Antiviral Agents, chapter 43

Different living organisms

Eucaryotes

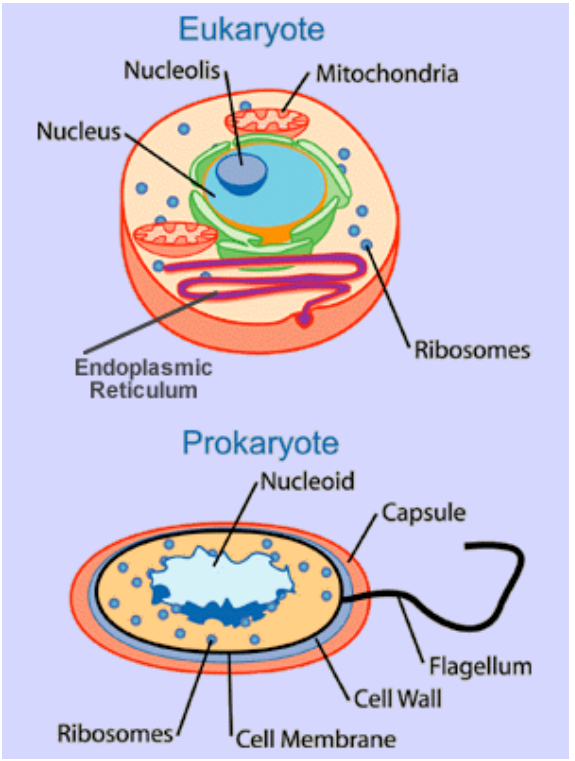
Mono or polycellular
Cell nucleus; DNA
May have cell wall
sexual and / or asexual replication

Animals

Plants

Fungi

Protocista: - Protozoea
- Algea

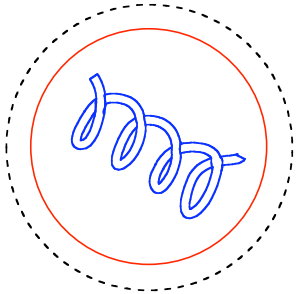


Procaryotes

Bakteriea:
Monocellular, no nucleus - DNA single strand, cell wall, asex. replic.

Virus

RNA or DNA + protein coating (not really a cell)
Use other oramisms ribosomes for protein synth

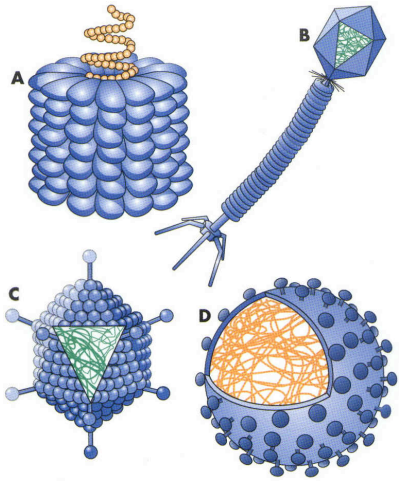


DNA or RNA

Protein Coat - Capsid

Protein coat - Envelope
(glycoproteins - antigens, not all viruses)

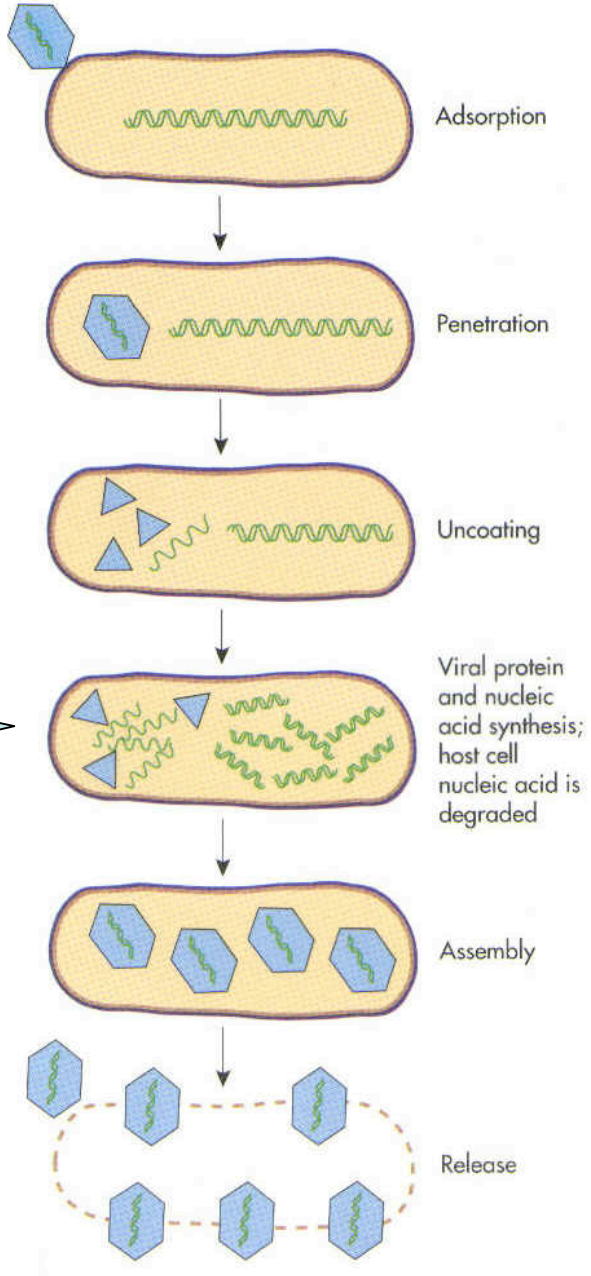
Many different shapes



May attack:

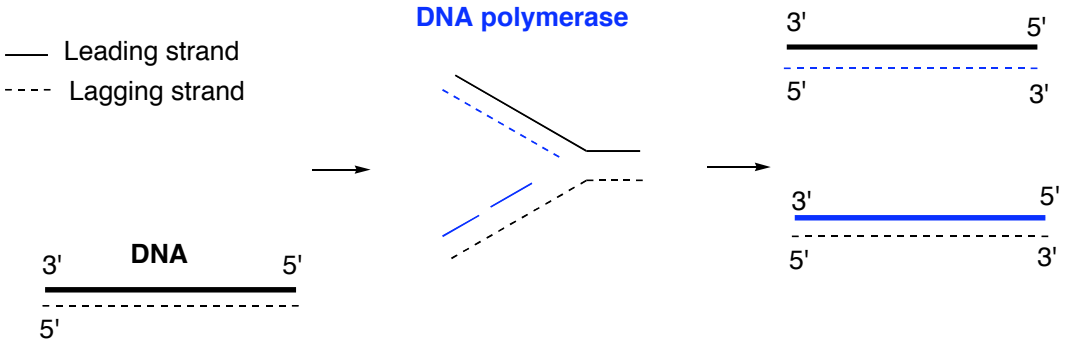
- **Animals**
- **Plants**
- **Bacteria (Phages)**

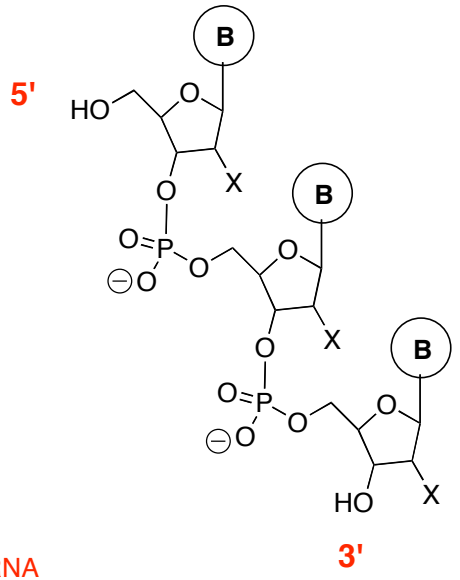
Stages of replication



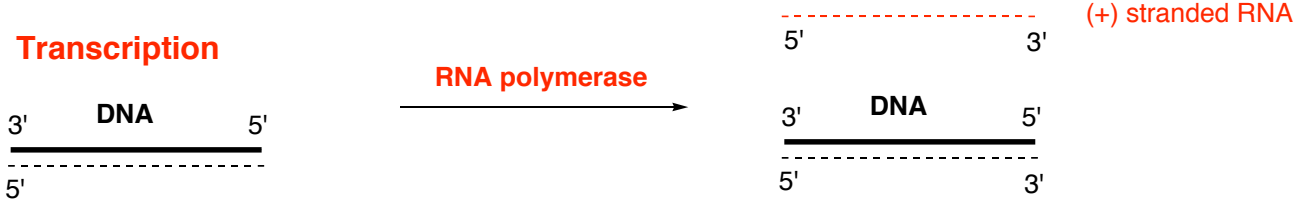
Procaryotes and eucaryotes

Replication

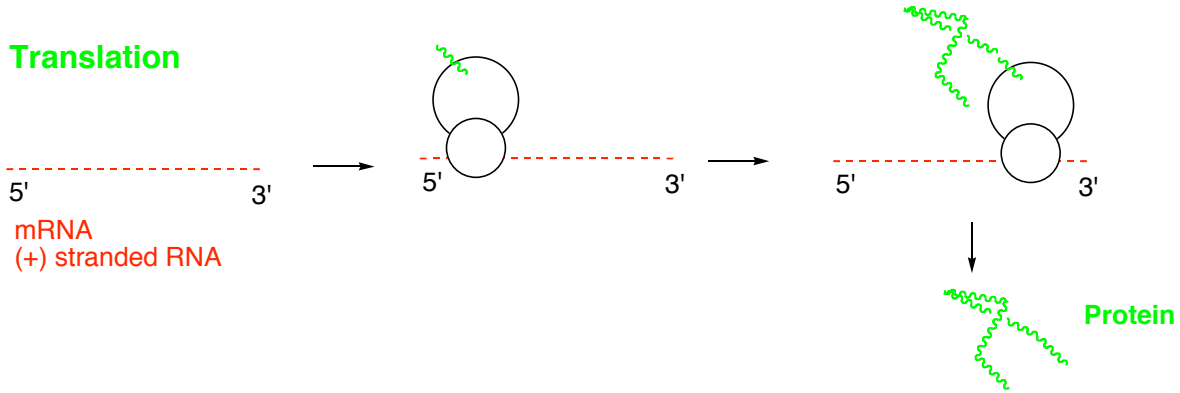




Transcription

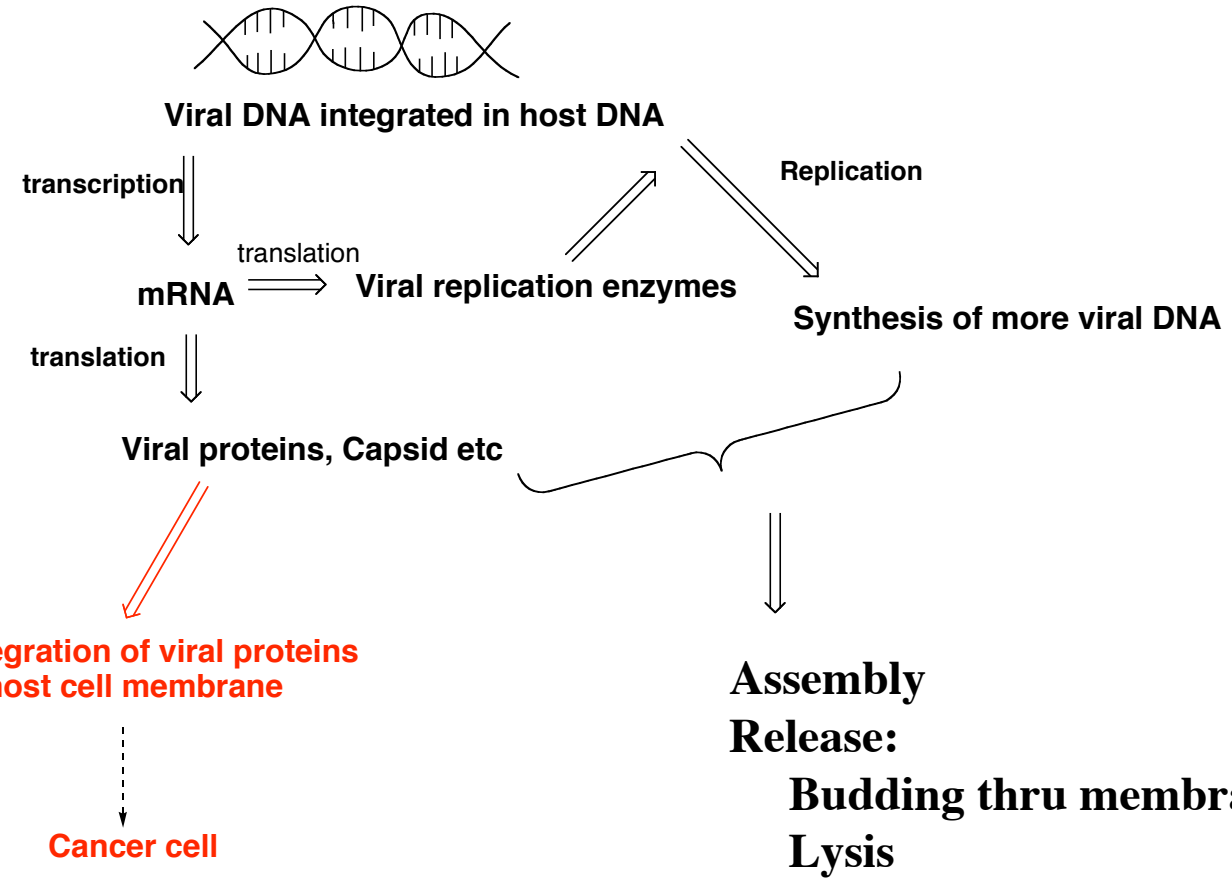


Translation



Stages of replication - DNA virus

Attachment, penetration, uncoating, transfer of DNA to cell nucleus



Assembly

Release:

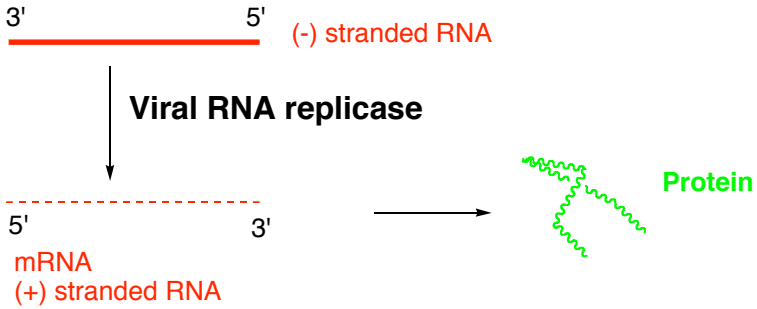
- **Budding thru membranes (knoppskyting)**
- **Lysis**

Oncogenic viruses

Stages of replication - RNA virus

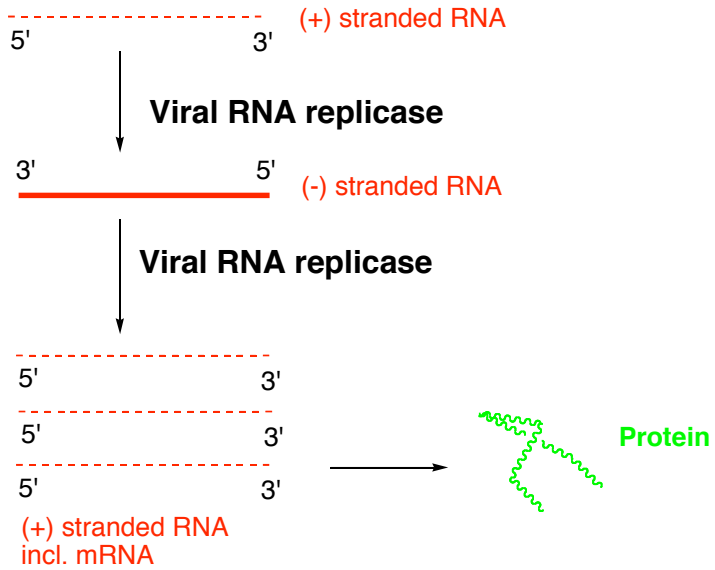
(+) stranded RNA = mRNA

Alternative A: (-) RNA virus

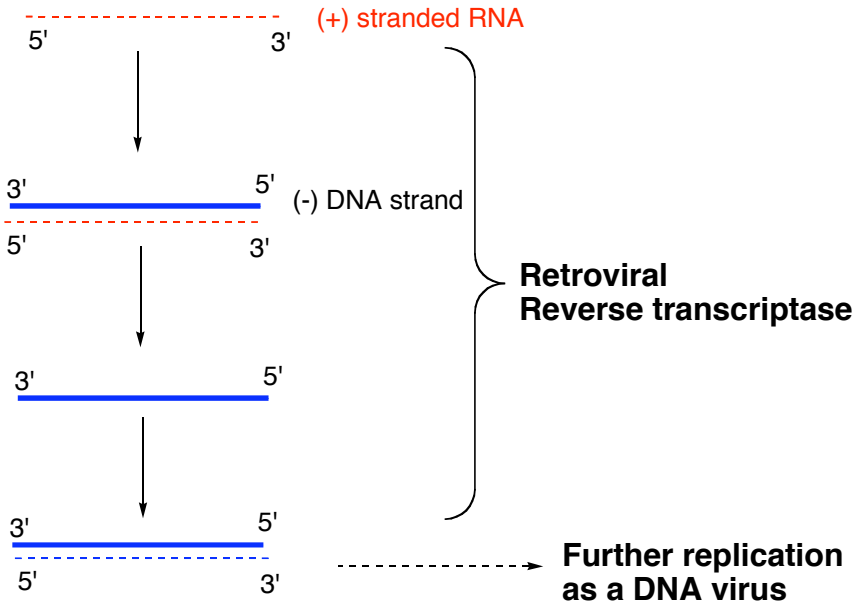


More difficult to treath RNA virus infect.
More mutation - Less repair mech. than with DNA

Alternative B: (+) RNA virus (≠Retrovirus)



Alternative C: Retrovirus; (+) RNA virus



Antiviral Drugs

- **Neuraminidase Inhibitors**
- **Nucleoside analogs - Antimetabolites**
- **Other comp. that interfere with replication**
- **Comp. that interfere with translation (protein synth)**
- **(Interferon / interferon inducers)**

Specific retroviral drugs

- **Reverse transcriptase inhibitors**
  - **Nucleosides (NRTIs)**
  - **Non-nucleosides (NNRTIs)**
- **Protease inhibitors**

Neuraminidase Inhibitors

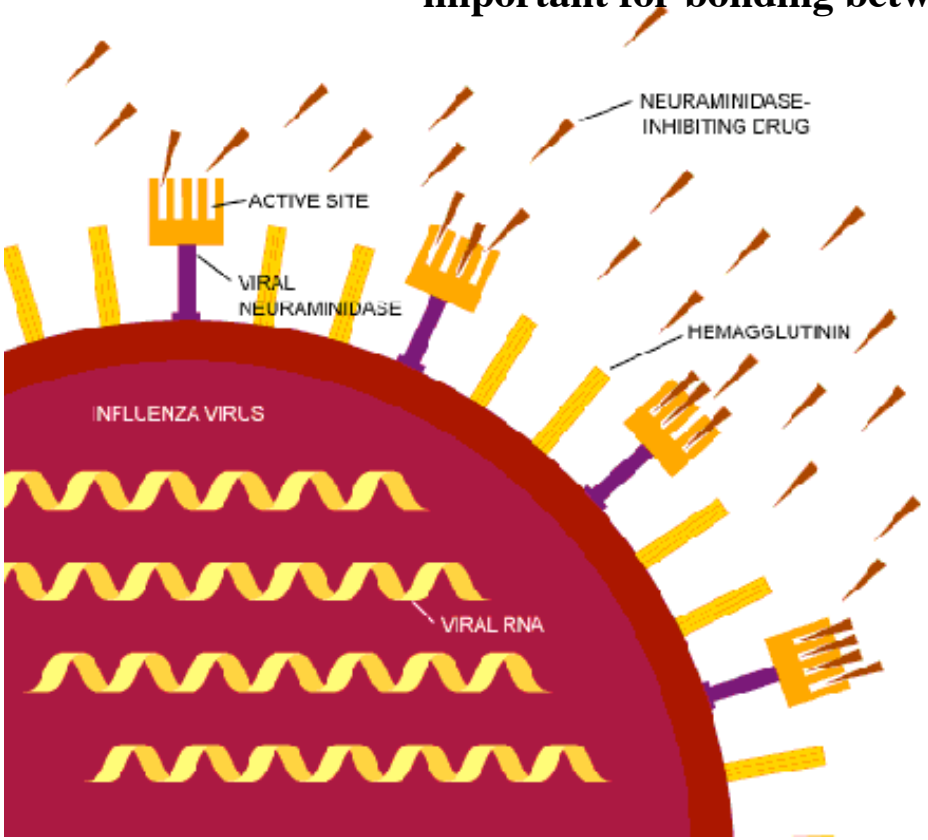
Effect on influenza virus A and B(?)

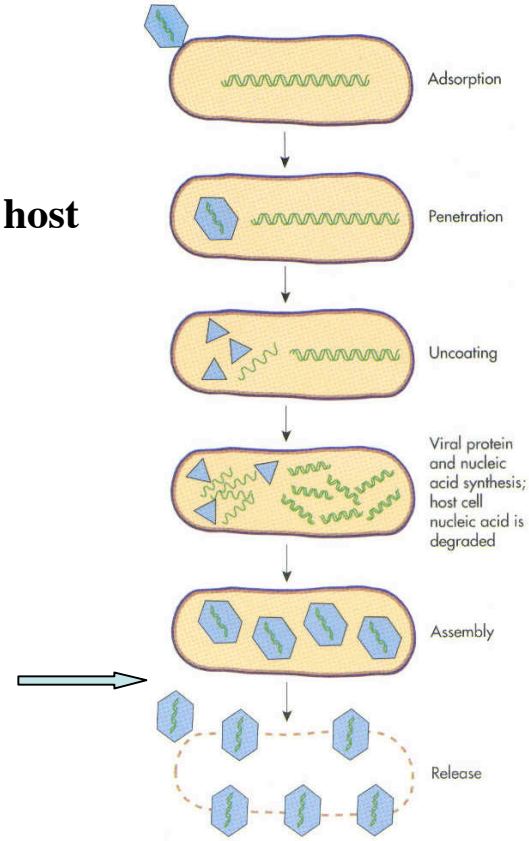
Inhib. neuraminidase

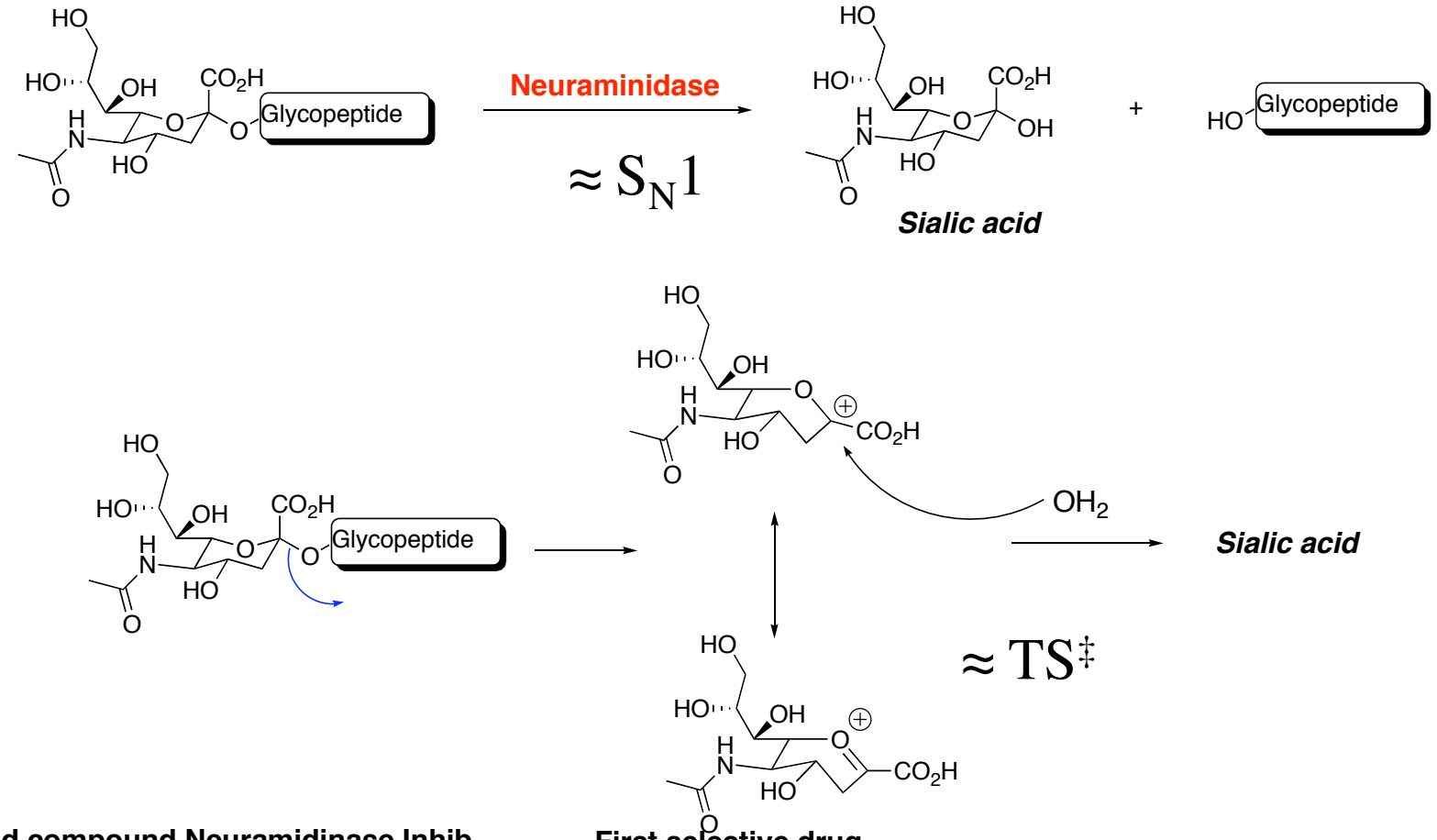
(enzyme that breaks bonds between HA* in newly HA in formed virus and host cell)

Prevents release of virus

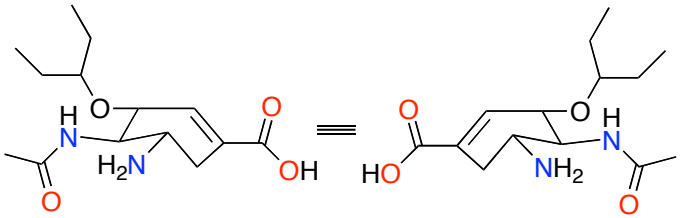
HA: Hemaglutinin, (glycoprotein)
important for bonding between influenza virus and host

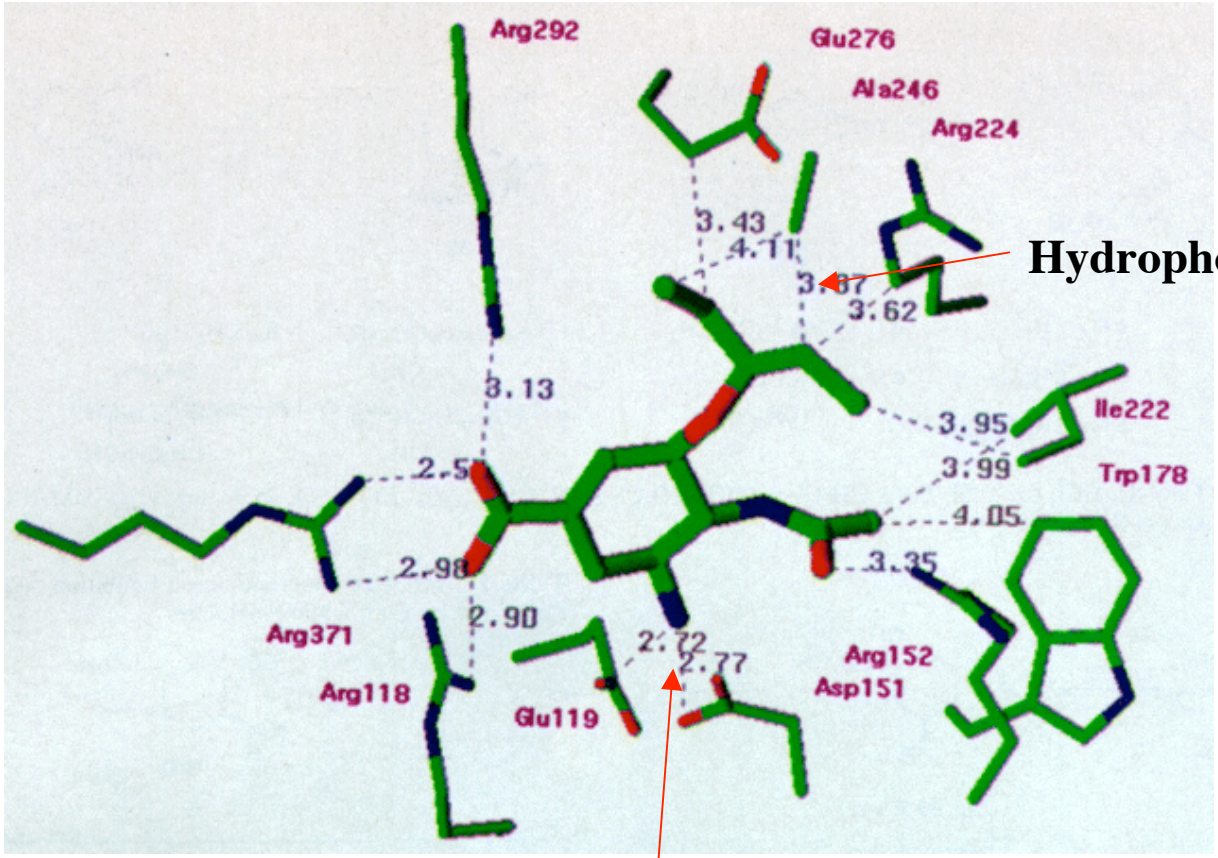





Neuraminidase
≈ S_N1
Sialic acid
Glycopeptide
OH2
≈ TS‡
Sialic acid
Lead compound Neuramidinase Inhib.
(not selective for viral NA)
First selective drug
Carbocyclic drug
DANA
Zanamivir
Relenza®
Oseltamivir
Tamiflu®
(“Take my flu”)

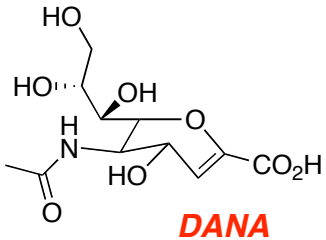
Binding of *oseltamivir* to NA



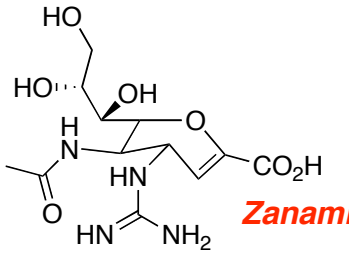


Hydrophobic pocket

Basic centre better binding than DANA



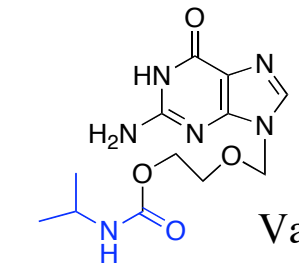
DANA



Zanamivir

Nucleoside analogs - Antimetabolites

(C.f. anticancer compounds)

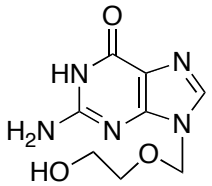


Valtrex®

Valacyclovir

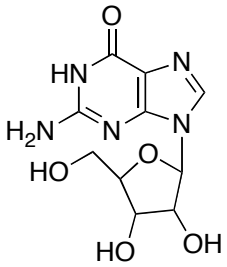
Increase GI absorbtion

Esterases



Aciclovir®
Zovirax®

Acyclovir



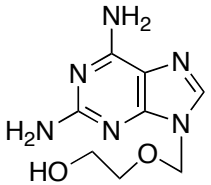
Guanosine

Xanthine oxidase

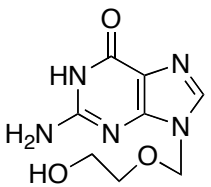
Adenosine deaminase

6-Deoxyacyclovir

Increased solubility

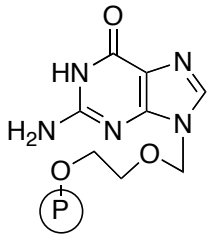


Guanosine analog
Activity: DNA Herpes viruses (ex. Herpes simplex, varicella, cytomegalo, epstein barr)

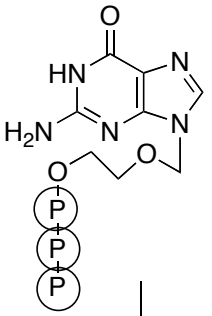


Acyclovir

Viral thymidine kinase



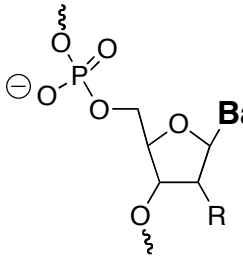
Normal cellular enzymes



Preference for the viral enzymes

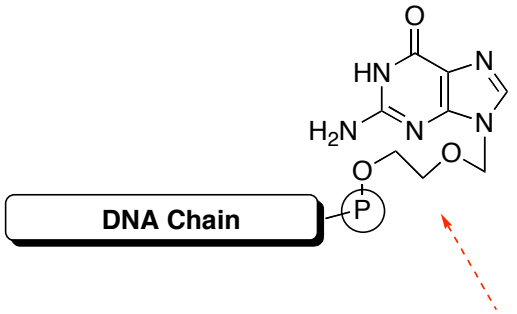
Viral DNA polymerase

Normal DNA / RNA chain



Base

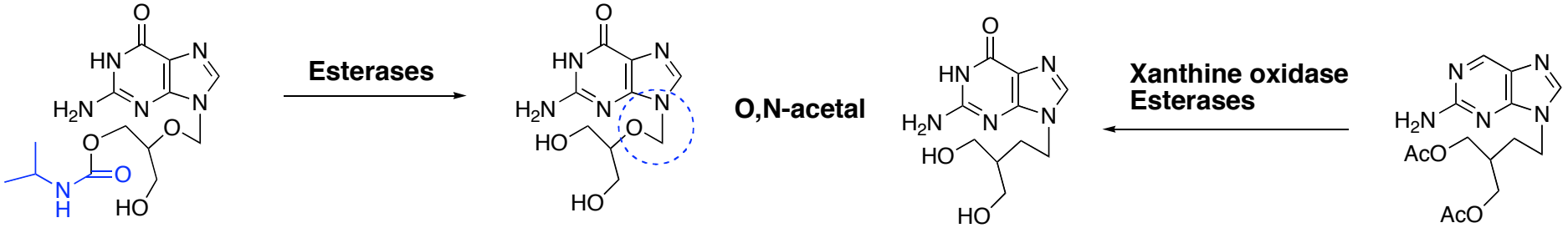
R=H in DNA
R=OH in RNA



DNA Chain

No 3'OH - No Chain elongation

Relatet Structures



Valgancyclovir

Valcyte®

Gancyclovir

Cymevene®

Peniciclovir

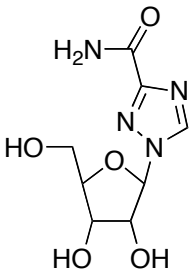
More stable
Low oral availability

Famciclovir

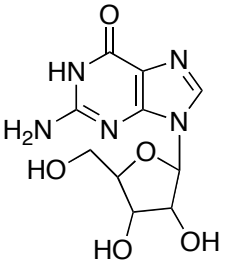
- **Converted to triphosphates**
- **Inhibitors of viral DNA polymerases**

- **Gancyclovir: Not dependent of viral thymine kinase (better effect CMV, EB)**

Ribavirin
Copegus®
Rebetol®

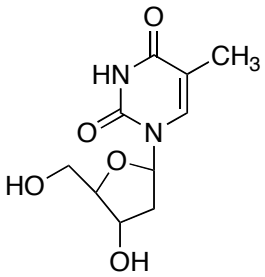


Guanosine analog
Fosforylated to triphosphate in vivo
Inhib. viral RNA polymerase, RNA / DNA synthesis
Broad spectrum (RNA and DNA viruses, some effect on HIV)
Used against Hepatitis in N., serious side effects

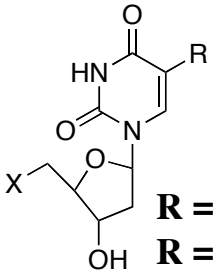


Guanosine

Thymidine analogs



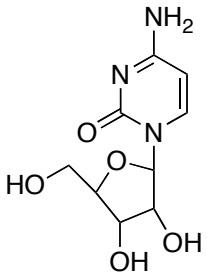
Thymidine



R = I, X = OH
R = I, X = NH_2 (less tox)
R = Br, X = OH
R = F, X = OH
R = CF_3, X = OH

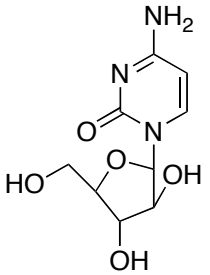
Incorp. DNA - faulty viral proteins

Cytosine analogs



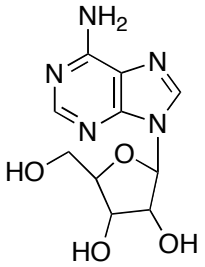
Cytosine

Cytarabine (ARA-C)
Cytarabin®, Cytosar®,

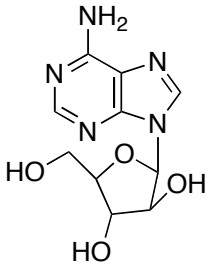


Only cancer ther in N.

Adenosine analogs



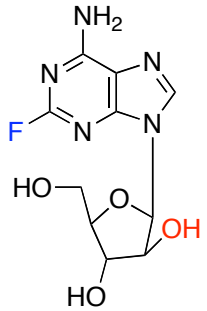
Adenosine



Vidarabine (Ara-A)

Isolated *Streptomyces antibioticus*
First studied as anticancer drug
Interfere with DNA synth
Tox.
Rapid metab. adenosine deaminase

Fludarabine
Fludara® **cancer ther.**

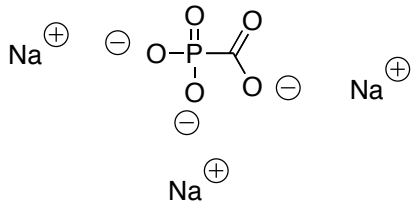


Not good substrate for adenosine deaminase

Antimetabolite

Other comp. that interfere with replication

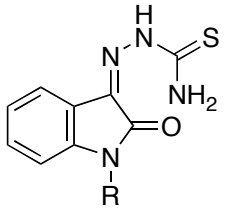
Foscarnet
Foscavir®



Not orally avail.
No in vivo activation required
Inhib. DNA polymerase
Neurotox.
Also active against HIV

Comp. that interfere with translation (protein synth)

Methisazone

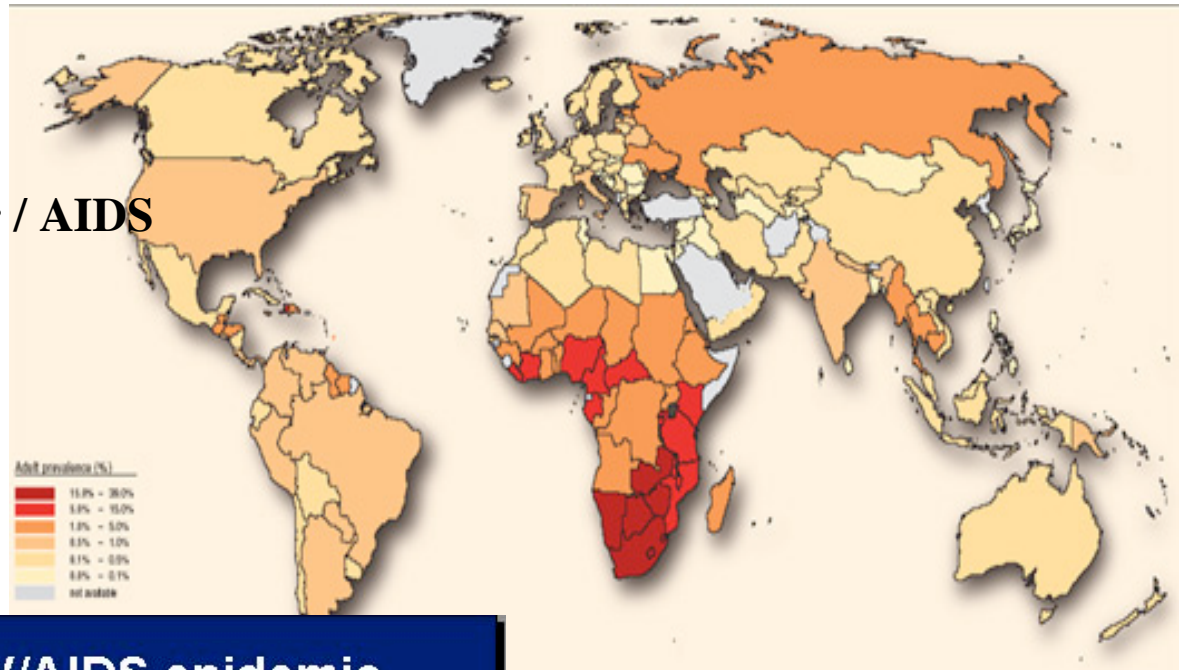


One of the oldest antiviral comp. known
Inhib protein synth

Retrovirus

HIV (humans)

Animal viruses resulting in cancer / AIDS



15-39%

http://www.who.int/hiv/facts/hiv2003/en/

Global summary of the HIV/AIDS epidemic, December 2003

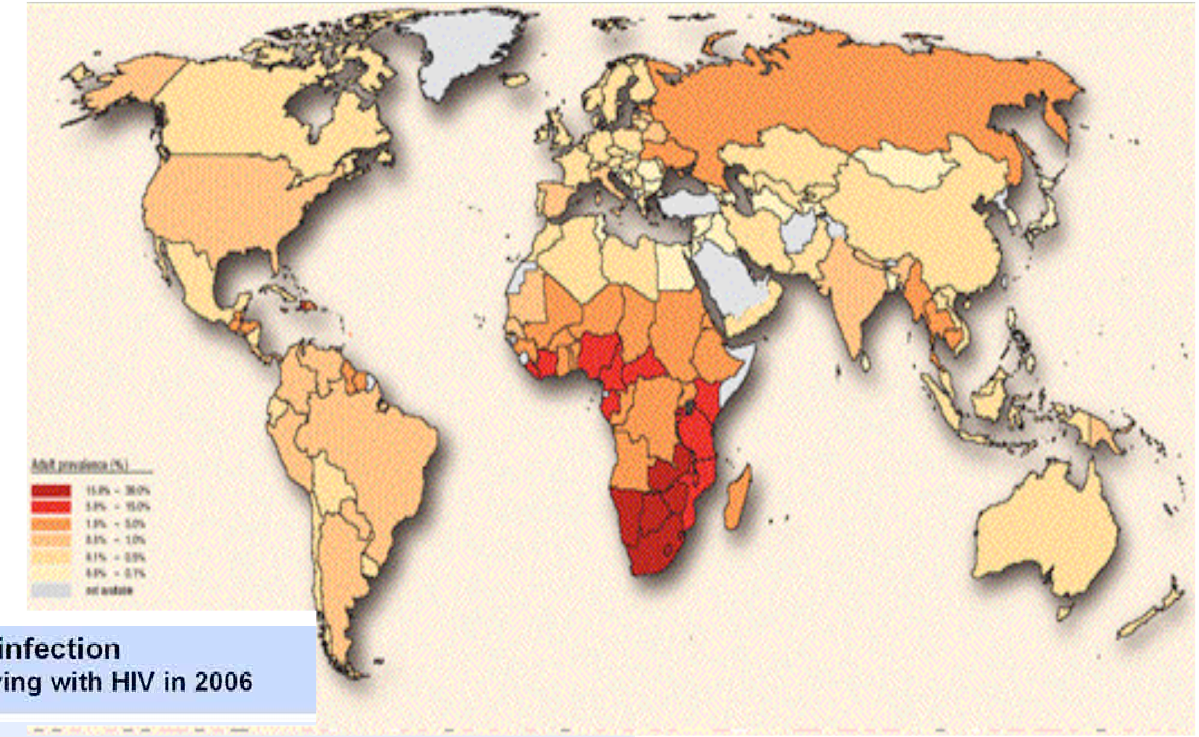
Number of people living with HIV/AIDS	**Total**	**40 million (34 – 46 million)**
	Adults	37 million (31 – 43 million)
	Children under 15 years	2.5 million (2.1 – 2.9 million)
People newly infected with HIV in 2003	**Total**	**5 million (4.2 – 5.8 million)**
	Adults	4.2 million (3.6 – 4.8 million)
	Children under 15 years	700 000 (590 000 – 810 000)
AIDS deaths in 2003	**Total**	**3 million (2.5 – 3.5 million)**
	Adults	2.5 million (2.1 – 2.9 million)
	Children under 15 years	500 000 (420 000 – 580 000)

UNAIDS

The ranges around the estimates in this table define the boundaries within which the actual numbers lie, based on the best available information. These ranges are more precise than those of previous years, and work is underway to increase even further the precision of the estimates that will be published mid-2004.

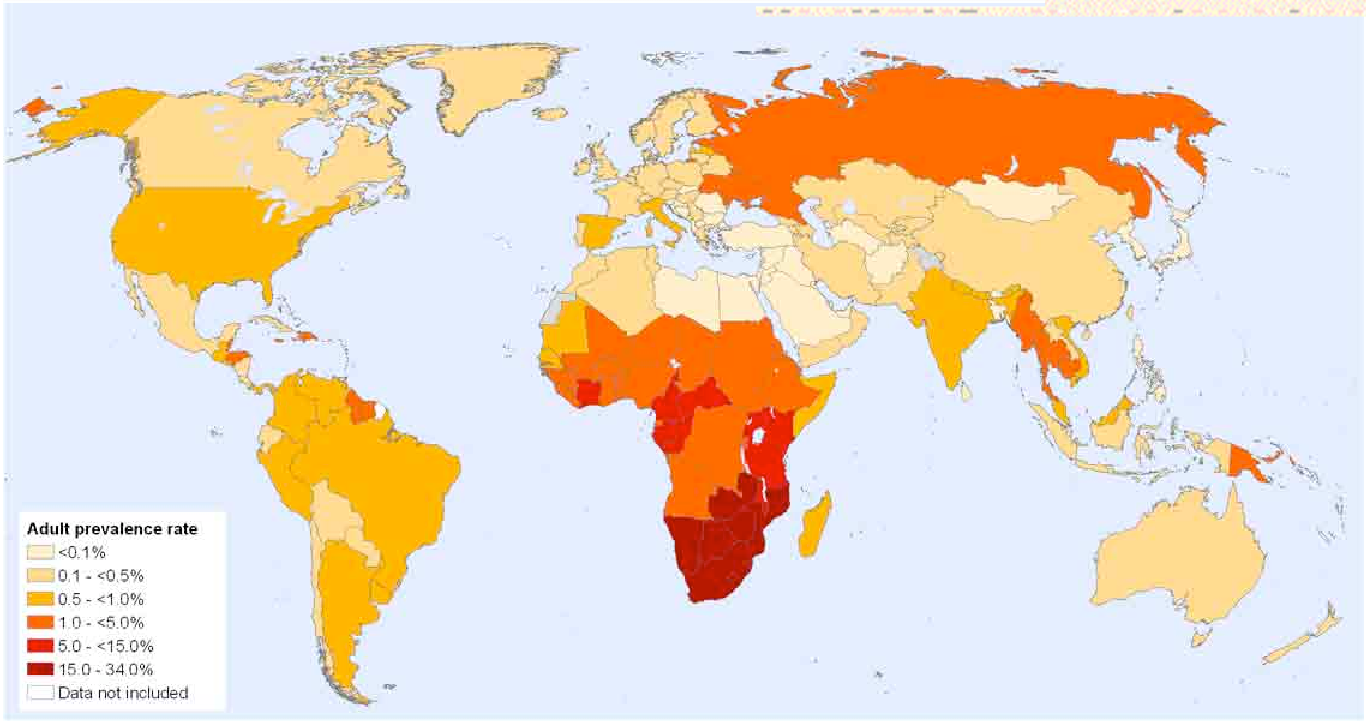
00002-E-1 – 1 December 2003

World Health Organization

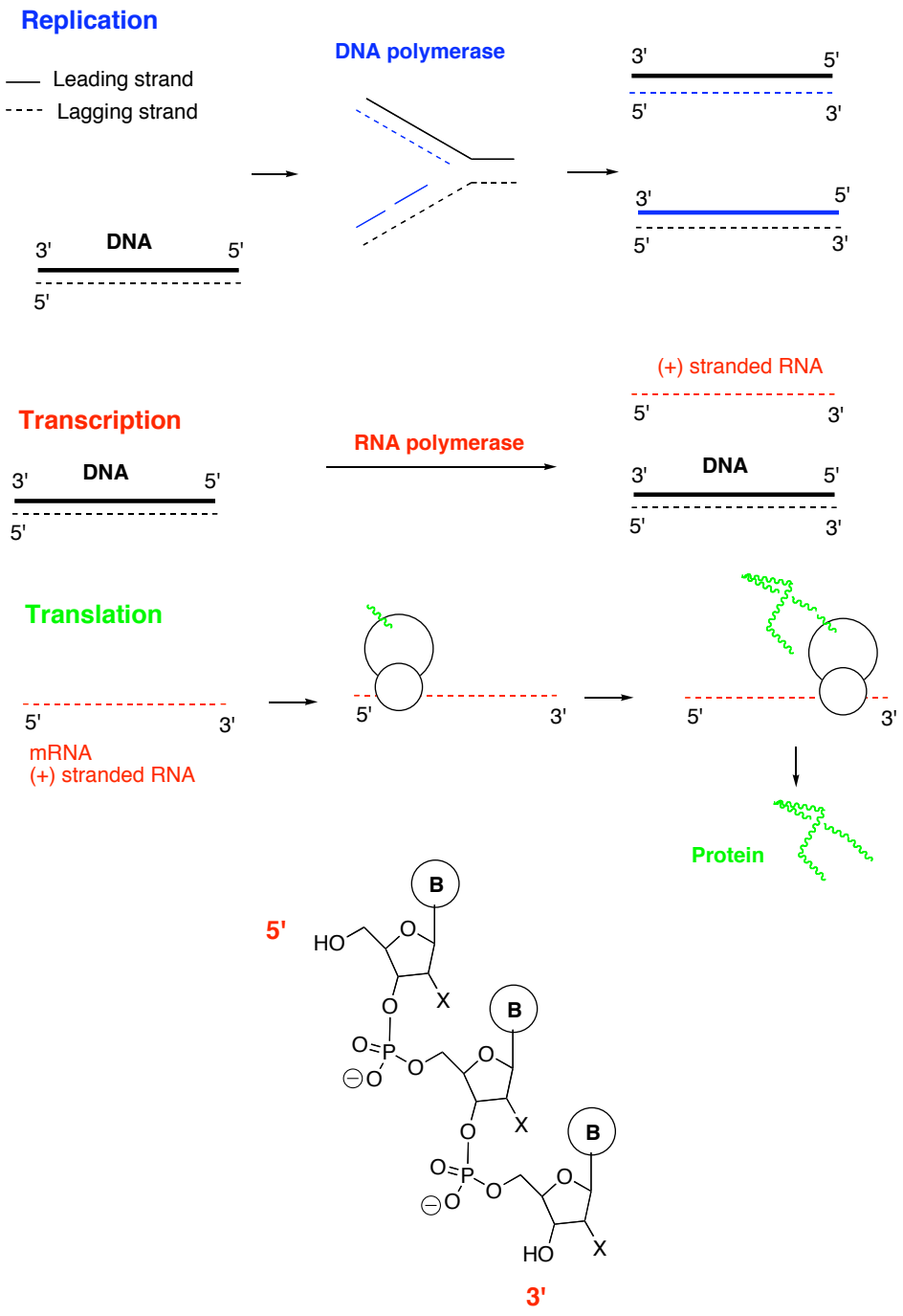


A global view of HIV infection

39.5 million people [34.1-47.1] living with HIV in 2006

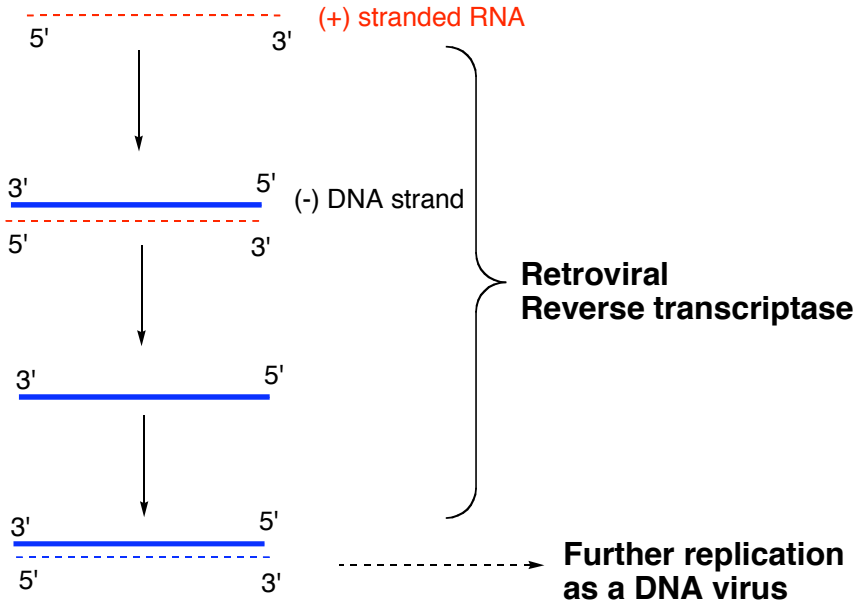


Procaryotes and eucaryotes



Stages of replication - RNA virus

Alternative C: Retrovirus; (+) RNA virus



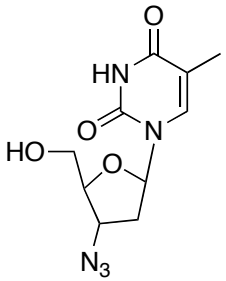
Specific retroviral drugs

- **Reverse transcriptase inhibitors**
  - **Nucleosides (NRTIs)**
  - **Non-nucleosides (NNRTIs)**
- **Protease inhibitors**

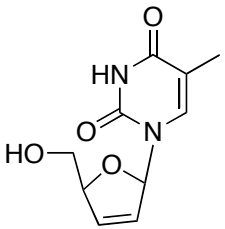
Nucleoside Reverse Transcriptase Inhibitors

Nucleoside analogs without 3' OH - DNA chain termination
Pro-drugs - Phosphorylated by kinases *in vivo*

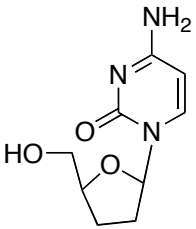
Zidovudine (AZT)
Retrovir®
Trizivir® Kombi prep.



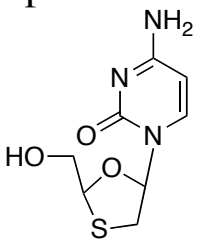
Stavudine
Zerit®



Zalcitabine (ddC)

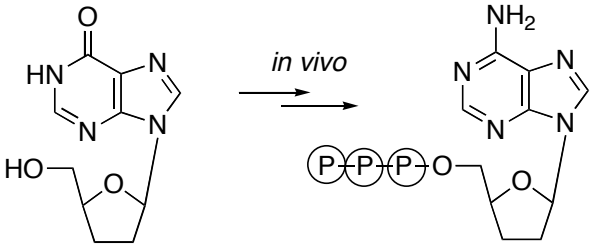


Lamividine (3TC)
Epivir®
Trizivir® Compivir ®
Kombi prep.

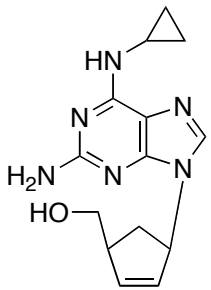


Higher bioavail. than ddC

Didanosine (ddI)
Videx®



Abacavir (ABC)
Trizivir® Kombi prep.

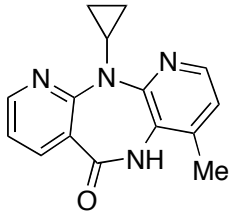


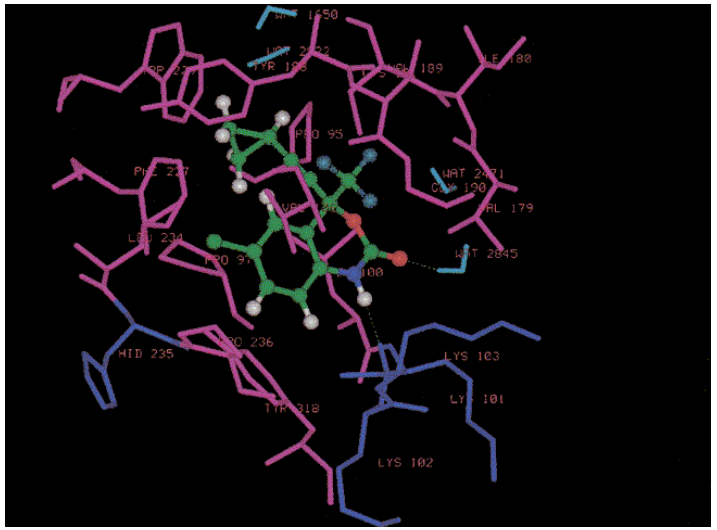
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

Binds directly to RT

Nevirapin

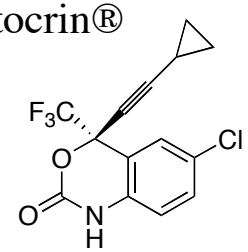
Viramune®



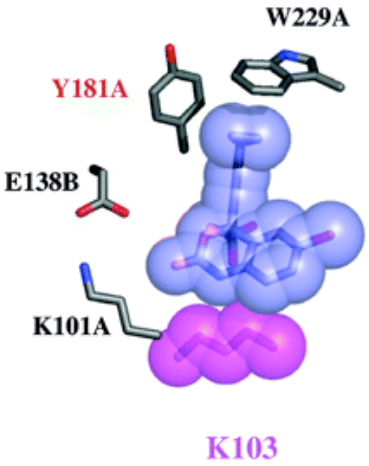


Efavirenz / Sustiva

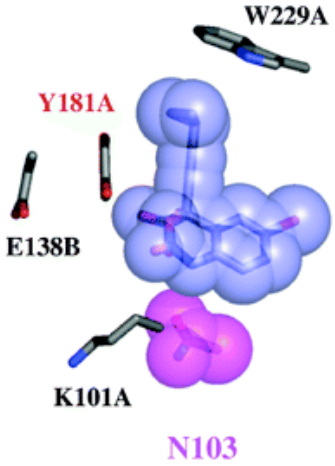
Stocrin®



FDA 1998
Already resistance

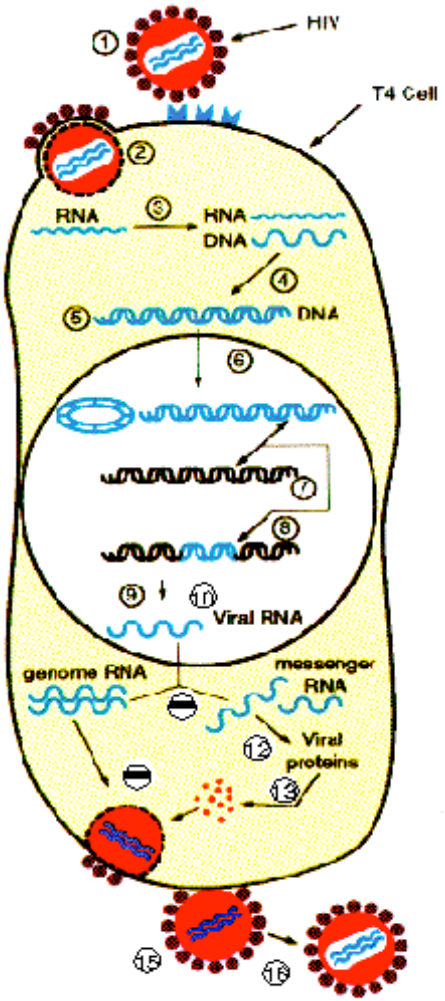


Wild type RT

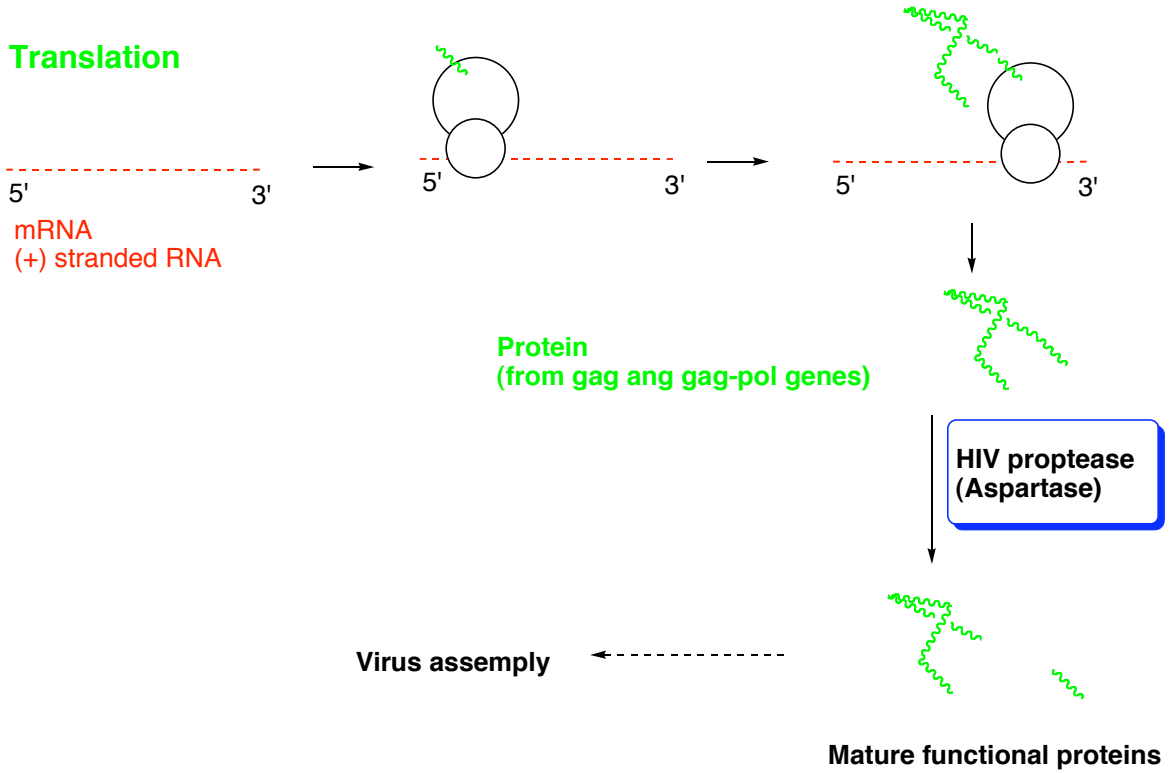


mutated

Protease Inhibitors



The **HIV**-1 **protease** is an enzyme crucial
for the maturation and assembly of infectious viral particles



X-ray:

HIV-1 protease - C2 symmetric homodimeric -Not C2-sym. in related human proteases!

Science **1990**, *249*, 527

The two subunits are rotated 180 from each other

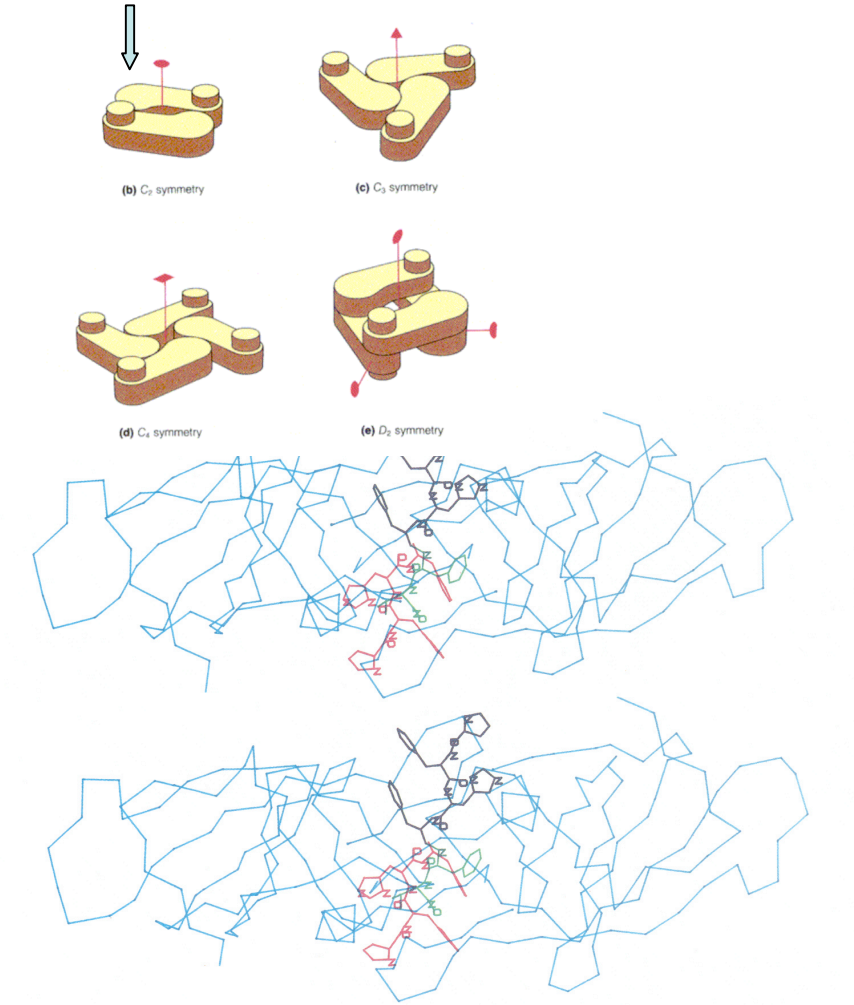


Fig. 1. Modeled structures of an asymmetric and an artificial symmetric inhibitor docked into the active site region of RSV protease. The RSV protease Cα backbone tracing (blue) is based on coordinates from Brookhaven file 2RSP (*10*). Coordinates of the reduced peptide inhibitor (green) were taken from Brookhaven file 3APR (*20*). An artificial, C_2 symmetric inhibitor (red) was produced by operating on the NH_2-terminal portion of the reduced peptide (which was truncated after the reduced methylene carbon atom) by the enzyme dyad. The approximate twofold symmetry axis (κ = 178.0°) for RSV protease was determined on the basis of least-squares superposition analysis of the two subunits (0.41 Å rms for 113 Cα pairs). The left halves of both molecules appear black because of the exact superposition of these regions; the peptide orientations of the right halves of the molecules are opposite to each other and are easily distinguished.

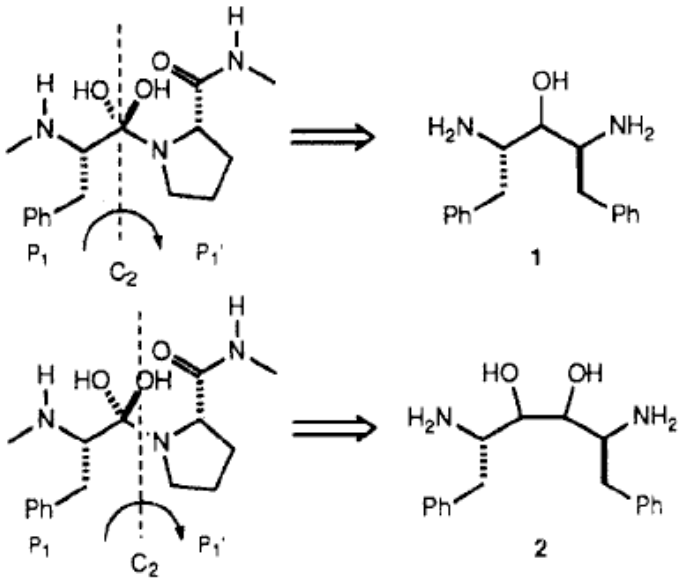
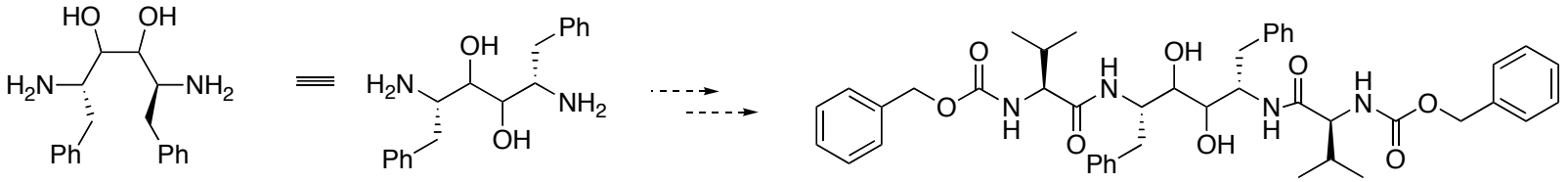


Figure 1. Design of C_2 symmetric HIV protease inhibitors.

J . Med. Chem. **1990**,*33*, 2687

Design of C2 sym. comp. as TS(Intermed) analog of Phe-Pro cleavage

(Type 1 comp. did not lead to drugs)

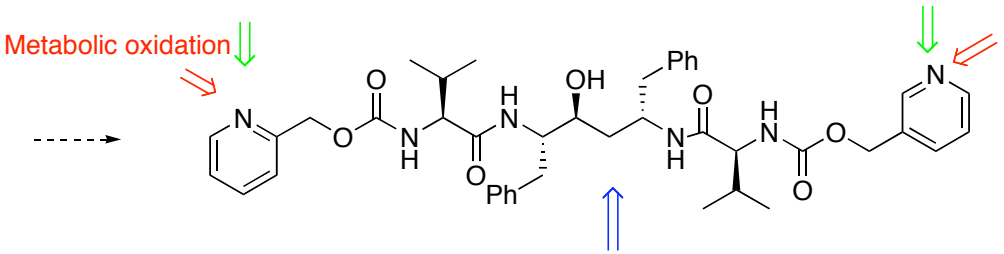


-Bad water sol. and oral bioavail.
-X-ray indicate modification of Cbz allowed

Good inhib *in vitro*
(both stereoisomers)

Increase water sol.

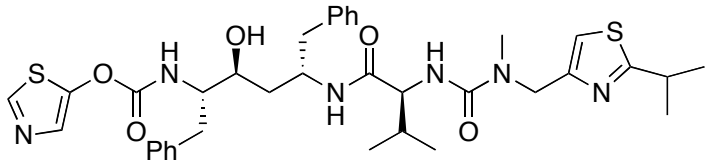
Metabolic oxidation



Somewhat increased bioavail. without OH

M_w >500!

Ritonavir
Norvir®

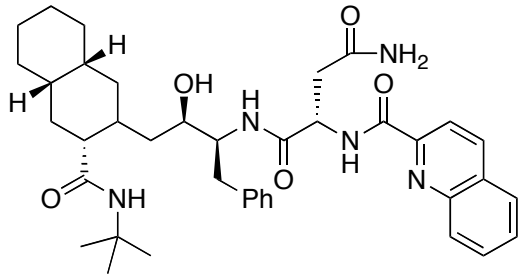


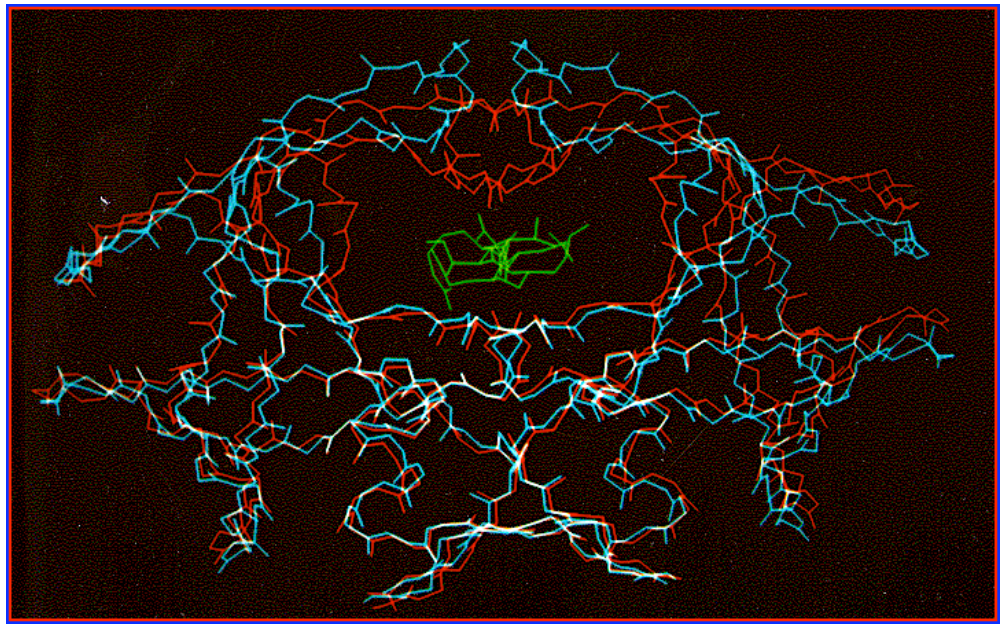
-Somewhat lower Mw
-Thiazol instead of pyridine

-FDA March 1996, now many resistant strains

-Ritonavir inhib. 3A4 isozyme of CypP450
Used in combi. with other protease inhib.
to suppress their metab.

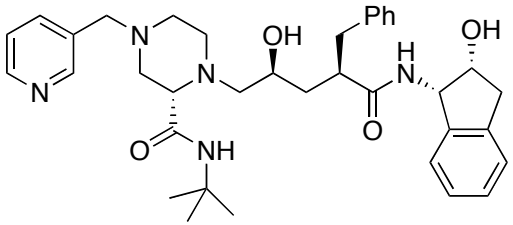
Saquinavir
Fortovase®



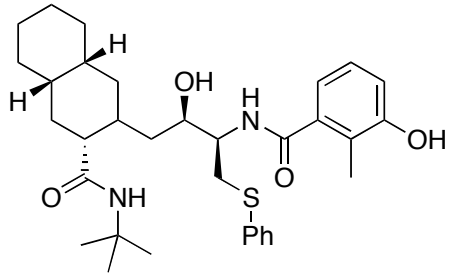


Saquinavir (green) bound to HIV-1 Protease

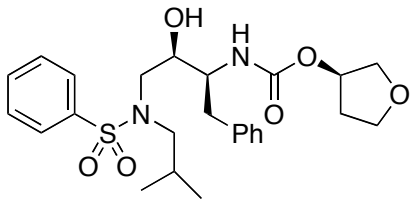
Indinavir
Crixivan®



Nelfinavir
Viracept®



Amprenavir
Agenerase®



Lopinavir
Kaletra®