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ADVANCES ON THE CHEMISTRY OF FURANO-DITERPENOIDS FROM *TEUCRIUM* GENUS

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Abstract – This paper updates the previous reviews, reporting the results published in the last six years on the chemistry of these diterpenoids.

Year after year, the chemistry of the neoclerodane diterpenoids isolated from the genus *Teucrium* (Lamiaceae) keeps on with repeated interest, and new contributions are introduced. Twenty-nine new natural products are here described in this review.

The investigation of these secondary metabolites was presented in previous reviews.¹⁻⁴ This paper aims to update the researches from 1998 to 2003. Recently an extensive and exhaustive chemical and biological evaluation of the genus was published by Ulubelen *et al.*⁵ Other information was given by Rodriguez-Hahn *et al.* in a global review on the neoclerodane diterpenoids⁶ and can be found in the periodical reports by Hanson.⁷

For reason of continuity, each new product will be indicated with the progressive number starting from the numbering of the last product in the prior review,⁴ and the numbering of the already described products remains the same of the previous reviews. In total, 29 new natural products were reported, and 2 previous structures were corrected.

Chronologically, the first paper appeared in these last years concerned a re-examination of *Teucrium massiliense*. Besides the diterpenoids described in previous papers,^{8,9} four new neoclerodanes were isolated¹⁰ as minor constituents: teumassilenin A (**207**), teumassilenin B (**208**), teumassilenin C (**209**) and teumassilenin D (**210**). All the new products have the usual β -furyl ring and a hydroxy function on C-12. Remarkable differences occur in the lower part of the decaline system: product (**207**) shows C-18 as an aldehydic group; product (**208**) has a hemiacetalic system between C-18 and C-19; product (**209**) has a C-4/C-19 oxetane ring; only in product (**210**) the usual C-4/C-18 epoxide ring is present.

The second paper reports on the isolation¹¹ of two new furanic neoclerodanes from a sample of *T. polium* (no subspecies indicated) collected in Southern Turkey: teulolin A (**211**) and teulolin B (**212**). The strong

polarity of both products must be remarked, as they contain four free hydroxy groups; moreover, teulolin B is the first diterpenoid from the genus *Teucrium* to retain an exocyclic C-4/C-18 double bond.

A chemotaxonomic problem was concerned with *T. polium*. In the past, many neoclerodane diterpenoids had been isolated from plants generically indicated as "*Teucrium polium*" and collected in different countries.^{1-4,11} The diterpenoids isolated from these sources differed qualitatively. It is known that the taxonomy of the section *Polium* of the genus *Teucrium* is complex and believed to contain 125 taxa;¹² moreover, for the species *T. polium* many subspecies were described. Now a paper was published¹³ reporting the neoclerodanes extracted from a material collected in Southern France and authenticated as *T. polium* subsp. *polium*. The compounds identified are the known auropolin and capitatin, and the new 20-epiauropolin (**213**). The problem, about the correct identification of all the other taxa examined previously, is still open.

A rich source of neoclerodanes was *T. maghrebinum* harvested in Algeria. The correct name of the taxon is still doubtful: surely, it belongs to the *Polium* section, and it could be a subspecies of *T. polium*. A first paper¹⁴ reported the identification of five known products: teucjaponin A, montanin D, montanin B, teusalvin and 19-deacetyl-teuscorodol. Three new products also occurred: 12-epiteucjaponin A (**214**), 12-epimontanin B (**215**) and 12-epimontanin D (**216**). It is very interesting that these eight diterpenoids constitute four pairs of epimers at carbon C-12. A reinvestigation of some chromatographic fractions let to isolate¹⁵ four minor products more: the known teukotschyn and the three new 12-epiteukotschyn (**217**), teughrebin (**218**) and 12-epiteughrebin (**219**). Also these four compounds constitute two pairs of epimers at C-12. The six 12-epi derivatives have the absolute 12*R** configuration, whereas the other six substances have the 12*S** configuration.

It has to be pointed out that the absolute configuration was not proved experimentally for the products from (**207**) to (**219**): however, on biogenetic grounds, it can be supposed that they belong to the neoclerodane series, like all the other diterpenoids isolated from the aerial parts of *Teucrium* plants.

A sample of *T. divaricatum* subsp. *divaricatum*, collected in Greece, was examined¹⁶ and the results compared with those obtained some years ago on a sample of the same subspecies harvested in Cyprus.¹⁷ The same known diterpenoids occurring in the Cyprus material were found, together also with teucvin and teucvidin.

The species *T. oliverianum*, growing in Saudi Arabia, had been examined several years ago¹⁸⁻²² and many neoclerodanes had been isolated. The plant was reinvestigated²³ and two new products were identified, teucrolin F (**220**) and teucrolin G (**221**). In the same paper, the structure assigned previously²¹⁻²² to teucrolin E was amended; the correct structure (**222**) substitutes the structure (**173**) reported in the precedent review.⁴

The species *T. arduini*, native of the western part of the Balkan peninsula, contained²⁴ only seven already

described products: teucvin, montanin D, 6 β -hydroxyteuscordin, isoteuflidin, teugin, dihydroteugin, 19-deacetylteuscorodol.

Ten furo-neoclerodanes were extracted²⁵ from *T. montbretii* subsp. *libanoticum*, native of Lebanon. Seven are known products: 6-keto-teuscordin, teuscordinon, 6 β -hydroxyteuscordin, montanin D, montanin G, 3-deacetylteugracilin A, 3,20-dideacetylteupyreinidin. Three are new: 3 β -hydroxyteubutilin A (**223**), 12-epimontanin G (**224**) and 20-epi-3,20-dideacetylteupyreinidin (**225**). In the present paper, the absolute configuration was determined for several products, by chemical correlation with other neoclerodanes whose absolute stereostructure was known.

Another investigation was performed²⁶ on a sample of *T. chamaedrys* of commercial origin (obtained from Europe and purchased from American Mercantile Corporation). A new furanic derivative (**226**) (no trivial name given) was isolated, beside the known teucrin A, dihydroteugin, isoteuflidin, teuflin, teucvidin, teucrin H1, teucrin G, 6 β -hydroxyteuscordin.

A recent paper was concerned with *T. tomentosum*, a species growing in Southern India:²⁷ a new furanic neoclerodane was isolated, teuctosin (**227**), together with the known teuflin, teucrin-H2, 6 β -hydroxyteuscordin, 6 β -acetylteuscordin and montanin-D, occurring in other *Teucrium* species. Montanin-D was confirmed to have the structure (**46**). The structure (**227**) of teuctosin was confirmed also by X-Ray analysis.²⁸ Another paper reported²⁹ the isolation of a second furanic neoclerodane (no trivial name given) from *T. tomentosum*, whose structure (**228**) was determined by X-Ray analysis.

Another species collected in Lebanon, *T. orientale*, was examined recently.³⁰ Six neoclerodanes were found: four are already known, teucrolivin A, teucrolivin B, teucrolivin C, teucrolivin H, previously¹⁸⁻²⁰ extracted from *T. oliverianum*; two are new natural products, 6-deacetylteucrolivin A (**229**) and 8 β -hydroxyteucrolivin B (**230**). It is worthy of remark the closeness, also geographic, of the two species *T. oliverianum* and *T. orientale*, whose secondary metabolites are identical or structurally similar.

Recently *T. fruticans* was the object of a reinvestigation: a sample collected in Southern Spain contained the same diterpenoids fruticolone, isofruticolone, 8 β -hydroxyfruticolone previously found in the material harvested in Sicily^{31,32} and four new products were isolated:³³ 7 β -hydroxyfruticolone (**231**), 11-hydroxyfruticolone (**232**), deacetylfruticolone (**233**), and 10-hydroxy-6-acetylteucjaponin B (**234**). Also the already known 6-acetylteucjaponin B was identified.

The species *T. marum*, growing in Sardinia, had been investigated previously,³⁴ and the neoclerodane teumarin (**34**) had been described. Now the occurrence of a second derivative, teumarin B (**235**) was reported.³⁵ A peculiarity of this new product is the fact that it is formed by a slow and spontaneous rearrangement of teumarin. A remarkable particularity of teumarin B is the rather rare occurrence of carbon 18 as an aldehydic 4 β -formyl group.

Recently, four other species of *Teucrium* were subjected to phytochemical investigation; only known

products were identified.³⁷ *T. dunense* from Majorca island (Spain) contained 19-acetylnaphalin, isoeriocephalin and 6-acetylpicropolin. *T. nuchense* from Georgia (Caucasus) yielded only teucrin A. *T. cylindraceum* from Algeria gave auropolin and 20-epiauropolin. On the contrary, *T. thymoides* from Algeria contained no diterpenoids, a case not very rare but unusual in the genus.

Only now we became acquainted with a series of papers³⁸⁻⁴⁰ published in Chinese language in local scientific journals, concerning *T. quadrifarium*. This species contains the known neoclerodanes teucvidin, 12-epiteucvidin, teuflin, teucvin, teuscorodonin, 19-acetylteuspinin and the new teuquadrin B (**236**).

In *Teucrium bidentatum* also teucvin and teupernin A were identified,⁴¹ together with the five diterpenoids already⁴ reported in the previous reviews.

Chinese researchers re-examined⁴² *T. viscidum*; they isolated the previously found teucvin, teucvidin, teuflin, and also teuspinin (**62**) and 6 α -hydroxyteuscordin (**79**).

A paper⁴³ reported the complete assignments of the ¹H and ¹³C NMR spectra of some neoclerodane diterpenoids, including chamaedroxide (**88**). A second paper⁴⁴ presented an extensive treatment of the ¹H and ¹³C spectral assignments and conformational analysis of some natural 19-norneoclerodanes from *Teucrium* and of some semisynthetic derivatives. This study allowed also to amend the structure of 2-hydroxyteucvidin: the previous one (**92**) with 2 β -hydroxy group configuration must be replaced by (**237**) with 2 α -hydroxy group.

Another paper,⁴⁵ published in 1994 in Chinese language and come to our knowledge only now, was related to the NMR stereochemistry determination of some 19-norneoclerodanes from *Teucrium*.

A quick TLC analysis was reported for the extract of *T. quadrifarium* and *T. pernyi*.⁴⁰ Also an HPLC examination was used for the quantitative determination of the diterpenoids occurring in an undetermined sample of *T. chamaedrys*.⁴⁶

Also in these last years, some papers reported results aiming at modifying the structures (rings and functional groups) of natural *Teucrium* neoclerodanes, to prepare semisynthetic derivatives to be tested for the antifeedant activity.⁴⁷⁻⁵²

In a case, a photochemical transformation was investigated:⁵³ irradiation at λ 313 nm of fruticolone (**38**) yielded fruticolide (**122**): both products occur^{31,54} in *T. fruticans* as natural products.

Something is moving also in the field of total synthesis. An excellent paper reported the first synthesis of a natural *Teucrium* diterpenoid,⁵⁵ teubrevin G (**166**), a rearranged neoclerodane of very unusual structure isolated from *T. brevifolium*.⁵⁶ Twenty-one steps from the starting material were required to obtain this intriguing target.

Also a very interesting total synthesis of racemic teucvin (**89**) and 12-epiteucvin (**90**) appeared recently.⁵⁷ The synthesis of neoclerodane models having a four-membered oxetane ring was studied.⁵⁸

The antifeedant activity of the neoclerodanes from *Teucrium* and semisynthetic derivatives against

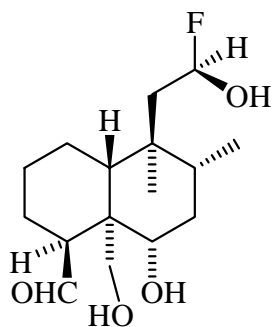
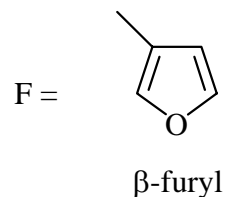
several insects was reported in some papers.^{13,24,27,49,60,61}

An exhaustive review on the insect antifeedant activity of neoclerodane diterpenoids, including also the natural compounds isolated from *Teucrium*, recently appeared in literature.⁶²

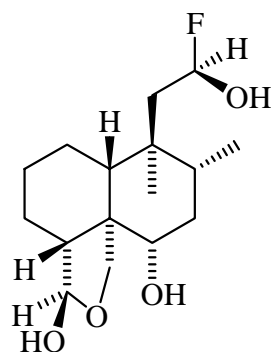
In a research⁶³ on the antitumor activity of several diterpenoids of different origin, it was found that teucvin and teucvidin are inactive against P388 lymphocyte leukemia.

The danger of the well ascertained hepatotoxicity in man of *T. chamaedrys*, due to teucrin A (**97**), was remembered in a safety data review⁶⁴ and emphasised in a careful experimental paper,⁶⁵ reporting also on the still permitted occurrence of extracts of this plant in soft drinks, vermouths, flavoured wines and bitters, with the aim of providing a bitter aromatic taste; an extensive use of HPLC is given. Another paper⁶⁶ was concerned with the hepatotoxicity of *T. polium*. It is probable that also other neoclerodane diterpenoids occurring in many species of *Teucrium* can be responsible for hepatotoxicity, that until now was reported only for *T. chamaedrys* and *T. polium*.

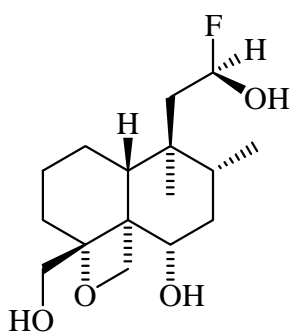
Structures



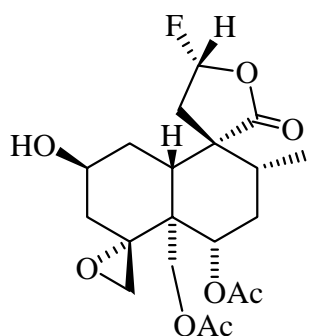
[207] teumassilenin A
*T. massiliense*¹⁰



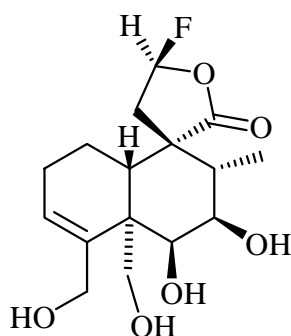
[208] teumassilenin B
*T. massiliense*¹⁰



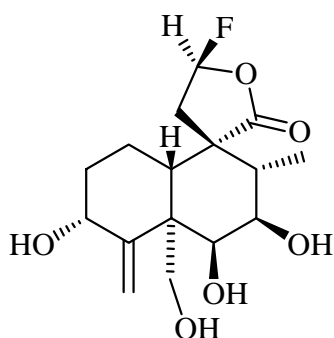
[209] teumassilenin C
*T. massiliense*¹⁰



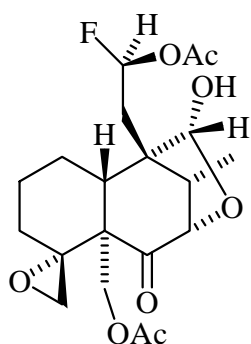
[210] teumassilenin D
*T. massiliense*¹⁰



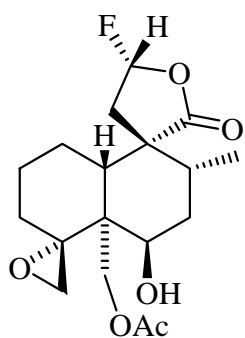
[211] teulolin A
*T. polium*¹¹



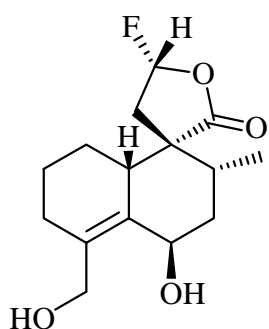
[212] teulolin B
*T. polium*¹¹



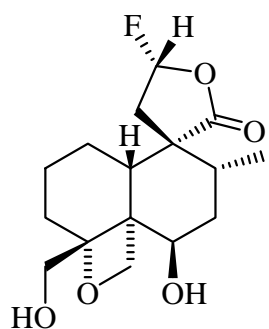
[213] 20-epiauropolin
T. polium ssp. *polium*¹³



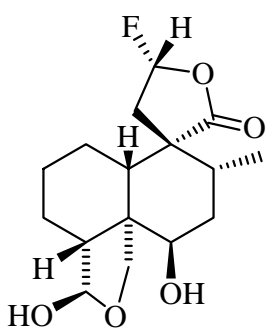
[214] 12-epiteujaponin A
*T. maghrebinum*¹⁴



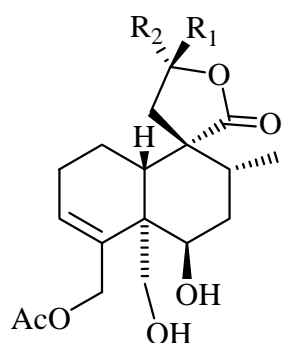
[215] 12-epimontanin B
*T. maghrebinum*¹⁴



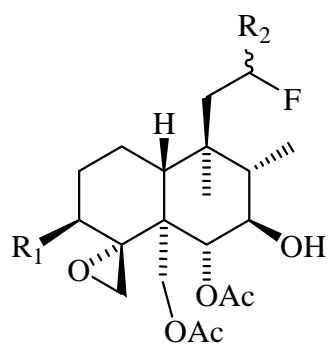
[216] 12-epimontanin D
*T. maghrebinum*¹⁴



[217] 12-epiteukotschyn
*T. maghrebinum*¹⁵



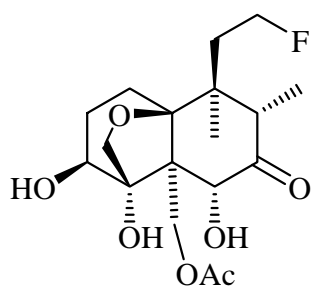
[218] teughrebin $R_1 = F$ $R_2 = H$
[219] 12-epiteughrebin $R_1 = H$ $R_2 = F$
*T. maghrebinum*¹⁵



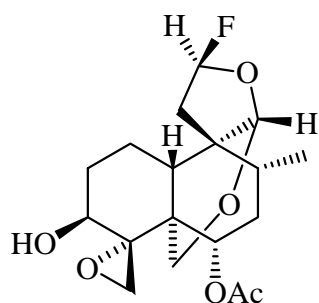
[220] teucrolin F

 $R_1 = \text{OH}$ $R_2 = \text{H}$

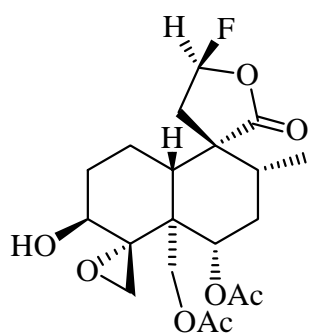
[221] teucrolin G

 $R_1 = \text{H}$ $R_2 = \text{OH}$ *T. oliverianum*²³

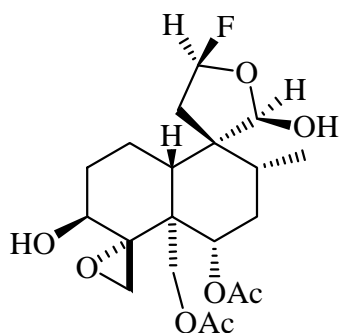
[222] teucrolin E

*T. oliverianum*²³

[223] 3β-hydroxyteubutilin A

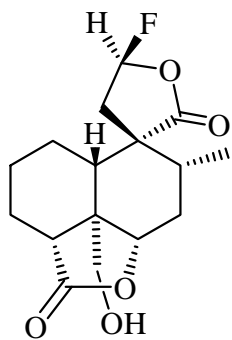
T. monbretii ssp. *libanoticum*²⁵

[224] 12-epimontanin G

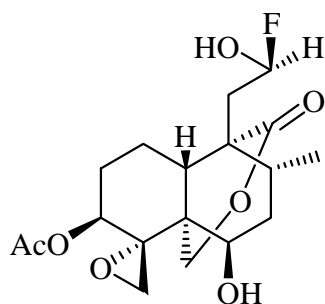
T. monbretii ssp. *libanoticum*²⁵

[225] 20-epi-3,20-dideacetylteupyreinidin

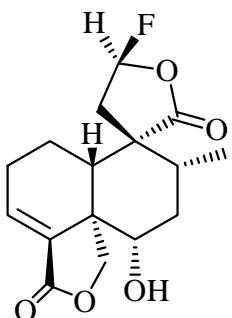
T. monbretii ssp. *libanoticum*²⁵



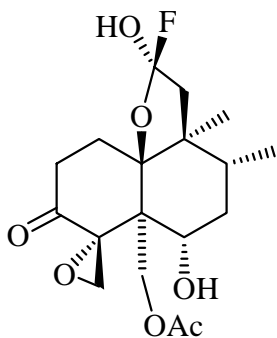
[226] no name
*T. chamaedrys*²⁶



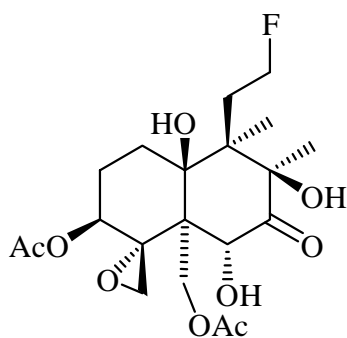
[227] teuctosin
T. tomentosum^{27,28}



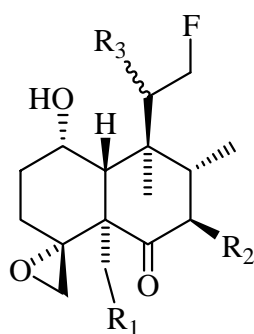
[228] no name
*T. tomentosum*²⁹



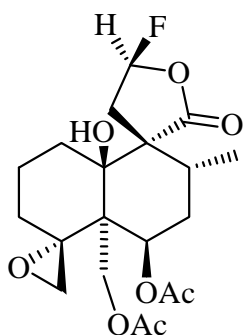
[229] 6-deacetylteucrolivin A
*T. orientale*³⁰



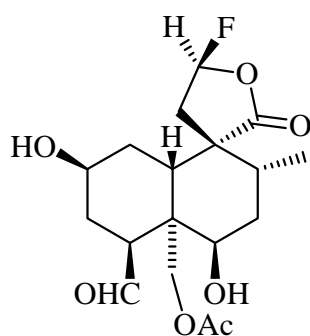
[230] 8 β -hydroxyteucrolivin B
*T. orientale*³⁰



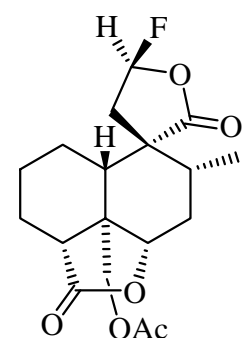
- [231] 7 β -hydroxyfruticolone R₁ = OAc R₂ = OH R₃ = H
 [232] 11-hydroxyfruticolone R₁ = OAc R₂ = H R₃ = OH
 [233] deacetylfruticolone R₁ = OH R₂ = H R₃ = H
*T. fruticans*³³



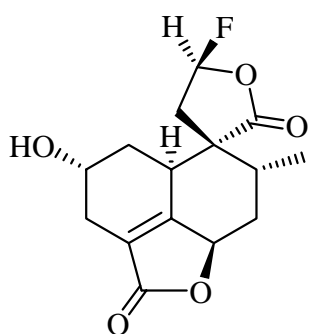
- [234] 10 β -hydroxy-6-acetylteucjaponin B
*T. fruticans*³³



- [235] teumarin B
*T. marum*³⁵



- [236] teuquadrin B
*T. quadrifarum*³⁹



- [237] 2 α -hydroxyteucvidin
*T. webbium*²

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