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Analytical Methods

Semi-synthesis of new antimicrobial esters from the natural oleanolic and maslinic acids



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ABSTRACT

In this article, we report an effective procedure for the selective isolation of oleanolic acid **1** and maslinic acid **2** (3.4 and 8.5 mg/g DW, respectively) from pomace olive (*Olea europaea* L.) using an ultrasonic bath, and the synthesis of a series of new triterpenic acid esters. The compounds were characterized by their spectral data and were evaluated for their antimicrobial activity. Among the compounds tested, those having sulfur and chlorine atoms were found to be antibacterial. They showed activity against two Gram-positive bacteria *Staphylococcus aureus* and *Enterococcus faecalis* and two Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa* (MICs within a range of 5–25 µg/mL). The fungus *Penicillium italicum* was found to be the most sensitive to both sulfur derivatives: (3β)-3-((thiophene-2-carbonyl)oxy)-olean-12-en-28-oic acid (**1a**) (IZ = 22 mm) and (2α,3β)-2,3-bis((thiophene-2-carbonyl)oxy)olean-12-en-28-oic acid (**2a**) (IZ = 24 mm).

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1. Introduction

Antibiotic resistance among bacterial pathogens is a serious problem for human and veterinary medicine, which necessitates the development of new therapeutics and antimicrobial strategies (Wright, 2010). Some plants derived secondary metabolites, e.g., pentacyclic triterpenoids have a potential as a new class of antibacterial agents as they are active against many bacterial species, both Gram-positive and Gram-negative, and they specifically target the cell envelope (Kurek, Nadkowska, Pliszka, & Wolska, 2012; Walencka et al., 2007). Triterpenoids are a large and structurally diversified group of natural products (Hill & Connolly, 2012) that display nearly 200 distinct skeletons. These compounds are found in food, medicinal herbs and various other plants in free form or bound to glycosides. The latter and their derivatives have been studied for their antineoplastic, anti-inflammatory, anti-ulcerogenic, antimicrobial, anti-plasmodial, antiviral (anti-HIV) characteristics. They are hepato- and cardio-protective, analgesic, anti-mycotic, immunomodulatory and they have tonic effects (Akihisa & Yasukawa, 2006; Cassels & Asencio, 2011; Kuo, Qian,

Morris-Natschke, & Lee, 2009; Ríos, 2010; Shanmugam, Nguyen, Kumar, Tan, & Sethi, 2012). In our previous research, we reported the synthesis and the antibacterial and anti-acetylcholinesterase activity of various oleanolic acid congeners as well as the structure–activity relationship conclusions (Hichri, Ben Jannet, Cheriaa, Jegham, & Mighri, 2003).

Oleanolic acid (3β-hydroxyolean-12-en-28-oic acid, **1**) and maslinic acid (2α,3β-dihydroxyolean-12-en-28-oic acid, **2**) are natural pentacyclic triterpenoid compounds (Fig. 1), widely distributed throughout the vegetable kingdom (Herrera, Rodríguez-Rodríguez, & Ruiz-Gutiérrez, 2006; Liu, 2005). These acids are present in olive-pomace oil (García-Granados, 1997), being the main components of the protective wax-like coating of the olive skin.

Both triterpenic acids and some closely related compounds display remarkable pharmacological characteristics such as being antitumor, antibacterial, anti-HIV, anti-inflammatory, antioxidant, and hepatoprotective (Huang et al., 2011; Parra, Rivas, Martín-Fonseca, García-Granados, & Martínez, 2011; Pollier & Goossens, 2012; Wang et al., 2010).

In this report, we describe the effective extraction of large amounts of these compounds from olive-pressing residues using an ultrasonic bath. To explore the roles of the introduced acyl

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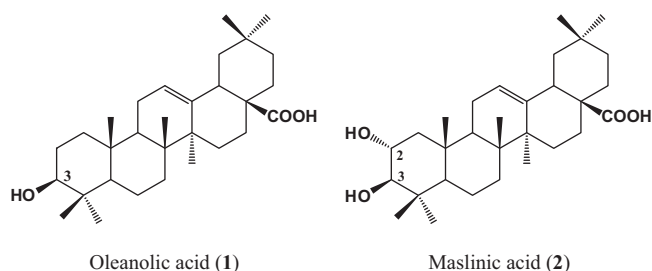


Fig. 1. Chemical structures of the natural triterpenic compounds **1** and **2**.

substituent at C-3 position, we prepared a series of new triterpenic acid esters **1a–j** from oleanolic acid **1** and **2a–o** from maslinic acid **2** using appropriate cyclic anhydrides and acid chlorides involving *N,N*-dimethyl-4-aminopyridine (DMAP) as a catalyst.

Compounds **1** and **2** and their acylated derivatives were screened for their antimicrobial activity towards two Gram-positive and two Gram-negative bacteria as well as against five fungal plant pathogens.

2. Materials and methods

2.1. General experimental procedures

Solvents were purified and dried using standard methods. Melting points were determined on a Büchi 510 apparatus using capillary tubes. Commercial TLC plates (Silica gel 60, F254, sds) were used to monitor the progress of the reaction. Column chromatography was performed with silica gel 60 (particle size 40–63 μm , sds). HRMS were acquired with a LCT Premier XE (Waters, ESI technique, positive mode) mass spectrometer. For ESI experiments, leucine-enkephalin peptide was employed as the LockSpray lockmass. ^1H (300 MHz, 16–32 scans) and BB-decoupled ^{13}C (75 MHz, 256–2048 scans) NMR spectra were recorded at room temperature (rt) on a Bruker AM-300 Fourier Transform spectrometer equipped with a 10 mm probe in deuterated chloroform, acetone and pyridine with all chemical shifts (δ), reported in ppm, referred to residual non deuterated solvent. Coupling constants were measured in Hz and signals are using the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet, etc.

2.2. Collection, extraction and isolation of compounds **1** and **2**

The chemlali pomace olive was collected from the factory of soap located in Sousse, Tunisia and kept at a temperature of 20 °C in the dark until its use. The solid olive oil waste (2 kg) resulting from olive fruit pressing was washed with hexane (1 mL/g) to

eliminate triglycerides. Then, dried at 35 °C for 24 h in an electrical furnace, milled and immersed in 4 L of methanol. The mixture was kept at room temperature and occasionally agitated to facilitate the maceration process. Five days after, the sample was decanted and filtered through a wire funnel. The methanolic solution was evaporated in vacuo to dryness in a rotary evaporator at 50 °C; this yielded 120 g of extract. This pasty extract was treated with hexane, and three fractions were collected using an ultrasonic bath (0.5 h, 50 °C): fraction **1** is composed of the hexane extract, fraction **2** oily consisting mainly of triglycerides and the drying of fraction **3** provided 25.5 g of a white solid formed according to TLC analysis by of two major compounds. About 25 g of this solid was separated by silica gel column chromatography (petroleum ether:EtOAc 8:2, 7:3 then 1:1) to give **1** and **2** (Table 1).

2.3. Synthesis

2.3.1. General procedure for the synthesis of oleanolic acid esters using acid chlorides

The appropriate acid chloride (1.1 equiv) was added to the mixture of **1** (0.01 g, 0.22 mmol) and *N,N*-dimethyl-4-aminopyridine (DMAP) (1 equiv), in refluxing anhydrous pyridine, and the mixture was refluxed for overnight and then concentrated in vacuum under reduced pressure. The resulting mixture was washed with water to remove salts then extracted with chloroform. The organic layer was dried over sodium sulfate. The solvent was removed under reduced pressure to give the esters **1a–e**, which were chromatographed over a column of silica gel using petroleum ether–ethyl acetate (9:1, v/v) as an eluent in 91–98% yield (Table 2).

2.3.2. General procedure for the synthesis of oleanolic acid esters using cyclic anhydrides

To a solution of **1** (0.01 g, 0.22 mmol) in 3 mL DMSO is added the appropriate cyclic anhydride (0.88 mmol) in 2 mL DMSO. The solution is thermostatted at 40 °C. *N,N*-Dimethyl-4-aminopyridine (DMAP) (0.22 mmol) is added to the solution while stirring. The reaction of the mixture is kept at 40 °C for 24 h. The reaction's product was diluted in distilled water, washed with a solution of HCl (3 M), then extracted with ethyl acetate. The organic layer was dried over sodium sulfate. After the evaporation of the solvent, the crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate 6:4) or recrystallization to give the esters **1f–j**, in 81–92% yield (Table 2).

2.3.3. General procedure for the synthesis of maslinic acid esters using acid chlorides

To a solution of **2** (0.01 g, 0.21 mmol) and of *N,N*-dimethyl-4-aminopyridine (DMAP) (2 equiv) in refluxing anhydrous pyridine,

Table 1
Methods and extraction yield of oleanolic acid **1** and maslinic acid **2** from different pomace olive cultivars.

Cultivar	Extraction methods	Yield of extraction (mg/g DW)		References
		Oleanolic acid 1	Maslinic acid 2	
Picual	Solid–liquid extraction (maceration)	0.500	1.200	Guinda, Rada, Delgado, Gutiérrez-Adán, and Castellano (2010)
Hojiblanca		0.500	1.300	
Arbequina		0.400	1.500	
Non indicated		0.015	0.034	
Manzanilla	Solid–liquid extraction (centrifugation)	0.274	0.824	Romero, García, Medina, Ruiz-Méndez, Castro, and Brenes (2010)
Hojiblanca		0.565	0.904	
Cacereña		0.185	0.295	
Kalamata		0.841	1.318	
Picual	Ultrasonic assisted extraction	1.003	2.440	Goulas and Manganaris (2011)
Kalamon		0.838	2.100	
Chemlali	Solid–liquid then ultrasonic assisted extractions	3.400	8.500	This work

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