Ministry of Health of the Russian Federation

Volgograd State Medical University

Department of Pharmaceutical, Toxicological Chemistry
Pharmacognosy and Botany

SPECIAL PHARMACEUTICAL CHEMISTRY

Antibiotics

Lesson 9

IX term

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GENERAL CHARACTERISTICS OF ANTIBIOTICS

Antibiotics are substances produced by microorganisms, higher plants, animal tissues in the process of their vital activity and possessing the ability to exert selective bacteriostatic or bactericidal action. Selectivity is manifested in the presence of a specific spectrum of each antibiotic.

The specificity of antibiotics is characterized by two main features:

1. Antibiotics have high biological activity against microorganisms sensitive to them.
2. Antibiotics are characterized by selectivity of their action.

There are antibiotics with antibacterial, antifungal, antiviral and antitumor effects. The ability of antibiotics to exhibit bacteriostatic or bactericidal action against pathogens without having a toxic effect on the human body is used to treat various diseases. It is known that this kind of drugs belong to chemotherapeutic agents.

The term "*antibiosis*" emerged in the late nineteenth century to refer to the phenomenon of oppression of microorganisms (and other living organisms), in particular, the function of their enzyme systems, respiration, nutrition, reproduction, etc.

The action of antibiotic substances is based on the phenomenon of antagonism, first discovered by L. Pasteur in the world of microorganisms. The essence of this phenomenon is that some microorganisms release into the environment various substances capable of suppressing the growth and reproduction of other microorganisms. This ensures their advantage in the struggle for existence.

One of the first attempts to use the phenomenon of antagonism was made by the remarkable Russian scientist I.I. Mechnikov, who used lactic acid bacteria in simple sourdough to suppress putrefactive bacteria in the intestine.

The first antibiotics were isolated from various strains of mold.

The fact that mold was used in folk medicine in Azerbaijan as early as in the 11th century is quite remarkable. Information about antibacterial properties of Penicillium mold is found in the works of L. Pasteur, carried out in 1862-1868.

In 1871-1872 Russian scientists V.A. Manassein and A.G. Polotebnov published interesting data on the effect of green mold (Penicillium glaucum) on bacteria. In particular, V.A. Manassein noted the absence of bacteria in the culture fluid when growing the above mold. Polotebnov experimentally proved that the removal of pus and healing of wounds is faster when mold is applied to it. He was the first to suggest the practical use of mold in medicine.

In 1877, Russian doctor P.V. Lebedinsky showed that under the influence of mold, the number of bacteria in the gastrointestinal tract decreases.

The antibiotic effect of mold was confirmed in 1904 by veterinarian M.G. Tartakovsky in experiments with the causative agent of chicken plague.

These remarkable discoveries of our Russian scientists were not widely known and developed. That is why the first study of the mold Penicillium notatum is associated with the name of the English microbiologist A. Fleming, who in 1928 discovered its antibiotic properties against Staphylococcus aureus. However, A. Fleming failed to isolate the antibiotic, which he named penicillin, in pure form. It was not until 1940 that H. Flory and J. Chein developed a method to isolate penicillin from culture fluid and demonstrated its therapeutic effect on cocci infections in mice.

The impetus for this research was the isolation and discovery of the antibiotic properties of tyrotricin by R. Dubo in 1939. Dubo in 1939.

The credit for the creation of Soviet penicillin, development of methods of its production from various strains of mold belongs to Prof. Z.V. Ermolieva, a native of Frolovo (Volgograd region). Frolovo (Volgograd region). These studies were conducted during the Great Patriotic War and were immediately introduced into the medical practice of hospitals through the efforts of the remarkable Soviet surgeon N.N. Burdenko.

Thus, the consistent accumulation of scientific facts and experimental material led to the greatest discovery of the twentieth century - the creation of a fundamentally new drug, penicillin. Since 1939-1940, research in the field of antibiotics has developed rapidly.

In 1942, scientists G.F. Gauze and M.G. Brazhnikova obtained gramicidin from soil bacteria. In 1944, A. Schatz, E. Bugi and Z.A. Waksman discovered streptomycin. In the following years, the radiating fungi producing it were the source of obtaining many new antibiotics (kanamycin, neomycin, novobiocin, etc.).

In 1947, J. Ehrlich and K. Bartz isolated chloromitecin. The elucidation of its chemical structure soon allowed the industrial synthesis of this group of antibiotics.

In 1947-1948 the first antibiotics from the group of polymyxins were discovered, and two years later a series of antibiotics known as tetracyclines was obtained. In the USSR, the biosynthesis of chlorotetracycline was realized in 1952.

In the following years the attention of researchers was drawn to a group of antibiotics of similar chemical structure based on a macrocyclic ring (erythromycin, olean-domycin, etc.). Scientists M.M. Shemyakin, A.S. Khokhlov, S.M. Navashin and others made a great contribution to the development of antibiotics research.

THE ROLE OF ANTIBIOTICS IN THE DEVELOPMENT OF CHEMOTHERAPY

After the successful use of chemotherapeutic agents from the classes of dyes, organoelement compounds, sulfonamide drugs, the introduction of antibiotics into medical practice was a kind of revolution, a new era in drug science, which helped man to defeat a number of serious diseases, to bring millions of people back to life.

It is enough to note that due to the use of antibiotics the mortality rate of pneumonia decreased by 10 times, acute dysentery - by 11 times, blood infections and peritoneal inflammations by 4-5 times. The reason for such a high efficiency of antibiotics lies in the selectivity of their action on pathogenic microorganisms.

The mandatory conditions for the suitability of an antibiotic for use as a drug are the presence of antimicrobial activity against microorganisms pathogenic to humans, the preservation of this activity under the conditions of the human body and, finally, the absence of toxic effects. For this reason, of the many hundreds of antibiotics described, only a few dozen have been used in medical practice. Scientists are constantly working not only to find new antibiotics, but also to improve the existing ones.

For example, studies on the creation of new drugs in the penicillin group are very illustrative. It is known that the first penicillin preparations were characterized by instability. At present, penicillin preparations have been developed that are quite effective when taken orally (phenoxymethylpenicillin). Sustained-release forms have been developed that are effective for several days after a single dose.

The most important stage in the study of penicillin, a kind of its "second birth", was the discovery in 1959 by a group of young English scientists of the method of synthesis of 6-aminopenicillanic acid. This substance is a kind of "penicillin nucleus" on the basis of which semi-synthetic penicillins can be created.

Created in recent years semi-synthetic penicillins - methicillin, oxacillin are not inactivated by the enzyme penicillinase, have a wider range of application and are successfully used for the treatment of infections caused by resistant staphylococci.

The availability of a large arsenal of antibiotics creates tremendous opportunities for the treatment of various diseases. However, the success of antibiotic therapy depends on skillful, rational use of drugs. It is necessary to take into account not only the form and stage of the disease, sensitivity to antibiotic microbe - pathogen, but also the state of the macroorganism, the possibility of complications and allergic reactions. Therefore, self-treatment with antibiotics without a doctor's prescription is absolutely inadmissible.

Widespread use of antibiotics as medicines gradually leads to increased resistance of pathogenic microorganisms initially sensitive to their action. To prevent this phenomenon, combinations of simultaneous use of different antibiotics are used, combining them with sulfonamide drugs. Increasingly important are the so-called reserve antibiotics, to which no resistant forms of microorganisms have yet

developed. They are used when commonly used antibiotics (penicillin, streptomycin, etc.) do not have the desired effect.

METHODS OF OBTAINING ANTIBIOTICS AND METHODS OF CONTROLLING ANTIBIOTICS

The high efficiency of antibiotics as drugs, their wide use in medicine, veterinary medicine, various branches of agriculture, food and canning industry have led to the creation of a special branch of production - the antibiotics industry. The peculiarity of this industry is the combination of biological (fermentation) and chemical processes.

The production of most antibiotics is based on microbial synthesis, which takes place in the cell of a microorganism. Microorganisms from the group of molds or ray fungi are most often used for biosynthesis.

uchistye fungi. The most important condition for the production of antibiotics is to find highly productive strains of microorganisms - antagonists, which produce substances that have a bacteriostatic effect on pathogenic microbes. Selected most active samples are subjected to selection by exposure to various physical factors (ultraviolet, X-rays, fast neutrons) or chemical substances - mutagens. In this way, it is possible to obtain a microorganism that produces tens or even hundreds of times more antibiotic than the original one.

The microbial cell acts as a complex chemical laboratory, where very subtle processes take place that are not yet available for organic synthesis. They also do not require high temperatures and pressures, catalysts, or other special conditions.

Biosynthesis is carried out in special equipment - fermenters with a capacity of several tens of thousands of liters. Fermentation is carried out by the "deep method", which means that mold growth and antibiotic formation occur throughout the entire thickness of the fermenting mass. Each of the microorganisms requires special conditions: temperature, air supply (aeration), nutrient medium, duration of the process. Special nutrient media are required to ensure microorganism viability and maximize antibiotic accumulation. By adjusting the qualitative and quantitative composition of their ingredients, it is possible to significantly influence the antibiotic yield.

Antibiotics are isolated from the culture broth by adsorption or ion-exchange chromatography, by extraction with various organic solvents and at different pH values of the medium, by precipitation. Purification of the crude antibiotic is carried out by chromatographic method or by countercurrent extraction in special apparatuses with subsequent recrystallization. The isolated crystalline antibiotic is subjected to careful chemical and biological control.

The entire process of antibiotic production is carried out under strictly observed aseptic conditions.

The methods of isolation and purification of antibiotics are very diverse and are determined by the chemical nature of the antibiotic. Ion exchange chromatography and other modern physicochemical methods are mainly used.

For ***identification of antibiotic***s, unlike a number of groups of natural compounds (alkaloids, glycosides), there are no common, group reactions. The qualitative characterization of antibiotics is based on the individuality of their chemical structure, the nature of functional groups, depending on which antibiotics give these or other reactions, mainly colored. Currently, spectral methods are widely used for the identification of antibiotics.

Various methods are used to ***quantify*** antibiotics: biological, chemical, physicochemical.

Biological methods are based on the direct biological effect of the antibiotic on the applied test microorganism sensitive to this antibiotic. Among the biological methods for quantitative determination of antibiotics, the most widely used is the method of diffusion in agar with turbidimetric determination, which is based on measuring the concentration of microbial cells that, as a result of their growth in the presence of a small amount of antibiotics, create a certain optical density of the medium (turbidity).

The *disadvantages* of the biological control method are the time required for analysis and the dependence of the accuracy of the analysis results on many external factors.

In recent years, ***chemical and physicochemical methods*** have become widely used for the quantitative determination of antibiotics, of which photocolorimetry is the most widely used. The latter is based on the use of certain properties of antibiotics: color reactions, appearance or disappearance of characteristic bands in the UV and IR spectral regions under the influence of various reagents (acids, hydroxides, etc.).

ANTIBIOTIC CLASSIFICATION

In the time that has passed since the discovery of A. Fleming (1929), more than 6000 different antibiotics have been obtained, so an important problem is the systematization of these drugs. There are several classifications of antibiotics, but none of them is universal. Currently, several approaches to classification have developed, which are determined by the professional interests of scientists. Thus, for biologists studying organisms-producers of antibiotic substances, the classification of antibiotics by source of isolation is the most acceptable. For pharmacologists, classification by mechanism of action is most acceptable. Physicians and health care practitioners prefer to classify antibiotics by spectrum of action and tactics of clinical use. For chemists and pharmacists who study the structure of antibiotic molecules and develop ways of their chemical synthesis, classification based on the chemical structure of antibiotics is acceptable.

Evaluating the above classification principles, one can find their own shortcomings in each of them. For example, from a chemist's point of view, the classification of antibiotics by biological origin has certain shortcomings due to the fact that sometimes substances close in structure and biological action may be produced by organisms belonging to different groups. It is not uncommon for organisms belonging to the same group (e.g. actinomycetes) to produce antibiotics with very different chemical structures. From a biologist's point of view, the classification of antibiotics on the basis of chemical structure also has its disadvantages: a group of antibiotics belonging to one class of chemical compounds includes substances produced by different groups of organisms.

Among the basic principles of antibiotic classification, consider the following.

Classification of antibiotics depending on chemical structure

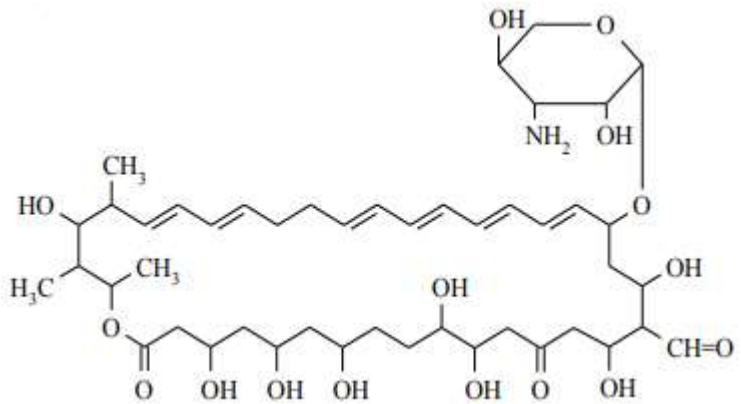
1. Acyclic antibiotics

Depending on their structure, the main groups of antibiotics are as follows:

- ***Antibiotics - Derivatives of fatty acids***.
- ***Polyene antibiotics***. This group of antibiotics is the most important among the acyclic antibiotics. They are characterized by the presence of a system containing three to eight conjugated double bonds. There are more than 150 polyene antibiotics. Many antibiotics of this group contain amino sugars (mycosamine, perosamine). Polyene antibiotics are divided into six subgroups according to the number of conjugated double bonds in the molecular structure:

  a) trienes (*microtriene, trienine, triene*);

  b) tetraenes, e.g., *nystatin*;



Nystatin

c) pentaenes (a subgroup of more than 40 antibiotics, including *roseofungin*, *aurenine, mycotycin, fungihromin*, etc.);

d) hexaenes (a small subgroup of only eight antibiotics, such as *dermostatin*);

e) heptaenes (a subgroup of more than 50 antibiotics, e.g., *candida, candicidin, trichomycin, levorin, mycoheptin*);

f) octaenes (*ochramycin*).

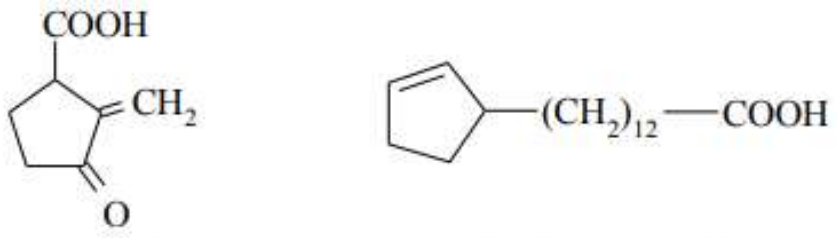
Most antifungal antibiotics of actinomycete origin are polyenes.

- ***Acetylene antibiotics.***
- ***Sulfur- and nitrogen-containing antibiotics***.

2. Alicyclic antibiotics

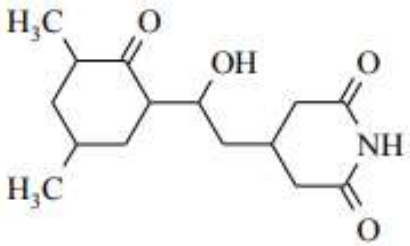
This group includes derivatives of cyclopentane, cyclohexane and cycloheptane:

- ***cyclopentane derivatives*** (*sarcomycin, haulmugric acid*);
- ***cyclohexane derivatives*** (*actidione*);
- ***cycloheptane derivatives*** (*thujic acid*).

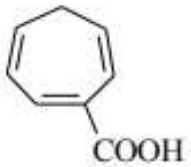


sarcomycin

haulmugric acid

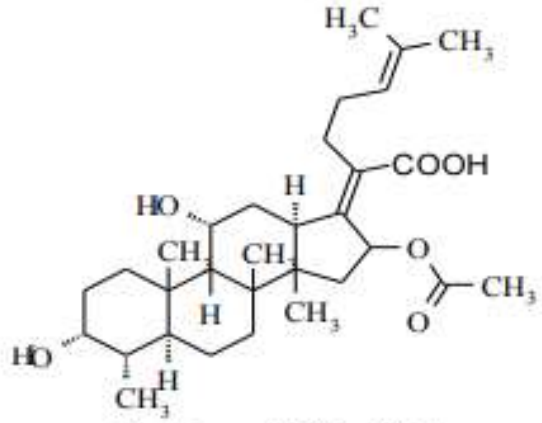


actidione



thujic acid

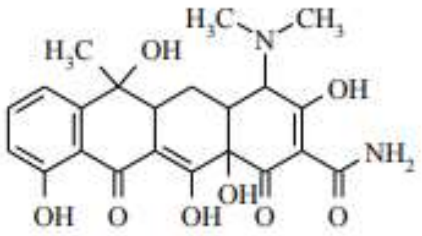
Alicyclic antibiotics include compounds called ***oligoterpenes***, which have a steroidal skeleton. An example is *fusidic acid (fusidin)*:



fusidic acid (fusidin)

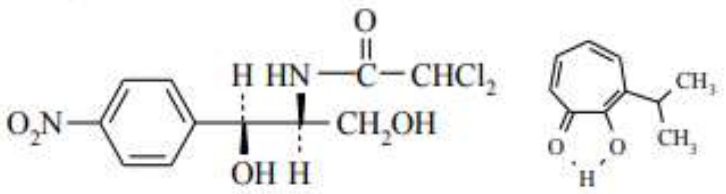
3. Polycyclic antibiotics – tetracyclines

This group includes antibiotics with close structural affinities. They are based on the structure of tetracycline, whose molecule is a system of four condensed six-membered cycles:



4. Aromatic antibiotics

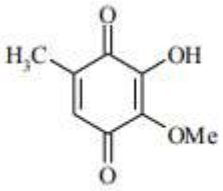
This group includes benzene derivatives (*levomycetin*, etc.) and non-benzoic aromatic compounds (*thujapricin*, found in the wood and essential oil of trees of the cypress family):



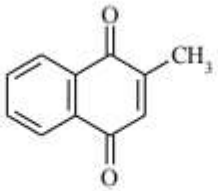
levomycetin *thujapricin*

5. Quinone antibiotics

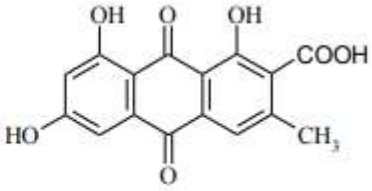
Many antibiotics in this group are generally of no practical importance. These are derivatives of benzoquinone, naphthoquinone, and anthraquinone, such as *fumigatin, plumbagin*, and *indocrocin*.



fumigatin

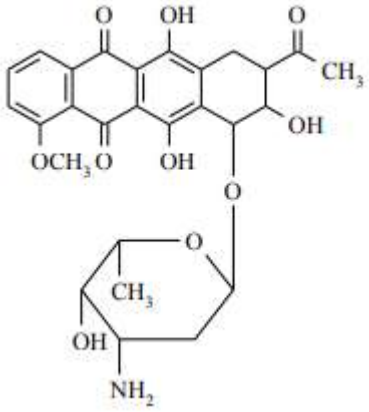


plumbagin



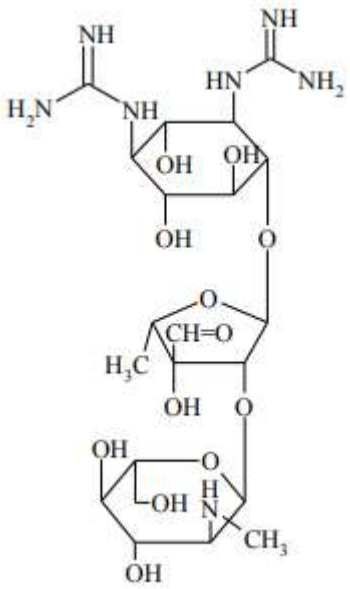
indocrocin

The group of quinone antibiotics also includes a subgroup of anthracyclines, consisting of more than 70 antibiotics. Many of these antibiotics, produced by streptomycetes, have antitumor activity. An example of such an antibiotic is *daunomycin*, which is used in medical practice:



6. Aminoglycoside antibiotics

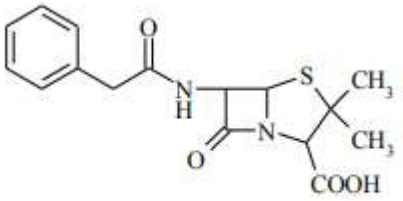
This group includes antibiotics that contain aminosugars in the molecule (e.g., *streptomycin*):



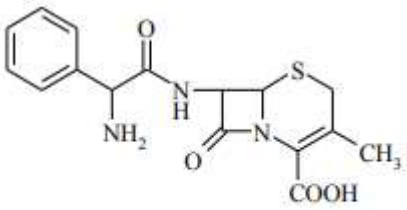
7. β-Lactam antibiotics

This group of antibiotics is characterized by the presence of the β-lactam cycle as part of the molecule and is of great practical and theoretical importance. β-Lactam antibiotics can be divided into the following subgroups:

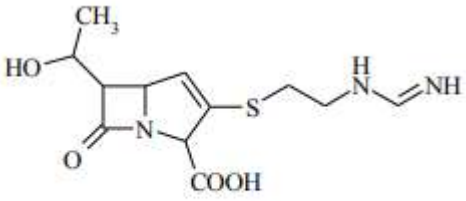
- ***penicillins*** (*benzylpenicillin*);
- ***cephalosporins*** (*cephalexin*);
- ***carbopenems*** (*imipenem*);
- ***monobactams*** (*aztreonem*).



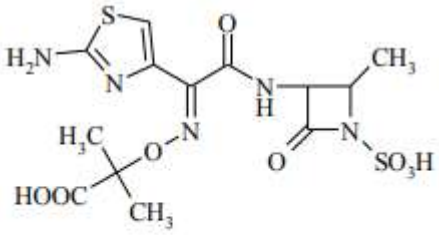
benzylpenicillin



cephalexin



imipenem



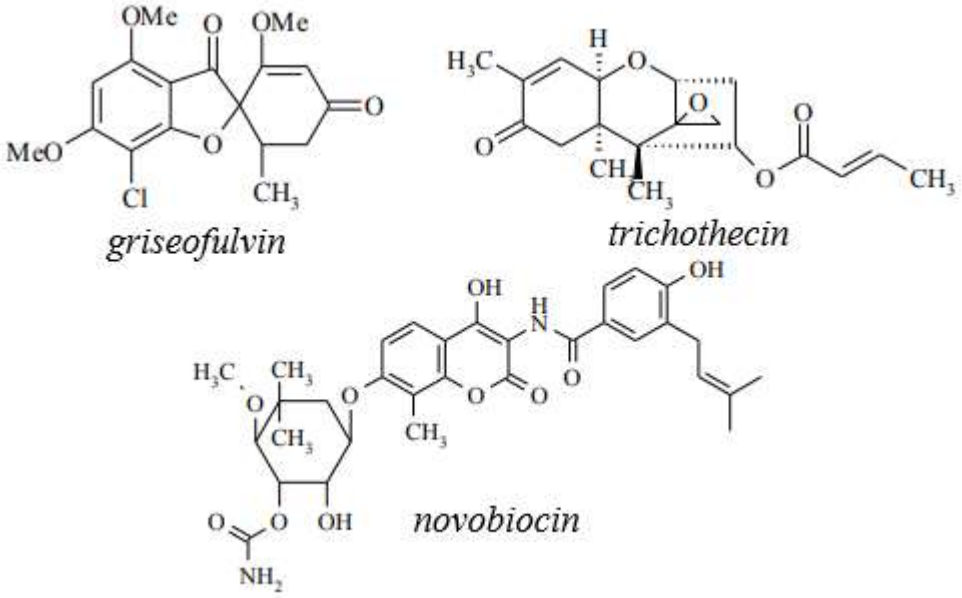
aztreonem

8. Oxygen-containing heterocyclic antibiotics

This group includes a large number of antibiotics, and among them *griseofulvin*, *novobiocin* and *trichothecin* are of the greatest practical interest.

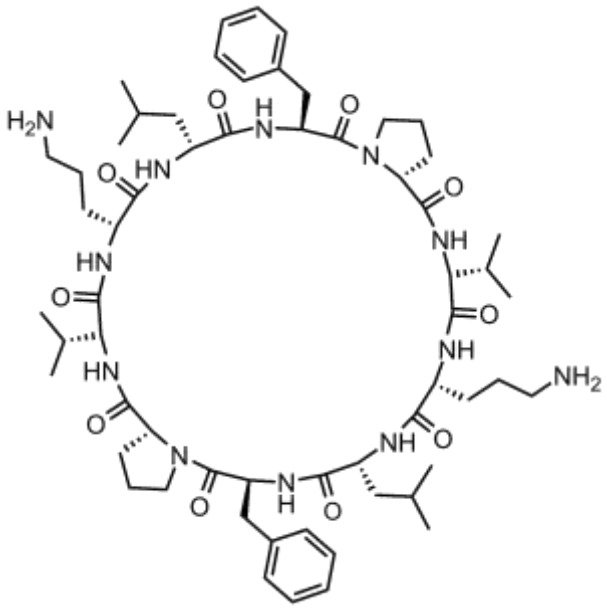
Oxygen-containing heterocyclic antibiotics can be categorized into three groups:

- ***antibiotics with a single five-membered O-heterocycle*** (*griseofulvin*);
- ***antibiotics with a single six-membered O-heterocycle*** (*novobiocin*);
- ***antibiotics with multiple O-heterocycles*** (*trichothecin*).



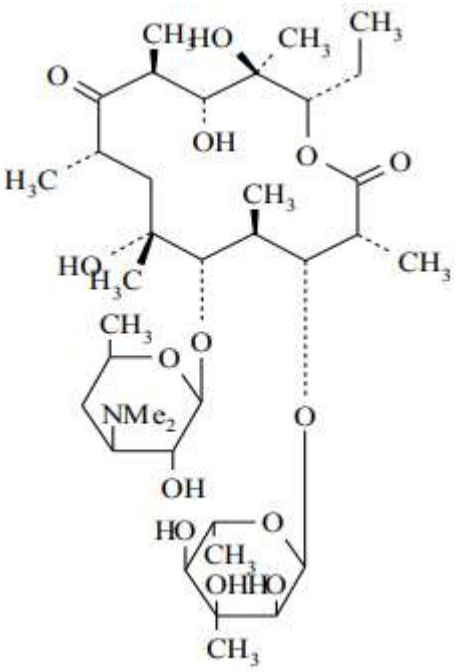
9. Antibiotic polypeptides

Among the chemically studied antibiotics in this group, cyclic peptides composed of L- and D-amino acid residues, such as *gramicidin*, are the most common:



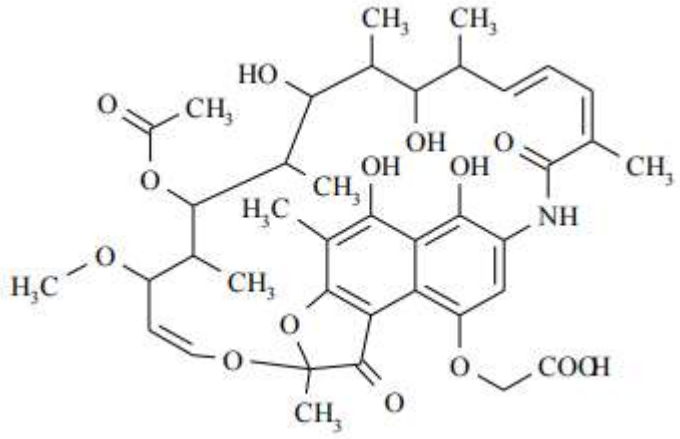
10. Macrolide antibiotics

A characteristic feature of antibiotics in this group is that their structure contains a macrocyclic lactone ring attached to one or more carbohydrate residues, usually aminosugars (e.g., *erythromycin*):



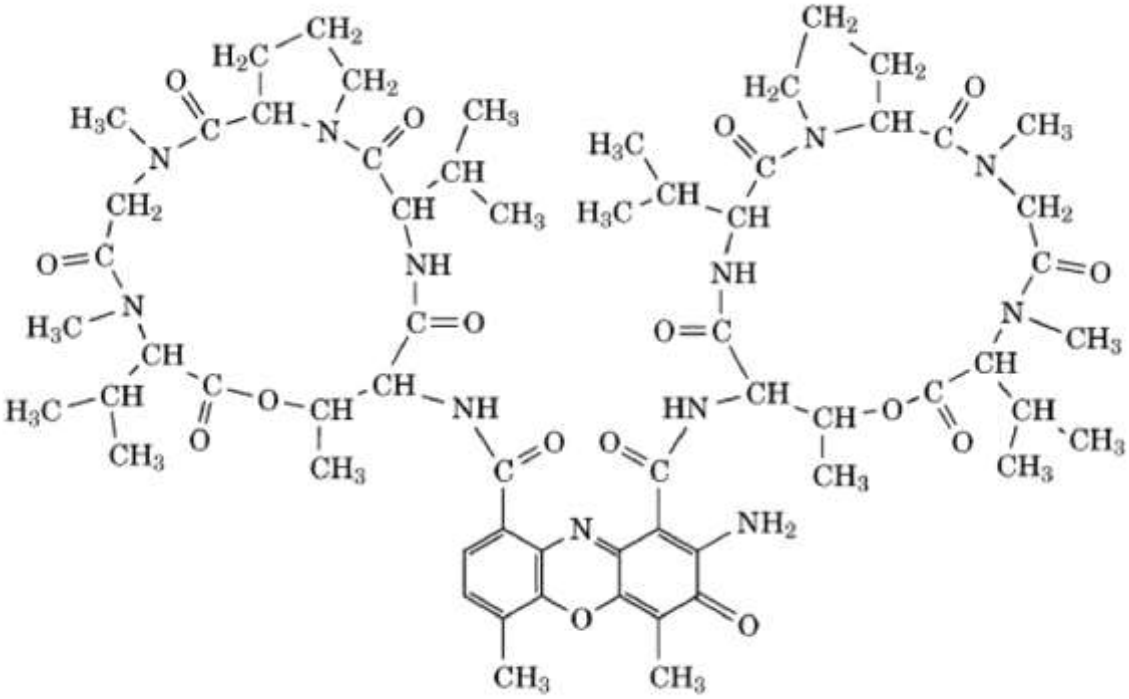
11. Macrolactam antibiotics (ansamycins)

This group includes compounds produced by Streptomycetes, Nocardia and micromonospores and containing a multimembered lactam cycle. Among them, the antibiotic *rifampicin* is of greatest practical interest:



12. Actinomycins

This group includes peptidolide antibiotics, which include the same phenoxazine chromophore group and different peptide chains for these substances:



actinomycin D

13. Metal-containing antibiotics

Among antibiotics there are iron and copper containing compounds. The former include *albomycin*, which contains trivalent iron bound to the organic part of the molecule, the polypeptide. When these antibiotics are treated with HCl or HBr, the iron is removed from the molecule, but the activity decreases 12-14 times. One copper-containing antibiotic is *phleomycin*. Copper can be removed by treatment with 8-oxyquinoline without loss of activity. This antibiotic consists of a carbohydrate and a peptide part. Metal antibiotics are stable compounds: they are not inactivated in the pH range of 2.0 - 7.0, even when heated. They are not affected by proteases.

Classification of antibiotics by mechanism of action

From a pharmacological point of view, the classification according to the mechanism of antibacterial action is more relevant.

The division of antibacterial agents into bacteriostatic and bactericidal agents also retains some significance. ***Bacteriostatic agents*** include *tetracyclines, levomycetin, erythromycin,* etc.; ***bactericidal agents*** include *penicillins, cephalosporins, aminoglycosides, rifampicin,* and others.

1. ***Antibiotics that are specific inhibitors of cell wall biosynthesis*** (*penicillins, cephalosporins, cycloserine*, etc.).
2. ***Antibiotics that disrupt the molecular organization and function of cell membranes***:

   - acting on the lipid layer - polyene antifungal antibiotics (*nystatin, levorin*);

   - acting on the protein layer - cyclic polypeptides (*polymyxins, gramicidin*).
3. ***Antibiotics that inhibit protein synthesis at the ribosome level:***

   - at the level of 30S ribosomal subparticles (*aminoglycosides, tetracyclines*);

   - at the level of 50S ribosomal subparticles (*macrolides, steroidal antibiotics, levomycetin*).
4. ***Antibiotics are inhibitors of purine and pyrimidine synthesis (****azaserin, deconin, sarcomycin,* etc.).
5. ***Antibiotics that selectively inhibit nucleic acid biosynthesis (metabolism):***

   - inhibitors of RNA synthesis at the level of RNA matrix (*rifampicin*);

   - inhibitors of RNA synthesis at the level of DNA matrix (*actinomycins*, etc.);

   - inhibitors of DNA synthesis at the level of DNA matrix (*anthracyclines, bleomycins*).
6. ***Antibiotics, specific respiratory inhibitors*** (*antimycin, oligomycin*, etc.).
7. ***Antibiotics, specific inhibitors of oxidative phosphorylation*** (*valinomycin, gramicidin*, etc.).
8. ***Antibiotics with antimetabolite properties*** (*furanomycin, thermophilus*).
9. ***Immunomodulatory antibiotics*** (*actinomycins, olivomycin, bruneomycin, rubomycin*, etc.)

Classification of antibiotics by spectrum of biological action

1. Antibacterial antibiotics with a narrow spectrum of action, active mainly against Gram-positive microorganisms and used in systemic infections:

1.1 Penicillin and cephalosporin groups:

- natural penicillins (*benzylpenicillin and its salts, phenoxymethylpenicillin*);
- semisynthetic penicillins, acid-resistant and resistant to penicillinase-forming staphylococci: *oxacillin*, etc.;

- semisynthetic cephalosporins: *cephalexi*n, etc.

1.2 Macrolide group: erythromycin and others.

1.3. Bacitracin.

1.4 Lincomycin.

1.5 Novobiocin.

1.6. Fusidine sodium.

2. Primarily targeting Gram-negative bacteria and used in systemic infections:

2.1 Group of aminoglycosides: *streptomycin, kanamycin, neomycin, gentomycin, tobramycin*, etc.

2.2. Group of cyclic polypeptides: *gramicidin C, cycloserine*.

3. Acting on Gram-positive and Gram-negative bacteria and used in systemic infections:

3.1. Semisynthetic penicillins: *ampicillin, carbenicillin*;

3.2. Semisynthetic cephalosporins.

4. Antituberculosis antibiotics:

4.1. Group of aminoglycosides: *streptomycin, kanamycin, cycloserine*.

5. Antifungal antibiotics:

5.1. Group of polyene antibiotics *nystatin, amphotericin B*, etc.

6. Antitumor antibiotics:

6.1. Group of anthracyclines.

6.2. Actinomycin group.

7. Antiprotozoal antibiotics (*trichomycin, fumagillin*).

8. Antiamoebic antibiotics (f*umagillin*).

Classification of antibiotics by tactics of clinical use

1. Primary antibiotics or first-line antibiotics (*penicillins, streptomycin, tetracyclines, cephalosporins*).

2. Reserve (auxiliary, supplementary) or second-line antibiotics (*macrolides, levomycetin, neomycin*, etc.).

Classification of antibiotics by source of excretion

Conventionally, all the most important antibiotics in practical terms can be divided into several groups according to the source of isolation.

1. Antibiotics produced by microorganisms belonging to the Eubacteria.

A. Antibiotics formed by representatives of the genus *Pseudomonas*:

- pyocyanin - *Ps. aeruginosa*.

B. Antibiotics formed by representatives of the genera *Vicrococcus, Streptococcus, Chromobacterium, Escherichia, and Proteus*.

C. Antibiotics formed by representatives of the genus *Bacillus*:

- gramicidins - *B. brevis*,
- polymyxins - *B. polymixa*

2. Antibiotics derived from actinomycetes (80% of all antibiotics):

A. Antibiotics formed by members of the genus *Streptomyces*:

- streptomycin - *S. grise*
- tetracyclines - *S. aureofaciens*,
- novobiocin - *S. spheroides*,
- erythromycin - *Saccharopolysphera erythraea*.

B. Antibiotics formed by members of the genus *Nocardia*:

- rifamycin - *N. mediterranei*.

C. Antibiotics formed by members of the genus *Actinomadura:*

- carminomycin - *A. carminata*.

D. Antibiotics formed by members of the genus *Micromonospora:*

- gentamicin - *M. purpurea*.

3. Antibiotics formed by cyanobacteria.

4. Antibiotics formed by imperfect fungi:

- penicillin - *Penicillium chrysogenum*,
- griseofulvin - P. *griseofulvum*,
- cephalosporin - *Cephalosporium acremonium*

5. Antibiotics formed by lichens, algae and lower plants:

- usninic acid (binanine) - by lichen *Usnea florida*,
- chlorelin - by alga *Clorella vulgaris*

6.Antibiotics of plant origin (phytoncides):

- allicin - *Allium sativum*,
- rafanin - *Rapfanus sativum*.

7. Antibiotics of animal origin:

- lysozyme,
- ecmolin,
- interferon.