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RESISTANCE TO TETRACYCLINE AND OLEANDOMYCIN OF A NUMBER OF STREPTOMYCETES — PRODUCERS OF POLYKETIDE ANTIBIOTICS

Recently, antibiotic resistance of pathogenic and opportunistic microorganisms is one of the primary problems of medicine. Scientists pay considerable attention to the study of genes for resistance of strains of streptomycetes as sources of such genes for microorganisms. ***The aim*** *of this study was to determine the sensitivity of 9 strains of streptomycetes producing polyketide antibiotics to tetracycline and oleandomycin and to identify possible correlations in resistant and sensitive strains between the level of their resistance and the presence of resistance genes in chromosomes.* ***Materials.*** *9 strains of producers of polyketide antibiotics were studied: Streptomyces cyanogenus S136, S. fradiae Tu2717, S. glaucescens Tu49, S. olivaceus Tu2353, S. antibioticus 35, S. globisporus 1912, S. aureofaciens 019, S. coelicolor A3(2), S. lividans TK24.* ***Methods.*** *Appropriate microbiological (method of serial dilution in agar) and biotechnological (method of computerized analysis of sequences) methods were used.* ***Results.*** *According to the sensitivity to oleandomycin and tetracycline, the studied strains of streptomycetes can be divided into 3 groups. The first group includes strains resistant to both antibiotics — S. coelicolor A3(2) and S. lividans TK24, the second group includes strains resistant to only one of the antibiotics: more resistant to oleandomycin — S. globisporus 1912, S. glaucescens Tu49, S antibiotic 35-1; more resistant to tetracycline — S. olivaceus Tu2353, S. fradiae Tu2717, S. aureofaciens 019. Strain S. cyanogenus S136 is sensitive to both antibiotics.* ***Conclusions****. A correlation was found between the level of tetracycline resistance and the presence (the number and similarity of structures) in the genomes of strains S. lividans TK24, S. globisporus 1912, and S. cyanogenus S136 sequences, which are similar to the sequences of tetracycline resistance genes of strain S. coelicolor A3(2).*

Keywords: *antibiotic, resistance, Streptomyces, gene.*

Antibiotics synthesized by members of the *Streptomyces* family are widely used in medicine and veterinary medicine. A special place among them is occupied by polyketide compounds, which are used as antibacterial, antitumor, and anthelmintic drugs as well as immunomodulators [1, 2].

It is known that the productivity of a producer strain depends on the functioning of all its

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necessary genes of the biosynthetic cluster and largely depends on the genes of resistance to its own antibiotic. Clusters of antibiotic biosynthesis genes typically include genes for resistance to the synthesized product. However, there may be individual resistance genes in the chromosomes of producers [3—5]. Non-producing cultures can also have resistance genes [6].

It was found, on the one hand, the increase in the level of resistance to its own antibiotic promotes increasing its productivity. On the other hand, there has been reported that an increase in resistance to the third-party antibiotics of industrial strains also increases their productivity.. For example, increase by two times in the level of landomycin E syntheses of variant 3-1 of strain *Streptomyces globisporus* 1912 after increasing its resistance to streptomycin from 2.5 μg/mL to 500.0 μg/mL medium was reported in [7].

It is known that there are several protection mechanisms of streptomycetes from antibiotics, both own and third-party: modification of the "targets" of biocides; enzymatic inactivation of antibiotics; active transport of metabolites from cells. The microorganism cell can simultaneously have several mechanisms of protection against the action of the same antibiotic. On the other hand, streptomycetes are known as carriers of the so-called multiple resistance, which simultaneously provide resistance to metabolites of different chemical nature, carried out by the same enzyme or transport complex [8].

The TransportBD database includes almost 800 transmembrane pumps in the strain *S. coelicolor* A3 (2) of different structures and mechanisms of action (for example, ABC family — The ATP-binding Cassette Superfamily and MFS family — The Major Facilitator Superfamily), which provide resistance to one specific antibiotic or a number of third-party and own antibiotics (http://www.membranetransport.org/transporter2.php?oOID=scoe1). Multiple mechanisms provide resistance to many antibiotics, including macrolides, streptogramins, fosmidomycin, and chloramphenicol [9, 10].

This paper presents the results of a study of sensitivity to tetracycline and oleandomycin of 9 streptomycetes strains producing polyketide antibiotics. Earlier, the results of studies of the resistance of these streptomycetes to landomycin A and E were published [11—13]. The authors hypothesized the existence of genetic determinants of multiple resistance in several of them (for example, in *S. globisporus* 1912) and showed a correlation between the level of their resistance to antibiotics and their synthesis of antibiotics [13].

Antibiotics used in the work (tetracycline and oleandomycin) inhibit protein biosynthesis by joining the components of ribosomes. Tetracycline molecules interact with the 30S subunit of ribosomes, blocking the binding of tRNA to the mRNA-ribosome complex, as well as disrupting the incorporation of new aminoacids into a polypeptide. Oleandomycin binds to the catalytic peptidyltransferase center of 50S subunits of ribosomes that inhibited protein synthesis. Self-protection of tetracycline and oleandomycin-producing streptomycetes from antibiotics is carried out both by enzymatic modification of the antibiotic (e.g. glycosylation of oleandomycin) and ribosomes (rRNA methylation) and by removal of biocides from the cell by transmembrane pumps [14]. Interestingly, the ribosomes of the oleandomycin producer *S. antibioticus* remain sensitive to their own antibiotic even in the super producer [15].

The **aim** of the study was to determine the sensitivity of 9 strains of streptomycetes producing polyketide antibiotics to tetracycline and oleandomycin and to identify possible correlations in resistant and sensitive strains between the level of their resistance and the presence of resistance genes in chromosomes.

Materials and methods. 9 streptomycetes strains producing polyketide antibiotics (Table 1) were tested in the work. The strains were obtained

from the museum of the Department of genetics of microorganisms of the Zabolotny Institute of Microbiology and Virology, NAS of Ukraine.

Streptomycetes were grown and stored on agar soy medium. Antibiotic susceptibility was determined on the Okanishi medium [13].

Method of sequential dilution of cells in liquid medium. Streptomycetes were grown in a liquid version of Okanishi medium at 28 ^{0}C with stirring. Two-day-old mycelium was separated from the culture fluid by centrifugation at 1.500 rpm, washed with sterile saline, ground in a glass Potter homogenizer, and filtered through a cotton gauze filter. The filtrates were diluted with saline to form a suspension with a titer of 10^7 CFU/mL.

Method of serial dilutions of antibiotics. The suspensions in appropriate dilutions were mixed with molten and cooled to 45 ^{0}C agar Okanishi medium, to which antibiotics with the required concentrations were added. 20 ml of such mixes were poured into each Petri dish. Commercial preparations of antibiotics oleandomycin and tetracycline (Borshchahivskyi Chemical Plant) were used in the work. After incubation of cultures at a temperature of 28 ^{0}C for 5—7 days, the number of colonies was counted.

Table 1. **List of used strains of streptomycetes — producers of polyketides**

Strains of streptomycetes	The main component of synthesized complex of antibiotics	Sources of information
S. cyanogenus S136	landomycin A	[16]
S. fradiae Tu2717	urdamycin A	[16]
S. glaucescens Tu49	tetracenomycin	[17]
S. olivaceus Tu2353	eloramycin	[18]
S. antibioticus 35-1	oleandomycin	[13]
S. globisporus 1912	landomycin E	[16]
S. aureofaciens 019	chlortetracycline	[19]
S. coelicolor A3(2)	actinorodine	[20]
S. lividans TK24.	actinorodine*	[20]

Note: * — trace quantities.

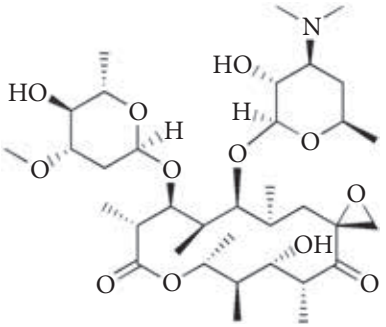
Computerized analysis of sequences of streptomycetes genomes was carried out by means of the BLASTN programs [www.ncbi.nlm.nih.gov/blast]. Tetracycline resistance genes SCO6805, SCO3898, SCO0900, SCO2046, SCO1892, SCO6427, SCO2264, SCO0783, SCO0252, SCO7705, SCO7659. SCO7625, and SCO0484 of strain *S. coelicolor* A3(2) were used in our BLAST-analyzes as reference sequences. Information on the genome primary structures of strains *S. lividans* TK24 (NZ_CP009124.1), *S. cyanogenus* S136 (NZ_CP071839.1), *S. globisporus* 1912 (QWFA00000000.1), and *S. coelicolor* A3(2) (NC_003888.3) were taken from NCBI databases [www.ncbi.nlm.nih.gov/nucleotide/]

Results. The resistance of 9 strains of streptomycetes to tetracycline and oleandomycin has been studied (Table 1, Fig. 1).

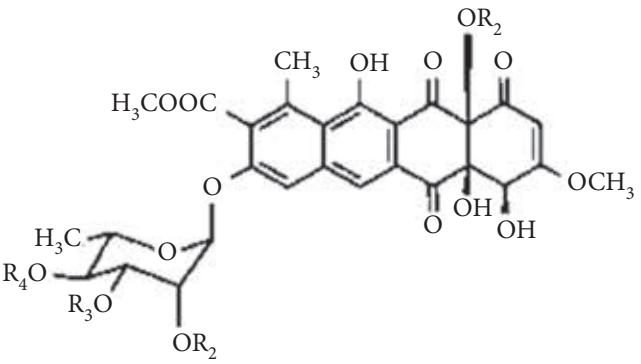
Three of them (strains of *S. fradiae* Tu2717, *S. cyanogenus* S136, and *S. globisporus* 1912) are producers of anthracycline antibiotics (urdamycin, landomycins A and E, respectively), 3 strains (*S. aureofaciens* 019, *S. glaucescens* Tu49, *S. olivaceus* Tu2353) synthesize tetracycline compounds (tetracycline, tetracenomycin, and eloramycin, respectively), *S. antibioticus* 35-1 strain produces the macrolide antibiotic oleandomycin. The antibiotic actinorodin is produced by *S. coelicolor* A3(2) and *S. lividans* TK24.

Resistance of streptomycetes to tetracycline and oleandomycin is provided by all known mechanisms, in particular via active removal of the antibiotic from the cell; inactivation of antibiotics and modification of the target by specific enzymes. Tetracycline and oleandomycin resistance genes exist not only in producer strains but also are widespread among microorganisms (including streptomycetes). Interestingly, the oleandomycin producer strain *S. antibioticus* lacks a mechanism to protect ribosomes from its own antibiotic and its ribosomes, even in the superproducer, are sensitive to the synthesized antibiotic.

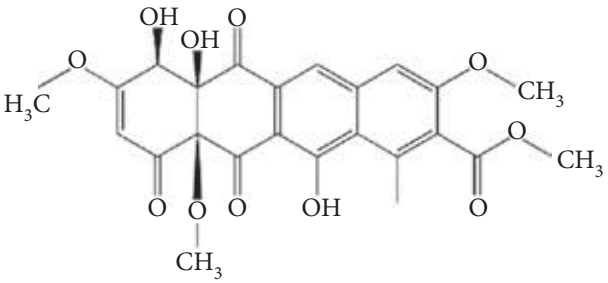
Resistance to antibiotics was investigated by the method of serial dilutions of antibiotics.



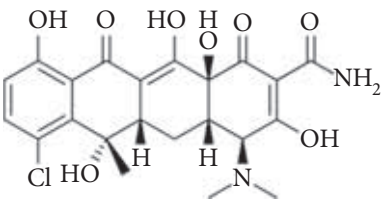
Oleandomycin



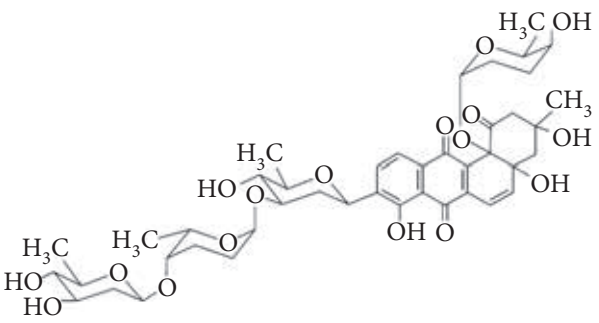
Eloramycin



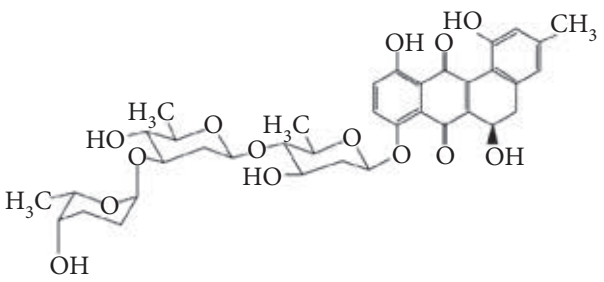
Tetracenomycin



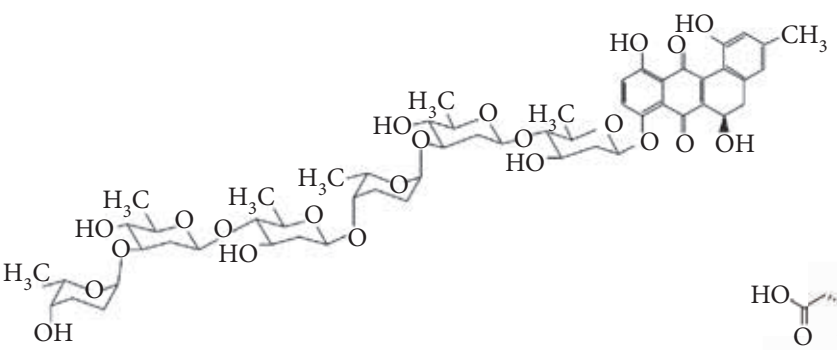
Chlortetracycline



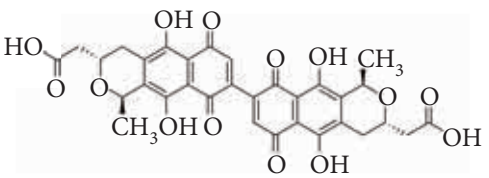
Urdamycin A



Landomycin E

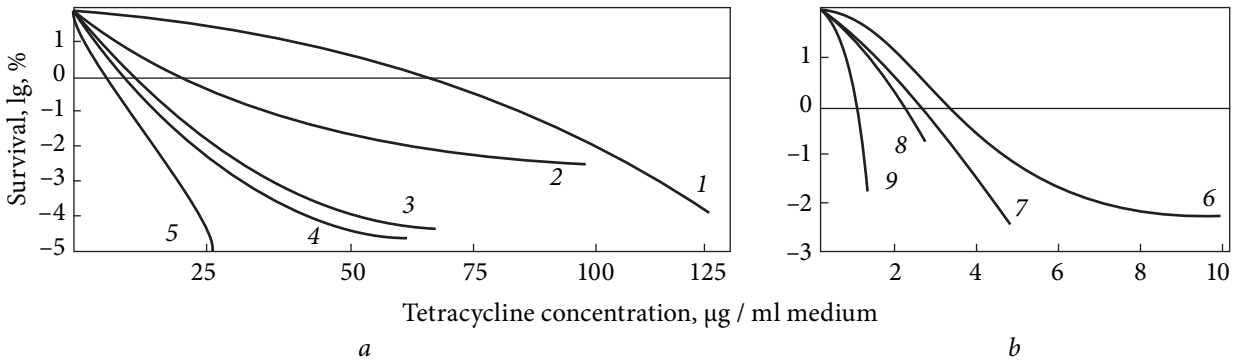


Landomycin A

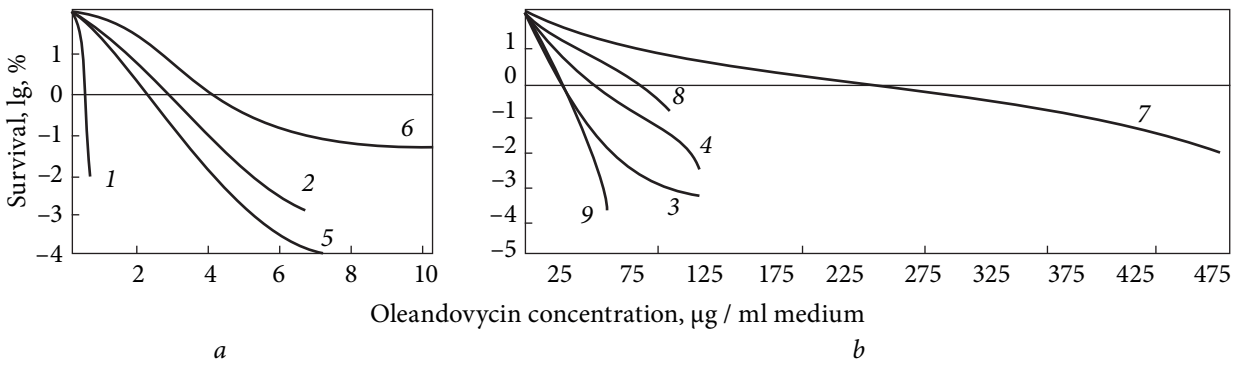


Actinorodine

Fig. 1. Structural formulas of polyketide antibiotics under study



Figs. 2. Dependence of streptomycete survival on the tetracycline concentration: 1 — *S. aureofaciens* 019, 2 — *S. fradiae* Tu2717, 3 — *S. coelicolor* A3(2), 4 — *S. lividans* TK24, 5 — *S. olivaceus* Tu2353, 6 — *S. cyanogenus* S136, 7 — *S. antibioticus* 35-1, 8 — *S. glaucescens* Tu49, 9 — *S. globisporus* 1912



Figs. 3. Dependence of streptomycete survival on the oleandomycin concentration: 1 — *S. aureofaciens* 019, 2 — *S. fradiae* Tu2717, 3 — *S. coelicolor* A3(2), 4 — *S. lividans* TK24, 5 — *S. olivaceus* Tu2353, 6 — *S. cyanogenus* S136, 7 — *S. antibioticus* 35-1, 8 — *S. glaucescens* Tu49, 9 — *S. globisporus* 1912

The maximum concentration of oleandomycin was 475 μg/mL of the Okanishi medium, and the maximum concentration of tetracycline was 150 μg/mL of medium (Fig. 2, *b*; 3, *a*). However, some of the strains were not able to grow on the medium with antibiotics at their concentrations (both and oleandomycin) above 10.0 μg/mL (Figs. 2, *a*; 3, *b*).

Figs. 2 and 3 show the dependence curves of cell survival of tetracycline 9 strains of streptomycetes, producers of polyketide antibiotics, on the concentration of tetracycline and oleandomycin in the Okanishi medium.

The studied strains of streptomycetes according to their sensitivity to antibiotics can be divided into 3 groups. The first group includes 2 strains, namely *S. coelicolor* A3(2), *S. lividans* TK24, which are most resistant to both antibiotics; the second group includes strains that are resistant to only one of the two antibiotics, namely the resistant to oleandomycin and sensitive to tetracycline strains *S. globisporus* 1912, *S glaucescens* Tu49, and *S. antibioticus* 35-1, as well as more resistant to tetracycline and sensitive to oleandomycin *S. olivaceus* Tu2353. *S. fradiae* Tu2717, and *S. aureofaciens* 019; the third group includes one strain only, namely strain *S. cyanogenus* S136, which is sensitive to both antibiotics.

In general, the studied strains of streptomycetes are more resistant to oleandomycin than to

tetracycline, although the structures of the molecules of their own antibiotics are more similar to those of tetracycline molecule (Fig. 1).

Significant sensitivity of *S. aureofaciens* 019 chlortetracycline producer to oleandomycin (0.5 μg/mL medium) has also been shown. It was previously reported that this strain is sensitive to landomycin E, as well as the producer of oleandomycin (*S. antibioticus* 35-1) [13].

As shown by our studies, strains of *S. lividans* TK24 and *S. coelicolor* A3(2) are more resistant than 7 strains to both antibiotics used. Both strains are the most studied streptomycetes. Strains of *S. lividans* TK24 and *S. coelicolor* A3(2) were found to be closely related streptomycetes [20]. It is known that the strain *S. coelicolor* A3(2) produces several antibiotics — actinorhodin, methyleneomycin, prodegiozin, coelimycin,

Table 2. **Similarity of gene sequences of *S. coelicolor* A3(2) (Query sequence) and *S. lividans* TK24, *S. cyanogenus* S136, *S. globisporus* 1912 (Subject sequence)**

Indicators of similarity of sequences* of analogous genes of streptomycetes			
S. coelicolor A3(2)	*S. lividans* TK24	*S. cyanogenus* S136	*S. globisporus* 1912
SCO6805	SLIV_RS04570 Qc=100%, I=99.62%	S1361_RS33455 Qc=92%, I=92,77%	N
SCO3898	SLIV_RS18790 Qc=100%, I=99.53%	S1361_RS20035 Qc=98%, I=78.86%	D3105_02060 Qc=93%, I=74.98%
SCO1892	SLIV_RS28255 Qc=100%, I=99.52%	S1361_RS10360 Qc=91%, I=75.02%	D3105_13870 Qc=85%, I=69.28%
SCO0900	SLIV_RS33385 Qc=100%, I=99.61%	S1361_RS35780 Qc=93%, I=75.85%	N
SCO0252	SLIV_RS36610 Qc=100%, I=99.36%	N	N
SCO0783	SLIV_RS33980 Qc=100%, I=98.70%	N	N
SCO2046	SLIV_RS27480 Qc=100%, I=99.65%	N	D3105_22805 Qc=95%, I=72.61%
SCO0484	SLIV_RS35470 Qc=100%, I=99.91%	S1361_RS37060 Qc =82%, I=63.77%	N
SCO7705	SLIV_RS00820 Qc=100%, I=99.50%	S1361_RS34970 Qc=88%, I=75.26%	N
SCO7659	SLIV_RS01070 Qc=100%, I=99.55%	S1361_RS00810 Qc=99%, I=85.93%	N
SCO7625	SLIV_RS01235 Qc=100%, I=99.82%	S1361_RS34970 Qc=88%, I=63.67%	N
SCO6427	SLIV_RS06350 Qc=100%, I=99.46%	N	D3105_16665 Qc=94%, I=79.74%
SCO2264	SLIV_RS26395 Qc=100%, I=99.61%	N	D3105_16665 Qc=95%, I=75.04%

Note: * — indicators of similarity of primary structures of similar genes: Qc (Query cover) — coverage, I (Identity) — identity, N — sequences not detected.

and calcium-dependent antibiotics. Trace synthesis of actinorodine by *S. lividans* TK24 has been reported. It was found that both strains contain genes for resistance to many foreign antibiotics [6,20].

The TransporterDB 2 database provides information on proteins that form transmembrane pumps of 2788 organisms of different taxonomic groups of the bacterial kingdom, including 19 strains of streptomycetes (of course and S. *coelicolor* A3(2)). The database presents information about 795 proteins of efflux of *S. coelicolor* A3(2). These pumps transport various substrates from and into the cell: carbohydrates, lipids, salts, peptides, antibiotics, and many others. By structure, effluxes that transport antibiotics from the cell belong to the ABC and MFS families of the class of ATP-dependent transporters.

The GenBank database contains information about the primary structures of 13 genes of *S. coelicolor* A3(2), which provide resistance of the strain to tetracycline: genes SCO6805, SCO3898, SCO0900, SCO2046, SCO1892, SCO6427, and SCO2264 determine proteins of transmembrane efflux of M-families; products of genes SCO0783, SCO0252, SCO7705, SCO7659. SCO7625, SCO0484 determine the modification of tetracycline and 30S ribosomal subunit.

Information on the primary structure of genomic DNA of strains *S. lividans* TK24 (NZ_CP009124.1), *S. cyanogenus* S136 (NZ_CP071839.1), *S. globisporus* 1912 (QWFA00000000.1), and mn*S. coelicolor* A3(2) (NC_003888.3) were in GenBank database. BLAST-analysis revealed in the genomic sequences of strains *S. lividans* TK24, *S. cyanogenus* S136 and *S. globisporus* 1912 structures similar to the sequences of tetracycline resistance genes of strain *S. coelicolor* A3(2) (Table 2). As reported above, strains of *S. coelicolor* A3(2) and *S. lividans* TK24 are the most resistant to the antibiotic, and strains of *S. cyanogenus* S136 and *S. globisporus* 1912 are the most sensitive to tetracycline.

While in the genome of strain S. lividans TK24, sequences with a significant degree of identity (over 98.7%) to the sequences of all reference genes of S. coelicolor A3(2) were revealed, in the genomes of sensitive strains (S. cyanogenus S136 and S. globisporus 1912) only 5 — 8 desired fragments with much smaller similarity of their sequences to the sequences of reference genes of S. coelicolor A3(2) were found. There is a definite correlation between, on the one hand, the resistance of strains to tetracycline and, on the other hand, the number of resistance genes present in the genomes and the similarity of the structures of these genes to the sequences of reference genes *S. coelicolor* A3(2). Interestingly, in the genome of strain *S. globisporus* 1912, there are no sequences similar to the sequences of the reference genes of *S. coelicolor* A3(2), which determine tetracycline resistance by enzymatic modification.

Discussion. In the experiments presented, the resistance of wild type strain of *S. globisporus* 1912 has been determined. It was found that the original culture is sensitive to tetracycline even in small doses (1.5 μg/mL). There is a sharp decrease in culture survival at a concentration of 15.0 μg/mL oleandomycin in the environment.

As previously reported, morphological variants of the strain *S. globisporus* 1912 differ in their resistance to tetracycline and oleandomycin [11]. For example, the "bald" mutant 3-1 of the strain *S. globisporus* 1912 (superproducer of landomycin E) has significant resistance to both of these antibiotics [12].

Our previous studies found that the resistance to landomycin E and A strain of *S. olivaceus* Tu2353 (producer of elaramicin) is not inferior to the producer of landomycin E and is superior to the producers of landomycin A and urdamycin [14]. At the same time, the strain is sensitive to low concentrations of oleandomycin and tetracycline (Fig. 2B, 3A). Interestingly, the strain of *S. lividans* TK24, which is resistant to oleandomycin and tetracycline (Figs. 2A, 3B), is one of the most resistant to landomycin A and at the same time sensitive to landomycin E [13]. Although close genetic affinities of *S. lividans*

TK24 and *S. coelicolor* A3(2) strains have been reported, there is a significant difference in their resistance to landomycins A and E [13]. At the same time, these strains are equally resistant to oleandomycin and tetracycline (Figs. 2A, 3B).

It was previously found that there is an association between increased levels of landomycin E synthesis and increased resistance to other foreign antibiotics. It was found that increasing the resistance to streptomycin (from 12.0 μg/mL to 500.0 μg/mL) of mutant 3-1 of the strain *S. globisporus* 1912 leads to doubling of the level of synthesis of landomycin E [11]. Streptomycin, an antibiotic from the group of glycosides, also inhibits protein synthesis by joining the 30S subunit of ribosomes. Mechanisms of resistance to streptomycin are enzymatic inactivation by phosphorylases, decreased permeability of the cell wall, modification of the target (30S subunit of bacterial ribosomes), and active excretion of the antibiotic from cells.

The Transporter database contains information on 109 efflux proteins from the MFS family of the strain *S. coelicolor* A3(2), of which 71 proteins are considered as components of multiple resistance pumps. According to information from the GenBank and Transporter databases, seven of the *S. coelicolor* A3(2) genes listed in Table 2 determine pump proteins from the MFS family. Most proteins (with the exception of the SCO6427 gene product) are components of efflux that provide multiple resistance.

Thus, the studied strains of streptomycetes, according to their sensitivity to oleandomycin and tetracycline, can be divided into 3 groups. The first group includes strains resistant to both antibiotics — S. coelicolor A3(2) and S. lividans TK24; the second group includes strains that are more resistant to only one of the antibiotics: S. globisporus 1912, S. glaucescens Tu49, S. antibioticus 35-1, S. olivaceus Tu2353. S. fradiae Tu2717, S. aureofaciens 019. Strain S. cyanogenus S136 is sensitive to low concentrations of both antibiotics.

Conclusions. A correlation between, on the one hand, the resistance of strains to tetracycline and, on the other hand, the number of resistance genes present in the genomes and the similarity of the structures of these genes to the sequences of reference genes *S. coelicolor* A3(2) has been established.

REFERENCES

1. Wencewicz TA. Crossroads of Antibiotic Resistance and Biosynthesis. J Mol Biol. 2019; 431(18):3370—3399. doi: 10.1016/j.jmb.2019.06.033
2. Trenin AS. [Methodology of screening new antibiotics: present status and prospects]. Antibiotics and chemotherapy. 2015; 60(7—8):34—46. Russian
3. Jian Z, Zeng L, Xu T, Sun S, et al. Antibiotic resistance genes in bacteria: Occurrence, spread, and control. J Basic Microbiol. 2021; 61(12):1049—1070. doi: 10.1002/jobm.202100201
4. Rebets Y, Ostash B, Gromyko O, et al. Resistance of recombinant *Streptomyces albus* cest 114 and *Streptomyces globisporus* strains to landomycins E. Visnyk of L'viv univ. Biology Series. 2003; 33:47—54.
5. Chen J, Wu Q, Hawas UW, Wang H. Genetic regulation and manipulation for natural product discovery. Appl Microbiol Biotechnol. 2016; 100(7):2953—2965. doi: 10.1007/s00253-016-7357-3.
6. Lewis RL, Laing E, Allenby N, et al. Metabolic and evolutionary insights into the closely-related species *Streptomyces coelicolor* and *Streptomyces lividans* deduced from high-resolution comparative genomic hybridization. BMC Genomics. 2010; 1(11):682—698 doi: 10.1186/1471-2164-11-682.
7. Gromyko O, Basiliya L, Kirichenko N, et al. Obtaining and characteristics of streptomycin resistant mutants of antitumor landomycin E producer *Streptomyces globisporus* 3-1. Visn Lviv Univ Ser Biol. 2000; 26(1):46—53.
8. Lee LF, Chen YJ, Kirby R, et al. A multidrug efflux system is involved in colony growth in *Streptomyces lividans*. Microbiology (Reading). 2007; 153 (Pt 4):924—934. doi: 10.1099/mic.0.2006/000018-0.
9. Vecchione JJ, Alexander B, Sello JK. Two distinct major facilitator superfamily drug efflux pumps mediate chloramphenicol resistance in *Streptomyces coelicolor.* Antimicrobial agents and chemotherapy. 2009; 53(11):4673—4677 doi:10.1128/AAC.00853-09

10. Nag A, Mehraa S. A Major Facilitator Superfamily (MFS) efflux pump, SCO4121, from *Streptomyces coelicolor* with roles in multidrug resistance and oxidative stress tolerance and its regulation by a MarR regulator. Applied and Environmental Microbiology. 2001; 87(7):2238—2250. doi: 10.1128/AEM.02238-20.
11. Dubinska L, Zavorotna S, Ostash B, et al. Characteristics of resistance of patterns to antibiotics of producers of antitumor antibiotics *Streptomyces globisporus* 1912, *Streptomyces peucetius* ATCC 29050 and *Streptomyces peucetius* supsp. caesius ATCC 27952. Visnyk Lviv Univ Ser. Biology. 2000; 25910:49—56.
12. Tymchik OV, Matselyukh BP, Lavrinchuk VYa. [Sensitivity of *Streptomyces globisporus* 3-1 — a highly active producer of landomycin E — to its own and other polyketide antibiotics]. Mikrobiol Z. 2004: 66(2):69—73. Ukrainian.
13. Matseliukh BP, Konovalova TA, Polishchuk LV, et al. [Sensitivity of streptomycetes, producers of polyketide antibiotics, to landomycins A and E]. Mikrobiol Z. 1998; 60(1):31—36. Ukrainian.
14. Vinogradova KA, Bulgakova VG, Polin AN, et al. [*Streptomycetes* Biofilms. I. Occurrence and Formation]. Antibiotics and Chemotherapy. 2015; 60(1—2):39—46. Russian.
15. Ogawara H. Comparison of Antibiotic Resistance Mechanisms in Antibiotic- Producing and Pathogenic Bacteria. Molecules. 2019; 24(19):3430. doi: 10.3390/molecules24193430
16. Zhang J, Duan Y, Zhu X, Yan X. [Novel angucycline/angucyclinone family of natural products discovered between 2010 and 2020] Chinese journal of biotechnolog. 2021; 37(6):2147—2165. doi: 10.13345/j.cjb.210033. Chinese.
17. Lazar G, Zahner H, Breiding S, et al. 3-Demethoxy-3-ethoxy-tetracenomycin C. J Antibiot (Tokyo). 1981; 34(8):1067—1068.
doi: 10.7164/antibiotics.34.1067.
18. Decker H, Rohr J, Motamedi H, et al. Identification of *Streptomyces olivaceus* Tu 2353 genes involved in the production of the polyketide elloramycin. Gene. 1995; 166(1):121—6. doi: 10.1016/0378-1119(95)00573-7.
19. Lavrinchuk VJa, Stryzhkova HM, Matseliukh BP. [The induction of mutations in *Streptomyces aureofaciens* by UV rays and nitrosoguanidine and the identification of the mutants obtained]. Mikrobiol Z. 1997; 59(2):20—24. Ukrainian.
20. Hopwood DA, Chater KF, Bibb MJ. Genetics of antibiotic production in *Streptomyces coelicolor* A3(2), a model streptomycete. Biotechnology. 1995; 28:65—102. doi: 10.1016/b978-0-7506-9095-9.50009-5.

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РЕЗИСТЕНТНІСТЬ ДО ТЕТРАЦИКЛІНУ ТА ОЛЕАНДОМІЦИНУ
РЯДУ СТРЕПТОМІЦЕТІВ — ПРОДУЦЕНТІВ ПОЛІКЕТИДНИХ АНТИБІОТИКІВ

Останнім часом резистентність до антибіотиків патогенних та умовнопатогенних мікроорганізмів є однією з першорядних проблем медицини. Значну увагу науковці приділяють вивченню генів стійкості штамів стрептоміцетів як джерел таких генів для мікроорганізмів. **Метою** роботи було визначити чутливість 9 штамів стрептоміцетів — продуцентів полікетидних антибіотиків до тетрацикліну та олеандоміцину та виявити можливу кореляцію у стійких та чутливих штамів рівня їх стійкості та присутності генів резистентності в хромосомах. **Матеріали.** Досліджували 9 штамів — продуцентів полікетидних антибіотиків: *S. cyanogenus* S136, *S. fradiae* Tu2717, *S. glaucescens* Tu49, *S. olivaceus* Tu2353, *S. antibioticus* 35, *S. globisporus* 1912, *S. aureofaciens* 019, *S. coelicolor* A3(2), *S. lividans* TK24. **Методи.** В роботі використовували відповідні мікробіологічні (метод серійного розведення в агарі) та біотехнологічний (метод комп'ютерного аналізу послідовностей) методи. **Результати.** За чутливістю до олеандоміцину і тетрацикліну досліджувані штами стрептоміцетів можливо розподілити на 3 групи. В першу віднесені штами, стійкі до обох антибіотиків — *S. coelicolor* A3(2), *S. lividans* TK24, у другу віднесені штами, що стійкі тільки до одного з антибіотиків: резистентніші до олеандоміцину — це *S. globisporus* 1912, *S. glaucescens* Tu49, *S. antibioticus* 35-1; стійкіші до тетрацикліну — *S. olivaceus* Tu2353. *S. fradiae* Tu2717, *S. aureofaciens* 019. Штам *S. cyanogenus* S136 є чутливим до обох антибіотиків. **Висновки.** Виявлена кореляція між рівнем стійкості до тетрацикліну та присутністю в геномах штамів *S. lividans* TK24, *S. globisporus* 1912 та *S. cyanogenus* S136 послідовностей, які подібні сиквенсам генів резистентності до тетрацикліну штаму *S. coelicolor* A3(2).

Ключові слова: *антибіотик, резистентність, стрептоміцет, ген.*