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by Mulyadi Tanjung

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Flavonoid and stilbene derivatives from *Macaranga trichocarpa*

Mulyadi Tanjung[a], Lia D. Juliawaty[b], Euis H. Hakim[b], Yana M. Syah[b,*]

[a] Chemistry Department, Airlangga University, Jalan Darmawangsa Dalam, Surabaya 60222, Indonesia
[b] Organic Chemistry Division, Faculty of Mathematics and Natural Sciences, Institut Teknologi Bandung, Jalan Ganesha 10, Bandung 40132, Indonesia

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ABSTRACT

A new farnesylated flavonol (4′-*O*-methylmacagigantin) and a new geranylated stilbene (macatrichocarpin H), together with eight known phenolic compounds, have been isolated from the leaves of *Macaranga trichocarpa*. Structures of these compounds were determined based on NMR and mass spectrroscopic data. Cytotoxic properties of the isolated compounds were tested against P-388 cells showing that mactrichocarpin G was the most active compound with IC_{50} was 3.5 μM.

1. Introduction

Macaranga (Euphorbiaceae) is the genus of plants inhabitated mostly in the tropical regions, including in the Indonesian archipelago [1]. The plants have been known to produce a variety of terpenylated flavonoids and stilbenes [2]. One of the species, namely *Macaranga trichocarpa* (Zoll.) Mull.Arg., is widely distributed in the western part of Indonesia, particularly in Sumatera and Kalimantan islands [3]. This plant is considered as a pioneer species for forest disturbances and is common to be found in a secondary forest [4]. Report on its medicinal use is a rather scarce, however, the people of Vietnam has used the decoction of the leaves to improve and maintain health [4]. Previous chemical investigation of the plant leaves collected from Kalimantan island has revealed a number of prenylated dihydrochalcone and flavanone derivatives [5,6]. Some of them were shown to have significant antibacterial properties [6]. In this paper we report the isolation of phenolic constituents from the leaves of this plant collected from Sumatera island. In addition to the previously isolated compounds, namely macatrichocarpins A-B (**1**–**2**), we succeded to isolate one new farnesylated flavonol, 4′-*O*-methylmacagigantin (**4**), and one new geranylated stilbene, macatrichocarpins H (**7**), together with other known stilbenes (**5** and **6**) and flavonoids (**3**, **8**–**10**) (Fig. 1). Structure elucidation of these new compounds will be the subject of this paper. In addition, preliminary cytotoxicity test of the isolated compounds against murine leukemia P-388 cells will also be described.

2. Experimental

2.1. General experimental procedure

^{1}H and ^{13}C NMR spectra were recorded with a JEOL ECA500 spectrometer operating at 500 (^{1}H) and 125 (^{13}C) MHz, using residual and deuterated solvent peaks (δ_H 7.26 and δ_C 77.0 for $CDCl_3$; δ_H 2.04 and δ_C 29.8 for acetone-d_6) as reference standards. High-resolution mass spectra were obtained with an ESI-TOF Waters LCT Premier XE mass spectrometer with either positive or negative mode.Vacuum liquid chromatography (VLC) and centrifugal planar (CPC) chromatography were carried out using Si gel 60 G (art. no. 1.07731.1000, Merck KgaA, 64,271 Darmstadt, Germany) and Si gel 60 PF_{254} (art. no. 1.07749.1000, Merck KgaA, 64,271 Darmstadt, Germany), respectively, and, for TLC analysis, precoated Si gel 60 F_{254} plates (art. no. 1.05554.0001, Merck KgaA, 64,271 Darmstadt, Germany) were used. Solvents used for extraction and separation were technical grades that were distilled before used.

2.2. Plant material

Samples of the leaves of *M. trichocarpa* were collected from Sungai Lilin District, South Sumatera, Indonesia, in December 2009. The specimen was identitified at the Herbarium Bogoriense, Center of Biological Research and Development, National Institute of Science,

* Corresponding author.
E-mail address: yana@chem.itb.ac.id (Y.M. Syah).

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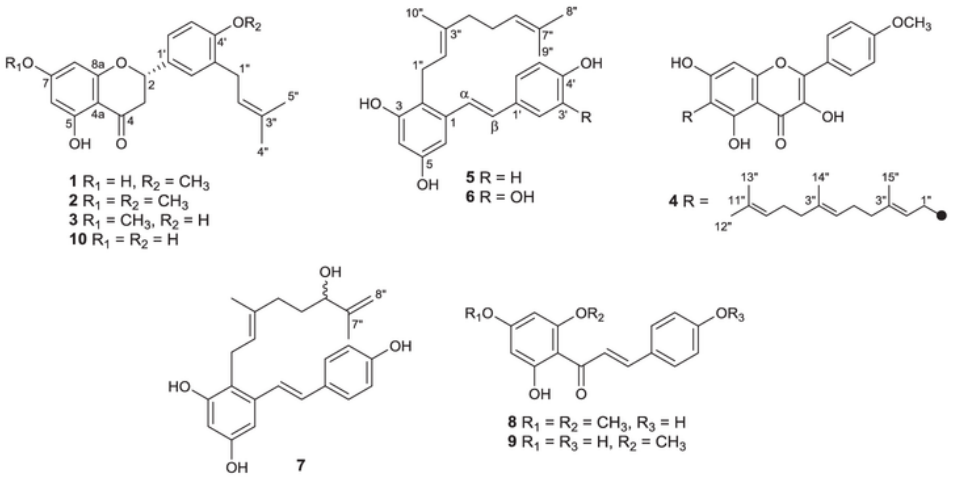

Fig. 1. Flavonoid and stilbene derivatives isolated from *M. trichocarpa*.

Bogor, Indonesia. The specimen (collection number HBG-13587), was deposited at herbarium Bandungense, School of Life Science and Technology, Institut Teknologi Bandung, Indonesia.

2.3. Extraction and isolation

The dried and powdered leaves of *M. trichocarpa* (650 g) was macerated with MeOH at room temperature (2 × 24 h) to give a dark MeOH extract (70 g) after solvent evaporation. The MeOH extract was dissolved MeOH-water (9:1) and was partitioned into *n*-hexane (48 g) and EtOAc (15 g) soluble fractions. The EtOAc soluble fraction was fractionated by VLC (Si gel 150 g; eluents *n*-hexane-EtOAc 9:1, 4:1, 7:3 and 1:1) into four fractions A-D. Purification of fraction A (1.9 g) by CPC (eluents: *n*-hexane-EtOAc 9:1, 17:3 and 4:1) gave compound **2** (10 mg, 0.0015%) and a fraction (1.2 g), which on purification by the same method (eluents: *n*-hexane-$CHCl_3$ 2:3, 1:1 and 3:2), yielded compounds **1** (120 mg, 0.018%), **3** (11 mg, 0.0017%), and **4** (17 mg, 0.0026%). Two steps purification of fraction B (1,7 g) using CPC (first eluents: *n*-hexane-acetone 4:1 and 7:3; second eluents *n*-hexane-acetone 9:1 and 4:1) gave compounds **8** (40 mg, 0.0061%), **9** (57 mg, 0.0086%) and **10** (35 mg, 0.0053%). The same method was also applied to purify fraction C (1.9 g) (eluent: *n*-hexane-$CHCl_3$ 1:4) to give compound **5** (480 mg, 0.0738%). CPC purification on fraction D (850 mg) (two steps; first eluents: *n*-hexane-EtOAc 7:3 and 2:3; second eluents: *n*-hexane-$CHCl_3$ 1:4 and $CHCl_3$-EtOAc 9:1) yielded compounds **6** (6 mg, 0.0009%) and **7** (45 mg, 0.0069%).

2.4. 4′-O-Methylmacagigantin (4)

Pale yellow solid; IR (KBr) ν_{max}: 3350 (OH), 2970, 2918 (alkyl-CH), 1649 (conj. C=O), 1606, 1560 (aromatic C=C), 1230, 1180, (C–O), 835, 819, 802 (alkene C=C) cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) see Table 1; ^{13}C NMR (acetone-d_6, 125 MHz) see Table 1; HRESIMS *m/z* $[M-H]^-$ 503.2438 (calcd $[M-H]^-$ for $C_{31}H_{36}O_6$, 503.2434).

2.5. Macatrichocarpin F (5)

Pale yellow solid; ^1H NMR ($CDCl_3$, 500 MHz) see Table 2; ^{13}C NMR ($CDCl_3$, 125 MHz) see Table 2; HRESIMS *m/z* $[M + H]^+$ 365.2102 (calcd $[M + H]^+$ for $C_{24}H_{28}O_3$, 365.2111).

2.6. Macatrichocarpin G (6)

Pale yellow solid; ^1H NMR (acetone-d_6, 500 MHz) see Table 1; ^{13}C NMR (acetone-d_6, 125 MHz) see Table 1; HRESIMS *m/z* $[M + H]^+$ 381.2058 (calcd $[M + H]^+$ for $C_{24}H_{28}O_4$, 381.2060).

Table 1
^1H and ^{13}C NMR data of 4′-*O*-methylmacagigantin (**4**) in acetone-d_6.

No	δ_H (*mult.*, *J* in Hz)	δ_C	No	δ_H (*mult.*, *J* in Hz)	δ_C
2	–	145.6	1”	3.47 (*d*, 6.7)	21.6
3	–	135.9	2”	5.29 (*tm*, 6.7)	121.1
4	–	175.4	3”	–	139.9
4a	–	103.7	4”	1.96 (*br t*, 7.3)	39.9
5	–	157.8	5”	2.13 (*br q*, 7.3)	26.4
6	–	109.6	6”	5.07 (*tm*, 6.8)	123.7
7	–	161.9	7”	–	135.9
8	6.62 (*s*)	94.5	8”	2.10 (*br t*, 7.3)	39.8
8a	–	155.2	9”	2.03 (*br q*, 7.3)	26.8
1’	–	123.5	10”	5.07 (*tm*, 6.8)	124.5
2′/6’	8.15 (*d*, 8.6)	129.5	11”	–	131.5
3′/5’	7.02 (*d*, 8.6)	114.2	12”	1.66 (*br s*)	25.9
4’	–	161.2	13”	1.55 (*br s*)	16.2
5-OH	12.10 (*s*)	–	14”	1.55 (*br s*)	17.9
4′-OCH_3	3.80 (*s*)	55.6	15”	1.84 (*br s*)	16.4

2.7. Macatrichocarpin H (7)

Pale yellow solid; IR (KBr) ν_{max}: 3412 (OH), 2924, 2855 (alkyl-CH), 1601, 1518 (aromatic C=C), 1140 (C–O), 960, 806 (alkene C=C) cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) see Table 1; ^{13}C NMR (acetone-d_6, 125 MHz) see Table 1; HRESIMS *m/z* $[M-H]^-$ 379.1911 (calcd $[M-H]^-$ for $C_{24}H_{28}O_4$, 379.1909).

2.8. cytotoxicity assay

Cytotoxic properties of the isolated compounds **1–10** against murine leukemia P-388 cells was done using MTT assay as previously described [7], with artonin E was used as the positive control.

3. Results and discussion

Compounds **1–3** were identified based on comparison of their NMR data with those previously reported [5,8]. 4′-*O*-Methylmacagigantin (**4**) has a molecular formula $C_{31}H_{36}O_6$ based on HRESIMS measurement ($[M-H]^-$: found *m/z* 503.2438, calcd *m/z* 503.2434). The IR absorptions showed vibrations for –OH (3350 cm^{-1}), alkyl C–H (2970, 2918 cm^{-1}). conjugated C=O (1649 cm^{-1}), aromatic C=C (1606,

Table 2
^{1}H and ^{13}C NMR data of macatrichocarpins F–H (**5**–**7**).

C No	δ_H (*multiplicity*, *J* in Hz)			δ_C		
	5*	6**	7***	5	6	7
1	–	–	–	138.8	139.3	139.3
2	–	–	–	117.7	118.3	118.3
3	–	–	–	155.4	156.6	156.7
4	6.31 (*d*, 2.5)	6.36 (*d*, 2.3)	6.36 (*d*, 2.4)	102.5	102.5	102.5
5	–	–	–	154.5	156.7	156.8
6	6.64 (*d*, 2.5)	6.64 (*d*, 2.3)	6.64 (*d*, 2.4)	105.2	104.2	104.3
α	7.12 (*d*, 16.2)	7.14 (*d*, 16.0)	7.19 (*d*, 16.1)	124.3	124.9	124.9
β	6.81 (*d*, 16.2)	6.82 (*d*, 16.0)	6.88 (*d*, 16.1)	130.3	130.4	130.1
1'	–	–	–	130.6	131.1	130.5
2'	7.35 (*d*, 8.7)	7.07 (*d*, 2.0)	7.39 (*d*, 8.6)	128.0	113.8	128.6
3'	6.82 (*d*, 8.7)	–	6.84 (*d*, 8.6)	115.6	146.0	116.3
4'	–	–	–	155.5	145.9	158.0
5'	6.82 (*d*, 8.7)	6.82 (*d*, 8.1)	6.84 (*d*, 8.6)	115.6	116.1	116.3
6'	7.35 (*d*, 8.7)	6.89 (*dd*, 8.1, 2.0)	7.39 (*d*, 8.6)	128.0	119.8	128.6
1"	3.41 (*d*, 6.7)	3.44 (*d*, 6.8)	3.44 (*d*, 6.8)	24.9	24.8	24.8
2"	5.18 (*tm*, 6.7)	5.16 (*tm*, 6.8)	5.18 (*tm*, 6.8)	122.5	125.3	125.3
3"	–	–	–	134.2	134.0	134.2
4"	2.03 (*m*)	1.96 (*m*)	2.03 (*m*); 1.97 (*m*)	39.6	40.4	36.5
5"	2.08 (*m*)	2.05 (*m*)	1.57 (*m*); 1.52 (*m*)	26.5	27.4	34.7
6"	5.04 (*tm*, 6.7)	5.05 (*tm*, 6.8)	3.94 (*m*)	123.8	125.0	75.2
7"	–	–	–	149.3	131.5	149.3
8"	1.64 (*br d*, 0.6)	1.57 (*br s*)	4.83 (*m*); 4.68 (*m*)	25.6	25.7	110.2
9"	1.56 (*br d*, 1.0)	1.52 (*br s*)	1.63 (*br d*, 0.9)	17.7	17.6	17.8
10"	1.80 (*br d*, 1.1)	1.82 (*br s*)	1.82 (*br s*)	16.3	16.4	16.5

* in $CDCl_3$; 3-OH/5-OH/4′-OH: δ_H 5.58, 5.42, 5.38 as broad singlets.
** in acetone-d_6; 3-OH/5-OH/3′-OH/4′-OH overlaped at δ_H 8.12 (4H) as a broad singlet.
*** in acetone-d_6; 3-OH/5-OH/4′-OH: δ_H 8.48, 8.16, 7.99 as broad singlets, 6″-OH: δ_H 3.64 (*brd*, 2.4 Hz).

1560 cm^{-1}), C–O (1230, 1180 cm^{-1}), and alkene C=C (835, 819, 802 cm^{-1}) groups. The ^{1}H and ^{13}C NMR data of compound **4** (Table 1) were very similar to those macagigantin [9], except that it showed additional signals of a methoxyl group (δ_H 3.80; δ_C 55.6). HMBC correlations observed between the methoxyl proton signal (δ_H 3.80) and an *ortho*-coupled aromatic proton signal (2H, δ_H 8.15) with an oxyaryl carbon signal (δ_C 161.2) allowed to place the methoxyl group at C-4′. Thus, structure **4** was assigned to 4′-*O*-methylmacagigantin.

HRESIMS measurement of macatrichocarpin F (**5**) showed a quasi-molecular $[M + H]^+$ ion at *m/z* 365.2102, consistent with a molecular formula $C_{24}H_{28}O_3$ (calcd *m/z* 365.2111). The ^{1}H NMR spectrum of compound **5** (Table 2) showed a pair of a *trans*-1,2-disubstituted-ethene signals at δ_H 7.12 and 6.81 (J = 16.2 Hz), typical for a stilbene structure [10]. The ^{1}H NMR spectrum also showed proton signals for a geranyl group as revealed by three methyl (δ_H 1.80, 1.64 and 1.56), three methylene (δ_H 3.41, 2.08 and 2.03) and two vinyl (δ_H 5.18 and 5.04) signals. In the ^{13}C NMR spectrum three carbon signals for three oxyaryl carbon atoms (δ_C 155.5, 155.4 and 154.5) were observed that accounted for all three oxygen atoms contained in the compound. These NMR data suggested that compound **5** has a structure of reveratrol bearing a geranyl group. The presence of two pairs of *ortho*-(J = 8.6 Hz) and *meta*-coupled (J = 2.5 Hz) aromatic proton signals at δ_H 7.35/6.82 (each 2H) and 6.64/6.31 (each 1H) consistent with the position of the geranyl group at C-2. Thus, compound **5** is assigned as 2-geranylresveratrol or trivially named macatrichocarpin F. Further evidences for structure **5** were obtained by one-bond and multiple-bonds correlations found in the HMQC and HMBC spectra as shown in Fig. 2. Compound **5** has been reported as a product of enzymatic synthesis *in vitro*[11], the evidence of which was based on ^{1}H NMR data only

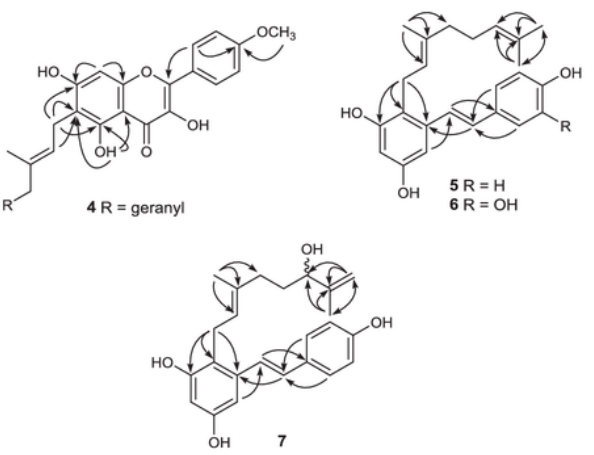

Fig. 2. Selected important HMBC correlations ($^{1}H \Leftrightarrow {}^{13}C$) in compounds **4**–**7**.

measured in DMSO-d_6. Table 2 presents ^{1}H and ^{13}C NMR data of this compound in acetone-d_6.

Macatrichoarpin G (**6**) has a molecular formula $C_{24}H_{28}O_4$ based on the presence of a quasimolecular $[M + H]^+$ ion peak at *m/z* 381.2058 in the positive mode of HRESIMS (calcd *m/z* 381.2060), indicating that this compound has one more oxygen atom than compound **5**. The NMR data (Table 2) of compound **6** were very close to those of compound **5**, the only difference is that the pair of *orto*-coupled aromatic proton signals at δ_H 7.35/6.82 (each 2H) in compound **5** were replaced in compound **6** with three proton signals at δ_H 7.07, 6.89 and 6.82 with their multiplicities are consistent for a 3,4-dihydroxyphenyl group (δ_C 146.0 and 145.9). Therefore, macatrichocarpin G (**6**) was deduced as 2-geranylpiceatannol. HMBC correlations supported structure **6** are shown in Fig. 2. Compound **6** has also been reported as a product of synthesis [12], and the structure was characterized by ^{1}H and ^{13}C NMR data in CD_3OD without assignments. Complete assignments of NMR data of this compound in acetone-d_6 are presented in Table 2.

Macatrichocarpin H (**7**) showed IR absorptions for –OH (3412 cm^{-1}), alkyl C–H (2924, 2855 cm^{-1}). aromatic C=C (1601, 1518 cm^{-1}), C–O (1140 cm^{-1}), and alkene C=C (960, 806 cm^{-1}) groups. This compound gave a quasimolecular $[M\text{-}H]^-$ ion peak in the negative mode of HRESIMS at *m/z* 379.1911, consistent with a molecular formula $C_{24}H_{28}O_4$ (calcd *m/z* 379.1909). Thus, compound **7** is an isomer of compound **6**. However, the ^{1}H NMR signals of compound **7** (Table 2) in the aromatic region were almost the same to that of compound **5**, suggesting that the additional one oxygenated functionality occurred at the geranyl group. In fact the vinyl and the methyl proton signals (δ_H 5.04 and 2.08, respectively) in compound **5** were replaced by proton signals of an oxymethine and a methylene alkene signals (δ_H 3.94 and 4.83/4.68, respectively). These changes were consistent with structure **7** for macatrichocarpin H, which was supported by long-range $^{1}H–{}^{13}C$ as shown in Fig. 2. The stereochemistry at C-6′ was not determined.

Compounds **8**–**10** were identified by comparison of their NMR data with those reported for flavokawain C [13], helichrysetin [14], and licoflavanon [15], respectively.

Compound **4** is one of a few examples of farnesylated phenolic compounds found in *Macaranga* species. Other farnesyl derivatives are macagigantin (6-farnesyl-4′,5,7-trihydroxyflavonol) from *M. gigantea* [9], schweinfurthin J (4-farnesylresveratrol) from *M. schweinfurthii*[16], 6-farnesyl-3′,4′,5,7-tetrahydroxyflavanone from *M. triloba*[17], and macarindicins A (6-farnesyl-3′,4′,5,7-tetrahydroxyflavonol) and B (6-farnesyl-4′,5,7-trihydroxyflavanone) from *M. indica*[18]. In the plant kingdom, the occurrence of farnesylated phenolic compounds are also very limited [19]. These compounds, however, are notably to be

Table 3
Cytotoxicity measurement of compounds **1–10** against P-388 cells.

Compounds	Types	IC_{50} (μM)
4′-*O*-Methylmacagigantin (**4**)	Flavonol	18.3 ± 0.5
Macatrichocarpin A (**1**)	Flavanone	18.0 ± 3.1
Macatrichocarpin B (**2**)	Flavanone	114.4 ± 9.7
Macatrichocarpin E (**3**)	Flavanone	16.7 ± 3.2
Licoflavanon (**10**)	Flavanone	33.6 ± 3.6
Flavokawain C (**8**)	Chalcone	8.4 ± 1.2
Helichrysetin (**9**)	Chalcone	18.6 ± 2.7
Macatrichocarpin F (**5**)	Stilbene	17.2 ± 1.4
Macatrichocarpin G (**6**)	Stilbene	3.5 ± 0.3
Macatrichocarpin H (**7**)	Stilbene	53.2 ± 5.3
Artonin E		1.3 ± 0.1

dominant secondary metabolites found in the plant species of genus *Ferula* (Apiaceae), particularly as derivatives of coumarins [20,21]. In these plants, the farnesyl groups are not only present in the acyclic form, but also in the form of mono- and biclyclic sesquiterpenyl groups. Therefore, the presence of farnesylated phenolic compounds in *Macaranga* species can be regarded as a unique chemical marker to some species in the genus. It is also worth to mention that one of *Macaranga* species, *M. pruinosa*, has been shown to produce phenolic compounds bearing an irregular sesquiterpenyl group containing a cyclobutane ring [10,22]. Unlike compound **4**, the presence of a geranyl substituent in compounds **5–7** are more common in the phenolic constituents of *Macaranga*[23]. The *Macaranga* species from Madagaskar, *M. schweinfurthii* and *M. alnifolia*, are noted for the dominance of geranylated stilbenes in their phenolic constituents.

Compounds **1–10** were tested for their cytotoxicity against murine leukemia P-388 cells according to MTT method previously described [7]. The results showed that compound **6** was the most active in inhibiting the cells growth with IC_{50} was 3.5 μM, while compounds **1**, **3–5**, **8** and **9** were moderately active with their IC_{50} were in the range of 8–19 μM, and compounds **2**, **7** and **10** were weakly active (IC_{50} 33–115 μM) (Table 3). The high cytotoxic activity of compound **6** could be due to the presence of a free 1,2-dihydroxy groups at the benzene ring, as noted in the cytotoxic properties of prenylated flavones bearing these groups in the ring B [24]. Lacking this group, such as in compound **5**, would diminish its cytotoxicity. The hydrophobicity of the geranyl group in compounds **5** and **6** seems to be important for activity, because its modification by oxygenation, such as in compound **7**, greatly lowered its cytotoxic properties. In general the chalcones (compounds **8** and **9**) were more active than the flavanone derivatives (compounds **1–3** and **10**), which is consistent with our previous results on the cytotoxicity of the flavonoids from *Cryptocarya costata*[25]. The effect of *O*-methylation in these compounds to their cytotoxic properties is confusing. However, by comparing cytotoxic properties of compound **4** with those macagigantin [9] suggested that a changing from a free 4′-OH to 4′-OCH_3 lowered its cytotoxicity.

Declaration of interest

Conflicts of interest: none.

Acknowledgments

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