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New anthraquinone glycosides from the roots of *Morinda citrifolia*

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ABSTRACT

Six new anthraquinone glycosides: digiferruginol-1-methylether-11-*O*-β-gentiobioside (**1**); digiferruginol-11-*O*-β-primeveroside (**2**); damnacanthol-11-*O*-β-primeveroside (**3**); 1-methoxy-2-primeverosyloxymethyl-anthraquinone-3-olate (**4**); 1-hydroxy-2-primeverosyloxymethyl-anthraquinone-3-olate (**5**); and 1-hydroxy-5,6-dimethoxy-2-methyl-7-primeverosyloxyanthraquinone (**6**) were isolated from *Morinda citrifolia* (Rubiaceae) roots together with four known anthraquinone glycosides. The structures of the new compounds were established using spectral methods. For five of the new compounds, the sugar is attached *via* the hydroxymethyl group of the anthraquinone C-2 carbon. This type of bond is rarely found for anthraquinone glycosides isolated from natural sources.

1. Introduction

The bush *Morinda citrifolia* L. is a member of the Rubiaceous family and is widely distributed throughout tropical Asia, India, and the Pacific islands. In Japan, it is called "Yaeyama-aoki" and grows in Okinawa Prefecture. Preparations of its roots, stems, bark, leaves, and fruits have been used as antibacterial, antiviral, antifungal, antitumor, antihelmin, analgesic, hypotensive, anti-inflammatory, and immune-enhancing agents; although, their efficacies are unproven [1]. Noni juice, which is made from *M. citrifolia* fruit, has become a popular tonic in recent years since it is reputed to prevent lifestyle-related diseases, such as diabetes, hypertension [2], and arteriosclerosis. In Japan and the USA, noni juice is widely distributed by several companies. As part of our studies on bioactive natural products, we are very interested in those compounds that might prevent or ameliorate lifestyle-related diseases. Previously, we isolated six lignanes from the fruit of *M. citrifolia* that inhibit LDL oxidation [3], which is part of the process leading to arteriosclerosis. We also isolated two anthraquinone glycosides from its roots that decrease blood sugar levels in diabetic mice [4]. Our on-going investigation of the natural products of *M. citrifolia* roots has resulted in the isolation of six new anthraquinone glycosides and the isolation of four known anthraquinone glycosides. We report herein the structures of the new anthraquinone glycosides (Fig. 1).

2. Experimental

2.1. General procedures and plant material

General experimental procedures and plant material have been described [4]. HR-ESI-MS were performed with a Bruker micrOTOF-Q instrument.

2.2. Extraction and Isolation

The extraction and partition processes have been published [4]. The *n*-BuOH soluble phase was chromatographed over Sephadex LH-20 with MeOH as the mobile phase to obtain a mixture of anthraquinone glycosides. This mixture was then repeatedly chromatographed over a SiO_2 column using EtOAc-MeOH-H_2O (90:7:3–85:10:5–77:13:10) and an Rp-18 column using MeOH–H_2O (1:3–1:2) to separate **1** (32 mg), **2** (20 mg), **3** (48 mg), **4** (10 mg), **5** (14 mg), **6** (3 mg) and the four previously characterized anthraquinone glycosides.

Digiferruginol-1-methylether-11-*O*-β-gentiobioside (**1**): Yellow amorphous powder, $[\alpha]_D^{23}$ −54.8° (c = 0.25, MeOH); HR-ESI-MS: m/z [M-H]$^-$ 591.1710 (calcd for $C_{28}H_{31}O_{14}$: 591.1719); IR ν_{max} cm^{-1}: 3391, 2920, 1674, 1553, 1450, 1331, 1275, 1075, 1050, 1028, 968; UV λ_{max}^{MeOH} nm (log ε): 275 (4.12), 255 (4.53),

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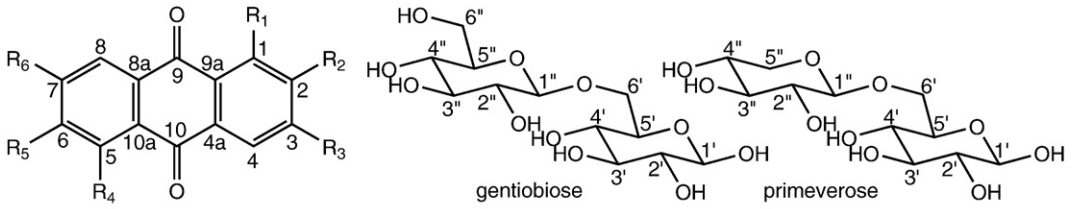

	R_1	R_2	R_3	R_4	R_5	R_6
1	OCH_3	CH_2O-gentiobiose	H	H	H	H
2	OH	CH_2O-primeverose	H	H	H	H
3	OCH_3	CH_2O-primeverose	OH	H	H	H
4	OCH_3	CH_2O-primeverose	O^-	H	H	H
5	OH	CH_2O-primeverose	O^-	H	H	H
6	OH	CH_3	H	OCH_3	OCH_3	O-primeverose

Fig. 1. Chemical structures of compounds **1**–**6**.

209 (4.41); ^{1}H and ^{13}C NMR (400 MHz and 100 MHz, DMSO-d_6): see Tables 1 and 2.

Digiferruginol-11-*O*-β-primeveroside (**2**): Yellow amorphous powder, $[\alpha]_D^{23}$ −23.2° (c = 0.03, MeOH); HR-ESI-MS: m/z [M-H]$^-$ 547.1451 (calcd for $C_{26}H_{27}O_{13}$: 547.1457); IR ν_{max} cm^{-1}: 3395, 1670, 1632, 1590, 1472, 1425, 1353, 1290, 1079, 1048, 1014; UV λ_{max}^{MeOH} nm (log ε): 406 (3.56), 254 (4.32), 223 (4.19), 202 (4.28); ^{1}H and ^{13}C NMR (400 MHz and 100 MHz, DMSO-d_6): see Table 1 and 2.

Damnacanthol-11-*O*-β-primeveroside (**3**): Yellow amorphous powder, $[\alpha]_D^{23}$ −46.2° (c = 0.1, MeOH); HR-ESI-MS: m/z [M-H]$^-$ 577.1550 (calcd for $C_{27}H_{29}O_{14}$: 577.1563); IR ν_{max} cm^{-1}: 3345, 2915, 1667, 1576, 1333, 1281, 1076, 1041, 977; UV λ_{max}^{MeOH} nm (log ε): 275 (4.32), 245 (4.28), 203 (4.37); ^{1}H and ^{13}C NMR (400 MHz and 100 MHz, DMSO-*d*6): see Tables 1 and 2.

1-Methoxy-2-primeverosyloxymethyl-anthraquinone-3-olate (**4**): Yellow amorphous powder, $[\alpha]_D^{23}$ −35.4° (c = 0.1, MeOH/H_2O = 1:1); HR-ESI-MS: m/z [M]$^-$ 577.1548 (calcd for $C_{27}H_{29}O_{14}$: 577.1563); IR ν_{max} cm^{-1}: 3427, 2920, 1666, 1651, 1574, 1558, 1330, 1276, 1076, 1041, 1028, 977; UV λ_{max}^{MeOH} nm (log ε): 278 (4.44), 245 (4.36), 203 (4.43); ^{1}H and ^{13}C NMR (400 MHz and 100 MHz, DMSO-d_6): see Tables 1 and 2.

Acid hydrolysis of **4**: Compound **4** (6 mg) was treated with 5% HCl (6 ml) under reflux for 6 h. The residue was purified by column chromatography on Sephadex LH-20 using MeOH to yield damnacanthol (**4a**) (2 mg). The solution was neutralized with Amberlite IRA and the resin was filtered off. The filtrate was purified by column chromatography on SiO_2 using EtOAc-MeOH–H_2O (90:7:3–85:10:5) to afford D-glucose (1 mg) and D-xylose (1 mg).

Damnacanthol (**4a**): ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.87 (3H, *s*, 1-OCH_3), 4.57 (2H, *s*, H-11), 7.52 (1H, *s*, H-4), 7.84 (1H, *td*, *J* 7.5, 1.5 Hz, H-6), 7.90 (1H, *td*, *J* 7.5, 1.5 Hz, H-7), 8.11 (1H, *dd*, *J* 7.5, 1.5 Hz, H-8), 8.16 (1H, *dd*, *J* 7.5, 1.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 182.56 (C-10), 179.98 (C-9), 162.17 (C-3), 161.66 (C-1), 135.37 (C-10a), 134.60 (C-8a), 134.56 (C-7), 133.36 (C-6), 132.09 (C-4a), 128.80 (C-2), 126.67 (C-8), 126.10 (C-5), 117.85 (C-9a), 109.80 (C-4), 62.40 (C-11), 52.15 (1-OCH_3). 1-Hydroxy-2-primeverosyloxymethyl-anthraquinone-3-olate (**5**): Yellow amorphous powder, $[\alpha]_D^{23}$ −64.3°(c = 0.1, MeOH/H_2O = 1:1); HR-ESI-MS: m/z [M]$^-$ 563.1390 (calcd for $C_{26}H_{27}O_{14}$: 563.1406); IR ν_{max} cm^{-1}: 3429, 1668, 1618, 1588, 1454, 1338, 1308, 1282, 1078, 1041, 964; UV λ_{max}^{MeOH} nm (log ε): 418 (3.56), 280 (4.13), 246 (4.22), 203 (4.29); ^{1}H

Table 1
^{1}H NMR spectral data for compounds **1**–**6** in DMSO-d_6.

No.	1	2	3	4	5	6
1-OH		12.78 (s)			14.08 (s)	12.70 (s)
3	8.10 (d, 8.0)	8.00 (d, 8.0)				7.67 (d, 7.7)
4	8.03 (d, 8.0)	7.74 (d, 8.0)	7.49 (s)	6.77 (s)	6.58 (s)	7.56 (d, 7.7)
5	8.15 (dd, 7.5, 1.5)	8.20 (m)	8.08 (dd, 7.5, 1.4)	8.01 (dd, 7.5, 1.2)	8.04 (dd, 7.6, 1.3)	
6	7.89 (td, 7.5, 1.4)	7.95 (m)	7.81 (td, 7.5, 1.3)	7.68 (td, 7.5, 1.1)	7.70 (td, 7.6, 1.3)	
7	7.93 (td, 7.5, 1.5)	7.95 (m)	7.87 (td, 7.5, 1.4)	7.79 (td, 7.6, 1.2)	7.80 (td, 7.6, 1.3)	
8	8.17 (dd, 7.5, 1.4)	8.25 (m)	8.14 (dd, 7.5, 1.3)	8.11 (dd, 7.6, 1.1)	8.11 (dd, 7.6, 1.3)	7.81 (s)
11	5.00 (d, 14.1)	4.93 (d, 14.8)	4.90 (d, 9.9)	4.74 (d, 9.5)	4.70 (d, 9.8)	2.29 (s)
	4.82 (d, 14.1)	4.76 (d, 14.8)	4.56 (d, 9.9)	4.53 (d, 9.5)	4.48 (d, 9.8)	
1-OCH_3	3.89 (s)		3.87 (s)	3.75 (s)		
5-OCH_3						3.84 (s)
6-OCH_3						3.94 (s)
1′	4.35 (d, 7.6)	4.32 (d, 7.6)	4.32 (d, 7.8)	4.27 (d, 7.4)	4.25 (d, 7.7)	5.17 (d, 7.3)
2′–6′	3.01–4.05 (m)	3.06–3.95 (m)	2.97–3.95 (m)	2.99–3.98 (m)	2.97–3.96 (m)	2.98–3.94 (m)
1″	4.31 (d, 7.8)	4.22 (d, 7.6)	4.31 (d, 7.5)	4.38 (d, 7.6)	4.33 (d, 7.6)	4.13 (d, 7.1)
2″–6″ (5″)	3.01–4.05 (m)	3.06–3.95 (m)	2.97–3.95 (m)	2.99–3.98 (m)	2.97–3.96 (m)	2.98–3.94 (m)

Coupling patterns and coupling constants (*J*) in Hz are given in parentheses.

Table 2
^{13}C NMR spectral data for compounds **1**–**6** in DMSO-d_6.

	1	2	3	4	5	6
1	157.88	158.72	162.58	163.26	165.29	159.42
2	140.41	133.87	125.82	125.38	115.16	132.67
3	134.36	135.17	163.42	177.89	179.33	137.45
4	122.67	118.59	110.11	116.25	117.24	118.35
4a	134.24 [1)]	131.91	133.95	135.57	133.12	132.48
5	126.21	126.86	126.09	126.14	126.12	154.51
6	133.92	134.60	133.30	131.50	132.03	149.07
7	134.60	135.08	134.65[2)]	133.84	134.07	154.90
8	126.75	126.60	126.67	125.11	125.43	100.05
8a	132.12	133.19	134.61[2)]	136.33	135.33	129.59
9	181.60	188.58	179.68	176.07	178.47	187.45
9a	124.97	115.22	117.24	107.71	102.00	114.44
10	182.40	181.77	182.69	185.07	184.21	179.82
10a	134.32[1)]	132.79	132.04	132.32	132.74	121.71
11	64.57	64.04	59.35	59.92	59.62	15.58
1-OCH_3	61.88		62.58	61.31		
5-OCH_3						61.37
6-OCH_3						61.37
1′	102.36	102.53	102.97	102.32	102.33	100.48
2′	73.56	73.41	73.38	72.82	72.99	73.20[3)]
3′	76.86	76.50	76.52	76.60	76.53	76.26[4)]
4′	70.10	69.86	69.97	70.20	70.20	69.49[5)]
5′	76.00	75.93	76.07	76.44	76.26	75.85
6′	68.47	68.23	68.15	68.44	68.47	68.11
1″	103.36	103.90	103.95	103.81	103.82	104.03
2″	73.48	73.30	73.38	73.41	73.40	73.16[3)]
3″	76.76	76.53	76.74	76.60	76.53	76.41[4)]
4″	70.07	69.52	69.59	69.61	69.60	69.32[5)]
5″	76.60	65.52	65.66	65.62	65.61	65.55
6″	61.06					

Symbols [1)–5)] in each column may be interchanged.

and ^{13}C NMR (400 MHz and 100 MHz, DMSO-d_6): see Tables 1 and 2. 1-Hydroxy-5,6-dimethoxy-2-methyl-7-primeverosyloxyanthraquinone (**6**): Yellow amorphous powder, $[\alpha]_D^{23}$ −131.65° (c = 0.1, MeOH); HR-ESI-MS: m/z [M-H]$^-$ 607.1645 (calcd for $C_{28}H_{31}O_{15}$: 607.1668); IR ν_{max} cm^{-1}: 3395, 2915, 1653, 1628, 1576, 1569, 1480, 1457, 1358, 1278, 1072, 1043, 985; UV λ_{max}^{MeOH} nm (log ε): 409 (3.91), 270 (4.56), 219 (4.45); ^{1}H and ^{13}C NMR (400 MHz and 100 MHz, DMSO-d_6): see Tables 1 and 2.

3. Results and discussion

Compound **1** was obtained as yellow amorphous powder. Its methanolic solution has a negative optical rotation ($[\alpha]_D^{23}$ −54.8°). The molecular formula of **1** is $C_{28}H_{32}O_{14}$ as deduced from the data of its HR-negative-ESI-MS. Its IR spectrum has absorption bands arising from a hydroxyl group (3391 cm^{-1}), a conjugated carbonyl group (1674 cm^{-1}), and an aromatic ring (1553, 1450 cm^{-1}). Its UV spectrum contains absorption maxima corresponding to those expected for an anthraquinone skeleton. The ^{1}H NMR spectrum of **1** shows an AA′BB′ coupling system [δ 8.17 (dd, J = 7.5, 1.4 Hz), 8.15 (dd, J = 7.5, 1.5 Hz), 7.93 (td, J = 7.5, 1.5 Hz), and 7.89 (td, J = 7.5, 1.4 Hz)] assigned to a 1,2-disubstituted phenyl group and ortho-coupled proton signals [δ 8.10 and 8.03 (d, J = 8.0 Hz for both signals)]. These observations suggest that one of the aromatic rings of the anthraquinone is unsubstituted and that the other ring possesses two substituents. Oxygen-bearing methylene proton signals at δ 5.00 and 4.82 (d, J = 14.1 Hz for both signals), a methoxy proton signal at δ 3.89 (s), and two anomeric proton signals at δ 4.35 (d, J = 7.6 Hz) and δ 4.31 (d, J = 7.8 Hz) are also present. Carbon signals with chemical shifts of 103.36, 102.36, 76.86, 76.76, 76.60, 76.00, 73.56, 73.48, 70.10, 70.07, 68.47, and 61.06 ppm are present in the ^{13}C NMR spectrum of **1** and correspond to those expected for two glucosyl moieties. In its HMBC spectrum, there is a cross peak between the anomeric proton signal at δ 4.31 and the C-6′ carbon signal at δ 68.47 (Fig. 2), which is consistent with the presence of a gentiobiosyl group [5]. The regiochemistry of the oxygen-bearing methylene, methoxy, and gentiobiosyl groups were determined using the connectivities of the HMBC spectrum. The anomeric proton signal of the gentiobiose at δ 4.35 correlates with the oxygen-bearing methylene carbon signal at δ 64.57. Another connectivity is observed between the methoxy proton signal at δ 3.89 and the aromatic carbon signal of C-1 at δ 157.88. Based on the aforementioned evidence, 1 is digiferruginol-1-methylether-11-*O*-β-gentiobioside. Compound **2** was also isolated as yellow amorphous powder and has a molecular formula of $C_{26}H_{28}O_{13}$ as deduced from the data of its HR-negative-ESI-MS. Its ^{1}H NMR spectrum is similar to that of **1**, except that the signal corresponding to the methoxyl group at δ 3.89 is absent; instead, a signal assignable to a chelated hydroxyl group at δ 12.78 is observed. The NMR data also support the presence of one unsubstituted anthraquinone aromatic ring and one disubstituted anthraquinone ring. The ^{13}C NMR spectrum of **2** differs somewhat from that of **1**. Signals at 102.53, 73.41, 76.50, 69.86, 75.39, and 68.23 ppm could be assigned to glucosyl carbons; whereas the ^{13}C signals at 103.90, 73.30, 76.53, 69.52, and 65.52 ppm are consistent with those expected for a xylosyl moiety. In the HMBC spectrum of **2**, there is a crosspeak involving the xylosyl anomeric proton signal at δ 4.22 and the glucosyl C-6′ carbon signal at δ 68.23; therefore, a primeverosyl group exists [6]. The glycosyl–anthraquinone linkage is β(1′→11) as a cross peak between the anomeric proton at δ 4.32 and the C-11 oxygen-bearing methylene carbon at δ 64.04 exists. Consequently, **2** is digiferruginol-11-*O*-β-primeveroside.

The molecular formula of compound **3** is $C_{27}H_{30}O_{14}$ as determined from the data of its HR-negative-ESI-MS (m/z 577.1550 [M-H]$^-$). For the ^{1}H NMR spectrum of **3**, the presence of an AA′BB′ coupling system and an isolated aromatic proton

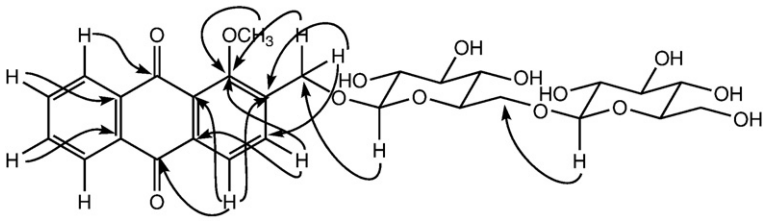

Fig. 2. Main HMBC (Arrows) correlations of **1**.

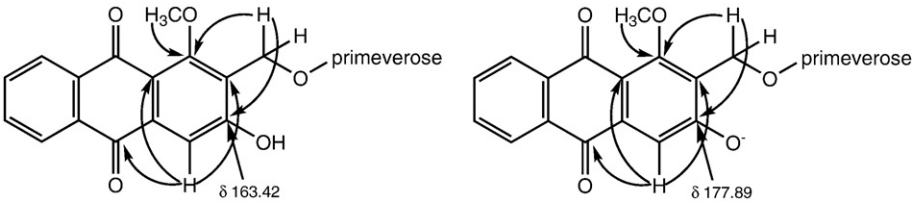

Fig. 3. Key HMBC (Arrows) correlations of **3** and **4**.

signal at δ 7.49 indicates that one anthraquinone aromatic is unsubstituted and the other ring is trisubstituted. A methoxy proton signal at δ 3.87 and oxygen-bearing methylene proton signals at δ 4.90 and 4.56 are also present. That two sugars exist is indicated by the presence of two anomeric proton signals at δ 4.32 and 4.31. The sugar carbon signals of **3** resemble those of **2**, indicating that the sugar is a primeverosyl moiety. The regiochemistry of each functional group was determined using the data of a HMBC experiment (Fig. 3). The isolated aromatic proton signal at δ 7.49 correlates with a carbonyl carbon at δ 182.69, proving that the anthraquinone is 1,2,3-trisubstituted. The anomeric proton signal of the premeverosyl group at δ 4.32 correlates with the oxygen-bearing methylene carbon signal at δ 59.35. The methoxy proton signal at δ 3.87 correlates with the aromatic carbon signal at δ 162.58 (C-1). Other HMBC correlations are shown in Fig. 3. From these observations, **3** is damnacanthol-11-*O*-β-primeveroside.

As found in the HR-negative-ESI-MS of compound **4**, the parent *m*/*z* value is 577.1548 (calcd for $C_{27}H_{29}O_{14}$: 577.1563), which is almost the same value as that found for the parent peak of **3**. The ^{1}H NMR spectrum of **4** is similar to that of **3**, indicating that the anthraquinone is also 1,2,3-trisubstituted, with a methoxy group, a primeverosyloxymethyl group, and an ionized hydroxyl (see below). The types of long-range connectivities found in the HMBC spectrum of **4** (Fig. 3) are almost identical to those found in the spectrum of **3**; however, the C-3 carbon signal of **4** is shifted downfield (177.89 ppm) of the corresponding signal (163.42 ppm) for **3**. This downfield shift indicates that the C-3 hydroxyl is ionized. The presence of ionized hydroxyl group was supported from obtaining damnacanthol (**4a**) as aglycone by the acid hydrolysis of **4**. Therefore, **4** is 1-methoxy-2-primeverosyloxymethyl-anthraquinone-3-olate.

The *m*/*z* of the parent MS peak of **5** is 563.1390 (calcd for $C_{26}H_{27}O_{14}$: 563.1406), which is 14 mass units less than that of **4**. The ^{1}H and ^{13}C NMR spectra of **5** mimic those of 4, except that signals for the methoxy group of **4** (δ 3.75 for the ^{1}H resonance and δ 61.31 for the ^{13}C resonance) are absent and a signal for a chelated hydroxyl group (δ 14.08) is present. Thus, **5** is 1-hydroxy-2-primeverosyloxymethyl-anthraquinone-3-olate. Compound **6** has the molecular formula $C_{28}H_{32}O_{15}$ as deduced from the data of its HR-negative-ESI-MS. Ortho-coupled proton signals at δ 7.67 and 7.56 (d, $J = 7.7$ Hz for both signals) and an isolated aryl proton signal at δ 7.81 (s) are present in the ^{1}H NMR spectrum of **6**. There are also singlets at δ 3.94, 3.84, 2,29, and 12.70 corresponding to two methoxy groups, a methyl group, and a chelated hydroxyl respectively. The ^{13}C-resonances of the sugar moiety of **6** are those expected for a primeverosyl group. An HMBC spectrum of 6 was used to determine the positions of the aforementioned functional groups on the anthraquinone skeleton. The ortho-coupled proton signal at δ 7.67 connects to the signal of a sp^2-type carbon that is attached to a hydroxyl group (δ 159.42) and also connects to a methyl carbon signal at δ 15.58. The other ortho-coupled proton signal at δ 7.56 correlates with the signal of the carbonyl carbon at δ 179.82. Connectivities exist between the isolated aryl proton signal at δ 7.81 and carbon signals at δ 187.45, 154.90, 149.07, 129.59, and 121.71. The two methoxy proton signals at δ 3.94 and 3.84 correlate with carbon signals at δ 149.07 and 154.51, respectively. The primeverosyl group is linked to the anthraquinone C-7 as shown by the existence of a cross peak between the anomeric proton signal at δ 5.17 and the aromatic carbon signal at δ 154.90. Therefore, **6** is 1-hydroxy-5,6-dimethoxy-2-methyl-7-primeverosyloxyanthraquinone. Most interestingly, for the new anthraquinone glycosides, the sugar moieties of compounds 1–5 are attached to the hydroxymethyl group at the C-2 position of the anthraquinone. This type of glycosidic linkage to an anthraquinone is rarely found naturally.

The other four anthraquinone glycosides were identified as lucidin-3-*O*-β-D-glucoside [7], damnacanthol-3-*O*-β-D-glucoside [8], rubiadin-1-methyether-3-*O*-β-primeveroside [9], and soranjidiol-6-*O*-β-primeveroside [10] by comparison of their spectral data with data obtained from the literature.

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