Supporting Information

A Novel Palladium Mediated Coupling Approach to 2,3-Disubstituted Benzo[*b*]thiophenes and its Application to the Synthesis of Tubulin Binding Agents.

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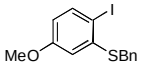
General methods:

Melting points were recorded with a Kofler hot-stage apparatus and are uncorrected. Proton (^{1}H) and (^{13}C) NMR spectra were recorded with a Varian Gemini 300 spectrometer operating at 300 MHz for proton and 75.5 MHz for carbon. All NMR spectra were recorded in (D)chloroform ($CDCl_3$) at 20 °C. The protonicities of the carbon atoms observed in the carbon NMR were determined using attached proton test (APT) experiments. Infrared spectra (IR) we obtained as KBr discs or as films on NaCl plates and were recorded on a Perkin-Elmer *Spectrum One* Fourier-transform infrared spectrophotometer. Low-resolution electron impact mass spectra (MS) were recorded at 70 eV on either a VG micromass 7070F instrument or a JEOL AX-505H mass spectrometer. High-resolution mass spectra (HRMS) were recorded on a VG micromass 7070F instrument. Elemental analyses were performed on a Carlo Erba 1106. Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Flash chromatography was performed on Merk Kieselgel 60.

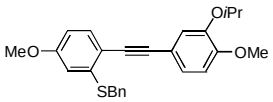


Benzyl 2-iodo-5-methoxyphenyl sulfide (4):

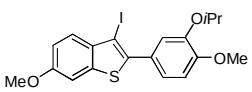
HBF_4 (50% w/v in H_2O, 14 mL) was added to a stirred suspension of 2-iodo-5-methoxyaniline (**3**)[10] (5.00 g, 21.5 mmol) in H_2O (30 ml) and the suspension stirred at room temperature for 0.5 h. The resultant clear solution was cooled in an ice bath, giving a white suspension. To this suspension $NaNO_2$ (1.55 g, 22.5 mmol) in H_2O (10 mL) was added dropwise over 0.1 h and the reaction mixture warmed to room temperature. The resulting suspension was filtered, rinsed with water (50 mL) and diethyl ether (25 mL) and dried under vacuum to give the corresponding diazonium tetrafluoroborate as a cream-colored solid 7.00 g (94 %).

The diazonium salt (7.00 g, 20.1 mmol) obtained above was added portionwise to a solution of potassium ethyl xanthate (3.42 g, 21.0 mmol) in acetone (50 mL) at 0 °C (ice bath) over 0.15 h. The reaction mixture was stirred at 0 °C for 0.75 h and at room temperature for 1.0 h. This mixture was concentrated under reduced pressure diluted with diethyl ether (50 mL) and washed sequently with H_2O (50 mL), KOH (2 % w/v in H_2O, 50 mL), brine (50 mL). The organic layer was died over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in methanol (50 mL) and powdered KOH (3.38 g, 60 mmol) added and the reaction mixture stirred vigoursly for 3 h. The methanol was then evaporated under reduced pressure. The residue was suspended in H_2O (40 mL) and CH_2Cl_2 (40 mL). Benzyl chloride (2.43 mL, 34.0 mmol) and *n*-Bu_4NHSO_4 (100 mg) were added and the biphasic mix stirred vigoursly for 1 h. The CH_2Cl_2 layer separated and the aqueous layer extracted with CH_2Cl_2 (50 mL). The combined

CH_2Cl_2 fractions dried over $MgSO_4$ and concentrated on to silica gel (8 g). The solid residue was subjected to flash chromatography (silica gel, hexane / diethyl ether 98:2) and **4** was obtained as a colorless oil which crystallized upon standing at 4 °C to afford a cream solid (4.22 g, 59 %), (55 % from 2-iodo-5-methoxyaniline) mp 72-4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.7 Hz, 1H), 7.29-7.46 (m, 5H), 6.82 (d, *J* = 3.0 Hz, 1H), 6.48 (dd, *J* = 3.0, 8.7 Hz, 1H), 4.16 (s, 2H), 3.70 (s, 3 H). ^{13}C NMR + APT (75.5 MHz, $CDCl_3$) δ 159.7 (C), 142.1 (C), 139.4 (CH), 135.5 (C), 128.7 (CH), 128.3 (CH), 127.1 (CH), 113.7 (CH), 112.6 (CH), 87.4 (C), 55.0 (CH_3), 38.5 (CH_2). IR (KBr disc, cm^{-1}) 2955, 2930, 1558, 1494, 1426, 1283, 1228, 1038. MS (70 eV) *m/z* (%): 356 ($M^{+\cdot}$, 45), 229 (10), 196 (22), 181 (6), 138 (15), 123 (20), 91 (100). HRMS calcd for $C_{14}H_{13}OSI$ 355.9732. Found 355.9728

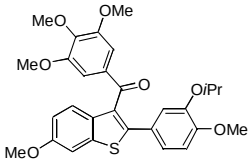


Benzyl 2-[2'-(3"-isopropoxy-4"-methoxyphenyl)-ethynyl]-5-methoxyphenyl sulfide:
n-Butyllithium (2.5 mL, 2.5 M in hexanes, 6.25 mmol) was added dropwise to a solution of *β,β*-dibromo-3-isopropoxy-4-methoxystyrene (**12**)[13a] (1.09 g, 3.12 mmol) in THF (10 mL) at -78 °C (dry-ice / acetone). After the addition was complete the cold bath was removed and the reaction mixture allowed to warm to room temperature over 0.33 h. Dry zinc chloride (426 mg, 3.12 mmol) was then added and after it dissolved (approximately 3 min), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.05 mmol) and 2-iodo-5-methoxyphenyl sulfide (**4**) (890 mg, 2.50 mmol) were added. The resultant solution was stirred at room temperature for 1 h then diluted with diethyl ether (30 mL) washed with $NH_4Cl_{(aq)}$ (saturated solution in H_2O, 30 mL) and brine (30 mL) dried over $MgSO_4$, and concentrated onto silica gel (3g). The solid residue was subjected to flash chromatography (silica gel, hexane / diethyl ether 9:1 then 3:1) to give the product (R*f* = 0.25, 3:1) as a white solid (1.00 g, 96 %) mp = 67-8 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 1H), 7.40-7.24 (m, 5H), 7.15 (dd, *J* = 1.8, 8.4 Hz, 1H), 7.09 (d, *J* = 1.8 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.79 (d, *J* = 2.4 Hz, 1H), 6.68 (dd, *J* = 2.4, 8.4 Hz, 1H), 4.55 (septet, *J* = 6.0 Hz, 1H), 4.23 (s, 2H), 3.88 (s, 3H), 3.75 (s, 3H), 1.38 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR + APT (75.5 MHz, $CDCl_3$) δ 159.5 (C), 150.8 (C), 146.9 (C), 141.1 (C), 136.8 (C), 133.6 (CH), 129.0 (CH), 128.6 (CH), 127.3 (CH), 125.1 (CH), 118.4 (CH), 115.6 (C), 115.4 (C), 113.3 (CH), 111.7 (CH), 111.2 (CH), 94.3 (C), 85.6 (C), 71.5 (CH), 56.0 (CH_3), 55.4 (CH_3), 37.5 (CH_2), 22.1 (CH_3). IR (KBr disc, cm^{-1}) 2973, 2835, 1594, 1509, 1471, 1410, 1324, 1288, 1263, 1246, 1136, 1116, 1053. MS (70 eV) *m/z* (%): 418 ($M^{+\cdot}$, 100), 376 ($M^{+\cdot}$ - CH_2=$CHCH_3$, 34), 341 (43), 299 (69), 253 (58) 91 (80). HRMS calcd for $C_{26}H_{26}O_3S$ 418.1603. Found 418.1601.



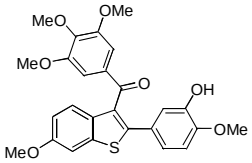
2-(3'-Isopropoxy-4'-methoxyphenyl)-3-iodo-6-methoxybenzo[*b*]thiophene:
Iodine (556 mg, 2.19 mmol) was added to a solution of benzyl 2-[2'-(3"-isopropoxy-4"-methoxyphenyl)-ethynyl]-5-methoxyphenyl sulfide (900 mg, 2.15 mmol) in CH_2Cl_2 (25 mL) and the solution stirred at room temperature for 1 h. After this time the solution was washed with $Na_2S_2O_5$ (5% w/v, 30 mL), dried over $MgSO_4$ and concentrated onto silica gel (5 g). The solid residue loaded onto a short column of (5 cm x 2 cm) and eluted with hexane and hexane / diethyl ether 3:1 to give the product (R_f = 0.33, 3:1)) as a white solid (950 mg, 97 %), mp = 102-3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.7 Hz, 1H), 7.30 (d, *J* = 2.1 Hz, 1H), 7.26 (d, *J* = 2.4

Hz, 1H), 7.21 (dd, *J* = 2.1 Hz, 8.4 Hz, 1H), 7.07 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 4.63 (septet, *J* = 6.3 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 1.45 (d, *J* = 6.3 Hz, 6H). ^{13}C NMR + APT (75.5 MHz, $CDCl_3$) δ 158.0 (C), 150.5 (C), 146.7 (C), 139.5 (C), 139.3 (C), 135.9 (C), 126.9 (C), 126.5 (CH), 122.6 (CH), 116.7 (CH), 115.1 (CH), 111.4 (CH), 104.3 (CH), 77.7 (C), 71.3 (CH), 55.9 (CH_3), 55.6 (CH_3), 22.1 (CH_3). IR (KBr disc, cm^{-1}) 2974, 2920, 2835, 1600, 1530, 1493, 1471, 1261, 1224, 1138, 1020. MS (70 eV) *m/z* (%): 454 ($M^{+\cdot}$, 66), 412 ($M^{+\cdot}$ - CH_2=$CHCH_3$, 58), 397 (26), 279 (24), 149 (100). Calcd for $C_{19}H_{19}O_3SI$ C: 50.23; H: 4.22. Found C: 50.27; H: 4.19.



2-(3'-Isopropoxy-4'-methoxyphenyl)-6-methoxy-3-(3",4",5"-trimethoxybenzoyl)benzo[*b*]thiophene (13):

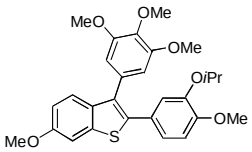
t-Butyllithium (0.52 mL, 1.7 M in hexanes, 0.88 mmol) was added to a solution 3-iodo-2-(3'-isopropoxy-4'-methoxyphenyl)-6-methoxybenzo[*b*]thiophene (200 mg, 0.44 mmol) in dry THF (4 mL) at –78 °C (dry-ice / acetone bath). To this was added a solution of 3,4,5-trimethoxybenzoyl chloride (**9**) (108 mg, 0.47 mmol) in dry THF (1.5 mL) and the reaction mixture warmed to room temperature. The mixture was diluted with diethyl ether (50 mL) and washed with $NH_4Cl_{(aq)}$ (sat., 50 mL), $NaHCO_{3(aq)}$ (5%, 60 mL) dried over $MgSO_4$ and concentrated onto silica gel (2 g). The residue was subject to flash chromatography (silca gel, hexane / diethyl ether 4:1, 2:1, 1:1) and the product, **13**, obtained as a colorless resin (200 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 9.0 Hz, 1H), 7.32 (d, *J* = 2.1 Hz, 1H), 7.10 (s, 2H), 7.00 (m, 2H), 6.85 (d, *J* = 2.1 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 4.30 (septet, *J* = 6.0 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.72 (s, 6H), 1.23 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR + APT (75.5 MHz, $CDCl_3$) δ 192.9 (C), 157.7 (C), 152.7 (C), 150.8 (C), 147.0 (C), 143.4 (C), 142.6 (C), 140.0 (C), 133.8 (C), 132.1 (C), 129.7 (C), 126.1 (C), 124.0 (CH), 121.8 (CH), 116.6 (CH), 114.9 (CH), 111.6 (CH), 107.3 (CH), 104.3 (CH), 71.5 (CH), 60.8 (CH_3), 56.0 (CH_3), 55.8 (CH_3), 55.5 (CH_3), 21.8 (CH_3). IR (NaCl film, cm^{-1}) 2936, 1644, 1581, 1531, 1501, 1473, 1413, 1228, 1126. MS (70 eV) *m/z* (%): 522 ($M^{+\cdot}$, 100), 480 ($M^{+\cdot}$ - CH_2=$CHCH_3$, 58), 301 (7), 195 (18). HRMS calcd for $C_{29}H_{30}O_7S$ 522.1712. Found 522.1716



2-(3'-Hydroxy-4'-methoxyphenyl)-6-methoxy-3-(3",4",5"-trimethoxybenzoyl)benzo[*b*]thiophene (14)

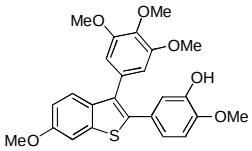
Aluminium trichloride (86 mg, 0.64 mmol) was added to a solution of **13** (140 mg, 0.27 mmol) in dry dichloromethane (4 mL) and the solution stirred at room temperature for 1.5 h. After this time $NH_4Cl_{(aq)}$ (sat., 20 mL) was added and the mixture extracted with diethyl ether (20 mL) dried over $MgSO_4$ and concentrated onto silica gel (1 g). The residue was subject to flash chromatography (silica gel, hexane / dichlormethane / diethyl ether 20:1) giving the product, **14**, as a white solid (112 mg, 87%), mp = 123-5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 9.0 Hz, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.06 (s, 2H), 7.00 (dd, *J* = 2.4, 9.0 Hz, 1H), 6.98 (d, *J* = 2.1

Hz, 1H), 6.83 (dd, *J* = 2.1, 9.0 Hz, 1H), 6.64 (d, *J* = 9.0 Hz, 1H), 5.68 (s, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.73 (s, 6H). ^{13}C NMR + APT (75.5 MHz, $CDCl_3$) δ 192.9 (C), 157.7 (C), 146.9 (C), 146.4 (C), 143.7 (C), 142.3 (C), 140.0 (C), 133.7 (C), 132.4 (C), 129.9 (C), 126.7 (C), 124.2 (CH), 121.3 (CH), 115.1 (CH), 114.9 (CH), 110.4 (CH), 107.3 (CH), 60.8 (CH_3), 56.0 (CH_3), 55.8 (CH_3), 55.5 (CH_3). IR (KBr disc, cm^{-1}) 3402, 2934, 1649, 1580, 1499, 1474, 1413, 1324, 1266, 1228, 1158, 1125. MS (70 eV) *m/z* (%): 480 ($M^{+\cdot}$, 100), 301 (6), 195 (7). HRMS calcd for $C_{26}H_{24}O_7S$ 480.1243. Found 480.1242.



2-(3'-Isopropoxy-4'-methoxyphenyl)-6-methoxy-3-(3",4",5"-trimethoxyphenyl)benzo[*b*]thiophene (15)

t-Butyllithium (0.78 mL, 1.7 M in hexanes, 1.33 mmol) was added to a solution 3,4,5-trimethoxyiodobenzene (194 mg, 0.66 mmol) in THF (3 mL) at –78 °C (dry-ice / acetone). Zinc chloride (90 mg, 0.66 mmol) was added and the reaction mixture warmed to room temperature. At this point $Pd(PPh_3)_2Cl_2$, (7.0 mg, 0.01 mmol) and 3-iodo-2-(3'-isopropoxy-4'-methoxyphenyl)-6-methoxybenzo[*b*]thiophene (200 mg, 0.44 mmol) were added and the resultant solution stirred at room temperature for 16 h. The reaction mixture was concentrated onto silica gel (2 g) and the residue subjected to flash chromatography (eluant hexane / diethyl ether 2:1, 1:1) and the relevant fractions collected (R*f* = 0.29, 1:1) giving **15** as white solid (188 mg, 86%), mp = 122-4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.7 Hz, 1H), 7.34 (d, *J* = 2.4 Hz, 1H), 7.02 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.98 (dd, *J* = 2.4, 8.4 Hz, 1H) 6.82 (d, *J* = 8.4 Hz, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 6.58 (s, 2H), 4.18 (septet, *J* = 6.0 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 3.76 (s, 6H), 1.21 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR + APT (75.5 MHz, $CDCl_3$) δ 157.5 (C), 153.5 (C), 149.3 (C), 146.6 (C), 139.5 (C), 137.2 (C), 136.7 (C), 135.1 (C), 131.6 (C), 126.8 (C), 123.7 (CH), 121.8 (CH), 116.0 (CH), 114.3 (CH), 111.5 (CH), 107.2 (CH), 104.6 (CH), 71.1 (CH), 60.9 (CH_3), 56.1 (CH_3), 55.9 (CH_3), 55.6 (CH_3), 21.8 (CH_3) (2 x C superimposed). IR (KBr disc, cm^{-1}) 2936, 2835, 1580, 1536, 1438, 1412, 1363, 1257, 1228, 1129. MS (70 eV) *m/z* (%): 494 ($M^{+\cdot}$, 100), 452 ($M^{+\cdot}$ - CH_2=$CHCH_3$, 52), 396 (12). HRMS calcd for $C_{28}H_{30}O_6S$ 494.1763. Found 494.1769.



2-(3'-Hydroxy-4'-methoxyphenyl)-6-methoxy-3-(3",4",5"-trimethoxyphenyl)benzo[*b*]thiophene (16):

Aluminium trichloride (40 mg, 0.30 mmol) was added to a solution of **15** (60 mg, 0.121 mmol) in dry dichloromethane (2 mL) and the solution stirred at room temperature for 1.5 h. After this time $NH_4Cl_{(aq)}$ (sat., 15 mL) was added and the mixture extracted with diethyl ether (15 mL) dried over $MgSO_4$ and concentrated onto silica gel (1 g). The residue was subject to flash chromatography (silica gel, hexane / dichlormethane / diethyl ether 5:5:1) giving the product, **16**, as a white solid (53 mg, 97%), mp = 210-1 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 9.0 Hz, 1H), 7.33 (d, *J* = 2.1 Hz, 1H), 6.97 (m, 2H), 6.78 (dd, *J* = 2.1, 8.4 Hz, 1H) 6.72 (d, *J* = 8.4 Hz, 1H), 6.55 (s, 2H), 4.58 (broad s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.75 (s, 6H).

^{13}C NMR + APT (75.5 MHz, $CDCl_3$) δ 157.4 (C), 153.3 (C), 146.1 (C), 145.2 (C), 139.8 (C), 137.2 (C), 136.5 (C), 134.9 (C), 131.9 (C), 131.2 (C), 127.6 (C), 123.8 (CH), 121.4 (CH), 115.5 (CH), 114.3 (CH), 110.4 (CH), 107.3 (CH), 104.6 (CH), 61.0 (CH_3), 56.1 (CH_3), 55.9 (CH_3), 55.7 (CH_3). IR (KBr disc, cm^{-1}) 3326, 2937, 2838, 1581, 1473, 1407, 1283, 1264, 1227, 1122. MS (70 eV) *m/z* (%): 452 ($M^{+\cdot}$, 100), 437 (8, $M^{+\cdot}$- CH_3). HRMS calcd for $C_{25}H_{24}O_6S$ 452.1294. Found 452.1292.