Note

Chemical Constituents from the Branches and Leaves of *Alchornea trewioides*

Nguyen Huu Toan Phan,^{*,a} Nguyen Thi Dieu Thuan,^a Nguyen Huu Huong Duyen,^a
Tran Thi Hong Hanh,^b Tran Hong Quang,^b Nguyen Xuan Cuong,^{*,b} and Nguyen Hoai Nam^b

^aTay Nguyen Institute for Scientific Research, Vietnam Academy of Science and Technology (VAST); 116 Xo Viet Nghe Tinh Street, 7th Ward, Dalat 671940, Vietnam; and ^bAdvanced Center for Bio-Organic Chemistry, Institute of Marine Biochemistry, VAST; 18 Hoang Quoc Viet, Cau Giay, Hanoi 10072, Vietnam.

Received August 6, 2020; accepted October 25, 2020; advance publication released online November 3, 2020

Two new megastigmane glucosides namely trewiosides A (1) and B (2), along with 20 α -hydroxypregn-4-en-3-one β -D-glucopyranoside (3), sugeroside (4), and schizandriside (5) were isolated from the branches and leaves of *Alchornea trewioides*. The structure elucidation was confirmed by extensive analysis of the one and two dimensional (1 and 2D) NMR, electronic circular dichroism (ECD) as well as high resolution electrospray ionization quadrupole time-of-flight (HR-ESI-QTOF) mass spectra. Noteworthy, the isolation of compounds 1 and 2 represents the second finding of megastigmane derivatives with a methoxy-carbonyl group at C-5 to date. In addition, compound 3 showed weak cytotoxicity against three human cancer cell lines as A549 (lung carcinoma), HepG2 (hepatocarcinoma), and MCF7 (breast carcinoma). Besides, compounds 2 and 3 exhibited moderate inhibitory effects on lipopolysaccharide (LPS)-induced nitric oxide (NO) production in RAW264.7 cells. Whereas, the remaining compounds 1, 4 and 5 showed weak inhibitory activity.

Key words *Alchornea trewioides*; Euphorbiaceae; megastigmane glucoside; cytotoxic activity; nitric oxide (NO) production

Introduction

Alchornea trewioides (Benth.) Müll. Arg. (Euphorbiaceae) is a 1–3 m tall and dioecious shrubs with puberulent or almost glabrous branchlets. The plant grows in plains, mountains, slopes, thickets, open scrub, and limestone hills up to 1200 m high in Cambodia, China, Japan, Laos, and Thailand. In Vietnam, this plant was found in northern provinces to Lam Dong province and used in folk medicine to treat dysentery, chronic bronchitis, urolithiasis, and hemorrhage uterine. It was also externally used to treat hemorrhage trauma, urticaria, and eczema.¹⁾ Previous investigations on chemical constituents of this plant resulted in isolation of flavonoid, phenylethanoid, phenolic acid, and quinic acid derivatives,^{2–5)} of which some compounds exhibited antioxidant activity.³⁾

As part of our current investigations on chemical constituents of the *Alchornea* species growing in Vietnam, this paper addresses the isolation and structure elucidation of two new megastigmane glucosides namely trewiosides A (1) and B (2), along with 20 α -hydroxypregn-4-en-3-one β -D-glucopyranoside (3), sugeroside (4), and schizandriside (5) from the branches and leaves of *A. trewioides*. Their *in vitro* cytotoxicity against three human cancer cell lines as A549 (lung carcinoma), HepG2 (hepatocarcinoma), and MCF7 (breast carcinoma) as well as inhibitory effects on lipopolysaccharide (LPS)-induced nitric oxide (NO) production in RAW264.7 cells were also evaluated.

Results and Discussion

The water-soluble part of *A. trewioides* yielded five compounds (1–5, Fig. 1) after subjecting it on various chromatographic separations. The known compounds, 20 α -hydroxypregn-4-en-3-one β -D-glucopyranoside (3),^{6,7)} sug-

eroside (4),⁸⁾ and schizandriside (5),⁹⁾ were identified by detailed analysis of their one and two dimensional (1- and 2D)-NMR spectroscopic data in comparison with those reported in the literature. Compound 3 was previously obtained by transformation of progesterone using suspension cultures of *Digitalis purpurea* cultured cells.⁷⁾ However, this is the first report of 3 from natural sources.

Trewioside A (1) was obtained as a white powder with the molecular formula of C₂₀H₃₂O₉, identified by high resolution electrospray ionization quadrupole time-of-flight (HR-ESI-QTOF)-MS containing a quasi-molecular ion peak at *m/z* 439.1941 [M + Na]⁺. The ¹H- and ¹³C-NMR spectra revealed typical signals of a β -D-glucopyranosyl moiety at δ_C 104.1 (C-1'), 75.2 (C-2'), 78.1 (C-3'), 71.6 (C-4'), 77.8 (C-5'), and 62.5 (C-6')/ δ_H 4.31 (d, *J* = 8.0 Hz, H-1'), 3.15 (dd, *J* = 8.0, 9.0 Hz, H-2'), 3.37 (t, *J* = 9.0 Hz, H-3'), 3.29 (t, *J* = 9.0 Hz, H-4'), 3.27 (m, H-5'), 3.67 (dd, *J* = 5.0, 12.0 Hz, H_a-6'), and 3.85 (dd, *J* = 2.0, 12.0 Hz, H_b-6')¹⁰⁾ and a methoxy group at δ_C 53.3/ δ_H 3.86 (3H, s). The D-glucopyranosyl moiety was further confirmed by acid hydrolysis followed by HPLC analysis of the thiocarbamoyl-thiazolidine derivatives of the hydrolysate of 1 in comparison with those of the standard sugars (see Experimental). Thus, with 13 remaining carbon atoms, 1 was suggested to be a megastigmane glucoside. The aglycon of 1 contained characteristic signals of one ketone [δ_C 202.2 (C-3)], one carbonyl carbon [δ_C 169.2 (C-13)], one oxymethine [δ_C 77.6 (C-9)/ δ_H 3.83 (m, H-9)], one doublet methyl [δ_C 22.0 (C-10)/ δ_H 1.22 (3H, d, *J* = 6.5 Hz, H-10)], and two singlet methyl [δ_C 28.5 (C-11) and 27.9 (C-12)/ δ_H 1.02 (H-11) and 1.17 (H-12), each 3H, s]. From the above observation, the ¹H- and ¹³C-NMR data of 1 were found to be similar as those of schinifolenol A,¹¹⁾ except for additional presence of

* To whom correspondence should be addressed. e-mail: phannht@tni.ac.vn; cuongnx@imbc.vast.vn

Fig. 1. Structures of Compounds 1–5

Fig. 2. Key Correlations for 2D-NMR of **1** and **2** Using COSY (—), HMBC (—), and NOESY (—).

3D structure for the aglycon of **2** was generated using PerkinElmer, Inc. Chem3D Ultra Version 18.2.0.48.

the glucose moiety. The correlation spectroscopy (COSY) connectivities of H-6/H-7/H-8/H-9/H-10 and heteronuclear multiple bond correlation (HMBC) cross-peaks of H-2 with C-3, C-4, C-6; H-4 with C-2, C-6, and C-13; H-6 with C-2, C-4, and C-13; H-11 and H-12 with C-1, C-2, and C-3; as well as H-9 with C-1' (Fig. 2), clearly confirmed the planar structure of **1**. The *S* configuration at C-9 was determined by using the empirical rules of ^{13}C -NMR chemical shift^{10,12,13} with the characteristic carbon signals of C-9, C-10, and C-1' at δ_{C} 77.6, 22.0, and 104.1, respectively; similar to those of 9*S* isomer at δ_{C} 77.7–78.1 (C-9), 21.8–22.0 (C-10), and 103.7–103.9 (C-1') and quite different from those of 9*R* isomer at δ_{C} 75.7–76.8 (C-9), 19.7–20.4 (C-10), and 102.0–102.9 (C-1').¹⁰ In addition, the absolute configuration at C-6 was elucidated as *S* by a good agreement of the electronic circular dichroism (ECD) data of **1** in MeOH (with a negative Cotton effect at 279 nm and a positive effect at 241 nm) and schinifolenol A in MeOH (with a negative Cotton effect at 270 nm and a positive effect at 235 nm)¹¹ as well as comparison of its experimental ECD spectrum with those calculated for both 6*R* and 6*S* isomers of the aglycon of **1** (Fig. 3).

Trewioside B (**2**) was also obtained as a white powder. Its ^1H - and ^{13}C -NMR data were similar to those of **1** (Table 1), except for the presence of a methylene and a methine in **2** instead of the trisubstituted double bond in **1**. Consideration the structure of **1** suggested that **2** is a 4,5-dihydrogenated derivative of **1**, further supported by HR-ESI-QTOF having a quasi-molecular ion peak at m/z 441.2075 $[\text{M} + \text{Na}]^+$ consistent with the molecular formula of $\text{C}_{20}\text{H}_{34}\text{O}_9$ as well as COSY and HMBC correlations (Fig. 2). The ^1H - and ^{13}C -NMR signals

for C-5 of **2** were strongly shifted downfield at δ_{H} 2.75/ δ_{C} 48.4 relative to those of sedumoside C at δ_{H} 1.78/ δ_{C} 37.7,¹⁴ indicating location of the methoxycarbonyl group at C-5. Similarly as in case of **1**, the carbon signals of C-9 (δ_{C} 77.2), C-10 (δ_{C} 21.7), and C-1' (δ_{C} 103.7) of **2** confirmed the 9*S* configurations.¹⁰ Moreover, comparison the experimental ECD spectrum of **2** with those calculated (Fig. 4) clearly confirmed the absolute configuration at C-6 as *S*. Detailed analysis of the ^1H -NMR coupling constants and nuclear Overhauser effect spectroscopy (NOESY) experiment led to elucidation of the configuration at C-5. The large coupling constant ($J = 10.0\text{ Hz}$) between H-5 and H-6 confirmed that they are in diaxial relationship. In addition, NOESY interactions of H-6 (δ_{H} 1.84) with H-12 (δ_{H} 1.11) and H $_{\alpha}$ -2 (δ_{H} 2.46) as well as that of H-5 (δ_{H} 2.75) with H-11 (δ_{H} 0.83) (Fig. 2) clearly confirmed the β -orientation of H-5.¹⁴

The sulforhodamine B (SRB) method¹⁵ was used to evaluate cytotoxic activity of compounds **1**–**5** against three human cancer cell lines as A549 (lung carcinoma), HepG2 (hepatocarcinoma), and MCF7 (breast carcinoma) following the previously described protocols.^{16,17} As the obtained results, only **3** showed weak cytotoxic effect on the three tested cell lines with corresponding IC_{50} values of 79.39 ± 1.44 , 85.70 ± 1.57 , and $68.32 \pm 2.29\ \mu\text{M}$, relative to those of the positive control. In addition, compounds **1**–**5** were evaluated for their inhibitory effects on LPS-induced NO production in RAW264.7 cells following the previously reported protocols.^{18,19} Compounds **2** and **3** exhibited moderate inhibitory effects with relevant IC_{50} values of 47.99 ± 1.43 and $45.69 \pm 2.42\ \mu\text{M}$, relative to that of the positive control *N*^G-methyl-L-arginine acetate (IC_{50} of $31.05 \pm 3.75\ \mu\text{M}$). Whereas, the remaining compounds **1**, **4** and **5** showed weak activity with IC_{50} values of 85.27 ± 2.33 , 61.29 ± 2.63 , and $85.94 \pm 8.01\ \mu\text{M}$, respectively.

In conclusion, two new megastigmane glucosides namely trewiosides A (**1**) and B (**2**), along with 20 α -hydroxypregn-4-en-3-one β -D-glucopyranoside (**3**), sugeroside (**4**), and schizandriside (**5**) were isolated from the branches and leaves of *A. trewioides*. The new compounds **1** and **2** possess a methoxycarbonyl group at C-5, rarely found from natural source. To the best of our knowledge, this is the second isolation of this megastigmane type to date. Compound **3** showed weak cytotoxicity against three human cancer cell lines as A549, HepG2, and MCF7. In addition, compounds **2** and **3** exhibited moderate inhibitory effects on LPS-induced NO production in RAW264.7 cells. Whereas, the remaining compounds **1**, **4**, and **5** showed weak inhibitory activity.

Fig. 3. Experimental ECD Spectrum of **1** and Calculated Spectra for the Two Isomers **6S** and **6R** of the Aglycon of **1**

Table 1. ^1H - (CD_3OD , 500 MHz) and ^{13}C -NMR (CD_3OD , 125 MHz) Spectroscopic Data of **1** and **2**

Pos.	1		2	
	δ_{C}	δ_{H} mult. (J in Hz)	δ_{C}	δ_{H} mult. (J in Hz)
1	37.4	—	39.9	—
2	47.9	2.67 d (17.0) 2.09 d (17.0)	56.2	α 2.46 d (14.0) β 2.08 dd (2.5, 14.0)
3	202.2	—	211.5	—
4	131.3	6.57 brs	44.2	α 2.67 ddd (1.0, 13.5, 12.0) β 2.38 ddd (2.0, 4.0, 13.5)
5	155.0	—	48.4	2.75 ddd (4.5, 10.0, 12.0)
6	46.1	2.64 dd (5.0, 7.5)	48.8	1.84 ddd (3.5, 6.0, 10.0)
7	27.9	1.66 m/1.92 m	25.4	1.36 m/1.68 m
8	36.3	1.53 m	37.9	1.56 m
9	77.6	3.82 q (6.0)	77.2	3.81 q (6.0)
10	22.0	1.22 d (6.0)	21.7	1.24 d (6.0)
11	28.5	1.02 s	21.4	0.83 s
12	27.9	1.17 s	30.1	1.11 s
13	169.2	—	176.6	—
OCH ₃	53.3	3.86 s	52.7	3.75 s
Glc				
1'	104.1	4.31 d (8.0)	103.7	4.33 d (8.0)
2'	75.2	3.15 dd (8.0, 9.0)	75.3	3.18 dd (8.0, 9.0)
3'	78.1	3.37 t (9.0)	78.2	3.36 t (9.0)
4'	71.6	3.29 t (9.0)	71.7	3.30 t (9.0)
5'	77.8	3.27 m	77.9	3.27 m
6'	62.5	3.67 dd (5.0, 12.0) 3.85 dd (2.0, 12.0)	62.9	3.68 dd (5.5, 12.0) 3.87 dd (2.0, 12.0)

All assignments were confirmed by HSQC, HMBC, COSY, and NOESY experiments.

Experimental

General Experimental Procedures Optical rotations were determined on a JASCO P-2000 polarimeter (Tokyo, Japan). Circular dichroism (CD) spectra were recorded with a Chirascan (Applied Photophysics, U.K.) spectropolarimeter. High resolution mass spectra were recorded on an Agilent 6530 Accurate-Mass spectrometer (CA, U.S.A.). The ^1H -NMR (500 MHz) and ^{13}C -NMR (125 MHz) spectra were recorded

on an AVANCE III HD 500 (Bruker, Germany) FT-NMR spectrometer with tetramethylsilane (TMS) was used as an internal standard. HPLC analysis was carried out on an Agilent 1200 series system equipped with a diode array detector (CA, U.S.A.). Medium pressure liquid chromatography (MPLC) was carried out on a Biotage-Isolera One system (SE-751 03 Uppsala, Sweden). Column chromatography (CC) was performed on silica gel (Kieselgel 60, 70–230 mesh and 230–400 mesh, Merck, Darmstadt, Germany) and reversed-phase silica gel (ODS-A, 12 nm S-150 mm, YMC Co., Ltd., Japan) resins. TLC used pre-coated silica gel 60F₂₅₄ (1.05554.0001, Merck) and RP-18F_{254S} plates (1.15685.0001, Merck), and compounds were visualized by spraying with aqueous 10% H_2SO_4 and heating for 3–5 min. ECD calculations were carried out on Dell Precision 5820 systems equipped with an Intel Xeon W-2175 2.50 GHz processor, 16 GB RAM, and Windows 10 Pro for Workstations.

Plant Material The branches and leaves of *Alchornea trewioides* (Benth.) Müll. Arg. (Euphorbiaceae) were collected at Me Linh Station for Biodiversity, Phuc Yen, Vinhphuc, Vietnam, in 06/2019 and identified by Dr. Nguyen The Cuong, Institute of Ecology and Biological Resources, VAST. The voucher specimens (No. 104.01-2015.39-4) were deposited at Herbarium of the Institute of Ecology and Biological Resources, VAST, Hanoi, Vietnam.

Extraction and Isolation The dried branches and leaves (1.6 kg) of *A. trewioides* were powdered and extracted with MeOH under ultrasonic condition (3×1 h) to obtain 150 g residue. This residue was suspended in distilled water (2 L) and partitioned in turn with *n*-hexane, CH_2Cl_2 , and EtOAc to give corresponding extracts *n*-hexane (H, 50 g), CH_2Cl_2 (D, 25 g) and EtOAc (E, 10 g), and water layer (W, 2 L). The W layer was passed through Diaion HP-20 CC using step-wise eluent of MeOH– H_2O (0:100, 25:75, 50:50, 75:25, and 100:0, v/v) to obtain four fractions W1–W4, after removal of the fraction eluted with 100% water. Fraction W4 (4 g) was separated on RP-18 MPLC using mobile phase of MeOH– H_2O (1:2.5, v/v) obtaining seven subfractions, W4A–W4G. Subfraction W4C (950 mg) was further separated on silica gel CC with CH_2Cl_2 –MeOH (15:1, v/v) to obtain three smaller fractions,

Fig. 4. Experimental ECD Spectrum of **2** and Calculated Spectra for the Isomers 5*S*,6*S*, 5*S*,6*R*, 5*R*,6*R*, and 5*R*,6*S* of the Aglycon of **2**

W4C1–W4C3. Fraction W4C2 (96 mg) was purified on silica gel CC with EtOAc–MeOH (15:1, v/v) and then on Sephadex LH-20 CC with MeOH–H₂O (1:1, v/v) to furnish compounds **1** (5.0 mg) and **2** (1.5 mg). Subfraction W4E (219 mg) was purified on silica gel CC with EtOAc–MeOH (8:1, v/v), followed by ODS-A CC with acetone–H₂O (1:1, v/v) to give compound **4** (5 mg). Subfraction W4F (270 mg) was separated into three smaller fractions, W4F1–F4F3, using ODS-A CC with MeOH–H₂O (1:1, v/v). Compounds **3** (3.0 mg) and **5** (3.5 mg) were purified from fraction W4F2 (52 mg) after subjecting it on Sephadex LH-20 CC with eluent of MeOH–H₂O (1:1, v/v).

Trewioside A (**1**): white powder, $[\alpha]_D^{25} +35.8$ (*c*, 0.05, MeOH); IR (KBr) $\nu_{\max}$ 3440, 2920, 1721, 1672, 1238, 1076, and 1030 cm⁻¹; UV (MeOH) $\lambda_{\max}$: 241 nm; CD (MeOH) $\lambda_{\max}$ (mdeg): 279 (–1.73) and 241 (+15.72) nm; ¹H-NMR (CD₃OD, 500 MHz) and ¹³C-NMR (CD₃OD, 125 MHz) are given in Table 1; HR-ESI-QTOF-MS *m/z* 439.1941 [M + Na]⁺ (Calcd for C₂₀H₃₂NaO₉⁺, 439.1939).

Trewioside B (**2**): white powder, $[\alpha]_D^{25} -95.3$ (*c*, 0.05, MeOH); IR (KBr) $\nu_{\max}$ 3440, 2919, 1721, 1635, 1076, and 1036 cm⁻¹; UV (MeOH) $\lambda_{\max}$: 289 nm; CD (MeOH) $\lambda_{\max}$ (mdeg): 290 (–2.80) and 232 (+1.14) nm; ¹H-NMR (CD₃OD, 500 MHz) and ¹³C-NMR (CD₃OD, 125 MHz) are given in Table 1; HR-ESI-QTOF-MS *m/z* 441.2075 [M + Na]⁺ (Calcd for C₂₀H₃₄NaO₉⁺, 441.2095).

Acid Hydrolysis and Sugar Identification Compound **1** (1.0 mg) was hydrolyzed with 1.0 M HCl (1.0 mL) for 3 h at 90 °C. After extracting the reaction mixture with ethyl acetate, the aqueous layer was obtained and evaporated *in vacuo* to give a dried and neutral residue. The residue was dissolved in pyridine (0.5 mL) containing L-cysteine methyl ester hydrochloride (3.0 mg) and the mixture was incubated at 60 °C for 1 h. Phenylisothiocyanate (15.0 μL) was then added and the reaction mixture was further heated at 60 °C for 1 h using hot plate stirrer. The reaction mixture was subsequently analyzed by comparing the retention times of derivatives of sugars obtained from the reaction mixture with those of standard samples using reversed-phase HPLC under the following conditions: detection wavelength: 250 nm, mobile phase: 25% acetonitrile–water (0.1% formic acid) and Agilent

Eclipse XDB-C18 column (5 μM, 4.6 × 250 mm). The sugar unit of **1** was identified as D-glucose by its observed peak at *t*_R = 14.71 min and comparison with the authentic standards: D-glucose (*t*_R = 14.75 min) and L-glucose (*t*_R = 13.73 min).²⁰⁾

Calculation of ECD Spectra The time-dependent density functional theory (TDDFT) ECD calculation was carried out using Gaussian 16W software.²¹⁾ Conformational analysis was initially performed using Spartan'18 software with the MMFF force field. The conformers with Boltzmann populations of over 1% were chosen for ECD calculations²²⁾ and re-optimized at the B3LYP/6-31G(d,p) level for MeOH using the IEFPCM model. The calculation of ECD was conducted in MeOH using TDDFT at the B3LYP/6-311++G(d,p) level with the solve for more states *N* = 25 for all conformers of compounds. ECD spectra were generated using the program SpecDis 1.71²³⁾ by applying Gaussian band shapes with sigma = 0.4 eV. ECD spectra of each conformer were weighted and summed according to a Boltzmann distribution and compared with the experimental data.

Acknowledgments This research is funded by Vietnam National Foundation for Science and Technology Development (NAFOSTED) under Grant number 104.01-2015.39. The authors are grateful to the Institute of Chemistry, VAST for measurement of the NMR spectra; to Dr. Bui Huu Tai, Institute of Marine Biochemistry, VAST for measurement of the CD and HR-ESI-QTOF mass spectra; and to Prof. Do Thi Thao, Institute of Biotechnology for evaluation of the biological activities.

Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials, one- and two-dimensional NMR (1 and 2D-NMR) spectra for the new compounds **1** and **2**.

References

- 1) Chi V. V., "Dictionary of Vietnamese Medicinal Plants," Vol. 2,

- Medicine Publishing House, Hanoi, Vietnam, 2012, pp. 377–378.
- 2) Huang Y.-L., Li D.-P., Yang Z.-M., *Guangxi Zhi Wu*, **35**, 564–568 (2015).
 - 3) Huang Y.-L., Chen Y.-Y., Liu J.-L., Yang Z.-M., Wang L., Li D.-P., *Guangxi Zhi Wu*, **35**, 105–108 (2015).
 - 4) Huang Y.-L., Liu J.-L., Chen Y.-Y., Yang Z.-M., Yan X.-J., Li D.-P., *Guangxi Zhi Wu*, **34**, 143–147 (2014).
 - 5) Huang Y.-L., Chen Y.-Y., Yan X.-J., Liu J.-L., Yang Z.-M., Li D.-P., *Guangxi Zhi Wu*, **34**, 126–129 (2014).
 - 6) Seo S., Tomita Y., Tori K., Yoshimura Y., *J. Am. Chem. Soc.*, **100**, 3331–3339 (1978).
 - 7) Furuya T., Kawaguchi K., Hirofumi M., *Phytochemistry*, **12**, 1621–1626 (1973).
 - 8) Li X. A., Zhang D. Z., Onda M., Konda Y., Iguchi M., Harigaya Y., *J. Nat. Prod.*, **53**, 657–661 (1990).
 - 9) Takani M., Ohya K., Takahashi K., *Chem. Pharm. Bull.*, **27**, 1422–1425 (1979).
 - 10) Matsunami K., Otsuka H., Takeda Y., *Chem. Pharm. Bull.*, **58**, 438–441 (2010).
 - 11) Hu L., Wang K., Wang Z., Liu J., Wang K., Zhang J., Luo Z., Xue Y., Zhang Y., Zhang Y., *Molecules*, **21**, 383–383 (2016).
 - 12) Yu L. L., Hu W. C., Ding G., Li R. T., Wei J. H., Zou Z. M., Wang M. H., *J. Nat. Prod.*, **74**, 1009–1014 (2011).
 - 13) Zhang Y., Yang L. J., Jiang K., Tan C. H., Tan J. J., Yang P. M., Zhu D. Y., *Carbohydr. Res.*, **361**, 114–119 (2012).
 - 14) Yoshikawa M., Morikawa T., Zhang Y., Nakamura S., Muraoka O., Matsuda H., *J. Nat. Prod.*, **70**, 575–583 (2007).
 - 15) Skehan P., Storeng R., Scudiero D., Monks A., McMahon J., Vistica D., Warren J. T., Bokesch H., Kenney S., Boyd M. R., *J. Natl. Cancer Inst.*, **82**, 1107–1112 (1990).
 - 16) Nam N. H., Kiem P. V., Ban N. K., Thao N. P., Nhiem N. X., Cuong N. X., Tistaert C., Dejaegher B., Heyden Y. V., Quetin-Leclercq J., Thao D. T., Minh C. V., *Phytochem. Lett.*, **4**, 348–352 (2011).
 - 17) Thao D. T., Phuong D. T., Hanh T. T. H., Thao N. P., Cuong N. X., Nam N. H., Minh C. V., *J. Asian Nat. Prod. Res.*, **16**, 364–369 (2014).
 - 18) Giang P. M., Thao D. T., Nga N. T., Van Trung B., Anh D. H., Viet P. H., *Pharm. Chem. J.*, **53**, 628–634 (2019).
 - 19) Cheenpracha S., Park E. J., Rostama B., Pezzuto J. M., Chang L. C., *Mar. Drugs*, **8**, 429–437 (2010).
 - 20) Tanaka T., Nakashima T., Ueda T., Tomii K., Kouno I., *Chem. Pharm. Bull.*, **55**, 899–901 (2007).
 - 21) Frisch M. J., Trucks G. W., Schlegel H. B., *et al.*, Gaussian, Inc., Wallingford, CT (2016).
 - 22) O'Boyle N. M., Vandermeersch T., Flynn C. J., Maguire A. R., Hutchison G. R., *J. Cheminformatics*, **3**, 1–9 (2011).
 - 23) Bruhn T., Schaumlöffel A., Hemberger Y., Pescitelli G., SpecDis Version 1.71 Berlin, Germany (2017). <<https://specdis-software.jimdo.com>>