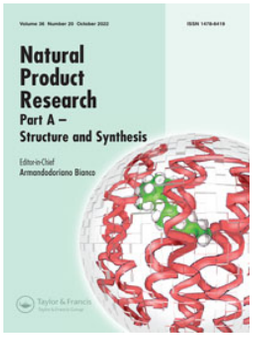

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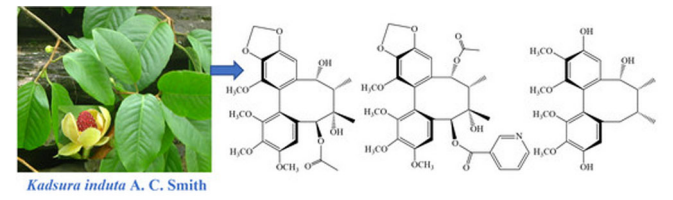
Kadsindutalignans A–C: three new dibenzocyclooctadiene lignans from *Kasura induta* A.C.Sm. and their nitric oxide production inhibitory activities

Truong Thi Thu Hien[a], Hoang Dac Thang[a], Hoang Anh Tuan[a], Nguyen Thanh Chung[a], Do Thanh Tuan[b], Nguyen Ba Hung[a], Nguyen Thi Kim Thuy[c], Nguyen Thi Thu Hien[d], Nguyen Huy Hoang[e], Dan Thi Thuy Hang[e], Bui Huu Tai[e,f], Nguyen Xuan Nhiem[e,f] and Phan Van Kiem[e,f]

[a]Centre for Toxicology and Radiology Teaching and Research, Vietnam Military Medical University, Hanoi, Vietnam; [b]Department of Quality Assurance and Testing, Thai Binh University of Medicine and Pharmacy, Thaibinh, Vietnam; [c]Center for High Technology Development, VAST, Hanoi, Vietnam; [d]Faculty of Basic Sciences, Hanoi University of Mining and Geology, Hanoi, Vietnam; [e]Institute of Marine Biochemistry, Vietnam Academy of Science and Technology (VAST), Hanoi, Vietnam; [f]Graduate University of Science and Technology, VAST, Hanoi, Viet Nam

ABSTRACT

Phytochemical study on the methanol extract of the stems and leaves of *Kadsura induta* led to the isolation of six dibenzocyclooctadiene lignans, including three new compounds named kadsindutalignans A–C (**1–3**), and three known ones, heteroclitalignan B (**4**), kadsuphilin C (**5**) and kadsulignan E (**6**). Their structures were elucidated based on extensive spectroscopic analyses, including HRESIMS, 1D- (^{1}H NMR and ^{13}C NMR), 2D-NMR (HSQC, HMBC, ^{1}H-^{1}H COSY and NOESY), and experimental circular dichroism (CD) spectra. All the isolates inhibited NO production in LPS-activated RAW264.7 cells with IC_{50} values in the range from 5.67 ± 0.54 μM to 38.19 ± 2.03 μM, compared to that of the positive control of N^G-monomethyl-L-arginine acetate (L-NMMA) with an IC_{50} value of 8.90 ± 0.48 μM. Interestingly, the new compound **2** showed potential inhibition of NO production with an IC_{50} value of 5.67 ± 0.54 μM, which was higher than that of the positive control.



Abbreviations: CD: circular dichroism spectroscopy; COSY: correlation spectroscopy; HMBC: heteronuclear multiple bond correlation; HR-ESI-MS: high-resolution electrospray ionization mass

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CONTACT Truong Thi Thu Hien truonghientruong@gmail.com; Phan Van Kiem phankiem@yahoo.com
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spectrometry; HSQC: heteronuclear single quantum coherence; L-NMMA: N^G-monomethyl-L-arginine acetate salt; LPS: lipopolysaccharide; NMR: nuclear magnetic resonance; NO: nitric oxide; NOESY: nuclear overhauser effect spectroscopy; Prep-HPLC: preparative high performance liquid chromatography

1. Introduction

The genus *Kadsura* (family Schisandraceae) comprises about 16 species, which is usually a climbing plant with separate male and female flowers growing on different plants. In Vietnam, there are six *Kadsura* species, *K. chinensis*, *K. coccinea*, *K. hetroclita*, *K. longipedunculata*, *K. oblongifolia* (Chi 2018), and *K. induta* A. C. Sm. a new record for the flora of Vietnam in 2012 (Thanh et al. 2012). In the traditional medicine of Vietnam, the leaves and stems of *K. induta* are used to treat arthritis, gastritis and duodenitis (Thanh et al. 2012). Previous phytochemical study on *Kadsura* species led to the isolation of lignans and triterpenes (Lu and Chen 2008; Liu et al. 2014; Su et al. 2014; Wang et al. 2021; Zhang et al. 2021; Tram et al. 2022). Notably, dibenzocyclooctadiene lignans, a typical substance of the genus *Kasura*, have been also found in *K. induta* and some of them exhibited antiviral and anti-HIV activities (Wenhui et al. 2007, 2009; Minh et al. 2014). In our continuing efforts toward discovering structurally interesting and biologically significant dibenzocyclooctadiene lignans from *Kadsura* species, six dibenzocyclooctadiene lignans (**1–6**) including three new ones (**1–3**) were isolated from the stem and leaves of this plant. All the isolates were found to inhibit NO production in LPS-activated RAW264.7 cells. Herein, we report the details of the isolation, structural elucidation, and the NO production inhibitory activities of these compounds.

2. Results and discussion

Compound **1** was obtained as colorless powder. Its molecular formula $C_{25}H_{30}O_{10}$ was determined by the HR-ESI-MS ion peak at *m/z* 513.1747 $[M+Na]^+$ (calcd. for $[C_{25}H_{30}O_{10}Na]^+$: 513.1731, $\Delta = +3.1$ ppm) indicating 11 degrees of unsaturation. The 1D and 2D NMR spectra of **1** exhibited two methyl groups [δ_C 29.0/δ_H 1.28 (3H, s) and δ_C 17.5/δ_H 1.34 (3H, d, $J = 7.5$ Hz)], two oxygenated methine groups [δ_C 84.9/δ_H 5.64 (1H, s) and δ_C 83.9/δ_H 4.84 (1H, s)], one oxygenated tertiary carbon (δ_C 74.2), one sp^3 methine [δ_C 43.0/δ_H 1.94 (1H, m)], one sp^3 dioxygenated methylene [δ_C 101.0/δ_H 5.93 and 5.95, each 1H, d, $J = 1.5$ Hz)], one acetoxy [δ_C 169.4 and δ_C 20.3/δ_H 1.62 (3H, s)], and four methoxy groups [δ_C 60.7/δ_H 3.73, δ_C 60.8/δ_H 3.88, δ_C 55.9/δ_H 3.89, δ_C 59.3/δ_H 3.85, each 3H, s)]. Two benzene rings were indicated from 12 olefinic carbon signals [δ_C 159.2, 151.0, 148.5, 141.3, 140.6, 136.2, 135.1, 130.9, 120.5, 120.2, 111.1 and 101.8] as similar to the most lignans found from the genus *Kadsura* (Li et al. 2006; Lu and Chen 2008; Liu et al. 2014; Minh et al. 2014). Of these, two carbons at δ_C 111.1 and 101.8 had HSQC cross peaks with the olefinic protons at δ_H 6.72 and 6.31, respectively. The abovementioned data suggested compound **1** was a dibenzocyclooctadiene lignan having one acetoxy, four methoxy, one dioxygenated methylene, and two

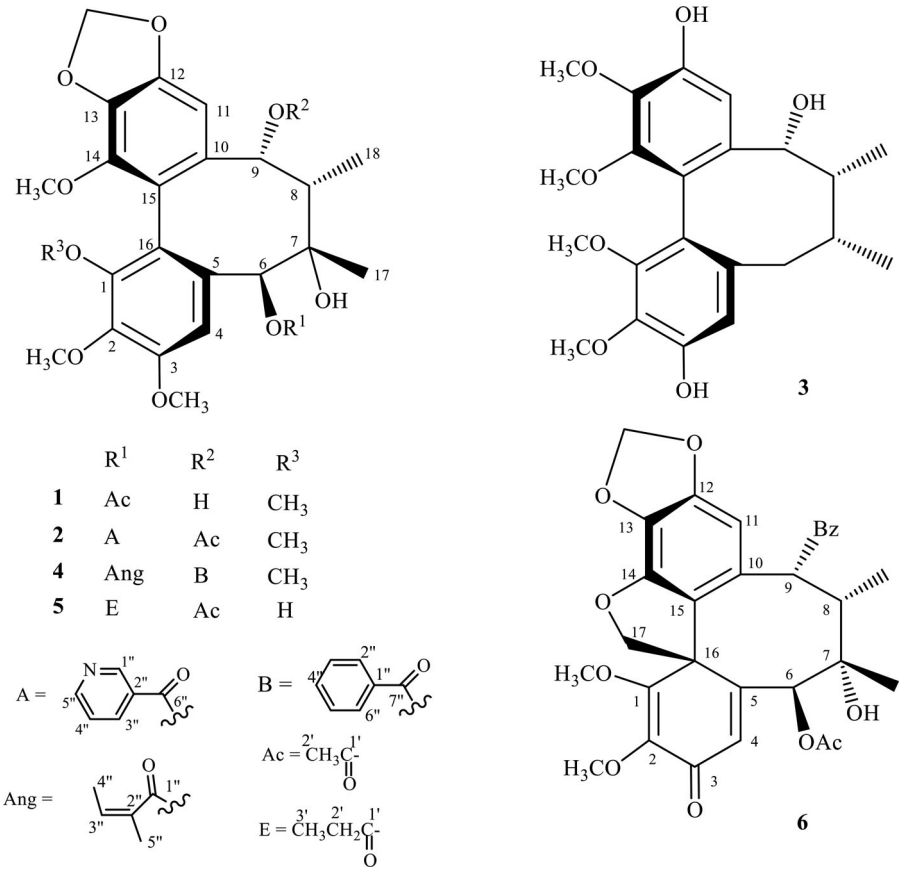

Figure 1. Chemical structures of compounds **1**–**6**.

hydroxy groups (Lu and Chen 2008; Minh et al. 2014). Detailed analysis of the NMR data (Table S1) showed that compound **1** was quite similar to *Kadsura*lignan B, which had two acetoxy groups at C-6 and C-9 (Li et al. 2006). In the HMBC spectrum, H-11 (δ_H 6.31) interacted with C-9 (δ_C 83.0)/C-12 (δ_C 148.5)/C-13 (δ_C 135.1), while dioxygenated methylene protons at 5.93/9.95 correlated with C-12 and C-13 indicating one hydroxy group at C-9 and the dioxygenated methylene group attached to C-12 and C-13. The 9-OH group was further indicated by ^{1}H-^{1}H COSY cross peak between H-8 (δ_H 1.94) and H-9 (δ_H 4.84). In addition, the HMBC correlations from H-4 (6.72) to C-2 (δ_C 141.3)/C-3 (δ_C 152.0)/C-5 (δ_C 130.9)/C-6 (δ_C 84.9)/C-16 (δ_C 120.5), from H-17 (δ_H 1.28) to C-6/C-7 (δ_C 74.2)/C-8 (δ_C 43.0), and from H-18 (δ_H 1.34) to C-7/C-8/C-9 were observed confirming the acetoxy group at C-6 and two hydroxy groups at C-7 and C-9. Four methoxy groups were at C-1, C-2, C-3 and C-14 as similar to the most of dibenzocyclooctadiene lignans from *Kadsura* species (Wang et al. 2021; Zhang et al. 2021) and further confirmed by HMBC spectrum as shown in Figure S1. The configuration of the biphenyl group of **1** was determined to be *S*, similar to all dibenzocyclooctadiene lignans found from the genus *Kadsura*, based on the positive cotton effects at 226 nm and negative cotton effects at 255 nm observed on the CD spectrum (Ikeya et al. 1988; Li et al. 2006; Wang et al. 2006; Shen et al. 2007). In the NOESY spectrum, the

cross peaks between H-11 (δ_H 6.31) and H-8 (δ_H 1.94) indicated twist-boat-chair conformation of cyclooctadiene ring and H-8 adopted *axial* position (β-configuration) (Wang et al. 2006; Shen et al. 2007). Thus, the NOESY cross peaks between H-8 (δ_H 1.94) and H-9 (δ_H 4.84)/H-17 (δ_H 1.28) suggested the same β-configuration of H-9 and methyl group C-17. On the other hand, the NOESY cross peaks between H-4 (δ_H 6.72) and H-6 (δ_H 5.64) demonstrated for *equatorial* position (α-configuration) of H-6 (Figure S2). Thus, the chemical structure of compound **1** was determined as shown in Figure 1, a new compound named kadsindutalignan A.

The molecular formula of compound **2** was elucidated as $C_{31}H_{33}NO_{11}$ by the exhibition of HR-ESI-MS ion peak at *m/z* 596.2136 $[M+H]^+$ (calcd. for $[C_{31}H_{34}NO_{11}]^+$: 596.2126 ($\Delta = +0.2$ ppm). The NMR spectra of compound **2** were similar to those of **1** except for the additional signals of one pyridinecarboxyl group [δ_C 149.8/δ_H 8.56 (1H, s), δ_C 137.6/δ_H 7.83 (1H, d, $J = 7.5$ Hz), δ_C 123.2/δ_H 7.33 (1H, dd, $J = 7.5$, 3.5 Hz), δ_C 152.5/δ_H 8.75 (1H, d, $J = 3.5$ Hz), δ_C 125.7 (C) and 163.0 (C = O)] (Shi et al. 2014; Table S1). The acetoxy group [δ_C 168.8 (C = O) and δ_C 20.5/δ_H 1.60 (3H, s)] attached to C-9 determined from the ^{1}H-^{1}H COSY correlations of H-18 (δ_H 1.32)/H-8 (δ_H 2.26)/H-9 (δ_H 5.74) as well as from HMBC correlations of H-17/C-8, H-17/C-9, and H-9/C-11. The pyridinecarboxyl group linked to C-6 evidenced from HMBC correlations between H-17 (δ_H 1.40) and C-6 (δ_C 85.9)/C-7 (δ_C 73.9)/C-8 (δ_C 43.4), between H-4 (δ_H 6.84) and C-6, and between H-6 (δ_H 5.88) and C-11. The CD spectrum of **2** showed the Cotton effects at (+) 228 and (−) 249 nm indicating *S*-configuration of the biphenyl groups (Li et al. 2006; Ikeya et al. 1988). In the NOESY spectrum, the cross peaks between H-8 (δ_H 2.26) and H-11 (δ_H 6.53)/H-9 (δ_H 5.74)/H-17 (δ_H 1.40), H-4 (δ_H 6.84) and H-6 (δ_H 5.88) demonstrated the same stereochemistry of dibenzo cyclooctadiene moiety between **2** and **1** (Figure S2). Therefore, the chemical structure of compound **2** was determined as shown in Figure 1, a new compound named kadsindutalignan B.

Compound **3** was obtained as colorless powder. Its molecular formula $C_{22}H_{28}O_7$ was determined by the HR-ESI-MS (found *m/z* 405.1919 $[M+H]^+$, calcd. for $[C_{22}H_{29}O_7]^+$: 405.1908), indicating 9 degrees of unsaturation. The 1D- and 2D-NMR spectra suggested **3** was a dibenzocyclooctadiene lignan with four methoxy groups [δ_C 60.1/δ_H 3.55 (s), 61.1/δ_H 3.95 (s), 60.9/δ_H 3.92 (s), δ_C 60.1/δ_H 3.64 (s)], two secondary methyl groups [δ_C 15.1/δ_H 0.93 (d, $J = 7.5$ Hz), δ_C 19.8/δ_H 1.17 (d, $J = 7.0$ Hz)], one oxygenated methine [δ_C 83.8/δ_H 34.62 (d, $J = 6.5$ Hz)], two sp^3 methine [δ_C 35.0/δ_H 2.08 (m) and δ_C 43.2/δ_H 1.92 (m), and one sp^3 methylene group [δ_C 38.4/δ_H 2.60 (m)]. Comparing the NMR data of **3** with those of **1** and **2** showed that the lower carbon chemical shifts of C-3 (δ_C 148.6) and C-12 (δ_C 148.7) together with the absence of the dioxygenated methylene signals in **3** suggested two hydroxy groups were at C-3 and C-12 (Li et al. 2006). The other hydroxy group at C-9 confirmed by the ^{1}H-^{1}H COSY correlations of H-6/H-7/H-8/H-9, H-7/H-17, H-8/H-18, and by HMBC correlations from H-9 to C-11 and from H-11 to C-9 as shown in Figure S1. Four methoxy groups were at C-1, C-2, C-13 and C-14 determined by HMBC spectrum. The CD spectrum of **3** showed the Cotton effects at (+) 215 and (−) 250 nm indicating *S*-configuration of the biphenyl groups (Li et al. 2006 and Ikeya et al. 1988). The NOESY cross peaks between H-17 (δ_H 0.93) and H-4 (δ_H 6.67)/H-18 (δ_H 1.17), H-8 (δ_H 1.92) and H-7 (δ_H 2.08)/H-9 (δ_H 4.62)/H-11 (δ_H 6.49), H-11 and H-9 were observed evidencing these protons were close

in proximity, indicating H-7, H-8, and H-9 groups in the same side of the molecule (Figure S2) (Wang et al. 2006; Shen et al. 2007). Thus, the chemical structure of compound **3** was determined as shown in Figure 1, a new compound named kadsindutalignan C.

The other compounds, heteroclitalignan B (**4**) (Wang et al. 2006), kadsuphilin C (**4**) (Shen et al. 2007), and kadsulignan E (**6**) (Liu and Huang 1992) were identified by comparison of their spectral data with those of the literature (Table S2).

The dibenzocyclooctadiene lignans have been reported for their potential anti-inflammatory activity (Li et al. 2006; Wang et al. 2021). Therefore, compounds **1**–**6** were evaluated for anti-inflammatory activity by their ability to inhibit NO production in LPS stimulated RAW 264.7 cells (Supporting information). At a concentration of 100 μM, compounds **1**–**6** did not significantly show cytotoxic activity by MTT assay (data not shown). Therefore, the levels of NO production in the cell medium were measured in the presence of **1**–**6** at serial diluted concentrations (0–100 μM). As shown in Table S3, all the tested compounds exhibited NO inhibitory activity with IC_{50} values in the range from 5.67 ± 0.54 to 38.19 ± 2.03 μM compared to that of the positive control L-NMMA (IC_{50} 8.90 ± 0.48 μM). Regarding structure activity relationship, our results suggested that the dibenzocyclooctadiene lignans which had a dioxygenated methylene group at C-12 and C-13 may have significant NO inhibitory activity and the compounds having benzyl or pyridinecarboxyl groups showed higher NO inhibitory activity than that of the other tested compounds. This result is well in agreement with those reported in literature (Li et al. 2006; Wang et al. 2021).

3. Experimental

3.1. General

Optical rotation was measured on a Jasco P2000 polarimeter. The CD spectra were measured on a Chirascan spectrometer (Applied Photophysics, Surrey, UK). The HR-ESI-MS was taken on an Agilent 6530 Accurate Mass Q-TOF LC/MS. The NMR spectra were recorded on a Bruker 500 MHz spectrometer using TMS as an internal Standard. Preparative HPLC were run on an Agilent 1100 system including quaternary pump, autosampler, DAD detector, and preparative HPLC column YMC J'sphere ODS-H80 (4 μm, 20 × 250 mm). Isocratic mobile phase with the flow rate of 3.0 mL/min was used in pre-HPLC. The compound was monitored at wavelengths of 205, 230, 254 and 280 nm. Flash column chromatographies were performed using silica gel (60, 70–230 mesh and 230–400 mesh, Merck, Darmstadt, Germany) or reversed phase C-18 (YMC, Kyoto, Japan) as stationary phase. Thin layer chromatographies (TLC) were carried out on pre-coated silica gel 60 F_{254} and RP-18 F_{254S} plates. The spots were detected by spraying with aqueous solution of H_2SO_4 5% followed by heating with a heat gun.

3.2. Plant material

The stems and leaves of *Kadsura induta* A.C.Sm. were collected from Sapa, Lao Cai, Vietnam, in April 2022 and authenticated by Dr Nguyen Van Thanh, Institute of

Ecology and Biological Resources, VAST. A voucher specimen (code NCCT-P149) is kept at the Herbarium, Institute of Ecology and Biological Resources, Hanoi, Vietnam.

3.3. Extraction and isolation

The dried stems and leaves (4.5 kg) were powdered and then sonicated with methanol (three times, each 15 L for 2 h) to get 300 g MeOH extract after removal of the solvent. This extract was suspended with distilled water and then partitioned in turn with *n*-hexane, dichloromethane and ethyl acetate to give residues, IKA (50.0 g), IKB (49.0 g), IKC (5.2 g) and water layer, respectively. After checking by TLC, fraction IKB (49.0 g) was further chromatographed on a silica gel column eluting with gradient of *n*-hexane/acetone (from 100/0 to 0/100, v/v) to obtain six fractions, IKB1-IKB6. IKB4 (5.8 g) was further chromatographed on a silica gel column eluting with *n*-hexane/acetone (5/1, v/v) to get seven sub-fractions, IKB4A-IKB4G. IKB4B (1.2 g) was chromatographed on an YMC column eluting with acetone/water (2/1, v/v) to get IKB4B1- IKB4B4 fractions. IKB4B4 was chromatographed on the HPLC (J'sphere H-80 column, 250 mm length × 20 mm ID, eluting with 75% acetonitrile (ACN) in water, a flow rate of 2.5 mL/min) to give compound **4** (t_R 43.50, 11.3 mg). IKB4F (1.7 g) was chromatographed on an YMC column eluting with MeOH/water (2/1, v/v) to get IKB4F1-IKB4F5 fractions. IKB4F1 was chromatographed on the HPLC eluting with 50% ACN in water to get compounds **3** (t_R 37.90, 12.4 mg), **1** (t_R 49.33, 14.1 mg), and **2** (t_R 67.67, 9.8 mg). IKB4F5 was chromatographed on the HPLC eluting with 55% ACN in water to get compound **5** (t_R 69.41, 10.6 mg). Compound **6** (21.3 mg) was obtained from IKB4G after crystallization.

3.3.1. Kadsindutalignan A (1)

Obtained as colorless powder, m.p. 118-120 °C; $[\alpha]_D^{25}$: +27.5 (*c* 0.1, MeOH); UV (MeOH) λ_{max} 217 nm; CD (MeOH, c 0.2 mg/mL) λ (θ: mdeg): 226 (+19.25), 225 (−17.97) nm. HR-ESI-MS *m/z* 513.1747 $[M+Na]^+$, calcd. for $[C_{25}H_{30}O_{10}Na]^+$: 513.1731 (Δ = +3.1 ppm). ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz) data, see Table S1.

3.3.2. Kadsindutalignan B (2)

Obtained as colorless powder, m.p. 123-125 °C; $[\alpha]_D^{25}$: + 18.2 (*c* 0.1, MeOH); UV (MeOH) λ_{max} 221 nm; CD (MeOH, c 0.2 mg/mL) λ (θ: mdeg): 228 (+15.09), 249 (19.63) nm. HR-ESI-MS *m/z* 596.2136 $[M+H]^+$, calcd. for $[C_{31}H_{34}NO_{11}]^+$: 596.2126 (Δ = +0.2 ppm). ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz) data, see Table S1.

3.3.3. Kadsindutalignan C (3)

Obtained as colorless powder, m.p. 107-109 °C; $[\alpha]_D^{25}$: + 23.6° (*c* 0.1, MeOH); UV (MeOH) λ_{max} 214 nm; CD (MeOH, c 0.2 mg/mL) λ (θ: mdeg): 215 (+19.66), 250 (20.05) nm. HR-ESI-MS *m/z* 405.1919 $[M+H]^+$, calcd. for $[C_{22}H_{29}O_7]^+$: 405.1908 (Δ = +2.7 ppm), *m/z* 422.2174 $[M+NH_4]^+$, calcd. for $[C_{22}H_{28}O_7{\cdot}NH_4]^+$: 422.2173 (Δ = +0.2 ppm), *m/z* 427.1730 $[M+Na]^+$, calcd. for $[C_{22}H_{28}O_7Na]^+$ 427.1727 (Δ = +0.7 ppm), *m/z* 439.1533

$[M+^{35}Cl]^-$, calcd. for $[C_{22}H_{28}O_7{}^{35}Cl]^-$: 439.1529 ($\Delta = +0.9$ ppm), *m/z* 441.1515 $[M+^{37}Cl]^-$, calcd. for $[C_{22}H_{28}O_7{}^{37}Cl]^-$: 441.1499 ($\Delta = +3.6$ ppm). ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz) data, see Table S1.

4. Conclusions

In the current study, three new dibenzocyclooctadiene lignans, kadsindutalignans A–C (**1–3**), and three known ones, heteroclitalignan B (**4**), kadsuphilin C (**5**), and kadsulignan E (**6**) were isolated from the methanol extract of the stems and leaves of *Kadsura induta*. Their chemical structures were evidenced by HRESIMS, 1D- and 2D-NMR and CD spectra. Compounds **1–6** inhibited NO production in LPS-activated RAW264.7 cells with IC_{50} values of 25.48 ± 1.69, 5.67 ± 0.54, 38.19 ± 2.03, 21.34 ± 1.73, 11.45 ± 1.12 and 14.37 ± 0.98 μM, respectively, compared to that of the positive control of N^G-monomethyl-L-arginine acetate (L-NMMA) with an IC_{50} value of 8.90 ± 0.48 μM. These results not only contributed three new dibenzocyclooctadiene lignans to science but also discovered some new compounds with potential NO production inhibition activity. These results suggested for further study on the anti-inflammatory activity of this medicinal plant in the future.

Disclosure statement

The authors declare no conflict of interest.

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ORCID

Phan Van Kiem http://orcid.org/0000-0003-0756-6990

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