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Angustifolinoid A, a macrocyclic flavonoid glycoside from *Elaeagnus angustifolia* flowers

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ABSTRACT

A novel macrocyclic flavonoid glycoside, angustifolinoid A (**1**), featuring an unprecedented 13-membered heterocyclic ring moiety, along with a known flavonoid glycoside, tiliroside (**2**), were isolated from *Elaeagnus angustifolia* flowers. Their structures were determined by extensive spectroscopic analysis and electronic circular dichroism (ECD) calculation. Biosynthesis analysis indicated that compound **1** might be derived from compound **2** via a key enzymatic intramolecular oxidative coupling. Compounds **1** and **2** showed inhibitory activities against cyclooxygenases, COX-1 and COX-2.

Elaeagnus angustifolia L. (Elaeagnaceae) is widely distributed in the northern regions of Asia and Europe.[1] In China, it is mainly planted in the northwest, such as Ningxia, Gansu, and Xinjiang Provinces, for wind break and sand fixation.[2] However, medicinal properties of *E. angustifolia* are also important. It has been used to treat inflammation and asthma, ease fever, release pains and cure ulcers in folk medicines.[3–5] As a traditional Uygur medicine, the flowers of *E. angustifolia* were used to treat disease of abnormal belghem hilit.[6] Previous phytochemical investigation on the flowers of this plant indicated the presence of essential oil and flavonoids, but most of researches focused on the determination of total flavonoids content, little has been reported on the isolation and structural elucidation of the flavonoids.[7–9] In our interesting on bioactive constituents from traditional Uygur medicine,[10,11] a novel macrocyclic flavonoid glycoside named angustifolinoid A (**1**) (Fig. 1), featuring an unprecedented 13-membered heterocyclic ring moiety, and a known flavonoid glycoside, tiliroside (**2**), were isolated from the flowers of *E. angustifolia*. Herein, we present the isolation, structural elucidation, and cyclooxygenase inhibitory activity of the compounds, as well as the plausible biosynthetic pathway of compound **1**.

Compound **1** was obtained as yellow amorphous solid with a $[\alpha]_D^{25}$ + 22 (*c* 0.05, MeOH). Its molecular formula was determined as $C_{30}H_{26}O_{13}$ by the HRESIMS at *m/z* 593.1278 $[M-H]^-$ (calcd for $C_{30}H_{25}O_{13}$, 593.1295), with 18 double-bond equivalents (DBEs). Its IR spectrum showed absorption bands for hydroxyl (3392 cm^{-1}) and carbonyl (1699, 1684 cm^{-1}). The ^1H NMR spectra (Table 1) of **1** showed signals for a set of *meta* aromatic protons at δ_H 6.45 (d, *J* = 1.6 Hz, H-8) and 6.24 (d, *J* = 1.6 Hz, H-6), a set of A_2B_2 system aromatic protons at δ_H 7.01 (d, *J* = 8.4 Hz, H-2‴ and H-6‴) and 6.63 (d, *J* = 8.4 Hz, H-3‴ and H-5‴), and a set of ABX spin system protons at δ_H 8.35 (d, *J* = 2.2 Hz, H-2′), 6.96 (d, *J* = 8.5 Hz, H-5′), and 7.75 (dd, *J* = 8.5, 2.2 Hz, H-6′), as well as some non-aromatic protons signals distributed from δ_H 2.50–5.00 ppm. Analyses of ^{13}C NMR (Table 1) and HSQC spectra revealed the presence of 30 carbon resonances attributable to two methylene, 15 methine, and 13 quaternary carbons (two of which are carbonyls). Notably, the carbon signals at δ_C 109.6, 76.9 (2 × C), 75.9, 72.6, 64.1, implied the presence of glucopyranose unit in compound **1**. Aforementioned NMR data and the UV absorption (205, 269, 357 nm), suggested that compound **1** is likely a 5,7-dihydroxy flavonoid glycoside.

To elucidate the structure of compound **1**, 2D NMR including ^1H-^1H COSY, HSQC, and HMBC, were employed. The HSQC spectrum permitted the assignment of all of the protons to their bonding carbons. The ^1H-^1H COSY and HMBC were then applied to construct the planar structure of compound **1**. The ^1H-^1H COSY

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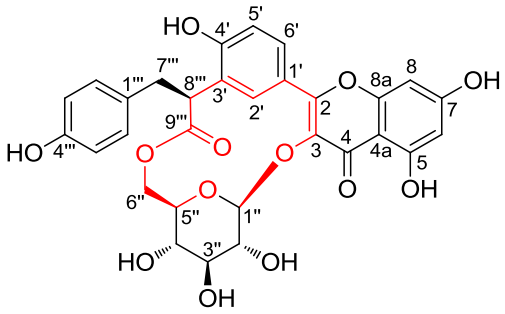


Fig. 1. Chemical structure of compound **1** and **2**.

Table 1
^{1}H and ^{13}C NMR spectroscopic data of **1**.[a]

Position	H (mult; *J*, Hz)	C
2		158.9
3		137.4
4		180.6
4a		105.5
5		163.1
6	6.24 (d, 1.6)	100.3
7		166.6
8	6.45 (d, 1.6)	95.0
8a		158.6
1		121.5
2	8.35 (d, 2.2)	131.4
3		128.2
4		159.5
5	6.96 (d, 8.5)	116.5
6	7.75 (dd, 8.5, 2.2)	129.7
1″	4.22 (d, 7.5)	109.6
2″	3.53 (t, 9.3)	75.9
3″	3.22 (t, 9.0)	76.9
4″	3.27 (t, 9.2)	72.6
5″	3.11 (m)	76.9
6″	4.98 (dd, 11.4, 10.1)	64.1
	3.90 (dd, 11.4, 2.7)	
1‴		131.9
2‴	7.01 (d, 8.4)	131.2
3‴	6.63 (d, 8.4)	115.8
4‴		156.7
5‴	6.63 (d, 8.4)	115.8
6‴	7.01 (d, 8.4)	131.2
7‴	3.14 (dd, 13.9, 8.9)	38.8
	2.75 (dd, 13.9, 5.8)	
8‴	4.47 (dd, 8.9, 5.8)	47.0
9‴		175.2

[a] Data were recorded in CD_3OD at 600 MHz (^{1}H) and 150 MHz (^{13}C).

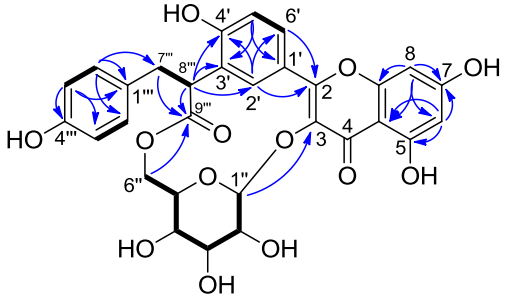
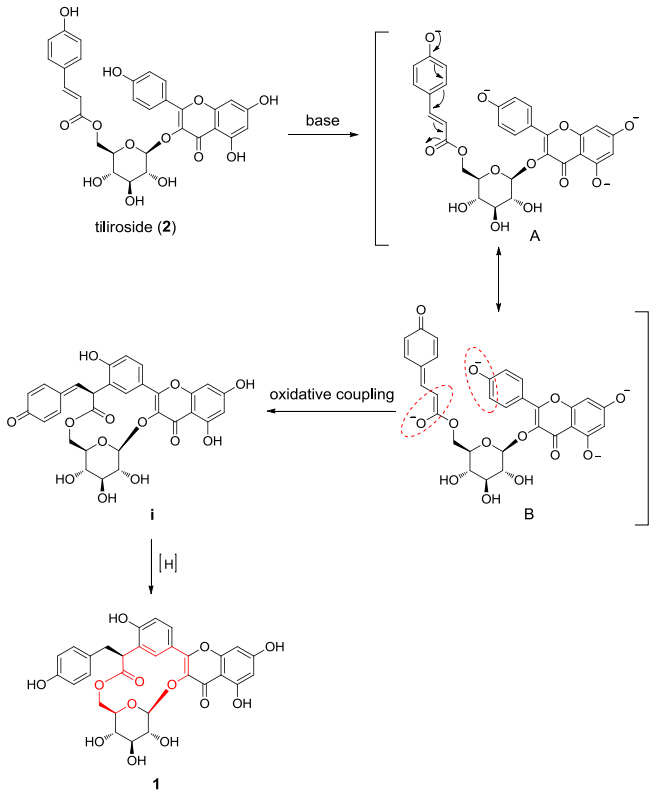


Fig. 2. Key ^{1}H-^{1}H COSY (–) and selected HMBC correlations (H → C) of **1**.

(Fig. 2) continuous correlations from H-1″ to H-6″, disclosed a glucopyranose moiety (C-1″ to C-6″), while other four structure units (drawn with bold bonds in Fig. 2) were also determined by the corresponding ^{1}H-^{1}H COSY correlations. Analysis of the HMBC spectrum enabled the connectivity of these structure units with other functional groups. The HMBC correlations (Fig. 2) from H-6 to C-4a (δ_C 105.5), C-5 (δ_C 163.1) and C-7 (δ_C 166.6), from H-8 to C-4a, C-6 (δ_C 100.3), C-7 and C-8a (δ_C 158.6), further supported the presence of 5,7-dihydroxy flavonoid skeleton. The HMBC correlations from H-2′ to C-2 (δ_C 158.9), C-4′ (δ_C 159.5) and C-6′ (δ_C 129.7), from H-5′ to C-1′ (δ_C 121.5) and C-3′ (δ_C 128.2), and from H-6′ to C-2, indicated that the B ring of the flavonoid was 1,3,4-trisubstituted benzene ring. The glucopyranose moiety was placed at C-3 by the HMBC correlation from H-1″ to C-3 (δ_C 137.4). The presence of a *p*- hydroxyphenylpropionoyl was determined by the HMBC correlations from H-2‴ to C-1‴ (δ_C 131.9), C-6‴ (δ_C 131.2) and C-7‴ (δ_C 38.8), from H-3‴ to C-1‴, C-4‴ (δ_C 156.7) and C-5‴ (δ_C 115.8), and from H-7‴ and H-8‴ to C-9‴ (δ_C 175.2), which was connected to C-6″ of glucose via ester bond by the HMBC correlation from H-6″ to C-9‴. The HMBC correlations from H-8‴ to C-2′ (δ_C 131.4), C-3′ and C-4′, and from H-2′ to C-8‴ (δ_C 47.0), assigned the attachment between C-8‴ and C-3′. Therefore, the planar structure of compound **1** was elucidated as depicted in Fig. 2, featuring an unprecedented 13-membered heterocyclic ring moiety.

Interestingly, a known flavonoid glycoside, tiliroside (**2**), was also isolated from the same fraction, which possessed the same molecular formula and similar structure with compound **1**. Biosynthetic analysis suggested that compound **2** might be a biosynthetic precursor of **1**. Thus, the possible biosynthetic pathway of **1** is postulated in Scheme 1. The compound **2** was transformed to a quinone **B** with several enolates sites in base condition, which would then be converted to intermediate **i** by a key enzymatic intramolecular oxidative coupling.[12] Although there are four enolates in **B**, the two enolates labeled as red cycle in Scheme 1 are readily intramolecular coupling reaction in space. The intermediate **i** was transformed to compound **1** by a reduction. Notably,



Scheme 1. Plausible Biosynthetic Pathway of **1**.