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A New Cardenolide and Other Compounds from *Salsola tetragona*Hamida Ghorab<sup>a</sup>, Abdelkrim Khettaf<sup>a</sup>, Meriem Lehbili<sup>a</sup>, Ahmed Kabouche<sup>a</sup>, Abdulmagid Alabdul Magid<sup>b</sup>, Dominique Harakat<sup>c</sup>, Laurence Voutquenne-Nazabadioko<sup>b\*</sup> and Zahia Kabouche<sup>a\*</sup>.<sup>a</sup>Université des frères Mentouri-Constantine, Laboratoire d'Obtention de Substances Thérapeutiques (LOST), Campus Chaabet Ersas, 25000 Constantine, Algeria<sup>b</sup>Groupe Isolement et Structure, Institut de Chimie Moléculaire de Reims (ICMR), CNRS UMR 7312, UFR de Pharmacie, BP 1039, 51687 Reims, France<sup>c</sup>Service Commun d'Analyses, ICMR-UMR CNRS 7312, Bât. 18 B.P.1039, 51687 Reims Cedex 2, France

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One new cardenolide, 3-*O*-β-D-allopyranosylcoroglaucigenin (salsotetragonin) (**1**), was isolated from the aerial parts of *Salsola tetragona* Delile with four known cardenolides (**2-5**), two known flavonoids (**6-7**), three known phenolic compounds (**8-10**) and two known fatty acids (**11-12**). Their structures were identified by spectroscopic analyses and by comparison of their spectral data with those reported in the literature. Compounds **1-5**, **7**, **10** and **12** were isolated from the genus *Salsola* for the first time. This is the first report on cardenolides identified in the Amaranthaceae family.

**Keywords:** *Salsola tetragona* Delile, Amaranthaceae, Cardenolides, Phenolic glycosides.

The genus *Salsola* (Amaranthaceae, ex. Chenopodiaceae) consists of over 174 species found in the arid regions of Asia, Europe and Africa [1]. *Salsola* species possess antihypertensive, anti-inflammatory, anticancer, antioxidant, anti-Alzheimer, antidepressant and antimicrobial activities [2-5]. Previous phytochemical investigations of this genus reported the isolation of flavonoids and other phenolic compounds [6], alkaloids [7], fatty acids [8] and triterpene glycosides [9]. In continuation of our works on plants from Algerian Septentrional Sahara [10-11], we report here the isolation and structural characterization of one new cardenolide, 3-*O*-β-D-allopyranosylcoroglaucigenin, named salsotetragonin (**1**), in addition to eleven known compounds from aerial parts of *S. tetragona* (Figure S1).

The hydromethanolic extract of the aerial parts of *S. tetragona* was partitioned successively with light petroleum, CH<sub>2</sub>Cl<sub>2</sub>, EtOAc and *n*-butanol to give four extracts. Purification of the *n*-butanol extract through repeated silica gel columns, flash chromatography and semi-prep HPLC led to the isolation and identification of a new cardenolide (**1**) and seven known compounds (**3**, **4**, **6-10**). The dichloromethane extract was fractionated by silica gel chromatography to give four known compounds (**2**, **5**, **11-12**). These compounds were identified by extensive spectroscopic methods including 1D-(<sup>1</sup>H and <sup>13</sup>C) and 2D-NMR (COSY, HSQC, HMBC and NOESY) experiments, as well as HR-ESI-MS analysis and by comparison of their spectral data with the literature. The eleven known compounds were identified as four cardenolides: uzarigenin (**2**) [12], desglucouzarin (**3**) [13], 12-dehydroxyghalakinoside (**4**), and calactin (**5**) [14] (Figure 1), two flavonoids: kaempferol-3-*O*-β-D-glucopyranoside (**6**) [15] and quercetin-3-*O*-β-D-glucopyranosyl-(1→6)-glucopyranoside (**7**) [16], three phenolic compounds: vanillic acid (**8**) [17], canthoside C (**9**), and canthoside D (**10**) [18] and two fatty acids: oleic acid (**11**) [19], and 2,3-dihydroxypropylpalmitate (**12**) [20] (Figure S1).

Compound **1** was isolated as a white amorphous powder. Its positive HR-ESI-MS showed a pseudomolecular ion peak at *m/z* 575.2829 [M+Na]<sup>+</sup>, corresponding to the molecular formula C<sub>29</sub>H<sub>44</sub>O<sub>10</sub>. The

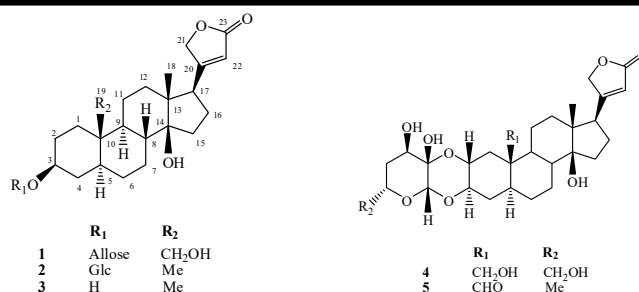


Figure 1: Structures of compounds 1-5.

<sup>1</sup>H NMR spectrum of compound **1** (Table 1) showed characteristic signals of a butenolactone ring at δ<sub>H</sub> 4.95 (1H, dd, *J* = 18.4, 1.6 Hz, H-21a), 5.07 (1H, dd, *J* = 18.4, 1.4 Hz, H-21b) and 5.93 (1H, s, H-22), one oxymethylene at δ<sub>H</sub> 3.74 (1H, d, *J* = 11.7 Hz, H-19a) and δ<sub>H</sub> 3.88 (1H, d, *J* = 11.7 Hz, H-19b), one oxymethine at δ<sub>H</sub> 3.78 (m, H-3), and one methyl signal at δ<sub>H</sub> 0.95 (3H, s, H-18). Its <sup>13</sup>C NMR spectrum (Table 1) showed twenty-nine carbon signals including six of the sugar part (Figure 1).

The <sup>1</sup>H NMR and <sup>13</sup>C NMR data of **1** were very similar to those of 3-β-D-glucopyranosylcoroglaucigenin [21]. The COSY and HSQC spectra showed one anomeric proton of a sugar moiety at δ<sub>H</sub> 4.78 (d, *J* = 7.9 Hz, H-1') and δ<sub>C</sub> 99.8 with five signals of an hexose unit [H-2' [δ 3.28 (dd, *J* = 7.9, 3.0 Hz)], H-3' [δ 4.06 (t, *J* = 3.0 Hz)], H-4' [δ 3.48 (dd, *J* = 9.5, 3.0 Hz)], H-5' [δ 3.69 (m)], and H<sub>2</sub>-6' [δ 3.66 (dd, *J* = 11.3, 5.7 Hz) and 3.85 (dd, *J* = 11.3, 1.8 Hz)]; the sugar was identified as an allopyranoside [22]. The large coupling constant (*J* = 7.9 Hz) of the anomeric proton at δ<sub>H</sub> 4.78 indicated that the allose had a β-configuration. The linkage of the allose at C-3 of the aglycone was established from the HMBC correlation between allo-H-1' (δ<sub>H</sub> 4.78) and C-3 (δ<sub>C</sub> 78.9) (Figure 2). The stereochemistry of **1** was confirmed by the NOE effect (Figure 2) between H-5/H-9 and H-3, which clearly established the α-orientation of H-5. The correlation of H<sub>3</sub>-18 to H-21 and H-22 in the

Noesy spectrum indicated the  $\beta$  orientation of the  $\gamma$  lactone at C-17. The chemical shifts of the carbons of the C and D rings of **1** are in agreement with those of coroglaucigenin and madagascarrenilid (A) recorded in deuterated pyridine and in  $\text{CD}_3\text{OD}$  [23,24], indicating a 14- $\beta$  hydroxy orientation. Thus compound **1** was identified as 3-O- $\beta$ -D-allopyranosylcoroglaucigenin, which we named salsotetragonin.

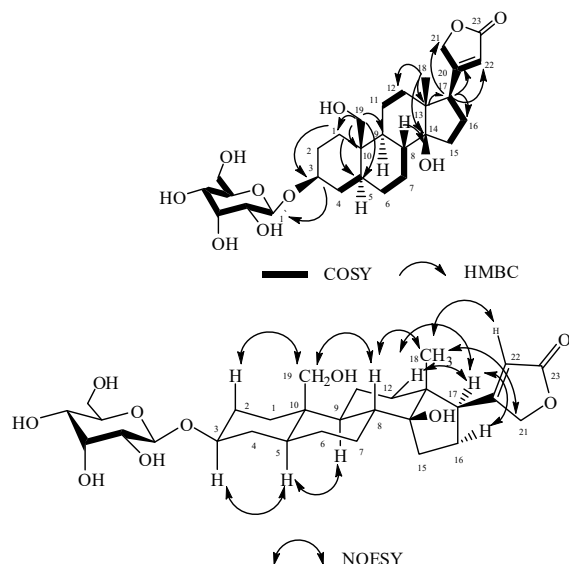


Figure 2:  $^1\text{H}$ - $^1\text{H}$  COSY, HMBC and NOESY correlations of **1**.

Table 1:  $^1\text{H}$  and  $^{13}\text{C}$  NMR data for compound **1** (in  $\text{CD}_3\text{OD}$ ;  $^{13}\text{C}$ : 150 MHz;  $^1\text{H}$ : 600 MHz).

Position	$\delta_{\text{H}}$ (m, J in Hz)	$\delta_{\text{C}}$
1	0.81 (td, 13.6, 3.5), 2.34 (dt, 13.3, 3.5)	32.8
2	1.57 (dm, 14.9), 1.91 (m)	30.9
3	3.78 (m)	78.9
4	1.44 (m), 1.82 (dd, 11.9, 3.4)	35.9
5	1.24 (m)	45.9
6	1.24 (m), 1.34 (m)	29.6
7	2.10 (dd, 12.3, 3.1), 1.15 (m)	28.8
8	1.82 (td, 11.9, 3.4)	43.1
9	1.03 (td, 13.5, 4.5)	51.5
10	-	40.6
11	1.65 (m)	24.1
12	1.41 (td, 13.6, 4.3), 1.53 (dt, 13.5, 3.0)	41.5
13	-	51.2
14	-	86.3
15	1.73 (dd, 11.6, 8.5), 2.14 (m)	33.5
16	2.16 (m), 1.90 (m)	28.1
17	2.85 (dd, 9.5, 5.8)	52.2
18	0.95 (s)	16.7
19	3.74 (d, 11.7), 3.88 (d, 11.7)	59.9
20	-	178.5
21	4.95 (dd, 18.4, 1.6), 5.07 (dd, 18.4, 1.4)	75.3
22	5.93 (s)	117.8
23	-	176.9
Allose (at C-3)		
1'	4.78 (d, 7.9)	99.8
2'	3.28 (dd, 7.9, 3.0)	72.4
3'	4.06 (t, 3.0)	73.1
4'	3.48 (dd, 9.5, 3.0)	69.1
5'	3.69 (m)	75.5
6'	3.66 (dd, 11.3, 5.7), 3.85 (dd, 11.3, 1.8)	63.3

## Experimental

**General:** Optical rotations were measured in DMSO with a Perkin-Elmer 241 polarimeter.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Avance DRX III 500 spectrometer ( $^1\text{H}$  at 500 MHz and  $^{13}\text{C}$  at 125 MHz) and on a Bruker Avance III-600 spectrometer equipped with a cryo platform ( $^1\text{H}$  at 600 MHz and  $^{13}\text{C}$  at 150 MHz). 2D-NMR experiments were performed using standard Bruker-microprograms (TopSpin version 3.2 software). HR-ESI-

MS and ESI-MS experiments were performed using a Micromass Q-TOF micro-instrument (Manchester, UK). TLC was carried out on pre-coated silica gel 60 F<sub>254</sub> (Merck). Vacuum liquid chromatography (VLC) was carried out on LiChroprep RP-18 (40-63  $\mu\text{m}$ , Merck). HPLC was performed on a Grace® Reveleris System using Grace® cartridges (Silica gel or RP-C<sub>18</sub>). The semi-preparative HPLC was performed on a Dionex apparatus equipped with an ASI-100 automated sample injector, a STH 585 column oven, a LPG-3400A pump, a diode array detector UVD-340U and Chromeleon® software.

**Plant material:** *Salsola tetragona* Delile was collected in Ghardaïa (Algerian Septentrional Sahara) in May 2011 and was identified by Pr. Gérard De Belair (University of Annaba, Algeria). A voucher specimen (LOST.St05/09) was deposited at the herbarium of the Faculty of Sciences, University frères Mentouri- Constantine.

**Extraction and isolation:** Air-dried and powdered aerial parts (1980 g) of *S. tetragona* were extracted with 80% MeOH (10 L). After evaporating the MeOH under *vacuum*, the residue was dissolved in water (900 mL) and partitioned with PE,  $\text{CH}_2\text{Cl}_2$ , EtOAc, and *n*-BuOH, successively (3 x 300 mL). The *n*-BuOH extract (6 g) was subjected to VLC over RP-18 eluted with  $\text{H}_2\text{O}$ -MeOH (6:4, 5:5, 4:6, 3:7, 2:8 and 0:10). Fractions of 150 mL were collected and pooled according to their similarity in TLC profile to give 6 fractions (F1–F6 respectively). F1 (1.2 g) was submitted to RP-18 flash chromatography eluting with MeCN:H<sub>2</sub>O (5:95 to 10:0) to afford 19 sub-fractions. Sub-fraction [20-23] (35 mg), was purified by semi-prep HPLC on RP-18 eluted with MeCN:H<sub>2</sub>O (6:94 to 1:9), affording compounds **9** (3 mg) and **10** (1.5 mg). F2 (1.5 g) was chromatographed on a silica gel column eluted with EtOAc:MeOH:H<sub>2</sub>O (20:2:1), giving 2 main sub-fractions. Sub-fraction [90] (180 mg) afforded **4** (22 mg) by silica gel CC ( $\text{CHCl}_3$ :MeOH, 9:1). Sub-fraction [115-119] (223 mg) was subjected to silica gel CC eluting with  $\text{CHCl}_3$ :MeOH (8:2) to afford **1** (27 mg) and sub-fraction [35-48] (100 mg), which was purified over silica gel using EtOAc:MeOH:H<sub>2</sub>O (20:2:1) to yield compounds **6** (15 mg) and **7** (18 mg). F3 (750 mg) was fractionated by silica gel CC eluted with  $\text{CHCl}_3$ :MeOH (0 to 100% of MeOH). The main sub-fraction [59-63] (212 mg) was further separated by silica gel CC ( $\text{CHCl}_3$ :MeOH, 0 to 100% of MeOH) and **3** (25 mg) was isolated. F4 (302 mg) was subjected to silica gel CC using  $\text{CHCl}_3$ :MeOH (0 to 100% of MeOH) to give 3 sub-fractions. Sub-fraction [72] (111.2 mg) was selected for silica gel CC eluted with  $\text{CHCl}_3$ :MeOH (0 to 100% of MeOH) to yield compound **8** (3 mg).

The  $\text{CH}_2\text{Cl}_2$  extract (2.5 g) was subjected to silica gel CC, eluted with toluene: $\text{CHCl}_3$  (0 to 100% of  $\text{CHCl}_3$ ) and  $\text{CHCl}_3$ :EtOAc (0 to 100% of EtOAc). Sub-fraction [27-32] (123 mg) was purified over silica gel using diethyl ether:EtOAc (9:1) to yield compound **11** (1.4 mg). Sub-fraction [160-173] (212 mg) was passed through a silica gel column ( $\text{CHCl}_3$ :EtOAc, 9:1) yielding compounds **2** (15 mg) and **5** (5 mg). Sub-fraction [234-257] (162 mg) was chromatographed on silica gel, eluted with ( $\text{CHCl}_3$ :MeOH, 9:1) that afforded compound **12** (2 mg).

**Acid hydrolysis:** The pure compounds were treated with 2 M HCl at 100°C for 1 h. The hydrolysates were extracted with EtOAc and the sugars identified in the aqueous residue by comparison with authentic samples by TLC using silica gel impregnated with 0.2 M  $\text{NaH}_2\text{PO}_4$  and a solvent system of  $\text{Me}_2\text{CO}$ -H<sub>2</sub>O (9:1); the compounds were revealed with aniline malonate. The optical rotation of the purified sugar was measured and compared with an authentic sample of D-allose.

**3-O-β-D-Allopyranosylcoroglaucigenin (salsotetragonin) (1)**

White amorphous powder.

 $[\alpha]_D^{20}$ : -16.9 (c 0.18, DMSO). $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 600 MHz): Table 1. $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 150 MHz): Table 1.HR-ESI-MS:  $[\text{M}+\text{Na}]^+$   $m/z$  575.2829 (calcd for  $\text{C}_{29}\text{H}_{44}\text{O}_{10}\text{Na}$ , 575.2832).

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**Supplementary data:** Figure S1 and Supplementary Data are included in the Supporting information.

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