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New lignans from the roots of *Datura metel* L

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ABSTRACT

Two new lignans (**1-2**) and a new natural product (**3**), as well as eighteen known compounds (**4-21**), were isolated from the roots of *Datura metel* L. Compounds **8**, **11**, **12**, **14**, **16**, **17**, **19** and **21** were isolated from *Datura metel* L for the first time. These compounds' chemical structures were elucidated by spectroscopic methods, including 1D and 2D NMR spectra with references to the literature, as well as high-resolution mass spectrometric analysis. All compounds were tested for cytotoxic activity using an MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenylt etrazolium bromide) assay.

1. Introduction

Datura metel L. is an annual herb that belongs to the Solanaceae family and is widely distributed in China (Jing et al., 2016; Al-Snafi, 2017). This herb was one of the most important anesthetics in ancient times. The flower of *Datura metel* L. is named "yangjinhua" in Chinese and is officially listed on the Chinese Pharmacopoeia (Shanghai Science and Technology Press, 1986; Yang et al., 2010a,b). As a Traditional Chinese Medicine, yangjinhua has been used for the treatment of bronchial asthma, chronic bronchitis, skin-ulcers, diarrhea, rheumatic pains, cough and convulsion in China (Yang et al., 2018). Modern pharmacological studies show that yangjinhua possesses various pharmacological activities, such as anti-cancer, anti-inflammatory, anti-itch, anti-proliferative, anti-microbial and anti-titillation of skin (Xue et al., 2015; Yang et al., 2014). The roots of *Datura metel* L. have been used in the treatment of such ailments as cough, pain, rheumatic arthralgia, and malignant sores in Chinese folk medicine (Shanghai Science and Technology Press, 1999; Xue et al., 2015). To achieve the most effective understanding of the basis of their pharmacodynamics, the chemical constituents of the roots of *Datura metel* L. were studied in the present experiment, mirroring the activity of traditional medicinal targets and expanding the medicinal roles of *Datura metel* L. In the results, two new compounds, a new natural product and eighteen known compounds (Fig. 1, Fig. S4) were elucidated, and the isolated compounds were evaluated for their cytotoxicities.

2. Results and discussion

Compound **1** was isolated as a white amorphous powder. This compound's molecular formula was indicated to be $C_{21}H_{22}O_7$ by its positive HRESIMS with *m/z* 387.1440 $[M+H]^+$ (calculated to be 387.1444). The ^{1}H NMR spectrum (Table 1) of compound **1** displayed two sets of meta-coupled aromatic proton signals at δ_H 7.20 (2H, s, H-2, 6), δ_H 6.99 (1H, d, J = 1.1 Hz, H-2′) and δ_H 7.31 (1H, d, J = 1.1 Hz, H-6′) and also showed the presence of 1,3,4,5-tetrasubstituted bezene and 1′,3′,4′,5′-tetrasubstituted benzene rings; the oxygenated methylene proton signals at δ_H 4.84 (2H, s, H-9); a set of signals due to the protons of a propenol group at δ_H 6.70 (1H, brd, J = 15.8 Hz, H-7′), 6.38 (1H, dt, J = 5.8, 15.8 Hz, H-8′), 4.25 (2H, dd, J = 1.3, 5.8 Hz, H-9′); two signals corresponding to three methoxy groups at δ_H 4.02 (3H, s, 3′-OCH_3) and 3.93 (6H, s, 3,5-OCH_3) (Fig. 1). The ^{13}C NMR spectrum (Table 1) of compound **1** had 21 signals assignable to three methoxy carbons (δ_C 56.5, 56.9 × 2) and 18 carbons (2 × C6 − C3) ascribable to a benzofuran-type lignin skeleton, structurally similar to herpetol (In et al., 2015), except for the signals arising from ring A. The ^{1}H NMR spectrum of compound **1** showed the symmetrical structure for ring A, rather than the ABX aromatic proton system of herpetol (δ_H 7.44 (1H, d, J = 2.0 Hz, H-2), 7.31 (1H, dd, J = 2.0, 8.0 Hz, H-6), 6.90 (1H, dd, J = 8.0 Hz, H-5)). The above speculation was further confirmed by long-range correlations of the methoxy protons at δ_H 3.93 (6H, s, 3,5-OCH_3) to the carbons at δ_C 149.6 (C-3, 5) and the correlations of the methoxy protons at δ_H 4.02 (3H, s, 3′-OCH_3) to the carbon at δ_C 146.5 (C-3′) in the HMBC spectrum (Fig. 2). Assignments of all functional groups of compound **1** were achieved by 2D NMR (DEPT, HMBC, HSQC, and ^{1}H-^{1}H COSY) spectra. Thus, compound **1** was identified as (3,3′,5-trimethoxy-4′,7-epoxy-8,5′-neolignan-7-ene-4,9,9′-triol), namely, herpetol B.

Compound **2** was also obtained as a white amorphous powder. This compound's molecular formula was indicated to be $C_{27}H_{32}O_{12}$ by its positive HRESIMS with *m/z* 549.1969 $[M+H]^+$ (calculated for

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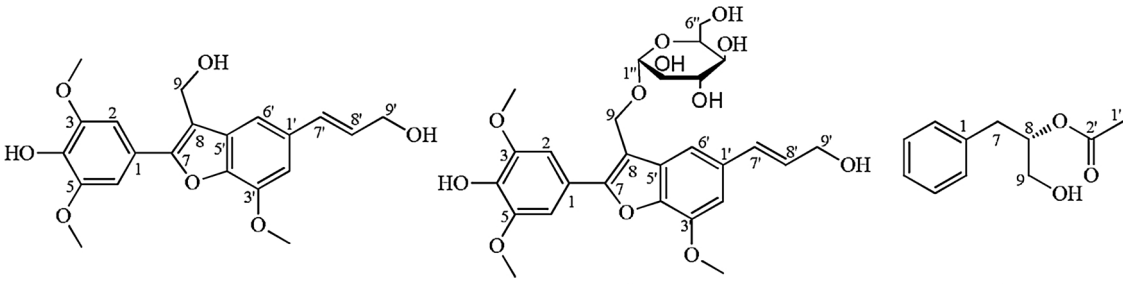

1 **2** **3**

Fig. 1. Structures of compounds **1-3**.

Table 1
^{1}H and ^{13}C-NMR Data of **1-3**(400 MHz in ^{1}H NMR and 100 MHz in ^{13}C NMR, in CD_3OD).

No.	1		2		3	
	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)
1	122.3	–	121.9	–	140.0	–
2	106.0	7.20 (1H, *s*)	106.1	7.23 (1H, *s*)	130.3	7.15–7.27 (*m*)
3	149.6	–	149.5	–	129.3	7.15–7.27 (*m*)
4	138.0	–	138.1	–	127.3	7.15–7.27 (*m*)
5	149.6	–	149.5	–	129.3	7.15–7.27 (*m*)
6	106.0	7.20 (1H, *s*)	106.1	7.23 (1H, *s*)	130.3	7.15–7.27 (*m*)
7	156.0	–	157.4	–	38.0	2.70 (1H, *dd*, 8.2, 13.7) 2.90 (1H, *dd*, 6.2, 13.7)
8	115.2	–	111.9	–	54.3	4.15 (1H, *m*)
9	55.4	4.84 (2H, *s*)	61.8	4.91 (1H, *d*, 11.6) 5.12 (1H, *d*, 11.6)	64.2	3.50 (2H, *d*, 5.3)
1'	134.7	–	134.9	–	22.6	1.78 (3H, *s*)
2'	106.0	6.99 (1H, *d*, 1.1)	105.9	6.99 (1H, *d*, 1.1)	173.1	–
3'	146.5	–	146.4	–	–	–
4'	143.9	–	143.8	–	–	–
5'	132.9	–	133.4	–	–	–
6'	111.3	7.31 (1H, *d*, 1.1)	111.4	7.37 (1H, *d*, 1.1)	–	–
7'	132.4	6.70 (1H, *brd*, 15.8)	132.3	6.71 (1H, *brd*, 15.8)	–	–
8'	128.9	6.38 (1H, *dt*, 5.8,15.8)	129.0	6.39 (1H, *dt*, 5.8,15.8)	–	–
9'	63.8	4.25 (2H, *dd*, 1.3, 5.8)	63.8	4.25 (2H, *dd*, 1.3, 5.8)	–	–
1"	–	–	103.1	4.49 (1H, *d*, 7.6)	–	–
2"	–	–	75.2	3.23 (1H, *m*)	–	–
3"	–	–	78.3	3.29 (1H, *m*)	–	–
4"	–	–	71.7	3.28 (1H, *m*)	–	–
5"	–	–	78.2	3.26 (1H, *m*)	–	–
6"	–	–	62.8	3.91 (1H, *O*) 3.71 (1H, *dd*, 5.3,11.9)	–	–
3-OCH_3	56.9	3.93 (3H, *s*)	57.1	3.94 (3H, *s*)	–	–
5-OCH_3	56.9	3.93 (3H, *s*)	57.1	3.94 (3H, *s*)	–	–
3'-OCH_3	56.5	4.02 (3H, *s*)	56.5	4.03 (3H, *s*)	–	–

549.1972). The ^{1}H NMR and ^{13}C NMR spectrum (Table 1) of compound **2** were similar to those of compound **1** except for the presence of a glucose moiety (δ_H 4.49 (1H, d, J = 7.6 Hz, H-1")). The structure of compound **2** was further confirmed from the HMBC correlations as shown in Fig. 2. The glucosyloxy group was located at C-9 by the long-range correlations between H-9 and C-1" in the HMBC spectrum of compound **2** (Fig. 2), suggesting an additional glucose moiety compared to compound **1**. This evidence coupled with the NMR spectroscopic data confirmed that compound **2** was (3,3′,5-trimethoxy-4′,7-epoxy-8,5′-neolignan-7-ene-4,9,9′-triol-9-β-D-glucopyranoside), namely, herpetol C.

Compound **3** was obtained as a white amorphous powder. This compound's molecular formula was assigned to be $C_{11}H_{14}O_3$ by its positive HRESIMS with m/z 195.1023 $[M+H]^+$ (calculated to be 195.1021). The ^{1}H NMR and ^{13}C NMR spectrum (Table 1) were similar to those of (S)-2-benzoyloxy-3-phenyl-1-propanol (Yaoita and Kikuchi, 1997) except for the substitution of a methyl group. The methyl group was located at C-2′ by the correlations between H-1′ and C-2′ in the HMBC spectrum of compound **3** (Fig. 2). The ^{1}H NMR and ^{13}C NMR spectroscopic data (Table 1) of compound **3** was completely interpreted. Consequently, compound **3** was named (8*R*)-2′-acetoxyl-7-phenyl-9-propanol, and defined as a new natural product, previously reported as a reactant in the total synthesis of γ-valerolactones (Nakano et al., 2008).

The known compounds were identified as N-trans-feruloyl tyramine (**4**) (Kan et al., 2011), N-trans-coumaroyltyramine (**5**) (Kim and Lee, 2003), N-trans-p-coumaroyloctopamine (**6**) (Feng et al., 2016), N-[2-(3,4-dihydroxyphenyl)-2 hydroxyethyl]-3-(4-methoxyphenyl)prop-2-enamide (**7**) (Khan et al., 2003), N-cis-p-coumaroyloctopamine (**8**) (Sun et al., 2015), N-cis-feruloyloctopamine (**9**) (Hwang et al., 2016), N-cis-coumaroyltyramine (**10**) (Yang et al., 2010a,b), N-benzoyl-L-phenylalaninol (**11**) (Zhang and Kong, 2009), ω-hydroxypropioguaiacone (**12**) (Yang et al., 2009), cannabisin G (**13**) (Yang et al., 2013), canabisine H (**14**) (Seca et al., 2001), canabisine F (**15**) (Yang et al., 2013), (-)de-4′,4″-O-dimethylepimagnolin A (**16**) (Yang et al., 2015), balanophonin B (**17**) (Ma et al., 2013), leptolepisol D (**18**) (Yang et al., 2017), thero-2,3-bis-(4-hydroxy-3-methoxypheyl)-3-methoxy-propanol (**19**) (Huang et al., 2012), eythero-2,3-bis-(4-hydroxy-3-methoxypheyl)-3-methoxy-propanol (**20**) (Huang et al., 2012), (+)-(7*R*,7′*R*,7″*R*,7‴*R*,8*S*,8′*S*,8″*S*,8‴*S*)-4″,4‴-Dihydroxy-3,3′,3″,3‴,5,5′-hexamethoxy-7,9′;7′,9-diepoxy-4,8″;4′,8‴-bisoxy-8,8′-dineolignan-7″,7‴,9″,9‴-tetraol (**21**) (Zhu et al., 2012) by extensive 1D and 2D NMR spectroscopy, and by comparison with literature data (Table 2). Compounds **8**, **11**, **12**, **14**, **16**, **17**, **19** and **21** were isolated from *Datura metel* L. for the first time.

The effects of compounds **1–21** on hela cells were tested for cytotoxic activities using an MTT assay. As shown in Table 3, the results suggested that compounds **1**, **2**, **14**, **15**, **16**, **18** and **21** exhibited weak cytotoxic activities, and the remaining compounds were inactive against HeLa cells.

3. Experimental

3.1. General experimental procedures

Melting points were measured on a CK-300 micromelting point apparatus. The CD was recorded on a Bio-LogicMOS-450. Optical rotations were measured on a JASCO P-2000 instrument. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX-400 spectrometer using TMS as