Naturally Occurring Rearranged Taxoids[1],*

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Abstract

The rearranged taxoids have recently been reported from different *Taxus* species. The literature concerning the chemistry, biogenesis, and bioactivity of such compounds is reviewed.

Key words

Rearranged taxoids, 11(15→1)-abeotaxoids, 2(3→20)-abeotaxoids, chemistry, biogenesis, bioactivity.

Introduction

Taxol (**1**) (1), a complex diterpenoid alkaloid, isolated originally from the pacific yew, *Taxus brevifolia* (Taxaceae) has emerged as a highly promising cancer chemotherapeutic agent. Its clinical activity against a broad spectrum of cancerous disease, such as refractory human ovarian, melanoma, and breast cancers (2–5) has spurred a worldwide search (6) for better sources and improved analogues of this compound. During the isolation of novel taxoids from different yew plants (*Taxus* species), some compounds have been observed with rearranged skeleta. These compounds represent a novel and rapidly growing group of taxoids. Here we review the chemistry, biogenesis, and bioactivity of the naturally occurring, rearranged taxoids.

Chemistry

Normal taxoids contain a 6/8/6-membered ring system (**A**), but the rearranged taxoids possess a 5/7/6- or a 6/10/6-membered ring system (**B** and **C**, respectively). Taxoids with the **B** ring system are known as 11(15→1)-abeotaxoids (7–9) or A-nortaxoids (10) and those with **C** ring system as 2(3→20)-abeotaxoids (11). They have been isolated from the bark, stems, needles, and seeds of several *Taxus* species. The reported naturally occurring rearranged taxoids and their physical properties are presented in Table **1**.

Most rearranged taxoids contain the 11(15→1)-abeotaxane skeleton (**B**) (7, 16, 8, 9) which was first observed (7) in a semisynthetic product from taxol (**1**). Brevifoliol (**2**), originally isolated (12, 13) from *T. brevifolia*, was the first natural taxoid isolated possessing this skeleton. It was initially considered (12, 13) to be a normal taxoid, and later proved (16, 8, 9) to be an 11(15→1)-abeotaxoid **2** after reinterpretation of its NMR spectra (mainly HMBC and ^{13}C-NMR) and by X-ray crystallographic analysis. Brevifoliol is the most abundant rearranged taxoid in the needles of *T. brevifolia* throughout most of the year (14). Taxchinin B (**16**) (20) isolated, from *T. chinensis*, was the first 11(15→1)-abeotaxoid isolated with an oxetane ring.

Thirteen derivatives of brevifoliol (**3–15**) and eleven derivatives of taxchinin B (**17–27**) have been isolated and characterised from different yew plants (Table **1**). Many compounds (**3–7** and **17–20**) were initially reported to have the normal taxoid skeleton but were later revised to 11(15→1)-abeotaxoids (references in the Table). In $CDCl_3$ solution the taxoids possessing a brevifoliol skeleton show conformational isomerisation (15, 8, 10, 23) which appears to be characteristic of this structural type. Besides the derivatives of brevifoliol and taxchinin B, three other novel 11(15→1)-abeotaxoids, wallifoliol (**28**) (17), taxuchin A (**29**) (29), and yunantaxusin A (**30**) (30) have been isolated. The former is the only taxoid, reported so far, which possesses the 5/6/6/6/4-membered ring system. Taxuchin A contains an epoxy ring at C-4. In yunantaxusin A the oxetane ring is open.

Four rearranged taxoids have been found with the 2 (3→20)-abeotaxane skeleton (Table **1**). Taxine A (**31**) (31, 32), the first compound of this group, was characterised by single crystal X-ray diffractometry. The structures of its three derivatives, **32–34**, were elucidated (11, 24, 33) by spectroscopic analysis and by comparison of the spectral data with those of taxine A (**31**).

Biogenesis

Taxoids and rearranged taxoids arise by two different biogenetic pathways (Scheme **1**) (29, 11) starting from a common precursor **a**. The generation of the 5- or 6-membered A-ring depends on the mode of ring closure for **b**. The formation of a 5-membered A-ring and

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* The paper is dedicated to Dr. A. V. Rama Rao on the occasion of his 60th birthday.

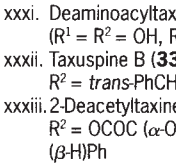
Table 1 Naturally occurring rearranged taxoids

Name, Structure	Mol. formula; M.p. (solvent); $[\alpha]_D$ (solvent)	Source
1. 11(15→1)-abeotaxoids		
A. *Brevifoliol and its derivatives*		
i. Brevifoliol (**2**) (R = R^4 = OH, R^1 = OBz, R^2 = R^3 = OAc, R^5 = H)	$C_{31}H_{40}O_9$; 200–203 °C (*n*-C_6H_{14}-Me_2CO) (12), 200–205 °C (*n*-C_6H_{14}-Me_2CO)(13), 200–202 °C (*n*-C_6H_{14}-Me_2CO)(15); −28.0° ($CHCl_3$) (13), −24.0° ($CHCl_3$) (15)	*T. brevifolia* Nutt. (needles, stembark and twigs) (12,13,9,14) *T. wallichiana* Zucc. (needles)(15,16,8,17) *T. baccata* Linn. (twigs) (18)
ii. Taxchinin A (**3**) (R = R^4 = OH, R^1 = OBz, R^2 = R^3 = R^5 = OAc)	$C_{33}H_{42}O_{11}$; 208–210 °C (Et_2O) (19,20), 198 °C (Me_2CO-Et_2O) (21); −34.62° (CH_2Cl_2) (20), −24,0° (CH_2Cl_2) (21)	*T. chinensis* (Pilgre) Rehd. (stems and neddles) (19,20) *T. baccata* Linn. (seeds) (21,8) *T. wallichiana* Zucc. (needles) (17)
iii. 13-Acetylbrevifoliol (**4**) (R = R^2 = R^3 = OAc, R^1 = OBz, R^4 = OH, R^5 = H)	$C_{33}H_{42}O_{10}$; thick oil (15); +8.0° (MeOH) (15), −26.0°($CHCl_3$) (9)	*T. wallichiana* Zucc. (needles) (15,8) *T. brevifolia* Nutt. (needles) (9)
iv. −*(**5**) (R = R^1 = R^4 = OH, R^2 = OAc, R^3 = R^5 = H)	$C_{22}H_{34}O_6$; 160–162 °C (*n*-C_6H_{14}-AcOMe) (15); −24.0° (MeOH) (15)	*T. wallichiana* Zucc. (needles) (15,8)
v. −* (**6**) (R = R^1 = R^4 = OH) R^2 = R^3 = OAc, R^5 = H)	$C_{24}H_{36}O_8$; non-cryst. (15); −5.0° (MeOH) (15)	Same as for **5**
vi. −* (**7**) (R = R^1 = R^4 = OH, R^2 = R^5 = OAc, R^3 = H)	$C_{24}H_{36}O_8$; 154 °C (22); −22.0° ($CHCl_3$) (22)	*T. baccata* Linn. (needles) (22,8)
vii. Taxchinin D (**8**) (R = R^2 = R^3 = R^5 = OAc, R^1 = OBz, R^4 = OH)	$C_{35}H_{40}O_{12}$; 138–141 °C (*n*-C_6H_{14}-Me_2CO);	*T. chinensis* (Pilgre) Rehd. (stems and needles) (23)
viii. Taxchinin G (**9**) (R = R^2 = R^3 = R^5 = OAc, R^1 = R^4 = OH)	$C_{28}H_{35}O_{11}$; 140–143 °C (Et_2O)	Same as for **8**
ix. 9-Deacetyl-9-benzoyl-10-debenzoyl-brevifoliol (**10**) (R = R^1 = R^4 = OH, R^2 = OBz, R^3 = OAc, R^5 = H)	$C_{29}H_{38}O_8$; 152 °C; +18.0° ($CHCl_3$)	*T. brevifolia* Nutt. (bark) (10)
x. 10β-Benzoxy-1β-hydroxy-5α-(3′-dimethylamino-3′phenyl)-propanoxy-1β-hydroxy-7β, 9α,13α-triacetoxy-11(15→1)-abeotaxa-4(20), 11-deine (**11**) [R = R^2 = R^3 = OAc, R^1 = OBz, R^4 = $OCOCH_2C$(α-NMe_2)(β-H)Ph, R^5 = H]	$C_{44}H_{55}O_{11}N$; Amorphous; −7.0° ($CHCl_3$)	*T. brevifolia* Nutt. (needles) (9)
xi. 10β-Benzoxy-1β-hydroxy-5α-(3′-methylamino-3′-phenyl)propanoxy-7β,9α,13α-triacetoxy-11(15→1)-abeotaxa-4(20),11-diene (**12**) [R = R^2 = R^3 = OAc, R^1 = OBz, R^4 = $OCOCH_2C$ (α-NHMe)(β-H)Ph,R^5 = H]	$C_{43}H_{53}O_{11}N$; Amorphous; −7.0° ($CHCl_3$)	Same as for **11**
xii. 10β-Benzoxy-5α-cinnamoxy-1β-hydroxy-7β,9α,13α-triacetoxy-11 (15→1)-abeotaxa-4(20),11-diene (Taxuspine A) (**13**) (R = R^2 = R^3 = OAc, R^1 = OBz, R^4 = *trans*-PhCH = CHOCO-, R^5 = H)	$C_{42}H_{48}O_{11}$; Amorphous (24); −26.0° ($CHCl_3$) (9), −3.4° ($CHCl_3$) (24)	Same as for **11** and *T. cuspidata* Sieb et Zucc. (stems) (24)
xiii. Taxchinin E (**14**) (R=*trans*-PhCH= CHOCO-, R^1=OBz, R^2=R^3=R^5=OAc, R^4=OH)	$C_{42}H_{48}O_{12}$; 134–136 °C; −17.49° ($CHCl_3$)	*T. chinensis* (Pilgre) Rehd. (stems and neddles) (25)
xiv. Taxchinin H (**15**) (R = OH, R^1 = OBz, R^2 = R^3 = OAc, R^4 = *trans*-PhCH = CHOCO-, R^5 = H)	$C_{40}H_{46}O_{10}$; 115–118 °C; −65.29° ($CHCl_3$)	Same as for **14**
B. *Taxchinin B and its derivatives*		
xv. Taxchinin B (**16**) (R = trans-PhCH = CHOCO-, R^1 = OBz,R^2 = R^3 = R^4 = OAc)	$C_{44}H_{48}O_{13}$; 176–178 °C (MeOH); +7.40° ($CHCl_3$)	*T. chinensis* (Pilgre) Rehd. (stems and neddles) (20)
xvi. 13-Decinnamoyltaxchinin B (**17**) (R = OH, R^1 = OBz, R^2 = R^3 = R^4 = OAc)	$C_{35}H_{44}O_{13}$; 225–226 °C (*n*-C_6H_{14}-AcOMe) (15), 227–228 °C (*n*-C_6H_{14}-Me_2CO) (26); −38.0° (MeOH) (15), −40.0° (MeOH) (26)	*T. wallichiana* Zucc. (needles) (15,8) *T. baccata* Linn. (twigs and needles) (18,26)
xvii. Taxchinin C (**18**) (R = R^3 = OAc, R^1 = R^2 = R^4 = OBz)	$C_{47}H_{50}O_{14}$; 212–214 °C (*n*-C_6H_{14}-Me_2CO) (20), Amorphous (27); −45.6° (CH_2Cl_2) (20)	*T. chinensis* (Pilgre) Rehd. (stems and needles) (20), *T. brevifolia* Nutt. (bark) (27,9)
xviii. −* (**19**) (R = R^2 = R^3 = OAc, R^1 = R^4 = OBz)	$C_{42}H_{48}O_{14}$; Amorphous (27); –	*T. brevifolia* Nutt. (bark) (27,9)
xix. −* (**20**) (R = R^1 = R^2 = OAc, R^3 = R^4 = OBz)	$C_{42}H_{48}O_{14}$; Amorphous (27); –	Same as for **19**
xx. 10-15-Epoxy-11(15→1)-abeo-10-deacetylbaccatin III (**21**)	$C_{29}H_{34}O_9$; Oil; −18.0° (CH_2Cl_2)	*T. wallichiana* Zucc. (needles) (28)
xxi. 7,9,10-Trideacetylabeobaccatin VI (**22**) R = OAc, R^1 = R^2 = R^3 = OH, R^4 = OBz)	$C_{31}H_{40}O_{11}$; Powder; −26.0° ($CHCl_3$)	*T. baccata* Linn. (twigs and needles) (11)
xxii. 7,13-Dideacetyl-9,10-debenzoyl-taxchinin C (**23**) (R = R^1 = R^2 = R^3 = OH, R^4 = OBz)	$C_{29}H_{38}O_{10}$; 162 °C; −15.0° ($CHCl_3$)	*T. brevifolia* Nutt. (bark) (10)

Table 1 Continued

Name, Structure	Mol. formula; M.p. (solvent); $[\alpha]_D$ (solvent)	Source
xxiii. 13-Acetyl-13-decinnamoyltaxchinin B (**24**) (R = R^2 = R^3 = R^4 = OAc, R^1 = OBz)	$C_{37}H_{46}O_{14}$; 243–244 °C (*n*-C_6H_{14}-Me_2CO); −54.0° ($CHCl_3$)	*T. baccata* Linn. (needles) (26)
xxiv. Taxchinin I (**25**) (R = R^3 = OAc, R^1 = OH, R^2 = R^4 = OBz)	$C_{40}H_{46}O_{13}$; 235–237 °C (Et_2O); −6.08° ($CHCl_3$)	*T. chinensis* (Pilgre) Rehd. (stems and needles) (25)
xxv. Taxchinin J (**26**) (R = *trans*-PhCH = CHOCO-, R^1 = OH, R^2 = OBz, R^3 = R^4 = OAc)	$C_{42}H_{48}O_{13}$; 238–240 °C (Et_2O); +23.36° ($CHCl_3$)	Same as for **25**
xxvi. Taxchinin K (**27**) (R = R^3 = R^4 = OAc, R^1 = R^2 = OBz)	$C_{42}H_{48}O_{14}$; 217–219° (*n*-C_6H_{14}-Et_2O); −30.0° ($CHCl_3$)	Same as for **25**
C. *Other*		
xxvii. Wallifoliol (**28**)	$C_{29}H_{34}O_{10}$; Amorphous; −10.8° (MeOH)	*T. wallichiana* Zucc. (needles) (17)
xxviii. Taxuchin A (**29**)	$C_{32}H_{44}O_{14}$; 248–250 °C (Et_2O); −64.8° (MeOH)	*T. chinensis* (Pilgre) Rehd. (bark) (29)
xxix. Yunantaxusin A (**30**)	$C_{35}H_{46}O_{14}$; 239–240 °C (Me_2CO); −52.0° (MeOH)	*T. yunnanensis* Cheng et L.K. Fu (stems and needles) (30)
2. 2(3→20)-abeotaxoids		
xxx. Taxine A (**31**) R^1 = OH, R^2 = OCOC(α-OH)(β-H) C(α-NMe_2)(β-H)Ph, R^3 = OAc]	$C_{35}H_{47}NO_{10}$; 204–206 °C (Et_2O); −140.0° ($CHCl_3$)	*T. baccata* Linn. (needles) (31,32)
xxxi. Deaminoacyltaxin A (**32**) (R^1 = R^2 = OH, R^3 = OAc)	$C_{24}H_{34}O_8$; Gum; –	*T. baccata* Linn. (needles and twigs) (11)
xxxii. Taxuspine B (**33**) (R^1 = R^3 = OAc, R^2 = *trans*-PhCH = CHOCO-)	$C_{35}H_{42}O_{10}$; Amorphous; −40.6° ($CHCl_3$)	*T. cuspidata* Sieb et Zucc. (stems) (24)
xxxiii. 2-Deacetyltaxine A (**34**) [R^1 = R^3 = OH, R^2 = OCOC (α-OH)(β-H) C(α-NMe_2) (β-H)Ph	$C_{33}H_{45}NO_9$; Amorphous; −106.0° ($CHCl_3$)	*T. baccata* Linn. (needles) (33)

*Originally proposed names based on the taxane skeleton were proved to be incorrect after revision of the structure.



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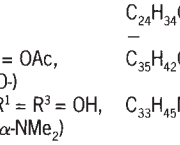

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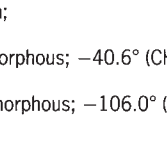

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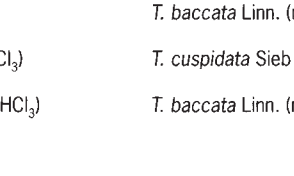

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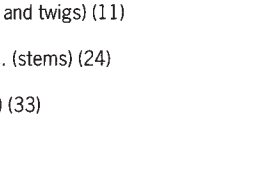

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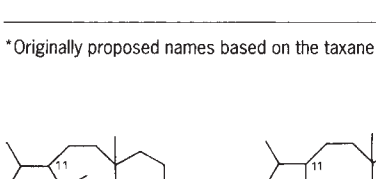

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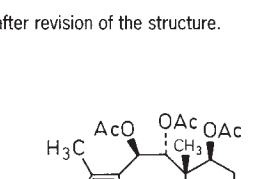
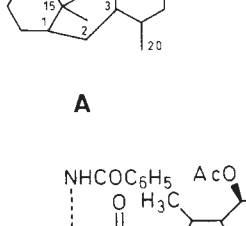


31-34



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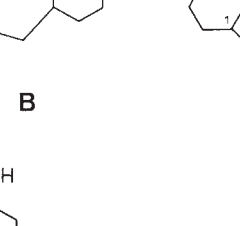
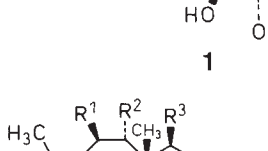


16-20, 22-27



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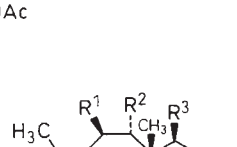

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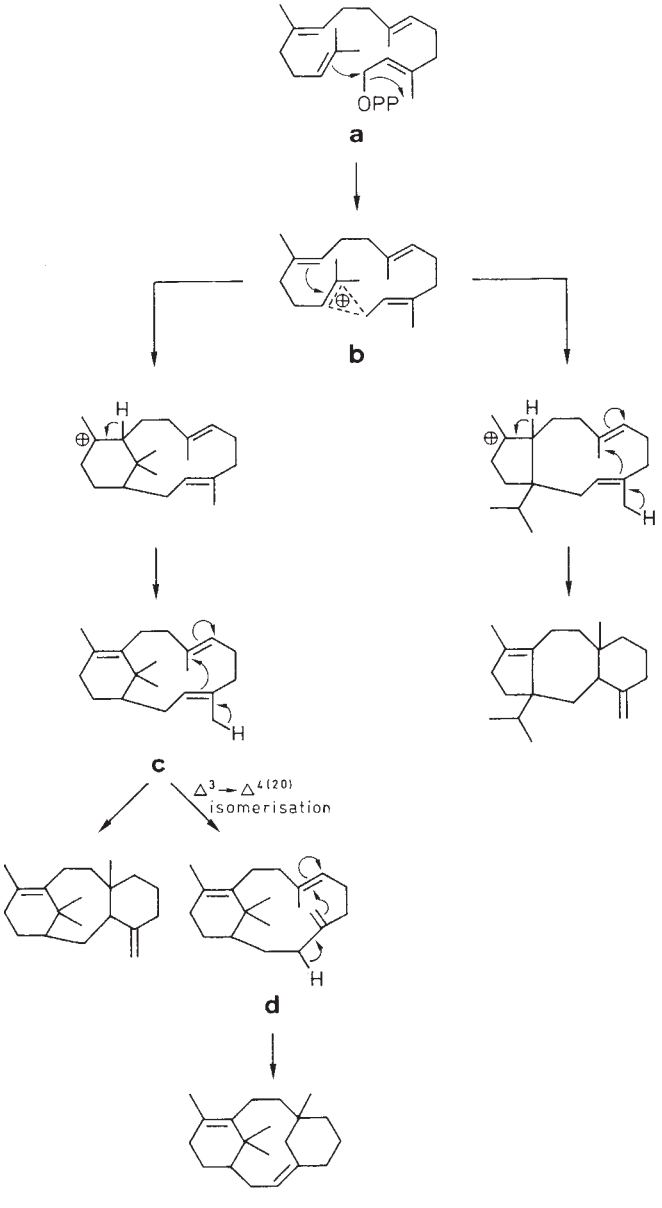
the subsequent formation of a 6-membered C-ring produces the 11(15→1)-abeotaxoid. On the other hand, the formation of a 6-membered A-ring first produces the verticilladiene precursor **c**, which then converts either to the taxoid, or to the isomeric verticilladiene **d** (by $\Delta^3 \rightarrow \Delta^{4(20)}$ isomerisation) to generate the 2(3→20)-abeotaxoid. However, all attempts to cyclise verticilladiene derivatives to taxoids have failed, suggesting (11) a more subtle biogenetic sequence.

Bioactivity

The biological activities of some naturally occurring rearranged taxoids have been studied. The synthetic 15-hydroxy-11(15→1)-abeotaxol derivatives showed a tubulin-binding activity (7, 34) but no *in vitro* cytotoxicity (7). This result created interest in the biological evaluation of the natural rearranged taxoids. Brevifoliol (**2**) itself showed no activity in tubulin assays (16). Brevifoliol-13[*N*-benzoyl-(2*R*′,3′*S*)-3′-phenylisoserinate] (35) in which the C-13 side chain of taxol has been attached to brevifoliol (**2**) was also found to be inactive in the microtubule binding assay and to have little cytotoxicity against B 16 melanoma cells. Taxchinins A (**3**), B (**16**), and C (**18**) had little effect on the microtubule binding assembly ($ID_{50} > 100\ \mu M$) (19, 20) compared t that of taxol ($ID_{50} = 0.29\ \mu M$).

The cytotoxicity of taxuspine A and B was evaluated (24) against murine lymphoma L 1210 and human epidermoid carcinoma KB cells. Taxuspine A (**13**) exhibited modest cytotoxicity against L 1210 cells (IC_{50} = 4.2 μg/ml) and taxuspine B (**33**) showed a weak cytotoxicity (IC_{50} = 18 μg/ml) although taxol (**1**) was found to be the most cytotoxic (IC_{50} = 0.33 μg/ml) under the experimental conditions. Taxuspine B (**33**) exhibited (24) appreciable taxol-like activity to reduce $CaCl_2$-induced depolymerisation of microtubules (36, 37). This compound also increased (24) the vincristine accumulation in multidrug-resistant tumour cells; it is as potent as verapamil (38, 39) and so may be useful for overcoming multidrug-resistance in tumour cells.



Scheme 1 Biogenetic pathways to taxoids and rearranged taxoids.

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References

[1] Wani, M. C., Taylor, H. L., Wall, M. E., Coggon, P., McPhail, A. T. (1971) J. Am. Chem. Soc. 93, 2325–2327.
[2] McGuire, W. P., Rowinsky, E. K., Rosenshein, N. B., Grumbine, F. C., Ettinger, D. S., Armstrong, D. K., Donehover, R. C. (1989) Ann. Int. Med. 111, 273–279.
[3] Rowinsky, E. K., Cazenave, L. A., Donehover, R. C. (1990) J. Natl. Cancer Inst. 82, 1247–1259.
[4] Kingston, D. G. I., Samaranayake, G., Ivey, C. A. (1990) J. Nat. Prod. 53, 1–12.
[5] Das, B., Das, R. (1994) Indian J. Pharm. Sci. 56, 199–204.
[6] Kingston, D. G. I., Molinero, A. A., Rimoldi, J. M. (1993) in: Progress in the Chemistry of Organic Natural Products, (Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, C., eds.), Vol. 61, pp. 1–206, Springer-Verlag, New York.
[7] Samaranayake, G., Magri, N. F., Jitrangsri, C., Kingston, D. G. I. (1991) J. Org. Chem. 56, 5114–5119.
[8] Appendino, G., Barboni, L., Gariboldi, P., Bombardielli, E., Gabetta, B., Viterbo, D. (1993) J. Chem. Soc., Chem. Commun. 1587–1589.
[9] Chu, A., Furlon, M., Davin, L. B., Zajicek, J., Towers, G. H. N., Soucy-Breau, C. M., Rettig, S. J., Croteau, R., Lewis, N. G. (1994) Phytochemistry 36, 975–985.
[10] Chen, R., Kingston, D. G. I. (1994) J. Nat. Prod. 57, 1017–1021.
[11] Appendino, G., Cravotto, G., Enriu, R., Jakupovic, J., Gariboldi, P., Gabetta, B., Bombardelli, E. (1994) Phytochemistry 36, 407–411.
[12] Balza, F., Tachibana, S., Barrios, H., Towers, G. H. N. (1991) Phytochemistry 30, 1613–1614.
[13] Chu, A., Jajicke, J., Towers, G. H. N., Soucy-Breau, C. M., Lewis, N. G., Croteau, R. (1993) Phytochemistry 34, 269–271.
[14] Vance, N. C., Kelsey, R. G., Sabin, T. E. (1994) Phytochemistry 36, 1241–1244.
[15] Barboni, L., Gariboldi, P., Torregiani, E., Appendino, G., Gabetta, B., Zini, G., Bombardelli, E. (1993) Phytochemistry 33, 145–150.
[16] Georg, G. I., Gollapudi, S. R., Grunewald, G. L., Gunn, C. W., Himes, R. H., Rao, B. K., Liang, X.-Z., Mirhom, Y. W., Mitscher, L. A., Velde, D. G. V., Ye, Q.-M. (1993) Bioorg. Med. Chem. Lett. 3, 1345–1348.
[17] Velde, D. G. V., Georg, G. I., Gollapudi, S. R., Jampani, H. B., Liang, X.-Z., Mitscher, L. A., Ye, Q.-M. (1994) J. Nat. Prod. 57, 862–867.
[18] Das, B., Rao, S. P., Srinivas, K. V. N. S., Yadav, J. S. (1995) Phytochemistry 38, 715–717.
[19] Fuji, K., Tanaka, K., Li, B., Shingu, T., Sun, H., Taga, T. (1992) Tetrahedron Lett. 33, 7915–7916.
[20] Fuji, K., Tanaka, K., Li, B., Shingu, T., Sun, H., Taga, T. (1993) J. Nat. Prod. 56, 1520–1531.
[21] Appendino, G., Tagliapietra, S., Özen, H. C., Gariboldi, P., Gabetta, B., Bombardelli, E. (1993) J. Nat. Prod. 56, 514–520.
[22] Appendino, G., Özen, H. C., Gariboldi, P., Gabetta, B., Bombardelli, E. (1993) Fitoterapie 64 (1-Suppl.), 47–51.
[23] Li, B., Tanaka, K., Fuji, K., Sun, H., Taga, T. (1993) Chem. Pharm. Bull. 41, 1672–1673.

[24] Kobayashi, J., Ogiwara, A., Hosoyama, H., Shigemori, H., Yoshida, N., Sasaki, T., Li, Y., Iwasaki, S., Naito, M., Tsuruo, T. (1994) Tetrahedron 50, 7401–7416.
[25] Tanaka, K., Fuji, K., Yokoi, T., Shingu, T., Li, B., Sun, H. (1994) Chem. Pharm. Bull. 42, 1539–1541.
[26] Das, B., Rao, S. P., Srinivas, K. V. N. S., Yadav, J. S., Das, R. (1995) Phytochemistry 38, 671–674.
[27] Chu, A., Zajicek, J., Davin, L. B., Lewis, N. G., Croteau, R. B. (1992) Phytochemistry 31, 4249–4252.
[28] Appendino, G., Özen, H. C., Gariboldi, P., Torregiani, E., Gabetta, B., Nizzola, R., Bombardelli, E. (1993) J. Chem. Soc., Perkin Trans. I, 1563–1566.
[29] Zhang, S., Lee, C. T.-L., Chen, K., Kashiwada, Y., Zhang, D.-C., McPhail, A. T., Lee, K.-H. (1994) J. Chem. Soc., Chem. Commun. 1561–1562.
[30] Zhang, S., Lee, C. T.-L., Kashiwada, Y., Chen, K., Zhang, D.-C., Lee, K.-H. (1994) J. Nat. Prod. 57, 1580–1583.
[31] Graf, E., Bertholdt, H. (1957) Pharma. Zentralhalle 96, 385–395.
[32] Graf, E., Kirfel, A., Wolff, G.-J., Breitmaier, E. (1982) Liebigs Ann. Chem. 376–381.
[33] Poupat, C., Ahond, A., Potier, P. (1994) J. Nat. Prod. 57, 1468–1469.
[34] Wahl, A., Guéritte-Voegelein, F., Guénard, D., le Goff, M. T., Potier, P. (1992) Tetrahedron 48, 6965–6974.
[35] Georg, G. I., Cheruvallath, Z. S., Velde, D. V., Ye, Q.-M., Mitscher, L. A., Himes, R. H. (1993) Bioorg. Med. Chem. Lett. 3, 1349–1350.
[36] Shetanski, M. L., Gaskin, F., Cantor, C. R. (1973) Proc. Natl. Acad. Sci. USA 70, 765–768.
[37] Shiff, P. B., Fant, J., Horwitz, S. B. (1979) Nature 277, 665–667.
[38] Tsuruo, T., Iida, H., Tsukagoshi, S., Sakurai, Y. (1982) Cancer Res. 42, 4730–4733.
[39] Yusa, K., Tsuruo, T. (1989) Cancer Res. 49, 5002–5006.