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Halogenation of Sesquiterpene γ -Lactone Molecules: New Compounds, Structure and Biological Activity

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Abstract

This article presents the results of halogenation studies on seven sesquiterpene γ -lactones readily obtainable from plant material: the germacranolide argolide, the eudesmanolide isoolantolactone, and the guaianolides arglabin, achillin, grossheimin, grossmisin, and leucomisin. Sesquiterpene γ -lactones occurring in plants of the *Asteraceae* (*Compositae*) family constitute an important class of terpenoids, among which chlorine-containing compounds are distinguished by pronounced biological activity. The aim of this study was to synthesize new biologically active halogen-containing derivatives of sesquiterpene γ -lactones. Thirty-four new halogen-containing compounds were synthesized by substitution and addition reactions, taking into account the structural features and reactive sites of the parent substrates, including the α -methylene- γ -lactone moiety, hydroxy and keto groups, exocyclic double bonds, and cyclopentadienone fragments. The structures of all synthesized compounds were established from physicochemical constants and spectroscopic data (IR, UV, ^1H NMR, ^{13}C NMR, COSY, NOESY, and COLOC). X-ray diffraction analysis was used for definitive structural assignment of the (E)- and (Z)-isomers. Biological screening demonstrated pronounced cytotoxic, antitumour, antifungal, and antimicrobial activities for several of the halogen-containing sesquiterpene lactones. Against *Artemia salina* (Linnaeus, 1758) larvae, the dichlorocarbene derivative of arglabin was 32.7-fold more cytotoxic than the parent arglabin, whereas $1\alpha,10\beta$ -dichloro- 14α -methoxyachillin was 2.6-fold more active than achillin.

1. Introduction

Sesquiterpene γ -lactones occurring in plants of the *Asteraceae* (*Compositae*) family constitute an important class of terpenoid compounds. More than 8,000 members of this class have been isolated from natural sources and characterized, making them a valuable source of potentially bioactive molecules.

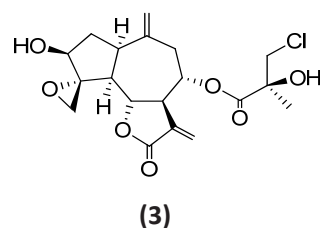
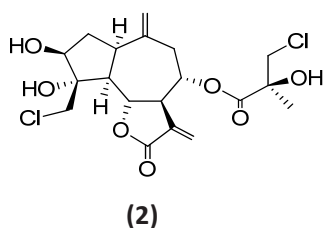
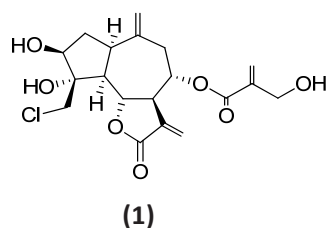
More than 100 halogenated sesquiterpene γ -lactones have been reported in plants [1]. Structurally, most naturally occurring chlorine-containing sesquiterpene lactones are of the guaiane type. In 45 guaianolides, chlorine is the only halogen present. To date, naturally occurring fluorine-, bromine-, and iodine-containing sesquiterpene lactones have

not been identified [2–4]. Accordingly, chlorinated sesquiterpene lactones appear to be the only halogenated members of this class biosynthesized in plants. Chlorine-containing guaianolides have been identified in species of *Centaurea* L., *Chartolapis* Cass., *Leuzea* DC., *Psephellus* (Cass.) Schmalh., *Rhaponticum* Adans., and *Saussurea* DC. [2, 5–9].

Plants of the subtribe *Centaureinae* are of particular interest because 19 chlorine-containing sesquiterpene γ -lactones have been identified in this group. The most widespread are chlorojanerin (**1**) and chlorohyssopifolins A (**2**) and C (**3**). Chlorojanerin (**1**) has been reported in 20 *Centaurea* L. species and 4 *Saussurea* DC. species; chlorohyssopifolin A (**2**) occurs in 12 *Centaurea* L. species and 2 *Rhaponticum* Adans. species; and chlorohyssopifolin C (acryptilin) has been found in 9 *Centaurea* L. species [7].

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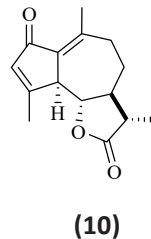
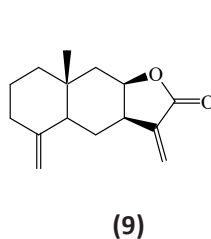
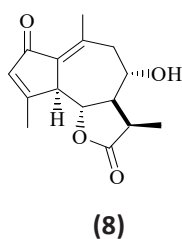
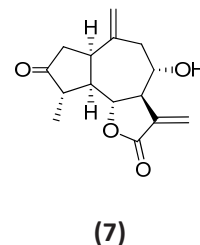
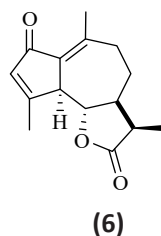
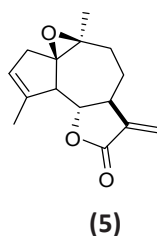
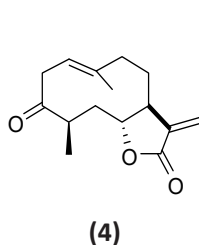
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Because chlorine-containing sesquiterpene lactones exhibit pronounced biological activity, chemical modification of natural sesquiterpene γ -lactones by introducing halogen atoms or halogen-containing functional groups is a promising approach to the synthesis of new pharmacologically active compounds [10, 11].

Among the most accessible and promising sesquiterpene γ -lactones for targeted chemical mod-

ification are argolide (**4**), arglabin (**5**), achillin (**6**), grossheimin (**7**), grossmisin (**8**), isalantolactone (**9**), and leucomisine (**10**) [12, 13]. Their polyfunctional structures contain several reactive sites, notably an α -methylene- γ -lactone moiety, hydroxy and keto groups, and exocyclic double bonds, which enable the preparation of heteroatom-containing derivatives with pronounced biological activity [14–16].



Zhao et al. [17] synthesized 60 isalantolactone (**9**) derivatives by SeO_2 oxidation followed by esterification with carboxylic acids using N,N' -dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP). The series included 18 new C-3 halogenated derivatives: ten fluorinated and eight chlorinated compounds.

The literature [18] also describes nucleophilic substitution of allylic bromides with alcohols, which has been used to prepare a series of 10-trifluoromethyl derivatives of artemisinin, as well as fluorinated amino derivatives of parthenolide.

Indian researchers [19] synthesized two bromocyclopropane derivatives at C11–C13 from alantolactone and isalantolactone (**9**) by reaction with bromoform (CHBr_3) in the presence of aqueous potassium hydroxide (KOH) and benzyltriethylammonium chloride (TEBAC).

Another study [20] described the synthesis of 28 new isalantolactone (**9**) derivatives by 1,3-dipolar cycloaddition of organic azides to the exocyclic double bond of the isalantolactone lactone ring. Six of these products were halogen-containing isalantolactone derivatives bearing a 4-fluorophenyl substituent at C-13.

The aim of the present study was the targeted halogenation of seven natural sesquiterpene γ -lactones – the germacranolide argolide (**4**), the eudesmanolide isalantolactone (**9**), and the guaianolides arglabin (**5**), achillin (**6**), grossheimin (**7**), grossmisin (**8**), and leucomisine (**10**) – and evaluation of the cytotoxic, antitumour, antimicrobial, and antifungal activities of the resulting halogenated derivatives. Compounds (**4–10**) are obtainable in preparative quantities from plant material. Their α -methylene- γ -lactone moieties, hydroxy and keto

groups, endo- and exocyclic double bonds, and cyclopentadienone fragments provide suitable reactive sites for targeted halogenation. The novelty of this study lies in the synthesis of 34 new biologically active halogen-containing sesquiterpene lactones and in the analysis of their structure–activity relationships.

2. Experimental

2.1. Starting materials

Compound **4** was isolated from the aerial part (buds, flower heads and leaves) of *Artemisia glabella* Kar. et Kir. as colorless crystals of composition $C_{15}H_{20}O_3$ with a melting point of 133–135 °C (CH_2Cl_2 – Et_2O), $[\alpha]_D^{23} +203.8^\circ$ (c 0.52; $CHCl_3$). According to its physicochemical constants and spectral data (IR, ^1H NMR, ^{13}C NMR), the isolated compound was identified as the germacranolide argolide (**4**) [21].

Compound **5** was isolated from the aerial part (buds, flower heads and leaves) of *Artemisia glabella* Kar. et Kir. as colorless crystals of composition $C_{15}H_{18}O_3$ with a melting point of 100–102 °C (hexane), $[\alpha]_D^{20} +45.6^\circ$ (c 0.3; $CHCl_3$). According to its physicochemical constants and spectral data (IR, ^1H NMR, ^{13}C NMR), the isolated compound was identified as the guaianolide arglabin (**5**) [22].

Compound **6** was isolated from the aerial part (buds, flower heads and leaves) of *Artemisia leucodes* Schrenk as colorless crystals of composition $C_{15}H_{18}O_3$ with a melting point of 144–146 °C (EtOH), $[\alpha]_D^{26} +151^\circ$. According to its physicochemical constants and spectral data (IR, ^1H NMR, ^{13}C NMR), the isolated compound was identified as the guaianolide achillin (**6**) [23].

Compound **7** was isolated from the aerial part (buds, flower heads and leaves) of *Chartolepis intermedia* Boiss. as colorless crystals of composition $C_{15}H_{18}O_4$ with a melting point of 200–202 °C (EtOH), $[\alpha]_D^{20} +159.9^\circ$ (c 1.14; $CHCl_3$). According to its physicochemical constants and spectral data (IR, ^1H NMR, ^{13}C NMR), the isolated compound was identified as the guaianolide grossheimin (**7**) [22].

Compound **8** was isolated from the aerial part (buds, flower heads and leaves) of *Artemisia leucodes* Schrenk as colorless crystals of composition $C_{15}H_{18}O_4$ with a melting point of 156–156.5 °C (EtOH), $[\alpha]_D^{20} +115.26^\circ$ (c 1.2; EtOH). According to its physicochemical constants and spectral data (IR, ^1H NMR, ^{13}C NMR), the isolated compound was identified as the guaianolide grossmisin (**8**) [23].

Compound **9** was isolated from the aerial part (buds, flower heads and leaves) of *Inula helenium* L. as colorless crystals of composition $C_{15}H_{20}O_2$ with a melting point of 117–119 °C (EtOH). According to its physicochemical constants and spectral data (IR, ^1H NMR, ^{13}C NMR), the isolated compound was identified as the eudesmanolide isoalantolactone (**9**) [22].

Compound **10** was isolated from the aerial part (buds, flower heads and leaves) of *Artemisia leucodes* Schrenk as colorless crystals of composition $C_{15}H_{18}O_3$ with a melting point of 196–198 °C (EtOH), $[\alpha]_D^{20} +56^\circ$ (c 1.14; $CHCl_3$). According to its physicochemical constants and spectral data (IR, ^1H NMR, ^{13}C NMR), the isolated compound was identified as the guaianolide leucomisine (**10**) [23].

2.2. General procedures

Reaction progress and product purity were monitored by thin-layer chromatography (TLC). “Sorbfil” plates were used for TLC; visualization – by spraying with a 2% aqueous solution of potassium permanganate. For column chromatography, KSK brand silica gel (fractions below 0.3 mm) was used. Melting points were determined using an OptiMelt device. IR spectra were recorded on an FSM-2201 spectrometer using KBr. UV absorption spectra were recorded on a CARY 60 UV–Vis spectrophotometer over the range 200–400 nm. Elemental analyses were performed using a Eurovector 3000 A analyzer. NMR spectra were recorded on a JEOL Resonance-500 spectrometer (500.16 MHz for ^1H and 125.76 MHz for ^{13}C ; δ scale). Specific optical rotations were measured using a Polax-2L polarimeter in a 0.5-dm, 3-mL cell.

A high-resolution DFS Thermo Scientific mass spectrometers operated at an ionization voltage of 70 V (evaporator temperature 210–280 °C) were used to record mass spectra and determine molecular masses and elemental compositions.

Solvents (dimethylformamide, chloroform, ethyl acetate), as well as triethylamine, were purified using standard methods and distilled under argon immediately before the reactions. The 1-chloro-4-iodobenzene, 3-iodobenzotrifluoride, 2-fluoro-1-iodobenzene, tris-(*o*-tolyl) phosphine, tetrabutylammonium bromide, and palladium acetate used in this work were purchased from Sigma-Aldrich.

2.3. Determination of cytotoxicity

The cytotoxicity of the synthesized compounds was determined using larvae of the marine crustacean *Artemia salina* (Linnaeus, 1758) in a lethality test (brine shrimp lethality bioassay) [24–25].

A 55 ml separatory funnel was filled with artificial seawater, and 200 mg of *Artemia salina* eggs was added. The eggs were incubated for three days under gentle aeration until hatching. One side of the funnel was covered with aluminum foil, and after 5 min, the larvae that had accumulated on the illuminated side were collected using a Pasteur pipette.

For each of the 24 microwells, 20–40 larvae were transferred into 990 ml of seawater. The number of dead larvae was determined microscopically before treatment. Subsequently, 10 ml of a dimethyl sulfoxide (DMSO) solution containing the test compound at a concentration of 10 mg/ml was added to each well. Dimethylaminoarglabin hydrochloride, the active ingredient of the antitumor drug Arglabin, was used as the reference compound, and its solution was prepared in the same manner as those of the test compounds. For the negative control, only 10 ml of DMSO was added.

Following 24 h of incubation and an additional 24 h of standing to ensure immobilization, the number of dead larvae was counted under a microscope. All experiments were performed in triplicate. Compounds exhibiting high cytotoxic activity (less than 5% larval survival) were subsequently retested at concentrations of 50, 10, 5, and 1 mg/ml.

Mortality (P) was calculated using the following equation:

$$P = \frac{A - N - B}{Z} * 100$$

where A is the number of dead larvae after 24 h; N is the number of dead larvae before the assay; B is the mean number of dead larvae in the negative control; and Z is the total number of larvae.

The mortality values were converted into probit units, and probit values were plotted against the base-10 logarithm of concentration using eight serial dilutions. Linear regression parameters were estimated by the least-squares method, and the median lethal concentration (LC_{50}) was determined as the concentration corresponding to a probit value of 5 (50% mortality). The 95% confidence intervals were calculated using Finney's probit analysis. LC_{50} values are reported with their corresponding 95% confidence intervals [26].

2.4. Antitumour activity

Antitumour activity was evaluated in outbred white rats bearing transplanted tumours. The animals received a five-day course of intraperitoneal

administration of the maximum tolerated doses of 2% solutions of the synthesized compounds in dimethyl sulfoxide at doses of 10–70 mg/kg.

Therapeutic efficacy was assessed using two parameters: percentage inhibition of tumour growth and increase in mean survival time, both determined immediately after completion of the experimental treatment course.

Ethical statement. The study was conducted in accordance with Order of the Minister of Health of the Republic of Kazakhstan No. KR DSM-181/2020 of 4 November 2020 (on compliance of preclinical studies with Good Laboratory Practice requirements) and was approved by the Local Bioethics Commission of the NJSC "Karaganda Medical University" (Protocol No. 18 of 21 October 2025) [27].

2.5. Antimicrobial activity

To evaluate the antimicrobial activity of the synthesized compounds, solutions of the test samples were assayed by the agar-well diffusion method against the strains *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Candida albicans*. Lincomycin hydrochloride and nystatin were used as reference drugs, while ethanol served as the negative control. The microorganisms were cultured in a slightly alkaline liquid nutrient medium at 30–35 °C for 18–20 hours.

The resulting cultures were adjusted to a concentration of 0.1% in sterile isotonic NaCl solution; 1 ml of the suspension was applied to Petri dishes with the selective agar media corresponding to each test culture and was spread by the continuous-lawn method. The agar surface was dried, wells (D = 6 mm) were cut, and solutions of the test and control samples were dispensed into them. The amount of each test compound was 1 μ g, and that of the reference drug 1 μ g. The seeded media were incubated at 37 °C, and the results were assessed quantitatively after 24 h from the diameter of the growth-inhibition zones (mm): no effect, <10 mm; weak activity, 10–15 mm; moderate, 15–20 mm; pronounced, >20 mm. Each sample was tested in three independent replicates [28].

Statistical processing of the results was carried out using parametric statistics with calculation of the arithmetic mean and standard error.

2.6. Halogenation of sesquiterpene lactones (4-10)

New halogenated derivatives of sesquiterpene lactones were synthesized according to published

procedures [29–32]. Full details of substrate-to-reagent molar ratios, reaction conditions and durations, product yields, and chromatographic separation and purification conditions are provided in the Supplementary Materials.

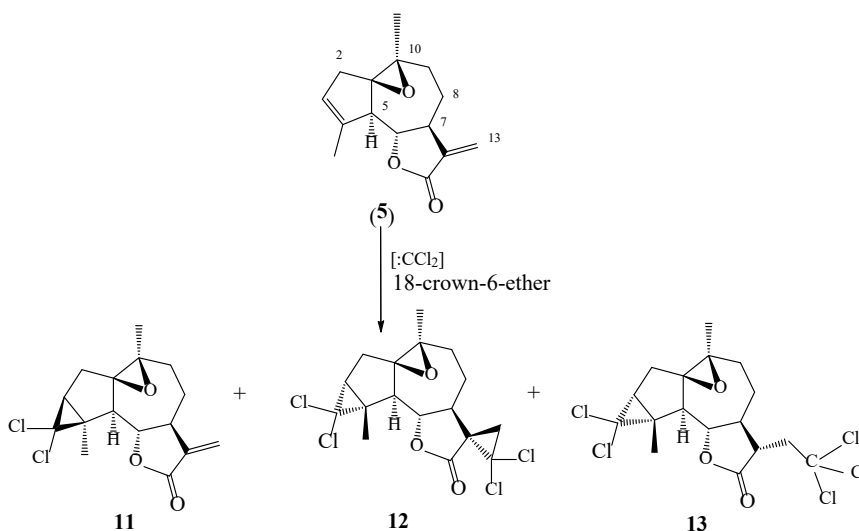
3. Results and Discussion

3.1. Synthesis of dichlorocarbene derivatives of arglabin (5)

Introduction of a halocyclopropane ring into a natural-metabolite scaffold can substantially affect the biological activity of the resulting compounds. In cyclopropanation reactions involving halocarbenes, functional groups adjacent to the unsaturated bond of the starting substrate can strongly influence the reaction outcome.

To expand the range of biologically active derivatives of the antitumor sesquiterpene lactone arglabin (**5**), we investigated the preparation of its dihalocarbene derivatives using dichloro- and dibromocarbene generated from chloroform and bromoform, respectively, under phase-transfer-catalysis conditions with dicyclohexyl-18-crown-6.

Reaction of arglabin (**5**) with dichlorocarbene afforded three compounds, with compound (**12**) being formed in the corresponding yield (Scheme 1). Compounds (**11**) and (**13**) were isolated as minor products in yields of 5 and 3%, respectively. According to the ^1H and ^{13}C NMR data, the less polar compound (**12**) resulted from addition of dichlorocarbene across the trisubstituted double bond: the exomethylene signals remained unchanged, whereas the C4=C5 signals disappeared and were replaced by signals attributable to the cyclopropane-ring carbons.



Scheme 1. Synthesis of compounds **11–13**.

The structure of compound (**13**) was established by X-ray diffraction analysis (XRD) (Fig. 1). Compound (**13**) is formed by addition of a trichloromethyl anion (CCl_3^-) and a proton, both generated from chloroform, to the exomethylene group of the starting compound (**5**).

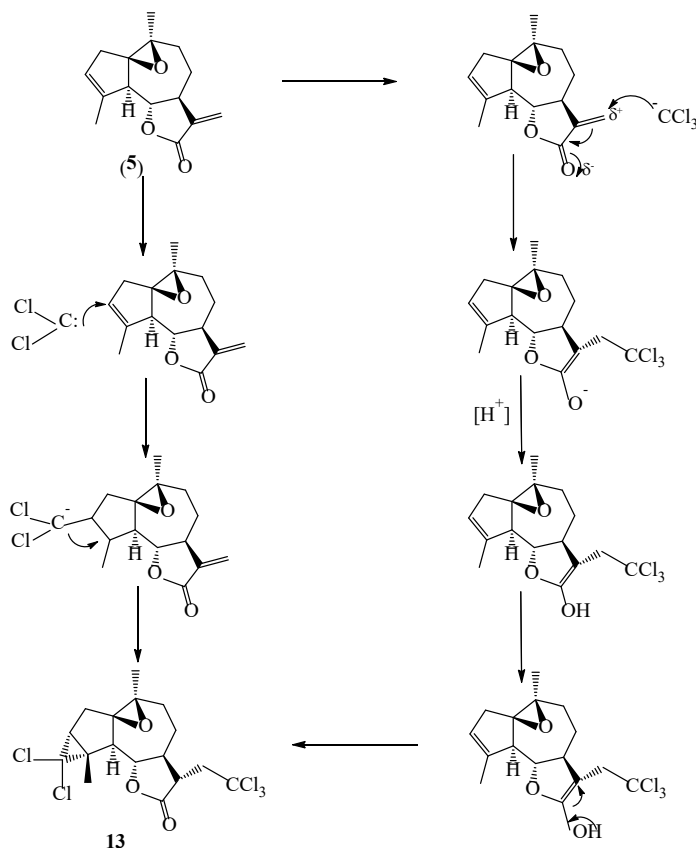
X-ray diffraction analysis showed that the asymmetric unit of crystal (**13**) contains two molecules with identical geometric and conformational parameters within experimental error. Bond lengths were within normal ranges. The seven-membered ring adopts a chair conformation, whereas the five-membered and lactone rings adopt envelope conformations, with C1 displaced from the corresponding planes by 0.49(2) and 0.49(2) Å and C7 by 0.62(1) and 0.61(2) Å. Crystal packing of (**13**) is characterized by the following shortened contacts: Cl1...O2A

3.18(1) Å (sum of van der Waals radii, 3.44 Å), Cl2...Cl5 3.478(6) Å, and Cl2...Cl4A 3.449(5) Å (sum of van der Waals radii, 3.52 Å) [33].

Unambiguous determination of the stereochemistry of cyclopropane-ring addition in compound (**13**) made it possible to assign the corresponding stereochemistry of compound (**11**). The C-16 signals in the ^{13}C NMR spectra of the two compounds differed markedly in position (by 8 ppm), indicating different environments of C-16. In compound (**11**), the epoxy ring exerts a strong deshielding effect, shifting the C-16 signal substantially downfield. Thus, the stereochemistry of dichlorocyclopropane-ring addition in compound (**11**) is opposite to that in lactone (**13**) and is assigned as 3 β ,4 β .

Comparison of the ^{13}C NMR spectra of derivatives (**11**) and (**13**) also enabled assignment of the

stereochemistry of compound (**12**). The C-16 chemical shift in compound (**12**) (76.25 ppm) is close to that of the 3 α ,4 α -cyclopropyl derivative (**13**) (78.90 ppm). Therefore, the major product of the reaction of dichlorocarbene with lactone (**5**), compound (**12**), has the same stereochemistry of cyclopropane-ring addition at C-3 and C-4 as compound (**13**).

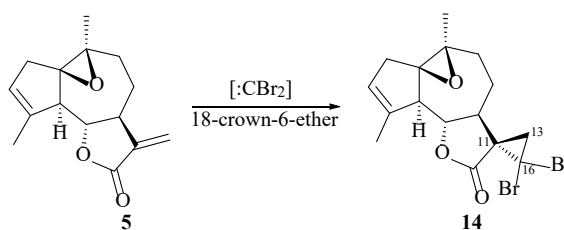


Scheme 2. Mechanism of formation of compound **13**.

As shown in Scheme 2, dihalocyclopropanation of arglabin (**5**) affords a trichloromethyl derivative of arglabin (**13**) in addition to the dichlorocyclopropane derivatives. The reaction proceeds with high stereoselectivity.

To obtain new biologically active arglabin derivatives, a new dibromocarbene derivative (**14**) was synthesized under phase-transfer-catalysis conditions (Scheme 3). Compound (**14**), $C_{16}H_{18}O_3Br_2$, was obtained in 28% yield, m.p. 182–185 °C. Its IR spectrum showed absorption bands attributable to the γ -lactone carbonyl group (1775 cm^{-1}) and C–Br bonds (661 cm^{-1}). Only one product, compound (**14**), was isolated from the reaction of arglabin (**5**) with dibromocarbene. Notably, under otherwise identical conditions, the yield of the dibromocarbene derivative was substantially lower than that of the corresponding dichlorocarbene derivative.

As shown in Fig. 1, rings A and B, and B and C,



Scheme 3. Synthesis of compound **14**.

in (**14**) are trans-fused (torsion angles $O_3C_1C_5H_5 = -145.1^\circ$, $H_6C_6C_7H_7 = -172.8^\circ$).

The conformation of the five-membered ring A was intermediate between the 1 β -envelope ($\Delta C_s^{1,1} = 5.7$, atoms C2, C3, C4 and C5 were coplanar within $\pm 0.02\text{ \AA}$, and the C1 atom extended out of this plane by $0.42\text{ \AA}$ to the β -side) and 1 β ,5 α - half-chair ($AC2^{5,1} = 6.1$, the C1 and C5 atoms moved out of the plane passing through the C2, C3 and C4 atoms by 0.32 and $0.12\text{ \AA}$ into the β - and α -sides, respectively).

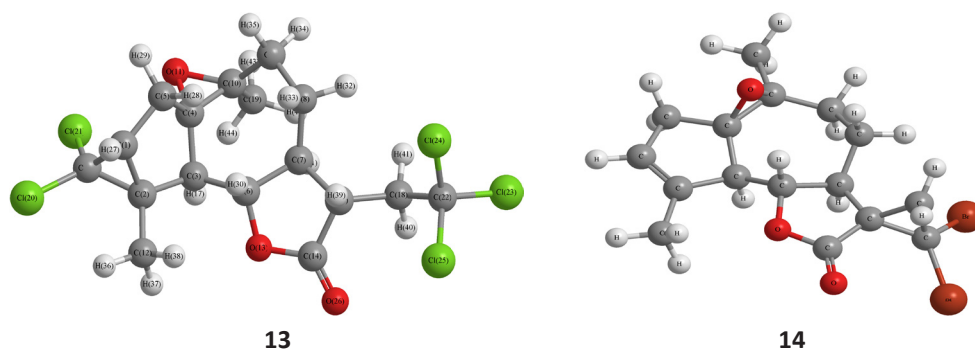


Fig. 1. Spatial structure of molecules (13) and (14) according to X-ray diffraction data.

The seven-membered ring B had a $7\alpha,1,10\beta$ -chair conformation ($\Delta C_s^7 = 3.6^\circ$). The conformation of the molecule (14) was close to the conformation of the arglabin molecules (5), the difference in the values of the corresponding torsion angles did not exceed 10° . The epoxy group at the C1 and C10 atoms was in the β -orientation.

The conformation of the lactone ring C was intermediate between the 6β -envelope (the C7, C11, C12 and O1 atoms were coplanar within ± 0.03 Å, and the C6 atom extended out of this plane by 0.44 Å to the β -side) and the $6\beta,7\alpha$ -half-chair (C6 atoms and C7 extended out of the plane formed by the C11, C12 and O1 atoms by 0.32 and 0.15 Å to the β - and α -sides ($\Delta C_s^6 = 5.7^\circ$ and $\Delta C_2^{6,7} = 6.7^\circ$, respectively).

Subsequent treatment of the dibromocyclopropane derivative of arglabin (14) with molecular bromine in anhydrous chloroform afforded 1,10 β -epoxy-3,4-dibromo-11,13 β -dibromomethylene-5,7 α (H),6 β (H)-guaia-6,12-olide (15) (Scheme 4), $C_{16}H_{18}O_3Br_4$, in 86% yield (116 mg), m.p. 141°C (dec.), R_f 0.43. The reaction proceeded regio- and stereoselectively.

The IR spectrum of molecule (15) contained absorption bands of the carbonyl group in the region of 1792 cm^{-1} , as well as C-Br bonds in the region of 659 cm^{-1} .

The ^1H NMR spectrum of molecule (15) contained a signal from the H-3 proton doublet at 4.91 ppm ($J=6.4\text{ Hz}$), the signal of the H-5 proton was a dou-

blet at 2.81 ppm ($J=10.0\text{ Hz}$) and the signal of the lactone proton H-6 triplet at 4.35 ppm ($J=10.0\text{ Hz}$). The signals of the methyl groups CH_3 -14 and CH_3 -15 appeared as a singlet and a broadened singlet in the region of 1.31 and 2.22 ppm, respectively. Signals of protons H-13b and H-13a were also observed at 2.13 and 2.04 ppm in the form of two doublets ($J=8.0\text{ Hz}$), respectively.

The spatial structure of the molecule (15) was established by X-ray diffraction analysis (Fig. 2).

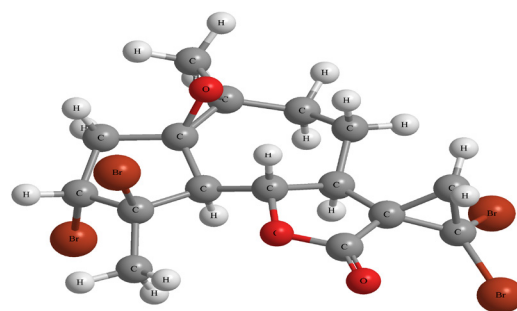
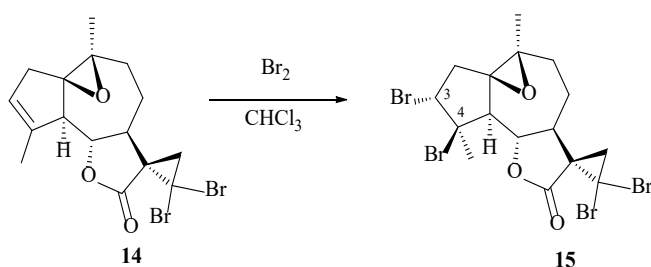


Fig. 2. Spatial structure of the molecule (15) according to X-ray diffraction data.

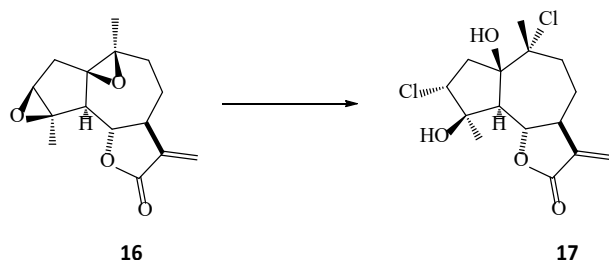
The bond lengths in compound (15) were close to the mean values reported in the literature [34–37]. The five-membered carbocycle adopts an E^4 -envelope conformation, with C-4 displaced by 0.57(1) Å from the plane. The seven-membered ring adopts a chair conformation, whereas the lactone ring adopts a $^6T_7$ twist conformation.

Thus, new bromo derivatives of arglabin (14) and (15) were synthesized, the structure of which was proven by spectral methods and X-ray diffraction analysis.

By reacting 3 β ,4 β -epoxyarglabin (16) with dry hydrogen chloride in an ether-acetone medium, a mixture of compounds was obtained, after chromatographic separation of which on a silica gel column, crystalline substance (17) was isolated with a yield of 60% based on the original compound (Scheme 5).



Scheme 4. Synthesis of compound (15).



Scheme 5. Synthesis of compound (17).

The IR spectrum of compound (17) showed an absorption band characteristic of the hydroxyl group. Mass spectrum of compound (17) with m/z 316, which corresponded to a fragment formed when a water molecule was eliminated by a molecular ion. In the ^1H NMR spectrum (17), when compared with the starting compound (16), a shift to the weak signals field was observed: methyl at C-10 – singlet 1.61 ppm. (3H); lactone proton – triplet 4.48 ppm. (1H; J 10 Hz); H-3 – doublet of doublets 4.42 ppm. (1H; J 10 and 7 Hz).

The elemental composition and spectroscopic data (IR, ^1H NMR, and mass spectra) indicate that compound (17) contains two tertiary hydroxyl groups and two chlorine atoms. Thus, reaction of compound (16) with hydrogen chloride is accompanied by opening of both epoxide rings and formation of isomeric chlorohydrin derivatives.

By X-ray diffraction analysis (Fig. 3), the structure and absolute configuration of 1 β ,4 β -dihydroxy-3 α ,10 α -dichloroarglabin (17) were established. The conformation of the 7-membered ring B was intermediate between a twist chair and a chair. The Me-group C14 was oriented equatorially relative to the ring, whereas the hydroxy group at C1 and the chlorine atom Cl-1 at C10 had an axial orientation. The five-membered carbocycle A and the lactone ring C had a trans-junction with the 7-membered ring (torsion angles O3–C1–C5–H5 = $-167(4)^\circ$ and H6–C6–O7–H7 = $-165(5)^\circ$). The conformation of the 5-membered carbocycle A was a distorted 1 β -envelope

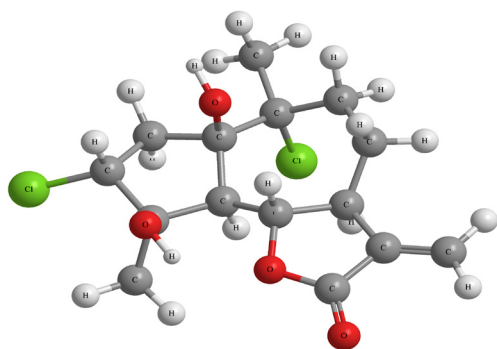


Fig. 3. Spatial structure of the molecule (17) according to X-ray diffraction data.

($C_2 = 7.5^\circ$). The C1 atom moved out of the plane of the C2, C3, C4 and C5 atoms, while the Cl-2, O-4 and C15 atoms were displaced to the α -, α - and β -sides, respectively. The conformation of the lactone ring was 6 β ,7 α -half-chair ($CS^{1,2} = 1.2$).

Thus, molecule (17) has the structure of 1,4 β -dihydroxy-3,10 α -dichloro-guai-11(13)-ene-6,12-olide.

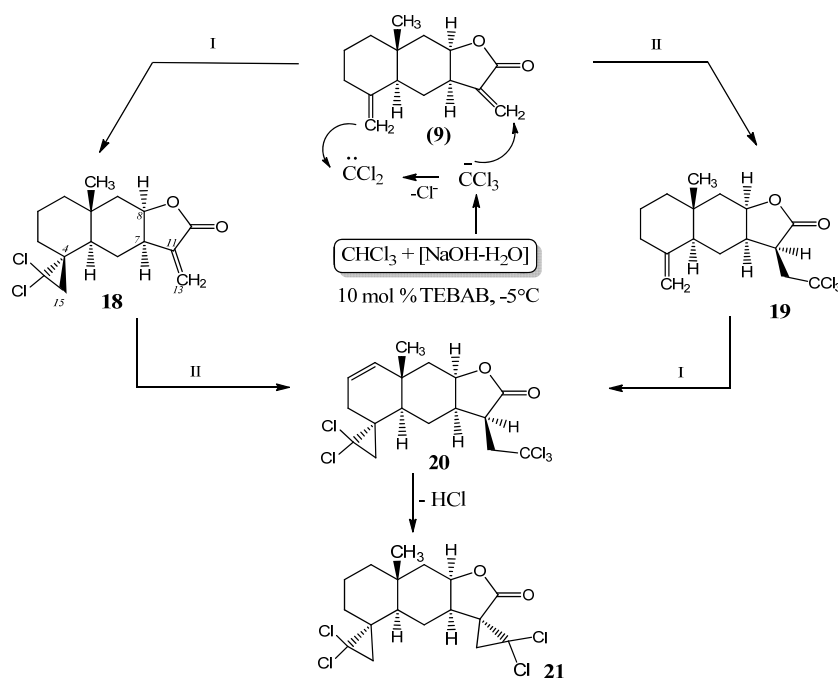
3.2. Chlorination of isoalantolactone (9)

Based on the available plant metabolite isoalantolactone (9), methods for the synthesis of its chlorine-containing derivatives were developed and the possibility of modifying trichloromethylisoalantolactone (19) using the Heck reaction was shown. The [2+1] cycloaddition of dihalocarbenes, generated *in situ* under phase-transfer catalysis, to olefins is an efficient preparative route to dihalocyclopropanes. Dichlorocyclopropanation afforded halogen-containing isoalantolactone derivatives (18–21), whose yields depended on the reaction time [38].

It was established that during the reaction four chlorine-containing compounds are formed: dichlorocyclopropaneisoalantolactone (18), trichloromethylisoalantolactone (19), pentachlorocyclopropaneisoalantolactone (20) and tetrachlorodicyclopropaneisoalantolactone (21). As can be seen, the reaction proceeded in two directions: (I) – addition of dichlorocarbene to the methylene group in ring A with the formation of compound (18); direction II, began with the attack of the $[\text{CCl}_3]^-$ anion at the activated double bond of methylene lactone, proceeded with the addition of a chloroform molecule and the formation of compound (19). Next, the formation of the pentachlorocyclopropane derivative (20) occurred. Intramolecular dehydrochlorination-cyclization in compound (20) led to the tetrachlorodicyclopropane derivative (21) (Scheme 6).

Thus, the reaction of isoalantolactone (9) with chloroform under the action of a phase transfer catalyst led to the formation of chlorine-containing compounds, the ratio of which depended on the reaction time. The dichlorocyclopropane derivative (18) exhibited high activity and selectivity in the Heck reaction with aryl halides.

A characteristic feature in the ^1H NMR spectra of compounds 18–21 is the signal of the axial proton H-6 in the upfield region (0.66–1.04 ppm), which is due to the shielding effect of the cyclopropane fragment. The protons of the methylene group at C13 in compound 20 have chemical shifts at 2.83 and 3.24 ppm, whereas for compound 21 they appear at 1.63 and 2.08 ppm. The multiplicity of the CH_2 group

Scheme 6. Synthesis of compounds **18-21**.

signals in compound **20** indicates the presence of an adjacent hydrogen atom. The $11R$ -configuration in compound **21** was established on the basis of NOESY spectroscopy, in which cross-peaks were observed for the methylene group protons at carbon atoms C6 and C13.

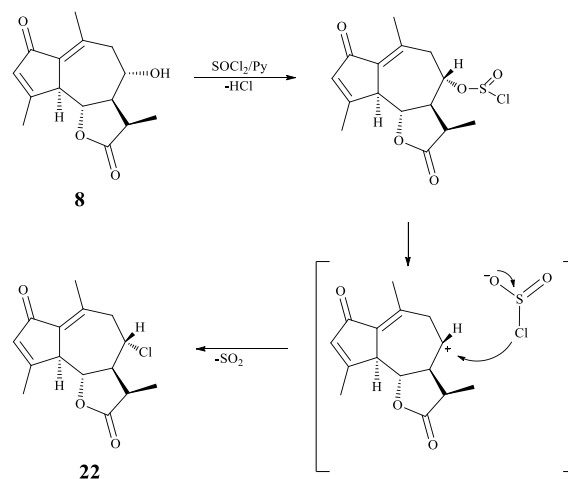
3.3. Chlorination of dienone guaianolides

The structural features of achillin (**6**), grossmisin (**8**), and leucomisin (**10**), particularly the presence of a hydroxyl group and a cyclopentadienone moiety, make these molecules suitable substrates for halogenation reactions.

Reaction of grossmisin (**8**) with thionyl chloride in chloroform at room temperature, in the presence of pyridine as an HCl acceptor, afforded compound (**22**) (Scheme 7), $C_{15}H_{17}O_3Cl$, M^+ 282 (Cl^{37}), M^+ 280 (Cl^{35}).

The IR spectrum of derivative (**22**) contained characteristic absorption bands caused by the C=O stretching vibrations of the γ -lactone ring at 1786 cm^{-1} , C=O at 1690 cm^{-1} , C=C bonds at 1643 and 1619 cm^{-1} .

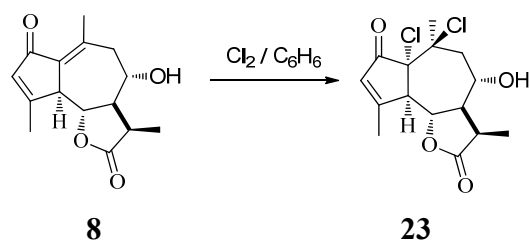
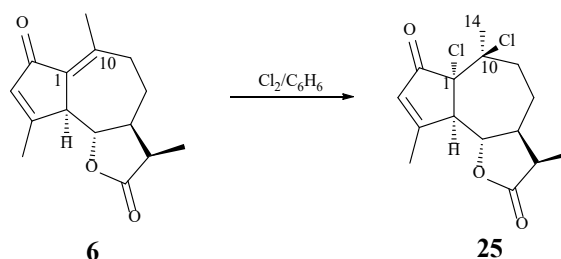
In the ^1H NMR spectrum of derivative (**22**), a three-proton doublet of the methyl group H-13 was observed at 1.23 ppm with a J of 7.0 Hz, also two singlets with an intensity of three protons each, belonging to methyl groups at C-4 and C-10. Doublets of doublets of protons H-9b and H-9a at 2.62 ppm. 13.0, 2.5 Hz and 2.73 ppm with J 13.5, 10.5 Hz, multiplet of methine proton H-7 at 2.80 ppm, triplet of lactone proton H-6 at 3.85 ppm with J 10.0 Hz.

Scheme 7. Synthesis of compound **22**.

A doublet of doublets of doublets of the gem chloride proton with $J_{7/8} = 13.0$ Hz indicated the α -orientation of the chlorine atom. It follows that in this case intramolecular nucleophilic substitution took place with preservation of the α -orientation of the original substituent at C-8.

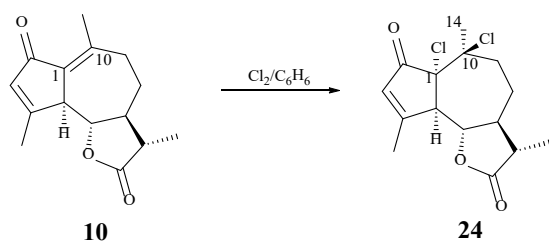
Accordingly, during the reaction of nucleophilic substitution with thionyl chloride in the grossmisin molecule (**8**), selective replacement of the hydroxyl function with a chlorine atom occurred while maintaining the configuration of the asymmetric center at C-8.

When grossmisin (**8**) reacted with chlorine gas in a benzene solution, its dichloride (**23**) was obtained in a yield of about 18% (Scheme 8).

Scheme 8. Synthesis of compound **23**.Scheme 10. Synthesis of compound **25**.

The unsaturated double bonds in dienone guaianolides account for their ability to undergo electrophilic addition reactions.

When leucomisine (**10**) was chlorinated in absolute benzene, its dichloride (**24**) was formed with the composition $C_{15}H_{18}O_3Cl_2$, M^+ 317 (^{37}Cl), M^+ 315 (^{35}Cl) (Scheme 9).

Scheme 9. Synthesis of compound **24**.

In the IR spectrum of chlorinated derivative (**24**), one of the two absorption bands in the region of $1640\text{--}1610\text{ cm}^{-1}$ was missing, which indicated saturation of the endocyclic double bond.

In the ^1H NMR spectrum, the signals of the H-3 protons and the C-15 methyl group did not change their position, and the singlet with the intensity of 3H, corresponding to the C-14 methyl group,

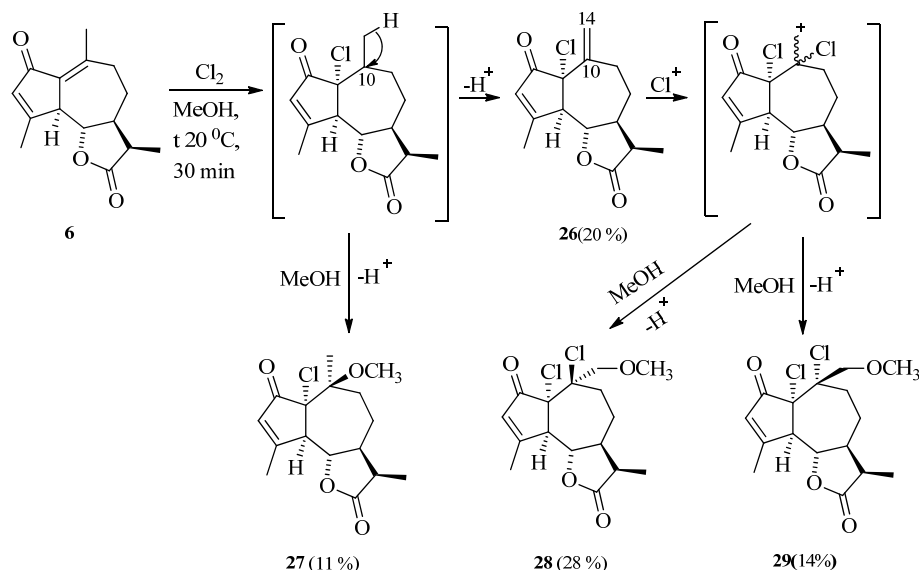
shifted to the upfield region by 0.51 ppm. It followed from this that selective addition of chlorine atoms occurred at the double $C(1)=C(10)$ bond.

Under similar conditions, when chlorinating achillin (**6**), we synthesized dichloride (**25**) (Scheme 10) in a yield of 0.20 g (63.3%).

When achillin (**6**) interacted with chlorine in a methanol solution at room temperature, it was found that achillin (**6**), upon its complete conversion in the reaction, formed four products (**26**–**29**) (Scheme 11) with derivative yields of 28, 11, 20 and 14% respectively.

Methoxychlorides (**28**) and (**29**) did not produce a molecular ion peak in their mass spectra, but the results of elemental analysis, taking into account ^{13}C NMR data, showed that they are isomers of the general formula $C_{16}H_{20}Cl_2O_4$.

The IR spectrum of lactones (**28**) and (**29**) contained absorption bands of the carbonyl group of the lactone ring (1780 cm^{-1}), the carbonyl group and the double bond of cyclopentenone (1710 cm^{-1} and 1625 cm^{-1} , respectively). In the UV spectrum (**28**), an intense absorption band was observed at 241 nm, and in the case of molecule (**29**) – 238 nm, corresponding to cyclopentenone. In a downfield, the ^1H NMR

Scheme 11. Synthesis of compounds **26**–**29**.

spectra of both derivatives (**28**) and (**29**) contained broadened signals of the H-3 olefinic protons and the methyl group at the double bond, therefore the C3-C4 double bond did not participate in the reaction.

In the ^1H NMR spectra of derivatives (**28**) and (**29**), there were no signals of the CH₃-14 methyl group and singlets of methoxy groups were observed – 3.38 ppm for (**28**) and 3.25 ppm for (**29**). Characteristic doublets in the region of 3.41–3.99 ppm indicated the presence of an isolated group (AB system with JAB = 11 Hz). Recording spectra with narrowing of signals allowed us to resolve the fine structure of multiplets and record long-range spin-spin interactions in lactone molecules (**28**) and (**29**).

The question of the configuration of the asymmetric centers C-1 and C-10 in the molecules of the studied chlorides (**28**) and (**29**) was resolved as follows. Monochloride (**26**) turned out to be an intermediate compound in the formation of dichlorides (**28**) and (**29**). For this monochloride, the α -orientation of the chlorine atom was established by X-ray diffraction, which is in agreement with the data on the steric preference of the α -side for attachment at the $\Delta^{10}(1)$ double bond in the guaian dienone-type molecule.

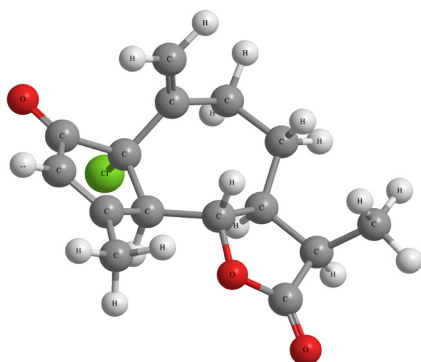


Fig. 4. Spatial structure of molecules (**26**) according to X-ray diffraction data.

The structure and absolute configuration of the molecule of compound (**26**) are presented in Fig. 4. The bond lengths in the molecule were close to the average statistical values. The seven-membered ring in it was in a slightly distorted chair conformation. The lactone ring had the shape of an envelope, the C-7 atom extends $-0.425(7)$ Å out of the plane of the other four atoms (average deviation from the plane is 0.019 Å). The cyclopentene fragment was flat within ± 0.05 Å. The closest analogue of the compound we studied in the Cambridge Structural Database (CSD) was 10-epi-8-deoxycoumambriane B. In general, the geometry and conformation of the

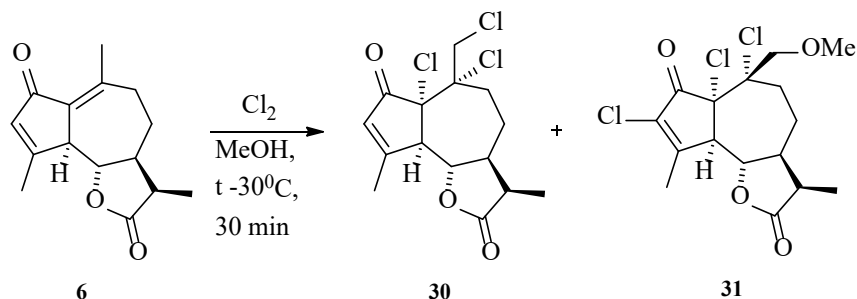
seven-membered ring of these molecules coincided. Let us only note that in the molecule of the mentioned lactone, in contrast to the lactone molecule (**26**), the cyclopentene fragment had the shape of a flattened envelope, and the twist conformation of the lactone ring was more pronounced.

When determining the stereochemistry of the environment at the C-10 atom of epimeric methoxydichlorides (**28-29**), we were based on the appearance of minor methoxydichloride in the ^1H NMR spectrum of long-range spin-spin interaction between the protons H-14 b and H-9 a ($J = 1.1$ Hz) and the absence of such in the ^1H NMR spectrum of basic methoxychloride. As is known, the cycloheptane ring can adopt chair, bathtub, twist-chair and twist-tub conformations. The seven-membered carbocycle in the molecules (**28-29**) was in one of two distorted chair conformations, which was very close to that observed for the methoxychloride molecule (**26**) in crystal.

In the mass spectrum of methoxy monochloride (**27**), the ion peak with the highest mass was $[\text{M}-\text{Cl}]$ ($\text{C}_{16}\text{H}_{21}\text{O}_4$). The presence of one chlorine atom in the molecule of the resulting derivative was confirmed by the results of elemental analysis, and its structure was established according to two-dimensional $^1\text{H}-^1\text{H}$ (COSY) and $^{13}\text{C}-^1\text{H}$ (COSY, COLOC) NMR-spectroscopy. The configuration of the C-1 and C-10 centers of the synthesized molecule was proposed as the most probable. It corresponds to the “normal” product of the trans-antiparallel addition of Cl^+ and MeO^- ions as a result of the primary attack of the Cl^+ cation on the achillin molecule from the sterically more favorable α -side.

For the methoxy monochloride under consideration, the structure of 1,10-diepi (**27**) is also possible. Such a product can be formed due to a similar sequential addition of Cl^+ and MeO^- ions, but with a primary attack of the Cl^+ ion on the achillin lactone molecule (**6**) from a sterically more shielded β -side.

Based on the structures of isolated compounds (**26-29**), the following reaction Scheme 11 can be proposed. The reaction began with the attack of the chloronium ion Cl^+ at the $\text{C1}=\text{C10}$ double bond to form a carbocation intermediate, the deprotonation of which led to a neutral intermediate (**26**). When the second Cl^+ ion attacked the exocyclic double bond $\text{C10}=\text{C14}$ of the vinyl chloride intermediate, a carbocation was formed, which interacted with the MeOH molecule and formed two epimeric C-10 dichloromethoxy derivatives of achillin (**28**) and (**29**). Compound (**27**) was apparently formed due to the addition of a methoxy group to the carbocation at C10.

Scheme 12. Synthesis of compounds **30-31**.

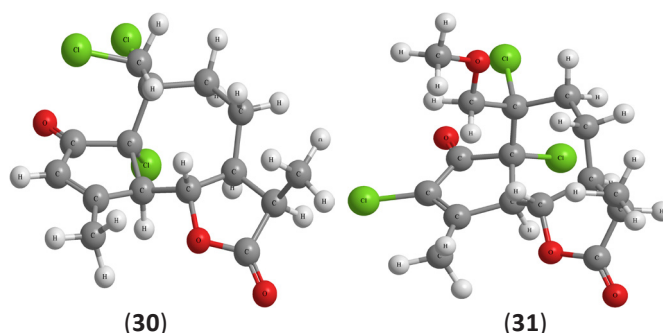
Continuing the study of the products formed by the interaction of chlorine with achillin (**6**) in methanol, we carried out the reaction at a low temperature (about -30°C) with the formation of two new products – 1,10,14-trichloro derivative of achillin (**30**) and 1,3,10-trichloro-14-methoxyachillin (**31**) with yields of 10% and 20%, respectively (Scheme 12).

The IR spectrum of the molecule (**30**) contained absorption bands of the carbonyl group of the lactone ring (1783 cm^{-1}), the carbonyl group and the double bond of cyclopentenone (1723 cm^{-1} and 1626 cm^{-1} , respectively). The UV spectrum of compound (**30**) exhibited an intense absorption band at 237 nm, corresponding to the cyclopentenone chromophore.

The IR spectrum of molecule (**31**) contained absorption bands of the carbonyl group of the lactone ring (1782 cm^{-1}), the carbonyl group and the double bond of cyclopentenone (1731 cm^{-1} and 1622 cm^{-1} , respectively). The UV spectrum of compound (**31**) exhibited an intense absorption band at 250 nm, corresponding to the cyclopentenone chromophore.

At the same time, thin layer chromatography (TLC) detected a substance that was not formed in a noticeable amount at room temperature. It was isolated as a result of chromatography on silica gel of the reaction products, and the structure of its molecule (**30**) (Fig. 5) was determined by X-ray diffraction analysis. The conformation of rings in the lactone molecule (**30**) is usual – a distorted chair (torsion angle $\text{C}(10)\text{--C}(1)\text{--C}(5)\text{--C}(6)$ $25.4(4)^\circ$) in a seven-membered ring, an envelope in five-membered ones (corresponding deviations $0.310(5)$ for $\text{C}(1)$ and $0.476(5)$ Å for $\text{C}(7)$). Almost the same ring conformation was found in 1,10-dihydro-1 α ,10 α (H)-achillin [39], and a slightly different one in the chlorolactone molecule (**26**). The bond lengths in the molecule (**30**) were close to the expected values. It should be noted that the $\text{C}(1)\text{--C}(2)$ and $\text{C}(1)\text{--C}(10)$ bonds were lengthened due to the introduction of chlorine atoms ($1.574(4)$, $1.579(4)$ Å) compared to the corresponding values of 1.519 , 1.550 Å in the molecule 1,10-dihydro-1 α ,10 α (H)-achillin and $1.550(7)$, $1.502(6)$ Å in

molecule (**26**). In the packing of molecules in the crystal there were slightly reduced [40] intermolecular contacts: $\text{O}(12) \dots \text{Cl}(1)$ – $3.127(3)$, $\text{Cl}(1) \dots \text{H}(3)$ – $2.87(5)$, $\text{H}(13\text{C}) \dots \text{O}(12)$ – $2.42(7)$ Å.

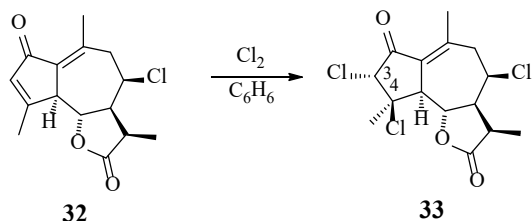
Fig. 5. Spatial structure of molecules (**30**) and (**31**) according to XRD data.

Sesquiterpene lactones, close to chloro-derivatives of achillin (**6**), containing a chlorine atom in the carbon skeleton at C-15, such as chlorojanerin (**1**), chlorohyssopifoline A (**2**), exhibited moderate antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Candida albicans* and *Candida parapsilosis* [9]. Chlorohyssopifolins A (**2**) and C (**3**) had pronounced antiprotozoal activity against *Entamoeba histolytica* and *Trichomonas vaginalis* [7]. Chlorojanerin (**1**) was active against the HSV-1 virus [8].

Using the previously discussed reactions of chlorination of achillin (**6**), it was proven that the double bond $\text{C}(1)=\text{C}(10)$ of the conjugated system in dienone guaianolides molecules was more reactive.

However, the addition of chlorine to the 8 β -chloroachillin molecule (**32**) in a benzene medium occurred through the double bond $\text{C}(3)=\text{C}(4)$ with the formation of trichloride (**33**) (Scheme 13), composition $\text{C}_{15}\text{H}_{17}\text{Cl}_3\text{O}_3$, M^+ 350 (Cl^{35}).

In the IR spectrum of (**33**), there was no absorption band in the region of $1640\text{--}1620\text{ cm}^{-1}$, caused by vibrations of the double endocyclic bond; in the NMR spectrum, the signals of the H-3 proton and the C-15 methyl group were shifted to the upfield region



Scheme 13. Synthesis of compound **33**.

by 2.00 and 0.27 ppm, respectively, in comparison with the spectral data (**32**), which indicated the saturation of the C(3)=C(4) bond.

The structure of the molecule (**33**) was determined by X-ray diffraction analysis (Fig. 6).

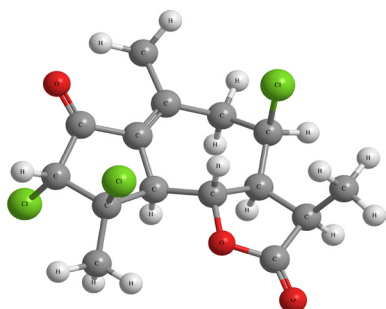


Fig. 6. Spatial structure (**33**) according to X-ray diffraction analysis.

The bond lengths in structure (**33**) were close, and the bond angles were distorted compared to usual ones. The articulation of the lactone ring with the guaiane skeleton was trans, the torsion angle H(7)C(7)C(8)H(8) was equal to -165.33° . The conformation of the lactone ring was a slightly distorted envelope ($\Delta C_s^7 = 3.6^\circ$), the C-7 atom moved out of the plane of the other atoms (coplanar within ± 0.01 Å) to the α side by 0.50 Å. The seven-membered ring C(5)C(6)C(7)C(8)C(9)C(10)C(1) took on a slightly distorted chair conformation ($\Delta C_s^7 = 3.0^\circ$), with C-7 atoms leaving α -side, and C-1 and C-10 in the β -side (from the plane of the remaining coplanar atoms within ± 0.01 Å), by 0.72 , 0.86 and 0.90 Å, respectively. The conformation of the five-membered ring C(1)C(2)C(3)C(4)C(5) was a distorted envelope ($\Delta C_s^4 = 13.4^\circ$), the C-4 atom moved out of the plane of the other atoms (coplanar within ± 0.05 Å) in the β -side

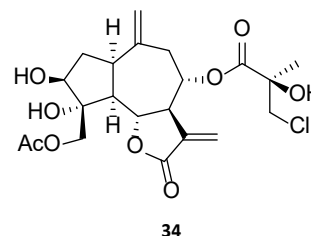
by 0.51 Å. The substituents were oriented as follows: Cl-2, Cl-3, as well as the methyl group at C-11 are β -directed, Cl-1 and the methyl group at C-4 were in the α -direction. The group at C-10 lay in the plane of the seven-membered ring.

The electrophilic addition of chlorine atoms to the 8 β -chloroachillin molecule (**32**) proceeded according to the classical laws of organic chemistry with the formation of vicinal trichloride (**33**). The only exception in this case was the attack on the double C(3)=C(4) bond.

The presence of a system of conjugated double bonds in the molecules of dienone guaianolides suggested the occurrence of addition reactions of electrophilic agents in two ways, with the formation of 1,10- or 3,4-addition products.

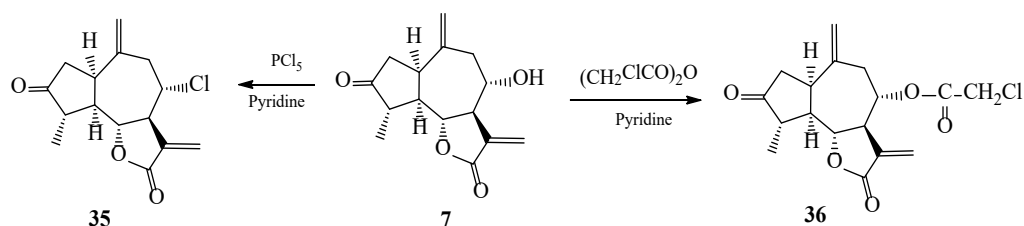
As a result of chlorination of achillin (**6**), grossmisin (**8**) and leucomisine (**10**) in benzene and methanol, 1,10-addition products were obtained. Consequently, the orientation of the methyl group did not affect the path of addition of the electrophilic agent, the hydroxyl group promotes its addition at the double bond C(1)=C(10), and its replacement with chlorine led to selective addition at the double bond C(3)=C(4).

The sesquiterpene γ -lactone raposerine (**34**), containing a chlorine atom in the ester group, inhibited the reproduction of influenza virus, herpes simplex virus 1 and parainfluenza [41].



3.4. Chlorination of grossheimin (7)

When the grossheimin molecule (**7**) interacted with phosphorus pentachloride in chloroform in the presence of pyridine at room temperature, its chloride (**35**) was formed – the product of substitution of the hydroxyl group with a chlorine atom at position C-8.



Scheme 14. Synthesis of compounds **35-36**.

In the IR spectrum of the synthesized compound (**35**), there was no absorption band characteristic of the hydroxyl group, while in the ^1H NMR spectrum (**35**) there was no signal of the proton geminal to the hydroxyl group, but a proton geminal to the chlorine atom is observed.

In addition, the presence of a chlorine atom at (**35**) was confirmed by elemental analysis data.

By reacting grossheimin (**7**) with chloroacetic anhydride in pyridine, a new derivative (**36**) was obtained containing a chlorine atom in the ester group.

Accordingly, based on grossheimin (**7**), new derivatives (**35**) and (**36**) were synthesized, containing a chlorine atom both at the C-8 position and in the ester group (Scheme 14).

3.5. Fluorinated derivatives of argolide (**4**) and grossheimin (**7**)

Fluorinated sesquiterpene lactones have not been found in natural sources to date. The synthesis of fluorine derivatives based on anhydroparthenin, parthenolide and artemisinin is known [42–45].

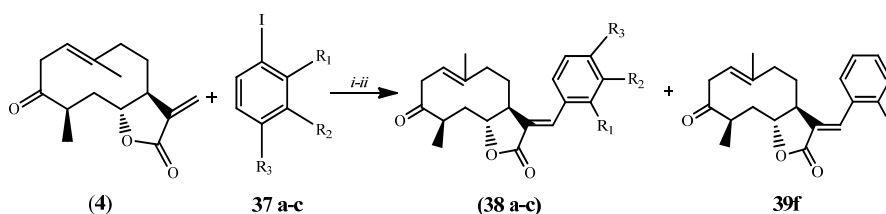
The exocyclic double bond of the lactone ring in the molecules of argolide (**4**) and grossheimin (**7**) allows synthesis according to the Heck reaction, due to the addition of an aryl substituent to the C-13 carbon

atom, which has a relatively high electron density.

The nature of substituents on the aryl halide has a significant effect on the composition of the reaction products and the conversion. The type of catalytic system also plays an important role: in particular, with a palladium catalyst, the less sterically hindered exocyclic double bond of the lactone ring in molecule (**4**) undergoes preferential arylation, ensuring a corresponding yield of halogen derivatives.

Thus, the reaction of compound (**4**) with aryl halides (**37a–c**) in the presence of the $\text{Pd}(\text{OAc})_2$ -(*o*-Tol) $_3\text{P}$ -Et $_3\text{N}$ -DMF (N,N-dimethylformamide) catalytic system proceeds regioselectively to yield exocyclic compounds of the (E)- (**38a–c**) and (Z)-configurations (**39f**) (Scheme 15).

The interaction of argolide (**4**) with aryl iodide (**37a**) in the presence of tetrabutylammonium bromide (conditions ii) led to the formation of the corresponding 13-(E)-aryl-3-oxogermacra-1(10),11(13)-diene-6,12-olide (**38a**), isolated in 26% yield after column chromatography on silica gel (an additional 48% of argolide (**4**) was isolated, respectively). The reaction of argolide (**4**) with 4-iodofluorobenzene (**37b**) or 4-iodochlorobenzene (**37c**) led to the formation of 13-(E)-aryl-3-oxogermacra-1(10),11(13)-diene-6,12-olides (**38b,c**) with yields of 32 and 28%, respectively.



38a: $\text{R}_1=\text{R}_3=\text{H}$, $\text{R}_2=\text{CF}_3$; **38b**: $\text{R}_1=\text{R}_2=\text{H}$, $\text{R}_3=\text{F}$; **38c**: $\text{R}_1=\text{R}_2=\text{H}$, $\text{R}_3=\text{Cl}$

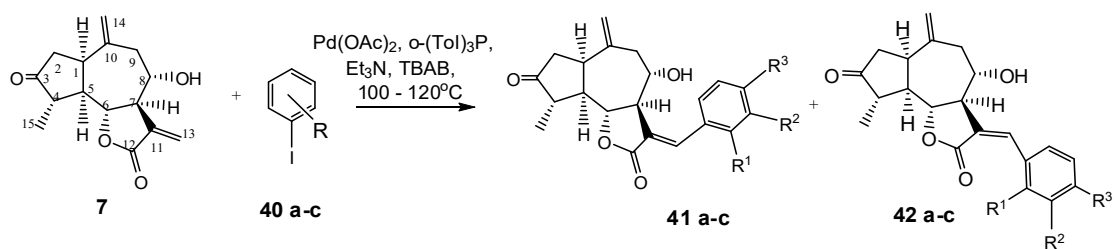
Scheme 15. Synthesis of compounds **38a–c**, **39f**.

The composition and structure of the obtained compounds (**38a–c**) and (**39f**) were confirmed by the data of elemental analysis, mass-, IR-, UV-, NMR- ^1H and ^{13}C spectra.

The ^1H and ^{13}C NMR spectra of compounds (**38a–c**) and (**39f**) were fully consistent with their structure and contained one set of signals for the germacranolide backbone and a substituent at position C-13, indicating the formation of one structural isomer. The assignment of signals in the ^1H NMR spectra of the synthesized compounds was carried out based on the analysis of two-dimensional ^1H NMR spectra of the studied samples using literature data for argolide [21]. (E)-Configuration of the double bond C11=C13 of lactones (**38 a–c**) followed from the presence in

the ^{13}C NMR spectrum (monoresonance mode) of a carbon-proton *cis*-J between the olefinic proton H-(13) and the carbonyl carbon C(12) ($^3J_{\text{C,H}}$ 4–6.9 Hz). A characteristic feature of the ^1H NMR spectra of lactone (**39 f**) was the downfield shift of the signal of the H-6 proton (4.78 ppm) compared to the location of the corresponding proton in the spectrum of lactone (**4**) (3.63 ppm) or in the spectrum of 13-(E)-aryl-substituted lactones (**38 a–c**) (3.66–3.75 ppm).

In terms of targeted chemical modification of the methylene lactone grossheimin (**7**), we studied the interaction (**7**) with chloro-, trifluoromethyl- and fluorine-substituted iodobenzenes (**40 a–c**) under the conditions of the Heck reaction. It was established that cross-coupling reactions (**7**) with iodarenes



$\text{R}^1=\text{H}, \text{R}^2=\text{H}, \text{R}^3=\text{Cl}$, (40a, 41a, 42a), 24h;
 $\text{R}^1=\text{H}, \text{R}^2=\text{CF}_3, \text{R}^3=\text{H}$ (40b, 41b, 42b), 25 h;
 $\text{R}^1=\text{F}, \text{R}^2=\text{H}, \text{R}^3=\text{H}$ (40c, 41c, 42c), 25h.

Scheme 16. Synthesis of compounds **41a-c**, **42a-c**.

(**40 a-c**) in the presence of a palladium acetate-ortho-tolylphosphine catalytic system, adding tetrabutylammonium bromide (TBAB) and triethylamine as a base in dimethylformamide, proceeded selectively at the C11-C13 double bonds and led to the formation of exocyclic products (*E*)- (**41 a-c**) and (*Z*)-configuration (**42 a-c**) (Scheme 16), separated by column chromatography on silica gel.

The H-13 proton signal of (*E*)-isomer products was located in a weaker field compared to the corresponding signal of the (*Z*)-isomer. The NMR spectrum of (*E*)-isomers (**41 a-c**) showed a downfield shift of the H-7 proton ($\delta = 3.70\text{--}3.85$ ppm) compared to the corresponding proton in the spectrum of (*Z*)-isomers (**42 a-c**) ($\delta = 3.08\text{--}3.15$ ppm).

In the ^{13}C NMR spectrum for molecules (**41a**, **41c**, **42a**, **42c**) signals of 21 carbon atoms were observed, and for molecules (**41b**), (**42b**) – signals of 22 carbon atoms. The signals of the carbonyl carbon atom C12

in the ^{13}C NMR spectra of (*E*)-isomers were located in a weaker field (δ 171.37; 171.11 and 171.10 ppm) than the corresponding signals of (*Z*)-isomers **42a-c** (δ 167.94; 167.72 and 167.72 ppm).

The molecular structures of compounds (**41a**), (**41b**), (**42a**), (**42b**), determined by X-ray diffraction analysis, are shown in Fig. 7.

Thus, grossheimin (**7**) was converted into new derivatives bearing 4-chlorophenyl (**41a**, **42a**), 3-(trifluoromethyl)phenyl (**41b**, **42b**), or 2-fluorophenyl (**41c**, **42c**) substituents at C-13. Arylation of grossheimin (**7**) afforded products with an exocyclic double bond. The structures of all synthesized compounds were established from physicochemical constants and spectroscopic data (IR, UV, ^1H NMR, ^{13}C NMR, and two-dimensional $^1\text{H}\text{--}^1\text{H}$ COSY/NOESY and $^{13}\text{C}\text{--}^1\text{H}$ COSY/COLOC spectra). The structures of the (*E*)- and (*Z*)-isomers (**41a,b**) and (**42a,b**) were finally confirmed by X-ray diffraction analysis (Fig. 7).

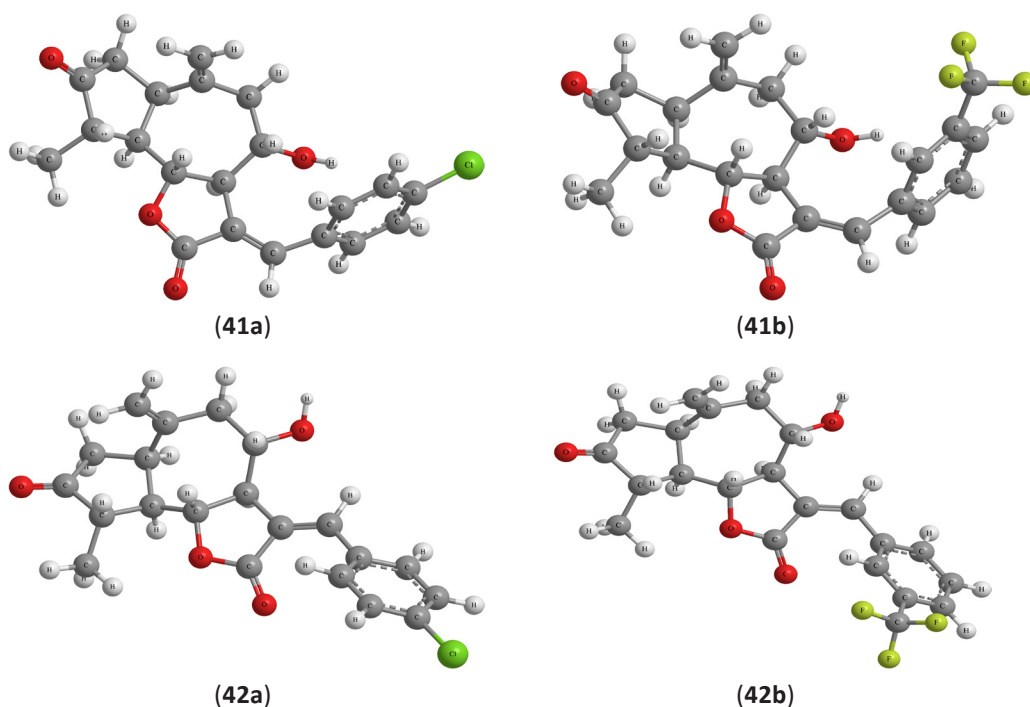


Fig. 7. Molecular structure and atomic numbering of compounds (**41a**), (**41b**), (**42a**) and (**42b**).

3.6. Biological activity of halogenated sesquiterpene lactones

A substantial proportion of naturally occurring halogen-containing sesquiterpene γ -lactones exhibit pronounced biological activity [11, 46]. Accordingly, targeted chemical modification of this terpenoid class through introduction of halogen atoms provides a means of modulating biological properties. In particular, considerable research interest has focused on the search for new sesquiterpene lactones with antitumor activity [47–49].

The synthesized halogenated derivatives of sesquiterpene lactones were evaluated for biological activity. Most of them exhibited antiviral, antimicrobial, antifungal, and antitumor effects, as well as cytotoxic activity.

Carbochlorination is a promising approach to chemical modification of arglabin (**5**). Reaction of arglabin with dichlorocarbene afforded the bis(dichloromethylene) derivative (**12**), which showed high cytotoxicity toward *Artemia salina* (Linnaeus, 1758) larvae at 100 $\mu\text{g/mL}$ and was 32.7-fold more active than the parent arglabin (**5**).

Dichlorocyclopropaneisoalantolactone (**18**) and trichloromethylisoalantolactone (**19**) at 50 mg/kg showed high cytotoxicity against three tumor cell lines: CEM-13, U-937, and MT-4.

Among the chlorinated achillin derivatives (**26–29**), compounds (**27**) and (**28**) showed comparatively high cytotoxicity toward murine myeloma P3X63. Ag8.653 cells. At 160 μM , the cytotoxicity indices were 97.2% for (**27**) and 77% for (**28**), compared with 67.9% for the parent achillin (**6**). In the *Artemia salina* (Linnaeus, 1758) assay, the LC_{50} of compound (**28**) was 68.6 $\mu\text{g/mL}$, whereas that of achillin (**6**) was 182.3 $\mu\text{g/mL}$, i.e., 2.6-fold higher.

8 α -Chloroacetoxy-3-oxo-5,7 α ,4,6,8 β (H)-guaio(14),11(13)-dien-6,12-olide (**36**) at 70 mg/kg showed high cytotoxicity against acute monocytic leukemia cells *in vitro* and at 100 $\mu\text{g/mL}$ against *Artemia salina* (Linnaeus, 1758) larvae.

Chlorination and bromination of arglabin (**5**) increased the cytotoxicity of the resulting derivatives toward tumor tissue. The 3,4-dibromo derivative of arglabin (**15**) at 50 mg/kg showed comparatively high antiproliferative activity, inhibiting the growth of Pliss lymphosarcoma (PLS), PC-1 alveolar hepatocellular carcinoma, and M-1 and sarcoma-45 tumors by 70–90%. Dichlorodihydroxyarglabin (**17**) at 50 mg/kg showed similar activity against sarcoma-45 and M-1 sarcoma, including a prospidine-resistant strain of Pliss lymphosarcoma, with maximal suppression of proliferation reaching 71%.

Compound (**36**) at 1 mg/mL showed moderate antimicrobial activity against the Gram-positive strains *Staphylococcus aureus* and *Bacillus subtilis*, as well as a weak anti-inflammatory effect in a model of acute exudative inflammation.

The brominated arglabin at 1 mg/mL derivative (**15**) exhibited antifungal activity against *Epidermophyton floccosum* and *Aspergillus flavus* and stimulated phagocytosis relative to the parent compound (**5**).

Based on the results of biological screening, it was established that 13E-(4'-chlorophenyl)-grossheimin (**41a**), 13Z-(4'-chlorophenyl)-grossheimin (**42a**), 13Z-(3'-trifluoromethylphenyl)-grossheimin (**42b**) at 1 mg/mL exhibited moderate antibacterial activity against Gram-positive strains of bacteria *Staphylococcus aureus* and *Bacillus subtilis*. A 13Z-(4'-chlorophenyl)-grossheimin (**42a**), 13Z-(2'-fluorophenyl)-grossheimin (**42c**) at 1 mg/mL had moderate antibacterial activity against Gram-negative microorganisms *Escherichia coli*.

Thus, introduction of halogen atoms into sesquiterpene γ -lactones results in directed changes in the biological activity of the parent molecules.

4. Conclusions

The complex, often chiral structures of natural sesquiterpene γ -lactones and the diversity of their functional groups encourage their use as substrates in organic synthesis, including for the development of new pharmacologically active agents.

On the basis of the structural features of germacranolides, eudesmanolides, and guaianolides, we carried out halogenation reactions of argolide, arglabin, achillin, grossheimin, grossmisin, isoalantolactone, and leucomisine.

The endo- and exocyclic double bonds in arglabin and isoalantolactone act as reactive centers for reactions with halocarbenes, affording the corresponding halogenated cyclopropane derivatives.

The hydroxyl group and cyclopentadienone moiety in achillin, grossmisin, and leucomisine enable halogenation to proceed through both nucleophilic substitution and electrophilic addition mechanisms.

Reaction of achillin, grossmisin, and leucomisine with chlorine in methanol proceeds as a multistep process, with predominant formation of a monochloride at the first stage, followed by two epimeric methoxydichlorides and one methoxytrichloro derivative.

Biological evaluation of the 34 new halogen-containing sesquiterpene γ -lactone derivatives synthesized in this study demonstrated pronounced

cytotoxic, antitumor, antifungal, and antimicrobial activities.

Among the chemical modifications examined, dihalocyclopropanation and gem-dihalogenation of arglabin (**5**) gave comparatively promising results. Thus, 3,4 α ,11,13 β -bis(dichloromethano)arglabin (**12**) showed a 32.7-fold increase in cytotoxicity relative to the parent arglabin (**5**), whereas 3,4-dihydro-3 α ,4 β -dibromo-11,13-dibromomethanoarglabin (**15**) displayed comparatively high antitumor activity, inhibiting the growth of various tumor lines by 70–90%. In turn, 1,4 β -dihydroxy-3,10 α -dichloroarglabin (**17**) retained activity against prospidine-resistant Pliss lymphosarcoma. The reactive sites involved in chlorination of dienone guaianolides were determined by the C1=C10 double bond of the conjugated system, whereas replacement of the C-8 hydroxyl group by chlorine redirected electrophilic addition to the C3=C4 bond. These findings indicate a structure–activity relationship in which halogenation adjacent to the α -methylene- γ -lactone/enone system enhances cytotoxicity. Because the biological-activity data reported here were obtained predominantly in primary screening assays, these relationships should be regarded as preliminary pending quantitative dose–response studies (LC₅₀/IC₅₀ with statistical analysis).

Declaration of competing interest

The author declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary material

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