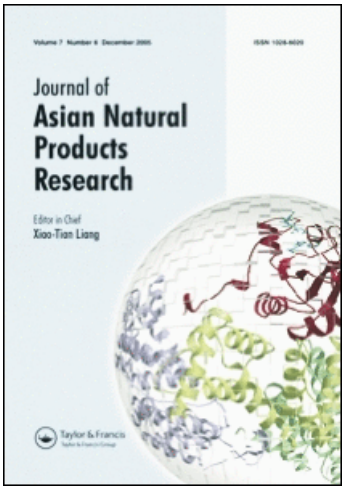

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New phenethyl alcohol glycosides from *Stachys parviflora*

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Phytochemical investigations of the whole plant of *Stachys parviflora* (Lamiaceae) resulted in the isolation of two new phenethyl alcohol glycosides. The structures of the new compounds named parviflorosides A and B were established as 2-(3,4-dihydroxyphenyl)-ethyl-*O*-α-L-rhamnopyranosyl-(1 → 2)-4-*O*-*E*-caffeoyl-β-D-glucopyranoside **(1)** and 2-(3,4-dihydroxyphenyl)-ethyl-*O*-α-L-rhamnopyranosyl-(1 → 2)-6-*O*-*E*-caffeoyl-β-D-glucopyranoside **(2)**, respectively. The structure elucidation of the new compounds was based primarily on 1D and 2D NMR analysis, including COSY, HMBC and HMQC correlations.

Keywords: *Stachys parviflora*; Lamiaceae; Phenethyl alcohol glycosides; 1D NMR spectroscopy; 2D NMR spectroscopy

1. Introduction

Stachys parviflora, commonly known as "Baggibuti", belongs to the Lamiaceae (Mint) family, distributed in the tropical and temperate regions of Pakistan [1]. Previous phytochemical investigations of genus revealed the presence of alkaloids, glucosides [2], terpenoids [3], flavonoids [4], phenethyl alcohol glycosides [5] and saponins. Phenethyl alcohol glycosides are widely distributed in the plant kingdom and have been found to have various biological activities, such as antibacterial [6], anti-feedant [7], cytotoxic [8], enzyme inhibitory activity against AMP phosphodiesterase and 5-lipoxygenase [9,10]. In this paper we describe the isolation and characterisation of two new phenethyl alcohol glycosides, **1** and **2**.

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2. Results and discussion

The two new phenethyl alcohol glycosides are closely related to verbascoside [11] and stachysosides A, B and C [12], the only difference being in the nature of the sugars and their linkages, since all such compounds have common caffeic acid and 3,4-dihydroxy phenyl ethanol units.

The BuOH-soluble fraction yielded compound **1**, which was recognised as phenethyl alcohol glycoside. It displayed pseudo molecular ion peak at *m/z* 625.5998 $[M + H]^+$ in its HR-MS spectrum. This information, combined with NMR data, allowed its molecular formula to be assigned as $C_{29}H_{36}O_{15}$. Its molecular formula was confirmed by observation of FAB mass spectrum. The positive-ion FAB mass spectrum exhibited the protonated molecular ion peak at *m/z* 625 and negative ion FAB mass spectrum exhibited the molecular ion peak at *m/z* 623, which confirms the mass of compound **1** as 624. The fragment ions at *m/z* 471 $[(M + H)\text{-aglycone}]^+$, 325 $[(M + H)\text{-(aglycone-Rham)}]^+$ and 163 $[(M + H)\text{-(aglycone-Rham-Glc)}]^+$ in the FAB-MS confirmed the presence of two sugar moieties in the

Table 1. NMR data of compound **1** in CD_3OD-d_4 (500 MHz for ^1H, 125 for ^{13}C, δ in ppm).

Carbon no.	*C[a] (multiplicity)*	δ_C	δ_H (*J in Hz*)
Aglycone			
1′	C	131.5	
2′	CH	116.3	6.68 (d, $J = 1.7$)
3′	C	144.7	
4′	C	146.1	
5′	CH	117.1	6.65 (d, $J = 8.0$)
6′	CH	121.3	6.56 (dd, $J = 7.9, 1.7$)
α′	CH_2	72.3	3.82 (dt, $J = 11.4, 7.9$)
β′	CH_2	36.6	2.80 (t, $J = 7.9$)
Caffeic acid			
1″	C	127.7	
2″	CH	115.2	7.04 (d, $J = 1.7$)
3″	C	146.8	
4″	C	149.8	
5″	CH	116.5	6.78 (d, $J = 8.1$)
6″	CH	123.2	6.93 (dd, $J = 8.2, 1.8$)
γ	CH	148.0	7.60 (d, $J = 15.8$)
β	CH	114.7	6.28 (d, $J = 15.8$)
α	C	168.3	
Glucose			
1	CH	104.2	4.37 (d, $J = 7.8$)
2	CH	81.6	3.38 (t, $J = 8.4$)
3	CH	76.2	3.60 (m)
4	CH	72.0	4.90 (t, $J = 9.3$)
5	CH	76.1	3.89 (m)
6	CH_2	62.4	3.75 (m)
			3.90 (m)
Rhamnose			
1″	CH	103.3	5.10 (s)
2″	CH	70.4	3.49 (m)
3″	CH	72.4	3.58 (m)
4″	CH	73.8	3.44 (m)
5″	CH	70.6	4.03 (m)
6″	CH_3	18.4	1.09 (d, $J = 6.6$)

[a] Assignment based on HMQC experiments.

molecule. Its IR spectrum exhibited absorptions of hydroxyls at ν_{max} (3454), α,β unsaturated ester (1702), C═C (1667) and aromatic rings (1604 and 1524 cm^{-1}).

The ^{13}C NMR spectrum of compound **1** (table 1) showed the presence of 29 carbons, which were resolved through DEPT experiment as one methyl, three methylene, 18 methine and seven quaternary carbons.

The ^{1}H NMR and ^{13}C NMR spectra of **1** exhibited signals arising from caffeic acid and 3,4-dihydroxy phenethyl alcohol moieties showing two ABX signals due to aromatic protons at δ 6.56 (dd, $J = 7.9$, 1.7 Hz), 6.65 (d, $J = 8.0$ Hz), 6.68 (d, $J = 1.7$ Hz) and δ 6.93 (dd, $J = 8.2$, 1.8 Hz), 6.78 (d, $J = 8.1$ Hz), 7.04 (d, $J = 1.7$ Hz), which were assigned to δ 121.25 (C-6′), 117.11 (C-5′), 116.30 (C-2′) and 123.20 (C-6″), 116.51 (C-5″), 115.23 (C-2″) respectively via HMQC correlation, which were also supported by $^{1}H-^{1}H$ COSY 45° and HMBC interactions [12]. A pair of *trans*-olefinic proton signals at δ 6.28 and 7.60 (each 1H, d, $J = 15.8$ Hz) resonated at δ 114.72 (C-β) and 148.00 (C-γ) and benzylic methylene proton signal at δ 2.80 (t, $J = 7.9$ Hz) assigned to δ 36.57 (C-β′) due to HMQC interaction [12,13].

Additionally a doublet and a singlet in ^{1}H NMR attributed to sugar anomeric protons observed at δ 4.37 (1H, d, $J = 7.8$ Hz, Glc-1) and 5.10 (1H, s, Rham-1‴) and resonated at δ 104.21 (C-1) and 103.02 (C-1‴) in ^{13}C NMR, respectively. The ^{1}H NMR spectrum also showed the presence of a secondary methyl group at δ 1.09 (3H, d, $J = 6.6$ Hz) which

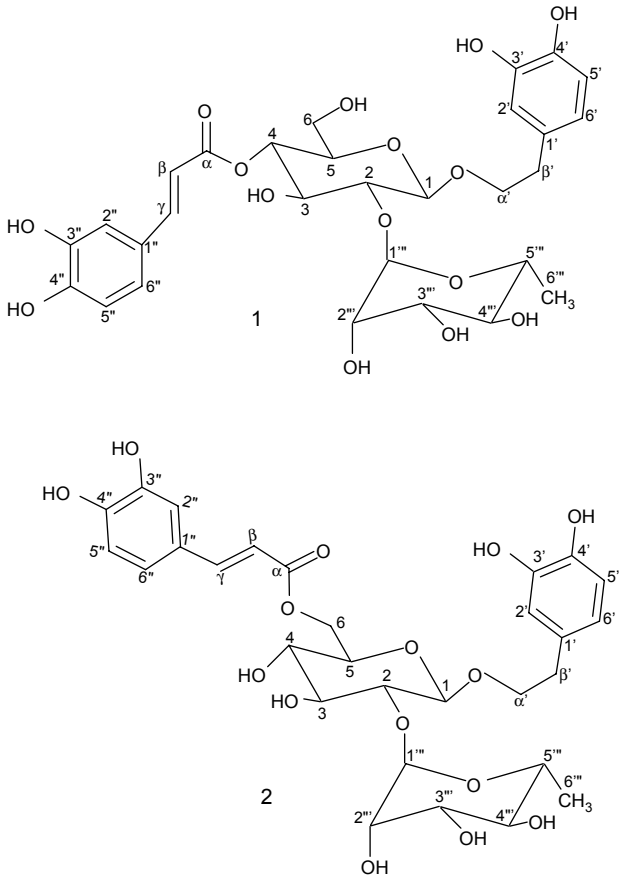

Figure 1. Structures of compounds **1** and **2**.

indicated the presence of rhamnose in the compound. The 1.9 ppm up-field shift of C-4 in the ^{13}C NMR spectrum indicated the attachment of caffeic acid moiety to C-4 of the glucose, this was also supported by the HMBC correlation of H-4 (δ 4.90, *t*, $J = 9.3$ Hz) and C-α (δ 168.28) of the caffeic acid [14]. The downfield shift of C-2 of glucose at δ 81.63 indicated the attachment of rhamnose to C-2 due to strong HMBC correlation of H-1‴ (δ 5.10) to δ 81.63 which was necessarily assigned to C-2 of glucose (1H, δ 3.38, *t*, $J = 8.4$ Hz, H-2) [11,15–17] from its coupling constant and ^{1}H–^{1}H COSY experiment with H-1 (δ 4.37) and H-3 (δ 3.60) of the glucose.

In light of all the above considerations, the structure of **1** was revealed as 2-(3,4-dihydroxyphenyl)-ethyl-*O*-α-L-rhamnopyranosyl-(1 → 2)-4-*O*-*E*-caffeoyl-β-D-glucopyranoside (figures 1 and 2).

Parvifloroside B (**2**) was similar to **1**, the only difference being the presence of caffeoyl moiety at C-6 of glucose rather than C-4 observed by downfield shift of C-6 (δ 64.63), which was further proved by HMBC correlation of H-6 at (δ 4.49, 4.34) with C-α at (δ 169.13) [18] (figure 3, table 2). The attachment of diglucosyl moiety with the aglycone was confirmed by ^3J interaction of H-1 (δ 4.37) of the substituted glucose to C-α′ (δ 72.26) of the aglycone.

Treatment of compounds **1** and **2** with aqueous 0.1 N HCl under refluxing conditions yielded aglycone, rhamnose and glucose as detectable sugars on TLC.

All these commutative results confirmed the structure of compound **2** as 2-(3,4-dihydroxyphenyl)-ethyl-*O*-α-L-rhamnopyranosyl-(1 → 2)-6-*O*-*E*-caffeoyl-β-D-glucopyranoside.

3. Experimental

3.1 General experimental procedures

For column chromatography, silica gel, 70–230 mesh and TLC were carried out on Merck silica gel plates and using the indicated solvents: BAW = 12:3:5 and detected at 254 nm, as well as by ceric sulphate reagent. The IR and UV spectra were recorded on a Jasco-320-A and Hitachi-UV-240, respectively. FAB-MS spectra were recorded on a double focusing Varian MAT-312 spectrometer. ^{1}H NMR and ^{13}C NMR, COSY, HMQC, HMBC spectra in CD_3OD for compounds **1** and **2** at 500 and 125 MHz, respectively, were recorded using an AM 500 Bruker Spectrometer. Chemical shifts (δ) are in ppm and coupling constants in Hz.

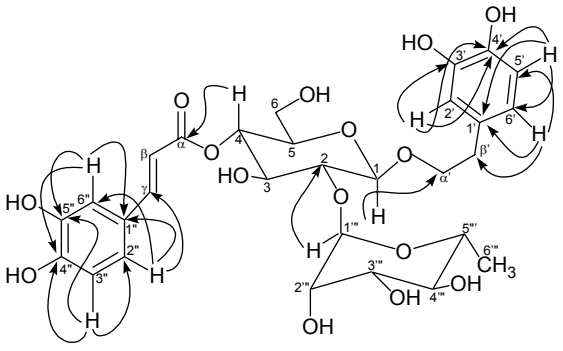

Figure 2. Selected HMBC correlations of compound **1**.

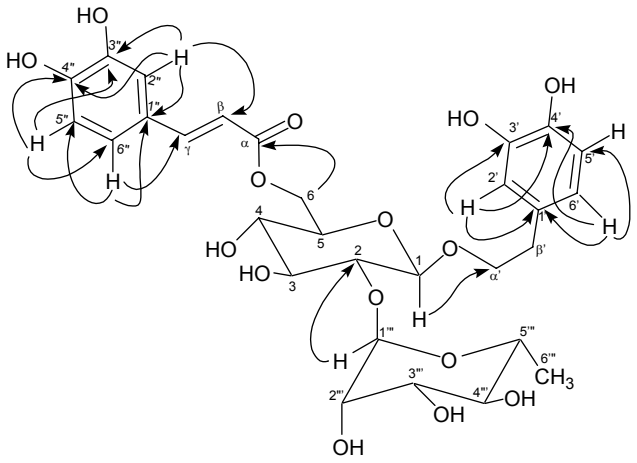

Figure 3. Selected HMBC correlations of compound **2**.

Table 2. NMR data of compound **2** in CD_3OD-d_4 (500 MHz for ^1H, 125 for ^{13}C, δ in ppm).

Carbon no.	*C[a] (multiplicity)*	δ_C	δ_H *(J in Hz)*
Aglycone			
1′	C	131.4	
2′	CH	116.4	6.66 (d, $J = 1.6$)
3′	C	144.7	
4′	C	146.1	
5′	CH	117.1	6.61 (d, $J = 8.0$)
6′	CH	121.3	6.51 (dd, $J = 8.0, 1.6$)
α′	CH_2	72.4	3.92 (m)
β′	CH_2	36.7	2.77 (t, $J = 7.2$)
Caffeic acid			
1″	C	127.7	
2″	CH	115.1	7.02 (d, $J = 1.6$)
3″	C	146.8	
4″	C	149.9	
5″	CH	116.5	6.74 (d, $J = 8.1$)
6″	CH	123.2	6.89 (dd, $J = 8.1, 1.6$)
α	CH	148.0	7.56 (d, $J = 15.8$)
β	CH	114.7	6.26 (d, $J = 15.8$)
γ	C	169.1	
Glucose			
1	CH	104.4	4.31 (d, $J = 7.8$)
2	CH	82.9	3.39 (t, $J = 8.9$)
3	CH	75.4	3.58 (m)
4	CH	70.0	3.93 (t, $J = 9.3$)
5	CH	75.7	3.32 (m)
6	CH_2	64.6	4.49 (dd, $J = 11.8, 1.6$)
			4.34 (d, $J = 11.9$)
Rhamnose			
1″	CH	102.7	5.16 (s)
2″	CH	72.3	3.99 (m)
3″	CH	72.4	3.58 (m)
4″	CH	73.9	3.44 (m)
5″	CH	70.4	4.03 (m)
6″	CH_3	17.9	1.28 (d, $J = 6.2$)

[a] Assignment based on HMQC experiments.

3.2 Plant material

The whole plant of *Stachys parviflora* (Lamiaceae) (18 kg) was collected from Quetta, Balochistan, Pakistan, in 2002, and was identified by one of us (R.B.T.). A voucher specimen (no.1572) has been deposited at the herbarium of the Botany Department, Balochistan University, Quetta.

3.3 Extraction and isolation

The shade-dried plant material (18 kg) was crushed and extracted three times with methanol (20 L each) at room temperature. The resulting methanol extract (304 g) was suspended in water and successively partitioned to provide *n*-hexane (50 g), chloroform (68 g), ethyl acetate (85 g), and *n*-butanol (45 g) fractions. The butanolic extract was subjected to column chromatography (CC) on silica gel column using a gradient of MeOH in $CHCl_3$. The fraction eluted with 30–40% methanol in $CHCl_3$ showed the presence of two partially overlapped yellow spots on TLC (*n* BuOH/AcOH/H_2O, 12:3:5) along with few impurities. The fraction was then subjected to Sephadex LH-20 and eluted with pure methanol; the resulting fraction contained two yellow spots free from impurities. From this fraction, compounds **1** and **2** were purified on recycling HPLC using a reverse-phase semi-preparative M-80 column. Elution was carried out at a flow rate of 4 ml/min under isocratic conditions with MeOH/H_2O (50:50). The peaks were detected by UV and RI detectors. The peaks obtained at retention time of 44 min and 48 min were due to compounds **1** (20 mg) and **2** (15 mg), respectively.

3.3.1 Parvifloroside A (1). Yield: 20 mg. Off-white amorphous powder, $C_{29}H_{36}O_{15}$; $R_f = 0.44$ (BAW), $[\alpha]_D^{25} - 14$ (*c* 0.01, MeOH); UV λ_{max}^{MeOH} (nm): 277, and 336 nm. Its IR spectrum (KBr) (cm^{-1}) exhibited absorptions at ν_{max} 3454, 1702, 1667, 1604 and 1524; ^{1}H NMR (500 MHz, CD_3OD-d_4) δ (ppm): 6.68 (1H, d, $J = 1.7$ Hz, H-2′), 6.65 (1H, d, $J = 8.0$ Hz, H-5′), 6.56 (1H, dd, $J = 7.9$,1.7 Hz, H-6′), 3.82 (2H, dt, $J = 11.4$, 7.9 Hz, H-α′), 2.80 (2H, *t*, $J = 7.9$ Hz, H-β′), 7.04 (1H, d, $J = 1.7$ Hz, H-2″), 6.78 (1H, d, $J = 8.1$ Hz, H-5″), 6.93 (2H, dd, $J = 8.2$, 1.8 Hz, H-6″), 7.60 (1H, d, $J = 15.8$ Hz, H-γ), 6.28 (1H, d, $J = 15.8$ Hz, H-β), 4.37 (1H, d, $J = 7.8$ Hz, Glc-1), 3.38 (1H, *t*, $J = 8.4$ Hz, Glc-2), 3.60 (m, Glc-3), 4.90 (1H, *t*, $J = 9.3$ Hz, Glc-4), 3.89 (m, Glc-5), 3.75, 3.90 (m, Glc-6), 5.10 (1H, s, Rham-1‴), 3.49 (m, Rham-2‴), 3.58 (m, Rham-3‴), 3.44 (m, Rham-4‴), 4.03 (m, Rham-5‴), 1.09 (3H, d, $J = 6.6$ Hz, Rham-6‴); ^{13}C NMR (125 MHz, CD_3OD-d_4) δ (ppm): 131.48 (C-1′), 116.30 (C-2′), 144.68 (C-3′), 146.14 (C-4′), 117.11 (C-5′), 121.25 (C-6′), 72.26 (C-α′), 36.57 (C-β′), 127.67 (C-1″), 115.23 (C-2″), 146.84 (C-3″), 149.79 (C-4″), 116.51 (C-5″), 123.20 (C-6″), 148.00 (C-γ), 114.72 (C-β), 168.28 (C-α), 104.21 (Glc-1), 81.63 (Glc-2), 76.22 (Glc-3), 72.04 (Glc-4), 76.05 (Glc-5), 62.38 (Glc-6), 103.32 (Rham-1‴), 70.40 (Rham-2‴), 72.35 (Rham-3‴), 73.80 (Rham-4‴), 70.60 (Rham-5‴), 18.44 (Rham-6‴); Positive FAB-MS: *m/z* 625, Negative FAB-MS *m/z* 623, 471 $[(M + H)\text{-aglycone}]^+$, 325 $[(M + H)\text{-(aglycone-Rham.)}]^+$ and 163 $[(M + H)\text{-(aglycone-Rham-Glc)}]^+$; HR-MS *m/z* 625.5998 $[M + H]^+$ (calcd for $C_{29}H_{36}O_{15} + H^+$, 625.6023).

3.3.2 Parvifloroside B (2). Yield: 15 mg. Off-white amorphous powder, $C_{29}H_{36}O_{15}$; $R_f = 0.45$ (BAW), $[\alpha]_D^{25} - 16$ (*c* 0.01, MeOH); UV λ_{max}^{MeOH} (nm): 277, and 336 nm. Its IR

spectrum (KBr) (cm^{-1}) exhibited absorptions at ν_{max} 3454, 1702, 1667, 1604 and 1524; ^{1}H NMR (500 MHz, CD_3OD-d_4) δ (ppm): 6.66 (1H, d, $J = 1.6$ Hz, H-2′), 6.61 (1H, d, $J = 8.0$ Hz, H-5′), 6.51 (1H, dd, $J = 8.0$,1.6 Hz, H-6′), 3.9 2 (2H, m, H-α′), 2.77 (2H, *t*, $J = 7.2$ Hz, H-β′), 7.02 (1H, d, $J = 1.6$ Hz, H-2″), 6.74 (1H, d, $J = 8.1$ Hz, H-5″), 6.89 (2H, dd, $J = 8.1$, 1.6 Hz, H-6″), 7.56 (1H, d, $J = 15.8$ Hz, H-γ), 6.26 (1H, d, $J = 15.8$ Hz, H-β), 4.31 (1H, d, $J = 7.8$ Hz, Glc-1), 3.39 (1H, *t*, $J = 8.9$ Hz, Glc-2), 3.58 (m, Glc-3), 3.93 (1H, *t*, $J = 9.3$ Hz, Glc-4), 3.32 (m, Glc-5), 4.49 (1H, dd, $J = 11.8$, 1.6 Hz, Glc-6a), 4.34 (1H, d, $J = 11.9$ Hz, Glc-6b), 5.16 (1H, s, Rham-1‴), 3.99 (m, Rham-2‴), 3.58 (m, Rham-3‴), 3.44 (m, Rham-4‴), 4.03 (m, Rham-5‴), 1.28 (3H, d, $J = 6.2$ Hz, Rham-6‴); ^{13}C NMR (125 MHz, CD_3OD-d_4) δ (ppm): 131.40 (C-1′), 116.35 (C-2′), 144.67 (C-3′), 146.14 (C-4′), 117.07 (C-5′), 121.25 (C-6′), 72.43 (C-α′), 36.69 (C-β′), 127.66 (C-1″), 115.06 (C-2″), 146.76 (C-3″), 149.98 (C-4″), 116.54 (C-5″), 123.20 (C-6″), 148.00 (C-γ), 114.72 (C-β), 169.13 (C-α), 104.40 (Glc-1), 82.91 (Glc-2), 75.43 (Glc-3), 70.04 (Glc-4), 75.70 (Glc-5), 64.63 (Glc-6), 102.72 (Rham-1‴), 72.25 (Rham-2‴), 72.35 (Rham-3‴), 73.95 (Rham-4‴), 70.37 (Rham-5‴), 17.86 (Rham-6‴); Positive FAB-MS: *m/z* 625, Negative FAB-MS *m/z* 623, 471 $[(M + H)$-aglycone$]^+$, 325 $[(M + H)$-(aglycone-Rham)$]^+$ and 163 $[(M + H)$-(aglycone-Rham-Glc)$]^+$; HR-MS *m/z* 625.5996 $[M + H]^+$ (calcd for $C_{29}H_{36}O_{15} + H^+$, 625.6023).

3.4 Acid hydrolysis of compounds 1 and 2

Each glycoside (5 mg each) was refluxed with 0.1 N aq. HCl for 3 h at 100°C. On cooling, the aglycone was extracted with AcOEt and sugars were isolated from the aqueous layer in the usual way and identified by co-TLC with authentic samples under the standard solvent system EtOAc/MeOH/HOAc/H_2O (11:2:2:2).

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