Farmacevtska kemija 3

Serotoninergični sistem

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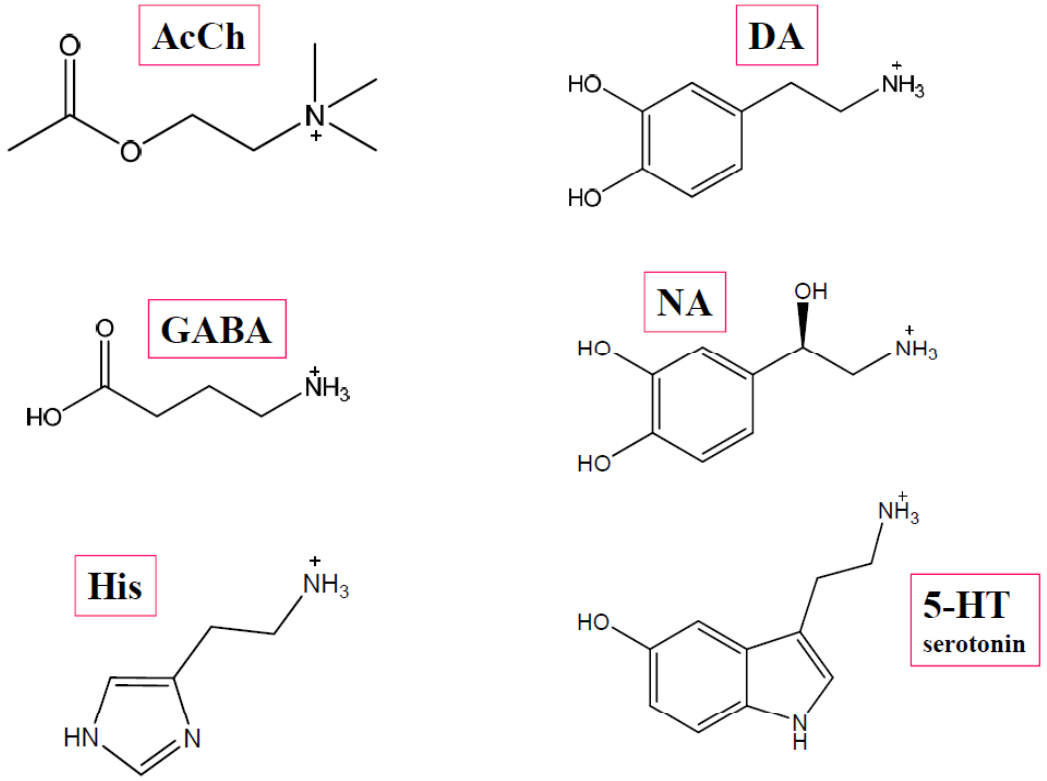
- http://www.youtube.com/watch?v=fvPpAPIIZyo
- http://www.youtube.com/watch?v=X0gyqsPdWFE

Serotonin = 5-hidroksitriptamin (5-HT)

- Kemizem prenašalcev



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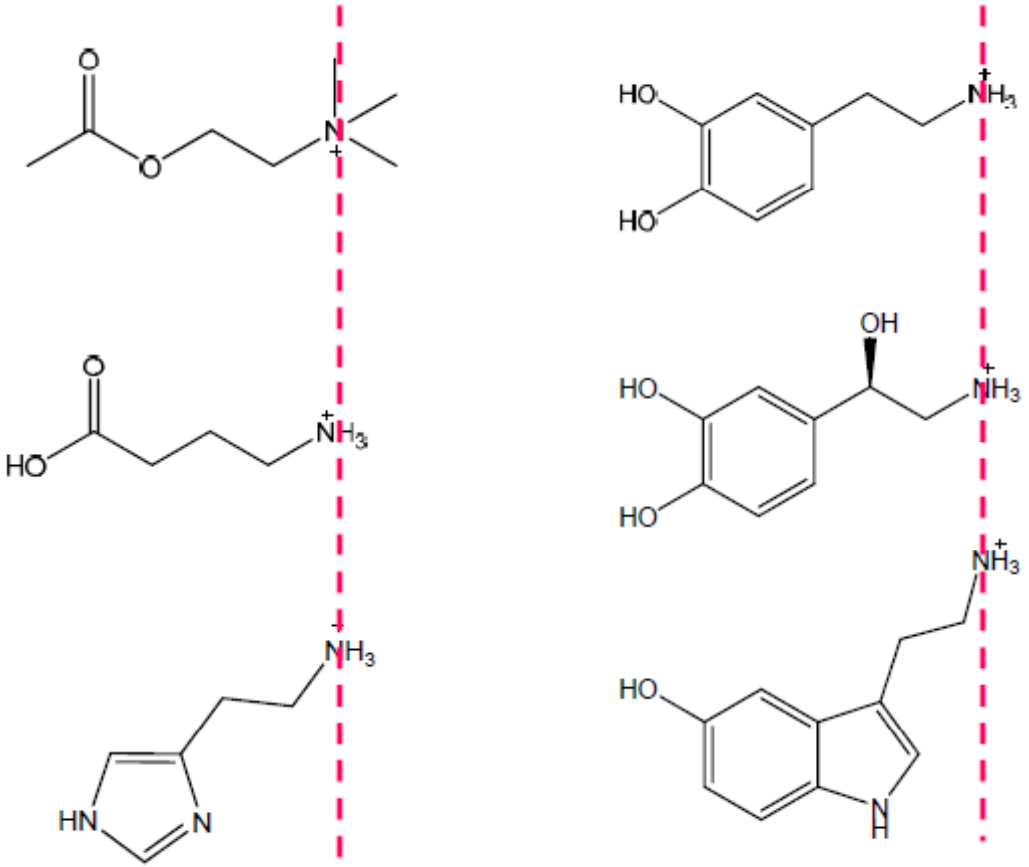

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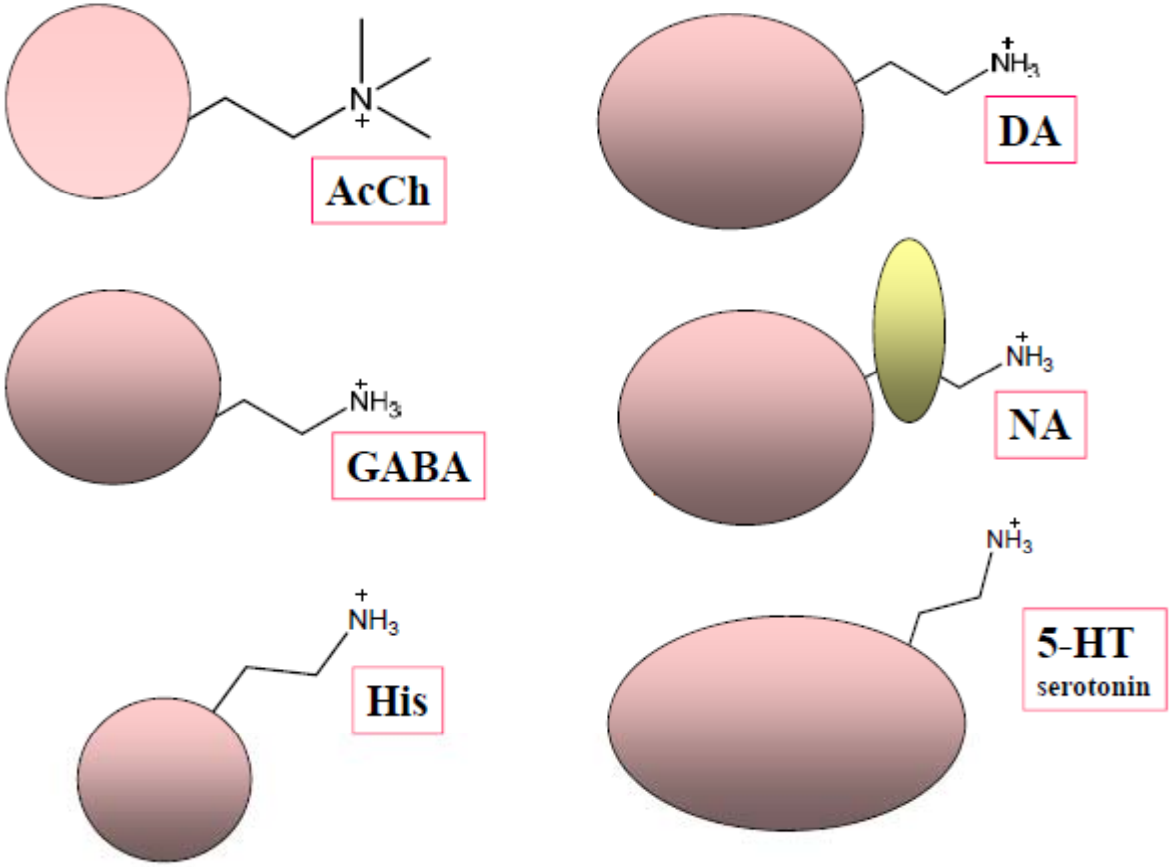

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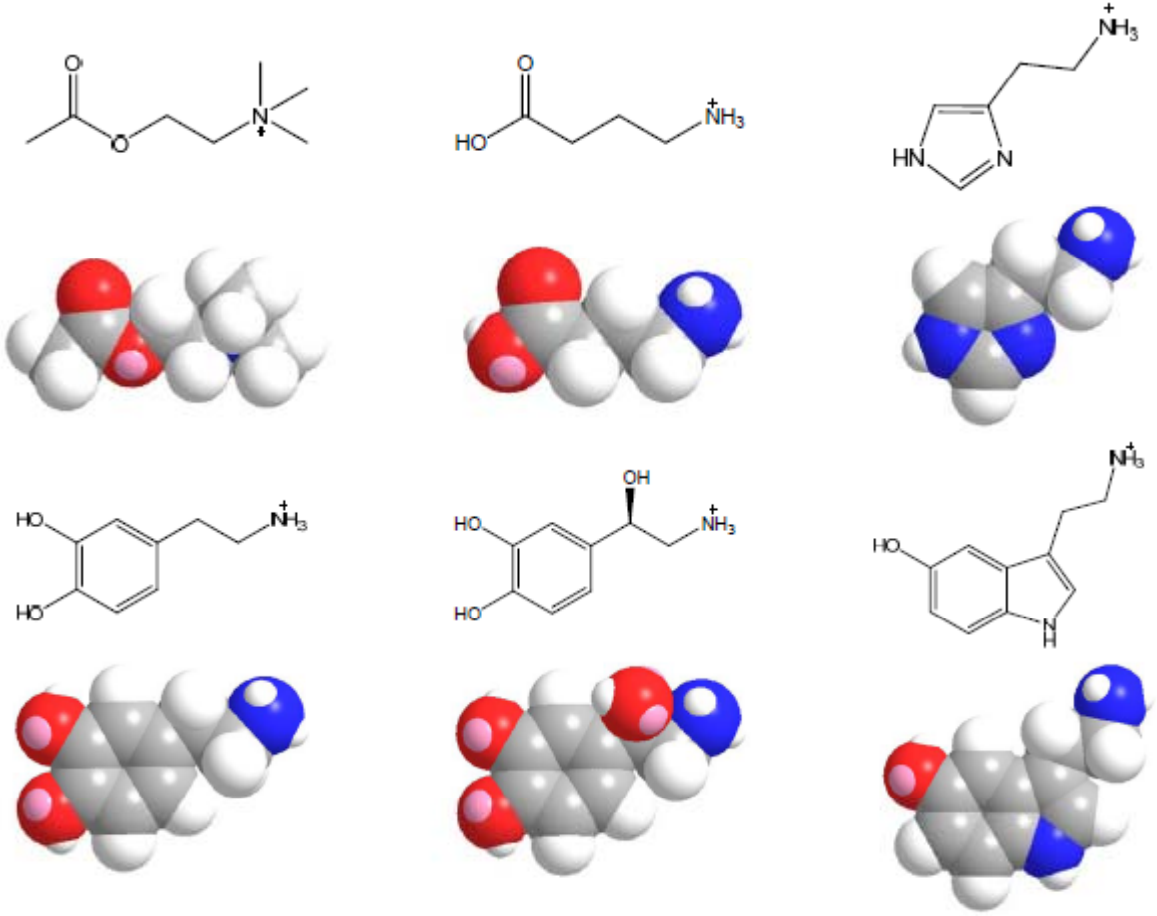
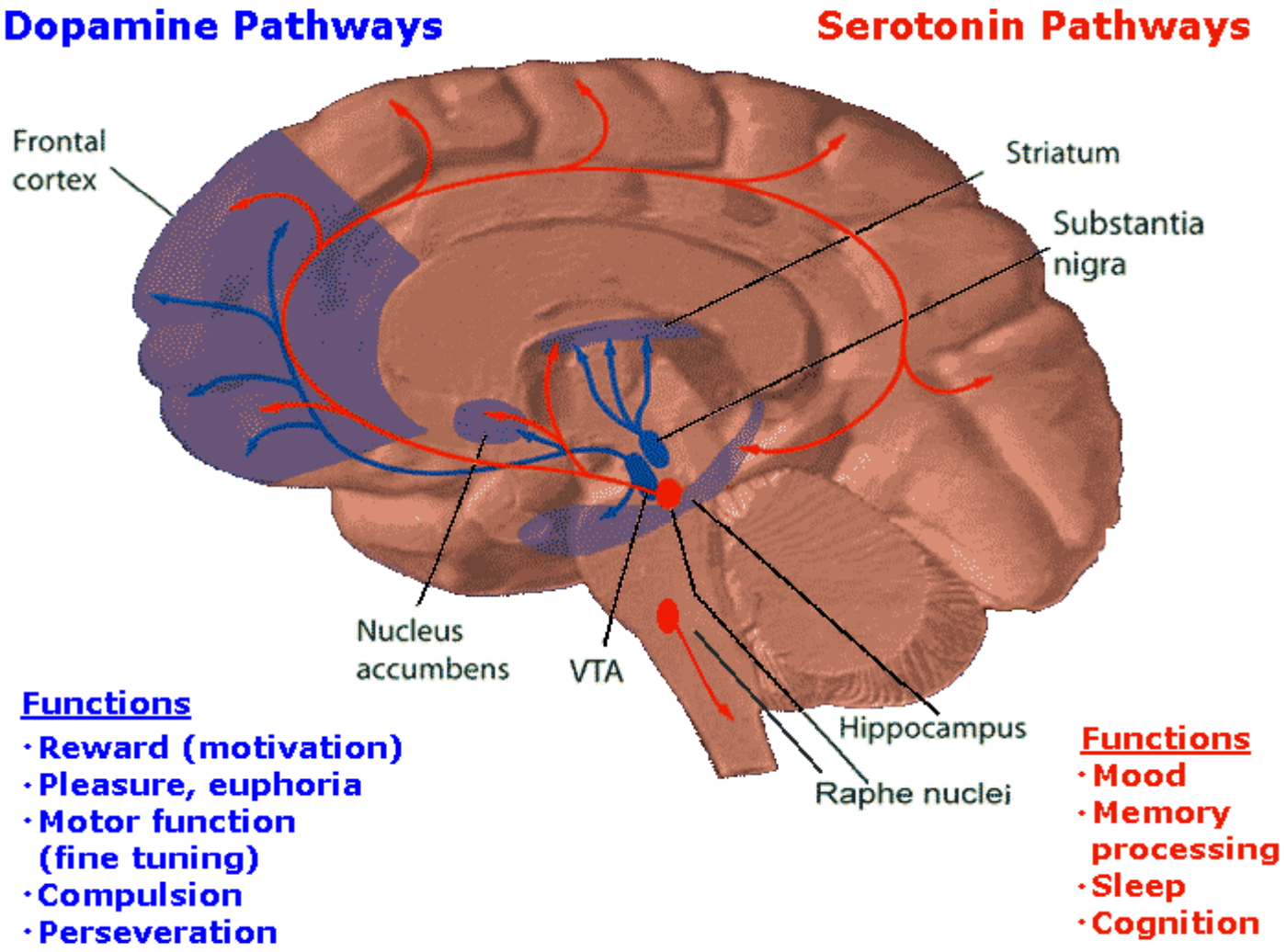


Serotonin v CŽS



Funkcije 5-HT

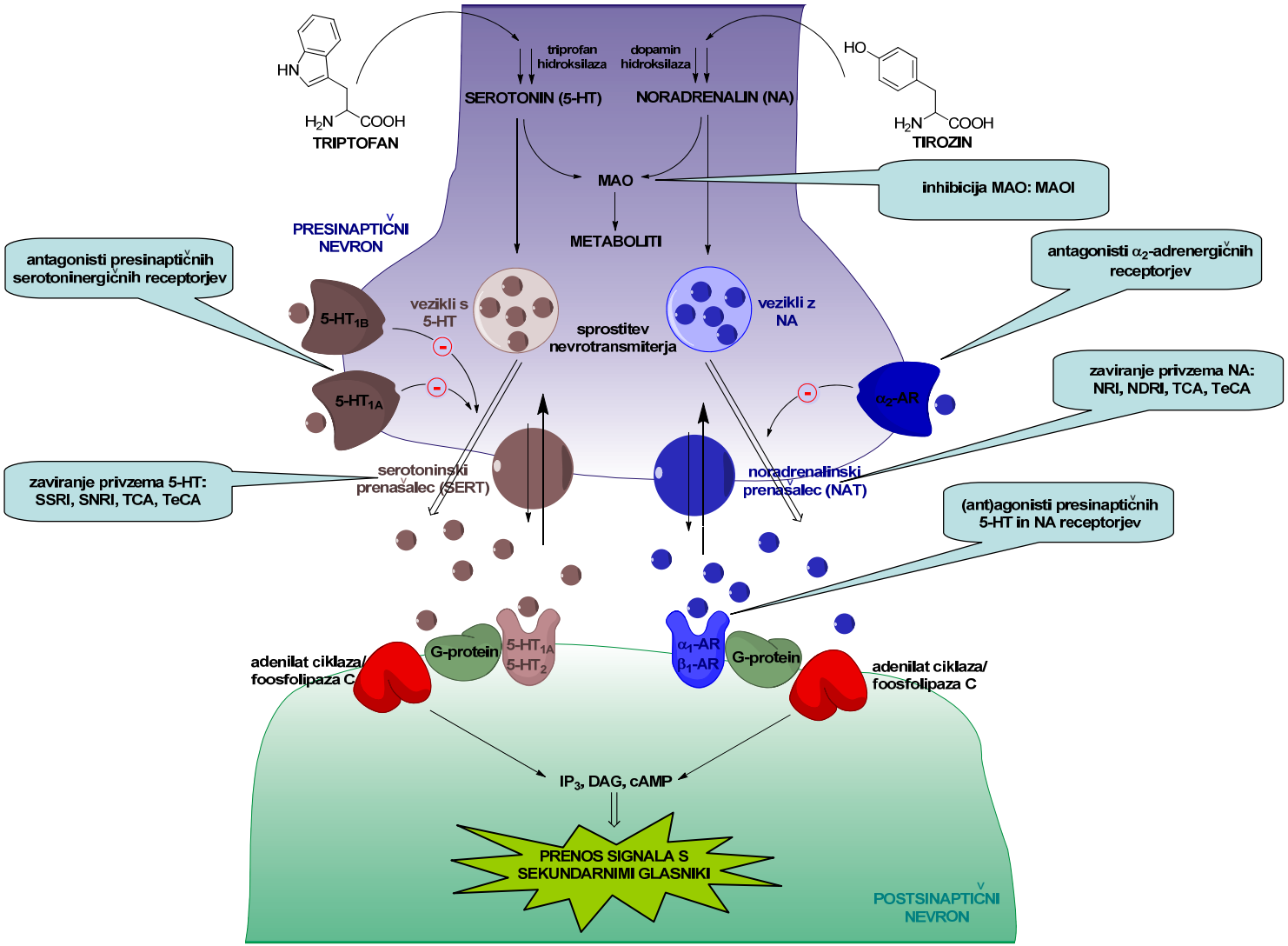
- Je prenašalec v CŽS
- **5% v CŽS**
- **95% na periferiji (večinoma v GIT nekaj v trombocitih)**
- Je predstopnja za sintezo hormona melatonina: uravnavanje spanja/budnosti
- V GIT vpliva na aktivnost mišic
- Trombociti - 5-HT_2 receptorji - strjevanje krvi in vazokonstricija

Funkcije 5-HT

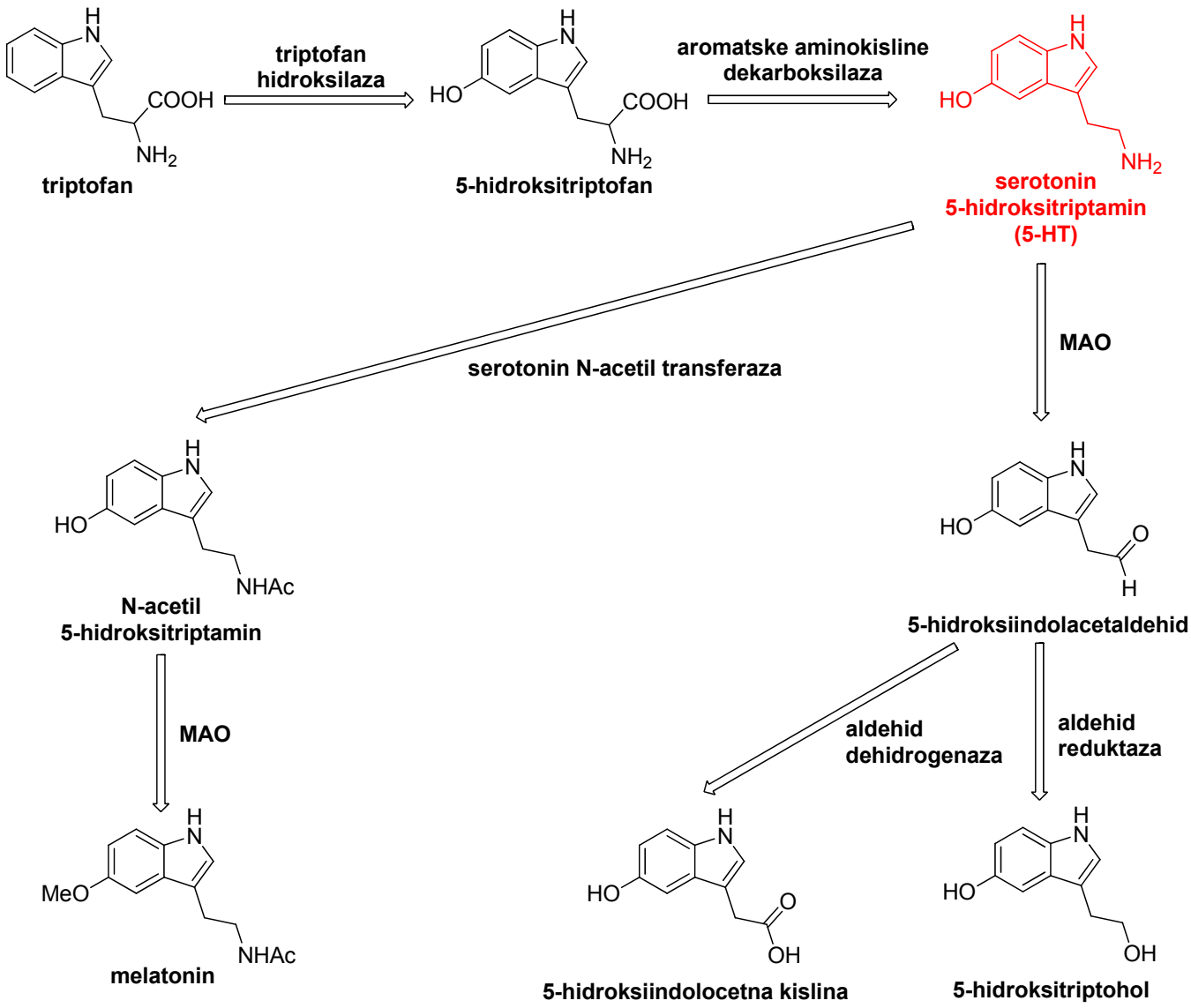
- Respiratorni sistem: bronhokonstrikcija
- GIT - tanko črevo: velika občutljivost na 5-HT→ močne ritmične kontrakcije.
- Stimulacija bruhanja (5-HT_3 receptorji)
- Kardiovaskularni sistem: različni neposredni in posredni učinki:

1. Neposredna vasokonstrikcija (velike arterije) in posredna vazodilatacija preko NO and PGI2
2. Srce: neposredni inotropni in kronotropni učinki

5-HT kot prenašalec v sinapsi



Biosinteza 5-HT



5-HT receptorji

- Najmanj 19 receptorskih tipov, vsi metabotropni in postsinaptični razen:
- 5-HT1A,B,D (avtoreceptorji)
- 5-HT3 (inhibitorni, ionotropni)

5-HT receptorji

receptor	5-HT_1	5-HT_2	5-HT_3	5-HT_4	5-HT_5	5-HT_6	5-HT_7
podtip	$5HT_{1A}$, $5HT_{1B}$, $5HT_{1D}$, $5HT_{1E}$, $5HT_{1F}$	$5HT_{2A}$, $5HT_{2B}$, $5HT_{2C}$	$5HT_{3A}$, $5HT_{3B}$		$5HT_{1A}$, $5HT_{1B}$		
mediator signalne poti	cAMP ↓	IP3↑	ionski kanal	cAMP↑	cAMP?	cAMP↑	cAMP ↑

Učinkovine v 5-HT sistemu

Pomen posameznih tipov receptorjev za 5-HT

- 5-HT1A: pomembni pri anksioznosti in depresiji
- 5-HT1D: pomembni pri migreni
- 5-HT2: so v CŽS, vplivajo na obnašanje in kardiovaskularni sistem
- 5-HT3: slabost in bruhanje, ki se pojavi pri kemoterapiji raka

Učinkovine v 5-HT sistemu

- 5-HT prekurzorji: triptofan
- Zaviralci biosinteze: *p*-klorofenilalanin inhibitor triptofan hidroksilaze
- Zaviralci razgradnje – MAO inhibitorji (moklobemid, selegilin)
- Zaviralci hranjenja v veziklih; fenfluramin
- Zavralci ponovnega privzema - antidepresivi

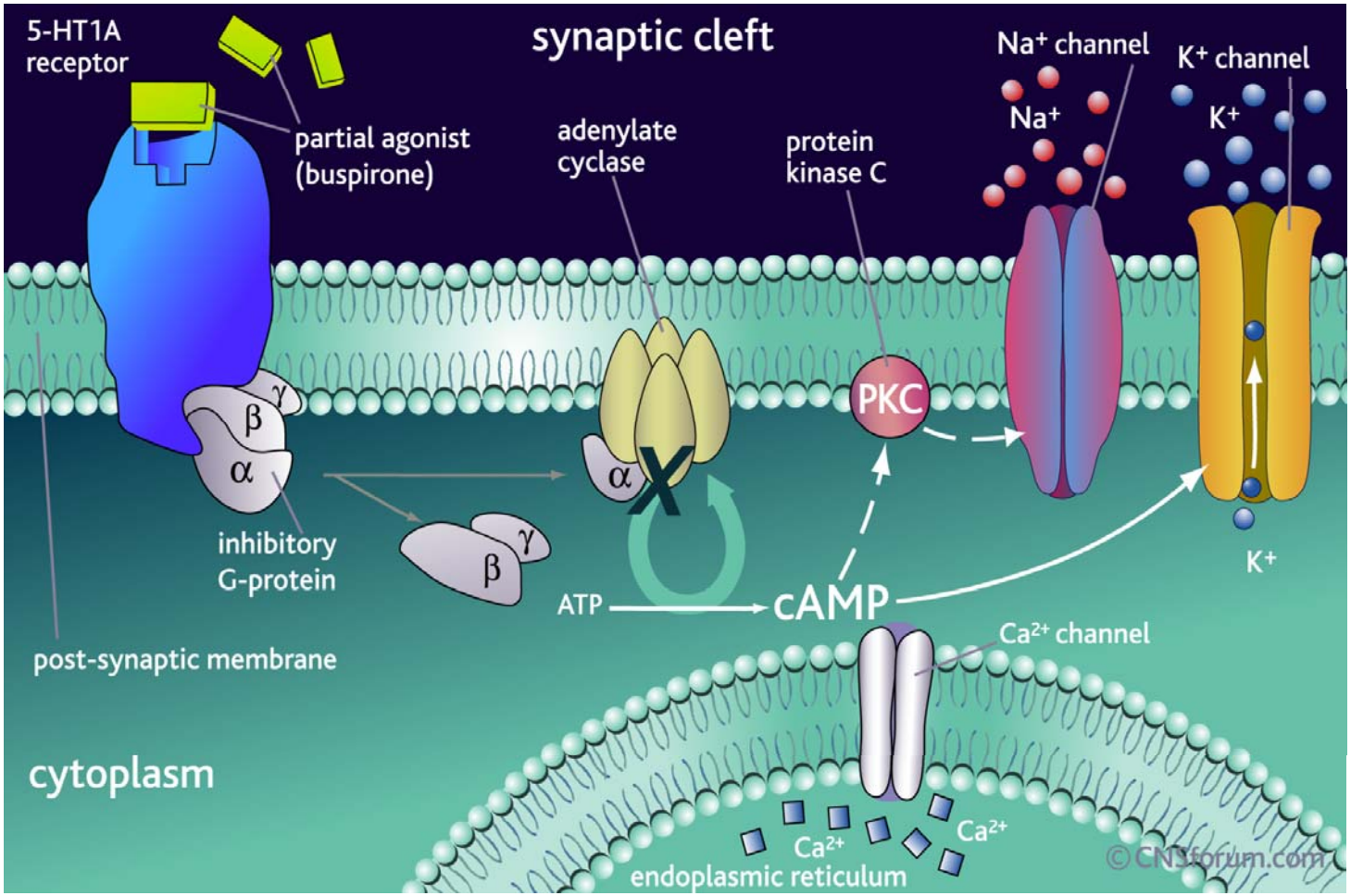
Učinkovine v 5-HT sistemu

5-HT – hormon sreče?

- Hormon sreče?

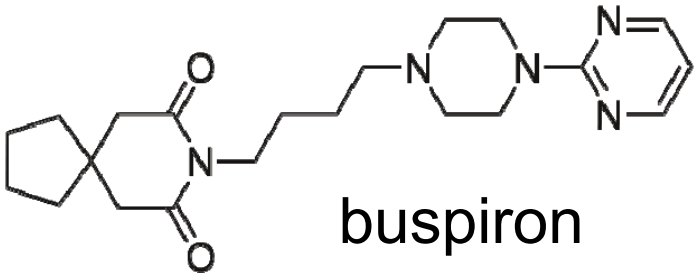
5-HT_{1A} delni agonisti

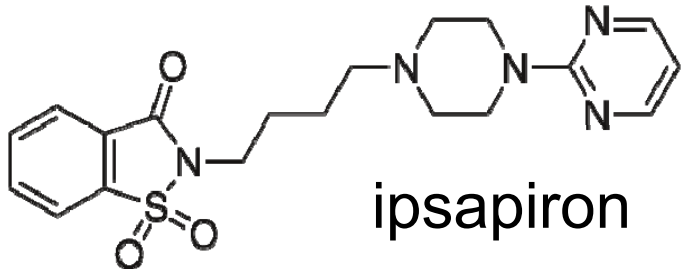
- Lokalizacija v CŽS
- Delovanje - 5-$HT1_A$ pre- postsinaptični inhibitorni receptor!

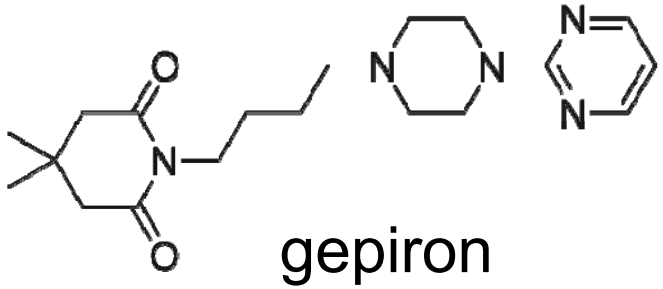


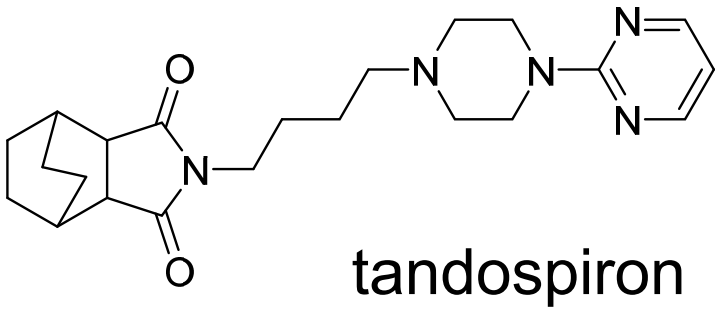
5-HT_{1A} delni agonisti

- terapija anksioznosti in depresije
- Tudi uravnavanje spolnosti, apetita
- arilpiperazinskega tipa (azapironi)


buspiron

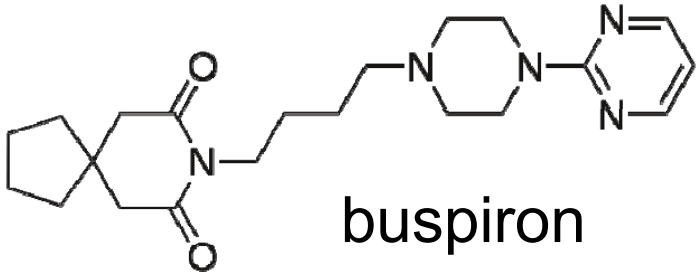

ipsapiron


gepiron


tandospiron

5-HT_{1A} delni agonisti

- Strukturna podobnost z butirofenoni?
- Delovanje na D_2 in α_1 receptorje
- Delovanje na 5-$HT1_A$ ugodno pri terapiji shizofrenije



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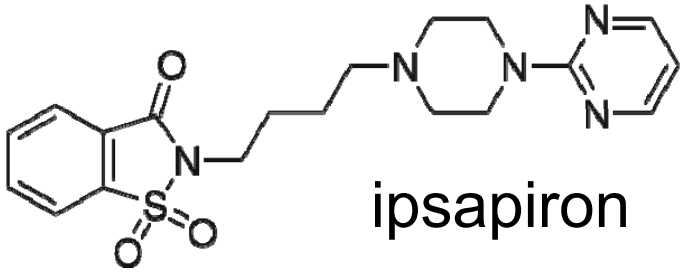

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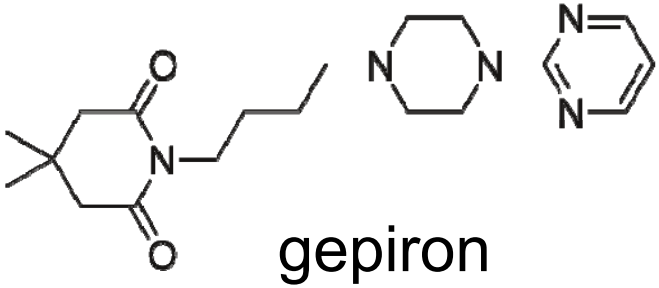

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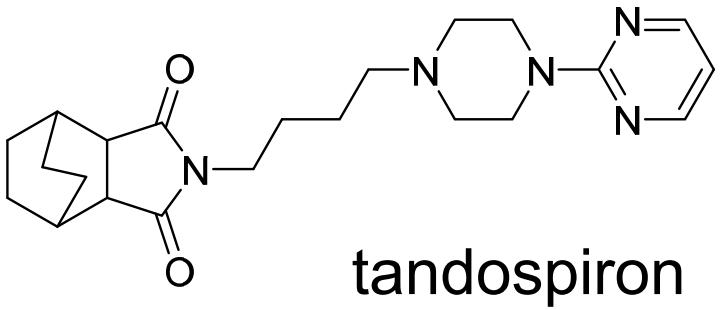


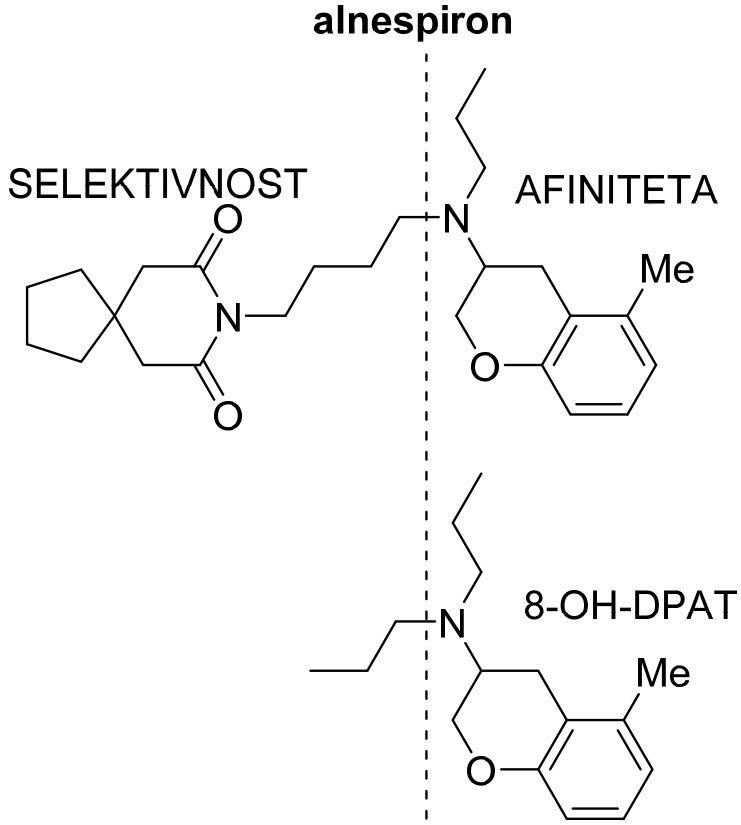
tandospiron

5-HT_{1A} delni agonisti

SAR arilpiperazinov

- Piperazin nujen, pirimidin ne (razni aromati)
- Tetrametilenski distančnik optimalen
- Imidna struktura

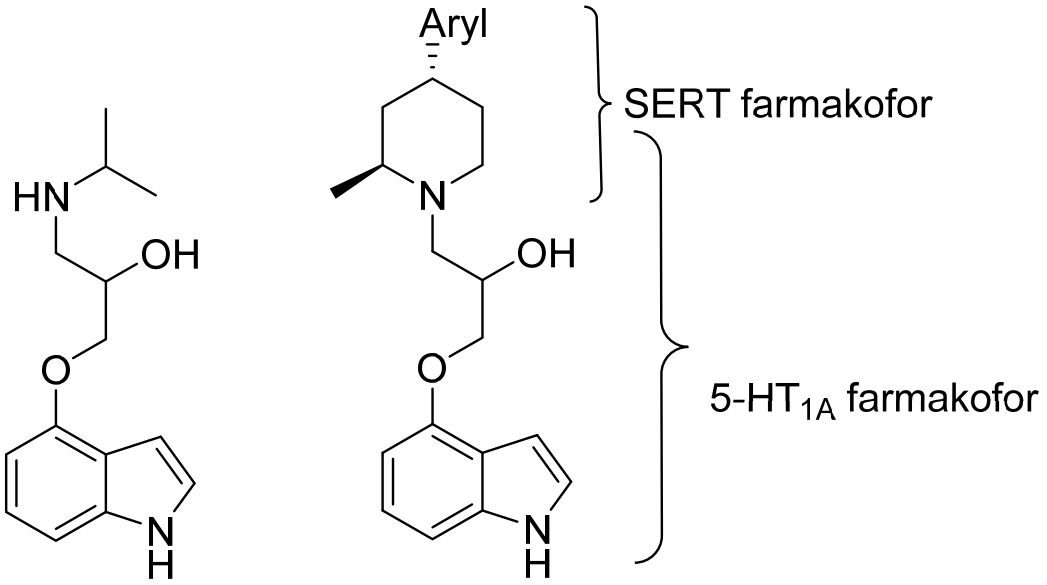
Primer **alnespiron**



5-HT_{1A} delni agonisti

Zanimivost – pindolol; 5-HT_{1A} antagonist

- skrajša začetek terapije s SSRI
- Kombinacija farmakofora?



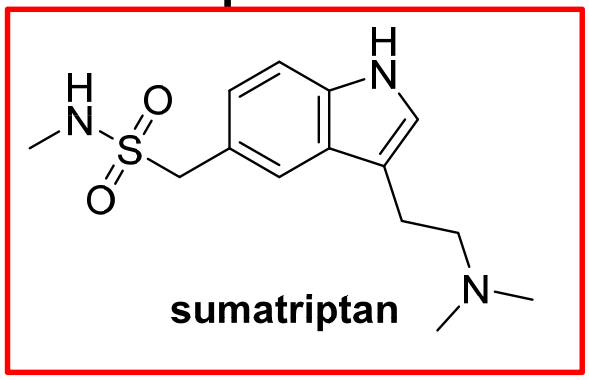
pindolol - β1 antagonist

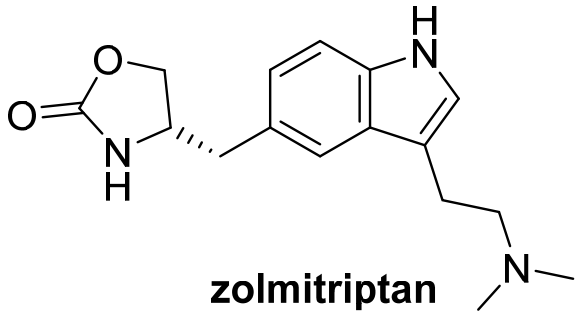
5-HT_{1D} agonisti

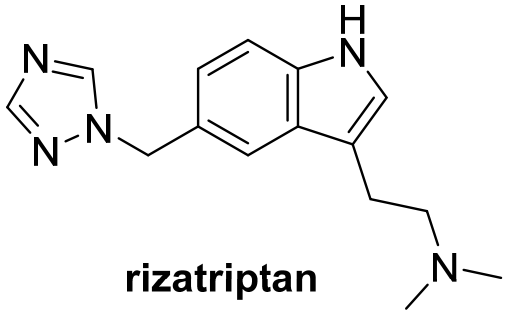
- Terapija migrene; agonisti 5-HT_{1D} agonisti cerebralnih žil – konstrikcija
- Ni delovanja v CŽS – ni prehoda HEB!
- Nevarnost – vazokonstrikcija koronark – kardiogeni šok

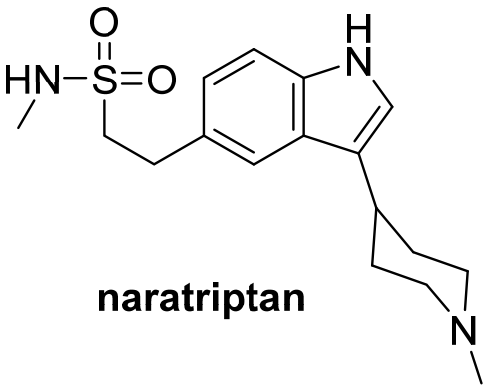
5-HT_{1D} agonisti

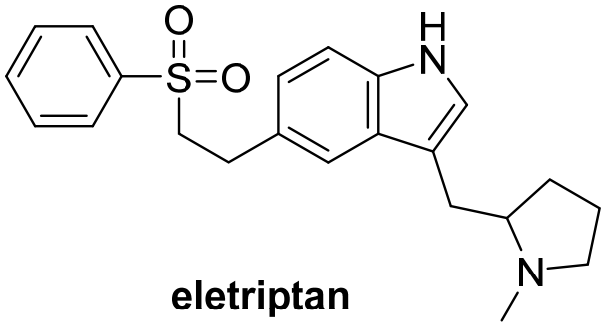
- triptani

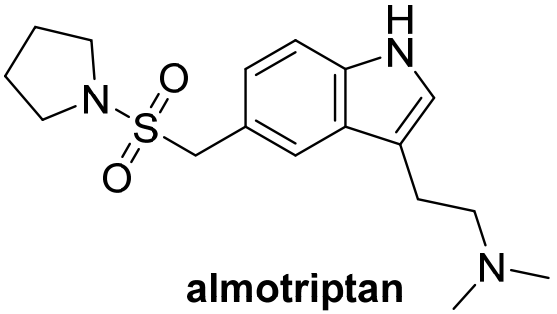












5-HT_{1D} agonisti

SAR

- Indoletilaminsko jedro
- Mesto 5: akceptor H-vezi

5-HT_{1D} agonisti

Table 14.3. Pharmacokinetics of the 5-HT_1 Agonists (the Triptans)

Parameters	Sumatriptan	Zolmitriptan	Naratriptan	Rizatriptan	Almotriptan	Frovatriptan	Eletriptan
Trade name	Imitrex	Zomig	Amerge	Maxalt	Axert	Frova	Relpax
Log P (calc)[a]	0.7 ± 0.6	1.6 ± 0.4	1.4 ± 0.6	0.9 ± 0.6	1.9 ± 0.6	0.9 ± 0.4	3.1 ± 0.6
Log D (pH 7) (calc)[a]	−1.7	−0.8	−1.2	−1.4	−0.5	−2.1	0.18
Bioavailability (%)							
Oral	14–15[b]	40–50[b]	70[c] Female: 75 Male: 60	40–50[b]	70–80	20–30[b] Female: ~30 Male: ~20	50[cd]
Nasal	17	102	—	—	—	—	—
SQ (subcutaneous)	97		—	—	—	—	—
Protein binding (%)	14–20	25	28–30	14	35	15	85
Volume of distribution (L/kg)	50	PO: 7 Nasal: 4	170	110–140	180–200	3–4	2.0–2.5
Elimination half-life (h)	PO: 2.5 SC: 2.5	PO: 2–3 Nasal: 3–4	5–6	2.3	PO: 3–4 SC: 3–4	25	4–5 Elderly: 6
Major metabolites (%)	Indoleacetic acid Glucuronides Hepatic: 60%	N-demethyl (act): 4 Indoleacetate: 31	Hepatic: 50%	Indolacetate N-demethyl (act) 6-OH	Indolacetate GABA N-demethyl Hepatic: 60%	N-demethyl (act) N-Ac demethyl	N-demethyl (act)
Metabolizing enzymes	MAO-A	CYP3A4	CYP3A4 MAO-A	MAO-A CYP3A4	CYP3A4/ CYP2D6:12% MAO-A: 27%	CYP1A2	CYP3A4
Excretion (%)	PO: Urine metab: ~60 Feces metab: ~40 Unchanged: 3–22	Urine metab: 60 Feces metab: 30 Unchanged: <10	Urine metab: 30 Feces metab: ~15	Urine metab: 80 Feces metab: 12 Unchanged: 14	Urine metab: 75 Feces metab: 10 Unchanged: 40–50	Urine metab: 10–30 Feces metab: 60	Urine metab: ~ 90% Unchanged: <10
Time to peak concentration (min)	SQ: 12 (5–20) Nasal: 60–90 PO: 60–120	PO: 120–240 Nasal: 180–240	PO: 60–180	PO: 60–90	PO: 60–240 SC: <30	120–240	60–90
Onset (min)	SQ: <10 Nasal: <15 PO: <30	PO: 60	PO: 60–180	PO: 30–120	PO: 60–120 SC: 60–120	PO: 120	PO: <60
Dosage range (mg)	SQ: 6 Nasal: 5–20 PO: 25–100 Max PO: 200/24 h Duration PO: 2–4 h	PO: 1.25–5.00 Max PO: 10/24 h	PO: 1.0–2.5 Max PO: 5/24 h Duration PO: <24 h	PO: 5–10 Max PO: 25/24 h Duration PO: 14–16 h	6.25–12.5 Max PO: 25/24 h	PO: 2.5–5.0 Max PO: 7.5/24 h Duration PO: <24 h	PO: 20–40 Max PO: 80/24 h Duration PO: 18 h

[a]Chemical Abstracts, American Chemical Society, calculated using Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris (1994-2006 ACD/Labs).
[b]First-pass metabolism.
[c]Delayed by food.
[d]Slower onset during migraine attack.

5-HT_2 agonisti

Klasični halucinogeni – t.i. “psihedelični” učinek

Slovenski Medicinski e-Slovar:

- psihedéličen -čna -o zavest razširjajoč, razgaljajoč duševnost; prim.
- razširjenje zavesti:
- ~a droga

Spremembe zavesti brez znatnih toksikomanogenih učinkov

Učinek posledica primarno agonizma na 5-HT_{2A}

5-HT_2 agonisti

Albert Hofmann, Sandoz, Basel – po sintezi pomotoma apliciral LSD:

"... affected by a remarkable restlessness, combined with a slight dizziness. At home I lay down and sank into a not unpleasant intoxicated[-]like condition, characterized by an extremely stimulated imagination. In a dreamlike state, with eyes closed (I found the daylight to be unpleasantly glaring), I perceived an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colors. After some two hours this condition faded away."

5-HT_2 agonisti

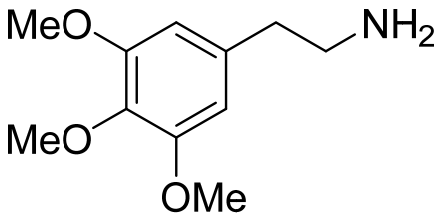
Albert Hofmann – “Kolesarski dan” ali prvi zavestni “trip” po zaužitju 250 mg LSD

"On the way home, my condition began to assume threatening forms. Everything in my field of vision wavered and was distorted as if seen in a curved mirror. I also had the sensation of being unable to move from the spot. Nevertheless, my assistant later told me that we had travelled very rapidly."

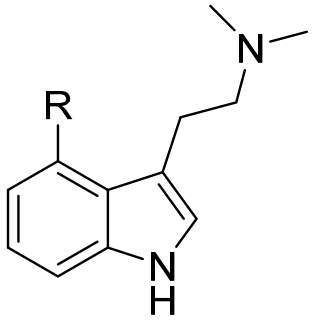
Back home, when a friendly neighbour brought round some milk, he perceived her as a "malevolent, insidious witch" wearing "a lurid mask". After six hours of highs and lows, the effects subsided.

5-HT_{2A} agonisti

Meskalin (feniletilamin), $t_{1/2}$ = 6h

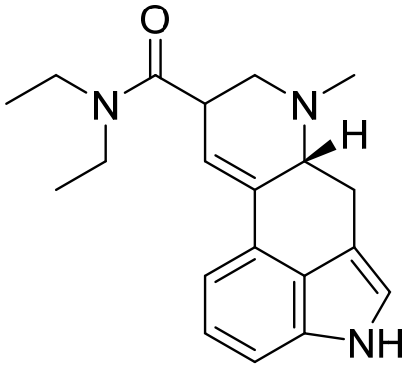


Triptamini: DMT (*N,N*-dimetiltriptamin), psilocibin, psilocin



R=H - DMT
R=OPO_3H_2 - psilocibin - predzdravilo
R=OH - psilocin, t1/2 = 2-3h

LSD, $t_{1/2}$ ~4h



$5\text{-}HT_{2A}$ agonisti

Načeloma nenevarni, pa vendar – serotoninski sindrom

- povišan srčni utrip, drgetanje, znojenje, razširjene zenice, mioklonus (občasno tresenje ali trzanje mišic), izraziti refleksi

primer Libby Zion:

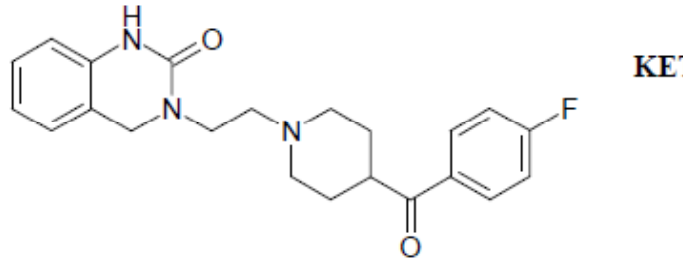
- Antidepresiv (MAOI) fenelzin
- Visoka telesna temperatura, visok krvni tlak, umrla zaradi zastoja srca

5-HT_2 antagonisti

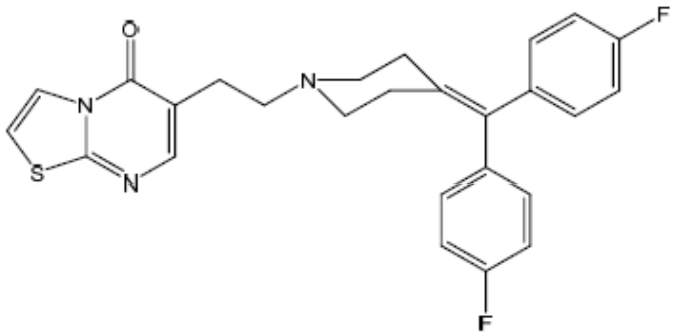
- 5-HT_{2A} receptor
- Anksiolitično, antipsihotično delovanje
- Kronična uporaba antagonistov – regulacija navzdol 5-HT_{2A} receptorjev
- 5-HT_{2A} receptorji na srčni mišici

5-HT_2 antagonisti

- 5-HT_{2A} antagonisti – antidepresivi, antihipertenzivi (α-adrenergični antagonisti), delovanje tudi na H_1 receptorje
- Delujejo na vse 5-HT_2 – slaba selektivnost



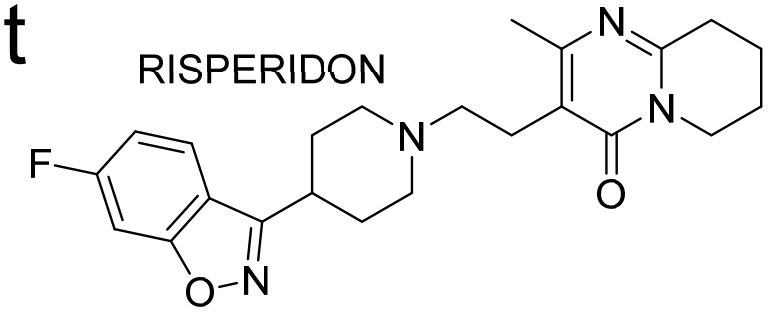
KETANSERIN

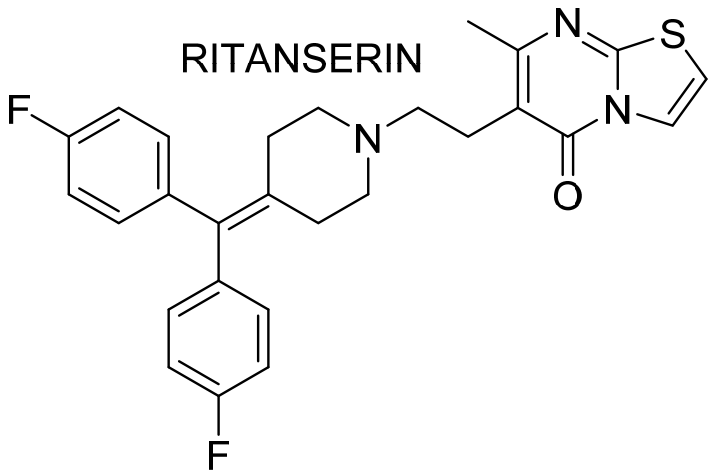


RITANSERIN

5-HT_2 antagonisti

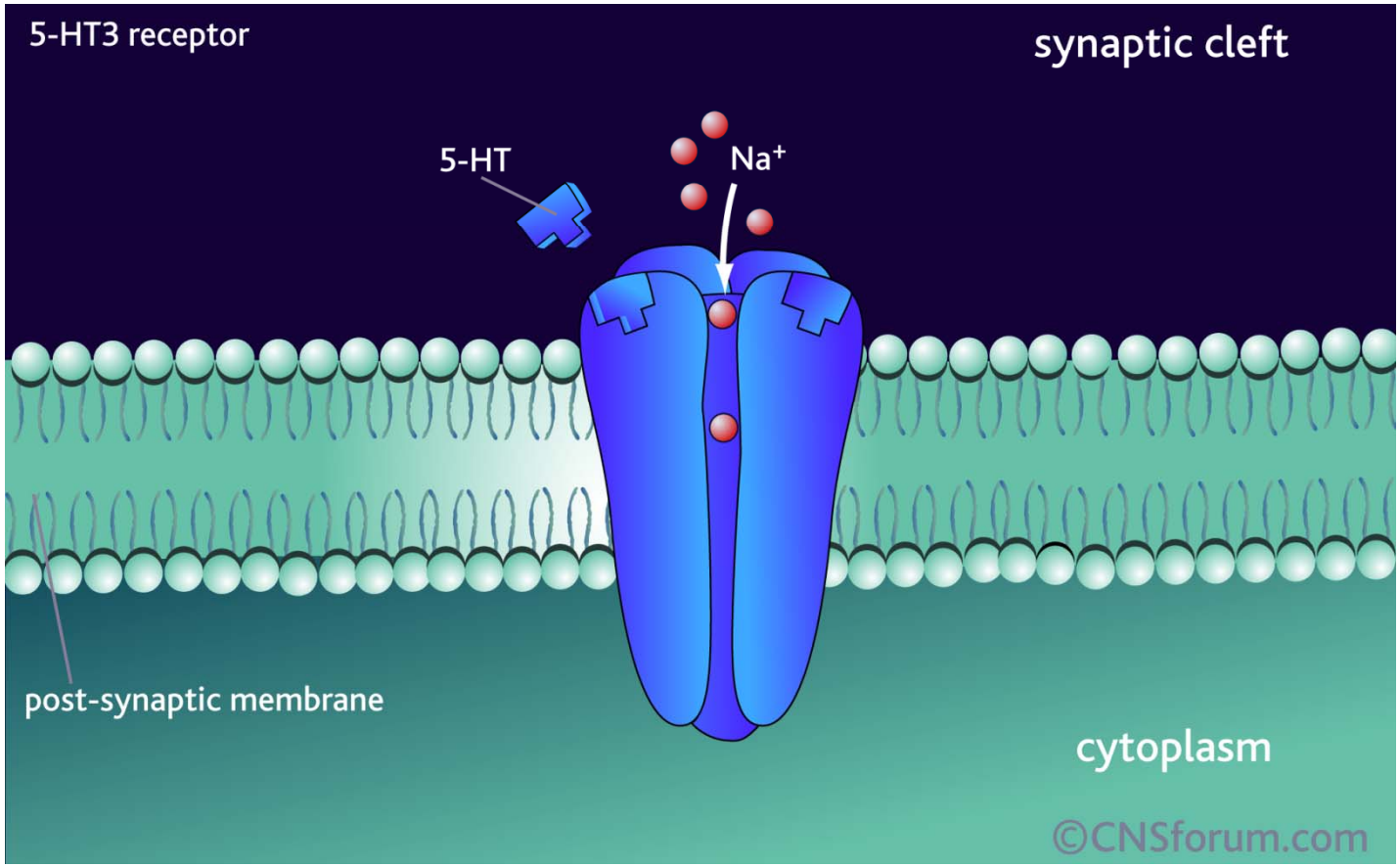
- Ritanserin – risperidon: 5-HT_2/D_2 selektivnost





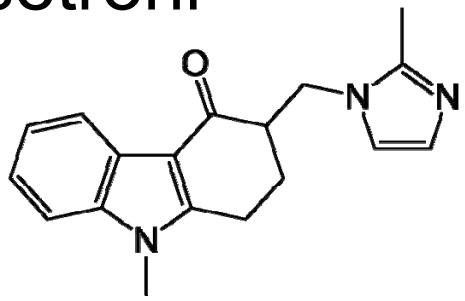
5-HT_3 antagonisti

- 5-HT_3 receptorji – ionofori (Na^+, Ca^{2+}, K^+)

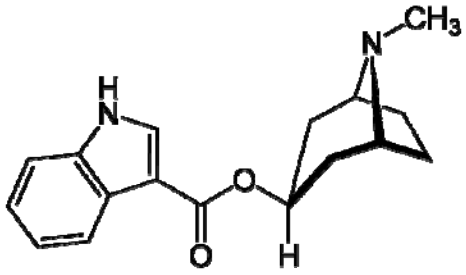


5-HT_3 antagonisti

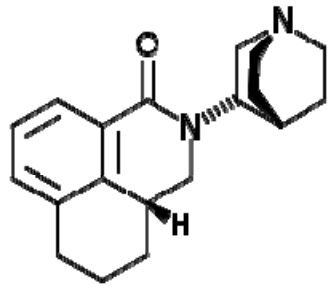
- 5-HT_3 receptorji – vagus, CŽS – vagus vzdraži enterokromafine celice v GIT
- Antiemetiki, koterapija s citostatiki
- setroni



ondansetron



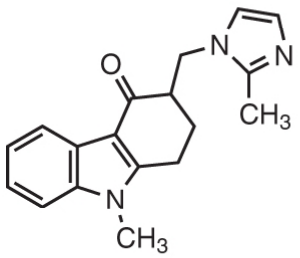
tropisetron



palonosetron

5-HT_3 antagonisti

- setroni



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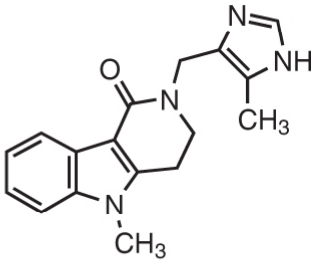

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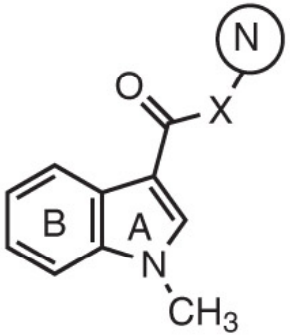
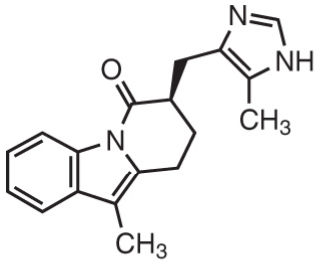
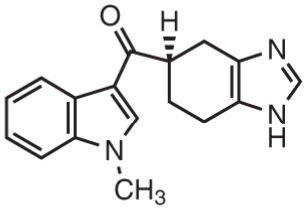




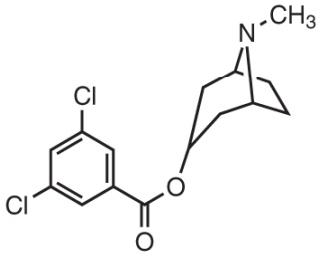
Fabesetron



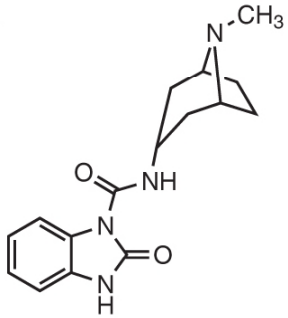
Ramosetron

5-HT_3 antagonisti

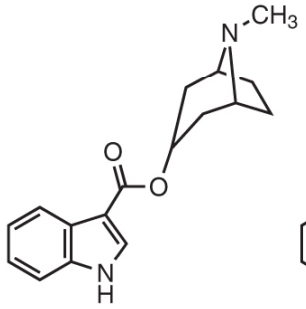
- setroni



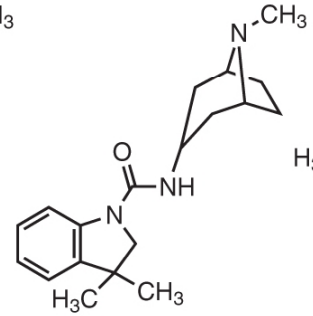
Bemesetron



Itasetron



Tropisetron



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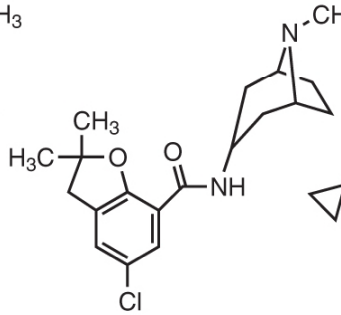

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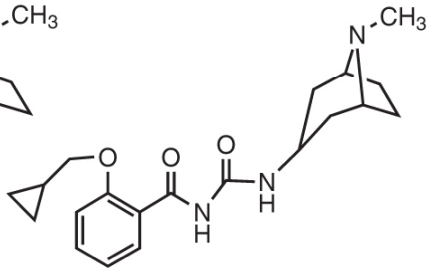
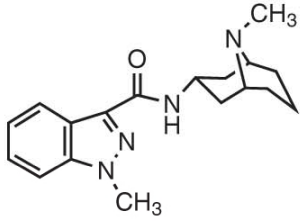
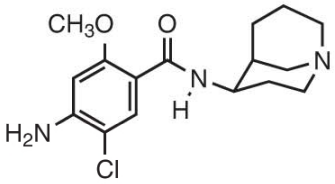


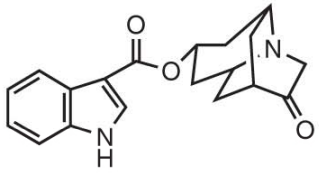
WAY-100289



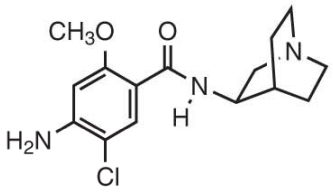
Granisetron



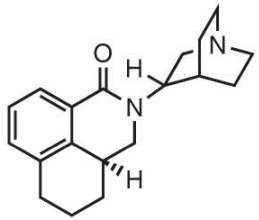
Renzapride



Dolasetron



Zacopride



Palonosetron

5-HT_3 antagonisti

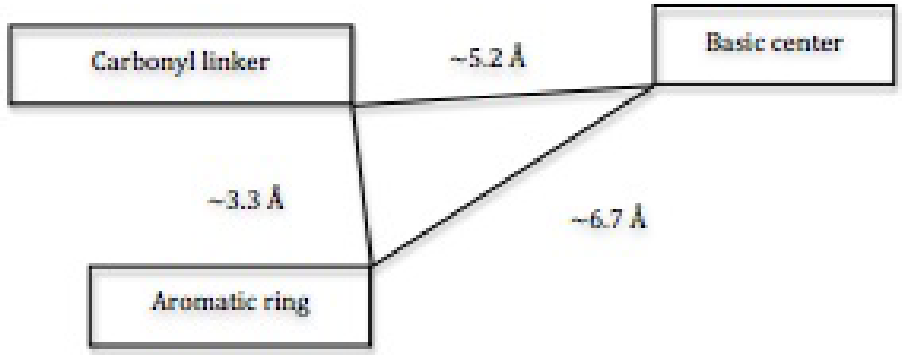
- FK lastnosti 5-HT_3 antagonistov

TABLE 11.4 Pharmacokinetics of the 5-HT3 Antagonists (Setrons)

Parameters	Ondansetron	Dolasetron	Granisetron	Alosetron	Palonosetron	Tropisetron
Trade name	Zofran	Anzemet	Kytril	Lotronex	Aloxi	Navoban
CLogP (calc)[a]	2.1 ± 0.5	2.8 ± 0.5	1.5 ± 0.5	0.88 ± 0.8	2.6 ± 0.5	3.6 ± 0.3
LogD (pH 7) (calc)[a]	1.5	2.8	−1.5	0.4	0.01	0.8
Bioavailability (%)	56–70[d]	Hydrodolasetron: 60–80	60[d]	50–60[bc]	IV	60 (60–100)
Protein binding (%)	70–76	Hydrodolasetron: 70–80	65	82	62	71
Volume of distribution (L/kg)	PO: 2.2–2.5	Hydrodolasetron: PO: 5.8–10	PO: 3.9	PO: 70 (65–95)	IV: 6.8–12.5	IV: 500
		PO: 6-7				
Elimination half-life (h)	PO: 3–6	PO: <10 min	IV: 4–5	PO: 1.5–2.0	PO: 30–40	EM: PO: 6–8
	Elderly: PO: 11	Hydrodolasetron: PO: 4–9	PO: ~6			PM: PO: 30
Major metabolites (%)	Hydroxylation	Hydrodolasetron	*N*-Demethyl	6-Hydroxylation	*N*-oxide	Hydrolyzation
	Glucuronidation	Hydroxylation	Hepatic	*N*-Demethyl	6S-Hydroxy	Glucuronides
	Hepatic	*N*-Demethyl			Hepatic: 50%	
Metabolizing enzyme (%)	CYP3A4	Carbonyl reductase	CYP3A4	CYP2C9: 30	CYP2D6	CYP2D6
	CYP2D6	CYP2D6		CYP3A4: 20	CYP3A4	
		CYP3A4 (*N*-oxide)		CYP1A2: 10	CYP1A2	
Time to peak plasma concentration (h)	PO: 1–2	Hydrodolasetron IV: <0.5	PO: 2–3	PO: 0.5–2	IV: 30 s	EM: PO: 3
		Hydrodolasetron PO: <1				PM: PO: 4
Excretion (%)	Urine metab: 40–60	Urine metab: 45	Urine metab: 48	Urine metab: 70	Urine metab: 80	Urine metab: ~70
	Feces metab: 25	Feces: 30	Feces metab: 38	Feces metab: 25		Feces metab: ~15
	Unchanged: <10	Unchanged hydrodolasetron: 60	Unchanged: <10	Unchanged: <10	Unchanged: 40	Unchanged: <10
Duration (h)	———	———	8–24	1–10	>24	———

5-HT_3 antagonisti

- SAR 5-HT_3 antagonistov



5-HT_3 antagonisti

Potencial 5-HT_3 antagonistov:

- Anksiolitiki
- Zloraba mamil
- Avtizem
- Bipolarna motnja
- Depresija
- Prebavne motnje

Literatura predavanj

Foye's Principles of Medicinal Chemistry, 6. izdaja:

- 14., 21. poglavje