Antibiotics

Are chemical substances produced by microorganism that has the capacity in low concentration to inhibit selectively or even to destroy bacteria by antimetabolite mechanism

Antibiotic is a word derived from the term antibiosis. Anti means against and biosis means life (against life)

M.O. producing A.B. called (Actinomycetes).

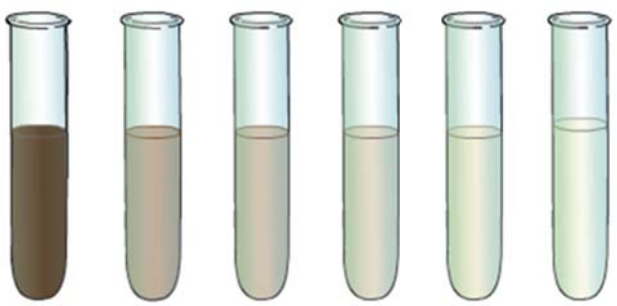
Antimicrobials are chemical compounds which produced by either chemical synthesis example triprim (methprim) or produce by some medicinal plant. They are not produce by microorganism

Screening for A.B.:

In searching for new A.B., relatively simple and rapid methods have seen developed for screening M.O., for A.B. producing ability soil sample are commonly employed in the screen because they are a rich source of A.B. producing organisms.

A general method for screening

first involves treating the soil sample with chemical that inhibit the growth of interfering bacteria and fungi but do not affect actinomycetes, cycloheximide is an as antifungal often employed for this purpose and 1:40 dilution of phenol is used as anti-bacterial agent.

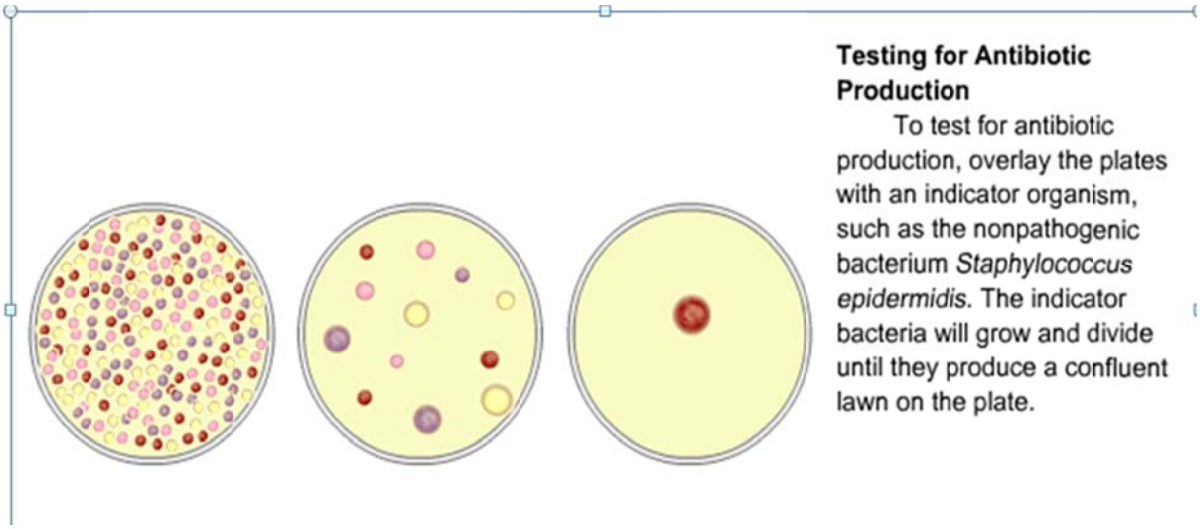


Select the most dilute mixtures and add 1 milliliter of the liquid to plates containing *Streptomyces*-selective media. Spread the sample evenly, and then incubate the plate for 5 to 7 days at room temperature. *Streptomyces* colonies appear white or colored and have a powdery or leathery appearance.

Varying dilution of the treated soil sample are streaked on agar plates containing medium that supports the growth of actinomycetes.

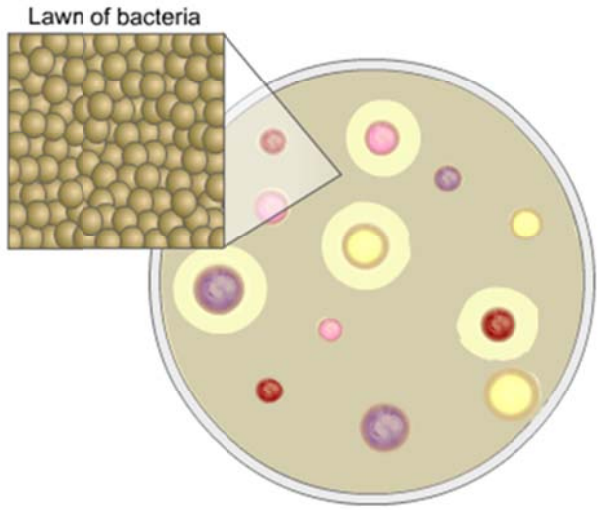
After incubation for 3-7 days at25-30C ◦the plates are examined for characteristic colonies of actinomycetes, these colonies then transferred on to fresh medium contain pathogenic M.O. for indication of the potential usefulness of the A,B.

For example activity against G+ve bacteria can be determined with Staphylococcus aureus or Bacillus subtilis, activity against G-ve bacteria can be determined with E. coil or Salmonella typhi and antifungal with Neurospora crassa .



Testing for Antibiotic Production

To test for antibiotic production, overlay the plates with an indicator organism, such as the nonpathogenic bacterium *Staphylococcus epidermidis*. The indicator bacteria will grow and divide until they produce a confluent lawn on the plate.



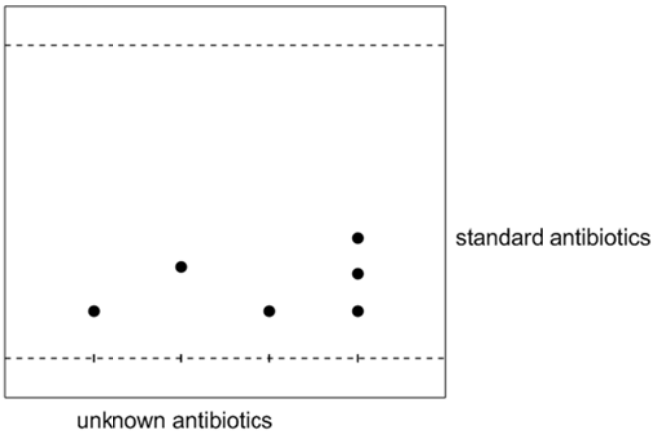
Some of the colonies are surrounded by zones of growth inhibition. The zones of inhibition surround potential antibiotic-producing organisms.

The next step in the screening is to determine whether the chemical substance that produced the inhibition is a new A.B. or a known compound , a rapid method that has been developed for this determination is termed (Bio autography assay).

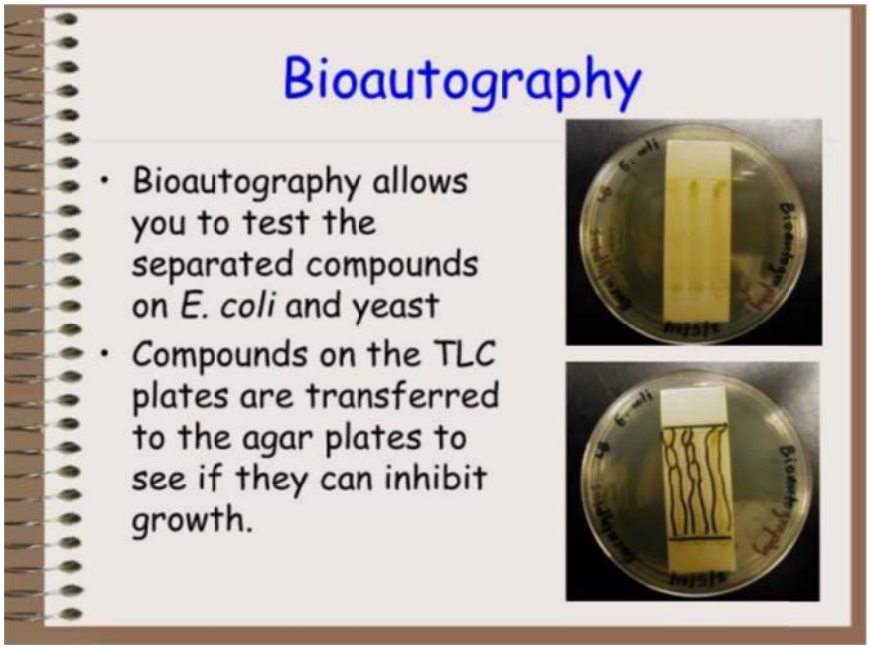
This assay employs paper or thin layer chromatography TLC and biologic assay.

Extract containing the newly discovered A.B. is chromatographed along with reference in different solvent systems.

Because each A.B. would possess a characteristic mobility on the chromatogram in a given solvent system, a comparison of the mobility of the unknown A.B. with those of known one in several solvent system would indicate whether the newly discovered A.B. was a known compound.



Because of the different type of chemical structures found in antibiotics there will be no spraying reagent found to detect the spot of the isolated antibiotics, therefore biological method used which is the introduction of agar media over the TLC profile. The antibiotics will diffuse from the plate to the agar. The inhibition zones indicate the activity and location of the spots of antibiotics.



Classification of antibiotics

According to spectrum:gram negative or gram positive or according to the mechanism of actionIn Pharmacognosy the more important classification is the biosynthetic pathways

1. A.B. derived from amino acid metabolism, like penicillin

2. A.B. derived from acetate metabolism like Tetracylines and erythromycins

3. A.B. derived from CHO metabolism. Like aminoglycoside antibiotics

Antibiotics derived from amino acid include the penicillin, cephalosporin and chloramphenicol

Pencillins: Penicillin is a group of antibiotics which include penicillin G(intravenous use), penicillin V (oral use), procaine penicillin, and benzathine penicillin (intramuscular use).

They are derived from Penicillium fungi.

Penicillin antibiotics were among the first medications to be effective against many bacterial infections caused by staphylococci and streptococci.

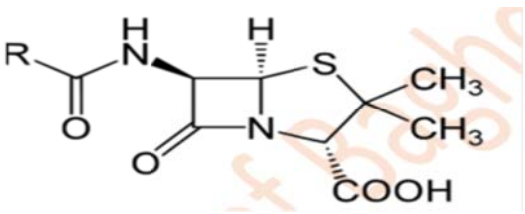
Penicillins are still widely used today, though many types of bacteria have developed resistance following extensive use. All penicillins are β-lactam antibiotics.

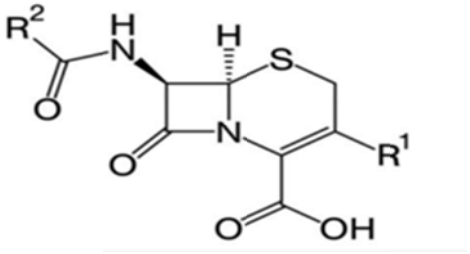
About 10% of people report that they are allergic to penicillin.

Basic structure of Penicillin : (5member)thiazolidine+(4member)lactam ring with viarable R group

Cephalosporin: β-lactam+ dihydrothiazin

• The cephalosporins are a class of β-lactam antibiotics originally derived from the fungus Acremonium, which was previously known as "Cephalosporium".





Classification

• The cephalosporin nucleus can be modified to gain different properties.

Cephalosporins are sometimes grouped into "generations" by their antimicrobial properties. The first cephalosporins were designated first generation cephalosporins, whereas,

later, more extended-spectrum cephalosporins were classified as second-generation cephalosporins.

• Each newer generation has significantly greater Gram-negative antimicrobial properties than the preceding generation, in most cases with decreased activity against Gram-positive organisms. Fourth-generation cephalosporins, however, have true broad-spectrum activity.

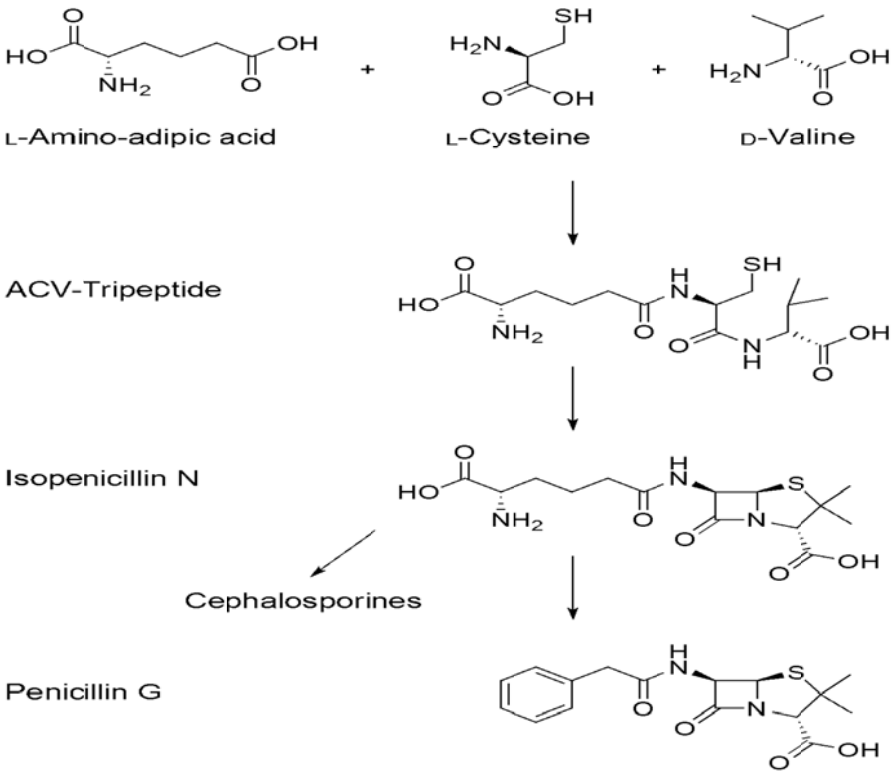
• 1. cephalothin. 2. cephoxitin. 3. Cephotaxim 4. cephepime.

Biosynthesis

There are three main and important steps to the biosynthesis of penicillin

1-The first step is the condensation of three amino acids—-aminoadipic acid ,L-cysteine, L-valine into a tripeptide (ACV).

2. The second step in the biosynthesis of penicillin is the oxidative conversion of linear ACV into the bicyclic intermediate isopenicillin N by isopenicillin N synthase (IPNS).



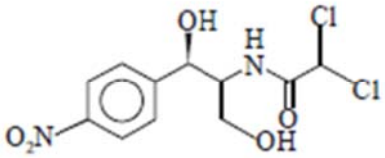
Chloramphenicol

is an antibiotic useful for the treatment of a number of bacterial infections. This includes meningitis, plague, cholera, and typhoid fever.

• Its use is only recommended when safer antibiotics cannot be used. Monitoring both blood levels of the medication and blood cell levels every two days is recommended during treatment.

It is available intravenously, by mouth, and as an eye ointment. Common side effects include bone marrow suppression, nausea, and diarrhea. The bone marrow suppression may result in death.

Chemical Structure



Chloramphenicol

Polypeptide antibiotics

• Polypeptide antibiotics are a chemically diverse class of anti-infective and antitumor antibiotics containing non-protein polypeptide chains.

Examples of this class include actinomycin, bacitracin, colistin, and polymyxin B.

Actinomycin-D has found use in cancer chemotherapy.

Most other polypeptide antibiotics are too toxic for systemic administration, but can safely be administered topically to the skin as an antiseptic for shallow cuts and abrasions.

Antibiotics derived from carbohydrate

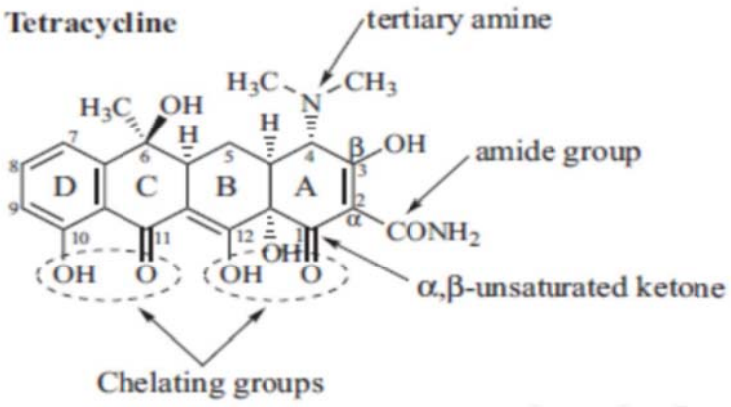
Tetracycline is an antibiotic used to treat a number of bacterial infections.

It is commonly used to treat acne and rosacea. Historically it was important in reducing the number of deaths from cholera.

• It is broad-spectrum and of the polyketide class.

It is produced by the Streptomyces genus of Actinobacteria.

It is a protein synthesis inhibitor



Although tetracycline has numerous functional groups, including a tertiary amine, hydroxyls, an amide, a phenolic hydroxy and keto groups

it is still possible to see that tetracycline is a member of the polyketide class of natural products by looking at the lower portion of the molecule. C10, C11, C12 and C1 are oxygenated, indicating that the precursor of this compound was a poly-b-keto ester.

C10 and C11 and C12 and C1 form part of a chelating system that is essential for antibiotic activity and may readily chelate metal ions such as calcium, magnesium, iron or aluminum and become inactive.

This is one of the reasons why oral formulations of the tetracycline antibiotics are never given with foodstuffs that are high in these ions e.g. Calcium in milk or with antacids which are high in cations such as Mg.

Minocycline and doxycycline are produced Semi synthetically from natural tetracyclines.

Minocycline has a very broad spectrum of activity and has been recommended for the treatment of respiratory and urinary tract infections and as a prophylaxis for meningitis caused by Neisseria meningitides.

Doxycycline (Vibramycin) has use in treating chest infections caused by Mycoplasma and Chlamydia and has also been used prophylactically against malaria in regions where there is a high incidence of drug resistance.

The macrolide antibiotics

The macrolide antibiotics are characterized by a macrolactone ring which is glycosidically linked to one or more sugars.

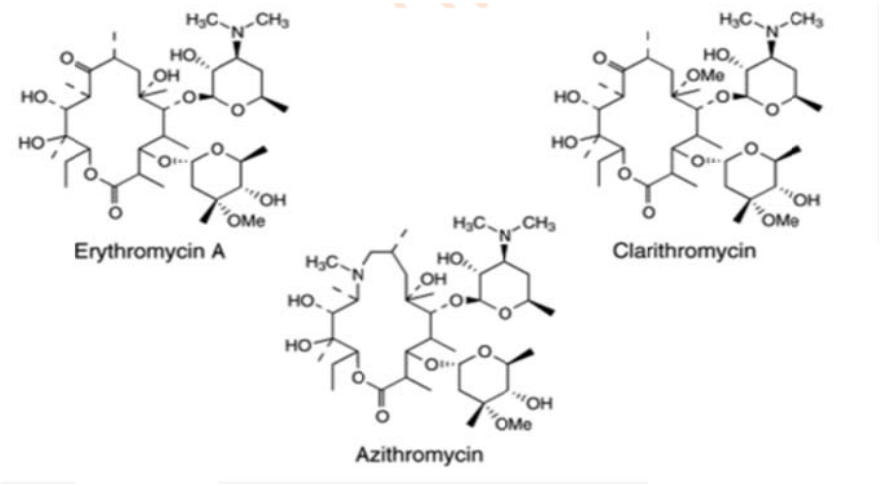
Biosynthetic studies have established that the macrolactone ring is formed by a condensation of acetate and/or propionate units.

Erythromycin

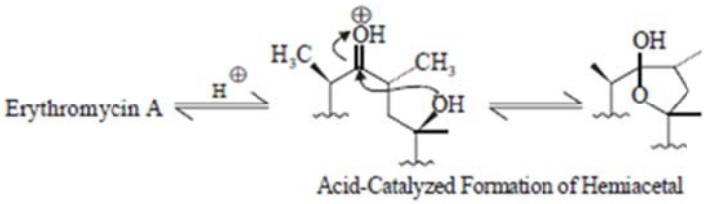
Biological Sources It is produced by cultures of Saccharopolyspora erythraea (formerly known as Streptomyces erythreus).

This compound is a member of the natural product class of macrolide antibiotics; these can contain 12 or more carbons in the main ring system.

As can be seen from, erythromycin A has the best features of natural products, being highly chiral and having many different functional groups, including a sugar, an amino sugar, lactone, ketone and hydroxyl groups.



Erythromycin is fairly unstable under acidic environment whereby it undergoes degradation to inactive molecules through the 6-hydroxyl attacking the 9- carbonyl function to form a hemiketal (or hemiacetal) as shown below:



However, a similar reaction may also take place between the C-12 hydroxyl function and the C-9 carbonyl moiety.

In order to minimize the particular acid instability, semisynthetic analouges of erythromycin have been developed by forming the corresponding 6-O-methyl derivatives of erythromycin (clarithromycin), thereby blocking the possibility of hemiacetal formation completely.

Azithromycin is a semi-synthetic aza-macrolide where in the organic chemistry the prefix aza refer to the replacement of the carbon atom by a nitrogen; and this sort of minor alternation lead to significantly increased in the activity when compared to the parent compound.

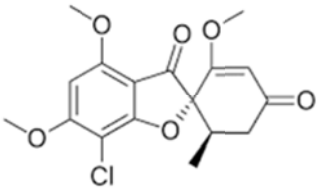
Griseofulvin

Another polyketide antibiotic is griseofulvin (Grisovin) from the fungus (mould) Penicillium griseofulvum.

Griseofulvin is a spiro compound; that is, it has two rings that are fused at one carbon.

Initially, the compound was used to treat fungal infections in animals and plants, but it is now recommended for the systemic treatment of fungal dermatophytic infections of the skin, hair, nails and feet caused by fungi belonging to the genera Trichophyton, Epidermophyton and Microsporum.

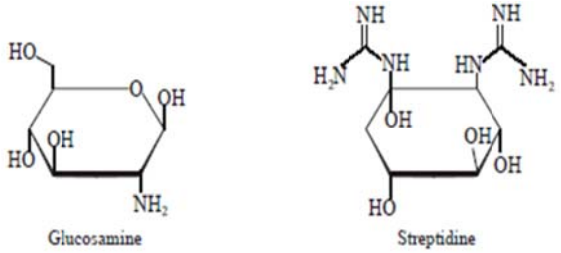
Its main use is in veterinary practice for the treatment of ringworm in animals; it is marketed as Fulcin and Grisovin.



Antibiotic derived from carbohydrate metabolism:

Gentamycin, kanamycin, amikacine and streptomycin

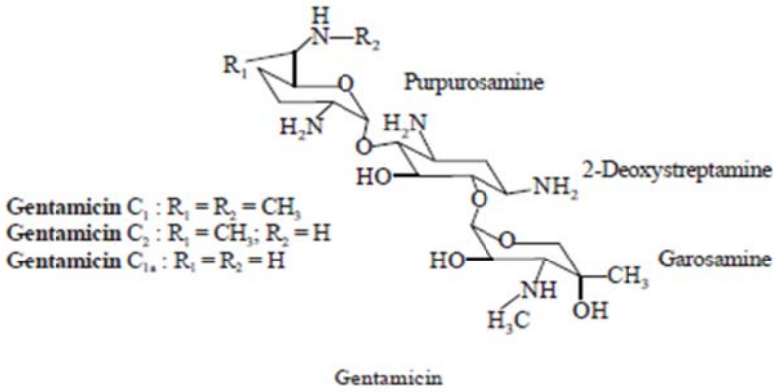
The aminoglycosides each contain one or more amino sugars, for instance: neosamine or glucosamine, bridged by glycoside linkage to basic, either amino or guanidino, six-membered carbon ring, such as: streptamine or streptidine as given below:



Gentamycin

is produced by Micromonospora purpurea, an actinomycete.

These antibiotic substances contain two aminosugar residues and a 2-deoxystreptamine unit. It is currently the most important drug of choice for the treatment of infections caused by most aerobic Gram-negative bacteria.

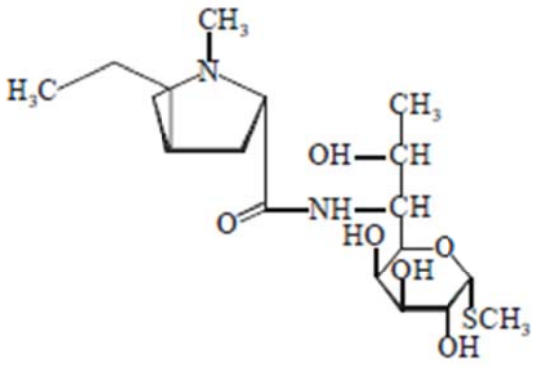


Gentamicin

Linkomycin

It is produced by Streptomyces lincolensis.

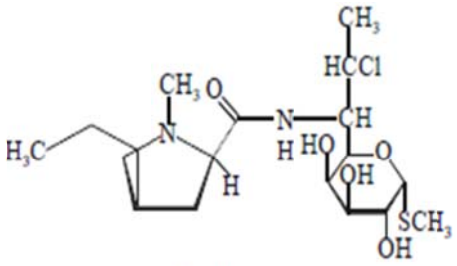
Linkomycin has an amide function group in its structure which may have been contributed by an unique strategic combination of an amino acid and carbohydrate metabolite.



Lincomycin

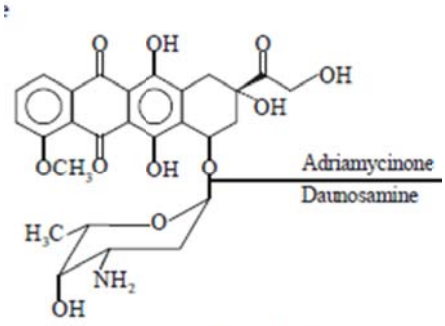
Clindamycin

Clindamycin is synthetic derived from lincomycin by chlorination.



Clindamycin

Doxorubicin



Doxorubicin

Uses

1. It has one of the broadest spectra of antitumour activity displayed by antitumour drugs.
2. It is extensively employed to treat acute leukemias, lymphomas, and a **l**arge number of solid tumours.
3. It has been found to inhibit the synthesis of RNA copies of DNA by virtue of the intercalation of the planar molecule between base pairs on the DNA helix.

Miscellaneous antibiotics

Ansamycin Antibiotics (or Ansamycins): These are a class of macrocyclic compounds where in the non-adjacent positions on an aromatic ring system are usually spanned by the long aliphatic bridge (**Latin:** ansa = handle). The aromatic portion may comprise of either a *substituted benzene* ring or a *substituted naphthalene* or *naphthaquinone* moiety. The macrocycle present in the **ansamycins** is normally closed by an *amide* rather an ester linkage, *i.e.*, ansamycins are **'Lactams'. Example rifadine**