Farmacevtska kemija 3

Kalcijevi kanalčki, zaviralci kalcijevih kanalčkov (kalcijevi antagonisti)

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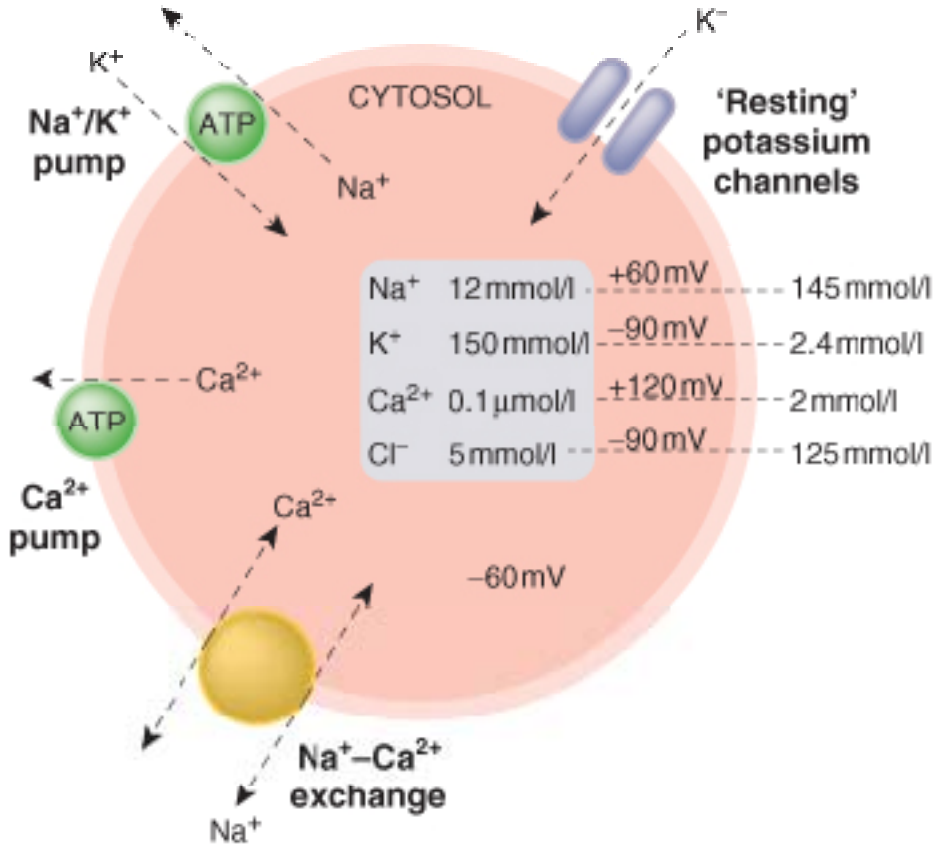
21. maj 2013

Ca^{2+} - kalcijevi ioni

- Izjemno nizka koncentracija v "nedejavni" celici (~10^{-7} mmol/L)
- Izjemno pomembni izven/znotrajcelični prenašalci
- Shranjeni v celičnih organelih (endoplazemski, sarkoplazemski retikulum), v intersticijski tekočini (~2,4 mmol/L)

EKSCITATORNI IONI!



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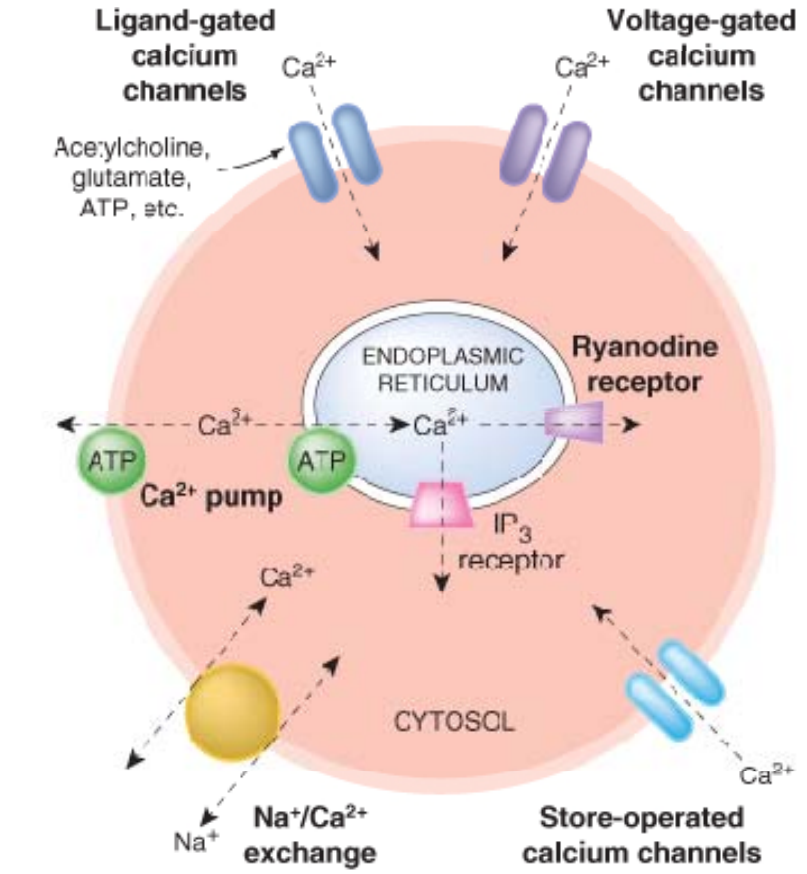
Ca^{2+} - kalcijevi ioni

Vnos Ca^{2+}:

- Napetostno odvisni Ca^{2+} kanali (L, N, T, Q/P, R)
- Od liganda odvisni Ca^{2+} kanali (AcCh, glutamat-NMDA)
- "Od zalog odvisni" Ca^{2+} kanali
- Na^{+}-Ca^{2+} izmenjava



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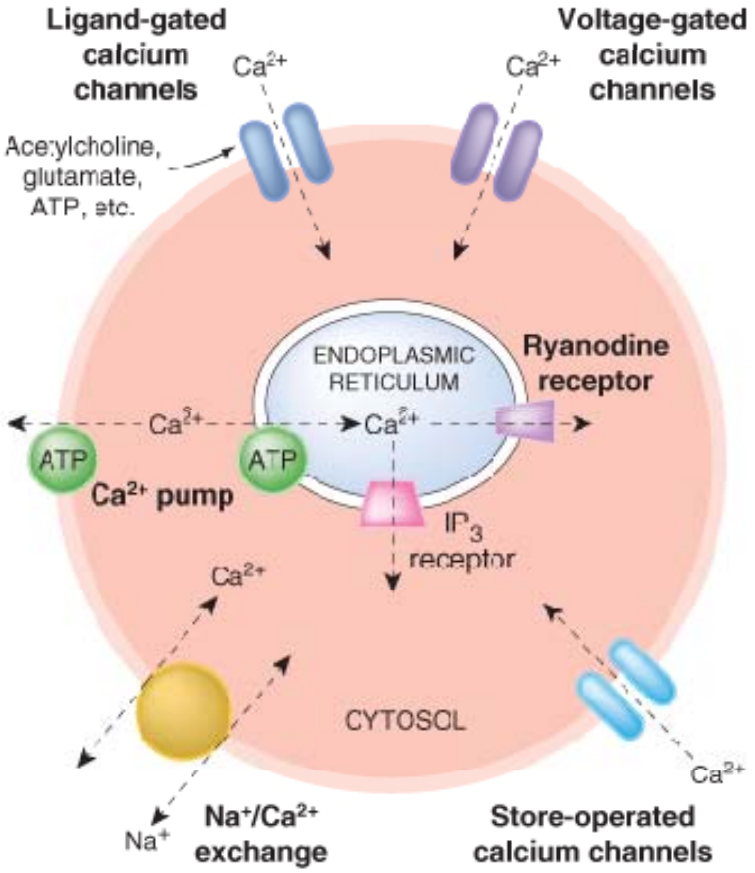
Ca^{2+} - kalcijevi ioni

Sproščanje Ca^{2+} iz ER/SR:

- Inozitol-trifosfatni (IP_3) "receptor" – aktivira ga IP_3, tvorba z GPCR
- Rianodinski receptor – sprožitev z visokimi konc. intracel. Ca^{2+} (+ povratna zanka)

Izločanje Ca^{2+} iz celice:

- Ca^{2+}-odvisna ATP-aza
- Na^+-Ca^{2+} izmenjava



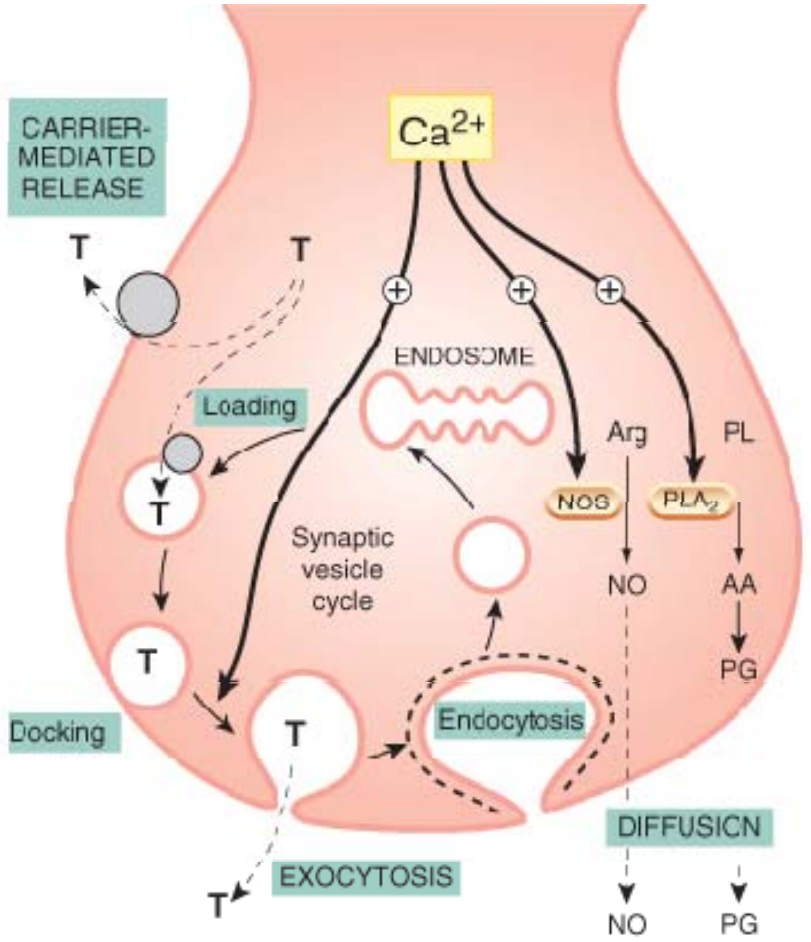
Ca^{2+} - modulacija prenosa

Epilepsija

- etosuksimid inhibira T-tip Ca^{2+} kanalov v CŽS

Eksocitoza transmitorjev

- N-tip Ca^{2+} kanalov v živčnih končičih, inhibicija: ω-konotoksin



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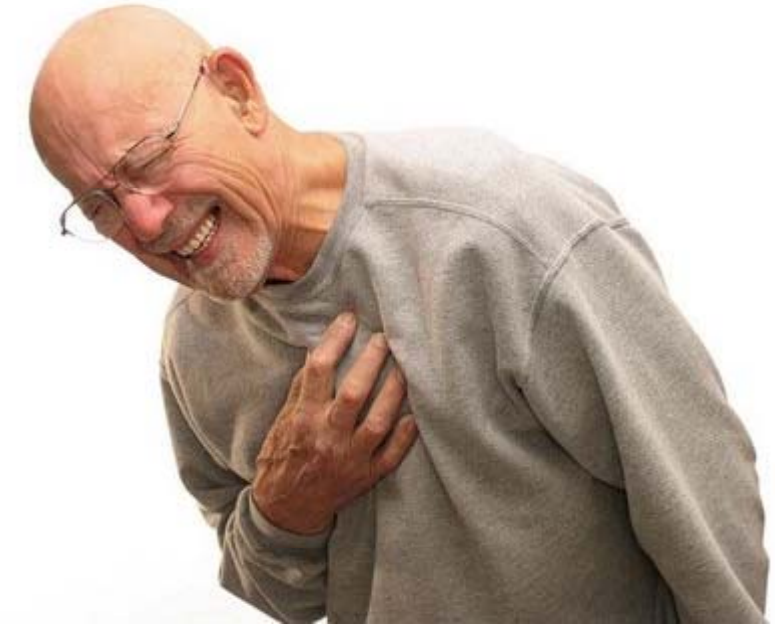
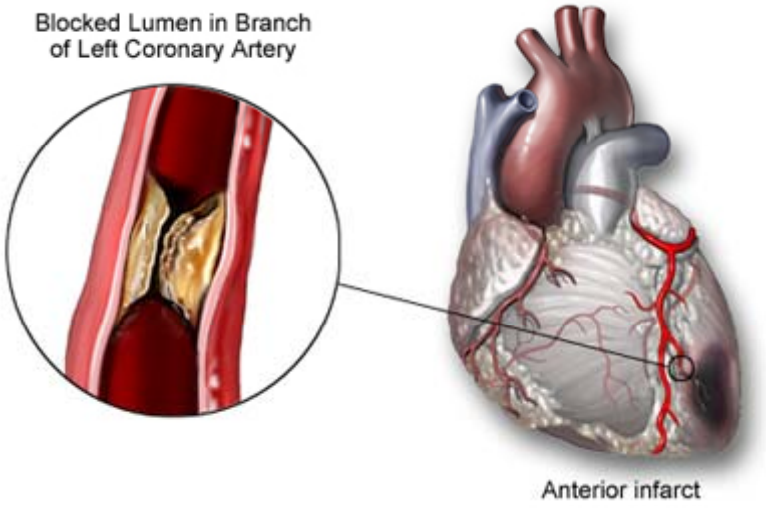
Ca^{2+} - kalcijevi ioni - funkcija

Funkcija – EKSCITACIJA!

- prevajanje impulza – vzdrževanje/proženje/ojačanje depolarizacije
- kontrakcija gladke, srčne in prečnoprogaste muskulature
- eksocitoza (npr. iz živčnih končičev) nevrotransmitorjev in hormonov
- kontrola encimov preko kalmodulina (najmanj 40 različnih encimov, npr. MLCK)
- strjevanje krvi (izvencelično)
- pri gibljivosti/adheziji celic

Angina pektoris?



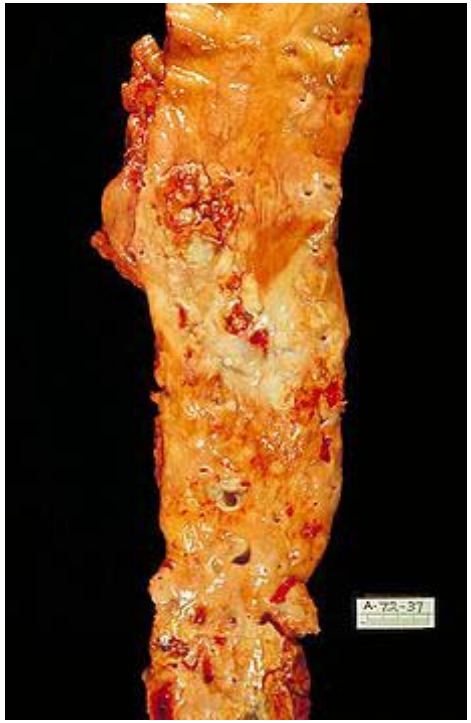


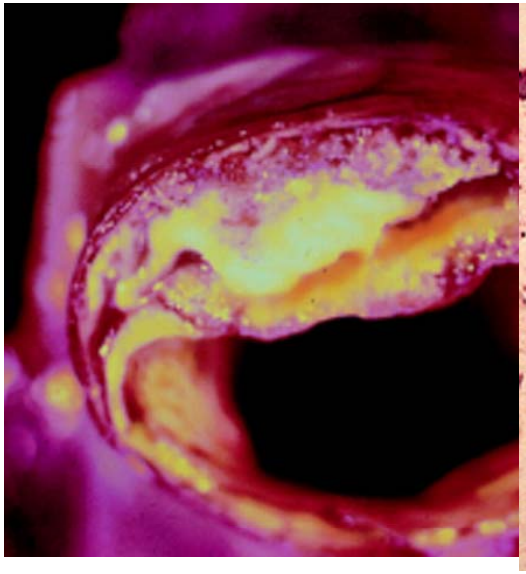
Angina pektoris?

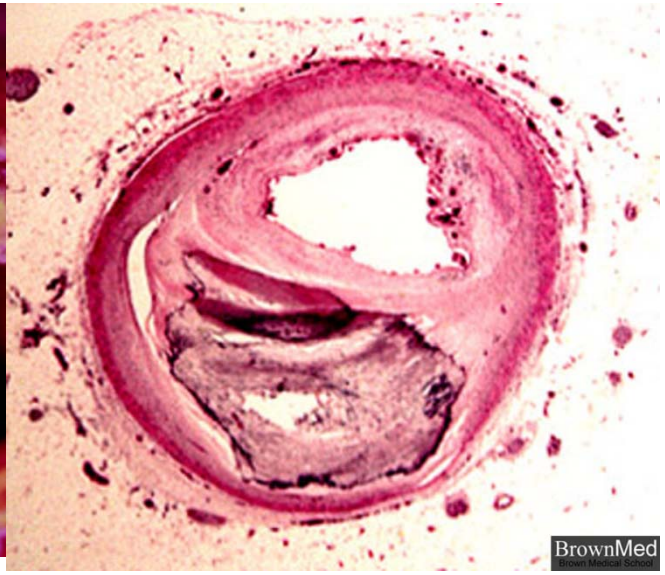
napad hude bolečine v prsnem košu za prsnico, ki pogosto izžareva v levi zgornji ud ali vrat ter je često povezana z občutkom dušenja in smrtnega strahu, pojavi se ob naporu ali razburjenju; sin. angina pectoris, koronarna bolečina, sindrom angine pektoris, stenocardia, stenokardična bolečina, stenokardija; prim. ishemična bolečina, stenokardični napad

Angina pektoris?

- Bolezen?
- Bolezen: koronarna srčna bolezen
- Vzroki za koronarno srčno bolezen?







Angina pektoris?

- Angina pektoris vs. Srčni infarkt?
- Nestabilna angina?

Terapija koronarne srčne bolezni/angine p.

Vazodilatorji

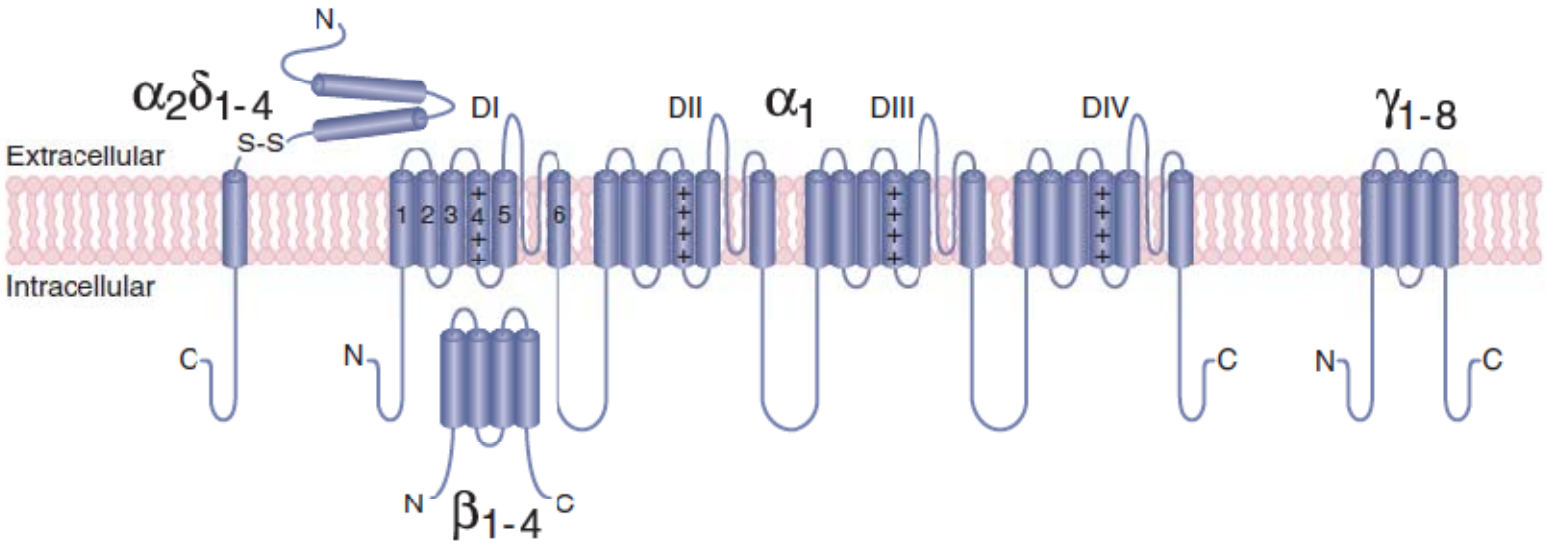
- Glicerol trinitrat = nitroglicerin
- Alkil nitriti

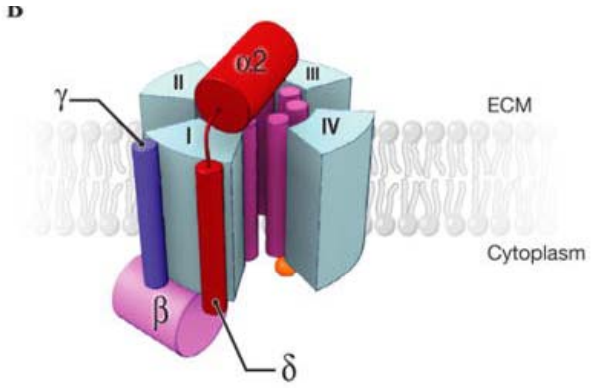
Terapija koronarne srčne bolezni/angine p.

Zmanjšanje srčne obremenitve

- Antagonisti adrenergičnih β1-receptorjev
- Antagonisti Ca^{2+} kanalčkov
- Zaviralci ACE

Napetostno odvisni Ca^{2+} kanali

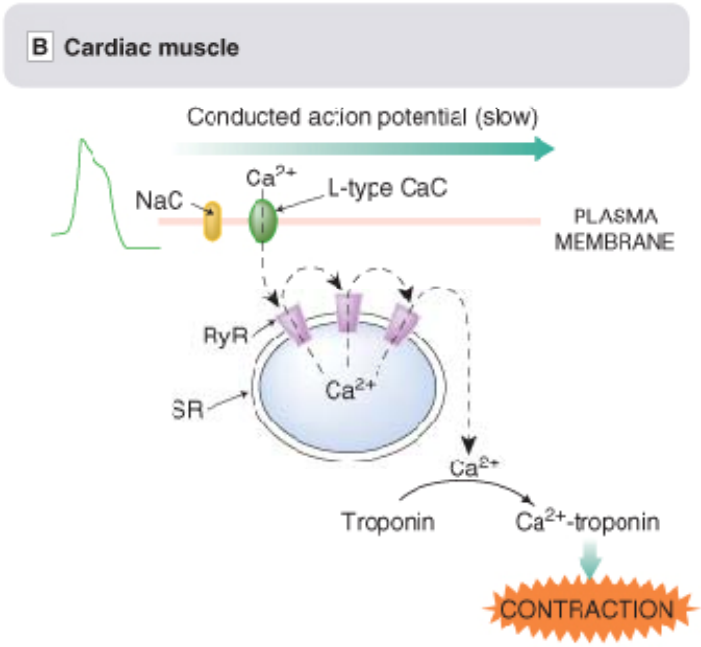


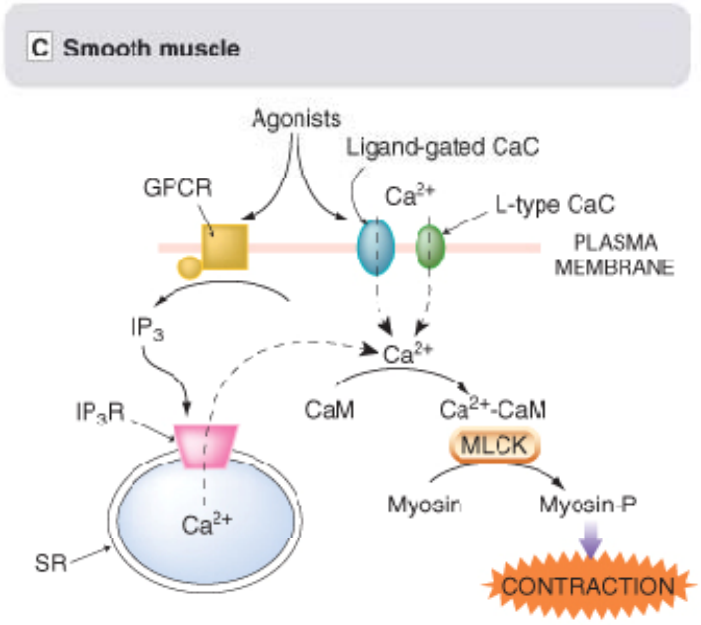


Ca^{2+} antagonisti

Ca^{2+} antagonisti – inhibicija kalcijevih kanalov

- L- tip Ca^{2+} kanalov: signal za kontrakcijo srčne in gladke mišice (žilni endotelij)
- Posledica: povišan krvni tlak, dis(a)ritmija srca, tahikardija
- Ca^{2+} antagonisti zavirajo napetostno, manj od liganda odvisne Ca^{2+} kanale (ATP receptorji ali P_{2x})
- Indikacije: aritmije, angina pektoris, hipertenzija





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Ca^{2+} antagonisti

= Zaviralci kalcijevih kanalčkov

- delujejo samo na L tip kalcijevih kanalov
- Zmanjšanje konstrikcije arterij – zniža se pritisk, zmanjša se srčno breme
- Povečan pretok krvi skozi koronarke

Ca^{2+} antagonisti - tipi

- 1,4-Dihidropiridini – nifedipin in analogi
- Fenilalkilamini – verapamil
- Benzotiazepini – diltiazem
- Diaminopropanolni etri – bepridil

Ca^{2+} antagonisti - selektivnost

Ca^{2+} antagonisti - selektivnost

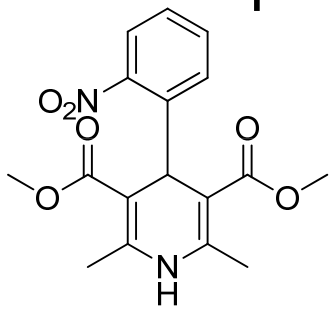
Table 28.10. Comparison of the Cardiovascular Effects of Verapamil, Diltiazem, and Nifedipine

Cardiovascular Effect	Verapamil	Diltiazem	Nifedipine (a 1,4-DHP)
Peripheral vasodilation	○○	○	○○○
Blood pressure	•	•	•
Heart rate	Variable	•	○○
Coronary vascular resistance	•	•	•
Coronary blood flow	○○	○○	○○○
Atrioventricular node conduction	••	•	NE
Contractility	•	NE/•	NE/○

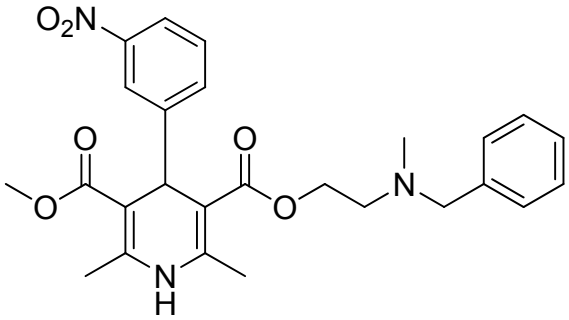
The number of circles represents the magnitude of response: ○, = increase; •, decrease; NE = no effect.
Adapted from Swamy VC, Triggle DJ. Calcium channel blockers. In: Craig CR, Stitzel RE, eds. Modern Pharmacology with Clinical Applications, 5th Ed. Boston: Little, Brown, 1997:229–234 and Triggle DJ. Drugs acting on ion channels and membranes. In: Hansch C, Sammes PG, Taylor JB, eds. Comprehensive Medicinal Chemistry, vol 3. Oxford, UK: Pergamon Press, 1990:1047–1099; with permission.

1,4-dihidropiridini

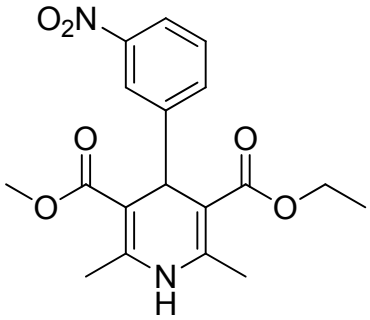
nifedipin



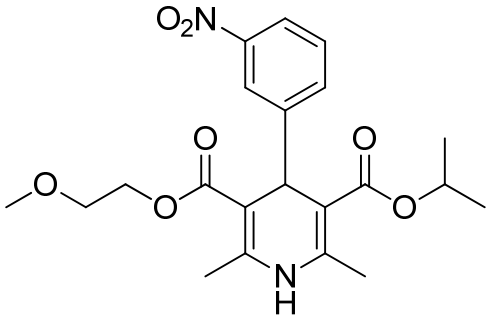
nikardipin



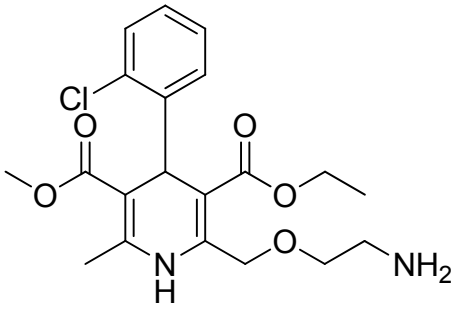
nitrendipin



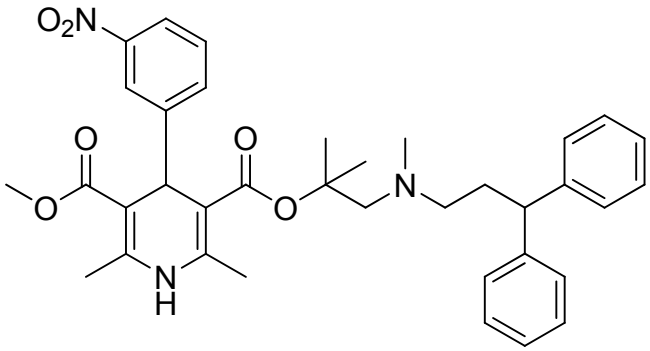
nimodipin



amlodipin

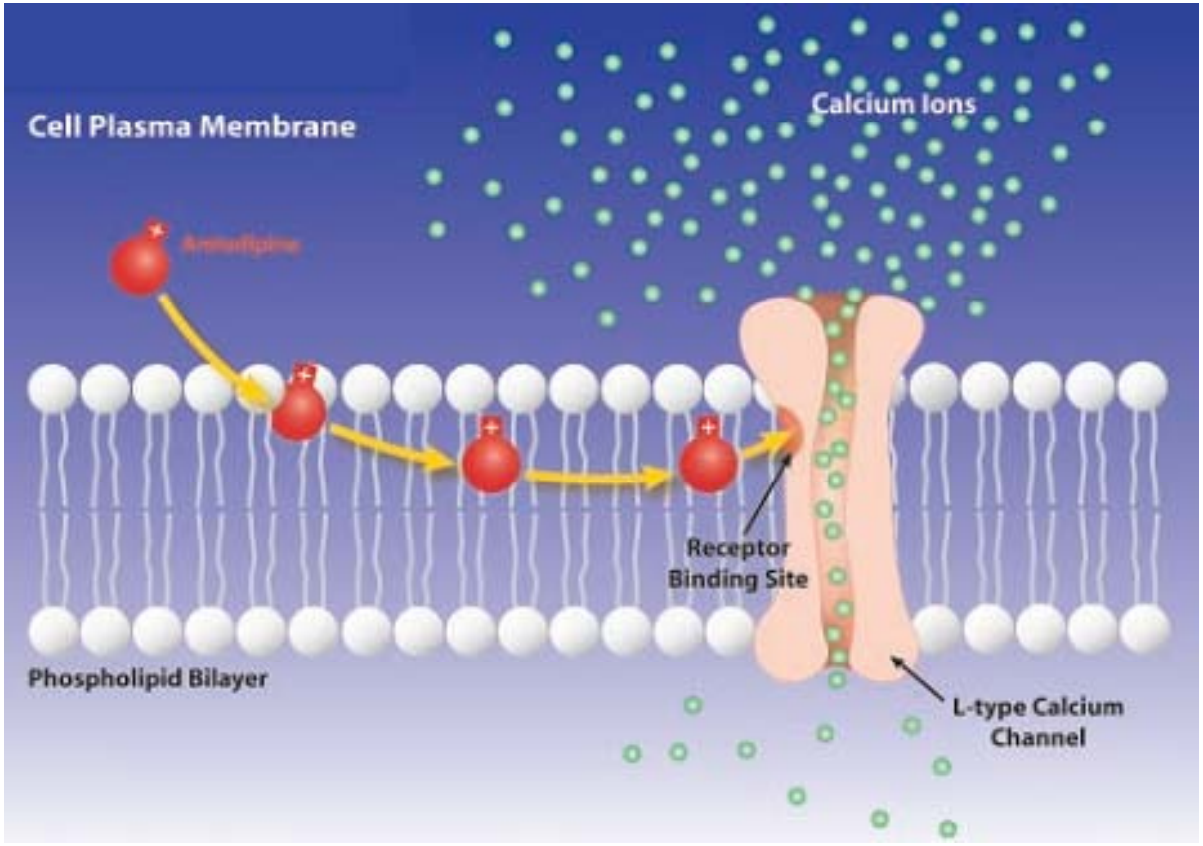


lerkanidipin

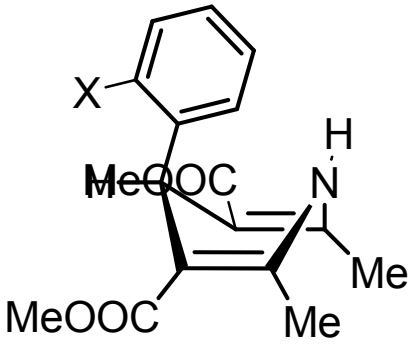


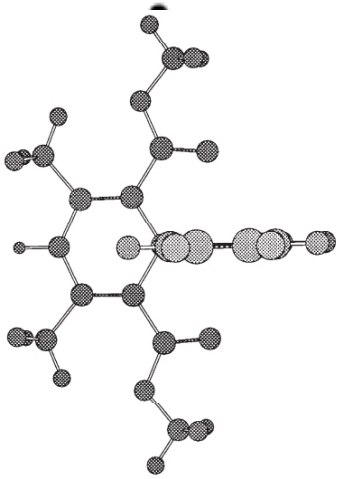
1,4-dihidropiridini

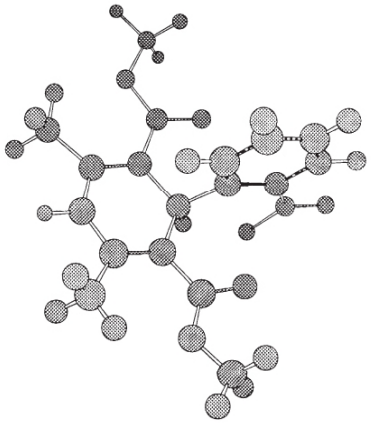
- Fiziološki ligandi za Ca^{2+} kanalčke?
- Lipofilne spojine



1,4-dihidropiridini

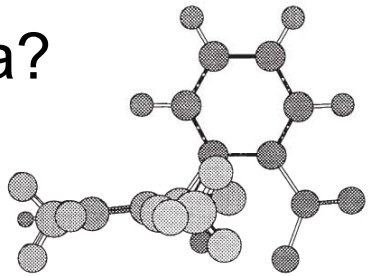






Sinperiplanarna

Antiperiplanarna lega?



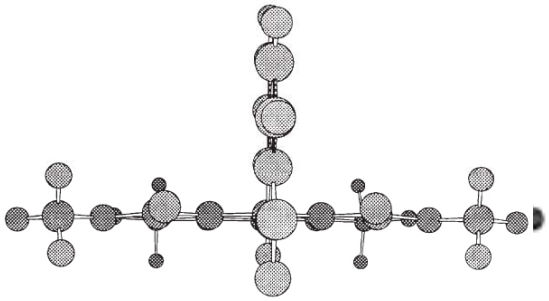


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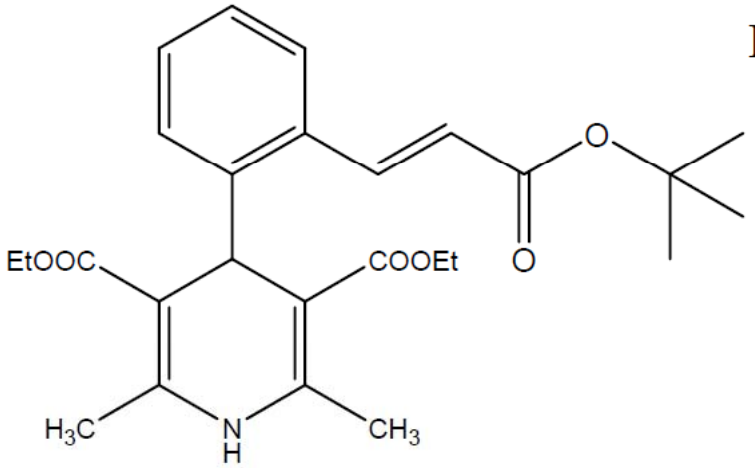
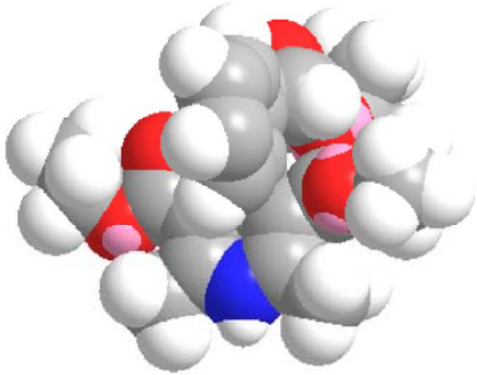
Fig. 28.23. Molecular models of nifedipine. The ortho-nitro group of nifedipine provides steric bulk and ensures that the required perpendicular nature of the phenyl and dihyropyridine rings is maintained.

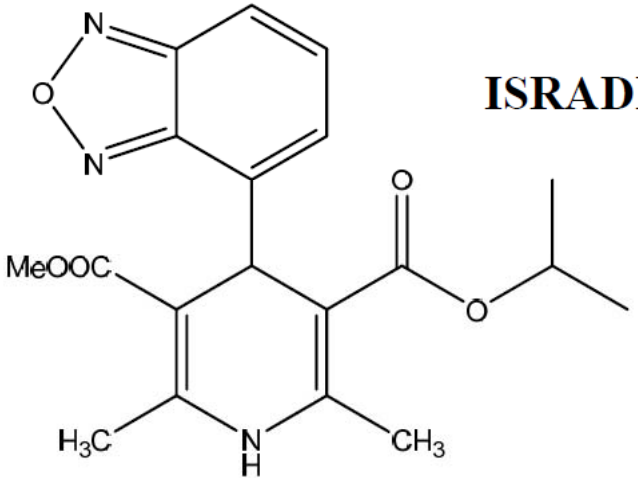
1,4-dihidropiridini

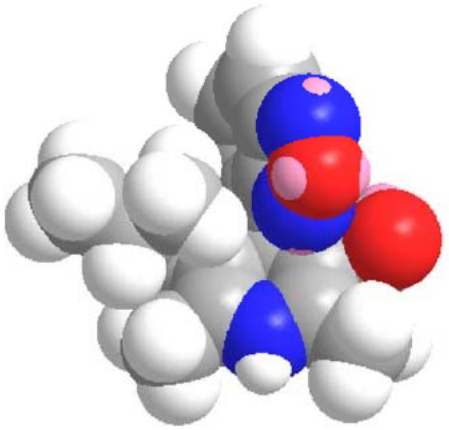
LACIDIPIN



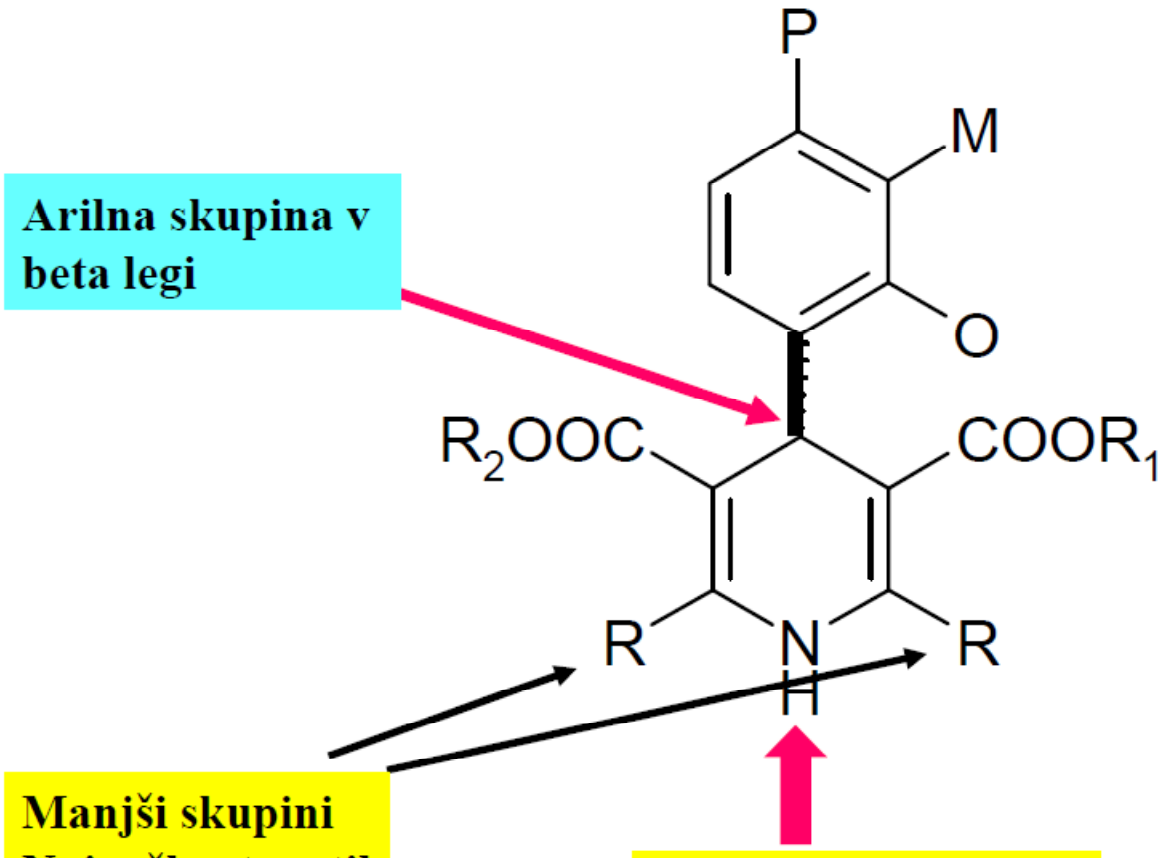


ISRADIPIN





SAR pri 1,4-dihidropiridinskih antagonistih



Arilna skupina v beta legi

O>M >P
Večje skupine

R_1 in R_2 enaki ali različni skupini

Manjši skupini
Največkrat metil

Sekundarni amin

1,4-dihidropiridini - SAR

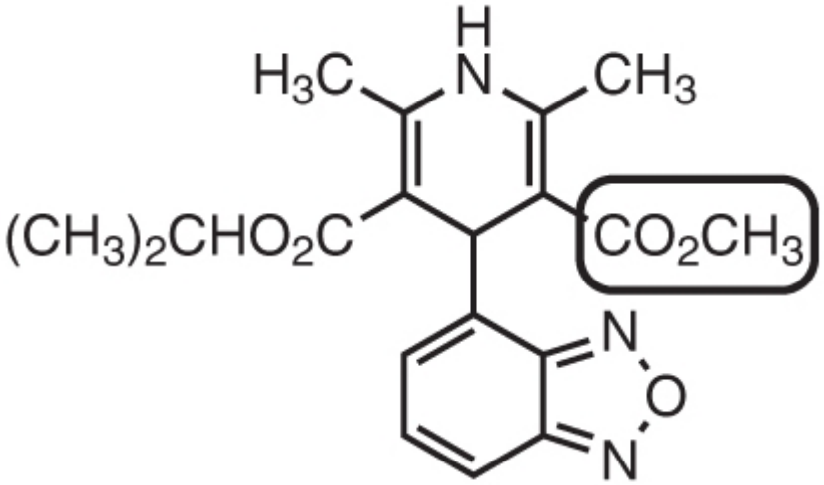
- 1,4-dihidropiridin, piridin NE!
- Neionizirani pri fiziol. pH, razen nikardipina in amlodipina
- Mesti 2,6 – kratki alkilni verigi – Me, redkeje Et
- Mesti 3,5 – optimalna estra:
    - Simetrična estra: ohranjeno šibko delovanje na srčno mišico (+ inotropi)
    - Nesimetrična estra: ni inotropnega učinka

1,4-dihidropiridini - SAR

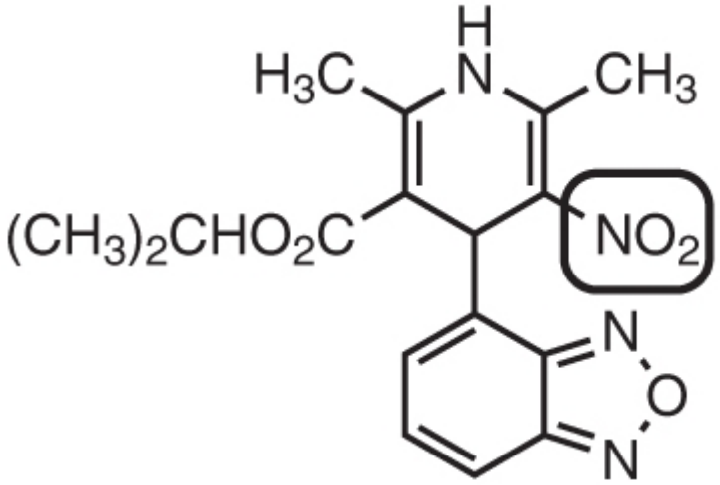
- Mesto 4 – Ph substituent, *o* ali *m*-substituiran: -NO_2, -Cl
- asimetričnost: v primeru nesimetričnih estrov stereogeni center, učinkovit R enantiomer

1,4-dihidropiridini

- Zamenjava estrske skupine z NO_2 ali laktonom → AGONISTI



Isradipine
(Calcium channel blocker)



PN 202.791
(Calcium channel activator)

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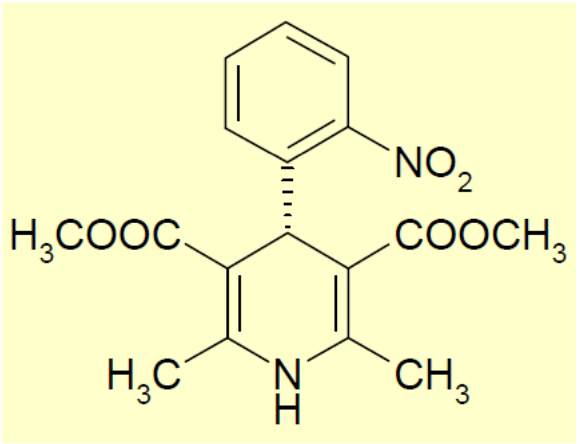
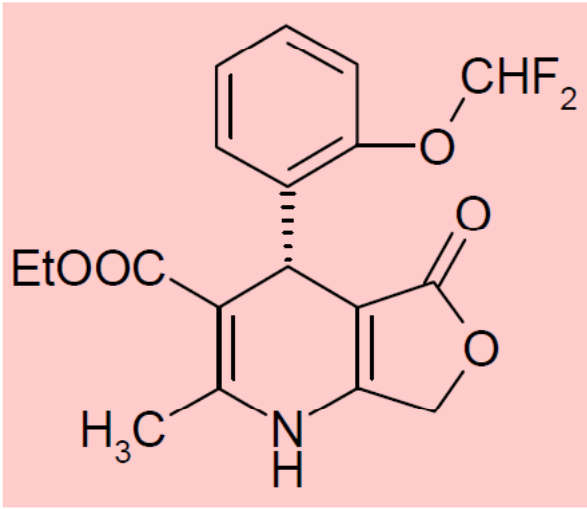


NIFEDIPIN
Inhibira prehod Ca^{2+}

CGP 28-392
Stimulira prehod Ca^{2+}



Alosterično povezana vezavna mesta za kalcijeve antagoniste

/vezava na različna mesta na α podenoti L kanala/

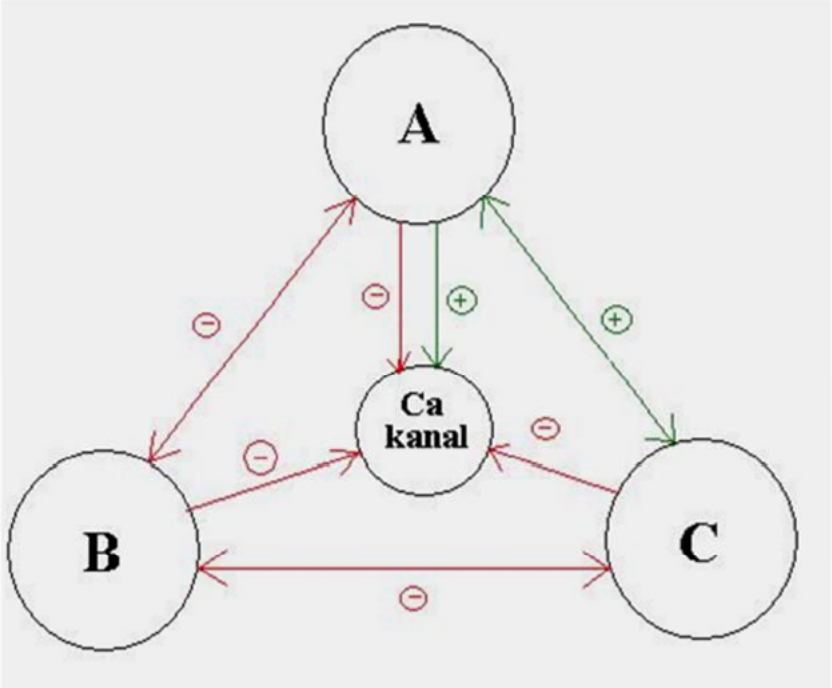
A: 1,4-dihidropiridini

B: fenilalkilamini

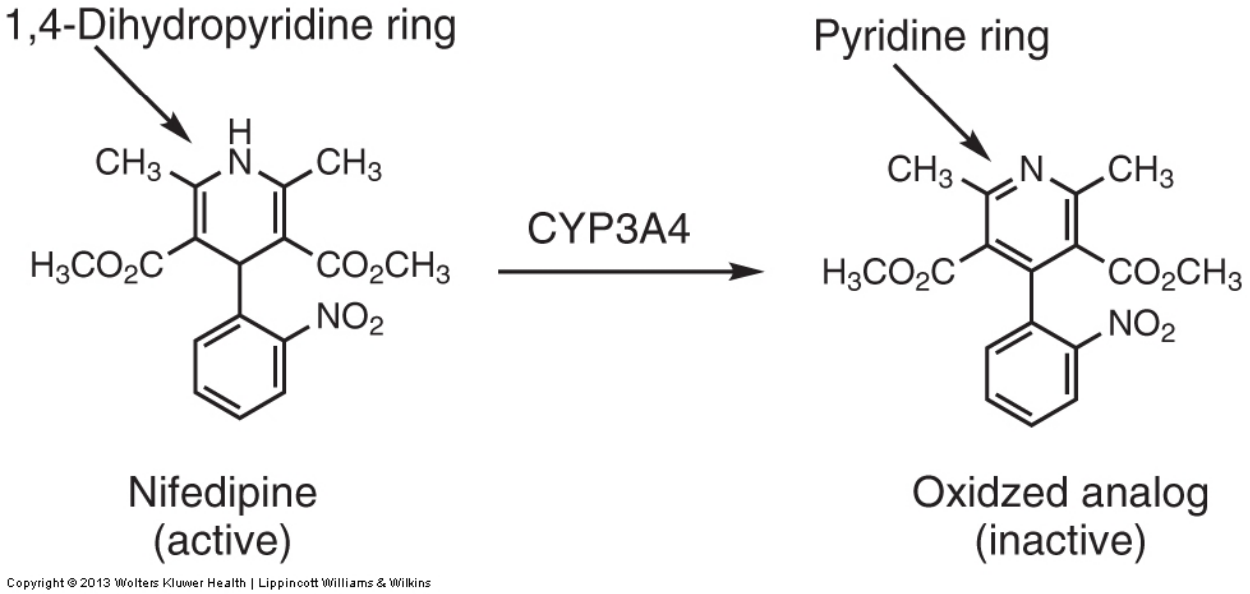
C: benziotiazepini

⊖ Alosterično izključevanje

⊕ Alosterično dopolnjevnje



Metabolizem 1,4-dihidropiridinov



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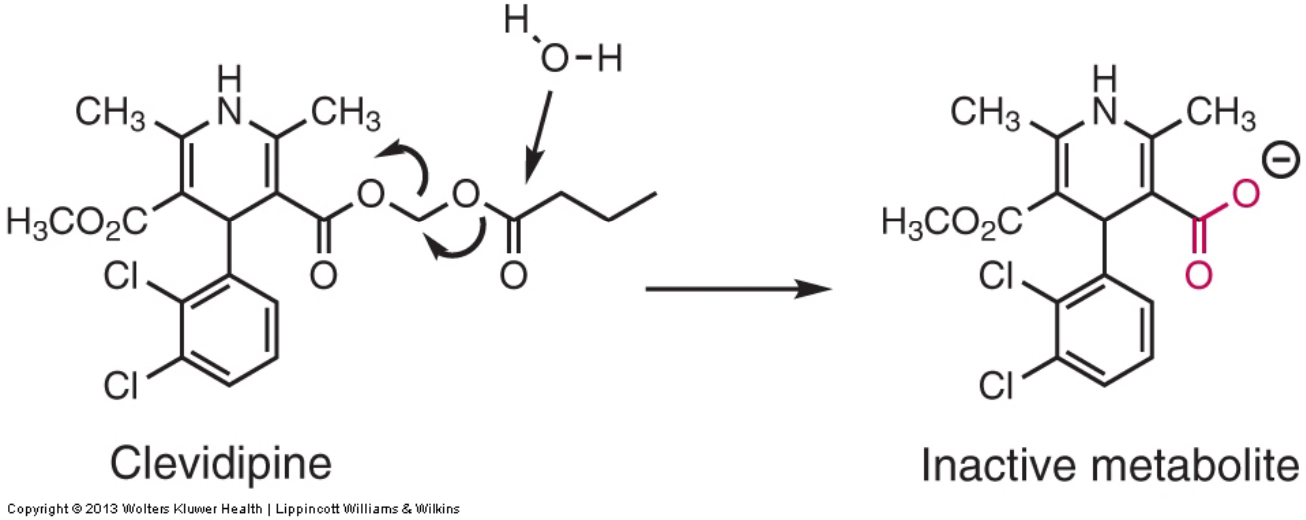

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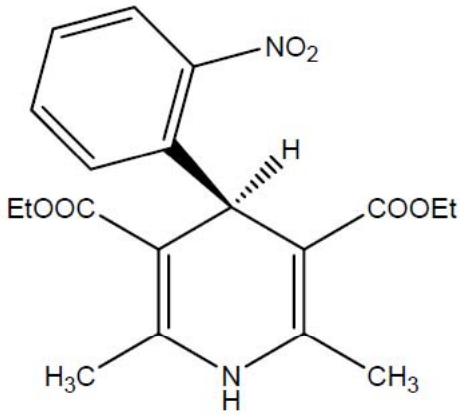
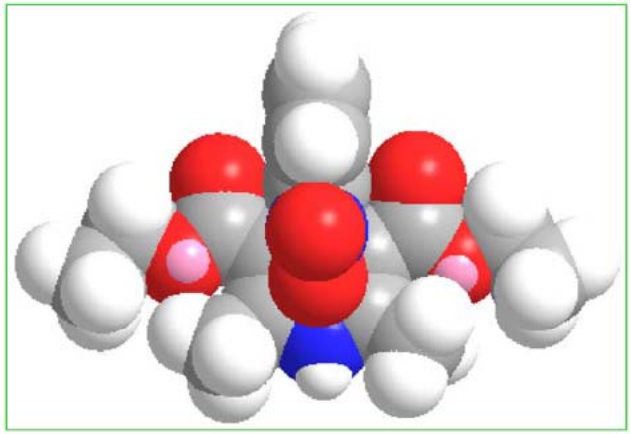
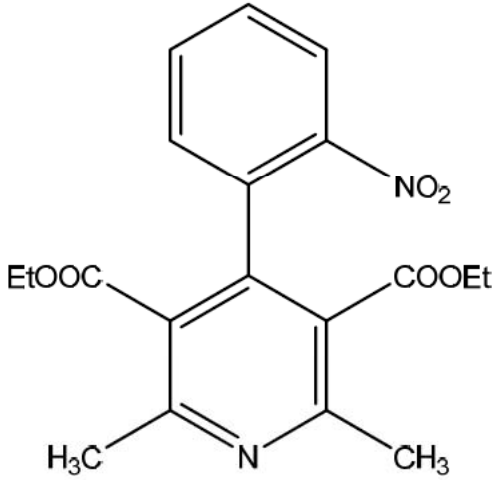
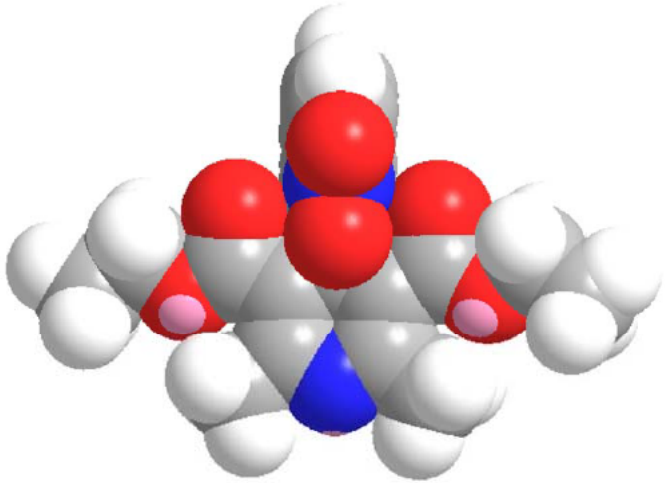

NO2
H
EtOOC
COOEt
H3C
N
H
CH3




NO2
EtOOC
COOEt
H3C
N
CH3



Primerjava FK lastnosti

- FK parametri

TABLE 23.11 Pharmacokinetic Parameters of Calcium Channel Blockers

Drug	Calculated LogP	Oral Bioavailability (%)	Effect of Food on Absorption	Active Metabolite	Protein Binding (%)	T_{max} (hours)	Elimination Half-Life (hours)	Major Route(s) of Elimination
1,4-Dihydropyridines								
Amlodipine	2.76	64–90	None	None	93–97	6–12	35–50	Renal (60%) Fecal (20%–25%)
Clevidipine	2,96	NA	NA	None	>99	2–4 (min)	0.15	Renal (63%–74%) Fecal (7%–22%)
Felodipine	4.69	10–25	Increase	None	>99	2.5–5.0	11–16	Renal (70%) Fecal (10%)
Isradipine	3.19	15–24	Reduced rate, same extent	None	95	7–18 (CR)	8	Renal (60%–65%) Fecal (25%–30%)
Nicardipine	4.27	35	Reduced	None	>95	0.5–2.0 (IR) 1–4 (SR)	2–4	Renal (60%) Fecal (35%)
Nifedipine	2.40	45–70 86 (SR)	None	None	92–98	0.5 (IR) 6 (SR)	2–5 (IR) 7 (SR)	Renal (60%–80%) Biliary/fecal (15%)
Nimodipine	3.14	13	Reduced	None	>95	1	8–9	Renal
Nisoldipine	3.86	5	High-fat meal increases immediate release but lowers overall amount	Hydroxylated analog	>99	6–12	7–12	Renal (70%–75%) Fecal (6%–12%)
Phenalkylamines								
Verapamil	3.53	20–35	Reduced (SR form only)	Norverapamil	90	1–2 (IR) 7–11 (SR) 0.1–0.2 (IV)	3–7 (IR) 12 (SR)	Renal (70%) Fecal (16%)
Benzothiazepines								
Diltiazem	3.55	40–60	None	Deacetyl-diltiazem	70–80	2–4 (IR) 6–14 (SR)	3.0–4.5 (IR) 4.0–9.5 (SR) 3.4 (IV)	Renal (35%) Fecal (60%–65%)

CR, controlled-release product; IR, immediate-release product; IV, intravenous administration; NA, not applicable; SR, sustained-release product; T_{max}, time to maximum blood concentration.

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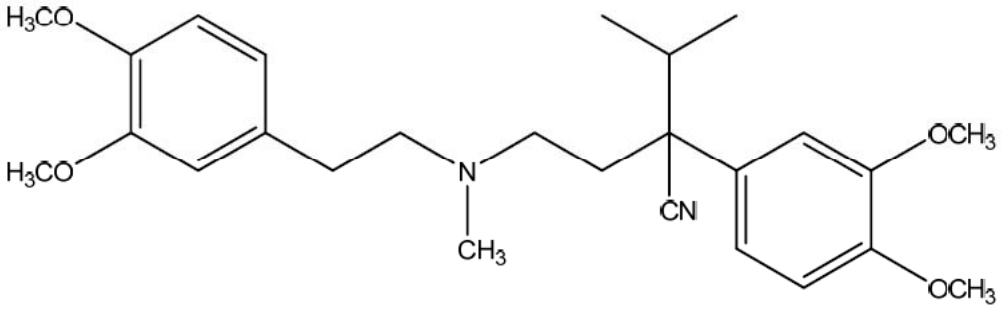
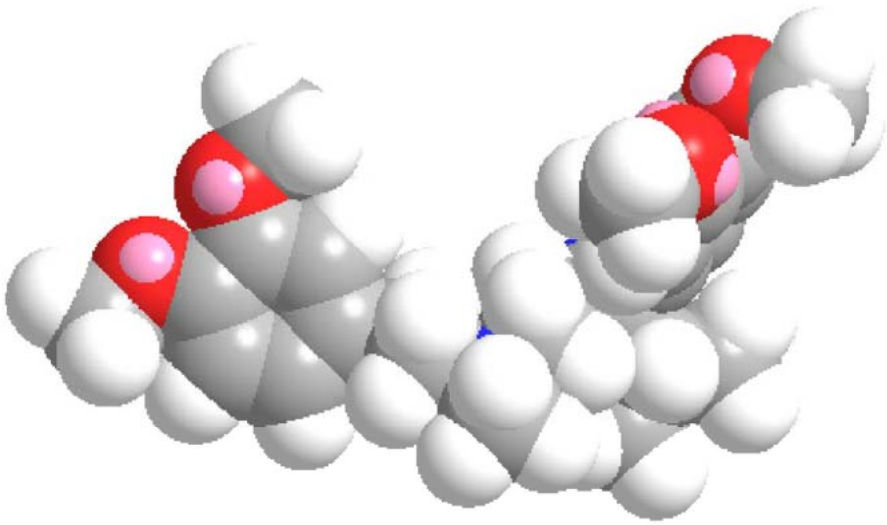
Fenilalkilamini

Verapamil

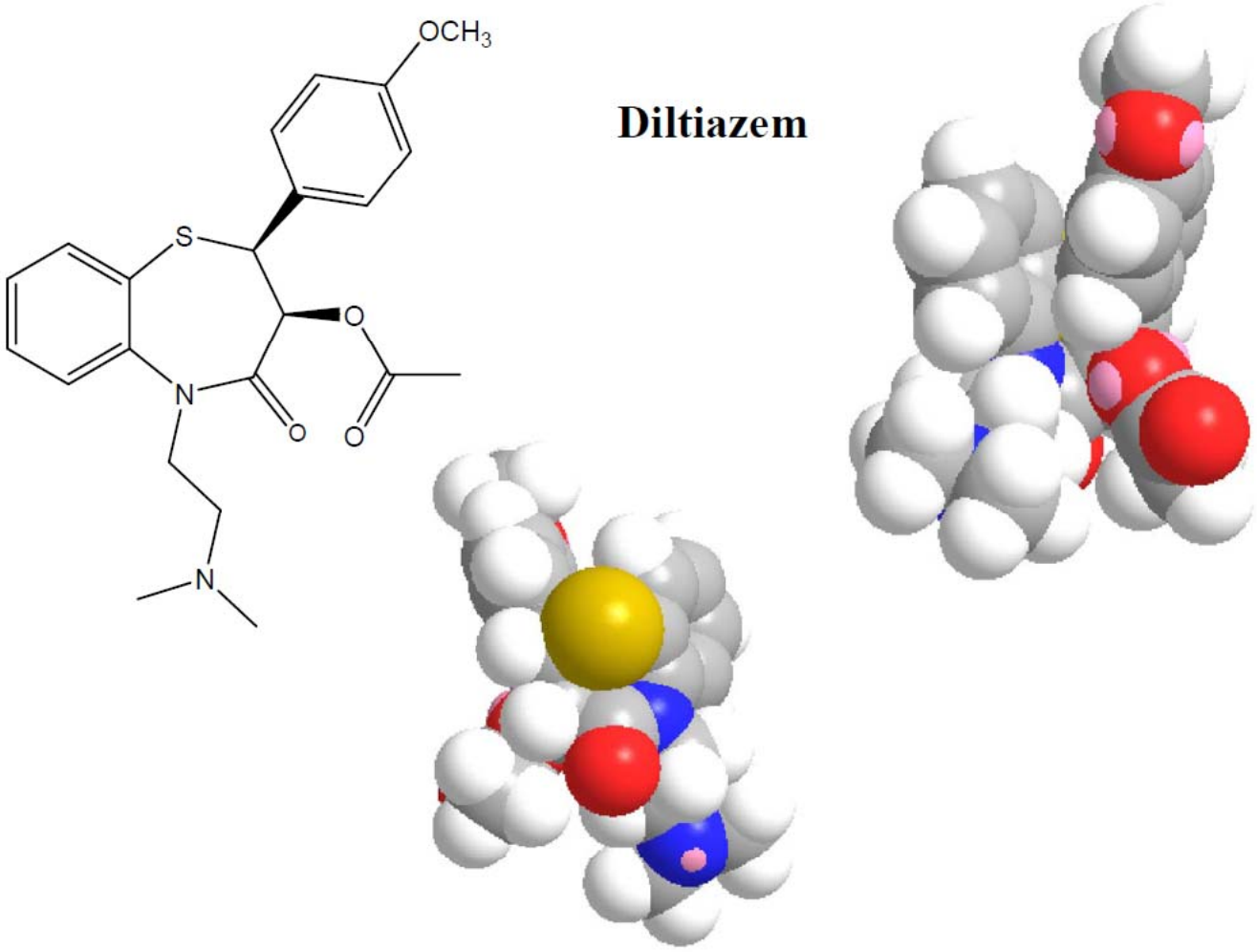




Fenilalkilamini

- Dva aromatska obroča, substituirana z –Ome
- terciarni amin
- Distančnik: 2C + 3C
- Stereogeni center – učinkoviti S enantiomeri
- Substituent na distančniku: -CN + alkil (3-12 C atomov)
- pKa = 8,9 (verapamil)

Benzotiazepini

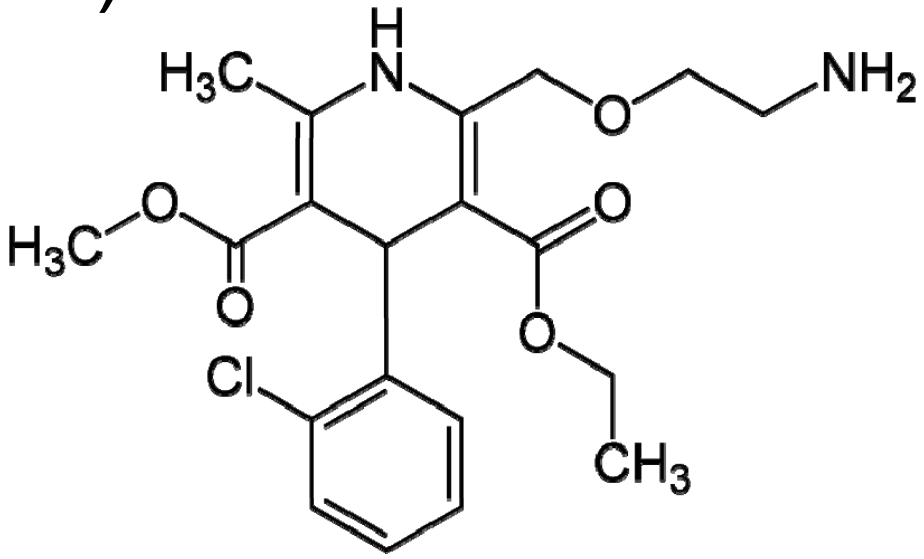


Benzotiazepini

- Učinek in strukturni elementi podobni kot pri fenilaklilaminih:
  - 2 Ar obroča
  - Ustrezna razdalja: distančnik
  - Terciarni amin
- Zamenjava S→N: benzodiazepini, šibkejši učinek, sedacija
- pKa = 7,7 (diltiazem)

Primerjava fiz.-kem. lastnosti

- Bazičnost: diltiazem, verapamil – bazi, 1,4-DHP zelo šibke baze (vinilogni karbamati)
- 1,4-DHP bazični amini v stranski verigi (npr. amlodipin)



Primerjava FK lastnosti

- FK parametri

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