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Cytotoxic oligophenols from the rhizome of *Wikstroemia indica*

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ABSTRACT

A new tricoumarin glycoside, triumbelletin-7-*O*-β-D-glucoside (**1**) and a new biflavonoid, wikstroflavone A (**2**), together with two known compounds, wikstaiwanone A (**3**) and wikstaiwanone B (**4**), were isolated from the rhizome of *Wikstroemia indica*. The structures of new compounds were elucidated by extensive spectroscopic techniques (UV, IR, HRESIMS, 1D, 2D NMR and CD), in combination with quantum chemical calculations of ^{13}C NMR and ECD spectra. All isolates were tested for their antineoplastic activities against cancer-derived cell lines HCT116, SW480, U87 and T98G. Compounds **2**–**4** exhibited moderate cytotoxic activities to the four cell lines. The flow cytometry assay and western blot analysis revealed that the cytotoxic effects were possibly attributed to the induced apoptotic cell death.

Wikstroemia indica (Thymelaeaceae) is a perennial shrub widely distributed in the southern region of China, including Guangdong, Guangxi and Fujian provinces.[1] The leaves, roots and rhizomes of *W. indica* have long been used as Chinese folk medicine for the treatment of parotitis, pertussis, subcutaneous hemorrhage and snake bite, etc.[2–4] Previous chemical research on this species has resulted in the discovery of a quantity of oligophenols, such as biflavonoids, dilignans, and biscoumarins, which are featured with the diverse combination modes between monophenols and with multiple stereogenic centers or chiral axes in the carbon skeletons.[5–7] In addition, some of the oligophenols exhibit promising biological effects, especially involved in anti-tumor, anti-inflammatory, antimalarial, antibacterial and antiviral activities.[8–12] Our preliminary study on the rhizome of *W. indica* had led to the isolation of a new chalcone-flavone bioflavonoid with moderate cytotoxicity.[13] In our continuing investigation for structurally novel oligophenols on this plant, a new tricoumarin glycoside, triumbelletin-7-*O*-β-D-glucoside (**1**) and a new biflavonoid, wikstroflavone A (**2**) (Fig. 1), together with two known compounds wikstaiwanone A (**3**) and wikstaiwanone B (**4**) were obtained.[5] Herein, we present the details of the structural characterization and the biological evaluation against several human cancer cells of these compounds.

Compound **1** was obtained as a pale yellow amorphous solid, [α]25 D −91.2 (*c* = 0.1, MeOH). Its molecular formula of $C_{33}H_{24}O_{14}$ with twenty-two degrees of unsaturation was assigned by the positive mode HRESIMS data at *m*/*z* 645.1239 (calcd for $C_{33}H_{25}O_{14}$, 645.1244). IR spectrum indicated the presence of hydroxyl (3418 cm^{-1}), conjugated carbonyl (1708 cm^{-1}) and aromatic (1600 cm^{-1}) groups. The exhibited blue fluorescence under UV-365 nm and the characteristic absorption maxima at 211 and 326 nm in UV spectrum assumed the 7-*O*-substituted coumarin skeleton for **1**.[14]

Inspection of the ^1H NMR and ^1H-^1H COSY spectra, twelve aromatic protons was classified into four AB systems, one ABX system and one singlet proton. Among them, two sets of doublets [δ_H 6.41 (1H, d, *J* = 9.6 Hz, H-3′), 7.79 (1H, d, *J* = 9.6 Hz, H-4′)] and [δ_H 6.26 (1H, d, *J* = 9.3 Hz, H-3″), 7.68 (1H, overlapped, H-4″)] were attributable to the typical signals of the coumarin. Proton resonances [δ_H 7.56 (1H, d, *J* = 8.4 Hz, H-5′), 7.07 (1H, dd, *J* = 8.4, 1.8 Hz, H-6′), 7.13 (1H, d, *J* = 1.8 Hz, H-8′)] indicated the presence of a 1, 3, 4-trisubstituted benzene ring in the structure. The downfield singlet at δ_H 7.85 (1H, s, H-4) suggested that **1** included one 3-*O*-substituted coumarin moiety. In addition, signals for a β-glucopyranose moiety [δ_H 5.80 (1H, d, *J* = 7.8 Hz, H-1‴)] was noted from the ^1H NMR spectral data. The ^{13}C NMR coupled with DEPT spectra displayed 33 carbons, apart from six carbons due to the glucoside moiety, the remain 27 aromatic carbons comprising twelve methines, six quaternary carbons and nine oxygenated quaternary carbons. Taken the three lactone carbonyls at δ_C 158.1 (C-2), 161.0 (C-2′)

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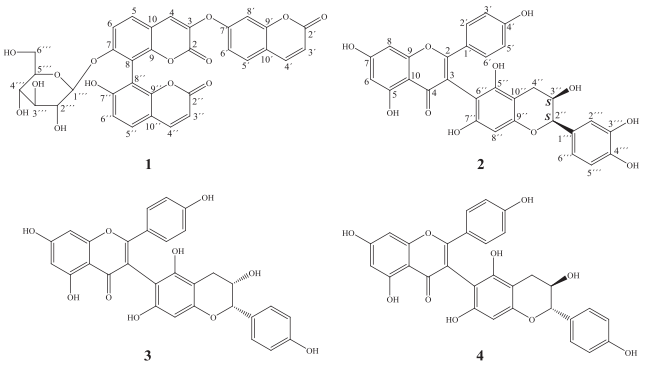

Fig. 1. Structures of compounds **1**–**4** from *W. indica*.

and 162.1 (C-2″), as well as the unsaturation into account, the aforementioned data suggested that **1** should be a trimeric coumarin glucoside. The sugar residue was deduced as D-glucose by comparing the HPLC retention time with the authentic sample after acid hydrolysis of **1** with 2 M HCl at 70 °C for 2 h. With the aid of 1D and 2D NMR experiments, the ^{1}H and ^{13}C NMR signals of **1** were fully assigned. Further comparison the NMR data of **1** (Table 1) with those of triumbellin strengthened that they had the identical tricoumarin skeleton, except for the replacement of a rhamnosyl group in triumbellin by a glucosyl group in **1**.[15]

The constructions of the four subunits in structure were evident from the HMBC experiment (Fig. 2A) and literature comparison. Cross-peaks from H-6 [δ_H 7.97 (1H, d, J = 8.7 Hz)] to C-8″ (δ_C 108.7) and from H-6″ [δ_H 7.22 (1H, d, J = 8.4 Hz)] to C-8 (δ_C 112.7) in HMBC spectrum supported the connectivity of two coumarin moieties via a carbon bond C_8-C_8''. The ether linkage between C-3 (δ_C 138.3) and C-7′ could be established with the aid of the unsaturation degree, as well as the obvious downfield ^{1}H NMR

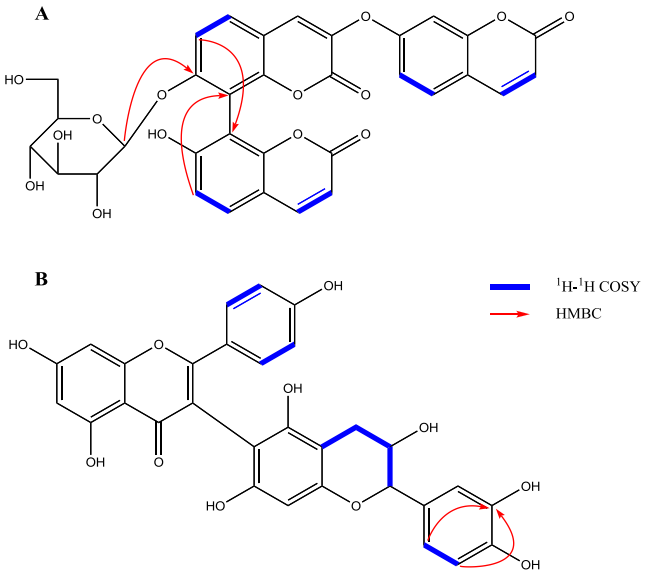

Fig. 2. Key ^{1}H-^{1}H COSY and HMBC correlations of **1** (A) and **2** (B).

Table 1
^{1}H (600 MHz) and ^{13}C (150 MHz) NMR spectroscopic data for 1 and 2 (δ in ppm, J values in Hz).

No.	**1**[a]		No.	**2**[b]	
	δ_H	δ_C		δ_H	δ_C
2		158.1	2		165.9
3		138.3	3		114.7
4	7.85 (s)	130.6	4		184.1
5	7.66 (overlapped)	129.8	5		100.2
6	7.97 (d, J = 8.7 Hz)	115.2	6	6.18 (d, J = 2.1 Hz)	163.8
7		160.1	7		166.1
8		112.7	8	6.33 (d, J = 2.1 Hz)	95.1
9		152.0	9		160.0
10		115.0	10		105.7
2′		161.0	1′		126.5
3′	6.41 (d, J = 9.6 Hz)	115.2	2′	7.24 (d, J = 8.7 Hz)	131.9
4′	7.79 (d, J = 9.6 Hz)	144.1	3′	6.66 (d, J = 8.7 Hz)	116.1
5′	7.56 (d, J = 8.4 Hz)	130.5	4′		161.1
6′	7.07 (d, J = 8.4, 1.8 Hz)	114.5	5′	6.66 (d, J = 8.7 Hz)	116.1
7′		160.5	6′	7.24 (d, J = 8.7 Hz)	131.9
8′	7.13 (d, J = 1.8 Hz)	105.6	2″	4.02 (d, J = 7.8 Hz)	83.3
9′		156.4	3″	3.87 (ddd, J = 9.1, 7.8, 5.6 Hz)	69.4
10′		115.8	4″	2.82 (dd, J = 15.8, 5.6 Hz)	29.3
				2.43 (dd, J = 15.8, 9.1 Hz)	
2″		162.1	5″		158.3
3″	6.26 (d, J = 9.3 Hz)	113.1	6″		101.2
4″	7.68 (overlapped)	144.6	7″		156.5
5''	7.42 (d, J = 8.4 Hz)	130.0	8″	6.04 (s)	97.1
6″	7.22 (d, J = 8.4 Hz)	114.0	9″		155.3
7″		161.4	10″		102.1
8″		108.7	1‴		132.6
9″		155.3	2‴	6.72 (d, J = 2.0 Hz)	115.6
10″		112.9	3‴		146.5
1‴	5.80 (d, J = 7.8 Hz)	103.8	4‴		146.4
2‴	4.02 (m)	75.2	5‴	6.68 (d, J = 8.1 Hz)	116.4
3‴	4.33 (m)	79.1	6‴	6.58 (dd, J = 8.1, 2.0 Hz)	120.6
4‴	4.16 (m)	71.8			
5‴	4.19 (m)	79.7			
6‴	4.37 (m)	63.0			
	4.62 (d, J = 12.0 Hz)				

[a] Data were measured in pyridine d_5.
[b] Data were measured in methanol d_4.