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FOUR NEW PRENYLATED FLAVONOIDS FROM THE FRUITS OF *Sinopodophyllum hexandrum*

Yan-jun Sun,[1,2,3]* Rui-jie Han,[1,2] Chen Zhao,[1,2] Hui Chen,[1,2] Yan-li Zhang,[1,2] and Wei-sheng Feng[1,2]*

*Four new prenylated flavonoids, sinoflavonoids NF–NI (**1**–**4**), were isolated from the fruits of* Sinopodophyllum hexandrum *by different chromatographic methods such as silica gel, Sephadex LH-20, ODS, and preparative high-performance liquid chromatography (HPLC). Their structures were elucidated on the basis of extensive spectroscopic data (UV, IR, HR-ESI-MS, ^{1}H NMR, ^{13}C NMR, HSQC, HMBC).*

Keywords: *Sinopodophyllum hexandrum*, prenylated flavonoids, structure identification.

With their chemical and pharmacological diversity, prenylated flavonoids have attracted much attention from natural product chemists [1]. *Sinopodophyllum hexandrum*, widely distributed in the Southwest of China, is a member of the Berberidaceae family [2]. Its roots and rhizomes are mainly used for extracting podophyllotoxin [3]. However, its fruits are clinically applied for the treatment of amenorrhea, dead fetus, and placental retention [4]. Previous phytochemical investigations revealed that *S. hexandrum* is particularly rich in aryltetralin lactone lignans and prenylated flavonoids [2, 4–12]. As part of our continuous efforts toward discovering new natural products, four new prenylated flavonoids, sinoflavonoids NF–NI (**1**–**4**), were isolated from the fruits of *S. hexandrum*. Details of the isolation and structure elucidation of all isolated compounds are described here (Fig. 1).

The EtOH extract of the fruits of *S. hexandrum* was partitioned between petroleum ether (PE), CH_2Cl_2, EtOAc, *n*-BuOH, and water. The EtOAc layer was fractionated and purified by repeated column chromatography, allowing the isolation of four new prenylated flavonoids, sinoflavonoids NF–NI (**1**–**4**). Their structures were elucidated on the basis of extensive spectroscopic data (UV, IR, HR-ESI-MS, ^{1}H NMR, ^{13}C NMR, HSQC, HMBC).

Compound **1** was obtained as a yellow amorphous powder and possesses the molecular formula $C_{21}H_{20}O_7$, as revealed from its HR-ESI-MS analysis (*m/z* 383.1129 $[M - H]^-$, calcd 383.1131). The ^{1}H NMR (Table 1) spectrum showed two aromatic systems including one 1,3,4-tri-substituted benzene ring at δ 7.53 (1H, d, J = 2.2 Hz), 6.89 (1H, d, J = 8.5 Hz), and 7.42 (1H, dd, J = 8.5, 2.2 Hz), one penta-substituted benzene ring at δ 6.42 (1H, s), one 2,2-dimethyldihydropyrano group [based on the HMBC correlations of methyl groups at δ 1.31 (6H, s, H-4″, 5″) with C-3″ (δ 76.2), and C-2″ (δ 30.9) and a methylene group at δ 1.81 (2H, t, J = 6.8 Hz, H-2″) with C-3″ (δ 76.2) and C-1″ (δ 15.7)], one aromatic methoxy group at δ 3.76 (3H, s), and three phenolic hydroxyl groups at δ 13.05 (1H, s), 9.76 (1H, s), and 9.37 (1H, s). The ^{13}C NMR (Table 2) spectrum revealed a flavonol skeleton, including one carbonyl group at δ 178.0, two benzene rings, two oxygen-bearing olefinic carbons at δ 155.3, 137.5, one 2,2-dimethyldihydropyrano group at δ 15.7, 30.9, 76.2, 26.3 (× 2), and one aromatic methoxy group at δ 59.6. These spectroscopic data indicated that compound **1** was a prenylated flavonol derivative. According to the reported literature [13], the chemical shifts of C-6 and C-8 in 3-*O*-methylquercetin are at δ 99.0 and 94.0, respectively. In combination with an intramolecular hydrogen-bonded phenolic hydroxyl group at δ 13.05 (1H, s, 5-OH), the chemical shift of C-6 (δ 104.3) and C-8 (δ 94.3) in compound **1** indicated that the 2,2-dimethyldihydropyrano group was located at C-6 and C-7.

1) Co-construction Collaborative Innovation Center for Chinese Medicine and Respiratory Diseases by Henan & Education Ministry of P. R. China, Henan University of Chinese Medicine, 450046, Zhengzhou, P. R. China, e-mail: sunyanjunily@126.com; 2) School of Pharmacy, Henan University of Chinese Medicine, 450046, Zhengzhou, P. R. China, e-mail: fwsh@hactcm.edu.cn; 3) Henan Research Center for Special Processing Technology of Chinese Medicine, 450046, Zhengzhou, P. R. China. Published in *Khimiya Prirodnykh Soedinenii*, No. 5, September–October, 2020, pp. 710–713. Original article submitted November 2, 2019.

TABLE 1. ^{1}H NMR Spectroscopic Data of Compounds **1–4** (500 MHz, DMSO-d_6, δ, ppm, J/Hz)

C atom	**1**	**2**	**3**	**4**
6	–	6.21 (s)	6.20 (s)	6.31 (s)
8	6.42 (s)	–	–	–
2′	7.53 (d, J = 2.2)	–	–	–
5′	6.89 (d, J = 8.5)	6.73 (d, J = 8.2)	6.76 (d, J = 8.2)	6.92 (d, J = 8.4)
6′	7.42 (dd, J = 8.5, 2.2)	6.86 (d, J = 8.2)	6.78 (d, J = 8.2)	7.58 (d, J = 8.4)
1″	2.61 (t, J = 6.8)	2.72 (d, J = 6.3)	5.32 (d, J = 6.3)	3.34 (d, J = 7.4)
2″	1.81 (t, J = 6.8)	4.10 (t, J = 6.3)	4.29 (d, J = 6.3)	5.10 (t, J = 7.4)
4″	1.31 (s)	4.57 (s); 4.53 (s)	1.17 (s)	1.51 (s)
5″	1.31 (s)	1.53 (s)	1.44 (s)	1.54 (s)
7″	–	–	1.05 (s)	–
8″	–	–	1.30 (s)	–
1‴	–	2.59 (m)	3.44 (d, J = 7.2)	7.04 (s)
2‴	–	1.72 (m)	5.00 (m)	–
4‴	–	1.29 (s)	1.27 (s)	5.78 (s); 5.30 (s)
5‴	–	1.31 (s)	1.44 (s)	2.08 (s)
OCH_3	3.76 (s)	3.57 (s)	3.55 (s)	3.67 (s)
5-OH	13.05 (s)	12.64 (s)	12.71 (s)	12.67 (s)

TABLE 2. ^{13}C NMR Spectroscopic Data of Compounds **1–4** (100 MHz, DMSO-d_6, δ, ppm)

C atom	**1**	**2**	**3**	**4**
2	155.3 (C)	158.2 (C)	158.1 (C)	156.6 (C)
3	137.5 (C)	139.2 (C)	139.2 (C)	137.8 (C)
4	178.0 (C)	178.0 (C)	178.1 (C)	178.2 (C)
5	158.1 (C)	159.1 (C)	159.8 (C)	158.6 (C)
6	104.3 (C)	99.1 (CH)	99.1 (CH)	98.2 (CH)
7	160.4 (C)	161.0 (C)	160.2 (C)	161.6 (C)
8	94.3 (CH)	105.6 (C)	101.6 (C)	105.9 (C)
9	154.3 (C)	154.9 (C)	155.8 (C)	153.9 (C)
10	103.9 (C)	104.7 (C)	106.2 (C)	104.1 (C)
1′	120.6 (C)	120.3 (C)	120.6 (C)	122.9 (C)
2′	115.7 (CH)	121.0 (C)	128.3 (C)	129.4 (C)
3′	145.2 (C)	142.1 (C)	143.2 (C)	142.7 (C)
4′	148.7 (C)	148.0 (C)	147.2 (C)	144.9 (C)
5′	115.5 (CH)	112.7 (CH)	112.3 (CH)	111.1 (CH)
6′	120.8 (CH)	121.2 (CH)	121.7 (CH)	126.0 (CH)
1″	15.7 (CH_2)	27.4 (CH_2)	65.9 (CH)	21.1 (CH_2)
2″	30.9 (CH_2)	73.9 (CH)	76.6 (CH)	122.3 (CH)
3″	76.2 (C)	148.0 (C)	77.4 (C)	130.8 (C)
4″	26.3 (CH_3)	110.8 (CH_2)	22.1 (CH_3)	17.4 (CH_3)
5″	26.3 (CH_3)	17.1 (CH_3)	24.7 (CH_3)	25.4 (CH_3)
6″			109.0 (C)	
7″			27.7 (CH_3)	
8″			26.4 (CH_3)	
1‴		20.5 (CH_2)	25.0 (CH_2)	104.4 (CH)
2‴		31.2 (CH_2)	123.0 (CH)	156.8 (C)
3‴		73.7 (C)	130.2 (C)	132.4 (C)
4‴		25.9 (CH_3)	17.3 (CH_3)	114.2 (CH_2)
5‴		26.8 (CH_3)	24.7 (CH_3)	18.8 (CH_3)
OCH_3	59.6 (CH_3)	60.1 (CH_3)	59.7 (CH_3)	60.1 (CH_3)

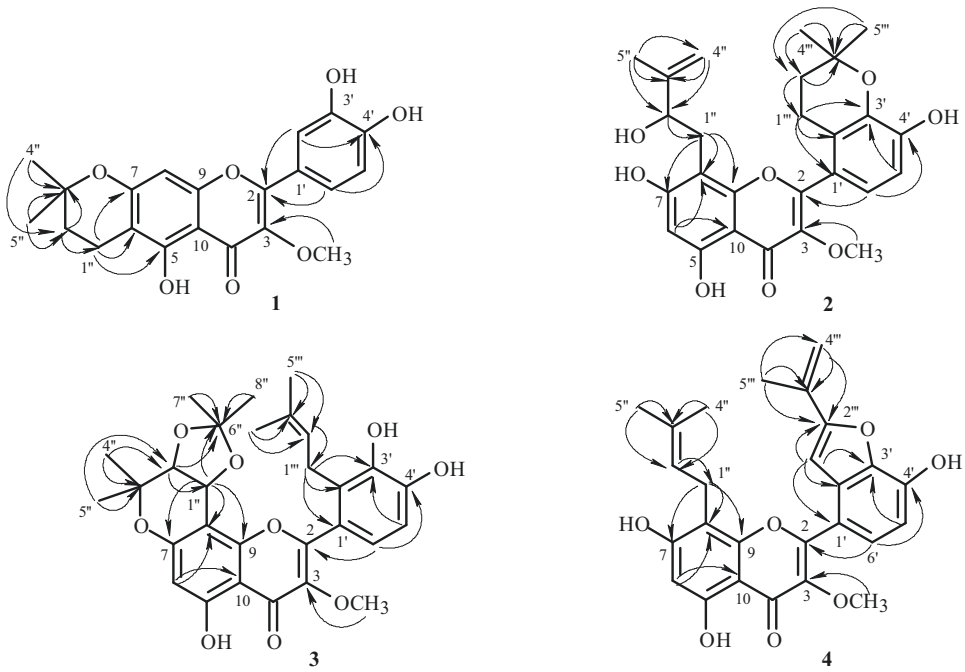

Fig. 1. Structures and key HMBC correlations of compounds **1**–**4**.

This was also supported by the HMBC correlations (Fig. 1) of the methylene group at δ 2.61 (2H, t, J = 6.8 Hz, H-1″) with C-5 (δ 158.1), C-6 (δ 104.3), and C-7 (δ 160.4). The methoxy group was located at C-3 from the HMBC correlation of the methoxy group at δ 3.76 (3H, s) with C-3 (δ 137.5). Thus, the structure of compound **1** was elucidated as 6,7-(2,2-dimethyldihydropyrano)-5,3′,4′-trihydroxy-3-methoxyflavone and named sinoflavonoid NF.

Compound **2** was obtained as a yellow amorphous powder. The ^{1}H NMR (Table 1) and ^{13}C NMR (Table 2) data of compound **2** are closely correlated to those of **1** but differ in the presence of one 2-hydroxy-3-methyl-3-butenyl and one olefinic carbon at δ 99.1 at lower field instead of C-8 (δ 94.3) in **1**. The HR-ESI-MS gave an $[M + Na]^{+}$ ion peak at *m/z* 491.1685 (calcd 491.1682), being 84 mass units greater than that of **1**. The detection of 2-hydroxy-3-methyl-3-butenyl was based on the HMBC correlations of the tertiary methyl group at δ 1.53 (3H, s, H-5″) and hydrogen protons of the terminal double bond at δ 4.57 (1H, s, H-4″) and 4.53 (1H, s, H-4″) with C-2″ (73.9) and C-3″ (δ 148.0) of the oxymethine group at δ 4.10 (1H, t, J = 6.3 Hz, H-2″) with C-1″ (27.4). The 2-hydroxy-3-methyl-3-butenyl group and the 2,2-dimethyldihydropyrano group were linked to C-8 and C-2′ and C-3′, respectively, due to the long-range correlations of the methylene group at δ 2.72 (2H, d, J = 6.3 Hz, H-1″) with C-7 (δ 161.0), C-8 (δ 105.6), and C-9 (δ 154.9), and at δ 2.59 (2H, m, H-1‴) with C-1′ (δ 120.3), C-2′ (δ 121.0), and C-3′ (δ 142.1) in the HMBC spectrum (Fig. 1). The methoxy group was located at C-3 from the HMBC correlation of the methoxy group at δ 3.57 (3H, s) with C-3 (δ 139.2). Thus, the structure of compound **2** was elucidated as 8-(2-hydroxy-3-methyl-3-butenyl)-2′,3′-(2,2-dimethyldihydropyrano)-5,7,4′-trihydroxy-3-methoxyflavone and named sinoflavonoid NG.

Compound **3** was obtained as a yellow amorphous powder and possesses the molecular formula $C_{29}H_{32}O_{9}$, as revealed from its HR-ESI-MS analysis (*m/z* 523.1967 $[M - H]^{-}$, calcd 523.1968). The ^{1}H NMR (Table 1) spectrum showed two aromatic systems, including one 1,2,3,4-tetra-substituted benzene ring at δ 6.76 (1H, d, J = 8.2 Hz) and 6.78 (1H, d, J = 8.2 Hz), one penta-substituted benzene ring at δ 6.20 (1H, s), one 3-methyl-2-butenyl [based on the HMBC correlations of two methyl groups at δ 1.27 (3H, s, H-4‴) and 1.44 (3H, s, H-5‴) with C-3‴ (130.2) and C-2‴ (δ 123.0), an olefinic proton at δ 5.00 (1H, m, H-2‴) with C-1‴ (δ 25.0)]. 3,4-Isopropyldioxy-2,2-dimethyldihydropyrano group [based on the HMBC correlations of two methyl groups at δ 1.17 (3H, s, H-4″) and 1.44 (3H, s, H-5″) with C-2″ (76.6) and C-3″ (δ 77.4), an oxymethine group at δ 4.29 (1H, d, J = 6.3 Hz, H-2″) with C-1″ (65.9), C-6″ (109.0), an oxymethine group at δ 5.32 (1H, d, J = 6.3 Hz, H-1″) with C-6″ (109.0), two methyl groups at δ 1.05 (3H, s, H-7″), 1.30 (3H, s, H-8″) with C-6″ (109.0), respectively], one aromatic methoxy group at δ 3.55 (3H, s), and three phenolic hydroxyl groups at δ 12.71 (1H, s), 9.92 (1H, s), and 8.56 (1H, s). The ^{13}C NMR (Table 2) spectrum revealed a flavonol skeleton including one carbonyl group at δ 178.1, two benzene rings, two oxygen-bearing olefinic carbons at δ 158.1, 139.2, and one 3-methyl-2-butenyl at δ 25.0, 123.0, 130.2, 17.3, 24.7, one 3,4-isopropyldioxy-2,2-dimethyldihydropyrano group at δ 65.9, 76.6, 77.4, 22.1, 24.7, 109.0, 27.7, 26.4, and one aromatic methoxy group at δ 59.7.

These spectroscopic data indicated that compound **3** was a prenylated flavonol derivative. The HMBC correlations (Fig. 1) of the oxymethine group at δ 5.32 (1H, d, J = 6.3 Hz, H-1″) with C-7 (δ 160.2), C-8 (δ 101.6), and C-9 (δ 155.8) and the methylene group at δ 3.44 (2H, d, J = 7.2 Hz, H-1‴) with C-1′ (δ 120.6), C-2′ (δ 128.3), and C-3′ (δ 143.2) indicated that 3,4-isopropyldioxy-2,2-dimethyldihydropyrano group and 3-methyl-2-butenyl were located at C-7 and C-8 and C-2′, respectively. The methoxy group was located at C-3 from the HMBC correlation of the methoxy group at δ 3.55 (3H, s) with C-3 (δ 139.2). Thus, the structure of compound **3** was elucidated as 7,8-(3,4-isopropyldioxy-2,2-dimethyldihydropyrano)-2′-(3-methyl-2-butenyl)-5,3′,4′-trihydroxy-3-methoxyflavone and named sinoflavonoid NH.

Compound **4** was obtained as a yellow amorphous powder. The molecular formula was found to be $C_{26}H_{24}O_7$, as deduced by analysis of the $[M + Na]^+$ molecular ion peak at *m/z* 471.1425 (calcd 471.1420) in the HR-ESI-MS. Its ^1H and ^{13}C NMR (Table 1 and 2) spectra were similar to those of **3**, except that one 2-isopropenylfurano group was observed instead of the 4-isopropyldioxy-2,2-dimethyldihydropyrano group in **3**. One tertiary methyl at δ 2.08 (3H, s), and one terminal double bond at δ 5.78 (1H, s), 5.30 (1H, s), δ_C 132.4, and 114.2 were evidence for the presence of one isopropenyl group. The olefinic proton at δ 7.04 (1H, s) and two olefinic carbons at δ 104.4 and 156.8 indicated the presence of one furan ring. The 2-isopropenylfurano group was deduced from the HMBC correlations (Fig. 1) of the tertiary methyl at δ 2.08 (3H, s, H-5‴) and olefinic protons 5.78 (1H, s, H-4‴) and 5.30 (1H, s, H-4‴) to C-2‴ (δ 156.8). The 2-isopropenylfurano group was located at C-2′ and C-3′ from the HMBC cross-peaks of the olefinic proton at δ 7.04 (1H, s, H-1‴) with C-1′ (δ 122.9), C-2′ (δ 129.4), and C-3′ (δ 142.7). The methylene group at δ 3.34 (2H, d, J = 7.4 Hz, H-1″) showed HMBC correlations with C-7 (δ 161.6), C-8 (δ 105.9), and C-9 (δ 153.9), indicating that the 3-methyl-2-butenyl was attached to C-8. Thus, compound **4** was deduced as 8-(3-methyl-2-butenyl)-2′,3′-(2-isopropenylfurano)-5,7,4′-trihydroxy-3-methoxyflavone, and named sinoflavonoid NI.

EXPERIMENTAL

General Methods. The UV spectra were measured on a Shimadzu UV-1700 spectrometer (Shimadzu Corporation, Kyoto, Japan). The IR spectra were taken on a Nicolet 10 microscope spectrometer (Thermo Scientific, San Jose, CA, USA). The 1D and 2D NMR spectra were recorded on a Bruker-AC (E)-500 spectrometer (Bruker AM 500, Fallanden, Switzerland) using TMS as internal standard. The HR-ESI-MS was determined on a Bruker microTOF-Q instrument (Bruker BioSpin, Rheinstetten, Germany). Column chromatography was performed with silica gel (200–300 mesh; Qingdao Marine Chemical Inc., Qingdao, China), Sephadex LH-20 (GE Healthcare), and ODS (50 μm; YMC Co., Ltd., Kyoto, Japan). Preparative HPLC separations were performed on a SEP system (Beijing Sepuruisi Scientific Co., Ltd., China) equipped with a variable-wavelength UV detector, using a YMC-Pack ODS-A column (250 × 20 mm, 5 μm). Chemical reagents for isolation were of analytical grade and purchased from Tianjin Siyou Co., Ltd., China.

Plant Material. The plant material was collected from Deqin, Yunnan Province, China, in September 2013, and identified by Prof. Chengming Dong as the fruits of *S. hexandrum*. A voucher specimen (SE 20130929) was deposited at the School of Pharmacy, Henan University of Chinese Medicine.

Extraction and Isolation. The powdered fruits of *S. hexandrum* (9.1 kg) were refluxed with 95% EtOH three times (each, 2h, 20L). The filtrate was concentrated under reduced pressure to yield a dark brown residue (1.6 kg). The residue was suspended in water and partitioned with petroleum ether (PE), CH_2Cl_2, EtOAc, and *n*-BuOH, successively. The EtOAc layer (142.71 g) was fractionated by silica gel column chromatography (CC, 100 × 10 cm) with a gradient of PE (60–90°)–acetone. Sixteen fractions E1–E16 were obtained on the basis of TLC monitoring. Fraction E2 (4.51 g) was subjected to Sephadex LH-20 CC (90 × 3.0 cm) eluted by methanol to yield subfractions E2-1–E2-3. Subfraction E2-2 (0.95 g) was subjected to preparative HPLC eluted with methanol–H_2O (70:30) at a flow rate of 7 mL/min to give **2** (2.7 mg, t_R 19 min). Fraction E7 (4.79 g) was chromatographed over open ODS (50 × 2 cm) eluted with a gradient of methanol–H_2O (60:40, 70:30, 80:20, 90:10) to obtain subfractions E7-1–E7-6. Subfraction E7-5 (1.06 g) was further purified by preparative HPLC eluted with MeOH–H_2O (80:20) at 7 mL/min to yield **1** (2.5 mg, t_R 39 min), **3** (3.3mg, t_R 42 min), and **4** (5.7 mg, t_R 58 min).

Sinoflavonoid NF (1), yellow amorphous powder. UV (MeOH, λ_{max}, nm) (log ε): 255 (4.62), 344 (4.45). IR (ν_{max}, cm^{-1}): 3419, 2976, 2930, 2853, 1655, 1617, 1571, 1354, 1288, 1242, 1159. HR-ESI-MS *m/z*: 383.1129 $[M - H]^-$ (calcd for $C_{21}H_{19}O_7$, 383.1131), 407.1105 $[M + Na]^+$ (calcd for $C_{21}H_{20}O_7Na$, 407.1107). For ^1H and ^{13}C NMR data (DMSO-d_6), see Tables 1 and 2.

Sinoflavonoid NG (2), yellow amorphous powder. UV (MeOH, λ_{max}, nm) (log ε): 264 (4.61), 350 (4.43). IR (ν_{max}, cm^{-1}): 3372, 2973, 2929, 2852, 1651, 1613, 1578, 1490, 1359, 1192. HR-ESI-MS *m*/*z* 491.1685 $[M + Na]^+$ (calcd for $C_{26}H_{28}O_8Na$, 491.1682). For ^1H and ^{13}C NMR data (DMSO-d_6), see Tables 1 and 2.

Sinoflavonoid NH (3), yellow amorphous powder. UV (MeOH, λ_{max}, nm) (log ε): 264 (4.61), 342 (4.44). IR (ν_{max}, cm^{-1}): 3370, 2976, 2927, 2854, 1648, 1590, 1451, 1353, 1263, 1157. HR-ESI-MS *m*/*z* 523.1967 $[M - H]^-$ (calcd for $C_{29}H_{31}O_9$, 523.1968). ^1H and ^{13}C NMR data (DMSO-d_6), see Tables 1 and 2.

Sinoflavonoid NI (4), yellow, amorphous powder. UV (MeOH, λ_{max}, nm) (log ε): 263 (4.62), 334 (4.46). IR (ν_{max}, cm^{-1}): 3384, 2956, 2925, 2854, 1653, 1593, 1456, 1377, 1350, 1261, 1161. HR-ESI-MS *m*/*z* 471.1425 $[M + Na]^+$ (calcd for $C_{26}H_{24}O_7Na$, 471.1420). For ^1H and ^{13}C NMR data (DMSO-d_6), see Tables 1 and 2.

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