Common antibiotics & their mode of action

Antibiotics are chemical agents that are microbial products or their derivatives, which can kill susceptible microorganisms or, inhibit their growth. In fact, antibiotics are special kind of chemotherapeutic agents usually obtained from living organisms. Originally, antibiotics are produced by microorganisms to kill other microbes in order to overcome the interspecific competetions.

The term "antibiotic" was proposed by Waksman in 1945 for those chemical substances of microbial origin which exert antimicrobial activity.

The first systematic search & study of antibiotics was done by Gradia & Dath (1924), who discovered Actinomycetia from soil bacteria Actinomycetes. This antibiotic was never used as chemotherapeutic agent but used to prepare vaccines.

In 1929, Alexander Flemming discovered Penicillin from a fungus Penicillium notatum. This discovery opened the era of antibiotics. In 1939, Rene Dubos discovered Gramicidin

& Tyrocidine from the gram +ve bacteria Bacillus brevis.

Several thousands of antibiotics has been discovered till date.

Characteristics of antibiotics required for them to be used as chemotherapeutic agents :-

To be useful as a chemotherapeutic agent or drug, an antibiotic must have following characteristics :-

(i) They should have the ability to destroy or inhibit many different species of pathogenic microbes, i.e. they must be a broad-spectrum antibiotic.

(ii) They should prevent the development of ~~resistance in the~~ resistant forms of the pathogenic microbe.

(iii) They should not produce harmful side effects in the host organism.

(iv) They should not eliminate the normal microbial flora of the host organism, so that the balance of nature should not get disturbed within the host body.

Mode of Action of Antibiotics :-

One of the most common ways of classification of antibiotics is their mode of action :-

[A] Inhibitors of cell wall synthesis :-

These antibiotics inhibit the bacterial cell wall synthesis. Some important ones are Penicillins, Bacitracin, Cephalosporins, vancomycin etc.

~~(b) Penicillins~~

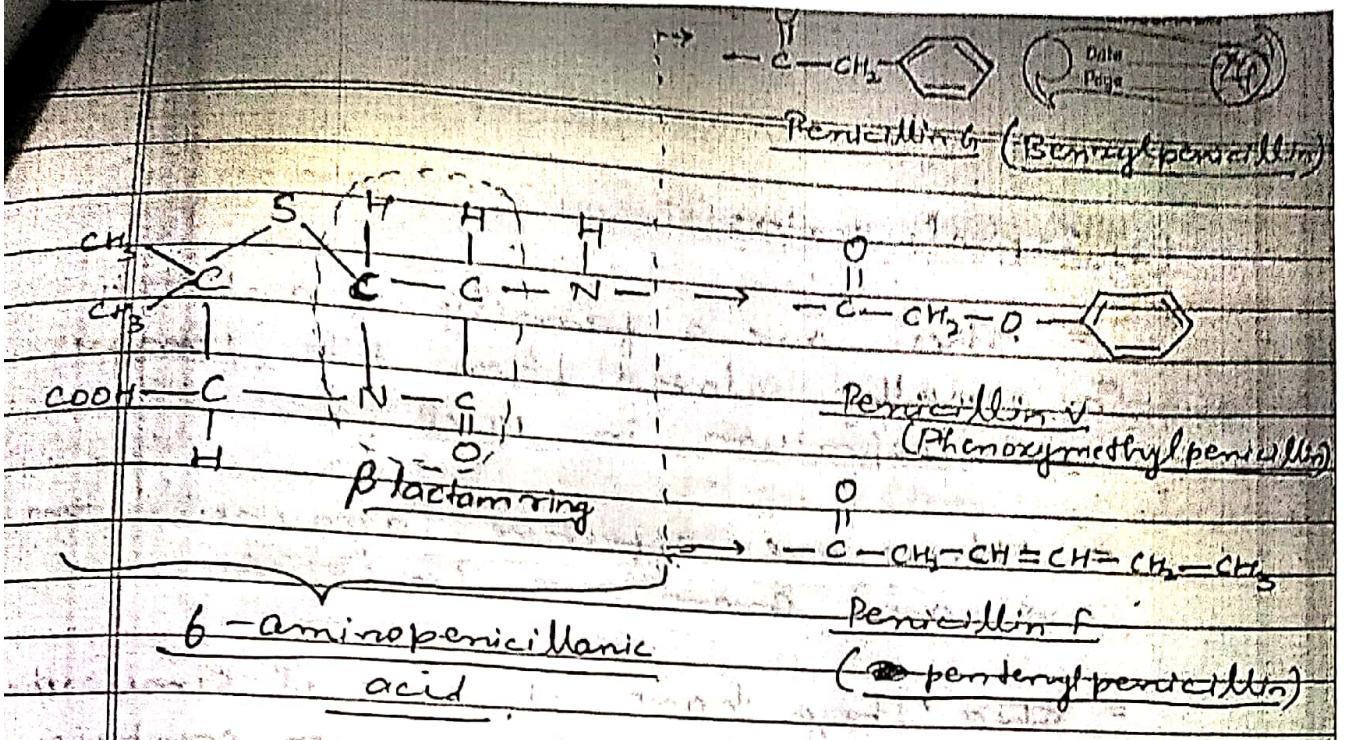
(b) Penicillins :-

= The penicillins (include Penicillin G, Penicillin V) are the first discovered antibiotics.

= Penicillin is selective for Gram +ve bacteria, some spirochetes and Gram -ve diplococci (Neisseria).

= Penicillins contain a β-Lactam ring which is essential for it's bioactivity.

= Most of the penicillins are derivatives of 6-aminopenicillanic acid.



Mode of action :-

The bacterial cell wall is stabilised by the formation of peptidoglycan cross-links (called transpeptidation reaction) during the synthesis of cell wall. Penicillins share structural similarities with the peptide side chain of the peptidoglycan sub-units. This structural similarity blocks the activity of the enzyme that is involved in the formation of peptidoglycan cross-links. As result, the formation of cross-links is hampered. Thus a complete cell wall is not formed, resulting into osmotic lysis of the cell.

However, the complete and even more complex mechanisms of actions of penicillins is not well known.

(2) Cephalosporins :-

= These are a family of antibiotics originally isolated from the fungus cephalosporium in 1948.

= These are effective against Gram +ve and Gram -ve bacteria.

= They have structural similarities with penicillins. They contain a β-lactam structure very similar to that of penicillins.

Mode of action :

As might be expected from the structural similarities to penicillin, the cephalosporins also inhibit the transpeptidation reaction thereby inhibiting the formation of peptidoglycan cross-linkings during bacterial cell wall synthesis. As result cell is not formed completely and the cell is lysed.

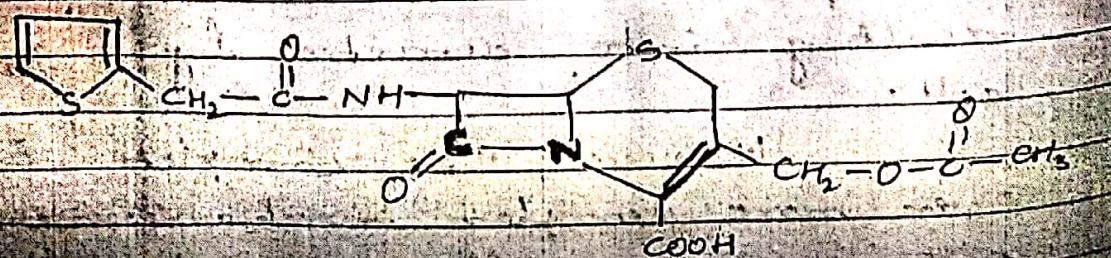


Fig:- Cephalothin (A cephalosporin antibiotic)

= The cephalosporins are derivatives of 7-aminocephalosporanic acid.

= The cephalosporins include:- ~~Cephalothin~~, ~~Cefoxitin~~

Cephalothin :- 1st generation cephalosporin

Cefoxitin :- 2nd " "

Cefoperazone :- 3rd " "

Cefpirazone :- 4th " "

[B] Protein synthesis inhibitors :-

Many antibiotics can inhibit the protein synthesis mechanism within the bacterial cell, by binding with prokaryotic ribosomes, or, by affecting ~~bind~~ aminoacyl t-RNA binding ~~on~~ peptide bond formation, mRNA reading etc.

(1) Tetracyclins :-

= Tetracyclins are a family of antibiotics including Chlortetracycline, Oxytetracycline, Tetracycline, doxycycline & Minocycline.

= These all have a common four ring

structure to which variety of side chains are attached.

= These are broad-spectrum antibiotics produced by Streptomyces bacteria.

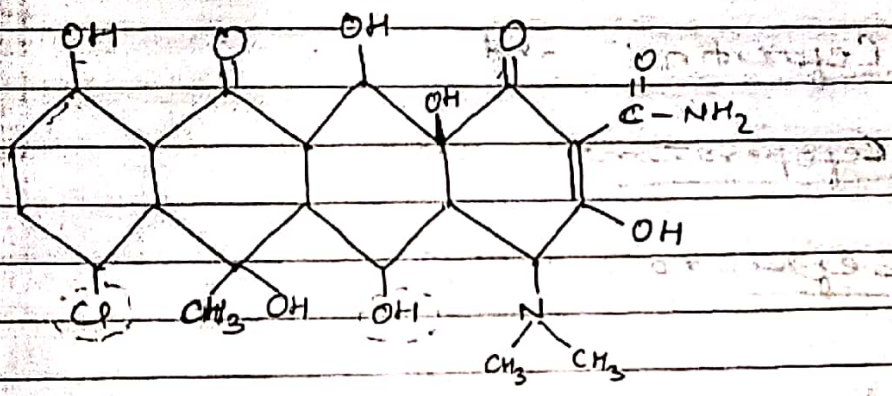


Fig. Tetracycline (Chlortetracycline, doxycycline)

[Tetracycline lack both –Cl & –OH groups that are circled.]

Mode of action :

These antibiotics will combine with the 30S (small) subunit of the prokaryotic ribosomes, this inhibits the binding of aminoacyl t-RNA molecule to the A-site of the ribosome. As result protein synthesis is inhibited.

= The tetracyclins are effective against Gram –ve & Gram +ve bacteria, Rickettsias, Mycoplasma etc. It is a bacteriostatic

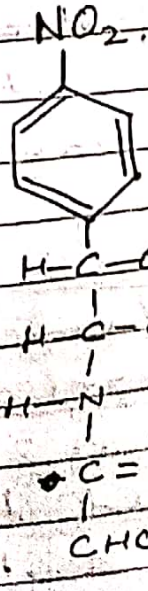
(antibiotic which limits the growth of bacteria, but not kills them) in function.

(2) Chloramphenicol :-

= It is also a broad-spectrum, bacterio-static antibiotic, effective against Gram +ve and Gram -ve bacteria.

= It was first produced from cultures of *streptomyces venezuelae*, but now it is synthesized chemically.

= Chemically, it is a nitrobenzene ring with non-ionic chlorine.



Mode of action :- Chloramphenicol binds to 23 S rRNA of the 50S (large) subunit

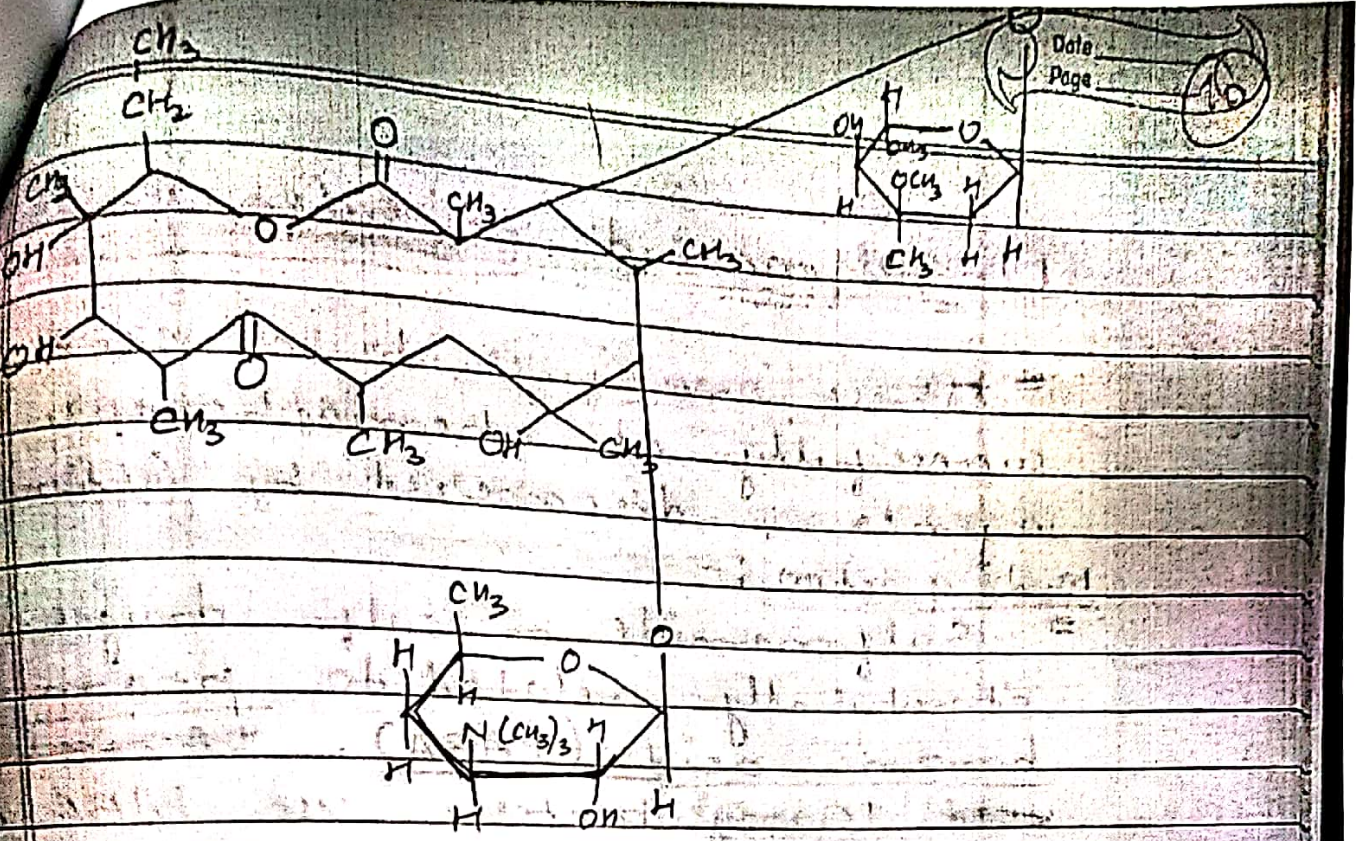
of the prokaryotic ribosome. As result the peptidyl transferase (enzyme involved in formation of peptide bonds) activity is inhibited. Also, transpeptidation and translocation functions associated with the 50S sub-unit are disturbed. Thus, the protein synthesis machinary fails to work.

(3) Erythromycin :-

= It is produced by a strain of ~~Erythromyces~~ Streptomyces erythraeus.

= It is effective against Gram +ve bacteria, some Gram -ve bacteria and pathogenic ~~spirochaetes~~ spirochetes. It is also active against those microbes which become resistant to penicillin or streptomycin.

= It belongs to a chemical group of antibiotics, called Macrolide antibiotics which contain 12- to 22- carbon lactone rings linked to one or more sugar. Other antibiotics of this group includes Clindamycin, Azithromycin etc.



Mode of action :-

Erythromycin = binds to the 50S sub-unit of the prokaryotic ribosomes, as result the process of transpeptidation and translocation are blocked, which result in to failure of protein synthesis.

[C] Inhibitors of specific enzyme systems (Metabolic antagonists) :-

Several drugs act as antimetabolites i.e., they block the functioning of metabolic pathways by competetively inhibiting the functioning of important enzymes.

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(1) Sulfonamide or Sulfa Drugs :-

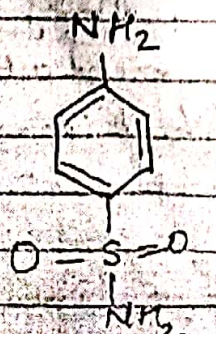
= These are first to be used successfully as chemotherapeutic agents, discovered by G. Domagk.

Mode of action :-

= Sulfonamide or sulfa drugs are structurally related to p-amino-benzoic acid (PABA). Many bacteria use PABA in the synthesis of a co-enzyme i.e. Folic acid (Tetrahydrofolic acid or THFA).

= These drugs compete with PABA and thereby block the synthesis of Folic acid. The Folic acid is a precursor of purines & pyrimidines thus synthesis of purines & pyrimidines are blocked.

= As result, the protein synthesis and DNA synthesis, within bacterial cell, are blocked and thus the pathogen dies.



Sulfanilamide

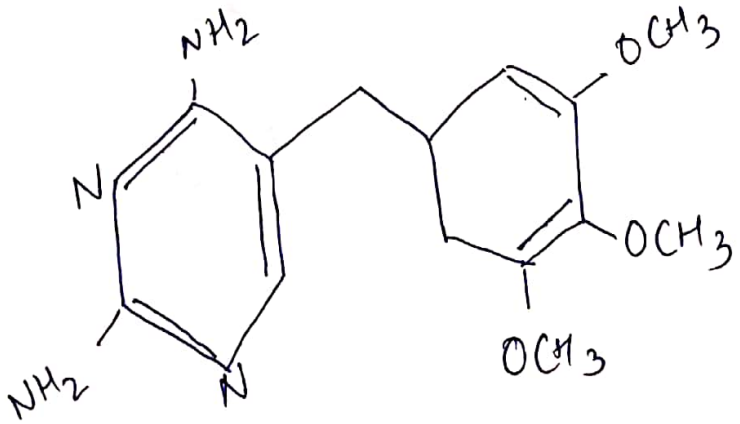
Trimethoprim

= It is a synthetic antibiotic
= It also interfere the synthesis of folic acid in bacteria.

Mode of action:

= It binds to dihydrofolate reductase (DHFR), the enzyme responsible for conversion of dihydrofolic acid into Tetrahydrofolic acid (THFA). Thus the enzyme activity is blocked and thereby the synthesis of folic acid is blocked.

= As a result the synthesis of purines and pyrimidines are blocked, which ultimately results into blockage of DNA + protein synthesis in the cell and finally the bacteria dies.



[D] Inhibitors of nucleic acid synthesis :-

These antibacterial drugs inhibit the functioning of enzymes like DNA Polymerase, helicase or RNA polymerase, thus blocking the process of replication or transcription. For Example :-

- Quinolones :-

= These are broad-spectrum antibiotics.

= These are synthetic drugs that contain 4 - quinolone ring.

= The first quinolone was Nalidixic acid which was synthesized in 1962. Since then, many of these drugs have been produced :- Ciprofloxacin, Norfloxacin and Ofloxacin, these drugs are currently used.

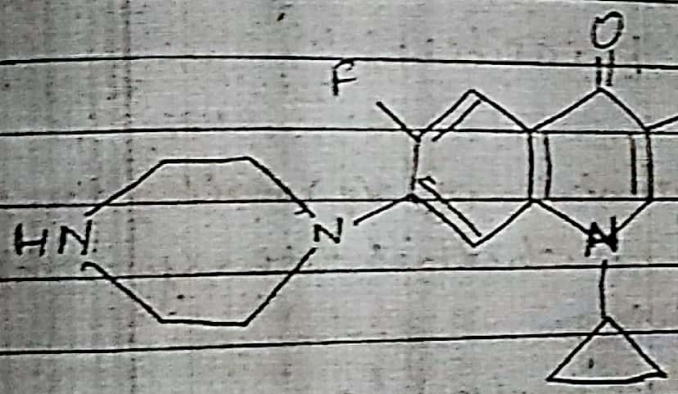
Mode of action :-

= These are highly effective against enteric bacteria and also against gram +ve bacteria.

Mode of action :-

Quinolones inhibit DNA gyrase and Topoisomerase II enzymes. Inhibition of these enzyme

disrupts the process of DNA replication and repair and also separation of bacterial chromosome during division and other cell processes involving DNA, thereby the bacteria dies.



Ciprofloxacin