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# Chemical constituents and cytotoxic effect from the barks of *Goniothalamus chinensis* Merr. & Chun. growing in Vietnam

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**ABSTRACT**

*Goniothalamus chinensis* Merr. & Chun is a medicinal plant which has cytotoxicity, antitumor, antifungal, antimalaria and antituberculosis and antioxidant activity. The styryl-lactone, alkaloid and acetogenin are the main group compounds in species of Goniothalamus. In this study, we aimed to investigate phytochemical and cytotoxic effect of compounds from bark of *Goniothalamus chinensis* Merr. & Chun. The bark of *Goniothalamus chinensis* Merr. & Chun grown in Vietnam was extracted by methanol. Three compounds were isolated using on Sephadex LH-20 and preparative glass-backed TLC plates. The compound's structure were characterized on the basis of spectroscopic data and by comparing their physicochemical and spectral data with those published in literatures. The cytotoxicity of three compounds was evaluated against four cancer cell lines: epithelial cancer (KB), liver (Hep G2); breast cancer (MCF-7) and lung (LU-1). We have been isolated three compounds. Their structures were identified as Goniothalamin (**1**), Aristolactam BII (**2**), 3-Methyl-1H-benz[f]indole-4,9-dione (**3**). Isolated compounds were tested cytotoxic activity against different cancer cell lines. The compound **1** demonstrated the highest potency against the epithelial cancer cell line with an $IC_{50}$ of 4.18 ± 0.60µg/mL. Other compounds have weak cytotoxic activity.

## INTRODUCTION

With the tropical climate, Vietnam has diversity of plant and animals species. In total, Vietnam has more than 12000 plant species; of which nearly 4000 species can be used in traditional medicine. The genus of *Goniothalamus* contains about 160 species in the world, mostly in Southeast Asia, among which about 19 are distributed in Vietnam (Wiart, 2007). Some species have been used as folk medicines for healing, for digestion and as a tonic plant. Main compounds in *Goniothalamus* are styryl-lactone, alkaloid and acetogenin which have cytotoxic, antitumor, insecticides, antifungal, antimalaria, antituberculosis and antioxidant activities (Blázquez *et al.*, 1999). Orlikova *et al.*, have showed goniothalamin, a styryl-lactone isolated from *Goniothalamus macrophyllus*, have cytotoxic and anti-inflammatory effects. Thí compound also inhibits the tumor necrosis factor-α-induced NF-κB activation and have anti-leukemic potential (Orlikova *et al.*, 2013). Other study demonstrated that goniolactone C, a styryl lactone, was extracted from *Goniothalamus cheliensis*, strongly inhibited platelet-derived growth factor-BB-induced vascular smooth muscle cell migration and proliferation (Sun *et al.*, 2014). Goniothalamin, an active compound extracted from *Goniothalamus griffithii*, also inhibits human leukemic cells undergo apoptosis via intrinsic and extrinsic pathways (Petsophonsakul *et al.*, 2013) and cervical cancer cells (HeLa) (Alabsi *et al.*, 2012). Furthermore, goniothalamin also showed potent gastroprotective activity on gastric ulcers models in rats. The mechanism is goniothalamin may induce the production of sulfhydryl compounds and prostaglandins (Vendramini-Costa *et al.*, 2014). For now, species of *Goniothalamus* continue being interested by many researches. However, there has been no report about the studies on the chemical constituents and bioactivity of this plant growing in Vietnam.

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Therefore a study about the chemical composition of *Goniothalamus chinensis* Merr. & Chun is much needed. In this study, from barks of *Goniothalamus chinensis* Merr. & Chun grown in Vietnam, have extracted, isolated and identified three compounds: Goniothalamin (**1**), Aristolactam BII (**2**),3-Methyl-1H-benz[f]indole-4,9-dione (**3**). Furthermore, we have evaluated the cytotoxic of these compounds on four cell line epithelial cancer (KB), liver (Hep G2); breast cancer (MCF-7) and lung (LU-1).

## MATERIALS AND METHODS

### Plant material

Barks of *Goniothalamus chinensis* Merr. & Chun. (Kingdom: Plantae; Phylum: Tracheophyta; Class: Magnoliopsida; Order: Magnoliales; Family: Annonaceae) were collected in Ha Giang province, Vietnam during 2013 and authenticated by the School of Medicine and Pharmacy, Vietnam National University, Hanoi, Vietnam (SMP-VNU). A voucher specimen (No. SMP-2013-0018) has been deposited at the Herbarium of SMP-VNU.

### General experimental procedures

Melting points were measured on Mikroskopheiztisch PHMK-50 (VEB WaegetechnikRapido, Germany). The FT-IR spectra were recorded on an IMPACT-410FT-IR spectrometer (CARL ZEISS JENA). The NMR [$^1$H (500 MHz), $^{13}$C (125 MHz), and DEPT-90 and 135 MHz)] spectra were recorded on an AVANCE spectrometer AV 500 (Brucker, Germany) in the Institute of Chemistry, Vietnam Academy of Science and Technology (VAST). Chemical shifts were reported in ppm downfield from TMS with *J* in Hz. Electrospray Ionization Mass Spectra (ESI-MS) were recorded on a Varian Agilent 1100 LC-MSD mass spectrometer. Analytical TLC was performed on Kieselgel 60 $F_{254}$ (Merck) plates (silica gel, 0.25 mm layer thickness) and RP-18 $F_{254}$ (Merck) plates (0.25 mm layer thickness). Spots were visualized using ultraviolet radiation (at 254 and 365 nm) and by spraying with 10% $H_2SO_4$, followed by heating with a heat gun. Column chromatography was performed on silica gel (70–230 and 230–400 mesh, Merck). Organic solvents were of analytical grade.

### Extraction and isolation

*Goniothalamus chinensis* Merr. & Chun barks of 1.7 kg was dried and extracted with methanol (5L × 24 hours × 3 times) at room temperature. The methanol extracts were combined and then evaporated to dryness *in vacuo* at 40°C to yield crude extract (40.3 g). This crude extract was chromatographed on Sephadex LH-20 column and eluted with gradient of $CH_2Cl_2$/MeOH to yield ten fractions F1-F10. Fraction F3 was further separated over a silica gel column and eluted with *n*-hexane/acetone (9:1) to yield eight subfractions F3.1-F3.8. Fraction 3.7 was further separated on Sephadex LH-20 column and eluted with MeOH/$CH_2Cl_2$ (95/5) to yield two fractions F3.7.1 and F3.7.2. Fraction F3.7.2 was applied on preparative glass-backed TLC plates, coated with silica gel 60 and eluted with gradient of *n*-hexane/acetone to yield compound **1** (14 mg). Fraction 3.8 was further separated on Sephadex LH-20 column and eluted with MeOH/$CH_2Cl_2$ (95/5) to yield compound **3** (17.5 mg). Fraction F4 was chromatographed over a silica gel column and eluted with *n*-hexane/acetone (9:1) to yield fifteen subfractions F4.1-F4.15. Fraction F4.13 was crystallized on solvents $CH_2Cl_2$-MeOH (1:1) to yield compound **2** (6.4mg).

**Goniothalamin (1):** was obtained as a light yellow, solid powder, melting point 82-84°C; $R_f$ = 0,44 (n-hexane-$CH_2Cl_2$ 20/80, v/v); $[\alpha]_D^{27}$ = +81,0° (C 0,2; EtOH). FT-IR (KBr) $\nu_{max}$ ($cm^{-1}$): 2925, 1707, 1664, 1627, 1454, 1382, 1244, 1066, 966, 822, 759, 699, 584, 512, 440. UV $\lambda_{max}$ MeOH nm (log ε): 210 (4.43); 251 (4.32); 282 (3.25); 290 (3.03). (+)-ESI-MS: m/z 223 [M+Na]+. $^1$H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.40 (2H, m, H-10, H-14); 7.34 (2H, m, H-11, H-13); 7.27 (1H, m, H-12); 6.92 (1H, ddd, J=4.0; 5.0; 9.5 Hz, H-4); 6.73 (1H, d, J=16.0 Hz, H-8); 6.27 (1H, dd, J=6.5; 16.0 Hz, H-7); 6.09 (1H, dt, J=2.0; 10.0 Hz, H-3); 5.10 (1H, ddd, J=1.0; 6.5; 15.5 Hz; H-6); 2,54 (2H, m, H-5). $^{13}$C-NMR (125 MHz, $CDCl_3$): δ (ppm) 163.8 (C-2); 144.5 (C-4); 135.8 (C-9); 133.1 (C-8); 128.7 (C-11, C-13); 128.3 (C-12); 126.7 (C-10, C-14'); 125.7(C-7); 121.7(C-3); 77.9 (C-6); 29.9 (C-5).

**Aristolactam BII (2):** was obtained as a yellow, crystalline powder, melting point 248-250°C; $R_f$= 0,38 (n-hexane-acetone 67/33, v/v). FT-IR (KBr) $\nu_{max}$($cm^{-1}$): 3449, 3194, 2926, 2855, 1717, 1644, 1607, 1462, 1379, 1031, 838, 720, 624, 530, 466. UV $\lambda_{max}$MeOH nm (log ε): 205 (3.59); 232 (3.56); 263 (3.49); 276 (3.54); 286 (3.53); 317 (2.97); 385 (2.94). (+)-ESI-MS: m/z 302 [M+Na]+; 581 [2M+Na]+. $^1$H-NMR (500 MHz, $CDCl_3$ + $CD_3OD$): δ (ppm) 9.12 (1H, m, H-5); 7.72 (1H, s, H-2); 7.72 (1H, m ,H-8); 7.47 (2H, m, H-6, H-7); 7.00 (1H, s, H-9); 4.02 (3H, s, 4-$OCH_3$); 3.98 (3H, s, 3-$OCH_3$). $^{13}$C-NMR (125 MHz, $CDCl_3$ + $CD_3OD$): δ (ppm) 170.2 (C=O); 154.4 (C-3); 151.5 (C-4), 134.8 (C-8a), 134.2 (C-10), 128.9 (C-8), 127.4 (C-5), 127.4 (C-7), 126.9 (C-5a), 125.8 (C-6), 124.2 (C-10a), 121.2 (C-1), 120.8 (C-4a), 109.5 (C-2), 106.2 (C-9), 60.2 (4-$OCH_3$), 56.8 (3-$OCH_3$).

**3-Methyl-1H-benz[f]indole-4,9-dione (3):** was obtained as a yellow, solid powder, melting point 248-249°C; $R_f$= 0,44 (n-hexane- $CH_2Cl_2$ 25/75, v/v). (+)-ESI-MS: m/z 210 $[MH]^+$, (+)-ESI-MS: m/z 212 [M+H]+; (+)-HR-ESI-MS m/z 212,0710 [M+H]+, FT-IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3429, 3322, 2938, 1647, 1588, 1507, 1403, 1238, 1031, 932, 714. UV (MeOH) $\lambda_{max}$ nm (log ε): 258 (4,07); 330 (3,32). $^1$H-NMR (500 MHz, $CDCl_3$+ $CD_3OD$): δ (ppm) 8.08 (1H, m, H-5); 8.01 (1H, m, H-8); 7.59 (2H, m, H-6, H-7); 6.83 (1H, m, H-2); 2.34 (3H, s, $CH_3$-10). $^1$H-NMR (500 MHz, DMSO): δ (ppm) 12.65 (1H, br s, H-1); 8.18 (2H, m, H-5, H-8); 7.76 (2H, m, H-6, H-7); 7.13 (1H, m, H-2); 2.31 (3H, s, $CH_3$-10). $^{13}$C-NMR (125 MHz, $CDCl_3$

+ $CD_3OD$): δ (ppm) 182.3 (C-9); 175.7 (C-4); 134.5 (C-8a); 133.4 (C-4a); 133.2 (C-6, C-7); 132.7 (C-9a); 126.5 (C-5); 126.0 (C-8); 125.5 (C-2); 125.1 (C-3a); 122.8 (C-3); 11.0 ($CH_3$-10).

**Cytotoxicity Assay**

Cytotoxicity of these compounds was evaluated against four types of cancer cell lines: epithelial cancer (KB), liver (Hep G2); breast cancer (MCF-7) and lung (LU-1) by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cell lines were cultured in Dulbecco's Modified Eagle medium (DMEM) with 10% foetal bovine serum, at 37°C, 5% CO2 and 95% humidity. Cells were plated in 96-well flat bottom tissue culture plates and allowed to density of approximately $3x10^4$/mL then begin experiment. The cells were incubated with 100 µL of compound at a range of concentration (from 1 µg/mL to 1000 µg/mL) for 72 hours. Then, 0.2 mg/mL MTT reagent was added to each well, and the plate was incubated for 4 hours at 37°C. Next, DMSO (100 uL) was added and the plates shaken for 5 min. The absorbance for each well was measured at 540 nm in a microtiter plate reader and the percentage cell viability (CV) was calculated manually using the formula:

$$CV=\frac{\text{Average abs of duplicate drug wells}}{\text{Average abs of control wells}}x100$$

The effects of compounds were expressed by $IC_{50}$ values (the drug concentration reducing the absorbance of treated cells by 50% with respect to untreated cells) (Monks *et al.*, 1991).

**RESULTS AND DISCUSSION**

**Isolation and Chemistry**

***Goniothalamin(1)***

Goniothalamin (**1**) was obtained as a light yellow, solid powder, melting point 82-84°C and the optical rotation$[\alpha]_D^{27}$= + 81,0° (c 0,2; EtOH). The ring γ-lactone α,β-unsaturated showed typical absorption bands arising from carbonyl group (1707 $cm^{-1}$) inIR spectrum, maximum absorption wavelength at $\lambda_{max}$ 210 nm (logε 4,43; MeOH) in UV spectrum and $\delta_C$ 163,8 in $^{13}$C-NMR spectrum. The molecular formula was established as $C_{13}H_{12}O_2$ based on a molecular ion peak at*m/z* 223 $[M + Na]^+$. The $^1$H-NMR spectrum showed the presence of phenyl group with five signals proton at $\delta_H$ 7,27- 7,40 (5H, m, $C_6H_5$), signals of 4 proton olefinic at $\delta_H$ 6,92 (1H, ddd, J=4.0; 5.0; 9.5 Hz, H-4); 6,73 (1H, d, J=16,0 Hz, H-8); 6,27 (1H, dd, J=6,5; 16,0 Hz, H-7); 6,09 (1H, dt, J=2,0; 10,0 Hz, H-3). The $^1$H-NMR spectrum of compound **1** also exhibited the presence of a methylen signal at $\delta_H$ 2,54 (m, 2H, H-5) and a methinoxy signal at $\delta_H$ 5,10 (1H, ddd, J=1.0; 6.5; 15.5 Hz; H-6). The $^{13}$C-NMR and DEPT spectra of compound **1** indicated the presence of 13 carbon atoms in the molecule. There are a carbonyl carbon ($\delta_C$ 163.8), one $CH_2$ group at $\delta_C$ 29.9, one $sp^3$ methine oxygenated carbons at $\delta_C$ 77.9; nine methine $sp^2$ group at $\delta_C$ 121.7-144.5 and one quaternary carbon $sp^3$ at $\delta_C$ 135.8. The signal in COSY spectra allowed correlating from C-3 to C-8. The coupling constants J(16.0 Hz) between H-7 and H-8 indicated that two protons are in trans position. The coupling constants J (9.5 Hz) between H-3 and H-4 indicated that two protons are in cis position. Based on the above evidence and the literature data (Wattanapiromsakul *et al.*, 2005)compound **1** was identified as goniothalamin. This compound is styryl lactone has been isolated from many Goniothalamus species. It has antitumor activity in vitro and in vivo (de Fátima *et al.*, 2005; Mereyala and Joe, 2001; Tian *et al.*, 2006). Furthermore, it has antifungal (Fatima *et al.*, 2008) and antioxidant activity (Kim *et al.*, 2012).

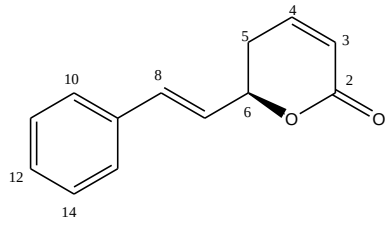


**Fig. 1:** Structures of compound **1.**

***Aristolactam BII (2)***

Compound **2** was obtained as a yellow, crystalline powder, melting point 248-250°C, gave positive result with Dragendorff agent. The IR spectrum showed typical absorption bands arising from NH ($\nu_{max}$ 3449 $cm^{-1}$) and C=O ($\nu_{max}$ 1717 $cm^{-1}$). The UV spectrum in solvent MeOH showed typical maximum absorption wavelength of phenanthrene structure at $\lambda_{max}$ nm (logε): 232 (3.56), 263 (3.49), 276 (3.54), 286 (3.53), 317 (2.97) and 385 (2.94). The molecular formula was established as $C_{17}H_{13}NO_3$ based on a molecular ion peak at *m/z* 302 $[M + Na]^+$. The $^{13}$C-NMR spectra of compound **2** indicated the presence of 17 carbon atoms in the molecule. There are a carbonyl carbon ($\delta_C$ 170.2), two methoxy groups ($\delta_C$ 60.2 and 56.8), six methine $sp^2$ group at $\delta_C$ 106.2; 109.5; 125.8; 127.4; 127.4; 128.9 and eight quaternary carbon $sp^3$.

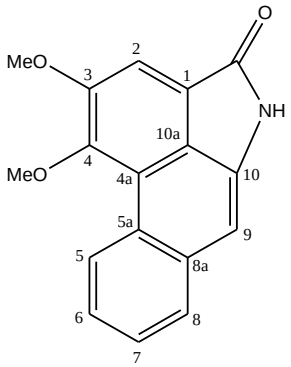


**Fig. 2:** Structures of compound Aristolactam BII (2);

The $^1$H-NMR spectrum of compound **2** exhibited the presence of 6 signals proton of aromatic ring at $\delta_H$ 9.12 (1H, m, H-5); 7.72 (1H, s, H-2); 7.72 (1H, m, H-8); 7.47 (2H, m, H-6 + H-7); 7.00 (1H, s, H-9) and two methoxy groups $OCH_3$at$\delta_H$ 4.02 (3H, s, $OCH_3$); 3.98 (3H, s, $OCH_3$). HMBC spectrum showed the correlation between H-9 with C-8, C-5a, C-8a, C-10a and C-10;

between H-5 with C-7, C-8a and C-5a, between H-8 with C-6, C-7, C-5a and C-9. Then it can deduced the correlation between C-8 with C-8a, C-9, C-10 and C-10a; C-5 with C-5a, C-8a and C-7.There is also the correlation between H-2 with C-3, C-4, C=O and C-1, hence C-2 correlates with C=O through C-1. The correlation between protons of methoxy group ($\delta_H$ 4.02) with C-3 ($\delta_C$ 154.4) and protons of methoxy group ($\delta_H$ 3.98) with C-4 ($\delta_C$ 151.5) indicated that two methoxy $OCH_3$ group linked with carbon C-3 and C-4. Based on the above evidence and the literature data(Marques *et al.,* 2011) compound **2** was identified as Aristolactam BII. This compound has neuroprotective (Kim *et al.,* 2004) and cytotoxicity with P-388 leukemia and A-549 lung adenocarcinoma epithelial cell line (Tsai *et al.,* 2005).

**3-Methyl-1H-benz[f]indole-4,9-dione (3)**

Compound **3** was obtained as a yellow, solid powder. The molecular formula was established as $C_{13}H_9O_2N$ based on a molecular ion peak at *m/z* 212,0710 $[M+H]^+$. The IR spectrum showed typical absorption bands arising from NH ($\nu_{max}$ 3429 $cm^{-1}$) and carbonyl C=O ($\nu_{max}$ 1647 $cm^{-1}$).

The $^1$H-NMR spectrum of compound **3** exhibited the presence of 5 signals proton of aromatic ring at $\delta_H$ 8.08 (1H, m, H-5); 8.01 (1H, m, H-8), 7.59 (2H, m, H-6 and H-7) and 6.83 (1H, m, H-2); and 1 methyl group at $\delta_H$ 2.31 (3H, s). The $^1$H-NMR spectrum of compound **3** also exhibited the presence of a proton NH signal at $\delta_H$ 12.65 (1H, br s, H-1). The $^{13}$C-NMR spectra of compound **3** indicated the presence of 13 carbon atoms in the molecule. There are a methyl group; 5 methine $sp^2$ groups; and 2 carbonyls group at $\delta_C$ 182.3 (C-9) và 175.7 (C-4) and 5 quaternary carbons in aromatic ring at $\delta_C$ 122.8 (C-3), 125.1 (C-3a), 133.4 (C-4a), 134.5 (C-8a) and 132.7 (C-9a).

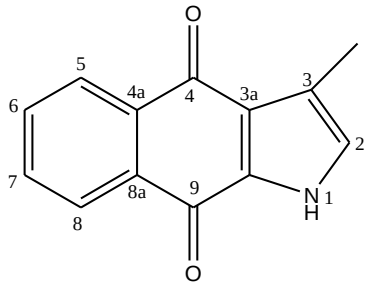


**Fig. 3:** Structures of compound 3-Methyl-1H-benz[f]indole-4,9-dione (**3**).

The signal in COSY spectra allowed determining the correlation from H-3 to H-8. HMBC spectrum showed the correlation between H-5 and H-8 with C-4a and C-8a, confirmed the presence of benzene A ring. Also there are correlations between 2 carbonyls C-4 and C-9 with H-5 and H-8 in HMBC spectrum respectively. It allowed confirming the C-4 and C-9 linked to ring A at position C-4a and C-8a. The pyrole C ring also is determined by HMBC spectrum: H-2 correlates with C-3, C-3a and C-9a; $CH_3$-10 correlates with C-2 and C-3a. The methyl group position at C-3 in pyrole C ring is also confirmed by NOE correlation between H-2 and $CH_3$-10. Based on the above evidence and the literature data (Efdi *et al.,* 2010) compound **3** was identified as 3-methyl-1H-benz[f]indole-4,9-dione. This compound was first isolated from Goniothalamustapis Miq (Efdi *et al.,* 2010).

***Bioactivity***

The result of cytotoxicity tests of isolated compounds against epithelial cancer (KB), liver (Hep G2), breast cancer (MCF-7) and lung (LU-1) cell lines are shown in Table 1.

**Table 1:** Cytotoxicity of isolated compounds

| Compounds | $IC_{50}$ (µg/mL) | | | |
|---|---|---|---|---|
| | KB | HepG2 | LU-1 | MCF7 |
| Compound **1** | 4.18 ± 0.60 | 8.62 ± 1.24 | 8.04 ± 1.18 | 13.31 ± 1.45 |
| Compound **2** | 52.32 ± 5.21 | 85.29 ± 3.47 | 98.34 ± 6.13 | 134.87 ± 7.97 |
| Compound **3** | 67.32 ± 3.73 | 94.53 ± 5.32 | 105.43 ± 2.41 | 167.89 ± 3.54 |

Only compound **1** exhibited strong cytotoxic activity against epithelial cancer (KB), liver (Hep G2), breast cancer (MCF-7) and lung (LU-1) cell lines. Previous study have demonstrated Goniothalamin possess anticancer potential activity through mechanism of induces apoptosis and inhibits TNF-α-induced NF-κB activation (Orlikova *et al.,* 2013; Seyed *et al.,* 2014). For the compounds **2**, **3**, we have found the $IC_{50}$ against fours tested cancer cell line were greater over than ten times as compared with compound **1**.

## CONCLUSION

From the bark of *Goniothalamus chinensis* Merr. & Chun. we have isolated three compounds, Goniothalamin (**1**), Aristolactam BII (**2**), 3-Methyl-1H-benz[f]indole-4,9-dione (**3**). The compound **1** showed the highest potency against the epithelial cancer (KB) cell line with an $IC_{50}$ of 4.18 ± 0.60 µg/mL. Others compounds have weak cytotoxic activity against all cell lines tested.

## CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this paper.

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