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EUDESMANE SESQUITERPENE LACTONES OF THE GENUS *INULA* AND THEIR BIOLOGICAL ACTIVITY

© ***S.A. Pukhov*, S.G. Klochkov, S.V. Afanas'yeva***

Institute of physiologically active compounds of the Russian academy of sciences, Severny proezd, 1, Chernogolovka, 142432 (Russia), e-mail: pukhov.sergey@gmail.com

Sesquiterpene lactones (SL) are widely distributed in nature (formed biosynthetically in plants from farnesyl pyrophosphate) and are a structurally diverse class of terpenoids with 15 carbon atoms in the skeleton and, in addition to the lactone cycle, can contain various functional groups. Some of them exhibit biological activity both in a rather wide range and in relation to a specific target. An increase in the number of undescribed natural plant compounds of this class, as well as detection in various plant species, opens up new possibilities for their use for the purposes of medical chemistry, phytochemistry, pharmacognosy, chemotaxonomy, and related fields. Using the example of SL of the eudesmane structural type found in plants of the genus *Inula*, this review attempts to show the relevance of studies of such compounds that investigate the mechanism of action on various biological models, including the goal of developing new effective antitumor agents.

Keywords: Sesquiterpene lactones, eudesmanes, Inula, biological activity.

Abbreviations: SL – Sesquiterpene lactones; ROS – Reactive oxygen species; p53 – tumor protein P53; NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K/AKT – phosphatidylinositol 3‑kinase/protein kinase B; Nrf2 – Nuclear factor erythroid 2-related factor 2.

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Introduction

SL are secondary metabolites of plants, the largest number of which is found in the Asteracea family. Interest in these compounds is associated with a wide range of their effects on various biological systems. Despite the absence of obvious functions in the basic metabolic processes, some representatives of SL play an important evolutionary and ecological role in plant protection demonstrating, in particular, antifeedant, allelopathic, and other properties [1].

The main types of SL are traditionally classified according to the types of carbocycles. Currently, more than 30 skeletal types are known, which differ in a cycle annelated to lactone. The most common are lactones, including a ten-membered hydrocarbon cycle – germacrane type (e.g. parthenolide), as well as two six-membered or five- and seven-membered cycles – eudesmane (e.g. santonin and vernolepin) and guaianolide types (e.g. arglabin) (Fig. 1). With the development of modern instrumental methods, the number of works devoted to the isolation, structure definition and the study of the biological activity of natural SL is constantly increasing [2]. One of the first generalizing works on this subject is considered to be a monograph [3], in which data on the biological activity of over 500 SL were presented. Most articles published before 1978 were summarized in a monograph [4] (in Russian). It described the physicochemical properties of 587 natural SL, as well as the names of over 70 plants in which they are found and brief information about their biological activity. The author also generalized literature data on the methods of isolation, separation and purification of these compounds.

After 10 years, almost 2,000 described SL were reported in [5] and detailed information was given on biological activity, and the structure – activity relationship. For example, almost 1,200 SL were found in

Pukhov Sergey Aleksandrovich – Senior Researcher, Candidate of Chemical Sciences, e-mail: pukhov.sergey@gmail.com
Klochkov Sergey Georgievich – Chief Researcher, Candidate of Biological Sciences, e-mail: klochkov@ipac.ac.ru
Afanasyeva Svetlana Vasilievna – Senior Researcher, Candidate of Chemical Sciences, e-mail: svafa@ipac.ac.ru

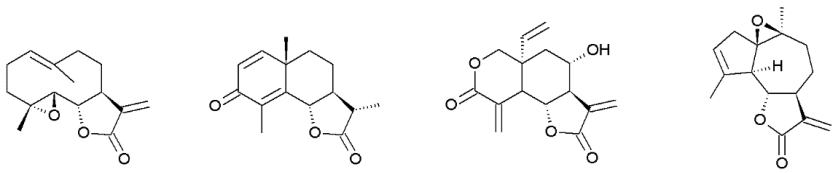
* Corresponding author.

plants in Central Kazakhstan alone by 1987 [6]. Of the recently published monographs, it should be noted [7], which describe SL structural diversity and biological activity. Some chapters of the book [8] are devoted to cytotoxicity, apoptosis, and new approaches to inhibit the growth of tumor cells using sesquiterpenoids; the authors of the chapter in the book [9] summarize current knowledge about the anti-inflammatory activity of these compounds. A review by Brazilian authors [10] considers lactones as protective compounds necessary for plant growth and development. In the review [11] the authors pay particular attention to the antitumor activity of lactones associated with cell cycle arrest, differentiation, induction of apoptosis through the internal pathway and sensitization of the external pathway by the example of parthenolide. The book [12] discusses some of the chemical and biological aspects associated with SL.

Among SL, compounds of the eudesmane structural type are actively studied. Such compounds are most often found in plants of the *Asteraceae* (*Compositae*) family. For example, an article [13] reports on 365 SL and their immediate predecessors from the tribe *Cichorieae* (*Lactuceae*). There is also a specialized review paper [14], devoted exclusively to this class of compounds, in which the structures of 494 eudesmane-type SL isolated from plants of the Asteraceae family are shown.

Plants of the genus *Inula* L. are one of the sources of SL that have been intensively studied recently [15]. So, in work [16] all compounds isolated from plants of the genus *Inula* were generalized and listed (22 of which belong the eudesmane type), including consideration of the biological activity of individual compounds. In the work [17] speaks of 28 eudesmane lactones. The review [18] contains information on isolated bioactive compounds of *I. britannica* and their pharmacological potential: antitumor, antioxidant, anti-inflammatory, neuro- and hepatoprotective. Other plants of the *Inula* genus are intensively studied. For example, out of 10 *Inula* species, one group of authors [19] isolated about 300 sesquiterpenoids of various structures, including about 30 dimers. The authors of [20] proposed a metabolic profile for plants of the genus *Inula*, which has 89 eudesmanolides. The article [21] provides information on various biological activities of SL found in *I. racemosa* Hook. F. In the review [22] information was collected on the effect of secondary metabolites of plants of the genus *Inula*, including sesquiterpenoids for diseases associated with oxidative stress. The authors of [23] focused on the cytotoxicity of SL and, in particular, the pathways of signal transduction of tumor cell death.

This review considers representatives of SL of the eudesmane structural type found in plants of the genus *Inula* until 2020 – alantolactone, isoalantolactone and their analogues, epoxy derivatives, hydroxyl-containing α-methylene and α-methyl-γ-lactones, natural lactones with various connections of lactone and decalin cycles, and with an unusual structure for a given class (a total of 116 substances of this class). The compounds are systematized according to the functional groups in the molecule: epoxy derivatives, mono alcohols and their esters, polyols and their esters, etc. The material is presented in accordance with the complexity of the structure. Data on biological activity are given. The search strategy was to find literature data on such key queries as: «sesquiterpene lactones» and «Inula», primarily using the Google Scholar Database.



Parthenolide **Santonin** **Vernolepin** **Arglabin**

Fig. 1. Examples of SL of various structural types

Natural lactones of eudesmane type

A large number of eudesmanolides were distinguished from plants of the *Inula* genus, differing in the type of connection of the lactone and decalin cycles, the position of the C=C double bond, the presence of an exomethylene or methyl group in the lactone cycle, and the presence, number and location of functional groups as well. The latter are most often hydroxyl and ester groups, less often epoxy cycles and hydroperoxide fragments.

This section discusses natural lactones isolated from various species of elecampane by various group of authors. The geography of studies of such compounds is quite extensive – the work of European, American, Arab, Chinese and Indian research groups is summarized.

1. Alantolactones

Alantolactone (**1**) is one of the most famous SL of the eudesmane type (the numbering of atoms in the formula is given in accordance with the traditionally established nomenclature). The first works on alantolactone appeared more than 120 years ago, but its structure was established only in 1964 [24]. Isoalantolactone (**2**) isomeric to alantolactone in terms of the double bond position is another widely studied eudesmanolide (Fig. 2).

Information on the isolation and properties of lactones **1** and **2** were first generalized in the early 20th century [25]. Among the review works, it is worth noting an article by Milman [26], which examined the issues of being in nature, the ecological role, isolation, synthesis, chemical and biological properties, postulating examples of conversion into lactones of other structural types (for example, artemisin, igalan, etc.). A review [27] details the history of the study on the isolation of alantolactone and its structure.

The largest number of compounds **1** and **2** were found in the roots of the plant *I. helenium* – up to 5% (it should be noted that this species also contains other eudesmanolides, for example, described in the work [28]). Recently, these lactones have also been isolated from *I. racemosa* [29, 30] and *I. royleana* [31].

The biological activity of alantolactones **1** and **2**, primarily antitumor, is being actively studied. A large number of works have been devoted to the study of their action on various tumor models *in vitro*. Thus, the review [32] compiles information on the description of the mechanisms of action of lactones on apoptotic pathways of tumor cell death: mitochondrial and reactive oxygen species (ROS)-dependent, caspase pathway, along with the participation of various caspase regulatory proteins: tumor protein P53 (p53), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), phosphatidylinositol 3‑kinase (PI3K)/protein kinase B (AKT), nuclear factor erythroid 2-related factor 2 (Nrf2), teratocarcinoma-derived growth factor-1 (Cripto-1) and signal transducer and activator of transcription 3 (STAT3) pathways. Alantolactone **1** induces dose-dependent induction of antioxidant enzymes such as quinone reductase, glutathione S-transferase, γ-glutamylcysteine synthase, glutathione reductase, and heme oxidase in mouse hepatocytes (hepa1c1c7) [33]. As the authors suggest, this lactone detoxifies these enzymes through activation of the PI3K and c-Jun N-terminal kinase (JNK) signaling pathways, which leads to translocation of the Nrf2 factor, followed by interaction between Nrf2 and antioxidant responsive element (ARE) in the coding genes. A study of the effect of compound **1** on human colorectal carcinoma (HCT-8) was complemented by a study on normal human liver cells. In the case of tumor cells, it induces specific activin/mothers against decapentaplegic homolog 3 (SMAD3) activation without toxicity to normal cells at the concentration of 5 $\mu g \cdot ml^{-1}$. The antitumor effect may be achieved by interrupting the interaction between Cripto-1 and activin receptors of type IIA in the activin signaling pathway [34]. At the concentration of 12.5 μM, alantolactone causes proliferation of non-small cell lung cancer (A549) and morphological changes in cells typical of apoptosis [35]. Alantolactone inhibits both constitutive and inducible activation of STAT3 by stimulating S-glutathioneylation of STAT3 through oxidative stress in A549 cells, and, as the authors of [36] found, induction of oxidative stress is the main mechanism of mediated mitochondrial dysfunction, endoplasmic reticulum, and, as a result apoptosis.

The cytotoxic activity of alantolactones with respect to the K562 line with IC50 values of 0.7 μM for compound **1** and 1.2 μM for isomer **2** was revealed in [37]. The study was supplemented by establishing an ID_{50} for both the natural lactone **2** and its diethylamine adduct on a panel of 9 tumor and normal cell lines (BT20, MCF7, COLO, A549, WiDR, K562, P388, H460, H520 and FF1). These compounds are able to inhibit cell growth in the submicromolar concentration range, but their effect is non-selective. Alantolactone **1** in micromolar concentrations inhibits proliferation and induces apoptosis of both imatinib-sensitive (K562) and resistant myeloid leukemia line (K562r), mainly through inhibition of the NF-κB signaling pathway and a decrease in regulation of the ABL proto-oncogene 1, non-receptor tyrosine kinase (BCR/ABL) [38].

1 **2**

Fig. 2. Structures of isomeric alantolactones

It was shown in [39] that alantolactone induces apoptosis of stem cells of myeloid leukemia by suppressing NF-κB and its downstream target proteins, selectively affects leukemia stem cells with little toxicity to normal cells, in addition to this, dimethylaminoalantolactone inhibits tumor growth *in vivo*. Alantolactone has an antitumor effect on multiple myeloma cells by inhibiting cell proliferation, triggering apoptosis, partially damaging the bone microenvironment, and overcoming resistance to proteasome inhibitors [40]. The ROS-regulated mitochondrial-dependent pathway is involved in the apoptosis of RKO 1 cells by treated with lactone **1**, which is associated with a change in regulation of the pro-apoptotic Bax protein and activation of caspases 3 and 9 [41]. Additionally, alantolactone was found as an inhibitor of promoter activity testicular-specific prosthesis 50 oncogen (TSP50) [42]. It was also shown that alantolactone inhibits thioredoxin reductase, causing oxidative stress-mediated apoptosis of HeLa cells [43]. At concentrations of 10^{-6}-10^{-8} g·ml^{-1} alantolactone does not significantly affect the viability of Vero cells (MTT test) and, based on the analysis of the cytopathic effect, exhibits an antiviral effect and protects cells from damage to HSV-1 [44]. In a dose-dependent manner (20–80 μM), alantolactone induces apoptosis and inhibits the growth of HepG2, Bel-7402, and SMMC-7721 cells due to the regulation of B-cell lymphoma 2 (Bcl-2) and the nuclear pathway factor B (NF-κB) signaling pathway, including activation inducer proteins p53, BCL2 Associated X Protein (Bax), BH3 domain–containing proapoptotic Bcl2 family member (t-Bid), caspases 8, 9 and 3 [45]. The IC_{50} value of lactone **1** for human glioblastoma cell lines U87, U373 and LN229M is 33, 35 and 36 μM, respectively. Against the U87 line, a mechanism of action has been proposed, which contributes to the effect on intracellular glutathione (GSH) and changes in the membrane mitochondrial potential (MMP), activation of the p53 signaling pathway, increase in the Bax/Bcl-2 ratio, release of cytochrome C, destruction of caspases (9 and 3) and poly(ADP-ribose)polymerase (PARP). In this case, the studied lactone does not have a significant toxic effect on normal mouse liver and kidney cells [46]. The continuation of this work was the study of the effect of alantolactone on HepG2 cells and clarification of its mechanism of action [47]. By inhibiting the activity of inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ) via NF-κB/cyclooxygenase-2 -mediated signaling cascades, alantolactone exerts its antitumor effects in human glioblastoma multiforme cells [48]. Apoptosis induced by alantolactone in MDA-MB-231 cells is mediated by activation of the mitochondrial dependent pathway (the ROS/mitogen-activated protein kinase) [49]. It was found in [50] that alantolactone is an inhibitor of autophagy in pancreatic cancer cells and significantly increases the chemosensitivity of these cells to oxaliplatin.

Data on the biological activity of the closest structural analogue of alantolactone – isoalantolactone (**2**) – are often interpreted as part of the structure-activity relationship. A higher antiproliferative activity of alantolactone **1** was noted in [51] compared to isomer **2** against to MK-1, HeLa, and B16F10 cell lines (GI_{50} for lactone **1** is 6.9, 6.9, 4.7, for lactone **2** is 44, 41, and 29 μM, respectively).

Isoalantolactone showed significant cytotoxic activity against SMMC-7721 and HO-8910 cells (IC_{50} is 6.2 and 5.28 μM, respectively), which the authors attribute to the presence in the structure of an α,β-unsaturated lactone moiety as the active center of this molecule. In addition, this compound has a toxic effect on human hepatocytes LO2 (IC_{50} = 9.77 μM) [52]. In this work, *I. japonica* was the raw material for production, however, the content of alantolactone was not mentioned. A number of studies have shown the selective effect of lactone **2** on various tumor lines, for example, on squamous cell carcinoma UM-SCC-10A, due to the induction of apoptosis. In this case, the process is associated with a disruption of the cell cycle in the G1 phase by modulation of factors p53, cyclin dependent kinase inhibitor 1A (p21) and cyclin D. The mitochondrial apoptosis pathway activates the expression of the pro-apoptotic Bax protein, decreases the expression of the anti-apoptotic Bcl-2 protein, releases cytochrome C from mitochondria, and decreases mitochondrial membrane the potential and activation of caspase-3. At the same time, no toxic effect was observed with lactone **2** at concentrations of 25 and 50 μM on mouse splenocytes [53]. For isoalantolactone, the effect of inhibiting the growth of human gastric adenocarcinoma cells (SGC-7901) with an IC_{50} of 40 μM was found, which is associated with inhibition of PI3K/AKT phosphorylation [54], which regulates such cellular processes as: cellular proliferation and growth, apoptosis and rearrangement of the cytoskeleton [55].

Lactone **2** is also an inhibitor of the growth of both androgen-sensitive (LNCaP, IC_{50} = 30 μM) and androgen-insensitive (PC3, IC_{50} = 28 μM and DU-145, IC_{50} = 34 μM) human prostate cancer cells, and may exhibit suppressive effect on the expression of antiapoptotic proteins in PC3 cells. The authors suggest that cell death occurs due to ROS-mediated apoptosis caused by this compound [56]. In addition, a significant inhibition of the growth of S180 ascites tumor in mice *in vivo* was revealed for this natural compound [57].

Lactones **1** and **2** (as well as 5α-epoxyalantolactone **10**) cause a significant increase in the activity of quinone reductase (chemopreventive biomarker) in Hepa1c1c7 and BPRc1 cells [58]. Our research group determined IC_{50} data for alantolactones on the following cell lines: MCF7, MS, HCT116 [59], A549, RD и HEK293 [60].

Other types of activity that alantolactones **1** and **2** have are described. Thus, these compounds exhibit a strong larvicidal effect against dengue carriers *A. albopictus* and *P. grimmii* (LC_{50} less than 12 mg·ml^{-1}) [61]. The study of the antibacterial properties of ala- and isoalantolactone in relation to strains of *E. coli* 25522 and *P. aeruginosa* U-16 did not reveal a delay in the growth of cultures at doses of 250, 500 and 1000 μg·ml^{-1} [62]. It was noted in [63] that compound **2** exerts a strong phytotoxic effect on wheat germ, as well as repellent and toxic activity on rice weevil (*S. oryzae*). Inhibition of growth in respect of a multi-phage plant pest *Spodoptera litura* [64]. Phytoncidal activity is shown for isoalantolactone – it exhibits absolute toxicity at the concentration of 500 μg·ml^{-1} against phytopathogenic fungi *G. graminis* var. *tritici*, *R. cerealis* and *P. capsici*, and for a number of pathogenic bacteria, the minimum inhibitory concentration (MIC) was 125, 425, 150, 150, and 100 μg·ml^{-1} for *B. subtilis*, *E. coli*, *P. fluorescense*, *S. lentus*, and *S. aureus*, respectively [65].

Isoalantolactone, as the authors of [66] found out, is able to enhance glucose uptake in L6 myotubes, and an antidiabetic drug can be developed on its basis.

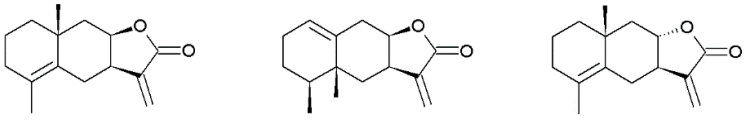
The isoalantolactone molecule can undergo general metabolic reactions: oxidation, hydration, hydrogenation, demethylation, conjugation with cysteine and N-acetylcysteine, as well as the addition of H_2S to the double bond at C-11 [67]. In [68], the metabolic pathway of molecules **1** and **2** was studied, the structure of the main metabolites and the pharmacokinetics of metabolites in rats (conjugation with glutathione and cysteine plays a dominant role in the metabolism of alantolactones). It was found that the main mechanism of penetration (into Caco-2 cells) of lactones **1** and **2** is passive diffusion with active outflow, mediated by proteins associated with multidrug resistance (MRs) and resistance to breast cancer (BCRP) [69].

Thus, the intensive research by many scientific groups of alanto- and isoalantolactone is associated primarily with their high and diverse biological activity.

1.1 α-Methylene-γ-lactones

In addition to isoalantolactone, other isomers of alantolactone containing an exomethylene group in the lactone cycle were found in plants of the genus *Inula* (Fig. 3).

The isomer of alantolactone at the position of the double bond alloalantolactone (**3**) was first isolated from the species *I. racemosa* [70]. It was later detected in *I. helenium* in a mixture with dugesialactone (**4**), which was separated using semi-preparative HPLC [71], and also isolated by column chromatography [72]. Another isomer of alantolactone – 1-desoxy-8-*epi*-ivangustine (**5**) – was found in the plant *I. royleana* DC [73].



3 **4** **5**

Fig. 3. Structures of α-methylene-γ-lactones **3–5**

1.2 α-Methyl-γ-lactones

A wide group of eudesmanolides is composed of analogues of alantolactone containing a methyl group in the lactone cycle instead of the exomethylene (Fig. 4).

Thus, 11,13β-dihydroalantolactone (**6**) was first found in the plant *I. helenium* [74], and was subsequently isolated from the species *I. macrophylla* [75]. The isomeric 11,13β-dihydroisoalantolactone (**7**) containing the exomethylene group in the decalin cycle, like the similar isoalantolactone (**2**), was isolated from the roots of *I. helenium* [76] and *I. japonica* [52]. Neoalantolactone (**8**) in minor amounts was found in two types of elecampane – *I. racemosa* [77] and *I. helenium* [78]. Information on eudesma-4(15),7(11)-diene-8β,12-olide (**9**), isolated from *I. helenium*, was presented in [78], but this lactone was not subsequently mentioned.

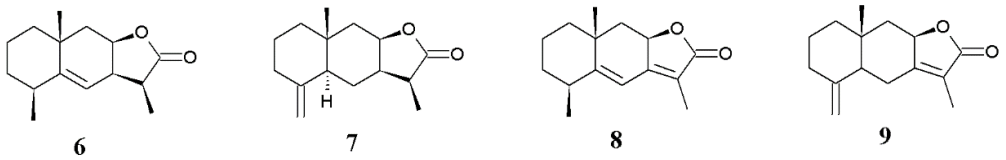


Fig. 4. Structures of α-methyl-γ-lactones **6–9**

2. Epoxy derivatives

Natural epoxidized SL of the *Inula* family usually contain an epoxy cycle in those positions in which alantolactones **1** and **2** have a double bond. Among these compounds, lactones with exomethylene and methyl groups in the lactone cycle are found (Fig. 5).

Thus, 5α-epoxyalantolactone (**10**) isolated from *I. racemosa* [29] and *I. helenium* [72] is alantolactone oxidized via the C=C bond. The new epoxylactone (**11**) was isolated from the *I. racemosa* plant relatively recently [79]. Originally discovered in *Ambrosia artemisioides* 4α,15-epoxyisoalantolactone (**12**) [80] was isolated from *I. helenium* [72]. The hydroxyl group-containing epoxidized lactone **13** and its isomer α-epoxyisotelekin (**14**) were found in *I. racemosa* (Fig. 5) [81]. Lactone **15** was named inujaponin G and isolated from *I. japonica* [82]. Recently, lactone 4α,15α-epoxypulchellin E (**16**) was found in *I. oculus-christi* L [83]. Two lactones of this class contain a methyl group in the lactone cycle: dihydroepoxyalantolactone (**17**) isolated from *I. racemosa* [84], dihydro-4(15)α-epoxyalantolactone (**18**) was found in *I. helenium* [85], and more recently in *I. racemosa* [86].

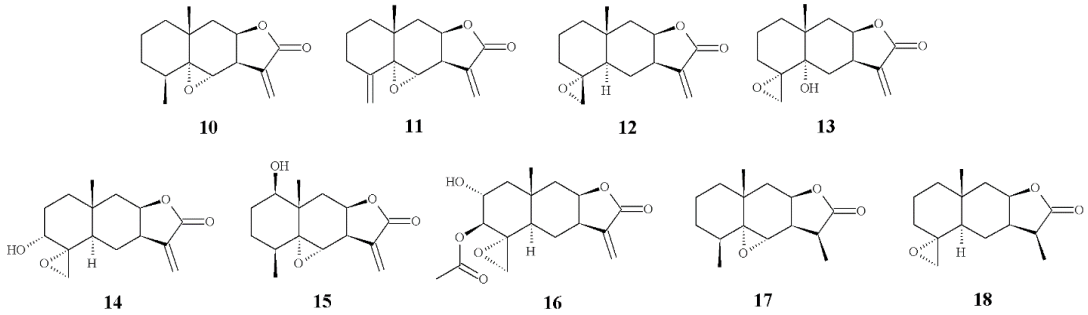


Fig. 5. Structures of epoxy derivatives **10–18**

3. Monohydroxyl-containing lactones and their esters

Some eudesmanolides of the genus *Inula* include various functional groups. Monoalcohols and corresponding esters predominate among such compounds.

3.1 Monohydroxyl-containing α-methylene-γ-lactones

Asperilin (**19**) was first found in *I. helenium* [73], and subsequently in *I. japonica* (Fig. 6) [52].

Lactone **20**, originally isolated from *Iva angustifolia* and named by the authors ivangulin [87], was subsequently discovered in *I. japonica* [52] and in *I. wissmanniana* [88], and most recently isolated from *I. britannica* [89]. The epimer of compound **20**, 8-*epi*-ivangustin (**21**), was isolated from the terrestrial part of the *I. britannica* plant using preparative liquid chromatography [90]. For the first time, this lactone, along with 8-*epi*-isoivangustin (**22**), were isolated from *I. royleana* DC [73]. A lactone similar to 8-*epi*-isoivangustine, but without stereochemistry, was found in *I. grandis* and described under the name grandulin [91]. 1β-Hydroxyalantolactone (**23a**) (Fig. 6) was first isolated from the roots of *I. helenium* [73], and was also found in other elecampane species: in *I. japonica* [52, 92] and *I. britannica* [90]. In addition, recently this lactone was isolated from *I. wissmanniana* [88] and *I. japonica* [82]. The isomer of lactone **23a** at the position of the hydroxyl group is 2α-hydroxyalantolactone (**24**), a component of *I. royleana* DC [73]. Ivalin (**25**), which is isoalantolactone oxidized at position 2, was first found in the plant *Iva microcephala* Nutt. and *Iva imbricata* Walt [93], and was subsequently found in the *Inula* species – *graveolens* [94] and *britannica* [95]. Ivalin acetate (**26**) was isolated from *I. royleana* DC [73]. In [96] the authors confirmed the

hypothesis that the first isolated isotelekin (**27a**) and telekin (**28a**) are products of biological oxidation of isoalantolactone (**2**), also found in *Telekia speciosa* (Schreb) Baumg. Later, isotelekin was also found in *I. racemosa* (Fig. 6) [81]. Both telekin **28a** and its stereoisomer, 5-*epi*-telekin **28b**, were isolated from *I. helenium* [97]. The isomer of lactone **27a** with the "β" orientation of the hydroxyl group was found in *I. britannica* and is named 3-*epi*-isotelekin (**27b**) [98]. This compound was first isolated in *Gaillardia aristata* [99]. Racemosalactone A (**29**) was obtained from *I. racemosa* (Fig. 6) [86] and it is also found in *I. helenium* [97]. The plant *I. viscosa* contains inuloxin C (**30**) [100]. 6α-Hydroxyisoalantolactone (**31**) was isolated from *I. hupehensis* [101]. Note that previously, lactone **31** was found in *Liriodendron tulipifera* [102]. 6α-Hydroxyisoalloalantolactone (**32**) was first described by the authors of [103]. Recently, this compound was isolated from *I. hupehensis* [101].

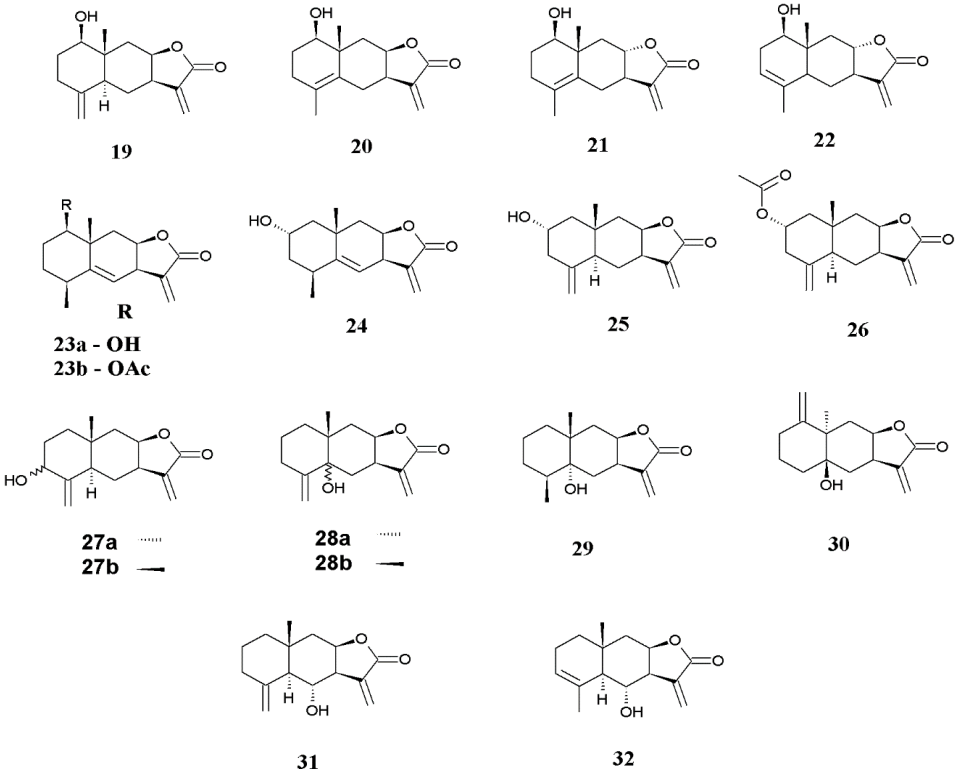


Fig. 6. Structures of hydroxy-substituted α-methylene lactones **19–32**

3.2 Monohydroxyl-containing α-methyl-γ-lactones

A number of hydroxyl-containing SL having a methyl group instead of an exocyclic double bond were found in plants of the *Inula* family. For example, a mixture of 1β-hydroxy-4β,11αH-eudesm-12,8α-olide (**33**) with 2-desacetoxy-11α,13-dihydroxanthuminol (Fig. 7) [104].

1β-Hydroxy-4α,11αH-eudesma-5-en-12,8β-olide (**34**) were found in two species of elecampane – *I. thapsoides* [105] and *I. japonica* [52], and its epimer at the position of the hydroxyl group 1α-hydroxy-11α,13-dihydroalantolactone (**35**) – only in the first of the mentioned plants [105]. 11,13-dihydroivalin (**36**) was isolated from *I. graveolens* (Fig. 7) [94] and recently lactone **36** was also found in *I. racemosa* [106] and isolated from the roots of *I. helenium* [57]. The isomer of lactone **36** at the position of the double bond in the decalin fragment is 11,13-dihydro-2α-hydroxyalantolactone (**37**), which was first found in the plant *Francoeuria crispa*, growing in Saudi Arabia [107]. Subsequently, lactone **37** was isolated from *I. racemosa* [29]. 3β-Hydroxy-11α,13-dihydroalantolactone (**38**), isolated from *I. racemosa*, was declared by the authors of [108] as a new eudesmanolide. This lactone was also found in *I. lineariifolia* [109]. The stereoisomeric 3α-hydroxy-11βH-eudesm-5-en-8β,12-olide (**39**) was found in *I. helenium* [28]. A similar lactone with undetermined stereochemistry of the methyl group at C-11 was cited by authors as new [110]. Lactones **40** and **41** contain an OH group not in the hydrocarbon fragment, but in the lactone cycle (Fig. 7) – racemosalactone C (**40**) [86] and 11α-hydroxy-eudesm-5-en-8β,12-olide (**41**) [29, 86, 108] are components of *I. racemosa*.

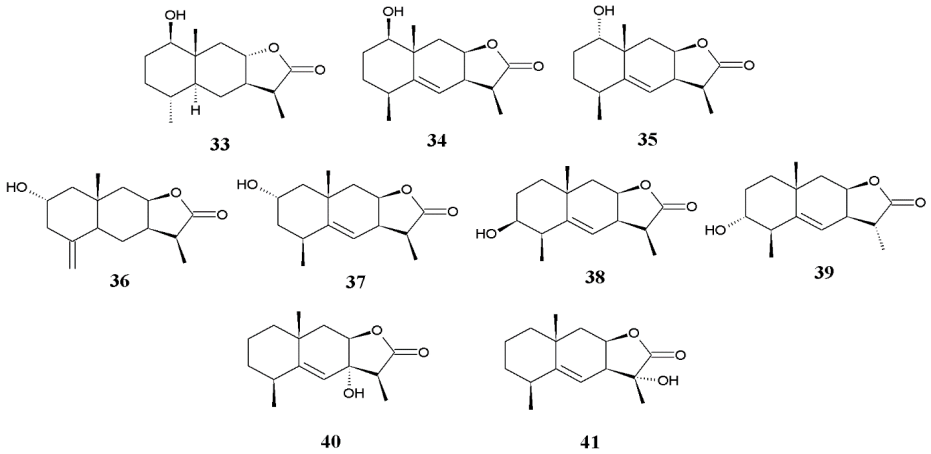


Fig. 7. Structures of hydroxy-substituted α-methyl lactones **33**–**41**

3.3 γ-Lactones with a hydroxyl group in the side chain

Described eudesmane alcohols in which the hydroxyl group is not connected to the tricyclic structure, but is located in the peripheral substituents (Fig. 8). Therefore, from the roots of *I. helenium*, 15-hydroxy-11βH-eudesma-4-en-8β,12-olide (**42**) [28] and eudesma-5,7(11)-diene-8β,12-olide (**43**) [78] was isolated. Compound **43a** and its stereoisomer with a trans-connection of the lactone and decalin cycles – (4S,8S,10R)-12-hydroxyeudesma-5(6),7(11)-diene-12,8-olide (**43b**) – were found in the plant *I. racemosa* [111].

Macrophyllilactone E (**44a**) and its acetate **44b** contain an unsaturated lactone cycle, which is rare in natural sesquiterpenoids (Fig. 8). The first was isolated from elecampane species – *I. macrophylla* [112] and *I. racemosa* [29]. Also found in *I. helenium* [97, 113]. 13-Acetyloxy-5,7(11)-eudesmadien-12,8-olide (**44b**) was recently discovered in *I. helenium* [78], and *I. racemosa* [106].

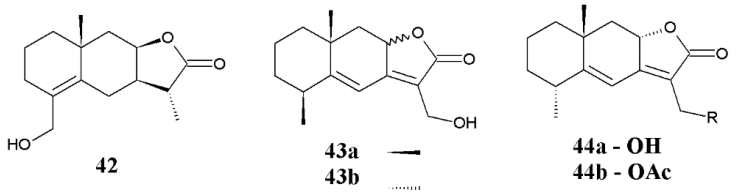


Fig. 8. Structures of hydroxy-substituted lactones **42**–**44**

4. Monohydroxyl-containing eudesmanes with a different connection of the lactone cycle

In plants of the genus *Inula*, several monohydroxyl-containing eudesmanolides were also found with a different lactone and decalin cycle from the C-6 – C-7 bond (Fig. 9). The authors of a study on the antitumor properties of lactones from *I. helenium* and *I. japonica* found santamarin (**45**) in *I. japonica* flowers [57]. This lactone was originally isolated from *Chrysantemum parthenium* [114]. It is also found in the leaves of *I. montana*, as well as its isomer, reynosin (**46**) [115], which was first discovered in *Ambrosia confertiflora* [116]. 11α,13-Dihydro-α-cyclocostunolide (**47**) was first found in wormwood *Artemisia herba-alba* [117], and later in elecampane *I. helenium* [28]. In the latest work, its isomer, 11α,13-dihydro-β-cyclocostunolide (**48**), which was previously isolated from the small-cone *Conyza aegyptiaea* [118] was also described.

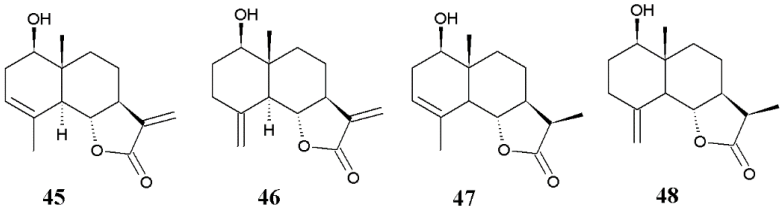


Fig. 9. Structures of α-methylene and methyl lactones **45**–**48**

5. Polyhydroxyl-containing lactones and their esters

In plants of the genus *Inula*, eudesmanolides containing more than one hydroxyl group or an ester function were found (most often two). Sesquiterpenoids with a large number of OH groups are extremely rare. As in the case of other eudesmane lactones, an exomethylene or methyl group is present in the five-membered ring of such compounds.

5.1 Polyhydroxyl-containing α-methylene-γ-lactones

A large number of eudesmane type SL contain two hydroxyl groups, one usually located at the C-1 atom and having an α configuration, and the other can occupy positions 2, 3, 5 with different stereochemistry. Vicinal diols **49** and **50** (Fig. 10) differ not only in the configuration of OH groups (cis and trans, respectively), but also in the arrangement of the double bond in the decalin fragment. 1β,2β-Dihydroxyeudesma-4(5),11(13)-diene-12,8β-olide (**49**) and its isomer isoivasperin (**50**) were isolated from *I. japonica* [92]. Lactone **50** was first discovered in the flowering plant *Hyaloseris andrade-limae*, common in the Andes [119].

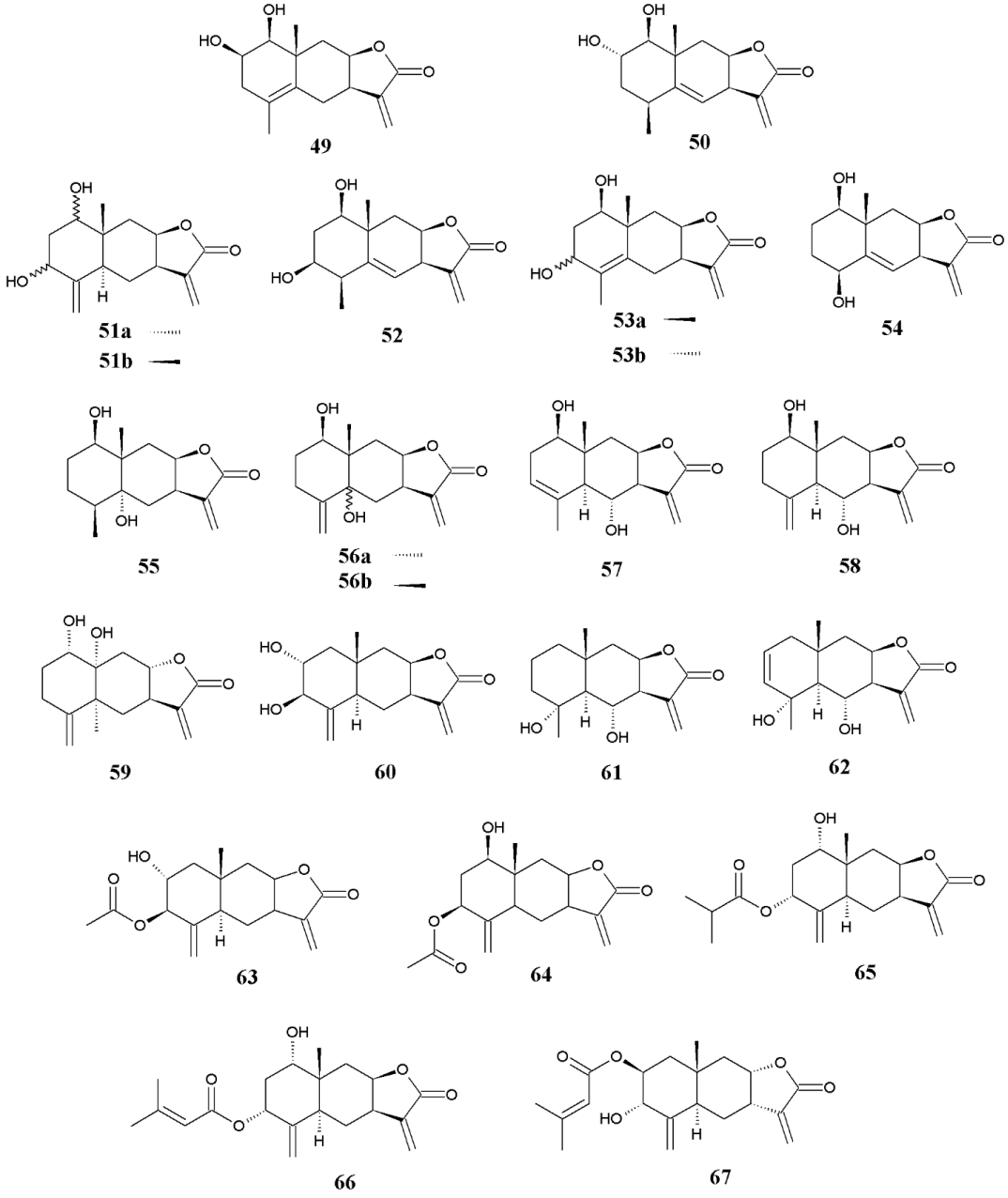


Fig. 10. Structures of diol α-methylene lactones **49**–**62** and containing ester group **63**–**67**

Eudesmanolides **51**–**53** contain the second hydroxyl group in the *meta* position, and lactone **54** in the *ortho* position (Fig. 10). Granilin (**51a**), originally found in *I. grandis* [120] was also found in *I. falconeri* [104]. The stereoisomeric granilin at the position of the hydroxyl groups of 1,3-*epi*-granilin (**51b**) was found in *I. Britannica* [121]. 1β,3β-Dihydroxy-4αH-eudesma-5(6),11(13)-dien-12,8α-olide (**52**) and its isomer 1β,3β-dihydroxy-eudesma-4(5),11(13)-dien-12,8β-olide (**53a**) was isolated from *I. japonica* [92]. The authors of [70] reported data on the isomers of 1β,3α-dihydroxyeudesma-4(5),11(13)-dien-12,8β-olide (**53b**), 1β,4β-dihydroxyeudesma-5(6),11(13)-dien-12,8β-olide (**54**) and (1R,4S,5R,7R,8R,10S)-1,5-dihydroxyeudesm-11(13)-en-12,8-olide (**55**) (Fig. 10). Lactone **55** is also found in *I. wissmanniana* and is described under the name 4α,15-dihydro-5α-hydroxy-asperilin [88]. 5α-Hydroxyasperilin (**56a**), isolated from *I. japonica* and containing the exomethylene group at C-4, was originally found in *Telekia speciosa* [122], and its content in *I. wissmanniana* was reported in [88]. The stereo-isomer at the hydroxyl group at C-5 – 5β-hydroxyasperilin (**56b**) was found in *I. japonica* [82], as well as in *I. britannica* [89]. 1β,6α-Dihydroxy-5αH-eudesma-3(4),11(13)-dien-12,8β-olide (**57**) and 1β,6α-dihydroxy-5αH-eudesma-4(15),11(13)-dien-12,8β-olide (**58**) from *I. britannica* are isomers of lactone **56** at the position of hydroxyl and methylene groups [123]. Eremobritanilin (**59**) is found in *I. britannica* var. *chinensis* (Fig. 10) [124]. As shown in Fig. 10, lactones **60**–**62** lack an axial OH group at position 1. These compounds include the vicinal diol pulchellin C (**60**). It was first isolated from the plant *Gaillardia pulchella* Foug. and before the publication of the work [125] it was assigned to pseudoguaninolides. Later, its structure was refined, and this lactone was found in various representatives of elecampane: in *I. montana* [126], *I. Britannica* [127], *I. caspica* [128] and *I. oculus-christi* [83]. In lactones **61** and **62**, OH groups are in different six-membered rings. 6α-Hydroxy-4-*epi*-septuplinolide (**61**), containing a methyl and hydroxyl group at one carbon atom, was isolated from the plant *I. hupehensis* [101]. Initially, lactone **61** was found in a tulip tree (*Liriodendron tulipifera)* [102], and later found in *I. britannica* [129]. A similar lactone containing a double bond at the C-2 atom – 4α,6α-dihydroxy-5-αH-eudesma-2(3),11(13)-dien-12,8β-olide (**62**), is isolated from *I. hupehensis* [101]. In the lactones of **63**–**67** OH groups are esterified and the remains of acetic, isobutyric and methacrylic acids act as ester groups (Fig. 10). Similarly to the situation with pulchellin C, pulchellin E (**63**) was referred to the pseudo-guainolide type of SL before the publication of [125]. The presence of compound **63** in plants of the genus *Inula* was reported in [126] (*I. montana)* and [130] (*I. oculus-christi*). Isomers of lactone **63** were isolated from *I. montana* according to the position of the hydroxyl group – 1β-hydroxy-3β-acetoxy-eudesma-4(15),11(13)-dien-12-8β-olide (**64**) [126], and from *I. falconeri* – 1α-hydroxy-3α-isobutyryloxy-isoalantolactone (**65**) [104]. Note that lactone **65** was first found in *Blumea densiflora* [131]. 1α-Hydroxy-3α-senecioyloxyisoalantolactone (**66**) was found in *I. falconeri* [104]. Article [98] establishes the content of 1α-hydroxy-3α-senecyioloxyisoalantolactone (**67**) in the ground part of *I. britannica*. The structure of this compound is distinguished by the α-junction of the decalin and lactone cycles, which is rare in the molecules of the eudesmane SL.

5.2 Polyhydroxyl-containing α-methyl-γ-lactones

Along with polyhydroxyl-containing α-methylene-γ-lactones, representatives of lactones of the genus *Inula* likewise contain α-methyl groups in the lactone cycle. In compounds **68**–**71**, one of the hydroxyl groups is in position 1, and in lactone **69**, in contrast to other examples, it occupies a *pseudo*-equatorial position (Fig. 11).

Three of the above lactones are 1β,3α-dihydroxy-11αH-eudesma-4(5)-en-12,8β-olide (**68**), 1β,5α-dihydroxy-4α,11αH-eudesma-12,8β-olide (**70**) and 1β,5α-dihydroxy-11αH-eudesma-4(15)-en-12,8β-olide (**71**) were identified in *I. japonica* Thunb [92]; also present are lactones **72** (inujaponin D – 1β,11α-dihydroxyeudesma-5-en-12,8β-olide) and **73** (inujaponin E – 1β,4α-dihydroxy-11αH-eudesma-12,8β-olide) [82]. 1β,4α-Dihydroxy-11α,13-dihydroalantolactone (**69**) was isolated from *I. thapsoides* [105]. 4α,6α-Dihydroxy-5α,11αH-eudesma-12,8β-olide (**74**) was isolated from *I. hupehensis* (Fig. 11), in which OH groups are located at C-4 and C-6 atoms [101]. An unusual position of the OH group at the α-carbon atom in the furanone cycle was recorded in lactones **75** and **76**. Interestingly, lactone **74** was found in the roots of *I. helenium* [28] and the racemosalactone D (**76**), which is close in structure, is found in *I. racemosa* [86]. 4α,13-Dihydroxy-5,7(11)-eudesmadiene-12,8-olide (**77**) was isolated from the same elecampane (Fig. 11) [106]. Macrophyllilactone F (**78**) and its acetate (**79**) were identified in *I. macrophylla* [112]. Recently, compound **76** was isolated from *I. helenium* [97].

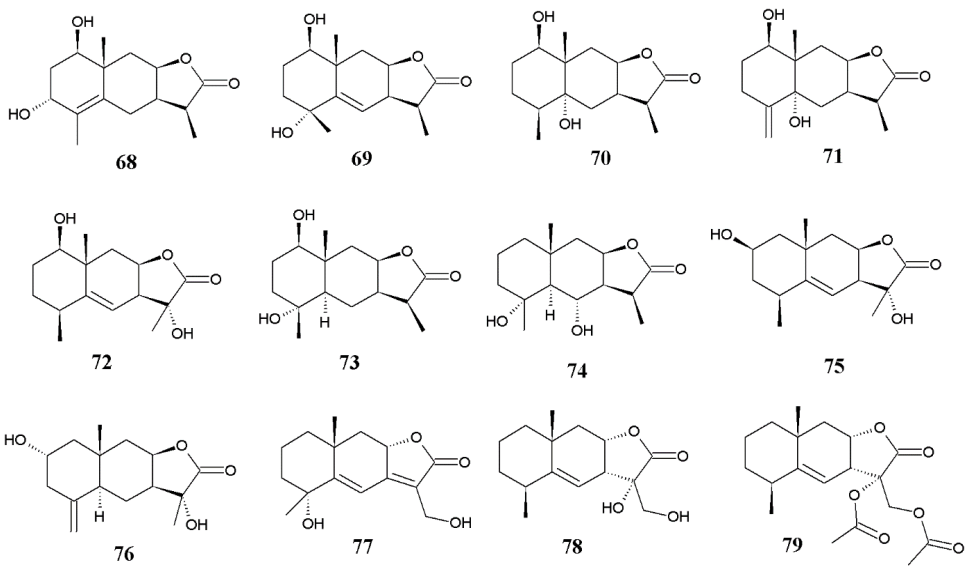


Fig. 11. Structures of polyhydroxy-α-methyllactones **68**–**79**

5.3 Polyhydroxyl-containing eudesmanes with a different conncection of the lactone cycle

In addition to the above examples of polyhydroxyl-containing SL with a position of lactone and decalin cycles at the C-7–C-8 atoms, a small number of their analogues are known via the C-6–C-7 bond. In lactones **80**–**84** lactone and decalin cycles have a trans-junction, the two hydroxyl groups are in positions 1 and 8; the first two containing exomethylene, and the last of the mentioned methyl group in the lactone cycle (Fig. 12). 8-*epi*-Dentatin A (**80**) was first described in [132], and later found in *I. japonica* [133] and *I. salsoloides* [134]. A compound with a similar formula is described by the authors using the name (8β)-8-hydroxysantamarin [135]. The isomer of lactone **80** is structure **81**, originally described in [136] and isolated from *I. japonica* [133].

1β-Hydroxyarbusculin A (**82**) was isolated from *I. montana* [116]; inucrithmolide (**83**) with two different ester groups from *I. crithmoides* [137], and 8-*epi*-11β,13-dihydrodentatin A (**84**) identified in *I. salsoloides* [134].

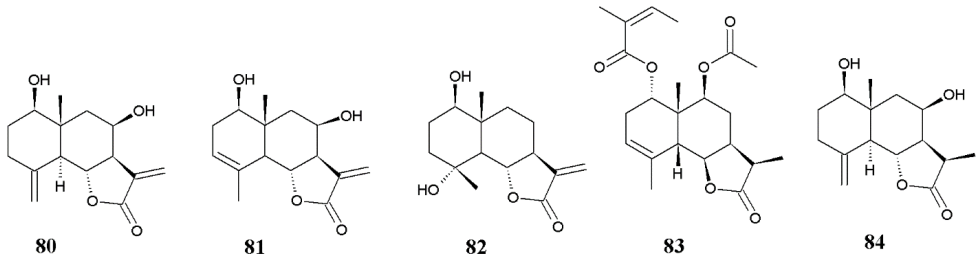
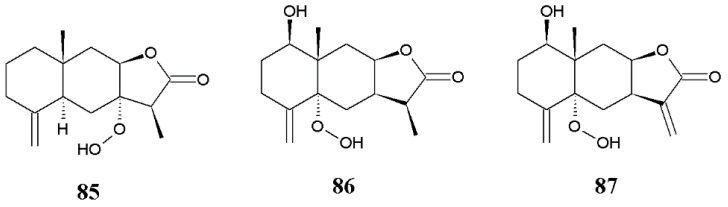


Fig. 12. Structures of dihydroxy (acetoxy) lactones **80**–**84** with a C-6–C-7 cycle connection

6. Eudesmanes with other functional groups

6.1 Lactones with a peroxide group

Examples of eudesmane SL containing a peroxide fragment as a functional group are described (Fig. 13). Thus, a compound with structure **85** was found in *I. racemosa* [81], 5-hydroperoxy-1-hydroxyeudesma-4(15)-eno-12,8-lactone (**86**) and (5a)-5-hydroperoxyasperylin (**87**) – in *I. japonica* [135]. Lactone **87** was first discovered in one of the representatives of the species *Eriocephalus* [138].



85 **86** **87**

Fig. 13. Structures of peroxylactones **85**–**87**

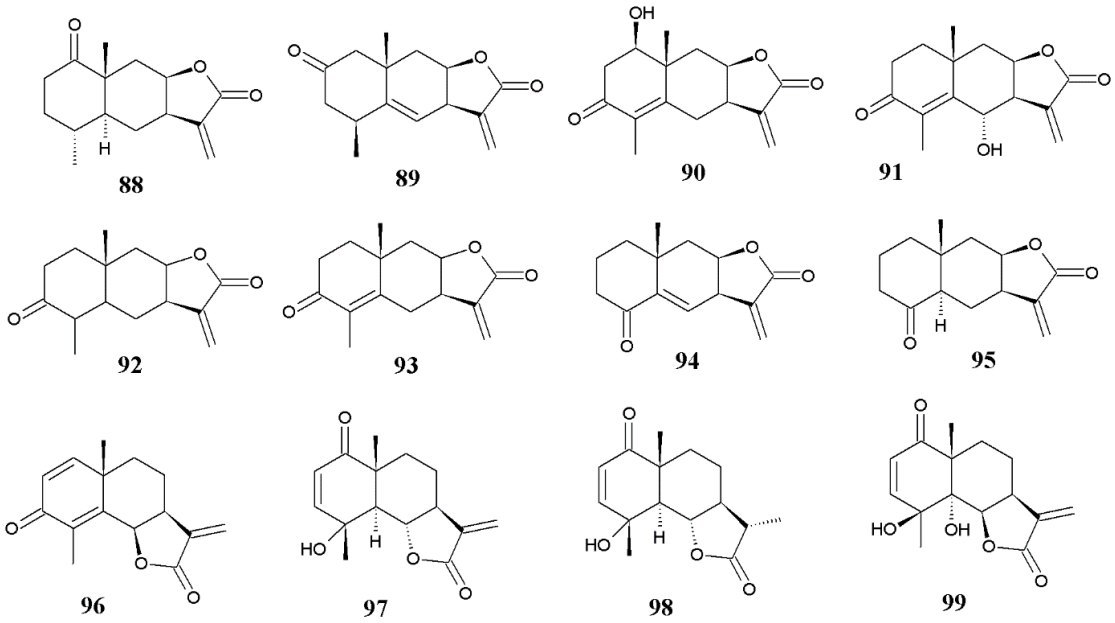
6.2 Lactones with a ketone group

A few examples described in the specialized literature indicate the content of eudesmanolides with a ketone functional group in the plants of the genus *Inula*. The oxygen atom of the carbonyl group can occur in positions 1–3. One such representative is 1-oxo-4-*epi*-alantolactone (**88**), isolated from *I. racemosa* (Fig. 14). Oxoalantolactone (**89**), found in *I. japonica* [135], contains a CO group at position 2.

Two 3-oxoeudesmanolides **90** and **91** are described, in the molecules of which there is also an additional hydroxyl group: 1β-hydroxy-3-oxo-eudesma-4(5),11(13)-dien-12,8β-olide (**90**) and 3-oxo-6α-hydroxyeudesma-4(5),11(13)-dien-12,8β-olide (**91**) from *I. japonica* [92] and *I. hupehensis* [101], respectively. Graveolide (**92**), also containing a ketone group at the C-3 atom, was discovered in *I. graveolens* as early as 1973 (Fig. 14) [139]. 3-Oxodiplofillin (**93**) was first found in *Chiloscyphus polyanthus* [140], and subsequently in *I. helenium* [113, 141]. Noralantolactone (**94**) and norisoalantolactone (**95**) found in *I. helenium* [142], differ from their analogues by the presence of an oxygen atom at position 4. Despite the structural similarity, they are not related to sesquiterpenoids.

Biologically active oxo-containing eudesmanolides of the genus *Inula* are also represented by structural types in which the lactone cycle is joined to the decalin via the C-6–C-7 bond (Fig. 14). For example, 3-oxoeudesma-1,4,11(13)-trien-12,6β-olide (**96**) isolated from *I. wissmanniana* was found [88].

Arglanin (**97**) was originally found in wormwood *Artemisia douglasiana* [143]. Recently, this lactone was discovered in *I. hupehensis* [101]. The SL tauremisin (**98**), known for the first time from *Artemisia taurica* Willd [144, 145], was subsequently recorded in *Artemisia vulgaris* and described under the name "vulgarin" [146] known since 1960. This lactone is reportedly identified in one species of elecampane – *I. hupehensis* [101]. 4β,5α-Dihydroxy-1-oxoeudesma-2,11(13)-diene-12,6β-olide (**99**), obtained from *I. wissmanniana*, along with the ketone function contains two hydroxyl groups at positions 4 and 5 [88].



88 **89** **90** **91**

92 **93** **94** **95**

96 **97** **98** **99**

Fig. 14. Structures of oxolactone **88**–**99**

7. Eudesmanes with an unusual structure

This section presents examples of SL isolated from plants of the genus *Inula*, with structures rare for compounds of this class, e.g., in lactones **100** and **101**, one of the six-membered cycles is aromatic (Fig. 15). These compounds were first characterized as derivatives of santonin and were named 11,13-dehydroisohyposantonin (**100**) and isohyposantonin (**101**) [147]. They have recently been isolated from *I. wissmanniana* Hand.-Mazz. [88].

The isomeric 1,4-dienes – isoalantodiene (**102**) and alantodiene (**103**) are components of *I. racemosa* [84]. The first SL with an amino acid residue (Fig. 15), isoheleproline (**104**), was recently isolated from the plant *I. helenium* [141]. In structure, it is an adduct of isoalantolactone **2** and proline. Such compounds were first discovered in *Saussurea lappa* [148]. Two chlorine-containing SL were isolated from plants of the genus *Inula*. Racemosalactone B (**105a**) was found in the *I. racemosa* plant [86]. In *I. helenium* 11β-hydroxy-13-chloroeudesma-5-en-12, 8-olide (**105b**) was found [97]. An inunal (**106**), in the structure of which an aldehyde group is present, was found in *I. racemosa* [149], and its isomer, isoinunal (**107**), was later isolated from the same plant source [150]. The acetal group includes (4S,8R,10R)-13-dimethoxyeudesma-5(6),7(11)-diene-12,8-olide (**108**), obtained from *I. racemosa* (**Fig. 15**) [111]. A very rare lactone, macrophyllilactone G (**109**), containing two hydroxyl and two hydroxymethyl groups, was isolated from *I. macrophylla* [112].

Thus at least 116 SL of the eudesmane structural type are present in plants of genus Inula. Some of them have been investigated in relation to different biological models, in particular – against to cell lines. IC_{50} values for natural SL given in this review are summarized in Table 1.

The content of the eudesmane SL in plants of the genus *Inula* is given in Table 2. Based on the analyzed literature data, it can be concluded that the most studied are such types of elecampane as *I. helenium, I. racemosa* and *I. japonica*. In these plants, the largest amount of SL of the eudesmane structure was found. Of course, the growth area of plant influences the content of one or another compound, but this goal was not pursued in this review.

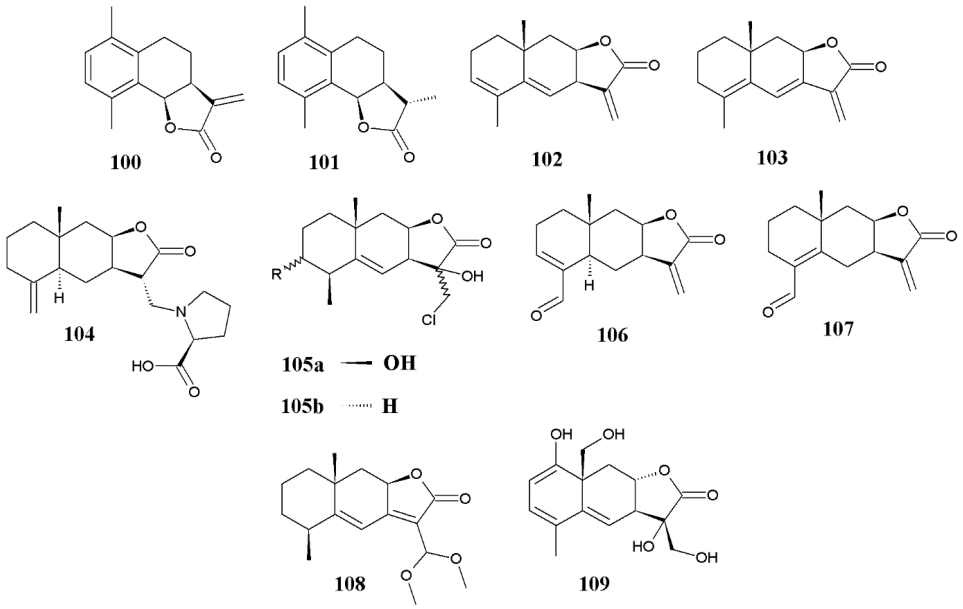


Fig. 15. Structures of unsaturated lactones **100**–**103** and with an unusual structure **104–109**

Table 1. IC_{50} indices on various lines for natural SL

SL	Cell line	IC_{50}, μM	Ref.	SL	Cell line	IC_{50}, μM	Ref.
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*
1	K562	1	[37]	**23a**	HepG2	7	[88]
		3	[39]		HeLa	34	[88]
	K562/A02	3	[39]		PC-3	22	[88]
	HL-60	3	[39]		MGC-803	3	[88]
	HL60/ADR	3	[39]		HL-60	4	[82]
	THP-1	2	[39]		SMMC-7721	4	[82]
	KG1a	3	[39]		A549	3	[82]

Continuation of table 1

1	2	3	4	5	6	7	8
	U87	33	[46]		MCF-7	4	[82]
	U373	35	[46]		SW-480	6	[82]
	LN229M	36	[46]	**25**	P-388	2	[94]
	MK-1	7	[51]		KB-3	7	[94]
	HeLa	7	[51]		KB-V1	5	[94]
	B16F10	5	[51]	**26**	P-388	1	[94]
	A549	45	[36]		KB-3	8	[94]
		32	[60]		KB-V1	7	[94]
	OPM2	4	[40]	**28a**	KG1a	46	[97]
	MM1S	4	[40]	**29**	A549	2	[86]
	MM1R	3	[40]	**29**	HepG2	3	[86]
	RPMI8226	4	[40]	**29**	HT1080	2	[86]
	NCI-H929	4	[40]	**36**	P-388	48	[94]
	IM-9	3	[40]		A549	25	[106]
	U266	6	[40]		Bel7402	25	[106]
	U87	20	[48]		BGC823	34	[106]
	U251	16	[48]		HCT-8	27	[106]
	U118	29	[48]		A2780	28	[106]
	SH-SY5Y	24	[48]	**37**	A549	28	[106]
	MDA-MB-231	10	[49]		Bel7402	32	[106]
	THP-1	2	[39]		HCT-8	27	[106]
	KG1a	3	[39]		A2780	39	[106]
	RD	10	[60]	**40**	A549	27	[86]
	HEK293	74	[60]	**41**	BEL-7402	38	[108]
	MCF7	33	[59]		HCT-8	37	[108]
	MS	23	[59]	**44a**	KG1a	49	[97]
	HCT116	13	[59]	**45**	SHIN3	12	[57]
2	K562	1	[37]		HOC-21	43	[57]
	MK-1	44	[51]	**53a**	HL-60	17	[82]
	HeLa	41	[51]		SMMC-7721	20	[82]
	B16F10	29	[51]		A549	18	[82]
	SMMC-7721	6	[52]		MCF-7	13	[82]
	HO-8910	5	[52]		SW-480	15	[82]
		23	[151]	**56a**	HepG2	11	[88]
	LO2	10	[52]		PC-3	22	[88]
	SGC-7901	40	[54]		MGC-803	10	[88]
	LNCaP	30	[56]		HL-60	17	[82]
	PC3	28	[56]		SMMC-7721	9	[82]
	DU-145	34	[56]		A549	8	[82]
	RD	5	[60]		MCF-7	11	[82]
	A549	37	[60]		SW-480	17	[82]
	HEK293	36	[60]	**56b**	HL-60	23	[82]
	MCF7	41	[59]		SMMC-7721	18	[82]
	MS	44	[59]		A549	18	[82]
	HCT116	38	[59]		MCF-7	11	[82]
	KG1a	4	[97]		SW-480	15	[82]
	HEC-1	33	[57]	**61**	HL-60	14	[129]
	HOC-21	20	[57]		MCF7	39	[129]
	HAC-2	12	[57]		HCT-15	15	[129]
7	B16F10	44	[51]		Malme-3M	17	[129]
10	MK-1	6.9	[51]	**80**	HL-60	12	[82]
	HeLa	6.5	[51]		SMMC-7721	17	[82]
	B16F10	3.6	[51]		A549	15	[82]
	MCF7	29	[152]		MCF-7	19	[82]
	MS	32	[152]		SW-480	12	[82]
	HCT116	14	[152]	**81**	HL-60	11	[82]
	K562	4	[152]		SMMC-7721	21	[82]
	KG1a	3	[97]		A549	20	[82]
17	A549	64	[86]		MCF-7	20	[82]
	HepG2	100	[86]		SW-480	13	[82]

End of table 1

1	2	3	4	**5**	6	7	8
	HT1080	68	[86]	**96**	HepG2	3	[88]
20	HepG2	39	[92]		HeLa	46	[88]
	HeLa	49	[92]		MGC-803	3	[88]
	PC-3	44	[92]	**99**	HepG2	23	[88]
	MGC-803	13	[92]		PC-3	41	[88]
	HL-60	18	[82]		MGC-803	12	[88]
	SMMC-7721	14	[82]	**100**	HepG2	3	[88]
	A549	13	[82]		HeLa	6	[88]
	MCF-7	18	[82]		PC-3	5	[88]
	SW-480	13	[82]		MGC-803	3	[88]
				105a	A549	123	[86]

Table 2. The content of the eudesmane SL in plants of the genus *Inula*

Source	SL, Reference
I. helenium	**1**,**2**,**3**,**4** [71, 72]; **6** [74]; **7** [76]; **8**,**9**,**43**,**44b** [78]; **10**,**12** [72]; **18** [85]; **19**,**23a** [73]; **28a**,**28b**,**29**,**76**,**105b** [97]; **39**,**42** [28]; **44a** [97, 113]; **47**,**74** [28]; **93** [113, 141]; **94**,**95** [142]; **104** [141]
I. racemosa	**1**,**2** [29, 30]; **3**,**53b**,**54**,**55** [70]; **8** [77]; **10**,**37**,**44a** [29]; **11** [79]; **13**,**14**,**27a** [81]; **17, 102**,**103**,**105a**,**102**,**103** [84]; **18**,**29**,**40**,**75**,**76**,**105a** [86]; **36**,**77**,**88** [106]; **38** [108]; **41** [29, 86, 108]; **43a**,**43b**,**108** [111]; **44b** [106]; **85** [81]; **106** [149]; **107** [150]
I. royleana	**1**,**2** [31]; **5**,**21**,**22**,**24**,**26** [73]
I. macrophylla	**6** [75]; **44a**,**78**,**79**,**109** [112]
I. japonica	**7**,**34**,**19**,**20** [52]; **2**,**15**,**23b**,**56b**,**72**,**73** [82]; **23a** [52, 92]; **45** [57]; **49**,**50**,**52**,**53a**,**68**,**70**,**71**,**90**,**91** [92]; **56a** [122]; **80**, **81** [133]; **80**,**86**,**87**,**89** [135]
I. oculus-christi	**16** [83]; **63** [130]
I. wissmanniana	**20**,**23a**,**55**,**56a**,**96**,**99**,**100**,**101** [88]
I. britannica	**20**,**56b** [89]; **21**,**23a** [90]; **25** [95]; **27b**,**67** [98]; **51b** [121]; **61** [129]
I. grandis	**22** [91]; **51a** [120]
I. graveolens	**25**,**36** [94]; **92** [139]
I. viscosa	**30** [100]
I. hupehensis	**31**,**32**,**61**,**62**,**74**,**90**,**91**,**97**,**98** [101]
I. falconeri	**33**,**51a**,**65**,**66** [104]
I. thapsoides	**34**,**35**,**69** [105]
I. lineariifolia	**28** [109]
I. montana	**45**,**46** [115], **63**,**64** [126], **82** [113]
I. salsoloides	**80**,**84** [134]
I. crithmoides	**83** [137]

Conclusion

Eudesmane SL of plants of the genus *Inula* represent an extensive group of natural compounds. The investigated sources of literature indicate that at least 116 SL of the eudesmane structural type are present in plants of this genus. Most of them contain an exocyclic methylene group activated by a conjugated lactone carbonyl function. In addition to the highly reactive double bond, these lactones may include hydroxyl, epoxy, peroxide, and ketone groups. The most characteristic annelation of the decalin fragment to the γ-lactone cycle is via the C-7–C-8 bond; joining at the C-6–C-7 bond is less common.

Alanto- and isoalantolactone are well studied both in plant raw material and specific activity thereof. This is due primarily to the history of these compounds, the ease of isolation and chemical modification. However, often the data on the antitumor effect of lactones **1** and **2** are contradictory in different research groups.

A comparison of the structures of the lactones presented in this review allows us to conclude that several reaction centers are present in the composition of many molecules. Together with the published data on the study of the effect on the cell lines *in vitro*, eudesmane-type SL can be considered as biologically active natural compounds, promising development of fundamentally new target-oriented drugs based on them.

The activity of lactones can be associated with the main chemical properties caused by the structural features of this class of compounds: the ability to act as an alkylating agent, the lipophilicity of the side chain, and also the dependence on the geometry of the molecule and its electronic characteristics. The primary basis of the diverse spectrum of biological action of SL, as mentioned above, is the presence of an α-methylene-γ-lactone functional

group in their structure. However, the transition to the stage of clinical studies of individual representatives of these compounds is hindered by their high hydrophobicity and non-selective binding (as Michael acceptors) in undesirable targets. In this regard, the development of approaches that will overcome these limitations remains relevant.

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