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CYTOTOXICITY AND ANTITUMOR ACTIVITY OF SESQUITERPENE LACTONES. STRUCTURE, ACTIVITY

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The article discusses the results of screening 19 samples of sesquiterpene γ-lactones argolide, grosheimin, estafiatin, and their derivatives for cytotoxicity and antitumor activity. The research results indicate significant cytotoxicity and selectivity of the action of sesquiterpene γ-lactones and their derivatives against most tumour cell lines.

The aim. *The aim of this study is to study the cytotoxicity and antitumor activity of the sesquiterpene γ-lactones argolide, grosheimin, estafiatin and their chemically modified derivatives as practically renewable materials.*

Methods. *The cytotoxicity of the compounds was determined using vero cells, THP-1, Pliss lymphosarcoma cell lines, Walker carcinosarcoma, sarcoma 45, sarcoma-180, alveolar liver cancer PC-1, P-388 leukemia, L-1210 leukemia, and sarcoma 45-resistant to 5-fluorouracil.*

The antitumor activity of the samples was studied in vivo experiments on white outbred rats with transplanted tumour strains and was assessed by inhibition of tumour growth and the magnitude of the increase in average life expectancy.

Statistical processing of the results was carried out using the program "GraphPad Prism v. 6.0» (GraphPad Software Inc., USA).

Conclusion. *When determining cytotoxicity in vitro samples of the sesquiterpene γ-lactones argolide, grosheimin and estafiatin showed selectivity of their action on cells of 8 tumor lines, on cells of human acute monocytic leukemia THP-1 and in relation to the larvae of sea crustaceans Artemia salina (Leach) .*

Samples of argolide, 8-acetylgrosheimin, 13-morpholinogrosheimin, 3-keto-4-methylene-cis-guaianolide, 3α-acetoxyisozaluzanin C, and 10α(14)-epoxy-1,5,7α,4,6β(H)-guai-11(13)-ene-4(3),6(12)-diolide in experiments in vivo possessed high antitumor activity against transplantable tumor strains of Pliss lymphosarcoma, Walker carcinosarcoma, sarcoma 45, sarcoma 37, sarcoma 180, alveolar liver cancer PC-1, leukemia P-388 and L-1210, sarcoma 45, resistant to 5-fluorouracil

Keywords: *sesquiterpene lactones, tumour cell culture, cytotoxicity, inoculated tumour lines, antitumor activity*

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1. Introduction

More than 8000 sesquiterpene lactones belonging to more than 40 structural types have been discovered and described from various sources [1].

Natural sesquiterpene lactones have a wide range of biological activities, including anti-inflammatory, antibacterial, cardiotonic, antitumor, anthelmintic, and antimutagenic activity [2, 3].

A large number of sesquiterpene lactones are known to have cytotoxicity and antitumor activity [4–8].

In the works, the cytotoxicity and antitumor effect of sesquiterpene lactones are determined by the presence in their molecule of such alkylating centers as α-methylene-γ-lactone, α,β-unsaturated keto group and epoxy ring [3, 9].

However, [10] notes that the carbocycle of the sesquiterpene lactone molecule also plays an important role in cytotoxicity. At the same time, he believes that germacranolides are more active among representatives of this group of natural terpenoids.

The structure-activity relationship was studied using QSAR analysis, which showed that the strength of the inhibitory activity against c-Myb-dependent transcription depends not only on the presence of signs of reaction acceptors according to the Michael reaction, but also on their optimal spatial arrangement in the molecule [11].

Considering that sesquiterpene γ-lactones exhibit a wide range of biological activities against many types of organisms, the studies of the structure-activity relationship for these compounds have not yet led to any general conclusion.

Of particular interest from the point of view of SAR-analysis are hybrid compounds containing two biologically active fragments in their structure that exhibit synergy between the known properties of these fragments and impart new types of activity to them.

One of the important features of sesquiterpene lactones is the presence in their structure of an α-methylene-γ-lactone fragment, which is responsible for biological activity, especially antitumor activity. An exocyclic

double bond conjugated to a carbonyl function is a Michael acceptor (alkylating) fragment and can act on transcription factors and enzymes in humans. It is suggested that the exomethylene group conjugated to the carbonyl group in the lactone ring is responsible for the cytotoxicity of sesquiterpene lactones.

Therefore, the aim of our research is to study the cytotoxicity and antitumor activity of the sesquiterpene γ-lactones argolide, grosheimin, estafiatin and their chemically modified derivatives as practically renewable materials.

2. Planning (methodology) of research

One of the stages of preclinical studies of the sesquiterpene γ-lactones argolide, grosheimin, estafiatin and their chemically modified derivatives is the study of their cytotoxicity and antitumor activity, as a result of which it is possible to evaluate the specific activity and advantages over existing drugs. Having set a goal, we developed a research algorithm, which consists of the following stages:

– the study of the cytotoxicity of compounds on cell lines of Pliss lymphosarcoma, Walker carcinosarcoma, sarcoma 45, sarcoma-180, alveolar liver cancer PC-1, leukemia P-388, leukemia L-1210 and 5-fluorouracil-resistant sarcoma 45;

– the study of the antitumor activity of compounds on a model of 60 cell lines of human tumour origin;

– selection of a reference drug and its prescription. Colchicine and 13-dimethylamino-1,10β-epoxy-5,7α,6,11β(H)-guai-3,4-en-6,12-olide hydrochloride, which is herbal medicine, were used as reference drugs;

– establishing the selectivity of the action of sesquiterpene γ-lactones argolide, grosheimin, estafiatin and their chemically modified derivatives of tumour strains;

– carrying out statistical processing of the results.

3. Materials and research methods

Argolide (**1**) – colourless crystalline substance, $C_{15}H_{20}O_3$, m.p. 133–135 °C (methylene chloride-diethyl ether), $[\alpha]_D^{23}$ +203.8° (c 0.52; chloroform) isolated from *Artemisia glabella* Kar. et Kir [12].

Argolide derivatives **(2–5)** were synthesized according to previously described methods [13].

Grosheimin **(7)** is a colourless crystalline substance, $C_{15}H_{18}O_4$, m.p. 200–202 °C (ethanol), $[\alpha]_D^{23}$ +159.9° (with 1.14; chloroform) isolated from *Chartolepis intermedia* Boiss [14].

Grosheimin derivatives **(8–13)** were synthesized according to previously described methods [15, 16].

Estafiatin **(14)** is a colourless crystalline substance, $C_{15}H_{18}O_3$, m.p. 102–104 °C (ether), $[\alpha]_D^{23}$ +10.3° (chloroform) isolated from *Achillea nobilis* L. Derivatives **(14)** were synthesized according to previously described methods [17].

Cytotoxicity in primary cell culture.

The cytotoxicity of the compounds was determined using the cell lines of Pliss lymphosarcoma, Walker carcinosarcoma, sarcoma 45, sarcoma-180, alveolar liver cancer PC-1, leukemia P-388, leukemia L-1210 and 5-fluorouracil-resistant sarcoma 45. Tests were performed in 96-well plates (Falcon) with an inoculum of 2.5×10^4 cells/ml. Test solutions were prepared as stock solutions in ethanol. The final ethanol concentration was 1 % (v/v) or less. To quantify cytotoxicity, 15 µl of an aqueous solution of methylthiazolyltetrazolium chloride (MTT, Fluka, 5 mg/ml in PBS) was added after 72 hours. When incubated at 37 °C for 4 h, surviving cells metabolized MTT into the insoluble formazan dye. The culture medium was removed, and the formazan dye was dissolved using 150 µl of 10 % SDS (sodium dodecyl sulfate) in water. After 24 h of incubation at room temperature, absorbance was measured at 540 nm using a microplate reader (MRX, Dynex Technologies). To determine IC_{50} values, absorbance was plotted against logarithmic concentration, and eight different concentrations were tested [18].

THP-1 cells were incubated for 24 hours with various concentrations of sesquiterpene lactones (from 50 µM and below). After 24 hours of incubation, cell viability was assessed by intracellular ATP levels (CellTiter-Glo Luminescent Cell Viability Assay Kit (Promega)).

Antitumor activity.

The antitumor activity of the compounds was studied in a model of 60 cell lines of human tumour origin. At the first stage of screening, the test substance in a standard concentration was added to three highly sensitive human cell lines MCF-7 (breast carcinoma), NCI-H460 (lung carcinoma) and SF-268 (glioma) and incubated for 48 hours. The basis of NCI60 is the SRB method for determining the viability of cell cultures using the pink anionic dye sulforhodamine B [19]. If the test substance inhibits the growth of at least one cell line, it moves on to the next stage of testing on a full panel of 60 cell lines. Afterwards, the substance under study was added to the cells in five different concentrations.

The study of antitumor activity on a model of transplantable tumours was carried out on white outbred rats with transplantable tumours of mice and rats. The antitumor effect of the studied compounds was determined by daily intraperitoneal administration in a 2 % dimethyl sulfoxide (DMSO) solution for 5 days at the maximum tolerated dose [20]. To assess the antitumor activity of the compounds, we used the percentage inhibition of tumour growth and the increase in average life expectancy (ILE), determined immediately after the end of treatment.

Statistical analysis.

Statistical processing of the results was carried out using the program “GraphPad Prism v. 6.0» (GraphPad Software Inc., USA). The results obtained are presented as “average value±standard error of the mean value”. Differences were considered significant at a significance level of $p<0.05$. The results are based on three to four independent experiments.

Institutional review board statement.

Animal study protocol approved by the Bioethics Committee of the NCJSC “Karaganda Medical University” (No. 4 dated 08 September 2020).

4. Research results

In the treatment of oncological diseases, cytotoxic drugs play an important role, since their mechanism of action is cellular destruction; the disadvantage is that such drugs also affect healthy cells, which leads to undesirable effects in tissues with a high rate of cell renewal. One of the most successful strategies for creating anticancer drugs is the design and synthesis of new compounds that induce tumor cell differentiation based on known chemical structures. An important class of differentiating compounds are antimetabolite derivatives, including secondary plant metabolites, which affect the synthesis and metabolism of nucleic acids by affecting key enzymes of DNA synthesis.

One of the promising groups of natural terpenoids in this area are sesquiterpene γ-lactones, many of which are cytotoxic *in vitro,* and some demonstrate an antitumor effect *in vivo.* A special place is occupied by γ-lactones with an activated double bond, which plays an important role in their chemical and biochemical transformations.

It is known that the epoxidation of sesquiterpene lactones stereoselectively produces their epoxy derivatives, the amination of which produces epoxyamino derivatives in quantitative yields. These compounds exhibit relatively high cytotoxicity and antitumor activity against lung cancer, glioma, breast cancer, and melanoma cell lines [21].

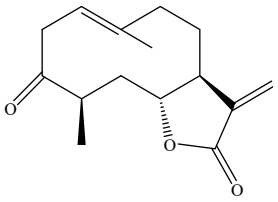
Based on the analysis of literature sources, we can conclude that the chemical modification of sesquiterpene lactones with the formation of new bonds and the production of hybrid compounds is a promising direction. In this case, chemical modification with the obtaining of structure combining fragments of sesquiterpene lactone and alkaloids, as well as epoxidation, which makes it possible to obtain new compounds with improved biological activity, is considered relevant.

Among them, promising molecules are considered to contain atoms in their structure, such as chlorine, fluorine, nitrogen, sulfur, etc., which are not found in natural sources. A number of chemical transformations have been carried out on the basis of sesquiterpene lactones, in particular grosheimin, estafiatin, and argolide: epoxidation, amination, acylation, hydrogenation, oxidation, substitution, and methoxylation [22].

One of the promising molecules is the germacrane-type sesquiterpene lactone argolide, a polyfunctional compound containing in its structure a γ-lactone ring with an exomethylene group, an olevinic double bond and a keto group in the carbocycle, acting as pharmacoformal and reaction centers.

Evaluation of the cytotoxicity of sesquiterpene lactones on human acute monocytic leukemia THP-1 cells (in vitro).

We conducted experiments on human cells of acute monocytic leukemia THP-1 (*in vitro*). For active compounds (argolide **(1),** 1,10-epoxyargolide **(2)**, anabasinyl argolide **(3)**, cytisinyl argolide **(4)**, *p*-chlorobenzylidene derivative of argolide **(5)**), IC_{50} values were calculated (the concentration of the compound at which the level of cell viability decreases by 50 %).



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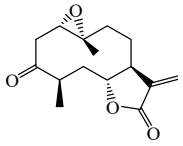

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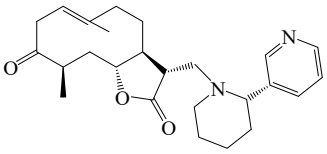

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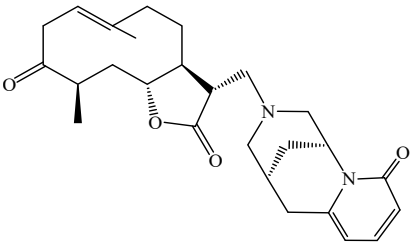

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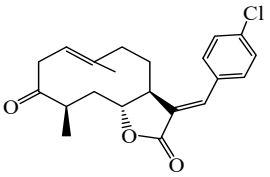

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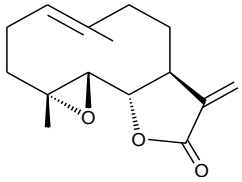


(6)

It was established that the epoxidation of argolide **(1)** with the formation of 1,10α-epoxyargolide **(2)** led to a directed increase in the cytotoxicity of the latter, IC_{50}=35.2 μM and IC_{50}=7.2 μM. And the introduction of an alkaloid function into the argolide molecule **(1)** reduces the selectivity of the action of the synthesized hybrid compound anabasinyl argolide **(3)** (Table 1).

The most active cytotoxic compound in this test in the range was the compound 1,10-epoxyargolide **(2)** with IC_{50}=7.2 μM, and the benzyl chloride derivative of argolide **(5)** turned out to be less active IC_{50}=42.2 μM. The remaining argolide derivatives **(1)** were inactive when tested for cytotoxicity (i.e., at concentrations of 50 μM and below, cytotoxicity did not reach 50 % cell survival compared to control, so the IC_{50} value cannot be calculated) (Table 1).

A structurally similar analogue of argolide **(1)** and its epoxy derivative **(2)** germacranolide parthenolide **(6),** contains an α-methylene-γ-butyrolactone group and an epoxide function, which are involved in interactions with target proteins, providing multiple therapeutic effects [23]. Parthenolide **(6)** reduces the pathogenicity of cancer in various types, including myeloma, colorectal, liver, prostate, pancreatic, thyroid, and breast cancer. In particular, parthenolide **(6)** has the effect of suppressing MDA-MB-231 breast cancer cells and reducing tumour size in a mouse xenograft model when used in combination with docetaxel [24]. When studied across a wide range of cancers cytotoxicity of parthenolide **(6)** has been associated with its directed effect on molecular targets, one of which causing anticancer activity is IκB β kinase (IKK-β), in which both IKK-β and nuclear factor κB (NF-κB) signaling is impaired due to a modified cysteine.. Parthenolide **(6)** affects additional cellular signalling pathways such as induction of oxidative stress and apoptosis, focal adhesion kinase 1 **(**FAK1) signalling, mitogen-activated protein kinase signalling, and mitochondrial function [7].

Table 1

Effect of argolide (1) and its derivatives on cell viability

Compounds	Cytotoxicity, IC_{50}, μM
Argolide **(1)**	35.2±0.08
1,10-epoxyargolide **(2)**	7.2± 0.02
Anabasinylargolide **(3)**	74.1±0.84
Cytisinylargolide **(4)**	84.3±0.91
p-Chlorobenzylidene derivative of argolide **(5)**	42.2±0.21

One of the advantages of parthenolide **(6)** is its selectivity for cancer stem cells while remaining noncytotoxic for normal cells. In this case, the molecular mechanism of action of parthenolide **(6)** includes the induction of apoptosis through mitochondrial and cascade signalling pathways, as well as an increase in cytosolic calcium concentration, cell cycle arrest, and inhibition of metastasis [25–29].

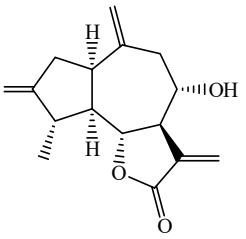
Glioblastoma, or glioblastoma multiforme (GBM), is the most aggressive type of brain cancer and is very difficult to treat. Parthenolide **(6)** was found to significantly inhibit the growth of transplanted glioblastoma cells relative to the control group [30].

Studies of parthenolide **(6)** have shown that it can inhibit the inflammation-carcinoma sequence and be critical in the experimental regulation of colitis-associated colon cancer (CAC). The mechanism of action involves downregulation of p65 NF-κB expression, blocking the phosphorylation and subsequent degradation of κB-α inhibitor (IκBα). Thus parthenolide **(6)** may be a chemopreventive agent for the treatment of CAC [31].

The guaian type sesquiterpene lactone, grosheimin **(7),** isolated from 12 plant species, is of interest as a renewable chemical material [14]. Previously, a number of its derivatives were obtained from the secondary hydroxyl group of grosheimin **(7)** at position C-8, which showed cytotoxic activity [32].

The cytostatic activity of grosheimin **(7)** and 17 of its derivatives was tested *in vitro* on the human nasopharyngeal carcinoma (KB) cell line. The results of studies of grosheimin **(7)** and its 17 derivatives are divided into three pharmacological groups: inactive, moderately active with a low cytostatic effect at a medium concentration of 5 μg/ml (corresponding to values greater than 10^{-5} M) and active compounds. Mechanism of action of substituted phenylthio derivatives of α,β-unsaturated cytotoxic lactones, acting as prodrugs for biological activity. They release the cytotoxic agent *in vitro* by stimulating sulfur oxidation and subsequent retroelimination of the thiosulfene moiety. The positions of R-substituents in the thiophenol ring on chemical and physicochemical properties provide a correlation with cytotoxic activity [33].

Sesquiterpene lactones exhibit their cytotoxic effect due to the presence of an electron-deficient double bond in the lactone cycle. The sesquiterpene lactone derivative with thiophenol lacks cytotoxicity. However, it acts as a prodrug of its corresponding parent lactone. Under the influence of intracellular ROS, the sulfide group of the thiophenol adduct is oxidized to sulfoxide or sulfone, which leads to subsequent gradual elimination with the formation of the initial active lactone and sulfinic or sulfonic acid. Thus, for the manifestation of the cytotoxic effect of thiophenol derivatives of sesquiterpene lactones, the concentration of ROS inside the cell, which can vary in different tumor lines, is crucial.



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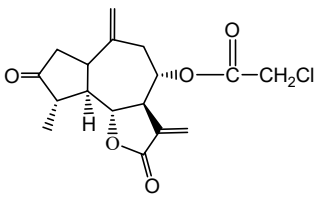

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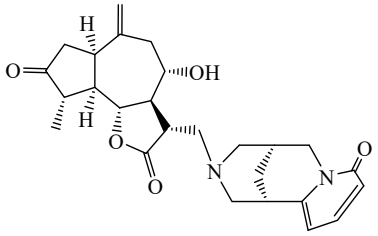

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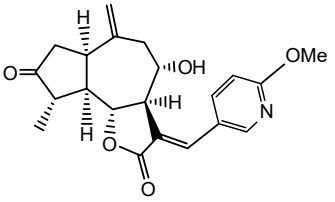

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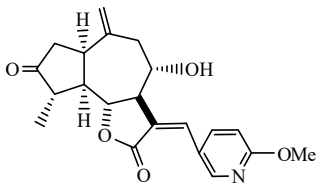

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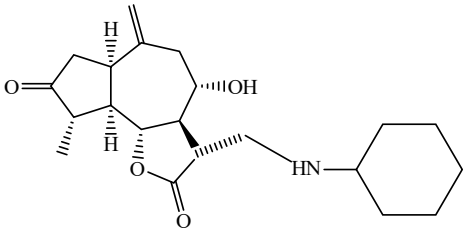

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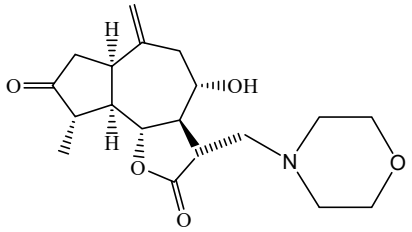

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Cytotoxicity of new grosheimin derivatives against human acute monocytic leukemia cells.

We determined the cytotoxicity of grosheimin **(7)** and a new derivative **(8)** based on it against THP-1 acute monocytic leukemia cells (*in vitro*). For active compounds, IC_{50} values were calculated (the concentration of a compound at which the level of cell viability decreases by 50 %). The results obtained are presented in Table 2.

The results of studying the biological activity showed that 8α-chloroacetoxy-3-oxo-5,7α,4,6,8β(H)-guai-10(14),11(13)-dien-6,12-olide (chloracetylgrosheimin) **(8)** at a dose of 50 μM has high cytotoxicity against acute monocytic leukemia (*in vitro*).

Table 2

Effect of grosheimin and its derivative on cell viability

Name of connections	Cytotoxicity, IC_{50}, μM
Grosheimin **(7)**	NA
Grosheimin chloroacetate **(8)**	0.59±0.02

Cytotoxic activity of new grosheimin derivatives against the larvae of the crustaceans Artemia salina (Leach).

A study was carried out on the cytotoxic activity of new grosheimin derivatives (grosheimin chloroacetate **(8)**, 3-oxo-8-hydroxy-1,5,7α,4,8β(H)-guai-10(14)-en-11(13-cytisinyl) -12,6-olide **(9)**, (E)-(13-(4-chlorophenyl)-8α-hydroxy-3-oxo-5,7α(H)-guai-10(14),11(13)-diene-12,6β-olide **(10),** (Z)-(13-(4-chlorophenyl)-8α-hydroxy-3-oxo-5,7α(H)-guai-10(14),11(13)-dien-12,6β-olide **(11),** (E)-13-(2-fluorophenyl)-8α-hydroxy-3-oxo-5,7α(H)-guai-10(14),11(13)-dien-12,6β-olide, (Z)-(13-(3-trifluoromethylphenyl)-8α-hydroxy-3-oxo-5,7α(H)-guai-10(14),11(13)-dien-12,6β-olide, (Z)-(13-(2-fluorophenyl)-8α-hydroxy-3-oxo-5,7α(H)-guai-10(14),11(13)-diene-12,6β-olid) against the larvae of the sea crustaceans *Artemia salina* (Leach).

The results of testing the cytotoxicity of samples of sesquiterpene lactones against the larvae of the sea crustaceans *Artemia salina* (Leach) *in vitro* are given in Table 3.

Table 3

Results of cytotoxicity testing against larvae of the crustaceans

Compounds	Cytotoxicity, LD_{50}, μg/ ml
Grosheimin **(7)**	IC_{50}>100 μM
Grosheimin chloroacetate **(8)**	104.2±1.02
3-oxo-8-hydroxy-1,5,7α,4,8β(H)-guai-10(14)-en-11(13-cytisinyl)-12,6-olide **(9)**	96.2±0.64
(E)-(13-(4-chlorophenyl)-8α-hydroxy-3-oxo-5,7α(H)-guai-10(14),11(13)-dien-12,6β-olide **(10)**	68.4±0.08
(Z)-(13-(4-chlorophenyl)-8α-hydroxy-3-oxo-5,7α(H)-guai-10(14),11(13)-dien-12,6β-olide **(11)**	49.5±0.04
13-cyclohexylaminogrosheimin **(12)**	78.4±0.61
13-morpholinogrosheimin **(13)**	56.4±0.41
(E)-13-(2-Fluorophenyl)-8α-hydroxy-3-oxo-5,7α(H)-guai-10(14),11(13)-dien-12,6β-olide	113.2±1.05
(Z)-(13-(3-trifluoromethylphenyl)-8α-hydroxy-3-oxo-5,7α(H)-guai-10(14),11(13)-dien-12,6β-olide	105.2±1.01
(Z)-(13-(2-Fluorophenyl)-8α-hydroxy-3-oxo-5,7α(H)-guai-10(14),11(13)-dien-12,6β-olide	127.7±1.09
Hydrochloride dimethylaminogrosheimin	109.5±1.01
Dimethylaminoacetogrosheimin hydrochloride	110.9±1.07
Compound drug: 13-dimethylamino-1,10β-epoxy-5,7α,6,11β(H)-guai-3,4-en-6,12-olide hydrochloride	

As can be seen from Table 3, derivatives of the sesquiterpene lactone **(7)** grosheimin chloroacetate **(8),** 3-oxo-8-hydroxy-1,5,7α,4,8β(H)-guai-10(14)-en-11(13-cytisinyl)-12,6-olide **(9)**, (E)-(13-(4-chlorophenyl)-8α-hydroxy-3-oxo-5,7α(H)-guai-10(14),11(13)-dien-12,6β-olide **(10),** (Z)-(13-(4-chlorophenyl)-8α-hydroxy-3-oxo-5,7α(H)-guai-10(14),11(13)-dien-12,6β-olide **(11)**, (E)-13-(2-fluorophenyl)-8α-hydroxy-3-oxo-5,7α(H)-guai-10(14),11(13)-dien-12,6β-olid,(Z)-(13-(3-trifluoromethylphenyl)-8α-hydroxy-3-oxo-5,7α(H)-guai-10(14),11(13)-dien-12,6β-olide and (Z)-(13-(2-fluorophenyl)-8α-hydroxy-3-oxo-5,7α(H)-guai-10(14),11(13)-dien-12,6β-olide exhibit cytotoxic activity against the larvae of the sea crustaceans *Artemia salina* (Leach). At the same time, (Z)-(13-(4-chlorophenyl)-8α-hydroxy-3-oxo-5,7α(H)-guai-10(14),11(13)-dien-12,6β-olide **(11)** LD_{50}=49.5±0.04 μg/ml, however, the original compound grosheimin itself does not show activity.

Thus, the introduction of a chloroacetate fragment into the groshemin molecule **(7)** leads to a targeted increase in cytotoxicity.

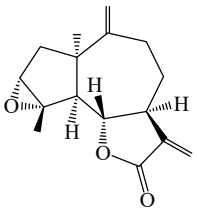
The results of determining the cytotoxicity of the grosheimin derivatives synthesized by us **(7)** against the larvae of the sea crustaceans *Artemia salina* (Leach) are presented in Table 3. It is quite expected that the cytotoxicity of chloro-, fluorine- and morpholine-containing grosheimin derivatives **(7)** is lower than that of the original lactone **(7)**. On the other hand,

from the literature [33], it is known that the thiophenol derivative of grosheimin **(7)** has moderate cytotoxicity (LD_{50}=11.2 μM) on the KB tumour line, which may be a consequence of the increased sensitivity of this cell line to the action of lactone **(7)**. The chloroacetylgrosheimin **(8)** synthesized by us retains moderate cytotoxicity (LD_{50}=104.2–113.2 μg/ml).

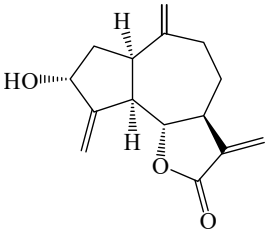
The disadvantage of this series of conjugates is their high hydrophobicity, even greater than that of the original substances. However, it can be eliminated in the future by using substituted thiophenols for the synthesis of prodrugs. In this work, we tested and confirmed the viability of the approach to the synthesis of ROS-activated chloro-, fluorine-, and amino-containing prodrugs from grosheimin **(7),** which exhibit cytotoxicity.

Cytotoxicity of the sesquiterpene lactone estafiatin and its derivatives in experiments in vitro.

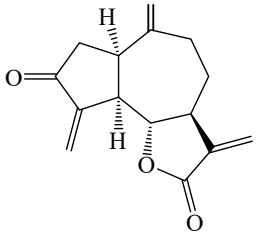
Using cell lines of Pliss lymphosarcoma, Walker carcinosarcoma, sarcoma 45, sarcoma-180, alveolar liver cancer PC-1, leukemia P-388, leukemia L-1210 and sarcoma 45, resistant to 5-fluorouracil, the following series of sesquiterpene lactones and their derivatives were studied: estafiatin **(14)**, isozaluzanin C **(15)**, 3-keto-4-methylene-cis-guaianolide **(16)**, 3α-acetoxy-isozaluzanin C **(17)**, estafiaton **(18)**, 10α(14)-epoxy-1,5,7α,4,6β(H)-guai-11(13)-ene-4(3),6(12)-diolide **(19)** (Table 4).



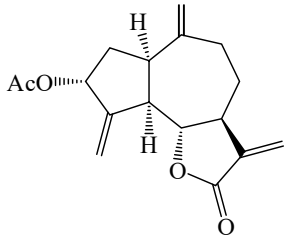
(14)



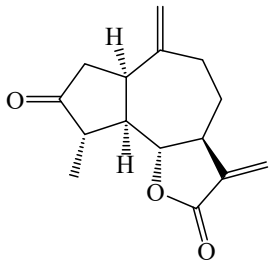
(15)



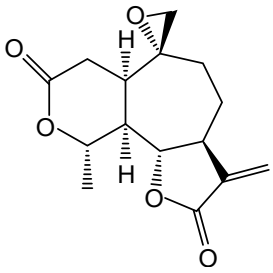
(16)



(17)



(18)



(19)

Study on the Pliss lymphosarcoma cell line estafiatin **(14)** and its derivatives, 3α-acetoxy-isozaluzanin C **(17)** turned out to be the most active (IC_{50}=0.04±0.01 μM), and estafiatin **(14)** was active in the Walker carcinosarcoma cell line (IC_{50}=2.13±0.94 μM) and its derivative estafiaton **(18)** (IC_{50}=1.34±0.12 μM).

Approximately the same effect on the sarcoma cell line 45 was shown by 3α-acetoxy-isozaluzanin C **(17)** and 10α(14)-epoxy-1,5,7α,4,6β(H)-guai-11(13)-ene-4(3),6(12)-diolide (19) with IC_{50}=2.96±0.75 μM and 2.59±0.75 μM, respectively, and also compound **(19)** turned out to be comparatively more active on the alveolar liver cancer cell line PC-1.

When studied on the sarcoma cell line 37, compounds **(14)** and **(18)** showed activity with an IC_{50} value of 2.20±0.09 μM and 2.96±1.15 μM, respectively.

In the experiment on the sarcoma cell line 180, the most active compound is estafiatone **(18)** with an IC_{50} value of 0.04±0.01 μM, while compound **(14)** (IC_{50} 3.05±1.10 μM) and others were less active.

On the leukemia cell line P-388, compounds **(14)** and its derivatives **(15), (16), (19)** showed relatively high activity from 1.69±0.15 to 3.62±1.21 μM, compared to compound **(17)** (IC_{50} 17.94±2.57 μM).

Experiments conducted on the leukemia cell line L-1210 showed relatively high activity of estafiatin **(14)** and derivative compounds are 3-keto-4-methylene-cis-guaianolide **(16),** 3α-acetoxy-isozaluzanin C **(17)** with IC_{50} 2.92±1.22 μM, 2.42±0.91 μM, 1.98±0.06 μM, respectively.

In the sarcoma 45 cell line, resistant to 5-fluorouracil, the δ-lactone epoxy-estafiatin **(19)** is relatively active (IC_{50} 1.30±0.08 μM).

Based on the results of experiments, it was established that the cytotoxicity of sesquiterpene lactones increases significantly with the introduction of an epoxy group and halogen atoms into the molecule, which enhances the effect of α-methylene-γ-lactone. Both the introduction of an epoxide group into the molecule of sesquiterpene lactones and the Heck arylation reaction generally affect the selectivity of the

action on the biological target and, consequently, the cytotoxicity.

Studies have shown the specificity of the action of argolide **(1),** grosheimin **(7)**, estafiatin **(14)** and their derivatives. For most tumour cell lines, Argolide **(1),** grosheimin **(7)**, estafiatin **(14),** and their derivatives have significant cytotoxicity. At the same time, for individual cell lines of Pliss lymphosarcoma, Walker carcinosarcoma, sarcoma 45, sarcoma 37, sarcoma 180, alveolar liver cancer PC-1, leukemia P-388 and L-1210, resistant to 5-fluorouracil sarcoma 45, the activity was in the IC_{50} range 1.30–4.69 μM.

Since the above-mentioned sesquiterpene lactones and their derivatives *in vitro* on cell culture showed relatively pronounced cytotoxicity, we studied their antitumor activity *in vivo* on transplantable tumor strains.

Antitumor activity.

All signalling cascades of antitumor activity are associated with Ras proteins. For the development of oncogenic activity of Ras proteins, their farnesylation is necessary. Farnesyltransferase inhibitors are not only able to return Ras-transformed cells to a normal phenotype, but also cause tumor regression.

Because farnesyltransferase inhibitors only affect cells with strong expression of the Ras oncogene, normal cells are unaffected and remain undamaged. Consequently, the antineoplasts being developed based on farnesyltransferase inhibitors will exhibit antiproliferative and proapoptotic effects selective only for cancer cells.

Samples of sesquiterpene lactones – argolide **(1)**, grosheimin **(7)**, estafiatin **(14)** and their derivatives were tested for antitumor activity on cultures of transplantable tumour strains. It was determined that most of the studied samples have moderate cytotoxicity.

It has been established that the presence of such alkylating moiety (Michael acceptor) in the sesquiterpene lactone molecule centres such as **α**-methylene-γ-lactone, enone moiety (**α**,β-unsaturated carbonyl moiety), epoxide ring, as well as hydroxyl function, halogen atoms help inhibit the growth of tumour strains.

Results of studies of argolide **(1)** in comparison with the reference drug showed relatively high antitumor activity on three tumour strains – they inhibited the growth of Pliss lymphosarcoma, Walker carcinosarcoma, and sarcoma 45 (Table 5).

Table 6 presents the results of a study of grosheimin **(7)** and its derivatives, which showed relatively high antitumor activity on five tumour strains – they inhibited the growth of sarcoma 45, Walker's carpinosarcoma and P-388 leukemia (increase in average life expectancy to 92 %).

Of the grosheimin derivatives, 8-acetylgrosheimin **(8)** and 13-morpholingrosheimin **(13)** showed significant inhibition of the growth of sarcoma 45 strains, Walker's carcinosarcoma. However, grosheimin **(7)** turned out to be relatively more active against Pliss lymphosarcoma and alveolar liver cancer than its acetate, morpholino and cyclohexylamino derivatives. A pronounced effect on P-388 leukemia was found in the morpholine derivative grosheimin: the increase in average life expectancy is 114.2 % (Table 6).

Based on the results of *in vitro* studies on KB 13 cell cultures of grosheimin derivatives (7), it was established that the presence of a selenium-phenyl group at C13 leads to the formation of more cytotoxic compounds [29].

Table 4

Effect of estafiatin **(14)** and its derivatives on cell viability

Name of sesquiterpene lactone	Lympho-sarcoma of Pliss	Walker's carcino-sarcoma	Sarcoma 45	Sarcoma 37	Sarcoma 180	Alveolar liver cancer PC-1	Leukemia P-388	Leukemia L-1210	Sarcoma 45 resistant to 5-fluorouracil
	IC_{50}, μM								
Estafiatin **(14)**	4.62±1.42	2.13±0.94	4.37±1.26	3.86±0.97	3.05±1.10	3.05±1.67	3.62±1.21	2.92±1.22	3.05±1.47
Isozaluzanin C **(15)**	4.65±1.01	4.27±1.58	3.69±1.05	2.20±0.09	4.52±1.42	5.09±1.75	2.92±1.09	–	–
3-keto-4-methylene-cis-guaianolide **(16)**	2.68±0.92	5.16±1.52	3.34±0.98	4.34±1.45	2.96±1.01	3.05±0.86	2.96±0.95	2.42±0.91	2.29±0.72
3α-acetoxy-isozaluzanin C **(17)**	0.04±0.01	4.93±0.92	2.96±0.75	3.05±1.08	2.96±1.07	4.69±1.01	17.94±2.57	1.98±0.06	5.09±2.03
estafiaton **(18)**	4.34±1.73	1.34±0.12	3.86±1.79	2.96±0.07	0.04±0.01	3.05±0.90	–	–	–
10α(14)-epoxy-1,5,7α,4,6β(H)-guai-11(13)-ene-4(3),6(12)-diolide **(19)**	1.84±0.18	8.37±1.92	2.59±0.75	3.17±1.22	4.52±1.68	2.80±0.38	1.69±0.15	4.52±1.59	1.30±0.11

Table 5

Antitumor activity of argolide **(1)**

Sesquiterpene lactone	Dose, mg/kg	Lymphosarcoma of Pliss	Walker's carcinosarcoma	Sarcoma 45	Sarcoma 37	Sarcoma 180	Alveolar liver cancer PC-1	Leukemia P-388	Leukemia L-1210	Sarcoma 45 resistant to 5-fluorouracil
Argolide **(1)**	25	69.0±1.45	41.0±0.98	67.0±1.91	–	–	–	–	–	–
Colchicine	2	54.4±1.24	30.1±1.47	20.4±0.12	36.0±0.58	–	26.5±1.52	81.0±1.55	–	75.7±1.90

Note: (-) – no activity occurred; (–) – significance of differences $p<0.05$ compared to the comparison group

The results obtained confirm the hypothesis that groshemin derivatives **(7),** containing in their structure an exomethylene group conjugated with a γ-lactone carbonyl, may be biologically active.

A study of the antitumor activity of estafiatin **(14)** and its 5 derivatives on 7 transplantable tumour strains and two types of leukemia – P-388 and L-1210 showed that the transformation of the epoxy cycle in the structure of estafiatin **(14)** into the keto group increases the inhibitory effect of the keto derivative **(18)** against Pliss lymphosarcoma and sarcoma-180 by 3–4 times than the activity of the parent estafiatin **(14)**. The introduction of a hydroxyl group at C-3 and an exomethylene group at C-4 instead of the epoxide ring of estafiatine increases the antitumor activity against Pliss lymphosarcoma by 4 times. In the presence of a conjugated 3-keto-4-methylene fragment in the molecule, the activity of such a derivative **(16)** against sarcoma-180, leukemia P-388 and L-I2I0 and sarcoma-45, resistant to 5-fluorouracil, increases 3–6 times than the effect of estafiatin **(14)** (Table 7).

As can be seen from Table 7, of the estafiatin derivatives **(14)**, 3-keto-4-methylene-cis-guaianolide **(16)**, 3α-acetoxy-isozaluzanin C **(17)** and 10α(14)-epoxy-1,5,7α,4,6β(H)-guai-11(13)-en-4(3),6(12)-diolide **(19)** showed a relatively high antitumor effect, which inhibit the growth of Pliss lymphosarcoma, Walker carcinosarcoma, sarcoma 45, alveolar liver cancer PC-1, sarcoma 180 by 68-90%, lymphocytic leukemia P-388 by 104 %.

5. Discussion

A structural analogue of estafiatin **(14)** is the guaianolide dehydroleucodine, which has antimicrobial activity against *Helicobacter pylori*, the main cause of chronic gastritis and peptic ulcers, as well as an important factor in the pathogenesis of gastric cancer [34, 35].

Antitumor activity sesquiterpene lactones manifests itself through induction apoptosis. An important role in this process is played by the influence of lactones on the cellular redox status, the formation of reactive oxygen species, and, as a consequence, oxidative damage in the cell and the initiation of the mitochondria-dependent apoptosis pathway [36].

Table 6

Antitumor activity of grosheimin **(7)** and its derivatives

Sesquiterpene lactone	Dose, mg/kg	Lympho-sarcoma of Pliss	Walker's carcino-sarcoma	Sarco-ma 45	Sarco-ma 37	Sarco-ma 180	Alveolar liver can-cer PC-1	Leukemia P-388	Leu-kemia L-1210	Sarco-ma 45 to 5-foruracil
Grosheimin **(7)**	70	68.6±1.45	–	41.4±1.97	–	–	52.5±1.06	59.3±1.04	–	–
Grosheimin chloroacetate **(8)**	50	36.0±0.83	82.1±1.53	71.1±1.90	–	–	48.0±1.02	92.1±2.03	–	–
	70	42.3±1.05	–	76.4±1.98	–	–	92.1±2.01	–	–	–
13-cyclohexylamino-gro-sheimin **(12)**	50	34.0±1.32	–	13.0±0.03	–	–	16.0±0.01	20.4±0.81	–	–
13-morpholinogro-sheimin **(13)**	50	41.0±0.98	24.0±0.05	81.0±1.55	–	–	40.0±0.07	114.2±2.91	–	–
	70	46.3±1.47	32.1±0.32	–	–	–	–	–	–	–
Dimethylamino-gro-sheimin hydrochloride	100	–	10.0±0.18	25.0±1.04	–	–	15.0±0.02	–	–	–
	150	27.0±1.45	32.0±0.34	27.0±1.12	–	–	37.0±0.54	–	–	–
Dimethylamino-acetogro-shemine hydrochloride	100	18.0±0.04	22.0±0.17	16.0±0.02	–	–	–	–	–	–
	150	42.0±1.05	29.0±0.05	34.0±0.51	–	–	26.0±0.54	–	–	–
Colchicine	2	54.4±1.24	30.1±1.47	20.4±0.12	36.0±0.58	–	26.5±1.52	81.0±1.55	–	75.7±1.90

Note: (-) – no activity occurred; (–) – significance of differences p<0.05 compared to the comparison group

Table 7

Antitumor activity of estafiatin **(14)** and its derivatives

Sesquiterpene lactone	Dose, mg/kg	Lympho-sarcoma of Pliss	Walker's carcino-sarcoma	Sarco-ma 45	Sarco-ma 37	Sarco-ma 180	Alveolar liver can-cer PC-1	Leu-kemia P-388	Leukemia L-1210	Sarcoma 45 resistant to 5-fluoro-uracil
Estafiatin **(14)**	20	23.3±1.45	59.9±1.04	31.2±0.32	15.1±0.14	26.4±0.17	55.0±1.77	16.1±0.02	12.4±1.12	23.3±0.19
Isozaluzanin C **(15)**	20	80.0±1.04	55.9±1.40	51.2±1.21	25.3±1.72	41.3±1.41	63.0±1.60	96.0±2.75	-	-
3-keto-4-methylene-cis-guaianolide **(16)**	20	68.7±0.94	69.1±1.26	68.9±1.10	29.6±1.50	81.5±1.72	68.2±1.33	81.5±2.07	45.0±1.06	88.9±1.64
3α-acetoxy-isozaluzanin C **(17)**	thirty	73.1±1.83	64.0±1.42	52.0±1.92	84.0±2.43	55.5±2.01	70.4±0.15	79.4±1.92	23.1±0.05	76.2±2.77
estafiaton **(18)**	25	71.1±1.93	59.0±1.61	48.1±0.47	36.0±1.05	74.1±2.32	79.0±0.09	–	–	–
10α(14)-epoxy-1,5,7α,4,6β(H)-guai-11(13)-ene-4(3),6 (12)-diolide **(19)**	25	68.9±0.71	83.0±1.53	90.9±1.01	49.4±1.47	72.1±2.04	43.6±2.01	104.0±2.9	62.0±1.70	75.7±2.70
Colchicine	2	54.4±1.24	30.1±1.47	20.4±0.12	36.0±0.58	–	26.5±1.52	81.0±1.55	–	75.7±1.90

Note: (-) – no activity occurred; (–) – significance of differences p<0.05 compared to the comparison group

All compounds tested exhibit approximately the same level of activity. It was noted that the effect of the sesquiterpene lactones and their derivatives studied by us on transplanted tumour strains consistently leads to the appearance of about 10 % of apoptotic cells, which is twice the number of apoptotic cells in control. Consequently, the action of sesquiterpene lactones and their derivatives on the cell is carried out mainly due to the inclusion of mechanisms for inducing apoptosis.

Limitations of the study. Pharmacological studies are limited to the sesquiterpene γ-lactones argolide, grosheimin, estafiatin and their chemically modified derivatives.

Prospects for further research. It is planned to develop, based on natural sesquiterpene lactones, effective and selective antineoplasts with antiproliferative and proapoptotic effects, acting through activation of the Ras signalling cascade regulating apoptosis.

6. Conclusion

A study of the antiproliferative activity of natural sesquiterpene lactones and their derivatives revealed the presence of both relatively high cytotoxicity for tumour cell lines and the specificity (selectivity) of their action. Much attention is paid to establishing the mechanisms of the antitumor action of synthesized derivatives based on sesquiterpene γ-lactones.

When determining cytotoxicity in *vitro* samples of the sesquiterpene γ-lactones argolide, grosheimin and estafiatin showed selectivity of their action on cells of 8 tumour strains, on cells of human acute monocytic leukemia THP-1 and in relation to the larvae of sea crustaceans *Artemia salina (Leach)*.

The antitumor activity of sesquiterpene lactones and their derivatives is associated with the inhibition of the enzyme farnesyltransferase (IC_{50} 1.30–4.69 μM) and modulation of the Ras signalling pathway. The cytotoxicity of such compounds is most often realized through the induction of apoptosis.

At the same time, cells from the lines of Pliss lymphosarcoma, Walker carcinosarcoma, sarcoma 45, sarcoma 37, sarcoma 180, alveolar liver cancer PC-1, leukemia P-388, L-1210, sarcoma 45, resistant to 5-fluorouracil, turned out to be the most sensitive to guaianolides and their derivatives. Compounds 3-keto-4-methylene-cis-guaianolide **(16),** 3α-acetoxy-isozaluzanin C **(17),** 10α(14)-epoxy-1,5,7α,4,6β(H)-guai-11(13)-en-4(3),6(12)-diolide **(18)** showed high antitumor activity against all tumor cell lines studied, and compounds grosheimin loracetate **(8)** and 13-morpholinogrosheimin **(13)** showed significant inhibition of growth of strains of sarcoma 45, Walker's carcinosarcoma. The above compounds contain in their structure an exomethylene group conjugated with the carbonyl of the γ-lactone, the presence of which is an important condition for cytotoxicity and antitumor activity.

Thus, the research results indicate the prospects of developing, based on natural sesquiterpene lactones, effective and selective antineoplasts with antiproliferative and proapoptotic effects, acting through the activation of the Ras signalling cascade regulating apoptosis.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this paper.

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Data availability

Data will be made available on reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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