1-1-2020

Styryllactones from Goniothalamus tamirensis

Pornphimol Meesakul
University of Wollongong, Mae Fah Luang University

Wuttichai Jaidee

Christopher Richardson
University of Wollongong, crichard@uow.edu.au

Raymond Andersen

Brian Patrick

See next page for additional authors

Publication Details Citation

Meesakul, P., Jaidee, W., Richardson, C., Andersen, R., Patrick, B., Willis, A., Muanprasat, C., Wang, J., Lei, X., Hadsadee, S., Jungsuttiwong, S., Pyne, S. G., & Laphookhieo, S. (2020). Styryllactones from Goniothalamus tamirensis. Faculty of Science, Medicine and Health - Papers: Part B. Retrieved from https://ro.uow.edu.au/smhpapers1/1101

Styryllactones from Goniothalamus tamirensis

Abstract

The phytochemical investigation of the twig and leaf extracts of Goniothalamus tamirensis led to the isolation and identification of 15 compounds including three rare previously undescribed styryllactones, goniotamirenones A-C, together with 12 known compounds. (Z)-6-Styryl-5,6-dihydro-2-pyranone and 5-(1-hydroxy-3-phenyl-allyl)-dihydro-furan-2-one are reported here for the first time as previously undescribed natural products. Their structures were elucidated by spectroscopic methods. Goniotamirenone A was synthesized via a [2 + 2] cycloaddition reaction of 6-styrrylpyran-2-one in quantitative yield. The absolute configurations of goniotamirenones B and C were identified from experimental and calculated ECD data, while the absolute configurations of (−)-5-acetoxygoniothalamin, (−)-isoaltholactone, parvistone E, and 5-(1-hydroxy-3-phenyl-allyl)-dihydro-furan-2-one were identified by single-crystal X-ray diffraction analysis using Cu Kα radiation. The absolute configurations of the other related compounds were determined from comparisons of their ECD spectra with relevant compounds reported in the literature. (−)-5-Acetoxygoniothalamin exhibited potent cytotoxicity against the colon cancer cell line (HCT116) with an IC50 value of 8.6 μM which was better than the standard control (doxorubicin, IC50 = 9.7 μM), while (Z)-6-styryl-5,6-dihydro-2-pyranone was less active with an IC50 value of 22.1 μM.

Publication Details

Meesakul, P., Jaidee, W., Richardson, C., Andersen, R., Patrick, B., Willis, A., Muanprasat, C., Wang, J., Lei, X., Hadsadee, S., Jungsuttiwong, S., Pyne, S. & Laphookhieo, S. (2020). Styryllactones from Goniothalamus tamirensis. Phytochemistry, 171

Authors

Pornphimol Meesakul, Wuttichai Jaidee, Christopher Richardson, Raymond Andersen, Brian Patrick, Anthony Willis, Chatchai Muanprasat, Jin Wang, Xiaoguang Lei, Sarinya Hadsadee, Siriporn Jungsuttiwong, Stephen G. Pyne, and Surat Laphookhieo

Styryllactones from *Goniothalamus tamirensis*

Pornphimol Meesakul[a,b,c], Wuttichai Jaidee[a,b], Christopher Richardson[c], Raymond J. Andersen[d], Brian O. Patrick[d], Anthony C. Willis[e], Chatchai Muanprasat[f,g], Jin Wang[h], Xiaoguang Lei[h,i], Sarinya Hadsadee[j], Siriporn Jungsuttiwong[j], Stephen G. Pyne[c,*], Surat Laphookhieo[a,b,*]

[a] Center of Chemical Innovation for Sustainability (CIS), Mae Fah Luang University, Chiang Rai 57100, Thailand

[b] School of Science, Mae Fah Luang University, Chiang Rai, 57100, Thailand

[c] School of Chemistry and Molecular Biosciences, University of Wollongong, Wollongong, New South Wales 2522, Australia

[d] Departments of Chemistry and Earth, Ocean & Atmospheric Sciences, University of British Columbia, 2036 Main Mall, Vancouver, BC, Canada V6T 1Z1

[e] Research School of Chemistry, The Australian National University, Canberra, ACT 2601, Australia

[f] Department of Physiology, Faculty of Science, Mahidol University, Rajathevi, Bangkok 10400, Thailand

[g] Excellent Center of Drug Discovery, Faculty of Science, Mahidol University, Rajathevi, Bangkok 10400, Thailand

[h] College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, China

[i] Peking-Tsinghua Center for Life Science, Peking University, Beijing 100871, China

[j] Center for Organic Electronic and Alternative Energy, Department of Chemistry and Center of Excellence for Innovation in Chemistry, Faculty of Science, Ubon Ratchathani University, Ubon Ratchathani 34190, Thailand

* Corresponding authors.

E-mail address: surat.lap@mfu.ac.th (S. Laphookhieo); spyne@uow.edu.au (S. Pyne)

ABSTRACT: The phytochemical investigation of the twig and leaf extracts of *Goniothalamus tamirensis* led to the isolation and identification of 15 compounds including three rare previouly undescribed styryllactones, goniotamirenones A-C, together with 12 known compounds. (*Z*)-6-Styryl-5,6-dihydro-2-pyranone and 5-(1-hydroxy-3-phenyl-allyl)-dihydro-furan-2 -one are reported here for the first time as previouly undescribed natural products. Their structures were elucidated by spectroscopic methods. Goniotamirenone A was synthesized *via* a [2+2] cycloaddition reaction of 6-styrrylpyran-2-one in quantitative yield. The absolute configurations of goniotamirenones B and C were identified from experimental and calculated ECD data, while the absolute configurations of (–) –5-acetoxygoniothalamin, (–)-isoaltholactone, parvistone E, and 5-(1-hydroxy-3-phenyl-allyl)-dihydro-furan-2-one were identified by single-crystal X-ray diffraction analysis using Cu Kα radiation. The absolute configurations of the other related compounds were determined from comparisons of their ECD spectra with relevant compounds reported in the literature. (–)–5-Acetoxygoniothalamin exhibited potent cytotoxicity against the colon cancer cell line (HCT116) with an IC_{50} value of 8.6 μM which was better than the standard control (doxorubicin, IC_{50} = 9.7 μM), while (*Z*)-6-styryl-5,6-dihydro-2-pyranone was less active with an IC_{50} value of 22.1 μM.

Keywords: *Goniothalamus tamirensis*; Annonaceae; Styryllactone dimer; Styryllactone; Cytotoxicity

1. Introduction

One of the largest genera in the family Annonaceae is *Goniothalamus* which comprises over 160 species (Saunders and Chalermglin, 2008). These plants are distributed thoughout tropical and subtropical countries. In Thailand, over 15 species have been found, mostly in the eastern, north-eastern and south-eastern regions (Soonthornchareonnon et al., 1999). Some species of *Goniothalamus* have been used in traditional medicines in Thailand. For example, the decoction of the stem bark of *G. laoticus* (Finet & Gagnep.) Bân has been used to reduce fever and as a tonic (Lekphrom et al., 2009), while *G. elegants* Ast has been used in the treatment of heart disease and diarrhea (Suchaichit et al., 2015). *G. tamirensis* Pierre ex Finet & Gagnep (syn. *G. marcanii* Craib) (Saunders and Chalermglin, 2008) is a small tree which is not known for its medcinal uses. Compounds reported from this plant have primarily been styryllactones (Ahmad et al., 1991; Fang et al., 1990; Goh et al., 1995) and alkaloids (Lekphrom et al., 2009; Tran et al., 2013). In this study, we report the isolation and identification of three rare and new styryllactones (**1**–**3**) together with 12 known compounds (**4**–**15**) from the twig and leaf extracts of *G. tamirensis* which were collected from a plant growing at Mae Fah Luang University, Chiang Rai Province, Thailand. The cytotoxicities of some of the isolated compounds against the colon cancer cell line HCT116 are also reported.

2. Results and Discussion

The twig and leaf extracts of *G. tamirensis* were subjected to column chromatography using various stationary phases to yield 15 compounds (Fig. 1). Eleven compounds (**1**–**4**, **6**–**10**, **14** and **15**) were obtained from the leaf extract and eight compounds (**2**, **4**–**6**, **10**, **12**, **13** and **14**) were obtained from the twig extract. The known compounds were characterized as (–)-goniothalamin (**4**) (de Fátima et al., 2006), (–)-5*β*-hydroxygoniothalamin (**5**) (Goh et al., 1995), (–)–5-acetoxygoniothalamin (**6**) (Ahmad et al., 1991), (–)-goniodiol (**7**) (Liou et al., 2014), 6-styrrylpyran-2-one (**8**) (Thibonnet et al., 2002), (*Z*)-6-styryl-5,6-dihydro-2-pyranone (**9**) (Gillard et al., 1988), (–)-isoaltholactone (**10**) (Nicolas et al., 2013), parvistone E (**11**) (Liou et al., 2014), 5-(1-hydroxy-3-phenyl-allyl)-dihydro-furan-2-one (**12**) (Zhang et al., 2012), 3,5-demethoxypiperolidine (**13**) (Tran et al., 2013), piperolactam C (**14**) (Danelutte et al., 2005) and aristolactam FII (**15**) (Sun et al., 1987).

Compound **1** was obtained as a pale yellow solid. The molecular formula $C_{26}H_{20}O_4$ was deduced from HREIMS data which showed a $[M + Na]^+$ ion peak at *m/z* 419.1267 (calcd. 419.1259). This compound was recrystallized from acetone to yield yellow single crystals. The X-ray structure of **1** (Fig. 3) confirmed a molecular structure as an achiral, head-to-tail symmetric styryllactone dimer. Its structure was supported by the following NMR data

(Table 1), which showed resonances for two identical mono-substituted aromatic rings [δ_H 7.25–7.31 (8H, m) and 7.19–7.21 (2H, m)], a pair of identical unsaturated δ-lactone units [δ_H 5.94 (2H, d, J = 7.2 Hz), 7.08 (2H, dd, J = 7.2, 8.8 Hz), and 5.96 (2H, d, J = 8.8 Hz)], and a symmetric cyclobutane [δ_H 4.36 (2H, dd, J = 6.8, 9.9 Hz) and 4.49 (2H, dd, J = 6.8, 9.9 Hz)]. Accordingly, compound **1** was identified as goniotamirenone A.

Compound **2** was obtained as a pale yellow solid which showed a $[M + Na]^+$ ion peak at *m/z* 419.1264 (calcd. 419.1259) in the HREIMS corresponding to a molecular formula of $C_{26}H_{20}O_4$. The NMR data of **2** (Table 1) suggested that this compound was an unsymmetrical styryllactone dimer similar to that of achyrodimer D, isolated from the aerial parts of *Achyrocline bogotensis* (Sagawa et al., 2005). The difference being that achyrodimer D contains a methoxy substituent at C-4/C-4′ of the δ-lactone and a hydroxy group at C-12/C-12′ of the aromatic ring whereas structure **2** contains no substituent groups (Sagawa et al., 2005). The ^{1}H and ^{13}C NMR data of **2** (Table 1) showed resonances for a cyclobutane, a mono-substituted aromatic ring, two different δ-lactones and a non-substituted styryl unit. The structure of **2** was confirmed by the the following HMBC correlations (Fig. 2): H-7 (δ_H 4.26) with C-5 (δ_C 105.1), C-6 (δ_C 159.6), C-8 (δ_C 39.0), C-9 (δ_C 134.7), and C-7′ (δ_C 124.4); H-7′ (δ_H 6.62) with C-6′ (δ_C 81.3) and C-9′ (δ_C 135.8); H-4′ (δ_H 6.46) with C-8 (δ_C 39.0), C-2′ (δ_C 160.7), C-5′ (δ_C 42.7), and C-6′ (δ_C 81.3), and H-8 (δ_H 4.42) with C-9 (δ_C 134.7) and C-10/C-14 (δ_C 127.4). The absolute configuration of **2** was determined from the experimental and calculated electronic circular dichroism (ECD) as shown in Fig. 4. The ECD spectra for (7*R*,8*R*,5′*S*,6′*S*)-**2,** (7*S*,8*S*,5′*S*,6′*S*)-**2,** (7*R*,8*S*,5′*S*,6′*S*)-**2**, and (7*S*,8*R*,5′*S*,6′*S*)-**2** were calculated at B3LYP/6 311++G(d,p) level in MeOH (CPCM) (Fig. 4). The experimental ECD spectrum of **2** was similar to that of the computed ECD spectrum of (7*S*,8*S*,5′*S*,6′*S*)-**2** (Fig. 10). Accordingly, the structure of compound **2** was identified as (–)-(7*S*,8*S*,5′*S*,6′*S*)-goniotamirenone B.

To help confirm the structures **1** and **2**, their syntheses were attempted *via* [2+2] cycloaddition reactions of compound **8**. Several screening conditions for these reactions are shown in Table S1 (Supplementary data). The best conditions for compound **1** are shown in entries 11 (neat, 24 W white LED, 11 h, 100% yield) and 12 (water (suspension), 24 W white LED, 11 h, 100% conversion). However, exposure of **8** to sunlight for 1 d (Table S1, entry 3) provided **1** in 50% isolated yield. ^{1}H NMR analysis of the crude reaction mixture indicated approximately 8% of compound **2** (presumably racemic) was also formed. The ^{1}H NMR data

(Table 1) of synthetic compound **1** as well as TLC mobility was indentical to those of natural product compound **1**.

Compound **3** was obtained as a pale yellow solid. The HREIMS of **3** showed a $[M + Na]^+$ ion peak at *m/z* 273.0292 (cald 273.0294) corresponding to the molecular formula of $C_{13}H_{11}O_3{}^{35}Cl$. The ^1H and ^{13}C NMR data of **3** were similar to those of **8** (Thibonnet et al., 2002). The main difference between these two compounds was found at C-7/C-8 of the styryllactone moiety. Compound **8** showed olefinic protons at C-7/C-8 [(δ_H 7.50 (1H, d, J = 16.0 Hz, H-7) and 6.57 (1H, d, J = 16.0 Hz, H-8)] (Thibonnet et al., 2002) whereas compound **3** was a chlorohydrin which showed resonances at δ_H 4.82 (1H, d, J = 6.2 Hz, H-7)/δ_C 74.9 and δ_H 5.28 (1H, d, J = 6.2 Hz, H-8)/δ_C 62.6. Key HMBC correlations (Fig. 2) between H-7 (δ_H 4.82) with C-5 (δ_C 104.1), C-6 (δ_C 161.3), C-8 (δ_C 62.6), and C-9 (δ_C 136.0) and H-8 (δ_H 5.28) with C-6 (δ_C 161.3), C-7 (δ_C 74.9), C-9 (δ_C 136.0), and C-10/C-14 (δ_C 128.1) supported this structure. Similar to that of **2**, the absolute configuration of **3** was determined from the experimental and calculated ECD spectra (Fig. 4). The absolute configuration of **3** was defined as (7*S*,8*S*) according to the same pattern of the experimental ECD spectrum of **3** and that calculated for (7*S*,8*S*)-**3** (Fig. 4). Thus, compound **3** was named as (–)-(7*S*,8*S*)-goniotamirenone C.

This study has resulted in the first report of compounds **9** and **12** as previously undescribed natural products. Compound **9** was identified as (*Z*)-6-styryl-5,6-dihydro-2-pyranone (Gillard et al., 1988) by comparing its ^1H NMR (Table 2) and MS data with the reference compound (Gillard et al., 1988). This compound was a by-product from a previous synthesis of its *E*-isomer, (*E*)-6-styryl-5,6-dihydro-2-pyranone (Gillard et al., 1988). Its ^{13}C NMR data (Table 2) as well as the absolute configuration at C-6 (6*S*) are reported here for the first time. Compound **12** was identified as (5*S*,6*R*)-5-(1-hydroxy-3-phenyl-allyl)dihydrofuran-2-one by X-ray diffraction and was identified as the compound synthesized by Zhang (Zhang et al., 2012). Its ^{13}C NMR data are reported here for the first time. Moreover, this work has resulted in the first reports of the absolute configurations of compounds **6** (5*R*,6*R*), **10** (5*R*,6*R*,7*R*,8*R*), **11** (4*S*,6*S*,7*S*,8*R*) and **12** (5*S*,6*R*) by X-ray diffraction using Cu Kα radiation with Flack parameters (Flack, 1983; Parsons et.al. 2013) of –0.2 (2), 0.00 (14), –0.01 (9), and 0.03 (18), respectively (Fig. 3) and their ECD spectra (Fig. 4).

The biosynthetic pathways of some styryllactones have been described (Fang et al., 1993; Suchaichit et al., 2015). A putative biogenetic pathway to many of these styryllactones could start from the intermediate A (Fig. 5) which could be converted to three key precursors

4 and **8** in multiple steps. Styryllactones **1**–**3** and **9** could be obtained from the common precursor styryllactone **8** which was isolated from this study. Styryllactone dimer **2** would be formed from the dimerization at C-5/C-6 of the first unit and at C-7/C-8 of the second unit of styryllactone **8**. While the symmetric styryllactone dimer **1** could be obtained from two units of styryllactone **8** *via* a [2+2]-coupling through C-7/C-8. Further, the epoxide of **8** could be the biosynthetic precursor to the chlorohydrin **3**. Hydroxylation of styryllactone **4** at C-5 followed by acetylation of the resulting lactone **5** could give styryllactone **6**, while selective dihydroxylation at C-7/C-8 would produce styryllactone **7**. On the otherhand, the reduction of the double bond (lactone ring) in the epimer of **5** would be a good precursor to **12** after rearrangement of the lactone ring size. The dehydration of styryllactone **12** would produce styryllactone **13**. Styryllactone **10** would be ontained from styryllactone **5** *via* intermediate **5A** whereas styryllactone **11** might be obtained from styryllactone **4** *via* intermediate **4A**.

Most of the isolated compounds were evaluated for their cytotoxicity against a colon cancer cell line (HCT116). Unfortunately, only compounds **6** and **9** displayed promising cytotoxicity. Compound **6** had an IC_{50} value of 8.6 μM which was better than standard control (doxorubicin, IC_{50} = 9.7 μM), while **9** had an IC_{50} value of 22.2 μM.

3. Conclusion

Three previously undescribed styryllactones were isolated and identified from the leaf and twig extracts of *G. tamirensis* including two cyclobutane styryllactones (**1** and **2**) and a halohydrin styryllactone (**3**). It should be noted that the cyclobutane styryllactones and chlorinated compounds have been reported as rare compounds in the family Annonaceae and other species of higher plants. A few compounds have been reported from Annonaceae, for example, parvistone A from *Polyalthia parviflora* (Liou et al., 2014), and velutinindimers A–C from *Miliusa velutina* (Wongsa et al., 2017). In this study, two cyclobutane styryllactones, goniotamirenone A (**1**) and (–)-(7*S*,8*S*,5′*S*,6′*S*)-goniotamirenone B (**2**), and a chlorinated styryllactone, (–)-(7*S*,8*S*)-goniotamirenone C, are the first examples of cyclobutane styryllactones and chlorinated compounds, respectively, from the *Goniothalamus* genus (Annonaceae).

4. Experimental section

4.1 General experimental procedures

Melting points were determined on a Stuart SMP3 Melting Point Apparatus and Gallenkamp Melting Point Apparatus. Optical rotations values were measured with a Bellingham and Stanley ADP400 polarimeter. UV−vis spectra were recorded with a BMG

LABTECH/SPECTRO star Nano spectrometer. The circular dichroism (CD) spectra were measured on a JASCO J-810 and JASCO J-815 CD spectropolarimeter. The IR spectra were determined on a PerkinElmer FTS FT-IR spectrometer and FTIR Shimadzu Single Reflection ATR MIRacle. The NMR spectra were recorded using a Bruker AM 400 NMR spectrometer in $CDCl_3$ with TMS as an internal standard; *J* values are reported in Hz. The HREIMS and LRMS were obtained on a Bruker microTOF and SHIMADZU LCMS-2010EV mass spectrometer. The chromatographic materials and other information of instruments were the same as previous reports. The 254 nm (6 W) and 365 nm (6 W) UV lamps were purchased from Beijing Pusaide Instrument Equipment Co., Ltd. The 302 nm (6 W) UV lamp was purchased from Shanghai Jiapeng Technology Co., Ltd. The 24 W white LED lamp (24W, E27, 3000 lm, 6500K) was purchased from Philips. The size of quartz tube for our photoreactions was as follows: 10 centimeters in length, 1.8 centimeters inner diameter, 2.2 centimeters outer diameter.

4.2 Plant material

The twigs and leaves of *Goniothalamus tamirensis* Pierre ex Finet & Gagnep. (Annonaceae) were collected in August 2015 from an authentic plant growing at Mae Fah Luang University, Chiang Rai Province, Thailand (GPS coordinates: 20°03′18.8″N, 99°53′37.9″E). The plant specimen (No. MFU-NPR0101) was deposited at the Natural Products Research Laboratory, School of Science, Mae Fah Luang University.

4.3 Extraction and isolation

Air-dried twigs of *G. tamirensis* (964.6 g) were extracted with EtOAc (5 L) over a period of 3 days at room temperature. Removal of the solvent provided the EtOAc extract (49.81 g), which was subjected to QCC over silica gel, eluting with a gradient of hexanes−EtOAc (100% hexanes to 100% EtOAc) to give 12 fractions (A−L). Fraction F (1.36 g) was separated by CC over Sephadex LH-20 (100% MeOH) to obtain four subfractions (FA−FD). Compounds **13** (21.7 mg) was obtained from subfraction FC (642.1 mg) by CC (1:4 EtOAc/hexanes). Fraction I (576.6 mg) was further separated by CC (4:1 DCM/hexanes) to give compounds **4** (6.5 mg) and **6** (9.7 mg). Fraction J (1.37 g) was subjected to CC using reverse phase silica gel (4:1 MeOH/H_2O) to afford five subfractions (JA−JE). Further purification of subfraction JE (43.3 mg) by repeated CC over reverse phase silica gel (3:2 MeOH/H_2O) gave compounds **2** (14.9 mg) and **14** (9.1 mg). Fraction K (1.76 g) was further separated by CC over Sephadex LH-20 (100% MeOH) to obtain four

subfractions (KA−KD). Subfractions KC (1.02 g) was chromatographed by CC (100% DCM), yielding compounds **5** (5.2 mg), **10** (8.2 mg) and **12** (13.1 mg).

Air-dried leaves of *G. tamirensis* (875.8 g) were extracted with EtOAc (5 L) over a period of 3 days at room temperature. Removal of the solvent provided the crude EtOAc extract (75.7 g), which was subjected to QCC over silica gel, eluting the same solvent system as described in the twig extract to give ten fractions (A−J). Fraction F (3.61 g) was subjected to CC using reverse phase silica gel (4:1 MeOH/H_2O) to afford two subfractions (FA−FB). Subfraction FA (639.8 g) was further purified by CC (4:1 DCM/hexanes), yielding compounds **8** (10.5 mg) and **9** (17.9 mg). Fraction H (15.53 g) was further separated by CC using reverse phase silica gel (4:1 MeOH/H_2O) to obtained four subfractions (HA−HB). Purification of subfraction HA (1.52 g) was purified by CC (1:4 acetone/hexanes) to give compounds **4** (16.3 mg) and **7** (22.7 mg) and two subfractions (HAA−HAB). Compounds **2** (7.5 mg) and **3** (7.4 mg) were obtained from subfraction HAA (56.1 mg) by repeated CC (100% DCM). Subfraction HAB (102.8 mg) was further separated by CC (1:4 acetone/hexanes) to give compounds **1** (13.7 mg), **14** (4.0 mg) and **15** (5.0 mg). Fraction I (8.54 g) was subjected to CC using reverse phase silica gel (4:1 MeOH/H_2O) to afford five subfractions (IA−IB). Compounds **6** (20.9 mg) and **11** (26.3 mg) were obtained from subfraction IA (181.8 mg) by repeated CC using reverse phase silica gel (3:2 MeOH/H_2O).

4.3.1 Goniotamirenone A (**1**)

Pale yellow solid: mp 168–170 ºC; UV (MeOH) λ_{max} (log ε) 234 (3.25), 312 (3.29) nm; IR (neat) ν_{max} 2988, 1717, 1628, 1550, 1496, 1450, 1093, 800 cm^{-1}; λ_{max} ($\Delta\varepsilon$); 230 (+0.28), 296 (−0.55) and 316 (+0.12) nm; see Table 1 for ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz); HREIMS *m/z* 419.1267 $[M + Na]^+$ (calcd for $C_{26}H_{20}O_4$, 419.1259).

4.3.2 (–)-(7*S*,8*S*,5′*S*,6′*S*)-*Goniotamirenone B* (**2**)

Pale yellow solid: mp 162–165 ºC; $[\alpha]_D^{25}$ –13.3 (*c* 1.5, CHC_{l3}); UV (MeOH) λ_{max} (log ε) 224 (3.42), 257 (2.99), 310 (2.73) nm; IR (neat) ν_{max} 2921, 2850, 1698, 1631, 1602, 1552, 1496, 1448, 1386, 1257, 1168, 1050, 800 cm^{-1}; ECD (*c* 1.7 × 10^{-3} M, MeOH) λ_{max} ($\Delta\varepsilon$); 228 (−1.26) and 213 (+0.25) nm; see Table 1 for ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz); HREIMS *m/z* 419.1264 $[M + Na]^+$ (calcd for $C_{26}H_{20}O_4$, 419.1259).

4.3.3 (–)-(7*S*,8*S*)-*Goniotamirenone C* (**3**)

Pale yellow solid: mp 121–123 ºC; $[\alpha]_D^{25}$ –56.9 (*c* 0.7, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 226 (3.66), 299 (3.17) nm; IR (neat) ν_{max} 3395, 2921, 1721, 1257, 808 cm^{-1}; ECD (*c* 0.9 ×

10^{-3} M, MeOH) λ_{max} ($\Delta\varepsilon$); 235 (+0.45), 294 (–3.08) nm. see Table 1 for ^{1}H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz); HREIMS *m/z* 273.0292 $[M + Na]^+$ (calcd for $C_{13}H_{11}O_3{}^{35}Cl$, 273.0294).

4.4 Computational methods

All structures of goniotamirenones B and C were optimized by the DFT method at the B3LYP/6-311G (d,p) level of theory. The ECD calculations were carried out by using TD-DFT at the B3LYP functional with 6–311++G(d,p) basis. Geometry optimization and TD-DFT computations were both performed with Continuum Model (PCM) solvation model with methanol. The rotary strengths of 90 excited states were calculated. All calculations were performed using Gaussian09 program package (Frisch, 2009). Gaussian bandshape with a bandwidth of 0.25 eV was used to simulate ECD spectra. The ECD curves were generated by softwares SpecDis 1.64 (University of Wurzburg, Wurzburg, Germany).

*4.5 X-ray Crystallographic Analysis of Compounds **1**, **6**, **10** and **11***

Single crystal X-ray diffraction data were collected on a Bruker APEX II area detector diffractometer with cross-coupled multilayer optics and Cu K*α* radiation. A multi-scan absorption correction was performed using SADABS-2016/2. The structure was solved by direct methods (Sheldrick et al., 2015) and was refined by full-matrix least-squares (Sheldrick et al., 2015). Crystallographic data for compounds **1**, **6**, **10** and **11** have been deposited with the Cambridge Crystallographic Data Center (CCDC 1839332, 1861849, 1861850 and 1861851 for compounds **1**, **6**, **10** and **11**, respectively). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. The detailed crystallographic information of compounds **1**, **6**, **10**, and **11** is described in Supplementary data.

*4.6 X-ray Crystallographic Analysis of Compound **8**.*

Single crystal X-ray diffraction data were collected on a XtaLAB Mini II diffractometer using Mo Kα radiation (λ 0.71073). Data were corrected for absorption effects using the SCALE3 ABSPACK scaling algorithm (CrysAlis PRO 1.171.39.46). Using Olex2, the structures were solved with the ShelXT structure solution program using Direct Methods (Sheldrick et al., 2015) and refined with the ShelXL refinement package using Least Squares minimization (Sheldrick et al., 2015). Crystallographic data for compound **8** has been deposited with the Cambridge Crystallographic Data Center (CCDC 1842574). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. The detailed crystallographic information of compound **8** is described in Supplementary data.

*4.7 X-ray Crystallographic Analysis of Compound **12***

Single crystal X-ray diffraction data were collected on a SuperNova, Dual, Cu at zero, EosS2 diffractometer with micro-focus sealed X-ray tube, SuperNova (Cu) X-ray Source. Data were corrected for absorption effects using the multi-scan method implemented in the SCALE3 ABSPACK scaling algorithm (CrysAlis PRO 1.171.39.46). The structure was solved by SIR92 (Altomare, et al. 1994) and refined using *CRYSTALS* (Betteridge, et al., 2003). Crystallographic data for compound **12** has been deposited with the Cambridge Crystallographic Data Center (CCDC 1860341). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. The detailed crystallographic information of compound **12** is described in Supplementary data.

4.8 Biological assay

4.8.1 Bioassay for Cytotoxicity

The cytotoxicities of selected compounds against the colon cancer cell HCT116 were determined using the previously described method (Sriyatep et al., 2017). Doxorubicin used as a positive control (IC_{50} = 9.74 μM).

Acknowledgements

This research was financially supported by the Thailand Research Fund (BRG5980012, DBG6280007, DBG5980001, and PHD/0010/2558) and Mae Fah Luang University. The University of Wollongong is also acknowledged for laboratory facilities.

Appendix A. Supplementary data

Supplementary data related to this article can be found at

References

Ahmad, F.B., Tukol, W.A., Omar, S., Sharif, A.M., 1991. 5-Acetyl goniothalamin, a styryl dihydropyrone from *Goniothalamus uvaroides*. Phytochemistry 30, 2430–2431.

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M.C., Polidori, G., Camalli, M., 1994. SIR92 – a program for automatic solution of crystal structures by direct methods. J. Appl. Crystallogr. 27, 435.

Betteridge, P.W., Carruthers, J.R. Cooper, R.I., Prout, K. Watkin, D.J., 2003. CRYSTALS version 12: software for guided crystal structure analysis J. Appl. Crystallogr. 36, 1487.

Danelutte, A.P., Costantin, M.B., Delgado, G.E., Braz-Filho, R., Kato, M.J., 2005. Divergence of secondary metabolism in cell suspension cultures and differentiated plants of *Piper cernuum* and *P. crassinervium*. J. Braz. Chem. Soc. 16, 1425–1430.

de Fátima, Â., Kohn, L.K., de Carvalho, J.E., Pilli, R.A., 2006. Cytotoxic activity of (*S*)-goniothalamin and analogues against human cancer cells. Bioorg. Med. Chem. 14, 622–631.

Fang, X.P., Anderson, J.E., Chang, C.J., Fanwick, P.E., McLaughlin, J.L., 1990. Novel bioactive styryl-lactones: goniofufurone, goniopypyrone, and 8-acetylgoniotriol from *Goniothalamus giganteus* (annonaceae). X-Ray molecular structure of goniofufurone and of goniopypyrone. J. Chem. Soc., Perkin Trans. 1. 1655–1661.

Fang, X.P., Anderson, J.E., Qiu, X.X., Kozlowski, J.F., Chang, C.J., McLaughlin, J.L., 1993. Gonioheptolides A and B: Novel eight-membered-ring lactones from *Goniothalamus giganteus* (Annonaceae). Tetrahedron 49, 1563–1570.

Flack, H.D. 1983. On Enantiomorph-Polarity Estimation. Acta Cryst. A 39, 876-881.

Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Scalmani, G., Barone, V., Petersson, G.A., Nakatsuji, H., Li, X., Caricato, M., Marenich, A., Bloino, J., Janesko, B.G., Gomperts, R., Mennucci, B., Hratchian, H.P., Ortiz, J.V., Izmaylov, A.F., Sonnenberg, J.L., Williams-Young, D., Ding, F., Lipparini, F., Egidi, F., Goings, J., Peng, B., Petrone, A., Henderson, T., Ranasinghe, D., Zakrzewski, V.G., Gao, J., Rega, N., Zheng, G., Liang, W., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Throssell, K., Montgomery, J.A., Jr., Peralta, J.E., Ogliaro, F., Bearpark, M., Heyd, J.J., Brothers, E., Kudin, K.N., Staroverov, V.N., Keith, T., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, J.C., Iyengar, S.S., Tomasi, J., Cossi, M., Millam, J.M., Klene, M., Adamo, C., Cammi, R., Ochterski, J.W., Martin, R.L., Morokuma, K., Farkas, O., Foresman, J.B., Fox, D.J., *Gaussian 09* (Revision A.02); Gaussian, Inc.; Wallingford, CT, 2009.

Gillard, F., Heissler, D., Riehl, J.J., 1988. Synthesis of the 5,6-dihydro-2-pyrone moiety of (+)-anamarin. J. Chem. Soc., Perkin Trans. 1, 2291–2295.

Goh, S.H., Ee, G.C.L., Chuah, C.H., Mak, T.C.W., 1995. 5*β*-hydroxygoniothalamin, a styrylpyrone derivative from *Goniothalamus dolichocarpus* (Annonaceae). Nat. Prod. Res. 5, 255–259.

Lekphrom, R., Kanokmedhakul, S., Kanokmedhakul, K., 2009. Bioactive styryllactones and alkaloid from flowers of *Goniothalamus laoticus*. J. Ethnopharmacol. 125, 47–50.

Liou, J.R., Wu, T.Y., Thang, T.D., Hwang, T.L., Wu, C.C., Cheng, Y.B., Chiang, M.Y., Lan, Y.H., El-Shazly, M., Wu, S.L., Beerhues, L., Yuan, S.S., Hou, M.F., Chen, S.L.,

Chang, F.R., Wu, Y.C., 2014. Bioactive 6*S*-styryllactone constituents of *Polyalthia parviflora*. J. Nat. Prod. 77, 2626–2632.

Nicolas, L., Izquierdo, E., Angibaud, P., Stansfield, I., Meerpoel, L., Reymond, S., Cossy, J., 2013. Cobalt-catalyzed diastereoselective synthesis of *C*-furanosides. Total synthesis of (−)-isoaltholactone. J. Org. Chem. 78, 11807–11814.

Parsons, S., Flack, H.D., Wagner, T. 2013. Use of intensity quotients and differences in absolute structure refinement. Acta Crystallogr., Sect. B 69, 249–259.

Sagawa, T., Takaishi, Y., Fujimoto, Y., Duque, C., Osorio, C., Ramos, F., Garzon, C., Sato, M., Okamoto, M., Oshikawa, T., Ahmed, S.U., 2005. Cyclobutane dimers from the colombian medicinal plant *Achyrocline bogotensis*. J. Nat. Prod. 68, 502–505.

Saunders, R.M.K., Chalermglin, P., 2008. A synopsis of *Goniothalamus* species (Annonaceae) in Thailand, with descriptions of three new species. Bot. J. Linean. Soc. 156, 355–384.

Sheldrick, G.M. 2015. Crystal structure refinement with SHELXL. Acta Crystallogr., Sect. C 71, 3–8.

Sheldrick, G.M. (2015). SHELXT–Integrated space-group and crystal-structure determination. Acta Crystallogr., Sect. A 71, 3–8.

Soonthornchareonnon, N., Suwanborirux, K., Bavovada, R., Patarapanich, C., Cassady, J. M., 1999. New cytotoxic 1-azaanthraquinones and 3-aminonaphthoquinone from the stem bark of *Goniothalamus marcanii*. J. Nat. Prod. 62, 1390–1394.

Sriyatep, T., Andersen, R.J., Patrick, B.O., Pyne, S.G., Muanprasat, C., Seemakhan, S., Borwornpinyo, S., Laphookhieo, S., 2017. Scalemic caged xanthones isolated from the stem bark extract of *Garcinia propinqua*. J. Nat. Prod. 80, 1658–1667.

Suchaichit, N., Kanokmedhakul, K., Panthama, N., Poopasit, K., Moosophon, P., Kanokmedhakul, S., 2015. A 2*H*-tetrahydropyran derivative and bioactive constituents from the bark of *Goniothalamus elegants* Ast. Fitoterapia 103, 206–212.

Sun, N.J., Antoun, M., Chang, C.J., Cassady, J.M., 1987. New cytotoxic aristolactams from *Pararistolochia flos-avis*. J. Nat. Prod. 50, 843–846.

Thibonnet, J., Abarbri, M., Parrain, J.-L., Duchêne, A., 2002. One-step synthesis of *α*-pyrones from acyl chlorides by the Stille reaction. J. Org. Chem. 67, 3941–3944.

Tran, D.T., Mai, H.D.T., Pham, V.C., Nguyen, V.H., Litaudon, M., Guéritte, F., Nguyen, Q. V., Tran, T.A., Chau, V.M., 2013. Alkaloids and styryllactones from the leaves of *Goniothalamus tamirensis*. Phytochem. Lett. 6, 79–83.

Wongsa, N., Kanokmedhakul, K., Boonmak, J., Youngme, S., Kanokmedhakul, S., 2017. Bicyclic lactones and racemic mixtures of dimeric styrylpyrones from the leaves of *Miliusa velutina*. RSC Adv. 7, 25285–25297.

Zhang, X., Guo, J., Hu, S., 2012. Facile and efficient synthesis of γ-lactone and butenolide derivatives. Synth. Commun. 42, 1551–1558.