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Taxoids from the Heartwood of *Taxus baccata* L. Growing in Turkey

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Abstract – The ethanolic extract of the heartwood of *Taxus baccata* L. afforded six taxoids, belonging to the skeletally three different groups, 2α, 5α, 10β-triacetoxy-14β-(2-methyl)-butryloxy-4(20),11-taxadiene (**1**), taxusin (**2**), baccatin VI (**3**), baccatin III (**4**), 1β-hydroxybaccatin I (**5**) and taxol (**6**). The isolation and structure elucidation of three taxoids (**3-5**) have been presented in this study. This is the first report for the presence of these taxoids in *Taxus baccata* L. growing in Turkey.
Key words – *Taxus baccata*, Taxaceae, taxoids, spectral data

Introduction

A large number of taxoids possessing various skeleton types have been isolated from various tissues of different *Taxus* species since the discovery of anticancer agent paclitaxel (Taxol®) (Baloğ lu and Kingston, 1999; Parmar *et al.*, 1999). A complex nitrogen-containing diterpenoid, paclitaxel was first isolated from the bark of the Pacific yew tree, *Taxus brevifolia* Nutt (Wani *et al.*, 1971). It is widely used as an anticancer drug for breast, ovarian, non-small lung cancer and Kaposi's sarcoma as alone or in combination with other anticancer agents. In the future, the efficacy of taxol may be shown for other types of malignancies (Rowinsky, 1997; Eisenhauer and Vermorken, 1998).

Genus *Taxus* L. (Taxaceae) is widely spread in the world which includes five genera and represented by seven or eight species. There is only one *Taxus* species growing in Turkey, namely *Taxus baccata* L. (European yew). It grows from Britain to North Iran (Davis and Cullen, 1965; Erdemğlu and Şener, 1998).

In this publication, the taxoids of *T. baccata* L. growing in Turkey were investigated. The occurrence of two (**1**, **2**) out of six taxoids was determined in our previous work (Erdemoğlu *et al.*, 1999). The spectroscopical features of taxol (**6**) were elucidated in detail previously (Chmurny *et al.*, 1992; Falzone *et al.*, 1992). The isolation and full structural elucidation of the other three taxoids, baccatin VI (**3**), baccatin III (**4**) and 1β-hydroxybaccatin I (**5**), from the heartwood of *Taxus baccata* L. growing in Turkey were presented in this study.

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Experimental

Plant material – *Taxus baccata* L. (Taxaceae) was collected from the vicinity of Çamlşhem, Rize, tTurkey, in June 1995. A voucher specimen (coded as GUE 1560) was kept in the Herbarium of the Faculty of Pharmacy, Gazi University, Ankara.

Instrumentation – The IR spectra were taken in KBr pellet on a Bruker Vector 22 FT-IR Spectrophotometer. The ^{1}H-, ^{13}C-NMR, DEPT 135, HMQC and HMBC spectra were obtained on a Jeol JNM-Alpha 500 (500 MHz) FT-NMR Spectrometer in $CDCl_3$, using TMS as an internal standard. The chemical shifts were expressed as ppm. The FAB-MS was measured on a Jeol JMS-SX 102A Tandem Mass Spectrometer. The DCI spectra were recorded on a MS 80 MASPEC Spectrometer. Column chromatography was carried out on Silica gel (Kieselgel 60, 0.063-0.200 mm, Art. 7734, Merck) and TLC was conducted on precoated plates (Kieselgel 60 F_{254}, Art. 5554, Merck). The spots were detected at UV (254 nm) and spraying with anisaldehyde reagent [methanol 76% (Merck), o-phosphoric acid 19% (Riedel-De Haën 85%), p-anisaldehyde 5% (Merck 98%)] followed by heating.

Extraction, isolation and purification – The air-dried and powdered heartwood of *T. baccata* (3078 g) was extracted with EtOH % 95 at room temperature. The EtOH extract was evaporated *in vacuo* and it was obtained as a reddish residue. This residue was diluted with H_2O and the aqueous solution was extracted with $CHCl_3$. The combined $CHCl_3$ extracts

were dried over anhydrous sodium sulfate. Thereafter, the solution was evaporated to dryness *in vacuo*. The $CHCl_3$ extract (49 g) was subjected to column chromatography on silica gel. Elution was carried out with increasing polarities of hexane→Me_2O→$CHCl_3$→MeOH mixtures. Seven main fractions (I-VII) were collected according to TLC analysis.

Exocyclic double bond containing taxoids, **1** and **2**, were obtained from the fractions I and II. Fractions I and II were further purified by CC, prep. tlc and recrystallization to give compounds **1** (3.6 mg, 0.0002%) and **2** (171 mg, 0.011%). Fraction III was chromatographed on prep. tlc to give **3** (40.5 mg, 0.0025%). Fraction IV was crystallized from hexane: acetone (1:1) mixture to afford **4** (155.4 mg, 0.0096%). Fraction V was subjected over a silica gel column to give fifteen subfractions. These subfractions were purified by CC and prep. tlc to provide **5** (76.4 mg, 0.0047%) and **6** (6.1 mg, 0.0004%).

Baccatin VI (3): Obtained as a light yellow amorphous powder; IR ν_{maks} (KBr)cm^{-1} : 3470 (OH), 1746, 1734, 1726, 1710 (ester CO); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ, ^{13}C-NMR ($CDCl_3$, 125 MHz) δ, DEPT 135 ($CDCl_3$, 125 MHz) ä, HMQC and HMBC were given in Table 1; FAB-MS (+) *m/z*: 715 $[M+H]^+$; DCI+(NH_3) m/z: 656 $[MH-CH_3COO^-]^+$, M^+: 714, $C_{37}H_{46}O_{14}$.

Baccatin III (4): Obtained as white needles from hexane:acetone (1:1) mixture; IR ν_{maks} (KBr) cm^{-1} : 3465 (OH), 1725, 1711, 1699 (ester CO), 1695 (CO), 1585, 1605 (C=C); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ, ^{13}C-NMR ($CDCl_3$, 125 MHz) δ, DEPT 135 ($CDCl_3$, 125 MHz) δ, HMQC and HMBC were given in Table 2; FAB-MS (+) *m/z*: 587 $[M+H]^+$; DCI + (NH_3) *m/z*: 604 $[M+NH_4]^+$, 587 $[M+H]^+$, M^+: 586, $C_{31}H_{38}O_{11}$.

1β-Hydroxybaccatin I (5): Obtained as a white crystalline compound from MeOH; IR ν_{maks} (KBr) cm^{-1} : 3568, 3510 (OH); 1751, 1743, 1740, 1734, 1730, 1719 (ester CO); 1140, 1030 (C-O-C); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ, ^{13}C-NMR ($CDCl_3$, 125 MHz) δ, DEPT 135 ($CDCl_3$, 125 MHz) δ, HMQC and HMBC were given in Table 3; FAB-MS (+) *m/z*: 593 $[MH-CH_3COOH]^+$; DCI+(NH_3) *m/z*: 670 $[M+NH_4]^+$, 653 $[M+H]^+$; M^+: 652, $C_{32}H_{44}O_{14}$.

Taxol (6): Obtained as a white amorphous powder. Taxol was identified by comparison with the reported data and its spectroscopical features were investigated in detail, previously (Chmurny *et al.*, 1992; Falzone *et al.*, 1992).

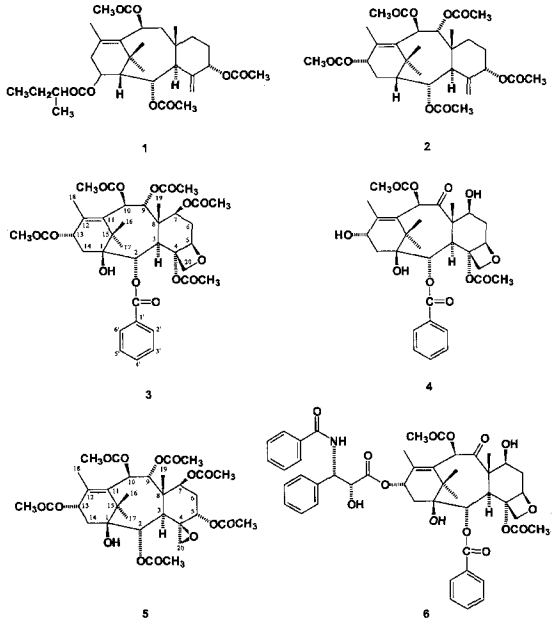

Fig. 1. Structures of compounds **1-6**.

Results

In our continuing research for bioactive compounds of *Taxus baccata* growing in Turkey, the heartwood of the plant was found to be richer than the other parts in terms of constituents (Erdemoğlu, 1993). According to the procedure described in the experimental section, six taxoids (**1-6**), representing skeletally three different groups, have been isolated using column chromatography and prep. tlc. The structures of these compounds were identified by comparison of their spectral data with to those in the literature. In addition, their structures confirmed by extensive 2D NMR methods. The spectral data of **6** has been reported in detail previously (Chmurny *et al.*, 1992; Falzone *et al.*, 1992). The spectral data of **3-5** were given in Tables 1-3. Besides all, this is the first report for the presence of taxoids in *Taxus baccata* L. growing in Turkey and their structures are summarized as follows:

a) 2α,5α,10β-triacetoxy-14β-(2-methyl)-butryloxy-4(20),11-taxadiene (**1**) and taxusin (**2**) were identified as exocyclic methylene containing taxoids.

b) baccatin VI (**3**), baccatin III (**4**) and taxol (**6**) were determined as an oxetane ring possesing taxoids.

c) 1β-hydroxy baccatin I (**5**) was elucidated as an epoxide ring possesing taxoid.

Table 1. Spectral data of baccatin VI (**3**)

Position	^{1}**H** (J,Hz)	^{13}C (HMQC)	DEPT	HMBC
1	–	78.89	C	–
2	5.89 d (6.10)	73.25	CH	2-O-COC$_6$H$_5$, C-3
3	3.19 d (6.10)	47.30	CH	C-4, C-8, C-1, C-20, C-2
4	–	81.50	C	–
5	4.99 d (8.85)	83.86	CH	C-7, C-4
6α	1.87 m	34.51	CH$_2$	C-5, C-7
6β	1.84 m			C-5, C-7, 7-OCOCH$_3$
7	5.57 t (8.85)	71.76	CH	7-OCOCH$_3$, C-19
8	–	45.78	C	–9-OCOCH3, C-7
9	6.03 d (11.29)	75.03	CH	C-15, C-9, C-12, 10-OCOCH$_3$, C-11
10	6.24 d (11.29)	70.38	CH	–
11	–	133.61	C	–
12	–	141.28	C	C-12, 13-OCOCH$_3$, C-11
13	6.19 t (8.85)	69.65	CH	C-13, C-12
14α	2.22 m	35.12	CH$_2$	C-1, C-2
14β	2.22 m			–
15	–	42.79	C	C-17, C-15, C-1, C-11
16	1.78 s	22.27	CH$_3$	C-16, C-15, C-1, C-11
17	1.23 s	28.27	CH$_3$	C-12, C-11, C-13
18	2.03 s	14.99	CH$_3$	C-9, C-7, C-8, C-3
19	1.59 s	12.77	CH$_3$	C-4
20α	4.35 d (9.0)	76.41	CH$_2$	C-5
20β	4.15 d (8.24)			–
4-O-COCH$_3$	–	170.48	C	4-OCOCH$_3$
4-O-COCH$_3$	2.19 s	21.23	CH$_3$	–
7-O-COCH$_3$	–	169.88	C	7-OCOCH$_3$
7-O-COCH$_3$	2.10 s	20.78	CH$_3$	–
9-O-COCH$_3$	–	170.20	C	9-OCOCH$_3$
9-O-COCH$_3$	2.10 s	21.40	CH$_3$	–
10-O-COCH$_3$	–	168.91	C	10-OCOCH$_3$
10-O-COCH$_3$	2.00 s	20.94	CH$_3$	–
13-O-COCH$_3$	–	169.14	C	13-OCOCH$_3$
13-O-COCH$_3$	2.28 s	22.74	CH$_3$	–
2-O-COC$_6$H$_5$	–	166.95	C	–
1'	–	129.22	C	C-2',6', C-4', 2-O-COC$_6$H$_5$
2', 6'	8.12 dd (8.24)	130.10	CH	C-1', C-3',5'
3', 5'	7.50 t (7.63)	128.64	CH	C-2',6'
4'	7.63 t (7.63)	133.72	CH	

Table 2. Spectral data of baccatin III (4)

Position	^{1}**H** (J,Hz)	^{13}C (HMQC)	DEPT	HMBC
1	–	78.93	C	–
2	5.61 d (7.02)	74.87	CH	C-14, C-3, C-8, C-1, 2-OCOC$_6$H$_5$
3	3.87 d (7.02)	46.15	CH	C-4, C-2, C-20, C-19, C-8, C-7, 9-CO
4	–	80.60	C	–
5	4.97 dd (9.46)	84.38	CH	C-7, C-4, C-3
6α	2.54 ddd (6.71, 14.65)	35.56	CH$_2$	C-8, C-7, C-5
6β	1.84 ddd (12.82)			C-7, C-5, C-4
7	4.45 m	72.11	CH	C-10, C-19
8	–	58.51	C	–
9	–	204.21	C	–
10	6.32 s	76.34	CH	C-15, C-11, C-12, C-9, 10-OCOCH$_3$
11	–	131.44	C	–
12	–	146.66	C	–

Table 2. Continued

Position	^{1}H (J,Hz)	^{13}C (HMQC)	DEPT	HMBC
13	4.85 brs	67.59	CH	C-12, C-11
14α	2.30 d (18.3)	38.66	CH_2	C-13, C-1, C-15, C-2
14β	2.26 d			C-13, C-1, C-2
15	–	42.58	C	–
16	1.09 s	20.84	CH_3	C-11, C-15, C-1, C-17
17	1.09 s	26.82	CH_3	C-11, C-15, C-1, C-16
18	2.03 s	15.48	CH_3	C-12, C-11, C-13, C-1
19	1.66 s	9.39	CH_3	C-7, C-8, C-3, 9-CO
20α	4.29 d (8.24)	76.23	CH_2	C-4, C-3
20β	4.15 d (8.54)			C-5, C-3, C-4
1-OH	2.85 brs	–	–	C-16
7-OH	2.77 d (4.27)	–	–	C-6
13-OH	1.95 brs	–	–	C-14
4-O-$\underline{CO}CH_3$	–	170.63	C	–
4-O-CO$\underline{CH_3}$	2.27 s	22.46	CH_3	4-O-$\underline{C}OCH_3$
10-O-$\underline{CO}CH_3$	–	171.32	C	–
10-O-CO$\underline{CH_3}$	2.23 s	20.84	CH_3	10-O-$\underline{C}OCH_3$, 9-$\underline{C}O$
2-O-$\underline{CO}C_6H_5$	–	166.91	C	–
1'	–	129.28	C	–
2', 6'	8.08 dd (7.02, 8.24)	129.99	CH	C-1', C-4', 2-O$\underline{C}OC_6H_5$
3', 5'	7.47 t (7.07)	128.56	CH	C-1'
4'	7.60 t (7.7)	133.59	CH	C-2',6', C-3',5'

Table 3. Spectral data of 1β-hydroxybaccatin I (**5**)

Position	^{1}H (J,Hz)	^{13}C (HMQC)	DEPT	HMBC
1	–	76.02	C	–
2	5.50 m	72.11	CH	C-14, C-1, C-3, 2-O$\underline{CO}CH_3$
3	3.19 d (3.05)	41.28	CH	C-19, C-4, C-8, C-2, C-1
4	–	58.25	C	–
5	4.22 brs	77.69	CH	C-7, C-4, C-3, 5-O$\underline{CO}CH_3$
6α	1.74 m	31.06	CH_2	C-7, 5-OCO$\underline{CH_3}$
6β	1.79 m			7-OCO$\underline{CH_3}$, C-8, C-4, C-7
7	5.50 m	68.67	CH	C-8, C-3, 7-O$\underline{CO}CH_3$
8	–	46.57	C	–
9	6.04 d (11.29)	75.14	CH	C-7, C-8, C-10, 7-O$\underline{CO}$CH3
10	6.22 d (10.99)	70.70	CH	C-15, C-9, C-12, C-11, 10-O$\underline{CO}CH_3$
11	–	135.62	C	–
12	–	140.31	C	–
13	6.09 bt (8.08)	71.11	CH	C-12
14α	1.90 dd (6.72, 14.65)	38.54	CH_2	C-17, C-15, C-13, C-1
14β	2.54 dd (9.76, 14.95)			C-12, C-1, C-10
15	–	43.24	C	–
16	1.24 s	28.40	CH_3	C-17, C-15, C-11
17	1.66 s	21.78	CH_3	C-16, C-15, C-1, C-11
18	2.23 s	15.37	CH_3	C-10, C-1, C-11, C-12
19	1.25 s	13.64	CH_3	C-9, C-8, C-3, C-7
20a	3.55 d (4.88)	49.88	CH_2	–
20b	2.32 d (5.19)			–
2-O-$\underline{CO}CH_3$	–	169.28	C	–
2-O-CO$\underline{CH_3}$	2.24 s	21.63	CH_3	2-O$\underline{CO}CH_3$
5-O-$\underline{CO}CH_3$	–	169.19	C	–
5-O-CO$\underline{CH_3}$	2.05 s	20.63	CH_3	5-O$\underline{CO}CH_3$
7-O-$\underline{CO}CH_3$	–	169.14	C	–
7-O-CO$\underline{CH_3}$	2.00 s	20.84	CH_3	7-O$\underline{CO}CH_3$

Table 3. Continued

Position	^{1}H (J,Hz)	^{13}C (HMQC)	DEPT	HMBC
9-O-COCH$_3$	–	170.04	C	–
9-O-COCH$_3$	2.12 s	21.39	CH$_3$	C-7, 9-OCOCH$_3$
10-O-COCH$_3$	–	169.73	C	–
10-O-COCH$_3$	2.06 s	20.63	CH$_3$	10-OCOCH$_3$, C-18
13-O-COCH$_3$	–	169.84	C	–
13-O-COCH$_3$	2.09 s	20.87	CH$_3$	C-18, 13-OCOCH$_3$

Among these, taxusin and baccatin III were found to be major compounds. Compound **3** was concluded to be baccatin VI by comparison of the spectral data with the reported ^{1}H-NMR spectral data (De Marcano and Halsall, 1975; Senilh *et al.*, 1984). The detailed spectral data of **3** was shown in Table 1. Compound **3** was previously isolated from *T. baccata* (De Marcano and Halsall, 1975; Senilh *et al.*, 1984), *T. brevifolia* (Koppaka and Juchum, 1996), *T. chinensis* (Fuji *et al.*, 1993) and *T. x media* (Barboni *et al.*, 1994).

Compound **4** was found to be one of the most abundant components in the ethanolic extract. It was identified as baccatin III by comparison of the spectral data with those reported ^{1}H-NMR spectral data in literature (De Marcano and Halsall, 1975; Miller *et al.*, 1981; Senilh *et al.*, 1984). The detailed spectral data of **4** was shown in Table 2. Compound **4** was previously obtained from *T. baccata* (Senilh *et al.*, 1984; Guo *et al.*, 1995; Soto *et al.*, 1996), *T. chinensis* (Fuji *et al.*, 1993), *T. cuspidata* (Choi *et al.*, 1995), *T. mairei* (Shen and Chen, 1996), *T. sumatrana* (Kitagawa *et al.*, 1995), *T. yunnanensis* (Zhang *et al.*, 1994; Yue *et al.*, 1995) and *T. wallichiana* (Miller *et al.*, 1981; Chattopadhyay *et al.*, 1998). *T. baccata* has been an important plant for the source of baccatin III used in the semisynthesis of anticancer drug paclitaxel (Taxol®) (Denis *et al.*, 1988).

The structure of compound **5** was identified as 1β-hydroxybaccatin I by comparison with the reported ^{1}H- and ^{13}C-NMR spectral data in the literature (Miller *et al.*, 1981; Barboni *et al.*, 1993). The detailed spectral data of **5** was given in Table 3. 1β-hydroxybaccatin I was previously isolated from *T. baccata* (Miller, 1980), *T. cuspidata* (Kobayashi *et al.*, 1995), *T. yunnanensis* (Zhang *et al.*, 1994; Yue *et al.*, 1995) and *T. wallichiana* (Miller *et al.*, 1981; Barboni *et al.*, 1993; Chattopadhyay *et al.*, 1998).

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