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THREE NEW ISOBENZOFURANS FROM THE ROOT OF YUNNAN LOCAL SUN CURED TOBACCO AND THEIR BIOACTIVITIES

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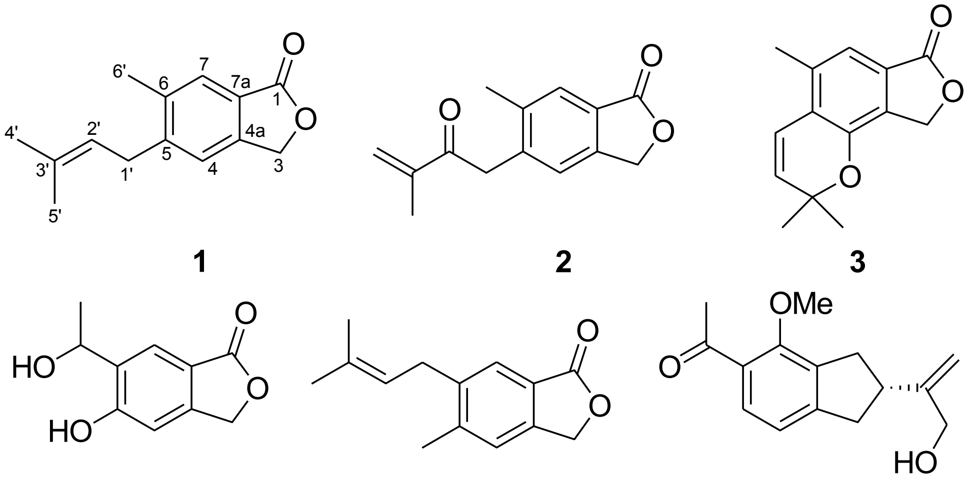
Abstract – Three new isobenzofurans (**1-3**), together with three known isobenzofurans (**4-6**) were isolated from the root of Yunnan local sun cured tobacco. Their structures were determined by means of HRESIMS and extensive 1D and 2D NMR spectroscopic studies. Compounds **1-4** were tested for their anti-tobacoo mosaic virus (TMV) activities and compounds **1-6** were tested for their cytotoxicity activities. The results revealed that compounds **1-4** showed high anti-TMV activity with inhibition rate of 31.4, 35.2 and 38.8, 29.6%. 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_{50} values in the range of 2.6 -9.5 μM.

Nicotiana tabacum is a stout herbaceous plant belonging to Nicotiana genus of the Solanaceace family. It 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.[1-3] Phytochemical investigation revealed that Nicotiana plants were rich in sesquiterpenes,[4-6] alkaloids,[7,8] lignans,[9,10] flavonoids,[11-14] phenylpropanoids,[15,16] chromanones,[17,18] biphenyls,[19,20] benzolactones,[21-23] isocoumarins,[24] and furan-2-carboxylic acids.[25] Our previous investigation of this species led to the discovery of a number of new compounds that showed various bioactivities, such as anti-HIV-1, anti-TMV, and cytotoxicity.[4-15] The roots and stems of *N. tabacum* are the main by-product in tobacco planting and are normally used as organic fertilizer. The multipurpose utilization of the roots and stems of tobacco is an interesting topic and has attracted more and more attentions.[2,12] As a continuous search for active compounds from natural sources, the phytochemistry investigation of roots of Yunnan local sun cured tobacco (Weishang Liuye tobacco, a variety of *Nicotiana tabacum*) led to the isolation of three new (**1**-**3**) and three known (**4**-**6**) isobenzofurans. This paper deals with the isolation, structural elucidation, and their bioactivities of these compounds.



1 **2** **3**

4 **5** **6**

Figure 1. The structures of isobenzofurans from the roots of Yunnan sun cured tobacco

A 70% aq. MeOH extract prepared from the root of tobacco was subjected repeatedly to column chromatography and preparative HPLC to afford three new isobenzofurans, 6-methyl-5-prenyl-isobenzofuran-1(3*H*)-one (**1**), 6-methyl-5-(3-methyl-2-oxobut-3-enyl)isobenzofuran-1(3*H*)-one (**2**), and 2,2,5-trimethyl-2*H*-furo[3,4-*h*]chromen-7(9*H*)-one (**3**), and three known isobenzofurans (**4**-**6**). The structures of the compounds **1**-**6** were as shown in Figure 1, and the ^{1}H and ^{13}C NMR data of **1**-**3** were listed in Table 1. The known compounds, compared with literature, were identified as erinaceolactone B (**4**),[26] 5-methyl-6-prenyl-isobenzofuran-1(3*H*)-one (**5**),[21] and (2*R*)-12-hydoxy-4-methoxy-tremeton (**6**).[24]

Compound **1** was obtained as a pale-yellow gum. Its molecular formula was determined as $C_{14}H_{16}O_2$ by HRESIMS (*m/z* 239.1041 $[M+Na]^+$; calcd 239.1048 for $C_{14}H_{16}NaO_2$), indicating the presence of seven degrees of unsaturation in the molecule. The UV spectrum showed absorption maxima at 210, 276 and 306 nm, and the IR spectrum showed absorption bands at 1738, 1610, 1556, 1438, and 1372 cm^{-1}, indicating the presence of carbonyl group and aromatic ring. The ^{1}H and ^{13}C NMR spectrum of **1** (Table 1) along with analysis of the DEPT spectra displayed 14 carbon signals and 16 proton signals, respectively, corresponding to a 1,2,4,5-tetrasubstituted phenyl ring (C-4~C-7, C-4a, and C-7a; H-4 and H-7),[21] a prenyl moiety (C-1'~C-5'; H_2-1', H-2', H_3-4', and H_3-5'), an ester carbonyl group (C-1), an oxygenated methylene (C-3, H_2-3), and a methyl group (C-6', H_3-6'). The HMBC correlations (Figure 2) from H_2-3 to C-1, C-4, C-4a, and C-7a; from H-4 to C-3, C-4a, and C-7a; and from H-7 to C-1, C-4a, and C-7a suggested the existence of a isobenzofuran-1(3*H*)-one moiety.[21] In addition, the position of the prenyl group at the C-5 of isobenzofuran-1(3*H*)-one was elucidated by the HMBC correlations from H_2-1' (δ_H 3.34) to C-4 (δ_C 125.4), C-5 (δ_C 139.5), and C-6 (δ_C 134.3), of H-2' (δ_H 5.17) to C-5 (δ_C 139.5), and of H-4 (δ_H 6.97) to C-1' (δ_C 28.5). The HMBC correlations from the H_3-6' (δ_H 2.33) to C-5 (δ_C 139.5), C-6 (δ_C 134.3), and C-7 (δ_C 129.5), and from H-7 (δ_H 7.51) to C-6 (δ_C 20.4)' supported the methyl group located at C-6. Thus, the structure of **1** was established as 6-methyl-5-prenyl-isobenzofuran-1(3*H*)-one.

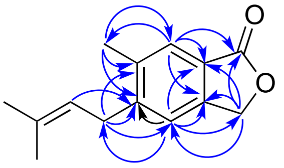


Figure 2. Key HMBC (↷) correlations of **1**

Compound **2** was also obtained as a pale-yellow gum. A molecular formula $C_{14}H_{14}O_3$ was assigned from HRESIMS (*m/z* 253.0847 $[M+Na]^+$, 253.0841 for $C_{14}H_{14}NaO_3$). The ^1H and ^{13}C NMR spectra of **2** were similar to those of **1**. The chemical shift differences resulted from the disappearance of a prenyl signal and appearance of a 3-methyl-2-oxobut-3-enyl resonance[28] (C-1'~C-5'; H_2-1', H_2-4', and H_3-5') in **2**. This indicated that the prenyl group in **1** was converted into a 3-methyl-2-oxobut-3-enyl group in **2**. The HMBC correlations of H_2-1′ to C-4, C-5, and C-6; of H-4 to C-1′ indicated that the 3-methyl-2-oxobut-3-enyl group was located at C-5. The HMBC correlations of H_3-6′ to C-5, C-6, and C-7, and of H-7 to C-6′ supported the methyl group located at C-6. Thus, the structure of 6-methyl-5-(3-methyl- 2-oxobut-3-enyl)isobenzofuran-1(3*H*)-one (**2**) was established.

Table 1. ^1H and ^{13}C NMR data for compounds **1**-**3** ($CDCl_3$, 125 and 500 MHz)

No.	**1**		**2**		**3**	
	δ_C	δ_H (m, *J*, Hz)	δ_C	δ_H (m, *J*, Hz)	δ_C	δ_H (m, *J*, Hz)
1	169.2 s		168.8 s		169.3 s	
3	69.8 t	5.39 s	71.3 t	5.33 s	66.5 t	5.18 s
4	125.4 d	6.97 s	126.3 d	6.90 s	151.9 s	
5	139.5 s		138.5 s		129.6 s	
6	134.3 s		135.2 s		136.5 s	
7	129.5 d	7.51 s	130.1 d	7.50 s	119.8 d	7.42 s
4a	140.1 s		142.9 s		130.3 s	
7a	124.3 s		125.2 s		124.9 s	
1′	28.5 t	3.34 (d) 6.8	47.8 t	4.65 s	116.7 d	6.53 (d) 9.9
2′	123.9 d	5.17 (t) 6.8	198.4 s		128.5 s	5.70 (d) 9.9
3′	133.2 s		144.6 s		76.1 s	
4′	17.6 q	1.57 s	123.1 t	5.96, 6.27 s	26.8 q	1.58 s
5′	25.3 q	1.80 s	16.5 q	1.96 s	26.8 q	1.58 s
6′	20.4 q	2.33 s	20.5 q	2.35 s	21.2 q	2.20 s

Compound **3** was also assigned the molecular formula of $C_{14}H_{14}O_3$ as supported by the HRESIMS (*m/z* 253.0833 $[M+Na]^+$). The ^1H and ^{13}C NMR spectroscopic data of **3** were also similar to those of compound **1**, except for the presence of a *gem*-dimethylchromene moiety[29] (C-1'~C-5'; H-1', H-2', and H_6-4',5'), and the absence of a prenyl group signals. The methyl group located at C-6 was supported by the HMBC correlations of H_3-6' with C-5, C-6, and C-7. Moreover, long-range correlations of H-1' to C-5, C-6, and C-7; and of H-2' to C-5 were observed. This led us to conclude that the *gem*-dimethylchromene moiety was fused in an angular manner at C-5 and C-4. Accordingly, the structure of **3** was determined, and gives the system name of 2,2,5- trimethyl-2*H*-furo[3,4-*h*]chromen-7(9*H*)-one.

Compounds **1-4** were tested for their anti-TMV activity at the concentration of 20 μM. The anti-TMV activity were tested using the half-leaf method.[29,30] 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 **1-4** showed high anti-TMV activity with inhibition rate of 31.4, 35.2 and 38.8, 29.6%. These rates are close to that of positive control.

The cytotoxicities of compounds **1-6** were also tested using a previously reported procedure.[31,32] 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 against some tested human tumor cell lines with IC_{50} values in the range of 2.6 -9.5 μM.

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

Compounds	Cell lines and IC_{50} (μM)				
	NB4	A549	SHSY5Y	PC3	MCF7
1	4.6	3.2	3.0	5.8	4.5
2	2.6	4.2	4.8	5.0	4.7
3	3.5	3.2	6.4	3.9	8.2
4	4.1	6.9	6.1	4.4	7.5
5	5.6	7.9	8.2	9.5	7.6
6	6.8	8.7	7.5	8.0	9.2
Taxol	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.

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 (δ) 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 × 25 cm, 7 μm) column or a Venusil MP C_{18} (20 mm × 25 cm, 5 μm) 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_2SO_4 in EtOH.

Plant Material. The roots of sun cured tobacco (Weishang Liuye 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 roots of sun cured tobacco (4.4 kg) were extracted four times with 70% aqueous MeOH (3 × 5 L) at room temperature and filtered. The solvent was evaporated in vacuo, and the crude extract was dissolved in H_2O and partitioned with EtOAc. The EtOAc partition (118 g) was applied to silica gel (200–300 mesh) column chromatography, eluting with a $CHCl_3$-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 A (9:1, 26.6 g) by silica gel column chromatography, eluted with $CHCl_3$ -Me_2CO (9:1-1:1), yielded mixtures A1–A6. Fraction A2 (8:2, 3.68 g) was subjected to silica gel column chromatography using petroleum ether-acetone and semi-preparative HPLC (58% MeOH-H_2O, flow rate 20 mL/min) to give **1** (13.6 mg), **2** (15.7 mg), **3** (10.5 mg), and **5** (15.4 mg). Fraction A3 (7:3, 3.18 g) was subjected to silica gel column chromatography using petroleum ether-acetone and semi-preparative HPLC (50% MeOH-H_2O, flow rate 20 mL/min) to give **6** (14.8 mg). Further separation of fraction B (8:2, 22.5 g) by silica gel column chromatography, eluted with $CHCl_3$ -Me_2CO (8:2-4:6), yielded mixtures B1-B6. Fraction B5 (1:1, 4.12 g) was subjected to silica gel column chromatography using petroleum ether-acetone and semi-preparative HPLC (38% MeOH-H_2O, flow rate 20 mL/min) to give **4** (14.3 mg).

Anti-TMV Assays. The anti-TMV activities were tested using the half-leaf method,[29,30] 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).[31,32]

6-Methyl-5- prenylisobenzofuran-1(3*H*)-one (**1**)**:** Obtained as pale-yellow gum; UV (MeOH), λ_{max} (log ε) 306 (2.86), 276 (3.72), 210 (4.11) nm; IR (KBr) λ_{max} 3014, 2926, 1738, 1610, 1556, 1438, 1372, 1260, 1146, 1058, 932, 856 cm^{-1}; ^{1}H NMR and ^{13}C NMR data ($CDCl_3$, 500 and 125 MHz, respectively), Table 1; ESIMS (positive ion mode) *m/z* 239 [M+Na]$^+$; HRESIMS (positive ion mode) *m/z* 239.1041 [M+Na]$^+$ (calcd 239.1048 for $C_{14}H_{16}NaO_2$).

6-Methyl-5-(3-methyl-2-oxobut-3-enyl)isobenzofuran-1(3*H*)-one (**2**): Obtained as pale-yellow gum; UV (MeOH), λ_{max} (log ε) 305 (2.92 6), 278 (3.75), 210 (4.16) nm; IR (KBr) λ_{max} 3026, 2938, 1742, 1658, 1610, 1560, 1454, 1376, 1262, 1149, 1059, 912, 867 cm^{-1}; ^{1}H NMR and ^{13}C NMR data ($CDCl_3$, 500 and 125 MHz, respectively), Table 1; ESIMS (positive ion mode) *m/z* 253 [M+Na]$^+$; HRESIMS (positive ion mode) *m/z* 253.0847 [M+Na]$^+$ (calcd 253.0841 for $C_{14}H_{14}NaO_3$).

2,2,5-Trimethyl-2*H*-furo[3,4-*h*]chromen-7(9*H*)-one (**3**)**:** Obtained as pale-yellow gum; UV (MeOH), λ_{max} (log ε) 316 (3.22), 276 (3.74), 210 (4.12) nm; IR (KBr) λ_{max} 3054, 2942, 1746, 1612, 1568, 1467, 1346, 1269, 1152, 1063, 895, 768 cm^{-1}; ^{1}H NMR and ^{13}C NMR data ($CDCl_3$, 500 and 125 MHz, respectively), Table 1; ESIMS (positive ion mode) *m/z* 253 [M+Na]$^+$; HRESIMS (positive ion mode) *m/z* 253.0833 [M+Na]$^+$ (calcd 253.0841 for $C_{14}H_{14}NaO_3$).

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