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EXPERIMENTAL PAPER

9α-hydroxyparthenolide in *Zoegea leptaurea* subsp. *mesopotamica* (Czerep.) Rech. (*Asteraceae*)

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Summary

From the aerial parts of *Zoegea leptaurea* subsp. *mesopotamica* (Czerep.) Rech. (syn. *Zoegea mesopotamica* Czerep.), 9α-hydroxyparthenolide was isolated. This compound was identified by spectral methods (^{1}H NMR and ^{13}C NMR). This research confirmed earlier indications about the presence of 4,5-epoxygermacranolides in the *Zoegea* L. genus. Thus, distinctive chemistry feature of plants in this taxon has chemotaxonomic implications.

Keywords: *Zoegea*, *Asteraceae, germacranolides, 9α-hydroxyparthenolide, chemotaxonomy*

INTRODUCTION

The main secondary metabolites of subtribe *Centaureinae* (*Asteraceae*) species are guaianolides and germacranolides [1]. Both of those types of sesquiterpene lactones are of vital chemotaxonomical importance for this taxon and all genera it includes [2]. Parthenolide and its semi-synthetic derivatives has proven pharmacological properties, mostly it has a migraine reducing effect [3]. There are some researches which show that parthenolide inhibits the release of serotonin (5-HT) from bovine platelets. 5-HT is believed to be a vasoactive

agent and main neurotransmitter in the etiology of migraine. Besides, they report stronger activity of germacranolides than popular migraine prophylactic drugs. Micromolar concentration of parthenolide necessary for 50% inhibition of 5-HT release from platelets (IC_{50}) was 3.03 μM, concentration of verapamil hydrochloride was 577.5 μM and concentration of propranolol hydrochloride was 939.8 μM [4]. In addition, parthenolide also manifests anticancer activities in ovarian cell lines [5].

9α-hydroxyparthenolide (fig. 1) can also be found in *Zoegea baldschuanica* C. Winkl. [6] as well as *Anvillea garcinii* (Burm.) DC., species from *Inulae* tribe. It possesses cytotoxic and antitumor activity [7, 8]. The significant cytotoxicity of 9α-hydroxyparthenolide was observed against leukemia, non-small cell lung, colon cancer and melanoma (ED_{50} 0.50-1.66 μg/ml) [8]. *Stizolophus balsamita* Lam. is also rich in 4,5-epoxygermacranolides but this species contains C8 and C8,9 parthenolide derivatives only [9].

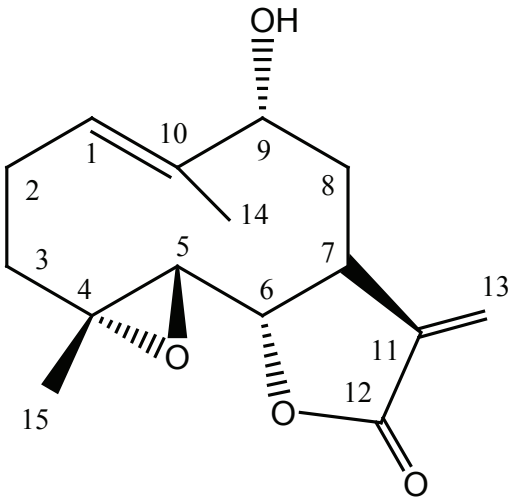

Figure 1.

The structure of 9α-hydroxyparthenolide

Lebanon, Syria, Iraq and Iran are the natural environment for *Zoegea leptaurea* subsp. *mesopotamica* (fig. 2). Our analysis showed that herb of this taxon contains one dominating compound from 4,5-epoxygermacranolides group with OH substituent at C9. This plant was examined for the first time.

Figure 2.

Zoegea leptaurea subsp. *mesopotamica* in the Garden of Department of Medicinal and Cosmetic Natural Products, Poznan University of Medicinal Sciences

MATERIAL AND METHODS

Plant material

Aerial parts of *Zoegea leptaurea* subsp. *mesopotamica* were collected in August 2010 from plants growing in the Garden of Department of Medicinal and Cosmetic Natural Products, Poznan University of Medical Sciences, where a voucher specimen is deposited in the herbarium of the mentioned above Department. Seeds of the plant were provided by the National Botanical Garden of Iran. The plant was identified according to description in Flora Iranica [10].

Phytochemical study

Extraction

The dried plant material (98 g) was ground and exhaustively extracted with methanol (MeOH). The solvent was removed under reduced pressure. The residue was dissolved in 500 ml of distilled water and extracted successively with dichloromethane (CH_2Cl_2). After drying and concentrating, 2.5 g of the CH_2Cl_2 extract were obtained.

Isolation and identification

The residue obtained after evaporation of the solvent under reduced pressure was chromatographed on a silica gel (Merck, Art. 7733) column eluted with CH_2Cl_2 – $(Me)_2CO$ mixture (8:1) yielded the compound (3.7 mg) in the form of short white needles. The compound was easily detectable on aluminium-backed silica gel plates DC Alufolien Kieselgel 60 (Merck, Art. 5553). 15-20 μg of isolated compound per plate was applied. Developed and dried chromatograms were sprayed by anisaldehyde-sulphuric acid reagent (0.5 ml p-anisaldehyde with 10 ml glacial acetic acid followed by 85 ml methanol and 5 ml concentrated sulphuric acid) and heated at 110° C for 3 minutes.

The structure of the isolated compound was identified on the basis of spectral methods: ^{1}H NMR (Bruker, 600 MHz, in $CDCl_3$), ^{13}C NMR (Bruker, 150 MHz, in $CDCl_3$), HMBC and by comparing the obtained data with those in literature [6]. Melting point (Büchi B-540) was also measured and compared with literature [6].

RESULTS AND DISCUSSION

Our chemical study of CH_2Cl_2 extract from aerial parts of *Zoegea leptaurea* subsp. *mesopotamica* (98 g) led to isolation of 9α-hydroxyparthenolide (3.7 mg). The crystalline compound (needles from ethyl ether, melting point. 140-142° C) was identified on the basis of the melting point, by TLC and by its ^{1}H NMR, ^{13}C NMR, HMBC data. (Table 1 and Table 2).

The presence of a trans-annelated exomethylene-γ-lactone, closed at C6 was proved by signals of exomethylene protons H-13 and H-13' and by interactions of protons H-5, H-6 and H-7. The presence of hydroxy group in position 9α showed signal of H-9 at δ 4.34. The configuration at C9 follows from the value of coupling constant $J_{9,8}$ for the germacrane ring conformation derived from vicinal coupling constants of protons. Isolated compound contains an epoxide grouping in position 4,5 (H-5 at δ 2.75 and C4 at δ 1.3 – CH_3).

TLC analysis showed that isolated compound gives violet colour, characteristic for derivatives of 9α-hydroxyparthenolide [11]. Control chromatograms show that C8 and C8,9 parthenolide derivatives have purple colour [12]. Figure 3 is an example of these differences. Stizolicin (C8 parthenolide derivative) – dominant sesquiterpene lactone occurring in *Stizolophus balsamita* - has characteristic purple colour.

Table 1.

^{1}H NMR data (600 MHz) of 9α-hydroxyparthenolide

H	δ_H [ppm]	*J* [Hz]
1	5.63 d	$J_{1,2'}$ 10.5
2	2.49 ddd	$J_{2,3}$ 6.1 $J_{2,3'}$ 2.1
2'	1.90 dd	$J_{2',3'}$ 6.9 $J_{2',3}$ 6.9
3	2.21 dd	$J_{3,2}$ 6.1
3'	1.62 m	
5	2.75 bd	$J_{5,6}$ 9.1
6	3.85 ddd	$J_{6,7}$ 8.4
7	3.41 m	
8	2.28 dd	$J_{8,9}$ 2.1
8'	1.41 m	$J_{8,7}$ 2.1
9	4.34 bd	$J_{9,8'}$ 5.6
13	6.32 d	$J_{13,7}$ 3.8
13'	5.63 d	$J_{13',7}$ 3.3
14	1.71 s	
15	1.30 s	

δ – chemical shifts, *J* – coupling constants

Table 2.

^{13}C NMR data (150 MHz) of 9α-hydroxyparthenolide

C	δ_C [ppm]
1	121.10
2	32.30
3	23.09
4	121.93
5	65.05
6	81.78
7	36.24
8	34.95
9	71.48
10	137.54
11	139.56
12	169.02
13	121.35
14	16.36
15	16.99

δ – chemical shifts

Figure 3.

Chromatogram and structures of 9α-hydroxyparthenolide and stizolicin. Mobile phase: CH_2Cl_2 – $(Me)_2CO$ 5:1

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9α-HYDROKSYPARTENOLID W *ZOEGEA LEPTAUREA* SUBSP. *MESOPOTAMICA* (CZEREP.) RECH. (*ASTERACEAE*)

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Streszczenie

Z ziela *Zoegea leptaurea* subsp. *mesopotamica* (Czerep.) Rech. (syn. *Zoegea mesopotamica* Czerep.) wyizolowano 9α-hydroksypartenolid. Związek ten zidentyfikowano za pomocą analiz spektralnych (^{1}H NMR i ^{13}C NMR). Potwierdzono tym samym wcześniejsze doniesienia o występowaniu 4,5-epoksygermakranolidów w rodzaju *Zoegea* L. Uzyskane dane mają walor chemotaksonomiczny.

Słowa kluczowe: *Zoegea*, *Asteraceae*, *germakranolidy, 9α-hydroksypartenolid, chemotaksonomia*