Supporting Information

Expanding the synthesizable multisubstituted benzo[b]thiophenes via 6,7-thienobenzynes generated from o-silylaryl triflate-type precursors

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General Remarks
All reactions were performed with dry glassware under atmosphere of argon, unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on precoated (0.25 mm) silica-gel plates (Merck Chemicals, Silica Gel 60 F254, Cat. No. 1.05715). Column chromatography was conducted using silica-gel (Kanto Chemical Co., Inc., Silica Gel 60, spherical, particle size 40–50 μm, Cat. No. 37562-85), or Biotage® ZIP-sphere cartridge 45 g (Cat. No. 445-4500-SZ-20), 80 g (Cat. No. 445-8000-JZ-20), 120 g (Cat. No. 445-120G-UZ-20), or Biotage® SNAP Ultra HP-sphere cartridge 10 g (Cat. No. FSUL-0442-0010) or 25 g (Cat. No. FSUL-0442-0025) with medium pressure liquid chromatography (Yamazen, W-Prep 2XY A-type). Preparative thin-layer chromatography (PTLC) was performed on silica-gel (Wako Pure Chemical Industries Ltd., Wakogel® B-5F, Cat. No. 230-00043). Melting points (Mp) were measured on an OptiMelt MPA100 (Stanford Research Systems), and are uncorrected.

1H NMR spectra were obtained with a Bruker ADVANCE 500 spectrometer at 500 MHz. 13C NMR spectra were obtained with a Bruker ADVANCE 500 spectrometer at 126 MHz. 19F NMR spectra (non-decoupling mode) were obtained with a Bruker ADVANCE 400 spectrometer at 376 MHz. 31P NMR spectra (non-decoupling mode) were obtained with a Bruker ADVANCE 400 spectrometer at 162 MHz. All NMR measurements were carried out at 25 °C. CDCl3 (Kanto Chemical Co., Inc., Cat. No. 07663-23) or DMSO-d6 (Kanto Chemical Co., Inc., Cat. No. 11560-43) was used as a solvent for obtaining NMR spectra. Chemical shifts (δ) are given in parts per million (ppm) downfield from (CH3)2Si (δ 0.00 for 1H NMR in CDCl3) or the solvent peak (δ 77.0 for 13C NMR in CDCl3), and δ 2.49 for 1H NMR and δ 39.5 for 13C NMR in DMSO-d6) as an internal reference, or a,a,a-trifluorotoluene (δ –63.0 ppm for 19F NMR in CDCl3) and 85%H3PO4 (δ 0.0 for 31P NMR in CDCl3) as an external standard with coupling constants (J) in hertz (Hz). The abbreviations s, d, t, q, sept, m, and br signify singlet, doublet, triplet, quartet, septet, multiplet, and broad, respectively. IR spectra were measured by diffuse reflectance method on a Shimadzu IRPrestige-21 spectrometer attached with DRS-8000A with the absorption band given in cm⁻¹. High-resolution mass spectra (HRMS) were measured on a Bruker micrOTOF mass spectrometer under positive electrospray ionization (ESI) conditions. Elemental analyses were carried out at A Rabbit Science Japan Co., Ltd.

n-Butyllithium (1.6 M in n-hexane) was used after titrimetric determination of the concentration by the 1,10-phenanthroline method. 2,3-Dibutyl-6-hydroxybenzo[b]thiophene (1a),6 sulfur-6-hydroxy-2-methylthio-3-(trifluoromethyl)benzo[b]thiophene (1b),6 6-hydroxy-2-methylthio-3-(trifluoromethyl)benzo[b]thiophene (1c),6 3-chloro-2-dimethylaminocarbonyl-6-hydroxybenzo[b]thiophene (1d),6 methyl 4-(azidomethyl)benzoate (5a),6 5-(4-tolyl)-5-(4-(trifluoromethyl)phenyl)sulfonoxime (16),6 2-bromophenyl 4-tolyl sulfoxide (18),54 and EP4 antagonist analog 20b were prepared according to the reported methods. All other chemical reagents used were commercial grade and used as received.

S1
Experimental Procedures

Preparation of 2,3-dibutyl-6-triflyloxy-7-(trimethylsilyl)benzo[b]thiophene (2a)

To a solution of 2,3-dibutyl-6-hydroxybenzo[b]thiophene (1a) (6.56 g, 25.0 mmol) dissolved in CH_2Cl_2 (50 mL) were slowly added isopropyl isocyanate (3.53 mL, 50.2 mmol, 2.01 equiv) and triethylamine (0.69 mL, 5.0 mmol, 20 mol%) at room temperature. After stirring for 3 h at the same temperature, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (Biotage® ZIP-sphere cartridge 120 g, n-hexane/CH_2Cl_2 = 80/20 to 50/50) to give 2,3-dibutyl-6-(isopropylcarbamyloxy)benzo[b]thiophene (7.95 g, 22.9 mmol, 91.6%) as a colorless solid.

Colorless solid; Mp 79–81 °C; TLC Rf 0.26 (n-hexane/CH_2Cl_2 = 1/1); 1H NMR (CDCl_3, 500 MHz) δ 0.87–0.99 (m, 6H, 2 CH_3), 1.24 (d, 6H, J = 6.6 Hz, 2 CH_3), 1.35–1.46 (m, 4H, aliphatic), 1.51–1.60 (m, 2H, aliphatic), 1.62–1.71 (m, 2H, aliphatic), 2.74 (t, 2H, J = 7.8 Hz, aliphatic), 2.83 (t, 2H, J = 7.7 Hz, aliphatic), 3.91 (dsept, 1H, J = 6.6, 6.6 Hz, CH), 4.87 (d, 1H, J = 6.6 Hz, NH), 7.09 (dd, 1H, J = 8.6, 2.1 Hz, aromatic), 7.52 (d, 1H, J = 2.1 Hz, aromatic), 7.55 (d, 1H, J = 8.6 Hz, aromatic); 13C NMR (CDCl_3, 126 MHz) δ 13.9 (1C), 14.0 (1C), 22.4 (1C), 22.8 (1C), 22.9 (2C), 26.2 (1C), 28.2 (1C), 32.2 (1C), 33.6 (1C), 43.4 (1C), 115.0 (1C), 118.3 (1C), 121.5 (1C), 131.1 (1C), 137.9 (1C), 138.8 (1C), 140.2 (1C), 147.3 (1C), 154.0 (1C); IR (KBr, cm⁻¹) 3029, 1057, 1175, 1206, 1238, 1466, 1526, 1717, 2859, 2930, 2957, 3323; Anal. calcd. for C_{32}H_{35}NO_2S: C, 79.6; H, 7.1; N, 4.03%; Found: C, 79.26; H, 7.0; N, 3.99.

To a solution of 2,3-dibutyl-6-(isopropylaminocarboxyloxy)benzo[b]thiophene (691 mg, 2.00 mmol) dissolved in EtO (20 mL) were added N,N,N',N'-tetramethylethylenediamine (TMEDA) (0.33 mL, 2.2 mmol, 1.1 equiv) and tert-butyl(dimethyl)silyl trifluoromethanesulfonate (TBSOTf) (0.51 mL, 2.2 mmol, 1.1 equiv) at 0 °C. After stirring for 5 min at the same temperature, the mixture was gradually warmed to room temperature, and the mixture was added TMEDA (0.60 mL, 4.0 mmol, 2.0 equiv). After cooling to –78 °C, the mixture was slowly added n-butyllithium (1.6 M in n-hexane, 2.5 mL, 4.0 mmol, 2.0 equiv), and stirred for 1 h at the same temperature. Then, the mixture was added trimethylsilyl chloride (Me_3SiCl) (0.90 mL, 7.0 mmol, 3.5 equiv) at –78 °C and the mixture was gradually warmed to room temperature. After stirring for 1.5 h at the same temperature, the mixture was added saturated aqueous NaHCO_3 (20 mL). The mixture was extracted with CH_2Cl_2 (20 mL × 3), and the combined organic extract was dried (Na_2SO_4), and after filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica-gel 10 g, n-hexane/EtOAc = 5/1) to give 2,3-dibutyl-6-(isopropylaminocarboxyloxy)-7-(trimethylsilyl)benzo[b]thiophene (689 mg, 1.64 mmol, 82.0%) as a colorless solid.

Colorless solid; Mp 120–122 °C; TLC Rf 0.18 (n-hexane/CH_2Cl_2 = 2/1); 1H NMR (CDCl_3, 500 MHz) δ 0.45 (s, 9H, 3 CH_3), 0.90–0.99 (m, 6H, 2 CH_3), 1.24 (d, 6H, J = 6.5 Hz, 2 CH_3), 1.35–1.47 (m, 4H, aliphatic), 1.51–1.59 (m, 2H, aliphatic), 1.64–1.72 (m, 2H, aliphatic), 2.73 (t, 2H, J = 7.8 Hz, aliphatic), 2.82 (t, 2H, J = 7.8 Hz, aliphatic), 3.93 (dsept, 1H, J = 6.5, 6.5 Hz, CH), 4.79 (br d, 1H, J = 6.5 Hz, NH), 7.05 (d, 1H, J = 8.6 Hz, aromatic), 7.58 (d, 1H, J = 8.6 Hz, aromatic); 13C NMR (CDCl_3, 126 MHz) δ 0.8 (3C), 13.9 (1C), 14.0 (1C), 22.5 (1C), 22.8 (1C), 23.0 (2C), 26.1 (1C), 28.1 (1C), 32.2 (1C), 33.8 (1C), 43.4 (1C), 119.1 (1C), 122.9 (1C), 124.3 (1C), 130.7 (1C), 137.6 (1C), 139.7 (1C), 144.5 (1C), 152.3 (1C), 154.2 (1C); IR (KBr, cm⁻¹) 843, 1040, 1173, 1204, 1250, 1438, 1520, 1713, 2859, 2930, 2955, 3325; HRMS (ESI⁺) m/z 442.2195 ([M+Na]⁺); C_{23}H_{27}NNaO_2Si requires 442.2206.
To a solution of 2,3-dibutyl-6-isopropylaminocarboxyloxy-7-(trimethylsilyl)benzo[b]thiophene (552 mg, 1.31 mmol) dissolved in MeCN (13 mL) were added 1.8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.30 mL, 2.0 mmol, 1.5 equiv) and Et3NH (0.16 mL, 1.6 mmol, 1.2 equiv) at room temperature. After stirring for 5 min at the same temperature, to the mixture was added a solution of N-phenylbis(trifluoromethanesulfonimide) (PhNTf2) (702 mg, 1.96 mmol, 1.50 equiv) dissolved in MeCN (4.0 mL) at 0 °C. After warming the mixture to room temperature, it was stirred for 30 min, and to the mixture was added aqueous NH4Cl (30 mL). The mixture was extracted with EtOAc (30 mL × 1), and the combined organic extract was washed with brine (10 mL × 3), dried (Na2SO4), and after filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (Biotage® ZIP-sphere cartridge 45 g, n-hexane) to give 2,3-dibutyl-6-trifluoroxy-7-(trimethylsilyl)benzo[b]thiophene (2a) (594 mg, 1.27 mmol, 97.1%) as a colorless oil.

Colorless oil; TLC Rf 0.25 (n-hexane); 1H NMR (CDCl3, 500 MHz) δ 0.58 (s, 9H, 3 CH3), 0.96–1.03 (m, 6H, 2 CH2), 1.40–1.52 (m, 4H, aliphatic), 1.54–1.62 (m, 2H, aliphatic), 1.68–1.77 (m, 2H, aliphatic), 2.78 (t, 2H, J = 7.8 Hz, aliphatic), 2.89 (t, 2H, J = 7.8 Hz, aliphatic), 7.34 (d, 1H, J = 8.9 Hz, aromatic), 7.66 (d, 1H, J = 8.9 Hz, aromatic); 13C NMR (CDCl3, 126 MHz) δ 0.8 (3C), 13.9 (1C), 14.0 (1C), 22.6 (1C), 22.8 (1C), 26.1 (1C), 28.2 (1C), 32.2 (1C), 33.7 (1C), 116.3 (1C), 118.6 (q, 1C, JCC = 321.2 Hz), 123.4 (1C), 125.6 (1C), 130.7 (1C), 139.2 (1C), 142.1 (1C), 145.2 (1C), 151.3 (1C); 19F NMR (CDCl3, 376 MHz) δ –73.5 (s); IR (KBr, cm⁻¹) 845, 910, 1142, 1211, 1250, 1418, 2860, 2932, 2957; Anal. calc. for C23H20F3O2S2Si: C, 51.48; H, 6.26%; Found: C, 51.40, H, 6.23%.

Preparation of 3-methyl-2-phenyl-6-trifluoroxy-7-(trimethylsilyl)benzo[b]thiophene (2b)

According to the synthetic procedure or 2a from 1a, 3-methyl-2-phenyl-6-trifluoroxy-7-(trimethylsilyl)benzo[b]thiophene (2b) was prepared using 6-hydroxy-3-methyl-2-phenylbenzo[b]thiophene (1b) instead of 1a.

6-Isopropylaminocarboxyloxy-3-methyl-2-phenylbenzo[b]thiophene
Colorless solid; Mp 158–159 °C; TLC Rf 0.27 (n-hexane/CH2Cl2 = 2/3); 1H NMR (CDCl3, 500 MHz) δ 1.24 (d, 6H, J = 6.7 Hz, 2 CH3), 2.44 (s, 3H, CH3), 3.92 (dsept, 1H, J = 6.7, 6.7 Hz, CH), 4.92 (br d, 1H, J = 6.7 Hz, NH), 7.18 (dd, 1H, J = 8.6, 1.8 Hz, aromatic), 7.34–7.39 (AA′BB′C, 1H, aromatic), 7.42–7.48 (AA′BB′C, 2H, aromatic), 7.50–7.55 (AA′BB′C, 2H, aromatic), 7.61 (d, 1H, J = 1.8 Hz, aromatic), 7.66 (d, 1H, J = 8.6 Hz, aromatic); 13C NMR (CDCl3, 126 MHz) δ 12.7 (1C), 22.9 (2C), 43.5 (1C), 114.9 (1C), 118.9 (1C), 122.4 (1C), 127.0 (1C), 127.8 (1C), 128.5 (2C), 129.6 (2C), 134.6 (1C), 139.7 (1C), 139.2 (1C), 148.2 (1C); IR (KBr, cm⁻¹) 694, 752, 1059, 1173, 1204, 1242, 1454, 1468, 1531, 1697, 2974, 3057, 3331; HRMS (ESI⁺) m/z 348.1028 ([M+Na]+), C18H16NaO2S⁺ requires 348.1029).

6-Isopropylaminocarboxyloxy-3-methyl-2-phenyl-7-(trimethylsilyl)benzo[b]thiophene
Colorless solid; Mp 158–159 °C; TLC Rf 0.18 (n-hexane/EtOAc = 10/1); 1H NMR (CDCl3, 500 MHz) δ 0.47 (s, 9H, 3 CH3), 1.26 (d, 6H, J = 6.6 Hz, 2 CH3), 2.43 (s, 3H, CH3), 3.95 (dsept, 1H, J = 6.6, 6.6 Hz, CH), 4.81 (br d, 1H, J = 6.6 Hz, NH), 7.15 (d, 1H, J = 8.5 Hz, aromatic), 7.34–7.39 (AA′BB′C, 1H, aromatic), 7.42–7.48 (AA′BB′C, 2H, aromatic), 7.51–7.56 (AA′BB′C, 2H, aromatic), 7.70 (d, 1H, J = 8.5 Hz, aromatic); 13C NMR (CDCl3, 126 MHz) δ 0.8 (3C), 12.6 (1C), 23.0 (2C), 43.5 (1C), 119.8 (1C), 123.8 (1C), 124.4 (1C), 126.6 (1C), 127.7 (1C), 128.5 (2C), 129.7 (2C), 134.7 (1C), 137.7 (1C), 138.5 (1C), 145.0 (1C), 153.1 (1C), 154.1 (1C); IR (KBr, cm⁻¹) 698, 737, 845, 912, 1042, 1173, 1206, 1250, 1350, 1439, 1502, 1713, 2972, 3331; HRMS (ESI⁺) m/z 420.1430 ([M+Na]+), C22H17NNaO2S· requires 420.1424.)
3-Methyl-2-phenyloxy-7-(trimethylsilyl)benzo[b]thiophene (2b)

Colorless solid; Mp 75–76 °C; TLC Rf 0.30 (n-hexane); 1H NMR (CDCl3, 500 MHz) δ 0.58 (s, 9H, 3 CH3), 2.45 (s, 3H, CH3), 7.38–7.43 (m, 2H, aromatic), 7.45–7.51 (AA'BB'C, 2H, aromatic), 7.52–7.56 (AA'BB'C, 2H, aromatic), 7.75 (d, 1H, J = 9.0 Hz, aromatic); 13C NMR (CDCl3, 126 MHz) δ 0.8 (3C), 12.5 (1C), 116.8 (1C), 118.6 (q, 1C, JCF = 321.2 Hz), 124.4 (1C), 125.8 (1C), 126.5 (1C), 128.2 (1C), 128.7 (2C), 134.0 (1C), 140.1 (1C), 145.6 (1C), 151.8 (1C); 19F NMR (CDCl3, 376 MHz) δ –73.4 (s). IR (KBrs): cm–1 696, 760, 843, 910, 1140, 1211, 1248, 1350, 1418, 2953; Anal. calcd. for C19H15F4O3S2Si: C, 51.33; H, 4.31%; Found: C, 51.43; H, 4.31%.

Preparation of 2-(methylthio)-6-trifluoryloxy-3-(trifluoromethyl)-7-(trimethylsilyl)benzo[b]thiophene (2c)

According to the synthetic procedure for 2a from 1a, 2-methylthio initial procedure for 2a from 1a, 2-methylthio-6-trifluoryloxy-3-(trifluoromethyl)-7-(trimethylsilyl)benzo[b]thiophene (2c) was prepared using 6-hydroxy-2-methylthio-3-(trifluoromethyl)-benzo[b]thiophene (1c) instead of 1a.

6-Isopropylaminoxy-2-methylthio-6-trifluoryloxy-3-(trifluoromethyl)-7-(trimethylsilyl)benzo[b]thiophene

Colorless solid; Mp 111–112 °C; TLC Rf 0.39 (n-hexane/EtOAc = 3:1); 1H NMR (CDCl3, 500 MHz) δ 1.25 (d, 6H, J = 6.8 Hz, 2 CH3), 2.65 (s, 3H, CH3), 3.61 (dsept, 1H, 1JH = 6.8, 6.8 Hz, CH), 4.91 (br d, 1H, 1JH = 6.8 Hz, NH), 7.17 (dd, 1H, J = 9.0, 2.0 Hz, aromatic), 7.56 (d, 1H, J = 2.0 Hz, aromatic), 7.77 (d, 1H, J = 9.0 Hz, aromatic); 13C NMR (CDCl3, 126 MHz) δ 18.7 (1C), 22.9 (2C), 43.6 (1C), 114.3 (1C), 119.7 (q, 1C, JCF = 34.3 Hz), 120.2 (1C), 122.3 (q, 1C, JCF = 2.4 Hz), 123.1 (q, 1C, JCF = 272.8 Hz), 134.3 (1C), 138.4 (1C), 145.1 (1C), 148.0 (1C), 153.4 (1C); 19F NMR (CDCl3, 376 MHz) δ –56.8 (s); IR (KBrs): cm–1 920, 1038, 1065, 1101, 1159, 1225, 1364, 1464, 1505, 1530, 1713, 2359, 2974, 3331; HRMS (ESI+): m/z 372.0313 ([M+Na]+), C19H15F4NNaO2S2Si+ requires 372.0310.

2-Methylthio-6-trifluoryloxy-3-trifluoromethyl-7-(trimethylsilyl)benzo[b]thiophene (2e)

Colorless solid; Mp 69–70 °C; TLC Rf 0.26 (n-hexane); 1H NMR (CDCl3, 500 MHz) δ 0.56 (s, 9H, 3 CH3), 2.70 (s, 3H, CH3), 7.40 (d, 1H, J = 9.0 Hz, aromatic), 7.83–7.87 (m, 1H, aromatic); 13C NMR (CDCl3, 126 MHz) δ 0.8 (3C), 18.4 (q, 1C, JCF = 1.5 Hz), 118.2 (1C), 118.5 (q, 1C, JCF = 321.3 Hz), 118.9 (q, 1C, JCF = 3.6 Hz), 123.1 (q, 1C, JCF = 272.6 Hz), 124.0 (q, 1C, JCF = 2.7 Hz), 125.8 (1C), 136.2 (1C), 144.5 (1C), 147.1 (q, 1C, JCF = 2.5 Hz), 151.4 (1C); 19F NMR (CDCl3, 376 MHz) δ –73.4 (s, 3F), –56.7 (s, 3F); IR (KBrs): cm–1 613, 843, 941, 1040, 1123, 1146, 1173, 1207, 1234, 1344, 1371, 1441, 1504, 1713, 2972, 3327; Anal. calcd. for C19H15F4O3S2Si: C, 54.84; H, 5.26; N, 3.32%; Found: C, 48.49; H, 5.45; N, 3.28%.
Preparation of 3-chloro-2-dimethylaminocarbonyl-6-triflyloxy-7-(trimethylsilyl)benzo[b]thiophene (2d)

To a solution of iodine (5.08 g, 20.0 mmol, 1.0 equiv) dissolved in benzene (72 mL) was added morpholine (7.83 g, 60.0 mmol, 3.0 equiv) at room temperature. After stirring for 30 min at the same temperature, to the mixture was added 3-chloro-2-dimethylaminocarbonyl-6-hydroxybenzo[b]thiophene (1d) (5.11 g, 20.0 mmol) at room temperature. After stirring for 1 h at the same temperature, the precipitate was collected by filtration and washed on the funnel with acetone (20 mL × 3), aqueous 1 M HCl (20 mL × 3), and H₂O (20 mL × 3). The solid was dried under reduced pressure to give 3-chloro-2-dimethylaminocarbonyl-6-hydroxy-7-iodobenzo[b]thiophene (3) (6.18 g, 16.2 mmol, 81.0%) as a colorless solid.

Colorless solid; Mp 200 °C (decomposed); TLC R₁: 0.43 (n-hexane/EtOAc = 1/1); ¹H NMR (DMSO-d₆, 500 MHz) δ 3.02 (br s, 6H, 2 CH₂), 7.11 (d, 1H, J = 8.5 Hz, aromatic), 7.69 (d, 1H, J = 8.5 Hz, aromatic), 10.94 (br s, 1H, OH); ¹³C NMR (DMSO-d₆, 126 MHz) δ 34.8 (1C), 38.1 (1C), 76.8 (1C), 114.6 (1C), 118.7 (1C), 123.1 (1C), 127.4 (1C), 127.7 (1C), 144.8 (1C), 156.9 (1C), 161.5 (1C); IR (KBr, cm⁻¹) 748, 772, 806, 1283, 1379, 1531, 1603, 3011; Anal. calcd. for C₁₅H₁₁ClIN₂O₂S: C, 34.62; H, 2.38; N, 3.67%; Found: C, 34.73; H 2.30; N, 3.62%.

To a solution of 3-chloro-2-dimethylaminocarbonyl-6-hydroxy-7-iodobenzo[b]thiophene (3) (3.81 g, 10.0 mmol) dissolved in THF (10 mL) was added HMDS (1.94 g, 12.0 mmol, 1.2 equiv) at room temperature. After stirring for 16 h at the same temperature, the mixture was concentrated under reduced pressure to give a crude product containing 3-chloro-2-dimethylaminocarbonyl-7-iodo-6-(trimethylsilyloxy)benzo[b]thiophene (4.58 g, ca. 10 mmol) as a yellow oil. This crude product was used in the next step without further purification.

To a solution of the crude of 3-chloro-2-dimethylaminocarbonyl-7-iodo-6-(trimethylsilyloxy)benzo[b]thiophene (4.58 g, ca. 10 mmol) dissolved in THF (100 mL) was added isopropylmagnesium chloride lithium chloride complex (1.34 M in THF, 11.2 mL, 15.0 mmol, 1.5 equiv) at −78 °C. After stirring for 1 h at the same temperature, to the mixture was added aqueous saturated NH₄Cl (100 mL). The mixture was extracted with EtOAc (30 mL × 3) and the combined organic extract was washed with brine, dried (Na₂SO₄), and after filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (Biotage® Z-53, silica gel 80–230 mesh, petroleum ether/EtOAc = 100/0 to 60/40) to give 3-chloro-2-dimethylaminocarbonyl-6-hydroxy-7-(trimethylsilyl)benzo[b]thiophene (4) (1.20 g, 3.66 mmol, 36.6%) as a colorless solid.

Colorless solid; Mp 145–147 °C; TLC R₁: 0.31 (n-hexane/EtOAc = 1/1); ¹H NMR (CDCl₃, 500 MHz) δ 0.49 (s, 9H, 3 CH₃), 3.13 (br s, 3H, CH₃), 3.19 (br s, 3H, CH₃), 5.67 (s, 1H, OH), 6.89 (d, 1H, J = 8.6 Hz, aromatic); ¹³C NMR (CDCl₃, 126 MHz) δ 0.6 (3C), 35.4 (1C), 38.7 (1C), 115.2 (1C), 117.4 (1C), 118.7 (1C), 124.5 (1C), 127.0 (1C), 129.5 (1C), 144.9 (1C), 160.1 (1C), 163.7 (1C); IR (KBr, cm⁻¹) 772, 843, 1265, 1362, 1531, 1614, 2949, 3225; HRMS (ESI⁺) m/z 350.0420 ([M+Na]+); C₁₅H₁₇ClINNaO₂Si requires 350.0408.

To a solution of 3-chloro-2-dimethylaminocarbonyl-6-hydroxy-7-(trimethylsilyl)benzo[b]thiophene (4) (328 mg, 1.00 mmol) dissolved in MeCN (3 mL) were added DBU (183 mg, 1.20 mmol, 1.20 equiv) and N-(2-pyridyl)bis(trifluoromethanesulfonimide) (537 mg, 1.50 mmol, 1.50 equiv) at 0 °C. After stirring for 5 min at the same temperature, to the mixture was added water (3 mL). The mixture was extracted with EtOAc (5 mL × 3) and the combined organic extract was washed with brine, dried (Na₂SO₄), and after filtration, the filtrate was
Colorless solid; Mp 92–93 °C; TLC Rf 0.33 (n-hexane/EtOAc = 3/1); 1H NMR (CDCl3, 500 MHz) δ 0.56 (s, 9H, 3 CH3), 3.09 (br s, 3H, CH3), 3.18 (br s, 3H, CH3), 7.48 (d, 1H, J = 9.0 Hz, aromatic), 7.90 (d, 1H, J = 9.0 Hz, aromatic); 13C NMR (CDCl3, 126 MHz) δ 0.7 (3C), 35.4 (1C), 38.5 (1C), 118.2 (1C), 118.5 (q, 1C, 1J/C,F = 321.4 Hz), 118.5 (1C), 125.1 (1C), 127.0 (1C), 132.3 (1C), 134.6 (1C), 144.2 (1C), 153.1 (1C), 162.4 (1C); 19F NMR (CDCl3, 376 MHz) δ –73.4 (s); IR (KBr, cm–1) 845, 910, 980, 1144, 1211, 1250, 1402, 1422, 1643, 2953; Anal. calcd. for C15H17ClFNO3S2Si: C, 39.17; H, 3.73; N, 3.05%; Found: C, 39.19; H, 3.64; N, 3.05%.

A typical procedure for the reaction via 6,7-thienobenzene

To a solution of 2,3-dibutyl-6-trifluoro-7-(trimethylsilyl)benzo[b]thiophene (2a) (46.7 mg, 0.100 mmol) and methyl 4-(azidomethyl)benzoate (5a) (96.5 mg, 0.504 mmol, 5.0 equiv) dissolved in THF (1.0 mL) was added cesium fluoride (30.5 mg, 0.201 mmol, 2.0 equiv) at room temperature. After stirring for 24 h at the same temperature, the mixture was filtrated through a pad of Celite® washing with CH3Cl (0.5 mL × 5), and the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (n-hexane/EtOAc = 4/1) to give a mixture of 6,7-dibutyl-3-(4-(methoxycarbonyl)benzyl)-3H-1,2,3-triazolo[3,4]benzo[1,2-d]thiophene (6a) and 6,7-dibutyl-1-(4-(methoxycarbonyl)benzyl)-1H-1,2,3-triazolo[3,4]benzo[1,2-d]thiophene (6a′) (36.8 mg, 84.4 µmol, 84.4%, 6a:6a′ = 90:10 as judged from 1H NMR analysis) as a colorless solid. Cycloadducts 6a and 6a′ were identical in spectral data with our previous report.52

Similarly, benzothiophenes 6b–d were prepared via the reaction of azide 5a with 6,7-thienobenzynes generated from precursors 2b–d, respectively. Benzothiophene derivatives 7–11 were also prepared via the reaction of thienobenzyne generated from 2a with 2,5-dimethylfuran, N-phenylpyrrole, N-(tert-buty1)-α-phenylnitrile, 1,1-dimethoxyethylen e, and morpholine, respectively. 3-(4-(Methoxycarbonyl)benzyl)-6-methyl-7-phenyl-3H-1,2,3-triazolo[3,4]benzo[1,2-d]thiophene (6b), 3-(4-(methoxycarbonyl)benzyl)-7-methylthio-6-trifluoromethyl-3H-1,2,3-triazolo[3,4]benzo[1,2-d]thiophene (6c), 6-chloro-7-dimethylamino-carbonyl-3-(4- (methoxycarbonyl)benzyl)-3H-1,2,3-triazolo[3,4]benzo[1,2-d]thiophene (6d), 2,3-dibutyl-6,9-dimethyl-6,9-dihydro-6,9-epoxyxantho[1,2-b]thiophene (7), 2,3-dibutyl-10-phenyl-6,9-dihydro-6,9-iminophtho[1,2-b]thiophene (8), 7-(tert-buty1)-2,3-dibutyl-8-phenyl-7,8-dihydroisoxazolo[4,5,6]benzo[1,2-d]thiophene (9), 2-(tert-buty1)-6,7-dibutyl-3-phenyl-2,3-dihydroisoxazolo[4,5,6]benzo[1,2-d]thiophene (9′), 2,3-dibutyl-7,7-dimethoxy-6,7-dihydrocyclobuta[3,4]benzo[1,2-d]thiophene (10), 2,3-dibutyl-6-morpholinobenzo[b]thiophene (11) and 2,3-dibutyl-7-morpholinobenzo[b]thiophene (11′) were identical in spectral data with our previous report.52

1-(4-(Methoxycarbonyl)benzyl)-6-methyl-7-phenyl-1H-1,2,3-triazolo[3,4]benzo[1,2-d]thiophene (6b′)
Synthesis of arylphosphonic diamide 13 via the reaction of 6,7-thienobenzene generated from 2a with alkoxyphosphine 12

![Chemical Structure](image)

To a mixture of 2,3-dibutyl-6-triflyoxy-7-(trimethylsilyl)benzo[\(b\)]thiophene (2a) (28.1 mg, 60.2 \(\mu\)mol, 1.20 equiv) and methyl \(N,N,N',N'\)-tetraisopropylphosphorodiamidite (12) (13.2 mg, 50.3 \(\mu\)mol) dissolved in THF (1.0 mL) were added tetrahexylammonium fluoride trihydrate (20.7 mg, 65.6 \(\mu\)mol, 1.30 equiv) at 0 °C. After stirring for 1 h at 0 °C, the mixture was filtered through a pad of Celite\(^8\) washing with CH\(_2\)Cl\(_2\) (0.5 mL \(\times\) 5), and the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (\(n\)-hexane/\(EtOAc\) = 4/1) to give \(N,N,N',N'\)-tetraisopropyl-\(P\)-(2,3-dibutylbenzo[\(b\)]thiophene-6-yl)phosphoric diamide (13) (21.6 mg, 43.8 \(\mu\)mol, 87.1%) as a colorless solid.

Colorless solid; Mp 82–83 °C; TLC R\(_f\): 0.35 (\(n\)-hexane/\(EtOAc\) = 4/1); \(\text{\textsuperscript{1}}H\) NMR (CDCl\(_3\), 500 MHz) \(\delta\) 0.97 (t, 3H+3H, \(J = 7.3 \text{ Hz}\), two signals overlapped, 2 CH\(_3\)), 1.11 (d, 12H, \(J = 6.8 \text{ Hz}\), 4 CH\(_2\)), 1.15–1.55 (m, 4H, \(J = 7.8 \text{ Hz}\), CH\(_2\)), 2.87 (t, 2H, \(J = 8.0 \text{ Hz}\), CH\(_2\)), 3.62–3.75 (m, 4H, \(J = 6.8 \text{ Hz}\)), 7.60 (dd, 1H, \(J = 8.4 \text{ Hz}\), aromatic), 8.29 (dd, 1H, \(J = 13.0 \text{ Hz}\), aromatic); \(\text{\textsuperscript{13}}C\) NMR (CDCl\(_3\), 126 MHz) \(\delta\) 13.9 (1C), 14.0 (1C), 22.6 (1C), 23.0 (1C), 23.1–23.4 (m, 4C+4C, two signals overlapped), 26.3 (1C), 28.4 (1C), 32.2 (1C), 33.7 (1C), 46.2 (d, 4C, \(J = 4.9 \text{ Hz}\), 120.3 (d, 1C, \(J = 2.4 \text{ Hz}\), 126.9 (d, 1C, \(J = 10.5 \text{ Hz}\), 127.3 (d, 1C, \(J = 9.8 \text{ Hz}\)), 131.4 (d, 1C, \(J = 151.6 \text{ Hz}\)), 131.7 (1C), 137.8 (d, 1C, \(J = 16.4 \text{ Hz}\)), 141.8 (d, 1C, \(J = 2.5 \text{ Hz}\), 142.9 (1C); \(\text{\textsuperscript{31}}P\) NMR (162 MHz) \(\delta\) 26.0–26.6 (m); IR (KBr, cm\(^{-1}\)) 980, 1113, 1138, 1155, 1173, 1188, 1211, 2872, 2930, 2961; HRMS (ESI) \(m/z\) 515.3181 ([\(M+Na\]^+) requires 515.3195).

The regiochemistry of 13 was determined by the COSY and NOESY experiments.

Synthesis of thioaminated products 15/15’ via the reaction of 6,7-thienobenzene generated from 2a with \(S,S\)-diphenylsulfilimine (14)

![Chemical Structure](image)

To a mixture of 2,3-dibutyl-6-triflyoxy-7-(trimethylsilyl)benzo[\(b\)]thiophene (2a) (46.6 mg, 0.100 mmol) and \(S,S\)-diphenylsulfilimine (14) (41.0 mg, 0.204 mmol, 2.04 equiv) dissolved in 1,4-dioxane (1.0 mL) were added 18-crown-6 (32.5 mg, 0.199 mmol, 1.99 equiv) and potassium fluoride (11.8 mg, 0.203 mmol, 2.03 equiv) at room temperature, and the mixture was stirred for 24 h with heating at 110 °C (oil bath temperature). After cooling to room temperature, the mixture was filtered through a pad of Celite\(^8\) washing with CH\(_2\)Cl\(_2\) (0.5 mL \(\times\) 5), and the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (\(n\)-hexane/\(EtOAc\) = 40/1) to give a mixture of 2,3-dibutyl-6-phenylamino-7-(phenylthio)benzo[\(b\)]thiophene (15) and 2,3-dibutyl-7-phenylamino-6-(phenylthio)benzo[\(b\)]thiophene (15’) (30.8 mg, 69.1 \(\mu\)mol, 69.1%, 15:15’ = 79:21 as judged from \(\text{\textsuperscript{1}}H\) NMR analysis) as an orange oil. For the characterization purpose, the isomers were separated by preparative TLC (\(n\)-hexane/\(EtOAc\) = 20/1) to afford 15 and 15’.
2.3-Dibutyl-6-phenylamino-7-(phenylthio)benzo[b]thiophene (15)

Orange oil; TLC Rf 0.42 (n-hexane/EtOAc = 20/1); 1H NMR (CDCl₃, 500 MHz) δ 0.90–0.99 (m, 6H, 2 CH₃), 1.36–1.46 (m, 4H, aliphatic), 1.52–1.60 (m, 2H, aliphatic), 1.60–1.69 (m, 2H, aliphatic), 2.71 (t, 2H, J = 8.0 Hz, aliphatic), 2.77 (t, 2H, J = 7.8 Hz, aliphatic), 6.75 (br s, 1H, NH), 6.96–7.01 (AA’BB’C, 1H, aromatic), 7.08–7.16 (m, 5H, aromatic), 7.17–7.22 (AA’BB’C, 2H, aromatic), 7.24–7.29 (AA’BB’C, 2H, aromatic), 7.37 (d, 1H, J = 8.5 Hz, aromatic), 7.53 (d, 1H, J = 8.8 Hz, aromatic), 13.3. C NMR (CDCl₃, 126 MHz) δ 13.9 (1C), 14.0 (1C), 14.0 (1C), 22.5 (1C), 22.9 (1C), 26.3 (1C), 28.1 (1C), 32.4 (1C), 33.6 (1C), 109.2 (1C), 113.2 (1C), 119.9 (2C), 122.2 (1C), 123.4 (1C), 125.8 (1C), 126.6 (2C), 129.1 (2C), 129.3 (2C), 132.3 (1C), 133.9 (1C), 135.0 (1C), 138.1 (1C), 142.5 (1C), 142.7 (1C), 147.6 (1C); IR (KBr, cm⁻¹) 689, 737, 1312, 1377, 1454, 1477, 1504, 1589, 2359, 2857, 2928, 2953, 3057, 3368; HRMS (ESI⁺) m/z 468.1793 ([M+Na⁺], C₂₆H₂₁NNaS₂⁺ requires 468.1790).

The regiochemistry of 15 was determined by the NOESY and the HMBC experiments.

2.3-Dibutyl-7-phenylamino-6-(phenylthio)benzo[b]thiophene (15')

Brown solid; Mp 72–74 °C; TLC Rf 0.39 (n-hexane/EtOAc = 20/1); 1H NMR (CDCl₃, 500 MHz) δ 0.90 (t, 3H, J = 7.3 Hz, CH₃), 0.97 (t, 3H, J = 7.5 Hz, CH₃), 1.32–1.40 (m, 2H, aliphatic), 1.40–1.48 (m, 2H, aliphatic), 1.55–1.63 (m, 4H, aliphatic), 2.71–2.80 (m, 4H, aliphatic), 6.52 (br s, 1H, NH), 6.76–6.81 (AA’BB’C, 2H, aromatic), 6.91–6.97 (AA’BB’C, 1H, aromatic), 7.07–7.12 (AA’BB’C, 1H, aromatic), 7.12–7.16 (AA’BB’C, 2H, aromatic), 7.16–7.22 (m, 4H, aliphatic), 7.35 (d, 1H, J = 8.5 Hz, aromatic), 7.51 (d, 1H, J = 8.5 Hz, aromatic); 13C NMR (CDCl₃, 126 MHz) δ 13.8 (1C), 14.0 (1C), 22.5 (1C), 22.9 (1C), 26.3 (1C), 28.2 (1C), 32.4 (1C), 33.6 (1C), 116.8 (1C), 118.2 (1C), 119.4 (2C), 121.6 (1C), 125.8 (1C), 127.7 (2C), 128.6 (2C), 129.0 (2C), 131.3 (1C), 131.7 (1C), 131.8 (1C), 137.3 (1C), 139.1 (1C), 142.4 (1C), 142.5 (1C), 143.3 (1C); IR (KBr, cm⁻¹) 691, 743, 912, 1393, 1450, 1495, 1599, 2857, 2928, 2955, 3348; HRMS (ESI⁺) m/z 468.1788 ([M+Na⁺], C₂₆H₂₁NNaS₂⁺ requires 468.1790).

The regiochemistry of 15' was determined by the NOESY and the HMBC experiments.

Synthesis of thioaminated product 17 via the reaction of 6,7-dienobenzene generated from 2a with S-(4-tolyl)-S-(4-(trifluoromethyl)phenyl)sulfoximine (16)

According to the synthetic procedure for 15 and 15', 2,3-dibutyl-7-(4-tolylsufanyl)-6-(4-(trifluoromethyl)phenylamino)benzo[b]thiophene (17) was prepared using S-(4-tolyl)-S-(4-(trifluoromethyl)phenyl)sulfoximine (16) instead of 14.

Pale brown solid; Mp 145–147 °C; TLC Rf 0.59 (CH₂Cl₂); 1H NMR (CDCl₃, 500 MHz) δ 0.91–1.02 (m, 6H, 2 CH₃), 1.37–1.52 (m, 4H, aliphatic), 1.51–1.61 (m, 2H, aliphatic), 1.68–1.76 (m, 2H, aliphatic), 2.24 (s, 3H, CH₃), 2.69–2.76 (m, 2H, aliphatic), 2.80–2.92 (m, 2H, aliphatic), 6.88–6.93 (AA’BB’C, 2H, aromatic), 7.04–7.08 (AA’BB’C, 2H, aromatic), 7.33 (d, 1H, J = 8.7 Hz, aromatic), 7.35–7.40 (AA’BB’C, 2H, aromatic), 7.45–7.50 (AA’BB’C, 2H, aromatic), 7.56 (d, 1H, J = 8.7 Hz, aromatic), 8.51 (s, 1H, NH); 13C NMR (CDCl₃, 126 MHz) δ.
13.9 (1C), 14.0 (1C), 21.1 (1C), 22.5 (1C), 22.8 (1C), 26.2 (1C), 28.2 (1C), 32.2 (1C), 33.6 (1C), 116.2 (2C), 117.7 (1C), 122.1 (q, 1C, \(^2J_{CF} = 32.8\) Hz), 122.8 (1C), 124.1 (2C), 124.5 (q, 1C, \(^2J_{CF} = 272.2\) Hz), 124.7 (1C), 126.4 (q, 2C, \(^1J_{CF} = 3.8\) Hz), 129.6 (2C), 131.5 (1C), 136.2 (1C), 139.4 (1C), 141.2 (1C), 145.7 (1C); \(^19\)F NMR (CDCl\(_3\), 376 MHz) \(\delta = 61.8\) (s); IR (KBr, cm\(^{-1}\)) 1067, 1113, 1165, 1323, 1524, 1597, 1614, 2930, 2957; HRMS (ESI) \(m/z = 566.1760\) ([M+Na]\(^+\), \(C_{30}H_{32}F_{3}N_{2}NaOS_{2}\) requires 566.1770).

The regiochemistry of 17 was determined by the NOESY experiment.

**Synthesis of oxythiolated product 19** via the reaction of 6,7-thienobenzyne generated from 2a with 2-bromophenyl 4-tolyl sulfoxide (18)

According to the synthetic procedure for 15 and 15', 6-(2-bromophenoxy)-2,3-dibutyl-7-(4-tolylthio)benzo[b]thiophene (19) was prepared using 2-bromophenyl 4-tolyl sulfoxide (18) instead of 14.

Yellow solid; Mp 44–46 °C; TLC \(R_f 0.55\) (n-hexane/CH\(_2\)Cl\(_2\) = 3/1); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta = 0.95\) (t, 3H+3H, \(J = 7.3\) Hz, two signals overlapped, 2 CH\(_3\)), 1.37–1.47 (m, 4H, aliphatic), 1.52–1.61 (m, 2H, aliphatic), 1.64–1.73 (m, 2H, aliphatic), 2.24 (s, 3H, CH\(_3\)), 2.73 (t, 2H, \(J = 7.8\) Hz, aliphatic), 2.82 (t, 2H, \(J = 7.8\) Hz, aliphatic), 6.62 (dd, 1H, \(J = 8.0, 1.3\) Hz, aromatic), 6.92 (ddd, 1H, \(J = 8.0, 8.0, 1.3\) Hz, aromatic), 6.94 (d, 1H, \(J = 8.5\) Hz, aromatic), 6.95–7.00 (AA’BB’, 2H, aromatic), 7.11 (ddd, 1H, \(J = 8.0, 8.0, 1.3\) Hz, aromatic), 7.22–7.28 (AA’BB’, 2H, aromatic), 7.54 (d, 1H, \(J = 8.5\) Hz, aromatic), 7.58 (dd, 1H, \(J = 8.0, 1.3\) Hz, aromatic); \(^13\)C NMR (CDCl\(_3\), 126 MHz) \(\delta = 13.9\) (1C), 14.0 (1C), 21.0 (1C), 22.5 (1C), 22.9 (1C), 26.4 (1C), 28.3 (1C), 32.3 (1C), 33.6 (1C), 113.5 (1C), 116.9 (1C), 118.3 (1C), 118.4 (1C), 122.8 (1C), 124.0 (1C), 128.3 (1C), 129.5 (2C), 130.0 (2C), 131.6 (1C), 132.0 (1C), 133.6 (1C), 136.3 (1C), 137.3 (1C), 141.3 (1C), 146.7 (1C), 153.2 (1C), 154.6 (1C); IR (KBr, cm\(^{-1}\)) 746, 1244, 1441, 1449, 1472, 1491, 2928, 2955; Anal. calcd. for C\(_{20}\)H\(_{13}\)BrO\(_2\): C, 64.55; H, 5.79%; Found: C, 64.63; H, 5.69%.

The regiochemistry of 19 was determined by the NOESY and the HMBC experiments.
**Synthesis of 6-chloro-7-(dimethylaminocarbonyl)-3-methyl-3H-1,2,3-triazolo[3,4]benzo[1,2-d]thiophene (21a)**

![Chemical structure of 21a]

According to the synthetic procedure for 6a and 6a', using 3-chloro-2-dimethylaminocarbonyl-6-triflyloxy-7-(trimethylsilyl)benzo[b]thiophene (2d) (45.8 mg, 99.6 μmol) and trimethylsilylmethyl azide (64.5 mg, 49.9 μmol) instead of 2a and 5a, the mixture of 6-chloro-7-dimethylaminocarbonyl-3-methyl-3H-1,2,3-triazolo[3,4]benzo[1,2-d]thiophene (21a) and 6-chloro-7-dimethylaminocarbonyl-1-methyl-1H-1,2,3-triazolo[3,4]benzo[1,2-d]thiophene (21a') was obtained (15.1 mg, 51.2 μmol, 51.4%). 21a:21a' = 90:10 as judged from 1H NMR analysis as a pale yellow solid. 6-Chloro-7-dimethylaminocarbonyl-3-methyl-3H-1,2,3-triazolo[3,4]benzo[1,2-d]thiophene (21a) was identical in spectra data with our previous report.52

Similarly, benzothenes 21b (22.3 mg, 72.9 mmol, 74.0%) and 21c/21c' (26.5 mg, 81.6 mmol, 80.8%), 21c:21c' = 71:29 as judged from 1H NMR analysis) were prepared from 2d using furan (33.9 mg, 0.498 mmol) and morpholine (44.9 mg, 0.515 mmol), respectively, instead of trimethylsilylmethyl azide.

### 3-Chloro-2-dimethylaminocarbonyl-6,9-dihydro-6,9-epoxynaphtho[1,2-b]thiophene (21b)

![Chemical structure of 21b]

Colorless solid; Mp 49–52 °C; TLC Rf 0.36 (n-hexane/EtOAc = 1/2); 1H NMR (CDCl3, 500 MHz) δ 3.08 (br s, 3H, CH3), 3.17 (br s, 3H, CH3), 5.88–5.92 (m, 1H, aliphatic), 5.93–5.97 (m, 1H, aliphatic), 7.13 (dd, 1H, J = 5.5, 1.5 Hz, olefin), 7.17 (dd, 1H, J = 5.5, 1.5 Hz, olefin), 7.46 (d, 1H, J = 8.0 Hz, aromatic), 7.53 (d, 1H, J = 8.0 Hz, aromatic); 13C NMR (CDCl3, 126 MHz) δ 35.3 (1C), 38.5 (1C), 81.5 (1C), 82.9 (1C), 118.2 (1C), 119.8 (1C), 119.9 (1C), 129.5 (1C), 129.8 (1C), 134.6 (1C), 142.2 (1C), 144.6 (1C), 144.8 (1C), 149.0 (1C), 162.9 (1C); IR (KBr, cm⁻¹) 714, 862, 874, 1188, 1393, 1537, 1634, 1639, 2928; HRMS (ESI⁺) m/z 328.0160 ([M+Na]+; C₁₈H₁₇ClN₂O₂S requires 328.0169).

### 3-Chloro-2-dimethylaminocarbonyl-6-morpholinobenzo[b]thiophene (21c)

![Chemical structure of 21c]

Colorless solid; Mp 165–167 °C; TLC Rf 0.48 (n-hexane/EtOAc = 2/1); 1H NMR (CDCl3, 500 MHz) δ 3.05–3.18 (br, 6H, 2 CH3), 3.21–3.27 (AA'BB', 4H, aliphatic), 3.86–3.93 (AA'BB', 4H, aliphatic), 7.13 (dd, 1H, J = 8.9, 2.2 Hz, aromatic), 7.21 (d, 1H, J = 2.2 Hz, aromatic), 7.70 (d, 1H, J = 8.9 Hz, aromatic); 13C NMR (CDCl3, 126 MHz) δ 35.3 (1C), 38.6 (1C), 49.5 (2C), 66.7 (2C), 107.3 (1C), 116.0 (1C), 119.0 (1C), 122.8 (1C), 126.9 (1C), 129.1 (1C), 139.4 (1C), 150.5 (1C), 163.3 (1C); IR (KBr, cm⁻¹) 743, 912, 1233, 1396, 1599, 1632, 2251, 2859, 2965; Anal. calcd. for C₁₈H₁₇ClN₂O₂S: C, 55.47; H, 5.28; N, 8.26%; Found: C, 55.40; H, 5.10; N, 8.50%.

The regiochemistry of 21c was determined by the COSY and NOESY experiments.
3-Chloro-2-dimethylaminocarbonyl-7-morpholinobenzo[\(b\)]thiophene (21c')

Colorless solid; Mp 114–116 °C; TLC \( R_f \) 0.65 (n-hexane/EtOAc = 2/1); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \( \delta \) 3.08 (br s, 3H, CH\(_3\)), 3.17 (br s, 3H, CH\(_3\)), 3.17–3.23 (AA'BB', 4H, aliphatic), 3.87–3.94 (AA'BB', 4H, aliphatic), 7.06 (dd, 1H, \( J = 7.7, 0.9 \) Hz, aromatic), 7.46 (dd, 1H, \( J = 7.7, 7.7 \) Hz, aromatic), 7.57 (dd, 1H, \( J = 7.7, 0.9 \) Hz, aromatic); \(^13\)C NMR (CDCl\(_3\), 126 MHz) \( \delta \) 35.3 (1C), 38.5 (1C), 51.6 (2C), 67.2 (2C), 115.1 (1C), 117.6 (1C), 119.6 (1C), 126.7 (1C), 130.3 (1C), 131.9 (1C), 137.1 (1C), 147.3 (1C), 163.1 (1C); IR (KBr, cm\(^{-1}\)) 743, 912, 1115, 1236, 1261, 1395, 1450, 1634, 2247, 2857, 2961; HRMS (ESI \(^+\)) \( m/z \) 347.0579 ([M+Na]\(^+\), C\(_{15}\)H\(_{17}\)ClN\(_2\)NaO\(_2\)S\(^+\) requires 347.0591).

The regiochemistry of 21c' was determined by the COSY and NOESY experiments.

**Synthesis of EP4 antagonist analog 20c**

According to the synthetic procedure for 21a and 21a', 3-chloro-2-(dimethylaminocarbonyl)-6,9-dihydro-6,9-epoxynaphtho[1,2-b]thiophene (21b) was prepared from 2d (276 mg, 0.600 mmol) using furan (203 mg, 2.98 mmol) instead of trimethylsilylmethyl azide. The mixture was filtrated through a short-pad of silica gel (n-hexane/EtOAc = 1/1), and the filtrate was concentrated under reduced pressure. The colorless residue containing 3-chloro-2-dimethylaminocarbonyl-6,9-dihydro-6,9-epoxynaphtho[1,2-b]thiophene (21b) (154 mg, ca. 0.50 mmol) was used in the next step without further purification.

To a mixture of crude 3-chloro-2-dimethylaminocarbonyl-6,9-dihydro-6,9-epoxynaphtho[1,2-b]thiophene (21b) (154 mg, ca. 0.50 mmol) and NaI (229 mg, 1.53 mmol, 3.04 equiv) in MeCN (9.2 mL) was added Me\(_3\)SiCl (0.20 mL, 1.6 mmol, 3.1 equiv) at room temperature. After stirring for 40 min at the same temperature, the mixture was added aqueous saturated Na\(_2\)SO\(_3\) (9.2 mL) and the mixture was extracted with EtOAc (10 mL \times 3). The combined organic extract was washed with brine (20 mL \times 1), dried (Na\(_2\)SO\(_4\)), and after filtration, the filtrate...
was concentrated under reduced pressure. The residue was purified by flash column chromatography (Biotage® SNAP Ultra HP-sphere cartridge 10 g, n-hexane/EtOAc = 100/0 to 80/20) to give 3-chloro-2-(dimethylaminocarbonyl)naphtho[1,2-b]thiophene (49.9 mg, 0.141 mmol, 23.5% from 2d) as a colorless solid.

Colorless solid; Mp 154–155 °C; TLC Rf 0.28 (n-hexane/EtOAc = 4/1); 1H NMR (CDCl3, 500 MHz) δ 3.14 (br s, 3H, CH3), 3.20 (br s, 3H, CH3), 7.58 (ddd, 1H, J = 8.0, 8.0, 0.8 Hz, aromatic), 7.62 (ddd, 1H, J = 8.0, 8.0, 1.5 Hz, aromatic), 7.82 (d, 1H, J = 9.0 Hz, aromatic), 7.85 (d, 1H, J = 9.0 Hz, aromatic), 7.97 (dd, 1H, J = 8.0, 1.5 Hz, aromatic), 8.01 (dd, 1H, J = 8.0, 0.8 Hz, aromatic); 13C NMR (CDCl3, 126 MHz) δ 35.5 (1C), 38.8 (1C), 119.9 (1C), 120.4 (1C), 123.0 (1C), 126.7 (1C), 126.9 (1C), 127.3 (1C), 128.3 (1C), 129.1 (1C), 129.2 (1C), 131.6 (1C), 133.5 (1C), 136.0 (1C), 161.1 (1C); IR (KBr, cm−1) 746, 810, 912, 1194, 1235, 1506, 1634, 2928, HRMS (ESI+) m/z 312.026 (M+[Na]+), C13H13ClN2NaO2S+ requires 312.0220.

To a mixture of 3-chloro-2-(dimethylaminocarbonyl)naphtho[1,2-b]thiophene (25.9 mg, 89.4 µmol), 4-(2-hydroxyethyl)phenylboronic acid (22.5 mg, 0.136 mmol, 1.52 equiv), [(Me2N)2C(Ph-Bu3)2PdCl2 (6.5 mg, 9.2 µmol, 10 mol %), and K2CO3 (37.2 mg, 0.269 mmol, 3.01 equiv) were added 1,4-dioxane (400 µL) and H2O (10 µL) at room temperature, and the mixture was heated at 100 °C (oil bath temperature) with stirring for 16 h. After cooling to room temperature, the mixture was filtrated through a pad of Celite® washing with EtOAc (0.5 mL × 5), and the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (n-hexane/EtOAc = 1/6) to give 3-(4-(2-hydroxyethyl)phenyl)naphtho[1,2-b]thiophene (14.6 mg, 38.9 µmol, 43.4%) as a colorless solid.

Colorless solid; Mp 65–68 °C; TLC Rf 0.20 (n-hexane/EtOAc = 3/1); 1H NMR (CDCl3, 500 MHz) δ 2.61 (br s, 3H, CH3), 2.90–3.04 (m, 5H, CH2+CH3), 3.92–4.00 (m, 2H, CH2), 7.35–7.39 (AA′BB′, 2H, aromatic), 7.47–7.53 (AA′BB′, 2H, aromatic), 7.56 (ddd, 1H, J = 8.0, 8.0, 1.1 Hz, aromatic), 7.61 (ddd, 1H, J = 8.0, 8.0, 1.4 Hz, aromatic), 7.75 (d, 1H, J = 8.8 Hz, aromatic), 7.77 (d, 1H, J = 8.8 Hz, aromatic), 7.94 (dd, 1H, J = 8.0, 1.4 Hz, aromatic), 8.15 (dd, 1H, J = 8.0, 1.1 Hz, aromatic) (the signal for the hydroxy proton was not observed clearly); 13C NMR (CDCl3, 126 MHz) δ 35.2 (1C), 38.5 (1C), 39.0 (1C), 63.6 (1C), 121.5 (1C), 123.7 (1C), 126.0 (1C), 126.4 (1C), 126.9 (1C), 128.7 (1C), 128.8 (1C), 129.3 (2C), 129.5 (2C), 131.3 (1C), 131.7 (1C), 132.6 (1C), 135.5 (1C), 136.6 (1C), 137.5 (1C), 138.6 (1C), 165.4 (1C); IR (KBr, cm−1) 750, 814, 1061, 1261, 1404, 1508, 1620, 2930, 3402; HRMS (ESI+) m/z 398.1185 (M+[Na]+), C21H13ClN2NaO2S+ requires 398.1185.

To a solution of 2-dimethylaminocarbonyl-3-(4-(2H-1,3-dioxoisocinolin-2-yl)ethyl)phenyl)naphtho[1,2-b]thiophene (11.0 mg, 21.8 µmol, 91%) as a colorless solid.

Colorless solid; Mp 166–168 °C; TLC Rf 0.57 (n-hexane/EtOAc = 1/2); 1H NMR (CDCl3, 500 MHz) δ 2.50 (br s, 3H, CH3), 2.92 (br s, 3H, CH3), 3.10 (t, 2H, J = 7.3 Hz, CH2), 4.02 (t, 2H, J = 7.3 Hz, CH2), 7.33–7.38 (AA′BB′, 2H, aromatic), 7.42–7.47 (AA′BB′, 2H, aromatic), 7.55 (ddd, 1H, J = 7.5, 7.5, 1.2 Hz, aromatic), 7.60 (ddd, 1H, J = 7.5, 7.5, 1.1 Hz, aromatic), 7.70–7.76 (m, 4H, aromatic), 7.81–7.85 (m, 2H, aromatic), 7.93 (dd, 1H, J = 7.5, 1.1 Hz, aromatic), 8.14 (dd, 1H, J = 7.5, 1.2 Hz, aromatic); 13C NMR (CDCl3, 126 MHz) δ 34.3 (1C), 35.0 (1C), 38.3 (1C), 39.2 (1C), 121.4 (1C), 123.2 (2C), 123.7 (1C), 126.0 (1C), 126.4 (1C), 126.9 (1C), 128.7 (1C), 128.8 (1C), 129.3 (2C), 129.4 (2C), 131.3 (1C), 131.9 (1C), 132.0 (2C), 132.9 (1C), 134.0 (2C), 135.3 (1C), 136.5 (1C), 137.6 (1C), 138.2 (1C), 165.3 (1C), 168.1 (2C); IR (KBr, cm−1) 719, 791, 1358, 1395, 1628, 1713, 1771, 2934; HRMS (ESI+) m/z 527.1409 ([M+Na]+), C21H15N2O2S+ requires 527.1400.

To a solution of 2-dimethylaminocarbonyl-3-(4-(2-(1,3-dioxoisocinolin-2-yl)ethyl)phenyl)naphtho[1,2-b]thiophene (6.8 mg, 13 µmol) in EtOH (0.32 mL) was added hydrazine monohydrate (7.7 µL, 0.16 mmol, 12 equiv) at room temperature and the mixture was heated at 80 °C (oil bath temperature) with stirring for 2 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. To the residue was added water (1 mL) and the mixture was extracted with EtOAc (1 mL × 3). The combined organic extract was washed with brine (1 mL), dried (Na2SO4), and after filtration, the filtrate was concentrated under reduced pressure. The residue was dissolved in CH2Cl2 (160 µL) and to this solution were added triethylamine (4.4 µL, 32 µmol, 2.5 equiv) and 2-(2-methoxyphenyl)acetil chloride (0.613 M, CH2Cl2 solution, 35 µL, 19 µmol, 1.5 equiv) at room temperature. After stirring for 16 h at the same temperature, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (CH2Cl2/MeOH = 20/1) to give 2-(dimethylaminocarbonyl)-3-(4-(2-(2-methoxyphenyl)acetamido)ethyl)phenyl)naphtho[1,2-b]thiophene (20e) (6.2 mg, 12 µmol, 88% in 2 steps from 2-(dimethylaminocarbonyl)-3-(4-(2-(1,3-dioxoisocinolin-2-yl)ethyl)phenyl)naphtho[1,2-b]thiophene) S12
as a colorless solid.

Colorless solid; Mp 59–62 °C; TLC Rf 0.45 (CH₂Cl₂/MeOH = 10/1); ¹H NMR (CDCl₃, 500 MHz) δ 2.57 (br s, 3H, CH₃), 3.80 (2H, J = 6.8 Hz, CH₂), 3.86 (2H, J = 6.8 Hz, CH₂), 3.87 (2H, J = 6.8 Hz, CH₂), 3.88 (2H, J = 6.8 Hz, CH₂), 3.89 (2H, J = 6.8 Hz, CH₂), 3.90–3.96 (br, 2H, CH₂), 7.05 (dd, 1H, J = 9.0, 2.0 Hz, aromatic), 7.31 (dd, 1H, J = 2.0 Hz, aromatic), 7.29–7.35 (AA’BB’, 2H, aromatic), 7.41–7.46 (AA’BB’, 2H, aromatic), 7.66 (dd, 1H, J = 9.0 Hz, aromatic) (the signal for the hydroxy proton was not observed clearly); ¹³C NMR (CDCl₃, 126 MHz) δ 35.1 (1C), 38.4 (1C), 40.5 (1C), 55.4 (1C), 110.8 (1C), 121.1 (1C), 121.4 (1C), 123.6 (1C), 123.7 (1C), 125.9 (1C), 126.4 (1C), 127.0 (1C), 128.7 (1C), 128.8 (1C), 128.9 (1C), 129.1 (2C), 129.4 (2C), 131.3 (1C+1C, two signals overlapped), 131.7 (1C), 132.5 (1C), 135.4 (1C), 136.5 (1C), 137.6 (1C), 139.1 (1C), 157.1 (1C), 165.3 (1C), 171.2 (1C); IR (KBr, cm⁻¹) 752, 1246, 1495, 1531, 1628, 2928, 3306; HRMS (ESI⁺) m/z 545.1865 ([M+Na]⁺, C₂₂H₁₆N₂NaO₄S⁺ requires 545.1869).

**Synthesis of EP4 antagonist analog 20d**

![Synthesis of EP4 antagonist analog 20d](image)

Ar = p-(HOCH₂CH₃)₂C₆H₄; L = p-(Me₂N)C₆H₄P(t-Bu)₂; DMEAD = di(2-methoxyethyl) azodicarboxylate.

To a mixture of 3-chloro-2-dimethylaminocarbonyl-6-morpholinobenzothiophene (21c) (35.2 mg, 0.108 mmol), 4-(2-hydroxyethyl)phenylboronic acid (28.0 mg, 0.169 mmol, 1.56 equiv), (4-(Me₂N)C₆H₄P(t-Bu)₂)₃PdCl₂ (8.2 mg, 12 µmol, 11 mol %), and K₂CO₃ (47.2 mg, 0.342 mmol, 3.17 equiv) were added 1,4-dioxane (0.43 mL) and H₂O (10 µL) at room temperature and the mixture was heated at 100 °C (oil bath temperature) with stirring for 16 h. After cooling to room temperature, the mixture was filtrated through a pad of Celite® washing with EtOAc (0.5 mL × 10), and the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (n-hexane/EtOAc = 1/5) to give 2-dimethylaminocarbonyl-3-(4-(2-hydroxyethyl)phenyl)-6-morpholinobenzothiophene (16.5 mg, 40.2 µmol, 37.2%) as a colorless solid.

Colorless solid; Mp 82–84 °C; TLC Rf 0.13 (n-hexane/EtOAc = 1/6); ¹H NMR (CDCl₃, 500 MHz) δ 2.56 (br s, 3H, CH₃), 3.80–3.98 (m, 5H, CH₂+CH₃), 3.20–3.26 (AA’BB’, 4H, aliphatic), 3.86–3.92 (AA’BB’, 4H, aliphatic), 3.90–3.96 (br, 2H, CH₂), 7.05 (dd, 1H, J = 9.0, 2.0 Hz, aromatic), 7.31 (dd, 1H, J = 2.0 Hz, aromatic), 7.29–7.35 (AA’BB’, 2H, aromatic), 7.41–7.46 (AA’BB’, 2H, aromatic), 7.66 (dd, 1H, J = 9.0 Hz, aromatic) (the signal for the hydroxy proton was not observed clearly); ¹³C NMR (CDCl₃, 126 MHz) δ 35.1 (1C), 38.4 (1C), 39.0 (1C), 49.7 (2C), 63.5 (1C), 66.8 (2C), 107.5 (1C), 115.7 (1C), 124.0 (1C), 129.2 (2C), 129.4 (2C), 129.6 (1C), 131.4 (1C), 132.7 (1C), 134.9 (1C), 138.5 (1C), 141.4 (1C), 149.7 (1C), 165.6 (1C), IR (KBr, cm⁻¹) 731, 951, 1034, 1121, 1233, 1398, 1449, 1537, 1601, 2241, 2857, 2926, 3406; HRMS (ESI⁺) m/z 433.1544 ([M+Na]⁺, C₂₂H₁₆N₂NaO₄S⁺ requires 433.1556).

To a solution of 2-dimethylaminocarbonyl-3-(4-(2-hydroxyethyl)phenyl)-6-morpholinobenzothiophene (16.5 mg, 40.3 µmol), di(2-methoxyethyl) azodicarboxylate (DMEAD) (14.8 mg, 63.2 µmol, 1.57 equiv), and
phthalimide (8.9 mg, 61 µmol, 1.5 equiv) dissolved in THF (0.40 mL) was added triphenylphosphine (17.0 mg, 64.8 µmol, 1.61 equiv) at room temperature. After stirring for 16 h at the same temperature, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (n-hexane/EtOAc = 1/5) to give 2-dimethylaminocarbonyl-3-(4-(2-(1,3-dioxoisoindolin-2-yl)ethyl)phenyl)-6-morpholinobenzothiophene (18.1 mg, 35.5 µmol, 83.1%) as a pale yellow solid.

Pallae yellow solid; Mp 82–84 °C; TLC Rf 0.38 (n-hexane/EtOAc = 1/6); 1H NMR (CDCl3, 500 MHz) δ 2.46 (br s, 3H, CH3), 2.87 (br s, 3H, CH3), 3.08 (t, 2H, J = 7.3 Hz, CH2), 3.20–3.27 (AA’BB’, 4H, aliphatic), 3.85–3.93 (AA’BB’, 4H, aliphatic), 4.00 (t, 2H, J = 7.3 Hz, CH2), 7.05 (dd, 1H, J = 9.0, 2.0 Hz, aromatic), 7.28–7.33 (m, 3H, aromatic), 7.36–7.40 (AA’BB’, 2H, aromatic), 7.62 (d, 1H, J = 9.0 Hz, aromatic), 7.68–7.74 (m, 2H, aromatic), 7.79–7.85 (m, 2H, aromatic); 13C NMR (CDCl3, 126 MHz) δ 34.2 (1C), 34.9 (1C), 35.0 (1C), 35.5 (1C), 38.3 (1C), 38.7 (1C), 40.5 (1C), 123.0 (2C), 130.0 (1C), 130.3 (1C), 134.0 (2C), 134.8 (1C), 138.0 (1C), 138.1 (1C), 141.4 (1C), 149.7 (1C), 165.4 (1C), 168.1 (2C); IR (KBr, cm–1) 741, 912, 1233, 1294, 1345, 1395, 1482, 1520, 1599, 1620, 1713, 2857, 2957; HRMS (ESI+) m/z 562.1756 ([M+Na]+, C31H29N4NaO4S+ requires 562.1771).

To a solution of 2-dimethylaminocarbonyl-3-(4-(2-(1,3-dioxoisoindolin-2-yl)ethyl)phenyl)-6-morpholinobenzothiophene (8.22 mg, 15.2 µmol) in EtOH (0.31 mL) was added hydrazine monohydrate (7.4 µL, 0.15 mmol, 10 equiv) at room temperature and the mixture was heated at 80 °C (oil bath temperature) with stirring for 2 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. To the residue was added water (1 mL) and the mixture was extracted with EtOAc (2 mL × 5). The combined organic extract was washed with brine (1 mL), dried (Na2SO4), and after filtration, the filtrate was concentrated under reduced pressure. The residue was dissolved in CH2Cl2 (0.15 mL) and to this solution was added triethylamine (4.2 µL, 30 µmol, 2.0 equiv) and 2-(2-methoxyphenyl)acetamide chloride (0.613 M CH2Cl2 solution, 34 µL, 0.12 mmol, 1.2 equiv) at room temperature. After stirring for 6 h at the same temperature, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (CH2Cl2/MeOH = 20/1) to give 2-dimethylaminocarbonyl-3-(4-(2-(2-methoxyphenyl)acetamido)ethyl)phenyl)-6-morpholinobenzothiophene (20d) (5.8 mg, 10 µmol, 68% in 2 steps from 2-dimethylaminocarbonyl-3-(4-(2-(1,3-dioxoisoindolin-2-yl)ethyl)phenyl)-6-morpholinobenzothiophene) as a colorless solid.

Colorless solid; Mp 72–75 °C; TLC Rf 0.54 (CH2Cl2/MeOH = 10/1); 1H NMR (CDCl3, 500 MHz) δ 2.52 (br s, 3H, CH3), 2.77 (t, 2H, J = 6.8 Hz, CH2), 2.92 (br s, 3H, CH3), 3.23–3.28 (AA’BB’, 4H, aliphatic), 3.50 (dt, 2H, J = 6.8, 6.8 Hz, CH2), 3.56 (s, 2H, CH2), 3.76 (s, 3H, CH3), 3.87–3.94 (AA’BB’, 4H, aliphatic), 5.79 (br t, 1H, J = 6.8 Hz, NH), 6.87 (dd, 1H, J = 7.8, 7.8 Hz, aromatic), 6.93 (ddd, 1H, J = 7.8, 7.8, 1.0 Hz, aromatic), 7.07 (dd, 1H, J = 9.0, 2.0 Hz, aromatic), 7.11–7.16 (AA’BB’, 2H, aromatic), 7.20 (dd, 1H, J = 7.8, 1.6 Hz, aromatic), 7.26 (ddd, 1H, J = 7.8, 7.8, 1.6 Hz, aromatic), 7.32 (d, 1H, J = 2.0 Hz, aromatic), 7.33–7.38 (AA’BB’, 2H, aromatic), 7.62 (d, 1H, J = 9.0 Hz, aromatic); 13C NMR (CDCl3, 126 MHz) δ 35.0 (1C), 35.5 (1C), 38.3 (1C), 38.7 (1C), 40.5 (1C), 49.8 (2C), 55.4 (1C), 66.8 (2C), 107.5 (1C), 110.7 (1C), 115.6 (1C), 121.1 (1C), 123.6 (1C), 123.9 (1C), 128.8 (1C), 129.06 (2C), 129.13 (2C), 129.7 (1C), 131.3 (1C), 131.4 (1C), 132.7 (1C), 134.8 (1C), 138.9 (1C), 141.4 (1C), 149.7 (1C), 157.1 (1C), 165.5 (1C), 171.2 (1C); IR (KBr, cm–1) 741, 912, 1233, 1246, 1601, 1622, 2241, 2857, 2926, 3308; HRMS (ESI+) m/z 580.2234 ([M+Na]+, C31H29N4NaO4S+ requires 580.2240).
Affinity determination of benzothiophene derivatives 20a–d to human EP4 receptor

(a) Specific binding of [³H]PGE₂ to the membrane of HEK293 cells expressing human EP4 receptor. Curve fitting shows that $K_d$ value is 6.6 nM. (b) Competition binding of [³H]PGE₂ by benzothiophene derivatives 20a–d. The $K_i$ values were calculated using the $K_d$ value determined in (a). Data are presented as mean ± s.e.m. of triplicate experiments.
Materials and methods of radioligand binding assays

Wild-type human EP4 cDNA was subcloned into the mammalian expression vector pcDNA3.1 (Thermo Fisher Scientific), and the resultant plasmid was transfected into HEK293 cells using Lipofectamine 2000 (Thermo Fisher Scientific). After culture for 24 h, the cells were harvested, and homogenized in a buffer comprising 25 mM Tris-HCl (pH 7.5), containing 0.25 M sucrose, 10 mM MgCl₂, 1 mM EDTA, and 0.1 mM phenylmethylsulfonyl fluoride. The homogenate was centrifuged at 100,000 g for 30 min, and the pellet was suspended in binding buffer (20 mM MES [pH 6.0], 10 mM MgCl₂ and 1 mM EDTA), and used as crude membranes in binding assays. Protein concentrations were determined using the BCA assay (Thermo Fisher Scientific).

[^3H]PGE₂ (PerkinElmer) affinity (K_d) was determined by saturation binding assay, performed by incubating varying concentrations of[^3H]PGE₂ with 50 µg of crude membranes at 30 ºC for 1 h, in a final volume of 100 µL binding buffer. Non-specific binding was determined using a 1,000-fold excess of non-radiolabelled PGE₂. Radioligand inhibition binding assays were performed by co-incubating 50 µg of crude membranes with 10 nM[^3H]PGE₂ and varying concentrations of non-radiolabelled test compounds. After the reaction, the mixture was rapidly filtered through Whatman GF/B glass filters presoaked in 0.3% (v/v) polyethylenimine. The filter was then washed twice with 5 mL of ice-cold K–P buffer (1.32 mM K₂HPO₄, 8.68 mM KH₂PO₄, 10 mM MgCl₂, 1 mM EDTA). The radioactivity associated with filter was measured in 2.5 mL of Clearsol I scintillation liquid (Nacalai Tesque) by an AccuFLEX LCS-8000 liquid scintillation counter (Hitachi). Specific binding was calculated by subtracting nonspecific binding from total binding. All binding assay measurements were analyzed using Prism (GraphPad).
References for Supporting Information

$^1$H and $^{13}$C NMR Spectra of Compounds

$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 2,3-dibutyl-6-(isopropylaminocarbonyloxy)-benzo[b]thiophene (CDCl₃)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 2,3-dibutyl-6-isopropylaminocarbonyloxy-7-(trimethylsilyl)benzo[b]thiophene (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 2a (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 3-methyl-6-isopropylaminocarbonyloxy-2-phenylbenzo[b]thiophene (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 3-methyl-6-isopropylaminocarbonyloxy-2-phenyl-7-(trimethylsilyl)benzo[b]thiophene (CDCl₃)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 2b (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 6-isopropylaminocarbonyloxy-2-methylthio-3-(trifluoromethyl)benzo[b]thiophene (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 6-isopropylaminocarbonyloxy-2-methylthio-3-trifluoromethyl-7-(trimethylsilyl)benzo[b]thiophene (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 2c (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 3 (DMSO-$d_6$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 4 (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 2d (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 6b' (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 13 (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 15 (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 15' (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 17 (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 19 (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 21b (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 3-chloro-2-(dimethylaminocarbonyl)naphtho[1,2-b]thiophene (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 2-(dimethylaminocarbonyl)-3-(4-(2-hydroxyethyl)-phenyl)naphtho[1,2-$b$]thiophene (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 2-dimethylaminocarbonyl-3-(4-(2-(1,3-dioxoisoindolin-2-yl)ethyl)phenyl)naphtho[1,2-b]thiophene (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 20c (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 21c (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 21c (CDCl$_3$)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 2-dimethylaminocarbonyl-3-(4-(2-hydroxyethyl)-phenyl)-6-morpholinobenzo[b]thiophene (CDCl₃)
$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra of 2-dimethylaminocarbonyl-3-(4-(2-(1,3-dioxoisindolin-2-yl)ethyl)phenyl)-6-morpholinobenzo[b]thiophene (CDCl₃)
\(^1\)H NMR (500 MHz) and \(^{13}\)C NMR (126 MHz) spectra of 20d (CDCl\(_3\))