Anti-oxidant and Anti-Inflammatory Cyclic Diarylheptanoids 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 the EtOAc fraction of *Alnus japonica* Steud (family: Betulaceae) stem bark. Their structures were established by different spectroscopic analyses, as well as optical rotation measurement. Compounds 1, 2, 4, and 5 are isolated for the first time from *A. japonica*. The antioxidant and anti-inflammatory activities of compounds (1-5) were assessed using DPPH assay and carrageenan induced rat paw edema model, respectively. They displayed significant antioxidant activity in relation to propyl gallate (standard antioxidant) at concentration 50 µM. Compound 2 demonstrated anti-inflammatory effect at a dose 10 mg/kg compared with indomethacin (positive control).

**Keywords:** *Alnus japonica*; Alnuheptanoid B; Cyclic diarylheptanoid; Antioxidant; Anti-inflammatory.

**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 benzene rings linked by a linear C\textsubscript{7}-aliphatic chain with varying functional groups on the aryl and 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 showed wide variety of biological activities as antioxidant, anti-inflammatory, antitumor, neuro-protective, estrogenic, hepatoprotective, anti-influenza, anti-trypanosomal, antiviral, and leishmanicidal...
(3, 5-15). In Japan, *Alnus japonica* (Betulaceae) is widely distributed in the low mountains (12, 13). Previous phytochemical study of *A. japonica* revealed the presence of diarylheptanoids, triterpenoids, flavonoids, and hydrolysable tannins (12-22). Continuing our study on *A. japonica* stem bark resulted in the isolation and characterization of alnuheptanoid B, a new cyclic diarylheptanoid, along with four known cyclic diarylheptanoids (Figure 1, Tables 1 and 2). They were assessed for their free radical scavenging activity using DPPH assay. Also, their anti-inflammatory effect was estimated using carrageenin induced paw edema method.

**Experimental**

**General**

Melting points were determined by Electrothermal Digital Melting Point 9100 instrument (England). Shimadzu 1601 UV/ VIS and Shimadzu Infrared-400 (Japan) spectrophotometers were used to measure the UV and IR spectra, respectively. Optical rotation was measured by Perkin-Elmer Polarimeter 341 LC Model (USA). LRMS spectra were assessed by a MATTSQ7000 Finnigan spectrometer. A Micromass Qtof 2 spectrometer was used for HRESIMS spectra measurements. Bruker Avance DRX 400 (Bruker, USA) was used to record NMR spectra. HPLC separations were performed on a HPLC system consisting of a UV L-7400 detector (280 nm) and a Lachrom-Merck L-7100 Hitachi pump using a C\textsubscript{18} column (250 × 8 mm i.d., Eurospher 100, Germany). A linear gradient (H\textsubscript{2}O:MeOH 80:20 % to MeOH 100 % over 45 min) was applied. Chromatographic separation was achieved using RP\textsubscript{18} (0.04-0.063 mm) and silica gel (0.04-0.063 mm) 60 (Merck, Germany).

The TLC analysis was performed using the following systems: MeOH:CHCl\textsubscript{3} (10:90, S\textsubscript{1}), MeOH:CHCl\textsubscript{3} (15:85, S\textsubscript{2}), and n-BuOH:H\textsubscript{2}O:HOAc (4:5:1, S\textsubscript{3}). Pre-coated silica gel 60 F\textsubscript{254} TLC plates (0.2 mm, Merck) was used for TLC. Propyl gallate (PG), 2,2-diphenyl-1-picrylhydrazyl (DPPH), carrageenin, and indomethacin were provided by Sigma-Aldrich Co. (Taufkirchen, Germany).
Table 1. $\textsuperscript{1}H$ and $\textsuperscript{13}C$ NMR data of compounds 1 and 2 (400 and 100 MHz, CDCl$_3$).

| No | $\delta$H [m, J (Hz)] | $\delta$C (Mult.) | $\delta$H [Mult., J (Hz)] | $\delta$C (Mult.) |
|----|---------------------|------------------|--------------------------|------------------|
| 1  | -                   | 125.4 C          | -                        | 124.7 C          |
| 2  | -                   | 123.1 C          | -                        | 122.6 C          |
| 3  | -                   | 145.9 C          | -                        | 145.8 C          |
| 4  | -                   | 138.7 C          | -                        | 138.6 C          |
| 5  | -                   | 147.8 C          | -                        | 147.7 C          |
| 6  | -                   | 123.0 C          | -                        | 123.4 C          |
| 7  | 2.72 m              | 26.8 CH$_2$      | 2.55 m                   | 1.93 m           |
|    |                     |                  |                          | 25.7 CH$_2$      |
| 8  | 1.94 m              | 24.4 CH$_2$      | 2.78 m                   | 1.92 m           |
|    |                     |                  |                          | 25.4 CH$_2$      |
| 9  | 1.87 m              | 21.8 CH$_2$      | 1.69 m                   | 1.55 m           |
|    |                     |                  |                          | 23.0 CH$_2$      |
| 10 | 2.77 m              | 46.1 CH$_2$      | 1.90 m                   | 1.54 m           |
|    |                     |                  |                          | 39.4 CH$_2$      |
| 11 | -                   | 213.6 C          | 4.08 m                   | 68.6 CH          |
| 12 | 2.81 m              | 42.5 CH$_2$      | 2.33 m                   | 1.72 m           |
|    |                     |                  |                          | 34.7 CH$_2$      |
| 13 | 3.03 m              | 28.8 CH$_2$      | 2.94 m                   |                 |
|    |                     |                  |                          | 26.9 CH$_2$      |
| 14 | -                   | 132.4 C          | -                        | 130.6 C          |
| 15 | 7.05 dd (6.6, 2.0)  | 128.9 CH         | 7.08 dd (7.0, 1.5)       | 129.9 CH         |
| 16 | 6.88 d (6.6)        | 116.9 CH         | 6.91 d (7.0)             | 116.8 CH         |
| 17 | -                   | 151.7 C          | -                        | 151.4 C          |
| 18 | 6.74 d (2.0)        | 132.4 CH         | 7.17 d (1.5)             | 133.1 CH         |
| 19 | 6.60 s              | 128.9 CH         | 6.90 s                   | 129.4 CH         |
| 3-OCH$_3$ | 3.81 s | 61.3 CH$_3$ | 3.87 s | 61.3 CH$_3$ |
| 4-OCH$_3$ | 3.98 s | 61.4 CH$_3$ | 3.99 s | 61.4 CH$_3$ |
| 17-OH | 7.66 brs | - | 7.70 brs | - |
| OH | 5.91 brs | - | 5.90 brs | - |

Plant material

The plant sample was obtained from the Heinrich-Heine University’s botanical garden (Düsseldorf, Germany) in March 2005. The plant was taxonomically authenticated and identified by Peter Westhoff, Prof. of Plants Molecular Biology and Development (Heinrich-Heine University, Germany). A specimen (Registration code AJB-2005) was kept at the Faculty of Pharmacy, Department of Pharmacognosy, Al-Azhar University, Egypt.

Extraction and isolation

The powdered stem bark (200 g) was extracted exhaustively with EtOH (70 %, 4 × 2 L). The EtOH extract was concentrated to afford 12 g brown residue. The residue was chromatographed over vacuum liquid chromatography (VLC) using 50 % CHCl$_3$:n-hexane (500 mL x 4) and EtOAc (500 mL x 4) to obtain 2.6 and 4.1 g, respectively. The VLC of the EtOAc (4.1 g) fraction using CHCl$_3$:MeOH gradient elution afforded 6 sub-fractions (A-F). Sub-fractions B-E were previously investigated by authors (13). SiO$_2$ column (2 cm × 50 cm × 50 g) of sub-fraction A (470 mg, CHCl$_3$:MeOH 90:10 v/v) with CHCl$_3$:MeOH gradient, followed by semi-preparative HPLC yielded 1 (22.1 mg, white needles) and 2 (14.8 mg, white needles). RP-18 column (2 cm × 50 cm × 60 g) of sub-
fraction F (392 mg, CHCl₃:MeOH 40:60 v/v) using MeOH:H₂O gradient elution followed by HPLC gave 3 (13.7 mg), 4 (15.3 mg), and 5 (18.9 mg).

**Myricanone (1)**
White needles (22.1 mg); m.p. 191-192 °C; UV (MeOH) λ_max: 215, 258, 295 nm; NMR data: see Table 1; ESIMS: m/z 357 [M + H]⁺.

**S-Myricanol (2)**
White needles (14.8 mg); m.p. 103-104 °C; [α]₀ +38.5 (c 0.5, CHCl₃); UV (MeOH) λ_max: 221, 259, 295 nm; NMR data: see Table 1; ESIMS: m/z 359 [M + H]⁺.

**Alnuheptanoids B (3)**
White amorphous powder (13.7 mg); UV (MeOH) λ_max (log ε): 219 (4.71), 251 (4.36), 293 (3.95) nm; IR (KBr) max: 3465, 1725, 1715, 1598 cm⁻¹; NMR data: see Table 2; ESIMS: m/z 561 [M + H]⁺, 398.9 [(M + H)-(Glu+Acetyl)]; HRESIMS: m/z 561.2339 (calc for C₂₉H₃₇O₁₁, 561.2336 [M + H]⁺).

**Myricanone 5-O-β-D-glucopyranoside (4)**
White amorphous powder (15.3 mg); UV (MeOH) λ_max: 220, 251, 294 nm; NMR data: see Table 2; ESIMS: m/z 519 [M + H]⁺, 357 [(M + H)-Glu]⁺.

**(+)-S-Myricanol 5-O-β-D-glucopyranoside (5)**
White amorphous powder (18.9 mg); [α]₀ +82.3 (c 0. 5, CH₃OH); UV (MeOH) λ_max: 231, 253, 294 nm; NMR data: see Table 2; ESIMS: m/z 521 [M + H]⁺, 359 [(M + H)-Glu]⁺.

**Antioxidant activity**
The antioxidant effect of compounds 1-5 was evaluated by 2,2`-diphenylpicrylhydrazyl (DPPH) assay as previously outlined (23, 24).

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

**Results and Discussion**
Compound 3 was isolated as white amorphous powder. A molecular formula C₂₉H₃₆O₁₁ was established from the HRESIMS quasi-molecular ion peak at m/z 561.2339 [M + H]⁺. The IR, UV, and NMR spectral data of 3 were in agreement with those of 4 except for the appearance of new signals at δ_H 2.08 /δ_C 20.8 (COCH₃) and 171.7 (COCH₃) characteristic for 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 ion peak at 357.2 [(M + H)-(Glu+Acetyl)]⁺. In addition, 3 was 4 mass units and one degree of unsaturation more than 4, confirming the presence of the acetyl moiety. The UV absorption maxima at 219, 251, and 293 nm indicated a diarylheptanoid structure of 3 (27). Its IR spectrum displayed bands ascribable to hydroxyl (3465 cm⁻¹), ester carbonyl (1725 cm⁻¹), ketone carbonyl (1715 cm⁻¹), and benzene (1598 cm⁻¹) functionalities (28). The ¹H NMR spectrum showed two singlet methoxy groups at δ_H 3.95 (4-OCH₃) and 3.79 (3-OCH₃) (Table 2). They correlated with the carbons resonating at δ_C 61.9 (4-OCH₃) and 61.7 (3-OCH₃), respectively in HMQC spectrum. Their connectivity at C-4 and C-3 was proven by the HMBC cross peaks of 4-OCH₃ to C-4 (δ_C 145.0) and 3-OCH₃ to 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 the carbons resonating at δ_C 129.6 (C-15), 122.8 (C-16), 132.4 (C-18), and 129.1 (C-19) in HMOC 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 COSY cross peaks of H-15 to H-16 and H-18 and further secured 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
Table 2. $^1$H and $^{13}$C NMR data of compounds 3-5 (400 and 100 MHz, DMSO-d$_6$).

| No | $\delta$$_H$ [m, J (Hz)] | $\delta$$_C$ (Mult.) | $\delta$$_C$ [Mult., J (Hz)] | $\delta$$_H$ [Mult., J (Hz)] | $\delta$$_C$ (Mult.) |
|----|---------------------------|----------------------|-------------------------------|------------------------------|----------------------|
| 1  | -                         | 130.9 C              | -                             | 128.9 C                     | -                    |
| 2  | -                         | 128.9 C              | -                             | 128.0 C                     | -                    |
| 3  | -                         | 146.9 C              | -                             | 148.5 C                     | -                    |
| 4  | -                         | 145.0 C              | -                             | 145.3 C                     | -                    |
| 5  | -                         | 148.7 C              | -                             | 148.7 C                     | -                    |
| 6  | -                         | 124.8 C              | -                             | 126.1 C                     | -                    |
| 7  | 2.82 m 2.72 m             | 27.8 CH$_2$          | 2.81 m 27.1 CH$_2$            | 2.54 m 25.8 CH$_2$          |
| 8  | 1.90 m 1.86 m             | 24.7 CH$_2$          | 1.75 m 24.2 CH$_2$            | 2.71 m 26.0 CH$_2$          |
| 9  | 1.80 m                    | 21.9 CH$_2$          | 1.51 m 21.2 CH$_2$            | 1.28 m 22.5 CH$_2$          |
| 10 | 2.75 m 2.67 m             | 45.8 CH$_2$          | 2.63 m 45.1 CH$_2$            | 1.63 m 39.3 CH$_2$          |
| 11 | -                         | 213.6 C              | -                             | 213.2 C                     | -                    |
| 12 | 2.77 m                    | 42.4 CH$_2$          | 2.74 m 41.7 CH$_2$            | 2.09 m 34.4 CH$_2$          |
| 13 | 3.07 m 2.95 m             | 28.6 CH$_2$          | 2.84 m 28.0 CH$_2$            | 2.83 m 26.8 CH$_2$          |
| 14 | -                         | 132.1 C              | -                             | 130.7 C                     | -                    |
| 15 | 7.06 dd (6.6, 1.5)        | 129.6 CH             | 6.95 dd (6.6, 1.7)            | 128.3 CH                     |
| 16 | 6.87 d (6.6)              | 122.7 CH             | 6.71 d (6.6)                  | 115.5 CH                     |
| 17 | -                         | 149.8 C              | -                             | 152.3 C                      |
| 18 | 6.69 d (1.5)              | 132.4 CH             | 6.45 d (1.7)                  | 133.2 CH                     |
| 19 | 6.67 s                    | 129.1 CH             | 6.35 s 128.5 CH               | 6.60 s 129.5 CH             |
| 1` | 4.80 d (7.6)              | 105.0 CH             | 4.79 d (7.6)                  | 103.4 CH                     |
| 2` | 3.33 m                    | 74.1 CH              | 3.19 m 74.0 CH                | 3.04 m 74.0 CH               |
| 3` | 3.37 m                    | 77.2 CH              | 3.06 m 77.0 CH                | 3.06 m 77.1 CH               |
| 4` | 3.95 m                    | 69.9 CH              | 3.16 m 69.9 CH                | 3.17 m 69.9 CH               |
| 5` | 3.67 m                    | 76.3 CH              | 3.24 m 76.4 CH                | 3.23 m 76.5 CH               |
| 6` | 3.86 m 3.70 m             | 62.0 CH$_3$          | 3.61 m 61.0 CH$_2$            | 3.58 m 60.9 CH$_2$           |
| 3-OCH$_3$ | 3.79 s | 61.7 CH$_2$ | 3.75 s 60.1 CH$_3$ | 3.81 s 60.1 CH$_3$ |
| 4-OCH$_3$ | 3.95 s | 61.9 CH$_2$ | 3.81 s 60.9 CH$_2$ | 3.83 s 60.8 CH3 |
| 17-OH | - | - | 8.91 brs | - | - |
| 2`-OH | - | - | 5.03 brs | - | 5.03 d (2.5) |
| 3`-OH | - | - | 4.93 d (4.3) | - | 4.93 d (4.1) |
| 4`-OH | - | - | 4.09 d (4.3) | - | 4.41 d (3.8) |
| 5`-OH | - | - | 5.28 d (3.5) | - | 5.22 d (3.5) |
| 6`-OH | - | - | 4.34 t (4.6) | - | 3.36 t (4.6) |
| 17-COCH$_3$ | 2.08 s | 20.8 CH$_2$ | 171.7 C | - | - |
Table 3. 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.

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, the doublet proton signal at $\delta_H 4.80$ ($J = 7.6$ Hz, H-1′) showed cross peak to the signal at $\delta_C 105.0$ (C-1′), indicating the presence of $\beta$-glucopyranoside moiety (23, 26). This was established by the observed ESIMS fragment peaks at $m/z$ 398.9 [(M + H)-Glu]$^+$ and 357.2 [(M + H)-(Glu+Acetyl)]$^+$. In the HMBC, the cross peak of H-1′ to C-5 ($\delta_C 148.7$) established the placement of glucose at C-5. Furthermore, signals for six methylene groups at $\delta_H 1.80-3.07$ and ketone carbonyl at $\delta_C 213.6$ (C-11), characteristic for heptanoid moiety in 3 were observed. In the 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 secured by the HMBC cross peaks of H-8/C-6, H-19/C-7, and H-18/C-13. Consequently, 3 was concluded to be 17-O-acetyl myricanone 5-O-$\beta$-glucopyranoside and named alnuheptanoid B.

Compounds 1-5 were identified to be myricanone (1) (29, 30), (+)-S-myricanol (2) (30,31), myricanone 5-O-$\beta$-D-glucopyranoside (4) (32), and (+)-S-myricanol 5-O-$\beta$-D-glucopyranoside (5) (27) by the interpretation.

![Figure 2. Important 1H-1H COSY and HMBC correlations of alnuheptanoid B (3).](image)

References

(1) Zhu J, Islas-Gonzalez G and Bois-Choussy M. Recent progress in isolation, bioactivity evaluation and total synthesis of diarylheptanoids. *Org. Prep. Proced. Int.* (2000) 32: 505-546.
Anti-oxidant and anti-inflammatory cyclic diarylheptanoids

The antioxidant activity of the isolated cyclic diarylheptanoids (1-5) was determined using DPPH free radical scavenging system at concentration 50 \( \mu \text{M} \). The results showed that, 1 and 2 had significant antioxidant activity. While, 3-5 showed moderate activity in comparison with propyl gallate (a known antioxidant) (Table 3). Their antioxidant effect was related to the number of free hydroxyl groups in their structures. Compounds 1 and 2 showed significant activities compared to propyl gallate at the same concentration. However, blocking of the hydroxyl group by an acetyl or glucose moiety leads to a decrease in the activity as in 3-5 (33).

Compounds 1-5 were evaluated for their anti-inflammatory effects using carrageenin induced paw edema model. Compound 2 showed the highest activity comparable to indomethacin (10 mg/kg) (Table 4). Also, 1, 3, 4, and 5 showed potent activity at dose 10 mg/kg after 4 h. The phenolic compounds are known to inhibit prostaglandins synthesis enzymes, more specifically the endoperoxide (26). It was reported that, prostaglandin like substances are released during the second phase of carrageenin induced edema (34, 35). So, the anti-inflammatory effects of the tested compounds may be due to inhibition of prostaglandin like substances.

The observed activity of these compounds might be through the inhibition of the inflammatory prostanooids (36, 37). In this work, 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 (36, 37). 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.

**Conclusions**

A new cyclic diarylheptanoid and four known compounds were isolated from *A. japonica* for the first time. Their chemical structures were established by different spectroscopic analyses.
Compounds 1 and 2 showed significant antioxidant activity. Compound 2 exhibited potent anti-inflammatory activity.

References

(1) Zhu J, Islas-Gonzalez G and Bois-Choussy M. Recent progress in isolation, bioactivity evaluation and total synthesis of diarylheptanoids. Org. Prep. Proced. Int. (2000) 32: 505-546.

(2) Lee YI, Lv H and She G. Naturally occurring diarylheptanoids. Nat. Prod. Commun. (2010) 5: 1687-1708.

(3) Lv H and She G. Naturally occurring diarylheptanoids-A supplementary version. Rec. Nat. Prod. (2012) 6: 321-333.

(4) Prasain JK, Tezuka Y, Li JX, Tanaka K, Basnet P, Dong H, Namba T and Kadota S. Six novel diarylheptanoids bearing chalcone or flavone moiety from seeds of *Alpinia blepharocalyx*. Tetrahedron (1997) 53: 7833-7842.

(5) Lee MW, Kim JH, Jeong DW, Ahn KH, Toh SH and Surh YJ. Inhibition of cyclooxygenase-2 expression by diarylheptanoids from the bark of *Alnus hirsuta* var. *sibirica*. Biol. Pharm. Bull. (2000) 23: 517-518.

(6) Shin D, Kinoshita K, Koyama Y and Takahashi K. Antiemetic principles of *Alpinia officinarum*. J. Nat. Prod. (2002) 65: 1315-1318.

(7) Agarwal BB, Kumar A and Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res. (2003) 23: 363-398.

(8) Kang GI, Kong PJ, Yuh YJ, Lim SY, Yim SV, Chun W and Kim SS. Curcumin suppresses lipopolysaccharide-induced cyclooxygenase-2 expression by inhibiting activator protein 1 and nuclear factor kappa B bindings in BV2 microglial cells. J. Pharmacol. Sci. (2004) 94: 325-328.

(9) Jeong YS. Hepatoprotective and antioxidant effects of *Alnus japonica* extracts on acetaminophen-induced hepatotoxicity in rats. Phytother. Res. (2004) 18: 971-975.

(10) Jin W, Cai XF, Na M, Lee JJ and Baek K. Diarylheptanoids from *Alnus hirsuta* inhibit the NF-κB activation and NO and TNF-α production. Biol. Pharm. Bull. (2007) 30: 810-813.

(11) Park D, Kim HJ, Jung SY, Yook C, Jin CH and Lee YS. A new diarylheptanoid glycoside from the stem bark of *Alnus hirsuta* and protective effects of diarylheptanoid derivatives in human HepG2 cells. Chem. Pharm. Bull. (2010) 58: 238-241.

(12) Wada H, Tachibana H, Fuchino H and Tanaka N. Three new diarylheptanoid glycosides from *Alnus japonica*. Chem. Pharm. Bull. (1998) 46: 1054-1055.

(13) Ibrahim SRM, Fouad MA, Abd-Elatef A, Okino T and Mohamed GA. Alnheptanoid A: A new diarylheptanoid derivative from *Alnus japonica*. Nat. Prod. Res. (2014) 28, 1765-1771.

(14) Tung NH, Kwon HJ, Kim JH, Ra JC, Ding Y, Kim JA and Kim YH. Anti-influenza diarylheptanoids from the bark of *Alnus japonica*. Bioorg. Med. Chem. Lett. (2010) 20: 1000-1003.

(15) Tung NH, Suzuki M, Uto T, Morinaga O, Kwofie KD, Ammah N, Koram KA, Aboagye F, Edoh D, Yamashita T, Yamaguchi Y, Setsu T, Yamaoka S, Ohita N and Shoyama Y. Anti-trypanosomal activity of diarylheptanoids isolated from the bark of *Alnus japonica*. Am. J. Chin. Med. (2014) 42: 1245-1260.

(16) Nomura M, Tokoroyama T and Kubotat T. Diarylheptanoids and other constituents from wood of *Alnus japonica*. Phytochem. (1981) 20: 1097-1104.

(17) Park J, Jeong HJ, Kim JH, Kim YM, Park S, Kim D, Park KH, Lee WS and Ryu YB. Diarylheptanoids from *Alnus japonica* inhibit papain-like protease of severe acute respiratory syndrome coronavirus. Biol. Pharm. Bull. (2012) 35: 2036-2042.

(18) Kim HJ, Yeom SH, Kim MK, Shim JG, Paek IN, and Lee MW. Nitric oxide and prostaglandin E2 synthesis inhibitory activities of diarylheptanoids from the barks of *Alnus japonica* steudel. Arch. Pharm. Res. (2005) 28: 177-179.

(19) Kuroyanagi M1, Shimomae M, Nagashima Y, Muto N, Okuda T, Kawahara N, Nakane T and Sano T. New diarylheptanoids from *Alnus japonica* and their antioxidative activity. Chem. Pharm. Bull. (2005) 53: 1519-1523.

(20) Sati SC, Sati N and Sati OP. Bioactive constituents and medicinal importance of genus *Alnus*. Pharmacogn. Rev. (2011) 5: 174-183.

(21) Lim SS, Lee MY, Ahn HR, Choi SJ, Lee J and Jung SH. Preparative isolation and purification of antioxidative diarylheptanoid derivatives from *Alnus japonica* by high-speed counter-current chromatography. J. Sep. Sci. (2011) 34: 3344-3352.

(22) Lee M, Tanaka T, Nonaka G and Nishioka I. Dimeric ellagitannins from *Alnus japonica*. Phytochemistry. (1992) 31: 2835-2839.

(23) Mohamed GA, Ibrahim SRM, Al-Musayeb NM and Ross SA. New anti-inflammatory flavonoids from *Cassia glandulosa* Forsk. Arch. Pharm. Res. (2014) 37: 459-466.

(24) Mohamed GA. New cytotoxic cycloartane triterpene from *Cassia italica* aerial parts. Nat. Prod. Res. (2014) 28: 976-983.

(25) Mohamed GA, Abd-Elrazek AEE, Hassanean HA, Youssef DTA and van Soest R. New compounds from the Red Sea marine sponge *Echinoclathria gibbosa*. Phytochem. Lett. (2014) 9: 51-58.

(26) Mohamed GA, Ibrahim SRM, Elkhayat ES, Ross SA, Sayed HM, El-Moghazy SAM and El-Shanawany MA. Blepharisides A and B, new flavonol glycosides from *Blepharis ciliaris* growing in Saudi Arabia. Phytochem. Lett. (2015) 11: 177-182.

(27) Matsuda H, Morikawa T, Tao J, Ueda K and Yoshikawa M. Bioactive constituents of Chinese natural medicines. VII) Inhibitors of degranulation in RBL-2H3 cells and absolute stereocounters of three new diarylheptanoid glycosides from the bark of *Myrica rubra*. Chem.
Anti-oxidant and anti-inflammatory cyclic diarylheptanoids

Silverstein RM and Webster FX. Spectrometric Identification of Organic Compounds. 6th ed., John Wiley, New York (1998) pages?

Morihara M, Sakurai N, Inoue T, Kawai K and Nagai M. Two novel diarylheptanoids from Myrica gale var. tomentosa and absolute structure of plant-chiral galleon. Chem. Pharm. Bull. (1997) 45: 820-823.

Kawai S, Nakata K, Ohashi M and Tomoaki N. Myricanol and myricanone biosynthesis in Myrica rubra: incorporation of two molecules of 4-coumaric acid. J. Wood Sci. (2008) 54: 256-260.

Joshiat B. Extensive 1D, 2D NMR spectra of same [7.0] metacyclophanes and X-ray analysis of (-)-myricanol. J. Nat. Prod. (1996) 59: 759-764.

Tao J, Morikawa T, Toguchida I, Ando S, Matsuda H and Yoshikawa M. Inhibitors of nitric oxide production from the bark of Myrica rubra: structures of new biphenyl type diarylheptanoid glycosides and taraxerane type triterpene. Bioorg. Med. Chem. (2002) 10: 4005-4012.

Dugas AJJ, Castañeda-Acosta J, Bonin GC, Price KL, Fischer NH and Winston GW. Evaluation of the total peroxyl radical-scavenging capacity of flavonoids: Structure-activity relationships. J. Nat. Prod. (2000) 63: 327-331.

Ibrahim SRM, Mohamed GA and Al-Musayeb NM. New constituents from the rhizomes of Egyptian Iris germanica L. Molecules (2012) 17: 2587-2598.

Alcaraz MJ and Jimenez MJ. Flavonoids as anti-inflammatory agents. Fitoterapia (1998) 59: 25-38.

Bellik Y, Boukrâ L, Alzahrani HA, Bakhotmah BA, Abdellah F, Hammoudi SM and Iguer-Ouada M. Molecular mechanism underlying anti-inflammatory and anti-allergic activities of phytochemicals: An update. Molecules (2013) 18: 322-353.

Tatli II, Akdemir ZS, Yesilada E and Küpeli E. Anti-inflammatory and antinociceptive potential of major phenolics from Verbascum salviifolium Boiss. Z. Naturforsch. (2008) 63c: 196-202.

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