Antiadrenergics

Lecture

Tomáš Goněc 2020

Antiadrenergics

direct – competitive inhibitors on NA binding site
indirect – inhibitors of release/uptake of NA

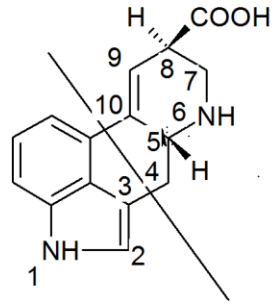
blocking of adrenergic receptor causes:
- vasodilation and bloog pressure decrease
- bradycardia (heart-rate decrease)
- increase of uterus tonicity
- prolactine release inhibition

Antiadrenergics

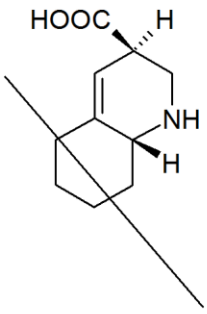
Antiadrenergics are used in therapy as:
- antihypertensives
- vasodilators
- antiarrhythmics
- antimigrenotics
- uterotonics

α-blockers (non-selective)

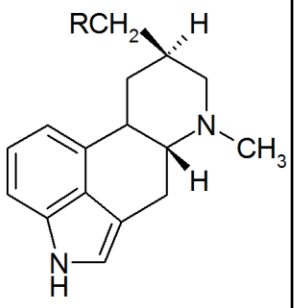
Natural drugs – ergot alkaloids



lysergic acid



isolysergic acid



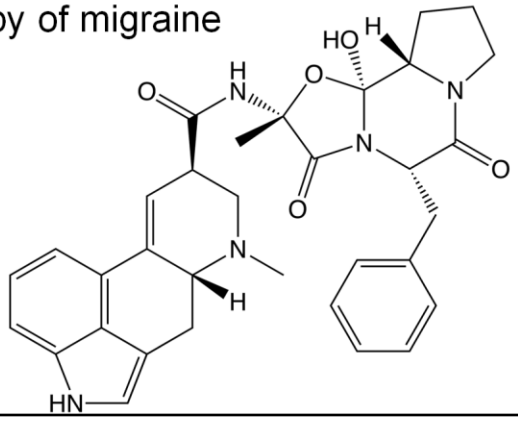
R=H, OH
clavine alkaloids

Three types of alkaloid. Isolysergic acid is optical isomer of lysergic acid. Clavine is without 9-10 double bond and carboxyl.

α-blockers (non-selective)

Ergotamine, Dihydroergotamine

- α antagonistic, 5HT, D agonistic effect
- therapy of migraine



Vasoconstrictors! Dihydroergotamine is without 9-10 double bond and is intended for nasal administration (rapid onset)

α-blockers (non-selective)

Dihydroergotoxine

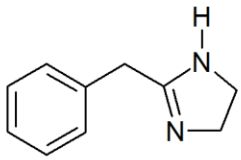
- α_1, 5HT antagonistic, D agonistic effect
- mixture of dihydroergocristine, dihydroergocryptine and dihydroergocornine
- therapy of insufficient limbs perfusion, insufficient CNS perfusion, insufficient internal ear perfusion, Menier disease

Vasodilators!

α-blockers (non-selective)

Tolazoline

- α antagonist, H_2 agonist
- therapy of neonatal pulmonar hypertension

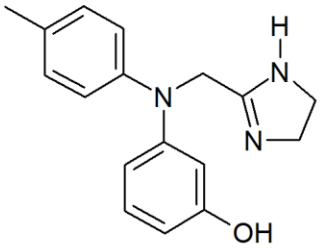


causes selective vasodilation in lungs

α-blockers (non-selective)

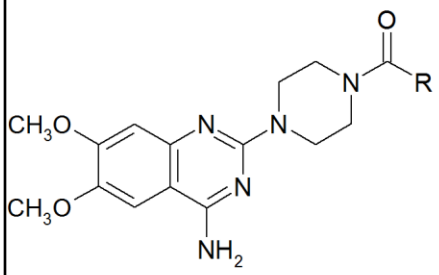
Phentolamine

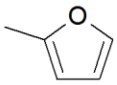
- dominantly α_1 antagonist - vasodilator
- antihypertensive agent
- limited use (hypertension crisis)



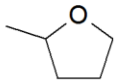
weak αlpha2 antagonist as well – risk of reflexive tachycardia

α_1-selective blockers

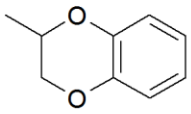




Prazosin
antihypertensive



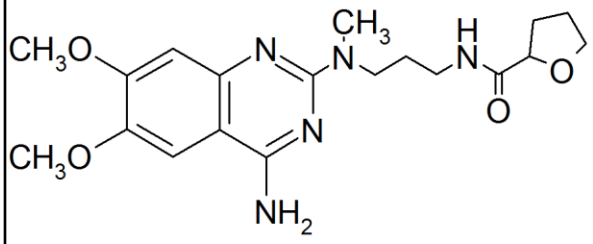
Terazosin
antihypertensive, BPH



Doxazosin
antihypertensive, BPH

Prazosin is not in clinical use, other derivatives posses better safety profiles. Terazosin and doxazosin has longer biological half-time (use 1x a day). Therapy of hypertension and benign prostatic hyperplasia (BPH)

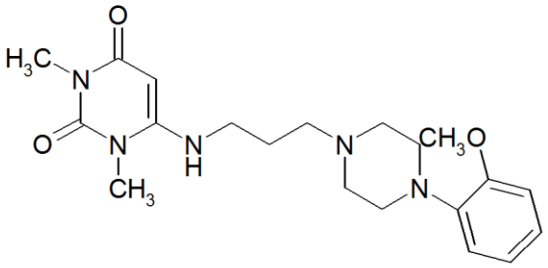
α_1-selective blockers



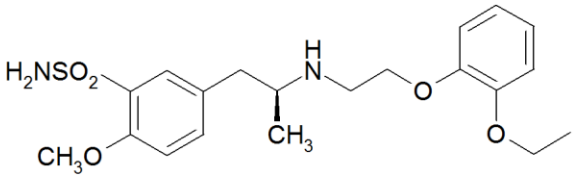
Alfuzosin
Uroselective
BPH

Selective decrease of urethral and prostatic tonus. Therapy of BPH

α_1-selective blockers



Urapidil
also $5HT_{1A}$ agonist
arterial hypertension



Tamsulosin
Uroselective
BPH
urinary incontinence

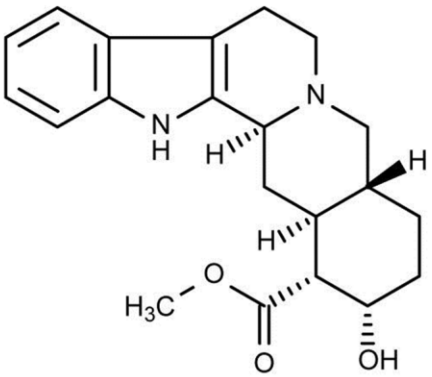
Urapidil is both alpha1 antagonist and central $5HT_{1A}$ agonist – combined central and peripheral antihypertensive effect
Tamsulosin selectively decreases urethral and prostatic tonus, improves bladder function

α_2-selective blockers

Yohimbine

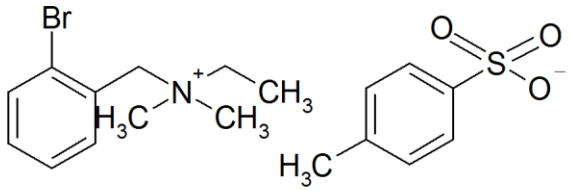
specific increase of pelvic perfusion

therapy of erectile dysfunction



Alkaloid of Yohimbe tree

Indirectly acting α-blockers



Bretylium tosylate
inhibits noradrenaline release in neural junction
III.class antidysrhythmic drug

β-blockers

Current Use

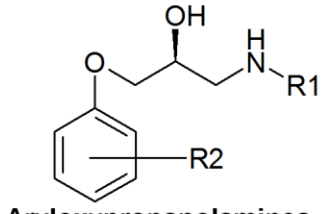
Treatment

·Angina pectoris (chest pain associated with lack of oxygen to the heart) ·Arrhythmias (irregular heart rhythms)·Heart attack ·Heart failure ·Hypertension (high blood pressure) ·Glaucoma ·Migraine

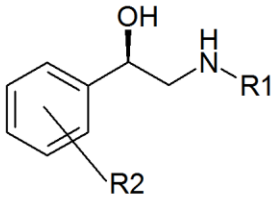
Prevention

·Protects the heart in people who have coronary artery disease ·Reduces risk of stroke ·Protective prior to non-cardiac surgery in persons at high risk of complications

β-blockers



Aryloxypropanolamines



Arylethanolamines

SAR: (-propoxy-) spacer -O- can be replaced by isosteric -COO-; -NHCOO- or =C=N- group

R1: isopropyl-, *terc*butyl- or arylalkyl-

R2: various substituents

o-substitution or another ring = non-selective

p-substitution = cardioselectivity

R1 is substituted with lipophillic group – isopropyl, tert-butyl or arylalkyl – selectivity towards beta receptors

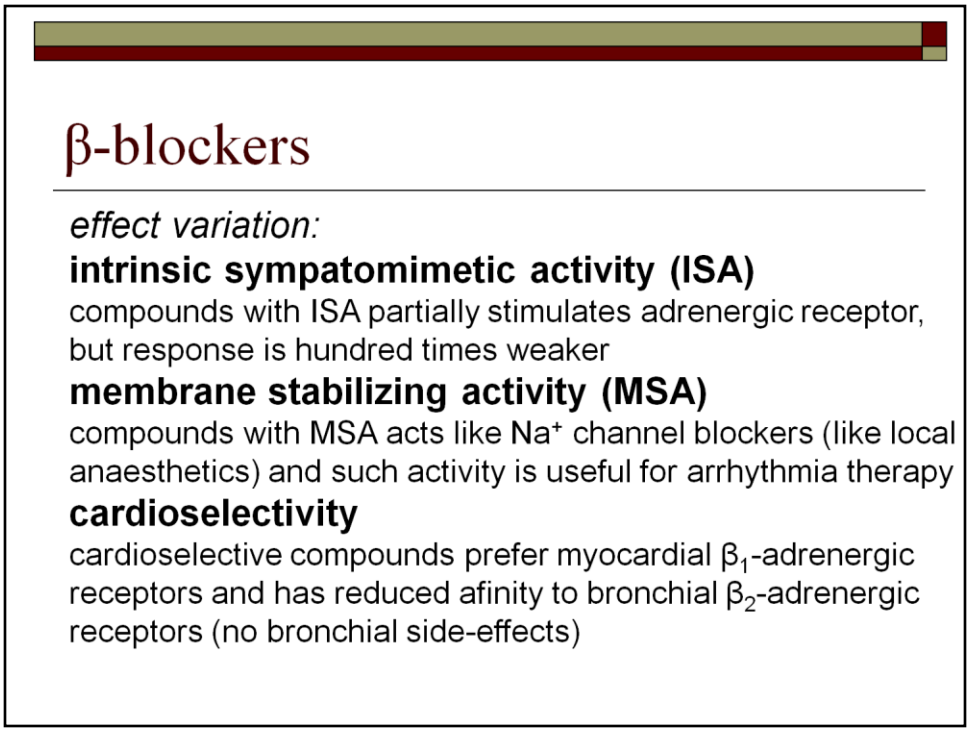
β-blockers

absolute configuration

R absolute configuration *S* absolute configuration

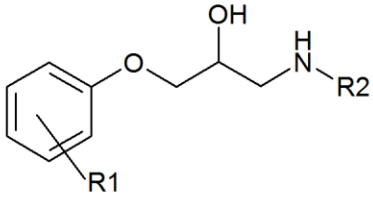
FIGURE 10.15 Stereochemical nomenclature for arylethanolamines versus aryloxypropanolamines. The relative positions in space of the four functional groups are the same in the two structures; however, one is designated *R* and the other *S*. This is because the introduction of an oxygen atom into the side chain of the aryloxypropanolamine changes the priority of two of the groups used in the nomenclature assignment.

Same space orientation but different R/S name! Different groups priority!



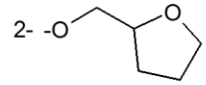
Non-cardioselective betablockers are contraindicated in cardiology (use only for migrain and glaucoma therapy)

non-selective β-blockers without ISA and MSA



metipranolol R1: 4- -O- CH_3 2,3,5- $-CH_3$ R2: $-CH(CH_3)_2$

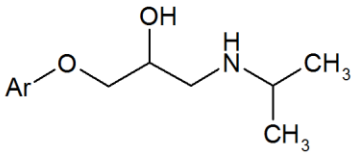
cloranolol R1: 2,5- Cl R2: $-C(CH_3)_3$

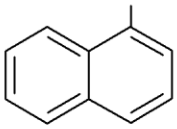
bufetolol R1: 2- -O-  R2: $-C(CH_3)_3$

Metipranolol – obsolent in cardiology; use for migraine prevention, stress urinary incontinence

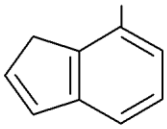
Cloranolol, Bufetolol – similar properties, less common

non-selective β-blockers without ISA and MSA





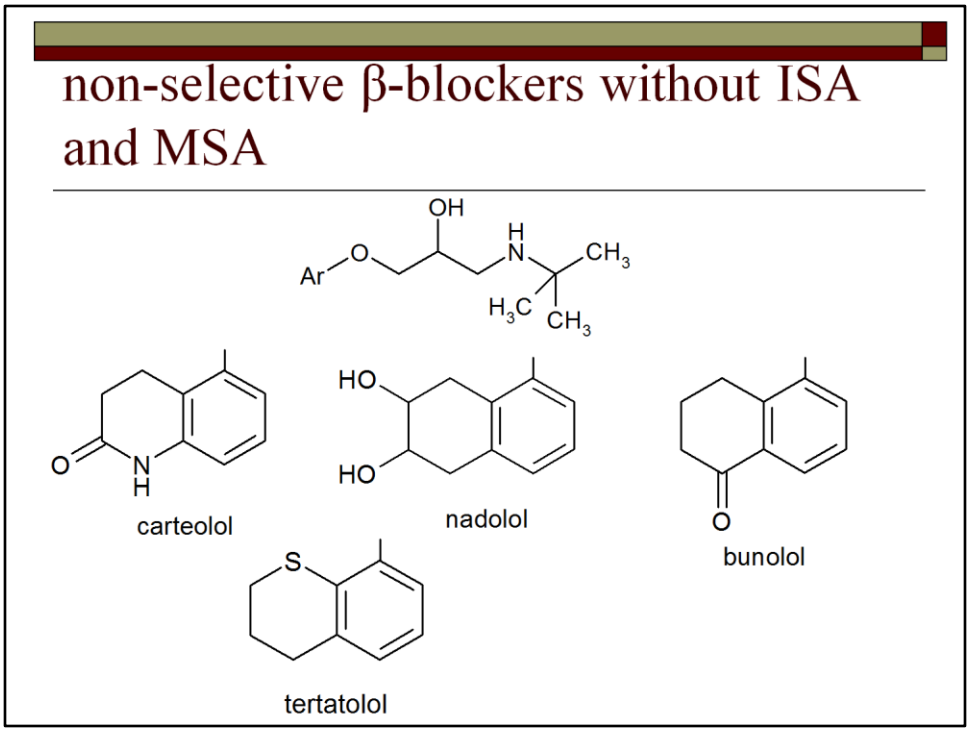
propranolol



indenalol

Propranolol is used in migraine prevention

Indenalol less common, same use



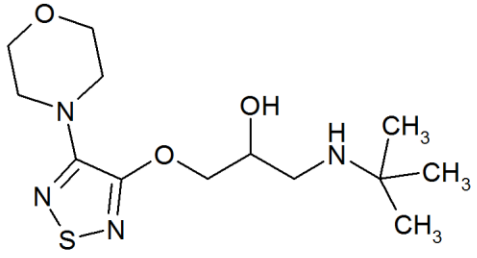
Carteolol – local application for glaucoma therapy

Nadolol – angina pectoris therapy

Bunolol / Levobunolol (pure S isomere) – local application in glaucoma therapy

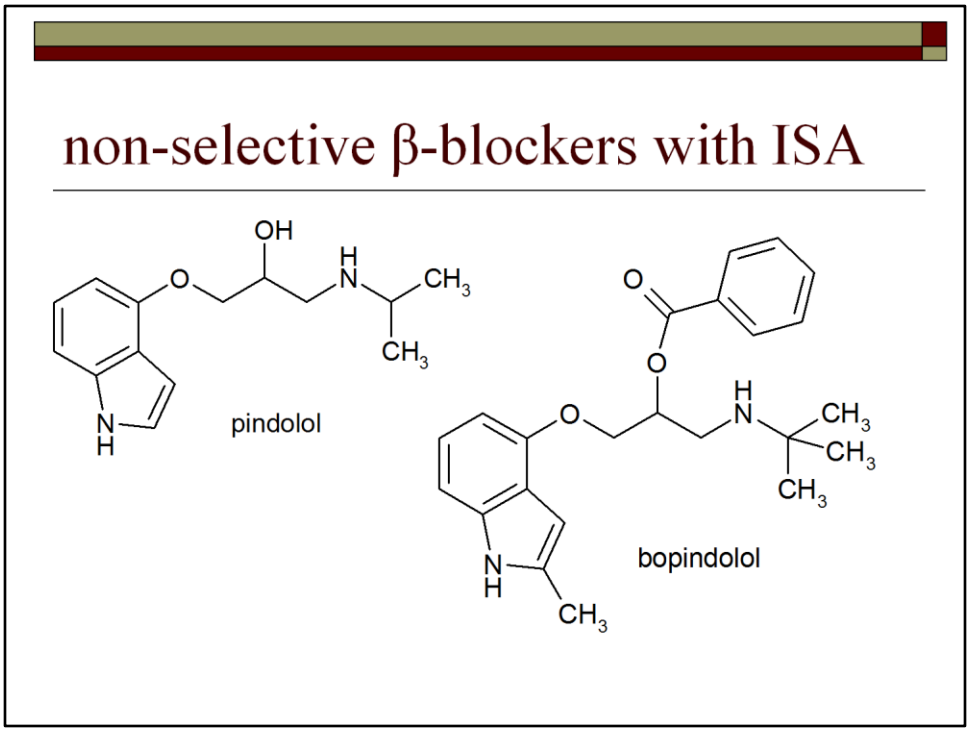
Tertatolol – used for hypertension therapy

non-selective β-blockers without ISA and MSA



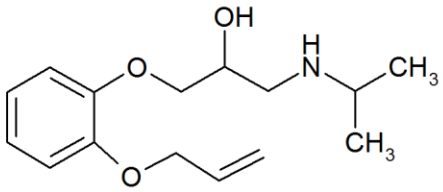
timolol

Local application in glaucoma therapy



Pindolol and Bopindolol (prodrug converted to dimethylpindolol) used for hypertension therapy. Use limited to angina pectoris therapy now.

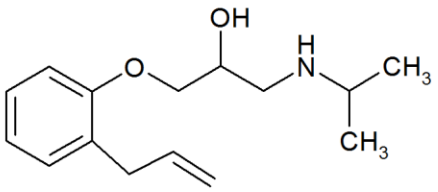
non-selective β-blockers with MSA



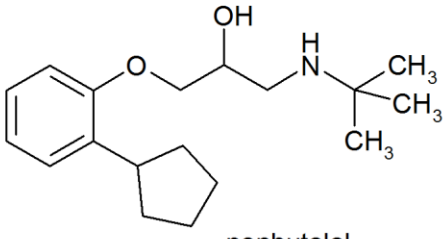
oxprenolol

Lipophillic compound passes through blood-brain barrier. Therapy of arrhythmias, angina pectoris

non-selective β-blockers with MSA and ISA



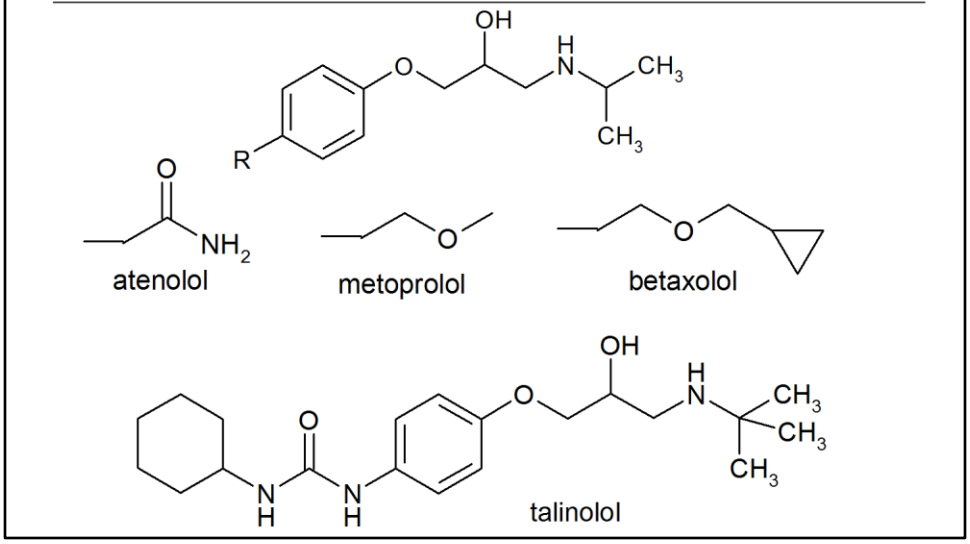
alprenolol



penbutolol

lipophillic compounds passes through blood-brain barrier – cerebral side-effects. Alprenolol was used for hypertension, penbutolol for angina pectoris therapy. Obsolent today.

selective β_1-blockers without ISA and MSA



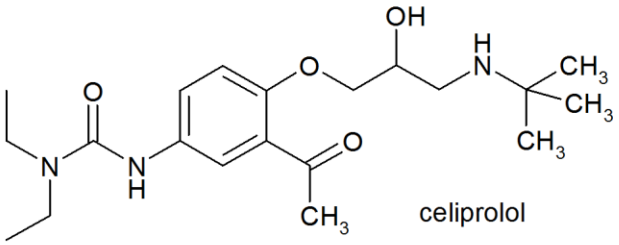
Atenolol is used for angina pectoris, myocardial infarction, arrhythmia and hypertension therapy.

Metoprolol is widely used in same indications as atenolol, additionaly for migraine prevention

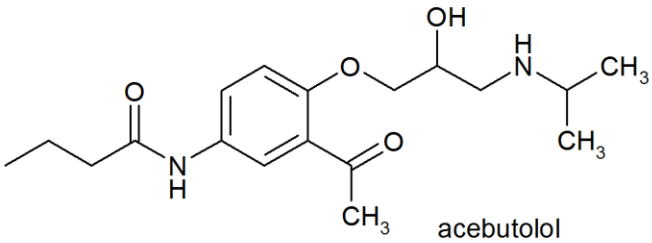
Betaxolol posses some additional Ca2+ channel blocking effect – used for therapy of glaucoma, angina pectoris and hypertension

Talinolol was used as antihypertensive agent.

selective β-blockers without ISA and MSA



celiprolol

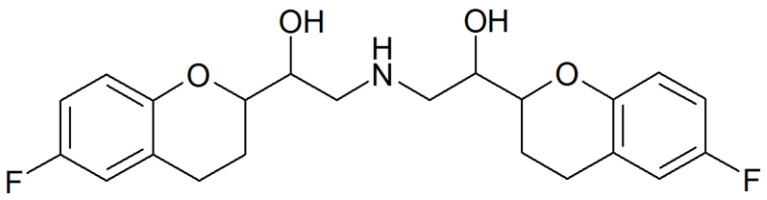


acebutolol

Celiprolol possess partial beta2 agonistic and alpha2 antagonistic effect. Used for hypertension and angina pectoris therapy.

Acebutolol is used for angina pectoris and arrhythmia therapy

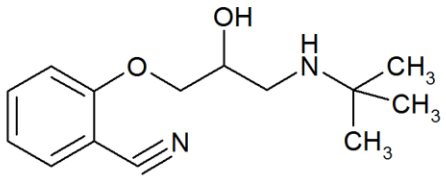
selective β-blockers without ISA and MSA



nebivolol

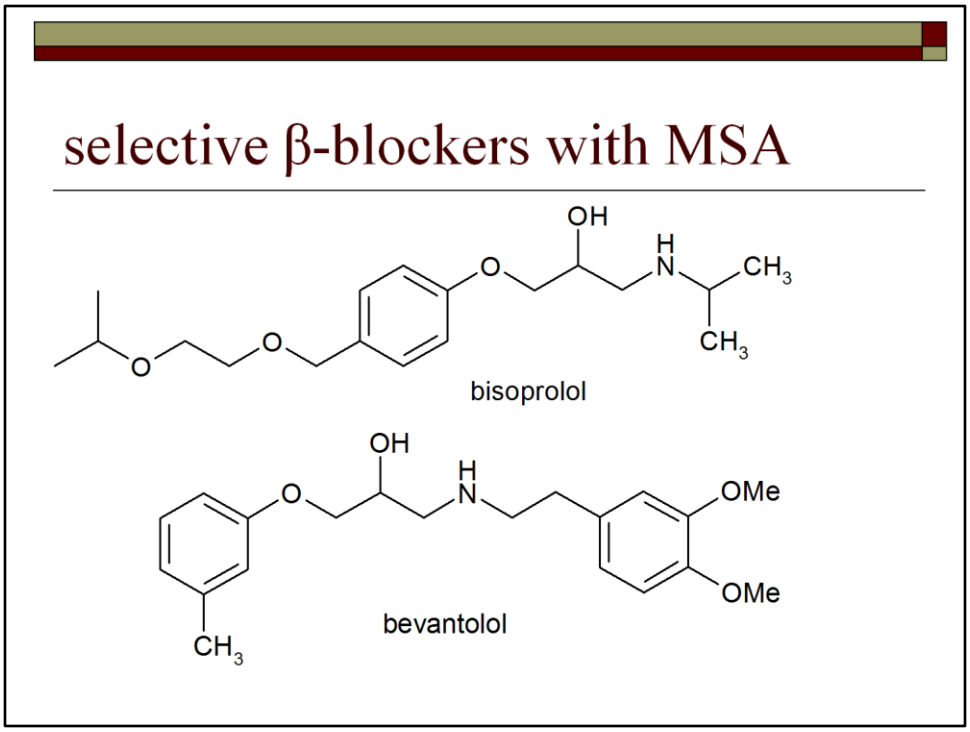
Nebivolol possess direct vasodilating effect (nitrate-like effect). Therapy of angina pectoris, heart insufficience.

selective β-blockers with ISA



bunitrolol

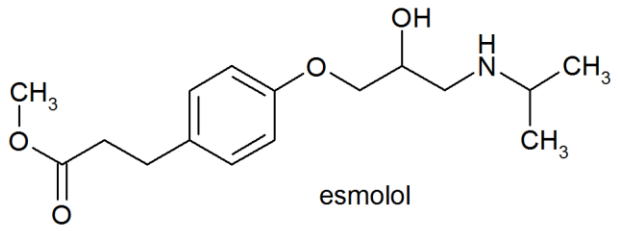
Used as antihypertensive and antiarrhythmic agent.



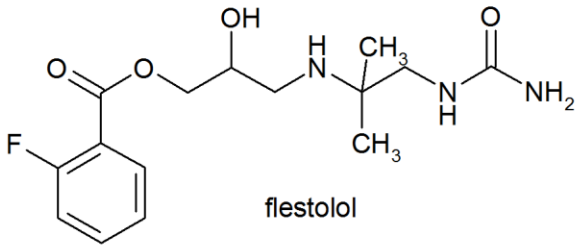
Bisoprolol possess long biological half-time (allows 1x day administration). Used against angina pectoris, arrhythmias, hypertension. Used in long term arrhythmia profylaxion, after myocardium infarction.

Bevantolol posses additional alpha agonistic and Ca2+ channel blocking activity (due to dimethoxy phenylethyl group). No renal side effects- suitable for patients with renal insufficience. Used for treatment of angina pectoris, arrhythmias, hypertension.

ultra-short-acting β-blockers



esmolol

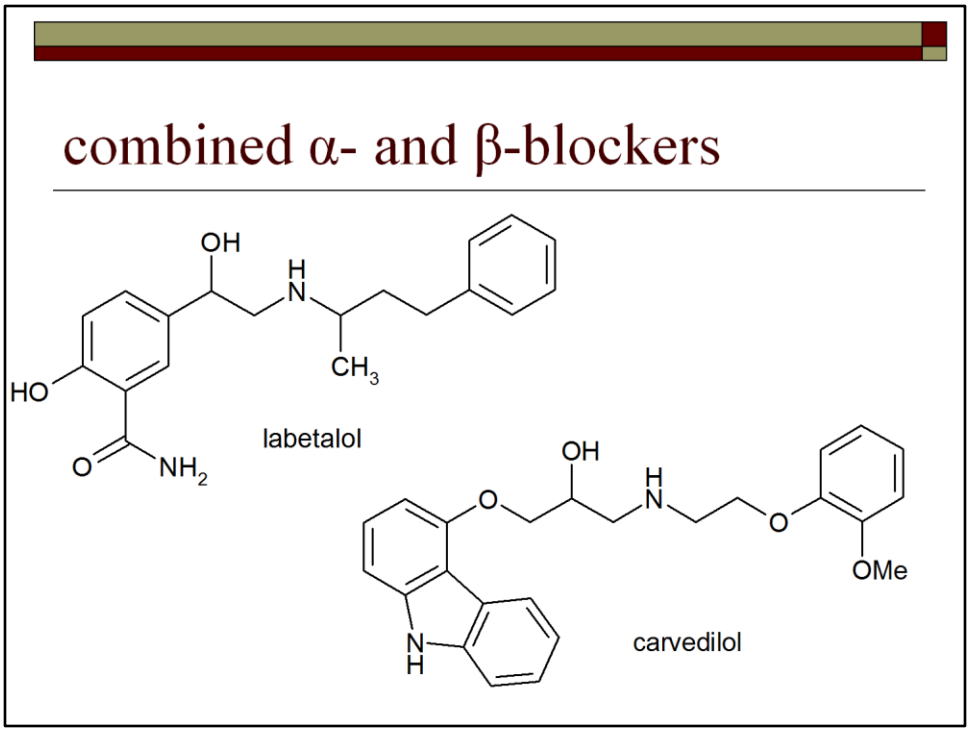


flestolol

Short acting betablockers. Continual intravenous infusion application.

Esmolol – biological half-time 9min, end of effect up to 30 min. Use in acute medicine for treating tachyarrhythmias and during myocardial infarction.

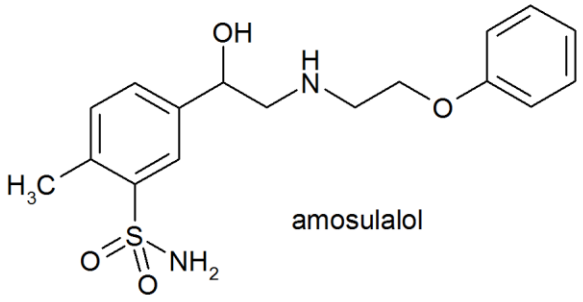
Flestolol – biological half-time 6min, not in clinical use.



Labetalol – not selective beta and selective alpha1 blocker. Only intravenous application. Hypertension crisis therapy, gravidity hypertension therapy.

Carvedilol – complex cardiovascular effect. non selective beta, but higher affinity for blocking of beta1. Selective alpha1 blocker. Best mortality index, remedy of first choice. Therapy of heart insufficience, angina pectoris, heart ischaemia and hypertension.

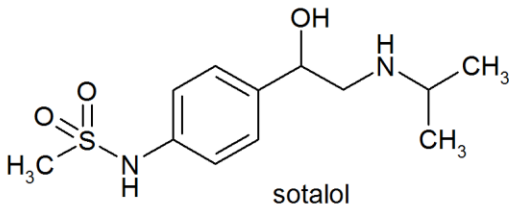
combined α- and β-blockers



amosulalol

Non selective beta, selective alpha1 blocker. Used widely in Japan and South Korea.

β-blockers with K^+channel blocking activity



sotalol

II. + III. class of antiarrhythmic agents (K+ channel blocker, non selective beta blocker). Used for therapy of tachyarrhythmias.