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Palladium Catalyzed Suzuki Cross-Coupling of 3-Iodo-2-(methylthio)-benzo[*b*]furan Derivatives: Synthesis of 3-Aryl-2-(methylthio)benzo[*b*]furans

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Experimental

Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 400 MHz. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$ or tetramethylsilane (TMS) as the external reference. Data are reported as follows: chemical shift (δ), multiplicity, coupling constant *(J)* in Hertz and integrated intensity. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 100 MHz. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet) and m (multiplet). High resolution mass spectra were recorded on a double focusing magnetic sector mass spectrometer using EI at 70 eV. Column chromatography was performed using silica gel (230-400 mesh) following the methods described by Still (Still, W.C.; Kahn, M.; Mitra, A.; *J. Org. Chem.* **1978**, *43*, 2923). Thin layer chromatography (TLC) was performed using silica gel GF_{254}, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapor, or acidic vanillin. The following solvents were dried and purified by distillation from the reagents indicated: tetrahydrofuran from sodium with a benzophenone ketyl indicator. All other solvents were ACS or HPLC grade unless otherwise noted. Air- and moisture-sensitive reactions were conducted in flame-dried or oven dried glassware equipped with tightly fitted rubber septa and under a positive atmosphere of dry nitrogen or argon. Reagents and solvents were handled using standard syringe techniques. Temperatures above room temperature were maintained by use of a mineral oil bath with an electrically heated coil connected to a controller.

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General procedure for the Suzuki coupling reaction

To a solution of appropriate 3-iodo-2-(methylthio) benzo[*b*]furan (0.5 mmol) in DMF (4.0 mL) and H_2O (0.4 mL) was added to $Pd(PPh_3)_4$ (0.011g, 2 mol%) and K_2CO_3 (1 mmol), under argon. After this time, boronic acid (0.75 mmol) was added. The mixture was then heated at 100 °C during 1-4 h, cooled to room temperature, diluted with dichloromethane (20 mL), and washed with brine (2 × 20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using hexane/ethyl acetate as eluent.

*2-(Methylthio)-3-phenylbenzofuran (**3a**)*

Yield: 0.111 g (93%). ^{1}H NMR: $CDCl_3$, 400 MHz, δ (ppm): 7.61-7.59 (m, 3H), 7.50-7.46 (m, 3H), 7.37 (t, *J* 7.3 Hz, 1H), 7.29 (t, *J* 7.3 Hz, 1H), 7.23 (dd, *J* 7.5 Hz and *J* 2.5 Hz, 1H), 2.52 (s, 3H). ^{13}C NMR: $CDCl_3$, 100 MHz, δ (ppm): 155.9, 147.5, 131.8, 129.1, 128.5, 128.3, 127.4, 124.4, 122.9, 122.5, 119.7, 110.8, 16.9. MS (EI, 70 eV) *m/z* (relative intensity): 238 (26), 222 (17), 194 (100), 163 (23), 151 (10), 76 (8). Anal. (%) Calc. for $C_{15}H_{12}OS$: C 74.97, H 5.03. Found: C 75.15, H 5.39.

*3-(4-Methoxyphenyl)-2-(methylthio)benzofuran (**3b**)*

Yield: 0.108 g (80%). ^{1}H NMR: $CDCl_3$, 400 MHz, δ(ppm): 7.59 (d, *J* 7.6 Hz, 1H), 7.53 (d, *J* 8.8 Hz, 2H), 7.47 (d, *J* 8.0 Hz, 1H), 7.30-7.20 (m, 2H), 7.03 (d, *J* 8.8 Hz, 2H), 3.85 (s, 3H), 2.49 (s, 3H). ^{13}C NMR: $CDCl_3$, 100 MHz, δ (ppm): 159.0, 155.4, 146.8, 130.2, 128.4, 124.4, 124.0, 122.8, 122.4, 119.7, 114.0, 110.8, 55.2, 17.1. MS (EI, 70 eV) *m/z* (relative intensity): 269 (14), 267 (100), 252 (48), 224 (46), 181 (14), 150 (21).

*2-(Methylthio)-3-p-tolylbenzofuran (**3c**)*

Yield: 0.116 g (92%). ^{1}H NMR: $CDCl_3$, 400 MHz, δ (ppm): 7.60 (d, *J* 7.6 Hz, 1H), 7.50 (d, *J* 7.8 Hz, 2H), 7.44 (d, *J* 8.0 Hz, 1H), 7.29 (d, *J* 7.8 Hz, 2H), 7.25-7.17 (m, 1H), 2.50 (s, 3H), 2.40 (s, 3H). ^{13}C NMR: $CDCl_3$, 100 MHz, δ (ppm): 155.4, 147.1, 137.2, 129.2, 128.9, 128.7, 128.3, 124.3, 122.8, 122.6, 119.7, 110.8, 21.2, 16.9. MS (EI, 70 eV) *m/z* (relative intensity): 254 (3), 251 (100), 236 (24), 208 (58), 176 (13), 150 (19).

*3-(4-Bromophenyl)-2-(methylthio)benzofuran (**3e**)*

Yield: 0.111 g (70%). ^{1}H NMR: ($CDCl_3$, 400 MHz) δ (ppm): 7.60 (d, *J* 8.5 Hz, 2H), 7.54 (d, *J* 7.6 Hz, 1H), 7.47-7.44 (m, 3H), 7.31-7.21 (m, 2H), 2.51 (s, 3H). ^{13}C NMR: ($CDCl_3$, 50 MHz), δ (ppm): 155.4, 147.7, 131.7, 130.7, 130.5, 124.6, 123.1, 121.4, 121.3, 119.4, 110.9, 16.8. MS (EI, 70 eV) *m/z* (relative intensity): 318 (10), 221 (100), 193 (11), 161 (14), 150 (33).

*1-(4-(2-(Methylthio)benzofuran-3-yl)phenyl)ethanone (**3f**)*

Yield: 0.098 g (70%). ^{1}H NMR: ($CDCl_3$, 400 MHz) δ (ppm): 8.08 (d, *J* 8.3 Hz, 2H), 7.70 (d, *J* 8.3 Hz, 2H), 7.61 (d, *J* 6.8 Hz, 1H), 7.50 (d, *J* 7.6 Hz, 1H), 7.34-7.25 (m, 2H), 2.65 (s, 3H), 2.56 (s, 3H). ^{13}C NMR: ($CDCl_3$, 50 MHz), δ (ppm): 197.5, 155.5, 148.7, 136.9, 135.8, 129.0, 128.6, 127.8, 124.6, 123.3, 121.1, 119.4, 111.0, 26.6, 16.6. MS (EI, 70 eV) *m/z* (relative intensity): 280 (17), 279 (100), 264 (35), 221 (12), 150 (21), 43 (58).

*1-(3-(2-(Methylthio)benzofuran-3-yl)phenyl)ethanone (**3g**)*

Yield: 0.126 g (90%). ^{1}H NMR: ($CDCl_3$, 400 MHz) δ (ppm): 8.02 (t, *J* 2.0 Hz, 1H), 7.95 (dt, *J* 7.3 Hz and *J* 1.2 Hz, 1H), 7.80 (dt, *J* 7.3 Hz and *J* 1.2 Hz, 1H), 7.59-7.54 (m, 2H), 7.49-7.47 (m, 1H), 7.30 (td, *J* 7.3 Hz and *J* 1.4 Hz, 1H), 7.25 (td, *J* 7.5 Hz and *J* 1.3 Hz, 1H), 2.64 (s, 3H), 2.53 (s, 3H). ^{13}C NMR: ($CDCl_3$, 50 MHz), δ (ppm): 197.6, 155.4, 148.0, 137.4, 133.4, 132.3, 128.8, 128.7, 127.8, 127.1, 124.6, 123.1, 121.4, 119.3, 110.9, 26.6, 16.7. MS (EI, 70 eV) *m/z* (relative intensity): 280 (17), 278 (100), 264 (7), 150 (19).

*2-(Methylthio)-3-(3-nitrophenyl)benzofuran (**3h**)*

Yield: 0.081 g (57%). ^{1}H NMR: ($CDCl_3$, 400 MHz) δ (ppm): 8.48 (t, *J* 2.0 Hz, 1H), 8.20 (dd, *J* 5.8 Hz and *J* 2.0 Hz, 1H), 7.94 (d, *J* 7.6 Hz, 1H), 7.64 (t, *J* 7.8 Hz, 1H), 7.59 (d, *J* 8.5 Hz, 1H), 7.50 (d, *J* 7.8 Hz, 1H), 7.35-7.24 (m, 2H), 2.57 (s, 3H). ^{13}C NMR: ($CDCl_3$, 50 MHz), δ (ppm): 155.4, 148.8, 148.4, 134.7, 133.6, 129.4, 127.4, 124.8, 123.5, 123.4, 122.0, 119.9, 119.0, 111.0, 16.5. MS (EI, 70 eV) *m/z* (relative intensity): 282 (100), 250 (10), 221 (43), 192 (15), 162 (18), 150 (30).

*2-(Methylthio)-3-(3-(trifluoromethyl)phenyl)benzofuran (**3i**)*

Yield: 0.137 g (89%). ^{1}H NMR: ($CDCl_3$, 400 MHz) δ (ppm): 7.88 (s, 1H), 7.78 (d, *J* 7.3 Hz, 1H), 7.63-7.55 (m, 3H), 7.49-7.47 (m, 1H), 7.33-7.23 (m, 2H), 2.53 (s, 3H). ^{13}C NMR: ($CDCl_3$, 50 MHz), δ (ppm): 155.5, 148.4, 132.8, 132.3, 130.8 (q, *J* 32 Hz), 129.9, 129.0, 125.7 (q, *J* 3.7 Hz), 124.7, 124.0 (q, *J* 3.6 Hz), 123.8 (q, *J* 273 Hz), 123.3, 119.3, 111.0, 16.7. MS (EI, 70 eV) *m/z* (relative intensity): 305 (100), 289 (8), 262 (95), 221 (15), 150 (13).

*5-Methyl-2-(methylthio)-3-(naphthalen-1-yl)benzofuran (**3o**)*

Yield: 0.139 g (92%). ^{1}H NMR: ($CDCl_3$, 400 MHz) δ (ppm): 7.89 (d, *J* 8.0 Hz, 2H), 7.73 (d, *J* 8.5 Hz, 1H), 7.54-7.34 (m, 5H), 7.08 (dd, *J* 7.1 Hz and *J* 1.5 Hz, 1H), 6.90 (s, 1H), 2.40 (s, 3H), 2.28 (s, 3H). ^{13}C NMR: ($CDCl_3$, 50 MHz), δ (ppm): 153.8, 148.9, 133.7, 132.4, 132.0, 129.9, 129.3, 128.4, 128.3, 128.2, 125.9, 125.8, 125.6, 125.4, 121.4, 119.9, 110.3, 21.1, 16.9. MS (EI, 70 eV) *m/z* (relative intensity): 300 (100), 285 (27), 270 (11), 258 (32), 242 (12), 223 (7).

*5-Fluoro-2-(methylthio)-3-phenylbenzofuran (**3p**)*

Yield: 0.103 g (80%). ^{1}H NMR: ($CDCl_3$, 400 MHz) δ (ppm): 7.55-7.53 (m, 2H), 7.46 (t, *J* 7.8 Hz, 2H), 7.37-7.33 (m, 2H), 7.24 (dd, *J* 6.1 Hz and *J* 2.5 Hz, 1H), 6.97 (td, *J* 6.3 Hz and *J* 2.9 Hz, 1H), 2.50 (s, 3H). ^{13}C NMR: ($CDCl_3$, 50 MHz), δ (ppm): 160.6, 158.2, 151.6, 149.5, 131.2, 128.7, 128.6, 127.6, 122.1, 111.8 (d, *J* 26.3 Hz), 111.4 (d, *J* 9.5 Hz), 105.3 (d, *J* 25.6 Hz), 16.5. MS (EI, 70 eV) *m/z* (relative intensity): 255 (100), 239 (64), 212 (92), 192 (12), 168 (30), 150 (6).

*5-Fluoro-3-(4-methoxyphenyl)-2-(methylthio)benzofuran (**3q**)*

Yield: 0.130 g (90%). ^{1}H NMR: ($CDCl_3$, 400 MHz) δ (ppm): 7.50 (d, *J* 8.5 Hz, 2H), 7.37 (dd, *J* 4.9 Hz and *J* 4.1 Hz, 1H), 7.24 (dd, *J* 6.1 Hz and *J* 2.7 Hz, 1H), 7.04-6.97 (m, 3H), 3.86 (s, 3H), 2.51 (s, 3H). ^{13}C NMR: ($CDCl_3$, 50 MHz), δ (ppm): 160.6, 159.1, 158.2, 151.6, 148.8, 130.0, 123.5, 122.3, 114.2, 111.9 (d, *J* 24.8 Hz), 111.4 (d, *J* 9.5 Hz), 105.3 (d, *J* 24.8 Hz), 55.3, 16.7. MS (EI, 70 eV) *m/z* (relative intensity): 285 (100), 269 (73), 242 (49), 226 (14), 155.6 (17).

*2-(Methylthio)-3-(thiophen-2-yl)benzofuran (**3x**)*

Yield: 0.074 g (60%). ^{1}H NMR: $CDCl_3$, 400 MHz, δ (ppm): 7.82-7.80 (m, 1H), 7.46-7.44 (m, 2H), 7.37 (dd, *J* 4.0 Hz and *J* 1.2 Hz, 1H), 7.32-7.25 (m, 2H), 7.16 (dd, *J* 4.0 Hz and *J* 1.4 Hz, 1H), 2.56 (s, 3H).^{13}C NMR: $CDCl_3$,

100 MHz, δ (ppm): 155.3, 147.6, 133.1, 127.6, 127.2, 126.0, 125.0, 124.6, 123.2, 120.0, 116.4, 110.8, 16.8. MS (EI, 70 eV) *m/z* (relative intensity): 243 (100), 228 (75), 200 (64), 169 (15), 114 (20). HRMS calc. for $C_{13}H_{10}OS_2$: 246.0173. Found: 246.0177.

Selected Spectra

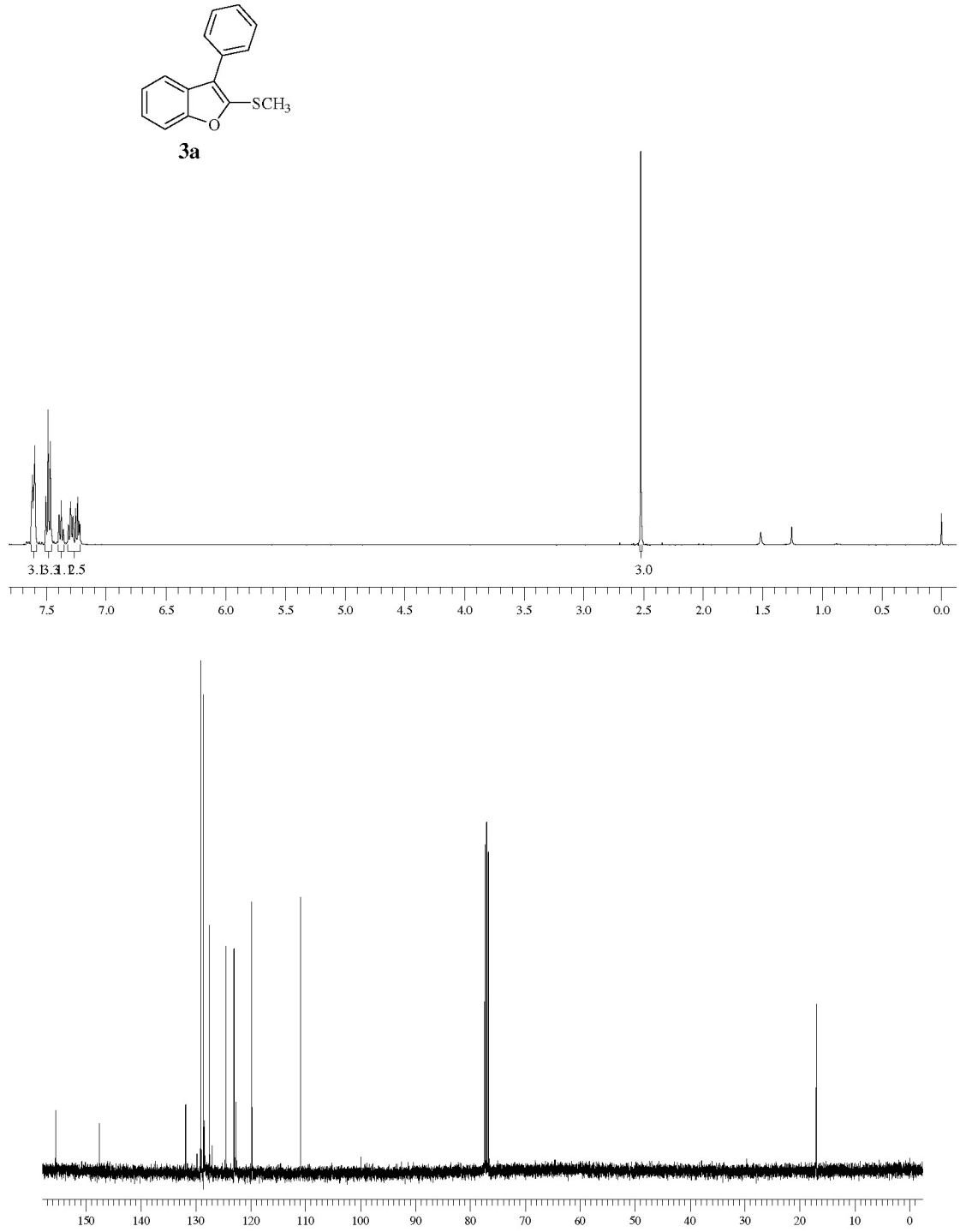


Figure S1. (up) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of compound **3a**; (down) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of compound **3a**.

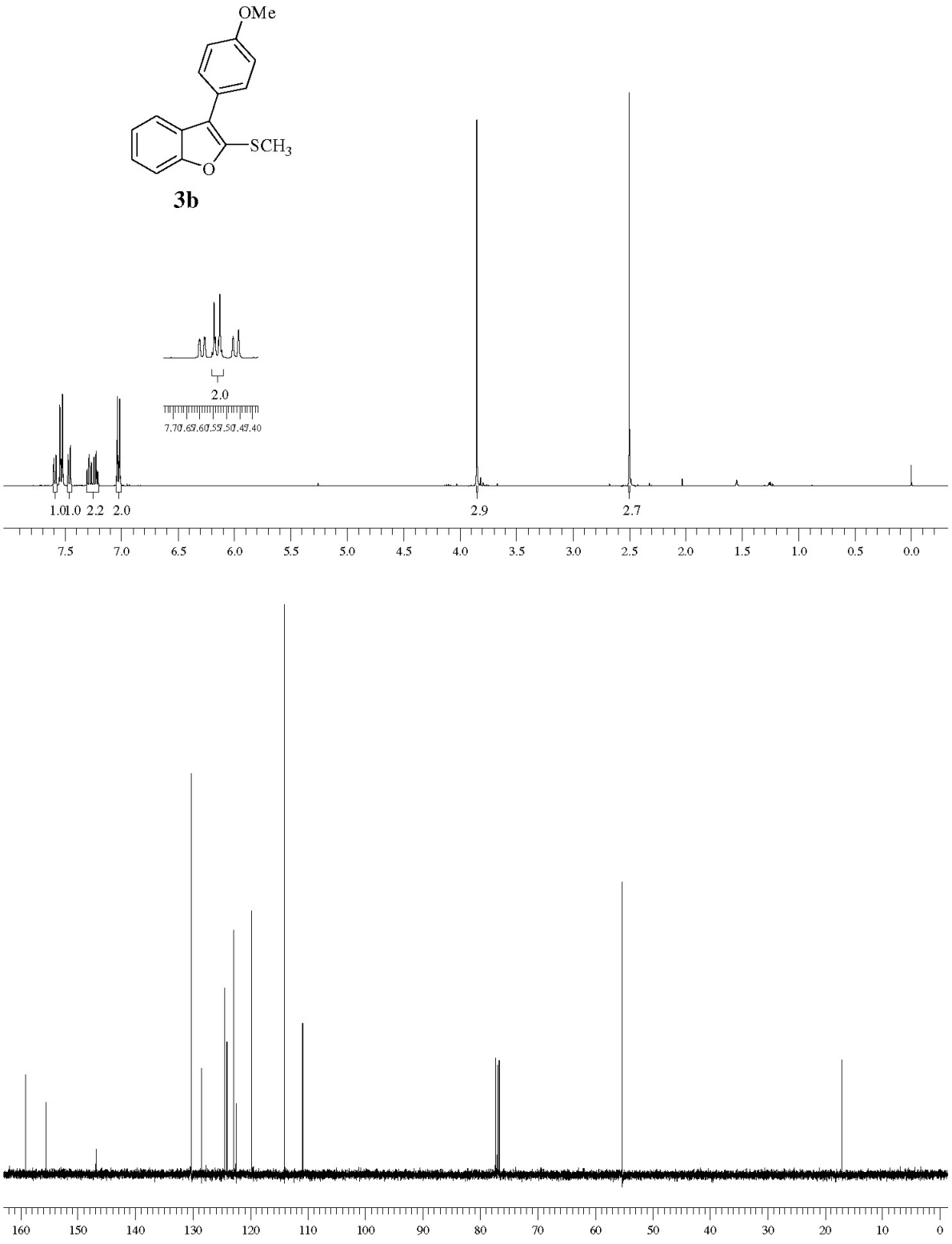


Figure S2. (up) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of compound **3b**; (down) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of compound **3b**.

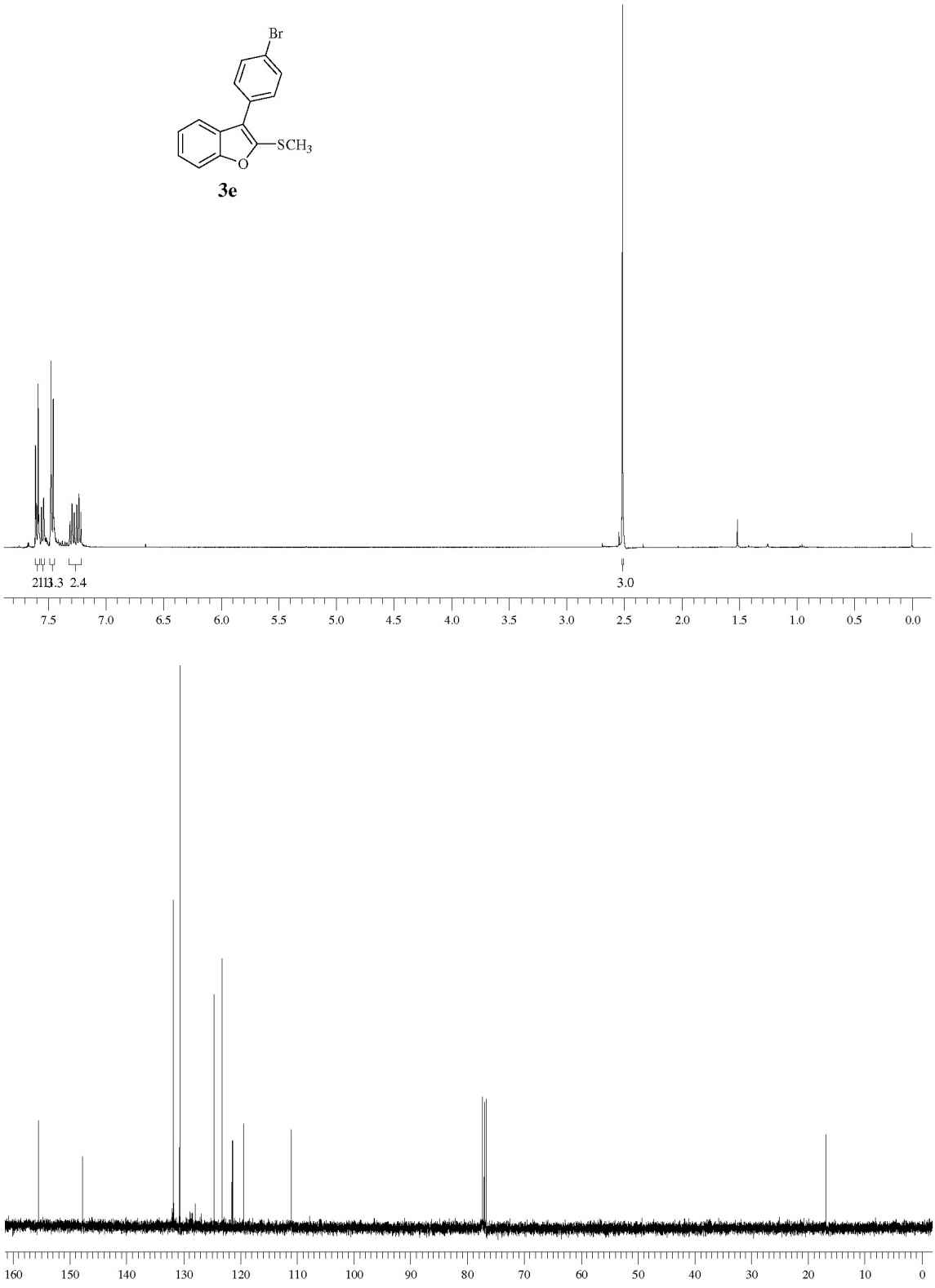


Figure S3. (up) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of compound **3e**; (down) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of compound **3e**.

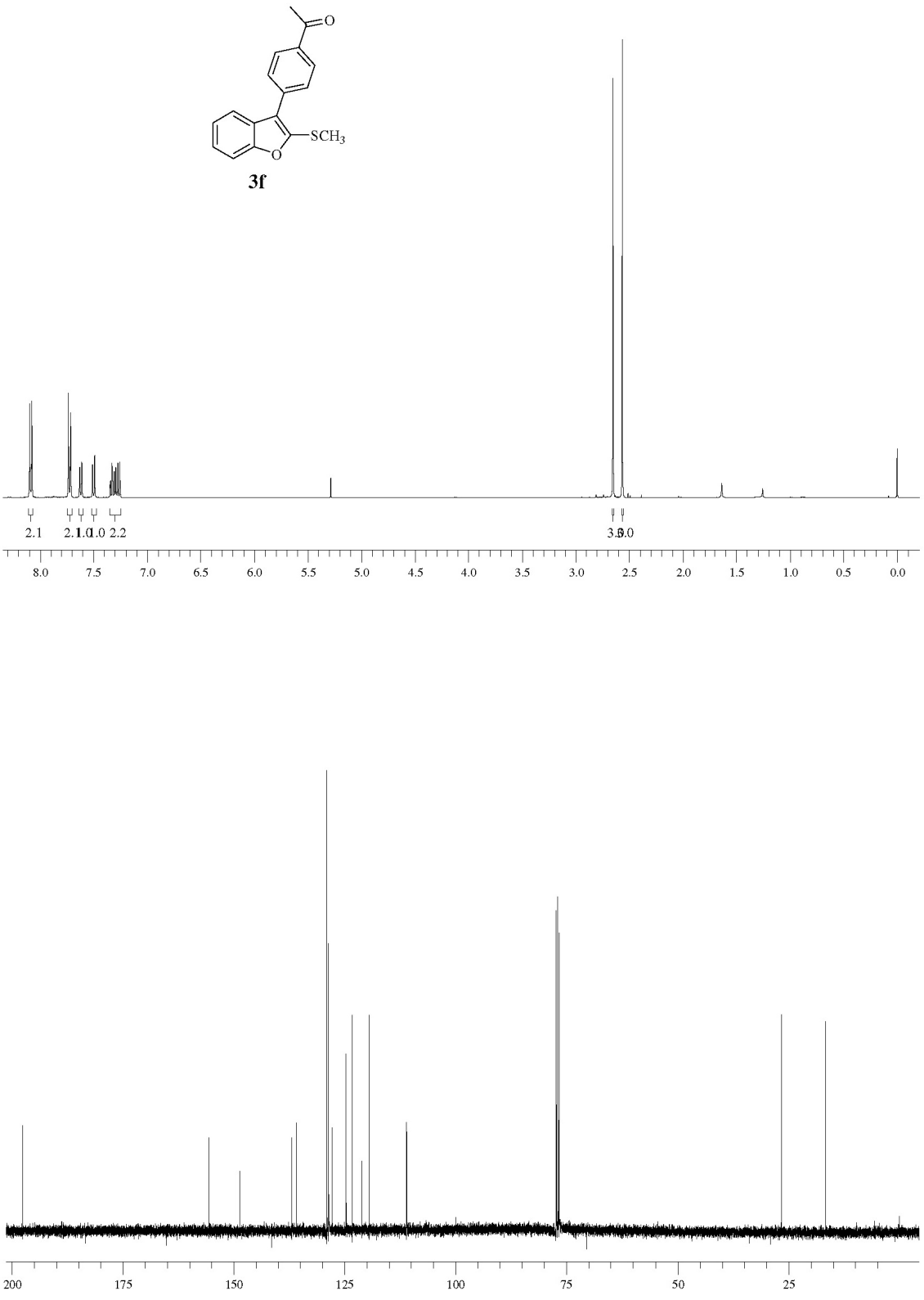


Figure S4. (up) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of compound **3f**; (down) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of compound **3f**.

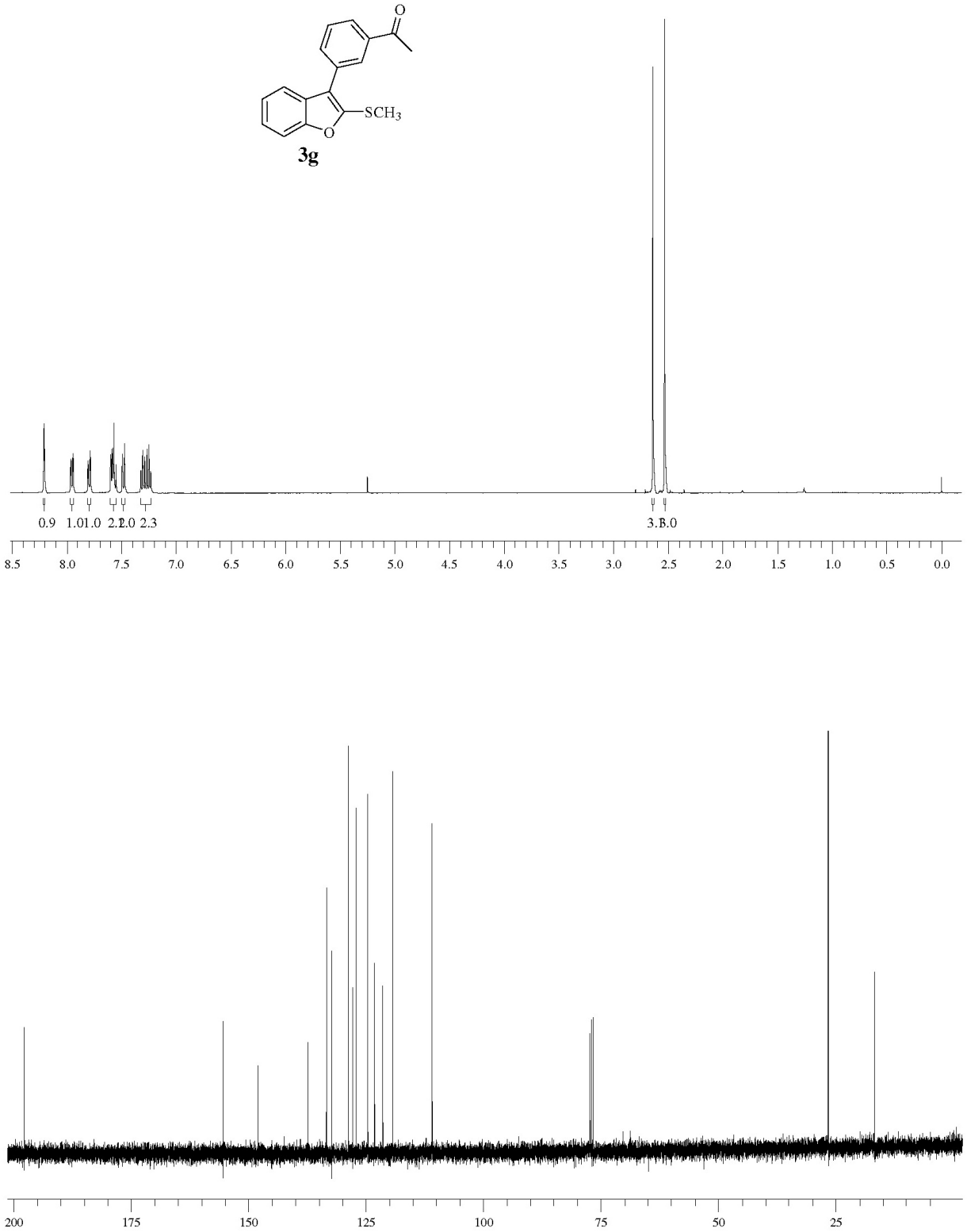


Figure S5. (up) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of compound **3g**; (down) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of compound **3g**.

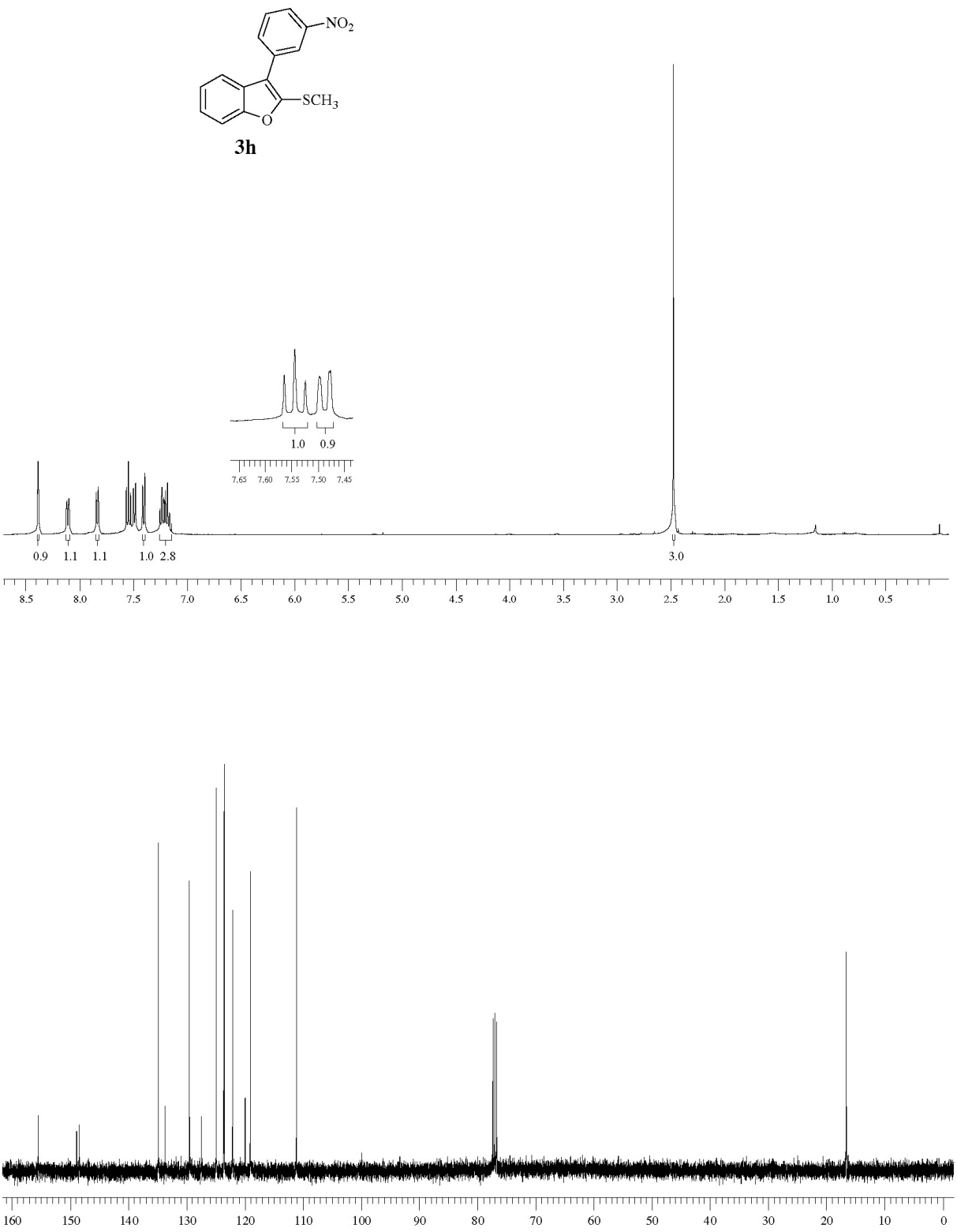


Figure S6. (up) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of compound **3h**; (down) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of compound **3h**.

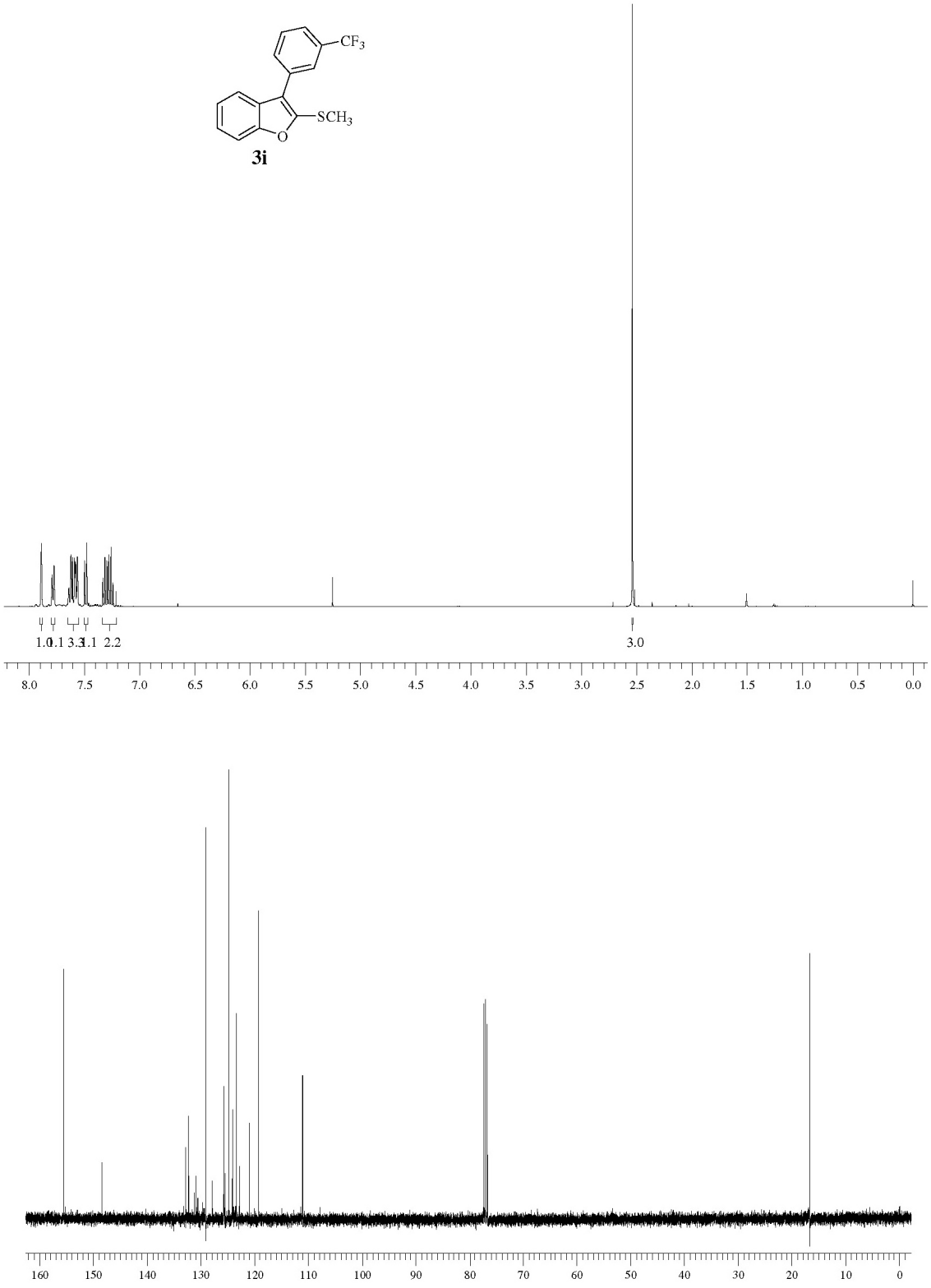


Figure S7. (up) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of compound **3i**; (down) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of compound **3i**.

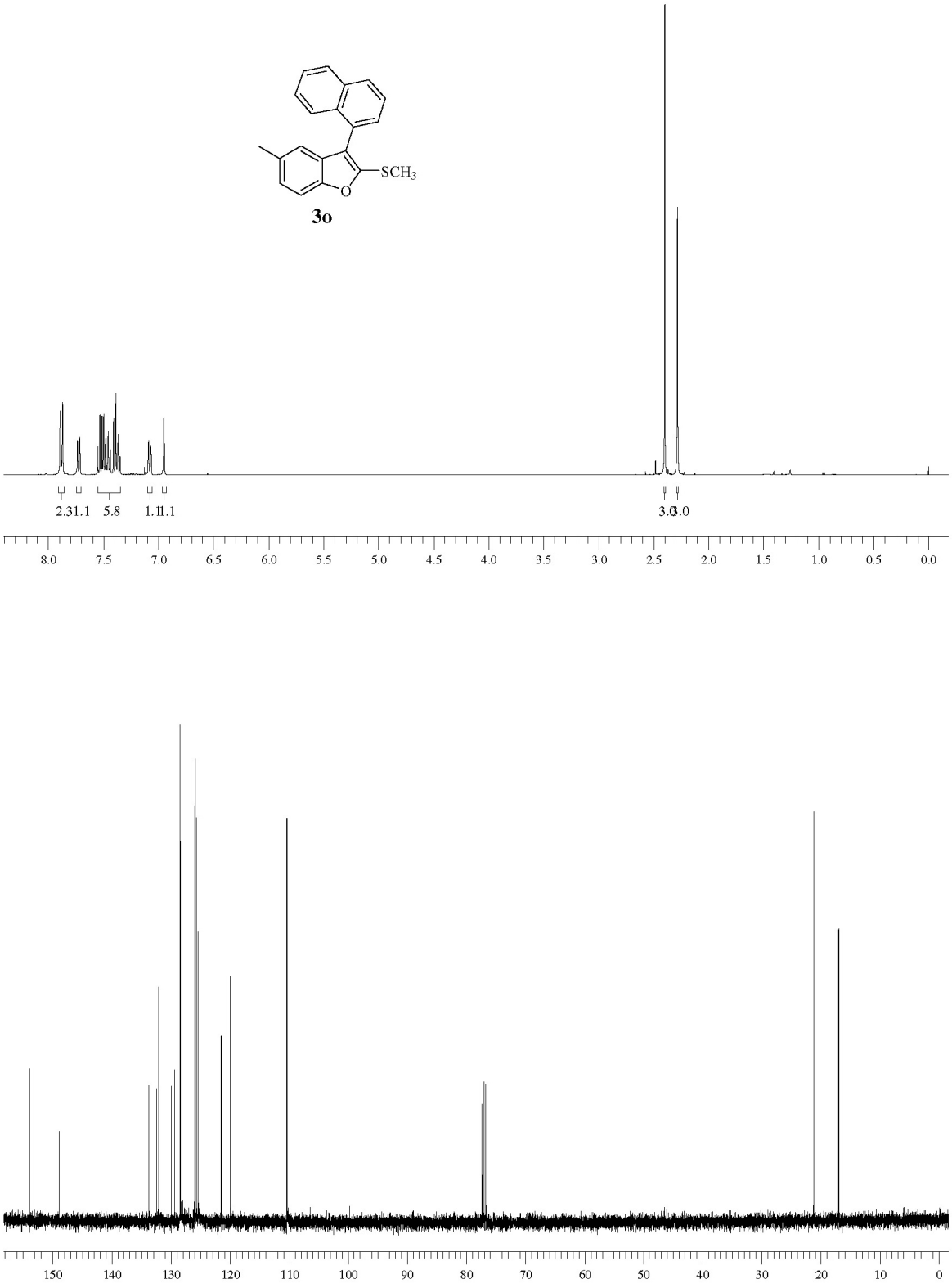
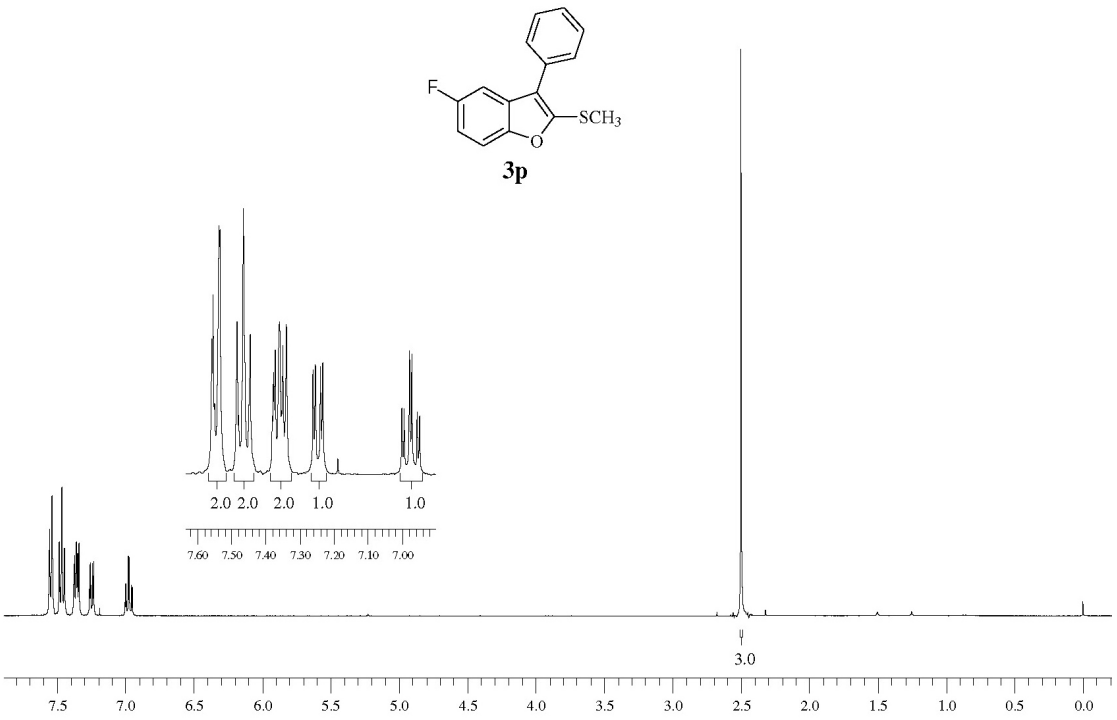


Figure S8. (up) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of compound **3o**; (down) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of compound **3o**.



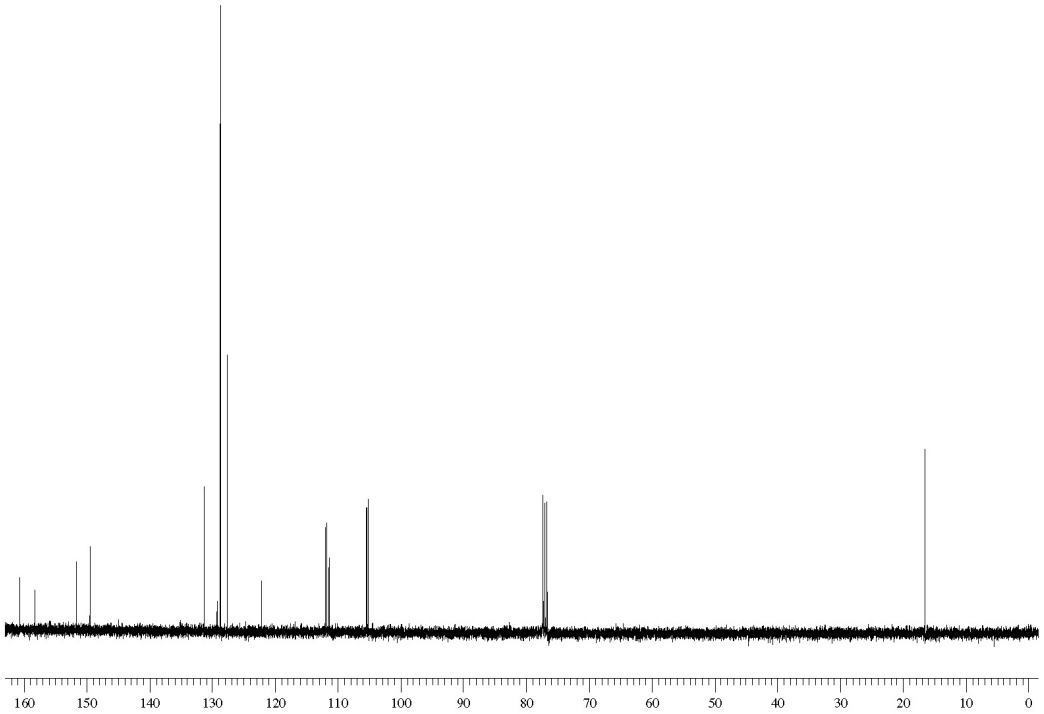
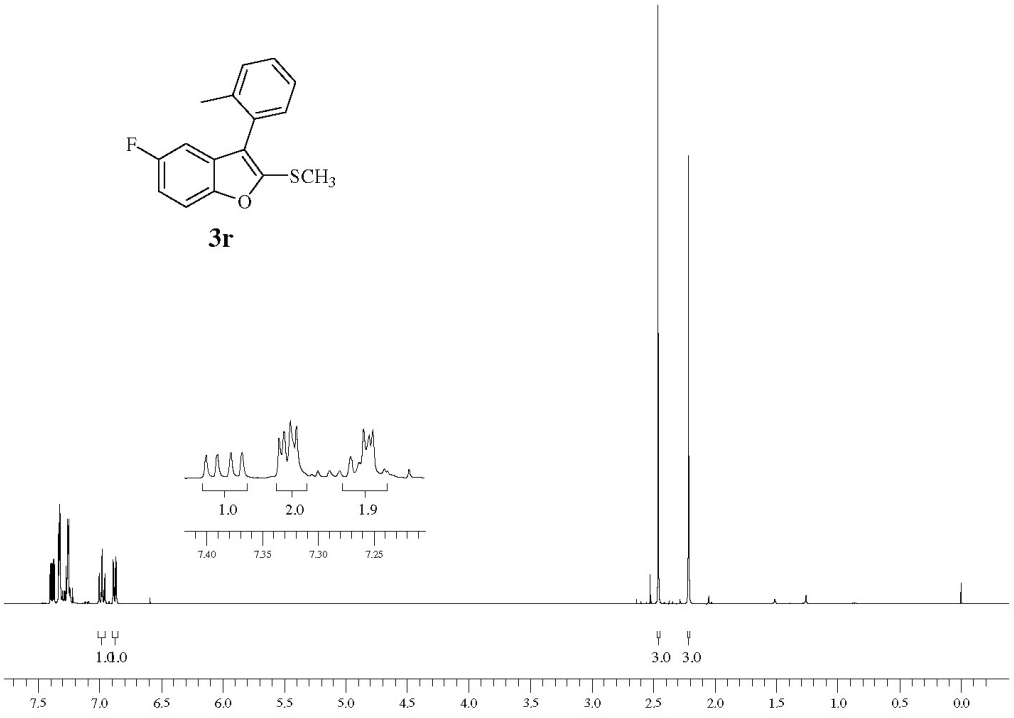


Figure S9. (up) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of compound **3p**; (down) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of compound **3p**.



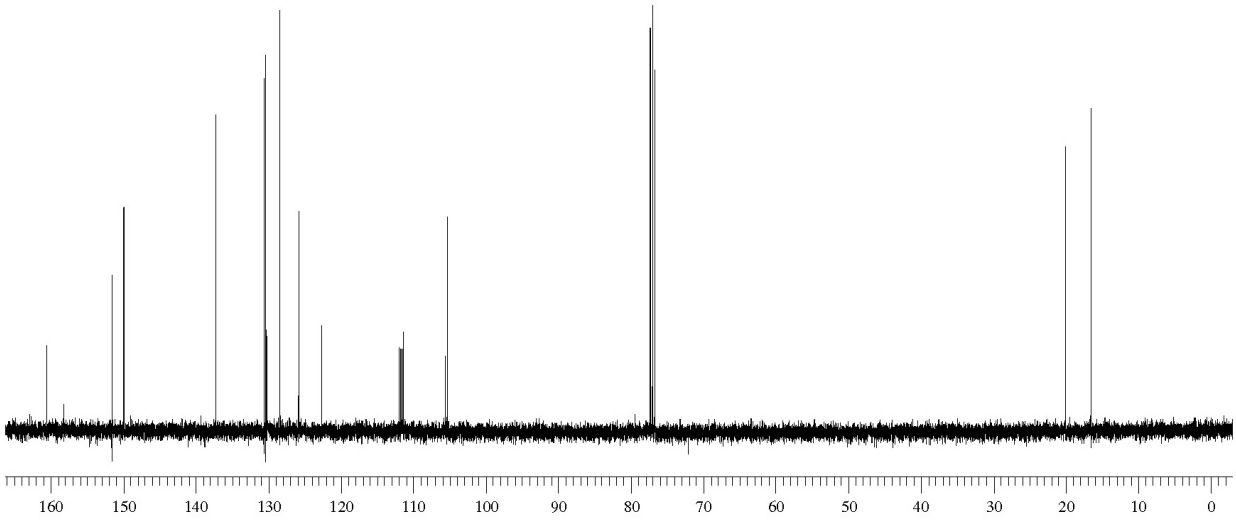


Figure S10. (up) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of compound **3r**; (down) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of compound **3r**.

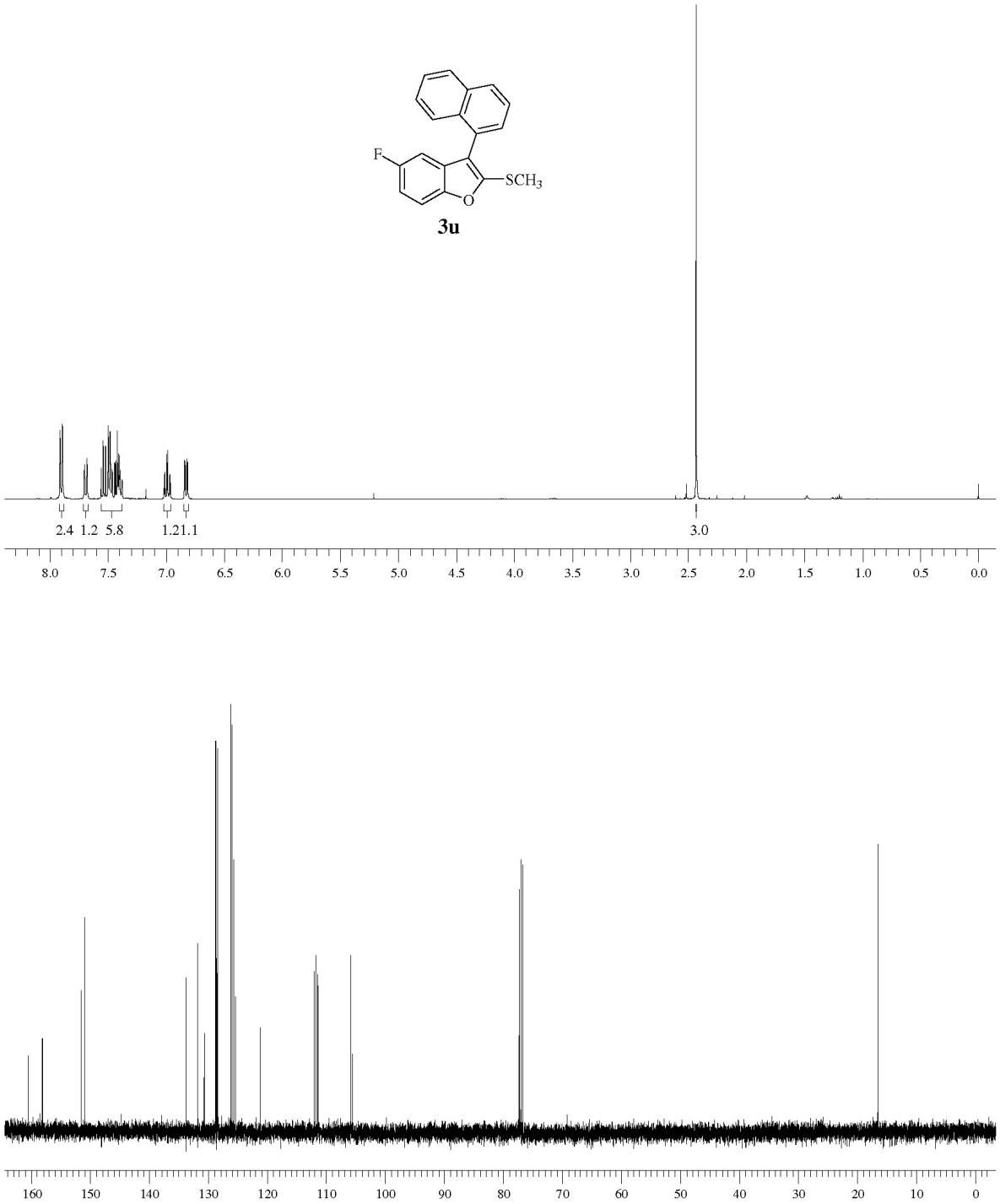


Figure S11. (up) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of compound **3u**; (down) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of compound **3u**.

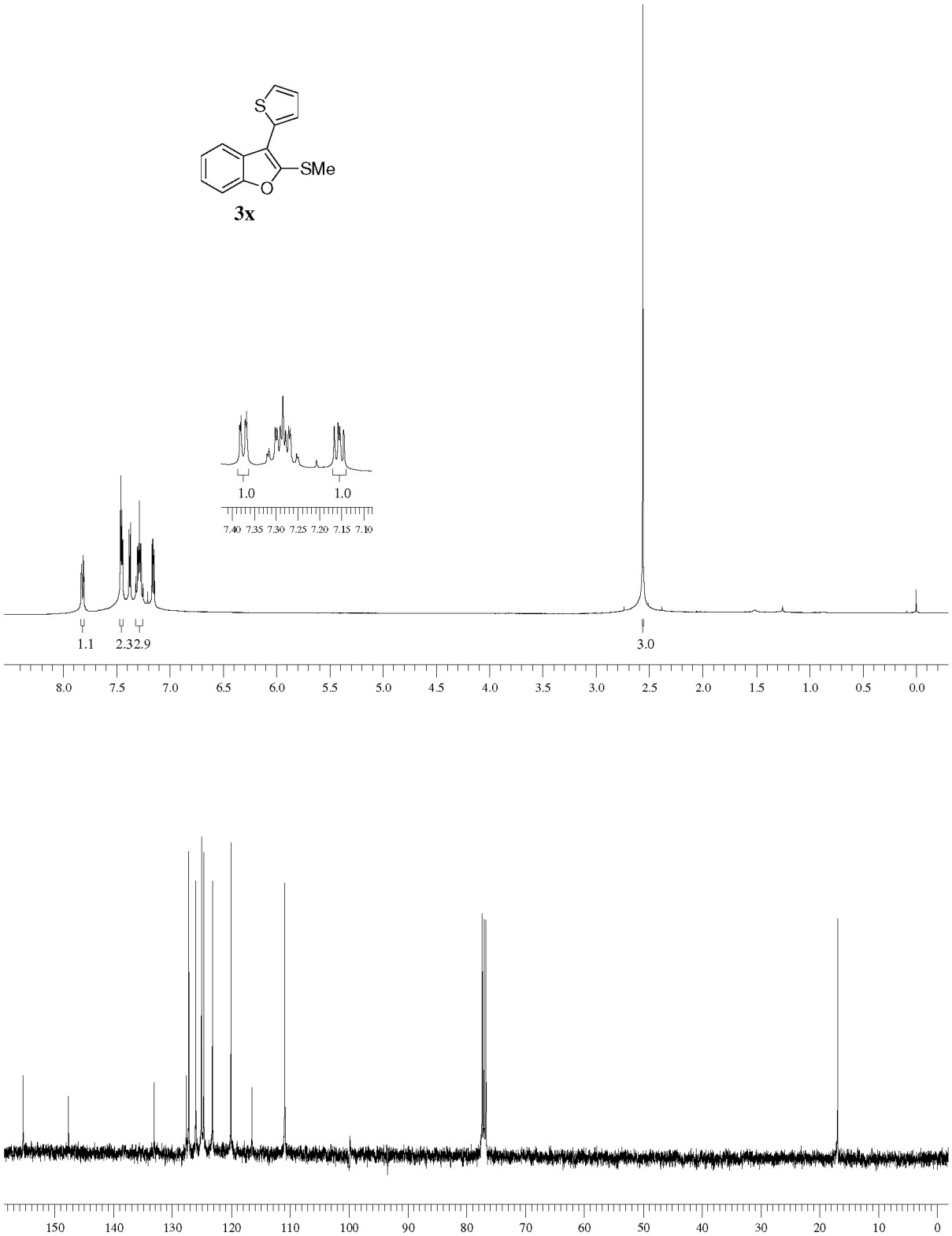


Figure S12. (up) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of compound **3x**; (down) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of compound **3x**.