Phytochemistry Letters 24 (2018) 1–5

Contents lists available at ScienceDirect

Phytochemistry Letters

journal homepage: www.elsevier.com/locate/phytol

Mini review

Secondary metabolites from the aerial parts of *Cytisus villosus* Pourr.

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ARTICLE INFO

Keywords:
Cytisus villosus
Isoflavonoids
Monoterpenoids
ECD

ABSTRACT

Phytochemical investigation of the aerial parts of *Cytisus villosus* Pourr. resulted in the isolation and characterization of a new isoflavan, (*3S, 4S*)-2′,4′-dihydroxy-3′-methoxy-6,7-methylenedioxyisoflavan-4-ol (**1**), and a new monoterpene, (*4R,6S*)-4-hydroxy-2,2,6-trimethyl-9-oxabicyclo [4.2.1] non-1(8)-en-7-one (**2**), together with four known flavonoids: geinstein **(3)**, chrysin **(4)**, chrysin −7-*O*-β-D-glucopyranoside **(5)** and 2"-*O*-α-L-rhamnosylorientin **(6)**. The structures of the new compounds were elucidated on the basis of extensive spectroscopic analysis, including 1D, 2D NMR (^{1}H, ^{13}C, COSY, TOCSY, HMBC and HSQC) and HRESIMS. The absolute configurations of **1** and **2** were established by the comparison of experimental and calculated electronic circular dichroism (ECD) spectra.

1. Introduction

The *Cytisus* genus (Fabaceae) has been used in folk medicine as a diuretic and in the treatment of mild hypertension, heart failure and cardiac edema (Bhakuni et al., 1969; Siegel, 1976; Weiss, 1988). It has been also reported as; anti-diabetic, hypnotic, sedative, antioxidant, hepatoprotective, antispasmodic, hypotensive and estrogenic agent (Jalili et al., 2013; Nirmal et al., 2008; Pereira et al., 2012). The therapeutic properties, particularly the antioxidant activity, of the different *Cytisus* species are related to their high concentration of phenolic compounds (Luís et al., 2009). The major compounds isolated from this genus include the lupin alkaloids: sparteine, lupanine and isosparteine (Iwu, 2014). Other important metabolites found in aerial part of this genus are tyramine, epinine, salsolidine, genisteine, quercetin, and their glycosides, and caffeic acid (Sundararajan and Koduru, 2014). Eugenol, phenol, cresol, isovaleric acid, benzoic acid, benzylalcohol, *cis*-3-hexen-1-ol and 1-octen-3-ol are the predominant compounds found in the seed-essential oil of several *Cytisus* species (Sundararajan and Koduru, 2014). The flavone 6"-*O*-acetyl-scoparin, the flavonols kaempferol, rutin, quercetin, quercitrin and isorhamnetin, and the isoflavones genistein and sarothamnoside have been found in *Cytisus scoparius* (Sundararajan and Koduru, 2014), while *Cytisus nigrians* and *Cytisus albus* contain the isoflavones ononin and genistein (Hanganu et al., 2010a, 2010b).

Cytisus villosus Pourr. is a Shrub of 1–2 m high with erect stems that spread into many twigs. Young twigs are angular and covered with long white hairs. The flowering takes place in April-May. The flowers are large, yellow streaked with papilionaceous corolla. *C. villosus* frequently grows in Algeria, France, Italy, Spain, Portugal, and Tunisia. In Algeria, it is common in the region of the Tell Algéro-Constantinois (Quezel et al., 1962) and locally known as "elugua." To the best of our knowledge, no phytochemical work on this species has been reported. As a part of our continuing study of Algerian medicinal plants (Larit et al., 2017), we have investigated an aqueous-ethanol extract of the aerial part of *C. villosus*, leading to the isolation of five flavonoids (**1, 3-6**) including the new isoflavan-4-ol (**1**) and a new monoterpene (**2**) (Fig. 1). The structures of the known compounds were confirmed through the comparison of their spectroscopic properties with the published data.

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https://doi.org/10.1016/j.phytol.2017.12.012
Received 21 September 2017; Received in revised form 12 December 2017; Accepted 19 December 2017
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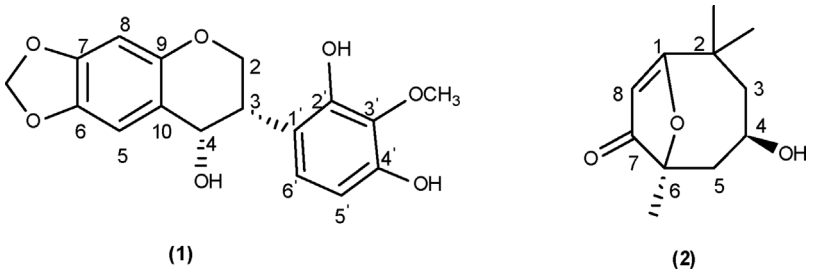

Fig. 1. Structures of compounds **1** and **2.**

2. Results and discussion

Dried powdered aerial parts (1 kg) of *C. villosus* were macerated at room temperature with EtOH–H_2O (80:20, v/v) for 24 h, three times. The filtered crude extracts were combined and evaporated under vacuum at 40 °C to yield 25 g of extract. The dried crude extract was suspended in water (800 mL) and partitioned with chloroform ($CHCl_3$), ethyl acetate (EtOAc) and n-butanol (*n*-but), yielding 500 mg ($CHCl_3$), 5 g (EtOAc) and 10 g (n-butanol) fractions, respectively. Chromatographic separation of the fractions led to the isolation of the isoflavan (**1**) and the monoterpene (**2**) along with four known flavonoids: genistein (**3**) (Coward et al., 1993), chrysin (**4**) (Mouffok et al., 2012), chrysin −7-*O*-β-D-glucopyranoside (**5**) (Antri et al., 2004) and 2"-*O*-α-L-rhamnosylorientin (**6**) (Kumamoto et al., 1985). Their chemical structures were elucidated using spectroscopic methods including 1D and 2D NMR experiments, and HRESIMS. Compound **6** was isolated from *Cytisus* genus for the first time.

Compound **1** was obtained as a white amorphous powder, the UV spectrum of **1** showed absorption maxima at 201.0 nm and 310.0 nm suggesting a flavonoid skeleton (Mabry et al., 1970). Its negative HRESIMS spectrum showed a peak at *m/z* 313.0734 $[M\text{-}H_2O\text{-}H]^-$ indicating the loss of H_2O from the molecular ion 332.0896. The molecular formula could be deduced as $C_{17}H_{16}O_7$. The ^{13}C NMR spectrum of 1 (Table 1) showed signals for 17 carbons. The DEPT spectra indicated the presence of a methylene carbon at δ_C 66.4, one methylenedioxy group at δ_C 101.5 ppm, two methine carbon at δ_C 40.0 and 78.5 ppm, one methoxy group at δ_C 60.6 ppm, four aromatic methine carbons at δ_C 93.6, 105.8, 110.3 and 126.0 ppm, and eight quaternary carbons. The ^1H NMR spectrum (Table 1) showed an oxygenated methylene signals at δ_H 4.30 ppm (m, H-2b) and 3.59 ppm (d br, J = 3.1 Hz, H-2a), a methine proton signal at δ_H 5.52 ppm (d, J = 6.8 Hz, H-4) and an aliphatic methine at δ_H 3.56 ppm (H-3), suggesting an 4-hydroxyisoflavan skeleton (Bojase et al., 2001). The ^1H NMR also showed signals for an ortho-coupled aromatic at δ_H 6.55 and 7.00 (J = 8.0 Hz), as well as, the presence of one methylenedioxy group δ_H 5.93 (d, J = 8.0 Hz, 2H). The COSY experiment (Fig. 2) disclosed a partial structure, CH_2CHCH corresponding to the C-2, C-3 and C-4 fragment. HMBC correlations between the proton at δ_H 6.52 (H-8) with the signals at δ_C 141.5 (C-6), 147.9 (C-7), and correlations between the proton at δ_H 6.98 (H-5) with the signals at δ_C 141.5 (C-6), 147.9 (C-7), and 78.5 (C-4), as well as, the correlations of the methylemedioxy signal at δ_H 5.93 with C-6 and C-7 assisted the placement of the methylendioxy group at the ring A of the isoflavan. The correlation of the methoxy signal at δ_H 3.56 with the carbon at δ_C 136.0 (C-3′), helped to position the methoxy group at the ring B. Consequently, structure **1** was determined to be 2′,4′-dihydroxy-3′-methoxy-6,7-methylenedioxyisoflavan-4-ol. The absolute configuration of **1** was elucidated using electronic circular dichroism (ECD) calculations. Compound **1** possess two stereogenic centers (C-3, C-4) and was optically active ($[\alpha]_D^{25} = -24$). Circular dichroism spectrum was taken to determine the absolute configuration at carbons C-3 and C-4 in the molecule. The calculated and experimental ECD spectra were compared for all possible stereoisomers (Fig. 3). The (*S, S*) isomer showed perfect fit with a negative cotton effect at λ_{max} ~200 nm. Only 34 conformers were obtained for the (*S, S*) and 12 of them contributed more than 90% in the Boltzmann distribution (Fig. 4). The intramolecular hydrogen bonds play significant role in ligand stabilization. Thus, the structure of **1** was determined as (*3S, 4S*)-2′,4′-dihydroxy-3′-methoxy-6,7-methylenedioxyisoflavan-4-ol.

Compound **2** was obtained as a yellowish white amorphous powder. Its molecular formula was revealed as $C_{11}H_{16}O_3$ with four degree of unsaturation, on the base of its positive HREISMS data *m/z* 197.122 ($[M + H]^+$ calcd. 197.120). The ^1H NMR spectrum (Table 2) showed three methyl singlets at δ_H 1.19, 1.38, and 1.67 ppm. The ^{13}C NMR and DEPT spectra (Table 2) of **2** disclosed 11 carbons including one carbonyl carbon at δ_C 183.5, one trisubstituted double bond at δ_C 171.5, one vinyl proton at δ_C 112.5, one oxygenated quaternary carbon at δ_C 86.9, one oxygenated methine at δ_C 65.3, one aliphatic quaternary carbon at δ_C 36.1, two methylene at δ_C 45.7, 47.0, and three tertiary methyl at δ_C 27.3, 26.6, 30.9 ppm. Extensive 2D NMR experiments allowed us to define the molecular connectivity. Thus, COSY experiment (Fig. 2) showed cross peak correlations of H_2-3 with H-4 and of H_2-5, revealing a $-CH_2$-CHOH-CH_2- fragment **2a**. HMBC experiment (Fig. 2) of **2** disclosed correlations of δ_H 1.38 (CH_3-10) and δ_C 47.0 (C-3); the signal at δ_H 1.19 (CH_3-11) with C-3; the proton at δ_H 5.79 (H-8), with the signals at δ_C 86.9 (C-6), 171.5 (C-1) and 36.1 (C-2), suggested the partial structure **2b**. The placement of the hydroxyl group in C-4 was deduced from its correlation in the COSY experiment (Fig. 2) with H-4 together with the HMBC (Fig. 2) experiment which showed correlations of the hydroxyl proton at δ_H 5.00 with C-4 and C-5. Additional HMBC correlations of H_2-5 with C-6 and C-7; H-4 with C-2 and C-6; and H_2-3 with C-2 and CH_3-10, required direct connections of C-3 to C-2, and of C-6 to C-5, respectively, so that **2a** and **2b** must be joined in the planar structure for **2**. These observations, in combination with the molecular formula, indicate one carbonyl, double bond and a ring, accounted three unsaturated degrees in **2**. The remaining one degree of unsaturation suggests the presence of an additional ring, the relatively downfield shifted of the ^{13}C NMR data at δ_C 171.5 (C-1) and the

Table 1
^1H NMR and ^{13}C NMR data of **1** (δ in ppm, in DMSO-d_6, 400 and 100 MHz).

Position	δ_H	δ_C
2	3.59, d, 3.1, 1H 4.30, m, 1H	66.4
3	3.50, m, 1H	40.0
4	5.52, *d*, 6.8, 1H	78.5
5	6.98, s, 1H	105.8
6	–	141.5
7	–	147.9
8	6.52, s, 1H	93.6
9	–	154.1
10	–	118.8
1'	–	113.0
2'	–	149.9
3'	–	136.0
4'	–	151.4
5'	6.55, d, 8.0,1H	110.3
6'	7.00, d, 8.0, 1H	126.0
3′-OCH_3	3.65, *s*, 3H	60.6
-O-CH_2-O-	5.93, d, 8.0, 2H	101.5
OH-4′	9.36, *br* s, 1H	151.4

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