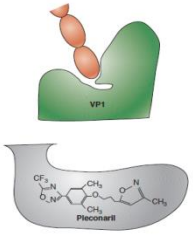
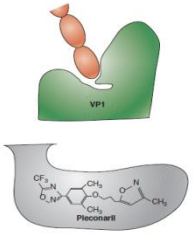


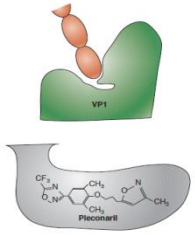
12

Antiviral Chemotherapy



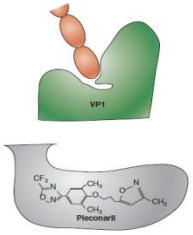
Why antiviral drugs?

- Vaccines have provided considerable success in preventing viral diseases; However, they have modest or often no therapeutic effect for individuals who are already infected
- Antiviral drugs can stop an infection once it has started. The development and use of antiviral drugs provide our second arm of antiviral defense
- Despite almost 50 years of research, our arsenal of antiviral drugs remains dangerously small; Only about 30 antiviral drugs (most against HIV and herpes viruses) are available on the market.



Why so few antiviral drugs?

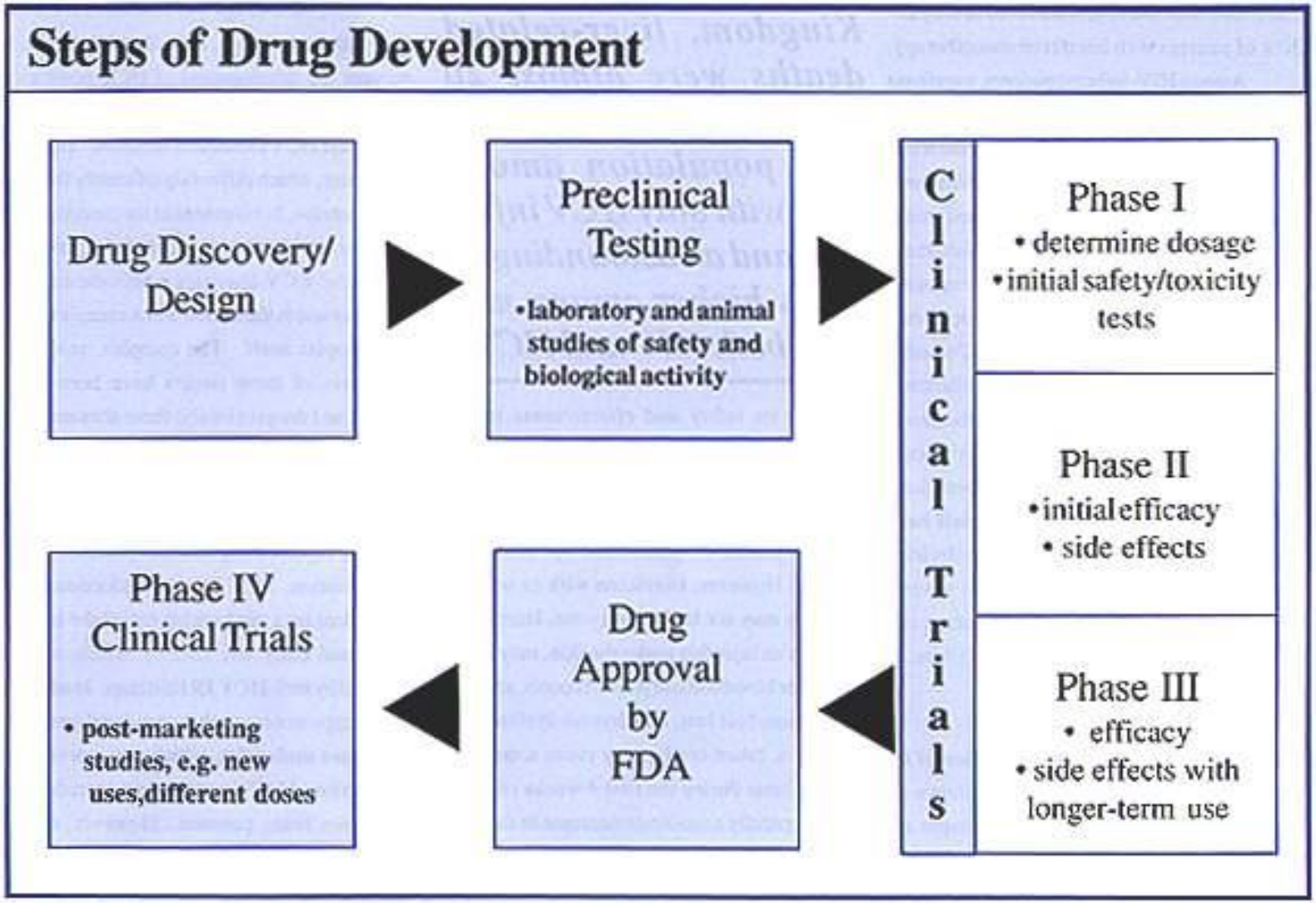
1. Compounds interfering with virus growth can adversely affect the host
   - All steps in viral life cycle engage host functions
   - Side effects are inevitable
2. Antiviral drugs must block viral replication completely
   - Partial inhibition is not acceptable because resistant viruses can emerge
3. Many medically important viruses are dangerous, can't be tested in model systems, or can't be propagated
   - Will accidently kill investigators (Ebola virus, Lassa fever virus)
   - Have no available animal model of human disease (HIV, measles virus)
   - Difficult or impossible to grow in the laboratory (HBV, HCV, HPV)
4. Antiviral drug discovery is time consuming and expensive
   - Fewer obvious targets for chemotherapy delayed antiviral discovery
   - Available vaccines also lessen the interest in developing an antiviral drug



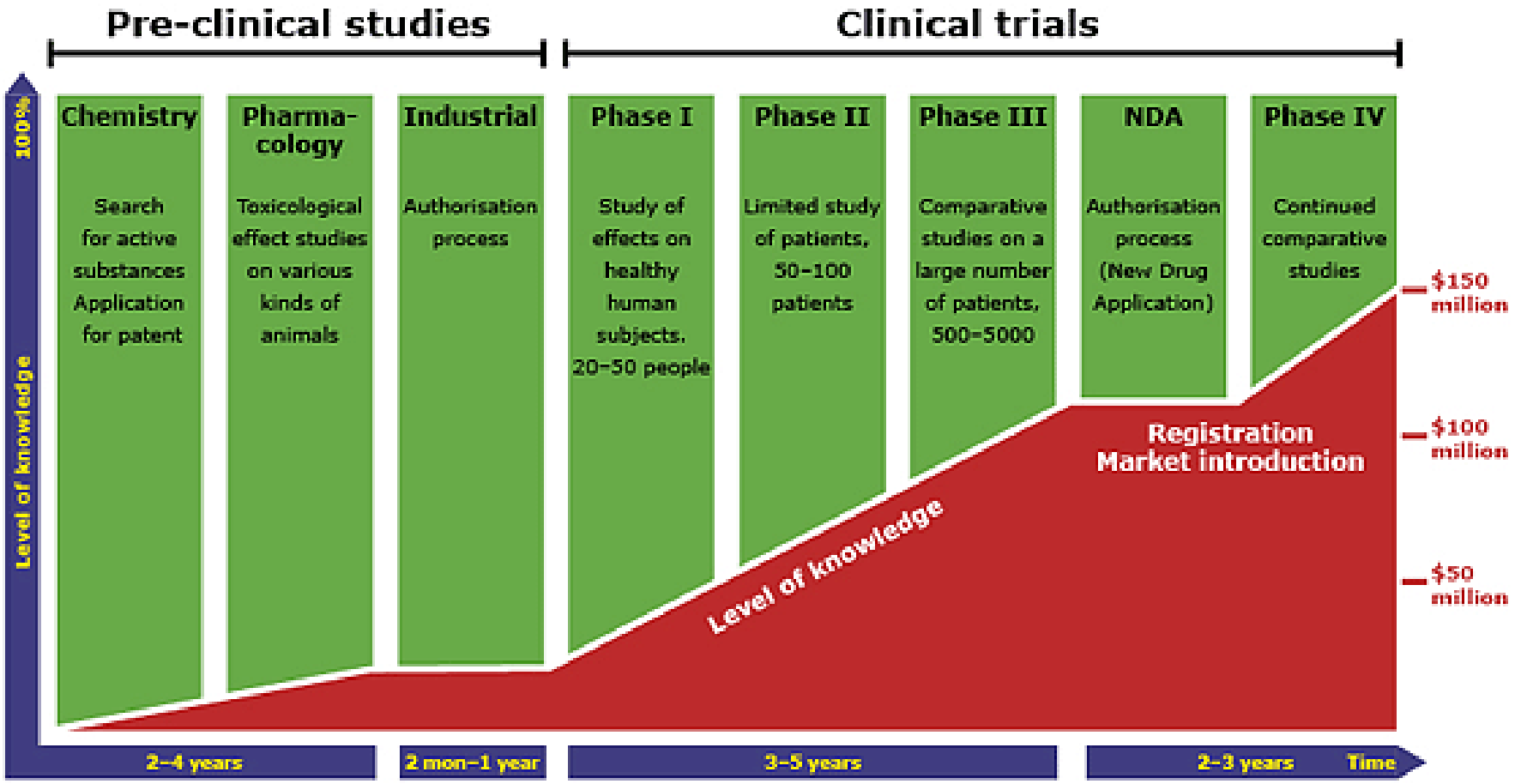
Viruses controlled by current antiviral therapy

- Cytomegalovirus (CMV)
- Hepatitis viruses B and C
- Herpes viruses
- Human immunodeficiency virus (HIV)
- Influenza viruses
- Respiratory syncytial virus (RSV)

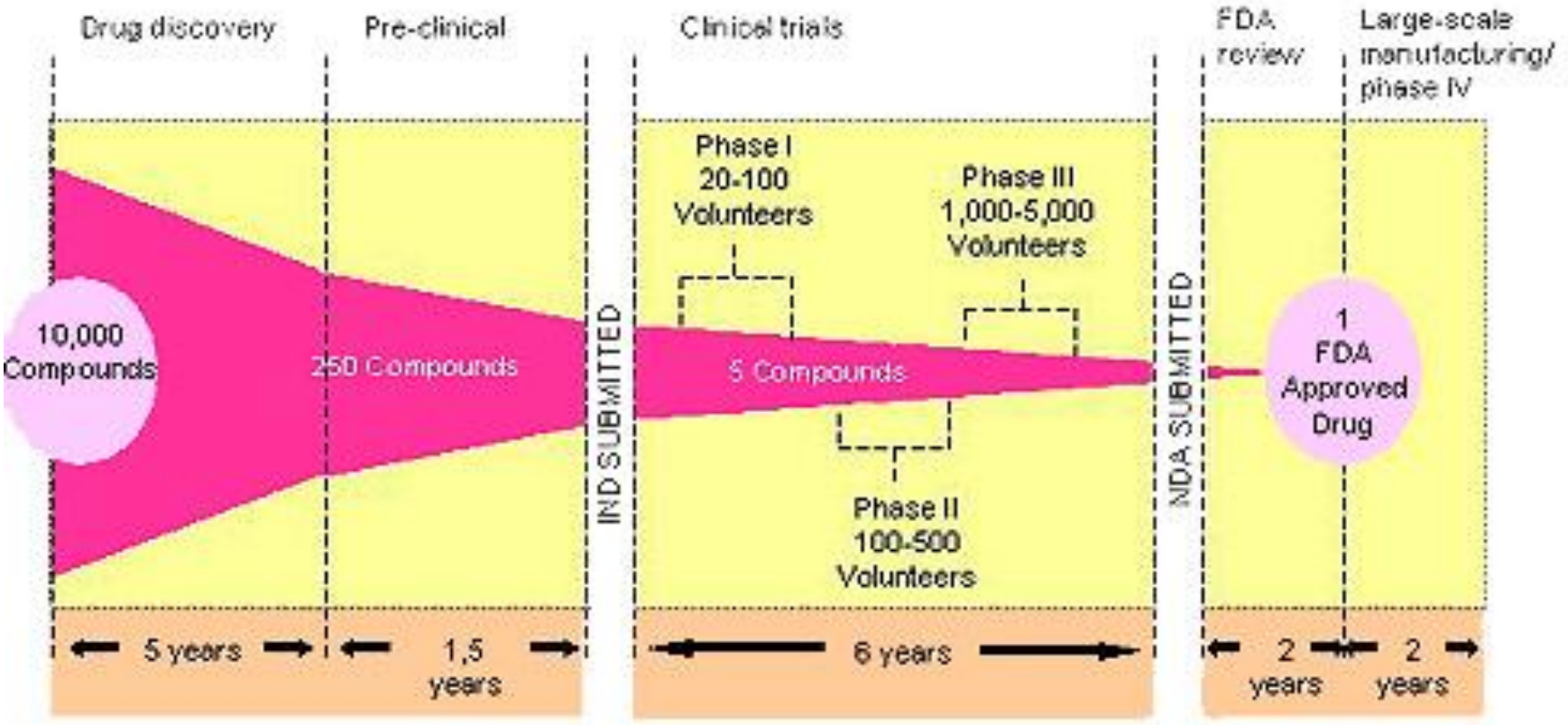
Steps of Drug Development



Steps of Drug Development

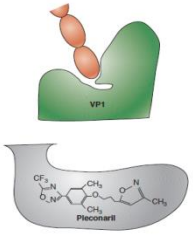


Steps of Drug Development



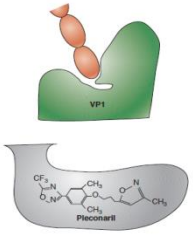
Investigational new drug

New drug application



Discovery of antiviral drugs

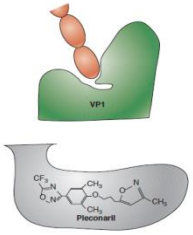
- The first modest search for antiviral drugs occurred in the early 1950's
  - Chemists looked at derivatives of the sulfonamide antibiotics
- In the 1960's and 1970's, drug companies launched huge "blind-screening" programs to find chemicals with antiviral activity
  - Random chemicals and natural product mixtures tested for ability to block replication of a variety of viruses in cell culture systems
  - The mechanism of how these compounds inhibit the virus is not given any importance
  - Despite considerable effects, very little success was achieved
  - Amantadine was discovered which is effective for treatment of influenza A virus infections



Discovery of antiviral drugs

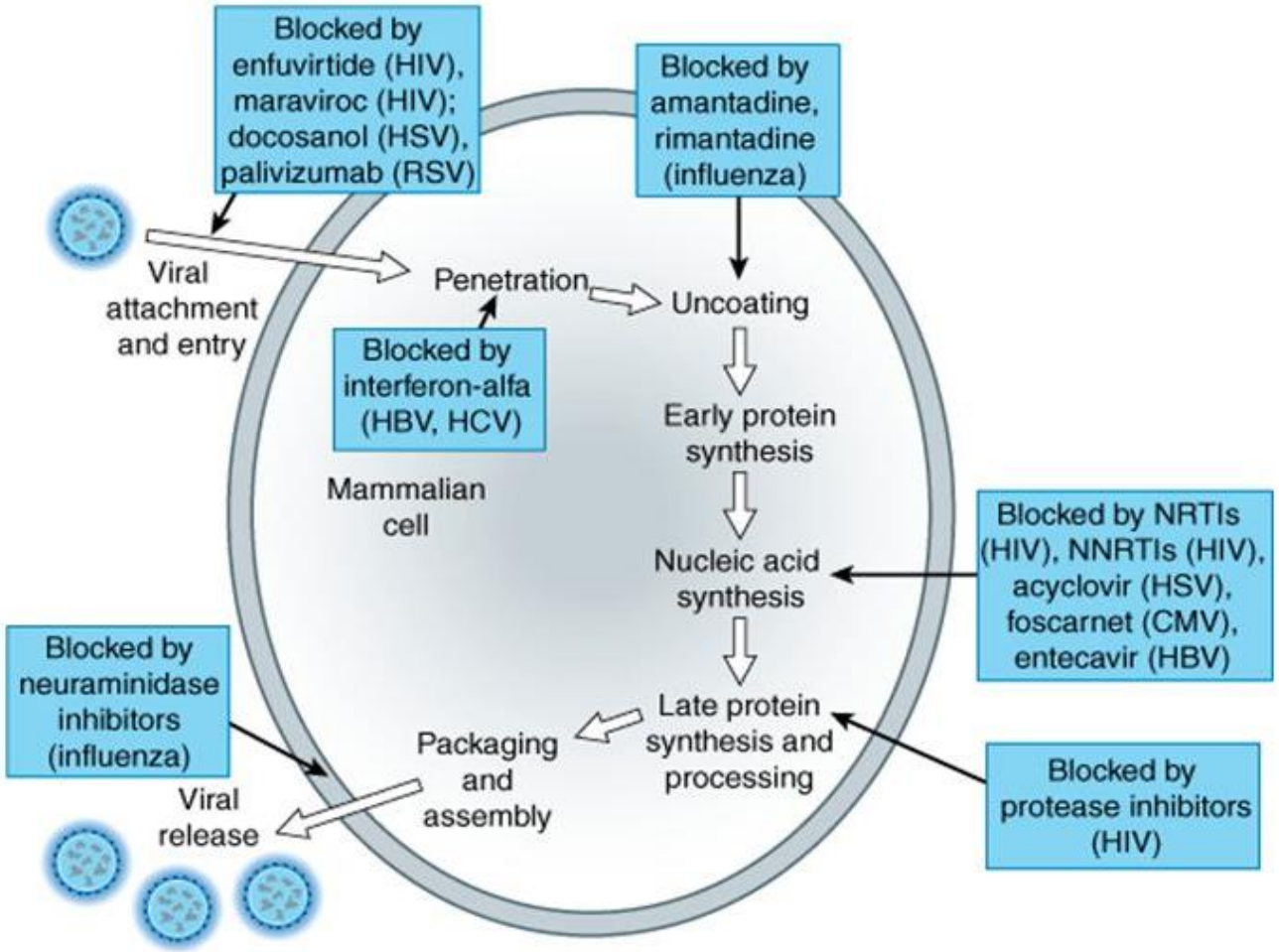
- The discovery and widespread use of antiviral compounds began relatively recently

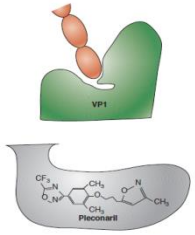
1. Chemical modification of known active compounds; ganciclovir, azidothymidine
2. High throughput screening assays of many compounds
    1) Cell-based HTS; herpes virus and HIV new replication inhibitors
    2) Target-based HTS; nevirapine (HIV RT inhibitor)
3. Rational design, often with the aid of three-dimensional structures of viral proteins; ritonavir (HIV protease inhibitor), zanamivir (influenza NA inhibitor)



Major antiviral drugs and their action sites

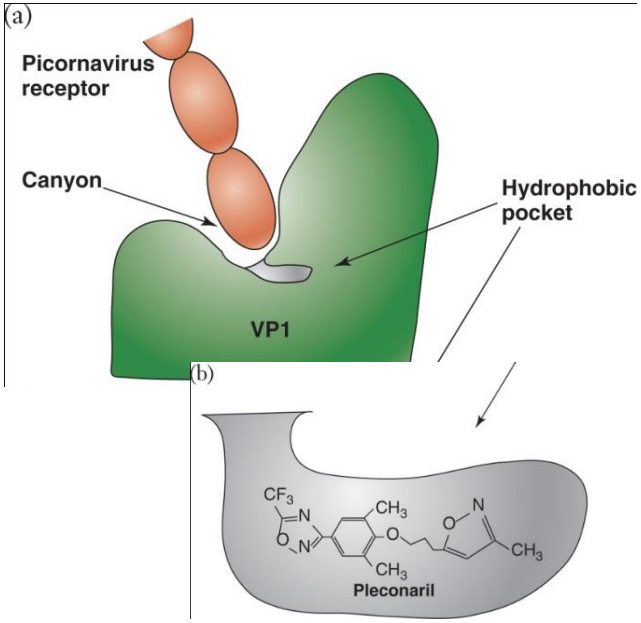
- Antiviral drugs are targeted to specific steps of virus replication

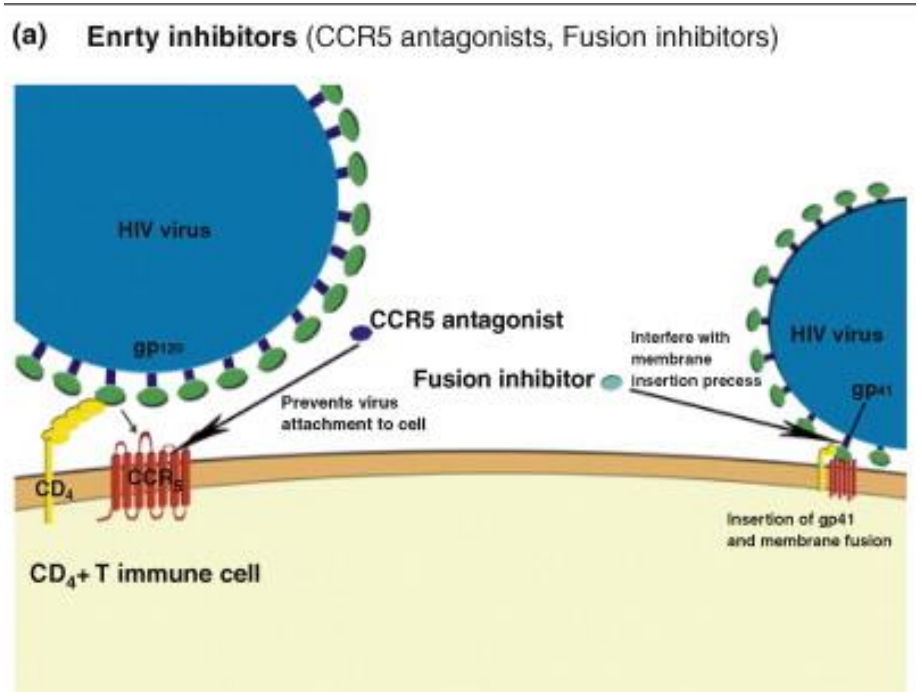


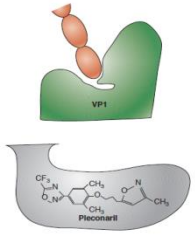


Targets of antiviral drugs

- Drugs preventing attachment and entry of virions
  - Pleconaril blocks many picornaviruses including rhinoviruses
  - Enfuvirtide binds to HIV-1 gp41 (fusion inhibitor)
  - Maraviroc binds to cellular HIV-1 receptor CCR5 (CCR5 antagonist)

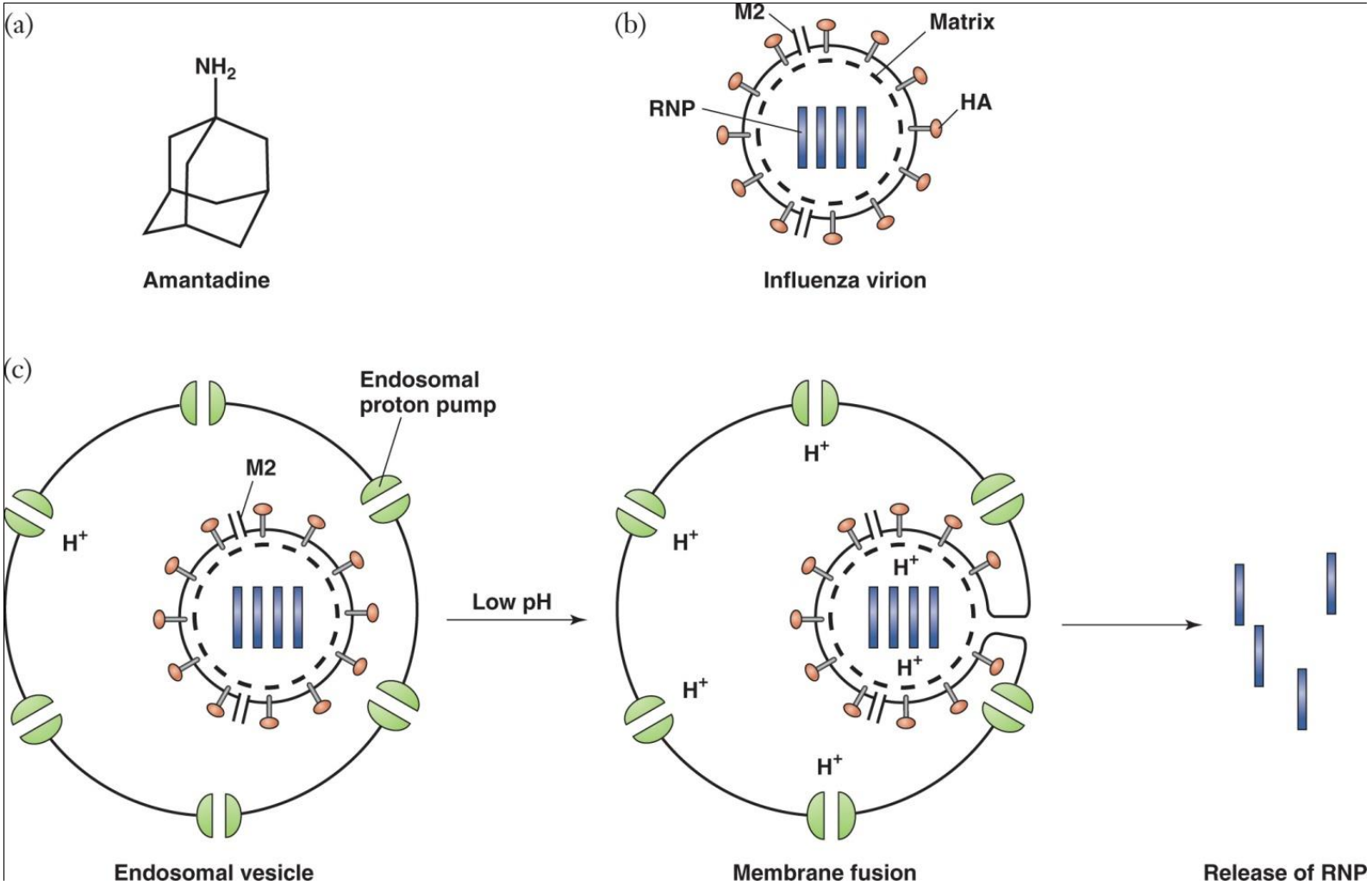


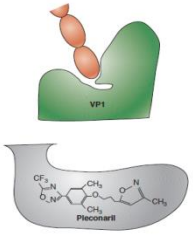




Targets of antiviral drugs

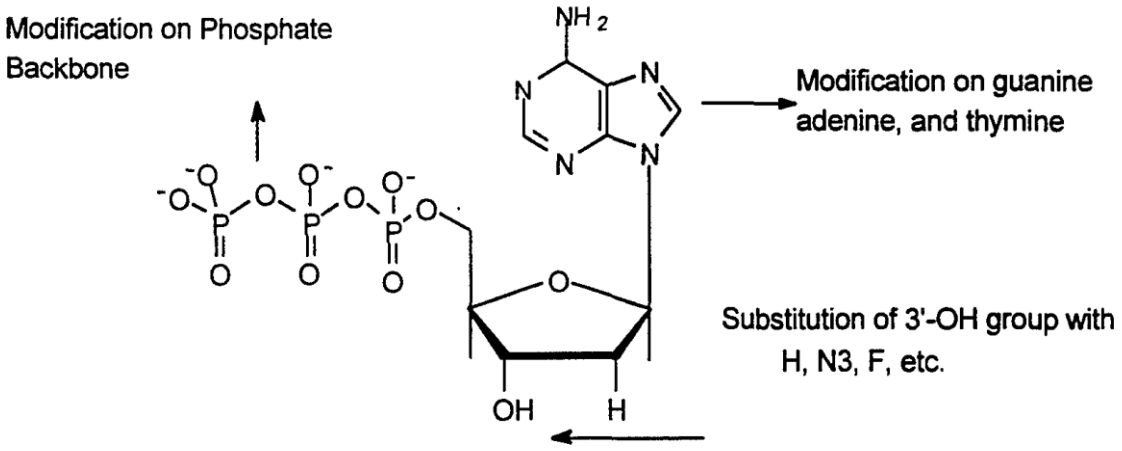
- Amantadine blocks ion channels and inhibits uncoating of influenza virions

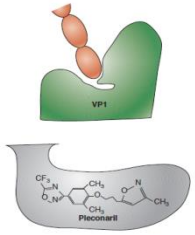




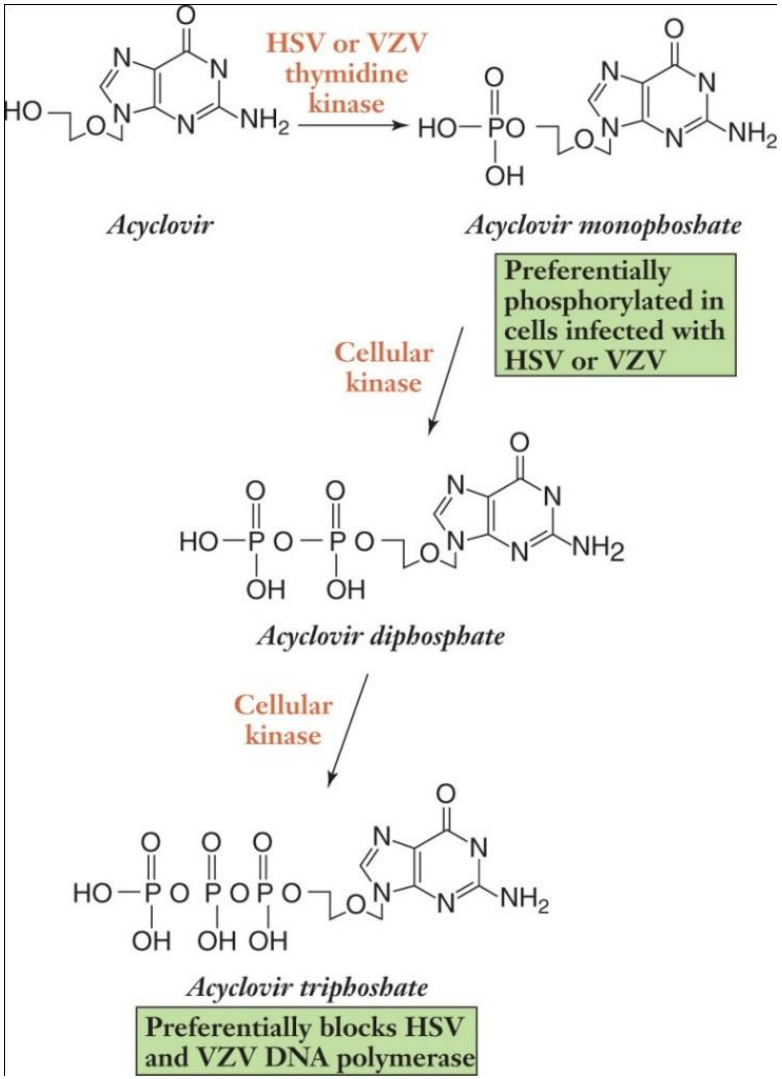
Targets of antiviral drugs

- Nucleoside analogues target viral DNA/RNA polymerases
  - Drugs must be specific to the viral polymerase to keep toxicity low
  - Competitive inhibitors or chain terminators
  - Activation by viral kinases will cause the drug to be activated only in infected cells
  - If viral polymerases are more sensitive to drug, then concentration of drug can be kept low (high **therapeutic index)**

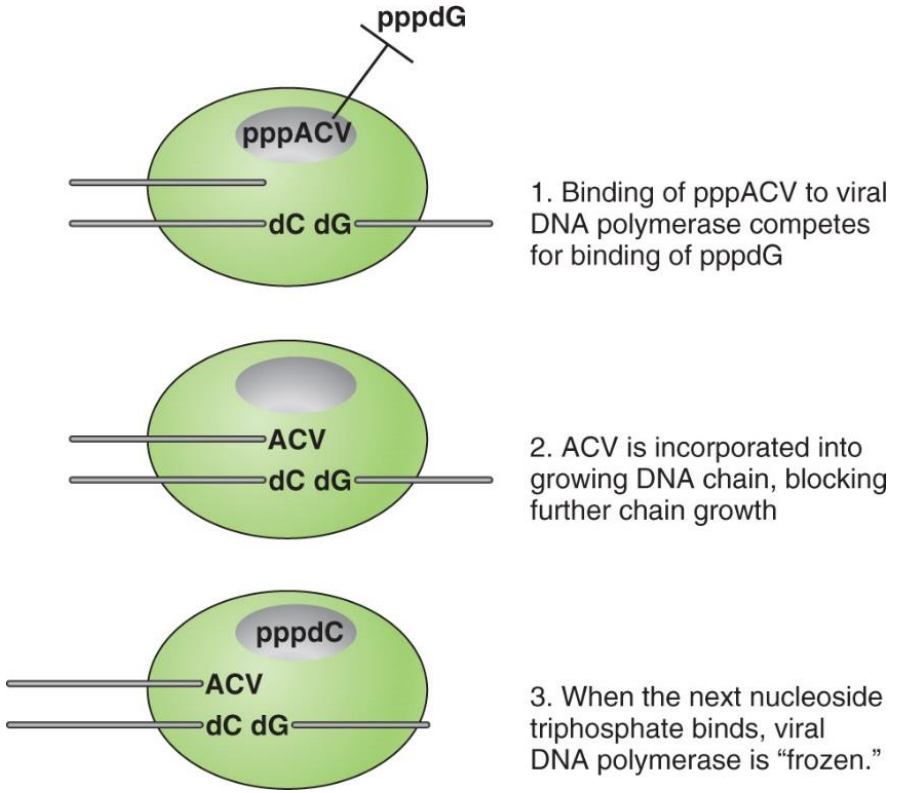


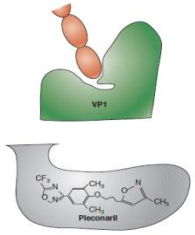


Targets of antiviral drugs



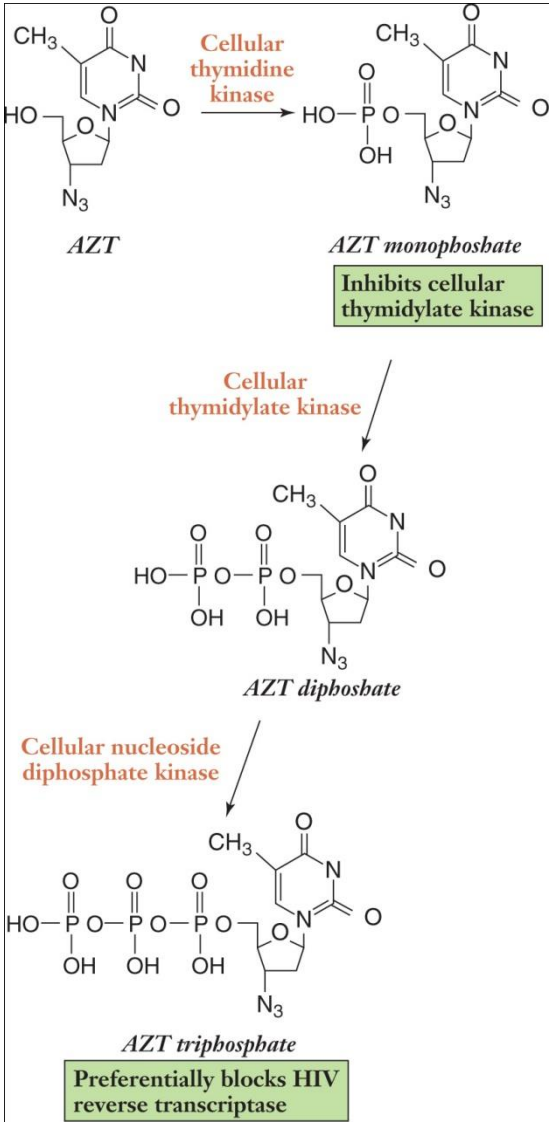
- Acyclovir is selectively phosphorylated by herpesvirus **thymidine kinase** to be activated
- Acyclovir is preferentially incorporated by herpesvirus DNA polymerase

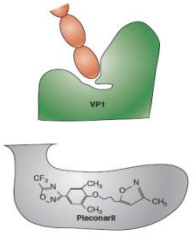




Targets of antiviral drugs

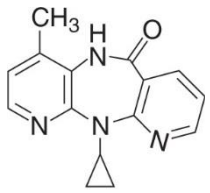
- HIV-1 RT preferentially incorporates azidothymidine (AZT) into DNA, leading to chain termination
  - A nucleoside analogue with an altered sugar moiety
  - Phosphorylated by cellular thymidylate kinase and nucleoside diphosphate kinase

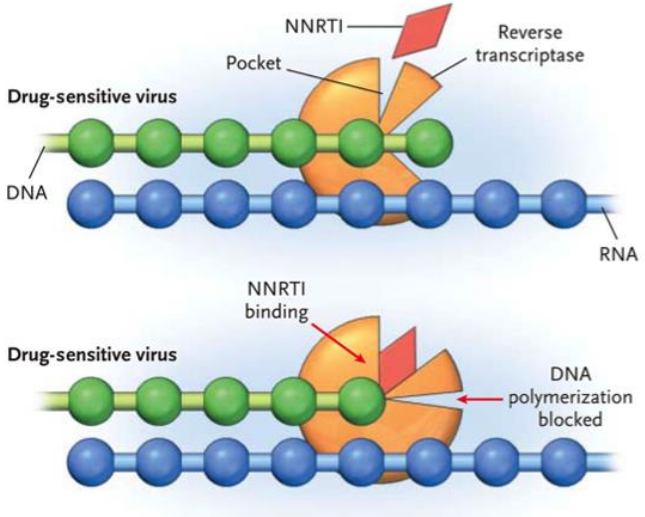


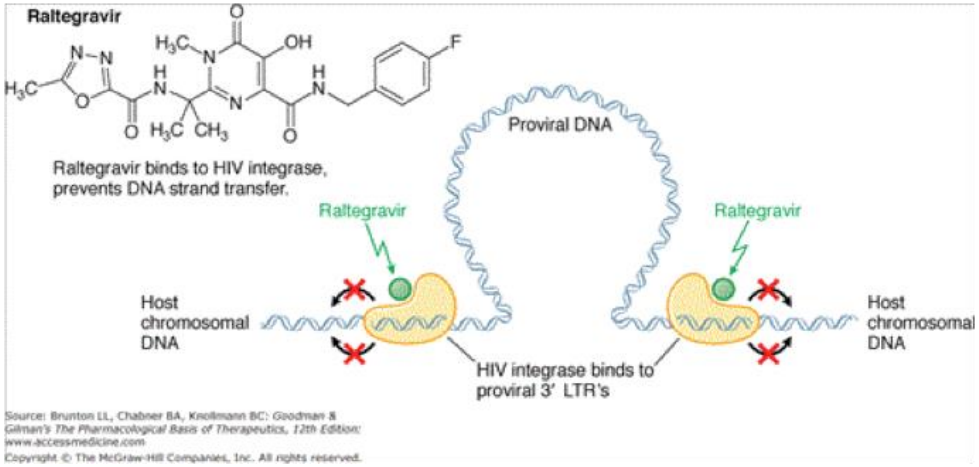


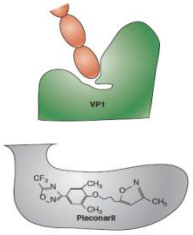
Targets of antiviral drugs

- Non-nucleoside inhibitors selectively (non-competitively) target viral replication enzymes
  - Do not require activation through phosphorylation
  - Nevirapine bind to a spot near the active site of HIV-1 RT and slow the rate of DNA polymerization
  - Raltegravir inhibits HIV-1 integrase



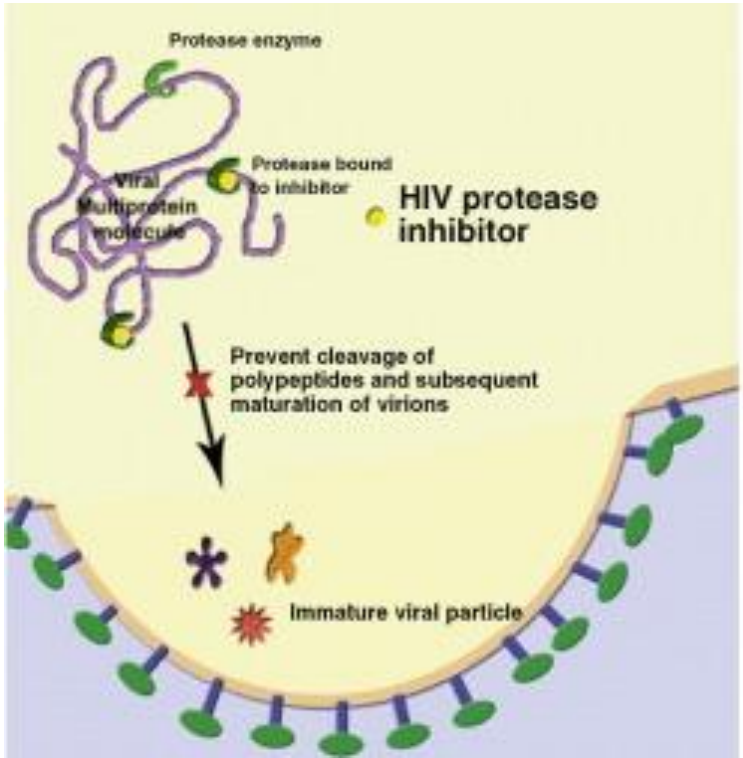


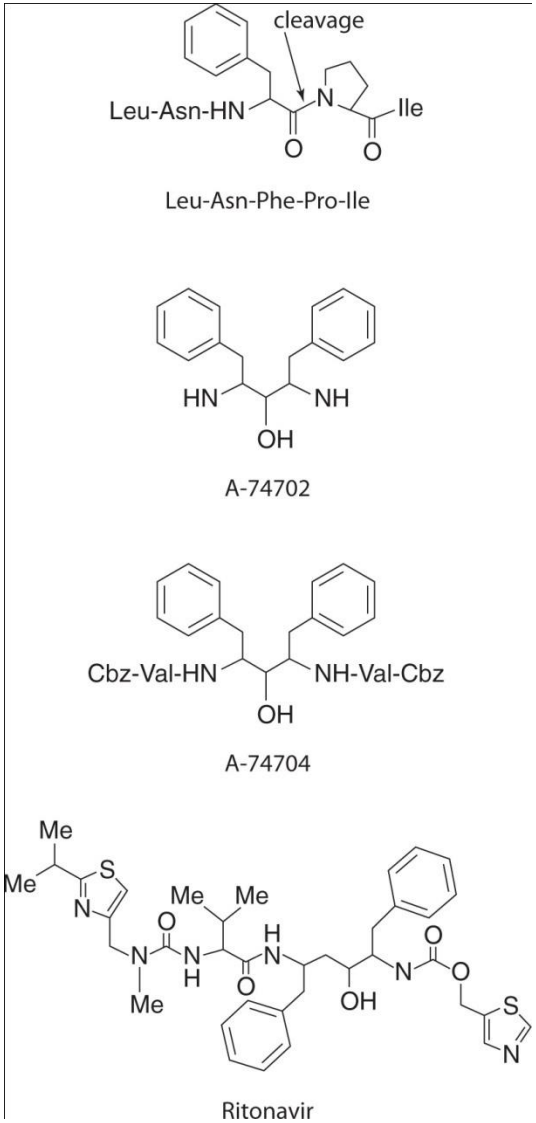


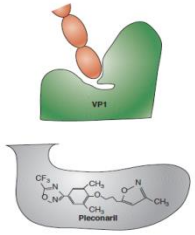


Targets of antiviral drugs

- Protease inhibitors can interfere with virus assembly and maturation
- Ritonavir: a successful protease inhibitor of HIV-1 that was developed by rational methods
  - It is a **peptidomimetic** drug that mimics a peptide
  - Modifications to drug improved its **pharmacokinetics**

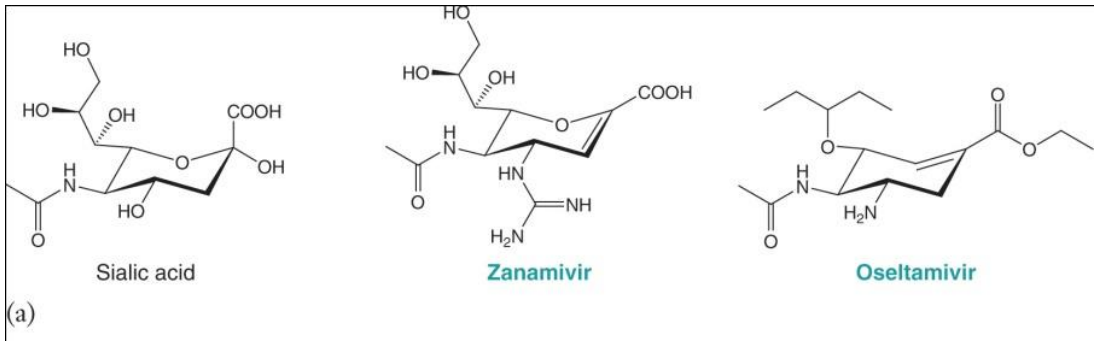


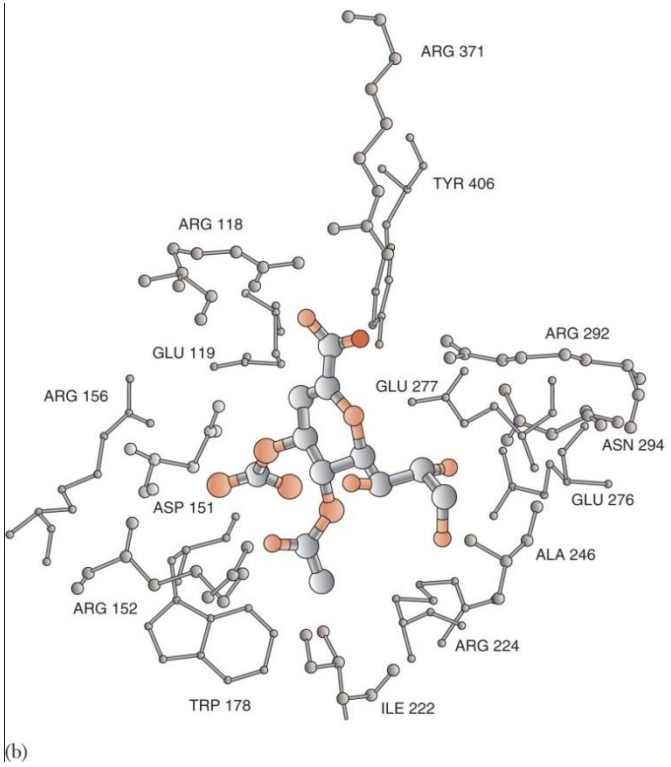


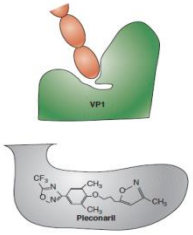


Targets of antiviral drugs

- **Neuraminidase** inhibitors release and spread of influenza virus
  - Influenza virus attaches to cellular **sialic acid** present on many glycoproteins and **gangliosides**
  - Zanamivir and **oseltamivir** inhibits NA to cleave sialic acid, releasing virus
- Rational design of neuraminidase inhibitors

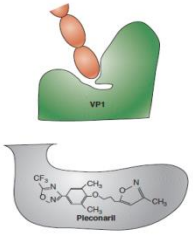






Key characteristics of anti-viral drugs

- Most anti-viral agents target specific viral proteins, usually an enzyme involved in viral multiplication
- Antiviral agents inhibits active replication so the viral growth resumes after drug removal.
- Current anti-viral agents do not eliminate non-replicating or latent virus
- Effective host immune response remains essential for the recovery from the viral infection
- Most anti-viral drugs affect the host cell and are associated with unacceptable toxicity
- Clinical efficacy depends on achieving inhibitory concentration at the site of infection (within the infected cells)



Global anti-viral drug market

KEY TREND

Combination therapy has proven to be beneficial to treat certain viral infections.

MARKET DRIVER

The CDC provides guidelines to improve access to antiviral drugs for the public through physicians.

MARKET DRIVER

The demand for antiviral drugs is due to the increasing mortality rate.

FORECAST

The market is projected to reach $91.58 billion by 2021.

technavio