ZAŠTO *SARTANI*

Prof Danica Agbaba

Renin-angiotenzin sistem

- Kompleks – visoko regulisan
- Integralni deo sistema koji reguliše zapreminu krvi, balans elektrolita i arterijski krvni pritisak

Renin-angiotenzin sistem

ANGIOTENZINOGEN – alfa 2- globulin
58 000-61000

(Glikokortikoidi, tireoidni hormon, i angiotenzinogen II – regulacija sinteze angiotenzinogena)

⇓ **Renin (Aspartil proteaza) 35 000 – 40000**

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-R

Leu 10-Val11

ANGIOTENZIN I **(dekapeptid) Phe8-His9**

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu

⇓ ACE enzim ≡
angiotenzin konvertujući enzim

ANGIOTENZIN II **(oktapeptid)**

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe

⇓ **efekti**

Renin-angiotenzin sistem

⇓ **efekti**

vazokonstrikcija
↑ nivo kateholamina
↑ reapsorpciju jona Na^+
↑ sekrecija aldosterona

∇

⇑⇑⇑ **krvni pritisak**

ACE-inhibitori-*PRILI*/Antagonisti AT-receptora-*SARTANI*)

ANGIOTENZINOGEN

⇓ **Renin**

ANGIOTENZIN I **(dekapeptid)**

⇓ ACE enzim ≡ angiotenzin konvertujući enzim

AT-receptore ⟵ ANGIOTENZIN II **(oktapeptid)**

⇓ **aminopeptidaza**

ACE-inhibitori-*PRILI*/Antagonisti AT-receptora-*SARTANI*)

⇓ **Aminopeptidaza A**

↑**Aldosteron** ← **ANGIOTENZIN III**

⇓ **endo- i egzopeptidaze**

INAKTIVNI PEPTIDI

ACE-inhibitori-*PRILI*/Antagonisti AT-receptora-*SARTANI*)

ANGIOTENZINOGEN

⇓ **Renin**

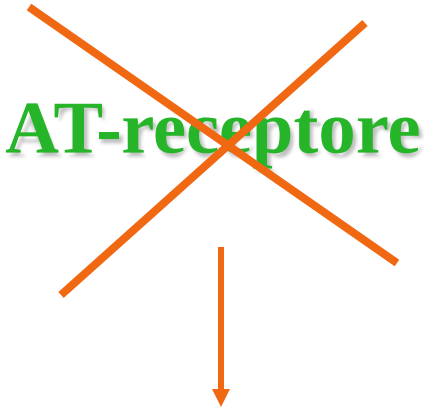
ANGIOTENZIN I (dekapeptid)

⇓ ACE enzim ≡ angiotenzin konvertujući enzim

ACE - inhibitori ←

ANGIOTENZIN II (oktapeptid)

ACE-inhibitori-*PRILI*/Antagonisti AT-receptora-*SARTANI*)



AT-receptore ← **ANGIOTENZIN II (oktapeptid)**

⇓ **aminopeptidaza**

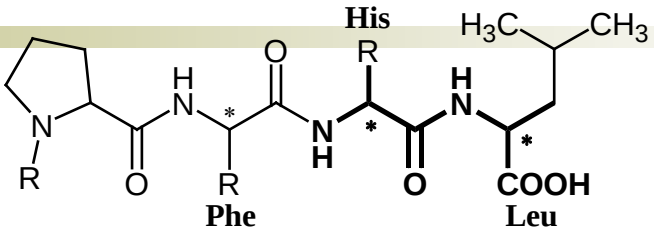
ANGIOTENZIN III

antagonisti AT-receptora (sartani)

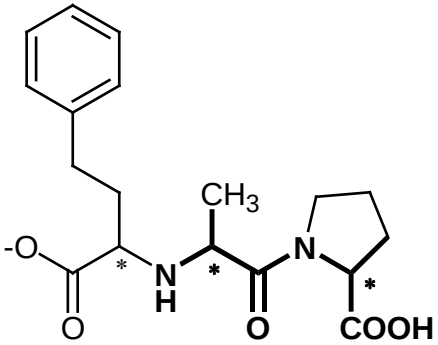
⇓ **endo- i egzopeptidaze**

INAKTIVNI PEPTIDI

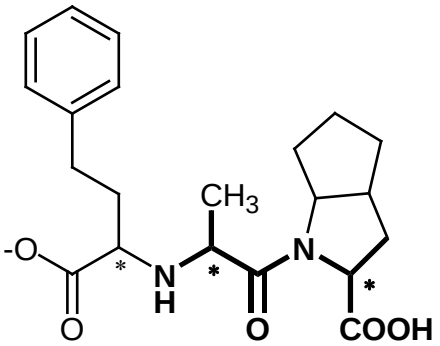
MOLEKULARNA OSNOVA - Strukturna sličnost - *PRILI*



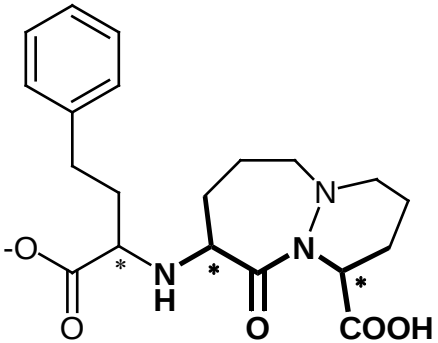
C-terminalni kraj Angiotenzina I



Enalaprilat

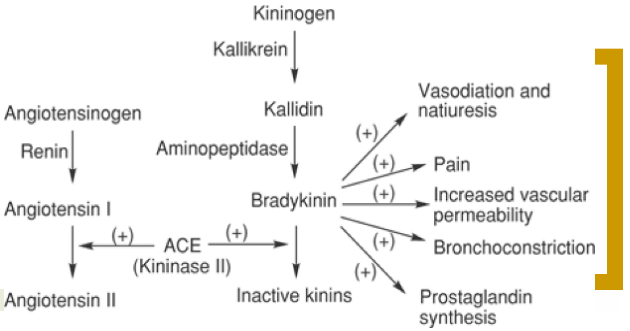


Ramiprilat



Cilazaprilat

ACE-inhibitori-*PRILI*-



- Kompletna inhibicija ACE ne sprečava konverziju ANGIOTENSIN I u ANGIOTENSIN II dejstvom drugih peptidaza
- U tkivu srca ANGIOTENZIN II nastaje dejstvom drugih enzima
- Inhibicija razgradnje bradikinina dejstvom ACE uzrok je sporednih efekata - kašalj i angioedem - - kod znatnog broja pacijenata

Antagonisti AT-receptora -*SARTANI* - ARBs

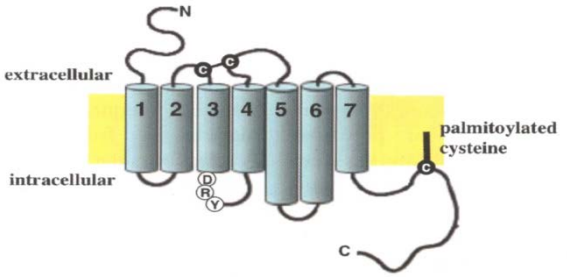
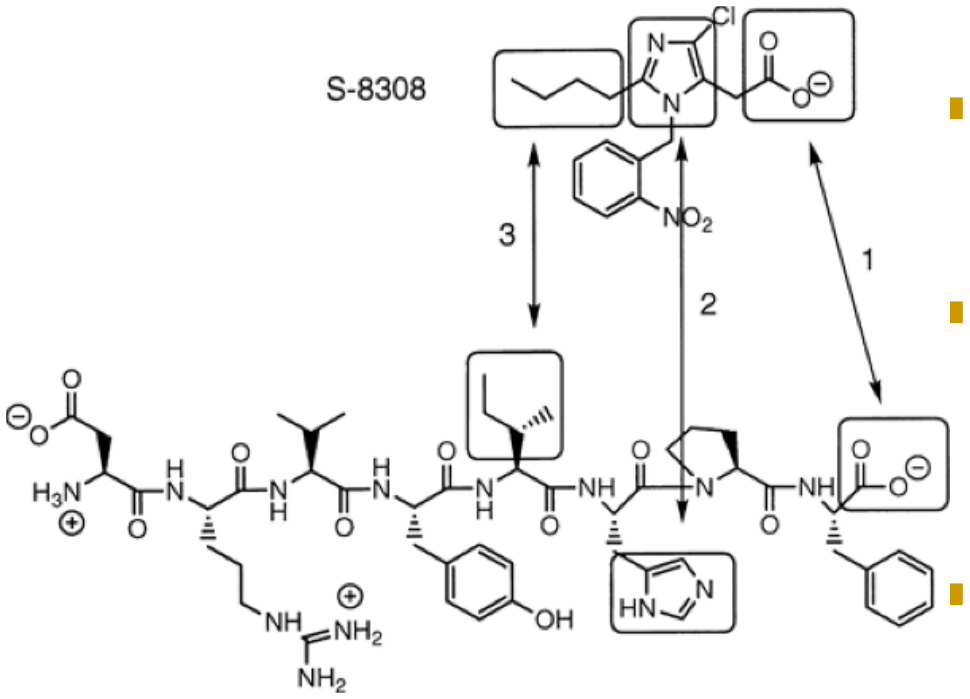


Figure 85 Two-dimensional structure of family A (Class 1) receptors and rhodopsin.

- Receptori angiotenzina
- AT_1, AT_2, AT_3, AT_4
- AT_1 lokalizovan mozgu, neuro, vaskularnom, hepatičnom i mišićnom tkivu i srži nadbubrežne žlezde
- AT_1 receptori odgovorni za kontrakcije glatkih mišića, adrenergičke presorne mehanizme i sekreciju aldosterona.

Structural comparison of S-8308, an imidazole-5-acetic acid analogue, with angiotensin II.

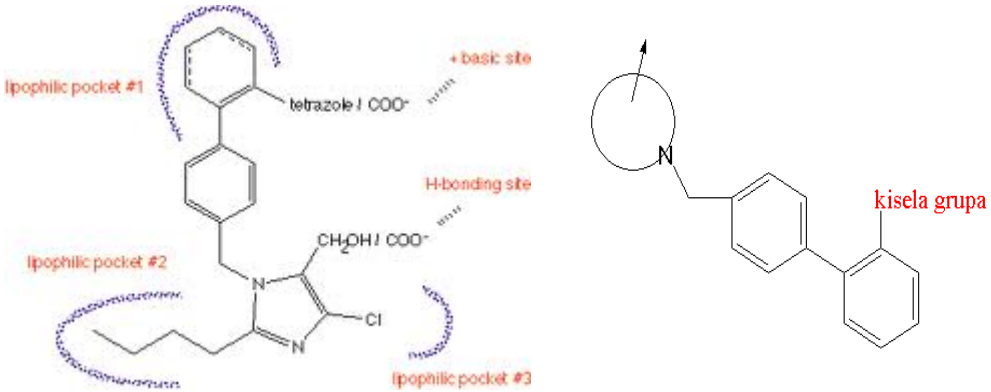


Asp - Arg- Val- Tyr- Ile- His- Pro- Phe

Timmermans PB, Wong PC, Chiu AT, et al. Angiotensin II receptors and angiotensin II receptor antagonists. Pharmacol Rev 1993;45:205–213

- Ionized carboxilate of S -8308 coorelate with the C-terminal carboxilate of angiotensin II
- Imidazole ring of S -8308 correlate with the imdazole side chain of the HIS $_5$ residue
- n-butil group of S -8308 correlate with the hydrocarbon side chain of the Ille
- A huge number of structural modification was done to improve receptor binding and lipid solubility important for oral absorption

Šta želimo? Da kompetitivno blokiramo ANGIOTENSIN II na njegov receptor

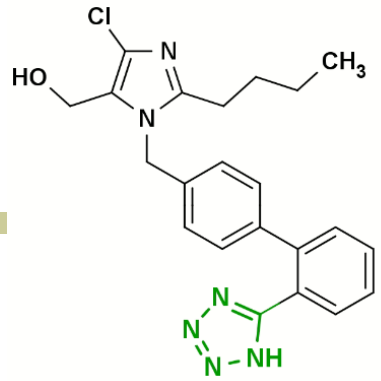


- The “acidic group” imitira odnosno liči na Tyr4 ili Asp1 karboksilat angiotensina II. Groups – karboksilna grupa (A),fenil teterazol (B), i fenil karboksilat (C).
- U bifenil seriji, tetrazol i karboksilati moraju biti u orto položaju za optimalnu aktivnost. Heterociklusi - imidazol ili izosterni ekvivalenti - imitiraju His6 angiotenzin II.

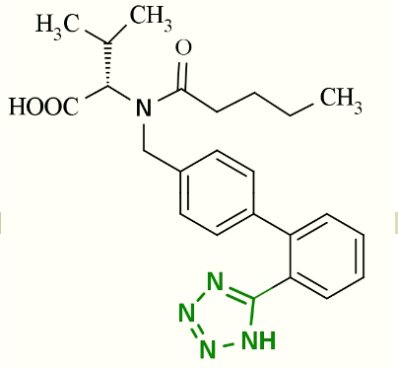
n-Butil, etil ili propil na heterociklusu omogućava hidrofobnu interakciju, imitiraju lanac Ile5 angiotenzin II.

ANGIOTENSIN II

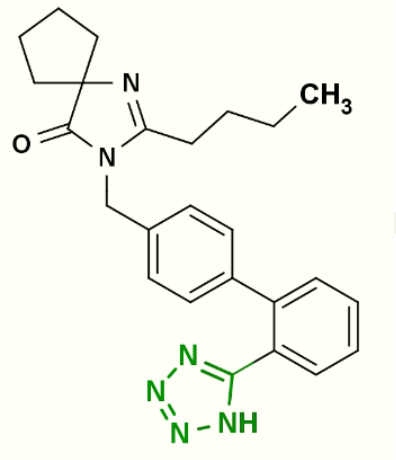
Asp-Arg-Val-Tyr-Ile-His-Pro-Phe



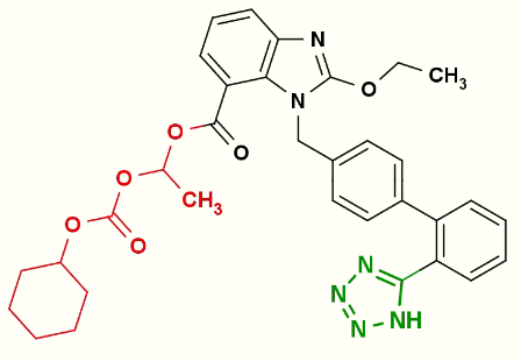
Losartan – 33%



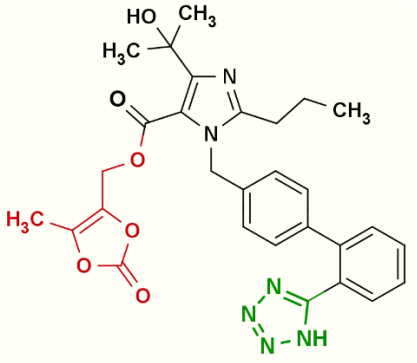
Valsartan – 23%



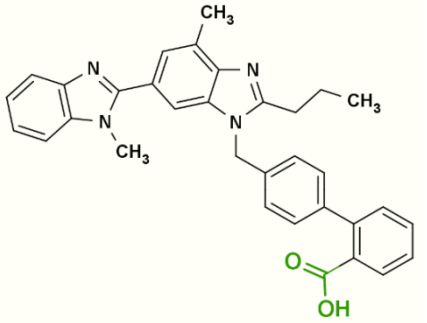
Irbesartan – 60-80%



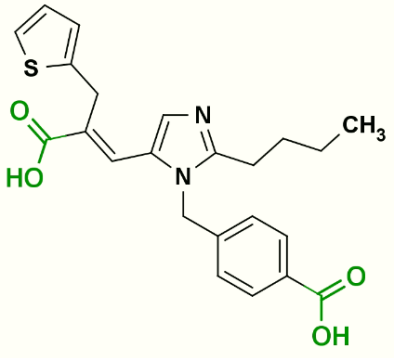
Candesartan cilexetil – 42%



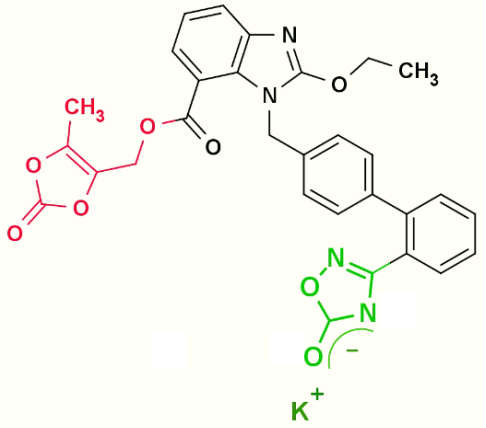
Olmesartan medoxomil – 40%



Telmisartan – 40-60%



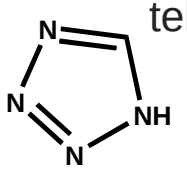
Eprosartan – 13%



Azilsartan kamedoxomi – 60%l

Osobine

KISELI LEKOVI – pKa – 3-4, COOH, (valsartan, eprosartan, kandesartan, olmesartan, telmisartan)

- pKa – 6, 

losartan, valsartan, irbesartan, kandesartan, olmesartan)

U fiziološkim uslovima potpuno protonovani

TETRAZOL

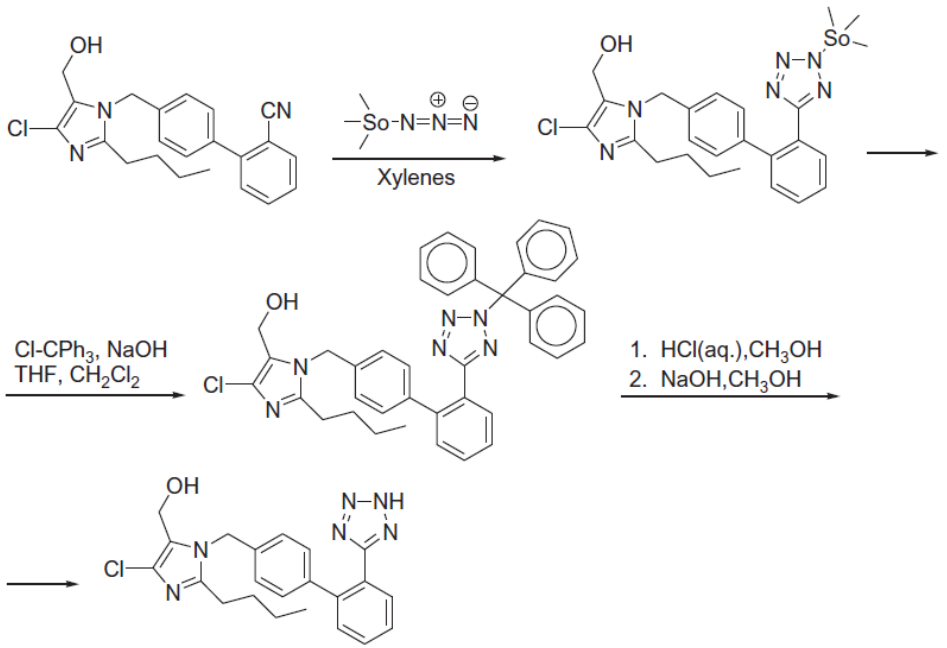
stabilan u kiseloj i baznoj sredini, na oksidaciju i redukciju, metabolički stabilan, četri nitrogena u tetrazolu mogu stvoriti veću distribuciju naboja/naelektrisanja ⟶ povećava vezivanje i bioraspoloživost

Lipofilnost tetrazola >>>> karboksilne grupe

Generalno imaju slabu bioraspoloživost

80 % se izlučuju nepromenjeni

TETRAZOL – sinteza- genotoksične nečistoće



Scheme 1 Preparation of Losartan according to Example 316 of U.S. Patent No. 5,138,069.

- Reakcija -C≡N + (azidima) **R-N=N=N**

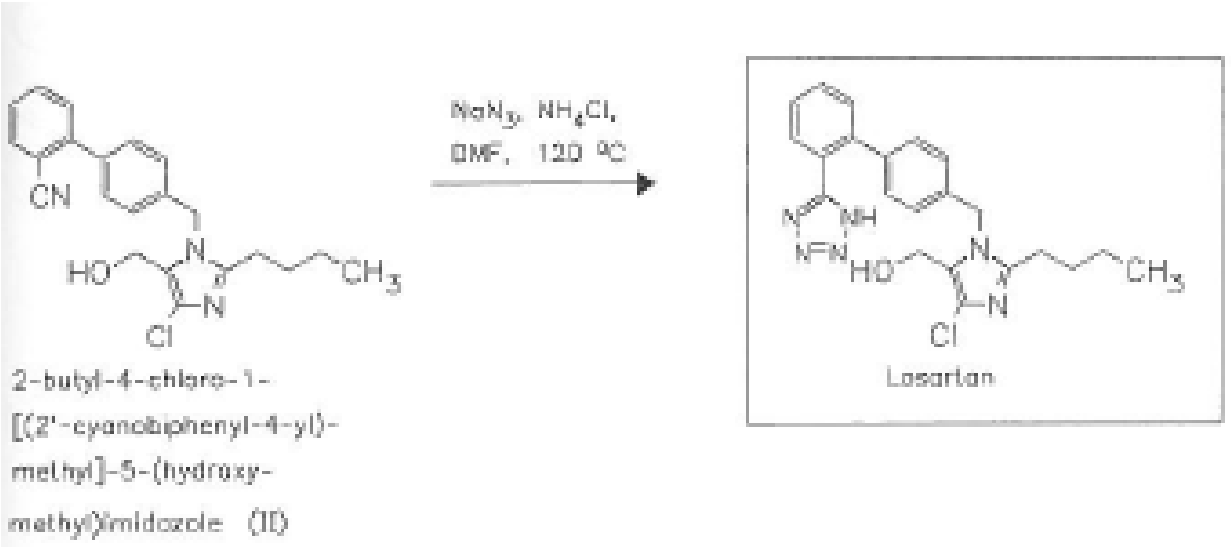
R –trimetilsililazid, trimetil/butil/fenil/stanil-/aluminijumazid +

rastvarač na visokoj temperaturi (stvaranje zapaljivih gasova)

TETRAAZOL

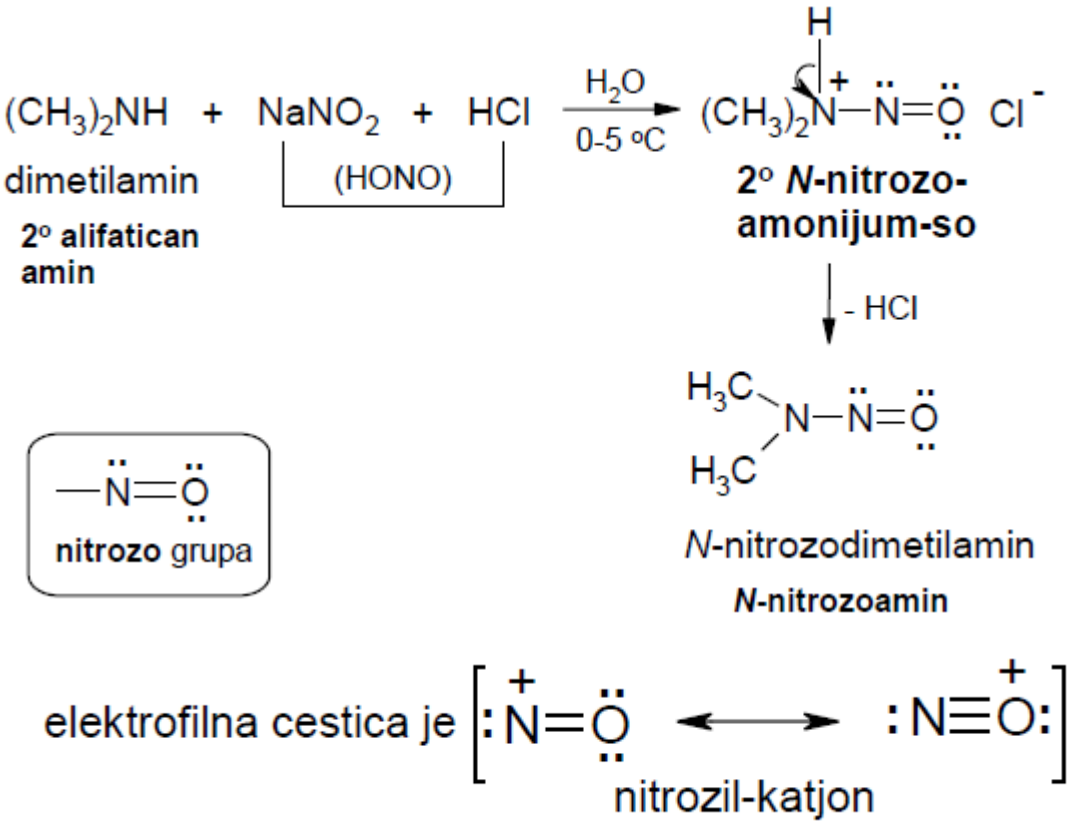
Click Chemistry

TETRAZOL – sinteza- genotoksične nečistoće



2012, EDQM i FDA – PROMENA PROCESA PROIZVODNJE *TRIBUTILINAZIDI*, ZAMENJENI TOKSIČNIJIM *NATRIJUMAZIDOM*
UZ DODATAK NaNO2 (neutralizacija viška azida) u kiseloj sredini se istisne azotasta kiselina koja sa aminima (nečistoće DMF) grade N-NITROZO JEDINJENJA. Gradi se i amonijumazid - sublimiše,eksplozivan

TETRAZOL – sinteza- genotoksične nečistoće



Sinteza- genotoksične nečistoće

PAT – Proces Analytical Technology, CM – kontinuirana proizvodnja,
RTRT – Real Time Release Testing, QbD – design space

Generisanje velikog broja merenja za vreme procesa proizvodnje,
off line, on line, in line
UV/Vis, NIR, Raman, X-ray fluorescence spectrometry
Hemijska, fizička i mikrobiološka merenja
Hemometrijski pristup
Kritični parametri- obezbedjenje kvaliteta