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Secondary Metabolites from Mexican Species of the Tribe Senecioneae (Asteraceae)

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Abstract. A revision of the Mexican species belonging to the tribe Senecioneae chemically studied so far, shows that the genera *Senecio* and *Packera* (subtribe Senecioninae), and the genera *Barkleyanthus*, *Pittocaulon*, *Psacalium*, and *Telanthophora* (subtribe Tussilagininae) contain pyrrolizidine alkaloids (PAs) and eremophilane derivatives as their main secondary metabolites. However, from *Roldana* and *Robinsonecio* (subtribe Tussilagininae) no PAs have been isolated. A special case is the genus *Pseudogynoxys* in which neither PAs nor eremophilanes are reported.
Keyword: Senecioneae, *Senecio, Packera, Barkleyanthus, Pittocaulon, Psacalium, Telanthophora,* pyrrolizidine alkaloids, eremophilane, *Roldana, Robinsonecio*.

Resumen. Una revisión de las especies mexicanas de la tribu Senecioneae estudiadas químicamente hasta el momento, muestra que los géneros *Senecio* y *Packera* (subtribu Senecioninae), y los géneros *Barkleyanthus*, *Pittocaulon*, *Psacalium* y *Telanthophora* (subtribu Tussilagininae) contienen alcaloides pirrolizidínicos (APs) y derivados de eremofilano como sus metabolitos secundarios principales. Sin embargo, de *Roldana* y *Robinsonecio* (subtribu Tussilagininae) no se han aislado APs. Un caso especial es el género *Pseudogynoxys* para el cual no se han reportado ni APs ni eremofilanos.
Palabras clave: Senecioneae, *Senecio, Packera, Barkleyanthus, Pittocaulon, Psacalium, Telanthophora,* alcaloides pirrolizidínicos, eremofilano, *Roldana, Robinsonecio*.

Introduction

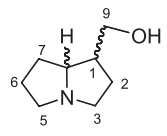
The tribe Senecioneae containing about 3000 species is the largest of the 13 tribes in which the family Asteraceae is divided [1]. This tribe is represented in the Mexican-Centroamerican region by 165 species [2] that belong to 19 genera [3], included the large genus *Senecio*. In the Mexican part there are about 102 species that constitute the 62 % of those of the Mexican-Centroamerican region.

The present review deals with the chemical studies of 44 Mexican species belonging to the subtribes Senecioninae and Tussilagininae that together with the subtribe Blennospermatinae, constitute the tribe Senecioneae. Chemical studies of species of *Senecio* and *Packera* (subtribe Senecioninae) show the pyrrolizidine alkaloids (PAs) and eremophilane derivatives as their main metabolites. Similar results have been obtained from species of *Barkleyanthus*, *Pittocaulon*, *Psacalium*, and *Telanthophora* (subtribe Tussilagininae) so far studied. Nevertheless from species of *Roldana* and *Robinsonecio*, which belong to the subtribe Tussilagininae as well, no PAs have been isolated. Sesquiterpenes such as eremophilanes, eremophilane derivatives, and oplopanes are the metabolites more frequently found in these genera. A special chemical composition presents *Pseudogynoxys chenopodioides* in which no PA neither eremophilane was found.

Since the pyrrolizidine alkaloids and eremophilanes are the main metabolites isolated from the above mentioned genera, these groups of compounds will be discussed. Then, the chemical composition of species belonging to the subtribe Senecioninae (genera *Senecio* and *Packera*) will be described followed by that of the genera of the subtribe Tussilagininae, arranged in alphabetical order.

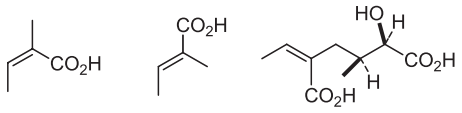
Pyrrolizidine Alkaloids

PAs are a group of natural products which contain any of the four isomers of the 1-hydroxymethylpyrrolizidine (**1**) in its molecule, which are named necines [4]. They may have a double bond at C-1, an OH group at C-7, and the positions 2 and 6 could be oxidized.



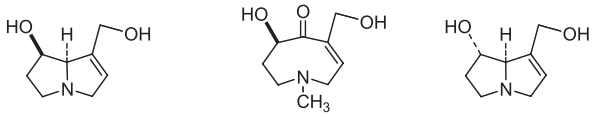
1

Hydroxyl groups can be esterified by monocarboxylic acids such as angelic (**2**) or tiglic (**3**) acids, or by dicarboxylic acid as senecionic acid (**4**).

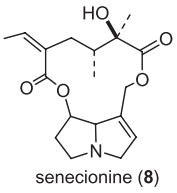


2 **3** **4**

PAs containing in their basic skeletons retronecine (**5**), otonecine (**6**), or heliotridine (**7**) are highly toxic. The toxicity increases when a cyclic ester is present as in senecionine (**8**) which is the more common PA in Senecioneae.



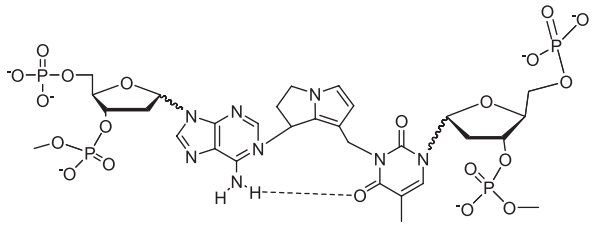
retronecine (**5**) otonecine (**6**) heliotridine (**7**)



senecionine (**8**)

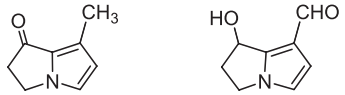
Nevertheless, saturated poly-hydroxy PAs mimics the structure of monosacharides and therefore have therapeutic potential in many diseases such as viral infections, cancer and diabetes [5].

Many of the 1,2 dehydro PAs are hepatotoxic, some of them are mutagenic and cause hepatomegalia and venooclusive disorders of the liver among other illnesses. The hazard begins when these substances are converted in the liver to the N-oxides or to hydroxylated compounds α to nitrogen. In both cases an elimination of water led to highly toxic dehydropyrrolizidines [4]. These compounds are electrophiles that could react with nucleophiles such as mercapto, hydroxyl, or amino groups present in enzymes, globulins, or hemoglobin. The purine or pyrimidine of DNA are able to act as nucleophiles creating a stable bridge inside the double helix of DNA (**9**), thus inducing cancer.



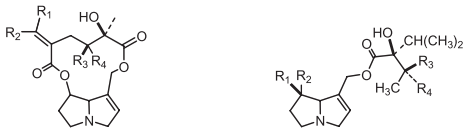
9

According to the above discussion, the consumption of herbs which contain PAs should be responsible for health problems and even for numerous deaths of cattle and human beings. However, what is risky for some organisms is good for others. The high toxicity is an advantage for many insects. The butterflies *Danaus gilippus* sequester PAs which are used as precursors of their pheromones such as danaidone (**10**) and hydroxydanaidal (**11**). The pheromones once synthesized are kept by the male and presented to the female by means of organs it has in the abdomen [6], the females do not accept the males unless they have the odor of the pheromone.



10 **11**

The chemical analysis of the body of monarch butterflies (*Danaus plexippus*) which spend the winter in Mexico [7] showed the presence of the highly toxic PAs: senecionine (**8**), integerrimine (**12a**), and seneciphyline (**12b**), and the open chain PAs intermedine (**13a**), lycopsamine (**13b**), and echinatine (**13c**). All these toxic alkaloids are probably used as defense compounds.

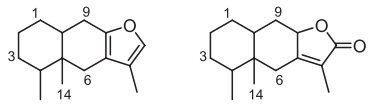


	R_1	R_2	R_3	R_4
integerrimine (**12a**)	CH_3	H	H	CH_3
seneciphyline (**12b**)	H	CH_3	CH_2	

	R_1	R_2	R_3	R_4
intermedine (**13a**)	OH	H	OH	H
lycopsamine (**13b**)	OH	H	H	OH
echinatine (**13c**)	H	OH	H	OH

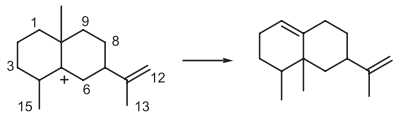
Eremophilanes

The sesquiterpenes known as eremophilanes contain, in its basic skeleton, a decalin system and most of them are found as furanoeremophilanes (**14**) or eremophilanolides (**15**).



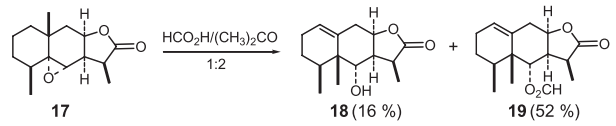
14 **15**

Eremophilanes could arise from an eudesmane precursor (**16**) by means of an 1,2 methyl migration, which it has been achieved *in vitro* by different authors.



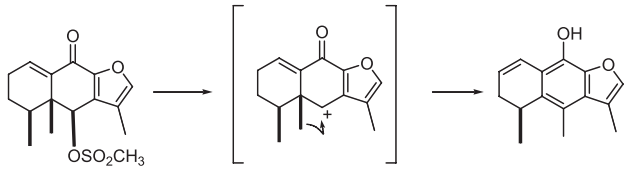
16

Kitagawa J. *et al.* [8] treated the 5,6-epoxi eudesmanolide **17** with formic acid in acetone. The reaction afforded a mixture of eremophilanolides in which the main products were the lactones **18** and **19**.



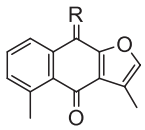
17 **18** (16 %) **19** (52 %)

Some species of Senecioneae contain modified eremophilanes as characteristic metabolites. There are many examples of transformation of eremophilanes into this type of compounds in the chemical literature, as that described by Romo J. [9]. The methylsulfonate of 6-*epi*-decompostine (**20**) on heating with collidine afforded the modified eremophilane **21**.



20 **21**

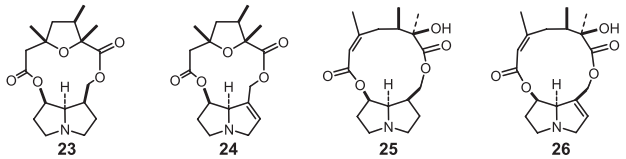
Further transformation of **21** led to *nor*-eremophilanes such as **22** which are present in many genera of Senecioneae.



22

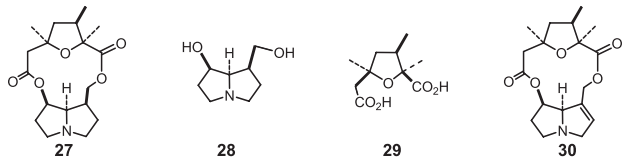
Genus *Senecio*

The genus *Senecio* includes about 1500 species with a broad spectrum of life forms. It is found world-wide and have in the Mexican-Centroamerican region an important diversification center. Barkley, Clark, and Funston in their study of *Senecio sl* [3] from the above region, recognized nineteen genera, most of them segregated from *Senecio* such as *Barkleyanthus*, *Packera*, *Pittocaulon*, *Psacalium*, *Pseudogynoxys*, *Robinsonecio*, *Roldana*, and *Telanthophora*. The same authors recognized that the genus *Senecio sensu stricto* is constituted by six sections; one of them is the section Mulgediifolii which contains 15 species [10] localized from Mexico to Guatemala. Some of its species contain the relative uncommon 13-membered macrocyclic PAs. Until 1995, these compounds have been isolated exclusively from European *Senecio* species [11-14], and only four were known: nemorencine (**23**), retroisosenine (**24**), bulgarsenine (**25**), and doronenine (**26**).



23 **24** **25** **26**

A systematic chemical examination of the section Mulgediifolii began in 1995 with the study of *S. mulgediifolius* [15]. In this work retroisosenine, its N-oxide, bulgarsenine (**25**) and mulgediifoline were isolated. Structure **27** was established for mulgediifoline on spectroscopic and chemical grounds, specially by the saponification products, platynecine (**28**) and *cis*-nemorencic acid (**29**). Similar considerations induced to propose structure **30** instead of **24** for retroisosenine.



27 **28** **29** **30**

The conformation of retroisosenine (**30**) was proposed on the basis of its NOE effects, especially those between CH_3-18 and H-2 (Fig. 1), which indicated a sandwich conformation with the tetrahydrofuran over the necine.

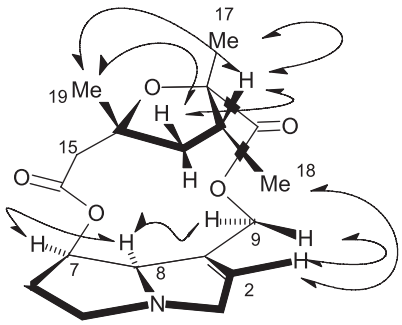
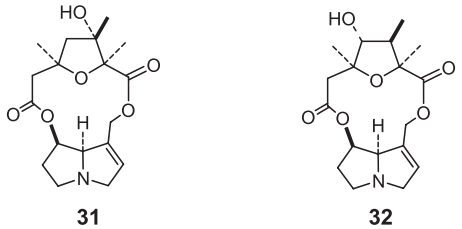


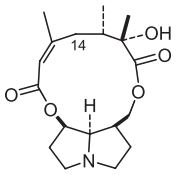
Fig. 1

The chemical examination of the species *S. helodes* and *S. roseus* afforded 13-membered macrocyclic PAs [16]. *S. helodes* yielded **30** and (12*S*)-12-hydroxyretroisosenine (**31**), and *S. roseus* produced **27**, **30**, **31**, and (13*R*)-13-hydroxyretroisosenine (**32**).



31 **32**

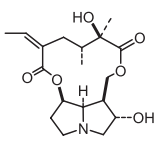
The next species of the section Mulgediifolii chemically analyzed were *S. iodanthus* and *S. bracteatus* [17], both species yielded iodanthine (**33**), bulgarsenine (**25**), retroisosenine (**30**), its hydrochloride and that of mulgediifoline (**27**). Additionally, **31** was obtained from *S. bracteatus*.



33

The diasteromeric relationship between bulgarsenine (**25**) and iodanthine (**33**) afforded differences in the chemical shift of CH_2-14 in their respective NMR spectra [17]. Even though the basic hydrolysis of **25** and **33** gave the same necine, platynecine (**28**), the necic acids were different. The structure of iodanthine was settled as **33** by X-ray crystallographic analysis of its hydrochloride.

All *Senecio* species of the section Mulgediifolii have a restricted distribution, except *S. callosus* which grows in an extensive area of Central and Southern Mexico. Collections from the States of Mexico, Michoacán and Oaxaca showed a different chemical composition. A sample from a place near Lagunas de Zempoala, State of Mexico, gave a high yield of rosmarinine (**34**) [18].



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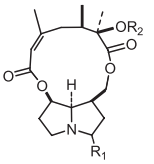
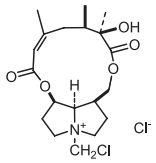
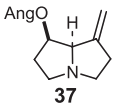


35a R_1 = H R_2 = Ac
35b R_1 = $CH_2CO_2CH_3$ R_2 = H



36

The plant collected in Michoacán [19] afforded 11-O-acetyl-bulgarsenine (**35a**), bulgarsenine (**25**), callosine (**35b**), and N-chloromethylbulgarsenine chloride (**36**). *S. callosus* from Oaxaca produced the opened chain PAs **37**-**38a**-**b**.



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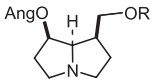
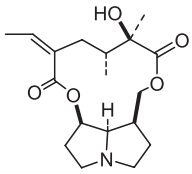


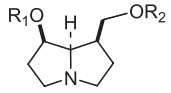
38a R = 5-hydroxyAng
38b R = 5-hydroxyTig

The species *S. jacalensis* [18], *S. polypodioides*, and *S. runcinatus* [20] gave 12-membered macrocyclic PAs. *S. jacalensis* afforded platyphylline (**39**) and senecionine (**8**), *S. polypodioides* yielded **39**, its hydrochloride, and its N-oxide, *S. runcinatus* gave rosmarinine (**34**) and its N-oxide.



platyphylline (**39**)

The three species *S. doratophyllus*, *S. conzattii*, and *S. deformis* [21] gave PAs with open chain esters and diesters. *S. doratophyllus* and *S. conzattii* afforded sarracine (**38a**) and neosarracine (**38b**) as hydrochlorides. Additionally, *S. doratophyllus* gave **37** and *S. conzattii* yielded 9-angelylplatynecine (**40a**) and 7β-tiglylplatynecine (**40b**). From *S. deformis* was isolated the **38a** N-oxide.



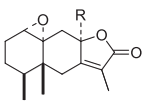
40a R_1= H R_2= Ang
40b R_1= Tig R_2= H

In summary, the twelve species of the section Mulgediifolii chemically studied gave PAs. Six of them gave 13-membered macrocyclic PAs, which constitute a relatively uncommon group.

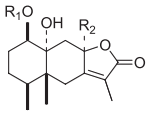
Additionally, the five Mexican *Senecio* species not grouped in the section Mulgediifolii which have been studied chemically (Table 1) exhibited 12-membered macrocyclic PAs with the only exception of *S. paricalia*. This species was not found in any taxonomic report neither as species nor as synonymous of other species.

Table 1. Chemical composition of five Mexican *Senecio* species.

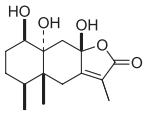
Species	Pyrrolizidine alkaloids	Eremophilane derivatives	Diverse compounds	Ref
S. madrensis	**8**, **39**			20
S. mairetianus	**8**, **12a**	**41**-**44**	**45**-**47a**-**e**	22
S. pericalia		**48a**-**d**, **49a**-**m**, **50a**-**c**	**51a**	23
S. prionopterus	**8**, **52**			20
S. procumbens	**8**, **52**, **53**		**47f**, **51b**, **54a**	24



41a R = H
41b R = OH
41c R = OMe



42a R_1 = Me R_2 = OMe
42b R_1 = Me R_2 = OH
42c R_1 = Me R_2 = H
42d R_1 = H R_2 = H
42e R_1 = H R_2 = OH



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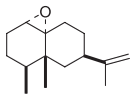

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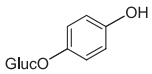

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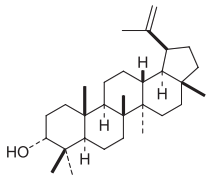

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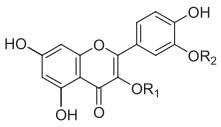
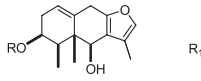
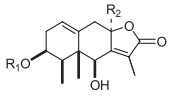


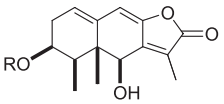
47a R_1 = H R_2 = H
47b R_1 = Gluc R_2 = H
47c R_1 = Gluc^6-OAc R_2 = H
47d R_1 = Gluc R_2 = Me
47e R_1 = Gluc^6-OAc R_2 = Me
47f R_1 = Gal R_2 = Me
47g R_1 = Gluc^3-Rhamn R_2 = H
47h R_1 = Rhamn R_2 = H
47i R_1 = Gal R_2 = H
47j R_1 = Gal^2-OAc R_2 = H



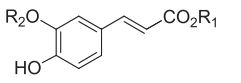
48a **48b** **48c** **48d**
R MeSen Ang Tig Sen



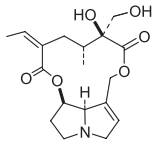
	49a	**49b**	**49c**	**49d**	**49e**
R_1	MeSen	MeSen	MeSen	Tig	Tig
R_2	H	OH	OMe	H	OH
	49f	**49g**	**49h**	**49i**	**49k**
R_1	Tig	Sen	Sen	Sen	Ang
R_2	OMe	H	OH	OMe	OH
	49l	**49m**	**49n**		
R_1	Ang	H	Ang		
R_2	OMe	OMe	H		



50a **50b** **50c**
R Ang Tig Sen



51a R_1 = Me R_2 = H
51b R_1 = H R_2 = Me



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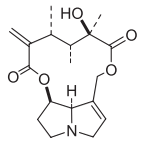

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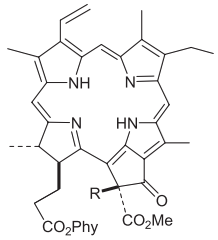
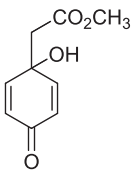


54a R = OH
54b R = H

Genus *Packera*

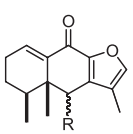
Genus *Packera* was considered as a part of the genus *Senecio* in a group called Aureoid. The *ca.* 60 species of the genus *Packera* [25-26] are distributed from Mexico to arctic regions and the east of Siberia. The genus *Packera* contains both annual and perennial herbs arising from rootstocks or a caudex, the basal leaves are well developed, the roots are fibrous thin and ramified. Fifteen species and three varieties of *Packera* are recognized in Mexico but only seven have been studied chemically (Table 2).

PAs, eremophilanes, and quinols such as jacaranone (**55a**) are the main secondary metabolites isolated from *Packera* species. The quinols are considered responsible of the antitumor properties of the non Mexican species *P. fendleri* [28].

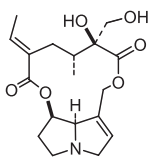


55a
55b 2,3,5,6-tetrahydro

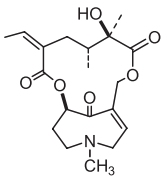
It is important to remark that many species of *Packera* are used as popular medicine, although some contain PAs with hepatotoxic activity. *P. candidissima* [29] is used by the people of the state of Chihuahua to treat several ailments. The bitter infusion is drunk hot or as drinking water in order to treat kidney disorders and ulcers. The plant contains furanoeremophilanes **56a** and **56b**, and the PAs senecionine (**8**), integerrimine (**12a**), retrorsine (**52**), usaramine (**57**), and senkirkine (**58**), which indicates that users of this herb are at high risk of poisoning.



56a R = βOAng
56b R = αOAng
56c R = βOiBut



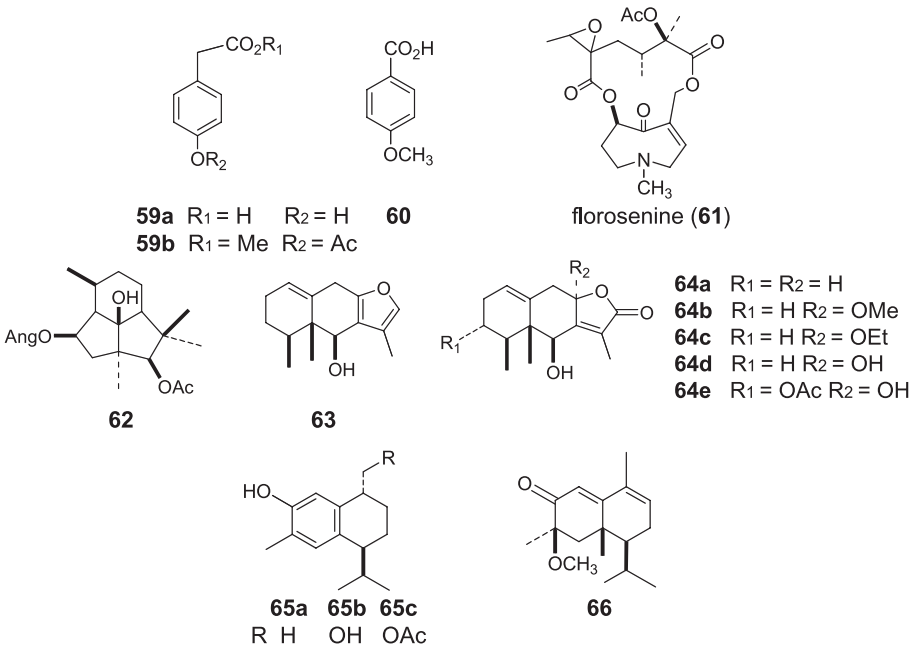
usaramine (**57**)



senkirkine (**58**)

Table 2. Chemical composition of Mexican *Packera* species.

Specie	Pyrrolizidine alkaloids	Eremophilanes and other sesquiterpenes	Quinols	Diverse compounds	Ref
P. bellidifolia			**55a-b**	**59a-b**, **60**	30
P. candidissima	**8**, **12a**, **52**, **57**, **58**	**56a-b**			29
P. coahuilensis	**8**, **52**		**55b**	**59b**	30
P. quebradensis	**58**, **61**				31
P. tampicana		**56c**, **62**	**55a**		23
P. toluccana		**63**, **64a-e**			32, 33
P. tomentosa		**65a-c**, **66**		**51a**	23

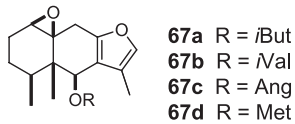


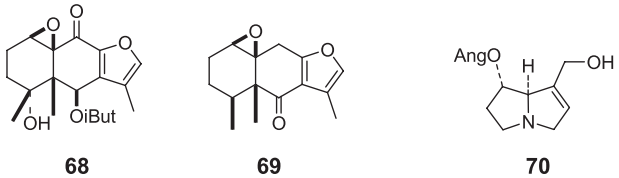
P. toluccana [25] worked as *Senecio toluccanus* [32, 33] did not show the presence of quinols or PAs, instead it contained furanoeremophilane 6β-hydroxyeuryopsin (**63**) and eremophilanolides **64a-e**.

Genus *Barkleyanthus*

Barkleyanthus (Tussilagininae) is a monotypic shrubby genus therefore is constituted of only *Barkleyanthus salicifolius*. It forms with the genera *Pittocaulon*, *Psacalium*, and *Robinsonecio* a well justified monophyletic group [26]. *B. salicifolius*, popularly known as jarilla, is a shrub very attractive when covered with yellow flowers at the end of the dry season. The infusion of this herb is used for rheumatism.

The first chemical study of *B. salicifolius* [34] worked as *Senecio salignus* afforded quercetin (**47a**). Bohlmann and Zdero [35] isolated in 1976 from the aerial parts of *Senecio salignus* epoxides **67a** and **68**. The roots gave mainly the 6-ketofuranoeremophilane **69** and in the polar fractions the mixtures **67b**/**67c** and **67c**/**68**. In a second study, the same authors [31] found the pyrrolizidine alkaloid 7-angelylheliotridine (**70**).





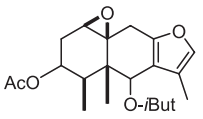
Genus *Pittocaulon*

The genus *Pittocaulon* (Tussilagininae) is made of only five species, *P. bombycophole*, *P. filare*, *P. hintonii*, *P. praecox*, and *velatum* which were segregated from the large genus

Senecio, [36]. The *Pittocaulon* popularly known as palo loco are shrubs or small trees growing in somewhat dry rocky places in Central Mexico. They live at altitude of 300 m in dry forests to 3000 m in temperate lands. Probably because the flowers of *Pittocaulon* appear at the end of the dry season they are called palo loco (crazy plant).

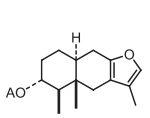
P. praecox is the more widely distributed, it can be found from Distrito Federal to regions as far north as Aguascalientes State. *P. velatum* has after *P. praecox* the widest range; it grows in Central and Western Mexico. *P. filare* is restricted to the State of Colima, it is smaller that *P. praecox* and its leaves are covered with wooly hair, it has beautiful yellow flowers and its seeds are maintained for a long time in the plant. *P. bombycophole* grows in the States of Michoacán, Guerrero, and Morelos. It has thick trunk and branches, its leaves like those of *P. filare* are covered with white wooly hair. *P. hintonii* is restricted to a few localities of States Michoacán and Colima, the species is scarcely ramified and live in small groups where pockets in the rock are filled with soil.

P. praecox is the only species of this genus chemically examined. In 1975 [37] the furanoeremophilane pracoxilin A (**71**) was isolated.

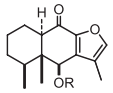


71

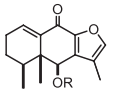
The following year Bohlmann and Zdero [35] isolated from the stem furanoeremophilane **72** and two complex mixtures of other furanoeremophilanes, **73a-c** and **74a-c**. In addition, the roots afforded **73d** and the mixtures: **73a-c**, **74a-c**, **67a-d**, and **75a-f**.



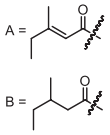
72

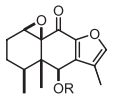


73a R = *i*Val
73b R = A
73c R = B
73d R = Sen



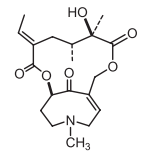
74a R = *i*Val
74b R = A
74c R = B



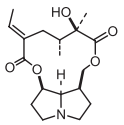


75a R = *i*Val
75b R = *i*But
75c R = Ang
75d R = Met
75e R = A
75f R = B

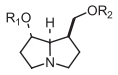
In 2007, Céspedes *et al.* reported the GC-MS analysis of *P. praecox* [38]. This analysis permitted to establish the presence of the PAs senecionine (**8**), integerrimine (**12a**), platyphylline (**39**), senkirkine (**58**), neosenkirkine (**76**), neoplatyphylline (**77**), 9-angeloyldihydroxyheliotridane (**78a**), and 7-angeloyldihydroxyheliotridane (**78b**) in the plant. These alkaloids are sequestered by the scale insect *Ceroplastes albolineatus* which infests the plant. A GC-MS analysis revealed the presence of the **58**, **76**, **78a**, and **78b** PAs found in *C.albolineatus*.



neosenkirkine (**76**)



neoplatyphylline (**77**)

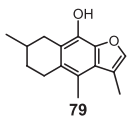


9-angeloyldihydroxyheliotridane (**78a**) R_1 = H R_2 = Ang
7-angeloyldihydroxyheliotridane (**78b**) R_1= Ang R_2 = H

Genus *Psacalium*

Genus *Psacalium* (Tussilagininae) is constituted by 40 species of scapiform perennial herbs distributed from southwest USA to Guatemala [3], most of them endemic to Mexico. Some *Psacalium* species from Western Sierra Madre are used by Tarahumaras and other Mexicans in the Matarique complex as a popular remedy for diabetes and for kidney ailments [39, 40]. The complex includes *Acourtia thurberi* and four species of *Pscalium*: *P. decompositum*, *P. palmeri*, *P. peltatum*, and *P. sinuatum.* In San Luis Potosí, *P. radulifolium* is used as a substitute for *P. decompositum* which is considered the most effective.

Even though the matarique complex is used by most Mexicans, the concept of sickness and cure is very especial for tarahumaras who consider that the sickness is due to natural or supernatural reasons. The illness is due to the lost of soul for his own fault or for the action of evil forces. The chaman makes a curative ceremony in search of the lost soul [40]. The reputation of this herbs specially *P. decompositum* induced J. Romo Armería in 1964, to initiate its chemical study [41]. The analysis of the roots of *P. decompositum* led to the isolation of the sesquiterpenes cacalol and cacalone whose structures were proposed as **79** and **80**, respectively. Later, these structures were revised to **81** [42] and **82** [43].



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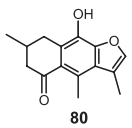

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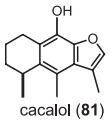
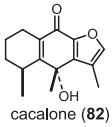
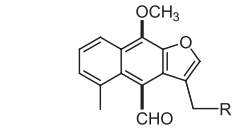


cacalol (**81**)

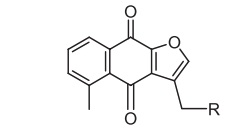


cacalone (**82**)

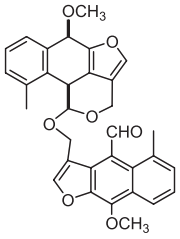
In a second study, Correa and Romo [44] isolated, from the same plant, four cacalol derivatives called maturin (**83a**), maturinin (**83b**), maturinone (**84a**), and maturone (**84b**). In the same study, the acetal **85** which is probably an artifact formed by the reaction between two molecules of maturin (**83a**) was isolated. The isolation of the furanoeremophilane decompostin (**86**) [45] indicates a biogenetic relationship between the eremophilanes and the cacalol derivatives which are common in *Psacalium*.



maturin (**83a**) R = OH
maturinin (**83b**) R = H
maturin acetate (**83c**) R = OAc



maturinone (**84a**) R = H
maturone (**84b**) R = OH
maturone acetate (**84c**) R = OAc



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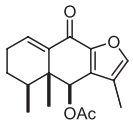
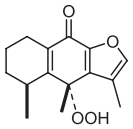


86

After several modifications, the structures were well established by Kakisawa, Inouye, and Romo [42]. They made correlations with furanoeremophilane derivatives and also made the total synthesis. Moreover, the absolute stereochemistry was established by Tarabe *et al.* [46].

In 1977, Jiménez-Estrada *et al.* [47] found in roots of *P. decompositum* the hydroperoxide **87** and a mixture of cacalone (**82**) and its epimer **88**, and in 2000, they obtained from the same species [48], the quinone 13-dehydromaturone **89** which was called romo A.



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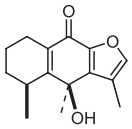

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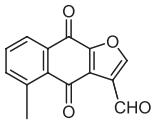
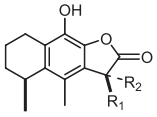


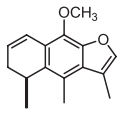
romo A (**89**)

On the other hand, Inman *et al*. [49] reported in 1999, the antihyperglycemic activity of an aqueous extract of roots of *P. decompositum*. They isolated **81**, **82**, **88**, and a mixture 1:1 of 3-hydroxycacalolide (**90a**) and *epi*-3-hydroxycacalolide (**90b**) and described that **81** and the mixture **90a**/**90b** resulted active in diabetic mice. They also reported the presence of PAs which were only detected by TLC. More recently, Alarcon-Aguilar *et al*. [50] tested the hypoglycemic activity of the aqueous extract of *P. decompositum* and that of its main metabolites **81**, **82**, and **83a**. The extract resulted active and the main metabolites inactive. The precipitate obtained from the dried water extract after treatment with methanol caused a significant decrease in fasting glycemia. In 2006, Jiménez-Estrada *et al*. [51] described the anti-inflammatory activity of **81** and **82**.



90a R_1 = Me R_2 = OH
90b R_1 = OH R_2 = Me

P. radulifolium is one of the species of the matarique complex, which is used for treatment of diabetes. A chemical study of the less polar constituent of roots from this species [52] afforded cacalol (**81**), cacalone (**82**), *epi*-cacalone (**88**), decompostin (**86**), O-methyl-1,2-dehydrocacalol (**91**), neoadenostylone (**92**), adenostin A (**93**), radulifolin A (**94a**), *epi*-radulifolin A (**94b**), radulifolin B (**95**), and radulifolin C (**96a**). Additionally, it was established the antimicrobial activity of cacalol.



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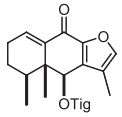

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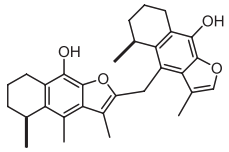

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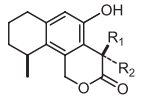
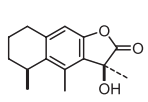


94a R_1 = Me R_2 = OH
94b R_1 = OH R_2 = Me



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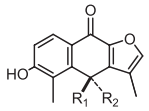
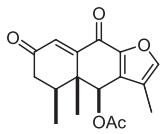


96a R_1 = Me R_2 = OH
96b R_1 = OH R_2 = Me

In a second work of *P. radulifolium* [53], the more polar extracts of roots were purified and yielded the modified eremophilanes: **81**, **82**, **83c**, **84a**, **85**, **86**, **88**, **90a-b**, **91**, radulifolins C-F (**96a,b**-**98a**), and *epi*-radulifolin F (**98b**). The extracts of this plant and some of its metabolites were evaluated as hypoglucemic and antihyperglycemic agents, but only the methanol extract displayed hypoglycemic activity. The anti-oxidant activity of the cacalol (**81**) was also reported.



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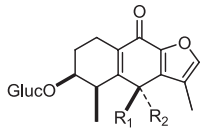
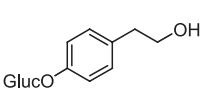
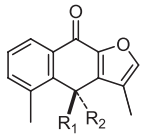


98a R_1 = Me R_2 = OH
98b R_1 = OH R_2 = Me

Analysis of *P. beamanii* [54] afforded the phenylethanoid icariside D_2 (**99**) and the modified eremophilanes: maturin (**83a**), maturin acetate (**83c**), maturinone (**84a**), maturone (**84b**), maturone acetate (**84c**), decompostin (**86**), cacalonol (**100a**/**100b**), and peroxycacalonol (**100c**/**100d**).

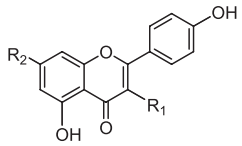


99



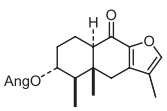
100a R_1 = Me R_2 = OH
100b R_1 = OH R_2 = Me
100c R_1 = Me R_2 = OOH
100d R_1 = OOH R_2 = Me

The aerial parts of *P. megaphyllum* [55] afforded kaempferol-3-O-α-L-(3-O-acetyl)rhamnopyranoside-7-O-α-L-rhamnopyranoside (**101a**). No sesquiterpenes were found.

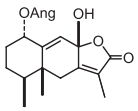


101a R_1 = Rhamn^3-OAc R_2 = Rhamn
101b R_1 = Gluc R_2 = H
101c R_1 = Gal R_2 = H

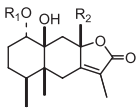
A chemical study of *P. paucicapitatum* [56], commonly known in Oaxaca state as hierba del venado and used as anti-inflammatory, revealed the presence of the furanoeremophilanone **102** and of four eremophilanolides **103-104a-c**; thus, differing from the chemical composition of other *Psacalium* species whose characteristic metabolites are the modified eremophilanes, also known as cacalol derivatives.



102



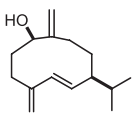
103



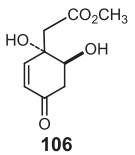
104a R_1 = Ang R_2 = H
104b R_1 = Ang R_2 = OH
104c R_1 = H R_2 = H

Genus *Pseudogynoxys*

Pseudogynoxys is constituted by 13 species distributed from Mexico to Guatemala [57]. The genus contains shrubby plants with orange flowers that become reddish with age; in some species the flowers are fragrant. *P. chenopodioides* is one of the four species that grow in Mexico (*P. fragans*, *P. chenopodiodes*, *P. cummingii*, and *P. haenkei*) which has been cultivated. Therefore its distribution might be partially the result of human intervention. A collection from the State of Nuevo Leon worked as *Senecio confusus* [23] resulted in the isolation of the germacrene D derivative (**105**) and the quinols **55a-b** and **106**.



105

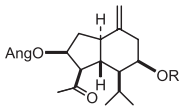


106

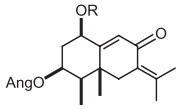
Genus *Robinsonecio*

Robinsonecio (subtribe Tussilagininae) is a genus of perennial herbs segregated from *Senecio* and established in 1996 by Barkey and Janovec [58]. The two new combinations proposed were *Robinsonecio gerberifolius* and *Robinsonecio porphyrestes*.

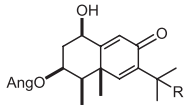
The chemical examination of leaves, roots, and rhizome of *R. gerberifolius* [59] collected near the alpine refuge of Pico de Orizaba at 4150 m, in October 2000, resulted in the isolation of two oplopanes (**107a-b**) and five eremophilane derivatives (**108-110**).



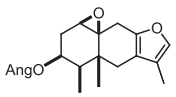
107a R = Epang
107b R = Ac



108a R = H
108b R = Ang

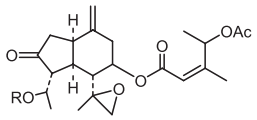


109a R = OH
109b R = OOH

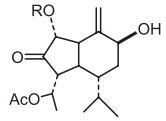


110

The presence of oplopanes in the genus *Robinsonecio* may have chemosystematic significance. Nevertheless, it is important to mention that this kind of compounds have been isolated from *Roldana mexicana* (Table 3) [60-62] and from several species of *Senecio* such as *S. ovirensis* (**111a-b**) [63] and *S. kleinia* (**112a-b**) [64].

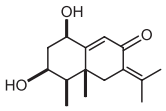


111a R = MeBut
111b R = Ang

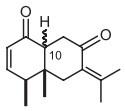


112a R = *i*Val
112b R = MeSen

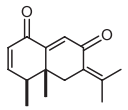
In a second work on *R. gerberifolius* [65], saponification of compounds **108a-b** yielded the expected diol **113** and the pair of epimers **114a-b**, in which a rearrangement and an elimination have occurred. The diketo compound **115** was formed by auto-oxidation of **108a** followed by β-elimination of the C-3 ester.



113

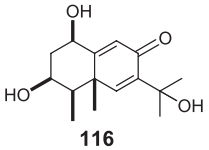


114a H-10 β
114b H-10 α

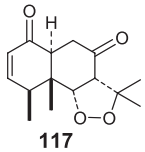


115

Basic hydrolysis of the hydroperoxide **109b** gave compounds **109a**, **116** and **117**. The last substance was produced by a rearrangement in which the OH group at C-1 was oxidized to a keto group with an elimination of the ester at C-3. In addition, the double bond at C-9 was reduced and the peroxide added to the C-6 double bond.



116



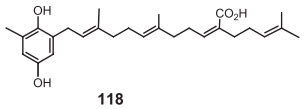
117

Genus *Roldana*

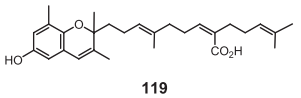
Roldana (subtribe Tussilagininae) is constituted of 48 species distributed from southeastern Arizona and southern New Mexico to Panama. These plants vary from low herbs of no more than 1 m tall to shrubs or trees that may reach 12 m tall and grow mostly in temperate forests at altitudes from 1000 to 4000 m. The genus has two centers of diversity in Mexico, one along the Volcanic Belt and Sierra Madre del Sur and the second along Sierra Madre de Chiapas [66]. The Mexican Tussilaginoid genera associated to *Roldana* are *Barkleyanthus*, *Pittocaulon*, *Psacalium*, and *Villasenoria*.

The chemical studies of *Roldana* have been carried out preferentially on the roots and the secondary metabolites more frequently found have been sesquiterpenes with variable structures, specially furanoeremophilanes and modified eremophilanes. The metabolites isolated from the aerial parts present diverse structures and some of them with important biological activities.

One of the more studied species is *R. barba-johannis* [67-69]. In 2003, several compounds from its aerial parts were reported, among them 3 plastoquinone derivatives (**118**-**120**) [68] with anti-inflammatory and antioxidant activities. These compounds were also tested as insect growth inhibitors [69]. They showed selective effects on the pre-emergence metabolism of the Fall armyworm (*Spodoptera fungiperda* J. F. Smith) which is an important pest of corn.



118



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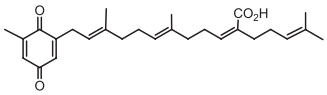
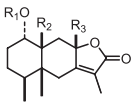


120

Other example is *Roldana sessilifolia* which belongs to the Cachana complex of medicinal plants [70]. This complex is used to treat some female ailments. The roots of *Roldana sessilifolia* [70-72] afforded the eremophilanolides **103**, **104a-c**, and **121a-c**.

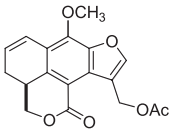


121a R1 = Ang R2 = H R3 = H
121b R1 = Ang R2 = H R3 = OH
121c R1 = H R2 = OH R3 = OH

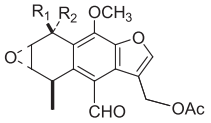
The results obtained from nine Mexican *Roldana* species, mainly of the roots, are shown in table 3.

Table 3. Chemical composition of Mexican *Roldana* species.

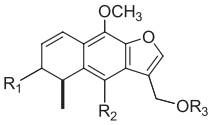
Species [Ref]	Eremophilane derivatives	Modified eremophilanes	Oplopanes	Diverse compounds
R. angulifolia				
roots [73]		**83c**,**122-124a-c**		**125**
aerial parts [73]	**126**			**47g**,**54a-b**,**127**
R. aschenborniana				
aerial parts [23,74]	**56a**,**128a-f**,**129**			**101b-c**,**130-135a-b**
R. barba-johannis				
roots[67		**124b-d**		
aerial parts [68,69]	**64b**			**118-120a-b**, **136a-b**
R. ehrenbergiana				
roots [75,76]	**137a-b-139a-b**			
leaves [75]				**47h**,**140**
flowers [76]				**136a-b**
R. heterogama				
roots [77]		**81**,**83b**,**91**,**124b**, **141a-b**		
R. lineolata				
roots [78,79]	**48b**,**48d**,**49k**,**49n**			
aerial parts [78]				**47i-j**,**136a-b**
R. mexicana				
roots [60,61]			**142-146**	
leaves [629]			**142a-b**,**144**,**147**	
R. sessilifolia				
roots [70-72]	**103**,**104a-c**,**121a-c**			**47h**
R. sundbergii				
aerial parts [23]				**51a**,**130**,**131**,**148**



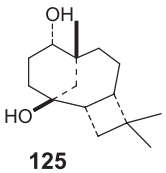
122



123a R_1 = H R_2 = OH
123b R_1 = OH R_2 = H



124a R_1 = OH R_2 = CHO R_3 = Ac
124b R_1 = H R_2 = CHO R_3 = Ac
124c R_1 = H R_2 = CHO R_3 = H
124d R_1 = H R_2 = Me R_3 = Ac



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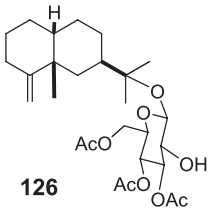

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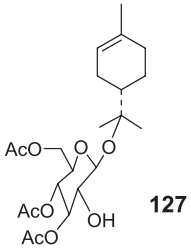

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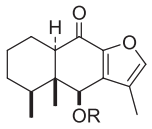
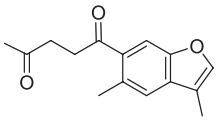
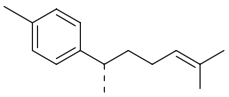


128a **128b** **128c** **128d** **128e** **128f**
R A MeBut Ang C MeBut *i*Val
Δ1,10 Δ1,10 Δ1,10

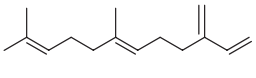
C =



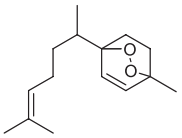
129



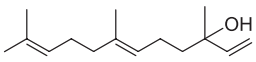
130



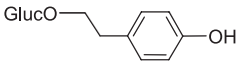
131



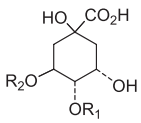
132



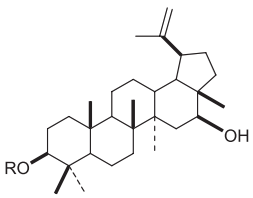
133



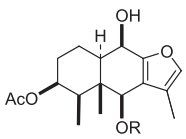
134



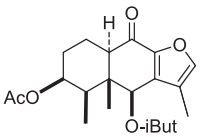
135a R_1 = R_2 = caffeoyl
135b R_1 = H R_2 = caffeoyl



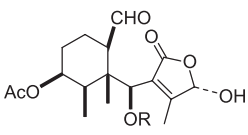
136a R = $CH_3(CH_2)_{12}CO$
136b R = $(CH_3)_2CH(CH_2)_{12}CO$



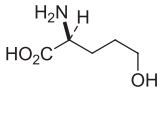
137a R = Ang
137b R = *i*But



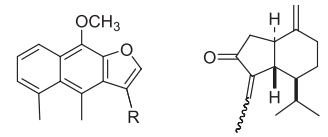
138



139a R= *i*But
139b R= Ang

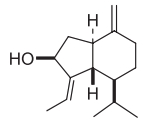


140

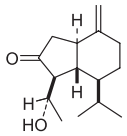


141a R = CH_2OAc
141b R = CHO

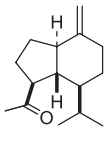
142a *Z*
142b *E*



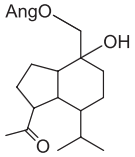
143



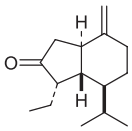
144



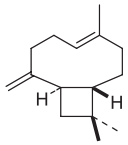
145



146



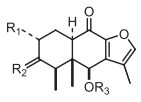
147



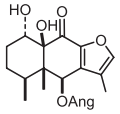
148

Genus *Telanthophora*

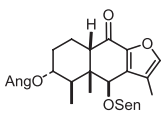
Telanthophora (Tussilagininae) includes 14 species of shrubs or trees distributed from northern Mexico to Panama [3]. Until the present time the only two species chemically analyzed are *T. grandifolia* [31], formerly *Senecio grandifolius*, and *T. andrieuxii* [80]. The chemical study of *T. grandifolia*, which is the most widespread of the genus, afforded the PAs senkirkine (**64**) and neosenkirkine (**82**) and the 9-ketofuranoeremophilanes **149a-h**. The species *T. andrieuxii* was worked as *Senecio andreuxii* and yielded compounds **150**-**152**. Considering the species of *Telanthophora* studied so far, the 9-ketofuranoeremofilane derivatives can be considered as the characteristic metabolites of the genus.



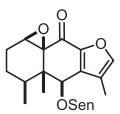
149a	R_1= H	R_2 = O	R_3 = Ang
149b	R_1= H	R_2 = β-OAc, H	R_3 = Ang
149c	R_1= H	R_2 = β-OAc, H	R_3 = α-MeSen
149d	R_1= OAc	R_2 = H, H,	R_3 = α-MeSen
149e	R_1= OH	R_2 = H, H	R_3 = α-MeSen
149f	R_1= H	R_2 = β-OH, H	R_3 = Ang
149g	R_1= H	R_2 = β-OH, H	R_3 = Sen
149h	R_1= H	R_2 = β-OH, H	R3 = α-MeSen



150



151



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