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Marthiapeptide A, an Anti-infective and Cytotoxic Polythiazole Cyclopeptide from a 60 L Scale Fermentation of the Deep Sea-Derived *Marinactinospora thermotolerans* SCSIO 00652

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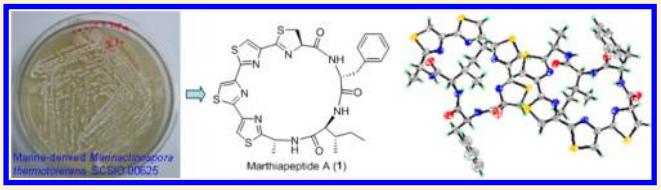
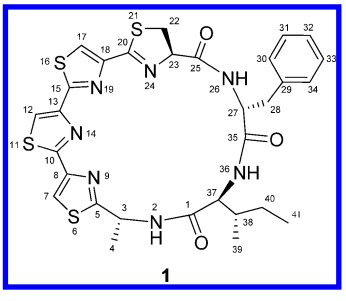
Supporting Information

ABSTRACT: A new sequential tristhiazole-thiazoline-containing cyclic peptide, marthiapeptide A (**1**), was isolated from a 60 L scale culture of the deep South China Sea-derived strain *Marinactinospora thermotolerans* SCSIO 00652. The planar structure and absolute configuration of **1** were elucidated by application of spectroscopic techniques, as well as by single-crystal X-ray diffraction and chiral-phase HPLC analysis of the acid hydrolysates. Marthiapeptide A (**1**) exhibited antibacterial activity against a panel of Gram-positive bacteria, with MIC values ranging from 2.0 to 8.0 μg/mL, and displayed strong cytotoxic activity against a panel of human cancer cell lines with IC_{50} values ranging from 0.38 to 0.52 μM.



Over the past decade marine-derived actinomycetes have been an important source of leads for drug discovery, as many novel metabolites with anti-infective and antitumor activities have been identified from such organisms.[1,2] Cyclic peptides are of great interest from the perspective of drug discovery and development due to their pharmacological efficacy.[3,4] In our efforts to explore anti-infective and cytotoxic metabolites from South China Sea-derived actinomycetes and fungi,[5,6] we have reported the cytotoxic cycloheptapeptides ordyheptapeptides C−D from the marine-derived fungus *Acremonium persicinum* SCSIO 115.[6] *Marinactinospora thermotolerans* SCSIO 00652 is a representative of a new actinomycete genus isolated from a deep South China Sea sediment.[5] Previous biological and chemical investigations of the fermentation broth of the strain SCSIO 00652 cultured using regular shaking flasks (6−8 L) led to the production and isolation of antimalarial β-carboline and indolactam alkaloids, as well as the known antibacterial antibiotic A201A.[5,7] Genome scanning of the strain SCSIO 00652 revealed that, besides the identified biosynthetic gene clusters for methylpendolmycin/pendolmycin[8] and antibiotic A201A,[7] at least 10 gene clusters responsible for nonribosomal peptide or alkaloid natural products exist in the genome.[9] However, these minor metabolites could not be detected by HPLC or purified due to the extremely small quantities produced. In order to capture these minor metabolites on a scale suitable for complete structure elucidation, the strain was fermented on a 60 L scale in a 100 L fermentor. Subsequent purification of the fermentation extract resulted in isolation of a new polythiazole cyclic peptide, designated marthiapeptide A (**1**). Herein, we report the isolation, structure elucidation, and biological activities of **1**.



1

Marthiapeptide A (**1**) was the major product in the fermentation broth as determined by HPLC and was obtained as colorless needles. Its molecular formula, $C_{30}H_{31}N_7O_3S_4$, was determined by the quasi-molecular ion peak at m/z 666.1425

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$[M + H]^+$ in the HRESIMS spectrum, requiring 19 degrees of unsaturation. The IR spectrum of **1** exhibited absorption bands at 3416 cm^{-1} (amide NH), 1670 cm^{-1} (amide C═O), and 1502, 1450 cm^{-1} (benzene ring). The ^1H, ^{13}C, and HSQC NMR spectroscopic data for **1** (Table 1) suggested the

Table 1. ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) Data of 1 in $CDCl_3$

	marthiapeptide A (**1**)	
position	δ_C	δ_H, multi. (*J* in Hz)
1	171.3, C	
2		6.99, d (8.1)
3	47.1, CH	5.50, m
4	23.0, CH_3	1.61, d (7.1)
5	174.3, C	
7	118.2, CH	7.74, s
8	147.2, C	
10	161.1, C	
12	118.3, CH	7.72, s
13	148.1, C	
15	161.0, C	
17	122.3, CH	7.66, s
18	148.9, C	
20	161.7, C	
22	36.3, CH_2	3.70, d (10.5)
23	78.8, CH	4.81, t (10.5)
25	170.3, C	
26		8.19, d (10.2)
27	56.4, CH	5.12, td (10.2, 3.8)
28	40.3, CH_2	2.98, dd (13.6, 10.2); 3.53, dd (13.6, 3.8)
29	137.1, C	
30/34	129.4, CH	7.34, d (7.4)
31/33	128.5, CH	7.27, t (7.4)
32	126.9, CH	7.20, t (7.4)
35	172.0, C	
36		8.48, d (9.6)
37	58.0, CH	4.70, dd (9.6, 3.7)
38	36.6, CH	2.12, m
39	16.0, CH_3	0.79, d (7.1)
40	24.8, CH_2	1.02, m; 1.34, m
41	11.8, CH_3	0.49, t (7.4)

presence of signals assignable to three exchangeable protons at δ_H 6.99 (NH-2), 8.19 (NH-26), and 8.48 (NH-36) and three methyls, three methylenes, five aliphatic and eight olefinic methines, and 11 olefinic quaternary carbons. One mono-substituted benzene ring was readily identified on the basis of a set of aromatic ^1H NMR signals at δ_H 7.34 (2H, d, *J* = 7.4 Hz, H-30, 34), 7.27 (2H, t, *J* = 7.4 Hz, H-31, 33), and 7.20 (1H, t, *J* = 7.4 Hz, H-32). Analysis of the COSY and HSQC spectra of **1** led to the assignments of the fragments X-NH-CH-CH_2-X′, X-NH-CH-(X′)CH(CH_3)-CH_2-CH_3, X-CH(CH_3)-NH-X′, and X-CH_2-CH-X′ (fragments A–D, respectively, Figure 1). The key HMBC correlations from H-28 in fragment A to C-29, C-30 (34), and C-35 (C═O), from H-30 (34) to C-28, and from H-27 to C-29 and C-35 (C═O) defined the presence of a Phe residue. The HMBC correlations of H-26/C-25 (C═O) and of H-27/C-25 (C═O) established the amide bond between the carbonyl carbon C-25 and the −NH of the Phe unit. Fragment B was deduced to be an Ile residue on the basis of COSY correlations between H-36/H-37/H-38/H-39 and H-38/H-40/H-41. The HMBC correlations from H-37 to C-1 (C═O) and

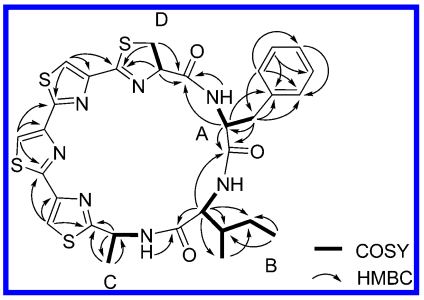

Figure 1. COSY and selected HMBC correlations of compound **1**.

C-35 (C═O) suggested that the Ile moiety was connected with the Phe residue. Fragment C was found to be linked with the Ile via an amide bond, as deduced on the basis of the HMBC correlation of H-2/C-1(C═O). These determined partial structures accounted for seven of the 19 double-bond equivalents. The remaining high degree of unsaturation, as well as the four nitrogen atoms and four sulfur atoms, inferred the presence of four thiazole/thiazoline rings in the molecule. The HMBC correlations from H_2-22 and H-23 in fragment D to the aromatic carbon C-20 with a downfield ^{13}C NMR chemical shift established a 4,5-dihydrothiazole unit. The HMBC correlations from H_2-22 and H-23 to the carbonyl carbon (C-25) and from H-26 and H-27 to C-25 suggested that the 4,5-dihydrothiazole moiety is connected with the Phe moiety through an amide linkage. The three singlet signals at δ_H 7.74 (H-7), 7.72 (H-12), and 7.66 (H-17) in the ^1H NMR spectrum were assigned to three protons on the three thiazole rings respectively. The HMBC correlations that originated from H-7, H-12, and H-17 permitted not only full assignment of the ^{13}C NMR data but also determination of the sequence of the three sequential thiazoles. Additional HMBC associations from H-3 and H_3-4 to C-5 defined the thiazole-Ala linkage, thus establishing the planar structure of **1**. The elucidated structure of **1** was confirmed by a single-crystal X-ray diffraction analysis using Cu Kα radiation (Figures 2, SI; Table S1). The absolute

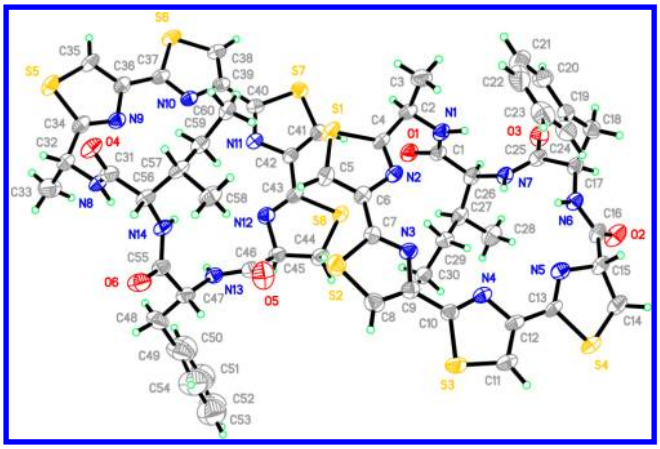

Figure 2. ORTEP structure of compound **1** (all solvent molecules are omitted for clarity).

configurations of the amino acid residues were assigned as D-Phe, L-Ile, and L-Cys through the refinement of the Flack parameter [*x* = 0.030(14)]. In addition, the presence of D-Phe and L-Ile units in **1** was unambiguously demonstrated by Marfey's analysis (Figure S2) and chiral-phase HPLC analysis of the acid hydrolysate of **1** (Figure S3).

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A literature survey reveals that **1** is categorized into a family of emerging macrocyclic natural products containing four or more sequential 2,4-disubstituted oxazoles/oxazolines and thiazoles/thiazolines. Members of this ever-expanding family include the telomerase inhibitor telomestatin (**2**) reported in 2001 from *Streptomyces anulatus*,[10,11] the cytotoxic mechercharstatin A (**3**, formerly named mechercharmycin A) reported in 2005 from the marine-derived *Thermoactinomyces* sp.,[12] and the cytotoxic urukthapelstatin A (**4**) reported in 2007 from the marine-derived *Mechercharimyces asporophorigenens*[13] (Figure S4). It has been reported that telomestatin (**2**) specifically interacts with the G-quadruplex but does not affect DNA polymerase or reverse transcriptase,[10,11] whereas compounds **3** and **4** have been found to show no telomerase inhibitory activity in TRAP assays at 2 μM,[13] consistent with the finding that the planar nature of **2** is important for telomerase inhibition.[14] Cyclic peptides **3** and **4** were reported to possess remarkable cytotoxic activity against a panel of human cancer cell lines (IC_{50} = 10 nM to 1 μM).[12,13] These previously reported data collectively demonstrate that the planar structure of **2** has telomerase inhibitory activity but weaker cytotoxicity than its congeners, whereas cyclic peptides **3** and **4** are potent cytotoxins.

Marthiapeptide A (**1**) possesses high structural similarity to **3** and **4** but possesses its own unusual features. In particular, marthiapeptide A bears a unique sequential tristhiazole-thiazoline moiety and an L-Ile residue rather than the D-*allo*-Ile residue characteristic of **3** and **4** (Figure 1). In this study, marthiapeptide A (**1**) was first tested for antibacterial activities against a panel of Gram-positive and Gram-negative bacteria (Table 2). Marthiapeptide A was found to exhibit antibacterial activities against *Micrococcus luteus*, *Staphylococcus aureus* ATCC 29213, *Bacillus subtilis* ATCC 6633, and *Bacillus thuringiensis*, with MIC values of 2.0, 8.0, 4.0, and 2.0 μg/mL, respectively.

Table 2. Antibacterial Activities (MIC, μg/mL) of Compound 1 against a Panel of Gram-Positive and Gram-Negative Bacteria

bacteria tested	compound **1**	erythromycin	kanamycin
Micrococcus luteus	2.0	<1.0	32.0
Staphylococcus aureus ATCC 29213	8.0	16.0	8.0
Bacillus subtilis ATCC 6633	4.0	<1.0	<1.0
Bacillus thuringiensis	2.0	<1.0	4.0
Aeromonas hydrophila subsp. hydrophila ATCC 7966	>128.0	4.0	<1.0
Escherichia coli ATCC 25922	>128.0	32.0	16.0
Escherichia coli DH5α	>128.0	64.0	32.0

Marthiapeptide A (**1**) was then tested for cytotoxic activity against the human glioblastoma cell line SF-268, the human breast adenocarcinoma cell line MCF-7, the human lung carcinoma cell line NCI-H460, and the human hepatocarcinoma cancer cell line HepG2 using the SRB method. Marthiapeptide A (**1**) significantly inhibited the growth of these tumor cells with IC_{50} values of 0.38 ± 0.02, 0.43 ± 0.005, 0.47 ± 0.003, and 0.52 ± 0.01 μM, respectively. These IC_{50} values indicate that **1** is roughly 5- to 10-fold more potent than cisplatin, which was used as a positive control.

Telomerase inhibition by **2** arises from its ability to interact with the human telomeric intramolecular G-quadruplex DNA.[11] Accordingly, we evaluated the ability of **1** to interact with this target using circular dichroism (CD) spectroscopy and fluorescence resonance energy transfer (FRET) melting assays.[15] In the presence of K^+, telomeric oligonucleotide HTG21 (d[G_3(T2AG_3)$_3$]) forms the hybrid-type G-quadruplex structure; the CD spectrum of this structure shows a strong positive band at 290 nm, a minor positive band at 265 nm, and a negative band at 235 nm. Titration of the target G-quadruplex with 5 equiv of **1** elicited little change in the quadruplex CD signal (Figure 3). Moreover, FRET melting data revealed that thermal stabilization of the telomeric G-quadruplex was minimally impacted by addition of **1**. The very slight increase in melting temperature (ΔT_m = 0.9 °C) observed upon addition of **1** to the quadruplex was much lower than that of **2** (Figure 4).[16] Thus, these data suggest that **1** has very little impact on, or interaction with, telomeric G-quadruplex DNA. This finding is in accordance with results obtained using **3** and **4** in TRAP assays.[13] These data reveal important information regarding the correlation of structure to biological functions and potential uses for **1**.

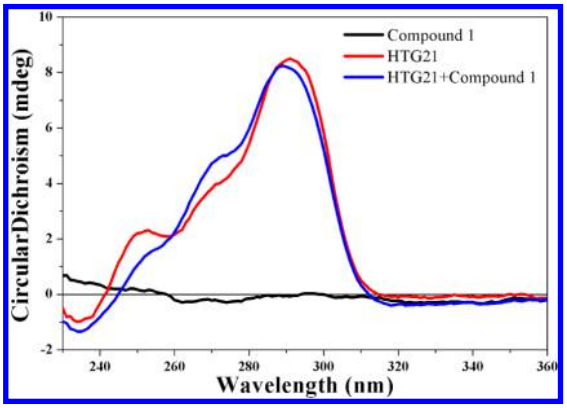

Figure 3. CD spectra of 4 μM HTG21 alone (red line) in 10 mM Tris-HCl buffer, pH 7.2, containing 100 mM KCl, and in the presence of 20 μM **1** (blue line).

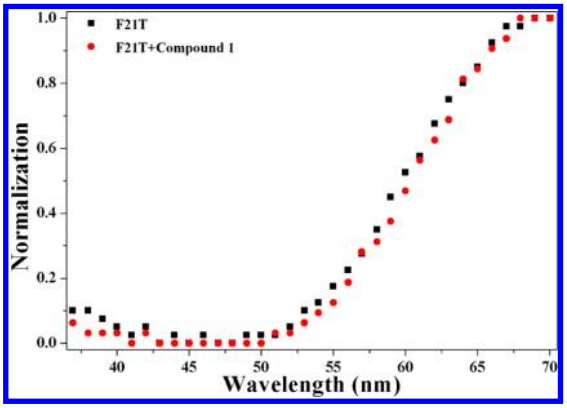

Figure 4. The melting behavior of 0.2 μM F21T alone (solid squares) and in the presence of 2 μM compound **1** (solid circles). T_m value of annealed F21T is 60.0 °C. Upon addition of 2 μM compound **1**, T_m value is 60.9 °C. $\Delta T_m = T_m$(DNA + ligand) − T_m(DNA).

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were determined with an SFW-X-4 apparatus and are uncorrected. Optical rotations were obtained with an MCP 300 polarimeter (Anton Paar). UV spectra were recorded with a U-2910 spectrometer (Hitachi). IR spectra were measured on an IRAffinity-1 Fourier transform infrared

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spectrophotometer (Shimadzu). NMR spectra were obtained with an AVANCE-500 spectrometer (Bruker). Thin-layer chromatography (TLC) was conducted with precoated glass plates (0.1−0.2 mm; silica gel GF_{254}, 10−40 nm, Jiangyou). Column chromatography (CC) was performed using silica gel (100−200 mesh; Jiangyou). Medium-pressure liquid chromatography (MPLC) was performed using a CHEETAH 100 automatic flash chromatograph (Bonna-Agela) with an ODS-A flash column (S-50 μm, 12 nm; 100 × 20 mm, YMC). Semipreparative HPLC was performed with two 210 solvent delivery modules equipped with a 335 photodiode array detector (Varian), using an ODS-A column (250 × 10 mm, 5 μm; YMC). Low-resolution and high-resolution mass spectra were obtained on an Amazon SL ion trap instrument and a Maxis quadrupole-time-of-flight mass spectrometer (Bruker), respectively. Single-crystal data were collected on an Xcalibur Onyx Nova diffractometer (Oxford) using Cu Kα radiation. All chemicals and solvents were of analytical or chromatographic grade.

Bacterium, Fermentation, and Isolation. The actinomycete strain *Marinactinospora thermotolerans* SCSIO 00652 has been described previously.[5] A portion of the mycelium and spore mixture of strain SCSIO 00652 grown on a modified ISP4 medium plate was inoculated into 100 mL of modified ISP4 medium (10g/L soluble starch, 2g/L $(NH_4)_2SO_4$, 1g/L K_2HPO_4, 1g/L $MgSO_4{\cdot}7H_2O$, 1g/L tryptone, 0.5g/L yeast extract, 30 g/L sea salt, trace element solution (0.1 mL/L), pH 7.0 before sterilization) in a 250 mL Erlenmeyer flask (six flasks were used). The flasks were incubated at 28 °C on a rotary shaker at 200 rpm for 2 days. Then the 600 mL of culture solution was inoculated into 6 L of modified ISP-4 medium for seed culture in a 10 L fermentor. Four days later, the 6 L seed culture in the 10 L fermentor was successively transferred into a 100 L fermentor containing 60 L of modified ISP-4 medium (herein 1 g/L sea salt was used, pH 7.0 adjusted after autoclave) and then incubated at 28 °C, 200 rpm, 30 L/min aseptic air, and 0.05 MPa for 7 days. During fermentation, 10 mL samples were withdrawn from the fermentor every 24 h and subjected to HPLC analysis.

On the seventh day, the entire culture broth (60 L) was harvested and filtered to yield the mycelium cake and liquid broth. The mycelium cake was extracted using 500 mL of EtOAc three times. The EtOAc layers were combined and evaporated to dryness to yield a residue (36.0 mg). The liquid broth was loaded onto an XAD-16 resin column (5 L), subsequently eluted with 30 L of H_2O and then 30 L of EtOH. The harvested EtOH eluates were evaporated in vacuo to yield a residue (8.1 g). The two residues were combined after HPLC analysis and subjected to a SiO_2 CC using gradient elution with $CHCl_3$ and MeOH mixtures (100:0, 98:2, 96:4, 94:6, 92:8, 9:1, 8:2, 5:5) to give eight fractions (Fr.1−Fr.8). The combined Fr.5−8 was purified by SiO_2 CC eluting with EtOAc/MeOH (94:6, 92:8, 90:10, 88:12, 85:15, 80:20) to give 20 fractions (Fr.2-1−Fr.2-20). Fr.2-1−Fr.2-3 were combined and further purified by semipreparative HPLC with an ODS column, eluted with CH_3CN/H_2O (30:70 to 100:0 over 30 min, 2.5 mL/min), to afford 2-acetamidobenzoic acid (22 mg, t_R = 13.0 min; see Supporting Information, Figure S5 and Table S2). Fr.2-4−Fr.2-15 were combined and further purified by MPLC with an ODS column, eluted with $MeOH/H_2O$ (10:90 to 100:0 over 60 min, 15 mL/min), to give 14 fractions (Fr.3-1−Fr.3-14). The subfractions were analyzed and grouped by TLC. Fr.3-1−Fr.3-7 and Fr.3-11−Fr.3-13 were separated by semipreparative HPLC with an ODS column, eluted with CH_3CN/H_2O (30:70 to 100:0 over 30 min, 2.5 mL/min), to afford **1** (16 mg, t_R = 22 min).

Marthiapeptide A (1): colorless needle crystals; mp 115−116 °C; $[\alpha]^{25}_D$ = +94 (*c* 0.8, MeOH); UV (MeOH) λ_{max} (log ε) 206 (4.49), 234 (4.34), 258 (4.26), 289 (4.25) nm; IR (KBr) ν_{max} 3415, 1674, 1502 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 1; (+)-HRESIMS *m*/*z* 666.1425 ($[M + H]^+$, calcd for 666.1444).

X-ray Crystallographic Analysis. Colorless crystals of **1** were obtained from MeOH. The crystal data of **1** were recorded on an Oxford Xcalibur single-crystal diffractometer with enhanced ultra Cu Kα radiation (λ = 1.54184 Å). The structure was solved by direct methods (SHELXS-97) and refined using full-matrix least-squares difference Fourier techniques.[17] Crystallographic data for **1** have been deposited in the Cambridge Crystallographic Data Center with the deposition number CCDC 895524. A copy of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1233-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Crystal data of **1**: monoclinic, chemical formula $C_{30.50}H_{36.50}N_7O_{5.25}S_4$, space group *C*2, a = 49.2617(10) Å, b = 9.2747(17) Å, c = 14.9726(3) Å, α = 90°, β = 93.113(18)°, γ = 90°, V = 6830.7(2) $Å^3$, Z = 8, D_{calcd} = 1.387 g/cm^3, μ = (Cu Kα) 2.981 mm^{-1}, and $F(000)$ = 2996. Crystal size: 0.30 × 0.30 × 0.10 mm^3. Independent reflections: 10 889 [R_{int} = 0.0395]. The final indices were R_1 = 0.0495, wR_2 = 0.1284 [$I > 2\sigma(I)$].

HPLC Analysis of the Acid Hydrolysates of 1 Using Marfey's Method. Compound **1** (0.5 mg) was dissolved in 6 N HCl (1 mL) and heated at 110 °C for 18 h. The downstream processing, derivatization with 1-fluoro-2,4-dinitrophenyl-5-L-alaninamide (FDAA) and HPLC analysis were performed in a fashion similar to that used for cordyheptapeptides C−E.[6] The retention times for FDAA derivatives of L-Ile, D-Ile, L-Phe, and D-Phe were 28.0, 31.2, 28.6, and 30.8 min, respectively. Accordingly, the amino acids were assigned in **1** as L-Ile (28.0 min) and D-Phe (30.8 min) (see Supporting Information, Figure S2).

Chiral-Phase HPLC Analysis of the Acid Hydrolysate of 1. Chiral-phase HPLC analysis of the acid hydrolysate was carried out to determine the absolute configurations of the Phe and Ile in **1**. Compound **1** (0.30 mg) was dissolved in 6 N HCl (1 mL) and heated at 110 °C for 18 h. After cooling to room temperature (rt), the solvent was removed under reduced pressure. The dried hydrolysate was dissolved in 400 μL of 2 mM $CuSO_4/H_2O$ solution. A 60 μL aliquot was analyzed by HPLC using a chiral-phase column (MCIGEL CRS10W, 4.6 × 50 mm, Mitsubishi Chemical Corporation) with 2 mM $CuSO_4/H_2O$ solution as the mobile phase at a flow rate of 0.5 mL/min with UV detection at 254 nm. L-Ile, D-Ile, L-*allo*-Ile, and D-*allo*-Ile were analyzed as references. The retention times of the L-Ile, D-Ile, L-*allo*-Ile, and D-*allo*-Ile were 25.1, 10.1, 17.5, and 10.2 min, respectively. Hence, the Ile residues in **1** were assigned as L-Ile (25.0 min) (Supporting Information, Figure S3).

Antibacterial Assay. Compound **1** was tested for antibacterial activity against a panel of Gram-positive and Gram-negative bacteria as listed in Table 2. MIC was determined using a dilution antibacterial susceptibility test for aerobic bacteria. Compound **1** was dissolved in DMSO, serially diluted to concentrations of 1.0−128.0 μg/mL, and tested in a 96-well plate in triplicate. Erythromycin and kanamycin were both used as controls.

Cytotoxicity Assays. Compound **1** was evaluated for its cytotoxic activities against SF-268, MCF-7, NCI-H460, and HepG2 cell lines using a previously reported SRB method.[18] All data were obtained in triplicate and are presented as means ± SD. Cisplatin was used as positive control, possessing potent cytotoxic activity against the four cell lines with IC_{50} values of 4.76 ± 0.27, 3.99 ± 0.13, 2.91 ± 0.18, and 2.45 ± 0.07, repectively.

CD Measurements. CD experiments were performed with a Chirascan circular dichroism spectrophotometer (Applied Photophysics). A quartz cuvette with 4 mm path length was used for the spectra recorded over a wavelength range of 230−360 at 1 nm bandwidth, 1 nm step size, and 0.5 s time per point. The oligomer HTG21 (5′-d(GGG[TTAGGG]$_3$)-3′) was diluted from stock solution to the correct concentration (4 μM in strand) in Tris-HCl buffer (10 mM, pH 7.2) with 100 mM KCl and then annealed by heating to 95 °C for 5 min followed by slow cooling to rt followed by overnight incubation at 4 °C. The CD spectra of preformed HTG21 (4 μM in strand) alone, compound **1** (20 μM) alone, and preformed HTG21 (4 μM) in the presence of 20 μM compound **1** were collected. A buffer baseline was collected in the same cuvette and subtracted from the sample spectra. Final analysis of data was carried out using Origin 7.5 (OriginLab Corp.).

Spectroscopy and Fluorescence Resonance Energy Transfer Melting Assay. The labeled oligonucleotide F21T, 5′-FAM-d(GGG-[TTAGGG]$_3$)-TAMRA-3′ (donor fluorophore FAM is 6-carboxy-

fluorescein; acceptor fluorophore TAMRA is 6-carboxytetramethylrhodamine), was used as the FRET probes. Fluorescence melting curves were determined with a Roche LightCycler 2 real-time PCR machine, using a total reaction volume of 20 μL, with 0.2 μM labeled oligonucleotide in Tris-HCl buffer (10 mM, pH 7.2) containing 60 mM KCl. Fluorescence readings with excitation at 470 nm and detection at 530 nm were taken at intervals of 1 °C over the range 37−99 °C, with a constant temperature being maintained for 30 s prior to each reading to ensure a stable value. The melting of the G-quadruplex was monitored alone or in the presence of 2 μM compound **1**. Final data analysis was carried out using Origin 7.5 (OriginLab Corp.).

■ ASSOCIATED CONTENT

Supporting Information

1D and 2D NMR, HRESITOFMS, and HRESIMS^2 spectra for compound **1**. Marfey's analysis and chiral-phase HPLC analysis of the acid hydrolysate of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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