UNIT-3

Anti-tubercular agents

Tuberculosis (TB) is an infective disease, most commonly affecting the lungs and caused by Mycobacterium tuberculosis and Mycobacterium bovis.

→ TB spreads via air in the form of small droplets

→ symptoms of TB include cough, weight loss, night sweats, fever, chest pain and fatigue.

→ TB bacteria can attack any part of the body such as kidney, spine and brain.

History

→ p-Aminosalicylic Acid (PAS) was the first discovered chemotherapeutic agent.

→ Selman Waksman found Actinomycetes effective against TB organism, in 1939

→ In 1943, Waksman isolalated streptomycin.

→ 1951 – development of isoniazid

→ 1959- development of rifamycins

→ 2012- development of delamanid and bedaquiline

Anti-tubercular Agents

First-line drugs	second-line drugs
– high anti-tubercular efficacy	– low anti-tubercular efficacy
– less toxic	– high toxicity
e.g. Isoniazid	e.g. Thiacetazone
Rifampin	PAS
Pyrazinamide	Ethionamide
Ethambutol	Cycloserine
Streptomycin	Kanamycin
	Amikacin
	Capriomycin

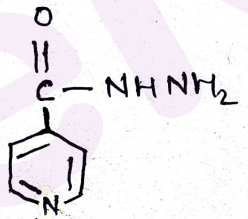
* The above classification is based on clinical utility of drugs.

Synthetic Anti-tubercular Agents

These drugs are:

1) Isoniazid
2) Ethionamide
3) Ethambutol
4) Pyrazinamide
5) Paraamino salicylic acid.

Isoniazid *



→ Isoniazid (also called as isonicotinylhydrazine, INH) is an organic compound used to treat TB.

→ Freely soluble in water

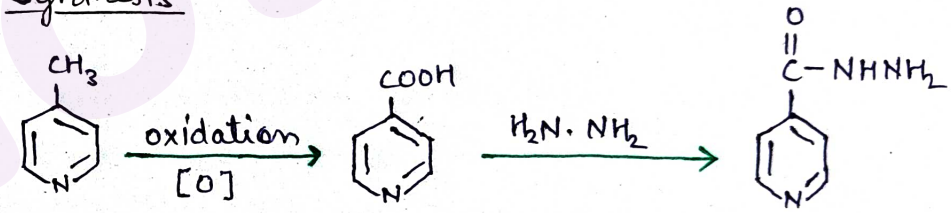
Mechanism of action

→ It inhibits synthesis of mycolic acids which are essential components of mycobacterial cell walls.

→ Isoniazid is either bacteriostatic or bactericidal depending upon the drug concentration at the infection site and susceptibility of organism.

Isoniazid (Prodrug)
↓
Activated by KatG
↓
Formation of covalent complex with AcpM and KasA. → Blocking mycolic acid synthesis

Synthesis

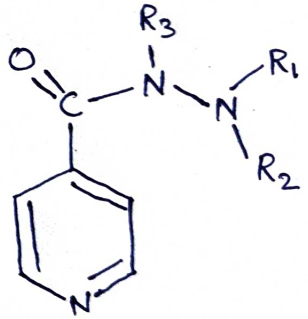


4-picoline → Isonicotinic acid → Isoniazid

SAR

→ Pyradine ring is essential for activity.

→ Substitution of R_1 and R_2 leads to variable activity.



→ Addition of isopropyl group at position R_2 results in loss of activity.

→ Any substitution (alkyl) at R_3 results in loss of activity.

Side effects

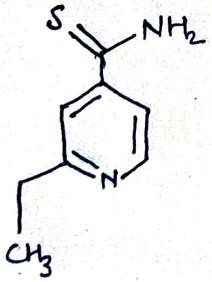
- neuritis (peripheral)
- fatal hepatitis
- Aplastic anaemia
- Hypersensitivity reaction (allergy)
- dark urine

Uses

- It is used in combination with other drugs in treating TB.
- It acts as an antibiotic and treats only bacterial infections.

Ethionamide

→ It is a nicotinamide derivative.



MOA

It undergoes intracellular modification and acts like isoniazid, i.e., it inhibits the synthesis of mycolic acid.

Adverse effects

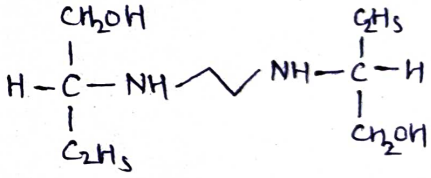
nausea, vomiting, diarrhoea, abdominal pain, increase saliva, loss of appetite, sores in mouth.

→ Used for treating tuberculosis resistant to isoniazid or rifampin.

Ethambutol

→ bacteriostatic against TB organism.

→ Used alongwith isoniazid, rifampin and pyrazinamide.



MOA

→ bacteriostatic against TB bacilli. (one of the TB causing bacteria)

→ It disrupts arabinogalactan (polymer) synthesis

by inhibiting the enzyme arabinosyl transferase leads to increased permeability of the cell wall.

Adverse effects

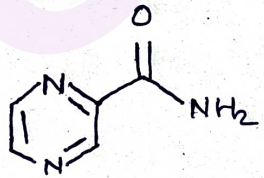
Optic neuritis, red-green colour blindness, peripheral neuropathy, hyperuricemia

Uses

→ Used with other drugs to treat TB.

→ Also used to treat MAC (Mycobacterium avium complex).

Pyrazinamide



→ close analogue of isoniazid.

→ It is a pro-drug.

MOA

→ Susceptible organisms produce pyrazinamidase, which is responsible for conversion of pyrazinamide (prodrug) to pyrazinoic acid (active) intracellularly.

→ Protonated pyrazinoic acid can permeate the mycobacterial membrane to lower the pH of the cytoplasm, hence disrupting basic chemical processes especially energy production.

Adverse effects

Arthralgia, gout, hepatotoxicity, Rash

↳ joint pain

Uses

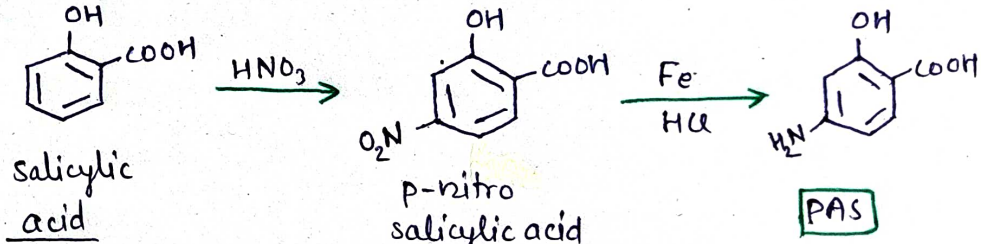
→ Used alongwith isoniazid and rifampin to treat TB.

→ Used alongwith rifampin to treat latent TB.

p-Amino Salicylic Acid *

PAS is an antibiotic used to treat inflammatory bowel diseases.

synthesis



salicylic acid

p-nitro salicylic acid

PAS

MOA

PAS inhibit folic acid synthesis or inhibition

of synthesis of the cell wall component, mycobactin, thus reducing iron uptake by M. tuberculosis.

SAR of PAS

1) Replacing the primary amino group with hydroxy, alkoxy, tertiary amines or amides yield inactive compounds.
2) Replacing the hydroxyl group with ether, ester, a thiol or an amino group also eliminates the anti-tubercular activity.
3) Converting the carboxylic acid group to alkyl esters, amidines, amides or nitrates also results in loss of activity.

Adverse effects

- GI irritation, allergic reactions

Uses

→ It is an antibiotic that is effective in treating tuberculosis.
→ Used in treatment of inflammatory bowel disease.

Anti-tubercular Antibiotics

Anti-tubercular drugs (antibiotics) are:

1) Rifampicin 2) Rifabutin 3) Cycloserine
4) Streptomycin 5) Capreomycin sulphate

Rifampicin

Rifampicin is a semi-synthetic antibiotic derived from streptomyces mediterranei.

MoA

Rifampicin inhibits the DNA-dependent RNA polymerase and thus suppresses RNA synthesis and cause cell death.

Adverse effects

Hepatotoxicity, breathlessness, pruritus (→ itching), flu-like symptoms.

Uses

→ Used in mycobacterium infections
→ Alongwith fusidic acid, it is useful in Methicillin-Resistant staphylococcus aureus (MRSA).
→ effective against vaccinia virus.

Rifabutin

Rifabutin is a broad-spectrum antibiotic that is used as prophylaxis against Micobacterium avium complex infection in HIV-positive patients.

MoA

similar to rifampicin.

Adverse effects

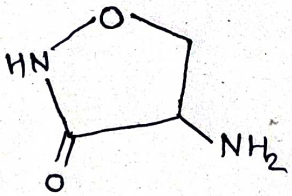
diarrhoea, stomach upset, change in taste, belching, bloating, loss of appetite.

Uses

prevents MAC (Micobacterium avium complex)

Cycloserine

Cycloserine is a broad-spectrum antibiotic which is used with other anti-tubercular drugs for treating drug-resistant TB.



MoA

Cycloserine inhibit cell-wall biosynthesis in bacteria. As a cyclic analogue of D-alanine, cycloserine acts against two crucial enzymes important in the cytosolic stages of peptidoglycan synthesis: alanine racemase and D-alanine ligase.

Adverse effects

confusion, dizziness, anxiety, drowsiness, mental depression, muscle twitching (quick sudden movement)

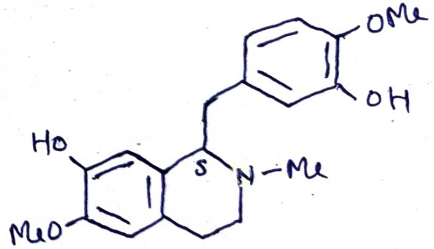
Uses

used in treating MAC and tuberculosis.

Streptomycin

It is an antibiotic produced by streptomyces griseus.

It is an aminoglycoside anti-bacterial and anti-microbial.



MOA

→ It inhibits protein synthesis of mycobacteria in the ribosome.

→ Streptomycin binds to the 30s subunit of the bacterial ribosome and leads to mistranslation and ultimately to a complete inhibition of translation.

Adverse effects

nausea, vomitting, vertigo, stomach upset, loss of appetite, tingling (face)
vertigo → dizziness

Uses

→ used to treat tuberculosis

→ In combination, it treat tularemia

Capreomycin Sulphate

Capreomycin is a cyclic peptide antibiotic produced by streptomyces capreolus.

MOA

Precise MOA is not known, but it is assumed that it inhibit protein synthesis by binding to the 70s ribosomal unit.

Adverse effects

black stools, blood in urine, change in frequency and amount of urine, chest pain, chills, cough.

Uses

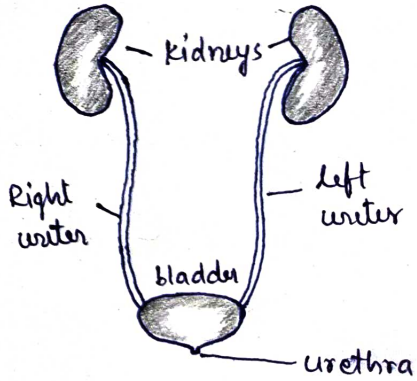
Capreomycin along with other drugs is used in the treatment of tuberculosis.

Urinary Tract Anti-Infective Agents

These are those agents which are used in the treatment of urinary tract infections (UTIs).

Urinary tract is divided into two parts.

1) Upper urinary tract
   a) kidneys
   b) ureters
2) Lower urinary tract
   a) bladder
   b) urethra



Common UTIs are cystitis (infection of bladder), urethritis (infection in urethra), prostatitis (infection in prostate gland) and pyelonephritis (infection of kidney).

The drug agents used as anti-infectives are:

1) Furazolidone
2) Nitrofurantoin
3) Methenamide

Quinolones

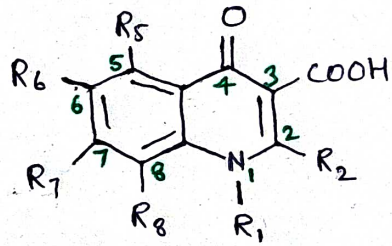
→ Quinolones are synthetic broad-spectrum antibiotics
→ Quinolones are therapeutically useful in the treatment of urinary tract infections.
→ Nalidixic acid is the first quinolone.

History

→ Nalidixic acid was introduced in 1964 for UTIs and GIT infections.
→ Oxolinic acid and rosoxacin with more potency in 1970s.
→ second generation called flouroquinolones with extended spectrum and systemic effects in 1980s.
→ Since then, many drugs have been synthesized.

SAR of Quinolones

The basic structure of quinolones is:



1) Replacing C-2 carbon is advantageous, e.g., C-2 methyl or C-2 hydroxyl.
2) Other acidic groups at C-3 other than carboxylic acid results in loss of activity.
3) Oxo group at C-4 is essential for activity.
4) Introducing an amino group at C-5 enhances the anti-bacterial activity.

5) Introducing a flourine at C-6 is excellent.
6) Introducing a piperazine moiety at C-7 was a landmark development.
7) A hydrogen atom or a nitrogen atom at C-8 is the most common.

MOA of quinolones

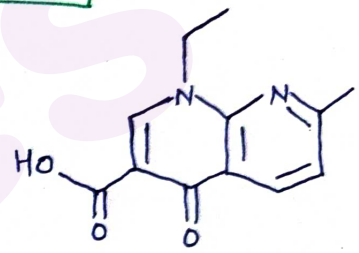
1) They block DNA synthesis in bacteria by inhibiting topoisomerase-II (DNA gyrase) and topoisomerase-IV.
2) Inhibition of DNA gyrase which ultimately prevents normal transcription and replication.
3) Inhibition of topoisomerase-IV interferes with separation of replicated chromosomal DNA into the respective daughter cells after cell division.

Uses

1) Nalidixic acid is used as a urinary antiseptic.
2) Nalidixic acid has been used in diarrhoea caused by Proteus, E. coli, Shigella or Salmonella.
3) Flouroquinolones are used in UTIs, gonorrhoea, chancroid, typhoid, TB.

Major Drugs

Nalidixic Acid



→ It is strongly active against gram -ve bacteria and shows minor activity towards gram +ve.
→ Acts as bacteriostatic or bactericidal depending upon concentration.

MOA

Binds with DNA reversibly and interferes with RNA and protein synthesis.

Uses

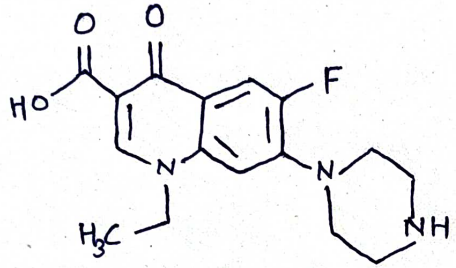
Used in the treatment of UTIs.

Adverse effects

allergic reactions, tightness in chest, swelling on mouth, face, lips, blurred vision, burning or tingling sensation.

Norfloxacin

It is a synthetic flouroquinolone with broad-spectrum antibacterial activity.



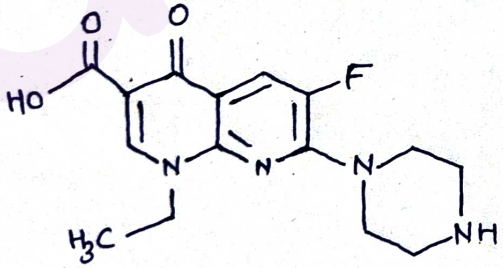
MOA

Inhibits topoisomerase-IV and DNA gyrase that are required for bacterial DNA replication, transcription, repair and recombination.

Uses

Used as first-line urinary anti-bacterial and is useful in genital infection.

Enoxacin



→ It is a broad-spectrum anti-bacterial agent.

→ structurally related to nalidixic acid.

MOA

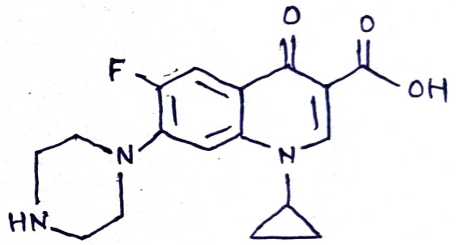
Enoxacin inhibits DNA gyrase which is an essential bacterial enzyme.

Uses

Enoxacin treats urethral or cervical gonorrhoea in adults, UTIs (cystitis),

Ciprofloxacin *

It is a synthetic chemotherapeutic antibiotic of flouro-quinolone class.



→ It is bactericidal.

MOA

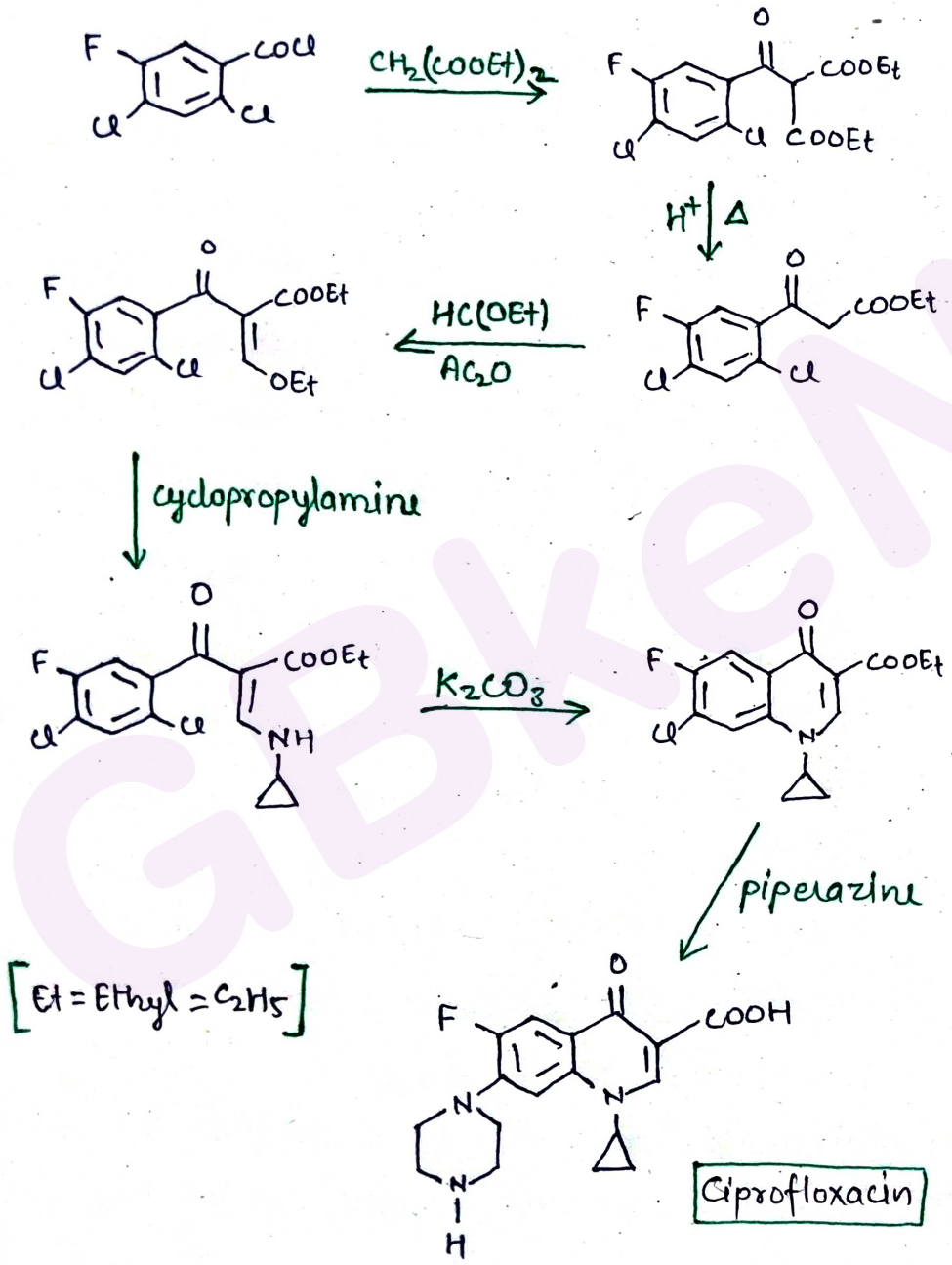
Ciprofloxacin acts on bacterial DNA gyrase and topoisomerase-IV.

Uses

→ treat infections of bones and joints, endocarditis, gastroenteritis, RTIs.

→ Treat the infections caused by gram-ve bacteria, Pseudomonas aeruginosa.

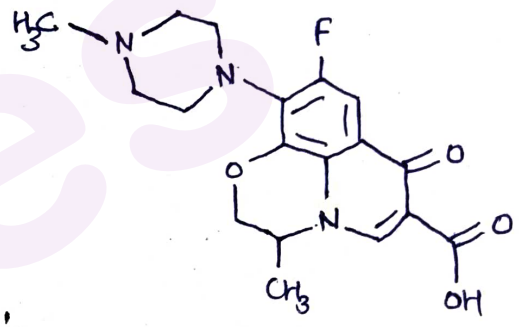
Synthesis



[Et = Ethyl = C_2H_5]

Ciprofloxacin

Ofloxacin



It is a synthetic chemotherapeutic antibiotic of flouroquinolone class.

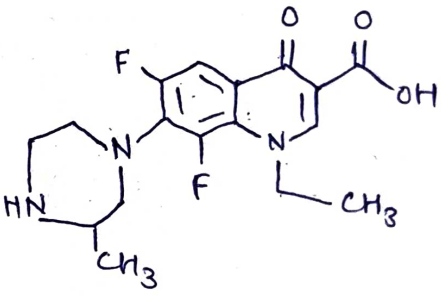
MoA

similar to ciprofloxacin.

Use

used to treat bronchitis, pneumonia, and infections of skin, urinary bladder and reproductive organs.

Lomefloxacin



→ It is a flouroquinolone antibiotic.

→ MOA is similar to ciprofloxacin.

Uses

Useful in RTIs and UTIs.

Antiviral Agents

Antiviral agents are a class of medication used specifically for treating viral infections. Viruses are intracellular obligate parasites, self-replicating able to pass through the filter that retain the smallest bacteria.

→ Virus conduct no metabolic process on their own.

→ They invade the host cell which may be bacteria, animal or plant cell.

Classification of anti-viral agents

On the basis of mechanism of action.

1) Anti-Herpes virus : Idoxuridine, Acyclovir, Famciclovi, Ganciclovir and Foscarnet.

2) Anti-retrovirus

(i) Nucleoside Reverse Transcriptase Inhibitors (NRTIs) : Zidovudine (AZT), Didanosine, Zalcitabine and stavudine.

(ii) Non-nucleoside reverse transcriptase inhibitors (NNRTIs) : Efavirenz and Delavirdine.

(iii) Protease Inhibitors : Indinavir, Nelfinavir, saquinavir, Amprenavir and Lopinavir.

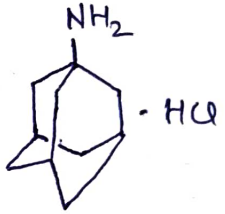
3) Anti-Influenza virus : Amantadine, Rimantadine

4) Non-selective anti-viral drugs : Ribavirin and Lamivudine

Major Drugs

Amantadine Hydrochloride

Amantadine consists of adamantane backbone substituted with an amino group at one of the four methyne positions.



MOA

It is found to interfere with the function of trans-membrane domain of the viral M2 protein, and prevent the release of infections viral nucleic acids into the host cell.

Uses

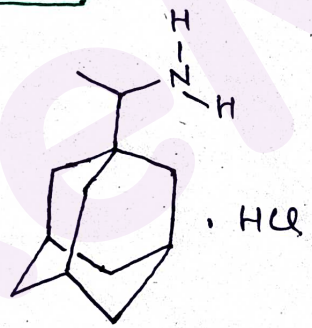
→ It is used in fatigue experienced by patients with multiple sclerosis.

→ Used in Parkinson's disease and similar conditions disease.

→ prevents and treats respiratory infections caused by influenza-A virus.

Rimantadine Hydrochloride

Rimantadine is an orally administered antiviral drug.



MOA

similar to Amantadine.

Uses

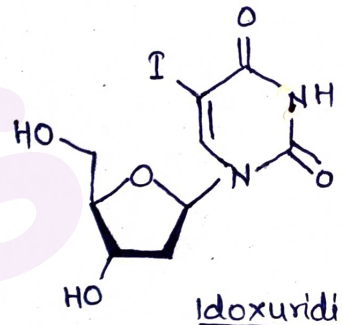
→ Used for the prophylaxis and treatment of infections caused by various strains of Influenza A virus in adults.

Idoxuridine Trifluoride

Idoxuridine is an analogue of dioxyuridine. It is used as an antiviral agent that inhibits the synthesis of viral DNA.

MOA

Idoxuridine exerts its antiviral activity by inhibiting viral replication by substituting thymidine in viral DNA. Virus loses its ability to reproduce.



Idoxuridine

Use

Idoxuridine is used in keratoconjunctivitis and keratitis caused by herpes simplex virus.

Acyclovir

Acyclovir is a nucleotide analog antiviral that is used for treating infections like herpes simplex, herpes zoster, herpes labialis. It is the first line drug to be used in the treatment of infections caused by these viruses.

MOA

Acyclovir cause DNA chain termination.

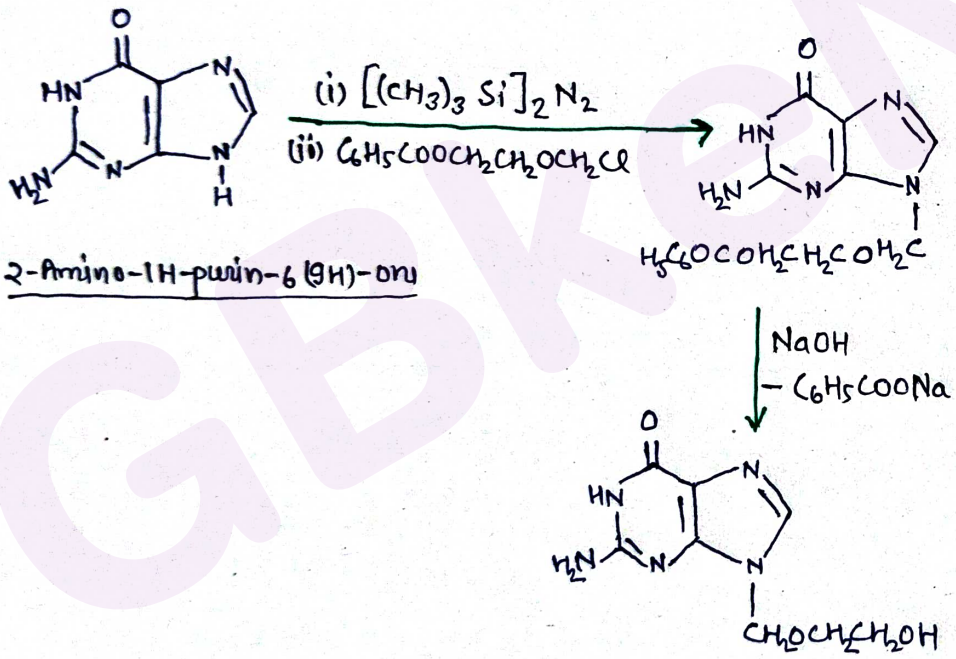
Use

→ Acyclovir opthalmic ointment is used in acute herpetic keratitis.

→ Acyclovir oral tablets, capsules, and suspensions are used in herpes zoster, genital herpes, chickenpox.

→ Acyclovir buccal tablet is used in recurrent herpes labialis.

Synthesis of Acyclovir



2-Amino-1H-purin-6(9H)-one

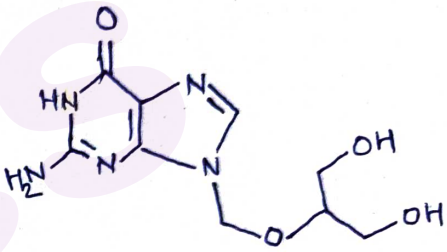
$H_5C_6OCOH_2CH_2COH_2C$

$CH_2OCH_2CH_2OH$

Acyclovir

Ganciclovir

Ganciclovir is an acyclovir analog and a potent inhibitor of Herpes virus family.



MOA

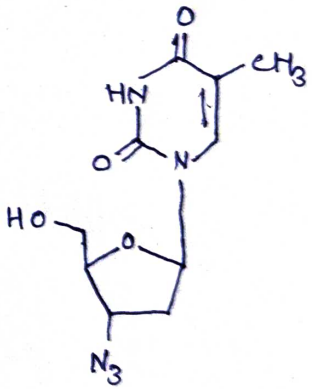
Ganciclovir prevents DNA synthesis.

Uses

It is used in severe cytomegalovirus (CMV) disease, including CMV pneumonia, CMV GI disease.

Zidovudine

Zidovudine is a potent inhibitor of HIV replication that acts as a chain terminator of viral DNA during reverse transcription.



MOA

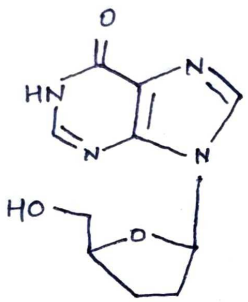
Inhibits the activity of HIV-1 Reverse Transcriptase via DNA chain termination.

Uses

HIV Infection prevention and control.

Didanosine

Didanosine is a reverse transcriptase inhibitor used to treat HIV.



MOA

It causes DNA chain termination.

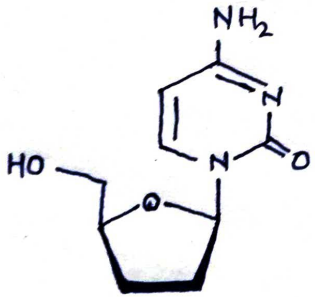
Uses

Didanosine is used alongwith other antiretroviral agents in the treatment of HIV-1 infection.

→ Side effects include pancreatitis, liver problems, peripheral neuropathy.

Zalcitabine

Zalcitabine is a dideoxynucleoside used to treat HIV.



MOA

It terminates viral DNA growth.

Uses

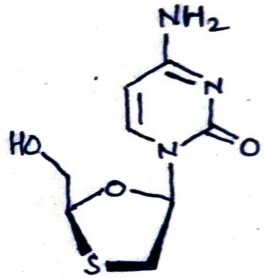
Zalcitabine is used in combination with other antivirals for treatment of HIV infections.

Lamivudine

Lamivudine is a reverse-transcriptase inhibitor used to treat HIV and Hepatitis-B Infections.

MOA

Lamivudine cause DNA chain termination.



Uses

Lamivudine is used in the treatment of HIV infection and Hepatitis-B.

Adverse effects

lactic acidosis, severe liver problems and pancreatitis.