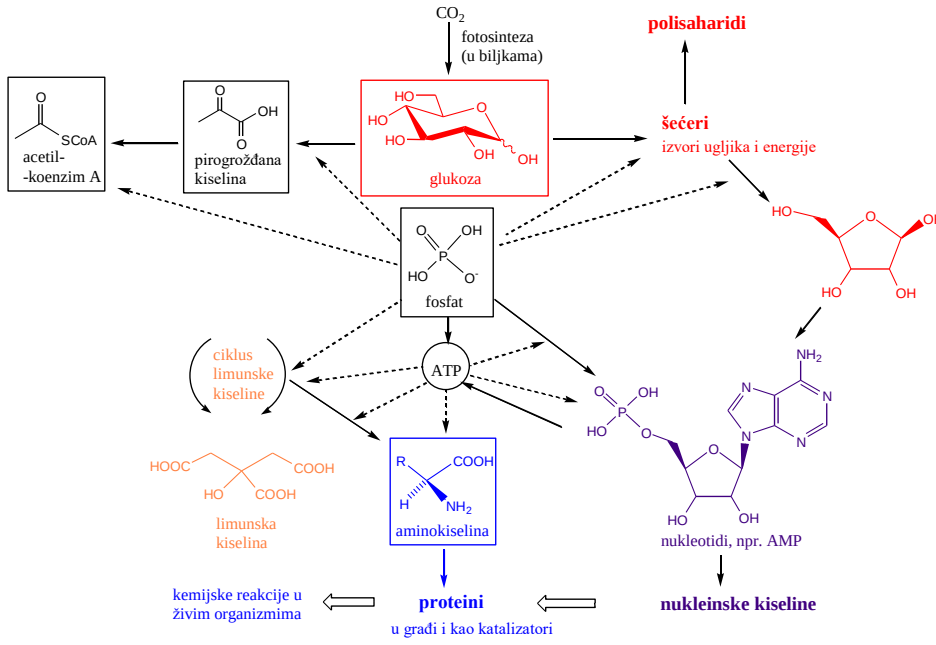


Nukleozidi, nukleotidi i nukleinske kiseline

Prof. dr. sc. Silvana Raić-Malić

Nukleozidi u primarnom metabolizmu

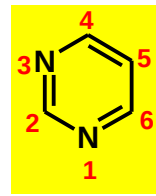


Nukleozidi

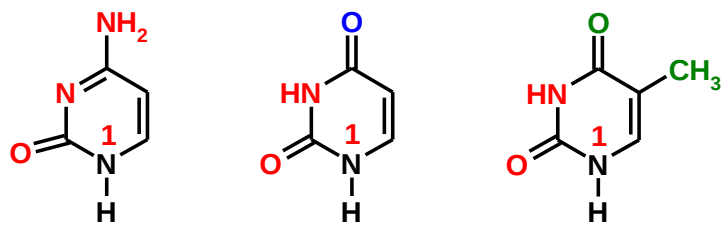
- 1869. g. MIESCHER otkrio nukleinske kiseline
- 1944. g. AVERY dokazao genetsku funkciju DNA
- 1953. g. WATSON i CRICK daju model dvostruke uzvojnice DNA

HETEROCIKLIČKE BAZE

PIRIMIDINSKE

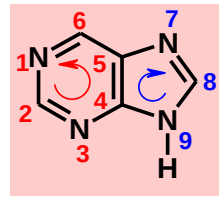


CITOZIN, URACIL, TIMIN (C, U, T)

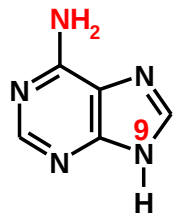


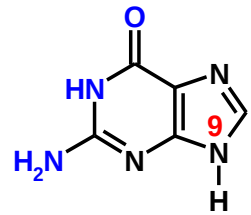
HETEROCIKLIČKE BAZE

PURINSKE

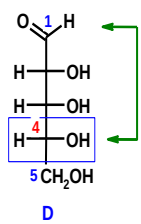


ADENIN, GVANIN (A, G)

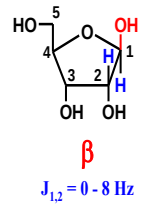




UGLJIKOHIDRATI - PENTOZE

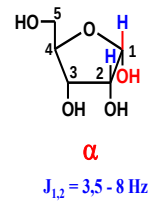


D



β

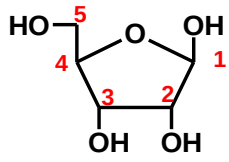
$J_{1,2}$ = 0 - 8 Hz



α

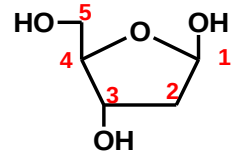
$J_{1,2}$ = 3,5 - 8 Hz

RIBOZA



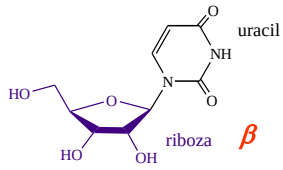
β-D-ribofuranoza

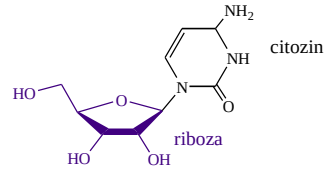
2-DEOKSIRIBOZA



2-deoksi-β-D-ribofuranoza

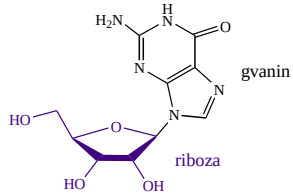
PIRIMIDINSKI RIBONUKLEOZIDI

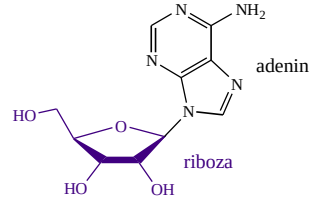




-IDIN **URIDIN** **CITIDIN**

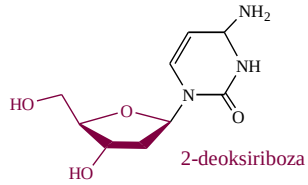
PURINSKI RIBONUKLEOZIDI

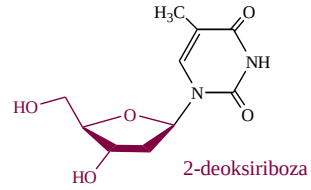




-OZIN **GVANOZIN** **ADENOZIN**

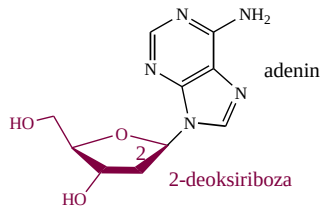
PIRIMIDINSKI DEOKSIRIBONUKLEOZIDI

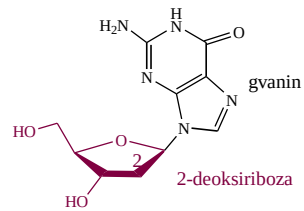




DEOKSICITIDIN **DEOKSITIMIDIN**

PURINSKI DEOKSIRIBONUKLEOZIDI

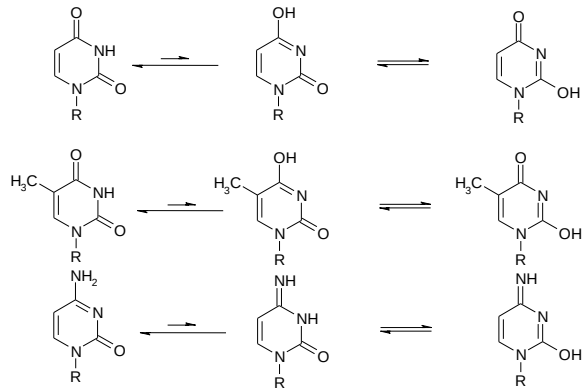




DEOKSIADENOZIN **DEOKSIGVANOZIN**

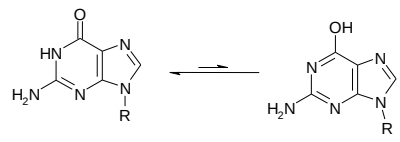
Tautomerija

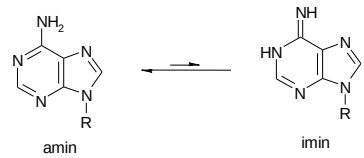
- Broj tautomernih oblika ovisi o broju egzocikličkih OH- i NH_2-skupina
- Tautomerna ravnoteža je jako pomaknuta na stranu diketo-oblika kod uridina i timidina, odnosno keto-amino-oblika citidina:



Tautomerija

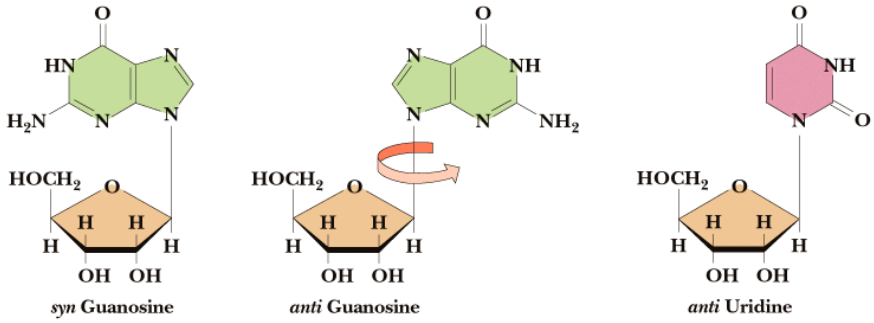
- Kod gvanozina ravnoteža je pomaknuta na stranu keto-amino- oblika, kod adenozina prema aminu:



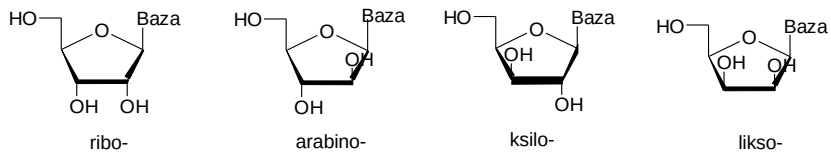


- Uvođenje elektronegativnih supstituenata pomiče ravnotežu prema enolu, odnosno iminu

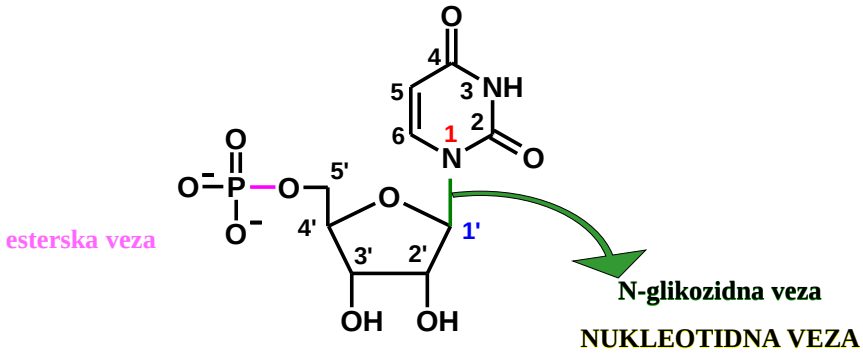
U molekuli DNA dušične baze mogu biti u *sin* ili *anti* konformaciji



Konfiguracijski izomeri šećernog prstena u nukleozidima



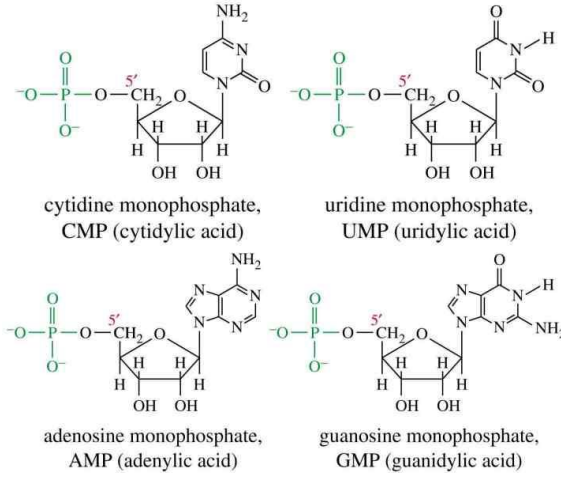
Nukleotidi



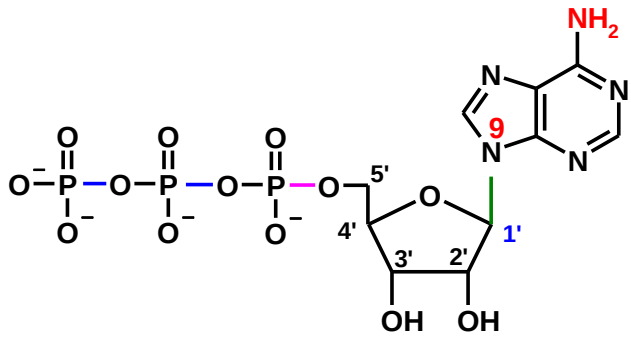
URIDIN-5'-FOSFAT (UMP)

Nukleotidi

- β-D-ribofuranoza i 2-deoksi-β-D-ribofuranoza vežu se preko anomernog ugljika na heterocikličku bazu ⇨ nukleozid
- Vezivanje fosfata na C-5' ⇨ nukleotid



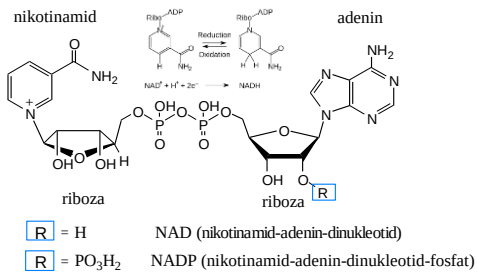
Nukleotidi

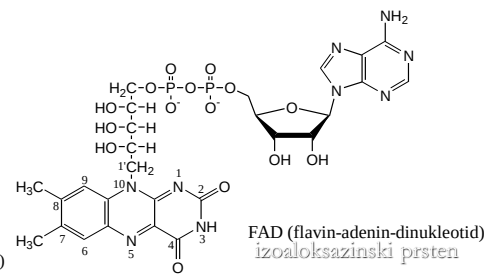


Adenozin-5’-trifosfat (ATP)

Fiziološki značajni nukleotidi

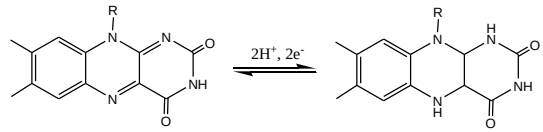
- NADH i $FADH_2$ – koenzimi, prijenosnici elektrona pri oksidaciji molekula
- Reaktivni dio molekule NADH - nikotinamidni prsten, NAD^+ prima vodikov atom i dva elektrona (NADH - reducirani oblik)
- Sudjeluje u stvaranju ATP-a





Fiziološki značajni nukleotidi

- Reaktivni dio FAD - izoaloksazinski prsten, prihvaća dva vodikova atoma sa supstrata ($FADH_2$ reducirani oblik) molekule
- NADPH (nikotinamid-adenin-dinukleotid-fosfat) - esterski vezan fosfat na 2'-hidroksilnu skupinu
- Prenosi elektrone, no većinom služi u reduktivnoj biosintezi, dok NADH sudjeluje u stvaranju ATP-a
- Flavoproteini sadrže FMN ili FAD kao prostetičke skupine

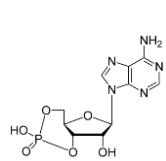


Fiziološki značajni nukleotidi

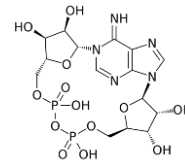
- Ciklički GMP (gvanozin-monofosfat) - sudjeluje u otvaranju i zatvaranju Na^+-kanala u vanjskoj staničnoj membrani, regulator stanične apoptoze

- Adenozin-trifosfat (ATP) - aktivni oblik molekule je kompleks s ionima Mg^{2+} ili Mn^{2+}, molekula bogata energijom koja se oslobađa hidrolizom u ADP i ortofosfat (Pi) ili u AMP i pirofosfat (PPi), služe kao kotransmitori u prijenosu signala

- cAMP (ciklički AMP) i cADPR (ciklička ADP-riboza)- posrednici (*second messengers*) u djelovanju hormona (adrenalina i glukagona)



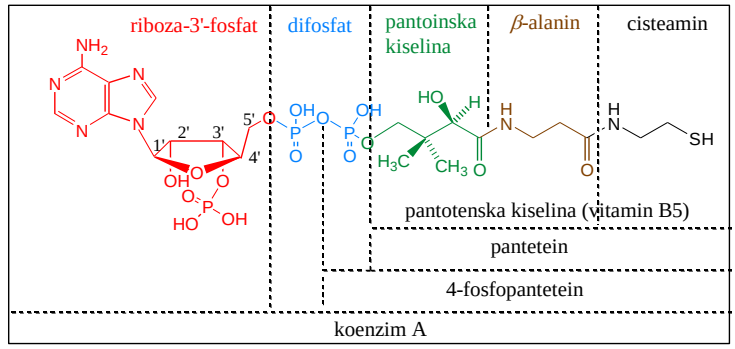
cAMP



cADPR

Fiziološki značajni nukleotidi

- Koenzim A (CoA) - nosač aktiviranih acetilnih i drugih acilnih skupina. Reaktivno mjesto CoA je skupina -SH preko koje se tioesterskim vezom vežu acilne skupine

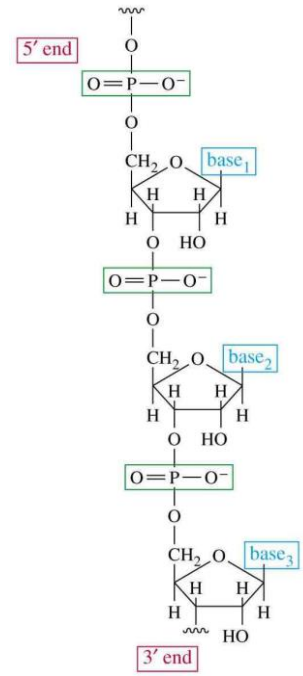


Koenzim A (CoA)

Nukleinske kiseline

- Polimeri ribofuranoznih prstena povezanih preko fosfatne esterske skupine
- Svaka riboza je povezana s bazom
- Ribonukleinska kiselina (RNA)
- Deoksiribonukleinska kiselina (DNA)

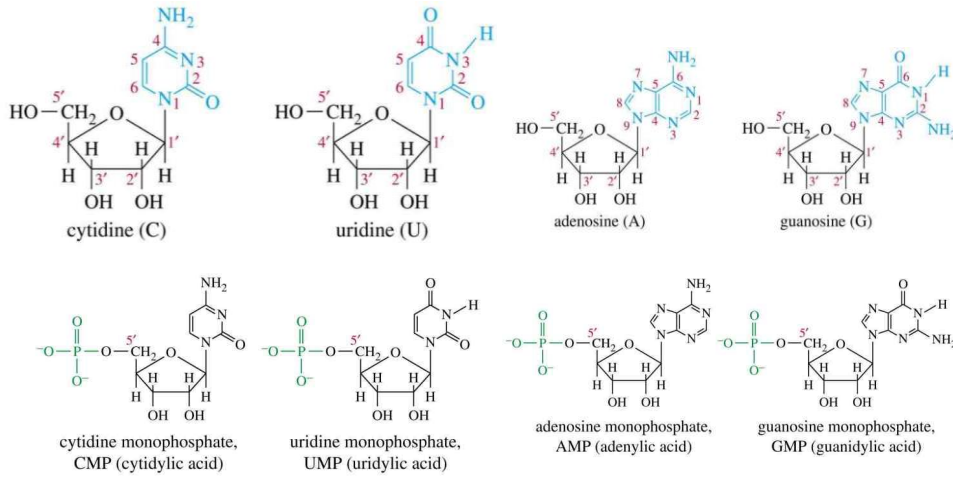
PRIMARNA STRUKTURA DNA – redoslijed nukleozida



=>

Ribonukleinska kiselina

- β-D-ribofuranozid vezan za heterocikličke baze (citozin, uracil, adenin i gvanin) preko anomernog C-atoma



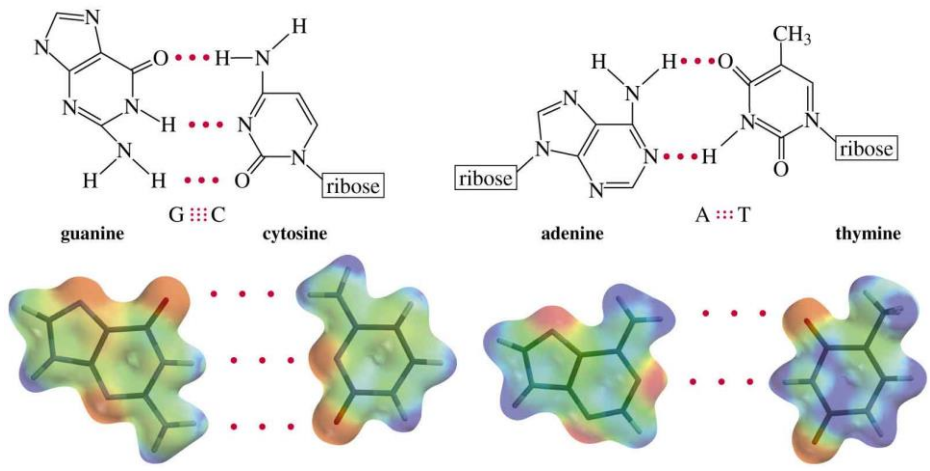
Deksiribonukleinska kiselina

- β-D-2-deoksiribofuranoza
- Heterocikličke baze: citozin, timin (umjesto uracila), adenin i gvanin
- Međusobno povezane preko fosfatne esterske skupine u primarnu strukturu

Osnovna svojstva strukture molekule DNA (Watson-Crickov model)

- DNA je desna dvostruka uzvojnica sačinjena od dvije niti polideoksiribonukleotida (promjer oko 2 nm)
  - okosnica molekule DNA sačinjena je od šećera deoksiriboze i fosfatnih skupina, a njezine dvije niti su antiparalelne (3'→ 5' i 5'→ 3')
- Nabijene fosfatne skupine okrenute su prema van
  - dvije niti DNA povezane su vodikovim vezama između dušikovih baza koje se nalaze u središtu uzvojnice
  - parovi baza uvijek su A=T i C≡G (dvije niti DNA su komplementarne)
  - hidrofobne interakcije između susjednih parova baza u DNA daju dodatnu čvrstinu dvostrukoj uzvojnici (engl.) *stacking*
  - razmak između susjednih baza je 0,34 nm
  - parovi baza su zakrenuti za 36° (10 parova baza = 1 okret = 3,4 nm)

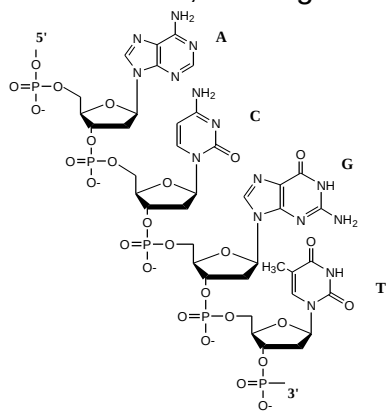
Sparivanje baza

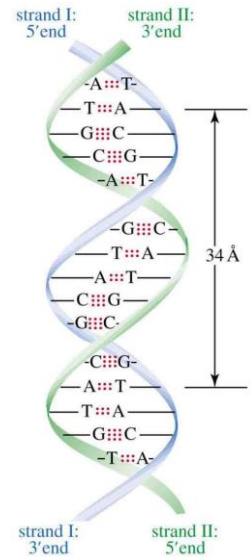


SEKUNDARNA STRUKTURA – definirana načinom sparivanja baza

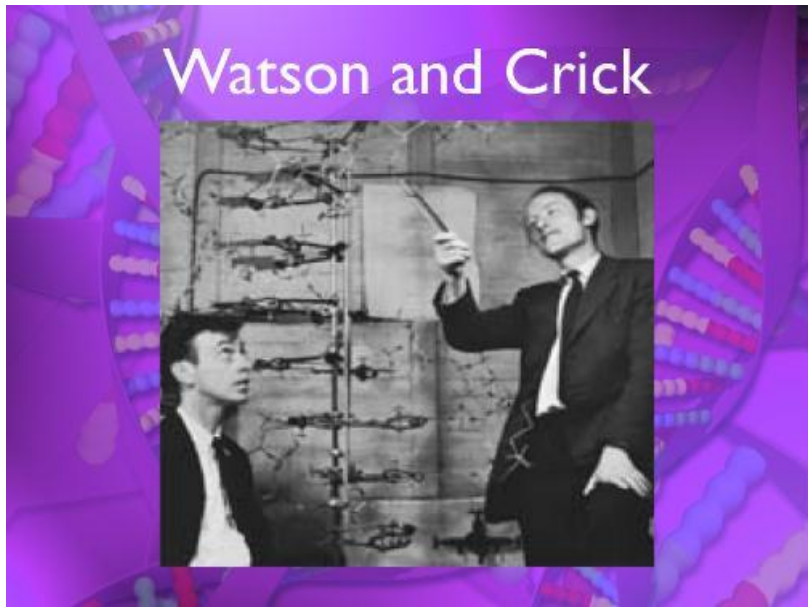
Međusobno povezivanje nukleotida u uzvojnicu DNA

- Antiparalelne uzvojnice, dva komplementarna polinukleotidna lanca tvore uzvojitu strukturu, helix
- Watson i Crick, 1953. god.





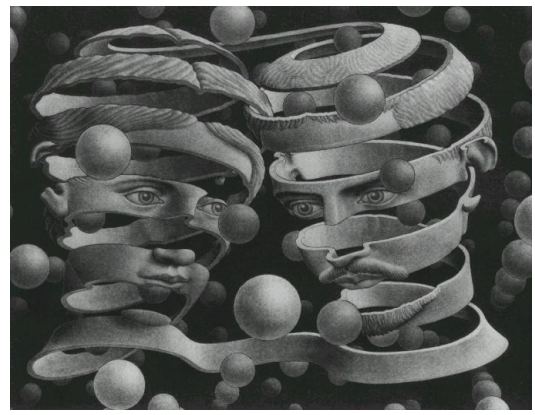
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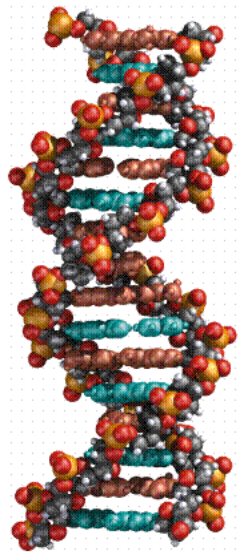
Model molekule DNA po Watsonu i Cricku

- Desna dvostruka uzvojnica promjera oko 2 nm
- Baze su smještene u unutrašnjosti, fosfati i šećeri na vanjskoj strani uzvojnice
- Ravnine baza približno su okomite na os uzvojnice
- Ravnine u kojima leži deoksiriboza gotovo su okomite na ravnine baza
- Razmak između susjednih baza je 0,34 nm
- Parovi baza međusobno su zakrenuti za 36°

Litografija «vrpca bez kraja» (M. C. Escher / Cordon Art, Nizozemska)



Međusobno povezivanje nukleotida u uzvojnicu DNA



DNA heliks

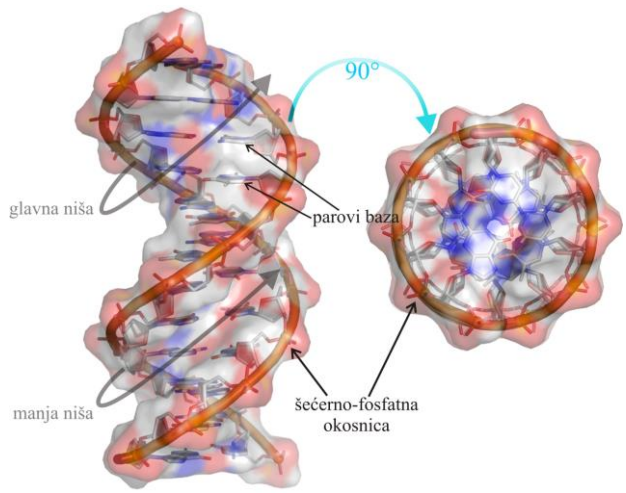
- Dva komplementarna polinukleotidna lanca tvore uzvojitu strukturu, heliks
- Watson i Crick, 1953.

TERCIJARNA STRUKTURA – raspored svih atoma u prostoru

Glavna i manja niša u DNA

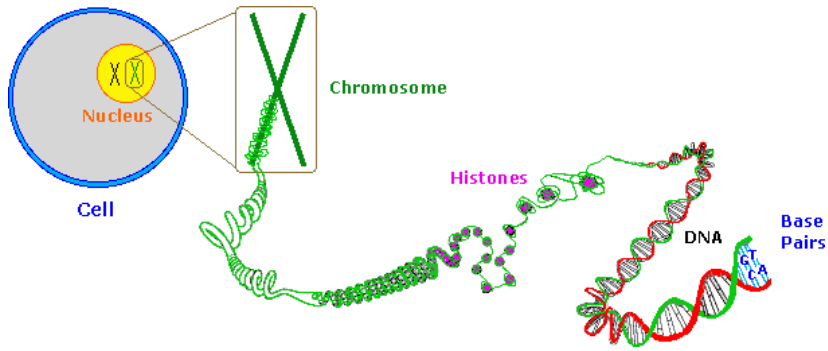
⇒ Razmak između dviju šećerno-fosfatnih okosnica uzduž osi dvostruke uzvojnice nije podjednak, pa stoga i niše (udubine) između dviju okosnica nisu podjednake veličine.

⇒ Veća udubina (niša) i manja udubina DNA



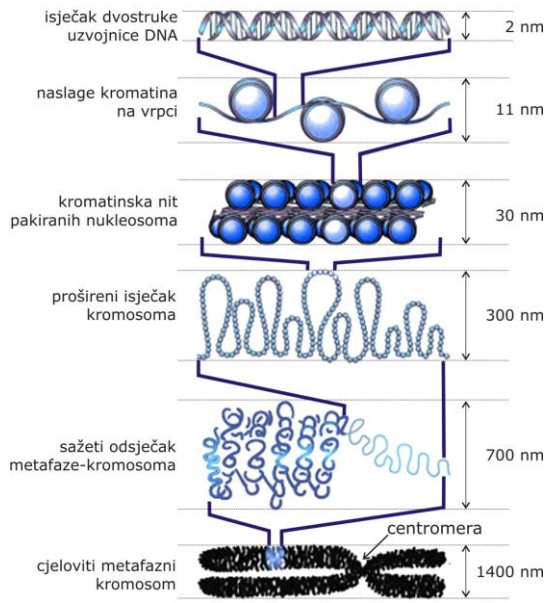
Organizacija staničnog genoma

- DNA pakirana u kromosome
- DNA omotana malim proteinima – histoni: H1, H2A, H2B, H3 i H4
- Kromatin – kompleks eukariotske DNA i proteina
- Udruživanje kromatina u kromosome
- Ukupna duljina DNA u ljudskoj stanici 2m, promjer jezgre 5-10 um

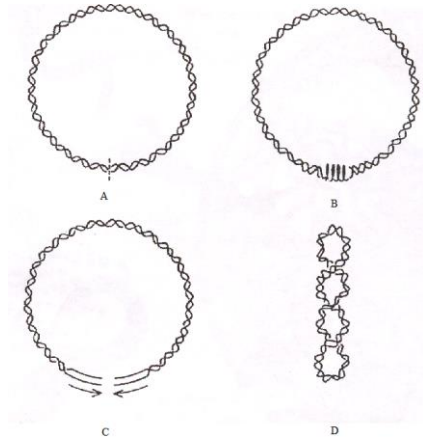


Stupnjevi stvaranja potpune metafaze-kromosoma

iz dvostruke uzvojnice DNA



Pretvorba dvostruke uzvojnice-DNA u superuzvojitu DNA



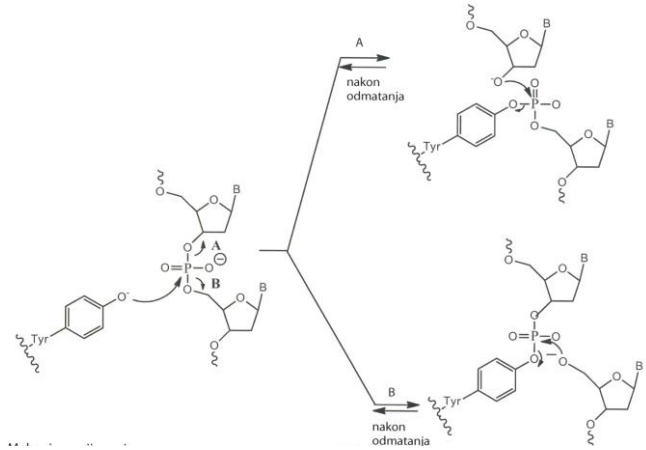
⇒ Linearna DNA može slobodno rotirati pri čemu se krajevi mogu povezati kovalentnom vezom i stvoriti kružnu (cirkularnu) DNA (**A**)

⇒ Cirkularna DNA se izvijanjem (poput gumene vrpce) može prevesti u super-uzvojitu DNA (**D**)

Pretvorba dvostruke uzvojnice-DNA u super-uzvojitu DNA

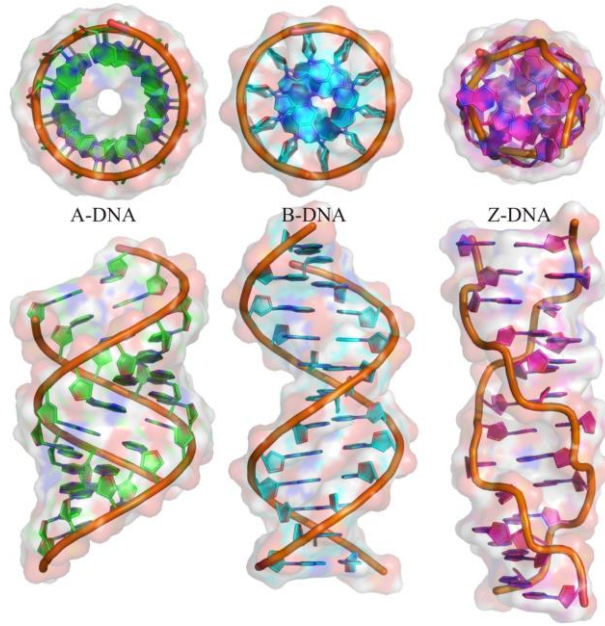
⇒ Cijepanje DNA kataliziraju enzimi DNA-*topoizomeraze* I i II

⇒ DNA-*topoizomeraza* I, katalizira cijepanje jedne uzvojnice od dvostruko uzvojite DNA, dok *topoizomeraza* II, katalizira prijelazno cijepanje obiju uzvojnica DNA



34

Konformacije DNA



35

Konformacije DNA

⇒ Tri su tipa općih DNA konformacija DNA: dvije su desno-usmjerene DNA (A-DNA i B-DNA) i jedna lijevo-usmjerena Z-DNA

⇒ Svaka se od tih konformacija sastoji od uzvojnice koju čine dva aniparalelna polinukleotidna lanca u Watson-Crickovim parovima baza povezanih vodikovim vezama.

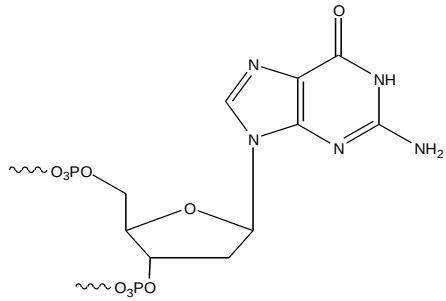
⇒ Desno-usmjerene uzvojnice se razlikuju od lijevo usmjerene DNA u razmaku potrebnom za jedan zakret (*pitch*), načinu slaganja šećernih grupa, kutu za koji su parovi baza izvijeni od osi uzvojnice i veličini niša

⇒ B-DNA je prevladavajući oblik dok je A-DNA kraća i zbijenija od B-DNA konformacije

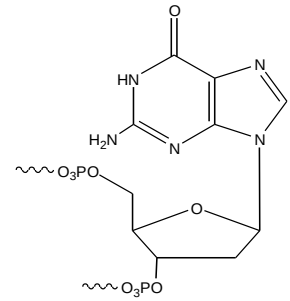
⇒ Z-DNA je manje zastupljena konformacija DNA u stanici sadrži samo manju nišu

36

Konformacije DNA



3

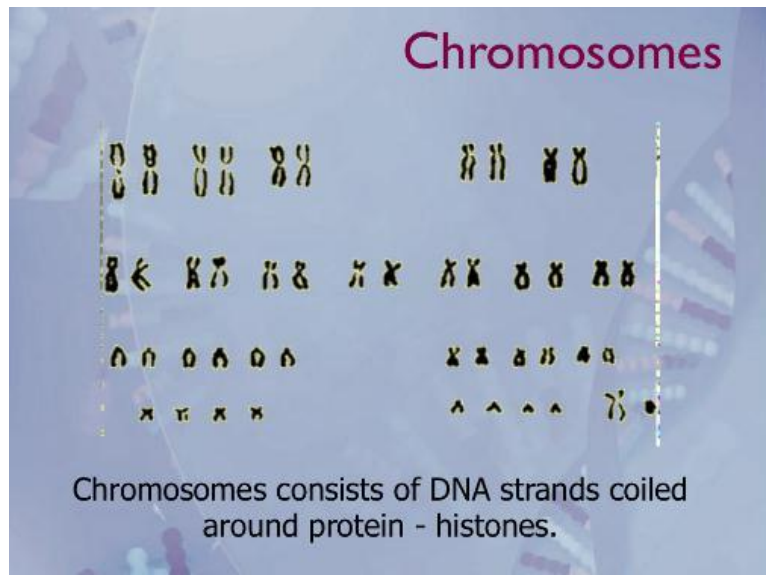


4

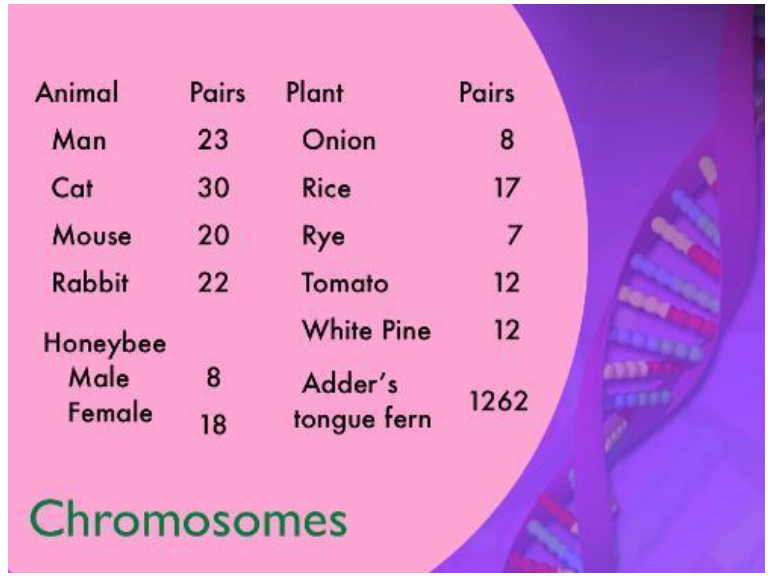
⇒ *Anti*-usmjerenje glikozidne veze u konformacijama A-DNA i B-DNA (**3**)

⇒ *Syn*-odnos deoksiriboze i purinskih jezgri i *anti*-usmjerenje deoksiriboze i pirimidinskih baza u Z-DNA

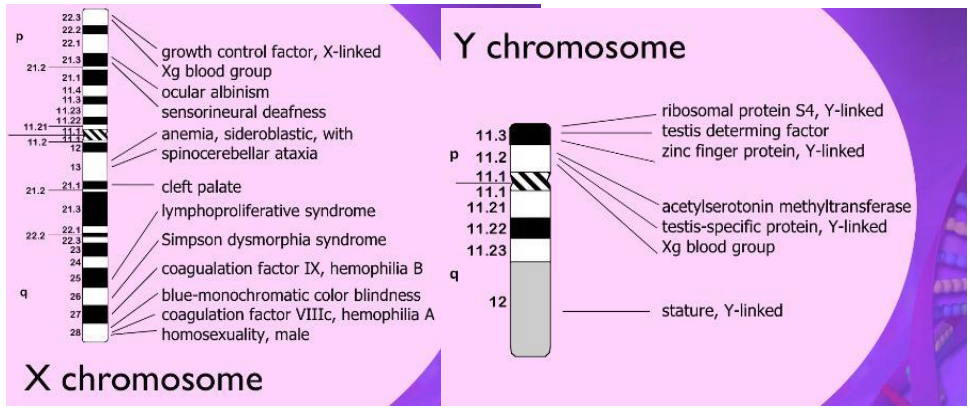
37



- Ljudski genom podijeljen je na 24 kromosoma (22 autosoma i 2 spolna kromosoma)

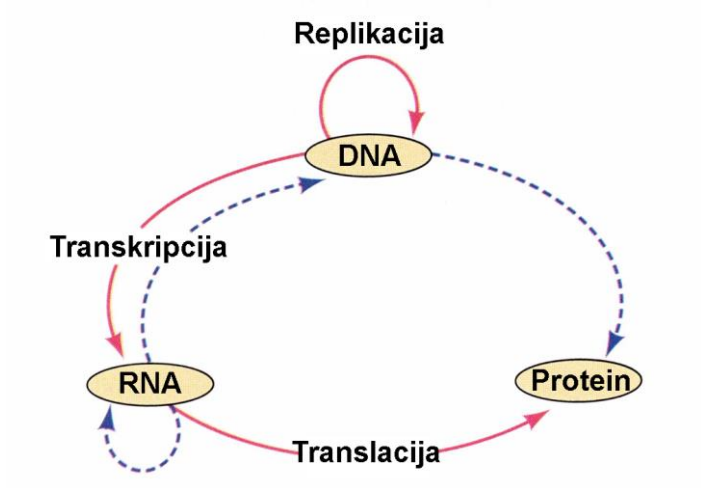


Geni na X i Y kromosomu

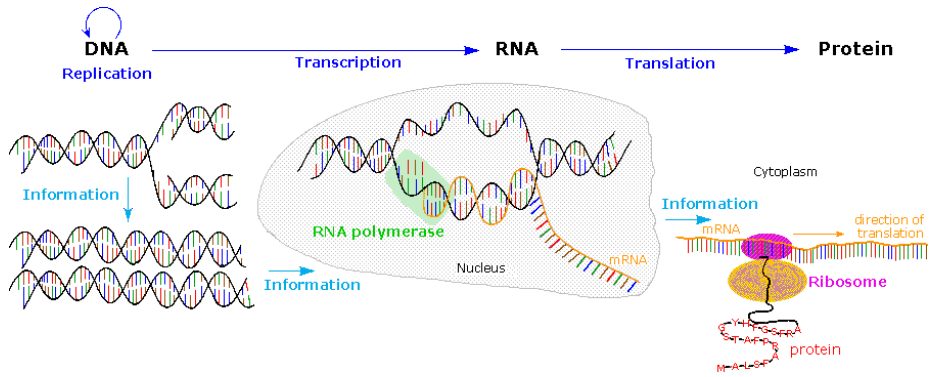


- Hemofilija - genetički poremećaj smanjenog zgrušavanja krvi zbog nedostatka supstrata tromboplastina
- Na kromosomu X – recesivno svojstvo (češće oboljevaju muškarci - 1:100.000, žene - 1:100 000 000)

Središnja dogma molekularne biologije



Replikacija, transkripcija i translacija

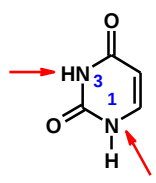


- Osnovni biološki proces razmnožavanja – zahtijeva vjerni prijenos genetičke informacije s roditelja na potomstvo, točna replikacija ključna za život
- Dijeljenje stanica – udvostručavanje genoma
- Mehanizmi za popravljanje pogrešaka
- Stanični genom podložan promjenama – prisutnost mutacija i preslagivanje gena važna za evolucijski razvoj (rekombinacija homolognih kromosoma u mejozi omogućuje stvaranje novih kombinacija u budućim generacijama)

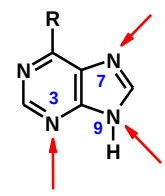
Kemija nukleozida

Kondenzacije šećera i nukleozidnih baza

- Prva sinteza 1914. god.
- Mjesta supstitucije na nukleozidnim bazama
- Metode kondenzacije:
  1. Metoda teških metala (Koenigs-Knorr)
  2. Fuzija (Helferich)
  3. Hilbert-Johnsonova i sililna metoda

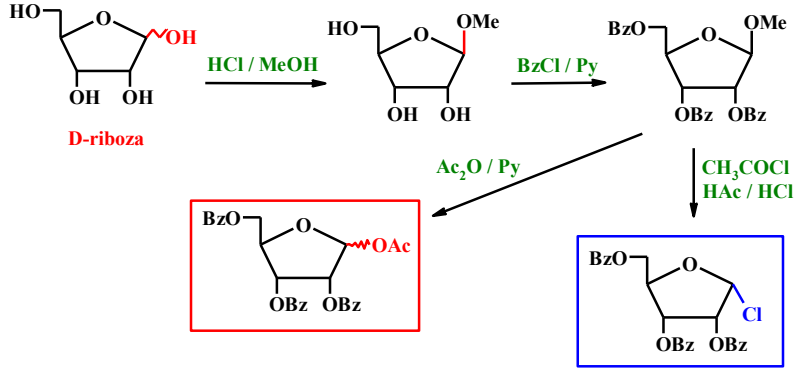


N-1
N-3
N-1,N-3 disupstituticija



N-3
N-9
N-7

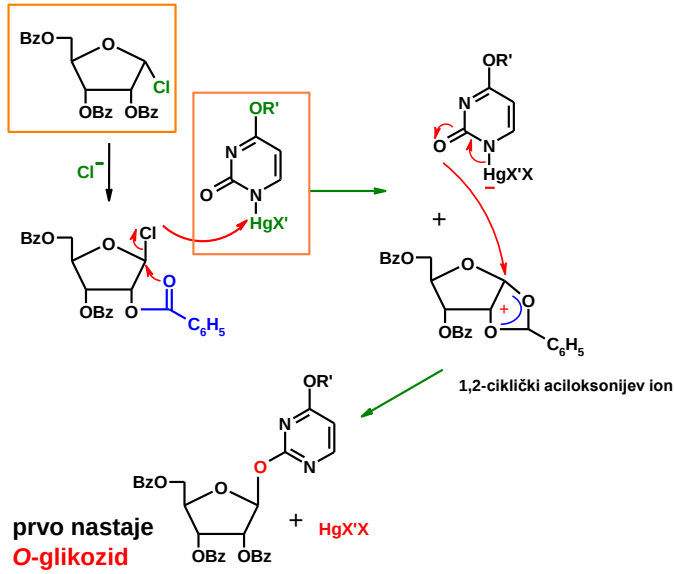
Zaštita funkcionalnih skupina šećera



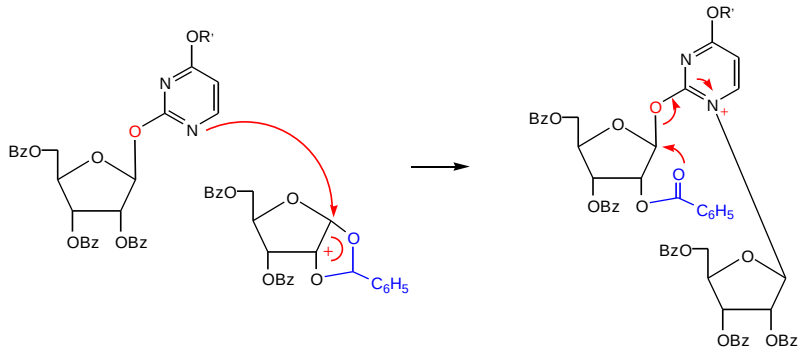
1. Metoda teških metala (Koenigs-Knorr)

- Koriste se soli žive i srebra
- Veza žive s heterocikličkim bazama ima više kovalentni karakter nego srebro → živa se ponaša kao odlazeća skupina u elektrofilnoj supstituciji pirimidina
- Živine soli su topljivije → kraće vrijeme reakcije!

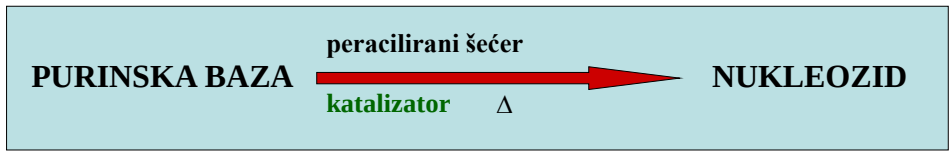
Sinteza pirimidinskih nukleozida metodom živinih soli



Pretvorba *O*-glikozida u nukleozid



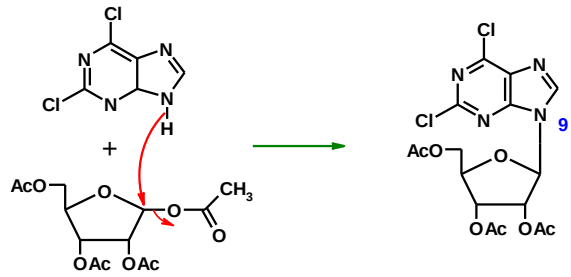
2. Fuzija (HELFERICH) - bez otapala



- **AMINO I HIDROKSI PURINI – visoka t.t. nereaktivni**
- **ACILIRANI DERIVATI – reagiraju**
- **KISELI PURINI (6-cijanopurin, 2,6-diklorpurin, 2,6,8-triklorpurin) – reagiraju**
- **SLABO KISELI (6-merkaptopurin) – ne reagira**

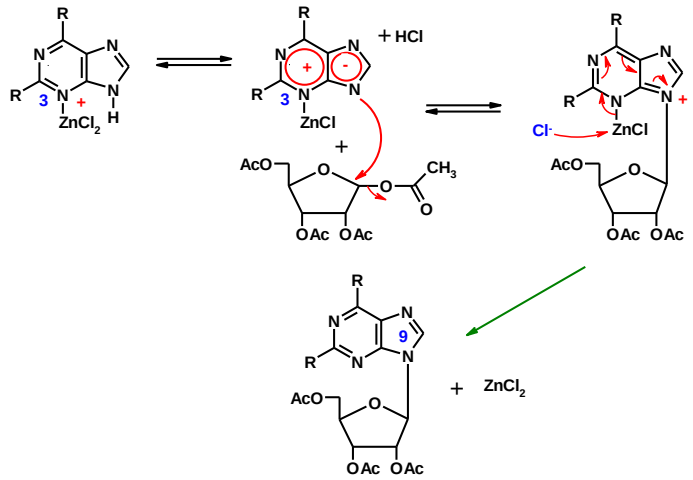
- **$TiCl_4$**
- **CH_3-C_6H_4-SO_3H**
- **$ZnCl_2$**
- **$CHCl_2COOH$**
- **I_2**

2. Fuzija (HELFERICH) - bez otapala



- **Slobodne, nezaštićene nukleozidne baze**
- **1-*O*-acilni derivati šećera**
- **Ne nastaju *N*-3 derivati purina**
- **Pirimidinski derivati – slaba iskorištenja**

Mehanizam aktiviranja purina katalizatorom

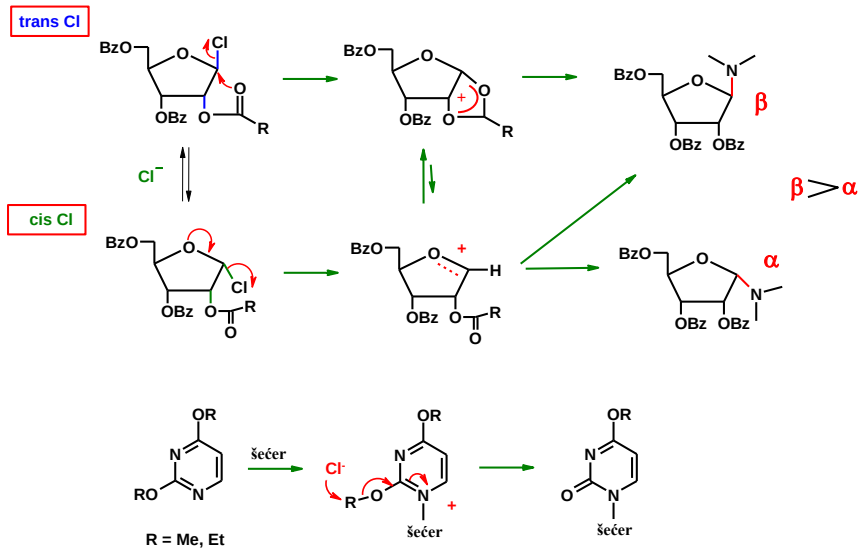


3. Hilbert-Johnsonova i sililna metoda

- **Koriste se:**
- **dialkoksi pirimidini - nisu komercijalni – sinteza u više stupnjeva**
- **1-halogenirani derivati šećera**
- **Metoda nije stereoselektivna – nastaju smjese α i β– nukleozida**

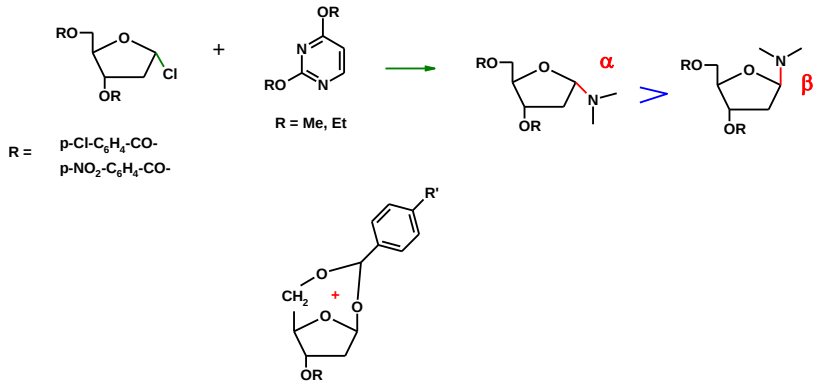
Mehanizam Hibert-Johnsonove kondenzacije dialkoksipirimidina

ribo-serija



Mehanizam Hilbert-Johnsonove kondenzacije dialkoksipirimidina

2-deoksiribo-serija



Sililna metoda kondenzacije

- **Sililna aktivacija baza – dobro topljivi heterocikli**
- **Peracilirani šećer – stabilniji od halogenida**
- **Nakon reakcije kondenzacije sililni derivati lagano hidroliziraju u blago kiselim uvjetima za vrijeme obrade produkta**
- **Nastaju uglavnom β-nukleozidi**

Reagensi za sililiranje: HMDS $Me_3SiNHSiMe_3$

TMSCl Me_3SiCl

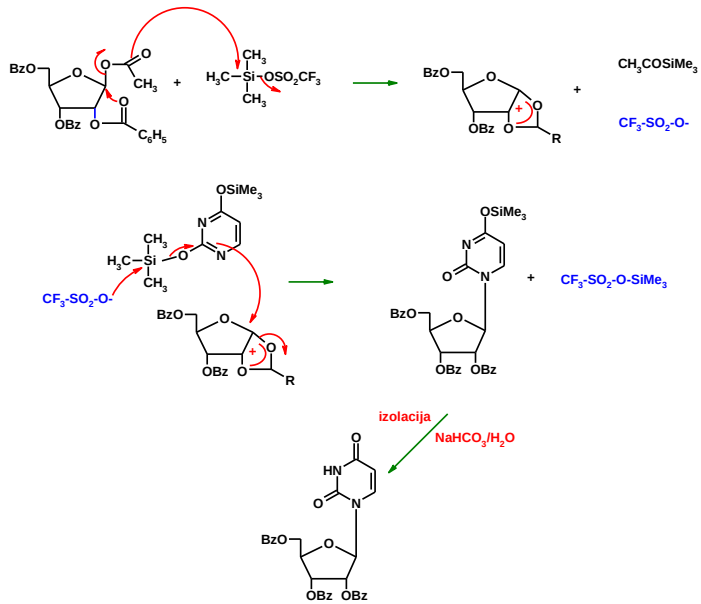
bis(trimetilsilil)acetamid BSA $CH_3C(=NSiMe_3)OSiMe_3$

Katalizatori $SnCl_4$

trimetilsilil triflat $Me_3SiO\text{-}SO_2CF_3$

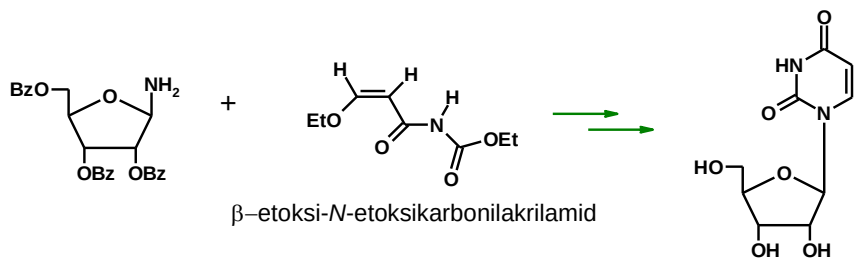
trimetilsililnonaflat $Me_3SiO\text{-}SO_2C_4H_9$

Sililna metoda kondenzacije



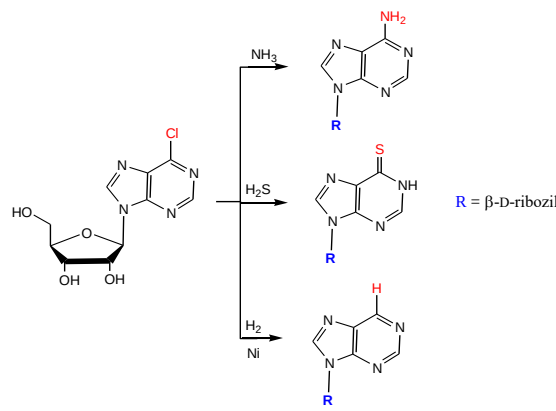
Sinteza nukleozida građenjem heterocikličkog prstena

- Koristi se kod pirimidinskih i purinskih nukleozida
- PREDNOST – mjesto vezivanja šećera na heterocikličku bazu je unaprijed određeno

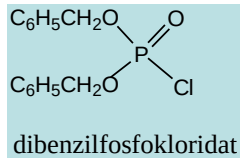


β–etoksi-*N*-etoksikarbonilakrilamid

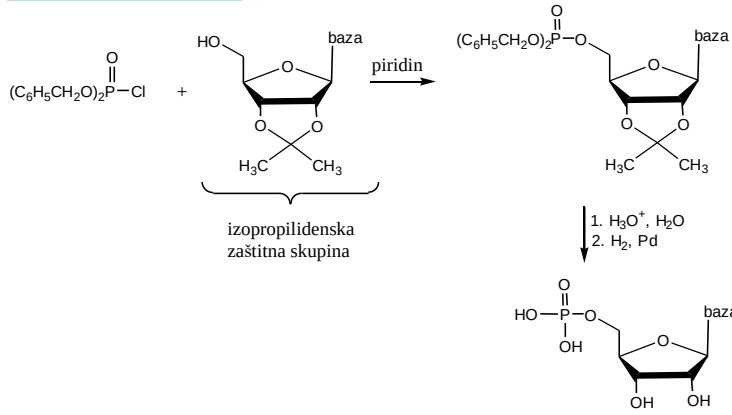
Transformacije funkcionalnih skupina nukleozida



Prevođenje nukleozida u nukleotide



dibenzilfosfokloridat



izopropilidenska
zaštitna skupina

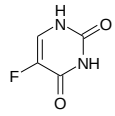
Modificirani nukleozidi kao lijekovi

- Polazne strukture za racionalni dizajn i razvoj novih antivirusnih i antitumorskih lijekova
- Nukleozidni analozi (mimetici):
  - antivirusni i antitumorski lijekovi
  - inhibiraju virusne polimeraze kao terminatori DNA/RNA lanca, ili kompetitivni inhibitori

Modificirani nukleozidi

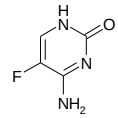
- Korelacija između promjena u strukturi i biološkog djelovanja analoga, u usporedbi s prirodnim nukleozidom
- Upoznavanje uloge nukleotida u staničnom metabolizmu, tj. koji je dio molekulske strukture bitan za proces prepoznavanja u stanici

Modifikacije pirimidinske jezgre
supstitucija u *C*(5)-položaju



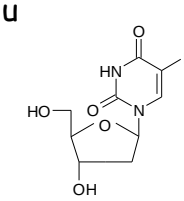
fluorouracil

antitumorsko djelovanje



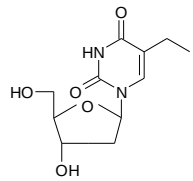
flucitozin

antifungalno djelovanje



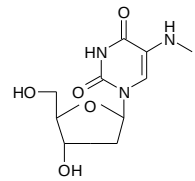
idoksuridin

IdU, prvi antivirusni agens, u oftalmologiji



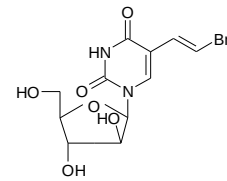
edoksudin

protiv virusa herpes simplexa



MADU

antitumorsko djelovanje

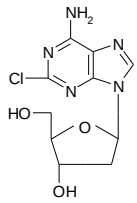


sorivudin

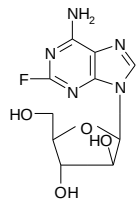
antivirusno djelovanje

Modifikacije purinske jezgre
supstitucija

- uvođenje halogena u purinsku jezgru



kladribin

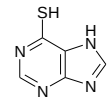


fludarabin

protiv leukemije

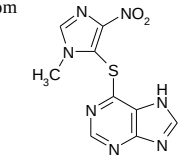
purinski nukleozidni antimetabolit,
otporan na deaminazu
antitumorski agens kao fosfat

- zamjena kisika sumporom



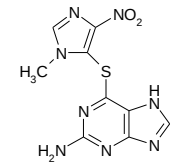
6-merkaptopurin

antitumorsko i
imunosupresivno
djelovanje



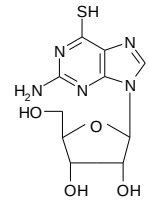
azatioprin

imunosupresant
i antireumatik

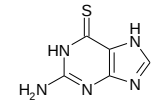


tiamiprin

antivirusno
djelovanje



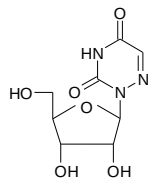
tiogvanozin



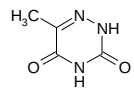
tiogvanin

antitumorsko
djelovanje

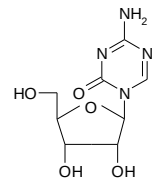
aza analozi



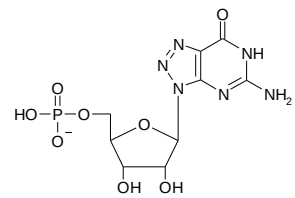
6-azauridin



6-azatimin

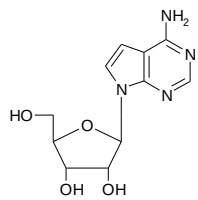


5-azacitidin

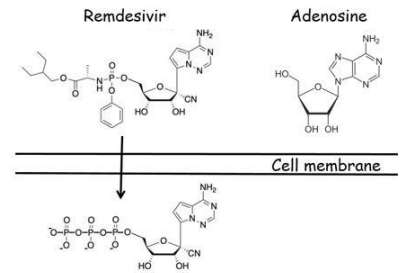


8-azagvanin kao baza

deaza analozi

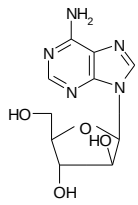


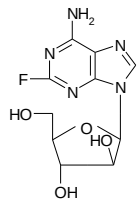
7-deazaadenozin
antibiotik tubercidin

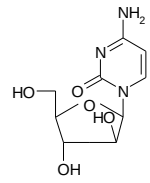


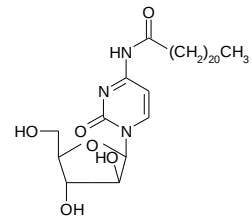
Modifikacije na šećernom dijelu molekule

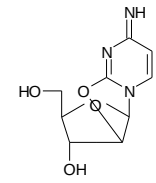
- promjena konfiguracije na C-2'


vidarabin


fludarabin

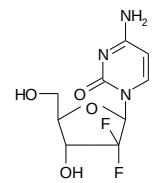

citarabin


enocitabin

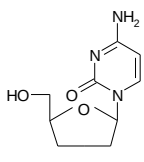

ancitabin

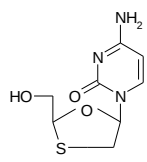
arabino - konfiguracija!

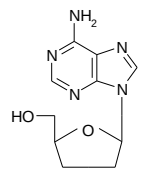
- supstitucija na riboznom prstenu

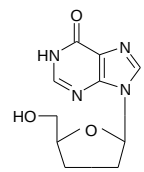

gemcitabin

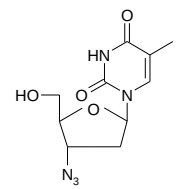
- analozi bez 2'- i 3'-hidroksilnih skupina

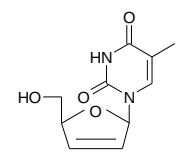

zalcitabin


lamivudin


dideoksiadenozin

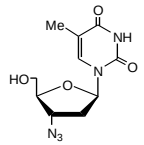

didanozin (DDI)


zidovudin (AZT)

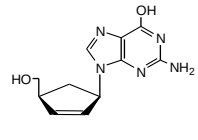

stavudin (d4T)

inhibitori reverzne transkriptaze

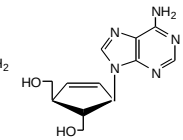
Antivirusni lijekovi koji sadrže karbocikličke ili furanske prstenove umjesto šećerne jezgre



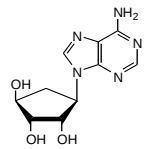
AZT



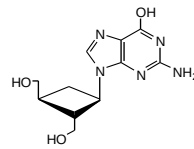
(−)-1*R*,4*S*-karbovir



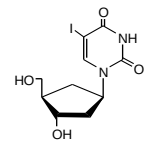
(+)-1*R*,4*S*,5*R*-BCA



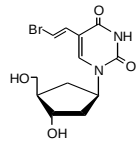
(−)-1*S*,2*R*,3*S*,4*R*-5'-noraristeromicin



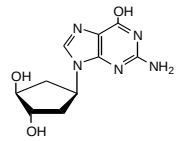
(+)-1*R*,2*R*,3*S*-BHCG



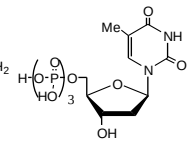
(+)-1*R*,3*S*,4*R*-C-IDU



(+)-1*R*,3*S*,4*R*-C-BVDU

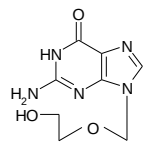


(+)-1*R*,3*S*,4*R*-CDG



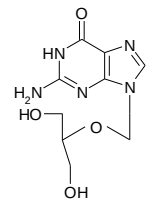
D-dTTP

Aciklički purinski analozi



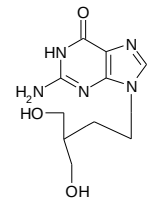
aciklovir

protiv virusa herpes simplex



ganciklovir

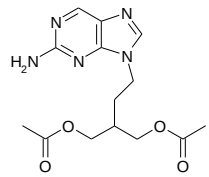
protiv citomegalovirusa



penciklovir

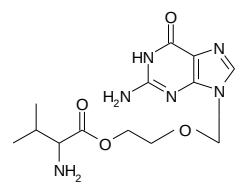
karba- analog,

protiv virusa herpesa



famciklovir

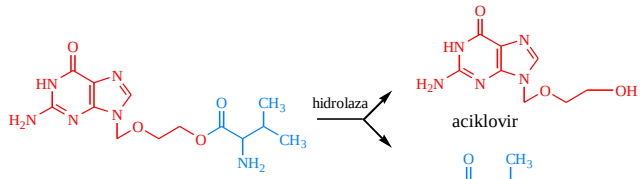
2-aminopurinski analog



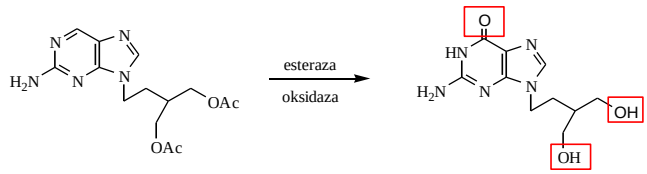
valaciklovir

L-valinski ester!

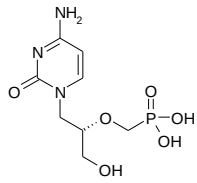
Prolijek valaciklovir



Prolijek famciklovir

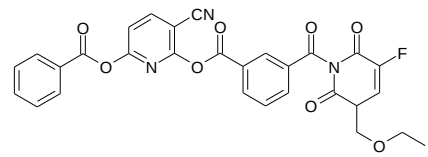


Aciklički pirimidinski analozi

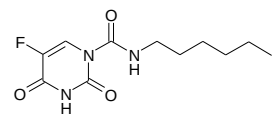


cidofovir

aciklički citidinski fosfonilni derivat,
djeluje protiv citomegalovirusa



emitefur



carmofur

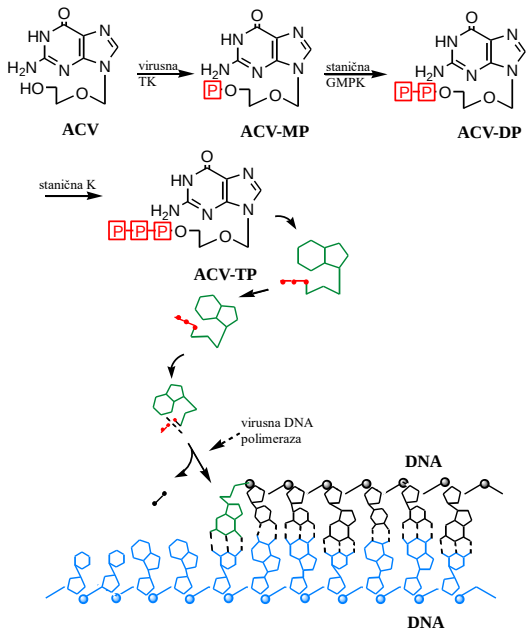
supstitucija u C-5 položaju!
antitumorsko djelovanje

ANALOZI NUKLEOZIDA
KAO ANTIVIRALNI AGENSI

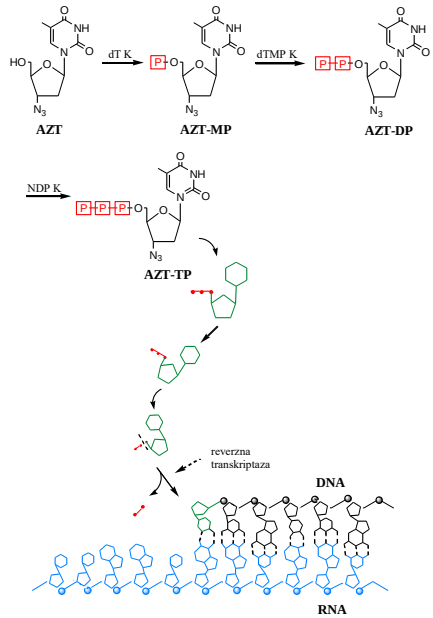
Virusi od medicinskog interesa:

	Virus	Bolesti
RNA-virusi	Human immunodeficiency virus (HIV)	AIDS
	Influenza virus	influenca
DNA-virusi	Herpes simplex virus type 1 (HSV-1)	infekcije ustiju
	Herpes simplex virus type 2 (HSV-2)	infekcije genitalija i očiju, encefalitis
	Varicella zoster virus (VZV)	vodene kozice, herpes zoster
	Epstein – Barr virus (EBV)	mononukleoza, glandularna groznica, sindrom kroničnog umora,
	Cytomegalovirus (CMV)	retinitis, pneumonia, bolesti probavnog trakta infekcija CNS-a
	Rhinovirus	prehlade
	Picornavirus	polio (dječja paraliza)
	Papillomavirus	bradavice

Biokemijski mehanizam djelovanja aciklovira na virusnu DNA-polimerazu

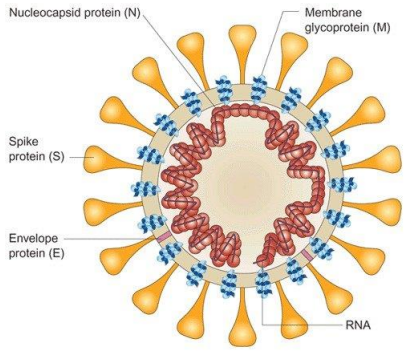


Biokemijski mehanizam djelovanja azidotimidina na reverznu transkriptazu



Corona virus

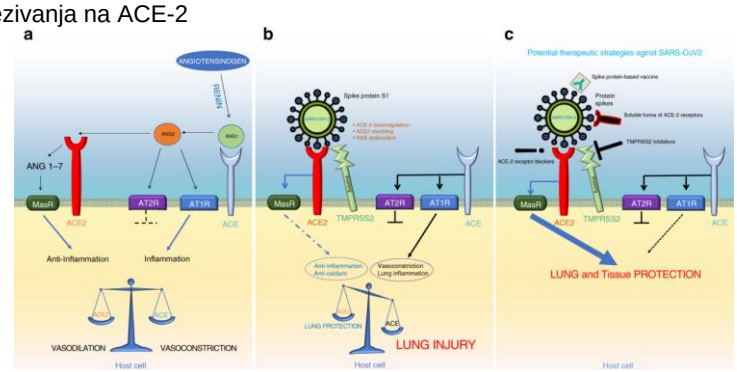
- **SARS-CoV-2** uzrok pandemije COVID-19 2019./20.
- preko 36 milijuna slučajeva zaraženih identificirani širom svijeta među kojima je oko 24 milijuna ozdravljenih, a više od 1 milijun smrtnih slučajeva
- > 625 milijuna slučajeva zaraženih identificirani širom svijeta među kojima je oko 605 milijuna ozdravljenih, a više od 6.55 milijuna smrtnih slučajeva (10. 2022)



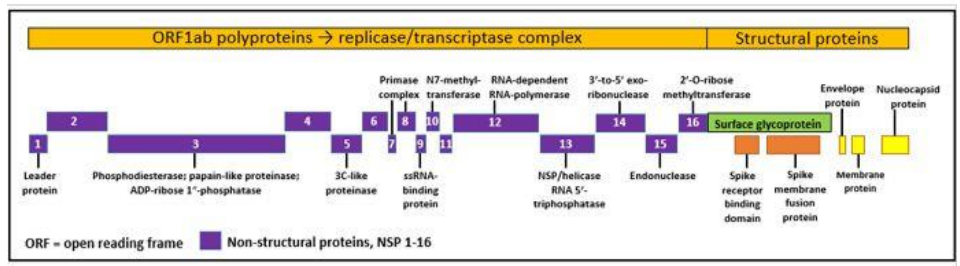
- **RNA** – jednolančana,
- 80-120 nm promjera, β-koronavirus (α-, β-, γ- i δ-koronavirusi)
- Virus se veže na enzim vezan za membranu, ACE-2 (*angiotensin-converting enzyme*) i aktivira se tranmsmembranskom serin-proteazom TM; obje su potencijalne mete, brza transmisija virusa zbog visokog afiniteta vezivanja na ACE-2

Potencijalne mete za antivirusne lijekove protiv COVID-19

- RNA virus, u replikaciji koristi stanične viruse i vlastitu RNA-ovisnu RNA polimerazu (RdRp)
- Fuzija koronavirusa zahtijeva "pristajanje" specijaliziranih glikoproteina, "bodlji", koji strše iz virusne površine i komuniciraju sa specifičnim molekulama na površini stanica domaćina
- Virus se veže na enzim vezan za membranu, ACE-2 (*angiotensin-converting enzyme*) i aktivira se tranmsmembranskom serin proteazom TM; obje su potencijalne mete, brza transmisija virusa zbog visokog afiniteta vezivanja na ACE-2



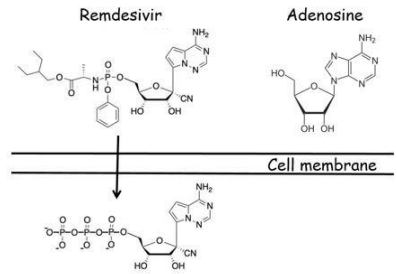
Genom virusa SARS-CoV-2



- Potencijalne mete uključuju papain-sličnu proteazu (PL pro, nsp 3), 3C-sličnu proteazu (3CL pro; nsp 5), N7-metiltransferazu (nsp 10), RNA-ovisnu RNA polimerazu (nsp 12), helikazu (nsp 13) i domenu na koju se veže receptor (RBD)

Remdesivir

- Derivat fosforamidata, remdesivir (GS-5734), zaobilazi ovaj stupanj i omogućuje ulazak u stanice, gdje se mogu akumulirati visoke koncentracije aktivnog trifosforiliranog derivata
- FDA odobrila primjenu antivirusnog lijeka remdesivira u bolničkom liječenju oboljelih od COVID-19 (intravenozna primjena)



- Remdesivir je fosforamidatni analog adenozina; ulazi u stanicu gdje se hidrolizira esterazama, a aktivni trifosforilirani analog adenozina nastaje pomoću unutarstaničnih nukleozid-fosfat kinaza

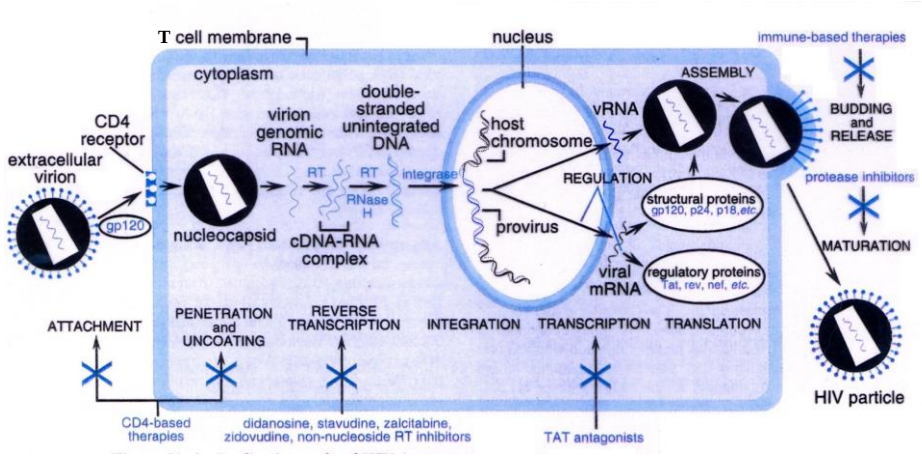
Selected stages of HIV replication that may be targets for therapeutic intervention.

Stage	Possible intervention
Binding to target cell	Antibodies to virus or cellular receptors; genetically engineered soluble CD4 proteins
Fusion of virus with target cell	Antibodies or drugs that block the fusogenic domain of virus
Entry into target cell and uncoating of RNA	Drugs (by analogy with uncoating inhibitors against rhinoviruses and related picornaviruses)
Transcription of RNA to DNA by reverse transcriptase	Reverse transcriptase inhibitors (for example, AZT and other dideoxy or didehydro-dideoxy nucleoside congeners)
Degradation of RNA by RNase activity (encoded by viral *pol* gene)	RNase H inhibitors
Migration of viral DNA to nucleus	Agents that block viral DNA migration into nucleus (as yet unidentified)
Integration of DNA into host genome	Agents that inhibit *pol*-encoded integrase function (as yet unidentified)
Transcriptional-translational efficiency of viral RNA	Inhibitors of Tat protein; mutant Tat protein molecules; TAR inhibitors; "pseudo-TAR" molecules; Rev protein inhibitors; antisense constructs against *tat* or *rev* mRNAs; activator of the *nef* gene (?)
Ribosomal frameshifting	Ribosomal frameshift inhibitors (as yet unidentified)
Viral component maturation Gag-Pol fusion polyprotein cleavage	Viral protease inhibitors (for example, transition state mimetics, synthetic peptides)
Myristoylation and glycosylation	Myristoylation and glycosylation inhibitors (for example, castanospermine and inhibitors of trimming glucosidase)
Packaging	Antisense construct against the packaging sequence
Viral budding	Interferons or interferon inducers; antibodies to viral antigens that may be associated with viral release; inhibitors of the *vpu* gene (?)

Odobreni lijekovi u tretmanu HIV-infekcije:

1. **Nukleozidni inhibitori reverzne transkriptaze (NiRT) 10 kom**
2. **Nenukleozidni inhibitori reverzne transkriptaze (NNiRT) 3 kom**
3. **Inhibitori proteaze (iP) 8 kom**
4. **Inhibitori fuzije (iF) 1 kom**

Replikacijski ciklus HIV-1 retrovirusa



- **RT-reverzna transkriptaza (RNA ovisna DNA polimeraza)**
- **cDNA-koplementarna DNA**
- **Tat-protein koji regulira viralnu transkripciju**
- **RNasaH-ribonukleaza H**
- **gp-glikoprotein envelope**