Tasumatrols P – T, Five New Taxoids from *Taxus sumatrana*

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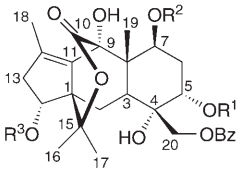
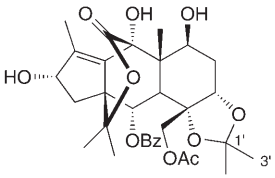
The phytochemical investigation of the more polar fractions from the leaves and twigs of *Taxus sumatrana* (Taxaceae) afforded five new taxane diterpene esters, tasumatrols P – T (**1** – **5**) possessing an 11(15 → 1),11(10 → 9)-diabeotaxane skeleton. Compounds **1**, **4**, and **5** contain an α-hydroxy group at C(14), while **3** has no OH group at either C(13) or C(14). Compound **2** is a natural 4,5-acetonide derivative, while **4** has an unusual spiro-connected 2-hydroxy-2-phenyl-1,3-dioxolane ring. Ten known taxoids, were also isolated in the course of the chromatographic fractionation. Five additional new *O*-acetyl derivatives **3a**, **4a**, **4b**, **5a**, and **5b** were prepared from the taxanes **3** – **5**. The structures of all new compounds were established on the basis of their spectroscopic analyses. Compound **1** showed mild cytotoxic activity against human Hela and Daoy tumor cells.

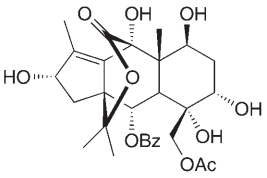
Introduction. – Taxoids are chemically diverse diterpenes isolated from different species of yew trees (family Taxaceae) [1 – 3]. The clinical effectiveness of paclitaxel (*Taxol*®) as a microtubule-stabilizing therapeutic agent for treatment of several malignancies has motivated many natural-product chemists and biologists to isolate new taxoids and investigate their antitumor activity [4 – 6]. A C_{21} taxane ester was recently reported from *Taxus sumatrana* (MIQ.) DE LAUB. (Taxaceae) growing in Taiwan [7]. In our continuing search for new and bioactive natural taxoids from the more polar fractions of *T. sumatrana* [8 – 10], a re-investigation of a taxoid-rich extract of this species was carried out. Herein, we report the isolation of five new taxane diterpene esters, tasumatrols P – T (**1** – **5**), all possessing the 11(15 → 1),11(10 → 9)-diabeotaxane skeleton. Compound **2** is a natural 4,5-acetonide derivative, whereas **4** displays a spiro-connected 2-hydroxy-2-phenyl-1,3-dioxolane moiety at C(4). Ten known taxoids were also isolated and identified as 5-decinnamoyltaxinin J [11], (2α,5α,7β,10β,13α)-2,7,13-tris(acetyloxy)-5,10-dihydroxy-2(3 → 20)-abeotaxa-4(20),11-dien-9-one [12], (2α,5α,7β,9α,13α)-2,7,13-tris(acetyloxy)-5,9-dihydroxy-2(3 → 20)-abeotaxa-4(20),11-dien-10-one [13], taxumairone A [14], tasumatrol K, taxezopidine F [15], taxachitriene A [16], 20-deacetyltaxachitriene A [17], tasumatrol J, and wallifoliol. The taxane structures were established on the basis of their spectroscopic analyses, especially by means of 1D- and 2D-NMR.



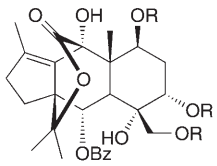
1 R^1 = Ac, R^2 = R^3 = H
5 R^1 = R^2 = R^3 = H
5a R^1 = R^2 = R^3 = Ac
5b R^1 = R^2 = Ac, R^3 = H



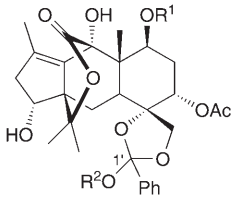
2



2a



3 R = H
3a R = Ac



4 R^1 = R^2 = H
4a R^1 = Ac, R^2 = H
4b R^1 = R^2 = Ac

Results and Discussion. – Solvent partition and extensive chromatographic separation over silica gel and *RP-C_{18}* of an acetone extract of the leaves and young twigs of *T. sumatrana* afforded five new taxanes **1**–**5** in addition to ten known taxoids. The molecular formula $C_{29}H_{36}O_{10}$ was established for **1** by the HR-ESI-MS that showed a pseudomolecular-ion peak at *m*/*z* 567.2208 ($[M + Na]^+$). The IR spectrum displayed absorption bands diagnostic of OH (3443 cm^{-1}) and ester (1734, 1716, 1700 cm^{-1}) functionalities. The ^{1}H- and ^{13}C-NMR (*Tables 1* and *2*), HMBC and NOESY (*Fig. 1*), and COSY data were in accord with the proposed structure **1**. Acetylation of **1** provided two products. One was a monoacetate (tasumatrol P 7-acetate), and was identical with tasumatrol T 5,7-diacetate (**5b**). The other was a diacetate (tasumatrol P 7,14-diacetate), and was identical with tasumatrol T 5,7,14-triacetate (**5a**). Consequently, the structure of **1** was established as tasumatrol P.

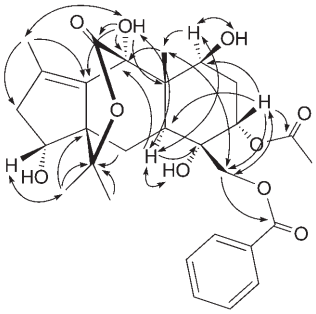


Fig. 1. *Significant HMBC* (→) *and NOESY* (↔) *correlations of* **1**

Table 1. *^{1}H-NMR Data* (300 MHz, $CDCl_3$) *of Compounds* **1**–**5**. δ in ppm, J in Hz.

	1	**2**	**3**	**4**	**5**
CH_2(2) or	2.37–2.41 (*m*),	5.78 (*d*, *J* = 11.4)	5.83 (*d*, *J* = 12.0)	2.39–2.45 (*m*),	2.40–2.52 (*m*),
H–C(2)	1.53–1.55 (*m*)			2.21–2.39 (*m*)	1.29–1.44 (*m*)
H–C(3)	2.19–2.23 (*m*)	2.65 (*d*, *J* = 11.4)	2.68 (*d*, *J* = 12.0)	2.20–2.38 (*m*)	2.14–2.32 (*m*)
H–C(5)	5.26 (br. *s*)	4.15 (br. *s*)	3.78 (br. *s*)	5.29 (br. *s*)	3.88 (br. *s*)
CH_2(6)	2.10–2.13 (*m*),	2.24 (*dd*, *J* = 11.0, 6.0),	2.04–2.20 (*m*), 1.76–1.81 (*m*)	2.09–2.15 (*m*),	2.20–2.28 (*m*),
	2.01–2.08 (*m*)	1.88–2.04 (*m*)		1.61–1.82 (*m*)	1.83–1.97 (*m*)
H–C(7)	4.18–4.23 (*m*)	4.22–4.28 (*m*)	4.32 (*dd*, *J* = 11.1, 4.6)	4.28 (*dd*, *J* = 11.4, 4.0)	4.28 (*dd*, *J* = 11.2. 4.5)
CH_2(13) or	2.18–2.23 (*m*),	4.56 (*dd*, *J* = 11.6, 6.3)	2.53–2.58 (*m*), 1.67–1.73 (*m*)	2.39–2.45 (*m*),	2.18–2.32 (*m*),
H–C(13)	1.48–1.53 (*m*)			1.54–1.61 (*m*)	1.49–1.67 (*m*)
H–C(14) or	4.40 (*dd*, *J* = 11.7, 4.5)	2.42 (*dd*, *J* = 14.7, 6.3),	2.39–2.58 (*m*), 1.61–1.68 (*m*)	4.55[a])	4.56 (br. *d*, *J* = 12.4)
CH_2(14)		2.12–2.17 (*m*)			
Me(16)	1.47 (*s*)	1.36 (*s*)	1.34 (*s*)	1.52 (*s*)	1.45 (*s*)
Me(17)	1.31 (*s*)	1.18 (*s*)	1.31 (*s*)	1.33 (*s*)	1.31 (*s*)
Me(18)	2.02 (*s*)	2.09 (*s*)	2.04 (*s*)	2.03 (*s*)	2.00 (*s*)
Me(19)	1.16 (*s*)	1.18 (*s*)	1.12 (*s*)	1.17 (*s*)	1.12 (*s*)
CH_2(20)	4.73 (*d*, *J* = 12.3),	4.40 (*d*, *J* = 12.6),	4.02 (*d*, *J* = 11.2),	4.56 (*d*, *J* = 7.9),	4.82 (*d*, *J* = 12.3),
	4.61 (*d*, *J* = 12.3)	4.19 (*d*, *J* = 12.6)	3.58 (*d*, *J* = 11.2)	3.74 (*d*, *J* = 7.9)	4.39 (*d*, *J* = 12.3)
OH–C(4)	3.64 (*s*)		1.25 (*s*)		
OH–C(7)	3.92 (*s*)	4.77 (*d*, *J* = 2.9)		4.16 (br. *s*)	4.27 (br. *s*)
OH–C(9)	4.18 (*s*)	5.84 (*s*)		3.82 (br. *s*)	
OH–C(14)	4.87 (*d*, *J* = 4.5)				
H_o (Ph)	8.10 (*d*, *J* = 7.5)	8.11 (*d*, *J* = 7.2)	8.03 (*d*, *J* = 7.5)	7.56 (br. *d*, *J* = 7.2)	8.05 (*d*, *J* = 7.3)
H_m (Ph)	7.47 (*t*, *J* = 7.5)	7.54 (*t*, *J* = 7.2)	7.48 (*t*, *J* = 7.5)	7.36 (br. *d*, *J* = 7.2)	7.46 (*t*, *J* = 7.3)
H_p (Ph)	7.59 (*t*, *J* = 7.5)	7.65 (*t*, *J* = 7.2)	7.60 (*t*, *J* = 7.5)	7.48–7.57 (*m*)	7.60 (*t*, *J* = 7.3)
Me–2′		1.17 (*s*)			
Me–3′		1.62 (*s*)			
AcO–C(5)	2.12 (*s*)			2.10 (*s*)	
AcO–C(20)		1.89 (*s*)			

[a]) Overlapped.

Table 2. *^{13}C-NMR Data* (300 MHz, $CDCl_3$) *of Compounds* **1**–**5**[a]). δ in ppm.

	1	**2**	**3**	**4**	**5**
C(1)	64.2 (*s*)	61.4 (*s*)	63.8 (*s*)	62.6 (*s*)	63.8 (*s*)
C(2)	39.1 (*t*)	68.5 (*d*)	69.5 (*d*)	39.6 (*t*)	39.1 (*t*)
C(3)	45.3 (*d*)	48.0 (*d*)	45.0 (*d*)	40.5 (*d*)	44.7 (*d*)
C(4)	76.5 (*s*)	81.8 (*s*)	74.9 (*s*)	81.6 (*s*)	75.9 (*s*)
C(5)	71.0 (*d*)	74.2 (*d*)	69.5 (*d*)	70.0 (*d*)	68.7 (*d*)
C(6)	32.4 (*t*)	31.2 (*t*)	33.5 (*t*)	33.9 (*t*)	33.8 (*t*)
C(7)	68.4 (*d*)	68.4 (*d*)	68.1 (*d*)	67.9 (*d*)	68.1 (*d*)
C(8)	48.4 (*s*)	47.4 (*s*)	48.4 (*s*)	46.6 (*s*)	48.1 (*s*)
C(9)	85.5 (*s*)	84.0 (*s*)	85.1 (*s*)	85.6 (*s*)	85.5 (*s*)
C(10)	175.8 (*s*)	172.5 (*s*)	174.9 (*s*)	175.7 (*s*)	175.7 (*s*)
C(11)	137.7 (*s*)	131.0 (*s*)	130.3 (*s*)	138.7 (*s*)	138.0 (*s*)
C(12)	129.3 (*s*)	139.9 (*s*)	138.3 (*s*)	129.6 (*s*)	129.6 (*s*)
C(13)	24.3 (*t*)	78.5 (*d*)	39.3 (*t*)	24.2 (*t*)	24.5 (*t*)
C(14)	68.4 (*d*)	36.2 (*t*)	25.5 (*t*)	67.9 (*d*)	68.9 (*d*)
C(15)	92.8 (*s*)	87.8 (*s*)	90.7 (*s*)	92.9 (*s*)	92.1 (*s*)
C(16)	22.6 (*q*)	22.3 (*q*)	21.3 (*q*)	22.5 (*q*)	22.5 (*q*)
C(17)	24.3 (*q*)	24.8 (*q*)	22.2 (*q*)	24.5 (*q*)	24.1 (*q*)
C(18)	13.8 (*q*)	10.4 (*q*)	14.0 (*q*)	13.8 (*q*)	13.9 (*q*)
C(19)	11.6 (*q*)	11.2 (*q*)	11.8 (*q*)	11.4 (*q*)	11.3 (*q*)
C(20)	65.8 (*t*)	61.6 (*t*)	61.6 (*t*)	70.0 (*t*)	66.4 (*t*)
Ph*C*O	166.4 (*s*)	165.1 (*s*)	165.6 (*s*)		167.2 (*s*)
C_i	129.2 (*s*)	139.9 (*s*)	130.1 (*s*)	136.3 (*s*)	128.4 (*s*)
C_o	129.9 (*d*)	130.9 (*d*)	128.8 (*d*)	125.9 (*d*)	129.8 (*d*)
C_m	128.7 (*d*)	128.4 (*d*)	128.6 (*d*)	128.6 (*d*)	128.7 (*d*)
C_p	133.6 (*d*)	133.2 (*d*)	133.4 (*d*)	129.5 (*d*)	133.6 (*d*)
*Ac*O–C(5)	171.6 (*s*), 21.1 (*q*)			169.8 (*s*), 21.2 (*q*)	
*Ac*O–C(20)		169.8 (*s*), 19.7 (*q*)			
C(1′)		107.2 (*s*)		118.8 (*s*)	
C(2′)		25.6 (*q*)			
C(3′)		28.3 (*q*)			

[a]) Assignments were aided by HMQC and DEPT techniques.

Both the ^{1}H- and ^{13}C-NMR data of **1** indicated the presence of an acetate ester at δ(H) 2.12 (δ(C) 21.1 and 171.6) along with a benzoate ester at δ(H) 8.10 (*d*, J = 7.5 Hz, 2 H), 7.59 (*t*, J = 7.5 Hz, 1 H), and 7.47 (*t*, J = 7.5 Hz, 2 H). Subtracting the C-atoms assignable to the two ester moieties from the molecular formula, a diterpene structure was suggested for the remaining part. The four Me *s* at δ(H) 1.31 (Me(17)), 1.47 (Me(16)), 1.16 (Me(19)), and 2.02 (Me(18)) and their corresponding C-signals at δ(C) 24.3, 22.6, 11.6, and 13.8 together with the two quaternary C-signals at δ(C) 64.2 (C(1)) and 92.8 (C(15)) were in agreement with an 11(15 → 1),11(10 → 9)-diabeotaxane skeleton [7][8][10][18–22]. The ^{1}H-NMR spectrum revealed 3 oxygenated CH groups at δ(H) 5.26 (br. *s*, H–C(5)), 4.18–4.23 (*m*, H–C(7)), and 4.40 (*dd*, J = 11.7, 4.5 Hz, H–C(14)) and an oxygenated CH_2 group at δ(H) 4.73 and 4.61 (2*d*, J = 12.3 Hz, CH_2(20)), and the absence of signals assignable to H–C(9) and H–C(10) (normally present in the 6,8,6-3-ring taxane skeleton and found between δ(H) 6.0 and 6.50). The relatively low-field chemical shift of H–C(5) implied acylation at C(5), which was supported by a HMBC correlation of H–C(5) with the acetate C=O at δ(C) 171.6. The low-field quaternary C-atom at δ 76.5 was assigned to the OH-bearing C(4), and further supported by its ^2J-correlations of C(4) with H–C(3) (δ(H) 2.19–

2.23) and H–C(5) (δ(H) 5.26). The benzoate C-atom at δ(C) 166.4 had HMBC correlation to CH_2(20) that, in turn, was correlated with C(4) and C(5), indicating the presence of a benzoyloxy group at C(20). The low-field shift of the quaternary C(15) (δ(C) 92.8) suggested its oxygenation, whereas its correlations with Me(16), Me(17), and H_β–C(2), along with a correlation Me(16)/C(1) confirmed the presence of the 11(15 → 1),11(10 → 9)-diabeotaxane skeleton. Another deshielded quaternary oxygenated C-atom resonating at δ(C) 85.5 was assigned to C(9) on the basis of its ^3J-correlation with Me(19). The *s* at δ(H) 4.18 was assigned to OH–C(9) as confirmed by its HMBC correlations with C(8), C(9), and C(11). The C=O signal at δ(C) 175.8 (C(10)) was assumed to arise from a 6-membered lactone ring involving C(15), C(1), C(11), and C(9). This finding was confirmed by a ^3J-correlation between C(10) and OH–C(9) as well as by comparison of the data of **1** with the corresponding data of wallifoliol and its analogues [7][8][23]. The proposed structure was supported by the COSY connectivities CH_2(13)/H–C(14), CH_2(2)/H–C(3), and H–C(5)/CH_2(6)/H–C(7), in addition to the HMBC correlations H–C(3)/C(9), H–C(5)/C(3), C(7), and C(20), H–C(7)/C(9) and C(19), Me(18)/C(11) and C(13), and H–C(14)/C(15) (*Fig. 1*). The relative configuration of **1** was determined with the aid of the NOESY experiment that showed the correlations Me(19)/H–C(5), Me(16) and CH_2(20), H–C(5)/CH_2(20) and H_o of the benzoate, and Me(16)/H–C(14), in accordance with the β-orientation of H–C(5), H–C(14), and CH_2(20), as well as the α-orientation of H–C(7) (*Fig. 1*).

The molecular formula of **2** was determined as $C_{32}H_{40}O_{11}$, as deduced from the HR-ESI-MS with $[M + Na]^+$ at *m*/*z* 623.2465. The MS and ^{1}H- and ^{13}C-NMR data (*Tables 1* and *2*) established the presence of the same 11(15 → 1),11(10 → 9)diabeotaxane skeleton in **2** as in **1**, with a six-membered lactone, a benzoyloxy and an acetyloxy moiety, in addition to extra three C-atoms. The latter were attributed to an acetonide moiety as confirmed by comparison with published data [24]. Compound **2** was identified as tasumatrol Q but might be an artifact derived from the nucleophilic attack of OH–C(4) and OH–C(5) of **2a** to acetone. However, the proposed **2a** was not isolated from the current experimental material [25].

The DEPT spectrum of **2** indicated three CH_2 groups instead of four in **1**. The two oxygenated quaternary C-atoms at δ(C) 84.0 and 87.8 were conveniently assigned to C(9) and C(15), respectively, whereas the C=O at δ(C) 172.5 was attributed to C(10). The acetate C=O at δ(C) 169.8 was correlated to two protons at δ(H) 4.40 and 4.19 (2*d*, J = 12.6 Hz, CH_2(20)) indicating the location of the acetate at C(20). The benzoate C=O at δ(C) 165.1 was correlated to an OCH group at δ(H) 5.78 (*d*, J = 11.4 Hz), that was, in turn, correlated to C(1) (δ(C) 61.4), C(8) (δ(C) 47.4), and C(14) (δ(C) 36.2), thus locating the benzoyloxy group at C(2). The HMBC correlation between the Me group at δ(H) 2.09 (Me(18)) and the oxymethine C-atom at δ(C) 78.5, and between the Me group at δ(H) 1.18 (Me(19)) and the oxymethine C-atom at δ(C) 68.4 indicated OH substitution at C(13) and C(7), respectively (*Fig. 2*). The proton at δ(C) 4.15 (br. *s*), assigned to H–C(5), was attached to a C-atom resonating at δ(C) 74.2 (C(5)) that was correlated to CH_2(20), confirming oxygenation at C(5). The ^2J-correlations between CH_2(20)

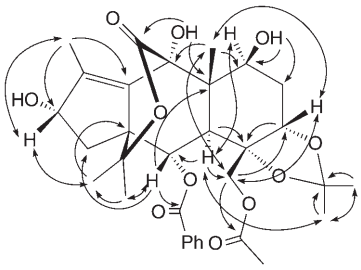


Fig. 2. *Selected HMBC* (→) *and NOESY* (↔) *correlations of* **2**

and the quaternary C-atom at δ(C) 81.8 (C(4)) established the oxygenation at C(4). On the other hand, the Me group at δ(H) 1.17 showed ^2J-correlations with an acetal C-atom at δ(C) 107.2 and a Me group at δ(C) 28.3. Alternatively, the Me group at δ(H) 1.62 was correlated with the acetal C-atom and another Me C-atom at δ(C) 25.6. It was suggested that the three C-atoms at δ(C) 25.6, 28.3, and 107.2 were involved in an acetonide moiety at C(4)–C(5) which was confirmed by the HR-ESI-MS (*m/z* 623.2465) and by comparison with published data [24]. The NOESY correlations (*Fig. 2*) Me_β(19)/H–C(2), H–C(5), Me(16), and CH_2(20), H–C(2)/Me(16), Me(16)/H–C(13), and H_α–C(3)/H–C(7) and Me(2′), together with the multiplicities of H–C(2), H–C(3), and H–C(5) were used to determine the relative configuration at the chiral centers of **2**.

Compound **3** was assigned the molecular formula $C_{27}H_{34}O_9$, as deduced from the HR-ESI-MS with $[M+Na]^+$ at *m/z* 525.2101 and the NMR data (*Tables 1* and *2*). Acetylation of **3** provided a product identical with tasumatrol I diacetate (**3a**) [7], confirming the proposed configuration of **3**. The structure of **3** was deduced as tasumatrol R.

The NMR data of **3** revealed one benzoate ester (δ(H) 8.03, 7.60, and 7.48, and δ(C) 165.6, 130.1, 128.8, 128.6, and 133.4) attached to the 11(15→1),11(10→9)-diabeotaxane skeleton. In addition to the OCH_2 protons at δ(H) 4.02 and 3.58 (2*d*, *J* = 11.2 Hz, CH_2(20)), the ^{1}H-NMR spectrum displayed three OCH protons at δ(H) 3.78 (br. *s*, H–C(5)), 4.32 (*dd*, *J* = 11.1, 4.6 Hz, H–C(7)), and 5.83 (*d*, *J* = 12.0 Hz, H–C(2)). The chemical shift and multiplicity of H–C(2) along with its HMBC correlation with the benzoate C=O at δ(C) 165.6 and C(1) allowed positioning the benzoyloxy group at C(2). The HMBC correlations H–C(2)/C(1), C(8), and C(15), H–C(3)/C(1) and C(8), Me(16)/C(1), Me(18)/C(11) and C(13), and Me(19)/C(7) and C(8) were in good agreement with the proposed structure of **3**. The large *J*(2,3) value (12.0 Hz) as well as the NOESY correlations Me(19)/H–C(2) and CH_2(20), and CH_2(20)/H–C(5) determined the β-orientation of H–C(2), H–C(5), and CH_2(20).

The molecular formula of **4**, $C_{29}H_{36}O_{10}$, was deduced from the HR-ESI-MS with $[M+Na]^+$ at *m/z* 567.2203 indicating twelve degrees of unsaturation. The ^{1}H- and ^{13}C-NMR (*Tables 1* and *2*), and HMBC and NOESY data (*Fig. 3*) were in accord with the proposed structure of **4**. Acetylation of **4** gave a monoacetate **4a** and a diacetate **4b**. The relative configuration of **4** was confirmed by an MM2 calculation of a three-dimensional molecular model of **4** which exhibited the lowest energy as illustrated in *Fig. 4*. The OH–C(1′) was tentatively deduced to be α-oriented based on the MM2-force field energy-minimized model that indicated that the (*S*)-configuration (steric energy 18.0 kcal/mol) is preferred to the (*R*)-isomer (23.6 kcal/mol). Thus the structure of **4** was established as tasumatrol S, an orthoester which could be formed by rearrangement of **1**.

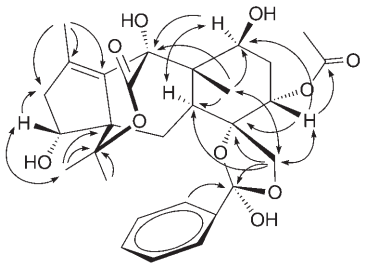


Fig. 3. *Selected HMBC* (→) *and NOESY* (↔) *correlations of* **4** (drawing based on an energy-minimized model)

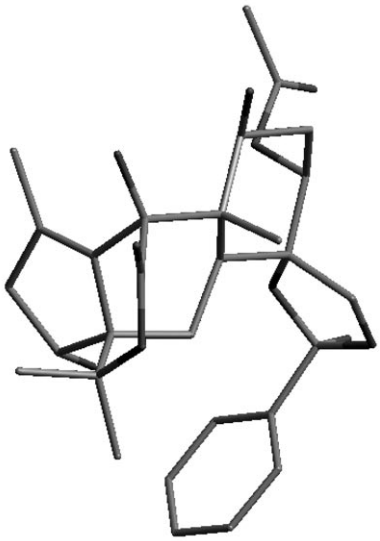


Fig. 4. *Lowest-energy Chem3D model of* **4**. Protons are omitted for clarity; $E = 18.0$ kcal/mol.

The NMR data of **4** were closely similar to those of **1** suggesting hydroxylation at C(7) and C(14) and acetyloxy substitution at C(5) (HMBC correlation δ(H) 5.29/δ(C) 169.8) of the modified taxane skeleton. The monoacetate **4a** and the diacetate **4b** exhibited additional acetyl *s*, and H–C(7) was shifted downfield to δ(H) 5.31. The presence of a monosubstituted benzene ring was demonstrated by proton signals at δ(H) 7.56 (2 H), 7.48–7.57 (1 H), and 7.36 (2 H) along with aromatic C-atom signals at δ(C) 136.3 (*s*), 125.9 (*d*), 128.6 (*d*), and 129.5 (*d*). However, the absence of a benzoate C=O and the downfield shift of the quaternary C-atom at δ(C) 136.3 (C_i) suggested a different attachment of the phenyl ring to the taxane skeleton than in **1**–**3**. Meticulous inspection of the HMBC data (*Fig. 3*) revealed that both the OCH_2 protons at δ(H) 4.56 and 3.74 (CH_2(20)) as well as the H protons of the phenyl group showed ^3J-correlations with an extremely downfield-shifted aliphatic C-atom at δ(C) 118.8 (C(1′)), suggesting the presence of an unusual heterocyclic ring. The downfield shift of C(1′) was ascribed to its attachment to three O-atoms, a rare case in natural products [26]. The proposed 2-hydroxy-2-phenyl-1,3-dioxolane ring spiro-connected at C(4) was supported by the relative downfield shift of C(4) (δ(C) 81.6, *Table 2*), as well as the relatively low coupling constant between the geminal protons of CH_2(20) (7.9 Hz) in comparison with related compounds (>11 Hz). The NOESY plot exhibited the correlations H–C(5)/H_β–C(6) and CH_2(20), H–C(7)/H–C(3), H–C(14)/H–C(16), and H–C(19)/H–CH_2(20), in agreement with the β-orientation of OH–C(7) and CH_2(20), as well as the α-orientation of AcO–C(5) and OH–C(14).

The HR-ESI-MS of **5** exhibited a quasi-molecular ion at *m*/*z* 525.2101 ($[M + Na]^+$), consistent with a molecular formula $C_{27}H_{34}O_9$, the same as compound **3**. By comparing the NMR data of **5** with those of **1** (*Tables 1* and *2*), it was concluded that **5** is the 5-*O*-deacetyl derivative of **1**, and the structure was further confirmed by chemical derivatization of **5**. Acetylation of **5** provided a triacetate **5a** whose spectral data were identical to those of tasumatrol P 7,14-diacetate, and a diacetate **5b**, identical with tasumatrol P 7-acetate. Thus, the structure of **5** was deduced as tasumatrol T.

The NMR data of **5** indicated a modified taxane skeleton similar to that of **1**–**4**, with one benzoate ester moiety. The OCH group at δ(H) 4.56 showed HMBC correlations to C(1) (δ(C) 63.8) and C(2)

(δ(C) 39.1) and was assigned to H–C(14). In addition, the HMBC correlations also established the substitution by OH groups at C(5) and C(7), and the correlations of the OCH_2 protons at δ(H) 4.82 and 4.39 (2*d*, $J = 12.3$ Hz, CH_2(20)) with C(4) (δ(C) 75.9) and the benzoate C=O (δ(C) 167.2) indicated the attachment of the benzoyloxy group at C(20).

The five novel wallifoliol-type compounds **1**–**5** may be intermediates or biogenetically related to wallifoliol [8], which was a major taxoid isolated from the leaves of *T. sumatrana* and other species of *Taxus*. All the isolated taxoids were tested against three human-cancer cell lines (Hela, Daoy, and DLD-1) *in vitro*. The results indicated that compounds **2**–**5** showed no activity against these cancer cells. Compound **1** exhibited very mild cytotoxicity toward Hela and Daoy cancer cells at ED_{50} 22.7 and 22.4 μg/ml, respectively.

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Experimental Part

General. Column chromatography (CC); silica gel *60* (*Merck*) and *Sephadex LH-20* (*Amersham Pharmacia Biotech AB*, Uppsala, Sweden). FC = flash chromatography. Prep. TLC: pre-coated silica gel plates (*Merc*k; silica gel *60 F-254*, 1 mm). Optical rotations: *Jasco DIP-1000* polarimeter. UV Spectra: *Hitachi U-3210* spectrometer; λ_{max} (log ε) in nm. IR Spectra: *Hitachi T-2001* spectrometer; in cm^{-1}. ^{1}H-, ^{13}C-NMR, COSY, HMQC, HMBC, and NOESY Experiments: *Bruker FT-300* spectrometer or *Varian Unity-Inova-500* FT-NMR spectrometers at 500 (^{1}H) and 125 MHz (^{13}C), $SiMe_4$ as internal standard; δ in ppm, coupling constants J in Hz. Low-resolution EI-MS and FAB-MS: *VG Quattro-5022* mass spectrometer; in *m*/*z* (rel. %).

Plant Material. Taxus sumatrana (MIQ.) DE LAUB. was collected from Kaohsiung county, Taiwan at an altitude of 1000 m in March 2002. A voucher specimen (TPG 8–7) has been deposited in the School of Pharmacy, National Taiwan University, Taipei, Taiwan.

Extraction and Isolation. Dried leaves and twigs (15.5 kg) were ground and extracted three times with acetone at r.t. The combined extracts were filtered and concentrated to obtain a crude extract (3.05 kg). The extract was stirred twice with H_2O (2 × 3.5 l), and the resulting emulsion was separated from the residue and partitioned between AcOEt/H_2O 1:1 to afford an AcOEt extract (173 g). The AcOEt extract was fractionated by CC (*Sephadex LH-20*, MeOH) into *Fractions* L_1 and L_2. *Fr.* L_1 (60 g) was subjected to CC (silica gel, hexane/CH_2Cl_2/MeOH 100:100:1 → 1:1:1): *Fr. F-1* to *F-10*. *Fr. F-1* (3.5 g) was subjected to CC (*RP*-silica gel, H_2O/MeOH/MeCN (70:25:5, 60:35:5, 50:45:5, 40:55:5, and 30:65:5, each 1000 ml): *Fr. F-1.A* to *F-1.J*. *Fr.F-1.G* (230 mg) was separated by reversed phase HPLC (MeOH/H_2O/MeCN (65:30:5): *20-deacetyltaxachitriene A* (5 mg) and a mixture. This mixture was subjected to HPLC (hexane/CH_2Cl_2/MeOH 20:15:1): *taxachitriene A* (35 mg), *5-decinnamoyltaxinin J* (30 mg), and a mixture (23 mg). The mixture (23 mg) was subjected to prep. TLC (silica gel plates, hexane/*n*-BuOH): *(2α,5α,7β,10β,13α)-2,7,13-tris(acetyloxy)-5,10-dihydroxy-2(3 → 20)-abeotaxa-4(20),11-dien-9-one* (6 mg). *Fr. F-1.H* (600 mg) was separated by FC (silica gel, hexane/CH_2Cl_2/MeOH 100:0:0 → 0:3:1): *Fr. F-1.H.1* to *Fr. F-1.H.4*, *Fr. F-1.H.3* (80 mg) was fractionated by HPLC (hexane/CH_2Cl_2/MeOH 20:15:1): *taxezopidine F* (2 mg). *Fr. F-2* (159 mg) was separated by reversed-phase HPLC (MeOH/H_2O/MeCN 55:40:5): *Fr. F-2.1* to *F-2.9*. *Fr. F-2.5* (35 mg) was subjected to reversed-phase HPLC (MeOH/H_2O/MeCN 50:50:5): *(2α,5α,7β,9α,13α)-2,7,13-tris(acetyloxy)-5,9-dihydroxy-2(3 → 20)-abeotaxa-4(20),11-dien-10-one* (15 mg). *Fr. F-4* (2.3 g) was separated by CC (*RP*-silica gel, H_2O/MeOH/MeCN 60:35:5, 50:45:5, 40:55:5, 30:65:5, 20:75:5, and 10:80:5, each 400 ml): *Fr. F-4.A* to *F-4.C*. *Fr. F-4.B* (200 mg out of 364 mg) was fractionated by reversed-phase HPLC (MeOH/H_2O/MeCN 55:40:5): *Fr. F-4.B.1* to *F-4.B.3*. *Fr. F-4.B.1* and *F-4.B.2* were separately purified by HPLC

(hexane/CH_2Cl_2/MeOH 8:8:1): **1** (6 mg) and **2** (7 mg). *Fr. F-4.B.3* was separated by prep. TLC (silica gel GF_{254}, hexane/CH_2Cl_2/MeOH 10:8:1): *taxumairone A* (3 mg) and *tasumatrol K* (5 mg). *Fr. F-9* (1.1 g) was purified by CC (*Sephadex LH-20*, MeOH) to yield a mixture (860 mg) that was divided into two unequal portions, *Fr. F-9.A* and *F-9.B*. *Fr. F-9.A* (40 mg) was separated by reversed-phase HPLC (MeOH/H_2O/MeCN (65:30:5) followed by HPLC (hexane/CH_2Cl_2/MeOH 7:7:1): **3** (5 mg). *Fr. F-9.B* (820 mg) was separated by FC (silica gel, gradient CH_2Cl_2/MeOH): *tasumatrol J* (260 mg) and two mixtures, *Fr. F-9.B.1* and *F-9.B.2*. Separation of *Fr. F-9.B.1* (30 mg) by reversed-phase HPLC (MeOH/H_2O/MeCN 65:30:5) yielded additional amounts of *tasumatrol J* (15 mg) and **1** (5 mg), while a similar separation of *Fr. F-9.B.2* (190 mg) afforded *wallifoliol* (10 mg) and **5** (27 mg). *Fr. L_2* (from the first *Sephadex* separation; 86 g) was fractionated by CC (silica gel, gradient hexane/AcOEt): *Fr. L_2.1* to *L_2.18*). *Fr. L_2.4* (1 g) was separated by CC (*Sephadex LH-20*, MeOH): *Fr. L_2.4.1* to *L_2.4.3*. Part of *Fr. L_2.4.1* 300 mg out of 875 mg) was subjected to reversed-phase HPLC (MeOH/H_2O/MeCN 65:30:5) followed by HPLC (hexane/CH_2Cl_2/MeOH 15:5:1): **4** (25 mg) and a third amount of *tasumatrol J* (32 mg).

Tasumatrol P (=*(3*R,*3a*R,*4a*S,*5*S,*6*S,*8*S,*8a*S,*9*S*)-6-(Acetyloxy)-5-[(benzoyloxy)methyl]-2,3,4,4a,5,6,7,8,8a,9-decahydro-3,5,8,9-tetrahydroxy-1,8a,12,12-tetramethyl-3a,9-(methanoxymethano)-3a*H*-benz[*f*]inden-10-one*; **1**). Colorless powder. $[\alpha]_D^{26} = -71.6$ ($c = 0.2$, CH_2Cl_2). UV (MeOH): 229 (4.08). IR (neat): 3443 (OH), 3062 (C=C−H), 2930 (C−H), 1734, 1716, 1700 (C=O, δ-lactone, Ac, Bz), 1601 (Ar), 1276, 1028 (C−O), 959, 854, 737. ^{1}H-NMR (300 MHz, $CDCl_3$) and ^{13}C-NMR (75 MHz, $CDCl_3$): *Tables 1* and *2*. ESI-MS: 567 ($[M+Na]^+$). HR-ESI-MS: 567.2208 ($C_{29}H_{36}Na^+O_{10}$; calc. 567.2206).

Acetylation of **1**. At r.t., **1** (12 mg) was treated with Ac_2O/pyridine 1:1 (1 ml) overnight. The mixture was purified by HPLC (silica gel, hexane/CH_2Cl_2/MeOH 15:5:1): *tasumatrol P 7-acetate* (2.5 mg) and *tasumatrol P 7,14-diactetate* (4 mg), identical with tasumatrol T 5,7-diacetate (**5b**) and tasumatrol T 5,7,14-triacetate (**5a**), respectively (see below).

Tasumatrol Q (=*(3a*S,*5*S,*5a*S,*6*S,*8*S,*9a*S,*10*S,*10a*R,*10b*S)-10b-[(Acetyloxy)methyl]-10-(benzoyloxy)-3a,4,5,5a,6,8,9,10,10a,10b-decahydro-5,6,8-trihydroxy-2,2,5a,7,11,11-hexamethyl-6,9a-(methanoxymethano)-9a*H*-cyclopenta[6,7]naphtho[1,2-*d*]-1,3-dioxol-13-one*; **2**). Colorless powder. $[\alpha]_D^{26} = -82.0$ ($c = 0.2$, CH_2Cl_2). UV (MeOH): 232 (4.05). IR (neat) 3442 (OH), 3060 (C=C−H), 2984, 2933 (C−H), 1733, 1715 (C=O, Ac, δ-lactone, Bz), 1601 (Bz), 1275, 1042 (C−O), 993, 736, 712. ^{1}H-NMR (300 MHz, $CDCl_3$) and ^{13}C-NMR (75 MHz, $CDCl_3$): *Tables 1* and *2*. EI-MS: 600 (M^+), 583, 542, 525, 524, 194, 148, 105, 77. ESI-MS: 623 ($[M+Na]^+$). HR-ESI-MS: 623.2465 ($C_{32}H_{40}Na^+O_{11}$; calc. 623.2468).

Tasumatrol R (=*(3a*S,*4*S,*4a*R,*5*S,*6*S,*8*S,*8a*S,*9*S*)-5-[(Acetyloxy)methyl]-4-(benzoyloxy)-2,3,4,4a,5,6,7,8,8a,9-decahydro-5,6,8,9-tetrahydroxy-1,8a,12,12-tetramethyl-3a,9-(methanoxymethano)-3a*H*-benz[*f*]inden-10-one*; **3**). Colorless powder. $[\alpha]_D^{26} = -52.1$ ($c = 0.2$, CH_2Cl_2). UV (MeOH): 229 (4.01). IR (neat): 3440 (OH), 2952 (C−H), 1730–1700 (C=O, δ-lactone, Bz), 1695, 1648 (C=C), 1277 (C−O), 1022, 780, 712. ^{1}H−NMR (300 MHz, $CDCl_3$) and ^{13}C-NMR (75 MHz, $CDCl_3$): *Tables 1* and *2*. EI-MS: 502 (0.1, M^+), 438, 326, 176, 149, 123, 105, 77. ESI-MS: 525 ($[M+Na]^+$). HR-ESI-MS: 525.2101 ($C_{27}H_{34}Na^+O_9$; calc. 525.2100).

Acetylation of **3**. With **3** (3 mg) and Ac_2O pyridine 1:1 (1 ml) for 5 h, followed by HPLC, as described for the acetylation of **1**: triactetate **3a** (2 mg), identical with tasumatrol I diacetate [7].

Tasumatrol S (=*3′*R,*3′a*R,*4′a*S,*5′*S,*6′*S,*8′*S,*8′a*S,*9′*S*)-6′-(Acetyloxy)-2′,3′,4′,4′a,7′,8′,8′a,9′-octahydro-2,3′,8′,9′-tetrahydroxy-1′,8′a,12′,12′-tetramethyl-2-phenylspiro[1,3-dioxolane-4,5′(6′*H*)-[3a,9](methanoxymethano)[3a*H*]benz[f]inden]-10′-one*; **4**). Colorless powder. $[\alpha]_D^{26} = -29.2$ ($c = 0.2$, MeOH). UV (MeOH): 229 (3.25). IR (neat): 3442 (OH), 3060 (C=C−H), 2983, 2938 (C−H), 1740 (δ-lactone), 1729 (C=O, Ac), 1466, 1451, 1374, 1328, 1237, 1160, 1026, 989, 852, 736, 700. ^{1}H-NMR (300 MHz, $CDCl_3$) and ^{13}C-NMR (75 MHz, $CDCl_3$): *Tables 1* and *2*. EI-MS: 544, 527, 482, 439, 423, 255, 213, 149, 121, 105, 104, 77. ESI-MS 567 ($[M+Na]^+$). HR-ESI-MS: 567.2203 ($C_{29}H_{36}Na^+O_{10}$; calc. 567.2206).

Acetylation of **4**. With **4** (10 mg) and Ac_2O/pyridine 1:1 (1 ml) overnight, followed by HPLC, as described for the acetylation of **1**: **4a** (3 mg) and **4b** (3.5 mg).

Tasumatrol S 7-Acetate (=*3′*R,*3′a*R,*4′a*S,*5′*S,*6′*S,*8′*S,*8′a*S,*9′*S*)-6′,8′-Bis(acetyloxy)-2′,3′,4′,4′a,7′,8′,8′a,9-octahydro-2,3′,9′-trihydroxy-1′,8′a,12′,12′-tetramethyl-2-phenylspiro[1,3-dioxolane-4,5′(6′*H*)-[3a,9](methanoxymethano)[3a*H*]benz[f]inden-10-one*; **4a**). Amorphous solid. $[\alpha]_D^{26} = -37.2$ ($c = 0.2$, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.55 (br. *s*, 2 H); 7.37 (br. *s*, 3 H); 5.31 (*dd*, $J = 11.1, 6.6$, H−C(7)); 5.27

(br. *s*, H–C(5)); 4.61, 3.75 (2*d*, *J* = 7.6, H_2(20)); 4.56 (*d*, *J* = 12, H–C(14)); 2.10, 2.05 (2*s*, 2 AcO); 2.05 (*s*, Me(18)); 1.51 (*s*, Me(17)); 1.34 (*s*, Me(16)); 1.26 (*s*, Me(19)). EI-MS: 86 (M^+), 508 ([*M* – AcOH – H_2O]$^+$), 362, 281, 221, 194, 149, 121, 105, 77. HR-ESI-MS: 609.2316 ($C_{31}H_{38}Na^+O_{11}$; calc. 609.2312).

Tasumatrol S 1′,7-Diacetate (= *3′*R,*3′a*R,*4′a*S,*5′*S,*6′*S,*8′*S,*8′a*S,*9′*S)*-2,6′,8′-Tris(acetyloxy)-2′,3′,4′,4′a,7′,8′,8′a,9-octahydro-3′,9′-dihydroxy-1′,8′a,12′,12′-tetramethyl-2-phenylspiro[1,3-dioxolane-4,5′(6′*H*)-[3*a*,9](methanoxymethano)[3*a*H]benz[f]inden-10-one*; **4b**). Amorphous solid. $[\alpha]_D^{26} = -27.4$ (*c* = 0.2, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.55 (br. *s*, 2 H); 7.37 (br. *s*, 3 H); 5.31 (*dd*, *J* = 11.1, 6.6, H–C(7)); 5.27 (br. *s*, H–C(5)); 4.61, 3.75 (2*d*, *J* = 7.6, CH_2(20)); 4.56 (*d*, *J* = 12, H–C(14)); 2.13, 2.05, 2.00 (3*s*, 3 AcO); 2.05 (s, Me(18)); 1.50 (*s*, Me(17)); 1.35 (*s*, Me(16)); 1.26 (*s*, Me(19)). EI-MS: 628 (M^+), 586, 508 ([*M* – 2 AcOH]$^+$, 362, 149, 121, 105, 77. HR-ESI-MS: 651.2415 ($C_{33}H_{40}Na^+O_{12}$; calc. 651.2417).

*Tasumatrol T (= 3*R,*3a*R,*4a*S,*5*S,*6*S,*8*S,*8a*S,*9*S*)-5-[(Benzoyloxy)methyl]-2,3,4,4a,5,6,7,8,8a,9-decahydro-3,5,6,8,9-pentahydroxy-1,8a,12,12-tetramethyl-3a,9-(methanoxymethano)-3a*H*-benz[f]inden-10-one*; **5**). Colorless powder. $[\alpha]_D^{26} = -44.3$ (*c* = 0.2, CH_2Cl_2). UV (MeOH): 228 (4.06). IR (neat): 3445 (OH), 3061 (C=C–H), 2950 (C–H), 1735, 1716 (C=O, δ-lactone, Bz), 1601 (Ar), 1454, 1276 (C–O), 1026, 962, 854, 739, 711. ^{1}H-NMR (300 MHz, $CDCl_3$) and ^{13}C-NMR (75 MHz, $CDCl_3$): *Tables 1* and *2*. EI-MS: 177, 149, 123, 105, 79, 77, 69. ESI-MS: 525 ([*M* + Na]$^+$). HR-ESI-MS: 525.2101 ($C_{27}H_{34}Na^+O_9$; calc. 525.2100).

Acetylation of **5**. With **5** (9 mg) and Ac_2O/pyridine 1:1 (1 ml) for 6 h, followed by HPLC, as described for the acetylation of **1**: **5a** (4 mg) and **5b** (3 mg).

Tasumatrol T 5,7,14-Triacetate (= *(3*R,*3a*R,*4a*S,*5*S,*6*S,*8*S,*8a*S,*9*S*)-3,6,8-Tris(acetyloxy)-5-[(benzoyloxy)-methyl]-2,3,4,4a,5,6,7,8,8a,9-decahydro-5,9-dihydroxy-1,8a,12,12-tetramethyl-3a,9-(methanoxymethano)-3a*H*-benz[f]inden-10-one*; **5a**). Amorphous solid. $[\alpha]_D^{26} = -14.6$ (*c* = 0.2, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 8.03 (*d*, *J* = 7.5, 2 H); 7.56 (*t*, *J* = 7.5, 1 H); 7.45 (*t*, *J* = 7.5, 2 H); 5.65 (*d*, *J* = 11.7, H–C(14)); 5.32 (br. *s*, H–C(5)); 5.27 (*m*, H–C(7)); 4.70, 4.59 (2*d*, *J* = 11.6, CH_2(20)); 2.14, 2.08, 2.06 (3*s*, 3 AcO); 2.02 (*s*, Me(18)); 1.35 (*s*, Me(16)); 1.32 (*s*, Me(17)); 1.26 (*s*, Me(19)). EI-MS: 628 (M^+), 568 ([*M* – AcOH]$^+$, 508 ([*M* – 2 HOAc]$^+$), 362, 194, 149, 121, 105, 77. HR-ESI-MS: 609.2316 ($C_{31}H_{38}Na^+O_{11}$; calc. 609.2312).

Tasumatrol T 5,7-Diacetate (= *(3*R,*3a*R,*4a*S,*5*S,*6*S,*8*S,*8a*S,*9*S*)-6,8-Bis(acetyloxy)-5-[(benzoyloxy)-methyl]-2,3,4,4a,5,6,7,8,8a,9-decahydro-3,5,9-trihydroxy-1,8a,12,12-tetramethyl-3a,9-(methanoxymethano)-3a*H*-benz[f]inden-10-one*; **5b**). Amorphous solid. $[\alpha]_D^{26} = -2.6$ (*c* = 0.2, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 8.06 (*d*, *J* = 7.5, 2 H); 7.58 (*d*, *J* = 7.5, 1 H); 7.47 (*t*, *J* = 7.5, 2 H); 5.28 (br. *s*, H–C(5)); 5.26 (*m*, H–C(7)); 4.81, 4.71 (2*d*, *J* = 11.1, CH_2(20)); 4.34 (*d*, *J* = 9.4, H–C(14)); 2.05, 2.03 (2*s*, 2 AcO); 1.99 (*s*, Me(18)); 1.47 (*s*, Me(16)); 1.32 (*s*, Me(17)); 1.26 (*s*, Me(19)). EI-MS: 586 (M^+), 526 ([*M* – AcOH]$^+$), 508 [*M* – AcOH–H_2O]$^+$), 362, 282, 194, 149, 121, 105, 77. HR-ESI-MS: 651.2419 ($C_{33}H_{40}Na^+O_{12}$; calc. 651.2417).

Molecular Modeling (MM2) *Calculation*. The model of compound **4** was optimized with Chem3D 8.0 (*ChambridgeSoft*) by using an MM2 force field. Minimization of energy was carried out to minimum RMS gradient of 0.100 which is a reasonable compromise between accuracy and speed. The MM2 force field computations were implemented based on the work of *Dudek* and *Ponder* [27]. An *Acer-TravelMate-280* computer was used during the whole process.

Cytotoxicity Assay. The cytotoxicity assay depends on the binding of methylene blue to fixed monolayers of four human-tumor cell lines. Samples and control standard drugs were prepared at a concentration of 1, 10, 40, and 100 μg/ml. After seeding 2880 cells/well in a 96-well microplate for 3 h, 20 μl of sample or standard agent was placed in each well and incubated at 37° for 3 days. The absorbance was measured on a microtiter plate reader (*Dynatech*, *MR 7000*) at a wavelength of 650 nm. The ED_{50} value was defined by a comparison with the untreated cells as the concentration of test sample resulting in 50% reduction of absorbance. Mitomycin was used as a standard.

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