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Heteroatom-Containing Natural Sesquiterpene Lactones and Methods for their Obtaining

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Abstract

This review shows the data about isolated heteroatom-containing sesquiterpene lactones from various genera of *Asteraceae* family, natural occurence, isolation methods and their biological activity. Chlorine-containing sesquiterpene lactones were isolated from genera of *Artemisia* L., *Achillea* L., *Acroptilon Cass*, *Centaurea* L., *Chartolepis* Cass, *Eupatorium* L., *Jurinea* Cass, *Rhaponticum* Adams, *Saussurea* DC. The greatest quantity of chlorine-containing sesquiterpene lactones were isolated from Centaurea genus. 25 new sesquiterpene lactones with chlorine atom in molecule were isolated and characterized. The sesquiterpene lactones, which in their structure contained a sulphur atom as a component of various alkoxyl-, thiohydroxygroups and acid residues, were isolated from genera of *Eupatorium* L., *Petasites* Mill, *Helenium* L., *Acritopappus* R.M. King and H. Rob., *Arctium* L., *Saussurea* DC. Nitrogen atom in the structure of natural sesquiterpene lactones is present in the form of amino groups as a part of ester groups as well as amino acids as Michael adducts. Nitrogen-containing sesquiterpene lactones were isolated from *Acanthospermum* Schrank, *Saussurea* DC. Isolated heteroatom-containing sesquiterpene lactones possess bactericidal, antifungal, cytotoxic, antiviral, virucidal, antiulcer and others activities. Another method for obtaining heteroatom-containing sesquiterpene lactones is a directed synthesis of chlorine-, fluorine-, bromine-, sulphur- and nitrogen-containing sesquiterpene lactones. On the basis of sesquiterpene lactone artemisinin known as an effective antimalarial preparation, we synthesized over 200 derivatives, among which fluorine-, chlorine-, bromine-, nitrogen-, sulphur- and azide-containing derivatives of artemisinin were obtained.

Introduction

The important and valuable group of natural terpenoids is represented by sesquiterpene γ-lactones which presently account for over 7000 compounds and generally found in plants of *Asteraceae* Dumort family (*Asteraceae or Compositae*) [1-12]. Among them, molecular structures containing heteroatoms such as chlorine, nitrogen, sulphur are of interest for researchers.

As the potential sources of heteroatom-containing sesquiterpene lactones from plants of *Asteraceae* family 243 species of Kazakhstan flora were determined. Among them 55 are endemic, 188 species are not chemically characterised yet, for example, in *Achillea* L. genus – 10 species; in *Artemisia* L. - over 50 species; *Centaurea* L. - 27 species etc.

Chlorine-Containing Sesquiterpene Lactones (Natural Occurence, Isolation Methods and Structural Particularities, Synthesis of Chlorine-Containing Sesquiterpene Lactones and Biological Activity)

At present, 85 chlorine-containing sesquiterpene lactones are known. Natural chlorine-containing sesquiterpene lactones are widespread in plant organisms and possess expressed biological activity. This type of sesquiterpene lactones is produced by plants of *Artemisia* L., *Achillea* L., *Acroptilon* Cass, *Centaurea* L., *Chartolepis* Cass, *Eupatorium* L., *Jurinea* Cass, *Rhaponticum* Adams, *Saussurea* DC and other genera.

The presence of covalently bound chlorine in plant compounds was first noticed in 1951 in the

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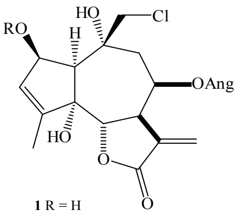
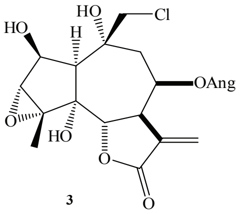
lactone of sceleratic acid isolated from highly toxic *Senecio sceleratus* Schweick. [13]. However, the accurate chemical structure was described for the first time in 1958 for acetylene chlorohydrine by a group of researchers under F. Bohlmann's supervision [14].

The first mention of isolated sesquiterpene lactones, containing chlorine atom in their molecule, was the information about eupachlorin 1, its acetate 2 and eupachloroxin 3 isolated from *Eupatorium rotundifolium* L. plant by Kupchan's group in 1968 [15, 16].



1 R = H
2 R = Ac



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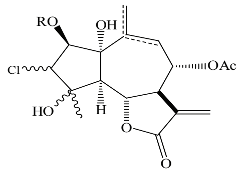
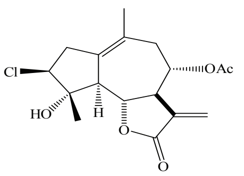
The isolated chlorine-containing sesquiterpene lactones belong to various types, for example, 63 sesquiterpene lactones belong to guaiane type, 17 lactones - to germacrane type, 1 each lactone belong to pseudoguaiane, drimane, eremophilane and absolutely new tanapartolide type.

Some isolated chlorine-containing sesquiterpene lactones from plants of genera of *Artemisia* L., *Centaurea* L., *Chartolepis* Cass., *Eupatorium* L., *Rhaponticum* Adans. belong to guaiane structural type. For example, the scientists from Egypt isolated four new lactones 4-7 from *Artemisia suksdorfii* Piper, which have chlorine atom in C-3 position in their structures [17].



4 α OH, β CH_3, β Cl, Δ^9
5 β OH, α CH_3, α Cl, Δ^9
4 α OH, β CH_3, β Cl, $\Delta^{10,\,14}$



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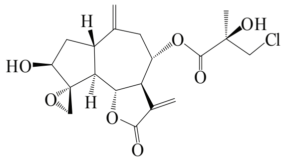
The greatest quantity of chlorine-containing sesquiterpene lactones was isolated from *Cynareae* tribe of *Asteraceae* family, for example, 25 new sesquiterpene lactones with chlorine atom in their molecules were characterized and isolated from *Centaurea* L. genus. Acroptiline 8 is a compound often occurring in plants of *Centaurea* L. (6 species), centaurepensine 9 is found in 20 species, linichlorine B 10 - in 12 species and chlorjanerine 11 - in 5 species [18]. A group of polish researchers under professor B. Drozdz's supervision studied the chlorine-containing lactones from plants of *Cynareae* tribe [19, 20].



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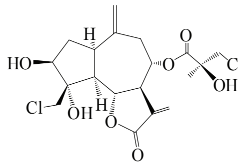

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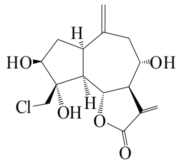

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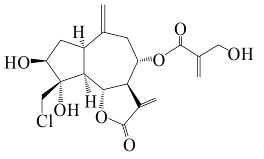

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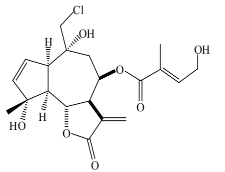
Chlorine atom is present in structures of sesquiterpene lactones mainly in the form of chlorohydrin function, for example, Chinese scientists isolated new chlorine-containing sesquiterpene lactones of guaiane type 12-18 from the ethanol extract of *Eupatorium lindleyanum* DC. [21].



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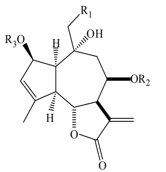
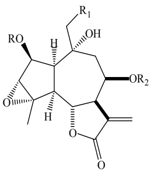
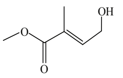


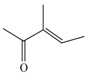
13 R_1=Cl, R_2=R_3 =H
14 R_1=Cl, R_2=**B**, R_3 =H
15 R_1=Cl, R_2=**A**, R_3 =H
16 R_1=Cl, R_2=**A**, R_3 =Ac



17 R=H, R_1=R_2 =**B**
18 R=H, R_1=OH, R_2 =**A**

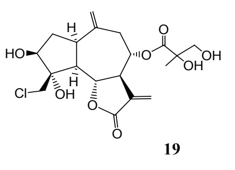


A



B

Position of the chlorine atom can be positioned as a part of ester-substituting groups, for example, ethanol extract of *Saussurea alata* DC produced chlorohyssopifolin E 19 and chlorohyssopifolin A 20 containing a chlorine atom in the ester group [22]. Sesquiterpene lactones of guaiane type 21 from *Saussurea elegans* Ldb. [23], cebelline J 22 and its epimer 23 from *Centaurea glastifolia* L. also contain a chlorine atom in ester-substituting groups [24].



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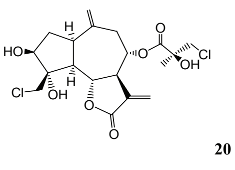

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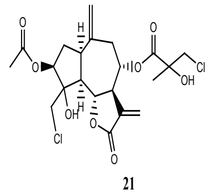

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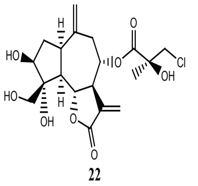

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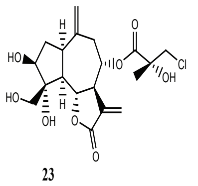

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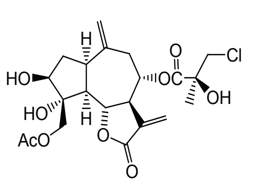
We isolated new chlorine-containing sesquiterpene lactones from *Rhaponticum serratuloides* (Georgi.) Bobr., collected at its bud-forming stage in Central Kazakhstan. The ethanol extract of air-dried and crushed plant material was cleaned from impurities (ballast substances) and the lactone concentrate obtained was chromatographed on silica gel. Fractions of substances containing cynaropicrin, known guaianolides of acroptiline and centaurepensine as well as two new lactones (yields of 0.03 % and 0.01 %, respectively) named as raposerine 24, 15-deacetylraposerine 25 were isolated [25].



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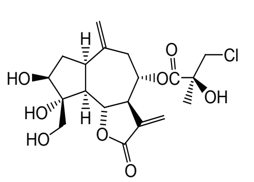

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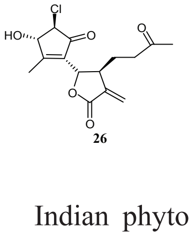
From methanol-dichloromethane (1:1) extract of *Achillea ligustica* All. we isolated two new chlorine-containing sesquiterpene lactones: 2α-chloro-iso-seco-tanapartolide 26 and 4α,10α-dihydroxy-1β,2β-epoxy-5α,7αH-guaiane12,6α-olide 27, whose structures were determined by nuclear magnetic resonance-spectroscopy [26]. Extraction was carried out at room temperature; further chromatographying afforded separate fractions with the following isolation on Sephadex LH-20 and preparative high performance liquid chromatography (eluent - hexane, dichloromethane, methanol, water).

Scientists from Saudi Arabia used the same species of *Achillea ligustica* All. to isolate a new chlorine-containing sesquiterpene lactone 3α-chloro-4β,10β-dihydroxy-1β,2β-epoxy-5α,7αH-guaiane11(13)-en-12,6-olide 28 – an epimer of the previously isolated compound 27 [27] whose structure was determined by IR-, UV-, mass-, ^{1}H- and ^{13}C NMR- spectroscopy and two-dimensional spectroscopy.



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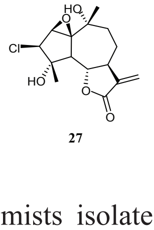

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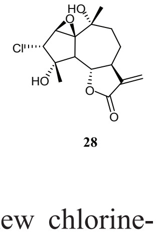
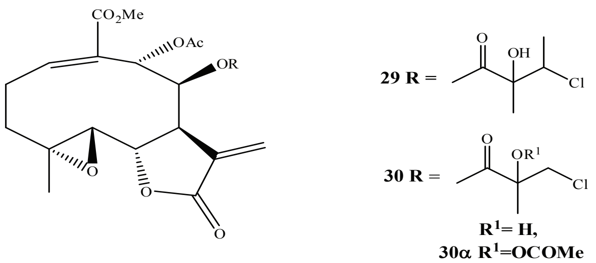
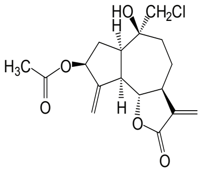


28

Indian phytochemists isolated a new chlorine-containing melampolide 29, 30 from the extract of *Enhydra fluctuans* Lour. leaves. Exhaustive extraction of raw plant material was performed by petrol at room temperature, further chromatography produced separate fractions with the following isolation by silica gel and preparative high performance liquid chromatography (eluent: benzene, benzene-chloroform, chloroform-methanol). Molecular structure and stereochemistry 29 were defined by IR-, NMR ^{1}H, mass- spectroscopy [28].



Spanish researchers isolated a new guaiane sesquiterpene lactone - 14-chlorine-10-hydroxy-10(14)-dihydrozaluzanine D 31 from *Centaurea acaulis* L. [29]. Compound 32 belonging to pseudoguaiane sesquiterpene lactones was isolated from *Ambrosia maritime* L. [30]. Sesquiterpene lactone chlorfastine 31 was isolated from the aerial part of *Ajania fastigiata* (C.Winkl.) Poljak and identified [31].



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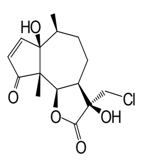

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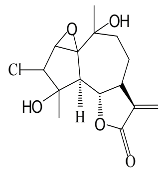
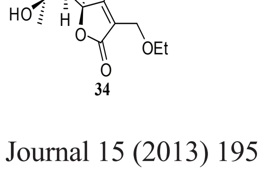


33

A new guaiane sesquiterpene lactone 34 containing a chlorine atom at C-8 in the ester residue was isolated from *Vernonia cinerea* (Linn.) Less [32].

New chlorine-containing sesquiterpene lactones 35-36 were isolated from the aerial part of *Achillea depressa* Janka, whose structures were determined by PMR-, 13C NMR- and mass-spectra [33]. Extraction was carried out by a standard technique at room temperature with the mixture of petroleum ether-ether-methanol (1:1:1) followed by treatment with methanol. Petroleum ether, and methanol were used for column chromatography. Then fractions were re-chromatographed on preparative TLC.



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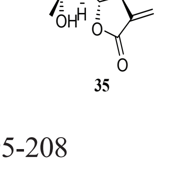

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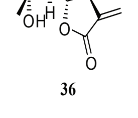

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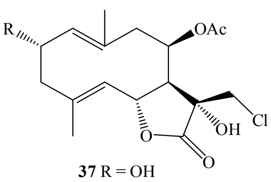
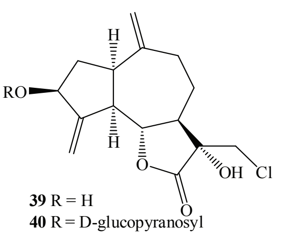
Authors [34] isolated germacrane chlorine-containing sesquiterpene lactone 37 and its acetate 38 from ethyl acetate fraction of methanol extract of Japanese species of *Eupatotium glehnii* Fr. Schmidt ex Trautv. using Sephadex LH-20 ($CHCl_3$-MeOH, 1:1) and HPLC (Nucleosil 50-5, $CHCl_3$-EtOAc). In this molecule, the chlorine atom is located in the lactone cycle.

New chlorine-containing sesquiterpene lactones of 39 and 40 containing a glycoside residue in their molecular structures were isolated from methanol extract of *Leontodon palisa*e Izuzquiza (*Asteraceae*, tribe *Lactuceae*) [35]. This type of lactones was isolated for the first time. The isolated lactones possess high cytotoxic activity.



37 R = OH
38 R = OAc



39 R = H
40 R = D-glucopyranosyl

Thus, the chlorine-containing sesquiterpene lactones were found in the plants of *Asteraceae* family, mainly, in the plants of *Cynareae* tribe.

Methods for Isolation and Structuale Particularities of Chlorine-Containing Sesquiterpene Lactones

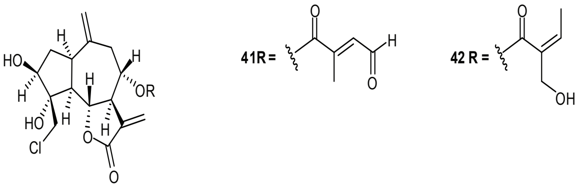
Methods for isolation of the chlorine-containing sesquiterpene lactones are based on the classical techniques of isolating natural compounds, where the basic stages are extraction of the crushed aerial parts of plant by organic solvents or water with the following precipitation of impurities (ballast substances). Various solvents are used as extracting agents. So, for example, *Eupatorium lindleyanum* DC. [21] and *Centaurea scoparia* Sieber ex Spreng [36] were extracted with ethanol, *Artemisia suksdorfii* Piper [17] and *Achillea ligustica* All. [26] with the mix of dichloromethane -methanol, *Achillea depressa* Janka [33] with the mixture of petroleum ether - diethyl ether - ethanol (1:1:1), etc. The choice of a solvent is based both on the polarity of the target product and on the prevention of the extraction of various ballast substances.

Essential limitation for using a solvent can be its ability or its impurity components to react chemically with lactones which can result in artifactual formation and decrease the yield of target products. So, the authors [37] address the unacceptability of the use of chloroform for the extraction of some reactive epoxyguaianolides by chloroform, because traces of HCl in this solvent lead to epoxide ring opening and artifactual formation with chlorohydrin moiety. The authors suggested to replace chloroform with chloride methylene free from chloride hydrogen.

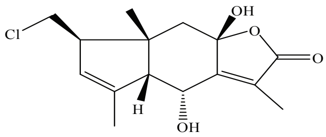
The more often used method for precipitating the hydrophobous components from crude extracts is the Drozdz-Petrovsky's method where the extract is treated with 50% hot ethanol followed by the extraction of lactones from water ethanol with organic solvents, most often with chloroform, diethyl ether, benzene [38]. Treatment of the extract by lead tetracetate was also used to precipitate the impurities (ballast substances). Subsequently, individual compounds were obtained by column chromatography separation method io normal phase sorbents such as silica gel and aluminium oxide.

Identification of compounds was carried out by the spectral methods: IR-, NMR ^{1}H, ^{13}C NMR, using two-dimensional spectroscopy of NMR ^{1}H-^{1}H (COSY), ^{13}C-1H (COSY, COLOC) etc. For example, lactones 9, 24, 25 are not sufficiently soluble in $CDCl_3$, therefore Py-d$_5$ was used to record their NMR ^{1}H and ^{13}C spectra. Interpretation of all signals was carried out using two-dimensional spectroscopy of NMR ^{1}H-^{1}H (COSY), ^{13}C-1H (COSY, COLOC) that permitted to establish molecular structures of new lactones 22 and 23 differing from each other only with the side chain structure. Important cross-peaks were noted in the COLOC spectrum of compound 24, which enabled to establish the position of acetoxygroups in its molecule: C(4)/H (5),2H (15); C (20)/3H (21),2H (15). According to NMR ^{13}C, the molecule of raposerine 24 has the same asymmetric center configuration at atom C(17) as centaurepensine 8 and acroptiline 9.

Absolute configuration of molecules of (1R,3S,4S,5S,6S,7R,8S)-4β-(chloromethyl)-3β,4α-dihydroxy-8α-OTig(4-oxo)-1αH, 5αH, 6βH, 7αH-guaian-10(14),11(13)-dien-6,12-olide 41 and (1R, 3S,4S,5S,6S,7R,8S)-4β-(chloromethyl)-3β,4α-dihydroxy-8α-OSarr-1αH, 5αH, 6βH, 7αH-guaian-10(14),11(13)-dien-6,12-olide 42, isolated from ethanol extract of *Centaurea scoparia* Sieb., were determined [39-40].



The absolute configuration of new chlorine-containing sesquiterpene lactone 43 was defined by quantum chemical methods. Conformational analysis was performed for the first time through Monte Carlo search program with MMFF94 using SPARTAN 04. The results were qualitatively analysed to confirm an absolute configuration of the molecule structure of 43 as 1*R*, 5*R*, 6*R*, 8*S*, 10*R*. Relative configuration is proved by the presence of cross- peak in NOESY spectra between H_3-14 and H_2-2, H-5, H-6 and H-9*β*. Correlation between H-9α and H-1 confirms their α-orientation [41].



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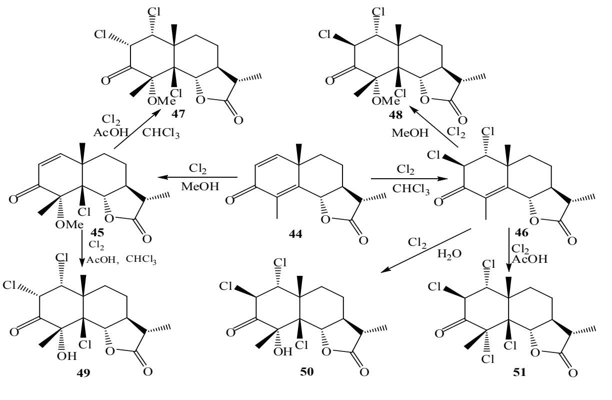
Thus, with the analysis of literature data we determined that there are no available express-methods to detect chlorine in the molecules of sesquiterpene lactones. Methods for isolating chlorine-containing sesquiterpene lactones are standard, however it is not recommended to use chlorine-containing solvents and HCl for the extraction processes to avoid artifactual formation.

Synthesis of Chlorine-Containing Sesquiterpene Lactones

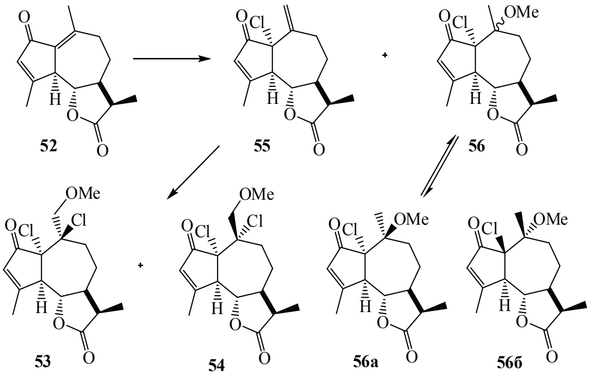
There are very few examples of chemically transformed chlorine derivatives of this class of natural compounds. The most suitable and simple procedure for the synthesis of chlorine-containing derivatives is the reaction of dienes with chlorine gas as was studied by Takayanagi, et al. on α-santonin [42-44]. They found out that chemo- and stereoselectivity of chlorine addition at double bond is strongly solvent-dependent. So, for example, chlorination of α-santonin 43 in methanol leads to the formation of 5β-chloro- 4-methoxysantonin 44, i.e. a double bond adduct at C4-C5. The use of $CHCl_3$ as solvent resulted in the formation of 1α, 2β-dichlorsantonin 45 i.e. trans-bonding product at double bond C1-C2.



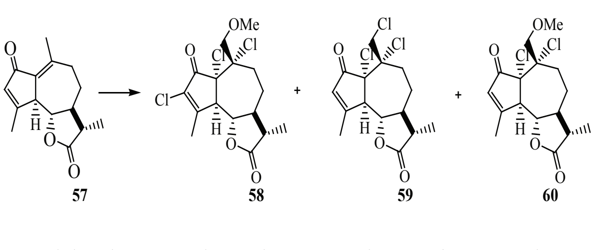
For a number of years, the scientists of Holding “Phytochemistry” have synthesized new chlorine-containing derivatives on the basis of available sesquiterpene lactones, whose structures were determined on the basis of IR-, UV-, ^{1}H-, ^{13}C NMR-spectra and X-ray analysis data.

We’ve carried out the reaction of dienes with chlorine gas using available guaianolides of achillin, grossmisin and leucomisin to obtain new chlorine derivatives [45-48].

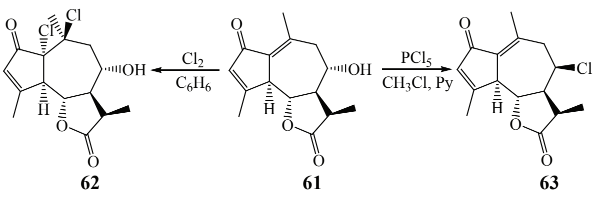
Chlorination of achillin 52 in MeOH at room temperature leads to the formation of several derivatives of 53-56a, 56b, whose yields were 28, 11, 20 and 14 % respectively (after chromatographic separation on silica gel).



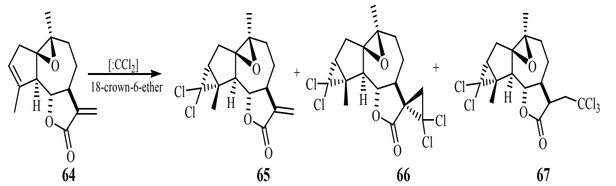
As a result of chlorination reaction of leucomisin 57 (achillin isomer at C-11 - C-13) in methanol at -10 °C we managed to isolate three products: 1b,3,10b -trichlorine-14-methoxy-1,10-dihydroleucomisin 58, 1b,10b,14-trichlorleucomisin 59 and 1b,10b-dichlorine-14-methoxy-1,10-dihydroleucomisin 60.



With the continued researches of natural and semisynthetic chloroguaianolides we obtained two chlorine derivatives of 62-63 on the basis of grossmisin (8α-hydroxyachillin) 61.

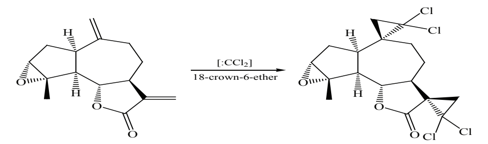


For example, for the synthesis of cyclopropane derivative we studied the interaction of arglabin 64 with dichlorocarbon generated from chloroform in the conditions of interphase catalysis with the presence of dicyclohexane-18-crown-6-ether. Thereat, compounds 65-67 were synthesized [49].



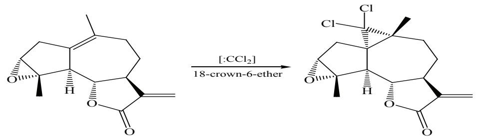
64 65 66 67

To study the cyclopropanation reaction we carried out the interaction of estafiatin 68 with dichlorocarbon [:CCl$_2$] generated from chloroform with the presence of dicyclohexane-18-crown-6-ether and alkali solution. Colourless crystalline substance 69 was obtained [50].



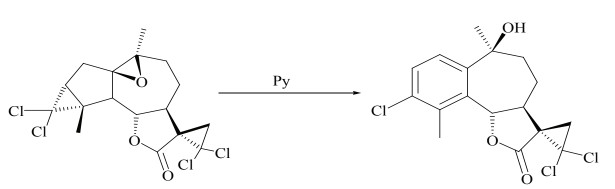
68 69

Interaction of ludartin 70 with dichlorocarbon in interphase conditions led to compound 71.



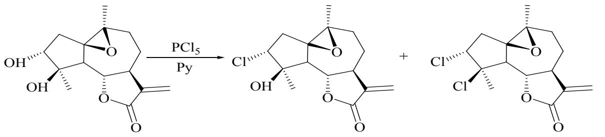
70 71

For further transformation of arglabin tetrachlorocarbene derivative, the molecule 66 was subjected to the interaction with pyridine. As a result, a new compound 72 containing an aromatic cycle was obtained [51].



66 72

On the basis of artefin molecule 73, we carried out the chlorination reaction with phosphorus pentachloride producing mono- and dichloroderivatives of 74, 75 for the first time.



73 74 75

Thus, chemical modification of natural compounds with the introduction of chlorine-containing functional groups in their molecules is extremely promising for receiving new data about chemical properties of terpenoids and for further application of their synthesized derivatives in practical medicine.

Biological Activity of Chlorine-Containing Sesquiterpene Lactones

One of the conditions for the cytotoxicity of compounds was the presence of chlorine atoms in their molecular structures.

Some of the chlorinated sesquiterpene lactones demonstrateed various biological activities. So, centaurepensine 9, acroptiline 8 have the bactericidal and antifungal activities for *Entamoeba hystolytica*, *Trichomonas vaginalis* [18]. Chlorogissopifolins A-D show cytotoxic and cytostatic activity. Acroptiline 8 at the concentration of 0.25 mkg/ml completely inhibits growth of the ascitic Ehrlich's tumor. High cytotoxic activity (2.5 times higher than that of 6-mercaptopurine) of the stated compound is caused by the presence of the chlorine atom in residual ester and 4α, 15-epoxide group. Epoxyderivatives of centaurepensine and chlorogissopifipolines B, D and E were established to show stronger cytotoxic activity in comparison with the initial ones [52].

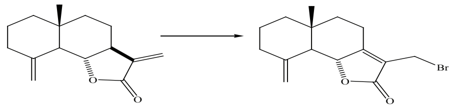
Centaurepensine 9 and raposerine 24 have antiviral properties. Both compounds are capable of effectively inhibiting the reproduction of flu virus (A/FPV/Rostock/34 strain) and causal virus of Newcastle disease (La Sota strain), besides, centaurepensine 9 and raposerine 24 reduce the infectivity of the two specified viruses. I.e. raposerine at concentrations from 5 mcM completely inhibits the flu virus reproduction and to 40% - the Newcastle disease virus and at the concentration of 100 mcM reduces the infectivity of Newcastle disease. Virucidal activity of these compounds is comparable to activity of widely applied commercial preparation "Remantadin" which is effective for flu virus A [53].

The isolated chlorine-containing sesquiterpene lactones possess high biological activity, for example, acroptiline 8 and centaurepensine 9 show bactericidal and antifungal activities for *Entamoeba hystolytica*, *Trichomonas vaginalis*. Acroptiline 8 at the concentration of 0.25 mkg/ml completely inhibits the growth of Ehrlich's ascites tumor. Acroptiline 8 and chlorjanerine 11 possess high antitumor activity [18].

Other Halogen-Containing Sesquiterpene Lactones

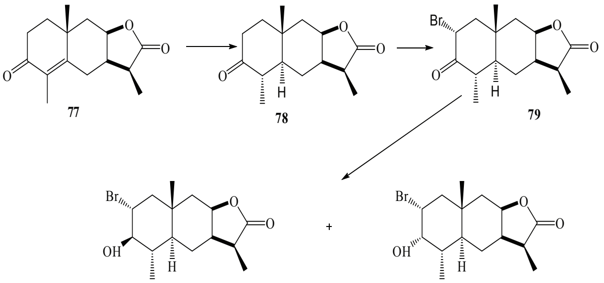
We have not found any information on the atoms of bromine, iodine and fluorine in molecules of sesquiterpene lactones in the available literature.

At the same time, there were attempts to introduce chlorine atoms in molecules of sesquiterpene lactones in order to synthesize their bromine-containing derivatives as well. The effective method for bromination of sesquiterpene lactones with the use of phenyltrimethylammonium perbromide was suggested by Spanish researchers I.G. Collado, et al. [54. Derivative 77 were obtained by bromination from β-cyclocostunolide 76.



76 77

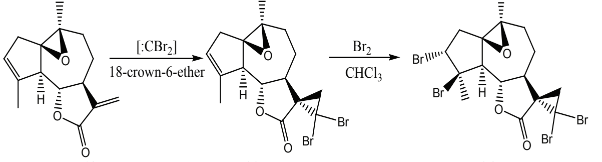
Examples of obtaining bromine-containing derivatives of sesquiterpene lactones is selective reduction of eudesmane sesquiterpene lactone 78 leading to hexahydrovomogine 79 which at further bromination produces bromo-ketone 80 with 92 % yield. Two bromohydrins are obtained by reduction of sodium borohydride: 47 % of cis-isomer 81 and 48 % of trans-isomer 82 [38].



77 78 79

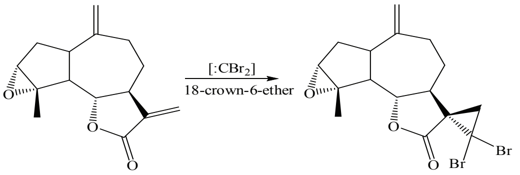
81 82

We performed similar reactions of cyclopropanation on the basis of arglabin and estafiatin to obtain new bromine-derivatives. Cyclopropanation reaction of arglabin 64 was carried out at room temperature at constant stirring. Thus a crystalline substance 83 was obtained. At bromination of 83 in absolute chloroform a colourless crystalline substance 84 was obtained in high yield.



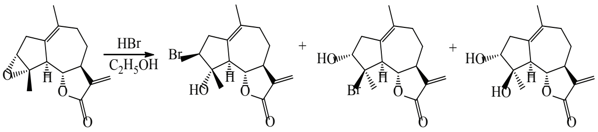
64 83 84

Compound 85 was obtained at interaction of guaianolide estafiatin 68 with dibromocarbene [:CBr$_2$].



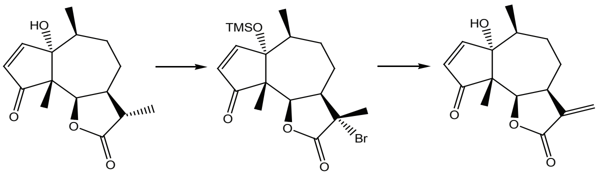
68 85

For obtaining bromohydrine analogues, we carried out the interaction of ludartin 70 with hydrogen bromide in alcohol. Thereat, a mixture of three substances 86-88 was produced.



69 86 87 88

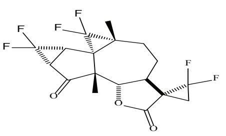
At the last stages of the synthesis of pseudoguaiane sesquiterpene lactone - partenine, Japanese chemists [38] bromated its lactone-cycle hydrogenated analogue– chimenoline 89. Bromation was carried out using phenyltrimethylammonium tribromide (PTAB).



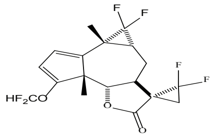
89 90 91

It is known that about 10 % of all marketed pharmaceuticals contain fluorine. Introduction of fluorine atoms in the molecules of natural compounds alters their physical and chemical properties, which are closely connected with the biological functions. Changes in properties effect the resorption, distribution and interaction with the biological target. This makes it possible to change the pharmaceutical profile of these compounds in a huge range and explain the importance of their use.

I. Salazar [55], et al. carried out the carbofluorination of anhydropartenine. At the of pyrolysis sodium chlorodiflouroacetate in boiling diglimethere is formed reactive difluorocarbene, attacking double bonds of this pseudoguaianolide with the formation of products 92-96.



92



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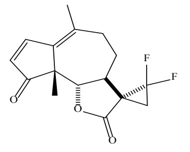

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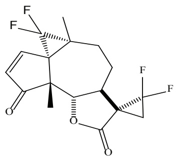

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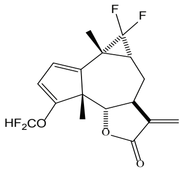
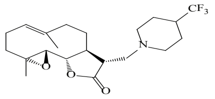


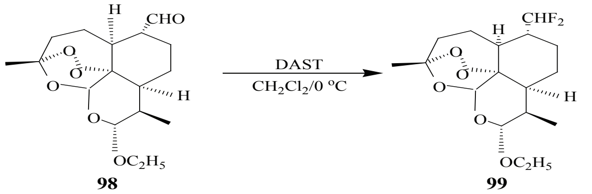
96

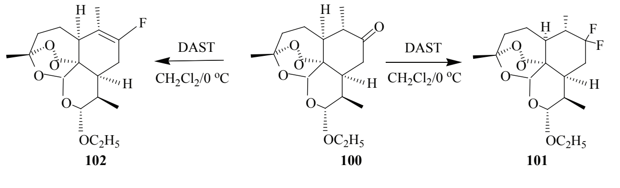
In 2011 J.R. Woods described the synthesis and biological activity of fluorinated amino-derivative 97 of sesquiterpene lactone partenolide [56].



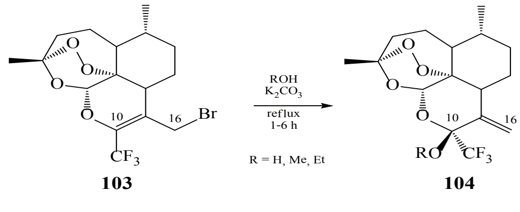
97

Artemisinin is an effective antimalarial preparation. It is used for treatment of multiple drug resistance of various forms of malarial plasmodium. American researchers H.Zifer, et al. [57] obtained fluorine-containing derivatives of sesquiterpene lactone artemisinin. Reaction of carbonyl derivatives of 98, 100 lactones with diethylaminosulfur trifluoride lead to difluoroderivatives of 99, 101 and 102.

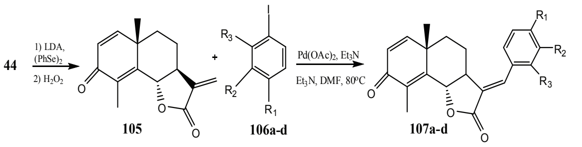




C. Chollet and co-authors [58] developed a simple method for obtaining new fluoroderivatives of artemisinin. Selectivity of substitution can be increased with the help of hexafluoroisopropanol. Preliminary screening of the derivative 104 showed its high antimalarial activity.



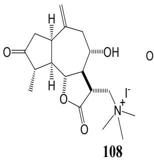
To carry out Heck reaction based on the sesquiterpene lactone of α-santonin 44 they obtained derivative 105. At the interaction of 11,13-dehydrosantonin 105 with aryl halides 106a-d in catalytical system Pd $(OAc)_2$-Et_3N in dimethylformamide solution the compounds 107a-d were obtained in high yield [59].



106a, 107a: R_1=Cl, R_2=H, R_3=H 106c, 107c: R_1=H, R_2=CO_2Me, R_3=H

106b, 107b: R_1=F, R_2=H, R_3=H 106d, 107d: R_1=H, R_2=H, R_3=F

We have not found any data on the synthesis of iodine-containing derivatives of sesquiterpene lactones in the literature available to us. We obtained quaternary ammonium salts 108-111 by reaction of grossheimin with secondary amines by Michael addition type followed by the reaction with alkyliodides in high yields [60].



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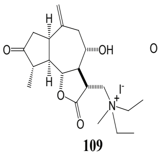

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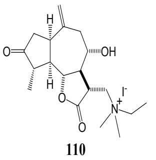

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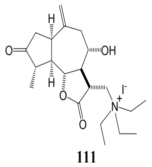
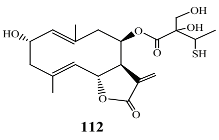


111

Analyzing the above-mentioned methods for obtaining chlorine-, bromine-, fluorine-, iodine-containing derivatives of sesquiterpene lactones we can make a conclusion that in modern organic chemistry there is quite a lot of methods for their obtaining and the choice of the latter depends, first of all, on the structural particularities of the initial natural compound.

Nitrogen- and Sulphur-Containing Sesquiterpene Lactones

Sesquiterpene lactones, containing sulphur atom in their structures as a component of various alkoxyl, thiohydroxy groups and residual acids were isolated as follows: 112 from *Eupatorium mikanioides* Chapm. [61], 113-114 - from *Petasites tricholobus* Franch. [62], 115 - from *Petasites japonicus* Maxim. [63], 116 - from *Helenium autumnale* L. [64], 117-118 - from *Arctium lappa* L. [65] and 119-120 - from *Saussurea lappa* Clarke [66].



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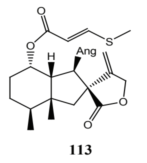

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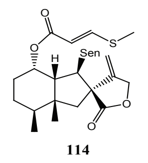

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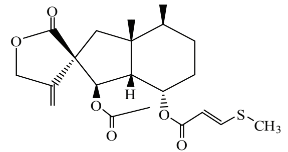

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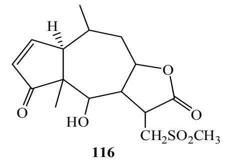

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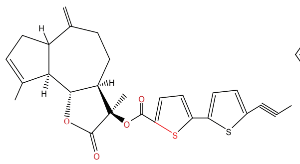

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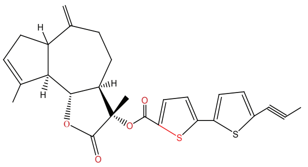

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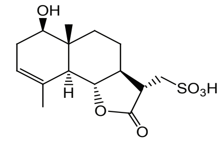

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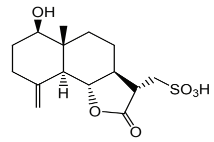
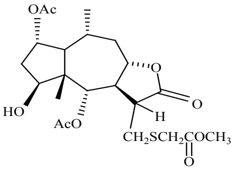


120

The works on chemical modification of sesquiterpene lactone britanin are carried out at the Kazan State Medical University (the Republic of Tatarstan, the Russian Federation). New sulphur-containing derivatives of britanin 121, 122 were produced [67].



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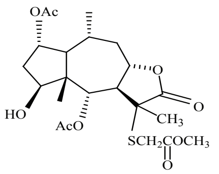
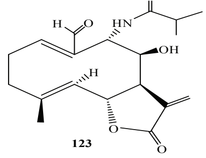


122

Nitrogen atom in structures of natural sesquiterpene lactones is present in the form of amino groups as a part of ester groups as well as amino acids in the form Michael adduct. Nitrogen-containing sesquiterpene lactones were isolated as follows: 123 - from *Acanthospermum glabratum* (DC.) Wild [68], 124-126 - from *Saussurea lappa* Clarke [69], 127-130 - from *Saussurea pulchella* Fisch. [70].



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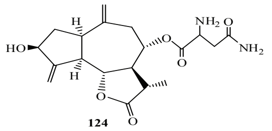

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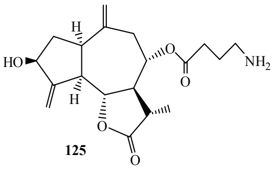

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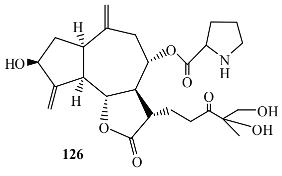

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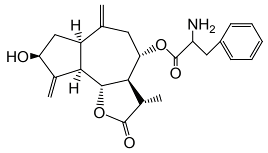

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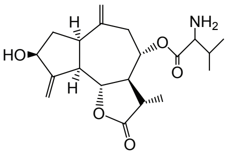

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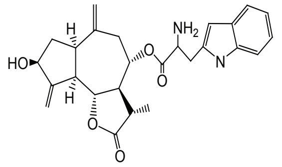

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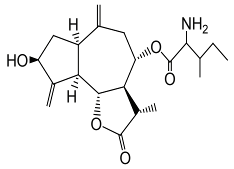
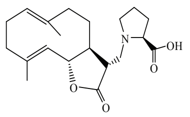


130

Sesquiterpene lactones saussureamines A-D 131-135 containing nitrogen atoms in their molecular structures of possessing anti-ulcer activity, were isolated from the roots of *Saussurea lappa* Clarke [71-72].



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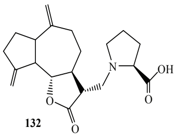

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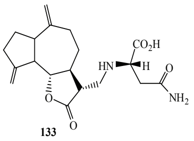

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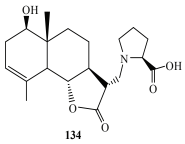

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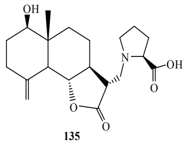
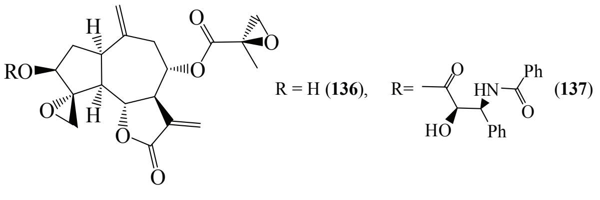


135

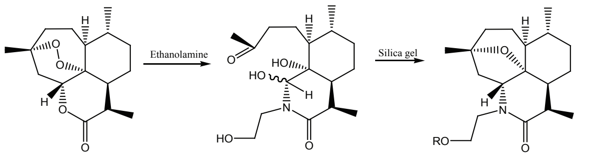
The presence of some reactionary centers in molecules of sesquiterpene lactones potentiates various chemical modifications with the help of which one can obtain various derivatives, including nitrogen-containing ones. Generalization of our own experiments and available literature data indicate that nitrogen-containing derivatives of sesquiterpene lactones are primarily obtained on following fragments of their molecules:

- α-methylene-γ-lactone cycle;
- keto-group;
- double bond.

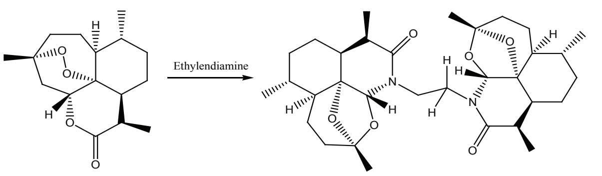
The necessity of further researches on the synthesis of nitrogen-containing derivatives of sesquiterpene lactones can be demonstrated on the work of M. Bruno, et al. [73]. Esterification of OH-group at C(3) of sesquiterpene lactone repine 136 with nitrogen-containing lateral chain of the known antitumor medicine "Paklitaxel" allowed to receive the compound 137 whose activity is 1.5-4.2 times higher than that of natural repine 136.



Except for Michael reaction of amination widely used among sesquiterpene α-methylene-γ-lactones, there are no sufficient literature data on other types of nitrogen-containing derivatives of these compounds. These works are partially generalized in thereview [74]. Among the most interesting works, the following should be noted. S. El-Feraly, et al. [75] carried out the reaction of artemisinin 138 with ethanolamine as a result of which the authors isolated its corresponding lactam 140 and diol 139 from the reaction mixture and identified them. When ethylenediamine was replaced by ethanolamine, dimeric lactam 142 was obtained. These compounds were evaluated for antimalarial and cytotoxic activities. Only the dimer 142 was found to possess antimalarial activity, while only diol 139 exhibited the cytotoxic activity against human breast ductal carcinoma.

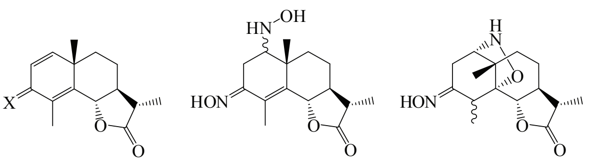


138 **139** **140,** R=H
141, R=COCH$_3$



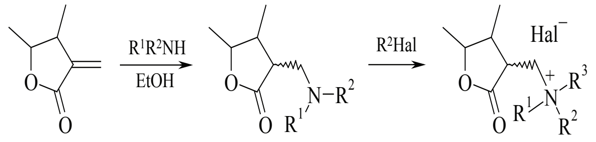
138 **142**

Unusually proceeding reaction of α-santonin 44 at boiling with hydroxylamine hydrochloride in the presence of sodium methylate was observed by Edward, et al. [76]. As a result, they accidentally isolated and identified heterocyclic compound 145 alongside with the derivatives 143 and 144.



44 X = O;
143 X = NOH
144
145

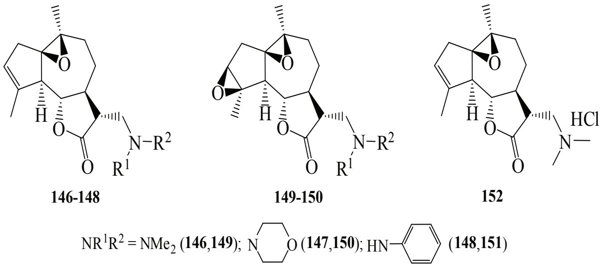
Introduction of nitrogen atom in molecules of sesquiterpene lactones is carried out by amination reaction or addition of primary and secondary amines to α-methylene-γ-lactone cycle by Michael reaction. This approach permits to receive water-soluble derivatives, which is rather essential for their practical application (Scheme 1). This reaction was used to obtain amine-derivatives of guaiane sesquiterpene lactones – arglabin 146-148, 3,4-epoxyarglabin 149-151; germacranolides - argolide 153-155 and stizolin 157-160.



Scheme 1.

One of accessible sesquiterpene lactones is guaianolide arglabin isolated from the aerial part of *Artemisia glabella* Kar. et Kir. [77]. On the basis of this compound some new amino derivatives 146-148 and epoxide - 149-150 were synthesized. The structure of hydrochloride 13-dimethylamino derivative arglabin 152 was determined by X-ray analysis [78].

The scientists at Holding “Phytochemistry”, developed an original antitumor preparation “Arglabin” from the compound 152 and that medicine had passed the final phases of clinical trials and is currently manufactured at Karaganda Pharmaceutical Factory. “Arglabin” is officially registered in the Russian Federation, Republic of Kazakhstan, Kyrgyzstan, Tajikistan, Uzbekistan and Georgia.



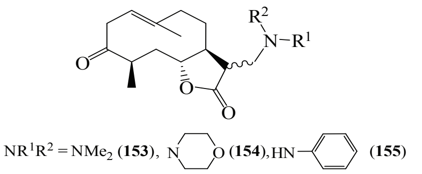
146-148 **149-150** **152**

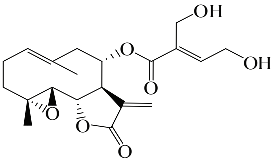
NR^{1}R^2 = NMe$_2$ (146,149); N O (147,150); HN– (148,151)

Corresponding amino derivatives 153-155 were obtained in quantitative yield from germacrane sesquiterpene lactone argolid isolated from the aerial part of *Artemisia glabella* Kar. et Kir. [79].

To study the correlation “structure-activity” and search for new potentially biologically active compounds we investigated the interaction of stizolicine 156 with dimethyl-, diethylamines- and morpholine. The corresponding crystal derivatives 157-159 were obtained. It was determined that de-esterification of dihydroxytiglic acid at C(8) occurs during this reaction.

By interaction of hydroiodic acid with stizolin 13-dimethylaminoderivative there was obtained a quaternary salt in the form hydroiodide 13-dimethylamino-stizolin 160, m.p. 321°C, 45 % yield. Spatial structures of compounds 157, 159 and 160 were determined by X-ray analysis [80].





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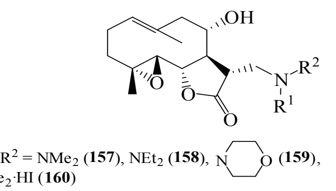
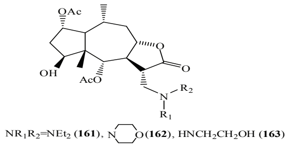
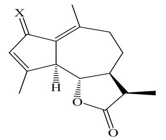


The quantitative yield of some derivatives 161-163 were obtained at amination with diethylamine, morpholine and ethanolamine of pseudoguaiane sesquiterpene lactone britanin isolated from the aerial part of *Inula caspica* Blume [81].



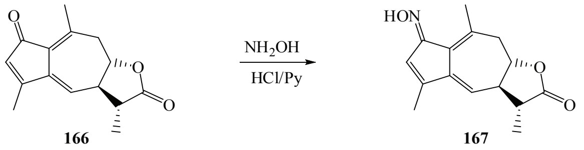


164 X=O;
165 X=NOH (E-isomer)

Oximation reaction of keto-group is the most widespread and often used on sesquiterpene lactones with saturated lactone cycle for obtaining the crystal derivatives as well as studying the influence of keto-group on biological activity. Oximes can be used as intermediate nitrogen-containing derivatives, which can be later transformed into other functional groups. Continuing the works on chemical modification of the accessible sesquiterpene lactone achillin 164 we obtained its oxime 165 – a promising initial compound for the synthesis of biologically active substances [82].

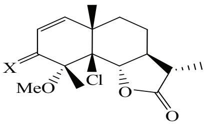
The problem of oximation of α-enones has been considered for a long time in the literature, and various conditions have been tested for reaction. In this case, reaction of ketone 165 with hydrochloride hydroxylamine in MeOH in the presence of Na_2CO_3 did not provide satisfactory yield of target oxime 165. We chose the conditions allowing to obtaining the target product in high yield - 87% (solvent Py, room temperature, reaction time was increased up to 12 h). Product 165 is formed regioselectivly - its geometrical isomer was not detected which was confirmed by X-ray analysis.

At interaction of linear guaianolide anhydroaustricin 166 with hydroxylaminohydrochloride in pyridin there was formed oxime 167 in quantitative yield whose structure was determined by X-ray analysis.



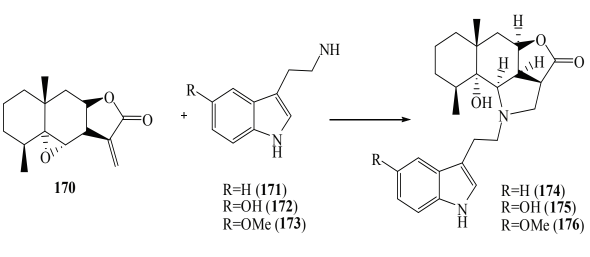
One of accessible method for obtaining nitrogen-containing derivatives of α-santonin is the oximation reaction which allows using further modifications to obtain new derivatives with potentially high biological activity.

As a result of reaction of 5β-chlorine-4α-methoxysantonin 168 with hydroxylamine hydrochloride in pyridin there was received a new derivative in 60% yield, whose structure was determined as 5β-chlorine-4α-methoxy-3-hydroxyimino-7α,6,11β(*H*)-eudesm-1-en-6,12-olide 169 based on the spectral data (IR, UV, NMR ^{1}H) [83].



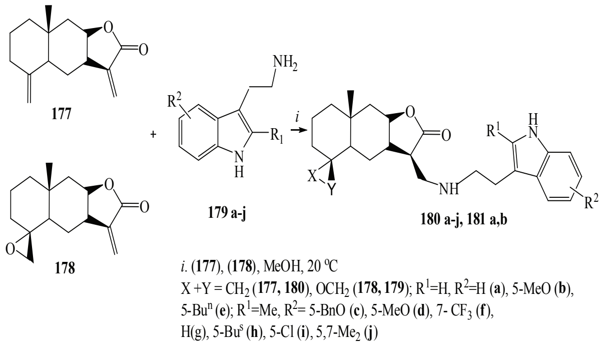
168 X = O;
169 X = NOH

Works on the synthesis of new biologically active compounds based on sesquiterpene lactones of alantolactone, isoalantolactone, santonin and britanin are carried out at the Institute of Physiologically Active Substances, Russian Academy of Sciences (Russia). Among them, we should note the reactions with alkaloids, in particular, their addition to exomethylene group of alantolactone epoxide 170 with epoxygroup opening at C5-C6 and formation of new heterocyclic system - hydrogenated benzo[g]furo[4, 3, 2-cd]indolone [84].



Isoalantolactone 177 and its epoxide 178 in the lactone cycle of exocyclic double bond were activated by carbonyl group. One of the ways to modify such derivatives is the use of Michael reaction – addition of nucleophilic reagents to electron-deficient alkenes. To introduce additional pharmacophore fragment into the lactone molecule, authors used substituted tryptamines (3(2-aminoethyl)indoles as

N-nucleophiles. The obtained tryptamine derivatives of isoalantolactones are of interest as effective antioxidants. The use of such compounds is promising for developing new neuroprotective medicines and cytoprotectors with wide spectrum of action [85].



i. (**177**), (**178**), MeOH, 20 °C
X +Y = CH_2 (**177, 180**), OCH_2 (**178, 179**); R^1=H, R^2=H (**a**), 5-MeO (**b**), 5-Bu^n (**e**); R^1=Me, R^2= 5-BnO (**c**), 5-MeO (**d**), 7- CF_3 (**f**), H(g), 5-Bu^s (**h**), 5-Cl (**i**), 5,7-Me_2 (**j**)

Thus, chemical modification of sesquiterpene lactones with the introduction of nitrogen-containing functional groups, in particular amino groups, is a promising direction for researches, permitting to obtain, first of all, water-soluble forms of these compounds. Introduction of others nitrogen-containing functions such as oxime-, nitrogroups represents certain interest for their further use as intermediate products for the reduction, synthesis of salts of water-soluble amines and studying of their biological activity.

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