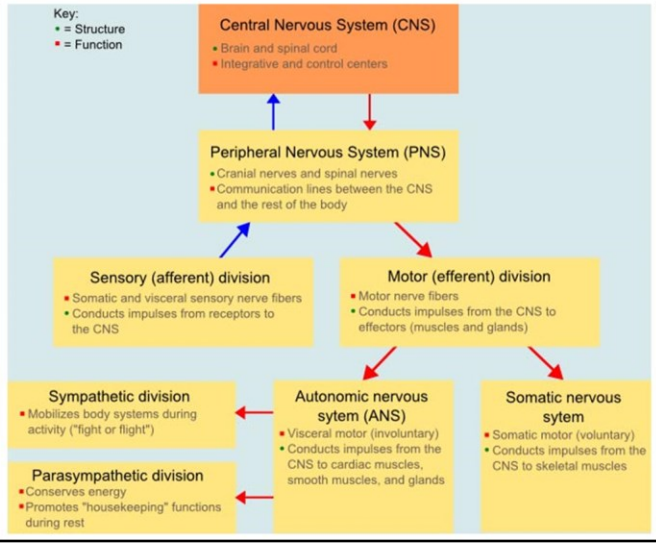
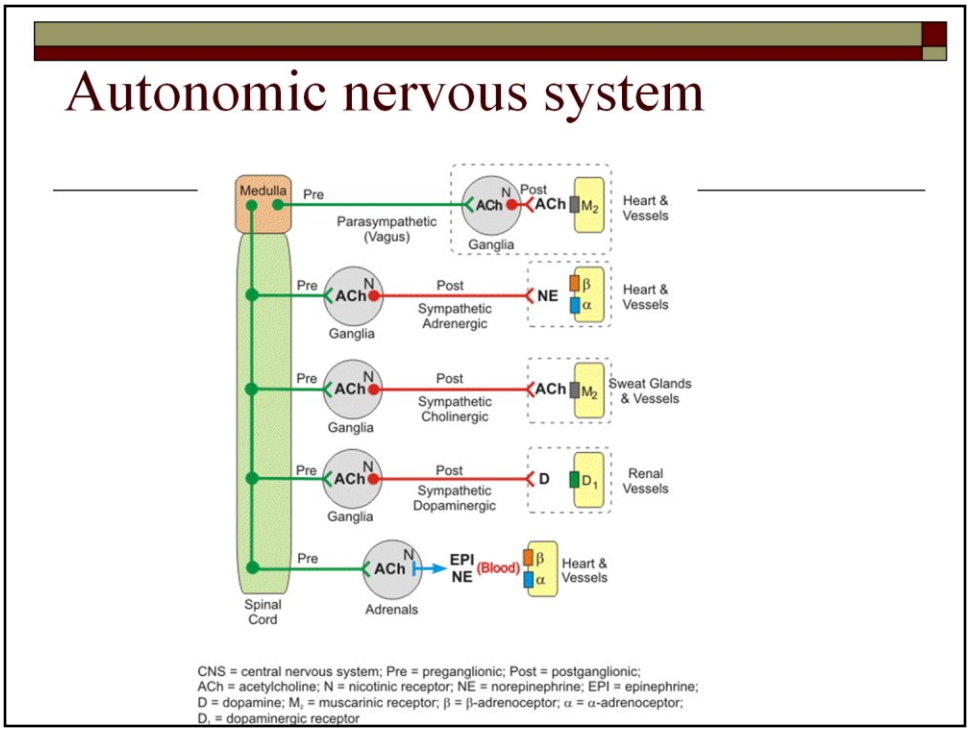
Adrenergic receptor agonists

Lecture

Tomáš Goněc 2020

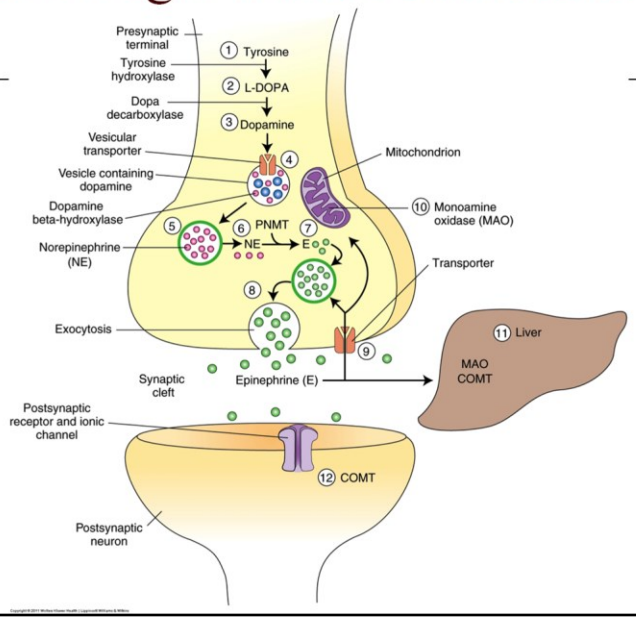
Nervous system

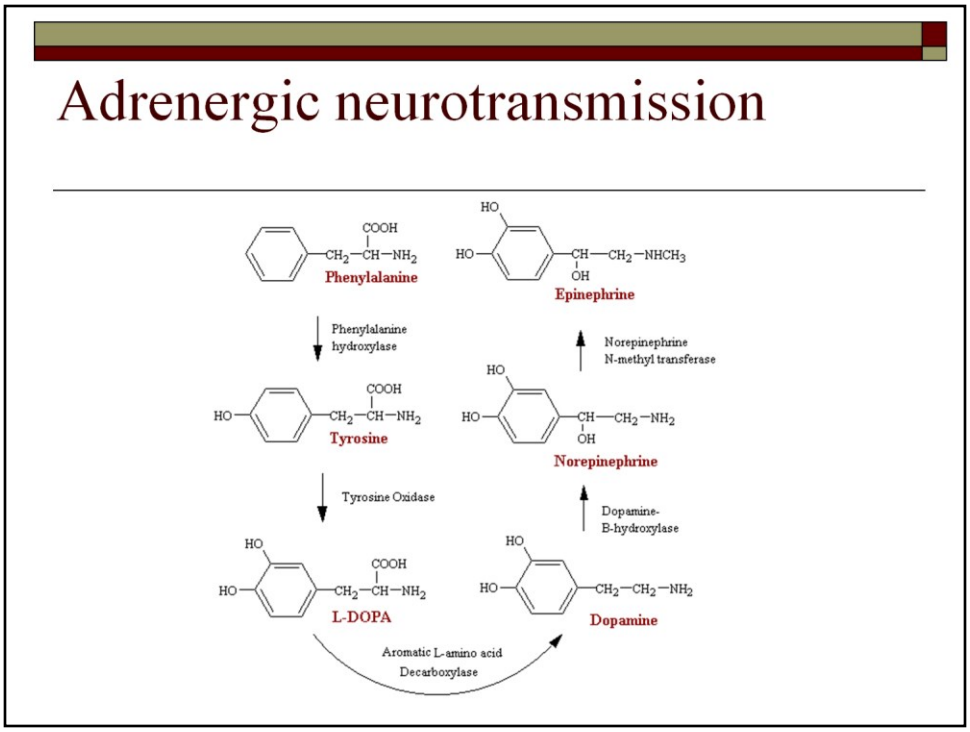




Adrenal galds release adrenalin (epinephrin) and noradrenalin (norepinephrin) into blood stream. Adrenergic receptor agonists and antagonists affects mainly receptors for circulating A and NA

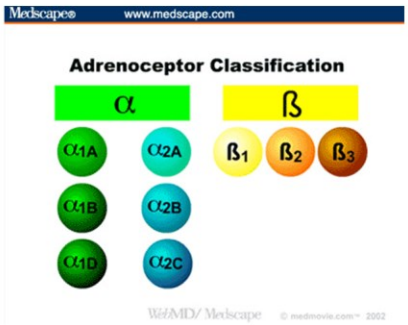
Adrenergic neurotransmission



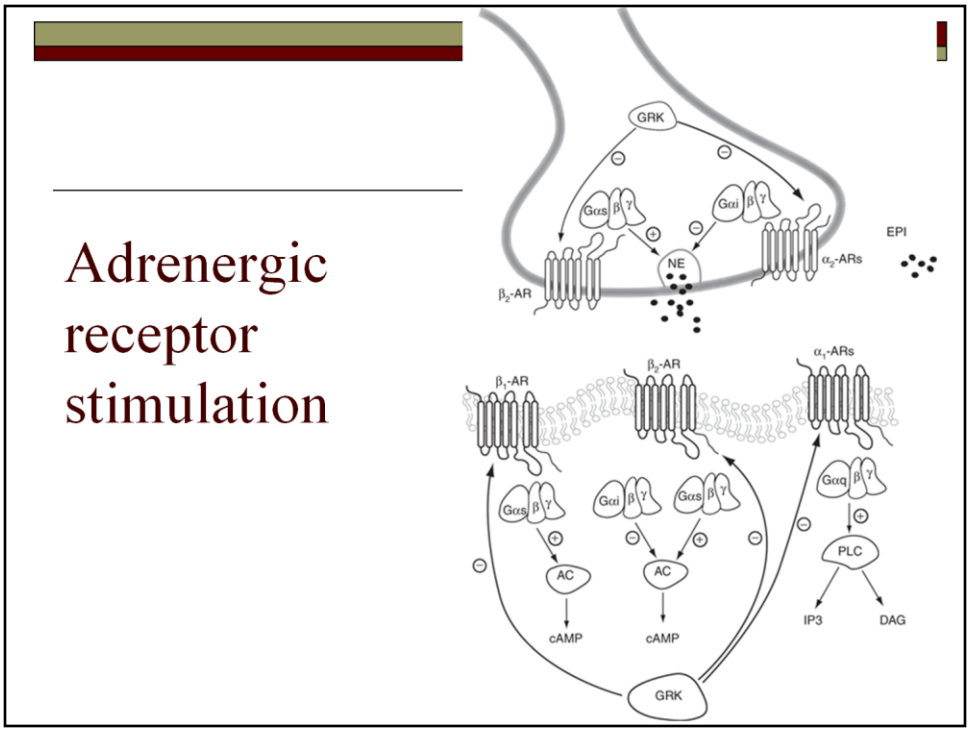


Biosynthesis of neurotransmitters Dopamine, Noradrenaline (Norepinephrine) and Adrenaline (Epinephrine)

Adrenergic receptor classification



3 gene families: alpha1, alpha2 and beta. All families consists of 3 subtypes (similar to each other)
together 9 different receptors with own genes on various chromozomes

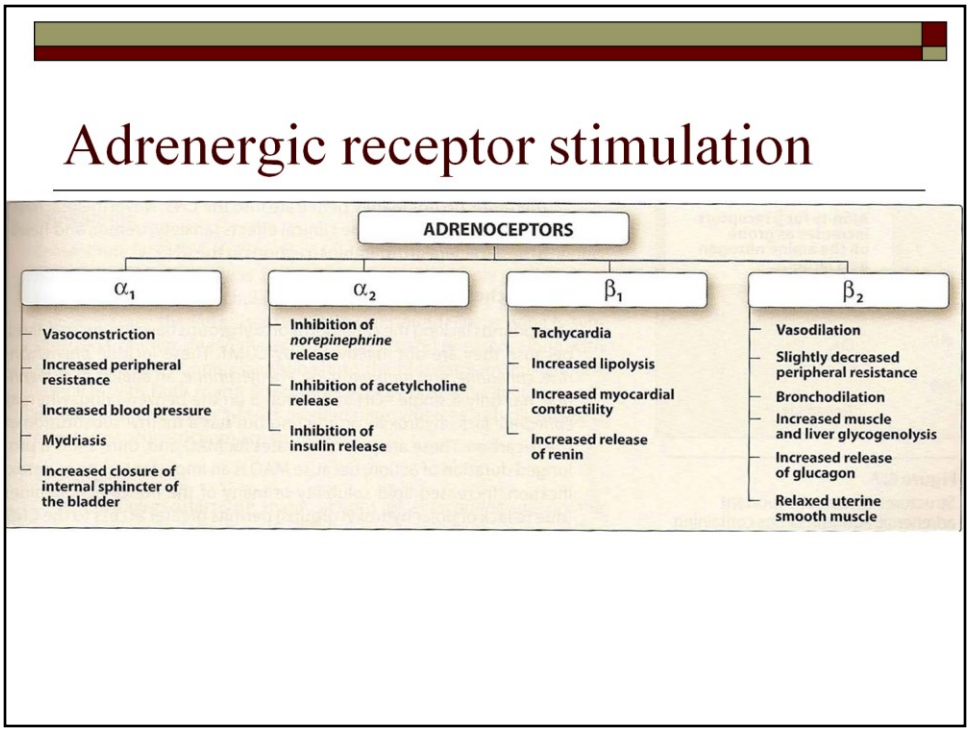


Receptors consists of 7 transmembrane loops and are connected with different G proteins

Gq protein activates PLC (proteinkinase C) - leads to increase of intracelular Ca2+

Gs protein activates AC (adenylylcyclase) – leads to increased cAMP

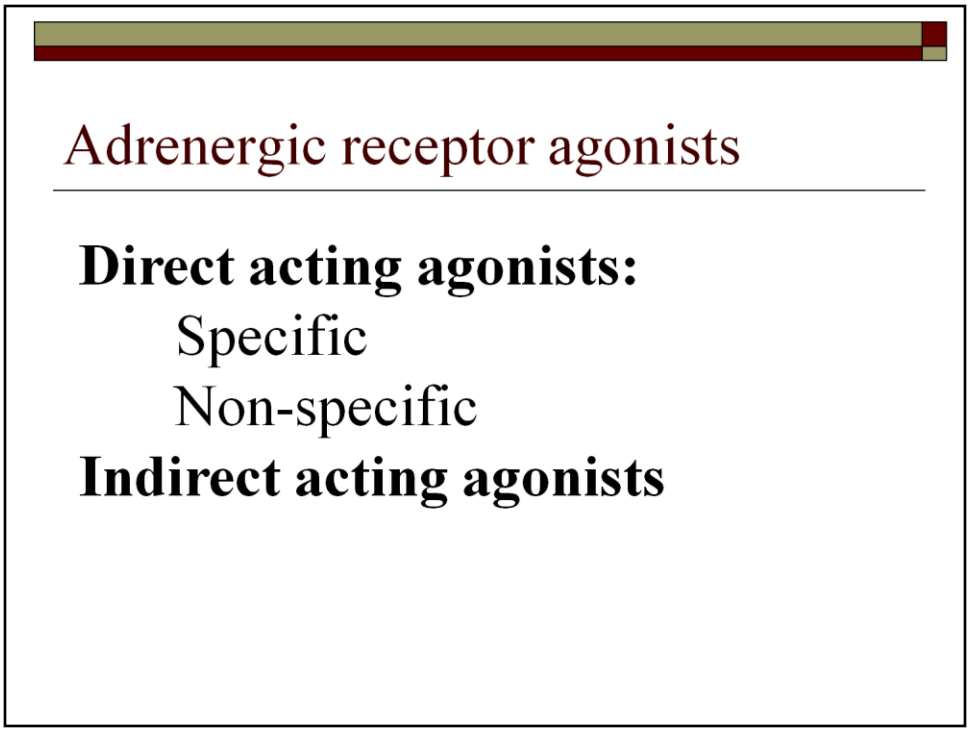
Gi protein inhibits AC – leads to decrease of c AMP



Tissue response. Most of mentioned effects are involved in clinical use of AR agonists and antagonists

Adrenoceptor	Drug Action	Therapeutic Uses
α_1	Agonists	Shock, hypotension (to raise blood pressure)
		Nasal decongestants
α_2	Agonists	Antihypertensives
		Glaucoma
		Analgesia
		Sedatives
β_2	Agonists	Bronchodilators (asthma and chronic obstructive pulmonary disorder)
		Glaucoma

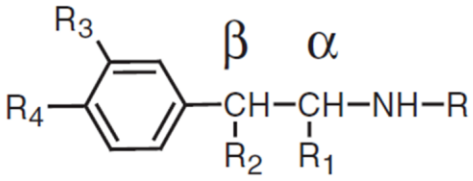
Therapeutic use of agonists



Direct agonists binds to receptor and activates it. Specifity can be focused to family or particular subtype.

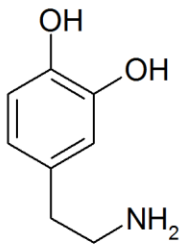
Adrenergic receptor agonists

Structure-activity relationships



Derivatives or analogues of phenylethylamine. Two carbons between phenyl and amino moiety is necessary.
The lesser degree of substitution on NH, the greatest selectivity for αlpha; increase volume of NH substituent adds the selectivity towards beta.
R1 substitution inhibits monoamino oxidase – prolonged action and facilitates indirect mechanism of action
R3, R4: OH groups necessary for activation of both alpha and beta. No hydroxyl increases central stimulation effect.

Non-specific α and β agonists



Dopamine

low dosis: renal vasodilatation via dopamine receptors

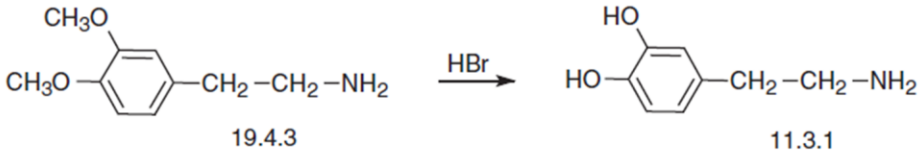
higher dosis: + cardial effect via β_1 stimulation

high dosis: cardial effect and peripheral vasoconstriction (α_1)

low dosis activates only D receptor (indication: cardiovascular shock prevention)
medium dosis activates D + beta1 (i: cardiotonic)
high dosis activates D + beta1 + alpha1 (i: severe hypotension, acute hearth failure)

Non-specific α and β agonists

Dopamine synthesis:



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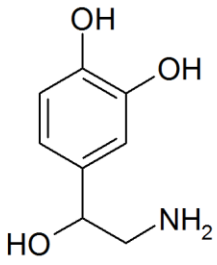
Non-specific α and β agonists



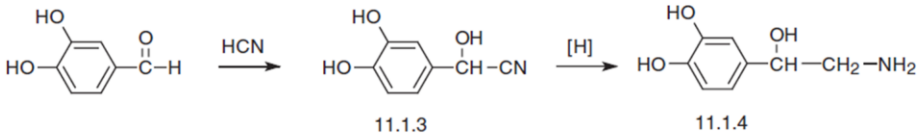
Noradrenaline

mainly peripheral vasoconstrictor (α)
partial effect on β_1 receptors in higher dosis

local decongescent
higher dosis i.v. severe hypotension, cardiovascular shock

Non-specific α and β agonists

Noradrenaline synthesis:



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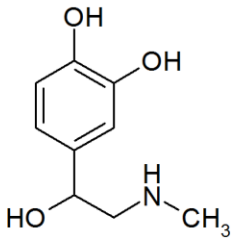
Non-specific α and β agonists



Adrenaline

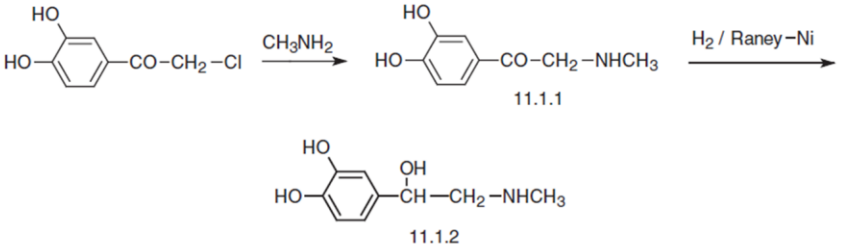
in lower dosis effect on β receptors, in higher both α and β

main effect is cardial stimulation and bronchodilation, only weak vasoconstriction

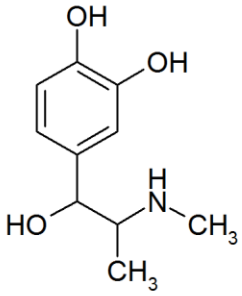
indication: cardiovascular shock, ventricle fibrilation; allergic shock

Non-specific α and β agonists

Adrenaline preparation:
isolation from adrenal glands tissue of livestock;
synthetic:



Non-specific α and β agonists

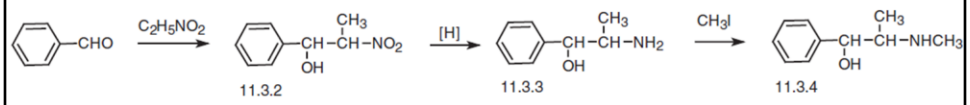


Ephedrine
(R,S configuration)
dominant effect on α, less β_1

Cardial effect, CNS stimulator, weak vasoconstrictor

Non-specific α and β agonists

Ephedrine synthesis:



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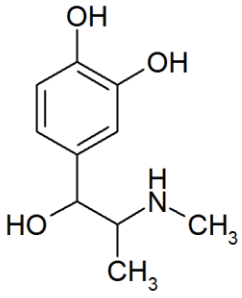
isomeres separated by salt crystallization

Non-specific α agonists

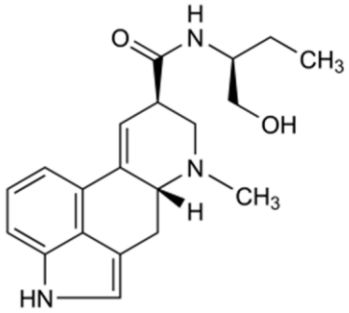


Pseudoephedrine
(R,R configuration)
peroral decongscent

vasoconstriction in mucosa reduces mucus production

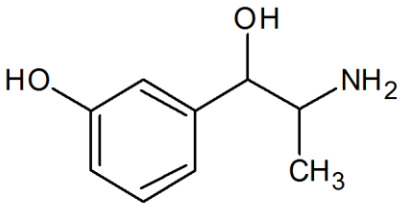
Non-specific α agonists

Methylergometrine
ergot alcaloid
uterotonic effect



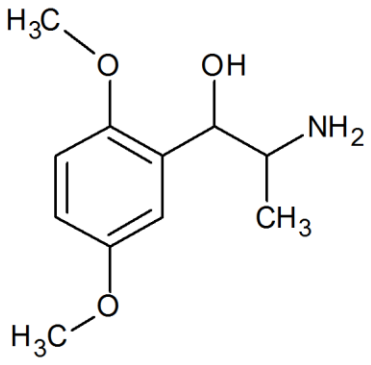
indication: atonic uterus (womb), uterus bleeding

Specific α_1 agonists



Metaraminol
strong vasoconstrictor
treatment of hypotension during surgery, cardivascular shock

Specific α_1 agonists



Methoxamine
strong vasoconstrictor
treatment of hypotension during surgery, cardivascular shock

Specific α_1 agonists

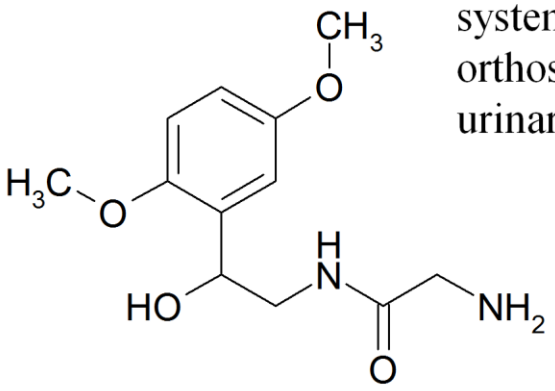
Midodrine

prodrug of deglymidodrine

system administration

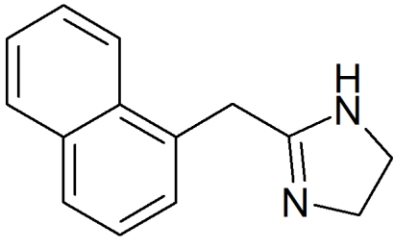
orthostatic hypotension

urinary incontinence



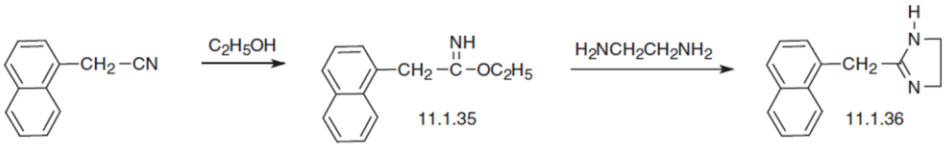
Specific α_1 agonists

Naphazoline
strong vasoconstrictor
local decongescent, ophthalmology



Specific α_1 agonists

Naphazoline synthesis:



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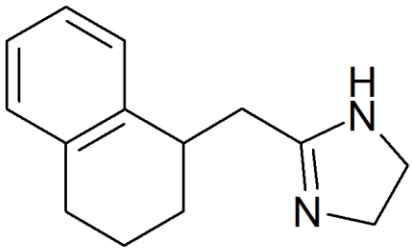
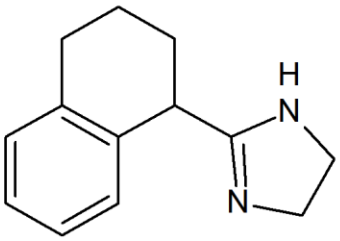
Specific α_1 agonists

Tetryzoline
local decongescent
synthesis similar to naphazoline



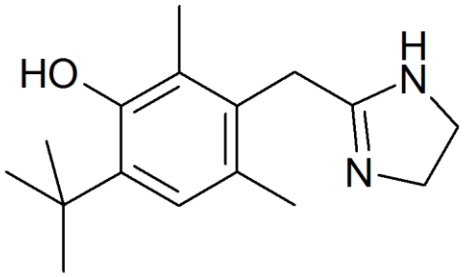
Specific α_1 agonists

Tetrahydrozoline
local decongescent
synthesis similar to naphazoline



Specific α_1 agonists

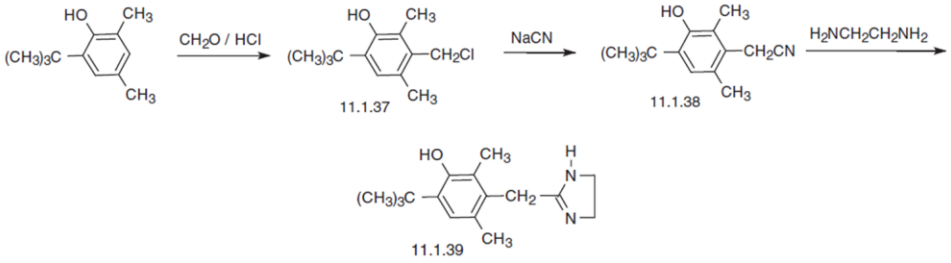
Oxymetazoline
local decongescent
prolonged effect



Prolonged effect due to higher lipophilicity and tissue accumulation

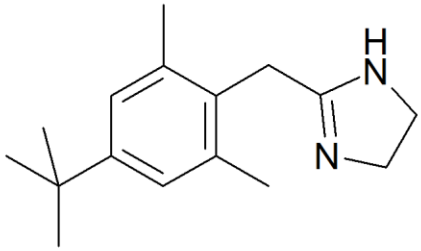
Specific α_1 agonists

Oxymetazoline synthesis:



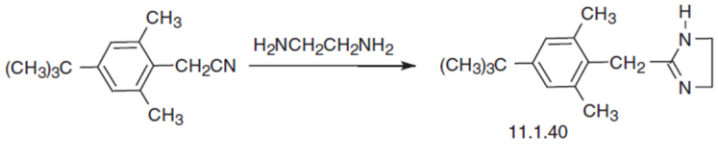
Specific α_1 agonists

Xylometazoline
local decongescent
prolonged effect



Specific α_1 agonists

Xylometazoline synthesis:



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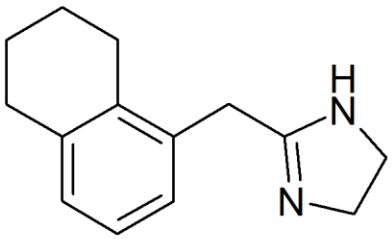
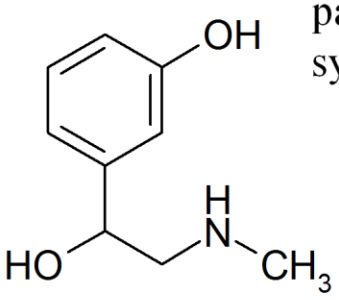
Specific α_1 agonists

Tramazoline
local decongescent
prolonged effect
synthesis similar to naphazoline



Specific α_1 agonists

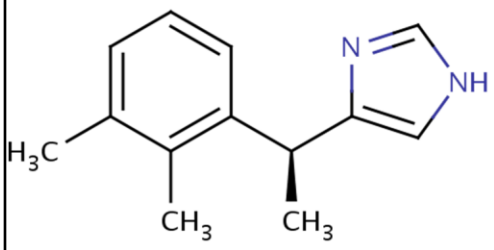
Phenylephrine
local decongescent
medium-lenght effect
partial system effect
synthesis similar to adrenaline



Due to partial system effect cardiovascular diseses are contraindicated

Specific α_2 agonists

Dexmedetomidine
central sedative & hypnotic effect
surgery – „artificial sleep“
↓ blood pressure and heart rate



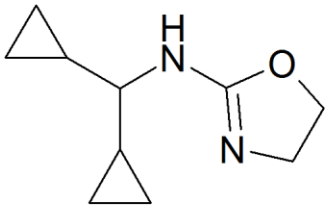
Specific α_2 and imidazoline I_1 agonists

Rilmenidine

dominant I_1 effect, weak α_2

long biological half-time (8-13h)

central antihypertensive agent



optimal lipophilicity to pass blood-brain barrier

indication: arterial hypertension

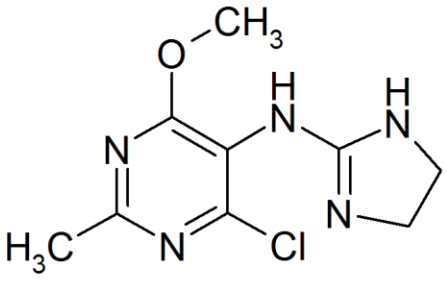
Specific α_2 and imidazoline I_1 agonists

Moxonidine

dominant I_1 effect, weak α_2

biological half-time (2-3h)

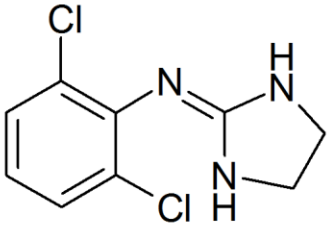
central antihypertensive agent



Specific α_2 and imidazoline I_1 agonists

Clonidine

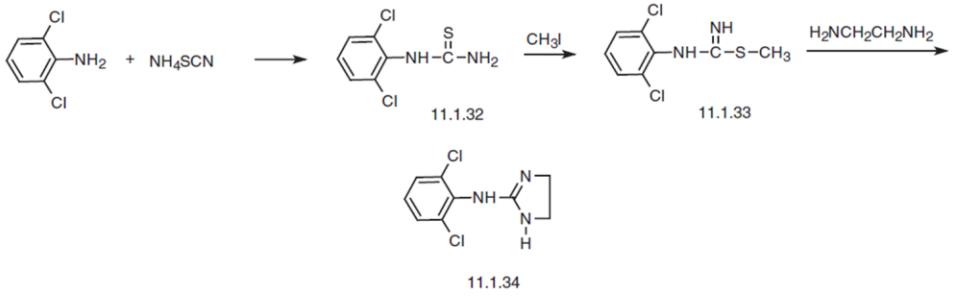
ballanced I_1 and α_2 effect
biological half-time (2-3h)
central antihypertensive agent
Ophthalmology: glaucoma therapy
central muscle relaxant



intravenous application in the case of hypertension crisis
local application in ophthalmology - reduces increased intraocular pressure

Specific α_2 and imidazoline I_1 agonists

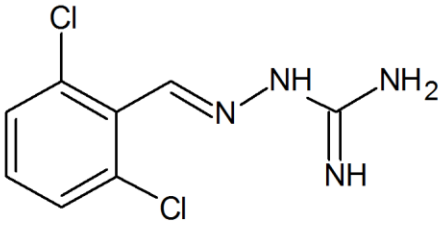
Clonidine synthesis:

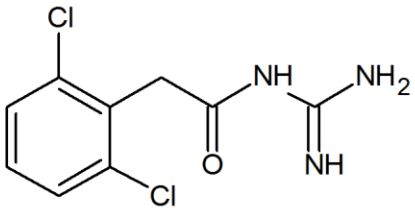


Specific α_2 and imidazoline I_1 agonists

Guanabenz, Guanfacine

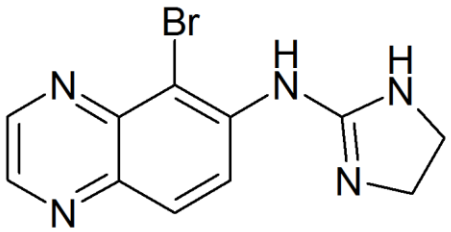
Centrally active antihypertensives





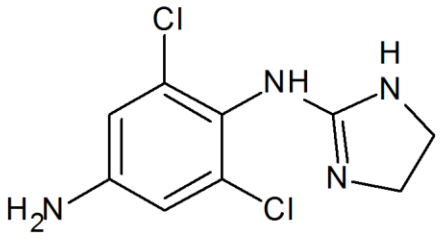
Specific α_2 and imidazoline I_1 agonists

Brimonidine
dominant α_2 effect
Ophthalmology: glaucoma therapy



Specific α_2 and imidazoline I_1 agonists

Apraclonidine
dominant α_2 effect
Ophthalmology: glaucoma therapy

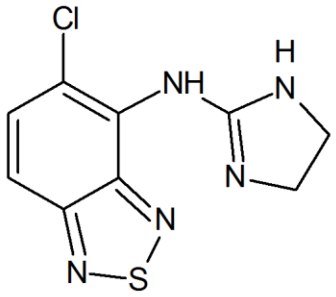


Specific α_2 and imidazoline I_1 agonists

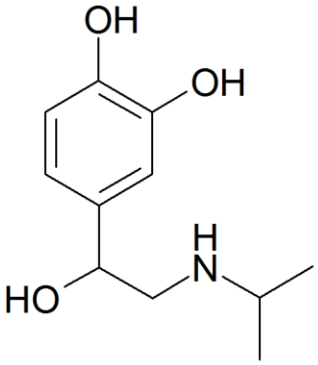
Tizanidine

dominant α_{2C} effect

Centrally active muscle relaxant



Non-specific β agonists

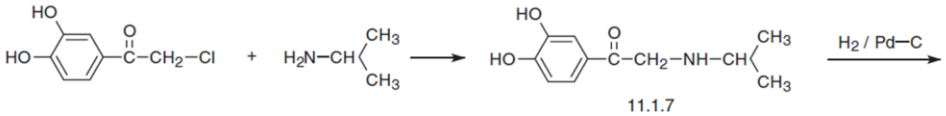


Isoprenaline
effect on all β receptor subtypes
very short biological half-time (2min)
+ cardial effect and bronchodilatation

administered by continual i.v. infusion
indication: heart insufficiency after transplantation, bradycardia

Non-specific β agonists

Isoprenaline synthesis:



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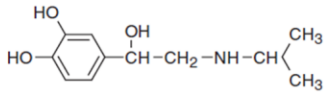

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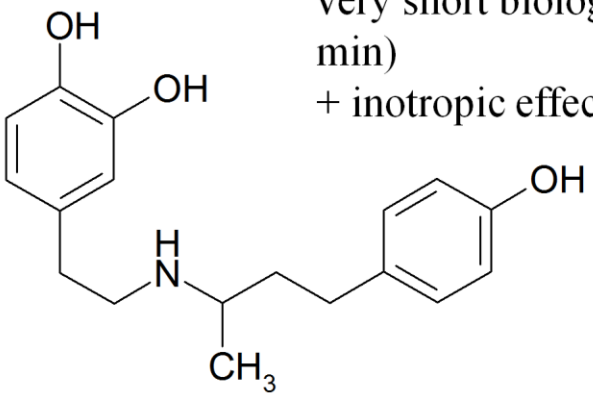
Non-specific β agonists

Dobutamine

dominant β_1 effect, weak β_2

very short biological half-time (1-2 min)

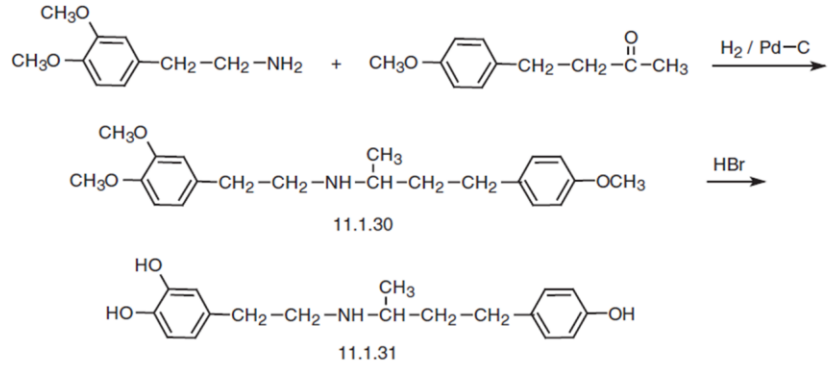
+ inotropic effect



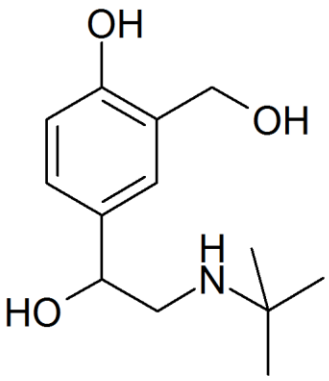
indication: hert failure

Non-specific β agonists

Dobutamine synthesis:



Specific β_2 agonists

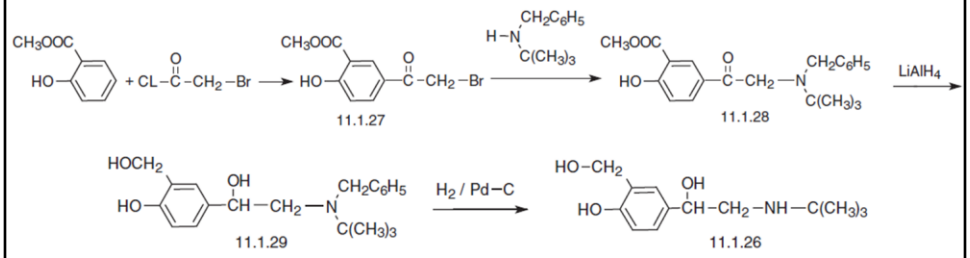


Salbutamol (Albuterol US)
selective β_2 agonist
oral and inhalatory way of administration
bronchodilator

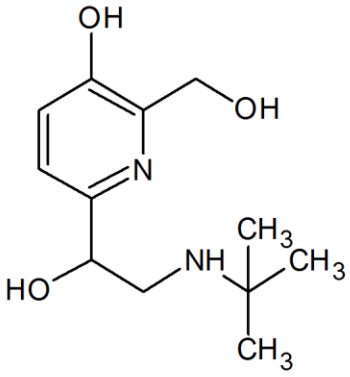
indication: bronchial asthma, ChOPN (chronical obstructive pulmonary disease)

Specific β_2 agonists

Salbutamol synthesis:

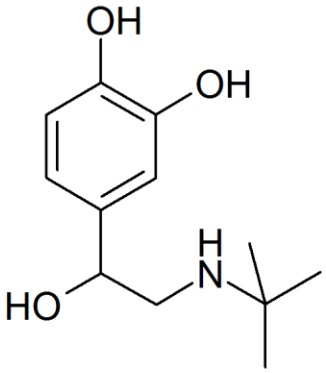


Specific β_2 agonists



Pirbuterol
pyridine analogue
only inhalatory way of administration

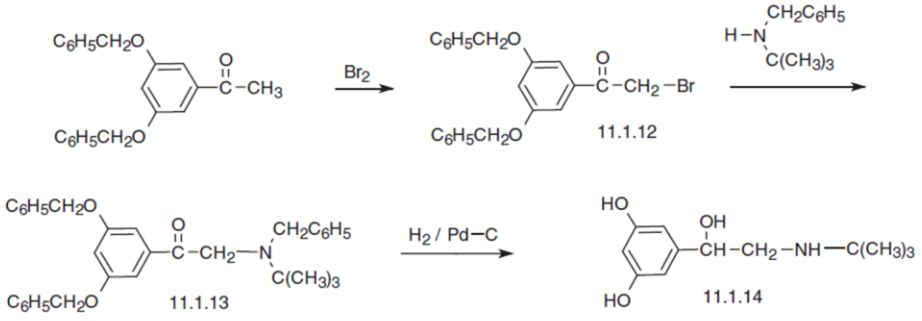
Specific β_2 agonists



Terbutaline
selective β_2 agonist
oral and inhalatory way of administration
bronchodilator

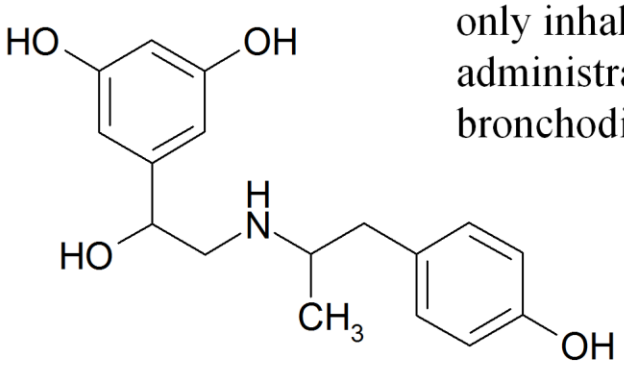
Specific β_2 agonists

Terbutaline synthesis:



Specific β_2 agonists

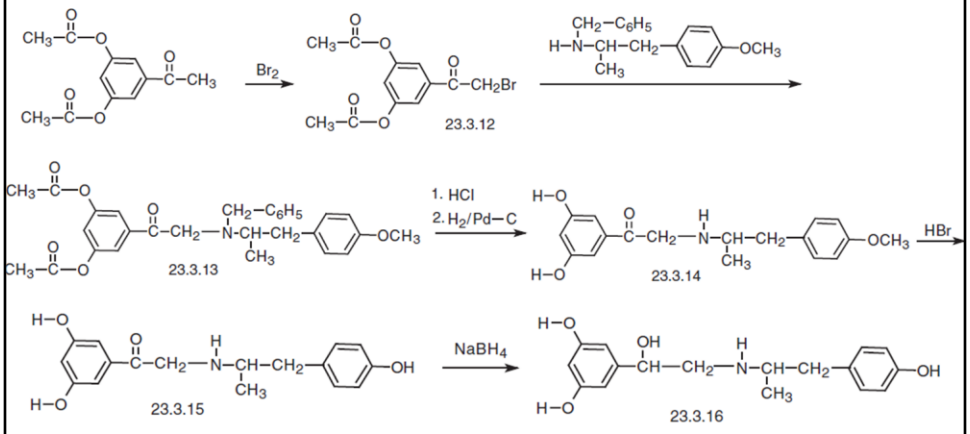
Fenoterol
selective β_2 agonist
only inhalatory way of administration
bronchodilator



p.o. administration is not possible due to partial system effect via beta1 activation

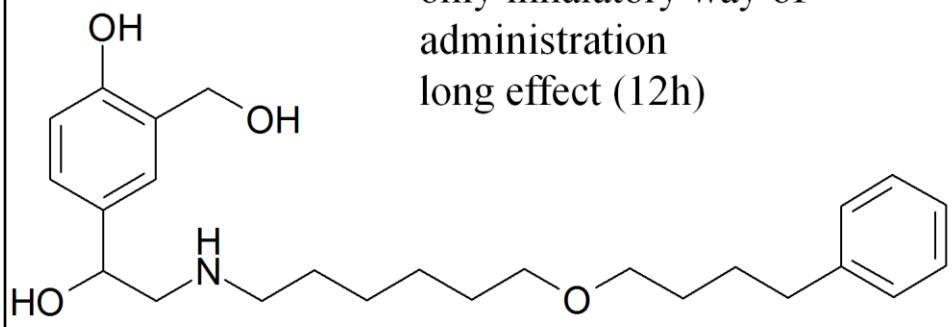
Specific β_2 agonists

Fenoterol synthesis:

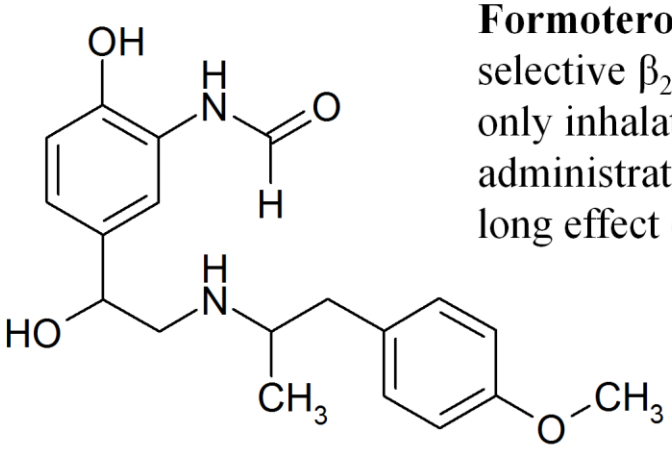


Specific β_2 agonists

Salmeterol
selective β_2 agonist
only inhalatory way of administration
long effect (12h)

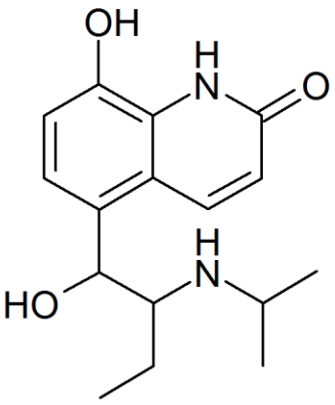


Specific β_2 agonists



Formoterol
selective β_2 agonist
only inhalatory way of administration
long effect (12h)

Specific β_2 agonists

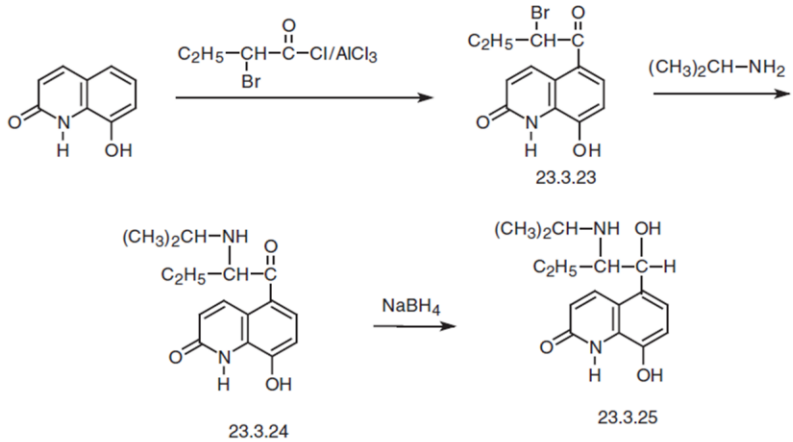


Procaterol
selective β_2 agonist
only peroral way of administration
long effect (12h)
long-term therapy

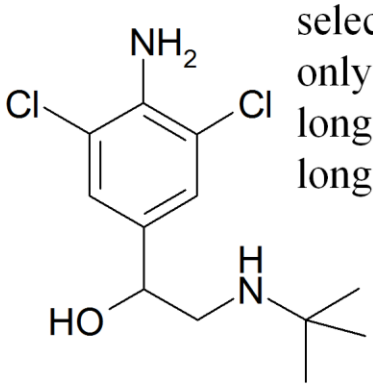
long term p.o. application for prevention of bronchial asthma symptoms

Specific β_2 agonists

Procaterol synthesis:



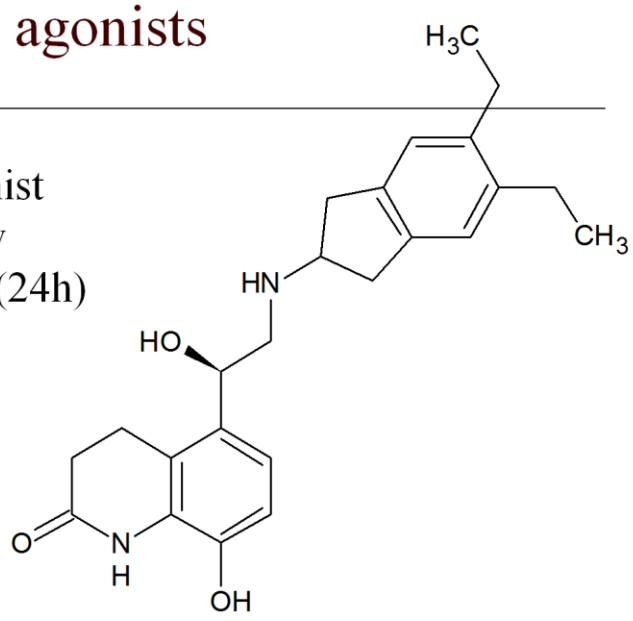
Specific β_2 agonists



Clenbuterol
selective β_2 agonist
only peroral way of administration
long effect (14h)
long-term therapy

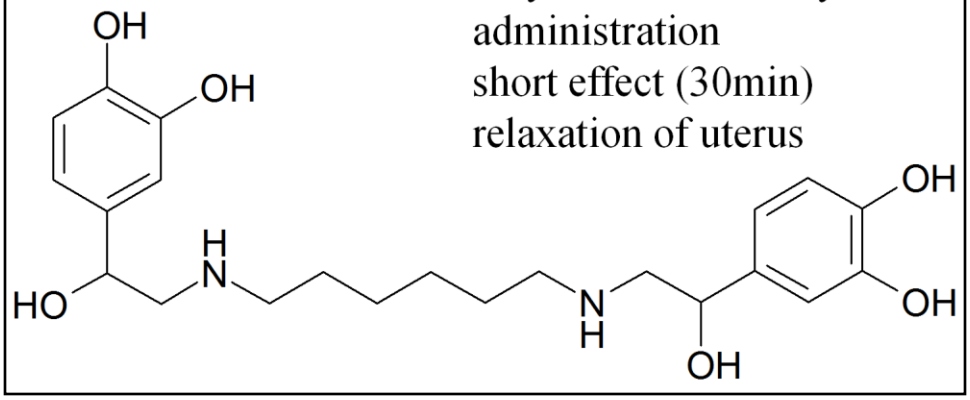
Specific β_2 agonists

Indacaterol
selective β_2 agonist
orally once a day
very long effect (24h)



Specific β_2 agonists

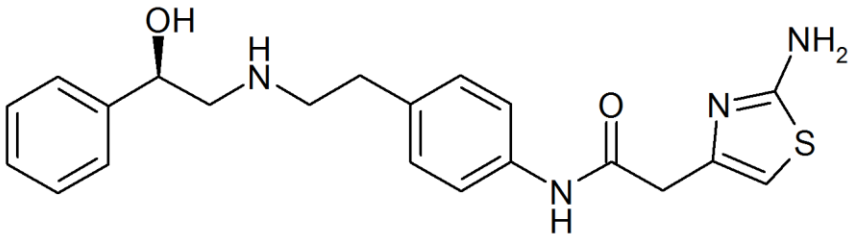
Hexoprenalin
selective β_2 agonist
only intravenous way of administration
short effect (30min)
relaxation of uterus



bronchodilation is weak

Specific β_3 agonists

Mirabegron
first on market (2012)
therapy of overactive bladder (OAB)



highly selective: only weak cardiovascular side effects, no bronchial side efect

Indirect acting adrenergic receptor agonists

- stimulation of NA release from vesicles or inhibition of NA reuptake

- psychic stimulants

- *Amphetamine and analogues used as anorectics (Antiobesity drugs lecture)*
- *Reuptake inhibitors and MAO inhibitors used as antidepressants (CNS agents lecture)*

Indirect acting adrenergic receptor agonists

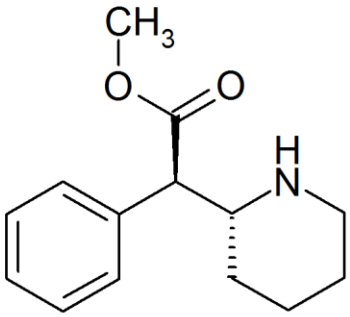
Methylphenidate

- NA and dopamine reuptake inhibitor
- Activation of reticular system in brain
- Therapy of ADHD (attention-deficit hyperactivity disorder) in children
- Therapy of narcolepsia in adults
- In modern therapy is used *R,R*-isomer (dexmethylphenidate) which is much more potent than racemate

ADHD – retarded dosage forms once a day
narcolepsia – non-retarded dosage forms 2-3x day

Indirect acting adrenergic receptor agonists

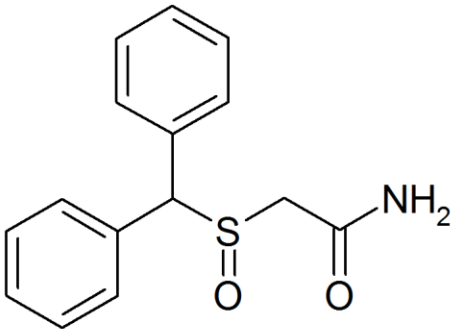
Dexmethylphenidate



Indirect acting adrenergic receptor agonists

Modafinyl

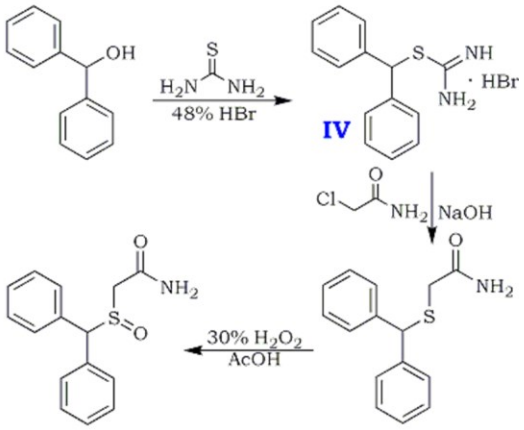
- Increasase α_1 activity via unknown mechanism
- Therapy of narcolepsy



increases motoric activity and wakefulness

Indirect acting adrenergic receptor agonists

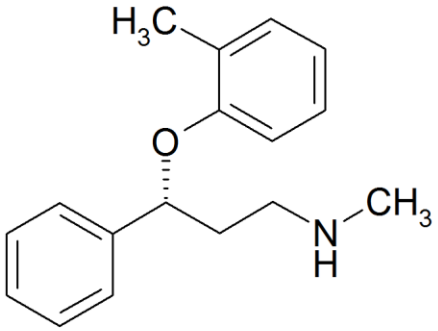
Modafinyl synthesis



Indirect acting adrenergic receptor agonists

Atomoxetine

- NA reuptake inhibitor
- Therapy of ADHD
- Only *R*-isomer active



Indirect acting adrenergic receptor agonists

Duloxetine

- NA and 5HT reuptake inhibitor, weak dopamine reuptake inhibitor
- Therapy of depression,
  stress urinary incontinence,
  diabetic neuropathy
- Only *S*-isomer active

antidepressive agent, diabetic neuropathy 60mg 1x a day
stress urinary incontinence 40mg 2x a day

Indirect acting adrenergic receptor agonists

Duloxetine