Chapter 11: Antiviral Agents

Antiviral agents:

Amantadine hydrochloride, Rimantadine hydrochloride, Idoxuridine trifluoride, Acyclovir*, Gancyclovir, Zidovudine, Didanosine, Zalcitabine, Lamivudine, Loviride, Delavirding, Ribavirin, Saquinavir, Indinavir, Ritonavir.

Pharmacology Lectures:

Antiviral Drugs and Infections: https://youtu.be/Q0Hkdd64F50

HIV infection and general mode of action of antiviral drugs: https://youtu.be/_wJextoOsos

Antiherpes Drugs (Acyclovir, Idoxorudine, and Ganciclovir): https://youtu.be/qYDYgX_m8P8

Antihepatitis Drugs: https://youtu.be/8z3ki8yHLag

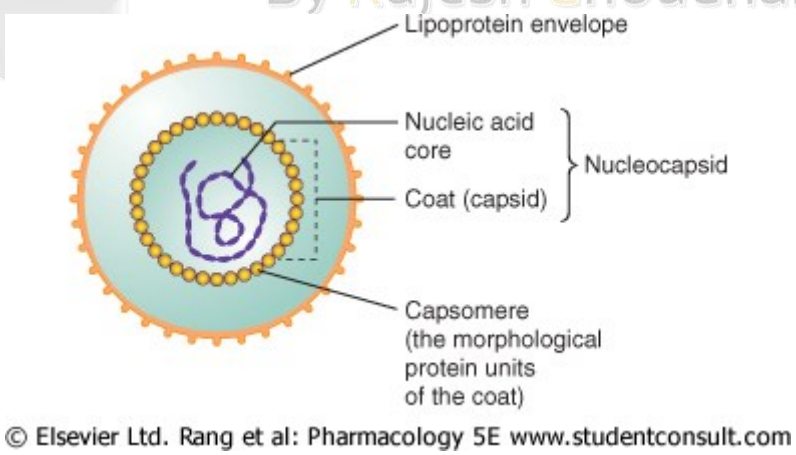
Anti influenzae Drugs (Amentadine, Rimentadine): https://youtu.be/1vWkGRQGyrw

Anti HIV Drugs (Zidovudine, Lamivudine, Indinavir, etc): https://youtu.be/JEqdmNAqL8s

11.1. ANTIVIRAL DRUGS AND GENERAL MECHANISM

These are the agents used in the treatment of viral infections.

Viruses are obligate intracellular parasites that depend on metabolic processes of host cells for their replication. Virus consist of either RNA or DNA enclosed in a protein coat and a lipoprotein coat.

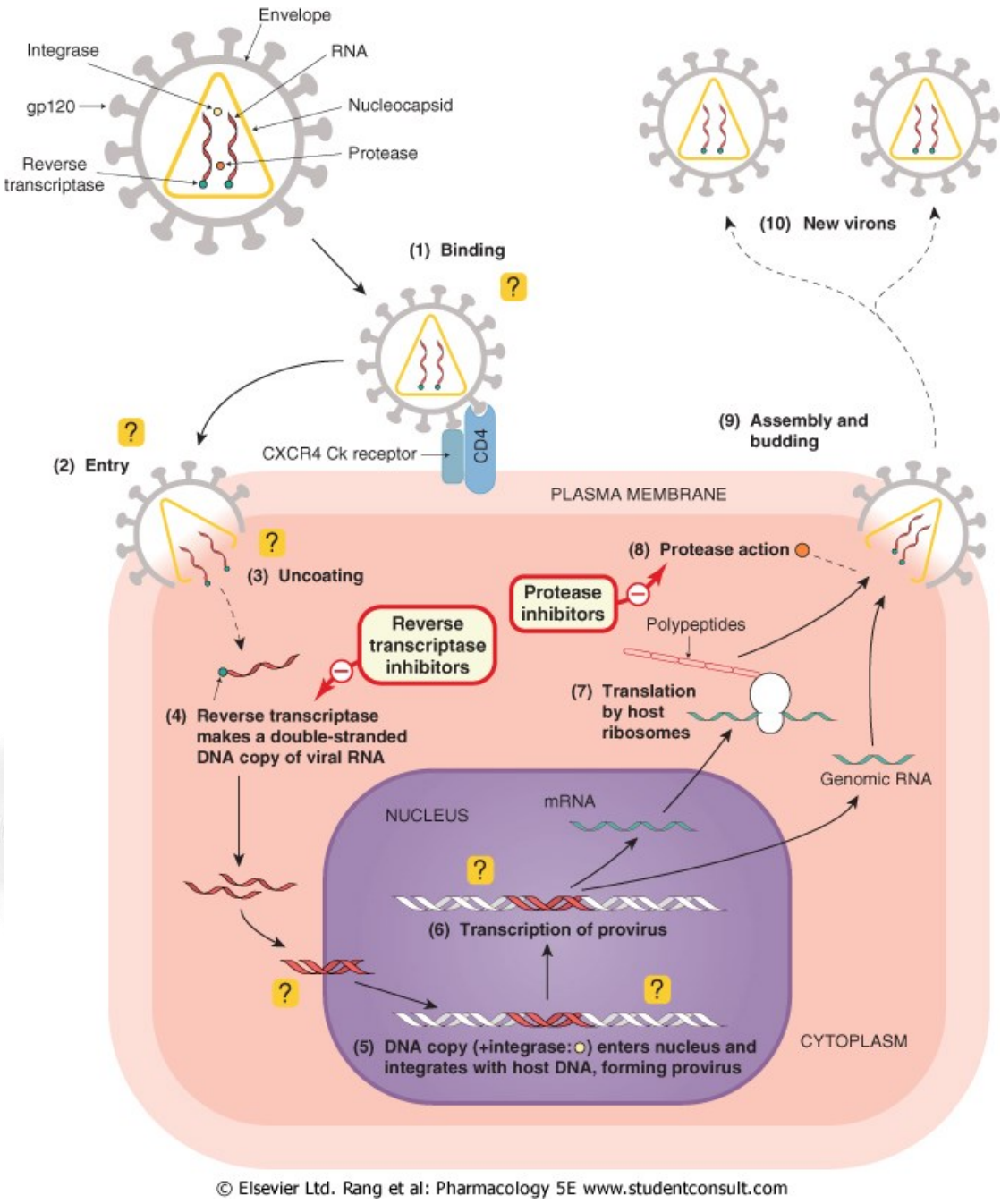


Source: Rang & Dale, Pharmacology

Component of virus particle or virion

PATHOGENIC VIRUSES:

- ***DNA viruses*:**
    - Poxviruses: smallpox,
    - Herpesviruses (Vercella Zoster, H. Simplex, CMV): chickenpox, shingles, cold sores, glandular fever),
    - adenoviruses (sore throat, conjunctivitis) and
    - papillomaviruses (warts).
- ***RNA viruses*:**
    - orthomyxoviruses (influenza),
    - paramyxoviruses (measles, mumps, respiratory tract infections),
    - rubella virus (German measles),
    - rhabdoviruses (rabies),
    - picornaviruses (colds, meningitis, poliomyelitis),
    - retroviruses (acquired immunodeficiency syndrome [AIDS], T-cell leukaemia),
    - arenaviruses (meningitis, Lassa fever),
    - hepadnaviruses (serum hepatitis) and
    - arboviruses (arthropod-borne encephalitis and various febrile illnesses, e.g. yellow fever).



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VIRUSES AND THEIR HOST CELLS:

1. ATTACHMENT

- ✓ Formed vacuoles. Attachment is facilitated by poly peptide binding site on the envelop or capside wich interact with the receptor of host cell.
- ✓ These receptors are generally for cytokines, NTs, hormone, and ion channels.
- ✓ **Reduce the attachment---- immune gamma-glycoproteins**
- ✓ Agents inhibiting host cell penetration by virus. e.g. HBIG (Hepatitis B immunoglobulin), HRIG (Human rabies immunoglobulin), Varicella-Zoster immunoglobulin.

Example of viral infection and Receptor

a. HIV: Helper T-lymphocytes CD4 glycoprotein,
CCR5 receptor for chemokines MCP-1 and RANTES,
CXCR4 chemokine receptor for cytokine SDF-1.

b. Rebies virus: Acetylcholine receptor on skeletal muscle.

c. Adenovirus: MHC molecules.

d. Infantile diarrhoea virus: β-Adrenoceptors.

2. UNCOATING – Uncoating of viral DNA/RNA by host cell

- ✓ The formed virus-receptor complex enter to the host cell by receptor mediated endocytosis after removal of coat by host enzyme.
- ✓ **Prevented by Amentadine/Rimentadine (used in RTI, influenza, Resp. Syncital virus)**
- ✓ Agents binding to surface coats of viruses and stabilising the protein coat so that subsequent uncoating of virus in host cell does not occur. e.g. Disoxaril.

3. **REPLICATION, SYNTHESIS AND PROTEIN SYNTHESIS:**

a. Reverse Transcriptase

- ✓ Viral RNA produces vDNA by Reverse transcriptase enzyme that is inhibited by Reverese transcriptase (vRNA dependent DNA polymerase) inhibitor (**Anti-retro virus—RNA virus)**:
  - NRTIs -Nucleoside RTIs: Zidovudine (AZT), Lamivudine, Stavudine, Didanosin, Abacavir
  - Non NRTIs: Nevirapine, Delavirdine, efavirenz

b. Protease Inhibitor (HIV 1- protease inhibitor)- "NAVIR"

- ✓ A **protease** (also called a **peptidase** or **proteinase**) is any enzyme that performs proteolysis; protein catabolism by hydrolysis of peptide bonds
- ✓ Protease inhibitors prevent viral replication by selectively binding to viral proteases (e.g. HIV-1 protease) and blocking proteolytic cleavage of protein precursors that are necessary for the production of infectious viral particles. **EX-Ritonavir, indinavir, Saquinavir, Lopinavir**
- ✓ **Hepatitis C virus NS3/4A protease inhibitor- "PREVIR"):** asunaprevir, boceprevir, grazoprevir, paritaprevir, simeprevir

c. DNA Synthesis Inhibitors

- ✓ Inhibit the DNA synthesis **(Anti-Herpes simplex and cytomegalovirus CMVvirus):** Idoxuridine, Vidarabine, Acyclovir, Ganciclovir.
- ✓ HSV1- oral, ocular, and Facial infection
- ✓ HSV2- Genital infection

d. **vRNA polymerase inhibitor** (**Anti-Herpes virus**)- Foscarnate

e. Protein Synthasis inhibitor

- ✓ Agent inducing production of intracellular enzymes which inhibit the translation of viral-mRNA to viral protein. e.g. **Human leucocyte interferon.**
- ✓ Agent inhibiting 'late' structural protein synthesis in Variola virus. e.g. Methisazone

4. ASSEMBLY- by virus particle and budding

- ✓ Agents preventing assembly of enveloped mature viral particles. e.g. Rifampicin
- ✓ **Amentadine: inhibit the maturation of viral protein**

5. RELEASE- by lysis

11.2. DRUG CLASSIFICATION

According to the treatment protocol antiviral agents are classified as follows:

I. Treatment of respiratory virus infection

Adamantane derivatives: Amantadine, Rimantadine

II. Treatment of herpes and cytomegalo viruse infection.

a. **Purine nucleotides**: Acyclovir, Ganciclovir, Vidarabine.

b. **Pyrimidine nucleosides**: Trifluouridine, Idoxuridine.

c. **Phosphorus derivatives**: Foscarnet sodium.

III. Treatment of HIV infections

a. RT inhibition.

1. **Purine derivatives**: Didanosine.
2. **Pyrimidine derivative**: Zidovudine, Stavudine.
3. **Non-nucleosides**: Nevirapine, Delaviridine, Efavirenz.

b. **Protease inhibition**: Saquinavir, Indinavir, Ritonavir, Nelfinavir, Amprenavir, Lopinavir.

c. **Integration inhibition**: Zintevir.

IV. **Treatment of Hepatitis C virus infections**

a. PREVIR: asunaprevir, boceprevir, grazoprevir, paritaprevir, simeprevir

11.3. MEDICINAL CHEMISTRY OF ANTIVIRAL DRUGS

I. Adamantane derivatives

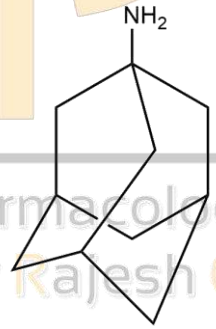
Active only against influenza - A virus. It is also used in the management of Parkinson's disease (Stimulates the release of dopamine nerve terminal and inhibit the presynaptic reuptake.

MOA

- ✓ Amantadine and Rimantadine inhibit the initiation of transcription (vRNA to vDNA) of an early stage between uncoating and viral specific RNA synthesis.
- ✓ They inhibit the viral replication by interfering with the influenza A virus M2 prortein (integral membrane protein) further leads to interfere with the uncoating process and prevent the viral particle assembling during replication.

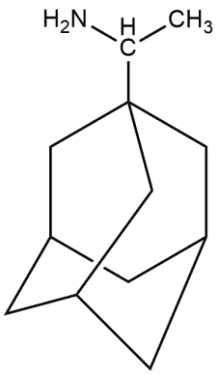
Uses: influenza, RTI, Resp. Syncital virus infection. Also used in idiopathic parkinsonism.

A) Amantadine hydrochloride



(3*s*,5*s*,7*s*)-adamantan-1-amine

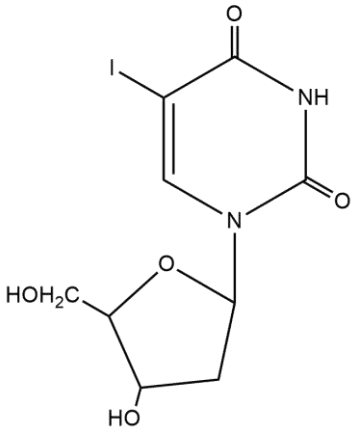
B) Rimantadine hydrochloride



1-((3*r*,5*r*,7*r*)-adamantan-1-yl)ethanamine

II. Anti-herpes Pyrimidine Nucleosides

C) Idoxuridine trifluoride



1-(4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-iodopyrimidine-2,4(1*H*,3*H*)-dione

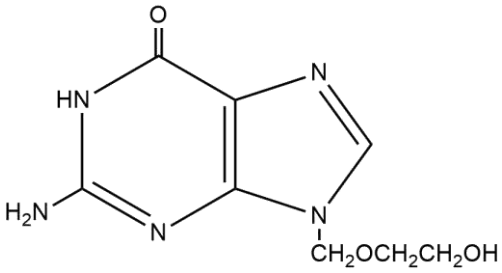
MOA:

- ✓ It is a substituted pyrimidine (Thymidine) analogue and Inhibit DNA synthesis by inhibiting the thymidylate phosphorylase and vDNA polymerase.
- ✓ Idoxuridine gets phosphorylated within the cell and the triphosphate derivative is incorporated into DNA (of both viral and mammalian). Such DNA is more susceptible to breakage and results in faulty transcription.

Uses : Used in the treatment of superficial ***H. simplex*** **keratoconjunctivitis** as 0.5% eye ointment applied every 4 hrs during day and once at bedtime or as 0.1% eyedrops, 1 drop instilled in conjunctival sac every hour during day and every 2 hours during night.

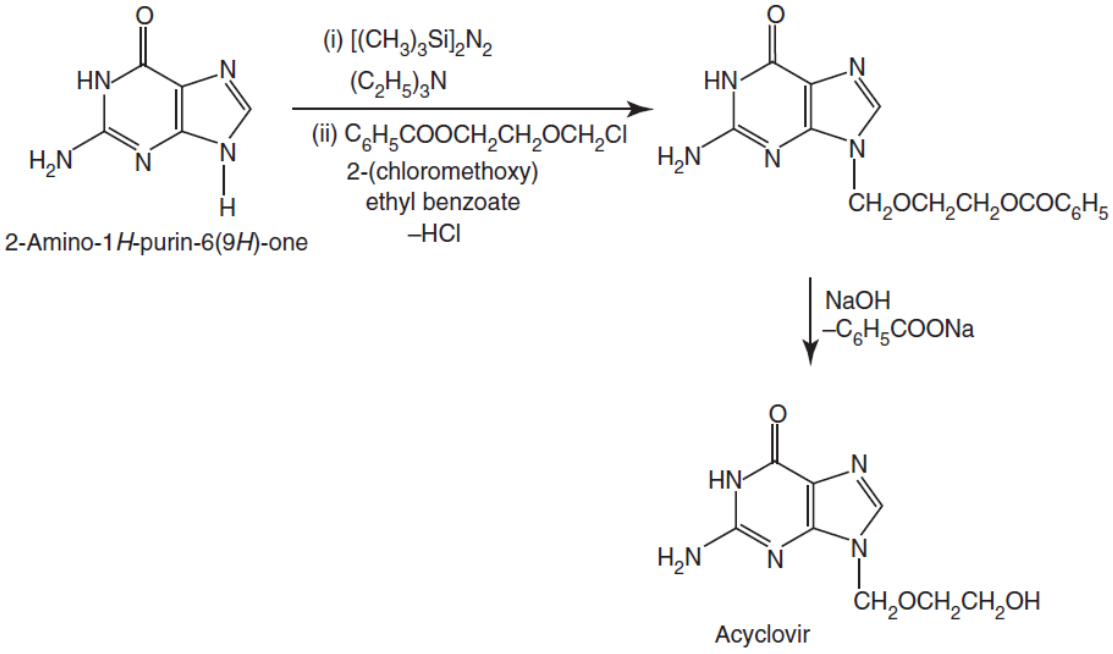
III. Anti-herpes Purine Nucleotides

D) Aciclovir*



2-amino-9-((2-hydroxyethoxy)methyl)-1*H*-purin-6(9*H*)-one

Synthesis:



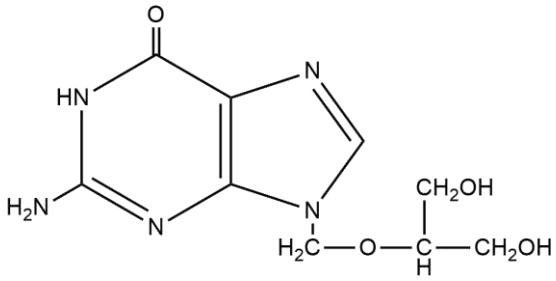
MOA:

- ✓ It is active against *Herpes* viruses particularly *Herpes simplex* virus (HSV) type-l and type-2.
- ✓ The Herpes viruses contain a specific ***thymidine kinase*** which phosphorylates acyclovir to its monophosphate. Further phosphorylation is by host cell ***guanosine monophosphate kinase*** to the diphosphate, which is then phosphorylated to acyclovir triphosphate. Acyclovir triphosphate inhibit ***Herpes* virus *DNA polymerase***. It also get incorporated into viral DNA and terminates biosynthesis of viral DNA strand.

Acyclovir----thymidine kinase (viral)-→**A. monophosphate-----**Guanosine monophosphate kinase---→ A.diP-----→ **Acyclovir triphosphate---inhibit virus *DNA polymerase***

Uses: It is used in the treatment of infections due to ***Herpes simplex* virus and *Varicella-Zoster* virus and Epstein virus.**

E) Gancyclovir



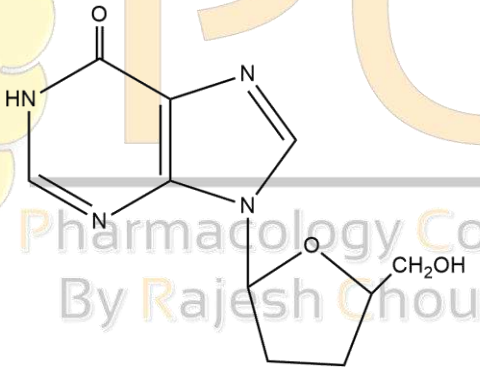
2-amino-9-(((1,3-dihydroxypropan-2-yl)oxy)methyl)-1*H*-purin-6(9*H*)-one

MOA: It is a synthetic guanine derivative. It converts into its active metabolite Ganciclovir-5-triphosphate which inhibits the vDNA polymerase.

Uses: Used to treatment of cytomegalovirus (CMV) infection in immune compromised patients.

IV. Anti-HIV Purine derivatives (RT inhibitor)

F) Didanosine



9-(5-(hydroxymethyl)tetrahydrofuran-2-yl)-1*H*-purin-6(9*H*)-one

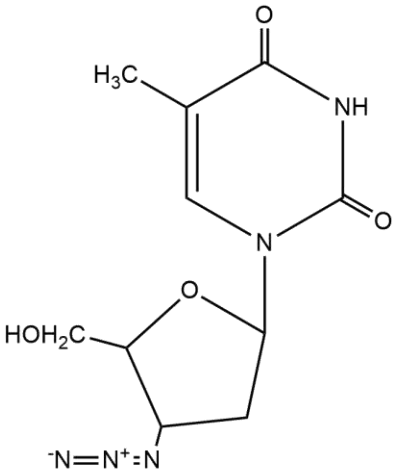
MOA: It is an **inosine analogue**. Mechanism of action is similar to zidovudine (Inhibits the Reverse Transcriptase Enzyme which responsible for conversion of vRNA to vDNA

Didanosine-------T. kinase----→ **Dideoxyadenosine triphosphate-----inhibit RT**

Uses : It is used in the treatment of AIDS. It is also used as an antiviral agent, antimetabolite, antineoplastic agents.

v. Anti-HIV Pyrimidine derivative (RT inhibitor)

G) Zidovudine



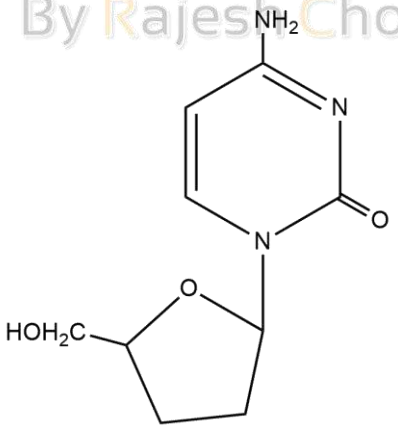
1-(4-azido-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione

.**Mechanism:** It is a thymidine analogue. It is incorporated into the virus and inhibit *vRNA dependent DNA polymerase (reverse transcriptase)* and thereby inhibit viral replication. It also inhibits the viral DNA Chain elongation and v RNA dependant DNA polymerase.

Ziduvudin (ATZ)-------T. kinase----→ **Z. triphosphate-----inhibit RT**

Uses: It is used in the treatment of **AIDS/HIV/retrovirus**. It is also used as an antiviral agent, antimetabolite, antineoplastic agents.

H) Zalcitabine

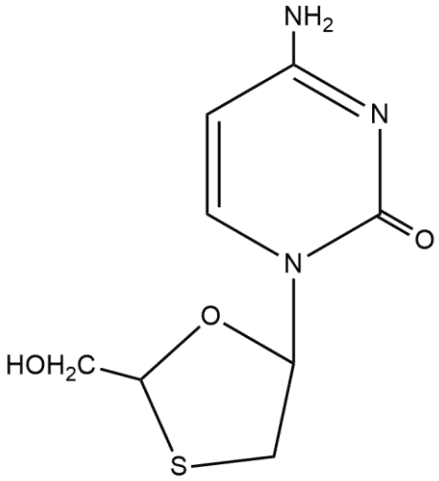


4-amino-1-(5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1*H*)-one

MOA: it converted into active metabolite dideoxycytidine 5'-triphosphate and interfere with the reverse transcriptase enzyme by competing for natural substrate deoxycytidine 5'-triphosphate and further inhibit the DNA Synthesis.

Uses: Along with Zidovudine (AZT), for treatment of HIV infection. And also, useful as antiretroviral protease inhibitor.

I) Lamivudine



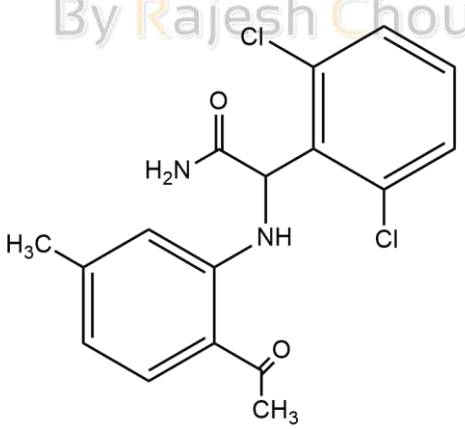
4-amino-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)pyrimidin-2(1*H*)-one

MOA: It is a synthetic nucleotide analogue and phosphorylated intracellularly to its active 5'-triphosphate derivative and inhibit the HIV reverse transcriptase enzyme and HBV polymerase, resulting in DNA chain termination.

Uses: Used in treatment of HIV infection and Hepatitis-B infection

VI. Anti-HIV Non-nucleosides (RT inhibitor)

J) Loviride

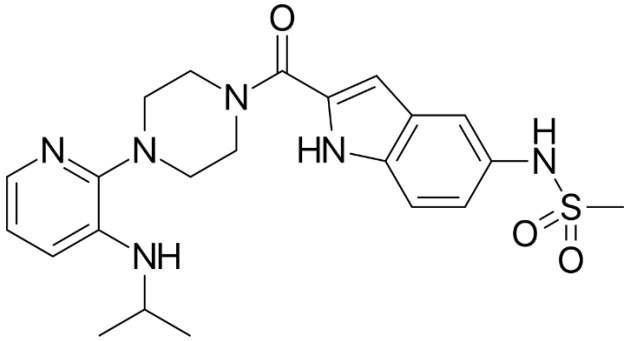


2-((2-acetyl-5-methylphenyl)amino)-2-(2,6-dichlorophenyl)acetamide

MOA: Inhibit the reverse transcriptase enzyme and inhibit the DNA replication

Uses: in HIV infection and chronic Hepatitis-B infection

K) Delavirdin



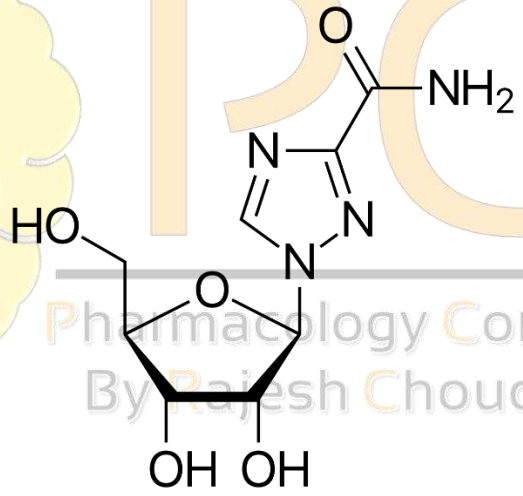
N-[2-[4-[3-(propan-2-ylamino)pyridin-2-yl]piperazine-1-carbonyl]-1H-indol-5-yl]methanesulfonamide

MOA: Inhibit the reverse transcriptase enzyme and inhibit the DNA replication

Uses: used in HIV infection along with other antiviral drugs.

VII. Viral mRNA Polymerase Inhibitor

L) Ribavirin



1-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxy methyl) oxolan-2-yl]-1,2,4-triazole-3-carboxamide

MOA: inhibits the viral mRNA polymerase

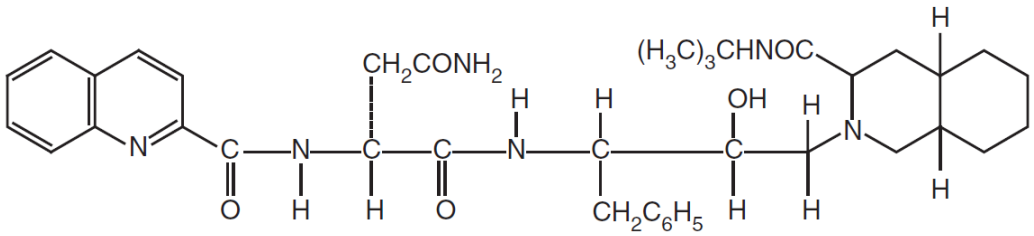
Uses: Treatment of Influenza A and B and used in sever RTI.

VIII. Retroviral Protease Inhibitors

MOA: They inhibit the viral protease enzyme which responsible for proteolysis of large of polyprotein molecules to functional viral protein particles.

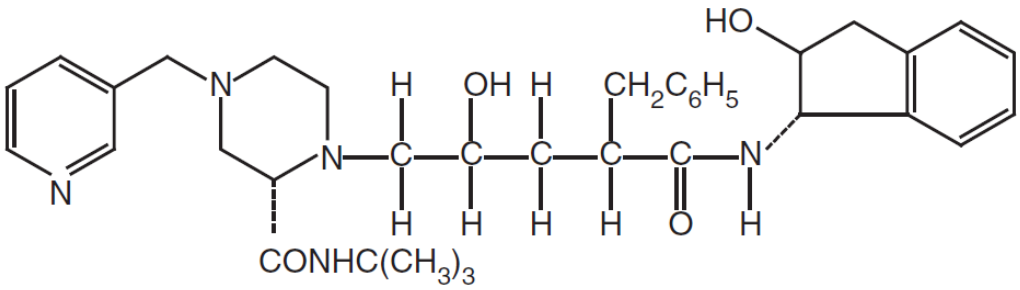
Uses: Mostly used in HIV-1 infection with immunodeficiency along with antiretroviral nucleoside analogues.

M) Saquinavir



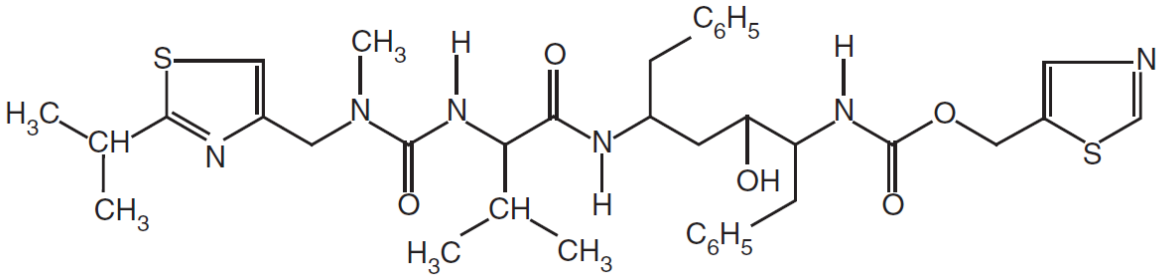
N-[4-[(3-(tert-butylcarbamoyl)-3,4,4a,5,6,7,8,8a-octahydro-1H-isoquinolin-2-yl]-3-hydroxy-1-phenylbutan-2-yl]-2-(quinoline-2-carbonylamino) butanediamide

N) Indinavir



1-[4-benzyl-2-hydroxy-5-[[(2-hydroxy-2,3-dihydro-1H-inden-1-yl]amino]-5-oxopentyl]-N-tert-butyl-4-(pyridin-3-yl methyl)piperazine-2-carboxamide

O) Ritonavir



1,3-thiazol-5-ylmethyl N-[3-hydroxy-5-(3-methyl-2-[[methyl-[(2-propan-2-yl-1,3-thiazol-4-yl)methyl]carbamoyl]amino]butanoyl]amino]-1,6-diphenylhexan-2-yl] carbamate