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Sesquiterpene Lactones

Advances in their Chemistry and Biological Aspects

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Cover illustration: The image corresponds to the leaf surface of *Artemisia annua*, showing glandular trichomes, the site of artemisinin biosynthesis. The image belongs to The CNAP Artemisia Research Project, University of York, UK

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We wish to dedicate this book to our dear colleague, Argentine botanist Gustavo Carlos Giberti, who was the mentor of many Argentine medicinal flora scholars.

Gustavo Giberti, PhD (September 7th, 1951–July 2nd, 2017), graduated as Agricultural Engineer from University of Buenos Aires (UBA) in 1976.

He attended a postgraduate specialization course at Royal Botanic Gardens, Plant Anatomy Section (Kew, Great Britain), directed by David F. Cutler, PhD (1980–1982), and at Escuela Técnica Superior de Ingenieros Agrónomos, Universidad Politécnica de Madrid (Spain), directed by Prof. César Gómez Campo, PhD (1882–1983). In 2002, he earned a PhD from the University of Buenos Aires in the field of pharmacobotany and pharmacognosy.

From 1984 up to 2017, he worked as an Independent Researcher of the Scientific and Technological Research Career of the National Council for Scientific and Technical Research (CONICET) at Instituto de Química y Metabolismo del Fármaco

(Institute for Drug Chemistry and Metabolism Studies) (IQUIMEFA-UBA-CONICET), and as curator at the Herbarium of Museo de Farmacobotánica (Pharmacobotany Museum) "Juan Aníbal Domínguez" at the School of Pharmacy and Biochemistry (UBA). He also specialized in economic botany and pharmacobotany. In Argentina, he was an expert in plants of the Aquifoliaceae family, especially, those belonging to the Ilex genus.

He has authored more than forty scientific papers and about thirteen book chapters and also contributed largely by helping collect and identify the plant materials employed in the research works carried out at the IQUIMEFA.

We will always remember Gustavo for his gentleness and kindness and for his immense generosity to share his knowledge with all of us.

Foreword

This book was originally conceived as a smaller project focused only on the antiparasitic activity of sesquiterpene lactones. After the evaluation of the proposal and taking into account the potential applications of this group of compounds, we decided to expand the scope and to explore chemical and biological aspects by including data on other biological activities and structure-activity studies.

Having obtained collaboration from renowned researchers in the field is, indeed, a dream come true. Virginia Martino, PhD, and César Catalan, PhD, deserve special mention, since they were my research directors and continue to be my mentors in the fields of pharmacognosy and chemistry, especially that of sesquiterpene lactones, respectively. Although they are both retired, they have given me support for the fulfillment of this project.

I am also grateful to those who have relied on and collaborated in this project: Marcus Tullius Scotti, PhD, and Fernando Batista da Costa, PhD (chemotaxonomy); Julián Rodriguez Talou, PhD, and Maria Perassolo, PhD (biotechnology); Francis Barrios, PhD (organic synthesis); Osvaldo Donadel, PhD (chemistry of natural products); Silvia Cazorla, PhD (trypanosomatids); Nubia Boechat, PhD (antiplasmodial compounds); María Elisa Lombardo, PhD (therapeutic targets and antitrypanosomal drugs); Miguel Sosa Escudero (microscopy); María Victoria Castelli, PhD, and Silvia Noelí López, PhD (antimicrobials); Claudia Anesini, PhD (antitumoral compounds); María Rosario Alonso, PhD (anti-inflammatory compounds); and Thomas J. Schmidt, Dr. rer. nat (structure-activity studies), who has given me access to Research Network Natural Products Against Neglected Diseases (ResNet NPND), which is devoted to the searching of novel natural drugs against neglected diseases.

Gustavo Giberti, PhD, also deserves a special mention in this Foreword. He has died unexpectedly in 2017 and to him we dedicate this book with all our affection. We will cherish in our hearts all the fieldwork and experiences we shared.

I believe the content of this book has met the goals. I would like to thank all the collaborating authors. As for me, I can only say: Mission accomplished!

Valeria P. Sülsen

Preface

Although some interesting reviews on sesquiterpene lactones have been published, many advances have recently been made in this field, which implies the necessity of an update.

The aim of this book is to review such recent advances made in the study of sesquiterpene lactones, discussing their potential medical applications.

Different aspects will be reviewed, such as the distribution and taxonomy; the biosynthetic pathways; their chemistry, including the synthesis and chemical and biological transformations as well as the analytical isolation and identification procedures most frequently employed. Their biological properties mainly focused on the antimicrobial, antiproliferative, and anti-inflammatory activities and structure-activity studies will be also summarized. An update on the main molecular targets for their antiprotozoal activity will also be presented.

It is expected that this book will serve as a source of information to scientific researchers and postgraduate students, being inspiring for the performance of further studies on the chemistry and the biological activities of this fascinating group of compounds. Finally, the aim of this book is to highlight the importance of sesquiterpene lactones as lead molecules for the development of new therapeutic drugs.

Valeria P. Sülsen
Virginia S. Martino

Acknowledgments

We thank Dr. Luis Fernando de O. Furtado, Springer Science + Business Media Editor – Applied Sciences, for inviting us to participate in this editorial project and for believing that we could materialize it.

We also acknowledge Panneerselvam Silembarasan, the Project Coordinator (Books) for Springer Nature, for his guidance and prompt reply to our queries.

We are very grateful to all contributing authors for having embarked in this project and for sharing their knowledge and expertise, as well as for having devoted their time to compiling the literature material and to writing each chapter. We would like to congratulate them for the high quality of their contributions and their predisposition to revise the manuscripts.

We thank Guillermo Nuñez Taquía, PhD, for English correction.

We kindly acknowledge Dr Caroline M. Calvert, CNAP Manager, HVCfP Network Manager, Department of Biology, University of York, York, UK, for providing the cover image.

We are profoundly thankful to the National Council for Scientific and Technical Research (CONICET), the University of Buenos Aries (UBA), and the National Agency for Scientific and Technological Promotion (ANPCyT) – Science, Technology and Productive Innovation Ministry for supporting this project.

This book entails a complex coordination of efforts and it is the embodiment of the work carried out by many people; we want to express our gratitude to all of them.

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Part I
Chemical and Biochemical Aspects of Sesquiterpene Lactones

Chapter 1
Overview

Valeria P. Sülsen and Virginia S. Martino

Abstract Sesquiterpene lactones (STLs) are a group of naturally occurring compounds, most of them found in the Asteraceae family but also present in Apiaceae, Magnoliaceae, and Lauraceae. To date about 8000 compounds have been reported. They consist of a C15 backbone with numerous modifications resulting in a variety of structures but with the common feature of a γ-lactone ring. They are classified in four major groups: germacranolides, eudesmanolides, guaianolides, and pseudoguaianolides, though there are other subtypes. There has been an increasing interest in sesquiterpene lactones due to the wide range of biological activities they present. Among the activities found, antimicrobial, antitumor, anti-inflammatory, antioxidant, antiulcerogenic, molluscicidal, antihelminthic, hepatoprotective and hepatotherapeutic, antiprotozoal, antidepressant, and bitter properties have been described. Besides, they play an important role in the interaction of plants with insects acting as attractants, deterrents, and antifeedants. These compounds were considered at first highly cytotoxic, but chemical transformations have enhanced their biological activities and diminished their cytotoxicity, so considerable attention has been drawn again on them as lead molecules. Artemisinin derivatives, artesunate, and artemether are drugs currently being employed, and dimethylaminoparthenolide, a parthenolide synthetic analogue, and mipsagargin, a prodrug from thapsigargin, are under clinical trials.

A summary with the most important findings about the known sesquiterpene lactones, artemisinin, parthenolide, cynaropicrin, dehydroleucodine, mexicanin, helenalin, costunolide, santonin, arglabin, and thapsigargin, will be given.

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Studies about the adverse health effects, toxicity, and ecological roles of some sesquiterpene lactones are also mentioned.

Keywords Sesquiterpene lactones · Chemical aspects · Biological activities · Adverse effects · Toxicity

1.1 Introduction

Since ancient times, natural products have played an important role in human health and have constituted one of the main sources of bioactive compounds and templates for synthetic modifications. According to Newman and Cragg (2016), the utilization of natural products and their derivatives in the development of new therapeutic drugs is still a promising approach. Recently, the 2015 Nobel Prize in Medicine has been awarded to Dr. Youyou Tu for the discovery of the natural product artemisinin, which is today an important component of the combined therapy for the treatment of malaria. This award highlighted the importance of the investigation of traditional medicine and drugs coming from natural sources (The Society for Medicinal Plant and Natural Product Research 2017). In the cancer research field, during the 1940–2014 period, 49% of all the small molecules approved for medical use were natural products or their derivatives. In other areas, such as the one corresponding to antimicrobial agents, the use of natural products is also frequent.

Sesquiterpene lactones (STLs) are a group of naturally occurring compounds, generally colorless and bitter in taste. Most of them are found in the Asteraceae family; however, they are also present in Apiaceae, Magnoliaceae, and Lauraceae families (Padilla González et al. 2016). They are mainly found in the leaves and in the flowering heads in a range from 0.001% to 8%/dry weight (Chaturvedi 2011). Some species store large amounts of STLs in leaf trichomes (Amorim et al. 2013).

Sesquiterpene lactones are present in food plants such as lettuce (*Lactuca sativa*) and chicory (*Cichorium intybus*), and star anise (*Illicium verum*) and in many medicinal plants such as feverfew (*Tanacetum parthenium*), qinghaosu (*Artemisia annua*), and yarrow (*Achillea* spp.) (Chaturvedi 2011).

There has been an increasing interest in STLs, mainly for their importance as chemical markers in biosystematic studies and for their wide range of biological activities. Among the activities explored for this group of compounds, antimicrobial, antitumor, anti-inflammatory, antioxidant, antiulcerogenic, molluscicidal, antihelminthic, hepatoprotective and hepatotherapeutic, antidepressant, and bitter properties have been described. Besides, they play an important role in the interaction of plants with insects acting as attractants, deterrents, and antifeedants (Chaturvedi 2011; Amorim et al. 2013).

Sesquiterpene lactones were considered at first highly cytotoxic. Chemical transformations have enhanced their biological activities and diminished their cytotoxicity, so considerable attention has been drawn again on them as lead molecules.

Artemisinin derivatives, artesunate, and artemether are drugs currently being employed, and dimethylaminoparthenolide, a parthenolide synthetic analogue, and mipsagargin, a prodrug from thapsigargin, are under clinical trials.

To date, about 8000 STLs have been reported (Macias et al. 2013). Some early reviews can be found in the literature about STLs which can be considered as a starting point for the present overview. In Yoshioka et al. (1973), the major skeleton types of STLs and the NMR spectra of 200 naturally occurring compounds are presented. Fischer et al. (1979) and Fischer (1990) summarize the biogenetic considerations concerning the different types of STLs as well as the regulation of their biosynthetic pathways. Rodriguez et al. (1976) and Picman (1986) disclose and discuss some of the more important biological activities of STLs. Other more recent reviews by Chaturvedi (2011) describe the structural characteristics and the biological activities of these compounds, while Chadwick et al. (2013) highlight the importance of STLs, not only for their potential as pharmaceutical agents but also for their importance as nutritional factors and for their physiological role in plants as antioxidants and growth factors, antifeedants, and allelochemicals and as the active constituents of many plants used in traditional medicine. Adekenov (2013) provides an overview of the available technology for the isolation of natural STLs and the chemical modifications to which STLs can be subjected and discusses their potential as source of new biologically active derivatives. In a subsequent publication, Adekenov and Atazhanova (2013) summarize the heteroatom-containing natural STLs, their natural occurrence, isolation methods, and biological activities, while Hohmann et al. (2016) disclose their anti-inflammatory effects. Padilla González et al. (2016) discuss the protective and physiological role of STLs in plants.

1.2 Chemical Aspects

Sesquiterpene lactones consist of a fifteen-carbon (C15) backbone, being the majority cyclic, with numerous modifications and resulting in a variety of structures. A distinctive feature of STLs is the presence of a γ-lactone ring closed toward either C-6 or C-8. This γ-lactone contains, in many cases, an *exo*-methylene group conjugated to the carbonyl group (Padilla González et al. 2016; Picman 1986). The stereochemistry of the lactonization can be either α or β, since the lactone ring can be fused to the remaining skeleton in either a *trans* or *cis* configuration (*trans*- or *cis*-fused STLs) (Padilla González et al. 2016; Ahern and Whitney 2014). The *trans*-configuration is the most common, and as a rule, the H-7 of STLs is α-oriented (Fischer 1990) (Fig. 1.1).

In some STLs, the exocyclic methylene is reduced, as is the case of artemisinin, matricin, achillin, and santonin, or the double bond can be endocyclic (Padilla González et al. 2016).

Sesquiterpene lactones are classified in four major groups: germacranolides (10-membered ring), eudesmanolides (6–6 bicyclic compounds), guaianolides, and pseudoguaianolides (5–7 bicyclic compounds) (Yoshioka et al. 1973) (Fig. 1.2). Nevertheless, according to their skeletal arrangement, there are other subtypes of

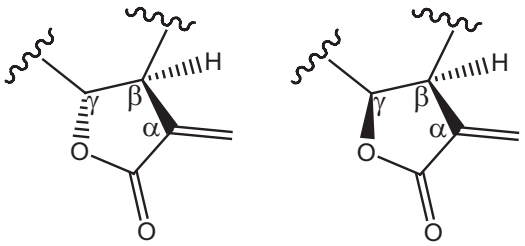


Fig. 1.1 α,β-unsaturated γ-lactone moiety present in the sesquiterpene lactones. (**a**) *trans*-fused lactone ring, (**b**) *cis*-fused lactone ring

STLs (Fischer et al. 1979; Rodriguez et al. 1976; Picman 1986; Padilla Gonzalez et al. 2016). The suffix "olide" indicates the presence of a lactone group in the structure. The presence of epoxy groups, hydroxyls, and hydroxyls esterified with acetate, which is the most frequent, propionate, isobutyrate, methacrylate, isovalerate, epoxymethacrylate, 2-methylbutanoate, tiglate, angelate, senecioate, epoxyangelate, sarracinate, acetylsarracinate, and other similar residues is frequently found in STLs. Only a few glycosylated lactones or lactones bearing halogen or sulfur atoms in their structures have been described. A cyclopentenone moiety (dehydroleucodin, achillin) and a second α,β-unsaturated lactone ring (mikanolide, deoxyelephantopin) can also be found in STLs (Rodriguez et al. 1976; Picman 1986; Schmidt et al. 2002).

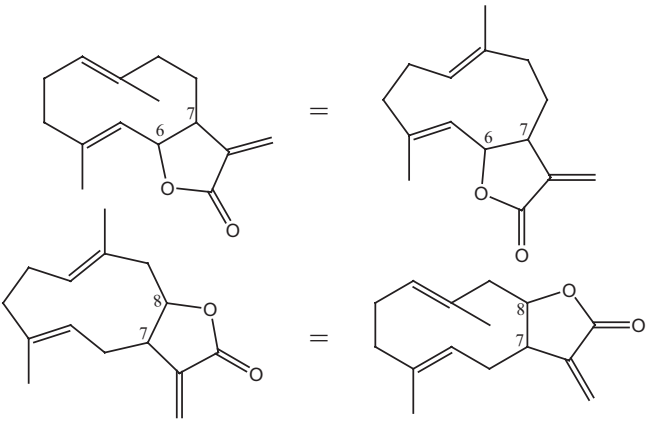
1.3 Some Representative Sesquiterpene Lactones

The STLs included in this chapter have been selected based upon the number of studies found in the literature, their biological activities, and/or the fact they are actually being used as medicines or are in clinical trials (Fig. 1.3).

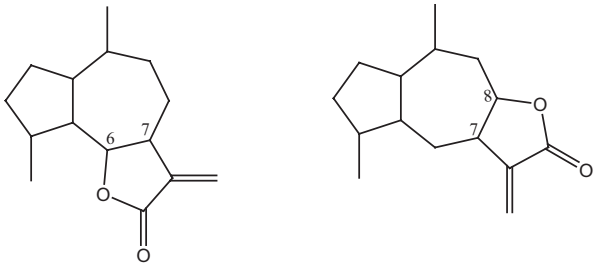
1.3.1 Santonin

Santonin **(1)** is an eudesmanolide present in *Artemisia santonica* and is one of the earliest STLs discovered (1830). This STL has been used as ascaricide and to remove all kind of worms and for the retention of urine and enuresis caused by atony or of other origins. Its pharmaceutical use was abandoned due to its toxic effects. Its anti-inflammatory, antipyretic, and analgesic effects have been reported (al-Harbi et al. 1994). Numerous chemical modifications have been introduced on the santonin structure in order to enhance its antiproliferative activity and cell differentiation on leukemia cells (Khazir et al. 2013; Kweon et al. 2011; Arantes et al. 2010) and its antimalarial activity (Tani et al. 1985). This molecule has been selected as the starting point for the synthesis of other guaianolides and eudesmanolides. Its structure was one of the first to be elucidated among STLs (Birladeanu 2003).

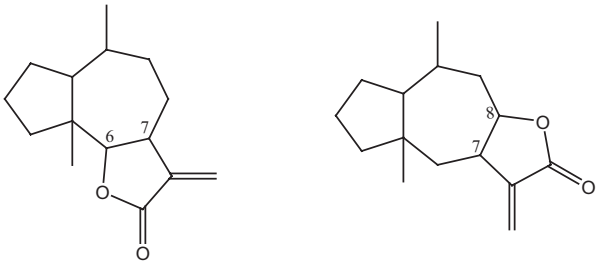
Germacranolides



Guaianolides



Pseudoguaianolides



Eudesmanolides

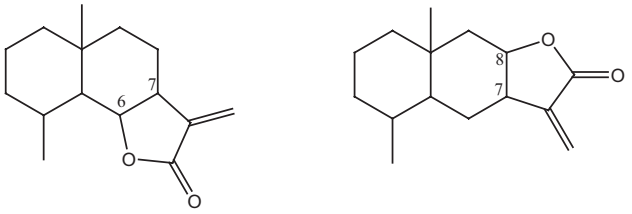


Fig. 1.2 Major skeletal types of sesquiterpene lactones

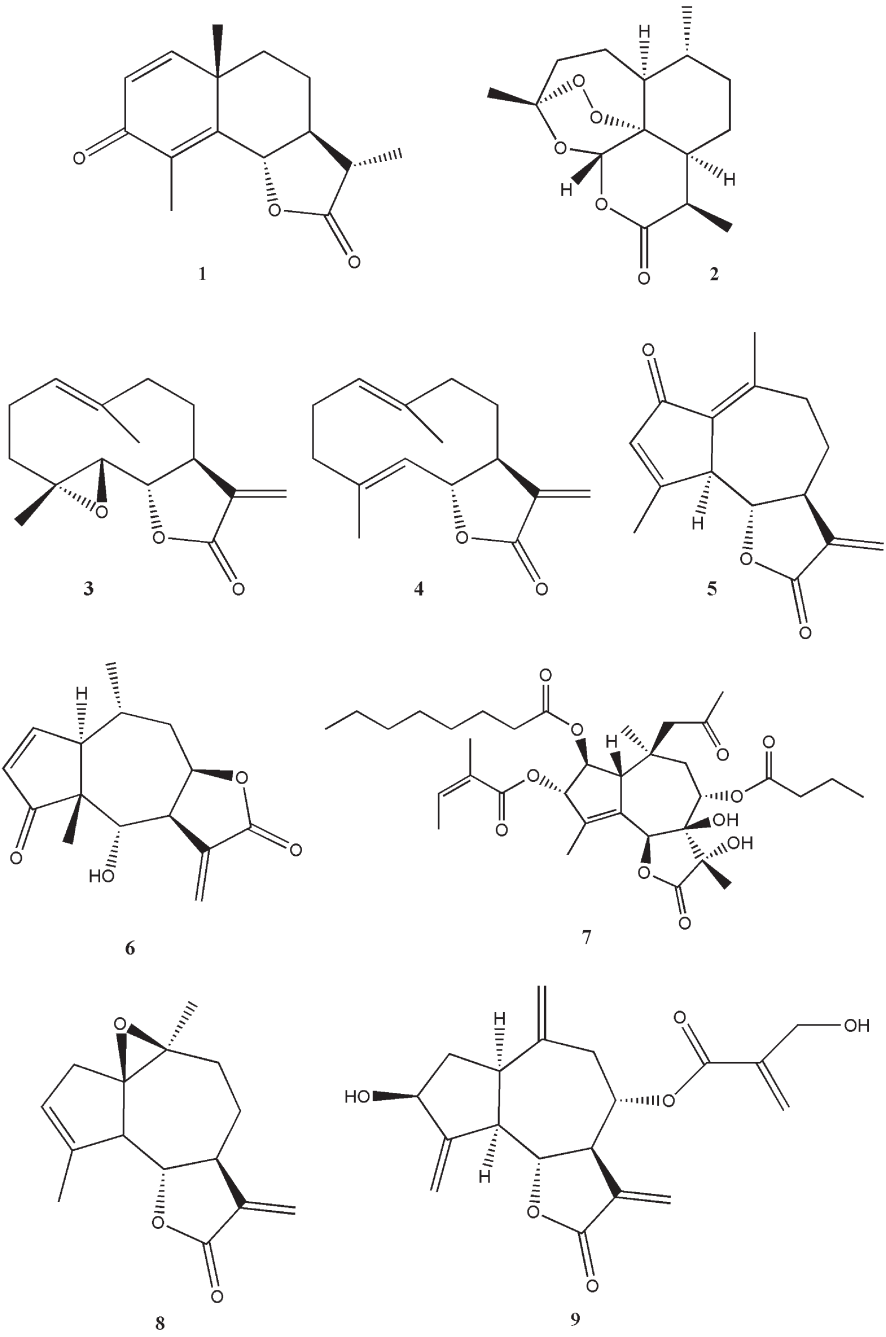


Fig. 1.3 Some representative sesquiterpene lactones

1.3.2 Artemisinin

Artemisinin **(2)** is a very a particular compound, for it presents an endoperoxide ring in its molecular structure. This STL has been isolated from *Artemisia annua* (Asteraceae). The aerial parts of this plant have been used as febrifuge in Chinese traditional medicine. Nowadays artemisinin and its derivatives are used as antimalarial against chloroquine-resistant *Plasmodium falciparum.* Other activities reported for this STL include leishmanicidal (Lezama Dávila et al. 2007; Ghaffarifar et al. 2015) and anticancer. The latter property is due to its capacity to inhibit cell growth and to induce apoptosis in human hepatocellular carcinoma cells (SMMC-7721) (Deng et al. 2013) and other cell lines (Crespo Ortiz and Wei 2012; Das 2015). Artemisinin also shows antischistosomal activity (Saeed et al. 2016). Activity against *Helicobacter pylori* has also been reported (Sisto et al. 2016).

Artemisinin derivatives are currently being assessed in phase I and II trials against lupus nephritis and breast, colorectal, and lung cancers (Lone et al. 2015).

1.3.3 Parthenolide

Parthenolide **(3)** is the active principle of feverfew (*Tanacetum parthenium*, Asteraceae). It is a traditional herbal medicine that has been used for centuries for the treatment of migraine, fever, and arthritis (Chaturvedi 2011). This STL has antiproliferative activity on multiple cancer cells such as melanoma; breast, colon, and lung cancer; and leukemia, among others (Wu et al. 2006; Parada Turska et al. 2007; Czyz et al. 2010: Gunn et al. 2011, Mathema et al. 2012). The compound selectivity to exert apoptosis in cancer cells provides an important and novel therapeutic strategy for the treatment of cancer and inflammation-related disorders (Liu 2013).

Other activities have been described for parthenolide such as antiprotozoal (against *Trypanosoma cruzi* and *Leishmania* spp.) (Izumi et al. 2008; Tiuman et al. 2005), anti-inflammatory (Wang and Li 2015), antiherpetic (Onozato et al. 2009), and antiosteoclastogenic (Kim et al. 2014).

1.3.4 Costunolide

Costunolide **(4)** is a germacranolide-type STL present in *Saussurea lappa* roots, a traditional Chinese medicinal herb that has anticancer and anti-inflammatory properties. This compound has also been isolated from other plant species such as *Magnolia* sp., *Laurus nobilis*, and *Costus speciosus*, among others. It exhibits a broad spectrum of bioactivities: antidiabetic and antioxidant (Eliza et al. 2009, 2010), anti-inflammatory (Butturini et al. 2014), antiulcerogenic (Zheng et al. 2016), anticlastogenic

(Cheon et al. 2014), and potential anticancer activity. Costunolide exerts its antiproliferative effect by inducing apoptosis through ROS generation (Wang et al. 2016) and cell cycle arrest (Liu et al. 2011; Lin et al. 2016), among other mechanisms. This STL is active on lung carcinoma (Wang et al. 2016; Hua et al. 2016); breast (Roy and Manikkam 2015), colon (Dong et al. 2015), bladder (Rasul et al. 2013), and platinum-resistant ovarian cancer (Yang et al. 2011); hepatoma (Liu et al. 2011); and leukemic (Choi and Lee 2009) cells.

1.3.5 Dehydroleucodine

Dehydroleucodine **(5)** is a STL isolated from *Artemisia douglasiana* which shows cytotoxic activity against human leukemia cells (Ordoñez et al. 2016) and inhibits the growth of melanoma cells in an animal model (Costantino et al. 2016). It reduces inflammation and gastrointestinal ethanol-induced damage, protecting the gastric mucosa, as demonstrated in in vivo models (Guardia et al. 2003; Wendel et al. 2008; Repetto and Boveris 2010). This compound has inhibitory effect on *T. cruzi* infective forms and *Leishmania mexicana* promastigotes (Jimenez Ortiz et al. 2005; Barrera et al. 2008). Antimicrobial activity against *Pseudomonas aeruginosa* multiresistant strains has also been reported for this compound (Mustafi et al. 2015).

1.3.6 Helenalin

Helenalin **(6)** is a guaianolide STL isolated from *Arnica montana* and other species of the Asteraceae family. It has been reported to possess cytotoxic (Grippo et al. 1992), hepatoprotective, anti-inflammatory, antioxidant (Lin et al. 2014), and antimicrobial properties against *Staphylococcus aureus* (Boulanger et al. 2007). It affects steroidogenesis in rat adrenocortical cells (Supornsilchai et al. 2006) and has cardiotonic activity (Itoigawa et al. 1987). Trypanocidal effects have also been reported (Schmidt et al. 2002; Jimenez-Ortiz et al. 2005).

1.3.7 Thapsigargin

Thapsigargin **(7)** is a guaianolide STL isolated from *Thapsia garganica* (Apiaceae). This Mediterranean medicinal plant was mentioned by Hippocrates, Theophrastus, Dioscorides, and Plinius as skin irritant, useful for pulmonary disease, catarrh, and fever and for the relief of rheumatic pains. In search for the skin-irritant principle, thapsigargin was isolated from the fruits and roots, and its structure and absolute configuration were determined between 1980 and 1985. This compound proved to be a potent histamine liberator and a cocarcinogen promoting skin cancer in mice

(Anderson et al. 2016). Nevertheless, the increasing interest in thapsigargin arose with the discovery of its ability to inhibit the sarco-endoplasmic reticulum calcium ATPase (SERCA) pump. The inhibition of this pump produces a high concentration of calcium in the cytosol, which leads to apoptosis. Several analogues have been obtained from thapsigargin, and a prodrug, termed mipsagargin, has been designed. Mipsagargin has shown an acceptable tolerability and a favorable pharmacokinetic profile in patients with solid tumors. Phase I clinical trials have been completed (Mahalingam et al. 2016). This compound has been authorized by the FDA to enter phase II clinical trials on patients suffering from hepatocellular carcinoma who had failed the first-line treatment with sorafenib and also on patients suffering from glioblastoma (Nhu and Christensen 2015). Inspyr Therapeutics Inc. (Texas, USA) has announced the initiation of a phase II clinical trial of mipsagargin for newly diagnosed prostate cancer patients (Inspyr 2016).

1.3.8 Arglabin

Arglabin **(8)** is a STL of the guaianolide type isolated for the first time by Adekenov et al. (1982) from *Artemisia glabella*, which is a plant species growing in Kazakhstan. It is present in the above ground parts (leaves, bud flowers, and stems). Later on, arglabin has been reported to be present in *A. myriantha* (Wong and Brown 2002), which is a well-known plant used in Chinese traditional medicine.

Arglabin shows promising antitumor activity against different tumor cell lines. Many derivatives have been obtained, and those bearing bromine and chlorine atoms and an epoxy group on the C(3)=C(4) double bond seem to have an increased antitumor activity. Dimethylamino arglabin, one of these derivatives, has been used to treat lung, liver, and ovarian cancers and is under study in phase I and II clinical trials (Lone et al. 2015). This STL has been patented in the USA and has been registered as an antitumor medicine in the Russian Federation, Kazakhstan, Uzbekistan, Tajikistan, the Kirghiz Republic, and Georgia (Adekenov 2016).

Arglabin acts as antitumor by a different mechanism from artemisinin, thapsigargin derivative, and parthenolide. It inhibits the farnesyl transferase, which is an enzyme that has been demonstrated to be involved in the formation of malignant tumors. Besides, this compound shows other biological activities: it has an inhibitory effect on influenza A virus, it can restore the synthesis of cytokines and other anti-inflammatory mediators acting as anti-inflammatory in in vivo models of inflammation (carrageenan, histame, and formalin models), and it has immunomodulatory activity (Lone et al. 2015). Abderrazak et al. (2016) have demonstrated that arglabin reduces inflammation in pancreatic β-cells in vivo and in the INS-1 cell line in vitro, thus concluding that it may represent a new promising compound to treat inflammation and type 2 diabetes mellitus.