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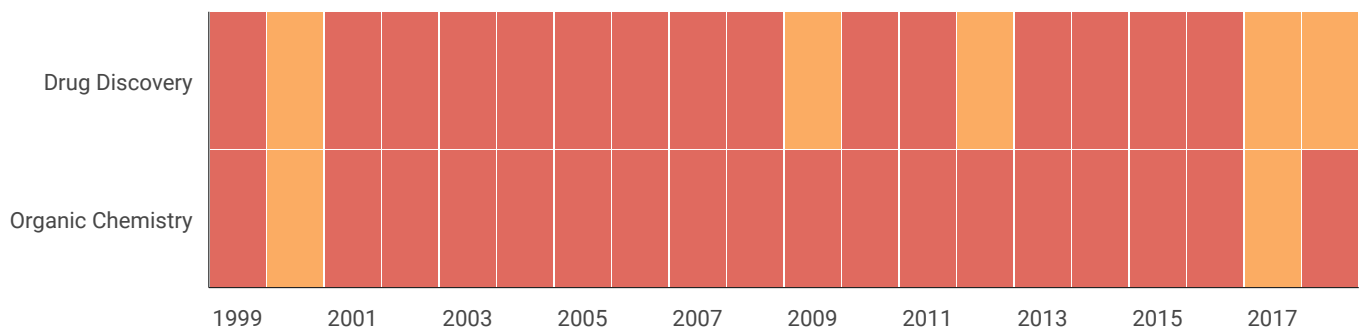
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# Natural Product Sciences

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<b>Subject Area and Category</b>	<a href="#">Chemistry</a> <a href="#">Organic Chemistry</a> <a href="#">Pharmacology, Toxicology and Pharmaceutics</a> <a href="#">Drug Discovery</a>	
<b>Publisher</b>	<a href="#">Korean Society of Pharmacognosy</a>	H Index
<b>Publication type</b>	Journals	
<b>ISSN</b>	12263907	
<b>Coverage</b>	1997-ongoing	
<b>Scope</b>	Natural Product Sciences is the official publication of the Korean Society of Pharmacognosy which was launched in 1995. Natural Product Sciences will primarily publish research papers on original work, either experimental or theoretical, that advance our understanding of natural product sciences, including important questions of phytochemistry, chemistry, and bio-chemistry of natural resources. Timely reviews and commentaries on recent progress in active areas of natural products will be also published.	
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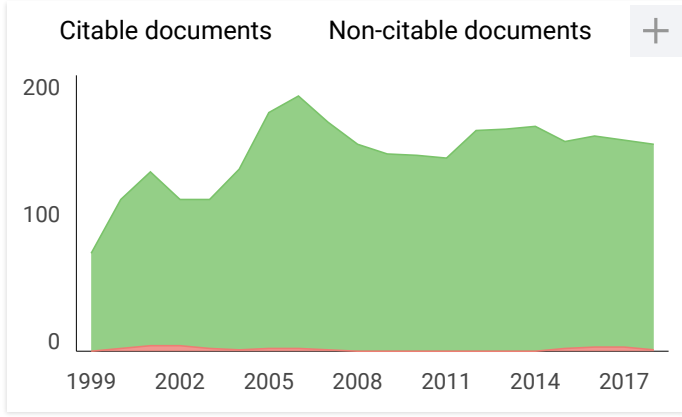
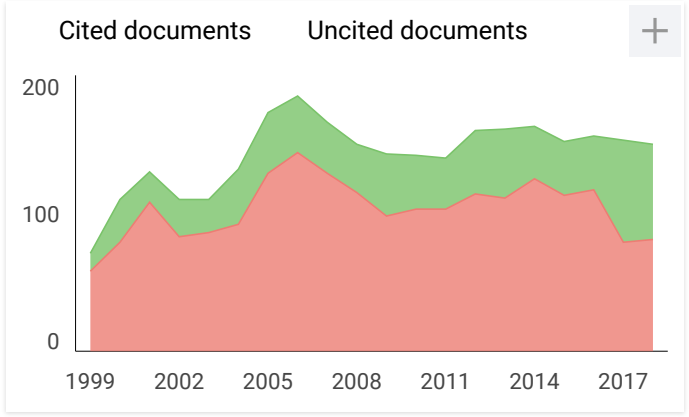
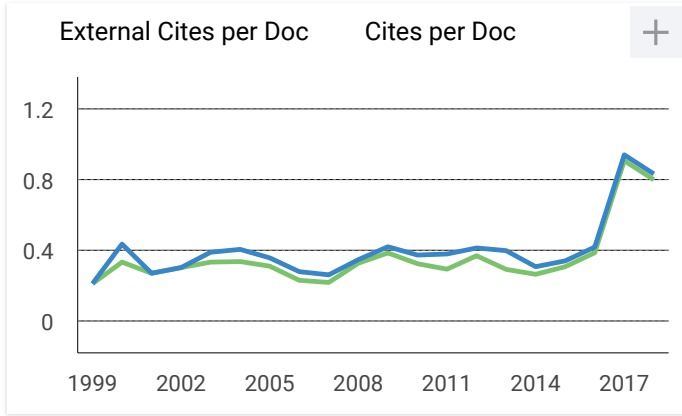
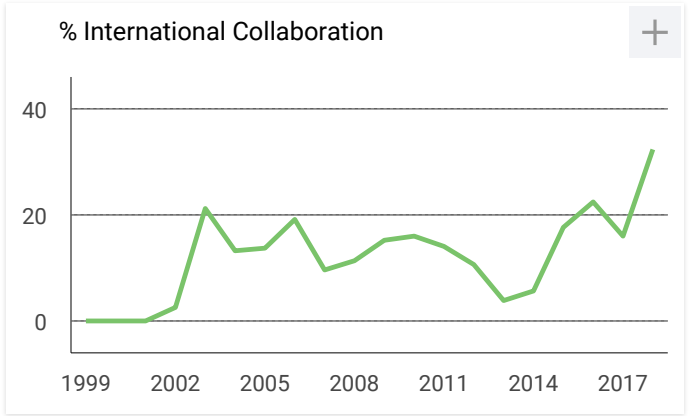
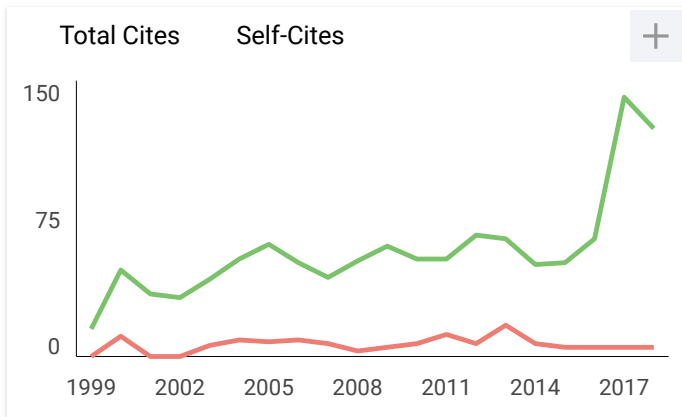
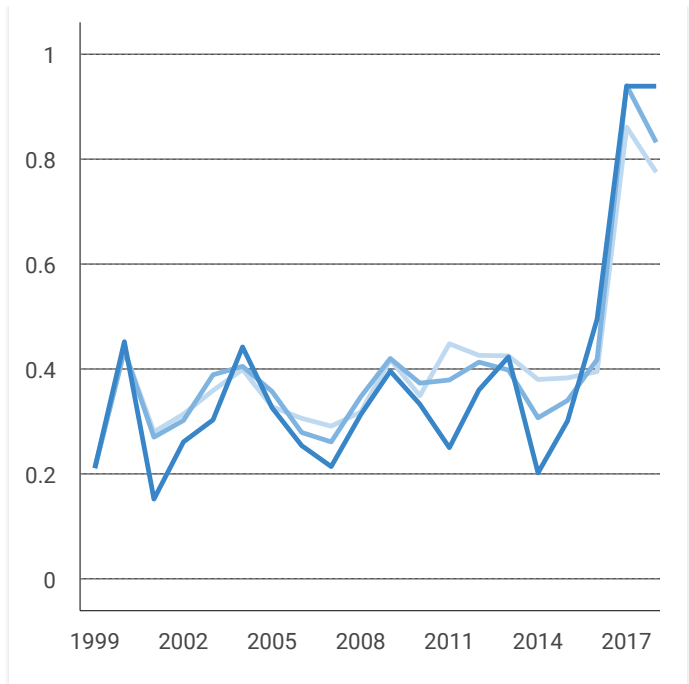
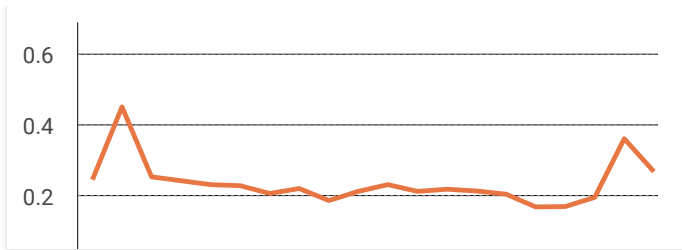


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**Actinofuranone C (1)** - White powder.  $[\alpha]_D^{20}$ : -10.5 (c 0.1, MeOH); UV (MeOH)  $\lambda_{\max}$  (log  $\epsilon$ ) 231 (3.9), 282 (3.7) nm; IR (neat)  $\nu_{\max}$  3383, 2924, 1601, 1357, 970  $\text{cm}^{-1}$ ;  $^1\text{H}$  and  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ ) see Table 1; HRFABMS  $m/z$  363.2162  $[\text{M}-\text{H}]^-$  (calcd for  $\text{C}_{21}\text{H}_{31}\text{O}_5$ , 363.2171).

**Valinic acid (2)** -  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz):  $\delta$  7.55 (1H, dd,  $J = 8.8, 2.0$  Hz, H-1), 7.55 (1H, d,  $J = 2.0$  Hz, H-2), 6.83 (1H, d,  $J = 8.8$  Hz, H-5), 3.89 (3H, s,  $\text{OCH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 100 MHz)  $\delta$  169.0 (C-7), 151.4 (C-4), 147.4 (C-3), 124.0 (C-6), 122.0 (C-1), 114.6 (C-5), 112.5 (C-2), 55.1 ( $\text{OCH}_3$ ); EI-MS  $m/z$  168  $[\text{M}]^+$ .

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## Flavestin K, An Isoprenylated Stilbene from the Leaves of *Macaranga recurvata* Gage

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**Abstract** – A new isoprenylated stilbene, flavestinK (**1**) together with two known isoprenylated stilbenes, flavestin B (**2**), flavestin G (**3**), and two isoprenylated flavanones, 4-*O*-methyl-8-isoprenylnaringenin (**4**) and 8-isoprenyl-5,7-dihydroxyflavanone (**5**) were isolated from the leaves of *Macaranga recurvata* Gage. All of the structures have been determined based on HRESIMS, 1D and 2D NMR spectral data. All of the isolated compounds were evaluated for their cytotoxicity against three human cancer cells (HeLa, T47D and WiDr). Compound **1** showed higher activity than doxorubicin against HeLa cells with IC<sub>50</sub> value of 13.1 µg/mL.

**Keywords** – Flavestin K, Stilbene, *Macaranga recurvata*, Cytotoxicity

### Introduction

*Macaranga recurvata* Gage (Euphorbiaceae), locally known as ‘Mahang merah’ is one pioneer plant and found endemic in Kalimantan Island, Indonesia. The genus *Macaranga* have been showed a number of phenolic compounds, predominantly flavonoids and stilbenes with terpenylated side chain (isoprenyl, geranyl and farnesyl) in aromatic ring.<sup>1-4</sup> Based on previously report, two isoprenylated dihydroflavonols, macarecurvatins A and B from the leaves of *M. recurvata* showed cytotoxicities against murine leukemia.<sup>5</sup> Isoprenylation of flavonoids and stilbenes seems to be a key factor to enhance their cytotoxicity.

In this research paper, we desiderate to report the isolation of a new isoprenylated stilbene, flavestin K (**1**) along with four known compounds, flavestin B (**2**), flavestin G (**3**), 4'-*O*-methyl-8-isoprenylnaringenin (**4**) and 8-isoprenyl-5,7-dihydroxyflavanone (**5**) from the leaves of *M. recurvata* (Fig. 1). The cytotoxic activities of compounds **1-5** against three human cancer cells (HeLa, T47D and WiDr) are also reported.

### Experimental

**General experimental procedures** – 1D NMR (<sup>1</sup>H and <sup>13</sup>C), 2D NMR (HMQC and HMBC) spectra were recorded with a JEOL JNM-ECA 400 FT NMR spectrometer operating at 400 MHz using deuterated solvent (peaks: δ<sub>H</sub> 2.04 and δ<sub>C</sub> 29.8 for acetone-*d*<sub>6</sub> as reference standard). High resolution mass spectra were measured on an ESI-TOF Waters LCT Premier X E mass spectrometer. All of compounds were dissolved in methanol and were measured by UV spectrophotometer Shimadzu 1900. The functional group of compounds in KBr were measured by IR Tracer-100 Shimadzu FT IR spectrophotometer. Column chromatography (CC) was performed using Si gel 60 G and centrifugal planar chromatography (CPC) was performed using Si gel 60 PF<sub>254</sub>. TLC analysis was performed using on pre-coated Si gel 60 GF<sub>254</sub> 0.25 mm thickness plates.

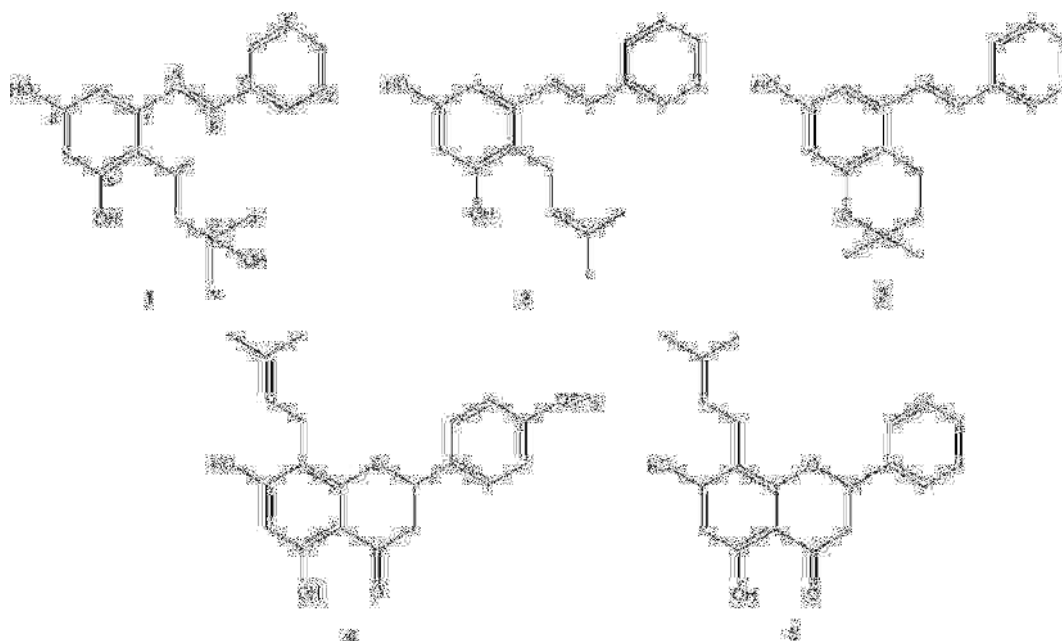
**Plant materials** – The leaves of *M. recurvata* were collected from Muara Teweh, North Barito Districts, East Kalimantan, Indonesia on Feb. 2018, and identified by senior botanist Mr. Ismail Rachman from the Herbarium Bogoriense, Center of Biological Research and Development, National Institute of Science, Bogor, Indonesia.

**Extraction and isolation** – The air-dried and powdered leaves of *M. recurvata* (3.5 kg) were extracted with MeOH (2 × 15 L) at room temperature for two days, and

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**Fig. 1.** Stilbenes and flavonoids **1 - 5** isolated from the leaves of *M. recurvata*.

after evaporation gave the viscous concentrated of MeOH extract (210 g). The suspended solids was redissolved in MeOH-H<sub>2</sub>O (9:1) and then partitioned with C<sub>6</sub>H<sub>14</sub> (45 g) and EtOAc (22 g), successively.

The EtOAc extract (20 g) was further fractionated by column chromatography on silica gel (800 g) eluted with C<sub>6</sub>H<sub>14</sub>-EtOAc (from 9:1 to 1:1) by gradient elution to give five major fractions A-E. Fraction B (2.10 g) was separated by sephadex LH-20 eluted with MeOH gave subfractions B<sub>1</sub>-B<sub>2</sub>. Subfraction B<sub>2</sub> was purified by centrifugal planar chromatography using C<sub>6</sub>H<sub>14</sub>-CHCl<sub>3</sub> (from 7:3 to 3:7) to yield compounds **4** (30 mg), and **5** (19 mg). Fraction C (2.8 g) was subjected to sephadex LH-20 and eluted with MeOH gave three subfractions C<sub>1</sub>-C<sub>3</sub>. Subfraction C<sub>1</sub> was purified by CPC using C<sub>6</sub>H<sub>14</sub>-EtOAc (from 9:1 to 4:1) gave compound **2** (40 mg) and purification of subfraction C<sub>2</sub> by the same methods using *n*-hexane-diisopropylether (from 1:1 to 1:4) to yield compounds **1** (5 mg), and **3** (21 mg).

**Flavestine K (1)** – Yellow solid, UV (MeOH)  $\lambda_{\max}$  nm (log  $\epsilon$ ): 212 (4.49), and 293 (4.26). IR (KBr)  $\text{vcm}^{-1}$ : 3400, 1604, 1521, 1438 and 1033. <sup>1</sup>H and <sup>13</sup>C NMR see Table 1. HRESIMS:  $m/z$  [M-H]<sup>-</sup> calcd. for C<sub>19</sub>H<sub>21</sub>O<sub>3</sub> 297.1491, found 297.1489.

**Flavestine B (2)** – Amorphous powder, UV (MeOH)  $\lambda_{\max}$  nm (log  $\epsilon$ ): 215 (4.39), and 303 (4.10). IR (KBr)  $\text{vcm}^{-1}$ : 3368, 1608, 1530, 1463 and 1028. HRESIMS:  $m/z$  [M-H]<sup>-</sup> calcd. for C<sub>19</sub>H<sub>19</sub>O<sub>2</sub> 279.1523, found 279.1519. The <sup>1</sup>H and <sup>13</sup>C NMR spectral data were compared and consistent with the published data.<sup>6</sup>

**Flavestine G (3)** – Amorphous powder, UV (MeOH)  $\lambda_{\max}$  nm (log  $\epsilon$ ): 214 (4.42), and 295 (4.17). IR (KBr)  $\text{vcm}^{-1}$ : 3340, 1602, 1548, 1459 and 1033. HRESIMS:  $m/z$  [M-H]<sup>-</sup> calcd. for C<sub>19</sub>H<sub>19</sub>O<sub>2</sub> 279.1489, found 279.1480. The <sup>1</sup>H and <sup>13</sup>C NMR spectral data were compared and consistent with the published data.<sup>6</sup>

**4'-O-Methyl-8-isoprenylnaringenin (4)** – White solid, m.p. 169 - 170 °C. UV (MeOH)  $\lambda_{\max}$  nm (log  $\epsilon$ ): 214 (4.46), and 293 (4.67). IR (KBr)  $\text{vcm}^{-1}$ : 3425, 1640, 1515, 1448 and 1170. HRESIMS:  $m/z$  [M-H]<sup>-</sup> calcd. for C<sub>21</sub>H<sub>21</sub>O<sub>5</sub> 353.1457, found 353.1452. The <sup>1</sup>H and <sup>13</sup>C NMR spectral data were compared and consistent with the published data.<sup>7</sup>

**8-Isoprenyl-5,7-dihydroxyflavanone (5)** – White solid, m.p. 165 - 167 °C. UV (MeOH)  $\lambda_{\max}$  nm (log  $\epsilon$ ): 224 (4.49), and 294 (4.73). IR (KBr)  $\text{vcm}^{-1}$ : 3418, 1638, 1520, 1446 and 1168. HRESIMS:  $m/z$  [M-H]<sup>-</sup> calcd. for C<sub>20</sub>H<sub>19</sub>O<sub>4</sub> 323.1362, found 323.1365. The <sup>1</sup>H and <sup>13</sup>C NMR spectral data were compared and consistent with published data.<sup>8</sup>

**Cytotoxic activity** – Compounds **1 - 5** were appraised for their cytotoxicity toward HeLa (human cervical carcinoma), T47D (human breast cancer), and WiDr (human colon carcinoma) according to the MTT method as well as doxorubicin as the positive control.<sup>9-12</sup> Briefly, before the compounds were added, cells were cultured in 96-well at a density of  $3 \times 10^4$  cells/well and incubated at 37 °C for 24 h. Compounds **1 - 5** with variations in concentration (100, 30, 10, 3, 1, 0.3, and 0.1  $\mu\text{g/mL}$ ) with triplicate were

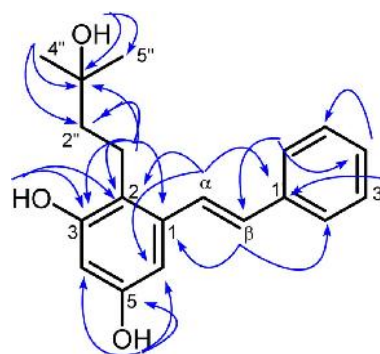
**Table 1.** NMR data of flavestin K (**1**)

No. C	$\delta_{\text{H}}$ (mult, $J$ in Hz)	$\delta_{\text{C}}$	HMBC (H $\leftrightarrow$ C)
1	-	138.8	-
2	-	120.2	-
3	-	156.9	-
4	6.35 ( <i>d</i> , 2.4)	103.2	C-2; C-3; C-6
5	-	156.7	-
6	6.69 ( <i>d</i> , 2.4)	104.4	C- $\alpha$ ; C-2; C-4; C-5
$\alpha$	7.52 ( <i>d</i> , 16.1)	127.5	C-2; C-6; C-1'
$\beta$	6.98 ( <i>d</i> , 16.1)	130.2	C-1; C-2'/6'
1'	-	138.2	-
2'/6'	7.57 ( <i>m</i> )	127.3	C- $\beta$ ; C-4'
3'/5'	7.34 ( <i>m</i> )	129.5	C-1'; C-3'/5'
4'	7.24 ( <i>m</i> )	128.2	C-3'/5'
1''	2.83 ( <i>m</i> )	20.7	C-1; C-2; C-3; C-2''; C-3''
2''	1.66 ( <i>m</i> )	45.0	C-2; C-1''; C-3''; C-4''; C-5''
3''	-	70.5	-
4''	1.25 ( <i>s</i> )	29.9	C-2''; C-3''; C-5''
5''	1.25 ( <i>s</i> )	29.9	C-2''; C-3''; C-4''
3-OH	8.19 ( <i>s</i> )	-	C-2; C-3; C-4
5-OH	7.99 ( <i>s</i> )	-	C-5; C-6
3''-OH	3.58 ( <i>s</i> )	-	C-2''; C-3''; C-4''; C-5''

added to each well and incubated at 37 °C for 48 h. After incubation, it was added MTT and let for 4 h, and the inhibition of cells by each of compounds **1** - **5** were recorded with microplate reader spectrophotometer at  $\lambda$  570 nm. The IC<sub>50</sub> values of all compounds were calculated by regression analysis.

## Result and Discussion

Flavestin K (**1**) obtained as yellow solid, and the chemical formula C<sub>19</sub>H<sub>22</sub>O<sub>3</sub> was deduced by HRESIMS spectra with ion peak [M-H]<sup>-</sup> at  $m/z$  297.1489 (calcd. for 297.1491). The UV spectrum showed two maximum absorption at  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 212 (4.49), and 293 (4.26) nm characteristic for a stilbene chromophore.<sup>13</sup> The IR spectrum displayed absorption band for hydroxyl (3400 cm<sup>-1</sup>), and aromatic ring (1521 - 1438 cm<sup>-1</sup>), respectively. The <sup>1</sup>H NMR spectrum of compound **1** (Table 1) exhibited two doublets ( $J$  = 16.1 Hz) at  $\delta_{\text{H}}$  7.52 (H- $\alpha$ ) and  $\delta_{\text{H}}$  6.98 (H- $\beta$ ) provided the evidence for a *trans* 1,2-disubstituted ethene connecting with two aromatic rings, revealed that compound **1** was (*E*)-stilbene.<sup>14</sup> The existence of *meta*-coupling doublets ( $J$  = 2.4 Hz) at  $\delta_{\text{H}}$  6.35 (H-4) and  $\delta_{\text{H}}$  6.69 (H-6) is characteristic for a 1,2,3,5-tetrasubstituted benzene. The presence of three multiplet signals at  $\delta_{\text{H}}$  7.57 (H-2'/H-6'),  $\delta_{\text{H}}$  7.34 (H-3'/H-5') and  $\delta_{\text{H}}$  7.24 (H-4') is consistent for a

**Fig. 2.** Selected HMBC correlations for flavestin K (**1**).

monosubstituted benzene. <sup>1</sup>H NMR spectrum of **1** also disclosed information two phenolic hydroxyl groups at  $\delta_{\text{H}}$  8.19 (3-OH), and  $\delta_{\text{H}}$  7.99 (5-OH). The proton signals for a 2-methylbutan-2-ol unit were observed at  $\delta_{\text{H}}$  3.58 (3''-OH), 2.83 (H<sub>2</sub>-1''), 1.66 (H<sub>2</sub>-2'') and 1.25 (H<sub>3</sub>-4'' and H<sub>3</sub>-5'') in the <sup>1</sup>H NMR spectrum. Sixteen carbon signals were observed in <sup>13</sup>C NMR spectrum. The carbon NMR signals including two oxyaryl carbon signals ( $\delta_{\text{C}}$  156.9 and  $\delta_{\text{C}}$  156.7) recommended that compound **1** has a structure of pinosylvin (*E*-3,5-dihydroxystilbene) bearing a 2-methylbutan-2-ol group.<sup>15</sup> Location of a 2-methylbutyl-2-ol group in pinosylvin structure was established by 2D NMR spectra (HMQC and HMBC) (Fig. 2). The H- $\alpha$  proton

**Table 2.** Cytotoxicity of compounds **1 - 5** of *M. recurvata*

Compounds	IC <sub>50</sub> (µg/mL)		
	HeLa	T47D	WiDr
Flavestine K ( <b>1</b> )	13.10 ± 0.87	51.12 ± 1.21	46.41 ± 1.25
Flavestine B ( <b>2</b> )	54.80 ± 1.15	>100	>100
Flavestine G ( <b>3</b> )	55.84 ± 2.68	73.04 ± 2.71	70.35 ± 2.58
4'- <i>O</i> -Methyl-8-isoprenylnaringenin ( <b>4</b> )	>100	>100	>100
8-Isoprenyl-5,7-dihydroxyflavanone ( <b>5</b> )	>100	>100	>100
Doxorubicin	46.11 ± 0.45	23.18 ± 0.45	12.44 ± 0.45

( $\delta_{\text{H}}$  7.52) of the ethene group correlated with a methine carbon at  $\delta_{\text{C}}$  104.4 (C-6) and two quaternary carbons at  $\delta_{\text{C}}$  120.2 (C-2) and at  $\delta_{\text{C}}$  138.2 (C-1') in the HMBC spectrum of **1**. The HMBC correlations of the methylene proton signal at  $\delta_{\text{H}}$  2.83 (H-1") to  $\delta_{\text{C}}$  138.8 (C-1), 120.2 (C-2), 156.9 (C-3), 45.0 (C-2"), and 70.5 (C-3") indicated that a 2-methylbutyl-2-ol chain was located at C-2. The presence of 2-methylbutan-2-ol chain was further supported by HMBC correlations between the hydroxyl proton signal at  $\delta_{\text{H}}$  3.58 (3"-OH) and the carbon signals at  $\delta_{\text{C}}$  29.9 (C-4" and C-5"), 45.0 (C-2") and 70.5 (C-3"). The structure of compound **1** was thus identified as 2-(3-hydroxy-3-methylbutyl)-pinosylvin. We designated the compound **1** as flavestine K.

The cytotoxicity activity of compounds **1 - 5** were appraised towards HeLa (human cervical carcinoma), T47D (human breast cancer), and WiDr (human colon carcinoma) by MTT method as well as doxorubicin (positive control).<sup>16</sup> Isoprenylated stilbenes (**1**, **2** and **3**) more active than isoprenylated flavonoids (**4** and **5**) (Table 2). Compound **1** exhibited higher activity than doxorubicin against HeLa with IC<sub>50</sub> value of 13.1 µg/mL. However, compounds **4 - 5** were inactive against HeLa, T47D, and WiDr cells.

### Acknowledgments

This study was supported by Penelitian Hibah Mandat, 2019, Universitas Airlangga, Surabaya, Indonesia.

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Received May 7, 2019

Revised July 15, 2019

Accepted July 18, 2019