Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Supporting Information

Improvement of the trypanocide activity of 3-arylthiophene farnesyltransferase inhibitors by modulation of their 3-aryl group

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SYNTHESIS

General methods

Unless otherwise indicated, all reactions were carried out with magnetic stirring and in case of air-sensitive compounds, reactions were carried out in oven-dried glassware under argon. Commercial compounds were used without any further purification. Tetrahydrofuran (THF) was freshly distilled over sodium/benzophenone. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), diisopropylamine and toluene were distilled over calcium hydride. N,N'-dimethylformamide (DMF) was dried over $MgSO_4$ followed by distillation under reduced pressure.

Analytical thin-layer chromatography was carried out on precoated silica gel aluminium plates (SDS TLC plates, silica gel $60F_{254}$). Column chromatography was performed with prepacked Redisep columns. Preparative TLC (PLC) was performed on Merck TLC with silica gel $60F_{254}$.

NMR spectra (^1H and ^{13}C) were recorded on a Brucker Avance 300 (300 MHz) and Avance 500 (500 MHz). Chemical shifts (δ) are given in ppm relative to $CDCl_3$ (7.26 ppm; 77.2 ppm), CD_3OD (3.34 ppm; 49.9 ppm), acetone-d_6 (2.05 ppm; 30.5 ppm) or DMSO-d_6 (2.50 ppm; 39.5 ppm). Splitting patterns are designed as: s, singlet; d, doublet; t, triplet; q, quartet; qi, quintuplet; h: heptuplet; m, multiplet; b, broad and combinations thereof. Coupling constants *J* are reported in hertz (Hz). IR spectra were recorded on a Perkin-Elmer Spectrum BX. Mass spectra were recorded on Thermofinnigan Automass with a quadripole detection (IE) and on Thermoquest AQA Navigator with a TOF detection (ESI-HRMS). UHPLC analyses were realized on Waters Acquity UPLC. Elemental analyses were performed by the Microanalytical Laboratory of the ICSN-Gif-sur-Yvette. Melting points were measured on Büchi b-450 and are uncorrected.

The purity of all target compounds was measured using reversed-phase UHPLC (HSS C-1_ 1;8 µm, 2.1 × 50 mm column): compounds were eluted with 95:5 A/B for 0.5 min then with a gradient of 5-100% B/A for 3.5 min followed by 0:100 isocratic for 1 min at a flow rate of 0.6

mL/min, where solvent A was 0.1% formic acid in H_2O and solvent B was 0.1% formic acid in CH_3CN. Purity was determined on TAC (total absorbance current from 200 to 400 nM).

Chemistry

Ethyl 4-cyano-5-(isopropylthio)-3-(4-methoxyphenyl)thiophene-2-carboxylate (3a)

To a solution (toluene/EtOH 9:1 (v/v), 20.3 mL) of **2** (0.709 g, 2.12 mmol, 1.0 equiv.), K_2CO_3 (2 M in water , 2.65 mL, 0.733 g, 5.30 mmol, 2.5 equiv.), $Pd(PPh_3)_4$ (0.245 g, 0.21 mmol, 0.1 equiv.) and 4-methoxyphenyl boronic acid (0.645 g, 4.24 mmol, 2 equiv.) were added. After stirring for 20 h under reflux, water was added to the reaction mixture which was extracted three times with EtOAc. Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 10:0 to 85:15 (v/v) in 35 min) to afford **3a** as a white amorphous solid (0.302 g, 50%). IR (film, ν , cm^{-1}) 2971, 2918, 2837, 2216, 1713, 1610, 1530, 1496, 1458, 1365, 1358, 1264, 1250, 1180, 1083, 1024, 828, 759, 732, 677. ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, 3H, J = 7.2 Hz), 1.46 (d, 6H, J = 6.6 Hz), 3.63 (h, 1H, J = 6.6 Hz), 3.85 (s, 3H), 4.22 (q, 2H, J = 7.2 Hz), 6.97 (d, 2H, J = 8.7 Hz), 7.38 (d, 2H, J = 8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 23.2, 42.1, 55.3, 61.6, 113.5, 113.8, 116.0, 124.2, 128.6, 130.8, 149.1, 152.7, 160.2, 160.3. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 384.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* calcd for $C_{18}H_{19}NO_3S_2Na^+$, $[M+Na]^+$: 384.0704 found 384.0722. UHPLC 6.17 min, 77%.

Ethyl 4-cyano-5-(isopropylthio)-3-(3-methoxyphenyl)thiophene-2-carboxylate (3b)

To a solution (toluene/EtOH 9:1 (v/v), 7.1 mL) of **2** (0.250 g, 0.75 mmol, 1.0 equiv.), K_2CO_3 (2 M in water , 0.93 mL, 0.258 g, 1.87 mmol, 2.5 equiv.), $Pd(PPh_3)_4$ (0.086 g, 0.07 mmol, 0.1 equiv.) and 3-methoxyphenyl boronic acid (0.227 g, 1.49 mmol, 2 equiv.) were added. After stirring for 5 h under reflux, water was added to the reaction mixture which was extracted three times with EtOAc. Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 10:0 to 85:15 (v/v) in 35 min) to afford **3b** as a white amorphous solid (0.111 g, 41%). Elemental analysis Found: C, 59.96; H, 5.30; N, 4.07; O, 13.29; S 17.94. Calc for $C_{18}H_{19}NO_3S_2$: C, 59.81; H, 5.30; N, 3.87; O, 13.28; S, 17.74%. IR (film, ν , cm^{-1}) 2976, 2899, 2223, 1721, 1608, 1578, 1527, 1449, 1399, 1353, 1274, 1228, 1184, 1161, 1045, 1018, 875, 779, 751, 715, 682. ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, 3H, J = 7.2 Hz), 1.48 (d, 6H, J = 6.6 Hz), 3.65 (h, 1H, J = 6.6 Hz), 3.85 (s, 3H), 4.22 (q, 2H, J = 7.2 Hz), 6.98 (m, 3H), 7.37 (t, 1H, J = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 23.1, 42.2, 55.3, 61.7, 113.6, 114.8, 114.9, 116.0, 121.6, 129.1, 129.4, 133.4, 148.9, 152.7, 159.2, 160.1. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 384.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* calcd for $C_{18}H_{19}NO_3S_2Na^+$, $[M+Na]^+$: 384.0704 found 384.0710.

Ethyl 4-cyano-5-(isopropylthio)-3-(2-methoxyphenyl)thiophene-2-carboxylate (3c)

To a solution (1,4-dioxane, 24 mL) of **2** (0.844 g, 2.53 mmol, 1.0 equiv.), Cs_2CO_3 (2.06 g, 6.31, 2.5 equiv.), $Pd(PPh_3)_4$ (0.292 g, 0.25 mmol, 0.1 equiv.) and 2-methoxyphenyl boronic acid (1.00 g, 5.05 mmol, 2 equiv.) were added. After stirring for 3 h under reflux, water was added to the reaction mixture which was extracted four times with EtOAc. Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/CH_2Cl_2 10:0 to 5:5 (v/v) in 45 min) to afford **3c** as a white amorphous solid (0.704 g, 68%). Elemental analysis. Found: C, 60.09; H, 5.27; N, 3.93. Calc for $C_{18}H_{19}NO_3S_2$: C, 59.81; H, 5.30; N 3.87%. IR (film, ν, cm^{-1}) 2983, 2909, 2224, 1717, 1601, 1537, 1486, 1470, 1367, 1270, 1245, 1180, 1083, 1023, 842, 756, 681. ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, 3H, J = 7.2 Hz), 1.42 (d, 6H, J = 6.9 Hz), 3.58 (h, 1H, J = 6.9 Hz), 3.78 (s, 3H), 4.15 (q, 2H, J = 7.2 Hz), 6.99 (m, 2H), 7.22 (m, 1H), 7.38 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 23.3, 42.2, 55.4, 61.4, 111.0, 113.7, 117.2, 120.2, 121.4, 130.5, 130.8, 130.9, 145.6, 151.4, 156.6, 160.2. MS (ESI^+, MeOH/CH_2Cl_2) *m/z* 384.1 $[M+Na]^+$. HRMS (ESI^+, MeOH/CH_2Cl_2) *m/z* calcd for $C_{18}H_{19}NO_3S_2Na^+$, $[M+Na]^+$: 384.0704 found 384.0712.

3-oxo-3-(3,4,5-trimethoxyphenyl)propanenitrile (4d)

n-Butyllithium 1.6M in hexane (14.6 mL, 23.4 mmol, 1 equiv.) was added in 47 mL of anhydrous THF at -78°C. After 15 min, a solution of acetonitrile (1.34 mL, 1.06 g, 25.7 mmol, 1.1 equiv.) in 47 mL of anhydrous THF was slowly added over 15 min. After 1 hour of stirring at -78°C, a solution of methyl 3,4,5-trimethoxybenzoate (5.29 g, 23.4 mmol, 1 equiv.) in 47 mL of anhydrous THF was slowly added over 15 min. After being stirred for 1 h at -78°C and 2 h at -45°C, the reaction mixture was cooled and treated slowly with aqueous HCl (2N, 25 mL). The reaction mixture was extracted four times with CH_2Cl_2. Combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (petroleum ether/EtOAc 10:0 to 5:5 (v/v) in 60 min) to afford **4d** as a white amorphous solid (2.55 g, conversion 55%, yield 46%). Elemental analysis. Found C, 61.31; H, 5.54; N, 5.86; O, 26.98. Calc for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95; O, 27.21%. IR (film, ν, cm^{-1}) 3105, 2944, 2926, 2840, 2253, 1676, 1579, 1503, 1453, 1412, 1394, 1336, 1158, 1114, 987, 930, 842, 831, 725.^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (s, 6H), 3.97 (s, 3H), 4.06 (s, 2H), 7.18 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.2, 56.5, 61.1, 106.2, 113.8, 129.3, 144.2, 153.4, 186.2. MS (ESI^+, MeOH/CH_2Cl_2) *m/z* 258.1 $[M+Na]^+$. HRMS (ESI^+, MeOH/CH_2Cl_2) *m/z* calcd for $C_{12}H_{13}NO_4Na^+$, $[M+Na]^+$: 258.0742 found 258.0736.

3-oxo-3-(3,4-dimethoxyphenyl)propanenitrile (4e)

n-Butyllithium 1.6M in hexane (17.0 mL, 27.1 mmol, 1 equiv.) was added in 54 mL of anhydrous THF at -78°C. After 15 min, a solution of acetonitrile (1.56 mL, 1.23 g, 29.8 mmol, 1.1 equiv.) in 54 mL of anhydrous THF was slowly added over 15 min. After 1 hour of stirring at -78°C, a solution of methyl 3,4-dimethoxybenzoate (5.32 g, 27.1 mmol, 1 equiv.) in 54 mL of anhydrous THF was slowly added over 15 min. After being stirred for 1 h at -78°C and 2 h at -45°C, the reaction mixture was cooled and treated slowly with aqueous HCl (2N, 25 mL). The reaction mixture was extracted four times with CH_2Cl_2. Combined organic layers

were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (petroleum ether/EtOAc 10:0 to 5:5 (v/v) in 60 min) to afford **4e** as a white amorphous solid (2.34 g, conversion 51%, yield 42%). Elemental analysis. Found: C, 64.31; H, 5.40; N, 6.80; O, 23.33. Calc for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83; O, 23.39%. IR (film, ν , cm^{-1}) 3088, 2988, 2942, 2914, 2251, 1671, 1585, 1516, 1445, 1422, 1393, 1325, 1262, 1244, 1154, 1016, 866, 801, 760, 634, 624 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.97 (s, 3H), 3.99 (s, 3H), 4.05 (s, 2H), 6.94 (d, 1H, J = 9.0 Hz), 7.50 (d, 1H, J = 9.0 Hz), 7.53 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.9, 56.1, 56.2, 110.2, 110.3, 114.0, 123.5, 127.5, 149.6, 154.7, 185.5. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 228.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{11}H_{11}NO_3Na^+$, $[M+Na]^+$: 228.0637 found 228.0645.

3-oxo-3-(3,5-dimethoxyphenyl)propanenitrile (4f)

n-Butyllithium 1.6M in hexane (9.78 mL, 15.7 mmol, 1 equiv.) was added in 31 mL of anhydrous THF at -78°C. After 15 min, a solution of acetonitrile (0.899 mL, 0.707 g, 17.2 mmol, 1.1 equiv.) in 31 mL of anhydrous THF was slowly added over 15 min. After 1.5 hour of stirring at -78°C, a solution of methyl 3,5-dimethoxybenzoate (3.07 g, 15.7 mmol, 1 equiv.) in 31 mL of anhydrous THF was slowly added over 15 min. After being stirred for 1.5 h at -78°C, 2.5 h at 0 °C and overnight from 0 °C to room temperature, the reaction mixture was cooled and treated slowly with aqueous HCl (2N, 20 mL). The reaction mixture was extracted four times with CH_2Cl_2. Combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (petroleum ether/EtOAc 10:0 to 5:5 (v/v) in 45 min) to afford **4f** as a white amorphous solid (2.34 g, conversion 67%, yield 36%). Elemental analysis. Found C, 64.32; H, 5.51; N, 6.73; O, 23.51. Calc for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83; O, 23.39%. IR (film, ν , cm^{-1}) 3079, 2994, 2946, 2910, 2256, 1685, 1588, 1465, 1427, 1350, 1207, 1159, 1067, 1021, 861, 830, 738, 683, 637. ^1H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 6H), 4.05 (s, 2H), 6.73 (t, 1H, J = 2.5 Hz), 7.04 (t, 2H, J = 2.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.5, 55.7, 106.3, 106.7, 113.6, 136.1, 161.2, 186.8. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 228.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{11}H_{11}NO_3Na^+$, $[M+Na]^+$: 228.0637 found 228.0630.

3-oxo-3-(2,4-dimethoxyphenyl)propanenitrile (4g)

n-Butyllithium 1,6M in hexane (12.0 mL, 19.2 mmol, 1 equiv.) was added in 39 mL of anhydrous THF at -78°C. After 15 min, a solution of acetonitrile (1.11 mL, 0.869 g, 21.2 mmol, 1.1 equiv.) in 39 mL of anhydrous THF was slowly added over 15 min. After 1 hour of stirring at -78 °C, a solution of methyl 2,4-dimethoxybenzoate (3.77 g, 19.2 mmol, 1 equiv.) in 39 mL of anhydrous THF was slowly added over 15 min. After being stirred for 1.5 h at -78°C, 2.5 h at 0 °C and overnight from 0 °C to room temperature, the reaction mixture was cooled and treated slowly with aqueous HCl (2N, 20 mL). The reaction mixture was extracted four times with CH_2Cl_2. Combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (petroleum ether/EtOAc 10:0 to 5:5 (v/v) in 60 min) to afford **4g** as a white amorphous solid (2.63 g, 67%). Elemental analysis. Found: C, 64.29; H, 5.35; N, 6.84; O, 23.19. Calc for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83; O, 23.39%. IR (film, ν , cm^{-1}) 3098, 2960, 2929,

2260, 1664, 1593, 1566, 1470, 1427, 1295, 1251, 1205, 1167, 1126, 1040, 1014, 854, 820, 651, 635. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (s, 3H), 3.97 (s, 3H), 4.04 (s, 2H), 6.49 (d, 1H, *J* = 2.0 Hz), 6.60 (dd, 1H, *J* = 2.0, 8.5 Hz), 7.94 (d, 1H, *J* = 8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.0, 55.7, 98.3, 106.2, 114.9, 117.8, 133.6, 161.3, 166.1, 185.9. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 228.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{11}H_{11}NO_3Na^+$, $[M+Na]^+$: 228.0637 found 228.0633.

3,3-bis(isopropylthio)-2-(3,4,5-trimethoxybenzoyl)acrylonitrile (5d)

To a solution (DMF, 19 mL) of **4d** (2.50 g, 10.6 mmol, 1.0 equiv.) was added NaH (60% in oil, 1.11 g, 27.6 mmol, 2.6 equiv.). After stirring for 45 min at room temperature carbon disulfide (0.64 mL, 10.6 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was stirred at room temperature for 2 h before *i*-propyl iodide (2.23 mL, 22.3 mmol, 2.1 equiv.) was added dropwise. After being stirred for 23 h at 60 °C, the reaction mixture was cooled and concentrated under reduced pressure. The residue was dissolved with water and extracted four times with diethyl ether. The organic layers were pooled, washed with sodium thiosulfate 5% and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 3:1 (v/v) in 45 min) to afford **5d** as a yellow amorphous solid (3.08 g, 73%). Elemental analysis. Found: C, 57.69; H, 6.45; N, 3.55; O, 16.04; S, 16.04. Calc for $C_{19}H_{25}NO_4S_2$: C, 57.69; H, 6.37; N, 3.54; O, 16.18, S 16.21%. IR (film, ν , cm^{-1}) 3000, 2968, 2926, 2864, 2203, 1638, 1582, 1455, 1412, 1328, 1222, 1126, 1056, 997, 914, 859, 766, 710, 651, 634. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, 6H, *J* = 6.9 Hz), 1.47 (d, 6H, *J* = 6.9 Hz), 3.73 (h, 1H, *J* = 6.9 Hz), 3.91 (h, 1H, *J* = 6.9 Hz), 3.93 (s, 6H), 3.96 (s, 3H), 7.22 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 23.0, 40.8, 42.0, 56.3, 61.0, 107.1, 112.2, 116.8, 130.7, 143.3, 153.1, 169.4, 185.9. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 418.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{19}H_{25}NO_4S_2Na^+$, $[M+Na]^+$: 418.1123 found 418.1123.

3,3-bis(isopropylthio)-2-(3,4-dimethoxybenzoyl)acrylonitrile (5e)

To a solution (DMF, 20 mL) of **4e** (2.34 g, 11.4 mmol, 1.0 equiv.) was added NaH (60% in oil, 1.19 g, 29.7 mmol, 2.6 equiv.). After stirring for 45 min at room temperature carbon disulfide (0.69 mL, 11.4 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was stirred at room temperature for 2 h before *i*-propyl iodide (2.39 mL, 24.0 mmol, 2.1 equiv.) was added dropwise. After being stirred for 23 h at 60 °C, the reaction mixture was cooled and concentrated under reduced pressure. The residue was dissolved with water and extracted four times with diethyl ether. The organic layers were pooled, washed with sodium thiosulfate 5% and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 3:1 (v/v) in 45 min) to afford **5e** as a yellow amorphous solid (3.21 g, 77%). Elemental analysis. Found: C, 59.08; H, 6.36; N, 3.92; O, 13.36; S, 17.59. Calc for $C_{18}H_{23}NO_3S_2$: C, 59.15; H, 6.34; N, 3.83; O, 13.13; S, 17.55%.. IR (film, ν , cm^{-1}) 2961, 2923, 2861, 2199, 1641, 1592, 1581, 1439, 1415, 1268, 1247, 1140, 1048, 1015, 914, 895, 818, 765, 712, 664, 629. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, 6H, *J* = 6.6 Hz), 1.46 (d, 6H, *J* = 6.6 Hz), 3.69 (h, 1H, *J* = 6.6 Hz), 3.91 (h, 1H, *J* = 6.6 Hz), 3.95 (s, 3H), 3.97 (s, 3H), 6.93 (d, 1H, *J* = 8.4 Hz), 7.51 (d, 1H, *J* = 2.1 Hz),

7.60 (dd, 1H, J = 2.1, 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 23.0, 40.6, 41.7, 56.0, 56.2, 110.1, 111.2, 113.1, 116.7, 124.9, 128.6, 149.3, 154.1, 167.3, 185.6. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 388.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{18}H_{23}NO_3S_2Na^+$, $[M+Na]^+$: 388.1017 found 388.1029

3,3-bis(isopropylthio)-2-(3,5-dimethoxybenzoyl)acrylonitrile (5f)

To a solution (DMF, 6 mL) of **4f** (0.655 g, 3.19 mmol, 1.0 equiv.) was added NaH (60% in oil, 0.332 g, 8.30 mmol, 2.6 equiv.). After stirring for 45 min at room temperature carbon disulfide (0.19 mL, 3.19 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was stirred at room temperature for 2 h before *i*-propyl iodide (0.67 mL, 6.70 mmol, 2.1 equiv.) was added dropwise. After being stirred for 23 h at 60 °C, the reaction mixture was cooled and concentrated under reduced pressure. The residue was dissolved with water and extracted four times with diethyl ether. The organic layers were pooled, washed with sodium thiosulfate 5% and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 3:1 (v/v) in 25 min) to afford **5f** as a yellow amorphous solid (0.948 g, 81%). Elemental analysis. Found: C, 59.00; H, 6.32; N, 3.83. Calc for $C_{18}H_{23}NO_3S_2$: C, 59.15; H, 6.34; N, 3.83%. IR (film, ν , cm^{-1}) 2965, 2926, 2864, 2206, 1670, 1589, 1455, 1425, 1319, 1299, 1204, 1155, 1052, 923, 846, 764, 678, 626. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, 6H, J = 6.6 Hz), 1.46 (d, 6H, J = 6.6 Hz), 3.73 (h, 1H, J = 6.6 Hz), 3.85 (s, 6H), 3.93 (h, 1H, J = 6.6 Hz), 6.69 (t, 1H, J = 2.4 Hz), 7.04 (t, 2H, J = 2.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 23.0, 40.8, 42.0, 55.6, 106.3, 107.1, 112.0, 116.7, 137.8, 160.8, 170.1, 187.0. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 388.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{18}H_{23}NO_3S_2Na^+$, $[M+Na]^+$: 388.1017 found 388.1004.

3,3-bis(isopropylthio)-2-(2,4-dimethoxybenzoyl)acrylonitrile (5g)

To a solution (DMF, 22 mL) of **4g** (2.62 g, 12.8 mmol, 1.0 equiv.) was added NaH (60% in oil, 1.33 g, 33.3 mmol, 2.6 equiv.). After stirring for 45 min at room temperature carbon disulfide (0.77 mL, 12.8 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was stirred at room temperature for 2 h before *i*-propyl iodide (2.68 mL, 26.9 mmol, 2.1 equiv.) was added dropwise. After being stirred for 23 h at 60 °C, the reaction mixture was cooled and concentrated under reduced pressure. The residue was dissolved with water and extracted four times with diethyl ether. The organic layers were pooled, washed with sodium thiosulfate 5% and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 3:1 (v/v) in 45 min) to afford **5g** as a yellow amorphous solid (1.59 g, 34%). Elemental analysis. Found: C, 59.33; H, 6.35; N, 3.66; S, 17.18. Calc for $C_{18}H_{23}NO_3S_2$: C, 59.15; H, 6.34; N, 3.83; S, 17.55%. IR (film, ν , cm^{-1}) 2964, 2924, 2863, 2205, 1641, 1594, 1451, 1435, 1417, 1264, 1209, 1159, 1125, 1020, 913, 832, 819, 767, 712, 651, 632. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, 6H, J = 6.6 Hz), 1.44 (d, 6H, J = 6.6 Hz), 3.78 (h, 1H, J = 6.6 Hz), 3.87 (s, 3H), 3.89 (s, 3H), 3.95 (h, 1H, J = 6.6 Hz), 6.46 (d, 1H, J = 2.4 Hz), 6.56 (dd, 1H, J = 2.4, 8.4 Hz), 7.61 (d, 1H, J = 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 22.9, 40.1, 41.8, 55.6, 55.7, 98.3, 105.8, 115.6, 117.5, 120.4, 133.1, 160.2, 165.0, 167.6, 185.6. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 388.1

$[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{18}H_{23}NO_3S_2Na^+$, $[M+Na]^+$: 388.1017 found 388.1018.

Ethyl 4-cyano-5-(isopropylthio)-3-(3,4,5-trimethoxyphenyl)thiophene-2-carboxylate (3d)

To a solution (EtOH, 33.0 mL) of **5d** (3.03 g, 7.66 mmol, 1.0 equiv.) were added dropwise ethyl thioglycolate (0.84 mL, 7.66 mmol, 1.0 equiv.) and Et_3N (1.17 mL, 8.42 mmol, 1.1 equiv.). After stirring for 3 h at room temperature, water was added to the reaction mixture which was extracted three times with EtOAc. The organic layers were pooled, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 3:1 (v/v) in 55 min) to afford **3d** as a white amorphous solid (2.34 g, 72%). Elemental analysis. Found: C, 57.04; H, 5.60; N, 3.28; S, 15.16. Calc for $C_{20}H_{23}NO_5S_2$: C, 56.99; H, 5.50; N, 3.32; S, 15.21%. IR (film, ν , cm^{-1}) 2971, 2940, 2838, 2221, 1722, 1588, 1501, 1410, 1352, 1248, 1234, 1182, 1156, 1123, 1100, 1004, 846, 762, 691. ^1H NMR (500 MHz, $CDCl_3$) δ 1.23 (t, 3H, J = 7.5 Hz), 1.48 (d, 6H, J = 7.0 Hz), 3.62 (h, 1H, J = 7.0 Hz), 3.90 (s, 6H), 3.92 (s, 3H), 4.24 (q, 2H, J = 7.5 Hz), 6.65 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 23.2, 42.2, 56.3, 61.0, 61.7, 107.0, 113.7, 115.8, 127.3, 129.0, 138.8, 148.9, 152.8, 153.0, 160.1. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 444.0 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{20}H_{23}NO_5S_2Na^+$, $[M+Na]^+$: 444.0915 found 444.0916.

Ethyl 4-cyano-5-(isopropylthio)-3-(3,4-dimethoxyphenyl)thiophene-2-carboxylate (3e)

To a solution (EtOH, 38.0 mL) of **5e** (3.20 g, 8.77 mmol, 1.0 equiv.) were added dropwise ethyl thioglycolate (0.96 mL, 8.77 mmol, 1.0 equiv.) and Et_3N (1.34 mL, 9.64 mmol, 1.1 equiv.). After stirring for 16 h at 50 °C, water was added to the reaction mixture which was extracted three times with EtOAc. The organic layers were pooled, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 3:1 (v/v) in 55 min) to afford **3e** as a white amorphous solid (2.94 g, 86%). Elemental analysis. Found: C, 58.14; H, 5.39; N, 3.58; O, 16.47; S, 16.34. Calc for $C_{19}H_{21}NO_4S_2$: C, 58.29; H, 5.41; N, 3.58; O, 16.35; S, 16.38%. IR (film, ν , cm^{-1}) 2964, 2934, 2834, 2214, 1715, 1704, 1503, 1360, 1255, 1225, 1182, 1140, 1085, 1024, 868, 760, 752, 698. ^1H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, 3H, J = 7.5 Hz), 1.48 (d, 6H, J = 6.5 Hz), 3.65 (h, 1H, J = 6.5 Hz), 3.92 (s, 3H), 3.96 (s, 3H), 4.24 (q, 2H, J = 7.5 Hz), 6.95 (d, 1H, J = 8.4 Hz), 6.97 (d, 1H, J = 2.1 Hz), 7.03 (dd, 1H, J = 2.1, 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 23.2, 42.2, 55.9, 56.0, 61.6, 110.6, 112.8, 113.8, 116.1, 122.3, 124.4, 128.6, 148.4, 149.1, 149.8, 152.8, 160.2. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 414.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{19}H_{21}NO_4S_2Na^+$, $[M+Na]^+$: 414.0810 found 414.0829.

Ethyl 4-cyano-5-(isopropylthio)-3-(3,5-dimethoxyphenyl)thiophene-2-carboxylate (3f)

To a solution (EtOH, 11.0 mL) of **5f** (0.904 g, 2.47 mmol, 1.0 equiv.) were added dropwise ethyl thioglycolate (0.27 mL, 2.47 mmol, 1.0 equiv.) and Et_3N (0.38 mL, 2.72 mmol, 1.1

equiv.). After stirring for 3.5 h at room temperature, water was added to the reaction mixture which was extracted three times with EtOAc. The organic layers were pooled, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 3:1 (v/v) in 25 min) to afford **3f** as a white amorphous solid (0.615 g, 64%). Elemental analysis. Found: C, 58.11; H, 5.45; N, 3.54; O, 16.51; S, 16.14. Calc for $C_{19}H_{21}NO_4S_2$: C, 58.29; H, 5.41; N, 3.58; O, 16.35; S, 16.38%. IR (film, ν , cm^{-1}) 2970, 2934, 2838, 2219, 1725, 1586, 1534, 1427, 1364, 1312, 1238, 1201, 1154, 1053, 945, 851, 832, 758, 696. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, 3H, *J* = 7.2 Hz), 1.47 (d, 6H, *J* = 6.6 Hz), 3.64 (h, 1H, *J* = 6.6 Hz), 3.83 (s, 6H), 4.23 (q, 2H, *J* = 7.2 Hz), 6.54 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 23.2, 42.2, 55.4, 61.7, 101.3, 107.5, 113.5, 116.0, 133.9, 148.8, 152.7, 160.1, 160.2, 160.3. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 414.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{19}H_{21}NO_4S_2Na^+$, $[M+Na]^+$: 414.0810 found 414.0811.

Ethyl 4-cyano-5-(isopropylthio)-3-(3,4-dimethoxyphenyl)thiophene-2-carboxylate (3g)

To a solution (EtOH, 18.0 mL) of **5g** (1.53 g, 4.19 mmol, 1.0 equiv.) were added dropwise ethyl thioglycolate (0.46 mL, 4.19 mmol, 1.0 equiv.) and Et_3N (0.64 mL, 4.61 mmol, 1.1 equiv.). After stirring for 3.5 h at room temperature, water was added to the reaction mixture which was extracted three times with EtOAc. The organic layers were pooled, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 3:1 (v/v) in 30 min) to afford **3g** as a white amorphous solid (0.559 g, 34%). Elemental analysis. Found: C, 58.56; H, 5.55; N, 3.51. Calc for $C_{19}H_{21}NO_4S_2$: C, 58.29; H, 5.41; N, 3.58%. IR (film, ν , cm^{-1}) 2964, 2934, 2836, 2221, 1721, 1694, 1609, 1496, 1462, 1369, 1247, 1207, 1182, 1159, 1080, 1030, 832, 764, 678. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (t, 3H, *J* = 7.5 Hz), 1.46 (d, 6H, *J* = 6.5 Hz), 3.61 (h, 1H, *J* = 6.5 Hz), 3.80 (s, 3H), 3.86 (s, 3H), 4.21 (q, 2H, *J* = 7.5 Hz), 6.55 (dd, 1H, *J* = 2.1, 8.4 Hz), 6.58 (d, 1H, *J* = 2.1 Hz), 7.19 (d, 1H, *J* = 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 23.2, 42.2, 55.4, 55.5, 61.4, 98.7, 104.4, 113.9, 117.5, 130.0, 131.6, 145.6, 151.2, 157.7, 160.3, 161.9. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 414.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{19}H_{21}NO_4S_2Na^+$, $[M+Na]^+$: 414.0810 found 414.0816.

4-cyano-5-(isopropylthio)-3-(4-methoxyphenyl)thiophene-2-carboxylic acid (6a)

To a solution (THF/EtOH 2/1, 2.1 mL) of **3a** (0.100 g, 0.28 mmol, 1.0 equiv.) was added aqueous NaOH (2M, 1.4 mL). After stirring 36 h at room temperature, the mixture was neutralized with aqueous HCl (1M, 3.0 mL) and extracted twice with CH_2Cl_2. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure.to afford acid **6a** as a white amorphous solid (0.092 g, quantitative yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (d, 6H, J = 6.6 Hz), 3.60 (h, 1H, J = 6.6 Hz), 3.79 (s, 3H), 6.88 (d, 2H, *J* = 7.7 Hz), 7.29 (d, 2H, *J* = 7.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 42.3, 55.4, 113.9, 115.1, 115.8, 124.2, 129.6, 131.0, 149.9, 154.4, 160.5, 165.3, 161.9.

In agreement with literature data[1]

4-cyano-5-(isopropylthio)-3-(3-methoxyphenyl)thiophene-2-carboxylic acid (6b)

To a solution (THF/EtOH 2/1, 0.8 mL) of **3b** (0.040 g, 0.11 mmol, 1.0 equiv.) was added aqueous NaOH (2M, 0.5 mL). After stirring 36 h at room temperature, the mixture was neutralized with aqueous HCl (1M, 1.0 mL) and extracted twice with CH_2Cl_2. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure.to afford acid **6b** as a white amorphous solid (0.031 g, 84%). ^{1}H NMR (300 MHz, acetone-d_6) δ 1.43 (d, 6H, J = 6.9 Hz), 3.66 (h, 1H, J = 6.9 Hz), 3.81 (s, 3H), 6.98 to 7.05 (m, 3H), 7.32 (t, 1H, *J* = 7.9 Hz). ^{13}C NMR (75 MHz, acetone-d_6) δ 23.5, 43.0, 55.7, 114.6, 115.2, 116.2, 117.3, 122.8, 129.7, 131.5, 135.3, 147.7, 150.9, 160.2, 165.7.

In agreement with literature data[1]

4-cyano-5-(isopropylthio)-3-(2-methoxyphenyl)thiophene-2-carboxylic acid (6c)

To a solution (THF/EtOH 2/1, 4.5 mL) of **3c** (0.211 g, 0.58 mmol, 1.0 equiv.) was added aqueous NaOH (2M, 3.0 mL). After stirring 36 h at room temperature, the mixture was neutralized with aqueous HCl (1M, 6.0 mL) and extracted twice with CH_2Cl_2. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure.to afford acid **6c** as a white amorphous solid (0.195 g, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (d, 6H, J = 6.6 Hz), 3.57 (h, 1H, J = 6.6 Hz), 3.72 (s, 3H), 6.90 (m, 2H), 7.12 (m, 1H), 7.31 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 42.4, 55.9, 111.6, 113.8, 117.0, 120.7, 121.5, 130.5, 131.1, 146.6, 153.1, 156.7, 165.0.

In agreement with literature data[1]

4-cyano-5-(isopropylthio)-3-(3,4,5-trimethoxyphenyl)thiophene-2-carboxylic acid (6d)

To a solution (THF/EtOH 2/1, 4.2 mL) of **3d** (0.240 g, 0.57 mmol, 1.0 equiv.) was added aqueous NaOH (2M, 2.8 mL). After stirring 36 h at room temperature, the mixture was neutralized with aqueous HCl (1M, 5.6 mL) and extracted twice with CH_2Cl_2. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure.to afford acid **6d** as a white amorphous solid (0.230 g, quantitative yield). IR (film, ν , cm^{-1}) 2971, 2836, 2221, 1644, 1587, 1500, 1439, 1358, 1300, 1237, 1124, 1101, 1011, 938, 865, 839, 764, 708, 691. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (d, 6H, *J* = 6.9 Hz), 3.66 (h, 1H, *J* = 6.9 Hz), 3.88 (s, 6H), 3.93 (s, 3H), 6.66 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 41.1, 52.3, 59.9, 106.0, 112.5, 114.0, 125.7, 125.8, 138.0, 149.4, 151.8, 154.5, 163.2. MS (ESI$^+$, MeOH/CH_2Cl_2) *m/z* 416.1 $[M+Na]^+$. HRMS (ESI$^+$, MeOH/CH_2Cl_2) calcd for $C_{18}H_{19}NO_5S_2Na^+$, $[M+Na]^+$: 416.0602 found 416.0601. UHPLC 4.84 min, 100%.

4-cyano-5-(isopropylthio)-3-(3,4-dimethoxyphenyl)thiophene-2-carboxylic acid (6e)

To a solution (THF/EtOH 2/1, 2.4 mL) of **3e** (0.132 g, 0.34 mmol, 1.0 equiv.) was added aqueous NaOH (2M, 1.6 mL). After stirring 36 h at room temperature, the mixture was neutralized with aqueous HCl (1M, 3.2 mL) and extracted twice with CH_2Cl_2. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure.to afford acid **6e** as a white amorphous solid (0.230 g, quantitative yield). IR (film, ν , cm^{-1}) 2951, 2928, 2827, 2228, 1680, 1533, 1505, 1454, 1356, 1247, 1232, 1167, 1140, 1021, 880, 811, 764, 697. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48 (d, 6H, *J* = 7.0 Hz), 3.67 (h, 1H, *J* = 7.0 Hz), 3.90 (s, 3H),

3.95 (s, 3H), 6.95 (d, 1H, J = 8.4 Hz), 6.96 (d, 1H, J = 2.1 Hz), 7.03 (dd, 1H, J = 2.1, 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 42.1, 55.9, 56.0, 110.8, 112.8, 113.5, 113.6, 122.3, 123.4, 124.0, 148.5, 150.1, 150.7, 155.3, 160.2. MS (ESI$^+$, MeOH/CH_2Cl_2) *m/z* 386.1 $[M+Na]^+$. HRMS (ESI$^+$, MeOH/CH_2Cl_2) calcd for $C_{17}H_{17}NO_4S_2Na^+$, $[M+Na]^+$: 386.0497 found 386.0514. UHPLC 4.73 min, 100%.

4-cyano-5-(isopropylthio)-3-(3,5-dimethoxyphenyl)thiophene-2-carboxylic acid (6f)

To a solution (THF/EtOH 2/1, 2.8 mL) of **3f** (0.146 g, 0.37 mmol, 1.0 equiv.) was added aqueous NaOH (2M, 1.9 mL). After stirring 36 h at room temperature, the mixture was neutralized with aqueous HCl (1M, 3.8 mL) and extracted twice with CH_2Cl_2. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure.to afford acid **6f** as a white amorphous solid (0.138 g, quantitative yield). IR (film, ν , cm^{-1}) 2965, 2933, 2841, 2224, 1666, 1592, 1527, 1450, 1421, 1356, 1309, 1265, 1206, 1156, 1065, 929, 845, 765, 714, 696. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (d, 6H, J = 6.9 Hz), 3.55 (h, 1H, J = 6.9 Hz), 3.73 (s, 6H), 6.45 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 42.1, 55.5, 101.6, 107.4, 113.2, 115.3, 127.3, 133.4, 150.4, 152.3, 160.4, 164.3. MS (ESI$^+$, MeOH/CH_2Cl_2) *m/z* 386.0 $[M+Na]^+$. HRMS (ESI$^+$, MeOH/CH_2Cl_2) calcd for $C_{17}H_{17}NO_4S_2Na^+$, $[M+Na]^+$: 386.0497 found 386.0506. UHPLC 4.99 min, 100%.

4-cyano-5-(isopropylthio)-3-(2,4-dimethoxyphenyl)thiophene-2-carboxylic acid (6g)

To a solution (THF/EtOH 2/1, 4.6 mL) of **3g** (0.241 g, 0.62 mmol, 1.0 equiv.) was added aqueous NaOH (2M, 3.1 mL). After stirring 36 h at room temperature, the mixture was neutralized with aqueous HCl (1M, 6.2 mL) and extracted twice with CH_2Cl_2. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure.to afford acid **6g** as a white amorphous solid (0.230 g, quantitative yield). IR (film, ν , cm^{-1}) 2966, 2931, 2841, 2222, 1664, 1579, 1534, 1495, 1417, 1354, 1302, 1284, 1256, 1158, 1031, 920, 831, 765, 731, 679. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, 6H, J = 6.9 Hz), 3.64 (h, 1H, J = 6.9 Hz), 3.80 (s, 3H), 3.88 (s, 3H), 6.58 (s, 1H), 6.59 (d, 1H, J = 8.1 Hz), 7.19 (d, 1H, J = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 42.1, 55.4, 55.5, 98.8, 104.7, 113.5, 116.7, 128.0, 131.6, 147.3, 153.7, 157.7, 162.1, 165.5. MS (ESI$^+$, MeOH/CH_2Cl_2) *m/z* 386.1 $[M+Na]^+$. HRMS (ESI$^+$, MeOH/CH_2Cl_2) calcd for $C_{17}H_{17}NO_4S_2Na^+$, $[M+Na]^+$: 386.0497 found 386.0496. UHPLC 4.91 min, 97%.

Ethyl 4-cyano-3-(4-hydroxyphenyl)-5-(isopropylthio)thiophene-2-carboxylate (7a)

The thiophene **3a** (0.117 g, 0.32 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (8.5 mL), cooled to 0°C and BBr_3 in CH_2Cl_2 (1M, 2.59 mL, 2.59 mmol, 8.0 equiv.) was added dropwise with stirring. Stirring continued at 0°C for 2 h and at room temperature for 2 h. The reaction was terminated by careful dropwise addition of water (8.5 mL). After 30 min of stirring, brine (10 mL) was added to the reaction mixture, which was extracted three times with CH_2Cl_2. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 3:1 (v/v) in 25 min) to afford **7a** as a yellowish amorphous solid (0.041 g, 37%). IR (film, ν , cm^{-1}) 3365, 2961, 2925, 2851, 2219, 1720, 1678, 1612, 1501, 1435, 1358, 1266, 1169, 1083,

1039, 842, 760, 679. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 3H, *J* = 7.2 Hz), 1.48 (d, 6H, *J* = 6.6 Hz), 3.65 (h, 1H, *J* = 6.6 Hz), 4.25 (q, 2H, *J* = 7.2 Hz), 5.81 (s, 1H), 6.85 (d, 2H, *J* = 8.7 Hz), 7.30 (d, 2H, *J* = 8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 23.2, 42.3, 61.8, 113.9, 115.2, 115.8, 124.0, 128.2, 130.8, 149.4, 153.1, 156.9, 160.5. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 370.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{17}H_{17}NO_3S_2Na^+$, $[M+Na]^+$: 370.0548 found 370.0559. UHPLC 5.47 min, 100%.

Ethyl 4-cyano-3-(3-hydroxyphenyl)-5-(isopropylthio)thiophene-2-carboxylate (7b)

The thiophene **3b** (0.035 g, 0.10 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (2.5 mL), cooled to 0°C and BBr_3 in CH_2Cl_2 (1M, 0.775 mL, 0.77 mmol, 8.0 equiv.) was added dropwise with stirring. Stirring continued at 0°C for 1.5 h and at room temperature for 2 h. The reaction was terminated by careful dropwise addition of water (2.5 mL). After 30 min of stirring, brine (3.0 mL) was added to the reaction mixture, which was extracted three times with CH_2Cl_2. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 3:1 (v/v) in 25 min) to afford **7b** as a yellowish amorphous solid (0.027 g, 64%). IR (film) 3208, 2966, 2934, 2223, 1699, 1584, 1532, 1446, 1369, 1295, 1158, 1092, 1043, 872, 760, 711. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, 3H, *J* = 7.2 Hz), 1.48 (d, 6H, *J* = 6.9 Hz), 3.64 (h, 1H, *J* = 6.9 Hz), 4.22 (q, 2H, *J* = 7.2 Hz), 6.87-6.99 (m, 3H), 7.32 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 23.2, 42.3, 61.8, 113.6, 115.7, 116.3, 116.7, 121.8, 129.4, 129.6, 133.6, 148.6, 153.0, 155.2, 160.2. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 370.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{17}H_{17}NO_3S_2Na^+$, $[M+Na]^+$: 370.0548 found 370.0544. UHPLC 5.48 min, 72%.

Ethyl 4-cyano-3-(2-hydroxyphenyl)-5-(isopropylthio)thiophene-2-carboxylate (7c)

The thiophene **3c** (0.250 g, 0.69 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (18.0 mL), cooled to 0°C and BBr_3 in CH_2Cl_2 (1M, 5.53 mL, 5.53 mmol, 8.0 equiv.) was added dropwise with stirring. Stirring continued at 0°C for 2 h and at room temperature for 2 h. The reaction was terminated by careful dropwise addition of water (18 mL). After 30 min of stirring, brine (10 mL) was added to the reaction mixture, which was extracted three times with CH_2Cl_2. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 3:1 (v/v) in 25 min) to afford **7c** as a yellowish amorphous solid (0.110 g, 46%). IR (film, ν, cm^{-1}) 3386, 2973, 2935, 2222, 1690, 1611, 1530, 1495, 1445, 1373, 1297, 1221, 1078, 1007, 824, 758, 709, 691. ^{1}H NMR (300 MHz, $CDCl_3$) δ 118 (t, 3H, *J* = 7.2 Hz), 1.44 (d, 6H, *J* = 6.6 Hz), 3.60 (h, 1H, *J* = 6.6 Hz), 4.20 (q, 2H, *J* = 7.2 Hz), 5.74 (s, 1H), 6.86-7.03 (m, 2H), 7.06-7.31 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 23.2, 42.3, 62.0, 113.6, 116.6, 116.9, 120.2, 120.8, 130.0, 130.7, 130.9, 145.2, 153.0, 153.2, 160.8. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 370.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{17}H_{17}NO_3S_2Na^+$, $[M+Na]^+$: 370.0548 found 370.0561. UHPLC 5.48 min, 86%.

Ethyl 4-cyano-3-(3,4,5-trihydroxyphenyl)-5-(isopropylthio)thiophene-2-carboxylate (7d)

The thiophene **3d** (0.067 g, 0.16 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (4.0 mL), cooled to 0°C and BBr_3 in CH_2Cl_2 (1M, 2.07 mL, 2.07 mmol, 13.0 equiv.) was added dropwise with stirring. Stirring continued at 0°C for 1.5 h and at room temperature for 2 h. The reaction was terminated by careful dropwise addition of water (4 mL). After 30 min of stirring, brine (15 mL) was added to the reaction mixture, which was extracted three times with CH_2Cl_2. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 1:1 (v/v) in 25 min) to afford **7d** as a yellowish amorphous solid (0.023 g, 35%). IR (film, ν, cm^{-1}) 3337, 2971, 2923, 2221, 1693, 1501, 1446, 1374, 1293, 1242, 1154, 1085, 1033, 844, 764. ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.0 Hz), 1.48 (d, 6H, J = 7.0 Hz), 3.63 (h, 1H, J = 7.0 Hz), 4.27 (q, 2H, J = 7.0 Hz), 5.62 (s, 1H), 5.69 (s, 2H), 6.57 (m, 2H). ^{13}C NMR (75 MHz, acetone-d_6) δ 14.2, 23.4, 42.9, 62.4, 109.7, 114.3, 117.1, 124.2, 130.0, 134.9, 146.0, 149.9, 152.3, 160.7. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 402.0 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{17}H_{17}NO_5S_2Na^+$, $[M+Na]^+$: 402.0446 found 402.0456. UHPLC 4.60 min, 100%.

Ethyl 4-cyano-3-(3,4-dihydroxyphenyl)-5-(isopropylthio)thiophene-2-carboxylate (7e)

The thiophene **3e** (0.060 g, 0.15 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (4.0 mL), cooled to 0°C and BBr_3 in CH_2Cl_2 (1M, 1.53 mL, 1.53 mmol, 10.0 equiv.) was added dropwise with stirring. Stirring continued at 0°C for 1 h and at room temperature for 1 h. The reaction was terminated by careful dropwise addition of water (4 mL). After 30 min of stirring, brine (15 mL) was added to the reaction mixture, which was extracted three times with CH_2Cl_2. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 7:3 (v/v) in 25 min) to afford **7e** as a yellowish amorphous solid (0.045 g, 80%). IR (film, ν, cm^{-1}) 3354, 2970, 2918, 2865, 2224, 1722, 1691, 1603, 1498, 1444, 1357, 1290, 1240, 1153, 1079, 1039, 871, 808, 755, 698. ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 6.9 Hz), 1.47 (d, 6H, J = 6.6 Hz), 3.64 (h, 1H, J = 6.6 Hz), 4.24 (q, 2H, J = 6.9 Hz), 5.85 (s, 1H), 6.05 (s, 1H), 6.86 (d, 1H, J = 8.4 Hz), 6.87 (s, 1H), 6.95 (d, 1H, J = 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 23.2, 42.2, 61.9, 113.8, 115.0, 115.6, 116.6, 122.3, 124.4, 128.3, 143.3, 145.0, 149.2, 153.2, 160.5. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 386.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{17}H_{18}NO_4S_2^+$, $[M+H]^+$: 364.0677 found 364.0686. UHPLC 5.07 min, 97%.

Ethyl 4-cyano-3-(3,5-dihydroxyphenyl)-5-(isopropylthio)thiophene-2-carboxylate (7f)

The thiophene **3f** (0.088 g, 0.22 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (6.0 mL), cooled to 0°C and BBr_3 in CH_2Cl_2 (1M, 2.25 mL, 2.25 mmol, 10.0 equiv.) was added dropwise with stirring. Stirring continued at 0°C for 1.5 h and at room temperature for 1.5 h. The reaction was terminated by careful dropwise addition of water (6 mL). After 30 min of stirring, brine (20 mL) was added to the reaction mixture, which was extracted three times with CH_2Cl_2. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 1:1 (v/v) in 25 min) to afford **7f** as a yellowish amorphous solid (0.028 g, 34%). IR (film, ν, cm^{-1})

3385, 2969, 2923, 2213, 1689, 1594, 1491, 1460, 1373, 1358, 1249, 1155, 1094, 1004, 846, 763, 703, 675. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.0 Hz), 1.48 (d, 6H, J = 6.5 Hz), 3.63 (h, 1H, J = 6.5 Hz), 4.25 (q, 2H, J = 7.0 Hz), 6.26 (s, 2H), 6.37 (s, 1H), 6.45 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 23.2, 42.3, 62.1, 104.1, 109.0, 113.5, 115.4, 128.9, 134.2, 148.9, 153.4, 156.6, 160.4. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 386.0 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{17}H_{17}NO_4S_2Na^+$, $[M+Na]^+$: 386.0497 found 386.0503. UHPLC 4.83 min, 100%.

Ethyl 4-cyano-3-(2,4-dihydroxyphenyl)-5-(isopropylthio)thiophene-2-carboxylate (7g)

The thiophene **3g** (0.041 g, 0.11 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (3.0 mL), cooled to 0°C and BBr_3 in CH_2Cl_2 (1M, 1.06 mL, 1.05 mmol, 10.0 equiv.) was added dropwise with stirring. Stirring continued at 0°C for 1.75 h and at room temperature for 1.75 h. The reaction was terminated by careful dropwise addition of water (3 mL). After 30 min of stirring, brine (10 mL) was added to the reaction mixture, which was extracted three times with CH_2Cl_2. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 1:1 (v/v) in 25 min) to afford **7g** as a yellowish amorphous solid (0.022 g, 58%). IR (film, ν , cm^{-1}) 3328, 2972, 2928, 2243, 1691, 1614, 1599, 1502, 1458, 1371, 1277, 1215, 1168, 1118, 1081, 977, 845, 801, 765. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, 3H, J = 7.0 Hz), 1.48 (d, 6H, J = 7.0 Hz), 3.64 (h, 1H, J = 7.0 Hz), 4.28 (q, 2H, J = 7.0 Hz), 6.40 (s, 1H), 6.45 (d, 1H, J = 1.5 Hz), 6.50 (dd, 1H, J = 1.5, 5.1 Hz), 7.09 (d, 1H, J = 5.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 23.2, 42.3, 62.2, 104.0, 108.4, 112.4, 113.9, 116.6, 129.1, 131.7, 146.1, 153.1, 154.4, 158.1, 161.1. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 386.0 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{17}H_{17}NO_4S_2Na^+$, $[M+Na]^+$: 386.0497 found 386.0504. UHPLC 4.90 min, 86%.

4-cyano-3-(4-hydroxyphenyl)-5-(isopropylthio)thiophene-2-carboxylic acid (8a)

The thiophene **6a** (0.093 g, 0.28 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (7.3 mL), cooled to 0°C and BBr_3 in CH_2Cl_2 (1M, 2.23 mL, 2.23 mmol, 8.0 equiv.) was added dropwise with stirring. Stirring continued at 0°C for 3 h and at room temperature for 1.5 h. The reaction was terminated by careful dropwise addition of water (7.3 mL). After 30 min of stirring, brine (10 mL) was added to the reaction mixture, which was extracted three times with EtOAc. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure. The solid was purified by partition of CH_3CN and pentane to afford **8a** as a yellowish amorphous solid (0.069 g, 78%). IR (film, ν , cm^{-1}) 3364, 2965, 2924, 2841, 2234, 1689, 1609, 1531, 1493, 1414, 1352, 1269, 1194, 1175, 837, 768, 678. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.45 (d, 6H, J = 6.9 Hz), 3.72 (h, 1H, J = 6.9 Hz), 6.92 (d, 2H, J = 8.7 Hz), 7.35 (d, 2H, J = 8.7 Hz). ^{13}C NMR (75 MHz, acetone-d_6) δ 23.4, 42.9, 114.4, 115.6, 117.1, 124.4, 130.0, 131.9, 150.0, 152.6, 159.0, 161.2. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 342.0 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{15}H_{13}NO_3S_2Na^+$, $[M+Na]^+$: 342.0235 found 342.0242. UHPLC 4.37 min, 100%.

4-cyano-3-(3-hydroxyphenyl)-5-(isopropylthio)thiophene-2-carboxylic acid (8b)

The thiophene **6b** (0.031 g, 0.09 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (2.4 mL), cooled to 0°C and BBr_3 in CH_2Cl_2 (1M, 0.744 mL, 0.74 mmol, 8.0 equiv.) was added dropwise with stirring. Stirring continued at 0°C for 2 h and at room temperature for 2 h. The reaction was terminated by careful dropwise addition of water (4 mL). After 30 min of stirring, brine (2 mL) was added to the reaction mixture, which was extracted three times with EtOAc. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure. The solid was purified by partition of CH_3CN and pentane to afford **8b** as a yellowish amorphous solid (0.027 g, 90%). IR (film, ν , cm^{-1}) 3384, 3197, 2971, 2928, 2856, 2228, 1681, 1652, 1596, 1524, 1490, 1441, 1295, 1187, 870, 791, 751, 706. ^1H NMR (300 MHz, acetone-d_6) δ 1.46 (d, 6H, J = 6.6 Hz), 3.73 (h, 1H, J = 6.6 Hz), 6.91-6.94 (m, 3H), 7.28 (m, 1H). ^{13}C NMR (75 MHz, acetone-d_6) δ 23.4, 42.9, 114.1, 116.8, 116.8, 117.3, 121.5, 129.9, 130.9, 134.8, 149.6, 152.6, 157.9, 161.1. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 342.0 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{15}H_{13}NO_3S_2Na^+$, $[M+Na]^+$: 342.0235 found 342.0240. UHPLC 4.38 min, 100%.

4-cyano-3-(2-hydroxyphenyl)-5-(isopropylthio)thiophene-2-carboxylic acid (8c)

The thiophene **6c** (0.200 g, 0.60 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (15.8 mL), cooled to 0°C and BBr_3 in CH_2Cl_2 (1M, 4.80 mL, 4.80 mmol, 8.0 equiv.) was added dropwise with stirring. Stirring continued at 0°C for 2 h and at room temperature for 2 h. The reaction was terminated by careful dropwise addition of water (16 mL). After 30 min of stirring, brine (5 mL) was added to the reaction mixture, which was extracted three times with CH_2Cl_2. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/HCOOH 1:0 to 98:2:0.4 (v/v) in 30 min) to afford **8c** as a yellowish amorphous solid (0.068 g, 35%). IR (film, ν , cm^{-1}) 3341, 2973, 2923, 2216, 1709, 1607, 1521, 1496, 1378, 1206, 1191, 1051, 877, 770, 746, 729, 658. ^1H NMR (300 MHz, acetone-d_6) δ 1.40 (d, 6H, J = 6.9 Hz), 3.65 (h, 1H, J = 6.9 Hz), 6.84-6.94 (m, 2H), 7.19-7.24 (m, 2H). ^{13}C NMR (75 MHz, acetone-d_6) δ 23.4, 42.9, 114.2, 116.6, 118.1, 120.1, 121.2, 131.2, 131.6, 132.3, 146.6, 151.5, 155.5, 161.3. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 342.0 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{15}H_{13}NO_3S_2Na^+$, $[M+Na]^+$: 342.0235 found 342.0239. UHPLC 4.37 min, 66%.

4-cyano-3-(3,4,5-trihydroxyphenyl)-5-(isopropylthio)thiophene-2-carboxylic acid (8d)

The thiophene **6d** (0.286 g, 0.73 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (19 mL), cooled to 0°C and BBr_3 in CH_2Cl_2 (1M, 9.45 mL, 9.45 mmol, 13.0 equiv.) was added dropwise with stirring. Stirring continued at 0°C for 1.75 h and at room temperature for 2.5 h. The reaction was terminated by careful dropwise addition of water (25 mL). After 30 min of stirring, brine (20 mL) was added to the reaction mixture, which was extracted three times with EtOAc. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure to afford **8d** as a yellow amorphous solid (0.182 g, 71%). IR (film, ν , cm^{-1}) 3321, 2969, 2912, 2224, 1671, 1610, 1506, 1437, 1360, 1300, 1240, 1155, 1079, 1025, 854, 767, 687. ^1H NMR (300 MHz, acetone-d_6) δ 1.44 (d, 6H, J = 6.6 Hz), 3.68 (h, 1H, J = 6.6 Hz), 6.53 (s, 2H), 7.54 (bs, 1H), 8.05 (bs, 2H). ^{13}C NMR (75 MHz, acetone-d_6) δ 23.4, 42.9, 109.9, 114.4, 117.0, 124.3, 130.1, 134.8, 146.1, 150.0, 152.5, 161.4. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 374.0

$[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{15}H_{13}NO_5S_2Na^+$, $[M+Na]^+$: 374.0133 found 374.0145. UHPLC 3.71 min, 100%.

4-cyano-3-(3,4-dihydroxyphenyl)-5-(isopropylthio)thiophene-2-carboxylic acid (8e)

The thiophene **6e** (0.169 g, 0.46 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (12.0 mL), cooled to 0°C and BBr_3 in CH_2Cl_2 (1M, 4.65 mL, 4.65 mmol, 10.0 equiv.) was added dropwise with stirring. Stirring continued at 0°C for 1.5 h and at room temperature for 1.5 h. The reaction was terminated by careful dropwise addition of water (13 mL). After 30 min of stirring, brine (30 mL) was added to the reaction mixture, which was extracted three times with EtOAc. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure. The solid was purified by partition of CH_3CN and pentane to afford **8e** as a yellowish amorphous solid (0.100 g, 64%). IR (film, ν , cm^{-1}) 3422, 3131, 2965, 2923, 2862, 2224, 1691, 1606, 1537, 1496, 1358, 1278, 1238, 1168, 781, 675. ^1H NMR (300 MHz, acetone-d_6) δ 1.46 (d, 6H, J = 6.9 Hz), 3.72 (h, 1H, J = 6.9 Hz), 6.83 (d, 1H, J = 8.4 Hz), 6.90 (s, 1H), 6.99 (d, 1H, J = 8.4 Hz). ^{13}C NMR (75 MHz, acetone-d_6) δ 22.2, 41.7, 113.2, 114.5, 116.0, 116.5, 121.3, 123.8, 128.8, 144.1, 145.7, 148.8, 151.3, 160.1. MS (ESI^-, $MeOH/CH_2Cl_2$) *m/z* 334.1 $[M-H]^-$. HRMS (ESI^-, $MeOH/CH_2Cl_2$) calcd for $C_{15}H_{12}NO_4S_2^-$, $[M-H]^-$:334.0208 found 334.0221. UHPLC 4.83 min, 95%.

4-cyano-3-(3,5-dihydroxyphenyl)-5-(isopropylthio)thiophene-2-carboxylic acid (8f)

The thiophene **6f** (0.066 g, 0.18 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (5.0 mL), cooled to 0°C and BBr_3 in CH_2Cl_2 (1M, 1.82 mL, 1.82 mmol, 10.0 equiv.) was added dropwise with stirring. Stirring continued at 0°C for 1.75 h and at room temperature for 2.5 h. The reaction was terminated by careful dropwise addition of water (6 mL). After 30 min of stirring, brine (20 mL) was added to the reaction mixture, which was extracted three times with EtOAc. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure to afford **8f** as a yellow amorphous solid (0.042 g, 69%). IR (film, ν , cm^{-1}) 3383, 2966, 2925, 2850, 2228, 1692, 1601, 1496, 1413, 1350, 1259, 1193, 1153, 1045, 1003, 840, 767. ^1H NMR (300 MHz, acetone-d_6) δ 1.45 (d, 6H, J = 6.6 Hz), 3.71 (h, 1H, J = 6.6 Hz), 6.43 (m, 3H), 8.40 (bs, 2H). ^{13}C NMR (75 MHz, acetone-d_6) δ 23.4, 42.9, 104.1, 108.9, 114.1, 116.9, 130.9, 135.4, 149.7, 152.5, 159.0, 161.2. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 358.0 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{15}H_{13}NO_4S_2Na^+$, $[M+Na]^+$: 358.0184 found 358.0197. UHPLC 3.92 min, 100%.

4-(2-bromoacetyl)benzonitrile (10a)

To a solution containing the 4-acetylbenzonitrile (1.03 g, 7.09 mmol, 1.0 equiv.) and *p*-toluenesulfonic acid monohydrate (2.02 g, 10.6 mmol, 1.5 equiv.) in acetonitrile (350 mL) was slowly added N-bromosuccinimide (1.26 g, 7.09 mmol, 1.0 equiv.). The reaction mixture was stirred for 2 h at reflux. After reaction mixture was cooled down to room temperature, the solvent was evaporated. The residue was dissolved in dichloromethane, washed twice with water and dried over $MgSO_4$. The crude product was purified by flash chromatography on

silica gel (heptane/CH_2Cl_2 8:2 to 5:5 (v/v) in 30 min) to afford **10a** as a white amorphous solid (1.24 g, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 (s, 2H), 7.82 (d, 2H, J = 8.0 Hz), 8.10 (d, 2H, J = 8.0 Hz).

In agreement with literature data[2]

3-(2-bromoacetyl)benzonitrile (10b)

To a solution containing the 3-acetylbenzonitrile (1.19 g, 8.20 mmol, 1.0 equiv.) and *p*-toluenesulfonic acid monohydrate (2.34 g, 12.3 mmol, 1.5 equiv.) in acetonitrile (410 mL) was slowly added N-bromosuccinimide (1.46 g, 8.20 mmol, 1.0 equiv.). The reaction mixture was stirred for 2.5 h at reflux. After reaction mixture was cooled down to room temperature, the solvent was evaporated. The residue was dissolved in dichloromethane, washed twice with water and dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel (heptane/CH_2Cl_2 8:2 to 5:5 (v/v) in 30 min) to afford **10b** as a white amorphous solid (1.64 g, 89%). Elemental analysis. Found: C, 48.33; H, 2.69; N, 6.16; O, 7.42. Calc for C_9H_6BrNO: C, 48.25; H, 2.70; N, 6.25; O, 7.16.. IR (film, ν , cm^{-1}) 3105, 3067, 2990, 2940, 2229, 1705, 1688, 1598, 1480, 1429, 1386, 1275, 1223, 1150, 1031, 938, 884, 801, 694, 681. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.45 (s, 2H), 7.67 (t, 1H, J = 7.5 Hz), 7.89 (d, 1H, J = 7.5 Hz), 8.22 (d, 1H, J = 7.5 Hz), 8.27 (s, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 32.2, 114.9, 119.3, 131.3, 133.2, 133.8, 134.3, 137.9, 190.3. MS (ESI$^-$, MeOH/CH_2Cl_2) *m/z* 222.0 [M-H]$^-$. HRMS (ESI$^-$, MeOH/CH_2Cl_2) calcd for $C_9H_5{}^{79}BrNO^-$, [M-H]$^-$: 221.9554 found 221.9562; calcd for $C_9H_5{}^{81}BrNO^-$: [M-H]$^-$, 223.9534 found 223.9542.

4-(2-cyanoacetyl)benzonitrile (11a)

A solution of **10a** (1.13 g, 5.05 mmol, 1.0 equiv.) was dissolved in ethanol (15 mL) and cooled to 0 °C. A solution of sodium cyanide (0.717 g, 14.6 mmol, 2.9 equiv.) in water (3.7 mL) was added dropwise over 0.5 h and the reaction was stirred for an additional 2 h. At that time, the mixture was diluted with water (15 mL) and filtered through Celite®. Acidification with 1N HCl of the filtrate gave a cloudy mixture, which was extracted with CH_2Cl_2. The pooled organic layers were dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 3:1 (v/v) in 35 min) to afford **11a** as a white amorphous solid (1.64 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (s, 2H), 7.78 (d, 2H, J = 8.4 Hz), 7.97 (d, 2H, J = 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.7, 112.9, 117.3, 118.1, 129.9, 133.0, 137.0, 186.0.

In agreement with literature data[3]

3-(2-cyanoacetyl)benzonitrile (11b)

A solution of **10b** (1.62 g, 7.22 mmol, 1.0 equiv.) was dissolved in ethanol (15 mL) and cooled to 0 °C. A solution of sodium cyanide (1.03 g, 20.9 mmol, 2.9 equiv.) in water (5.2 mL) was added dropwise over 0.5 h and the reaction was stirred for an additional 2.5 h. At that time, the mixture was diluted with water (15 mL) and filtered through Celite®. Acidification with 1N HCl of the filtrate gave a cloudy mixture, which was extracted with CH_2Cl_2. The pooled organic layers were dried over $MgSO_4$. The crude product was purified

by flash chromatography on silica gel (heptane/EtOAc 1:0 to 3:1 (v/v) in 50 min) to afford **11b** as a white amorphous solid (0.742 g, 60%). Elemental analysis. Found: C, 70.56; H, 3.52; N, 16.26; O, 9.56. Calc for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46; O, 9.40. IR (film, ν, cm^{-1}) 3111, 3067, 2923, 2256, 2232, 1700, 1601, 1480, 1430, 1392, 1239, 1156, 1040, 944, 909, 805, 753, 684, 662. ^1H NMR (500 MHz, $CDCl_3$) δ 4.12 (s, 2H), 7.67 (t, 1H, J = 7.5 Hz), 7.89 (d, 1H, J = 7.5 Hz), 8.22 (d, 1H, J = 7.5 Hz), 8.27 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.6, 112.9, 114.0, 117.2, 130.3, 132.0, 132.2, 135.0, 137.5, 185.4. MS (IE) *m/z* 172.0 $[M]^+$.

4-(2-cyano-3,3-bis(isopropylthio)acryloyl)benzonitrile (12a)

To a solution (DMF, 3 mL) of **11a** (0.326 g, 1.92 mmol, 1.0 equiv.) was added NaH (60% in oil, 0.199 g, 4.98 mmol, 2.6 equiv.). After stirring for 45 min at room temperature, carbon disulfide (0.115 mL, 1.92 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was stirred at room temperature for 2 h before *i*-propyl iodide (0.402 mL, 4.02 mmol, 2.1 equiv.) was added dropwise. After being stirred for 23 h at 60°C, the reaction mixture was cooled and concentrated under reduced pressure. The residue was dissolved with water and extracted four times with diethyl ether. The organic layers were pooled, washed with sodium thiosulfate 5% and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 3:1 (v/v) in 45 min) to afford **12a** as a yellow oil (0.330 g, 52%). Elemental analysis. Found: C, 61.68; H, 5.56; N, 8.51; O, 5.05; S, 19.37. Calc for $C_{17}H_{18}N_2OS_2$: C, 61.79; H, 5.49; N, 8.48; O, 4.84; S, 19.41. IR (film, ν, cm^{-1}) 2969, 2928, 2865, 2231, 2205, 1646, 1449, 1403, 1368, 1257, 1153, 1052, 994, 916, 854, 764, 700. ^1H NMR (500 MHz, $CDCl_3$) δ 1.36 (d, 6H, J = 7.0 Hz), 1.47 (d, 6H, J = 7.0 Hz), 3.86 (h, 1H, J = 7.0 Hz), 4.06 (h, 1H, J = 7.0 Hz), 7.79 (d, 2H, J = 8.0 Hz), 7.96 (d, 2H, J = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 23.0, 41.1, 43.1, 108.8, 116.3, 117.3, 117.8, 129.4, 132.4, 140.2, 176.7, 185.9. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 353.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{17}H_{18}N_2OS_2Na^+$, $[M+Na]^+$: 353.0758 found 353.0753.

3-(2-cyano-3,3-bis(isopropylthio)acryloyl)benzonitrile (12b)

To a solution (DMF, 7 mL) of **11b** (0.715 g, 4.20 mmol, 1.0 equiv.) was added NaH (60% in oil, 0.437 g, 10.9 mmol, 2.6 equiv.). After stirring for 45 min at room temperature, carbon disulfide (0.253 mL, 4.20 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was stirred at room temperature for 2 h before *i*-propyl iodide (0.881 mL, 8.82 mmol, 2.1 equiv.) was added dropwise. After being stirred for 23 h at 60°C, the reaction mixture was cooled and concentrated under reduced pressure. The residue was dissolved with water and extracted four times with diethyl ether. The organic layers were pooled, washed with sodium thiosulfate 5% and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 3:1 (v/v) in 45 min) to afford **12b** as a yellow oil (0.966 g, 70%). Elemental analysis. Found: C, 61.87; H, 5.61; N, 8.44; O, 4.99; S, 19.53. Calc for $C_{17}H_{18}N_2OS_2$: C, 61.79; H, 5.49; N, 8.48; O, 4.84; S, 19.41. IR (film, ν, cm^{-1}) 2969, 2931, 2861, 2232, 2204, 1647, 1420, 1368, 1267, 1153, 1051, 1012, 917, 813, 754, 683, 665. ^1H NMR (500 MHz, $CDCl_3$) δ 1.36 (d, 6H, J = 7.0 Hz), 1.47 (d, 6H, J = 7.0 Hz), 3.85 (h, 1H, J = 7.0 Hz), 4.05 (h, 1H, J = 7.0 Hz), 7.63 (t, 1H, J = 7.5 Hz), 7.86

(d, 1H, J = 7.5 Hz), 8.11 (d, 1H, J = 7.5 Hz), 8.14 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 23.0, 41.1, 43.1, 108.8, 113.2, 117.2, 117.7, 129.6, 132.6, 133.0, 136.0, 137.7, 176.2, 185.3. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 353.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{17}H_{18}N_2OS_2Na^+$, $[M+Na]^+$: 353.0758 found 353.0757.

Ethyl 4-cyano-3-(4-cyanophenyl)-5-(isopropylthio)thiophene-2-carboxylate (13a)

To a solution (EtOH, 3.5 mL) of **12a** (0.312 g, 0.79 mmol, 1.0 equiv.) were added dropwise ethyl thioglycolate (0.086 mL, 0.79 mmol, 1.0 equiv.) and Et_3N (0.121 mL, 0.87 mmol, 1.1 equiv.). After stirring for 3.7 h at room temperature, water was added to the reaction mixture which was extracted three times with EtOAc. The organic layers were pooled, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 3:1 (v/v) in 25 min) to afford **13a** as a white amorphous solid (0.157 g, 56%). Elemental analysis. Found: C, 60.81; H, 4.44; N, 7.76; O, 8.76; S, 18.11. Calc for $C_{18}H_{16}N_2O_2S_2$: C, 60.65; H, 4.52; N, 7.86; O, 8.98; S, 17.99. IR (film, ν , cm^{-1}) 2975, 2923, 2233, 1720, 1527, 1499, 1473, 1391, 1356, 1269, 1192, 1179, 1083, 1042, 1017, 849, 762, 675. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, 3H, J = 7.2 Hz), 1.49 (d, 6H, J = 6.6 Hz), 3.66 (h, 1H, J = 6.6 Hz), 4.23 (q, 2H, J = 7.2 Hz), 7.54 (d, 2H, J = 8.4 Hz), 7.77 (d, 2H, J = 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 23.1, 42.4, 62.0, 113.1, 114.8, 116.1, 129.7, 130.2, 131.9, 136.9, 146.7, 154.2, 159.6. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 379.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{18}H_{16}N_2O_2S_2Na^+$, $[M+Na]^+$: 379.0551 found 379.0555.

Ethyl 4-cyano-3-(3-cyanophenyl)-5-(isopropylthio)thiophene-2-carboxylate (13b)

To a solution (EtOH, 10 mL) of **12b** (0.940 g, 2.38 mmol, 1.0 equiv.) were added dropwise ethyl thioglycolate (0.261 mL, 2.38 mmol, 1.0 equiv.) and Et_3N (0.364 mL, 2.61 mmol, 1.1 equiv.). After stirring for 3.7 h at room temperature, water was added to the reaction mixture which was extracted three times with EtOAc. The organic layers were pooled, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/EtOAc 1:0 to 3:1 (v/v) in 40 min) to afford **13b** as a white amorphous solid (0.772 g, 91%). Elemental analysis. Found: C, 60.61; H, 4.56; N, 7.78; O, 8.86; S, 18.01. Calc for $C_{18}H_{16}N_2O_2S_2$: C, 60.65; H, 4.52; N, 7.86; O, 8.98; S, 17.99. IR (film, ν , cm^{-1}) 2967, 2928, 2233, 1723, 1520, 1487, 1366, 1273, 1163, 1085, 1042, 1017, 905, 806, 761, 705, 680. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, 3H, J = 7.2 Hz), 1.49 (d, 6H, J = 6.6 Hz), 3.66 (h, 1H, J = 6.6 Hz), 4.23 (q, 2H, J = 7.2 Hz), 7.57 to 7.77 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 23.1, 42.4, 62.0, 113.1, 114.8, 116.1, 129.1, 129.9, 132.6, 133.1, 133.7, 135.4, 146.1, 154.1, 159.7. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 379.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{18}H_{16}N_2O_2S_2Na^+$, $[M+Na]^+$: 379.0551 found 379.0556.

4-cyano-3-(4-cyanophenyl)-5-(isopropylthio)thiophene-2-carboxylic acid (14a)

To a solution (THF/EtOH 2/1, 2.3 mL) of **13a** (0.109 g, 0.31 mmol, 1.0 equiv.) was added aqueous NaOH (2M, 1.5 mL). After stirring 36 h at room temperature, the mixture was neutralized with aqueous HCl (1M, 3.0 mL) and extracted two times with CH_2Cl_2. The

organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure.to afford acid **14a** as a white amorphous solid (0.100 g, quantitative yield). IR (film, ν , cm^{-1}) 2966, 2925, 2861, 2227, 1695, 1674, 1533, 1494, 1368, 1266, 1196, 1156, 1039, 873, 837, 789, 769, 673. ^1H NMR (300 MHz, acetone-d_6) δ 1.46 (d, 6H, J = 6.9 Hz), 3.74 (h, 1H, J = 6.9 Hz), 7.72 (d, 2H, J = 8.4 Hz), 7.88 (d, 2H, J = 8.4 Hz). ^{13}C NMR (75 MHz, MeOD) δ 23.4, 43.6, 113.8, 114.2, 119.5, 130.4, 131.7, 133.0, 139.0, 147.7, 154.1, 162.3. MS (ESI^+, MeOH/CH_2Cl_2) *m/z* 327.0 $[M-H]^-$. HRMS (ESI^-, MeOH/CH_2Cl_2) calcd for $C_{16}H_{11}N_2O_2S_2^-$, $[M-H]^-$: 327.0262 found 327.0268. UHPLC 4.77 min, 80%.

4-cyano-3-(3-cyanophenyl)-5-(isopropylthio)thiophene-2-carboxylic acid (14b)

To a solution (THF/EtOH 2/1, 15.0mL) of **13b** (0.721 g, 2.02 mmol, 1.0 equiv.) was added aqueous NaOH (2M, 10.0 mL). After stirring 36 h at room temperature, the mixture was neutralized with aqueous HCl (1M, 20.0 mL) and extracted two times with CH_2Cl_2. The organic layers were pooled, dried over $MgSO_4$ and concentrated under reduced pressure.to afford acid **14b** as a white amorphous solid (0.557 g, 84 %). IR (film, ν , cm^{-1}) 2969, 2933, 2253, 2207, 1690, 1530, 1472, 1419, 1350, 1261, 1229, 1157, 1082, 822, 799, 688, 671. ^1H NMR (300 MHz, acetone-d_6) δ 1.47 (d, 6H, J = 6.9 Hz), 3.75 (h, 1H, J = 6.9 Hz), 7.69-7.97 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 43.3, 113.1, 114.0, 116.6, 119.0, 130.2, 130.2, 133.4, 134.2, 135.0, 135.1, 147.2, 153.4, 160.9. MS (ESI^+, MeOH/CH_2Cl_2) *m/z* 351.0 $[M+Na]^+$. HRMS (ESI^+, MeOH/CH_2Cl_2) calcd for $C_{16}H_{12}N_2O_2S_2Na^+$, $[M+Na]^+$: 351.0238 found 351.0244. UHPLC 4.75 min, 97%.

Ethyl 4-cyano-5-(isopropylthio)-3-(phenylamino)thiophene-2-carboxylate (15a)

To the bromothiophene **2** (0.100 g, 0.30 mmol, 1.0 equiv.), Cs_2CO_3 (0.137 g, 0.42 mmol, 1.4 equiv.), $Pd(PPh_3)_4$ (0.347 g, 0.03 mmol, 10 mol%) and aniline (0.033 mL, 0.36 mmol, 1.2 equiv.) under argon was added toluene (3 mL) and the reaction was stirred at reflux for 3 h. After cooling to room temperature, the reaction mixture was diluted with THF (5 mL), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/CH_2Cl_2 1:0 to 7:3 (v/v) in 25 min) to afford **15a** as a white solid (0.064 g, 50%). MP = 91 °C. IR (film, ν , cm^{-1}) 3325, 2962, 2223, 1665, 1548, 1236, 1173. ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, 3H, J = 7.1 Hz), 1.41 (d, 6H, J = 6.7 Hz), 3.57 (h, 1H, J = 6.7 Hz), 4.31 (q, 2H, J = 7.1 Hz), 7.15 (d, 2H, J = 7.6 Hz), 7.19 (t, 1H, J = 7.6 Hz), 7.34 (t, 2H, J = 7.6 Hz), 8.62 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 23.3, 41.7, 61.2, 103.8, 104.4, 112.4, 124.0, 126.0, 129.3, 139.6, 151.5, 156.0, 163.2. MS (ESI^+, MeOH/CH_2Cl_2) *m/z* 369.1 $[M+Na]^+$. HRMS (ESI^+, MeOH/CH_2Cl_2) calcd for $C_{17}H_{18}N_2O_2S_2Na^+$, $[M+Na]^+$: 369.0707 found 369.0703.

Ethyl 3-(4-chlorophenylamino)-4-cyano-5-(isopropylthio)thiophene-2-carboxylate (15b)

To the bromothiophene **2** (0.300 g, 0.90 mmol, 1.0 equiv.), Cs_2CO_3 (0.411 g, 1.26 mmol, 1.4 equiv.), $Pd(PPh_3)_4$ (0.104 g, 0.09 mmol, 10 mol%) and *p*-chloroaniline (0.138 g, 1.08 mmol, 1.2 equiv.) under argon was added toluene (10 mL) and the reaction was stirred at reflux for 46 h. After cooling to room temperature, the reaction mixture was diluted with THF (10 mL), filtered and concentrated under reduced pressure. The crude product was purified by flash

chromatography on silica gel (heptane/CH_2Cl_2 1:0 to 4:6 (v/v) in 40 min) to afford **15b** as a white solid (0.257 g, 75%). MP = 130 °C. Elemental analysis. Found: C, 53.25; H, 4.50; N, 7.12; O, 8.49; S, 16.76. Calc for $C_{17}H_{17}ClN_2O_2S_2$: C, 53.60; H, 4.50; N, 7.35; O, 8.40; S, 16.84. IR (film, ν , cm^{-1}) 3313, 2975, 2926, 2901, 2219, 1650, 1556, 1380, 1241. ^1H NMR (500 MHz, $CDCl_3$) δ 1.37 (t, 3H, J = 7.1 Hz), 1.44 (d, 6H, J = 6.7 Hz), 3.60 (h, 1H, J = 6.7 Hz), 4.33 (q, 2H, J = 7.1 Hz), 7.08 (d, 2H, J = 8.6 Hz), 7.31 (d, 2H, J = 8.6 Hz), 8.57 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 23.3, 41.8, 61.3, 103.7, 105.3, 112.5, 124.9, 129.5, 131.1, 138.3, 150.9, 156.3, 163.2. MS (ESI^+, MeOH/CH_2Cl_2) *m/z* 403.0 $[M+Na]^+$. HRMS (ESI^+, MeOH/CH_2Cl_2) calcd for $C_{17}H_{17}{}^{35}ClN_2O_2S_2Na^+$, $[M+Na]^+$: 403.0318 found 403.030; calcd for $C_{17}H_{17}{}^{37}ClN_2O_2S_2Na^+$, $[M+Na]^+$: 405.0288 found 405.0305.

Ethyl 4-cyano-5-(isopropylthio)-3-phenoxythiophene-2-carboxylate (15c)

To the bromothiophene **2** (0.100 g, 0.30 mmol, 1.0 equiv.), Cs_2CO_3 (0.137 g, 0.42 mmol, 1.4 equiv.), $Pd(PPh_3)_4$ (0.347 g, 0.03 mmol, 10 mol%) and phenol (0.034 g, 0.36 mmol, 1.2 equiv.) under argon was added toluene (3 mL) and the reaction was stirred at reflux for 6 h. After cooling to room temperature, the reaction mixture was diluted with THF (5 mL), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/CH_2Cl_2 1:0 to 1:1 (v/v) in 30 min) to afford **15c** as a yellowish solid (0.082 g, 79%). MP = 61 °C. IR (film, ν , cm^{-1}) 2981, 2928, 2220, 1686, 1384, 1309, 1156, 752. ^1H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, 3H, J = 7.1 Hz), 1.45 (d, 6H, J = 6.7 Hz), 3.63 (h, 1H, J = 6.7 Hz), 4.20 (q, 2H, J = 7.1 Hz), 6.95 (d, 2H, J = 7.7 Hz), 7.10 (t, 1H, J = 7.7 Hz), 7.32 (t, 2H, J = 7.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 23.3, 42.1, 61.8, 109.7, 111.5, 116.2, 120.4, 123.8, 129.9, 152.8, 154.5, 157.6, 159.2. MS (ESI^+, MeOH/CH_2Cl_2) *m/z* 370.1 $[M+Na]^+$. HRMS (ESI^+, MeOH/CH_2Cl_2) calcd for $C_{17}H_{17}NO_3S_2Na^+$, $[M+Na]^+$: 370.0548 found 370.0544.

Ethyl 3-(4-chlorophenoxy)-4-cyano-5-(isopropylthio)thiophene-2-carboxylate (15d)

To the bromothiophene **2** (0.100 g, 0.30 mmol, 1.0 equiv.), Cs_2CO_3 (0.137 g, 0.42 mmol, 1.4 equiv.), $Pd(PPh_3)_4$ (0.347 g, 0.03 mmol, 10 mol%) and *p*-chlorophenol (0.046 g, 0.36 mmol, 1.2 equiv.) under argon was added toluene (3 mL) and the reaction was stirred at reflux for 2.5 h. After cooling to room temperature, the reaction mixture was diluted with THF (5 mL), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (heptane/CH_2Cl_2 1:0 to 4:6 (v/v) in 30 min) to afford **15d** as a yellowish solid (0.097 g, 84%). MP = 123 °C. IR (film, ν , cm^{-1}) 2977, 2927, 2223, 1686, 1483, 1383, 1311. ^1H NMR (500 MHz, $CDCl_3$) δ 1.18 (t, 3H, J = 7.1 Hz), 1.45 (d, 6H, J = 6.7 Hz), 3.63 (h, 1H, J = 6.7 Hz), 4.20 (q, 2H, J = 7.1 Hz), 6.89 (d, 2H, J = 8.6 Hz), 7.28 (d, 2H, J = 8.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 23.3, 42.2, 62.0, 109.3, 111.4, 117.5, 129.5, 128.9, 129.9, 153.2, 154.1, 156.2, 159.0. MS (ESI^+, MeOH/CH_2Cl_2) *m/z* 404.0 $[M+Na]^+$. HRMS (ESI^+, MeOH/CH_2Cl_2) calcd for $C_{17}H_{16}{}^{35}ClN_2O_3S_2Na^+$, $[M+Na]^+$: 404.0158 found 404.0159.

Ethyl 3-benzyl-4-cyano-5-(isopropylthio)thiophene-2-carboxylate (15e)

To a suspension of potassium benzyltrifluoroborate (0.118 g, 0.60 mmol, 2.0 equiv.), aqueous Cs_2CO_3 (2M, 0.37 mL, 0.75 mmol, 2.5 equiv.), $PdCl_2(dppf).CH_2Cl_2$ (0.025 g, 0.030 mmol, 10 mol%) in toluene/EtOH (THF/EtOH 9/1, 2.0 mL) was added bromothiophene **2** (0.100 g, 0.30 mmol, 1.0 equiv.) under argon. The reaction mixture was stirred at reflux temperature for 22 h, then cooled to room temperature, and diluted with water (5 mL) followed by extraction with EtOAc (3 × 10 mL). The organic solution was dried over magnesium sulfate. The solvent was removed in vacuo and the crude product was purified by flash chromatography on silica gel (heptane/AcOEt 1:0 to 0:1 (v/v) in 30 min) to afford **15e** as a yellow amorphous solid (0.057 g, 55%). IR (film, ν , cm^{-1}) 2976, 2926, 2222, 1712, 1250, 1132. ^1H NMR (500 MHz, $CDCl_3$) δ 1.35 (t, 3H, J = 7.1 Hz), 1.45 (d, 6H, J = 6.7 Hz), 3.56 (h, 1H, J = 6.7 Hz), 4.35 (q, 2H, J = 7.1 Hz), 4.46 (s, 2H), 7.20 (t, 1H, J = 7.5 Hz), 7.28 (t, 2H, J = 7.5 Hz), 7.33 (d, 2H, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 23.4, 34.2, 42.4, 61.9, 114.0, 116.3, 126.9, 128.8, 129.0, 129.3, 138.3, 149.7, 153.3, 160.8. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 368.1 $[M+Na]^+$. HRMS (ESI^+, $MeOH/CH_2Cl_2$) calcd for $C_{18}H_{19}NO_2S_2Na^+$, $[M+Na]^+$: 368.0755 found 368.0753.

3-(4-chlorophenylamino)-4-cyano-5-(isopropylthio)thiophene-2-carboxylic acid (16b)

To a solution (THF/EtOH 2/1, 1.2 mL) of **15b** (0.057 g, 0.15 mmol, 1.0 equiv.) was added aqueous NaOH (2M, 0.7 mL). After stirring 16 h at room temperature, the mixture was neutralized with aqueous HCl (1M, 1.4 mL) and extracted twice with CH_2Cl_2. The organic layers were pooled, dried over MgSO4 and concentrated under reduced pressure.to afford acid **16b** as a yellow solid (0.053 g, quantitative yield). MP = 156 °C. IR (film, ν , cm^{-1}) 3327, 2969, 2861, 2528, 2214, 1631. ^1H NMR (500 MHz, $CDCl_3$) δ 1.46 (d, 6H, J = 6.7 Hz), 3.62 (h, 1H, J = 6.7 Hz), 7.12 (d, 2H, J = 8.6 Hz), 7.34 (d, 2H, J = 8.6 Hz), 8.53 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 42.5, 105.9, 108.2, 113.0, 124.9, 130.0, 130.2, 140.6, 151.1, 155.6, 164.0. MS (ESI^+, $MeOH/CH_2Cl_2$) *m/z* 351.0 $[M-H]^-$. HRMS (ESI^-, $MeOH/CH_2Cl_2$) calcd for $C_{15}H_{12}{}^{35}ClN_2O_2S_2^-$, $[M+-H]^-$: 351.0029 found 351.0027.

4-cyano-5-(isopropylthio)-3-phenoxythiophene-2-carboxylic acid (16c)

To a solution (EtOH, 1.5 mL) of **15c** (0.025 g, 0.072 mmol, 1.0 equiv.) was added aqueous NaOH (2M, 1.5 mL). After stirring 19 h at room temperature, the mixture was neutralized with aqueous HCl (1M, 3.0 mL). The precipitate was filtered, washed with water and solubilized in CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure.to afford acid **16c** as a white amorphous solid (0.017 g, 75%). ^1H NMR (500 MHz, acetone-d_6) δ 1.42 (d, 6H, J = 6.6 Hz), 3.66 (h, 1H, J = 6.6 Hz), 6.99 (d, 2H, J = 7.5 Hz), 7.06 (t, 1H, J = 7.5 Hz), 7.32 (t, 2H, J = 7.5 Hz).

3-(4-chlorophenoxy)-4-cyano-5-(isopropylthio)thiophene-2-carboxylic acid (16d)

To a solution (THF/EtOH 2/1, 1.4 mL) of **15d** (0.070 g, 0.18 mmol, 1.0 equiv.) was added aqueous NaOH (2M, 0.8 mL). After stirring 16 h at room temperature, the mixture was neutralized with aqueous HCl (1M, 1.6 mL) and extracted two times with CH_2Cl_2. The organic layers were pooled, dried over MgSO4 and concentrated under reduced pressure.to afford acid **16d** as a white solid (0.065 g, quantitative yield). IR (film, ν , cm^{-1}) 2965, 2924,

2225, 1634, 1482, 1400. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (d, 6H, *J* = 6.7 Hz), 3.63 (h, 1H, *J* = 6.7 Hz), 6.92 (d, 2H, *J* = 8.9 Hz), 7.29 (d, 2H, *J* = 8.9 Hz). MS (ESI^-, MeOH/DMF) *m/z* 352.0 $[M-H]^-$. HRMS (ESI^-, MeOH/DMF) calcd for $C_{15}H_{11}{}^{35}ClNO_3S_2^-$, $[M-H]^-$: 351.9869 found 351.9884.

3-benzyl-4-cyano-5-(isopropylthio)thiophene-2-carboxylic acid (16e)

To a solution (THF/EtOH 2/1, 0.6 mL) of **15e** (0.029 g, 0.085 mmol, 1.0 equiv.) was added aqueous NaOH (2M, 0.4 mL). After stirring 16 h at room temperature, the mixture was neutralized with aqueous HCl (1M, 0.8 mL) and extracted two times with CH_2Cl_2. The organic layers were pooled, dried over MgSO4 and concentrated under reduced pressure.to afford acid **16e** as a yellow amorphous solid (0.027 g, quantitative yield). IR (film) 2959, 2921, 2851, 2526, 2218, 1665, 1527, 1374, 1292, 706. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (d, 6H, *J* = 6.7 Hz), 3.55 (h, 1H, *J* = 6.7 Hz), 4.43 (s, 2H), 7.18-7.31 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 34.2, 42.4, 113.7, 115.5, 127.0, 128.8, 129.0, 137.2, 151.4, 155.7, 166.0. MS (ESI^+, MeOH/CH_2Cl_2) *m/z* 340.0 $[M+Na]^+$. HRMS (ESI^+, MeOH/CH_2Cl_2) calcd for $C_{16}H_{15}NO_2S_2Na^+$, $[M+Na]^+$: 340.0442 found 340.0442. UHPLC 2.94 min, 97%.

BIOLOGICAL ASSAYS

Human FTase assay

Assays were realized on 96-well plates, prepared with Biomek NKMC and Biomek 3000 from Beckman Coulter and read on Wallac Victor fluorimeter from Perkin-Elmer. Per well 20 µL of farnesyl pyrophosphate (10 µM) was added to 180 µL of a solution containing 2 µL of varied concentrations of potential inhibitors (dissolved in DMSO) and 178 µL of a solution composed by 5 µL of partially purified human FTase (1.5 mg/mL) and 1.0 mL of Dansyl-GCVLS peptide (in the following buffer: 5.8 mM DTT, 6 mM $MgCl_2$, 12 µM $ZnCl_2$ and 0.18% (w/v) Octyl-D-glucopyranoside, 53 mM Tris/HCl, pH 7.5).[4] Then the fluorescence development was recorded for 15 min (0.7 seconds per well, 15 repeats) at 30°C with an excitation filter at 340 nm and an emission filter at 486 nm. Each measurement was realized twice as duplicate or triplicate.

T. brucei FTase assay

Assays were realized on 96-well plates, as described for human FTase with the dansylated peptide Dansyl-GCAIM and the solution contains 15 µL of partially purified *Tb*FTase (1.0 mg/mL) in 1 mL peptide solution.[1]

Assay for *in vitro* inhibition of *P. falciparum* growth

The chloroquine-resistant strain FcB1/Colombia of *Plasmodium falciparum* was maintained in vitro on human erythrocytes in RPMI 1640 medium supplemented by 8% (v/v) heat-inactivated human serum, at 37°C, under an atmosphere of 3% CO_2, 6% O_2, 91% N_2. *In vitro*

drug susceptibility assays was measured by [^{3}H]-hypoxanthine incorporation as described.[6, 7] Drugs were prepared in DMSO at a 10 mM concentration. Compounds were serially diluted two-fold with 100 µL culture medium in 96-well plates. Asynchronous parasite cultures (100 µL, 1% parasitaemia and 1% final hematocrite) were then added to each well and incubated for 24 h at 37°C prior to the addition of 0.5 µCi of [^{3}H]-hypoxanthine (GE Healthcare, France, 1 to 5 Ci·mmol/mL) per well. After a further incubation of 24 h, plates were frozen and thawed. Cell lysates were then collected onto glass-fiber filters and counted in a liquid scintillation spectrometer. The growth inhibition for each drug concentration was determined by comparison of the radioactivity incorporated in the treated culture with that in the control culture maintained on the same plate. The concentration causing 50% growth inhibition (IC_{50}) was obtained from the drug concentration-response curve and the results were expressed as the mean values ± standard deviations determined from several independent experiments.

Assay for *in vitro* inhibition of *T. brucei* growth

Bloodstream forms of *Trypanosoma brucei brucei* strain 93 were cultured in HMI9 medium supplemented with 10% FCS at 37°C under an atmosphere of 5% CO_2.[8] In all experiments, log-phage cell cultures were harvested by centrifugation at 3,000 x *g* and immediately used. Drug assays were based on the conversion of a redox-sensitive dye (resazurin) to a fluorescent product by viable cells[9]. Drug stock solutions were prepared in pure DMSO. *T. b. brucei* bloodstream forms ($3x10^4$ cells/ml) were cultured as described above in 96-well plates (200 µL per well) either in the absence or in the presence of different concentrations of inhibitors and with a final DMSO concentration that did not exceeded 1%. After a 72-h incubation, resazurin solution was added in each well at the final concentration of 45 µM. Fluorescence was measured at 530 nm excitation and 590 nm emission wavelengths after a further 4-h incubation. Each inhibitor concentration was tested in triplicate and the experiment repeated twice. The percentage of inhibition of parasite growth rate was calculated by comparing the fluorescence of parasites maintained in the presence of drug to that of in the absence of drug. DMSO was used as a control. IC_{50}s were determined from the dose-response curves with drug concentrations ranging from 100 µM to 50 nM. IC_{50} value is the mean +/- the standard deviation of three independent experiments.

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