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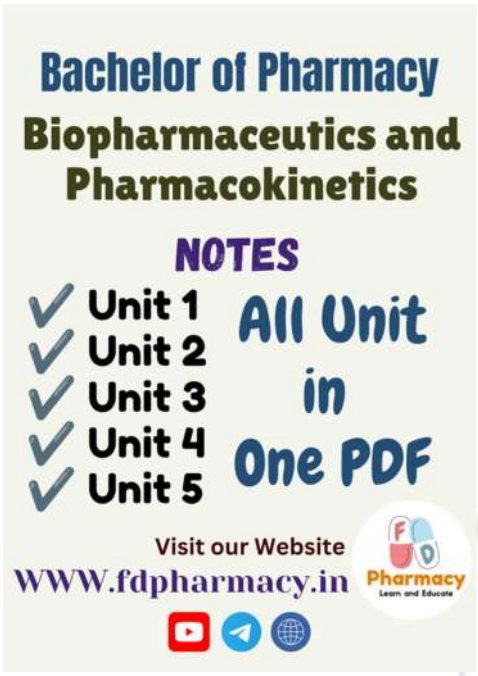
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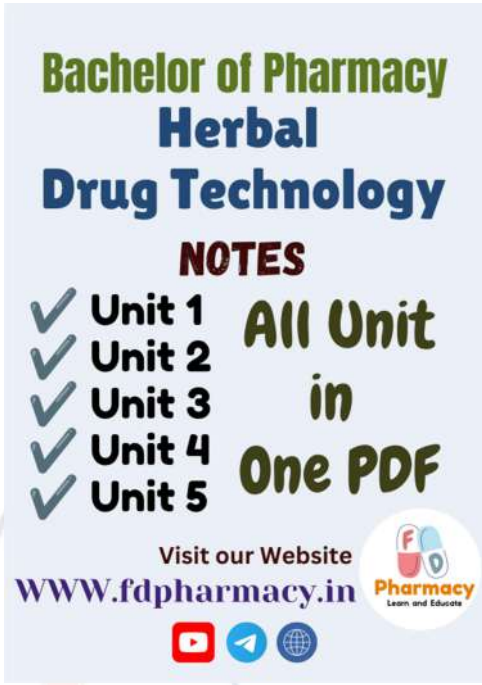
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MEDICINAL CHEMISTRY - III

UNIT 3

TOPIC :

- **Antiviral agents :**

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

Antiviral Agents

- Antiviral agents are drugs that inhibit the growth or replication of viruses.
- Unlike antibiotics, they do not kill the virus directly but prevent virus multiplication in host cells.
- They are used to treat viral infections like:
    - Influenza
    - Herpes simplex virus (HSV) infections
    - HIV/AIDS
    - Hepatitis B and C
    - Varicella-Zoster virus infections

Characteristics of Antiviral Agents

- Act inside the host cell where viruses replicate
- May be virustatic (inhibit replication) or virucidal (kill virus)
- Often have narrow spectrum of activity
- Can cause toxicity to host cells due to selective action

Classification of Antiviral Agents

Antiviral agents can be classified based on **mechanism of action** or **type of virus**.

A. Based on Mechanism of Action

Entry Inhibitors

- Block virus from entering host cells
- Example: Maraviroc (HIV), Enfuvirtide (HIV)

Nucleoside/Nucleotide Analogues

- Mimic viral nucleotides, inhibit viral DNA/RNA synthesis

- Examples: Acyclovir (HSV), Ganciclovir (CMV), Tenofovir (HIV, HBV)

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- Bind to reverse transcriptase and inhibit viral replication
- Example: Nevirapine, Efavirenz (HIV)

Protease Inhibitors

- Inhibit viral protease enzyme, preventing maturation of viral particles
- Examples: Ritonavir, Saquinavir (HIV)

Integrase Inhibitors

- Inhibit viral integrase enzyme, preventing viral DNA integration into host genome
- Examples: Raltegravir, Dolutegravir (HIV)

Neuraminidase Inhibitors

- Inhibit neuraminidase enzyme, preventing release of influenza virus
- Examples: Oseltamivir, Zanamivir

Interferons

- Proteins produced naturally by host cells
- Enhance immune response against viruses
- Examples: IFN-α (Hepatitis B & C)

B. Based on Type of Virus

- **Anti-Herpesvirus Agents** – Acyclovir, Ganciclovir
- **Anti-Influenza Agents** – Oseltamivir, Zanamivir, Amantadine
- **Anti-HIV Agents** – Zidovudine, Tenofovir, Ritonavir
- **Anti-Hepatitis Agents** – Lamivudine, Interferons
- **Anti-Cytomegalovirus (CMV) Agents** – Ganciclovir, Foscarnet

Mechanism of Action (Examples)

Drug	Virus	Mechanism
Acyclovir	HSV, VZV	Nucleoside analogue → inhibits viral DNA polymerase
Oseltamivir	Influenza	Neuraminidase inhibitor → prevents virus release
Zidovudine (AZT)	HIV	Nucleoside reverse transcriptase inhibitor → inhibits viral DNA synthesis
Ritonavir	HIV	Protease inhibitor → prevents viral maturation
Interferon-α	HBV, HCV	Enhances host antiviral immune response

Indications

- Herpes simplex infections – Acyclovir
- Varicella-Zoster virus – Acyclovir, Valacyclovir
- HIV/AIDS – Zidovudine, Tenofovir, Ritonavir
- Hepatitis B and C – Lamivudine, Interferon-α
- Influenza – Oseltamivir, Zanamivir

Adverse Effects

Drug	Adverse Effects
Acyclovir	Nausea, vomiting, nephrotoxicity (IV)
Ganciclovir	Bone marrow suppression, neutropenia
Zidovudine	Anemia, myopathy
Protease inhibitors	Hyperlipidemia, insulin resistance
Interferons	Flu-like symptoms, depression, hepatotoxicity
Oseltamivir	Nausea, vomiting, headache

Amantadine Hydrochloride

- Amantadine hydrochloride is a synthetic antiviral agent with activity against influenza A virus.
- It is also used in neurology for Parkinson's disease and drug-induced extrapyramidal symptoms due to its dopaminergic activity.
- Amantadine is well absorbed orally, widely distributed, and excreted unchanged in urine.

Classification

Based on Chemical Class

- Tricyclic amine
- Adamantane derivative

Based on Antiviral Action

- Inhibits viral replication of influenza A
- Ineffective against influenza B

Based on Neurological Use

- Dopamine-releasing agent for Parkinson's disease

Structure

- Consists of a rigid adamantane cage with a primary amino group.

Molecular formula: $C_{10}H_{17}N{\cdot}HCl$

Structural Characteristics

- Tricyclic structure → lipophilic → crosses cell membranes
- Amino group → protonated in acidic medium, aids solubility

Nomenclature

- Amantadine → adamantane derivative with amino substitution
- Hydrochloride → salt form for oral administration
- Available as tablets, capsules, and syrup

Mechanism of Action

Antiviral Action

- Blocks M2 protein ion channel of influenza A virus.
- Prevents acidification of viral interior required for viral uncoating.
- Stops viral replication.

Neurological Action

- Increases dopamine release in CNS.
- Blocks dopamine reuptake, enhancing dopaminergic activity.
- Hence, amantadine has dual action: antiviral and dopaminergic.

Spectrum of Activity

- Influenza viruses: Influenza A (not B)
- Neurological: Parkinson's disease, drug-induced extrapyramidal symptoms

Uses

Antiviral

- Prophylaxis and treatment of influenza A infections

Neurological

- Parkinson's disease (mild to moderate)

Adverse Effects

- CNS: dizziness, insomnia, nervousness, hallucinations
- Gastrointestinal: nausea, vomiting, dry mouth
- Rare: livedo reticularis (skin mottling), edema

Chemical Degradation

- Stable in solid form
- Sensitive to strong acids and bases, Store in cool, dry place

Structure–Activity Relationship (SAR)

- ❖ Adamantane cage → lipophilic, allows membrane penetration
- ❖ Primary amino group → essential for antiviral activity (blocks M2 ion channel)
- ❖ Lipophilicity → enables CNS penetration for Parkinson's effect
- ❖ Dual activity depends on both cage structure and amino substitution

Rimantadine Hydrochloride

- Rimantadine hydrochloride is a synthetic antiviral agent, structurally related to amantadine, with activity primarily against influenza A virus.
- It is better tolerated than amantadine and has less CNS toxicity.
- Rimantadine is orally active, metabolized in the liver, and excreted as metabolites and unchanged drug in urine.

Classification

Based on Chemical Class

- Adamantane derivative
- Tricyclic amine

Based on Antiviral Action

- Inhibits replication of influenza A virus
- Ineffective against influenza B

Based on Use

- Antiviral prophylaxis and treatment

Structure

- Consists of a rigid adamantane cage with a methyl-amino substitution.

Molecular formula: $C_{12}H_{21}N{\cdot}HCl$

Structural Characteristics

- Lipophilic adamantane core → facilitates membrane penetration
- Amino group → protonated at acidic pH, aiding solubility and activity
- Structural modification reduces CNS side effects compared to amantadine

Nomenclature

- Rimantadine → derivative of adamantane with methyl-amino substitution
- Hydrochloride → salt form for oral use
- Available as tablets or syrup

Mechanism of Action

- Inhibits M2 protein ion channel of influenza A virus.
- Prevents acidification of viral interior, blocking viral uncoating.
- Stops viral replication.
- Hence, rimantadine is a specific antiviral against influenza A.

Spectrum of Activity

- Influenza viruses: Influenza A (not B)
- No activity against other viruses

Uses

- Prophylaxis of influenza A infections
- Treatment of influenza A infections in adults and children

Adverse Effects

- CNS: headache, dizziness, insomnia, nervousness (less frequent than amantadine)
- Gastrointestinal: nausea, vomiting, dry mouth
- Rare: mild liver enzyme elevation, allergic reactions
- Caution in renal impairment (dose adjustment may be needed)

Chemical Degradation

- Stable in solid form
- Sensitive to strong acids and bases
- Store in cool, dry place

Structure–Activity Relationship (SAR)

- Adamantane cage → lipophilic, allows viral penetration
- Methyl-amino substitution → enhances antiviral activity, reduces CNS toxicity
- Prevents viral uncoating by blocking M2 ion channel
- Lipophilicity → ensures oral absorption and tissue penetration

Idoxuridine Trifluoride

- Idoxuridine trifluoride is a synthetic antiviral agent primarily used for herpes simplex virus (HSV) infections, especially ocular HSV infections.
- It is a nucleoside analogue that inhibits viral DNA synthesis. Administered topically as eye drops, it is poorly absorbed systemically.

Classification

Based on Chemical Class

- Pyrimidine nucleoside analogue

Based on Antiviral Action

- Inhibits viral DNA replication
- Active against herpes simplex virus (HSV-1 and HSV-2)

Based on Use

- Ophthalmic antiviral agent

Structure

→ Analog of deoxyuridine with:

- Iodine substitution at C-5 → enhances antiviral activity
- Trifluoride modification → increases stability and potency

Molecular formula: $C_9H_{11}F_3IN_2O_5$

Structural Characteristics

- Halogen substitution → interferes with viral DNA polymerase
- Trifluoride → increases chemical stability and ocular retention

Nomenclature

- Ido → iodine substitution
- Xuridine → uridine nucleoside analogue
- Trifluoride → fluorine modification

- Available as 0.1–0.5% ophthalmic solution

Mechanism of Action

- Phosphorylated by viral thymidine kinase to triphosphate form.
- Incorporated into viral DNA during replication.
- Causes base-pairing errors, preventing DNA chain elongation.
- Selectively inhibits viral DNA synthesis without affecting host DNA significantly.
- Hence, idoxuridine trifluoride is a viral DNA synthesis inhibitor.

Spectrum of Activity

- Herpes simplex virus: HSV-1 (ocular), HSV-2 (less common)
- Limited or no activity against varicella-zoster virus, CMV, or systemic viruses

Uses

- Herpes simplex keratitis (ocular infection)
- Corneal epithelial HSV infections
- Topical prophylaxis in recurrent ocular HSV

Adverse Effects

- Local ocular irritation, redness, and burning sensation
- Rare: transient punctate keratitis
- Avoid systemic use due to poor selectivity and bone marrow toxicity

Chemical Degradation

- Sensitive to light and moisture
- Store in refrigerated, dark containers
- Maintain aseptic handling for ophthalmic preparations

Structure–Activity Relationship (SAR)

- Iodine at C-5 → essential for antiviral activity
- Trifluoride group → increases stability and potency
- Acts as thymidine analogue, incorporated into viral DNA → inhibits replication
- Topical application maximizes ocular concentration and minimizes systemic toxicity

Ganciclovir

→ Ganciclovir is a synthetic nucleoside analogue antiviral primarily active against cytomegalovirus (CMV) and other herpesviruses.
It is structurally similar to guanosine and inhibits viral DNA synthesis.
→ Ganciclovir is used in immunocompromised patients, including transplant recipients and those with HIV/AIDS.

Classification

Based on Chemical Class

- Purine nucleoside analogue
- Guanine derivative

Based on Antiviral Action

- Inhibits viral DNA polymerase
- Selective for virus-infected cells

Based on Use

- Anti-CMV and anti-herpesvirus agent

Structure

- Acyclic nucleoside analogue of 2'-deoxyguanosine
- Contains:
  - Guanine base
  - Open-chain sugar moiety (acyclic)

Molecular formula: $C_9H_{13}N_5O_4$

Structural Characteristics

- Acyclic sugar → allows incorporation into viral DNA
- Guanine base → recognized by viral DNA polymerase
- Hydroxyl groups → allow phosphorylation by viral kinases

Nomenclature

- Gan → guanine analogue
- Cyclovir → antiviral activity
- Available as oral capsules, IV infusion, and ophthalmic gel

Mechanism of Action

- Ganciclovir is monophosphorylated by viral kinases (e.g., CMV UL97 kinase).
- Converted to ganciclovir triphosphate by cellular kinases.
- Triphosphate form is incorporated into viral DNA by viral DNA polymerase.
- Causes chain termination due to lack of 3'-OH group.
- Selectively inhibits viral DNA synthesis in infected cells.
- Hence, ganciclovir is a viral DNA synthesis inhibitor.

Spectrum of Activity

- Cytomegalovirus (CMV) – main activity
- Herpes simplex virus (HSV-1, HSV-2) – moderate activity
- Varicella-zoster virus (VZV) – moderate activity
- Limited activity against other DNA viruses

Uses

- CMV retinitis in immunocompromised patients
- CMV prophylaxis in organ transplant recipients
- HSV and VZV infections (in immunocompromised patients)

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- CNS: headache, confusion, tremor

Chemical Degradation

- Sensitive to light and moisture, Stable at acidic and neutral pH
- Store in cool, dry place, protected from light

Structure–Activity Relationship (SAR)

- Acyclic sugar moiety → allows incorporation into viral DNA → chain termination
- Guanine base → recognized by viral DNA polymerase
- Phosphorylation by viral kinases → confers selectivity for infected cells
- Triphosphate form → active form incorporated into viral DNA
- Enhanced activity against CMV compared to acyclovir due to better phosphorylation by CMV kinase

Zidovudine (AZT – Azidothymidine)

- Zidovudine (AZT) is a synthetic nucleoside reverse transcriptase inhibitor (NRTI) used for HIV infection.
- It is a thymidine analogue that inhibits viral reverse transcriptase, preventing viral DNA synthesis from RNA.
- Zidovudine is orally active and also available for IV use, with good tissue penetration including the CNS.

Classification

Based on Chemical Class

- Nucleoside analogue
- Thymidine derivative

Based on Antiviral Action

- Reverse transcriptase inhibitor (NRTI)
- Inhibits HIV replication

Based on Use

- Anti-HIV agent
- Used for prophylaxis and treatment

Structure

- Thymidine analogue with azido ($-N_3$) group at 3'-position

Molecular formula: $C_{10}H_{13}N_5O_4$

Structural Characteristics

- Azido group → prevents formation of 3'-5' phosphodiester bond → chain termination
- Hydroxyl and sugar moieties → allow phosphorylation by cellular kinases

Nomenclature

- Zido → azido substitution
- Vudine → thymidine derivative
- Available as oral capsules, tablets, syrup, and IV infusion

Mechanism of Action

- Zidovudine is phosphorylated by cellular kinases to zidovudine triphosphate.
- Triphosphate form competes with thymidine triphosphate for incorporation into viral DNA.
- Incorporation into viral DNA causes chain termination (absence of 3'-OH).
- Selectively inhibits HIV reverse transcriptase without affecting host DNA significantly.
- Hence, zidovudine is a viral DNA chain terminator and reverse transcriptase inhibitor.

Spectrum of Activity

- Human immunodeficiency virus type 1 (HIV-1)
- Human immunodeficiency virus type 2 (HIV-2) (less potent)
- Minimal activity against other retroviruses

Uses

- Treatment of HIV infection (part of HAART)
- Prevention of mother-to-child transmission (PMTCT) of HIV

Adverse Effects

- Hematologic: anemia, neutropenia (dose-related)
- Gastrointestinal: nausea, vomiting, diarrhea
- CNS: headache, insomnia, myopathy
- Rare: lactic acidosis, hepatomegaly with steatosis

Chemical Degradation

- Sensitive to light and moisture, Stable at acidic and neutral pH
- Store in cool, dry place, protected from light

Structure–Activity Relationship (SAR)

- Azido group at 3'-position → prevents DNA chain elongation
- Thymidine base → recognized by HIV reverse transcriptase
- Triphosphate form → active moiety incorporated into viral DNA
- Selectivity depends on preference of viral reverse transcriptase over host DNA polymerase
- Oral absorption and tissue penetration facilitated by sugar moiety

Didanosine (ddI)

- Didanosine (ddI) is a synthetic nucleoside reverse transcriptase inhibitor (NRTI) used for HIV infection.
- It is a purine nucleoside analogue that inhibits viral reverse transcriptase, preventing conversion of viral RNA to DNA.
- Didanosine is orally active, often formulated as enteric-coated tablets or buffered powder to improve stability in acidic gastric conditions.

Classification

Based on Chemical Class
- Purine nucleoside analogue
- Hypoxanthine derivative

Based on Antiviral Action
- Reverse transcriptase inhibitor (NRTI)
- Prevents viral DNA synthesis

Based on Use
- Anti-HIV agent
- Used in combination therapy (HAART)

Structure

- Nucleoside analogue of inosine
- Lacks 3'-OH group → prevents DNA chain elongation
- Molecular formula: $C_{10}H_{12}N_4O_3$

Structural Characteristics

- 3'-deoxy structure → causes chain termination
- Purine base (hypoxanthine) → recognized by HIV reverse transcriptase
- Sugar moiety allows phosphorylation by cellular kinases

Nomenclature

- Didanosine → "di" (two modifications) + "danosine" (analogue of inosine)
- Available as enteric-coated tablets, buffered powder for oral suspension, and IV formulation

Mechanism of Action

- Didanosine is phosphorylated by cellular kinases to didanosine triphosphate (ddATP).
- ddATP competes with natural deoxyadenosine triphosphate for incorporation into viral DNA.
- Incorporation results in DNA chain termination due to absence of 3'-OH.
- Selectively inhibits HIV reverse transcriptase without affecting host DNA significantly.
- Hence, didanosine is a viral DNA chain terminator and NRTI.

Spectrum of Activity

- HIV-1 – primary target
- HIV-2 – less potent
- Minimal activity against other retroviruses

Uses

- Treatment of HIV infection (as part of combination HAART therapy)
- Post-exposure prophylaxis (PEP) in combination with other NRTIs

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea, abdominal pain
- Pancreatitis (serious, dose-related)
- Peripheral neuropathy

Chemical Degradation

- Unstable in acidic medium → must be enteric-coated or buffered
- Sensitive to moisture and heat, Store in cool, dry place

Structure–Activity Relationship (SAR)

- 3'-deoxy sugar → prevents DNA chain elongation → chain termination
- Purine (inosine) base → recognized by HIV reverse transcriptase
- Triphosphate form → active moiety incorporated into viral DNA
- Enteric coating → protects drug from acid degradation
- Selectivity depends on preference of viral reverse transcriptase over host DNA polymerase

Zalcitabine (ddC)

- Zalcitabine (ddC) is a synthetic nucleoside reverse transcriptase inhibitor (NRTI) used for HIV infection.
- It is a cytidine analogue that inhibits HIV reverse transcriptase, preventing conversion of viral RNA to DNA.
- Zalcitabine is orally active, rapidly absorbed, and primarily excreted unchanged in urine.

Classification

Based on Chemical Class

- Pyrimidine nucleoside analogue
- Cytidine derivative

Based on Antiviral Action

- Reverse transcriptase inhibitor (NRTI)
- Prevents viral DNA synthesis

Based on Use

- Anti-HIV agent
- Used in combination therapy (HAART)

Structure

- Nucleoside analogue of cytidine
- Lacks 3'-OH group → prevents DNA chain elongation

Molecular formula: $C_9H_{13}N_3O_3$

Structural Characteristics

- 3'-deoxy structure → causes chain termination
- Cytosine base → recognized by HIV reverse transcriptase
- Sugar moiety → allows phosphorylation by cellular kinases

Nomenclature

- Zalcitabine → "zal" (modified) + "citabine" (cytidine analogue)
- Available as oral tablets and oral solution

Mechanism of Action

- Zalcitabine is phosphorylated by cellular kinases to zalcitabine triphosphate (ddCTP).
- ddCTP competes with natural deoxycytidine triphosphate for incorporation into viral DNA.
- Incorporation results in DNA chain termination due to absence of 3'-OH.
- Selectively inhibits HIV reverse transcriptase without affecting host DNA significantly.
- Hence, zalcitabine is a viral DNA chain terminator and NRTI.

Spectrum of Activity

- HIV-1 – primary target
- HIV-2 – less potent
- Minimal activity against other retroviruses

Uses

- Treatment of HIV infection (in combination therapy)
- Often combined with zidovudine (AZT) for synergistic effect
- Reserved for patients with resistance or intolerance to other NRTIs

Adverse Effects

- Peripheral neuropathy (dose-limiting, most common)
- Gastrointestinal: nausea, vomiting, diarrhea
- Oral ulcers

Chemical Degradation

- Stable in solid form, Sensitive to light and moisture
- Store in cool, dry place

Structure–Activity Relationship (SAR)

- 3'-deoxy sugar → prevents DNA chain elongation → chain termination
- Cytosine base → recognized by HIV reverse transcriptase
- Triphosphate form → active moiety incorporated into viral DNA
- High oral absorption → allows systemic activity
- Selectivity depends on preference of viral reverse transcriptase over host DNA polymerase

Lamivudine (3TC)

- Lamivudine (3TC) is a synthetic nucleoside reverse transcriptase inhibitor (NRTI) used in HIV and hepatitis B virus (HBV) infections.
- It is a cytidine analogue that inhibits viral reverse transcriptase, preventing viral RNA conversion to DNA.
- Lamivudine is well absorbed orally, has good bioavailability, and is primarily excreted unchanged in urine.

Classification

Based on Chemical Class

- Pyrimidine nucleoside analogue
- Cytidine derivative

Based on Antiviral Action

- Reverse transcriptase inhibitor (NRTI)
- Causes viral DNA chain termination

Based on Use

- Anti-HIV agent
- Anti-HBV agent

Structure

- Analogue of cytidine
- Contains modified sugar with 3'-thio group

Molecular formula: $C_8H_{11}N_3O_3S$

Structural Characteristics

- 3'-thio modification → prevents DNA chain elongation
- Cytosine base → recognized by viral reverse transcriptase
- Sugar moiety → allows phosphorylation by cellular kinases

Nomenclature

- Lami → lamivudine
- Vudine → nucleoside analogue suffix
- Available as oral tablets, oral solution, and combination formulations (e.g., with zidovudine or tenofovir)

Mechanism of Action

- Lamivudine is phosphorylated by cellular kinases to lamivudine triphosphate (3TCTP).
- 3TCTP competes with natural deoxycytidine triphosphate for incorporation into viral DNA.
- Incorporation results in DNA chain termination due to absence of 3'-OH.
- Selectively inhibits HIV reverse transcriptase and HBV polymerase.
- Hence, lamivudine is a viral DNA chain terminator and NRTI.

Spectrum of Activity

- HIV-1 – primary activity
- HIV-2 – moderate activity
- Hepatitis B virus (HBV) – inhibits DNA polymerase
- Minimal activity against other viruses

Uses

- Treatment of HIV infection (part of HAART)
- Treatment of chronic hepatitis B infection

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- CNS: headache, fatigue, dizziness
- Rare: pancreatitis, hepatic dysfunction

Chemical Degradation

- Stable in solid form, Sensitive to light and moisture
- Store in cool, dry place

Structure–Activity Relationship (SAR)

- 3'-thio modification → prevents DNA chain elongation → chain termination
- Cytosine base → recognized by viral reverse transcriptase and HBV polymerase
- Triphosphate form → active moiety incorporated into viral DNA
- High oral absorption → systemic activity
- Selectivity depends on preference of viral polymerases over host DNA polymerase

Loviride

- Loviride (Delavirdine) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used for HIV-1 infection.
- It binds directly to HIV-1 reverse transcriptase, causing a conformational change that inhibits viral DNA synthesis.
- Loviride is orally active, metabolized in the liver, and primarily excreted via feces.

Classification

Based on Chemical Class

- Non-nucleoside reverse transcriptase inhibitor (NNRTI)
- Pyrimidine derivative

Based on Antiviral Action

- Allosteric inhibitor of HIV-1 reverse transcriptase
- Does not require phosphorylation

Based on Use

- Anti-HIV-1 agent (used in combination therapy)

Structure

- Pyrimidine derivative with diarylpyrimidine moiety

Molecular formula: $C_{18}H_{20}N_6S$

Structural Characteristics

- Lipophilic structure → good oral absorption
- Binds to hydrophobic pocket of HIV-1 reverse transcriptase
- No need for phosphorylation → rapid onset of action

Nomenclature

- Delavirdine → generic name
- Loviride → brand name

- Available as oral tablets (100–200 mg)

Mechanism of Action

- Loviride binds non-competitively to HIV-1 reverse transcriptase at the allosteric site.
- Causes conformational change in the enzyme.
- Prevents RNA-dependent and DNA-dependent DNA polymerase activity.
- Inhibits viral DNA synthesis.
- Hence, loviride is a non-nucleoside reverse transcriptase inhibitor (NNRTI).

Spectrum of Activity

- HIV-1 – effective
- HIV-2 – not effective
- No activity against other viruses

Uses

- Treatment of HIV-1 infection in combination with NRTIs
- Part of HAART regimen
- Often used when patients are resistant or intolerant to other NRTIs

Adverse Effects

- Rash (common, mild to moderate)
- Gastrointestinal: nausea, vomiting, diarrhea
- Hepatotoxicity (rare)

Chemical Degradation

- Stable in solid form
- Sensitive to light and moisture
- Store in cool, dry place

Structure–Activity Relationship (SAR)

- Diarylpyrimidine moiety → essential for allosteric binding to HIV-1 reverse transcriptase
- Lipophilic structure → oral bioavailability and tissue penetration
- Non-nucleoside structure → does not require phosphorylation
- Selectivity due to binding to hydrophobic pocket present only in HIV-1 reverse transcriptase

Ribavirin

- Ribavirin is a synthetic broad-spectrum antiviral nucleoside analogue effective against RNA and some DNA viruses.
- It is a guanosine analogue that inhibits viral RNA synthesis and replication.
- Ribavirin is used systemically (oral or IV) and inhalationally for respiratory viral infections.

Classification

Based on Chemical Class

- Purine nucleoside analogue
- Guanosine derivative

Based on Antiviral Action

- Inhibits viral RNA polymerase
- Interferes with viral mRNA synthesis

Based on Use

- Broad-spectrum antiviral agent
- Used for respiratory syncytial virus (RSV), hepatitis C (with interferon), and viral hemorrhagic fevers

Structure

- Guanosine analogue with a triazole carboxamide moiety

Molecular formula: $C_8H_{12}N_4O_5$

Structural Characteristics

- Triazole ring → interferes with viral polymerase
- Sugar moiety → allows phosphorylation by cellular kinases
- Mimics guanosine → incorporated into viral RNA

Nomenclature

- Riba → ribose analogue
- Virin → antiviral
- Available as oral tablets, capsules, IV solution, and aerosol

Mechanism of Action

- Ribavirin is phosphorylated by cellular kinases to ribavirin triphosphate.
- Competes with GTP → inhibits viral RNA-dependent RNA polymerase.
- Causes impaired viral RNA synthesis and mutagenesis of viral genome.
- Broad-spectrum action due to interference with viral RNA replication.
- Hence, ribavirin is a viral RNA synthesis inhibitor.

Spectrum of Activity

- RNA viruses: RSV, influenza A & B, HCV, Lassa virus, Hantavirus
- Some DNA viruses: limited activity
- Not effective against all viruses → best for respiratory and hemorrhagic viral infections

Uses

- ❖ Respiratory syncytial virus (RSV) infections in infants
- ❖ Chronic hepatitis C (with interferon)
- ❖ Lassa fever, Hantavirus infections
- ❖ Occasionally for other severe viral hemorrhagic fevers

Adverse Effects

- Hematologic: hemolytic anemia
- Gastrointestinal: nausea, vomiting, diarrhea
- CNS: headache, fatigue

Chemical Degradation

- Sensitive to light and moisture, Stable at acidic pH
- Store in cool, dry place, protected from light

Structure–Activity Relationship (SAR)

- Triazole carboxamide moiety → inhibits viral RNA polymerase
- Guanosine mimic → incorporated into viral RNA → mutagenesis
- Triphosphate form → active form inhibiting viral RNA synthesis
- Broad-spectrum activity due to interference with multiple RNA viruses

SAQUINAVIR

- Saquinavir is a synthetic antiretroviral agent classified as a protease inhibitor (PI).
- It inhibits HIV-1 and HIV-2 protease, preventing viral polyprotein processing into mature, infectious virions.
- Saquinavir is used orally in combination with other antiretrovirals as part of HAART therapy.

Classification

Based on Chemical Class

- Peptidomimetic protease inhibitor
- Structurally mimics polypeptide substrate of HIV protease

Based on Antiviral Action

- HIV protease inhibitor
- Prevents viral maturation

Based on Use

- Anti-HIV agent
- Used in combination therapy (HAART)

Structure

- Peptidomimetic structure with hydroxyethylene scaffold
- Contains:
  - Aromatic groups
  - Polar hydroxyl group
  - Amide bonds mimicking natural peptide substrate

Molecular formula: $C_{38}H_{50}N_6O_5$

Structural Characteristics

- Hydroxyethylene group → mimics the transition state of protease cleavage
- Aromatic side chains → increase lipophilicity and protease binding
- Peptidomimetic backbone → resists enzymatic degradation

Nomenclature

- Saquinavir → generic name
- Available as oral soft-gel capsules or tablets

Mechanism of Action

- Saquinavir binds reversibly to the active site of HIV protease.
- Prevents cleavage of Gag and Gag-Pol polyproteins.
- Results in incomplete, non-infectious virions.
- Does not affect host proteases significantly.
- Hence, saquinavir is a viral maturation inhibitor.

Spectrum of Activity

- HIV-1 – primary activity
- HIV-2 – moderate activity
- No activity against other viruses

Uses

- Treatment of HIV-1 infection in combination with NRTIs and/or NNRTIs
- Part of HAART regimen to reduce viral load and increase CD4 counts
- Used for treatment-experienced patients

Adverse Effects

- Gastrointestinal: nausea, diarrhea, abdominal discomfort
- CNS: headache, insomnia, dizziness
- Metabolic: hyperlipidemia, hyperglycemia

Chemical Degradation

- Sensitive to light and moisture
- Stable at acidic pH
- Store in cool, dry place, protected from light

Structure–Activity Relationship (SAR)

- Hydroxyethylene scaffold → mimics peptide bond cleavage transition state → inhibits protease
- Aromatic side chains → enhance binding to hydrophobic pockets of HIV protease
- Peptidomimetic backbone → resists enzymatic degradation → improves bioavailability
- Combination with ritonavir → inhibits CYP3A4 metabolism → increases saquinavir plasma levels

Indinavir

- Indinavir is a synthetic antiretroviral agent classified as a HIV protease inhibitor (PI).
- It inhibits HIV-1 and HIV-2 protease, preventing cleavage of viral polyproteins into mature, infectious virions.
- Indinavir is orally active and used in combination with other antiretrovirals as part of HAART therapy.

Classification

Based on Chemical Class

- Peptidomimetic protease inhibitor
- Mimics natural polypeptide substrate of HIV protease

Based on Antiviral Action

- HIV protease inhibitor
- Prevents viral maturation

Based on Use

- Anti-HIV agent
- Used in combination therapy (HAART)

Structure

- Peptidomimetic structure with hydroxyethylene scaffold
- Contains:
  - Aromatic groups
  - Polar hydroxyl group
  - Amide bonds mimicking protease substrate

Molecular formula: $C_{36}H_{47}N_5O_4$

Structural Characteristics

- Hydroxyethylene group → mimics transition state of protease cleavage
- Aromatic side chains → improve lipophilicity and binding
- Peptidomimetic backbone → resists enzymatic degradation

Nomenclature

- Indinavir → generic name
- Available as oral capsules and solution

Mechanism of Action

- Indinavir binds to the active site of HIV protease.
- Prevents cleavage of Gag and Gag-Pol polyproteins.
- Results in immature, non-infectious virions.
- Does not significantly affect host proteases.Hence, indinavir is a viral
- maturation inhibitor.

Spectrum of Activity

- HIV-1 – primary activity
- HIV-2 – moderate activity
- No activity against other viruses

Uses

- Treatment of HIV-1 infection in combination with NRTIs and/or NNRTIs
- Part of HAART regimen to reduce viral load and increase CD4 counts
- Used for treatment-experienced patients

Adverse Effects

- Gastrointestinal: nausea, diarrhea, abdominal discomfort
- CNS: headache, dizziness, insomnia
- Metabolic: hyperbilirubinemia, nephrolithiasis, hyperlipidemia

Chemical Degradation

- Sensitive to light and moisture
- Stable at acidic pH, Store in cool, dry place, protected from light

Structure–Activity Relationship (SAR)

- Hydroxyethylene scaffold → mimics peptide bond cleavage transition state → inhibits protease
- Aromatic side chains → enhance hydrophobic binding in HIV protease
- Peptidomimetic backbone → resists enzymatic degradation → improves bioavailability
- Administered with ritonavir → CYP3A4 inhibition increases indinavir plasma levels

Ritonavir

- Ritonavir is a synthetic antiretroviral agent classified as a HIV protease inhibitor (PI).
- It inhibits HIV-1 and HIV-2 protease, preventing cleavage of viral polyproteins into mature, infectious virions.
- Additionally, ritonavir is widely used as a pharmacokinetic booster due to its CYP3A4 inhibitory activity, increasing plasma levels of other protease inhibitors.

Classification

Based on Chemical Class

- Peptidomimetic protease inhibitor
- Contains hydroxyethylene scaffold

Based on Antiviral Action

- HIV protease inhibitor
- Prevents viral maturation
- CYP3A4 inhibitor → boosts other PIs

Based on Use

- Anti-HIV agent
- Pharmacokinetic enhancer (booster) in HAART

Structure

- Peptidomimetic with **hydroxyethylene scaffold**
- Contains:
  - Aromatic groups
  - Polar hydroxyl group
  - Amide bonds mimicking HIV protease substrate

Molecular formula: $C_{37}H_{48}N_6O_5S$

Structural Characteristics

- Hydroxyethylene group → mimics transition state of protease cleavage
- Aromatic and sulfur-containing side chains → increase lipophilicity and protease binding
- Peptidomimetic backbone → resistant to enzymatic degradation

Nomenclature

- Ritonavir → generic name
- Brand names include Norvir
- Available as oral capsules, tablets, and solution

Mechanism of Action

- ❖ Ritonavir binds reversibly to the active site of HIV protease.
- ❖ Prevents cleavage of Gag and Gag-Pol polyproteins.
- ❖ Leads to immature, non-infectious viral particles.
- ❖ Inhibits CYP3A4 enzyme → increases plasma concentration of co-administered protease inhibitors.
- ❖ Hence, ritonavir acts as both a viral maturation inhibitor and a pharmacokinetic enhancer.

Spectrum of Activity

- HIV-1 – primary activity
- HIV-2 – moderate activity
- No activity against other viruses

Uses

- Treatment of HIV-1 infection in combination with other NRTIs or NNRTIs
- Boosting other protease inhibitors (e.g., lopinavir, saquinavir, indinavir)
- Part of HAART regimen to reduce viral load and increase CD4 counts

Adverse Effects

- Gastrointestinal: nausea, diarrhea, vomiting
- CNS: headache, dizziness, paresthesia
- Metabolic: hyperlipidemia, hyperglycemia, insulin resistance
- Hepatotoxicity (rare)
- Long-term use → fat redistribution, lipodystrophy
- Drug interactions due to CYP3A4 inhibition

Chemical Degradation

- Sensitive to light and moisture
- Stable in solid form
- Store in cool, dry place, protected from light

Structure–Activity Relationship (SAR)

- ⇨ Hydroxyethylene scaffold → mimics peptide bond cleavage transition state → inhibits protease
- ⇨ Aromatic and sulfur side chains → enhance binding to hydrophobic pocket of HIV protease
- ⇨ Peptidomimetic backbone → resists enzymatic degradation → improves bioavailability
- ⇨ CYP3A4 inhibitory property → boosts plasma levels of other protease inhibitors