Chapter 12
Effects on Other Microorganisms

María Victoria Castelli and Silvia Noelí López

Abstract Sesquiterpene lactones (STLs) are natural and semisynthetic compounds displaying interesting biological activities, including antiprotozoal, anti-inflammatory, and cytotoxic among the most studied. Some compounds belonging to this group have recently been described as promising antimicrobial hits. In this chapter, the antifungal, antibacterial, and antiviral properties will be discussed, taking into account their basic chemical scaffolds.

Keywords Sesquiterpene lactones · Antimicrobial · Antifungal · Antibacterial · Antiviral

Abbreviations

ATCC	American Type Culture Collection
DNA	Deoxyribonucleic acid
EC_{50}	Half maximal effective concentration
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
IC_{50}	Half-maximal inhibitory concentration
MIC	Minimum inhibitory concentration
MTCC	Microbial Type Culture Collection

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12.1 Introduction

Sesquiterpene lactones (STLs) constitute a large group of secondary plant metabolites comprising about 8000 members, mostly isolated from the Asteraceae family (Macias et al. 2013; Zhang et al. 2012). They have been described as the active constituents of several medicinal plants traditionally used to treat inflammatory diseases. However, not only do they have anti-inflammatory properties but also a broad spectrum of biological activities, including antimicrobial, antifungal, antiviral, antiparasitic (anthelmintic, antimalarial), uterus contracting, cytotoxic, antifeedant, and anticancer, among others (Merfort 2011).

Microorganisms, fungi, and bacteria have been in contact with humans since ancient times (Hancock 2007). Although some of them are beneficial to humans, a small fraction of them is responsible for devastating diseases affecting crops, food security, and human health. The continuous development of antibiotic resistance by microbes is alarming; therefore, there is an urgent need for new active molecules to fight such microorganisms (Demain and Sanchez 2009). The main classes of antibiotic drugs in current use were mainly discovered through empirical screening programs carried out more than 50 years ago. Most drugs currently in use (β-lactamic, azoles, etc.) derive from these precursors and encompass a limited number of chemical skeletons, offering, in some cases, few improvements over existing therapies. The increasing emergence of fungal and bacterial diseases is further promoted by human activity, primarily through global trade, and may be exacerbated by the impact of climate change (Jampilek 2016).

Viruses are responsible for a number of human diseases including cancer. Due to globalization, epidemic outbreaks caused by emerging and reemerging viruses (e.g. dengue virus, influenza virus, severe acute respiratory syndrome virus, etc.) represent a threat to public health. Despite progress has been made in the development of immunization therapies and antiviral drug development, vaccines to prevent infections and efficient antiviral therapies against many viral infections are still lacking. In addition, drug-resistant mutants can arise, especially when viral enzyme-specific inhibitors are employed (Lin et al. 2014).

Taking this information into account, it can be deduced that the need for new drugs to target emerging multidrug-resistant microorganisms is imperative. These drugs should also be less toxic and cheaper than the existing ones. In this sense, nature continues to provide an unparalleled source of small molecules that may be useful to comply with this need.

In this chapter, the antifungal, antibacterial, and antiviral properties of natural sesquiterpene lactones, including some examples of semisynthetic derivatives, will be discussed.

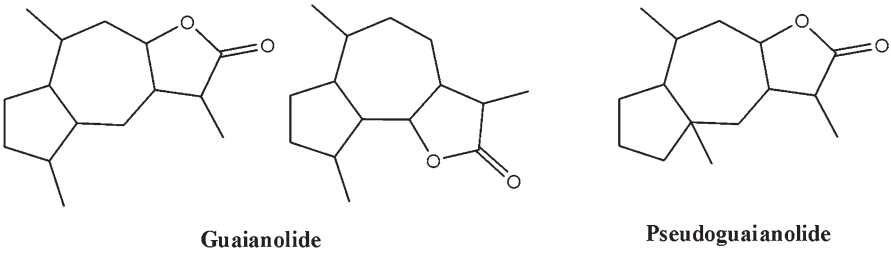


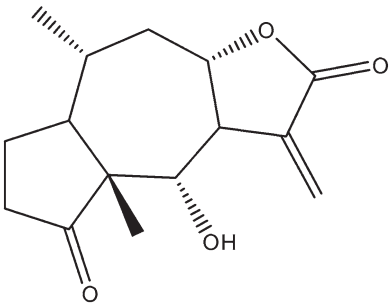
Fig. 12.1 Guaianolide and pseudoguaianolide skeleton

12.2 Antifungal, Antibacterial, and Antiviral Activity

12.2.1 Guaianolides and Pseudoguaianolides

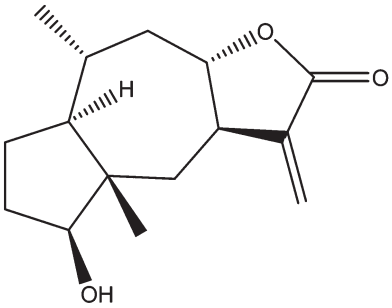
Guaianolides and pseudoguaianolides (Fig. 12.1) are regular tricyclic sesquiterpene lactones that contain a five-membered γ-lactone ring fused to a seven-membered carbocycle in positions 6,7 or 7,8 (*cis* or *trans* configurations, respectively), which in turn, is fused to a five-member carbocycle (Macías et al. 2013; Zhang et al. 2015). Pseudoguaianolides contain methylated *trans*-perhydroazulene scaffolds.

Carpesiolin (**1**) is a pseudoguaianolide sesquiterpene lactone isolated from the ethanolic extract of *Carpesium abrotanoides* L. (Asteraceae) along with other eudesmanolide sesquiterpene lactones (see below). The bioassay-guided fractionation of the extract has shown that carpesiolin has a potent activity against *Cochliobolus miyabeanus* and *Xanthomonas oryzae*, which are two infectious agents of rice cultures (Maruyama and Shibata 1975; Maruyama and Omura 1977).



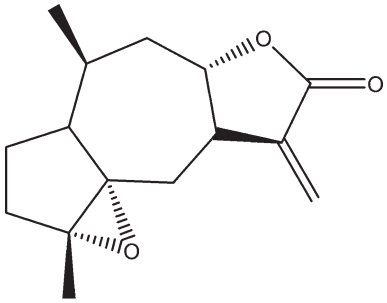
carpesiolin (1)

Further studies performed on the same plant have led to the isolation of 2-desoxy-4-epi-pulchellin (**2**), which has shown significant antimycobacterial activity (MIC: 7.6 μM) (Wang et al. 2015).



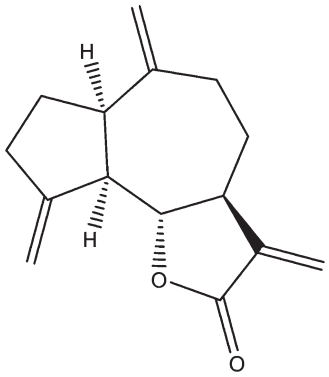
2-desoxy-4-epi-pulchellin (**2**)

The guaianolide 4α,5α-epoxy-10α,14H-1-epi-inuviscolide (**3**) has been isolated from *Carpesium macrocephalum* Franch. & Sav. (Asteraceae), which is a widely distributed plant in China and Korea used as fungicide against phytopathogenic fungi. When the antifungal activity was tested in vitro against *Candida albicans*, it did not show activity at 256 μg/ml. However, in an anti-virulence assay, the compound strongly inhibited biofilm formation with an IC_{50} value of 38 μg/ml, also inhibiting the yeast to hyphae morphogenetic transition with an IC_{50} value of 106.5 μg/ml (Xie et al. 2015).



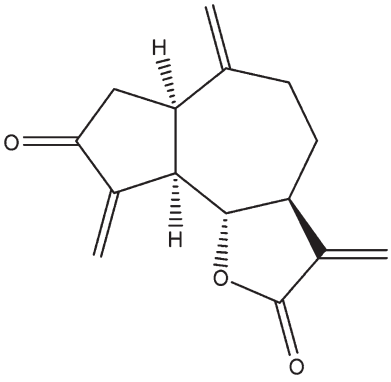
4α,5α-epoxy-10α,14H-1-epi-inuviscolide (**3**)

When (-)-dehydrocostuslactone (**4**), which was isolated from a commercially available roots extract of *Saussurea lappa* (Asteraceae), was tested against *Cunninghamella echinulata*, the lactone inhibited fungal growth with an EC_{50} value of 6 μg/ml, which is a value that is similar to that obtained with ketoconazole (EC_{50} 1.5 μg/ml) (Barrero et al. 2000).



(-)-dehydro-costuslactone (4)

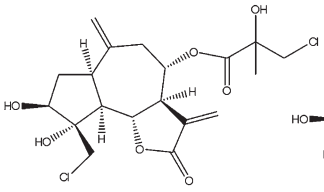
Dehydrozaluzanin C (**5**) has been isolated from many different species from the Asteraceae family; however, this compound can also be semisynthesized from dehydrocostus lactone (Macías et al. 2000; Galindo et al. 1999). In a bioautographic assay, compound (**5**) has shown fungicidal activity against *Colletotrichum gloeosporioides*, *Colletotrichum acutatum*, *Colletotrichum fragariae*, *Phomopsis* sp., and *Botrytis cinerea*. When evaluated in a 96-well bioassay system, dehydrozaluzanin C (30 μM) inhibited the growth of *C. fragariae*, *C. gloeosporioides*, and *C. acutatum* by 90%, 89%, and 29%, respectively (Wedge et al. 2000).



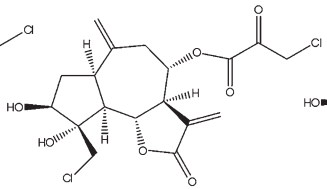
dehydrozaluzanin C (5)

The genus *Centaurea* (Asteraceae) comprises many species that are used in folk medicine. Plants belonging to this genus have sesquiterpene lactones as characteristic constituents (Ciric et al. 2012). *Centaurea solstitialis* L. subsp. *solstitialis* is commonly used in Turkish folk medicine to treat orofacial herpes infections, peptic ulcer, malaria, common colds, and stomach and abdominal pain (Honda et al. 1996). Three sesquiterpene lactones centaurepensin (**6**), chlorojanerin (**7**), and 13-acetyl solstitialin A (**8**) have been isolated from the aerial parts as major

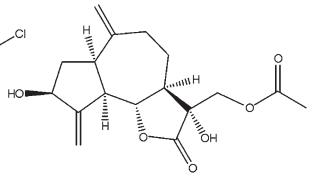
constituents, and their antimicrobial, antifungal, and antiviral profiles have been determined (Özçelik et al. 2009). These compounds have been tested against *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Candida albicans*, and *Candida parapsilosis* by the microdilution method and against type 1 herpes simplex virus (HSV-1) and parainfluenza virus using Vero cells. These compounds have shown weak activity against fungi (MIC = 64 μg/ml), Gram-negative bacteria (MIC = 64–256 μg/ml), and Gram-positive *E. faecalis* (MIC = 64–128 μg/ml). However, 13-acetyl solstitialin A (**8**) and to a lesser degree centaurepensin (**6**) and chlorojanerin (**7**) have shown moderate activity on standard and isolated strains of *S. aureus* (MIC = 16 and 32 μg/ml, respectively). These compounds were also active against HSV-1, being **8** the most active when tested in a microdilution antiviral test using Vero cells (MIC ≤ 60 pg/ml).



centaurepensin (6)

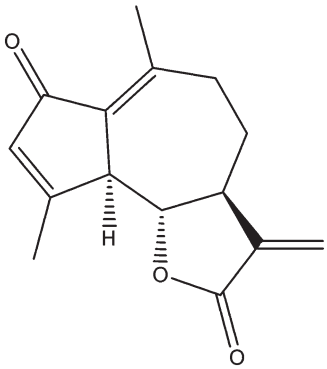


chlorojanerin (7)



13-acetyl solstitialin A (8)

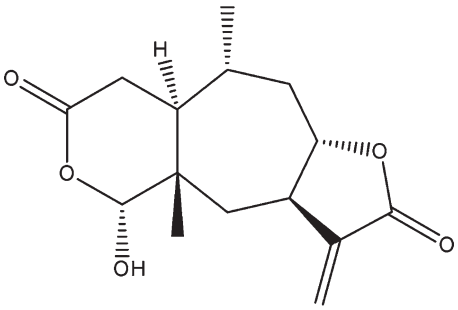
Artemisia douglasiana (Asteraceae) leaves, also known as "matico," are used in Argentinian folk medicine for their beneficial effects against gastroduodenal disorders like peptic ulcer and for the treatment of external sores (Vega et al. 2009). Dehydroleucodine (**9**) is the main active cytoprotective principle isolated from the plant, which has been demonstrated to increase the synthesis of glycoproteins of the gastric mucosa and to prevent the formation of gastric mucous lesions induced by absolute ethanol or other necrotizing agents. The compound has been tested for its in vitro antibacterial activity on one *Helicobacter pylori* reference strain (NCTC 11638) and six antral biopsy clinical isolates by the agar dilution method. Dehydroleucodine (**9**) was active against all strains tested, with MIC values ranging from 1 to 8 μg/ml.



dehydroleucodine (9)

Seco-pseudoguaianolides are common compounds found in the genus *Hymenoxys* (Asteraceae). Herz (1977) categorized *seco*-pseudoguaianolides at the fourth level of biogenetic complexity (from 1 to 4). The biosynthesis of these compounds starts by a cyclization of either a germacrolide precursor or melampolide precursor (see below), which generates the guaianolide skeleton. After a number of structural rearrangements, the guaianolide is transformed into a pseudoguaianolide skeleton followed by a five-membered ring opening to produce the *seco*-pseudoguaianolide one. Generally, the lower complexity level skeletons have broader distributions within the family than the higher complexity level skeletons (Herz 1977, 1978).

Vermeerin (**10**) and other sesquiterpene lactones presenting a *seco*-pseudoguaianolide backbone have been isolated from *Hymenoxys robusta* (Rusby) K.F. Parker, also known in Bolivia as "q'illu q'illu" (Fortuna et al. 2011). When these *seco*-pseudoguaianolide sesquiterpene lactones were tested against a panel of bacterial and fungal pathogen strains, only vermeerin (**10**) was found to be active, showing a specific antibacterial activity on *S. aureus* with a MIC value of 10 μg/ml.



vermeerin (**10**)

12.2.2 Eudesmanolides

As for the antimicrobial activity, eudesmane sesquiterpene lactones constitute the most represented group among sesquiterpene lactones. They are tricyclic sesquiterpenoid lactones containing a five-membered γ-butyrolactone ring (Fig. 12.2) and can be divided in two structural classes according to the lactone ring annulation, 6,12- or 8,12-olides (Zhang et al. 2015).

Granilin (**11**) is an eudesmane-type sesquiterpene lactone which has been isolated from a methanolic extract of the whole *C. abrotanoides* plant and has shown in vitro activity against *Cochliobolus miyabeanus* and *Xanthomonas oryzae* (Maruyama and Shibata 1975).

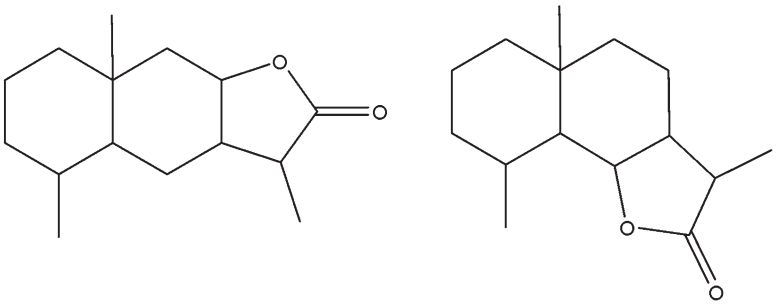
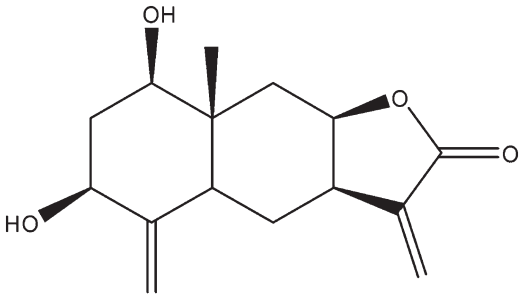


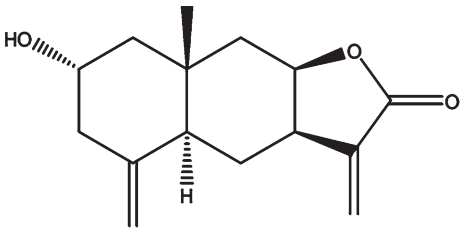
Fig. 12.2 Eudesmanolide skeletons



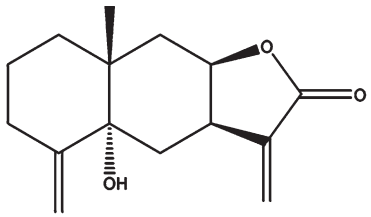
granilin (**11**)

Ten eudesmanolide sesquiterpene lactones have been isolated from the seeds of *C. macrocephalum*. Six of them have been tested for their antibacterial activity against *Bacillus subtilis*, *S. aureus*, and *E. coli.* Ivalin (**12**), telekin (**13**), and 2-(β-D-glucopyranosyloxy)-5,11⟨H-eudesma-4(15)-en-12,8-β-olide (**14**) have shown moderate antibacterial activity, while telekin (**13**) and ivalin (**12**) strongly inhibited *C. albicans* biofilm formation with IC_{50} values ranging from 15.4 to 36.0 μg/ml (Yang et al. 2002; Xie et al. 2015).

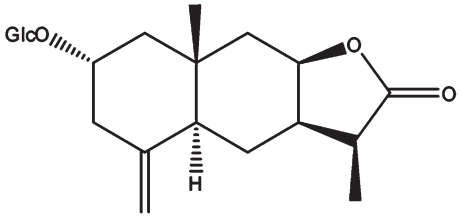
Other sesquiterpene lactones also isolated from *C. macrocephalum* have also been evaluated in vitro for their antifungal capacity to inhibit growth, biofilm formation, and yeast-hyphal transition of *C. albicans*. The eudesmane 5α-epoxyalantolactone (**15**) did not show neither antifungal activity ($MIC_{50} > 256$ μg/ml) nor inhibitory capacity on biofilm formation ($IC_{50} > 128$ μg/ml); however, the compound inhibited the morphogenetic transition yeast-to-hyphae with an IC_{50} value of 118.4 μg/ml (Xie et al. 2015).



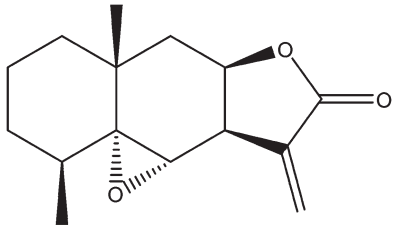
ivalin (12)



telekin (13)

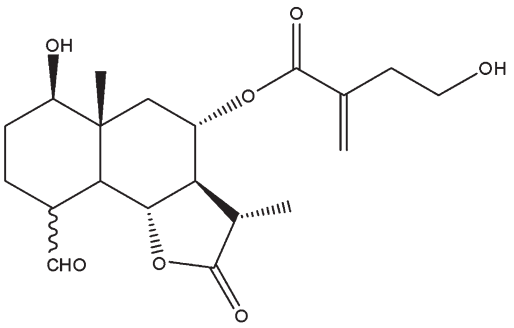


2α-(β-D-Glucopyranosyloxy)-5α,11αH-eudesma-4(15)-en-12,8-β-olide (14)



5α-epoxyalantolactone (15)

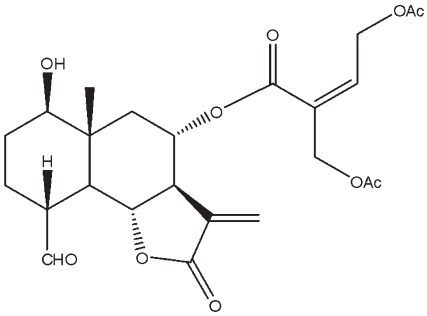
Antimicrobial eudesmane sesquiterpene lactones have been isolated from the aerial parts of *Centaurea pullata* (Djeddi et al. 2007). Two eudesmanolides (**16**) and (**17**), which had not previously been described, showed in vitro antibacterial and antifungal activities when tested against Gram-negative bacteria such as *Pseudomonas tolaasii* and *E. coli* ATCC 35210; Gram-positive bacteria such as *B. subtilis* ATCC 10907, *Micrococcus flavus* ATCC 10240, and *Staphylococcus epidermidis* ATCC 12228; and eight fungi (*Aspergillus niger* ATCC 6275, *Aspergillus ochraceus* ATCC 12066, *Aspergillus flavus* ATCC 9643, *Penicillium ochrochloron* ATCC 9112, *Penicillium funiculosum* ATCC 36839, *Trichoderma viride* IAM 5061, *Fusarium tricinctum* CBS 514478, and *Alternaria alternata* DSM 2006). Minimum inhibitory bactericidal or fungicidal concentrations obtained using the microdilution method ranged from 0.2 to 0.5 μg/ml, being the compounds more potent than the positive controls streptomycin and miconazole.

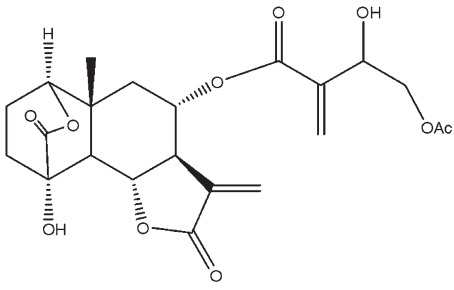


α-CHO **8α-O-(4-hydroxy-2-methylenebutanoyloxy)-11β,13-dihydrosonchucarpolide (16)**

β-CHO **8α-O-(4-hydroxy-2-methylenebutanoyloxy)-11β,13-dihydro-4-epi-sonchucarpolide (17)**

The sesquiterpene lactones 8α-O-(4,5-diacetoxyangeloyl)sonchucarpolide (**18**) and zuccarinin (**19**) have been isolated from *Centaurea zuccariniana* and evaluated by the broth microdilution method against Gram-negative bacteria (*E. coli*, *Proteus mirabilis*, *P. aeruginosa*, *Salmonella typhimurium*), Gram-positive bacteria (*Bacillus cereus*, *Micrococcus flavus*, *Listeria monocytogenes*, *S. aureus*), and fungi (*Aspergillus niger*, *Aspergillus versicolor*, *A. flavus*, *Aspergillus fumigatus*, *C. albicans*, *Penicillium funiculosum*, *Penicillium ochrochloron*, *T. viride*). The tested compounds exhibited moderate antibacterial activity when compared to streptomycin and amoxicillin, with MIC values ranging from 222 to 450 nmol/ml, and similar or higher antifungal activities than the fungicides, bifonazole, and ketoconazole (MIC = 222 to 900 nmol/ml) (Ciric et al. 2012).

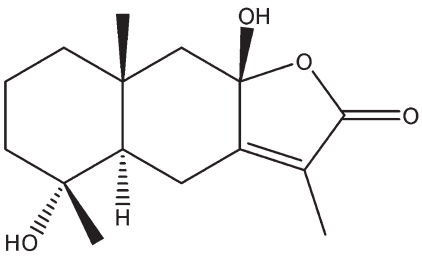




8α-**O-(4,5-diacetoxyangeloyl) sonchucarpolide (18)** **zuccarinin (19)**

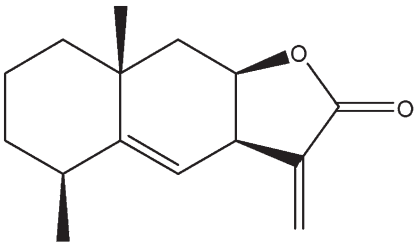
Plants from the genus *Chloranthus* (Chloranthaceae) such as *C. angustifolius* have been used as herbal medicines in China for the treatment of traumatic injury, blood stasis, and *tinea* infections (Yang et al. 2014). Sesquiterpenes and their dimers have been described as the major secondary metabolites in this genus, exhibiting a variety of biological activities like antifungal and cytotoxic, among others (Xu 2013). A bioassay-guided phytochemical investigation

carried out on *C. angustifolius* roots has led to the isolation of the eudesmane sesquiterpene lactone 4α,8β-dihydroxy-5α(H)-eudesm-7(11)-en-8,12-olide (**20**), among others. When tested against a panel of five bacterial and six fungal strains, the lactone exhibited moderate inhibitory activity on *C. albicans* with a MIC value of 16 μg/ml.

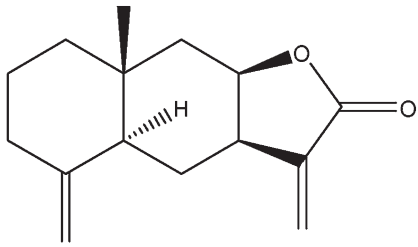


4α,8β-dihydroxy-5α(H)-eudesm-7(11)-en-8,12-olide (20)

The sesquiterpene lactones alantolactone (**21**) and isoalantolactone (**22**) have been isolated from *Inula helenium* (Asteraceae). Actually, these compounds have been isolated from their natural source as a mixture known as helenin (Gökbulut and Şarer 2013). These lactones have been reported to inhibit the growth of dermatophytes *Microsporum gypseum*, *Trichophyton acuminatum*, and *Epidermophyton* sp. When tested against a panel of 16 fungi in a macrodilution agar test, both lactones showed antifungal activity against all fungi tested at least at the highest concentration used (1000 μg/ml), being strongly active against *Microsporum cookei* and *Trichophyton mentagrophytes*, whose growth was completely inhibited when used at 10 μg/ml (Picman 1983).



alantolactone (21)

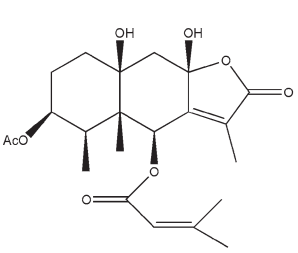


iso-alantolatone (22)

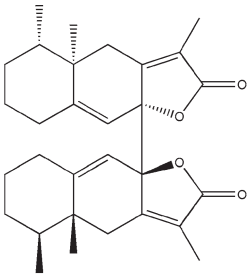
Alantolactone (**21**) has also shown antiviral activity in vitro on herpes simplex virus 1 (HSV-1) (Rezeng et al. 2015). The effect of the compound was determined using a cytopathic effect-based assay, and results indicated that alantolactone markedly inhibited viral infections at 0.01-1 μg/ml, showing the more potent antiviral activity at 0.1 μg/ml. Besides Vero cells viability was not affected at concentrations below 1 μg/ml.

Plants of the genus *Senecio* L. (Asteraceae) are traditionally used in China for the treatment of hepatitis B, dermatosis, and inflammation. Studies performed on extracts

from *S. tsoongianus* and *S. saluenensis* have shown a suppressor activity on the secretion of hepatitis B virus surface antigen (HBsAg) and hepatitis B virus e antigen (HBeAg) in HepG2.2.15 cells. The bioguided fractionation of *S. saluensis* has led to the isolation of saluenolide A (**23**) and compounds **24** and **25** from *S. tsoongianus*. These compounds displayed significant inhibitory activity on the expression of HBsAg and HBeAg in HepG2.2.15 and reduced the hepatitis B virus (HBV) DNA in the culture medium without inhibiting intracellular HBV DNA, suggesting that these compounds may interfere with virion release from cells (Li et al. 2005).



saluenolide A (23)



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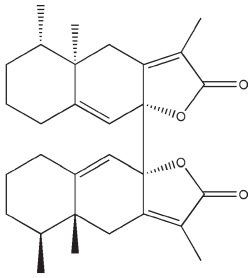


25

12.2.3 Germacranolides and Other Related Structures

The parent nucleus of the germacranes contains a special ten-member ring (Fig. 12.3), thus creating a complex and diverse stereo configuration. The Asteraceae family presents several types of germacranolides (Zhang et al. 2015).

Smallanthus sonchifolius (Poepp.) H. Rob. (Asteraceae), also known as "yacon," is a medicinal plant originally cultivated in the Andean highlands. It has been reported that its tubers contain high amounts of oligofructans and polyphenols, and that the leaf extract has antidiabetic effects. Its tubers are also used as food, whereas the aerial parts are used as fodder for animals (Inoue et al. 1995). Since for the cultivation of "yacon," it is not necessary to use antifungal and pesticide compounds; it has been suggested that the aerial parts of the plant should contain some antifungal and pesticide compounds (Lin et al. 2003). The ethanolic extract of yacon leaves has been studied by a bioassay-guided fractionation using a spore suspension of

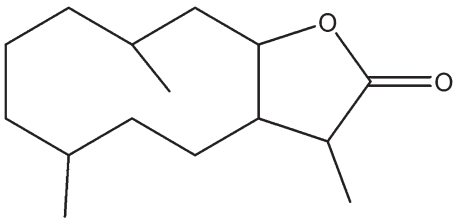
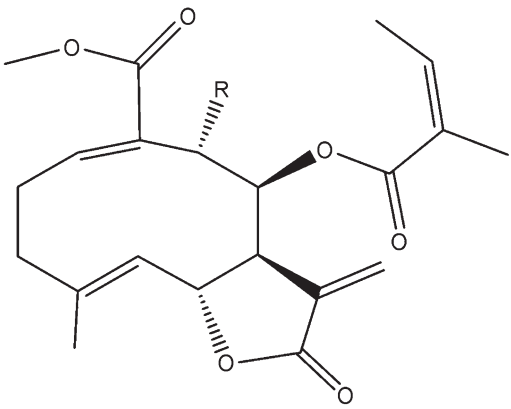
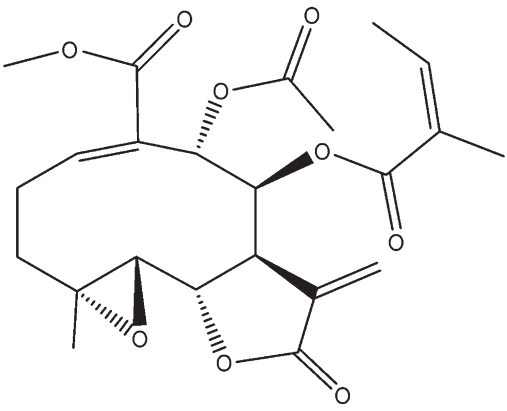


Fig. 12.3 Germacranolide skeleton

Pyricularia oryzae (Akatsuka et al. 1985). The active fractions obtained proved to contain the melampolides sonchifolin (**26**) and polymatin B (**27**), among other melampolides. The complete inhibition of spore germination was obtained at 100 ppm and 250 ppm for sonchifolin (**26**) and polymatin B (**27**), respectively.

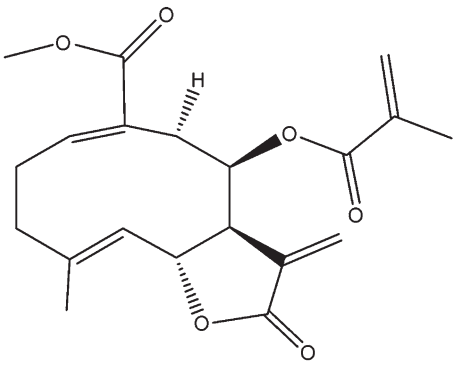


R=H **sonchifolin** (**26**), **R**=OAc **polymatin B** (**27**)



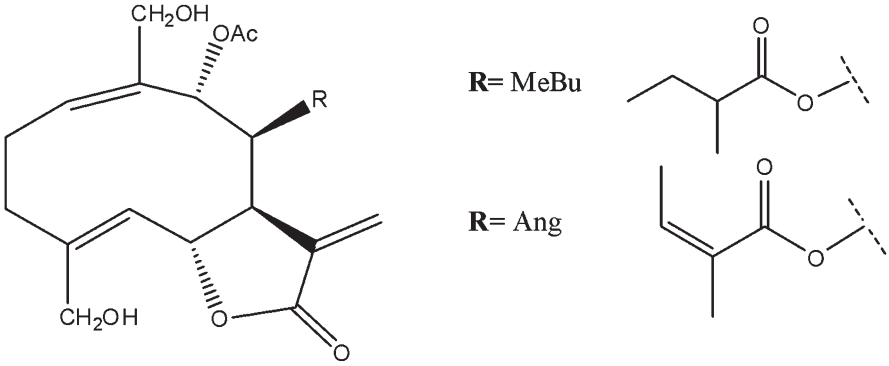
fluctuanin (**28**)

The extraction and chromatographic separation of "yacon" leaves extract yielded two melampolide-type sesquiterpene lactones that had not previously been described and the known melampolides sonchifolin (**26**), fluctuanin (**28**), uvedalin, and enhydrin (structures not shown) (Lin et al. 2003). These compounds were tested for their antibacterial activity against *B. subtilis* and for their antifungal properties against *P. oryzae*. The new compound 8β-methacryloyloxymelampolid-14-oic acid methyl ester (**29**) and sonchifolin (**26**) exhibited potent antifungal activity on *P. oryzae*, inhibiting 100% of spore germination at 200 ppm. Fluctuanin (**28**) was the most active compound on *B. subtilis*, and the minimum inhibitory weight to give a bacterial growth inhibition zone greater than 10 mm diameter was 25 μg.



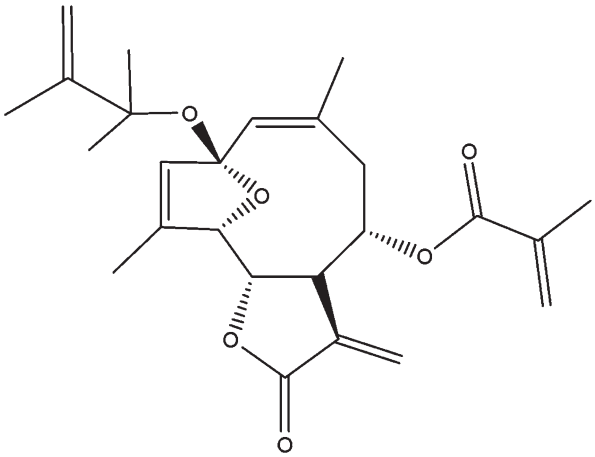
8β-methacryloyloxy melampolid-14-oic acid methyl ester (29)

The dihydroxy melampolides (**30**) and (**31**) isolated from *Acanthospermum hispidum* (Asteraceae) have shown activity on *P. aeruginosa* biofilm formation. These compounds were active at the two concentrations tested (0.25 μg/ml and 2.5 μg/ml), reducing biofilm formation by roughly 50%, when compared to the control after 1 or 6 h of bacteria-compound contact (Cartagena et al. 2007).



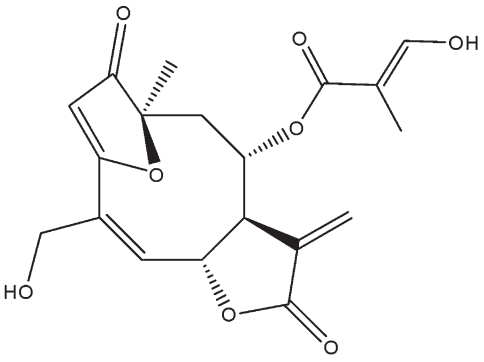
R=MeBu **9α-acetyloxy-14,15-dihydroxy-8β-(2-methylbutanoyloxy)-acanthospermolide (30)**
R= Ang **9α-acetyloxy-14,15-dihydroxy-8β-(2-angeloyloxy)-acanthospermolide (31)**

Elephantopus tomentosus (Asteraceae) is a traditional plant medicine growing in the south of China. The whole plant is used for the treatment of hepatitis, bronchitis, fever, the cough associated with pneumonia, and arthralgia. Three germacranolide sesquiterpene lactones have been isolated from the whole plant and their antibacterial properties evaluated by the agar diffusion assay on *S. aureus* employing kanamycin sulfate as positive control. Tomenphantopin H (**32**), 2β-methoxy-2-de-ethoxy-8-O-deacylphanto-molin-8-O-tiglinate, and 2-de-ethoxy-2-hydroxyphantomolin (structure not shown) inhibited the growth of *S. aureus* at 500 μg/disk with inhibition halos of 14.2 mm, 13.4 mm, and 31.0 mm, respectively (positive control 6.4 μg/disk, 32.6 mm) (Wang et al. 2012).



tomenphantopin H (32)

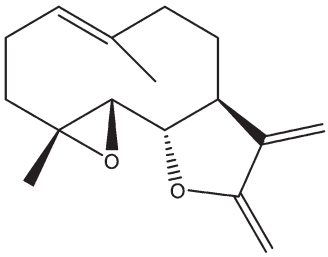
Six sesquiterpene lactones of the goyazensolide-type and the isogoyazensolide-type have been isolated from *Centratherum punctatum* subsp. *punctatum* (Asteraceae). The compounds were tested for their inhibitory capacity on *P. aeruginosa* biofilm formation, elastase activity, and production of N-acyl-homoserinelactones, which act as intercellular signal molecules. All the compounds assayed inhibited bacterial growth at the highest concentration tested. At 200 μg/ml the inhibitory effect of the compounds ranged from 11% to 71%. The biofilm formation and N-acyl-homoserinelactones production were also inhibited by all the compounds tested, being 1-oxo-3,10-epoxy-8-epoxymethacryloyloxy-15-hydroxygermacra-2,4,11(13)-trien-6,12-olide (**33**) the most potent compound causing a 42% inhibition of biofilm formation at 0.5 μg/ml and 66% inhibition on N-acyl-homoserinelactones production at 200 μg/ml (Amaya et al. 2012).



1-oxo-3,10-epoxy-8-epoxymethacryloyloxy-15-hydroxygermacra-2,4,11(13)-trien-6,12-olide(33)

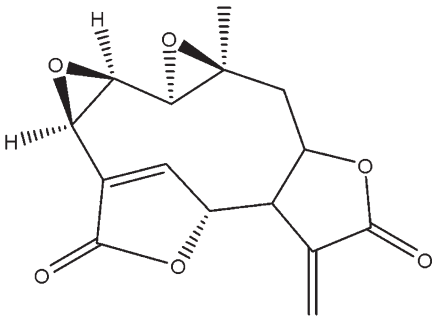
Parthenolide-like sesquiterpene lactones are germacranolides which bear a ten-membered ring with a five-membered fused lactone, an α-methylene group in the lactone ring, and a C_4-C_5 epoxide ring (Seca et al. 2017). Parthenolide (**34**) was the first

sesquiterpene lactone isolated from feverfew leaves, *Tanacetum parthenium* (Asteraceae), and from other asteraceous species such as *Tarchonanthus camphoratus*. The species *T. camphoratus* is used in Yemen to treat wounds and urinary tract infections, while in South Africa, the plant is used to relieve toothache and to treat respiratory disorders. Parthenolide has been tested for its in vitro growth inhibitory activity against *C. albicans* ATCC 2091, *S. aureus* ATCC 6538P, *B. subtilis* ATCC 6633, *Mycobacterium smegmatis* ATCC 14468, *E. coli* ATCC 25922, and *P. aeruginosa* MTCC 741. The molecule showed activity against *S. aureus* and *B. subtilis* with MIC values of 25 μg/ml, while the MIC for *C. albicans* was 300 μg/ml (Jamal et al. 2014).

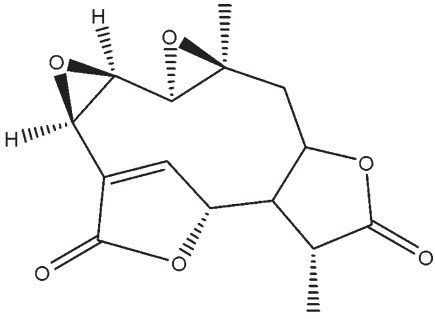


parthenolide (34)

The plant *Mikania micrantha* (Asteraceae) is an extremely fast growing perennial creeping weed native to Central and South America, where it is traditionally used to treat skin diseases and athlete's foot (Rios et al. 2014). Sesquiterpene lactones of the germacrane type have been described as constituents of the plant. Mikanolide (**35**) and dihydromikanolide (**36**) have been isolated from the aerial parts as the major constituents which are responsible for the antimicrobial activity of the plant. In an agar diffusion test, both compounds showed antibacterial and antifungal activities on *S. aureus* (45–48 mg/disc) and *C. albicans* (6–42 mg/disc), being the dihydro derivative seven times more active against *C. albicans* (Facey et al. 1999).



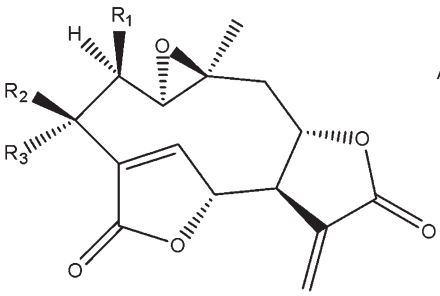
mikanolide (35)



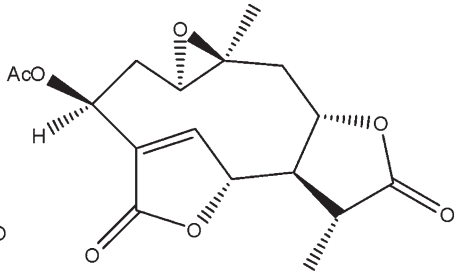
dihydromikanolide (36)

Further studies have led to the isolation of deoxymikanolide (**37**), scandenolide (**38**), and dihydroscandenolide (**39**) in addition to mikanolide (**35**) and dihydromikanolide (**36**). The compounds were evaluated by the hypha growth inhibition and

the spore germination inhibition methods against eight phytopathogenic fungal strains. All compounds showed antimicrobial activity, and the MIC values for the tested strains (*S. aureus*, *B. subtilis*, *Micrococcus luteus*, *Bacillus cereus*, *Ralstonia dolaanacearum*, *Xanthomonas oryzae* pv. *oryza*, *Xanthomonas campestris* pv. *vesicatoria*, *Xanthomonas campestris* pv. *citri*) ranged from 62.5 to 125 μg/ml. In the hypha growth inhibition method, EC_{50} values for the four strains tested (*Fusarium solani*, *Rhizoctonia solani*, *Pythium aphanidermatum*, *Phytophthora parasítica*) ranged from 82.4 to 347.33 μg/ml. Deoxymikanolide (**37**) was the most active compound in the spore germination assay, and the IC_{50} ranged from 21.44 to 53.18 μg/ml for the four strains tested (*Exserohilum turcicum*, *Botrytis cinerea*, *Pseudoperonospora cubensis*, *Colletotrichum lagenarium*) (Li et al. 2013).

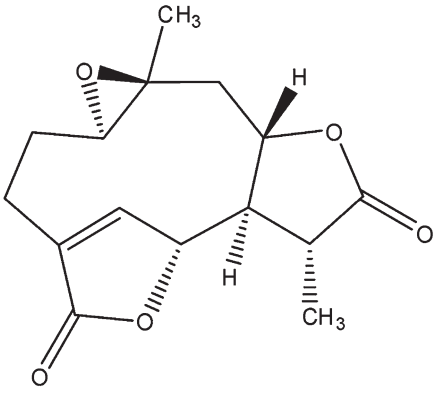


R_1=R_2=R_3=H **deoxymikanolide (37)**
R_1=R_3=H R_2=OAc **scandenolide (38)**



dihydroscandenolide (39)

In another study (But et al. 2009), the methanolic extract from the dried aerial parts of *M. micrantha* has shown inhibitory activity on respiratory syncytial virus (RSV) with an IC_{50} of 60 μg/ml. Further studies led to the isolation of sesquiterpene lactones **36**, **39,** and **40**. These sesquiterpene lactones showed weak antitype A influenza activities, while compound **40** showed moderate activity against RSV (IC_{50} = 37.4 μM) and parainfluenza type 3 virus (IC_{50} = 37.4 μM) with a therapeutic index of 10 for both viruses.



1,10-epox-4-germacrane-12,8;15,6-diolide (40)

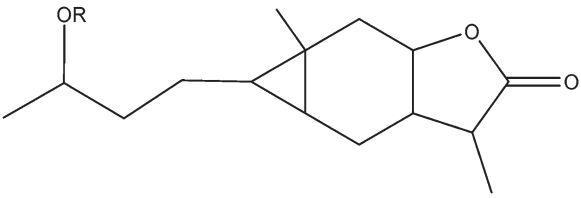
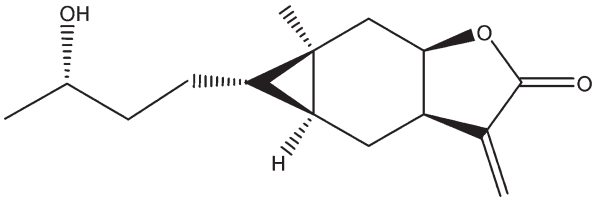


Fig. 12.4 Carabranolide skeleton

12.2.4 Carabranolides

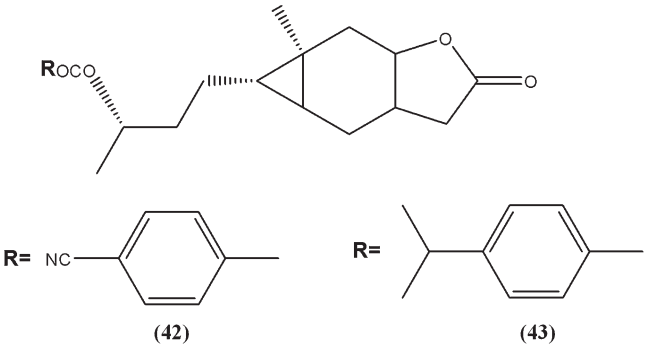
Carabranolide sesquiterpene lactones (Fig. 12.4) are secoregular sesquiterpenoids that can be biosynthesized from a xanthanolide carbon skeleton by creating a bond between C-5 and C-10 to form a ring (Zhang et al. 2015). Interestingly, carabrol (**41**) is the only compound presenting antimicrobial activity (see below).

The sesquiterpene lactone carabrol (**41**) has been isolated from *C. abrotanoides*. This compound has shown antifungal activity against *Colletotrichum lagenarium* with an IC_{50} value of 20.14 μg/ml in a spore germination assay. The fungus *C. lagenarium* is the causative agent of anthracnose of leaves and fruits of cucurbit crops, resulting in severe yield losses and reduction in the quality of the fruits (Feng et al. 2012).



carabrol (41)

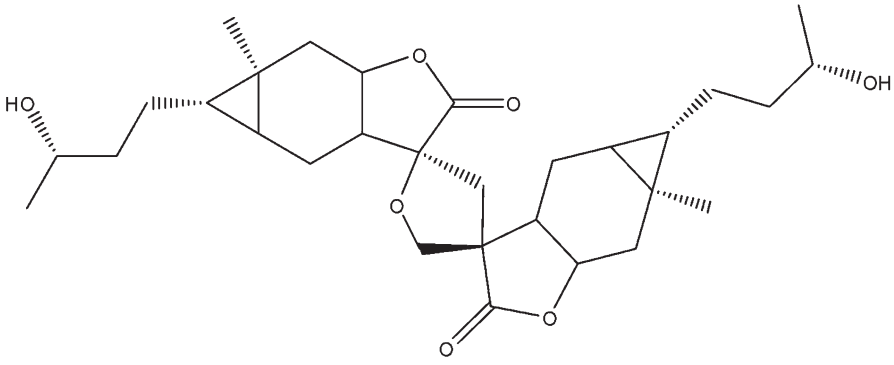
Because carabrol has great potential as a template for developing more effective fungicides that may be environmentally safe, Feng et al. (2012) prepared 38 ester derivatives and tested them on *C. lagenarium*, 16 of which showed higher antifungal activity than that of carabrol. The authors found that the C-4 position of carabrol was key for the biological activity. When that position was substituted by a phenyl ring, the ester derivatives bearing electron-attracting groups showed higher activity than those bearing electron-donating ones. Two ester derivatives, carabryl 4-cyanobenzoate (**42**, IC_{50} = 2.70 μg/ml) and carabryl 4-isopropylbenzoate (**43**, IC_{50} = 2.82 μg/ml), showed an antifungal activity that was near to chlorothalonil used as positive control (IC_{50} = 0.87 μg/ml) (Feng et al. 2012).



(42) (43)

12.2.5 *Dimeric Sesquiterpene Lactones*

Sesquiterpene dimers, which are also called disesquiterpenoids, can be classified into three major classes based on their biosynthetic origins, namely, true disesquiterpenoids, pseudo-disesquiterpenoids, and dimerosesquiterpenoids. Sesquiterpene dimers are mainly synthetized by Diels-Alder, hetero-Diels-Alder, [2 + 2] cycloaddition, or free-radical coupling reactions (Zhang et al. 2015). Sesquiterpenoid dimers with unusual carbon skeletons have been reported. The complex linkage patterns, along with their multiple chiral centers, make them to exhibit more "biologically friendly" and "drug-like" molecular features than the corresponding monomers (Wu et al. 2017), as is the case of dimeric sesquiterpene lactones.

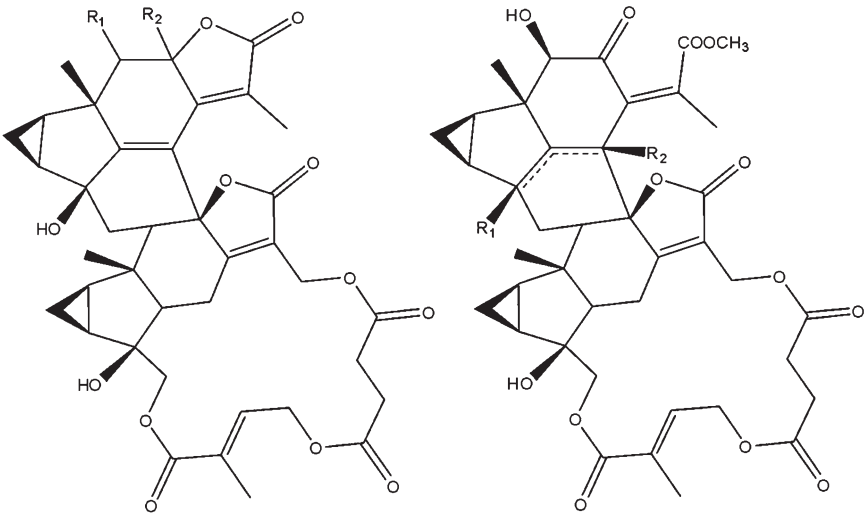


dicarabrol (44)

Dicarabrol (**44**) is a dimeric sesquiterpene lactone which has been isolated from *C. abrotanoides* along with other dimeric and monomeric sesquiterpene lactones. Dicarabrol (**44**) possesses an unusual carbon skeleton with two carabranolide moieties linked through a spirotetrahydrofuran ring, presumably generated by a [4 + 2]

cycloaddition (Wu et al. 2015). The molecule displayed significant antimycobacterial activity on *Mycobacterium tuberculosis* H37Rv with an IC_{50} value of 3.7 μM (1.91 μg/ml), control isoniazid IC_{50} = 2.0 μM (0.2 μg/ml) employing the alamar blue microdilution test (Wang et al. 2015).

Mycobacterium tuberculosis has been a major human pathogen since the dawn of modern human existence. The prognosis for patients with tuberculosis has improved dramatically with the discovery and introduction of antitubercular drugs, starting with streptomycin in 1946 and subsequent research that produced today's frontline therapies for drug-sensitive *M. tuberculosis*. Despite having an effective treatment regimen, tuberculosis is still causing millions of infections and deaths. There are a few drugs that are currently being assessed in clinical trials. Besides, major pharmacological redundancies exist, with many of the new agents in the pipeline that share a similar mechanism of action, cross-resistance, and/or side effect profiles, which makes them unsuitable to be used in combination (Hoagland et al. 2016). Taking into account these facts, the search for new drugs within the plant kingdom can certainly give interesting results, as occurs with dicarabrol.



	R_1	R_2
henriol A(45)	β-OH	α-OH
spicachlorantin A(46)	=O	α-OH
8 tianmushanol (47)	β-OH	β-OH
8-O-methyltianmushanol (48)	β-OH	β-OCH_3

	R_1	R_2	Δ
chloramultilide A (49)	OH	--	5,6
shizukaol B (50)	--	H	4,5

The dimeric carabranolide sesquiterpene lactones henriol A (**45**), spirachlorantin A (**46**), 8-tianmushanol (**47**), 8-O-methyltianmushanol (**48**), chloramultilide A (**49**), and shizukaol B (**50**) have been isolated from *C. angustifolius*, which was cited above as a producer of antimicrobial eudesmanolide sesquiterpene lactones. The compounds were tested in vitro using a microdilution assay against a panel of five bacterial strains including *S. aureus* (ATCC 29213), *E. coli* (ATCC 25922),

S. typhimurium (ATCC 13311), *P. aeruginosa* (ATCC 27853), and *Klebsiella pneumoniae* (ATCC 18433), as well as six fungal strains including *C. albicans* (ATCC 90028), *C. neoformans* (ATCC 22402), *Candida glabrata* (ATCC 90030), *Candida krusei* (ATCC 6258), *Candida parapsilosis* (ATCC 22019), and *Aspergillus* spp. (ATCC 293). None of the compounds were active on bacteria at 256 μg/ml; however, the compounds showed activity on the fungal strains tested. All compounds displayed significant antifungal activity against *C. albicans*, with MIC values ranging from 4 to 8 μg/ml (MIC itraconazole = 0.125 μg/ml). Shizukaol B (**37**) was active on *C. neoformans* (MIC itraconazole = 2.0 μg/ml) and on *Aspergillus* spp. with a MIC value of 8 μg/ml (MIC itraconazole = 2.0 μg/ml) (Yang et al. 2014).

12.2.6 Seco-prezizaane Sesquiterpene Lactones

Seco-prezizaane-type sesquiterpenoids (Fig. 12.5) constitute a biosynthetically fascinating, architecturally variegated, and rapidly growing class of natural products that are found as characteristic chemical markers of *Illicium* spp. (Schisandraceae) (Liu et al. 2015). This genus is widely distributed in southern regions of China.

The cortex and root bark of *Illicium* spp. such as *I. merrillianum*, *I. jiadifengpi*, and *I. minwanense* have been used in folk medicine for the treatment of rheumatoid arthritis. Studies performed on the ethanolic extract of the fruits of *I. jiadifengpi*, a tree found in South China, led to the isolation of two new *seco*-prezizaane sesquiterpene lactones 2*S*-hydroxyl-jiadifenolide (**51**) and jiadifenlactone acid (**52**) along with other known *seco*-prezizaane sesquiterpene lactones (**53** and **54**). The compounds were tested for their potential anti-HBV activities regarding their capacity to inhibit the secretion of HBsAg and HBeAg to the culture medium of HBV-infected HepG2.2.15 cells under non-cytotoxic concentrations (Liu et al. 2015). The compounds **53** and **54** were the most active, inhibiting 15.53 to 37.93% of HBeAg and HBsAg expression at 64.94 and 61.35 μM, respectively. These results suggest that the carbonyl group at position 2 enhanced the antiviral activity (Liu et al. 2015).

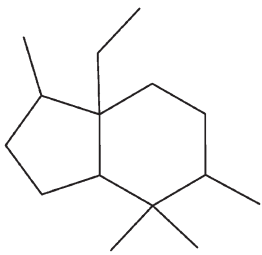
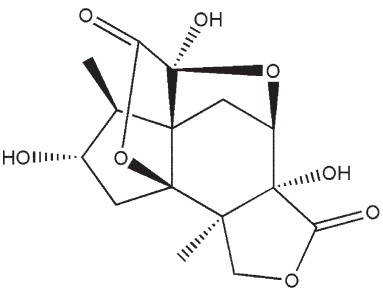
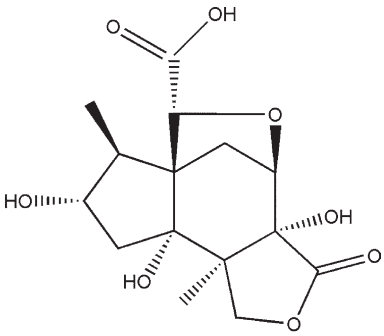


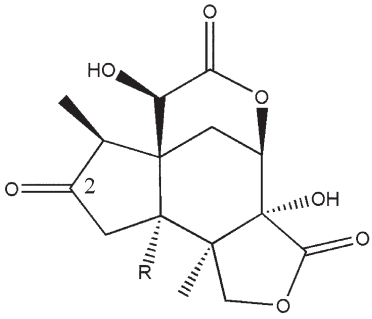
Fig. 12.5 Seco-prezizaane skeleton



2S-hydroxyl-jiadifenolide (51)



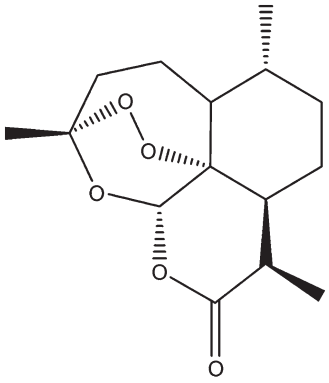
jiadifenlactone acid (52)



R=OH 2-oxoneomajucin (53)
2-oxo-3,4-dehydroxyneomajucin (54)

12.2.7 Cadinanolides

Artemisia annua (Asteraceae), also known as "sweet wormwood," is a traditional Chinese herbal medicine which has been used for hundreds of years for its antimalarial properties, among others. Artemisinin (**55),** a cadinane-type sesquiterpene containing a unique peroxide bridge, has been identified in China in 1972 as the active compound (Efferth et al. 2008); and since then, artemisinin and its derivatives have been used against multidrug-resistant *Plasmodium falciparum* strains.

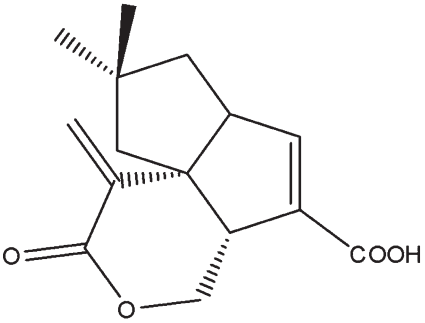


artemisinin (55)

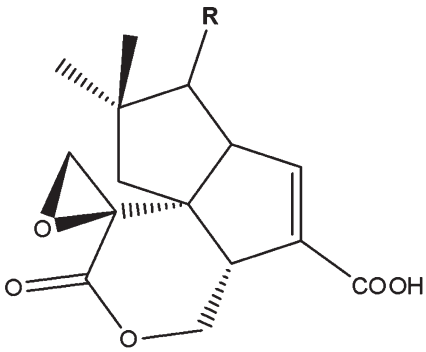
Apart from its potent antimalarial activity, artemisinin has immunomodulatory and antitumor properties. In addition, several in vitro studies have demonstrated that the compound has also antiviral activities (Goswami et al. 2012, Ivanescu et al. 2015). Artemisinin (**55**) has shown considerable anti-HBV activity, when tested on HBV-transfected HepG2 2.2.15 cells, inhibiting HBsAg secretion with an IC_{50} = 55 μg/ml (Romero et al. 2005). The compound inhibited HCV replication in Huh5–2 cells, with an EC_{50} = 78 μM (Paeshuyse et al. 2006). The compound has also demonstrated strong activity against *Helicobacter pylori*, which is one of the causative agents of peptic ulcer disease. When tested against standard strains and clinical isolates of *H. pylori*, artemisinin (**55**) generated a 1.5 to 2.5 cm inhibition zone diameter at a dose of 1 to 5 μg/disc and MIC values that ranged from 0.5 to ≥8 μg/ml (Goswami et al. 2012).

12.2.8 Microbial Sesquiterpene Lactones

Pentalenolactones, also known as arenaemycins, are a sesquiterpenoid family of antibiotics discovered in 1957 in the culture extracts of *Streptomyces roseogriseus* and subsequently isolated from numerous *Streptomyces* species such as *S. avermitilis* and *S. arenae* (Takamatsu et al. 2011).



pentalenolactone E (56)



R=H **pentalenolactone F (57)**
R= =O **pentalenolactone G (58)**
R=OH **pentalenolactone H (59)**

Pentalenolactones (**56–59**) are active against both Gram-positive and Gram-negative bacteria, as well as pathogenic and saprophytic fungi (Takamatsu et al. 2011). The mechanism of action of pentalenolactone E (**56**) has been reported by Hartmann et al. (1978). These authors have demonstrated that pentalenolactone exerts its antimicrobial activity by selective irreversible inhibition of glyceraldehyde-3-phosphate dehydrogenase (EC 1.2.1.12), an enzyme from the glycolytic pathway, with no affectation of other glycolytic reactions or enzymes of the intermediary metabolism. The study showed that pentalenolactone E (**56**) inhibits the enzyme of both prokaryotic and eukaryotic organisms (Hartmann et al. 1978).

12.3 Conclusion

Sesquiterpene lactones constitute a great group of natural products with an outstanding chemical diversity. Derived from the common biosynthetic precursor farnesyl diphosphate (FPP), they can undergo many chemical changes to produce several different backbones.

The antimicrobial and antiviral properties of 59 natural and semisynthetic sesquiterpene lactones were included in this chapter. All the natural structures discussed herein have been isolated from plants, with the exception of pentalenolactones, which are the only sesquiterpene lactones of microbial origin. Semisynthetic molecules dehydrozaluzanin and carabrol esters have also been included, and their antimicrobial properties were discussed.

As for the sesquiterpene lactones isolated from plants, most of them were from the Asteraceae family, followed by a few molecules from the Chloranthaceae and Schisandraceae families. These compounds may play a role in the defense of these

plants against pathogens, herbivorous insects, and mammals and in competition with other plants. Regarding sesquiterpene lactones of bacterial origin, they were from *Streptomyces* spp.

Different methods have been used to evaluate the antibacterial or antifungal activity of sesquiterpene lactones. It is known that the use of standardized methods is extremely important in order to perform comparisons of antimicrobial activities both intra- and inter-laboratory. It must be taken into account that the results corresponding to each research have been presented in different units. In addition, in many examples included in this chapter, no information regarding the values obtained for positive controls was provided. Thus, comparison of antimicrobial activities to establish valid relationships becomes difficult.

The biological activities of sesquiterpene lactones, including the antimicrobial activity, are generally the result of their interaction with the thiol groups present in proteins. When the relationship between the biological activity and the chemical structure was studied, no major generalizations could be obtained. In addition to the α-methylene-γ-lactone moiety, suspected to be responsible for many activities, other functionalities and their position on a skeleton and/or configuration may also enhance or reduce the activity of sesquiterpene lactones. Differences in the physiology and biochemistry among the target organisms must also be considered in order to draw valid conclusions.

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