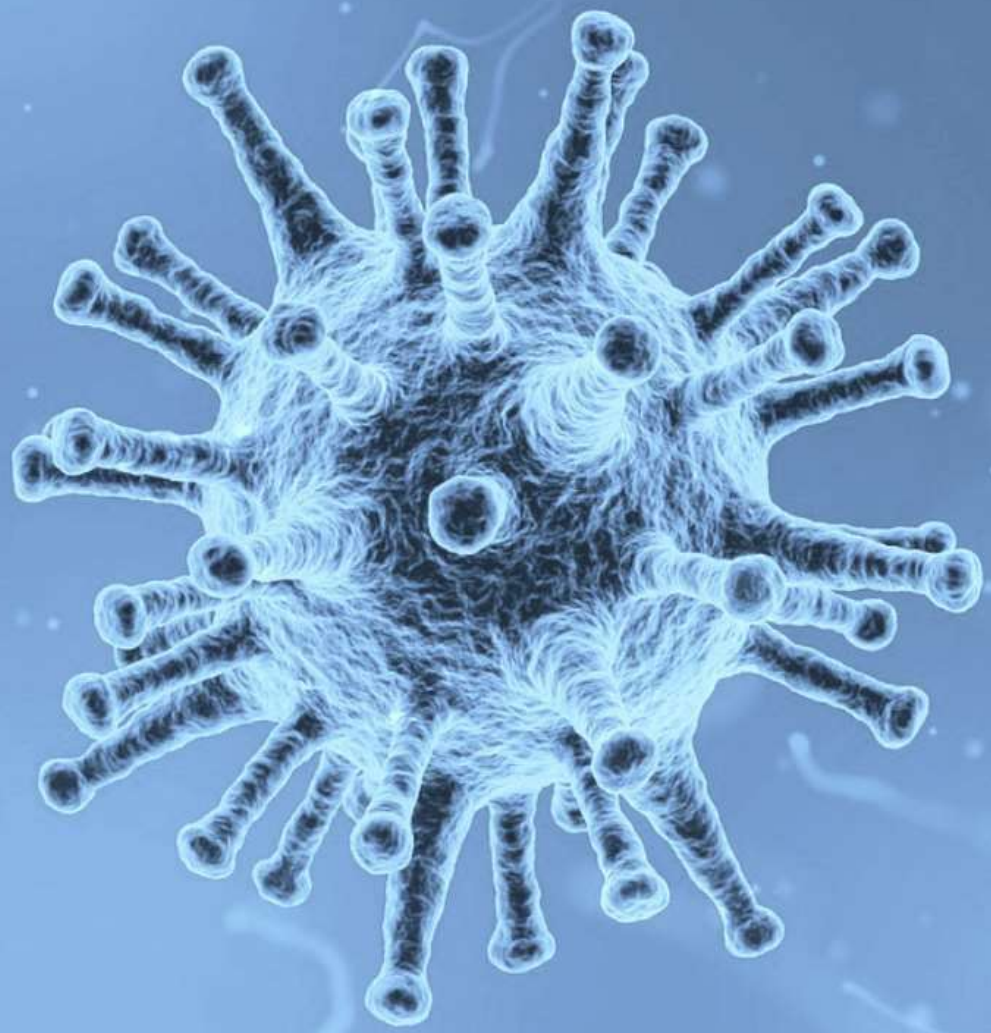
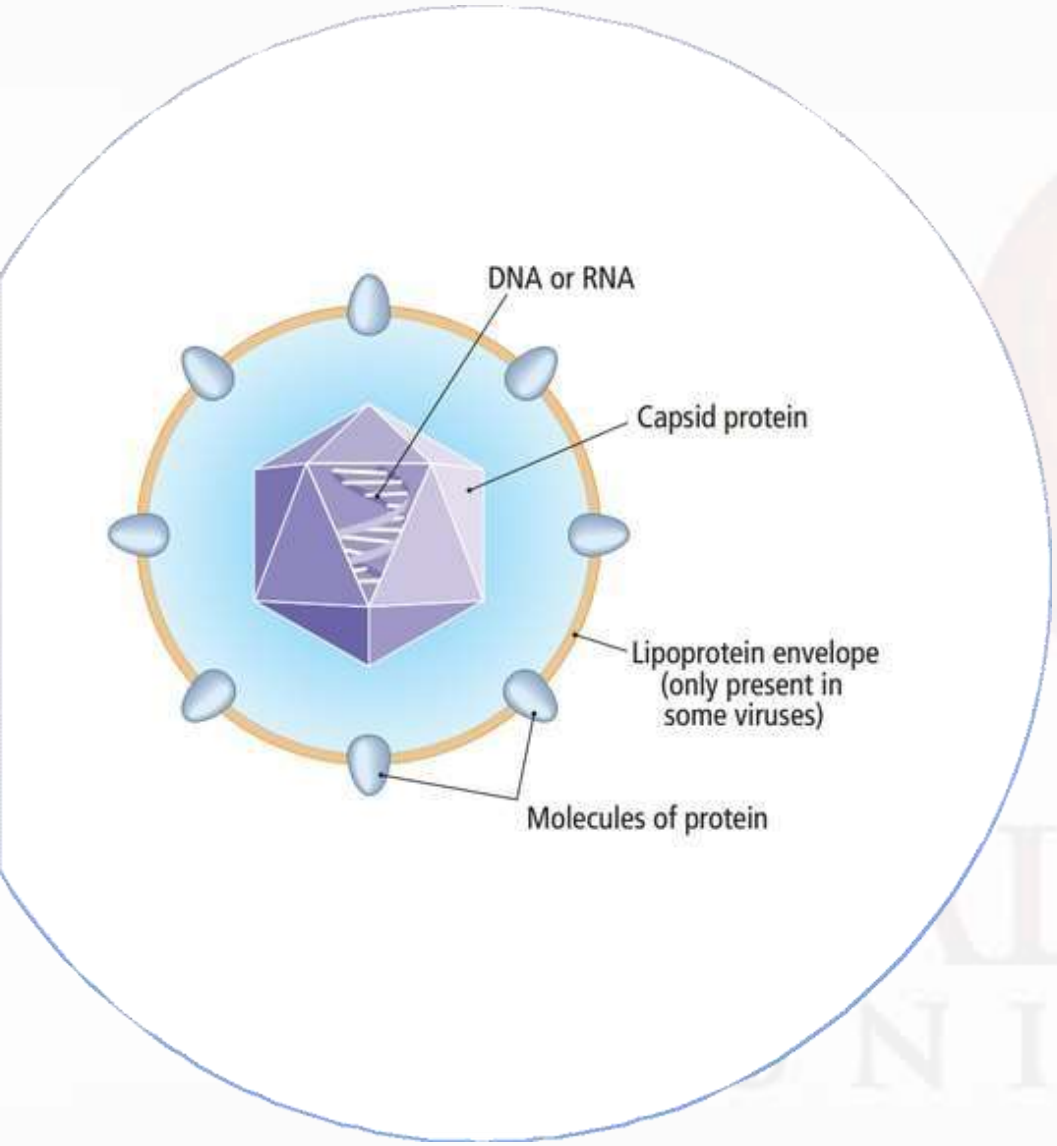
Anti-viral Drugs

- **Viruses** is a small infectious agents that replicates only inside the living cells of other organisms.
- **Viruses** are lack both a cell wall and cell membrane and they do not carry out metabolic process





Viral particles consist of two to three parts :

1. Genetic material , either DNA or RNA
2. Protein coat (Capsid), which surrounds and protects the genetic material
3. Envelope of lipid , lipid layer that surround the protein coat when they are outside cell

- Viruses cannot reproduce on their

Own , they use host's metabolic processes and so few drugs are selective enough to prevent viral replication

Viral attachment and entry are blocked by:

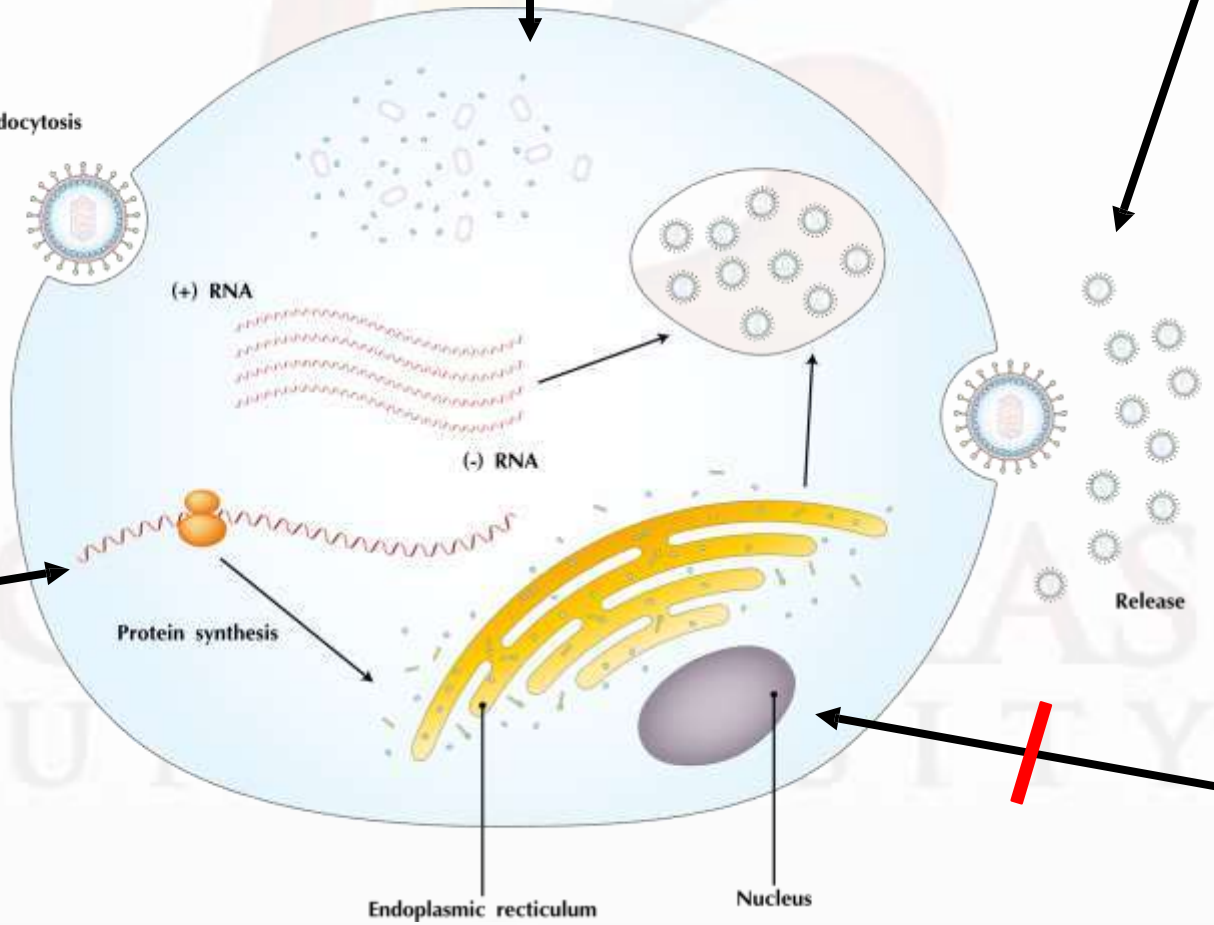
- Enfuvirtide(HIV)
- Maraviroc(HIV)
- Docosanol(HSV)
- Palivizumab (RSV)

Uncoating are blocked by:

- Amantadine (influenza)
- Rimantadine(influenza)

Viral release are blocked by:

- Neuraminidase inhibitors(Influenzas)

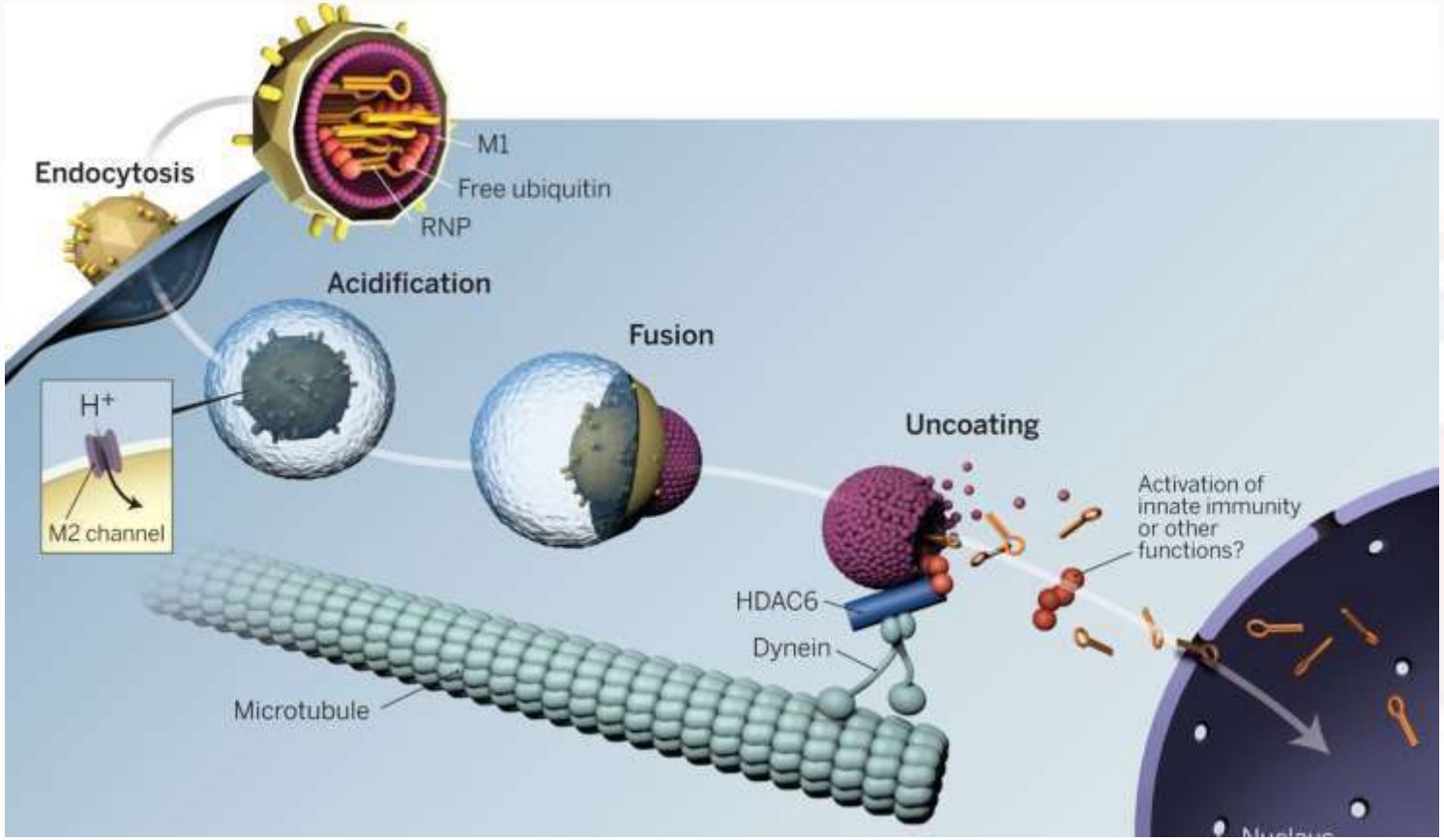


Protein processing are blocked by:

- Protease inhibitors (HIV)

Nucleic acid synthesis are blocked by:

- Nucleoside reverse transcriptase Inhibitors NRTI (HIV,HBV)
- Non-Nucleoside reverse transcriptase Inhibitors NNRTI (HIV)
- Acyclovir (HSV)
- Foscarnet(CMV)



Uncoating Inhibitors

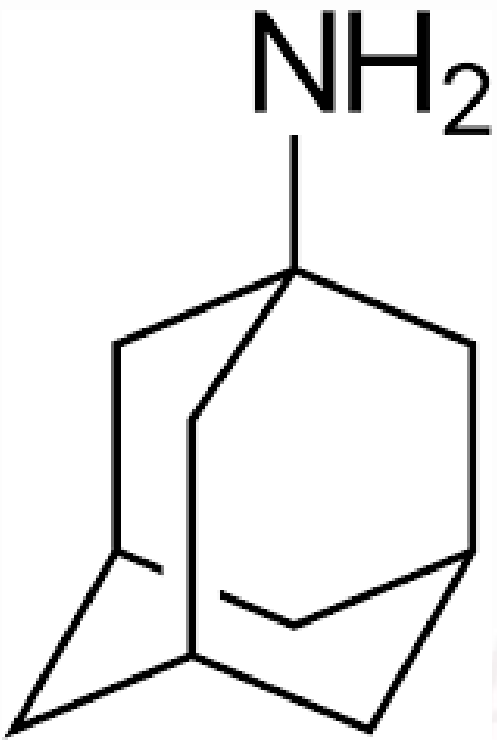
Amantadine and Rimantadine :

They are hydrophobic amines (weak organic bases) with clinical against influenza **A** only.

Their specificity stems from their ability to bind to block the proton channel formed by the M2 matix protein.

Can reduce severity of illness if started within 48 hrs of onset of symptoms .

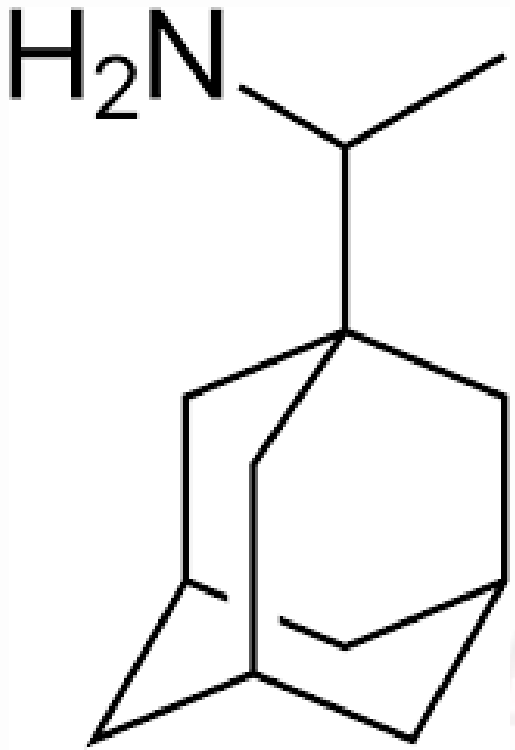
Uncoating inhibitors



Amantadine :

Amantadine (1-aminoadamantane) and its methyl derivative inhibit the uncoating of the viral RNA within the infected host cells thus preventing its replication

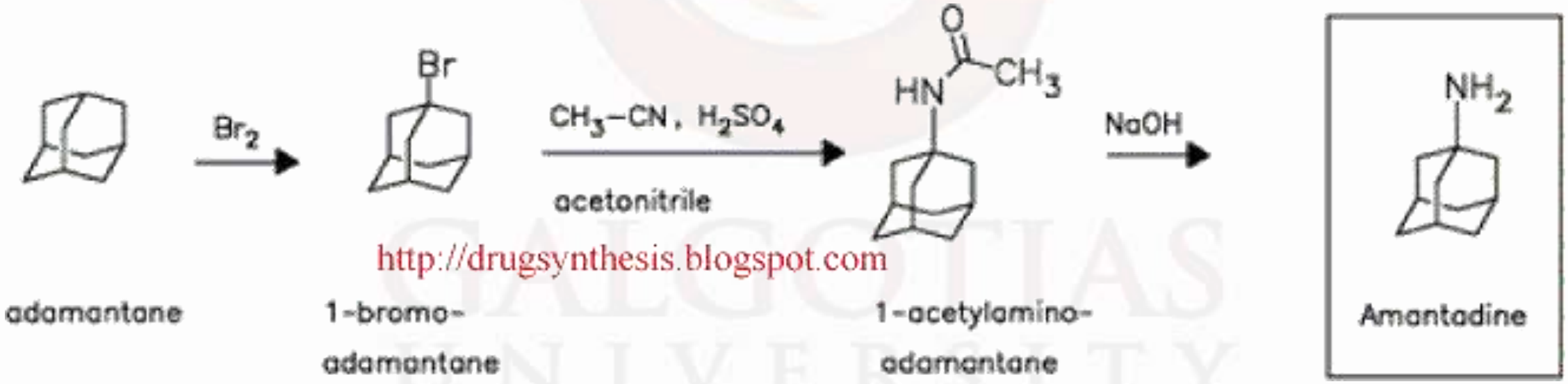
Uncoating inhibitors



Rimantadine:

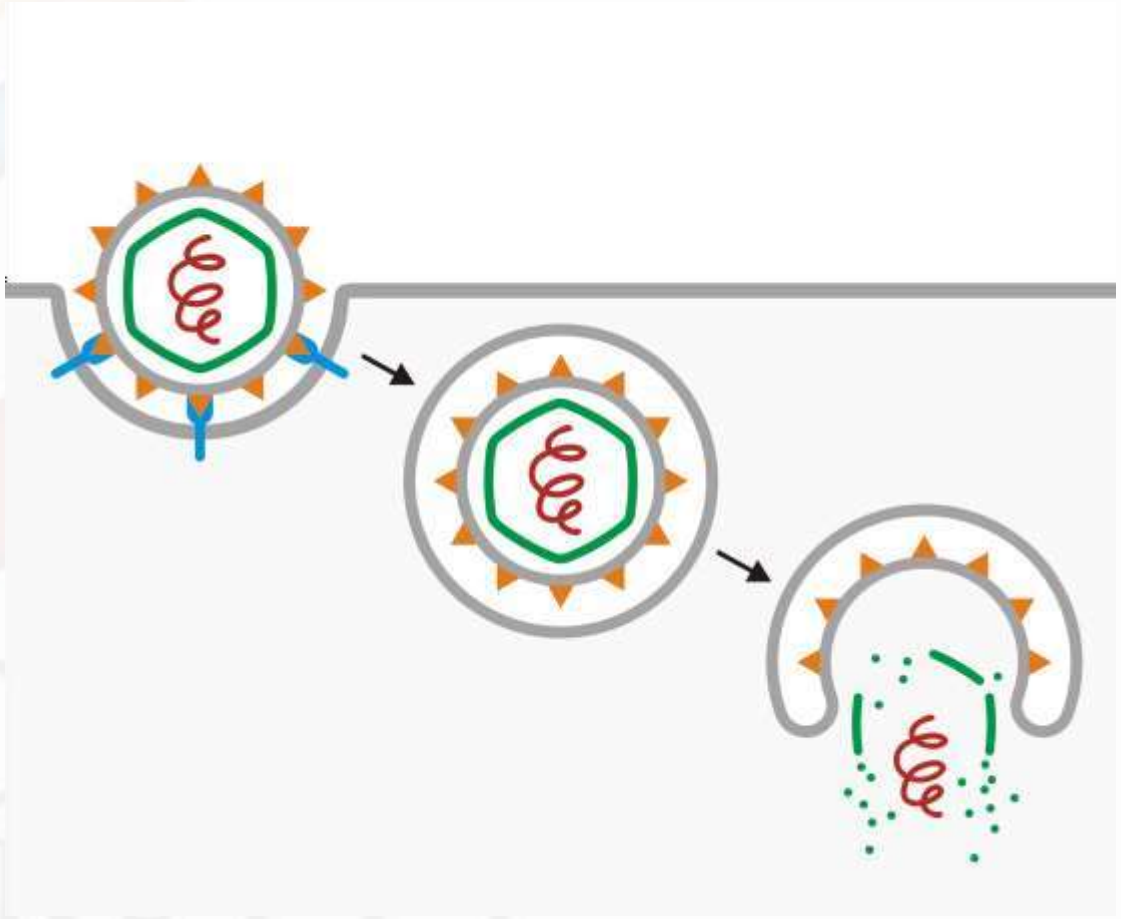
Interfere with virus uncoating by inhibiting release of specific protein also its more effective than amantadine .

Synthesis of Amantadine



Entry Inhibitors:

- The most common drugs that prevent the virus from entering CD4 cells are:
  -Maraviroc
  -Enfuvirtide
  -Docosanol

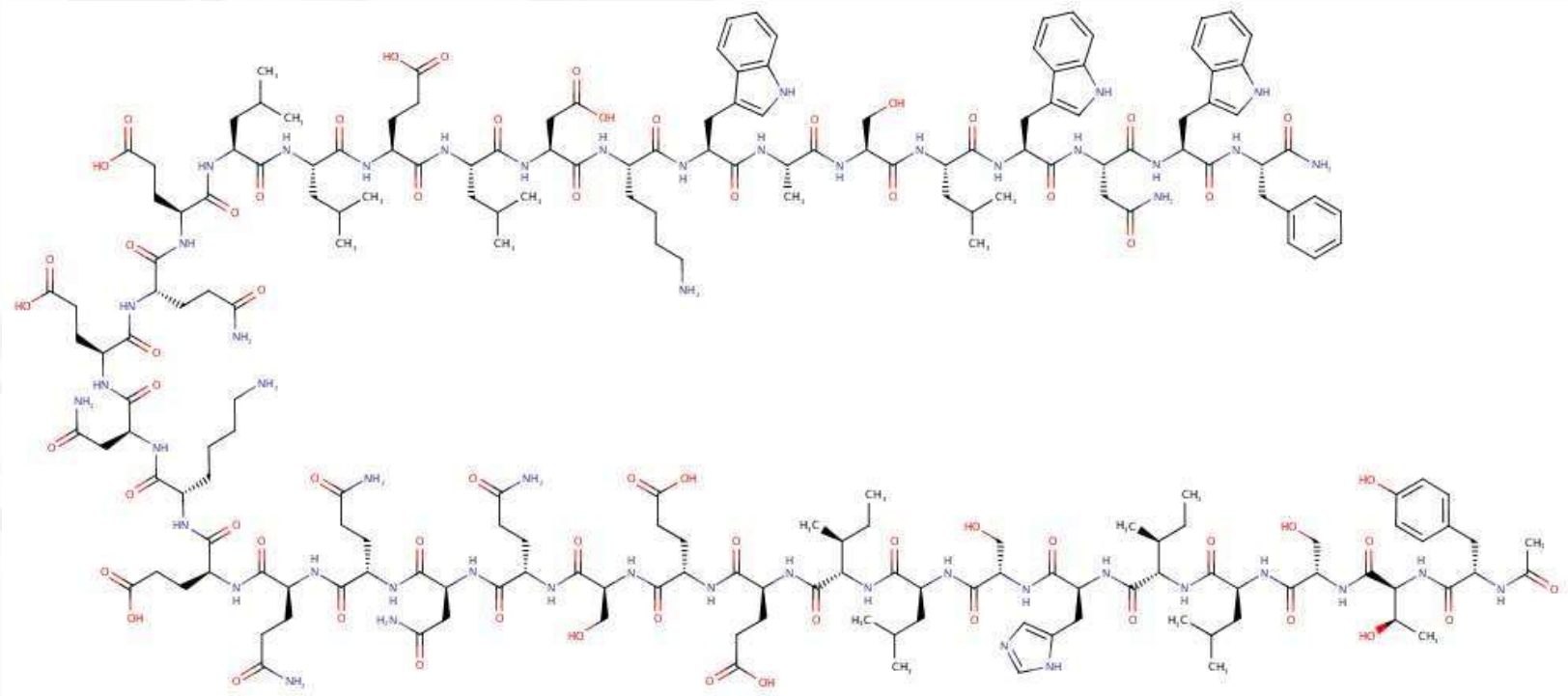


Enfuvirtide

•New class of antiviral drug, fusion inhibitors, which interferate with penetration of HIV-1 in the cells.

•Exhibits potent and selective inhibition of membrane of viral and cells.

•Showed significantly efficacy in the combination with other antiviral drugs in early stadium of HIV infection and in patients with antiretroviral resistention

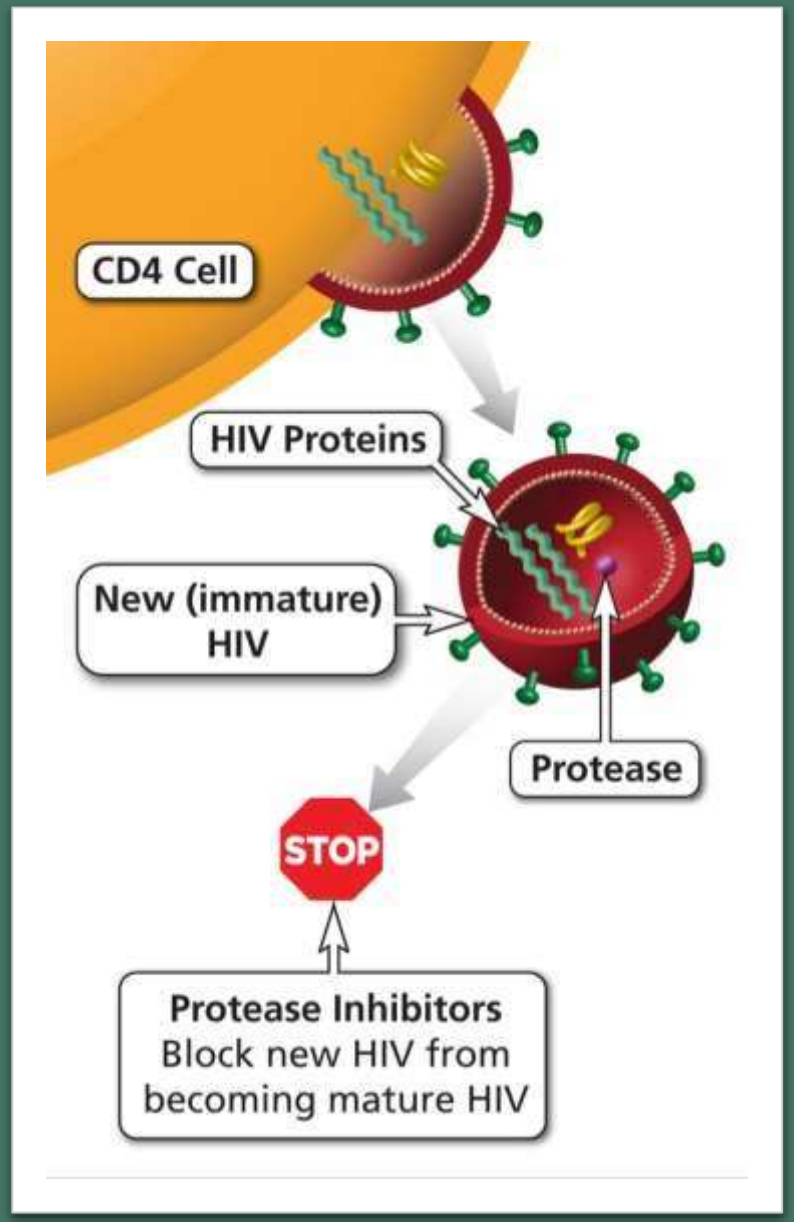


Protease inhibitors:

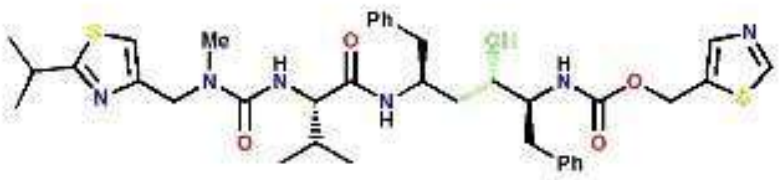
-the use of X-ray crystallography and molecular modelling led to the structure-based design of a series of inhibitors which act on the viral enzyme HIV protease.

-They have a short-term benefit when they are used alone, but resistance soon develops.

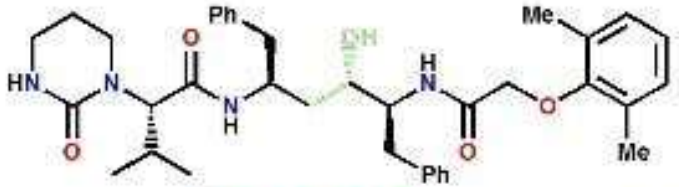
-When protease and reverse transcriptase inhibitors are used together, the antiviral activity is enhanced and viral resistance is slower to develop.



Saquinavir



Ritonavir



Lopinavir

Indinavir

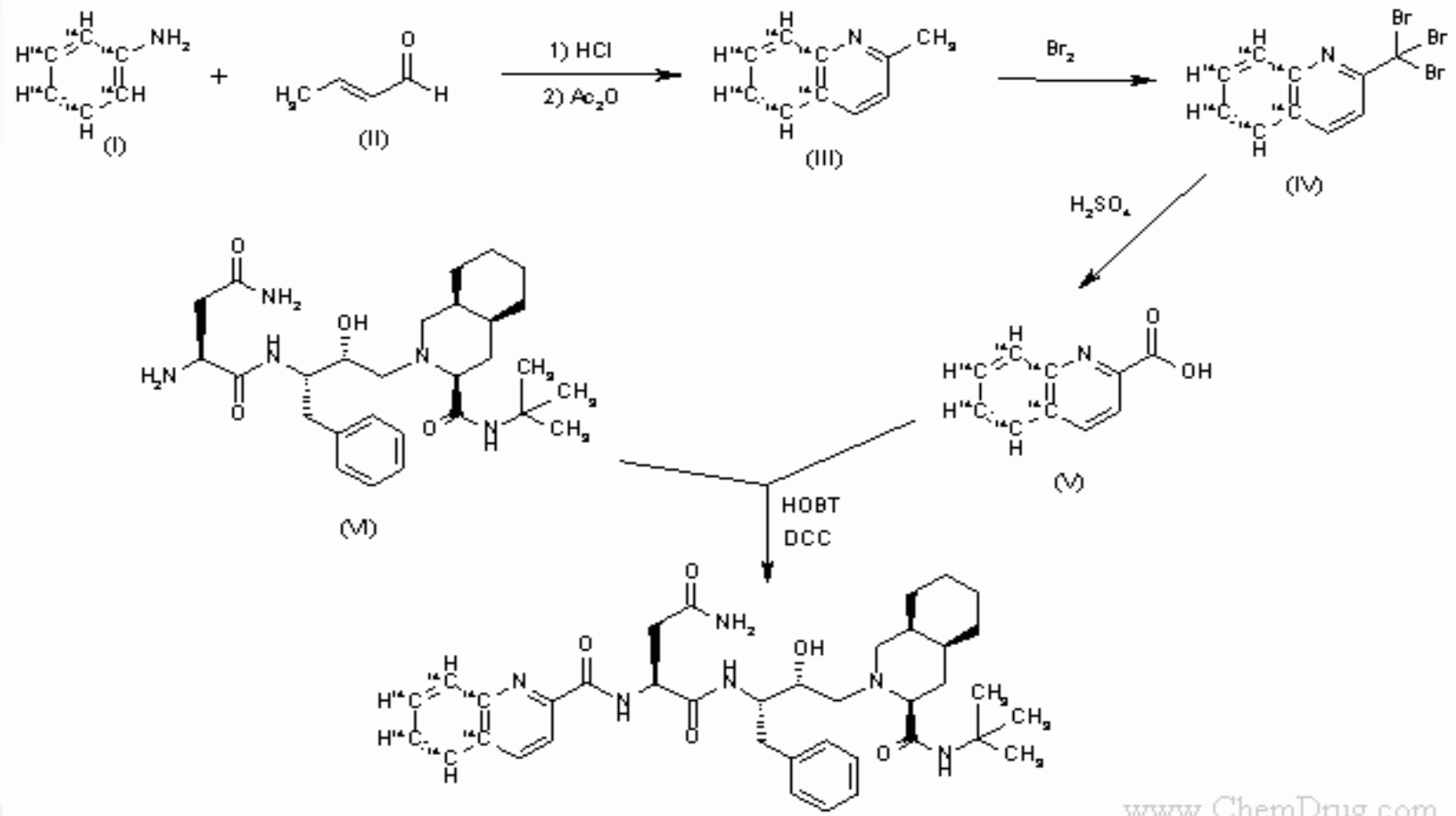
Nelfinavir

Saquinavir

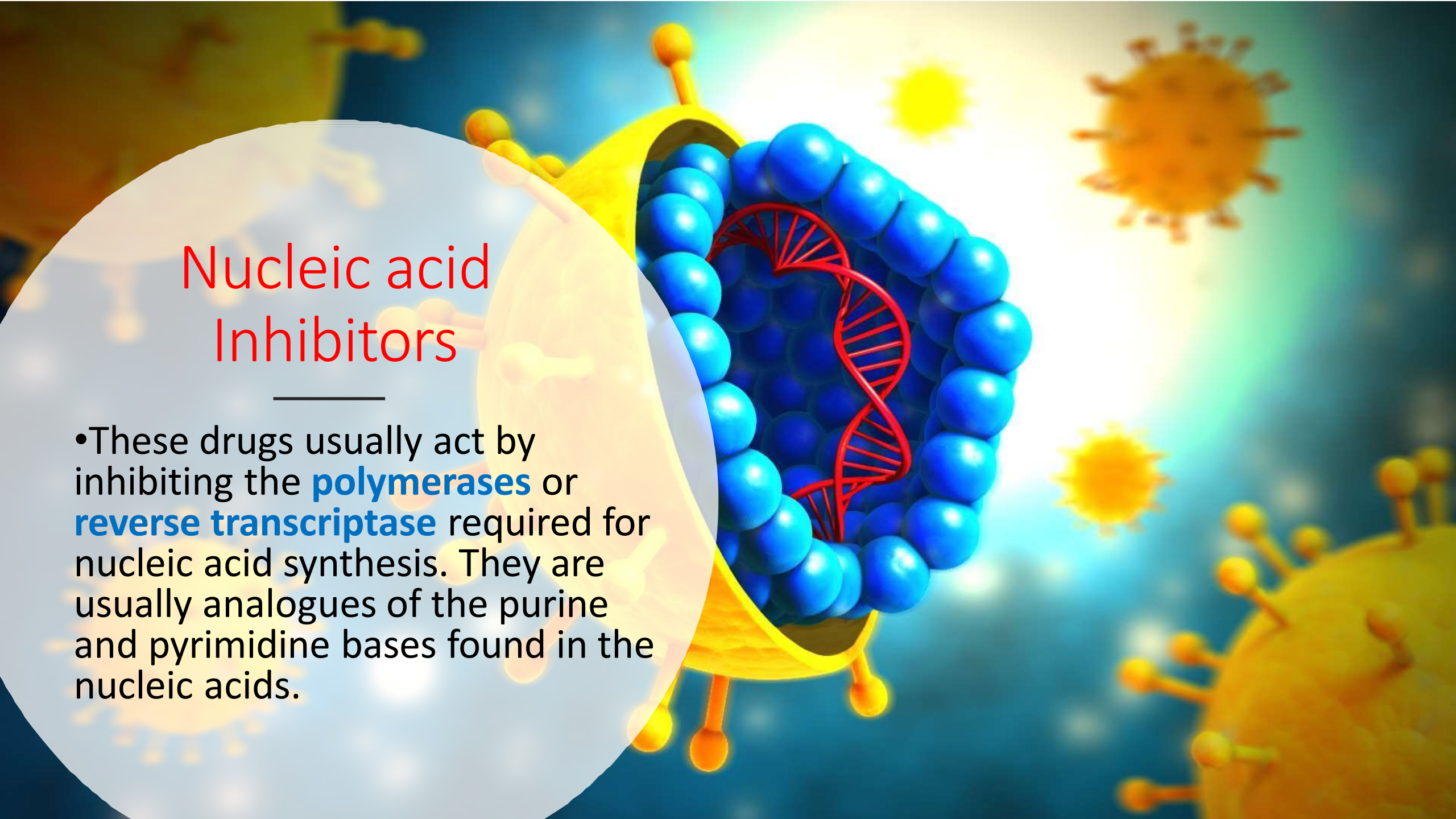
-the first PI to reach the market

-it has high molecular weight and peptide-like character

- oral bioavailability

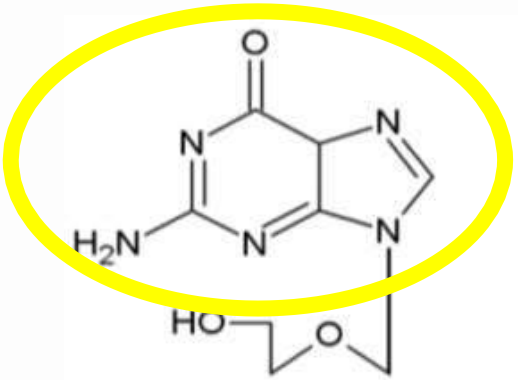


Nucleic acid Inhibitors

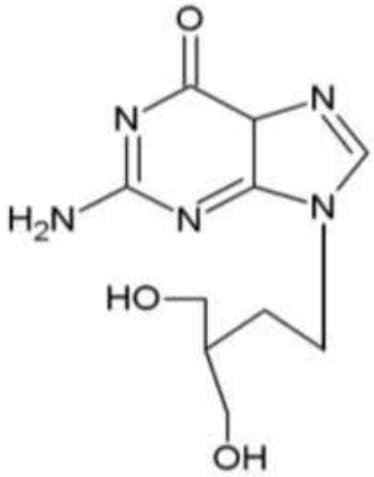


- These drugs usually act by inhibiting the **polymerases** or **reverse transcriptase** required for nucleic acid synthesis. They are usually analogues of the purine and pyrimidine bases found in the nucleic acids.

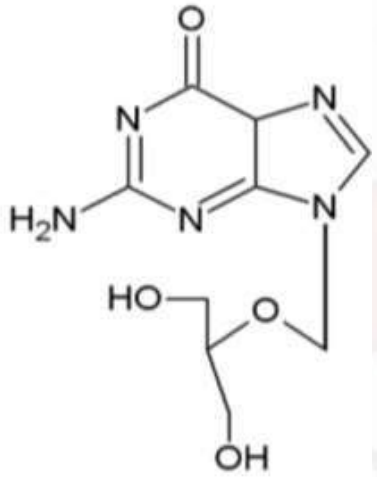
Inhibitors of viral DNA polymerase



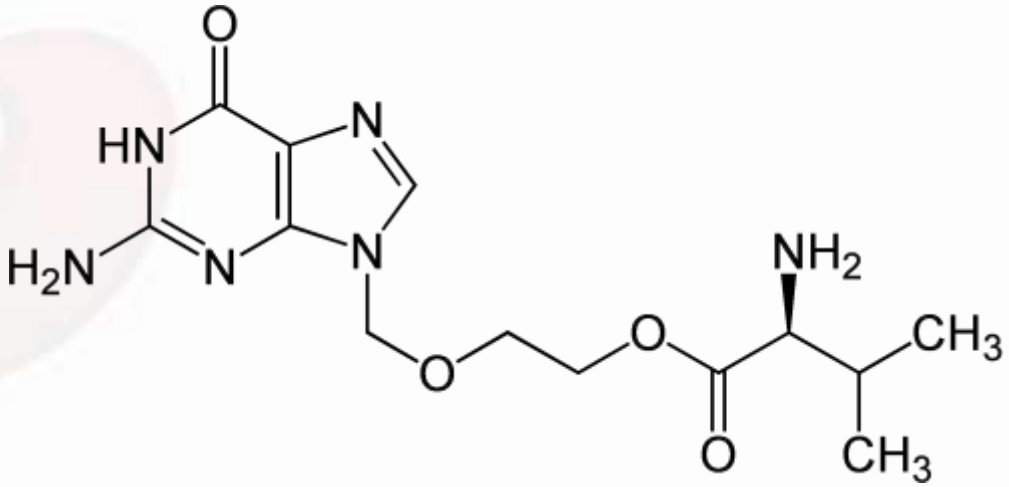
Acyclovir (ACV)



Penciclovir (PCV)



Ganciclovir (GCV)



Valaciclovir (prodrug of ACV)

Acyclovir

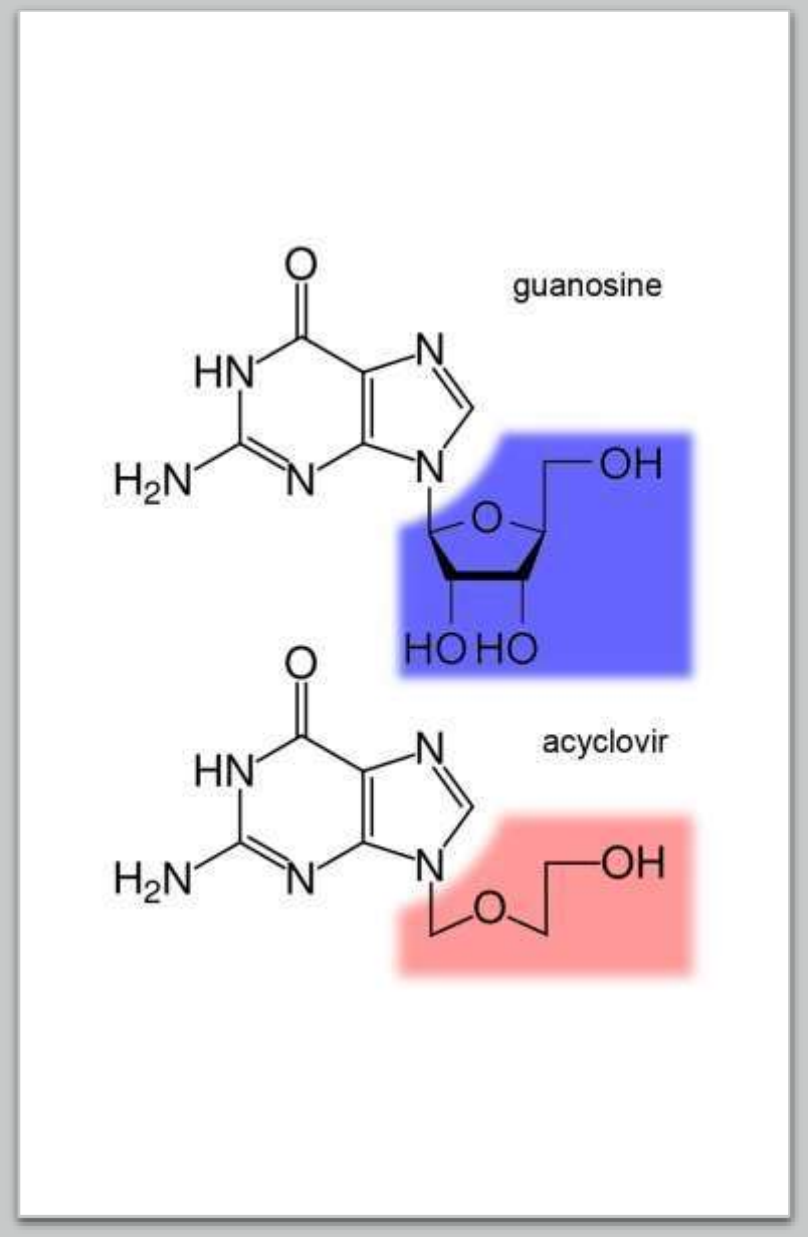
- is the prototypic antiherpetic therapeutic agent. Herpes simplex virus (HSV) types 1 and 2,varicella-zoster virus (VZV) (i.e. chickenpox and shingles).

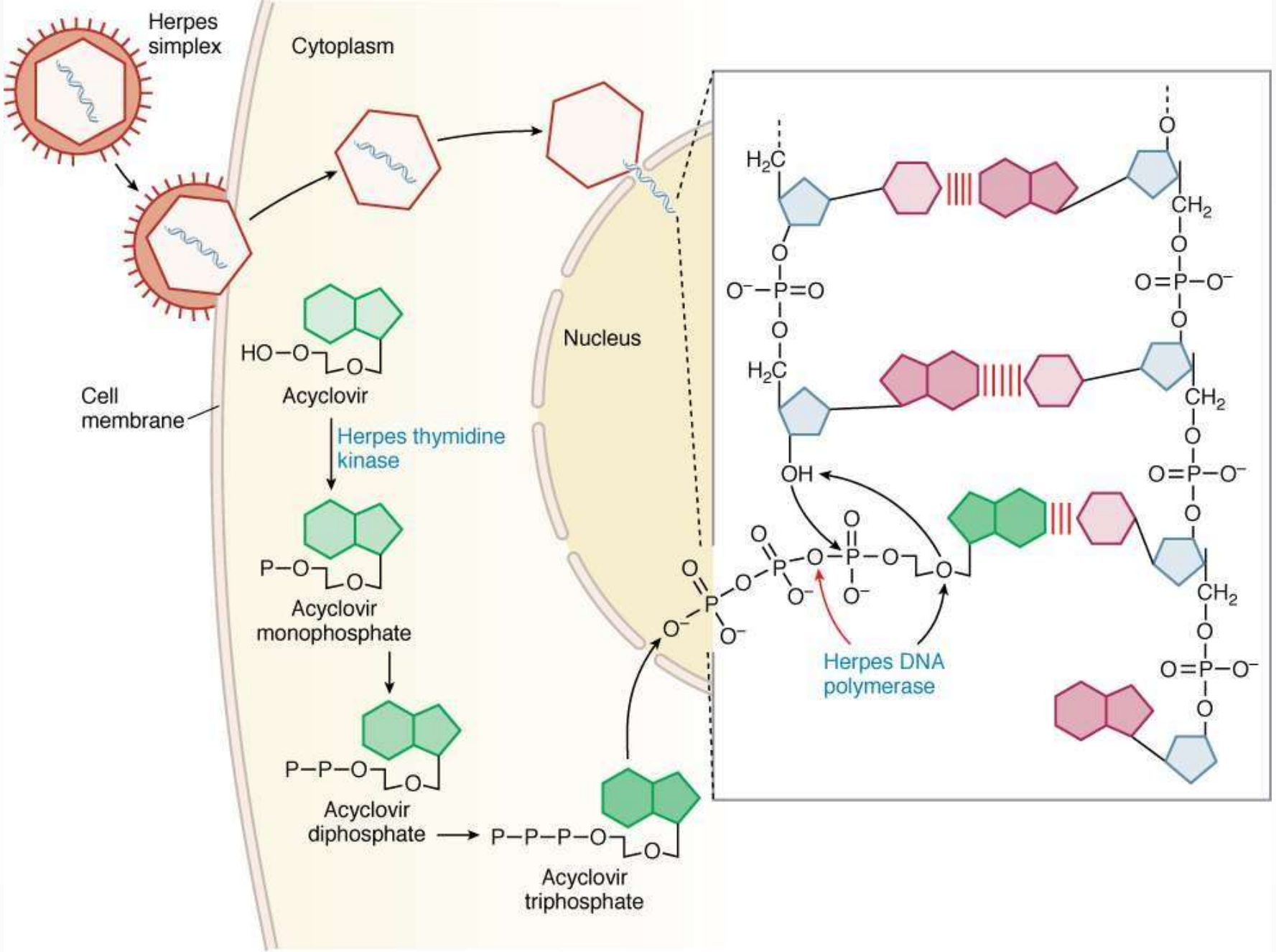
- Acyclovir has a nucleoside-like structure
- it lacks the complete sugar ring.
- In virally infected cells, it is phosphorylated to form a triphosphate which is the active agent, and so acyclovir is a prodrug

- Acyclovir triphosphate prevents DNA replication in two ways.

Firstly, it can bind to DNA polymerase and inhibit it.

Secondly, the drug acts as a chain terminator





Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

Valacyclovir

- The oral bioavailability of acyclovir is quite low (15– 30%).
- To overcome this, various prodrugs were developed to increase water solubility. Valacyclovir is an **l-valyl ester prodrug** absorbed from the gut far more effectively than acyclovir.

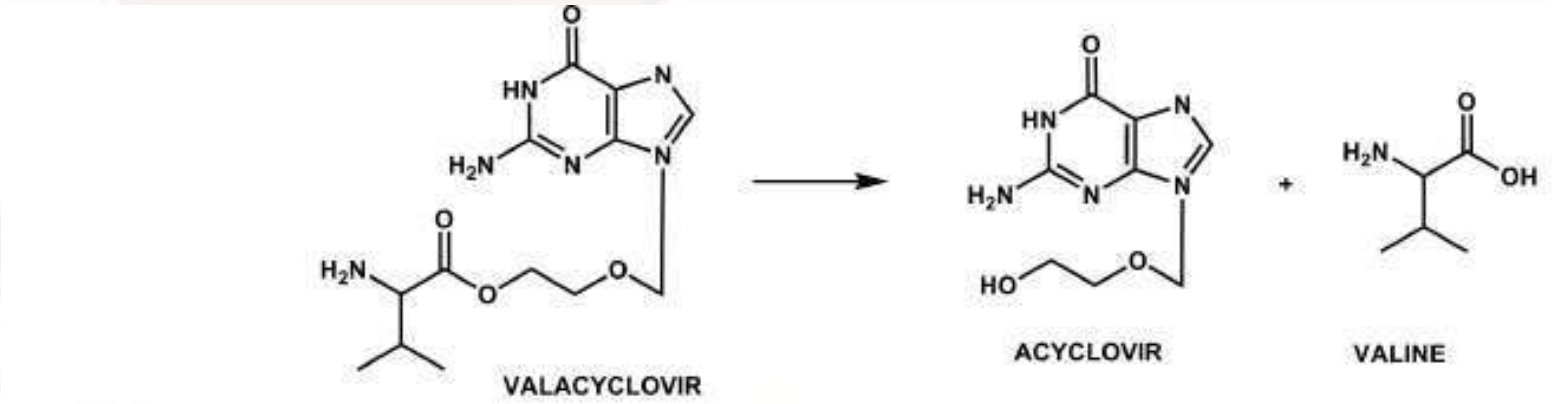
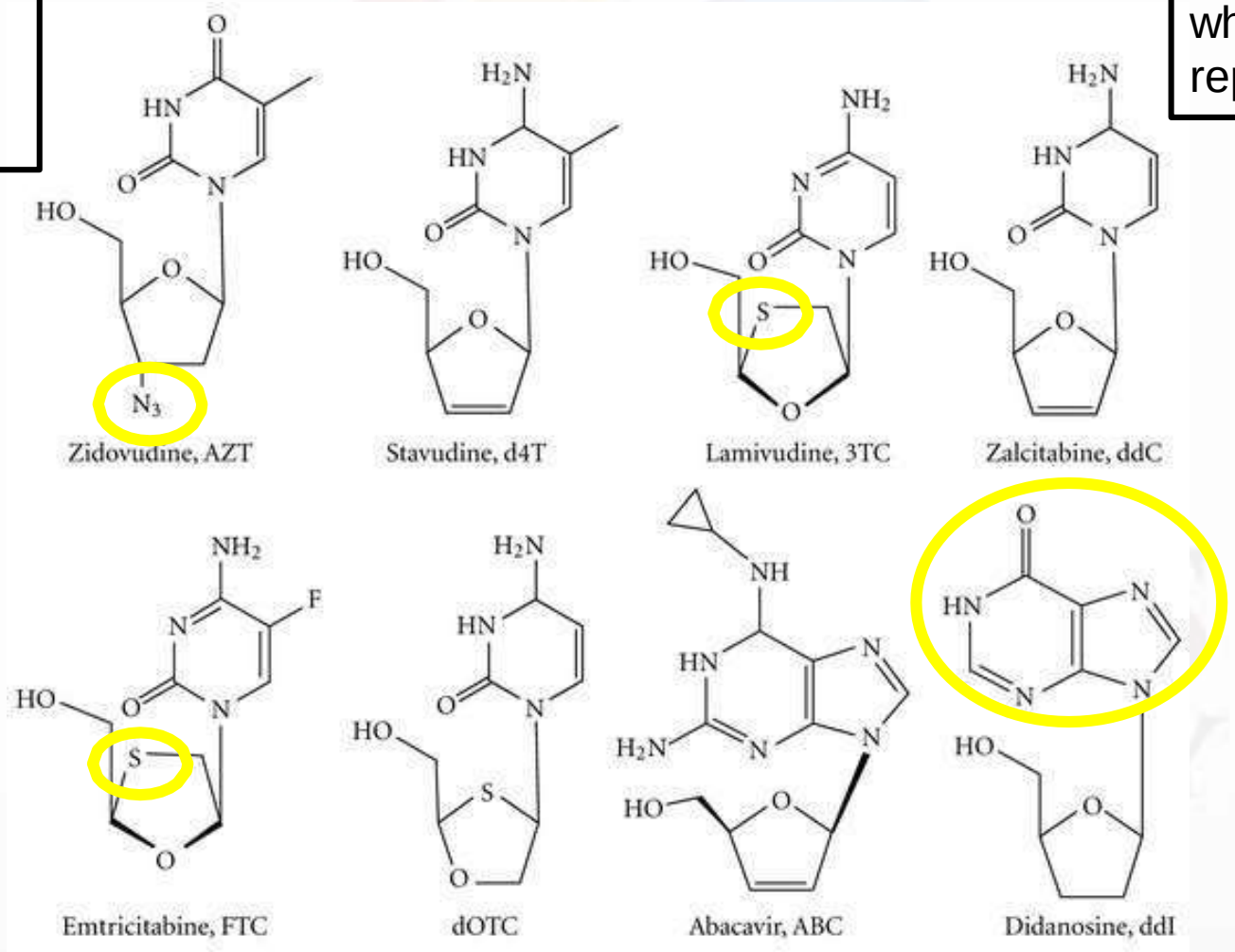


FIGURE 14 - Reaction illustrating the release of acyclovir from its prodrug.

Nucleoside reverse transcriptase inhibitors (NRTI)

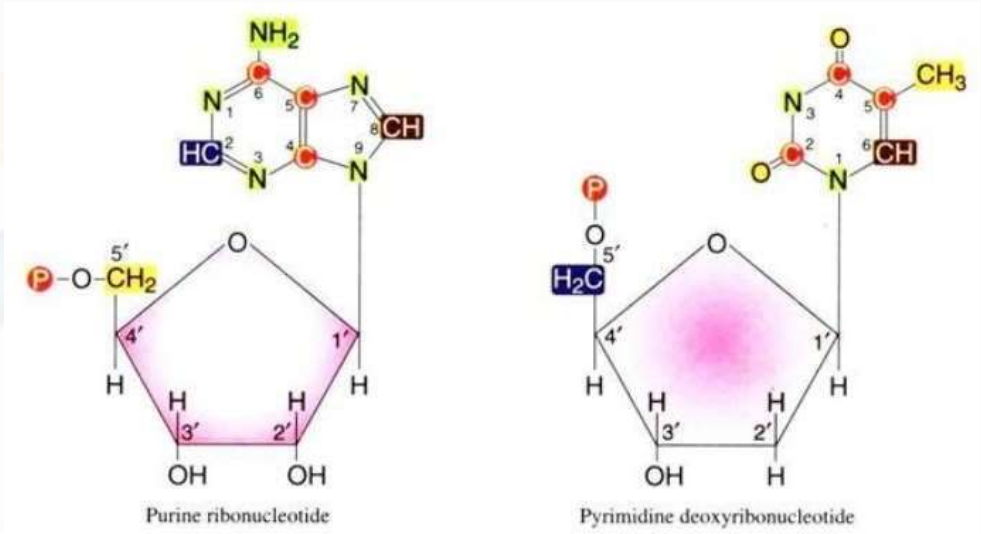
Zidovudine:
sugar 3′-hydroxyl group
has been replaced by an azido group

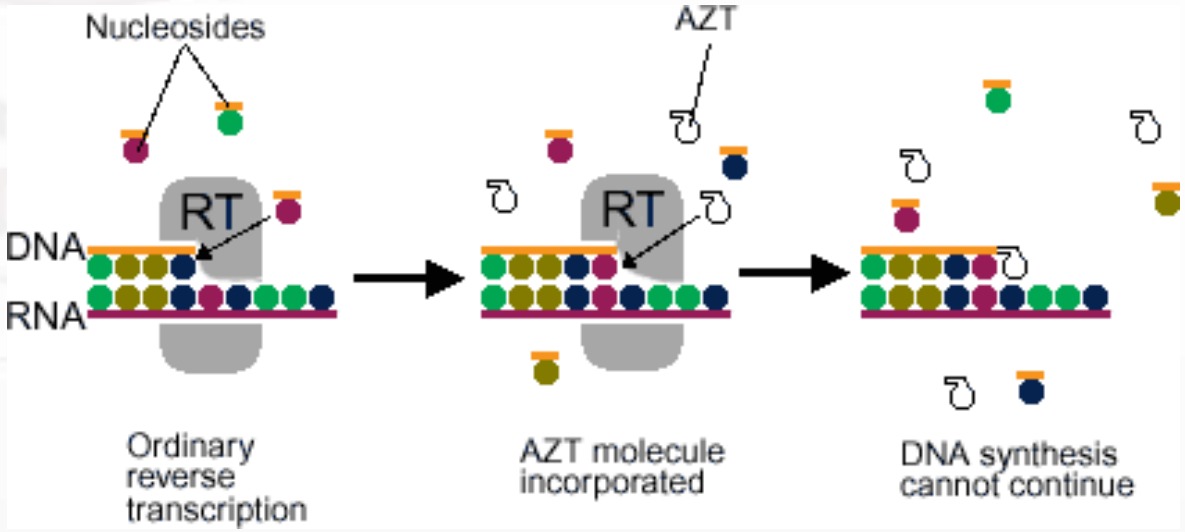
lamivudine and **emtricitabine:**
analogues of deoxycytidine where the 3′ carbon has been replaced by sulphur.



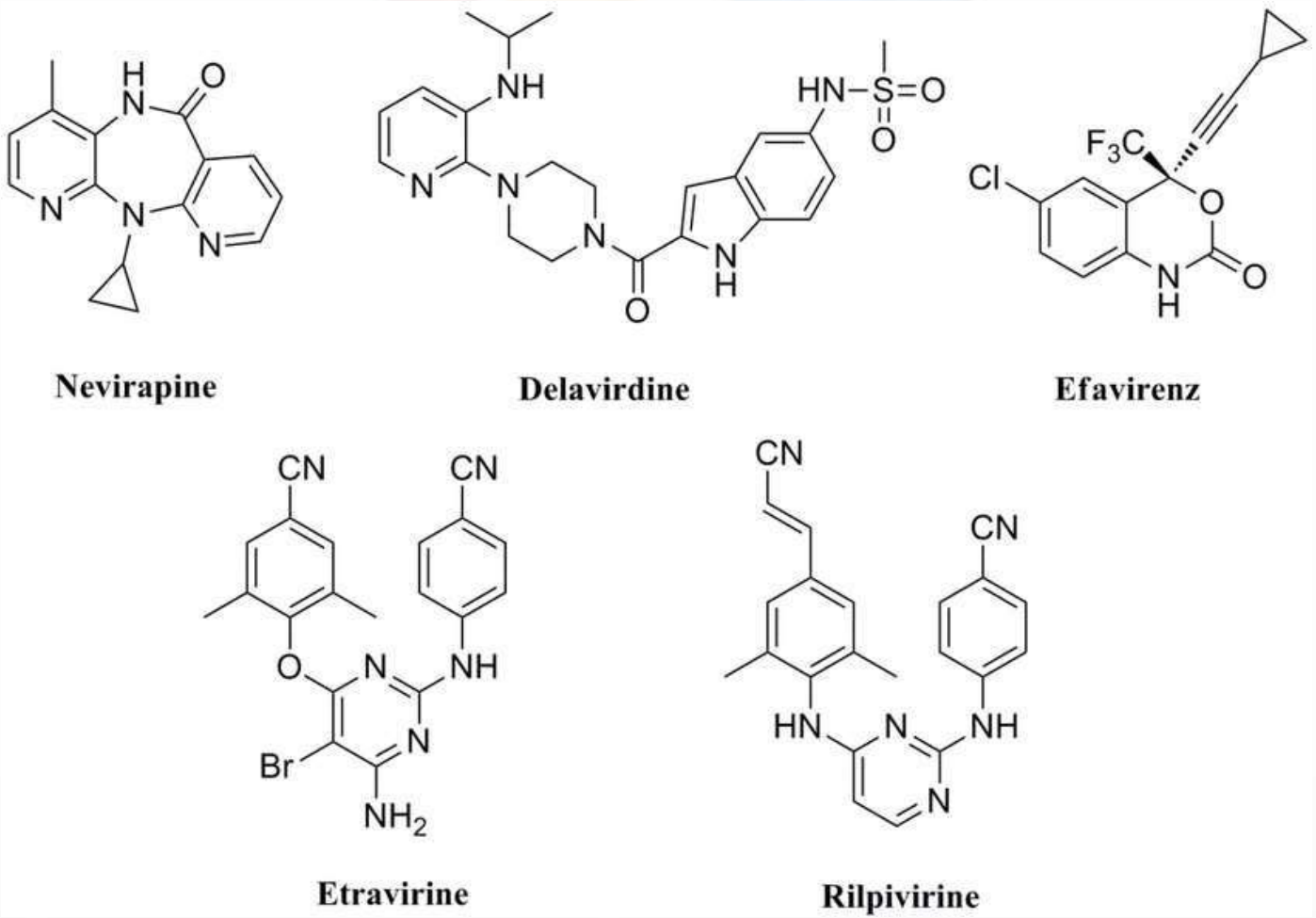
Didanosine:
nucleic acid base present is inosine base

- are analogs of native ribosides which **all lack a 3′-hydroxyl group**.
- Once they enter cells, they are phosphorylated to triphosphate analog which is incorporated into the viral DNA by Reverse Transcriptase . Because the 3′-hydroxyl group is not present, a 3′,5′-phosphodiester bond between an incoming nucleoside triphosphate and the growing DNA chain cannot be formed, and DNA chain elongation is terminated





Non-nucleoside reverse transcriptase inhibitors (NNRTI)



REFRENCES

- An Introduction to Medicinal Chemistry (5th edition), Graham L. Patrick
- Fundamentals of Medicinal Chemistry,Gareth Thomas
- *Wilson and Gisvold's Textbook of* ORGANIC MEDICINAL AND PHARMACEUTICAL CHEMISTRY (12th edition)
- https://www.ncbi.nlm.nih.gov/pubmed/16134757
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC438_0148/