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Original Article

Lignans from *Gymnema sylvestre*

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Abstract: Seven known lignans, tortoside A (1), (+)-syringaresinol (2), (+)-medioresinol (3), (+)-pinoresinol (4), (+)-lyoniresin-6-yl *β*-D-glucopyranoside (5), (-)-lyoniresinol 3*α*-*O*-*β*-D-glucopyranoside (6), and (-)-lyoniresinol (7) were isolated from the leaves of *Gymnema sylvestre* (Retz.) R.Br. ex Schult. Their structures were identified on the basis of spectroscopic evidence and in comparison with those reported in the literature. All compounds were reported from *G. sylvestre* for the first time.

Keywords: Gymnema sylvestre, lignan, NMR.

1. Introduction

In previous papers [1-4], we have reported the isolation and structural elucidation of pregnane glycosides and oleanane saponins from *Gymnema sylvestre.* In continuation of our chemical investigation on *G. sylvestre* species, this paper describes the isolation and structural elucidation of seven known lignans, tortoside A (1), (+)-syringaresinol (2), (+)-medioresinol (3), (+)-pinoresinol (4), (+)-lyoniresin-6-yl *β*-D-glucopyranoside (5), (-)-lyoniresinol 3*α*-*O*-*β*-D-glucopyranoside (6) and (-)-lyoniresinol (7) from the leaves of *G. sylvestre* (Figure 1).

2. Methodology

2.1. Plant Materials

The leaves of *Gymnema sylvestre* (Retz.) R.Br. ex Schult. were collected in Hai Loc, Hai Hau, Nam Dinh in November, 2019, and identified by Dr. Nguyen The Cuong, Institute

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of Ecology and Biological Resources, VAST. A voucher specimen (NCCT-P20) was deposited at the Herbarium of the Institute of Marine Biochemistry, VAST.

2.2. General Experimental Procedures

Optical rotations were determined on a Jasco DIP-370 automatic polarimeter. NMR spectra were recorded on a Bruker AM500FT-NMR spectrometer (500 MHz for ^{1}H-NMR and 125 MHz for ^{13}C-NMR). ESI mass spectra were recorded on an Agilent 6530 Accurate-Mass Q-TOF LC/MS system. Column chromatography was performed using silica gel (Kieselgel 60, 70-230 mesh and 230 - 400 mesh, Merck) or RP-18 resins (150 µm, Fuji Silysia Chemical Ltd.), and thin layer chromatography (TLC) was done by using pre-coated silica-gel 60 F_{254} (0.25 mm, Merck) and RP-18 F_{254S} plates (0.25 mm, Merck).

2.3. Extraction and Isolation

The dried powder of *G. sylvestre* leaves (5.0 kg) was sonicated with methanol at room temperature (3 times × 10 L, each 3 h) to give 550 g extract after evaporation of the solvent. This extract was suspended in H_2O and successively partitioned with *n*-hexane, CH_2Cl_2, and EtOAc to obtain *n*-hexane (GS1, 62.0 g), CH_2Cl_2 (GS2, 74.0 g), and EtOAc extracts (GS3, 43.0 g) and water layer (GS4). The water layer (GS4) was chromatographed on a Diaion HP-20 column eluting with water to remove sugars, then with increasing concentrations of methanol in water (25, 50, 75, and 100%) to obtain four fractions, GS4A-GS4D. Fraction GC4C (12.0 g) was chromatographed on a silica gel column eluting with CH_2Cl_2/MeOH/water (5/1/0.1, v/v/v) to give five fractions, GS4C1-GS4C5. Fraction GS4C2 was chromatographed on a YMC RP-18 column eluting with acetone/water (1/2, v/v) to give two fractions, GS4C2A and GS4C2B. Compounds 1 (12.0 mg) and 2 (18.0 mg) were yielded from fraction GS4C2A using the HPLC system: J'sphere H-80 column (150 × 20 mm), solvent ACN-H_2O (22-78%, v/v) and a flow rate of 3 mL/min).

Fraction GS4C2B was chromatographed by HPLC using the same above conditions but eluting with ACN-H_2O (30-70, v/v) to obtain 3 (13.4 mg) and 4 (15.0 mg). Fraction GS4C4 was chromatographed on a YMC RP-18 column eluting with acetone/water (1/7, v/v) to give four fractions, GS4C4A-GS4C4D. Compounds 5 (11.0 mg) and 6 (10.4 mg) were isolat ed from fraction GS4C4A by using silica gel eluted with CH_2Cl_2/MeOH/water (4/1/0.1, v/v/v). Compound 7 (12.5 mg) was isolated from GS4C4D using an RP-18 column eluted with acetone/water (1/5, v/v).

Tortoside A (1)

White amorphous powder, mp 173-175 °C, $[\alpha]_D^{25}$: + 30.0 (*c* 0.1 MeOH); Lit: $[\alpha]_D^{25}$: + 28.3 [5].

ESI-MS: *m/z* 581 $[M+H]^+$, $C_{28}H_{36}O_{13}$

^{1}H- and ^{13}C-NMR (CD_3OD), see Table 1.

(+)-Syringaresinol (2)

White amorphous powder, mp 180.1-183.5 °C, $[\alpha]_D^{25}$: +44.0 (*c* 0.1, $CHCI_3$).

ESI-MS: *m/z* 419.2 $[M+H]^+$, $C_{22}H_{26}O_8$.

^{1}H- and ^{13}C-NMR (CD_3OD), see Table 1.

(+)-Medioresinol (3)

White amorphous powder, mp 170-172 °C, $[\alpha]_D^{25}$: +77.7 (MeOH; *c* 0.7).

ESI-MS: *m/z* 389.3 $[M+H]^+$, $C_{21}H_{24}O_7$.

^{1}H- and ^{13}C-NMR (CD_3OD), see Table 1.

(+)-Pinoresinol (4)

White amorphous powder, $[\alpha]_D^{25}$: +71.1 (MeOH; *c* 0.1)

ESI-MS: *m/z* 359.1 $[M+H]^+$, $C_{20}H_{22}O_6$.

^{1}H- and ^{13}C-NMR (CD_3OD), see Table 1.

(+)-Lyoniresin-6-yl-*O*-*β*-D-glucopyranoside (5)

White amorphous powder, mp 178-179 °C, $[\alpha]_D^{25}$: +22.7 (MeOH; *c* 0.1).

ESI-MS: *m/z* 583.2 $[M+H]^+$, $C_{28}H_{38}O_{13}$.

^{1}H- NMR (500 MHz, CD_3OD), δ (ppm): 2.63 (1H, dd, J = 6.5, 15.0 Hz, H_a-1), 2.78 (1H, dd, J = 5.0, 15.0 Hz, H_b-1), 1.65 (1H, m, H-2), 2.03 (1H, m, H-3), 4.37 (1H, d, J = 5.5 Hz, H-4), 6.72 (1H, s, H-8), 6.40 (2H, s, H-2′,H-6′), 3.52 (1H, m, H_a-2α), 3.63 (1H, m, H_b-2α), 3.53 (2H, d, J = 5.5 Hz, H-3α), 3.46 (3H, s, 5-OC$\underline{H}_3$), 3.89 (3H, s, 7-OC$\underline{H}_3$), 3.76 (6H, s, 3'-OC$\underline{H}_3$, 5'-OC$\underline{H}_3$), 4.92 (1H, d, J = 7.5 Hz,

H-1′′), 3.41 (1H, dd, *J* = 7.5, 9.0 Hz, H-2′′), 3.45 (1H, t, *J* = 9.0 Hz, H-3′′), 3.45 (1H, t, *J* = 9.0 Hz, H-4′′), 3.19 (1H, m, H -5′′), 3.62 (1H, dd, *J* = 5.0, 12.5 Hz, H_a-6′′), 3.72 (1H, dd, *J* = 2.5, 12.5 Hz, H_b-6′′).

^{13}C-NMR (125 MHz, CD_3OD), *δ* (ppm): 33.7 (C-1), 40.7 (C-2), 48.8 (C-3), 42.2 (C-4), 153.1 (C-5), 138.7 (C-6), 153.1 (C-7), 109.4 (C-8), 136.4 (C-9), 126.8 (C-10), 138.9 (C-1′), 106.9 (C-2′, C-6′), 149.1 (C-3′, C-5′), 134.6 (C-4′), 66.7 (C-2α), 64.2 (C-3α), 61.6 (5-O$\underline{C}H_3$), 57.0 (7-O$\underline{C}H_3$), 56.8 (3'-O$\underline{C}H_3$, 5'-O$\underline{C}H_3$), 104.9 (C-1′′), 75.8 (C-2′′), 77.9 (C-3′′), 71.3 (C-4′′), 78.2 (C-5′′), 62.4 (C-6′′).

(-)-Lyoniresinol 3*α*-*O*-*β*-D-glucopyranoside (6)

White amorphous powder, mp 178-179 ºC, $[\alpha]_D^{25}$: -110.7 (MeOH; *c* 0.7)

ESI-MS: *m/z* 583.2 $[M+H]^+$, $C_{28}H_{38}O_{13}$.

^{1}H-NMR (500 MHz, CD_3OD), *δ* (ppm): 2.69 (1H, dd, *J* = 6.5, 15.0 Hz, H_a-1), 2.70 (1H, dd, *J* = 5.0, 15.0 Hz, H_b-1), 1.71 (1H, m, H-2), 2.16 (1H, m, H-3), 4.25 (1H, d, *J* = 5.5 Hz, H-4), 6.60 (1H, s, H-8), 6.43 (2H, s, H-2′, H-6′), 3.51 (1H, m, H_a-2α), 3.62 (1H, m, H_b-2α), 3.62 (1H, dd, *J* = 5.0, 10.0 Hz, H_a-3α), 3.90 (1H, dd, *J* = 5.5, 10.0 Hz, H_b-3α), 3.36 (3H, s, 5-O$\underline{C}H_3$), 3.87 (3H, s, 7-O$\underline{C}H_3$), 3.76 (6H, s, 3'-O$\underline{C}H_3$, 5'-O$\underline{C}H_3$), 4.16 (1H, d, *J* = 7.5 Hz, H-1′′), 3.21 (1H, dd, *J* = 7.5, 9.0 Hz, H-2′′), 3.38 (1H, t, *J* = 9.0 Hz, H-3′′), 3.30 (1H, t *J* = 9.0 Hz, H-4′′), 3.20 (1H, m, H -5′′), 3.83 (1H, dd, *J* = 12.0, 2.5 Hz, H_a-6), 3.71 (1H, dd, *J* = 12.0, 5.0 Hz, H_b-6).

^{13}C-NMR (125 MHz, CD_3OD), *δ* (ppm): 33.8 (C-1), 41.3 (C-2), 46.6 (C-3), 43.2 (C-4), 147.6 (C-5), 139.5 (C-6), 148.7 (C-7), 107.8 (C-8), 130.2 (C-9), 126.2 (C-10), 138.9 (C-1′), 107.1 (C-2′, C-6′), 149.0 (C-3′, C-5′), 134.6 (C-4′), 66.2 (C-2α), 72.0 (C-3α), 60.1 (5-O$\underline{C}H_3$), 56.6 (7-O$\underline{C}H_3$), 56.9 (3'-O$\underline{C}H_3$, 5'-O$\underline{C}H_3$), 104.3 (C-1′′), 75.1 (C-2′′), 78.2 (C-3′′), 71.6 (C-4′′), 78.0 (C-5′′), 62.7 (C-6′′).

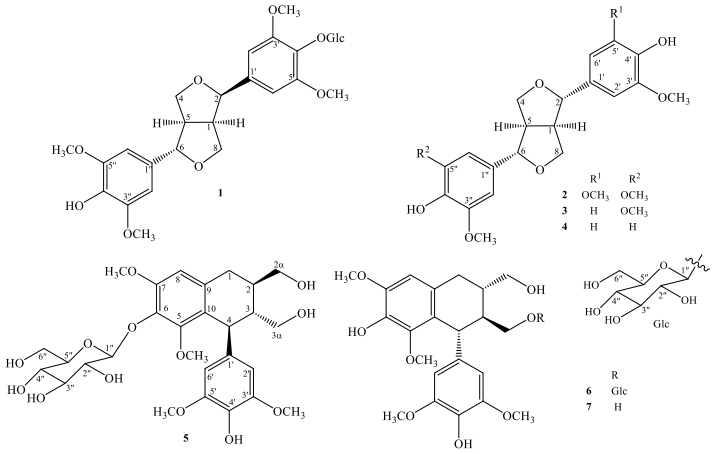

Figure 1. The chemical structures of compounds 1-7.

(-)-Lyoniresinol (7): White amorphous powder; $[\alpha]_D^{25}$ -56.0 (*c* 0.25, MeOH);

ESI-MS: *m/z* 421.2 $[M+H]^+$, $C_{22}H_{28}O_8$.

^{1}H- NMR (500 MHz, CD_3OD), *δ* (ppm): 2.59 (1H, dd, *J* = 6.5, 15.0 Hz, H_a-1), 2.72 (1H, dd, *J* = 5.0, 15.0 Hz, H_b-1), 1.63 (1H, m, H-2), 2.00 (1H, m, H-3), 4.33 (1H, d, *J* = 5.5 Hz, H-4), 6.60 (1H, s, H-8), 6.40 (2H, s, H-2′, H-6′), 3.51 (1H, m, H_a-2α), 3.61 (1H, m, H_b-2α), 3.51 (2H, d, *J* = 5.5 Hz, H-3α), 3.40 (3H, s, 5-O$\underline{C}H_3$), 3.89 (3H, s, 7-O$\underline{C}H_3$), 3.74 (6H, s, 3'-O$\underline{C}H_3$, 5'-O$\underline{C}H_3$).

^{13}C-NMR (125 MHz, CD_3OD), *δ* (ppm):33.6 (C-1), 40.9 (C-2), 49.9 (C-3), 42.3 (C-4), 147.7 (C-5), 138.9 (C-6), 148.7 (C-7), 107.8 (C-8), 130.2 (C-9), 126.2 (C-10), 139.3

(C-1′), 106.9 (C-2′, C-6′), 149.0 (C-3′, C-5′), 134.5 (C-4′), 66.8 (C-2α), 64.2 (C-3α), 60.2 (5-O<u>C</u>H$_3$), 56.6 (7-O<u>C</u>H$_3$), 56.8 (3'-O<u>C</u>H$_3$, 5'-O<u>C</u>H$_3$).

3. Results and Discussion

Compound 1 was found to have the molecular formula $C_{28}H_{36}O_{13}$ from ESI-MS mass spectral and 1D, 2D-NMR data. The ^{1}H-NMR spectrum of 1 (Table 1) clearly indicated the presence of two pairs of *meta* aromatic protons at δ_H 6.68 (s) and 6.74 (s); two oxymethine groups at δ_H 4.74 (1H, d, J = 4.5 Hz) and 4.79 (1H, d, J = 4.5 Hz); two oxymethylene groups at δ_H 3.93 (m) and 4.31 (m); two methine groups at δ_H 3.15 (m), and four aromatic methoxy groups at δ_H 3.87 (s) and 3.88 (s). In addition, a signal of one anomeric proton of a glucose moiety was observed at δ_H 4.88 (d, J = 7.5). The ^{13}C-NMR and DEPT spectra of 1 displayed signals of 28 carbons, including eight non-protonated carbons, thirteen methines, three methylenes, and four methyl carbons. The positions of the functional groups and the sugar moiety were assigned using analysis of the HSQC and HMBC spectra (Table 1). Eight non-protonated carbons at δ_C 133.1 (C), 135.7 (C), 136.3 (C), 139.6 (C), 149.4 (2C), 154.4 (2C), 148,3 (C) and four methines 104.5 (2C), 104.9 (2C) were assigned for two aromatic rings. The six signals of δ_C 55.5 (CH), 87.2 (CH-O), 72.8 (CH$_2$-O), 55.7 (CH), 87.6 (CH-O), 72.9 (CH$_2$-O) were indicated for a bis-tetrahydrofuran ring. The HMBC correlations from H-2′ (δ_H 6.74) to C-2 (δ_C 87.2) and from H-2′′ (δ_H 6.68) to C-6 (δ_C 87.6) were observed confirming that the two benzene rings were linked to C-2 and C-6 of the bis-tetrahydrofuran ring. Thus, the aglycone of 1 was identified to be 2,6-bis (4'-hydroxy-3',5-dimethoxy-phenyl) -3,7-dioxabicyclo [3,3,0] octane. The ^{13}C-NMR data set [δ_C 105.4 (CH), 75.7 (CH), 77.9 (CH), 71.4 (CH), 77.8 (CH) and 62.6 (CH$_2$)] and the multiplicity of the anomeric proton in the ^{1}H-NMR spectrum [δ_H 4.88 (d, J = 7.5)] confirmed that the sugar moiety was β-D-glucopyranosyl. Furthermore, the HMBC correlations between Glc H-1′′′′ (δ_H 4.88) and C-4′ (δ_C 135.7) proved the sugar linkage position at C-4′ of the aglycone. The NMR data and the optical rotation of 1 were compared to those of tortoside A [5] and found to match. Based on the above evidence, the structure of 1 was elucidated as tortoside A, a compound was previously reported from *Pedicularis torta* [5].

Table 1. The ^{1}H- and ^{13}C-NMR data for compounds 1-4

C	1		2		3		4	
	δ_C[a,b]	δ_H[a,c] (mult., J in Hz)	δ_C[a,b]	δ_H[a,c] (mult., J in Hz)	δ_C[a,b]	δ_H[a,c] (mult., J in Hz)	δ_C[a,b]	δ_H[a,c] (mult., J in Hz)
1	55.5	3.15 (m)	54.4	3.09 (m)	55.3	3.12 (m)	55.2	3.09 (m)
2	87.2	4.79 (d, 4.5)	86.1	4.73 (d, 4.5)	87.5	4.69 (d, 4.5)	86.6	4.67 (d, 4.5)
4	72.8	3.93 (m) 4.31 (m)	71.3	3.90 (m) 4.28 (m)	72.6	3.83 (m) 4.23 (m)	72.2	3.79 (m) 4.21 (m)
5	55.7	3.15 (m)	54.4	3.09 (m)	55.6	3.12 (m)	55.2	3.09 (m)
6	87.6	4.74 (d, 4.5)	86.1	4.73 (d, 4.5)	87.7	4.69 (d, 4.5)	86.6	4.67 (d, 4.5)
8	72.9	3.93 (m) 4.31 (m)	71.3	3.90 (m) 4.28 (m)	72.7	3.83 (m) 4.23 (m)	72.2	3.79 (m) 4.21 (m)
1'	139.6	-	132.3	-	133.8	-	134.1	-
2'	104.9	6.74 (s)	102.8	6.58 (s)	111.0	6.93 (br s)	110.6	6.99 (d, 2.0)
3'	154.4	-	148.2	-	149.1	-	148.3	-
4'	135.7	-	134.5	-	147.3	-	146.9	-
5'	154.4	-	148.2	-	116.1	6.74 (d, 8.0)	115.5	6.79 (d, 8.0)
6'	104.9	6.74 (s)	102.8	6.58 (s)	120.1	6.79 (d, 8.0)	119.6	6.84 (dd, 2.0.

								8.0)
3'-OMe	59.6	3.88 (s)	56.4	3.90 (s)	56.4	3.82 (s)	56.2	3.84 (s)
5'-OMe	59.6	3.88 (s)	56.4	3.90 (s)				
1"	133.1	-	132.3	-	133.1	-	134.1	-
2"	104.5	6.68 (s)	102.8	6.58 (s)	104.5	6.63 (s)	110.6	6.99 (d, 2.0)
3"	149.4	-	148.2	-	149.3	-	148.3	-
4"	136.3	-	134.5	-	136.2	-	146.9	-
5"	149.4	-	148.2	-	149.3	-	115.5	6.79 (d, 8.0)
6"	104.5	6.68 (s)	102.8	6.58 (s)	104.5	6.63 (s)	119.6	6.84 (dd, 2.0. 8.0)
3"-OMe	57.1	3.87 (s)	56.4	3.90 (s)	56.8	3.82 (s)	56.2	3.84 (s)
5"-OMe	57.1	3.87 (s)	56.4	3.90 (s)	56.8	3.82 (s)		
4′-*O*-Glc								
1"'	105.4	4.88 (d, 7.5)						
2"'	75.7	3.49 (dd, 7.5, 9.0)						
3"'	77.9	3.43 (t, 9.0)						
4"'	71.4	3.43 (t, 9.0)						
5"'	78.4	3.22 (m)						
6"'	62.6	3.68 (dd, 5.5, 12.0) 3.80 (dd, 2.5, 12.0)						

Recorded in [a]CD_3OD, [b]125 MHz, [c]500 MHz, Glc: β-D-glucopyranosyl.

Compound 2 was obtained as a white amorphous powder. The NMR spectra of 2 were similar to the corresponding spectra of 1, except for the loss of the sugar moiety signals in the NMR spectra of 2. The ^{1}H-NMR spectrum of 2 exhibited the following proton signals: two *meta* aromatic protons at δ_H 6.58 (s), one oxymethine group at δ_H 4.73 (d, J = 4.5 Hz), one oxymethylene group at δ_H 3.90 (m) and δ_H 4.28 (m), one methine groups at δ_H 3.09 (m), and two aromatic methoxyl groups at δ_H 3.90 (s). The ^{13}C-NMR and DEPT spectra of 2 displayed tetra-substituted aromatic signals at δ_C 102.8 (2xCH), 132.3 (C), 134.5 (C), and 148,2 (2xC), and the bis-tetrahydrofuran ring signals at δ_C 56.4 (2xOCH_3), 54.4 (CH), 86.1 (CH-O), 71.3 (CH_2-O). The chemical shift values of H-C were accurately assigned and given in Table 1 based on HSQC spectra. In addition, the existence of two groups CH(O)-CH-CH_2(O) was determined from the ^{1}H-^{1}H COSY cross peaks of H-1/H-2/H-8 and H-4/H-5/H-6. Besides, the HMBC correlations from H-1 (δ_H 3.09) to C-5 (δ_C 54.4), from H-2 (δ_H 4.67) to C-1 (δ_C 54.4)/ C-4 (δ_C 71.3), and from H-4 (δ_H 4.28 /3.90) to C-2 (δ_C 86.1)/C-5 (δ_C 54.4) were observed. The above evidence confirmed that the two aromatic rings were attached to C-2 and C-6 of the bis-tetrahydrofuran ring. In addition, the ESI-MS mass spectrometry of 2 exhibited the ion peak at *m/z* 419.2 $[M+H]^+$, corresponding to the molecular formula of $C_{22}H_{26}O_8$. This result showed that the molecule of compound 2 was symmetrical with the second axis and was completely consistent with NMR spectra. The HMBC correlations from the methoxy protons (δ_H 3.90) to C-3'/C-5' (δ_C 148.2), from H-2 (δ_H 4.73) to C-1'/C-1" (δ_C 132.3), and from H-1 (δ_H 3.09) to C-1' (δ_C 132.3) demonstrated the structure of compound 2 as shown in Fig. 1. Based on the above evidence and the matching of the optical

rotations of 2 with those of the reported compound, compound 2 was elucidated as (+)-syringaresinol [6].

Compounds 3-7 were identified as (+)-medioresinol,[7] (+)-pinoresinol [8] (+)-lyoniresin-6-yl-*O*-*β*-D-glucopyranoside [9], (-)-lyoniresinol 3*α*-*O*-*β*-D-glucopyranoside [10], and (-)-lyoniresinol [11] by comparing their NMR data and the optical rotations with the corresponding data reported in the literature, and further confirmed by their ESI-MS, HSQC and HMBC spectra. To the best of our knowledge, this is the first time these compounds were isolated from *G. sylvestre*.

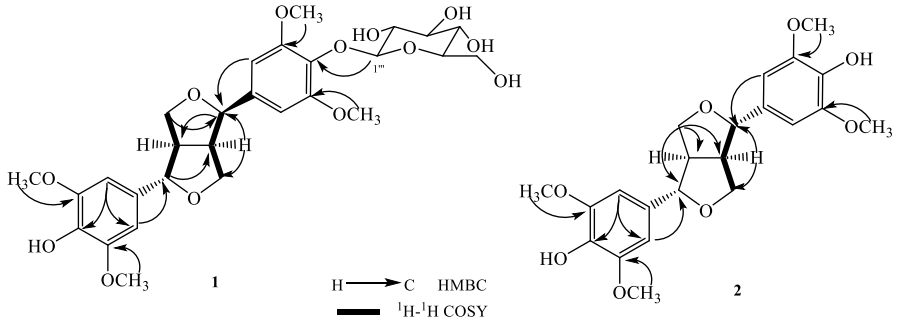

Figure 2. The key HMBC and ^{1}H-^{1}H COSY correlations of compounds 1 and 2.

4. Conclusion

Gymnema sylvestre is a medicinal plant used in folk medicine for diabetes. By the combination of various chromatographic methods, seven lignans, tortoside A (1), (+)-syringaresinol (2), (+)-medioresinol (3), (+)-pinoresinol (4), (+)-lyoniresin-6-yl *β*-D-glucopyranoside (5), (-)-lyoniresinol 3*α*-*O*-*β*-D-glucopyranoside (6), and (-)-lyoniresinol (7) were isolated for the first time from the leaves of this plant. Their structures were identified on the basis of spectroscopic evidence and in comparison with those reported in the literature.

Acknowledgements

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