

REVIEW

Sesquiterpene lactones from the Yugoslavian wild growing plant families Asteraceae and Apiaceae

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Key words: Sesquiterpene lactones, Yugoslavian wild growing plants, Asteraceae, Apiaceae.

1. INTRODUCTION

Sesquiterpene lactones (SLs) constitute one of the biggest group of natural products. Up to now, the structures of *ca.* 5000 SLs of natural origin plus hundreds of synthetic ones have been reported. Their chemotaxonomic importance, together with various biological activities (antitumor, allergenic, phytotoxic, antimicrobial, insecticidal, *etc.*) are the major reasons for the continuing interests in these compounds. The great majority of SLs have been isolated from higher plants, mainly those belonging to the large, species-rich family of Asteraceae, but they have also been found in some other plant families, as well as in some fungi.

The common structural feature of SLs is the γ -lactone function (**A - D**, Fig. 1).

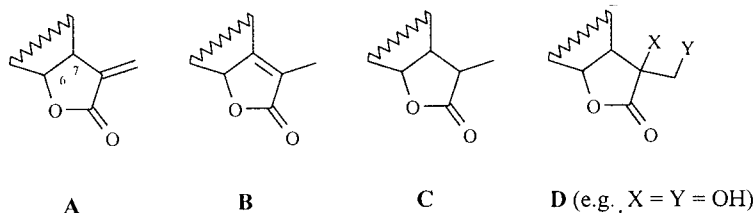
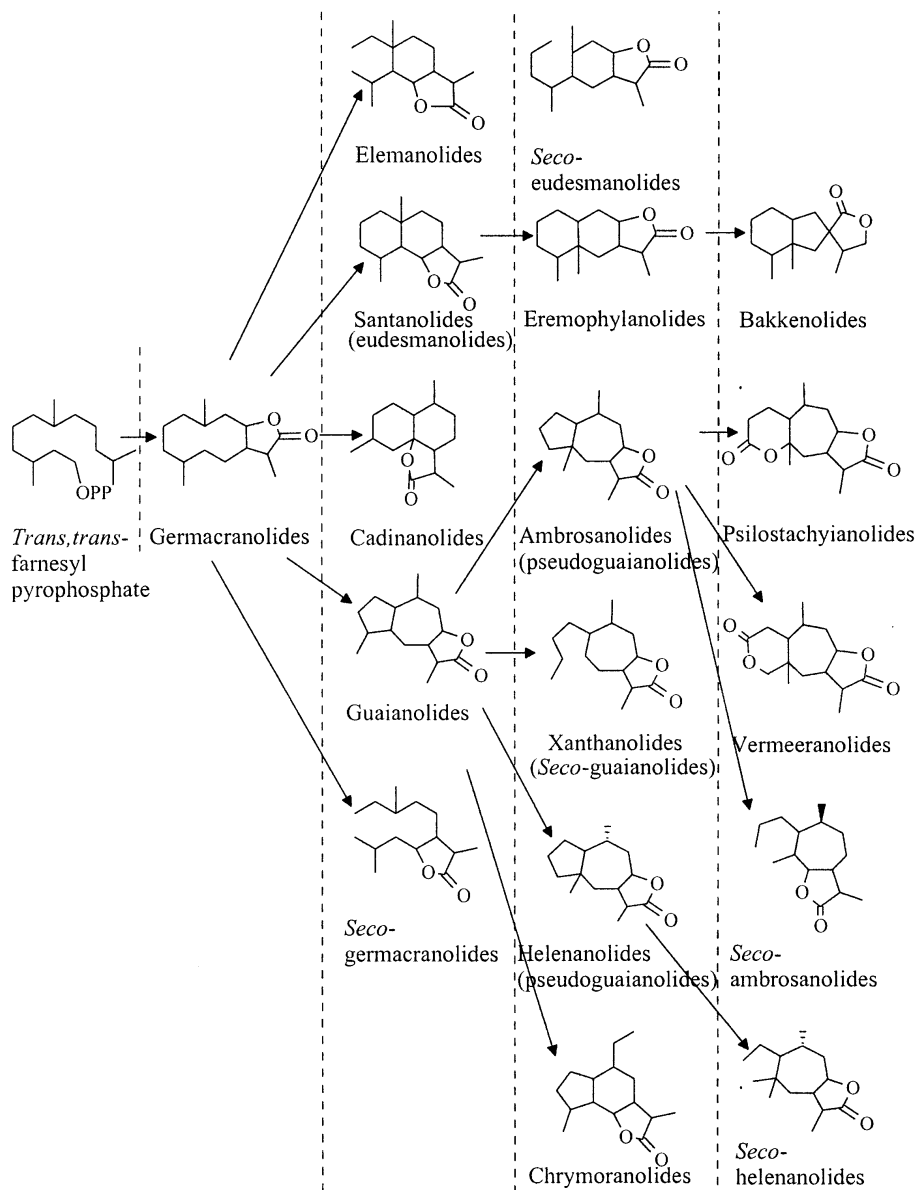


Figure 1.

The majority of SLs from higher plants contain the α -methylene- γ -lactone ring (**A**) with an α -oriented H-7. Despite the great diversity of sesquiterpene skeletons, the number of carbocyclic ring types of SLs is relatively small (Scheme 1), which could be explained by a common cyclodecadiene precursor, such as germacrene A obtained by the cyclisation of (*E,E*)-farnesyl pyrophosphate. An individual plant species generally yields a limited number of skeleton types, with



Scheme 1. Major skeletal types of sesquiterpene lactones and their biogenesis

oxidative variations on these skeletons. In general, having a broad geographical distribution, a given species may exhibit considerable intraspecific variation in its sesquiterpene lactone structures.

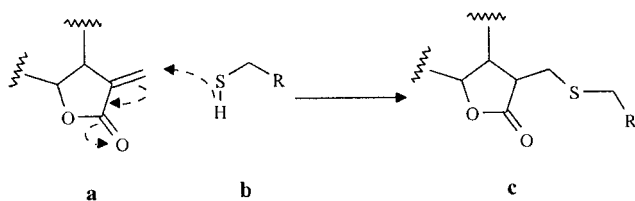
In the early 1960s, major emphasis was on the use of SLs as taxonomic markers in systematic biochemical studies within the Asteraceae. This provided the impetus for many detailed structural studies of SLs in these plant families. In recent years, an increasing number of publications describing the ecological functions of SLs has been reported. The first report of the antifeedant properties of SLs in *Vernonia* species (Asteraceae) upon herbivorous insects created an awareness of a possible ecological role of SLs as natural deterrents against insects and mammals, as toxins against plant pathogens and as allelopathic agents in plant-plant interactions.¹

In recent studies, the major structural feature of these bitter substances, an α,β -unsaturated- γ -lactone, has been shown to be associated with antitumor, cytotoxic, antimicrobial and phytotoxic activity. Sesquiterpene lactones are known to poison livestock, to act as insect feeding deterrents and to cause allergic contact dermatitis in humans.

The biological and therapeutical applications of the plants of the Compositae are more the results of systematically conducted chemical and pharmacological research than of tradition. In addition to drugs known since antiquity, from plants such as *Chammomilla*, *Cynara* and *Silybum*, there are over 25 species in the family which have found therapeutic application due to their antihepatotoxic, choleric, spasmolytic, anthelmintic, antiphlogistic, antibiotic or antimicrobial activity. In food technology some drugs containing bitter principles have achieved industrial significance. The insecticide pyrethrins from *Pyrethrum* species exemplify how plant products serve as models for the development of more active synthetic agents. The cytotoxic sesquiterpene lactones of certain species may act as pointers for future development of anticancer drugs.

The biological activity of sesquiterpene lactones results from the presence of highly electrophilic functional groups. These selectively alkylate, by a Michael type addition, sulphhydryl proteins, specifically thiol groups in preference to other nucleophiles.² A classical reaction of an α -methylenebutyrolactone function **a**, as a Michael acceptor of thiols **b**, led to the adducts **c**, as pointed out by the Kupchan group (Scheme 2). It could be assumed that exactly such a reaction is responsible for the pharmacological properties.³

Plant extracts that exhibit antineoplastic (anticancer) activity have received considerable attention. In a further study of the structure-activity relationship of sesquiterpene lactones, it was noted that the presence of exocyclic 11(13)-double bond conjugated to the γ -lactone (Scheme 2) was essential for cytotoxicity. Compounds having endocyclic double bonds gave unstable cysteine adducts and were inactive. However, sesquiterpene lactones which incorporated a cyclopentanone, or α -methylene lactone (in addition to the α,β -methylene- γ -lactone) appeared to pro-



Scheme 2.

duce enhanced cytotoxicity. None of the monofunctional sesquiterpenes containing only an α,β -unsaturated ester of cyclopentanone displayed significant activity.

The examples of sesquiterpene lactones exhibiting antitumor and cytotoxic activity are:

- germacranolides:
 - ridentin (*Artemisia cana*⁴)
 - parthenolide (*Chrysanthemum parthenium*^{5,6})
 - tamaulipin A⁷, tamaulipin B⁸ (*Ambrosia confertiflora*)
 - eupacunin (*Eupatorium cuneifolium*⁹)
 - eupatolide (*Eupatorium formosanum* and *E. cannabinum*^{10,11})
- guaianolides:
 - eupachlorin acetate (*Eupatorin* sp.¹²)
 - deacetoxymatricarin (*Achillea lanulosa*, *Artemisia leukoides*¹³)
 - canin (*Artemisia cana*¹⁴)
- pseudoguaianolides:
 - helenalin (*Helenium autumnale*¹⁵)
 - ambrosin (*Hymenoclea salsola*, *Ambrosia maritima*¹⁶)
- eudesmanolides:
 - α -santonin (*Artemisia* sp.¹⁷)
 - vulgarin (*Artemisia vulgaris*¹⁸)

Some sesquiterpene lactones have been shown to possess antibacterial or anthelmintic properties. Helenalin, a helenanolide common in species of *Helenium*, was shown to exhibit activity against the human pathogenic fungi, *Trichophyton mentagrophytes*, *T. acriminatum* and *Epidermophyton* sp.¹⁹

Over 80 sesquiterpene lactones were used in patch tests to determine their allergenic potential. Bioassay tests, carried out on several classes of sesquiterpene lactones, germacranolides, eudesmanolides and pseudoguaianolides (ambrosanolides), showed that alantolactone and guaianolide 8-deoxycumambrin B possessed considerable activity.^{2,20-23} All the known allergenic sesquiterpene lactones contain an exocyclic α -methylene function which may conjugate with sulphydryl groups of proteins in cells by a Michael-type addition (see Scheme 2) to form complete antigens capable of producing cell-mediated contact allergic reactions. Plants of the family Asteraceae that have been reported to cause contact dermatitis are: *Achillea*

millefolium, *Ambrosia* spp., *Anthemis nobilis*, *Artemisia* spp., *Eupatorium serotinum*, *Inula britannica*, *Inula graveolens*, *Tanacetum vulgare*, *Telekia* sp.

Some sesquiterpene lactones that have been reported to cause allergic contact dermatitis in humans are:

- parthenin (*Parthenium hysterophorus*¹⁶)
- alantolactone (*Inula helenium*, *I. racemosa*²⁴)
- costunolide (*Saussurea lappa*, *Laurus nobilis*²⁵)

The sesquiterpene lactones, arbusculine-A, achillin, deacetoxymatricarin, viscidulin-B and -C obtained from *Artemisa tridentata* var. *vaseyana* and other species of *Artemisa* were shown to inhibit lateral root growth but to stimulate respiration in *Cucumis sativum*. Alantolactone was shown to be a potent inhibitor of seed germination and seedling growth. It was postulated that this lactone inhibits the enzymes associated with the degradation of starch (amylases) and of protein (proteases), but there is no evidence to support this.

An examination of the sesquiterpene lactones that exhibit growth inhibitory properties indicates that the following structural configurations are the least principal requirements for biological activity:

- the presence of an exocyclic methylene conjugated to a γ -lactone;
- the presence of a functional group, such as an epoxide, hydroxy, chlorohydrin, unsaturated ketone or O-acyl adjacent to the α -CH₂ of the γ -lactone, which can enhance the reactivity of the conjugated lactone toward biological nucleophiles.

2. RESULTS

The sesquiterpene lactones so far isolated from the Yugoslavian wild growing plant families Asteraceae and Apiaceae, together with their biological activities, are presented in Table I and II, respectively.

TABLE I. Sesquiterpene lactones isolated from the families Asteraceae and Apiaceae in Yugoslavia (new compounds are marked with *)

Species/Locality	Compound	References
ASTERACEAE		
Genus <i>Artemisia</i> L.		27, 29, 30, 31, 47, 51, 57, 73, 78, 79
<i>A. annua</i> L./Belgrade, 1970	arteannuin B (1) artemisinin, or qinghaosu (2)	27, 29, 31, 47
<i>A. vulgaris</i> L./Belgrade, 1970	psylostachyin (3) psilostachyin C (4)	51
<i>A. absinthium</i> L./Golubac, 1971	ketopelenolide-A(5)	57
<i>A. scoparia</i> W. et K./Belgrade	no SLs	73
<i>A. campestris</i> L./Deliblatska peščara	no SLs	78, 79

TABLE I. Cont

Species/Locality	Compound	References
Genus <i>Ambrosia</i> L.:		27, 51, 84, 86
<i>A. artemisiifolia</i> L./Novi Sad, 1970, Pančevo, 1983	psylostachyin (3) psilostachyin C (4) lactone 6* lactone 7* lactone 8* cumanin (9) cumanin diacetate (10)	27, 51 27, 34, 84 27, 83, 84 83 84 84 84
Genus <i>Tanacetum</i> L.:		94–99
<i>T. parthenium</i> L./Kučevo, 1977	santamarin (11) magnolialolide (12), reynosin (13), 1 β -hydroxyarbusculin (14) 8 β -hydroxyreynosin (15)	94, 95
<i>T. serotinum</i> L./Belgrade, 1980	beogradolide A (16*) beogradolide B (17*)	94, 96
<i>T. vulgare</i> L./Ugrinovci, 1979	germacranolide 20* germacranolide 21* guaianolide 22* chrysartemin A (24)	94, 97
<i>T. macrophyllum</i> Willd./Goč, 1978	chrysartemin A (24)	94, 98
<i>T. corymbosum</i> L./Stolovi, 1978	no SLs	94
Genus <i>Telekia</i> Baumg.		
<i>T. speciosa</i> L./Goč, 1978	isoalantolactone (26) telekin (27) asperilin (29) eudesmanolide 30* eudesmanolide 33* pseudoguaianolide 35* pseudoguaianolide 36* parthenolide (37)	133
Genus <i>Inula</i> L.		
<i>I. helenium</i> L./Boleč, 1985	isoalantolactone (26) alantolactone (38) guaianolide 39 carabrone (40) diepoxygermacranolide 41 2 α -hydroxyalantolactone (42)	139, 141
<i>I. spiraeifolia</i> L./Boleč, 1981	no SLs	150, 151
Genus <i>Eupatorium</i> L.		
<i>E. cannabinum</i> L./Sevojno, 1978	eupaformonin (43)	162

TABLE I. Cont

Species/Locality	Compound	References
Genus <i>Achillea</i> L.		
<i>A. abrotanoides</i> Vis./Bjelasica, 1987	deacetoxymatricarin (46) deacetylmatricarin (47) 1 β ,10 β -epoxydeacetoxymatricarin (48*)	164
<i>A. millefolium</i> subsp. <i>pannonica</i> Vis./Bjelasica, 1987	deacetoxymatricarin (46) 1 β ,10 β -epoxydeacetoxymatricarin (48*)	177
<i>A. crithmifolia</i> W. et K./Rtanj, 1988, Donji Milanovac, 1990	rupicolin A (51) rupicolin B (53) germacranolide 55* guaianolide 56 guaianolide 57* rupin A (58) ridentin (60) ridentin B (61)	175, 182
<i>A. clypeolata</i> Sibth. et Sm./Sićevačka klisura, 1994	no SLs	188
<i>A. serbica</i> Nyman/Donja Studena, 1992	rupicolin B (53) guaianolide 65 guaianolide 66* guaianolide 67* guaianolide 68* guaianolide 69* guaianolide 70* guaianolide 71* guaianolide 72* lactone 73*	189
<i>A. depressa</i> Janka/Oblačinsko jezero, 1994	guaianolide 70* guaianolide 71* guaianolide 72* lactone 73*	189
Genus <i>Anthemis</i> :		
<i>A. carpatica</i> Wild./Lavlja vrata, 1994	anthemolide A (76*) 8- <i>O</i> -acetylanthemolide B (77*) 9- <i>O</i> -acetylanthemolide B (78*) 8,9-di- <i>O</i> -acetylanthemolide B (79*) 8- <i>O</i> -isobutyryl-9- <i>O</i> -acetylanthemolide. B (80*) 8-deoxy-9- <i>O</i> -acetylanthemolide B (81*) 8- <i>O</i> -tigloyl-9- <i>O</i> -acetylanthemolide B (82*) 9 α -acetoxycumambrin B (84*) 9 α -hydroxycumambrin A (85*) 9 α -acetoxycumambrin B (86*) 2 α -hydroperoxy-8- <i>O</i> -isobutyryl-9 α -acetoxycumambrin B (87*)	217, 220

TABLE I. Cont

Species/Locality	Compound	References
	cumambrin B (88 [*])	
	anthemolide C (95 [*])	
	anthemolide D (96 [*])	
	anthemolide E (97 [*])	
<i>A. creticae</i> L. subsp. <i>cretica</i> /Ošljak, 1994	anthemolide B (75 [*])	217
	8- <i>O</i> -acetylanthemolide B (77 [*])	
	8,9-di- <i>O</i> -acetylanthemolide B (79 [*])	
	8- <i>O</i> -isobutyryl-9- <i>O</i> -acetylanthemolide B (80 [*])	
	8- <i>O</i> -angeloyl-9- <i>O</i> -acetylanthemolide B (83 [*])	
	9 α -acetoxycumambrin B (84 [*])	
	9 α -hydroxycumambrin A (85 [*])	
	hydruntinolide B (89)	
	2 β ,9 α -diacetoxy-8 α ,10 α -dihydroxyguaia-3,11(13)-dien-6,12 α -olide (90)	
	10 α -hydroxy-2 β ,8 α ,9 α -triacetoxyguaia-3,11(13)-dien-6,12 α -olide (91)	
	2 β -acetoxy-8 α ,10 α -dihydroxy-9 α -(2-methylpropanoyloxy)-guaia-3,11(13)-dien-6,12 α -olide (92)	
	2 β -acetoxy-8 α ,10 α -dihydroxy-9 α -(2-methylbutanoyloxy)-guaia-3,11(13)-dien-6,12 α -olide (93)	
	2 β -acetoxy-8 α ,10 α -dihydroxy-9 α -(2-methylbutanoyloxy)-guaia-3,11(13)-dien-6,12 α -olide (94)	
	anthemolide D (96 [*])	
Genus <i>Centaurea</i> L.		
<i>C. derventana</i> Vis. et Panč./Bajina Bašta, 1996	salonitenolide (98)	221–231
	cnicin (99)	
	cnicin-4'- <i>O</i> -acetate (100)	
	salonitenolide-8- <i>O</i> -(4'-acetoxo-5-hydroxyangelate (101)	
<i>C. kosaninii</i> Hayek/Brezovica, 1994	no SLs	226
<i>C. solstitialis</i> L./New Belgrade, 1995	solstitialin A (102)	221–239
	solstitialin A 13-acetate (103)	
	cynaropicrin (104)	
	11 β ,13-dihydrodeacetylcynaropicrin (105)	
	linichlorin B (106)	
	19-deoxychlorojanerin (107)	
	8-deacylcentaurepensin-8- <i>O</i> -(4-hydroxy)-tiglate (108)	

TABLE I. Cont.

Species/Locality	Compound	References
	17- <i>epi</i> -centaurepensin (109) centaurepensin (110)	
APIACEAE		
Genus <i>Laserpitium</i> :		
<i>L. siler</i> L./Tara, 1975	acetylisomontanolid (111) isomontanolid (112) montanolid (113) silerolid (114) tarolid (115 [*])	245,255
<i>L. marginatum</i> L./Kopaonik, 1976	guaianolid 119 [*] guaianolid 120 [*]	245, 258, 259
<i>L. latifolium</i> L./Ibarska klisura, 1977	guaianolid 119 [*] guaianolid 120 [*] laserpitin (121)	245
<i>L. alpinum</i> W.K./Vranica, 1979	lactone 122 [*] compound 123 [*]	245, 263
Genus <i>Angelica</i> L.		
<i>A. silvestris</i> L.	no SLs	264–269
Genus <i>Peucedanum</i> L.		
<i>P. austriacum</i> (Jacq) Koch	no SLs	265, 270

TABLE II. Biological activities of sesquiterpene lactones isolated from the family Asteraceae in Yugoslavia

Compound	Biological activity	Ref.
2 (artemisinin)	Antimalaric activity	35–38, 41
12, 13	Stimulation of seed germination	99
16–24	Antibacterial activity	94, 99
26 (isoalantolactone)	Allergenic activity Cause photosensitivity Inhibition of lateral root growth of <i>Phaseolus annuus</i> Fungicide action Antibacterial activity	2, 20–24, 148 149
37 (parthenolid)	In the prophylaxis of migraine and arthritis Antimicrobial activity Phototoxic effect Antitumor activity	3, 114–120
38 (alantolactone)	Allergenic activity Cause photosensitivity Inhibition of seed germination of <i>Phaseolus annuus</i> Fungicide action	148, 149, 2 20–24

TABLE II. Cont.

Compound	Biological activity	Ref.
	Antibacterial activity	
41	Antibacterial activity	142
43 (eupaformonin)	Cytostatic activity	162
46 (deacetoxymatricarin)	Inhibition of lateral root growth of <i>Cucumis sativum</i>	2, 20-23
60 (ridentin)	Antitumor activity	4
	Cytostatic activity	
99 (cnicin)	Cytotoxic activity	222
	Cytostatic activity	
	Antibiotic activity	
103 (solstitialin A 13-acetate)	Neurotoxic activity	221
104 (cynaropicrin)	Cytotoxic activity to HeLa cells	221, 223
110 (centaurepensin)	Cytotoxic activity to 9 KB cells	221

3. ASTERACEAE

3.1. *Genus Artemisia L.*

The genus *Artemisia L.* is one of the largest and most widely distributed of approximately 60 genera in the tribe *Anthemideae* of the Asteraceae. This genus, with nearly 300 species, is found predominately in the northern temperate regions of the world (North America, Europe, Asia and North Africa).

Our systematic examinations of the SLs content in the family Asteraceae commenced with this genus, involving the following species: *A. annua L.*, *A. vulgaris L.*, *A. absinthium L.*, *A. scoparia W. et K.* and *A. campestris L.* In all cases, extraction of air-dried aerial parts was carried out with CHCl_3 at room temperature. The extracts were worked up using a slightly modified previously reported procedure.²⁶ The constituents of the extracts were separated by means of silica gel column chromatography.

3.1.1. *Artemisia annua L.*

A herb, that was featured prominently in Chinese pharmacopoeia, especially in relation to decoctions used to treat fever, was qinghao, the "blue green" herb. Recorded use of qinghao spans over 2000 years, with written descriptions first appearing in 168 B.C. in the *Treatments for 52 Sicknesses* and as late as 1798 in the *Book of Fevers*. The most detailed description appears in the mammoth *Compendium of Materia Medica* compiled in 1596 by the great Ming Dynasty physician Li Shi-Zem, and which is still printed in China today.

From an extract of the aerial parts of *A. annua*, collected in October 1970 at a locality close to the center of Belgrade, called "Staro sajmište" (The Old Fairgrounds), two novel crystalline sesquiterpene lactones (**1** and **2**) were isolated (Fig. 2).²⁷ In the same extract a polyacetylene known as pontica epoxide, previously detected in the

essential oil of *A. annua*,²⁸ was also found. According to ¹H-NMR, IR, MS, ORD and CD data of **1** and **2**, as well as those of their derivatives, these lactones were assigned as the first members of a new series with cadinane and *seco*-cadinane skeletons.²⁹⁻³¹ Whereas the structure of **1**, named arteannuin B,^{29,30} was subsequently confirmed,^{32,33} the initially proposed³¹ ozonide structure (**2A**) of the *seco*-lactone was later revised. The correct (endoperoxide) structure of this lactone (**2B**), together with its absolute configuration was determined in 1980 by means of X-ray diffraction of a sample isolated from *A. annua* originating from China.³⁴

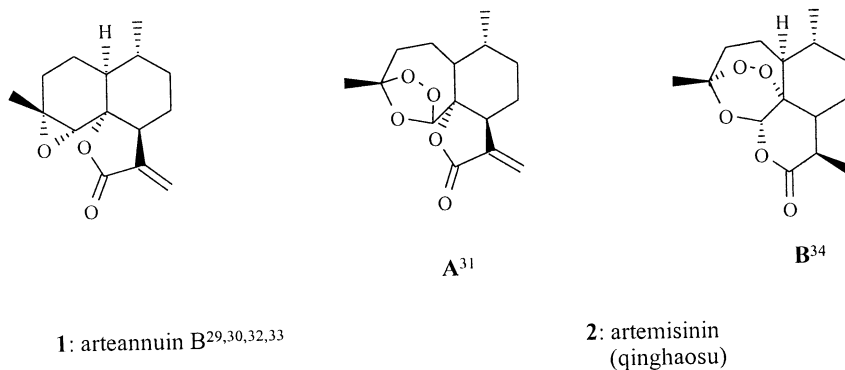


Figure 2.

Lactone **2**, shown to be the carrier of antimalarial activity (*vide infra*), was named qinghaosu (according to the Chinese name for the herb, *Qinghao*), and, alternatively, artemisinin, the name adopted today in the *Chemical Abstracts*. It should be noted that the chemical examinations of *A. annua* in China, occurring approximately at the same time as our investigations in Belgrade, were part of a comprehensive research program embracing both synthetic compounds and traditional herbal drugs for new antimalarials. After extensive screening, several groups of Chinese chemists, pharmacologists and botanists focused their joint research of *A. annua* because this herb had been used for many centuries in traditional Chinese medicine for the treatment of fever and malaria. Finally, it was proved by Chinese researchers that artemisinin (**2**, qinghaosu),^{35,36} contained in the extract of *A. annua* was the active antimalarial principle, being much more active towards both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* in comparison to usual antimalarials, such as quinine and chloroquine.* This discovery prompted many groups throughout the world to research this topic. Since that time, quite a few papers and reviews (*e.g.* Refs. 37, 38), about the chemistry, pharmacology and clinical application of artemisinin and its derivatives have appeared. Up to recently, qinghaosu had been considered to be a specific kind of compound belonging to the cardanolide group, and isolated only from *A. annua*. However, in 1986, this lactone was isolated from *A. apiacea* and *A. lancea*.²⁹ Since *A. annua* still remains

* However, it should be noted that artemisinin (qinghaosu) has not yet been registered as a drug against malaria (FDA)

the main source of artemisinin, now the efforts of geneticists are concentrated towards the development of new clones of this herb producing a more active principle.

Qinghaosu is a sesquiterpene lactone that bears a peroxide group and, unlike most other antimalarials, lacks a nitrogen-containing heterocyclic ring system. Derivatives of qinghaosu, such as dihydroqinghaosu, artemether, the water soluble sodium artesunate, and the oil soluble arteether appear to be more potent than qinghaosu itself. Sodium artesunate acts rapidly in restoring to consciousness comatose patients with cerebral malaria. Thus, qinghaosu and its derivatives offer promise as a new class of antimalarials. Recent studies have suggested that artemisinin B, another metabolite of this plant, could serve as a precursor for artemisinin. Qinghao acid, one of the major sesquiterpene constituents of *A. annua* was converted to artemisinin B by singlet oxygen, which plays a role in biogenetic reactions, generated by sensitized photo-oxygenation.⁴⁰

The advent of the qinghaosu class of antimalarial has ushered in a new era for treatment of malaria, and work in all areas, involving the preparation of new derivatives, uncovering the mode of action, pharmacokinetic studies, drug formulation, clinical studies and field trials, continuing apace. The herb of antiquity, qinghao, has provided a fascinating compound whose trioxane nucleus is the focus of development of new methodology to provide structures containing this moiety.⁴¹

Besides the number of pharmacologically active sesquiterpene lactones based on cadinane and closely related carbon skeletons, chromenes, phenolic constituents, mainly coumarins and both flavonoid aglycones and glycosides, have also been isolated by different groups.^{37,42-46} These results are noteworthy from the pharmacological point of view for they may impart new medicinal applications to *A. annua*. Some of these compounds have been shown to be antiviral, cardiovascular, anti-hepatotoxic and antiinflammatory agents. Some others were found to exhibit cytotoxic activity against specific carcinoma cells or to control the expression of certain genes. Flavonoids, *e.g.*, artemetin, chrysosplenol-D, chrysosplenetin, casticin and cirsilineol, markedly enhanced the antimalarial activity of artemisinin.

Our repeated examination of *A. annua*⁴⁷ (originating from Belgrade and Kovin) yielded, in addition to **1**, **2** and pontica epoxide, camphor, pinocarvon, pinocarveol, artemisia alcohol, artemisia ketone (monoterpenes), scopoletin (coumarin) and two isomeric flavonols,⁴⁸ *i.e.*, chrysosplenetin and casticin. These flavonols, together with pinocarvone and pinocarveol were isolated for the first time from *A. annua*. From this plant, the new flavonol, quercetagenin 6,7,3',4',-tetramethyl ether has also been isolated.⁴⁹

3.1.2. *Artemisia vulgaris* L.

It is known that the pollen of mugwort (*A. vulgaris* L.) is one of the main causes of allergenic reactions in late summer in Europe. Extracts of mugwort pollen contain about eleven different allergens of variable clinical importance.⁵⁰

The plant material was collected in October 1970 near Belgrade. The standard isolation procedure,²⁶ yielded⁵¹ two known *seco*-pseudoguaianolides, psilostachyin (**3**) and psilostachyin C (**4**) (previously isolated from *Ambrosia psilostachya*^{52,53}), the usual constituents of the genus *Ambrosia* (Fig. 3). These compounds are considered to be interesting from the chemotaxonomic point of view, because the psilostachyinolides are supposedly biosynthesized from ambrosanolides which have not yet been isolated in this genus. Repeated examination of *A. vulgaris*, collected in September 1978 at Deliblatska peščara (Vojvodina) afforded only 5,3'-dihydroxy-3,7,4'-trimethoxyflavone, 7,8-methylenedioxy-9-methoxycoumarin and a triterpene, 3 β -hydroxy-urs-12-ene-27,28-dionic acid.⁵⁴ The sesquiterpene lactones were not detected.

However, eudesmanolide vulgarin, first reported in 1961 (Rybalko and Dolejs investigated *Artemisia taurica* Willd. and isolated a compound which they assigned the same structure as that of vulgarin, but named it tauremisin; furthermore, the compounds barrelin and judaicin were proved to be identical with vulgarin⁵⁵), isolated previously from the Australian *A. vulgaris* was not detected in this extract.¹⁸

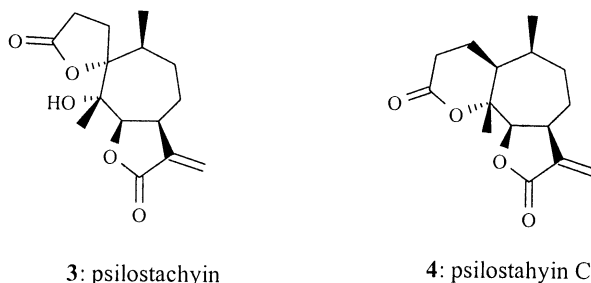


Figure 3.

3.1.3. *Artemisia absinthium* L (warmwood)

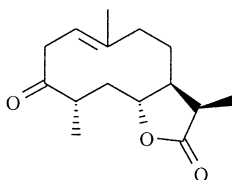
Guaianolides of the proazulogenes type were found in the group *Absinthium* of the genus *Artemisia*.⁵⁶

The usual isolation procedure,²⁶ applied to the aerial parts of *A. absinthium*, collected in November 1971 at Golubac (Eastern Serbia), afforded⁵⁷ a germacranolide (Fig. 4), ketopelenolide-A (**5**) and two known⁵⁸ diastereomeric lignans (isolated for the first time from this plant) with 2,6-aryl disubstituted 3,7-dioxabicyclo [3.3.0]octane ring, *i.e.*, dimethyl ethers of liriouresinol A and liriouresinol C.

Lactone **5** was previously isolated from the same plant originating from Czechoslovakia.⁵⁹ Neither artabsin (guaianolide) and absinthin (dimeric guaianolide), previously isolated from *A. absinthium*, nor the other sesquiterpene lactones (guaianolide dimers: absintholide, artabsinolides, arlatin, anabsin, artenolide, aryemolin⁶⁰⁻⁷⁰) were detected in our sample.

In 1992, new diastereomeric homoditerpene peroxides were isolated from the aerial parts of warmwood by Rücker *et al.*⁷¹ The mixture of these compounds

showed antimalarial activity against *Plasmodium falciparum*. The aerial parts of warmwood are used against dyspeptic diseases, fever and gastrointestinal worms. The bitter sesquiterpene lactones absinthin, anabsinthin and anabsin are known to be major compounds of warmwood, as well as thujone, which showed neurotoxic activity. Antitumor, cytostatic and other pharmacological properties have been reported for this plant.⁷² *A. absinthium* was used until the 1920's to prepare the narcotic and now illegal drink absinth.



5: ketopelenolide-A

Figure 4.

3.1.4. *Artemisia scoparia* W. et K.

Chloroform extraction of the leaves and flower heads of *A. scoparia* (collected south of Belgrade), using the usual techniques,²⁶ resulted⁷³ in the isolation of coumarin, scoparone (*i.e.*, 6,7-dimethoxycoumarin, isolated previously from *A. scoparia*⁷⁴), two polyacetilenes (capillin and 1-phenyl-2,4-hexadiin-1-ol, the constituents of *A. capillaris*⁷⁵) and vanillin. Sesquiterpene lactones were not detected.

From the extract of *A. scoparia*, examined by Ryakhovskya and Chandrosckharan^{76,77} only flavonoids and coumarins were isolated.

3.1.5. *Artemisia campestris* L.

Examination of the CHCl_3 extract of the aerial parts of *A. campestris* (collected at Deliblatska peščara, Vojvodina) revealed two coumarins (scoparon and scopoletin)⁷⁸ and a mixture of *p*-coumaric acid esters of various fatty alcohols.⁷⁹ None of these compounds had been detected before in *A. campestris*. Sesquiterpene lactones were not detected in the examined extract.

Subsequent studies of the related *A. campestris* subsp. *maritima* (Ranter *et al.*⁸⁰) and *A. campestris* subsp. *glutinosa* (De Pascual *et al.*⁸¹ and Hurakielle *et al.*⁸²) revealed only flavonoids and acetophenone derivatives and no SLs.

3.2. Genus *Ambrosia* L.

3.2.1. *Ambrosia artemisiifolia* L. (the common rag weed)

The plant material (aerial parts) of *A. artemisiifolia* was collected at two localities in the Province of Vojvodina, *i.e.*, near Novi Sad (October 1970)^{27,51,83} and near Pančevo (August 1983).⁸⁴ As expected, according to previous examination of the genus

Ambrosia,^{85,86} these investigations revealed (*seco*)pseudoguaian-6,12-olides, known as (*seco*)ambrosanolides (3),^{27,51} 4,^{27,55,84} 6,^{27,83,84} 7,⁸³ 8,⁸⁴ Fig. 5). At the time they were identified, lactones 6–8 were new compounds. Lactone 8 was the first 3,4-*seco*-ambrosanolide. This type of oxidative 3,4-fragmentation in a pseudoguaianolide precursor was previously encountered only in the helenanolide series (*i.e.*, pseudoguaian-8,12-olides with a 10 α -positioned methyl). Two pseudoguaian-8,12-olides, also previously detected in the genus *Ambrosia*, *i.e.*, cumanin (9)^{84,85} and its diacetate (10),⁸⁵ were identified in the plant originating from Pančevo.⁸⁴

The genus *Ambrosia* is known to produce numerous sesquiterpene lactones of the germacranolide, psilostachyanolide, pseudoguaianolide, ambrosanolide and eudesmanolide types. Germacranolides, such as artemisiifolin,⁸⁷ isabelin,^{88,89} dihydroparthenolide,⁹⁰ pseudoguaianolides peruvian⁹¹ and coronopilin (W. Herz *et al.* determined its structure²⁶), modified pseudoguaianolide ambrosic acid,⁹² guaianolides cumambrins A and B,⁹³ isolated from the extracts of other species belonging to this genus by other authors, were not detected in the examined extracts. In the connection with studies on the physiologically active substances in the genus of *Gaillardia*, *Artemisia* and their relatives in Compositae, the poisonous principle in *A. artemisiifolia* has recently been investigated (H. Ogura *et al.*⁹²). It was shown that this plant is responsible for the pollen allergy, assigned to ambrosic acid isolated from its pollen.

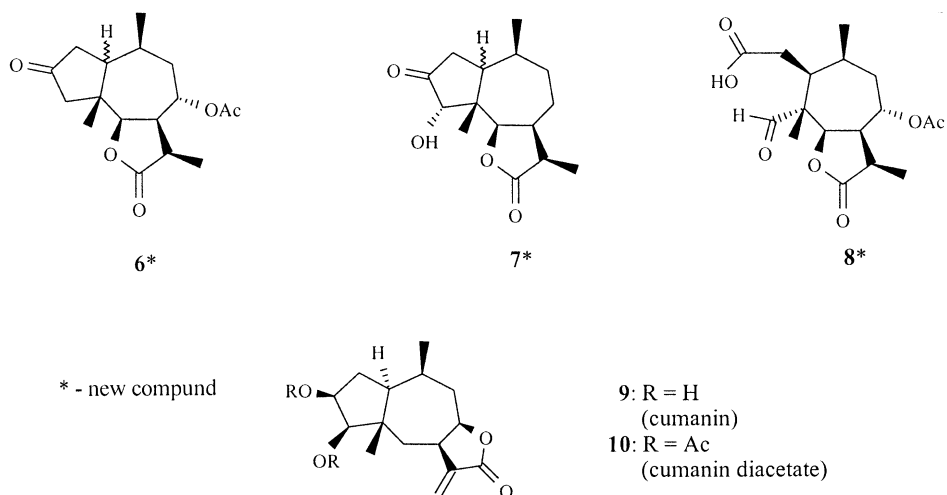


Figure 5.

3.3. Genus *Tanacetum* L. (syn. *Chrysanthemum* L.)

Investigation of the aerial parts of five species of this genus, *i.e.*, *T. serotinum* L., *T. parthenium* L., *T. macrophyllum* Willd., *T. vulgare* L. and *T. corymbosum* L., using the usual procedure,²⁶ revealed three types of SLs, *i.e.*, germacranolides,

eudesmanolides and guaianolides.⁹⁴⁻⁹⁸ In addition, the antimicrobial and antitumor activities of the isolated compounds were studied.^{94,99}

3.3.1. *Tanacetum parthenium* L. (feverfew)

The herb feverfew has been recognized since ancient times as having significant beneficial medicinal properties. The herb has been used as a general febrifuge and for the treatment of a wide range of disorders, including psoriasis, toothache, insect bites, rheumatism, asthma, stomach ache, menstrual problems, and threatened miscarriage. The herb was successfully used as a prophylaxis for both migraine and arthritis. This plant has been referred to as the "mediaeval aspirin".¹⁰⁰

The overall picture of the constituents of *T. parthenium* shows that this species produces a large variety of highly oxygenated compounds, especially in the aerial parts.

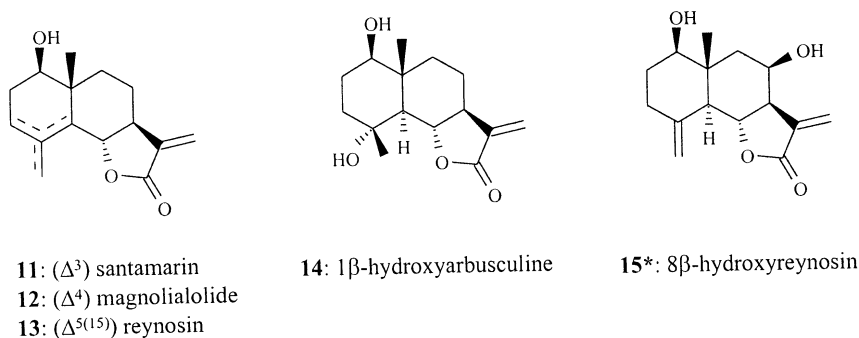
Previous studies of this species originating from different places revealed the following SLs:

- germacranolides – parthenolide^{5,6,101-103} and its metabolites, 3 β -hydroxy-parthenolide, costunolide, 3 β -hydroxycostunolide,¹⁰⁴ artemorin¹⁰⁴⁻¹⁰⁶ and a derivative of artemorin, epoxyartemorin¹⁰⁷ and anhydroverlotrin-4 α ,5 β -epoxide;
- eudesmanolides – santamarin and reynosin;
- guaianolides – 3,4-epoxy-8-deoxycumambrin B,¹⁰⁸ chrysartemin A (**24**) and chysartemin B, and, in addition to these widespread compounds, two groups of rare and closely related guaianolides, the " α -series" represented by the endoperoxide tanaparthin- α -peroxide, canin, 10-*epi*-canin and seco-tanaparthin- α -peroxide, together with the corresponding " β -series", tanaparthin- β -peroxide, artemcanin and *seco*-tanaparthin- β -peroxide, and finally, two very unusual, chlorine-containing guaianolides.^{104,109,110}

Achillea millefolium also contains the α - and β -endoperoxides, related to the tanaparthenins, and this provided some circumstantial evidence for the proposed biogenetic pathway in feverfew.

From the aerial parts of *T. parthenium*, collected in the vicinity of Kučevo (eastern Serbia, July 1977) we isolated five eudesmanolides (Fig. 6), such as santamarin (**11**), magnolialolide (**12**), reynosin (**13**), 1 β -hydroxyarbusculin (**14**) and 8 β -hydroxyreynosin (**15**).^{94,95} Whereas lactone **15** was a new compound, compounds **12** and **14** (detected for the first time in *T. parthenium*) were isolated previously from *Magnolia grandiflora*¹¹¹ and *Tanacetum vulgare*,¹¹² respectively. Santamarin was detected (1965) in *T. parthenium*,¹¹³ and reynosin in *Ambrosia confertiflora* (1970).¹⁰⁹

The Antitumor activity KB test (human epidermal carcinoma of nasopharynx-cell culture) and PS test (P 388 lymphocytic leukemia), carried out in the National



* - new compound

Figure 6.

Cancer Institute, Bethesda, Maryland, USA, showed that **12** and **13** have insufficient activity to warrant further testing.⁹⁹

T. parthenium has been successfully used as a prophylaxis for migraine and a link between blood platelet chemistry and migraine has been suggested in a number of reports in the literature.^{114,115} Hence, initial studies of various groups focused on the effects of feverfew extracts on blood platelets, which led to the conclusion that α -methylenebutylolactone groups were responsible for the inhibitory effect of feverfew extracts on blood platelet function. Upon agonist-induced aggregation, blood platelets release 5-hydroxytryptamine (serotonin) which has been linked to the onset of migraine and which further augments the aggregation induced by the original agonist. The bioactivity is based on the inhibition of 5-hydroxytryptamine secretion.¹¹⁶ Perhaps of more relevance to migraine prophylaxis is the ability of feverfew extracts and parthenolide to inhibit prostaglandin production, as these are mediators of inflammation. Crude extracts of feverfew have recently been shown to selectively block voltage-dependant potassium channels in smooth muscle cells; the implications of this observation with respect to migraine prophylaxis are as yet unclear. Parthenolide and epoxyartemisin showed high levels of activity whereas tanaparthenin- α -peroxide was much less active.^{3,117,118}

Parthenolide was shown to be the major antimicrobial constituents in the CHCl_3 extracts of *T. parthenium*. In inhibited growth of Gram (+) bacteria, yeasts and filamentous fungi *in vitro*. Gram (–) bacteria were unaffected. This compound was not phytotoxic except at very high concentrations, but crude extracts from the whole plant were strongly phytotoxic.¹¹⁹

In addition, the CHCl_3 extracts of fresh leaves of *T. parthenium* caused a progressive loss of tone of pre-contracted aortic rings, strongly inhibited its responses to phenylephrine, 5-HT, the thromboxane mimetic U46619 and angiotensin

II, and appeared to impair the ability of acetylcholine to induce endothelium dependent relaxations of the tissue.¹²⁰

Parthenolide inhibits the incorporation of thymidine into DNA and, thus, antitumour activity may occur at the DNA replication level.

A mixture of the two eudesmanolides, santamarin and reynosin, displayed activity equal to or greater than the germacranolides at most of the concentrations tested in the stimulation of witchweed germination.¹²¹ The high activity of the eudesmanolides is noteworthy, because these compounds are less prone to undergo further structural changes by intramolecular cyclization reaction than the germacranolides.

In identifying the active principles of this plant, it is important to be aware of the nature of the other chemical constituents since there is the possibility of synergistic action. Although the sesquiterpene lactones have been fully identified in *T. parthenium*, little work has been carried out on the lipophilic flavonoids. However, several flavonoid methyl ethers have been isolated from other *Tanacetum* species. The new lipophilic flavonols, santin and its 7-methyl derivative, 6-hydroxy kaempferol 3,7,4'-trimethyl ether, called tanetin,^{122,123} have been characterized in the leaf, flower and seed of *T. parthenium*. Pharmacological tests indicate that tanetin could contribute to the antiinflammatory properties of feverfew by inhibiting the generation of pro-inflammatory eicosanoids, although it is unlikely to be the only biologically active compound within the plant.

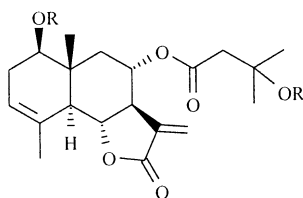
3.3.2. *Tanacetum serotinum* L.

It should be noted that this was the first study of this species. From the plant material, collected near Belgrade (August 1980), two novel eudesmanolides, named beogradolide A (**16**) and beogradolide B (**17**) were isolated.^{94,96} Both compounds were also converted, using acetic acid anhydride, to the corresponding diacetates **18** and **19** (Fig. 7).

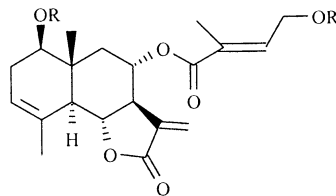
The isolated sesquiterpene lactones, the new ones, were tested for antibacterial activity. All the tested compounds displayed an inhibitory effect against *Staphylococcus aureus* (E-169), Gram-positive. Lactone **16** showed the most intensive inhibition zones. An additional test, using Gram-negative *Escherichia coli* (B-82354), was performed, in which only beogradolide A developed a slight inhibition zone. Its acetate exhibited considerable inhibition against *Salmonella sp.*^{94,99}

3.3.3. *Tanacetum vulgare* L. (*tansy*)

T. vulgare, exhibiting medicinal properties (vermifuge, cholagogue), has been used in traditional medicine.¹²⁴ In Bulgaria tea prepared from dry leaves and flowers is used as an antiseptic and a spasmolytic remedy, also against insects in cattle and for protecting hair against dandruff; powdered, dry leaves and flowers are also utilized as insecticides.



16*: R = H
(beogradolide A)
18: R = Ac



17*: R = H
(beogradolide B)
19: R = Ac

* - new compound

Figure 7.

During previous examinations of the aerial parts of botanically non-specified forms or varieties of *T. vulgare*, originating from different localities, over fifteen different sesquiterpene lactones have been isolated:^{112, 125-129}

- germacranolides – tamarin, tanacin, tabulin, tatridin-A and B, parthenolide, costunolide diepoxide and artemorin
- eudesmanolides – reynosin (**12**), 1 β -hydroxyarbasculin-A (**13**), dentain, chrysanin, tanacetin (5-hydroxyreynosin) and santamarin (**11**).

In our sample, collected in the village Ugrinovci near Kraljevo (southwest Serbia, September 1979)^{94,97} we isolated four SLs, *i.e.*, two new germacranolides (**20** and **21**) and two guaianolides **22** and **24** (Fig. 8). Compound **22** was a new one and **24** (chrysartemin A) had been detected previously in *T. parthenium*.^{109,130} In addition, a flavone eupatilin, *i.e.*, 5,7-dihydroxy-3',4',6-trimethoxyflavone (tumor inhibitor) identified for the first time in *Eupatorium cuneifolium* (Tourn) L.,¹³¹ was isolated from this extract.

The isolated sesquiterpene lactones (**20–24**) were tested for antibacterial activity, as was done with the compounds **16–19**. With the exception of **24**, all the tested compounds displayed an inhibitory effect against *Staphylococcus aureus* (E-169), Gram-positive. Lactone **22** showed the most intensive inhibition zones. Chrysartemin A inhibited *Salmonella* sp. All of these compounds were inactive on *Escherichia coli* (B-82354), Gram-negative.^{94,99}

3.3.4. *Tanacetum macrophyllum* Willd.

The usual procedure²⁶ applied to the CHCl₃ extract of the aerial parts *T. macrophyllum*, collected at the Goč mountain (1978) (East Serbia), yielded diepoxylguaianolide chrysartemin A (**24**),^{94,98} which was converted, upon treatment with hot acetic acid anhydride, to the corresponding acetate (**25**). This was the first study of secondary metabolites of this species.

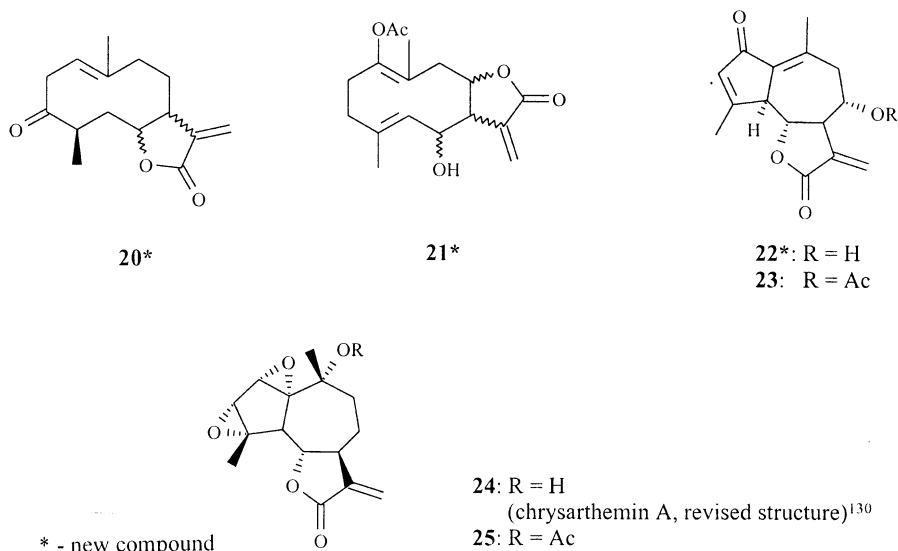


Figure 8.

3.3.5. *Tanacetum corymbosum* L.

Sesquiterpene lactones were not detected in the CHCl_3 extract of the aerial parts of *T. corymbosum*, originating from a locality under the plateau Stolovi (Mountain Goč).⁹⁴ This was not unexpected, since previous examination of 14 species of the genus *Tanacetum* had shown that the lowest sesquiterpene lactone content was noted in *T. carinatum*, *T. anethifolium* and *T. corymbosum*.¹³²

3.4. Genus *Telekia* Baumg.

3.4.1. *Telekia speciosa* (Schreb.) Baumg.

The Genus *Telekia* is a small one, and is chemically characterized by the occurrence of sesquiterpene lactones similar to those from *Inula* species.

In course of our investigations of the CHCl_3 extract of the aerial parts of *T. speciosa*, collected at the mountain Goč (East Serbia, July 1978), in addition to the eudesmanolides (**26**, **27**, **29**, **30** and **33**), we isolated two pseudoguaianolides (**35** and **36**) and a germacranolide (**37**).¹³³ The lactones **30**, **33**, **35** and **36** were new compounds (Fig. 9). Asperilin (**29**), isolated for the first time (1964) from *Iva asperifolia* (whole plant, St. Marks, Florida)¹³⁴ was found for the first time in this species. Acetylation and epoxidation of **29** afforded the lactones **31** and **34**.¹³³ Diol **30** was also converted to the corresponding diacetate (**32**). Isoalantolactone (**26**)¹³⁵ was isolated for the first time from *I. helenium* in 1957 and telekin (**27**) from *T. speciosa* in 1961.¹³⁶ Parthenolide (**37**) was detected for the first time in the crude extract of *T. parthenium* in 1961⁶ (see 3.3.1.).

In the previous chemotaxonomic study of this species, originating from Bulgaria and Czechoslovakia, the eudesmanolides isoolantolactone (**26**), telekin (**27**) and isotelekin (**28**) were identified.^{136,137} At the same time, only lactone **26** was detected in the roots. Helenin was isolated from *T. speciosa* as an inseparable mixture of isomers **26** and **38**, in the ratio of 2:1,¹³⁸ respectively.

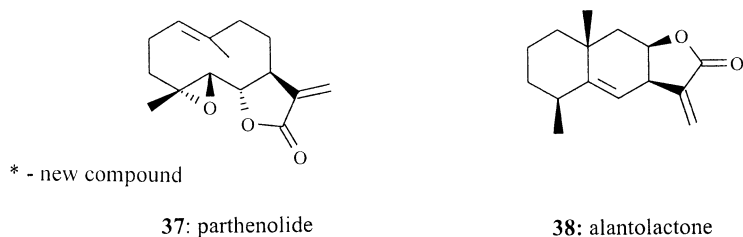
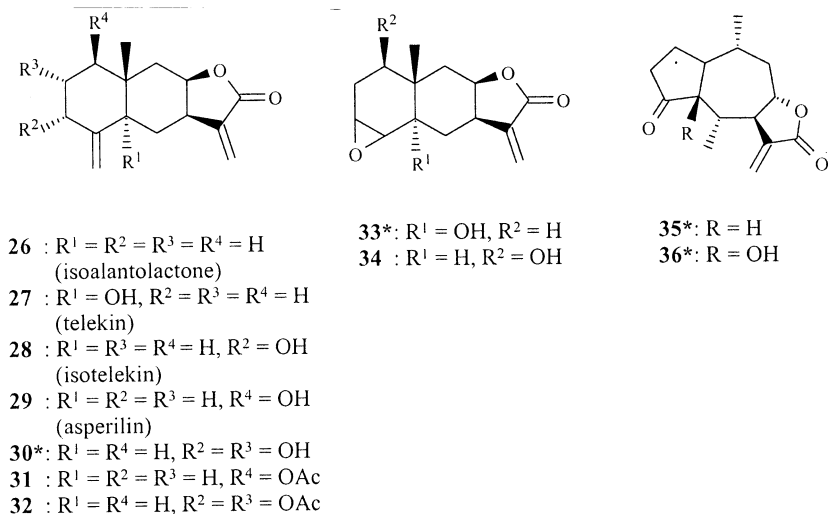


Figure 9.

3.5. Genus *Inula* L.

3.5.1. *Inula helenium* L.

Plant material (roots and aerial parts) was collected in Boleč (ca. 10 km south-east from Belgrade) in the summer of 1985. The usual CHCl₃ extraction²⁶ of the roots afforded a high yield of the isomeric eudesmanolides **26** and **38**,¹³⁹ which was in agreement with previous results (Figure 10).¹⁴⁰ The same isolation procedure applied to the aerial parts yielded four SLs (**39–42**), belonging to different types.¹⁴¹ Whereas the lactones **39** and **40** had been previously isolated from *I. helenium*,¹⁴⁰ diepoxygermacranolide **41** had not been found in this species before. This lactone, exhibiting antibacterial properties,¹⁴² was isolated previously from *Carpesium*

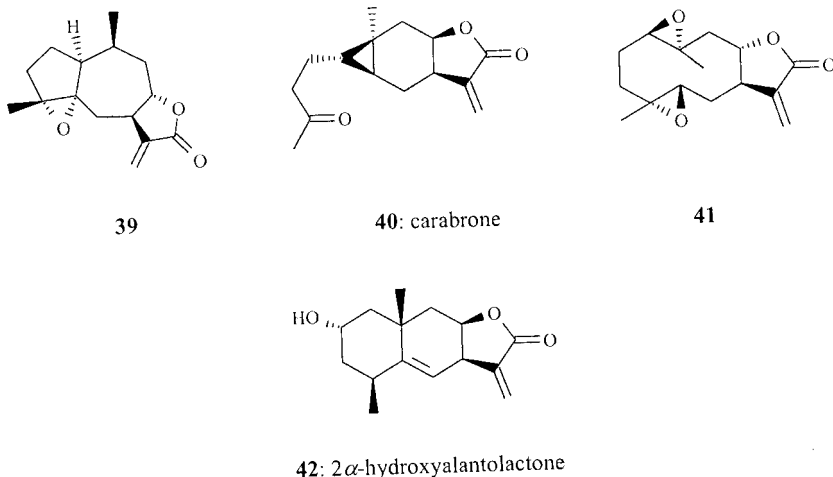


Figure 10.

abrotanoides,¹⁴² as well as from some *Schkhuria* species.¹⁴³ 2 α -Hydroxyalantolactone (**42**) was found previously in the aerial parts of *I. royleana*.¹⁴⁰

The acetone extract of the root of *I. helenium* by Kerimov *et al.*, yielded **26**, **38**, dihydroisoalantolactone and dihydroalantolactone.¹⁴⁴ In addition to these mentioned constituents of the underground parts, an EtOH extract from the aerial parts afforded coumarines, scopoletin and umbelliferone.¹⁴⁵ Kowalewska and Lutowski isolated, from *I. helenium*, quercetin, quercetin-7-triglucoside and 3-methylquercetin (obtained for the first time from the genus *Inula*).⁴⁶

The isolated compounds showed activity in promoting root formation on stem cuttings of *Phaseolus aureus* L. Isoalantolactone and inunal (an aldehydolactone), isolated from some *Inula sp.*, displayed considerable biological activity as plant growth regulators.¹⁴ Alantolactone was distinctly less active than either isoalantolactone, or isoalloyalantolactone. This could be due to the fact that an isolated double bond can affect the activity.

An investigation of the biological properties of these compounds (Schlemer *et al.*)¹⁴⁸ led to the striking result of the absence of cross allergy between the sesquiterpene lactone-sensitized groups of guinea pigs and the one sensitized to a smaller molecule, α -methylene- γ -butyrolactone. The observation concerns alantolactone and isoalantolactone. These are double bond positional isomers and a good cross reactivity between them could be expected. The study shows that both compounds do indeed give reactions, confirming earlier results. It should be noted that isoalantolactone sensitization seems a little weaker than that of alantolactone. These lactones might react differently because of discrepancies in their penetration capacity, elimination rate, metabolism rate, solubility, *etc.*¹⁴⁸ Alantolactone and isoalantolactone exhibited high bactericidal and fungicidal properties. These lactones were generally most active against *Chycobacterium tuberculosis*.¹⁴⁹

3.5.2. *Inula spiraeifolia* L.

The aerial parts of *I. spiraeifolia* were collected in summer 1981 at the same locality as *I. helenium* (3.5.1). An analogous procedure to the above (CHCl₃ extraction) yielded two novel isomeric trioxxygenated caryophyllenes.^{150,151} Almost simultaneously, the same compounds were isolated from *Pulicaria dysenterica* (Bohlmann and Zdero).¹³²

3.6. Genus *Eupatorium* L.

3.6.1. *Eupatorium cannabinum* L.

E. cannabinum L. (Asteraceae), a widespread wild plant growing in Europe, is a well known traditional medicinal plant since antiquity. Extracts of this species are used in traditional medicine against influenza and other diseases (cholagogue, laxative, diurethic and diaphoretic).

The following sesquiterpene lactones^{153,154} were previously isolated from *E. cannabinum*, originating from different localities:

- germacranolides – eupatoriopicrin, eupatolid, eucannabinolid, eupasimplicin B, chromolenid, giodorilactone E
- eudesmanolides – alantolactone and isoalantolactone
- guaianolide – eupahifolin C.

Chemical examination of several *Eupatorium* species has produced a number of sesquiterpene lactones with cytotoxic and antitumor properties, as determined in *in vivo* and *in vitro* test systems. Eucannabinolide exhibits *in vivo* antileukemic activity against lympholytic leukemia P 388 in mice.¹⁵⁵ Pharmacological studies of the sesquiterpene lactones confirmed the antitumor activity of eupatoriopicrin.¹⁵⁶ This lactone was active against KB (human nasopharynx carcinoma), He La (human carcinoma cervix uteri), EA (Ehrlich ascites carcinoma) and R KB (a normal human cell strain) cells. Recently, cytotoxicity against GLC-4 (Gromingen lung carcinoma, a human small cell lung carcinoma cell line) has been reported for eupatoriopicrin and related sesquiterpene lactones.^{157,158} Eupatilin and eupafolin showed cytotoxic activity.¹⁵⁹ The sesquiterpene lactone of *E. cannabinum* releases an acrylic acid (2,3-dihydroxymethylacrylic acid) which can be found in the plant in the free state. This, together with lactic, malic and citric acids present in *E. cannabinum*, has protective effects against acute toxicity induced by ethanol in mice. Other compounds could also be involved in this antinecrotic activity, such as phenolic acids, flavonoids, and triterpenoids which are present in *E. cannabinum*: caffeic and chlorogenic acids have been shown to inhibit the elevation of glutamic pyruvic transaminase in rat *in vivo*.¹⁶⁰ Also, it had been shown that polysaccharides of *E. cannabinum* and *E. perfoliatum* have immunological activity.¹⁶¹

Our investigation of the CHCl₃ extract of the aerial parts of plant material collected near Sevojno (West Serbia) in June 1978 revealed the presence of only one lactone, eupaformonin (**43**, Fig. 11).⁶² This cytotoxic lactone, belonging to a

new subgroup of germacranolides with (*E*)- $\Delta^{1(10)}$ and (*Z*)- Δ^4 double bonds, so called heliangolides, was isolated previously, together with eupatolide, from *E. formosanum* (Tainan, Taiwan).^{10,11} Eupaformonin was converted to the corresponding acetate (**44**) using the standard procedure. In addition the benzofuran (**45**), known as euparin, was isolated from our extract.

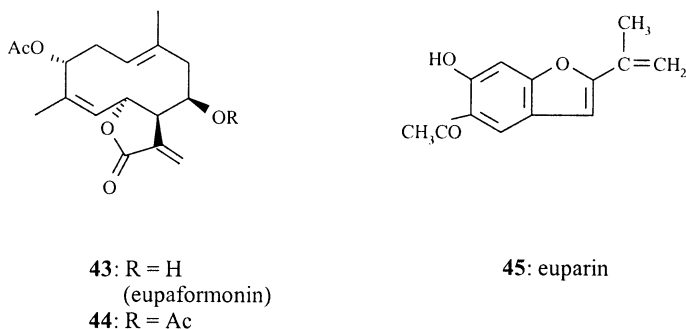


Figure 11.

3.7. Genus *Achillea* L.

The genus *Achillea* has received much attention so far because of various medicinal properties of some members. A number of SLs, mostly guaianolides with cross-conjugated cyclopentadienone systems, have been isolated from *Achillea* species.¹⁶³ According to the configuration at C-11, they were divided into the achillin (11 β -Me) and matricarin (11 α -Me) series. These types of guaianolides have also been found in numerous *Artemisia* and other species. Hitherto, our studies involved 6 species, collected in east Serbia and Montenegro.

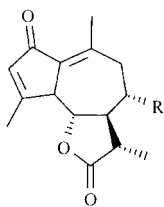
3.7.1. *Achillea abrotanoides* Vis.

Our investigations of this genus started with *A. abrotanoides*, collected in summer 1987 on the mountain Bjelasica (Montenegro). From the CHCl₃ extract, using the same procedure as above, we isolated three guaianolides (**46** – **48**, Fig. 12), all belonging to the same matricarin type.¹⁶⁴ Lactones **46** and **47**, i.e., deacetoxy-matricarin and deacetylmaticarin, respectively, have been found before in several *artemisia* and *Achillea* species.^{110,85,165-167} The structure of 1 β ,10 β -epoxydeacetoxy-matricarin (**48**) was established by comparison of its ¹H- and ¹³C-NMR spectral data to those of the diastereomeric lactone **49** (1 α , 10 α -epoxydeacetoxy-matricarin), obtained as the main product of the epoxidation of **46**, using *m*-chloroperbenzoic acid.

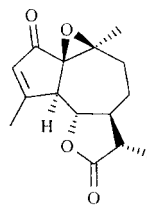
In addition, a flavonoid centaureidin was isolated from this extract (Fig. 13).

3.7.2. *Achillea millefolium* subsp. *pannonica* L.

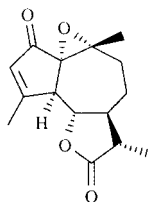
Since the Trojan war (1200 BC), *A. millefolium* has been used extensively by many cultures on different continents as a herbal remedy for various afflictions.¹⁶⁸



- 46: R = H
(deacetoxymatricarin)
47: R = OH
(deacetylmatricarin)



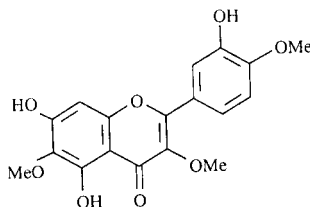
- 48*: 1β,10β-epoxydeacetoxymatricarin



* - new compound

- 49: 1α,10α-epoxydeacetoxymatricarin

Figure 12.



- 50: centaureidin

Figure 13.

Its antiinflammatory properties and the use of the extracts of the plant in the treatment of dental disorders have been investigated.¹⁶⁹

Previously, the following sesquiterpene lactones^{6,170-175} have been isolated from this plant originating from different regions:

- germacranolides – dihydroparthenolide, millefin, balchanolide and acetyl-balchanolide;
- eudesmanolide – dihydroreynosin;
- guaianolides – achillifolin, achillin, achillicin (the first azulene type compound), deacetylmatricarin, 2,3-dihydro-deacetoxymatricin, acetoxartab-sine and lactones of 3-oxaguaianolid type.

The aerial parts of *A. millefolium* also yielded acetylenic compounds and amides. The essential oil of *A. millefolium* subsp. *panonica* has been investigated and austriecin (azulene) was isolated.¹⁷⁶

In our laboratory, the lactones **46** and **48** were also detected in the aerial parts of *A. millefolium* subsp. *pannonica*,¹⁷⁷ collected at the same locality and at the same time as *A. abrotanoides* (3.7.1.).

3.7.3. *Achillea crithmifolia* W. et K.

Sesquiterpene lactones from *A. crithmifolia* have not been investigated so far.

The chemical constituents of *A. crithmifolia* originating from two different localities, and collected at different times were studied. In the first case from the aerial parts of this species collected at Rtanj mountain (East Serbia, September 1988), using the usual CHCl_3 extraction,²⁶ we isolated the known guaianolides rupicolin A (**51**), rupicolin B (**53**), their acetates (**52** and **54**), as well as a novel germacranolide (**55**) whose structure was deduced by means of COSY and NOESY

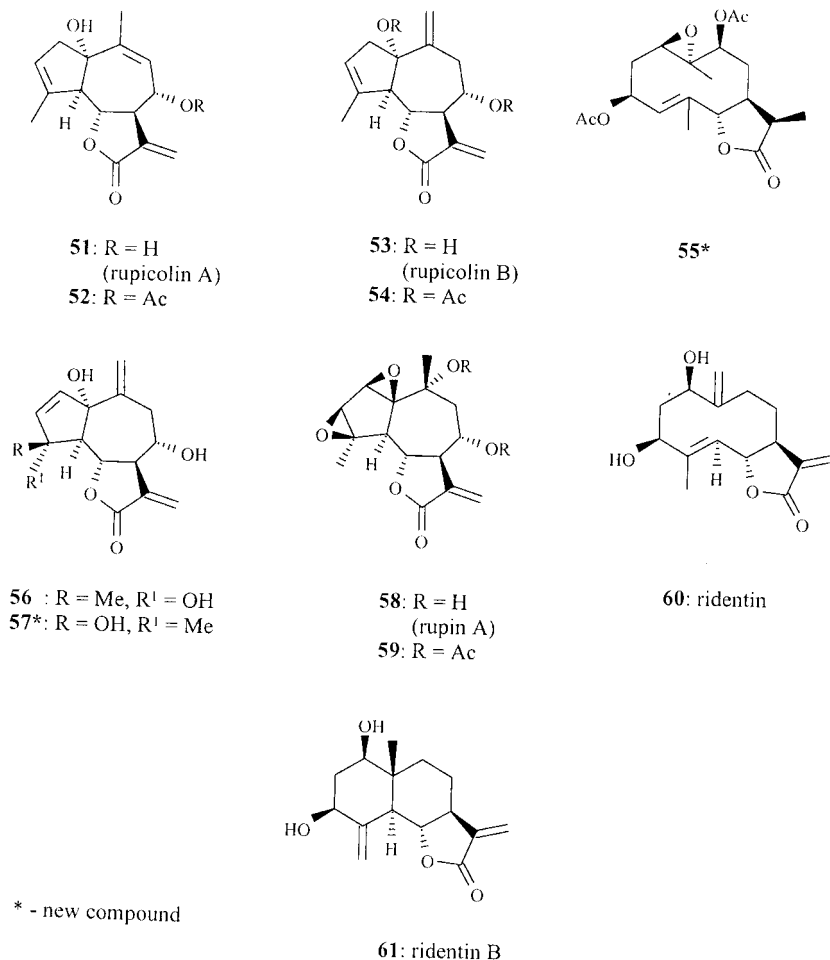


Figure 14

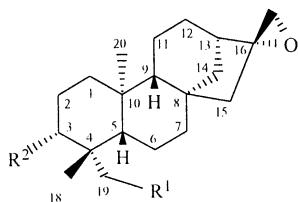
(Fig. 14).¹⁷⁸ Rupicolin A had been previously isolated from *Artemisia tripartita* subsp. *rupicola*,¹⁷⁹ and rupicolin B was isolated for the first time in 1968, but under the name ligustrin, from *Eupatorium ligustrinum*.¹⁸⁰

The second investigation of the aerial parts of *A. crithmifolia* collected in the vicinity of Donji Milanovac (East Serbia, July 1990) and using petrol ether-Et₂O-MeOH (1:1:1) for extraction (applied for the first time by Bohlmann *et al.*¹⁸¹) afforded three guaianolides (**56–58**), a known germacranolide ridentin (**60**) and a known eudesmanolide ridentin B (**61**).¹⁸² Lactone **56** had been isolated previously from the aerial parts of *Artemisia afra* (grown at the experimental station of the University of Fort Hare),¹⁸³ but the co-occurring 4-epimeric lactone **57** (assigned by means of COSY and NOESY) was a new compound (Fig. 14). Diepoxylactone, rupin A (**58**) was isolated previously from *Artemisia tripartita* subsp. *rupicola*.¹⁷⁹ Acetylation of **58** afforded **59**, exhibiting almost identical ¹H-NMR data as 1 β ,2 β :3 β ,4 β -diepoxyguaianolide, yomogiartemin, isolated from *Artemisia feddei*.¹⁸⁴ This indicated that the original assumption¹⁷⁹ of a 1 α ,2 α :3 α ,4 α -diepoxy stereochemistry of rupins A and B had to be revised to the 1 β ,2 β :3 β ,4 β -diepoxy-configuration. Rupin-A was also isolated previously from *Achillea biebersteinii*.¹⁸⁵

Ridentin (**60**) was previously isolated from *Artemisia cana* and *A. tripartita* subsp. *rupicola*,⁴ and ridentin B (**61**) from *A. tripartita*.^{179,186}

3.7.4. *Achillea clypeolata* Sibth. *et* Sm.

The plant material was collected at Sićevačka Klisura (Southeast Serbia) during the flowering season (May 1994). The roots and aerial parts were extracted according to the usual procedures used for the isolation of alkamides, (Et₂O-petrol ether 1:2)¹⁸⁷ and sesquiterpene lactones (Et₂O-petrol ether-MeOH, 1:1:1)¹⁸¹ respectively.¹⁸⁸ Neither the expected SLs, nor the alkamides (the usual constituents of the roots of *Achillea* species) were isolated from the extracts. Silica gel CC of the extract of the roots yielded three diterpenes belonging to the same *ent*-kaurane groups, *i.e.*, 16 α ,17-epoxy-*ent*-kaurane and its 19-acetoxy and 3 α -acetoxy analogues (**62–64**, Fig. 15).



- 62:** R¹ = R² = H
63: R¹ = OAc, R² = H
64: R¹ = H, R² = OAc

Figure 15.

3.7.5. *Achillea serbica* Nyman

In a continuation of the chemical investigation of the secondary metabolites in the species of genus *Achillea*, the extract of the aerial parts of *A. serbica* has been examined. The plant material was collected in 1992 from the locality Donja Studena (Jelašnica). The usual procedure¹⁸¹ was applied for the isolation of sesquiterpene lactones. Six guaianolides were obtained from the petrol ether-Et₂O-MeOH (1:1:1) extract of the air-dried aerial parts by CC (Fig. 16).¹⁸⁹ Rupicolin B (**53**) and 1 α ,4 β -dihydroxy-8 α -acetoxyguaia-11(13),9-dien-12,6 α -olide (**65**) were known compounds. 1 α ,4 β -Dihydroxy-8 α -acetoxyguaia-11(13)10(14)-dien-12,6 α -olide (**66**), two diastereomeric 1,2-epoxy-3-chloro-4,10-dihydroxy-8 α -acetoxy-(11(13)-en-12,6 α -olides (**67**, **68**) and 1,10-dihydroxy-2-chloro-3,4-epoxy-11(13)-en-12,6 α -olide (**69**) were new ones. All compounds were identified by means of spectroscopic data (IR, MS(1D and 2D) ¹H- and ¹³C-NMR). The determination of the relative configurations of **67**–**69** is still in progress.

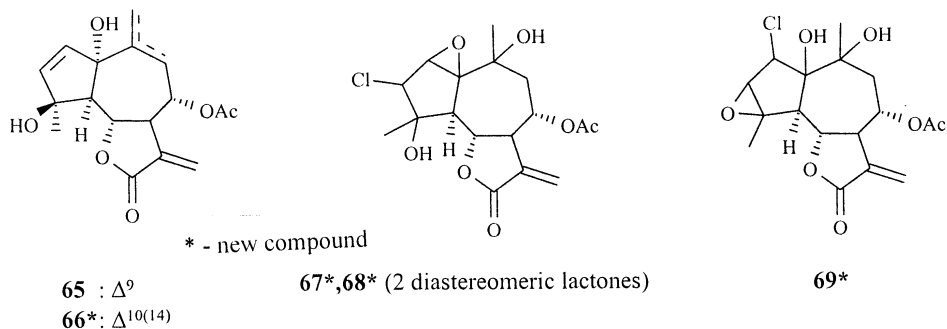
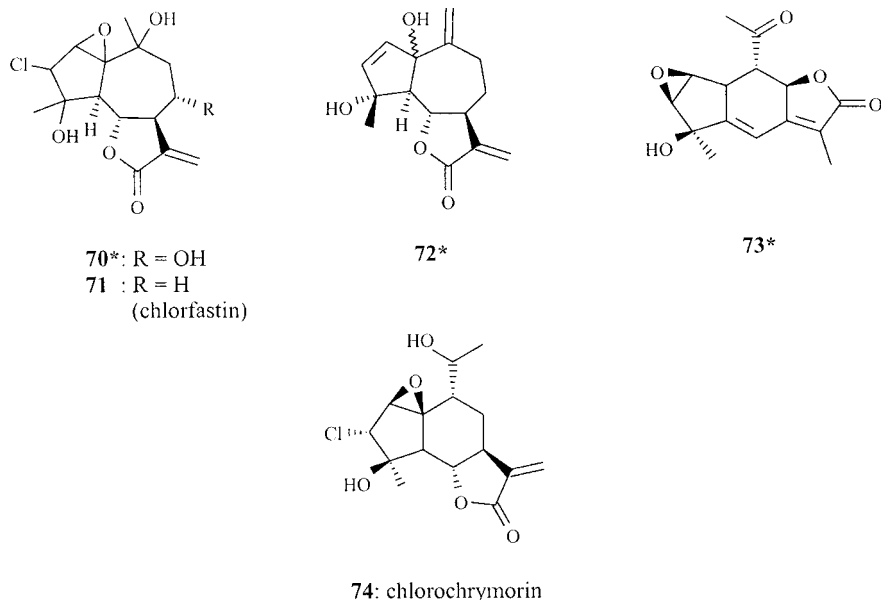


Figure 16.

3.7.6. *Achillea depressa* Janka

The plant material was collected from the locality Oblačinsko jezero (Me-rošina, Niš) during the flowering season at the end of May 1994. Using the usual previously mentioned procedure,¹⁸¹ the sesquiterpene lactones **70** – **73** were isolated (Fig. 17). Lactone **71** was previously isolated from *Ajania fastigata* (C. Winkl.) Poljak.¹⁹⁰ Compounds **70**, **72** and **73** have not been found in plant material before. Compound **73** is the rarely occurring type of sesquiterpene lactone in which the seven-membered ring of a guaianolide skeleton has undergone biogenetic ring contraction involving a 1,2-shift of C-1 from C-10 to C-9. Previously, a compound with a similar skeleton – chlorochrymorin, a sesquiterpene lactone with rooting promoter activity (**74**)¹⁹¹ was isolated from *Chrysanthemum morifolium* Ram. Similar chemical 1,2-shifts have been observed previously for sesquiterpenes and steroids.¹⁹² Rabi and coworkers¹⁹³ studied the Lewis acid catalyzed rearrangement of the 9,10- α -epoxide, which was obtained by peracid oxidation of eremanthin. Treatment of this epoxide with one equivalent of BF₃·Et₂O did not give an analogue of chlorochrymorin, but resulted in the aldehyde, derived from a shift of C-8 to C-10.



* - new compound

Figure 17.

Recently, a sesquiterpene lactone apressin, a guaianolide with an endoperoxide moiety¹⁹⁴ was isolated from the flowers of *A. depressa* originating from Bulgaria. From the leaves, besides the well-known monoterpenoids and flavonoids, the guaianolides achillin and 1,10-epoxyachillin were isolated.¹⁹⁵⁻¹⁹⁸ The complete analysis of the sesquiterpene-coumarin ethers from the roots of *A. depressa* had led to the isolation of eleven different compounds – all belonging to the isofraxidin series. According to morphological characters, these chemical findings support the close alliance between *A. depressa* and the *A. odiolenca* – *A. pseudopectinata* complex.¹⁹⁹

3.8. Genus *Anthemis* L.

Three main classes of compounds of chemosystematic interest, polyacetylenes, flavonoids and sesquiterpene lactones, typical for *Anthemidae*, have been detected in the genus *Anthemis*. Three types of sesquiterpene lactones, germacranolides (and secogermacranolides),²⁰⁰⁻²¹⁰ eudesmanolides²¹⁰⁻²¹² and guaianolides^{206,210,211,213,214} have been isolated from the genus. The exception was an allergenic lactone with an unusual structure (anthecotuloides), the constituent of *A. cotula*.^{215,216}

Continuing the chemotaxonomic examinations of the Yugoslavian wild-growing species belonging to Asteraceae,²¹⁷ the aerial parts of *A. carpatica* Willd. and *A. cretica* subs. *cretica* (syn. *A. montana* L.) were investigated. The flavonoids (from

leaves)²¹⁸ and polyacetylenes (roots)²¹⁹ are the only secondary metabolites of these species reported so far. Sesquiterpene lactones of these two species have not yet been investigated.

Repeated silica gel column chromatography of the extract, obtained using the usual extraction procedure for the isolation of sesquiterpene lactones,¹⁸¹ combined with preparative TLC of some fractions, yielded sesquiterpene lactones of guaianolide series, the majority of them with 8 α -acyloxy (or hydroxy) functionality.

3.8.1. *Anthemis carpatica* Wild.

The plant material was collected during the flowering season, in July, in 1994 from the Šara mountain, at location Lavlja vrata, altitude of *ca.* 1900m.

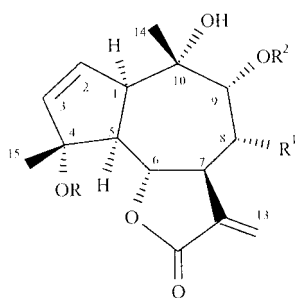
Fifteen new highly oxygenated guaianolides (**76–82**, **84–85**, **95–97**) were isolated from the extract of the aerial parts. The structures of the isolated compounds were established by spectroscopic methods, namely ¹H-NMR, ¹³C-NMR, MS, IR and in some cases also by 2D NMR spectroscopy (COSY, TOCSY, NOESY, HSQC and HMBC).²²⁰ Some of them (**77–82**, **87**, **97**) contained a hydroperoxy group, a functionality known to play an important role in the biological activities of many natural products (Fig. 18).

3.8.2. *Anthemis cretica* L. *subsp.* *cretica*

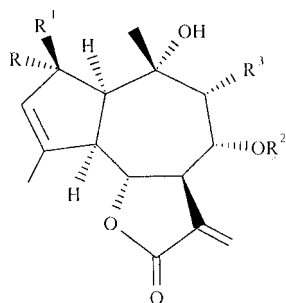
The same procedure¹⁸¹ applied to the extract of the aerial parts of *A. cretica* subsp. *cretica* (Ošljak, altitude 2210 m, Šara Mountain, 1994) afforded two new guaianolides, *i.e.*, anthemolide B (**75**) and 8-*O*-angeloyl-9-*O*-acetylanthemolide B (**83**) in addition to twelve sesquiterpene lactones of the guaianolide series **77**, **79**, **80**, **84**, **85**, **89–94** and **96** (Fig. 18). Whereas the lactones **77**, **79**, **80**, **84** and **85** had also been isolated from *A. carpatica*, **89** was a constituent of *A. hydruntina* (southern Italy)²¹³ and lactones **89–94** have recently been found in *A. aetnensis* (Mountain Etna, Sicily).²²¹ The structure determination of the isolated sesquiterpene lactones was based on the ¹H-NMR, ¹³C-NMR, IR, MS and 2D NMR methods – COSY, TOCSY, NOESY, HSQC and HMBC.

3.9. Genus *Centaurea* L.

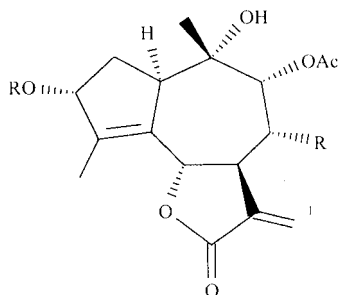
Extensive chemotaxonomic investigations of the large genus *Centaurea* revealed quite a few sesquiterpene lactones, comprising four types, *i.e.* guaianolides, germacranolides, elemanolides and eudesmanolides.²²¹ Many of them exhibited various biological activities (*e.g.* cytotoxicity, antibioticity, phytotoxicity, neurotoxicity, *etc.*)^{221–224} Our study of this genus involved three species, originating from Yugoslavia: *C. derwentana* Vis. & Pančić, *C. kosaninii* Hayek and *C. solstitialis* L. The chemical constituents of *C. derwentana* and *C. kosaninii*, both endemic species,²²⁵ growing in west Serbia (and Bosnia) and south Serbia (and Albania), respectively, had not been studied before. However, *C. solstitialis* (yellow starthistle) could be found throughout the world, *i.e.*, southern Europe, western and central



	R	R ⁱ	R ^j
75* m :	OH	OH	H
76* c :	H	H	Ac
77* m,c :	OH	OAc	H
78* c :	OH	OH	Ac
79* m,c :	OH	OAc	Ac
80* m,c :	OH	O- <i>i</i> -But	Ac
81* c :	OH	H	Ac
82* c :	OH	OTig	Ac
83* m :	OH	OAng	Ac



	R	R ⁱ	R ²	R ³
84* m,c :	H	H	H	OAc
85* m,c :	H	H	Ac	OH
86* c :	H	H	Ac	OAc
87* c :	OOH	H	<i>i</i> -But	OAc
88* c :	H	H	H	H
89 m,h,a :	H	OAc	<i>i</i> -But	OAc
90 m,a :	H	OAc	H	OAc
91 m,a :	H	OAc	Ac	OAc
92 m,a :	H	OAc	H	O- <i>i</i> -But
93 m,a :	H	OAc	H	O- <i>i</i> -Val
94 m,a :	H	OAc	H	O-2-MeBut



	R	R ⁱ
95* c :	H	H
96* m,c :	H	OAc
97* c :	OH	OAc

c - guaianolides isolated from *A. carpatica*

m - guaianolides isolated from *A. cretica* subsp. *cretica* (syn. *A. montana*)

h - guaianolides isolated from *A. hydruntina*

a - guaianolides isolated from *A. aetnensis*

* - new compound

Figure 18.

Asia, South America and also in the western United States where it is a major weed problem.

All extracts, whose investigation is reported in this paper, were prepared from the aerial parts of plant material collected during the flowering season using the usual extraction procedure for the isolation of sesquiterpene lactones,¹⁸¹ followed by silica gel column chromatography of the extract.

3.9.1. *Centaurea derwentana* Vis. et Panč.

From the extract of the aerial parts of *C. derwentana*, collected at the canyon of the brook Derventa close to Bajina Bašta (W. Serbia, 1996) four closely related germacranolides, commonly found in *Centaurea* species, such as salonitenolide (**98**), cnicin (**99**), cnicin-4'-*O*-acetate (**100**) and salonitenolide-8-*O*-(4'-acetoxy-5'-hydroxyangelate) (**101**) were isolated²²⁶ and identified by comparison of their spectral data to those published (Fig. 19).²²⁷⁻²³¹ The major constituent, cnicin was obtained in an appreciable yield (0.2%, calc. per weight of dried plant material). This compound, found before in sixteen *Centaurea* species originating from different localities,^{221,232-235} is known to exhibit considerable cytotoxic,²²² cytostatic²²³ and antibiotic²²² activities. Cnicin was also rather abundant in the extracts of *C. stoebe* (Germany, 0.45%),²²⁹ *C. brugeriana* (Iran, 0.16%),²³⁰ *C. nicaensis* (Sicily, Italy 0.19%)²³¹ and *C. calcitrapa* (Argentina, 0.06%).²²⁸ The related germacranolides **98** and **100** were co-occurring species of **99** in *C. calcitrapa*,²²⁸ whereas in *C. stoebe*, **99** was accompanied by **98** and **101**.²²⁸ The lactones **98** – **101** had also been isolated previously from *C. alba* (Spain).²³²

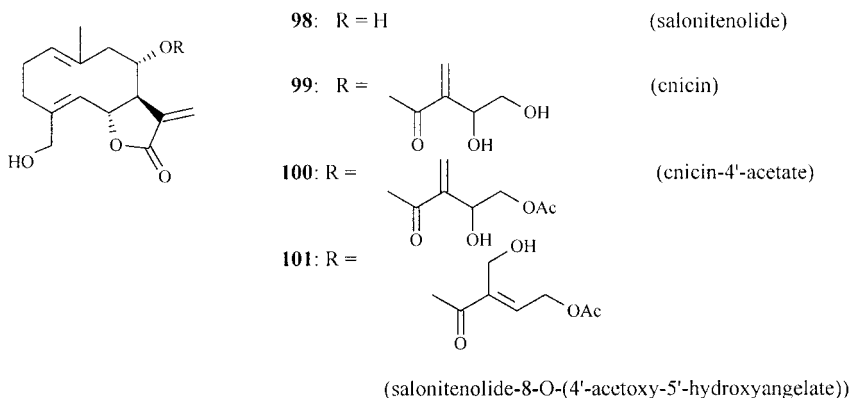


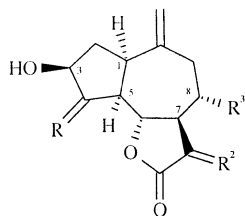
Figure 19.

3.9.2. *Centaurea kosaninii* Hayek

The same procedure applied to the extract of the aerial parts of *C. kosaninii* (Brezovica, Kosovo, 1994) afforded a mixture of α - and β -amyrin and also a mixture of stigmasterol and β -sitosterol. No sesquiterpene lactones were detected in this extract.²²⁶

3.9.3. *Centaurea solstitialis* L.

Due to their neurotoxicity, allelopathic activity and cytotoxicity, the chemical constituents of *C. solstitialis*, originating from different parts of the world (California, Argentina, Europe) have been extensively studied so far.^{221,224,227,228} Hitherto, several sesquiterpene lactones, almost exclusively highly oxygenated guaianolides have been isolated from the aerial parts of this species. In addition, some alkaloids, triterpenes and flavonoids were reported as the constituents of *C. solstitialis*.²²¹



	R ¹	R ²	R ³	
102:	CH ₂		H	(solsitalin A)
103:	CH ₂		H	(solsitalin A 13-acetate)
104:	CH ₂	CH ₂		(cynaropicrin)
105:	CH ₂		OH	(11β,13-dihydro deacylcynaropicrin)
106:	CH ₂	CH ₂		(linichlorin B)
107:		CH ₂		(19-desoxychlorojanerin)
108:		CH ₂		(8-deacylcentaurepsin -8-O-(4-hydroxy)-tiglate
109:		CH ₂		(17- <i>epi</i> -centaurepsin)
110:		CH ₂		(centaurepsin)

Figure 20

From the aerial parts of *C. solstitialis* (New Belgrade, 1995), eight known guaianolides (**102** – **110**), typical for this genus, were isolated and identified by comparison of their spectral data to those published (Fig. 20). Whereas solstitialin A and its 13-acetate (**102** and **103**),^{221,227} cynaropicrin (**104**)^{221,227,228} and linichlorin B (**106**)^{221,228,236} had been found before in this species, the remaining lactones had been isolated previously from other *Centaurea* species.²²⁷ The identification of lactone **105** was based on a close similarity of its ¹H-NMR data to those of 11 β ,13-dihydrodeacylcynaropicrin, isolated (together with **104**) from *Tricholepis glaberimma* (Uttar Pradesh, India).²³⁷ Lactone **107**, 19-deoxychlorojanerin, was isolated for the first time from *C. aegyptica* (originating from the Sinai desert).²³⁸ Lactone **108**, exhibiting almost identical ¹H-NMR data to those of 8-deacylcentaurepensin-8-*O*-(4-hydroxy)-tiglate, a constituent of *C. imperialis* (collected northwest of Teheran, Iran),²³⁹ was an additional guaianolide isolated for the first time from *C. solstitialis*. Lactone **109** had identical ¹H-NMR data to those of a lactone isolated from *C. conifera* (collected in Spain),²³² and so was identified as the 17-epimer of centaurepensin (or chlorohyssopifolin A, **110**), a constituent of the previously studied aerial parts of *C. solstitialis*,^{227,228} shown to be toxic to 9 KB (human nasopharynx carcinoma) cells.

4. APIACEAE

The plant family Apiaceae, encompassing *ca* 3000 species, occurs throughout the northern hemisphere in the temperate zones. In Serbia, this family is represented by 138 species (53 genera).²⁴⁰ Hitherto, the chemical constituents of Apiaceae species have received considerable attention, which is due to various bioactivities of their extracts and essential oils. Many of the medicinal properties of these species are ascribed to aromatic δ -lactones – coumarins which are common secondary metabolites of Apiaceae. Among these compounds, the most active are furocoumarins which exhibit phototoxicity.

Another group of secondary metabolites of Apiaceae are SLs. The majority of the SLs isolated from species of the family Apiaceae have a different stereostructure to that predominating in Asteraceae. This could be explained in terms of the different conformations of the *trans*, *trans*-farnesyl diphosphate precursor prior to the cyclization steps (Holub & Budesinsky and the refs therein).²⁴¹⁻²⁴³ Thus, in one of the most abundant groups of lactones produced by Apiaceae, such as the guaianolides, a slovanolide type structure (*i.e.*, 1 β H, 5 β H, 6 α H-6,12-olide) predominates, whereas in the eudesmanolides, a selinanolide type structure (*i.e.* 5 β H, 6 α H, 7 α H, 10 α Me-12,6-olide) is the basic structure.

4.1. Genus *Laserpitium* L.

The study of this genus revealed almost exclusively guaianolides of the slovanolide type.²⁴⁴⁻²⁵⁴

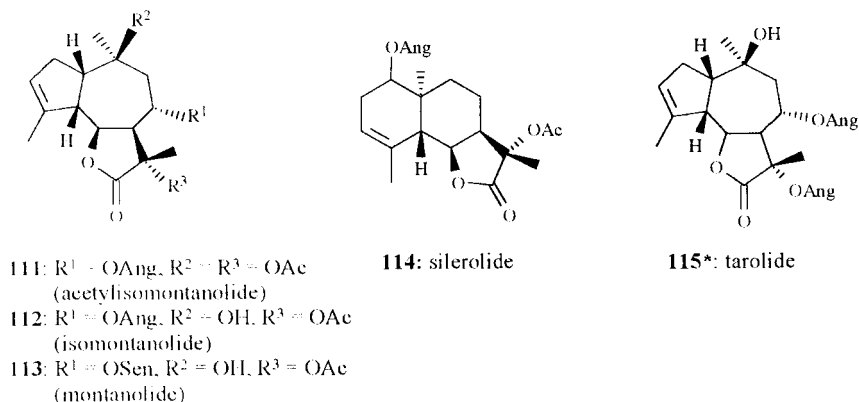
4.1.1. *Laserpitium siler* L.

L. siler was collected on the Tara mountain, in 1975. From the aerial parts of the plant, using the usual procedure of isolation,²⁶ the sesquiterpene lactones acetylismontanolid (111), isomontanolid (112), montanolid (113), silerolid (114) and a new guaianolide tarolid (115)²⁴⁵ were isolated and identified (Fig. 21). All the isolated lactones exhibited stereostructural features typical for the genus *Laserpitium*, which was the main subject of research work carried out by a group of Czechoslovak authors and by Bohlmann *et al.*²⁴⁴⁻²⁵⁴ The structure of a non-crystalline sesquiterpene lactone of the selinane type, silerolid (114), for the first time found in the same species in 1970, was established by correlation with lasolide.

In addition to the sesquiterpene lactones an aromatic compound latifolone (116) and its derivatives were also isolated (Fig. 22). α -Angeloyloxy-latifolone (117) is a new derivative of latifolone.^{245,255} Artemetin (118), the flavonol, was also isolated from the extract of this origin.

Earlier examination of this plant of Slovakian origin showed that the fruit gave 4.2% essential oil rich in limonene and perilladehyde. The light petroleum extract contained the C₁₆–C₃₁ paraffin hydrocarbons, sesquiterpene hydrocarbons, fatty acids (palmitic, linoleic, oleic) and phytosterol (mainly β -sitosterol).^{247,256}

From a comparison of the components, especially sesquiterpene lactones which were identified in the fruits,^{247,253} in the aerial part^{245,255} and the underground part of *L. siler*, it follows (disregarding the localities of the material investigated) that some substances (montanolid, isomontanolid and acetylismontanolid), which occur in relatively high concentrations, are present in all the plants investigated, while some others, usually present in the given part in lower amounts, have been detected so far only in some parts of the plant. It may be concluded that, from a quantitative point of view, no fundamental difference exists



* - new compound

Figure 21.

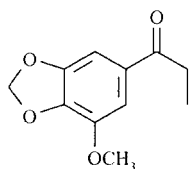
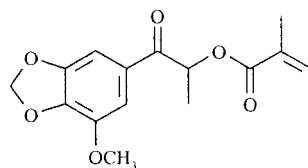
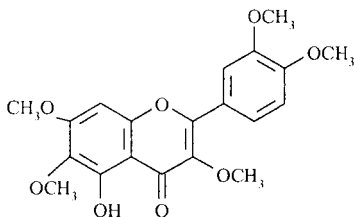
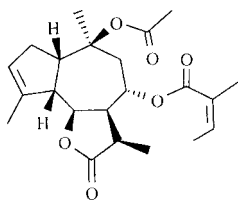
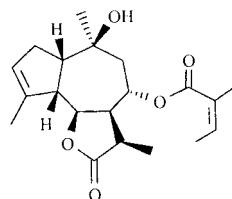
**116:** latifolone**117:** α-angeloyloxy-latifolone**118:** artemetin

Figure 22.

with the exception of isosilerolide, present only in the underground parts.²⁵⁷ The acid parts of the ester residues in all the products isolated from *L. siler* are formed from only three acids, *i.e.*, acetic, β,β-dimethylacrylic and α-methyl-isocrotonic acid. It could be significant to correlate the occurrence of these acids to the geographical origin of the species.

4.1.2. *Laserpitium marginatum* L.

L. marginatum had not been investigated previously. From this plant, collected 1976, in July on the mountain Kopaonik, using the usual CHCl_3 extraction,²⁶ two new guaianolides (Fig. 23), **119** and **120**, as colourless crystalline compounds were isolated. Their structures were deduced by means of $^1\text{H-NMR}$, IR and X-ray

**119*:** 10β-acetoxy-8α-angeloyloxy-6αH,
7αH-guaian-3-en-6,12-olide**120*:** 8α-angeloyloxy-10β-hydroxy-6αH,
7αH-guaian-3-en-6,12-olide

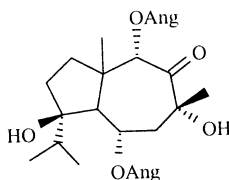
* - new compound

Figure 23.

crystallographic analysis.^{258,259} Acetylation of **120** yielded **119**, thus confirming the proposed structure of these lactones.

4.1.3. *Laserpitium latifolium* L.

From the extract of *L. latifolium*, collected in Ibarska klisura, in 1977, obtained by the usual procedure,²⁶ three crystalline compounds, *i.e.*, laserpitin (Fig. 24), **121**, previously isolated by Holub *et al.* from the same species,²⁶⁰ and two sesquiterpene lactones identical with the compounds from *L. marginatum* (**119** and **120**) were isolated by CC.



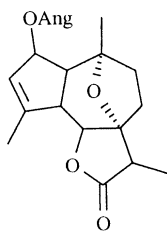
121: laserpitin

Figure 24.

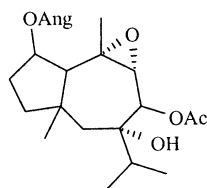
Previous chemical investigations of this species afforded laserpitin, laserol-monoangeloyloxy,²⁶¹ laserol,²⁶² isolaserpitin²⁶⁰ and latifolon.²⁶⁰

4.1.4. *Laserpitium alpinum* W. K.

From the rare plant, *L. alpinum* collected in 1979, on the mountain Vranica, two new crystalline products (**122** and **123**, Fig. 25) were isolated by a previously described method.²⁶³



122*: 2 β -angeloyloxy-7 α ,10 α -epoxy-6 β H-guaian-3-en-6,12-olide



123*: 8-acetoxy-2 β -angeloyloxy-9 α ,10 α -epoxy-7 α -hydroxy-*pseudo*-guaiane

* - new compound

Figure 25.

4.2. Genus *Angelica* L.

4.2.1. *Angelica silvestris* L.

The study of EtOAc-extracts of roots of *A. silvestris*, originating from Holme (east Serbia) and fruits from the Tara Mountain (West Serbia) revealed nine known linear furocoumarins (four in the roots and five in the fruits), two of them (heraclenol and heraclenin) found for the first time in this species.^{264,265} This was in accordance with previous reports concerning the chemical constituents of *A. silvestris*, also yielding quite a few linear furocoumarins.²⁶⁶⁻²⁶⁸ Neither sesquiterpene lactones, nor a sesquiterpene ketoalcohol, bisabolangelone, the latter previously found in *A. silvestris*,²⁶⁹ were detected in our extracts.

4.3. Genus *Peucedanum* L.

4.3.1. *Peucedanum austriacum* (Jacq.) Koch

Three reduced (dihydro) angular pyranocoumarins (so-called khellactones), together with two linear dihydro(furo- and pyrano-)chromones were isolated from the aerial parts of *P. austriacum* (Stolovi Mountain, W. Serbia).²⁷⁰ Subsequent investigation of the roots of this species (Tara Mountain, W. Serbia)²⁶⁵ yielded three known dihydrofurocoumarins and a dihydropyranocoumarin, all of them isolated for the first time from *P. austriacum*. No sesquiterpene lactones were detected in these experiments.

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SUMMARY

Investigations regarding the isolation, structure determination and, in some cases, the biological activities of sesquiterpene lactones from Yugoslavian plant species carried out at the Institute of Chemistry, Faculty of Science (now Faculty of Chemistry), University of Belgrade, since the beginning of seventies, involving nine genera of the family of Asteraceae and three of Apiaceae are reviewed in this paper. Results of other groups concerning the same and related species, originating from different localities throughout the world, are also presented.

ИЗВОД

СЕСКВИТЕРПИНСКИ ЛАКТОНИ САМОНИКЛИХ ЈУГОСЛОВЕНСКИХ БИЉНИХ ВРСТА ФАМИЛИЈА ASTERACEAE И APIACEAE

СЛОБОДАН МИЛОСАВЉЕВИЋ,¹ ВАЊА БУЛАТОВИЋ² И МИЛУТИН СТЕФАНОВИЋ¹

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Приказана су хемијска испитивања самониклих биљних врста фамилија Asteraceae (девет родова) и Apiaceae (три рода) са подручја Југославије рађена на Хемијском институту

Природно-математичког факултета (данашњем Хемијском факултету) Универзитета у Београду од почетка седамдесетих година. Њима су углавном обухваћени изоловање и идентификација сесквитерпенских лакотна, а у неким случајевима и испитивање биолошке активности изолованих једињења. Такође је дат преглед и резултата других група који се односе на исте и сродне врсте са различитих локалитета у свету.

(Примљено 4. фебруара 1999)

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