المملكة العربية السعودية

جامعة الملك سعود

كلية العلوم

قسم الكيمياء الحيوية

المضادات الحيوية (BCH 476)

Antibiotics

Lectures 7-13: Classification of antibiotics

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Lec No.	Topics
7	Classification of antibiotics on the basis of biological effect. Classification of antibiotics according to chemical structure. The code system of Bérdy. Carbohydrate antibiotic structure and characteristics e.g. Streptomycin and neomycins.

Classification of antibiotics

- There are many ways to classify antibiotics, like classification according to :
  - the producing microorganism,
  - mode of action,
  - biological or spectral activity, and
  - physicochemical properties.
- The most convincing method of classification depends on the chemical structure:

Classification according to mode action

1.Antibiotics which interfere with cell-wall synthesis

1.beta-lactams, including penicillins and cephalosporins; mono-lactams, such as vancomycin, bacitracin

2.Antibiotics which interfere with bacterial protein synthesis

3.Antibiotics which bind to the 50S ribosomal unit

lincosamides/lincosides including clindamycin and lincomycin; chloramphenicol, macrolides

4.Antibiotics which interfere the 30S ribosomal unit

tetracyclines; aminoglycosides including gentamicin

5. Drugs which interfere with DNA synthesis

rifampin, metronidazole, quinolines, novobiocin

6.Drugs which interfere with cell membrane function

polymyxin B, gramicidin

Classification of antibiotics according to chemical structure

- Bérdy (1974) proposed a detailed system for the chemical classification of antibiotics consisting of primary and secondary classification, method of classification and appropriate code system.

Primary classification

1. Sugar-containing antibiotics in which the carbohydrate moiety is not predominant.
2. Macrocyclic lactones
3. Quinone-indicator and similar antibiotics
4. Amino acid & peptide antibiotics (one or more amino acids)
5. Nitrogen-containing heterocyclic antibiotics
6. Oxygen-containing heterocyclic antibiotics
7. Alicyclic antibiotics (having aromatic or aliphatic chain)
8. Aromatic antibiotics (non-quinoid compounds containing aromatic system as well as aliphatic side-chain)
9. Aliphatic antibiotics

Secondary classification

Within the families, the antibiotics are placed into subgroups according to their individual characteristics

Eight main rules are taken into account. They were:

1. Size of the molecule
2. Variants of similar skeleton
3. Variants of identical skeleton
4. Antibiotics of practical importance
5. Specific type of linkage
6. Specific type of quality of chromophore
7. Similarities in antibiotics
8. Biological activity.

The Code System

- The individual group of antibiotics received code numbers which can be used in punched-card system or in computers.
- **The code system consists of four digits:**
  - The first element shows the family to which the antibiotic belongs. There are 9 families.
  - The second element indicates the subfamily.
  - The third element indicates the group
  - The fourth gives the type.

Carbohydrate antibiotics

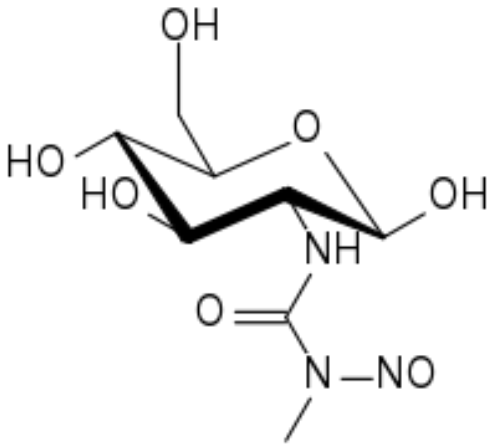
Carbohydrate antibiotic family is classified into 4 subfamilies

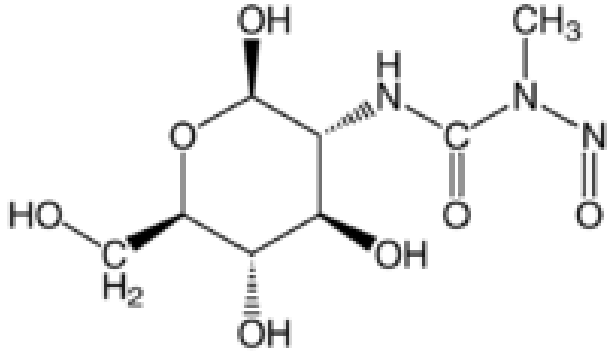
Primary code number	Family
1	**CARBOHYDRATE ANTIBIOTICS**
1.1	Pure saccharides
1.2	Aminoglycosides
1.3	Other (N- and C-) glycosides
1.4	Various sugar derivatives

Family 1:Carbohydrate antibiotics (Cont.)

1.1 Subfamily: pure saccharides

Example, Streptozotocin
It has antibacterial,
anti-leukaemic and
diabetogenic properties.





Streptozotocin

- **Streptozotocin** is a naturally occurring chemical that is particularly toxic to the insulin-producing beta cells of the pancreas in mammals.
- It is used in medicine for treating certain cancers of the Islets of Langerhans (especially hypoglycemia due to excessive insulin secretion by insulinomas) and used in medical research to produce an animal model for Type 1 diabetes by damaging the DNA of beta cells.
- **Why streptozotocin damages Beta cells but not other cells?**
- Because it is similar enough to glucose to be transported into the cell by the glucose transport protein GLUT2 characteristic of beta cells, but is not recognized by the other glucose transporters present in others tissues.

Reference, Some parts of the text were copied from. Wikipedia http://en.wikipedia.org

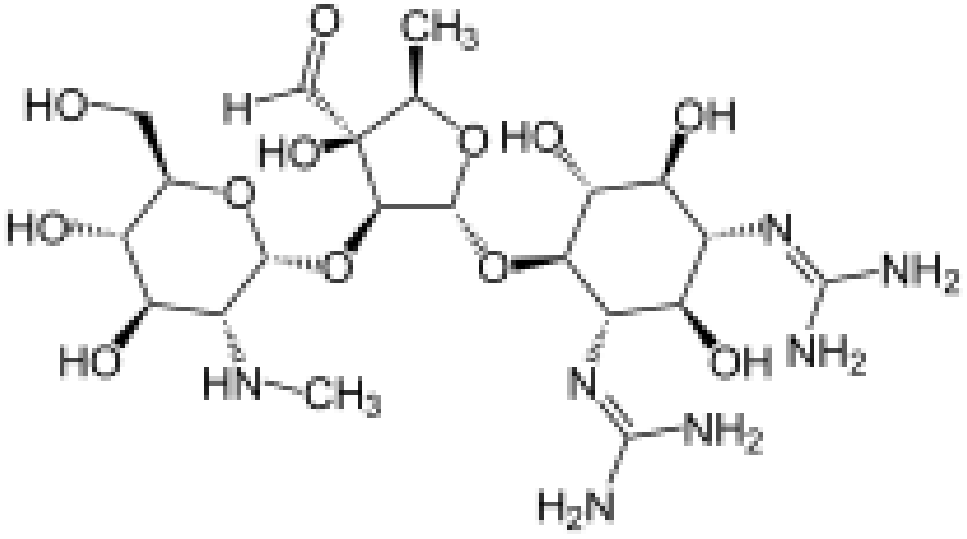
Family 1:Carbohydrate antibiotics

1.2 Subfamily: Aminoglycosides

-The name aminoglycoside means that they contain monosaccharides joined by glycosidic bond.

-It is also called amino cyclitol due to the presence of at least one aminohexanol (aminocyclitol) ring in its structure.

- examples. Streptomycin,
- Neomycin, Kanamycin,
- Paromomycin, gentamycin



Streptomycin

- **Streptomycin** is an aminoglycosides and was the first antibiotic remedy for tuberculosis.
- It is a bactericidal antibiotic.

  It kills microbes by inhibiting protein synthesis, it binds to the 16S rRNA of the bacterial ribosome, interfering with the binding of formyl-methionyl-tRNA to the 30S subunit. This prevents initiation of protein synthesis and leads to death of bacteria.

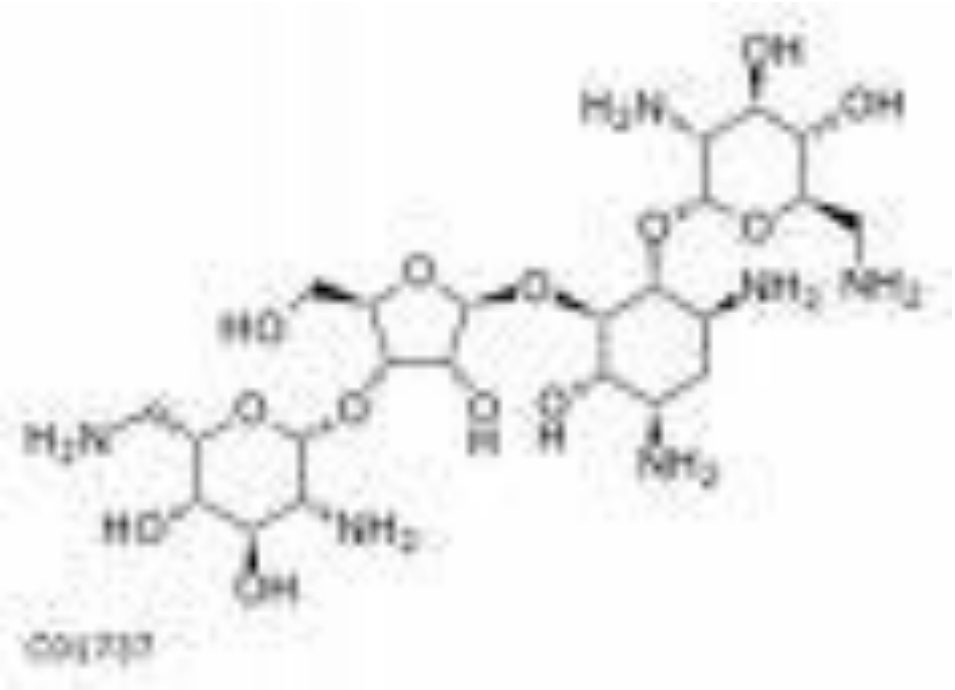
- **Why streptomycin kills bacteria but doesnot affect human?**
- Because humans ribosomes are structurally different from bacteria, thereby allowing the selectivity of this antibiotic for bacteria.
- Streptomycin cannot be given orally, but must be administered by regular intramuscular injection.

Reference, Some parts of the text were copied from. Wikipedia http://en.wikipedia.org

Family 1:Carbohydrate antibiotics

1.3 Subfamily: Other (N- and C-) glycosides

-N- glycosides e.g. Streptothricin
-C-glycosides e.g. ristocetin, vancomycin, chromomycin

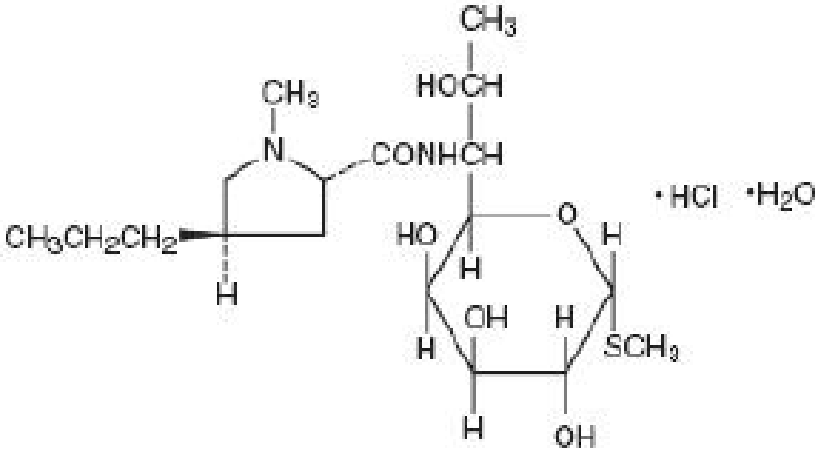


Streptothricin

Family 1:Carbohydrate antibiotics

1.4 Subfamily: Various sugar derivatives

e.g. lincomycin antibiotics
e.g. orthosomycin compound (everninomicin, flambamycin, avilamycin, curamycin) that contain one or more orthoester linkages in its structure associated with carbohydrate residues.



lincomycin

Family 2: Macrocyclic lactone (lactam) antibiotics

Lactam antibiotic family is classified into 4 subfamilies

Primary code No.	Family
2	**LACTAM ANTIBIOTICS**
2.1	Macrolide antibiotics
2.2	Polyene antibiotics
2.3	Other macrocyclic lactone antibiotics
2.4	Ansamycin antibiotics

Family 2: Lactam antibiotics

2.1 Subfamily: Macrolide antibiotics

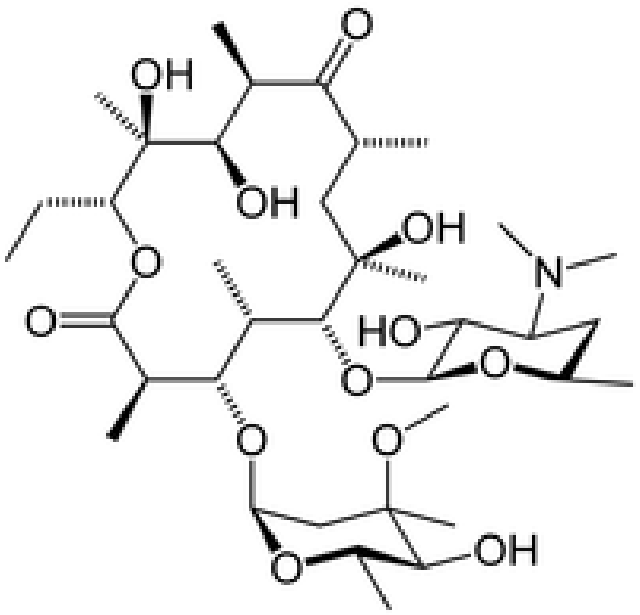
According to Woodward (1957) they are:

-14-16 membered compounds.

-have substituents which are linked to lactone ring.

-one or more saccharide moieties are present in its structure.

-at least one sugar contain nitrogen



Erythromycin

-It may called polyoxomacrolides

-ex. Erythromycin, lancamycin (14 memb. Ring)

-Carbomycin, leokomycin (16 memb. ring)

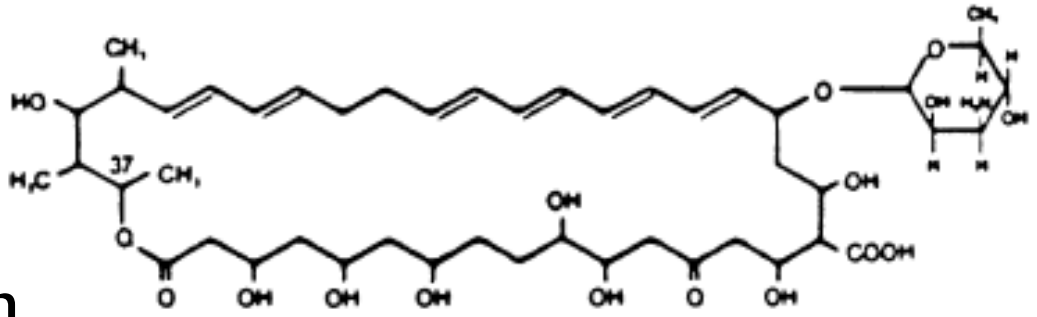
- **Erythromycin** is a macrolide antibiotic that contains a 14-membered lactone ring with ten asymmetric centers and two sugars, making it a compound very difficult to produce via synthetic methods.
- It is produced from a strain of the actinomycete *Saccharopolyspora erythraea*, and has an antimicrobial spectrum similar to or slightly wider than that of penicillin, and is often used for people who have an allergy to penicillins.
- It has better coverage for atypical respiratory tract infections, including mycoplasma and Legionellosis.
- The mechanism of action is not fully elucidated. It may act by binding to the 50S subunit of the bacterial 70S rRNA complex. So, protein synthesis and subsequently structure/ function processes critical for bacterial life or replication are inhibited.
- This interferes with the production of functionally useful proteins and is therefore the basis of antimicrobial action.

Reference, Some parts of the text were copied from. Wikipedia http://en.wikipedia.org

Family 2: Lactam antibiotics

2.2 Subfamily: Polyene antibiotics

They contain many conjugated double bonds (3-8).
So, they have a highly characteristic UV spectra.
Higher double bond contents=higher density of compound color
3 = colorless or very pale yellow 4= pale yellow
5 = yellow 7 = orange
Some of them has glycosidically linked sugar moiety
Examples: Nystatin, rimocidin,, filipin , candidin and fungichromin



Nystatin

Nystatin is a polyene lactam antifungal to which many molds and yeast infections are sensitive, including *Candida* spp.
Nystatin has some toxicity when given intravenously, but it is not absorbed across intact skin or mucous membranes
It is considered a relatively safe drug for treating oral or gastrointestinal infection.
Nystatin binds to ergosterol, a major component of the fungal cell membrane. When present in sufficient concentrations, it forms pores in the membrane that lead to K^+ leakage and death of the fungus.

- **Why Nystatin kills fungus but not affect human?**

Because its target is ergosterol which is fairly unique to fungi, and not exist in animals. So it does not have such catastrophic effects on animals.

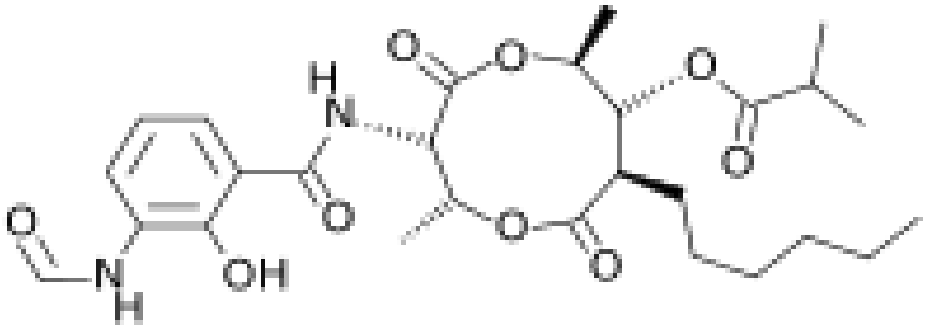
Reference, Some parts of the text were copied from. Wikipedia http://en.wikipedia.org

Family 2: Lactam antibiotics

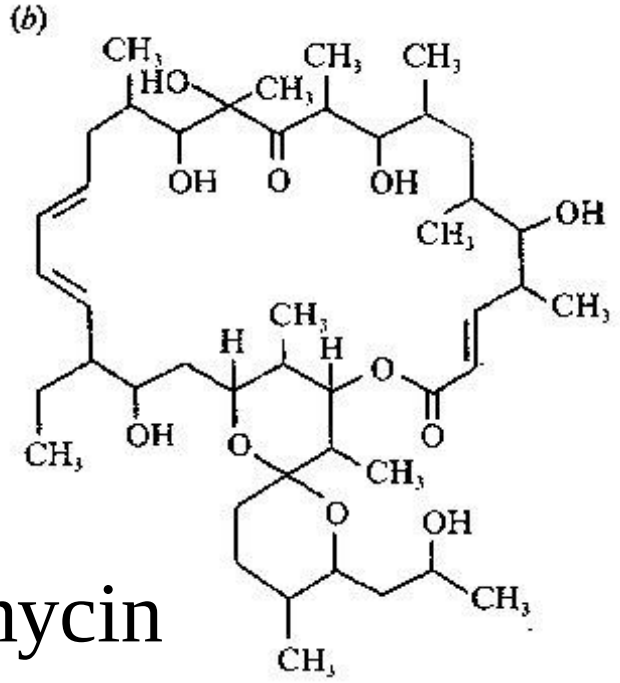
2.3 Subfamily: Other macrocyclic lactone antibiotics

They contain many groups with various structures and biological properties.

Oligomycin and antimycin are inhibitors of oxidative phosphorylation and respiration.



antimycin



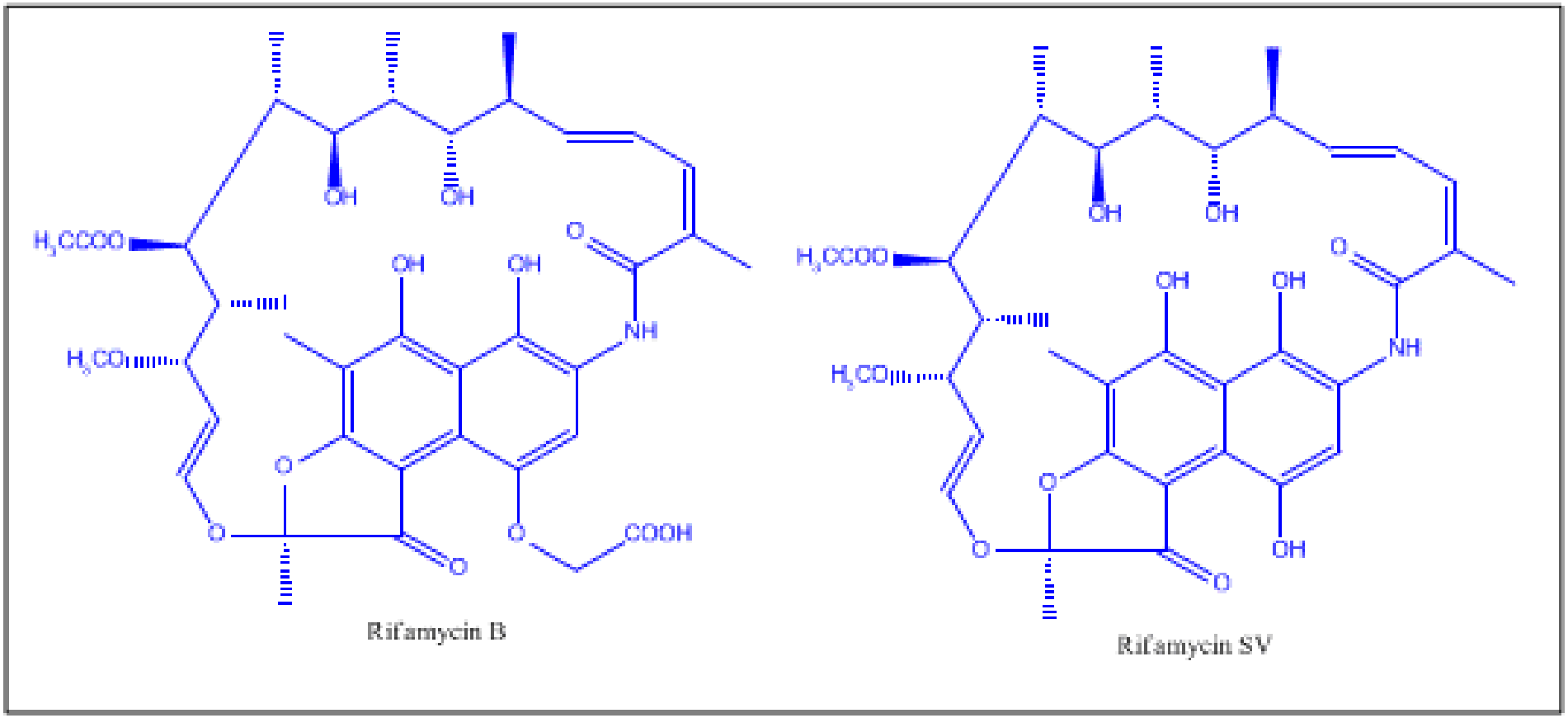
Oligomycin

Family 2: Lactam antibiotics

2.4 Subfamily: Ansamycin

They are group having aromatic moiety spanned by an aliphatic bridge (ansa).

Rifamycins are separated from actinomycete and they are potent drug against tuberculosis and gram positive pathogens
Derivatives of rifamycin and streptovaricin are inhibitors of DNA-dependent RNA polymerase.
Maytansine and related compounds are separated from higher plants and they are potent antitumor agents.


H3CCOO
OH
OH
O
NH
H3CO
OH
OH
O
O
O
O
COOH
Rifamycin B
H3CCOO
OH
OH
O
NH
H3CO
OH
OH
O
O
O
OH
Rifamycin SV

Rifamycin

Family 3: Quinone and similar antibiotics

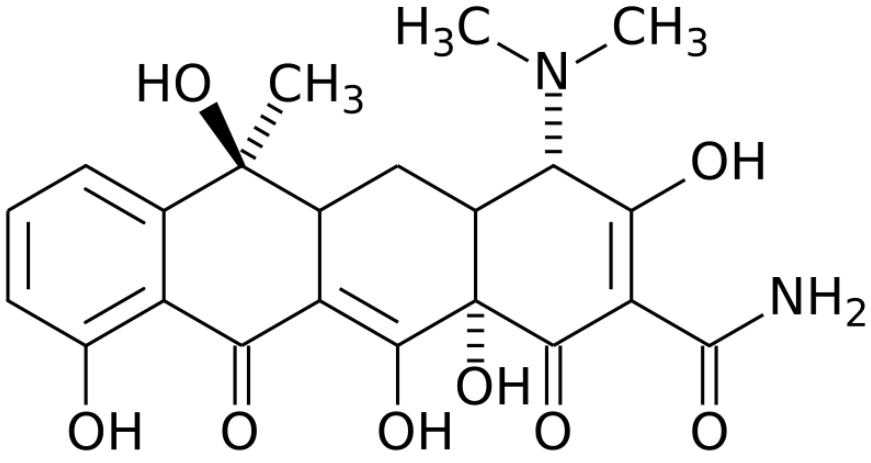
Quinone and similar antibiotic family is classified into 4 subfamilies

Primary code number	Family
3	**QUINONE AND SIMILAR ANTIBIOTICS**
3.1	Linearly condensed polycyclic compounds
3.2	Naphthoquinone derivatives
3.3	Benzoquinone derivatives
3.4	Various quinone-like compounds

Family 3: Quinone and similar antibiotics

3.1 Subfamily: Linearly condensed polycyclic compounds

Tetracyclins are derived from 4 linearly condensed 6-membered rings with characteristic arrangement of double bonds and two chromophoric regions.
It is yellow, light-sensitive fluorescing compounds.
There are many tertracycline derivatives like rolitetracycline, metacycline, doxycycline and minocycline.



tetracycline

- **Tetracycline** is a broad-spectrum antibiotic produced by the *Streptomyces* genus of Actinobacteria, indicated for use against many bacterial infections.

- It works by inhibiting action of the prokaryotic 30S ribosome, by binding the 16S rRNA thereby blocking the aminoacyl-tRNA. However, bacterial strains can acquire resistance against tetracycline and its derivates by encoding a resistance operon.

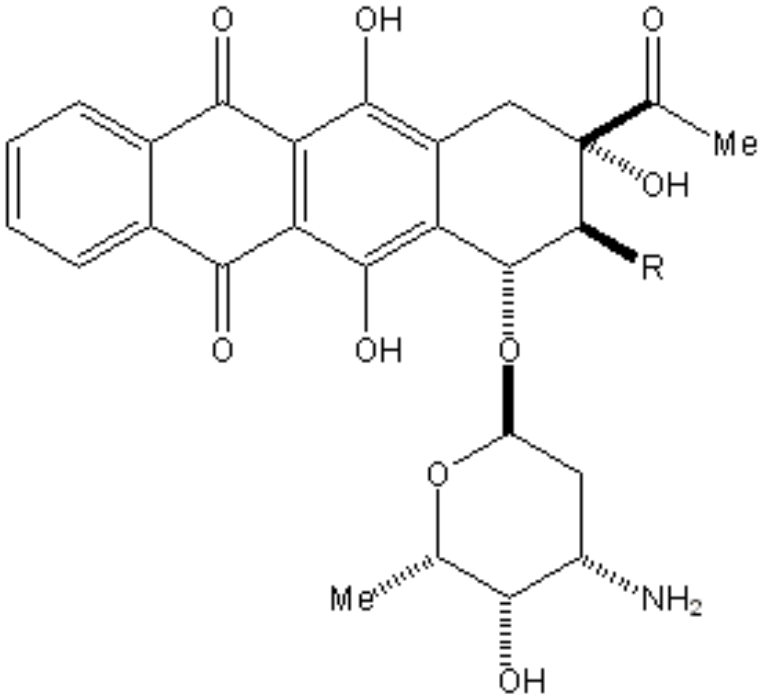
- In eukaryotic cells, toxicity may be the result of inactivation of mitochondrial 30S ribosomes.

Reference, Some parts of the text were copied from. Wikipedia http://en.wikipedia.org

Family 3: Quinone and similar antibiotics

3.2 Subfamily: Naphthoquinone derivatives

Anthracyclines have antibacterial and some have antitumor activity. They derive from actinomycetes (mostly *Streptomyces*).
E.g. Daunomycin, adriamycin and carminomycin are antitumors.



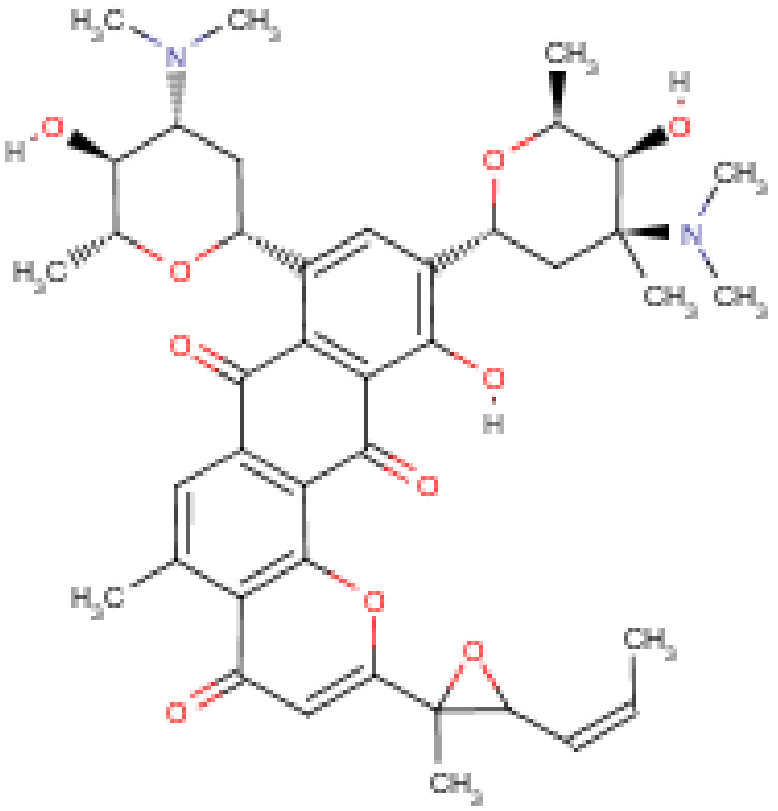
1; R = H
2; R = OH

Anthracycline

Family 3: Quinone and similar antibiotics

3.4 Subfamily: Other quinone antibiotics

The most famous one is pluramycin type antibiotics. It has antitumor activity. It binds to DNA. e.g. rubiflavin A and B



rubiflavin

Family 4: Amino acid, Peptide antibiotics

Amino acid, peptide antibiotic family is classified into 5 subfamilies

Primary code No.	Family
4	**AMINO ACID, PEPTIDE ANTIBIOTICS**
4.1	Amino acid derivatives
4.2	Homopeptides
4.3	Heteromer peptides
4.4	Peptolides
4.5	High molecular weight peptides

Family 4: Amino acid, Peptide antibiotics

a- amino acid derivatives

β-Lactam antibiotics are the most important of this class.

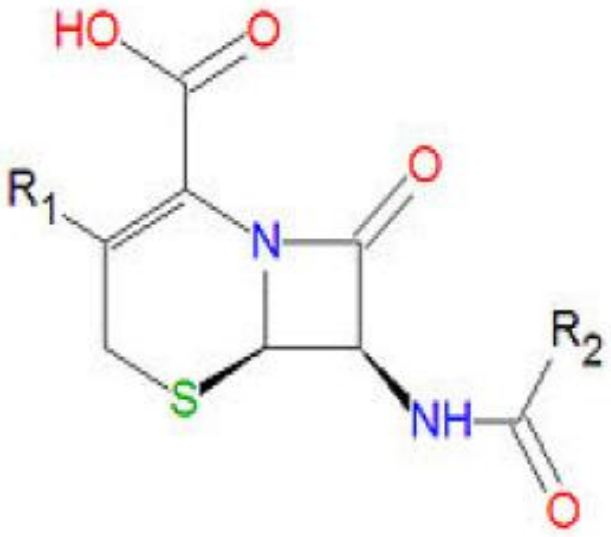
β-Lactam group consists of three subgroups:

1- Penicillins
2- Cephalosporin C and cephamycins
3- Novel β- lactam antibiotics

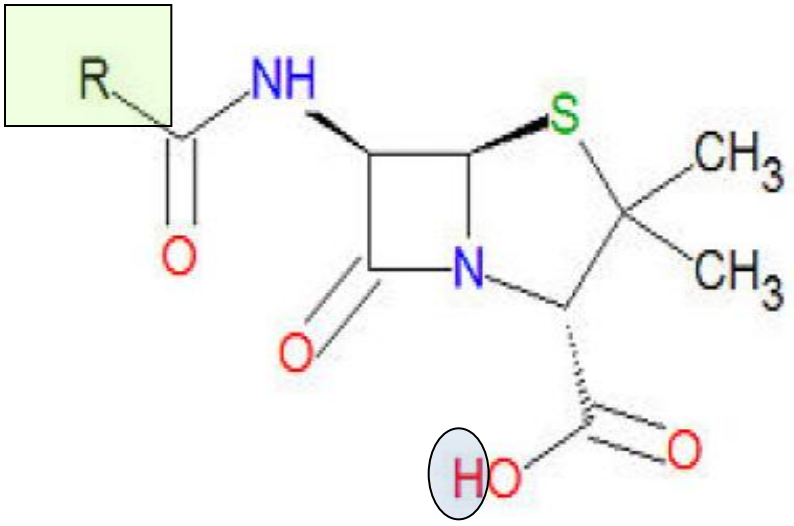
Penicillins contain the basic structure named penam skeleton.

All penicillins (natural, synthetic or semisynthetic) differ in the structure of the side chain which is responsible of the spectral activities of penicillin.

The hydrogen atom of the carboxyl group attached to the thiazolidine ring can be substituted by organic or inorganic cation which influence the solubility of this antibiotic.



Cephalosporin



Penicillin

- **Penicillins** are used in the treatment of bacterial infections caused by susceptible, usually Gram-positive, organisms.
- β-lactam antibiotics work by inhibiting the formation of peptidoglycan cross-links in the bacterial cell wall.

- Penicillin shows a synergistic effect with aminoglycosides, since the inhibition of peptidoglycan synthesis allows aminoglycosides to penetrate the bacterial cell wall more easily, allowing its disruption of bacterial protein synthesis within the cell.

- **Cephalosporins** are bactericidal and have the same mode of action as other beta-lactam antibiotics such as penicillins.

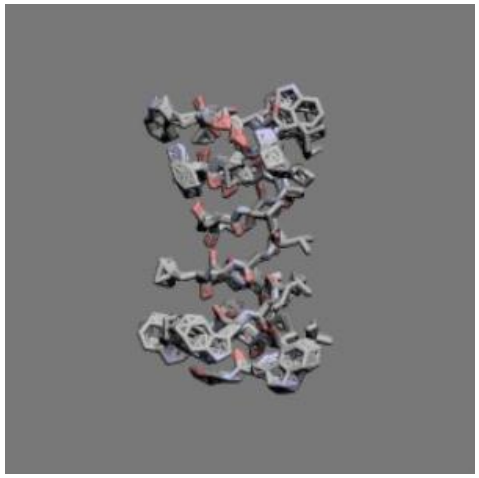
Reference, Some parts of the text were copied from. Wikipedia http://en.wikipedia.org

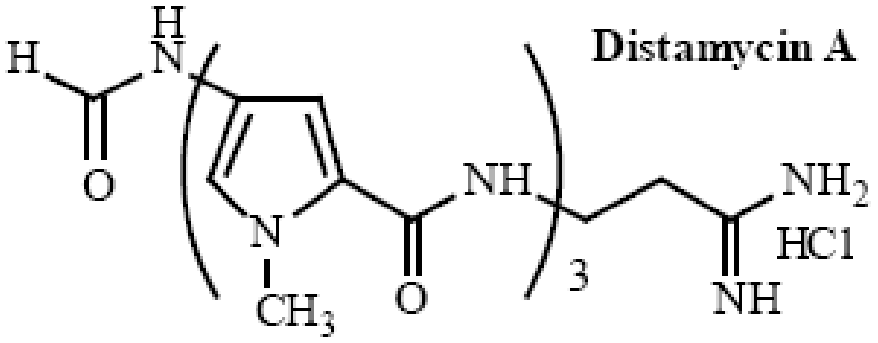
Family 4: Amino acid, Peptide antibiotics

b -Peptide antibiotics

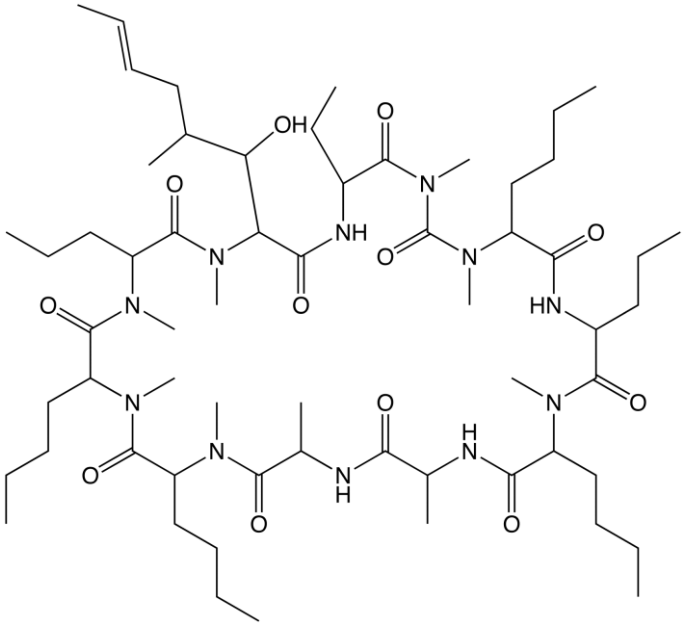
- Small molecular weight (350-3000 D)
- Homopeptide antibiotics are composed of entirely amino acids.
- Heteropeptide antibiotics contain pyrimidines, aminosugars, fatty acids, hydroxyacids, and other constituents.
- Many peptide antibiotics contain amino acids that are not present in protein (D-aa, β-aa. Ornithin etc.).
- Some peptide antibiotics have linear structures whereas others are cyclic or may have unusual linkages.

- Ex. homopeptide: distamycin A and congocidin, they interact with various types of DNA, thus inhibiting DNA-dependent syntheses.
- Gramicidine A, B, and D are linear pentadecapeptides produced by *Bacillus brevis.*
- Cyclosporin has antifungal and immunosuppressive properties.





Gramicidin



Cyclosporin

- **Gramicidin** is a heterogeneous mixture of six antibiotic compounds.
- Gramicidin D are linear pentadecapeptides; that is chains made up of 15 amino acids. This is in contrast to Gramicidin S which is a cyclic peptide chain.
- Gramicidin is active against Gram-positive bacteria, except for the Gram-positive bacilli, and against select Gram-negative organisms, such as *Neisseria* bacteria.
- Its therapeutic use is limited to topical application as it induces hemolysis in lower concentrations than bacteria cell death thus cannot be administered internally. The exterior epidermis is composed of dead cells, thus applying it to the surface of the skin will not cause harm.
- Gramicidin's bactericidal activity is a result of increasing the permeability of the bacterial cell wall allowing inorganic monovalent cations (e.g. H^+) to travel through unrestricted, thereby destroying the ion gradient between the cytoplasm and the extracellular environment.

Reference, Some parts of the text were copied from. Wikipedia http://en.wikipedia.org

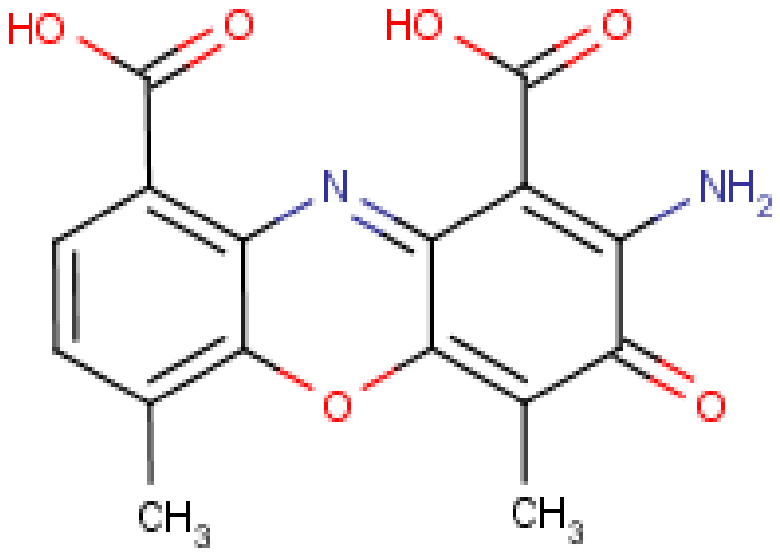
- **Cyclosporin**, is an immunosuppressant drug widely used in post-allogeneic organ transplant to reduce the activity of the patient's immune system and so the risk of organ rejection. It has been studied in transplants of skin, heart, kidney, liver, lung, pancreas, bone marrow and small intestine.
- **Cyclosporin A**, the main form of the drug, is a cyclic nonribosomal peptide of 11 amino acids (an undecapeptide) produced by the fungus *Tolypocladium inflatum Gams*, and contains D-amino acids.
- Cyclosporin is thought to bind to the cytosolic protein cyclophilin (immunophilin) of , especially T-lymphocytes. This complex of cyclosporin and cyclophilin inhibits calcineurin, which under normal circumstances is responsible for activating the transcription of interleukin 2.
- It also inhibits lymphokine production and interleukin release.

Reference, Some parts of the text were copied from. Wikipedia http://en.wikipedia.org

Family 4: Amino acid, Peptide antibiotics

c - Peptolide antibiotics

- They are a series of chromopeptides produced by a variety of *Streptomyces* sp.
- They consist of a hetero-tricyclic chromophore called **actinocin,** which is responsible for the yellow to red color of the antibiotics, linked to two pentapeptide lactone ring that determine the solubility.
- Actinocins possess antimicrobial and antineoplastic effect and are used as antitumor agents. They have the capacity to bind nuclear dsDNA, so they are used as specific inhibitor of DNA-primed synthesis of RNA and protein synthesis. They are also used in molecular biology to study virus replication and properties of DNA molecule.



Actinocin

Family 5: Nitrogen containing heterocycle antibiotics

Nitrogen containing antibiotic family is classified into 3 subfamilies

Primary code number	Family
5	**NITROGEN-CONTAINING HETEROCYCLE ANTIBIOTICS**
5.1	Non condensed (single) heterocycles
5.2	Condensed (fused) heterocycles
5.3	Alkaloids with antibiotic (antitumor) activity

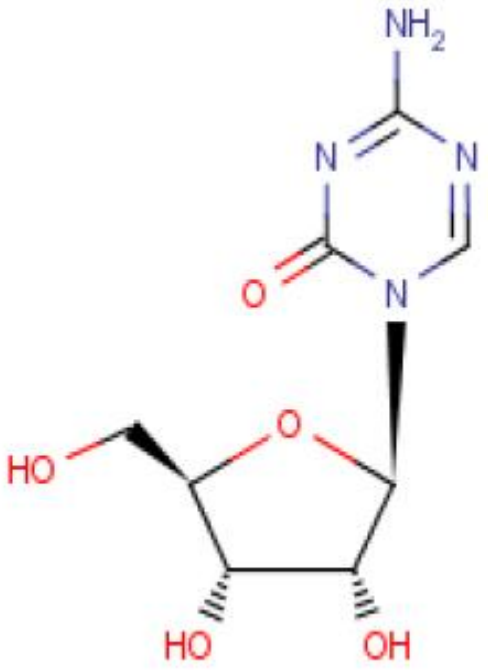
Family 5: Nitrogen containing heterocycle antibiotics

There are three subfamilies belonging to this group.
Nucleoside antibiotics are the best known members of this family

They differ from the normal nucleosides in three possible ways. It may contain:

- -a normal base + abnormal saccharide or
- -abnormal base + normal saccharide or
- -both abnormal base and saccharide

e.g. azacytidine, cordycepin, gougerotin and plicacetin



5-Azacytidine

- Azacytidine is a chemical analogue of cytidine, a nucleoside present in DNA and RNA .
- Azacytidine and its deoxy derivative decitabine are used in the treatment of myelodysplastic syndrome. Both drugs were first synthesized as potential chemotherapeutic agents for cancer
- Cells in the presence of azacytidine incorporate it into DNA during replication and RNA during transcription. The incorporation of azacytidine into DNA or RNA inhibits methyltransferase thereby causing demethylation in that sequence, affecting the way that cell regulation proteins are able to bind to the DNA/RNA substrate.
- Inhibition of DNA methylation occurs through the formation of stable complexes between the molecule and with DNA methyltransferases, thereby saturating the cells methylation machinery.

Reference, Some parts of the text were copied from. Wikipedia http://en.wikipedia.org

Family 6: Oxygen-containing heterocyclic antibiotics

Oxygen-containing heterocyclic antibiotics are classified into 5 subfamilies

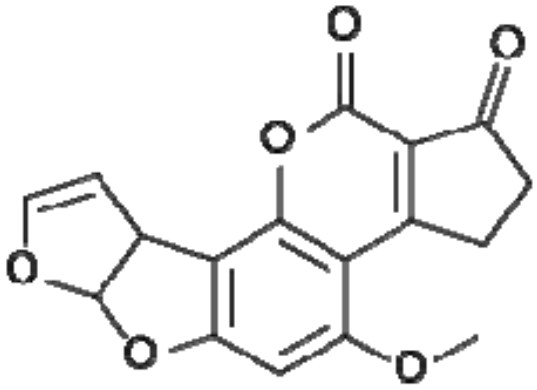
Primary code No.	Family
6	**OXYGEN-CONTAINING HETEROCYLE ANTIBIOTICS**
6.1	Furan derivatives
6.2	Pyran derivatives
6.3	Benzo{γ}pyran derivatives
6.4	Small lactones
6.5	Polyether antibiotics

Family 6: Oxygen-containing heterocyclic antibiotics

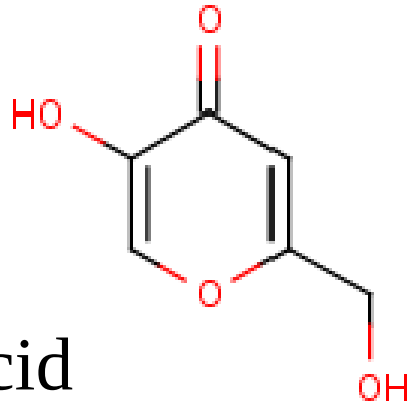
This family includes various metabolites of fungi and actinomycetes with a variety of biological activities.

Aflatoxins are mycotoxins that are toxic to higher animals and man.

Aflatoxins belonging to condensed furans like kojic acid have weak antibiotic activity.



Aflatoxin



Kojic acid

- **Aflatoxins** are naturally occurring mycotoxins that are produced by many species of the fungus *Aspergillus*.
- Aflatoxins are toxic and among the most carcinogenic substances known. After entering the body, aflatoxins are metabolized by the liver to an epoxide (a reactive intermediate) aflatoxin M1, .
- Aflatoxin-producing members of *Aspergillus* are common and widespread in nature. They can colonize and contaminate grain before harvest or during storage.
- High-level aflatoxin exposure produces an acute hepatic necrosis, resulting later in cirrhosis, and/or carcinoma of the liver.
- No animal species is immune to the acute toxic effects of aflatoxins including humans; however, humans have an extraordinarily high tolerance for aflatoxin exposure and rarely succumb to acute aflatoxicosis.

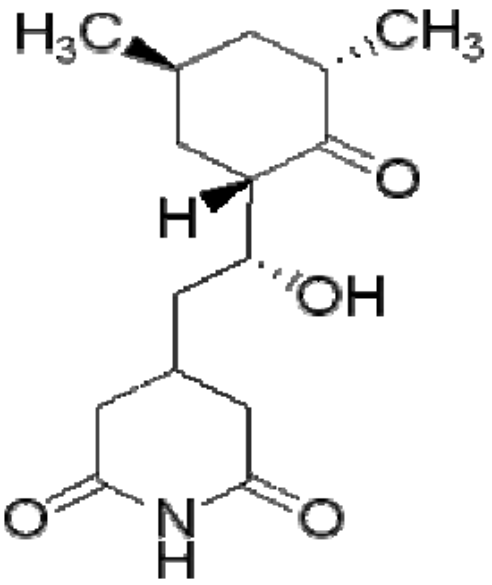
Reference, Some parts of the text were copied from. Wikipedia http://en.wikipedia.org

Family 7: Alicyclic antibiotics

Alicyclic antibiotics family is classified into 3 subfamilies

Primary code number	Family
7	**ALICYCLIC ANTIBIOTICS**
7.1	Cycloalkane derivatives
7.2	Small terpenes
7.3	Oligoterpenes antibiotics

The subfamily of cycloalkane derivatives contain a large group of glutarmide antibiotics, ex. Cycloheximide.
They possess antifungal activity and inhibit protein synthesis on eukaryotic ribosomes.



Cyclohixamide derivatives

Oligoterpene antibiotics includes many types like cephalosporin and fusidic acid

- **Cycloheximide** inhibits protein biosynthesis in **eukaryotic organisms (including human)**, by interfering with the translocation step in protein synthesis thus blocking translational elongation.
- Due to significant toxic side effects, including DNA damage, and interfering sperm production and other reproductive effects, cycloheximide is generally used only in *in vitro* research applications, **and is not suitable for human use as a therapeutic antibiotic compound**.
- Although it has been used as a fungicide in agricultural applications, this application is now decreasing as the health risks have become better understood.
- Since cycloheximide is an effective inhibitor of protein biosynthesis in Eukaryotes only (in nucleus), it may be used to distinguish between genes expressed in organelles and genes expressed in the nucleus. Genes expressed in the eukaryotic nucleus will not be expressed in the presence of cycloheximide. Conversely, organelle transcription is unaffected by cycloheximide, and organelle genes will continue to be expressed.

Reference, Some parts of the text were copied from. Wikipedia http://en.wikipedia.org

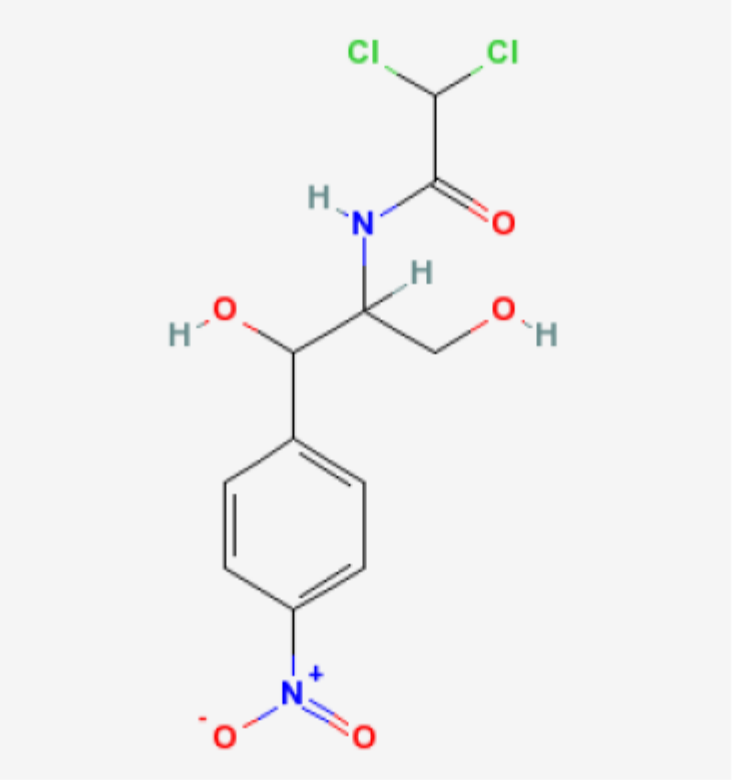
Family 8: Aromatic antibiotics

Aromatic antibiotics family is classified into 4 subfamilies

Primary code No.	Family
8	**AROMATIC ANTIBIOTICS**
8.1	Benzene compounds
8.2	Condensed aromatic compounds
8.3	Non-benzenoid aromatic compounds
8.4	Various derivatives of aromatic compounds

Aromatic antibiotics

Ex chloramphenicol
Griseofulvin and
novobiocin



Chloramphenicol

- **Chloramphenicol** is a bacteriostatic antimicrobial originally derived from the bacterium *Streptomyces venezuelae*.
- It is effective against a wide variety of microorganisms; it is still very widely used in low income countries because it is exceedingly inexpensive, but has fallen out of favour in the West due to a very rare but very serious side effect: aplastic anemia.
- In the West, the main use of chloramphenicol is in topical use as eye drops or ointment for bacterial conjunctivitis because of the worries about the risk of aplastic anaemia.
- It has a very broad spectrum of activity: it is active against Gram-positive bacteria, Gram-negative bacteria and anaerobes.
- Chloramphenicol may be used as a second-line agent in the treatment of tetracycline-resistant cholera.
- Chloramphenicol is active against the main bacterial causes of meningitis. In the West, It remains the drug of choice in the treatment of meningitis in patients with severe penicillin or cephalosporin allergy because it is the antibiotic that can penetrate the cerebro spinal fluid.

Reference, Some parts of the text were copied from. Wikipedia http://en.wikipedia.org

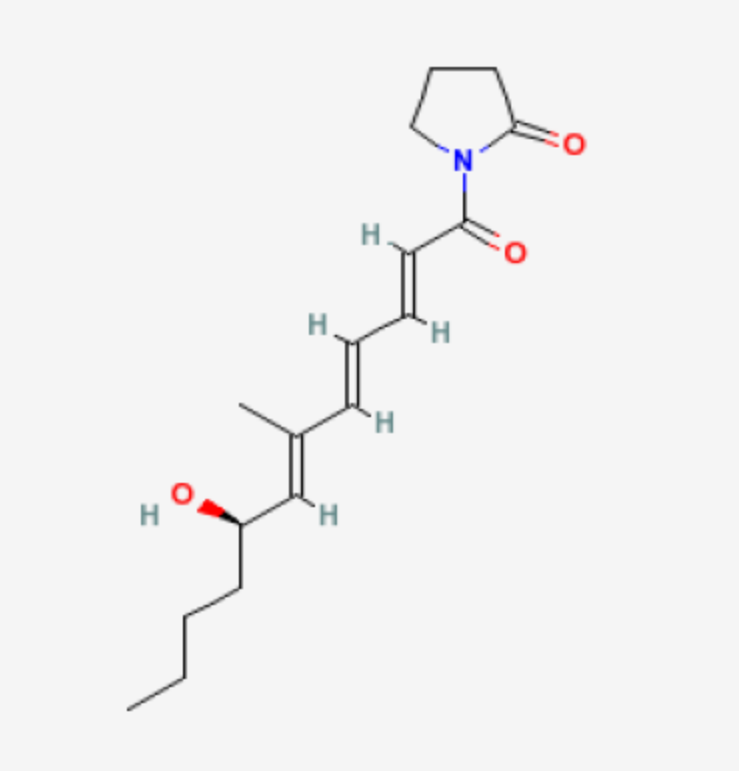
Family 9: Aliphatic antibiotics

Aliphatic antibiotics family is classified into 3 subfamilies

Primary code number	Family
9	**ALIPHATIC ANTIBIOTICS**
9.1	Alkane derivatives
9.2	Aliphatic carboxylic acid derivatives
9.3	Aliphatic compounds containing S and P

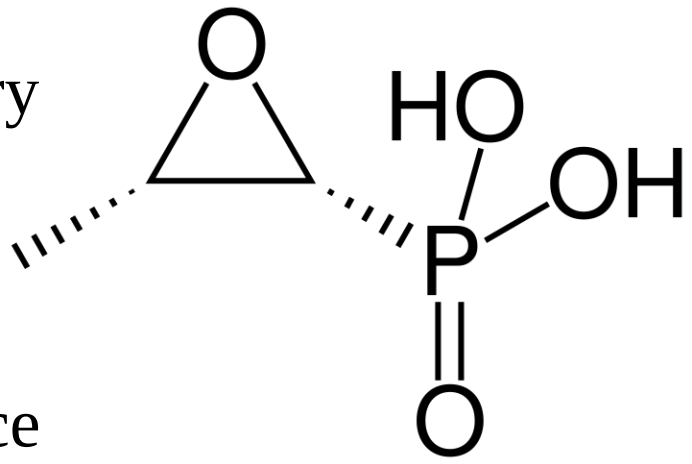
Aliphatic antibiotics

Variotin belongs to fatty acid derivatives and is used for treatment of dermatomycosis.



Variotin

- Phosphonomycin or Fosfomycin is indicated in the treatment of urinary tract infections, where it is usually administered as a single dose.
- Development of bacterial resistance under therapy is a frequent occurrence and makes fosfomycin unsuitable for sustained therapy of severe infections.



- Fosfomycin is an antimetabolite of phosphoenolpyruvate in the enzymatic synthesis of N-Acetylmuramic acid via enolpyruvate transferase, a component of the bacterial cell wall glycopeptide murein.
- The epoxide ring of fosfomycin covalently reacts with a cystein residue in the bacterial enzyme's active site, which results in the enzyme's irreversible inactivation.

Reference, Some parts of the text were copied from. Wikipedia http://en.wikipedia.org

Family 0: Miscellaneous antibiotics

Primary code number	Family
0	**MISCELLANEOUS ANTIBIOTICS**
may be distributed according to physical, chemical and microbiological properties	

References

- Wikipedia
- Chemistry and Biology of Antibiotics. By Vladimir Betina (1983).