Beilschglabrines A and B: Two new bioactive phenanthrene alkaloids from the stem bark of *Beilschmiedia glabra*

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ABSTRACT

Two new phenanthrene alkaloids, beilschglabrines A (**1**) and B (**2**) were isolated from the stem bark of *Beilschmiedia glabra*, together with lupeol, taraxerol, and 24-methylenelanosta-7,9-diene-3β-15α-diol. The structures of the isolated compounds were elucidated by extensive spectroscopic data analysis and comparison with respective literature data. The compounds were tested for DPPH radical scavenging, acetylcholinesterase and lipoxygenase inhibitory activities. Compound **1** displayed considerable activity in the acetylcholinesterase (IC_{50} 50.4 µM), the DPPH radical scavenging (IC_{50} 115.9 µM) and the lipoxygenase (IC_{50} 32.8 µM) assays.

Keywords:

Beilschmiedia glabra

Lauraceae

Phenanthrene alkaloid

DPPH radical scavenging activity

Acetylcholinesterase

Anti-inflammatory

1. Introduction

Beilschmiedia is a genus of the family Lauraceae with 250 species, which are distributed in tropical and subtropical Australia, New Zealand, North America, South America and Asia (Nishida, 1999). The chemical analyses of *Beilschmiedia* species have revealed the presence of alkaloids, endiandric acid derivatives, essential oils, fatty acids, epoxyfuranoid lignans, flavonoids and terpenoids, which have been shown to possess anti-oxidant, antibacterial, cytotoxic, antimalarial and antitubercular activities (Chen et al., 2007; Lenta et al., 2009; Chouna et al., 2010; Salleh et al., 2016a).

Beilschmiedia glabra Kosterm, locally known as *kayau temblouh* or *kayuh tefuluh*, is distributed in Peninsular Malaysia, Sumatra and Borneo. It can be found in mixed dipterocarp forests up to 600 m altitude, often along rivers. In secondary forests, it is usually present as a pre-disturbance remnant tree. The leaves are alternate to opposite, simple, penni-veined and glabrous, while the fruits are rusty brown and fleshy drupes (Nishida, 2008). We have recently reported the chemical composition and biological activity of the leaf and bark oil (Salleh et al., 2015). The leaf and bark oil contained mainly β-eudesmol (15.4-19.3%) and β-selinene (12.2-16.9%). The leaf oil had the highest phenolic content (233.4 mg GA/g), while the bark oil showed potent activity in the β-carotene/linoleic acid bleaching assay (77.6%). Both the leaf and bark oils were active against *Candida glabrata* and *Saccharomyces cerevisiae* with MIC values of 31.3 and 62.5 µg/mL, respectively. Tyrosinase (leaf 73.7%; bark 76.0%) and acetylcholinesterase (leaf 48.1%; bark 45.2%) inhibitory activities, and anti-inflammatory (leaf 59.7%; bark 48.9%) property were also identified (Salleh et al., 2015).

In continuation of phytochemical and bioactivity studies on this genus (Salleh et al., 2016b), herein we report the isolation, identification of phenanthrene alkaloids, named beilschglabrines A (**1**) and B (**2**) (**Fig. 1**) from the stem bark of *B. glabra* and assessment of

their potential free radical scavenging, acetylcholinesterase inhibitory and anti-inflammatory activities.

2. Results and discussion

Compound **1** was obtained as a yellow amorphous powder. The HREIMS spectrum revealed the molecular ion peak at *m/z* 421.1517 (calculated for 421.1525) and the molecular formula was deduced as $C_{24}H_{23}O_6N$. The IR spectrum showed the absorption bands at 3367, 1637, 1600 and 1462 cm^{-1} ascribable to hydroxyl, conjugated double bonds, and aromatic functional groups, respectively, while the peak assignable to the carbonyl group of an aldehyde functionality was observed at 1727 cm^{-1}. The UV spectrum exhibited absorption bands at 212 and 260 nm, typical of a phenanthrene skeleton (Castro et al., 1986). The ^{1}H NMR spectrum (**Table 1**) showed signals for two AB systems for four aromatic protons, at δ_H 7.58 (1H, J = 9.2 Hz), 8.03 (1H, J = 9.2 Hz), 6.97 (1H, J = 4.0 Hz) and 6.20 (1H, J = 4.0 Hz), corresponding to the aromatic protons of H-9, H-10, H-2′ and H-3′, respectively. Three singlets resonating at δ_H 8.96 (1H), 7.36 (1H) and 7.14 (1H) were assigned to aromatic protons H-5, H-8, and H-2, respectively. In addition, each of the two triplets centered at δ_H 3.51 (J = 8.4 Hz) and 4.67 (J = 7.6 Hz) integrating for two protons were assigned to H-11 and H-12, respectively, and those are typical signals for a phenanthrene alkaloid (Shamma, 1972). A singlet resonating at δ_H 4.35 (1H) was attributed to H-5′ of a cyclopenta-1,3-diene group. Two sharp singlets appeared at δ_H 3.87 (3H) and 4.11 (3H), and were assigned to two methoxyl groups. The presence of hydroxyl groups was revealed by a broad signal at δ_H 6.02. Besides, a singlet at δ_H 9.65 was characteristic for the proton of an aldehyde group. The COSY spectrum exhibited correlations between H-2′ (δ_H 6.97) and H-3′ (δ_H 6.20), and between H-9 (δ_H 7.58) and H-10 (δ_H 8.03). Futhermore, H-12 (δ_H 4.67) was found to correlate with H-11 (δ_H 3.51). The ^{13}C NMR spectrum exhibited 24 signals corresponding to twenty four carbons. The DEPT spectrum showed the presence of two

methoxyls, seven methines, three methylenes, one carbonyl and eleven quaternary carbons. The HMBC long-range correlations (**Fig. 2**) furnished correlations of H-9 (δ_H 7.58) to C-8/C-8a/C-4b/C-10a; H-10 (δ_H 8.03) to C-4b/C-4a/C-10a/C-1/; H-5 (δ_H 8.97) to C-4b/C-4a/C-8a/C-7/C-6; H-8 (δ_H 7.36) to C-4b/C-7/C-6; H-2 (δ_H 7.14) to C-11/C-10a/C-4/C-3; H-12 (δ_H 4.67) to C-11/C-1/C-4′; H-11 (δ_H 3.51) to C-2/C-10a/C-1/C-12, and H-5′ (δ_H 4.35) to C-3′/C-4′. The positions of two methoxyl groups were confirmed by a NOESY experiment, in which a series of correlations were observed between H-5/4-OCH_3 and H-5/6-OCH_3, in addition to H-11−H-12/2/10, H-5′/H-12, H-12−H-5′/H-10, H-2−H-11, and H-8/H-9. On the basis of the above findings and detailed spectral analyses, the structure of compound **1** was established as 4'-((12-(3,7-dihydroxy-4,6-dimethoxyphenanthren-1-yl)ethyl)(hydroxy)amino)cyclopenta-1',3'-dienecarbaldehyde, and given a trivial name of beilschglabrine A.

Compound **2** was obtained as a yellow amorphous powder. The HREIMS spectrum revealed the molecular formula $C_{25}H_{25}O_6N$, corresponding to the molecular ion peak at *m/z* 435.1672 (calculated 435.1681). The ^{1}H NMR and COSY spectra (**Table 1**) displayed similar profile with those of compound **1** except for one of the hydroxyl group position which was replaced by a methoxyl group. This was consistent with the addition of another singlet signal at δ_H 4.08 (3H) in the ^{1}H NMR spectrum. The presence of hydroxyl groups was revealed by a broad signal at δ_H 6.16. The ^{13}C NMR and DEPT spectra indicated the presence of twenty five carbons, with one carbonyl, eleven quaternary, seven methines, three methylenes, and three methoxyls carbons. The location of the third methoxyl group was confirmed at C-7 by NOESY spectrum (**Fig. 3**) in which good correlation was observed between 7-OCH_3 with H-8. Thus, the structure of compound **2** was established as 4'-(hydroxy(12-(3-hydroxy-4,6,7-trimethoxyphenanthren-1-yl)ethyl)amino)cyclopenta-1',3'-dienecarbaldehyde, and given a trivial name of beilschglabrine B. The known compounds, lupeol (Yang et al., 2009), taraxerol

(Chen et al. 1998) and 24-methylenelanosta-7,9-diene-3β-15α-diol (Lue et al., 1998), were identified by comparison of their spectroscopic data with published data.

Beilschmiedia like other genera in the Lauraceae, is an important source of isoquinoline alkaloids (e.g., benzylisoquinoline, aporphine) which are widely distributed in the plant kingdom, and more rarely, phenanthrene alkaloids. Some phenanthrene alkaloids possess various biological properties such as antiplatelet (Jantan et al., 2006), anti-inflammatory (Estellés et al., 2005), antimicrobial (Okwu and Nnamdi, 2011), and acetylcholinesterase inhibitory activity (Chiou et al., 1998). In this study, the isolated phenanthrene alkaloids (**1** and **2**) were tested for free radical scavenging, acetylcholinesterase inhibitory and anti-inflammatory activities. The results are shown in **Table 2**. The free radical scavenging activity was evaluated by the DPPH assay with a series of different concentrations (Chima et al., 2014). Compounds **1** and **2** showed a moderate level of activity as compared to that of ascorbic acid with IC_{50} values of 115.9 and 134.4 µM, respectively. The compounds were also screened for AChE inhibitory activity using the Ellman's colorimetric method in a 96-well plate (Ellman et al., 1961). Both **1** and **2** displayed strong activity against AChE with IC_{50} values of 50.4 and 84.6 µM, respectively. In the LOX assay (Salleh et al., 2016), compounds **1** and **2** exhibited significant activity with IC_{50} values of 32.8 and 40.4 µM, respectively. Compound **1** showed slightly higher activity than that of **2** in all assays.

3. Experimental

3.1. General experimental procedures

The mass spectra were recorded on the EPSRC UK National Mass Spectrometry Facility (Swansea University). The UV spectra were obtained in methanol on a Shimadzu UV 1601PC spectrophotometer. The IR spectra were obtained on a Perkin-Elmer 1600 FTIR spectrophotometer. The 1D and 2D NMR spectra were recorded in deuterated chloroform on a

Bruker Avance 400 MHz spectrometer, chemical shifts (δ) are reported in ppm on δ scale, and the coupling constants (*J*) are given in Hz. Vacuum liquid chromatography (VLC) was performed using Merck silica gel 230-400 mesh, while column chromatography (CC) was performed using Merck silica gel 70-230 mesh. Preparative thin layer chromatography (PTLC) was prepared using silica gel 60 PF_{254}. Thin layer chromatography (TLC) aluminum sheets pre-coated with silica gel 60 F_{254} (0.2 mm thickness) was used to detect and monitor components presence in the crude samples or fractions. The TLC and PTLC spots were visualized under UV light (254 and 366 nm) followed by spraying with 5% H_2SO_4 and 1% vanillin in MeOH and heating at 120°C for 5 min. All solvents were AR grade.

3.2. Plant material

The stem bark of *B. glabra* was collected from Kluang, Johor in October 2014. The species was identified by Dr. Shamsul Khamis from the Institute of Bioscience (IBS), UPM and the voucher specimen (SK2570/14) deposited at the Herbarium of IBS.

3.3. Extraction and isolation

Cold extraction of the powdered stem bark (2 kg) of *B. glabra,* sequentially, with *n*-hexane, EtOAc and MeOH yielded the crude extracts, *n*-hexane (BGBH: 15.4 g, 0.77%), EtOAc (BGBE: 18.9 g, 0.95%) and MeOH (BGBM: 25.3 g, 1.27%). The MeOH extract (BGBM) (20.0 g) was subjected to VLC on silica gel eluted with *n*-hexane:$CHCl_3$:EtOAc to afford 15 major fractions. Fraction BGBM5-10 were combined and purified by multiple CC on silica gel and preparative TLC to yield (**1**) (10.2 mg) and (**2**) (11.0 mg). The EtOAc extract (15.0 g) was fractionated by VLC on silica gel, eluted with *n*-hexane:$CHCl_3$:EtOAc to afford eight major fractions (BGBE1-8). Fractions BGBE2-5 and BGBE6-8 were purified by CC on silica gel to obtain taraxerol (25.5 mg) and 24-methylenelanosta-7,9-diene-3β-15α-diol (14.5 mg), respectively. Similar VLC (on silica gel) purification of the *n*-hexane extract (15.0 g) eluted

with *n*-hexane:$CHCl_3$:EtOAc afforded 10 major fractions (BGBH1-10). The combined fractions BMBH1-5 was subjected to multiple CC on silica gel to yield lupeol (5.6 mg).

*3.3.1 Beilschglabrine A (**1**)*

Yellow amorphous powder; IR (KBr): 3367, 2917, 2849, 1727, 1637, 1600, 1515, 1462, 1399, 1273, 1088 cm^{-1}; UV_{max} (MeOH) nm (log ε) 212 (2.15), 264 (2.85); HREIMS *m/z* 421.1517 (calculated 421.1525 for $C_{24}H_{23}O_6N$); ^1H NMR ($CDCl_3$, 400 MHz), ^{13}C NMR ($CDCl_3$, 100 MHz), COSY, NOESY and HMBC data see **Table 1**.

*3.3.2 Beilschglabrine B (**2**)*

Yellow amorphous powder; IR (KBr): 3312, 2925, 2867, 1715, 1636, 1602, 1514, 1454, 1388, 1223, 1009 cm^{-1}; UV_{max} (MeOH) nm (log ε) 208 (1.55), 263 (2.62); HREIMS *m/z* 435.1672 (calculated 435.1681 for $C_{25}H_{25}O_6N$); ^1H NMR ($CDCl_3$, 400 MHz), ^{13}C NMR ($CDCl_3$, 100 MHz), COSY, NOESY and HMBC data see **Table 1**.

3.4. Biological activities

3.4.1. Solvents and chemicals

Anti-oxidant: 1,1-Diphenyl-2-picrylhydrazyl (DPPH), and acsorbic acid were obtained from Sigma-Aldrich (Germany). Analytical grade ethanol (EtOAc), methanol (MeOH), ethyl acetate (EtOAc), *n*-hexane and dimethylsulfoxide (DMSO) were purchased from Merck (Germany). *Acetylcholinesterase:* AChE enzyme (Type-VI-S, EC3.1.1.7), acetylthiocholine iodide (AChI), 5,5′-dithio-bis(2-nitrobenzoic) acid (DTNB), and galantamine were purchased from Sigma-Aldrich (Germany). *Anti-inflammatory:* Lipoxygenase inhibitor screening assay kit, Cayman Chemicals Co. (Item No. 760700) was purchased from Cayman Chemical Company (Ann Arbor, MI, USA)

3.4.2. Free radical scavenging activity

The anti-oxidant activity was determined using DPPH free radical scavenging assay as described previously with minor modifications (Shimada et al., 1992; Chima et al., 2014).

Briefly, 0.1 mM DPPH (1 mL) dissolved in EtOH was added to an EtOH solution (3 mL) of the test samples or ascorbic acid at different concentrations. An equal volume of EtOH was added in the control test. The mixture was shaken vigorously and allowed to stand at room temperature for 30 min. Then the absorbance at 517 nm was measured with a UV–vis spectrophotometer. The percentage of scavenging of DPPH was calculated using the following equation:

$$I\% = [\ A_{blank} - A_{sample} / A_{blank}\ ] \times 100$$

where A_{blank} is the absorbance value of the control reaction (containing all reagents except the test compound) and A_{sample} is the absorbance value of the test compound. The sample concentration providing 50% inhibition (IC_{50}) was calculated by plotting inhibition percentages against concentrations of the sample. All tests were carried out in triplicate and inhibition values were reported as means ± SD of triplicates.

3.4.3 Acetylcholinesterase (AChE) inhibitory activity

AChE inhibitory activity of the compounds was measured by slightly modifying the spectrophotometric method (Ellman et al., 1961; Salleh et al., 2016b). Electric eel AChE was used, while acetylthiocholine iodide (AChI) was employed as the substrate of the reaction. DTNB acid was used for the measurement of the AChE activity. Briefly, 140 µL of sodium phosphate buffer (pH 8.0), 20 µL of DTNB, 20 µL of test compounds and 20 µL of AChE solution were added by multichannel automatic pipette in a 96-well microplate and incubated for 15 min at 25°C. The reaction was then initiated with the addition of 10 µL of AChI. Hydrolysis of AChI was monitored by the formation of the yellow 5-thio-2-nitrobenzoate anion as a result of the reaction of DTNB with thiocholines, catalysed by enzymes at 412 nm utilizing a 96-well microplate reader (Epoch Micro-Volume Spectrophotometer, USA). Percentage of inhibition (I%) of AChE was determined by comparison of rates of reaction of samples relative to blank sample (EtOH in phosphate buffer pH = 8) using the formula:

$$I\% = [\ E - S / E\ ] \times 100$$

where *E* is the activity of enzyme without test sample and *S* is the activity of enzyme with test sample. The experiments were done in triplicate. Galantamine was used as the positive controls.

3.4.4 Anti-inflammatory activity

The reagents were prepared according to the standard protocol (Lipoxygenase inhibitor screening assay kit, Item No. 760700). Stock solutions of samples were prepared so as to obtain concentrations of 100 - 6.25 µM in the respective wells. The prepared solutions were then introduced onto 96 well plates where the cells were distributed as blanks 1A-2A-1D (triplicate), positive control 1B-2B (duplicate), and 100% initial activity wells 1C-2C-2D (triplicate). The remaining wells were designated for inhibitor (compounds) solutions in duplicate. The addition of the reagents was done according to the standard protocol, according to which, 100 µL of assay buffer was added to the blank wells and 90 µL of lipoxygenase (5-LOX) enzyme and 10 µL of assay buffer were added to positive control wells. For the 100% initial activity wells, 90 µL of lipoxygenase enzyme and 10 µL of solvent (DMSO) were added. The inhibitor (compounds) wells were charged with 90 µL of lipoxygenase enzyme and 10 µL of respective stock (compounds) solution. The reaction was initiated by adding 10 µL of the substrate (AA) to all wells. The plate was then shaken for 5 min on an orbital shaker. Ultimately, 100 µL of chromogen solution (prepared according to standard protocol) was added to each well to stop the enzyme catalysis. The plate was incubated for half an hour and was read at 500 nm. The percentage inhibitions (I%) of the compounds were calculated using the following equation:

$$I\% = [\ A_{\text{initial activity}} - A_{\text{inhibitor}} / A_{\text{initial activity}}\ ] \times 100$$

where $A_{\text{initial activity}}$ is the absorbance of 100% initial activity wells without sample and $A_{\text{inhibitor}}$ is the absorbance of compounds/reference. Analyses were expressed as means ±SD of triplicates.

3.5 Statistical analysis

Data obtained from biological activities were expressed as mean values. The statistical analyses were carried out using one way ANOVA ($p<0.05$). A statistical package (SPSS version 16.0) was used for the data analysis.

Appendix A. Supplementary data

Supplementary data including IR, 1D/2D NMR, UV and MS for compound (**1**-**2**) are available as supporting information.

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