# Semisynthesis and Antitumor Activities of New Styryl-Lactone Derivatives

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**Nineteen new derivatives (2—20) of the naturally occurring compound, goniothalamin (1), were prepared by chemical modification and semi-synthetic methods. The antitumor activities of these derivatives and goniothalamin were evaluated *in vitro* against human tumor cell lines, and most of them showed an inhibitory effect against HL-60 cancer cells. The derivatives 10-nitro-goniothalamin (2) and 10-amino-goniothalamin (4) gave selective inhibition concentration ($IC_{50}$) of 1.10 and 1.14 $\mu$g/ml, respectively, against human stomach cancer SGC-7901 cells, while that of etoposide (vp-16) as the positive control was 6.07 $\mu$g/ml. Finally, the partition coefficients, logP ($\pi$ values), of these derivative molecules, were evaluated by calculating the additive approximate organic fragment logP value.**

**Key words** styryl-lactone; semisynthesis; goniothalamin; antitumor activity

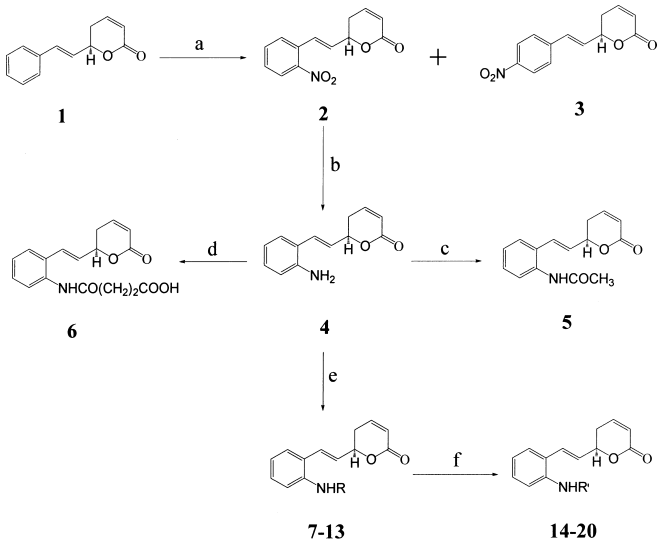
The natural styryl-lactones from *Goniothalamus* species (Annonaceae) possess potent antitumor activities.[1—4] Goniothalamin (**1**), which has been found to have good activity against various tumor cell lines,[5,6] was first isolated as a plant styryl-lactone in 1967 and later obtained from *Goniothalamus griffithii* and other Annonaceae species.[7—9] However, semisynthesis study of goniothalamin derivatives has been scant so far, and none of them advanced to activity experiments.[3,10] Goniothalamin is a good starting material, because it is abundant in several *Goniothalamus* species and possesses lower oxidation activity compared with other styryl-lactones.[7] Some derivatives of 10- and 12-substituted goniothalamin were synthesized. Furthermore, in order to improve the water solubility of the compounds, a series of derivatives with a variety of different $\alpha$-amino acid groups were also prepared with moderate yield, and their partition coefficients, logP or $\pi$ values were calculated by the approximate additive organic fragmental method.

The present paper concerns the semi-synthesis and antitumor activities of nineteen new styryl-lactone derivatives in the goniothalamin series (**2**—**20**).

## Results and Discussion

The general methods employed for the preparation of styryl-lactone derivatives **2**—**20** are outlined in Chart 1. The nitration of **1** in acetic anhydride with a mixture of concentrated nitric acid and glacial acetic acid afforded two nitro-goniothalamin derivatives, 10-nitro-goniothalamin (**2**) and 12-nitro-goniothalamin (**3**) in 52% and 11% yields, respectively.[11] Subsequent reduction of the nitro group in **2** was attempted under different sets of conditions.[12,13] Firstly, when Fe/HCl was used as the reductant, the reactant disappeared but no target product was obtained. Then, by sodium hydrosulfite in methanol/water (90%) at room temperature (rt), **2** was reduced to 10-amino-goniothalamin (**4**) in a low yield of 5%. In the condition using 0.5 M stannous chloride dihydrate (14 eq) in *N*,*N*-dimethylformamide (DMF)/dichloromethane (1 : 1), **2** was successfully reduced to **4** in moderate yield (61%). Acetylization of **4** with $Ac_2O$ at rt gave 10-acetyl-amino-goniothalamin (**5**) in satisfactory yield (92%).[14] A suspension of the amine **4** and succinic anhydride in dry $CH_2Cl_2$ was stirred at rt for 6 h to give 10-(hydroxysuccinyl)-amino-goniothalamin (**6**) in 60% yield.[15] The amino acid derivatives **14**—**20** were obtained as trifluoroacetate salts in good yield by reacting **4** with various *N*-*tert*-butoxycarbonyl (*t*-Boc)-protected amino acids in the presence of dicyclohexylcarbodiimide (DCC), and successive deprotection by trifluoroacetic acid (TFA) in dichloromethane.[16] All compounds were unambiguously confirmed by spectroscopic methods.

The antitumor activities of these derivatives were measured *in vitro* using a SRB (Sulforhodamine B) assay against human promyelocytic leukemia HL-60 and human hepatoma BEL-7402 cells. Compounds **2**—**5**, which possessed significant activity against HL-60 cells, were selected for further evaluation against human lung carcinoma A549 and human stomach cancer SGC-7901 cells with the reference com-




Reagents and conditions:

a. $HNO_3/Ac_2O$, rt, 2 h; b. $SnCl_2 2H_2O$, DMF-$CH_2Cl_2$ (1:1), rt, 3 h; c. $Ac_2O$, rt, 40 min; d. succinic anhydride, $CH_2Cl_2$, rt, 6 h; e. RCOOH, DCC/$CH_2Cl_2$, rt; f. TFA, $CH_2Cl_2$, rt.

Chart 1. The Scheme of the Semisynthesis of Goniothalamin Derivatives

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pound, goniothalamin. For two reasons, VP-16 (etoposide, **21**) was chosen as a positive control standard. First, the etoposide is also the derivative of a naturally originated compound. Secondly, it had consecutively been used as the control standard in our previous antitumor tests of the natural styryllactones isolated from Goniothalamus plants.[9] The results, expressed as $IC_{50}$ values, are summarized in Table 2.

In the antitumor tests, the semi-synthetic styryllactone derivatives **2**, **3** and **4**, as well as goniothalamin (**1**) showed stronger inhibitory effects ($IC_{50}$ 1.07—1.56 $\mu$g/ml) than the positive control drug etoposide ($IC_{50}$ 6.07 $\mu$g/ml) against the tumor cell strain SGC-7901 (human stomach tumor), even though most of the derivatives generally gave lower inhibition to HL-60, Bel-7402 tumor cell lines (Table 2).

The compounds **2**, **3** and **4**, however, showed comparable or superior activity against HL-60, A549 or SGC-7901 cells in comparison to their parent **1** (Table 2). Compound **2** of the main product in nitration was chosen as the starting material for the next step reaction, and subsequent reduction easily gave the amine **4**. Its antitumor activity was similar to **3**. It was noticeable that the formation of the acylamino group of the 10-position made the $IC_{50}$ of the derivatives increase dramatically, from 0.64 to 3.30 $\mu$g/ml for A549 cells, and from 1.14 to 25 $\mu$g/ml for SGC-7901 cells (Table 2). It was assumed that the carbonyl group in the acylamide distributed the lone electrons in the nitrogen because of the conjugated effect, and this indicated that the free amino group at the 10-position was favorable for its antitumor activity. Further study could explore in detail how the substituents at C-10 affect the antitumor activity after the conversion of an amino group in the amine **4** to other substituted groups. Additionally, several amino acid trifluoroacetate derivatives (**15**, **17**, **18**, **20**) showed comparable activity against HL-60 cells to the amine **4**, but were less active than parent **1**. The data obtained indicated that the introduction of amino acid groups could not enhance the antitumor activity *in vitro*.

Table 1. Styryl-lactone Derivatives **7**—**20** and Their Corresponding Yields

| Compd. | R | % Yield | Compd. | R′ | % Yield |
|---|---|---|---|---|---|
| **7** | NHBoc-L-Gly | 77 | **14** | L-Gly[a] | 59 |
| **8** | NHBoc-L-Ala | 81 | **15** | L-Ala[a] | 69 |
| **9** | NHBoc-L-Val | 90 | **16** | L-Val[a] | 85 |
| **10** | NHBoc-L-Leu | 68 | **17** | L-Leu[a] | 85 |
| **11** | NHBoc-L-Ile | 92 | **18** | L-Ile[a] | 91 |
| **12** | NHBoc-L-Gln | 80 | **19** | L-Gln[a] | 65 |
| **13** | NHBoc-L-Phe | 78 | **20** | L-Phe[a] | 59 |

*a*) Obtained as trifluoroacetate salt.

The approximate calculating logP ($\pi$ value), or log of the partition coefficient, for a molecule was used for evaluating the water solubility of the derivatives. P is logarithmically related to free energy, generally expressed as logP, and is therefore the sum of the hydrophobic and hydrophilic characteristics of the organic functional groups making up the structure of the molecule.[17] According to the $\pi$ value for organic fragments,[18—20] each derivative compound in this experiment was calculated and included in Table 2. The higher logP value corresponds to the stronger hydrophobic or weaker hydrophilic nature of the molecule.

After the chemical modification, most of the amino acid derivatives of gonithalamin which possessed higher logP values (+4.8 to +7.3), expressed poor antitumor activities against HL-60 cells ($IC_{50}$ was 2—3 $\mu$g/ml); meanwhile the compounds **1**, **2** and **3**, whose logP values were +4.4 to +4.7, possessed good activities ($IC_{50}$ was 0.18—0.68 $\mu$g/ml). In addition, different amino moieties in the styryllactone derivatives resulted in little difference in antitumor activity.

## Experimental

**General** $^1$H- and $^{13}$C-NMR spectra ($\delta$ ppm, $J$ in Hz) were run at 400 and 100 MHz on a Mercury Plus 400 NMR spectrometer. EI/MS were recorded on an Agilent 5973 spectrometer. ESI/MS and HR- (high resolution) ESI/MS were performed on a Q-Tof microspectrometer. MALDI/MS (matrix-assisted laser desorption-ionization) and HR-MALDI/MS were taken on an IonSpec 4.7 Tesla FT (Fourier transform) spectrometer. Silica gel TLC plates were observed under UV light (254 nm) and after being sprayed with 20% (v/v) $H_2SO_4$ in ethanol.

**Extraction and Isolation** Dried and powdered leaves (10 kg) of *G. griffithii* were extracted with alcohol and concentrated. The extract was dissolved in MeOH–$H_2O$ (1 : 9) and was extracted with petroleum. After being concentrated, 120 g of brown resin was subjected to silica gel chromatography, eluted with a gradient of petroleum/ethyl acetate, which gave goniothalamin (**1**) 8.0 g (colorless crystal, *Rf*=0.22 petroleum/ethyl acetate (v/v 8 : 2)), structurally confirmed by comparing its $^1$H- and $^{13}$C-NMR data with those reported.[6]

**Bioassays** Live cancer cells were established by using Trypan blue stain, and cell generation was measured by means of the SRB method. All test compounds were solubilized in DMSO. Each compound concentration was tested in quadruplicate wells. The cancer cells, cultured in 10% bovine serum, were digested with trypsin solution. The cancer cells at a concentration of $1\times10^5$ cells/ml were inoculated into every cell of a 96-well dish and cultured at 37 °C in 5% $CO_2$ for 48 h. The cellular proteins were precipitated to the plates with trichloroacetic acid and stained with 0.4% SRB. Protein bound SRB was solubilized with Tris base and read at 515 nm in an ELISA reader. The protein content of the compound-treated cells was compared to that of the DMSO control, and $IC_{50}$ values were obtained.

**Preparation of Compounds 2 and 3** To an acetic anhydride (45 ml) solution of **1** (3050 mg, 15 mmol) was added dropwise at 0 °C concentrated nitric acid and glacial acetic acid (18 ml 1 : 3) for 1.5 h. After the addition was complete, the mixture was stirred at rt for 2 h, then ice and $CH_2Cl_2$ was added, and the reaction products were extracted into $CH_2Cl_2$. The residue

Table 2. Antitumor Activities of Styryl-lactone Derivatives[a]

| Compd. | HL-60[b] | BEL-7402[c] | A549[d] | SGC-7901[e] | LogP[g] | Compd. | HL-60[b] | BEL-7402[c] | LogP[g] |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 0.58 | 4.13 | 0.35 | 1.07 | +4.7 | **8** | 3.92 | 31.34 | +5.3 |
| **2** | 0.68 | 8.17 | 0.33 | 1.10 | +4.4 | **9** | 3.81 | | +6.0 |
| **3** | 0.18 | 26.88 | 1.90 | 1.56 | +4.4 | **13** | 2.51 | 26.27 | +7.3 |
| **4** | 2.27 | 24.08 | 0.64 | 1.14 | +3.3 | **15** | 2.54 | | +4.0 |
| **5** | 2.45 | 32.62 | 3.30 | 25.00 | +3.4 | **17** | 3.21 | 31.00 | +5.5 |
| **7** | 3.11 | 29.90 | | | +4.8 | **18** | 3.21 | | +5.5 |
| **21**[f] | 0.13 | 15.28 | 0.19 | 6.07 | | **20** | 2.28 | 13.96 | +6.3 |

*a*) Inhibition of HL-60, BEL-7402, A549, and SGC-7901 proliferation as measured by SRB assay, $IC_{50}$, $\mu$g/ml. *b*) $IC_{50}$ of compounds **6**, **10**, **11**, **14**, **16** and **19** with $IC_{50}$ >5 $\mu$g/ml. *c*) $IC_{50}$ of compounds **6**, **9**—**12**, **14**—**16**, and **18**—**19** with $IC_{50}$ >40 $\mu$g/ml. *d*) Compounds **6**—**20** not tested. *e*) Compounds **6**—**20** not tested. *f*) Positive control standard (VP-16). *g*) The approximate fragment $\pi$ values for the calculations is listed in Experimental.

was subjected to column chromatography on silica gel (petroleum : ethyl acetate=37 : 19) to afford 1901 mg of **2** (52%) and 400 mg of **3** (11%).

10-Nitro-goniothalamin (**2**): Yellow solid, *Rf*=0.24 petroleum/ethyl acetate (v/v 66 : 34) $^1$H-NMR (acetone-$d_6$) $\delta$: 7.98 (1H, dd, *J*=8.05, 1.22 Hz, Ar-H), 7.81 (1H, dd, *J*=8.04, 1.22 Hz, Ar-H), 7.70 (1H, ddd, *J*=7.80, 7.30, 1.22 Hz, Ar-H), 7.55 (1H, ddd, *J*=7.80, 7.60, 1.22 Hz, Ar-H), 7.11 (1H, d, *J*=15.85 Hz, H-8), 7.07—7.03 (1H, m, H-4), 6.47 (1H, dd, *J*=15.85, 6.09 Hz, H-7), 5.99—5.96 (1H, m, H-3), 5.24—5.19 (1H, m, H-6), 2.73—2.65 (1H, m, H-5), 2.60—2.51 (1H, m, H-5). EI/MS *m/z* 246 $(M+H)^+$. HR-MALDI/MS Calcd $C_{13}H_{12}NO_4$ $(M+H)^+$: 246.0761, Found 246.0770.

12-Nitro-goniothalamin (**3**): Yellow powder, *Rf*=0.23 petroleum/ethyl acetate (v/v 65 : 35) $^1$H-NMR (acetone-$d_6$) $\delta$: 8.22 (2H, dt, *J*=8.84, 2.46, 1.96 Hz, Ar-H), 7.78 (2H, dt, *J*=8.59, 2.46, 1.96 Hz, Ar-H), 7.08—7.04 (1H, m, H-4), 6.91 (1H, d, *J*=15.97 Hz, H-8), 6.71 (1H, dd, *J*=15.97, 5.89 Hz, H-7), 5.99 (1H, m, H-3), 5.24—5.19 (1H, m, H-6), 2.74—2.52 (2H, m, H-5). EI/MS *m/z* 245 $M^+$ HR-MALDI/MS Calcd $C_{13}H_{12}NO_4$ $(M+H)^+$: 246.0761, Found 246.0750.

**10-Amino-goniothalamin (4)** **2** (800 mg, 3.3 mmol) was treated with tin(II) chloride dihydrate (10310 mg, 45.7 mmol) in DMF/$CH_2Cl_2$ (91 ml, 1 : 1) under $N_2$ for 3 h at rt. The $CH_2Cl_2$ was removed *in vacuo* at rt. The remaining solution was adjusted to pH 8 with 10% $Na_2CO_3$ (aq.), and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, then dried over anhydrous $Na_2SO_4$. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel (petroleum : ethyl acetate=3 : 2) to afford **4** as a yellow solid (425 mg, 61%). Compound **4**: *Rf*=0.25 petroleum/ethyl acetate (v/v 58 : 42) $^1$H-NMR ($CDCl_3$) $\delta$: 7.25 (1H, dd, *J*=7.42, 1.17 Hz, Ar-H), 7.10 (1H, ddd, *J*=7.80, 7.42, 1.17 Hz), 6.95—6.90 (1H, m, H-4), 6.80 (1H, d, *J*=15.61 Hz, H-8), 6.76 (1H, t, *J*=7.42 Hz, Ar-H), 6.69 (1H, dd, *J*=7.80, 1.17 Hz, Ar-H), 6.16 (1H, dd, *J*=15.61, 6.25 Hz, H-7), 6.09 (1H, dt, *J*=9.75, 1.95, 1.57 Hz, H-3), 5.12—5.07 (1H, m, H-6), 3.81 (2H, br s, N$\underline{H}_2$), 2.56—2.52 (2H, m, H-5). EI/MS *m/z* 215 $M^+$ HR-MALDI/MS Calcd $C_{13}H_{14}NO_2$ $(M+H)^+$: 216.1038, Found 216.1029.

**10-Acetylamino-goniothalamin (5)** The mixture of **4** (20 mg, 0.09 mmol) and $Ac_2O$ (1.0 ml). was stirred for 40 min at rt. Water and $CHCl_3$ was added to the reaction mixture and the organic layer was washed with water. The organic solvent was evaporated under reduced pressure. The residue was purified by silical gel column chromatography ($CHCl_3$ : MeOH= 96 : 1.5) to give **5** (22 mg, 92%) as a yellow amorphous powder. Compound **5**: *Rf*=0.22 petroleum/ethyl acetate (v/v 17 : 83) $^1$H-NMR ($CDCl_3$) $\delta$: 7.67 (1H, d, *J*=7.65 Hz, Ar-H), 7.42 (1H, br, N$\underline{H}$), 7.39 (1H, d, *J*=7.75 Hz, Ar-H), 7.27 (1H, t, *J*=7.75 Hz, Ar-H), 7.14 (1H, t, *J*=7.75 Hz, Ar-H), 6.94—6.90 (1H, m, H-4), 6.83 (1H, d, *J*=15.92 Hz, H-8), 6.15 (1H, dd, *J*=15.91, 6.13 Hz, H-7), 6.07 (1H, d, *J*=9.79 Hz, H-3), 5.12—5.07 (1H, m, H-6), 2.55—2.52 (2H, m, H-5), 2.20 (3H, s, C$\underline{H}_3$). $^{13}$C-NMR ($CDCl_3$) $\delta$: 168.3 (NH$\underline{C}$O), 163.3 (C-2), 144.4 (C-4), 134.2 (C-9), 128.8 (C-10), 128.6 (s), 128.3 (s×2), 126.4 (s), 125.4 (s), 124.5 (s), 121.2 (C-3), 77.9 (C-6), 30.1 (C-5), 24.5 ($\underline{C}H_3$). EI/MS *m/z* 257 $M^+$ HR-MALDI/MS Calcd $C_{15}H_{15}NO_3Na$ $(M+Na)^+$: 280.0944, Found 280.0955.

**10-(Hydroxysuccinyl)amino-goniothalamin (6)** A suspension of the amine **4** (15 mg, 0.07 mmol) and succinic anhydride (120 mg, 1.20 mmol) in dry $CH_2Cl_2$ (3 ml) was stirred for 6 h at rt. The solids were filtered and the filtrate was concentrated and chromatographed ($CHCl_3$ : MeOH=46 : 4) to give **6** as a yellow amorphous solid (13 mg, 60%). Compound **6**: *Rf*=0.25 $CHCl_3$/MeOH (v/v 9 : 1) $^1$H-NMR ($CDCl_3$) $\delta$: 8.21 (1H, br s, N$\underline{H}$), 7.65 (1H, d, *J*=7.80 Hz, Ar-H), 7.45 (1H, d, *J*=6.64 Hz, Ar-H), 7.28 (1H, t, *J*= 7.60 Hz, Ar-H), 7.14 (1H, t, *J*=7.81 Hz, Ar-H), 7.04—7.00 (1H, m, H-4), 6.95 (1H, d, *J*=16.00 Hz, H-8), 6.16—6.11 (2H, m, H-4, H-7), 5.21—5.16 (1H, m, H-6), 2.84—2.45 (6H, m, H-5, COC$\underline{H}_2$C$\underline{H}_2$COOH). $^{13}$C-NMR ($CDCl_3$) $\delta$: 174.9 ($\underline{C}$OOH), 170.5 (NH$\underline{C}$O), 165.5 (C-2), 145.9 (C-4), 134.1 (C-9), 128.6 (C-10), 128.3 (s), 126.3 (s), 126.0 (s), 125.3 (s), 125.0 (s), 124.9 (s), 120.8 (C-3), 77.2 (C-6), 32.5 (s), 30.6 (s), 30.4 (s). EI/MS *m/z* 315 $M^+$ HR-MALDI/MS Calcd $C_{17}H_{18}NO_5$ $(M+H)^+$: 316.1180, Found 316.1190.

**10-(*N*-$\alpha$-*tert*-Butoxycarbonyl-L-glycyl)amino-goniothalamin (7)** To a stirred solution of **4** (30 mg, 0.14 mmol) and *N-tert*-butoxycarbonyl-L-glycine (147 mg, 0.84 mmol) in $CH_2Cl_2$ (3.5 ml), DCC (173 mg, 0.84 mmol) was added. The reaction mixture was stirred at rt for 1.5 h and the solids were filtered. The filtrate was concentrated *in vacuo* and the residue was chromatographed (petroleum : ethyl acetate=8 : 5). Initially obtained was **7** as a white amorphous solid (40 mg, 77%). Compound **7**: *Rf*=0.24 petroleum/ethyl acetate (v/v 53 : 47) $^1$H-NMR ($CDCl_3$) $\delta$: 8.37 (1H, br s, N$\underline{H}$CO), 7.64 (1H, d, *J*=8.22 Hz, Ar-H), 7.39 (1H, d, *J*=7.44 Hz, Ar-H), 7.25 (1H, t, *J*=7.43 Hz, Ar-H), 7.13 (1H, t, *J*=7.43 Hz, Ar-H), 6.94—6.89 (1H, m, H-4), 6.80 (1H, d, *J*=15.65 Hz, H-8), 6.15 (1H, dd, *J*=15.65, 6.24 Hz, H-7), 6.06 (1H, d, *J*=10.18 Hz, H-3), 5.64 (1H, br, N$\underline{H}$Boc), 5.10—5.05 (1H, m, H-6), 3.95 (2H, d, *J*=4.30 Hz, Gly C$\underline{H}_2$), 2.56—2.54 (2H, m, H-5), 1.43 (9H, s, Boc C$\underline{H}_3$×3). MALDI/MS *m/z* 395 $(M+Na)^+$ HR-MALDI/MS Calcd $C_{20}H_{24}N_2O_5$ $(M+Na)^+$: 395.1577, Found 395.1585.

**10-(*N*-$\alpha$-*tert*-Butoxycarbonyl-L-alanyl)amino-goniothalamin (8)** A mixture of DCC (35 mg, 0.17 mmol), compound **4** (24 mg, 0.11 mmol), and *N-tert*-butoxycarbonyl-L-alanine (32 mg, 0.17 mmol) in $CH_2Cl_2$ (2.0 ml) was stirred for 1 h at rt. The solids were filtered and the filtrate was concentrated and chromatographed (petroleum : ethyl acetate=3 : 2) to give **8** as a yellow amorphous solid (35 mg, 81%). Compound **8**: *Rf*=0.23 petroleum/ethyl acetate (v/v 6 : 4) $^1$H-NMR ($CDCl_3$) $\delta$: 8.42 (1H, br s, N$\underline{H}$CO), 7.70 (1H, t, *J*= 7.82 Hz, Ar-H), 7.40 (1H, d, *J*=7.82 Hz, Ar-H), 7.25 (1H, t, *J*=7.43 Hz, Ar-H), 7.13 (1H, t, *J*=7.83, 7.43 Hz, Ar-H), 6.94—6.87 (1H, m, H-4), 6.82 (1H, d, *J*=16.04 Hz, H-8), 6.17 (1H, dd, *J*=15.65, 6.65 Hz, H-7), 6.07—6.04 (1H, dm, H-3), 5.31—5.28 (1H, br, N$\underline{H}$Boc), 5.11—5.04 (1H, m, H-6), 4.34 (1H, d, Ala $\alpha$-C$\underline{H}$), 2.56—2.54 (2H, m, H-5), 1.45—1.41 (12H, m, Ala $\beta$-C$\underline{H}_3$ and Boc C$\underline{H}_3$×3). Compound **8**: ESI/MS *m/z* 387 $(M+H)^+$ HR-ESI/MS Calcd $C_{21}H_{26}N_2O_5Na$ $(M+Na)^+$: 409.1742, Found 409.1739.

**10-(*N*-$\alpha$-*tert*-Butoxycarbonyl-L-valyl)amino-goniothalamin (9)** To a solution of **4** (25 mg, 0.12 mmol), *N-tert*-butoxycarbonyl-L-valine (78 mg, 0.36 mmol) and $CH_2Cl_2$ (3.0 ml) was added DCC (74 mg, 0.36 mmol). The solution was stirred for 12 h at rt, filtered, and concentrated. The residue was chromatographed (petroleum : ethyl acetate=32 : 18) to give **9** as a yellow amorphous solid (43 mg, 90%). Compound **9**: *Rf*=0.26 petroleum/ethyl acetate (v/v 6 : 4) $^1$H-NMR ($CDCl_3$) $\delta$: 8.39 (1H, br, N$\underline{H}$CO), 7.60 (1H, t, *J*= 9.39, 8.21 Hz, Ar-H), 7.41 (1H, d, *J*=7.83 Hz, Ar-H), 7.24 (1H, t, *J*=7.82, 7.43 Hz, Ar-H), 7.13 (1H, t, *J*=7.82, 7.43 Hz, Ar-H), 6.90—6.80 (1H, m, H-4), 6.78 (1H, d, *J*=16.00 Hz, H-8), 6.15 (1H, dd, *J*=16.00, 6.66 Hz, H-7), 6.01 (1H, t, *J*=9.39, 8.61 Hz, H-3), 5.37 (1H, br, N$\underline{H}$Boc), 5.03—4.93 (1H, m, H-6), 4.16—4.10 (1H, m, Val $\alpha$-C$\underline{H}$), 2.49—2.39 (2H, m, H-5), 2.25—2.19 (1H, m, Val $\beta$-C$\underline{H}$), 1.39 (9H, d, *J*=5.86 Hz, Boc C$\underline{H}_3$×3), 1.04—0.98 (6H, m, Val $\beta$-C$\underline{H}_3$ and $\gamma$-C$\underline{H}_3$). MALDI/MS *m/z* 437 $(M+Na)^+$ HR-MALDI/MS Calcd $C_{23}H_{30}N_2O_5Na$ $(M+Na)^+$: 437.2047, Found 437.2053.

**10-(*N*-$\alpha$-*tert*-Butoxycarbonyl-L-leucyl)amino-goniothalamin (10)** A mixture of DCC (49 mg, 0.24 mmol), compound **4** (25 mg, 0.12 mmol), *N-tert*-butoxycarbonyl-L-leucine (55 mg, 0.24 mmol), and $CH_2Cl_2$ (2.0 ml) was stirred at rt for 12 h. The solids were filtered and the filtrate was concentrated and chromatographed (petroleum : ethyl acetate=35 : 15) to give **10** as a white powder (34 mg, 68%). Compound **10**: *Rf*=0.32 petroleum/ethyl acetate (v/v 6 : 4) $^1$H-NMR ($CDCl_3$) $\delta$: 8.40 (1H, br, N$\underline{H}$CO), 7.69 (1H, d, *J*= 8.22 Hz, Ar-H), 7.40 (1H, d, *J*=7.44 Hz, Ar-H), 7.25 (1H, t, *J*=7.83 Hz, Ar-H), 7.13 (1H, t, *J*=7.83, 7.43 Hz, Ar-H), 6.93—6.84 (1H, m, H-4), 6.82 (1H, d, *J*=16.04 Hz, H-8), 6.27 (1H, dd, *J*=16.04, 6.26 Hz, H-7), 6.07—6.03 (1H, m, H-3), 5.21 (1H, br, N$\underline{H}$Boc), 5.09—5.00 (1H, m, H-6), 4.30 (1H, s, Leu $\alpha$-C$\underline{H}$), 2.56—2.48 (2H, m, H-5), 1.78—1.74 (2H, m, Leu $\beta$-C$\underline{H}_2$), 1.61—1.57 (1H, m, Leu $\gamma$-C$\underline{H}$), 1.41 (9H, d, *J*=5.09 Hz, Boc C$\underline{H}_3$×3), 0.98—0.94 (6H, m, Leu C$\underline{H}_3$×2). MALDI/MS *m/z* 451 $(M+Na)^+$ HR-MALDI/MS Calcd $C_{24}H_{32}N_2O_5Na$ $(M+Na)^+$: 451.2203, Found 451.2208.

**10-(*N*-$\alpha$-*tert*-Butoxycarbonyl-L-isoleucyl)amino-goniothalamin (11)** A mixture of DCC (62 mg, 0.30 mmol), compound **4** (17 mg, 0.08 mmol), *N-tert*-butoxycarbonyl-L-isoleucine (70 mg, 0.30 mmol), and $CH_2Cl_2$ (2.0 ml) was stirred at rt for 24 h. The solids were filtered and the filtrate was concentrated and chromatographed (petroleum : ethyl acetate=35 : 15) to give **11** as a white amorphous powder (31 mg, 92%). Compound **11**: *Rf*=0.29 petroleum/ethyl acetate (v/v 6 : 4) $^1$H-NMR ($CDCl_3$) $\delta$: 8.26 (1H, br, N$\underline{H}$CO), 7.64 (1H, t, *J*=8.21 Hz, Ar-H), 7.42 (1H, d, *J*=7.83 Hz, Ar-H), 7.26 (1H, t, *J*=8.21 Hz, Ar-H), 7.15 (1H, t, *J*=7.83, 7.43 Hz, Ar-H), 6.92—6.82 (1H, m, H-4), 6.80 (1H, d, *J*=15.65 Hz, H-8), 6.17 (1H, dd, *J*=16.04, 6.55 Hz, H-7), 5.28 (1H, br, N$\underline{H}$Boc), 5.06—4.97 (1H, m, H-6), 4.18—4.08 (1H, m, Ile $\alpha$-C$\underline{H}$), 2.53—2.43 (2H, m, H-5), 2.03—1.97 (1H, m, Ile $\beta$-C$\underline{H}$), 1.59 ( m, 1H, Ile $\gamma$-C$\underline{H}_{2a}$), 1.41 (9H, d, *J*=5.87 Hz, Boc C$\underline{H}_3$×3), 1.26—1.16 (2H, m, Ile $\gamma$-C$\underline{H}_{2b}$), 1.01 (3H, dd, *J*=7.65, 2.34 Hz, Ile $\beta$-C$\underline{H}_3$), 0.92 (3H, t, *J*=7.44 Hz, Ile $\gamma$-C$\underline{H}_3$). MALDI/MS *m/z* 451 $(M+Na)^+$ HR-MALDI/MS Calcd $C_{24}H_{32}N_2O_5Na$ $(M+Na)^+$: 451.2203, Found 451.2207.

**10-(*N*-$\alpha$-*tert*-Butoxycarbonyl-L-glutaminyl)amino-goniothalamin (12)** A mixture of DCC (62 mg, 0.30 mmol), compound **4** (21 mg, 0.10 mmol), *N-tert*-butoxycarbonyl-L-glutamine (74 mg, 0.30 mmol), and $CH_2Cl_2$ (2.0 ml) was stirred at rt for 2 h. The solids were filtered and the filtrate was concentrated and chromatographed ($CHCl_3$ : $CH_3OH$=50 : 1) to give **12** as a foam (34 mg, 80%). Compound **12**: *Rf*=0.20 $CHCl_3$/MeOH (v/v 96 : 4) $^1$H-NMR ($CDCl_3$) $\delta$: 9.01 (1H, br, N$\underline{H}$CO), 7.51 (1H, s, Ar-H), 7.41 (1H, dd, *J*=7.83, 7.43 Hz, Ar-H), 7.22 (1H, t, *J*=7.43 Hz, Ar-H), 7.13 (1H, t, *J*=7.43 Hz, Ar-H), 6.93—6.82 (2H, m, H-8, H-4), 6.75 (1H, br, N$\underline{H}$Boc), 6.34 (1H, br, N$\underline{H}$),

6.17—6.00 (3H, m, NH, H-7, H-3), 5.11—5.06 (1H, m, H-6), 4.41—4.37 (1H, m, Gln α-CH), 2.54—2.42 (4H, m, H-5, Gln γ-$CH_2$), 2.18—2.01 (2H, m, Gln β-$CH_2$), 1.42 (9H, s, Boc $CH_3$×3). ESI/MS *m/z* 444 $(M+H)^+$ HR-ESI/MS Calcd $C_{23}H_{29}N_3O_6Na$ $(M+Na)^+$: 466.1954, Found 466.1956.

**10-(*N*-α-*tert*-Butoxycarbonyl-L-phenylalanyl)amino-goniothalamin (13)** A mixture of DCC (56 mg, 0.27 mmol), compound **4** (19 mg, 0.09 mmol), *N-tert*-butoxycarbonyl-L-phenylalanine (72 mg, 0.27 mmol) and $CH_2Cl_2$ (2.0 ml) was stirred at rt for 2 h. The solids were filtered, the filtrate concentrated and then chromatographed (petroleum : ethyl acetate = 33 : 17) to give **13** as a white powder (32 mg, 78%). Compound **13**: *Rf*=0.22 petroleum/ethyl acetate (v/v 64 : 36) $^1$H-NMR ($CDCl_3$) δ: 7.93 (1H, br, NHCO), 7.66—7.59 (1H, m, Ar-H), 7.38 (1H, d, *J*=7.81 Hz, Ar-H), 7.31—7.22 (6H, m, Ar-H, Phe-H), 7.15 (1H, t, *J*=7.42 Hz, Ar-H), 6.94—6.88 (1H, m, H-4), 6.53 (1H, d, *J*=16.00 Hz, H-8), 6.11 (1H, dd, *J*=16.00, 6.63 Hz, H-7), 6.10—6.06 (1H, m, H-3), 5.25 (1H, br, NHBoc), 5.04—4.96 (1H, m, H-6), 4.50 (1H, d, *J*=6.25 Hz, Phe α-CH), 3.23—3.10 (2H, m, Phe β-$CH_2$), 2.53—2.50 (2H, m, H-5), 1.41 (9H, s, Boc $CH_3$×3). MALDI/MS *m/z* 485 $(M+Na)^+$ HR-MALDI/MS Calcd $C_{27}H_{30}N_2O_5Na$ $(M+Na)^+$: 485.2047, Found. 485.2047.

**10-(α-L-Glycyl)amino-goniothalamin Trifluoroacetate (14)** To a solution of trifluoroacetic acid (0.5 ml) and methylene chloride (1.5 ml) was added **7** (18 mg, 0.05 mmol), and the mixture was stirred 1 h at rt. The solvent was removed *in vacuo* and the residue was chromatographed ($CHCl_3$ : MeOH = 50 : 2) to give **14** as a yellow solid (11 mg, 59%). Compound **14**: *Rf*=0.21 $CHCl_3$/MeOH (v/v 92 : 8) $^1$H-NMR ($CD_3OD$) δ: 7.63 (1H, dd, *J*=7.81, 1.58 Hz, Ar-H), 7.44 (1H, d, *J*=7.81 Hz, Ar-H), 7.32 (1H, t, *J*=7.81, 7.41 Hz, Ar-H), 7.26 (1H, t, *J*=7.41 Hz, Ar-H), 7.09 (1H, m, H-4), 6.90 (1H, d, *J*=16.00 Hz, H-8), 6.36 (1H, dd, *J*=16.00, 6.24 Hz, H-7), 6.06—6.03 (1H, m, H-3), 5.21—5.16 (1H, m, H-6), 3.85 (2H, s, Gly $CH_2$), 2.70—2.52 (2H, m, H-5). ESI/MS *m/z* 385 $(M-H)^-$ HR-ESI/MS Calcd $C_{17}H_{16}F_3N_2O_5$ $(M-H)^-$: 385.1011, Found 385.1015.

**10-(α-L-Alanyl)amino-goniothalamin Trifluoroacetate (15)** **8** (38 mg, 0.10 mmol) was dissolved in $CH_2Cl_2$ (1.0 ml) and added to a stirring solution of TFA (0.5 ml) and $CH_2Cl_2$ (0.5 ml). The mixture was stirred 1 h at rt, then the solvent was removed *in vacuo* and chromatographed ($CHCl_3$ : MeOH = 45 : 5) to give **15** (27 mg, 69%) as a foam. Compound **15**: *Rf*=0.18 $CHCl_3$/MeOH (v/v 94 : 6) $^1$H-NMR ($CD_3OD$) δ: 7.64 (1H, d, *J*=7.82 Hz, Ar-H), 7.38 (1H, d, *J*=7.83 Hz, Ar-H), 7.34—7.26 (2H, m, Ar-H), 7.10—7.06 (1H, m, H-4), 6.87 (1H, d, *J*=15.65 Hz, H-8), 6.36 (1H, dd, *J*=15.65, 6.26 Hz, H-7), 6.04 (1H, dd, *J*=9.78, 1.17 Hz, H-3), 5.20—5.15 (1H, m, H-6), 4.04 (1H, q, *J*=7.42 Hz, Ala α-CH), 2.60 (2H, m, H-5), 1.60 (3H, d, *J*=7.04 Hz, Ala β-$CH_3$). ESI/MS *m/z* 399 $(M-H)^-$ HR-ESI/MS Calcd $C_{18}H_{18}F_3N_2O_5$ $(M-H)^-$: 399.1168, Found 399.1171.

**10-(α-L-Valyl)amino-goniothalamin Trifluoroacetate (16)** To a solution of TFA (0.5 ml) and $CH_2Cl_2$ (1.5 ml) was added **9** (32 mg, 0.08 mmol), and the mixture was stirred 1 h at rt. The solvent was removed under reduced pressure and the residue was chromatographed ($CHCl_3$ : MeOH = 48 : 2) to give **16** as a yellow solid (28 mg, 85%). Compound **16**: *Rf*=0.19 $CHCl_3$/MeOH (v/v 97 : 3) $^1$H-NMR ($CD_3OD$) δ: 7.61 (1H, dd, *J*=7.80, 1.17 Hz, Ar-H), 7.45 (1H, dd, *J*=7.81, 1.17 Hz, Ar-H), 7.31 (1H, t, *J*=7.81, 7.41 Hz, Ar-H), 7.24 (1H, t, *J*=7.41 Hz, Ar-H), 7.10—7.05 (1H, m, H-4), 6.92 (1H, d, *J*=15.61 Hz, H-8), 6.35 (1H, dd, *J*=15.61, 6.22 Hz, H-7), 6.04 (1H, m, H-3), 5.20—5.15 (1H, m, H-6), 3.37 (1H, d, *J*=5.07 Hz, Val α-CH), 2.69—2.51 (2H, m, H-5), 2.17—2.12 (1H, m, Val β-CH), 1.09 (3H, d, *J*=7.02 Hz, Val β-$CH_3$), 1.02 (3H, d, *J*=6.63 Hz, Val γ-$CH_3$). ESI/MS *m/z* 427 $(M-H)^-$ HR-ESI/MS Calcd $C_{20}H_{22}F_3N_2O_5$ $(M-H)^-$: 427.1484, Found 427.1476.

**10-(α-L-Leucyl)amino-goniothalamin Trifluoroacetate (17)** A mixture of **10** (17 mg, 0.04 mmol) and TFA/$CH_2Cl_2$ (2 ml, 1 : 3) was stirred 1 h at rt and concentrated to dryness. The residue was chromatographed ($CHCl_3$ : MeOH = 46 : 4) to give **17** as a foam (15 mg, 85%). Compound **17**: *Rf*=0.21 $CHCl_3$/MeOH (v/v 97 : 3) $^1$H-NMR ($CD_3OD$) δ: 7.65 (1H, d, *J*=7.42 Hz, Ar-H), 7.37—7.27 (3H, m, Ar-H), 7.10—7.06 (1H, m, H-4), 6.90 (1H, d, *J*=15.61 Hz, H-8), 6.37 (1H, dd, *J*=15.61, 5.47 Hz, H-7), 6.06—6.03 (1H, m, H-3), 5.20—5.14 (1H, m, H-6), 4.15—4.10 (1H, m, Leu α-CH), 2.71—2.63 (1H, m, H-5), 2.58—2.49 (1H, m, H-5), 1.90—1.81 (3H, m, Leu β-$CH_2$, γ-CH), 1.09 (6H, m, Leu $CH_3$×2). ESI/MS *m/z* 441 $(M-H)^-$ HR-ESI/MS Calcd $C_{21}H_{24}F_3N_2O_5$ $(M-H)^-$: 441.1637, Found 441.1638.

**10-(α-L-Isoleucyl)amino-goniothalamin Trifluoroacetate (18)** A mixture of **11** (17 mg, 0.04 mmol), TFA (0.5 ml) and $CH_2Cl_2$ (1.5 ml) was stirred 0.5 h at rt and concentrated to dryness. The residue was chromatographed ($CHCl_3$ : MeOH = 48 : 4) to give **18** as an amorphous solid (16 mg, 91%). Compound **18**: *Rf*=0.22 $CHCl_3$/MeOH (v/v 95 : 5) $^1$H-NMR ($CDCl_3$) δ: 9.72 (1H, br, NHCO), 8.33 (2H, br s, $NH_2$), 7.38—7.32 (2H, m, Ar-H), 7.14—7.05 (2H, m, Ar-H), 6.90—6.78 (2H, m, H-8, H-4), 6.07—6.00 (2H, m, H-7, H-3), 5.02 (1H, m, H-6), 4.28 (1H, t, *J*=7.43 Hz, Ile α-CH), 2.47—2.41 (2H, m, H-5), 1.91 (1H, m, Ile β-CH), 1.48 (1H, m, Ile γ-$CH_{2a}$), 0.95 (4H, m, Ile γ-$CH_{2b}$, β-$CH_3$), 0.79—0.72 (3H, m, Ile γ-$CH_3$). ESI/MS *m/z* 427 $(M-H)^-$ HR-ESI/MS Calcd $C_{21}H_{24}F_3N_2O_5$ $(M-H)^-$: 441.1637, Found 441.1641.

**10-(α-L-Glutaminyl)amino-goniothalamin Trifluoroacetate (19)** A mixture of **12** (18 mg, 0.04 mmol), TFA (0.2 ml) and $CH_2Cl_2$ (1.5 ml) was stirred 2 h at rt and concentrated to dryness. The residue was chromatographed ($CHCl_3$ : MeOH = 46 : 6) to give **19** as a foam (12 mg, 65%). Compound **19**: *Rf*=0.20 $CHCl_3$/MeOH (v/v 86 : 14) $^1$H-NMR ($CD_3OD$) δ: 7.65 (1H, d, *J*=7.43 Hz, Ar-H), 7.45 (1H, d, *J*=7.82 Hz, Ar-H), 7.36—7.27 (2H, m, Ar-H), 7.11—7.06 (1H, m, H-4), 6.92 (1H, d, *J*=16.04 Hz, H-8), 6.36 (1H, m, H-7), 6.05 (1H, dd, *J*=9.78, 1.56 Hz, H-3), 5.22—5.17 (1H, m, H-6), 4.19 (1H, t, *J*=6.26 Hz, Gln α-CH), 2.71—2.50 (4H, m, H-5 and Gln γ-$CH_2$), 2.31—2.21 (2H, m, Gln β-$CH_2$). ESI/MS *m/z* 456 $(M-H)^-$ HR-ESI/MS Calcd $C_{20}H_{21}F_3N_3O_6$ $(M-H)^-$: 456.1382, Found 456.1386.

**10-(α-L-Phenylalanyl)amino-goniothalamin Trifluoroacetate (20)** A mixture of **13** (28 mg, 0.06 mmol), TFA (0.5 ml) and $CH_2Cl_2$ (1.5 ml) was stirred 1 h at rt and concentrated to dryness. The residue was chromatographed ($CHCl_3$ : MeOH = 49 : 2) to give **20** as an amorphous powder (17 mg, 59%). Compound **20**: *Rf*=0.20 $CHCl_3$/MeOH (v/v 97 : 3) $^1$H-NMR ($CDCl_3$) δ: 9.57 (1H, br, NHCO), 7.55 (1H, d, *J*=7.83 Hz, Ar-H), 7.33 (1H, d, *J*=7.82 Hz, Ar-H), 7.29—7.14 (6H, m, Ar-H, Ph-H), 7.07 (1H, t, *J*=7.83 Hz, Ar-H), 6.90—6.85 (1H, m, H-4), 6.64 (1H, dd, *J*=15.65, 5.87 Hz, H-8), 6.06 (1H, dd, *J*=15.65, 6.62 Hz, H-7), 6.02 (1H, m, H-3), 5.04—4.99 (1H, m, H-6), 4.20 (2H, br s, $NH_2$), 4.20 (1H, m, Phe α-CH), 3.26 (1H, dd, *J*=13.69, 5.87 Hz, Phe β-$CH_{2a}$), 3.06—2.99 (1H, m, Phe β-$CH_{2b}$), 2.51—2.43 (2H, m, H-5). ESI/MS *m/z* 475 $(M-H)^-$ HR-ESI/MS Calcd $C_{24}H_{22}F_3N_2O_5$ $(M-H)^-$: 475.1481, Found 475.1484.

Approximate organic fragments π value for the Calculating the π Value of the Derivative Molecules[17—20]: C (aliphatic) +0.5, phenyl +0.2, Cl +0.5, O=C–O (carboxyl) −0.7, O=C–N (amide, imide) −0.7, O (hydroxyl, phenol, ether) −0.1, N (amine) −1.0, $NO_2$ (aromatic) −0.28.

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