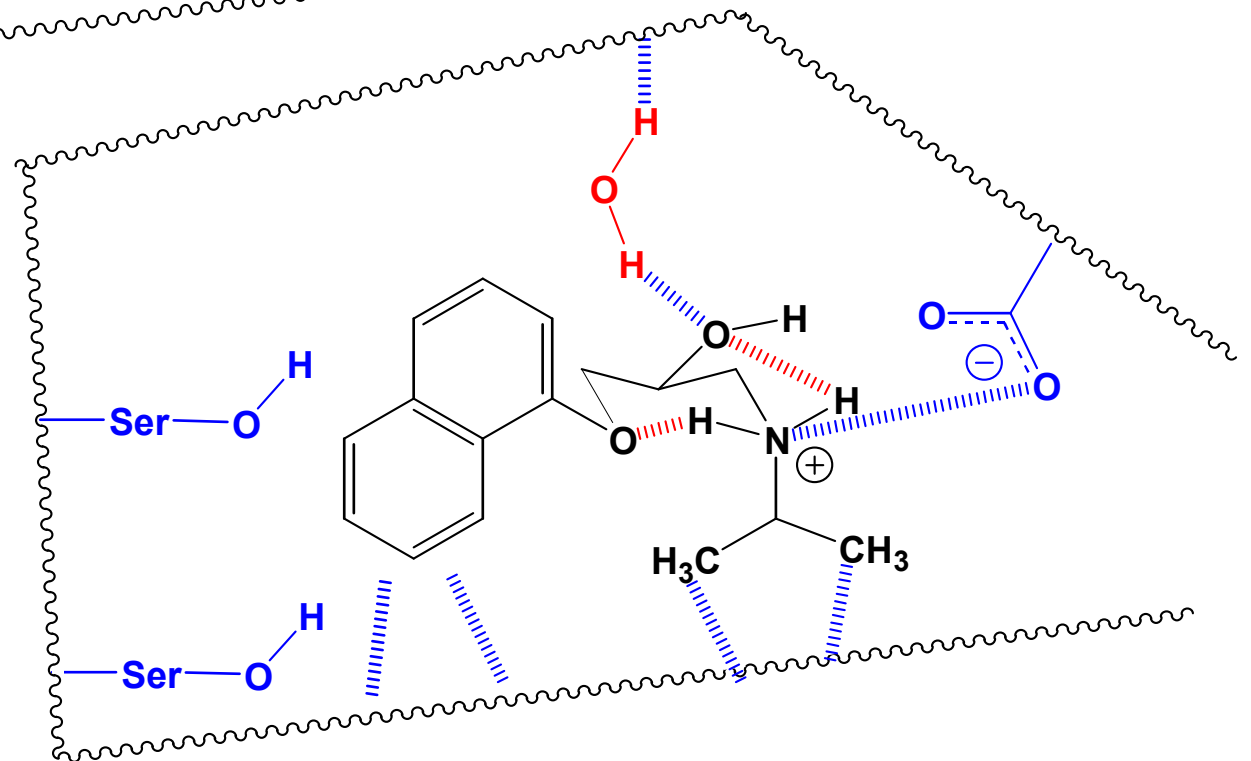
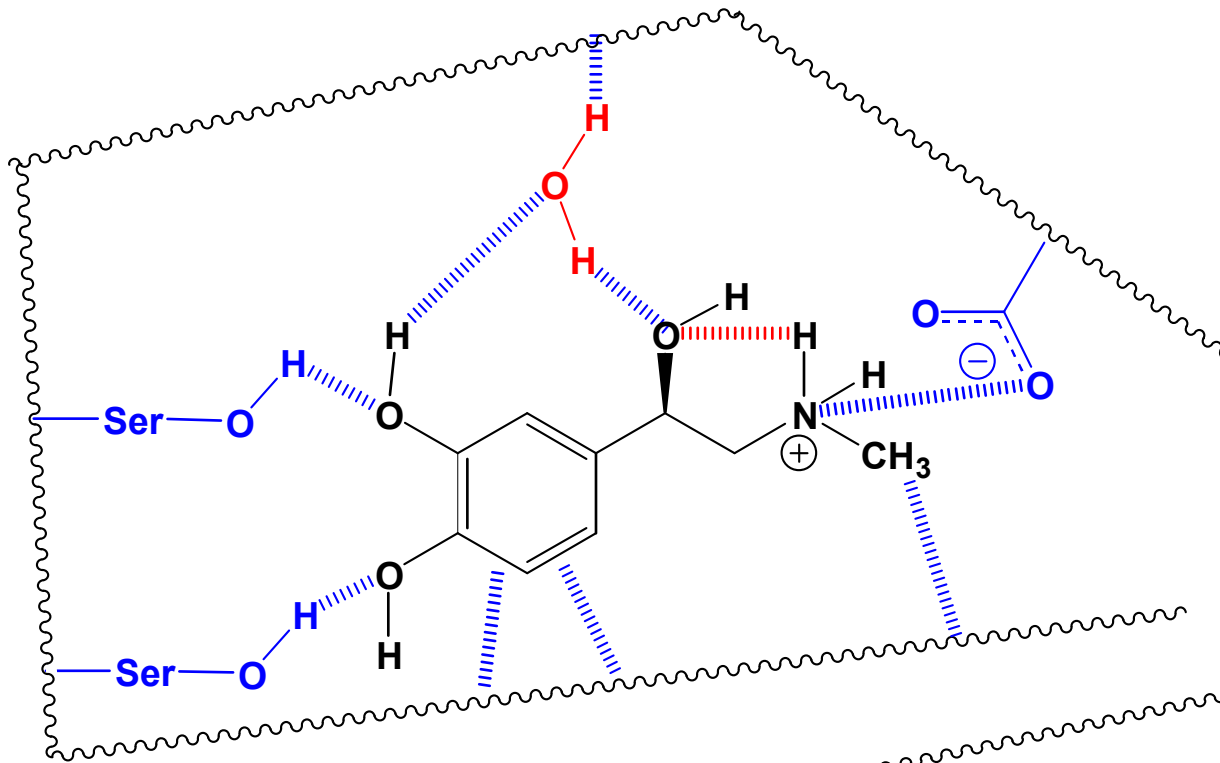
interações hidrofóbicas



interações hidrofóbicas

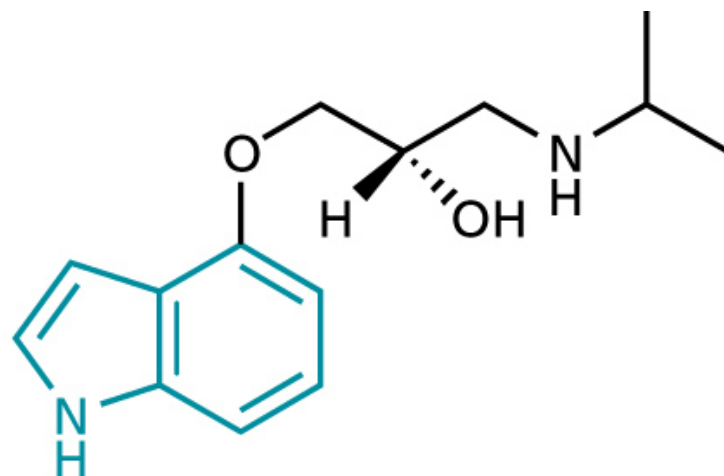


Representação esquemática da interação da adrenalina e do propranolol com o receptor β -adrenérgico

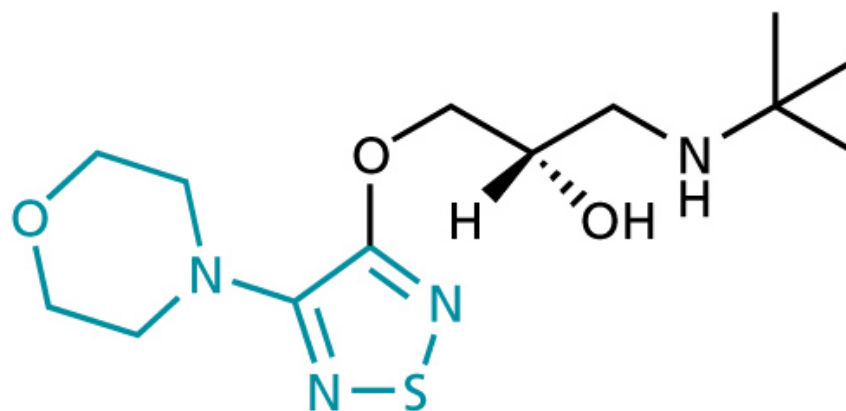




Antagonistas beta contendo anéis heterocíclicos



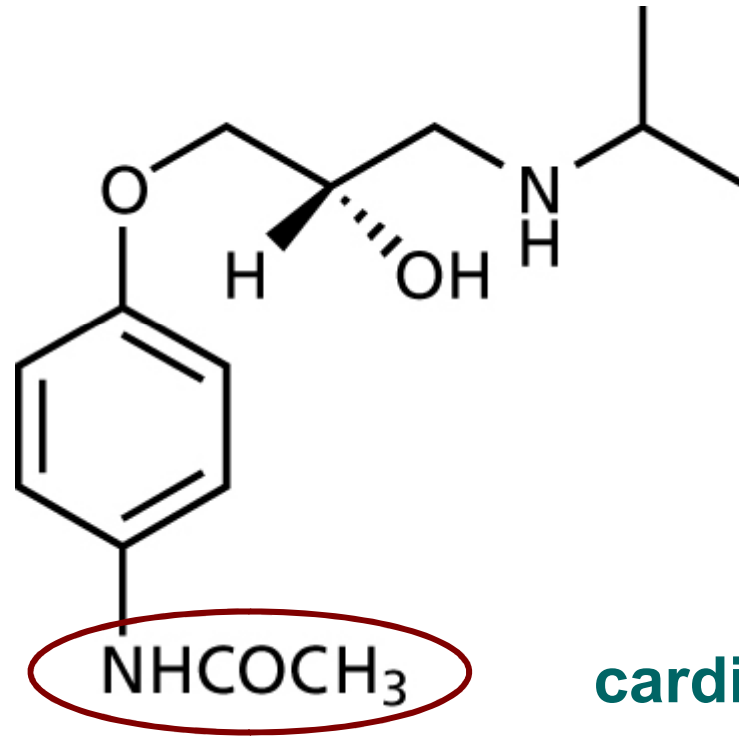
Pindolol



Timololol



Bloqueadores beta-1 seletivos (2ª geração)



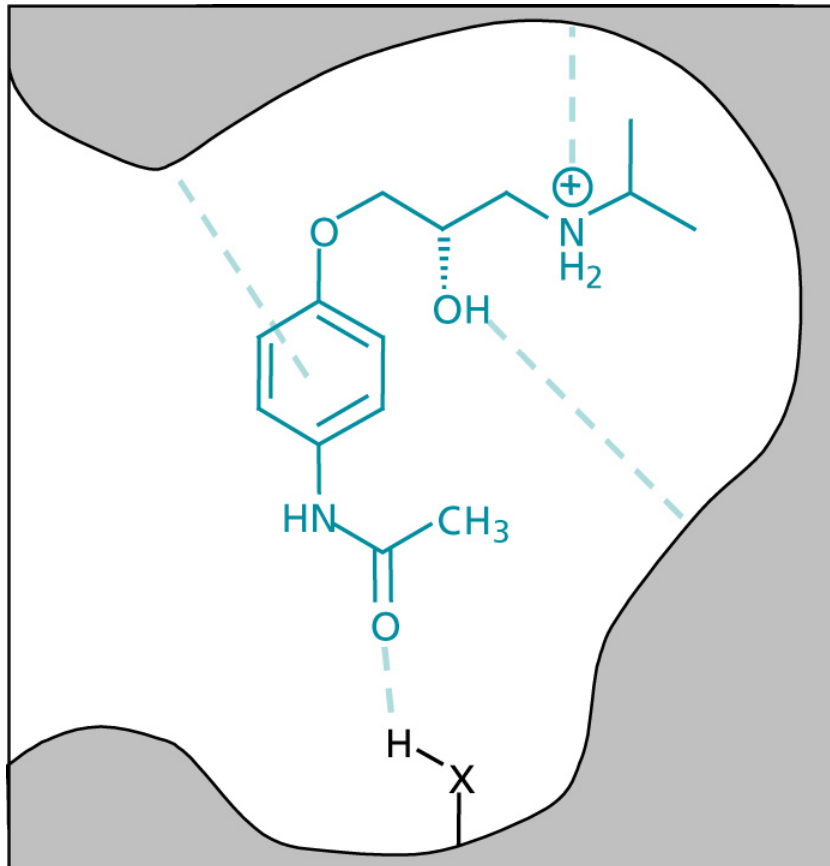
Amida em *para*
seletividade β_1

cardiosseletivo

Practolol

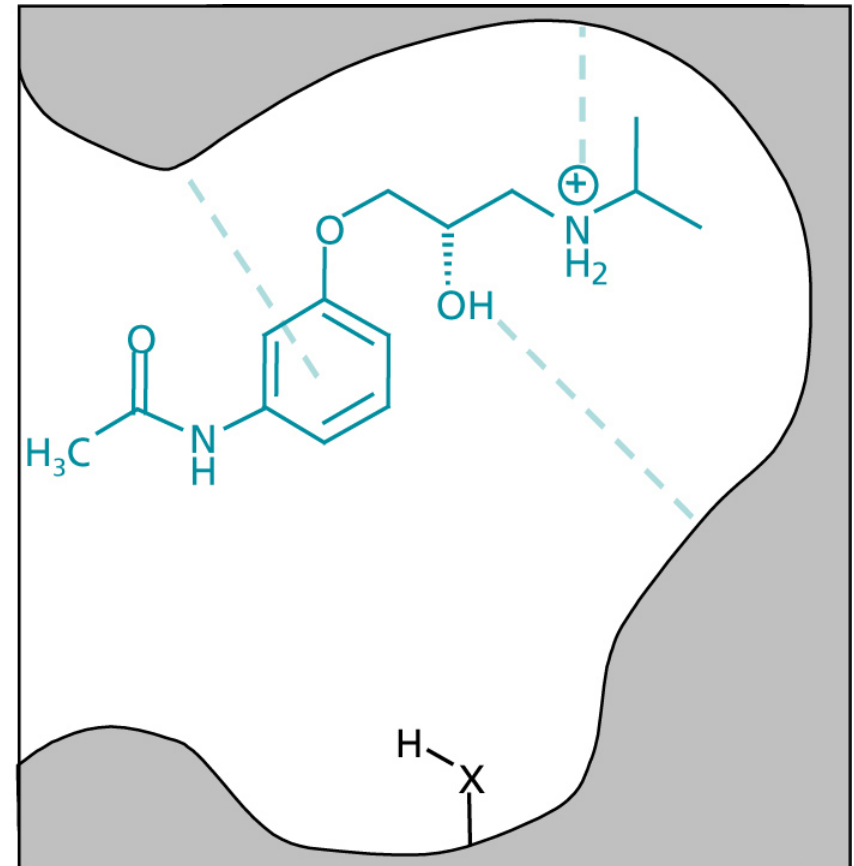


Interações no receptor beta-1



para substitution

**Interação extra por
ligação de hidrogênio**



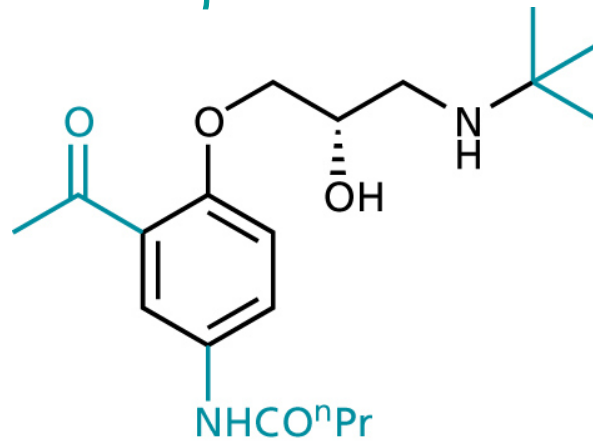
meta substitution

**Não ocorre interação por
lig. H da amida**

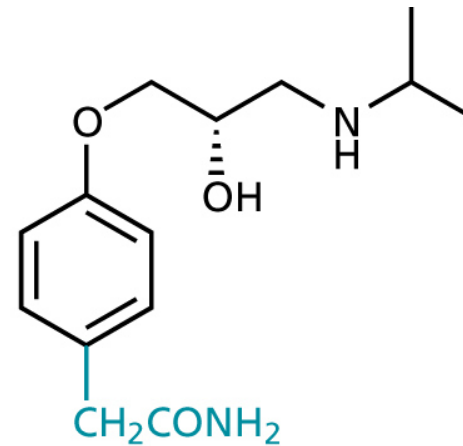


Segunda geração de bloqueadores seletivos beta-1

Grupos em *para* capazes de estabelecer lig. de H -
seletividade β_1

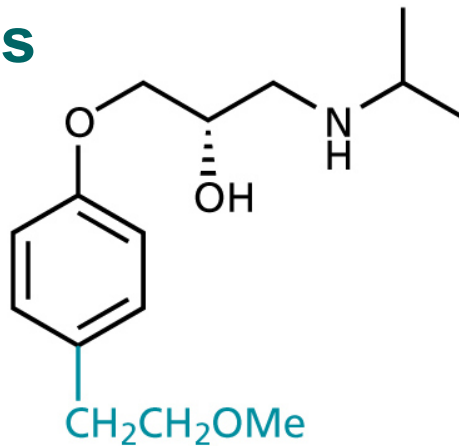


Acebutolol

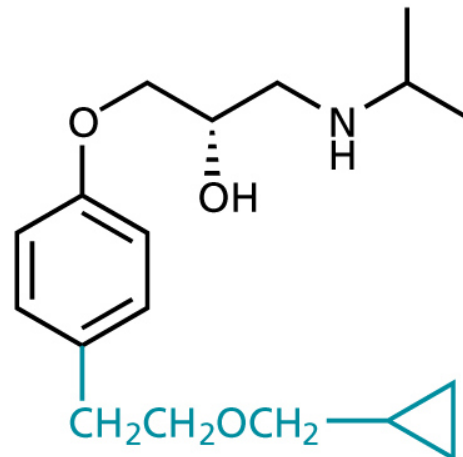


Atenolol

cardiosseletivos



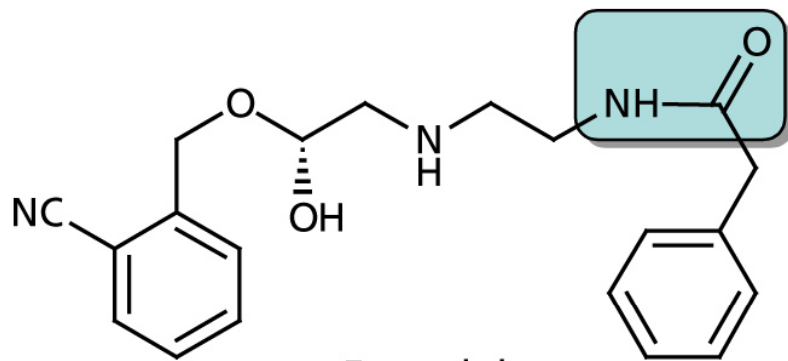
Metoprolol



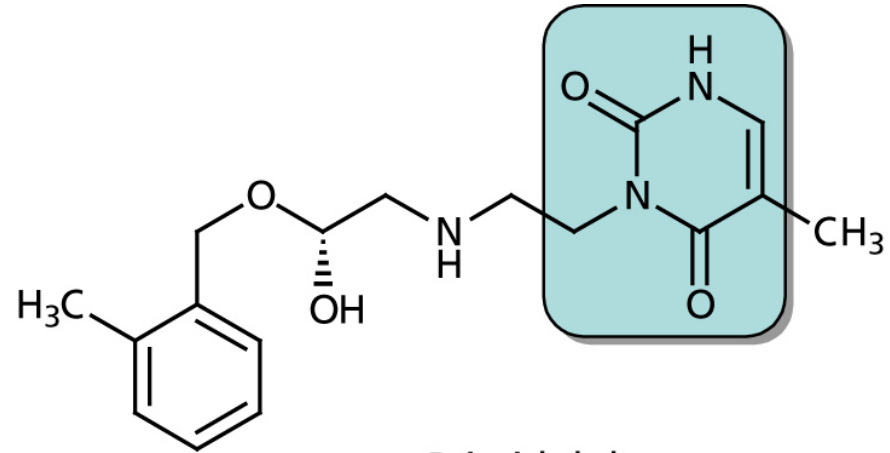
Betaxolol



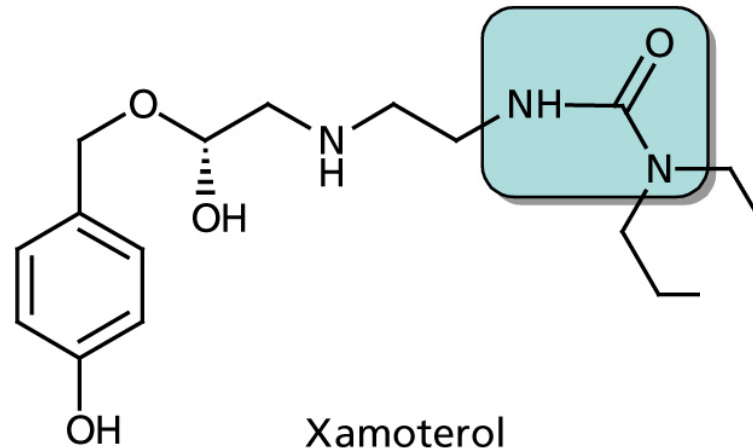
Terceira geração de bloqueadores beta-1



Epanolol



Primidolol



Xamoterol

**Grupos envolvidos
em ligações de
hidrogênio adicionais na
cadeia lateral**