Supporting information for:

**Miyaura Borylation Suzuki-Miyaura Coupling (BSC) Sequence of 4-bromo-2,4'-bithiazoles with Halides: Straightforward Access to Heterocyclic Cluster of D-series of Thiopeptide GE2270**

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**Table of contents**

*General information:* ....................................................................................................................................... S2

*Experimental section* ..................................................................................................................................... S3

1.  **Synthesis of the 2’alkyl and 2’aryl 4-bromo-2,4’-bithiazole 4a-c**................................................................... S3

   *General procedure A:* .............................................................................................................................. S4

2.  **Borylation Suzuki-Miyaura Coupling (BSC) of 4-bromo-2,4’-bithiazoles with various halides**............. S6

   *General procedure B:* .............................................................................................................................. S6

3.  **Novel synthetic route to heterocyclic cluster of thiopeptide GE2270**................................................. S9
General information:

tert-Butyl 2-(2-chloro-6-(4-(ethoxycarbonyl)thiazol-2-yl)pyridine-3-yl)thiazole-4-carboxylate 2,\(^1\) Benzyl (2S,3S)-1-amino-3-(tert-butyldimethylsilyloxy)-3-phenyl-1-thioxopropan-2-ylcarbamate 8d\(^1\) were prepared according to procedures reported in the literature.

1. Solvents and reagents

All commercially available reagents were used as received, except otherwise specified. Palladium catalyst and phosphine ligands were stored in desiccators. Extra dry solvents were obtained from Accros Organic® in sealed bottles over 3Å or 4Å molecular sieves and stored under N₂.

2. Purification

Chromatography columns were performed using silica gel (mesh size 60-80 mesh). TLC were performed using Merck® TLC silica gel 60 F₂₅₄ and product revealed by UV irradiation (\(\lambda = 254\) nm).

3. Analysis

\(^1\)H and \(^{13}\)C NMR spectra were recorded at room temperature on a Brucker Advance spectrometer operating at 300 MHz and 75 MHz respectively. Chemical shifts (δ) are given as ppm relative to the residual solvent peak (7.26 for \(^1\)H and 77.16 for \(^{13}\)C in CDCl₃). Splitting patterns are indicating as fellow: br: broad; s: singulet; d: doublet; t: triplet; q: quartet; qt: quintuplet; sp: septuplet; dd: doublet of doublet; dt: doublet of triplet; tt: triplet of triplet; qt: quintuplet; m: multiplet.

IR spectra were obtained with Bomen MB-100 (KBr pellet) or Perkin Elmer Spectrum 100 FT IR spectrometers.

Microanalyses were carried out on the flash 2000 series from Thermo Fisher.

Melting Point were measured on a Fisher Scientific hot stage melting point apparatus and are uncorrected.

GC/MS analysis (EI, 70 Ev) were performed on the Agilent GC: 6850, MS: 5975 using HP-5MS column (30 m x 0.25 mm x 0.25 µm) with the following method: 50 °C (2 min) to 250 °C (15 min) with an increase of 25 °C.min⁻¹.

Mass analysis (ESI) were performed on a LCQ Advantage.

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Experimental section

1. Synthesis of the 2'-alkyl and 2'-aryl 4-bromo-2,4'-bithiazole 4a-c

Prepared according to Cossy’s procedure.² To a solution of 2,4-dibromothiazole (6.0 g, 24.7 mmol) in Et₂O (60 mL) was added nBuLi 2.5 M in hexanes (27.2 mmol, 1.1 equiv.) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C and N-acetylmorpholine (4.3 mL, 37.05 mmol, 1.5 equiv) was then added dropwise at −78 °C. The reaction mixture was warmed up to room temperature, stirred for 12 h and then quenched with H₂O and extracted with Et₂O (3 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (PE/CH₂Cl₂ from 8:2 to 6:4) to afford 6 (4.39 g, 21.3 mmol) in 86% yield as a colorless solid. Exhibited spectra data identical to previous reports.³

¹H-NMR (300 MHz, CDCl₃): δ (ppm) = 7.57 (s, 1 H), 2.71 (s, 3 H).
¹³C-NMR (75 MHz, CDCl₃): δ (ppm) = 190.4 (C), 166.9 (C), 126.8 (CH), 124.9 (C), 25.8 (CH₃).

Prepared according to Natile’s procedure⁴ To a solution of 4-bromo-2-(bromoacetyl)thiazole 6 (1.263 g, 6.13 mmol) in 20 mL of anhydrous THF was added pyridinium bromide perbromide (2.056 g, 1.1 equiv). Then the

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solution was heated at 45 °C for 14h. After cooling, the crude mixture was diluted with H₂O and extracted three times with Et₂O. The combined organic layers were washed with 10 % Na₂S₂O₃ aq. soln., brine and dried over MgSO₄. The crude product was purified by flash column chromatography (PE/CH₂Cl₂ from to 8:2 to 6:4) afforded 7 (1.45 g, 5.09 mmol) in 83% yield as colorless solid.

Exhibited spectra data identical to previous reports.⁵

\(^{1}\text{H-NMR (300 MHz, CDCl₃)}\): δ (ppm) = 7.68 (s, 1 H), 4.69 (s, 2 H).

\(^{13}\text{C-NMR (75 MHz, CDCl₃)}\): δ (ppm) = 183.8 (C), 163.6 (C), 127.7 (C), 126.4 (CH), 30.6 (CH₂).

General procedure A:

To a solution of α-bromoketone 7 (1 equiv) and CaCO₃ (1 equiv) in EtOH (0.25 M) was added thiobenzamide 8 (1.2 equiv), and the resulting solution was stirred for 6 h at reflux. After cooling, the solution was filtered and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated in vacuo.

According to general procedure A, using 7 (1.34 g, 4.70 mmol) and 2-methylpropanethioamide 8a (583 mg, 5.65 mmol, 1.2 equiv) and CaCO₃ (471 mg, 4.71 mmol, 1 equiv). Standard treatment (see general procedure A), and the crude product was purified by flash column chromatography (PE/EtOAc 8:2) afforded 4a (1.25 g, 4.32 mmol) in 92% yield as a pale brown needles.

Mp = 78–80°C (Et₂O).

\(^{1}\text{H-NMR (300 MHz, CDCl₃)}\): δ (ppm) = 7.87 (s, 1H), 7.21 (s, 1H), 3.34 (sept, J = 6.9 Hz, 1H) 1.43 (d, J = 6.9 Hz, 6H).

\(^{13}\text{C-NMR (75 MHz, CDCl₃)}\): δ (ppm) = 179.0 (C), 163.9 (C), 147.5 (C), 125.9 (C), 117.2 (CH), 115.7 (CH), 33.4 (CH), 23.2 (2xCH₃).

IR (neat): 3116, 2957, 2923, 2865, 1483, 1442, 1305, 1283, 1181, 1072, 1020, 793 cm⁻¹.

MS (ES-TOF) m/z 288.9 [M+H⁺; ⁷⁹Br] and 290.9 [M+H⁺; ⁸¹Br].


According to general procedure A, using 7 (415 mg, 1.46 mmol) and thiobenzamide 8b (220 mg, 1.75 mmol, 1.2 equiv) and CaCO₃ (146 mg, 1.46 mmol, 1 equiv). Standard treatment (see general procedure A), and the crude product was purified by flash column chromatography (PE/CH₂Cl₂ 9:1 to 6:4) afforded 4b (390 mg, 1.21 mmol) in 83% yield as a colorless solid. 

Mp = 196–197°C (PE/Et₂O).

¹H-NMR (300 MHz, CDCl₃): δ (ppm) = 8.02–7.99 (m, 3 H), 7.48–7.45 (m, 3 H), 7.27 (s, 1 H).

¹³C-NMR (75 MHz, CDCl₃): δ (ppm) = 168.9 (C), 163.7 (C), 149.0 (C), 132.8 (C), 130.8 (CH), 129.1 (2xCH), 126.8 (2xCH), 126.0 (C), 117.7 (CH), 116.6 (CH).

IR (neat): 3126, 3111, 1474, 1451, 1298, 1253, 1184, 1179, 1087 cm⁻¹.

HRMS (ESI+): calcd for C₁₂H₈BrN₂S: 322.9307; found 322.9305.

According to general procedure A, using 7 (415 mg, 1.46 mmol) and thionicotinamide 8c (222 mg, 1.75 mmol, 1.2 equiv) and CaCO₃ (146 mg, 1.46 mmol, 1 equiv). Standard treatment (see general procedure A), and the crude product was purified by flash column chromatography (PE/EtOAc 9:1 to 7:3) afforded 4c (306 mg, 0.94 mmol) in 65% yield as colorless solid.

Mp = 224–225°C (PE/Et₂O).

¹H-NMR (300 MHz, CDCl₃): δ (ppm) = 9.22 (d, J = 1.7 Hz, 1 H), 8.70 (dd, J = 4.8 and 1.6 Hz, 1 H), 8.30 (dt, J = 8.0 and 1.9 Hz, 1H), 8.07 (s, 1 H), 7.43 (ddd, J = 7.9, 4.8 and 0.5 Hz, 1 H), 7.29 (s, 1 H).

¹³C-NMR (75 MHz, CDCl₃): δ (ppm) = 165.5 (C), 163.2 (C), 151.5 (CH), 149.4 (C), 147.9 (CH), 133.9 (CH), 128.9 (C), 126.2 (C), 123.9 (CH), 117.9 (CH), 117.2 (CH).

IR (neat): 3127, 3117, 1573, 1465, 1442, 1422, 1308, 1256, 1187, 1083 cm⁻¹.

HRMS (ESI+): calcd for C₁₁H₇BrN₃S₂: 323.9259, found 323.9254.
2. Borylation Suzuki-Miyaura Coupling (BSC) of 4-bromo-2,4’-bithiazoles with various halides

Scheme 2

General procedure B:

The 4-bromo-2,4’-bithiazole (0.25 mmol, 1.2 equiv) was weighed in a sealed tube, followed by bis(pinacolato)diboron (64 mg, 1.2 equiv), potassium acetate (50 mg, 2.4 equiv), Pd(OAc)$_2$ (5 mol%) and dpff (5 mol%). The tube was evacuated and backfilled three times with N$_2$ and degassed anhydrous 1,4-dioxane (0.85 mL) was added. Then, the reaction mixture was heated at 110 °C until completion of the starting material (checked by TLC). Once, the reaction is completed, the sealing cap was removed and, the appropriate halide (1 equiv) and K$_3$PO$_4$ (5 equiv) were added. The tube was re-sealed and flushed with dry N$_2$, then degassed 1,4-dioxane (0.21 mL) and degassed water (0.21 mL) were added. The resulting mixture was stirred for 12 h at 110 °C. The crude mixture was cooled to room temperature, filtered through a short pad of Celite®, washed with EtOAc (50 mL) and the solvents were removed under reduced pressure. The crude product was then purified by flash column chromatography.

$\text{5aA}$

$2'$-isopropyl-4-(pyridin-2-yl)-2,4'-bithiazole 5aA: Compound 5aA was prepared according to the procedure B using 4a (72 mg, 0.25 mmol, 1.2 eq) and 2-chloropyridine (20 µL, 0.21 mmol, 1 eq). The crude product was purified by flash chromatography (PE/EtOAc 8:2) to afford 5aA in 98% (59 mg, 0.20 mmol) as a colorless solid.

$\text{Mp} = 113–114°C$ (PE/EtOAc)

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ (ppm) = 8.63 (ddd, $J = 4.8, 1.7$ and 0.9 Hz, 1H), 8.20 (dt, $J = 8.0$ and 0.9 Hz, 1H), 8.08 (s, 1H), 7.92 (s, 1H), 7.77 (td, $J = 7.7$ and 1.8 Hz, 1H), 7.23 (ddd, $J = 7.5$, 4.8 and 1.2 Hz, 1H), 3.38 (hept, $J = 6.9$ Hz, 1H), 1.45 (d, $J = 6.9$ Hz, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ (ppm) = 178.8 (C), 163.1 (C), 156.1 (C), 152.7 (C), 149.5 (CH), 148.8 (C), 137.1 (CH), 122.9 (CH), 121.3 (CH), 117.6 (CH), 115.0 (CH), 33.5 (CH), 23.3
IR (neat): 3118, 3087, 2925, 2868, 1588, 1570, 1489, 1464, 1422, 1178, 1030 cm\(^{-1}\).

HRMS (ESI\(^+\)): calcd for C\(_{14}\)H\(_{14}\)N\(_3\)S\(_2\): 288.0624; found 288.0622.

5aB

2'-isopropyl-4-(6-methoxypyridin-2-yl)-2,4'-bithiazole 5aB: Compound 5aB was prepared according to the procedure B using 4a (72 mg, 0.25 mmol, 1.2 eq) and 2-bromo-6-methoxypyridine (26 \(\mu\)L, 0.21 mmol, 1 eq). The crude product was purified by flash chromatography (PE/EtOAc 95:5) to afford 5aB in 88% (59 mg, 0.19 mmol) as a colorless solid.

\(\text{Mp} = 90–91^\circ\text{C (PE/EtOAc)}\)

\(^1\text{H-NMR (300 MHz, CDCl}_3\)): \(\delta (\text{ppm}) = 8.07 (s, 1\text{H}), 7.91 (s, 1\text{H}), 7.81 (dd, J = 7.4 \text{ and } 0.8 \text{ Hz, 1H}), 7.66 (dd, J = 8.2 \text{ and } 7.4 \text{ Hz, 1H}), 6.70 (dd, J = 8.2 \text{ and } 0.8 \text{ Hz, 1H}), 4.02 (s, 3\text{H}), 3.39 (\text{hept, } J = 6.9 \text{ Hz, 1H}), 1.45 (d, J = 6.9 \text{ Hz, 6H}).\)

\(^{13}\text{C-NMR (75 MHz, CDCl}_3\)): \(\delta (\text{ppm}) = 178.8 (C), 163.7 (C), 162.9 (C), 156.2 (C), 150.0 (C), 148.8 (C), 139.5 (CH), 117.3 (CH), 114.8 (CH), 113.8 (CH), 110.2 (CH), 53.3 (CH\(_3\)), 33.4 (CH), 23.2 (2xCH\(_3\)).\)

IR (neat): 3118, 2943, 2869,2852, 1605, 1593, 1577, 1492, 1461, 1409, 1316, 1299, 1258, 1180, 1027 cm\(^{-1}\).

HRMS (ESI\(^+\)): calcd for C\(_{15}\)H\(_{16}\)N\(_3\)OS\(_2\): 318.0729; found 318.0734.

5aC

4-(6-chloropyridin-3-yl)-2'-isopropyl-2,4'-bithiazole 5aC: Compound 5aC was prepared according to the procedure B using 4a (72 mg, 0.25 mmol, 1.2 eq) and 2-chloro-5-iodopyridine (50 mg, 0.21 mmol, 1 eq). The crude product was purified by flash chromatography (PE/EtOAc 9:1) to afford 5aC in 76% (51 mg, 0.16 mmol) as a colorless solid.

\(\text{Mp} = 157–158^\circ\text{C (PE/EtOAc)}\)

\(^1\text{H-NMR (300 MHz, CDCl}_3\)): \(\delta (\text{ppm}) = 8.94 (dd, J = 2.5 \text{ and } 0.7 \text{ Hz, 1H}), 8.22 (dd, J = 8.3 \text{ Hz, 1H}), 7.96 (s, 1\text{H}), 7.82 (dd, J = 7.4 \text{ and } 0.8 \text{ Hz, 1H}), 6.87 (dd, J = 8.2 \text{ and } 7.4 \text{ Hz, 1H}), 4.03 (s, 3\text{H}), 3.43 (\text{hept, } J = 7.2 \text{ Hz, 1H}), 1.43 (d, J = 7.2 \text{ Hz, 6H}).\)
and 2.5 Hz, 1H), 7.92 (s, 1H), 7.57 (s, 1H), 7.39 (dd, \( J = 8.3 \) and 0.7 Hz, 1H), 3.38 (hept, \( J = 6.8 \) Hz, 1H), 1.45 (d, \( J = 6.9 \) Hz, 6H).

\(^{13}\text{C-NMR (75 MHz, CDCl}_3\)): \( \delta \) (ppm) = 179.0 (C), 163.8 (C), 151.9 (C), 150.6 (C), 148.4 (C), 147.6 (CH), 136.5 (CH), 129.4 (C), 124.3 (CH), 115.4 (CH), 114.9 (CH), 33.4 (CH), 23.2 (2xCH\(_3\)).

IR (neat): 3113, 3081, 3040, 2958, 1566, 1534, 1487, 1450, 1377, 1308, 1277, 1176, 1101 cm\(^{-1}\).

HRMS (ESI\(^+\)): calcd for \( \text{C}_{14}\text{H}_{13}\text{ClN}_3\text{S}_2 \): 322.0234; found 322.0237.

\( \text{5aD} \)

**4-(5-chloropyridin-2-yl)-2'-isopropyl-2,4'-bithiazole 5aD:** Compound **5aD** was prepared according to the procedure B using **4a** (72 mg, 0.25 mmol, 1.2 eq) and 2,5-dichloropyridine (31 mg, 0.21 mmol, 1 eq). The crude product was purified by flash chromatography (PE/EtOAc 9:1) to afford **5aD** in 68% (46 mg, 0.14 mmol) as a colorless solid.

\( \text{Mp} = 155–156^\circ\text{C (PE/EtOAc)} \)

\(^1\text{H-NMR (300 MHz, CDCl}_3\)): \( \delta \) (ppm) = 8.57 (dd, \( J = 2.5 \) and 0.7 Hz, 1H), 8.17 (dd, \( J = 8.4 \) and 0.7 Hz, 1H), 8.07 (s, 1H), 7.91 (s, 1H), 7.75 (dd, \( J = 8.5 \) and 2.5 Hz, 1H), 3.39 (hept, \( J = 6.9 \) Hz, 1H), 1.46 (d, \( J = 6.9 \) Hz, 6H).

\(^{13}\text{C-NMR (75 MHz, CDCl}_3\)): \( \delta \) (ppm) = 178.9 (C), 163.3 (C), 155.0 (C), 150.8 (C), 148.6 (C), 148.4 (CH), 136.6 (CH), 130.9 (C), 122.0 (CH), 118.0 (CH), 115.0 (CH), 33.4 (CH), 23.2 (2xCH\(_3\)).

IR (neat): 3123, 2969, 2865, 1581, 1539, 1491, 1455, 1369, 1306, 1172, 1105, 1011 cm\(^{-1}\).

HRMS (ESI\(^+\)): calcd for \( \text{C}_{14}\text{H}_{13}\text{ClN}_3\text{S}_2 \): 322.0234; found 322.0238.

\( \text{5aE} \)

**2'-isopropyl-4-(pyrimidin-5-yl)-2,4'-bithiazole 5aE:** Compound **5aE** was prepared according to the procedure B using **4a** (72 mg, 0.25 mmol, 1.2 eq) and 5-bromopyrimidine (33.4 mg, 0.21 mmol, 1 eq). The crude product was purified by flash chromatography (PE/EtOAc 6:4) to afford...
5aE in 98% (59 mg, 0.205 mmol) as a pale yellow solid.

Mp = 166-167 °C (CH₂Cl₂/Pentane)

¹H-NMR (300 MHz, CDCl₃): δ (ppm) = 9.28 (s, 2H), 9.18 (s, 1H), 7.94 (s, 1H), 7.66 (s, 1H), 3.38 (hept, J = 6.9 Hz, 1H), 1.45 (d, J = 6.9 Hz, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ (ppm) = 179.1 (C), 164.3 (C), 157.9 (CH), 154.5 (CH), 149.9 (C), 148.3 (C), 128.4 (C), 115.8 (CH), 115.7 (CH), 33.5 (CH), 23.3 (2xCH₃).

IR (neat): 3118, 2961, 2927, 2866, 1588, 1488, 1308, 1031, 797, 761

HRMS (ESI+): calcd for C₁₃H₁₃N₄S₂: 289.0582; found 289.0568.

5aF

2'-isopropyl-4-(pyrazine-2-yl)-2,4'-bithiazole 5aF: Compound 5aF was prepared according to the procedure B using 4a (72 mg, 0.25 mmol, 1.2 eq) and 2-chloropyrazine (19 µL, 0.21 mmol, 1 eq). The crude product was purified by flash chromatography (PE/EtOAc 7:3) to afford 5aF in 82% (50 mg, 0.17 mmol) as a colorless solid.

Mp = 83–84°C (PE/EtOAc)

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 9.42 (s, 1H), 8.54 (s, 1H), 8.50 (s, 1H), 8.11 (s, 1H), 7.94 (s, 1H), 3.36 (hept, J = 6.9 Hz, 1H), 1.43 (d, J = 6.9 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 179.0 (C), 163.8 (C), 153.5 (C), 148.4 (C), 148.1 (C), 144.0 (CH), 143.63 (CH), 143.1 (CH), 119.4 (CH), 115.4 (CH), 33.4 (CH), 23.2 (2xCH₃).

IR (neat): 3129, 3115, 2971, 2920, 2852, 1679, 1602, 1533, 1495, 1383, 1311, 1066 cm⁻¹.

MS (ES-TOF) m/z 289.0 [M+H⁺].


5aG

Ethyl 2''-isopropyl-[2,4':2',4''-terthiazole]-4-carboxylate 5aG: Compound 5aG was prepared according to the procedure B using 4a (72 mg, 0.25 mmol, 1.2 eq) and ethyl 2-bromothiazole-4-carboxylate (49 mg, 0.208 mmol, 1 eq). The crude product was purified by
flash chromatography (PE/Et₂O 7:3) to afford 5aG in 60% (45 mg, 0.125 mmol) as a colorless solid.

\[ \text{Mp} = 187–188°C (\text{PE/Et₂O}). \]

\[ ^1\text{H}-\text{NMR} (300 \text{ MHz, CDCl₃}): \delta (\text{ppm}) = 8.19 (s, 1H), 8.14 (s, 1H), 7.93 (s, 1H), 4.45 (q, J = 7.0 Hz, 2H), 3.37 (hept, J = 7.0 Hz, 1H), 1.44 (d, J = 7.0 Hz, 6H), 1.43 (t, J = 7.0 Hz, 3H). \]

\[ ^{13}\text{C}-\text{NMR} (75 \text{ MHz, CDCl₃}): \delta (\text{ppm}) = 179.0 (C), 163.6 (C), 163.5 (C), 161.6 (C), 149.1 (C), 148.1 (C), 148.0 (C), 127.9 (CH), 117.9 (CH), 115.8 (CH), 61.7 (CH₂), 33.4 (CH), 23.2 (2xCH₃), 14.5 (CH₃). \]

\[ \text{IR (neat): 3125, 2957, 2865, 1729, 1540, 1484, 1420, 1197, 1199 cm}^{-1}. \]

\[ \text{HRMS (ESI⁺): calcd for C}_{15}\text{H}_{16}\text{N}_{3}\text{O}_{2}\text{S}_{3}: 366.0405; \text{found 366.0393.} \]

2'-isopropyl-4-phenyl-2,4'-bithiazole 5aH: Compound 5aH was prepared according to the procedure B using 4a (72 mg, 0.25 mmol, 1.2 eq) and iodobenzene (24 µL, 0.208 mmol, 1 eq). The crude product was purified by flash chromatography (PE/Et₂O 95:5) to afford 5aH in 95% (56 mg, 0.20 mmol) as a colorless solid.

\[ \text{Mp} = 81–82°C (\text{CH}_2\text{Cl}_2/\text{pentane}) \]

\[ ^1\text{H}-\text{NMR} (300 \text{ MHz, CDCl₃}): \delta (\text{ppm}) = 7.99-7.96 (m, 2H), 7.93 (s, 1H), 7.49 (s, 1H), 7.47-7.42 (m, 2H), 7.37–7.32 (m, 1H), 3.37 (hept, J = 7.0 Hz, 1H), 1.44 (d, J = 7.0 Hz, 6H). \]

\[ ^{13}\text{C}-\text{NMR} (75 \text{ MHz, CDCl₃}): \delta (\text{ppm}) = 178.7 (C), 162.9 (C), 156.3 (C), 148.9 (C), 134.6 (C), 128.8 (2xCH), 128.2 (CH), 126.5 (2xCH), 114.8 (CH), 113.4 (CH), 33.4 (CH), 23.2 (2xCH₃). \]

\[ \text{IR (neat): 3110, 2959, 2865, 1443, 1179, 759, 686 cm}^{-1}. \]

\[ \text{MS (ES-TOF) m/z 287.0} \ [\text{M+H}^+] \]

\[ \text{HRMS (ESI-TOF): calcd for C}_{13}\text{H}_{15}\text{N}_{2}\text{S}_{2}: 287.0677; \text{found 287.0684.} \]

(E)-4-(3,4-dimethoxystyril)-2'-isopropyl-2,4'-bithiazole 5aI: Compound 5aI was prepared according to the procedure B using 4a (72 mg, 0.25 mmol, 1.2 eq) and (E)-4-(2-bromovinyl)-
1,2-dimethoxybenzene (51 mg, 0.208 mmol, 1 eq). The crude product was purified by flash chromatography (PE/EtO 95:5) to afford 5a in 96% (74 mg, 0.20 mmol) as a yellow foam.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ (ppm) = 7.91 (s, 1H), 7.48 (d, $J = 15.9$ Hz, 1H), 7.15 (s, 1H), 7.10-7.08 (m, 2H), 7.01 (d, $J = 15.9$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.39 (hept, $J = 7.0$ Hz, 1H), 1.45 (d, $J = 7.0$ Hz, 6H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ (ppm) = 178.8 (C), 162.9 (C), 155.2 (C), 149.1 (2xC), 148.7 (C), 131.3 (CH), 130.1 (C), 120.2 (CH), 119.6 (CH), 115.0 (CH), 114.9 (CH), 11.2 (CH), 108.8 (CH), 56.0 (CH$_3$), 55.9 (CH$_3$), 33.4 (CH), 23.2 (2xCH$_3$).

IR (neat): 3103, 2961, 2928, 2833, 1599, 1512, 1261, 1245, 1136, 1023 cm$^{-1}$.

HRMS (ES-TOF): calcd for C$_{19}$H$_{21}$N$_2$O$_2$S$_2$: 373.1044; found 373.1055.

2'-Phenyl-4-(pyridin-2-yl)-2,4'-bithiazole 5b: Compound 5b was prepared according to the procedure B using 4b (81 mg, 0.25 mmol, 1.2 eq) and 2-chloropyridine (20 µL, 0.208 mmol, 1 eq). The crude product was purified by flash chromatography (PE/EtOAc 8:2) to afford 5b in 64% (43 mg, 0.13 mmol) as a colorless solid.

$\text{M}p = 194–195^\circ\text{C (Et}_2\text{O)}$.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ (ppm) = 8.65 (ddd, $J = 4.5$, 1.5 and 0.6 Hz, 1H), 8.23 (d, $J = 7.8$ Hz, 1H), 8.13 (s, 1H), 8.07 (s, 1H), 8.06–8.03 (m, 2H), 7.81 (td, $J = 7.8$ and 1.5 Hz, 1H), 7.51–7.47 (m, 3H), 7.28–7.24 (m, 1H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ (ppm) = 168.7 (C), 163.0 (C), 156.2 (C), 152.7 (C), 150.3 (C), 149.6 (CH), 137.2 (CH), 133.1 (C), 130.7 (CH), 129.2 (2xCH), 126.8 (2xCH), 123.0 (CH), 121.4 (CH), 118.1 (CH), 115.9 (CH).

IR (neat): 3113, 3066, 3007, 1588, 1571, 1478, 1465, 1448, 1420, 1186 cm$^{-1}$.

HRMS (ESI+): calcd for C$_{17}$H$_{12}$N$_3$S$_2$: 322.0467 found 322.0461.

4-(pyridin-2-yl)-2'-(pyridin-3-yl)-2,4'-bithiazole 5c: Compound 5c was prepared according to the procedure B using 4c (81 mg, 0.25 mmol, 1.2 eq) and 2-chloropyridine (20
μL, 0.208 mmol, 1 eq). The crude product was purified by flash chromatography (CH₂Cl₂/EtOAc from 95:5 to 9:1) to afford 5cA in 49% (33 mg, 0.10 mmol) as a yellow solid. Mp = 232–233 °C (CH₂Cl₂/pentane).

¹H-NMR (300 MHz, CDCl₃): δ (ppm) = 9.24 (d, J = 2.0 Hz, 1H), 8.70 (dd, J = 1.5 and 4.8 Hz, 1H), 8.66 (d, J = 4.1 Hz, 1H), 8.35 (dt, J = 2.0 and 7.9 Hz, 1H), 8.23 (d, J = 7.9 Hz, 1H), 8.15 (s, 1H), 8.13 (s, 1H), 7.81 (td, J = 1.8 and 7.8 Hz, 1H), 7.44 (dd, J = 4.8 and 7.9 Hz, 1H), 7.28–7.25 (m, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ (ppm) = 165.2 (C), 162.0 (C), 156.4 (C), 152.5 (C), 151.3 (CH), 150.7 (C), 149.6 (CH), 147.9 (CH), 137.1 (CH), 133.9 (CH), 129.1 (C), 123.9 (CH), 123.0 (CH), 121.3 (CH), 118.1 (CH), 116.4 (CH).

IR (neat): 3664, 2988, 2901, 1406, 1066, 1056, 700 cm⁻¹.

MS (ES-TOF) m/z 323.0 [M+H⁺].

HRMS (ES-TOF): calcd for C₁₆H₁₁N₄S₂: 323.0425; found 323.0413.

3. Novel synthetic route to heterocyclic cluster of thiopeptide GE2270

![Scheme 3](image-url)
To a stirred solution of thioamide $8d$ (1.12 g, 2.50 mmol, 1 equiv) in anhydrous DMF (10 mL) at $-20 \, ^\circ C$ were added MS $4^\circ$ (2.5 g) and bromoketone $7$ (0.86 g, 3.02 mmol, 1.2 equiv). The mixture was allowed to warm to $0 \, ^\circ C$ and was stirred at this temperature for 14 hours. Then the mixture was filtered through a Celite® pad and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (eluent: PE/EtOAc 9:1 to 8:2) affording the title compound (1.27 g, 1.96 mmol, 78%) which was dissolved in anhydrous DME (20 mL) and cooled at $-40 \, ^\circ C$ before 2,6-lutidine (2.3 mL, 19.60 mmol) and trifluoroacetic anhydride (1.0 mL, 7.84 mmol) were added. The mixture was allowed to warm to $-20 \, ^\circ C$ and stirred at this temperature for 12 hours. Then NEt$_3$ was added until pH 8-9, water was added and the aqueous layer was extracted three times with CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (eluent: PE/EtOAc, 95:5 to 8:2) affording 3 (1.20 g, 1.90 mmol, 76% over two steps) as a yellow solid.

\[\text{Mp} = 66–67 \, ^\circ C\]
\[\alpha_20^\circ = -4.9 \, (c \ 1.03, \text{CHCl}_3).\]

$^1$H-NMR (300 MHz, CD$_3$CN): $\delta$ (ppm) = 7.96 (s, 1H), 7.44 (s, 1H), 7.37–7.29 (m, 8H), 7.21–7.17 (m, 2H), 6.30 (br s, 1H), 5.21–5.13 (m, 2H), 5.03–4.90 (m, 2H), 0.75 (s, 9H), $-0.14$ (s, 3H), $-0.26$ (s, 3H).

$^{13}$C-NMR (75 MHz, CD$_3$CN): $\delta$ (ppm) = 170.9 (C), 164.3 (C), 156.3 (C), 148.3 (C), 141.8 (C), 137.8 (C), 129.4 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.4 (CH), 128.0 (CH), 126.3 (C), 119.3 (CH), 118.6 (CH), 77.2 (CH), 67.2 (CH$_2$), 60.5 (CH), 25.9 (3×CH$_3$), 18.6 (C), $-4.6$ (CH$_3$), $-5.1$ (CH$_3$).

IR (neat): 3430, 3330, 3120, 3050, 3020, 2960, 2930, 2900, 2860, 1720, 1710, 1500 cm$^{-1}$.

Anal. Calcd for C$_{28}$H$_{32}$BrN$_3$O$_3$Si: C, 53.32; H, 5.11; N, 6.66. Found: C, 53.38; H, 5.17; N, 6.54.

HPLC Chromatograms

HPLC: Chiralpak IA (heptane/isopronol, 7/3), $\lambda = 254 \, \text{nm}$, 1 mL.min$^{-1}$.

$t_R$ (major) = 4.84 min, $t_R$ (minor) = 9.29 min. ee > 99%, dr = 84:16.
Racemic 99% ee, dr : 84:16
Bromothiazole 3 (378 mg, 0.60 mmol, 1.2 equiv), bis(pinacolato)diboron (152 mg, 0.60 mmol, 1.2 equiv), Pd(OAc)$_2$ (6 mg, 0.025 mmol), CyJohnPhos (35 mg, 0.10 mmol) and freshly dried KOAc (118 mg, 1.20 mmol) were charged in a Schlenk flask. It was then evacuated and backfilled three times with N$_2$ and then anhydrous degassed 1,4-dioxane (2.0 mL) was added and the reaction mixture was stirred at 110 °C in a preheated oil bath for 1 hour. Then the mixture was cooled to room temperature and chloropyridine 2 (229 mg, 0.50 mmol, 1 equiv), freshly dried K$_3$PO$_4$ (531 mg, 2.50 mmol), degassed dioxane (0.5 mL) and degassed water (0.5 mL) were added and the mixture was stirred at 110 °C for further 14 hours. Then the mixture was filtered through a Celite® pad and washed with EtOAc. Water was added and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with water, brine, dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (eluent: PE/EtOAc 95:5 to 7:3) affording GE2270A core (210 mg, 0.22 mmol, 43%) as a pale beige solid.

Mp 119–120 °C.

$[\alpha]_D^{20}$ -10.2 (c 1.05, CHCl$_3$).

HPLC: Chiralpak IA (heptane/isopropanol, 8/2), $\lambda = 254$ nm, 1 mL.min$^{-1}$. t$_R$ (major) = 27.859 min, t$_R$ (minor) = 32.804 min. ee > 99%, dr = 91:9.

IR (ATR diamond): 3430, 3330, 3120, 3050, 3020, 2960, 2930, 2900, 2860, 1710, 1500, 1370, 1330, 1250, 1200, 1160, 1100, 1020 cm$^{-1}$.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ (ppm) = 8.42 (s, 2H), 8.32 (s, 1H), 8.09 (s, 1H), 7.95 (s, 1H), 7.49 (s, 1H), 7.33 (br s, 5H), 7.26 (br s, 5H), 5.74 (d, $J = 7.7$ Hz, 1H), 5.31-5.25 (m, 2H), 5.08 (s, 2H), 4.48 (q, $J = 7.0$ Hz, 2H), 1.59 (s, 9H), 1.45 (t, $J = 7.1$ Hz, 5H), 0.85 (s, 9H), –0.02 (s, 3H), –0.17 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ (ppm) = 169.0 (C), 167.7 (C), 165.2 (C), 162.2 (C), 161.5 (C), 160.5 (C), 155.5 (C), 153.5 (C), 150.9 (C), 150.7 (C), 148.6 (C), 148.5 (C), 148.5 (C), 140.2
(CH), 139.8 (C), 136.2 (C), 130.2 (CH), 129.5 (C), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 126.7 (CH), 122.0 (CH), 119.2 (CH), 116.4 (CH), 82.3 (C), 76.4 (CH), 67.2 (CH$_2$), 61.8 (CH$_2$), 59.7 (CH), 28.3 (3xCH$_3$), 25.8 (3xCH$_3$), 18.2 (C), 14.5 (CH$_3$), −4.6 (CH$_3$), −5.2 (CH$_3$).

**MS** (ESI$^+$): $m/z$ 966.8 [(M+H)$^+$], 988.9 [(M+Na)$^+$], 1949.9 [(M+NH$_4$)$^+$].

**HRMS** (ESI$^+$) Calcd for C$_{47}$H$_{51}$N$_6$O$_7$S$_4$Si: 967.2471. Found: 967.2461 [(M+H)$^+$].

HPLC Chromatograms
GE2270A core

![HPLC Chromatogram](image)

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