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## THREE NEW PHENYLPROPANOIDS FROM THE LEAVES OF YUNNAN LOCAL SUN CURED TOBACCO AND THEIR BIOACTIVITIES

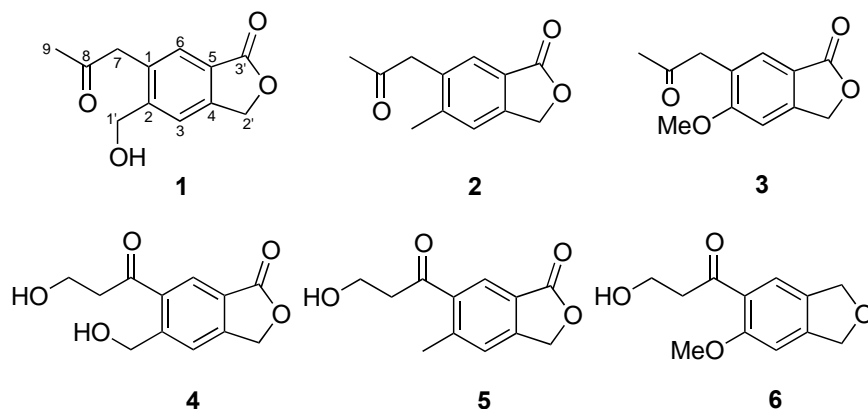
Feng-Mei Zhang,<sup>1,2</sup> Jian-Jun Xia,<sup>1,2</sup> Pei-Song Yang,<sup>1,2</sup> Qin-Peng Shen,<sup>1</sup> Chun-Bo Liu,<sup>1</sup> Pei He,<sup>1</sup> Jia-Qiang Wang,<sup>1</sup> Zhi-Hua Liu,<sup>2,\*</sup> and Zhong-Tao Ding<sup>1,\*</sup>

<sup>1</sup> School of Chemical Science and Technology, Yunnan University, Kunming 650091, P.R. China; <sup>2</sup> Key Laboratory of Tobacco Chemistry of Yunnan Province, Research and Development of Center, China Tobacco Yunnan Industrial Co., Ltd., Kunming 650231, P.R. China; E-mail: zhihualiu@163.com; ygy1110@163.com

**Abstract** – Three new phenylpropanoids, 5-(hydroxymethyl)-6-(2-oxopropyl)-isobenzofuran-1(3*H*)-one (**1**), 5-methyl-6-(2-oxopropyl)isobenzofuran-1(3*H*)-one (**2**), and 5-methoxy-6-(2-oxopropyl)isobenzofuran-1(3*H*)-one (**3**), together with three known phenylpropanoids (**4-6**) were isolated from the leaves of Yunnan local sun cured tobacco. Their structures were determined by means of HRESIMS and extensive 1D and 2D NMR spectroscopic studies. Compounds **1-3** were tested for their anti-tobacco mosaic virus (TMV) activities and compounds **1-6** were tested for their cytotoxicity activities. The results revealed that compounds **1-3** showed high anti-TMV activity with inhibition rate of 28.6, 31.2 and 32.7%. These rates are close to that of positive control. Compounds **1-6** also showed moderate-to-weak inhibitory activities against some tested human tumor cell lines with IC<sub>50</sub> values in the range of 2.5-8.5 μM.

*Nicotiana tabacum* belonging to *Nicotiana* genus of the Solanaceae family, is a stout herbaceous plant that originated in the tropical Americas (South America, Mexico, and the West Indies) and now cultivated worldwide as the primary commercial source of tobacco, which is smoked or chewed as a drug for its mild stimulant effects.<sup>1-3</sup> Phytochemical investigations revealed that many new bioactive compounds, such as, sesquiterpenes,<sup>4-6</sup> alkaloids,<sup>7,8</sup> lignans,<sup>9,10</sup> flavonoids,<sup>11-14</sup> phenylpropanoids,<sup>15,16</sup> chromanones,<sup>17,18</sup> biphenyls,<sup>19</sup> phenolic amides,<sup>20</sup> isocoumarins,<sup>21</sup> were isolated from the genus of this plants. Some of which showed various bioactivities, such as anti-HIV-1, anti-TMV, and cytotoxicity.

Therefore, the multipurpose utilization of this plant is an interesting topical and attracts more and more attentions. As a continuous search for active compounds from these plants, the phytochemistry investigation on the leaves Yunnan local sun cured tobacco (a variant of *N. tabacum*) led to the isolation of three new (**1-3**) and three known (**4-6**) phenylpropanoids. This paper deals with the isolation, structural elucidation, and their anti-TMV activity of these compounds.

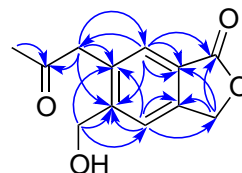


**Figure 1.** The structures of phenylpropanoids from sun cured tobacco

A 70% aq. MeOH extract prepared from the leaves of tobacco was subjected repeatedly to column chromatography and preparative HPLC to afford three new phenylpropanoids, 5-(hydroxymethyl)-6-(2-oxopropyl)isobenzofuran-1(3*H*)-one (**1**), 5-methyl-6-(2-oxopropyl)isobenzofuran-1(3*H*)-one (**2**), and 5-methoxy-6-(2-oxopropyl)isobenzofuran-1(3*H*)-one (**3**), and three known phenylpropanoids (**4-6**). The structures of the compounds **1-6** were as shown in Figure 1, and the  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of **1-3** were listed in Table 1. The known compounds, compared with literature, were identified as 6-(3-hydroxypropanoyl)-5-hydroxymethyl-isobenzofuran-1(3*H*)-one (**4**),<sup>22</sup> 6-(3-hydroxypropanoyl)-5-methylisobenzofuran-1(3*H*)-one (**5**),<sup>23</sup> and 3-hydroxy-1-(6-methoxy-1,3-dihydroisobenzofuran-5-yl)propan-1-one (**6**).<sup>24</sup>

Compound **1** was obtained as a pale-yellow gum. Its molecular formula was determined as  $\text{C}_{12}\text{H}_{12}\text{O}_4$  by HRESIMS ( $m/z$  243.0639  $[\text{M}+\text{H}]^+$ ; calcd for  $\text{C}_{12}\text{H}_{12}\text{NaO}_4$ , 243.0633),

indicating the presence of seven degrees of unsaturation in the molecule. The UV spectrum showed absorption maxima at 210, 282 and 310 nm, and the IR spectrum showed absorption bands at 3382, 1728, 1654, 1615, 1574, and  $1450\text{ cm}^{-1}$ , indicating the presence of hydroxy group, carbonyl group, and aromatic ring. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectrum of **1** (Table 1) along with analysis of the DEPT spectra displayed 12 carbon signals and 12 proton signals, respectively, corresponding to a 1,2,4,5-tetrasubstituted phenyl ring ( $\delta_{\text{C}}$  128.9 s, 146.5 s, 127.6 d, 145.3 s, 124.9 s, and 130.1 d), an 2-oxopropyl  $[-\text{CH}_2\text{C}(\text{O})\text{CH}_3]$  moiety ( $\delta_{\text{C}}$  49.2 t, 206.6 s and 30.4 q;  $\delta_{\text{H}}$  2.28 s and 4.51 s),<sup>25</sup> an ester carbonyl group ( $\delta_{\text{C}}$  168.5 s), an oxygenated methylene ( $\delta_{\text{C}}$  72.2 t;  $\delta_{\text{H}}$  5.26 s), and a hydroxymethyl



**Figure 2.** Key HMBC ( $\curvearrowright$ ) correlations of **1**

group ( $\delta_C$  63.6 t;  $\delta_H$  4.51 s). The HMBC correlations from H<sub>2</sub>-2' to C-3', C-3, C-4, C-5; from H-3 to C-2'; and from H-6 to C-3' (Figure 2) suggested the existence of a benzolactone moiety.<sup>23</sup> The HMBC correlations of H<sub>2</sub>-7 with C-1, C-2, and C-6; of H-6 with C-7 suggested the 2-oxopropyl moiety should be located at C-1. The location of the hydroxymethyl group was assigned to C-2 on the basis of HMBC correlations of H<sub>2</sub>-1' with C-1, C-2 and C-3. Thus, the structure of 5-(hydroxymethyl)-6-(2-oxopropyl)isobenzofuran-1(3*H*)-one (**1**) was established as shown.

**Table 1.** <sup>1</sup>H and <sup>13</sup>C NMR data for compounds **1-3** (125 and 500 MHz)

No.	<b>1</b> <sup>a</sup>		<b>2</b> <sup>a</sup>		<b>3</b> <sup>b</sup>	
	$\delta_C$	$\delta_H$ (m, <i>J</i> , Hz)	$\delta_C$	$\delta_H$ (m, <i>J</i> , Hz)	$\delta_C$	$\delta_H$ (m, <i>J</i> , Hz)
1	128.9 s		130.9 s		125.0 s	
2	146.5 s		142.8 s		164.2 s	
3	127.6 d	7.09 s	128.5 d	6.95 s	113.5 d	6.65 s
4	145.3 s		145.0 s		147.2 s	
5	124.9 s		123.1 s		116.8 s	
6	130.1 d	7.81 s	129.3 d	7.76 s	131.6 d	7.74 s
7	49.2 t	4.16 s	49.3 t	4.19 s	49.4 s	4.20 s
8	206.6 s		206.8 s		206.4 t	
9	30.4 q	2.28 s	30.1 q	2.30 s	30.6 q	2.26 s
1'	63.6 t	4.51 s	22.2 q	2.51 s		
2'	72.2 t	5.26 s	72.0 t	5.23 s	70.2 t	5.38 s
3'	168.5 s		168.8 s		169.1 s	
-OMe					55.8 q	3.84 s
1'-OH		4.96 s				

<sup>a</sup>obtained in CDCl<sub>3</sub>; <sup>b</sup>obtained in C<sub>5</sub>D<sub>5</sub>N.

Compound **2** was also obtained as a pale-yellow gum. A molecular formula C<sub>12</sub>H<sub>12</sub>O<sub>3</sub> was assigned from HRESIMS ( $m/z$  227.0676 [M+Na]<sup>+</sup>, calcd 227.0684 for C<sub>12</sub>H<sub>12</sub>NaO<sub>3</sub>). The <sup>1</sup>H and <sup>13</sup>C NMR spectra of **2** were similar to those of **1**. The chemical shift differences resulted from the disappearance of a hydroxymethyl signal ( $\delta_C$  63.6 t;  $\delta_H$  4.51 s) and appearance of a methyl resonance ( $\delta_C$  22.2 q;  $\delta_H$  2.51 s) in **2**. This indicated that the hydroxymethyl group in **1** was converted into a methyl group in **2**. The HMBC correlations of H<sub>3</sub>-1' to C-1, C-2 and C-3 indicated that the methyl group was located at C-2. Thus, the structure of **2** was established as 5-methyl-6-(2-oxopropyl)isobenzofuran-1(3*H*)-one.

Compound **3** was also assigned the molecular formula of C<sub>12</sub>H<sub>12</sub>O<sub>4</sub> as supported by the HRESIMS ( $m/z$  243.0624 [M+Na]<sup>+</sup>). Its <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic data were very similar to those of compound **2**, except for the presence of a methoxy group ( $\delta_C$  55.8 q;  $\delta_H$  3.84 s), and the absence of a methyl group ( $\delta_C$  22.2 q;  $\delta_H$  2.51 s). The HMBC correlations from the methoxy protons ( $\delta_H$  3.84) to C-2 ( $\delta_C$  164.2) suggested this methoxy group located at C-2. Accordingly, the structure of **3** was determined, and gives the system name of 5-methoxy-6-(2-oxopropyl)isobenzofuran-1(3*H*)-one.

Compounds **1-3** were tested for their anti-TMV activity at the concentration of 20  $\mu\text{M}$ . The anti-TMV activity were tested using the half-leaf method.<sup>26,27</sup> Ningnanmycin (a commercial product for plant disease in China, with inhibition rate of 33.6%), was used as a positive control. The results showed that compounds **1-3** showed high anti-TMV activity with inhibition rate of 28.6, 31.2 and 32.7%. These rates are close to that of positive control.

The cytotoxicities of compounds **1-6** were also tested using a previously reported procedure.<sup>28,29</sup> The cytotoxic abilities against five human tumor cell lines (NB4, A549, SHSY5Y, PC3, and MCF7) by MTT-assay were summarized in **Table 2**. The results revealed that compounds **1-6** showed moderate-to-weak inhibitory activities

**Table 2.** Cytotoxic activity of compounds **1-6**

Compounds	Cell lines and IC <sub>50</sub> ( $\mu\text{M}$ )				
	NB4	A549	SHSY5Y	PC3	MCF7
<b>1</b>	3.4	2.8	3.6	5.4	4.2
<b>2</b>	2.5	4.2	4.0	3.3	3.5
<b>3</b>	3.4	5.6	6.2	4.9	6.2
<b>4</b>	3.6	>10	6.8	4.6	>10
<b>5</b>	>10	5.5	>10	7.3	8.2
<b>6</b>	8.5	6.0	7.0	7.8	>10
<b>Taxol</b>	0.03	0.02	0.05	0.05	0.05

NB4, human leukemia cell; A549, carcinomic human alveolar basal epithelial cell; SHSY5Y, human neuroblastoma cell; PC3, human prostate cancer cell; MCF7, human breast adenocarcinoma cell.

against some tested human tumor cell lines with IC<sub>50</sub> values in the range of 2.5–8.5  $\mu\text{M}$ .

## EXPERIMENTAL

**General.** UV spectra were obtained using a Shimadzu UV-2401A spectrophotometer. A Tenor 27 spectrophotometer was used for scanning IR spectroscopy with KBr pellets. 1D and 2D NMR spectra were recorded on DRX-500 spectrometers with TMS as internal standard, and the chemical shifts ( $\delta$ ) were expressed in ppm. HRESIMS was performed on an API QSTAR time-of-flight spectrometer and a VG Autospec-3000 spectrometer, respectively. Preparative HPLC was performed on a Shimadzu LC-8A preparative liquid chromatograph with a ZORBAX PrepHT GF (21.2 mm  $\times$  25 cm, 7  $\mu\text{m}$ ) column or a Venusil MP C<sub>18</sub> (20 mm  $\times$  25 cm, 5  $\mu\text{m}$ ) column. Column chromatography was performed with Si gel (200–300 mesh, Qing-dao Marine Chemical, Inc., Qingdao, China). The fractions were monitored by TLC, and spots were visualized by heating Si gel plates sprayed with 5% H<sub>2</sub>SO<sub>4</sub> in EtOH.

**Plant Material.** The sun cured tobacco leaves (Nanjian Leju tobacco, a variety of *Nicotiana tabacum*) were collected in Dali Prefecture, Yunnan Province, People's Republic of China, in September 2014. The identification of the plant material was verified by Prof. H. W. Yang (School of Tobacco, Yunnan Agriculture University).

**Extraction and Isolation.** The air-dried and powdered leaves of sun cured tobacco (3.8 kg) were extracted four times with 70% aqueous MeOH (3  $\times$  5 L) at room temperature and filtered. The solvent was evaporated in vacuo, and the crude extract was dissolved in H<sub>2</sub>O and partitioned with EtOAc. The EtOAc partition (126 g) was applied to silica gel (200–300 mesh) column chromatography, eluting with a

CHCl<sub>3</sub>-MeOH gradient system (9:1, 8:2, 7:3, 6:4, 5:5, 4:6), to give six fractions A–F. Further separation of fraction C (7:3, 32.6 g) by silica gel column chromatography, eluted with CHCl<sub>3</sub>-Me<sub>2</sub>CO (8:2 - 2:1), yielded mixtures C1–C6. Fraction C3 (6:4, 2.94 g) was subjected to silica gel column chromatography using petroleum ether-acetone and semi-preparative HPLC (36% MeOH-H<sub>2</sub>O, flow rate 12 mL/min) to give **3** (12.2 mg) and **4** (15.4 mg). Fraction C4 (1:1, 4.48 g) was subjected to silica gel column chromatography using petroleum ether-acetone and semi-preparative HPLC (30% MeOH-H<sub>2</sub>O, flow rate 12 mL/min) to give **1** (10.2 mg), **2** (13.5 mg), **5** (18.4 mg), and **6** (10.2 mg).

**Anti-TMV Assays.** The anti-TMV activities were tested using the half-leaf method,<sup>26,27</sup> and Ningnanmycin (2% water solution), a commercial product for plant disease in China, was used as a positive control.

**Cytotoxicity Assay.** The cytotoxicity tests for the isolates were performed by against NB4, A549, SHSY5Y, PC3, and MCF7 tumor cell lines by MTT-assay (with taxol as the positive control).<sup>28,29</sup>

**5-(Hydroxymethyl)-6-(2-oxopropyl)isobenzofuran-1(3H)-one (1):** C<sub>12</sub>H<sub>12</sub>O<sub>4</sub>, obtained as pale yellow gum; UV (MeOH), λ<sub>max</sub> (log ε) 310 (3.62), 282 (3.86), 210 (4.05) nm; IR (KBr) ν<sub>max</sub> 3382, 3080, 2942, 1728, 1654, 1615, 1574, 1450, 1342, 1263, 1167, 1032, 870 cm<sup>-1</sup>; <sup>1</sup>H NMR and <sup>13</sup>C NMR data (CDCl<sub>3</sub>, 500 and 125 MHz, respectively), see Table 1; ESI-MS (positive ion mode) *m/z* 243 [M+Na]<sup>+</sup>; HR-ESI-MS (positive mode) *m/z* [M + Na]<sup>+</sup> 243.0639 (calcd 243.0633 for C<sub>12</sub>H<sub>12</sub>NaO<sub>4</sub>).

**5-Methyl-6-(2-oxopropyl)isobenzofuran-1(3H)-one (2):** C<sub>12</sub>H<sub>12</sub>O<sub>3</sub>, obtained as pale yellow gum; UV (MeOH), λ<sub>max</sub> (log ε) 308 (3.81), 280 (3.64), 210 (4.12) nm; IR (KBr) ν<sub>max</sub> 3072, 2960, 1729, 1657, 1615, 1560, 1455, 1353, 1216, 1156, 1045, 869 cm<sup>-1</sup>; <sup>1</sup>H NMR and <sup>13</sup>C NMR data (CDCl<sub>3</sub>, 500 and 125 MHz, respectively), see Table 1; ESI-MS (positive ion mode) *m/z* 227 [M + Na]<sup>+</sup>; HR-ESI-MS (positive mode) *m/z* [M + Na]<sup>+</sup> 227.0676 (calcd 227.0684 for C<sub>12</sub>H<sub>12</sub>NaO<sub>3</sub>).

**5-Methoxy-6-(2-oxopropyl)isobenzofuran-1(3H)-one (3):** C<sub>12</sub>H<sub>12</sub>NaO<sub>4</sub>, obtained as pale-yellow gum; UV (MeOH), λ<sub>max</sub> (log ε) 312 (3.38), 283 (3.68), 210 (4.11) nm; IR (KBr) λ<sub>max</sub> 2932, 1730, 1659, 1615, 1537, 1478, 1264, 1119, 1063, 987, 836 cm<sup>-1</sup>; <sup>1</sup>H NMR and <sup>13</sup>C NMR data (C<sub>5</sub>D<sub>5</sub>N, 500 and 125 MHz, respectively), Table 1; ESIMS (positive ion mode) *m/z* 243 [M+Na]<sup>+</sup>; HRESIMS (positive ion mode) *m/z* 243.0624 [M+Na]<sup>+</sup> (calcd 243.0633 for C<sub>12</sub>H<sub>12</sub>NaO<sub>4</sub>).

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