*Bulgarian Chemical Communications, Volume 52, Issue 2 (pp. 250 - 258) 2020* *DOI: 10.34049/bcc.52.2.5153*

# Clerodane diterpenoids isolated from Bulgarian species of genus *Teucrium* (Lamiaceae)

P. I. Bozov

*Department of Biochemistry and Microbiology, Plovdiv University, 24 Tzar Asen St., 4000, Plovdiv, Bulgaria*

Received May 15, 2019; Revised March, 4, 2020

*Neo*-clerodane diterpenoids have attracted interest in a variety of skeletons owing to the many stereochemical problems arising during their identification and structural characterization and to the wide range of biological activity, especially their operation as insect-antifeedant agents. The present review reports on the clerodane diterpenoids isolated from Bulgarian *Teucrium* species (Lamiaceae), and the systematization of their characteristic structural features. The changes in the antifeedant activity due to chemical transformations of the compounds and some significant aspects of the structure-activity relationship are discussed.

**Keywords:** Lamiaceae, *Teucrium, T. botrys* L., *T. lamiifolium* D'Urv, *T. polium* L., *T. montanum* L., *T. scordium* L, *T. chamaedris* L., neo-clerodane diterpenes, antifeedant activity, hemisynthetic derivatives.

## INTRODUCTION

The Lamiaceae genus *Teucrium* covers about 360 species spread in different climatic zones.

In Bulgaria the genus is represented by six species [1]. Since 1906 the species *T. botrys* L. is not confirmed in Bulgaria and it is probably extinct species for the country. Three of the species of genus *Teucrium* are represented by two subspecies. Common types of *T. polium* L. are the subspecies *capitatum* (L.) Arcangeli and subspecies *vincentinum* (Rouy) D. Wood; of *T. scordium* L. – subspecies *scordium* and subspecies *scordioides* (Schreb.) Maire et Petitmengin; of *T. montanum* L. – subspecies *montanum* and subspecies *skorpilii* (vel.) D. Peev.

The *Teucrium* species are honey-bearing with medical use. For thousands of years, paws and infusions of the plants are applied in open-wound healing, treatment of gastrointestinal pains, diabetes, inflammations, rheumatism and other disorders. They are also used as diuretic, antipyretic, tonic, diaphoretic, analgesic agents [2].

The species of the genus *Teucrium* are a rich source of biologically active compounds as diterpenes, flavonoids, phenols, iridoids. Clerodane diterpenoids are the main chemical constituents of the genus. For clarity and in order to classify all clerodane diterpenoids, their bicyclic basic skeleton is divided in two substructures: combined C-1–C-10 atoms into a decalin ring and a C-11–C-16 (with C-16 attached at C-13, i.e., 3-methylpentyl) six-carbon side chain at C-9. The rest four carbons (C-17–C-20) are linked up with C-8, C-4, C-5, and C-9, respectively, on the decalin core as it is illustrated on Fig. 1 [3, 4].

Approximately 25% of clerodanes have a 5:10 cis ring fusion as presented in columbin (Fig. 1). The rest 75% of clerodanes have a 5:10 trans ring fusion as demonstrated in clerodin.

Depending on the relative configuration of C-8 and C-9, in the molecule four substructures of the clerodane skeleton are defined as shown in Fig. 2: *trans–cis* (TC), *trans–trans* (TT), *cis–cis* (CC) and *cis–trans* (CT).

Merritt and Ley [5] have revised the absolute stereochemistry of clerodin, the first member of the clerodane series of the diterpenes, and offer a new nomenclature for the clerodane diterpenoids: *neo*-clerodanes (formerly *ent*-clerodanes) have the same absolute stereochemistry as clerodin, while *ent*-*neo*-clerodanes are enantiomeric to clerodin (Fig. 3).

The major compounds, isolated from the genus *Teucrium*, are furo-*neo*-clerodane diterpenes with 5:10 trans ring fusion, as more than 90 % of them are of the TC type.

The intensive study of *Teucrium* species for presence of *neo*-clerodane diterpenoids has started in the sixties of the twentieth century. First received *neo*-clerodanes from this genus in Bulgaria are montanins A (**1**) and B (**2**), isolated in 1978 from *T. montanum* by Malakov *et al.* (Table 1) [6].

This review summarizes more than 40 years of scientific studies of clerodane diterpenoid content in Bulgarian *Teucrium* species, systematizing their skeletons and the change of the antifeedant activity of the clerodanes in chemically modified hemisynthetic derivatives. The activity of the natural clerodane diterpenoids was compared with that of non-natural hemisynthetic derivatives and of the potent *neo*-clerodane antifeedant ajugarin I (Fig. 3) isolated by Kubo *et al.* from *Ajuga remota* [7].

---

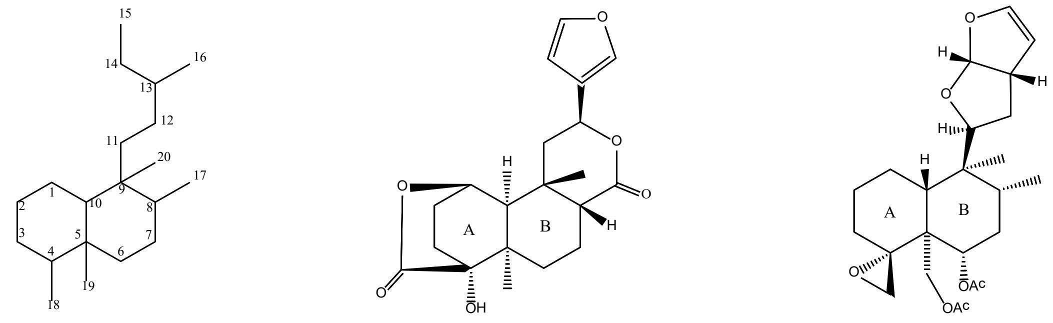
* To whom all correspondence should be sent:
E-mail: bozov@uniplovdiv.bg

© 2020 Bulgarian Academy of Sciences, Union of Chemists in Bulgaria

## ISOLATED DITERPENOIDS

The first paper on the *neo*-clerodane diterpenoids from the Bulgarian genus *Teucrium*, which appeared in 1987, concerned *T. montanum* L. The group of Malakov [6] have isolated the *nor*-clerodane furanoid diterpenoids – montanines A (**1**) and B (**2**). The absolute configuration of **2** has been proved by correlation with teucvin (Fig. 3), a *nor*-clerodane diterpenoid isolated by Fujita *et al.* from *T. viacidum* var. *miquelianum* [8], whose construction had been determined by X-ray crystallographic analysis of the bromo-derivative and by some of its reactions. Later that year, the same team [9, 10] reported obtaining of two more constituents of this species, the *neo*-clerodane diterpenes montanine C (**4**) and D (**7**).

In the next year five furanoid clerodane diterpenes, the known teucrin P$_1$ (**9**), teucrin H$_3$ (**10**, = 19-acetylgnafalin) montanine B (**2**) and the new teupolin I (**5**) and teupolin II (**12**), have been isolated for the first time from the bitter fraction of the aerial parts of *Teucrium polium* L. from Bulgaria by the same team [11]. Compound **9** has been found in Moldovian *T. polium* L. by Popa *et al.* [12] and compound **10** - in *T. hyrcanicum* by Gacs-Baitz *et al.* [13]. Only montanine B is a *nor*-clerodane diterpenoid, the other four terpenes are *neo*-clerodanes.



clerodane skeleton

columbin (*cis*)

clerodin (*trans*)

**Figure 1.** Basic clerodane skeleton and compounds with 5:10 *cis*- and *trans*- fusion of rings A and B.

<u>trans-</u>clerodane diterpenes

<u>cis-</u>clerodane diterpenes

type TC

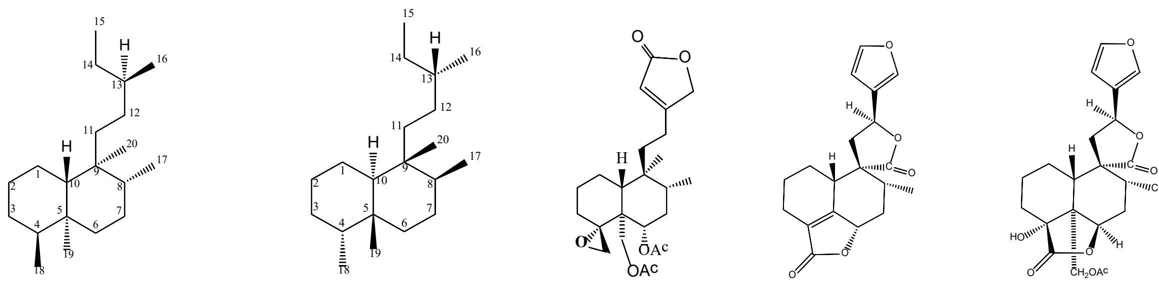
type TT

type CC

type CT

**Note:** in the figure neo-absolute configurations are given, ent-neo-forms possess reversed configurations for all asymmetric carbon atoms.

**Figure 2.** Absolute configurations at C-8 and C-9 of the clerodane skeleton.



*neo*-clerodane ≡ *ent*-clerodane

*ent-neo*-clerodane

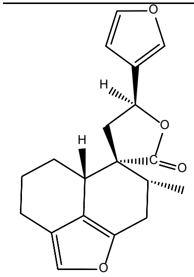
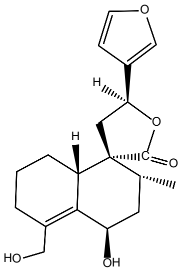
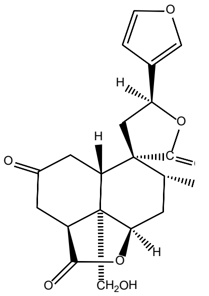
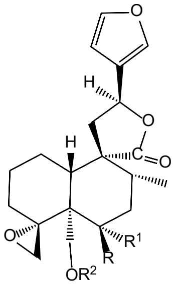
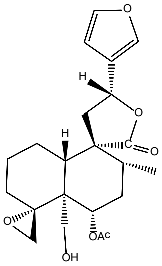
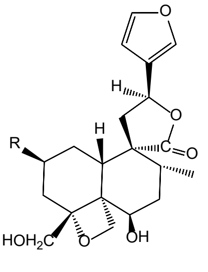
ajugarin I

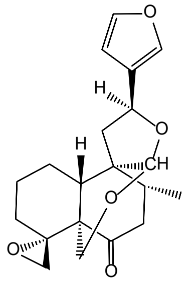
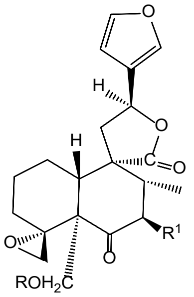
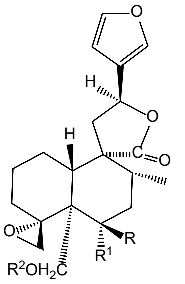
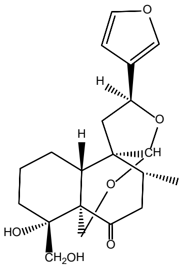
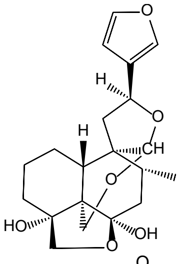
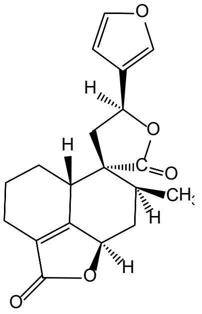
teucvin

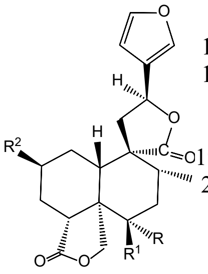
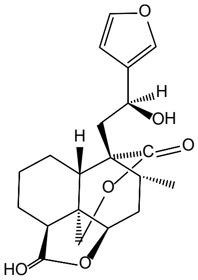
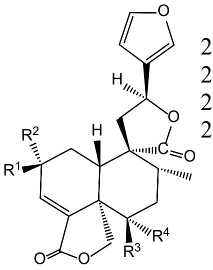
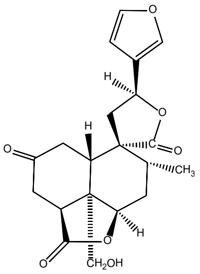
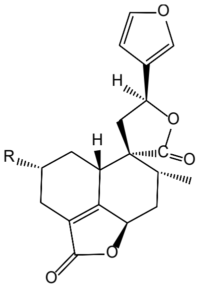
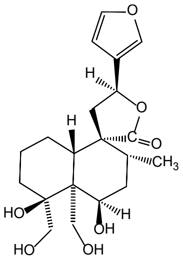
teuspinin

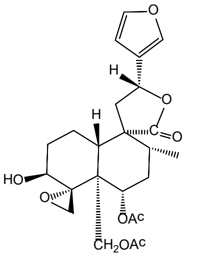
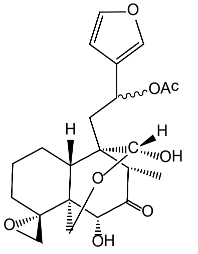
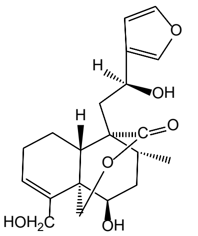
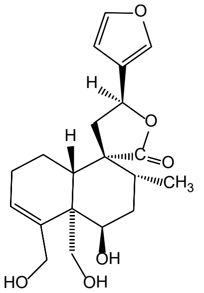
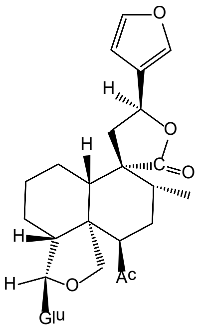
**Figure 3.** *Neo*-absolute configurations of clerodanes and structures of the compounds used in the discussion.

**Table 1.** Natural *neo*-clerodane diterpenoids isolated from Bulgarian *Teucrium* species.

| Compounds | | | | | Name | Source | Ref. |
|---|---|---|---|---|---|---|---|
|  | 1 | | | | Montanine A | *T. montanum* L. | 6 |
|  | 2 | | | | Montanine B | *T. montanum* L. | 6 |
|  | 3 | | | | Teucrin A | *T. chamaedrys* L.<br>*T. chamaedrys* L. | 16<br>***18***$^*$ |
|  | 4 | R = OAc | $R^1$ = H | $R^2$ = Ac | Montanine C | *T. montanum* L. | 9 |
| | 5 | R = OH | $R^1$ = H | $R^2$ = Ac | Teupolin I | *T. polium* L. | 38 |
| | | | | | | | 11 |
| | | | | | | | 38 |
|  | 6 | R = H | $R^1$ = Ac | $R^2$ = H | 12-епитеуполин II | *T. lamiifolium* D'Urv | 33 |
|  | 7 | R = H | | | Montanine D | *T. montanum L.* | 10 |
| | 8 | R = OH | | | Teucroxide | *T polium subsp. polium* | 30 |
| | | | | | | ***T. chamaedrys L.*** | ***32*** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
|  | 9 | | | | Teucrin $P_1$ | *T. polium* L.<br>***T. polium* L.** | 11<br>***12*** |
|  | 10 | R = Ac | $R^1$ = H | | 19-acetylgnaphalin<br>(= Teucrin $H_3$) | *T. polium* L.<br>***T. hyrcaicum*** | 11<br>***13*** |
| | 11 | R = H | $R^1$ = OAc | | Teupolin IV | *T. polium* subsp. *polium* | 15 |
|  | 12 | R = H | $R^1$ = OAc | $R^2$ = H | Teupolin II | *T. polium* L. | 11 |
| | 13 | R = OH | $R^1$ = H | $R^2$ = Ac | Montanine F<br>(teucjaponin A) | *T. montanum* subsp. *skorpilii* (vel.) D. Peev<br>***Teucrium japonicum Hov TT*** | 25<br>***28*** |
|  | 14 | | | | Teupolin III | *T. polium* subsp. *polium* | 14 |
|  | 15 | | | | Teupolin V | *T. polium* subsp. *polium*<br>***T. japonicum Hov T`*T*** | 15<br>***28*** |
|  | 16 | | | | Teuchamaedryn A | *T. chamaedrys* L. | 16 |

| | | | | | | |
|---|---|---|---|---|---|---|
|  | 17 R = H | R$^1$ = OH | R$^2$ = H | Teuchamaedryn B | *T. chamaedrys* L. | 16 |
| | 18 R = OH | R$^1$ = H | R$^2$ = H | Teucrin E | *T. chamaedrys* L. | 16 |
| | | | | | *T. scordium subsp. scordium* | 24 |
| | 19 R = H | R$^1$ = OH | R$^2$ = OH | Dihydroteugin | ***T. chamaedrys* L.** | ***19*** |
| | 20 R = R$^1$ = O | R$^2$ = H | | 6-Ketoteuscordin | *T. chamaedrys* L. | 17 |
| | | | | | ***T. chamaedrys* L.** | ***20*** |
| | | | | | *T. scordium subsp. scordium* | 22 |
|  | 21 | | | Teuchamaedryn C | *T. chamaedrys* L. | 17 |
|  | 22 R$^1$ = R$^2$ = H | R$^3$ = R$^4$ = O | | Teuscordinon | | |
| | 23 R$^1$ = R$^2$ = H | R$^3$ = H | R$^4$ = OH | 6$\alpha$-Hydroxyteuscordin | *T. scordium subsp. scordium* | 21 |
| | 24 R$^1$ = R$^2$ = H | R$^3$ = OH | R$^4$ = H | 6$\beta$-Hydroxyteuscordin | | |
| | 25 R$^1$ = OH | R$^2$=H, R$^3$= OH | R$^4$ = H | 2$\beta$,6$\beta$-Dihydroxyteuscordin | *T. scordium subsp. scordium* | 22 |
| | | | | | *T. scordium subsp. scordium* | 23 |
| | | | | | *T. scordium subsp. scordium* | 23 |
|  | 26 R + R$^1$ = O | R$^2$ = H | R$^3$ = H | 2-Keto-19-hydroxyteuscordin | *T. scordium subsp. scordium* | 24 |
|  | 27 R = OH | | | Teucrin $H_4$ | *T. scordium subsp. scordium* | 24 |
| | 28 R = H | | | Teuflin | *T. hyrcanicum* | ***13*** |
| | | | | | *T. lamiifolium* D'Urv | 31 |
| | | | | | ***Teucrium flavurn*** | ***32*** |
|  | 29 | | | Montanine E | *T. montanum* subsp. *skorpilii* (vel.) D. Peev | 25 |

| | | | | |
|---|---|---|---|---|
|  | 30 | Montanine G | *T. montanum* subsp. *skorpilii* (vel.) D. Peev | 26 |
|  | 31 | Montanine H | *T. montanum* subsp. *skorpilii* (vel.) D. Peev | 27 |
|  | 32 | Teulamifin B (= teubotrin) | *T. polium subsp. polium*<br>*T. lamiifolium*<br>***T. botrys*** | 29<br>30<br>***31*** |
|  | 33 | 19-Deacetylteuscorodol | *T. lamiifolium*<br>***T. botrys*** | 29<br>***31*** |
|  | 34 | Teulamioside | *T. lamiifolium* | 36 |

[*] Bold-italic: species from which the compound has been isolated for the first time, when it is not new.

From 1982 to 1987 Malakov published in various collectives the data of three more new furo-*neo*-clerodane diterpenoids isolated from *T. polium* subsp. *polium*: teupolin III (**14**) [14], teupolins IV (**11**) and V (**15**) [15]. Their structures were established by spectroscopic and chemical means and for teupolin V by partial synthesis from teucrin $P_1$ (**9**).

From the aerial parts of *T. chamaedrys* six *neo*-clerodanes have been obtained by Malakov and Papanov. Three of them, Teuchamaedryns A (**16**), B (**17**) [16] and C (**21**) [17] are new compounds; the rest three diterpenoids were previously isolated: teucrin A (**3**) and teucrin E (**18**) from Moldavian *T. chamaedrys* [18, 19], while dihydroteugin (**19**) has been found in Spanish *T. chamaedrys* [20]. Teuchamaedryn A (**16**) is with *nor*-clerodane skeleton and the only diterpene, isolated from Bulgarian *Teucrium* species, with clerodane skeleton of the TT type. Teuchamaedrin C (**21**) is the first diterpenoid, isolated from a *Teucrium* species, which possesses a C-18 – C-6*β* hemiacetalic function.

The research of the species *T. scordium* subsp. *scordium* was conducted by Papanov and Malakov through the period 1981–1985. Six new furanoid *neo*-clerodane diterpenoids were described: teuscordinon (**22**) [21], 6-ketoteuscordin (**20**) and 6*α*-hydroxyteuscordin (**23**) [22], 6*β*-hydroxy-teuscordin (**24**) and 2*β*,6*β*-dihydroxyteuscordin (**25**) [23], 2-keto-19-hydroxyteuscordin (**26**) [24], besides the previously known diterpenoids teucrin E (**18**) [24] and teucrin $H_4$ (**27**) [24]. The structures of the compounds and their stereochemistry were determined on the basis of chemical reactions and spectroscopic evidence.

The study of the aerial parts of *T. lamiifolium* and *T. polium* subsp. *polium* [30] resulted in simultaneous isolation from both species of a *neo*-clerodane diterpenoid teulamifin B (**32**), besides the known dlterpenolds 19-deacetyl-teuscorodol (**33**) previously isolated from *T. botrys* [31] and teucroxide (**8**) for the first time found in *T. chamaedrys* [32]. The structure of teulamifin B was established by chemical and spectroscopic means and by correlation with 19-deacetylteuscorodol. Later it was found that teulamifin B was identical to teubotrin previously isolated from *T. botrys*.

Three new *neo*-clerodane diterpenoids – montanines E (**29**) [25], G (**30**) [26] and H (**31**) [27], have been isolated from the aerial parts of *T. montanum* subsp. *skorpilii* (vel.) by D. Peev. In addition, two more previously known diterpenoids, montanine F (**13**) (which was identical to teucjaponin A [25, 28]) and teubotrin (**32**) (which was identical to teulamifin B [30, 31]) were obtained.

A new *neo*-clerodane diterpenoid, 12-epiteupolin II (**6**), was obtained from *T. lamiifolium* D'Urv by Boneva *et al.* [33], together with the previously known diterpenes teuscordinon (**22**) [21], teuflin (**28**) [34], montanine C (**4**) [9] and 19-acetylgnaphalin (= teucrin $H_3$, **10**) [35]. The structure of 12-epiteupolin II was established by chemical and spectroscopic means and by correlation with montanine C. Five years later Boneva, in another team [36], isolated a new *neo*-clerodane glucoside teulamioside (**34**), in addition to the previously known diterpenes montanine E (**29**) [25] and teuspinin (Fig. 3) previously isolated by Savona *et al.* from *T. spinosum* L. [37].

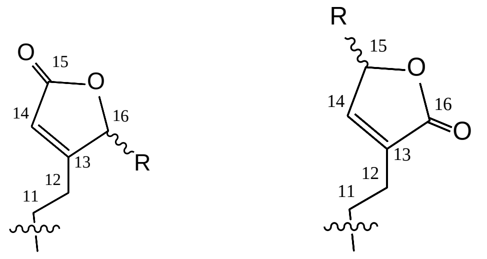
Fayos *et al.* [38] proposed the reported stereochemistry of montanine C (**4**) and teupolin I (**5**) structures with C-12S configuration to be corrected to C-12R configuration. Three years later, Gacs-Baitz *et al.* [39] established that the absolute stereochemistry of the C-12 chiral center must be maintained in an S configuration. This statement was based on chemical correlations with compounds of known C-12(S) absolute stereochemistry proven by X-ray analysis and studies using a variety of $^1$H NOE experiments.

From the Bulgarian *Teucrium* species thirty-four furoclerodane diterpenoids were isolated. Five of them, **1**, **2**, **16**, **27** and **28**, had a *nor*-clerodane skeleton and the rest were *neo*-clerodanes. All compounds were of the TC type except **16** which was of the TT type.

## ANTIFEEDANT ACTIVITY

In 1994 Malakov *et al.* [40] have subjected the *neo*-clerodane diterpenes montanine C (**4**), teucrin $P_1$ (**9**) and teupolin III (**14**) to a series of chemical transformations to obtain *α*,*β*-unsaturated 15,16-(**Aa**) and 16,15-*γ*-lactones (**Ab**), 13,14,15,16-tetranor-*neo*-clerodanes (**B**), chlorohydrins (**C**), vinyl chlorides (**D**), amine (**Ea**), 1-pyrroline (**Eb**) and 2-pyridazoline (**Ec**) derivatives (Fig. 4). These non-natural hemisynthetic derivatives have been assayed as insect antifeedants against larvae of the lepidopteran *Spodoptera littoralis* (Boisduval) in order to investigate how the changes in the structure influence the antifeedant activity. The results of the bioassays have been compared with the activity of the potent antifeedant ajugarin I.

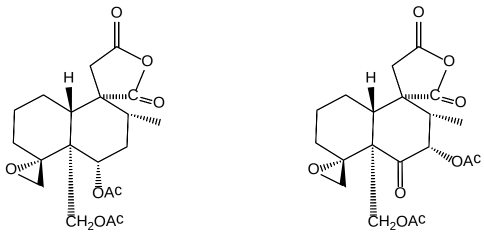
Bioassay data showed that ajugarin I was the most potent agent among the 17 tested diterpenes (3 natural and 14 hemi-synthetic). Modification of the functional groups present in the ajugarin I molecule resulted in a decrease of antifeedant activity. For example, a comparison of the activity of ajugarin I with that of montanine C (**4**) and its chemical derivatives having an identical decalin core, bearing 4α,18-oxirane ring and two acetoxy groups at 6α and 19 position, indicates that the functional groups on the C-9 side-chain influence the antifeedant activity of the compound. The results of the biological tests indicate that the presence of a lactone instead of the furan ring in the C-1 – C-16 substructure increases the activity of the compounds and that the regiochemistry of the lactone is important. Compounds having identical 15,16-*γ*-lactone (Aa, Fig. 4) moiety as that occuring in ajugarin I showed more potent antifeedant activity than the compounds having 16,15-*γ*-lactone (Ab, Fig. 4).



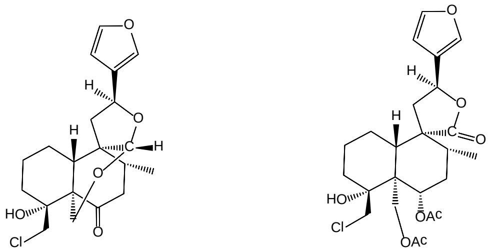
R = 2H; *α*,*β*-OH,H; =O; *α*,*β*-OAc,H; *α*,*β*-OMe,H.

a) 15,16-*γ*-lactone b) 16,15-*γ*-lactone

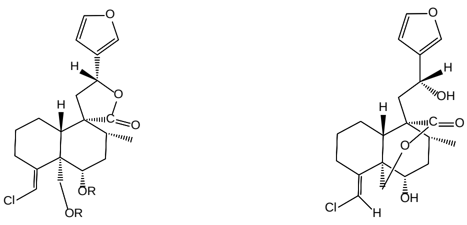
**A:** *α*,*β*-Unsaturated -*γ*-lactones



**B:** 13,14,15,16-Tetranor-neo-clerodanes

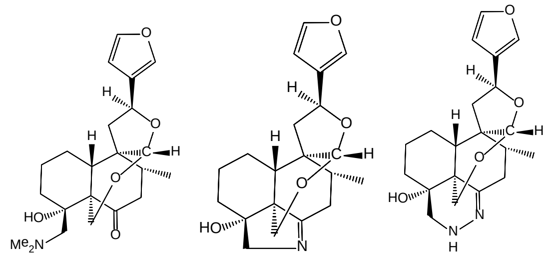


**C:** Chlorohydrins



R = H;
R = OAc

**D:** vinyl chlorides



a) Amine b) 1-Pyrroline c) 2-Pyridazoline

**E:** N-containing derivatives

**Fig. 4.** Hemi-synthetic derivatives of the *neo*-clerodane diterpenes montanine C (**7**), teucrin $P_1$ (**12**) and teupolin III (**17**).

The chemical reactions leading to the opening of the 4*α*,l8-oxirane ring result in an antifeedant index with a negative value. Diterpenoids that are bridged by an oxygen atom between C-19 and C-20 either stimulate feeding or are inactive. Activity of all 13,14,15,16-tetranor-*neo*-clerodanes was drastically decreased.

Consequently, in order to optimize the antifeedant activity of natural *neo*-clerodanes from *Teucrium* by chemical transformations, the 4α,l8-oxirane needs to be maintained and the furan ring should be oxidized.

## REFERENCES

1. B. Kuzmanov, Flora Reipublicae Popularis Bulgaricae, **IX**, 241 (1989).
2. A. Ulubelen, G. Topgu, U. Sonmez, *Studies in Natural Products Chemistry*, **23**, 591, (2000).
3. M. Bruno, Piozzi F., Rosselli S., *Nat. Prod. Rep.*, **19**, 357 (2002).
4. R. Li, S. L. Morris-Natschke, Kuo-Hsiung Lee, *Nat. Prod. Rep.*, **33**, 1166, (2016).
5. A. T. Merritt, S. V. Ley, *Nat. Prod. Rep.*, **9**, 243 (1992).
6. P. Y. Malakov, G. Y. Papanov, N. M. Mollov. *Tetrahedron *Lett.*, **23**, 2025 (1978).
7. I. Kubo, Y. W. Lee, V. Balogh-Nair, K. Nakanishi, A. Chapia, *J. Chem. Soc. Chem. Commun.*, **22**, 949 (1976).
8. E. Fujita, I. Uchida, T. Fujita, N. Masaki, K. Osaki, *J. Chem. Soc. Chem. Commun.*, **0** (20), 793 (1973).
9. P. Y. Malakov, G. Y. Papanov, N. M. Mollov, S. L. Spassov, *Z. Naturforsch.*, **33b**, 789 (1978).
10. P. Y. Malakov, G. Y. Papanov, N. M. Mollov, S. L. Spassov. Z. *Naturforsch.*, **33b**, 1142 (1978).
11. P. Y. Malakov, G. Y. Papanov., N. M. Mollov, *Z. Naturforsch.*, **34b**, 1370 (1979).
12. D. P. Popa, A. F. Tkhuk, *Chem. Nat. Compd.*, **13** (1), 42 (1977).
13. E. Gacs-Baitz, L. Radics, G. B. Oganessian, V. A. Mnatsakanian, *Phytochemistry*, **17**, 1967 (1978).

16. G. Y. Papanov, P. Y. Malakov, *Z. Naturforsch*., **35b**, 764 (1980).
17. P. Y. Malakov, G. Y. Papanov, *Phytochemistry*, **24** (2), 301 (1985).
18. D. P. Popa, A. M. Reinbol'd, *Khim. Prirodn. Soedin*., **67**, 27 (1972).
19. A. M. Reinbol'd, D. P. Popa, *Khim. Prirodn. Soedin*., **10**, 589 (1974).
20. G. Savona, M. C. Garcia-Alvarez, B. Rodriguez. *Phytochemistry*, **21** (3), 721 (1982).
21. G. Y. Papanov, P. Y. Malakov, F. Bohlmann, *Phytochemistry*, **20**, 170 (1981).
22. G. Y. Papanov, P. Y. Malakov, *Z. Naturforsch*., **36b**, 112 (1981)
23. G. Y. Papanov, P. Y. Malakov, *Z. Naturforsch*., **37b**, 519 (1982)
24. P. Y. Malakov, G. Y. Papanov, *Phytochemistry*, **24** (2), 297 (1985).
25. G. Y. Papanov, P. Y. Malakov, *Phyrochemistry*, **22** (12), 2787 (1983).
26. P. Y. Malakov, G. Y. Papanov, *Z. Naturforsch.*, **42b**, 1000 (1987).
27. P. Y. Malakov, G. Y. Papanov, I. M. Boneva, *Phytochemistry*, **31** (11), 4029 (1992).
28. T. Miyase, H. Kawasaki, T. Noro, A. Ueno, S. Fukushima, T. Takemoto, *Chem. Pharm. Bull.*, **29** (12), 3561 (1981).
29. A. Fiorentino, B. D'Abrosca, S. Pacifico, M. Scognamiglio, G. D'Angelo, M. Gallicchio, A. Chambery, P. Monaco, *Phytochemistry*, **72**, 2037 (2011).
30. P. Y. Malakov, I. M. Boneva, G. Y. Papanov, S. L. Spasov, *Phytochemistry*, **27**, 1141 (1988).
31. M. C. De La Torre, F. Fernandez-Gadea, A. Michavila, B. Rodriguez, F. Piozzi, G. Savona, *Phytochemistry*, **25** (10), 2385 (1986).
32. M. C. Garcia-Alvarez, G. Lukacs, A. Neszmelyi, F. Piozzi, B. Rodriguez, G. Savona, *J. Org. Chem.,* **48**, 5123 (1983).
33. I. V. Boneva, P. Y. Malakov, G. Y. Papanov, *Phytochemistry*, **27**, 295 (1988).
34. G. Savona, M. P. Paternostro, F. Piotzi, J. R. Hanson, P. B. Hitchcock, S. A. Thomas, *J. Chem. Soc. Perkin Trans. I*, **6**, 1915 (1979).
35. G. Savona, M. Paternostro, F. Piozzi, B. Rodriguez, *Tetrahedron Letters*, **4**, 379 (1979).
36. P. Y. Malakov, G. Y. Papanov, I. M. Boneva, M. C. De La Torre, B. Rodriguez, *Phytochemistry*, **34** (4), 1095 (1993).
37. G. Savona, M. Paternostro, F. Piozzi, B. Rodriguez, *Heterocycles*, **14**, 193 (1980).
38. J. Fayos, F. Fernandez-Gadea, C. Pascual, A. Perales, F. Piozzi, M. Rico, B. Rodriguez, G. Savona, *J. Org. Chem.*, **49**, 1789 (1984).
39. E. Gacs-Baitz, G. Y. Papanov, P. Y. Malakov, L. Szilagy, *Phytochemistry*, 26 (7), 2110 (1987).
40. P. Y. Malakov, G. Y. Papanov, B. Rodriguez, M. C. De La Torre, M. S. J. Simmonds, W. M. Blaney, I. M. Boneva, *Phytochemistry*, **37** (1), 147 (1994).