Izosterija in bioizosterija

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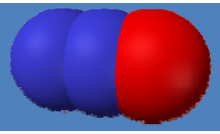
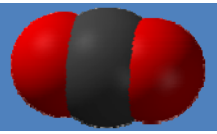
Izosterija

Gr. Izo = enak, steros = trden, oprijemljiv, prostorski

1919 fizik Langmuir definira:

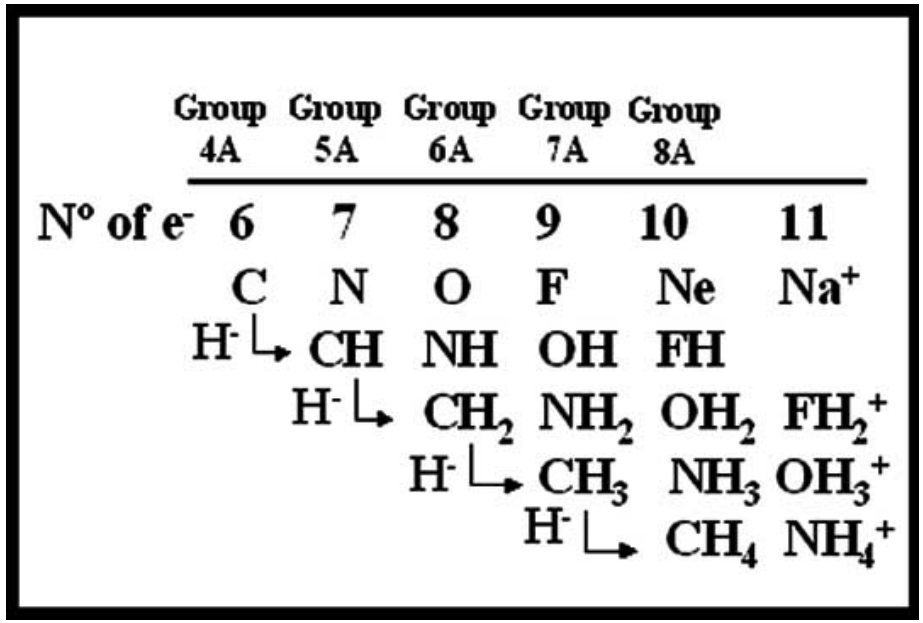
- Izosterične skupine (atomi, ioni, molekule) – enako število elektronov in enako št. atomov
- Izosterija = fizikalno-kemijska podobnost, zamenjava ne povzroči sprememb v fiz.-kem lastnostih

	N_2O 	CO_2 
Gostota (10 °C)	0,856	0,858
Ref. Indeks (16 °C)	1,193	1,190
Dielektrična konstanta	1,593	1,582
Topnost v etanolu (15°C)	3,250	3,130

Izosterija

1925 Grimmov "zakon" hidridnih zamenjav:

- "Atoms anywhere up to four places in the periodic system before an inert gas change their properties by uniting with one to four hydrogen atoms, in such a manner that the resulting combinations behave like **pseudoatoms**, which are similar to elements in the groups one to four places respectively, to their right."



Izosterija

Grimmov “zakon” – ali drži?

	Pentan	Dietileter	Dietilamin
Vrelišče	36,1 °C	34,6 °C	55,5 °C
Viskoznost (20°C)	0,240 cP	0,224 cP	~0,35 cP
Ref. Indeks *n*20/D	1,358	1,353	1,385
Gostota	0,626 g/cm^3	0,7134 g/cm^3	0,7074 g/cm^3

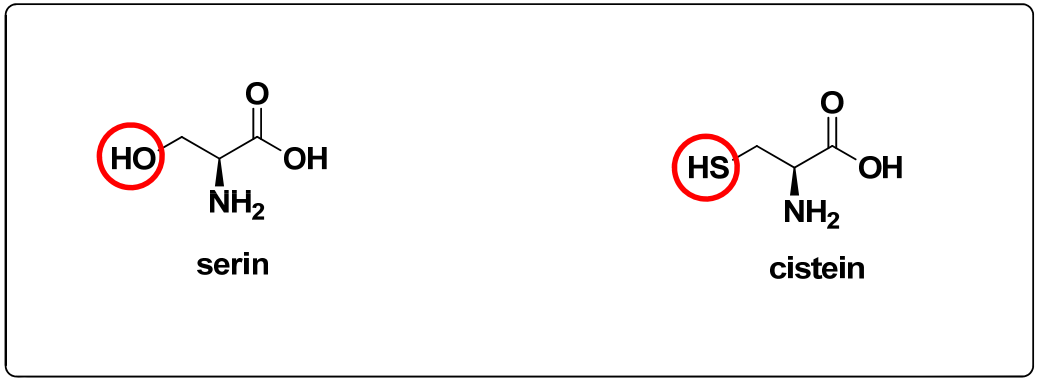
Izosterija

1932 Erlenmeyer razširi pojem:

- Izosteri so elementi, funkcionalne skupine, ioni in molekule z enakim številom valenčnih elektronov
- Elementi iste skupine so izosteri

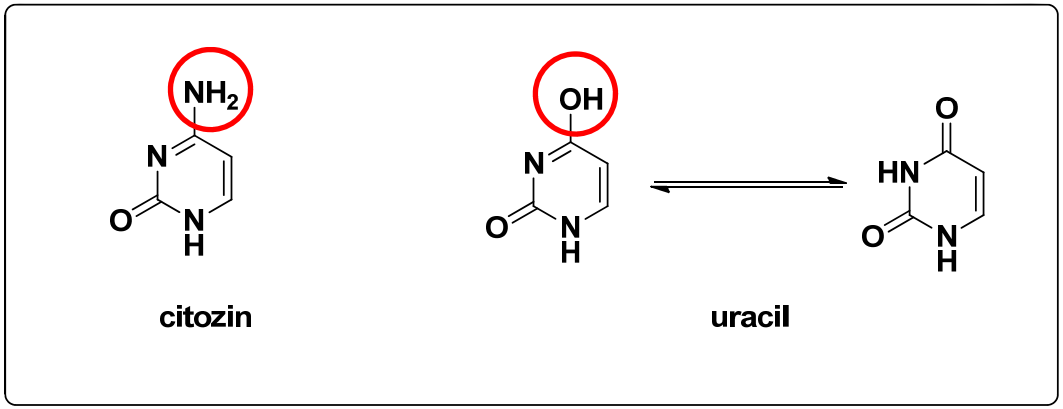
Št. Valenčnih el.	4	5	6	7	8
	N+	P	S	Cl	ClH
	P+	As	Se	Br	BrH
	S+	Sb	Te	I	IH
	As+		PH	SH	SH_2
	Sb+			PH_2	PH_3

Izosterija v naravi



POSLEDICE?

- disulfidne vezi (proteini)
- nukleofilnost (aktivno mesto encimov)
- velikost
- lipofilnost



POSLEDICE

- AT/U (2 H-vezi)
- CG (3 H-vezi)

Izosteri

Izosteri = atomi, skupine, ioni, molekule

- **imajo podoben volumen,**
- **podobno obliko,**
- **enako število elektronov in njihovo razporeditev v zunanji lupini**

Bioizosteri

Friedman 1951:

Bioizosteri = izosteri z enakim (podobnim) biološkim učinkom

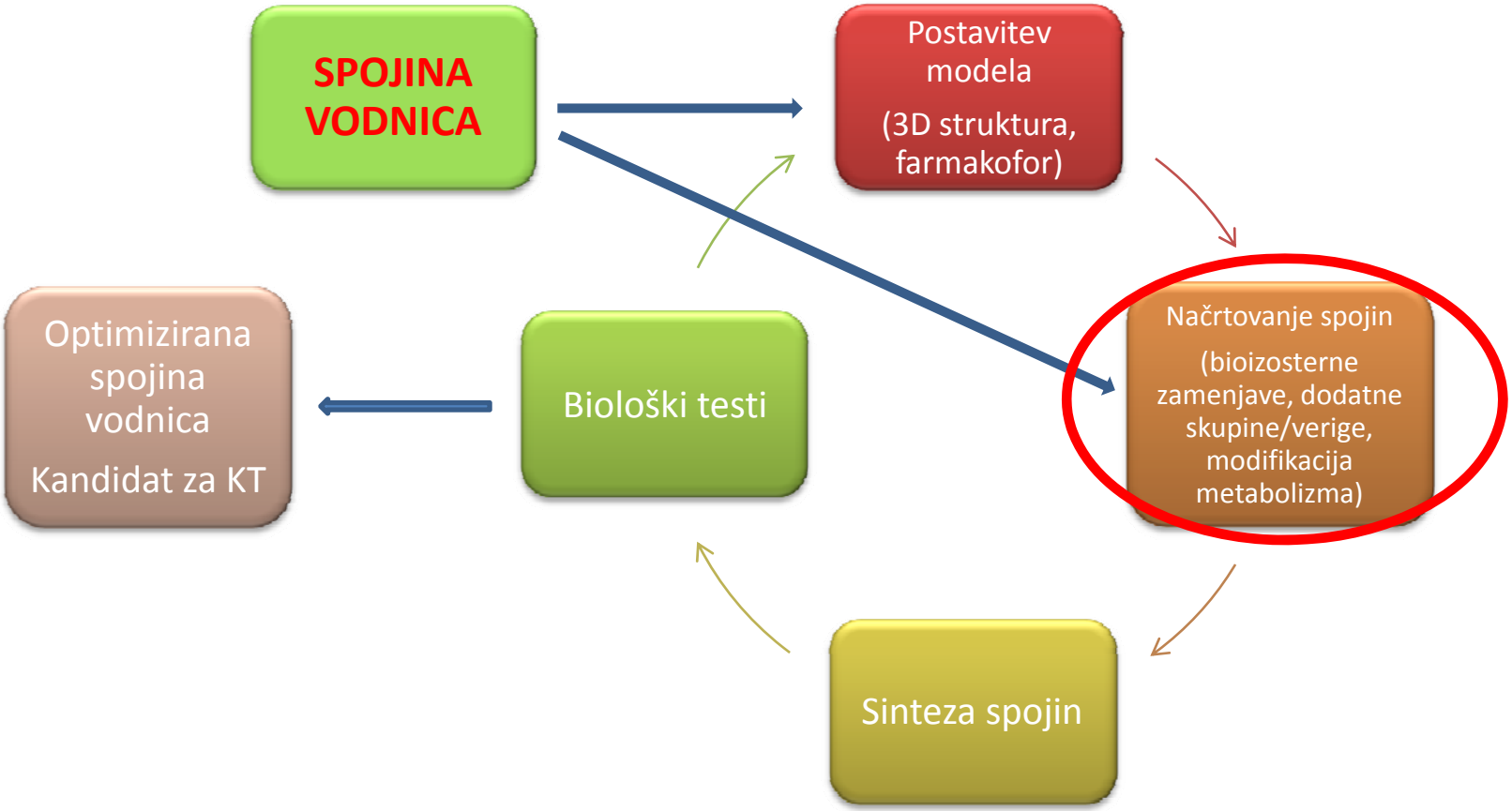
Burger 1990:

= atomi, skupine, ioni, molekule

- **imajo podoben volumen,**
- **podobno obliko,**
- **podobno število elektronov in njihovo razporeditev v zunanji lupini,**
- **enako tarčo,**
- **agonisti/antagonisti.**

podobne fiz-kem. lastnosti

Optimizacija spojine vodnice – racionalno načrtovanje učinkovin



Čemu bioizosterne zamenjave?

Nove spojine

- “me too” princip – nove, patentibilne spojine

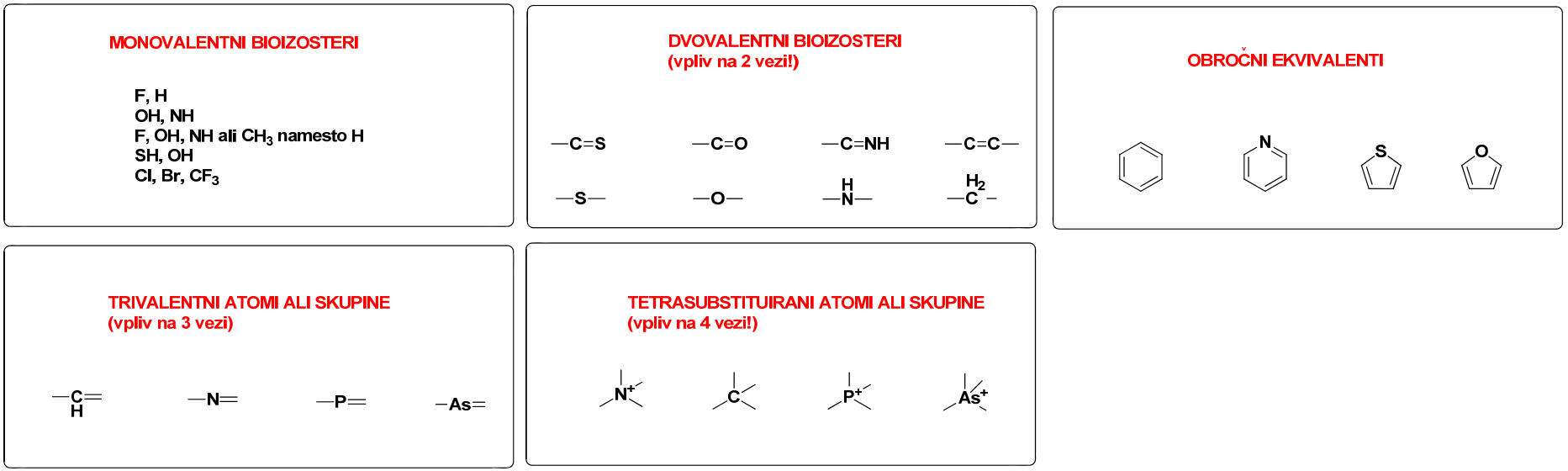
Modifikacije spojine vodnice – načrtovanje analogov

- Sprememba učinka
- Jakost
- Selektivnost
- Biol. uporabnost, boljše ADME lastnosti
- Zmanjšanje str. učinkov
- Kemijska stabilnost
- Stroški sinteze

Delitev bioizosterov

Klasični

- Ustrezajo osnovnim pogojem izosterov (Langmuir, Grimm)
- Delitev na podskupine



Neklasični

Monovalentni bioizosteri

Vodik – fluor

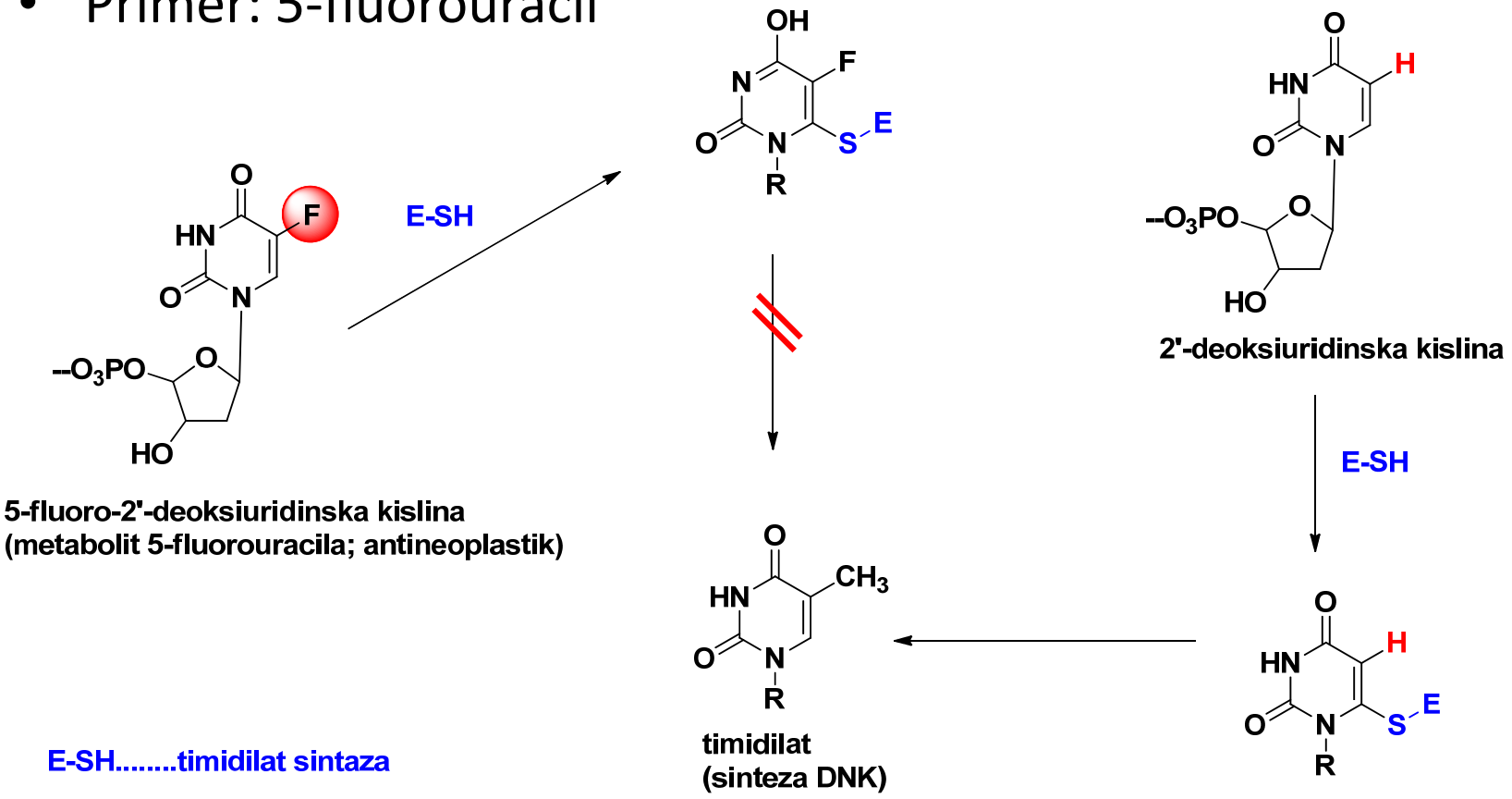
- Podobna radija (1,2 – 1,35 Å), ohranjena lipofilnost
- Povečana elektronegativnost
- Metabolična obstrukcija

	H	F	Cl	CH_3	CF_3
VdW radius	1.2	1.35	1.80	2	2
MR	1.03	0.92	6.03	5.65	5.02
induktivni efekt	-	3.08	2.68	0.00	2.85
π	0	0.14	0.71	0.56	0.88

Monovalentni bioizosteri

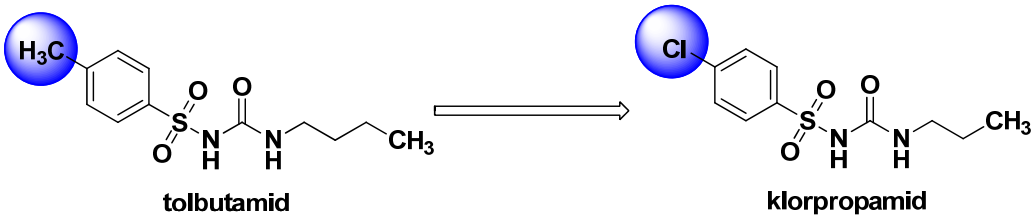
Vodik – fluor

- Primer: 5-fluorouracil



Monovalentni bioizosteri

-F, - OH, -NH_2, -CH_3



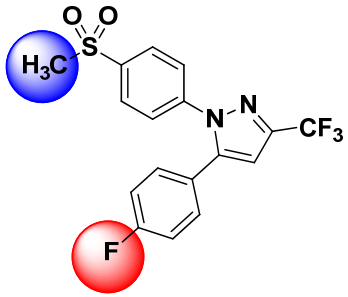
tolbutamid

klorpropamid

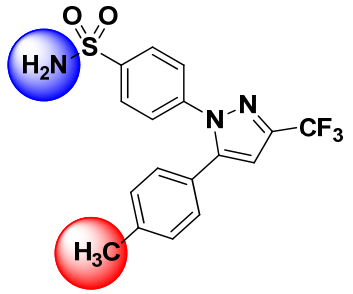
$t_{1/2}$ = 4-5 h

METABOLNA STABILNOST
-daljši razpolovni čas

$t_{1/2}$ = 36 h



uvedba metabolne
šibke tocke



celekoksib

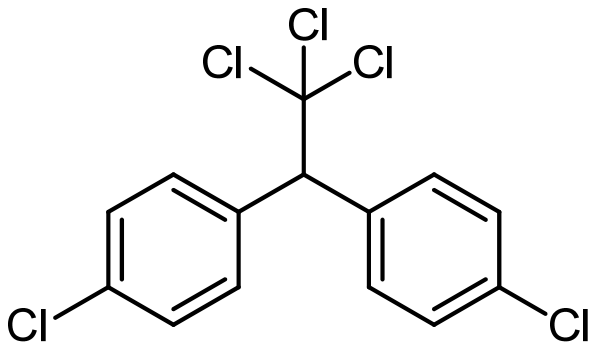
$t_{1/2}$ = 211h
selektivnost (COX-2/COX-1) > 1000

$t_{1/2}$ = 8-12h
selektivnost (COX-2/COX-1) = 375

Monovalentni bioizosteri

-Cl, - OH, -CH_3

- Grimmov “zakon” + Erlenmayerjeva razširitev
- DDT = **d**iklorо**d**ifenil**t**rikloroetan



Monovalentni bioizosteri

-OH, -NH_2 skupina

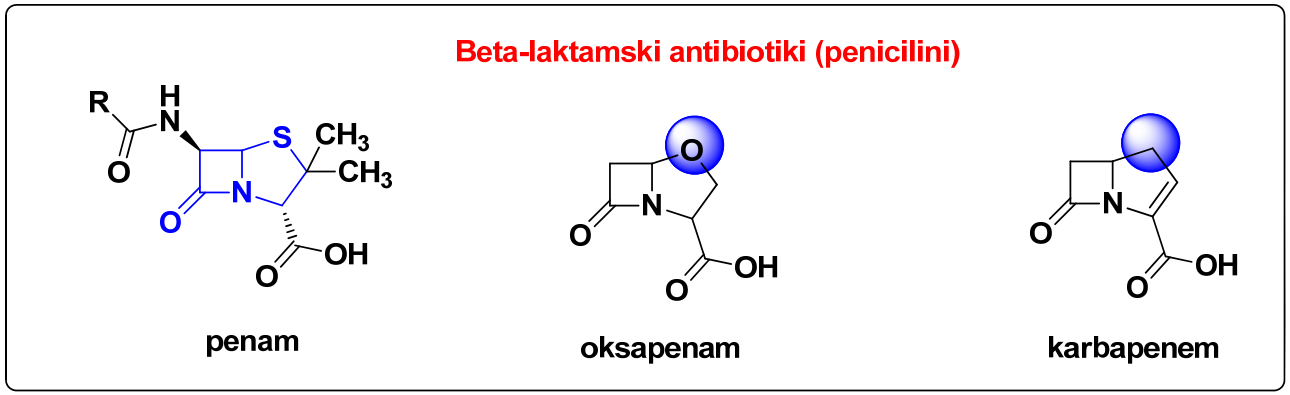
- Podobna velikost
- Polarnost
- Akceptorji/donorji H-vezi
- Folna kislina/aminopterin/metotreksat

- -OH, -SH skupina
- Podobna polarnost
- Različna tvorba H-vezi
- Gvanin/tiogvanin

Dvovalentni bioizosteri

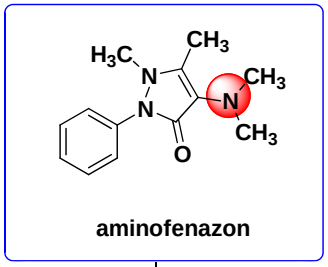
-CH_2-, -NH-, -O-, -S-

- β-laktamski antibiotiki

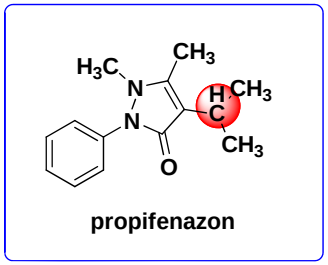


Trivalentni bioizosteri

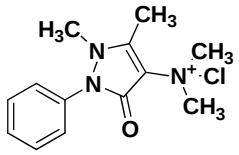
-CH=, -N=, -P=, -As=



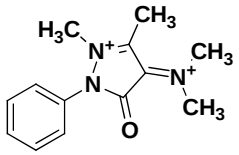
-antipiretika



HOCl
(nevtrofilci)

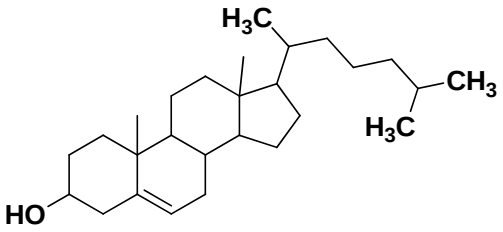


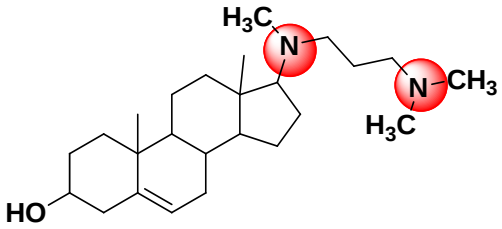
-Cl⁻



TOKSIČNI
METABOLITI!

NI TOKSIČNIH
METABOLITOV!



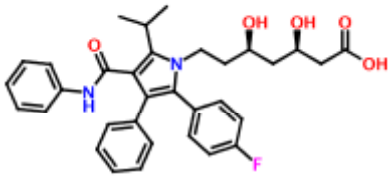


-inhibitor biosinteze holesterola

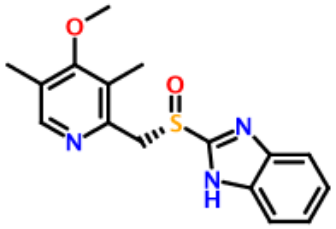
Obročni ekvivalenti

- Najpogosteje uporabljan koncept bioizosterije
- 8/10 najbolje prodajanih zdravil (2006):

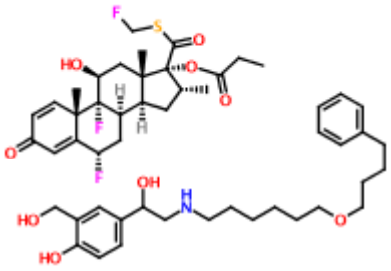
atorvastatin



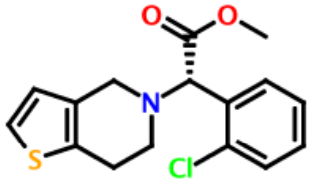
esomeprazol



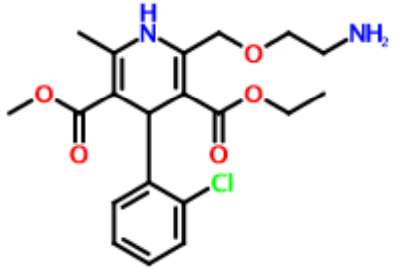
Flutikazol/
salmeterol



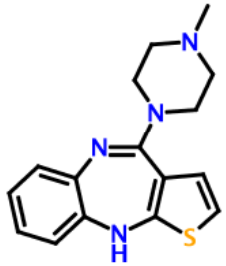
klopidogrel



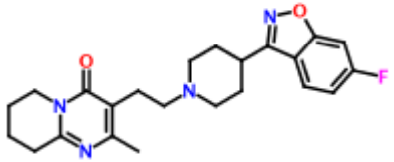
amlodopin



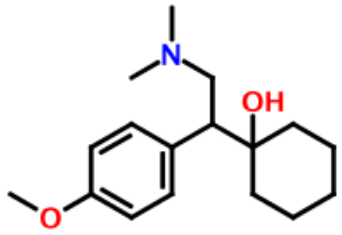
olanzapin



risperidon



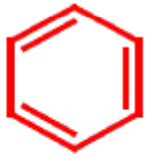
venlafaksin



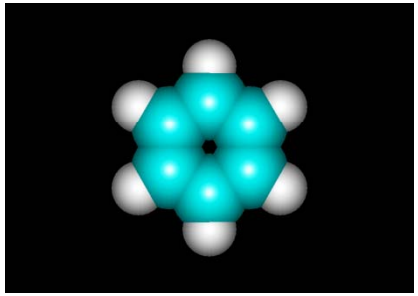
Obročni ekvivalenti

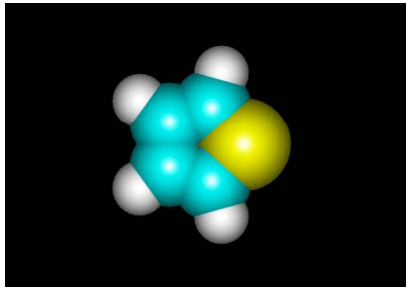
Tiofen – bezen (Meyer 1883)

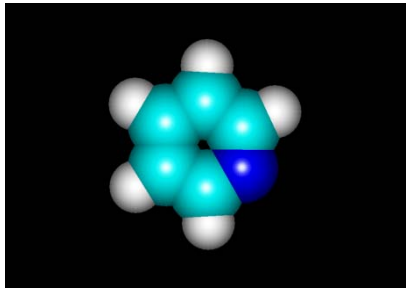
MW = 78.11
mp. = 5.5°C
bp. = 80.15°C
Log P = 2.13
MR = 26.4
d = 0.879



MW = 84.14
mp. = -38°C
bp. = 84°C
Log P = 1.81
MR = 25.0
d = 1.057



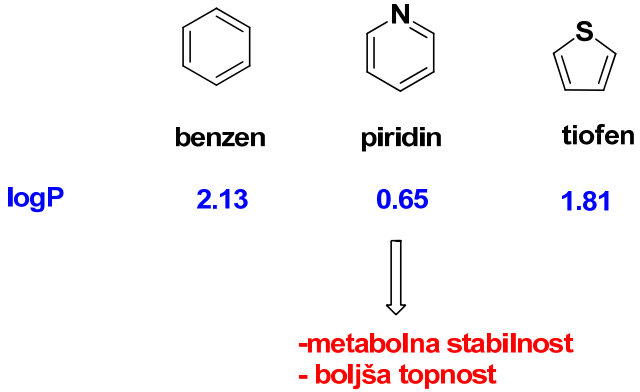


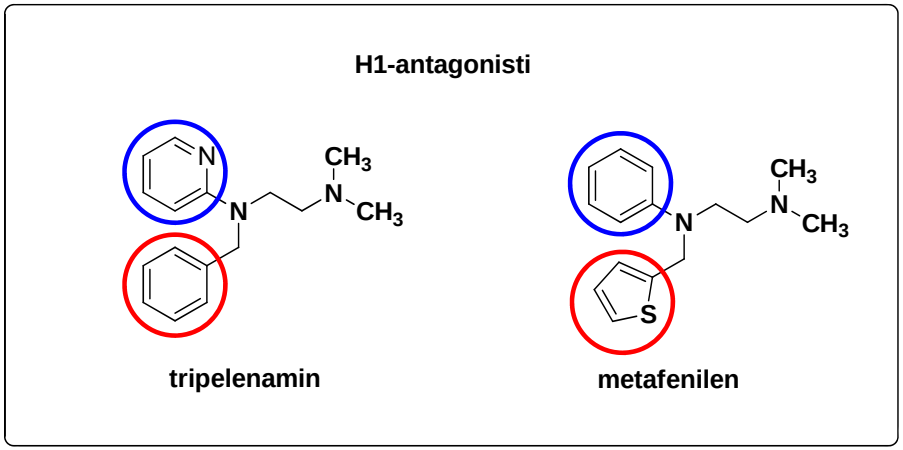


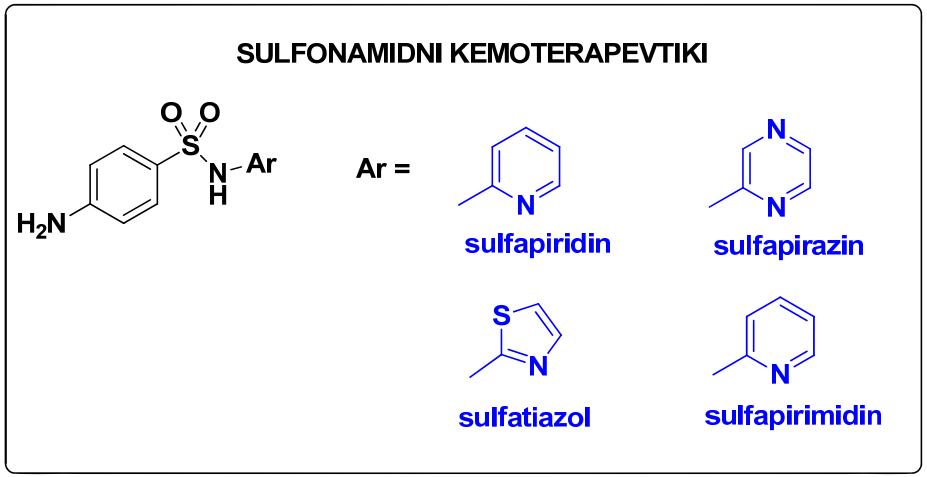
Obročni ekvivalenti

Klonidin – tiamenidin (α2-agonista)

Obročni ekvivalenti

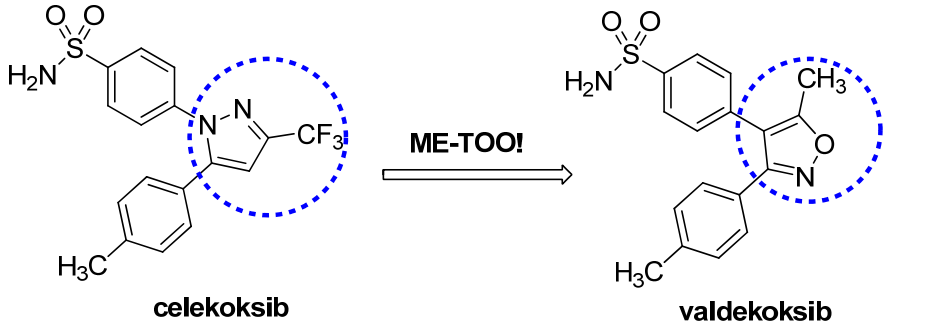


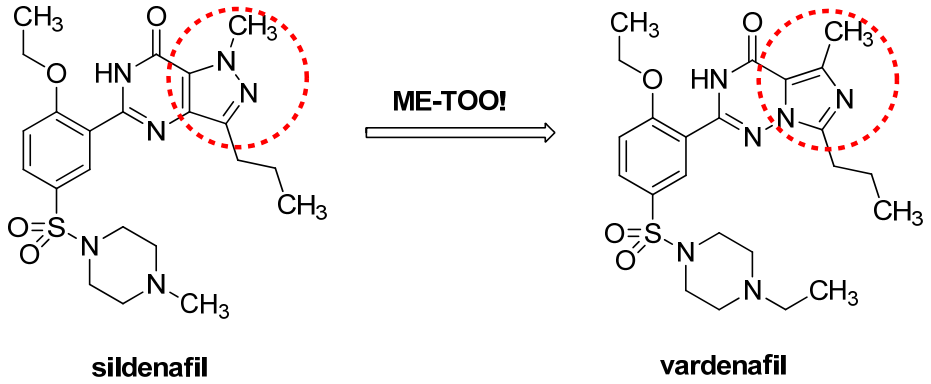




Obročni ekvivalenti

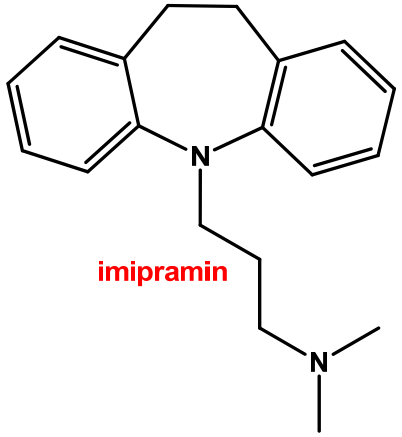
- “Me-too”



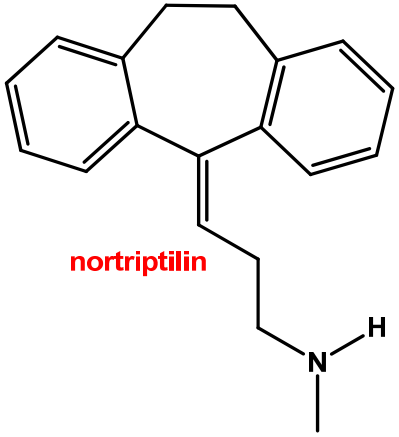


Obročni ekvivalenti

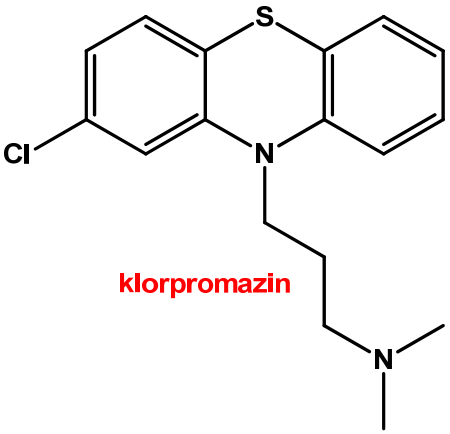
- Triciklični antidepresivi/nevroleptiki



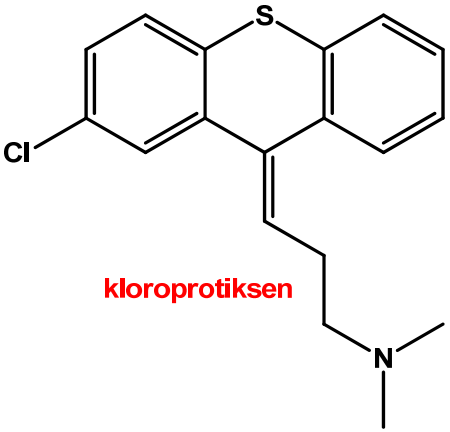
imipramin



nortriptilin



klorpromazin



kloroprotiksen

Neklasični bioizosteri

Neklasični bioizosteri - klasični

- **<u>Podobna</u>** prostorska razporeditev ali elektronske lastnosti ali drugi fiz-kem parametri molekule/skupine
- Zamenjave funkcionalnih skupin , ki ne ustrezajo klasični definiciji; ni nujno, da imajo isto št.atomov
- Večina spada med neklasične BI

Neklasični bioizosteri funkcionalnih skupin

Karboksilna skupina

- pKa ~ 4-5
- H-vezi

Direktni bioizosteri

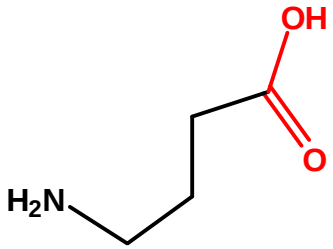
- **Hidroksamska skupina, (acil-)sulfonamidi**
- **Ibuprofen-ibuproksan**

Neklasični bioizosteri funkcionalnih skupin

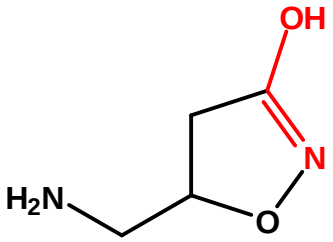
Karboksilna skupina

Planarni obročni bioizosteri

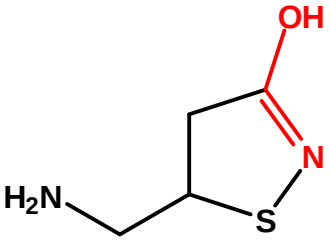
- **GABA agonisti**



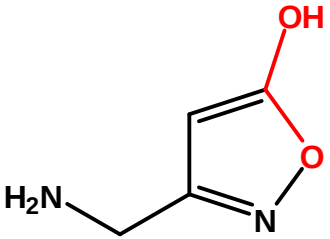
GABA



muscimol (+)



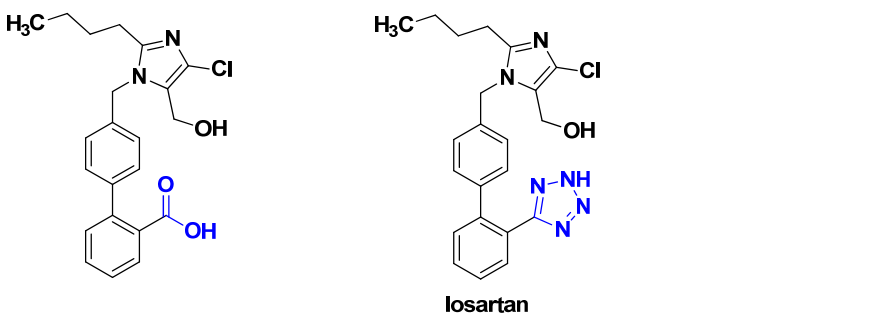
tiomuscimol (+)

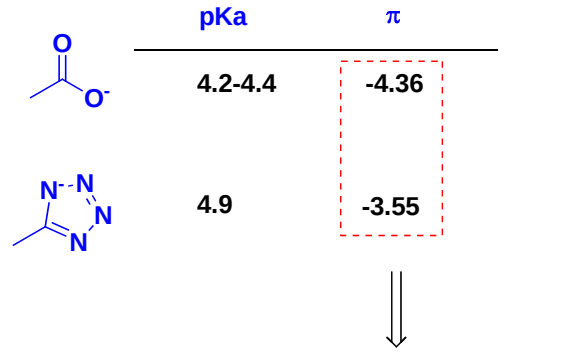


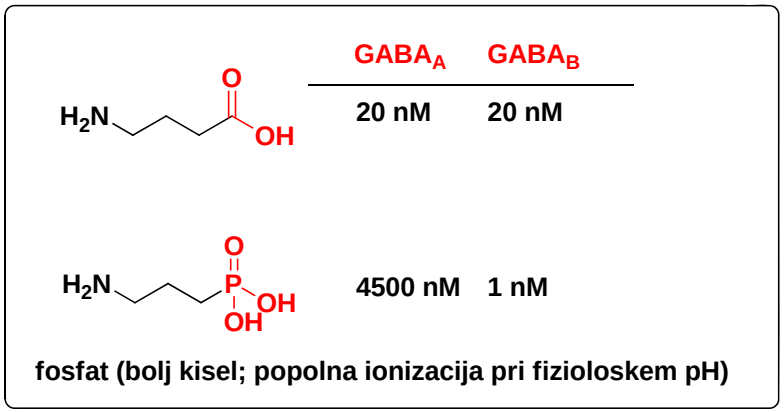
izomuscimol (-)

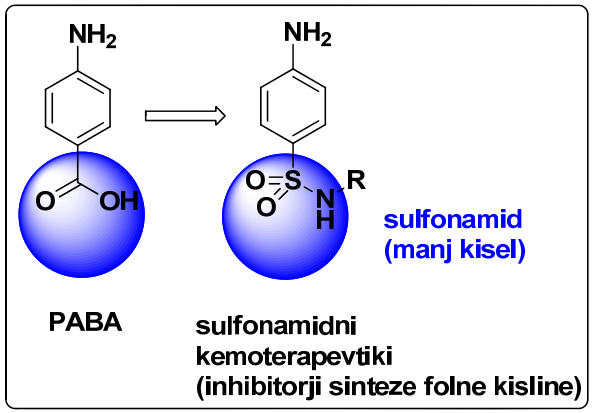
Neklasični bioizosteri funkcionalnih skupin

Karboksilna skupina





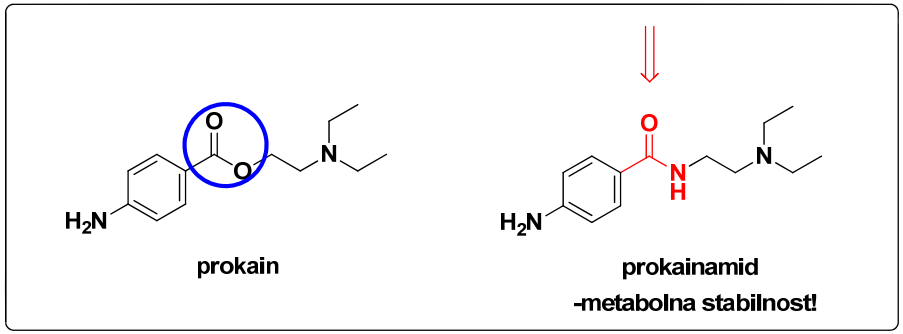


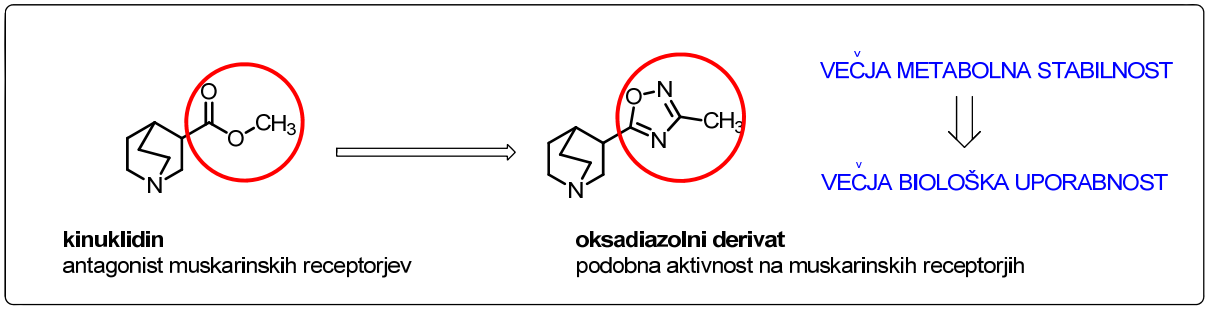


Neklasični bioizosteri funkcionalnih skupin

Estri

- Labilni *in vivo;* metabolično stabilni analogi
- Prokain - prokainamid

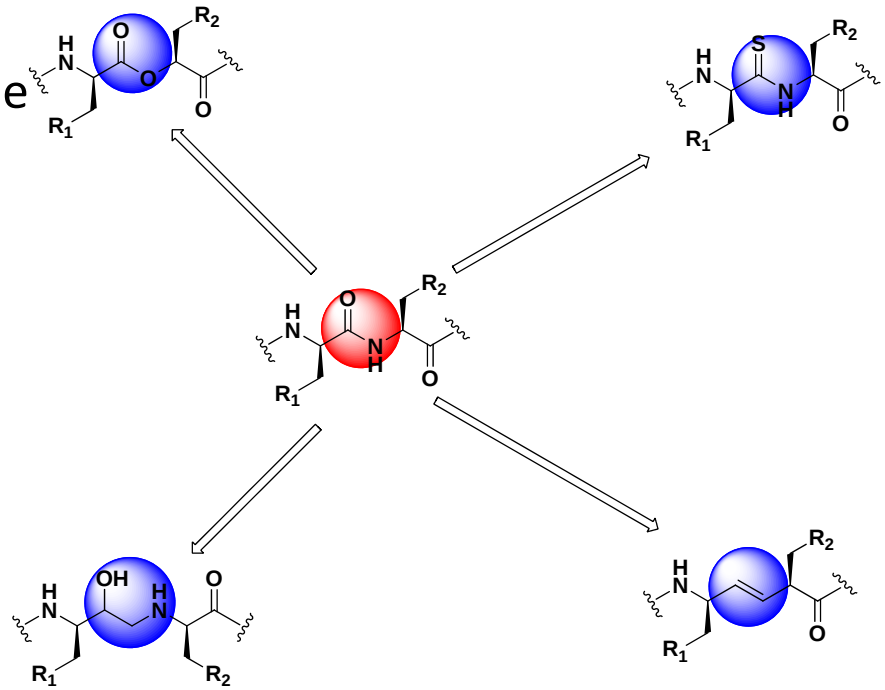


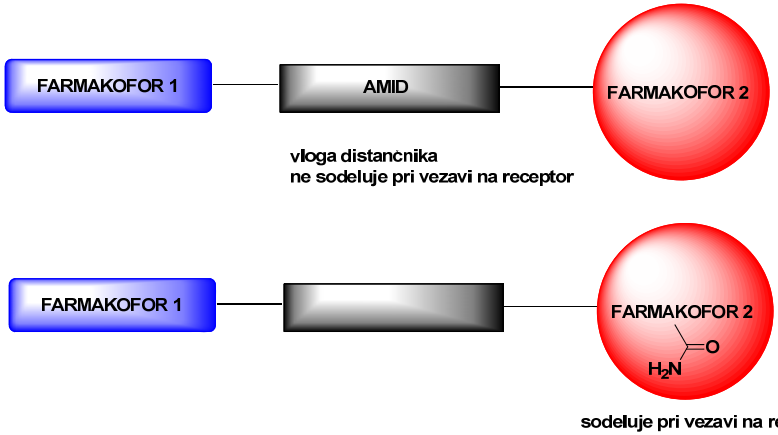


Neklasični bioizosteri funkcionalnih skupin

(Karboks)amidi

- Cela vrsta bioizosterov – naslednje predavanje
- Razgradnja amidov v organizmu
- Plazemske amidaze! ➔ labilnost amidov ➔ slaba BU
- Peptidne ZU (problem peroralne uporabe)



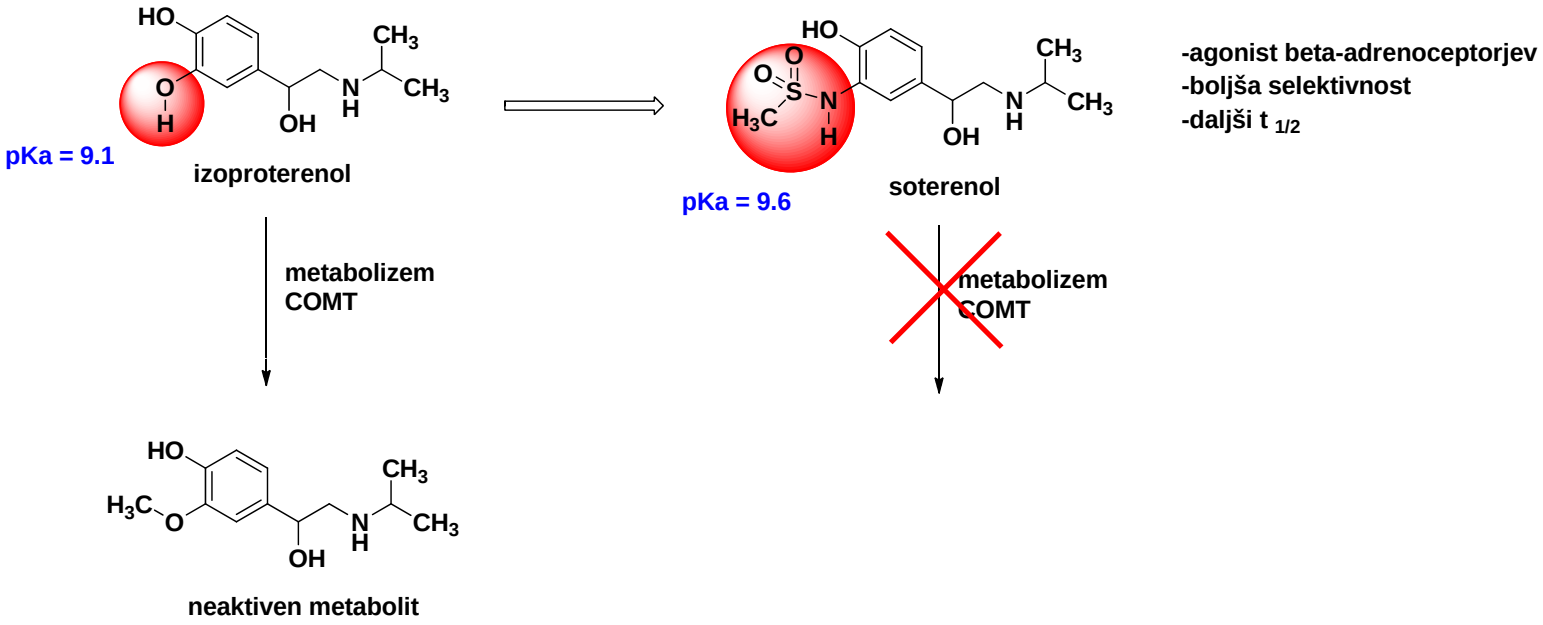


Neklasični bioizosteri funkcionalnih skupin

Fenoli

- **Izoproterenol – soterenol**

Adrenergični sistem:



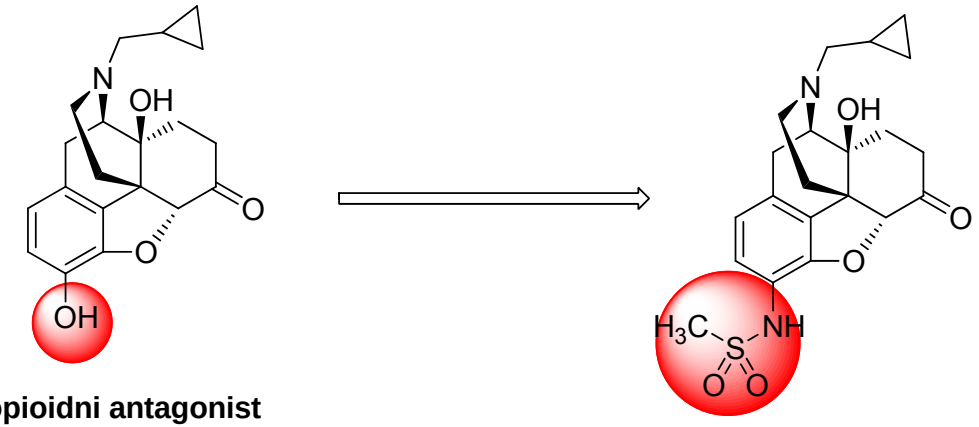
-agonist beta-adrenoceptorjev
-boljša selektivnost
-daljši $t_{1/2}$

Neklasični bioizosteri funkcionalnih skupin

Fenoli

- **-OH -> -SO_2NH; ni zagotovilo za uspeh!**

Opioidni sistem:

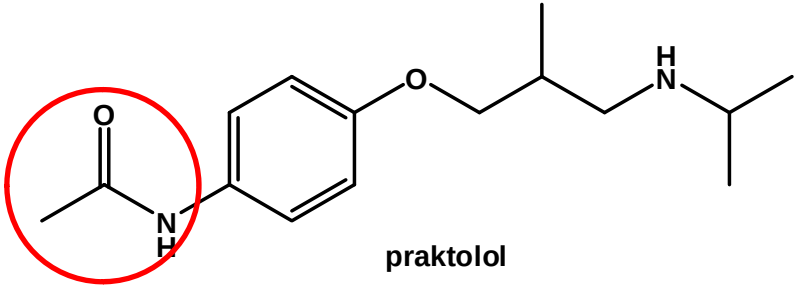


opioidni antagonist

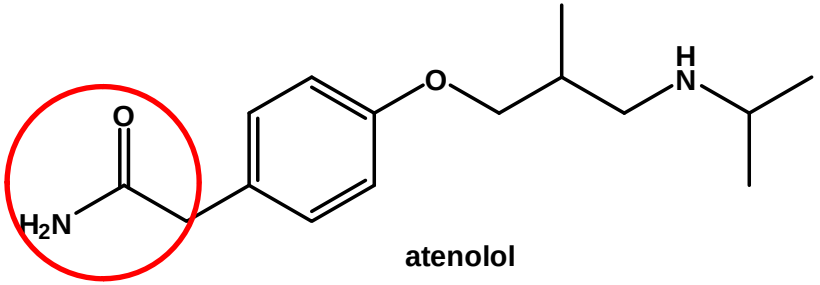
POPOLNA IZGUBA AFINITETE

Retro-bioizosteri

- β-blokatorji praktolol – atenolol



praktolol



atenolol

Ciklični – neciklični analogi

Zamenjava cikličnega dela molekule z necikličnim – posnemanje iste prostorske usmeritve/razporeditve

- Primer estradiol – dietilstilbestrol, heksestrol

Ciklični – neciklični analogi

Primer - propranolol (izumitelj sir James W. Black – Nobelova nagrada 1988)

“Bioizosteri” kitajskega porekla

- Izosteri – podobna analitika
- http://www.sciencedaily.com/releases/2008/04/080423171529.htm

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

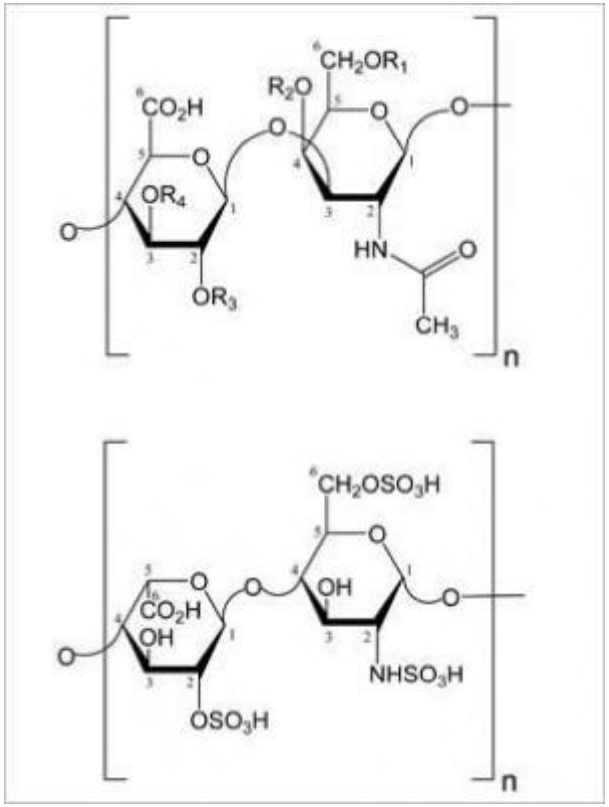
Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System

Takashi Kei Kishimoto, Ph.D., Karthik Viswanathan, Ph.D., Tanmoy Ganguly, Ph.D., Subbiah Elankumaran, Ph.D., Sean Smith, B.S., Kevin Pelzer, Ph.D., Jonathan C. Lansing, Ph.D., Nammalwar Sriranganathan, Ph.D., Ganlin Zhao, M.D., Zoya Galcheva-Gargova, Ph.D., Ali Al-Hakim, Ph.D., Gregory Scott Bailey, B.S., Blair Fraser, Ph.D., Sucharita Roy, Ph.D., Thomas Rogers-Cotrone, M.S., Lucinda Buhse, Ph.D., Mark Whary, Ph.D., James Fox, Ph.D., Moheb Nasr, Ph.D., Gerald J. Dal Pan, M.D., Zachary Shriver, Ph.D., Robert S. Langer, Sc.D., Ganesh Venkataraman, Ph.D., K. Frank Austen, M.D., Janet Woodcock, M.D., and Ram Sasisekharan, Ph.D.

ABSTRACT

BACKGROUND

There is an urgent need to determine whether oversulfated chondroitin sulfate (OSCS), a compound contaminating heparin supplies worldwide, is the cause of the severe anaphylactoid reactions that have occurred after intravenous heparin administration in the United States and Germany.



Sklepi

- Razmeroma stroga pravila pri klasičnih bioizosterih
- Pri neklasičnih bioizosterih obratno
- Velika vloga bioizosterov pri razvoju ZU (jakost, ADME, str.učinki); spremembe funkc.skupin (ne celih molekul)
- Uporaba bioizosternih zamenjav odvisna od dane farmakološke skupine!
- Ni preprostih pravil! (izkušnje, intuicija)