Antiviral agents

Dr. Mai Ramadan

Introduction

The main characteristics of viruses:

All viruses are obligate intracellular parasite [rely on host for the growth, development, and replication]

Consist of a core genome in a protein shell and some are surrounded by a lipoprotein

Lack cell membrane or cell wall (Not cell)

Do not carry out metabolic process (Can not make food, take in food, or produce waste)

Don not grow or respond to stimuli.

Introduction

The main characteristics of viruses:

Replication depends on host cell machinery causing acute infections such as Influenza virus as well as chronic such as herpes virus

Nucleic acid is DNA or RNA (never both)

Viral genome can be single or double stranded, linear or circular

Viral genome and nucleoproteins may be surrounded by a capsid [Nucleocapsid] which can comprises the entire virus

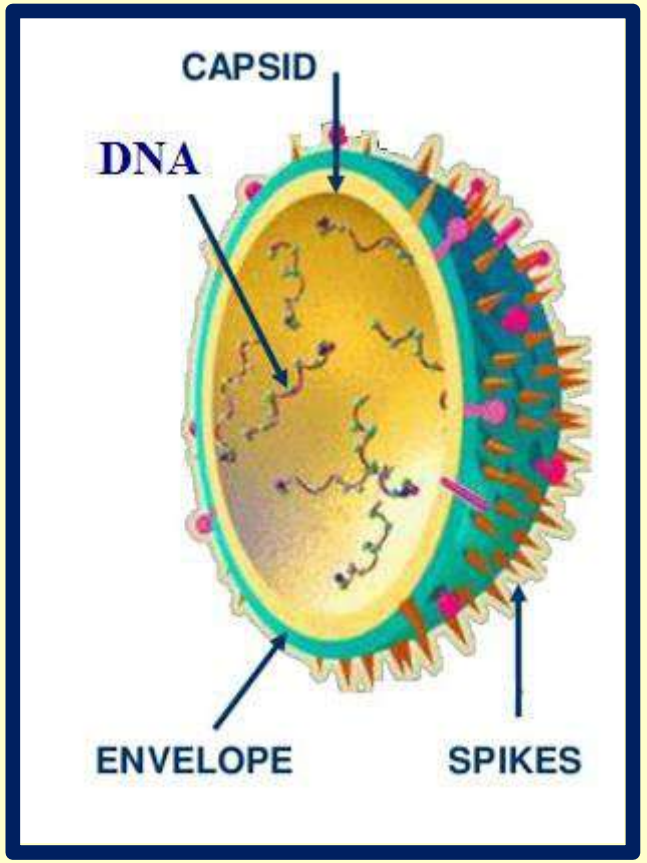
Nucleocapsid maybe surrounded by an envelop

Introduction

The main characteristics of viruses:

Some viruses have spikes to help attach host cell

Most viruses infected only specified host cell type.



Introduction

Read about

Viral diseases: Aids, influenza, hepatitis

HIV: Life cycle, reverse transcriptase (RT), integrase

Influenza: Types A and B, life cycle

Hepatitis viruses: A, B, and C

Interferon α

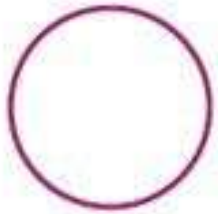
Introduction

According to genome

Single / double/ linear / circular

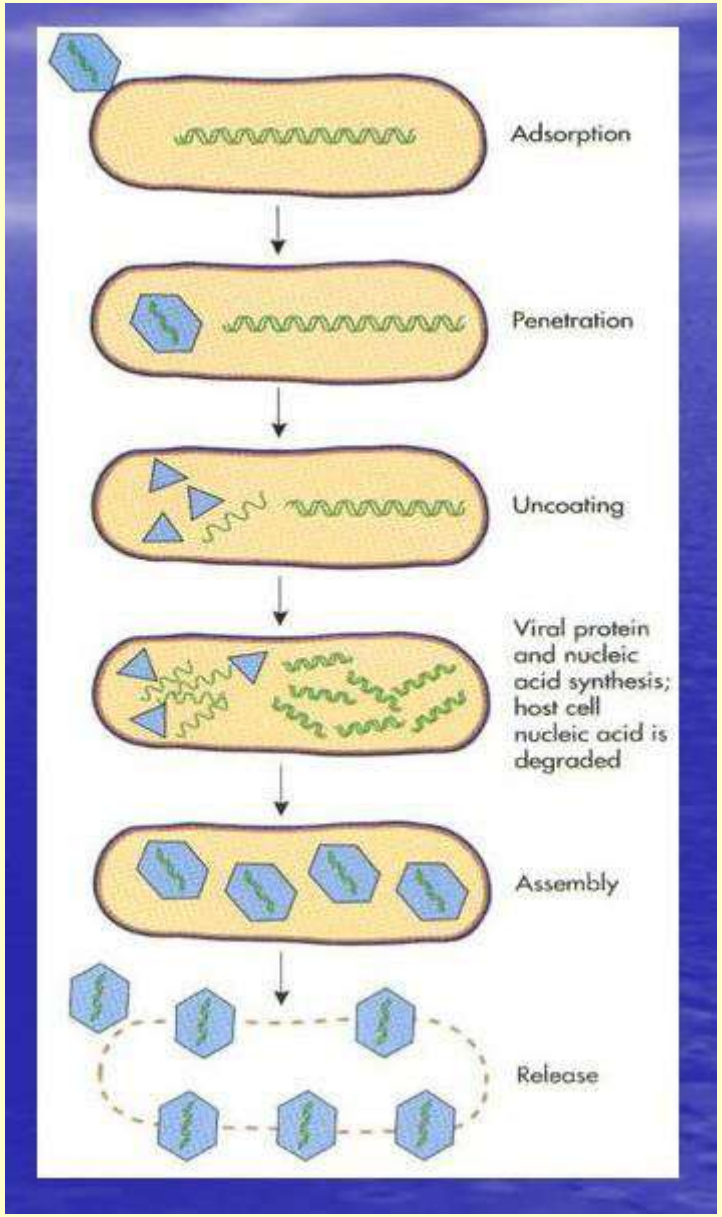
DNA virus	RNA virus
Adenovirus	HIV-1 & HIV-2
Herpes simplex type 1, & 2	HAV, HCV
HBV	Influenza virus A,B, C
Epstein-Barr virus	Ebola virus
Poxvirus	
Human papillomavirus	

Viral genome

DNA genomes		Examples
	ss, linear	Parvoviruses
	ds, linear	Poxviruses
	ss, circular	Phage φX174
	ds, circular	Baculoviruses
RNA genomes		
	ss, linear	Tobacco mosaic virus
	ds, linear	Reoviruses
	ss, circular	Hepatitis delta virus

Introduction: Replication cycle

1. Attachment (Adsorption)
2. Penetration (Viral entry)
3. Uncoating
4. Replication (Viral genome and protein synthesis)
5. Assembely
6. Release



Introduction: Replication cycle

Attachment:

is a specific binding between viral capsid proteins and specific receptors on the host cellular surface

Example: viral extracellular gp-120 of HIV attaches to CD 4 receptor on T-lymphocyte.

Penetration :

Virions enter the host cell through receptor-mediated **endocytosis** or **membrane fusion**. This is often called viral entry.

Uncoating:

It is a process in which the viral capsid is removed.

The viral genomic nucleic acid is released

Introduction: Replication cycle

Replication

primarily involves multiplication of the genome (DNA or RNA) and viral protein synthesis (Transcription and translation)

Self-*assembly* of the virus particles

:Release

Release from the host cell by lysis, a process that kills the cell by bursting its membrane and cell wall if present or by budding.

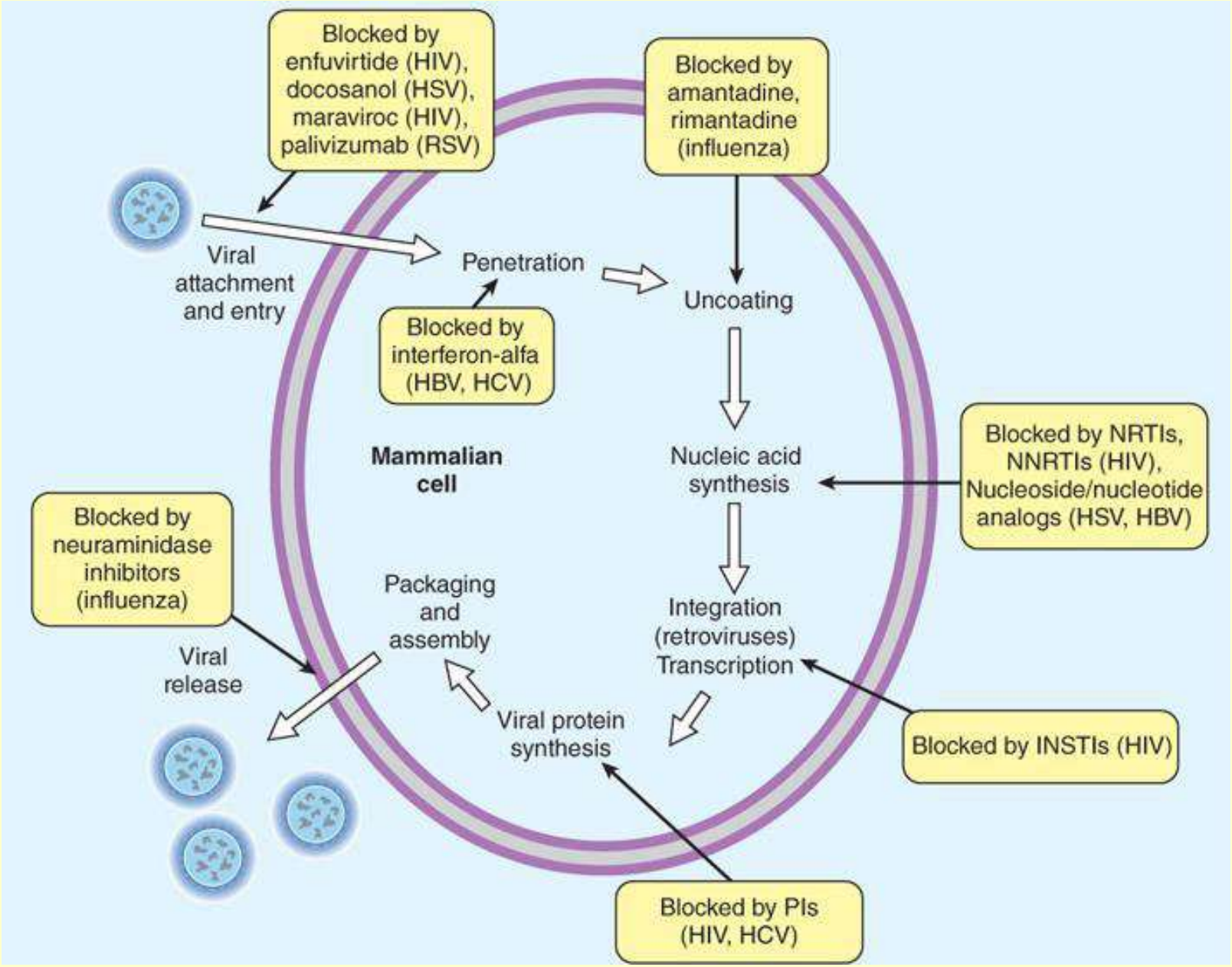
Introduction: Antiviral treatment

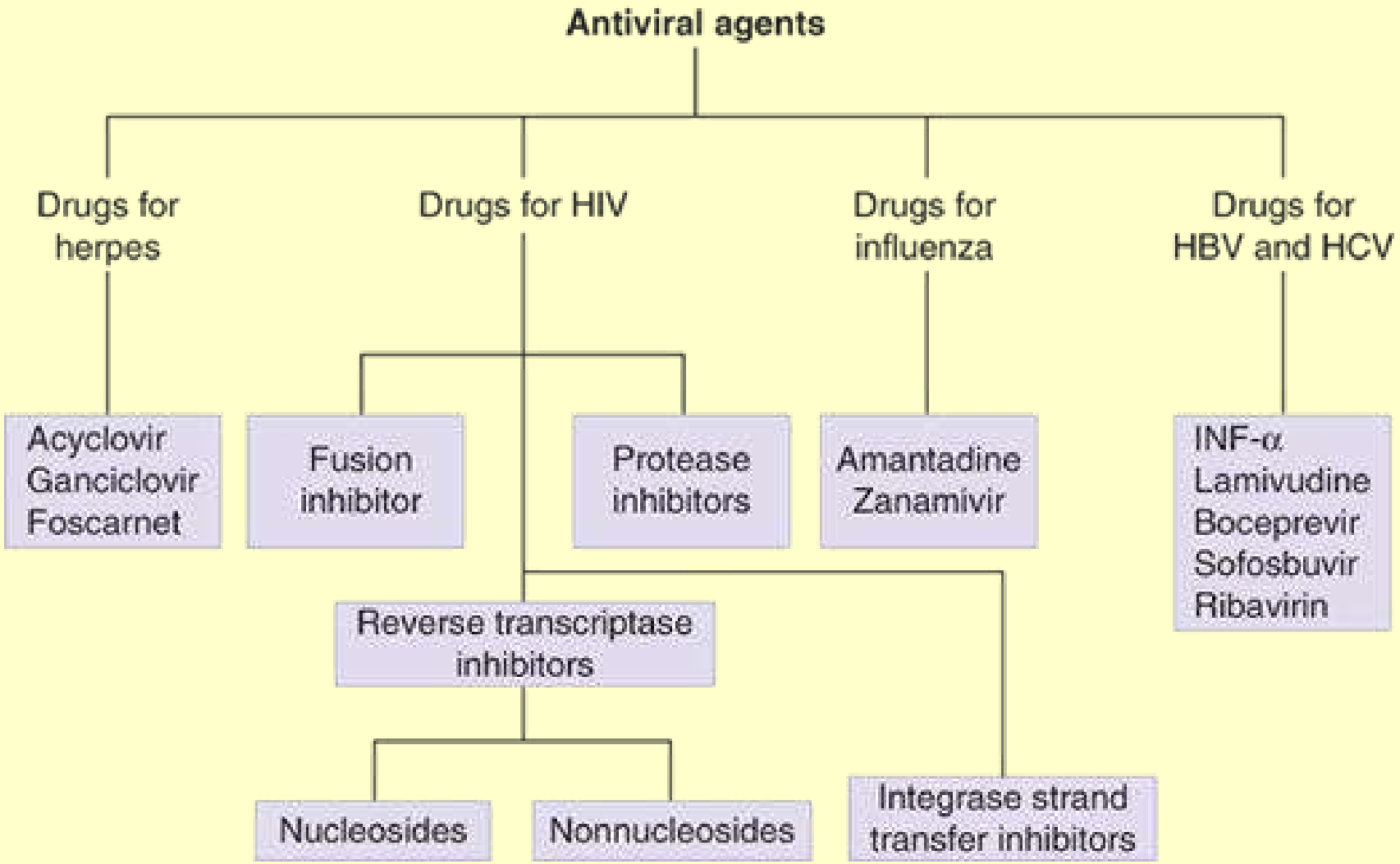
- **Prevention**

Immunization
Chemoprophylaxis

- **Chemotherapeutics**

Introduction: Sites of drug action




Antiviral agents
Drugs for herpes
Drugs for HIV
Drugs for influenza
Drugs for HBV and HCV
Acyclovir
Ganciclovir
Foscarnet
Fusion inhibitor
Protease inhibitors
Amantadine
Zanamivir
INF-α
Lamivudine
Boceprevir
Sofosbuvir
Ribavirin
Reverse transcriptase inhibitors
Nucleosides
Nonnucleosides
Integrase strand transfer inhibitors

Viral Chemotherapy

❑ **Inhibiting viral attachment and entry/ penetration**

Enfuvirtide, maraviroc: HIV

Interferon α: Chronic hepatitis B and C, others

❑ **Inhibiting viral uncoating**

Amantadine and Rimantadine: Influenza A

❑ **Inhibiting viral release**

Zanamavir and Oseltamivir: Influenza A, and B

Viral Chemotherapy

❑ Inhibiting viral replication:

DNA Polymerase inhibition: For Herpes

Nucleoside antimetabolite (Purine-, pyrimidine analogue)

Reverse transcriptase inhibition (RTI) For HIV

Nucleoside reverse transcriptase inhibition: NRTI

Nonnucleoside reverse transcriptase inhibition: NNRTI

Direct inhibitor of DNA polymerase and RT

Foscarnet

Viral Chemotherapy

❑ **Protease Inhibitor: For HIV**

Peptidomimetic inhibitor: Saquinavir

Nonpeptidomimetic inhibitor: Tipranavir

❑ **Integrase Inhibitor: For HIV**

Raltegravir

Introduction

Classification according to genome replication

Class I viruses

Double-stranded DNA genomes

Genome is double-stranded DNA

mRNA is synthesized in the normal fashion using negative-strand DNA as a template.

Examples: Adenovirus, Hepatitis B virus

Introduction

Classification according to genome replication

Class II viruses

Single-stranded DNA genones

Form a double stranded DNA intermediate during replication and this intermediate used for transcription.

Examples: parvovirus, maize streak virus.

Introduction

Classification according to genome replication

Class III viruses

Double-stranded RNA genomes

Genome is double-stranded RNA, one strand of which is therefore equivalent to mRNA.

Examples: reovirus, rotavirus

Introduction

Classification according to genome replication

Class IV viruses

Positive-strand RNA genomes

Genome is single-stranded RNA that can serve as mRNA directly, so these are positive-strand viruses.

Examples: poliovirus

Introduction

Classification according to genome replication

Class V viruses

Negative-strand RNA genomes

Genome is single-stranded RNA that serve as template for synthesis of viral mRNA.

Since genome is complementary to mRNAs, these are negative-strand viruses. Therefore, complementary positive strand is synthesized by RNA polymerase and used as mRNA.

Examples: rabies virus, mumps virus

Introduction

Classification according to genome replication

Class VI viruses

Retroviruses

Genome is positive-strand RNA.
This RNA virus require reverse transcriptase to copy the information found in RNA to DNA but its expression and replication require synthesis of a double- stranded DNA molecule

Example: Human Immunodeficiency Virus (HIV).

Introduction

Classification according to genome replication

Class VII viruses

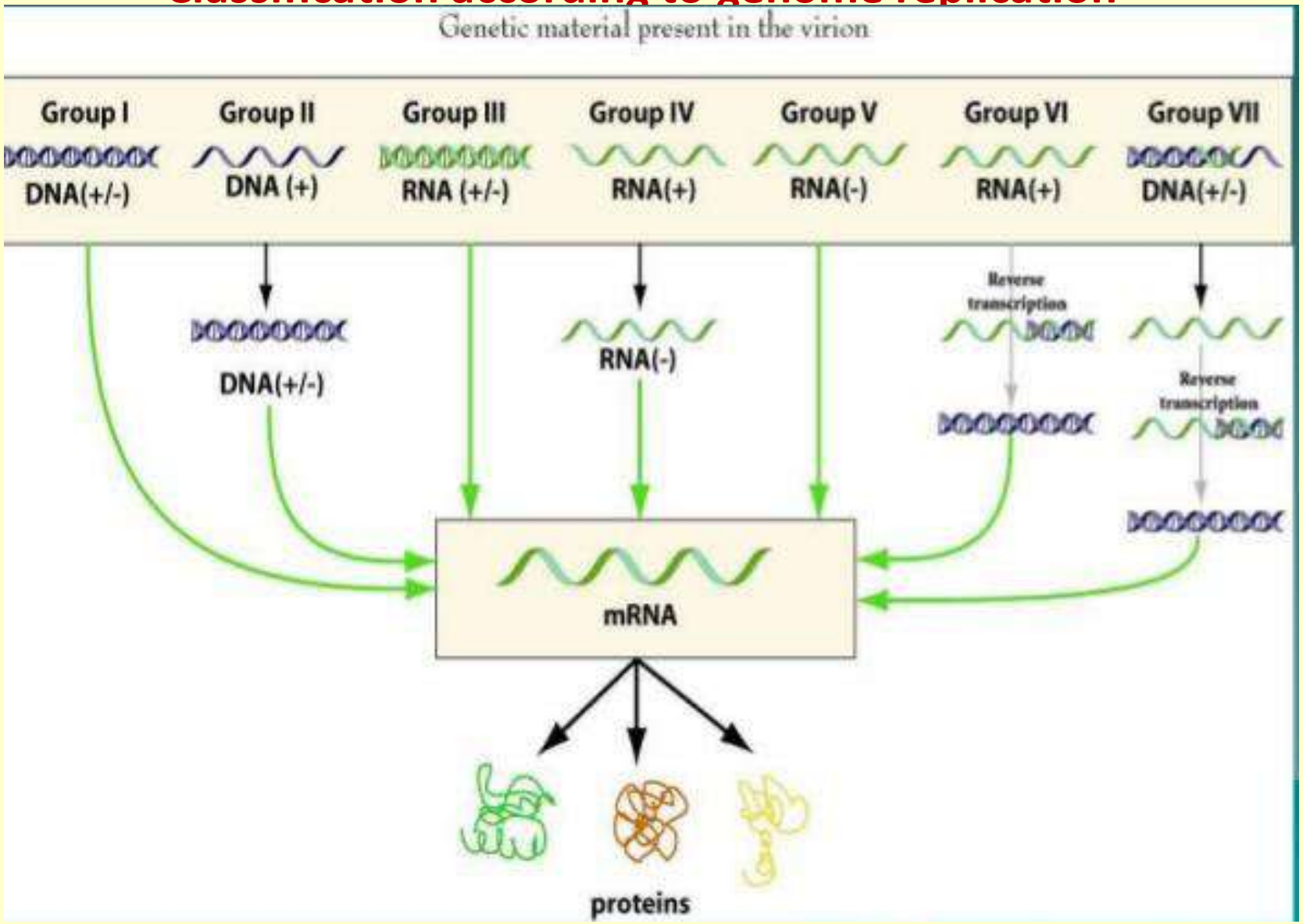
Double-stranded DNA with RNA intermediate

Double-stranded DNA genome that replicates with RNA intermediate.

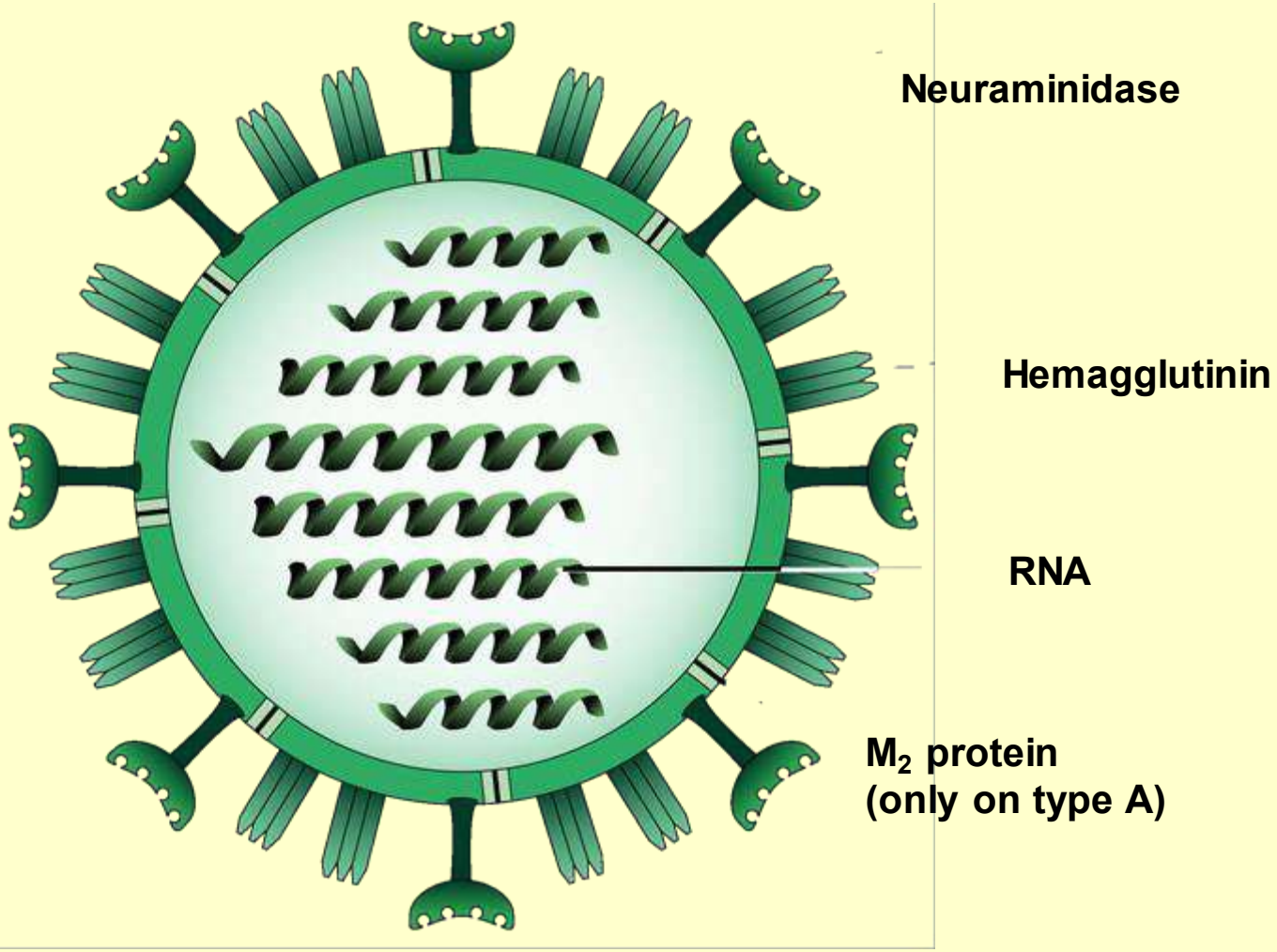
Required reverse transcriptase

Introduction

Classification according to genome replication

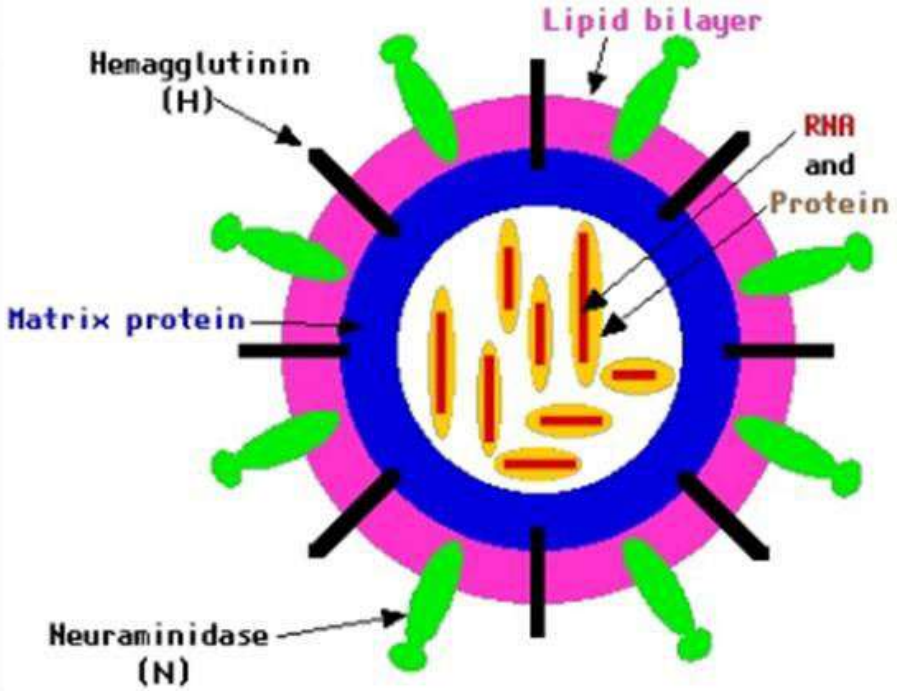


Influenza virus: Structure



Influenza virus: Surface protein

Flu A virus



Influenza A Subtypes:
-Based on:
Hemagglutinin (HA)
H1 to H16

Neuraminidase (NA)
N1 to N9

144 different combinations

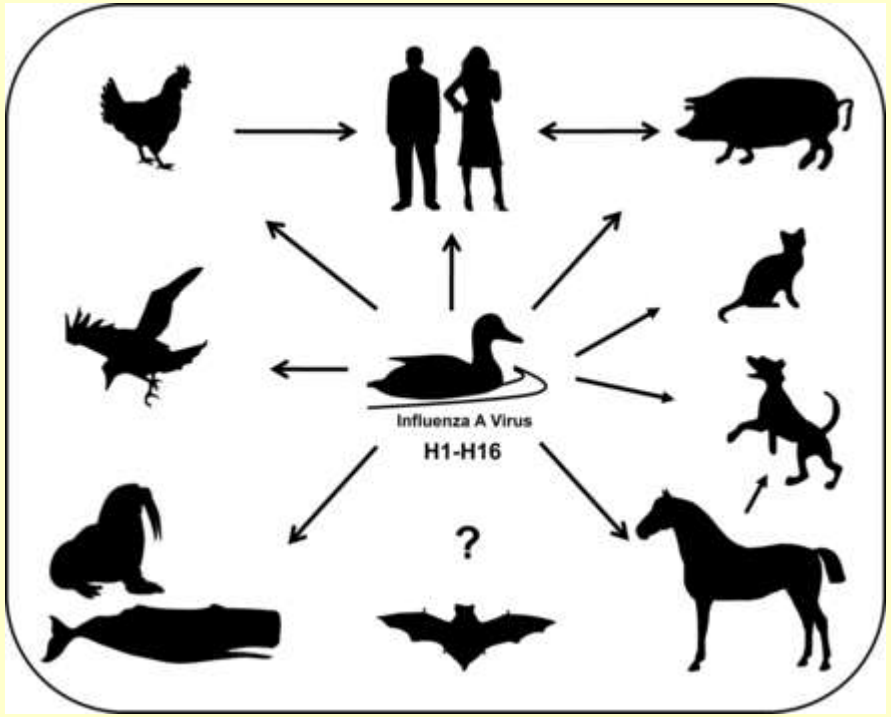
The role of haemagglutinin is to bind to the cells of the infected person
The role of neuraminidase is to release the virus from the cell surface

Influenza virus: Subtypes

Influenza virus is classified into:

- **Influenza A**: Most important (Wild water birds, chicken, flying birds, cats , dogs, horses, pigs, human, marine mammals, bats????)
- **Influenza B:** Known only in man
- **Influenza C:** Uncommon, Known only in man

Influenza A virus: Subtypes



Host range of influenza A viruses. Wild water birds represent the natural reservoir of influenza A viruses, from which they can be transmitted to a wide variety of other hosts

Influenza A virus: Subtypes

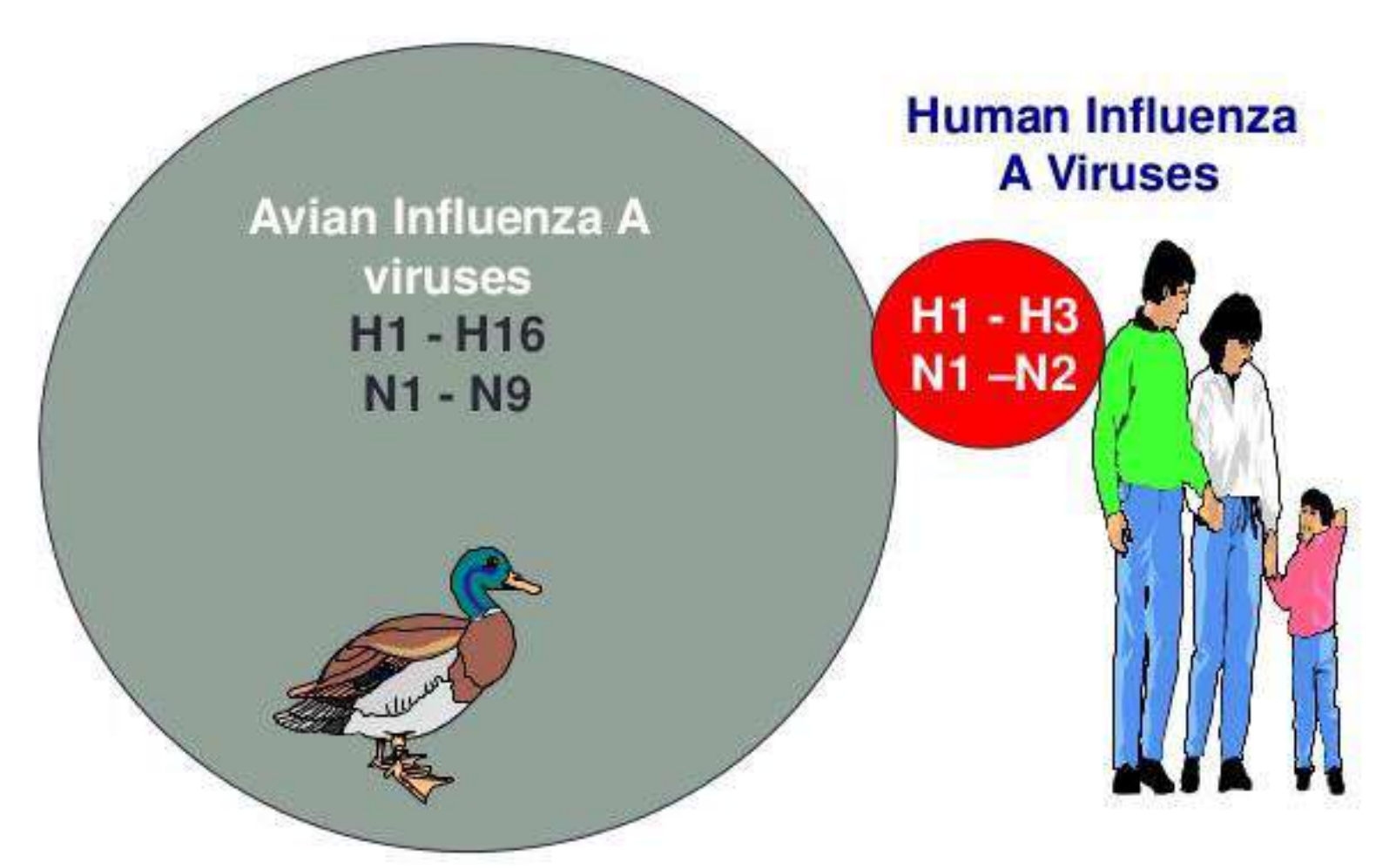
Influenza virus Type A

- Influenza A viruses are further classified into subtypes based on the antigenicity of their surface glycoproteins (HA & NA)

Hemagglutinin (HA)	Neuraminidase (NA)
H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15, H16	N1, N2, N3, N4, N5, N6, N7, N8, N9

So far at least **84 serotypes** (HA &NA combination) are found in resivour

Influenza A virus: Subtypes



Influenza A virus: Subtypes

Spanish flu

Spanish flu: Known as **1918 influenza pandemic**

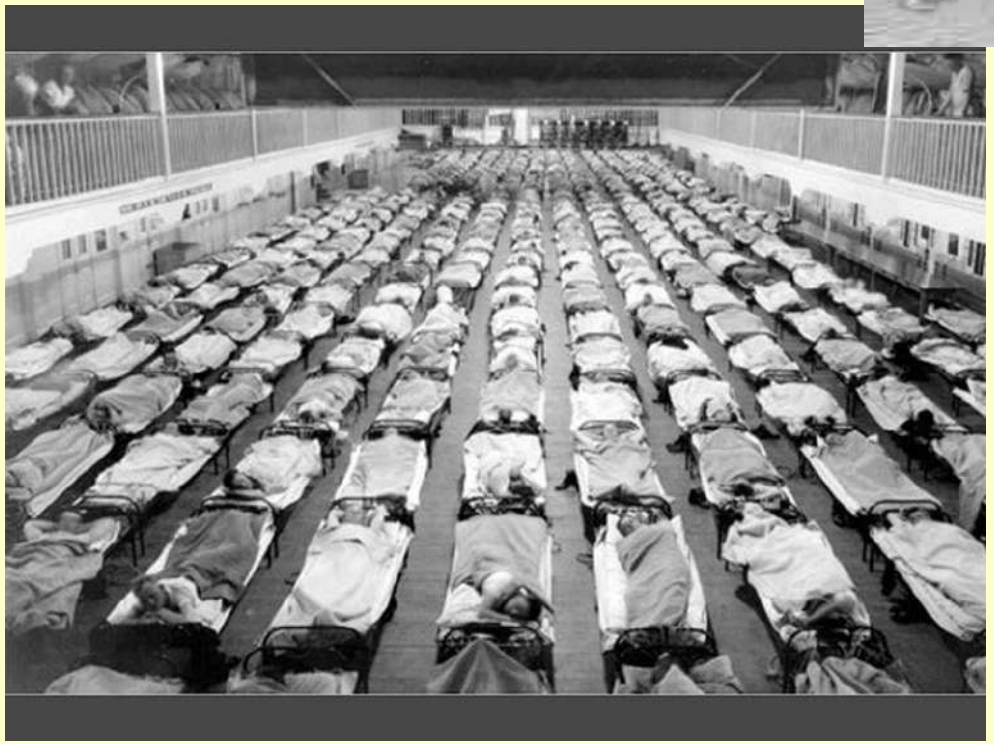
February 1918 to April 1920

Influenza pandemic caused by the H1N1 influenza A virus.

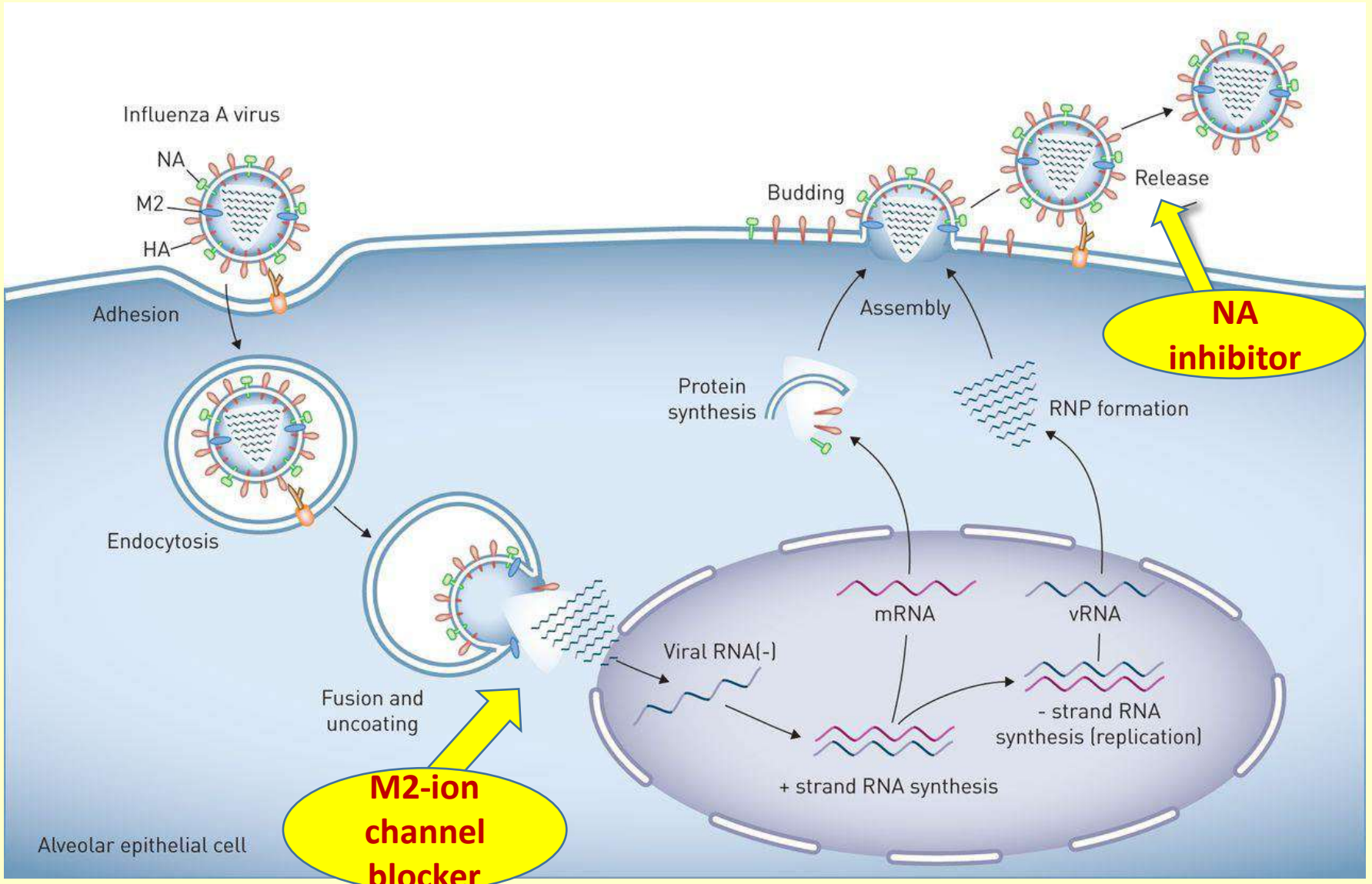
Infected 500 million people – about a third of the world's population at the time.

Death ca. 100 million (One of the **deadliest pandemics** in human history.

Spanish flu



Life cycle of Influenza virus



Life cycle of Influenza virus

Replication of influenza A viruses in the lung epithelium. Binding of **haemagglutinin** (**HA**), expressed on the surface of the influenza virion, with **sialic acid residues linked to cell surface glycans induces binding and fusion of the virion with the plasma membrane of the target cell**. The HA in human viruses interacts with sialic acid residues linked to surface glycans *via* an α-2,6 linkage, which is found in the upper and lower human airway epithelium and in alveolar type II cells.

The virus then enters the cell *via* endocytosis or micropinocytosis and is trafficked to the lysosome where acidification activates the proton selective **matrix protein-2 viral channel (M2),** inducing membrane fusion and dissociation of the viral **ribonucleoprotein** (**RNP**) core, which is then transported to the nucleus where viral RNA replication occurs. Progeny viral RNP cores are generated in the cytosol and, with the viral surface proteins, HA and neuraminidase (NA), and other viral proteins, are concentrated in and near lipid rafts at the plasma membrane. Budding of these plasma membrane regions forms complete viral progeny, which is linked to the plasma membrane by HA/sialic acid interactions.

Cleavage of sialic acid residues by neuraminidase releases the viral progeny so they are then free to infect other cells, which can be **prevented by NA inhibitors**.

Viral Chemotherapy: Influenza virus

1. M2- Ion channel inhibitor

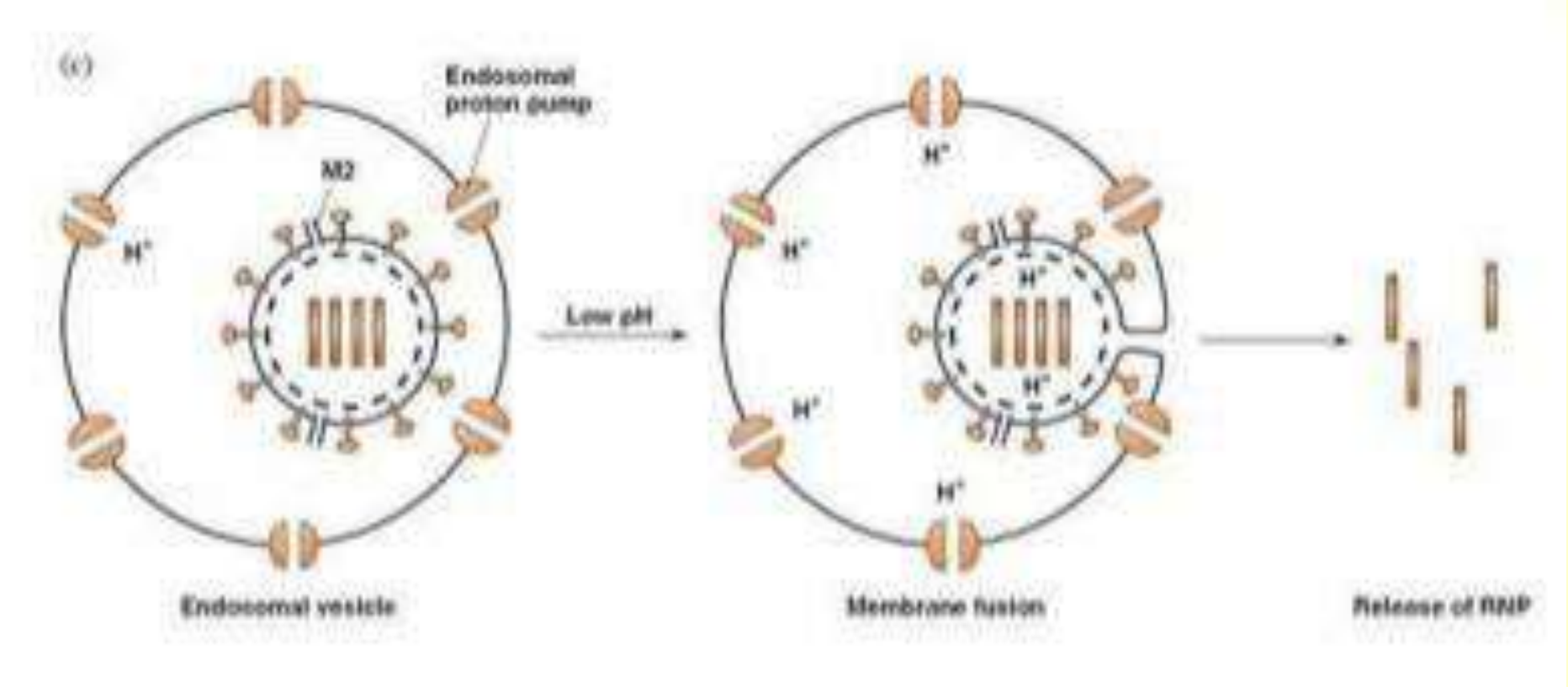
Drugs: Adamantanes and Rimantadine

M2-ion channel is only in Influenza A

Influenza A virion in endosome undergoes fusion with endosomal membrane upon drop in pH. M2-ion channels allow hydrogen ion to enter in virion, releasing RNP from the matrix protein, leading to viral uncoating.

M2 proton channel blockers protect only against the A viruses

Viral Chemotherapy: Influenza virus



Influenza virions in endosomes undergo fusion with endosomal membrane upon drop in pH induced by an endosomal proton pump.

The M2 protein allows hydrogen ions to enter virion, releasing the RNP from the matrix protein. Amantadine blocks the M2 channel, inhibiting this process.

Viral Chemotherapy

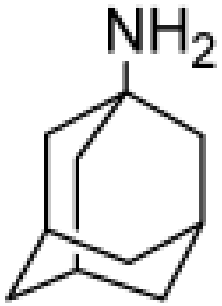
Amantadine:

Amantadine: 1-adamantanamine hydrochloride

A symmetric tricyclic primary amine

Inhibits penetration of RNA viral particles into the host cell, and viral genome uncotaing.

Prophylaxis of Influenza A



Amantadine

Side effect:

Cross BBB--------CNS (Dopamine release)

GIT

Viral Chemotherapy

Rimantadine:

α-methyl derivative of amantadine,

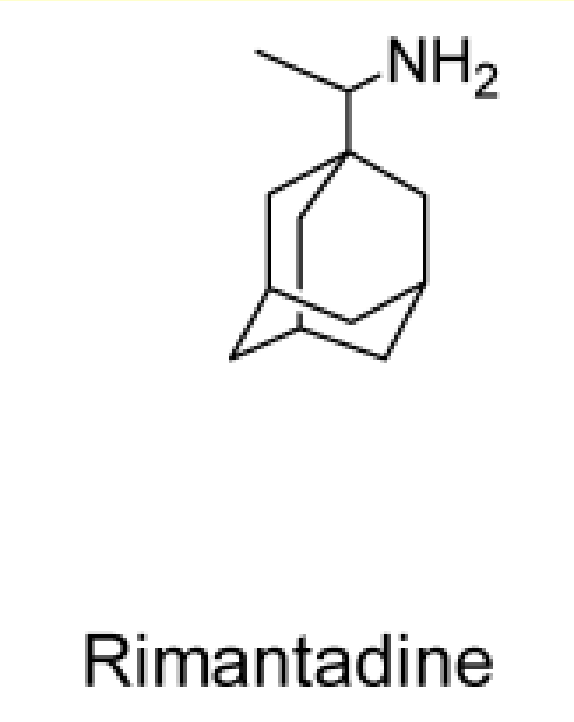
4 to 10 times more active than amantadine

Interfere with virus uncoating. It does not interfere with viral adsorption or penetration

It has similar uses like amantadine HCl.

Side effect: fewer CNS side effects than amantadine

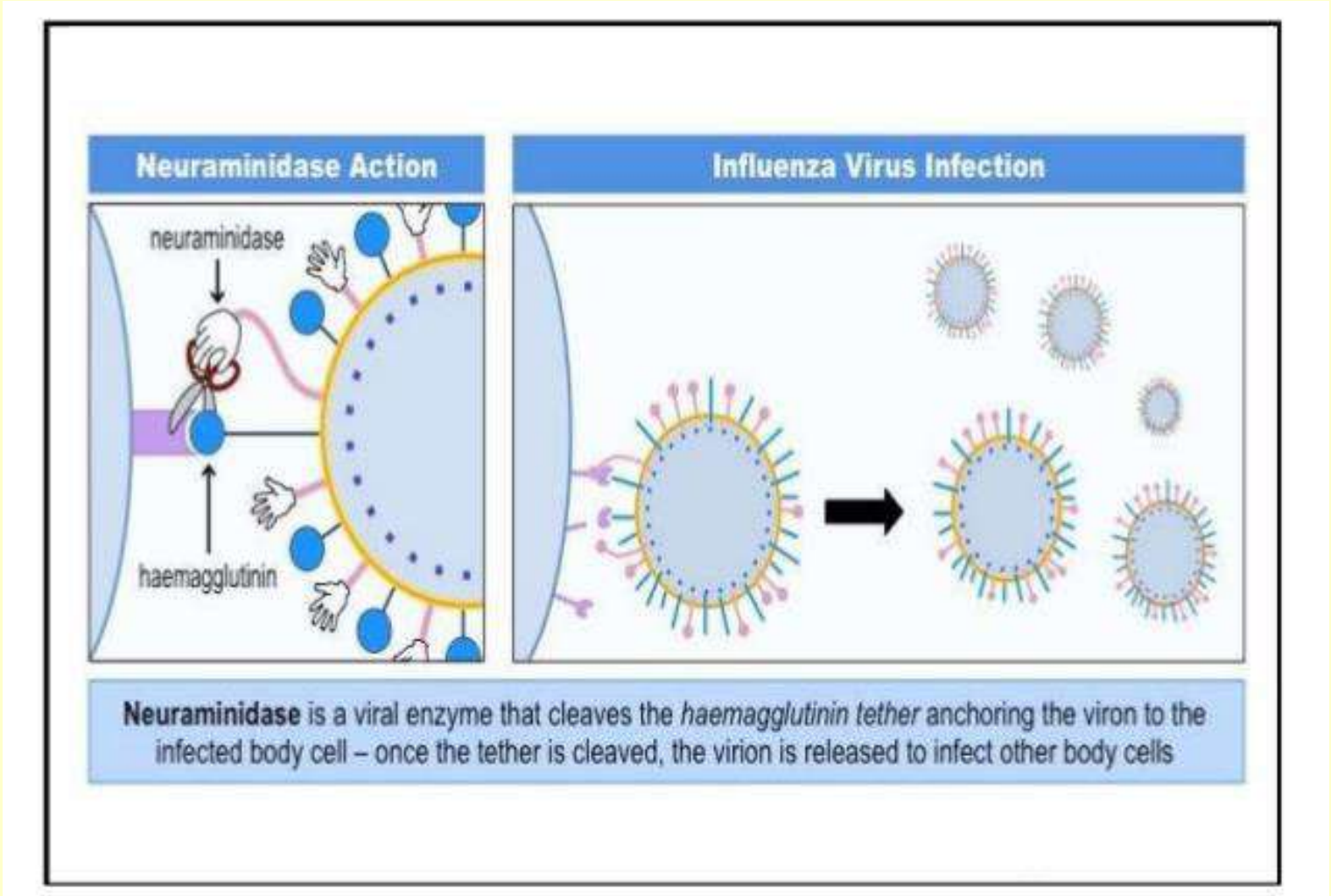
Amnatadine and rimantadine interfere with **M2 protein an ion channel in influenza A**



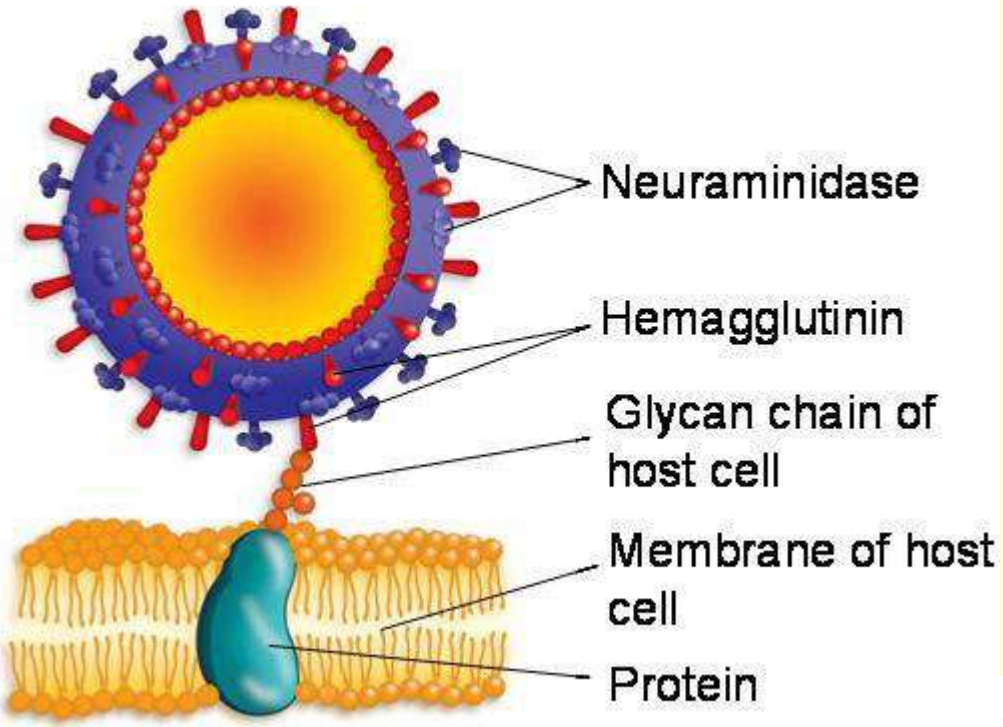
Rimantadine

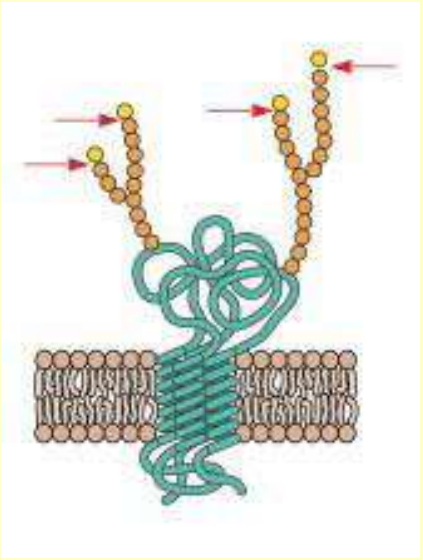
Viral Chemotherapy: Influenza virus

2. Neuroaminidase inhibitor (NAI)

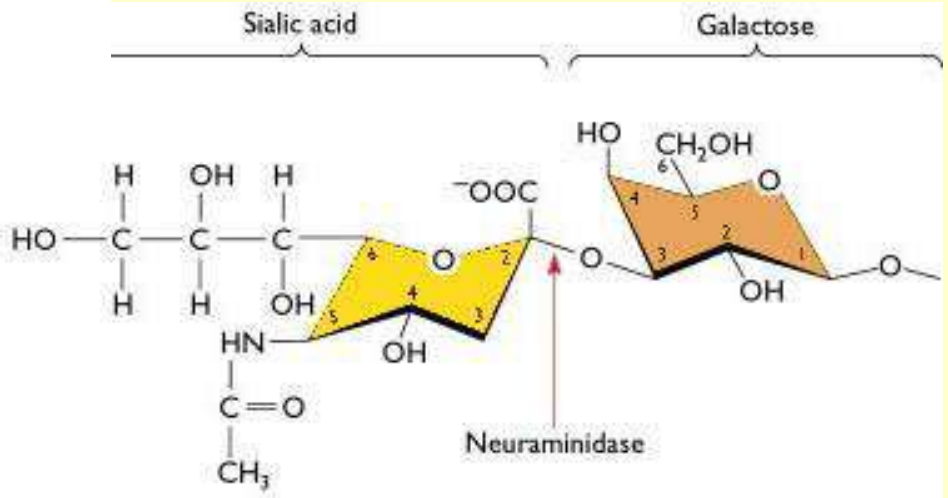


Influenza A virus infects a host cell





Neuramindase and hemagglutinin are a glycoprotein embedded in envelop of Influenza virus A and B.



Viral Chemotherapy: Influenza virus

Neuroaminidase inhibitor (NAI)

- Neuroamidinase (NA) is an enzyme -a sialidase-, cleaving a bond between a terminal sialic acid unit and a sugar which results in release of new virions and their spread from cell to cell.

- **Neuraminidase inhibitors** block viral neuraminidase enzyme, which is critical in releasing virions from the infected host's cells.

- **These drugs are active against influenza A and B**

- Neuraminidase inhibitors, are not cures and do not ‘kill’ the flu virus but merely slow the virus replication down to a level where the immune system can more easily destroy it.

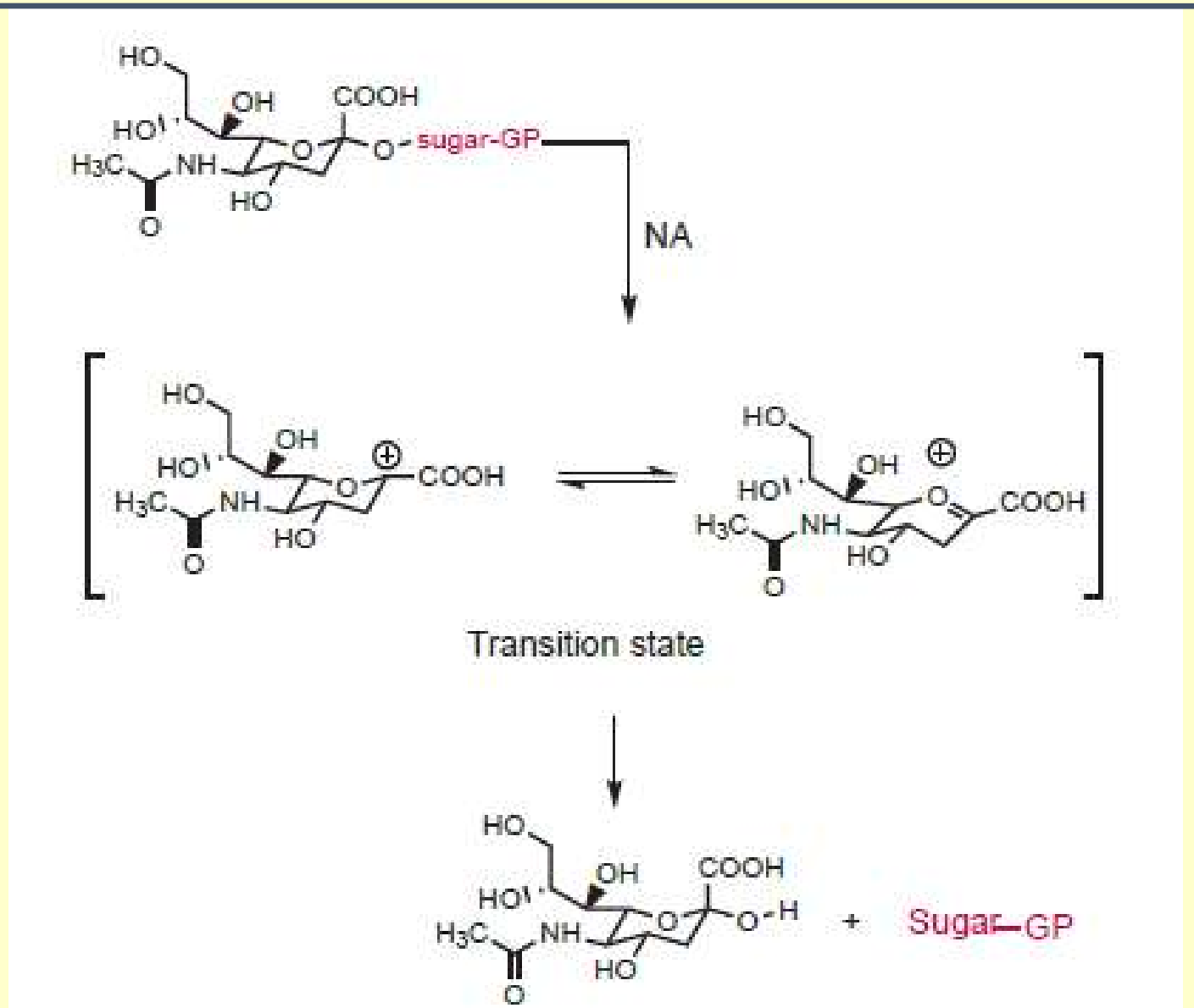
Viral Chemotherapy: Influenza virus

Neuroaminidase inhibitor (NAI)

- Ideally, they should be given as early as possible especially within 48 hours of influenza illness onset.
- They can reduce the severity and duration of a flu illness.
- There are three FDA-approved influenza antiviral drugs (Neuraminidase inhibitors)

1. Oseltamivir (trade name Tamiflu®)
2. Zanamivir (trade name Relenza®)
3. Peramivir (trade name Rapivab®).

Mechanism of Neuroaminidase



Sialic acid, N-Acetylneuraminic acid , Neu5Ac

Neuroaminidase inhibitor (NAI): Transition state inhibitors

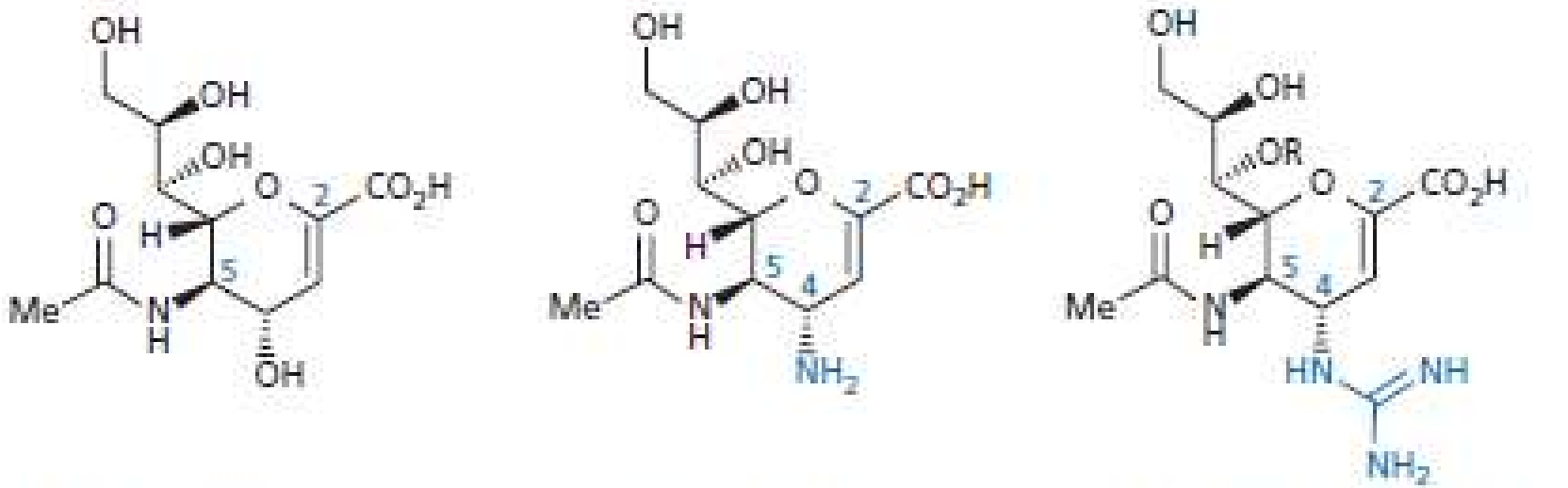
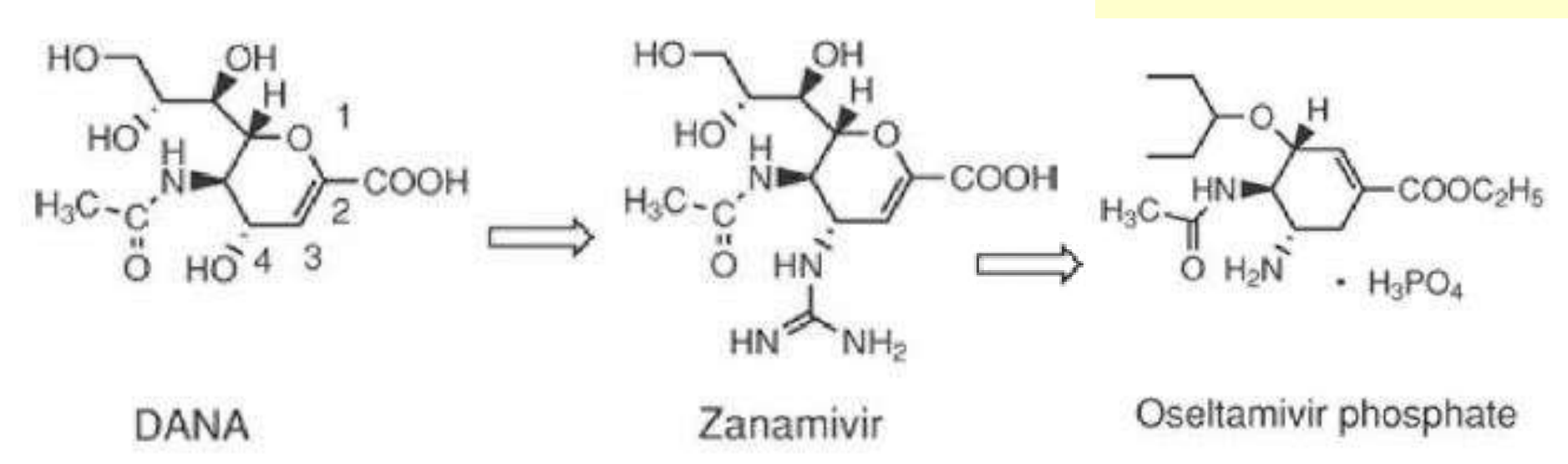


FIGURE 20.44 Transition-state inhibitors for the enzyme neuraminidase.

Neu5Ac2en (DANA): 2-deoxy-2,3-dehydro-*N-acetylneuraminic acid, is a highly active* neuraminidase inhibitor (<u>not specific for the viral enzyme</u>).

DANA: Lead compound

Neuroaminidase inhibitor (NAI): Transition state inhibitors



(Not selective for the viral NA).
Inactive in vivo

First selective drug
Powder
Inhalation

Carbocyclic drug
Oral
Tablet

Neuroaminidase inhibitor (NAI): Transition state inhibitors/ development of Zanamivir

- The transition state has a planar trigonal centre at C-2 and so sialic acid analogues containing a double bond between positions C-2 and C-3 were synthesized to achieve that same trigonal geometry at C-2. Discovery of the inhibitor **2-deoxy-2,3-dehydro- *N* -acetylneuraminic acid** **(Neu5Ac2en, DANA)**.

- **4-Amino-Neu5Ac2en** contains the aminium group / more potent than Neu5Ac2en/ selective against the viral enzyme

- Substitution at C 4 with larger guanidinium group was 100 X more potent than aminogroup

Neuroaminidase inhibitor (NAI): Transition state inhibitors/ development of Zanamivir

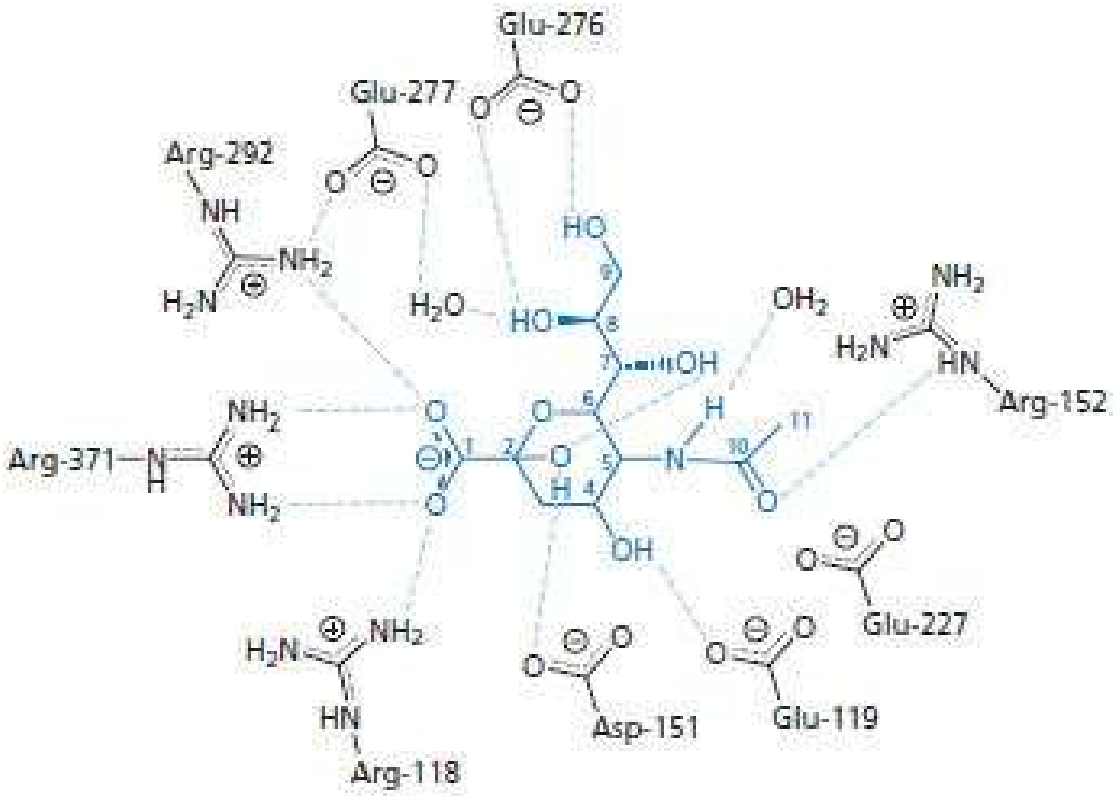


FIGURE 20.42 Hydrogen bonding interactions between sialic acid and the active site of neuraminidase.

Neuroaminidase inhibitor (NAI): Transition state inhibitors/ development of Zanamivir

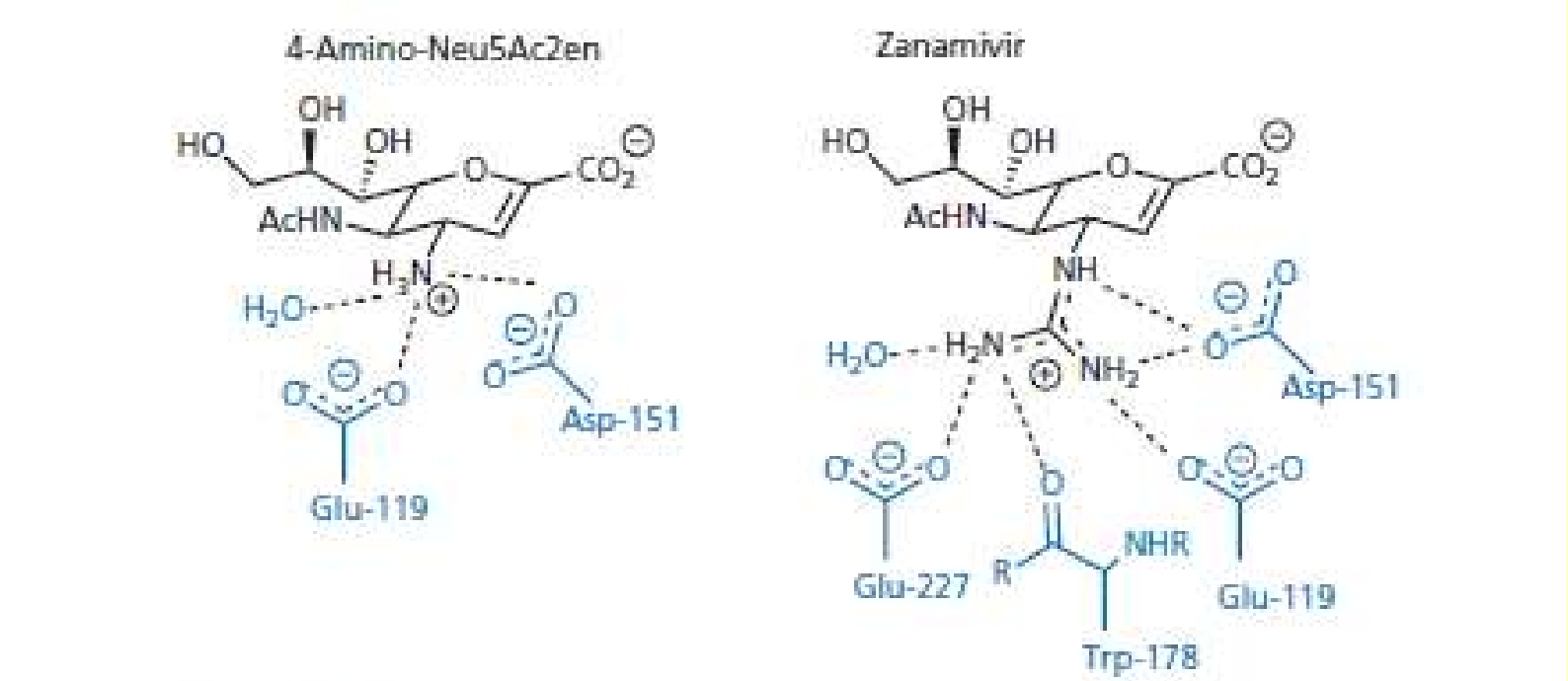
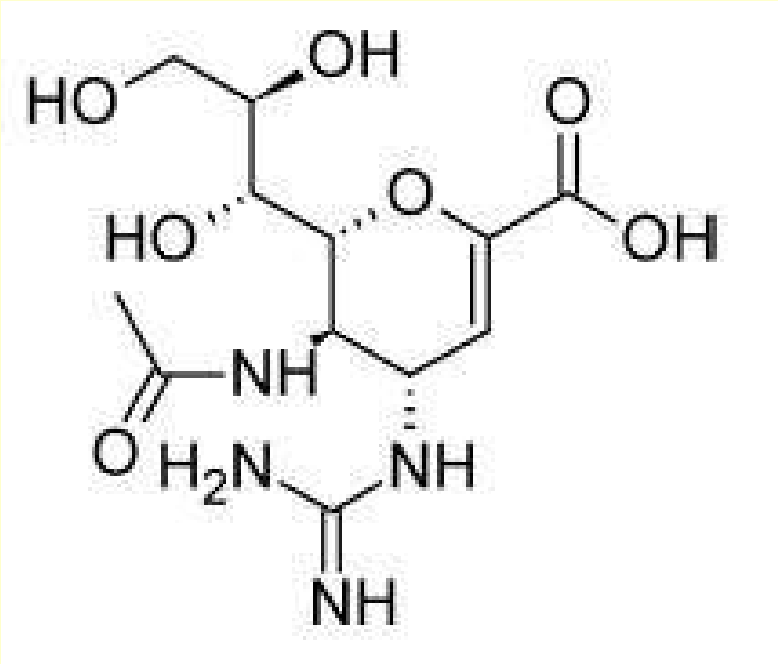


FIGURE 20.45 Binding interactions of aminium and guanidinium moieties at C-4 with the active site of neuraminidase.

Neuroamidinase Inhibitor

Zanamivir



A sialic acid analog, replacement of the 4’ OH with an amino- or guanidinyl group

Selective for viral neuroamidinase

Prophylactic for the prevent ion of influenza A and B infections

Neuroamidinase Inhibitor

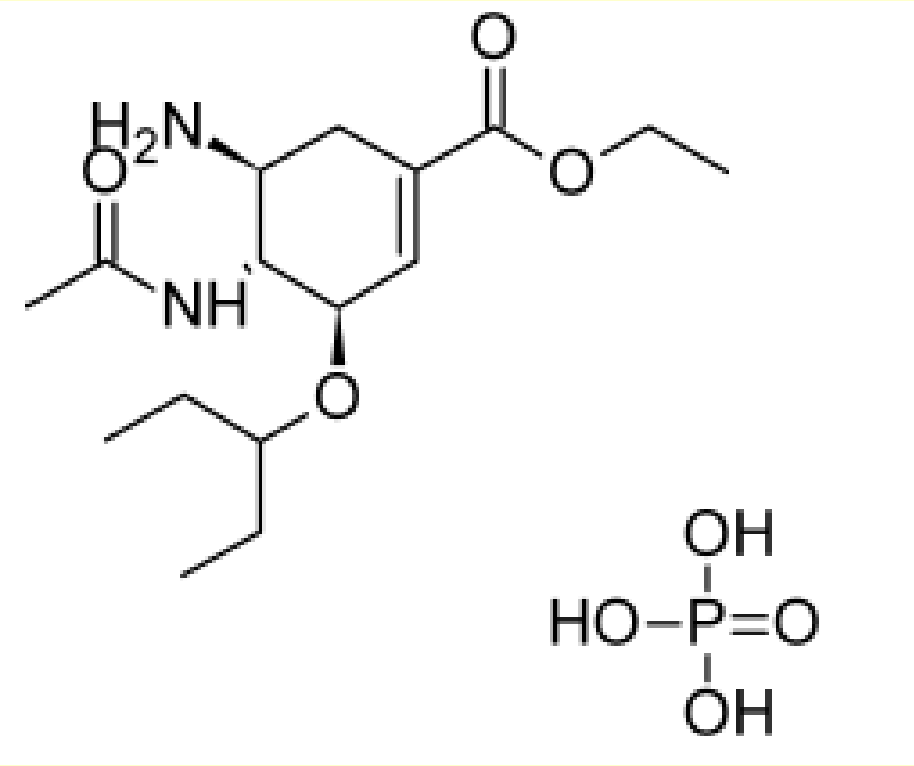
Oseltamivir phosphate

It is given orally

Oseltamivir is actually a **prodrug** in its ethyl ester form.

Ester hydrolysis releases the active oseltamivir molecules.

If administered within 2 days after the onset of influenza symptoms, the drug is effective



Neuroamidinase Inhibitor

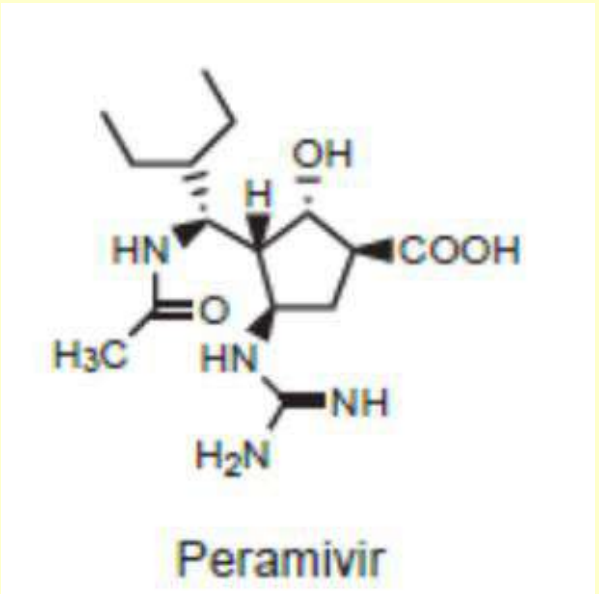
Peramivir

In Japan: 2010

FDA approval 2012

Peramivir is a **cyclopentane** derivative with activity against influenza A and B viruses.

Intravenous (IV) medication



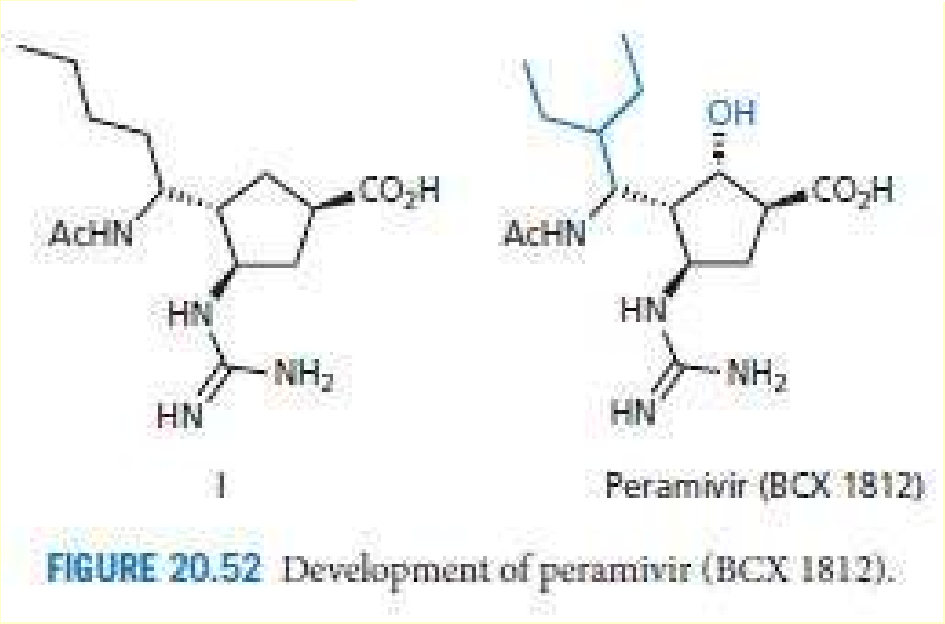


FIGURE 20.52 Development of peramivir (BCX 1812).

Antiviral agents

Part 2

Dr. Mai Ramadan

Viral Chemotherapy

Inhibiting viral replication:

DNA Polymerase inhibition: For Herpes

Nucleoside antimetabolite (Purine and pyrimidine analogue)

Reverse transcriptase inhibition (RTI) For HIV

Nucleoside reverse transcriptase inhibition: NRTI

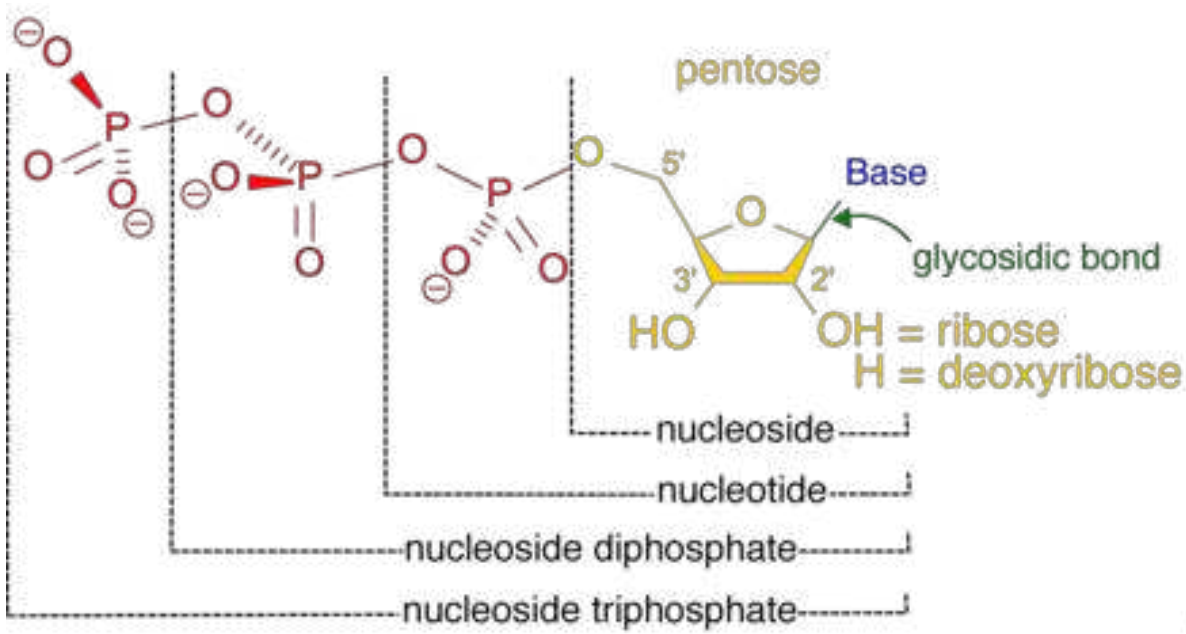
Nonnucleoside reverse transcriptase inhibition: NNRTI

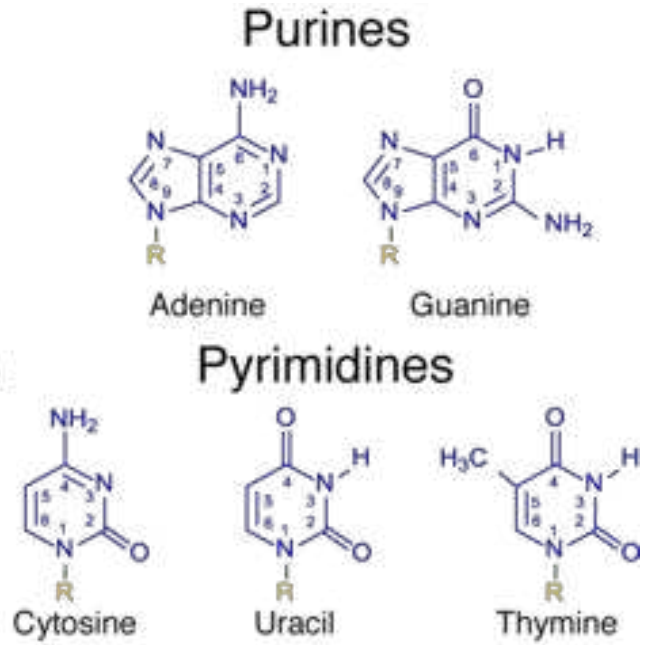
Direct inhibitor of DNA polymerase and RT

Foscarnet

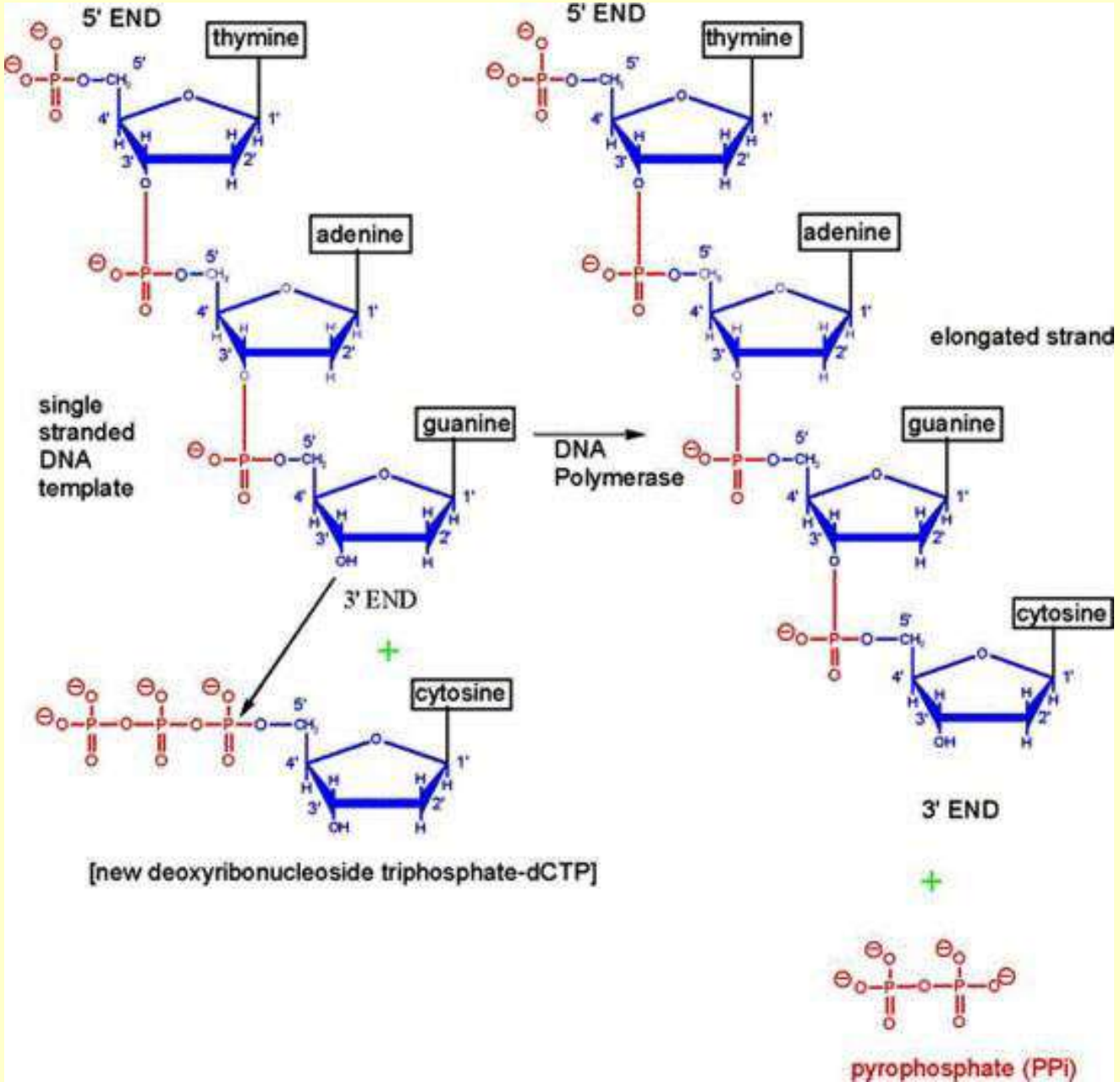
Review

Synthesis of DNA/ Role of DNA polymerase

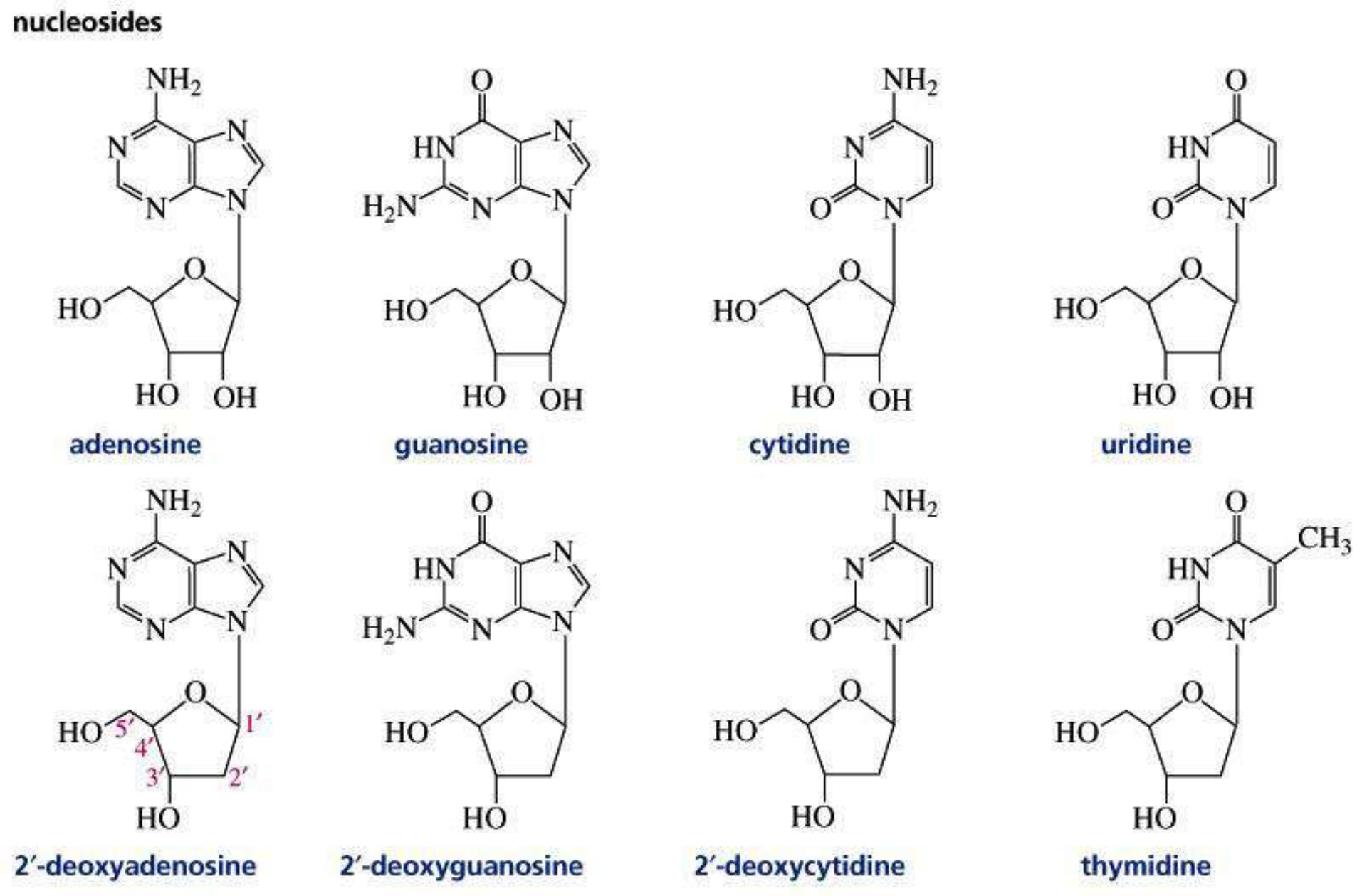




Synthesis of DNA/ Role of DNA polymerase

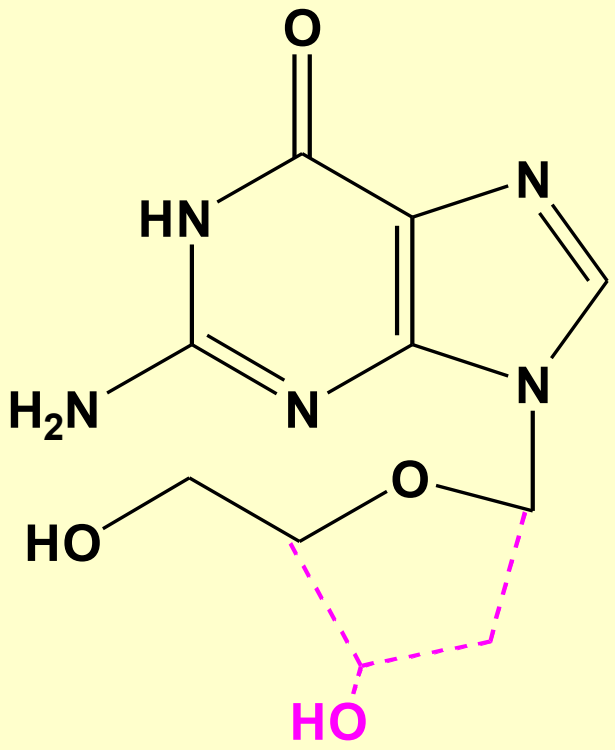


Nucleosides = Base + Sugar



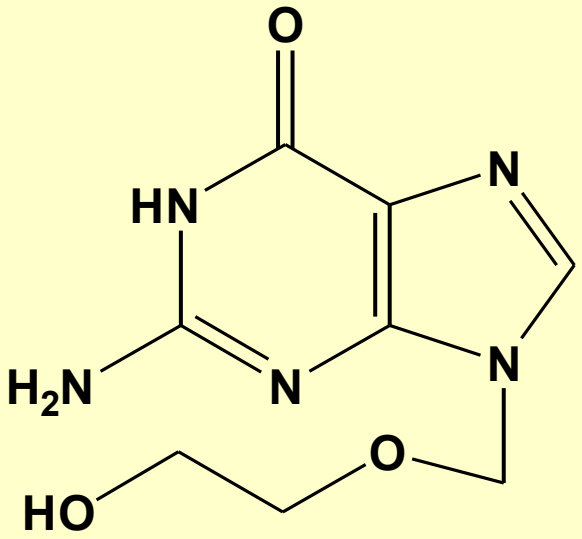
Nucleoside antimetabolite (Purine analogue)

Acyclovir (Zovirax):



2’-deoxyguanosine

DNA component



Acyclovir

DNA terminator

Nucleoside antimetabolite (Purine analogue)

Acyclovir (Zovirax):

Acyclovir is a purine **nucleoside analog**

One of the most successful antiviral drugs

Targets herpes virus infection (HSV-1&2, and VZV)

It lacks C-2', C-3' and the **3'-OH**

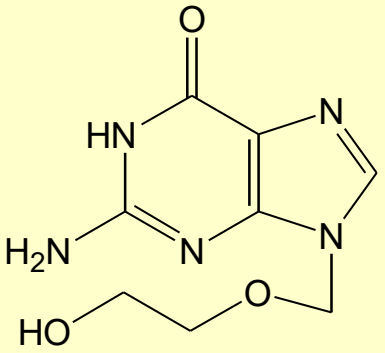
It is a prodrug.

Activation by **viral** thymidine kinase, and cellular kinase to acyclguanosine triphosphate **(Acyclo-GTP)**

Inhibit DNA polymerase and terminate DNA elongation (lack 3^{-} OH necessary for phosphodiester formation, Chain terminator)

Nucleoside antimetabolite (Purine analogue)

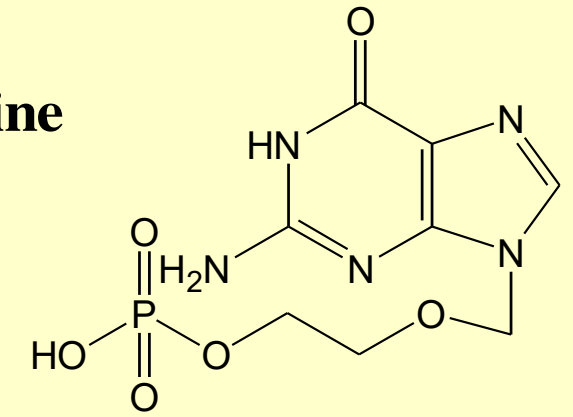
Acyclovir Mode of Action



Acyclovir

Viral thymidine Kinase

ATP

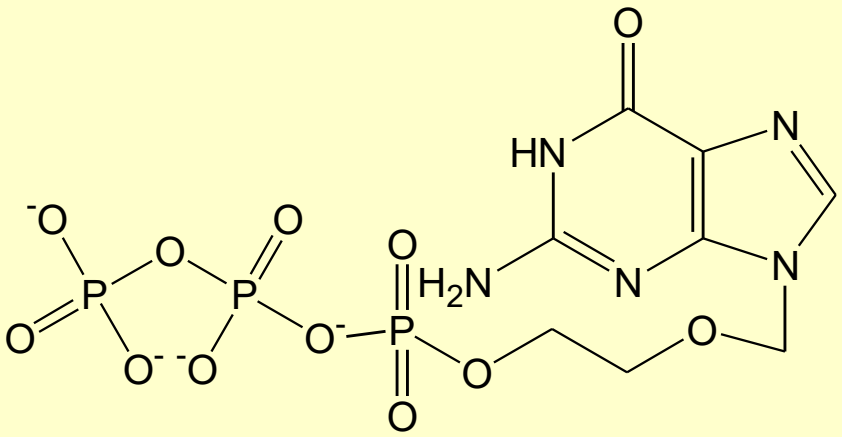


Acycloguanosine monophosphate

(acyclo GMP)

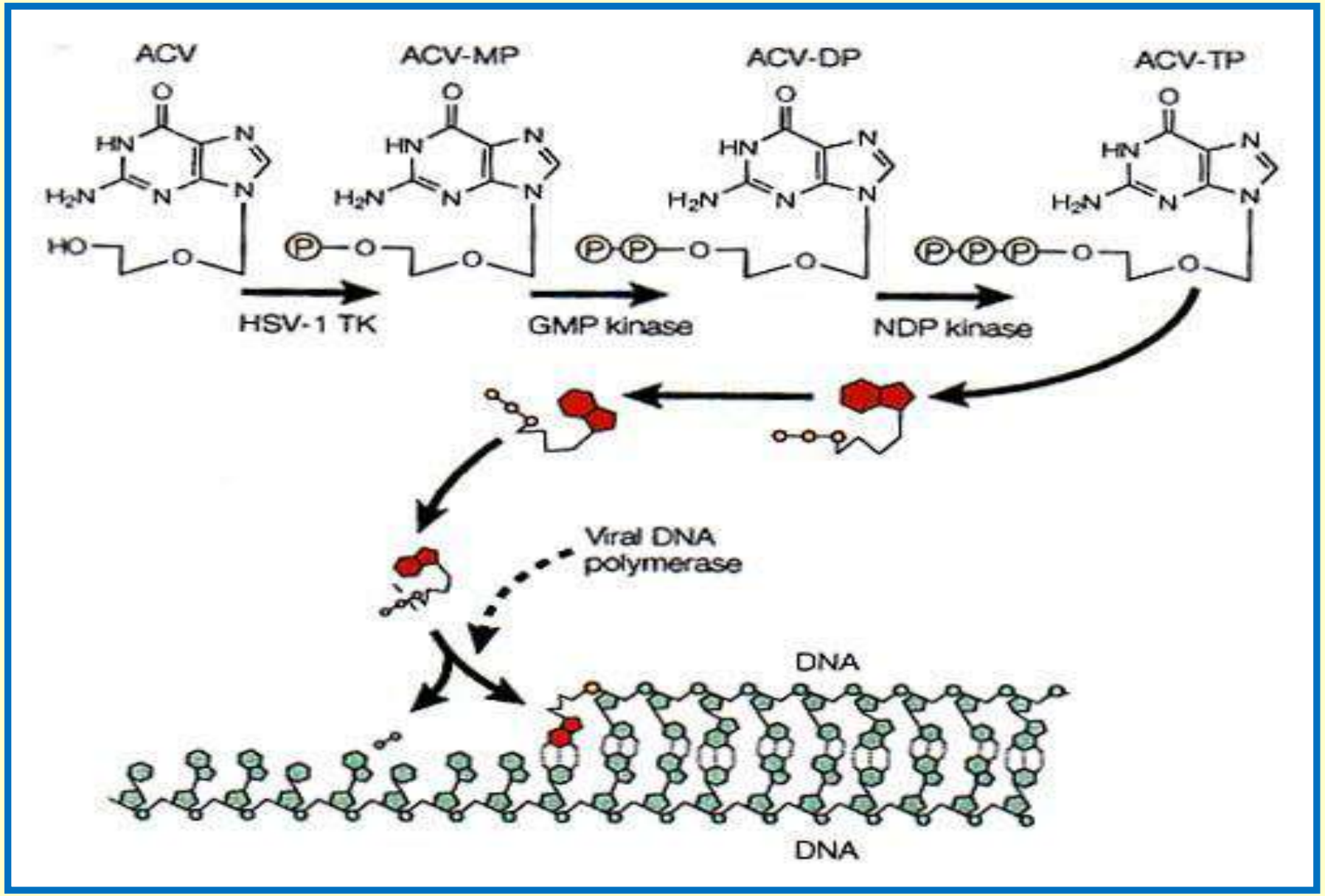
Cellular Kinase

2 ATP

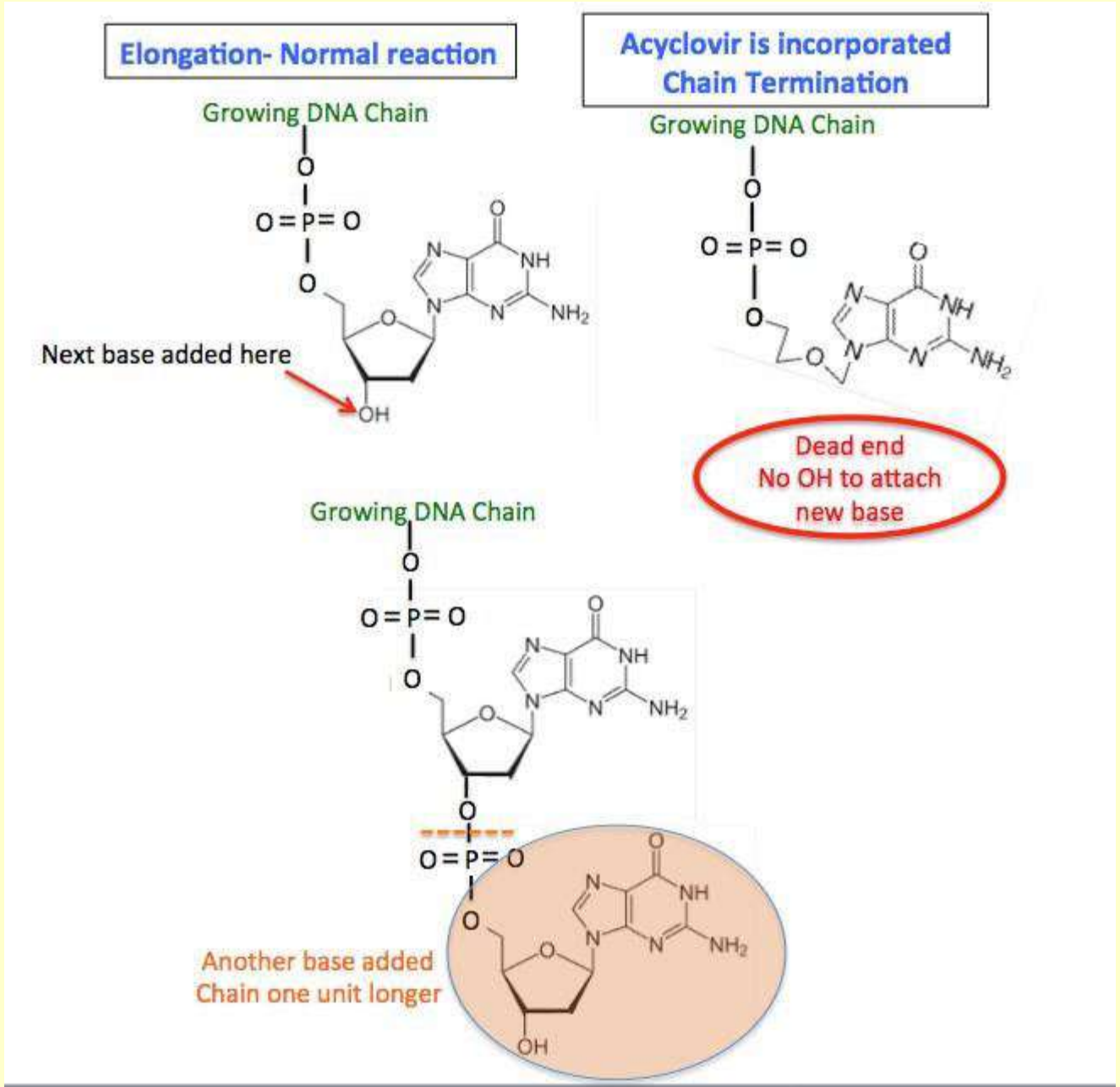


Acycloguanosine triphosphate
(acyclo GTP)

Acyclovir Mode of Action



Acyclovir Mode of Action



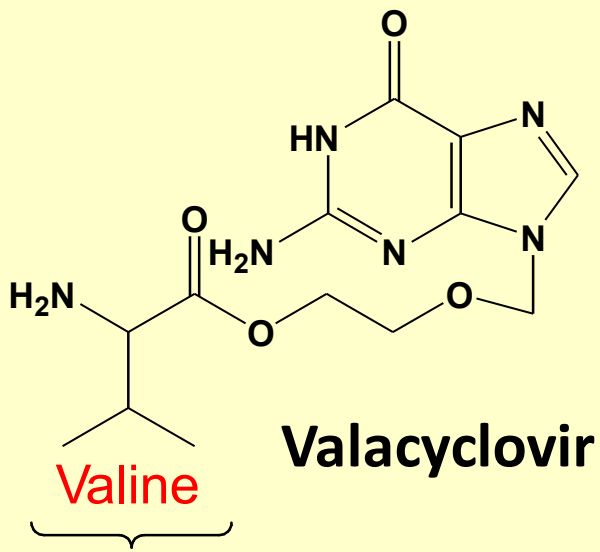
Nucleoside antimetabolite (Purine analogue)

Valacylovir (Valtrex):

Apro-prodrug

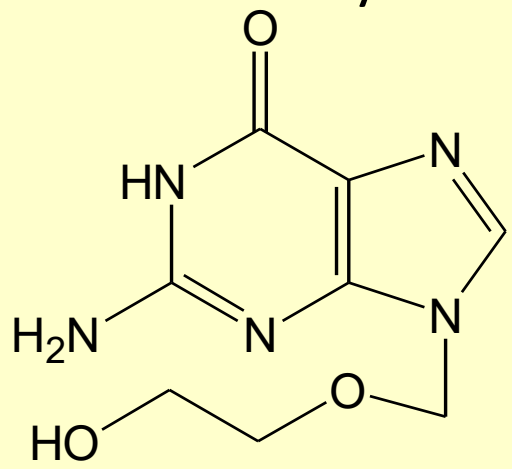
L-Valylester of acyclovir

Improve oral bioavailability (3-5 times higher than that of acyclovir)



Valacyclovir

Esterase

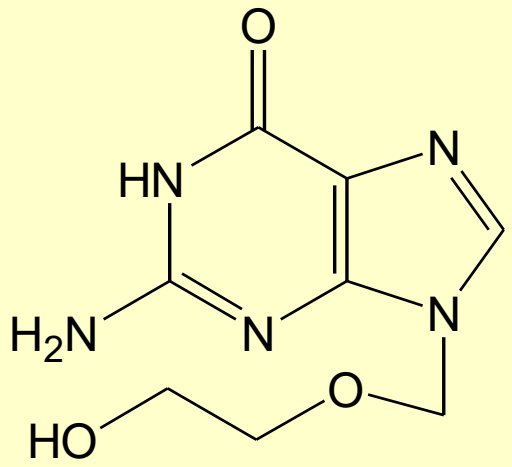


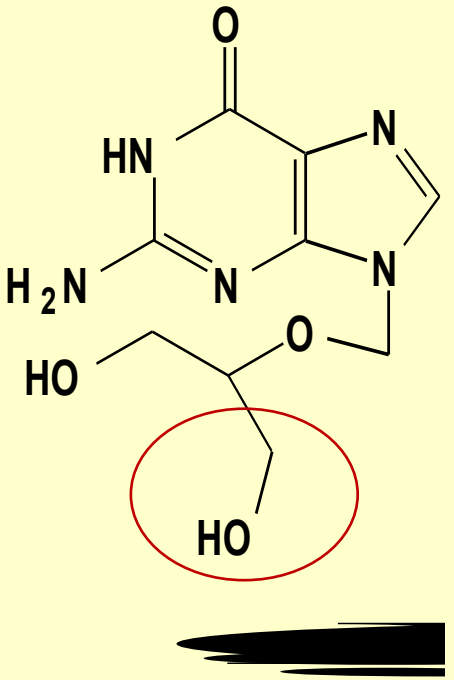
Acyclovir

Oral bioavailability 15-30%

Nucleoside antimetabolite (Purine analogue)

Gancyclovir:





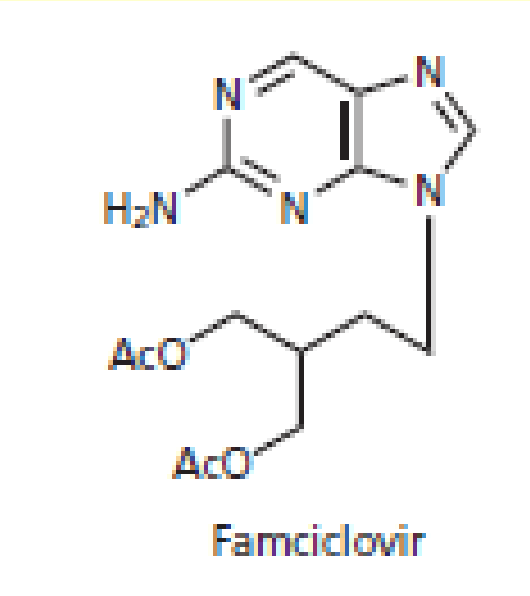
Oral bioavailability less than 10%.

Difference: Presence of hydroxyl methyl moiety on acyclic part

Greater activity against CMV (Cytomegalovirus), while maintaining the activity of acyclovir towards Varicella-Zoster virus (VZV) and (HSV)

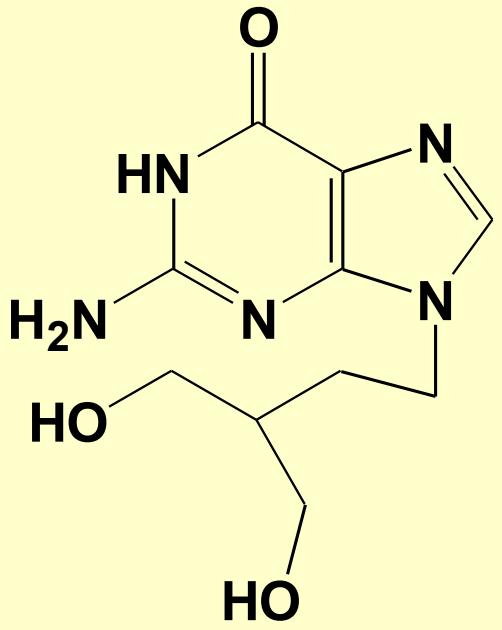
Nucleoside antimetabolite (Purine analogue)

Famciclovir and penciclovir:



Famciclovir

METABOLIC ACTIVATION

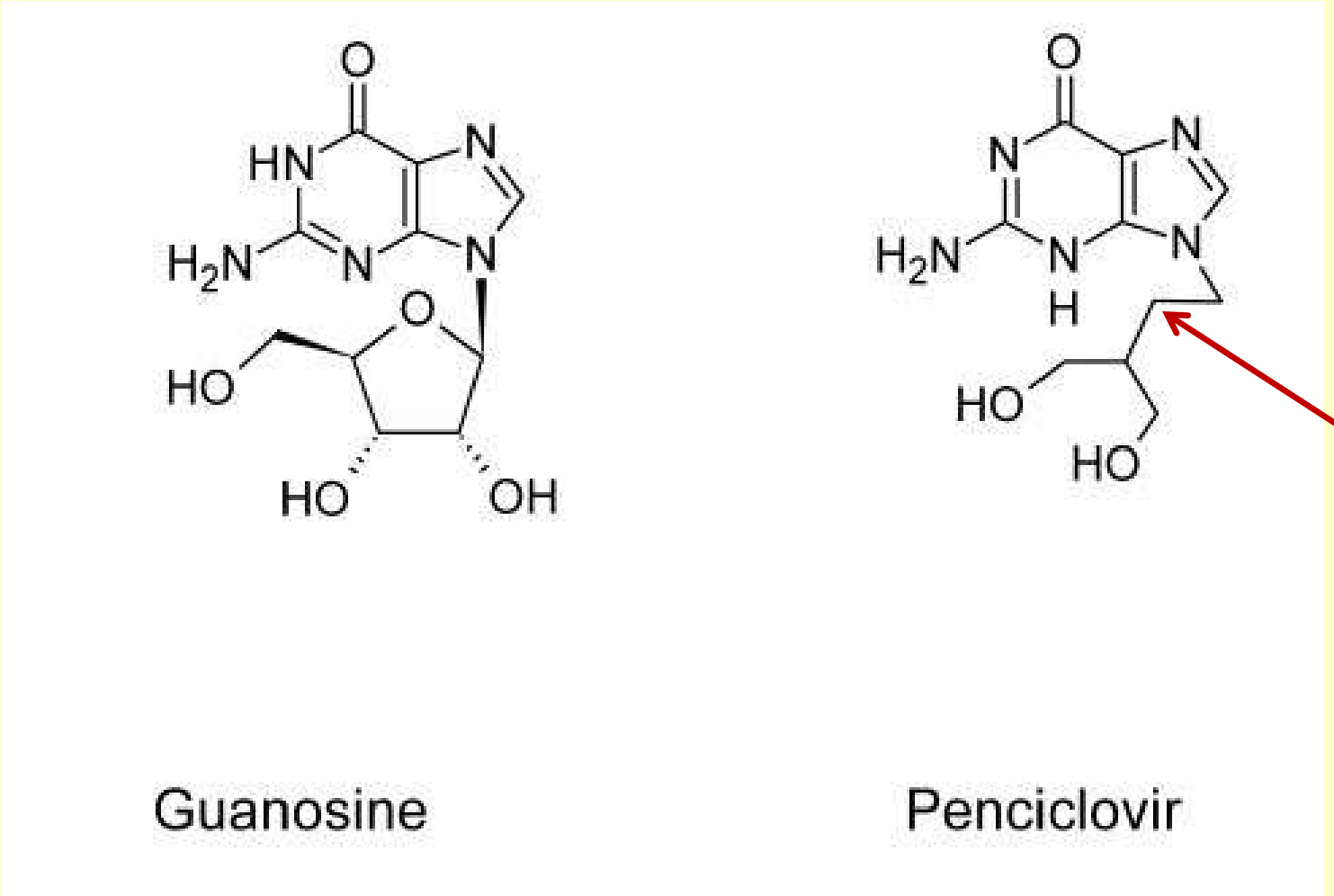


Penciclovir

Famciclovir(oral): Diacetyl prodrug of penciclovir.
The mechanism of action like acyclovir.
Penciclovir (topical): less oral bioavaialbility

Nucleoside antimetabolite (Purine analogue)

Famciclovir and penciclovir:



Nucleoside antimetabolite (Purine analogue)

Famciclovir and penciclovir:

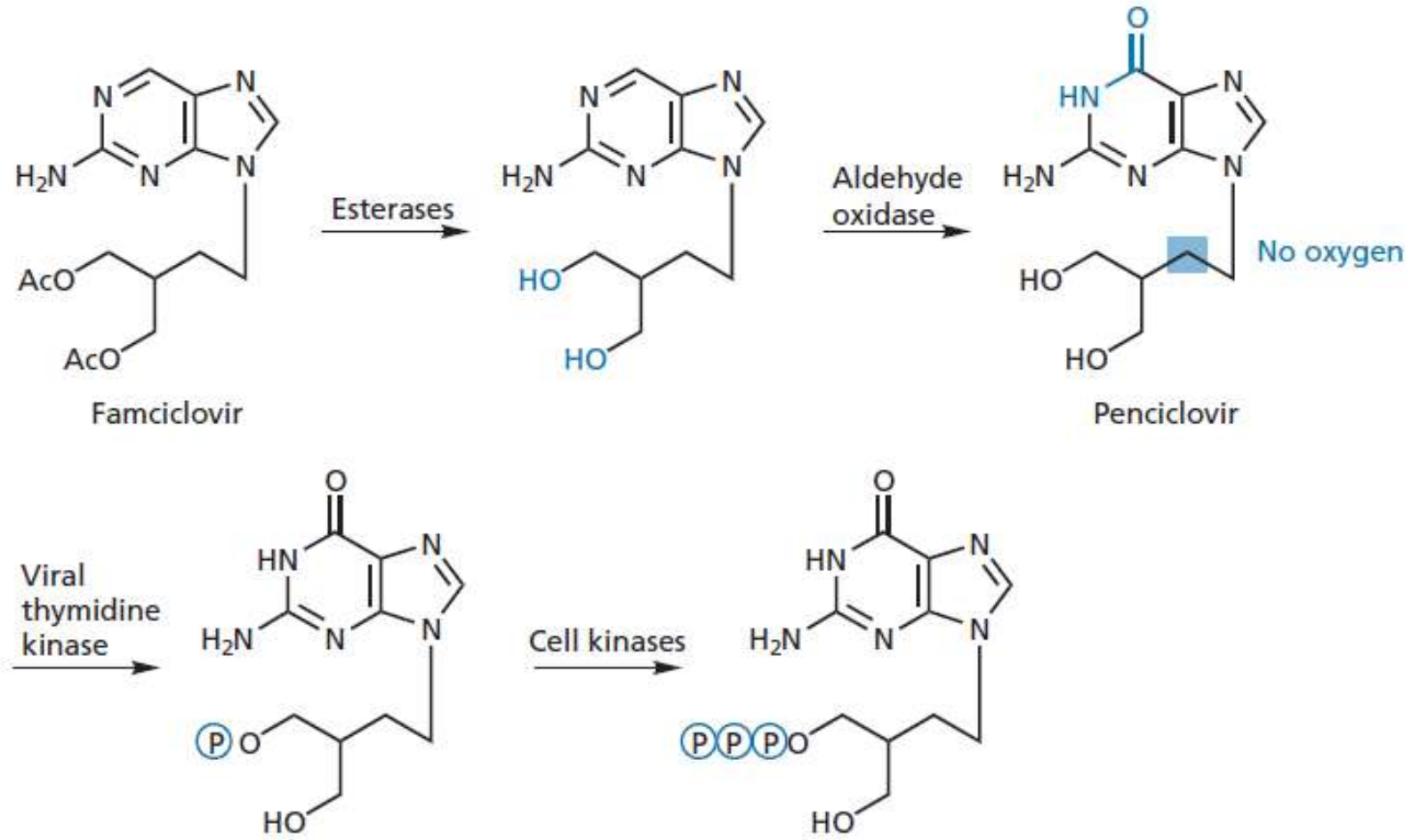


FIGURE 20.6 Penciclovir and famciclovir. (P) represents a phosphate group.

Nucleoside antimetabolite (Purine analogue)

Vidarabine(ara-A)

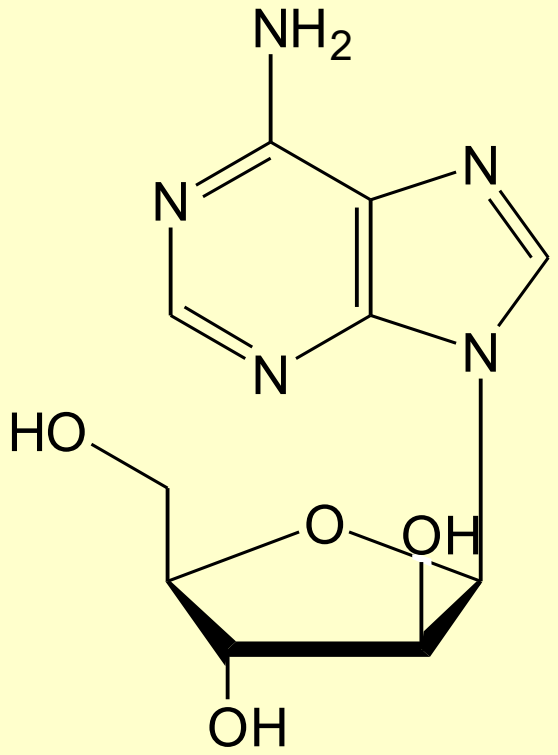
is an adenosine nucleoside

arabinose instead of ribose (differ in the stereochemistry of the **2'-OH**.

It is activated to mono- , di- and triphosphate derivative

Competitive inhibitor of viral DNA polymerase, incorporation into and inhibition of the growing viral DNA (Formation of faulty DNA)

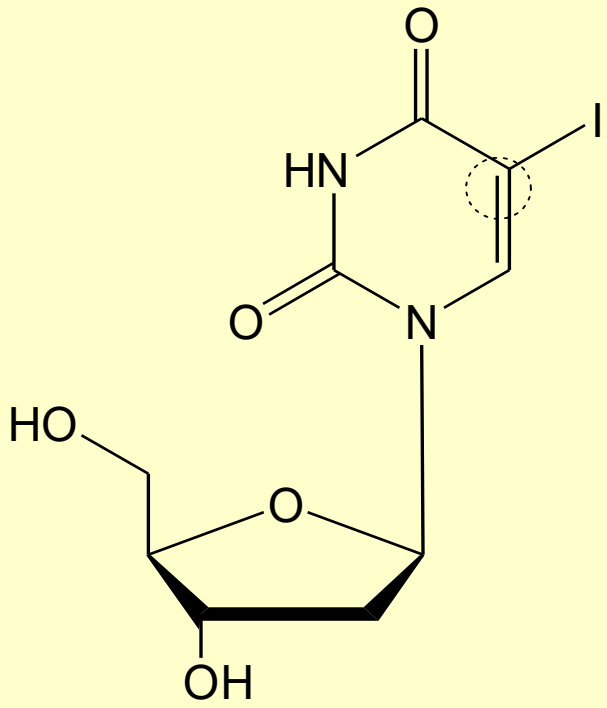
Originally used as antineoplastic, but found effective antiviral superior to that of idoxuridine.



Vidarabine (ara-A)

Nucleoside antimetabolite (Pyrimidine analogue)

Idoxuridine (Stoxil)
5-iodo-2-deoxyuridine



The drug is an iodinated analog of thymidine

It is converted in cell to mono-, di-, and triphosphate.

Activation is not selective to virally infected cells

kinases in both virus and normal cells convert idoxuridine to the corresponding nucleotide monophosphate, nucleotide diphosphate, and nucleoside triphosphate (NTP)

Nucleoside antimetabolite (Pyrimidine analogue)

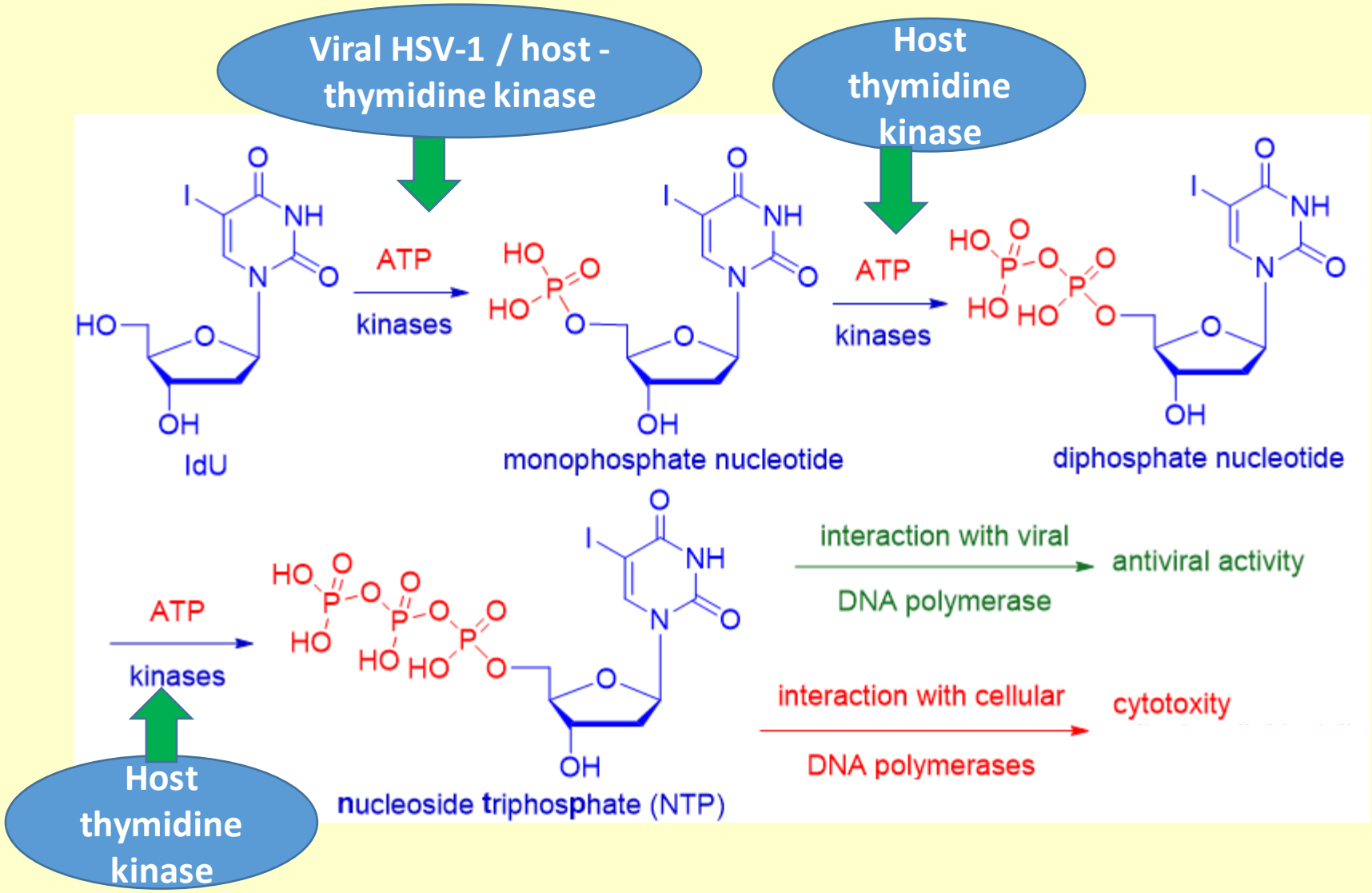
Idoxuridine (Stoxil)

The triphosphate is believed to be both a substrate and inhibitor of viral DNA polymerase.

It is used **only topically** due to cardiotoxicity

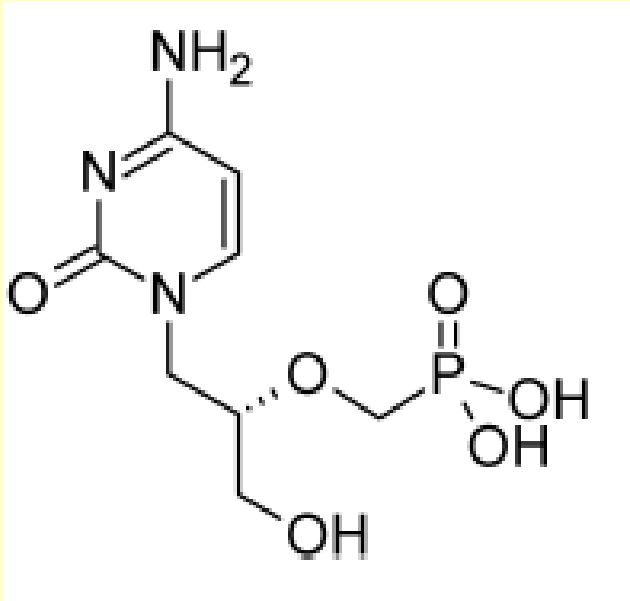
The ability of idoxuridine to substitute for deoxythymidine in viral DNA may be a result of the similar van der Waals radii of iodine (2.15 Å) and the thymidine methyl group (2.00 Å). The resulting DA is faulty and breakable.

Nucleoside antimetabolite (Pyrimidine analogue)



Nucleoside antimetabolite (Pyrimidine analogue)

Cidofovir (Vistide)
(*S)-3-hydroxy-2-phosphonomethoxypropyl cytosine* (HPMPC)



An acyclonucleotide analog (dexycytidine-5-monophosphate analogue)

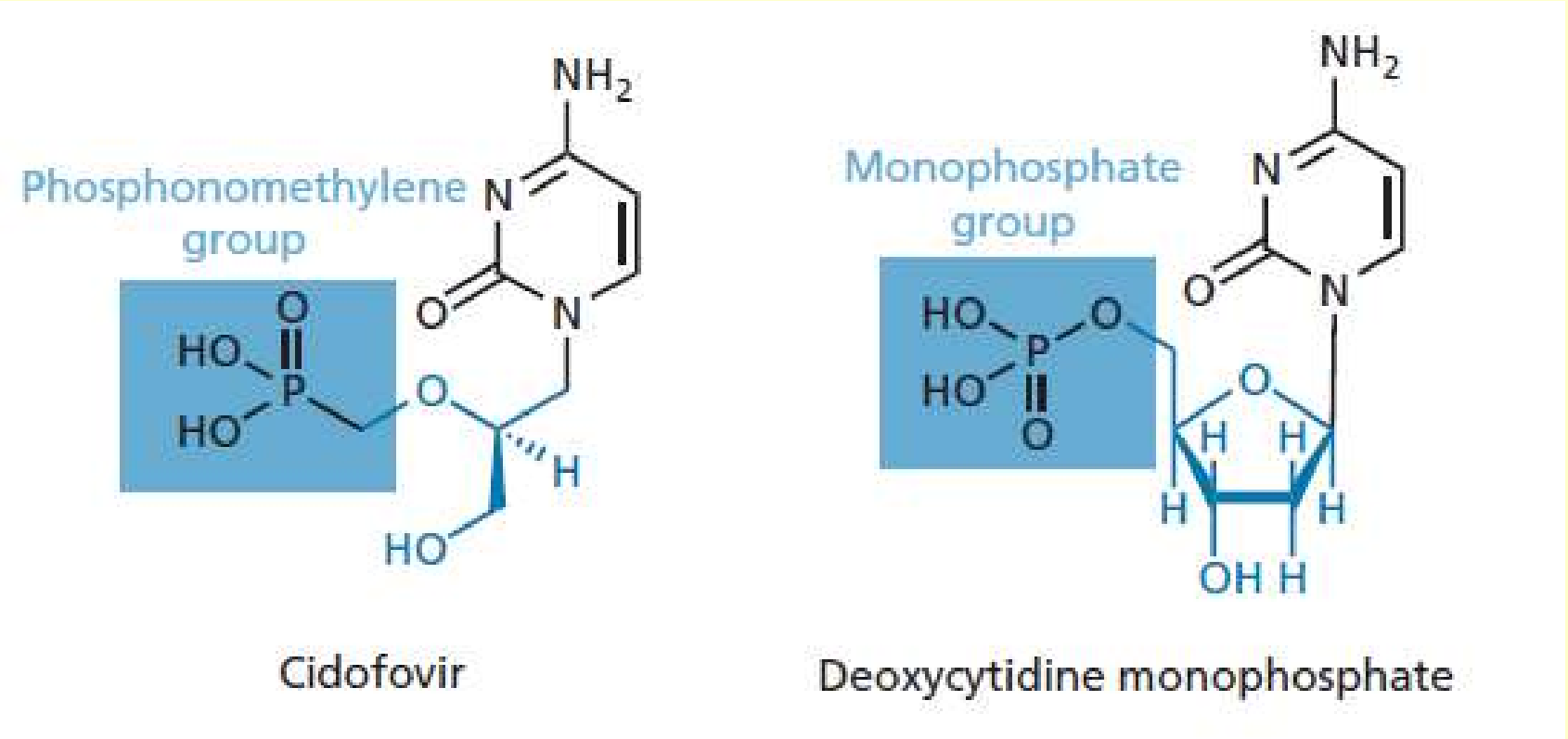
A phosphonic acid derivative.

The phosphonic acid is not hydrolyzed by phosphatases in vivo

Phosphorylated by cellular kinases to yield a diphosphate. [antimetabolite to deoxycytosine triphosphate (dCTP).

Approved for treating CMV retinitis in patients with AIDS.

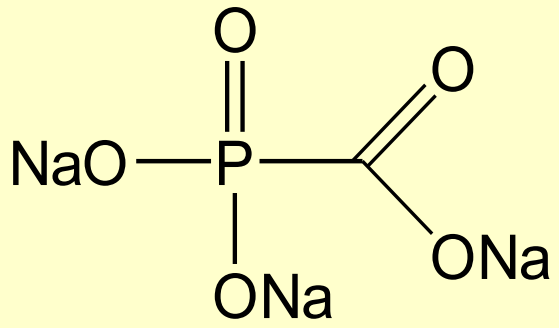
Nucleoside antimetabolite (Pyrimidine analogue)



Direct inhibitor of DNA polymerase and RT

Foscarnet

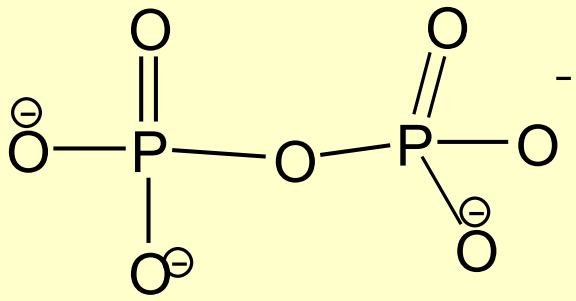
Trisodium phosphonoformate is an inorganic pyrophosphate analog



Trisodiumphosphonoformate

Not requiring an activation step before attacking the target viral enzyme (**Not a prodrug)**

It is a reversible, noncompetitive inhibitor with respect to nucleoside triphosphate , that binds to pyrophosphate binding site of viral DNA polymerase and reverse transcriptase (RT).



Pyrophosphate

Direct inhibitor of DNA polymerase and RT

Foscarnet

It is non selective and toxic.

Difficult crossing cell membrane due to its high charge.

Synergistic effect with nucleoside antimetabolite.

Antiviral agents

Part 3

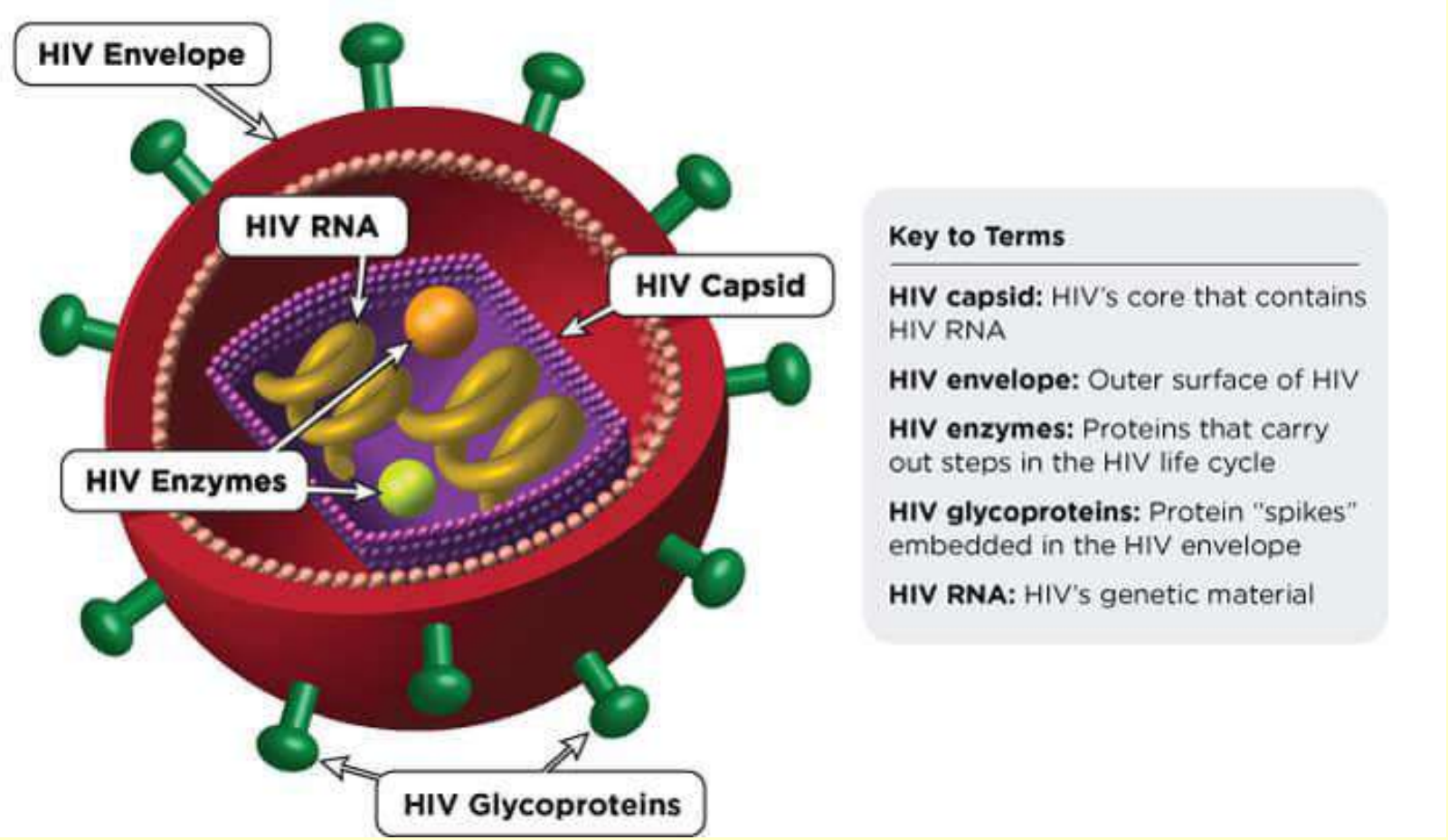
Dr. Mai Ramadan

Antiretroviral agents

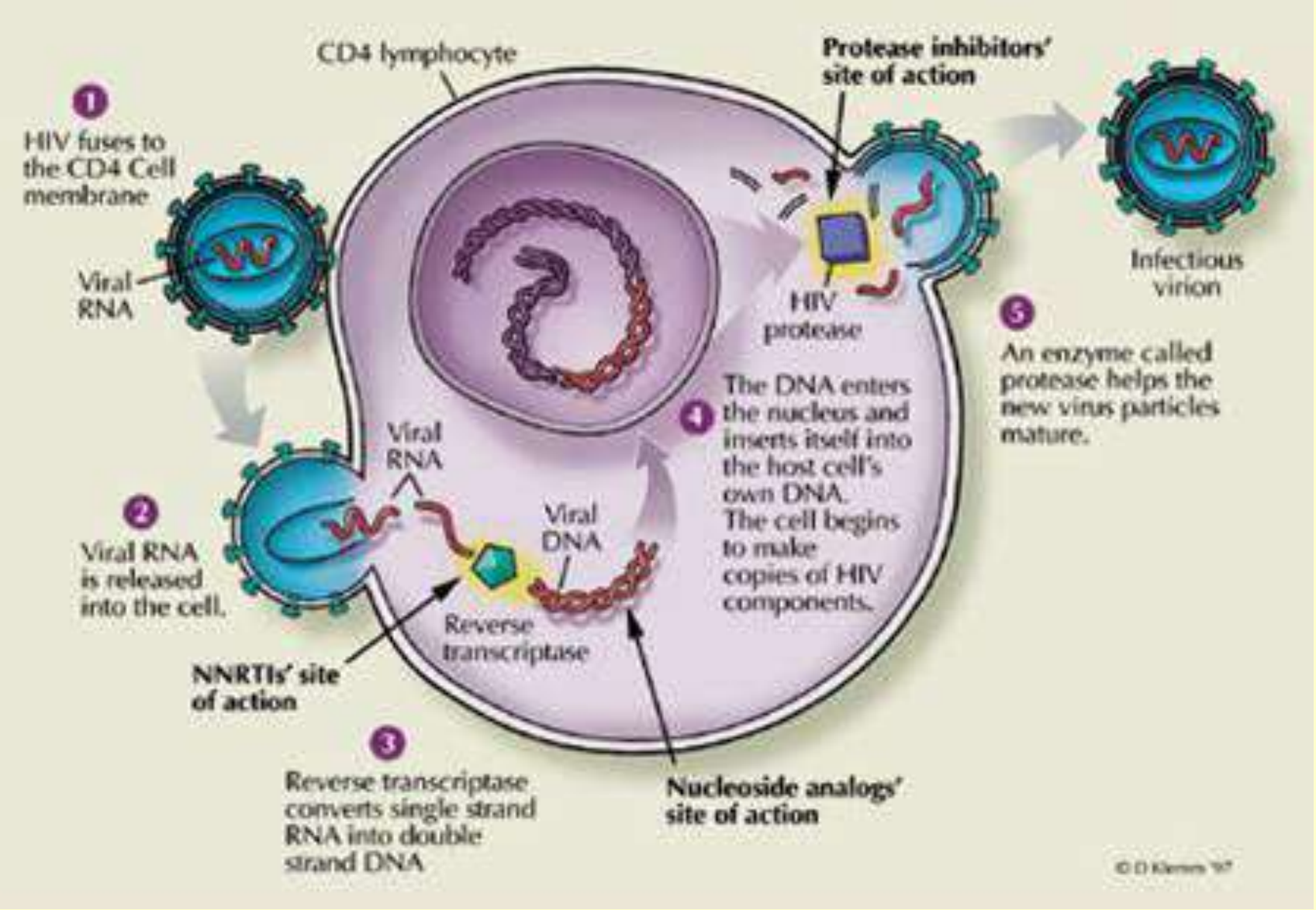
Retrovirus: HIV

- Nucleoside reverse transcriptase inhibitor: NRTI
- Nonnucleoside reverse transcriptase inhibitor (NNRTI)
- Protease inhibitor
- Integrase inhibitor

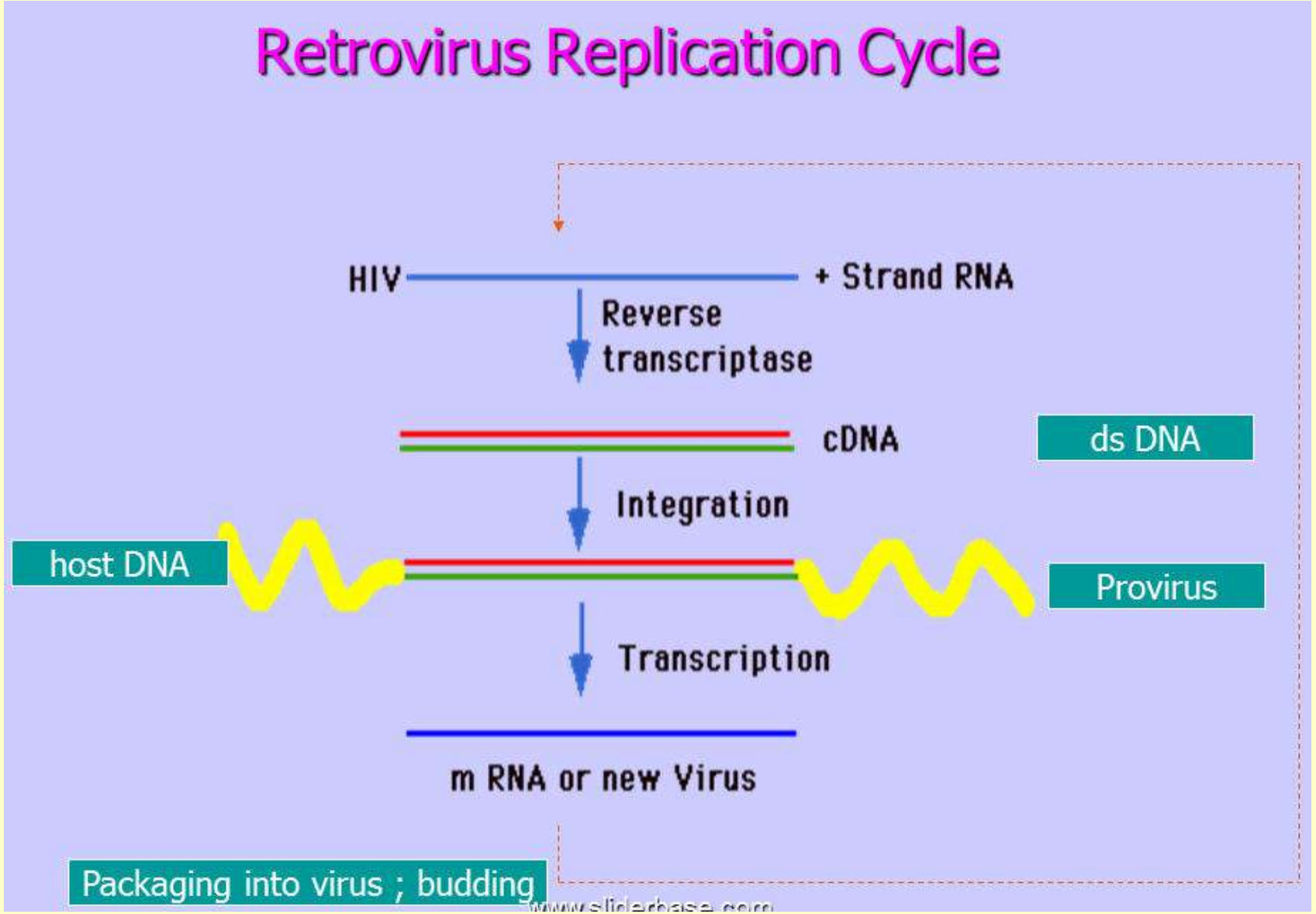
Retrovirus: HIV



HIV Lifecycle (RNA virus)

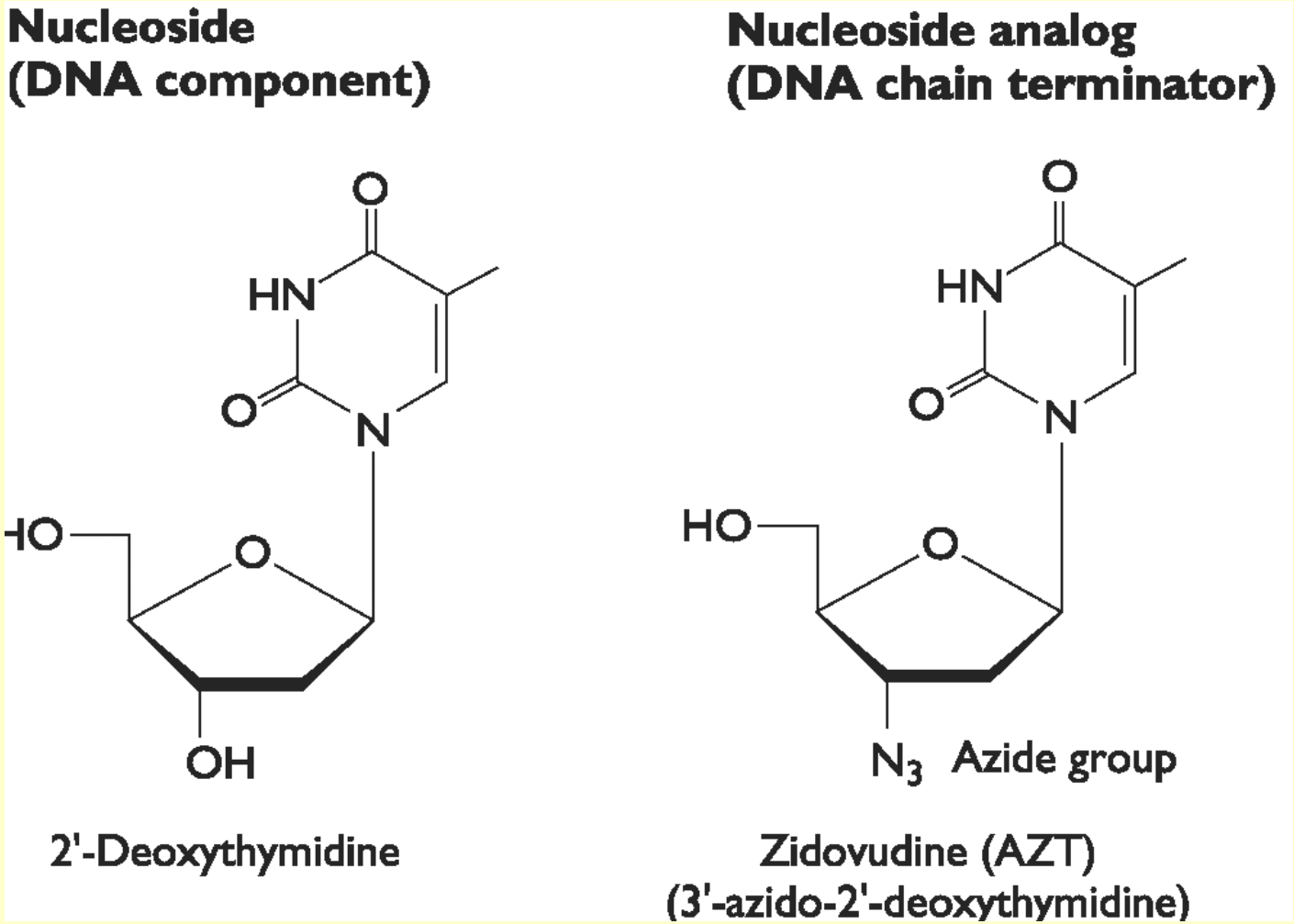


Nucleoside reverse transcriptase inhibitor: NRTI

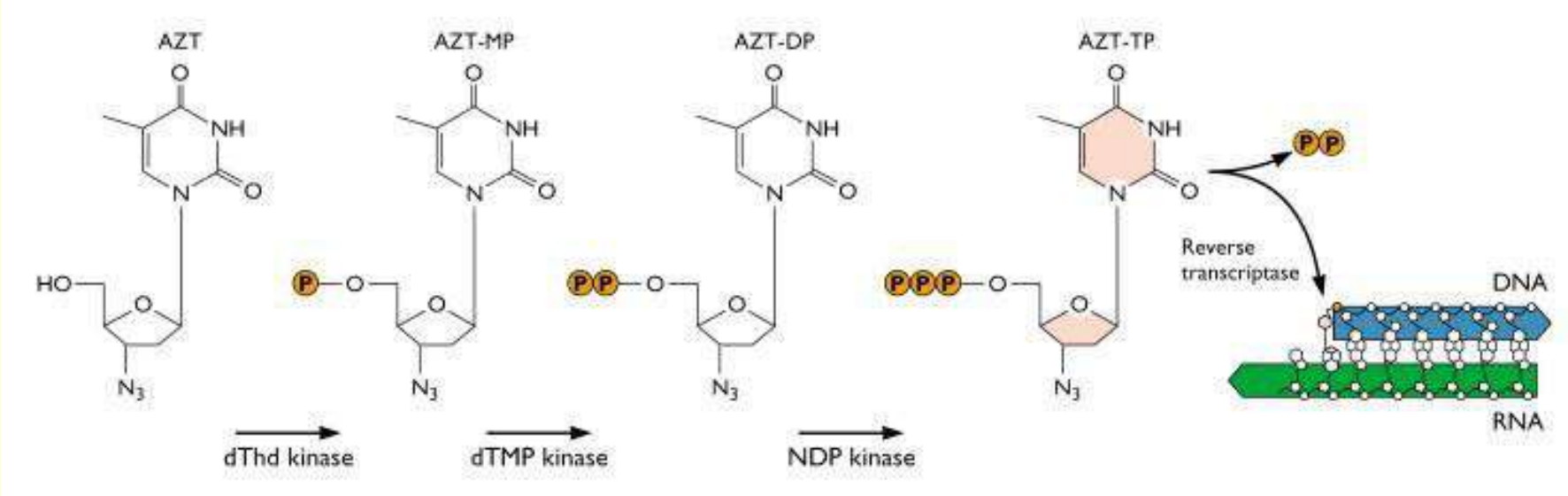


Nucleoside reverse transcriptase inhibitor: NRTI

Zidovudine



Nucleoside reverse transcriptase inhibitor: NRTI



DNA chain termination

The affinity of AZT to RT is much higher than cellular DNA polymerase (Selective to viral enzyme)

Nucleoside reverse transcriptase inhibitor: NRTI

Zidovudine

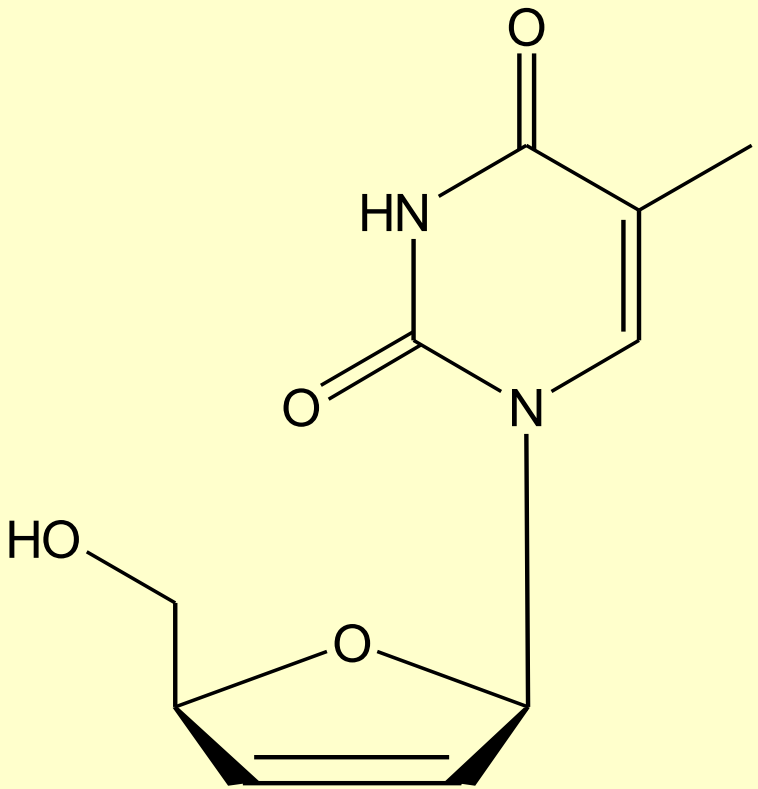
Zidovudine (ZDV,AZT) : One of the first anti-HIV drugs

The drug enters the host cells by diffusion and is phosphorylated by cellular enzymes to mono-, di-, and triphosphates.

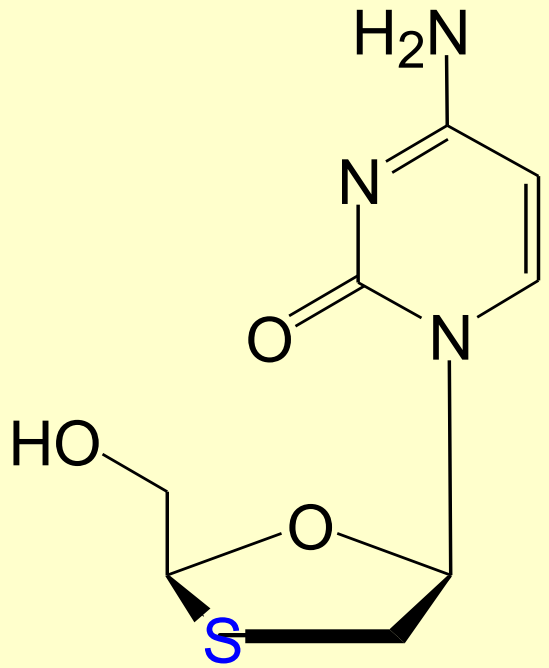
The 3’-OH in thymidine is replaced by Azido group, thus the 5’,3’-diester formation is inhibited

AZT causes DNA chain termination, yielding an incomplete proviral DNA (chain terminator)

Nucleoside reverse transcriptase inhibitor: NRTI



Stavudine
2’,3’-Dideoxy-2’,3’-didehydrothymidine
(D4T)



Lamivudine
2'-Deoxy-3'-thiacytidine, 3TC

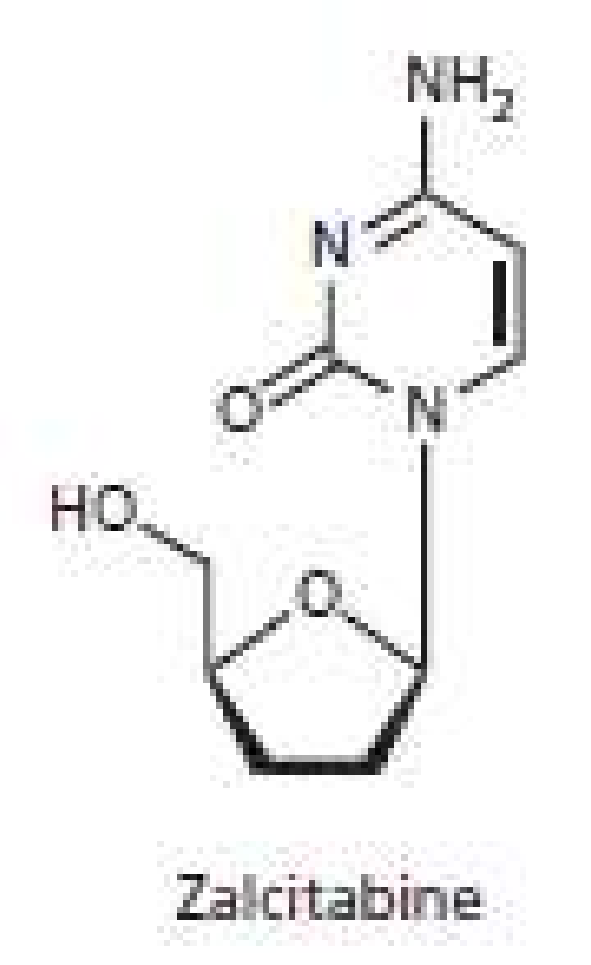
Nucleoside reverse transcriptase inhibitor: NRTI

Zalcitabine

2`, 3`-dideoxycytidine

Cytosine analogue

Causes peripheral neuropathy.



Zalcitabine

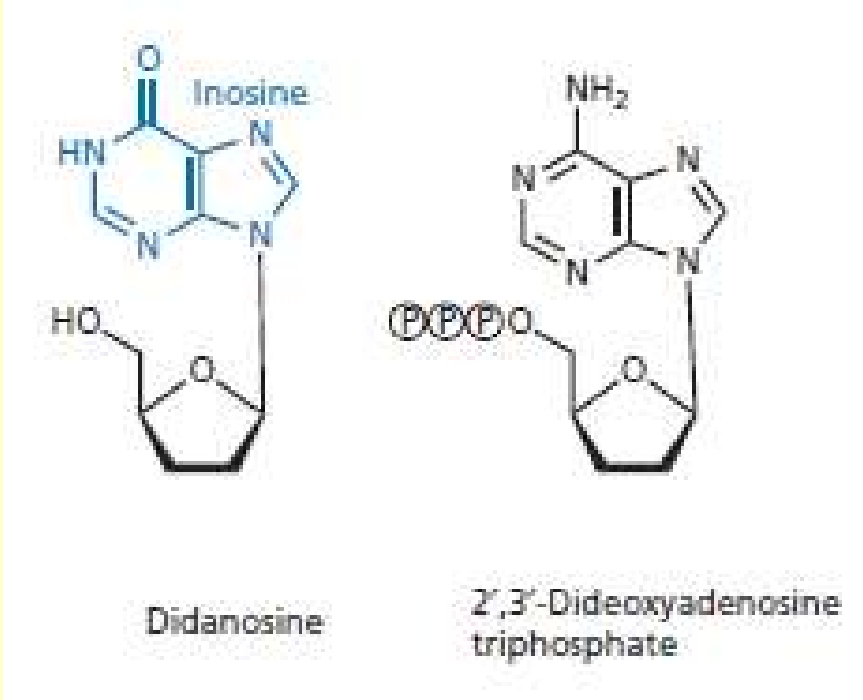
Nucleoside reverse transcriptase inhibitor: NRTI

Others

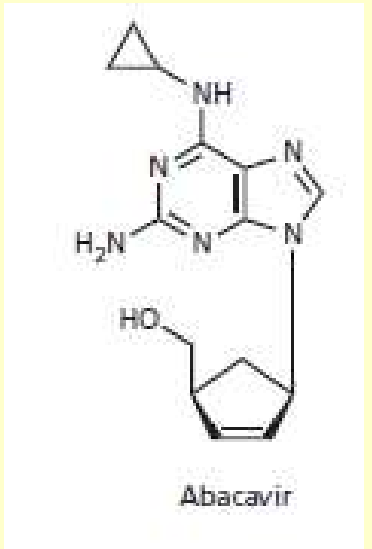
- **Didanosine:**

2`, 3`-dideoxyinosine

In vivo transform by metabolic activation to 2`, 3`-dideoxyadenosine triphosphate



Abacavir: Carbocyclic nucleoside analoge



Nonnucleoside reverse transcriptase inhibitor: NNRTI

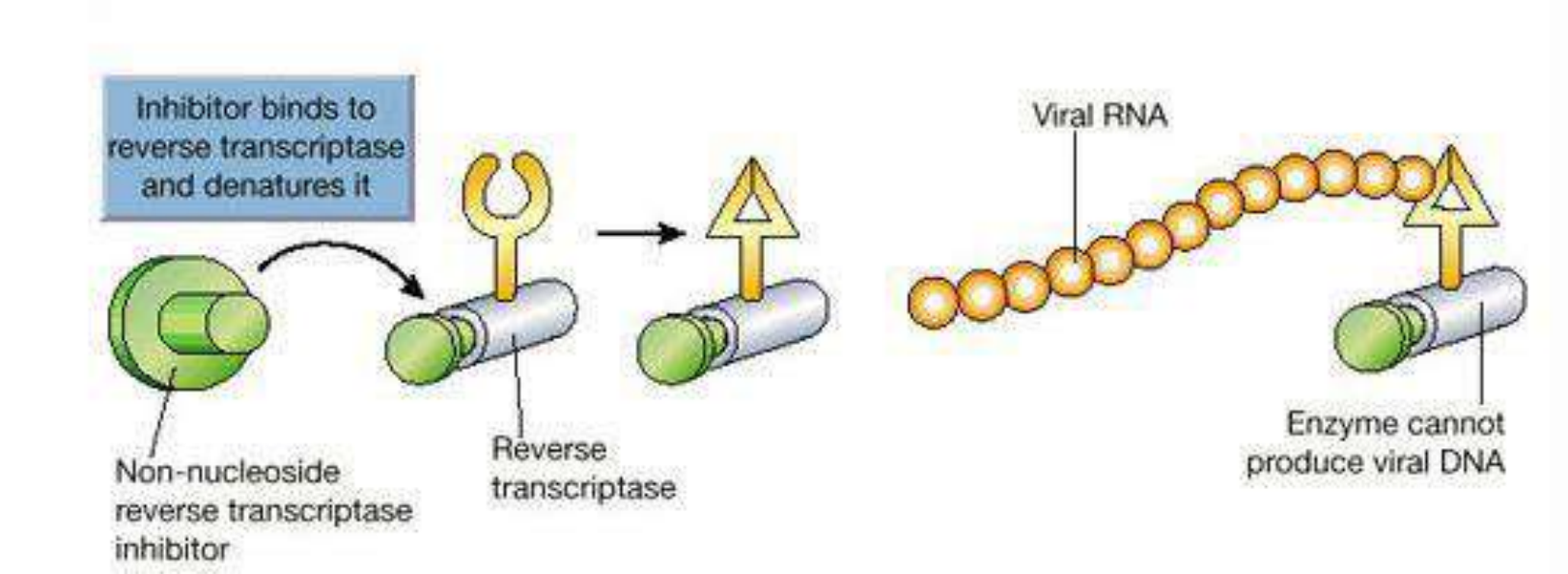
- Not prodrug (Do not require bioactivation by kinases/ phosphorylation).
- Binding directly to RT.
- Not incorporated in DNA.
- They are more selective
- They have high therapeutic index
- Orally bioavailable

Problem of NNRTI: Resistance among HIV isolates

Nonnucleoside reverse transcriptase inhibitor: NNRTI

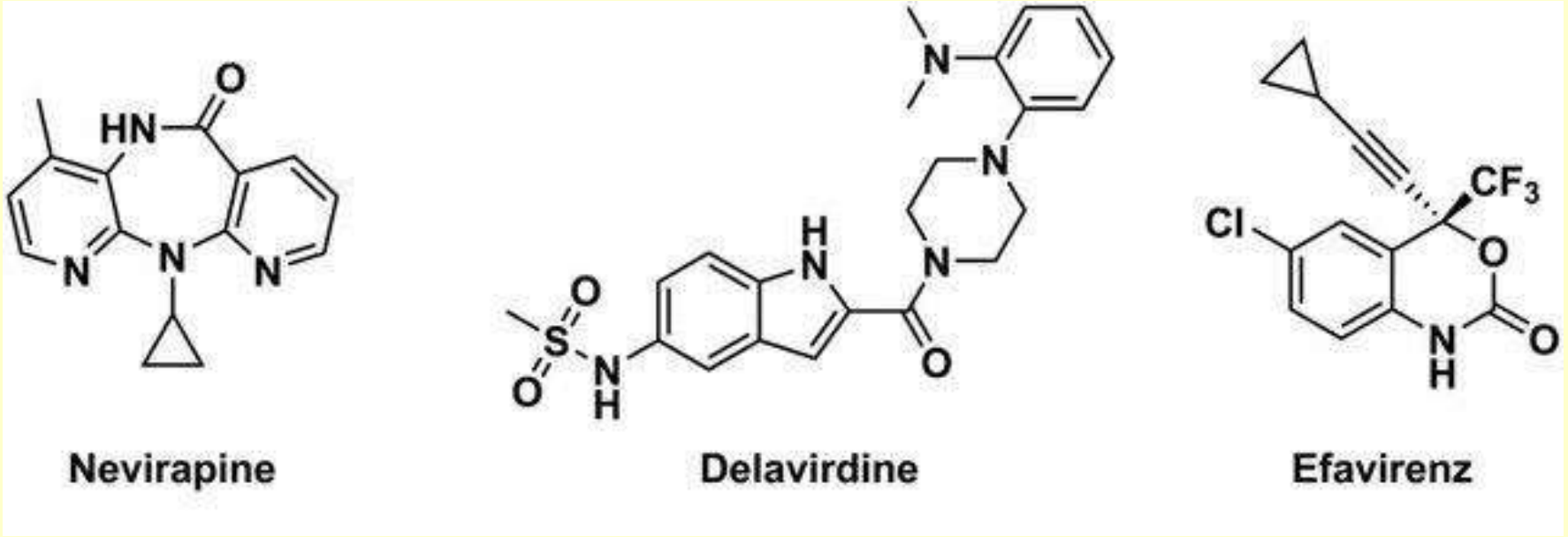
Mechanism of action

NNRTIs bind to an **allosteric site** (a hydrophobic pocket) that is distinct from the substrate (nucleoside triphosphate)-binding site (Active site) of RT, which causes conformational change in the three-dimensional structure of the enzyme, and affecting the catalytic activity of enzyme, and blocking HIV viral replication.



Nonnucleoside reverse transcriptase inhibitor: NNRTI

Diazepinone | **Piperazine** | **Benzoxazin-2-one**



Nevirapine	Delavirdine	Efavirenz
Approved in 1996	Approved in 1997	Approved in 1998
First generation	First generation	Second generation

NNRTIs show a wide variety of different structures. Despite the structural diversity, the NNRTIs show high specificity for the HIV-1 reverse transcriptase (RT), as they do not inhibit the HIV-2.

Nonnucleoside reverse transcriptase inhibitor: NNRTI

NNRTIs have lipophilic aromatic ring system which interact with the hydrophobic pocket in the binding site.

Second-generation NNRTIs were developed specifically to find agents that were active against resistant variants as well as wild-type viruses

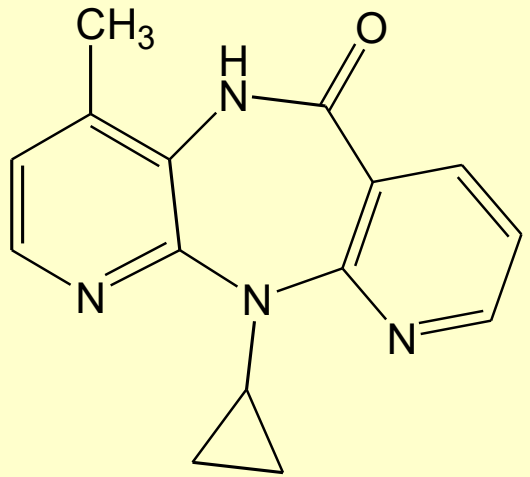
Efavirenz (For Wild type and resistant mutant HIV-1)

Efavirenz: Teratogenicity

Nonnucleoside reverse transcriptase inhibitor: NNRTI

Nevirapine

Noncompetitive binding to RT and direct inhibition at a site different from AZT and others.



May be active against AZT-resistant strains.

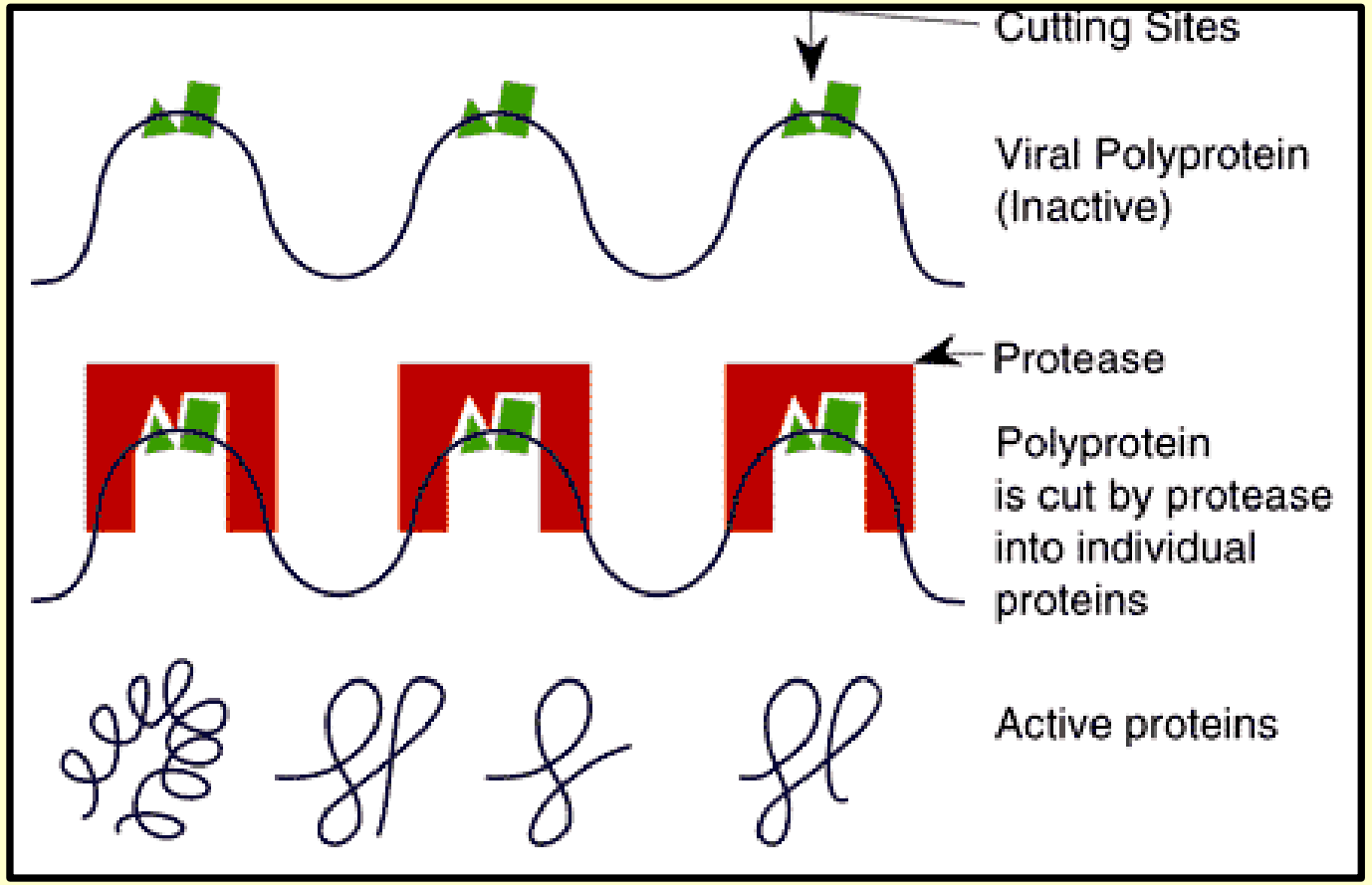
Can be used in combination.

Main adverse effect is rash.

Neverapine prevent transmission of HIV from mother to newborn when given at onset of labor and to the neonate at delivery

HIV Protease Inhibitors (PIs)

HIV-1 protease is a crucial enzyme for the maturation and assembely of infectious viral particles



Role of HIV protease

HIV protease cleaves a peptide bond of Tyr-Pro OR Phe-Pro

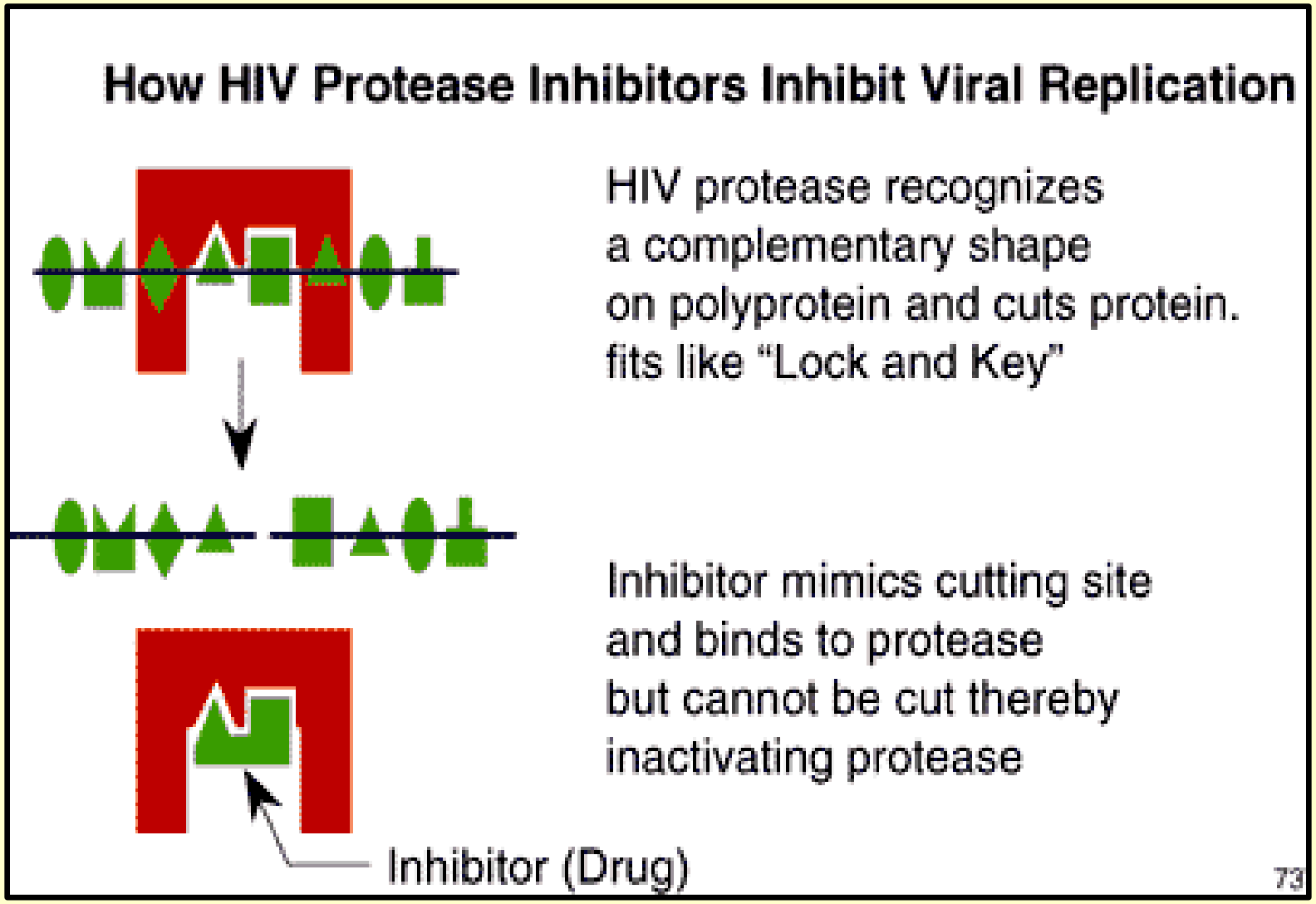
HIV protease belongs to aspartyl proteases enzymes (Aspartic acid in the active site)

Mammalian peptidase do not cleave amide bonds of prolines (Selectivity to HIV protease)

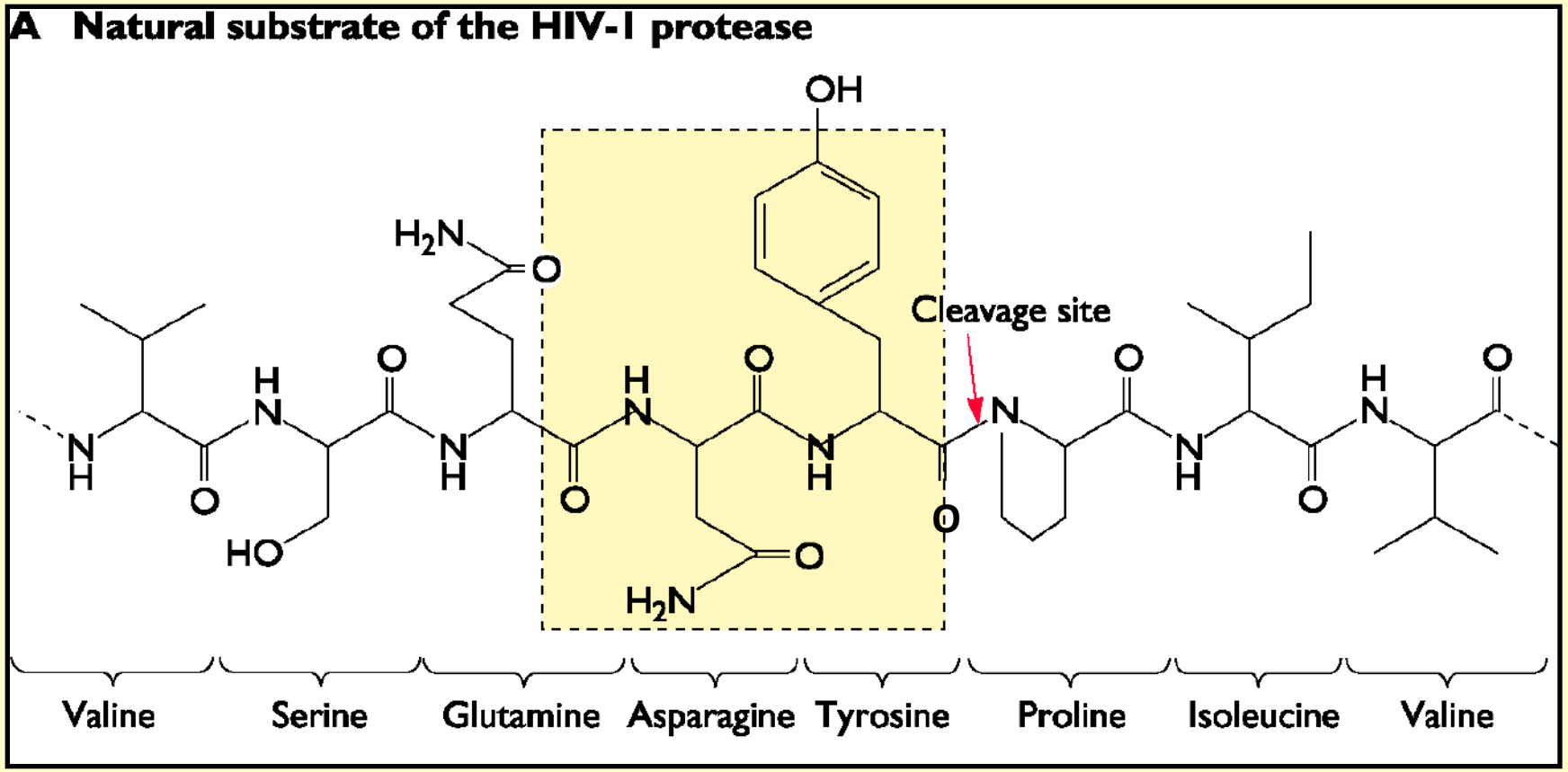
Inactivation of protease leads to production of immature, noninfectious particles

Protease inhibitors work by mimicking the transition state of the peptide –peptidase complex

HIV Protease Inhibitors (PIs)



HIV protease inhibitor: PI



HIV protease inhibitor: PI

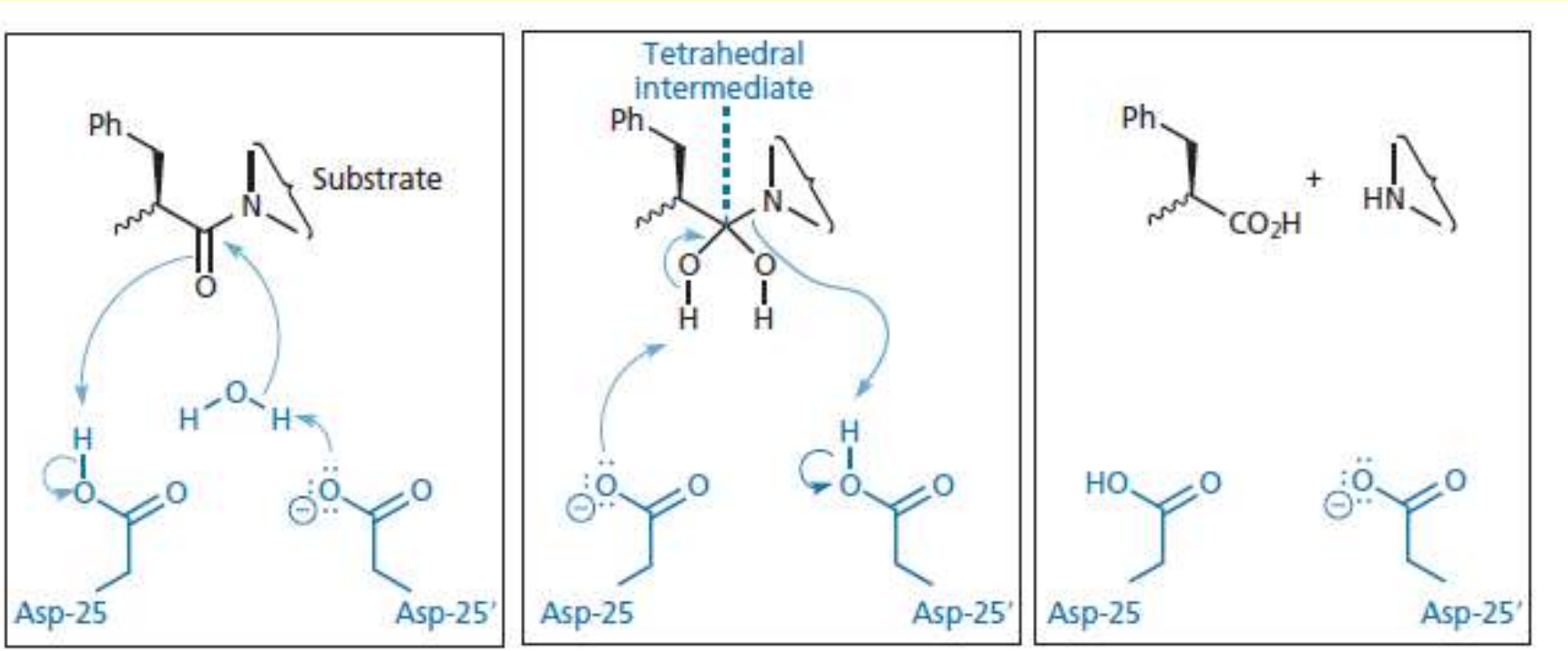
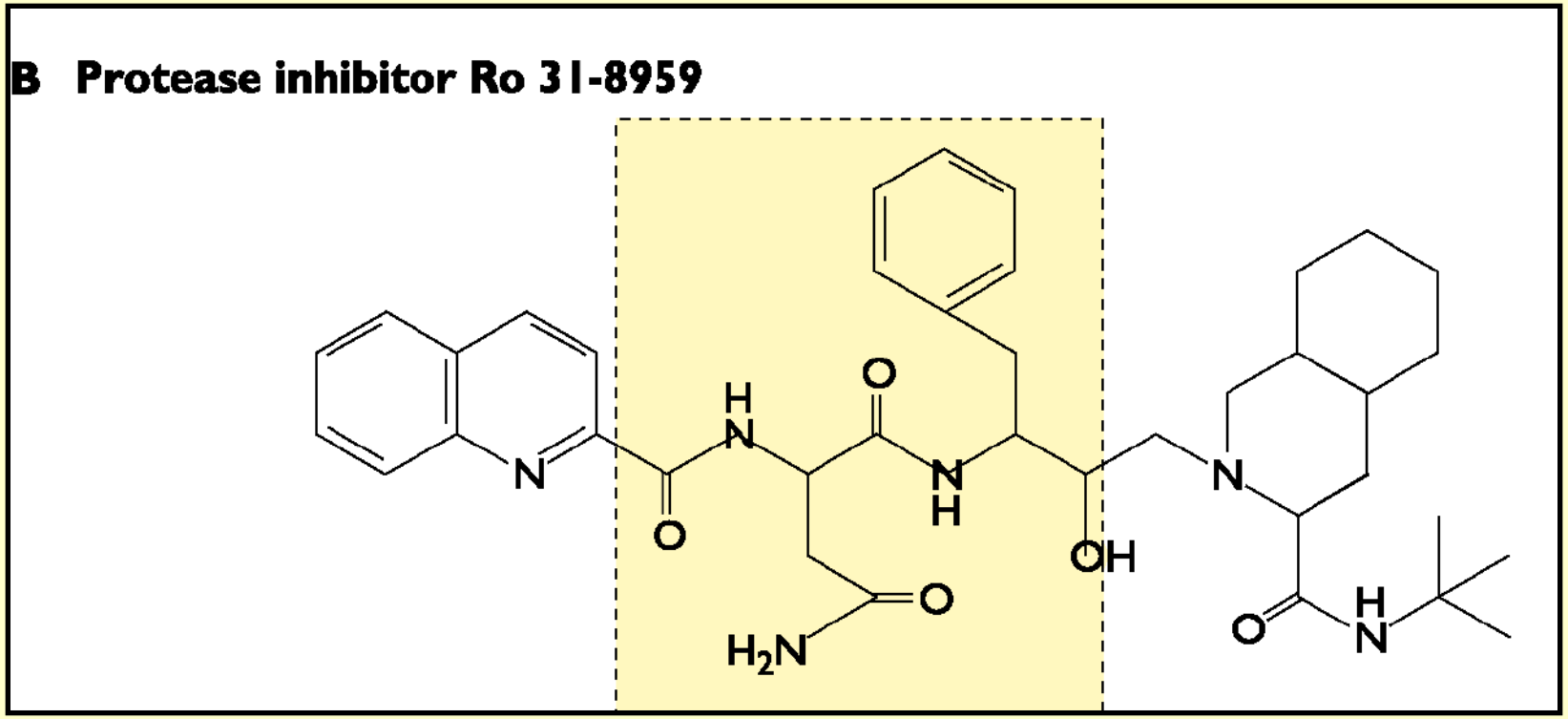


FIGURE 20.18 Mechanism of the reaction catalysed by HIV protease.

HIV protease inhibitor: PI



Replace CO-NH peptide bond with ethylene alcohol (-CH2-CHOH-)

An isosteric replacement for the scissible peptide bond that mimics the transition state for the hydrolysis of that bond but is not scissible.

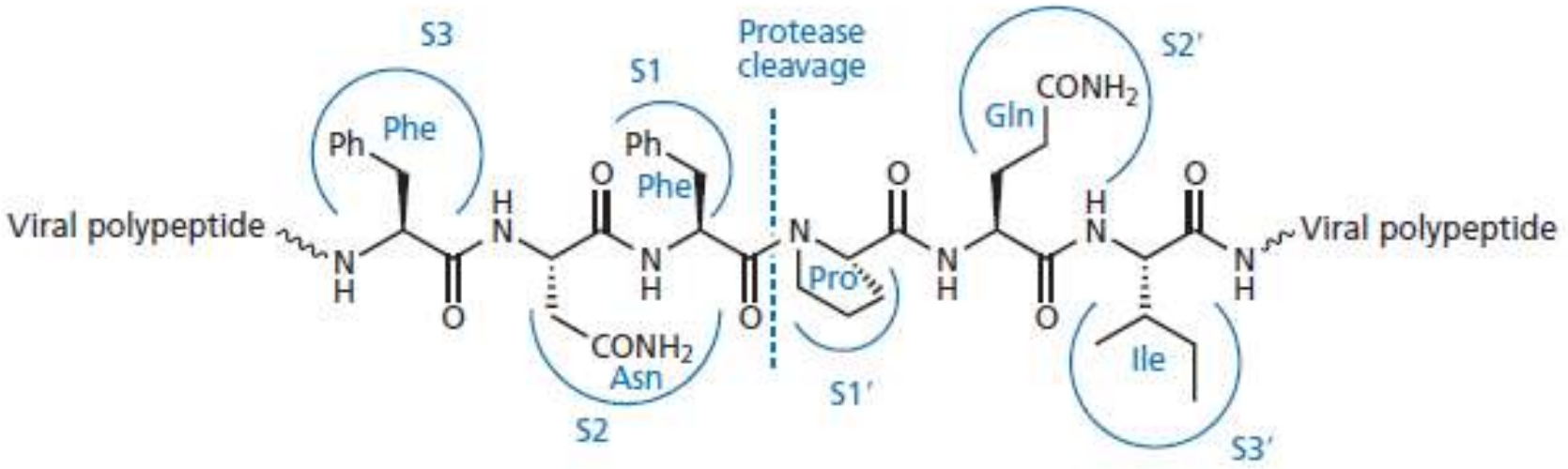
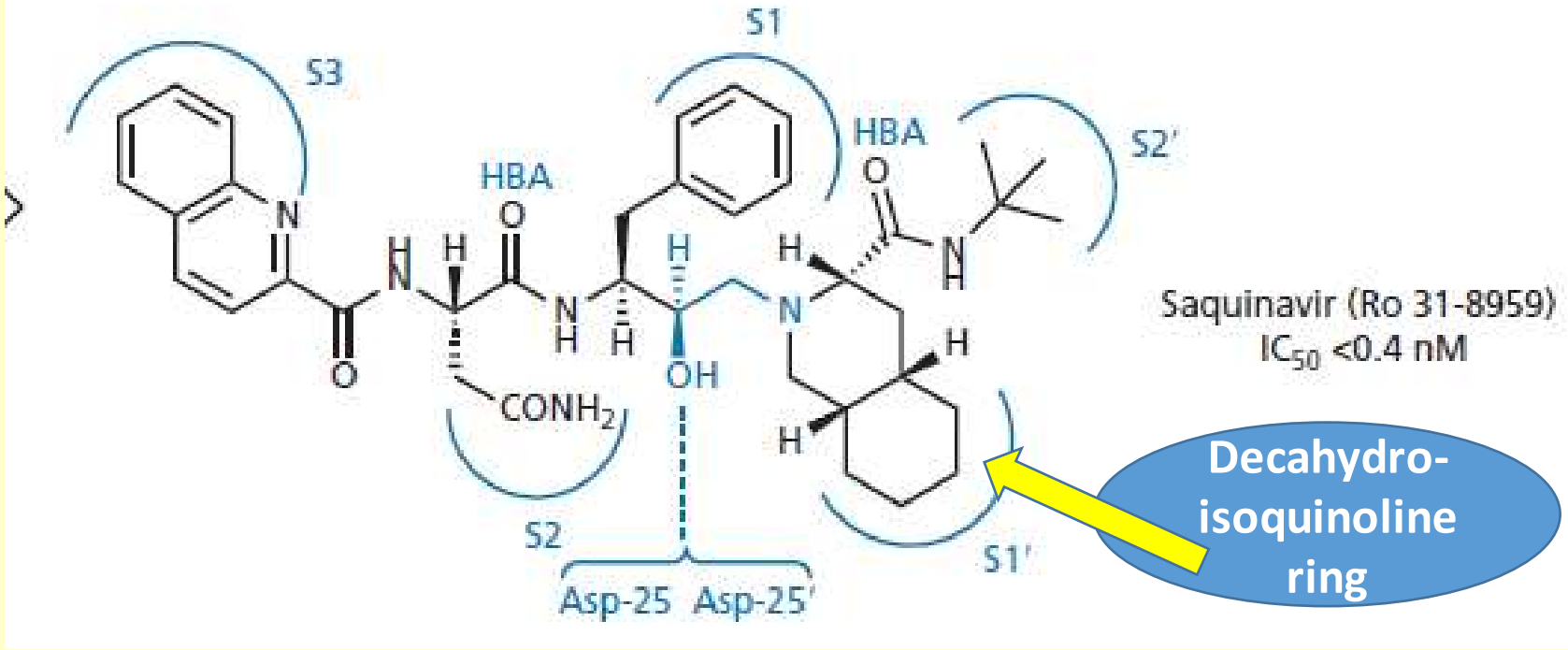
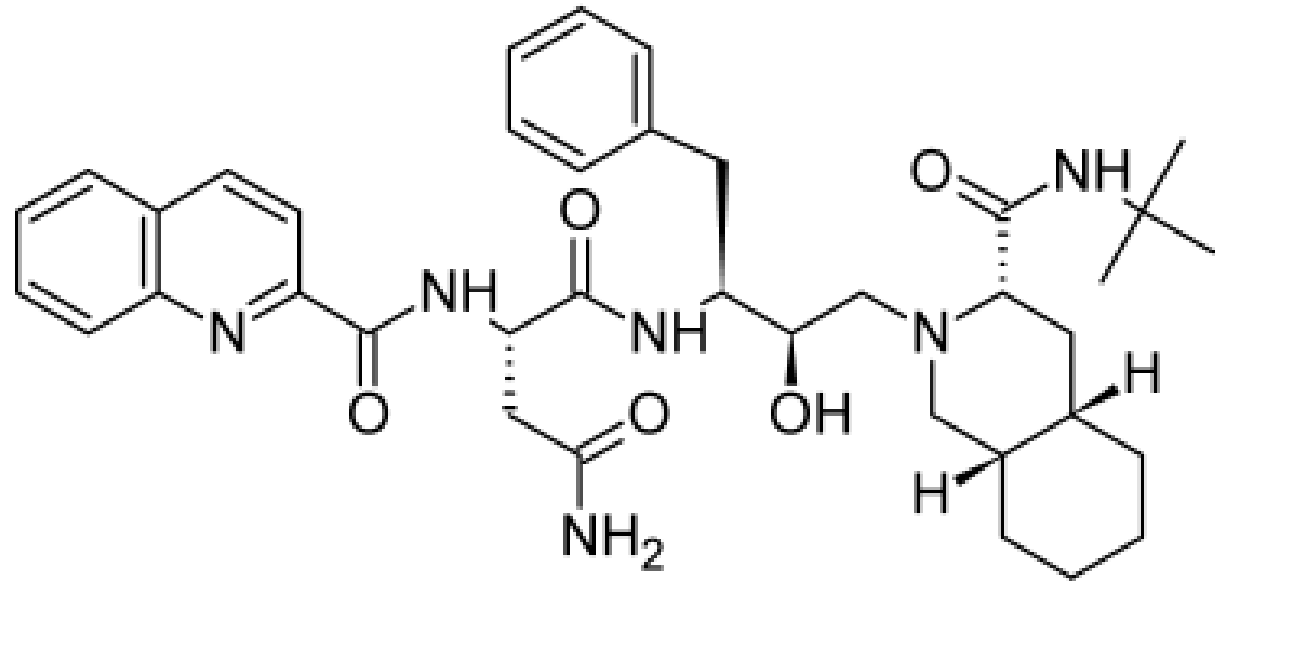


FIGURE 20.16 The aromatic–proline peptide bond that is cleaved by HIV protease



HIV protease inhibitor: PI [Peptidomimetic]

Saquinavir

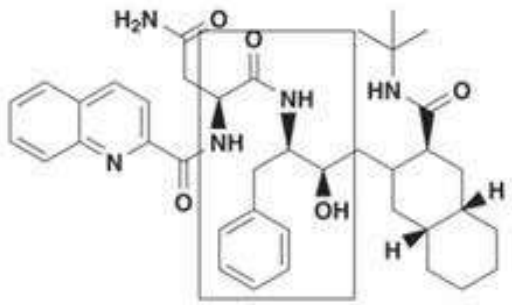


MW: 670

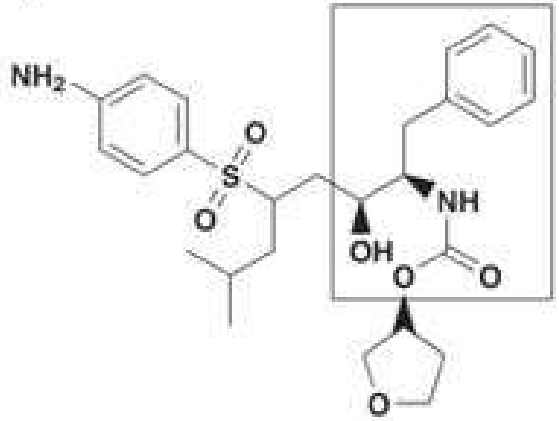
Absorption of saquinavir is poor but is increased with a fatty meal.

Others: Indinavir, amprinavir, ritonavir

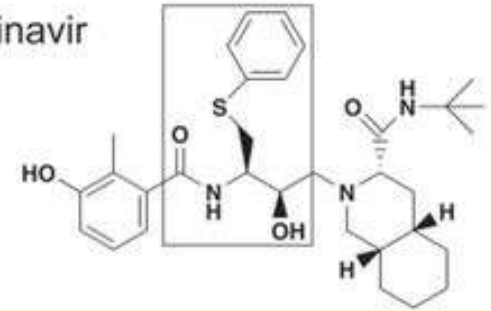
Saquinavir



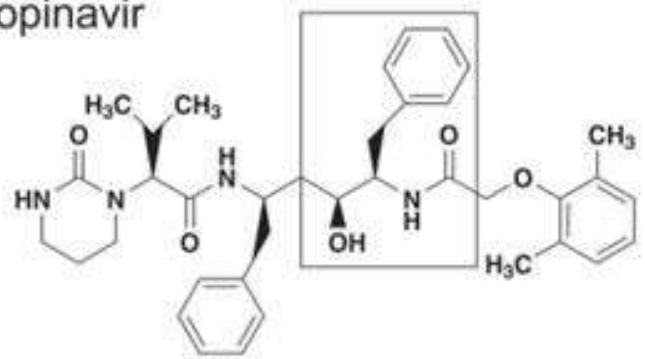
Amprenavir



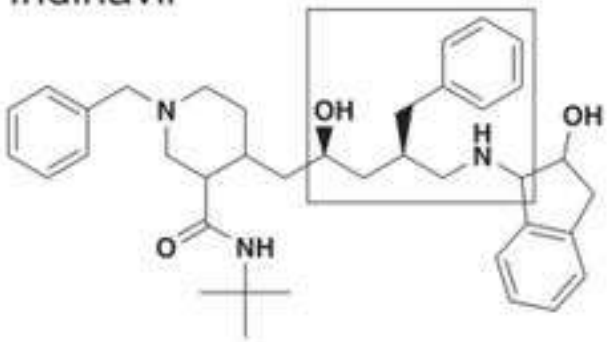
Nelfinavir



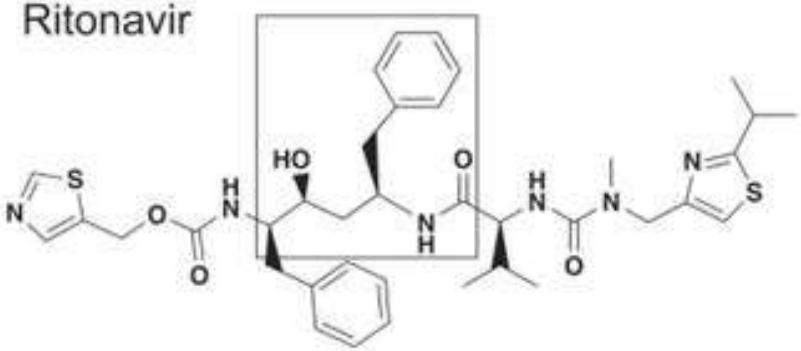
Lopinavir



Indinavir



Ritonavir



HIV protease inhibitor: PI [Non-Peptidomimetic]

Tipranavir

Tipranavir **is not a peptidomimetic compound**.

It does appear to bind to the active site of HIV-1 protease the same as the peptidomimetics do.

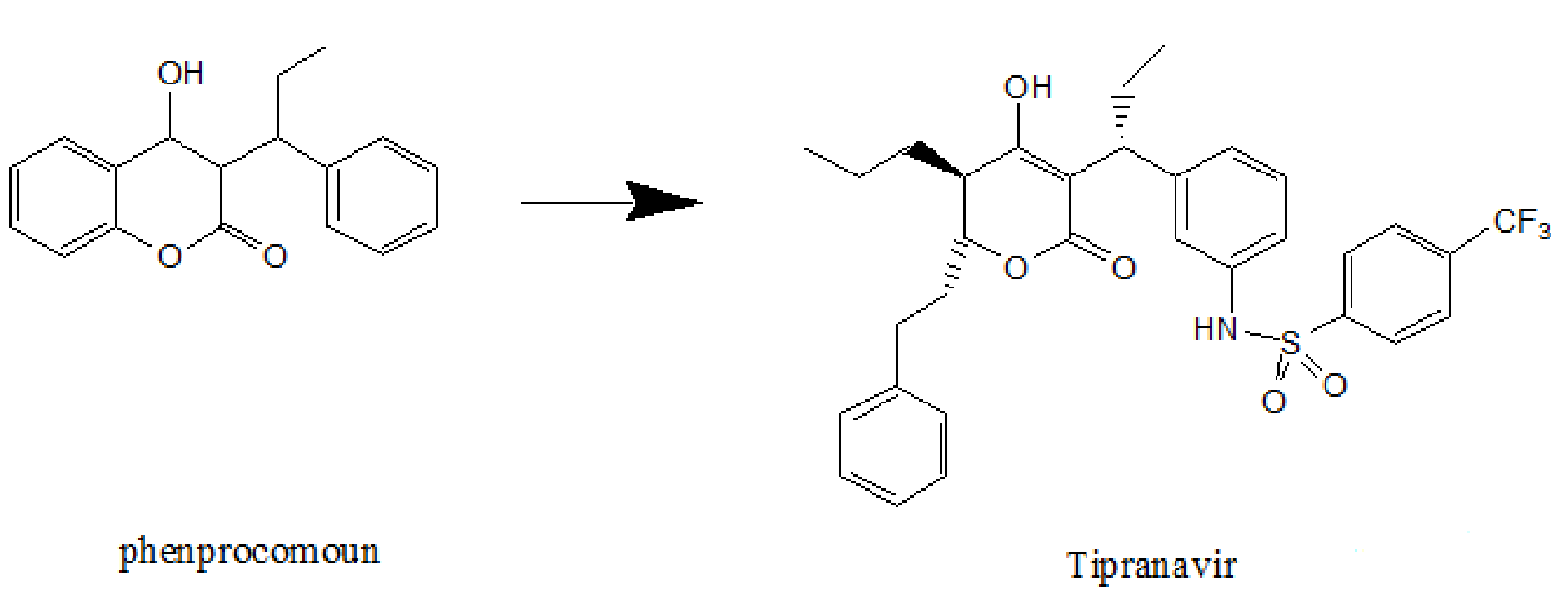
Lead compound is Phenprocomoun, an anticoagulant

Cross-resistance does not develop to the same extent as seen with the peptidomimetics.

The drug is administered with a booster dose of ritonavir. This protocol inhibits CYP3A4, causing the levels of tipranavir to increase.

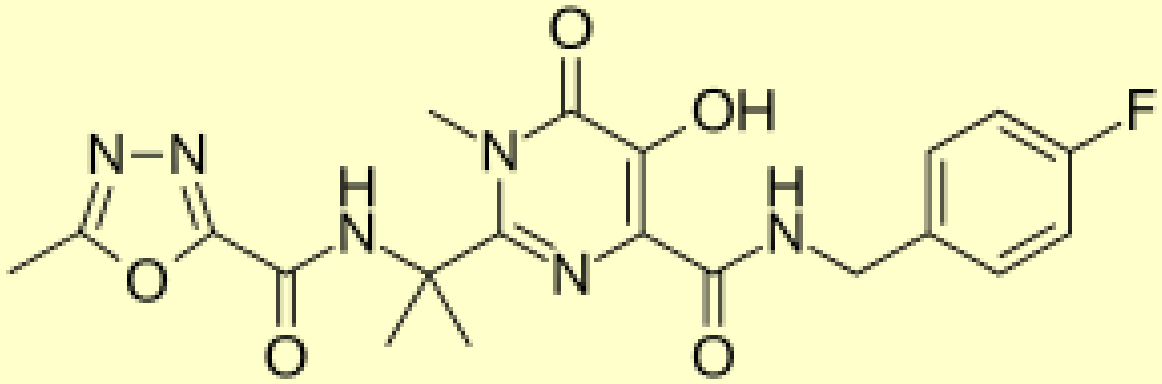
HIV protease inhibitor: PI [Non-Peptidomimetic]

Tipranavir



Integrase Inhibitor

Raltegravir



Integrase is a viral enzyme that inserts the viral genome into the DNA of the host cell

For HIV treatment

HIV entry and fusion inhibitor

Enfuvirtide: HIV

Entry inhibitors, also known as fusion inhibitors, are a new class of drugs for the treatment of HIV infection (Inhibitor of gp 41 activity)

Enfuvirtide
It is a 36-mer synthetic peptide that is derived from the C-terminal repeat of gp41.

The drug is administered twice daily, SC

Used in combination with other anti-HIV medicines.

HIV entry inhibitor

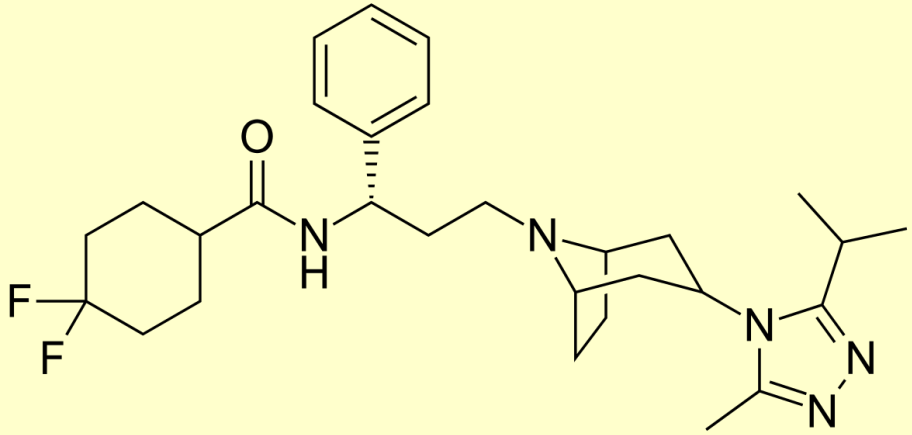
Maraviroc

An entry inhibitor

CCR5 receptor antagonist for HIV treatment

FDA approved 2007

Hepatotoxicity



Interferon

Read about INF-α

Next subject