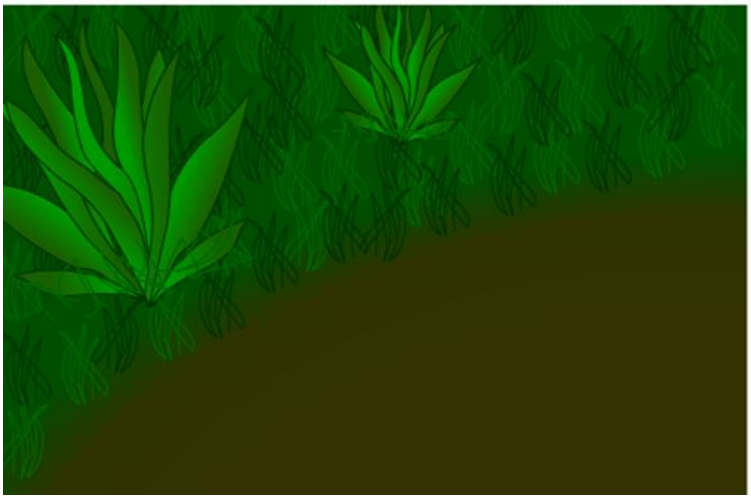
Antibiotics

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

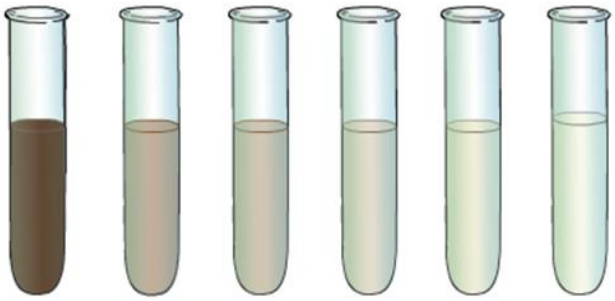
Antibiotic is a word derived from the term antibiosis. Anti means against and biosis means life (against life)

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

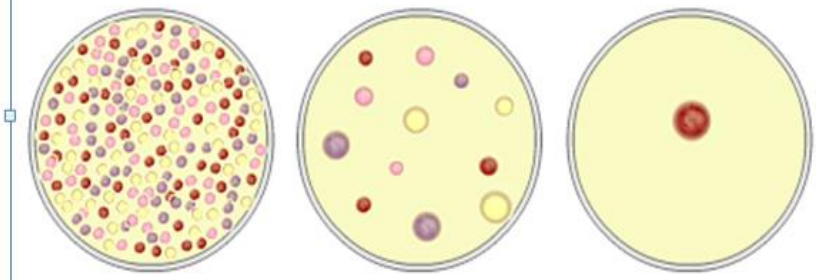


Collecting and Growing Bacteria

Soil bacteria known as *Streptomyces* produce many clinically useful antibiotics. More than 500 *Streptomyces* species are recognized, and nearly half of them produce antibiotics, according to some studies. Here is a method for isolating and screening antibiotic producers.

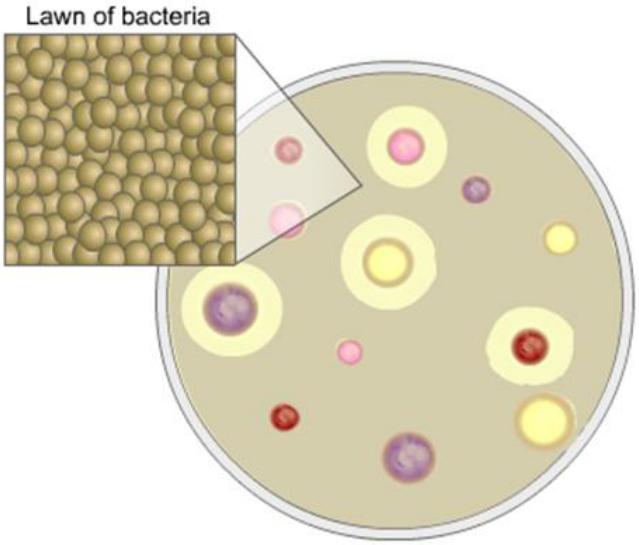


Select the most dilute mixtures and add 1 milliliter of the liquid to plates containing *Streptomyces*-selective media. Spread the sample evenly, and then incubate the plate for 5 to 7 days at room temperature. *Streptomyces* colonies appear white or colored and have a powdery or leathery appearance.



Testing for Antibiotic Production

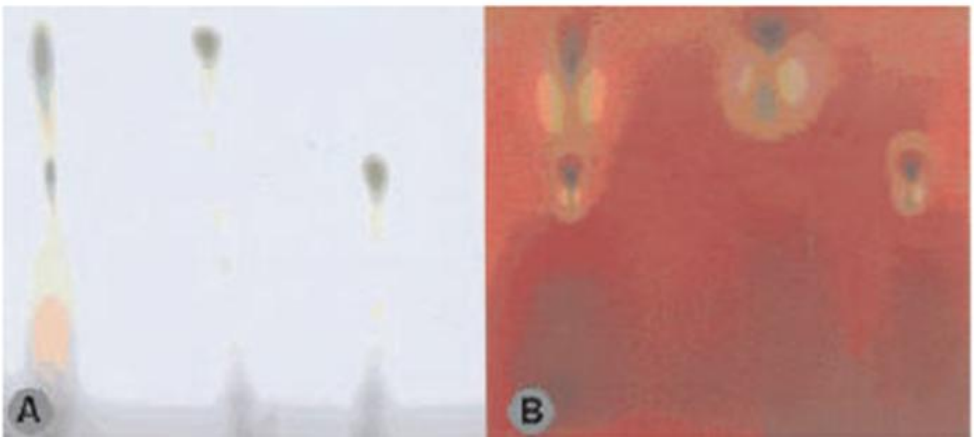
To test for antibiotic production, overlay the plates with an indicator organism, such as the nonpathogenic bacterium *Staphylococcus epidermidis*. The indicator bacteria will grow and divide until they produce a confluent lawn on the plate.

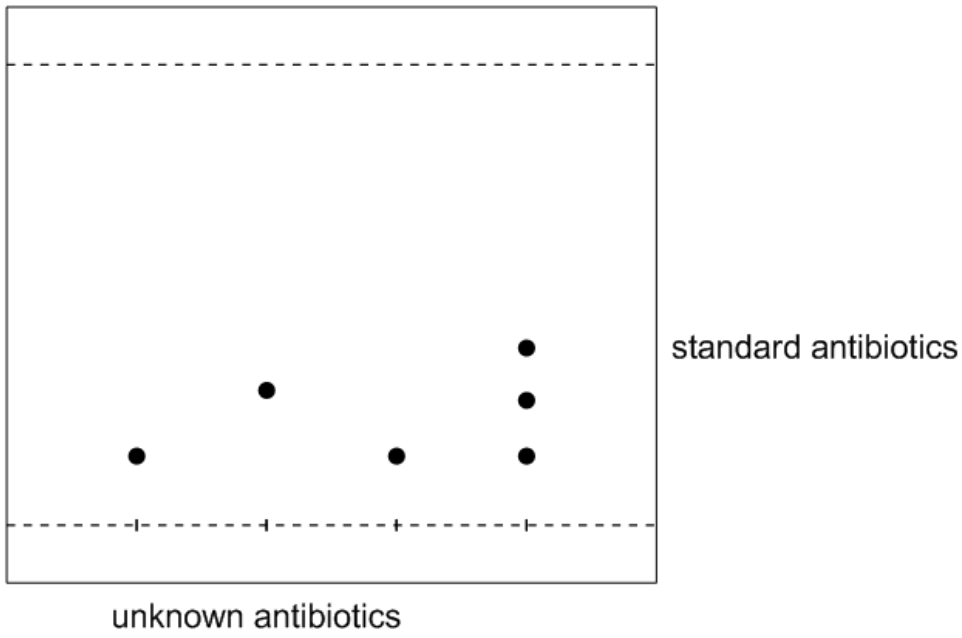


Some of the colonies are surrounded by zones of growth inhibition. The zones of inhibition surround potential antibiotic-producing organisms.

Screening of antibiotics

the next step in screening procedure is to determine whether the chemical substance that produce the inhibition is a new antibiotic or a known compound. **Bioautography** is the method use to determine this. The assay employ paper chromatography or thin layer chromatography and biological assay.





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

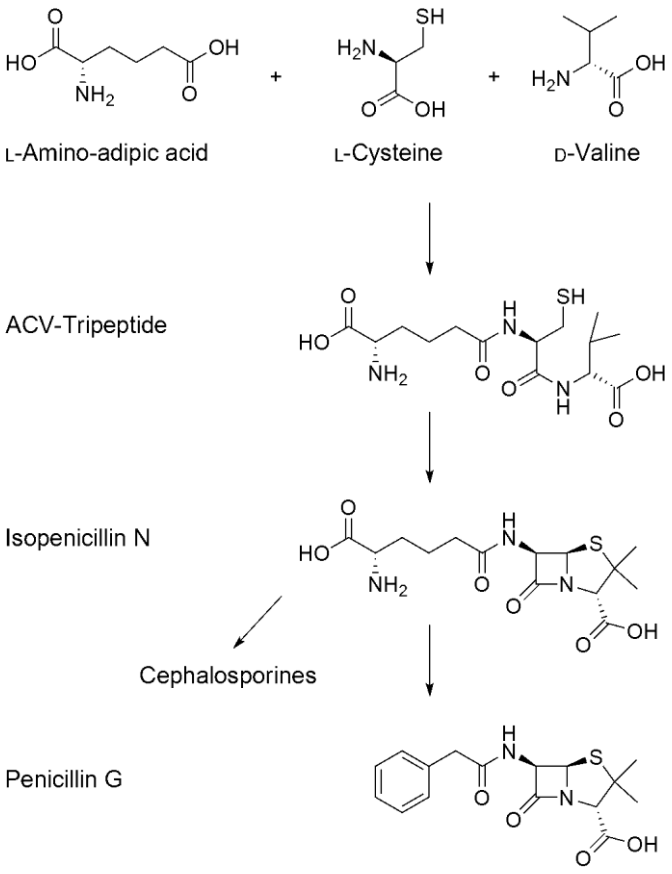
Actions: gram negative or gram positive

In Pharmacognosy the more important classification **is the biosynthetic pathways**

Biosynthesis of antibiotics

The useful microbial metabolites are produced from amino acid, like penicillin. Tetracylines and erythromycins are produced via acetate pathway. Carbohydrate is the source of aminoglycoside antibiotics.

Antibiotics derive from amino acid include the penicillin cephalosporin and chloramphinicol

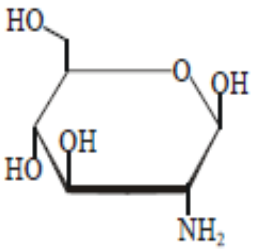


Is a product of *Penicillium notatum*, The β-**lactams** essentially comprise of the **penicillins, cephalosporins, clavulanic acid,** and **moxalactam** Interestingly,the β-lactam heterocyclic nucleus consists of a 4-membered cyclic ring with a N-atom. There exist a number of structural variants of β-lactam ring whereby the highly-strained β-lactam nucleus is strategically stabilized by means of the fusion of a variety of either 5-membered or 6-membered heterocyclic moieties to give rise to a wide spectrum of newer antibiotics

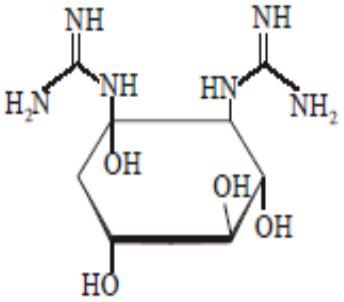
Antibiotics derived from carbohydrate

Gentamycin, kanamycin, amikacine and sterptomycin

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



Glucosamine



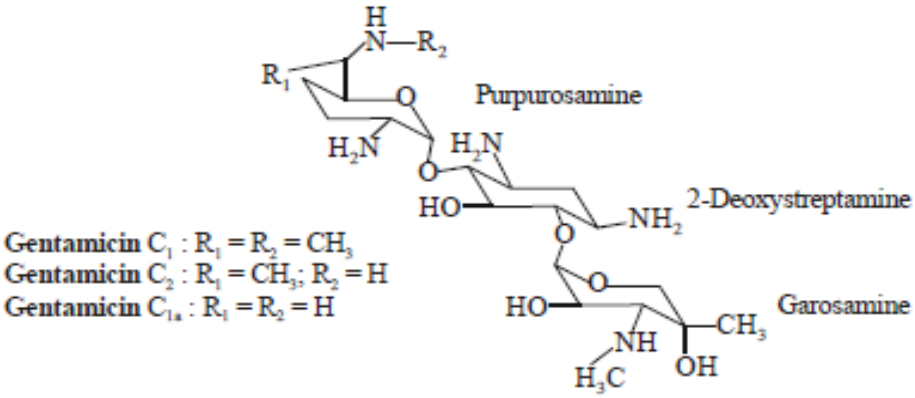
Streptidine

9.3.1.2 Gentamicin

Synonym Gentamycin.

Biological Sources It is an antibiotic complex produced by the fermentation of *Micromonospora purpurea* and *M. echinospora;* and a number of variants thereof.

Chemical Structure

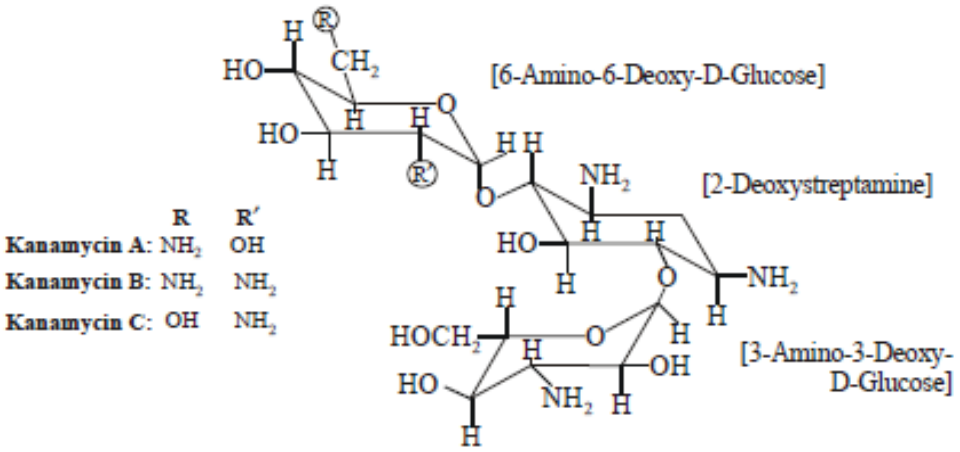


Gentamicin C_1 : $R_1 = R_2 = CH_3$
Gentamicin C_2 : $R_1 = CH_3$; $R_2 = H$
Gentamicin C_{1a} : $R_1 = R_2 = H$

Gentamicin

Preparation **Gentamycin** is normally recovered from a fermentation broth produced when submerged cultures of two subspecies of *Micromonospora purpurea* are grown in the yeast extract-cerelose medium.

It is currently the most important drug of choice for the treatment of infections caused by most aerobic Gram-negative bacteria.



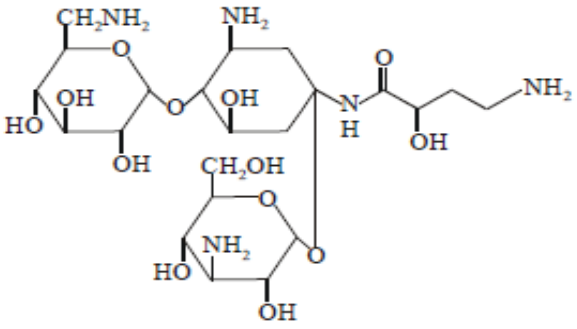
Interestingly, these *three* antibiotics essentially comprise of *two* aminosugars (*i.e.*, 6-amino-6-deoxy-D-glucose) which are linked individually to one single 2-deoxystreptamine aglycone (*i.e.*, non-sugar) residue.

9.3.1.1 Amikacin

Synonyms Lukadin.

Biological Source It is a **semisynthetic aminoglycoside antibiotic** derived from **Kanamycin A.**

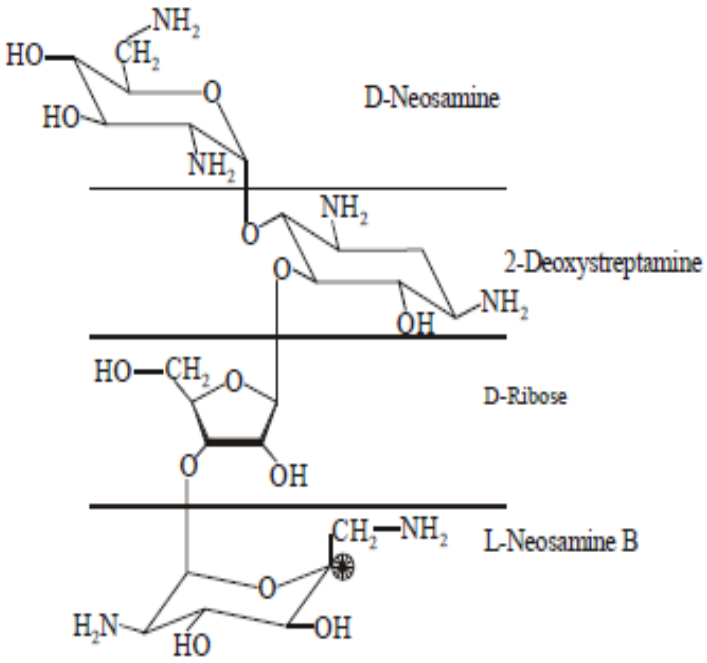
Chemical Structure



Amikacin

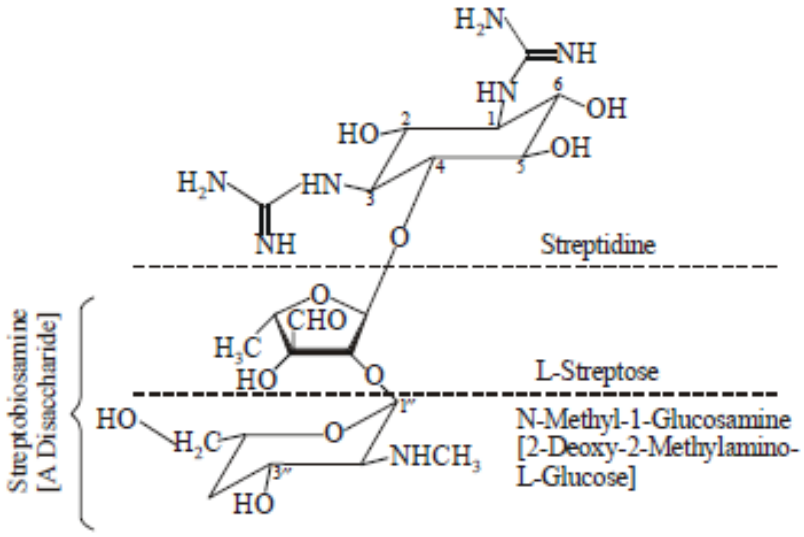
Preparation Amikacin is obtained by acylation of the C-1 amino function of the 2-deoxystreptamine group of **kanamycin** with L-(-)-4-amino-2-hydroxy-butyric acid.

It is mostly employed in a wide range of infections, such as: septicemia, serious infections due to burns, urinary tract, respiratory tract and various soft tissues, meningitis, peritonitis, osteomyelitis, omphalitis in neonates, and other serious surgical infections.



Neomycin B (Framycetin)
[Neomycin C is Epimer at ✱]

Neomycin is usually obtained as a mixture of neomycin B (*Framycetin*) and its epimer **neomycin C**, the latter constitutes 5-15% of the mixture. Interestingly, in contrast to the other clinically useful aminoglycosides, neomycin is observed to comprise essentially of *three* sugar residues strategically attached to *2-deoxystreptamine* as shown above. One of the three sugars present is the *D-ribose* (a common sugar).



Streptomycin

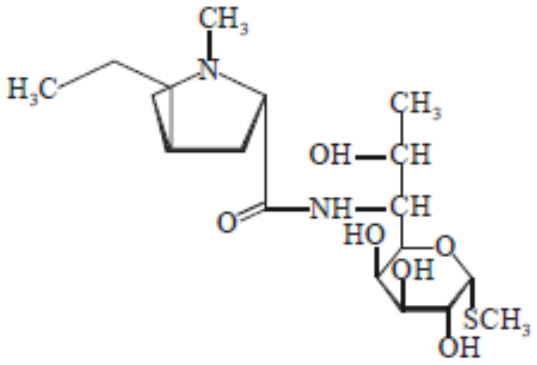
Streptomycin has essentially *two* sugar components, namely: L-streptose and 2-deoxy-2-methylamino-L-glucose, which are linked to a non-sugar moiety streptidine evidently through *two* ether-linkages.

9.3.5.1 Lincomycin

Synonyms Lincolnensin; Lincolcina; U-10149; NSC-70731;

Biological Source It is produced by *Streptomyces lincolensis* var. *lincolensis*.

Chemical Structure **Lincomycin** has an amide function in its molecule which may have been contributed essentially by an unique strategic combination of amino acid and carbohydrate metabolites. It is also obtained through **stereoselective synthesis** by the method of Knapp and Kukkola.***



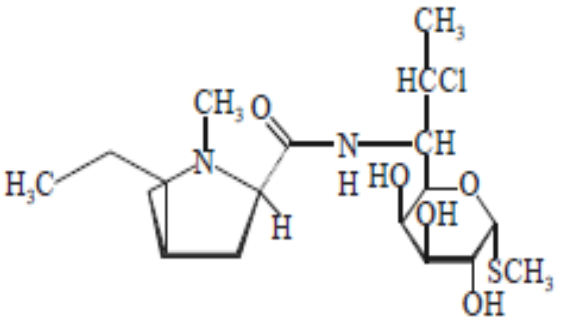
Lincomycin

9.3.5.2 Clindamycin

Synonyms Antirobe; Cleocin; Dalacin C; Klimicin; Sobelin; Clinimycin (rescinded); 7-Deoxy-7(S)-chloro-lincomycin.

Biological Source **Clindamycin** (7-chloro-7-deoxy-lincomycin) is synthetically derived from **lincomycin,** which is obtained from the cultures of *Streptomyces lincolensis* var *lincolensis*.

Chemical Structure The semi-synthetic derivative is obtained by the chlorination of the *lincomycin* with resultant inversion of stereochemistry.

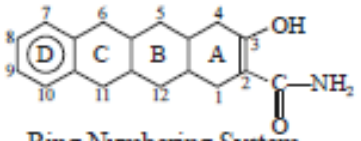


Clindamycin

Acetate derived antibiotics

The **tetracyclines** are a conglomerate of broad spectrum orally active **actinomycete antibiotics** produced by cultures of *Streptomyces* species, and possessing appreciable therapeutic value. **Chlortetracycline** was the first true or real member of this group isolated

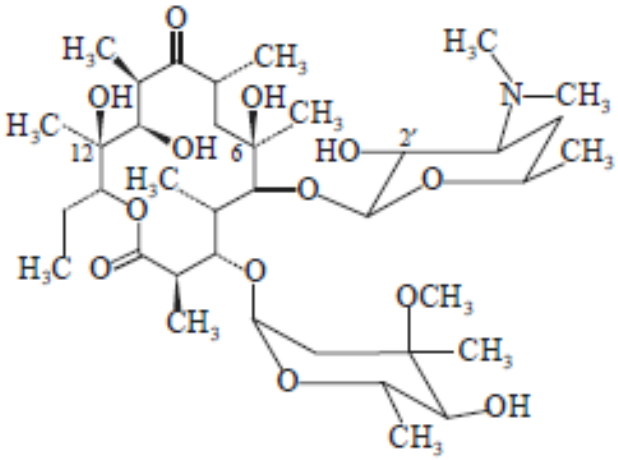
from *Streptomyces aureofaciens* and discovered by Duggar in 1948. It was immediately followed by **oxy-tetracycline** in 1950 from the cultures of *Streptomyces rimosus*.



Ring Numbering System (IUPAC)

Macrolide antibiotics

Erythromycin



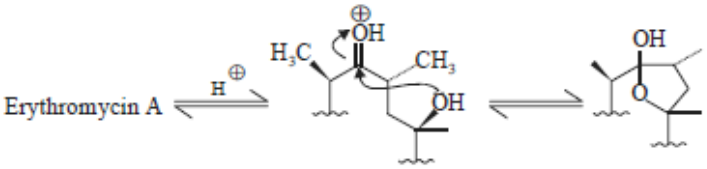
Erythromycin

Biological Sources It is produced by cultures of *Saccharopolyspora erythraea* (formerly known as *Streptomyces erythreus*). Waksman and Henrici were the pioneer in finding this antibiotic in a soil sample collected from the Philippine Archipelago.

Clarithomycin

Biological Source It is a semi-synthetic derivative of erythromycin which is obtained from *Saccharopolyspora erythraea.*

Chemical Features 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:

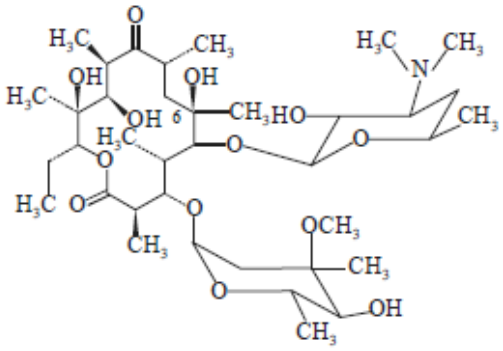


Acid-Catalyzed Formation of Hemiacetal

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

In order to minimise this particular acid-instability semi-synthetic structural analogues of **erythromycin** have been developed by forming the corresponding 6-O-methyl derivative of **erythromycin A**, thereby blocking the possibility of **hemiacetal formation** completely.

Chemical Structure **Clarithromycin** is nothing but a simple structural variant of **erythromycin A** having a 6-O-methyl substituent.



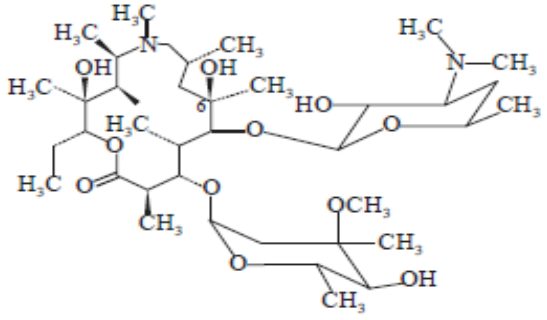
Clarithromycin

Biological Source It is a semi-synthetic derivative of erythromycin which is obtained from *Saccharopolyspora erythraea.*

Azithromycin

Biological Source It is a semi-synthetic **macrolide antibiotic** related to **erythromycin A** which is obtained from *Saccharopolyspora erythraae.*

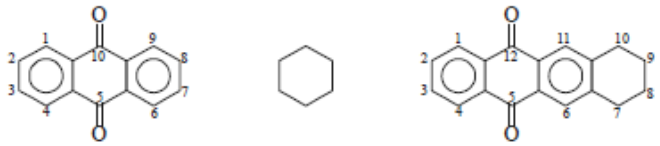
Chemical Structure Azithromycin is a tailor-made ring-expanded aza-macrolide wherein the carbonyl moiety at C-6 has been subjected to reduction; and this sort of minor alternation means the complex structure has significantly increased the activity when compared to the parent compound.



Azithromycin

9.3.2 Anthracyclines

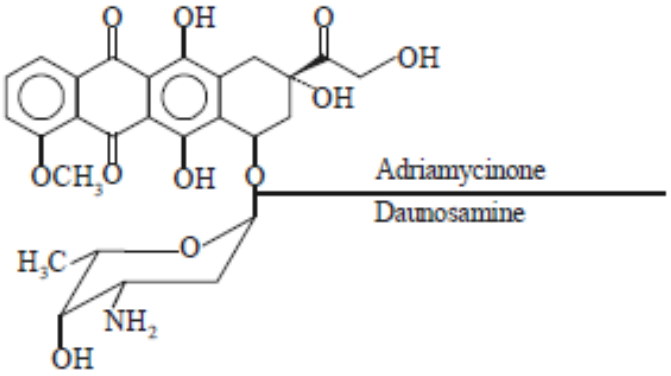
The **anthracyclines** *i.e.*, the **anthracycline antibiotics** essentially contain an anthraquinone moiety fused with a non-aromatic ring:



Anthraquinone Non-Aromatic Ring Anthracycline

Doxorubicin

I Structure



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 large 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.

Cephalosporins

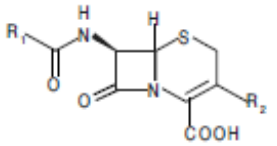
Is belonging to the three categorized generations are available in the therapeutic armamentarium, besides the cephamycins, which are given as under:

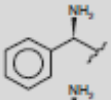
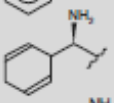
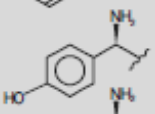
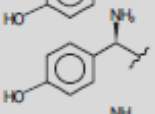
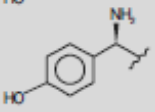
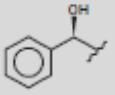
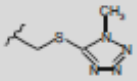
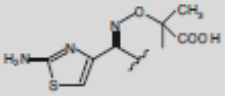
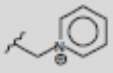
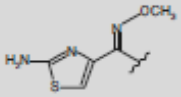
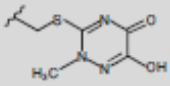
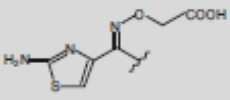
(*i*) ***First generation Cephalosporins:*** **Cefalotin (Cephalothin); D-Cephalexin (D-Cefalexin); Cephapirin; Cefazolin; D-Cephradine (D-Cefradine); D-Cefadroxil;**

(*ii*) ***Second Generation Cephalosporins*****: D-Cefactor; D-Cefamandole; Cefuroxime; DCefonicid; Ceforanide;**

(*iii*) ***Third Generation Cephalosphorins*****: Cefotaxime; Ceftizoxime; D-Cefoperazone;**

Ceftazidime; Ceftriaxone; Cefmonoxime, Moxalactam;



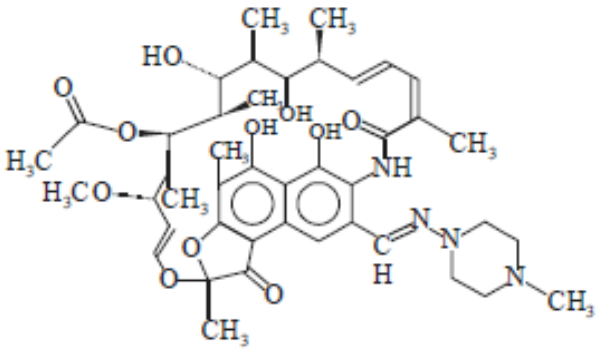
Class	Sl. No.	R_1	R_2	Name (Synonyms)	Special Remarks
First Generation	1		—CH_3	Cefalexin [Cephalexin]	Orally Active
	2		—CH_3	Cefradine [Cephradine]	Orally Active, superseded generally
	3		—CH_3	Cefadroxil	Orally Active
Second Generation	4		—Cl	Cefaclor	Orally Active
	5		—CH=CH—CH_3	Cefprozil	Orally Active,
	6			Cefamandole [Cephamandole]	High Resistance to β-lactamases
Third Generation	7			Caftazidime	Broad-Spectrum Gram-Negative Activity; good Activity against Pseudomonas
	8			Ceftriaxone	Broad-Spectrum Gram-Negative Activity; Longer Half-Life Than Other Cephalosporins
	9		—CH=CH_2	Cefixime	II/III Generation, Orally Active, Long Duration

Miscellaneous antibiotics

Ansamycin Antibiotics (or Ansamycins): These are a class of macrocyclic compounds wherein 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

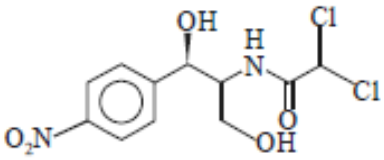
substituted benzene ring or a *substituted naphthalene* or *naphthaquinone* moiety. The macrocycle present in the **ansamycins** is normally closed by an *amide* rather an ester linkage, *i.e.*, ansamycins are **'Lactams'. Example rifadine**

Chemical Structure



Chloramphinicol

Chemical Structure



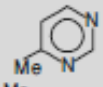
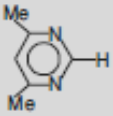
Chloramphenicol

a) **Natural Source:** It may be obtained from the filtrate of a *Streptomyces venezuelae* culture by extraction with ethyl acetate. In case, the charcoal extract is rich in **chloramphenicol,** the latter may be crystallized from the ethyl acetate by affecting dilution with several volumes of deodourized kerosene oil.

(*b*) **Synthetic Route: Chloramphenicol** may be synthesized by many different routes of preparation, but one of the better known starts with *para*-nitroacetophenone and, and after due conversion it into *para*-nitro-2-amino-acetophenone.

Sulphonamides and Trimethoprim Sulphonamides—the first and foremost antimicrobial agents, since discovered in 1930s, still hold the glory and fame of the modern antibiotic era. In general,

sulfanilamide (*i.e.*, *para*-aminobenzene sulphonamide), obtained as a structural analogue of ***para*-aminobenzoic acid (PABA),** is basically the core compound from which hundreds of congeners were synthesized over the years by suitable modifications at N_1 (amide) or N_4 (*p*-amino function) so as to alter the pharmacological characteristics of the parent compound (sulphanilamide). The following table summarizes some of the approved and clinically useful widespread sulphonamides

S. No.	Classification	Drug(s)	R1	R2	Brand Name	Theraputic Uses
I	**Sulphonamides for general Infections**	1. Sulpha-nilamide	H	H	Rhinamid	Obsolete
		2. Sulpha-pyridine		H	M2B 693	Pneumonia; *Dermatitis herpetiformis.*
		3. Sulpha-Thiazole		H	Cibazol	Bubonic plague staph. infections
		4. Sulpha-Diazine		H	Diazyl	Rheumatic fever; Chancroid due to *Haemophilus ducneyi.*
		5. Sulpha-merazine		H	Solume-dine	General infection
		6. Sulpha-dimidine (sulpha-methazine)		H	Pirmazin	Meningal infections