A new dihydrobenzofuran lignan and potential $\alpha$-glucosidase inhibitory activity of isolated compounds from *Mitrephora teysmannii*

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**ABSTRACT**

A new dihydrobenzofuran lignan, $(2R,3S)-2-(3',4'-\text{dimethoxyphenyl})-5-(3\text{-hydroxypropyl})-7\text{-methoxy}-2,3\text{-dihydrobenzofuran}-3\text{-methyl acetate}$, named as mitredrusin (1), was isolated from the leaves of *Mitrephora teysmannii* (Annonaceae) together with 12 known compounds including a related dihydrobenzofuran lignan: $(-)-3',4'\text{-di-O-methylcedrusin}$ (2), four polyacetylenic acids: $13(E)$-octadecene-9,11-diyinoic acid (3), $13(E),17$-octadecadiene-9,11-diyinoic acid (4), octadeca-9,11,13-triyinoic acid (5) and octadeca-17-en-9,11,13-triyinoic acid (6), five lignans: $(-)-\text{eudesmin}$ (7), $(-)-\text{epieudesmin}$ (8), $(-)-\text{phillygenin}$ (9), magnone A (10) and forsythian B (11) and two megastigmans: $(3S,5R,6S,7E,9R)-7\text{-megastigmene-3,6,9-triol}$ (12) and annoionol A (13). The chemical structures of these compounds were established on the basis of their 1-D and 2-D NMR spectroscopic data. All compounds were evaluated for their $\alpha$-glucosidase inhibitory activity. Among these isolates, polyacetylenic acids 3 and 4 showed more than 20-fold much higher activity compared with that of the antidiabetic drug acarbose.

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been used as a Thai folk medicine for tonic purposes (Smitinand 2001). Previous phytochemical investigations of the bark and twigs of *M. teysmannii* have resulted in the isolation of alkaloids, polyacetylenes, lignans and terpenoids (Lee et al. 1999; Yu et al. 2005; Deepralard et al. 2007; Zhang et al. 2010). However, there have not been any previous studies of extracts from the leaves of this plant. As part of our search for new natural products and bioactive compounds from Thai *Mitrephora* plants (Rayanil et al. 2013), extracts from the leaves of *M. teysmannii* became of interest due to their inhibitory activity against \( \alpha \)-glucosidase in our preliminary screening. Therefore, a chemical investigation of the \( \alpha \)-glucosidase inhibition guided fractions was undertaken, aiming to discover new potent antidiabetic drugs. We describe herein the isolation, characterisation and \( \alpha \)-glucosidase inhibitory assay of all isolated compounds.

2. Results and discussion

A combination of various chromatographic separations of the bioactive hexane and EtOAc extracts from the leaves of *M. teysmannii* led to the isolation of 13 compounds including a new dihydrobenzofuran lignan (1). By comparison of spectral and physical data with those in the literature, the known compounds were identified as (−)-3′,4-di-O-methylcedrusin (2, Yuen et al. 1998), 13(\( E \))-octadecene-9,11-diyinoic acid (3, El-Jaber et al. 2003),

![Figure 1. Structures of compounds 1–13.](image-url)
13(E),17-octadecadiene-9,11-diynoic acid (4, Zgoda et al. 2001), octadeca-9,11,13-triynoic acid (5, Kanokmedhakul et al. 2007), octadeca-17-en-9,11,13-triynoic acid (6, Cavin et al. 1998), (−)-eudesmin (7, Latip et al. 1999), (−)-epieudesmin (8, Ahmed et al. 2002), (−)-phillygenin (9, Messiano et al. 2008), magnone A (10, Jung et al. 1998), forsythialan B (11, Piao et al. 2008), (3S,5R,6S,7E,9R)-7-megastigmen-3,6,9-triol (12, Kawakami et al. 2011) and annono A (13, Matsushige et al. 2012) (Figure 1).

Compound 1 was obtained as an optically active colourless liquid, [α]D25 −22.3° (c 0.038, CHCl3). The molecular formula of compound 1 was determined to be C23H28O7 by ESI-TOF-MS, consistent with the molecular ion peak at m/z 439.1734 [M + Na]+ (Calcd for C23H28O7Na, 439.1733). The UV spectrum of 1 showed absorption bands at λmax 278, 237 and 207 nm and the IR signals at 3501, 1738, 1595 and 1516 cm−1 suggested the presence of hydroxyl, carbonyl and aromatic functionalities. The 13C NMR, DEPT and HMBC spectra revealed 23 carbon signals, which corresponded to 12 carbons of two benzene rings, a carbonyl carbon (δC 170.8), a methyl carbon (δC 20.8), three methoxy carbons (δC 50.6 × 2C and 56.1), two oxygenated methylene carbons (δC 65.4 and 62.2), an oxygenated methine carbon (δC 88.3), two methylene carbons (δC 34.6 and 32.0) and a methine carbon (δC 50.6). For aromatic ring A, the 1H NMR spectrum showed two broad singlets at δ 6.67 (1H, H-4) and 6.68 (1H, H-6) indicated the presence of two meta aromatic hydrogens. For aromatic ring C, the appearance of a typical ABX system at δ 6.83 (1H, d, J = 8.7 Hz, H-5′), 6.94 (1H, dd, J = 8.7, 1.8 Hz, H-6′) and 6.93 (1H, br s, H-2′) corresponded to a 1, 3, 4-trisubstituted phenyl moiety. The 1H NMR spectrum of 1 also exhibited three aromatic methoxy groups at δ 3.86, 3.87 and 3.89 (each 3H, s) and signals of an oxygenated methylene group at δ 5.46 (2H, t, J = 6.3 Hz, H-5c), a methylene group at δ 1.89 (2H, m, H-5b) and a benzylic methylene group at δ 2.68 (2H, t, J = 7.5 Hz, H-5a), suggesting the linkage of a 3-hydroxypropyl moiety on a benzene ring. The salient features in the 1H NMR spectrum of an oxygenated methine proton at δ 5.46 (1H, d, J = 7.5 Hz, H-2), a methine proton at δ 3.77 (1H, m, H-3) and oxygenated methylene protons at δ 4.32 (1H, dd, J = 11.1, 7.5 Hz, Hα-3a) and δ 4.43 (1H, dd, J = 11.1, 5.4 Hz, Hβ-3a) indicated the presence of a C3 unit, –OCHCH2O–, which was supported by the 1H−1H COSY correlations. Important long-range correlations were observed between H-2 (δH 5.46) and C-2′ (δC 109.3), C-6′ (δC 118.8), C-3a (δC 65.4), C-4a (δC 127.3) and C-7a (δC 146.3); H-3 (δH 3.77) and C-1′ (δC 133.2), C-4a (δC 127.3) and C-7a (δC 146.3) and H-3a (δH 4.32 and 4.43) and C-2 (δC 88.3), C-3 (δC 50.6) and C-4a (δC 127.3) in the HMBC spectrum of 1. These results suggested the formation of a dihydrobenzofuran ring (ring B) at the C-4a and C-7a of ring A and the connection of a phenyl ring C at C-2 of the dihydrobenzofuran ring. In ring C, the HMBC correlations of a broad singlet at δH 6.93 to C-2 (δC 88.3), a doublet at δH 6.83 to C-1′ (δC 133.2) and a doublet of doublet at δH 6.94 to C-4′ (δC 149.1) indicated that the three aromatic protons were placed at H-2′, H-5′ and H-6′, respectively. In addition, the HMBC correlations of signals at δH 3.87 to C-3′ (δC 149.2) and δH 3.86 to C-4′ (δC 149.1) confirmed location of the two methoxy groups at C-3′ and C-4′. In ring A, the key HMBC correlations of the signals at δH 6.68 to C-7a (δC 146.3) and δH 6.67 to C-3 (δC 50.6) suggested that the two protons were H-6 and H-4, respectively. Irradiation of the methoxy group at δH 3.89 in the NOE difference experiment enhanced the signal of H-6 (2.6%), indicating the placement of the third methoxy group at the C-7 position, which was supported by the HMBC correlation of the signal at δH 3.89 to C-7 (δC 144.2). The correlations between the benzylic methylene protons at δH 2.68 (H-5a) and C-4 (δC 116.2), C-5 (δC 135.5) and C-6 (δC 112.6) in the HMBC spectrum indicated that the 3-hydroxypropyl moiety was linked to C-5 of ring A. Additionally, the NMR spectrum
of 1 contained a singlet at $\delta_H$ 2.03, which showed one bond $^1$H/$^1$C connectivity with the carbon at $\delta_C$ 20.8 and HMBC correlation with a carbonyl signal at $\delta_C$ 170.8, confirming the presence of an acetyl group. The HMBC correlation between H-3a ($\delta_H$ 4.32, 4.43) and carbonyl carbon ($\delta_C$ 170.8) indicated that the acetyl group was attached to C-3a. Compound 1 was elucidated as 2-(3′,4′-dimethoxyphenyl)-5-(3-hydroxypropyl)-7-methoxy-2,3-dihydrobenzofuran-3-methyl acetate. Comparison of the NMR spectroscopic data of 1 with that of the known (−)-3′,4-di-O-methylcedrusin (2) or 3-[(2R,3S)-2-(3′,4′-dimethoxyphenyl)-3-(hydroxymethyl)-7-methoxy-2,3-dihydrobenzofuran-5-yl]propan-1-ol (Yuen et al. 1998), established that they were closely related. The main difference between 1 and 2 was the presence of an acetyl group in the former instead of a hydroxyl group at C-3a. The configuration for C-2 and C-3 in 1 was determined by the coupling constant value ($J$ = 7.5 Hz), which was a characteristic for a trans H-2, H-3 stereochemistry of dihydrobenzofuran lignans (Pieters et al. 1990). As the optical rotation value of 1 was $[\alpha]_D^{25}$ −22.3°, compared with that of (−)-3′,4-di-O-methylcedrusin (2) isolated from this plant ($[\alpha]_D^{25}$ −7.4°) and synthesised by Yuen et al. (1998, $[\alpha]_D^{25}$ −8.5°), the absolute configuration of 1 was thus determined to be 2$R$,3$S$. Our assumption was further confirmed by hydrolysis of compound 1 under mild alkaline condition to give compound 2. Therefore, compound 1 was proposed as (2$R$,3$S$)-2-(3′,4′-dimethoxyphenyl)-5-(3-hydroxypropyl)-7-methoxy-2,3-dihydrobenzofuran-3-methyl acetate and called mitredrusin, hitherto unreported in the literature.

All isolated compounds (1–13) were evaluated for their in vitro α-glucosidase inhibitory activity. The results revealed that all polyacetylenic acids (3–6) were more potent than the positive control acarbose. Especially, compounds 3 and 4 were both found to inhibit α-glucosidase with IC$_{50}$ values of 53 ± 1.7 and 59 ± 1.0 μM, respectively, which was about 20-fold more potent than acarbose (IC$_{50}$ value of 1457 ± 121.8 μM). Whereas, compounds 5 and 6 also showed strong potent α-glucosidase inhibitory activity with IC$_{50}$ values of 128 ± 2.5 and 274 ± 7.3 μM, respectively. This indicated that polyacetylenic acids acted as the major active constituents in the hexane extract. Although some polyacetylenic acids have been isolated from this plant and some other Mitrephora species (Zgoda et al. 2001; Supudompol et al. 2004; Li et al. 2009; Zhang et al. 2010), this is the first evaluation of polyacetylenic acids for α-glucosidase inhibitory activity. Unfortunately, the rest of the compounds (1, 2 and 7–13) showed less than 30% inhibitory effect at the concentration of 1 mg/mL.

3. Experimental

3.1. General experimental procedures

Melting points were measured on a Kofler hot stage apparatus and are uncorrected. Optical rotations were obtained using a Jasco P1010 digital polarimeter. IR spectra were obtained on a Perkin Elmer GX FT-IR spectrophotometer. UV spectra were recorded on a Hewlett Packard 8453 UV–vis spectrometer. 1-D and 2-D NMR experiments were recorded on a Bruker AVANCE 300 MHz spectrometer operating at 300 MHz for proton and 75 MHz for carbon, respectively. Mass spectra were acquired on a Micromass lCT mass spectrometer and the lock mass calibration was applied for the determination of accurate masses. Column chromatography (CC) was carried out on silica gel (Merck, 70–230 mesh or 230–400 mesh) or RP-18 (Merck, 40–63 mesh). TLC was performed on Merck precoated silica gel 60 F$_{254}$ plates and spots were visualised under UV light (254 and 365 nm) or by spraying with 1% CeSO$_4$ in 10% aqueous H$_2$SO$_4$ followed by heating.
3.2. Plant material

The leaves of *M. teysmannii* were collected in February 2011 from Ton Pariwat Wildlife Conservation Area, Phang-nga Province, Thailand and were identified by Dr. Piya Chalermglin of the Thailand Institute of Scientific and Technological Research. A voucher specimen (SS614/272) was deposited at the Herbarium of the Faculty of Science and Technology, Phuket Rajabhat University, Phuket, Thailand.

3.3. Extraction, isolation and characterisation

Air-dried leaves of *M. teysmannii* (3.7 kg) were extracted with 95% EtOH (3 × 10 L) at room temperature to afford a crude extract of 200.4 g after evaporation of the solvent under vacuum. The crude extract was diluted with water and partitioned into hexane, EtOAc and *n*-BuOH. Evaporation of the respective solvents gave the hexane (50.6 g), EtOAc (40.4 g) and *n*-BuOH (33.5 g) extracts. The hexane extract was subjected to silica gel flash column chromatographic separation, using a gradient system of hexane-EtOAc as the eluent to afford 30 fractions (H1–H30). Fraction H13 (2.59 g) was chromatographed on a silica gel column using hexane-EtOAc-benzene (7:1:2) as the eluent to give 19 subfractions (H13.1–19). Subfraction H13.7 (131.5 mg) was rechromatographed using RP-18 CC eluted with CH₃CN–H₂O (8:2) to provide compound 3 (31.2 mg) and compound 4 (43.3 mg). Subfraction H13.9 (73.4 mg) was further purified by RP-18 CC employing CH₃CN–H₂O (8:2) as the eluent to afford compound 5 (6.6 mg). Fraction H18 (3.26 g) was separated by silica gel CC using EtOAc in hexane as gradient mixtures (10, 20 and 40%) to give 17 subfractions (H18.1–17) and subfraction H18.11 (65.6 mg) was further purified by RP-18 CC employing CH₃CN–H₂O (8:2) as the eluent to afford compound 6 (27.3 mg). Fraction H25 (2.67 g) was chromatographed on a silica gel column eluted with hexane–EtOAc–benzene (2:1:1) to provide compound 7 (34.4 mg), compound 8 (67.0 mg) and compound 9 (16.8 mg). Fraction H30 (3.46 g) was subjected to silica gel CC employing CH₂Cl₂–MeOH–H₂O as gradient mixtures (50:3:1 and 20:1:1) to afford 44 subfractions (H30.1–44). Subfraction H30.21 (95.7 mg) was further separated by RP-18 CC employing MeOH–H₂O (1:1.5) as the eluent to furnish compound 10 (29.3 mg) and compound 1 (5.6 mg). Subfraction H30.23 (82.3 mg) was purified by RP-18 CC using MeOH–H₂O (1:1.5) to give compound 11 (47.4 mg).

The EtOAc extract was chromatographed on a silica gel flash column eluted with EtOAc in hexane (10–100%) and MeOH in EtOAc (1–10%) gradient mixtures to provide 25 fractions (E1–E25). Fraction E19 (4.64 g) was rechromatographed on a silica gel column using CH₂Cl₂–MeOH–H₂O (70:3:1 and 50:3:1) as the eluent to yield 27 subfractions (E19.1–27). Subfraction E19.8 (0.206 g) was subjected to RP-18 CC with MeOH–H₂O (1:1.5) to give compound 2 (100.6 mg). Subfraction E19.23 (0.166 g) was separated by RP-18 CC employing MeOH–H₂O (1:2) as the eluent to yield compound 12 (5.4 mg) and compound 13 (7.2 mg).

Mitredrusin (1): colourless liquid. [α]D²⁵ = -22.3° (c 0.038, CHCl₃). IR (neat): v max 3501, 2938, 1738, 1595, 1516. UV (MeOH): λ max (log ε) 278 (3.00), 237 (3.10), 207 (3.40) nm. ESI-TOF-MS m/z 439.1734 [M + Na]⁺ (Calcd for C₂₃H₂₈O₇Na, 439.1733). 1H NMR (300 MHz, CDCl₃): δ 1.89 (2H, m, H-5b), 2.03 (3H, s, C(O)CH₃), 2.68 (2H, t, J = 7.5 Hz, H-5a), 3.69 (2H, t, J = 6.3 Hz, H-5c), 3.77 (1H, m, H-3), 3.86 (3H, s, 4′-OCH₃), 3.87 (3H, s, 3′-OCH₃), 3.89 (3H, s, 7-OCH₃), 4.32 (1H, dd, J = 11.1, 7.5 Hz, H-3a), 4.43 (1H, dd, J = 11.1, 5.4 Hz, H-5b), 5.46 (1H, d, J = 7.5 Hz, H-2), 6.67 (1H, br s, H-4), 6.68 (1H, br s, H-6), 6.83 (1H, d, J = 8.7 Hz, H-5′), 6.93 (1H, br s, H-2′), 6.94 (1H,
dd, J = 8.7, 1.8 Hz, H-6’). 13C NMR (75 MHz, CDCl3): δ 20.8 (C(O)CH3), 32.0 (C-5a), 34.6 (C-5b), 50.6 (C-3), 56.0 (×2C, 3’-OCH3, 4’-OCH3), 56.1 (7–OCH3), 62.2 (C-5c), 65.4 (C-3a), 88.3 (C-2), 109.3 (C-2’), 111.0 (C-5’), 112.6 (C-6), 116.2 (C-4), 118.8 (C-6’), 127.3 (C-4a), 133.2 (C-1’), 135.5 (C-5), 144.2 (C-7), 146.3 (C-7a), 149.1 (C-4’), 149.2 (C-3’), 170.8 (C=O).

3.4. Basic hydrolysis of mitredrusin (1)

To a solution of compound 1 (4.3 mg) in MeOH (0.5 mL), 1.0 mL of 0.5 M NaOH/H2O solution was added and the mixture was stirred for 5 h at room temperature. The mixture was acidified with 1.0 mL of 1.0 M HCl and extracted with CH2Cl2 (1.0 mL × 3). The combined organic layer was concentrated and purified by preparative TLC to afford (−)-3’,4-di-O-methylcedrusin (2, 3.2 mg) as colourless liquid. [α]D 25 −7.4° (c 0.060, CHCl3). IR (neat): υmax 3390, 2935, 1606, 1515 cm−1. UV (MeOH): λmax (log ε) 280 (3.08), 237 (3.23), 205 (3.59) nm. ESI-TOF-MS m/z 397.1634 [M + Na]+ (Calcd for C21H26O6Na, 397.1627). 1H and 13C NMR spectral data were in good agreement with the previously published data (Yuen et al. 1998).

3.5. α-Glucosidase inhibitory assay

The α-glucosidase (from Saccharomyces cerevisiae; Sigma-Aldrich, St. Louis, MO, USA) inhibitory activity was determined by the method described by Worawalai et al. (2012). Briefly, 20 μL of the test compound was mixed with 20 μL of the enzyme solution (1 U/mL) in 0.01 M phosphate buffer (pH 6.8). The mixture was pre-incubated at 25 °C for 15 min and then a p-nitrophenyl-α-D-glycopyranoside (PNPG) solution (20 μL) was added. After 15 min of continuous incubation, a 0.5 M Na2CO3 solution (40 μL) was added to quench the reaction. The enzymatic activity was evaluated by monitoring the absorbance at 405 nm of released p-nitrophenol. The per cent inhibition was calculated according to the equation: % inhibition = (Ablank − Asample)/Ablank × 100; where Asample and Ablank are the absorbances of the solutions containing PNPG and α-glucosidase with and without the sample, respectively. The IC50 values of the samples possessing an inhibition rate >50% were then determined. Acarbose was used as the positive control.

4. Conclusion

The chemical investigation of the leaves of M. teysmannii resulted in the isolation of 13 compounds (1–13). Compound 1 was a new natural product and the known compounds 2–5, 8, 9 and 11–13 were isolated for the first time from M. teysmannii. In addition, the strong α-glucosidase inhibitory activity of polyacetylenic acids (3–6) presented here encouraged us to further develop this type of compounds as potent α-glucosidase inhibitors.

Disclosure statement

No potential conflict of interest was reported by the authors.

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