Program	B. Pharmacy
Semester	VI
Subject /Course	Medicinal Chemistry III
Subject/Course ID	BP 601T
Module No.	03
Module Title	Anti-infective agents
Course coordinator	Noel
Mobile No.	6280907651
Email id	noelchem00@gmail.com

Learning Outcome of module-3

LO	Learning Outcome (LO)	Course Outcome Code
LO1	To Understand the metabolism, adverse effects and therapeutic value of drugs.	BP601.1
LO2	To Understand the mechanism of action & importance of SAR of drugs.	BP601.3 BP601.4

CONTENT OF MODULE

Topics
Anti-Tubercular Agents Synthetic Anti-Tubercular Agents Isoniozid*, Ethionamide, Ethambutol, Pyrazinamide, Para amino salicylic acid*. Anti-Tubercular Antibiotics Rifampicin, Rifabutin, Cycloserine Streptomycine, Capreomycin sulphate.
Urinary Tract Anti-Infective Agents Quinolones SAR of quinolones, Nalidixic Acid, Norfloxacin, Enoxacin, Ciprofloxacin*, Ofloxacin, Lomefloxacin, Sparfloxacin, Gatifloxacin, Moxifloxacin. Miscellaneous Furazoloidine, Nitrofurantoin*, Methanamine.
Antiviral Agents Amantadine hydrochloride, Rimantadine hydrochloride, Idoxuridine trifluoride, Acyclovir*, Gancyclovir, Zidovudine, Didanosine, Zalcitabine, Lamivudine, Loviride, Delavirding, Ribavirin, Saquinavir, Indinavir, Ritonavir.

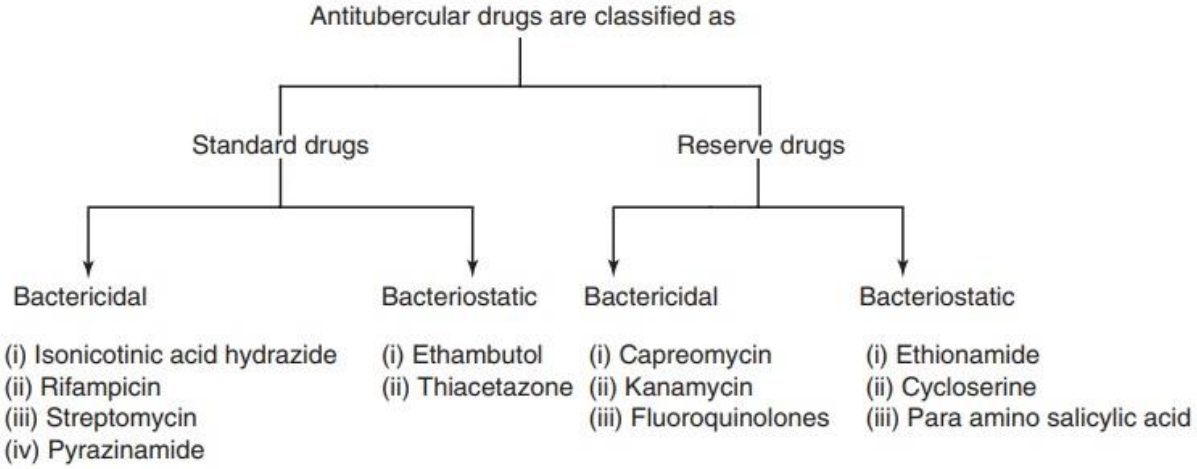
ANTI-TUBERCULAR AGENTS

Tuberculosis is the most prevalent infectious disease worldwide and a leading killer caused by a single infectious agent, that is, Mycobacterium tuberculosis. According to World Health Organization (WHO) report, M. tuberculosis currently infects over 2 billion people worldwide, with 30 million new cases reported every year. This intracellular infection accounts for at least 3 million deaths annually. Common infection sites of the tuberculosis are lungs (primary site), brain, bone, liver, and kidney. The main symptoms are cough, tachycardia, cyanosis, and respiratory failure. Depending upon the site of infection, the disease can be categorized as follows:

- Pulmonary tuberculosis (respiratory tract).
- Genitourinary tuberculosis (genitourinary tract).
- Tuberculous meningitis (nervous system).
- Miliary tuberculosis (a widespread infection).

Drugs used in the treatment of tuberculosis can be divided into two major categories.

1. First-line drugs: Isoniazid, streptomycin, rifampicin, ethambutol, and pyrazinamide.
2. Second-line drugs: Ethionamide, p-amino salicylic acid, ofloxacin, ciprofloxacin, cycloserine, amikacin, kanamycin, viomycin, and capreomycin.



Mode of action: Antitubercular drug is a prodrug that is activated on the surface of M. tuberculosis by katG enzyme to isonicotinic acid. Isonicotinic acid inhibits the bacterial cell wall mycolic acid, thereby making M. tuberculosis susceptible to reactive oxygen radicals. Isoniazid

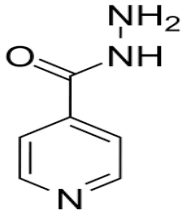
may be bacteriostatic or bactericidal in action, depending on the concentration of the drug attained at the site of infection and the susceptibility of the infecting organism. The drug is active against susceptible bacteria only during bacterial cell division.

USES

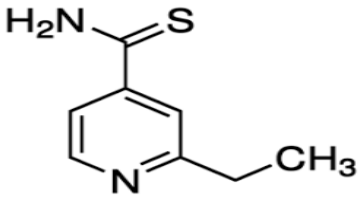
Antitubercular medications are a group of drugs used **to treat tuberculosis**. Tuberculosis (TB) is a disease caused by Mycobacterium tuberculosis (M-TB), an acid-fast aerobic bacterium that can grow on gram stain as either gram-positive or gram-negative.

Structure of Drugs

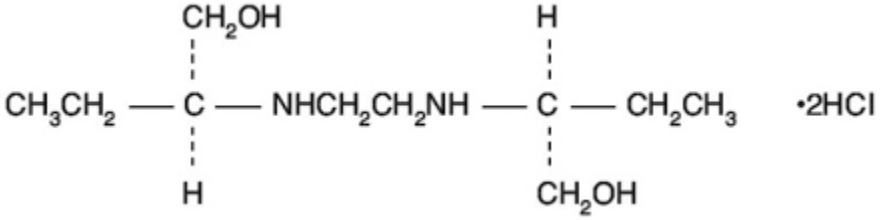
1. **Isoniazid**



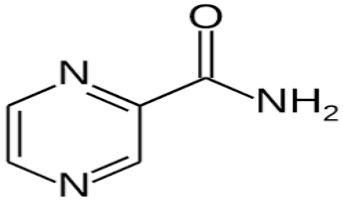
2. Ethionamide



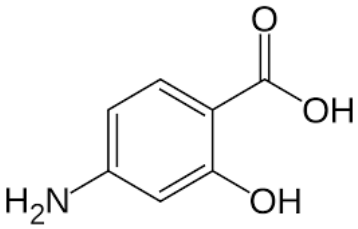
3 **Ethambutol**



4 **Pyrazinamide**

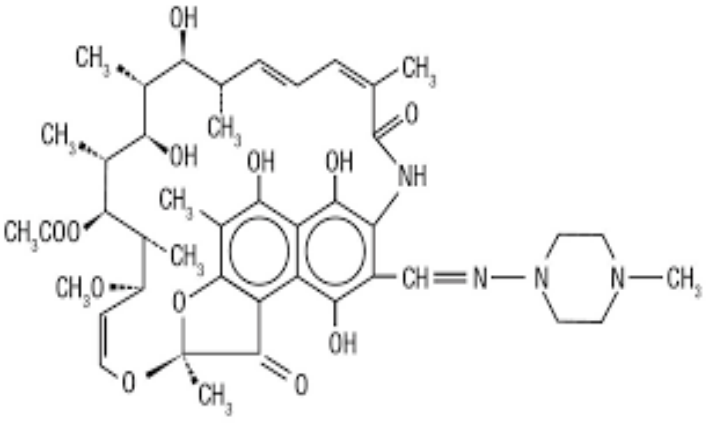


5. Para amino salicylic acid

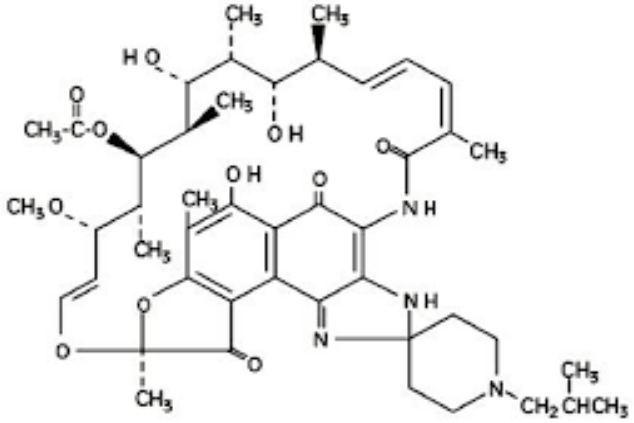


Anti-Tubercular Antibiotics

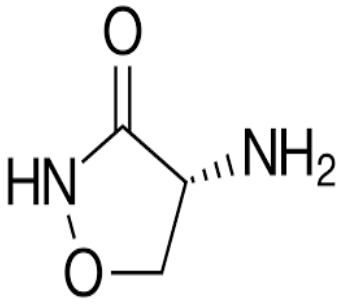
1. **Rifampicin**



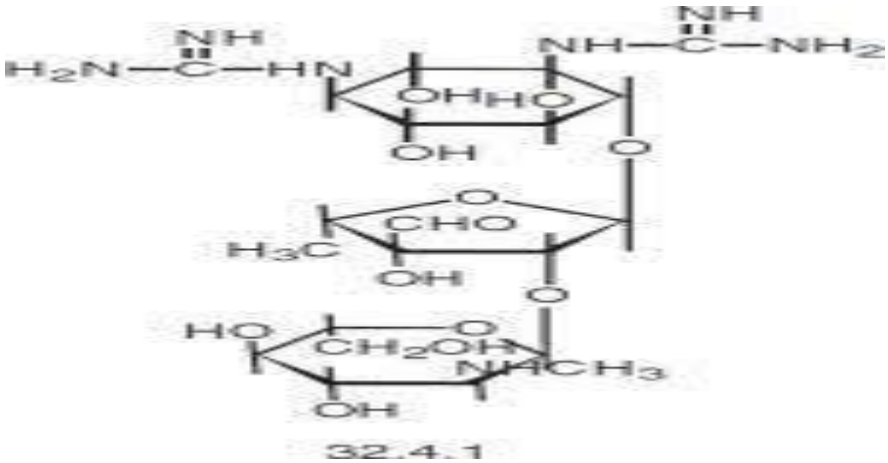
2. **Rifabutin**



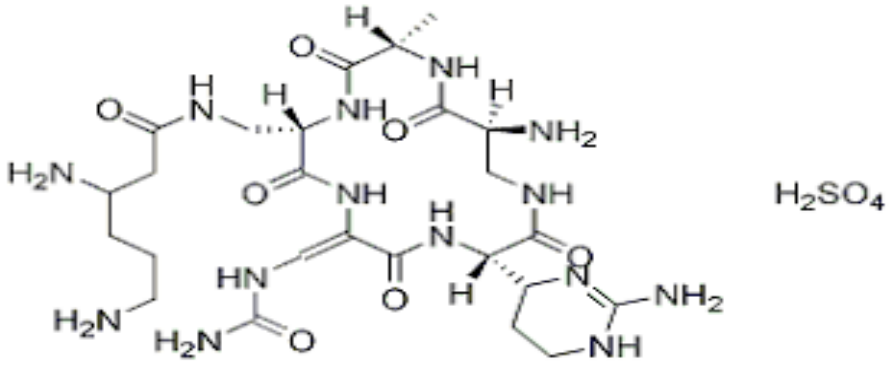
3. **Cycloserine**



4. Streptomycine



5. Capreomycin sulphate



URINARY TRACT ANTI-INFECTIVE AGENTS

Introduction

The kidneys do the major work of urinary system. The structural and functional units of kidneys are nephron. The clinical importance of urinary system includes hypertension, heart failure, renal failure, nephritic syndrome, and cirrhosis. The haemodynamics of renal system has a capability to alter the aforesaid pathological conditions.

Functions of Renal System

The functions of renal system are as follows:

Regulation of blood ionic compounds: The kidneys help to regulate the blood ions, i.e., sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), chloride (Cl^-) and phosphate ions (HPO_4^{2-})

Regulation of blood pH: The kidneys excrete a variable amount of hydrogen ions (H^+) into the urine and conserve bicarbonate (HCO_3^-) ions, which regulate pH of blood.

Regulation of fluid volume: The kidneys adjust blood volume by eliminating water in urine.

Regulation of blood pressure (BP): BP is regulated by the kidneys through an enzyme called renin secreted by extra glomerular cells, which activates the renin-angiotensin-aldosterone (RAA) pathway. Increased renin causes increase in BP.

Maintenance of blood osmolarity: The kidneys produce two hormones, calcitrol and erythropoietin. Calcitrol, the active form of vitamin D helps to regulate calcitrol homeostasis and erythropoietin stimulates the production of red blood cells (RBCs).

Regulation of blood glucose level: The kidneys can use the amino acid of glutamine in gluconeogenesis and release blood to maintain sugar level.

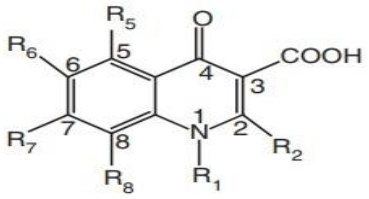
Excretion of metabolite waste products and foreign substances: Metabolic products like ammonia, urea, bilirubin, creatinine, uric acid, and other substances, i.e., toxins of exogenous compounds and drug metabolites, etc., are excreted through urine. Renal haemodynamics is altered by diuretics in clinical medicine. The therapeutic applications of diuretics are mainly concerned with hypertension and heart failure.

The normal renal physiological process includes glomerulus filtration and tubular reabsorption.

PRINCIPLE OF GLOMERULAR FILTRATION

In glomerulus capillaries, a portion of plasma water is formed through a filter, which functions due to the fenestrated capillary epithelial cells and the filtration diaphragm formed by epithelial cells; solutes of small size flow with filtered water into the urinary space whereas formed elements and macromolecules are retained by the filtration barrier. The glomerulus filtration depends on the hydrostatic pressure in Bowman's capsule space. Glomerular filtration rate (GFR) averages 125 ml/min in males and 105 ml/min in females. The mechanism regulates GFR in two ways—(i) by adjusting blood flow into and out of glomerulus and (ii) by altering glomerular capillary surface area available for filtration.

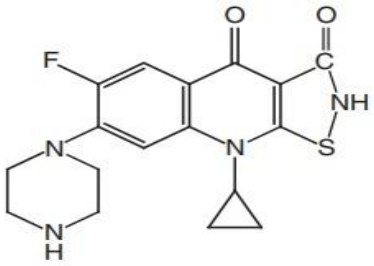
SAR of quinolines



1. Substituent at N-1 position: The optimum substituents at position 1 appear to be ethyl, butyl, cyclopropyl, and difluorophenyl, and these substituents have resulted in potent compounds. Addition of a fluorine atom into the N-1 cyclopropyl group or the 1-butyl substituent resulted in compounds with overall improved activity against gram-positive bacteria.

2. The simple replacement of C-2 hydrogen has been generally disadvantageous (e.g. C-2 methyl or hydroxyl groups); however, some derivatives containing a suitable C-1, C-2 ring have shown to possess notable activity.

3. The carboxy functions at position: Modification of C-3 carboxylic acid group leads to decrease in antibacterial activity. However, replacement of C-3 carboxylic group with isothiazolo group afforded most active isothiazolo quinolone, which has been 4–10 times greater in *in vitro* antibacterial activity than ciprofloxacin.



4. The C-4-oxo group of the quinolone nucleus appears to be essential for antibacterial activity. Replacement with 4-thioxo or sulphonyl group leads to a loss of activity.

5. The incorporation of a group at the C-5 position has proven beneficial in terms of antibacterial activity. The order of activity is NH_2: CH_3>F, H>OH, or SH, SR.

6. The incorporation of a fluorine atom at the C-6 position of the quinolone is monumental. The order of activity is F>Cl, Br, CH_3>CN.

7. In general, a C-8 fluoro substituent offers good potency against gram-negative pathogens, while a C-8 methoxy moiety is active against gram-positive bacteria. The order of activity is F, Cl, OCH_3>H, CF_3>methyl, vinyl, propargyl.

8. A halogen (F or Cl) at the C-8 position improves oral absorption.

9. Linking of N-1 group to the C-8 position with oxazine ring leads to active oflaxacin.

Mechanism of action

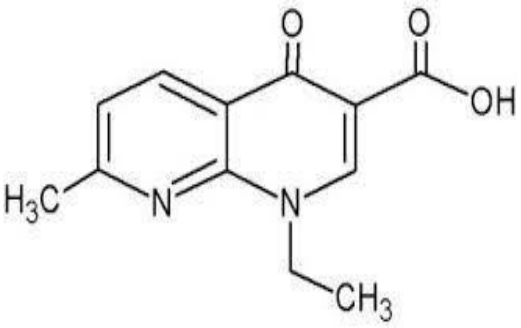
1. They block bacterial DNA synthesis by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV.
2. Inhibition of DNA gyrase prevents the relaxation of positively supercoiled DNA that is required for normal transcription and replication.
3. Inhibiton of topoisomerase IV probably interferes with separation of replicated chromosomal DNA into the respective daughter cells during cell division.

Therapeutic Uses of Quinolones

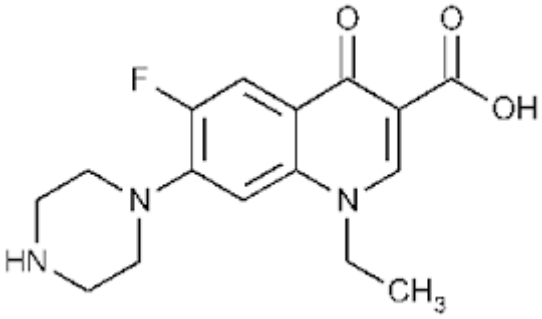
- Bone and joint infections caused by gram-negative organisms
- Infectious diarrhea
- Ophthalmic infections
- Some sexually transmitted diseases
- Upper respiratory infections
- UTIs

DRUGS

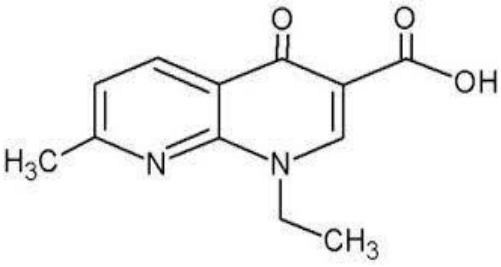
Nalidixic Acid



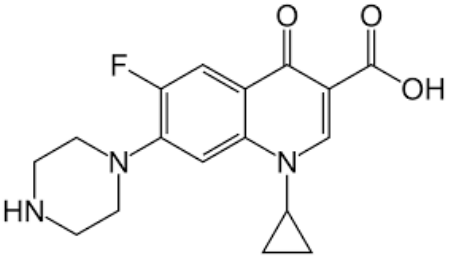
Norfloxacin



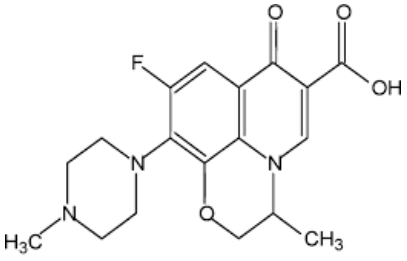
Enoxacin



Ciprofloxacin

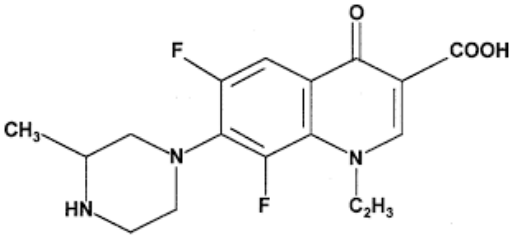


Ofloxacin



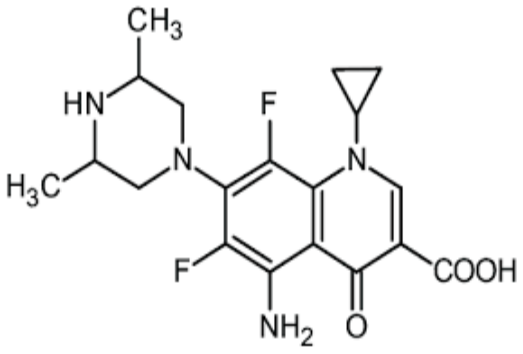
Ofloxacin

Lomefloxacin

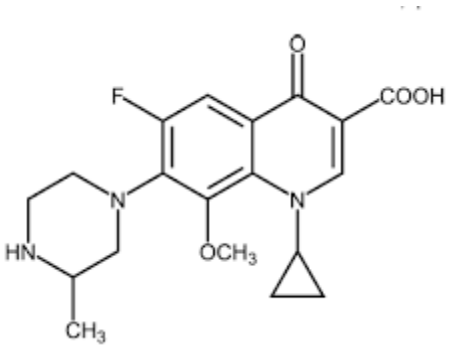


Lomefloxacin

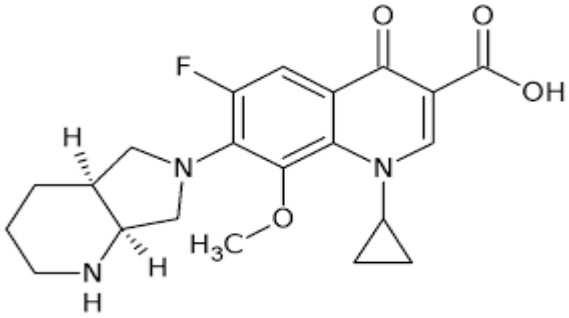
Sparfloxacin



Gatifloxacin

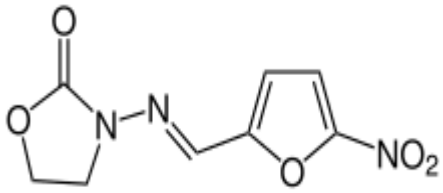


Moxifloxacin

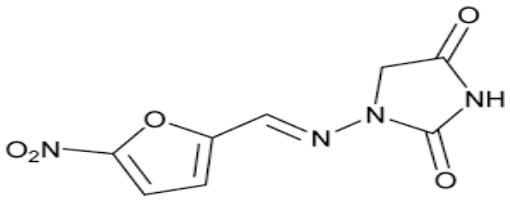


Miscellaneous Drugs

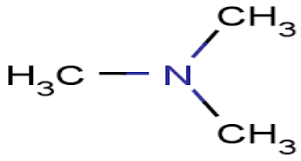
Furazoloidine



Nitrofurantoin



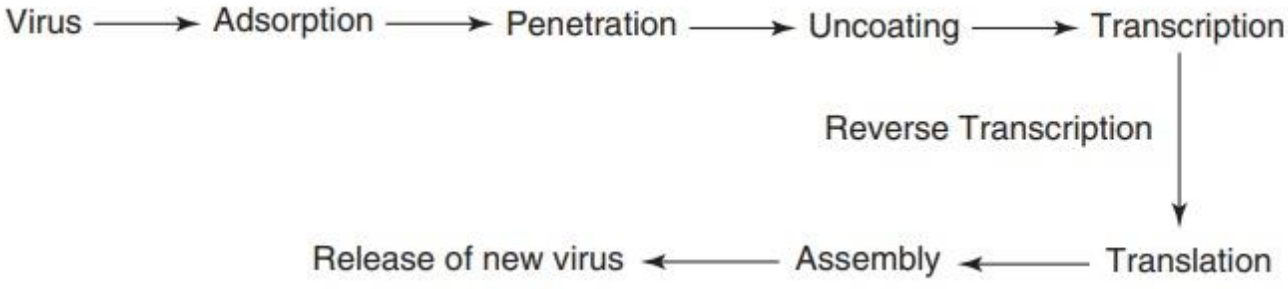
Methanamine



ANTIVIRAL AGENTS

Introduction

Antiviral agents are substances used in the treatment and prophylaxis of diseases caused by viruses. Viral diseases include influenza, rabies, yellow fever, poliomyelitis, ornithosis, mumps, measles, ebola, human immuno deficiency virus (HIV), herpes, warts, and small pox. Viruses are not proper living things, but consist of a genome; they are smaller in size with simple chemical composition, sometimes a few enzymes stored in a capsule made up of protein and rarely covered with a lipid layer. The viruses only replicate within the host cell and the viral replication depends primarily on the metabolic processes of the invaded cell. A virus does not possess cell wall, but they have RNA or DNA enclosed in a shell of protein known as capsid. The capsid is composed of several subunits known as capsomers. In certain cases, capsid may be surrounded by an outer protein or lipoprotein envelope. One group of RNA virus that deserves special mention is reteroviruses. They are responsible for acquired immuno deficiency syndrome (AIDS) and T-leukaemias. Reteroviruses contain reverse transcriptase (RT) enzyme activity that makes a DNA copy of the viral RNA template. Then, the DNA copy is integrated into the host genome, at which it is referred to as provirus and is transcribed into both the genomic RNA and mRNA for translocation into the viral proteins, giving generation to new virus particles. Viral life cycle varies according to the species, but they all share a general pattern that can be sequenced as follows:

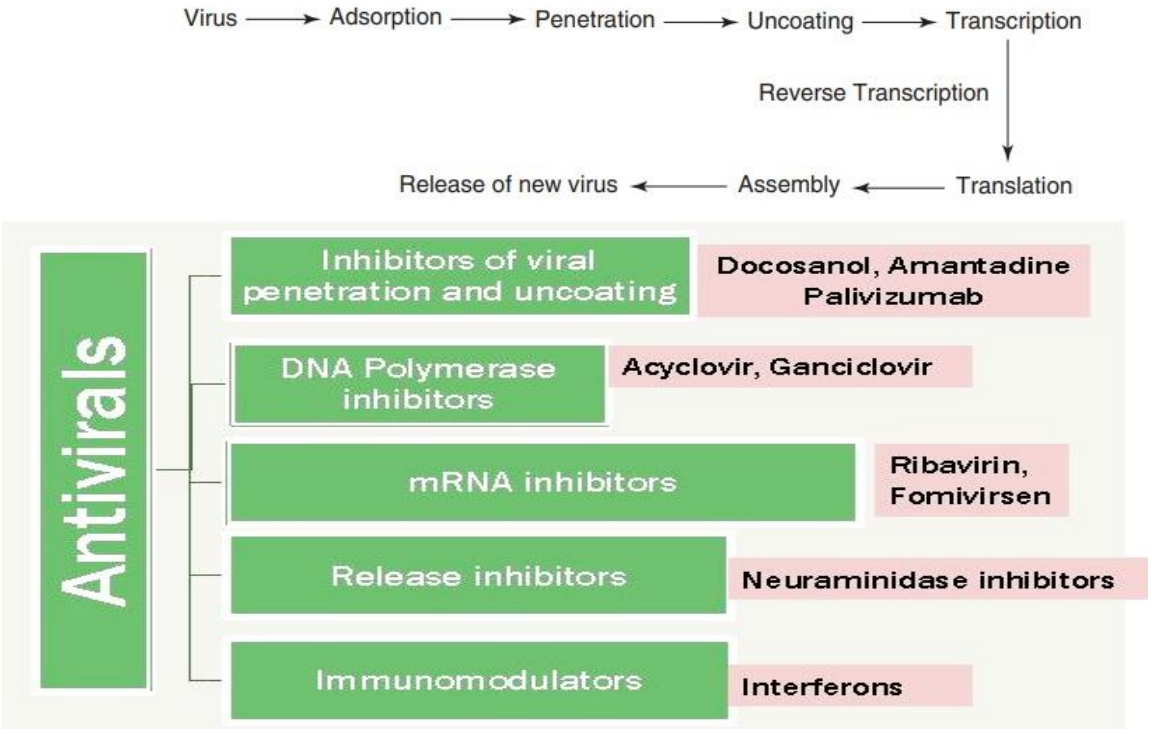


VIRUS LIFE CYCLE

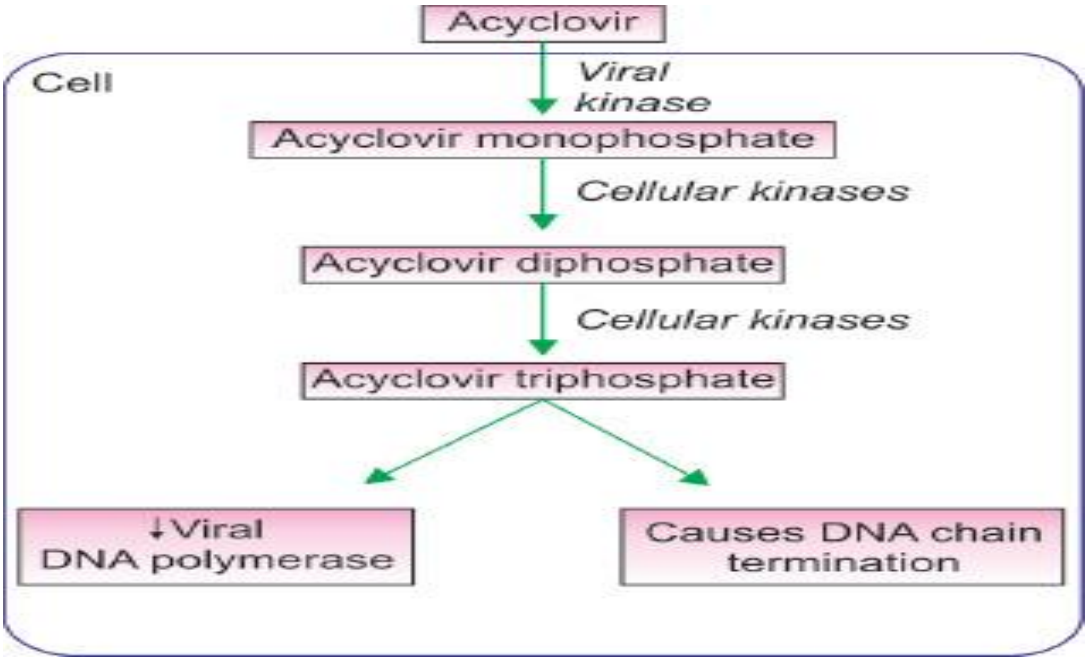
- ✓ **Adsorption:** Attachment of the virus to the host cell.
- ✓ **Penetration:** Penetration of virus into the cell.

- ✓ **Uncoating:** The genetic material or viral genome (DNA or RNA) passes into the host cell leaving the capsid covering outside the host cell.
- ✓ **Transcription:** Production of the viral mRNA from the viral genome.
- ✓ **Translation:** The viral genome enters the cytoplasm or the nucleoplasma and directs or utilizes the host nucleic acid machinery for the synthesis of the new viral protein and for the production of more viral genome. The viral protein modifies the host cell and allows the viral genome to replicate by using host and viral enzyme. This is often the stage at which the cell is irreversibly modified and eventually killed.
- ✓ **Assembly of the viral particle:** New viral coat protein assembles into capsid and viral genomes.
- ✓ Release of the mature virus from the cell and the budding process or rupture of the cell and repeat of the process, in a fresh host cell.
- ✓ Since the host cell machinery is totally utilized for the production of new virions, the normal cell function is affected. Antiviral agents have been developed to act at various stages in the viral replication cycle, such as attachments, replication, and release of the virus.

Some virus types together with diseases that they cause are listed as follows.



MECHANISM OF ACTION

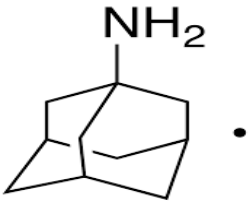


USES

Antiviral medications **help the body fight off harmful viruses**. The drugs can ease symptoms and shorten the length of a viral infection. Antiviral also lower the risk of getting or spreading viruses that cause herpes and HIV.

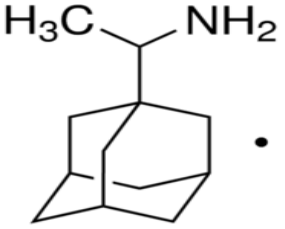
Drugs

Amantadine hydrochloride



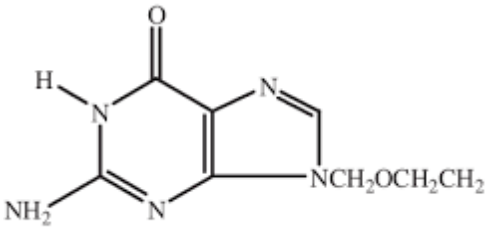
• HCl

Rimantadine hydrochloride

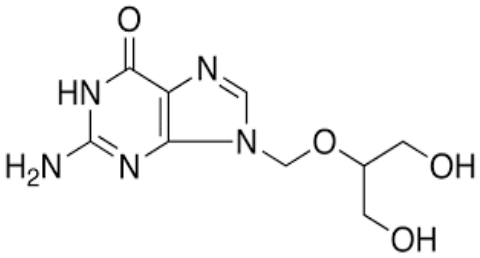


• HCl

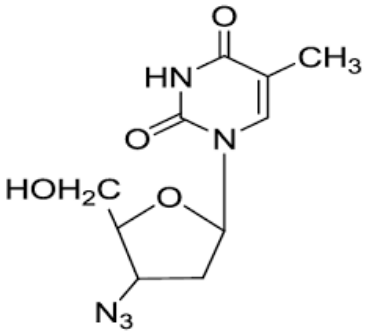
Acyclovir



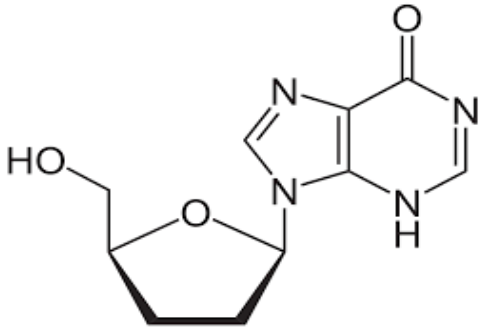
Gancyclovir



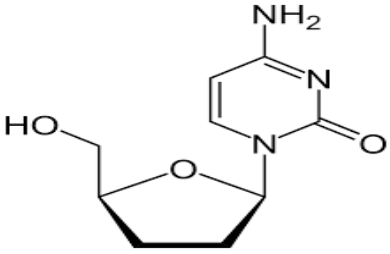
Zidovudine



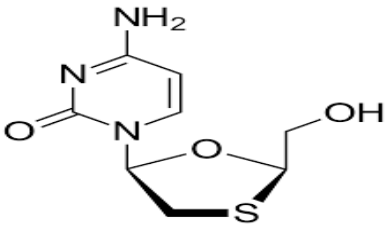
Didanosine



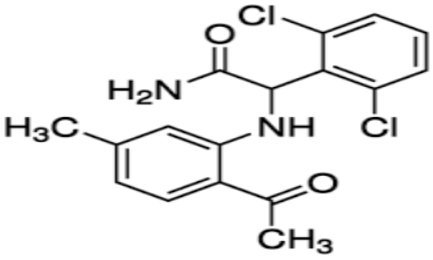
Zalcitabine



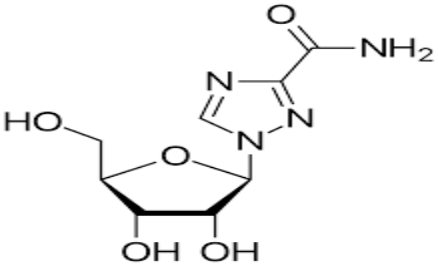
Lamivudine



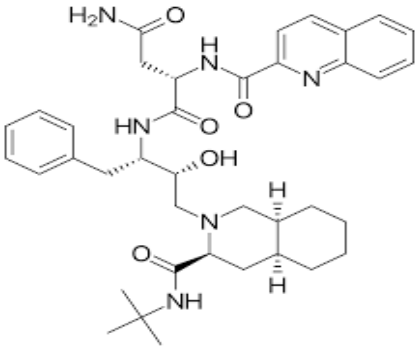
Loviride



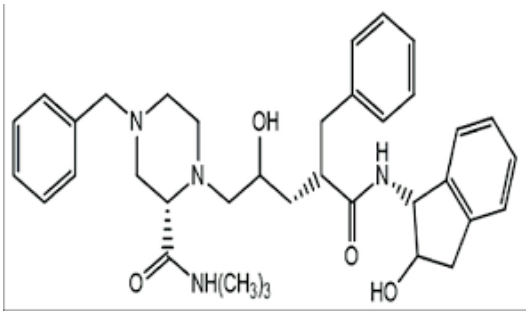
Ribavirin



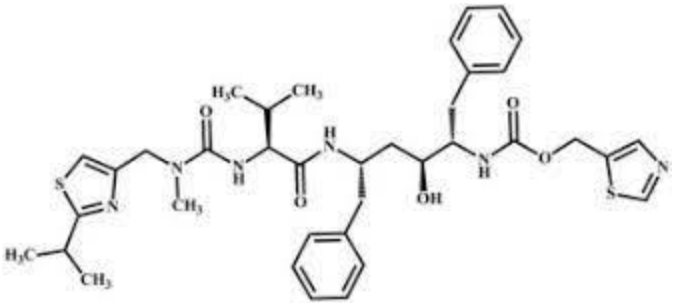
Saquinavir



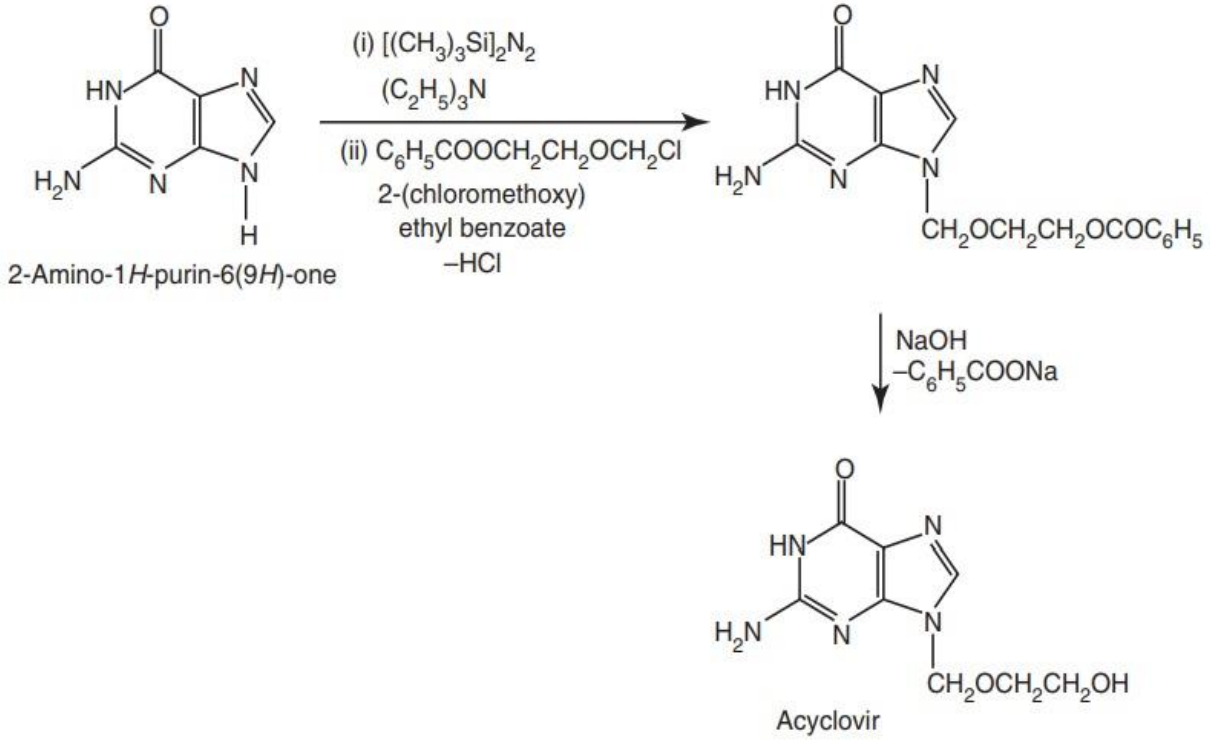
Indinavir



Ritonavir



Synthesis of Acyclovir



IMPORTANT QUESTIONS

VERY SHORT ANSWER TYPE QUESTIONS

Q1 Acidic urine augments the antibacterial action of which drug?

Q2 Give the name of antimicrobial drug which is used orally only for UTI .

Q3 Iodovuridine is indicated in for which disease?

Q4 The high virus selectivity of acyclovir is due to?

Q5 which viruses are most susceptible to acyclovir?

SHORT ANSWER TYPE QUESTIONS

Q6 what is UTI?

Q7 what are urinary tract anti-infective agents?

Q8 Classify urinary tract anti-infective agents

Q9 Write a note on SAR of Quinolone as urinary tract ant- infective agents

Q10 what are antiviral agents?

Q11 Classify antiviral agents?

Q12 Explain the mechanism of action of Iodoxuridine & Amantadine.

LONG ANSWER TYPE QUESTIONS

Q13 Explain urinary tract anti-infective agents. Classily them. Explain any two drugs in this Category.

Q14 Give synthesis of

a) Nitrofurantoin

b) Ciprofloxacin

Q15 Give uses and mechanism of action of urinary tract anti-infective agents.

Q16 Explain SAR of Quinolone as urinary tract anti-infective agents giving suitable examples

Q17 what are antiviral agents? Give its classification. Explain any two drugs in this category.

Q18 Give synthesis, mechanism of action & uses of Acyclovir.

Q19 Explain Antiretroviral agents in detail giving suitable examples.