

# Chlorine-Containing Sesquiterpenes of Higher Plants

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(Received January 21, 2002)

## Abstract

The structures of chlorine-containing sesquiterpenes produced by higher plants and data on the biological activity of some compounds are presented.

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## INTRODUCTION

Sesquiterpenes as a class of terpenoids are widespread in nature. They are produced by plants, microorganisms and inhabitants of the world ocean [1]. Sesquiterpenes containing haloid atoms have begun to be studied comparatively recently. The data available nowadays witness to the fact that halogenized sesquiterpenes, unlike halomonoterpenes and haloditerpenes produced almost exclusively by marine organisms [2, 3], are found among the metabolites of higher plants. In the present review, the structures and partly the biological activity of chlorine-containing sesquiterpenes isolated from plants widespread in nature [4] are considered.

## SESQUITERPENIC LACTONES

The first chlorine-containing sesquiterpenoids were eupachlorin (**1**), its acetate (**2**) and eupachloroxin (**3**) isolated in 1968 from the plant *Eupatorium rotundifolium* [5, 6]. All the three compounds have supplemented the series of sesquiterpenic lactones characterized by a high anticancerogenic activity.

The genus *Centaurea* belongs to perennial grasses widespread in Eurasia, North America and Africa. More than 500 species of this genus are known. In West Siberia, *Centaurea adpressa* Ledeb., *C. Cyanus* L., *C. Jacea* L., *C. Scabiosa* L. and *C. Sibirica* L. grow.

Plants of the genus *Centaurea* have turned out to be producers of a whole group of chlo-

rine-containing sesquiterpenic lactones. As one can see from the structures presented herein below, sesquiterpenic lactones from plants of the genus *Centaurea* belong to Guianic structural type. Their characteristic property is that they belong to esters.

In this connection, the lactones of *Centaurea* may be conditionally divided into three groups depending on the position of the chlorine atom. So, lactones of group 1 contain the chlorine atom in the guianic skeleton. In lactones of group 2, the chlorine atom is situated in the acid substituent. Sesquiterpenes of group 3 are esters of chlorine-containing guianolides and chlorine-containing oxyacids.

*Centaurea repens* which is poisonous to cattle contains centaurepensin (**4**) whereby its toxicity is mainly accounted for [7, 8]. The same lactonoester has been isolated from the plant *C. solstitialis* [9]. The mentioned plant *C. repens* produces also chlororepdiolide (**5**) [10].

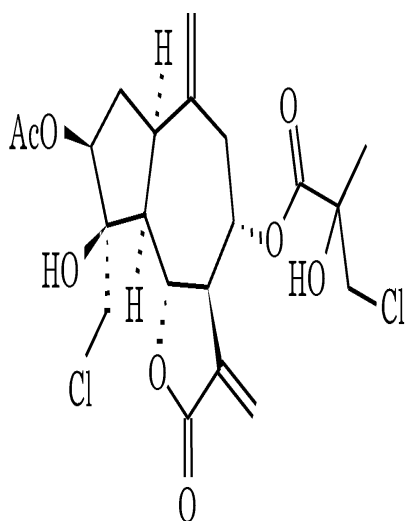
Lactone acroptilin (**6**) or chlorhyssopifolin C has been found in plants *C. repens*, *C. hyrcanica* [11, 12] and *C. hyssopifolium* [13–15].

Extracts from the plants *C. hyssopifolium* [14] and *C. linifolia* [16] contain chlorhyssopifolins B (**7**), D (**8**) and E (**9**). The plant *C. linifolia* is also a producer of linichlorins A (**10**), B (**11**) and C (**12**) [16].

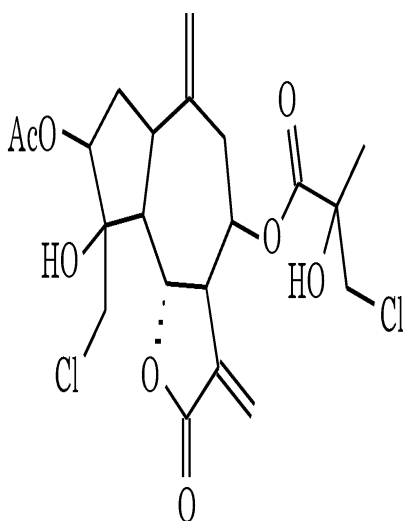
Salegin (**13**) isolated from the plant *Saussurea elegans* [17] is an epimer of linichlorin C. Solstitiolide (**14**) and episolstitiolide (**15**) have been isolated from the plant *C. solstitialis* [9].

*C. janeri* and *C. nigra* growing in Latin America synthesize the already mentioned lactone (**4**) and chlorjanerin (**16**) [18].

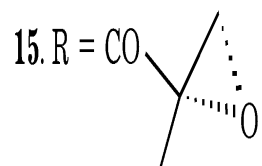
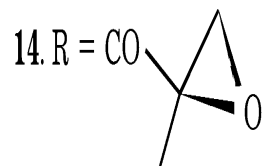
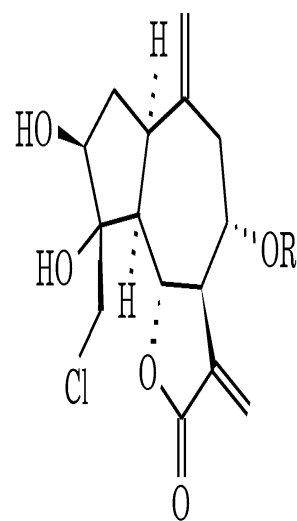
*C. aegyptica* growing in North Africa contains guianolides (**4**), (**7**), (**9**), (**10**), (**14**) and (**15**) [19]. The Argentinian species of *C. repens*, apart from the above mentioned lactones (**5**), (**10**) and (**16**), produces also trihydroxylactone repensolide (**17**) [20].

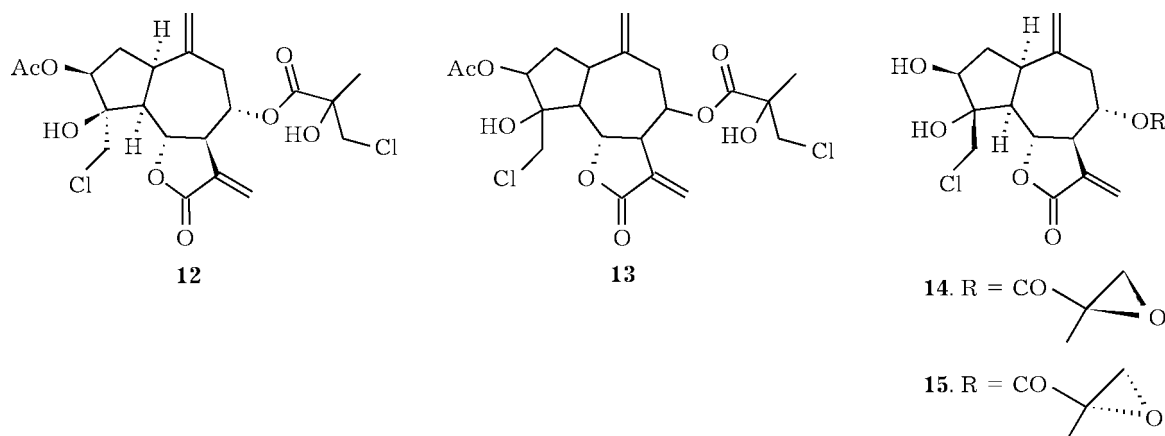


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In South America there is a plant *C. scoparia* which is a source of lactones (**7**), (**10**), (**16**) and of cebellin D (**18**), its acetate (**19**) and a lactone of abnormal structure (**20**) which carbon skeleton may be formally considered as belonging to *tris*-homosessquiterpenoid or *bis*-norditerpenoid types [21–23].

The species *C. sinaica* widespread in North Africa and Middle East produces lactones (**4**) and (**5**) [24, 25]. In the same regions, the species *C. bella* grows which contains, besides the already mentioned lactones (**4–6**), (**16**) and (**19**), lactone cebellin J (**21**). The latter compound (**21**), just like lactones (**10**), (**14**) and (**15**), is synthesized by the plant *C. adriatica* growing on the shores of the Adriatic Sea [26–28].

In other species of genus *Cenraurea*, the above mentioned lactones have also been found. So, *C. hermannii* contains compounds (**10**) and (**16**) [29], *C. imperialis* produces lactones (**4**) and (**19**) [30], from *C. incana* three lactones – (**6**), (**14**) and (**15**) [31] – have been isolated, and *C. marshaliana* contains compounds (**6**), (**16**) and (**18**) [26].

Plants *C. kotschyi*, *C. phaeopappoides* and *C. thracica* are interesting for containing the only lactone (**11**) [32].

Plants of genera *Chartolepsis*, *Leuzea* and *Psephellus* growing in Eurasia are related to plants of genus *Centaurea*. This is confirmed by identity of their metabolites to lactones produced by plants of this genus.

So, plants *Chartolepsis biebersteinii*, *Ch. Glasatifolia* and *Ch. Pterocaula* produce as the main components lactones (**4**), (**6**) and (**16**), and as minor ones, lactones (**12**) and (**21**) [28].

Three species – *Leuzea carthamoides*, *L. rhapontica* ssp. *helenifolia* and *L. rhaponti-*

*coides* – contain chlorjanerin (**16**) and an abnormal lactone (**20**) [28].

Eight species of genus *Psephellus* – *P. carthalinicus*, *P. colchicus*, *P. dagestanicus*, *P. deabatus*, *P. karabaghensis*, *P. nogmovii*, *P. somcheticus* and *P. zangezuri* – contain lactones (**4**), (**6**) and (**11**), and three species – *P. declinatus*, *P. hypolecus* and *P. leucophyllus* – are sources of lactone linichlorin B (**11**) [28, 33].

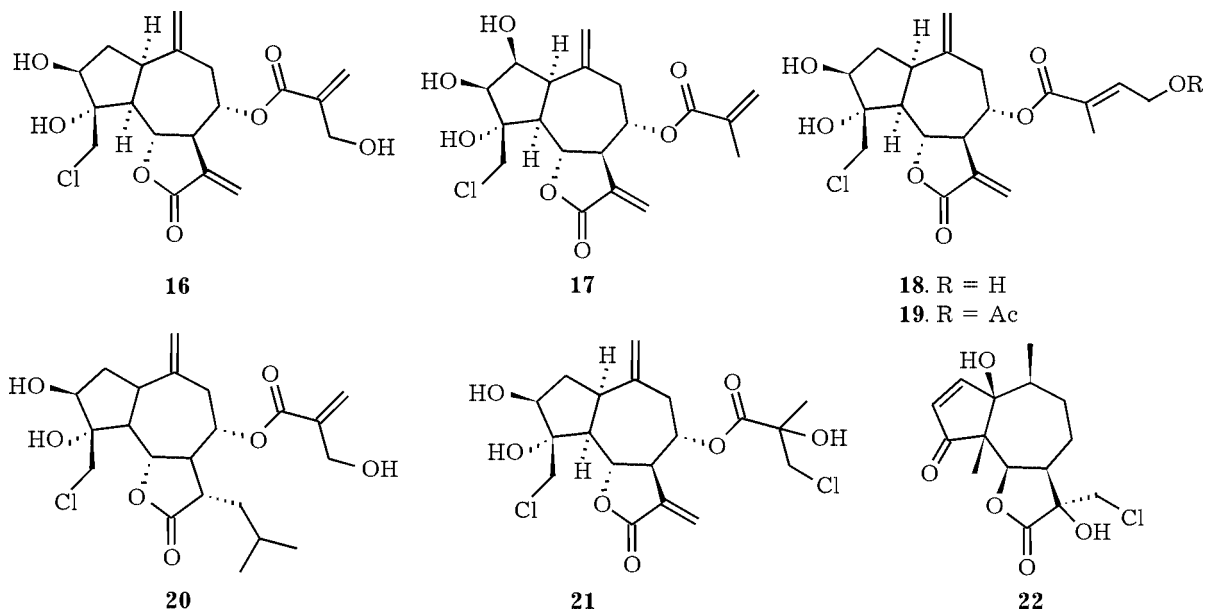
Perennial plants of genus *Saussurea* growing both in Europe and in Asia contain chlorinated lactones. For example, *Saussurea candidans* produces the above mentioned lactones (**4**), (**10**) and (**16**) [34]. The latter of the three mentioned lactones has been isolated from the Mongolian species *S. lipshitzii* [35], whereas *S. elegans* contains compounds (**10**) and (**13**) [17].

The plant *Ambrosia maritima* is used in the traditional medicine of Egypt [36]. From the leaves of this plant, 11- $\beta$ -hydroxy-13-chloro-11,13-dihydrochymenine (**22**) has been isolated which displays a high cytotoxic activity with respect to cancerous cells P-388, L-1210, KB and V-79 [37]. Noteworthy is the fact that the lactone (**22**) differs from other lactones in the configuration of angular carbon atoms.

A study of two related plant species *Cousinia canescens* and *C. pitocephala* has demonstrated that they synthesize the known lactones (**10**) and (**16**), and lactone (**25**) [38]. In extracts of leaves of *Gutenbergia marginata* (Veronicae), angelate (**23**) and dihydrochloroangelate (**24**) have been detected [39].

From the Middle Asia plant *Achillea biebersteinii*, biesanine (**26**) has been isolated [40].

Brazilian population of the plant *Lasiolaela santonii* contains ketolactones (**27–29**) char-



acterized by the presence of a dienone group [41]. In Brazil, the plant *Lasiolaena morii* producing, besides the lactone (28), also lactone (30) which molecule contains such a specific fragment as an hydroxy group at C 15, has been found [42].

It is noteworthy that the only chlorine-containing sesquiterpene contained in the leaves of Brazilian plant *Trichogonia gerdneri* is acetate (31) [43].

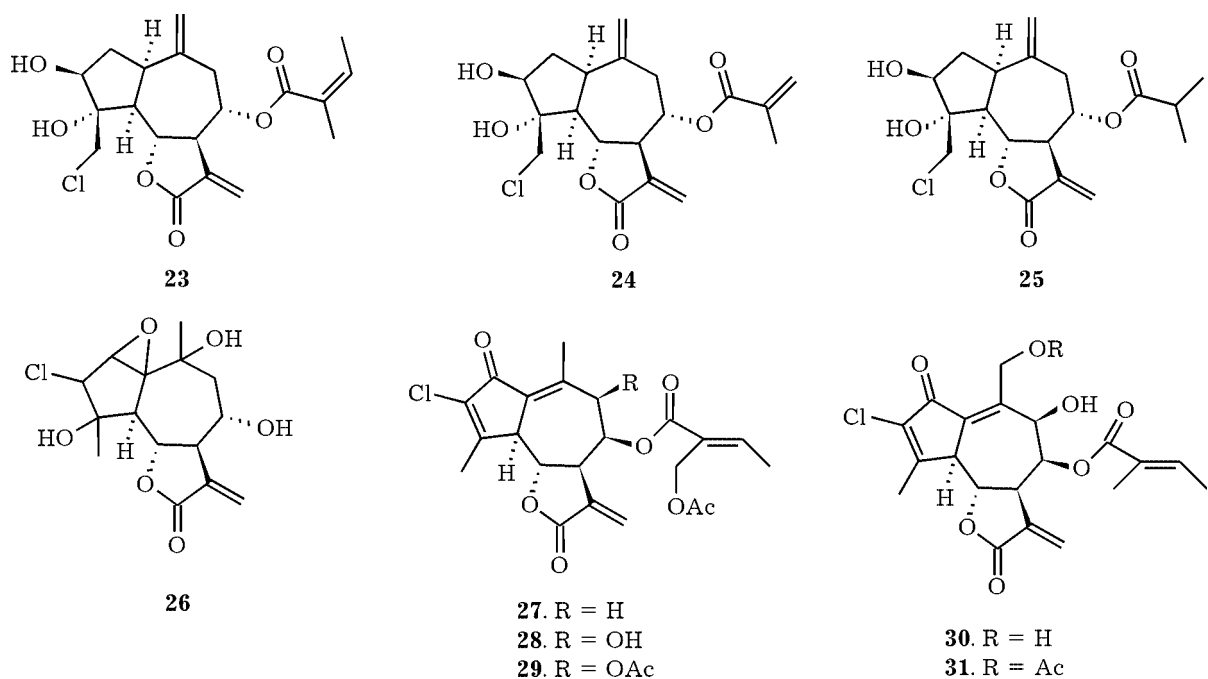
The same structural peculiarity is characteristic of lactones (32) and (33) isolated from

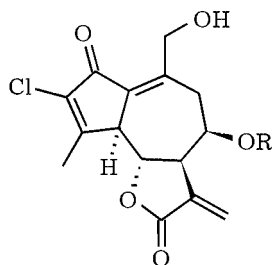
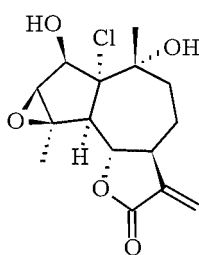
the leaves of Costa Rican plant *Mikania viti-fovia* [44].

Among six sesquiterpene lactones produced by the Mexican wormwood species *Artemisia klotzchiana*, one - chloroklotzchin (34) - contains chlorine [45].

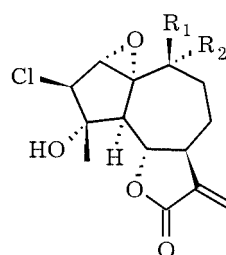
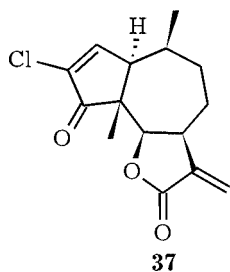
Epimer epoxy lactones - dihydroxybievani-nes (35) and (36) - have been isolated from the medicinal plant *Chrysanthemum parthenium* [46].

The medicinal plant *Ambrosia maritima* widespread in Egypt synthesizes chloroketo-lactone chlorambrosine (37) [47].

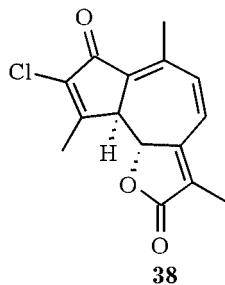


32. R = COC(CH<sub>3</sub>)OHCH<sub>2</sub>Cl33. R = COC(CH<sub>3</sub>)=CH<sub>2</sub>

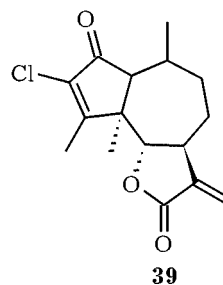
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35. R<sub>1</sub> = OH, R<sub>2</sub> = CH<sub>3</sub>36. R<sub>1</sub> = CH<sub>3</sub>, R<sub>2</sub> = OH

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38



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An interesting component of the Argentinian species of the plant *Stevia sanguinea* is the cross-conjugate ketolactone (**38**) [48].

Leaves of plant *Kaunia lasiophthalma* contain 19 sesquiterpenic lactones one of which (**39**) contains a chlorine atom [49].

The 13-chlorosolstitiplin (**40**) and its acetate (**41**) isolated from the Portuguese plant *Cynara humilis* differ from all the earlier described guianolides by the presence of a chlorine atom at C<sub>13</sub> [50].

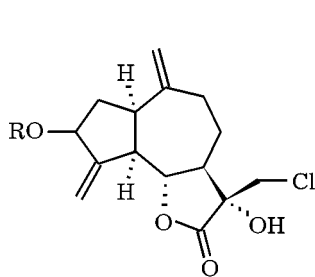
Chlorovenidol (**42**) and chlorovenidin (**43**) are produced by the grassy plant *Vinidium fastuosum* widespread in Egypt [51]. These compounds differ from the above mentioned guianolides by the position of the lactone fragment.

Isolation of chlorine-containing hermactranolides has been described. Epoxy lactone

poskephnolide (**44**) is produced by the plant *Critoniopsis huaircajana* growing in Costa Rica [52]. Diepoxide (**45**) has been identified in extracts from the North American plant *Liatrix acidota* [53]. Derivates of hermactrane containing an oxide fragment C<sub>11</sub>-C<sub>14</sub> form a new type of sesquiterpenic lactones referred to heliangolides. Chlorine-containing heliangolides (**46**) and (**47**) have been isolated from the plant *Calea morri* [54], whereas the plant *Calea villosa* produces lactones (**48**) and (**49**) [55].

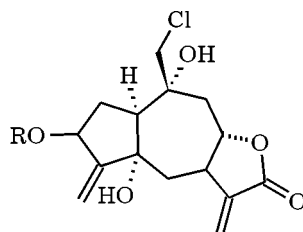
#### INDANONIC SESQUITERPENES

Indanonic sesquiterpenes (**50-58**) were discovered more than 30 years ago [56]. They have been found in Chinese and Japanese ferns *Pte-*



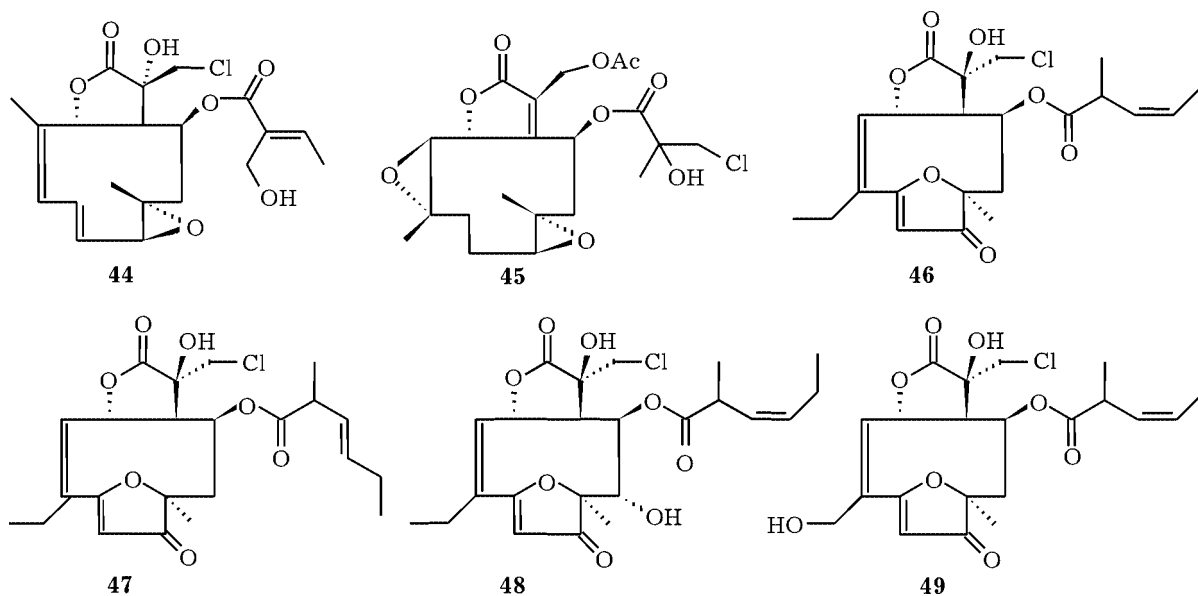
40. R = H

41. R = Ac



42. R = H

43. R = COCH<sub>2</sub>CH<sub>3</sub>



*ridium aquilinum* var. *latiusculum* which are toxic to cattle. The indanonic sesquiterpenes themselves display a cytotoxic effect and inhibit the development of sea urchin embryos and infusoria [57].

Pterosine F (**50**) has been detected in many species of fern: *Pteridium* var. *latiusculum* [56–59], *Pteridium* subsp. *wightianum* [60], *Microlepia strigosa* and *M. substrigosa* [61], and in species belonging to the genus *Pteris*: *P. angustipinna*, *P. cretica*, *P. dactylina*, *P. multifida* and *P. tremula* [62].

Pterosine H (or hypolepine A) (**51**) has been found in plants *Dennstaedtia scaba* [63], *Hypolepis punctata* [64], *Pteridium aquilinum* [59],

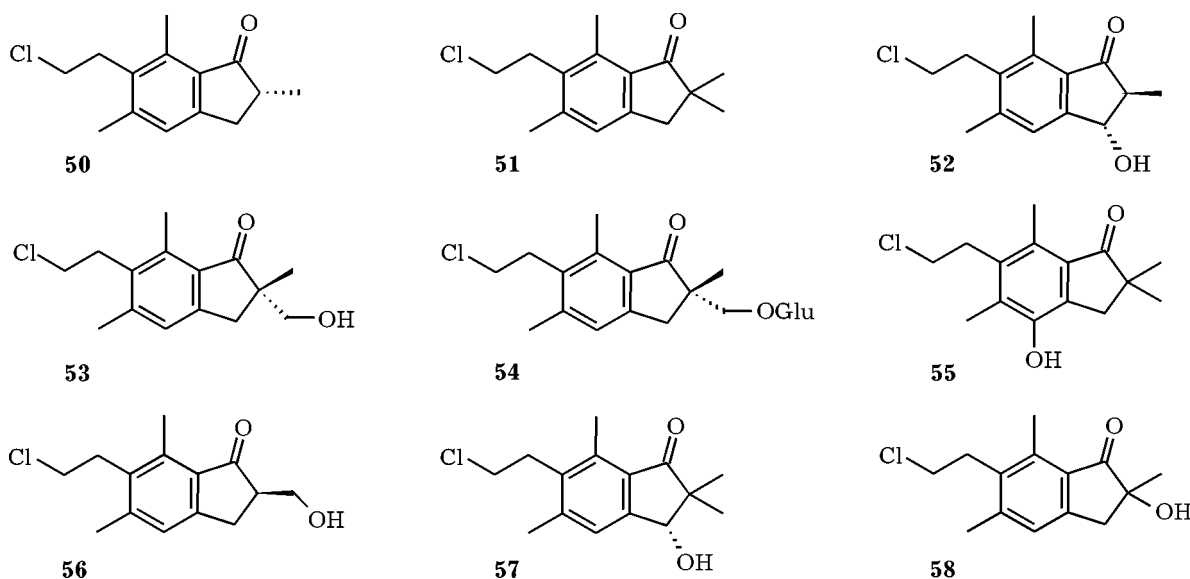
*Pteridium* subsp. *wightianum* [60], *Microlepia substrigosa*, *M. obtusiloba*, *M. trapeziformis* and *M. speluncae* [61].

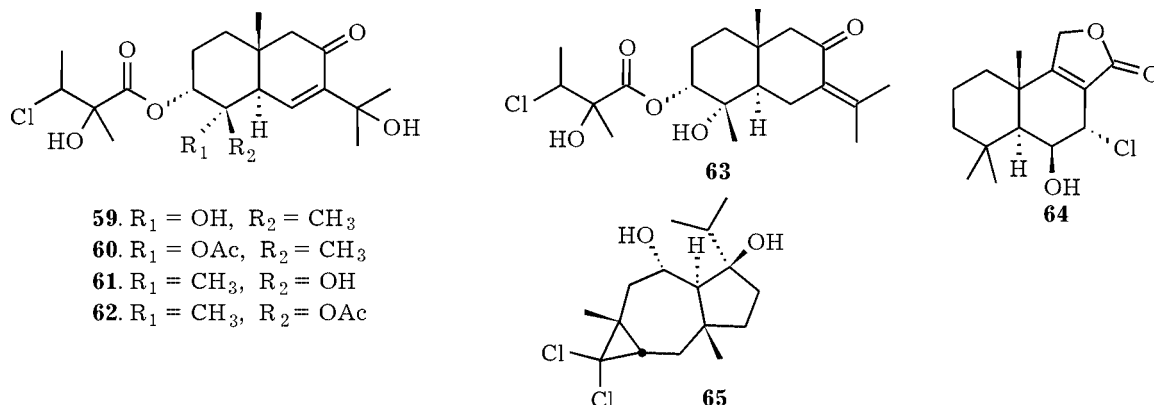
Pterosine J (**52**) has been isolated from two fern species – *Pteridium aquilinum* var. *latiusculum* [58, 65] and *Pteris tremula* [62].

Pterosine K (**53**) has been detected in the leaves of ferns *Pteridium aquilinum* var. *latiusculum* [58, 65], *Dennstaedtia scaba* [63] and *Hypolepis punctata* [64].

Pteroside K (**54**) is produced as a glucoside by the fern *Pteridium aquilinum* var. *latiusculum* [57].

Pterosine R (**55**) has been found in extracts from *Cibolium barometz* [66]; two other ses-





quiterpenes – (56) and (57) – have been found in *Pteris podophylla* [67] and *Pteridium* subsp. *wightianum* [60], respectively. Histiopetrosine B has been isolated from the leaves of fern *Histiopteris incisa* [68]. The chemistry and the biological activity of metabolites of indanone type have been described in a review published in 1988 [68].

#### OTHER TYPES OF SESQUITERPENES

The family *Pluchea* (Asteraceae) is comparatively small and contains 28 genera and approximately 22 species of plants characteristic of South and Central America. Some species have been discovered also in Africa, tropical Asia and Australia [69]. These plants produce sesquiterpenes of eudesmane type among which there are chlorine-containing compounds. For example, two chlorinated derivatives of eudesmane – (59) and (60) – have been found in the plant *Pluchea odorata* widespread in Salvador [70], and two other representatives of this type – (61) and (62) – have been isolated from the leaves of *Pluchea arguta* collected in Pakistan [71]. Out of twelve various sesquiterpenes isolated from the extract of the plant *Laggera crispata* (*Pluchea*) growing in Ethiopia, chlorine is contained in ketoester cuauhtemon (63) [72].

A sesquiterpene of drimane type (64) has been detected in the plant *Makinoa crispata* belonging to the class Bryophyta (liverworts) [73]. Jaeschkenol (65) – a sesquiterpene containing a cyclopropane ring and two chlorine atoms – has been isolated from the plant *Ferula jaeschkeana* (Umbelliferae) growing in the Himalayas (Nepal) [74].

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