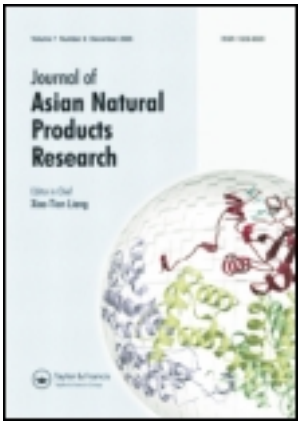

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Salvicins A and B, new lignans from *Salvia santolinifolia*

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Salvicins A and B, new lignans from *Salvia santolinifolia*

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Phytochemical investigation on the $CHCl_3$ soluble fraction of the ethanolic extract from the whole plants of *Salvia santolinifolia* led to two new lignans salvicins A (**1**) and B (**2**). Their structures were elucidated on the basis of spectral data.

Keywords: *Salvia santolinifolia*; lignans; salvicins A and B

1. Introduction

The genus *Salvia* (Labiateae) comprises 24 species. These are herbs and under-shrubs distributed in Pakistan, India, and Afghanistan. One of these species *Salvia santolinifolia* is an under shrub that commonly grows in rocky arid areas. In Pakistan, it is found in Peshawar, Balochistan, and Karachi [1]. Its leaves and seeds are used by the local people as demulcent in diarrhea and hemorrhoids and for the treatment of inflammation [2]. Our previous studies on this species resulted in the isolation of a new lignan and new epoxydammarane triterpenes [3,4]. The ethnopharmacological and chemotaxanomic importance of the genus *Salvia* prompted us to reinvestigate the chemical constituent of *S. santolinifolia*. In this study, two new lignans salvicins A (**1**) and B (**2**) (Figure 1) were isolated. Herein, we report the isolation and structure elucidation of compounds **1** and **2**.

2. Results and discussion

Salvicin A (**1**) was isolated as white amorphous solid and gave violet coloration with $FeCl_3$ for phenols. The absorptions at 3400, 1720, and 1610–1515 cm^{-1} in the IR spectrum showed the presence of hydroxyl, ester, and aromatic moieties, respectively. The UV absorption maxima at 235, 272, and 280 nm were typical for substituted aromatic system of lignans [5,6]. The molecular formula was determined as $C_{24}H_{30}O_8$ through HR-EI-MS showing an $[M]^+$ peak at *m/z* 446.1940, with 10 degrees of unsaturation. The ^1H and ^{13}C NMR spectra showed striking resemblance to those of santolinol [3] and lariciresinol C [5]. Twenty-four signals in the broad band (BB) ^{13}C NMR spectrum were resolved through a DEPT experiment into three methyl, five methylene, eight methine, and eight quaternary signals (Table 1). The most downfield signal at δ 173.0 was assigned to the ester carbonyl. Four oxygenated aromatic carbons resonated at δ 146.1–147.1, whereas aromatic methine carbons were observed at δ 111.5–123.8. The tetrahydrofuran moiety gave signals at δ 61.8–85.7, whereas the remaining signals were due to butanoyl moiety (Table 1). In the ^1H NMR spectrum, the signals for tetrahydrofuran ring appeared at δ 4.70 (1H, d, $J = 7.2$ Hz, H-7), 2.27 (1H, ddd, $J = 8.0$, 7.2, 5.4 Hz, H-8) as well as oxymethylene

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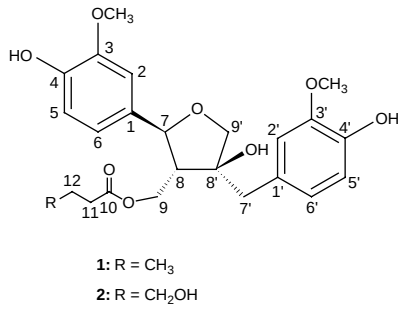

Figure 1. Structures of salvicins A (**1**) and B (**2**).

signal as a pair of doublets at δ 3.76 and 3.56 (1H each, d, $J = 9.2$ Hz). Signals for oxymethylene at δ 3.71 (1H, dd, $J = 11.2$, 5.4 Hz, H-9a), 3.67 (1H, dd, $J = 11.2$, 8.0 Hz, H-9b) and for methylene at δ 2.96 and 2.88 (1H each, $J = 13.9$ Hz, H-7′) were observed. Two trisubstituted phenyl rings at δ 7.12 (1H, d, $J = 1.2$ Hz, H-2), 6.79 (1H, dd, $J = 8.0$, 1.2 Hz, H-6), 6.70 (1H, d, $J = 8.0$ Hz, H-5), 6.87 (1H, d, $J = 1.2$ Hz, H-2′), 6.84 (1H, dd, $J = 8.1$, 1.2 Hz, H-6′), and 6.72 (1H, d, $J = 8.1$ Hz, H-5′), as well as two methoxyl groups resonated at δ 3.84 and 3.82 as singlets were also displayed. A butanoyl moiety could also be inferred by signals at δ 2.58 (2H, t, $J = 7.0$ Hz, H-11), 1.97 (2H, m, H-12), and 0.76 (3H, t, $J = 6.6$ Hz, H-13). The substitutions and linkages at various positions were confirmed by ^{1}H–^{1}H COSY spectrum and HMBC correlations (Figure 2). The methoxyl groups at C-3 and C-3′ were determined based on HR-EI-MS peaks at *m/z* 137.0602 ($C_8H_9O_2$, 137.0607) for 4-hydroxy-3-methoxybenzyl moiety and at *m/z* 151.0395 ($C_8H_7O_3$, 151.0399) for

Table 1. ^{1}H and ^{13}C NMR spectral data of **1** and **2** ($CDCl_3$, δ in ppm, J in Hz).

Position	δ_H	δ_C	δ_H	δ_C
1	–	130.3 (s)	–	130.5 (s)
2	7.12 (d, 1.2)	111.5 (d)	7.13 (d, 1.1)	111.5 (d)
3	–	146.1 (s)	–	146.2 (s)
4	–	145.0 (s)	–	145.0 (s)
5	6.70 (d, 8.0)	115.7 (d)	6.72 (d, 8.0)	115.6 (d)
6	6.79 (dd, 8.0, 1.2)	123.8 (d)	6.85 (d, 8.0, 1.1)	123.8 (d)
7	4.70 (d, 7.2)	85.7 (d)	4.71 (d, 7.2)	85.2 (d)
8	2.27 (ddd, 8.0, 7.2, 5.4)	61.8 (d)	2.24 (ddd, 8.1, 7.2, 5.4)	61.4 (d)
9	3.67 (dd, 11.2, 8.0) 3.71 (dd, 11.2, 5.4)	60.5 (t)	3.66 (dd, 11.1, 8.3) 3.70 (dd, 11.1, 5.4)	60.7 (t)
10	–	173.0 (s)	–	173.4 (s)
11	2.58 (t, 7.0)	34.8 (t)	2.53 (t, 7.1)	33.4 (t)
12	1.97 (m)	19.2 (t)	1.27 (m)	28.0 (t)
13	0.76 (t, 6.6)	13.1 (q)	3.34 (t, 6.3)	64.2 (t)
1′	–	135.3 (s)	–	135.5 (s)
2′	6.87 (d, 1.2)	111.5 (d)	6.87 (d, 1.2)	111.5 (d)
3′	–	147.1 (s)	–	147.0 (s)
4′	–	146.8 (s)	–	146.8 (s)
5′	6.72 (d, 8.1)	115.7 (d)	6.75 (d, 8.1)	115.7 (d)
6′	6.84 (dd, 8.1, 1.2)	120.9 (d)	6.80 (dd, 8.1, 1.2)	120.7 (d)
7′	2.88 (d, 13.9) 2.96 (d, 13.9)	40.6 (t)	2.88 (d, 13.9) 2.96 (d, 13.9)	40.0 (t)
8′	–	82.5 (s)	–	82.5 (s)
9′	3.56 (d, 9.2) 3.76 (d, 9.2)	77.9 (t)	3.51 (d, 9.0) 3.78 (d, 9.0)	77.2 (t)
OMe-3	3.84 (s)	56.5 (q)	3.84 (s)	56.5 (q)
OMe-3′	3.82 (s)	56.8 (q)	3.80 (s)	56.8 (q)

4-hydroxy-3-methoxybenzoyl group, and were further confirmed by NOESY cross peaks of methoxyl protons at δ 3.84 with H-2 and remaining methoxyl signal at δ 3.82 with H-2′. Close similarity of NMR chemical shifts to those of known lignans [5,6] allowed us to assign the same relative stereochemistry at tetrahydrofuran ring, which could further be confirmed by NOESY correlations of H_2-7 (δ 4.70) with H_2-9 (δ 3.67 and 3.71) and H_2-9 (δ 3.67 and 3.71) with H_2-7′ (δ 2.88 and 2.96). Additionally, the positive optical rotation of **1** suggested 8*R*, 7*S,* and 8′*R* stereochemistry [6], which is similar to those reported for similar lignans [5,6]. Thus, the structure of salvicin A (**1**) could be assigned as [(2*S*,3*R*,4*R*)-4-hydroxy-4-(4-hydroxy-3-methoxy-benzyl)-2-(4-hydroxy-3-methoxyphenyl)tetrahydro-3-furanyl]methyl butyrate.

Compound **2** was also obtained as a white amorphous solid and gave a positive test for a phenol. The UV and IR spectra were similar to those of **1**. The HR-EI-MS showed a molecular ion peak at *m/z* 462.1889, consistent with the molecular formula $C_{24}H_{30}O_9$ with 10 degrees of unsaturation. It was confirmed by ^{13}C NMR spectrum (BB and DEPT) that showed 24 signals comprising two methyl, six methylene, eight methine, and eight quaternary carbons. The spectrum showed striking resemblance to those of **1** except for replacement of one methyl by an oxymethylene carbon at δ 64.2. The ^1H NMR spectrum also showed close similarity to that of **1** except for the absence of methyl protons at δ 3.43 and the presence of oxymethylene protons at δ 3.34 (t, $J = 6.3$ Hz). Compound **2**, therefore, differs from **1** in having a 3-hydroxy butanoyloxy moiety connected to C-9, which could further be authenticated by HMBC correlations (Figure 2). Similarity of chemical shifts and coupling constants of the protons of tetrahydrofuran moiety with those of **1** allowed us to retain the same relative configuration. Conclusive evidence was provided by NOE and NOESY spectra, which showed similar interactions as salvicin A (**1**). Thus, the structure of salvicin B (**2**) could be assigned as [(2*S*,3*R*,4*R*)-4-hydroxy-4-(4-hydroxy-3-methoxybenzyl)-2-(4-hydroxy-3-methoxyphenyl)tetrahydro-3-furanyl] methyl-4-hydroxy-butanoate.

3. Experimental

3.1 General experimental procedures

Optical rotation was measured by using a JASCO DIP-360 digital polarimeter. IR spectra were measured with a Shimadzu IR-460 spectrometer. UV spectra were recorded on a Hitachi UV-3200 spectrometer. NMR spectra were measured on

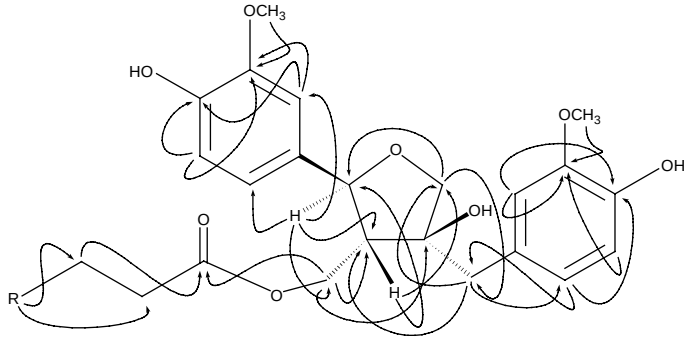

Figure 2. Important HMBC correlations of salvicins A (**1**) and B (**2**).

a Bruker AMX-400 MHz FT-NMR in $CDCl_3$ with TMS as internal standard. HR-EI-MS were recorded on a JEOL JMS-HX 110 mass spectrometer. TLC analysis was carried out on precoated aluminum sheets with silica gel $60F_{254}$ (20×20 cm, 0.2 mm layer thickness, E. Merck Darmstadt, Germany). Column chromatography (CC) was performed with silica gel 250–400 mesh (E. Merck. Darmstadt, Germany).

3.2 Plant material

The whole plant of *S. santolinifolia* Boiss (20 kg) was collected from Karachi (Pakistan) in July 2008 and identified by Dr Surraiya Khatoon, Plant Taxonomist, Department of Botany, University of Karachi, where a voucher specimen (No. LS 831) has been deposited.

3.3 Extraction and isolation

The whole plant of *S. santolinifolia* (20 kg) was shade dried, ground, and extracted with EtOH (3×50 l) at room temperature. The combined ethanolic extract was evaporated under reduced pressure to obtain a thick gummy residue (450 g). This residue was suspended in H_2O and successively fractionated with *n*-hexane (80 g), $CHCl_3$ (50 g), EtOAc (70 g), and *n*-BuOH (130 g). The $CHCl_3$ soluble fraction was subjected to CC over silica gel eluted gradiently with *n*-hexane, *n*-hexane–$CHCl_3$, $CHCl_3$, $CHCl_3$–MeOH, and MeOH. The fraction obtained from chloroform was a binary mixture. The mixture was subjected to flash chromatography, eluted with $CHCl_3$–MeOH (9.8:0.2) to provide compound **1** (18 mg), and eluted with $CHCl_3$–MeOH (9.6:0.4) to afford compound **2** (14 mg).

3.3.1 Salvicin A (*1*)

White amorphous solid; $[\alpha]_D^{25} + 38.2$ (*c* 0.032, CH_3OH); UV (CH_3OH) λ_{max} nm (log ε): 235 (3.91), 272 (3.45), 280 (3.61, sh); IR (KBr) ν_{max}: 3400, 1720, 7610–1515 cm^{-1}. For ^1H and ^{13}C NMR spectral data (see Table 1). HR-EI-MS *m/z*: 446.1933 $[M]^+$ (calcd for $C_{24}H_{30}O_8$, 446.1940).

3.3.2 Salvicin B (*2*)

White amorphous solid; $[\alpha]_D^{25} + 51.1$ (*c* 0.041, CH_3OH); UV (CH_3OH) λ_{max} nm (log ε): 235 (3.91), 272 (3.45), 280 (3.61, sh). IR (KBr) ν_{max}: 3420, 1720, 1612–1512 cm^{-1}. For ^1H and ^{13}C NMR spectral data (see Table 1). HR-EI-MS *m/z*: 462.1880 $[M]^+$ (calcd for $C_{24}H_{30}O_9$, 462.1889).

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