Funkcionalne skupine
Terapogene strukture

doc.dr. Marko Anderluh

27. oktober 2009

Diskretizacija glazbenega/ kemijskega fenomena

Nota	Atom, funkcionalna skupina
Akord	Kemijska struktura

Diskretizacija farmacevtsko-kemijskega fenomena

Smoter: “razbiti” kemijsko strukturo učinkovine na manjše dele (diskretne strukture) => algoritem, ki omogoča kvalitativno predvidevanje ali celo izračun določenih bioloških in fiz.-kem. lastnosti učinkovin (pKa, logP, QSAR)

Terapogene strukture

Skupine odgovorne za biološko aktivnost!

Farmakofor = skupine, ki sestavljajo učinkovino in so odgovorne za vezavo na receptor in zato biološko aktivnost (Gund, 1977)

Terapogene strukture

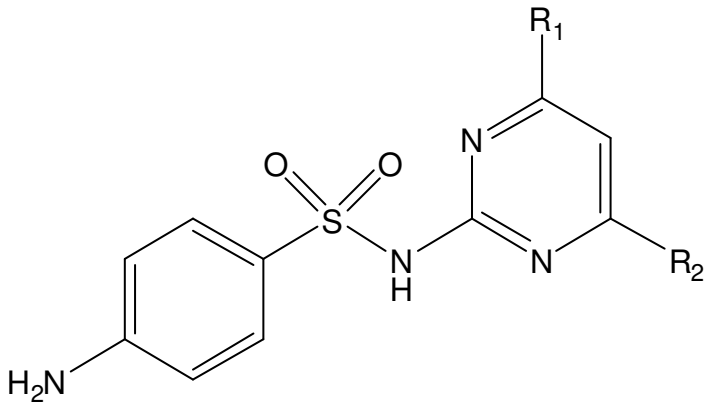
Auksofor = skupine, ki sestavljajo učinkovino in **niso** odgovorne za vezavo na receptor

- Interagirajo z vezavo farmakofornih skupin - odstranitev
- Ni interakcij z receptorjem
- Modifikacije - izboljšanje ADME lastnosti

Alkilne skupine

Fizikalno – kemijske lastnosti

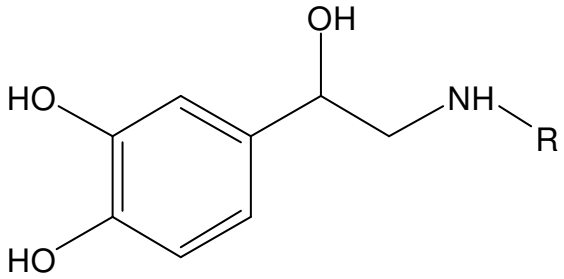
- C-C vez 348 kJ/mol
- Lipofilnost (logP)
- Elektronski efekti: +I, +M



Učinkovina	R_1	R_2	pKa	Ionizacija (pH=5,2)
sulfadiazin	H	H	6,5	3,9%
sulfamerazin	H	CH_3	7,1	1,4%
sulfametazin	CH_3	CH_3	7,4	0,7%

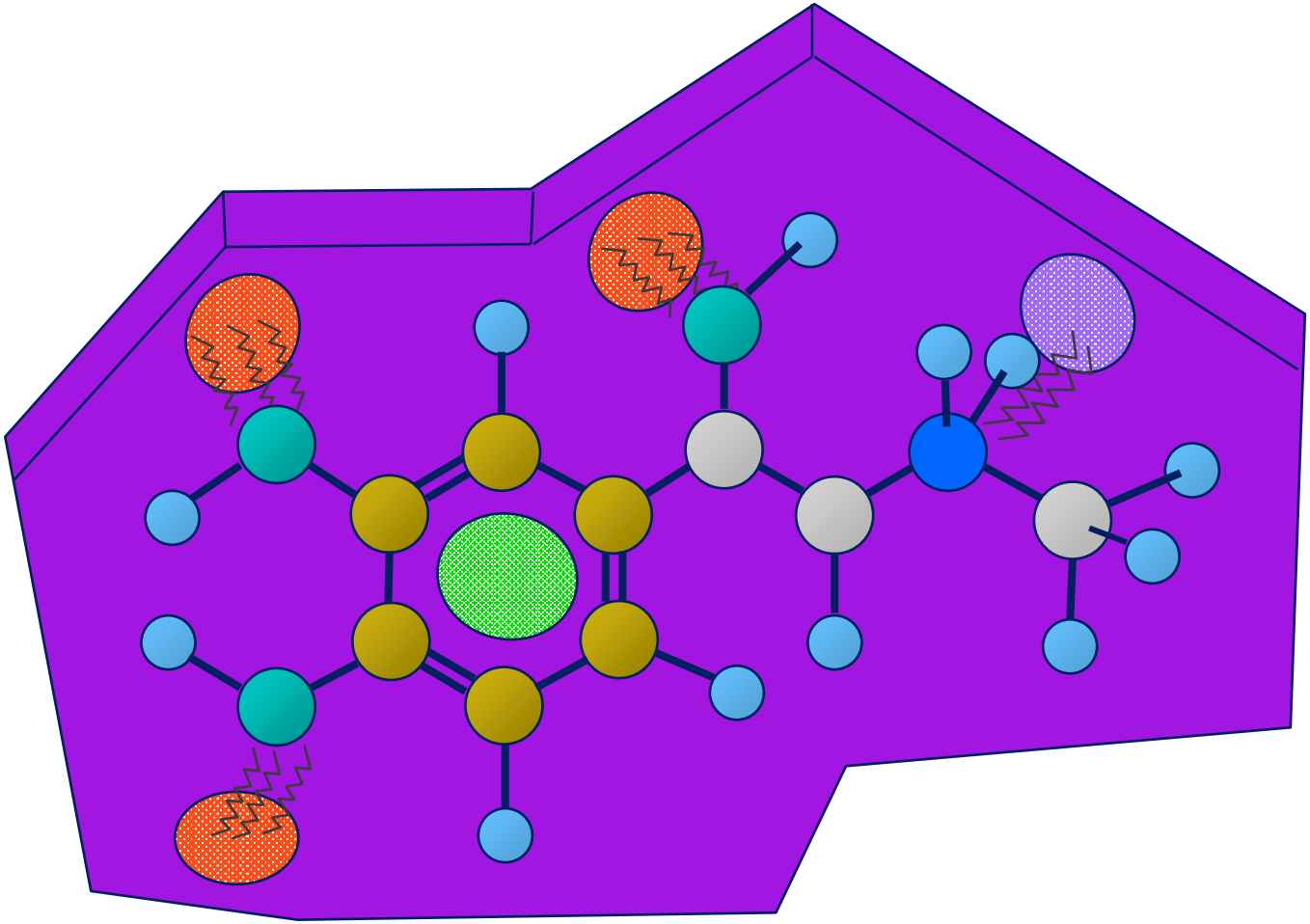
Alkilne skupine

- Sterični efekti – selektivnost na receptorje



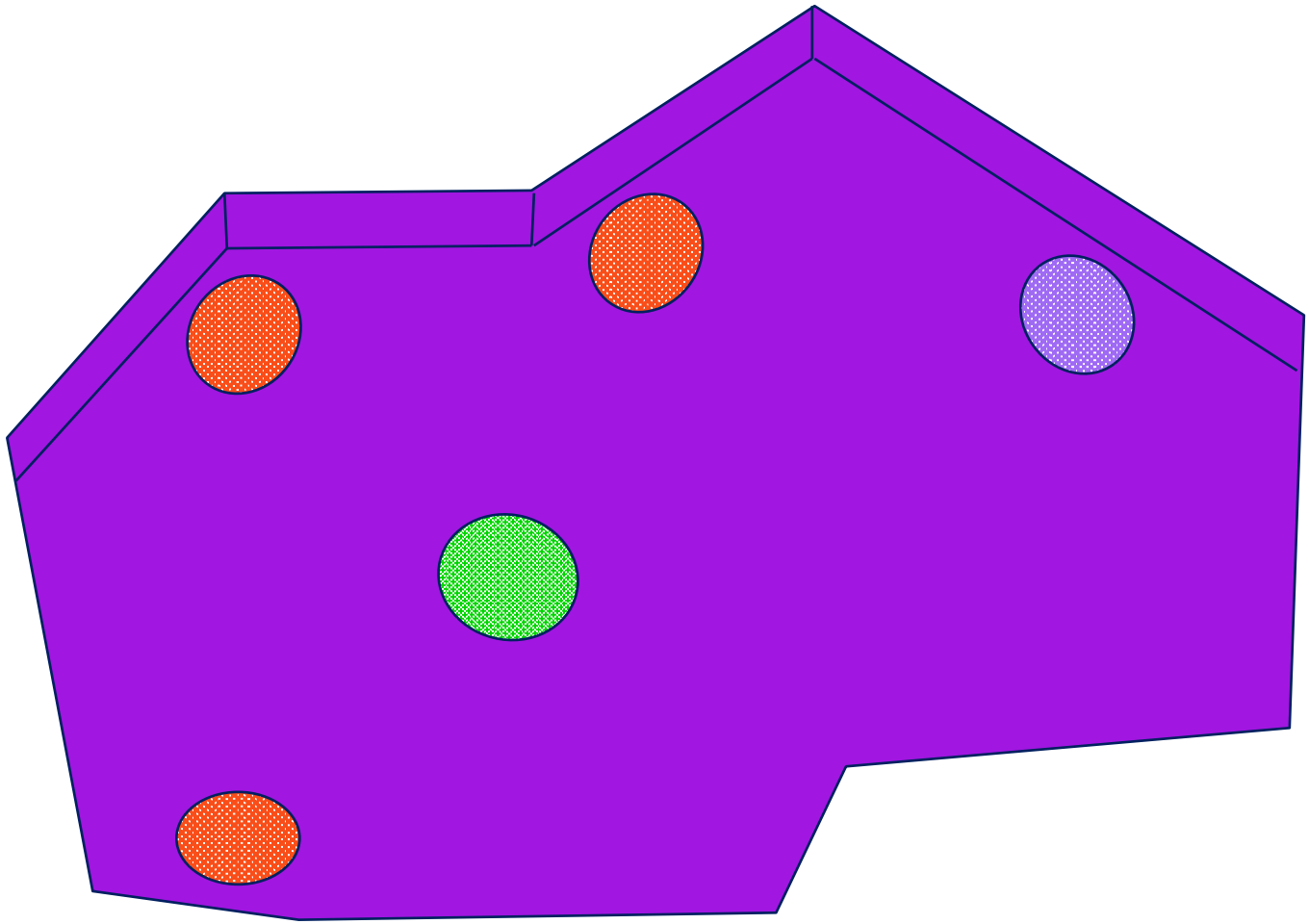
R	Hipertenzivno delovanje	Hipotenzivno delovanje
H	++	-
metil	++	-
etil	+	+
propil	+	+
izopropil	-	++
butil	-	++
izobutil	-	++

α-Adrenoceptor

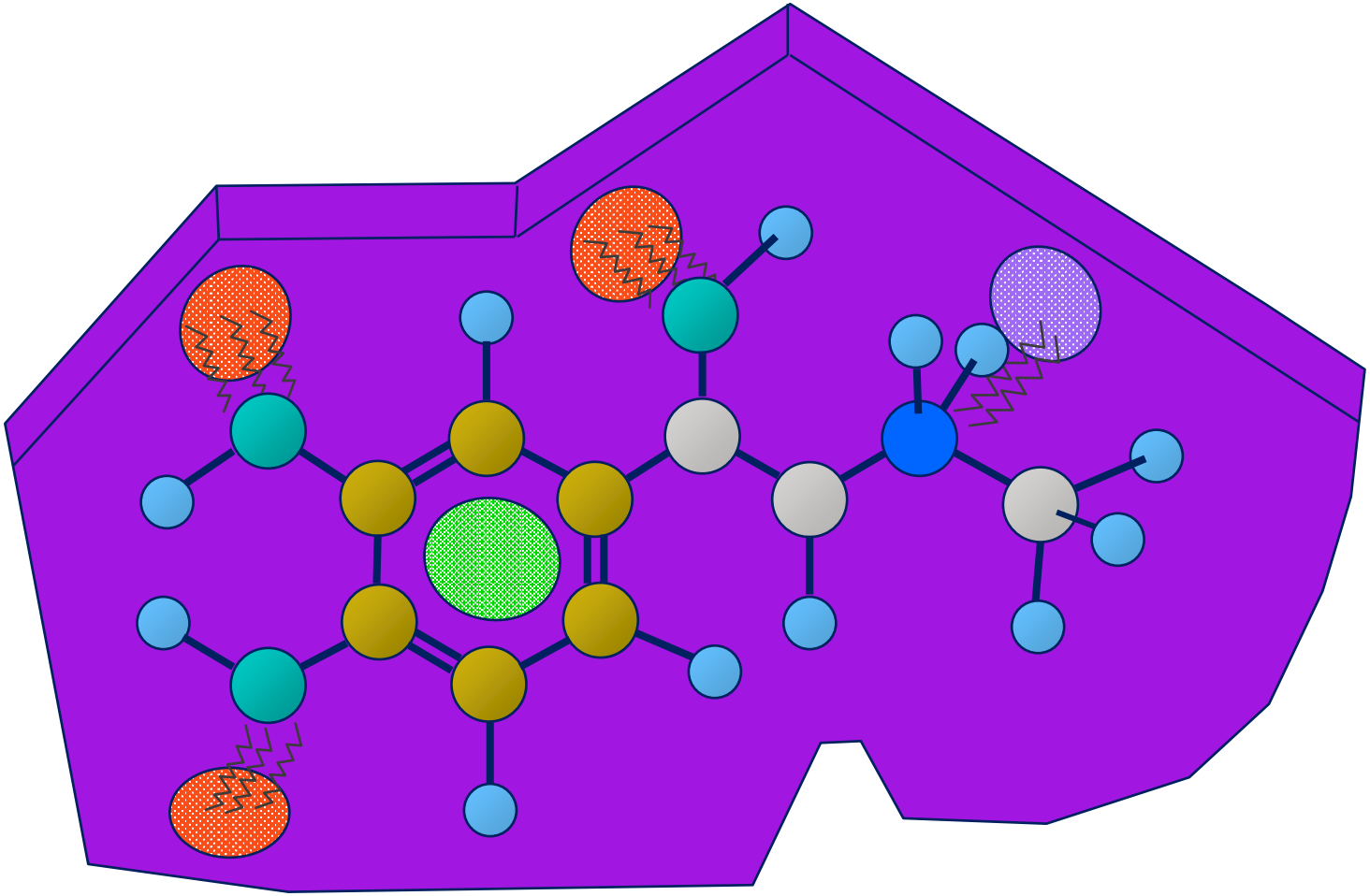


ADRENALIN

α-Adrenoceptor

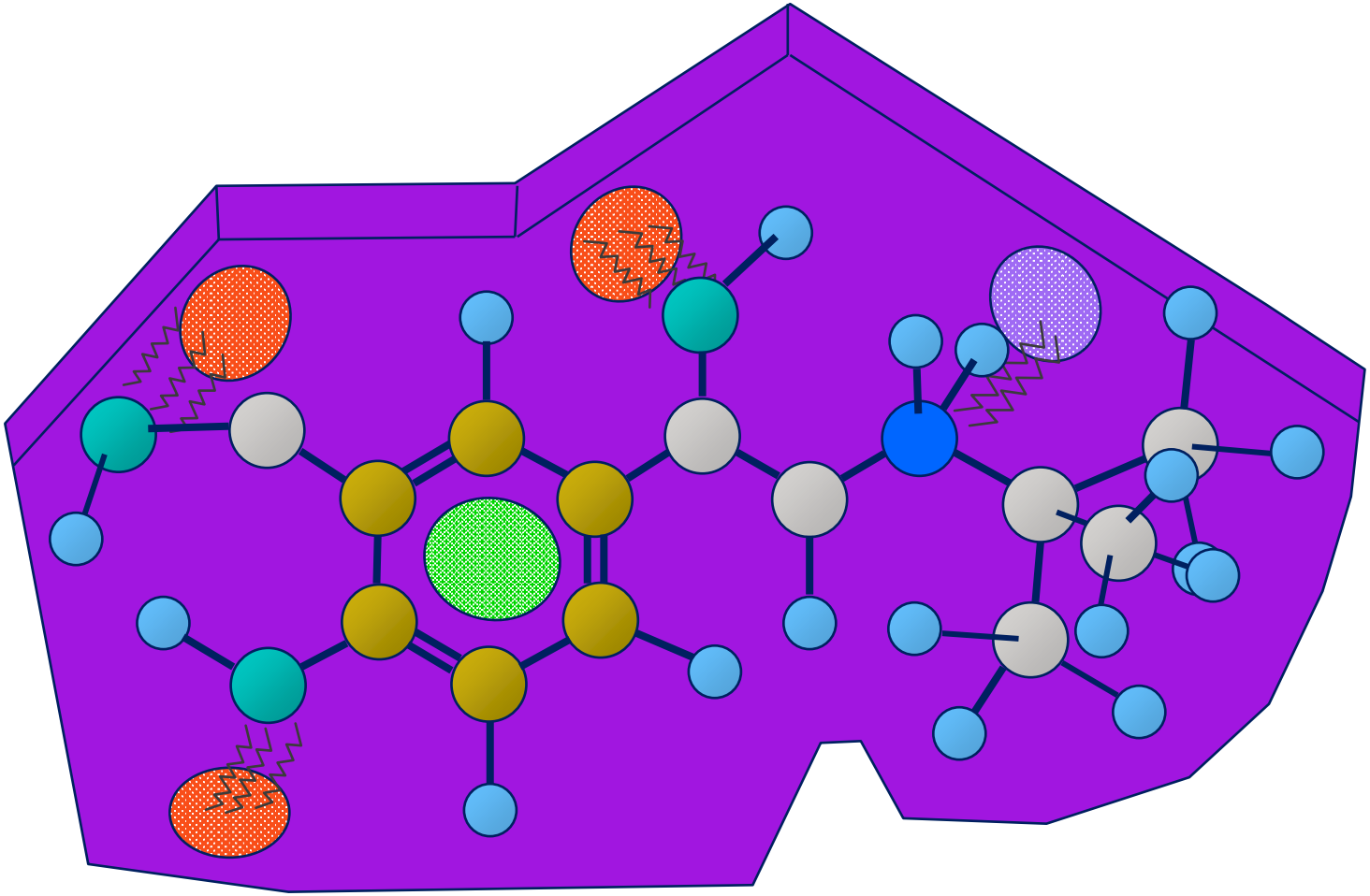


β-Adrenoceptor



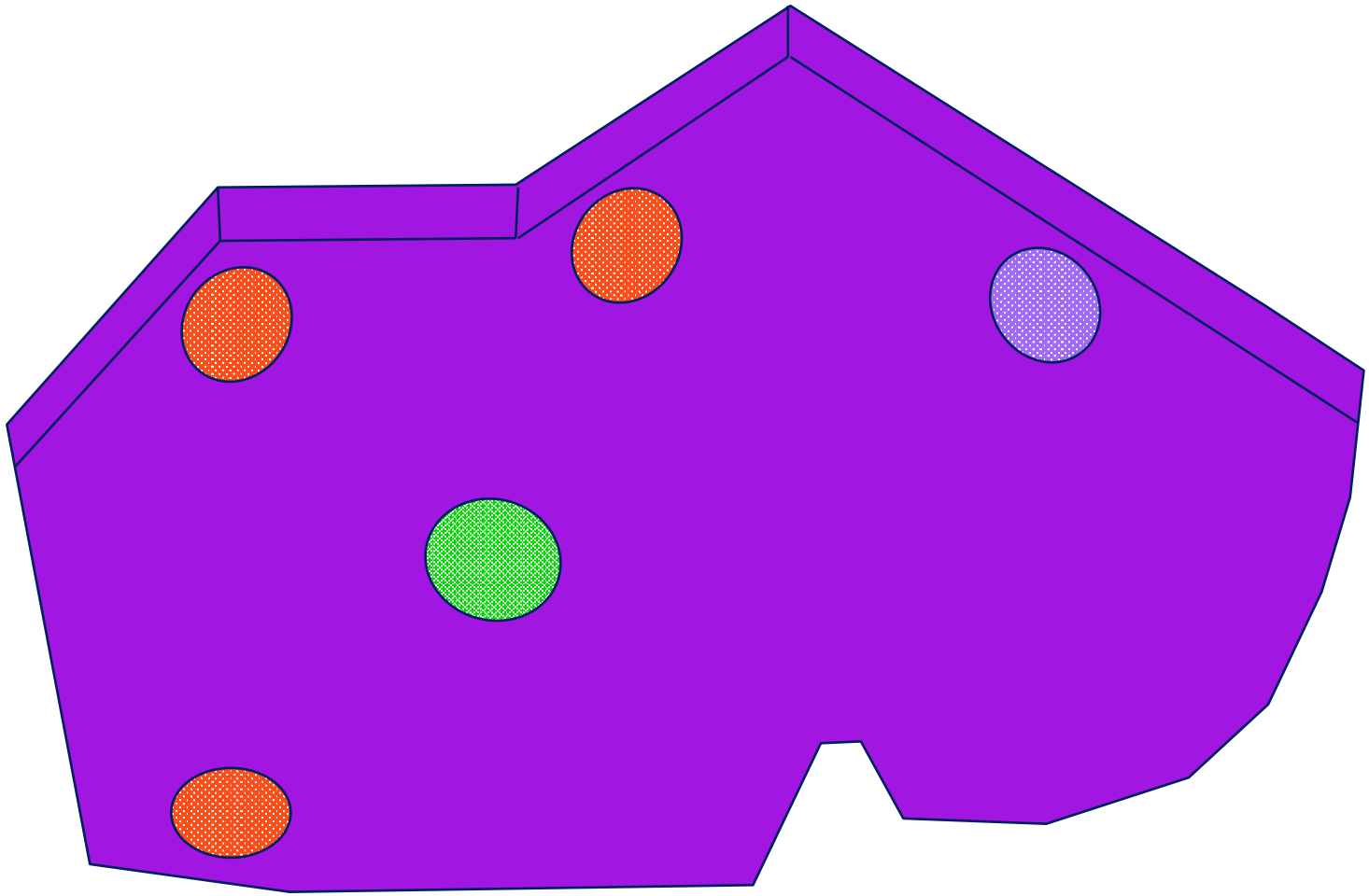
ADRENALIN

β-Adrenoceptor

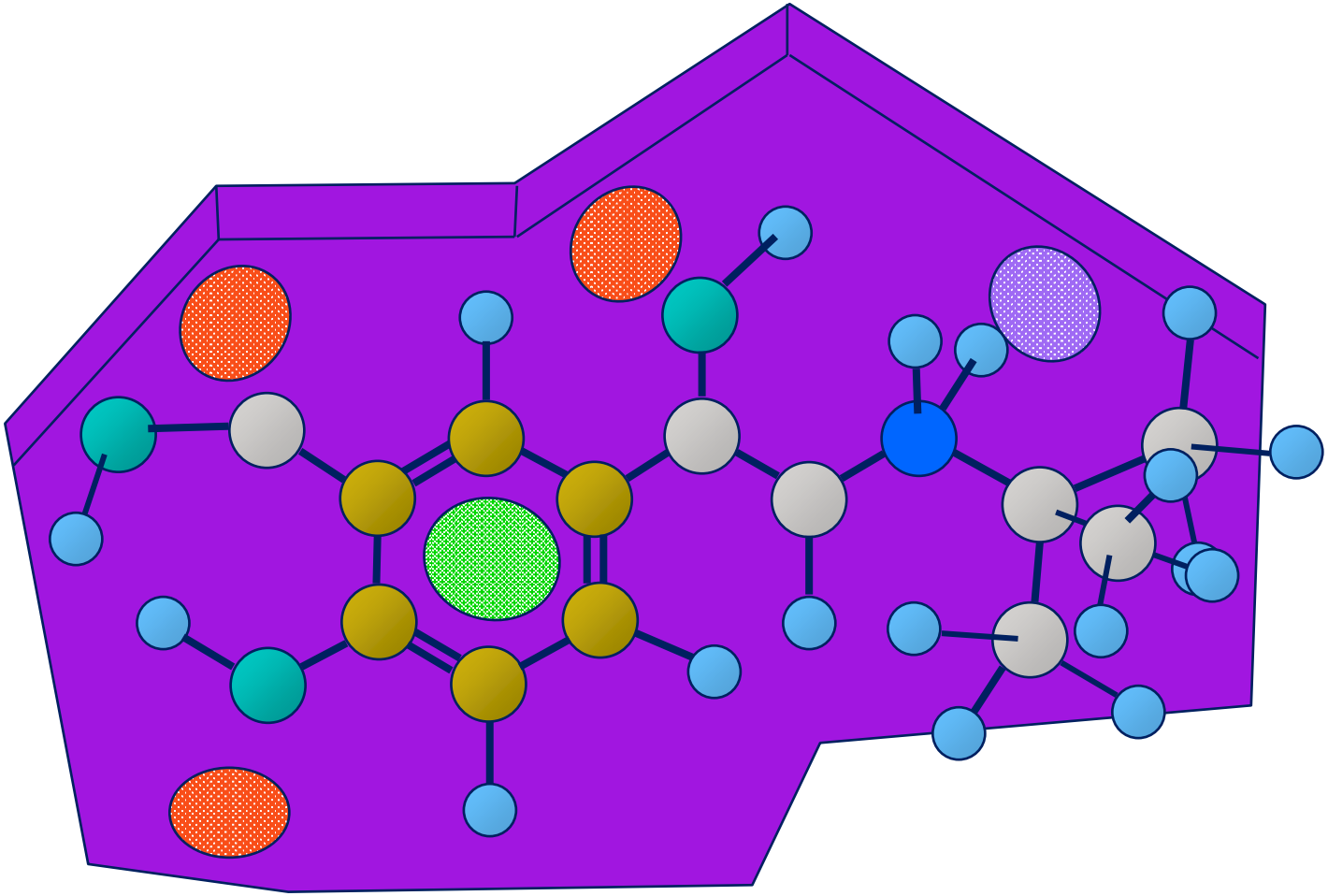


SALBUTAMOL

β-Adrenoceptor

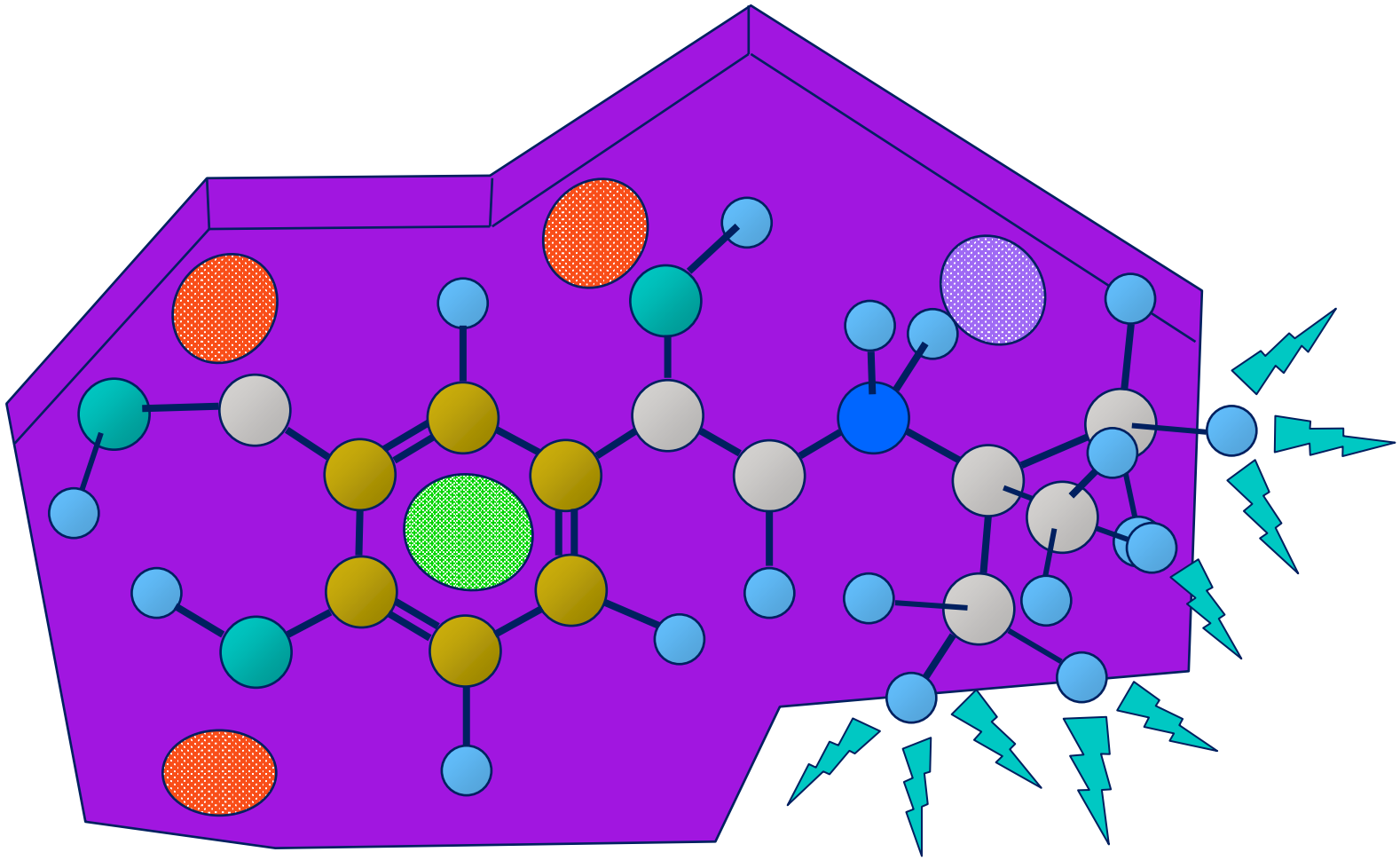


α-Adrenoceptor



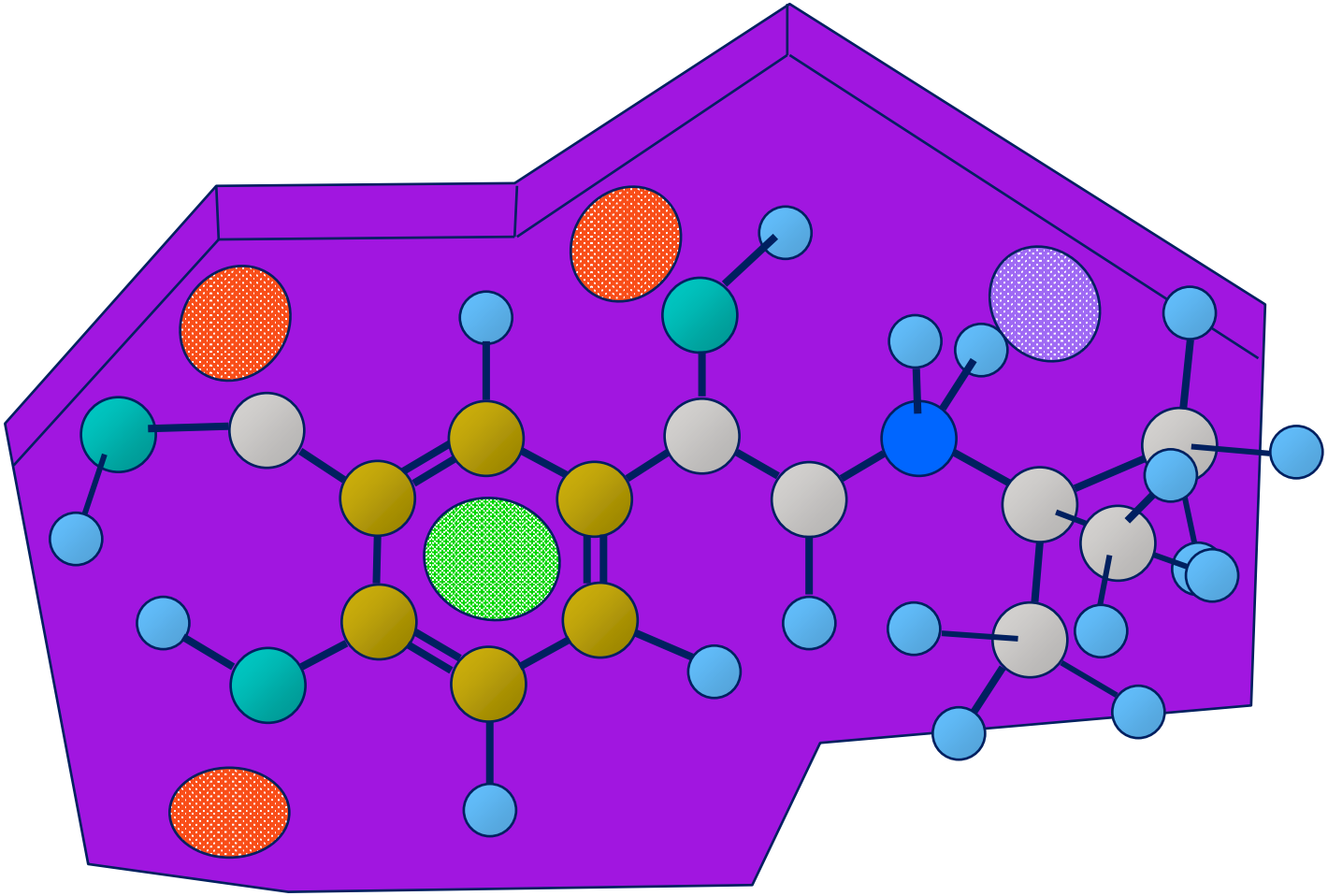
SALBUTAMOL

α-Adrenoceptor



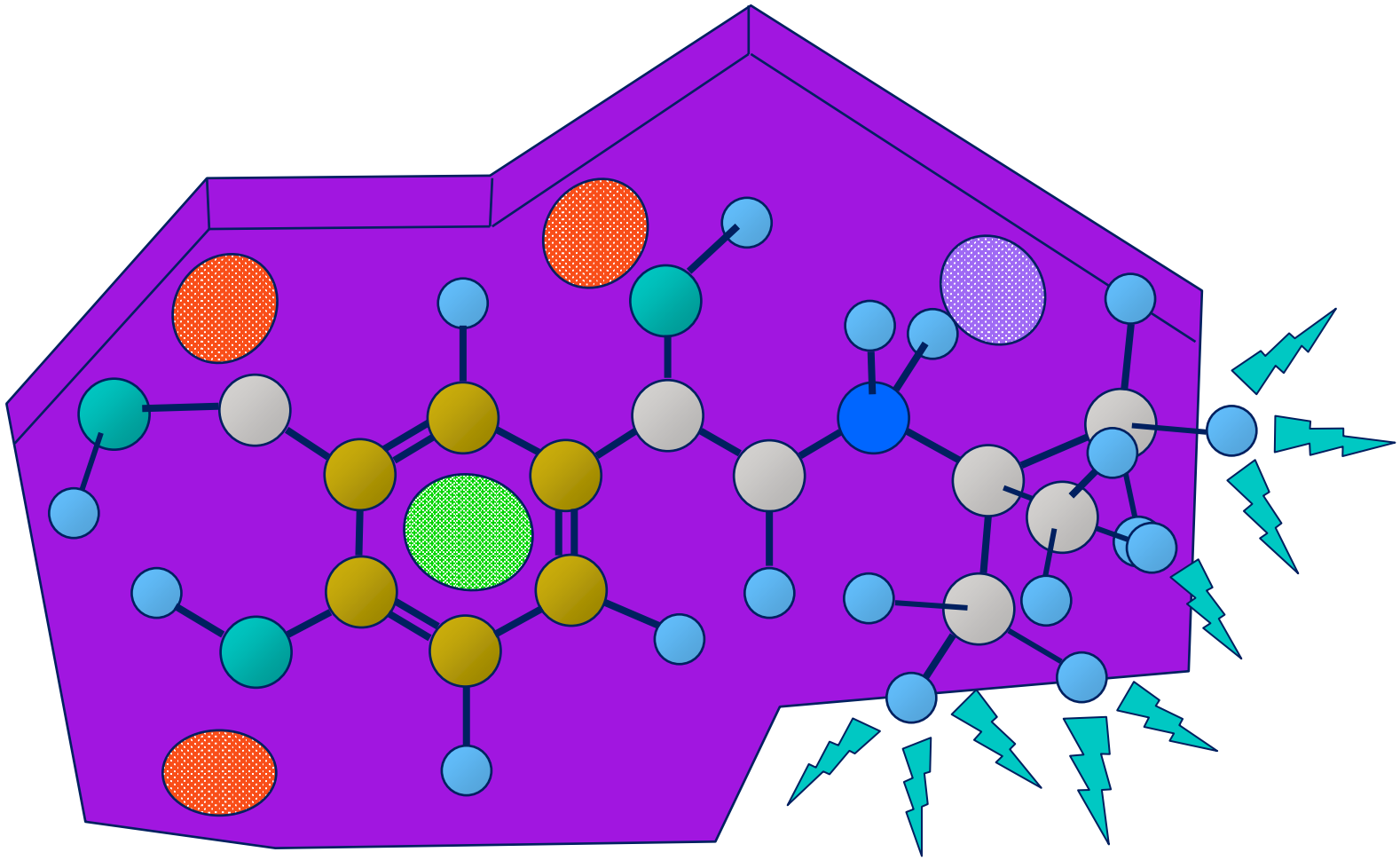
SALBUTAMOL

α-Adrenoceptor



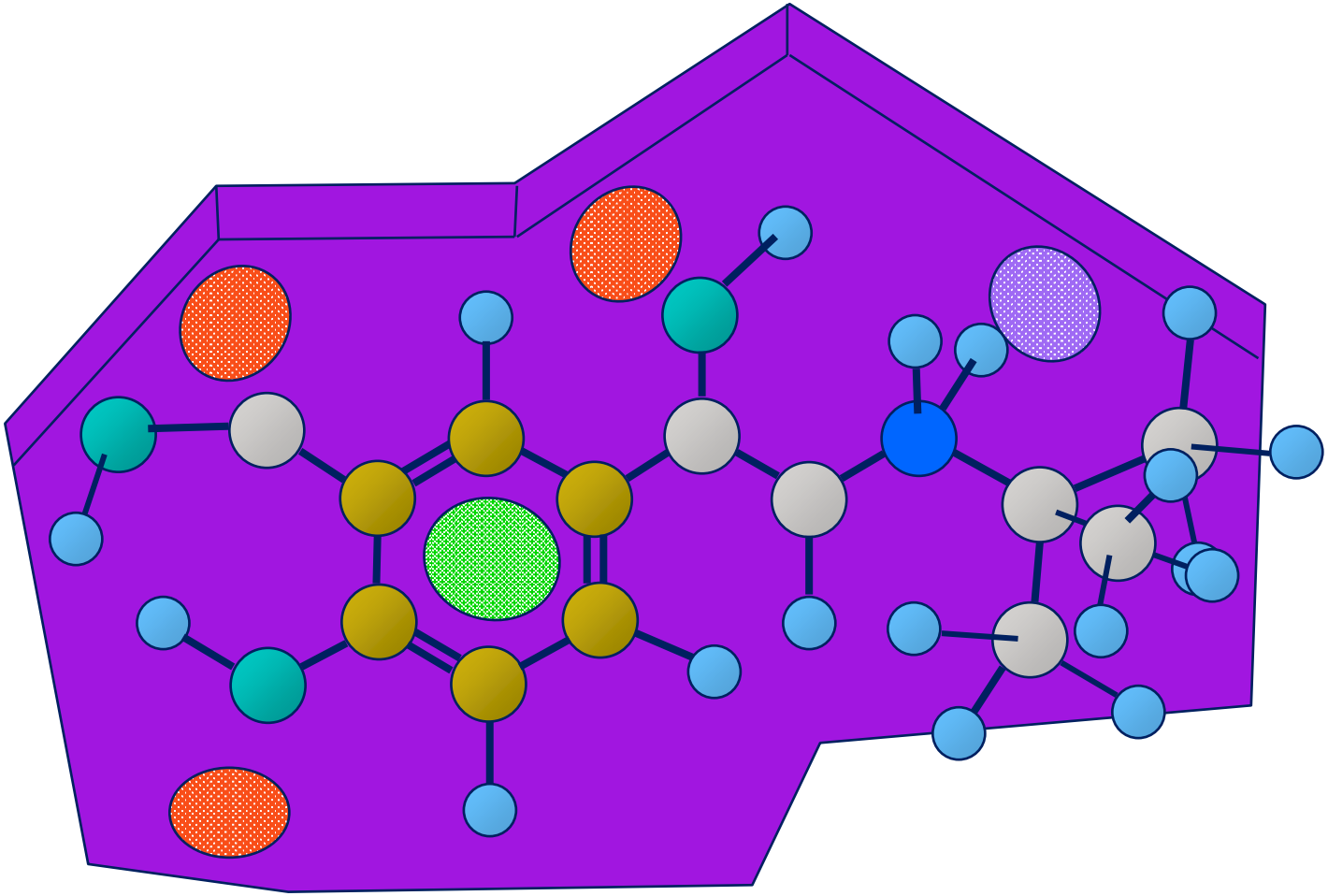
SALBUTAMOL

α-Adrenoceptor



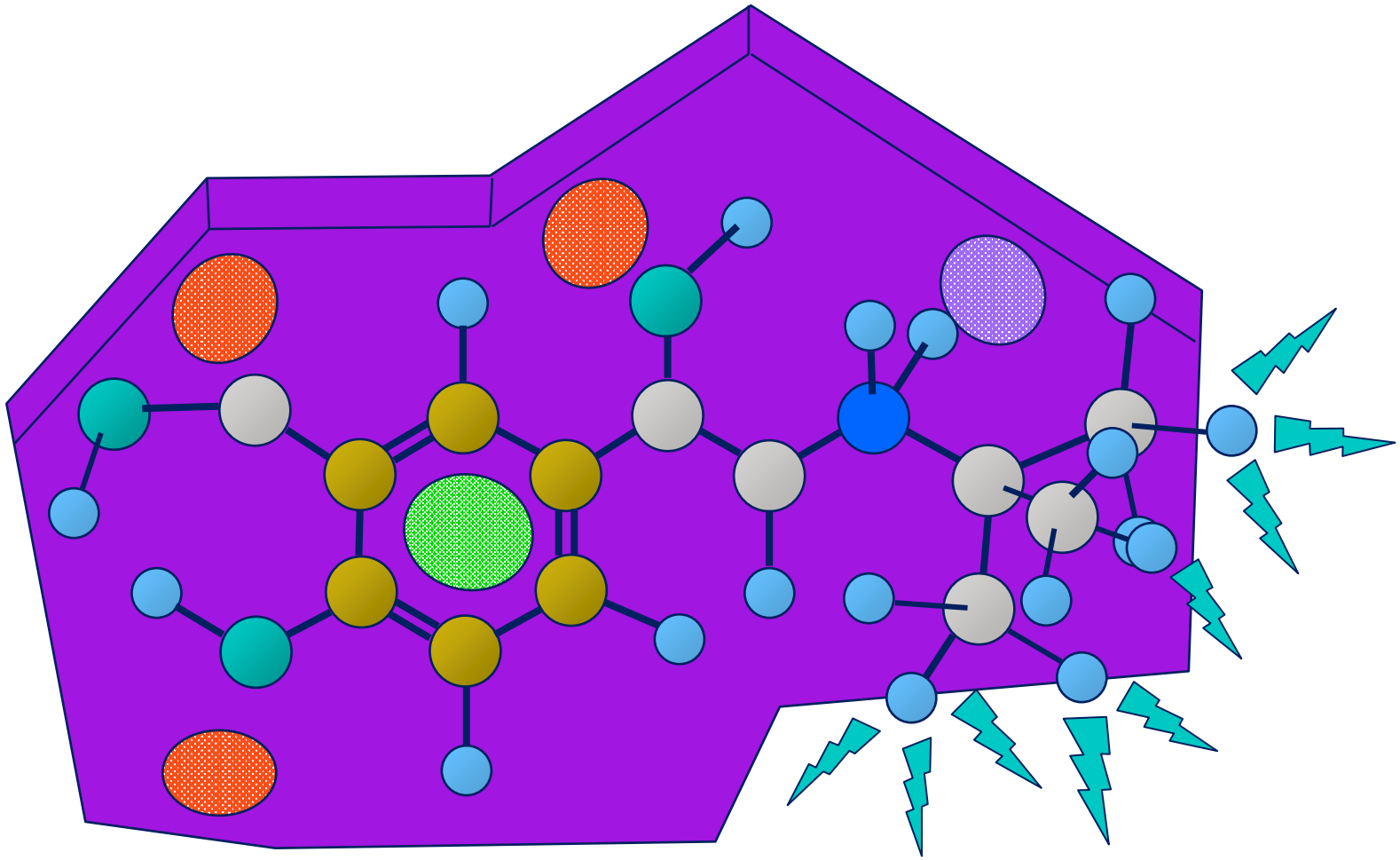
SALBUTAMOL

α-Adrenoceptor



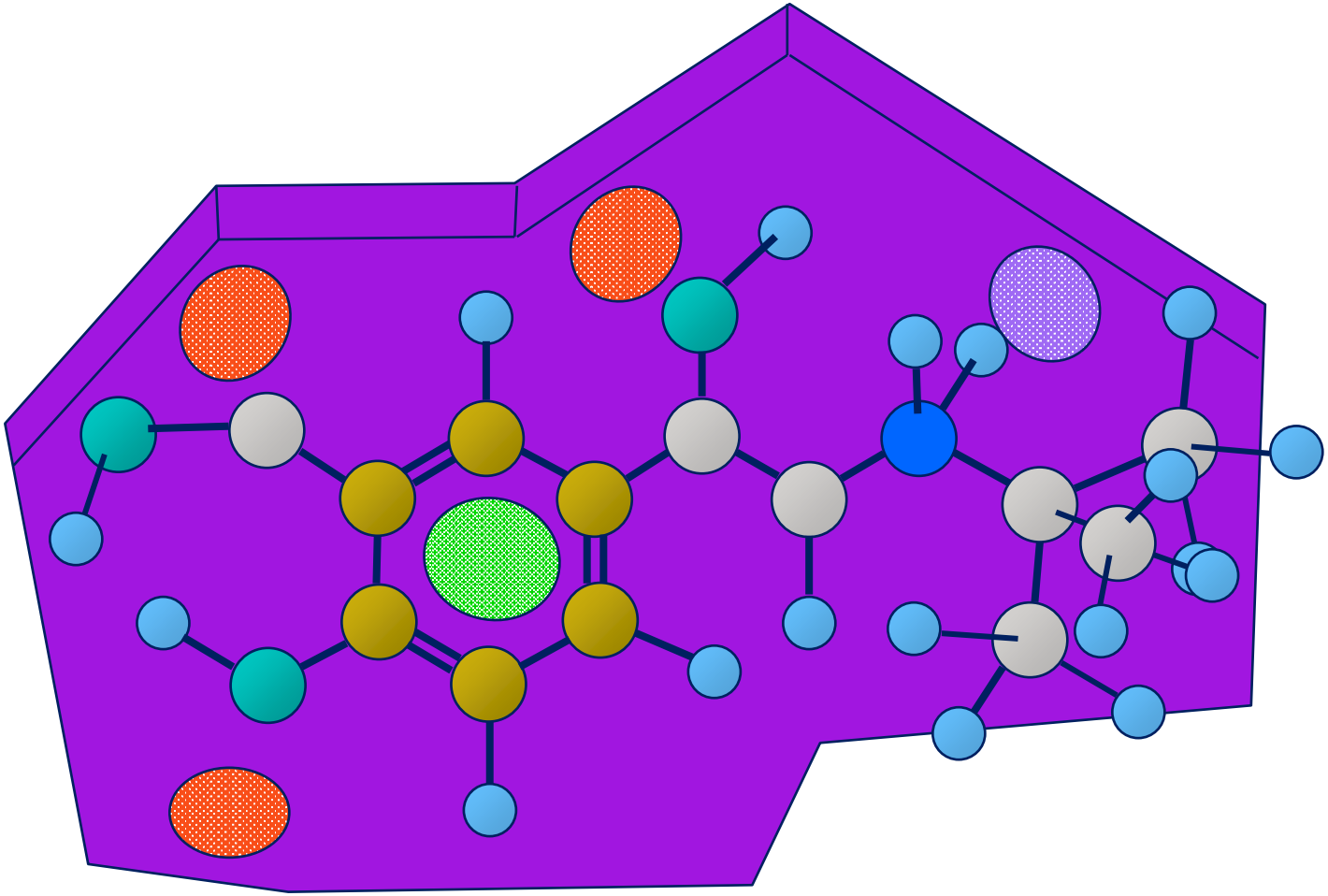
SALBUTAMOL

α-Adrenoceptor



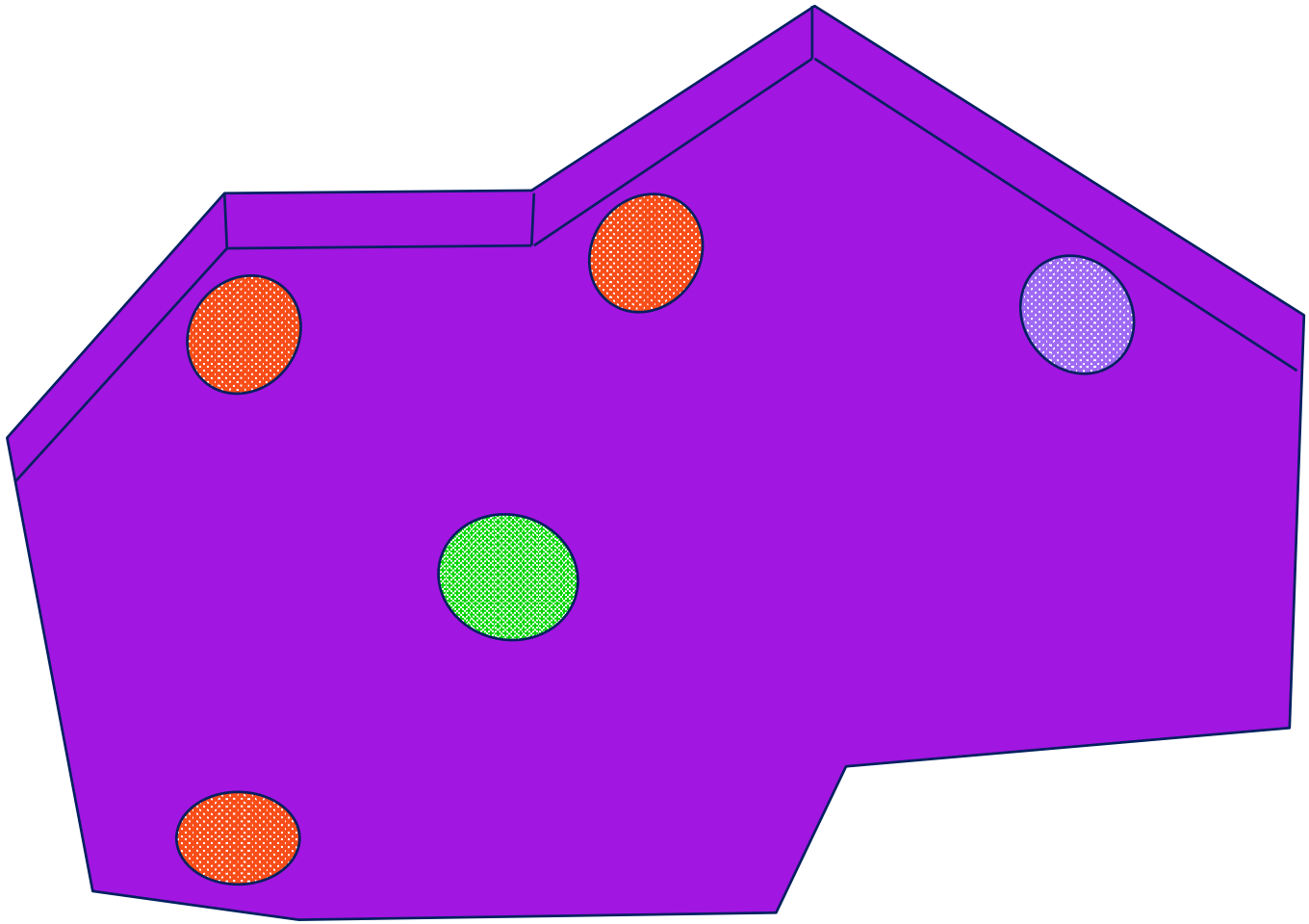
SALBUTAMOL

α-Adrenoceptor



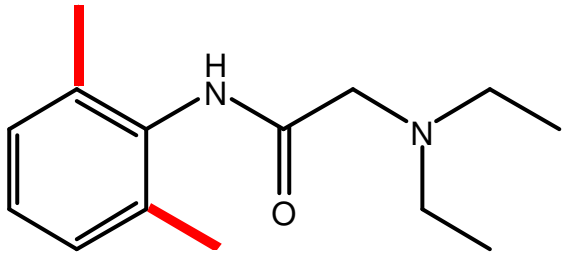
SALBUTAMOL

α-Adrenoceptor



Alkilne skupine

- Oviranje metabolizma



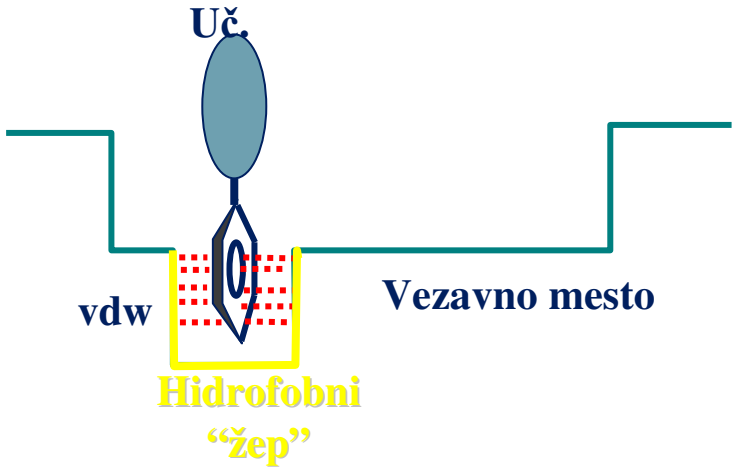
Lidokain
$t_{1/2}$ =1,5-2h

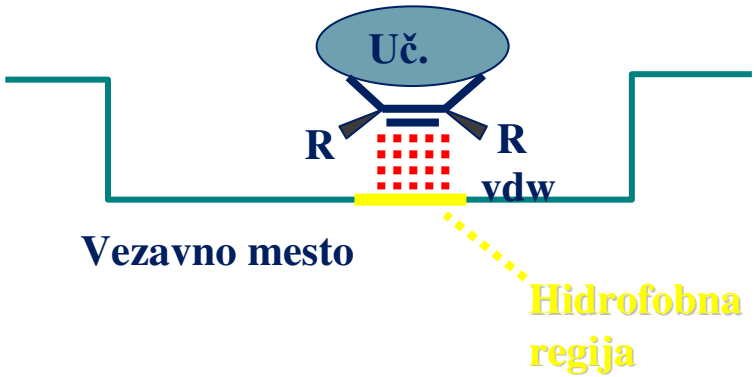
Obročni sistemi

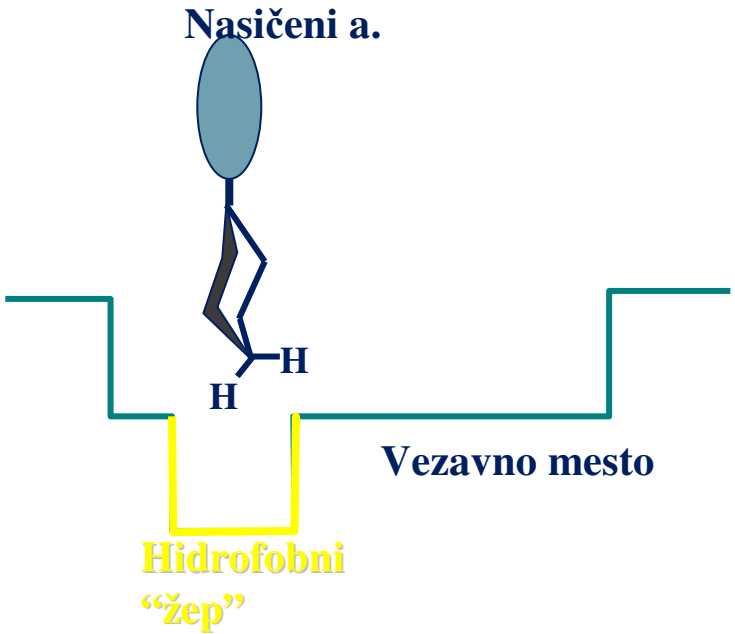
- Nasičeni, nenasičeni
- Primerjava cikloheksan-benzen: lipofilnost (logP), elektronski efekti, sterični učinki, π- π interakcije

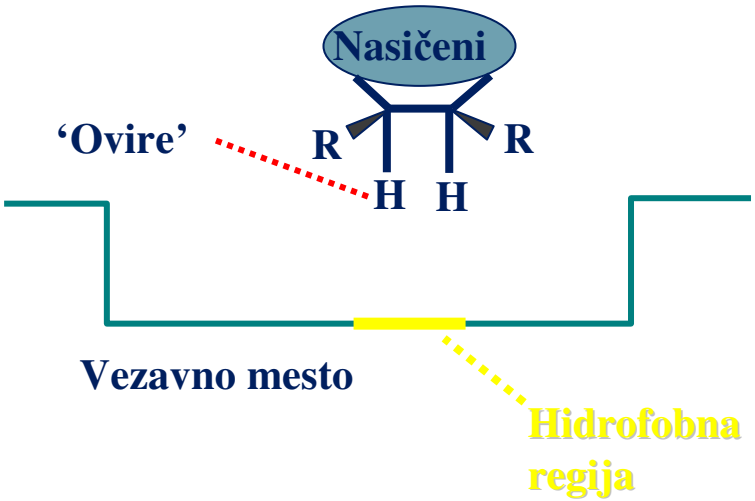
	cikloheksan	benzen
Vrelišče [°C]	80,74	80,1
Tališče [°C]	6,55	5,5
Gostota [g/ml]	0,779	0,8786
Topnost v vodi	/	1.79 g/L (25 °C)

Obročni sistemi



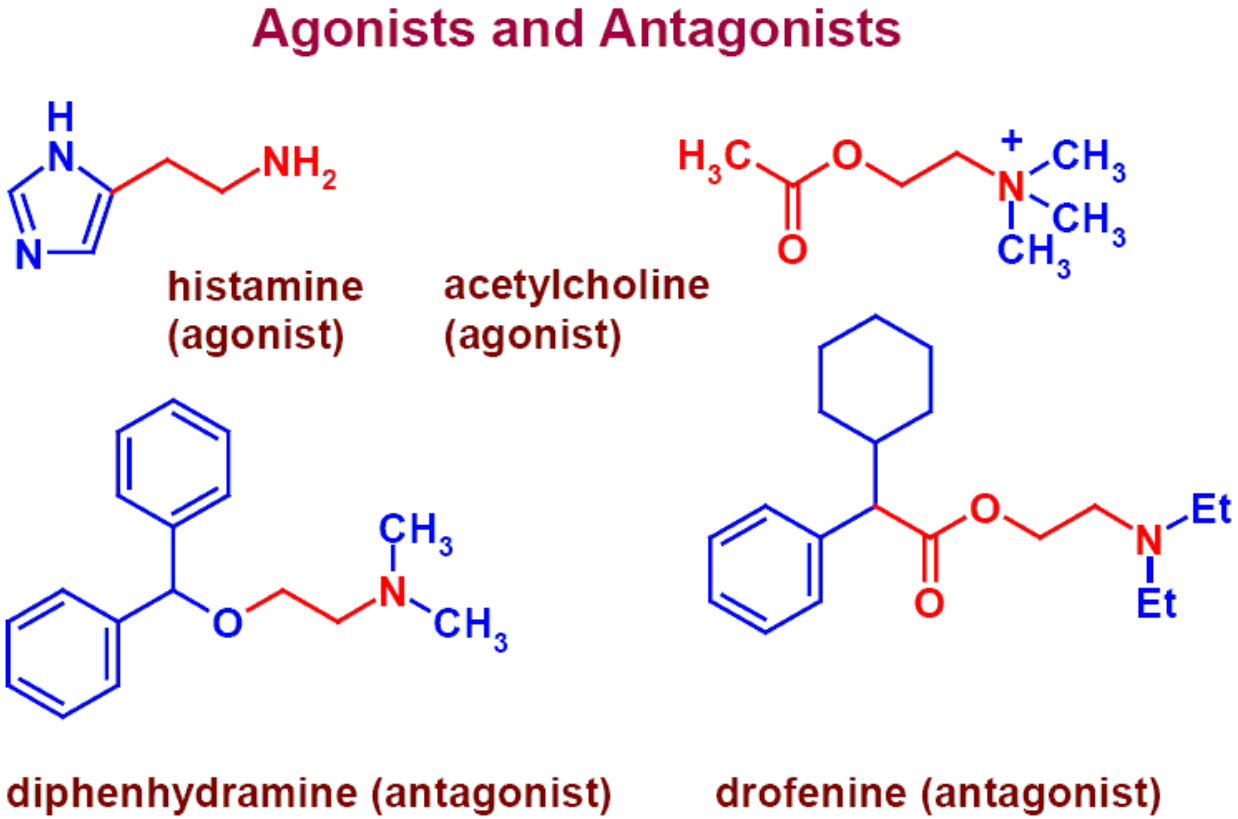






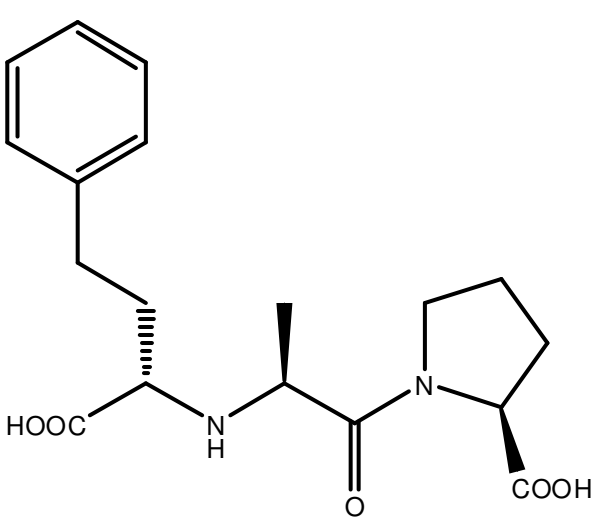
Obročni sistemi

- Sprememba delovanja

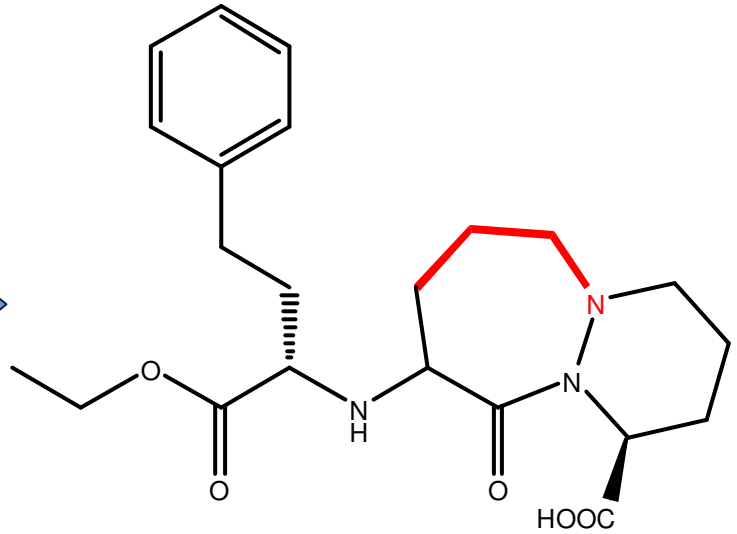


Obročni sistemi

- Rigidizacija strukture



enalaprilat



Cilazapril
4,5 x močnejši!

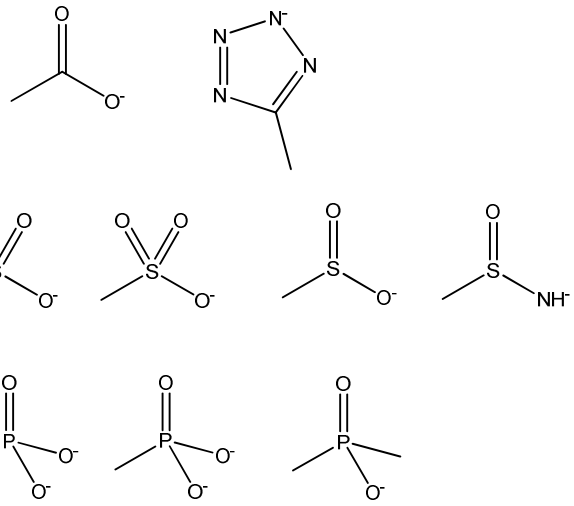
Obročni sistemi

- Napeti obročni sistemi: β-laktami, aziridini

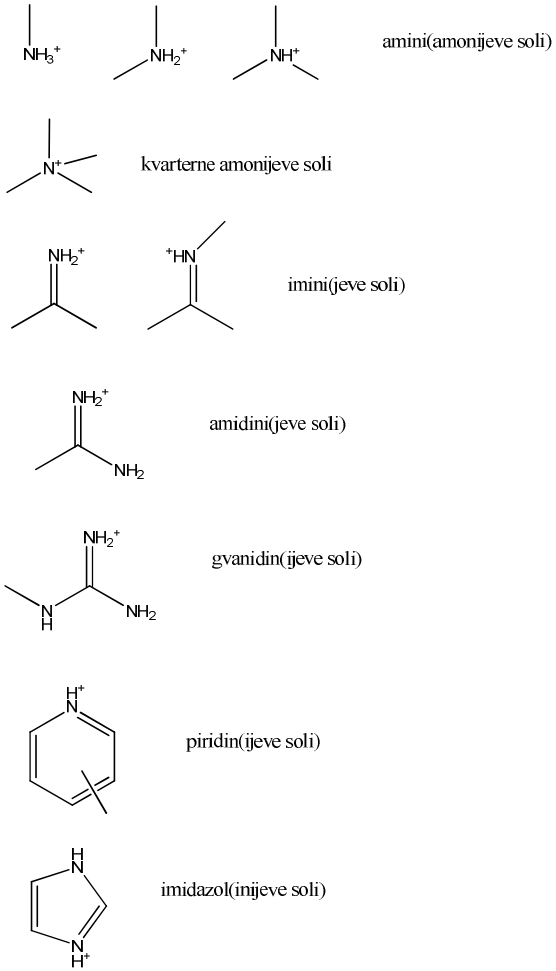
Heteroatomi

- Skupine z O, N, P, S, halogeni
- Močno polarizirane vezi
- Možnost tvorbe H-vezi
- Možnost ionizacije

Anionske skupine R^-

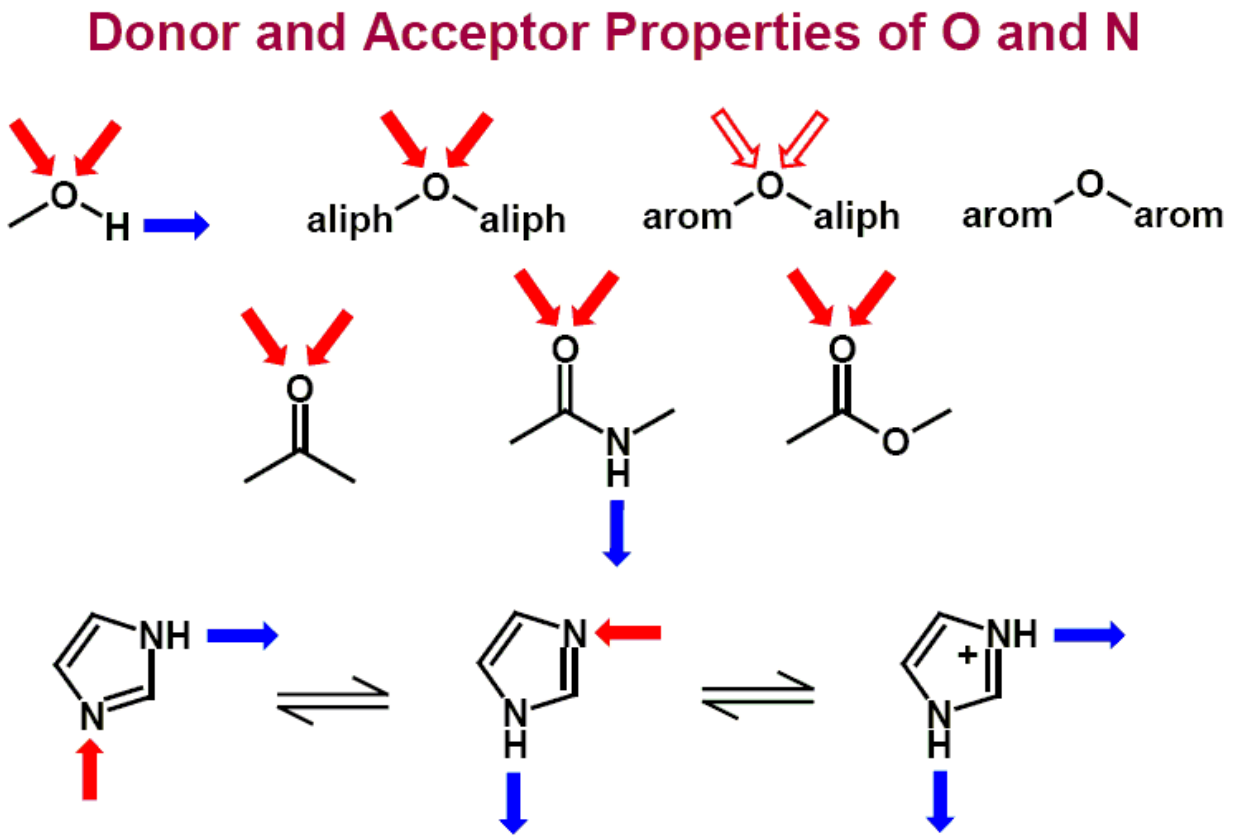


Kationske skupine R^+



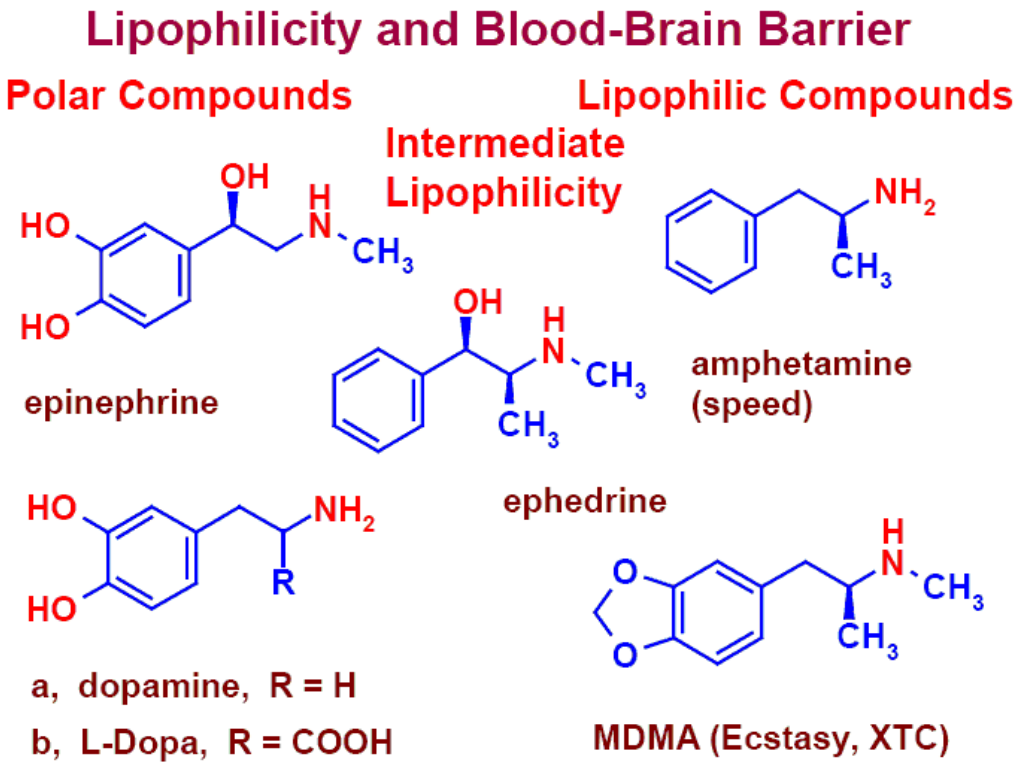
Heteroatomi

Vodikove vezi



Heteroatomi

- Polarnost
- Izločanje heteroatomov



Halogeni

Jakost vezi $C_{(alkil)}$-X

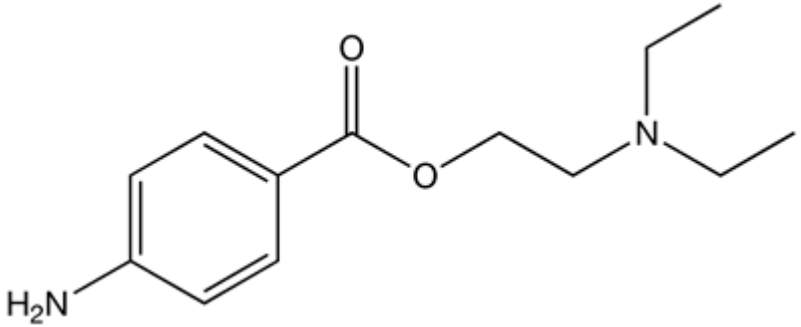
X	Jakost vezi C-X [kJ/mol]	Atomski radij [G]
H	415	0,29
F	485	0,64
Cl	331	0,99
Br	276	1,14
J	248	1,33

- F velikokrat zamenjava za H, ostali halogenidi alkilanti
- Arilhalogenidi večinoma stabilni (F-, Cl-, Br-)

Halogeni

Elektronski učinki

- -I; močno elektronegativni, C-X vez reaktivna
- +M

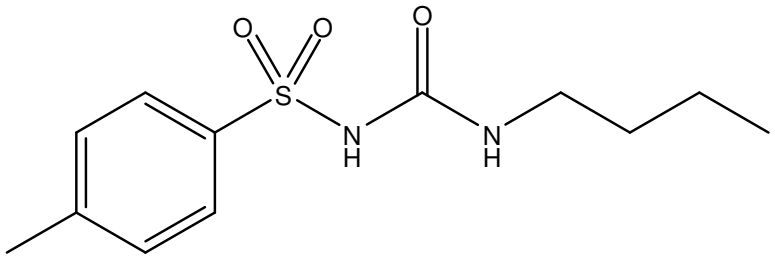


spojina	Relativna hitrost hidrolize
prokain	1,00
2-kloroprokain	4,63
2-bromoprokain	2,44
3,5-dikloroprokain	0,26

Halogeni

Metabolična stabilizacija (obstruktivna halogenacija)

- **Tolbutamid**; $t_{1/2}$ = 5,7h



- *p*-kloro derivat, **klorpropamid**; $t_{1/2}$ = 33h

Transportne skupine

- Povečanje biološke uporabnosti – predzdravila

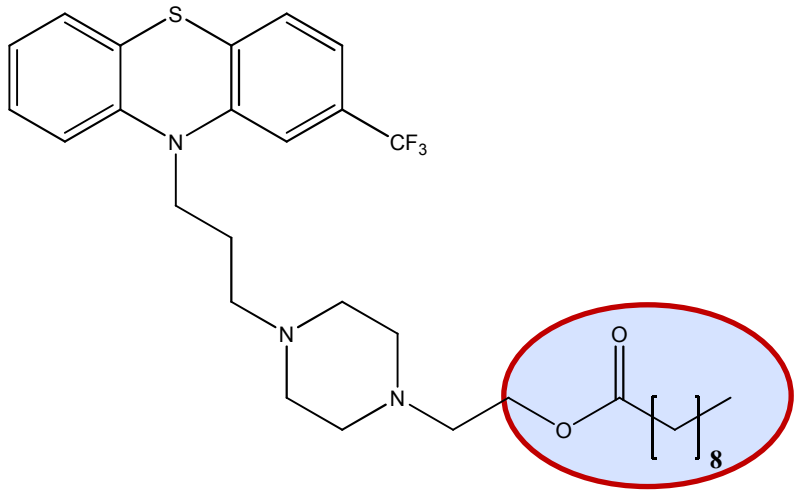
Aktivna oblika	Predzdravilna oblika
R-OH	R-OCOR' R-fosfat
R-SH	R-SCOR' R-fosfat
R-COOH	RCOOR
RR'NH	RR'NCOR'

- Primer – enalapril(at)

Transportne skupine

- Predzdravila – povečanje $t_{1/2}$

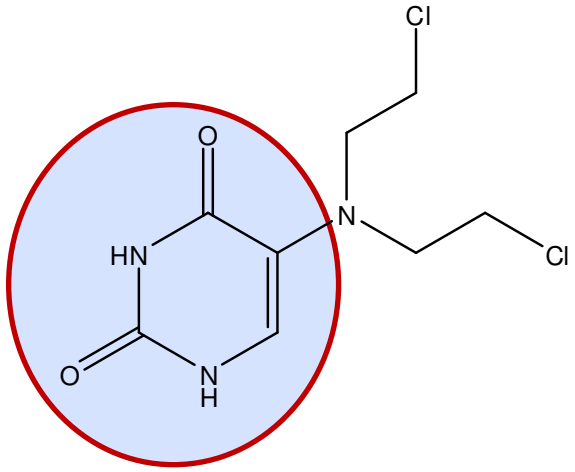
Flufenazin dekanoat



Transportne skupine

Specifične transportne skupine

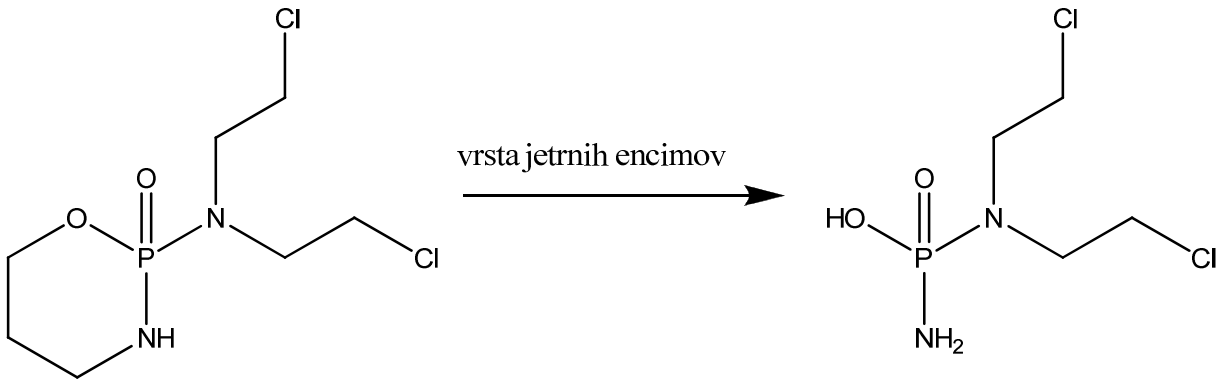
- Uracil iperit (uramustin)



Transportne skupine

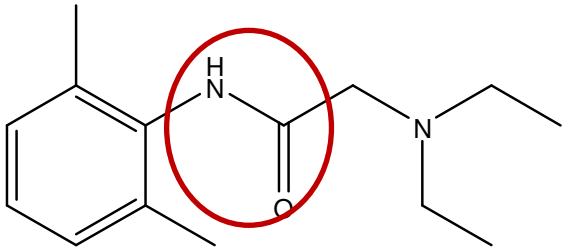
Specifične transportne skupine

- Ciklofosfamid; predzdravilo

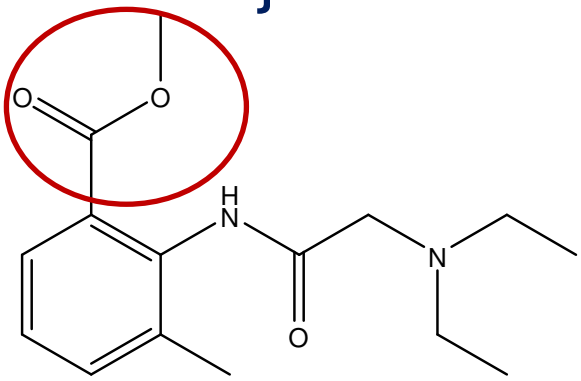


"Ranljive" skupine

- Občutljive na encimsko delovanje/hidrolizo



lidokain



Tolikain
"soft drug"