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Synthesis and Antiproliferative Activity Evaluation of the Disulfide-Containing Cyclic Peptide Thiochondrilline C and Derivatives

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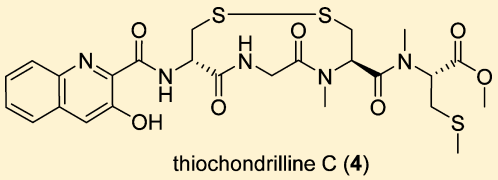
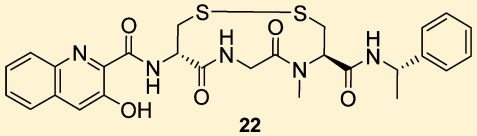
Supporting Information

ABSTRACT: Thiochondrilline C (**4**) was previously isolated from *Verrucisispora* sp. and reported to have moderate cytotoxicity against human lung adenocarcinoma cells. Herein, we report the synthesis of thiochondrilline C by N-terminal peptide extension, oxidative disulfide bond formation, and heterocycle installation as key steps. Antiproliferative activities for the prepared natural product and several derivatives against the NCI 60 cancer cell line panel are also described. Derivative **22** was identified as a moderately potent antiproliferative agent (50% growth inhibition (GI_{50}) = 0.2−12.2 μM) with leukemia (average GI_{50} = 1.8 ± 0.1 μM) and colon (average GI_{50} = 2.4 ± 0.3 μM) cells being most sensitive.



thiochondrilline C (**4**)



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Thiodepsipeptides (e.g., thiocoraline A, **1**) and other structurally related depsipeptide natural products (e.g., triostin A, **2**, and echinomycin, **3**) exhibit a broad range of biological activities, including as antitumor, antibiotic, and anti-inflammatory agents.[1] However, clinical advancement of echinomycin for the treatment of cancer has been hindered by significant dose-limiting toxicities.[2] One of the primary obstacles in surpassing this hurdle has been inadequate availability of derivatives that would permit extensive structure−activity relationship (SAR) studies to be conducted in order to optimize the selective toxicity for malignant cells and to improve physiochemical and absorption, distribution metabolism, and excretion (ADME) properties. Most of the current approaches in this field aim to modify their structures through extensive synthesis[3,4] or to alter biosynthesis pathways for the generation of thiodepsipeptide and depsipeptide derivatives.[5] However, these strategies will likely produce equally complex structures with similar liabilities.

Thiocoraline A, isolated from the mycelium of *Micromonospora* sp.,[6] has been reported to exhibit potent antiproliferative activity against an array of cancer cells, including lung, breast, colon, renal, and melanoma (Figure 1).[7] The mechanism of action for thiocoraline A, like many structurally similar thiodepsipeptides and depsipeptides, is bis-intercalation-induced DNA damage. Thiocoraline A also has been reported to inhibit DNA polymerase α and hypoxia-inducible factor 1α (HIF-1α).[8] In addition, preliminary SAR studies of antiproliferative activity for thiocoraline A and related molecules have revealed that the 3-hydroxyquinaldic or 2-quinoxalinecarboxylic substituents are a key contributor to biological activity by providing a structural motif for DNA intercalation.[9,10]

Thiochondrilline C is a marine-derived natural product recently isolated from *Verrucisispora* sp., along with thiocoraline A.[11] Thiochondrilline C is composed of a disulfide-containing cyclic peptide with one 3-hydroxylquinaldic moiety and is a substructure of thiocoraline A, but with a significantly lower molecular weight (MW = 609 versus 1156). Thiochondrilline C has been reported to demonstrate moderate cytotoxicity (EC_{50} = 2.9 μM) against human A549 lung adenocarcinoma cells. Although the potency of thiochondrilline C is less than thiocoraline A (EC_{50} = 0.010 μM),[11] its ligand efficiency (defined as the −log IC_{50} in molarity/number of heavy atoms) is greater (0.14 versus 0.11) due to lower molecular weight. On the basis of its greater ligand efficiency and synthetic tractability we sought to develop a versatile synthetic route to thiochondrilline C that would also be amenable to the preparation of derivatives to further study the antiproliferative activity and physiochemical and ADME properties of this natural product and its non-natural derivatives.

RESULTS AND DISCUSSION

A divergent approach for the synthesis of thiochondrilline C was envisioned that consisted of coupling **5** and **6** in the final step, which would provide efficient flexibility for modification of the exocyclic portion of the molecule (Scheme 1). Cyclic intermediate **5** would be prepared by oxidative disulfide bond formation of **7**, which would be generated by N-terminal peptide extension starting from **8**.

An efficient synthesis of 3-hydroxyquinoline-2-carboxylic acid, **13**, was initially developed (Scheme 2). *ortho*-Nitrobenzaldehyde, **9**, was selectively reduced with iron to provide

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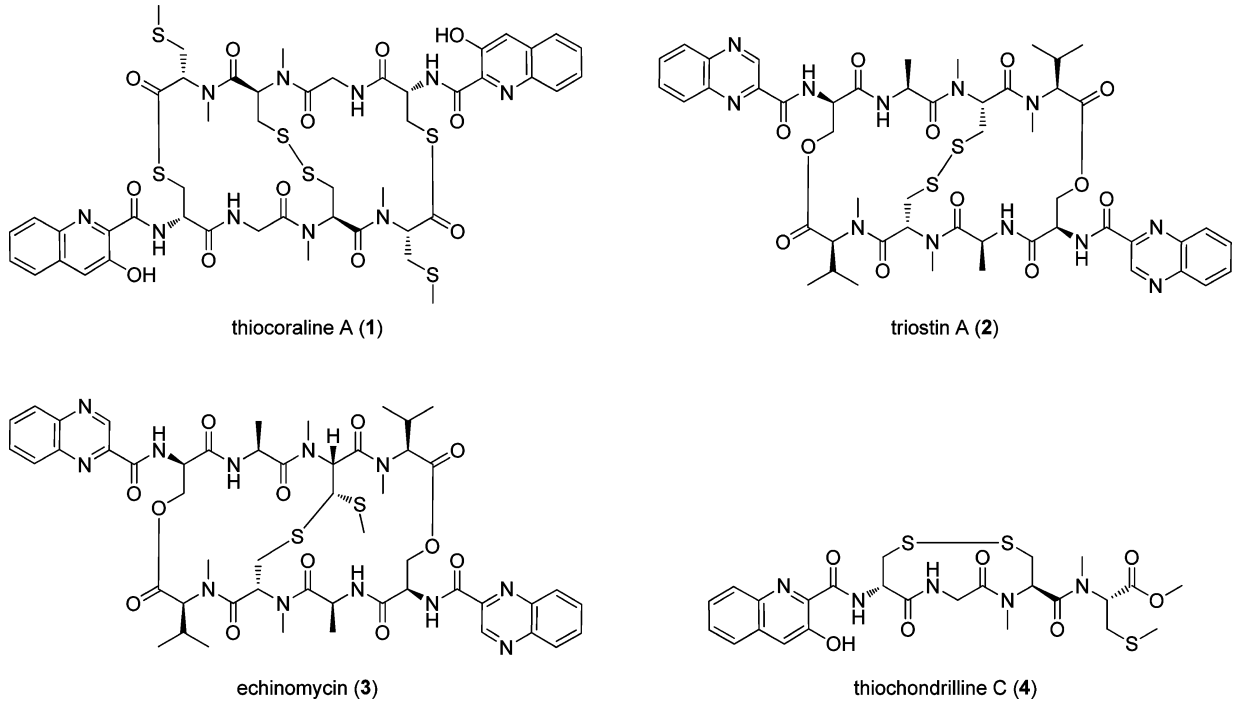
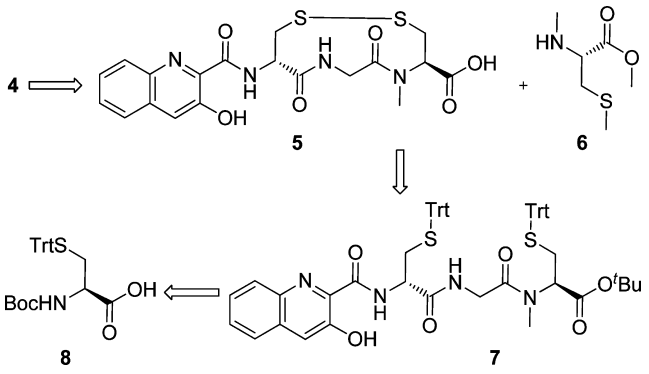


Figure 1. Structures of thiocoraline A (**1**), triostin A (**2**), echinomycin (**3**), and thiochondrilline C (**4**).

Scheme 1. Retrosynthetic Analysis of Thiochondrilline C

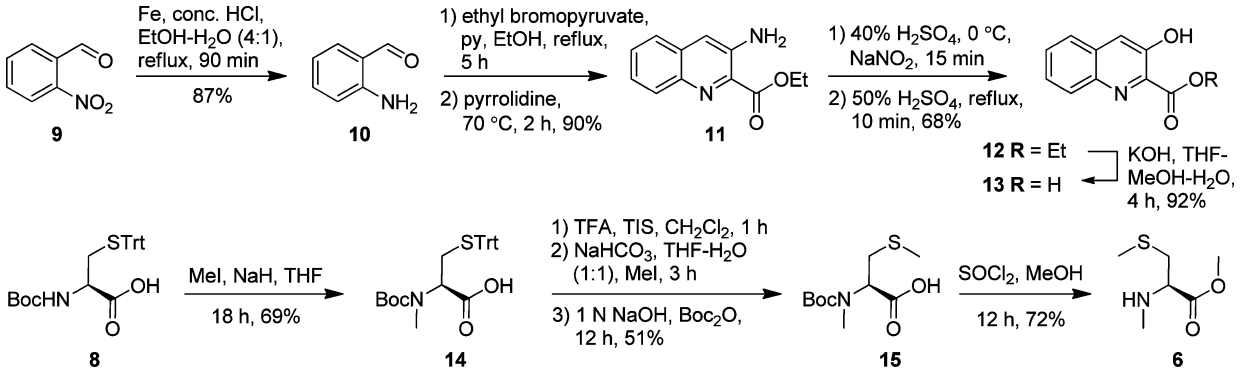


ortho-aminobenzaldehyde, **10** (87%).[12] Subsequent condensation with ethyl bromopyruvate generated ethyl 3-amino-2-quinolinecarboxylate, **11**, in 90% yield.[13] A Sandmeyer reaction was employed to convert the amine to a hydroxy in 68% yield in the presence of H_2SO_4 and sodium nitrite, followed by ester hydrolysis with aqueous potassium hydroxide, which furnished **13** in 92% yield.

The synthesis of cysteine derivative **6** started with N-methylation of **8** in the presence of NaH and MeI in THF to generate **14** in 69% yield.[14] Compound **14** was treated with trifluoroacetic acid (TFA) in the presence of triisopropylsilane (TIS) to remove the trityl, which was accompanied by loss of the Boc protecting group. This step was followed by selective S-methylation with MeI in the presence of sodium bicarbonate, followed by reintroducing Boc protection of the amine to give **15** in 51% yield.[15] Acid **15** was treated with thionyl chloride in methanol to generate **6** in 72% yield.

Assembly of the natural product and derivatives began by esterification of acid **14** with *tert*-butyl-2,2,2-trichloroacetamidate to give the corresponding *tert*-butyl ester **16** in 85% yield (Scheme 3). Selective removal of the Boc group with 1 N HCl provided **17** in 84% yield. The secondary amine **17** was coupled with Fmoc-Gly-OH using 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) and 1-hydroxy-7-azabenzotriazole (HOAt) to provide dipeptide **18** in 96% yield. Fmoc removal

Scheme 2. Synthesis of 3-Hydroxy quinoline-2-carboxylic Acid (13) and N-Me-L-Cys(Me)-OMe (6)



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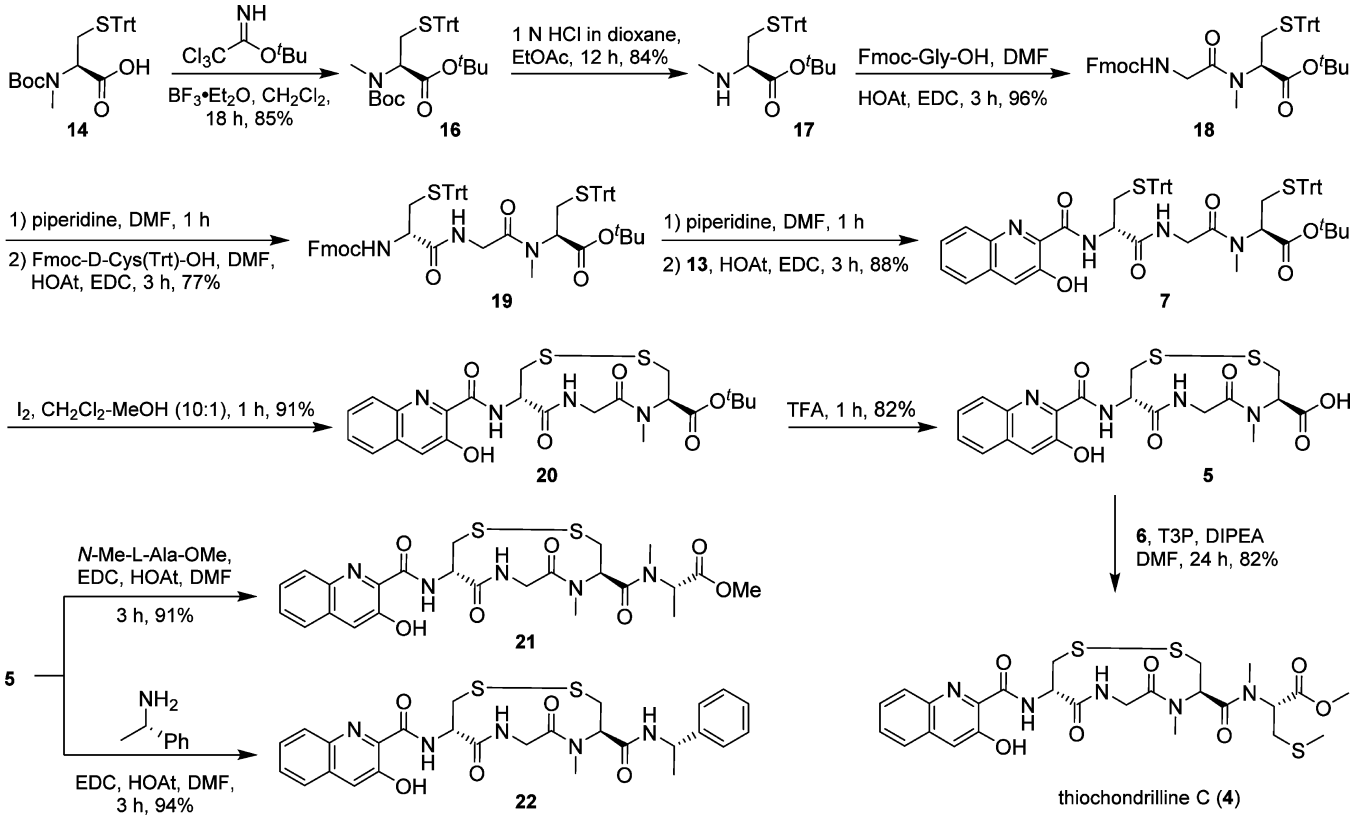
Scheme 3. Synthesis of Thiochondrilline C (4) and Derivatives



from the dipeptide was carried out with piperidine, and subsequent coupling with Fmoc-D-Cys(Trt)-OH using EDC and HOAt furnished tripeptide **19** in 77% yield. The tripeptide was treated with piperidine to remove the Fmoc protecting group followed by coupling with 3-hydroxyquinoline-2-carboxylic acid, **13**, using EDC and HOAt, which generated **7** in 88% yield. The oxidative disulfide bond formation was mediated with iodine to afford cyclic peptide **20** in 91% yield.[15,16] This material was treated with TFA to generate acid **5** in 82% yield.

Initial attempts to couple acid **5** and the secondary amine **6** with EDC and HOAt did generate thiochondrilline C, but only in <10% yield. Efforts to increase the efficiency of this reaction employing various coupling reagents, such as DCC, HBTU, HATU, and PyBOP, did not generate the desired product. However, the coupling reagent T3P (e.g., propylphosphonic anhydride) furnished thiochondrilline C in 82% yield. The optical rotation, NMR, and HRMS data of the synthetic material were consistent with the reported data for the isolated natural product.[11] In order to demonstrate the versatility of intermediate **5** and to examine the scope of the coupling procedure in more detail, the structurally similar amine N-Me-L-Ala-OMe and the primary amine (*S*)-1-phenylethylamine were employed. In both cases the coupling reaction using EDC/HOAt proceeded well to give **21** (91%) and **22** (94%) in excellent yields.

Although thiochondrilline C's activity in human A549 lung adenocarcinoma cells has been reported, broader profiling of this natural product has not been described. Therefore, thiochondrilline C and three derivatives (**5**, **21**, and **22**) were profiled for antiproliferative activity utilizing the National Cancer Institute (NCI) 60 cancer cell line assay (Table 1).[17] Thiochondrilline C and two of the other derivatives (**5** and **21**) did not show significant activity, including human A549 lung adenocarcinoma cells (e.g., <30% inhibition of growth at 10 μM). However, derivative **22** demonstrated moderate growth inhibition (GI) activity against the 60 cancer cell lines (GI_{50} = 0.2−12.2 μM), with leukemia (GI_{50} range = 0.2−5.7 μM; average GI_{50} = 1.8 ± 0.1 μM) and colon (GI_{50} range = 0.6−7.9 μM; average GI_{50} = 2.4 ± 0.3 μM) cells being the most sensitive. Total growth inhibition (TGI) could generally be achieved in these cells at ≤10 μM (leukemia: average TGI_{50} = 7.5 ± 0.2 μM; colon: average TGI_{50} = 7.8 ± 0.7 μM).

Derivative **22** was also evaluated in several *in vitro* ADME assays. The compound demonstrated moderate mouse liver microsomal stability ($t_{1/2}$ = 27 min) and good mouse plasma stability ($t_{1/2}$ = 294 min). However, it had poor permeability in Caco-2 cells (A → B P_{app} = 0.11 nm/s and B → A P_{app} = 0.62 nm/s) and aqueous solubility (4.5 μg/mL).

In conclusion, the first synthesis of thiochondrilline C has been accomplished using N-terminal peptide extension, oxidative disulfide bond formation, and heterocycle installation as key steps. The natural product was prepared in 28% overall yield starting from **14**. Several derivatives of thiochondrilline C were also prepared. Although the natural product did not demonstrate significant activity in the NCI 60 cancer cell line assay, derivative **22** showed moderate antiproliferative activity against the cell line panel, with leukemia and colon cells being most sensitive. The activity of **22** may stem from the phenyl ring providing a structural motif to achieve bis-intercalation. However, this will need to be verified with more extensive SAR and biophysical studies. Collectively, this preliminary study supports continued optimization of thiochondrilline C

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Table 1. *In Vitro* Antiproliferative Activity of 22 against the NCI-60 Human Tumor Cell Lines

	activity (μM)[a]		
panel/cell line	GI_{50}	TGI	LC_{50}
Leukemia			
CCRF-CEM	1.9 ± 0.2	10.5 ± 0.6	>50
HL-60(TB)	1.2 ± 0.1	5.1 ± 1.7	38.8 ± 1.5
K-562	0.7 ± 0.0	3.1 ± 0.1	> 50
MOLT-4	0.9 ± 0.2	3.3 ± 0.2	> 50
RPMI-8226	5.7 ± 0.2	21.6 ± 2.1	> 50
SR	0.2 ± 0.1	1.2 ± 0.9	> 50
Non-Small-Cell Lung			
A549/ATCC	7.1 ± 0.4	15.7 ± 1.1	35.3 ± 3.0
EKVX	3.8 ± 1.5	11.8 ± 0.9	31.4 ± 0.9
HOP-62	12.2 ± 3.5	21.0 ± 3.9	36.8 ± 2.6
HOP-92	9.7 ± 1.0	18.6 ± 1.3	35.6 ± 1.6
NCI-H226	8.9 ± 0.6	17.4 ± 1.1	34.2 ± 1.9
NCI-H23	5.2 ± 0.6	12.6 ± 0.8	29.7 ± 1.0
NCI-H322M	7.1 ± 1.0	20.1 ± 3.6	>50
NCI-H460	1.3 ± 0.0	8.0 ± 0.8	30.5 ± 7.0
NCI-H522	3.6 ± 1.9	10.5 ± 2.6	29.1 ± 2.4
Colon Cancer			
COLO 205	1.0 ± 0.0	2.3 ± 0.0	7.2 ± 0.3
HCC-2998	7.9 ± 2.3	17.9 ± 5.6	>50
HCT-116	1.8 ± 0.7	6.0 ± 3.1	18.3 ± 6.9
HCT-15	2.6 ± 0.4	9.7 ± 1.2	25.9 ± 3.9
HT29	1.2 ± 0.3	3.9 ± 1.9	12.4 ± 8.0
KM12	0.6 ± 0.0	8.6 ± 0.2	28.3 ± 3.9
SW-620	1.9 ± 0.1	6.3 ± 0.7	33.2 ± 9.2
CNS Cancer			
SF-268	0.4 ± 0.1	11.1 ± 1.3	35.6 ± 3.8
SF-295	7.4 ± 0.1	16.3 ± 0.2	35.8 ± 0.3
SF-539	2.0 ± 1.2	9.4 ± 2.4	27.3 ± 4.5
SNB-19	7.3 ± 1.0	19.5 ± 1.8	>50
SNB-75	7.7 ± 1.3	>50	>50
U251	2.5 ± 0.8	7.7 ± 2.0	20.4 ± 3.0
Melanoma			
LOX IMVI	0.7 ± 0.0	1.5 ± 0.2	3.6 ± 0.6
MALME-3M	6.1 ± 0.0	14.0 ± 0.5	32.3 ± 2.1
M14	0.3 ± 0.1	10.3 ± 3.3	>50
MDA-MB-435	0.8 ± 0.3	6.6 ± 0.8	22.0 ± 0.4
Melanoma			
SK-MEL-2	2.6 ± 0.4	10.1 ± 0.6	27.1 ± 0.1
SK-MEL-28	0.9 ± 0.2	9.9 ± 1.0	31.8 ± 5.3
SK-MEL-5	0.6 ± 0.1	3.8 ± 0.0	15.6 ± 0.2
UACC-257	8.3 ± 3.3	27.8 ± 13.0	>50
UACC-62	5.7 ± 1.2	13.3 ± 1.6	30.2 ± 2.0
Ovarian Cancer			
IGROVI	4.0 ± 3.0	12.9 ± 3.8	37.6 ± 1.8
OVCAR-3	0.6 ± 0.1	1.4 ± 0.0	3.1 ± 0.1
OVCAR-4	8.0 ± 0.9	18.4 ± 1.8	42.4 ± 3.7
OVCAR-5	5.2 ± 2.8	12.6 ± 3.7	29.6 ± 3.6
OVCAR-8	5.2 ± 0.5	17.8 ± 1.3	>50
NCI/ADR-RES	11.0 ± 0.2	>50	>50
SK-OV-3	5.8 ± 1.4	21.3 ± 2.6	>50
Renal Cancer			
786-0	2.5 ± 0.3	9.8 ± 1.1	33.5 ± 4.0
A498	15.0 ± 0.6	33.5 ± 0.2	>50
ACHN	4.9 ± 1.6	13.0 ± 2.3	31.5 ± 4.5
CAKI-1	7.3 ± 0.2	18.5 ± 0.1	47.4 ± 0.6
RXF 393	1.3 ± 0.1	3.1 ± 0.4	13.0 ± 4.1
SN12C	5.6 ± 0.2	14.1 ± 0.2	35.4 ± 2.2
TK-10	8.1 ± 0.0	15.4 ± 0.1	29.7 ± 0.5
UO-31	5.8 ± 0.6	13.3 ± 1.0	30.8 ± 1.6
Prostate Cancer			
PC-3	6.1 ± 1.0	13.5 ± 1.3	30.3 ± 0.6
DU-145	5.8 ± 0.4	12.7 ± 0.5	27.7 ± 0.3
Breast Cancer			
MCF7	0.9 ± 0.1	2.6 ± 0.7	16.1 ± 11.2
MDA-MB-231/ATCC	1.9 ± 0.1	7.9 ± 0.5	26.0 ± 0.3
HS 578T	11.3 ± 1.5	34.5 ± 5.5	>50
BT-549	6.9	16.1	37.6
T-47D	1.1 ± 0.0	3.8 ± 0.4	24.8 ± 1.0
MDA-MB-468	6.0 ± 0.9	13.3 ± 1.7	29.8 ± 3.0

[a] GI_{50}: concentration causing 50% growth inhibition. TGI: concentration causing total growth inhibition. LC_{50}: concentration causing 50% net cell killing. Average values ± SEM from two independent determinations.

derivatives as antiproliferative agents utilizing the versatile synthetic method now established.

EXPERIMENTAL SECTION

General Experimental Procedures. All reactions involving air-sensitive reagents were carried out with magnetic stirring and oven-dried glassware with rubber septa under argon, unless otherwise stated. All commercially available chemicals and reagent-grade solvents were used directly without further purification, unless otherwise specified. Reactions were monitored by thin-layer chromatography (TLC) on Baker-flex silica gel plates (IB2-F) using UV-light (254 and 365 nm) detection or visualizing agents (e.g., iodine, ninhydrin, or phosphomolybdic acid stain). Flash chromatography was conducted on a silica gel (230−400 mesh) or C_{18} column using a Teledyne ISCO CombiFlash Rf. Melting points were measured using a Thomas-Hoover Uni-Melt capillary melting point apparatus and are uncorrected. NMR spectra were recorded at room temperature using a JEOL ECA-500 or -400 instrument (^{1}H NMR at 500 or 400 MHz and ^{13}C NMR at 125 or 100 MHz) with tetramethylsilane as an internal standard. High-resolution mass spectra (HRMS) were obtained from University of Connecticut mass spectral facility using an AccuTOF-DART or Qstar Elite-ESI and are reported as m/z (relative intensity) for the molecular ion [M]. Optical rotations were measured on ATAGO's polarimeter (POLAX-2L). Specific rotation $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}.

2-Aminobenzaldehyde (10). To a solution of 2-nitrobenzaldehyde (1.51 g, 10 mmol) in ethanol (30 mL) and water (7.5 mL) was added iron powder (5.6 g, 100 mmol) and concentrated HCl (0.1 mL). The reaction mixture was refluxed for 90 min, diluted with ethyl acetate, and dried over anhydrous sodium sulfate. The insoluble materials were removed by filtration, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80) to give **10** (1.05 g, 87%) as a pale yellow solid: mp 38−40 °C (lit.[12] 38−40 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.48 (dd, J = 1.8, 7.8 Hz, 1H), 7.34−7.29 (m, 1H), 6.77−6.73 (m, 1H), 6.65 (d, J = 8.2 Hz, 1H), 6.12 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 149.8, 135.7, 135.2, 118.8, 116.4, 116.0.

Ethyl 3-Amino-2-quinolinecarboxylate (11). To a solution of pyridine (685 mg, 8.68 mmol) in ethanol (24 mL) was added a solution of ethyl bromopyruvate (1.69 g, 8.68 mmol) in ethanol (16 mL) dropwise. The resulting mixture was heated at 60 °C for 1 h and then allowed to cool to room temperature. 2-Aminobenzaldehyde (1 g, 8.26 mmol) and pyridine (1.6 mL) were added to the reaction mixture, which was then refluxed for 5 h. Pyrrolidine (1.41 g, 19.8 mmol) was added to the reaction mixture, which was then heated at 70

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°C for 2 h. The reaction mixture was allowed to cool and then concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 30:70) to obtain **11** (1.6 g, 90%) as a yellow solid: mp 149−151 °C (lit.[13] 148−150 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, J = 2.0, 7.6 Hz, 1H), 7.56−7.54 (m, 1H), 7.47−7.40 (m, 2H), 7.35 (s, 1H), 5.60 (brs, 2H), 4.54 (q, J = 7.6 Hz, 2H), 1.50 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 142.7, 141.4, 134.1, 131.2, 130.4, 128.9, 126.0, 125.1, 118.6, 62.1, 14.3; HRMS (DART-TOF) m/z calculated for $C_{12}H_{13}N_2O_2$ $[M + H]^+$ 217.0977, found 217.0966.

Ethyl 3-Hydroxy-2-quinolinecarboxylate (12). Compound **11** (864 mg, 4.0 mmol) was added to 3 mL of 40% sulfuric acid at room temperature, and then 3 g of ice was added. The mixture was stirred for 5 min to form a homogeneous paste. The slurry was cooled to 0−5 °C, and then a cold solution of $NaNO_2$ (304 mg, 4.4 mmol) in 1 mL of water was added dropwise. The reaction mixture was stirred for 15 min and then added to a boiling solution of 50% sulfuric acid (20 mL) dropwise. After the addition, the solution was boiled for 10 min and poured into ice−water. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80) to give **12** (590 mg, 68%) as a white solid: mp 108−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (s, 1H), 8.16−8.13 (m, 1H), 7.73−7.70 (m, 2H), 7.60−7.53, 4.63 (q, J = 6.8 Hz, 2H), 1.54 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 153.9, 142.5, 133.7, 132.0, 130.5, 129.4, 127.5, 126.2, 120.7, 63.1, 14.2; HRMS (DART-TOF) m/z calculated for $C_{12}H_{12}NO_3$ $[M + H]^+$ 218.0817, found 218.0822.

3-Hydroxy Quinoline-2-carboxylic acid (13). Potassium hydroxide (336 mg, 6.0 mmol) was added to a solution of **12** (434 mg, 2.0 mmol) in 10 mL of a 3:1:1 mixture of THF/MeOH/H_2O at room temperature and stirred for 4 h. The reaction mixture was concentrated and acidified with 1 N $HCl_{(aq)}$. The solid was filtered and washed with ice cold water and cold Et_2O to afford **13** (347 mg, 92%) as a yellow solid: mp 189−191 °C (dec) (lit.[18] 187−190 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (d, J = 7.6 Hz, 1H), 8.05 (s, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.72−7.65 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.3, 152.8, 138.9, 138.5, 131.3, 129.4, 129.1, 127.2, 126.7, 122.9; HRMS (DART-TOF) m/z calculated for $C_{10}H_8NO_3$ $[M + H]^+$ 190.0504, found 190.0544.

Boc-N-Me-L-Cys(Trt)-OH (14). To a solution of NaH (60% in mineral oil, 432 mg, 10.8 mmol) in THF (10 mL) was added Boc-Cys(Trt)-OH (2.0 g, 4.32 mmol) in THF (3 mL) dropwise at 0−5 °C. After 15 min MeI was added dropwise to the reaction mixture and was stirred for 18 h. The reaction mixture was quenched with MeOH, acidified with 1 N HCl, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 40:60) to give **14** (1.42 g, 69%) as a white foam: $[\alpha]^{26}_D$ −26 (c 3.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), mixture of two rotamers, δ 10.81 (brs, 1H), 7.43−7.41 (m, 6H), 7.28−7.17 (m, 9H), 3.93 (dd, J = 5.2 Hz, 10 Hz, 0.45), 3.61 (dd, J = 5.2 Hz, 8.4 Hz, 0.55H), 2.85−2.80 (m, 1H), 2.67−2.58 (m, 4H), 1.42 and 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of two rotamers, δ 175.8 and 175.6, 155.8 and 154.7, 144.3, 129.4, 127.9, 126.7, 81.1 and 80.5, 66.91 and 66.81, 60.3 and 59.2, 34.1 and 33.3, 31.4 and 30.7, 28.2 and 28.1; HRMS (ESI-Qstar Elite) m/z calculated for $C_{28}H_{31}NNaO_4S$ $[M + Na]^+$ 500.1871, found 500.1890.

Boc-N-Me-L-Cys(Me)-OH (15). To a solution of **14** (1.0 g, 2.1 mmol) in dichloromethane (5 mL) were added triisopropylsilane (1.7 g, 10.5 mmol) and TFA (6.2 g, 54.6 mmol) at room temperature. The reaction mixture was stirred for 1 h and then concentrated. The crude reaction mixture was washed with diethyl ether and dried *in vacuo* to afford a colorless oil, which was used directly in the next step. The crude oil was dissolved in a 1:1 mixture of THF/water (20 mL) and was treated with $NaHCO_3$ (353 mg, 4.2 mmol) and MeI (328 mg, 2.3 mmol). The reaction mixture was stirred for 3 h and then basified with 1 N $NaOH_{(aq)}$. To the reaction mixture was added $(Boc)_2O$ (550 mg, 2.52 mmol); then the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was concentrated, acidified with 1 N HCl, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (MeOH/CH_2Cl_2, 5:95) to give **15** (265 g, 51%) as a colorless oil: $[\alpha]^{24}_D$ −53.3 (c 4.5, $CHCl_3$) [lit.[15] $[\alpha]^{25}_D$ −53 (c 1.0, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of two rotamers, δ 10.2 (brs, 1H), 4.80 and 4.46 (dd, J = 4.8, 10.4 Hz, 1H), 3.07 and 3.04 (d, J = 4.8 Hz, 1H), 2.89−2.83 (m, 4H), 2.11 (s, 3H), 1.44 and 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of two rotamers, δ 175.5 and 175.4, 156.4 and 155.2, 81.3 and 80.8, 59.5 and 57.7, 33.8 and 33.0, 32.6 and 31.9, 28.2, 15.7 and 15.3; HRMS (DART-TOF) m/z calculated for $C_{10}H_{20}NO_4S$ $[M + H]^+$ 250.1113, found 250.1116.

Methyl *N,S*-Dimethyl-L-cysteinate (6). To a solution of **15** (250 mg, 1.0 mmol) in methanol (3 mL) at 0 °C was added thionyl chloride (131 mg, 1.1 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was concentrated, quenched with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (MeOH/CH_2Cl_2, 5:95) to give **6** (117 mg, 72%) as a colorless oil: $[\alpha]^{25}_D$ +5.4 (c 5.5, $CHCl_3$) [lit.[15] $[\alpha]^{25}_D$ +5.6 (c 1.1, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.39 (t, J = 6.4 Hz, 1H), 2.84−2.77 (m, 1H), 2.42 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 62.3, 51.9, 36.9, 34.6, 16.0; HRMS (DART-TOF) m/z calculated for $C_6H_{14}NO_2S$ $[M + H]^+$ 164.0745, found 164.0761.

Boc-N-Me-L-Cys(Trt)-O^{t}Bu (16). To a solution of **14** (1.0 g, 2.1 mmol) and *tert*-butyl-2,2,2-trichloroacetamidate (911 mg, 4.2 mmol) in CH_2Cl_2 (15 mL) was added $BF_3{\cdot}Et_2O$ (30 mg, 0.21 mmol) at room temperature, and then the mixture was stirred for 18 h. The reaction mixture was quenched with solid $NaHCO_3$ (617 mg, 7.35 mmol) and stirred for 10 min. The insoluble material was removed by filtration, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80) to give **16** (950 mg, 85%) as a colorless oil: $[\alpha]^{27}_D$ −5.2 (c 2.87, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), mixture of two rotamers, δ 7.45−7.42 (m, 6H), 7.31−7.26 (m, 6H), 7.23−7.18 (m, 3H), 3.85−3.75 (m, 1H), 2.87−2.54 (m, 5H), 1.45 and 1.40 (s, 9H), 1.37 and 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of two rotamers, δ 169.4 and 169.2, 155.6 and 155.1, 144.63 and 144.56, 129.58 and 129.50, 127.91 and 127.88, 126.65 and 126.60, 81.6 and 81.4, 80.3 and 79.9, 66.8, 60.6 and 60.3, 33.4 and 33.3, 31.7 and 31.3, 28.32 and 28.29, 27.90 and 27.83; HRMS (ESI- Qstar Elite) m/z calculated for $C_{32}H_{39}NNaO_4S$ $[M + Na]^+$ 556.2497, found 556.2524.

N-Me-L-Cys(Trt)-O^{t}Bu (17). To a solution of **16** (950 mg, 1.78 mmol) in ethyl acetate (9 mL) was added 4 N HCl in dioxane (3 mL). The reaction mixture was stirred for 12 h, concentrated, neutralized with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 50:50) to give **17** (648 mg, 84%) as a colorless oil: $[\alpha]^{22}_D$ +22.6 (c 1.77, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.41 (m, 6H), 7.29−7.26 (m, 6H), 7.22−7.18 (m, 3H), 2.83 (dd, J = 6.0 Hz, 7.2 Hz, 1H), 2.42−2.32 (m, 1H), 2.26 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 144.6, 129.6, 127.8, 126.6, 81.4, 66.5, 62.8, 34.6, 34.4, 28.0; HRMS (DART-TOF) m/z calculated for $C_{27}H_{32}NO_2S$ $[M + H]^+$ 434.2154, found 434.2140.

Fmoc-Gly-N-Me-L-Cys(Trt)-O^{t}Bu (18). To a solution of **17** (648 mg, 1.5 mmol) and Fmoc-Gly-OH (445 mg, 1.5 mmol) in DMF (7.5 mL) were added HOAt (245 mg, 1.8 mmol) and EDC (345 mg, 1.8 mmol). The reaction mixture was stirred for 3 h at room temperature and then quenched by the addition of 1 N $HCl_{(aq)}$. The aqueous layer was extracted with EtOAc (2 × 25 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 50:50) to afford **18** as a white foam (1.02 g, 96%): $[\alpha]^{26}_D$ −14.8 (c 2.71, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), mixture of two rotamers,

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δ 7.76 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 7.2 Hz, 2H), 7.45−7.38 (m, 8H), 7.33−7.20 (m, 11H), 5.82 (m, 1H), 4.46−4.21 (m, 4H), 4.10−3.53 (m, 2H), 2.83−2.60 (m, 5H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of two rotamers, δ 168.6 and 168.5, 168.2 and 167.5, 156.0 and 155.9, 144.3 and 144.1, 143.8, 141.2, 129.5 and 129.4, 128.1 and 128.0, 127.6, 127.0 and 126.9, 126.8, 125.2, 119.9, 83.1 and 82.3, 67.5 and 67.1, 67.0, 59.1 and 59.0, 47.1, 42.9 and 42.8, 32.3 and 30.3, 30.5 and 28.6, 27.84 and 27.79; HRMS (DART-TOF) *m*/*z* calculated for $C_{44}H_{45}N_2O_5S$ $[M + H]^+$ 713.3049, found 713.3066.

Fmoc-D-Cys(Trt)-Gly-NMe-L-Cys(Trt)-O^{t}Bu (19). To a solution of **18** (925 mg, 1.3 mmol) in DMF (13 mL) was added piperidine (110 mg, 1.3 mmol) at room temperature. The reaction mixture was stirred for 1 h, evaporated, and purified by flash column chromatography on silica gel and then used for the next step directly. To a solution of dipeptide and Fmoc-D-Cys(Trt)-OH (760 mg, 1.3 mmol) in DMF (6.5 mL) were added HOAt (212 mg, 1.56 mmol) and EDC (299 mg, 1.56 mmol). The reaction mixture was stirred for 3 h at room temperature and then quenched by the addition of 1 N $HCl_{(aq)}$. The aqueous layer was extracted with EtOAc (2 × 25 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 50:50) to afford **19** as a white foam (1.06 g, 77%): $[\alpha]^{22}_D$ −11.95 (*c* 2.93, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), mixture of two rotamers, δ 7.74 (t, J = 8.4 Hz, 2H), 7.59 (t, J = 5.6 Hz, 2H), 7.42−7.18 (m, 34H), 6.85 (brs, 1H), 5.09 (m, 1H), 4.38−4.19 (m, 4H), 3.98−3.52 (m, 3H), 2.82−2.57 (m, 7H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of two rotamers, δ 169.7 and 169.5, 168.2 and 168.0, 167.9 and 167.5, 155.7, 144.3 and 144.0, 144.3 and 143.8, 143.6, 141.2, 129.5 and 129.4, 128.1 and 128.0, 127.9, 127.6, 127.1 and 127.0, 126.9, 126.8, 125.13 and 125.11, 119.9, 83.2 and 82.3, 67.6 and 67.2, 67.1, 67.0, 59.1 and 58.9, 53.7, 47.0, 41.6 and 41.5, 34.2, 32.2 and 30.3, 30.5 and 28.6, 27.82 and 27.78; HRMS (ESI- Qstar Elite) *m*/*z* calculated for $C_{66}H_{63}NaN_3O_6S_2$ $[M + Na]^+$ 1080.4056, found 1080.4014.

***tert*-Butyl *N*,*N*-(3-Hydroxyquinoline-2-carbonyl)-*S*-trityl-D-cysteinylglycyl-*N*-methyl-*S*-trityl-L-cysteinate (7).** To a solution of **19** (1.06 mg, 1.0 mmol) in DMF (10 mL) was added piperidine (85 mg, 1.0 mmol) at room temperature. The reaction mixture was stirred for 1 h, concentrated, purified by flash column chromatographed on silica gel, and used for the next step directly. To a solution of tripeptide and **13** (189 mg, 1.0 mmol) in DMF (5 mL) were added HOAt (163 mg, 1.2 mmol) and EDC (230 mg, 1.2 mmol). The reaction mixture was stirred for 3 h at room temperature and then quenched by the addition of 1 N $HCl_{(aq)}$. The aqueous layer was extracted with EtOAc (2 × 25 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 50:50) to afford **7** as a white foam (885 mg, 88%): mp 104−106 °C; $[\alpha]^{27}_D$ +8.0 (*c* 5.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), mixture of two rotamers, δ 11.61 and 11.59 (s, 1H), 8.81 (d, J = 8.4 Hz, 1H), 8.01−7.99 (m, 1H), 7.72−7.70 (m, 1H), 7.63 (s, 1H), 7.57−7.50 (m, 2H), 7.45−7.17 (m, 29H), 6.87 (brs, 1H), 4.33−4.24 (m, 1.7H), 3.79 (d, J = 3.6 Hz, 1.35H), 3.82 (d, J = 3.6 Hz, 0.65H), 3.50 (dd, J = 4.8, 9.6 Hz, 0.3H), 2.97−2.88 (m, 1H), 2.79−2.52 (m, 6H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of two rotamers, δ 168.9 and 168.7, 168.2, 168.1 and 168.0, 167.9 and 167.4, 153.7, 144.3, 144.2 and 144.0, 141.4, 134.2, 132.1, 129.7, 129.6, 129.5 and 129.4, 128.7, 128.2 and 128.1, 127.9, 127.2, 127.0 and 126.9, 126.7, 126.3, 120.3, 83.2 and 82.3, 67.6 and 67.3, 67.1, 59.2 and 58.9, 51.9 and 51.8, 41.7, 34.0 and 33.9, 32.2 and 30.3, 30.5 and 28.7, 27.82 and 27.78; HRMS (ESI-Qstar Elite) *m*/*z* calculated for $C_{61}H_{58}N_4NaO_6S_2$ $[M + Na]^+$ 1029.3695, found 1029.3637.

***tert*-Butyl (4*R*,10*S*)-10-(3-Hydroxyquinoline-2-carboxamido)-5-methyl-6,9-dioxo-1,2-dithia-5,8-diazacycloundecane-4-carboxylate (20).** To a solution of iodine (380 mg, 1.5 mmol) in a 10:1 mixture of dichloromethane/methanol (143 mL) was added a solution of **7** (150 mg, 0.15 mmol) in dichloromethane (40 mL) dropwise at room temperature. The reaction mixture was stirred for 1 h, cooled to ice cold temperature, and quenched with saturated aqueous sodium bisulfite. The reaction mixture was concentrated and then partitioned between H_2O and EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 50:50) to afford **20** as a colorless oil (70 mg, 91%): $[\alpha]^{24}_D$ −141.66 (*c* 5.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.54 (s, 1H), 9.29 (d, J = 5.5 Hz, 1H), 8.73 (d, J = 9.5 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.70−7.68 (m, 1H), 7.62 (s, 1H), 7.57−7.50 (m, 2H), 5.24 (dd, J = 10.0, 15.0 Hz, 1H), 5.07−5.04 (m, 1H), 4.99 (t, J = 7.5 Hz, 1H), 3.84 (dd, J = 6.0, 15.0 Hz, 1H), 3.65−3.62 (m, 1H), 3.45−3.41 (m, 2H), 3.05 (dd, J = 8.0, 15.0 Hz, 1H), 2.77 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 168.1, 168.0, 167.4, 153.5, 141.5, 134.0, 132.0, 129.8, 128.7, 127.2, 126.2, 120.4, 83.7, 58.8, 53.0, 43.6, 43.1, 40.1, 29.2, 27.9; HRMS (DART-TOF) *m*/*z* calculated for $C_{23}H_{29}N_4O_6S_2$ $[M + H]^+$ 521.1529, found 521.1514.

(4*R*,10*S*)-10-(3-Hydroxyquinoline-2-carboxamido)-5-methyl-6,9-dioxo-1,2-dithia-5,8-diazacycloundecane-4-carboxylic acid (5). Compound **20** (62 mg, 0.12 mmol) was treated with TFA (2 mL) for 1 h at room temperature. The reaction mixture was concentrated and purified by column chromatography on silica gel (MeOH/CH_2Cl_2, 10:90) to afford **5** as a white solid (45 mg, 82%): mp 210−212 °C; $[\alpha]^{25}_D$ −120.2 (*c* 0.79, CH_3COCH_3); ^{1}H NMR (400 MHz, CD_3COCD_3) δ 11.75 (s, 1H), 9.33 (d, J = 6.4 Hz, 1H), 8.67 (d, J = 9.6 Hz, 1H), 8.04−8.02 (m, 1H), 7.86−7.83 (m, 1H), 7.74 (s, 1H), 7.64−7.58 (m, 2H), 5.11−5.02 (m, 3H), 3.84 (dd, J = 5.6, 14.8 Hz, 1H), 3.57 (d, J = 14.8 Hz, 1H), 3.50 (dd, J = 6.4, 15.2 Hz, 1H), 3.33 (dd, J = 2.8, 15.2 Hz, 1H), 3.18 (dd, J = 8.0, 15.2 Hz, 1H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 170.6, 169.5, 168.0, 167.5, 153.9, 141.4, 134.5, 132.3, 129.5, 129.0, 127.6, 126.6, 120.3, 57.8, 53.0, 43.7, 43.0, 40.1, 28.4; HRMS (DART-TOF) *m*/*z* calculated for $C_{19}H_{21}N_4O_6S_2$ $[M + H]^+$ 465.0903, found 465.0908.

Methyl *N*-((4*R*,10*S*)-10-(3-Hydroxyquinoline-2-carboxamido)-5-methyl-6,9-dioxo-1,2-dithia-5,8-diazacycloundecane-4-carbonyl)-*N*-methyl-L-alaninate (21). To a solution of *N*-methyl-L-alanine methyl ester (7.0 mg, 0.06 mmol) and **5** (24 mg, 0.05 mmol) in DMF (1 mL) were added HOAt (8.5 mg, 0.06 mmol), EDC (11.5 mg, 0.06 mmol), and diisopropyl ethylamine (8.0 mg, 0.06 mmol). The reaction mixture was stirred for 3 h at room temperature and then quenched by the addition of 1 N $HCl_{(aq)}$. The aqueous layer was extracted with EtOAc (2 × 15 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (MeOH/CH_2Cl_2, 5:95) to give **21** as a pale yellow solid (26 mg, 90%): $[\alpha]^{25}_D$ −30 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), mixture of two rotamers, δ 11.37 and 11.36 (s, 1H), 8.98−8.95 (m, 1H), 8.01−7.99 (m, 1H), 7.75−7.70 (m, 2H), 7.66 (s, 1H), 7.59−7.52 (m, 2H), 5.23−5.14 (m, 2H), 4.97−4.81 (m, 2H), 3.93−3.69 (m, 6H), 3.19−3.17 (m, 3.3H), 3.00 (s, 1H), 2.85−2.74 (m, 3.7H), 1.69 and 1.47 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of two rotamers, δ 171.3, 168.92, 168.87, 168.1, 167.9, 153.5, 141.5 and 141.0, 133.7, 132.4 and 132.2, 129.6 and 129.5, 129.0, 127.6 and 127.5, 126.4, 120.7, 57.8, 54.54 and 54.50, 54.24 and 54.22, 52.8 and 52.5, 44.4 and 44.2, 43.6, 43.3, 32.2 and 30.2, 30.1 and 29.9, 16.3 and 14.4; HRMS (DART-TOF) *m*/*z* calculated for $C_{24}H_{30}N_5O_7S_2$ $[M + H]^+$ 564.1587, found 564.1609.

(4*R*,10*S*)-10-(3-Hydroxyquinoline-2-carboxamido)-5-methyl-6,9-dioxo-*N*-((*S*)-1-phenylethyl)-1,2-dithia-5,8-diazacycloundecane-4-carboxamide (22). To a solution of (*S*)-phenylethylamine (6.5 mg, 0.05 mmol) and **5** (24 mg, 0.05 mmol) in DMF (1 mL) were added HOAt (8.5 mg, 0.06 mmol) and EDC (11.5 mg, 0.06 mmol). The reaction mixture was stirred for 3 h at room temperature and then quenched by the addition of 1 N $HCl_{(aq)}$. The aqueous layer was extracted with EtOAc (2 × 15 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 50:50) to give **22** as a pale yellow solid (27 mg, 94%): mp 146−148 °C; $[\alpha]^{26}_D$ −43.3 (*c* 2.08, $CHCl_3$); ^{1}H NMR

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(400 MHz, $CDCl_3$) δ 11.43 (s, 1H), 9.13 (d, J = 3.2 Hz, 1H), 8.41 (brs, 1H), 8.00 (d, J = 7.6 Hz, 1H), 7.71−7.68 (m, 1H), 7.63 (s, 1H), 7.58−7.51 (m, 2H), 7.37−7.28 (m, 6H), 5.12−5.08 (m, 2H), 4.97 (brs, 1H), 4.77 (t, J = 7.2 Hz, 1H), 3.76 (dd, J = 6.4, 14.4 Hz, 1H), 3.62 (d, J = 14.8 Hz, 1H), 3.41 (brs, 1H), 3.29 (d, J = 14.8, 1H), 3.09−2.95 (m, 1H), 2.96 (s, 1H), 1.57 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 168.6, 167.9, 167.3, 153.5, 142.3, 141.5, 133.9, 132.1, 129.8, 128.9, 128.7, 127.6, 127.4, 126.3, 120.6, 58.4, 53.2, 49.4, 43.9, 43.3, 41.0, 30.0, 22.0; HRMS (DART-TOF) m/z calculated for $C_{27}H_{30}N_5O_5S_2$ $[M + H]^+$ 568.1688, found 568.1696.

Thiochondrilline C (4). To a solution of **6** (17 mg, 0.1 mmol), **5** (24 mg, 0.05 mmol), and diisopropyl ethylamine (13 mg, 0.1 mmol) in DMF (1 mL) was added T3P (50% in DMF, 127 mg, 0.2 mmol) dropwise at 0 °C. The reaction mixture was stirred for 24 h and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (MeOH/CH_2Cl_2, 10:90) and then by reversed-phase C_{18}-column (MeOH/H_2O, 60:40) to afford thiochondrilline C as a white solid (26 mg, 82%): $[\alpha]^{23}_D$ −76.0 (c 0.46, $CHCl_3$) [lit.[11] $[\alpha]^{25}_D$ −77.0 (c 0.0011, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of rotamers, δ 11.45 and 11.38, 9.15, and 8.96 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.91 (brd, J = 9.6 Hz, 1H), 7.74−7.70 (m, 1H), 7.65 (s, 1H), 7.60−7.52 (m, 2H), 5.30−5.15 (m, 2H), 5.08 (dd, J = 4.0, 11.2 Hz, 1H), 4.90 (brt, J = 8.0 Hz, 1H), 3.96 (brs, 1H), 3.83−3.76 (m, 4H), 3.70 (dd, J = 9.6, 14.4 Hz, 1H), 3.30−3.13 (m, 5H), 2.97−2.90 (m, 4H), 2.78 (brd, J = 11.6 Hz, 1H), 2.40 and 2.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 168.9 (2C), 168.6, 167.9, 153.5, 141.5, 133.8, 132.2, 129.6, 128.9, 127.5, 126.4,120.7, 57.9, 57.7, 54.3, 52.7, 44.3, 43.8, 43.3, 32.9, 32.8, 30.5, 15.6; HRMS (DART-TOF) m/z calculated for $C_{25}H_{32}N_5O_7S_3$ $[M + H]^+$ 610.1464, found 610.1471.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.5b00428.

NMR spectral data of **4**, **5**, **7**, **12**, **14**, and **16**−**22**, as well as the LC-MS of **4** (PDF)

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Notes

The authors declare no competing financial interest.

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