

# Comparative Study of *Tanacetum* Species Growing in Bulgaria

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Chemical investigation of the Bulgarian species *Tanacetum. parthenium*, *T. millefolium*, *T. achilleifolium*, *T. corymbosum* and *T. macrophyllum* afforded in addition to 24 known sesquiterpene lactones a new 12, 8-eudesmanolide **22**. Besides, four known highly oxygenated terpenoids and a new keto-diol **30** of the rare iphionane skeleton were also isolated. The structures were elucidated on the basis of their spectral properties. The accumulation of the different sesquiterpene lactones in the studied species and there classification is discussed.

## Introduction

The genus *Tanacetum* is one of the largest genera in Asteraceae family comprising 14 species distributed in Europe (Heywood, 1976). However, its exact position is not yet determined as it is considered to be quite heterogenous regarding the botanical classification. Thus, some of the *Tanacetum* species are believed to belong to the genus *Chrysanthemum*, while others are classified under the genus *Pyrethrum*. The taxonomical rank of some *Tanacetum* species is also under discussion. Thus, Heywood described *T. millefolium* and *T. achilleifolium* as two different species although they are not always clearly separated (Heywood, 1976), while Stojanov *et al.* based on the close morphological grounds treats them as varieties of *T. millefolium* – *var. millefolium* and *var. achilleifolium* (Stojanov *et al.*, 1967). The chemical composition of *Tanacetum* species have received much attention because the terpenoids, in particular the sesquiterpene lactones, are believed to play a substantial role in the plant taxonomy. Moreover, most of them have shown to possess different biological activities (Abad *et al.*, 1995).

The *Tanacetum* genus is represented in Bulgaria by six species (Andreev *et al.*, 1992), of which *T. vulgare* L and *T. macrophyllum* (Waldst. & Kit.) Schultz Bip. have been previously studied by us (Todorova and Ognyanov, 1985; Todorova and Ognyanov, 1999; Ognyanov and Todorova, 1983). Continuing the chemical investigation of Bulgarian medicinal plants of the Asteraceae family we

extended our examination on the other four species – *T. achilleifolium* (Bieb.) Schultz Bip., *T. millefolium* (L) Tzvelev, *T. corymbosum* (L) Schultz Bip., *T. parthenium* (L) Schultz Bip. The literature search revealed that *T. parthenium* had been subject of many scientific papers reviewed by Milbrodt *et al.* (1997) and Knight *et al.* (1995). However, no work had been reported so far on *T. millefolium* and *T. achilleifolium*. Very recently the study appeared on *T. corymbosum* (Milosavljevic *et al.*, 1999).

The present study focuses on the sesquiterpene lactone profile of the Bulgarian *Tanacetum* species.

## Experimental

### Plant material

The aerial parts of the studied samples were collected at flowering stage in July, 1999 from the following locations: Black Sea coast near Kavarna (*T. achilleifolium* and *T. millefolium*) and Losenka mountain (*T. corymbosum*, *T. macrophyllum* and *T. parthenium*). Voucher specimens (L 9931–9935, respectively) were deposited in the Herbarium of the Institute of Botany, Bulgarian Academy of Sciences, Sofia.

### Extraction and isolation

The air-dried leaves and flowers of each sample (the amounts are given below) were extracted exhaustively with CHCl<sub>3</sub> (3 × 600 ml) at room tem-

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perature. After evaporation of the solvent under reduced pressure the resulting extracts were worked up as described earlier (Todorova and Ognyanov, 1985). The crude lactone fractions (see below) were separated by column chromatography (CC) on silica gel, using solvent mixtures (n-hexane / acetone) with increasing polarity. The fractions containing lactones (IR control) were further subjected to repeated CC and/or prep.TLC (silica gel) to yield the individual components. The known compounds were identified by spectroscopic methods and TLC comparison using authentic samples as references.

*T. parthenium* (340 g) afforded 5.0 g lactone fraction which yielded: **1** (24 mg), **2** (6 mg), **3** (5 mg), **4** (4 mg), **5** (5 mg), **6** (6 mg), **7** (15 mg), **8** (11 mg), **9** (4 mg), **10** (3 mg), **11** (4 mg), **12** (6 mg), **13** (5 mg), **14** (3 mg) and **15** (7 mg).

*T. millefolium* (240 g) afforded 2.1 g lactone fraction which yielded: **16** (160 mg), **17** (4 mg), **18** (15 mg), **19** (15 mg) and **20** (12 mg).

*T. corymbosum* (134 g) afforded 2.2 g lactone fraction which yielded: **21** (8 mg) and **22** (10 mg)

#### *1β,4α-Dihydroxy-6α-tigloyloxy-11 (13)-eudesmen-12,8-olide (22)*

Colourless oil, CIMS (APCI)  $m/z$  (rel. int.) 365  $[M+1]^+$  (8), 347  $[M+1-18]^+$  (42), 265  $[M+1-100]^+$  (48), 247  $[347-100]^+$  (100), 229  $[247-18]^+$  (93), 182 (52).  $^1H$  NMR (250 MHz, in  $CDCl_3$ )  $\delta$ : 3.49 (1H, dd, 4.0, 9.7, H-1), 1.93 (1H, d, 10.8, H-5), 4.05 (1H, ddd, 3.9, 11.8, 11.8, H-8), 2.87 (1H, br. t., 11.8, H-7), 5.79 (1H, dd, 10.8, 11.8, H-6), 5.25 (1H, d, 2.9, H-13), 6.07 (1H, d, 3.1, H-13'), 2.54 (1H, dd, 3.8, 11.8, H-9), 1.48 (1H, t, 11.8, H-9'), 1.60–1.80 (4H, m, 2H-2 and 2H-3), 1.05 (3H, s, H-14), 1.26 (3H, s, H-15), 6.95 (1H, qq, 1.3, 7.0, H-3'), 1.83 (3H, dq, 7.0, 1.3, H-4'). 1.88 (3H, dq, 1.3, 1.3, H-5').

*T. macrophyllum* (117 g) afforded 2.0 g lactone fraction which yielded: **2** (5 mg), **3** (3 mg), **5** (4 mg), **6** (6 mg), **23** (9 mg), **24** (2 mg), **25** (7 mg), **26** (3 mg), **27** (7 mg), **28** (12 mg), **29** (11 mg), **30** (8 mg).

#### *5β,11-Dihydroxy-iphionan-4-one (30)*

White powder; EIMS (70 eV)  $m/z$  (rel. int.) 254  $[M]^+$  (1), 236  $[M-18]^+$  (3), 221  $[236-15]^+$  (8), 203  $[221-18]^+$  (10.5), 195  $[M-(CH_3)_2COH]^+$  (8), 178

$[221-CH_3CO]^+$  (67.7), 170 (95.2), 152 (92.7), 135 (87.9), 109 (74.2), 97 (30.6), 95 (28.2), 93 (29.8), 81 (41.1), 71 (38.7), 59 (61.3), 55 (33.3), 43 (100);  $^1H$  NMR (250 MHz, in  $CDCl_3$ )  $\delta$ : 1.00 (s, 3H, H-14), 1.18 (s, 6H, H-12 and H-13), 2.18 (s, 3H, H-15), 3.35 (dd, 1H, H-3,  $J^1=J^2=10$  Hz).

## Results and Discussion

Each of the plant samples was extracted with chloroform and the fractions enriched in sesquiterpene lactones were worked up as described in the experimental section to give the individual components. Their identification and structure elucidation were achieved using spectral methods.

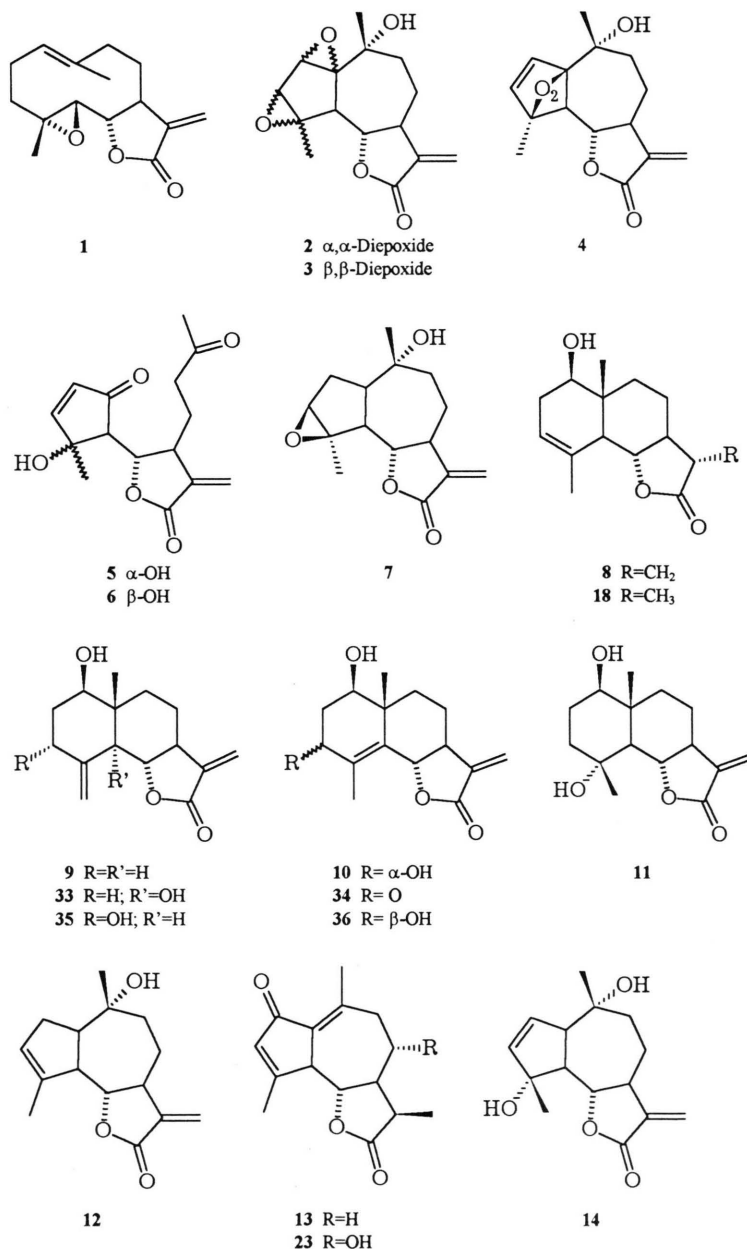
*T. parthenium* afforded fifteen sesquiterpene lactones, including the single germacranolide parthenolide (**1**) (Govindachari *et al.*, 1964) which was the major one. The latter, as well as canin (**2**) artecamin (**3**), tanapartin- $\beta$ -peroxide (**4**), secotanapartholides – A (**5**) and -B (**6**) (Bohlmann and Zdero, 1982), 3,4- $\beta$ -epoxy-8-deoxycumambrin B (**7**) (Milbrodt *et al.*, 1997), santamarin (**8**) (Appendino *et al.*, 1982) and reynosin (**9**) (Samek *et al.*, 1973) are known constituents for *T. parthenium*. However, the eudesmanolides armefolin (**10**) (Mata *et al.*, 1984) and  $1\beta$ -hydroxyarbusculin A (**11**) (Samek *et al.*, 1973) were found for the first time in this species. Furthermore, the guaianolides 8-deoxycumambrin B (**12**) (Sosa *et al.*, 1989), achillin (**13**) (Marco *et al.*, 1988),  $4\alpha,10\alpha$ -dihydroxy-1,5H-guaia-2,11(13)dien-12,6 $\alpha$ -olide (**14**) (Zdero *et al.*, 1987) and  $10\beta$ -hydroxycichopumelide (**15**) (El-Masry *et al.*, 1984) have not been reported so far as constituents of any *Tanacetum* species.

This is the first study of *T. achilleifolium* and *T. millefolium*. Surprisingly, the lactone fractions of these two species proved to be practically identical regarding the main components which were identified as the eudesmanolides vulgarin (**16**) (Ohno *et al.*, 1980), 4-*epi*-vulgarin (**17**) (González *et al.*, 1983) and 11,13-dihydro-santamarine (**18**) (Shafizadeh *et al.*, 1971). Among them, the lactone **16** was the principal constituent. In addition, two davanone derivatives **19** and **20** (Appendino *et al.*, 1984) were also isolated.

*T. corymbosum* of Serbian origin is reported to be free of sesquiterpene lactones (Milosavljevic *et al.*, 1999). However, two closely related lactones

**21** and **22** were isolated from this species of Bulgarian origin. Whereas the eudesmanolide 1 $\beta$ ,4 $\alpha$ ,6 $\alpha$ -trihydroxy-11(13)-eudesmen-12,8-olide (**21**) had been found previously in *T. densum* (Gören *et al.*, 1993), the lactone **22** proved to be a new natural product. Its structure followed easily from the MS and  $^1\text{H}$  NMR spectra which revealed that the only difference in **21** and **22** is the presence of an ester side chain in **22**. The latter was

identified as a tigloyloxy group the position of which at C-6 followed from the downfield shift of H-6 signal and its vicinal interactions with H-5 and H-7. COSY experiments allowed the assignment of all the proton signals. The relative stereochemistry at the chiral centres was derived from the observed spectral data and NOE measurements. Thus, the lactone no. **22** was 1 $\beta$ ,4 $\alpha$ -dihydroxy-6 $\alpha$ -tigloyloxy-11(13)-eudesmen-12,8-olide.



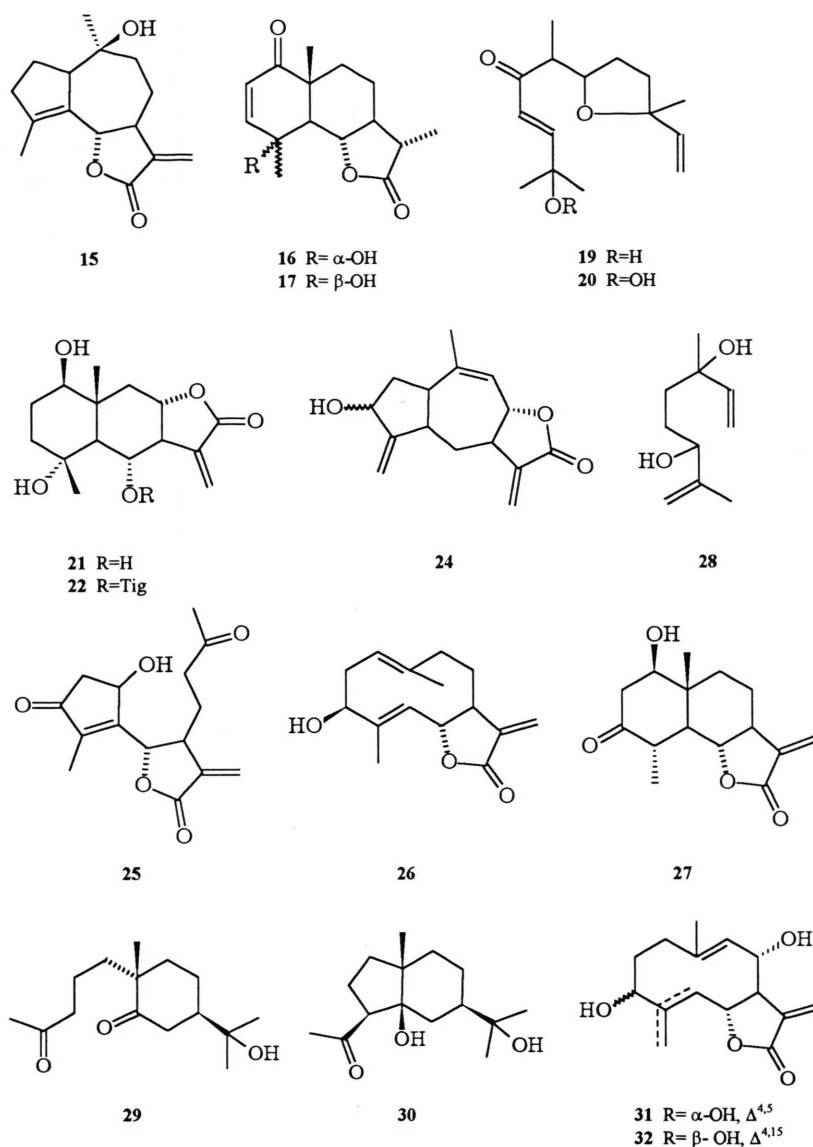


Fig. 1. **1**: parthenolide; **2**: canin; **3**: artemisin; **4**: tanapartin- $\beta$ -peroxide; **5**: secotanaparthalide-A; **6**: secotanaparthalide-B; **7**: 3,4- $\beta$ -epoxy-8-deoxycumambrin B; **8**: santamarin; **9**: reynosin; **10**: armefolin; **11**: 1 $\beta$ -hydroxyarbusculin A; **12**: 8-deoxycumambrin B; **13**: achillin; **14**: 4 $\alpha$ , 10 $\alpha$ -dihydroxy-1,5H-guaia-2,11(13)dien-12,6 $\alpha$ -olide; **15**: 10 $\beta$ -hydroxycichopumelide; **16**: vulgarin; **17**: 4-*epi*-vulgarin; **18**: 11,13-dihydro-santamarine; **19**: hydroxydavanone; **20**: hydroperoxy davanone; **21**: 1 $\beta$ ,4 $\alpha$ ,6 $\alpha$ -trihydroxy-11(13)-eudesman-12,8-olide; **22**: 1 $\beta$ ,4 $\alpha$ -dihydroxy-6 $\alpha$ -tigloyloxy-11(13)-eudesman-12,8-olide; **23**: 8 $\alpha$ -hydroxyachillin; **24**: macrotanacin; **25**: tanaphillin; **26**: hanfillin; **27**: artemalin; **28**: 2,6-dimethyl-1,7-octadien-3,6-diol; **29**: 11-hydroxy-4,5-secoeudesmane-4,5-dione; **30**: 5 $\beta$ ,11-dihydroxy-iphionan-4-one; **31**: tatridin-A; **32**: tatridin B; **33**: tanacetin; **34**: 1-*epi*-ludovicin C; **35**: 3 $\alpha$ -hydroxyreynosin; **36**: 3-*epi*-armefolin.

The repeated examination of *T. macrophyllum* yielded, in addition to the previously isolated lactones **2**, **3**, **23–26** (Todorova and Ognyanov, 1985), secotanaparthalides – A (**5**) and -B (**6**) (Bohlmann *et al.*, 1982) and artemalin (**27**) (Geissman *et*

*al.*, 1969). Whereas the lactones **5** and **6** are known constituents of *Tanacetum* species, artemalin (**27**) has not been found so far in the genus *Tanacetum*. Furthermore, three non-lactonic terpenoids, **28–30** were also isolated which proved to be new for

the genus *Tanacetum*. Of them, the acyclic monoterpene diol **28** has been found in *Cinnamomum camphora* (Takaoka, 1976), and the secoeudesmane **29** has been isolated from *Eriocephalus* species (Asteraceae) (Zdero *et al.*, 1987). The compound **30** had not been found before. Its structure was deduced by means of the following spectroscopic data. The EI mass spectrum was very informative showing besides the molecular peak  $[M]^+$  at  $m/z$  254 consistent with a molecular formula  $C_{15}H_{26}O_3$ , the fragments at  $m/z$  236  $[M-H_2O]^+$ , 221  $[236-CH_3]^+$ , 218  $[236-H_2O]^+$ , 195  $[M-(CH_3)_2COH]^+$  and 178  $[221-CH_3CO]^+$ , which revealed the presence of one OH group, one hydroxyisopropyl moiety and a methyl ketone group. The  $^1H$  NMR spectrum exhibited signals for four methyl groups – an angular methyl ( $\delta$  1.00), two methyls of a hydroxyisopropyl group ( $\delta$  1.18, s, 6H), and a methyl ketone ( $\delta$  2.18). Further, a proton triplet is visible at  $\delta$  3.32, which was assigned to H-3. These data were accommodated by the carbocyclic iphionane skeleton, bearing a ketone group at C-4 and two hydroxyl groups at C-5 and C-11. Hence, the new terpenoid **30** was identified as 5 $\beta$ ,11-dihydroxy-iphionan-4-one. The latter is a representative of the rarely occurring type of sesquiterpenoids in which the six-membered ring of an eudesmane skeleton has undergone ring contraction. The co-occurrence of 4,5-seco-eudesmane compounds and that with iphionane skeleton, reported also in other species of Asteraceae family (El-Ghazouly *et al.*, 1987; Castilo *et al.*, 1995; Jaku-

povic *et al.*, 1992) supports their biogenetic relationship.

The overall picture of the sesquiterpene lactones found in the *Tanacetum* species growing in Bulgaria is presented in Table I. The studied taxa are classified under two different sections according to the botanical characteristics. To a certain extent the results of our investigation are in agreement with this classification. Thus, *T. achilleifolium* and *T. millefolium* belonging to section *Tanacetum* produce one skeletal type of lactones only. Moreover, they are the only Bulgarian *Tanacetum* species producing 11,13-dihydroeudesmanolides, a fact which could be of chemotaxonomical interest. The other member of this section, *T. vulgare* was studied by us earlier, and the results revealed that this species is also producing lactones of one skeletal type only (Todorova and Ognyanov, 1999). Moreover, as can be seen in Table I, the existence of three chemotypes is demonstrated – germacranolide (sample *T. vulgare* 1), eudesmanolide (sample *T. vulgare* 2) and lactone free (sample *T. vulgare* 3). The identical chemical composition of *T. achilleifolium* and *T. millefolium* found by us could indicate the close relationship between these two taxa. Many intermediate forms observed as well as lack of any chemical evidence for the differentiation of these two species strongly support the classification of Stojanov *et al.* (1967) who described two varieties of *A. millefolium* – var. *millefolium* and var. *achilleifolium*.

Table I. Sesquiterpene lactones found in the Bulgarian *Tanacetum* species.

I. Sect. <i>Tanacetum</i>			
	Ger	Gu	Eu
<i>T. vulgare</i> -1*	<b>31, 32</b>	–	–
<i>T. vulgare</i> -2*	–	–	<b>9, 10, 11, 18, 33, 34, 35, 36</b>
<i>T. vulgare</i> -3*	–	–	–
<i>T. achilleifolium</i>	–	–	<b>16, 17, 18</b>
<i>T. millefolium</i>	–	–	<b>16, 17, 18</b>
II. Sect. <i>Pyrethrum</i>			
<i>T. corymbosum</i>	–	–	<b>21, 22</b>
<i>T. macrophyllum</i>	<b>26</b>	<b>2, 3, 5, 6, 23, 24, 25</b>	<b>27</b>
<i>T. parthenium</i>	<b>1</b>	<b>2, 3, 4, 5, 6, 7, 12, 13, 14, 15</b>	<b>8, 9, 10, 11</b>

\* Published data (Todorova and Ognyanov, 1999).

Ger – germacranolides; Gu – guaianolides; Eu – eudesmanolides.



Further, two of the species belonging to Sect. *Pyrethrum* (*T. parthenium* and *T. macrophyllum*) produce lactones of all the three skeletal types. Of them, the guaianolides are the most abundant and with a large variety of oxygen containing functional groups, although the germacranolide parthenolide (**1**) is the major lactone in *T. parthenium*. Surprisingly, the third member of this section, *T. corymbosum* contained only lactones of the considerably small group of eudesman-12,8-olides which are not typical for the genus *Tanacetum*.

Hence, the sesquiterpene lactone profile of the Bulgarian *Tanacetum* species studied is in agreement with the botanical classification with

the only exception – *T. corymbosum*. This species, producing one skeletal type of lactones appears to be closer to the species of sect. *Tanacetum*. Moreover, similar to sample *T. vulgare* 3, a collection of *T. corymbosum* from Serbia was reported to be free of lactones. All these results could be an indication for reconsideration the position of *T. corymbosum*.

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