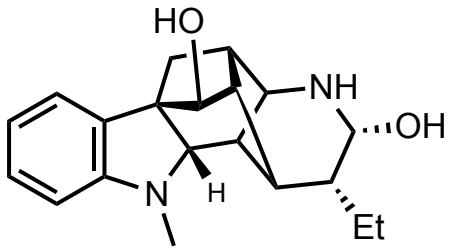
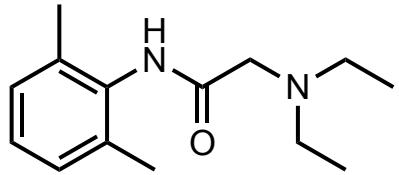
Antiarrhythmika

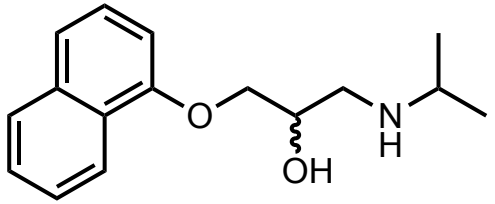
HerzMech; WirkMech; **Klassen; SAR; Ph/M Chem**



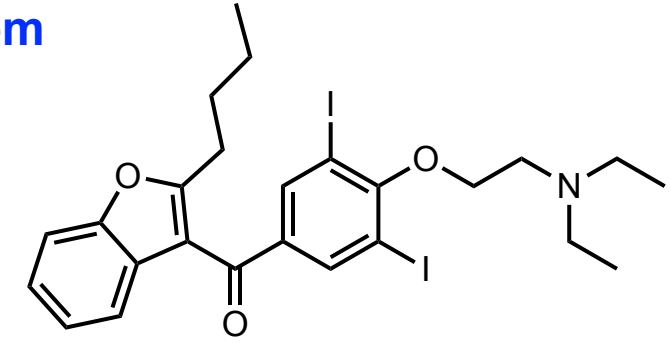
Ajmalin



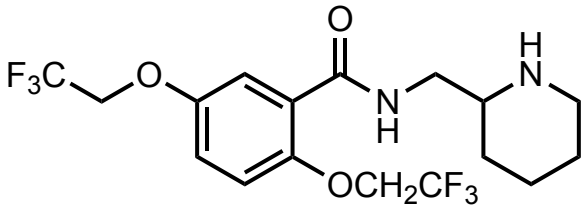
Lidocain



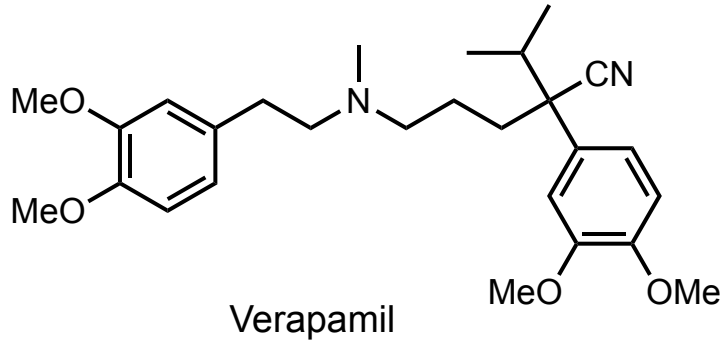
Propranolol



Amiodarone



Flecainid

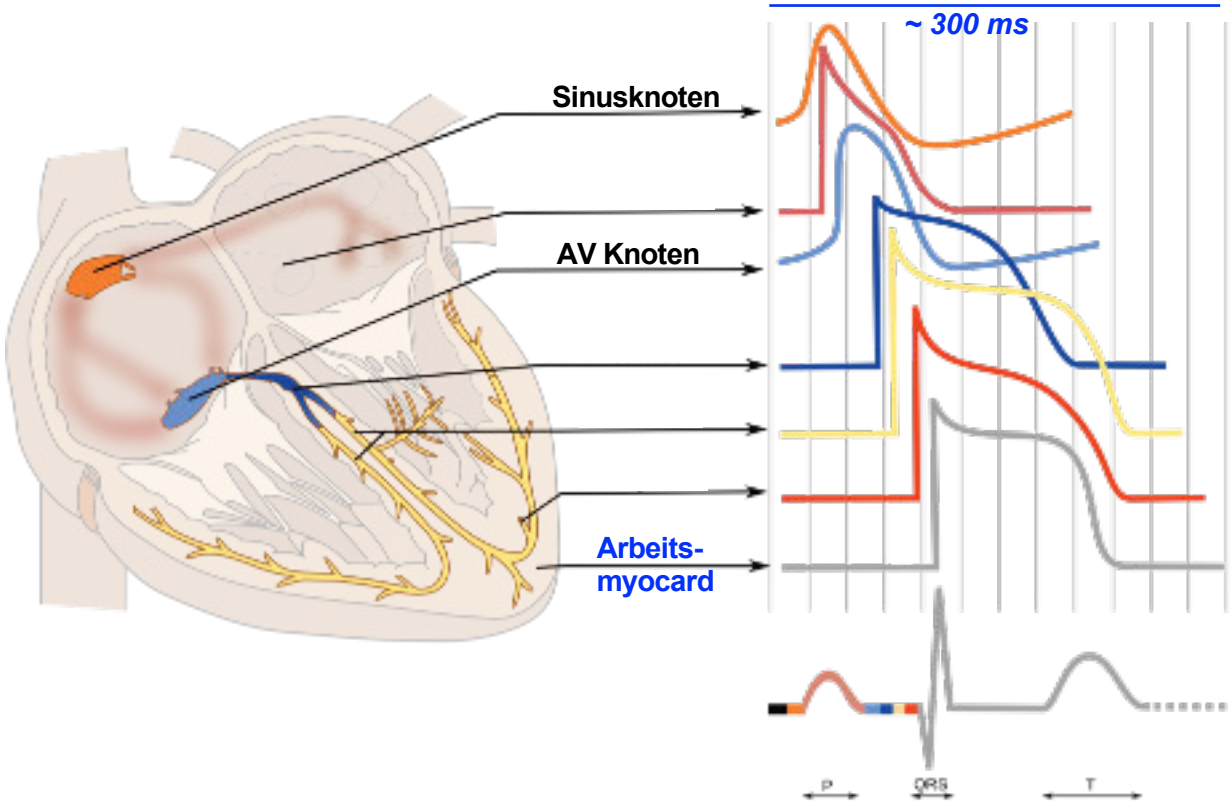


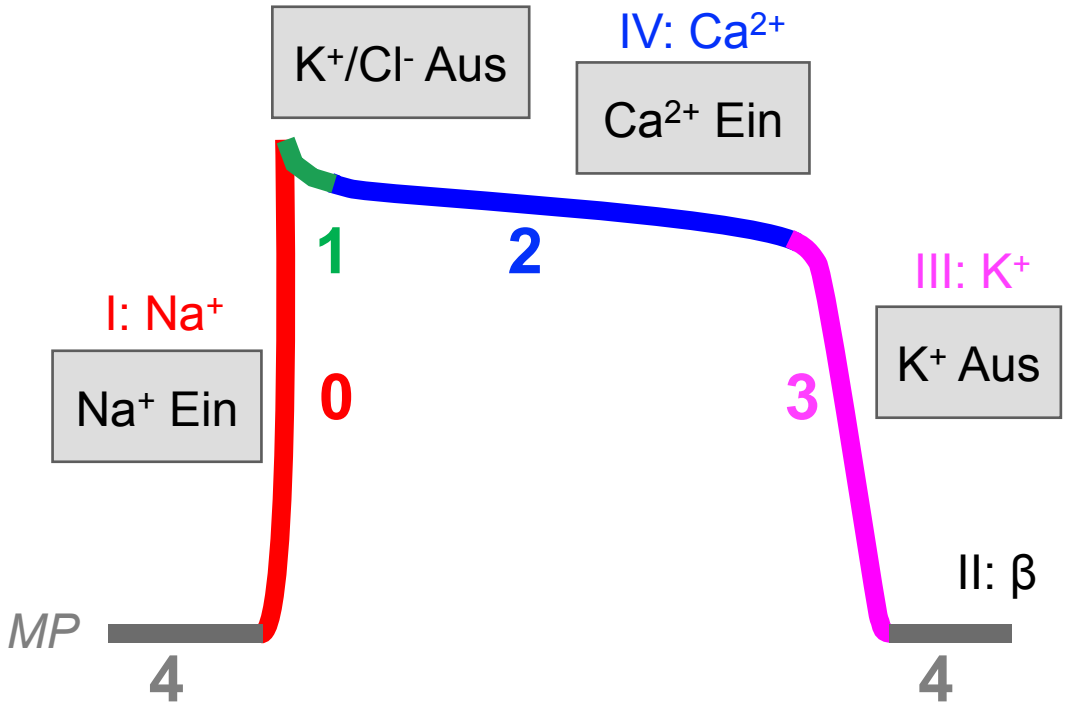
Verapamil

Dr. Oliver Thorn-Seshold; LMU München

Herzrhythmus

Aktionspotenzial: von Schrittmacher zu Arbeitsmyocard

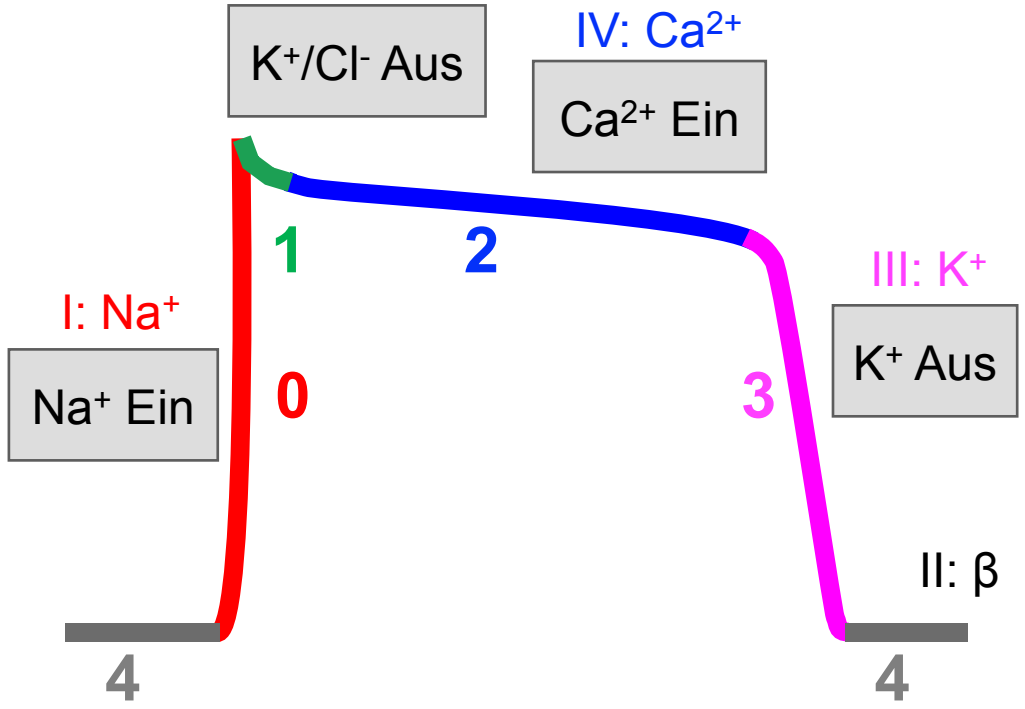




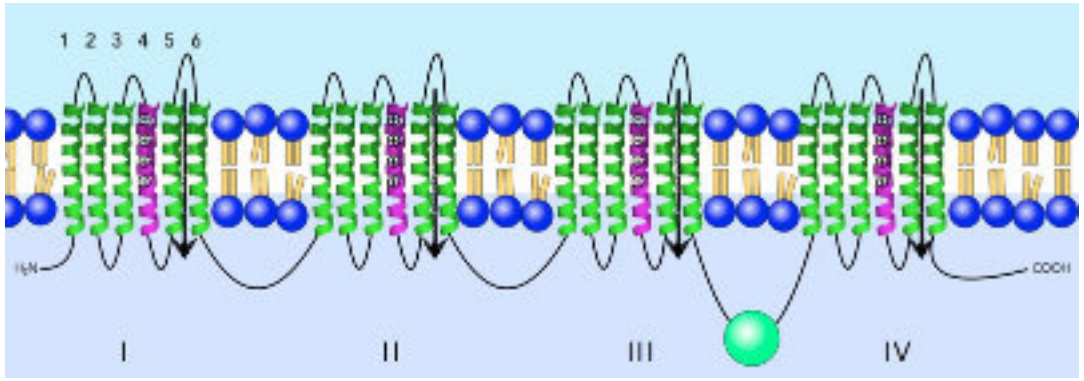
Herzarrhythmien

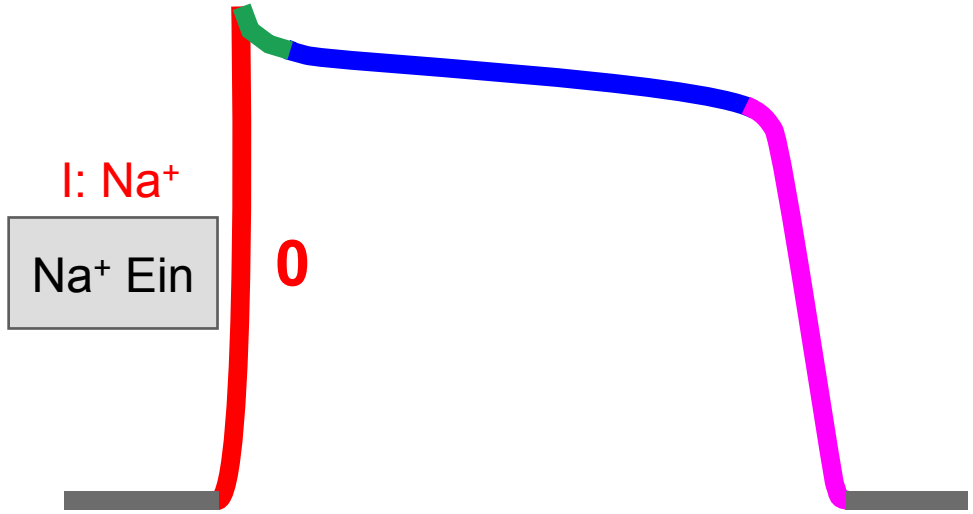
Tachykardien: supraventrikuläre, ventrikuläre, Vorhofflimmern

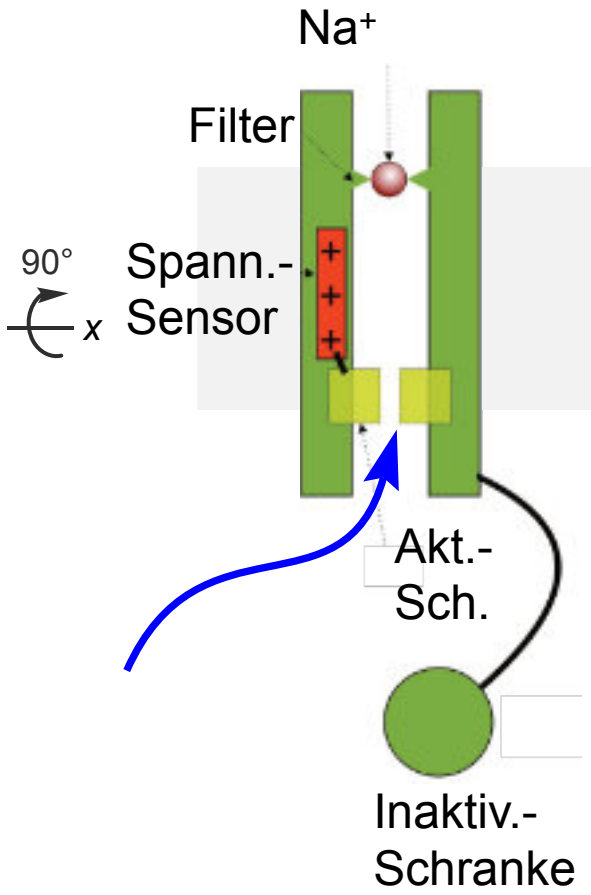
- Vaughan-Williams System
  - I: VG Na^+ Kanalblocker
  - II: β-Blocker
  - III: K^+-Kanalblocker
  - IV: Ca^{2+}-Kanalblocker
  - *& andere*



Spannungsabhängige Na^+-Kanäle : Na_V

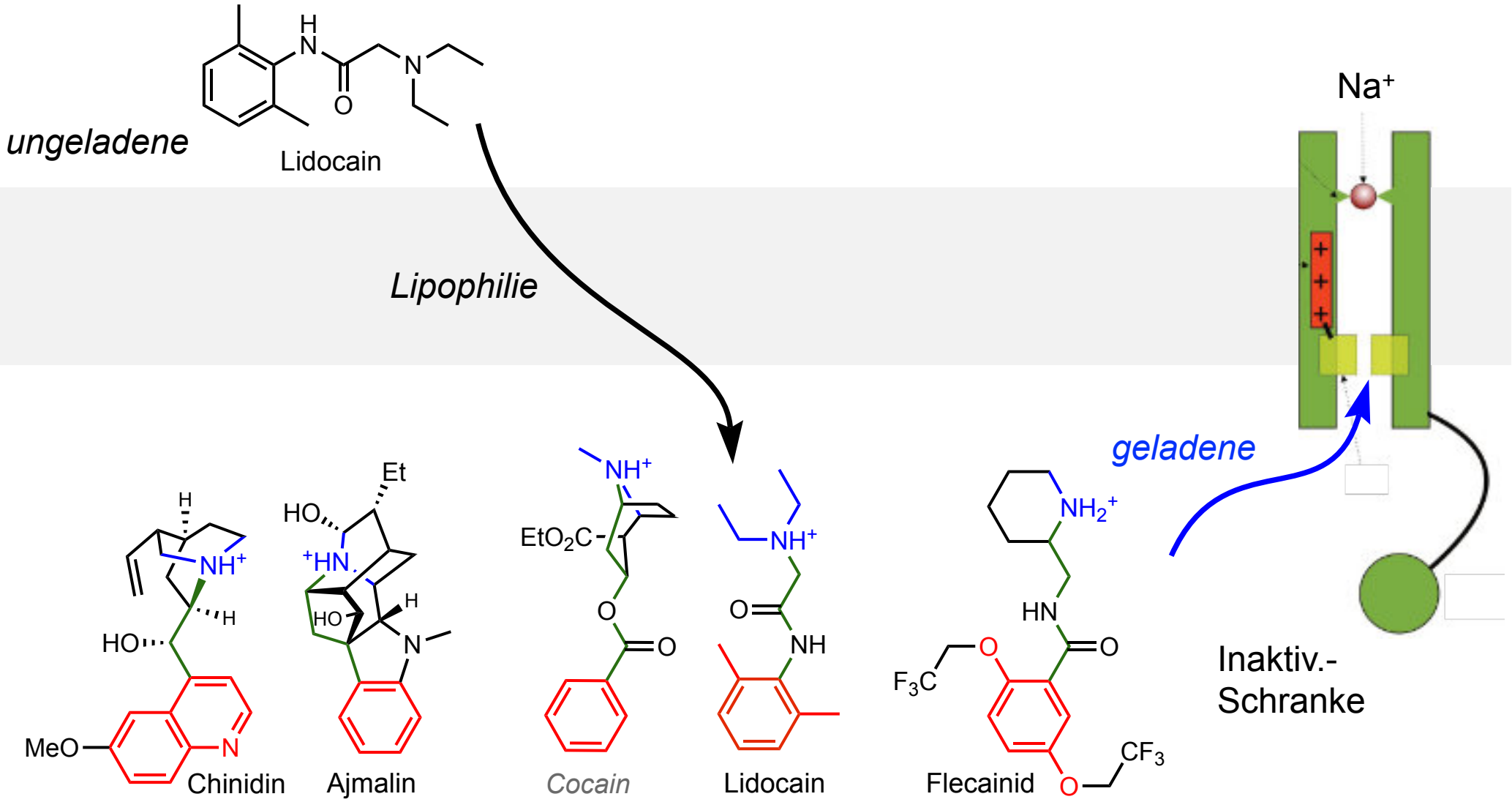






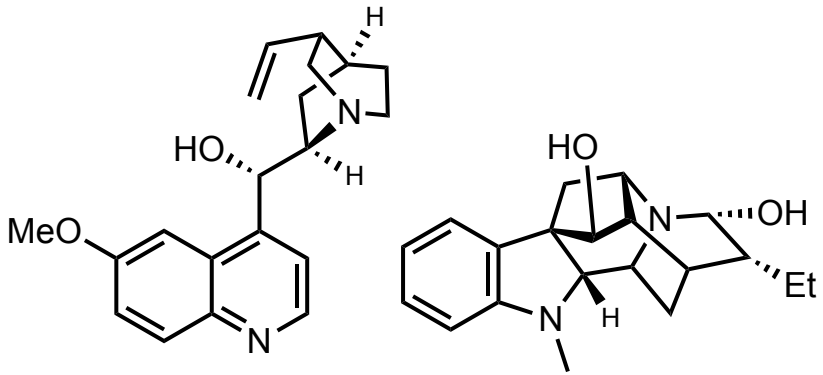
Bildquelle: Ulrich Helmich, 2021

Klasse I: Na^+-Kanalblocker



Klasse I: Na^+-Kanalblocker

IA: Chinidinartig



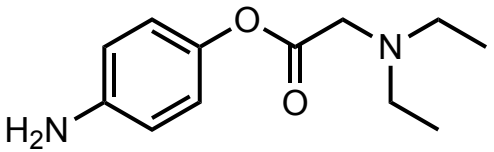
Chinidin Ajmalin

binden $VGSC_O$: AP verlängert

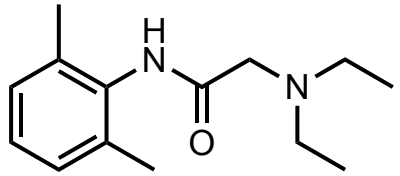
auch VGKC: QT verlängert

wenn keine andere Option:
Akut / bedroh. Vorhofflimmern

IB: Lidocainartig



Procain

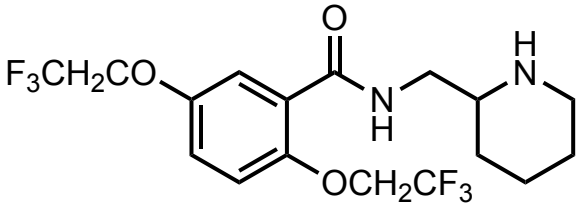


Lidocain

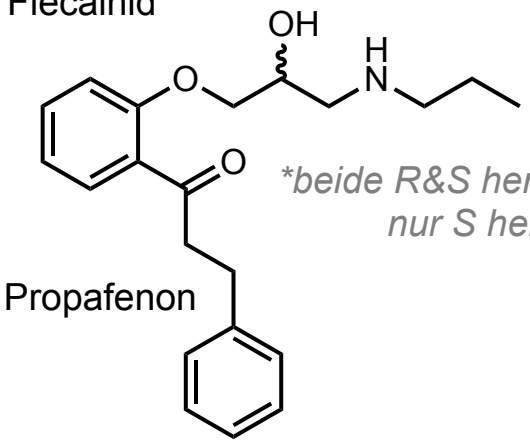
binden $VGSC_i$: AP kaum verkürzt

wenn keine andere Option:
Akut ventrik. Arrhythmien

IC: "Mischtyp"



Flecainid

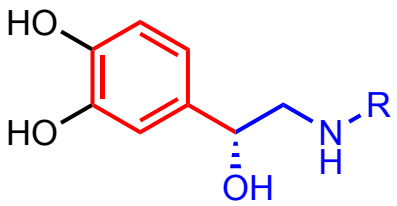


Propafenon

**beide R&S hemmen VGSC*
nur S hemmt β

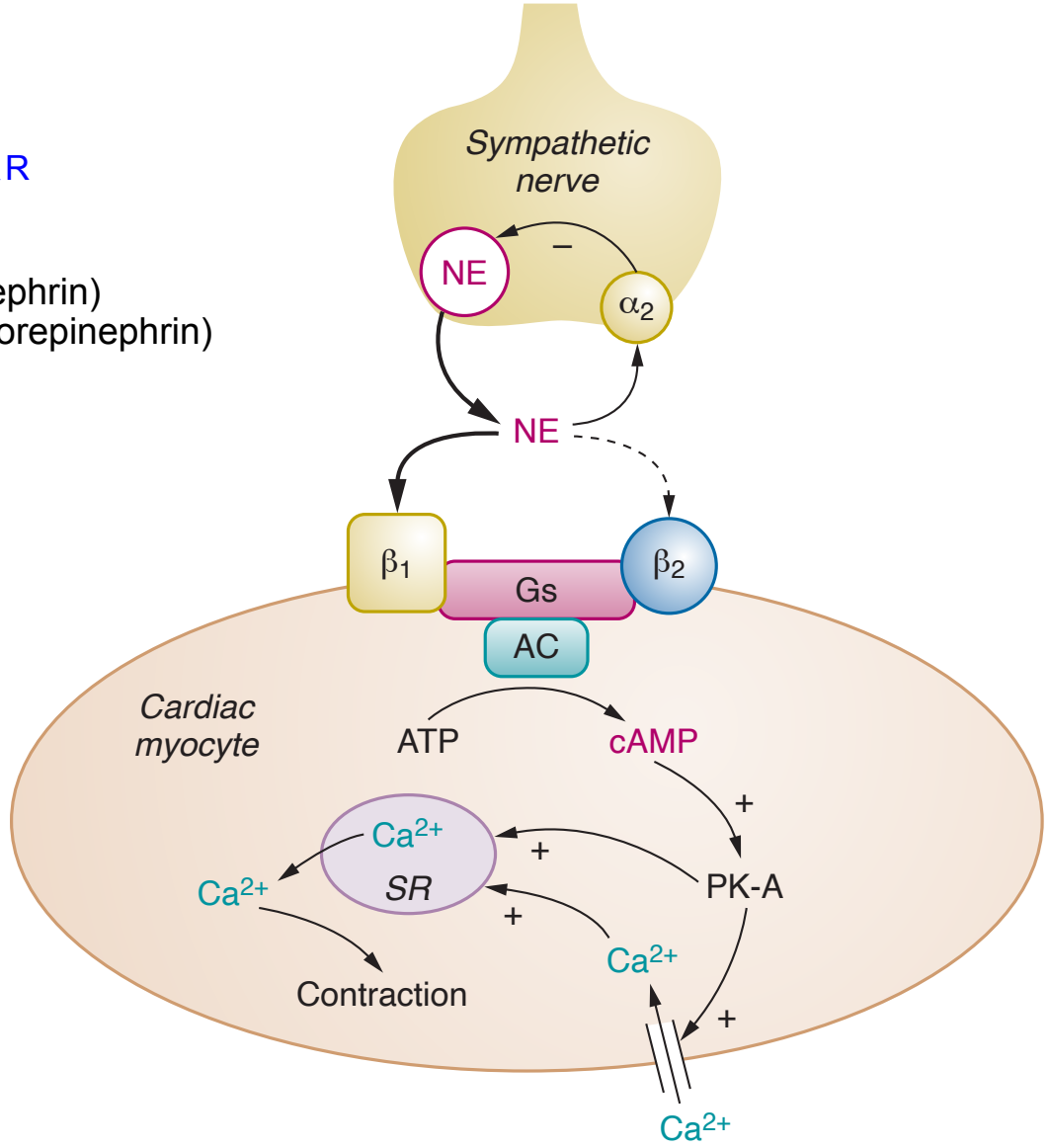
wenn keine andere Option:
Akut supraventrik. Arr.

β-Adrenozeptoren : $\beta_{1[2]}$

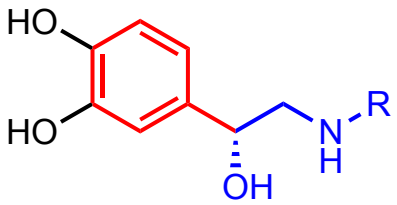


R = CH_3: Adrenalin (Epinephrin)
R = H: Noradrenalin (Norepinephrin)

Agonisten

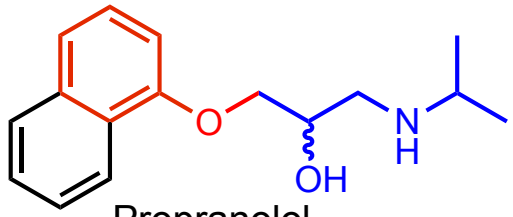


Klasse II: Betablocker



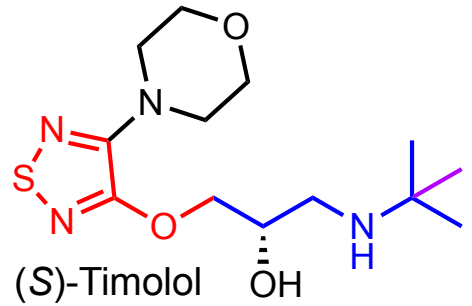
R = CH_3: Adrenalin (Epinephrin)
R = H: Noradrenalin (Norepinephrin)

Agonisten



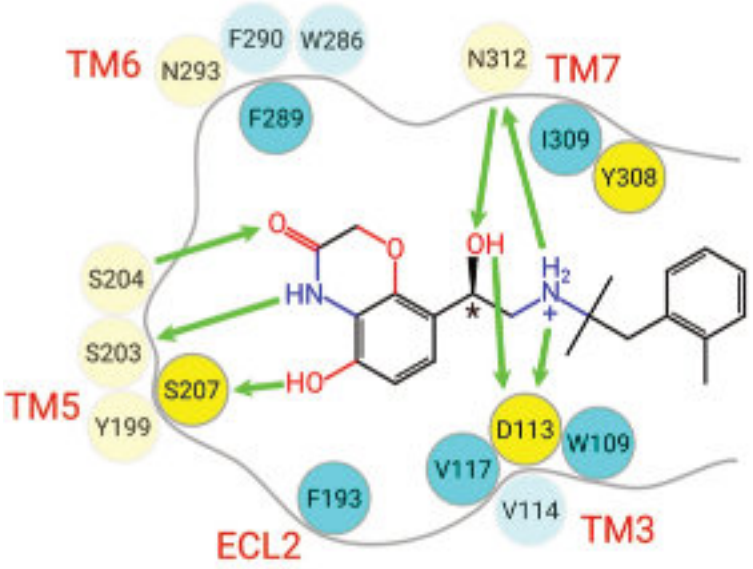
Propranolol

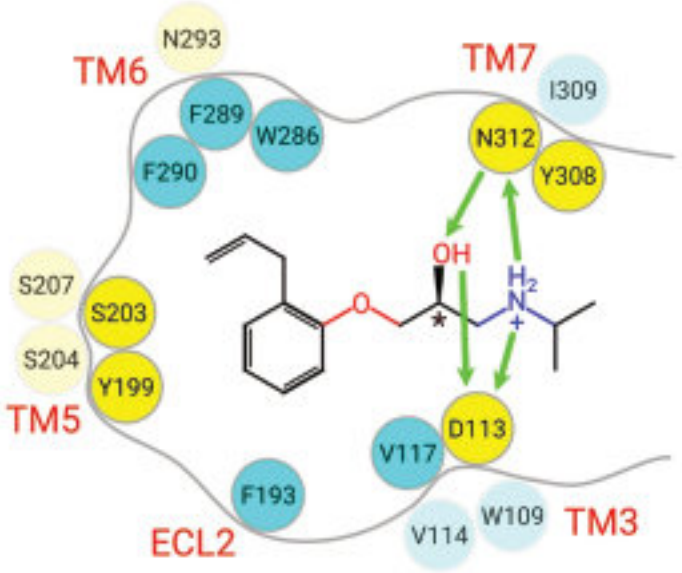
Antagonisten

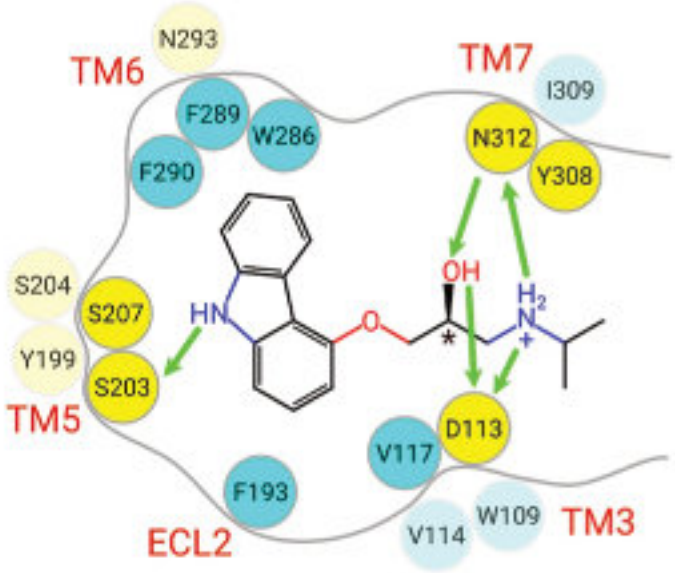


(*S*)-Timolol

inverse Agonisten

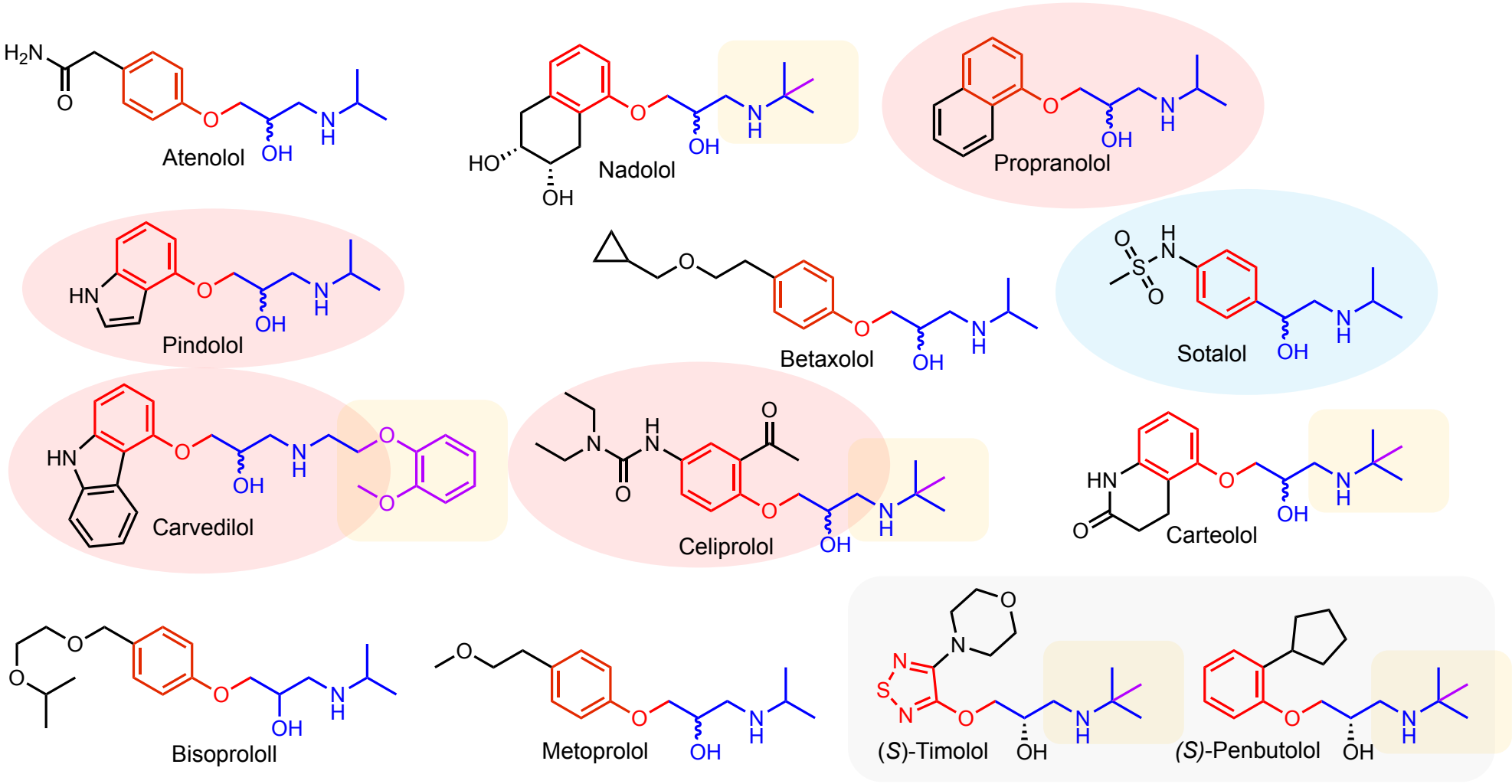






Experimentelle synthetische Derivate im β_2-AR Komplex: Chan et al, Sci Rep 2016, 10.1038/srep34736

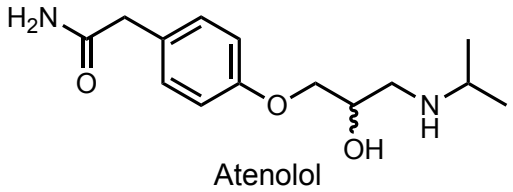
Klasse II: Betablocker



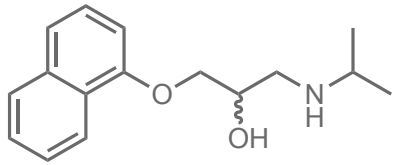
v.a. β_1-selektive: tachykarde Rhythmusstörung (! β_2 bei Asthma/COPD)

(+ chronische Herzinsuffizienz, koronare Herzkrankheit, arterielle Hypertonie)

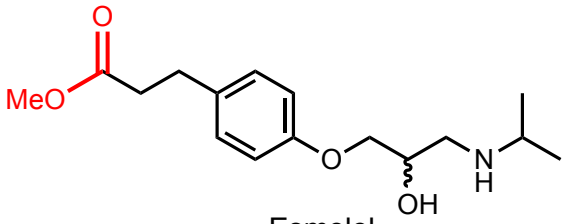
Klasse II: Betablocker



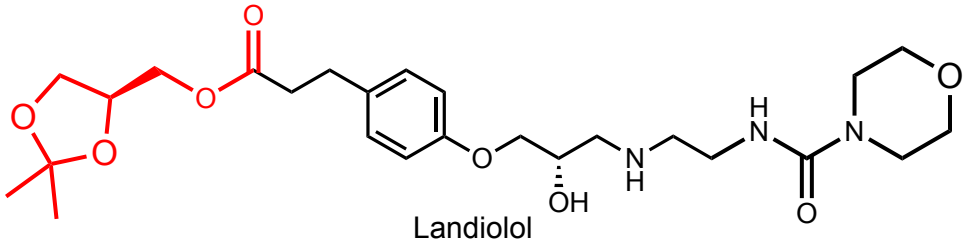
Atenolol



Propranolol



Esmolol

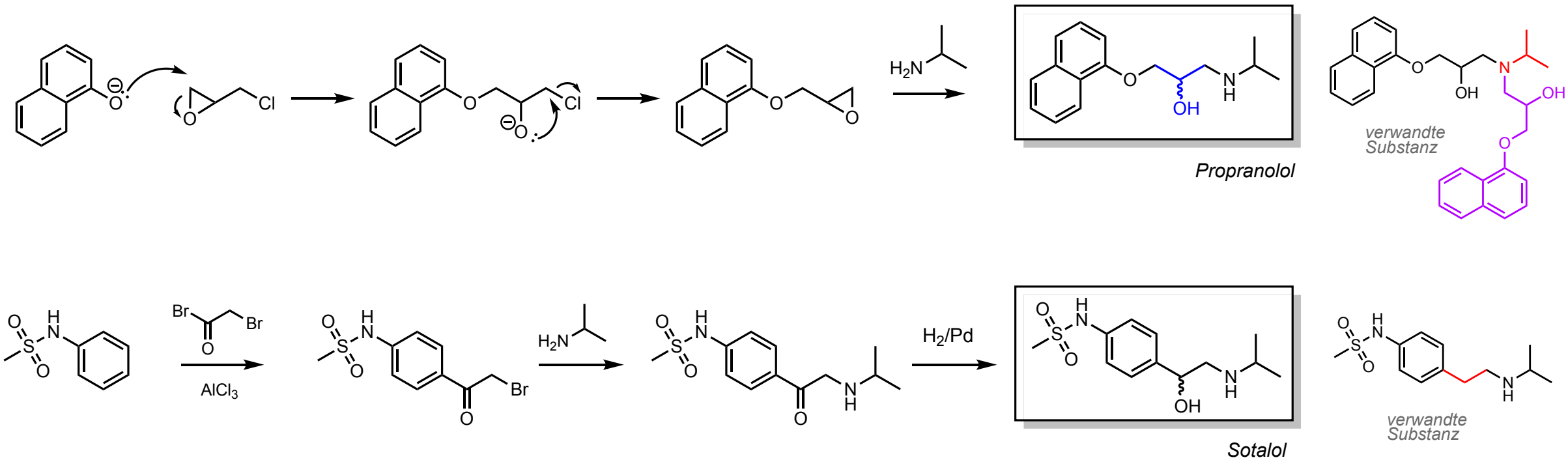


Landiolol

Softdrugs

ultrakurz wirksam: nicht als Dauertherapie, aber während OPs (supraventrikuläre Tachykardien)

Synthese



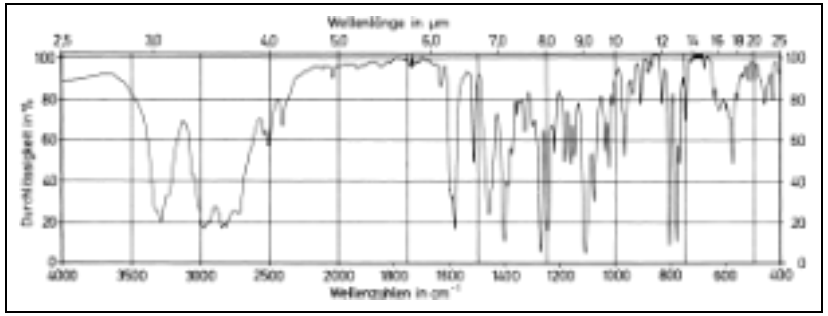
ggf: Raz.-Spaltung mit Weinsäure / Mandelsäure, oder asymm. Synthese

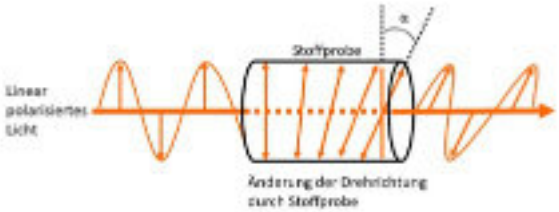
Arzneibuchanalytik

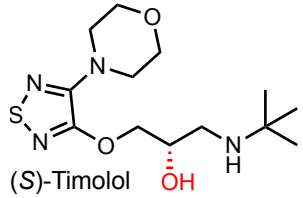
Identität

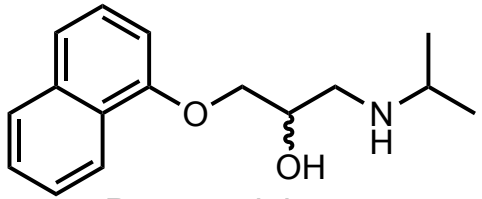
1°: **IR, gegenion, [α]**

2°: **DC, Smp, ion**







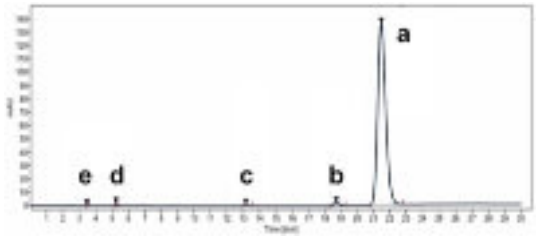


Propranolol (HCl)

Reinheit

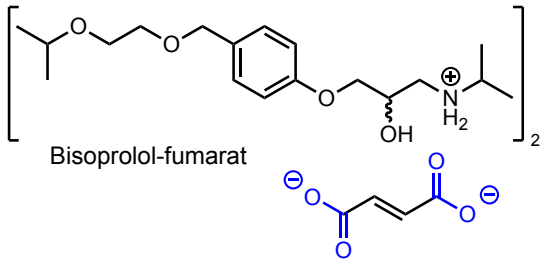
VS: **HPLC***

Prüflösung...



Gehalt

Titration



Bisoprolol-fumarat

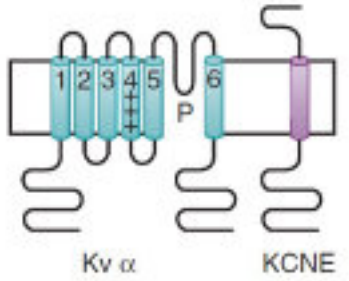
2 Äq $HClO_4$

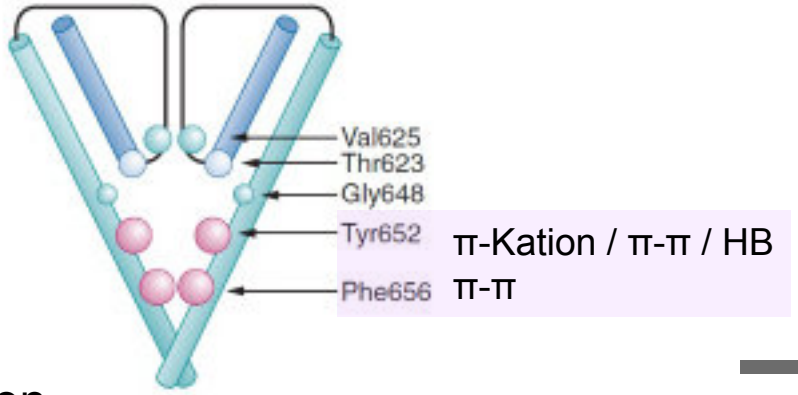
(AcOH)

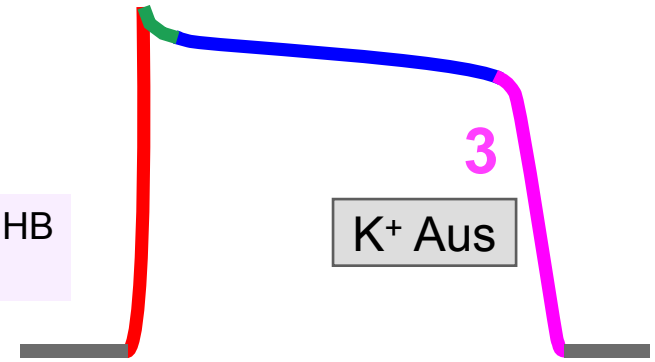
Spannungsabhängige Kaliumkanäle : K_Vn

allgemein

K_V11.1 / hERG







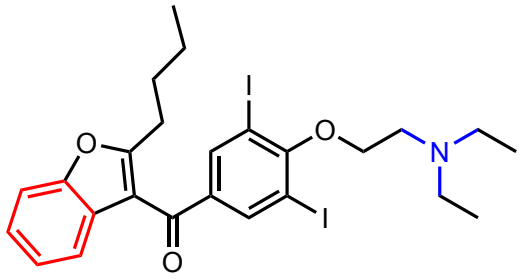
Bindestellen

- ***Pore (Ionenkanalblocker)***
- *Außenseite (Skorpion-peptid)*
- *Spannungssensor (Vogelspinnen-peptid)*

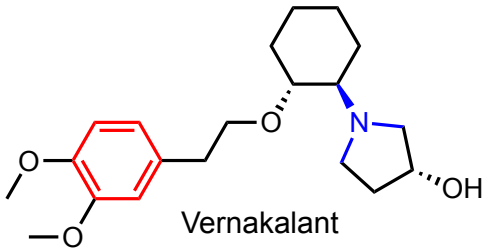
K+ channel; MacKinnon *et al,* Science 1998, 10.1126/science.280.5360.69

III: Kaliumkanalblocker

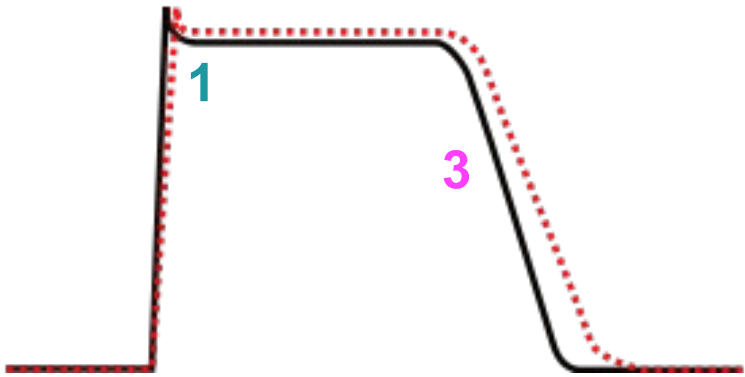
I_{Kr} Strom, K⁺, *rapid delayed rectifier [gleichrichter]*
→ **K_V11.1 : hERG** *(human ether-a-go-go related gene)*
→ **QT**



Amiodarone
(auch Klasse I, IV)



Vernakalant

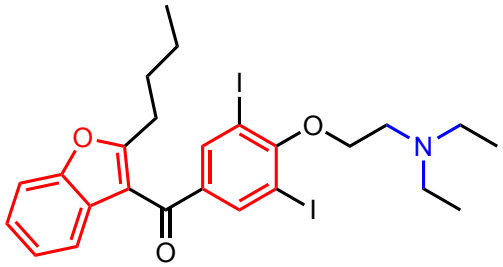


langsame Repolarisation (K^+ Aus)
→ **QT verlängert**

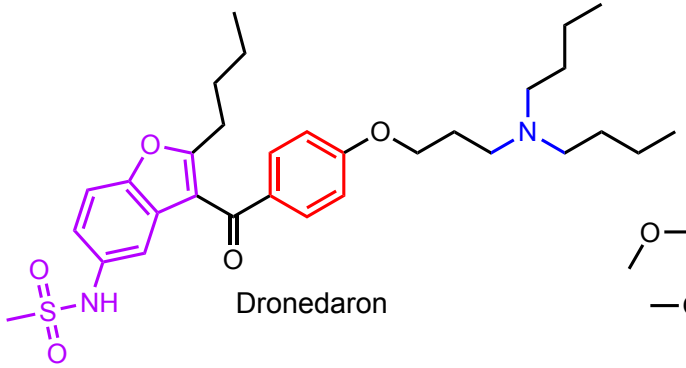
I_{to1} Strom, *transient outward K^+ current*
→ K_V4.2/K_V4.3; **Phase 1**

I_{Kur} Strom, K⁺, *ultra-rapid rectifier*
→ K_V1.5; **Phase 3**

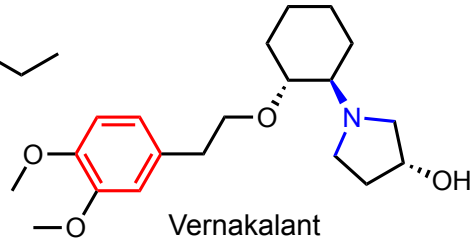
III: Kaliumkanalblocker



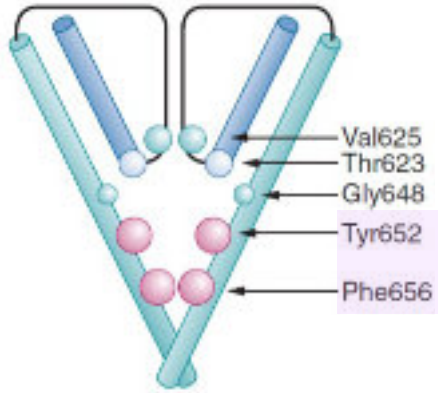
Amiodaron
(auch Klasse I, II, IV)



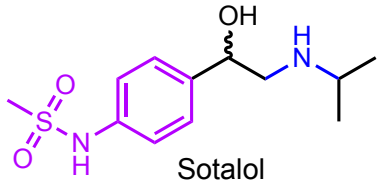
Dronedaron



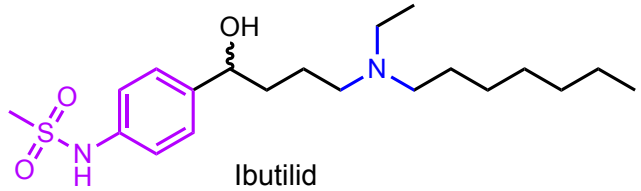
Vernakalant



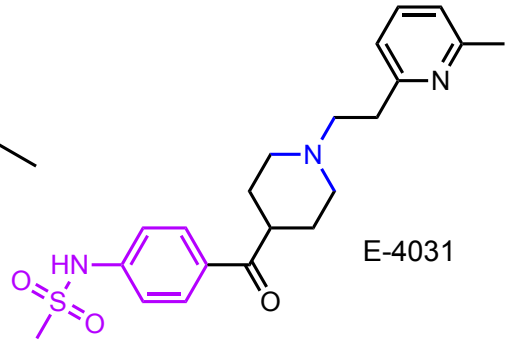
π-Kation / π-π / HB
π-π



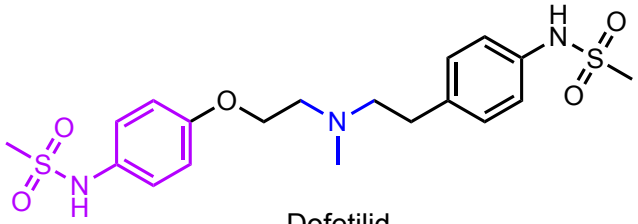
Sotalol
(auch Klasse II)



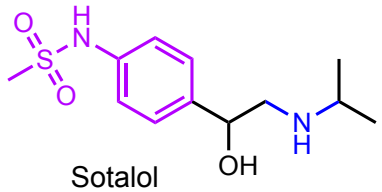
Ibutilid



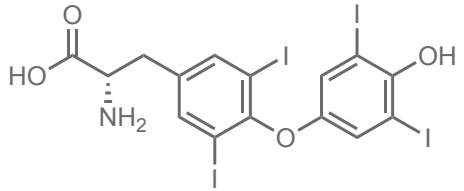
E-4031



Dofetilid



Sotalol

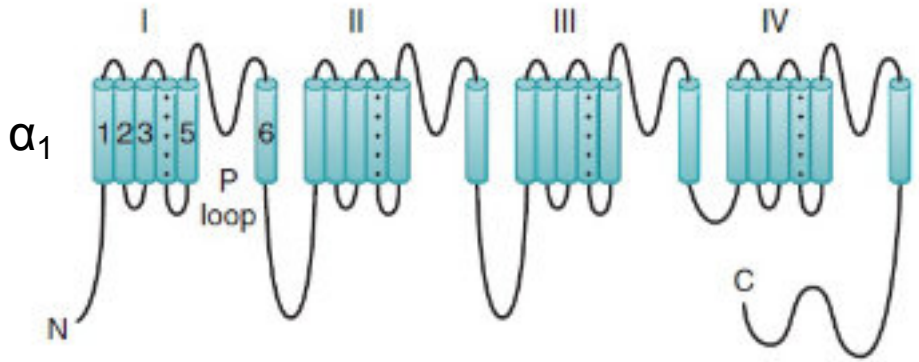


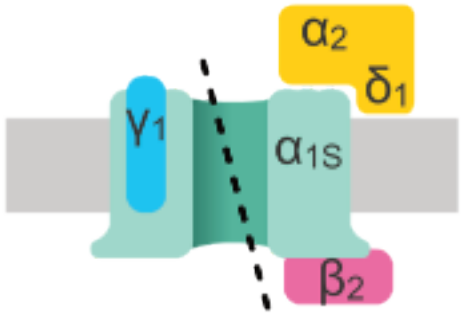
Thyroxine

Amiodaron: akute supraven. [Vorhofflimmern] & ven. Tachykardie
Vernakalant: Renormalisierung des Sinusrhythmus nach Vorhofflimmern

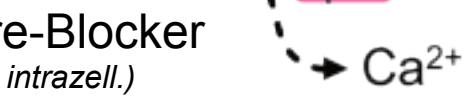
L-Typ spannungsabhängige Calciumkanal : $Ca_V1.n$

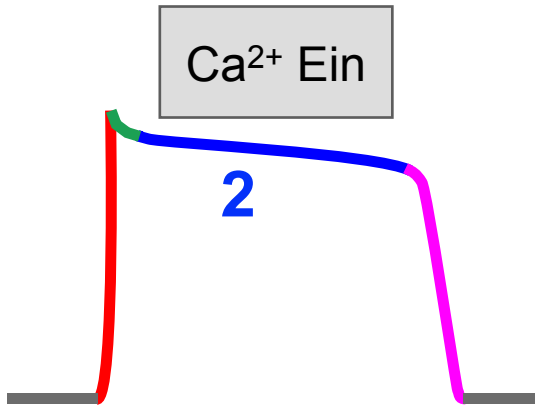
für Arrhythmien: Hemmung des kardialen Kanals





→ Pore-Blocker
(von intrazell.)

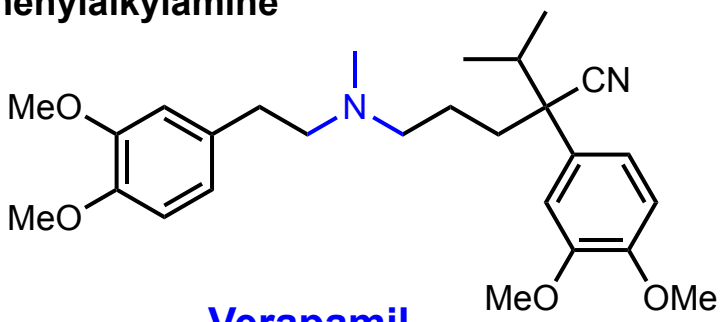




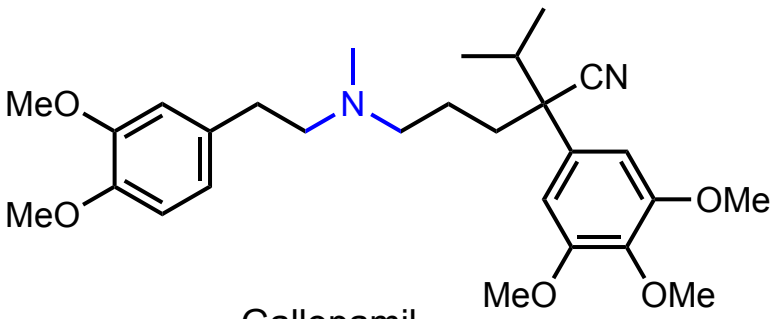
Bildquelle: Aktories et al., Pharm/Tox, Abb. 18.14

IV: L-Typ Calciumkanalblocker

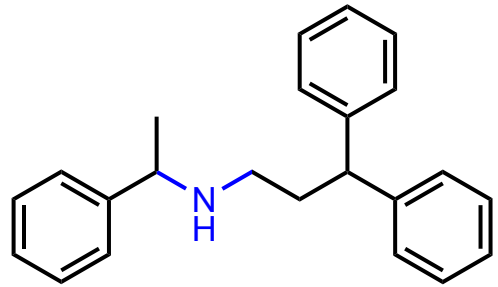
Phenylalkylamine



Verapamil

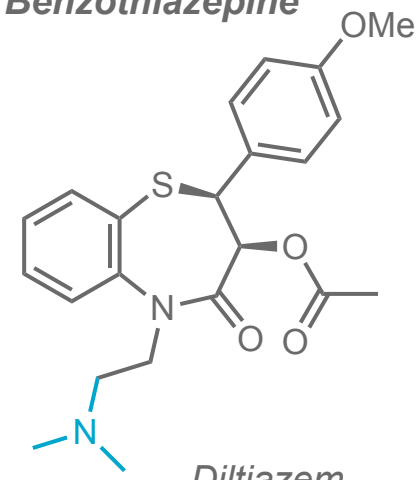


Gallopamil



Fendiline

Benzothiazepine



Diltiazem

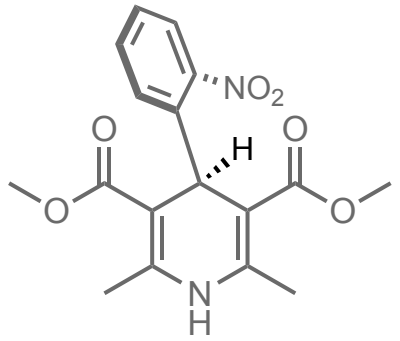
Kanalblocker (protoniert)

negativ: inotrop, chronotrop, dromotrop

gegen supraventrikulärer Tachykardie

(auch arterielle Hypertonie, koronare Herzkrankheit & Angina)

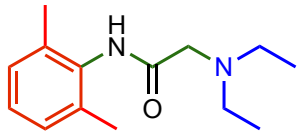
Dihydropyridine



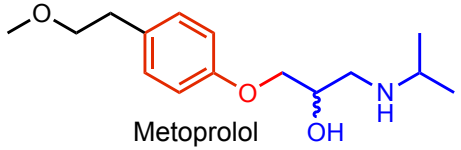
Nifedipin

Antiarrhythmika

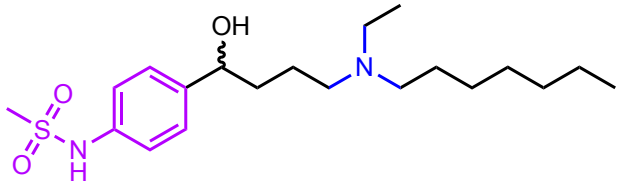
- I: Na^+ II: β-AR III: K^+ IV: Ca^{2+}



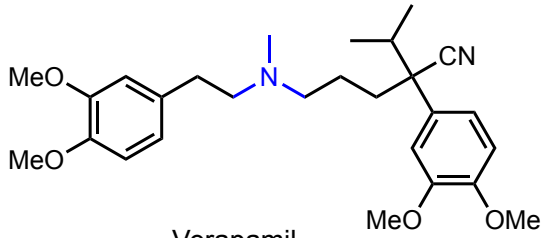
Lidocain



Metoprolol



Ibutilid



Verapamil

- Wirkungsmechanismus; SAR; Entwicklung
- ADME-PK; Merkmale; Einsatz & Gefahren

Andere Herztherapeutika

Adenosin [A_1], Digoxin/Digitoxin [Na^+/K^+]...
HCN-Kanalblocker (ivabradine)
ACE-inhibitoren (captopril, benazepril)
Angiotensin Rezeptor Blocker: losartan, valsartan...