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Alnuheptanoid B: A New Cyclic Diarylheptanoid from *Alnus japonica* Stem Bark

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Abstract: A new cyclic diarylheptanoid namely alnuheptanoid B (**3**), along with four known cyclic diarylheptanoids: myricanone (**1**), (+)-*S*-myricanol (**2**), myricanone 5-*O*-*β*-D-glucopyranoside (**4**), and (+)-*S*-myricanol 5-*O*-*β*-D-glucopyranoside (**5**) were isolated from *Alnus japonica* Steud (Betulaceae) stem bark. Their structures were determined by spectroscopic analyses, including UV, IR, 1D (^{1}H and ^{13}C), 2D (COSY, HMQC, and HMBC), and HRESIMS, as well as optical rotation measurement. Compounds **1**, **2**, **4**, and **5** are reported for the first time from the plant. All isolated compounds **1-5** were tested for their antioxidant and anti-inflammatory activities using DPPH assay and carrageenin induced rat paw edema model, respectively. They displayed significant antioxidant activity in relation to propyl gallate (positive control). Compound **2** demonstrated anti-inflammatory effect at a dose 10 mg/kg.

Keywords: *Alnus japonica*; Betulaceae; alnuheptanoid B; cyclic diarylheptanoid; antioxidant; anti-inflammatory. © 2015 ACG Publications. All rights reserved.

1. Introduction

Diarylheptanoids have been isolated from various genera such as *Acer* (Aceraceae), *Platycarya* (Juglandaceae), *Myrica* (Myricaceae), *Centrolobium* (Leguminosae), *Alpinia*, *Curcuma* and *Zingiber* (Zingiberaceae), and *Alnus* and *Betula* (Betulaceae) [1, 2]. The structure of diarylheptanoids consists of two aromatic rings linked by a linear seven-carbon aliphatic chain with varying functional groups on the aryl and C7-aliphatic moieties. They can be sub-grouped into open chain linear or cyclic compounds [2, 3]. The latter group includes *meta-meta* bridged biphenyls and *meta-para* diphenyl ethers [2, 3]. In addition, more complex diarylheptanoids with the basic skeleton extended by fragments such as arylbutyl, chalcone or flavonoid moieties have been isolated [4]. They

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were recognized as potential therapeutic agents with different biological activities as anti-inflammatory, antioxidant, antitumor, estrogenic, leishmanicidal, hepatoprotective, and neuro-protective [3, 5-11]. *Alnus japonica* (Betulaceae, Japanese name; Hannoki) is a common tree in low mountainous areas of Japan [12, 13]. Our previous phytochemical study of *A. japonica* stem bark led to isolation of diarylheptanoids and triterpenes [13]. In continuation of our investigation of *A. japonica* stem bark, a new cyclic diarylheptanoid named alnuheptanoid B, along with four known cyclic diarylheptanoids were isolated (Figure 1). The isolated compounds were evaluated for their antioxidant activity using DPPH. Also, their anti-inflammatory activity was determined using carrageenin induced rat paw edema method.

2. Materials and Methods

2.1. General

Electrothermal 9100 Digital Melting Point apparatus (Electrothermal Engineering Ltd, Essex, England) was used for measuring melting points. The UV spectra were recorded using Perkin Elmer double beam spectrophotometer Model 550S, attached to a Hitachi recorder Model 561, using 1 cm quartz cell. The IR spectra were carried out on a Shimadzu Infrared-400 spectrophotometer (Shimadzu, Kyoto, Japan). Optical rotations were recorded on a Perkin-Elmer Model 341 LC Polarimeter (Perkin-Elmer, Waltham, MA, USA). ESIMS spectra were obtained with a LCQ DECA mass spectrometer (Thermo Finnigan, Bremen, Germany) coupled to an Agilent 1100 HPLC system equipped with a photodiode array detector. HRESIMS was recorded on a LTQ Orbitrap (Thermo Finnigan, Bremen, Germany). 1D (^{1}H and ^{13}C) and 2D (COSY, HMQC, and HMBC) NMR spectra were recorded on Bruker ARX 400 NMR spectrometers (Bruker BioSpin, Massachusetts, USA). HPLC separations were performed on a HPLC system consisting of a Lachrom-Merck Hitachi L-7100 pump and a L-7400 UV detector (UV detection at 280 nm) using a C-18 column (250 × 8 mm i.d., prefilled with Eurospher 100, Knauer, Berlin, Germany), applying a linear gradient from 80 % H_2O (pH 2.0) and 20 % MeOH to 100 % MeOH over 45 min. Column chromatographic separations were performed on silica gel 60 (0.04-0.063 mm, Merck, Darmstadt, Germany) and RP-18 (0.04-0.063 mm, Merck, Darmstadt, Germany). TLC analysis was performed on pre-coated TLC plates with silica gel 60 F_{254} (0.2 mm, Merck, Darmstadt, Germany). The compounds were detected by UV absorption at λ_{max} 255 and 366 nm followed by spraying with *p*-anisaldehyde:H_2SO_4 reagent and heating at 110 ºC for 1-2 min. 2,2-Diphenyl-1-picrylhydrazyl (DPPH), propyl gallate (PG), carrageenin, and indomethacin were purchased from Sigma Chemical Co. (Germany).

2.2. Plant material

Alnus japonica stem bark was collected in March 2005 from the authorized trees growing in the botanical garden, Heinrich-Heine University, Düsseldorf, Germany. The plant was taxonomically identified by Prof. Dr. Peter Westhoff (Prof. of Development and Molecular Biology of Plants, Heinrich-Heine University, Düsseldorf, Germany). A voucher specimen was deposited at the Department of Pharmacognosy, Faculty of Pharmacy, Al-Azhar University, Assiut, Egypt (Registration code AJB-2005).

2.3. Extraction and Isolation

The air-dried powdered stem bark of *A. japonica* (200 g) was exhaustively extracted with 70 % EtOH (4 × 2 L). The combined extracts were concentrated under reduced pressure to afford a dark brown residue (12 g). The EtOH extract was subjected to vacuum liquid chromatography (VLC) using 50 % *n*-hexane:$CHCl_3$ (4 x 500 mL) and EtOAc (4 x 500 mL) to give 2.6 and 4.1 g, respectively. The VLC of the EtOAc fraction (4.1 g) using $CHCl_3$:MeOH gradient elution afforded six sub-fractions (A-F). Sub-fractions B-E were previously investigated by authors [13]. Silica gel column chromatography (50 g × 50 cm × 2 cm) of sub-fraction A (470 mg) using $CHCl_3$:MeOH gradient gave impure **1** and **2**.

They were further purified by semi-preparative HPLC to yield **1** (22.1 mg, white needles) and **2** (14.8 mg, white needles). Sub-fraction F (392 mg) was chromatographed on RP-18 column (60 g × 50 cm × 2 cm) using MeOH:H_2O gradient elution followed by semi-preparative HPLC to give **3** (13.7 mg, white amorphous powder), **4** (15.3 mg, white amorphous powder), and **5** (18.9 mg, white amorphous powder).

2.4. Spectral Data

*Alnuheptanoid B (**3**)*: white amorphous powder (13.7 mg); $[\alpha]_D$ + 43.1 (*c* 0.50, MeOH); UV (MeOH) λ_{max} (log ε): 219 (4.71), 251 (4.36), 293 (3.95) nm; IR (KBr) γ_{max}: 3465, 1725, 1715, 1598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.82 (1H, m, H-7A), 2.72 (1H, m, H-7A), 1.90 (1H, m, H-8A), 1.86 (1H, m, H-8A), 1.80 (2H, m, H-9), 2.75 (1H, m, H-10A), 2.67 (1H, m, H-10B), 2.77 (2H, m, H-12), 3.07 (1H, m, H-13A), 2.95 (1H, m, H-13B), 7.06 (1H, dd, *J* = 6.6, 1.5 Hz, H-15), 6.87 (1H, d, *J* = 6.6 Hz, H-16), 6.69 (1H, d, *J* = 1.5 Hz, H-18), 6.67 (1H, s, H-19), 4.80 (1H, d, *J* = 7.6 Hz, H-1`), 3.33 (1H, m, H-2`), 3.37 (1H, m, H-3`), 3.95 (1H, m, H-4`), 3.67 (1H, m, H-5`), 3.86 (1H, m, H-6`A), 3.70 (1H, m, H-6`B), 3.95 (3H, s, 4-OCH_3), 3.79 (3H, s, 3-OCH_3), 2.08 (3H, s, 17-CO$\underline{CH_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 130.9 (s, C-1), 128.9 (s, C-2), 146.9 (s, C-3), 145.0 (s, C-4), 148.7 (s, C-5), 124.8 (s, C-6), 27.8 (t, C-7), 24.7 (t, C-8), 21.9 (t, C-9), 45.8 (t, C-10), 213.6 (s, C-11), 42.4 (t, C-12), 28.6 (t, C-13), 132.1 (s, C-14), 129.6 (d, C-15), 122.7 (d, C-16), 149.8 (s, C-17), 132.4 (d, C-18), 129.1 (d, C-19), 105.0 (d, C-1`), 74.1 (d, C-2`), 77.2 (d, C-3`), 69.9 (d, C-4`), 76.3 (d, C-5`), 62.0 (t, C-6`), 61.7 (q, 3-OCH_3), 61.9 (q, 4-OCH_3), 20.8 (q, 17-CO$\underline{CH_3}$), 171.7 (s, 17-$\underline{CO}CH_3$); ESIMS: *m/z* 561.2 $[M + H]^+$, 398.9 $[(M + H)\text{-Glu}]^+$, 357.2 $[(M + H)\text{-(Glu+Acetyl)}]^+$; HRESIMS: *m/z* 561.2339 (calc for $C_{29}H_{37}O_{11}$, 561.2336 $[M + H]^+$).

2.5. Antioxidant Activity

The antioxidant activity of the isolated compounds was evaluated using 2,2`-diphenylpicrylhydrazyl (DPPH) assay as previously outlined [14, 15]. The detailed procedure was mentioned in Supporting Information.

2.6. Pharmacological Study

2.6.1. Animal

Adult male albino rats (120-150 g body weight) were used. All animal procedures were conducted in accordance with the internationally accepted principles for laboratory animals' use and care as found in the European community guidelines. An institutional ethical committee approval was obtained. The study protocol was approved by the animal ethical committee of Assiut University. The animals were housed under standardized environmental conditions in the pre-clinical animal house, Pharmacology Department, Faculty of Medicine, Assuit University. The animals were fed with standard diet and free access to water. They were kept at 24-28°C, 60-70% relative humidity, 12 hr day and night cycle for one week to acclimatize to the environmental conditions.

2.6.2. Carrageenin Induced Rat Paw Edema

The anti-inflammatory activity was evaluated as previously described [14, 16, 17] (See Supporting Information).

2.7. Statistical Analysis

All data were expressed as mean ± standard error of mean using the student *t* test. The statistical significance was evaluated by one-way analysis of variance (ANOVA). The values were considered to be significantly different when *P* values were less than 0.01 ($P < 0.01$).

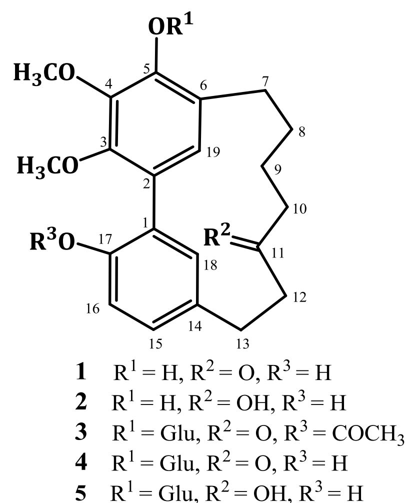

Figure 1. Structures of compounds **1-5**

3. Results and Discussion

3.1. Structure elucidation

Compound **3** was obtained as white amorphous powder. Its molecular formula was established as $C_{29}H_{36}O_{11}$ from the HRESIMS quasi-molecular ion peak at *m/z* 561.2339 $[M + H]^+$. The IR, UV, and NMR spectral data of **3** were similar to those of **4** except for the appearance of new signals at δ_H 2.08 /δ_C 20.8 (CO$\underline{CH_3}$) and 171.7 ($\underline{CO}CH_3$) characteristic for the presence of an acetyl group in **3**. Its attachment at C-17 was confirmed by the ^3J HMBC cross peak of H-16 to the carbonyl group of acetyl moiety at δ_C 171.7 and further secured by the ESIMS fragment ion peak at 357.2 $[(M + H)\text{-}(Glu+Acetyl)]^+$. In addition, **3** was 42 mass units and one degree of unsaturation more than **4**, confirming the presence of the acetyl moiety. In the UV spectrum, absorption maxima at 219, 251, and 293 nm indicated a diarylheptanoid structure of **3** [18]. Its IR spectrum showed absorption bands ascribable to hydroxyl (3465 cm^{-1}), ester carbonyl (1725 cm^{-1}), ketone carbonyl (1715 cm^{-1}), and benzene (1598 cm^{-1}) functionalities [19]. The ^{1}H NMR spectrum showed two methoxy groups singlets at δ_H 3.95 (4-OCH_3) and 3.79 (3-OCH_3). They correlated with the carbons resonating at δ_C 61.9 (4-OCH_3) and 61.7 (3-OCH_3), respectively in HMQC spectrum. Their connectivity at C-4 and C-3 was confirmed by the HMBC cross peaks of 4-OCH_3/C-4 (δ_C 145.0) and 3-OCH_3/C-3 (δ_C 146.9). Four aromatic proton signals at δ_H 7.06 (dd, J = 6.6, 1.5 Hz, H-15), 6.87 (d, J = 6.6 Hz, H-16), 6.69 (d, J = 1.5 Hz, H-18), and 6.67 (s, H-19), which correlated with carbons at δ_C 129.6 (C-15), 122.8 (C-16), 132.4 (C-18), and 129.1 (C-19) in HMQC spectrum, indicating the presence of 1,2,4-*tri*-substituted and 1,2,3,4,5-*penta*-substituted benzene moieties in **3** [20, 21]. They were established by the ^{1}H-^{1}H COSY cross peaks of H-15 to H-16 and H-18 and further confirmed by the HMBC correlations of H-15 to C-17 and C-18, H-16 to C-1 and C-14, H-18 to C-14 and C-17, and H-19 to C-3 and C-5 (Figure 2). The connectivity of two phenyl moieties at C_1-C_2 was secured based on the HMBC cross peaks of H-19 to C-1 and H-18 to C-2 (Figure 2). Moreover, an anomeric proton signal at δ_H 4.80 (d, J = 7.6 Hz, H-1`) showed cross peak to the carbon signal at $\delta_C$ 105.0 (C-1`), indicating the presence of β-glucopyranose moiety [14, 16]. This was confirmed by the observed fragment ion peaks at *m/z* 398.9 $[(M + H)\text{-}Glu]^+$ and 357.2 $[(M + H)\text{-}(Glu+Acetyl)]^+$ in the ESIMS spectrum. In the HMBC, the cross peak of H-1` to C-5 (δ_C 148.7) established the attachment of glucose moiety at C-5. Furthermore, signals for six methylene groups at δ_H 1.80-3.07 and ketone carbonyl at δ_C 213.6 (C-11), characteristic for the presence of heptanoid moiety in **3** were observed. In the ^{1}H-^{1}H COSY spectrum, the spin system started from H-7 to H-10 and cross peak of H-12 to H-13 established this moiety. It was secured by the observed HMBC cross peaks of H-9/C-7 and C-11, H-10/C-8, H-12/C-13, and H-13/C-

11. The attachment of heptanoid moiety at C6-C14 of the biphenyl moiety was confirmed by the HMBC cross peaks of H-8/C-6, H-19/C-7, and H-18/C-13. Consequently, the structure of **3** was concluded to be 17-*O*-acetyl myricanone 5-*O*-*β*-glucopyranoside and named alnuheptanoid B.

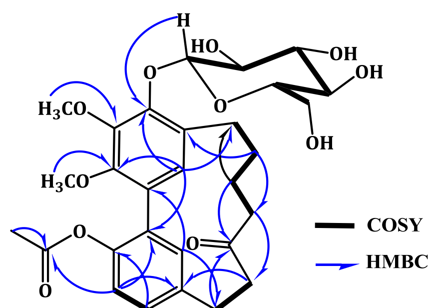

Figure 2. Important ^{1}H-^{1}H COSY and HMBC correlations of alnuheptanoid B (**3**)

The known compounds were identified to be myricanone (**1**) [20, 21], (+)-*S*-myricanol (**2**) [21, 22], myricanone 5-*O*-*β*-D-glucopyranoside (**4**) [23], and (+)-*S*-myricanol 5-*O*-*β*-D-glucopyranoside (**5**) [18] by the analysis of the spectroscopic data (1D, 2D NMR, and MS) and comparison of their data with literature.

3.2. Biological activities

3.2.1. Antioxidant activity

The antioxidant activity of the isolated cyclic diarylheptanoids (**1**-**5**) was determined using a 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging system at concentration 50 *μ*M. The results showed that, **1** and **2** had significant antioxidant activity. While, **3**-**5** showed moderate activity in comparison with propyl gallate (a known synthetic antioxidant) (Table 1).

Table 1. The DPPH radical scavenging activity results

Sample	DPPH (% Inhibition)
1	63.10 ± 0.81
2	70.14 ± 0.55
3	41.16 ± 0.64
4	49.09 ± 0.76
5	52.11 ± 0.59
Propyl gallate	97.31 ± 0.37

Conc. 50 μM; Each value represents the mean ± S.D.; *n* = 3.

3.2.1. Anti-inflammatory activity

Compounds **1**-**5** were evaluated for their anti-inflammatory effects using carrageenin induced rat paw edema model. Compound **2** showed the highest activity comparable to indomethacin (10 mg/kg, p.o) (Table 2). Also, **1**, **3**, **4**, and **5** showed potent activity at dose 10 mg/kg after 4 hr. The phenolic compounds are known to inhibit prostaglandins synthesis enzymes, more specifically the endoperoxide [16]. It was reported that, prostaglandin like substances are released during the second phase of carrageenin induced edema [24, 25]. So, the anti-inflammatory effects of the tested compounds may be due to inhibition of prostaglandin like substances

Table 2. The anti-inflammatory activity results.

Groups n = 6	Dose mg/kg	0 hr		1 hr		2 hr		4 hr		6 hr	
		PET[a]	% IN[b]	PET[a]	% IN[b]	PET[a]	% IN[b]	PET[a]	% IN[b]	PET[a]	% IN[b]
Inflamed		3.95±0.09	0.00	5.76±0.12	0.00	6.51±0.11	0.00	6.97±0.10	0.00	4.88±0.13	0.00
Inflamed + Indom.[c]	10	3.94±0.14	0.25	5.39±0.14*	6.42	3.41±0.15*	47.62	3.12±0.08*	55.24	2.99±0.07*	38.73
Inflamed + **1**	10	3.89±0.12	1.52	3.97±0.11*	29.98	3.77±0.12*	42.09	3.51±0.07*	49.64	3.24±0.11*	33.61
Inflamed + **2**	10	3.87±0.07	2.03	3.94±0.10*	31.60	3.62±0.06*	44.39	3.38±0.13*	51.51	3.08±0.12*	36.89
Inflamed + **3**	10	3.93±0.12	0.51	4.37±0.10*	24.13	3.99±0.13*	38.71	3.74±0.11*	46.34	3.49±0.13*	28.48
Inflamed + **4**	10	3.94±0.14	0.25	4.32±0.15*	25.00	3.91±0.11*	39.94	3.70±0.09*	46.92	3.42±0.15*	29.92
Inflamed + **5**	10	3.91±0.08	1.01	4.07±0.14*	29.34	3.87±0.09*	40.55	3.69±0.11*	47.06	3.31±0.08*	32.17

Each value represents the mean ± S.E.M., n = 6; *Significant different from inflamed control group at $P < 0.01$; [a]PET: Paw edema thickness; [b]% IN: % Inhibition; [c]Indom: Indomethacin.

These results indicated that, the anti-inflammatory activity of these compounds might be through the inhibition of the inflammatory prostanoids [26, 27]. In the present study, we can make a conclusion on the SAR of the tested cyclic diarylheptanoids. It was observed that, the phenolic hydroxyl groups are responsible for anti-inflammatory activity as in **1** and **2** [26, 27]. Glucosidation of phenolic OH group leads to reduce the activity as in **3**-**5**. Secondary alcoholic hydroxyl group in aliphatic chain might increase the activity as in **1** and **5** in comparison to the other compounds.

4. Conclusions

A new cyclic diarylheptanoid and four known compounds were isolated for the first time from the stem bark of *Alnus japonica*. Their structures were elucidated using different spectroscopic methods. Compounds **1** and **2** showed significant antioxidant activity. Compound **2** exhibited potent anti-inflammatory activity.

Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/RNP

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