Date
25/4/21

Day - Monday

UNIT - 3rd

Anti - Tubercular Agent

These are the drugs used for the treatment of mycobacterium Tuberculo infections or group of drugs used to the treat tuberculosis (TB).

Tuberculosis [TB] - It is an acute or chronic communicable disease caused by mycobacterium tuberculosis (acid fast aerobic bacteria) and mycobacterium Bovis (In animal)

It mainly affects the respiratory tract (mainly lungs) can also spread to other parts of your body like brain and spinal cord.

Symptoms - Chronic cough, fever, cough with bloody mucous, weight loss.

Extra pulmonary TB - (A disease involving any part of body other than lung parenchyma (like pleura, pericardium, lymph node)

Is more commen in patients suffering from AIDS/HIV dose smoke.

Classification of Anti - Tubercular Agent

1st line drugs
- R - Rifampin
- I - Isoniazid
- P - Pyrazinamide
- E - Ethambutal
- S - Streptomycin

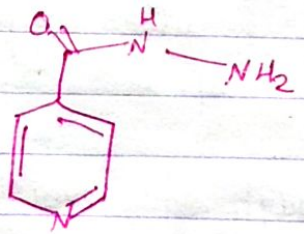
2nd line drugs
- K - Kanamycin
- E - Ethionamide
- P - Paraamino salicylic acid
- T - Thiacetazone.

Newer Drugs (Antibiotics)
- O - Ofloxacin
- C - Ciprofloxacin
- C - Clarithromycin
- R - Rifabutin
- A - Azethromycin.

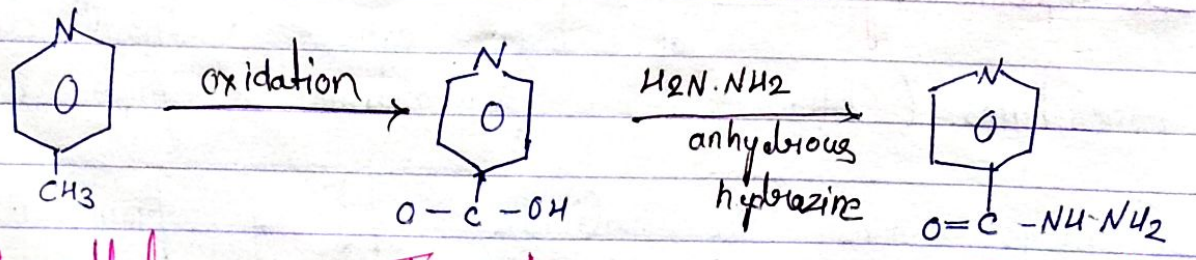
Trick - पकी रखी इंडी

[1] Isoniazid

Structure -

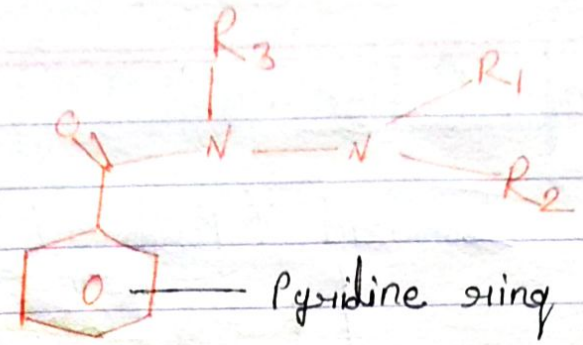


Synthesis -



4 - methyl pyridine → Isonicotinic acid → Isoniazid

SAR-

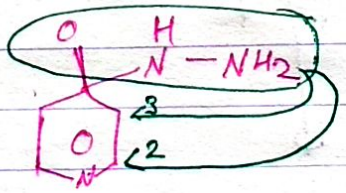


[1] Pyriding ring is essential for activity.

[2] R_1, R_2, and R_3 substitution - leads to variable activity.

[3] If pyridine ring is repleced by piperidine - less active compound

[4] If hydrazine is shifted to position 2 or 3 p instead of 4 — less active compound.



[5] Addition of isopropyl group at position R-2 — results in loss of anti-tubercular activity.

[6] Substitution of alkyl group at R-3 — results in loss of affinity.

Mechanism of Action -

Isoniazid (Prodrug)

↓ Kat G [Catalase peroxidase in mycobacterium]

Isoniazid (active form)

↓ Interacts with

AcpM and Kas

(Acyl carrier Protein)

→ Kas A (β-Keto Acyl carrier protein Synthesis)

↓

Interferes with elongation of fatty acid

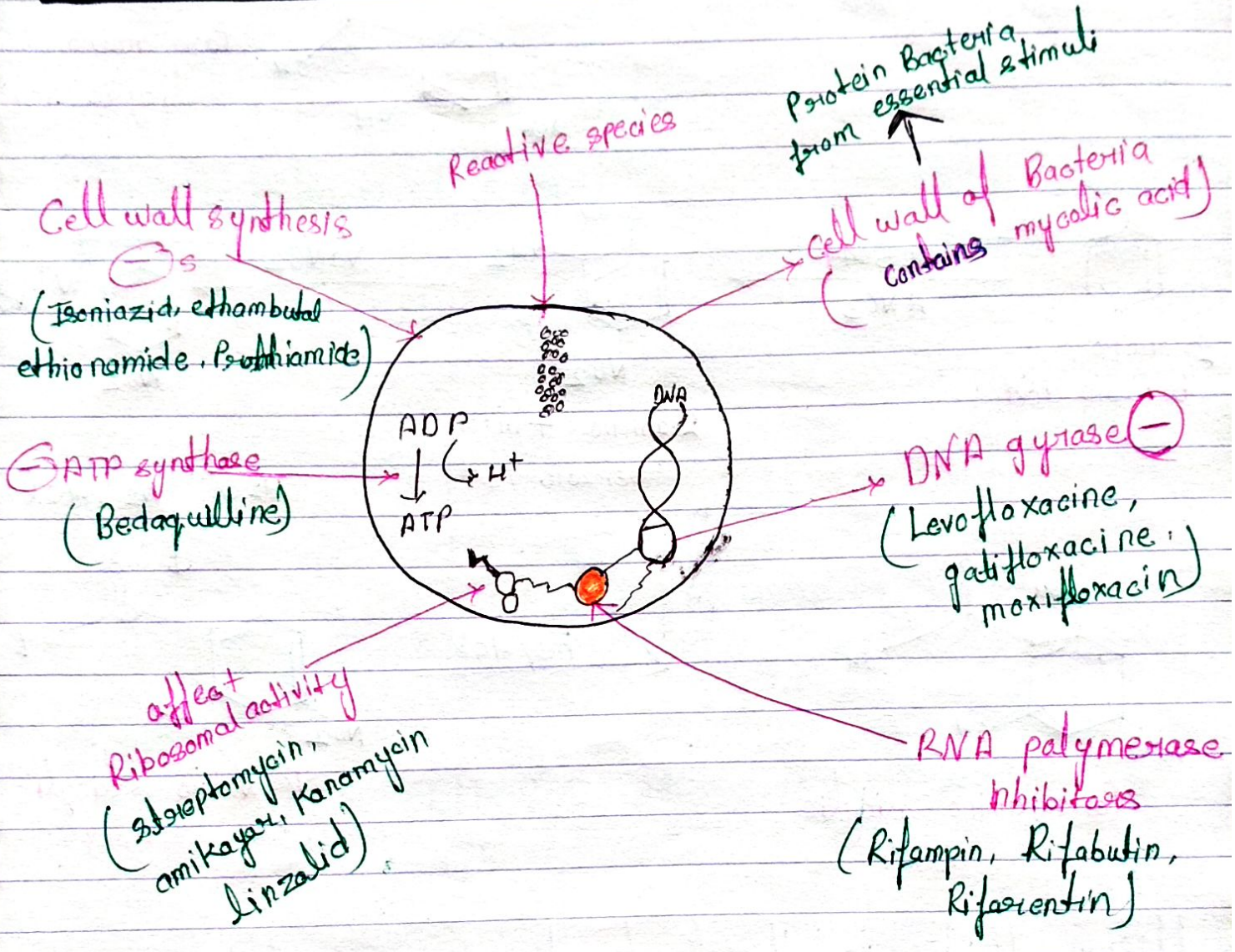
↓

Os cell wall synthesis.

↓

Kills Bacilli.

Mechanism of Action of Antitubercular drugs



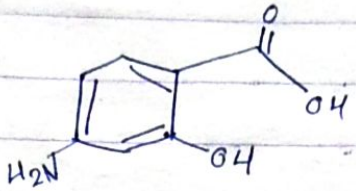
Uses- It is used to treat and to prevent TB.

[2] Para amino salicylic Acid (PASA)

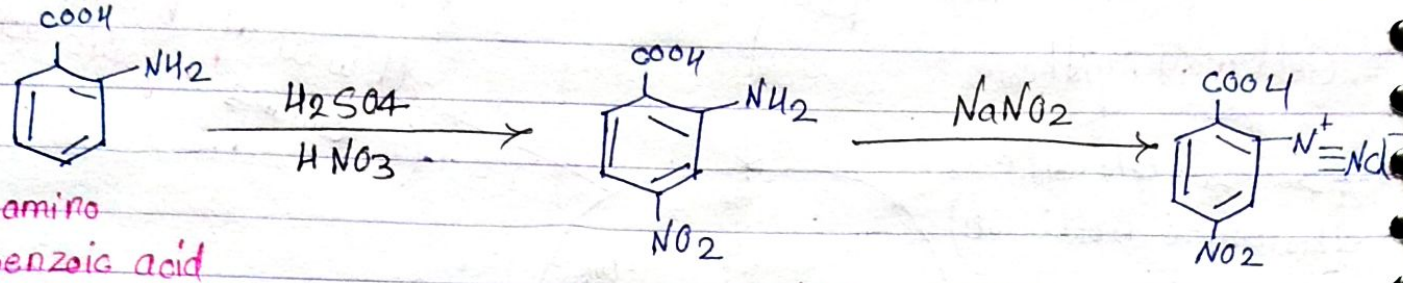
It is also known as 4-amino salcylic acid, is an antibiotic primarily used to treat TB, was introduced at in 1946 and are sefated to sulphonamide.

Synthesis-

Structure-



Para amino salicylic acid



2-amino benzoic acid

2-amino, 4 nitro benzoic acid

P-Nitro salicylic acid

Para amino salicylic acid

Uses- Used in the treatment of TB infections. Also used in the treatment of inflammatory bowl disease.

Mechanism of Action-

It is a structural analogue of PABA [Para amino bubaric acid], hence inhibiting ($\ominus_3$) the synthesis of folate in Mitrochondria [MT] can

separable action

distinguish b/w PABA and sulfonamides but not b/w PABA and PASA.

Pteridine + PABA

Dihydropteroate di PO4 + PABA

dihydropteroate synthase ← ⊖ Sulfonamides

Sulfonamides ↔ PABA : structurally similar

Dihydropteroic acid

DHFA (dihydro folic acid)

Dihydrofolate reductase ← ⊖ Trimethoprim

Tetra hydro folic acid (THFA) / Folate

Thymidine → DNA

Purines → DNA, RNA

Methionine → ↓ RNA, Proteins

* PASA binds to pteridine synthetase with greater affinity than PABA, thus inhibiting [⊖ing] the synthesis of folic acid in MT.

→ PASA are tuberculastatic - one of the ~~least~~ least active drug.
→ They delay the sustaince resistance development.
→ PASA are distributed widely except in CSF.
→ Metabolised in liver and secreted through urine.

Note:-
- PASA is used only in resistance TB.
- Adverse drug reaction (ADR) of PASA - Hypothyroidism.
- GIT irritation can be reduced by food and antacid.

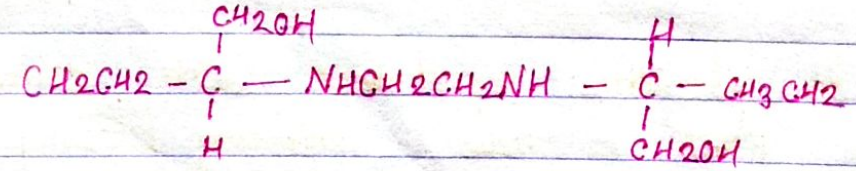
[3] Ethambutol

Due to its efficacy and less adverse effects it is included in first-line therapy of Tuberculosis.

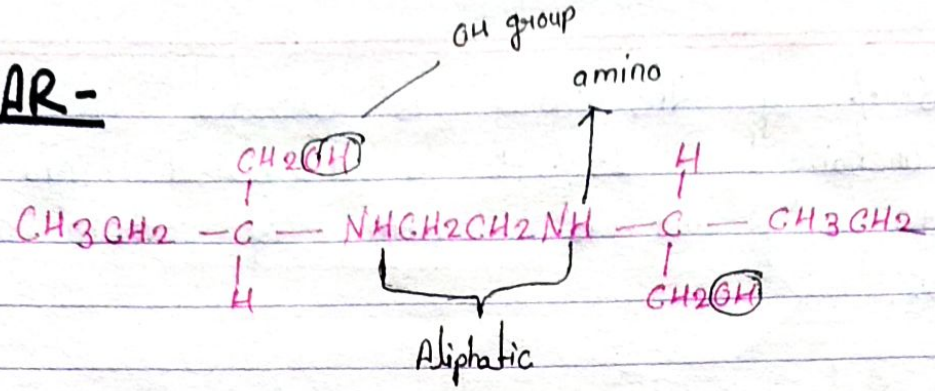
It has synergistic action with other anti-Tb drugs.

It contains 2 asymmetric carban atoms.

It is more active on dividing cells, whereas, less or inactive on non-dividing cells. It inhibits the formation of cell wall.



SAR-



- OH group at CH2
- Aliphatic chain
- NH group.

[1] If OH group are replaced by OCH_3 or OC_2H_5, the compounds remain active, and if replaced by aromatic system (Phenyl or pyridine) the compound become inactive.

[2] By removing OH groups activity is lost.

[3] Extension of ethane diamine results in loss of activity.

[4] Removal of either of the amino group activity is lost.

[5] Increase in size of N- substituents activity is lost.

Antibacterial spectrum / Pharmacokinetics-

- Bacteriostatic
- Absorption - Well absorbed after oral absorption.
- Distribution - Well distributed in all body fluids and tissues including CNS.

Metabolism - 73 % of the drug is excreted in urine as unchanged, 15% is metabolised into metabolite A and B, both of them are inactive.

Mechanism of Action - The mechanism of action of Ethambutol is not fully understood, but has been found to inhibit arbinosyl transferases involved in arbinogalactan synthesis and to interfere with mycolic acid incorporation in mycobacterial cell wall.

~~Therapeutic~~ Uses - Adverse Reactions -

- Optic Neuritis
- Red green color blindness.
- Arthralgia (due to decreased urate excretion)
- Milk skin reaction.

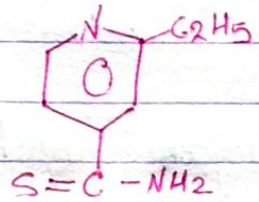
Therapeutic Uses -

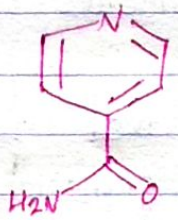
- Used in combination INH and PZA and Rifampicin.
- Its ~~is~~ action is synergistic with other drugs because it disrupts cell wall and facilitates the penetration of other drugs.

[4] Ethionamides

A 2nd line anti TB agent, analogue of isonicotinamide but it is di-substituted and contains S in place of O.

It contains ethyl group at position 2.





In vitro it is less active but in vivo more active because of increased lipocity due to C_2H_5.

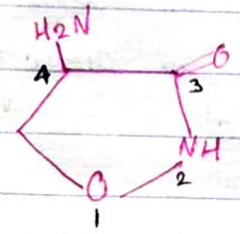
Mechanism of action is similar to isoniazid (INH)

Mechanism of Action- MOA of ethionamides is unknown, it may inhibit the synthesis of mycolic acid, thereby inhibiting bacterial cell wall synthesis.

Metabolism- Less than 1% of the drug is excreted unchanged in urine.

Rest of the drug excreted as one of the following metabolites

[5] Cycloserine



- Analogue of amino acid serine and it exists in cyclic form - a five member ring containing O and N at an adjacent positions.
- It was first isolated from streptomyces orchidaceous. but now being synthesized in laboratory.
- It causes CNS toxicity.
- It acts on cell wall of bacteria and is not selective against MT because all bacteria contain peptidoglycon.
- It acts on normal peptidoglycon portion of cell wall rather than acting on outer layer of mycolic acid.

[6] Rifampicin / Rifampin

- Are group of macrocyclic antibiotics which are produced by streptomyces mediterraei (1957 first time).
- Are useful in treating tuberculosis, leprosy, Mycobacterium avium complex [MAC] infection and staphylococcus infections.

Mechanism of Action-

- It is bactericidal in nature.
- Inhibiting gram +ve bacteria.
- Rifampin completly bind to DNA dependent RNA polymerase enzyme (DDRP) of mycobacteria and interferes with the RNA synthesis.

Uses- First line drug in TB treatment.
Also used to treat leprosy (in combination with Dapsone)
Also used in stephylo cocci infection.

[7] Rifabutin

Known as rifamycin antibiotic.

Related to rifampin in structure.

Mechanism of Action-

Same as of Rifampin.

Uses-
- is used for prophylaxis of MAC (mycobacterium ovium complex) infection.
- Used in combination with other medications to eliminate H. Pylori (causes ulcers).
- less active against MT.

Urinary tract Anti - infective agent

Anti - infective are the drugs that can either kill an infective agent and or it prevent from spreading

UTI is an infection in any part of the urinary system like kidney, Uterus, bladder and urethra.
Ureter

It is defined as the presence of at least 1 lakh bacteria per ml of urine (normal bacterial count = 1000 per ml of urine)

Most infections involve the lower urinary tract (the bladder and urethra).

It is a common disorder at all ages in both males and females.

Epidemology-

UTI is the 2nd most common infections present in community practice.

World wide about 150 million people are diagnosed with UTI each year.

Prevalence 35% of healthy women suffer symptoms of UTI at some time in their life.

Etiology-

- The causative organism causing UTI are -

  E. Coli, Pseudomonas aeroginosa, Streptococcus faecalis, staphylococcus epidermis and proteus mirabilis.

- Waiting for long to urinate.
- Sexual transmitted diseases (STD) like gonorrhea causes urethritis.
- Presence of tumor / stones / foreign bodies in urinary tract.
- Following can cause germs to enter into bladder or kidney and cause UTI. -

  - Having bubble bath.
  - Wearing tight fitting clothes.

Risk factors-

- Being Pregnant.
- Wearing tight fitting clothes.
- Diabetic.

Sign and Symptoms-

Abrupt onset of micturation.

- Pain in urethra during voiding.
- Supra pubic pain and tenderness.
- Haematuria (blood in urine)
- Dysuria.
- Fever, feeling tired, apathy, shaky.
- Pressure in lower belly.

Part of urinary tract affected	Sign and symptoms
Kidney (acute pyelonephritis)	Upper back and side pain High fever Shaking and chills Nausea Vomiting.
Bladder (cystitis)	Pelvic pressure Lower abdomen discomfort Frequent painful urination Blood in urine.
Urethra (urethritis)	Burning with urination Discharge.

Pathogenesis-

- In many cases, bacteria first travel to the urethra, when bacteria multiply, an infection can occur.

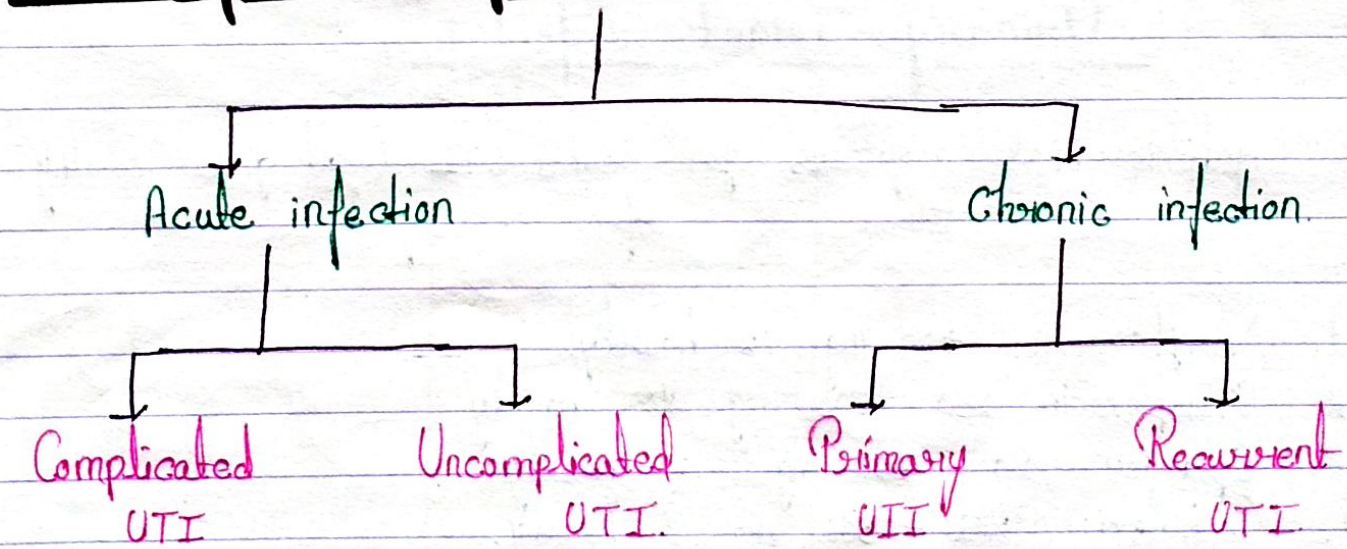
  An infection limited to the urethra is called urethritis.

- If bacteria move to bladder and multiply, a bladder infection called cystitis.

- If the infection is not treated promptly, bacteria may then travel further up the ureters to multiply and infect the kidneys.

  A kidney infection is called pyelonephritis.

Classification of UTI-



Drug Therapy / Treatment

Agents	Examples
1. Bacteriostatics agents.	Sulfonamides Tetracycline Nitrofurantion.
2. Bactericidal agents.	Cotrimaxazole Ampicillin Fluroquinolones Cephalosporins Aminoglycosides
3. Urinary Antiseptic	Nitrofurantoin Nalidixic acid Methanamine. mandelate

Urinary Tract Infection

Antimicrobial regimens for acute UTI (all given orally for 3-5days)

1. Norfloxacin 400 mg 12 hourly.
2. Ciprofloxacin 250 - 500 mg 12 hourly
3. Oflaxacin 200 - 400 mg 12 hourly
4. Cephalexin 250 - 500 mg 6 hourly.
5. Amoxicillin + clavulanic acid (500 + 125 mg) 8 hourly.
6. Nitrofurantoin 50 mg 8 hourly or 100 mg 12 hourly

x x 5 - 7 days.

QUINOLONES

- Quinolones are broad spectrum antibiotics, that are active against both gram +ve and gram -ve bacteria including mycobacteria and anaerobes.
- Quinolones are widely used for treating a variety of infections [community acquired and hospital acquired].
- Quinolones are a family of antibiotics containing a bicyclic core structure related to the compound 4- quinolones.
- Discovered in 1960.

Classification -

They are classified as follows -

Generation	Drugs	Characteristic factor
Quinolones [1st generation]	Nalidixic acid Pipemidic acid Oxolinic acid Cinoxacin.	Active against some gram-ve bacteria, highly protein bound drugs, short half life [Pseudomonas] species - Not active]
Fluroquinolones (2nd generation)	Norfloxacin Ciprofloxacin	Active against gram -ve bacteria [including pseudomonas

	- Ofloxacin - Enoxacin.	Species] some gram +ve bacteria [S. aureus]
3rd generation	- Levofloxacin - Sparfloxacin - Moxifloxacin - Gatifloxacin.	Some as 2nd generation with extended gram +ve and atypical coverage.
4th generation	Trovafloxacin [withdrawn from market in 1999.	Some as 3rd generation with broad anaerobic coverage.

SAR of Quinolones-

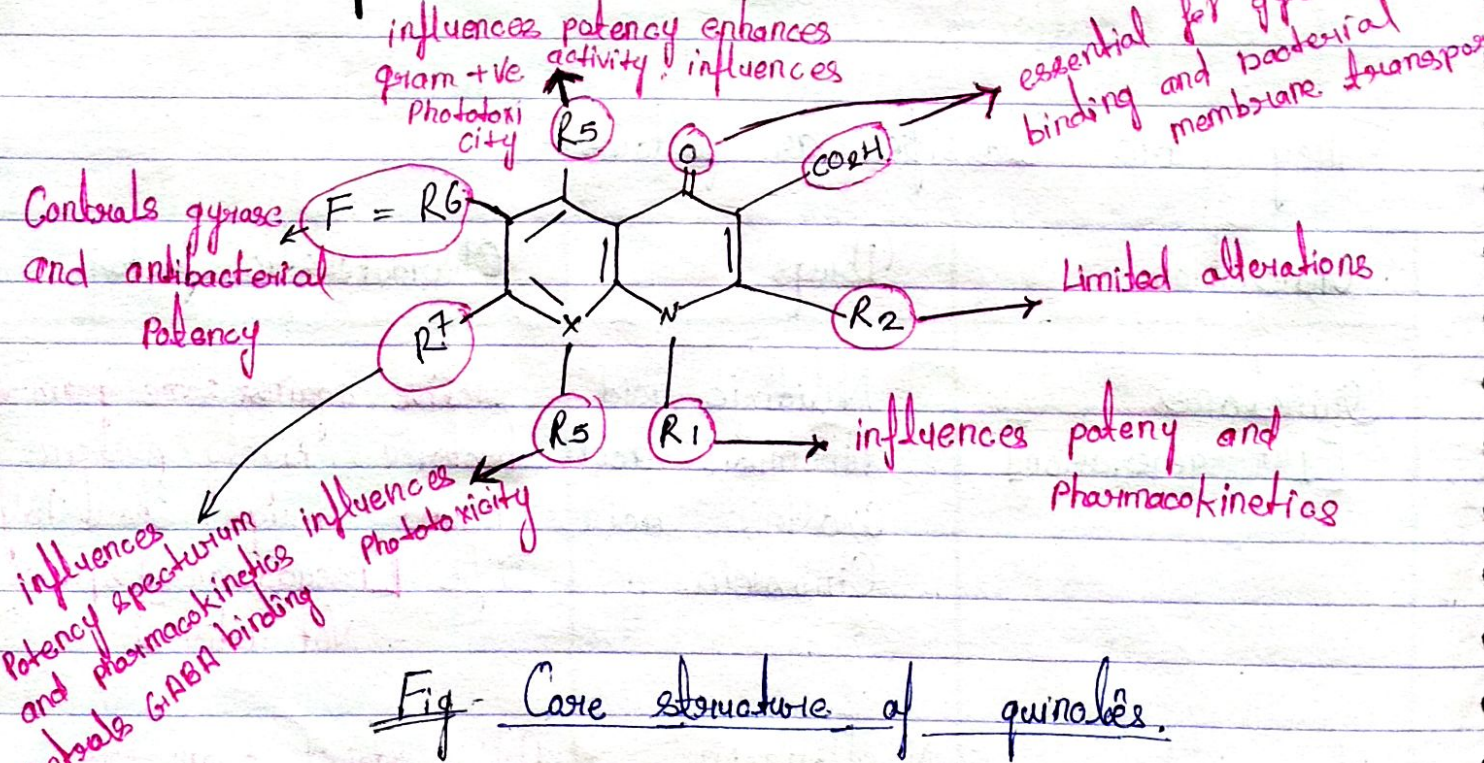


Fig- Core structure of quinolones.

[1] There are 6 imp. positions for modification to improve the activity of the drug -

R_1, R_5, R_6, R_7, R_8 and X.

X = C —— defines quinalones.
X = N —— defines naphthyridones.

[2] Introduction of flourine (F) atom at R_6 position — Tes spectrum of activity [facilitates penetration into the bacterial cells]

[3] Introduction of substituents of position 2 gradly reduces or abalises the activity.

- But substitution at position 5, 6, 7 (especially) and 8 produces good effect.

[6] At position 7 substitution — bacterial tissue penetration and improve the half life.

Eg Piperazinyl & 3-amino pyrolidine substitution at position 7 - enhances activity against P aeruginosa.

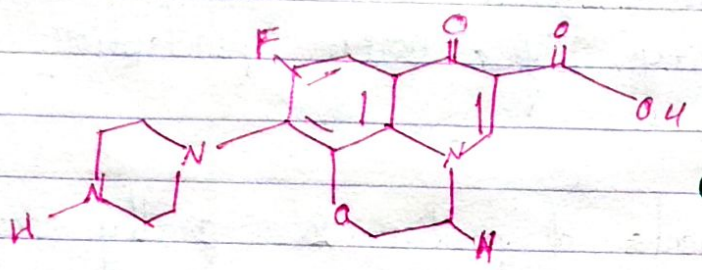
[C] at position 5 an amino group Tes the activity (sparfloxacin).

[3] Alkyl substitution at position - 1 - essential for activity.

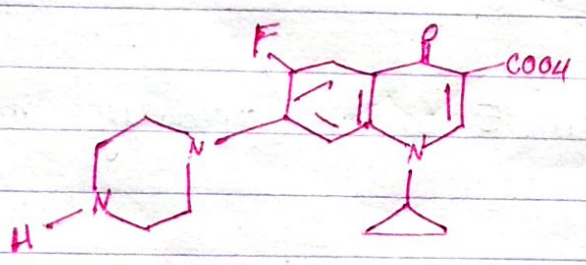
(a) Lower alkyl (methyl, ethyl, cyclopropyl) compounds have greater potency.

[4] Ring condensation at 1,8, 5,6, and 6,7 & 7,8 position leads to ~~to~~ ~~ett~~ active compound.

Eg-



Ofloxacine.



Ciprofloxacin.

The replacement of 'N' at position 8 by -CH (Ciprofloxacin), -CF (Lomefloxacine), -CCl (Sparfloxacine) or by $-COOH_3$ moeity lead to masked improvements in activity against anaerobic bacteria.

Mechanism of Action

Inhibition of DNA gyrase also prevents the relaxation of positively supercoiled DNA.

Inhibition of DNA nicking - closing enzyme responsible for

DNA elongation, which leads to break in double stranded DNA.

Inhibition of topoisomerase IV interferes with the separation of replicated chromosomal DNA into respective daughter cells during cell division.

Or

Fluroquinolones

Inhibiting

DNA gyrase enzyme (topoisomerase II type) enzyme in gram -ve bacteria

→ Nicks double stranded DNA

which

Introduces -ve super coils & themselves the nicked ends.

as

Such +ve supercoiling of DNA strands are presented and replication or transcription is inhibit.

Topoisomerase IV enzyme in gram +ve bacteria.

It interferes with the separation of replicated chromosomal DNA into respective daughter cells during cell devision.

Inhibiting of enzymes may lead to

⇒ Premature cell devision
⇒ Delayed cell devision
⇒ Total failure of cell devision
⇒ Leading to lysis of cell.

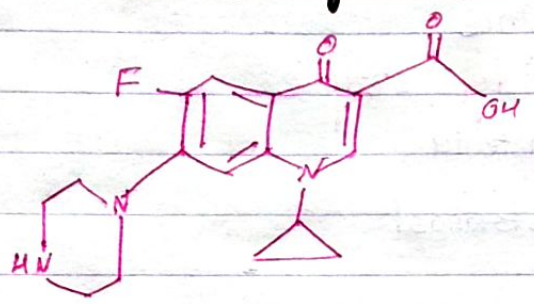
Uses-

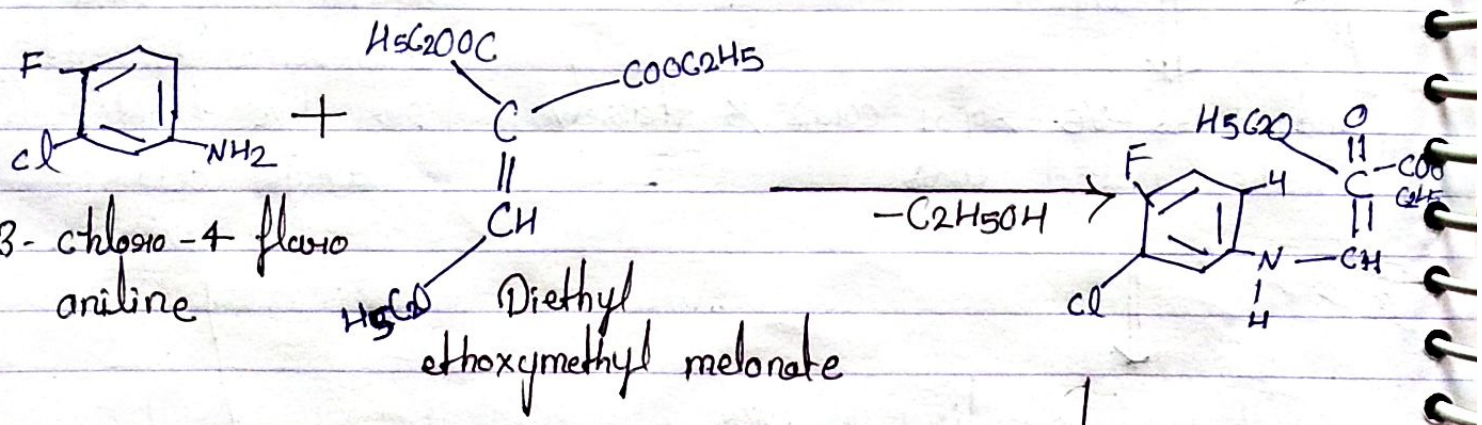
- Opthalmic infections.
- Infection of bone joints & soft tissues.
- Respiratory infections (inhaled anthrax mycobacteria (TB))
- GI and abdominal infections.
- Prostatitis UTIs & STDs

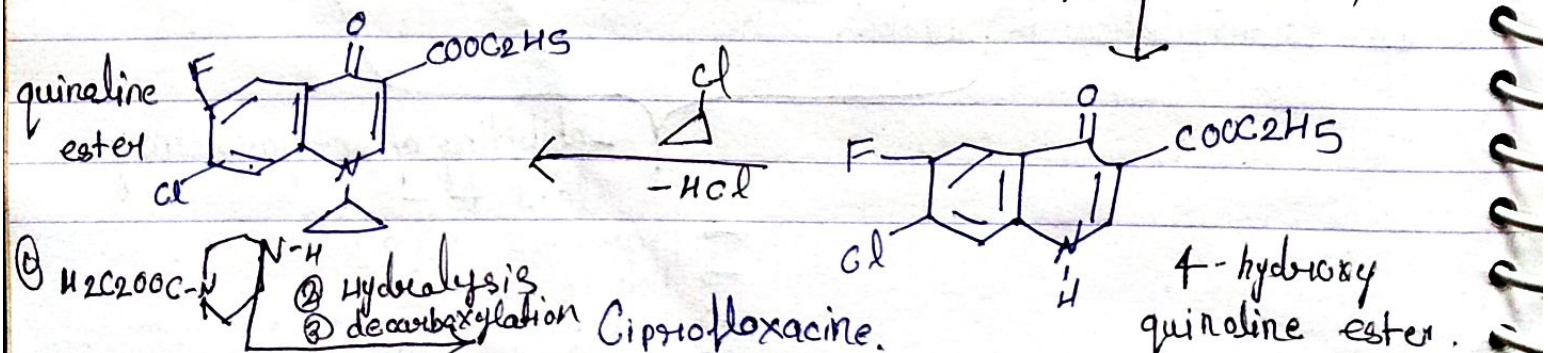
Adverse effect-

Tendon rupture
Children < 18 (cartilage)
Seizures, Confusion, Dizziness.
Photosensitivity.

Synthesis- [1] Ciprofloxacine

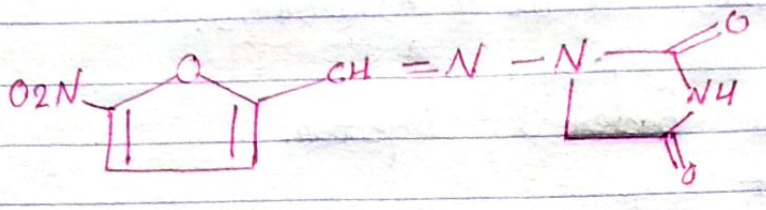




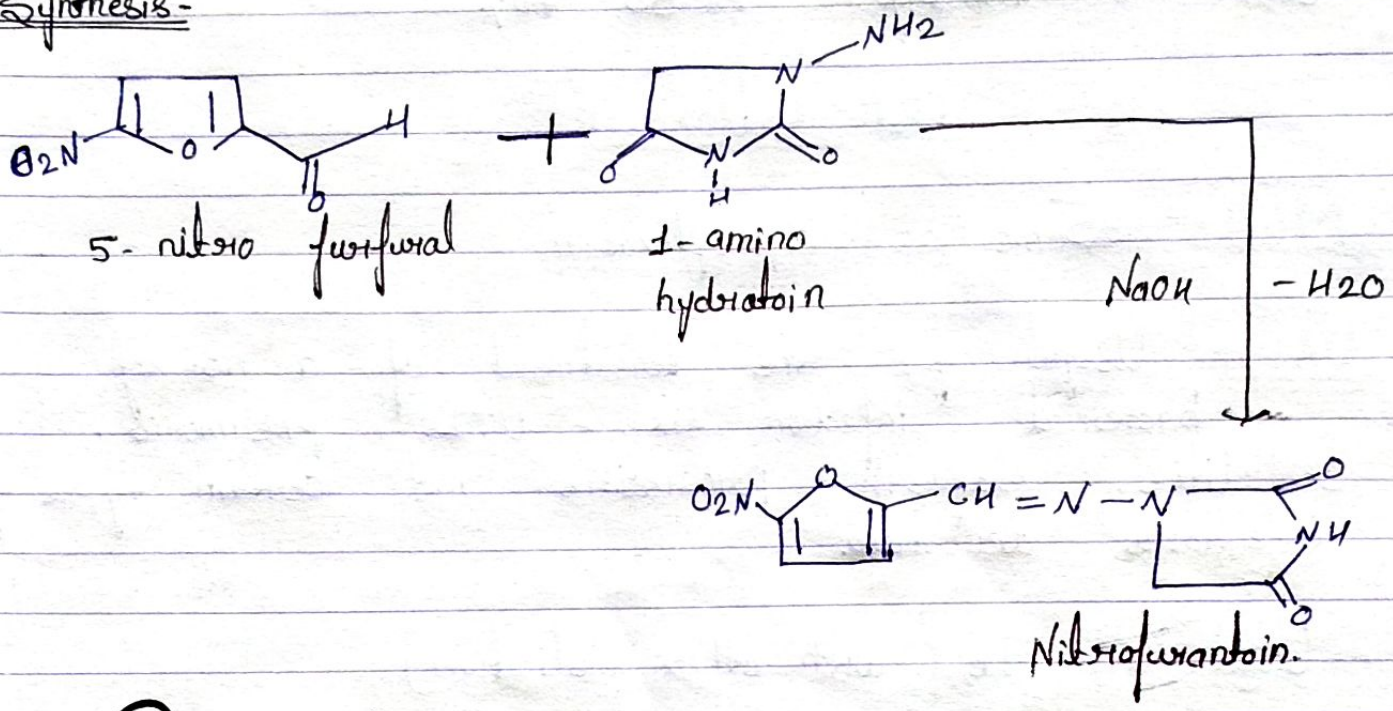


[2] Nitrofurantoin

Structure-



Synthesis-



Brief Notes of Anti- UTI Drugs

[1] Ciprofloxacin

MOA-

Interferes bacterial topoisomerase II enzyme (DNA gyrase) and topoisomerase IV enzyme.

Ciprofloxacin drugs are involved in supercoiling of DNA that is nessary for the duplication, transcription and repair of bacterial DNA.

Uses- - Useful in gram -ve d septicaemia, skin and bone infection urinary and respiratory tract infection, some STDs (gonorrhea).

- Safe drop for bacterial infection.
- Half life 4 hrs.
- Oral bioavailibility → 50 - 70%.

[2] Ofloxacin

MOA- Same as ciprofloxacin.

Uses- Useful for the treatment of a no. of bacterial infection like - UTIs, pneumonia, cellulitis, plague, prostatitis and certain types of infectious diarrhoea.

- Used in TB (with other medication).
- Also used in treatment of syphilis.

[3] Enoxacin

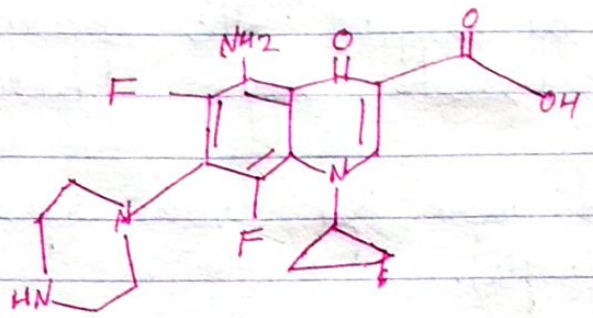
It is an oral broad-spectrum fluroquinalone antibacterial agent.

MOA- Same as ciprofloxacin.

Uses- Used to treat a wide variety of infections like- Gastroenteritis including infectious diarrhoea, RTIs

(Respiratory tract infections), UTIs and gonorrhoea.

[4] Sparfloxacin



Are bactericidal drugs, actively killing bacteria, they inhibit the bacterial DNA gyrase or topoisomerase IV enzyme, thereby inhibiting the DNA replication and transcription.

Uses- Used in treatment of skin and soft tissue infections, lower RTIs and pelvic inflammatory disease (caused by gonorrhoea and chlomydia).

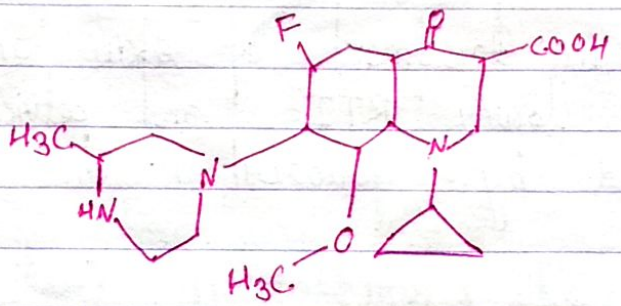
[5] Moxifloxacin, Grafloxacin, Norfloxacin

Mechanism of Action - Same as quinolones.

Uses- Moxifloxacin is used to treat a number of infections, including Respiratory tract infections, cellulitis, anthrax, intra-abdominal infections, endocarditis, meningitis, and tuberculosis.

- Norfloxacin is used to treat a variety of bacterial infections.
- This medication belongs to a class of drugs known as quinolones antibiotics.
- It works by stopping the growth of bacteria. this antibiotic treats only bacterial infections.
- It will not work for viral infections (such as common cold, flu).
- Using any antibiotic when it is not needed can cause it to not work for future infections.

[6] Gatifloxacin



Uses - This medication is a quinolone antibioti used for eye infections (such as conjuctivitis).

This medication treats only bacterial eye infections

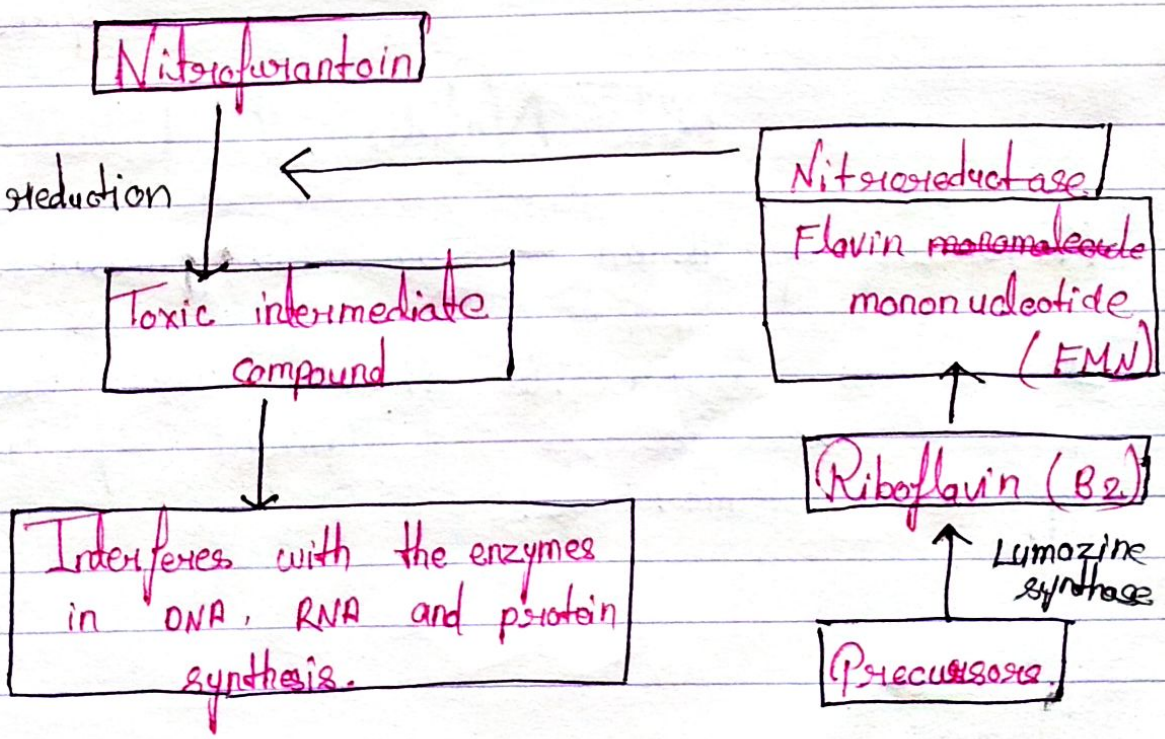
It will not work for the other types of eye infections.

Unnecessary use or misuse of any antibiotic can lead to its decreased effectiveness.

[7] Nitrofurantoin

Mechanism of Action -

- Bacteriostatic, but may be cidal at higher concentration in acidic urine.
- Activity is enhanced at lower pH.
- Inhibiting many gram -ve bacteria.
- Its mechanism of action is unique.
- It is reduced by bacterial flavoproteins to reactive intermediates that inhibit bacterial ribosomes & other macromolecules, protein synthesis, aerobic energy metabolism, DNA & RNA synthesis & cellwall synthesis are inhibited.



Uses- An antibiotic used to treat -
- UTIs
- Cystitis.
- Kidney infections.

[7] Methanamine

Methanamine is hexamethylene-tetramine, inactive as such. decomposes slowly in urine (~~acidic~~ acidic) to release formaldehyde which inhibits all bacteria.

Methanamine
↓ decomposes at pH 5.5, less in urine & gets converted to -
Ammonia & formaldehyde.
↓ acts locally &
⊖ or inhibit bacteria (interferes with protein synthesis)

[8] Nalidixic Acid

Mechanism of Action - Same as quinalones.

It is no longer in clinical use due to bacterial resistance & development of more effective antimicrobials.

Date
25/5/24

Day - Tuesday

ANTIVIRAL AGENT

Are drugs / medications used for treating viral infection.

Unlike most antibiotics, antiviral drugs don't destroy their target pathogens, instead they inhibits its development.

Virus

Virus is a submicroscopic infectious agent that replicates only inside the living cells of an organism, it infects all types of life forms (Plant, animals, microorganism).

When infected, a host cell is forced to rapidly produce thousands of copies of the original virus.

When not inside an infected cell or in the process of infecting a cell, viruses exist in the form of independent particles or virions, consisting of -

(i) The genetic material, that is long molecules of DNA or RNA that encode the structure of the proteins by which ~~surrounds and protects~~ the virus acts.

(ii) A protein coat, the capsid, which surrounds and protects the genetic material, and in some cases.

[iii] An outside envelope of lipids.

The shapes of these virus particles range from simple helical and icosahedral forms to more complex structures.

Most virus species have virions too small to be seen with an optical microscope, as they are one-hundredth the size of most bacteria.

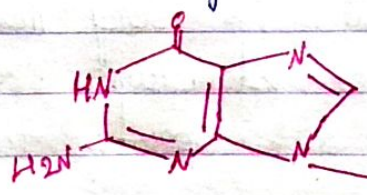
The origins of viruses in the evolutionary history of life are unclear - some may have evolved from plasmids - pieces of DNA that can move b/w cells - while others may have evolved from bacteria.

Classification of Antiviral drugs

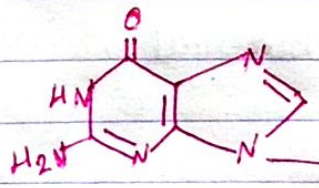
The antiviral agents are classified as follows -

[1] Anti-Herpes Virus -

Ex- Idoxuridine, Acyclovir, Famciclovir, Gancyclovir.



(Acyclovir)

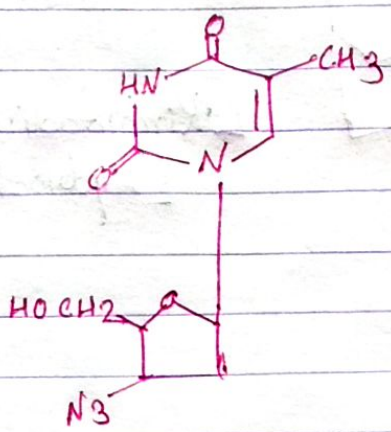


(Gancicloviz)

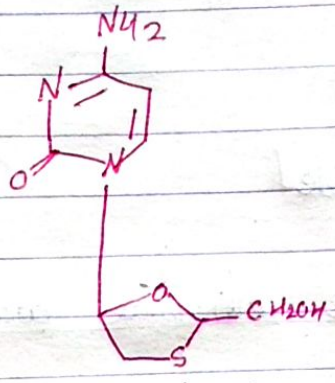
[B] Anti-Retrovirus / Anti-HIV virus-

[A] Nucleoside reverse transcriptase inhibitor (NRTIs)-

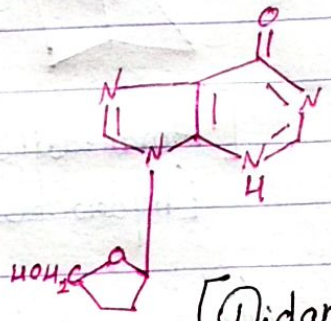
Ex- Zidovudine, Stavudine, Didonosine, Zalcitabine, Lamivudine.



[Zidovudine]



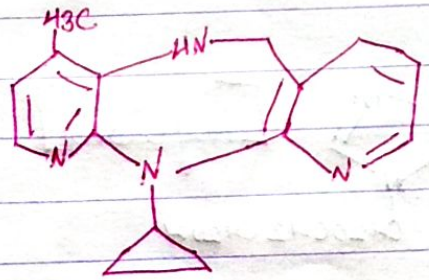
[Lamivudine]



[Didanosine]

[B] Non nucleoside reverse transcriptase inhibitors (NNRTIs)

Ex- Nevirapine, Delavirdine.



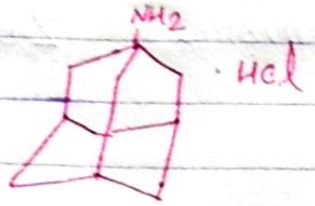
[Nevirapine]

[C] Protease inhibitors-

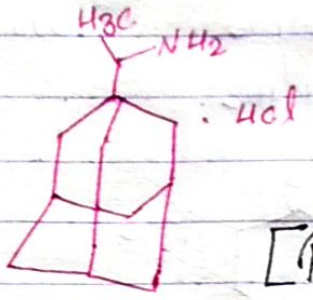
Ex- Indinavir, Saquinavir
Lopinavir.

[3] Anti - Influenza Virus -

Ex- Amantadine, Rimantadine.



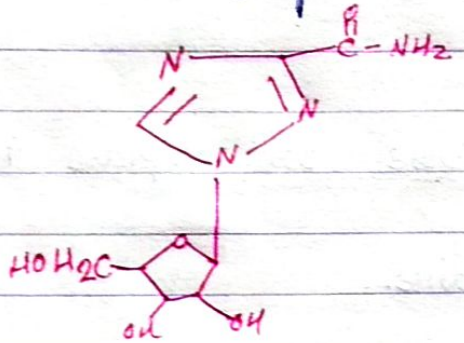
[Amantadine]
[Hydrochloride]



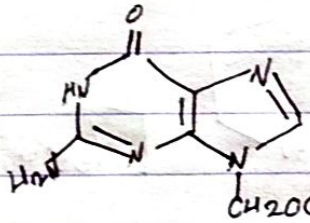
[Rimantadine]
[Hydrochloride]

[4] Non - selective antiviral drugs -

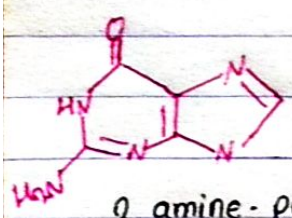
Ex- Ribavirin, interferon α.



Synthesis -



[Acyclovir]

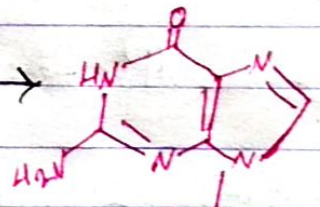


2 amine - purine - 4 - one

+ $C_6H_5COOCH_2CH_2OCH_2Cl$

2 - (chloromethyl) ethyl benzoate

$\xrightarrow[-HCl]{(C_2H_5)_3-N}$



$\xrightarrow[-C_6H_5COONa]{NaOH}$

Acyclovir.