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# Alkaloids and styryllactones from Goniothalamus cheliensis

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**Abstract**

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**Alkaloids and styryllactones from *Goniothalamus cheliensis***

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**ABSTRACT**

Eight previously undescribed compounds, including four alkaloids and five styryllactones together with 36 known compounds were isolated from the twig and leaf extracts of *Goniothalamus cheliensis*. Their structures were elucidated by extensive analysis of their spectroscopic data. The absolute configuration of (−)-(4*S*,5*S*,6*R*,7*S*,8*S*)-goniochelienlactone and (−)-(4*S*,5*S*,6*R*,7*S*,8*S*)-7-acetylgoniochelienlactone were established from single crystal X-ray analysis using Cu Kα radiation. The absolute configurations of the other related compounds were identified by comparisons of their ECD spectra with those of related known compounds. Most of the isolated compounds were evaluated for their cytotoxicities against human colorectal cancer cells (HCT-116). Griffithazanone A was the most potent with an $IC_{50}$ value of 2.39 $\mu$M.

**Keywords:** *Goniothalamus cheliensis,* Annonaceae, Alkaloids, Styryllactones

## 1. Introduction

*Goniothalamus* is the one of the largest genera of the family Annonaceae. It is distributed throughout the world and is found predominately in Southeast Asia (Duc et al., 2016). This genus includes about 160 species, of which 25 are found in Thailand (Saunders et al., 2008). Some species have been used as traditional medicines for the treatment of fever (Surivet and Vatèle, 1999), scabies (Heyne, 1950), edema, rheumatism (Jiang et al., 2011), tympanites (Quismbing, 1951), and typhoid fever (Efdi et al., 2010). *Goniothalamus cheliensis* Hu is a large green tree which is distributed throughout the forested slopes at 1500 m, in South Yunnan, China (Saunders et al., 2008). This plant is found in the Northern parts of Thailand, especially in Chiang Rai and Nan Provinces. Previous phytochemical investigations of *G. cheliensis*, resulted in the isolation and identification of various types of compounds, including styryllactones (Jiang et al., 2011; Wang et al., 2002; Zhu et al., 2012, Duc et al., 2016; Wang et al., 2003, Si et al., 2002), alkaloids (Jiang et al., 2008; Duc et al., 2016), flavonoids (Wang et al., 2003, Sun et al., 2014), and acetogenins (Duc et al., 2016). Many of these isolated compounds exhibited a variety of biological activities such as antiproliferative (Sun et al., 2014), antifungal (Duc et al., 2016), antimalarial (Duc et al., 2016) and cytotoxic activities (Wang et al., 2002; Zhu et al., 2012). In this study, we describe the isolation and identification of eight previously undescribed compounds (**1–3** and **5–9**) and 36 known compounds (**4** and **10–44**) (Fig. 1) from the twig and leaf extracts of *G. cheliensis* collected from Doi Tung, Chiang Rai Province, Thailand. Their cytotoxicities against the colon cancer cell line HCT-116 are also reported.

## 2. Results and Discussion

The acetone extracts of the leaves and twigs of *G. cheliensis* were individually subjected to separation by silica gel and Sephadex LH-20 column chromatography (CC) followed by semipreparative RP-HPLC to afford eight previously undescribed compounds (**1–3** and **5–9**) and 36 known compounds (**4** and **10–44**). The known compounds were identified as 3-methyl-1*H*-benz[*f*]indole-4,9-dione (**4**) (Efdi et al., 2010), (−)-goniobutenolide B (**10**) (Xu et al., 1994), 7-*epi*-(−)-goniobutenolide B (**11**) (Popsavin et al., 2012), (+)-goniodiol (**12**) (Fang et al., 1991), goniodiol-8-monoacetate (**13**) (Wu et al., 1992), (+)-7-*O*-acetylgoniodiol (**14**) (Kampong et al., 2013), 8-acetoxy goniofufurone (**15**) (Zhang et al., 1998), isoaltholactone (**16**) (Colegate et al., 1990), (+)-glaberide I (**17**) (Wu et al., 2013), (−)-glaberide I (**18**) (Chang et al., 2015), (+)-syringaresinol (**19**) (Rahman et al., 2007; Yamauchi et al., 2015), (+)-medioresinol (**20**) (Nakasone et al., 1996; Yamauchi et al., 2015), (+)-episyringaresinol (**21**) (Chen et al., 1998), (−)-syringaresinol (**22**) (Rahman et al., 2007; Yamauchi et al., 2015), (−)-episyringaresinol (**23**) (Lui et al., 2015), (−)-pinoresinol (**24**) (Ming et al., 2001; Yamauchi et al., 2015), griffithazanone A (**25**) (Zhang et al., 1999), cleistopholine (**26**) (Waterman and Muhammad, 1985), vanillic acid (**27**) (Wu et al., 2000), *p*-hydroxybenzoic acid (**28**) (Rukachaisirikul et al., 2010), *p*-methylbenzoicacid (**29**) (Zhou et al., 2013), 4-hydroxy-3-methoxypropiophenone (**30**) (Ito et al., 2001), 3,5-dimethoxy-4-hydroxypropiophenone (**31**) (Zdero et al., 1986), *p*-hydroxybenzaldehyde (**32**) (Zhou et al., 2013), ethyl-4-hydrozybenzoate (**33**)

(Fan et al., 2016), *trans*-ferulic acid (**34**) (Salum et al., 2010), (–)-(3*R*)-mellein methyl ether (**35**) (Li et al., 2017), derrusnin (**36**) (East et al., 1969), 5-hydroxy-7-methoxy-3',4'-methylene dioxy isoflavone (**37**) (Liping et al., 1996), derrustone (**38**) (Singh and Muthukrishnan, 2005), robustone methyl ether (**39**) (East et al., 1969), derrugenin (**40**) (Ortega et al., 2015), robustigenin (**41**) (Pancharoen et al., 2008), methyl-BRM-5 (**42**) (Tahara et al., 1986), *trans*-*N*-coumaroyltyramine (**43**) (Holzbach and Lopes, 2010), and *N*-trans-feruloyl tyramine (**44**) (Holzbach and Lopes, 2010) by comparison of their spectroscopic data with those published.

Compound **1**, goniochelienic acid A, was obtained as yellow needles. The core structure of compound **1** was a benzo[*f*]indole-4,9-dinone (Efdi et al., 2010) which was confirmed by a single-crystal X-ray diffraction analysis using Mo K$\alpha$ radiation (Fig. 5). The HRESIMS spectrum showed a $[M + Na]^+$ ion peak at *m/z* 294.0379 (calcd. for $C_{14}H_9NO_5Na$, 294.0378) which also supported this structural assignment. The $^1H$ NMR spectrum of **1** (Table 1) showed resonances for a hydroxy proton of a carboxylic acid [$\delta_H$ 13.68 (CO*OH*)], a H-bonded hydroxy proton [$\delta_H$ 12.20 (1H, s, 8-OH)], aromatic protons of an ABC spin system [$\delta_H$ 7.82 (1H, d, $J$ = 7.4 Hz, H-5)/$\delta_C$ 120.7, 7.64 (1H, dd, $J$ = 7.8, 7.4 Hz, H-6)/$\delta_C$ 136.0, 7.32 (1H, d, $J$ = 7.8 Hz, H-7)/$\delta_C$ 126.1], an olefinic proton [$\delta_H$ 7.74 (1H, s, H-2)/$\delta_C$ 138.0], and a *N*-methyl group [$\delta_H$ 4.15 (3H, s, *N*-$CH_3$)/$\delta_C$ 37.5]. The structure of **1** was further supported by the following key HMBC correlations (Fig. 3): $\delta_H$ 12.20 (8-OH) with C-7 ($\delta_C$ 126.1), C-8 ($\delta_C$ 162.5), and C-8a ($\delta_C$ 114.5); $\delta_H$ 7.82 (H-5) with C-4 ($\delta_C$ 183.1) and C-6 ($\delta_C$ 136.0); $\delta_H$ 4.15 (*N*-Me) with C-9a ($\delta_C$ 130.9), C-2 ($\delta_C$ 138.0); $\delta_H$ 7.74 (H-2) with C-3 ($\delta_C$ 114.5), C-3a ($\delta_C$ 123.5), C-9a ($\delta_C$ 130.9), and C-10 ($\delta_C$ 161.5). From these data, the structure of compound **1** was assigned as 8-hydroxyl-1-methyl-4,9-dioxy-1*H*-benz[*f*]indole-3-catboxylic acid. Full assignments of the $^1H$ and $^{13}C$ NMR spectroscopic data are shown in Table 1.

Compound **2**, goniochelienic acid B, was isolated as a yellow powder. Its molecular formula, $C_{14}H_9NO_4$, was established by the HRESIMS which showed a $[M + Na]^+$ ion peak at *m/z* 278.0436 (calcd. for $C_{14}H_9NO_4Na$, 278.0429). The $^1H$ and $^{13}C$ NMR spectroscopic data (Table 1) of **2** were similar to those of **1**. The main difference between these two compounds was that the H-bonded proton at $\delta_H$ 12.22 (OH-8) was not observed in the $^1H$ NMR spectrum of **2**. Compound **2** showed $^1H$ NMR resonances for four aromatic protons, that formed part of a 1,2-disubstituted aromatic ring, at $\delta_H$ 8.26 (1H, dd, $J$ = 1.3, 7.4 Hz, H-5), 7.79 (1H, td, $J$ = 1.5, 7.5 Hz, H-6), 7.81 (1H, td, $J$ = 1.5, 7.5 Hz, H-7), 8.21 (1H, dd, $J$ = 7.4, 1.3 Hz, H-8) instead of the ABC spin system observed in the $^1H$ NMR spectrum of compound **1**. Finally, the structure of **2** was supported with the following key HMBC correlations (Fig. 3): $\delta_H$ 8.26 (H-5) with C-4 ($\delta_C$ 184.0) and C-6 ($\delta_C$ 134.5); $\delta_H$ 4.16 (*N*-Me) with C-9a ($\delta_C$ 131.8), C-2 ($\delta_C$ 137.5); $\delta_H$ 7.73 (H-2) with C-3 ($\delta_C$ 116.4), C-3a ($\delta_C$ 123.1), C-9a ($\delta_C$ 131.8), and C-10 ($\delta_C$ 162.1). Therefore, compound **2** was assigned as 1-methyl-4,9-dioxy-1*H*-ben[*f*]indole-3-carboxylic acid.

Compound **3**, methyl goniochelienate, was isolated as a yellow amorphous powder. The molecular formula $C_{14}H_9NO_4$ was deduced from HRESIMS analysis which showed a $[M + Na]^+$ at *m/z* 278.0435 (calcd for $C_{14}H_9NO_4Na$, 278.0429). The

$^1$H NMR spectroscopic data of **3** (Table 1) were similar to those of **4**; whose structure was determined by single crystal X-ray structural analysis (Fig. 6). The difference between compounds **3** and **4** is that **3** has a C-3 methoxy carbonyl substituent ($\delta_H$ 3.89) and **4** has a C-3 methyl group. The position of the methoxy group in **3** was confirmed by the HMBC correlation from $\delta_H$ 3.89 (3-$CO_2$*Me*) with C-10 ($\delta_C$ 163.2) (Fig. 3). The other key HMBC correlations were shown in Fig. 3. Therefore, the structure of **3** was identified as methyl 4,9-dioxo-1*H*-benz[*f*]indole-3-catboxylate.

Compound **5** was obtained as a yellow solid. The molecular formula of **5** was established as $C_{13}H_{11}NO_5$ based on the HRESIMS (*m/z* 284.0530 $[M + Na]^+$, calcd for $C_{13}H_{11}NO_5Na$ 284.0535). The $^1$H and $^{13}$C NMR spectra of **5** in $CDCl_3$ solution shown resonances characteristic of a naphthoquinone derivative (Table 2), which were similar to those of goniothalaminone B (**45**), previously isolated from *Goniothalamus scortechinii* (Prawat et al., 2012). The significant difference between these two compounds was observed for the chemical shift of H-7/C-7 and H-8/C-8. Compound **5** displayed these resonances at $\delta_H$ 7.05 (1H, d, $J$ = 8.4 Hz, H-7)/$\delta_C$ 113.2 and 7.75 (1H, d, $J$ = 8.4 Hz, H-8)/$\delta_C$ 121.0, whereas for goniothalaminone B these appeared at $\delta_H$ 7.22 (1H, d, $J$ = 8.4 Hz, H-7)/$\delta_C$ 117.8 and $\delta_H$ 7.76 (1H, d, $J$ = 8.4 Hz, H-8)/$\delta_C$ 120.7 (Table 2). In addition, the chemical shifts for C-2, C-3 and C-6 were also different; $\delta_C$ 106.9 (C-2) and $\delta_C$ 158.4 (C-3) 155.8 (C-6) for compound **5** and $\delta_C$ 109.4 (C-2), $\delta_C$ 152.5 (C-3) and $\delta_C$ 152.1 (C-6) for goniothalaminone B. These data indicated that compound **5** was a structural isomer of goniothalamin B. To help further assign all $^1$H NMR resonances as well as to confirm the location of amino group, the NMR spectra of compound **5** were also recorded in DMSO-$d_6$. The $^1$H NMR spectrum in DMSO-$d_6$ (Table 2) showed addition downfield resonances at $\delta_H$ 9.12 (1H, br s) and $\delta_H$ 10.68 (1H, br s) assignable to the primary amine protons. Finally, the structure was further confirmed from the following HMBC correlations: $\delta_H$ 10.68 (2-$NH_2$) with C-1 ($\delta_C$ 178.1); $\delta_H$ 3.91 (6-OMe) with C-6 ($\delta_C$ 155.8); $\delta_H$ 13.94 (5-OH) with C-6 ($\delta_C$ 155.8), C-5 ($\delta_C$ 151.6), C-4a ($\delta_C$ 114.3); $\delta_H$ 7.62 (H-8) with C-1 ($\delta_C$ 178.1), C-8a ($\delta_C$ 121.8), and C-7 ($\delta_C$ 114.7) (Fig. 3 and S27). Thus, the structure of **5** was identified as goniochelieninone, a structural isomer of goniothalamin B. Full assignments of the $^1$H and $^{13}$C NMR spectroscopic data are shown in Table 2 and the COSY and selected HMBC correlations in Fig. 3.

Plausible biosynthetic pathways of compounds **1**–**5** are shown in Fig.11. Compounds **1**–**4** and **5** might arise from difference polyketide units (Wagoner et al., 2008; King et al., 2009; Bauer et al., 2010). The benzo[*f*]indole-4,9-diones **1**–**4** could be obtain from a hexaketide generated from an isobutyryl-CoA starter and a five acetyl-CoA extender (Zhou et al., 2016) involving multi-steps including the incorporation of nitrogen (Fig. 11a) (Wagoner et al., 2008; Bauer et al., 2010). Compound **4** undergoes oxidation of the methyl group to give the carboxylic acid derivative **(4a)**, esterification of **4a** would yield compound **3**. Alternatively, **4a** was regioselectively *N*-methylated to obtain compound **2** which was then oxidized at C-8 to give compound **1**. The naphthoquinone **5** might arise from heptaketide (Fig. 11b) with the similar process of **4**.

Compound **6** was isolated as a colorless prism. Analysis of its HRESIMS showed a $[M + Na]^+$ ion peak at *m/z* 273.0749 (calcd for $C_{13}H_{14}O_5Na$, 273.0739) which established the molecular formula $C_{13}H_{14}O_5$. The 5,7-dihydroxy-8-phenylbicyclo[3.3.1]nonan-2-one based structure and the absolute configuration (4*S*,5*S*,6*R*,7*S*,8*S*) of compound **6** were established by single-crystal X-ray diffraction analysis using Cu K$\alpha$ radiation (Fig. 7) with the flack parameter of -0.04(7). The ECD spectrum of **6** (Fig. 9) displayed a negative Cotton effect at 227 nm, similar to that of parvistone D and parvistone E (Liuo et al., 2014) which also supported the identification of its absolute configuration. The $^1$H NMR spectrum further supported this structure and showed resonances for the mono substituted aromatic ring at $\delta_H$ 7.38 (2H, d, $J$ = 7.9 Hz, H-2′/6′), 7.30 (2H, d, $J$ = 7.6 Hz, H-3′/5′) and 7.26 (1H, d, $J$ = 7.2 Hz, H-4′). The structure of compound **6** was almost identical to that of (+)-goniopypyrone except for the configuration at C-7 which was 7*S* for compound **6** and 7*R* for (+)-goniopypyrone (Tsubuki et al., 1999; Zhang et al., 1998). The $^1$H NMR spectroscopic data of these two compounds were significantly different, except for the aromatic proton chemical shifts, as shown in Table S1. Thus, compound **6** was assigned as (−)-(4*S*,5*S*,6*R*,7*S*,8*S*)-goniochelienlactone, the C-7 epimer of (+)-goniopypyrone.

Compound **7** was isolated as a colorless prism. Its molecular formula $C_{15}H_{16}O_6$ was established the HRESIMS analysis which showed a $[M + Na]^+$ ion peak at *m/z* 315.0854 (calcd for $C_{15}H_{16}O_6Na$, 315.0845). The core structure of compound **7** was a [3.3.1] bicyclic, similar to that found in compound **6**. A single-crystal X-ray diffraction analysis of compound **7** using Cu K$\alpha$ radiation established the structure of compound **7** and its absolute configuration as 4*S*,5*S*,6*R*,7*S*,8*S* (Fig. 8) with the Flack parameter 0.00 (11). Its ECD spectrum (Fig. 9) was similar to that of compound **6** which showed the Cotton effect at 232 nm to support the 4*S*,5*S*,6*R*,7*S*,8*S* configuration. The full assignments of its $^1$H and $^{13}$C NMR spectroscopic data are summarized in Table 3. It should be noted that compound **7** is the C-7 is epimer of 7-acetylgoniopypyrone (Zhang et al., 1998). Differences were also observed between these epimers from their $^1$H NMR spectra, especially the chemical shifts for the [3.3.1] bicyclic protons as shown in Table S2. Thus, the structure of **7** was identified as (−)-(4*S*,5*S*,6*R*,7*S*,8*S*)-7-acetylgoniochelienlactone.

Compound **8**, (+)-(7*S*,8*S*)-goniochelienbutenolide A, was obtained as a colorless viscous oil. Its molecular formula $C_{15}H_{14}O_5$ was deduced from its HRESIMS (*m/z* 297.0730 $[M + Na]^+$, calcd for $C_{15}H_{14}O_5Na$, 297.0739). The $^1$H and $^{13}$C NMR spectroscopic data of **8** were similar to those of goniobutenolide A (Fang et al., 1991). The main difference between compounds **8** and goniobutenolide A was that compound **8** displayed an additional $^1$H NMR resonance for acetoxy protons at $\delta_H$ 2.12. Additionally, the resonances for H-7 ($\delta_H$ 5.10) and H-8 ($\delta_H$ 5.88) of compound **8** were shifted downfield compared to the same protons of goniobutenolide A, [$\delta_H$ 4.98 (H-7) and 4.94 (H-8)], (SI Table S3 and S4). The HMBC correlations between H-8 ($\delta_H$ 5.85) with the acetate carbonyl carbon ($\delta_C$ 168.0), H-2′/H-6′ ($\delta_H$ 7.40) with C-8 ($\delta_C$ 76.5) and H-7 ($\delta_H$ 4.98) with C-8 ($\delta_C$ 76.5) supported the position of the acetoxy group

at C-8 (Fig. 3). The relative stereochemistry of **8** was proposed to be *ethyro* based on the coupling constant of H-7/H-8 ($J_{7,8}$ = 6.0 Hz) indicating their *syn* orientation ($J_{7,8}$ = 6–8 Hz) (Fang et al., 1991, Shing et al., 1994; Xu et al., 1994). The *Z*-geometry of C-5/C-6 was determined from a comparison of the $^1$H NMR spectroscopic data to those of 7-*epi*-goniobutenolide A and B (SI Table S3 and S4). The absolute configuration of **8** (7*S*,8*S*) was proposed by the comparison of its ECD spectrum to that of compound **11** which showed a negative Cotton effect at 230 and 274 nm (Fig. 10). Thus, the structure of compound **8** was deduced as (7*S*,8*S*,*Z*)-5-(3-acetyl-2-hydroxy-3-phenylpropylidene)-2(5*H*)-furanone.

Compound **9**, (−)-(7*S*,8*R*)-goniochelienbutenolide B, was obtained as a colorless viscous oil. It molecular formula $C_{15}H_{14}O_5$ was established by HRESIMS (*m/z* 297.0746 $[M + Na]^+$, calcd for $C_{15}H_{14}O_5Na$, 297.0739). The $^1$H NMR spectroscopic data of **9** were similar to that of **8** (Table 4 and SI Fig.S3), but H-3 ($\delta_H$ 6.19) of compound **9** showed long range coupling with that of H-6 ($\delta_H$ 5.82) with the *J* value of 1.5 Hz indicating the *E*-geomety at the exo-cyclic alkene isomer of compound **9** (Fang et al., 1991; Popsavin et al., 2012). The oxymethine protons of C-7 and C-8 were assigned the *threo* configuration on the basis of their coupling constant $J_{7,8}$ = 4.2 Hz (Fang et al., 1991; Shing et al., 1995; Popsavin et al., 2012). The absolute configuration of **9** as 7*S*,8*R* was proposed from the comparison of its ECD spectrum to that of **10** (Fig. 10). Therefore, the structure was characterized as (7*S*, 8*R*, *E*)-5-(3-acetyl-2-hydroxy-3-phenylpropylidene)-2(5*H*)-furanone.

Annonaceae is a large family containing over 120 genera (Saripalli and Dixit, 2013). Each genus produces different major phytochemicals. For example, polyoxygenated cyclohexenes are commonly found in many species of *Uvaria* (Awale et al., 2017; Lekphrom et al., 2018; Hsu et al., 2016; Kaweetripob et al., 2015; Auranwiwat et al., 2017; Macabeo et al., 2017), but they are also found in some species of *Artabotrys* (Liu et al., 2018), *Cleistochlamys* (Nyandoro et al., 2017), *Dasymaschalon* (Hongthong et al., 2015), *Ellipeiopsis* (Kijjoa et al., 2002), and *Monanthotaxis* (Starks et al., 2012) genera. Flavonoids are major compounds from many genera including *Desmos* (Clement et al., 2017; Tuntipaleepun et al., 2012; Kuo et al., 2015; Prachyawarakorn et al., 2013; Bajgai et al., 2011; Rittiwong et al., 2011), and *Friesodielsia* (Meesakul et al., 2017; Prawat et al., 2012; Fleischer et al., 1997; Joseph et al., 2007), while alkaloids, including aristololactams, aporphines and oxoprotoberberine, are commonly found in the *Miliusa* (Promchai et al., 2018; Promchai et al., 2016; Hasan et al., 2000; Chen et al., 2003; Harrigan et al., 1994) and *Fissistigma* (Ge et al., 2013; Zhou et al., 2016; Zhou et al., 2018; Chia et al., 2000) genera. Styryllactones are the major compounds found in *Goniothalamus* (Moharam et al., 2012; Macobeo et al., 2013; Zhang et al., 1998; Fang et al., 1991., Suchaichit et al., 2015, Hisham et al., 2000; Uma et al., 2012) and *Polyalthia* (Nantapap et al., 2015; Nurunajah et al., 2001; Samoath and Vasanthi, 2013) whereas acetogenin (Moghadamtousi et al., 2015; Dang et al., 2011; Melot et al., 2009; Liaw et al., 2008; Sun et al., 2017; Guzmán et al., 2009; Liaw et al., 2004; Queiroz et al., 2003) and diterpenoids (Supudompol et al., 2004; Li et al., 2005; Li et al., 2009; Deepralard et al., 2007; Meng et al., 2007) were found in *Annona* and *Mitrephora*.

Most of the isolated compounds (**1**, **2**, **4**, **6**, **7**, **10**, **12**–**14**, **16**, **19**, **22**, **25**, **27**, **28**, **30**, **31**, **34**, **36**–**39**) were evaluated for their cytotoxicities against the colon cancer cell line HCT-116. Only compound **25** (griffithazanone A) showed potent cytotoxicity with an $IC_{50}$ value of 2.39 $\mu$M (doxorubicin as a positive control had an $IC_{50}$ value of 9.74 $\mu$M). All remaining compounds were inactive ($IC_{50}$ >50 $\mu$M). The $IC_{50}$ value of compound **25** against HCT-116 is less than those against human cervical cancer cells (20.2 μM and 11.7 μM for KB cells and HeLa cells, respectively) (Tip-pyang et al., 2010). Indicating that the cytotoxic effect of compound **25** is not cell-line specific and that compound **25** may be more effective against colorectal cancer cell lines than cervical cancer cell lines.

## 3. Conclusions

The phytochemical investigation of the extracts of the *G. cheliensis* led to the identification of 44 compounds, of which eight were previously undescribed compounds (**1**–**3**, **5**, and **6**–**9**). The discovery of styryllactones as the major compounds was in good agreement with the previous report of this genus (Moharam et al., 2012; Macobeo et al., 2013; Zhang et al., 1998; Fang et al., 1991., Suchaichit et al., 2015, Hisham et al., 2000; Uma et al., 2012). To the best of our knowledge, the indole alkaloids **1**–**3** and alkaloid **5** were found in this species for the first time. In a previous paper, the [3.3.1] bicyclic core structure of compounds **6** and **7** was reported as having the 7*R* configuration (Fang et al., 1991; Tsubuki et al., 1999; Zhang et al., 1998), however, we report herein related compounds having the 7*S* configuration with their absolute configurations being confirmed by single-crystal X-ray diffraction analysis. The isolated compounds were found to have no cytotoxicities against the colon cancer cell line HCT-116 at 50 μM except for griffithazanone A (**25**) which had potent cytotoxicities. This compound may have potential as a lead compound for the development of new anti-cancer agents.

## 4. Experiment section

### *4.1. General experiment procedures*

The optical rotation $[\alpha]_D$ values were determined with a Bellingham and Stanley ADP400 polarimeter. Melting points were measured with a Buchi B-540 melting point apparatus. UV-vis spectra were recorded with Varian Cary 5000 UV-vis-NIR spectrophotometer. The IR spectra were recorded using a Perkin-Elmer FTS FT-IR spectrophotometer. Electronic circular dichroism spectra were recorded on a JASCO J-815 CD spectropolarimeter. The NMR spectra were recorded using Bruker Avance 600 MHz spectrometers. Chemical shifts are reported in parts per million ($\delta$), and coupling constants ($J$) are expressed in hertz. HRESIMS spectra were obtained on a Bruker-Hewlett-Packard 1100 Esquire-LC system mass spectrometer. Single-crystal X-ray diffraction measurements were made on a Bruker APEX DUO diffractometer with cross-coupled multilayer optics Cu-Kα radiation. HPLC was performed on a Waters 1525 HPLC pump system, equipped with a Waters 2487 dual λ absorbance detector using the following column: Phenomenex Luna 5u $C_8$ column (10 × 250 mm)

and CHIRALCEL OD-H column (4.6 × 250 mm). Quick column chromatography (QCC) and column chromatography (CC) were carried out on Si gel 60 H (5−40 $\mu$m, Merck), Si gel 100 (63−200 $\mu$m, Merck) or silica gel 100 (63−200 $\mu$m, SiliCycle® Inc.), respectively. Waters 10 g Sep-Pak's were used for reversed-phase flash chromatography. Sephadex LH-20 was also used for CC. Precoated plates of silica gel 60 $F_{254}$ were used for analytical purposes.

*4.2 Plant material*

The twigs and leaves of *Goniothalamus cheliensis* Hu (Annonaceae) were collected from Doi Tung, Chiang Rai Province, Thailand (GPS coordinates: 20°17.351′ N, 99°48.661′ E), in October 2015, winter. The plant material was authenticated by Mr. Martin van de Bult (Doi Tung Development Project, Chiang Rai, Thailand), and a voucher specimen (MFU-NPR0146) was deposited at the Natural Products Research Laboratory, School of Science, Mae Fah Luang University.

*4.3 Extraction and isolation*

The dried twigs of *G. cheliensis* (5.1 kg) were extracted with acetone. The acetone extract (41.2 g) was subjected to QCC eluting with a gradient solvent system of *n*-hexanes-acetone (1:0 to 0:1, v/v) to afford 11 fractions (A−K). Fraction D (2.3 g) was subjected to Sephadex LH-20 (100% MeOH) to yield seven subfractions ($D_1$−$D_7$). Fraction $D_4$ (95.8 mg) was subjected to Sep-Pak $C_{18}$ CC, eluted with MeOH-$H_2O$ (3:2, v/v) to yield subfraction $D_1A$. Fraction $D_1A$ (61.6 mg) was separated over Sephadex LH-20 to give 4 subfractions ($D_1A$-1−$D_1A$-4). Fraction $D_1A$-2 (40.4 mg) was fractionated using silica gel CC eluting with *n*-hexanes-acetone (7:3, v/v) to obtained 6 subfractions ($D_1A$-2-1−$D_1A$-2-6). Fraction $D_1A$-2-2 (4.5 mg) was chromatographed using RP $C_{18}$ HPLC (eluted with $CH_3CN/H_2O$ with 0.05% TFA, 1:1, 2 mL/min) to give compounds **29** and **32** (0.3 mg, $t_R$ = 11.6 min), **30** (1.0 mg, $t_R$ = 15.6 min), and **33** (0.9 mg, $t_R$ = 18.5 min). Compound **31** (2.1 mg, $t_R$ = 15.6 min) was obtained from $D_1A$-2-3 by RP $C_{18}$ HPLC (eluted with $CH_3CN/H_2O$ with 0.05% TFA, 1:1, 2 mL/min). Fraction $D_5$ (205.0 mg) was subjected to Sep-Pak $C_{18}$ CC, eluted with MeOH-$H_2O$ (3:2, v/v) to give subfraction $D_5A$ (172.6 mg) following separated by Sephadex LH-20 (100% MeOH) to yield 4 subfractions ($D_5A$-1−$D_5A$-4). Compound **35** (3.9 mg) and **28** (1.4 mg) were purified from $D_5A$-2 (47.5 mg) by silica gel CC eluting with *n*-hexanes-acetone (7:3, v/v). Fraction $D_7$ (29.4 mg) was subjected to Sep-Pak $C_{18}$ CC eluting with MeOH-$H_2O$ (3:2, v/v) to give $D_7A$ (26.1 mg) and further separation on a silica gel CC eluting with $CH_2Cl_2$-MeOH (97:3, v/v) to yield compound **5** (0.8 mg). Fraction E (14.9 mg) was subjected to RP $C_8$ HPLC (eluted with $CH_3CN/H_2O$ with 0.05% TFA, 3:2, 2 mL/min) to give compound **2** (1.0 mg, $t_R$ = 12.8 min) and compound **1** (2.1 mg, $t_R$ = 13.6 min). Fraction F (8.9 g) was partition with $CH_2Cl_2$ and water, the $CH_2Cl_2$ soluble fraction (7.9 g) was subjected to silica gel CC, eluting with a gradient of $CH_2Cl_2$-MeOH (99:1 to 19:1, v/v) to afford 7 subfractions (F1−F7). Fraction F2 (912.8 mg) was chromatographed on a silica gel CC eluting with $CH_2Cl_2$-MeOH (99:1, v/v) to afford compound **4** (1.1 mg) and 4 subfractions (F2-1−F2-4). Fraction F2-2 (588.0 mg) was subjected to Sephadex LH-

20 CC (100% MeOH) to afford 5 subfractions (F2-2-1–F2-2-5). Fraction F2-2-1 (114.5 mg) was purified using RP $C_8$ HPLC (eluted with $CH_3CN/H_2O$ with 0.05% TFA, 3:7, 2 mL/min) to afford compounds **8** (1.1 mg, $t_R$ = 34.9 min), **9** (0.3 mg, $t_R$ = 48.7 min), and seven subfractions (F2-2-1-1–F2-2-1-7). Fraction F2-2-1-3 and F2-2-1-6 were subjected to RP $C_8$ HPLC (eluted with $CH_3CN/H_2O$ with 0.05% TFA, 3:7, 2 mL/min) to yield compounds **16** (7.7 mg, $t_R$ = 40.5 min), **13** (1.3 mg, $t_R$ = 62.9 min), **7** (0.9 mg, $t_R$ = 70.0 min), **14** (1.7 mg, $t_R$ = 81.9 min), and **15** (1.1 mg, $t_R$ = 91.4 min). Fraction F2-2-2 (257.7 mg) was chromatographed on silica CC eluting with *n*-hexanes-acetone (7:3, v/v) to give 5 subfractions (F2-2-2-1–F2-2-2-5). Fraction F2-2-2-2 (11.8 mg) was subjected to RP $C_8$ HPLC (eluted with $CH_3CN/H_2O$ with 0.05% TFA, 3:7, 2 mL/min) to yield compound **26** (0.7 mg, $t_R$ = 20.6 min). Compound **20** (3.9 mg, $t_R$ = 29.1 min), enantiomeric mixtures of **17** and **18** (1.9 mg, $t_R$ = 15.2 min), **23** and **21** (0.7 mg, $t_R$ = 29.1 min) and **19** and **22** (15.7 mg) were obtained from fraction F2-2-2-4 (28.5 mg). The chiral column OD-H (eluted with *n*-hexanes/MeOH, 3:2, 2 mL/min) was used to yield compounds **17** (0.2 mg, $t_R$ = 10.9 min) and **18** (0.4 mg, $t_R$ = 11.4 min), **23** (0.3 mg, $t_R$ = 9.2 min) and **21** (0.2 mg, $t_R$ = 10.9 min), and **19** (5.2 mg, $t_R$ = 6.3 min) and **22** (6.9 mg, $t_R$ = 7.4 min). Fraction F2-2-4 (13.7 mg) was subjected to RP $C_{18}$ HPLC (eluted with $CH_3CN/H_2O$ with 0.05% TFA, 2:3, 2 mL/min) to give compounds **24** (0.5 mg, $t_R$ = 14.1 min) and **25** (1.9 mg, $t_R$ = 11.8 min). Compound **3** (1.8 mg, $t_R$ = 15.9 min) was purified by RP $C_8$ HPLC (eluted with $CH_3CN/H_2O$ with 0.05% TFA, 3:7, 2 mL/min) from fraction F2-2-5 (8.4 mg). Compound **34** (1.0 mg, $t_R$ = 9.9 min) was purified from fraction F3 (435.7 mg) by QCC over silica gel, eluting with a gradient of $CH_2Cl_2$-MeOH gradient (99:1 to 97:3, v/v) to give 4 subfractions (F3-1–F3-4), with each of these purified with RP $C_{18}$ HPLC (eluted with $CH_3CN/H_2O$ with 0.05% TFA, 2:3, 2 mL/min) and Sephadex LH-20 (100% MeOH). Fraction G (10.8 g) was chromatographed on a silica gel CC eluting with $CH_2Cl_2$-MeOH (95:5, v/v) to give 10 subfractions (G1–G10). Fraction G3 (15.7 mg) was purify using RP $C_8$ HPLC (eluted with $CH_3CN/H_2O$ with 0.05% TFA, 3:7, 2 mL/min) to give compound **12** (1.7 mg, $t_R$ = 7.4 min). Fraction G4 (142.3 mg) was subjected to silica gel CC, eluted with $CH_2Cl_2$-MeOH (97:3, v/v) following RP $C_8$ HPLC (eluted with $CH_3CN/H_2O$ with 0.05% TFA, 1:3, 2 mL/min) to give compounds **27** (5.2 mg, $t_R$ = 14.2 min), **10** (0.4 mg, $t_R$ = 23.3 min), and **11** (0.3 mg, $t_R$ = 24.6 min). Compound **6** (36.9 mg) was recrystallized from *n*-hexanes-acetone (1:1, v/v) from subfraction G6 (234.7 mg).

The dried leaves of *G. cheliensis* (412.1 g) were extracted with acetone (3 × 3 L) at room temperature. The acetone extract (33.8 g) was subjected to QCC over silica gel, eluting with a gradient of *n*-hexanes-acetone gradient (1:0 to 0:1, v/v) to afford fourteen fractions (A–N). The combined of fraction E–H were further separated on a Sep-Pak $C_{18}$ CC eluting with MeOH-$H_2O$ (1:1, v/v) to give fraction B1 (819.4 mg) and further separation by silica gel CC, eluting with *n*-hexanes-acetone (9:1, v/v) gave 5 subfractions (B1-1–B1-5). Fraction B1-3 (73.2 mg) was purified by RP $C_8$ HPLC (eluted with $CH_3CN/H_2O$ with 0.05% TFA, 3:2, 2 mL/min) to yield compounds **37** (2.0 mg, $t_R$ = 24.7 min) and **42** (1.3 mg, $t_R$ = 37.3 min). The combination of fraction I–K was subjected to Sep-Pak $C_{18}$ CC eluting with MeOH-$H_2O$ (1:1, v/v) to give

fraction C1 (806.4 mg) and further separation by Sephadex LH-20 CC (100% MeOH) to yield six subfractions (C1-1–C1-6). Fraction C1-3 (8.7 mg) was purified by silica gel CC, eluting with *n*-hexanes-acetone (7:3, v/v) to give compound **39** (1.7 mg) and 5 subfractions (C1-3-1–C1-3-5). Compounds **36** (1.4 mg, $t_R$ = 32.8 min) and **41** (0.9 mg, $t_R$ = 34.0 min) were obtained from subfraction C1-3-5 (4.5 mg), by a RP $C_8$ HPLC (eluted with $CH_3CN/H_2O$ with 0.05% TFA, 1:1, 2 mL/min). After further purification by RP $C_8$ HPLC (eluted with $CH_3CN/H_2O$ with 0.05% TFA, 1:1, 2 mL/min), compounds **38** (2.1 mg, $t_R$ = 20.7 min) and **40** (0.4 mg, $t_R$ = 23.5 min) were obtained from subfraction C1-4 (6.1 mg). The combined of fractions L–N were further separated by Sephadex LH-20 CC (100% MeOH) to give nine subfractions (D1–D9). Fraction D6 (18.2 mg) was isolated by RP $C_{18}$ HPLC (eluted with $CH_3CN/H_2O$ with 0.05% TFA, 3:7, 2 mL/min) to afford compounds **43** (0.3 mg, $t_R$ = 28.9 min) and **44** (0.8 mg, $t_R$ = 30.5 min).

*4.3.1 Goniochelienic acid A* (**1**)

Yellow needle; mp 215–217 °C; UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 253 (3.47), 287 (3.08), 328 (2.51) nm; IR (neat) $\upsilon_{max}$ 2920, 2850, 1721, 1451, 1236, 747 $cm^{-1}$; For $^1$H-NMR (600 MHz, $CDCl_3$) and $^{13}$C-NMR (125 MHz, $CDCl_3$), see Table 1; HRESIMS (positive-ion mode) *m/z* 294.0379 $[M + Na]^+$ (calcd for $C_{14}H_9NO_5Na$, 294.0378).

*4.3.2 Goniochelienic acid B (**2**)*

Yellow amorphous solid; mp 220–222 °C; UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 253 (3.74), 278 (3.33), 331 (2.95) nm; IR (neat) $\upsilon_{max}$ 2918, 2850, 1727, 1459, 1228, 717 $cm^{-1}$; For $^1$H-NMR (600 MHz, $CDCl_3$) and $^{13}$C-NMR (125 MHz, $CDCl_3$), see Table 1; HRESIMS (positive-ion mode) *m/z* 278.0436 $[M + Na]^+$ (calcd for $C_{14}H_9NO_4Na$, 278.0429).

*4.3.3 Methyl goniochelienate* (**3**)

Yellow solid; mp 214–216 °C; UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 251 (4.37), 276 (3.95), 309 (3.53), 3.74 (3.13) nm; IR (neat) $\upsilon_{max}$ 2924, 2853, 1678, 1208, 1135 $cm^{-1}$; For $^1$H-NMR (600 MHz, MeOH-$d_4$) and $^{13}$C-NMR (125 MHz, MeOH-$d_4$), see Table 1; HRESIMS (positive-ion mode) *m/z* 278.0435 $[M + Na]^+$ (cald for $C_{14}H_9NO_4Na$, 278.0429).

*4.3.4 Goniochelieninone* (**5**)

Yellow solid; mp 162–165 °C; UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 215 (3.53), 282 (3.20), 417 (2.59) nm; IR (neat) $\upsilon_{max}$ 3335, 3215, 2920, 2851, 1615, 1452, 1371, 1260 $cm^{-1}$; For $^1$H-NMR (600 MHz, $CDCl_3$) and $^{13}$C-NMR (125 MHz, $CDCl_3$), see Table 2; HRESIMS (positive-ion mode) *m/z* 284.0530 $[M + Na]^+$ (calcd for $C_{13}H_{11}NO_5Na$, 284.0535).

*4.3.5* (–)-(4*S*,5*S*,6*R*,7*S*,8*S*)-*Goniochelienlactone* (**6**)

Colorless solid; mp 215–217 °C; $[\alpha]^{25}_D$ –47.0 (*c* 0.1, EtOH); UV (EtOH) $\lambda_{max}$ (log $\varepsilon$) 215 (2.76), 255 (1.51) nm; CD (EtOH) $\lambda_{max}$ ($\Delta\varepsilon$) 227 (–0.89) nm; IR (neat)

$\upsilon_{max}$ 3395, 2925, 2873, 2853, 1713, 1177, 1081 $cm^{-1}$; $^1H$ NMR (600 MHz, DMSO-$d_6$) and $^{13}C$ NMR (125 MHz, DMSO-$d_6$) data, see Table 3; HRESIMS (positive-ion mode) *m/z* 273.0749 $[M + Na]^+$ (calcd for $C_{13}H_{14}O_5Na$, 273.0739).

*4.3.6* (−)-(4*S*,5*S*,6*R*,7*S*,8*S*)-*7-acetylgoniochelienlactone* (**7**)

Colorless solid; mp 152−155 °C; $[\alpha]^{25}_D$ −58.0 (*c* 0.1, EtOH); UV (EtOH) $\lambda_{max}$ (log $\varepsilon$) 212 (2.69), 249 (0.97) nm; CD (EtOH) $\lambda_{max}$ ($\Delta\varepsilon$) 232 (−0.26) nm; IR (neat) $\upsilon_{max}$ 3422, 2924, 1731, 1220, 1054 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) and $^{13}C$ NMR (125 MHz, $CDCl_3$) data, see Table 3; HRESIMS (positive-ion mode) *m/z* 315.0854 $[M + Na]^+$ (calcd for $C_{15}H_{16}O_6Na$, 315.0845).

*4.3.7* (+)-(7*S*,8*S*)-*Goniochelienbutenolide A* (**8**)

Colorless viscous; $[\alpha]^{25}_D$ +55.0 (*c* 0.1 EtOH); UV (EtOH) $\lambda_{max}$ (log $\varepsilon$) 206 (2.9), 273 (2.8) nm; CD (EtOH) $\lambda_{max}$ ($\Delta\varepsilon$) 227 (−0.30), 274 (−0.59) nm; IR (neat) $\upsilon_{max}$ 3419, 2926, 1682, 1750, 1208, 1135 $cm^{-1}$; $^1H$ NMR (600 MHz, acetone-$d_6$) and $^{13}C$ NMR (125 MHz, acetone-$d_6$) data, see Table 4; HRESIMS (positive-ion mode) *m/z* 297.0730 $[M + Na]^+$ (calcd for $C_{15}H_{14}O_5Na$, 297.0739).

*4.3.8* (−)-(7*S*,8*R*)-*Goniochelienbutenolide B* (**9**)

Colorless viscous; $[\alpha]^{25}_D$ −34.0 (*c* 0.1 $CHCl_3$); UV ($CHCl_3$) $\lambda_{max}$ (log $\varepsilon$) 225 (2.9), 274 (2.8) nm; CD ($CHCl_3$) $\lambda_{max}$ ($\Delta\varepsilon$) 228 (+0.04), 281 (+0.76) nm; IR (neat) $\upsilon_{max}$ 3472, 2922, 2852, 1743, 1236 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) and $^{13}C$ NMR (125 MHz, $CDCl_3$) data, see Table 4; HRESIMS (positive-ion mode) *m/z* 297.0746 $[M + Na]^+$ (calcd for $C_{15}H_{14}O_5Na$, 297.0739).

*4.4 X-ray crystal analysis of compounds **1, 4, 6,*** and ***7***

X-ray diffraction data were collected using Mo Kα radiation (λ = 0.71073 Å) and Cu Kα radiation (λ = 1.54178 Å) on a Bruker APEX-II CCD diffractometer. Using Olex2 (Dolomanov et al., 2009), the structure was solved with the XT (Sheldrick, 2015) structure solution program, using the Intrinsic Phasing solution method. The model was refined with version 2018/1 of XL (Sheldrick, 2015) using Least Squares minimisation. Crystallographic data of compounds **1, 4, 6**, and **7** have been deposited at the Cambridge Crystallographic Data Center under the reference number CCDC 1846457 (**1**), 1846454 (**4**), 1846455 (**6**), and 1846456 (**7**). These data can be obtained, free of charge, from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

*4.4.1 Crystal data of **1***

Crystals of **1** were obtained as orange irregular-shaped crystals from $Me_2CO$-hexanes. $C_{31}H_{24}N_2O_{11}$, $M_r$ = 600.52, monoclinic, space group C2/c (No. 15), a = 13.549(6) Å, *b* = 26.964(12) Å, *c* = 8.522(4) Å, $\beta$ = 122.191(10)°, $\alpha = \gamma$ = 90°, *V* = 2635(2) $Å^3$, *T* = 90(2) K, *Z* = 4, *Z′* = 0.5, $\mu$(Mo $K_\alpha$) = 0.117, 9693 reflections

measured, 1731 unique ($R_{int}$ = 0.0813) which were used in all calculations. The final $wR_2$ was 0.1937 (all data) and $R_1$ was 0.0692 (I > 2(I)).

*4.4.2 Crystal data of* ***4***

Crystals of **4** were obtained as orange needle-shaped crystals from $Me_2CO$-hexanes. $C_{13}H_9NO_2$, $M_r$ = 211.21, monoclinic, space group $P2_1/c$ (No. 14), a = 15.1793(14) Å, b = 3.8477(5) Å, c = 17.6197(18) Å, $\beta$ = 109.578(5)°, $\alpha = \gamma = 90°$, $V$ = 969.59(19) Å$^3$, $T$ = 100(2) K, $Z$ = 4, $Z'$ = 1, $\mu$(Mo $K_\alpha$) = 0.099, 9656 reflections measured, 2298 unique ($R_{int}$ = 0.0343) which were used in all calculations. The final $wR_2$ was 0.1790 (all data) and $R_1$ was 0.0602 (I > 2(I)).

*4.4.3 Crystal data of* ***6***

Crystals of **6** were obtained as colourless irregular-shaped crystals from $Me_2CO$-hexanes. $C_{13}H_{14}O_5$, $M_r$ = 250.24, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 9.4413(5) Å, b = 10.3844(6) Å, c = 11.6131(6) Å, $\alpha = \beta = \gamma = 90°$, $V$ = 1138.57(11) Å$^3$, $T$ = 90(2) K, $Z$ = 4, $Z'$ = 1, $\mu$(Cu $K_\alpha$) = 0.948, 9069 reflections measured, 2012 unique ($R_{int}$ = 0.0325) which were used in all calculations. The final $wR_2$ was 0.0615 (all data) and $R_1$ was 0.0241 (I > 2(I)). Flack parameter = -0.04(7).

*4.4.4 Crystal data of* ***7***

Crystals of **7** were obtained as colourless irregular-shaped crystals from $Me_2CO$-hexanes. $C_{15}H_{16}O_6$, $M_r$ = 292.28, monoclinic, $P2_1$ (No. 4), a = 10.9487(4) Å, b = 6.8358(3) Å, c = 18.6909(7) Å, $\beta$ = 90.243(2)°, $\alpha = \gamma = 90°$, $V$ = 1398.87(10) Å$^3$, $T$ = 90(2) K, $Z$ = 4, $Z'$ = 2, $\mu$(Cu $K_\alpha$) = 0.910, 20213 reflections measured, 4945 unique ($R_{int}$ = 0.0351) which were used in all calculations. The final $wR_2$ was 0.0900 (all data) and $R_1$ was 0.0336 (I > 2(I)). Flack parameter = 0.00(11).

*4.5 Biological assay*

*4.5.1 Bioassay for Cytotoxicity*

The cytotoxicities of compounds on colon cancer cell were performed following by the previous method (Sriyatep et al., 2017). Doxorubicin used as a positive control ($IC_{50}$ = 9.74 µM).

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**Appendix A. Supplementary data**

Supplementary data related to this article can be found at

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922 23, 583–586.
923

# Graphical abstract

## Alkaloids and styryllactones from *Goniothalamus cheliensis*

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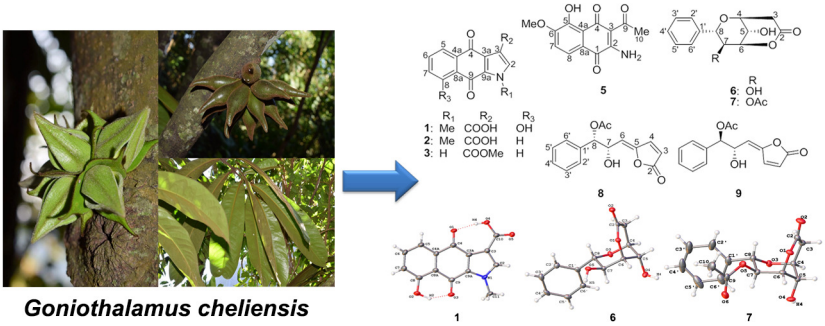


Eight previously undescribed compounds were isolated and characterized from *Goniothalamus cheliensis*. Griffithazanone A showed potent cytotoxicities against human colorectal cancer cells (HCT-116).

**Figure legends**

**Fig. 1.** The structures of compounds from *G. cheliensis* twigs.

**Fig. 2.** The structures of compounds from *G. cheliensis* leaves.

**Fig. 3.** The key COSY and HMBC correlations of **1**–**3** and **5**–**9**.

**Fig.4.** The key NOESY correlations of **6** and **7** (molecular structures generated using 3D structure ChemBioDraw Ultra 11.0).

**Fig. 5.** Single crystal X-ray structure of **1.**

**Fig. 6.** Single crystal X-ray structure of **4.**

**Fig. 7.** Single crystal X-ray structure of **6.**

**Fig. 8.** Single crystal X-ray structure of **7.**

**Fig. 9.** ECD spectra of **6** and **7.**

**Fig. 10.** ECD spectra of **8–11.**

**Fig. 11.** Plausible biosynthetic pathway of **1–4** (**a**) and **5** (**b**)**.**

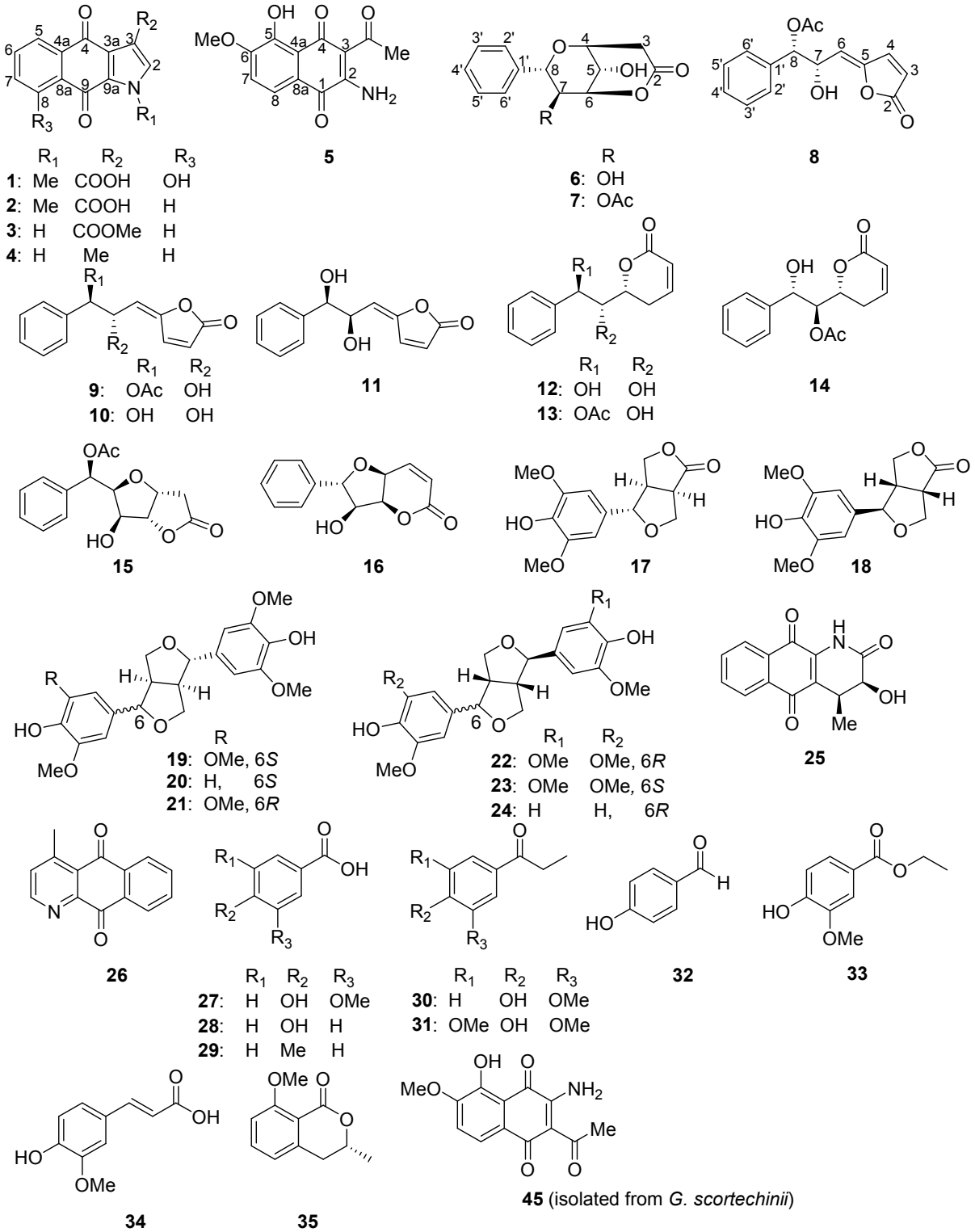
R1 R2 R3
1: Me COOH OH
2: Me COOH H
3: H COOMe H
4: H Me H
5
R
6: OH
7: OAc
8
R1 R2
9: OAc OH
10: OH OH
11
R1 R2
12: OH OH
13: OAc OH
14
15
16
17
18
R
19: OMe, 6S
20: H, 6S
21: OMe, 6R
R1 R2
22: OMe OMe, 6R
23: OMe OMe, 6S
24: H H, 6R
25
26
R1 R2 R3
27: H OH OMe
28: H OH H
29: H Me H
R1 R2 R3
30: H OH OMe
31: OMe OH OMe
32
33
34
35
45 (isolated from G. scortechinii)

**Fig. 1.**

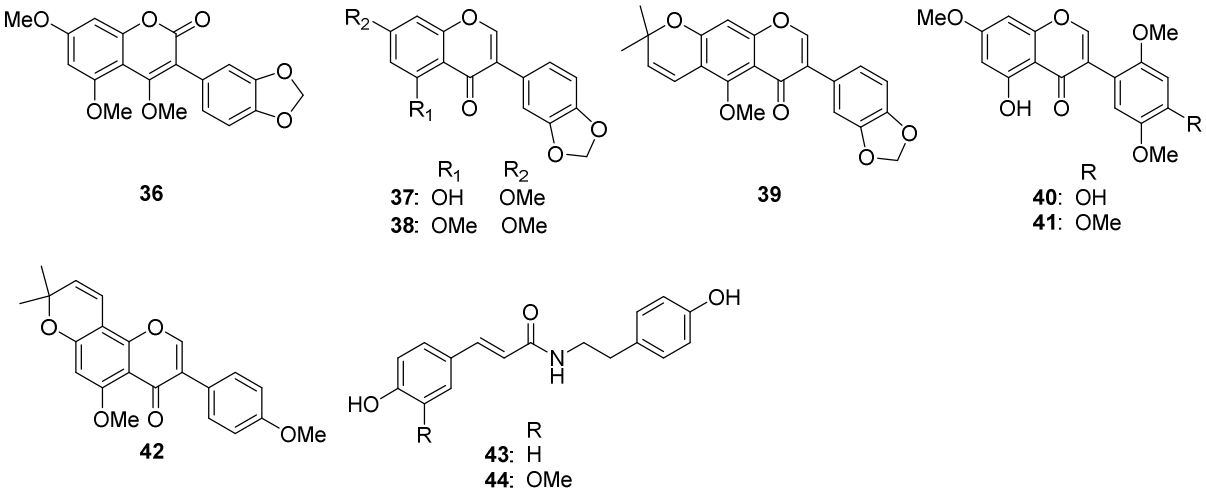
MeO
OMe OMe
36
R2
R1
R1 R2
37: OH OMe
38: OMe OMe
39
MeO
OMe
OH
R
OMe
40: OH
41: OMe
OMe
OMe
42
HO
R
43: H
44: OMe

**Fig. 2.**

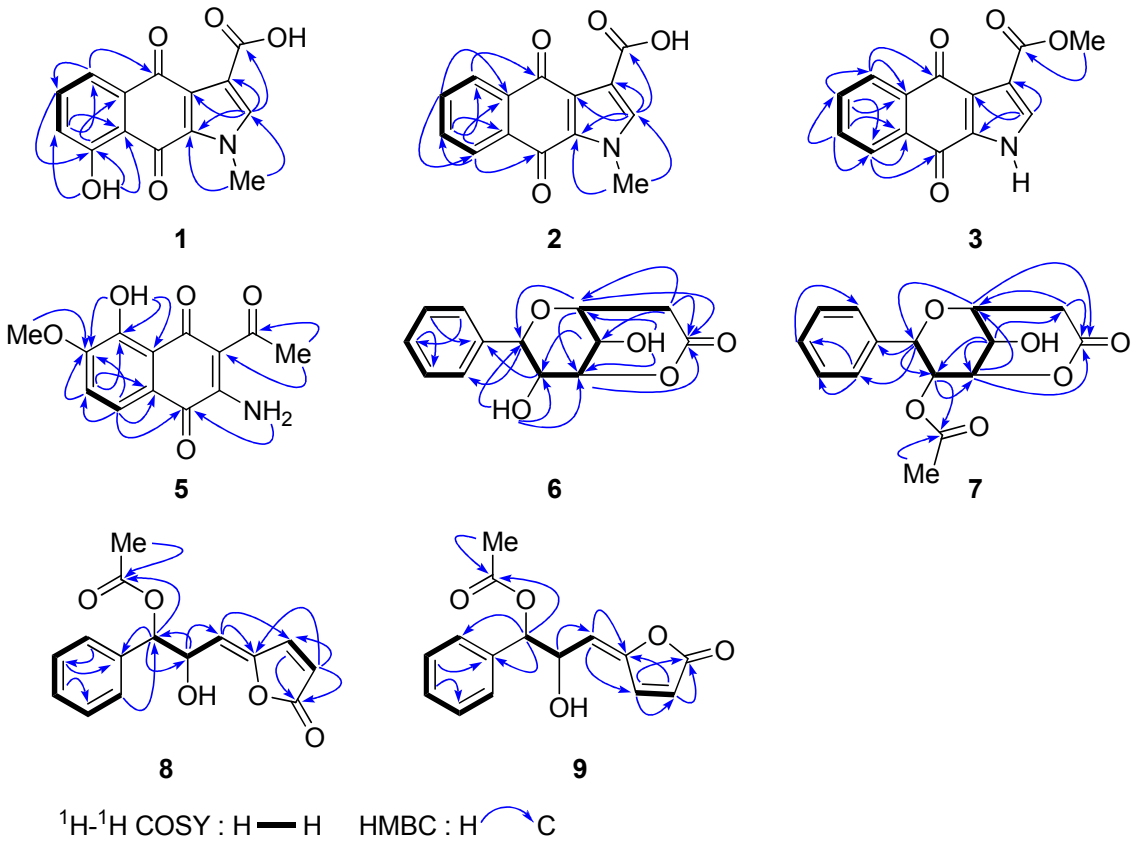
1
2
3
MeO
Me
NH2
5
6
7
8
9
1H-1H COSY : H — H
HMBC : H C

**Fig. 3.**

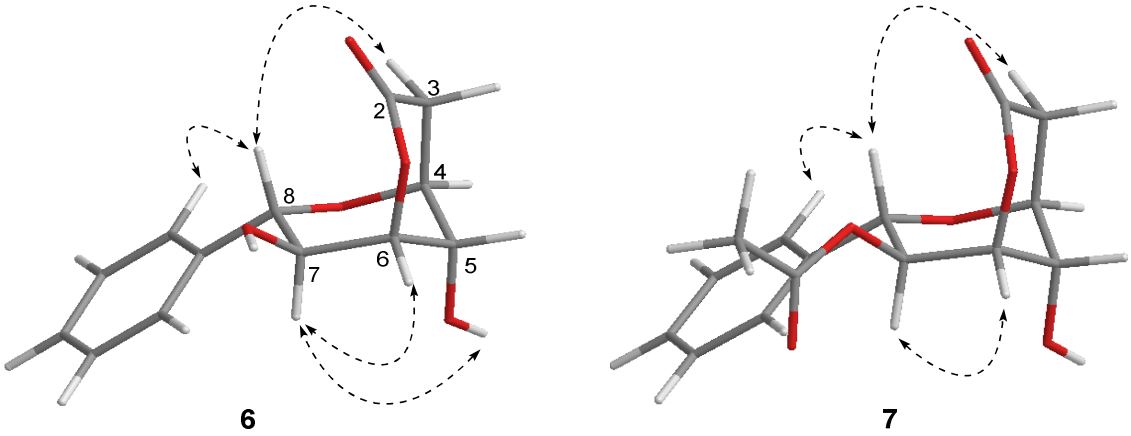
3
2
4
8
6
5
7
6
7

**Fig.4.**

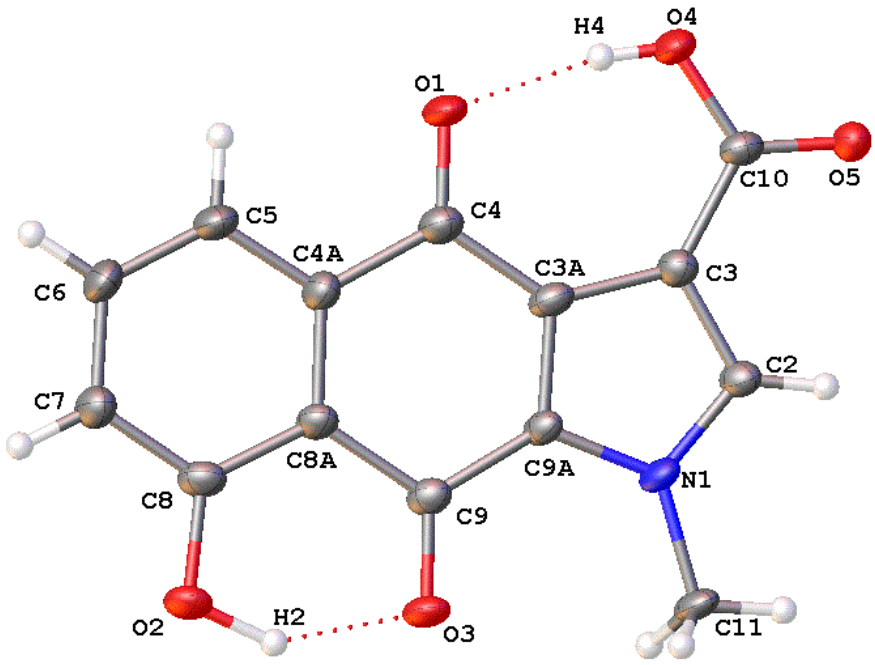
H4
O4
O1
C10
O5
C5
C4
C4A
C3A
C3
C6
C2
C7
C8A
C9A
N1
C8
C9
O2
H2
O3
C11

**Fig. 5.**

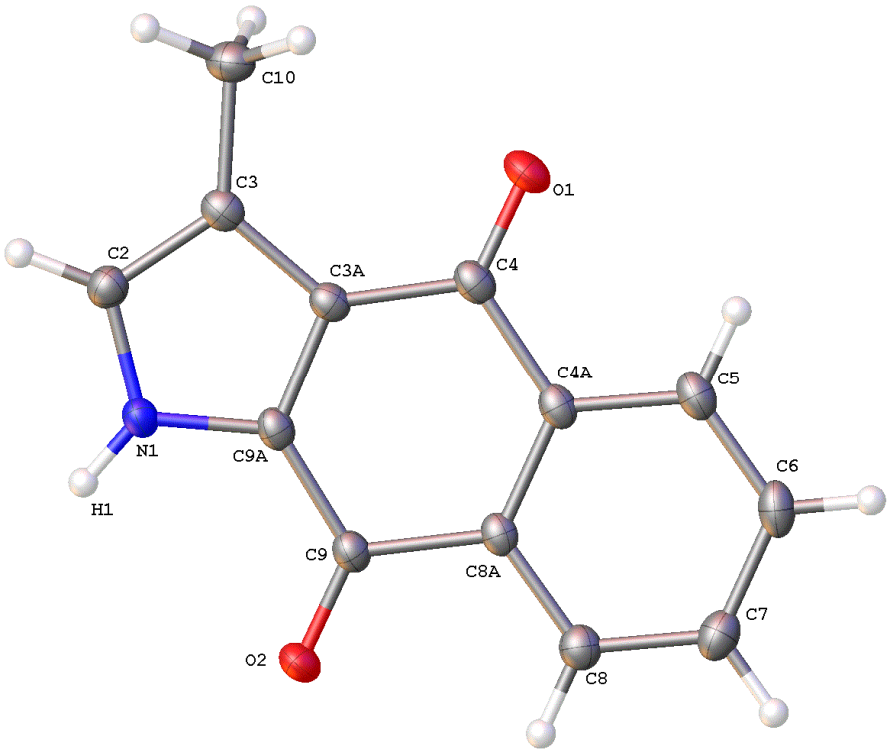
C10
C3
O1
C2
C3A
C4
C4A
C5
N1
C9A
C6
H1
C9
C8A
C7
O2
C8

**Fig. 6.**

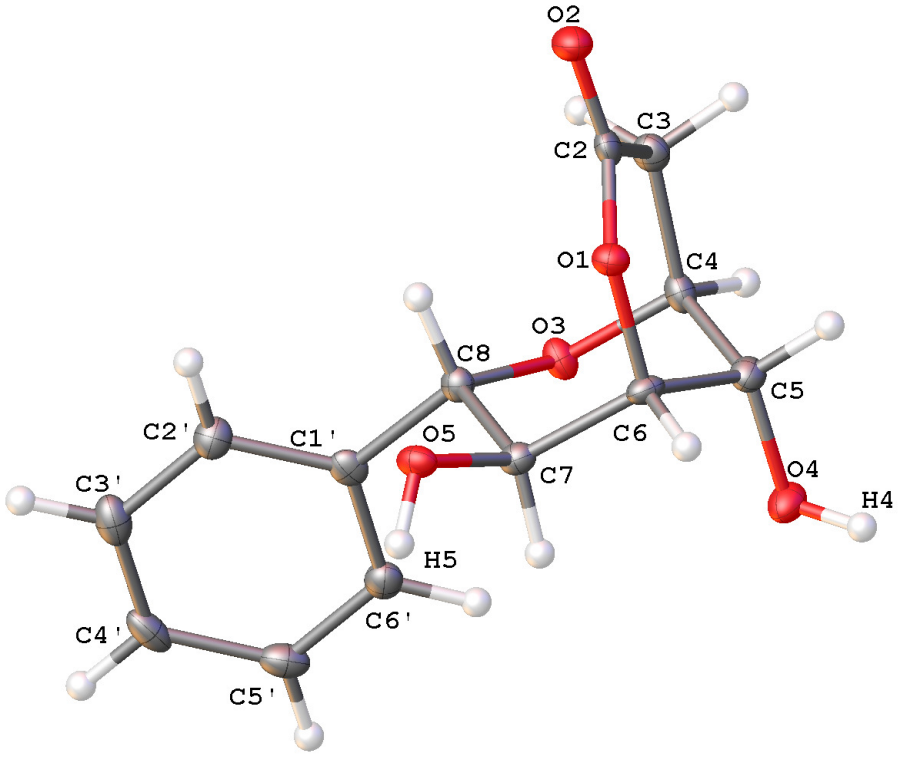
O2
C3
C2
O1
C4
O3
C8
C5
C2'
C1'
O5
C6
C7
O4
C3'
H4
H5
C6'
C4'
C5'

**Fig. 7.**

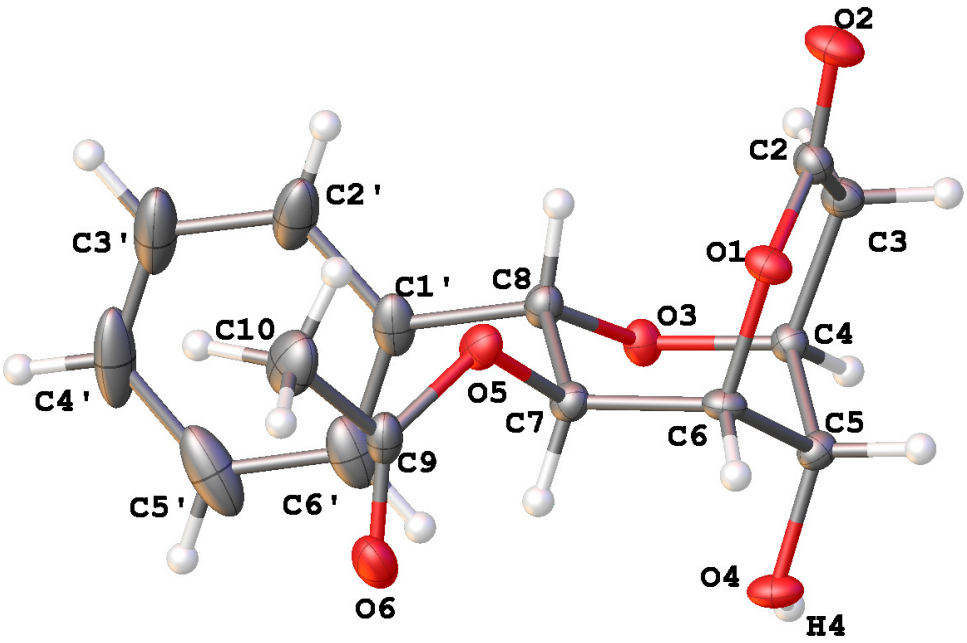
O2
C2
C3
O1
C2'
C3'
C1'
C8
O3
C4
C10
O5
C4'
C7
C6
C5
C9
C5'
C6'
O4
O6
H4

**Fig. 8**.

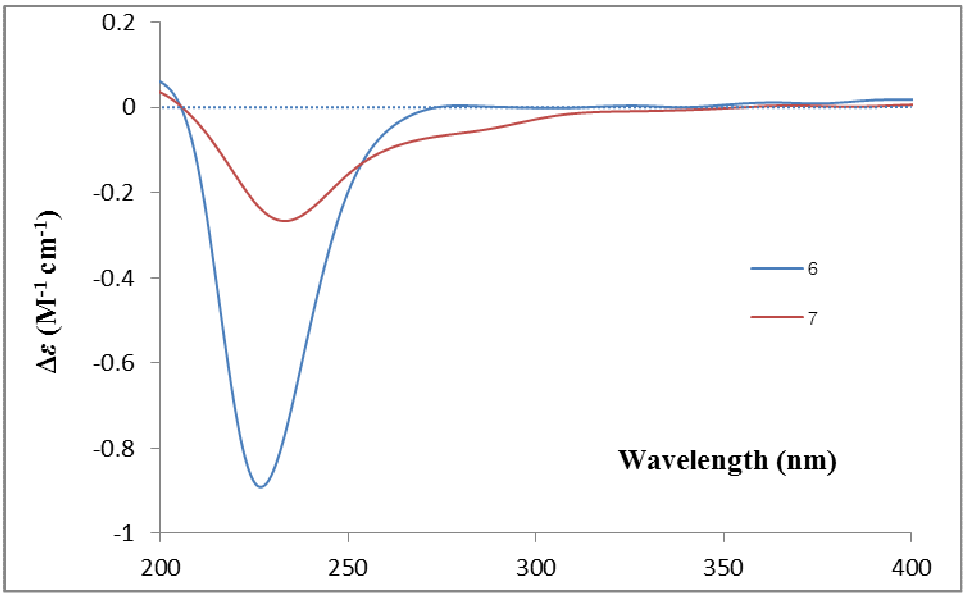
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
Δε (M-1 cm-1)
200
250
300
350
400
Wavelength (nm)
6
7

**Fig. 9**.

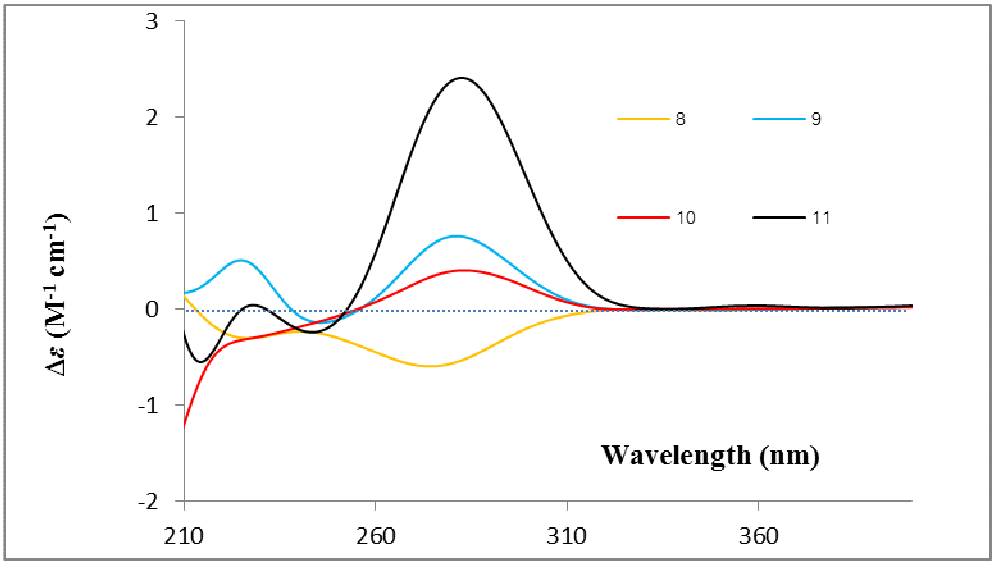


**Fig. 10**.

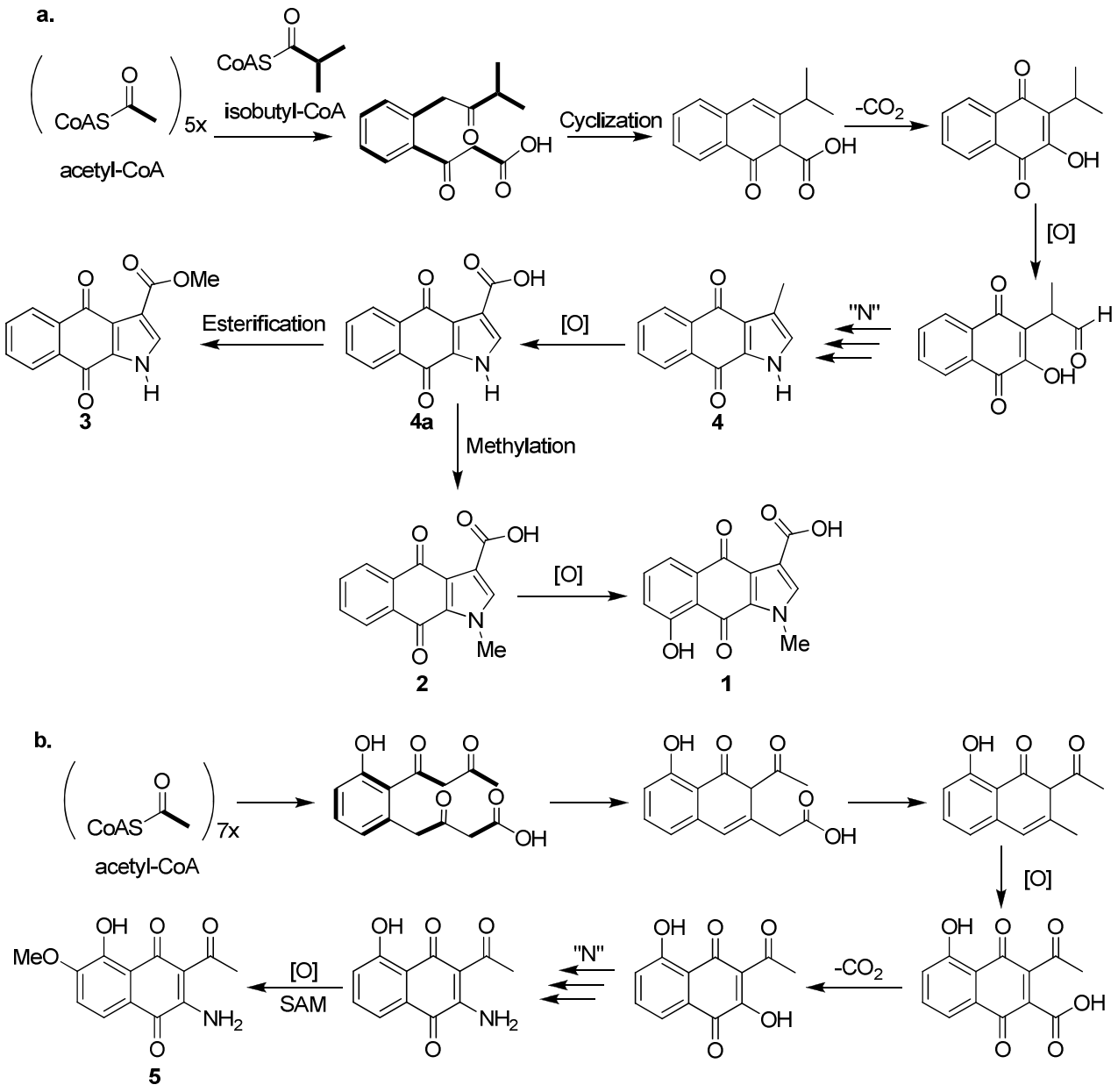
a.
CoAS
5x
acetyl-CoA
isobutyl-CoA
Cyclization
-CO2
[O]
"N"
[O]
Esterification
OMe
3
4a
4
Methylation
[O]
2
1
Me
b.
CoAS
7x
acetyl-CoA
[O]
SAM
"N"
-CO2
MeO
NH2
5

**Fig. 11**.

**Table 1**

$^{1}H$ (600 MHz) and $^{13}C$ (150 MHz) NMR Spectroscopic data of **1–3**.

| | **1** ($CDCl_3$) | | **2** ($CDCl_3$) | | **3** (methanol-$d_4$) | |
|---|---|---|---|---|---|---|
| position | $\delta_C$, type | $\delta_H$ (*J* in Hz) | $\delta_C$, type | $\delta_H$ (*J* in Hz) | $\delta_C$, type | $\delta_H$ (*J* in Hz) |
| 2 | 138.0, CH | 7.74, s | 137.5, CH | 7.73, s | 130.2, CH | 7.81, s |
| 3 | 114.5, C | | 116.4, C | | 115.2, C | |
| 3a | 123.5, C | | 123.1, C | | 124.0, C | |
| 4 | 183.1, C | | 184.0, C | | 179.1, C | |
| 4a | 132.0, C | | 132.6, C | | 133.7, C | |
| 5 | 120.7, CH | 7.82, d (7.4) | 127.4, CH | 8.26, dd (7.4, 1.3) | 124.0, CH | 8.14, dd (7.8, 1.2) |
| 6 | 136.0, CH | 7.64, dd (7.8, 7.4) | 134.5, CH | 7.79, td (7.5, 1.5) | 132.1, CH | 7.78, dd (7.2, 1.2) |
| 7 | 126.1, CH | 7.32, d (7.8) | 133.6, CH | 7.81, td (7.5, 1.5) | 131.4, CH | 7.77, ddd (7.8, 7.2, 1.2) |
| 8 | 162.5, C | | 126.6, CH | 8.21, dd (7.4, 1.3) | 125.2, CH | 8.19, dd (7.8, 1.2) |
| 8a | 114.5, C | | 132.6, C | | 133.0, C | |
| 9 | 180.9, C | | 175.5, C | | 175.3, C | |
| 9a | 130.9, C | | 131.8, C | | 134.4, C | |
| 10 | 161.5, C | | 162.1, C | | 163.2, C | |
| *N*-Me | 37.5, $CH_3$ | 4.15, s | 37.3, $CH_3$ | 4.16, s | | |
| 8-OH | | 12.20, s | | | | |
| 3-$CO_2$*Me* | | | | | 49.3, $CH_3$ | 3.89, s |
| 3-CO*OH* | | 13.68, s | | 13.70, s | | |

**Table 2**
$^{1}$H (600 MHz) and $^{13}$C (150 MHz) NMR Spectroscopic data of **5** and goniothalaminone B.

| | **5** (DMSO-$d_6$) | | **5** ($CDCl_3$) | | goniothalaminone B ($CDCl_3$) | |
|---|---|---|---|---|---|---|
| position | $\delta_C$, type | $\delta_H$ (*J* in Hz) | $\delta_C$, type | $\delta_H$ (*J* in Hz) | $\delta_C$, type | $\delta_H$ (*J* in Hz) |
| 1 | 178.1, C | | 178.0, C | | 180.2, C | |
| 2 | 107.5, C | | 106.9, C | | 109.4, C | |
| 3 | 155.0, C | | 158.4, C | | 152.5, C | |
| 4 | 187.7, C | | 186.3, C | | 185.5, C | |
| 4a | 114.3, C | | 113.4, C | | 114.0, C | |
| 5 | 151.6, C | | 151.8, C | | 152.0, C | |
| 6 | 155.8, C | | 155.8, C | | 152.1, C | |
| 7 | 114.7, CH | 7.29, d (8.4) | 113.2, CH | 7.05, d (8.4) | 117.8, C | 7.22, d (8.4) |
| 8 | 120.7, CH | 7.62, d (8.4) | 121.0, CH | 7.75, d (8.4) | 120.7, C | 7.76, d (8.4) |
| 8a | 121.8, C | | 126.7, CH | | 125.0, C | |
| 5-OH | | 13.94, s | | 13.97, s | | 11.71, s |
| 6-OMe | 56.2, $CH_3$ | 3.91, s | 56.0, $CH_3$ | 4.02, s | 56.4, $CH_3$ | 3.99, s |
| $NH_2$ | | 9.12, br s | | | | 7.07, br s |
| | | 10.68, br s | | | | 10.66, br s |
| *CO*Me | 199.9, C | | 200.7, C | | 202.4, C | |
| CO*Me* | 33.2, $CH_3$ | 2.56, s | 33.0, $CH_3$ | 2.73, s | 33.2, $CH_3$ | 2.73, s |

**Table 3**
$^{1}$H (600 MHz) and $^{13}$C (150 MHz) NMR Spectroscopic data of **6** and **7**.

| | **6** (DMSO-$d_6$) | | **7** ($CDCl_3$) | |
|---|---|---|---|---|
| position | $\delta_C$, type | $\delta_H$ (*J* in Hz) | $\delta_C$, type | $\delta_H$ (*J* in Hz) |
| 2 | 168.7, C | | 167.0, C | |
| $3_{ax}$ | 35.2, $CH_2$ | 2.78, d (19.3) | 34.6, $CH_2$ | 3.15, dd (19.6, 1.2) |
| $3_{eq}$ | | 3.07, d (19.3, 5.2) | | 3.02, dd (19.6, 5.2) |
| 4 | 69.3, CH | 4.07, d (4.6) | 69.7, CH | 4.38, m |
| 5 | 64.7, CH | 4.15, td (4.3, 1.6) | 65.3, CH | 4.33, dd (4.6, 1.6) |
| 6 | 78.4, CH | 4.45, m | 74.5, CH | 4.91, dt (4.6, 2.6) |
| 7 | 67.2, CH | 3.87, ddd (9.8, 7.2, 2.3) | 69.1, CH | 5.37, dd (10.3, 2.6) |
| 8 | 72.9, CH | 4.24, d (9.8) | 70.6, CH | 4.67, d (10.3) |
| 1′ | 139.7, C | | 136.0, C | |
| 2′ | 128.7, CH | 7.38, d (7.9) | 126.7, CH | 7.41, m |
| 3′ | 127.7, CH | 7.30, t (7.6) | 128.1, CH | 7.37, m |
| 4′ | 127.6, CH | 7.26, t (7.2) | 128.6, CH | 7.34, m |
| 5′ | 127.7, CH | 7.30, t (7.6) | | 7.37, m |
| 6′ | 128.7, CH | 7.38, d (7.9) | | 7.41, m |
| 5-OH | | 5.70, d (4.0) | | |
| 7-OH | | 5.16, d (6.9) | | |
| 7-O*CO*Me | | | 169.1, C | |
| 7-OCO*Me* | | | 20.2, $CH_3$ | 1.94, s |

**Table 4**
$^{1}$H (600 MHz) and $^{13}$C (150 MHz) NMR Spectroscopic data of **8** and **9**.

| | **8** (acetone-$d_6$) | | **9** ($CDCl_3$) | |
|---|---|---|---|---|
| position | $\delta_C$, type | $\delta_H$ ($J$ in Hz) | $\delta_C$, type | $\delta_H$ ($J$ in Hz) |
| 2 | 168.2, C | | 169.6, C | |
| 3 | 119.6, CH | 6.31, d (5.5) | 121.2, CH | 6.19, dd (5.6, 1.5) |
| 4 | 114.0, CH | 7.74, d (5.5) | 139.6, CH | 7.50, d, (5.6) |
| 5 | 149.8, C | | 152.4, C | |
| 6 | 112.9, CH | 5.46, d (9.2) | 107.0, CH | 5.82, dd (10.0, 1.5) |
| 7 | 67.8, CH | 4.98, dd (9.2, 5.3) | 72.3, CH | 5.69, dd (10.0, 4.2) |
| 8 | 76.5, CH | 5.85, d (5.3) | 74.8, CH | 5.06, d (4.2) |
| 1′ | 135.8, C | | 137.4, C | |
| 2′ | 126.7, CH | 7.40, d (7.4) | 125.9, CH | |
| 3′ | 127.5, CH | 7.33, t (7.4) | 128.1, CH | 7.34-7.38, m |
| 4′ | 127.3, CH | 7.27, t (7.3) | 128.8, CH | |
| 5′ | 127.5, CH | 7.33, t (7.4) | 128.1, CH | |
| 6′ | 126.7, CH | 7.40, d (7.4) | 125.9, CH | |
| 8-O*CO*Me | 168.0, C | | 168.2, C | |
| 8-OCO*Me* | 19.5, $CH_3$ | 2.00, overlapped | 21.0, $CH_3$ | 2.07, s |