Supplemental Information

SYNTHESIS

All reagents, catalysts, and solvents were purchased from Sigma-Aldrich and Fisher Scientific and used as received. Unless stated otherwise, all reactions were carried out under an atmosphere of dry argon in oven dried glassware. Indicated reaction temperatures refer to those of the reaction bath, while room temperature (rt) is noted as 25 °C. Reaction progress was monitored by means of analytical thin layer chromatography (TLC) on silica gel plates (5 x 20 cm, 60 Å, 250 μm) with UV visualization at 254 nm. NMR spectra were recorded on either a Bruker Avance 400 MHz spectrometer or Bruker DPX 400 MHz spectrophotometer. Chemical shifts are reported in ppm with the solvent resonance as internal standard ([$CDCl_3$ 7.27 ppm, 77.23 ppm] [DMSO-d_6 2.5 ppm, 39.51 ppm] and [MeOD-d_4 4.78, 49.0] for ^1H, ^{13}C respectively). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, br. s = broad singlet, m = multiplet), number of protons, and coupling constants. Low resolution mass spectra (electrospray ionization) were acquired on a Hewlitt Packard MSD single quad.

The syntheses of **3,2-TDP, 3,3-TDP**, and **4,4-TDP** were performed according to the procedure reported by Pirali *et al.*(*1*)

3- and 4-azidophenols. To a suspension of 1.09 g (10 mmol) of the corresponding aminophenol in water (25 mL) concentrated HCl (2.28 mL) was added. The resulting clear solution was cooled to -3 ^oC by means of ice-NaCl bath followed by careful addition of sodium nitrite (0.83 g, 12 mmol) in water (2 mL) at such rate that the reaction temperature did not exceed 0 ^oC. Upon completion of the addition, the reaction mixture was stirred at -3 ^oC for 20 min, followed by careful addition of sodium azide (0.78 g, 12 mmol) in water (10 mL) (CAUTION: vigorous gas evolution!) The cold bath was removed, and the resulting mixture was stirred for 1 hr while gradually warming up to room temperature, followed by extraction with ethyl acetate (3 x 80 mL). Combined organic extracts were washed with 0.01 N HCl (20 mL), water (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford product which was stored at -20 ^oC.

3-azidophenol. Obtained 1.04 g (77%) ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (t, *J* = 8.1 Hz, 1 H), 6.62 (m, 2 H), 6.51 (t, *J* = 2.2 Hz, 1 H), 5.14 (br. s, 1 H)

4-azidophenol. Obtained 1.12 g (83%) ^1H NMR (400 MHz, $CDCl_3$) δ 6.91 (d, *J* = 8.8 Hz, 2 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 5.31 (br. s, 1H)

2-, 3-, and 4-[(2-trimethylsilyl)ethynyl]phenols. To a solution of 1.56 g (7 mmol) of the corresponding iodophenol in anhydrous toluene (16 mL) dichloro*bis*(triphenylphosphine)palladium(II) (148 mg, 0.21 mmol), copper(I) iodide (118 mg, 0.62 mmol), N,N-diisopropylethylamine (1.21 mL, 7 mmol), and ethynyl(trimethyl)silane (0.97 mL, 7 mmol) were added subsequently. The resulting mixture was stirred at room temperature for 24 hrs. The solvent was evaporated and the residue was purified by flash column chromatography (hexanes with ethyl acetate eluting from 9% to 14%) to afford the product as reddish-brown oil.

2-[(2-trimethylsilyl)ethynyl]phenol. Obtained 1.08 g (80%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.25 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.95 (d, *J* = 8.0 Hz, 1 H), 6.87 (dt, *J* = 7.6, 0.8 Hz, 1 H), 5.84 (br. s, 1 H), 0.29 (s, 9 H)

3-[(2-trimethylsilyl)ethynyl]phenol. Obtained 0.88 g (66%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (m, 1 H), 7.05 (m, 1 H), 6.93 (m, 1 H), 6.80 (m, 1 H), 4.90 (br. s, 1 H), 0.23 (s, 9 H)

4-[(2-trimethylsilyl)ethynyl]phenol. Obtained 1.14 g (85%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 2 H), 6.75 (d, *J* = 8.4 Hz, 2 H), 5.56 (br. s, 1 H), 0.23 (s, 9 H)

2-, 3-, and 4-ethynylphenols. To a solution of 190 mg (1 mmol) of the corresponding (2-trimethylsilyl)ethynylphenol iodophenol in methanol (15 mL) anhydrous potassium carbonate (1.07 g, 7.7 mmol) was added. The reaction mixture was stirred at reflux for 18 hr, then cooled down to room temperature, diluted with water (10 mL), and acidified with 1 M HCl (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 25 mL); organic extracts were combined, washed with water (2 x 10 mL), sodium bicarbonate (10 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford the product as a waxy solid.

2-ethynylphenol. Obtained 68 mg (57%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.29 (m, 1 H), 6.96 (dd, *J* = 8.0, 0.8 Hz, 1 H), 6.87 (dt, *J* = 7.6, 1.2 Hz, 1 H), 5.78 (br. s, 1 H), 3.47 (s, 1 H)

3-ethynylphenol. Obtained 72 mg (60%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 1 H), 7.12 (m, 1 H), 7.00 (m, 1 H), 6.84 (m, 1 H), 5.78 (br. s, 1 H), 3.72 (s, 1 H)

4-ethynylphenol. Obtained 65 mg (55%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 2 H), 6.78 (d, *J* = 8.4 Hz, 2 H), 5.04 (br. s, 1 H), 2.98 (s, 1 H)

3,2-TDP, 3,3-TDP, and **4,4-TDP**. The corresponding azidophenol (1 eq.) and ethynyl phenol (1 eq.) were dissolved in *tert*-butanol (2 mL) under argon atmosphere. A freshly prepared solution of sodium ascorbate (0.1 eq) in water (2 mL) was added. To the resulting suspension 0.01 eq. of $CuSO_4$ in water (0.2 mL) was added. The reaction mixture was stirred at 60 ^oC for 20 hrs, then cooled down and diluted with water (20 mL). The precipitate was filtered, shaken in 20 mL of dichloromethane/methanol mixture (10:1), and filtered through a silica plug. The eluent was evaporated to afford pure product.

2-(1-(3-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)phenol. Obtained 42 mg (29%) ^{1}H NMR (400 MHz, CD_3OD) δ 8.77 (s, 1 H), 7.98 (d, *J* = 6.8 Hz, 1 H), 7.35 (m, 3 H), 7.29 (m, 1 H), 6.93 (m, 3 H); M/S *m/z* (ESI+) 254 $(M+H)^+$; *m/z* (ESI-) 252 $(M-H)^-$

3,3'-(1H-1,2,3-triazole-1,4-diyl)diphenol. Obtained 45 mg (23%) ^{1}H NMR (400 MHz, CD_3OD) δ 8.79 (s, 1 H), 7.37 (m, 5 H), 7.29 (t, *J* = 8.4 Hz, 1 H), 6.94 (m, 1 H), 6.83 (m, 3 H); M/S *m/z* (ESI+) 254 $(M+H)^+$; *m/z* (ESI-) 252 $(M-H)^-$

4,4'-(1H-1,2,3-triazole-1,4-diyl)diphenol. Obtained 60 mg (54%) ^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1 H), 7.71 (d, *J* = 8.4 Hz, 2 H), 7.67 (d, *J* = 9.2 Hz, 2 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 6.87 (d, *J* = 8.4 Hz, 2 H); M/S *m/z* (ESI+) 254 $(M+H)^+$; *m/z* (ESI-) 252 $(M-H)^-$

4-(6-bromobenzo[1,3]dioxol-5-yl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (G15).[41]
To a mixture of 6-bromopiperanal (0.916 g, 4 mmol), aniline (0.372 g, 4 mmol), and freshly distilled cyclopentadiene (1.32 g, 20 mmol) in acetonitrile (12 mL) a solution of $Sc(OTf)_3$ (0.196 g, 0.4 mmol) in anhydrous acetonitrile (4 mL) was added. The reaction mixture was stirred for 3 hrs. The volatiles were removed *in vacuo.* The residue was dissolved in dichloromethane (40 mL) and precipitated by dropwise addition of methanol (5 mL). The precipitated product was purified by HPLC to afford the desired product.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.24 (s, 1 H), 7.14 (s, 1 H), 6.97 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.87 (dt, *J* = 7.6, 1.2 Hz, 2 H), 6.70 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.61 (dt, *J* = 7.6, 1.2 Hz, 1 H); 6.09 (dd, *J* = 9.2, 0.8 Hz, 2 H), 5.86 (m, 1 H), 5.59 (d, *J* = 4.8 Hz, 1 H) , 5.57 (s, 1 H), 4.67 (d, *J* = 2.8 Hz, 1 H), 4.00 (d, *J* = 8.4 Hz, 1 H), 3.03 (m, 1H), 2.46 (m, 1 H), 1.67 (m, 1 H); M/S *m/z* (ESI+) 370 $(M+H)^+$

(6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)(*p*-tolyl)methanone. *p*-toluoyl chloride (343 mg, 2.22 mmol) was added to a solution of 6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (400 mg, 1.48 mmol) in anhydrous CH_2Cl_2 (60 mL) at 0 °C. To this mixture, $AlCl_3$ (296 mg, 2.22 mmol) was added and the reaction was stirred at 0 °C for 2 hr and at room temperature for 1 hr. The reaction mixture was poured into ice water (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic layer was washed with 1 M NaOH and brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and the crude product was purified by flash chromatography (hexanes/ethyl acetate, 8:1) to yield 438 mg (76%) of the the desired product. ^{1}H NMR (400 MHz, acetone-d_6): δ 2.31 (s, 3H), 3.75 (s, 3H), 3.90 (s, 3H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.01 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.17 (d, *J* = 8 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.56 (d, *J* = 2.4 Hz, 1H), 7.67 (d, *J* = 8 Hz, 2H).

(6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl)(*p*-tolyl)methanone (Tol-BTC). To a stirred solution of (6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)(*p*-tolyl)methanone (200 mg, 0.52 mmol) in anhydrous CH_2Cl_2 (40 mL) was added BBr_3 (1.0 M, in CH_2Cl_2, 2.06 mL, 2.06 mmol) at -78 °C. The reaction was allowed to warm to room temperature over the course of 6 hr, after which period it was carefully quenched by the addition of saturated $NaHCO_3$ (20 mL) at 0 °C. CH_2Cl_2 was removed under reduced pressure, and the residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate several times, and the organic extracts were combined and dried over Na_2SO_4. Solvent was removed under reduced pressure and the crude product was purified by flash chromatography (hexanes/ethyl acetate, 2:1) to afford 132 mg (66%) of the desired compound. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.29 (s, 3H), 6.66 (d, *J* = 8.4 Hz, 2H), 6.85 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 1H), 7.34 (d, *J* = 2 Hz, 1H), 7.59 (d, *J* = 8 Hz, 1H), 9.72 (s, 1H), 9.78 (s, 1H).

1,7-bis(6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)heptane-1,7-dione. Anhydrous $AlCl_3$ (269 mg, 2.02 mmol) was added in small portions to a stirred solution of 6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (500 mg, 1.85 mmol) in anhydrous CH_2Cl_2 (60 mL) at 0 °C. To this solution, pimeloyl chloride (165 mg, 0.83 mmol) was added slowly, and the mixture was stirred at 0 °C for 2 hr and at room temperature for 2 hr. The reaction mixture was poured into ice water (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic layer was washed with 1 M NaOH and brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and the crude product was purified by flash chromatography (hexanes/ethyl acetate 6:1) to yield 264 mg (48%) of the desired compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (quin, *J* = 2.8 Hz, 2H), 1.40 (quin, *J* = 7.6 Hz, 4H), 2.31 (t, *J* = 7.2 Hz, 4H), 3.86 (s, 6H), 3.89 (s, 6H), 6.94 (d, *J* = 8.8 Hz, 4H), 7.04 (dd, *J* = 8.8, 2.4 Hz, 2H), 7.27 (d, *J* = 2.4 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 4H), 7.90 (d, *J* = 9.2 Hz, 2H).

1,7-bis(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)heptane-1,7-dione (bisBTChd). To a stirred solution of 1,7-bis(6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)heptane-1,7-dione (72 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (30 mL) was added BBr_3 (1.0 M, in CH_2Cl_2, 888 μL, 0.89 mmol) at -78 °C. The reaction was allowed to warm to room temperature over the course of 6 hr, after which period it was carefully quenched by the addition of saturated $NaHCO_3$ (20 mL) at 0 °C. CH_2Cl_2 was removed under reduced pressure, and the residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate several times, and the organic extracts were combined and dried over Na_2SO_4. Solvent was removed under reduced pressure and the crude product was purified by flash chromatography (hexanes/ethyl acetate, 2:1) to afford 58 mg (86%) of the desired compound. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 0.86 (quin, *J* = 2.8 Hz, 2H), 1.28 (quin, *J* = 7.2 Hz, 4H), 2.26 (t, *J* = 7.2 Hz, 4H), 6.84 (d, *J* = 8.8 Hz, 4H), 6.91 (dd, *J* = 8.8, 2.4 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 4H), 7.28 (d, *J* = 2 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 2H), 9.76 (s, 2H), 9.91 (s, 2H); ^{13}C NMR (400 MHz, DMSO-*d*$_6$): δ 24.3, 28.2, 42.5, 107.2, 115.8, 116.3, 124.5, 130.8, 131.3, 132.0, 139.6, 144.7, 155.9, 201.5; Positive ion electrospray HRMS *m/z* 609.1430 $[M + H]^+$, calculated for $C_{35}H_{29}O_6S_2$ 609.1361.

3-isopropyl-6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene. Anhydrous $AlCl_3$ (617 mg, 4.63 mmol) was added in small portions to a stirred solution of 6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (500 mg, 1.85 mmol) in anhydrous CH_2Cl_2 (60 mL) at 0 °C. To this solution, 2-bromopropane (569 mg, 4.63 mmol) was added slowly, and the mixture was stirred at 0 °C for 2 hr and at room temperature for 4 hr. The reaction mixture was poured into ice water (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic layer was washed with 1 M NaOH and brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and the crude product was purified by flash chromatography (hexanes/ethyl acetate 10:1) to yield 242 mg (42%) of the desired compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 3H), 1.45 (s, 3H), 3.42 (sep, *J* = 7.2 Hz, 1H), 3.88 (s, 3H), 3.90 (s, 3H) 6.99 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 2.4 Hz, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.87 (d, *J* = 9.2 Hz, 1H).

2-(4-hydroxyphenyl)-3-isopropylbenzo[b]thiophen-6-ol (iPr-BTC). To a stirred solution of 3-isopropyl-6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene (114 mg, 0.37 mmol) in anhydrous CH_2Cl_2 (40 mL) was added BBr_3 (1.0 M, in CH_2Cl_2, 1.46 mL, 1.46 mmol) at -78 °C. The reaction was allowed to warm to room temperature over the course of 6 hr, after which period it was carefully quenched by the addition of saturated $NaHCO_3$ (20 mL) at 0 °C. CH_2Cl_2 was removed under reduced pressure, and the residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate several times, and the organic extracts were combined and dried over Na_2SO_4. Solvent was removed under reduced pressure and the crude product was purified by flash chromatography (hexanes/ethyl acetate, 4:1) to afford 60 mg (58%) of the desired compound. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 1.33 (s, 3H), 1.35 (s 3H), 3.31 (sep, *J* = 7.2 Hz, 1H), 6.83-6.88 (m, 3H), 7.20 (d, *J* = 2.4 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 1H), 9.54 (s, 1H), 9.68 (s, 1H). ^{13}C NMR (400 MHz, DMSO-*d*$_6$): δ 21.8, 27.7, 107.3, 114.0, 115.5, 124.1, 125.1, 130.9, 131.4, 133.3, 136.1, 140.2, 154.4, 157.3; Positive ion electrospray HRMS *m/z* 285.0938 $[M + H]^+$, calculated for $C_{17}H_{17}O_2S$ 285.0905.

pent-4-ynyl 4-methylbenzenesulfonate. The compound was synthesized as previously described by Deschamps, et al.(*2*) to give 3.71 g (65%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.83-2.01 (m, 3H), 2.29 (m, 2H), 2.49 (s, 3H), 4.18 (t, *J* = 6.1 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.83 ppm (d, *J* =

8.3 Hz, 2H).

4-(pent-4-ynyloxy)phenol. To a stirred solution of DMSO (10 mL) and 5M NaOH (4.2 mL) was added hydroquinone (1.11 g, 10.1 mmol) in one portion. The solution was heated to 50 ^{o}C and pent-4-ynyl 4-methylbenzenesulfonate (2g, 8.4 mmol) was added slowly over the course 0.5 hr. The mixture was stirred at 50 ^{o}C for 6 hr and then at room temperature for 12 hr. After cooling to 0 ^{o}C, deionized water (40 mL) was added, and the pH was adjusted to 7 with concentrated HCl. The resulting mixture was partitioned between water and ethyl acetate. The organic layer was isolated, washed with brine, and then dried over Na_2SO_4. Solvent was removed under reduced pressure and the crude product was purified by flash chromatography (hexanes/ethyl acetate, 6:1) to afford 502 mg (34%) of the desired monoarylated compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95-2.02 (m, 3H), 2.41 (td, *J* = 6.8, 2.4 Hz, 2H), 4.02 (t, *J* = 6 Hz, 2H), 5.06 (s, 1H), 6.79 (m, 3H).

3-bromo-2-(4-fluorophenyl)-6-methoxybenzo[b]thiophene S-oxide. The compound was synthesized as previously described by Liu, et al(*3*) to give 812 mg (86%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) 3.91 (s, 3H), 7.32 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.43 (t, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.81 (m, 3H).

2-(4-fluorophenyl)-6-methoxy-3-(4-(pent-4-ynyloxy)phenoxy)benzo[b]thiophene S-oxide. NaH (57 mg, 2.38 mmol, 60% dispersion in mineral oil) was added to a solution of 4-(pent-4-ynyloxy)phenol (250 mg, 1.42 mmol) in 10 mL of anhydrous DMF at room temperature. After stirring for 15 minutes, 3-bromo-2-(4-fluorophenyl)-6-methoxybenzo[b]thiophene S-oxide (495 mg, 1.40 mmol) was added in small portions, and the solution was stirred for 1.5 hr. Ethyl acetate and water were added, and the organic layer was washed several times with water and then dried over Na_2SO_4. The crude product was purified by flash chromatography (hexanes/ethyl acetate, 2:1) to afford 268 mg (43%) of the desired compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96-2.02 (m, 3H), 2.41 (td, *J* = 7.2, 2.8 Hz, 2H), 3.89 (s, 3H), 4.03 (t, *J* = 6.4 Hz, 2H), 6.83 (d, *J* = 9.2 Hz, 2H), 7.01 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.09 (d, *J* = 9.2 Hz, 2H), 7.14 (t, *J* = 8.8 Hz, 2H), 7.27 (m, 1H), 7.42 (d, *J* = 2.4 Hz, 1H), 7.50 (m, 2H).

2-(4-fluorophenyl)-6-methoxy-3-(4-(pent-4-ynyloxy)phenoxy)benzo[b]thiophene. $LiAlH_4$ (45 mg, 1.12 mmol) was added in small portions to a solution of 2-(4-fluorophenyl)-6-methoxy-3-(4-(pent-4-ynyloxy)phenoxy)benzo[b]thiophene S-oxide (268 mg, 0.60 mmol) in 10 mL of anhydrous THF under N_2 at 0 °C. After the mixture was stirred for 60 min, the reaction was quenched by the slow addition of 1 mL of 2.0 M NaOH. The mixture was stirred vigorously for 30 min, and a minimal amount of 2.0 M NaOH was added to dissolve salts. The mixture was partitioned between water and ethyl acetate, and the aqueous layer was isolated and then extracted several times with ethyl acetate. The organic layers were combined, dried over anhydrous Na_2SO_4, and then concentrated in vacuo to an oil. The crude product was purified by flash chromatography (hexanes/ethyl acetate, 10:1) to afford 217 mg (84%) of the desired compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97-2.03 (m, 3H), 2.42 (td, *J* = 7.2, 2.8 Hz, 2H), 3.88 (s, 3H), 4.04 (t, *J* = 6 Hz, 2H), 6.84 (d, *J* = 4.8 Hz, 2H), 6.99 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 2H), 7.14 (t, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.53 (m, 3H).

2-(4-fluorophenyl)-3-(4-hydroxyphenoxy)benzo[b]thiophen-6-ol (HP-BTF). To a stirred solution of 2-(4-fluorophenyl)-6-methoxy-3-(4-(pent-4-ynyloxy)phenoxy)benzo[b]thiophene (93 mg, 0.22 mmol) in anhydrous CH_2Cl_2 (10 mL) was added BBr_3 (1.0 M, in CH_2Cl_2, 430 µL, 0.43 mmol) at -78 ^{o}C. The reaction was allowed to warm to room temperature over the course of 6 hr, after which period it was carefully quenched by the addition of saturated $NaHCO_3$ (10 mL) at 0 °C. CH_2Cl_2 was removed under reduced pressure, and the residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate several times, and the organic extracts were combined and dried over Na_2SO_4. Solvent was removed under reduced pressure and the crude product was purified by flash chromatography (chloroform, methanol 9:1) to afford 24 mg (32%) of the desired compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.96 (s, 1H), 5.14 (s, 1H), 6.77 (d, J = 8.8 Hz, 2H), 6.90 (dd, J = 8.4, 2.4 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 7.14 (t, J = 8.8 Hz, 2H), 7.17 (d, J = 2.4 Hz, 1H), 7.51 (m, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 99.6, 107.9, 113.9, 115.1, 115.3, 115.7, 118.3, 120.1, 122.7, 130.7, 134.1, 151.7, 151.9, 152.6, 152.7, 162.9; Positive ion electrospray HRMS *m/z* 353.0638 $[M + H]^+$, calculated for $C_{20}H_{14}FO_3S$ 353.0642.

IMMUNOASSAY

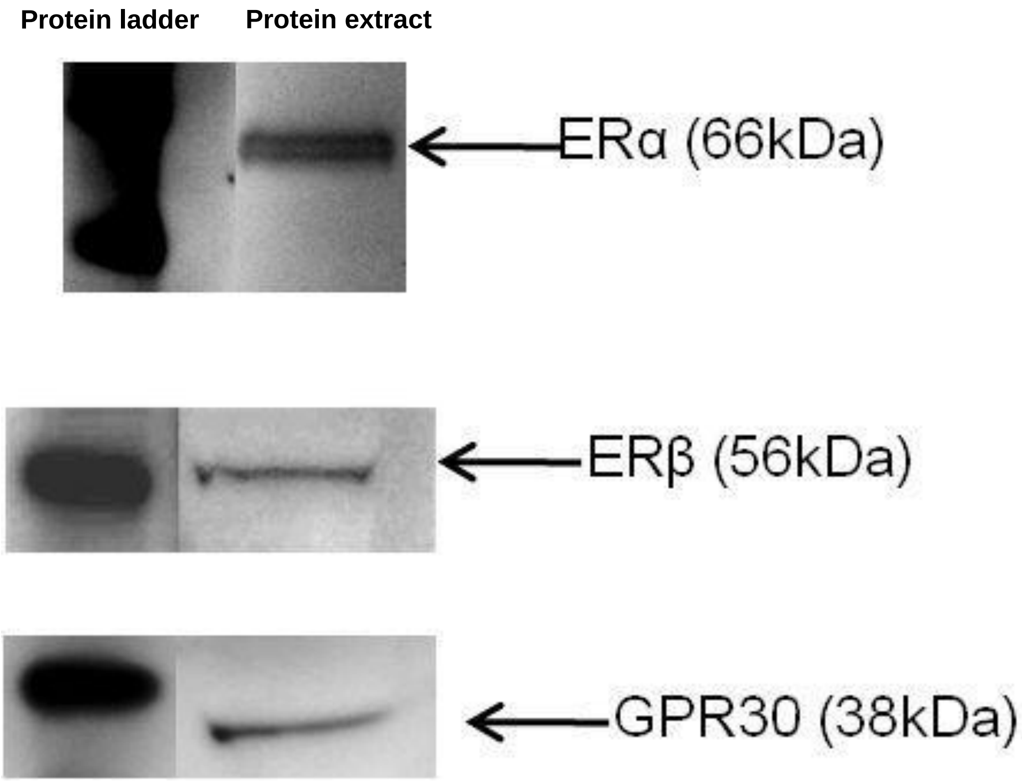
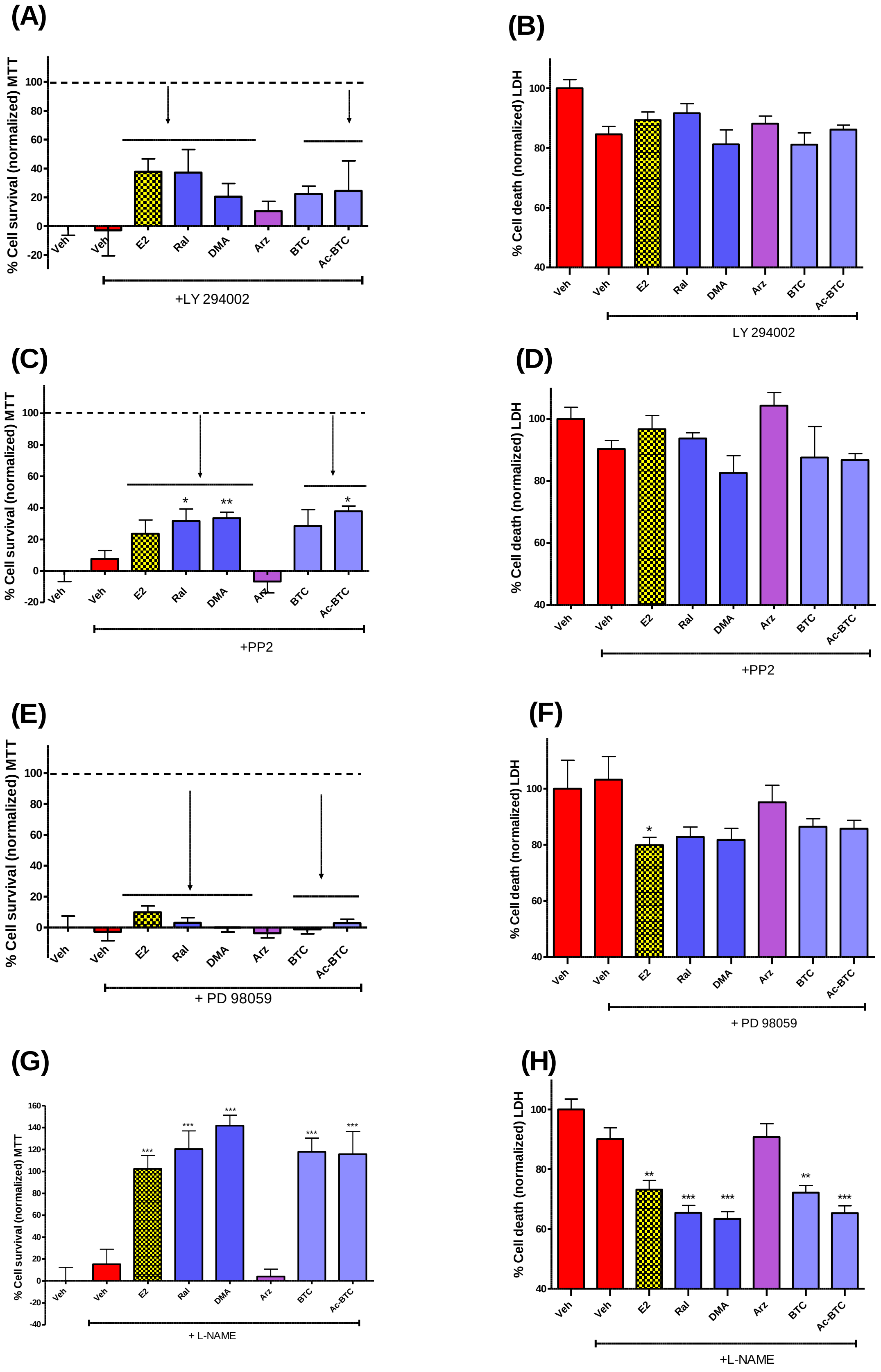


Fig. 1 Primary cortical neurons were harvested, and proteins were run on an SDS gel to determine the presence of ERα, ERβ, and GPR30 as described in Methods. ERα was detected at 66kDa, ERβ was detected at 56kDa and GPR30 was detected at 38kDa.

(A)
% Cell survival (normalized) MTT
100
80
60
40
20
0
-20
Veh
Veh
E2
Ral
DMA
Arz
BTC
Ac-BTC
+LY 294002
(B)
% Cell death (normalized) LDH
100
80
60
40
Veh
Veh
E2
Ral
DMA
Arz
BTC
Ac-BTC
LY 294002
(C)
% Cell survival (normalized) MTT
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+PP2
(D)
% Cell death (normalized) LDH
+PP2
(E)
% Cell survival (normalized) MTT
+ PD 98059
(F)
% Cell death (normalized) LDH
*
+ PD 98059
(G)
% Cell survival (normalized) MTT
160
140
120
100
80
60
40
20
0
-20
-40
***
***
***
***
***
+ L-NAME
(H)
% Cell death (normalized) LDH
**
***
***
**
***
+L-NAME

Fig. 2. Estrogen neuroprotection is attenuated by inhibition of PI3K/AkT and Src/MEK signaling, but not by inhibition of NOS. OGD induced cell death in 10-12 day primary neuronal cultures measured by MTT or LDH assays after pre-treatment with antagonists (-45 min) and treatment with test compounds (SERMs 100nM; E_2 10nM) immediately before OGD. **A-B.** PI3K inhibitor LY294002 (10 µM), **C-D**. SRC inhibitor PP2 (10 µM), **E-F.** MEK inhibitor PD 98059 (10 µM), **G-H**. NOS inhibitor L-NAME (100 µM). LDH data was normalized to veh. control as 100% cell death; MTT data was normalized to veh. control as 0% and E_2 (in the absence of antagonist) as 100% cell survival. Data show mean and s.e.m. (N = 6); ***$P<0.0001$, **$P<0.001$, *$P<0.01$ compared to veh. control using one way ANOVA with Dunnett's post hoc test.

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