DIARYLHEPTANOIDS FROM THE RHIZOMES OF *ZINGIBER OFFICINALE*

MỘT SỐ HỢP CHẤT DIARYLHEPTANOIT TỪ CỦ GỪNG (*ZINGIBER OFFICINALE*)

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ABSTRACT

Ginger (*Zingiber officinale* rhizome) is commonly used as a spice in food. It is also used as an herbal medicine for thousands of years to treat headaches, colds, arthritis, pains, hypertension, infectious diseases. The broad range of biological activity of Ginger was explained due to the rich of terpenoids and phenolics as well as polyphenol and arylalkanes. This paper describes the isolation and identification of three diarylheptanoids including (3*R*)-1,7-bis(3,4-dihydroxyphenyl)heptan-3-ol (**1**), (3*R*,5*R*)-1,7-bis(3,4-dihydroxyphenyl)heptan-3,5-diol (**2**), and *trans*-1,7-bis(3,4-dihydroxyphenyl)hept-4-en-3-one (**3**) from less polar soluble fraction of the rhizome of *Z. officinale*. Their chemical structures were determined by analysis of ESI-MS and NMR spectra.

Keywords: *Ginger, Zingiber officinale, chemical constituent, diarylheptanoid.*

TÓM TẮT

Củ gừng được sử dụng phổ biến làm gia vị trong thực phẩm. Bên cạnh đó, củ gừng cũng được sử dụng như một loại thảo dược từ lâu đời để điều trị đau đầu, cảm lạnh, đau nhức xương, cao huyết áp, hay một số bệnh truyền nhiễm. Phổ hoạt tính rộng của củ gừng phần nào đó được giải thích do nó chứa nhiều các hợp chất terpenoids, phenolics mà cụ thể là các polyphenol và arylankanes. Bài báo này công bố phân lập và xác định cấu trúc ba hợp chất dạng diarylheptanoids bao gồm (3*R*)-1,7-bis(3,4-dihydroxyphenyl)heptan-3-ol (**1**), (3*R*,5*R*)-1,7-bis(3,4-dihydroxyphenyl) heptan-3,5-diol (**2**), and *trans*-1,7-bis(3,4-dihydroxyphenyl)hept-4-en-3-one (**3**) từ phân đoạn kém phân cực của củ gừng. Cấu trúc hóa học của các hợp chất được minh chứng dựa trên phân tích phổ ESI-MS và phổ cộng hưởng từ hạt nhân.

Từ khóa: *Gừng, củ gừng, thành phần hóa học, diarylheptanoid.*

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1. INTRODUCTION

Zingiber genus (Zingiberaceae) comprises more than 100 species and widely distributes in tropical and warm temperate regions of the Asia [1]. A lot of *Zingiber* species have been use in the traditional medicine with anti-inflammation, anti-fungal, and anti-bacterial properties [2]. Ginger, a popular spice, is the rhizome of *Z. officinale*. It has been used both in food and folk medicine for thousands of years. Ginger essential oil was identified rich in β-sesquiphellandrene, caryophyllene and α-zingiberene which exhibited high anti-inflammatory effects as well as prevention of rheumatism and musculoskeletal disorders [2-3]. Chemical study on ginger revealed the presence of gingerols (arylankanes), diarylheptanoids, and their derivatives. Almost the reports focused in the volatile components of the ginger [4]. In the aim to clarify chemical constituents of ginger, this paper describes the isolation and structural determination of three diarrylheptanoids from the dichloromethane soluble fraction of dried ginger.

2. MATERIAL AND METHODS

2.1. General experimental procedures.

ESI-MS were recorded on an Agilent 1100 LC-MSD Trap. NMR spectra were measured on a Jeol 400 MHz FT-NMR spectrometer. Column chromatography was performed using a silica gel (Kieselgel 60, 70 - 230 mesh and 230 - 400 mesh, Merck). Thin layer chromatography (TLC) was carried out on pre-coated silica gel 60 F_{254} (0.25mm, Merck). The spots were visualized under UV radiation (254 and 365nm) and by spraying with aqueous solution of H_2SO_4 (10%) followed by heating with a hot plate.

2.2. Plant material

Rhizomes of *Zingiber officinale* Roscoe were collected at Hoa Binh province in October 2018 and taxonomically identified by PhD. Nguyen The Cuong at the Institute of Ecology and Biological Resources, Vietnam Academy of Science and Technology (VAST). A voucher specimen (coded: NCCT-HB31018) was kept at the Department of Structural Research, Institute of Marine Biochemistry, VAST.

2.3. Extraction and isolation.

Air-dried rhizome of *Zingiber officinale* (2.5kg) was ultrasonically extracted with methanol at room temperature (three times, each 5L, 30 minutes). The combined methanol soluble extracts were concentrated in *vacuo* to dryness. The methanol residue (150g) was suspended in 2.0L of water and successively partitioned with n-hexane, dichloromethane, ethyl acetate (each 2.0L × 3 times) to obtain soluble fractions of hexane (43g), dichloromethane (32 g), EtOAc (14g). The dichloromethane soluble fraction was separated over a silica gel column using a gradient of n-hexane/acetone (40:1-0:1, v/v) to give

seven fractions (ZOD1-ZOD7). Fraction ZOD3 was chromatographed over silica gel column using dichloromethane/ethyl acetate (5:1, v/v) to obtain four subfractions (ZOD3A-ZOD3D). Fraction ZOD3A was purified on a silica gel column, eluting with n-hexane/ethyl acetate (3/1, v/v) to give compound **3** (37mg). Fraction ZOD3C was purified on a silica gel column, eluting with n-hexane/acetone (5/1, v/v) to give compound **1** (26mg). Fraction ZOD5 was loaded on a silica gel column and eluted with n-hexane/ethyl acetate (2/1, v/v) to give five fractions ZOD5A-ZOD5E. Compound **2** (19mg) was obtained from the fraction ZOD5B by silica gel column chromatography with dichloromethane/acetone (7/1, v/v) as the eluent.

(3*R*)-1,7-bis(3,4-dihydroxyphenyl)heptan-3-ol (**1**): Colourless gum; $[\alpha]_D^{25}$:–17.2 (*c* = 0.1, MeOH); $C_{19}H_{24}O_5$; ESI-MS *m/z*: 333 $[M+H]^+$; ^{1}H-NMR (400MHz, CD_3OD) and ^{13}C-NMR (100MHz, CD_3OD) are given in the Table 1.

(3*R*,5*R*)-1,7-bis(3,4-dihydroxyphenyl)heptan-3,5-diol (**2**): Colourless gum; $[\alpha]_D^{25}$:+12.8 (*c* = 0.1, MeOH); $C_{19}H_{24}O_6$; ESI-MS *m/z*: 349 $[M+H]^+$; ^{1}H-NMR (400MHz, CD_3OD) and ^{13}C-NMR (100MHz, CD_3OD) are given in the Table 1.

***Trans*-1,7-bis(3,4-dihydroxyphenyl)hept-4-en-3-one (3)**:Yellow gum; $C_{19}H_{20}O_5$; ESI-MS *m/z*: 329 $[M+H]^+$^{1}H-NMR (400MHz, CD_3OD) and ^{13}C-NMR (100MHz, CD_3OD) are given in the Table 1.

3. RESULTS AND DISCUSSION

Compound **1** was isolated as a colourless gum. The ^{1}H-NMR spectrum of **1** contained aromatic proton signals corresponding with two ABX coupled protons [δ_H 6.33 (1H, dd, *J* = 8.0, 1.6Hz), 6.44 (1H, d, *J* = 1.6Hz), 6.50 (1H, d, *J* = 8.0Hz), 6.34 (1H, dd, *J* = 8.0, 1.6Hz), 6.46 (1H, d, *J* = 1.6Hz), and 6.51 (1H, d, *J* = 8.0Hz)], an oxygenated methine proton [δ_H 3.35 (1H, m)], and six upfield shifted protons δ_H 1.20~2.44ppm. The ^{13}C-NMR and DEPT spectrum of **1** revealed signal of 19 carbons. Among them, 12 aromatic carbons δ_C 116.3~146.2 suggested the presence of two benzene rings. An oxygenated methine group was assigned at δ_C 71.8ppm. Remaining six methylene groups was observed at δ_C 40.5, 38.2, 36.2, 32.9, 32.3, and 26.2. Aforementioned NMR data suggested compound **1** to be a diarylheptanoid.

Table 1. NMR spectral data for compounds **1**-**3** in CD_3OD.

No	1		2		3	
	$^a\delta_C$	$^b\delta_H$ (mult. *J* in Hz)	$^a\delta_C$	$^b\delta_H$ (mult. *J* in Hz)	$^a\delta_C$	$^b\delta_H$ (mult. *J* in Hz)
1	32.3	2.44 (m)	32.3	2.31 (m); 2.44 (m)	30.9	2.69 (t, 6.4)
2	40.5	1.49 (m)	41.3	1.50 (m)	42.7	2.78 (t, 6.4)
3	71.8	3.35 (m)	68.7	3.64 (quin, 6.4)	203.1	-
4	38.2	1.26 (m)	45.6	1.36 (t, 6.4)	131.7	6.04 (d, 16.0)
5	26.2	1.20 (m)	68.7	3.64 (quin, 6.4)	149.4	6.85 (dt, 6.4, 16.0)
6	32.9	1.40 (m)	41.3	1.50 (m)	34.8	2.44 (q, 6.4)
7	36.2	2.30 (m)	32.4	2.31 (m); 2.44 (m)	35.6	2.60 (t, 6.4)
1′	135.5	-	135.4	-	133.9	-
2′	116.6	6.44 (d, 1.6)	116.4	6.46 (d, 1.6)	116.4	6.58 (d, 1.6)
3′	146.1	-	146.2	-	146.3	-
4′	144.2	-	144.3	-	144.6	-
5′	116.3	6.50 (d, 8.0)	116.6	6.48 (d, 8.0)	116.6	6.64 (d, 8.0)
6′	120.7	6.33 (dd, 8.0, 1.6)	120.7	6.33 (dd, 8.0, 1.6)	120.7	6.46 (dd, 8.0, 1.6)
1″	135.7	-	135.4	-	134.1	-
2″	116.6	6.46 (d, 1.6)	116.4	6.46 (d, 1.6)	116.4	6.60 (d, 1.6)
3″	146.2	-	146.2	-	146.3	-
4″	144.2	-	144.3	-	144.6	-
5″	116.4	6.51 (d, 8.0)	116.6	6.48 (d, 8.0)	116.6	6.65 (d, 8.0)
6″	120.7	6.34 (dd, 8.0, 1.6)	120.7	6.33 (dd, 8.0, 1.6)	120.7	6.48 (dd, 8.0, 1.6)

Measured at [a]100MHz, [b]400MHz

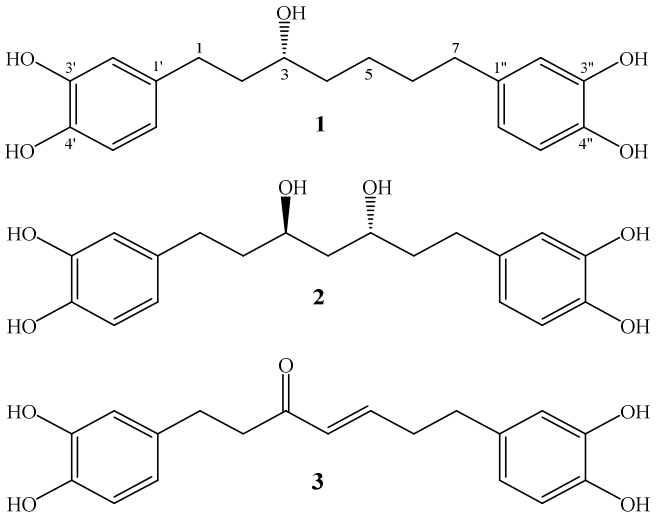

Figure 1. Chemical structures of compounds **1-3**from Zingiber officinale

The HMBC interactions from H-1 (δ_H 2.44) to C-2 (δ_C 116.6)/ C-6 (δ_C 120.7), from H-2 (δ_H 1.49) to C-1 (δ_C 135.5), and from H-1 to C-3 (δ_C 71.8) indicated location of hydroxy group at C-3 and connection of the benzene ring with heptane chain via C-1/C-1. The downfield shifted of C-3 (δ_C 146.1) and C-4 (δ_C 144.2) suggested for the presence of two hydroxy groups at C-3 and C-4 which formed a 1,3,4-trisubstituted benzene ring (an ABX coupled protons). Similarly, the HMBC correlations from H-7 (δ_H 2.30) to C-2 (δ_C 116.6)/ C-6 (δ_C 120.7) supported for the binding of other benzene ring at C-7 of heptane chain. And the downfield shifted of C-3 (δ_C 146.2) and C-4 (δ_C 144.2) suggested for the presence of two hydroxy groups at C-3 and C-4. Configuration at C-3 was deduced to be 3*R* by negative optical rotation ($[\alpha]_D^{25}$:-17.2) as previous report [5]. Therefore, compound **1** was determined to be (3*R*)-1,7-bis(3,4-dihydroxyphenyl)heptan-3-ol. This deduction was well agreed with a quasi-molecular ion peak at *m/z* 333 $[M+H]^+$ corresponding with molecular formula of **1** as

$C_{19}H_{24}O_5$. This compound was previously isolated from several plants such as *Pinus flexilis*[6], *Alnus rubra*[7], and *Alnus formosana*[8] showing potential anti-inflammatory activity by inhibiting NO production in macrophages RAW264.7 [8].

Compound **2** was obtained as a colourless gum. The ^{1}H-NMR spectrum of **2** also observed ABX aromatic coupled protons [δ_H 6.33 (dd, *J* = 8.0, 1.6Hz), 6.46 (d, *J* = 1.6Hz), and 6.48 (d, *J* = 8.0Hz)], oxygenated methine proton [δ_H 3.64 (quin, *J* = 6.4Hz)]. The ^{13}C-NMR and DEPT spectrum of **2** contained ten carbon signals including six aromatic signals (δ_C 146.2, 144.3, 135.4, 120.7, 116.6, 116.4), an oxygenated methine signal (δ_C 68.7), and three methylene signals (δ_C 45.6, 41.3, 32.3). However, the ESI-MS data of compound **2** with a quasi-molecular ion peaks at *m/z* 349 $[M+H]^+$ suggested structure of compound **2** also to be a symmetric diarylheptanoid. Accordingly, six aromatic carbon signals corresponded for two benzene rings. Oxygenated carbon signal and three methylene carbon signals corresponded to seven carbons of heptane chain. Like compound **1**, the presence of ABX aromatic coupled proton signals and two downfield carbons (δ_C 146.2, 144.3) characterized for the 3,4-dihydroxyphenyl group. The HMBC correlations from H-1/H-7 (δ_H 2.44, 2.31) to C-2/C-2 (δ_C 116.4); C-6 /C-6 (δ_C 120.7); C-3/C-5 (δ_C 68.7) suggested location of 3,4-dihydroxyphenyl groups at C-1 and C-7, two hydroxy group at C-3 and C-5 which formed a symmetric structure. Carbon chemical shift of C-3 and C-5 ($\delta_{C\text{-}3,C\text{-}5}$ = 68.7) suggested (3*β*,5*α*)-relative configurations which were good consistence with literature [(3*β*,5*α*)-relative configurations $\delta_{C\text{-}3,C\text{-}5}$ = 68.8 [9] and (3*β*,5*β*)-relative configurations $\delta_{C\text{-}3,C\text{-}5}$ = 71.0 [10]]. Additionally, positive optical rotation of **2** ($[\alpha]_D^{25}$:+12.8) expected (3*R*,5*R*)-absolute configurations as previously described [9]. Consequently, compound **2** was determined as (3*R*,5*R*)-1,7-bis(3,4-dihydroxyphenyl)heptan-3,5-diol. This compound was previously reported from *Alpina officinarum*[11], *Tacca chantrieri*[9] which showing cytotoxic activity and inhibiting aggregation of α-synuclein [11].

Compound **3** was isolated as yellow gum. The ^{1}H-NMR spectrum of **3** showed eight downfield protons including six protons belonging to two sets of ABX coupled protons [δ_H 6.64 (d, *J* = 8.0Hz), 6.58 (d, *J* = 1.6Hz), 6.46 (dd, *J* = 8.0, 1.6Hz), 6.65 (d, *J* = 8.0Hz), 6.60 (d, *J* = 1.6Hz), 6.48 (dd, *J* = 8.0, 1.6Hz)] and two olefinic protons [δ_H 6.85 (dt, *J* = 6.4, 16.0Hz), 6.04 (d, *J* = 16.0Hz)]. The lager of *J* coupling constant (*J* = 16.0Hz) indicated the presence of *trans*-disubtituted CH=CH double bond. The ^{13}C-NMR spectrum of **3** observed signals of 19 carbons including 14 sp^2 hybridised olefinic carbons (δ_C 116.4~149.4), one ketone carbon (δ_C 203.1), and four methylene (δ_C 42.7, 35.6, 34.8, 30.9). Above NMR data suggested that compound **3** also to be a diarylheptanoid containing two sets of 1,3,4-trisubtituted benzene rings, a ketone functional group, a *trans* CH=CH double bond, and four methylene carbons. By analysis of HSQC, two olefinic carbon signals at δ_C 131.7/ δ_H 6.04and δ_C 149.4/ δ_H 6.85 were assigned for *trans* CH=CH double bond. Furthermore, HMBC correlations from H-4 (δ_H 6.04)/H-5 (δ_H 6.85) to ketone carbon (δ_C 203.1) indicated for α,β-unsaturated ketone moiety. The similarity between NMR data corresponding to benzene rings (C-1~C-6, and C-1~C-6) of compound **3** and compounds **1**-**2**indicated the same structure of two 3,4-dihydroxyphenyl groups. Also, the HMBC correlations from H-1 (δ_H 2.69) to C-2 (δ_C 116.4)/ C-6 (δ_C 120.7), from H-7 (δ_H 2.60) to C-2 (δ_C 116.4)/ C-6 (δ_C 120.7) confirmed location of two 3,4-dihydroxyphenyl groups at C-1 and C-7. Multiplicity of H-1/ H-2 (triplet, *J* = 6.4 Hz) and HMBC correlation from H-1 (δ_H 2.69) to C-3 (δ_C 203.1) supported for position of ketone functional group at C-3. Therefore, compound **3** was established as *trans*-1,7-bis(3,4-dihydroxyphenyl)hept-4-en-3-one. Its NMR data was well agreed with those reported in the literature [12]. This compound was also previously isolated from *Pinus flexilis*[6], *Amonmum muricarpum*[13], and various medicinal plant belonging *Alnus* species [12, 14]. Compound **3** was reported to have potential anti-inflammation activity [8, 15-16].

4. CONCLUSIONS

Three diarylheptanoids including (3*R*)-1,7-bis(3,4-dihydroxyphenyl)heptan-3-ol (**1**), (3*R*,5*R*)-1,7-bis(3,4-dihydroxyphenyl)heptan-3,5-diol (**2**), and *trans*-1,7-bis(3,4-dihydroxyphenyl)hept-4-en-3-one (**3**) from dichloromethane soluble fraction of the dried rhizome of *Z. officinale*. Their chemical structures were determined by analysis of ESI-MS and NMR spectra which well matched with those reported in the literature. To the best of our knowledge, this is the first report on isolation of compounds **1**-**3** from ginger.

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THÔNG TIN TÁC GIẢ

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