Clerodane diterpenes: sources, structures, and biological activities†

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Abstract

The clerodane diterpenoids are a widespread class of secondary metabolites and have been found in several hundreds of plant species from various families and in organisms from other taxonomic groups. These substances have attracted interest in recent years due to their notable biological activities, particularly insect antifeedant properties. In addition, the major active clerodanes of Salvia divinorum can be used as novel opioid receptor probes, allowing greater insight into opioid receptor-mediated phenomena, as well as opening additional areas for chemical investigation. This article provides extensive coverage of naturally occurring clerodane diterpenes discovered from 1990 until 2015, and follows up on the 1992 review by Merritt and Ley in this same journal. The distribution, chemotaxonomic significance, chemical structures, and biological activities of clerodane diterpenes are summarized. In the cases where sufficient information is available, structure activity relationship (SAR) correlations and mode of action of active clerodanes have been presented.

1. Background and introduction

1.1. The sources of clerodane diterpenes

Clerodane diterpenes are a large group of naturally occurring secondary metabolites found in several hundreds of plant species from various families and in organisms from other taxonomic groups, such as fungi, bacteria, and marine sponges. Table 1 illustrates the occurrence of clerodane diterpenes in the plant kingdom and marine animals.

Clerodane diterpenes have attracted interest in recent years as a result of their noteworthy biological activities, particularly as agents modifying the feeding behavior of many economically important insect phytophagous pests. Various genera from the plant family Salvia have been shown to accumulate relatively high levels of clerodane diterpenes, including Salvia divinorum and Salvia horminum.

†Electronic supplementary information (ESI) available: Tables 2–32: compound structures arranged by chemical classifications of clerodane diterpenes arranged by source. See DOI: 10.1039/c5np00137d
Lamiaceae have been identified as rich sources of antifeedant clerodanes, with species of the genus *Scutellaria* producing some of the most potent clerodane antifeedants known so far. In addition, the major active clerodanes of *Salvia divinorum* can serve as opioid receptor probes, enabling better understanding of opioid receptor-mediated phenomena, as well as providing additional areas for chemical investigation.

### 1.2. The basic structures of clerodane diterpenes

Clerodane diterpenes are bicyclic diterpenoids. The basic skeleton is divided into two fragments: a fused ring decalin moiety (C-1–C-10) and a six-carbon side chain at C-9 (C-11–C-16, with C-16 attached at C-13, *i.e.*, 3-methylpentyl). The remaining four carbons (C-17–C-20) are attached at C-8, C-4, C-5, and C-9, respectively, on the decalin system as illustrated below.

Approximately 25% of clerodanes have a 5 : 10 *cis* ring fusion as represented by columbin (1). This diterpenoid furanolactone has been isolated from several plants, including *Sphenocentrum jollyanum* Pierre (Menispermaceae) and *Jateorhiza calumba* Miers (Menispermaceae). It is sold in a crude drug preparation called calumbae radix or tinosporae radix. Columbin exhibited dose dependent anti-inflammatory activity as well as chemopreventative activity against colorectal cancer.1–3 The remaining 75% of clerodanes have a 5 : 10 *trans* ring fusion as exemplified by clerodin (2). This compound was originally isolated from *Clerodendrum infortunatum* L. (Lamiaceae) and has potential as a natural pesticide due to its insect antifeedant activity.4 Clerodanes with a 5 : 10 *trans* ring junction are characteristic of the Lamiaceae family and to a lesser extent the Compositae (Asteraceae) family, while clerodanes with a 5 : 10 *cis* ring junction are more commonly found in the Euphorbiaceae, Flacouriaceae (Salicaceae), and Menispermaceae families.

In addition to the relative configuration of the *trans* or *cis* junction of the fused rings, clerodanes are further classified by their relative configurations at C-8 and C-9.

Consequently, as shown in Fig. 1, four types of clerodane skeletons are defined with respect to the configuration at the ring fusion and of the substituents at C-8 and C-9: *trans*–*cis* (TC), *trans*–*trans* (TT), *cis*–*cis* (CC), and *cis*–*trans* (CT).5 In the majority of clerodanes, the C-17 and C-20 substituents on C-8 and C-9 are *cis*.5

In their 1992 review, Merritt and Ley noted that confusion exists in the literature over the absolute stereochemistry of the clerodanes.6 The absolute stereochemistry of clerodin (2), the first member of the clerodane series, was revised leading to the following terminology. *neo*-Clerodanes (formerly *ent*-clerodanes) have the same absolute stereochemistry as clerodin, while *entneo*-clerodanes are enantiomeric to clerodin.6,7 The former compounds
predominate in number over the latter compounds.\textsuperscript{5} We have used \textit{neo}-clerodane in this paper, except for compound names already given with the \textit{ent}-clerodane terminology.

Biosynthetically, the clerodanes likely arise from geranylgeranylpyrophosphate (3) as shown in Scheme 1. However, this overall biogenetic route is simplified as many parallel pathways are needed to yield the multiplicity of clerodane natural products.\textsuperscript{8} Initially, plant cyclases catalyze a proton-initiated cationic cycloisomerization of 3 to generate a labdane-type precursor skeleton, such as 4 [one of four possible structures (‘normal’, ‘\textit{ent}’, ‘\textit{syn}-normal’, ‘\textit{syn-ent}’), depending on the conformation of 3].\textsuperscript{5b}

\begin{center}
\begin{tikzpicture}
\begin{scope}[xscale=0.7,yscale=0.7]
\node at (0,0) {\textbf{\textit{neo}-clerodane} = \textbf{\textit{ent}-clerodane}};
\node at (2.5,0) {\textbf{\textit{ant-\textit{neo}-clerodane}}};
\end{scope}
\end{tikzpicture}
\end{center}

Subsequently, this intermediate can undergo either a concerted or stepwise migration process of methyl and hydride shifts. A concerted process, with a C-4\textalpha{} to C-5\textalpha{} methyl group migration,\textsuperscript{9} gives clerodane-type intermediate 5 and results in only $\textit{trans}$ clerodanes. A stepwise process ‘pauses’ at a halimane-type intermediate (6) that retains both gem-dimethyl groups on C-4. Intermediate 6 can then progress to either $\textit{cis}$ or $\textit{trans}$ clerodanes. The general scheme without specific stereochemistry is also shown. Examples to support this proposed biosynthetic pathway include the isolation of the partially rearranged labdane compounds chettaphanin (7) from \textit{Adenochlaena siamensis} (Compositae)\textsuperscript{10} and salmantic acid (8) from \textit{Cistus laurifolius} (Cistaceae).\textsuperscript{11}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\textbf{(7)}};
\node at (2.5,0) {\textbf{(8)}};
\end{tikzpicture}
\end{center}

1.3. The biological activities of clerodane diterpenes

The most important biological activities of clerodanes are insect antifeedant effects\textsuperscript{12} and action as novel opioid receptor probes.\textsuperscript{13}

1.3.1. Insect antifeedant activity—Clerodane diterpenes are best-known and most extensively studied for their insect anti-feeding and related insecticidal properties, with an emphasis placed on the safety aspects of such natural insect antifeedants in relation to the lives of mammals and fish. To date, over 400 natural and semi-synthetic clerodanes have
been examined in laboratory assays, yielding several compounds with potent antifeedant activity against various insect species.\textsuperscript{12}

1.3.2. Probes in opioid pharmacology—In 2002, opioid receptors were implicated in the actions of the psychoactive mint \textit{Salvia divinorum}.\textsuperscript{13} The main active constituent isolated from the leaves of \textit{S. divinorum} is the neoclerodane diterpene salvinorin A (9). This molecule is interesting to pharmacologists, because it is a non-serotonergic hallucinogen that lacks a basic nitrogen and is a potent and selective agonist for $\kappa$ opioid receptors. Synthetic organic chemists also find it an attractive target because of its unique structure containing seven chiral centers and a diterpene scaffold.

Opioid agonists based on 9 have the potential to treat pain, cough, diarrhea, stimulant dependence, and mood disorders. Antagonists derived from 9 have potential use in treating several medical conditions, including drug dependence, depression, opioid-induced constipation, and obesity. Thus, analogues of 9 may prove to be excellent research tools and provide greater insight into opioid receptor-mediated phenomena.

![](image)

\textit{salvinorin A (9)}

1.3.3. Other bioactivities—Besides insect antifeedant activity and opioid receptor agonist effects, clerodane diterpenes can exhibit other pharmacological activities, including antitumor,\textsuperscript{14} antifungal, NGF-potentiating, antibiotic, anti-peptic ulcer, antiplasmodial, as well as hypoglycemic, hypolipidemic, and anti-thrombin inhibitory activity.

This review provides extensive coverage of naturally occurring clerodane diterpenes discovered in the last 25 years (1990–2015) along with their various bioactivities. The distribution, chemotaxonomic significance, chemical structures, and biological activities of clerodane diterpenes are summarized. In the cases where sufficient information is available, the structure activity relationship (SAR) correlations and mode of action of active clerodanes have been presented.

2. Structure classifications and sources of clerodane diterpenes

During the last 25 years, over 1300 diterpenoids and nor-diterpenoids with the clerodane carbon skeleton have been isolated. For clarity and the purposes of this review, they have been grouped together by particular structural features as described below.

Firstly, the C-11–C-16 fragment can be acyclic or occur as several different bi- and monocyclic substructures (Fig. 2). Substructures a–c contain a bicyclic furofuran system, either tetrahydro (a) or hexahydro (b and c). Moreover, the two latter systems can have oxygen
moieties present on C-13 and C-14 (b) or C-15 (c), forming a hemiacetal or acetal. Furthermore, when OR is methoxy or ethoxy in substructure c, the compound could be an artifact resulting from the use of methanol or ethanol using the isolation procedure. Substructure d possesses one furan ring (C-11–C-13, C-16) and a two-carbon open chain system (C-14–C-15), formally arising from the opening of the acetal moiety and subsequent reduction of the C-15 aldehyde to a primary alcohol. Alternatively, carbons C-11 and C-12 are present as a two-carbon ethyl chain, while carbons C-13–C-16 form an attached single ring, either an α,β-unsaturated-γ-lactone (e) or lactol (f). Sometimes, Δ11,12 unsaturation is present or carbons C-11 and C-12 can bear oxygenated groups. Finally, bicyclic spiro substructures can be found. The tetrahydropyran incorporates C-8 and C-9, as well as C-11–C-13, and the γ-lactone (C-13–C-16) can assume both possible configurations (g, h) at C-13.

Secondly, the decalin moiety contains some consistent functional features. The decalin junction is mostly trans, and the two groups (C-17 and C-20) on positions C-8 and C-9, respectively, are primarily cis, as well as α-oriented (type TC neo-clerodanes in Section 1.2). Six classifications (A–F) have been made based on the formal oxidation number of carbon C-18 in the decalin moiety (Fig. 3). Groups A and B contain a C-4α/C-18 epoxide, while C-18 is present as a hydroxymethyl in group C. Furthermore, in groups A and B, carbon C-19 is often hydroxylated, either esterified (A) or forming a hemiacetal or acetal bridge with the α-hydroxy group on carbon C-2 (B). In a few cases, carbon C-19 is a methyl or a carboxylic group. In substructure D, C-4 and C-18 form an exocyclic double bond. In this case, carbon C-19 is always a methyl. When C-18 is a methyl, C-19 is also always a methyl. Finally, carbon C-18 can have a higher oxidation number as in an aldehyde (E) or acetal (F). Again, in this case, carbon C-19 is always a methyl.

Finally, all of the natural neo-clerodanes have been classified into seven different types (I–VII, Fig. 4) on the basis of their two fragments, the C-11–C-16 moiety (a–h) and the decalin moiety (A–F). Unless otherwise indicated, the diterpenes possess the neo-clerodane absolute stereochemistry.

2.1. Type I with an acyclic side chain at C-9

Type I clerodane diterpenoids are characterized firstly by having an acyclic side chain at C-9, and then are further divided into three subtypes related to the decalin system. The first subtype has an O-containing five-membered cyclic ring attached to the decalin ring A (18,19-oxide), the second subtype has a double bond between C-3 and C-4 or at another (or no) position of either decalin ring (without an 18,19-oxide), and the third subtype has an epoxy ring in the decalin system.

2.1.1. Type I subtype I with an O-containing five-membered ring at C-18 and C-19—In this subtype, most of the representative compounds are based on two derivations of the 18,19-oxide clerodane nucleus – zuelanin (double bonds at C-12/C-13 and C-14/C-15) and isozauelanin (double bonds at C-13/C-16 and C-14/C-15) (Fig. 5). Various substituents are found at C-2, C-6, C-7, C-18 and C-19, as well as sometimes at C-12, in the isozauelanin
subtype, and the decalin system can be saturated. Compounds with other skeletons also exist.

### 2.1.1.1. Type I subtype Ia with the isozuelanin skeleton\(^\text{15–33}\) (Table 2 – compounds 10–86 found in ESI†): The new clerodanes from type I subtype Ia are all 5 : 10 cis and 17 : 20 trans, mostly isolated from genera *Casearia* and *Zuelania* in the family Salicaceae. The structures of zuelaguidins A–D (17–20) from *Z. guidonia* are typical of this subtype.\(^\text{16}\) Corymbulosins A–C (25–27) from *Laetia corymbulosa* were elucidated as clerodane diterpenes unsaturated at C-3, C-13(16), and C-14.\(^\text{18}\) Corymbulosin A (25) has a decadienoate ester at C-2, while corymbulosins B and C (26–27) have a saturated decanoate ester at C-6. The latter two compounds are identical except for the configuration at C-2. As based on coupling constant and NOE data, H-2 is equatorial in the former and axial in the latter. However, the study was unable to assign the absolute or relative stereochemistry of the three compounds. Corymbulosin A was the most cytotoxic with IC\(_{50}\) values of 0.6 μM against SF539 human CNS tumor cells and 8 μM against the LOX melanoma cell line in two-day cytotoxicity tests.\(^\text{18}\)

Two other compounds in this structural subtype, intrapetacins A (35) and B (36) from *Licania intrapetiolaris*, with a p-hydroxybenzoate group at C-2, displayed moderate cytotoxicity against KB cells, with IC\(_{50}\) values of 2.0 and 0.8 μg mL\(^{-1}\).\(^\text{20}\) Caseanigrescens A–D (37–40) from *C. nigrescens* showed moderate cytotoxicity against the A2780 human ovarian cancer cell line, with an IC\(_{50}\) range of 0.83–1.4 μM.\(^\text{21}\) Unlike most compounds in this subtype, compounds 37–39 are substituted at C-7 (37, acetoxy; 38–39, hydroxy). When 37–40 were stored in CDCl\(_3\) for varying times during NMR analysis, their hemiacetal resonances disappeared and aldehyde resonances appeared. This result indicated that all four compounds slowly hydrolyzed to corresponding unstable dialdehydes. The hydrolysis was likely caused by traces of acid in the specific CDCl\(_3\) used, and did not occur when the compounds were allowed to stand in a fresh sample of CDCl\(_3\).\(^\text{21}\) Argutins F–H (41–43) with a unique hydroperoxide moiety at C-12 were isolated from *C. arguta*.\(^\text{22}\)

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\(^\text{†}\)Electronic supplementary information (ESI) available: Tables 2–32: compound structures arranged by chemical classifications structures of clerodane diterpenes arranged by source. See DOI: 10.1039/c5np00137d

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It should be noted that the clerodane absolute stereochemistry was not determined in every structural characterization study. For example, esculentin A (76) has been reported in both ent–neo\(^1\,^6\) and neo\(^3\,^2\) configurations. In addition, while caseargrewiin A (74) was shown as a neo-clerodane, caseargrewiins B–D (1256–1258, structures in Section 3.5) co-isolated from C. grewiifolia were shown as ent-neo-clerodanes. The absolute configuration of C-2 in 1258 established as \(R\) by a modified Mosher’s method, and the absolute stereochemistry in the rest of the molecule based on NMR coupling constants and NOESY correlations.\(^3\,^1\) Generally, this review has focused on relative configurations only.

Caseabalansin A and 18-epicaseabalansin A (85–86) are the first examples of clerodane diterpenoids with an oxygen bridge between C-2 and C-19.\(^3\,^3\) They were initially isolated as an inseparable 1.3 : 1 isomeric mixture from C. balansae and identified based on NMR spectroscopy. Conversion to the 18-acetates allowed separation of the two compounds by HPLC.

2.1.1.2. Type I subtype Ib with the zuelanin skeleton\(^1\,^4\,^2\,^2\,^3\,^4\,^2\,^5\,^2\,^8\,^2\,^9\,^3\,^4\,^0\) (Table 3 – compounds 87–135 found in ESI\(^\dagger\)): The newly reported type I subtype Ib compounds are also 5 : 10 cis and 17 : 20 trans, mostly isolated from the family Salicaceae. They are structurally similar to type I subtype Ia compounds, but with a different double bond pattern.
in the C-11–C-16 acyclic side chain. Casearvestrins A–C (87–89) from *Casearia sylvestris* show the typical zuelanin skeleton, with acetoxy groups at both C-18 and C-19, in addition to a 18,19-oxide. In these three compounds, C-2 and C-6 are also substituted with various four to six carbon esters and a hydroxy group, respectively. Compounds 87–89 displayed promising bioactivity in cytotoxicity assays against a panel of tumor cell lines and antifungal assays against *Aspergillus niger* in a disk diffusion assay. Argutins A–E (90–94) from *C. arguta* contain the same cyclic ether with varying combinations of decadienoyloxy, hydroxy, and hydrogen at C-2, C-6, and C-7. Among them, argutin B (91) showed the highest degree of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) sensitization. Furthermore, the synergistic effect of 91 and TRAIL together was three-fold greater than that of 91 alone. Like the type I subtype Ia compounds 35–36 mentioned above, type Ib case-arborins A–E (96–100) from *C. arborea* contain structurally novel aromatic esters, either at C-2 or C-6. When evaluated against LOX and SF539 cell lines using a two-day cytotoxicity assay, compounds 96–100 exhibited IC$_{50}$ values ranging from 0.29 to 9.7 μM. 

Caseobliquins A (127) and B (128) from *C. obliqua* have different substituents at C-6, a p-hydroxybenzoate moiety in 127 and a cinnamoate moiety in 128. Meanwhile, the acetoxy groups on C-18 and C-19 are trans, rather than cis as in the above-mentioned compounds.

**2.1.1.3. Type I subtype Ic with other skeletons**

Type I subtype Ic includes compounds with acyclic side chains different from 3-methylenepent-4-ene or (E)-3-methylpenta-2,4-diene, which are found in subtypes Ia and Ib, respectively. Most of the type I subtype Ic compounds contain a 18,19-lactone ring. Compounds 136–138 from the aerial parts of *Olearia teretijdia* contain a $\Delta^{13E}$ double bond, while this position is saturated in 139–149. The terminal carbon in the side chain is
generally hydroxymethyl, malonyloxymethyl, or carboxy rather than methyl. Compound 149 also has a Δ² rather than Δ³ double bond.  

*Baccharis linearis* was the source of three new clerodanes: baclinal (150) with a 3-formyl-3E-pentenyl side chain and epimeric baclinepoxides (151–152) with an interesting 13,16-spiro-oxirane in the C-9 side chain. 42 Zuelaguidins E, G, and H (153–155), isolated from *Zuelania guidonia* (family Salicaceae),  

were the first reported diterpenoids containing a 3,6-dihydro-1,2-dioxin moiety. This endoperoxide may result from a Diels–Alder reaction between zuelaguidin A (17, see Section 2.1.1.1), also found in *Z. guidonia*, and molecular oxygen. 16 Compounds 153–155 are 5 : 10 cis and 17 : 20 trans. The remaining compounds in type I subtype Ic are 5 : 10 trans and 17 : 20 cis, as typical of clerodanes isolated from the family Asteraceae.

2.1.2. Type I subtype II with a double bond between C-3 and C-4 or another position

2.1.2.1. Type I subtype IIa with a double bond between C-3 and C-4 (ref. 14, 15, 18, 26, 41 and 43–88) (Table 5 – compounds 156–253 found in ESI†): Type I subtype IIa compounds contain many of the same acyclic side chains as type I subtype Ia–Ie compounds. For instance, both 3-methylenepent-4-ene (156–158) and 3-methylpenta-2,4-diene (164–167) side chains are found in type I subtype IIa. Interestingly, compounds 164–166 with a Δ¹²Z double bond were isolated from both Schistochila acuminata and *Heteroscyphus planus*, 45–47 while heteroscyphol (167) with an assigned Δ¹²E double bond was found only in *Heteroscyphus planus*. 47

Terpenetetriene (159) was produced from a transformant of *Streptomyces lividans* and postulated to be a probable biosynthetic intermediate of terpentecin (160), a diterpenoid
antibiotic previously isolated from the bacterium *Streptomyces griseosporus*. This study was the first to report a bacterial diterpene cyclase. Compound 159 was also isolated together with 161 from *Jungermannia infusca*. These two compounds have the same planar structure but different stereochemical structures. Both are 5:10 trans, but the former compound is 17:20 trans while the latter is 17:20 cis.

Compounds 193 and 194 have a neo-clerodane skeleton with a Δ3,4 C=C bond and a C=O group at C-2. Compounds 197 (2-oxokolavenic acid) and 198, isolated from different plant species, are identical, except for the orientation of the C-20 methyl group, β in the former compound and α in the latter compound. The cis-decalin (5α Me, 10α H) and trans orientation of C-8 and C-9 (17α Me, 20β Me) in 197 were confirmed by X-ray crystallographic analysis. Furthermore, 2-oxokolavenic acid with a trans-decalin (5β Me, 10α H) and cis orientation of C-8 and C-9 (17β Me, 20β Me) was co-isolated at the same time from the fruits of *Detarium microcarpum*, as well as previously from the bark and leaves of the same plant.

Portulene acetal (199) with a caged hemiacetal [6.6]-ring was isolated as a minor constituent from *Portulaca grandiflora*. The structures of 200 and 201 were quite similar, except for a tigloyl group in 200 and an angeloyl group in 201. Seven new clerodanes, exemplified by 207, were obtained from *Baccharis trinervis*. Although no double bond is present between C-13/C-14, the stereochemistry of C-13 in these compounds and their analogue 214 from *B. gaudichaudiana* could not be deduced spectroscopically.
The four new clerodanes (227–230) isolated from *Nuxia sphaerocephala* were assigned to the *ent*-series (now *neo*-series) based on optical rotation values, plus the absolute configuration of C-13 in 227 was established as *S* based on its phenylglycine methyl ester (PGME) amide derivatives. In addition to having a free carboxylic acid rather than ethyl ester at the side chain terminus, compounds 231 and 232 have a formyloxy group and an acetyloxy group, respectively, on C-2 compared with the hydrogen in 233. All three compounds were isolated from *Clausena dumiana*.

Compounds 240–242 were established as hydroxy and peroxy derivatives of the 2-oxo group 239, based on X-ray and CD analysis. Compounds 249–252, isolated as 3 : 1 or 4 : 1 mixtures from *Linaria saxatilis*, are the (12E)- and (12Z)-stereo-isomers of the Δ^3^-endocyclic analogues.

2.1.2.2. Type I subtype IIb with a double bond at another (or no) position (Table 6 – compounds 254–289 found in ESI†): The decalin double bonds in type I subtype IIb compounds can be either endocyclic at C-1/C-2 (e.g., 277), C-2/C-3 (276), or C-7/C-8 (272) or exocyclic at C-4/C-18 (281) or C-8/C-17 (258). Alternatively, some compounds in this subtype do not have a decalin double bond, but instead often have dihydroxy substitution (e.g., 266–267). Like in type I subtype IIa, various acyclic side chains are present.

Leojaponin A (276), characterized by a C4-C7 oxa-bridge and a double bond between C-2 and C-3, is the first clerodane diterpenoid obtained from *Leonurus japonicus*. Palmadorins
A and B (288–289), from the Antarctic nudibranch *Austrodoris kerguelenensis*, were the first two of a new series of clerodane diterpene glycerides.88

2.1.3. Type I subtype III with an epoxy ring46,65,90,99,103–105 (Table 7 – compounds 290–296 found in ESI†)—Among all compounds with an acyclic side chain, seven compounds are classified as type I subtype III with a epoxy ring either at C-3/C-4 (290–294)46,65,90,103,104 or C-4/C-18 (295–296).99,105 The β-orientations of the four methyl groups (C17–C20), as well as H-10, in *291* from *Detarium microcarpum* are shown as reported.65 The assignments were based on NOE correlations, but seem uncommon from a biogenetic viewpoint. Compound 292 from *Heteroscyphus planus* is a possible intermediate in the biosynthesis of diterpenes that have a spiro-γ-lactone group at the C-9 position.46 Compounds 293 from *Jungermannia paroica* and 294 from *Stachys glutinosa* have almost identical structures with a hydroxy group at C-13, but a hydrogen and α-hydroxy group, respectively, at C-2.103,104 The orientation of the epoxy methylene H2-18 in *295* from *Polyalthia longifolia* was deduced to be β, based on comparison of the chemical shifts and coupling constants with those of similar structures in the literature.99 Highly oxygenated compound 296 from *Ajuga decumbens* inhibited lipopolysaccharide (LPS)-induced nitric oxide production in RAW 264.7 macrophages.105

2.2. Type II with a 2-ethylfuran-based side chain at C-9

Type II clerodane diterpenoids are characterized initially by a 2-ethylfuran-based, rather than acyclic, side chain at C-9. When viewed simplistically, an oxygen atom has been inserted between C-15 and C-16 of a 3-methylenepent-4-ene side chain.
Type II compounds then are further split into various subtypes. Subtypes Ia and Ib generally have more complex or multiple O-containing rings at various positions of the decalin moiety, as compared with subtype Ic with only one simple epoxy ring on the decalin moiety. Subtypes IIa and IIb do not have an O-containing ring, but instead have one or more double bonds in the decalin moiety (IIa) or saturated decalin or oxodecalin moiety (IIb). Finally, subtype III compounds have a distinctive tetrahydrofuran rather than furan in the C-9 side chain, along with various decalin moieties.

2.2.1. Type II with various O-containing rings

2.2.1.1. Type II subtype Ia with various O-containing rings\textsuperscript{75,106–127} (Table 8 – compounds 297–323 found in ESI\textsuperscript{†}): Nasimalun A (297) from Barringtonia racemosa illustrates a type II subtype Ia clerodane with a C-18/C-19 \(\gamma\)-lactone ring,\textsuperscript{106} while teumassilenin B (302) from Teucrium massiliense is a type II subtype Ia with a similar \(\gamma\)-lactol ring.\textsuperscript{111} T. massiliense also yielded new clerodane diterpenes from two additional type II subtypes: teumassilenin C (336) (type II subtype Ib with an oxetane ring, see Section 2.2.1.2) and teumassilenin A (423) (type II subtype IIb with an oxodecalin, see Section 2.2.2.2; the first example of an 18\(\beta\)-aldehyde from Teucrium species).\textsuperscript{111}

A furan ring is present between C-18 and C-6 in clerodanes 314–316,\textsuperscript{122,123} while plaunol E (306) has a \(\gamma\)-lactone ring at this same position, as well as a \(\delta\)-lactol ring between C-20 and C-19.\textsuperscript{115} Compound 306 significantly inhibited LPS-induced NO production with an IC\textsubscript{50} value of 2.79 \(\mu\)M.\textsuperscript{115}
Other new clerodanes in this subtype also had oxygenated rings incorporating C-20. Sacacarin (318) from Croton cajucara has a C-19/C-20 δ-lactone ring. Compound 319 from Salvia miniata has an oxygenated structure containing C-19/C-20 and C-7/C-20 acetalic bridges. The C-20/C-19 δ-lactone in 321 (ref. 116) from Teucrium oxylepis and the C-20/C-6 δ-lactol ring in 323 (ref. 75) from Pteronia eenii are also accompanied by C-4/C-18 and C-3/C-4 epoxide rings, respectively.

2.2.1.2. Type II subtype Ib with other O-containing rings\(^8\),\(^\text{111}\),\(^\text{112}\)–\(^\text{140}\) (Table 9 – compounds 324–355 found in ESI†): Clerodane diterpenoids with an axial oxyfunction at the C-7 position are rare, but a few examples, such as 326–329, have been reported. The structure of 326 from Tecritum cossonii distinctly contained a 4,18-spiro-oxirane compared with those of 327–329 from Psychopetalum olacoides.\(^\text{129}\),\(^\text{130}\) Methyl dodonates A–C (330–332), three new modified clerodanes containing a tricyclo [5.4.0.0\(^1\)3]undecane ring system, were isolated from Dodonaea viscosa.\(^\text{131}\) They have been proposed as putative intermediates in the biogenetic pathway to diterpenes possessing a bicyclo[5.4.0]undecane or bicyclo[5.3.0]decane ring system.

Teucrolin E (335) from Teucrium oliverianum contains an oxo group (C=O) at C-7.\(^\text{133}\),\(^\text{134}\) Its originally proposed structure also contained an oxetane ring with the oxygen connecting C-4 to C-10, leaving C-18 as a hydroxymethyl group.\(^\text{133}\) However, additional NMR analysis of the diacetate, including NOE studies, indicated that C-18 is instead part of a tetrahydrofuran ring that includes C-10 and a tertiary OH group is present at C-4.\(^\text{134}\) As mentioned previously, teumassilenin C (336) from Teucrium massiliense does possess an
oxetane ring; however, the oxygen connects C-4α and C-19.\textsuperscript{111} Anastreptin (337) from \textit{Adelanthus lindenbergi} contains a cyclic ketal moiety with oxygen bridges from C-12 to C-7 and C-12 to C-8 of the decalin moiety.\textsuperscript{84} Three type II subtype Ib clerodanes (bafoudiosbulbins A, D, and E; 339–341) were isolated from \textit{Dioscorea bulbifera}.\textsuperscript{135,136} Compound 339 is a stereoisomer of 340; both compounds contain a lactone bridge (OC=O) between C-2 and C-5, as well as between C-6 and C-8.\textsuperscript{135,136} Compound 341 is identical to 340, but also contains a 3α,4α-epoxide.\textsuperscript{136}

Scaparvin A (343), a novel caged \textit{cis}-clerodane diterpenoid with an unprecedented C-6/C-11 bond, was isolated together with scaparvins B–E (344–346, 350), without the C-6/C-11 bond, from the Chinese liverwort \textit{Scapania parva}.\textsuperscript{138} Their absolute structures were elucidated by analysis of NMR and CD data coupled with electronic circular dichroism (ECD) calculations. The authors proposed an enzymatic intramolecular aldol reaction as the key step in the biogenetic pathway of 343.\textsuperscript{138} Parvitexins A–C (347–349) from \textit{S. parvitexta} were the first natural products identified with an unusual 2,8-dioxobicyclo[3.2.1]octane moiety.\textsuperscript{139}

2.2.1.3. Type II subtype Ic with a simple epoxy ring\textsuperscript{123,129,139,141–148} (Table 10 – compounds 356–376 found in ESI†): Clerodane diterpenes in this subtype generally have either a 3,4 epoxide (\textit{e.g.}, 357 from \textit{Scapania parvitexta},\textsuperscript{139} 359 from \textit{Croton eluteria},\textsuperscript{142} 364 from \textit{Thysanathus spathulistipus}\textsuperscript{143}) or a 4,18-spiro-oxirane (\textit{e.g.}, 369 from \textit{Teucrium oliverianum},\textsuperscript{146} 375 from \textit{T. fruticans}\textsuperscript{123}). Their structural differences are mainly in the linkages between the carbocyclic and heterocyclic moieties and the functionalization of the decalin core. However, the β-oriented epoxide of phlomeoic acid (376) from \textit{Phlomis bracteosa} is uniquely at C-1/C-10.\textsuperscript{148}

2.2.2. Type II with or without a C=C double bond in the decalin moiety

2.2.2.1. Type II subtype IIa with one or more decalin C=C double bonds\textsuperscript{74,106,110,130,149–168} (Table 11 – compounds 377–419 found in ESI†): Vishautriwatic acid (377) from \textit{Dodonaea viscosa}
was identified with different stereochemistry at C-5 and C-9 from the known neo-clerodane hautriwatic acid (378) found in *Eremocarpus setigerus*.\textsuperscript{149,150} The cis-relationship of H-10 and Me-20 in 377 is uncommon compared with the trans-relationship found in 378. Crotonolide G (404, *Croton laui*), with a unique 2,5-dihydrofuran rather than furan in the C-9 side chain, displayed significant antibacterial activity with an MIC value of 43.4 μM against four strains of Gram-positive bacteria, including *Staphylococcus aureus* ATCC 25923, *Staphylococcus epidermidis* ATCC 12228, *Micrococcus luteus* ATCC 9341, and *Bacillus subtilis* CMCC 63501.\textsuperscript{165} Crotomembranafuran (414, *Croton membranaceus*), which has a less common ethanone rather than ethyl or ethylene linkage between the decalin and furan ring systems, had an IC\textsubscript{50} value of 10.6 μM against PC-3 cells.\textsuperscript{168}

In addition to the C-3/C-4 double bond, compounds 415 and 418 found in *Caryophyllales* also contain a second double bond (C-1/C-2 in 415;\textsuperscript{155} C-1/C-10 plus C-2 oxo in 418 (ref. 169)). Finally, eluterin B (419) from *Croton eluteria* contains an exocyclic C-4/C-18 double bond.\textsuperscript{142}
2.2.2. Type II subtype IIb without a decalin C=C double bond\(^\text{89,111,142,151,165,170–172}\) (Table 12 – compounds 420–428 found in ESI†): Crolechinic acid (422) is representative of type II subtype IIb compounds and was found as a minor constituent in *Croton lechleri* based on TLC profiles and NMR spectra.\(^\text{89}\) Eluterin A (425) differs structurally from eluterin B (419) only in the functionalities at C-3, C-4, and C-18: oxo and \(\beta\)-methyl in the former, but \(\alpha\)-hydroxy and exocyclic double bond in the latter.\(^\text{142}\) Four new tricyclic clerodane type diterpene aldehydes (423 and 426–428) were characterized through modern spectroscopic techniques and comparison with literature data.\(^\text{111,170–172}\) 20\(\alpha\)-Aldehydes are present in 426 and 427 from *C. hovarum*.\(^\text{170,171}\) Compounds 423 and 428 both contain a 18-aldehyde and the same relative stereochemistry, but the former was reported as a *neo*-clerodane from *Teucrium massiliense* and the latter as an *ent-neo*-clerodane from *Nepeta juncea*.\(^\text{111,172}\)

\[
\begin{align*}
\text{422} & \quad \text{HO} \quad \text{C} \\
\text{423} & \quad \text{OH} \quad \text{OCH}_2\text{Ac} \\
\text{425} & \quad \text{CH}_2\text{OH} \\
\text{426} & \quad R_1 = \text{O}, \quad R_2 = \text{H}, \quad R_3 = \text{Me} \\
\text{427} & \quad R_1 = \text{OH}, \quad R_2 = \text{Me}, \quad R_3 = \text{OH}
\end{align*}
\]

2.2.3. Type II subtype III with a tetrahydrofuran ring\(^\text{72,89,149,173–179}\) (Table 13 – compounds 429–445 found in ESI†): Compounds 429 and 430 from *Baccharis trinervis* were determined as trinerolide and 15-\(\text{epi}\)-trinerolide, respectively, based on the number of split peaks and coupling constant of the acetal H at C-15.\(^\text{72}\) Compound 434 was a possible artifact from *B. articulata*, with the true natural product being its hemiacetal analogue.\(^\text{173}\) Two new *neo*-clerodane diterpenoids with multiple O-containing rings, compounds 439 and 440, were isolated from an acetone extract of the aerial parts of *Scutellaria galericulata*.\(^\text{176,177}\)

\[
\begin{align*}
\text{429} & \quad R = \text{o-OAc} \\
\text{430} & \quad R = \text{b-OMe} \\
\text{434} & \quad R_1 = \text{OH}, \quad R_2 = \text{b-OMe} \\
\text{439} & \quad R_1 = \text{OH}, \quad R_2 = \text{OMe} \\
\text{440} & \quad R_1 = \text{OMe}, \quad R_2 = \text{OH}
\end{align*}
\]

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2.3. Type III with a 3-ethyl-2-butenolide-based side chain at C-9

Type III clerodane diterpenoids bear a 3-ethyl-2-butenolide-based side chain at C-9, with various O-containing rings or double bonds at different positions. Comparison of the type II and type III general structures shows that the furan ring in the former has been replaced by a furan-2(5H)-one (or 2-butenolide) in the latter.

2.3.1. Type III subtype I with O-containing rings

2.3.1.1. Type III subtype Ia with five-membered cyclic O-containing rings

(Tables 14 – compounds 446–480 found in ESI†): Amphiacrolides A–E, I, J, L, and M (446–454), isolated from *Amphiachyris dracunculoides*, have an ethyl butenolide side chain attached at C-9, as supported by characteristic MS fragments (*m/z* 111, 98, and 97) and 1H and 13C-NMR peaks.180–182 The stereochemistries of the amphiacrolides were established from the chemical correlation of these compounds to gutierolide, a compound with absolute stereochemistry determined by X-ray analysis.180–182

The planar structures of 460 and 461, isolated from different Baccharis species are identical, but the compounds are epimeric at C-8.173,186 The absolute stereochemistry (neo-series, 5 : 10 trans, 17 : 20 trans) of gaudichanolide A (461) from *B. gaudichaudiana* was established by X-ray crystallographic analysis.186

Several new clerodanes, exemplified by 463 from *Cephaloziella kiaeri*, have a unique unsaturated γ-lactone moiety incorporating C-18 and C-6.84,182,187–191 Three 1 : 1 mixtures (470–475) of epimeric clerodane diterpenes with a C-8/C-12 ether bridge were isolated from *Adelanthus lindenberghianus*.84 Structures 474–476 contain a second ether bridge between C-12 and C-7 forming a cyclic ketal at C-12.84 A C-1/C-12 ether bridge is present in 477 also from *A. lindenberghianus*,84 while a C-10/C-12 ether bridge is found in 478–480 from *Scapania ciliata*.191

2.3.1.2. Type III subtype Ib with other O-containing rings

(Tables 15 – compounds 481–527 found in ESI†): Many compounds in this subtype contain the typical functional groups of neo-clerodane diterpenoids, including a C-4/C-18 (e.g., 505) or C-3/C-4 epoxide (e.g., 515, 516) and cis C-17α and C-20α methyl groups.192–209 Among them, hastifolin A (505) from *Scutellaria hastifolia* showed significant antifeedant activity against larvae of *Spodoptera littoralis* at a concentration of 100 ppm; its feeding index was 60 ± 15.2 and FI50 concentration was 45 ppm.204 Seguiniilactones A and B (515–516) from *Colquhounia seguinii* differ structurally only in where the butenolide ring is connected to C-12. This connection is at the β position of the
butenolide ring in the former compound and at the α position in the latter compound.209 Thus, the carbonyl moiety of the lactone ring is at C-15 (a 15,16-olide) in 515 and at C-16 (a 16,15-olide) in 516. A β-substituted α,β-unsaturated γ-lactone functionality was found to be crucial for the strong antifeedant activity of this compound class, and 515 was approximately 17-fold more potent than commercial neem oil insecticide against the generalist plant-feeding insect *Spodoptera exigua.*208,209

The C-2/C-19 ether bridges of amphiacrolide K (518; *Amphiachyris dracunculoides*) and conyzalactone (519; *Conyza blinii*) have opposite relative configurations, and these two compounds are also the two *ent-neo-clerodane* exceptions in this subtype.181,210 *Neo-*Clerodane-type diterpenoid 520 from *Ajuga decumbens* has a C-1/C-19 ether bridge.211 Compounds 521–525 contain a C-20/C-7 γ-lactone/lactol bridge,52,212 compounds 526 has
a C-18/C-7 δ-lactone bridge, and finally, microdon B (527) possesses a C-17/C-12 δ-lactone bridge.

2.3.1.3. Type III subtype IIa with C3/C4 double bond

A wide range of substituents are found on the decalin and butenolide moieties in type III subtype IIa compounds. With CO$_2$H at the decalin C-4 position and OMe or H, respectively, at the butenolide C-4 position, limbatolides B (533) and C (534) from *Otostegia limbata* inhibited acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes in a concentration-dependent manner with IC$_{50}$ values of 47.2, 103.7 and 17.5, 14.2 μM, respectively. Polylongifoliaon B (543) from *Polyalthia longifolia* is one of a few type III subtype IIa compounds with an α,β-unsaturated ketone in the decalin ring A. This compound improved the viability of human neuroblastoma cells (SK-N-MC cells) under Aβ-induced neurotoxicity with an IC$_{50}$ value of 3.75 μM.
The H-10 of compounds 558–571 has the more unusual $\alpha$-orientation (ent-neo-clerodane).\textsuperscript{163,164,183,213,226} Both cis–trans (e.g., 558–564), trans–cis (e.g., 566), and cis–cis (e.g., 571) configurations of the decalin ring junction and C-17/C-20 orientation, respectively, are found. Solidagoic acids C–I (558–564) from *Solidago virgaurea* contain a carboxylic acid at C-19, a motif that is relatively uncommon among the clerodanes.\textsuperscript{183} Compared with the standard drug deoxynojirimycin (425.6 ± 8.1 $\mu$M), compound 566 from *Duranta repens* showed significant $\alpha$-glucosidase inhibitory activity (IC\textsubscript{50} 577.7 ± 19.0 $\mu$M).\textsuperscript{226} Structurally, it has a 6$\beta$-OH and opposite stereochemistry at C-8 to C-10 compared with 534 mentioned above.

Scutebata A (574), as well as scutebatas B and C (994 and 995; see Section 2.9.1), from *Scutellaria barbata* possess a rare hydroxy group at the $\alpha$-position of the $\alpha,\beta$-unsaturated lactone ring. Scutebata A showed weak cytotoxic activity against SK-BR-3 cells with an IC\textsubscript{50} value of 15.2 $\mu$M.\textsuperscript{228} Compound 575 from *Baccharis trinervis* has a saturated, rather than unsaturated, $\gamma$-lactone in its side chain.\textsuperscript{72}

### 2.3.1.4. Type III subtype IIb with double bonds in other positions

Compounds 577–579, 584, and 888 (see Section 2.7) from *Scutellaria barbata* showed significant cytotoxic activities against three human cancer lines, HONE-1 nasopharyngeal, KB oral epidermoid carcinoma, and HT29 colorectal carcinoma, with IC\textsubscript{50} values in the range of 2.0–8.1 $\mu$M.\textsuperscript{220,230,232} Compound 584 has a 2,3-epoxy-2-isopropyl-$\alpha$-proproxy moiety attached at C-6, and its possible biosynthesis was proposed.\textsuperscript{230} Salvidivins C (587) and D (588) from *Salvia*
Divinorum are unique neo-clerodane diterpenes that possess a \(\gamma\)-hydroxy-\(\alpha,\beta\)-unsaturated \(\gamma\)-lactone moiety, and are geometrical isomers at the \(\gamma\)-lactone moiety.\textsuperscript{235}

Several compounds in this subtype have a 4,18-exo-methylene group (\textit{e.g.}, \textsuperscript{589} \textsuperscript{597} \textsuperscript{598} \textsuperscript{600}),\textsuperscript{217,231,236–242} while compounds \textsuperscript{612}–\textsuperscript{614} have a unique \(\alpha\)-oriented cyclopropane ring formed from C-4, C-5, and C-19.\textsuperscript{247,248} The latter three compounds were isolated from two different marine organisms, an Okinawa tunicate \textit{Cystodytes} sp and a Formosan gorgonian coral \textit{Echinomuricea} sp. Echinoclerodane A (\textsuperscript{614}) was found to be the C-8 epimer of dytesinin A (\textsuperscript{612}), and the chiral carbons in \textsuperscript{614} were assigned as 4\(S^*\), 5\(S^*\), 8\(S^*\), 9\(S^*\) and 10\(R^*\).\textsuperscript{248}

### 2.4. Type IV with a 5-(3-furyl)-\(\delta\)-valerolactone-based side chain at C-9

Compounds in this group are characterized by a 5-(3-furyl)-\(\delta\)-valerolactone-based side chain at C-9, together with lactone and epoxy rings, hydroxy and acetoxy groups, as well as double bonds. Both type II and type IV compounds contain a furan ring in the C-9 side chain but differ by the presence of a 17,12-\(\delta\)-lactone ring in the latter class. Thus, as seen below, position 17 is generally a free methyl group in type II compounds, while it is incorporated into the \(\delta\)-lactone ring as the carbonyl group in type IV compounds.

#### 2.4.1. Type IV subtype I with O-containing rings\textsuperscript{108,109,113,120,249–262} (Table 19 – compounds 615–655 found in ESI†) —In addition to the 17,12-\(\delta\)-lactone ring characteristic of type IV clerodanes, many new subtype I compounds from \textit{Salvia} species...
have a 18,19-γ-lactone ring. Their decalin moieties also contain various numbers and locations of double bonds (see 615, 617, 622–624) and oxygenated groups. The 1β,10β-epoxy group of 627–630 from *Salvia herbacea* was deduced by analysis of spectroscopic data.249 Tehuanin G (630) exhibited anti-inflammatory activity (IC₅₀ 0.24 μM/ear) comparable to that of indomethacin, the reference compound.249 In contrast, the C-1(2)-epoxy group of 632–634 from *S. reptans* has an α-orientation.252,253 Except for the stereochemistry of the C-18–C-19 lactone ring fusion (trans in 632, cis in 633), compounds 632 and 633 have identical structures with both A/B and B/C cis ring fusions, as established by X-ray analysis.252,253 Furthermore, tehuanins A–C (635–637) from *S. herbacea* contain a 1,8-oxygen bridge; this unusual structural feature was confirmed by X-ray diffraction of 635.249

In addition to the C-12–C-17 δ-lactone ring found in the type IV class, compounds 638–640 from *Jamesoniella autumnalis* have a second lactone ring at C-18/C-6,120 while fibrauretin A (641) from *Fibraurea tinctoria* has a second lactone ring at C-1/C-18 as well as an epoxide ring at C-2/C-3.254 Compound 647, a stereoisomer of 8-hydroxycolumbin at the C-12 position, contains the same C-1(18)-lactone ring as 641 rather than the C-2(18)-lactone ring of compounds 648 and 649.258 Compounds

650–653 are novel furano-clerodanes from *Dioscorea antaly* and *D. bulbifera* with a second δ-lactone ring bridging carbonyl C-19 to C-2.259,260

![Image](https://example.com/image.png)
2.4.2. Type IV subtype II other compounds—Compound 665 from *Salvia divinorum* is a C-17 epimeric mixture of the hemiacetal salvinorin J, and is an example of a neo-clerodane hemiacetal (lactol) susceptible to mutarotation with the formation of an equilibrium mixture of C-17 epimers. Salvinicins A (684) and B (685) from the same plant are unique neo-clerodanes with a 3,4-dihydroxy-2,5-dimethoxytetrahydrofuran ring. Their absolute stereochemistry (neo-series, A/B ring *trans*, B/C ring *trans*) was based on X-ray crystallographic analysis. Interestingly, salvinacin A (684) exhibited partial κ agonist activity with an EC$_{50}$ value of 4.1 ± 0.6 μM ($E_{\text{max}}$ = 80% relative to (-)-U50,488H), while salvinicin B (685) exhibited antagonist activity at μ receptors with a $K_{i}$ of >1.9 μM. This report provided a new lead in the development of opioid receptor antagonists.

Salvidivins A (686) and B (687) are a pair of geometrical isomers of the γ-hydroxy-α,β-unsaturated γ-lactone, differing from each other in the linkage position to C-12. It appears that 686 and 687 are important precursors of 684 (a partial agonist of the κ-opioid receptor) and 685 (the first μ-opioid antagonist with a neo-clerodane skeleton).

Compounds 688–691 are type IV subtype II compounds with variations on the δ-lactone structure. Compound 688

from *Cornutia granditolia* and 689 from *Adelanthus lindenbergianus* are distinguished by a unique ether linkage between C-1 and C-12. Remarkably, the structures of orcadensin (690) also from *A. lindenbergianus*, as well as salvianduline D (691) from *Salvia miniata*, contain cyclic ketal functions with two oxygen bridges from C-12 to different positions of the decalin moiety.
2.5. Type V with an $\alpha$-spiro-attached 4-(3-furyl)-$\gamma$-butyrolactone-based side chain at C-9

Clerodane diterpenoids of this group contain an unusual C-9-spiro-$\gamma$-lactone substituted at C-12 with a furan ring or are compounds arising from rearrangements of this structure. As contrasted in the below figure, the $\gamma$-lactone ring of type V compounds includes C-20 (C=O), C-9 (as the one carbon link to the decalin system), C-11, and C-12, while the $\delta$-lactone ring of type IV compounds incorporates C-17 (C=O), C-8, C-9, C-11, and C-12. Type V compounds have a free Me-17, while type IV compounds have a free Me-20.

2.5.1. Type V subtype I with various O-containing rings$^{75,108,113,165,187,275–281}$ (Table 21 – compounds 692–719 found in ESI†)—Compound 692 from *Salvia fulgens* exemplifies a variation on the basic type V structure. In it, C-20 is connected to C-7 as well as C-12 by oxygen atoms, forming two tetrahydrofuran rings joined at the C-20 acetal. This interesting structure was confirmed by X-ray crystallographic analysis as a dihydro derivative of the known salvifaricin, which has a double bond at C-1/C-2, as well as C-3/C-4.$^{275}$ Like salvifaricin, salvifolin (695; *S. tiliaefolia*)$^{276}$ and dugesin F (696; *S. dugesii*),$^{113}$ also have two double bonds in the decalin A-ring. However, unlike salvifaricin and 692, the second ether bridge from C-20 to C-7 is missing in 695 and 696, and instead a cyclic hemiacetal (spiro-$\gamma$-lactol) and C-7 oxo groups are present. An A/B cis ring fusion was elucidated in 695, in comparison with linearolactone whose structure was established by X-ray diffraction analysis, while the structurally similar 696 has a trans decalin ring fusion. Dugesin F (696) exhibited an inhibitory effect on influenza virus FM1, a strain that causes a cytopathic effect (CPE) in MDCK cells.$^{113}$ The results [TC$_{50}$ 45.67 μg mL$^{-1}$, IC$_{50}$ 9.43 μg mL$^{-1}$, therapeutic index (TI) 4.84] implied that 696 is a non-toxic antiviral compound against influenza virus FM1.
Teusandrin A–D (708–711) isolated from *Teucrium sandrasicum* contain a non-rearranged C-9-spiro-γ-lactone. Notably, such diterpenoids containing an oxetane ring involving positions 4α,19 (e.g., 708 and 709) and 4β,10β (e.g., 710 and 711), as well as 4β,6β (not illustrated) of the neo-clerodane skeleton are relatively frequent among the constituents of *Teucrium* plants.281

Several new clerodane diterpenoids, crotonolides A–D (713–714, 716, 718) and isocrotonolides B–D (715, 717, 719), were isolated from the aerial parts of *Croton laui.*165 They contain a variation on the C-9-spiro-γ-lactone with the two oxygen atoms on C-20 incorporated into both a tetrahydrofuran ring through C-12 and a six-membered lactone/lactol ring between C-19 and C-20. Crotonolide A (713) also contains a Δ3,4 double bond, a Δ8,17 exocyclic double bond, and a 18,6-γ-lactone. In 714–719, the latter lactone ring is absent, and also C-19 is hydroxylated rather than present as an oxo group. Compounds 714/715, 716/717, and 718/719 are epimeric pairs at C-19 and were obtained as 3 : 1 interconverting mixtures.

2.5.2. Type V subtype II with 4,18-; 3,4-; or 8,17-oxirane moieties75,123,126,142,144,145,262,280–294 (Table 22 – compounds 720–767 found in ESI†) — Most of the new compounds in this subtype have a C-12 furan, a spiro-20,12-hemiacetal function involving the C-9, C-11, C-12, and C-20 carbons, a 4α,18-oxirane, and a trans decalin ring junction. Teumassin (720) from *Teucrium massiliense* contains the rare feature of a C-2 hydroxy group.282 The diterpenes 729–732 isolated from *T. polium* possess the same absolute configuration, and belong to the neo-clerodane series.285 In this clerodane subtype, the C-12 stereocenter can have an R-configuration (e.g.,...
743 from T. maghrebinum), as well as an S-configuration (e.g., 729).\textsuperscript{126,144,280} New C-10 oxygenated type V subtype III neo-clerodane derivatives, sandrasin A (744) and 6-deacetyl-sandrasin A (745) were isolated from the aerial parts of T. sandrasicum.\textsuperscript{289} Analysis of spectroscopic data revealed ether linkages between both C4α, C18 and C19α, C20α in 750 obtained from T. abutiloides.\textsuperscript{287}

The investigation of different Pteronia species afforded 28 new diterpenes, including five cis-clerodanes in this subtype (751–753, 758–759).\textsuperscript{75} Compounds 751–753 have a 8,17-oxirane and C-10 is hydroxylated. Compounds 758–759 have a 3,4-oxirane and C-10 bears a hydrogen. An extract of the aerial parts of Microglossa pyrrhopappa afforded cis-clerodanes 760–763 as well as 767 with a Δ\textsuperscript{1,10} double bond.\textsuperscript{128}

Cascarilla, the bitter bark of the South American tree Croton eluteria, is a commercially available and inexpensive source of polyfunctionalized clerodane diterpenoids. In addition to the bitter triol cascarillin, ten additional new diterpenoids, including eluterins J and I (756–757) in this subtype, were isolated and characterized.\textsuperscript{142} The structural differences among cascarilla clerodanes mainly involve the linkage between the carbocyclic and the heterocyclic moieties and the functional groups on C-3, C-4, and C-6. Although cascarillin was previously reported to be a γ-hydroxyaldehyde, this study showed that it is actually a mixture of interconverting γ-lactols.\textsuperscript{142} Compound 756 is set apart by the oxygenation of C-11, a very unusual feature in furoclerodanes.\textsuperscript{142}

Crotopene A (764), which has a rare 2,3-dihydrofuran ring with a spiro-carbon at C-9 and an oxygen connecting C-12 and C-20, may be formed by oxidation or enzyme catalysis of crotopene B (765). Both compounds are found in Croton yanhuii.\textsuperscript{204}
2.5.3. Type V subtype III with a C-9-spiro-γ-lactone/lactol moiety and opened furan ring\(^{47,61}\) (Table 23 – compounds 768–773 found in ESI†)—Clerodane-type diterpenoids (768–773) with a C-9-spiro-γ-lactone/lactol moiety bearing an opened furan ring (2-hydroxy-3-buten-2-yl) at C-12 are rare and found only in *Heteroscyphus* plants. In the decalin portion, compounds 768 and 769 possess a 3,4-epoxide, 770 contains a 3,4-epoxy and 2-oxo groups, and compounds 771–773 have a 3,4-double bond and 2-oxo moiety.\(^{47,61}\)

![Chemical Structures](image)

2.5.4. Type V subtype IV other compounds\(^{75,142,277,289,292,295–299}\) (Table 24 – compounds 774–793 found in ESI†)—Compounds in this subtype possess the furanyl substituted C-9-spiro-γ-lactone/lactol together with various substituents and unsaturation (\(\Delta^3,4\) 777, \(\Delta^4,18\) 778, \(\Delta^1,10\) 779, \(\Delta^1,2\) 780,\(^{277}\) saturated 781 (ref. 297)) in the decalin system. A small coupling constant between H-6 and H-7 proved that these protons were in \(\alpha,\alpha\)-equatorial positions in 777, which consequently contains a cis-6β,7β-diol. Teulolin B (778) is the first neo-clerodane diterpene with an exocyclic double bond at C-4/C-18 isolated from *Teucrium* species.\(^{297}\) In sandrasin B (781), C-4 bears \(\alpha\)-OH and \(\beta\)-CH\(_2\)OH groups, rather than being involved in a spiro-oxirane with C-18 as found in 744 and 745, which are type V subtype II compounds (see Section 2.5.2.) co-isolated from *T. sandrasicum*.\(^{289}\)

![Chemical Structures](image)

2.6. Type VI with a furofuran-based side chain at C-9

Type VI compounds contain a bicyclic furofuran system, either hexahydro or tetrahydro, attached at C-9. As contrasted below, an oxygen bridge between C-11 and C-16 differentiates the bicyclic type IV from the monocyclic type II compounds.

![Chemical Structures](image)
2.6.1. Type VI subtype I with a hexahydrofurofuran-based side chain at C-9 (ref. 176, 193, 195, 207 and 300–319) (Table 25 – compounds 794–845 found in ESI†)—Most neo-clerodanes in this group possess a hexahydrofurofuran side chain at C-9 and a 4α,18-spiro-oxirane group, while some compounds also contain an additional C-19,2α-hemiacetal function (compare the structures of 815 and 834 obtained from Scutellaria discolor).311 Interestingly, compound 819, isolated from S. columnae, was the first neo-clerodane diterpene reported to have a hexahydrofurofuran moiety with an 11R-configuration.313

Generally, clerodin hemiacetal derivatives are found as C-15 epimeric mixtures. Scupolin K (811) from S. polyodon was found as a mixture of the C-15 epimers of the 14,15-dihydro-15-hydroxy derivative of scupolin J,310 and scutalsin (818) from S. altissima was also a 1 : 1 epimeric mixture of the C-15 hemiacetal function.312 Compounds 812–814 and 832–833, which have ethoxy acetal groups, are considered to be artifacts from Scutellaria discolor formed in the course of extraction or separation using ethanol.311 Compounds 824 and 825 from Ajuga salicifolia are the C-15 epimers of the 14,15-dihydro-15-hydroxy derivative of 826.316 Compound 831 from Clerodendrum inerme was assigned as a mixture of C-15 epimers of 14,15-dihydro-15-hydroxy-3-epicaryoptin.319 Two pairs of diastereomeric hemiacetals, scutecyprols A (838) and B (810), were detected in the aerial parts of S. cypria. After oxidation, they were isolated as their γ-lactone derivatives.309

Compound 837 from S. alpine contains an isobutyroyloxy group at C-19, while a rarer propanoyloxy substituent is present in 836 from S. barbata; however, their absolute configurations were not ascertained.195,321 Scupontins C, D, and F (839–841) from S. pontica possess unusual [(3’S,3”S)-3’-[(3”-acetoxybutyryl) oxy]butyryloxy and [(3’S,3”S, 3’”S)-3’-[(3’”-hydroxybutyryl) oxy]butyryl]oxy substituents, respectively, attached to the C-19 position of the neo-clerodane nucleus.322 Scutalpin M (842) also from
S. alpine is the first 14-oxidized hexahydrofuro-furan-neo-clerodane derivative isolated from natural sources. Compound 843 from A. lupulina has a C-4/18 exocyclic double bond, which is unusual in this type of clerodane diterpenes. Inermes A (844) and B (845) from C. inerme are dimeric neo-clerodanes with the two hexahydrofurofuran rings joined through an ether linkage at C-15, the latter compound contains a C-1 methoxy group not found in the former compound.

2.6.2. Type VI subtype II with a tetrahydrofurofuran-based side chain at C-9 (ref. 207, 300–302, 306, 310, 311, 320 and 322–328) (Table 26 – compounds 846–874 found in ESI†)—The tetrahydrofurofuran system with a 14,15 double bond is the same in compounds of this subtype, and their clerodendrin skeletons also contain a 4α, 18-spiro-oxirane. They differ in other substitutions on the decalin system. Certain compounds [e.g., jodrellins A and B (860–861) from Scutellaria species] also
contain an additional C-19,2α-hemiacetal function, as found in the type VI subtype I compounds mentioned in the prior section. The spectroscopic differences observed between 853 and 854 found in S. laterifora suggested the presence of an acetoxyl substituent in the former and a 2-methylbutanoyloxy group in the latter. Clerodendrum trichotomum yielded clerodendrins I, E, F, G (868–871) all having a double bond at C-7/C-8 in their decalin skeleton are substituted with 2α-hydroxy, 4α,18-epoxy, 6α,19-diacetoxy, 7,8-ene and 11,12,13,16-tetrahydrofurofuran functions, but with different 3β-acyloxy groups. Like 839–841, scupontins A, B, and E (872–874) from S. pontica are esterified at C-19 with diand tri-esters of 3-hydroxybutanoic acid.

2.7. Type VII with a 13-spiro-15,16-γ-lactone moiety (Table 27 – compounds 875–902 found in ESI†) The defining structural characteristics of type VII neo-clerodane structures are a 8,13-ether bridge creating a tetrahydropyran that incorporates C-8 and C-9, as well as C-11–C-13, and a 13-spiro-15,16-γ-lactone moiety. Both possible configurations are found at the spiro C-13. A comparison with type III compounds is shown below.

Scutorientalin C (876) is the first neo-clerodane with a free C-11 axial hydroxy group in ring C (tetrahydropyran) to be isolated from a Scutellaria species. The observed spectroscopic differences between 877 and 878 were consistent with the presence of a C-6α-isobutyric ester in the former compound rather than the tigloyloxy group found in the latter. From a chemotaxonomic point of view, compound 879 is the first 8β,13S-epoxy-neo-clerodan-15,16-olide derivative found in European Scutellaria species, although these structural features are shown by several neo-clerodanes isolated from Asian Scutellaria species.

Opposite absolute configurations have been found at C-13 (e.g., 13S and 13R in 884 and 898, respectively). The aerial parts of Scutellaria hastifolia yielded several clerodanes similar structurally to the known scuteparvin, but distinguished by being trans-cinnamoyl derivatives. Some of these compounds are epimeric at C-13, and it was not possible to separate the 4 : 1 mixture of hastifolin G (886) and hastifolin F (894). Likewise, barbatellarine E (888) is a C-13 epimer of barbatellarine F (892), as confirmed by NOESY
and optical rotation data. Comparison of spectroscopic data for 896 and 897 indicated the presence of C-6α and C-7β equatorial isobutyryloxy groups and a free C-19 hydroxy group in the former compound instead of C-6α tiglate and C-7β and C-19 acetates in the latter compound.

2.8. Clerodane diterpene glycosides (Table 28 – compounds 903–981 found in ESI†)

The clerodane diterpene glycosides come from many of the above types but have been placed into a separate category based on the presence of one or more sugar groups at various positions on both the decalin and C-9 side chain. *Gleichenia japonica* and *Dicranopteris pedata* yielded new glycosylated type I clerodane diterpenes with an acyclic C-9 side chain (903–904 and 905–906, 910–913, respectively). The only structural difference between 903 and 904 is the presence of only glucopyranosyl at C-6 in the former, but glucopyranosyl linked to rhamnopyranosyl in the latter. However, compound 903 inhibited the growth of lettuce, whereas 904 accelerated growth. The related glycoside 905 with sugars on both C-6 and C-13 also accelerated lettuce stem growth, but inhibited root growth. Compounds 907–909 are the first clerodane diterpenes with l-arabinoside at C-13 isolated from the family Compositae (species *Nannoglottis carpesioides*). Compounds 910–913 are monodesmosidic clerodane diterpene glycosides containing two monosaccharides, glucopyranosyl and rhamnopyranosyl. Compounds 918–922 possess a 1,4-dihydroxy-2-buten-2-yl-ethyl group at C-9, which is characteristic of the diterpenoids found in *Portulaca* and *Salvia* plants.

Examples of glycosylated clerodanes with type II structures are 924–925 from *Elsholtzia bodinieri*, 926 from *Salvia amarissima*, and 927–928 from *Tinospora tuberculata*. Amarisolide (926) was the first reported diterpene glucoside found in *Salvia* species.

Compounds 930 and 931, both found in *Baccharis sagittalis*, were separated and characterized as C-18 β-D-glucopyranosyl peracetylated derivatives. The former compound can be classed as a type I clerodane glycoside, while the latter compound is a type III clerodane glycoside with a 3-ethyl-2-butenolide side chain.

Clerodane diterpene glycosides with various five-membered O-containing rings attached at C-12 were isolated from three *Tinospora* species. Compounds 934 and 935 with an unsubstituted butenolide ring exhibited moderate anti-settling...
activity against the sea barnacle *Balanus amphitrite*, and are the first clerodane diterpenes to be reported with antifouling activity.\textsuperscript{350} Rumphiosides A and B (936 and 937) contain hydroxy- and methoxy-butenolide rings, while the tetrahydrofuran rings attached to C-12 in the epimeric 939 and 940 were possibly artifacts formed from a dialdehyde during the extraction of the plant material with methanol.\textsuperscript{351} Compounds 941 and 942 have a 17,6-γ-lactone,\textsuperscript{351} while compounds 936–937, 939–940, and 943–944 contain a 17,12-δ-lactone as well as an 18β,1β-δ-lactone. In cordifolides B and C (943 and 944) the butenolide ring located on C-12 is rotated nearly 180° from the C-12/C-13 bond, resulting in different
orientations. Their structures were determined on the basis of spectroscopic data interpretation.

In addition to cordifolides B and C, *Tinospora cordifolia* also yielded a novel unique sulfur-containing type IV clerodane furanoditerpene glycoside, cordifolide A (**948**). Its structure and configurations at chiral centers were confirmed by single-crystal X-ray crystallographic analysis. Cordioside (**949**) is a 19-*nor-*clerodane furanoditerpene glucoside with a C-3/C-4 double bond, and hence, no C-19 carbon. Phytochemical investigations on

![Chemical structures of various compounds](image)

the aerial parts of *Tinospora crispa* led to the isolation of several new *cis-*clerodane type IV furanoditerpene glycosides (e.g., **950, 966, 967**). In addition, spectroscopic assignments of a previously reported compound, borapetoside A (**947**), were revised on the basis of HMQC and HMBC correlations. Type IV glucoside **968** adopted a unique all boat conformation of its tricyclic ring system, as also indicated by energy calculations.

Compounds **970** and **973** are type IV 18-*nor-*clerodane glucosides, whereas **971** and **972** are 18,19-*dinor-*clerodane-type diterpene glucosides. Compounds **970–972**, isolated from *Tinospora sinensis*, were subjected to an α-glucosidase inhibition assay, and exhibited IC₅₀
values of 2.9, 3.8, 3.3, and 1.9 mM, respectively. Meanwhile, the positive control, acarbose, demonstrated an IC$_{50}$ value of 0.84 µM. Compounds 974–976 are three new type V 19-nor-neo-clerodane diterpene glucosides. Compounds 978–981 are described by a novel macrocyclic skeleton containing an neo-clerodane diterpenoid moiety, one or two d-glucose units, and a 3-hydroxy-3-methylglutaric residue. Two long nine-atom extended strands are connected by two “cyclohexane-chairlike” two atom junctions to create a unique three-dimensional construction. The structure and the absolute stereochemistry of 978 were elucidated through a combination of spectroscopic techniques, degradation reactions, and conformational analysis methods. Compound 978 inhibited high density induced apoptosis in several human and murine carcinoma cell lines.

2.9. Clerodane derivatives

2.9.1. N (or S or Cl)-containing derivatives (Table 29 – compounds 982–1054 found in ESI†) — Compounds 982 and 983 from Polyalthia longifolia contain a succinic diamide moiety attached at C-12; the former compound also has a double bond between C-13 and C-14. Other N-containing clerodane diterpenes have a heterocyclic group attached at the terminal carbon (C-15) of a 3-methyl-3-pentenyl side chain. For example, when the marine sponge Agelas axifera was investigated for cancer cell growth inhibitory constituents, pyrimidine diterpenes (e.g., 986) were isolated. Other compounds from Agelas species possess both a 9-N-methyladenine moiety at C-15 as well as a 2-carboxy-4-bromopyrrole linked through an ester at C-18 (e.g., 990), whereas compound 991 with a C4/C18 exocyclic methylene has only the former moiety. Scutellaria barbata is a major source of neo-clerodane diterpenoid alkaloids. Nicotinic acid (also known as niacin or vitamin B3) is a frequent N-containing component of ester groups found at various positions on the decalin, as shown in the following examples: 994–995 (mentioned in Section 2.3.1.3.), 998, 1008, 1012.
Two similar \( N \)-containing clerodanes (1013 and 1014) were isolated from \( P. \) longifolia.\(^{362}\) The former compound has a molecular weight two units greater than the latter, consistent with a pyrrolidine-15,16-dione in 1013 and a \( 1H \)-pyrrole-15,16-dione attached at C-12 in 1014. New clerodanes 1015–1021 with either a dihydro-\( 2H \)-pyrrol-15-one, dihydro-\( 2H \)-pyrrol-16-one, or \( 1H \)-pyrrole-15,16-dione at C-12 were isolated from Echinodorus macrophyllus and Casearia sylvestris.\(^{218,373,374}\) Compounds 1022–1024 isolated from the twigs and leaves of Cleidion brevipetiolatum have a type IV clerodane skeleton with an infrequent methylsulfinyl group present at C-3.\(^{375}\) Rare \( \text{Cl} \)-containing clerodanes 1025 and 1026 were isolated from Teucrium pernyi and \( T. \) racemosum, respectively.\(^{376,377}\) The Cl is part of a chlorohydrin in both compounds, with the \( \text{CH}_2\text{Cl} \) at C-17 in 1025 and at C-18 in 1026. Because they were present in acetone extracts of the plant material, these two compounds were not regarded as artifacts of the isolation procedure.

Other compounds with nicotinoyl esters were isolated from \( S. \) barbara as described below. Compound 1031, with an \( \alpha \)-configuration of the ethoxy group, is the epimer of 1030.\(^{370}\) Compared with 1033, compound 1032 lacks a 13-spiro-15,16-\( \gamma \)-lactone moiety, as the result of oxidative cleavage between C-13 and C-14.\(^{368}\) NMR spectroscopy confirmed the presence of hydroxy and hydroxymethyl groups at C-13 in 1032, as well as the absence of carbon signals for C-14 and C-15. The originally reported structures of 1036–1043 were revised.\(^{366}\) The absolute stereochemistry \( 1R,5R,6R,7S,8R,9R,10R,13S \) was assigned to compounds 1045 (1048) and 1049, whereas compound 1050 has the same \( 5R,6R,7S,8R,9R,10R,11S,13R \) absolute configuration as 1051.\(^{379}\) Barbatine A (1050) also showed significant capability to protect cells against \( \text{H}_2\text{O}_2 \) with an \( \text{ED}_{50} \) value of 16.8 \( \mu \)M.\(^{379}\) Barbatellarine C (1053) is a C-13 epimer of...
barbatellarine D (1054), as confirmed by a NOE difference experiment and the respective NOESY spectra.

2.9.2. Degraded derivatives

Compounds in this subtype have fewer than the normal 20 carbons of the basic clerodane skeleton. Firstly, in pentandranic acid B (1055) from *Callicarpa pentandra*, a new contracted ring-A (cyclopentanone rather than cyclohexanone) is present.98 Secondly, various one-carbon substituents can be absent, primarily, but not exclusively, C-18 or C-19. Compounds 1056–1061 are rare 18-nor-clerodane diterpenoids with a C-4 oxo or hydroxy group.258,293,380,381

19-nor-Clerodanes constitute the majority of the degraded clerodanes, and the following examples come primarily from *Croton* and *Teucrium* species. One of the simplest 19-nor-clerodanes is cajucarin B (1062) isolated from *Croton cajucara*.158 The 19-nor-clerodane 1063 with a C-5/C-10 double bond could be formed by a retro Diels–Alder reaction.170 Except for an opened 17,12-γ-lactone ring and C-12 oxidation, compound 1064 from *Croton euryphyllus* is quite structurally similar to 1070 and 1071, which have a butenolide moiety spanning C-19 to C-6, from *Teucrium viscidum*.278,382 Crassifolin H (1073) from *C. crassifolius* has a similar structure except for the presence of a C-5/C-10 rather than C-4/C-5 double bond.387 It demonstrated anti-angiogenic activity by reducing vessel formation to 59.3% of the control value at a concentration of 15 μg mL\(^{-1}\). Notably, the bioactive type V 19-nor-clerodane-type diterpenoid trans-dehydrocrotonin (1076), with a cyclohexenone decalin ring A, is one of the most investigated clerodanes in the current literature.389 Two of the three hydroxy groups in syspiresin A (1078) from *T. chamaedrys* are replaced by hydrogen (C-2) and a methoxy group (C-6) in teupolin IX (1079) from *T. polium*.92,277 Crotoeurin A (1084) from *C. euryphyllus* was the first nor-clerodane diterpenoid dimer connected through a unique cyclobutane ring via a [2 + 2]
cycloaddition; its structure was confirmed by single-crystal X-ray diffraction analysis.\(^{382}\)

Compound \(1085\) is a 14,15,16-trinor-clerodane isolated from \(Sindora sumatrana\).\(^{163}\) Isolated from several different plant species, compounds \(1086-1089\) are unusual 14,15-bisnor clerodanes with a C-4/C-5 double bond,\(^ {44,79,219,391}\) and compounds \(1090-1096\) are 13,14,15,16-tetranor-clerodanes. Among the latter tetranor-clerodanes, C-12 is present as a free carboxylic acid (e.g., \(1090-1092\))\(^ {227,342}\) or as part of a lactone ring. Croinsulactone (\(1093\)) from \(C. insularis\) contains a 12,13-\(\gamma\)-lactone with a spiro-carbon at C-9,\(^ {132}\) while ciliatolide A (\(1094\)) from \(Scapania ciliata\) contains a 12,10-\(\gamma\)-lactone as well as a 14,6-\(\gamma\)-lactone (the latter ring is comparable with a 18,6-\(\gamma\)-lactone in a non-degraded clerodane).\(^ {191}\) Teucrolin D (\(1095\)) and teucrolivin F (\(1096\)) from \(T. oliverianum\) also contain a 12,10-\(\gamma\)-lactone as well as a 4,14-spiro-oxirane (identical to a 4,18-spiro-oxirane in a non-degraded clerodane).\(^ {133,146}\) Compound \(1097\) from \(Jamesoniella colorata\) is a degraded clerodane (rearranged drimane)-type sesquiterpenoid.\(^ {392}\)

**2.9.3. Ring-seco**

derivatives\(^ {75,108,119,121,128,131,144,155,187,250,252,263,270,393-398}\) (Table
31 – compounds 1098–1145 found in ESI†—seco-Derivatives have an opened ring at some point in the structure, creating multiple interesting compounds, depending on which bond is broken and what additional rearrangements are present. The first examples are 9,10-seco-clerodane diterpenoids. Although the configuration of the C-8/C-9 epoxide in jamesoniellide F (1098) from the liverwort Jamiesoniella autumnalis could not be determined absolutely by NMR, this 9,10-seco-clerodane likely is a biogenetic product of cis-clerodane found in the same plant. Salvianduline A (1102) and pyrrhopappolide from Salvia lavanduloides and Microglossa pyrrhopappa, respectively, are both 9,10-seco-clerodanes, but contain a 17,12-δ-lactone and a 20,12-γ-lactone, respectively. Compound 1111 is a 9,10-seco-clerodane with a fully saturated benzofuran rather than decalin bicyclic skeleton. Among several compounds of this type from Cephaloziella kiaeri, cephaloziellins H and I (1115–1116) are C-8/C-10 hemiketals, while one additional degree of unsaturation in cephaloziellin J (1117) was indicative of a second ether bridge between the C-10 ketal carbon and the C-11 oxygenated methine. Furthermore, in cephaloziellin K (1118), the hemiketal bridge found in 1115 and 1116 is absent. Both jamesoniellides B (1121) and A (1120), from J. autumnalis, have a C-8/C-10 ether bridge; however, the B-ring in the former compound is opened between C-9 and C-10, while that in the latter compound is fragmented between C-8 and C-9.

In various 5,10-seco-neo-clerodanes, the unsaturated patterns of the “opened” decalins include 2,4,10(1)-triene (cyclodeca-1,3,5-triene) (e.g. 1122), 10-oxo-2,4-diene (cyclodeca-3,5-dien-1-one) (e.g., 1123), and 1,3,5(19)-triene (5-methylenecyclodeca-1,3-diene) (e.g., 1124) conjugated systems. Salvimicrophyllin A (1122) from S. microphylla was unstable in solution and decomposed on exposure to light and heat. The relative configuration of salvimicrophyllin B (1123) was confirmed by single-crystal X-ray diffraction crystallography. The epimeric hemiacetals 1125/1126 and acetals 1127/1128 could not be separated when isolated from Conyza welwitschi. Compounds 1132 and 1135 from Conyza and Dodonaea species, respectively, have the same ethylfuran side chain at C-9 but different double bond patterns in the cyclodecane ring, 1,3,5(19) and 2,4,10(1), respectively. Tonalensin (1136) from S. tonalensis is an interesting 5,10-seco-neo-clerodane containing an acetal at C-20 with oxygens from C-7 and C-11 forming two fused tetrahydrofuran rings. Its trans,cis,cis-cyclodecatriene ring adopts a boat-chair conformation in which the Δ1,3,5-triene system is no longer coplanar.
Tinosporafuranol (1137) and tinosporafuranadiol (1138), obtained from the stem bark of *Tinospora cordifolia*, are 4,5-seco-clerodane-type diterpenoids. The single-crystal X-ray diffraction analysis of 5,6-seco-compound 1139 established a 5α-configuration for the C-19 acetoxymethylene group, as well as the absolute stereochemistry. In the crystalline state, the substituted cyclohexane ring of 1139 is in a chair conformation, with a mean torsion angle of 57°. Both rhyacophiline (1140) and salvireptanolide (1141) from *S. rhyacophila* and *S. reptans*, respectively, have novel skeletons characterized by cleavage of the C-5/C-6 bond and aromatization of the A-ring. Compound 1140’s structure was fully established by spectroscopic and X-ray diffraction analyses. Jamesoniellide J (1142) from *J. autumnalis* is a seco-clerodane diterpenoid cleaved between C-8 and C-9.
2.9.4. Rearranged derivatives — The clerodanes in this group have a vast scope of ring numbers, sizes, and fusions. The “usual” decalin systems are especially affected, but rearranged C-9 side chains also occur. In various abeoclerodane diterpenes with a (4→2) rearranged ring A moiety, C-3 is generally an aldehyde (e.g., 1149) or carboxylic acid (e.g., 1152) attached to the five-membered ring A. However, compound 1146 from Solidago altissima is also a homoditerpene with 21 carbons [a methyl (C-21) is attached to a C-3 oxo group] and could have resulted from reaction of a C-3 aldehyde with diazomethane used to esterify the extract. In addition to the rare contracted ring A, pentandranoic acid A (1153) from Callicarpa pentandra also contains an 12-oxo-13(16)-methylene in a C-9 pentanoic acid side chain rather than the C-9 ethyl-α,β-unsaturated-γ-lactone of pentandralactone (1154), also found in the same plant. Compound 1155 was isolated from Polyalthia viridis as a 1 : 1 mixture of C-16 epimers.

Compounds 1157–1160 contain an expanded seven-membered A-ring where C-19 is inserted between C-4 and C-5. In 1157 from Portulaca pilosa, this novel bicyclo[5.4.0] undecane trans-clerodane skeleton also has an ether bridge at C-3→C-5 in the A-ring. Scapanialide B (1160) from Scapania parva is the first cis-clerodane diterpenoid with a bicyclo[5.4.0] undecane skeleton isolated from liverworts. Compounds 1161–1163 from two Salvia species also contain a seven-membered A-ring; however, this ring includes C-6, rather than C-19. In addition, C-11 has been inserted between C-8 and C-9, creating a phenyl B-ring fused to a γ-lactone, in a tricyclic skeleton.

Notably, compounds 1164–1166 from three different Salvia species have a novel rearranged A/B ring spiro-fused neo-clerodane skeleton with the spirocyclic junction at C-10. The structure of spiroleucantholide (1164) might be derived biogenetically by a ring contraction of the seven-membered ring in a precursor benzocycloheptatriene skeleton to form a spiro-fused junction. This report was the first to identify a spiro-6/6 A/B ring diterpenoid derived from a neoclerodane skeleton.
Compounds 1167–1171, also from various *Salvia* species, contain a salvigenane skeleton with a seven-membered B-ring, which contains C-11 inserted between C-8 and C-9. Like in 1161–1163, a fused γ-lactone is also present. However, the A/B ring sizes are 7/6 in 1161–1163, but 6/7 in 1167–1171.

X-ray crystal structure determination of blepharolide A (1172) showed a 5,6-unsaturated octahydro-1H-cyclopropa[α] naphthalene derivative, which presented a new rearranged clerodane structure with a C6–C6–C3 ring system. This new skeleton was named isosalvigenane. The isolation of salvigenane (blepharolide B, 1167) and isosalvigenane (blepharolide A, 1172) diterpenoids from *Salvia blepharophylla* suggested a botanical chemotaxonomic relation between sections Fulgentes, Albolanatae and Brandegeia of subgenus Calosphae. Tilifodiolide (1173) from *Salvia dugesii* was the first natural product with a substituted tetralin skeleton; its unusual structure was confirmed by X-ray diffraction analysis. A biogenetic derivation of both 1173 and the co-isolated 1161 from a clerodane precursor was postulated.

The rearranged clerodane diterpenes baenzigerides A (1174) and B (1176) and the related open-ring glucosides, baenzigerosides A (1175) and B (1177), were isolated from the stems of *Tinospora baenzigeri*. The novel skeleton of baenzigeride A (1174) could be produced from the cis-ent-neoclerodane epoxide (A) (Scheme 2). Rearrangement with ring-A contraction through migration of either the 1–2 or 3–4 bond would give the aldehyde (B). Reduction of B should give the primary alcohol (C), which could lactonize to 1174. Although epoxides such as (A) have not been found as natural products, the known clerodane 2,3-epoxides, e.g., jateorin, do have a 1,18-lactone group.408
The vapor and condensed solid resulting from heating salvinorin A (9) to 245 °C for 10 min were combined as a chloroform extract, from which two new rearranged clerodanes (1178–1179), were isolated. The major structural changes to 9 were epimerizations at C-2 and C-8, eliminations of acetoxy and methyl ester groups, and carbon–carbon rearrangements at C-1, C-2, and C-10. Compounds 1178 and 1179 are unique salvinorin derivatives with interlocking five-membered cyclopentane and six-membered anhydride rings; the 3-oxabicyclo[3.2.1]octane-2,4-dione systeme was confirmed by X-ray analysis.²⁷¹

Microphyllandiolide (1180) from *Salvia microphylla* represents the first example of a new framework with a 9/3 bicyclic ring system (microphyllane skeleton). A plausible biogenetic pathway to this new skeleton arises from proposed transformations of other neo-clerodane diterpenes isolated from *Salvia* species, involving pericyclic reactions. As shown in Scheme 3, an electrocyclic opening of the decalin ring of the diene (a) would give the triene (b). Cyclopropanation of (b) would give (c), and finally, allylic oxidation of (c) would provide the C-3 hydroxy group of 1180.⁴¹⁰

Compound 1181 from *Teucrium betonicum* is a biogenetically unexpected diterpenoid with a new 7β-homo-19(5→18)abeo-neo-clerodane skeleton.⁴¹¹ Its structure was established by spectroscopic means, including an X-ray diffraction analysis.
Both *Microglossa pyrrhopappa* (e.g., 1182, 1186) and *Pteronia divaricata* (e.g., 1190) provided rearranged clerodanes with a 2-oxabicyclo[2.2.1]heptan-3-one system most likely formed by Wagner–Meerwein rearrangement; compound 1182 also has a 7,8-epoxide.\(^75,128\)

Ring-A of 1194 (*M. pyrrhopappa*) and 1195 (*P. incana*) is a cyclopentene ring substituted with hydroxymethyl (C-3), and the former compound has an additional hydroxy group at C-6.\(^75,128\)

Pteroniatrilactone (1198) from *P. eeni* has the same rearranged carbon skeleton as 1186 with the addition of a third lactone between C-2 and C-19 (OC=O). An inseparable mixture of related 3:1 epimeric hemiacetals 19-α- and 19-β-hydroxypteronia dilactone (1196, 1197) was also isolated.\(^75\)

Eenioliolide (1199), also from *P. eeni*, was probably formed biogenetically from an 8,10-dihydroxyclerodane diterpenoid, with cleavage of the C-9/C-10 bond and formation of a C-9/C-8 double bond, followed by ring-A/B reclosure at C-17/C-10.\(^75\)

Jamesoniellide C (1200) with the same side chain (furanymethylene-dihydrofuranone) as 1199 but a 5/6 rather than 6/6 skeleton was isolated from the liverwort *Jamesoniella autumnale* along with the interesting 8,9 and 9,10-seco-clerodanes 1120 and 1121 (see
Compounds 1201–1206 with a novel rearranged tetrahydrobenzofuran fused to the decalin through a C8–C16 bond were isolated from Teucrin alyssifolium. Although 1205 and 1206 were structurally quite similar to 1201–1204, the presence of a C-7/C-19 hemiketal bridge in the former compounds was the main difference between these two related groups. Salvilanguiduline A (1207) from Salvia languidula illustrates a rearranged clerodane skeleton containing an epoxy spiro γ-lactone function and a C1–C13 bond. The structure of the rearranged clerodane cephaloziielin O (1215) isolated from the Chinese liverwort Cephaloziella kiaeri was confirmed by single-crystal X-ray diffraction analyses, and the absolute configurations of 16 new clerodane diterpenoids, cephaloziiellins A–P, were established by comparing experimental and calculated electronic circular dichroism spectra.

Teucrium brevifolium yielded several clerodanes containing an unusual rearranged skeleton with an eight-membered ring carbocycle (e.g., 1217, 1219, 1221). The ring conformation in each compound was established by exhaustive NMR spectroscopic studies as well as X-ray data on 1221. A biogenetic pathway from teubrevin D (747) was postulated to explain the formation of the 5,10-seco-9(8→19)abeo-neo-clerodane skeleton (1219, 1221) and the 7,8,17-trinor derivatives (1217). The leaves of Salvia xalapensis yielded two new clerodane-type diterpenoids with an opened (C5–C6) unsaturated ring-B skeleton, salvixaladiene (1223) and isosalvixaladiene (1224). Both compounds have a phenyl A-ring and two double bonds in the opened B-ring at C6–7/C8–11 and C7–8/C9–11, respectively. Their unprecedented rearranged skeleton may be derived biogenetically from a salvigenane precursor. Salvixalapoxide (1222) with a languardulane skeleton was also isolated at the same time.

### 2.10. NMR features of clerodane diterpenes

NMR spectroscopy, especially 13C NMR analysis, has been widely employed for the characterization of the different skeletons of clerodane diterpenes. The assignments of carbon signals of a new clerodane diterpene by comparison with the data of known compounds require the 13C data of appropriate model compounds. It would appear to be of value to provide an easy access to an extensive list of 13C data of these diterpenes. Inspection of the chemical shifts of different types of clerodanes revealed that the main differences among the seven structural types (I–VII) are related to the number of methyl groups (C-17 or C-20 are absent, in the IV and V structural types, respectively), and chemical shifts of C-8, C-12, C-17, and C-20. The characteristic spectroscopic features associated with these seven different structural types I–VII are summarized in Table 2.
Clerodanes that possess a furan ring at C-12 show carbon resonances between $\delta_{C} 123 \rightarrow 132$ (C-13), $\delta_{C} 107 \rightarrow 114$ (C-14), $\delta_{C} 138 \rightarrow 146$ (C-15), and $\delta_{C} 137 \rightarrow 148$ (C-16). In clerodane diterpenes containing a $\Delta^{3}$ double bond (C-3: $\delta_{C} 120 \rightarrow 130$; C-4: $\delta_{C} 130 \rightarrow 145$), the chemical shifts of these carbons are affected by the presence of the substituents at C-18. When this carbon contains a carboxyl or carboxymethyl group, C-3 ($ca. \delta_{C} 133$) and C-4 ($ca. \delta_{C} 149$), are deshielded. However, when C-18 is an aldehyde group, C-3 ($\delta_{C} 152.4$) and C-4 ($\delta_{C} 151.7$) are more deshielded. On the other hand, in clerodane diterpenes containing a $\Delta^{1,3}$ double bond and a carboxymethyl group at C-18, resonances occur between $\delta_{C} 133 \rightarrow 134$ (C-1), $\delta_{C} 123 \rightarrow 125$ (C-2), $\delta_{C} 132 \rightarrow 136$ (C-3), and $\delta_{C} 134 \rightarrow 137$ (C-4). In the structural type IV containing a $\Delta^{7}$ double bond, carbon resonances appear at $\delta_{C} 172$ (C-7) and $\delta_{C} 100$ (C-8). For compounds having a $\Delta^{4}$ double bond and C-18 as a methyl group, C-4 and C-5 resonate at $\delta_{C} 125.7$ and 134, respectively. If C-18 is part of a lactone ring, these carbons are deshielded [$\delta_{C} 127.6$ (C-4) and 162 (C-5)]. An epoxy ring at C-4 and C-18 leads to carbon signals at $\delta_{C} 63 \rightarrow 67$ (C-4) and $\delta_{C} 43 \rightarrow 51$ (C-18).
2.11. Abbreviation of functional groups

3. Biological activities

Clerodane secondary metabolites may benefit a plant species by acting as a chemical defense mechanism against phytophagous animals or diseases. Apart from insect antifeedant properties, several clerodane diterpenes display other effects against insects. Insecticidal activity has been reported for ajugarins I and IV.\textsuperscript{416,417} Ajugarin IV also displays insect growth regulating activity, as do 3-\textit{epi}-caryoptin\textsuperscript{418} and the 19-\textit{nor}-clerodanes \textit{cis}-and \textit{trans}-dehydrocrotonin.\textsuperscript{419} Fungicidal activity against plant pathogenic fungi has been reported for clerodin and the related jodrellins A and B.\textsuperscript{326}

Besides insect antifeedant and antifungal activities, many clerodane diterpenes possess various pharmacological activities beneficial to humans, including action as opioid receptor probes, as well as NGF-potentiating, anti-ulcer, cytotoxic, anti-inflammatory, antiparasitic, and antibacterial activities.
3.1. Insect antifeedant activities

3.1.1. Insect antifeedant and related plant protective activities of clerodane diterpenes—Clerodane-type secondary metabolites have attracted considerable attention as insect antifeedants, which is by far the most extensively studied bioactivity of these diterpenes. Clerodane diterpenoids have been found in several hundreds of plant species from various families and in organisms from other taxonomic groups, such as fungi, bacteria, and marine sponges.\textsuperscript{420–422} Especially, various genera from the plant families Lamiaceae have been identified as rich sources of antifeedant clerodanes, with species of the genus \textit{Scutellaria} producing some of the most potent clerodane antifeedants known so far.\textsuperscript{306,330,423–426} The most active compounds from these species against larvae of \textit{Spodoptera littoralis} (cotton leafworm) were scutalpin C (497), scutecyprol B (810), jodrellin A (860), jodrellin B (861), and dihydroclerodin (1225), with corresponding feeding index (FI) values of 92 ± 8, 100 ± 0, 95 ± 16, 100 ± 0, and 97 1, respectively. In addition, 810 showed potent activity against ± several other species of Lepidoptera.\textsuperscript{426}

Ajugractins A–E (855–856, 795–797) and 15-epi-lupulin B (821) were isolated from a dichloromethane extract of \textit{Ajuga bracteosa}.\textsuperscript{301} Among them, 795–797 and 821 showed moderately high antifeedant activities (FR = 0.14–0.15). Data analysis from the behavioral responses of \textit{S. littoralis} exposed to the clerodane diterpenoids hativenes A–C (827–829), from \textit{Ajuga pseudoiva}, showed that the all of the compounds tested had strong antifeedant activity at 100, 10, and 1 mg\textsuperscript{−1}, which began to dissipate at 0.1 mg\textsuperscript{−1}.\textsuperscript{317} Comparison of the antifeedant index at the latter two concentrations also indicated that a change in the relative configuration of carbons C-12 and C-15 did not modify the activity considerably. 14,15-Dehydroajugareptansin (859), from \textit{Ajuga reptans}, had significant activity against sixth stadium larvae of \textit{Spodoptera littoralis}.\textsuperscript{207} Overall, these data, compared to those of other clerodanes isolated from \textit{Ajuga} and \textit{Salvia} species, helped to clarify different authors’ suggestions and conclusions, which related the antifeedant activity of clerodanes to the presence of a perhydrofuranoferan moiety, a \textit{trans} decalin ring system bearing an epoxide, and acetate groups.

Clerodin (2), 15-methoxy-14,15-dihydroclerodin (1226), and 15-hydroxy-14,15-dihydroclerodin (1227) exhibited growth inhibitory activity against \textit{Helicoverpa armigera} (cotton boll-worm) with growth inhibition index (GI\textsubscript{50}) values of 13, 21, and 11 ppm, respectively, compared to azadirachtin, the active ingredient of many pesticides, with a GI\textsubscript{50} value of 15 ppm.\textsuperscript{427} Clerodin (2), clerodendrin B (849), 3-epicaryoptin (1228), and 15-hydroxyepicaryoptin (1229) were effective antifeedants at 10 μg cm\textsuperscript{−3} of diet against \textit{Earias vitella} and at 10 μg cm\textsuperscript{−2} of leaf against \textit{Spodoptera littoralis}.\textsuperscript{428} In addition, 2, 122, 849–850, 1229, and 2-acetoxyclerodendrin B (1230) showed good insect growth inhibitory activity,
even at lower concentrations. In contrast, clerodendrin H (851), from *Clerodendron trichotomum*, distinctly stimulated feeding activity in adult turnip sawflies.325

Jodrellins A and B (860–861) and the reference compound clerodin (2) also reduced the growth of the plant pathogenic fungus *Fusarium oxysporum* f. sp. *Lycopersici* after 18 h, and 861 and 2 maintained growth inhibition at 50 and 100 ppm after 66 h. Compound 2 delayed germination of *Verticillium tricorpus* spores at 25, 50 and 100 ppm after 42 h, and 861 had similar effects even at 66 h. This study suggests that certain neo-clerodane diterpenoids may contribute to antifungal, as well as anti-insect, protection in plants.326 Clerod-14-ene-3α,4β, 13ζ-tiol (1231) from *Viguiera tucumanensis* inhibited both germination and root growth of *Sorghum halepense* and *Chenopodium album* and also slightly inhibited *Ipomoea purpurea*.429 Allelopathic agents with phytogrowth inhibitory effects are attractive new leads for development of agrochemicals.

3.1.2. Compilation of structure–activity relationships of clerodane insect antifeedants—To date, over 300 natural and semi-synthetic clerodanes have been examined in laboratory assays, yielding several compounds with potent antifeedant activity against various insect species, but it is not known whether this activity will be retained under field conditions. A comprehensive compilation of all test results on the insect antifeedant activity of clerodane diterpenes resulted in some interesting trends based on only the 10–20% of the most active clerodanes per insect species.12,430

(i) Active clerodanes generally have a trans-decalin neo-clerodane skeleton.

(ii) In the most potent clerodanes, the C-9 side chain fragment contains an oxygenated ring system. A furofuran-based structure appears to be most favorable for strong activity against many Lepidopteran insect species. Furan and butenolide side chains are also frequently found in the most potent clerodanes,
and hydrogenation of these unsaturated moieties usually results in lower potency.

(iii) Structural elements from (i) and (ii) must be present simultaneously to produce high activity. However, a number of exceptions to this general observation are known. For example, while decalin 1233, which has the more common 4α-O-epoxide, but no C-9 side chain, was inactive against *L. migratoria*, the decalin 1232 with a 4β-O-epoxide showed equal antifeedant activity under no-choice conditions as the clerodin derivative 1234.12

(iv) In addition to (iii), the key structural elements from (i) and (ii) must be able to adopt a certain spatial orientation for the compound to exert high activity. Indeed, the stereoelectronic factors are more important than the hydrophobic aspects as determinants of antifeedant activity. In addition, a furan ring in the side chain and a carbonyl α,β-unsaturated (or spiro-epoxide) group appear to be crucial. A conformational study indicated that the optimum interatomic distance between these two moieties ranged from 9.5 to 10.5 Å.431,432

For example, bacchotricuneatin A (1235), 7α-hydroxybacchotricuneatin A (1236), 1237, azadirachtin (1238), and the D-ring aromatic withanolide 1239 exhibited remarkable feedant-deterrent activity against *T. molitor* with PFI values of 22.62, 26.60, 25.03, 29.57, and 29.89, respectively.431

(v) Both rings in the decalin fragment are often substituted with hydroxy, epoxy, or ester groups, but none of these moieties can be concluded to be essential for antifeedant activity. However, slight changes in the exact identities and orientations of such groups can affect the potency of the antifeedance effect.

The general observations in (i)–(v) represent a reasonable summary of the structural features involved in the overall antifeedant activity of clerodane diterpenes. However, the underlying mechanisms of insect antifeedant activity are certainly more complex than implied by this abridged picture.
3.2. Opioid receptor agonist

3.2.1. Salvinorin A as a probe in opioid pharmacology and other salvinorin analogues—The discovery of salvinorin A ([9] as the first non-nitrogenous natural product with high affinity and efficacy at the κ-opioid receptors (KORs or KOP receptors) led to a reevaluation of whether a basic nitrogen is necessary for opioid receptor affinity and efficacy. With similar potency to LSD, compound 9 is one of the most potent naturally occurring hallucinogens, and appears to have distinctive properties at KOR, including ultra-high efficacy in particular transduction systems and a lower tendency to cause receptor desensitization.433–442 In mice, it produces antinociception that can be blocked by KOR antagonists.443,444 It also produced an aversive response in the conditioned place preference assay,445 blocked the locomotor-stimulant effects of cocaine,446 and did not exert 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM)-like effects in nonhuman primates.447 Interestingly, compound 9 has low affinity for the μ-opioid receptor (MOR), although it does show allosteric MOR modulation.448 It exhibited deleterious effects on learning and memory, acting via a KOR mechanism.448–450

Phytochemical studies on S. divinorum led to the isolation of many clerodanes, including salvinorins C–J (659–662, 1240, 663–665), divinatorins A–F (405–407, 409–410, 1241), salvinicins A (684) and B (685), and salvidivins A–D (686–687, 587–588).166,167,235,263–266,273,451 (The structures of 409–410, 659, 686, 1240, and 1241 are specifically shown, the remaining compounds can be found in the Structure Tables in ESI†.) In a modification study of 9,
salvinorin C (659) had 250-fold lower KOR affinity compared with 9 (Ki = 1022 nM vs. Ki = 4 nM).452 Divinatorins D (409) and E (410) also had reduced KOR affinity compared with 9 (Ki = 230 nM and Ki = 418 nM, respectively, vs. Ki = 1.0 nM).167 Uniquely, salvidivin A (686) was identified as the first naturally occurring neoclerodane with KOR antagonist activity (Ke = 440 nM).453 Among dicarboxylic acid esters of 9, the methyl malonyl derivative (1242) showed the highest binding affinity (Ki = 2 nM), although analogues 1243–1245 still exhibited significant KOR affinity (Ki = 21, 36, and 39 nM).454 12-epi-Salvinorin A (1246), synthesized in four steps from 9, was a selective partial KOR agonist. It partially activated signaling through G proteins, yet acted as a full agonist in the β-arrestin 2 DiscoveRx assay.455,456

Of the derivatives of 9 reported to date, salvinorin B ethoxymethyl ether (EOM–SB) is the most potent. It exhibited ten-fold greater potency than 9 in vitro and in rodents, and had a longer duration of action in rodents.457–460 In addition, 22-thiocyanato-(RB–64) and 22-chloro-salvinorin A (RB–48) were both extremely potent and selective KOR agonists in vitro and in vivo.461

3.2.2. Structure–activity relationships of salvinorin A analogues—The general SAR studies of 9 have been performed by semi-synthetic structure modifications, and have mainly focused on 9’s high affinity and selectivity for the KOP receptor. Some of these analogues have interesting pharmacological profiles, from full KOR agonist to partial δ-opioid receptor (DOR) or μ-opioid receptor (MOR) agonists and antagonists.13,448,453,462–464 The SAR is summarized in Fig. 5.13,457,465–471

At the C-1 position, the reduction or removal of the carbonyl is tolerated, and introduction of a 1,10-alkene increases the possibility of antagonist activity.

At the C-2 position, (1) the size and electronegativity of the substituent at the C-2 position is critical for activity at opioid receptors. Bioisosteric replacements of the ester moiety are tolerated. (2) α-Substituents are preferred over the corresponding β-substituents. (3) In general, small alkyl esters favor binding to KORs. The compounds with methoxymethyl (1247) and ethoxymethyl (1248) ethers at this position are among the most potent 9-derived KOR agonists reported to date, while aromatic esters favor MOR binding.13,472 Different aromatic groups attached directly to the decalin core can be allowed by KOR.473

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At the C-4 position, (1) small alkyl chains are preferential for KOR binding, while (2) hydrolysis or reduction of the carbomethoxy group leads to reduced KOR affinity, and (3) conversion to an amide is generally not tolerated.\(^\text{13,472}\)

Furthermore, the furan ring at C-12 may be reduced or replaced, but KOR affinity is reduced. The reduction or removal of the carbonyl at C-17 and the introduction of an 8,17-alkene are tolerated.\(^\text{13,472}\)

Finally, degradation of the furan ring and/or replacement with other heterocycles is tolerated. Moreover, such a modification produced the first DOR selective ligand (1249) with the scaffold of 9.\(^\text{13,472}\)

### 3.3. NGF-potentiating activities

With EC\(_{50}\) values of 20.2, 12.7, 4.0 and 2.4 µg mL\(^{-1}\), balanspenes D–G (13–16), which have a 18,19-exoxy clerodane-type diterpene skeleton with an additional double bond at C-3 and C-4, markedly increased the nerve growth factor NGF (20 ng mL\(^{-1}\))-induced quantity of neurite-bearing cells.\(^\text{15}\) An equilibrium mixture of pychonal (380) and pychonal hemiacetal (329), 6α,7α-dihydroxyannonone (382), and 7α,20-dihydroxyannonone (383), significantly enhanced NGF-mediated neurite outgrowth in PC12 cells at concentrations ranging from 0.1 to 50.0 µM, 0.1 to 30.0 µM, and 0.1 to 10.0 µM, respectively.\(^\text{130,474}\) At 10, 30, and 100 µmol, compounds 435 and 436 had no effect on neurite outgrowth from PC12D cells in the absence of NGF, but at 100 µmol, decidedly increased the NGF (2 ng mL\(^{-1}\))-induced proportion of neurite-bearing PC 12D cells by 49% and 53%, respectively.\(^\text{174}\)
Both crotopenes A and B (764 and 765) exhibited potentiating activities on NGF-mediated neurite outgrowth from PC12 cells. At a concentration of 10 μM, degraded clerodane compounds 1064, 1083, and 1084 exhibited neurite outgrowth-promoting activity in NGF mediated PC12 cells.

13-epi-15,16-Epoxy-15α-methoxy-ent-clerod-3-en-18-oic acid (1250) and 15,16-epoxy-7α, 18-dihydroxy-15-methoxy-ent-clerod-3-ene (1251) also markedly increased the NGF (2 ng mL⁻¹)-induced proportion of neurite-bearing cells by 49%, 53%, and 68%, respectively.

3.4. Antiulcer activities

trans-Dehydrocrotonin (1076), trans-crotonin (1252), cordatin (1253), and aparisthman (1254) exhibited significant anti-ulcer activities, comparable with those of cimetidine. At a dose of 100 mg kg⁻¹ (p.o.), the four compounds significantly reduced gastric injury induced by stress (67% or 72%), indomethacin/bethanechol (29%, 78%, 71%, 78%, respectively), ethanol (71% or 76%), pylorus ligature (30%, 35%, 59%, 50%, respectively), and hypothermic restraint (50% or 66%) in mice and rats. In the HCl/ethanol-induced gastric ulcer model, at 100 and 250 mg kg⁻¹ (p.o.), gastric lesion formation was decreased by 48.1%, 52.3%; 50.8%, 55.8%; 70%, 59% and 77%, 66%, respectively, when compared to the control group. In the pylorus-ligature model, 1076 and 1252 (p.o.), like cimetidine, increased the volume of gastric fluid when compared to the control group, while 1253 and 1254 (p.o.) decreased the volume of gastric fluid. Compound 1076 exhibited low acute toxicity in mice (LD₅₀ 876 mg kg⁻¹) when administered orally, however, hepatotoxicity resulted from its long-term use.

3.5. Cytotoxic activities

Casearupestrins A (21), B (22) and D (24) showed significant cytotoxicity against four cell lines (HL-60, HCT-8, MDA/MB-435, and SF-295), with IC₅₀ values ranging from 0.10 to 1.3 μM.
Intrapetacins A (38) and B (39) displayed moderate cytotoxicity against KB cells, with IC$_{50}$ values of 2.0 and 0.8 μg mL$^{-1}$ \cite{21}. In addition, compound 39 caused a significant (21 mm) zone of inhibition of fungal growth. Bioassay-guided fractionation of the EtOAc extracts of *Casearia membranacea* afforded case-amembrins A–E (60–64), M–O (65–67), and caseamembrols A (119) and B (68) as active principles. Compounds 60 and 62–64 exhibited cytotoxic activity against PC-3 and Hep 3B, with IC$_{50}$ values below 3 μM. Compounds 66 and 67 showed significant activity against KB, DLD-1, and Med tumor cell lines (1.94–8.94 μg mL$^{-1}$). Compounds 119 and 68 were cytotoxic against PC-3 human prostate cancer cells with IC$_{50}$ values of 2.45 and 5.66 μM, respectively.\cite{28}

Laetiaprocerines A–D (101–103, 274) were cytotoxic toward the MCF7 human tumor cell line. The structurally similar zuleanin-type compound caseamembrin G (1255) was cytotoxic against KB, HeLa, and Hep59T/VGH carcinoma cell lines.\cite{483}

Esculentin B (95) from *Casearia esculenta* and caseargrewiins A–H (74, 1256–1258, 104–107) from *C. grewiifolia* showed significant cytotoxicity against three cancer cell lines (KB, BC1, and NCI-H187) with IC$_{50}$ values ranging from 0.1 to 8.7 μg mL$^{-1}$\cite{31,37}. The most potent compounds were 104 and 106.
against KB (IC$_{50}$ 0.66, 0.67 μg mL$^{-1}$), 1258, 95, 105, and 107 against BC1 (IC$_{50}$ 0.1, 0.17, 0.20, 0.21 μg mL$^{-1}$), and 104 and 1257 against NCI-H187 (IC$_{50}$ 0.15, 0.3 μg mL$^{-1}$), respectively, similar values to those for the control drug ellipticine. Bucidarinas A–C (133–135) showed potent cytotoxicity against nine human tumor cell lines with IC$_{50}$ values ranging from 0.5 to 1.9 μM.$^{14}$

Compound 203 from Brazilian propolis reduced the incidence of skin tumors by inhibiting DNA synthesis via a de novo pathway, and suppressed the tumor growth by decreasing DNA synthesis via a salvage pathway.$^{69}$ Premnones A–C (234–236) exhibited cytotoxic activity when evaluated against three human cancer cell lines (Lu1, LNCaP, and MCF-7), and one normal cell line (HUVEC) in the range of ED$_{50}$ of 0.7–7.0 μg mL$^{-1}$.$^{80}$
However, 234 was not active when evaluated in a follow-up in vivo hollow fiber assay at the highest dose tested (50 mg kg\(^{-1}\)), using LNCaP, Lu1, and MCF-7 cells.

Crispene E (468) inhibited STAT3 dimerization in a cell-free fluorescent polarization assay and displayed significant toxicity against the STAT3-dependent MDA-MB 231 breast cancer cell line with selective inhibition of the expression of STAT3 and STAT3 target genes cyclin D1, fascin and bcl-2.\(^{190}\) Ajugalide B (507) exhibited broad spectrum antiproliferative activity against A549, AGS, HepG2, and HT29 human cancer cell lines, with GI\(_{50}\) values ranging from 3.18 to 5.94 μM.\(^{384}\) Below its cytotoxic concentration, 507 also reduced the tumorigenic and metastatic ability of A549 cancer cells by inhibiting anchorage-independent growth and cell migration; thus, 507 could be a lead for development of potential cancer chemotherapy.

Clerodermic acid (548) induced potent apoptosis against human leukemia HL60 cells.\(^{485}\) Compounds 590, 609, and 1260 from Polyalthia barnesii exhibited their highest potency against LNCaP and U373 cell lines, but generally showed broad spectrum cytotoxicity, with ED\(_{50}\) values of less than 4 μg mL\(^{-1}\) toward several cell lines.\(^{237}\) Scutebata L (597) exhibited moderate activity against several human cancer cell lines with IC\(_{50}\) values ranging from 12.6 to 26.1 μM.\(^{231}\) Calcicolins A (598) and C (600) showed significant cytotoxic effects against the D.mel-II and HepG2 cell lines with IC\(_{50}\) values of 2.06, 2.10, and 9.04, 8.30 μg mL\(^{-1}\), respectively.\(^{242}\) Calcicolin B (599) also showed good toxicity against D.mel-II cells (IC\(_{50}\) = 3.09 μg mL\(^{-1}\)) but was not as potent against HepG2 cells (IC\(_{50}\) = 16.16 μg mL\(^{-1}\)).\(^{242}\) Echinoclerodane A (614) exhibited moderate cytotoxicity against MOLT-4, HL-60, DLD-1 and LoVo tumor cells and inhibited superoxide anion generation and elastase release by human neutrophils.\(^{248}\) Tinosporin A (643) showed low cytotoxicity against HL-60 and MCF-7 cells, with IC\(_{50}\) values of 18.63 and 23.58 μM, respectively.\(^{256}\) Crotonlide A (713)
exhibited moderate cytotoxicity against HL-60 (IC$_{50}$ 9.42 μM) and P-388 (IC$_{50}$ 7.45 μM) tumor cell lines.$^{165}$

Many neo-clerodane diterpene alkaloids from *Scutellaria barbata* showed significant cytotoxic activity against three human cancer lines (HONE-1 nasopharyngeal, KB oral epidermoid carcinoma, and HT29 colorectal carcinoma cells) (IC$_{50}$ 2.0–8.1 μM) in various studies.$^{230,232,233,367,370,371,378}$ Examples are shown below (1001, 1004, 1027, 1034, 1052) as well as in prior Section 2.9.1 (998, 1008, 1009, 1012, 1030, 1031, 1036–1042).

The rearranged clerodane polylongifoliaic A (1156) exhibited potent activity against SK-N-MC human neuroblastoma cells with an IC$_{50}$ value of 1.64 μM.$^{220}$ 16-Oxo-cleroda-3,13(14)-E-dienl5-oic acid (1259)$^{486}$ and polyalthialdoic acid (189) showed antiproliferative activity against human leukemia HL-60 cells, with IC$_{50}$ values of 13.7 and 21.8 μM, respectively, compared with 5-fluorouracil’s IC$_{50}$ of 9.5 μM.$^{60,487}$

Table 3 lists cytotoxicity results found for casearins A–R (1261–1278) against V-79 cells.$^{488,489}$ Three compounds without an oxygenated substituent at C-6, casearins G (1267), H (1268) and I (1269) showed the highest potency (IC$_{50}$ 0.17–0.51 μM). Casearins J (1270) and K (1271) with a hydroxy moiety at C-6 exhibited similar or slightly weaker activity (IC$_{50}$ 0.52 and 1.1 μM, respectively) than 1267–1269. Casearins L (1272) and M (1273) have a hydroxy moiety at C-7 rather than C-6, and showed slightly reduced activity (IC$_{50}$ 1.6 and 1.8 μM, respectively). Casearin C (1263), with an interesting decanoate at C-7 exhibited significant potency (IC$_{50}$ 0.77 μM), while a related compound, casearin E (1265) with the same decanoate group but slightly different oxygenated substituents at C-6 and C-18 was much less potent (IC$_{50}$ 4.7 μM). The authors postulated that the greater hydrophobicity of 1263 might increase its affinity for the V-79 cell membrane leading to significant activity. Furthermore, casearins A (1261) and D (1264) were converted to derivatives A$_{a}$ (1279), A$_{b}$ (1280), A$_{c}$ (1281) with oxo, propionate, and butanoate groups, respectively, at C-6 and D$_{a}$ (1282) with oxo groups at both C-2 and C-6. Only compound 1279 retained cytotoxic potency (IC$_{50}$ 0.55 μM); compounds 1280–1282 had greatly reduced activity (IC$_{50}$ 17, 38, 19 μM, respectively). Thus, the bulkiness of the C-6 group could greatly influence the activity.$^{489,490}$ In other studies, the structurally similar casearin X (1283) and caseargrewiin F (105), which do not have an oxygenated group at C-7, showed cytotoxic activity against MOLT-4, MDA-MB-435, HCT-8, and SF-295 human cell lines, with IC$_{50}$ values from 0.22 to 0.97 and 0.09 to 0.17 μM, respectively. Their lower cytotoxicity against L-929 cells (IC$_{50}$ 1.52 and 1.06 μM) perhaps indicated a more selective cytotoxic response to tumor cell lines.$^{490}$ Other zuleanin-type clerodanes, case-arvestrins A–C (87–89), had comparable IC$_{50}$ values between 0.2 and 0.8 μM against a panel of tumor cell lines, including LX-1, HCT116, and A2780.$^{34}$
Mechanistic investigations showed that 1264 can protect DNA against different types of damage and act as an antioxidant by inducing detoxificant enzymes in HepG2 cells; these actions give rise to interesting chemopreventive characteristics in both HepG2 cells and the *Salmonella typhimurium* bacterial strain.\(^{491}\) Finally, casearin X (1283) showed potent cytotoxic effects against CEM and HL-60 lines (IC\(_{50}\) 0.4 μM) and PBMC cells (IC\(_{50}\) 1.2 μM) and caused cell death via apoptotic pathways. These data further substantiated the promising antitumor-related properties of casearins.\(^{492}\) In addition, 1283 exhibited chemopreventive activity against DNA damage induced by the particulates formed from burning sugarcane, which implied that 1283 can act by different mechanisms to protect DNA against damage, including repairable and non-repairable damages.\(^{493}\)

Compounds 1284–1286 showed potent and selective cytotoxicity against P-388, A-549, HT-29, Mel-28 cell lines, with IC\(_{50}\) values of 0.2–2.4 μM.\(^{494}\) (−)-Kolavenol (1287) increased lifespan (I.L.S.) in mice with IMC carcinoma, and was twice as effective (I.L.S. 98%, 41 mg per kg per day, 4 days) as 5-FU (46%, 30 mg per kg per day, 4 days).\(^{495}\) (−)-7β-Acetoxy-15,16-epoxycleroda-3,13(16),14-trien-18-oic acid (1288) strongly inhibited P-glyco-protein and likely has promise for development as an MDR-reversing agent.\(^{496}\) (5\(R\), 10\(R\))-4\(R\),8\(R\)-Dihydroxy-2\(S\),3\(R\):15,16-diepoxycleroda-13(16),17,12\(S\):18,1\(S\)-dilactone (1289) exhibited a preventive effect against chemically-induced hepatocellular carcinoma (HCC) in rats, and could be a potent chemopreventive drug for HCC.\(^{497}\)

\(\text{trans-Dehydrocrotonin (1076) and trans-crotonin (1252)}\) (see structures in Section 3.4) were evaluated for their effects on the survival of mice bearing Sarcoma 180 and Ehrlich
carcinoma ascitic tumors, as well as the proliferation of cultured Ehrlich cells and TNFα activity. When the mice were treated with 80 and 120 mg kg\(^{-1}\) of 1076 or 38 mg kg\(^{-1}\) of 5-FU, substantial antitumor activity was observed (%T/C 128–140). Both compounds showed a cytotoxic value of 16 μM against Ehrlich carcinoma in 48 h cell culture. In vitro electrophoresis of DNA extracted from the treated tumor cells showed no apoptosis. But significant TNFα activity was detected in Ehrlich tumor-bearing mice treated with 1076, likely due to enhanced immune function.498

3.6. Anti-inflammatory activities

The hallucinogenic compound salvinorin A (9) (see structure in Section 3.2) is a potent KOR agonist. However, its multiple pharmacological effects are likely due to action on other targets, such as the cannabinoid CB1 receptor (CB1R). For instance, it exerted potent anti-inflammatory and antinociceptive effects, as mediated by KOR and CB1R,\(^{499}\) and thus, is an interesting new lead compound for the development of novel anti-inflammatory agents targeting KOR and CB1R. This observation also encourages further studies on 9 leading to the development of novel peripherally restricted derivatives with similar potency and selectivity. Thus, 9-related compounds may be useful future drugs, especially in patients with inflammatory bowel disease, in which pain is the most pronounced symptom during maintenance of remissions.\(^{500}\)

Compound 485 inhibited LPS-induced NO production in BV-2 cells dose-dependently with an IC\(_{50}\) value of 28.6 ± 2.6 μM.\(^{194}\) Tinospinosides B (956) and C (957) also showed inhibitory effects against NO production.\(^{355}\)

\(E\)-Isolinaridial (1290) and \(E\)-isolinaridial methylketone (1291) inhibited human synovial sPLA\(_{2}\) in a concentration-dependent manner with IC\(_{50}\) values of 0.20 and 0.49 μM, respectively, similar to that of scalaradial, an anti-inflammatory marine natural product that selectively inhibits 14 kDa type II phospholipase A2 (PLA2).\(^{501}\) In addition, these compounds reduced cell-free 5-lipoxygenase activity and A23187-induced neutrophil LTB4 biosynthesis, and significantly decreased receptor-mediated degranulation. 6-Oxocleroda-3,13(14)\(E\)-dien-15-oic acid methyl ester (1292) and 16-hydroxy-cleroda-3,13(14) \(E\)-dien-15-oic acid (1293), displayed significant activity against fMLP/CB induced superoxide generation by neutrophils with IC\(_{50}\) values of 0.6 ± 0.09 and 1.49 ± 0.28 μg mL\(^{-1}\), respectively.\(^{246,436}\) The suppressive effects of 1293 on human neutrophil respiratory burst and degranulation were due, at least partially, to inhibition of calcium, AKT, and p38 signaling pathways.\(^{457,502}\) 3β,4β:15,16-Diepoxy-13(16),14-clerodadiene (1294) and thysaspathone (365) inhibited NO production in LPS-stimulated RAW 264.7 cells with IC\(_{50}\) values of 20.1 and 11.6 μM, respectively.\(^{143,438}\)
3.7. Antiparasitic/antiprotozoal activities

Caseargrewiins A–D (74, 1256–1258, see structures in Section 3.5) were active in vitro against Plasmodium falciparum in vitro, with respective IC$_{50}$ values of 2.9, 2.4, 3.0, and 3.3 μg mL$^{-1}$. Clerodane diterpenoids 227–230 also inhibited the growth of the chloroquine-resistant strain FeB1, with IC$_{50}$ values between 4.3 and 14.6 μg mL$^{-1}$. Penianthic acid (1295) and epicordatine (1296) exhibited weak activity against chloroquine-resistant strain K1. Casearlucine A (1297), caseamembrol A (119, see structure in Section 3.5), and laetiaprocerines A–D (101–103, 274, see structures in Section 3.5) displayed activity against P. falciparum with IC$_{50}$ values as low as 0.5 μM against FeB1 and F-32 strains. In addition, compounds 119 and 1297 also showed activity against Leishmania amazonensis amastigote axenic stages and promastigote. Ajugarin-1 (1298) showed moderate in vivo antiparasomal activity, with an IC$_{50}$ of 23.0 ± 3.0 μM, against FCA 20/GHA P. falciparum. At a dose of 200 mg kg$^{-1}$ in mice, the clerodane diterpenoid gomphostenin-A (1299) exhibited an impressive 93% chemosuppression against P. berghei.

Clerodane 182, a diastereoisomer of kolavenol, exhibited trypanocidal activity (IC$_{50}$ 2.5 μg mL$^{-1}$) against Trypanosoma brucei rhodesiense, the parasitic cause of acute human African trypanosomiasis (sleeping sickness). This compound was isolated from the root bark of Entada abyssinica, which is used by traditional healers in Uganda to treat sleeping sickness.

Infuscatin (626) and sepulturins A, C, D and E (1300, 1302–1304) showed antiprotozoal activity against clinically isolated strains of Entamoeba histolytica and Giardia lamblia with similar potency to (+)-catechin and tyramine, but much less than metronidazole. Sepulturins A–F (1300–1305) were isolated from Saliva shannoni J.D. Smith, which is used as a traditional medicine in El Salvador against malaria. The structure of 626 (ref. 251) was also revised based on NOESY data and structural similarity to 1302. These new clerodane diterpenes contain a tertiary hydroxy group at C-8 or C-10 or both positions.

3.8. Antifungal and antibacterial activities

A fruit pulp extract of Detarium microcarpum inhibited the growth of the plant pathogenic fungus Cladosporium cucumerinum and of the enzyme acetylcholinesterase, which has been
implicated in Alzheimer’s disease. Fractionation of this extract led to the isolation of four new clerodane diterpenes, 197 (see Section 2.1.2.1), 266–267 (see Section 2.1.2.2), and 291 (see Section 2.1.3). Their structures were elucidated from spectroscopic data and X-ray crystallography of 197 and 266. Compounds 197, 267, and 291 showed both antifungal activity and inhibition of acetylcholinesterase. 65

Caseanigrescen C (39) caused a significant (21 mm) zone of inhibition of fungal growth, 21 and 16-oxo-cleroda-3,13(\(E\))-diene-15-oic acid (204) also exhibited high antifungal activities, with MIC values of 25 to 50 \(\mu\)g, as compared with fungicide Dithane M-45. 70 Caseargrewiins A–D (74, 1256–1258, see Section 3.5) exhibited moderate activity against *Mycobacterium tuberculosis*, with MIC values of 12.5, 12.5, 25.0, and 12.5 \(\mu\)g mL\(^{-1}\), respectively. 31
Compounds 205 and 206 were isolated as active antibacterial principles from *Haplopappus foliosus*. They were active against six Gram-positive bacteria, but inactive against five Gram-negative bacteria. 18-Acetoxy-cis-cleroda-3-en-15-oic acid (226) also showed antibacterial activity against five Gram-positive bacteria. 16α-Hydroxy-cleroda-3,13(\(Z\))-diene-15,16-olide (551) was highly active against Gram-negative bacteria, including *Escherichia coli*, *Klebsiella aerogenes*, and *Pseudomonas* species, with MICs in the range 0.78–1.5 mg. Among Gram-positive bacteria, compound 551 was also highly active against *Bacillus* species with MIC of less than 2 μg. Interestingly, against Gram-positive methicillin-resistant *Staphylococcus aureus*, compound 551 showed both *in vivo* efficacy in infected mice due to bacterial membrane disruption as well as synergistic activity with clinically used antibiotics, such as tetracycline, linezolid, and daptomycin.

Furthermore, neo-clerodanes-(5\(R\),8\(R\),9\(S\),10\(R\))-15,16-diol-15,16-dihydrohardwickiic acid (1306) and (2\(S\),5\(R\),8\(R\),9\(S\),10\(R\))-2β-hydroxy-16-oxo-15,16-dihydrohardwickiic acid (1307) from *Salvia adenophora* showed strain-dependent activity against Gram-positive *Staph. epidermidis*. In contrast, lupulin A (822) showed clear activity against Gram-negative *Ps. aeruginosa* and *E. coli* (inhibitory zone 3–5 mm), and hativenes A–C (827–829) showed potent activity against three Gram-negative rods (*E. coli*, *Ps. aeruginosa* and *Salmonella typhimurium*). Lupulin F (794) also showed antibacterial activity against *Ps. aeruginosa* and *E. coli*. 
3.9. Other bioactivities

\textit{trans}-Dehydrocrotonin (t-DCTN, 1076, see structure in Section 3.4) exhibits multiple biological effects, including antitumor, antiulcerogenic, hypolipidaemic, antiatherogenic, anti-oestrogen, antigenotoxicity, anti-inflammatory, and insect growth inhibitory property activities.\textsuperscript{511–518} The anti-hyperglycemic potential of this compound was supported by its reported hypoglycemic effect, which was almost comparable to that produced by glibenclamide (2 mg kg\textsuperscript{-1}), a clinically useful drug.\textsuperscript{519} Compound 1076 can also be used as a potent analgesic agent in case of peripheral algesia, without CNS effects.\textsuperscript{520} The hypotensive and bradycardia effects of 1076 are possibly related to some extent to the release of nitric oxide as well as direct effects on vascular smooth muscle, and cardiac pacemaker activity.\textsuperscript{521}

Casearinols A (1308) and B (1309) and casearinones A (1310) and B (1311), inhibited the binding of T-cell leukocyte function antigen 1 to intercellular adhesion molecule 1, with an \textit{IC}\textsubscript{50} of 50 μM.\textsuperscript{522} This report is the first to link this diterpene class with immunomodulatory activity. Diterpene 1312, an active principle of \textit{Baccharis trimeta}, blocked vascular smooth muscle contractions induced by extracellular Ca\textsuperscript{2+} in KCl-depolarized preparations.\textsuperscript{523}

Interestingly, 16α-hydroxycleroda-3,13Z-dien-15,16-olide (551, see structure in Section 3.8) is the first clerodane diterpene reported to have potential as a lipid lowering agent. It represents a new structural class of HMG-CoA reductase inhibitor.\textsuperscript{524}
3.10. Toxicity

Some neo-clerodane diterpenoids, especially furan-containing diterpenoids, are highly hepatotoxic in mice, causing mid zonal hepatic necrosis. They have also been alleged to cause fulminant hepatitis, chronic hepatitis, or cirrhosis in humans.

Diosbulbin D (1313, DBD) was the first hepatotoxic furano norclerodane diterpenoid isolated from Dioscorea bulbifera. The effects of DBD on the growth of normal human liver L-02 cells may be due to its induction of cell apoptosis, which may also explain the toxicity observed with plants containing furano clerodane diterpenoids. Diosbulbin B (1314, DB) is another hepatotoxic compound found in high quantity in D. bulbifera. The hepatotoxic effects of the ornamental and medicinal germander plant (Teucrium chamaedrys) were attributed to the furano neo-clerodanes teucrin A (1315) and teuchamaedryn A (1316). Plants in the genus Teucrium have been used as erroneously “safe” herbal hypoglycemic and slimming aids. Other furanoclerodane diterpenoids have not been assayed for hepatotoxicity, with more attention put on other pharmacological properties. Determination of toxicity is an important criterium for both consumer safety and clinical candidacy. For instance, the possible development of 8-epidiosbulbin E acetate (1317) (with a δ-lactone cis-fused to the decalin system rather than trans-fused as in the hepatotoxic 1313, DBD) as a potential plasmid-curing agent against multidrug-resistant bacteria, which pose a tremendous current health challenge.

4. Conclusion

In this review, discoveries of clerodane diterpenes from 1990–2015 were categorized by their chemical structures. During the last 25 years, over 1300 diterpenoids and nor-diterpenoids with the clerodane carbon skeleton have been isolated. These natural neo-clerodanes have been classified into seven different groups on the basis two fragments, the C-11–C-16 moiety and the decalin moiety. In addition, clerodane-type diterpene glycosides and clerodane derivatives, including N-containing derivatives, degraded derivatives, ring-seco derivatives, and rearranged derivatives reported in the literature were considered in this review. Although their insect antifeedant activity and opioid receptor agonist effects are generally considered most important, clerodane diterpenes exhibit many other pharmacological activities. The distribution, chemotaxonomic significance, biological activity, structure activity relationship correlations, and modes of action of active clerodanes have also been summarized.

The body of knowledge on the chemistry, biological activity, and pharmacology of clerodane diterpenes continues to grow rapidly. Despite such advances, continued investigations into the biological mechanisms involved in insect antifeedant activity, as well as extended research into the chemistry and pharmacology of opioid receptor ligands, such as salvinorin.
A (9) or other natural products, may provide the means to differentiate among different types of antifeedants and give better defined sets of clerodanes with a distinct mode of action from which more detailed structure–activity relationships can be deduced, and may yet yield the holy grail of opioids.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgements**

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**Biography**

Rong-Tao Li received her Ph.D at Kunming Institute of Botany, Chinese Academy of Science (CAS) in 2004, under the guidance of Prof. Han-Dong Sun. She worked with Prof. Kuo-Hsiung Lee from March 2013 to June 2014, as a Visiting Professor at the UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill. She has been awarded several prizes conferred by national, CAS, provincial, or ministerial authorities, including the “National Excellent Doctoral Dissertation of P.R. China” in 2006, the “New Century Excellent Talents on University” in 2006, the “Young Academic and Technical Leader of Yunnan Province” in 2009, and the “Excellent Doctoral Dissertation of the Chinese Academy of Science” and “CPA-Servier Yong Investigator Award in Medicinal Chemistry” 2005. She has performed phytochemical studies on about 50 plants, published 12 patents, and over 130 scientific papers. She is now Professor, Kunming University of Science and Technology (2005-present). Her current research interests involve the activity-directed isolation, structure elucidation and the structure–activity relationships of natural products from medically important plants.
Susan L. Morris-Natschke received her B.S. in chemistry from the University of Maryland-College Park in 1975 and her Ph.D. in organic chemistry from the University of North Carolina-Chapel Hill (UNC-CH) in 1982. She is currently Research Professor in the Division of Chemical Biology and Medicinal Chemistry, UNC Eshelman School of Pharmacy, UNC-CH, where she has been on the faculty since 1983. Her interests include scientific writing/editing, as well as the synthesis and structure-activity relationships of bioactive natural products.

Kuo-Hsiung Lee received his B.S. in pharmacy from Kaohsiung Medical University, Taiwan (1961), M.S. in pharmaceutical chemistry from Kyoto University, Japan (1965), and Ph.D. in medicinal chemistry from University of Minnesota, Minneapolis (1968). He joined the faculty of UNC Eshelman School of Pharmacy, University of North Carolina-Chapel Hill, in 1970 and is now Kenan Distinguished Professor of Medicinal Chemistry and Director of the Natural Products Research Laboratories. He has published over 848 research articles, been granted over 114 patents, and received numerous awards, including most recently, the Third Cheung On Tak International Award for Outstanding Achievement in Chinese Medicine from Hong Kong Baptist University, School of Chinese Medicine in 2016.

6. References


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Fig. 1.
Stereochemical variety in clerodane diterpenoids.
Fig. 2.
C_{11}–C_{16} moiety of clerodane diterpenoids.
Fig. 3.
The decalin moiety of clerodane diterpenoids.
Fig. 4.
Basic skeletal classifications of clerodane diterpenoids.
Fig. 5.
Zuelanin and isozuelanin skeletons.
Fig. 5.
General SAR for salvinorin A activity at KOP receptors.
Scheme 1.
Scheme 2.
Possible biogenesis of baenzigeride A (1174).
Scheme 3.
A plausible biogenetic pathway to 1180.
**Table 1**

The occurrence of clerodane diterpenes in the plant kingdom and marine animals

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Table 2
Characteristic $^{13}$C NMR chemical shifts of types I–VII ($\delta_{C}$, ppm)

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<td>40–42</td>
<td>75–77</td>
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<tr>
<td>C-17</td>
<td>16–18</td>
<td>13–18</td>
<td></td>
<td>169–177</td>
<td>14–20</td>
<td></td>
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</tr>
<tr>
<td>C-20</td>
<td>18</td>
<td>16–18</td>
<td></td>
<td>14–26</td>
<td>172–178</td>
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</tr>
<tr>
<td></td>
<td>$\Delta^{5,10}$: 140</td>
<td></td>
<td></td>
<td>$\Delta^{7,8}$: 170, 100</td>
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</table>
Table 3
Structures and cytotoxic data (V-79 cells) of casearins and their derivatives

<table>
<thead>
<tr>
<th>Casearin</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>R₅</th>
<th>IC₅₀ (µmol L⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (1261)</td>
<td>OCH₃</td>
<td>Ac</td>
<td>Ac</td>
<td>OH</td>
<td>OBu</td>
<td>1.0</td>
</tr>
<tr>
<td>B (1262)</td>
<td>OCH₃</td>
<td>Ac</td>
<td>Ac</td>
<td>OAc</td>
<td>OBu</td>
<td>8.5</td>
</tr>
<tr>
<td>C (1263)</td>
<td>OH</td>
<td>Ac</td>
<td>Ac</td>
<td>OAc</td>
<td>ODe</td>
<td>0.77</td>
</tr>
<tr>
<td>D (1264)</td>
<td>OH</td>
<td>Bu</td>
<td>Ac</td>
<td>OH</td>
<td>OBu</td>
<td>1.8</td>
</tr>
<tr>
<td>E (1265)</td>
<td>OH</td>
<td>Et</td>
<td>Ac</td>
<td>OH</td>
<td>ODe</td>
<td>4.7</td>
</tr>
<tr>
<td>F (1266)</td>
<td>OH</td>
<td>Et</td>
<td>Ac</td>
<td>OH</td>
<td>OBu</td>
<td>29</td>
</tr>
<tr>
<td>G (1267)</td>
<td>OCH₃</td>
<td>Ac</td>
<td>Ac</td>
<td>H</td>
<td>OBu</td>
<td>0.17</td>
</tr>
<tr>
<td>H (1268)</td>
<td>OH</td>
<td>Ac</td>
<td>Ac</td>
<td>H</td>
<td>OBu</td>
<td>0.37</td>
</tr>
<tr>
<td>I (1269)</td>
<td>OH</td>
<td>Ac</td>
<td>Bu</td>
<td>H</td>
<td>OBu</td>
<td>0.51</td>
</tr>
<tr>
<td>J (1270)</td>
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<td>Bu</td>
<td>Ac</td>
<td>OH</td>
<td>OBu</td>
<td>1.1</td>
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<tr>
<td>K (1271)</td>
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<td>Ac</td>
<td>Ac</td>
<td>OH</td>
<td>OBu</td>
<td>0.52</td>
</tr>
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<td>L (1272)</td>
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<td>Ac</td>
<td>OAc</td>
<td>OH</td>
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</tr>
<tr>
<td>M (1273)</td>
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<td>Bu</td>
<td>Bu</td>
<td>OAc</td>
<td>OH</td>
<td>1.8</td>
</tr>
<tr>
<td>N (1274)</td>
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<td>Ac</td>
<td>Bu</td>
<td>OAc</td>
<td>OBu</td>
<td>5.9</td>
</tr>
<tr>
<td>O (1275)</td>
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<td>Bu</td>
<td>Ac</td>
<td>OAc</td>
<td>OBu</td>
<td>6.0</td>
</tr>
<tr>
<td>P (1276)</td>
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<td>Ac</td>
<td>Ac</td>
<td>OAc</td>
<td>OAc</td>
<td>7.8</td>
</tr>
<tr>
<td>Q (1277)</td>
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<td>Ac</td>
<td>Ac</td>
<td>OAc</td>
<td>OBu</td>
<td>4.3</td>
</tr>
<tr>
<td>R (1278)</td>
<td>=O</td>
<td>Ac</td>
<td>Ac</td>
<td>OH</td>
<td>OBu</td>
<td>5.4</td>
</tr>
<tr>
<td>Aₐ (1279)</td>
<td>OCH₃</td>
<td>Ac</td>
<td>Ac</td>
<td>=O</td>
<td>OBu</td>
<td>0.55</td>
</tr>
<tr>
<td>Aₐ (1280)</td>
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<td>Ac</td>
<td>Ac</td>
<td>OPt</td>
<td>OBu</td>
<td>17</td>
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<tr>
<td>Aₐ (1281)</td>
<td>OCH₃</td>
<td>Ac</td>
<td>Ac</td>
<td>OBu</td>
<td>OBu</td>
<td>38</td>
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<tr>
<td>Dₐ (1282)</td>
<td>=O</td>
<td>Bu</td>
<td>Ac</td>
<td>=O</td>
<td>OBu</td>
<td>19</td>
</tr>
<tr>
<td>X (1283)</td>
<td>Bu</td>
<td>Bu</td>
<td>Ac</td>
<td>OH</td>
<td>H</td>
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Structures of Compounds 1261-1283
$^a$Ac = acetate, Bu = butanoate, Dc = decanoate.