Insights into the Mechanism of the Site-Selective Sequential Palladium-Catalyzed Cross-Coupling Reactions of Dibromothiophenes/Dibromothiazoles and Arylboronic Acids. Synthesis of PPARβ/δ Agonists

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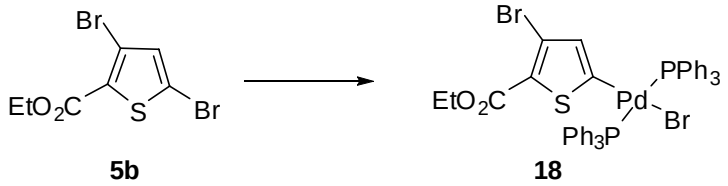
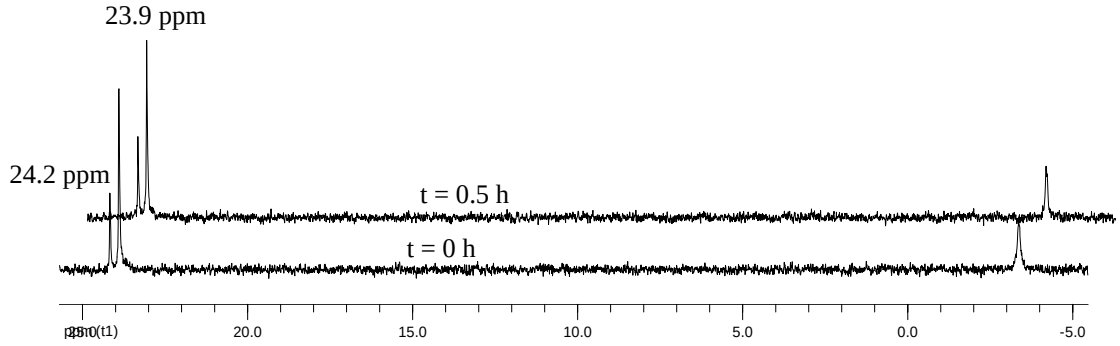
Electronic Supplementary Information

^{31}P NMR Monitoring of the Oxidative Addition of 5b. The experiment was performed at 25 °C.

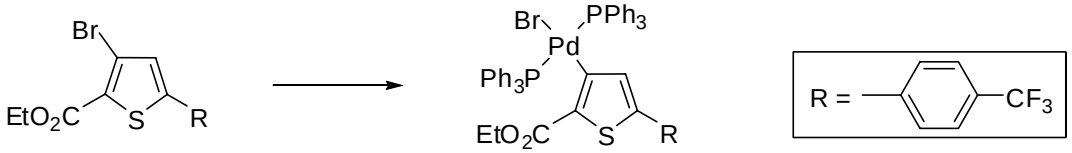


5b **18**

^{31}P NMR δ 23.9 ppm

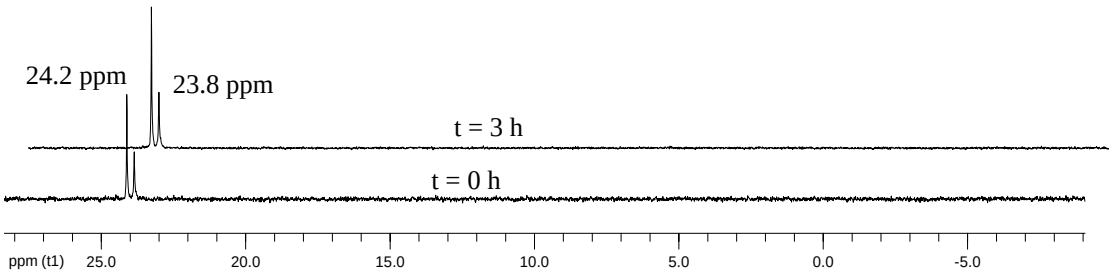


^{31}P NMR Monitoring of the Oxidative Addition of 7b. The experiment was performed at 90 °C.

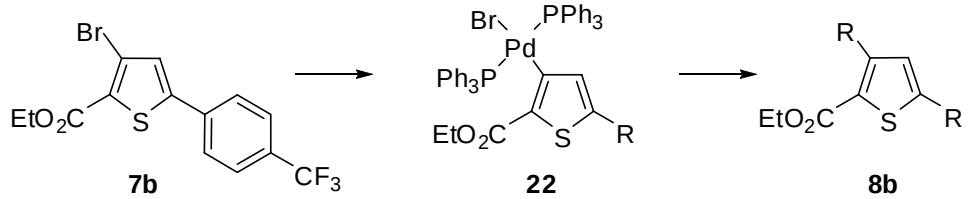


7b **22**

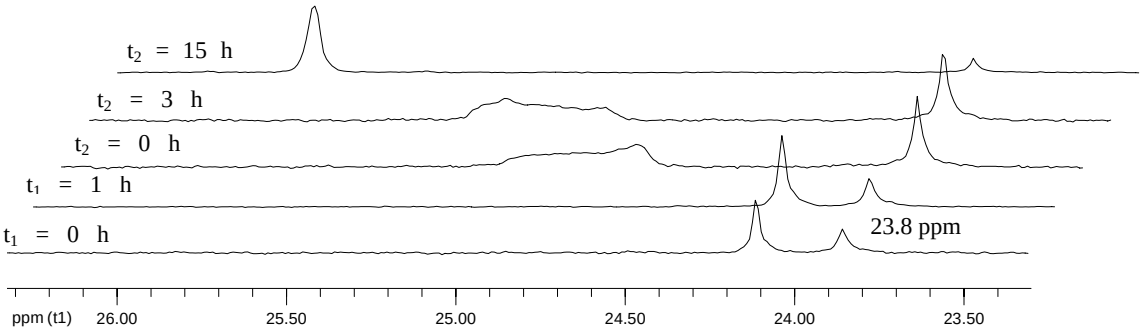
^{31}P NMR δ 23.8 ppm



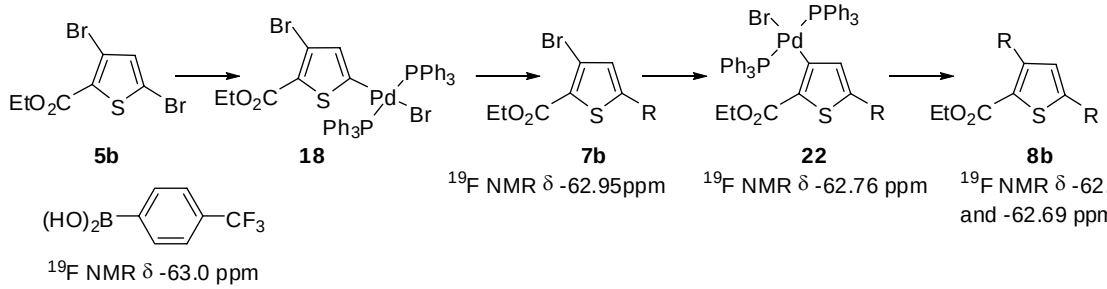
^{31}P NMR Monitoring of the Cross-Coupling Reaction of 7b. The experiment was performed at 90 °C.



^{31}P NMR δ 23.8 ppm



^{19}F NMR Monitoring of the Cross-Coupling Reaction of 5b. The experiment was performed at 90 °C.

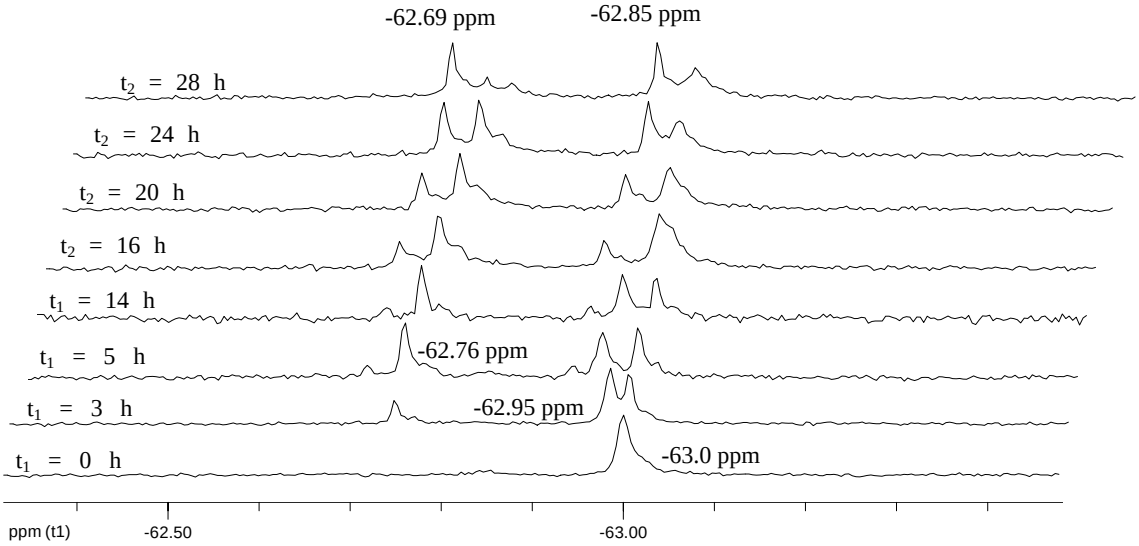


^{19}F NMR δ -62.95ppm

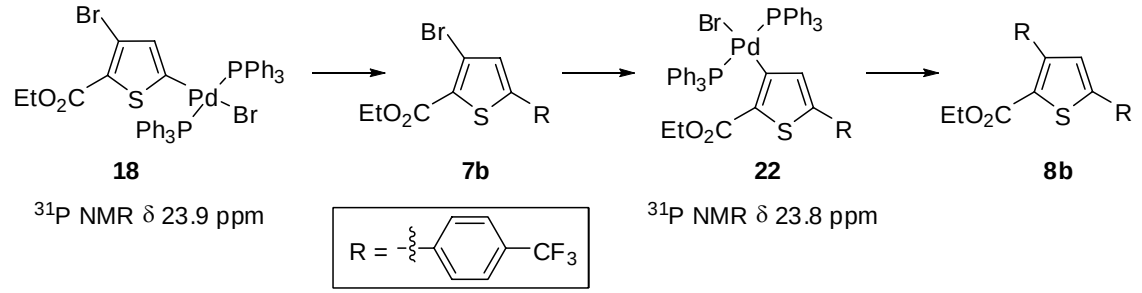
^{19}F NMR δ -62.76 ppm

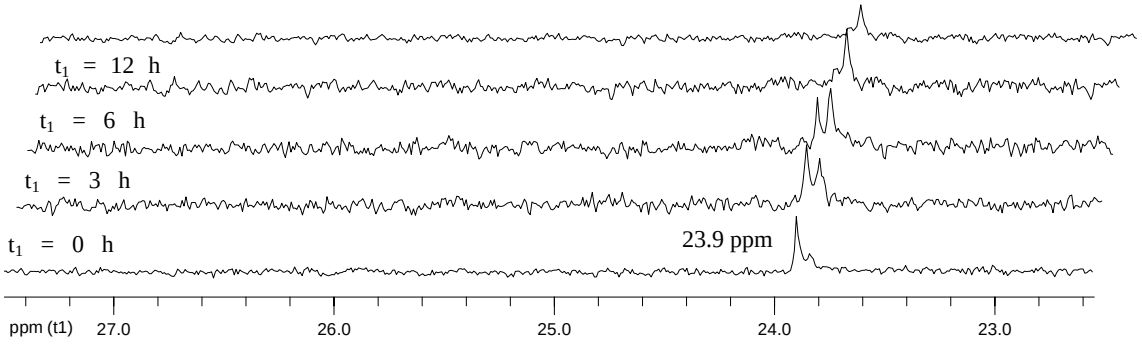
^{19}F NMR δ -62.85 and -62.69 ppm

^{19}F NMR δ -63.0 ppm

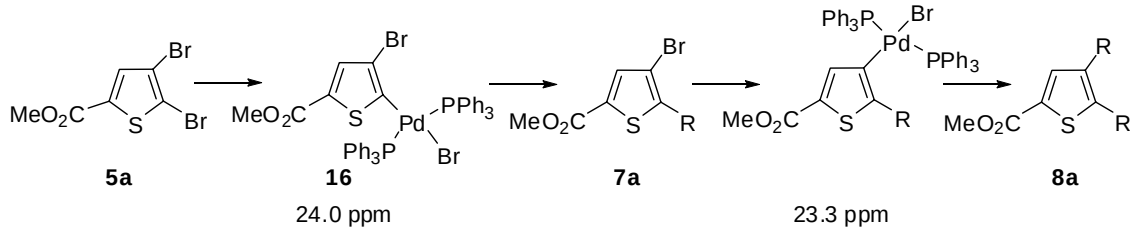


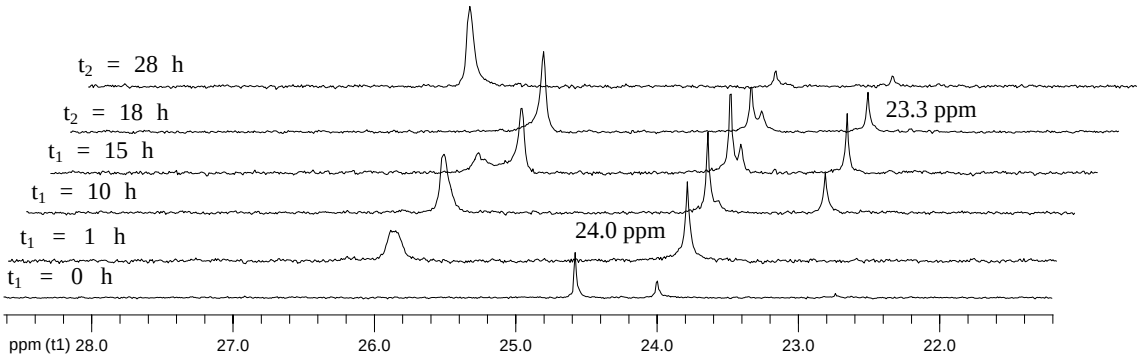
^{31}P NMR Monitoring of the Cross-Coupling Reaction of Complex 18. The experiment was performed at 90 °C.



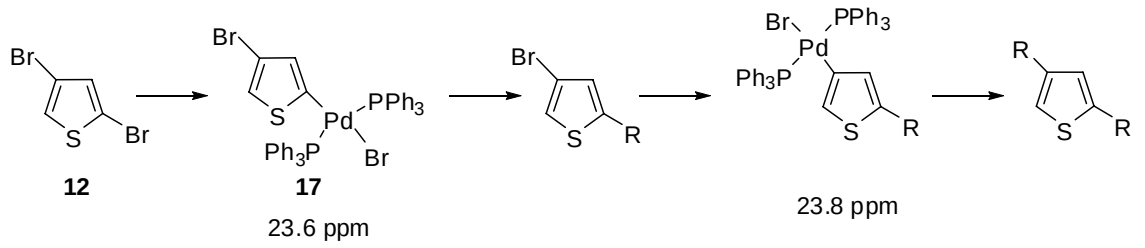


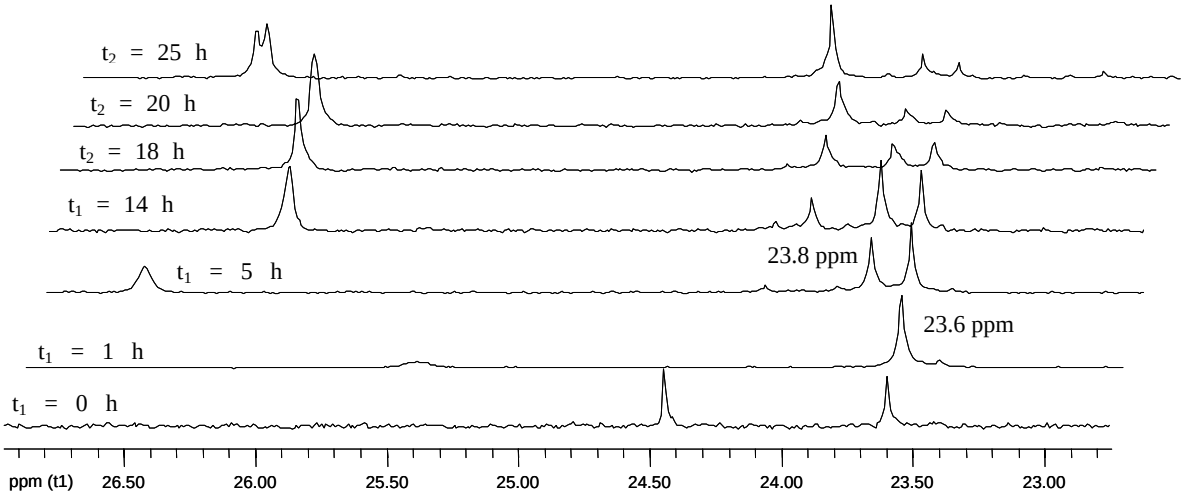
^{31}P NMR Monitoring of the Cross-Coupling Reaction of 5a. The experiment was performed at 90 °C.



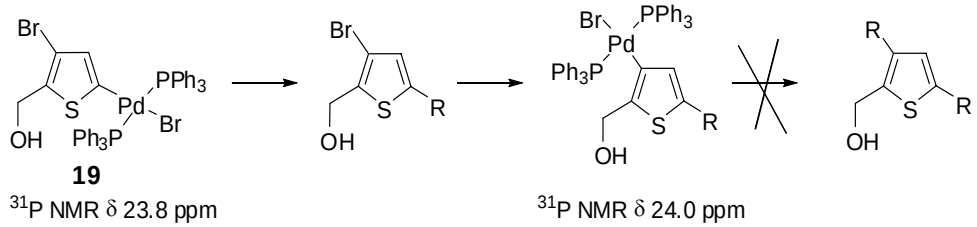


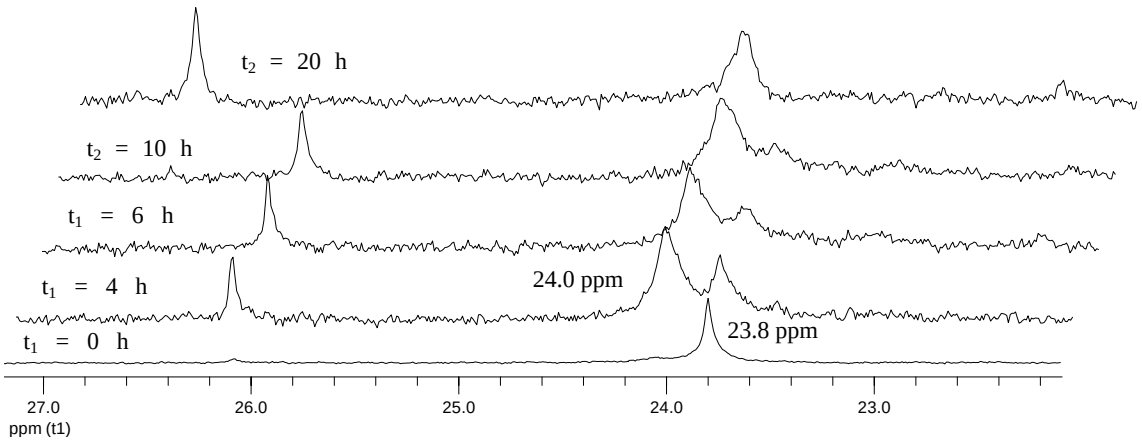
^{31}P NMR Monitoring of the Cross-Coupling Reaction of 12. The experiment was performed at 90 °C.



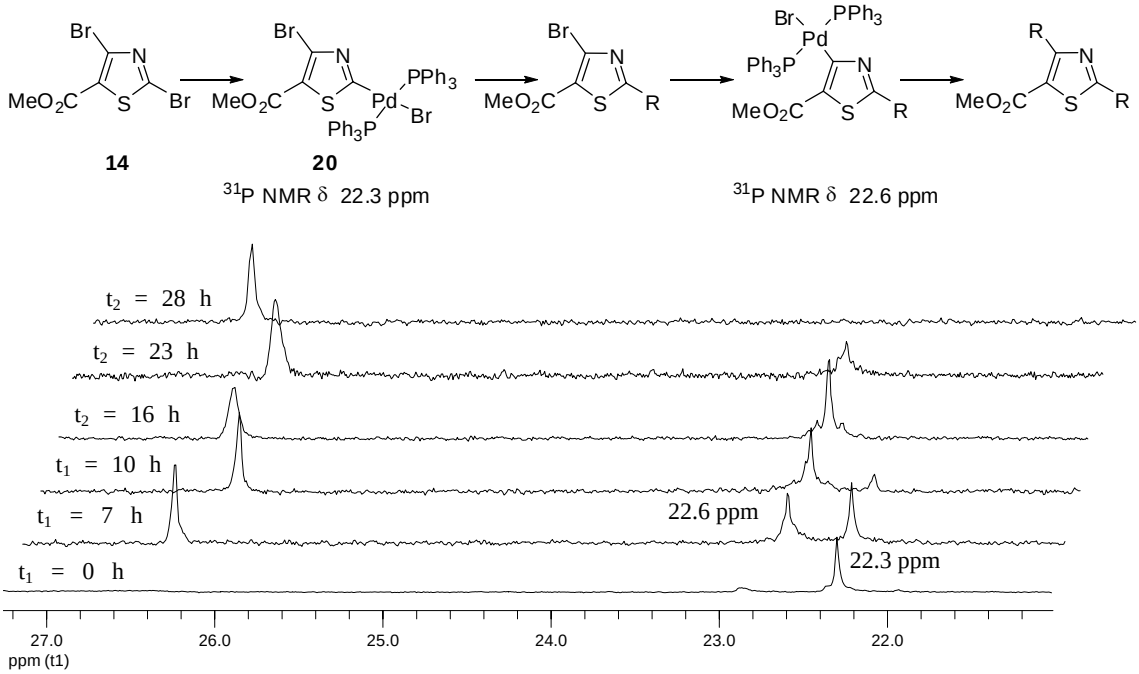


^{31}P NMR Monitoring of the Cross-Coupling Reaction of Complex 19. The experiment was performed at 90 °C. There is no evidence of reaction at position C3.

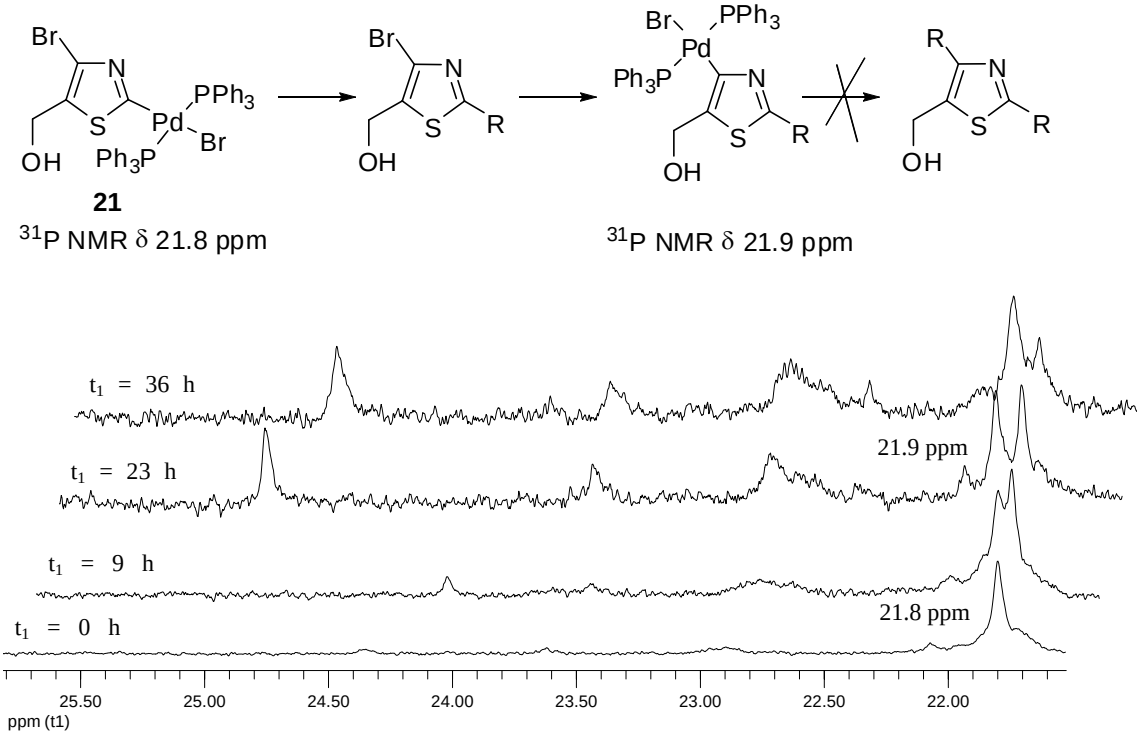




^{31}P NMR Monitoring of the Cross-Coupling Reaction of 14. The experiment was performed at 90 °C.



^{31}P NMR Monitoring of the Cross-Coupling Reaction of Complex 21. The experiment was performed at 120 °C in order to facilitate reaction at position C4, although no evidence of reaction at this position could be observed.



Preparation of Methyl 4,5-Dibromothiophene-2-carboxylate (5a).[1] Addition of H_2SO_4(c) (0.01 mL) to a solution of 4,5-dibromothiophene-2-carboxylic acid (0.2 g, 0.70 mmol) in anhydrous MeOH (1 mL), followed by heating the mixture to reflux for 6 h, quenching to neutral pH with 3 M K_2CO_3, extraction with AcOEt (2x), drying over sodium sulphate and solvent evaporation furnished methyl 4,5-dibromothiophene-2-carboxylate **5a** (0.19 g, 92%).

Preparation of Ethyl 3,5-Dibromothiophene-2-carboxylate (5b).[2] The carboxylic acid was prepared following the reported procedure (Meth-Cohn, O.; van Vuuren, G. *J. Chem. Soc. Perkin Trans. I* **1986**, 233-243): *n*-BuLi (3.9 mL, 1.6 M in hexane, 6.5 mmol) was added dropwise to a solution of 2,3,5-tribromothiophene (2.0 g, 6.2 mmol) in anhydrous diethyl ether (20 mL) under argon at –78 ºC. The resulting solution was added to excess CO_2. Water was then added, followed by the dropwise addition of HCl(c). The solid was filtered off and recrystallized from aqueous ethanol to afford 3,5-dibromothiophene-2-carboxylic acid (1.2 g, 66%). Addition of H_2SO_4(c) (0.1 mL) to a solution of 3,5-dibromothiophene-2-carboxylic acid (1.2 g, 1.76 mmol) in anhydrous EtOH (5 mL) followed by heating the mixture to reflux for 6 h, quenching to neutral pH with 3 M K_2CO_3, extraction with AcOEt (2x), drying over sodium sulphate and solvent evaporation furnished ethyl 3,5-dibromothiophene-2-carboxylate **5b** (1.19 g, 90%).

Preparation of Ethyl 3-Bromo-5-(4-trifluoromethylphenyl)thiophene-2-carboxylate (7b). According to the general procedure for Stille reactions, ethyl 3,5-dibromothiophene-2-carboxylate **5b** (0.05 g, 0.16 mmol) in NMP (2 mL) was treated with $Pd_2(dba)_3$ (0.002 g, 0.002 mmol), $AsPh_3$ (0.01 g, 0.03 mmol) and tributyl(4-trifluoromethylphenyl)stannane **6** (0.09 g, 0.21 mmol) during 4 h at 60 ºC, to provide, after purification by chromatography (SiO_2, 98:2 hexane/AcOEt), 0.02 g (40%) of a mixture of thiophenes **7b** and **8b** in a 57:43 ratio. Partial separation of this mixture for characterization purposes was accomplished by chromatography (SiO_2, 75:25 hexane/CH_2Cl_2). *Spectroscopic data for **7b***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7. 2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 4.39 (q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 7.35 (s, 1H, H4), 7.68 (d, J_{AB} = 9.2 Hz, 2H, ArH), 7.70 (d, J_{AB} = 9.2 Hz, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (q, $CO_2CH_2\underline{C}H_3$), 61.6 (t, $CO_2\underline{C}H_2CH_3$), 117.5 (s), 123.7 (s, CF_3, $^1J_{C\text{-}F}$ = 272.1 Hz), 126.2 (d, 2x, C2' + C6'), 126.2 (d, 2x, C3' + C5', $^3J_{C\text{-}F}$ = 3.8 Hz), 127.5 (s), 129.7 (d, C4), 131.1 (s, C4', $^2J_{C\text{-}F}$ = 33.2 Hz), 135.6 (s), 147.0 (s), 160.5 (s, CO_2Et) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.95 ppm. IR (NaCl) ν 3090 (w, C-H), 2994 (w, C-H), 1685 (s, C=O), 1612 (w), 1445 (w), 1327 (m), 1295 (m), 1158 (m), 1120 (s), 841 (m) cm^{-1}. MS *m/z* (%) 381 ([M+1]$^+$ [^{81}Br], 5), 380 (M$^+$ [^{81}Br], 44), 379 ([M+1]$^+$ [^{79}Br], 6), 378 (M$^+$ [^{79}Br], 45), 352 (24), 350 (24), 335 ([M-OC_2H_5]$^+$ [^{81}Br], 97), 333 ([M-OC_2H_5]$^+$ [^{79}Br], 100), 308 (22), 306 (23), 226 (42). HRMS (EI$^+$) calcd for $C_{14}H_{10}{}^{81}BrF_3O_2S$ 379.9517 and $C_{14}H_{10}{}^{79}BrF_3O_2S$ 377.9537, found 379.9509 and 377.9523. Anal. Calcd for $C_{14}H_{10}BrF_3O_2S$: C, 44.34; H, 2.66; S, 8.46. Found: C, 44.47; H, 2.70; S, 8.47. *Spectroscopic data for ethyl 3,5-bis(4-trifluromethylphenyl)thiophene-2-carboxylate (**8b**)*: ^{1}H NMR (400

[1] Elbe, H.-L.; Assmann, L.; Tiemann, R.; Schulz, U.; Haenssler, H.; Dehne, H.-W. European Patent No. EP 0755185, 1995; *Chem. Abstr*. **1995**, *124*, 55787.
[2] Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. *Heterocycles* **1983**, *20*, 2035-2037.

MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 4.27 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 7.34 (s, 1H, H4), 7.61 (d, *J* = 8.1 Hz, 2H, ArH), 7.69 (d, *J* = 8.4 Hz, 4H, H3' + H5' + H3'' + H5''), 7.77 (d, *J* = 8.1 Hz, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (q, $CO_2CH_2\underline{C}H_3$), 61.4 (t, $CO_2\underline{C}H_2CH_3$), 123.8 (s, CF_3, $^1J_{C\text{-}F}$ = 272.1 Hz), 124.1 (s, CF_3, $^1J_{C\text{-}F}$ = 272.0 Hz), 124.8 (d, 2x, ArCH, $^3J_{C\text{-}F}$ = 3.7 Hz), 126.2 (d, 2x, ArCH, $^3J_{C\text{-}F}$ = 3.7 Hz), 126.3 (d, 2x, ArCH), 128.0 (d, C4), 128.2 (s), 129.6 (d, 2x, ArCH), 130.2 (s, C4' or C4'', $^2J_{C\text{-}F}$ = 32.7 Hz), 130.8 (s, C4'' or C4', $^2J_{C\text{-}F}$ = 32.7 Hz), 136.3 (s), 139.1 (s), 146.7 (s), 147.6 (s), 161.5 (s, CO_2Et) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.85, -62.69 ppm. IR (NaCl) ν 2956 (w, C-H), 2928 (w, C-H), 1718 (s, C=O), 1617 (m), 1451 (m), 1325 (s), 1292 (s), 1251 (s), 1167 (s), 1124 (s), 1068 (s), 1018 (m), 839 (m) cm^{-1}. MS *m/z* (%) 446 ([M+2]$^+$, 6), 445 ([M+1]$^+$, 18), 444 (M$^+$, 70), 416 (30), 415 ([M-C_2H_5]$^+$, 24), 400 (23), 399 ([M-OC_2H_5]$^+$, 100), 372 (39), 327 (16), 302 (21). HRMS (EI$^+$) calcd for $C_{21}H_{14}F_6O_2S$ 444.0619, found 444.0635. Anal. Calcd for $C_{21}H_{14}F_6O_2S$: C, 56.76; H, 3.18; S, 7.22. Found: C, 56.69; H, 3.24; S, 7.36.

Preparation of 7b. According to the general procedure for Suzuki reactions, 4-bromotrifluoromethylbenzene (0.05 g, 0.19 mmol) in THF (1 mL) was treated with *n*-BuLi (0.12 mL, 1.75 M in hexane, 0.21 mmol) and $B(OMe)_3$ (0.02 mL, 0.21 mmol) to afford the boronate, which was reacted with ethyl 3,5-dibromothiophene-2-carboxylate **5b** (0.05 g, 0.16 mmol), $Pd(PPh_3)_4$ (0.009 g, 0.009 mmol) and K_2CO_3 (0.11 mL, 3 M in H_2O, 0.33 mmol) in toluene (1.5 mL), at 70 °C for 24 h, providing, after purification by chromatography (SiO_2, 98:2 hexane/AcOEt), 0.05 g (90%) of thiophene **7b** as a slightly yellow solid (mp 121 ºC, hexane/AcOEt).

Preparation of Ethyl 3-Methyl-5-(4-trifluoromethylphenyl)thiophene-2-carboxylate (10b). In accordance to the general procedure for the second Stille coupling, ethyl 3-bromo-5-(4-trifluoromethylphenyl)thiophene-2-carboxylate (**7b**) (0.27 g, 0.70 mmol) was reacted with $PdCl_2(PPh_3)_2$ (0.02 g, 0.01 mmol) and $SnMe_4$ (0.25 g, 0.53 mmol) in DMA (5 mL), for 15 h at 90 ºC, to yield, after purification by chromatography (SiO_2, 95:5 hexane/AcOEt), 0.18 g (83%) of ethyl 3-methyl-5-(4-trifluoromethylphenyl)thiophene-2-carboxylate (**10b)** as a white solid (mp 81 ºC, hexane/TBME). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 2.57 (s, 3H, C3-CH_3), 4.35 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 7.19 (s, 1H, H4), 7.64 (d, *J* = 8.3 Hz, 2H, H3' + H5'), 7.71 (d, *J* = 8.3 Hz, 2H, H2' + H6') ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (q, $CO_2CH_2\underline{C}H_3$), 16.1 (q, C3-CH_3), 60.9 (t, $CO_2\underline{C}H_2CH_3$), 123.9 (s, CF_3, $^1J_{C\text{-}F}$ = 272.0 Hz), 126.0 (d, 2x, C3' + C5', $^3J_{C\text{-}F}$ = 3.7 Hz), 126.1 (d, 2x, C2' + C6'), 127.2 (s), 128.8 (d, C4), 130.3 (s, C4', $^2J_{C\text{-}F}$ = 32.7 Hz), 136.8 (s), 145.8 (s), 146.9 (s), 162.6 (s, CO_2Et) ppm. IR (NaCl) ν 2985 (w, C-H), 1708 (s, C=O), 1615 (w), 1446 (w), 1412 (w), 1378 (w), 1326 (s), 1256 (s), 1168 (m), 1123 (s), 1091 (s), 1069 (s), 831 (m) cm^{-1}. MS *m/z* (%) 316 ([M+2]$^+$, 6), 315 ([M+1]$^+$, 12), 314 (M$^+$, 89), 286 (41), 285 ([M-C_2H_5]$^+$, 41), 270 (23), 269 ([M-OC_2H_5]$^+$, 100), 242 (21), 197 (25), 171 (11). HRMS (EI$^+$) calcd for $C_{15}H_{13}F_3O_2S$ 314.0588, found 314.0586. Anal. Calcd for $C_{15}H_{13}F_3O_2S$: C, 57.32; H, 4.17; S, 10.20. Found: C, 57.56; H, 4.17; S, 10.21.

Preparation of [3-Methyl-5-(4-trifluoromethylphenyl)thien-2-yl]methanol (11b). According to the general procedure for the reduction of esters to alcohols, ethyl ester **10b** (0.12 g, 0.40 mmol) was treated with a suspension of $LiAlH_4$ (0.02 g, 0.49 mmol) in THF (1 mL) at 0 ºC for 2 h, to afford, after purification by chromatography (SiO_2, 75:25 hexane/AcOEt), 0.09 g (79%) of a white solid (mp 122 ºC, hexane/TBME) identified as alcohol **11b**.[3]

Preparation of 2,4-Dibromothiazole-5-carboxylic acid. A solution of $NaClO_2$ (0.30 g, 3.33 mmol) and NaH_2PO_4 (0.36 g, 2.53 mmol) in H_2O (3.3 mL) was added to the mixture of 2,4-dibromothiazole-5-carbaldehyde (0.18 g, 0.67 mmol) and 2-methylbut-2-ene (3.5 mL, 33.3 mmol) in *t*-BuOH (13 mL) by means of a syringe pump programmed at a rate of 0.01 mL/min. The resulting mixture was stirred at 25 ºC for 15 min, after which time 2 M NaOH was added until pH 10. *t*-BuOH was evaporated, water was added and the mixture was extracted with TBME. The aqueous layer was treated with 10% HCl until pH 3 and it was extracted with AcOEt (3x). The combined organic extracts were dried (Na_2SO_4) and evaporated. Crystallization from MeOH/$CHCl_3$ afforded 0.18 g (94%) of the carboxylic acid as a white solid (mp 165 ºC). MS *m/z* (%) 289 (M^+ [2 x ^{81}Br], 54), 288 ([M+1]$^+$ [^{81}Br + ^{79}Br], 6), 287 (M^+ [^{81}Br + ^{79}Br], 100), 285 (M^+ [2 x ^{79}Br], 48), 210 (10), 243 (14), 208 (30), 206 (31), 180 (18), 178 (16), 138 (10), 137 (15), 135 (15). HRMS calcd. for $C_4H^{81}Br_2NO_2S$ 288.8054, $C_4H^{81}Br^{79}BrNO_2S$ 286.8074 and $C_4H^{79}Br_2NO_2S$ 284.8095; found 288.8050, 286.8068 and 284.8087.

Preparation of Methyl 2,4-Dibromothiazole-5-carboxylate (14). To a solution of 2,4-dibromothiazole-5-carboxylic acid (0.07 g, 0.25 mmol) in MeOH (2 mL) H_2SO_4 (0.03 mL) was added and the mixture was stirred at 80 ºC for 4 h. It was then neutralized with 2 M NaOH and extracted with AcOEt (4x). The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (SiO_2, 95:5 hexane/AcOEt) to yield methyl ester **14** (0.06 g, 87 %) as a yellow solid (mp 60 ºC, hexane/AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H, CO_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.8 (q, $CO_2\underline{C}H_3$), 127.0 (s), 130.4 (s), 141.4 (s, C2), 159.1 (s, $\underline{C}OCH_3$) ppm. IR (NaCl) ν 2956 (m, C-H), 2853 (w, C-H), 1731 (s, C=O), 1710 (s, C=O), 1567 (w), 1489 (s), 1433 (m), 1381 (s), 1300 (s), 1252 (s), 1217 (s), 1083 (s), 1030 (s), 846 (m), 797 (m), 757 (m) cm^{-1}. MS *m/z* (%) 303 (M^+ [2 x ^{81}Br], 10), 301 (M^+ [^{81}Br + ^{79}Br], 16), 299 (M^+ [2 x ^{79}Br], 10), 272 ([M-OCH_3]$^+$ [2 x ^{81}Br], 56), 270 ([M-OCH_3]$^+$ [^{81}Br + ^{79}Br], 56), 268 ([M-OCH_3]$^+$ [2 x ^{79}Br], 28), 242 (11), 147 (28), 137 (26), 135 (41), 110 (12), 82 (100), 78 (12), 73 (88). HRMS calcd. for $C_5H_3{}^{81}Br_2NO_2S$ 302.8210, $C_5H_3{}^{81}Br^{79}BrNO_2S$ 300.8231 and $C_5H_3{}^{79}Br_2NO_2S$ 298.8251; found 302.8229, 300.8236 and 298.8261.

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[3] Beswick, P. J.; Hamlett, C. C. F.; Patel, V.; Sierra, M. L.; Ramsden, N. G. European Patent No. WO 0292590, 2002; *Chem. Abstr*. **2002**, *137*, 384743.

Table 2. Data Collection and Refinement Parameters for X-Ray Structures of **16**, **17**, **20**, **21** and **22**

	16[a]	**17**	**20**[b]	**21**	**22**
Empirical formula	$C_{43}H_{36}Br_2Cl_2O_2P_2PdS$	$C_{40}H_{32}Br_2P_2PdS$	$C_{42}H_{34}Br_2Cl_3NO_2P_2PdS$	$C_{40}H_{33}Br_2NOP_2PdS$	$C_{50}H_{40}BrF_3O_2P_2PdS$
Formula weight	1015.84	872.88	1051.27	903.89	1010.13
Crystal system	Triclinic	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space group	P-1	C2/c	P-1	C2/c	P2(1)/n
Unit cell dimensions					
a (Å)	11.5181(9)	25.7511(18)	11.6242(8)	25.775(4)	21.459(3)
b (Å)	11.8484(9)	13.0925(9)	11.8469(9)	13.4291(19)	11.2009(16)
c (Å)	18.2094(14)	18.2094(14)	16.6140(13)	11.7221(16)	22.854(3)
α (º)	96.201(2)		90.3990(10)		
β (º)	105.5040(10)	113.7810(10)	105.424(2)	113.582(3)	102.583(4)
γ (º)	113.5420(10)		98.5010(10)		
Volume	2129.4(3) $Å^3$	3570.8(4) $Å^3$	2178.7(3) $Å^3$	3718.6(9) $Å^3$	5361.4(13) $Å^3$
Z	2	4	2	4	4
Calculated density	1.584 mg/m^3	1.624 mg/m^3	1.602 mg/m^3	1.615 mg/m^3	1.251 mg/m^3
Goodness-of-fit on F^2	0.843	1.157	0.909	1.142	0.986
Final R indices	R1 = 0.0470	R1 = 0.0709	R1 = 0.0548	R1 = 0.0794	R1 = 0.0940
[I>2sigma(I)]	wR2 = 0.0900	wR2 = 0.2024	wR2 = 0.1358	wR2 = 0.2022	wR2 = 0.2117
R indices (all data)	R1 = 0.0953 wR2 = 0.0998	R1 = 0.1024 wR2 = 0.2102	R1 = 0.0916 wR2 = 0.1539	R1 = 0.1219 wR2 = 0.2156	R1 = 0.1949 wR2 = 0.2483

[a] A molecule of CH_2Cl_2 cocrystallized with **16**.
[b] A molecule of $CHCl_3$ cocrystallized with **20**.

Preparation of *trans*-Bromo[3-bromo-5-(methoxycarbonyl)thien-2-yl]bis(triphenylphosphine)palladium(II) (16). $Pd(PPh_3)_4$ (0.19 g, 0.17 mmol), methyl 4,5-dibromothiophene-2-carboxylate **5a** (0.05 g, 0.17 mmol), toluene (2 mL). Yield: 0.12 g (76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H, CO_2CH_3), 6.80 (s, 1H, H4), 7.2-7.3 (m, 12H, PPh_3), 7.3-7.4 (m, 6H, PPh_3), 7.6-7.7 (m, 12H, PPh_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.03 ppm. Anal. Calcd. for $C_{42}H_{34}Br_2O_2P_2PdS$: C, 54.19; H, 3.68; S, 3.44. Found: C, 54.29; H, 3.77; S, 3.06. Selected bond distances and angles for **16** are given in Table 3.

Preparation of *trans*-Bromo(4-bromothien-2-yl)bis(triphenylphosphine)palladium(II) (17). $Pd(PPh_3)_4$ (0.05 g, 0.04 mmol), 2,4-dibromothiophene **12** (0.01 g, 0.04 mmol), toluene (0.8 mL). Yield: 0.03 g (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (d, J = 0.9 Hz, 1H, ArH), 6.61 (s, 1H, ArH), 7.2-7.4 (m, 18H, PPh_3), 7.5-7.6 (m, 12H, PPh_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.60 ppm. Selected bond distances and angles for **17** are given in Table 3.[4]

Preparation of *trans*-Bromo[4-bromo-5-(ethoxycarbonyl)thien-2-yl]bis(triphenylphosphine)palladium(II) (18). $Pd(PPh_3)_4$ (0.18 g, 0.16 mmol), ethyl 3,5-dibromothiophene-2-carboxylate **5b** (0.05 g, 0.16 mmol), toluene (2 mL). Yield: 0.12 g (80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 4.14 (q, J = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 5.85 (s, 1H, H3), 7.3-7.4 (m, 18H, PPh_3), 7.5-7.6 (m, 12H, PPh_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.90 ppm. Anal. Calcd. for $C_{43}H_{36}Br_2O_2P_2PdS$: C, 54.65; H, 3.84; S, 3.39. Found: C, 54.31; H, 3.66; S, 3.46.

Preparation of *trans*-Bromo[4-bromo-5-(hydroxymethyl)thien-2-yl]bis(triphenylphosphine)palladium(II) (19). $Pd(PPh_3)_4$ (0.33 g, 0.28 mmol), (3,5-dibromothien-2-yl)methanol **13** (0.08 g, 0.28 mmol), toluene (3 mL). Yield: 0.16 g (62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (s, 2H, $C\underline{H}_2OH$), 5.71 (s, 1H, H3), 7.2-7.3 (m, 12H, PPh_3), 7.3-7.4 (m, 6H, PPh_3), 7.5-7.6 (m, 12H, PPh_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.82 ppm. Anal. Calcd. for $C_{41}H_{34}Br_2OP_2PdS$: C, 54.54; H, 3.80; S, 3.55. Found: C, 54.57; H, 4.05; S, 3.22.

Preparation of *trans*-Bromo[4-bromo-5-(methoxycarbonyl)thiazol-2-yl]bis(triphenylphosphine)palladium(II) (20). $Pd(PPh_3)_4$ (0.11 g, 0.10 mmol), methyl 2,4-dibromothiazole-5-carboxylate **14** (0.03 g, 0.10 mmol), toluene (1 mL). Yield: 0.07 g (80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 3H, CO_2CH_3), 7.3-7.4 (m, 18H, PPh_3), 7.6-7.7 (m, 12H, PPh_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.28 ppm. Anal. Calcd. for

[4] **17** and **21** crystallize in the monoclinic system. Systematic absences in the intensity data indicated space groups C2/c or Cc. The space group C2/c was eventually confirmed by the successful data solution and refinement. The asymmetric unit contains half of the molecule located on a two-fold rotational axis (e position in the Wyckoff notation). Pd and Br are on the two-fold axis. The molecule is consequently disordered about the two-fold axis such that ring atoms are interchanged [S, C(2), C(3) and C(4) for **17**; S, N, C(2) and C(3) for **21**]. Occupancies for these atoms were initially refined and yielded values near the expected 0.5. Subsequently these occupancies were fixed at 0.5 for the final refinement cycles. Refinement in Cc with the two-fold axis removed resulted in the same ring disorder with one complete molecule per asymmetric unit, therefore the higher space group C2/c was retained. Careful examination of the intensity data showed no evidence of a larger unit cell which might resolve the disorder.

$C_{41}H_{33}Br_2NO_2P_2PdS$: C, 52.84; H, 3.57; N, 1.50; S, 3.44. Found: C, 52.89; H, 3.50; N, 1.52; S, 3.25. Selected bond distances and angles for **20** are given in Table 3.

Preparation of *trans*-Bromo[4-bromo-5-(hydroxymethyl)thiazol-2-yl]bis(triphenylphosphine)palladium(II) (21). $Pd(PPh_3)_4$ (0.21 g, 0.18 mmol), (2,4-dibromothiazol-5-yl)methanol **15** (0.05 g, 0.18 mmol), toluene (2 mL). Yield: 0.15 g (91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (d, *J* = 5.7 Hz, 2H, C<u>H</u>$_2$OH), 5.30 (s, 1H, OH), 7.3-7.4 (m, 18H, PPh_3), 7.6-7.7 (m, 12H, PPh_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.80 ppm. Anal. Calcd. for $C_{40}H_{33}Br_2NOP_2PdS$: C, 53.15; H, 3.68; N, 1.55; S, 3.55. Found: C, 53.17; H, 3.60; N, 1.62; S, 3.46. Selected bond distances and angles for **21** are given in Table 3.[4]

Preparation of *trans*-Bromo[5-(4-trifluoromethylphenyl)-2-(ethoxycarbonyl)thien-3-yl]bis(triphenylphosphine)palladium(II) (22). $Pd(PPh_3)_4$ (0.09 g, 0.08 mmol), ethyl 3-bromo-5-(4-trifluoromethylphenyl)thiophene-2-carboxylate **7b** (0.03 g, 0.08 mmol), toluene (1 mL). Yield: 0.07 g (88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.1 Hz, 3H, CO_2CH_2C<u>H</u>$_3$), 4.07 (q, *J* = 7.1 Hz, 2H, CO_2C<u>H</u>$_2CH_3$), 6.70 (s, 1H, H4), 7.2-7.4 (m, 18H, ArH), 7.50 (d, *J* = 8.4 Hz, 2H, ArH), 7.6-7.7 (m, 14H, ArH) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.80 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.76 ppm. Anal. Calcd. for $C_{50}H_{40}BrF_3O_2P_2PdS$: C, 59.45; H, 3.99; S, 3.17. Found: C, 59.59; H, 3.95; S, 2.96. Selected bond distances and angles for **22** are given in Table 3. **22** presents disorder in the CF_3 group which was modelled by refinement of the fluorine atoms in two alternative positions. Final refinement cycles showed occupancy factors of 46 and 54%.

Table 3. Selected Intramolecular Bond Distances (Å) and Angles (°) for **16**, **17**, **20**, **21** and **22**

	16	**17**	**20**	**21**	**22**
Pd-C1	2.029(5)	2.03(2)	1.979(6)	1.979(12)	1.960(9)
Pd-P1	2.3341(12)	2.323(2)	2.3321(15)	2.347(2)	2.315(3)
Pd-P2	2.3430(12)		2.3341(15)		2.337(3)
Pd-Br2	2.4867(7)	2.5068(18)	2.4886(8)	2.5123(18)	2.5084(14)
S-C1	1.709(5)	1.54(2)	1.737(7)	1.770(7)	
C1-C2	1.351(7)	1.490(19)			1.463(14)
C1-C4					1.378(14)
N-C1			1.328(7)	1.288(19)	
Br1-C2	1.919(5)		1.882(6)	1.87(2)	
Br1-C3		1.90(2)			
C1-Pd-P1	89.34(12)	88.1(5)	89.65(17)	89.74(7)	89.7(3)
C1-Pd-P2/P1^i	89.05(13)	91.5(5)	88.25(17)	89.74(7)	88.6(3)
P1-Pd-P2/P1^i	177.97(5)	179.6(13)	176.55(6)	179.48(13)	176.73(12)
C1-Pd-Br2	173.89(13)	166.8(4)	172.06(19)	180.000(1)	170.5(3)
P1-Pd-Br2	91.06(4)	90.21(7)	89.85(4)	90.26(7)	91.02(8)
P2/P1^i-Pd-Br2	90.68(4)	90.21(7)	92.60(5)	90.26(7)	91.08(8)

Symmetry code, i: –x+1, y, -z+1/2 in **17** and –x, y, -z+3/2 in **21**

Preparation of 2-Chloromethyl-3-methyl-5-(4-trifluoromethylphenyl)thiophene (26b). According to the general procedure for the preparation of chlorides from alcohols, a solution of [3-methyl-5-(4-trifluoromethylphenyl)thiophen-2-yl]methanol **11b** (0.20 g, 0.76 mmol) and Et_3N (0.40 mL, 3.00 mmol) in CH_2Cl_2 (7.5 mL) was treated with methanesulfonyl chloride (0.20 mL, 3.00 mmol) for 2 h at 0 ºC, followed by 16 h at 25 ºC, to afford 0.19 g (90%) of chloride **26b** as a yellow oil, which was used in the next step without further purification, due to its instability. A small sample was purified by column chromatography (SiO_2, 95:3:2 hexane/AcOEt/Et_3N) for characterization purposes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H, C3-CH_3), 4.76 (s, 2H, CH_2Cl), 7.11 (s, 1H, H4), 7.61 (d, *J* = 8.6 Hz, 2H, ArH), 7.63 (d, *J* = 8.6 Hz, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (q, C3-$\underline{C}H_3$), 38.7 (t, CH_2Cl), 124.1 (s, CF_3, $^1J_{C\text{-}F}$ = 272.0 Hz), 125.6 (d, 2x, C2' + C6'), 125.9 (d, 2x, C3' + C5', $^3J_{C\text{-}F}$ = 4.0 Hz), 127.5 (d, C4), 129.4 (s, C4', $^2J_{C\text{-}F}$ = 32.6 Hz), 133.8 (s), 137.2 (s), 138.5 (s), 141.5 (s) ppm. IR (NaCl) ν 3020 (w, C-H), 2926 (w, C-H), 2861 (w, C-H), 1614 (m), 1411 (w), 1325 (s), 1167 (s), 1123 (s), 1067 (m), 1015 (w), 831 (m), 761 (m) cm^{-1}. MS *m/z* (%) 292 (M^+ [^{37}Cl], 2), 290 (M^+ [^{35}Cl], 5), 270 (36), 269 (64), 256 (17), 255 ([M-Cl]$^+$, 100), 254 (62), 197 (17), 184 (17), 128 (12). HRMS (EI$^+$) calcd for $C_{13}H_{10}{}^{35}ClF_3S$ 290.0144 and $C_{13}H_{10}{}^{37}ClF_3S$ 292.0114, found 290.0156 and 292.0111.

Preparation of Methyl (2-Methyl-4-[3-methyl-5-(4-trifluoromethylphenyl)thien-2-ylmethylthio]phenoxy)acetate (29b). In accordance to the general procedure for the nucleophilic displacement of chlorides by thiols, chloride **26b** (0.09 g, 0.32 mmol) was reacted with Cs_2CO_3 (0.23 g, 0.70 mmol) and methyl (4-mercapto-2-methylphenoxy)acetate **27** (0.09 g, 0.42 mmol) in CH_3CN (3 mL) for 2 h at 25 ºC to afford, after purification by chromatography (SiO_2, 87:10:3 hexane/AcOEt/Et_3N), 0.12 g (77%) of thiophene **29a** as a yellow solid (mp 86 ºC, hexane/AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 3H, Ar-CH_3), 2.24 (s, 3H, Ar-CH_3), 3.79 (s, 3H, CO_2CH_3), 4.11 (s, 2H, CH_2S), 4.64 (s, 2H, 2H2), 6.60 (d, *J* = 8.4 Hz, 1H, H6'), 7.04 (s, 1H, H4''), 7.17 (dd, *J* = 8.4, 2.0 Hz, 1H, H5'), 7.21 (br s, 1H, H3'), 7.58 (d, *J* = 8.6 Hz, 2H, ArH), 7.61 (d, *J* = 8.6 Hz, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (q, Ar-CH_3), 16.1 (q, Ar-CH_3), 33.9 (t, CH_2S), 52.2 (q, $CO_2\underline{C}H_3$), 65.5 (t, C2), 111.5 (d, C6'), 124.1 (s, CF_3, $^1J_{C\text{-}F}$ = 271.7 Hz), 125.4 (d, 2x, C2''' + C6'''), 125.8 (d, 2x, C3''' + C5''', $^3J_{C\text{-}F}$ = 3.7 Hz), 126.2 (s), 127.1 (d, C4''), 128.2 (s), 128.9 (s, C4''', $^2J_{C\text{-}F}$ = 32.6 Hz), 131.7 (d, C5'), 135.6 (s), 135.8 (d, C3'), 136.4 (s), 137.7 (s), 139.5 (s), 156.1 (s), 169.3 (s, C1) ppm. IR (NaCl) ν 2954 (w, C-H), 1763 (s, C=O), 1614 (m), 1489 (s), 1438 (w), 1325 (s), 1121 (m), 1166 (m), 1119 (s), 1068 (s), 831 (m) cm^{-1}. MS *m/z* (%) 466 (M^+, 1), 256 (84), 255 ([M-$C_{10}H_{11}O_3S$]$^+$, 100), 254 (26), 211 (30), 189 (14), 153 (22), 152 (14), 139 (13), 73 (31). HRMS (EI$^+$) calcd for $C_{23}H_{21}F_3O_3S_2$ 466.0884, found 466.0880.

Preparation of 4-Hydroxyphenyl Disulfide. After heating a solution of 4-hydroxybenzenethiol (0.20 g, 1.60 mmol) in DMSO (2.3 mL) to 65 ºC for 4 h, the mixture was allowed to cool down to 25 °C and the solvent was distilled using a Kugelrohr (10 mmHg, 65 ºC). Purification of the residue by chromatography on silica gel using hexane/AcOEt (70:30) as eluent afforded 4-hydroxyphenyl disulfide (0.19 g, 95%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.92 (s, 2H), 6.74 (d, *J* = 8.1 Hz, 4H), 7.27 (d, *J* = 8.1 Hz, 4H) ppm. All other analytical data are in agreement whith those reported in the literature: McMorris, T. C.; Yu, J. *Tetrahedron* **1997**, *53*, 14579-14590.

Preparation of Methyl [4-(4-[Methoxycarbonylmethoxy]phenyldithio)phenoxy]acetate. NaH (0.07 g, 1.70 mmol) was added in small portions to a solution of 4-hydroxyphenyl disulfide (0.19 g, 0.76 mmol) in DMF (4 mL) under argon at 0 ºC. The mixture was stirred at 25 ºC for 2 h and then cooled down to 0 ºC. Methyl bromoacetate (0.16 mL, 1.67 mmol) was added and the solution was stirred at 25 ºC for 4 h. After the addition of water, the mixture was extracted with AcOEt (2x). The organic extracts were dried (Na_2SO_4), and the solvent was evaporated. Purification of the residue by chromatography (SiO_2, 70:30 hexane/AcOEt) yielded 0.25 g (82%) of methyl **[**4-(4-[methoxycarbonylmethoxy]phenyldithio)phenoxy]acetate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 6H, 2x, CO_2CH_3), 4.61 (s, 4H, 2x, $C\underline{H}_2CO_2Me$), 6.83 (d, *J* = 8.9 Hz, 4H, ArH), 7.39 (d, *J* = 8.9 Hz, 4H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2 (q, 2x, $CO_2\underline{C}H_3$), 65.2 (t, 2x, $\underline{C}H_2CO_2Me$), 115.3 (d, 4x, ArCH), 129.6 (s, 2x, ArC), 131.9 (d, 4x, ArCH), 157.9 (s, 2x, ArC), 168.9 (s, 2x, CO_2Me) ppm. IR (NaCl) ν 2953 (w, C-H), 1760 (s, C=O), 1590 (s), 1490 (s), 1437 (m), 1292 (m), 1210 (s), 1175 (s), 1076 (m), 826 (m) cm^{-1}. MS *m/z* (%) 396 ([M+2]$^+$, 11), 395 ([M+1]$^+$, 19), 394 (M$^+$, 89), 198 (15), 197 (100), 86 (34), 84 (52), 73 (32). HRMS (EI$^+$) calcd for $C_{18}H_{18}O_6S_2$ 394.0545, found 394.0538.

Preparation of Methyl (4-Mercaptophenoxy)acetate (28). 10% HCl (20 mL) was added to a solution of methyl [4-(4-[methoxycarbonylmethoxy]phenyldithio)phenoxy]acetate (0.20 g, 0.51 mmol) and Zn (1.20 g, 18.20 mmol) in CH_2Cl_2 (50 mL). After stirring the solution at 25 ºC for 2 h, the layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (2x). The organic extracts were dried (Na_2SO_4) and the solvent was evaporated. Purification of the residue by column chromatography (SiO_2, 75:25 hexane/AcOEt) afforded 0.17 g (85%) of methyl (4-mercaptophenoxy)acetate **28**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (s, 1H, SH), 3.79 (s, 3H, CO_2CH_3), 4.59 (s, 2H, 2H2), 6.79 (d, *J* = 8.7 Hz, 2H, H2' + H6'), 7.24 (d, *J* = 8.7 Hz, 2H, H3' + H5') ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2 (q, $CO_2\underline{C}H_3$), 65.3 (t, C2), 115.4 (d, 2x, C2' + C6'), 121.6 (s, C4'), 132.1 (d, 2x, C3' + C5'), 156.5 (s, C1'), 169.1 (s, CO_2Me) ppm. IR (NaCl) ν 2953 (w, C-H), 2564 (w, S-H), 1759 (s, C=O), 1594 (m), 1492 (s), 1437 (m), 1293 (m), 1207 (s), 1177 (s), 1080 (s), 821 (m) cm^{-1}. MS *m/z* (%) 200 ([M+2]$^+$, 12), 199 ([M+1]$^+$, 25), 198 (M$^+$, 100), 139 (51), 125 (76), 109 (49), 97 (28), 69 (22), 65 (22). HRMS (EI$^+$) calcd for $C_9H_{10}O_3S$ 198.0351, found 198.0347.

Preparation of Methyl (4-[4-Methyl-5-(4-trifluoromethylphenyl)thien-2-ylmethylthio]phenoxy)acetate (30a). In accordance to the general procedure for the nucleophilic displacement of chlorides by thiols, chloride **26a** (0.02 g, 0.09 mmol) was reacted with Cs_2CO_3 (0.06 g, 0.02 mmol) and methyl (4-mercaptophenoxy)acetate **28** (0.02 g, 0.1 mmol) in CH_3CN (0.5 mL) for 3 h at 25 ºC to afford, after purification by chromatography (SiO_2, 80:20 hexane/AcOEt), 0.02 g (67%) of thiophene **30a** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H, C4''-CH_3), 3.80 (s, 3H, CO_2CH_3), 4.16 (s, 2H, SCH_2), 4.62 (s, 2H, 2H2), 6.65 (s, 1H, H3''), 6.84 (m, 2H, ArH), 7.36 (m, 2H, ArH), 7.52 (d, *J* = 8.2 Hz, 2H, H2''' + H6'''), 7.63 (d, *J* = 8.2 Hz, 2H, H3''' + H5''') ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0 (q, C4''-$\underline{C}H_3$), 35.4 (t, CH_2S), 52.2 (q, $CO_2\underline{C}H_3$), 65.2 (t, C2), 115.2 (d, 2x, ArCH), 124.1 (s, CF_3, $^1J_{C\text{-}F}$ = 271.7 Hz), 125.3 (d, 2x, C3''' + C5''', $^3J_{C\text{-}F}$ = 3.7 Hz), 127.2 (s), 128.7 (d, 2x, C2''' + C6'''), 128.8 (s, C4''', $^2J_{C\text{-}F}$ = 32.4 Hz), 130.6 (d, C3''), 133.8 (d, 2x, ArCH), 133.9 (s), 135.4 (s), 138.2 (s), 140.2 (s), 157.4 (s), 169.0 (s, C1) ppm. IR (NaCl) ν

2954 (m, C-H), 2923 (s, C-H), 2853 (m, C-H), 1759 (s, C=O), 1612 (m), 1591 (m), 1491 (s), 1439 (s), 1407 (m), 1379 (w), 1322 (s), 1204 (s), 1166 (s), 1111 (s), 1067 (s), 1014 (m), 825 (s) cm^{-1}. MS *m/z* (%) 452 (M^+, 12), 257 (9), 256 (27), 255 ([M-$C_9H_9O_3S$]$^+$, 100). HRMS (EI$^+$) calcd for $C_{22}H_{19}F_3O_3S_2$ 452.0728, found 452.0710.

Preparation of Methyl (4-[3-Methyl-5-(4-trifluoromethylphenyl)thien-2-ylmethylthio]phenoxy)acetate (30b). In accordance to the general procedure for the nucleophilic displacement of chlorides by thiols, chloride **26b** (0.07 g, 0.28 mmol) was reacted with Cs_2CO_3 (0.18 g, 0.56 mmol) and methyl (4-mercaptophenoxy)acetate **28** (0.06 g, 0.26 mmol) in CH_3CN (3 mL) for 2 h at 25 ºC to afford, after purification by chromatography (SiO_2, 87:10:3 hexane/AcOEt/Et_3N), 0.09 g (80%) of thiophene **30b** as a yellow solid (mp 83 ºC, hexane/AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (s, 3H, C3''-CH_3), 3.79 (s, 3H, CO_2CH_3), 4.11 (s, 2H, CH_2S), 4.62 (s, 2H, 2H2), 6.82 (d, *J* = 8.6 Hz, 2H, H2' + H6'), 7.03 (s, 1H, H4''), 7.33 (d, *J* = 8.6 Hz, 2H, H3' + H5'), 7.58 (d, *J* = 8.7 Hz, 2H, ArH), 7.60 (d, *J* = 8.7 Hz, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5 (q, C3''-$\underline{C}H_3$), 33.9 (t, CH_2S), 52.2 (q, $CO_2\underline{C}H_3$), 65.2 (t, C2), 115.2 (d, 2x, C2' + C6'), 124.1 (s, CF_3, $^1J_{C\text{-}F}$ = 271.7 Hz), 125.4 (d, 2x, C2''' + C6'''), 125.8 (d, 2x, C3''' + C5''', $^3J_{C\text{-}F}$ = 4.0 Hz), 126.7 (s), 127.1 (d, C4''), 128.9 (s, C4''', $^2J_{C\text{-}F}$ = 32.5 Hz), 134.8 (d, 2x, C3' + C5'), 135.5 (s), 136.4 (s), 137.6 (s), 139.5 (s), 157.8 (s), 169.0 (s, C1) ppm. IR (NaCl) ν 2954 (w, C-H), 1762 (s, C=O), 1614 (m), 1592 (m), 1492 (s), 1326 (s), 1209 (s), 1172 (s), 1114 (s), 1068 (s), 829 (s) cm^{-1}. MS *m/z* (%) 452 (M^+, 0.3), 270 (57), 269 (70), 256 (23), 255 ([M-$C_9H_9O_3S$]$^+$, 100), 254 (20), 197 (20). HRMS (EI$^+$) calcd for $C_{22}H_{19}F_3O_3S_2$ 452.0728, found 452.0727. Anal. Calcd for $C_{22}H_{19}F_3O_3S_2$: C, 58.39; H, 4.23; S, 14.17. Found: C, 58.30; H, 4.30; S, 13.74.

Preparation of (2-Methyl-4-[3-methyl-5-(4-trifluoromethylphenyl)thien-2-ylmethylthio]phenoxy)acetic Acid (3b). According to the general procedure for the hydrolysis of esters, a solution of methyl ester **29b** (0.05 g, 0.11 mmol) in MeOH (1.0 mL) was treated with 3 M K_2CO_3 (0.40 mL) at 80 ºC for 1 h, to afford, after purification by recrystallization (hexane/AcOEt), 0.04 g (88%) of acid **3b** as a yellow solid (mp 145 ºC, hexane/$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 3H, Ar-CH_3), 2.23 (s, 3H, Ar-CH_3), 4.11 (s, 2H, CH_2S), 4.68 (s, 2H, 2H2), 6.63 (d, *J* = 8.4 Hz, 1H, H6'), 7.04 (s, 1H, H4''), 7.18 (dd, *J* = 8.4, 2.1 Hz, 1H, H5'), 7.21 (br s, 1H, H3'), 7.58 (d, *J* = 8.8 Hz, 2H, ArH), 7.60 (d, *J* = 8.8 Hz, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (q, Ar-CH_3), 16.0 (q, Ar-CH_3), 33.8 (t, CH_2S), 65.0 (t, C2), 111.5 (d, C6'), 124.1 (s, CF_3, $^1J_{C\text{-}F}$ = 271.9 Hz), 125.4 (d, 2x, C2''' + C6'''), 125.8 (d, 2x, C3''' + C5'''), $^3J_{C\text{-}F}$ = 3.7 Hz), 126.7 (s), 127.1 (d, C4''), 128.1 (s), 128.9 (s, C4''', $^2J_{C\text{-}F}$ = 32.4 Hz), 131.6 (d, C5'), 135.6 (s), 135.8 (d, C3'), 136.4 (s), 137.7 (s), 139.5 (s), 155.6 (s), 173.4 (s, C1) ppm. IR (NaCl) ν 3500-3000 (br, O-H), 2922 (w, C-H), 1736 (m, C=O), 1614 (m), 1490 (m), 1325 (s), 1229 (m), 1122 (m), 1068 (m), 830 (w) cm^{-1}. MS *m/z* (%) 453 ([M+1]$^+$, 2), 452 (M^+, 13), 257 (32), 256 ([M-$C_9H_9O_3S$]$^+$, 100), 241 (13), 139 (19), 95 (11), 83 (11). HRMS (EI$^+$) calcd for $C_{22}H_{19}F_3O_3S_2$ 452.0728, found 452.0733.

Preparation of (4-[4-Methyl-5-(4-trifluoromethylphenyl)thien-2-ylmethylthio]phenoxy)acetic Acid (4a). According to the general procedure for the hydrolysis of esters, a solution of **30a** (0.08 g, 0.18 mmol) in MeOH (2 mL) was treated with 3 M K_2CO_3 (0.6 mL, 1.8 mmol) at 80 °C for 1.5 h, to afford, after purification by

recrystallization (hexane/TBME), 0.07 g (89%) of acid **4a** as a white solid (mp 131 ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H, C4''-CH_3), 4.17 (s, 2H, SCH_2), 4.65 (br s, 2H, 2H2), 6.66 (s, 1H, H3''), 6.86 (d, *J* = 8.2 Hz, 2H, ArH), 7.37 (d, *J* = 8.2 Hz, 2H, ArH), 7.52 (d, *J* = 8.1 Hz, 2H, H2''' + H6'''), 7.63 (d, *J* = 8.1 Hz, 2H, H3''' + H5''') ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2 (q, C4''-$\underline{C}H_3$), 36.2 (t, CH_2S), 66.3 (t, C2), 117.1 (d, 2x, ArCH), 126.3 (s, CF_3, $^{1}J_{C\text{-}F}$ = 271.7 Hz), 127.3 (d, 2x, C3''' + C5''', $^{3}J_{C\text{-}F}$ = 4.0 Hz), 128.4 (s), 130.0 (s, C4''', $^{2}J_{C\text{-}F}$ = 32.2 Hz), 130.7 (d, 2x, C2''' + C6'''), 132.8 (d, C3''), 135.1 (d, 2x, ArCH), 136.0 (s), 136.6 (s), 140.5 (s), 142.9 (s), 159.7 (s), 171.0 (s, C1) ppm. IR (NaCl) ν 3200-2600 (br, O-H), 2923 (w, C-H), 1702 (s, C=O), 1611 (w), 1493 (m), 1321 (s), 1234 (s), 1179 (m), 1124 (s), 837 (s), 772 (s) cm^{-1}. MS *m/z* (%) 438 (M^+, 2), 257 (5), 256 (17), 255 ([M-$C_8H_7O_3S$]$^+$, 100), 185 (2), 153 (2), 125 (3). HRMS (EI$^+$) calcd for $C_{21}H_{17}F_3O_3S_2$ 438.0571, found 438.0565. Anal. Calcd for $C_{21}H_{17}F_3O_3S_2$: C, 57.52; H, 3.91; S, 14.63. Found: C, 57.36; H, 3.83; S, 14.20.

Preparation of (4-[3-Methyl-5-(4-trifluoromethylphenyl)thien-2-ylmethylthio]phenoxy)acetic Acid (4b). According to the general procedure for the hydrolysis of esters, a solution of **30b** (0.05 g, 0.11 mmol) in MeOH (1 mL) was treated with 3 M K_2CO_3 (0.40 mL) at 80 °C for 1 h, to afford, after purification by recrystallization (hexane/$CHCl_3$), 0.04 g (91%) of acid **4b** as a yellow solid (mp 131 ºC). ^{1}H NMR (400 MHz, CD_3COCD_3) δ 2.01 (s, 3H, C3''-CH_3), 4.11 (s, 2H, CH_2S), 4.66 (s, 2H, 2H2), 6.84 (d, *J* = 8.5 Hz, 2H, H2' + H6'), 7.04 (s, 1H, H4''), 7.35 (d, *J* = 8.5 Hz, 2H, H3' + H5'), 7.58 (d, *J* = 8.7 Hz, 2H, H3''' + H5'''), 7.60 (d, *J* = 8.7 Hz, 2H, H2''' + H6''') ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (q, C3''-$\underline{C}H_3$), 33.9 (t, CH_2S), 64.7 (t, C2), 115.2 (d, 2x, C2' + C6'), 124.1 (s, CF_3, $^{1}J_{C\text{-}F}$ = 271.4 Hz), 125.4 (d, 2x, C2''' + C6'''), 125.8 (d, 2x, C3''' + C5''', $^{3}J_{C\text{-}F}$ = 3.7 Hz), 127.1 (d, C4''), 127.3 (s), 128.9 (s, C4''', $^{2}J_{C\text{-}F}$ = 32.4 Hz), 134.8 (d, 2x, C3' + C5'), 135.5 (s), 136.4 (s), 137.6 (s), 139.6 (s), 157.3 (s), 172.2 (s, C1) ppm. IR (NaCl) ν 3300-2500 (br, O-H), 2922 (m, C-H), 1727 (s, C=O), 1614 (m), 1591 (m), 1491 (s), 1430 (w), 1326 (s), 1240 (s), 1165 (s), 1110 (s), 1068 (s), 1013 (w), 827 (s) cm^{-1}. MS *m/z* (%) 439 ([M+1]$^+$, 3), 438 (M^+, 11), 257 (35), 256 ([M-$C_8H_7O_3S$]$^+$, 100), 241 (15), 189 (8), 183 (9), 125 (18). HRMS (EI$^+$) calcd for $C_{21}H_{17}F_3O_3S_2$ 438.0571, found 438.0569.

Preparation of 4-Bromo-2-(4-trifluoromethylphenyl)thiophene. In accordance to the procedure for the Suzuki coupling, the reaction of boronate **6** with 2,4-dibromothiophene **12** (0.06 g, 0.25 mmol), in the presence of $Pd(PPh_3)_4$ (0.01 g, 0.01 mmol) and K_2CO_3 (3 M in H_2O, 0.14 mL, 0.36 mmol) in toluene (2 mL), for 15 h at 100 ºC afforded, after purification by chromatography (SiO_2, hexane), 0.03 g (50%) of 4-bromo-2-(4-trifluoromethylphenyl)thiophene as a colourless oil and 0.007 g (7%) of 2,4-bis(4-trifluoromethylphenyl)thiophene as a white solid. *Spectroscopic data for 4-bromo-2-(4-trifluoromethylphenyl)thiophene.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 2.4 Hz, 1H, H3 or H5), 7.29 (d, *J* = 2.4 Hz, 1H, H5 or H3), 7.65 (ap. s, 4H, H2' + H3' + H5' + H6') ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.9 (s, C4), 123.2 (d, C3 or C5), 123.8 (s, CF_3, $^{1}J_{C\text{-}F}$ = 272.0 Hz), 125.7 (d, 2x, C2' + C6'), 125.9 (d, 2x, C3' + C5', $^{3}J_{C\text{-}F}$ = 3.7 Hz), 126.9 (d, C5 or C3), 129.9 (s, C4', $^{2}J_{C\text{-}F}$ = 32.5 Hz), 136.3 (s), 143.4 (s) ppm. IR (NaCl) ν 2926 (s, C-H), 2854 (m, C-H), 1616 (m), 1501 (m), 1409 (w), 1324 (s), 1168 (s), 1127 (s), 1068 (s), 1017 (m), 823 (s) cm^{-1}. MS *m/z* (%) 309 ([M+1]$^+$ [^{81}Br], 13), 308 (M^+ [^{81}Br], 90), 307 ([M+1]$^+$ [^{79}Br], 10), 306

(M^+ [^{79}Br], 84), 228 (13), 189 (27), 184 (10), 183 (100), 182 (11), 158 (16), 133 (13), 129 (12), 128 (11), 74 (10). HRMS calcd. for $C_{11}H_6{}^{81}BrF_3S$ 307.9305 and $C_{11}H_6{}^{79}BrF_3S$ 305.9326; found 307.9308 and 305.9334. *Spectroscopic data for 2,4-bis(4-trifluoromethylphenyl)thiophene*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H, ArH), 7.6-7.8 (m, 9H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.4 (d), 123.3 (d), 124.0 (s, CF_3, $^1J_{C\text{-}F}$ = 271.9 Hz), 124.1 (s, CF_3, $^1J_{C\text{-}F}$ = 271.9 Hz), 125.9 (d, 2x, $^3J_{C\text{-}F}$ = 3.7 Hz), 125.9 (d, 2x), 126.0 (d, 2x, $^3J_{C\text{-}F}$ = 4.0 Hz), 126.5 (d, 2x), 129.7 (s, $^2J_{C\text{-}F}$ = 32.6 Hz), 129.7 (s, $^2J_{C\text{-}F}$ = 31.6 Hz), 137.3 (s), 138.8 (s), 141.9 (s), 143.9 (s) ppm. IR (NaCl) ν 2923 (s, C-H), 2853 (m, C-H), 1613 (w), 1463 (w), 1327 (m), 1167 (m), 1129 (m), 1070 (w), 827 (w) cm^{-1}. MS *m/z* (%) 373 ([M+1]$^+$, 15), 372 (M^+, 100), 353 (8), 327 (8), 302 (6), 234 (8), 207 (16), 191 (7), 189 (20), 186 (7). HRMS calcd. for $C_{18}H_{10}F_6S$ 372.0407; found 372.0419.

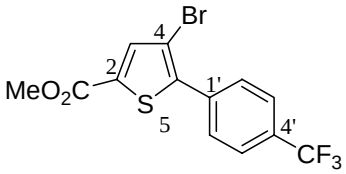
Preparation of [3-Bromo-5-(4-trifluoromethylphenyl)thien-2-yl]methanol. In accordance to the procedure for the Suzuki coupling, the reaction of boronate **6** with (3,5-dibromothien-2-yl)methanol **13** (0.05 g, 0.18 mmol), in the presence of $Pd(PPh_3)_4$ (0.01 g, 0.009 mmol) and K_2CO_3 (3 M in H_2O, 0.12 mL, 0.36 mmol) in toluene (1 mL), for 19 h at 100 ºC afforded, after purification by chromatography (SiO_2, 78:20:2 hexane/AcOEt/Et_3N), 0.04 g (68%) of the alcohol as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (br. s, 1H, OH), 4.82 (s, 2H, 2H1), 7.22 (s, 1H, H4'), 7.63 (ap. s, 4H, H2'' + H3'' + H5'' + H6'') ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.3 (t, C1), 109.6 (s, C3'), 123.9 (s, CF_3, $^1J_{C\text{-}F}$ = 272.0 Hz), 125.6 (d, 2x, C2'' + C6''), 126.1 (d, 2x, C3'' + C5'', $^3J_{C\text{-}F}$ = 3.7 Hz), 127.1 (d, C4'), 130.0 (s, C4'', $^2J_{C\text{-}F}$ = 32.5 Hz), 136.5 (s), 138.9 (s), 142.0 (s) ppm. IR (NaCl) ν 3500-3100 (br, O-H), 2923 (m, C-H), 1615 (w), 1325 (s), 1168 (m), 1125 (m), 1069 (m), 823 (m) cm^{-1}. MS *m/z* (%) 339 ([M+1]$^+$ [^{81}Br], 2), 338 (M^+ [^{81}Br], 23), 337 ([M+1]$^+$ [^{79}Br], 4), 336 (M^+ [^{79}Br], 29), 321 (54), 319 (58), 257 (28), 229 (100), 228 (24), 196 (18), 189 (61), 183 (14), 145 (10). HRMS calcd. for $C_{10}H_8{}^{81}BrF_3OS$ 337.9411 and $C_{10}H_8{}^{79}BrF_3OS$ 335.9431; found 337.9410 and 335.9433. Anal. Calcd. for $C_{10}H_8BrF_3OS$: C, 42.75; H, 2.39; S, 9.51. Found: C, 42.68; H, 2.30; S, 9.40.

Preparation of Methyl 4-Bromo-2-(4-trifluoromethylphenyl)thiazole-5-carboxylate. In accordance to the procedure for the Suzuki coupling, the reaction of boronate **6** with methyl 2,4-dibromothiazole-5-carboxylate **14** (0.08 g, 0.27 mmol), in the presence of $Pd(PPh_3)_4$ (0.015 g, 0.013 mmol) and K_2CO_3 (3 M in H_2O, 0.18 mL, 0.36 mmol) in toluene (1.5 mL), for 17 h at 80 ºC afforded, after purification by chromatography (SiO_2, 95:5 hexane/AcOEt), 0.09 g (92%) of the ester as a white solid (mp 144 ºC, hexane/AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3H, CO_2CH_3), 7.73 (d, *J* = 7.7 Hz, 2H, H3' + H5'), 8.08 (d, *J* = 7.7 Hz, 2H, H2' + H6') ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.8 (q, $CO_2\underline{C}H_3$), 123.5 (s, CF_3, $^1J_{C\text{-}F}$ = 272.4 Hz), 123.8 (s), 126.2 (d, 2x, C3' + C5', $^3J_{C\text{-}F}$ = 4.0 Hz), 127.0 (d, 2x, C2' + C6'), 132.9 (s), 133.3 (s, C4', $^2J_{C\text{-}F}$ = 32.7 Hz), 134.8 (s), 160.3 (s, C2), 169.5 (s, CO_2Me) ppm. IR (NaCl) ν 1727 (s, C=O), 1615 (w), 1483 (m), 1437 (m), 1318 (s), 1248 (s), 1159 (m), 1113 (s), 1066 (m), 1015 (w), 845 (m), 753 (w), 603 (w) cm^{-1}. MS *m/z* (%) 368 ([M+1]$^+$ [^{81}Br], 4), 367 (M^+ [^{81}Br], 47), 366 ([M+1]$^+$ [^{79}Br], 4), 365 (M^+ [^{79}Br], 49), 336 ([M-OCH_3]$^+$ [^{81}Br], 51), 334 ([M-OCH_3]$^+$ [^{79}Br], 50), 308 (18), 306 (17), 287 (16), 189 (19), 171 (31), 152 (22), 145 (22), 137 (99), 135 (100), 121 (25). HRMS calcd. for $C_{12}H_7{}^{81}BrF_3NO_2S$ 366.9313 and $C_{14}H_{10}{}^{79}BrF_3NO_2S$ 364.9333; found 366.9298 and 364.9315. Anal. Calcd. for

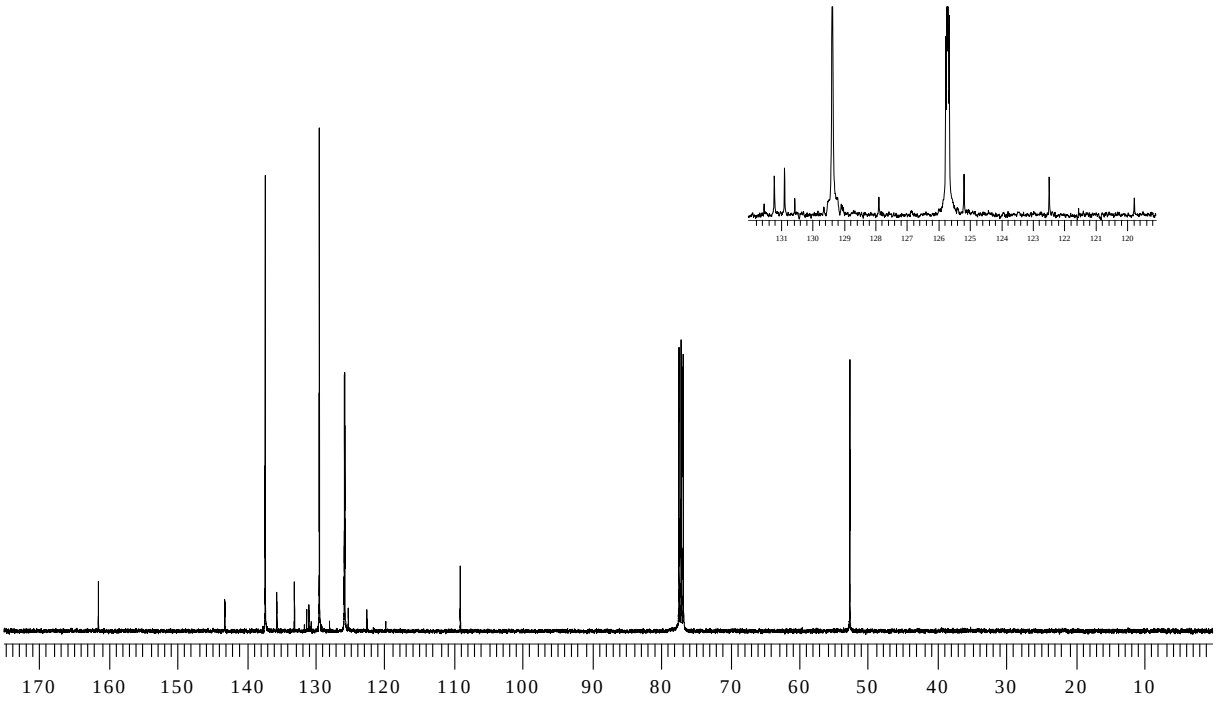
$C_{12}H_7BrF_3NO_2S$: C, 39.36; H, 1.93; S, 8.76; N, 3.83. Found: C, 39.52; H, 1.95; S, 8.43; N, 3.77.

Preparation of [4-Bromo-2-(4-trifluoromethylphenyl)thiazol-5-yl]methanol. In accordance to the procedure for the Suzuki coupling, the reaction of boronate **6** with (2,4-dibromothiazol-5-yl)methanol **15** (0.05 g, 0.18 mmol), in the presence of $Pd(PPh_3)_4$ (0.01 g, 0.009 mmol) and K_2CO_3 (3 M in H_2O, 0.12 mL, 0.36 mmol) in toluene (1 mL), for 19 h at 100 ºC afforded, after purification by chromatography (SiO_2, 78:20:2 hexane/AcOEt/Et_3N), 0.05 g (87%) of the alcohol as a yellow solid (mp 117 ºC, hexane/AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (d, *J* = 6.0 Hz, 2H, 2H1), 7.71 (d, *J* = 8.2 Hz, 2H, H3'' + H5''), 8.03 (d, *J* = 8.2 Hz, 2H, H2'' + H6'') ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.9 (t, C_1), 123.6 (s, CF_3, $^1J_{C\text{-}F}$ = 272.4 Hz), 124.5 (s), 125.9 (d, 2x, C3'' + C5'', $^3J_{C\text{-}F}$ = 3.7 Hz), 126.2 (d, 2x, C2'' + C6''), 132.1 (s, C4'', $^2J_{C\text{-}F}$ = 32.5 Hz), 134.6 (s), 135.4 (s), 165.8 (s, C2') ppm. IR (NaCl) ν 3500-3000 (br, O-H), 1616 (w), 1510 (w), 1440 (w), 1406 (w), 1329 (s), 1197 (m), 1112 (s), 1070 (s), 1047 (m), 994 (w), 835 (m) cm^{-1}. MS *m/z* (%) 339 (M^+ [^{81}Br], 7), 338 ($[M+1]^+$ [^{79}Br], 1), 377 (M^+ [^{79}Br], 8), 189 (100), 172 (9), 145 (12), 137 (11), 135 (9). HRMS calcd. for $C_{14}H_{10}{}^{81}BrF_3O_2S$ 338.9363 and $C_{14}H_{10}{}^{79}BrF_3O_2S$ 336.9384; found 338.9379 and 336.9381. Anal. Calcd. for $C_{14}H_{10}BrF_3O_2S$: C, 39.07; H, 2.09; S, 9.48; N, 4.14. Found: C, 39.15; H, 1.91; S, 9.36; N, 4.11.

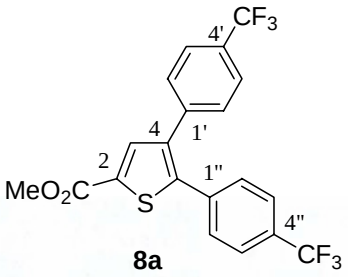
Methyl 4-Bromo-5-(4-trifluoromethylphenyl)thiophene-2-carboxylate (7a)



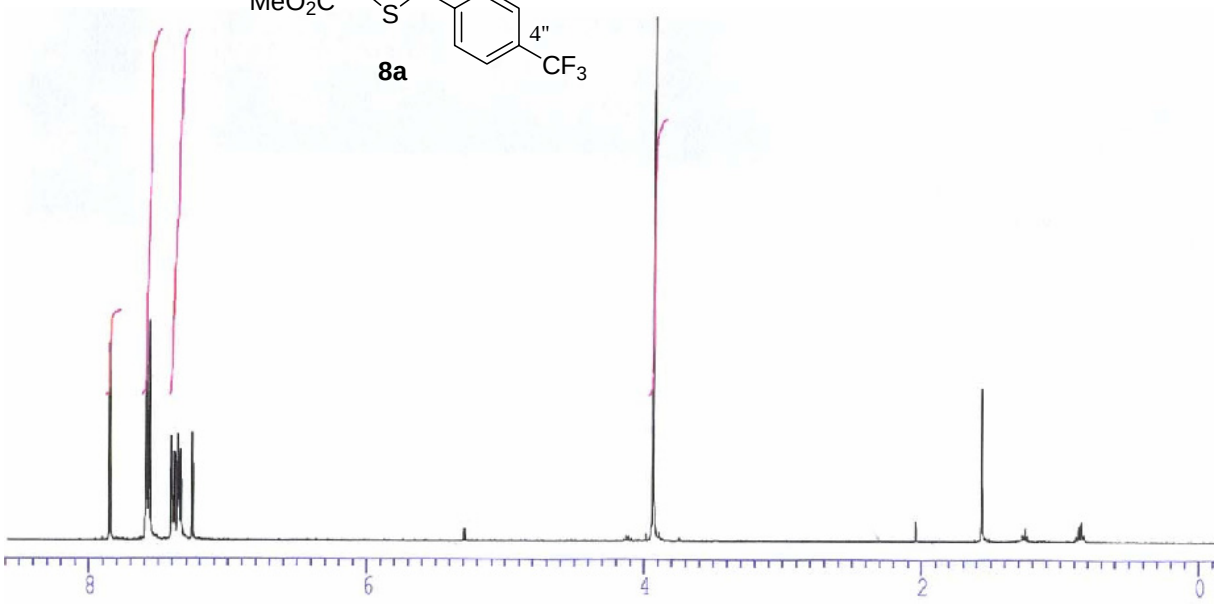
7a

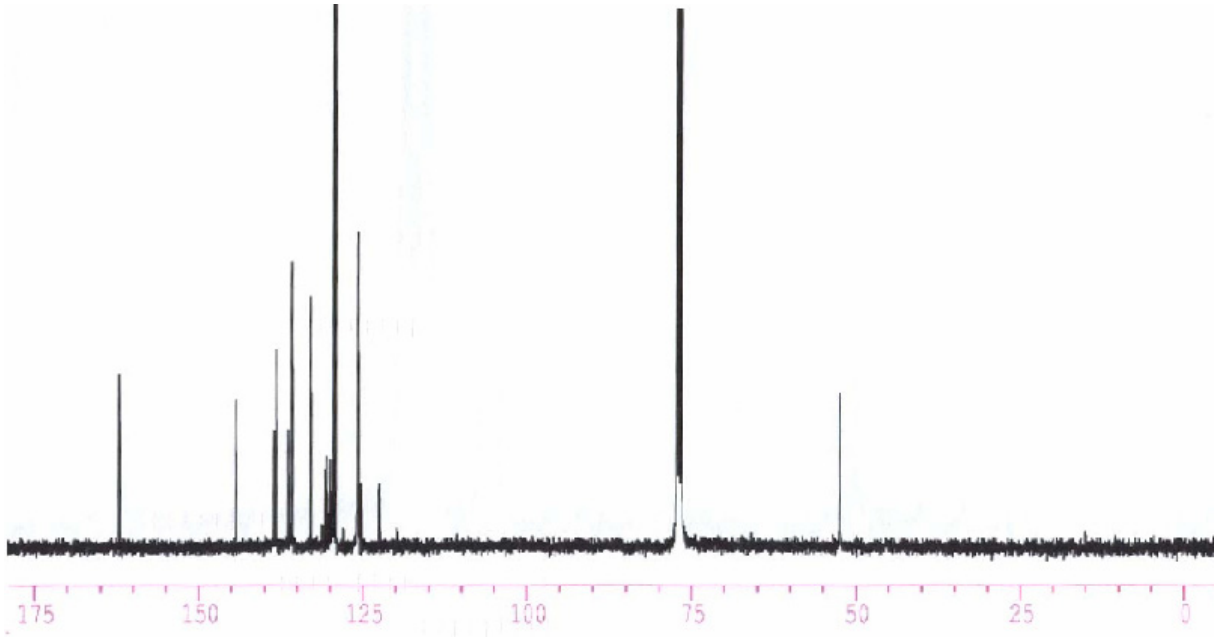


Methyl 4,5-Bis(4-trifluoromethylphenyl)thiophene-2-carboxylate (8a)

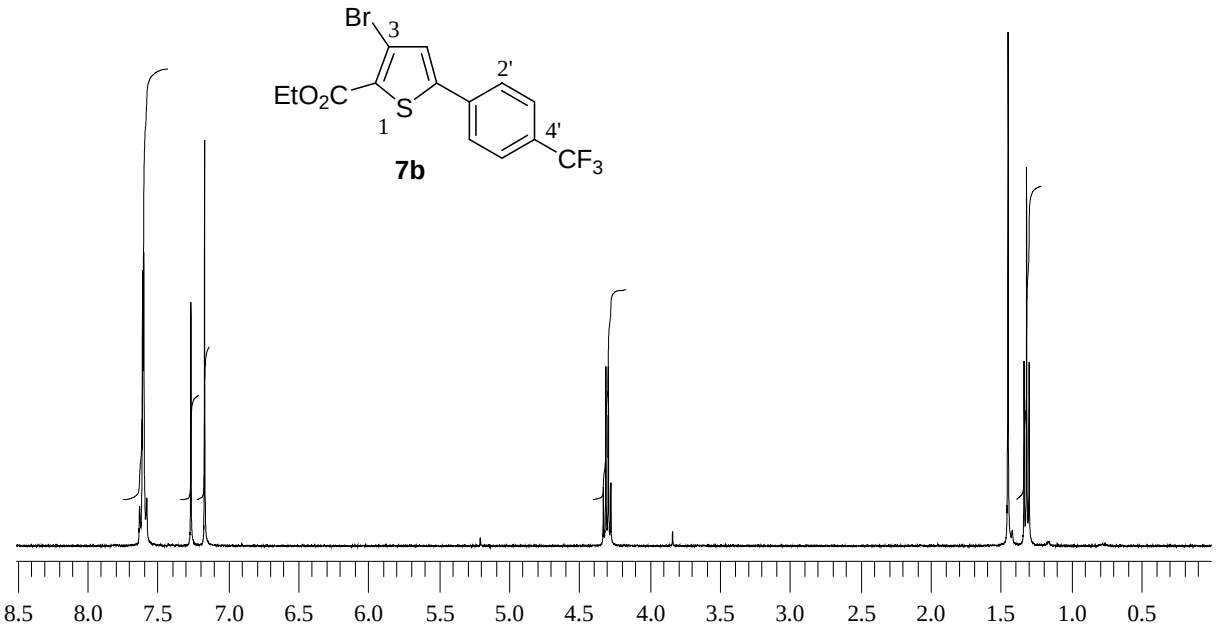


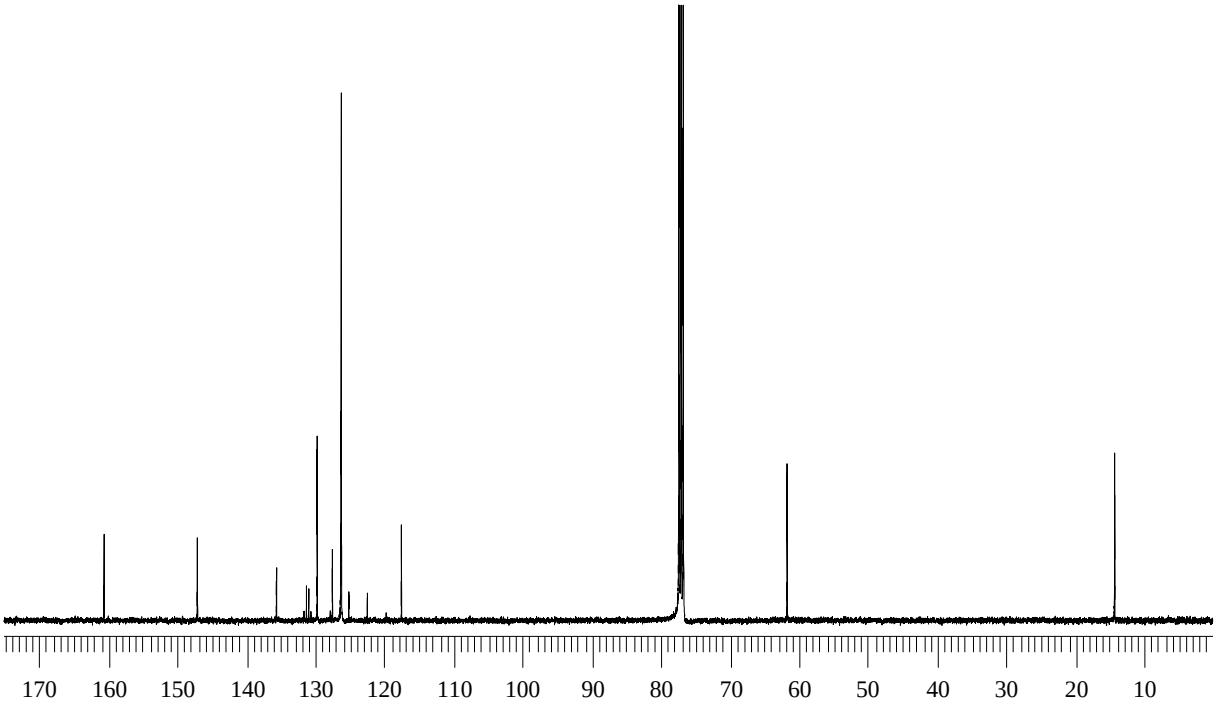
8a



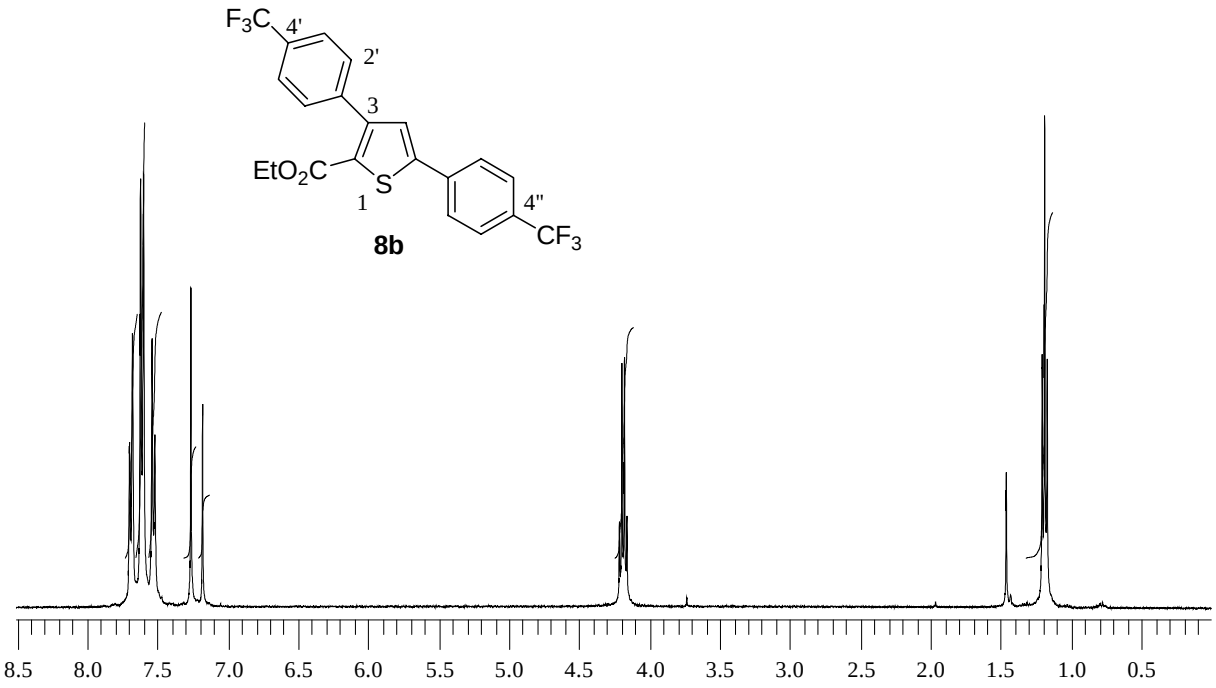


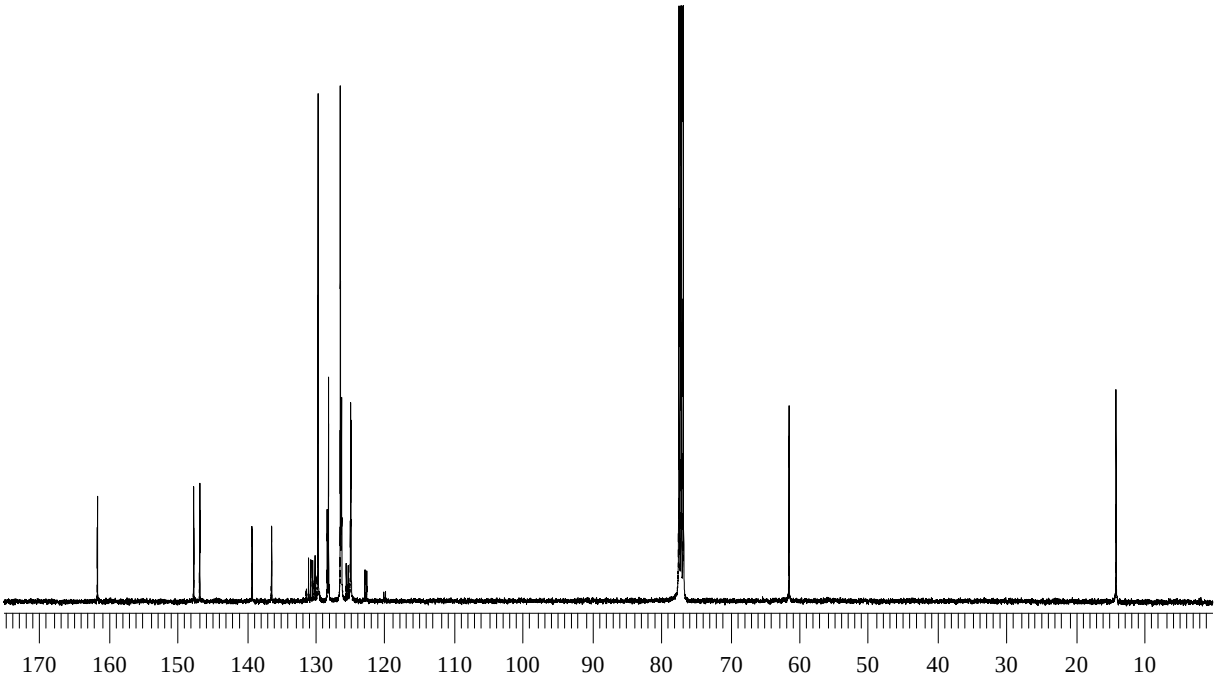
Ethyl 3-Bromo-5-(4-trifluoromethylphenyl)thiophene-2-carboxylate (7b)



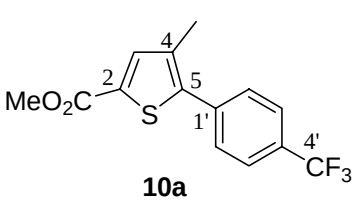


Ethyl 3,5-Bis(4-trifluoromethylphenyl)thiophene-2-carboxylate (8b)

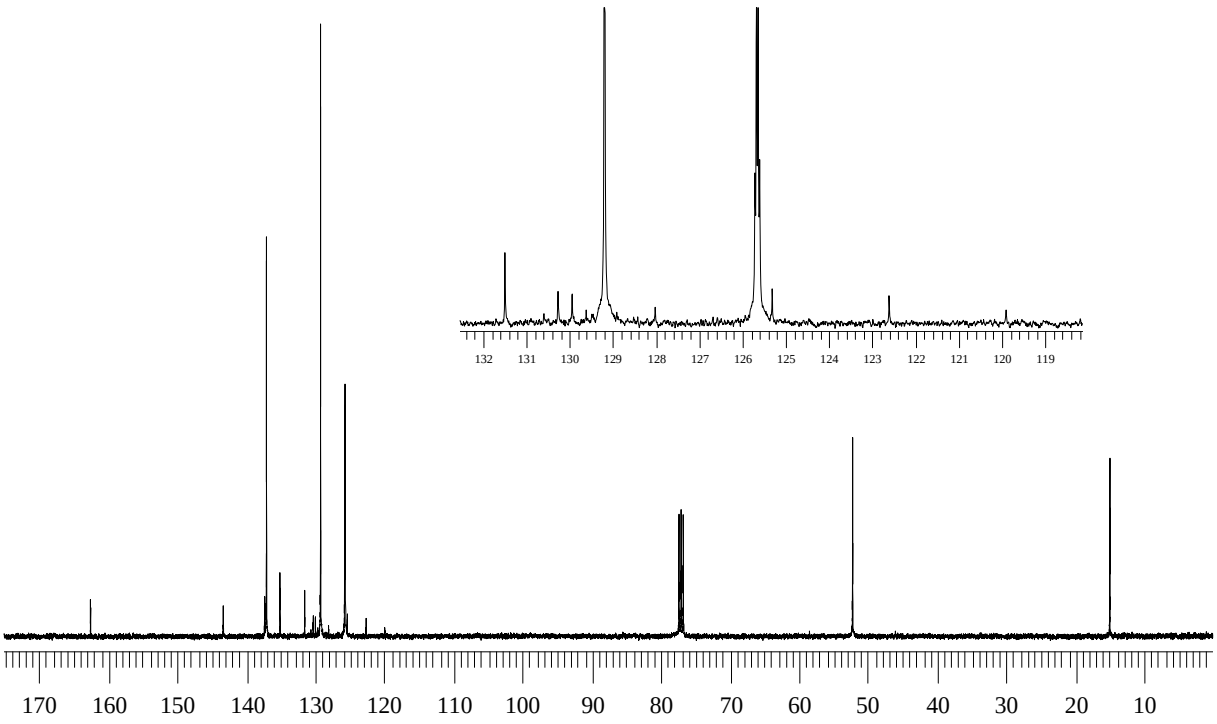




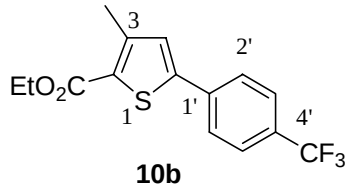
Methyl 4-Methyl-5-(4-trifluoromethylphenyl)thiophene-2-carboxylate (10a)



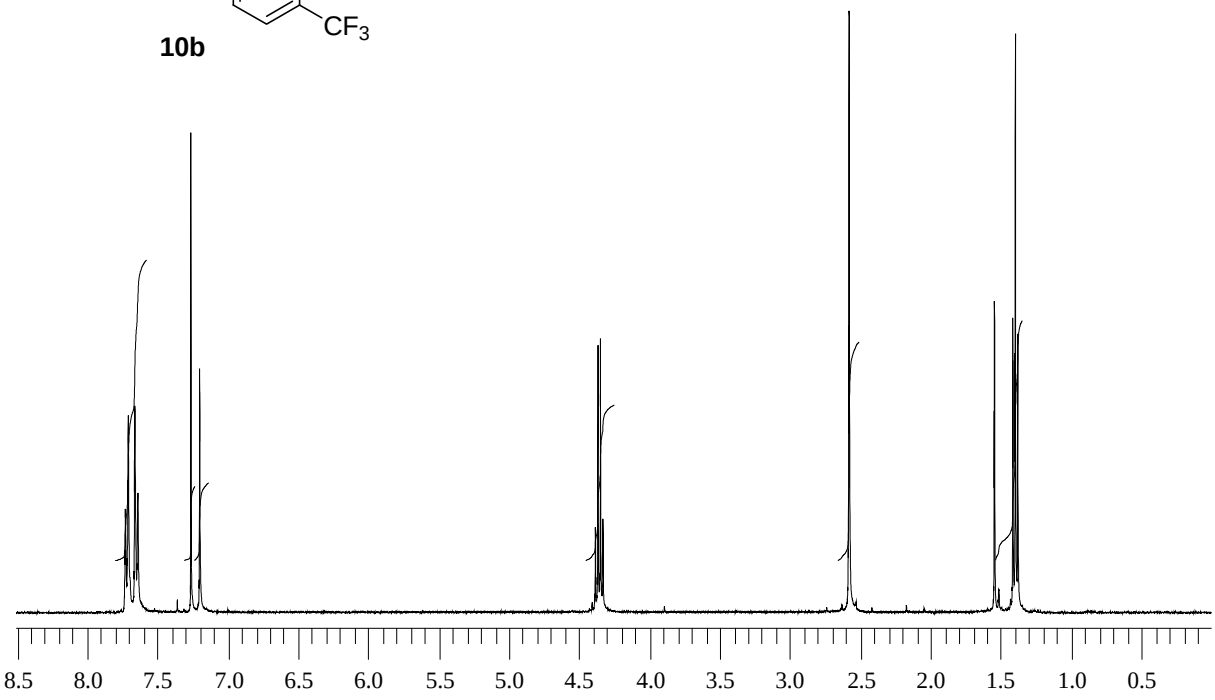
10a

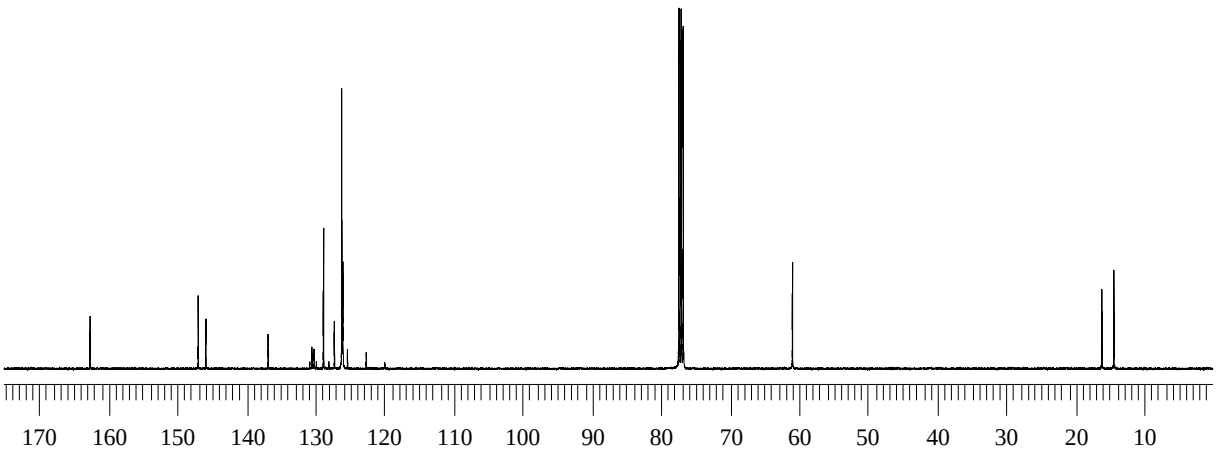


Ethyl 3-Methyl-5-(4-trifluoromethylphenyl)thiophene-2-carboxylate (10b)

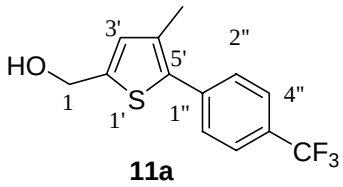


10b

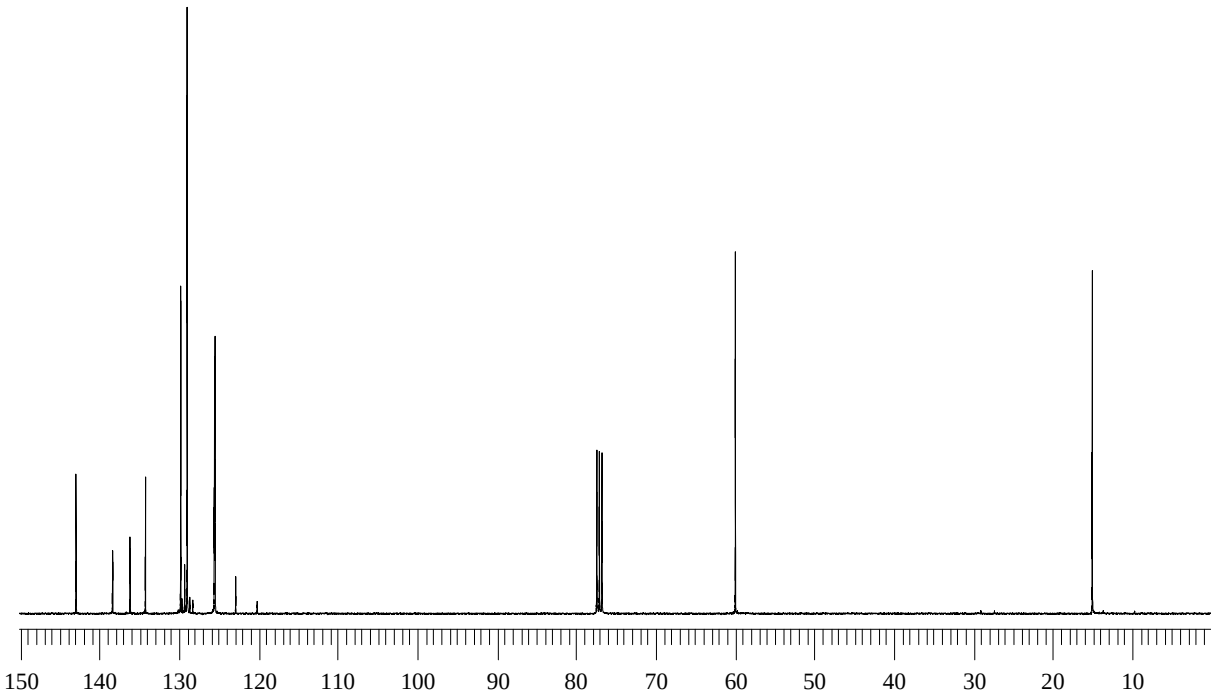




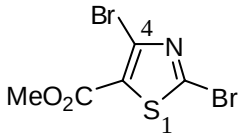
[4-Methyl-5-(4-trifluoromethylphenyl)thiophen-2-yl]methanol (11a)



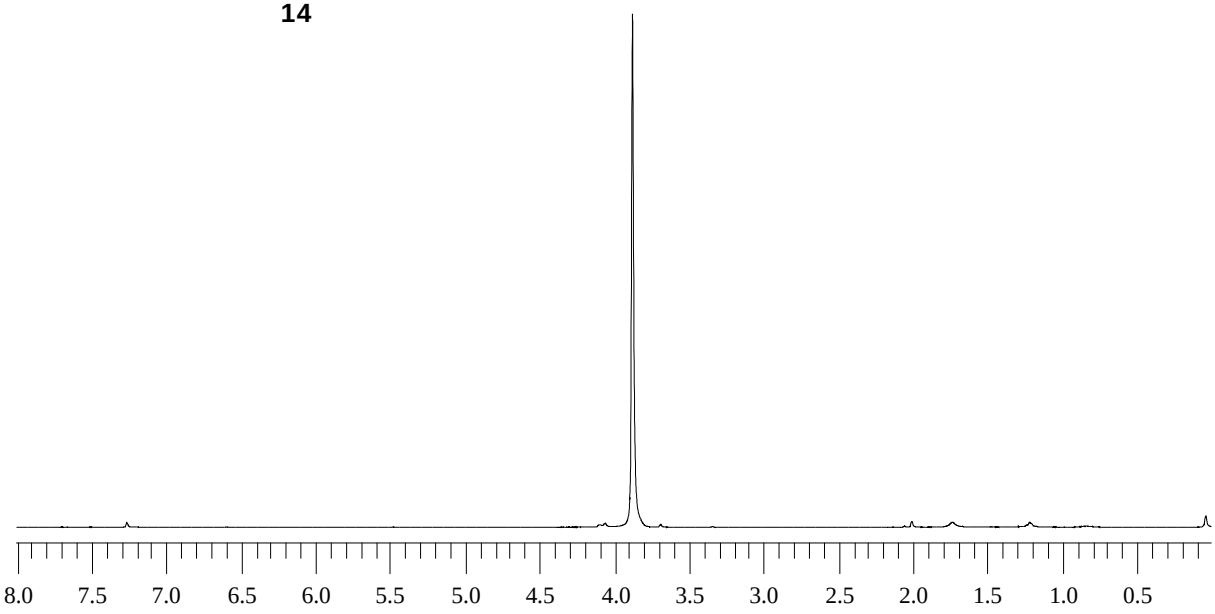
11a

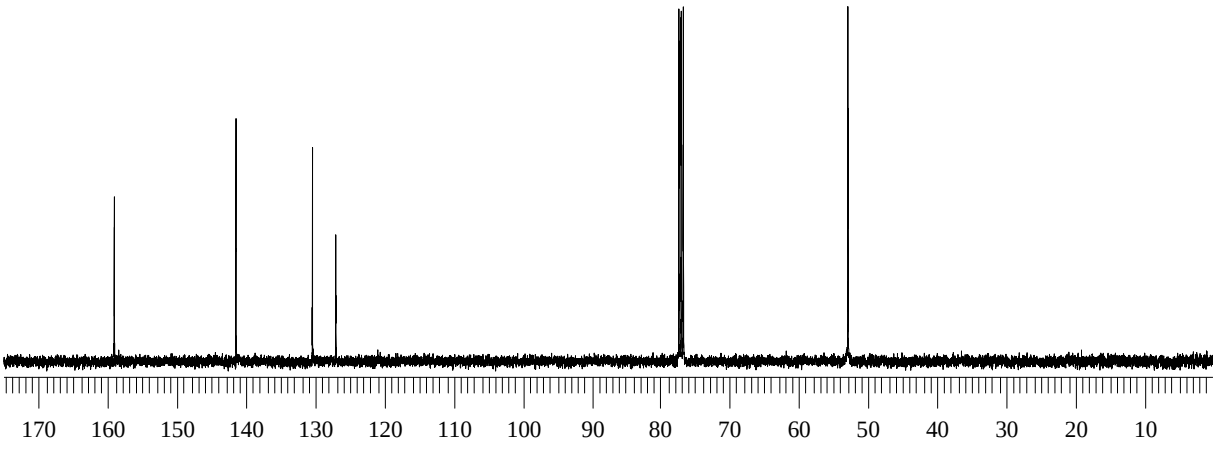


Methyl 2,4-Dibromothiazole-5-carboxylate (14)

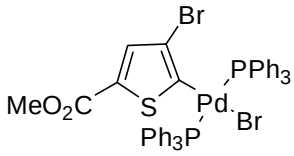


14

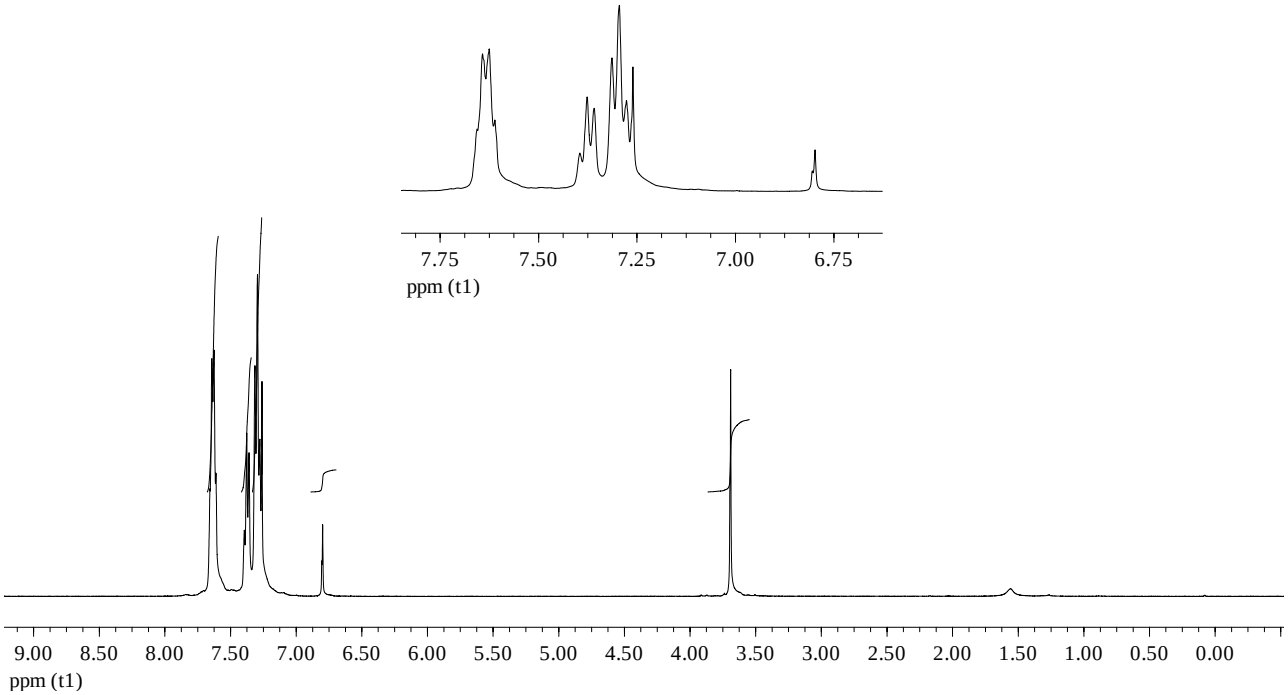




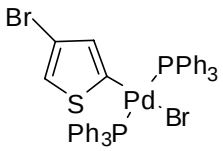
***trans*-Bromo[3-bromo-5-(methoxycarbonyl)thien-2-yl]bis(triphenylphosphine)palladium(II) (16)**



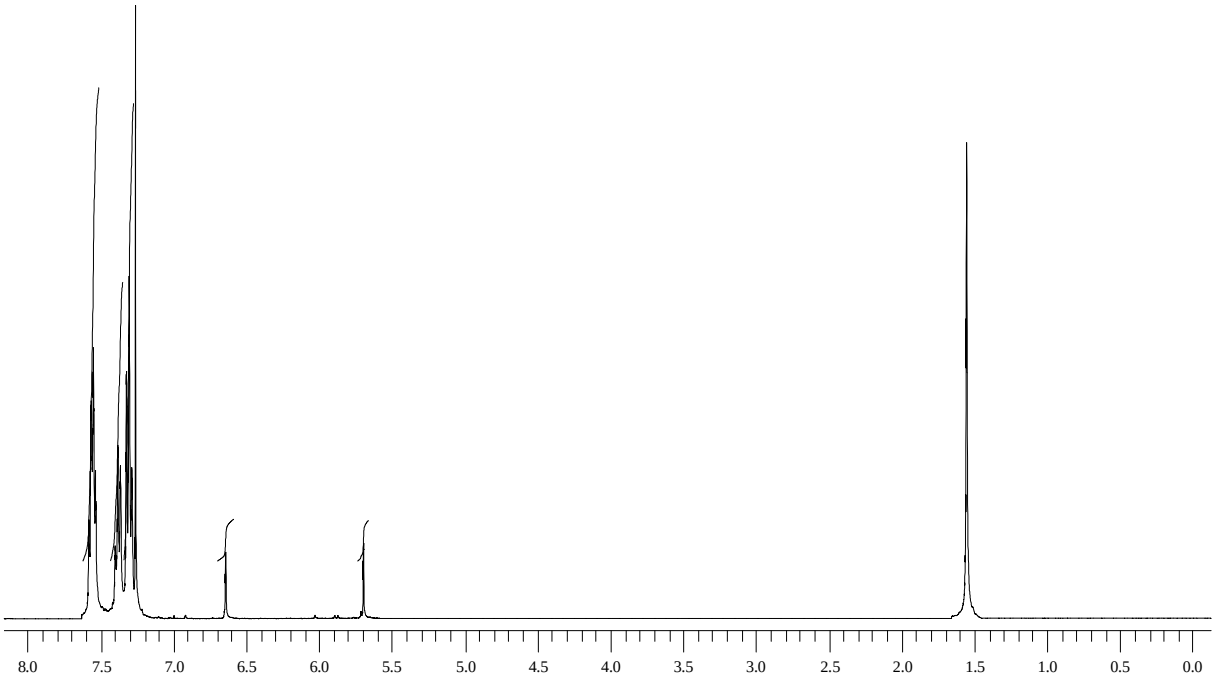
16



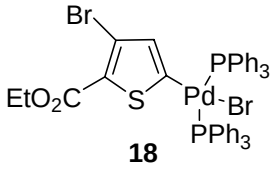
***trans*-Bromo(4-bromothien-2-yl)bis(triphenylphosphine)palladium(II) (17)**



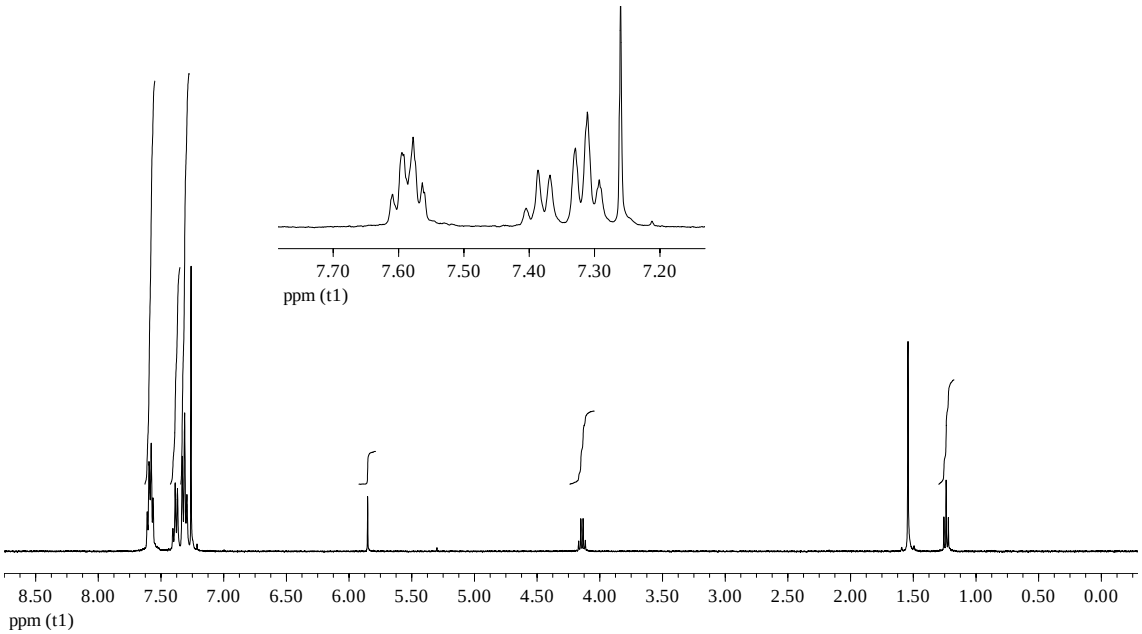
17

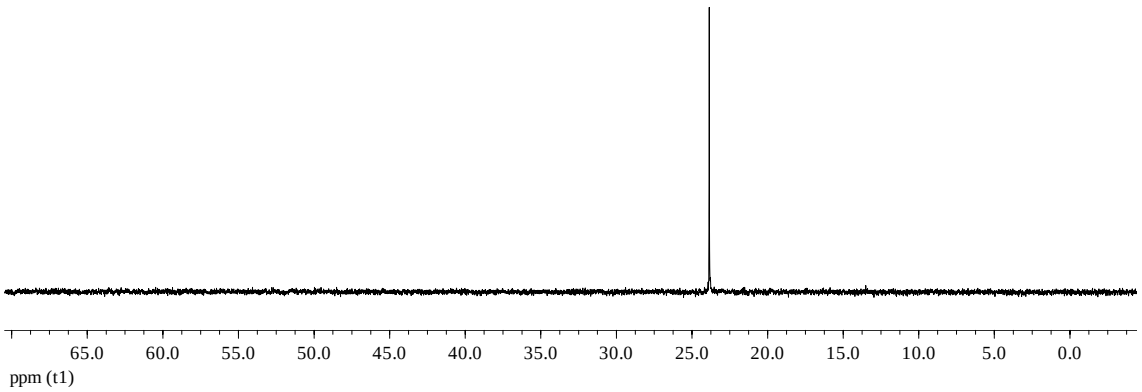


***trans*-Bromo[4-bromo-5-(ethoxycarbonyl)thien-2-yl]bis(triphenylphosphine)palladium(II) (18)**

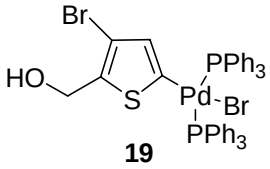


18

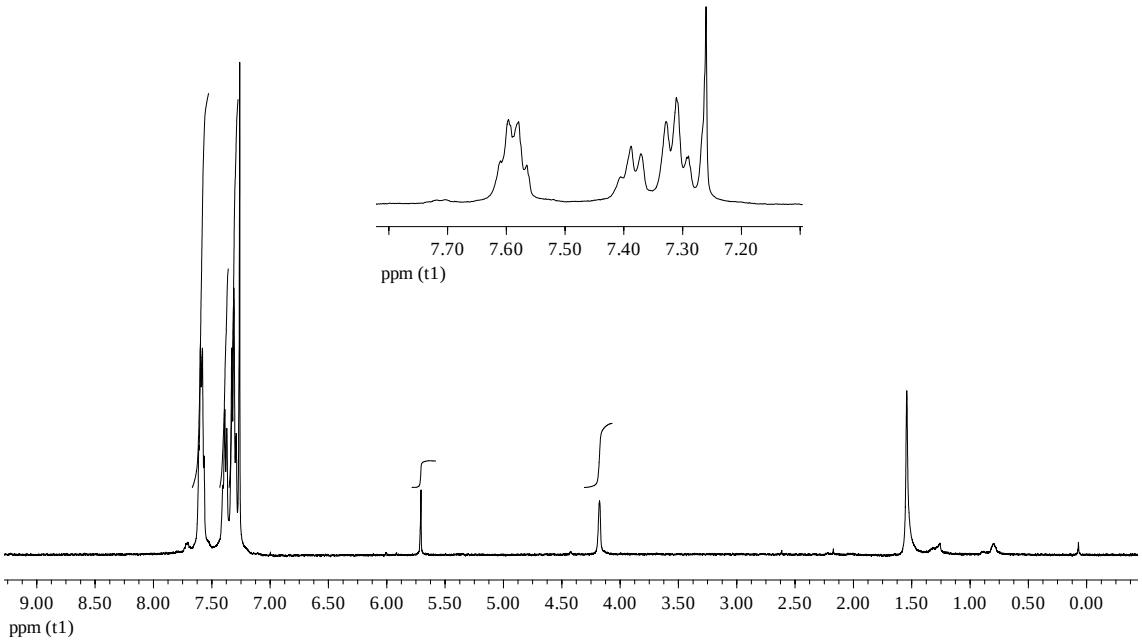


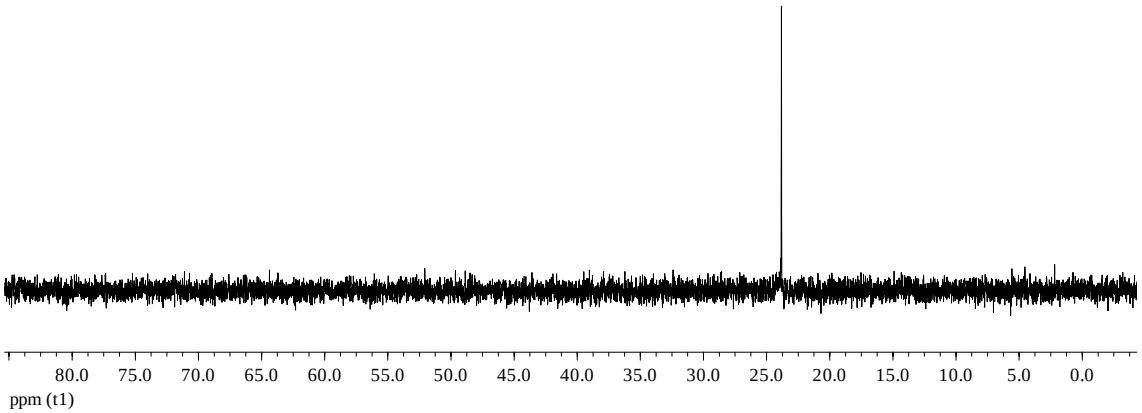


***trans*-Bromo[4-bromo-5-(hydroxymethyl)thien-2-yl]bis(triphenylphosphine)palladium(II) (19)**

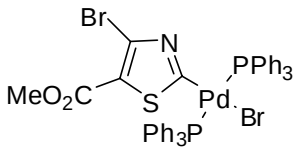


19





***trans*-Bromo[4-bromo-5-(methoxycarbonyl)thiazol-2-yl]bis(triphenylphosphine)palladium(II) (20)**



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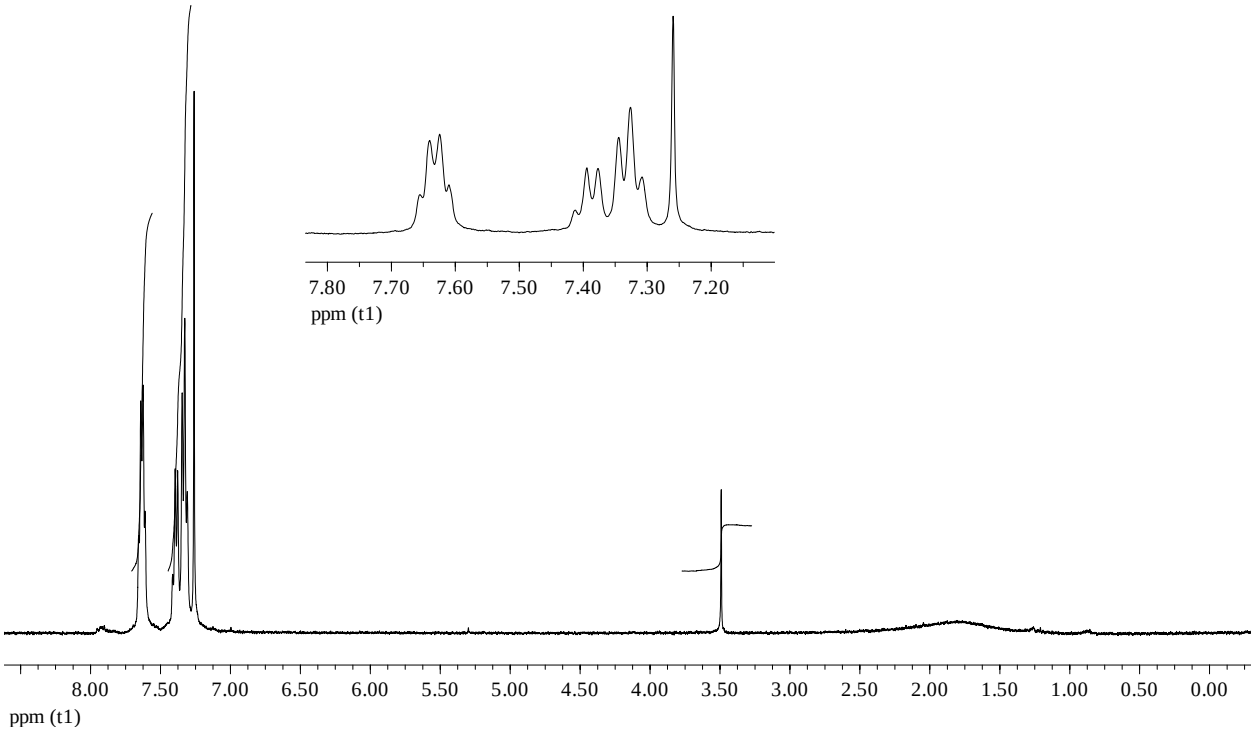
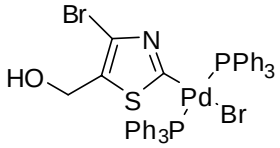
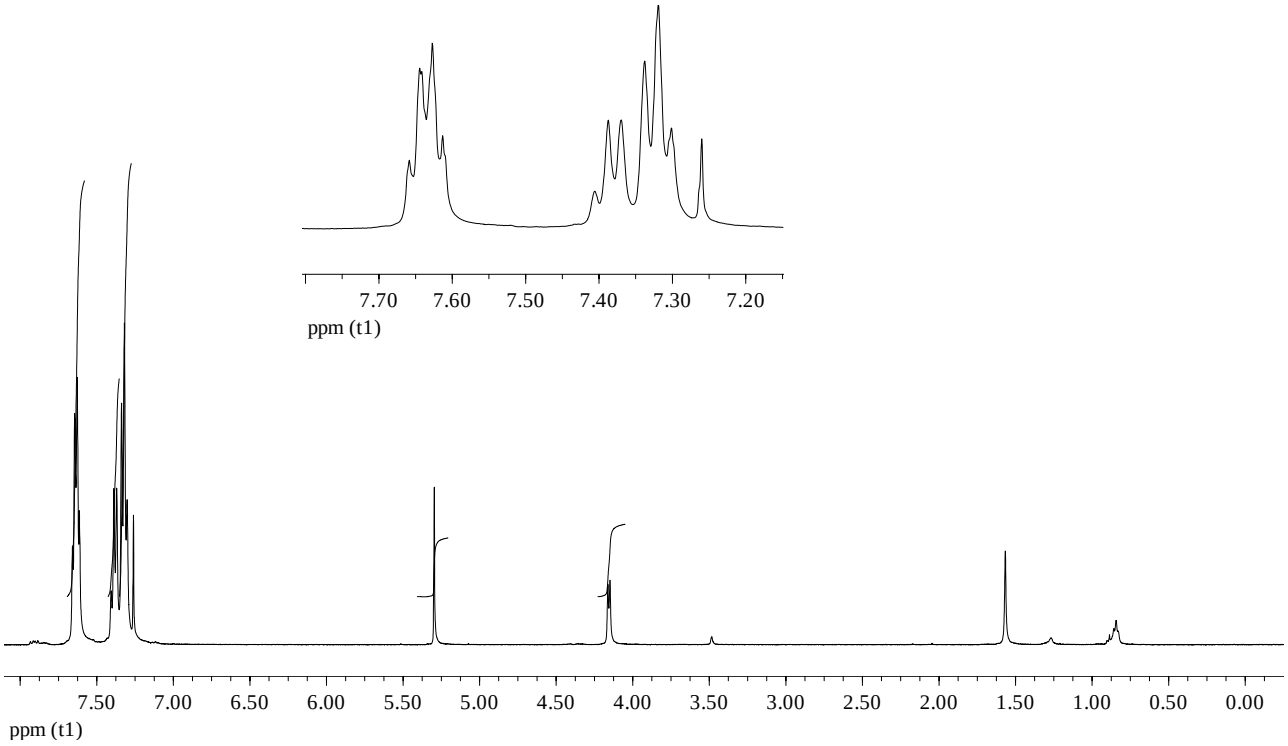


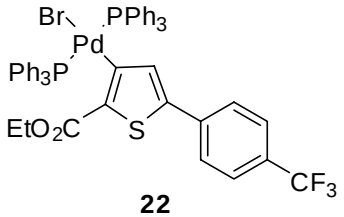
***trans*-Bromo[4-bromo-5-(hydroxymethyl)thiazol-2-yl]bis(triphenylphosphine)palladium(II) (21)**



21



***trans*-Bromo[5-(4-trifluoromethylphenyl)-2-(ethoxycarbonyl)thien-3-yl]bis(triphenylphosphine) palladium(II) (22)**



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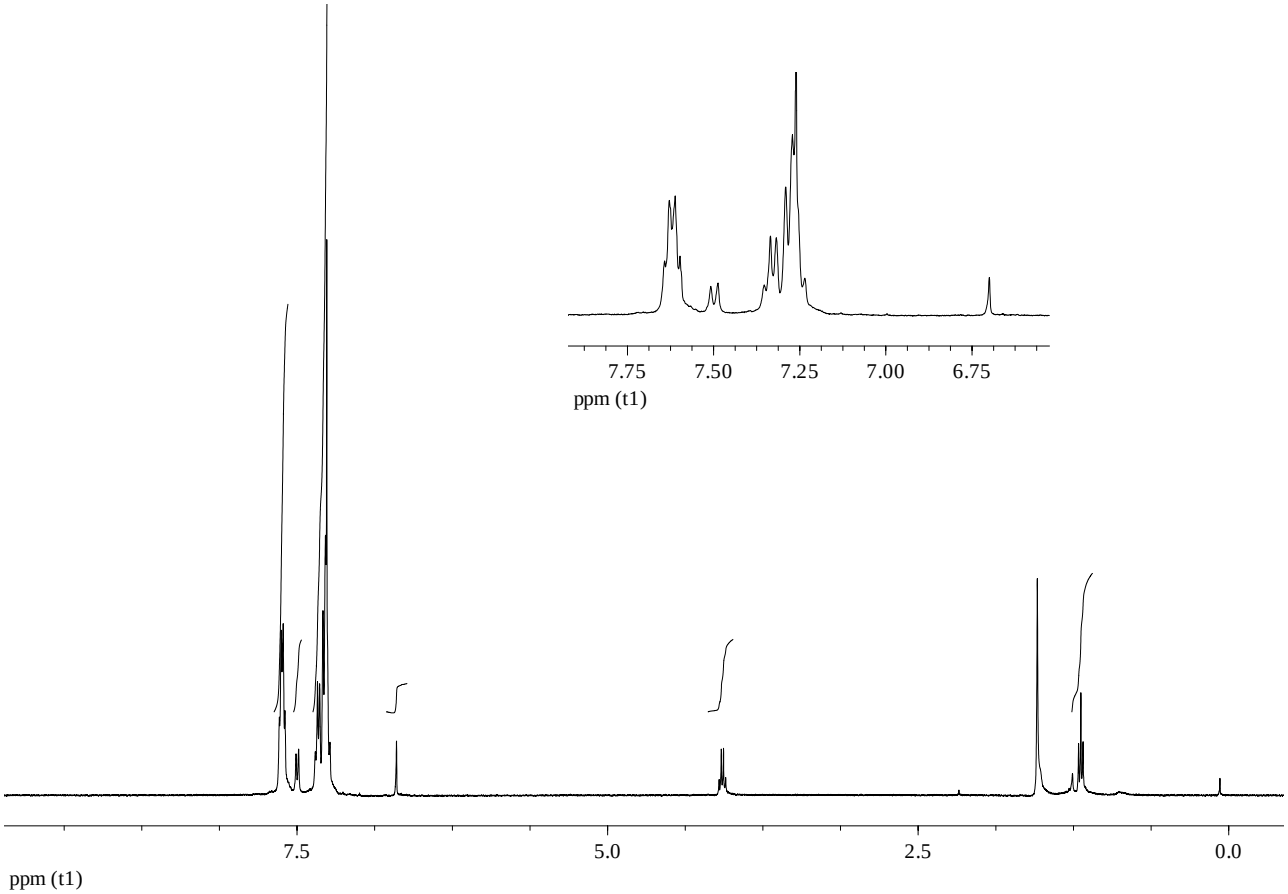
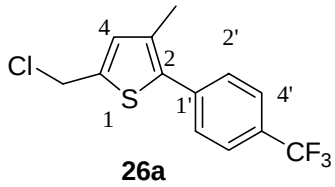
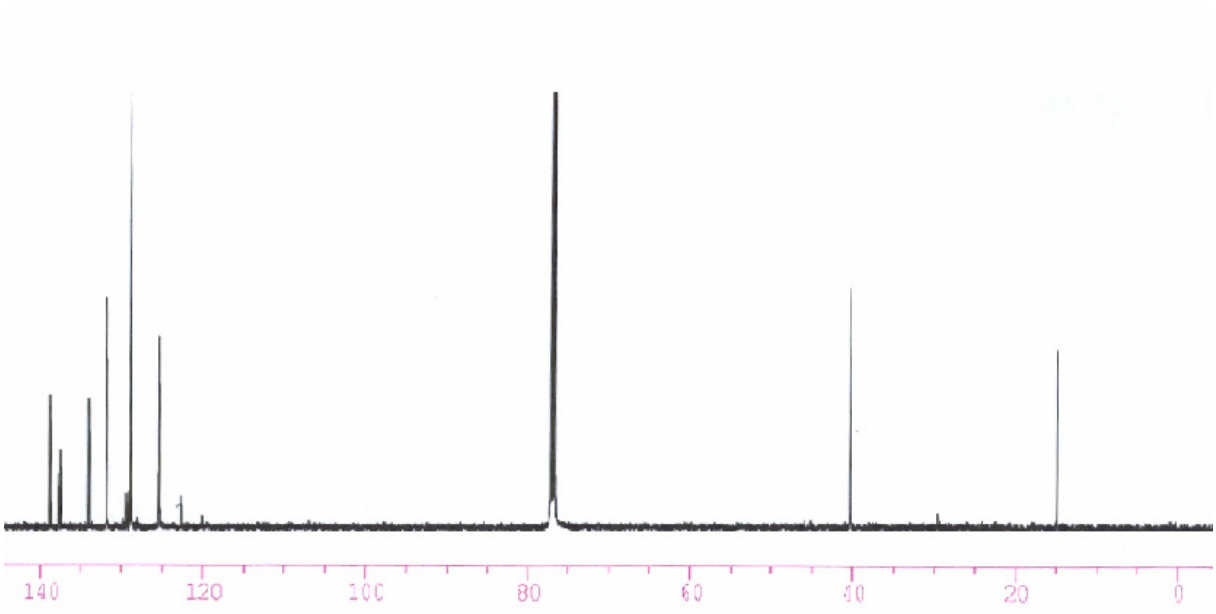


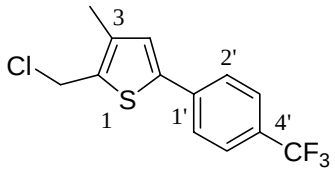
5-Chloromethyl-3-methyl-2-(4-trifluoromethylphenyl)thiophene (26a)



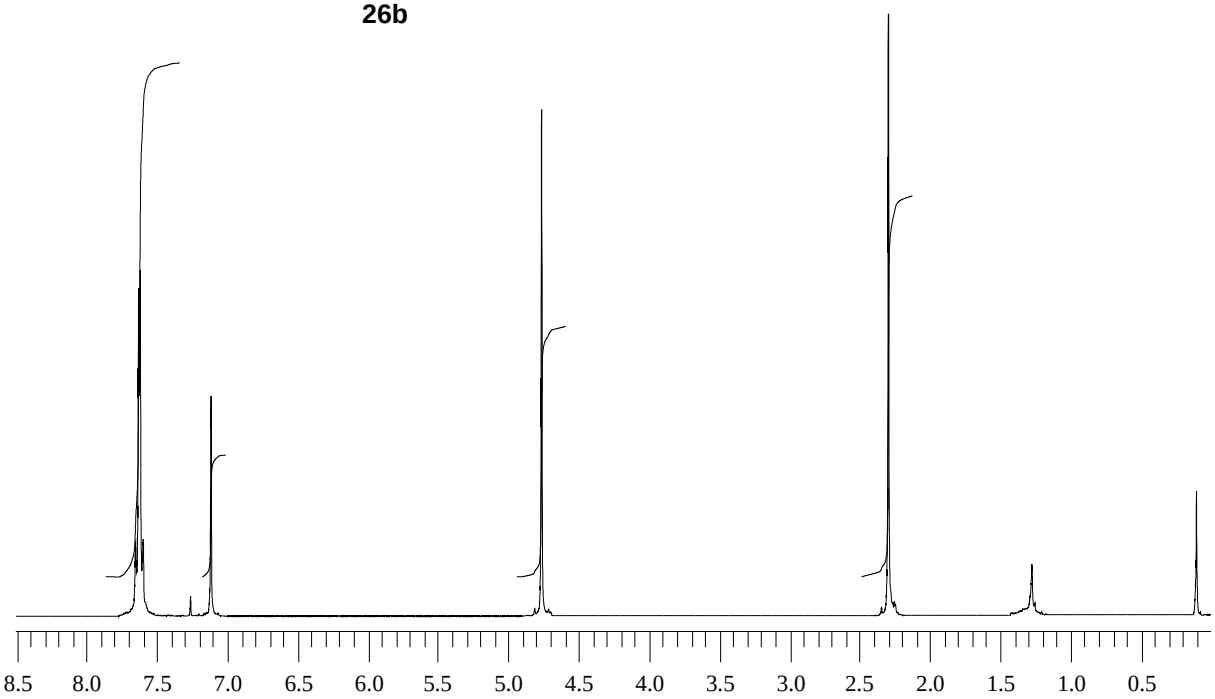
26a

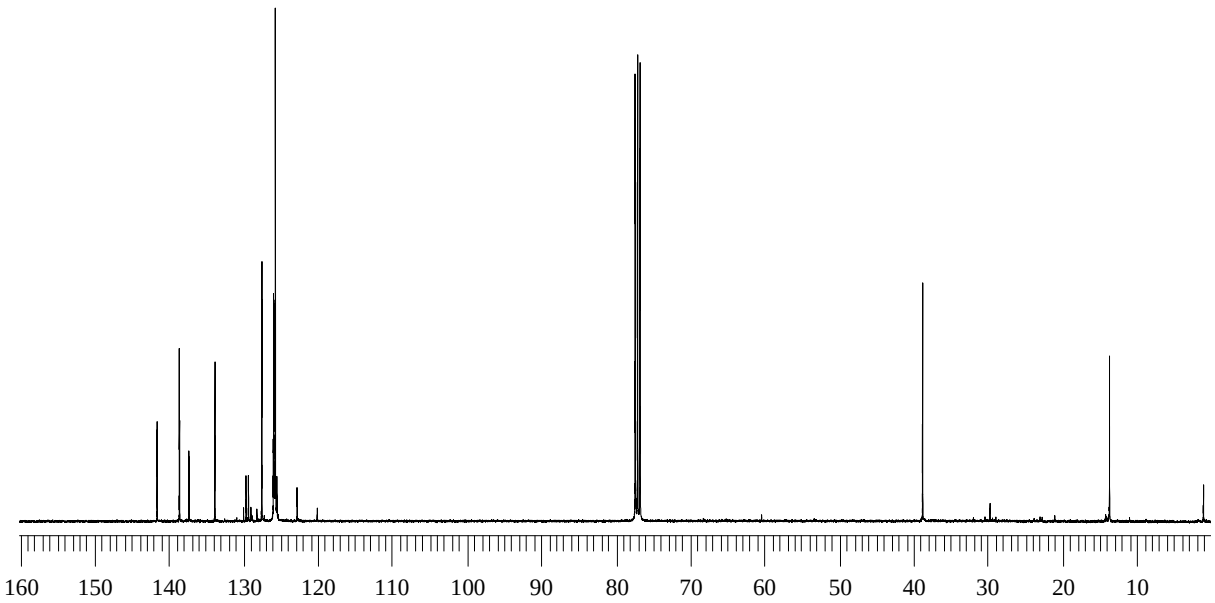


2-Chloromethyl-3-methyl-5-(4-trifluoromethylphenyl)thiophene (26b)

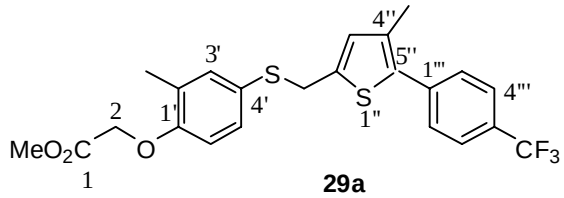


26b

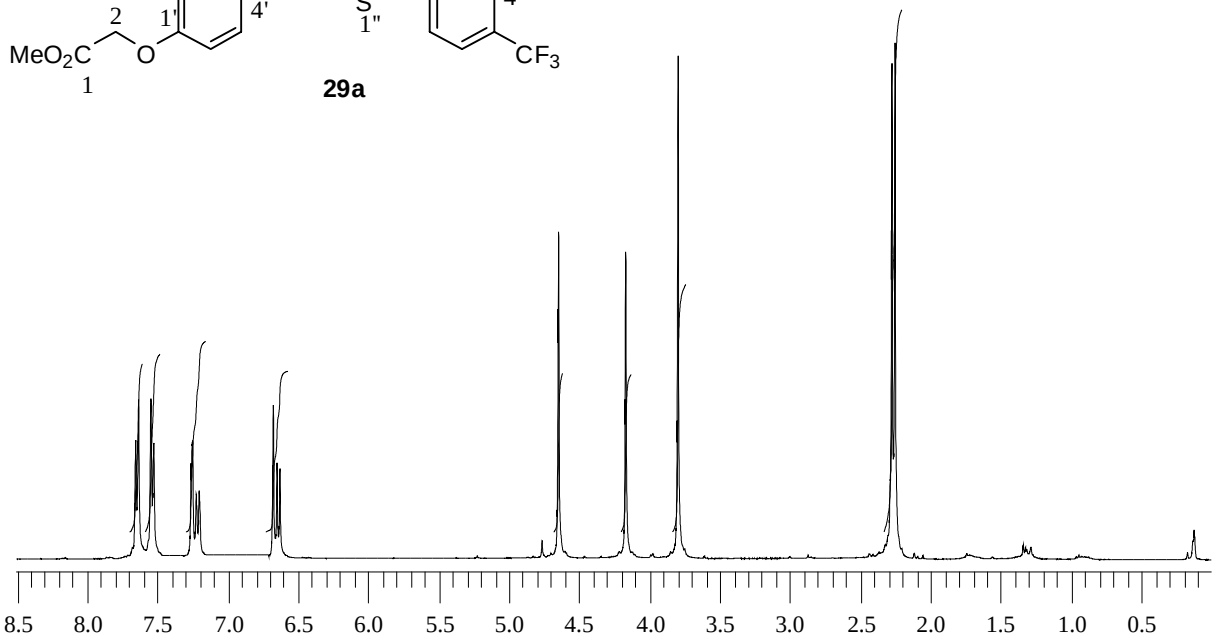


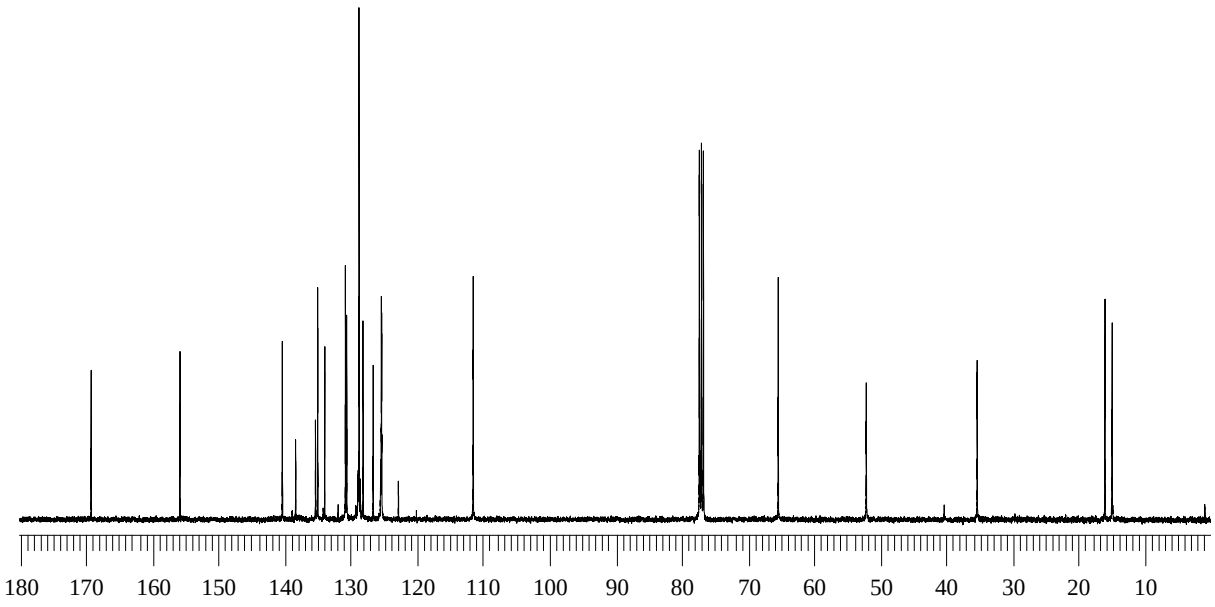


Methyl (2-Methyl-4-[4-methyl-5-(4-trifluoromethylphenyl)thien-2-ylmethylthio]phenoxy)acetate (29a)

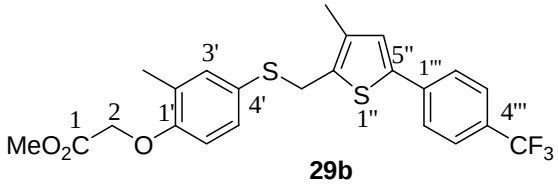


29a

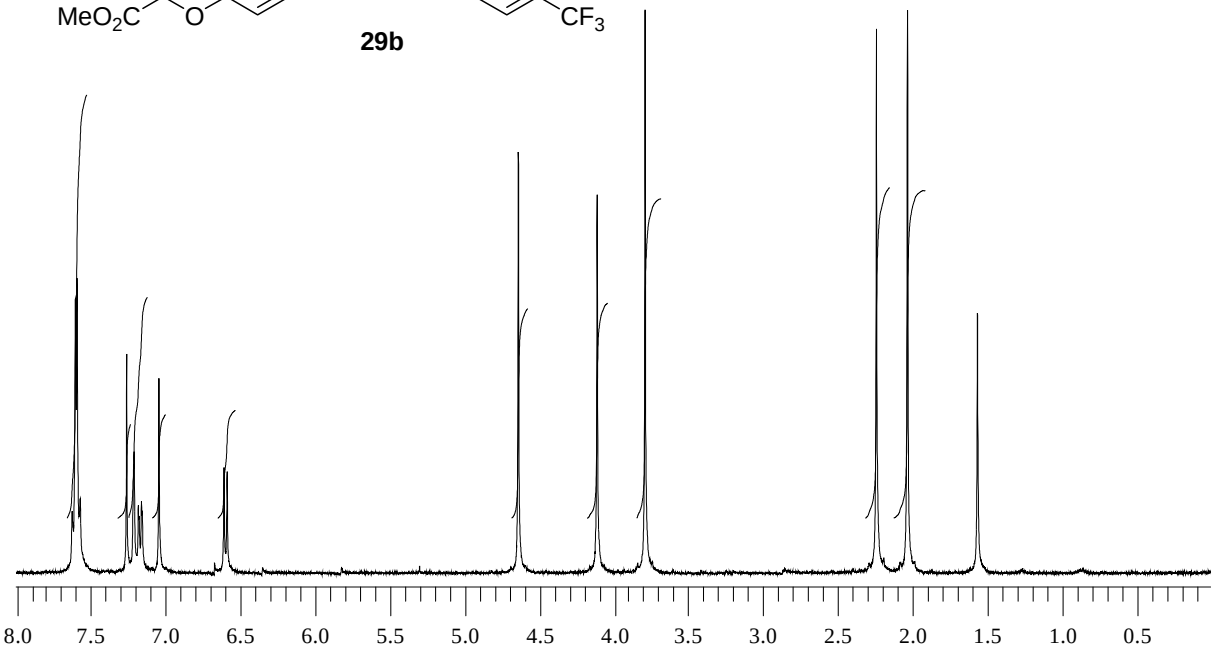


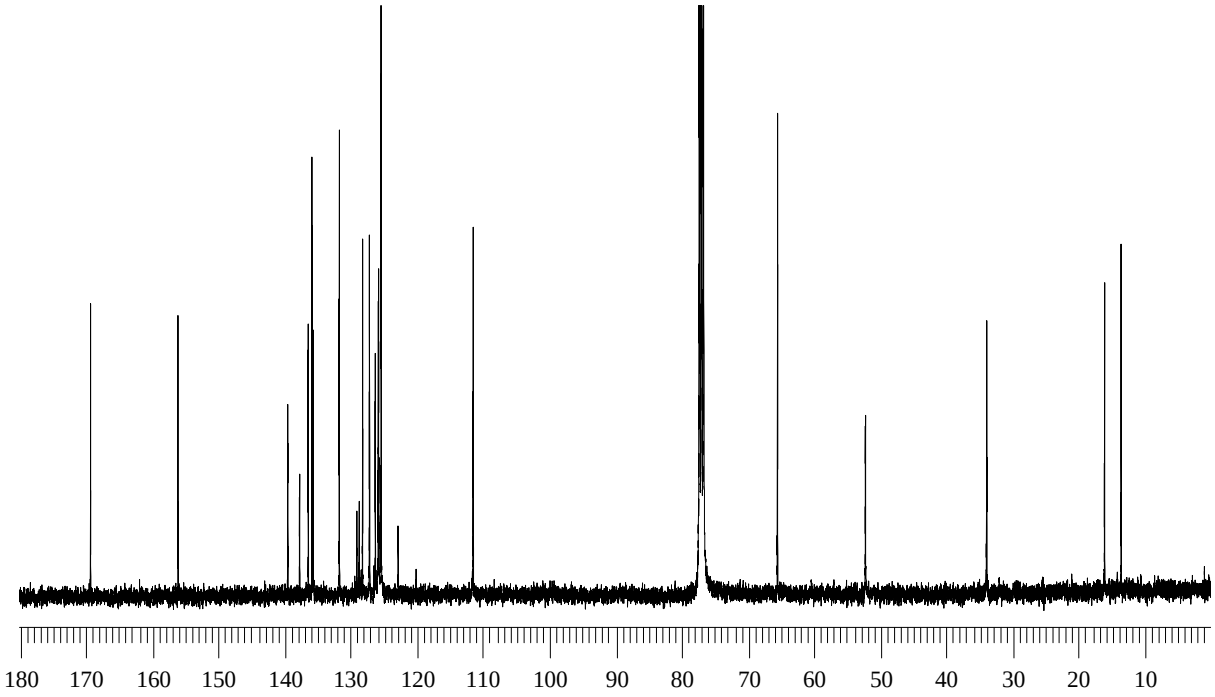


Methyl (2-Methyl-4-[3-methyl-5-(4-trifluoromethylphenyl)thien-2-ylmethylthio]phenoxy)acetate (29b)

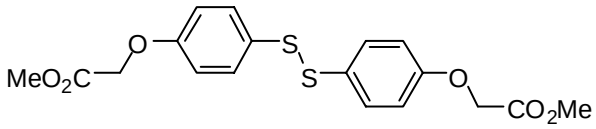


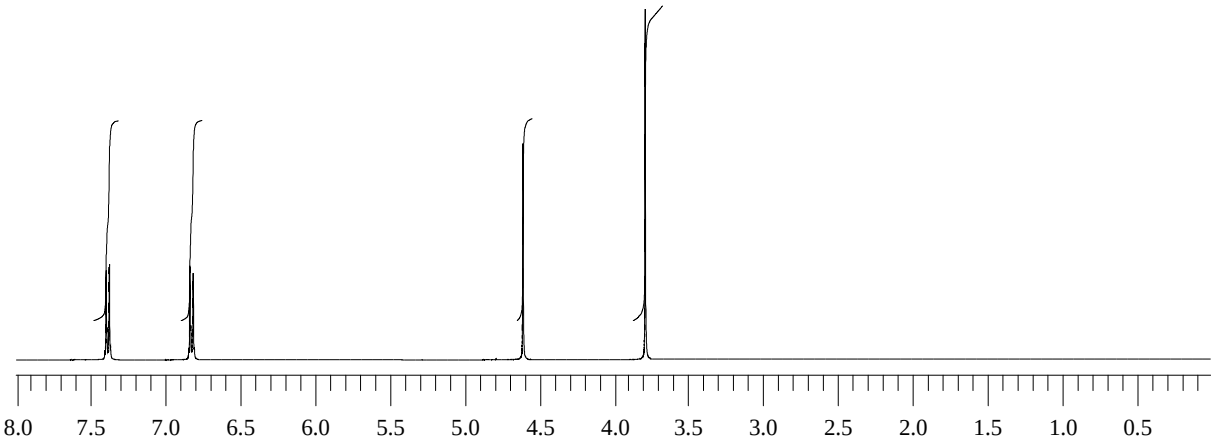
29b

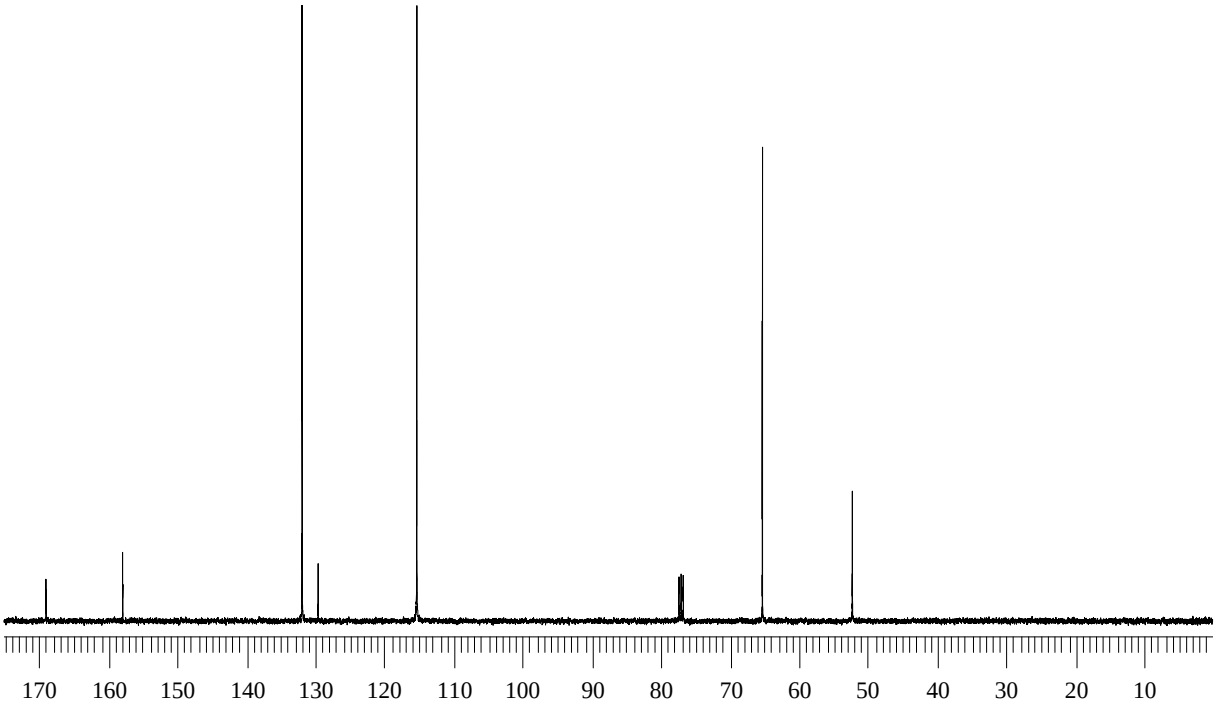




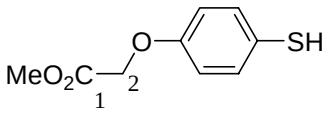
Methyl [4-(4-[Methoxycarbonylmethoxy]phenyldithio)phenoxy]acetate



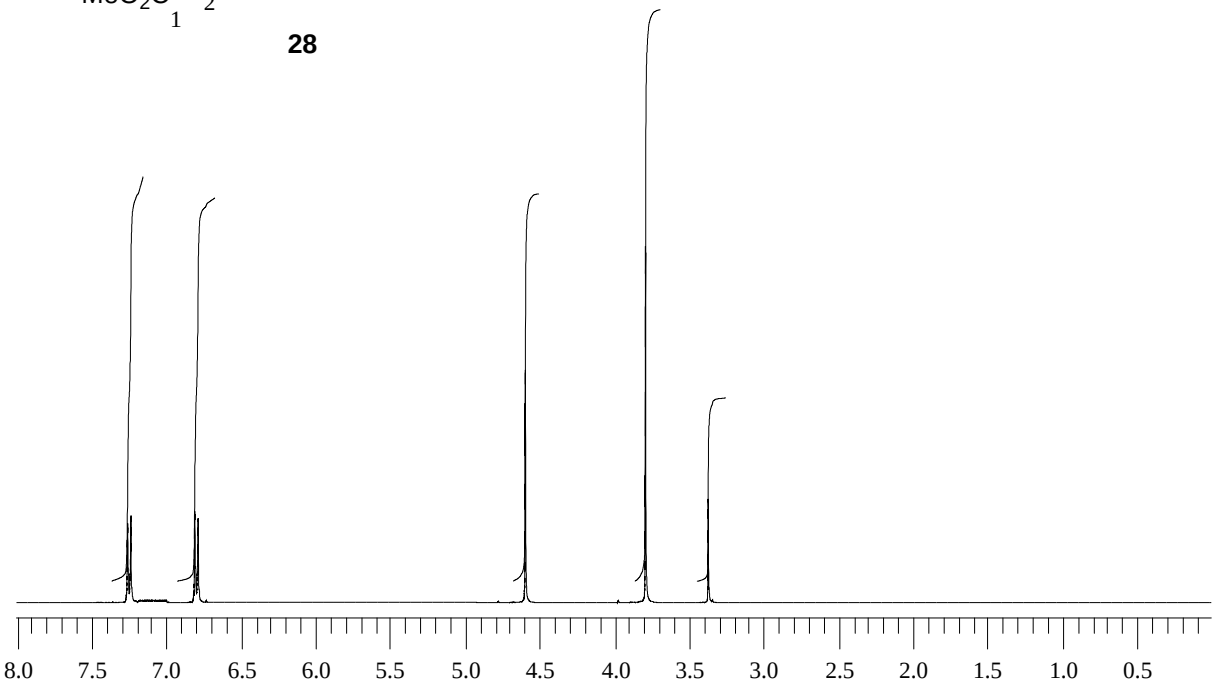


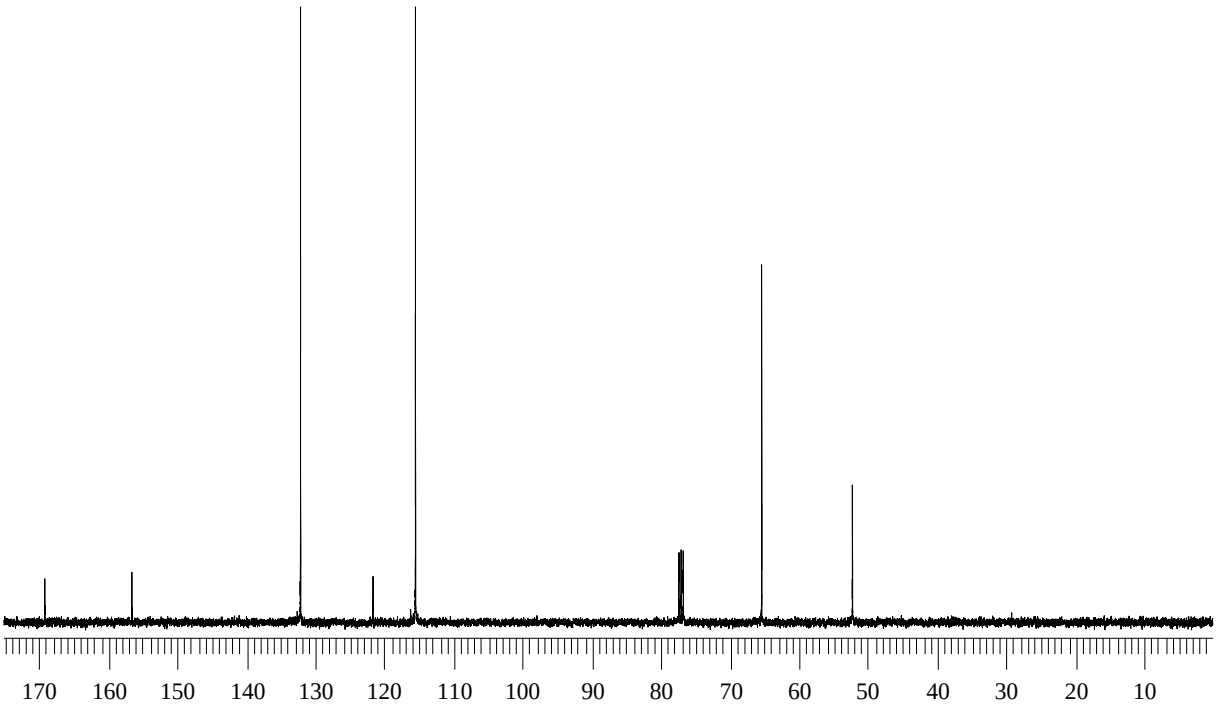


Methyl 2-(4-Mercaptophenoxy)acetate (28)

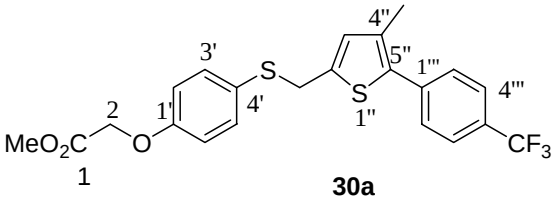


28

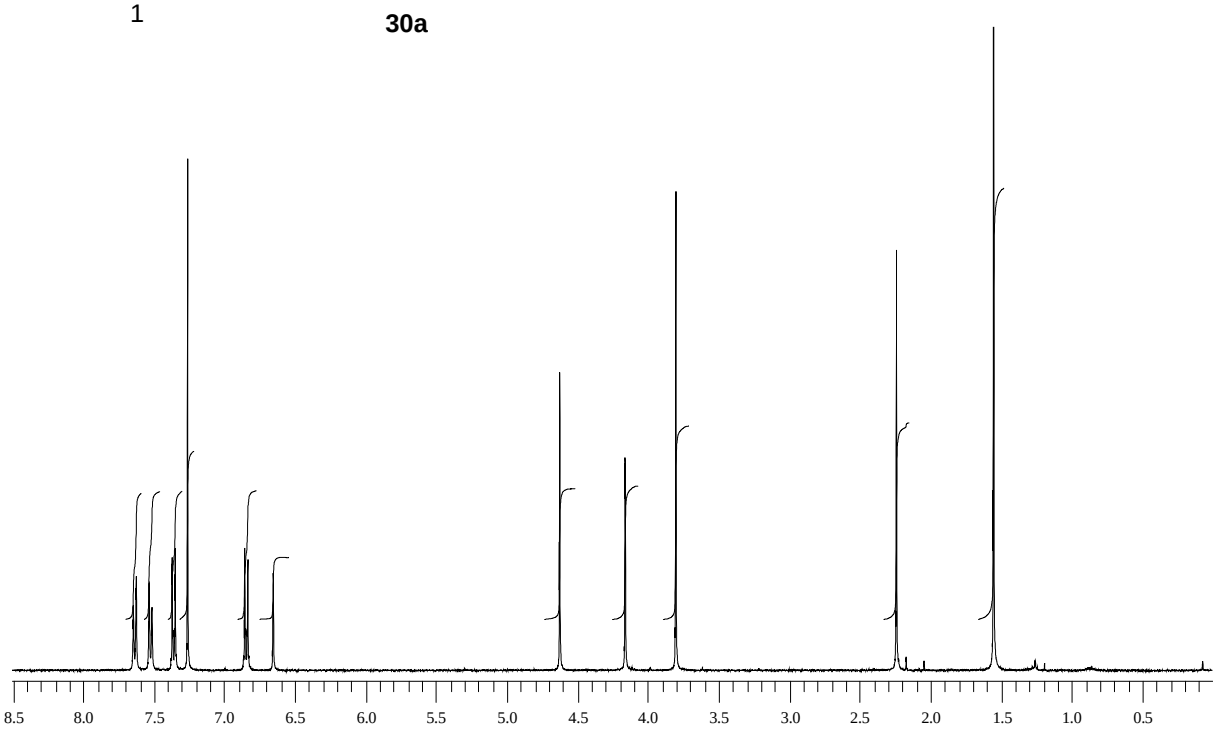


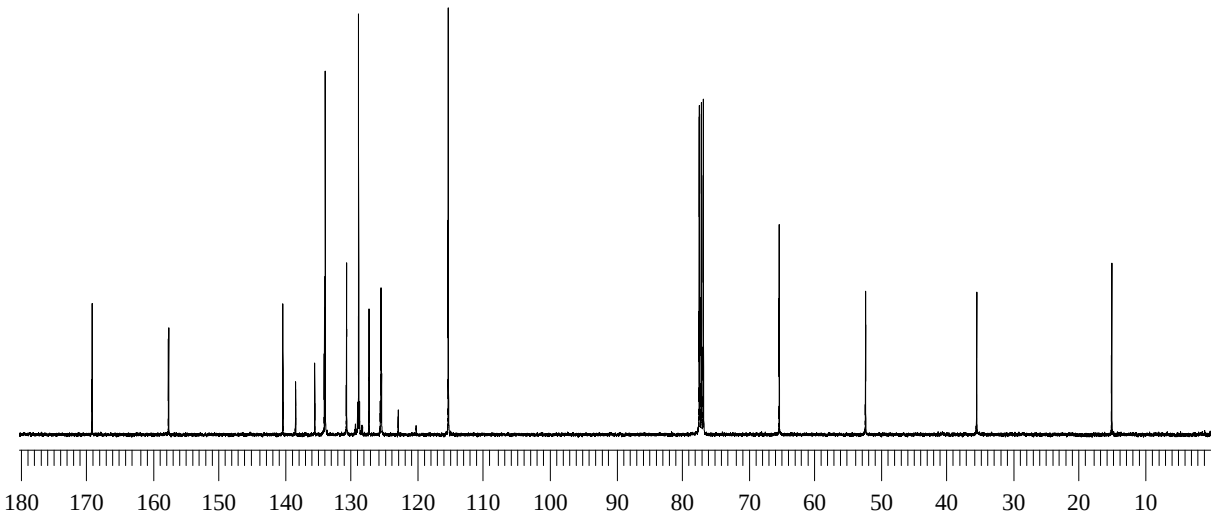


Methyl (4-[4-Methyl-5-(4-trifluoromethylphenyl)thien-2-ylmethylthio]phenoxy)acetate (30a)

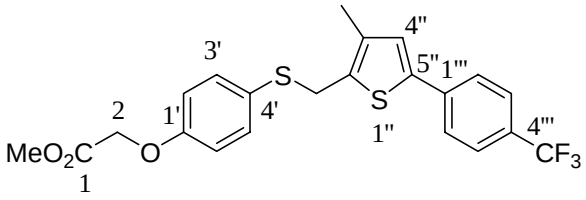


30a

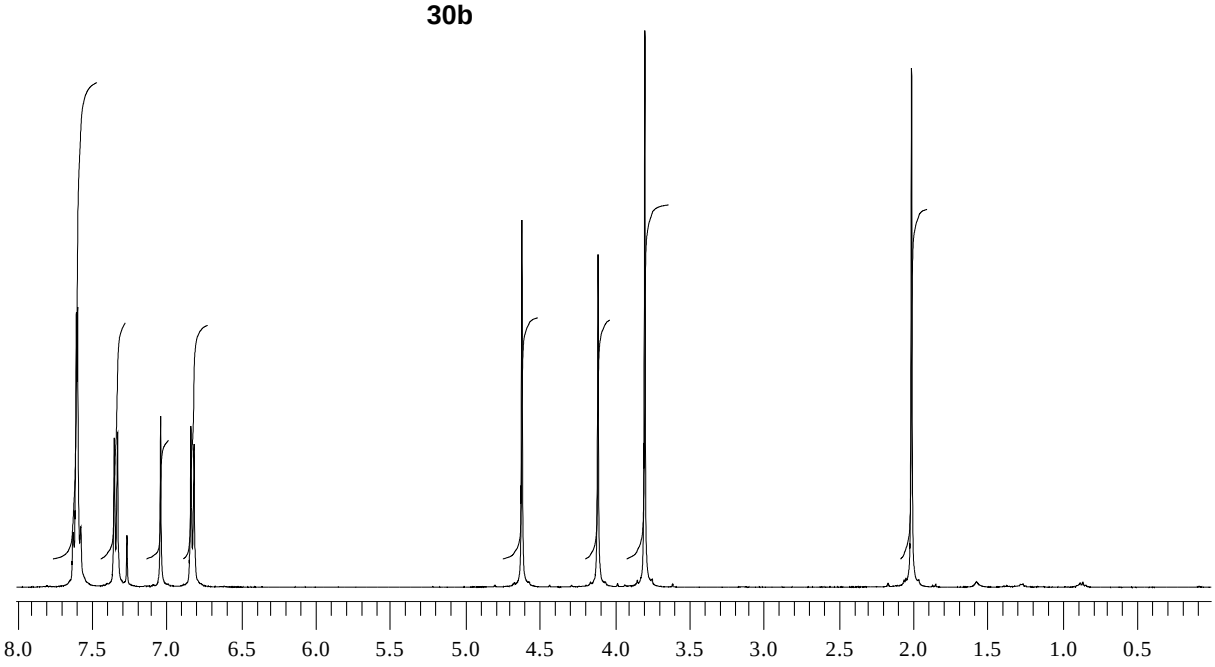


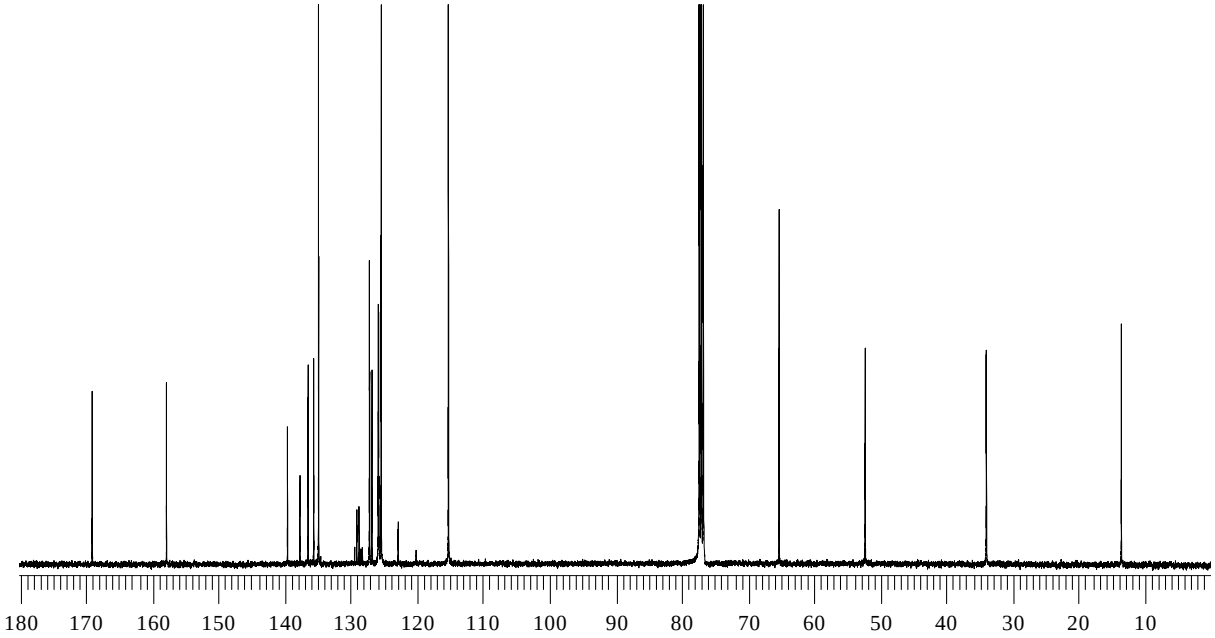


Methyl (4-[3-Methyl-5-(4-trifluoromethylphenyl)thien-2-ylmethylthio]phenoxy)acetate (30b)

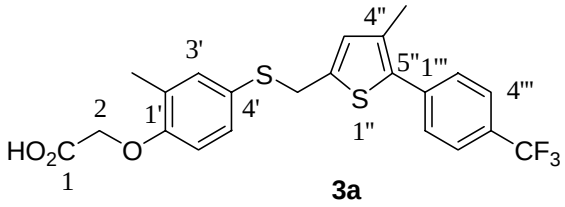


30b





(2-Methyl-4-[4-methyl-5-(4-trifluoromethylphenyl)thien-2-ylmethylthio]phenoxy)acetic Acid (3a)



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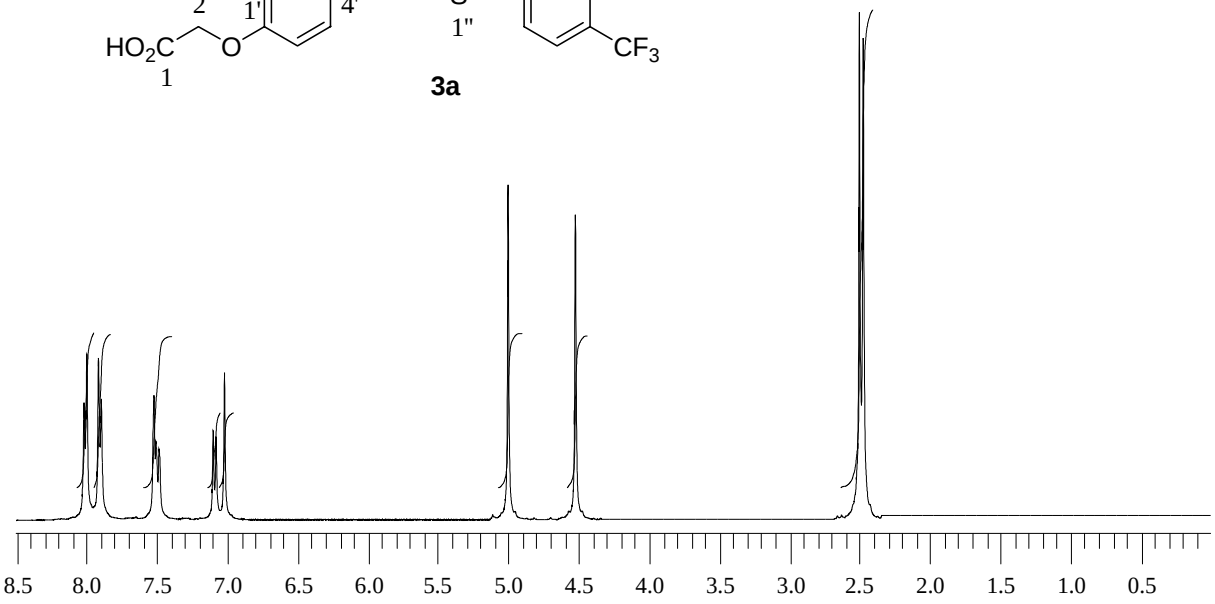

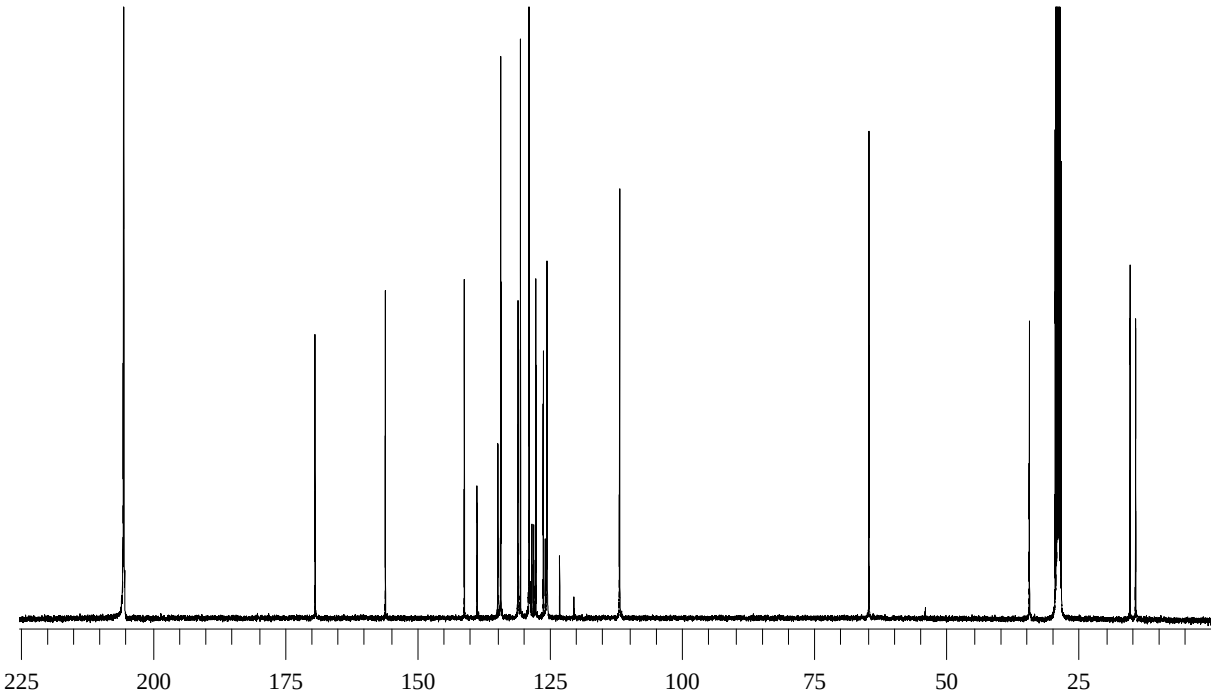

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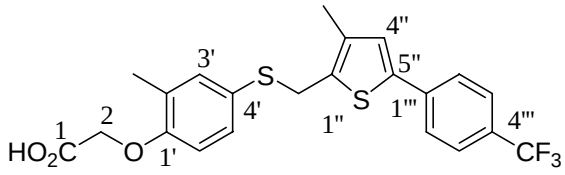
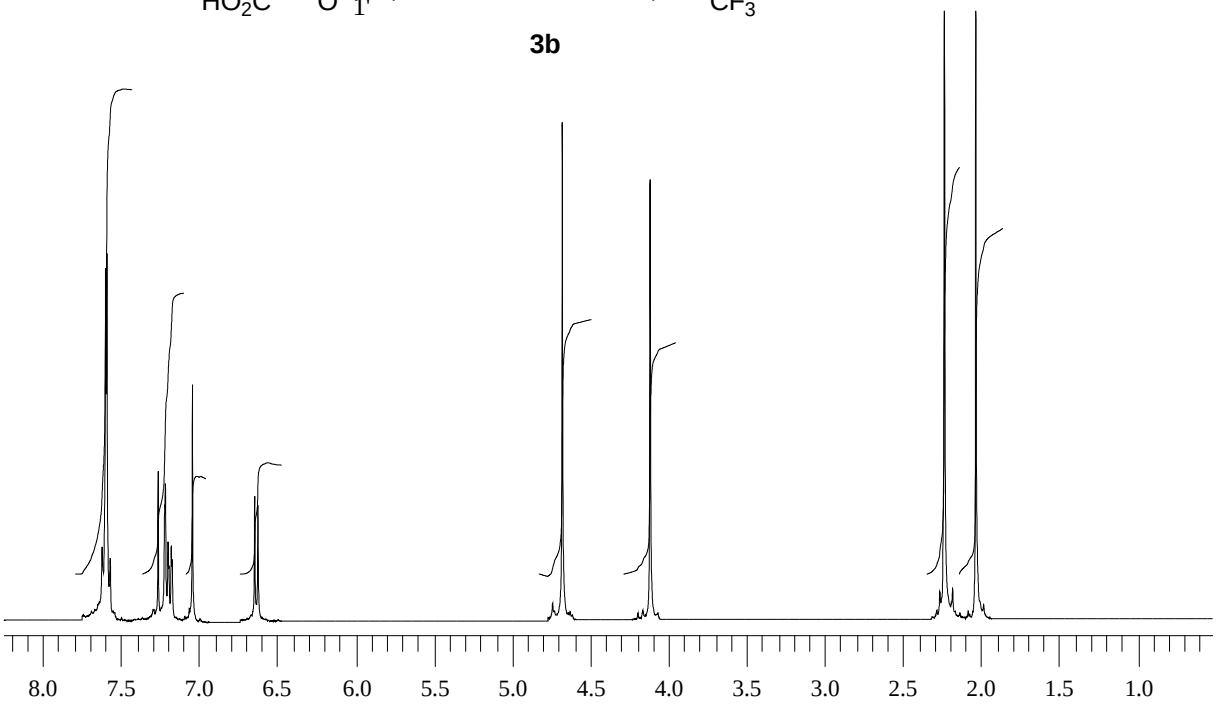
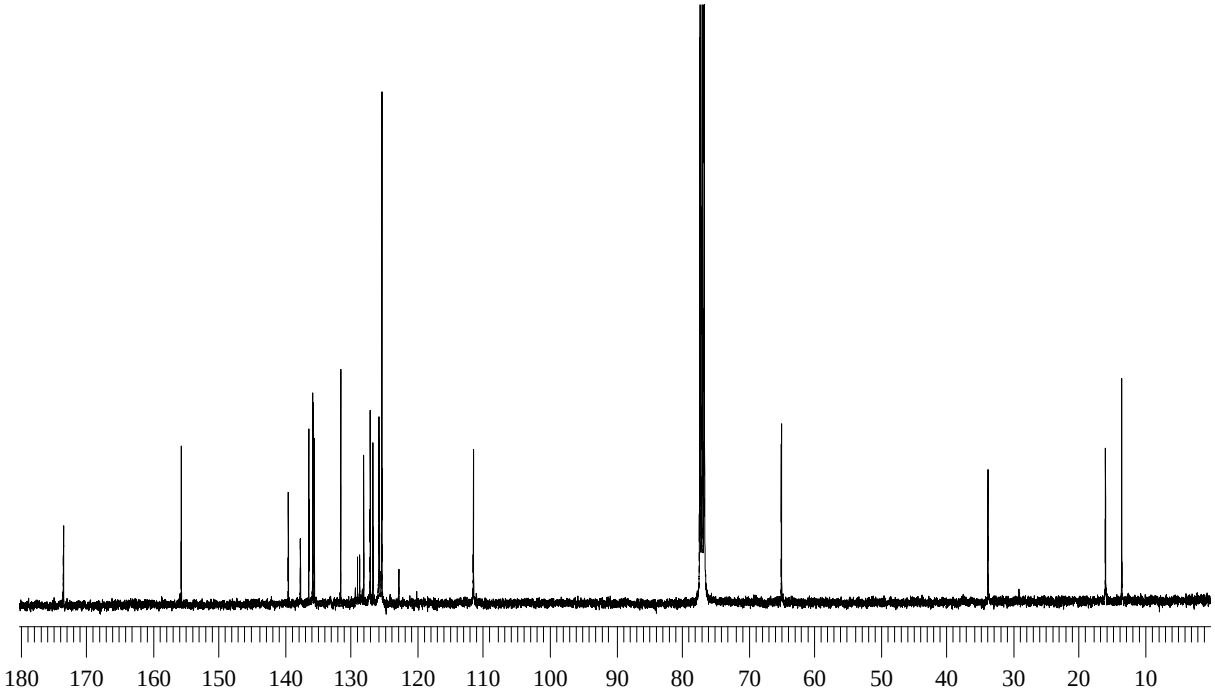
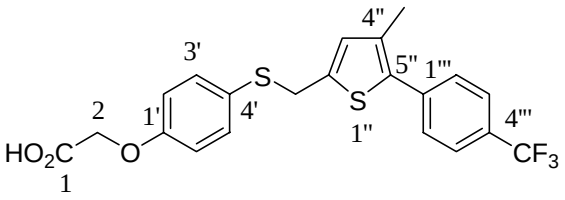


3b

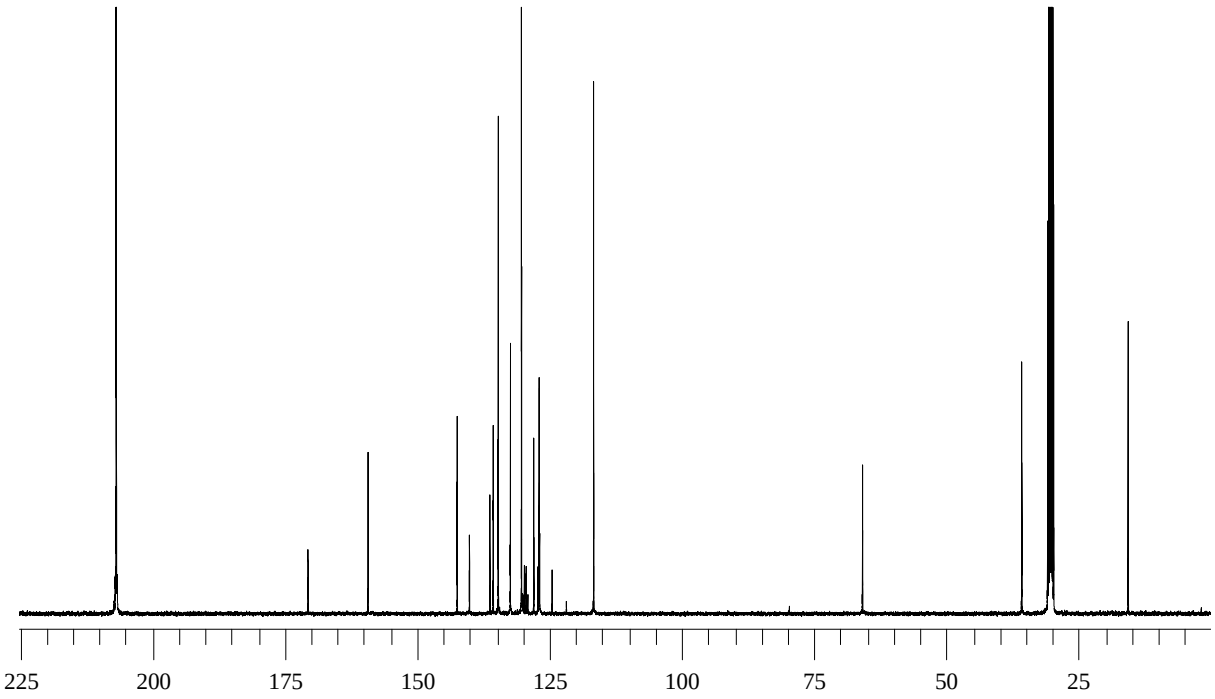




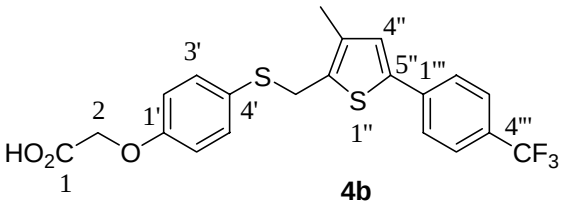
(4-[4-Methyl-5-(4-trifluoromethylphenyl)thien-2-ylmethylthio]phenoxy)acetic Acid (4a)



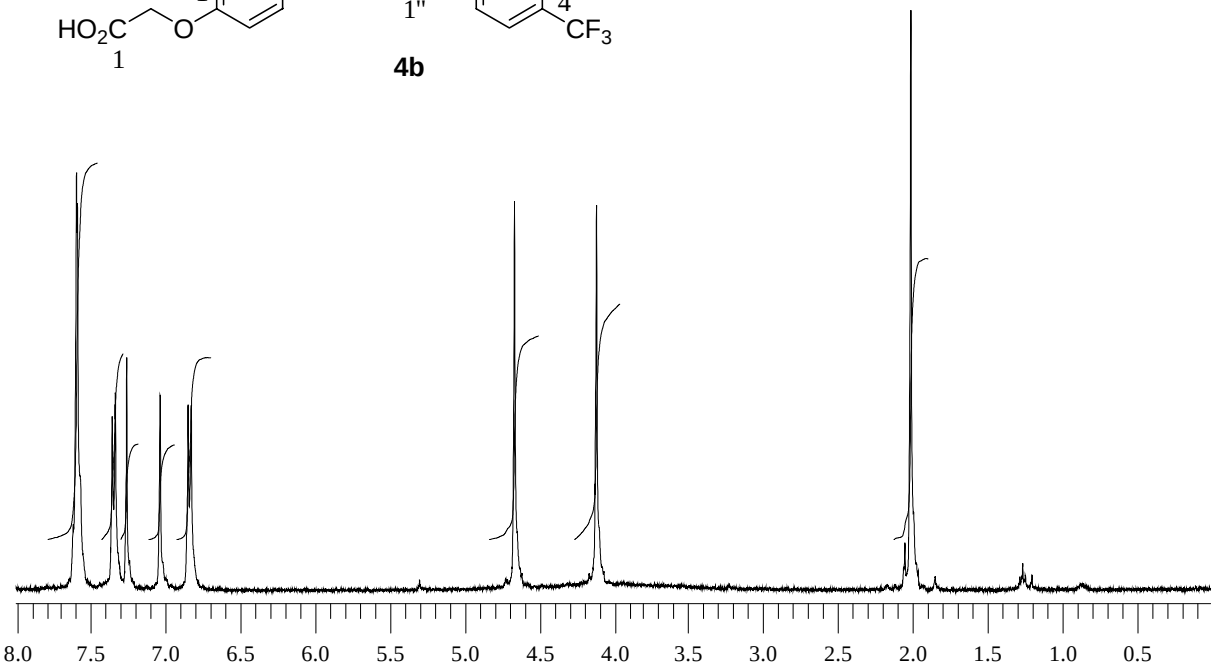
4a

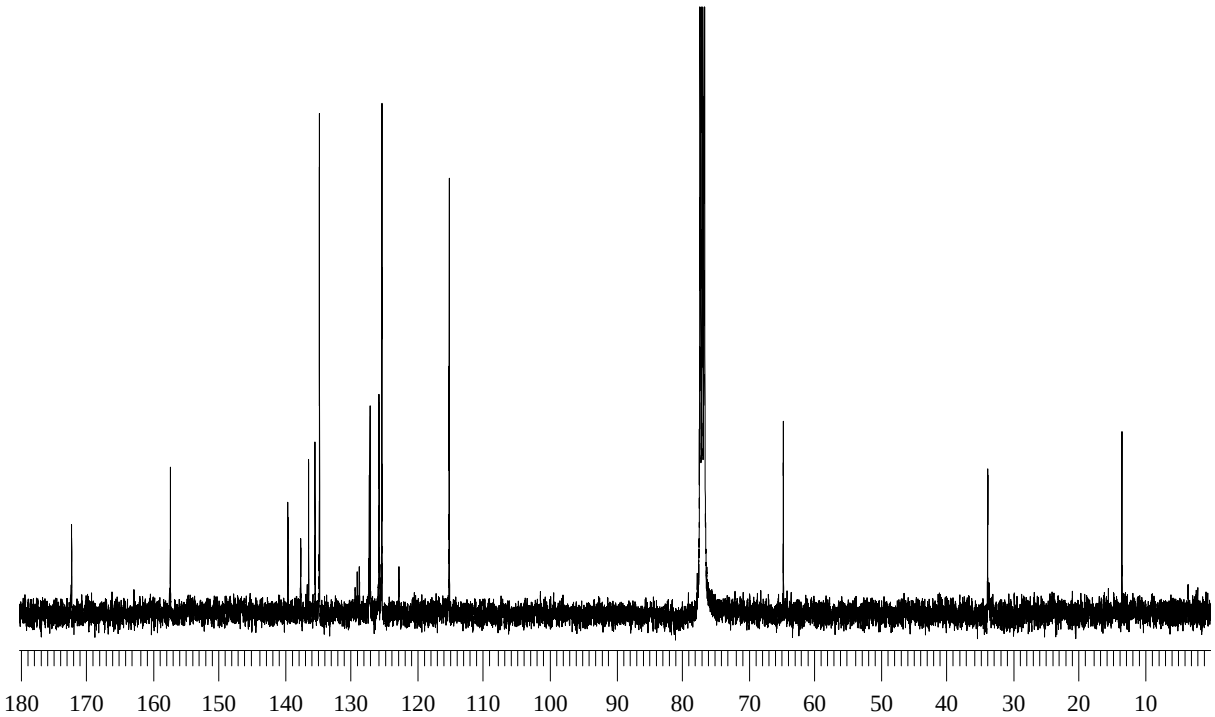


(4-[3-Methyl-5-(4-trifluoromethylphenyl)thien-2-ylmethylthio]phenoxy)acetic Acid (4b)

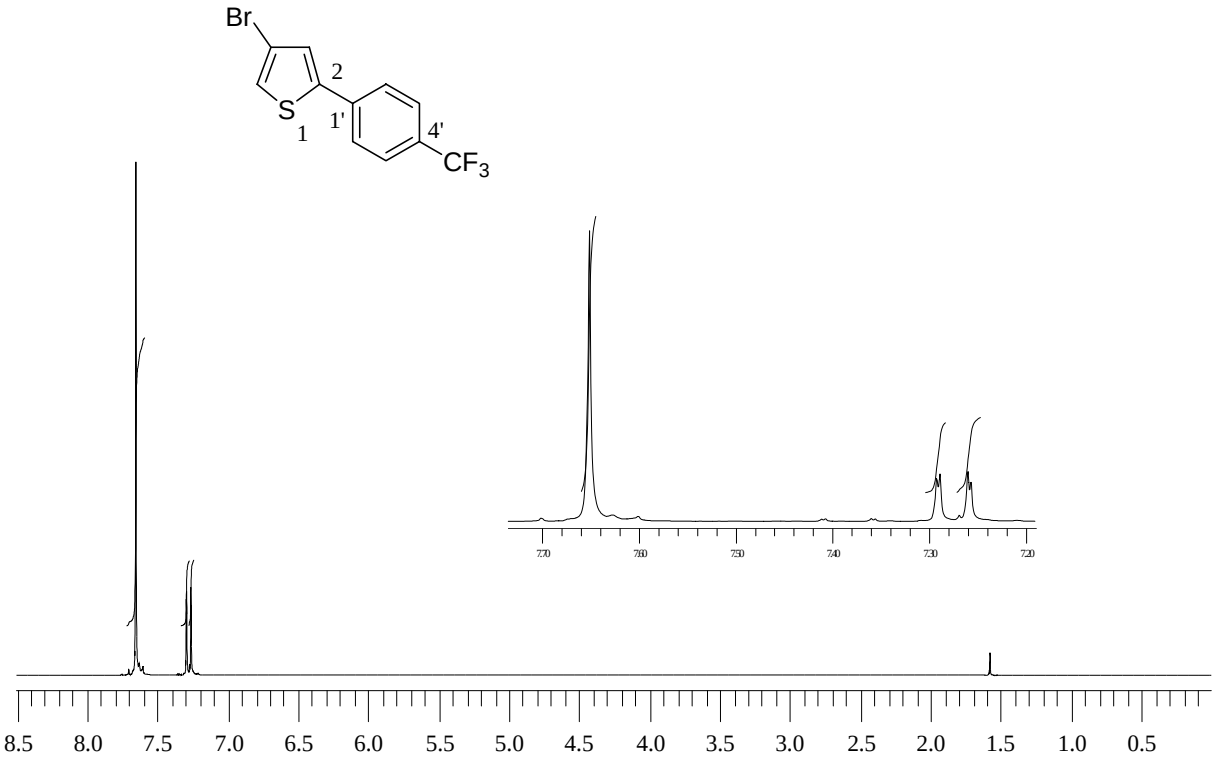


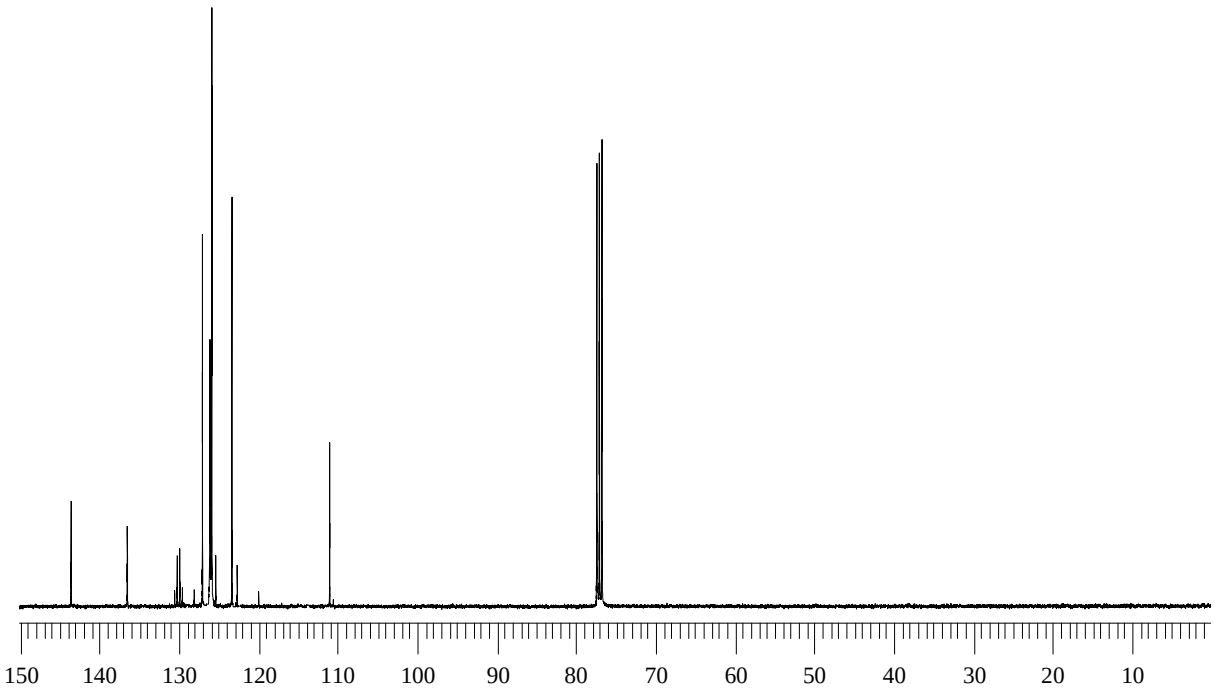
4b



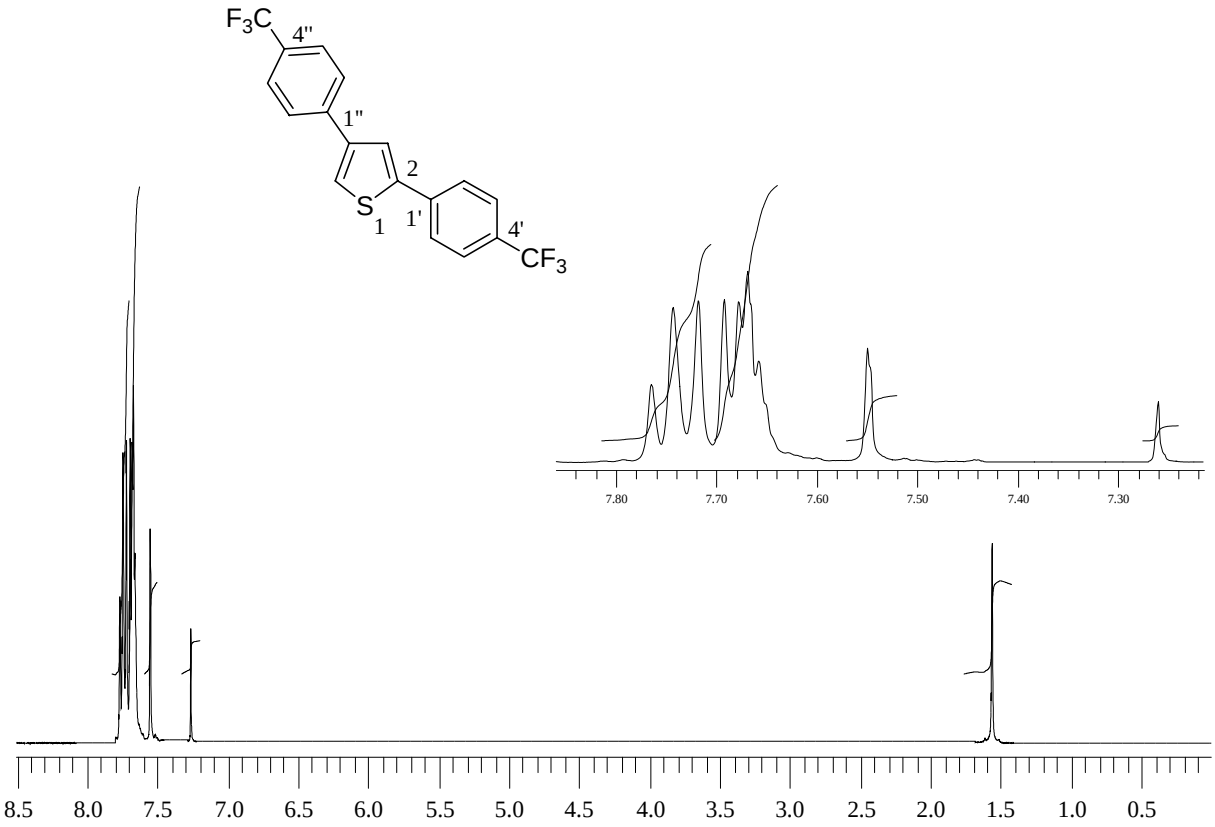


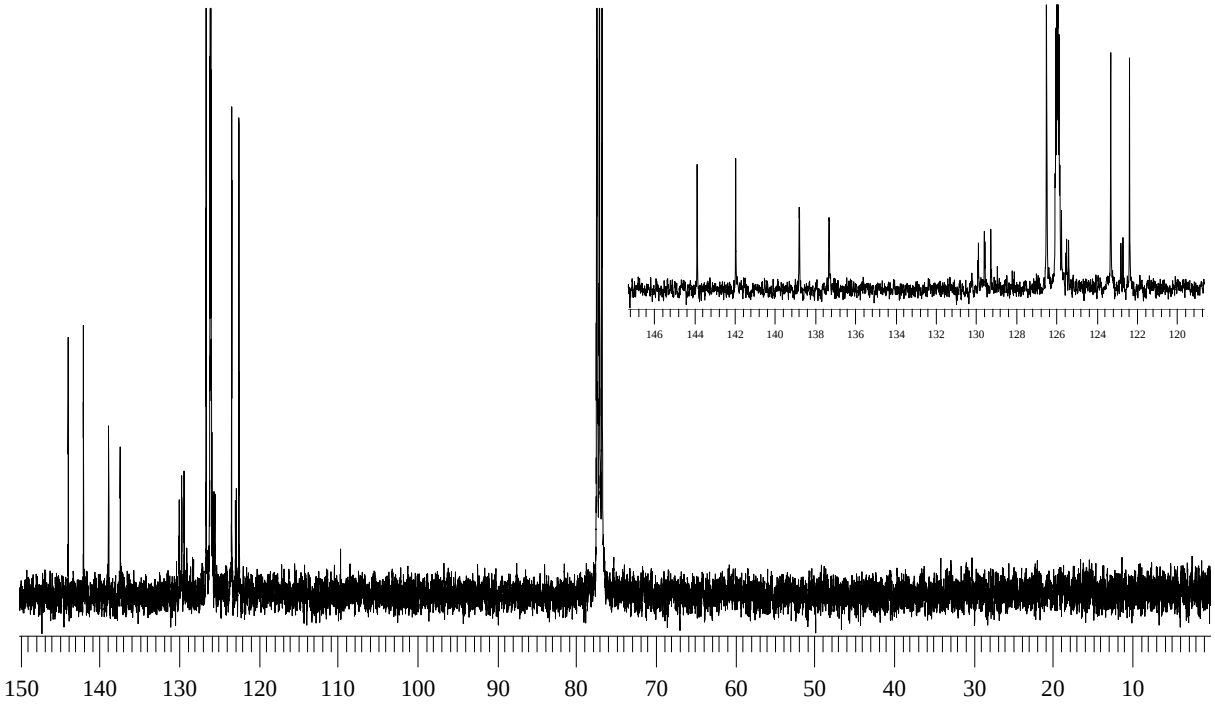
4-Bromo-2-(4-trifluoromethylphenyl)thiophene



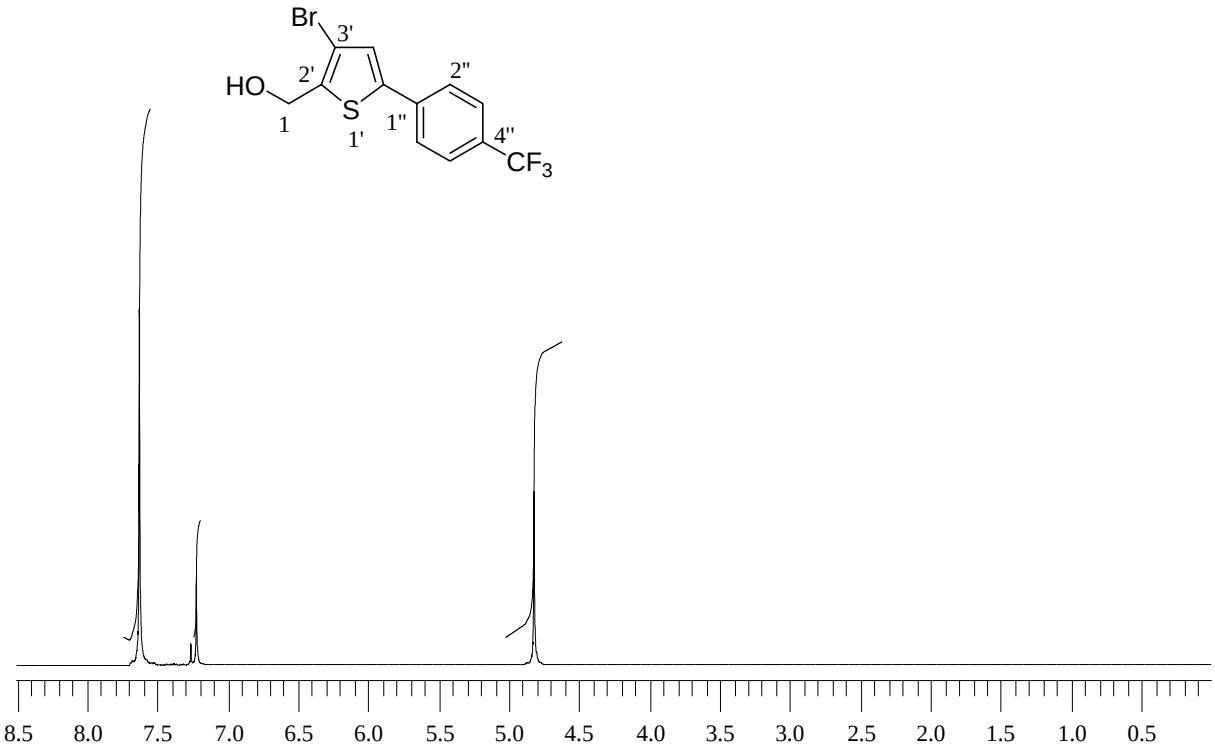


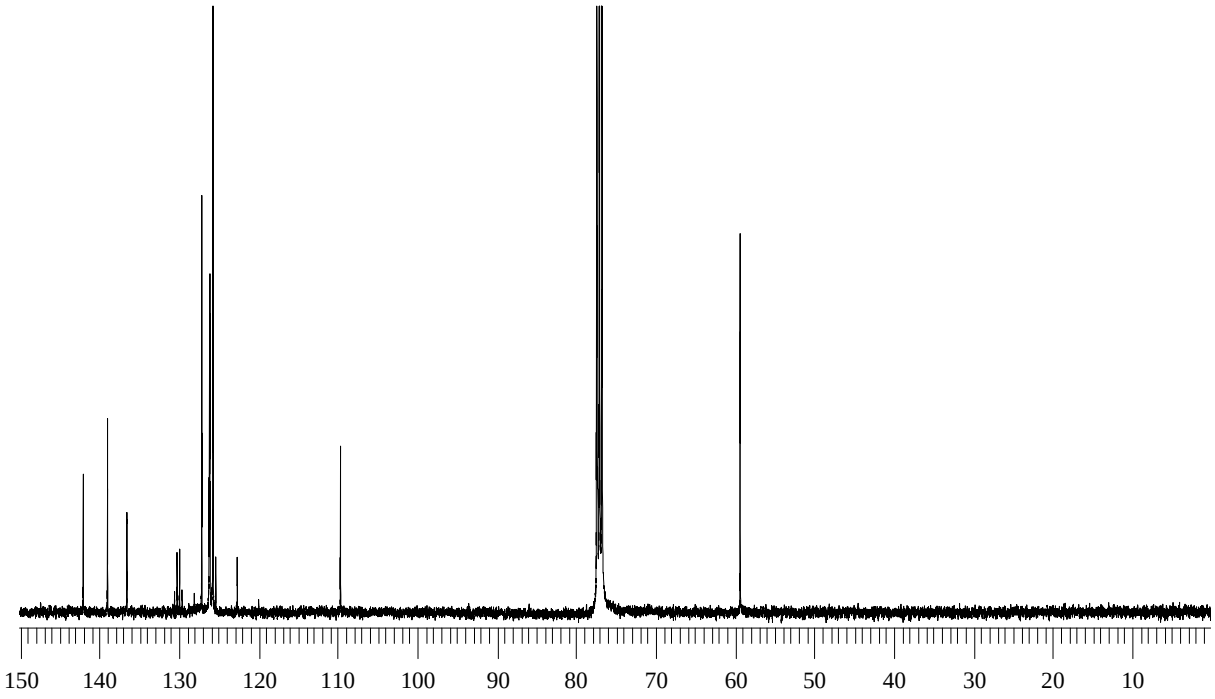
2,4-Bis(4-trifluoromethylphenyl)thiophene



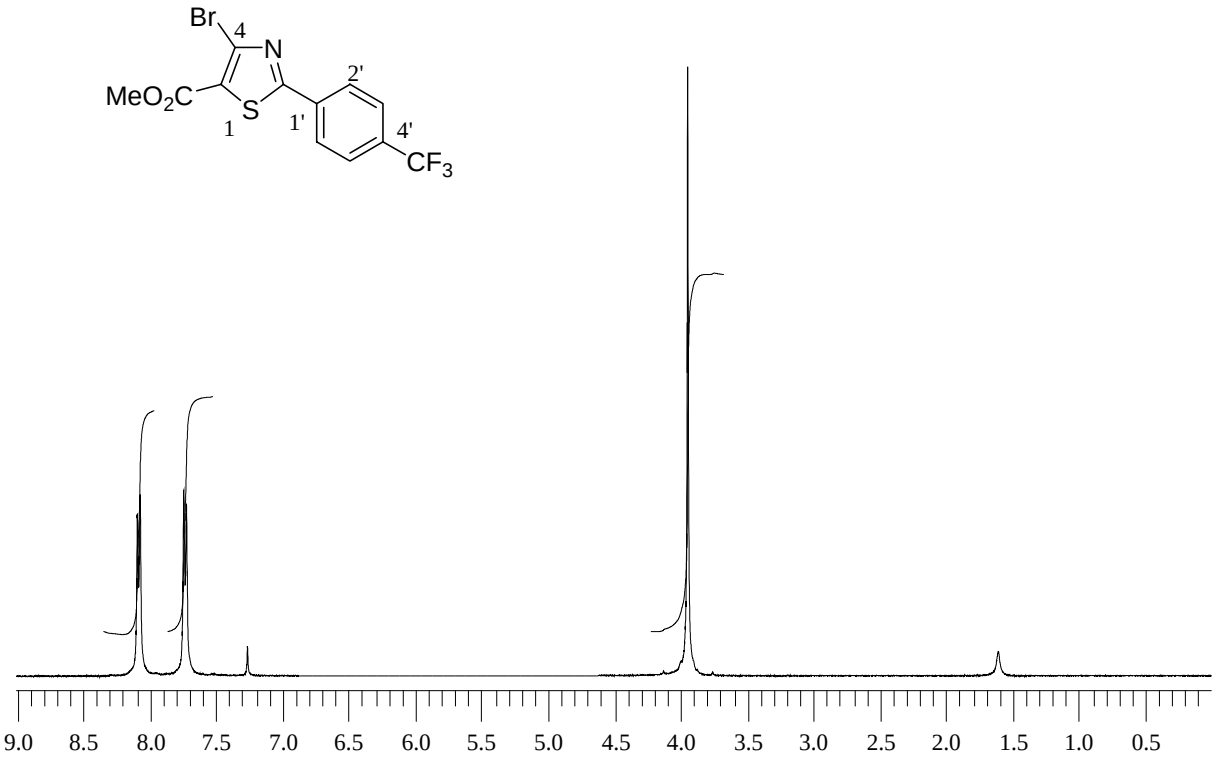


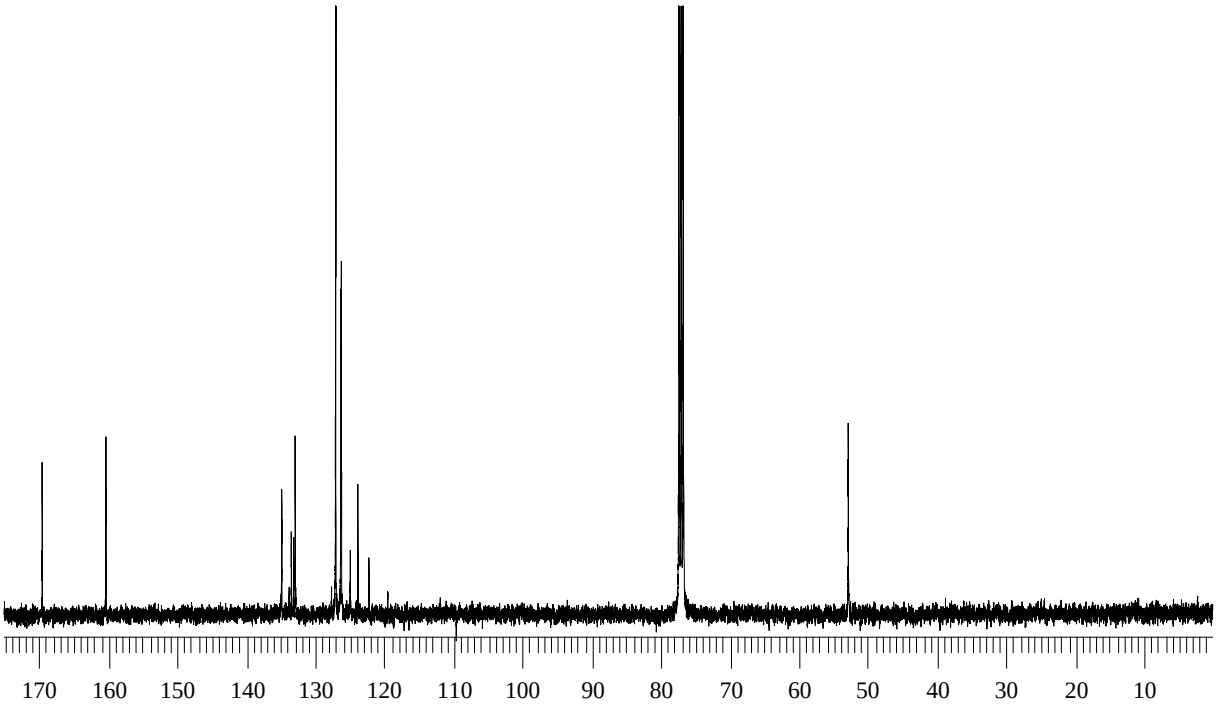
[3-Bromo-5-(4-trifluoromethylphenyl)thien-2-yl]methanol





Methyl 4-Bromo-2-(4-trifluoromethylphenyl)thiazole-5-carboxylate





[4-Bromo-2-(4-trifluoromethylphenyl)thiazol-5-yl]methanol