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# Non-catalytic alkylation of the 2-positioned methyl group in 3-acyl-2-methylindoles

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## Content

## Experimental

### Methods and materials

Starting compounds **1a-h** were synthesized according to the known methods: Vilsmeier acylation [S1] of 2-methylindole followed by alkylation [S2] of 3-acylindoles. Tetrahydrofuran was refluxed over $CaH_2$, distilled, and then redistilled directly into the reaction vessel from sodium benzophenone ketyl under an argon atmosphere. LDA (AcroSeal) was used as received. NMR spectra were recorded on a Bruker DPX-250 (250 MHz for $^1H$, 63 MHz for $^{13}C$) spectrometer. All resonances are reported relative to TMS. Spectra were calibrated relative to the solvents' residual proton and carbon chemical shifts: $CHCl_3$ ($\delta$ = 7.26 ppm for $^1H$ NMR and $\delta$ = 77.16 ppm for $^{13}C$ NMR). NMR spectra were analyzed using MestReNova NMR data processing software (www.mestrelab.com). Coupling constants (J) are reported in hertz (Hz). The multiplicity of the signals is given as s (singlet), d (doublet), t (triplet), and m (multiplet). Copies of $^1H$ NMR and $^{13}C$ NMR spectra are provided in the Supporting Information. The content of chlorine was determined separately by the Schöniger method. Melting points were determined in open capillaries on a Khimlaborpribor PTP apparatus.

**General procedure for the synthesis of 3-acyl-2-ethylindoles 7a-c (GP1)**. All reactions were carried out in dried glassware under a slightly positive pressure of dry, prepurified argon. Compound **1a-c** (1 equiv.) was dissolved in THF or $Et_2O$, cooled down to −32 °C, and treated with lithium diisopropylamide (2 equiv., 2 M in THF/*n*-heptane/ethylbenzene). The reaction mixture was kept for 3 h. Methyl iodide (5 equiv) was added, and the reaction mixture was left overnight at room temperature. The reaction was quenched with water (30-50 mL), and product **7a-c** was precipitated and purified by multiple recrystallizations.

*4.2.1. (2-Ethyl-1-methyl-1H-indol-3-yl)(phenyl)methanone* (**7a**): was obtained according to **GP1** using (1,2-dimethyl-1*H*-indol-3-yl)(phenyl)methanone **1a** (0.50 g, 2.01 mmol), LDA (2.00 mL of 2 M sol., 4.02 mmol) and $CH_3I$ (0.63 mL, 10.05 mmol). White solid, 43% isolated yield (0.23 g); mp 100−103 °C (iPrOH). $^1$H NMR (250 MHz, $CDCl_3$) δ: 1.32 (t, 3H, $CH_3$, J=7.5), 3.11 (q, 2H, $CH_2$, J=7.5), 3.79 (s, 3H, $CH_3$), 7.01-7.07 (m, 1H, $CH_{arom}$), 7.13-7.25 (m, 2H, $CH_{arom}$), 7.33-7.36 (d, 1H, $CH_{arom}$), 7.42-7.59 (m, 3H, $CH_{arom}$), 7.76-7.80 (m, 2H, $CH_{arom}$). $^{13}C\{^1H\}$ NMR (63 MHz, CDCl3) δ: 14.00; 19.21; 29.61; 109.35; 112.80; 121.07; 121.33; 122.00; 127.05; 128.23; 129.10; 131.48; 136.62; 141.52; 150.49; 192.78.

*4.2.2. (1-Benzyl-2-ethyl-1H-indol-3-yl)(p-tolyl)methanone* (**7b**) was obtained according to **GP1** using (1-benzyl-2-methyl-1*H*-indol-3-yl)(*p*-tolyl)methanone **1b** (0.50 g, 1.47 mmol), LDA (1.50 mL of 2 M sol., 2.94 mmol) and $CH_3I$ (0.46 mL, 7.35 mmol). White solid, 46% isolated yield (0.23 g); mp 115−117 °C (iPrOH). $^1$H NMR (250 MHz, $CDCl_3$) δ: 1.25 (t, 3H, $CH_3$, J=7.5), 2.61 (s, 3H, $CH_3$), 3.07 (q, 2H, $CH_2$, J=7.5), 5.44 (s, 2H, $CH_2$), 7.01-7.07 (m, 3H, $CH_{arom}$, J=1.8; 7.4), 7.09-7.16 (m, 1H, $CH_{arom}$), 7.20-7.25 (m, 3H, $CH_{arom}$), 7.27-7.35 (m, 4H, $CH_{arom}$), 7.71-7.77 (m, 2H, $CH_{arom}$, J=8.1). $^{13}C\{^1H\}$ NMR (63 MHz, CDCl3) δ: 14.49; 19.29; 21.72; 46.59; 110.06; 113.49; 121.19; 121.31; 122.14; 125.95; 127.28; 127.71; 128.91; 128.99; 129.47; 136.25; 136.63; 138.53; 142.20; 150.05; 192.66.

*4.2.3. (1-Benzyl-2-ethyl-1H-indol-3-yl)(phenyl)methanone* (**7c**) was obtained according to **GP1** using (1-benzyl-2-methyl-1*H*-indol-3-yl)(phenyl)methanone **1c** (0.50 g, 1.54 mmol), LDA (1.54 mL of 2 M sol., 3.08 mmol) and $CH_3I$ (0.48 mL, 7.70 mmol). White solid, 52% isolated yield (0.27 g); mp 132−135 °C (iPrOH). $^1$H NMR (250 MHz, $CDCl_3$) δ: 1.25 (t, 3H, $CH_3$, J=7.5), 3.07 (q, 2H, $CH_2$, J=7.5), 5.45 (s, 2H, $CH_2$), 7.00-7.24 (m, 6H, $CH_{arom}$), 7.27-7.35 (m, 3H, $CH_{arom}$), 7.43-7.50 (m, 2H, $CH_{arom}$), 7.53-7.60 (m, 1H, $CH_{arom}$), 7.79-7.83 (m, 2H, $CH_{arom}$). $^{13}C\{^1H\}$ NMR (63 MHz, CDCl3) δ: 14.40; 19.32; 46.60; 110.10; 113.30; 121.14; 121.45; 122.23; 125.93; 127.24; 127.74; 128.25; 129.01; 129.15; 131.57; 136.29; 136.53; 141.39; 150.45; 192.85.

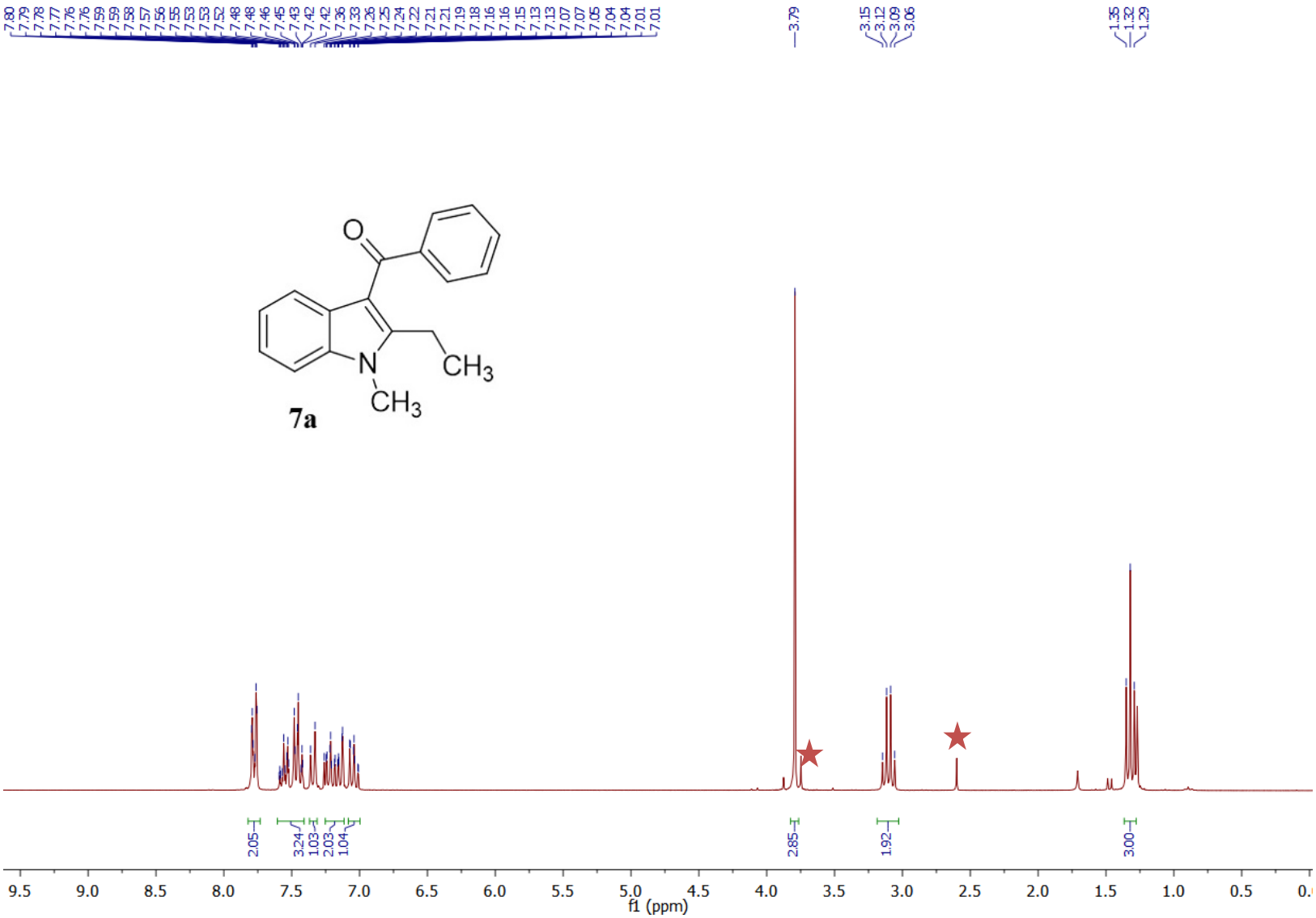


**Figure S1** $^{1}$H NMR of **7a**, $CDCl_3$, 250 MHz (Signals from starting compound **1a** are marked by red asterisk (for ref. see S2))

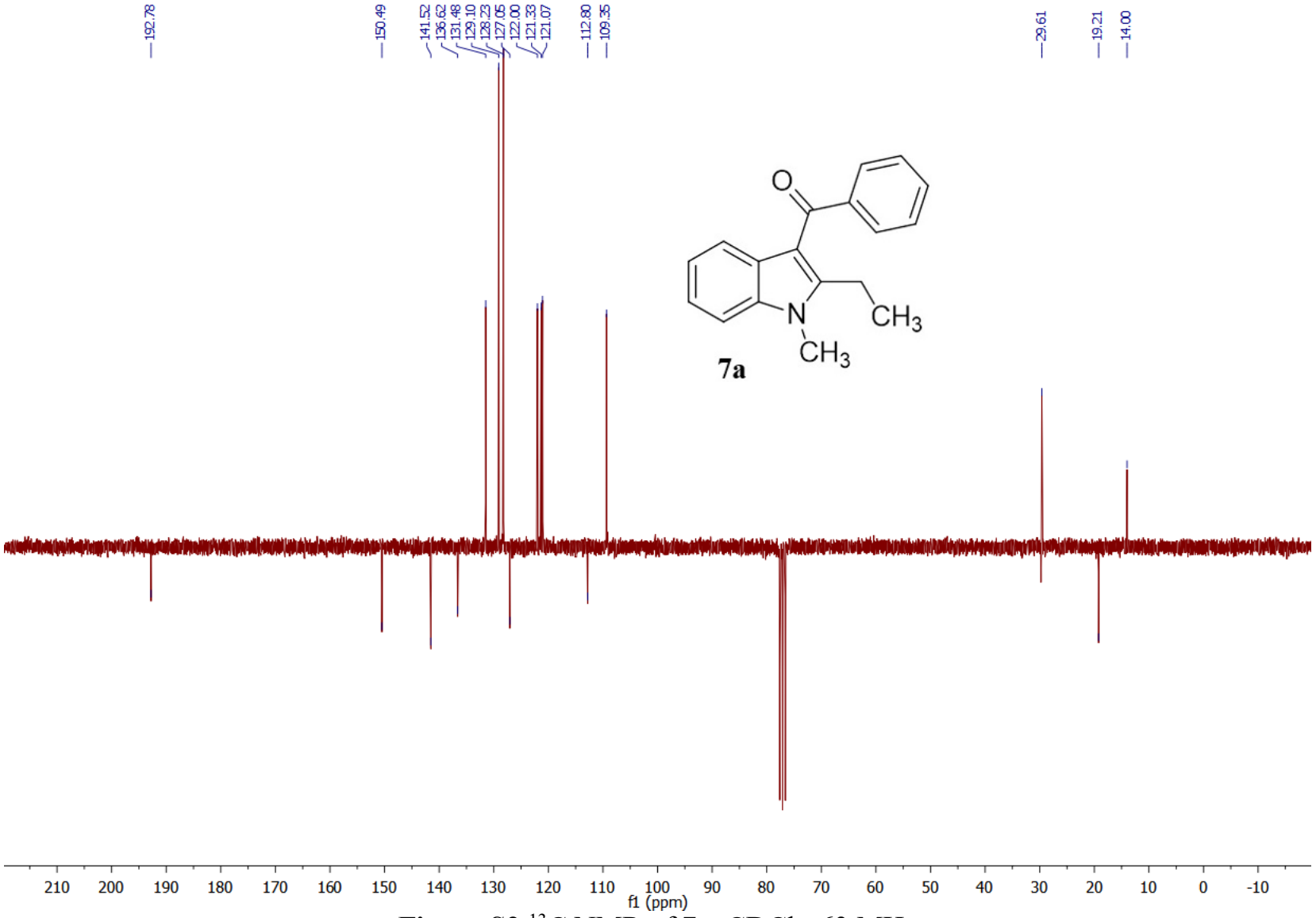


**Figure S2** $^{13}C$ NMR of **7a**, $CDCl_3$, 63 MHz

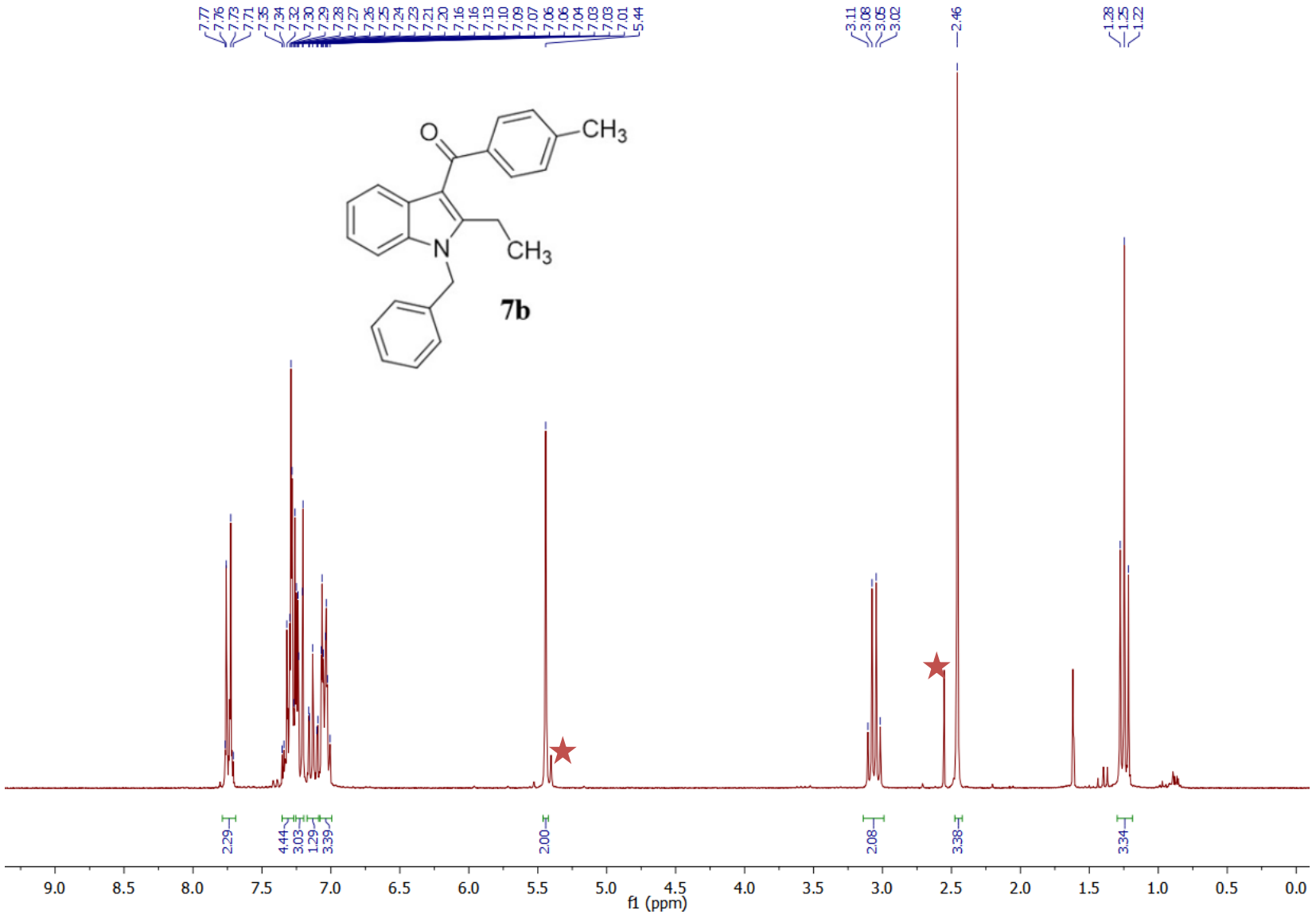


**Figure S3** $^{1}$H NMR of **7b**, $CDCl_3$, 250 MHz (Signals from starting compound **1b** are marked by red asterisk (for ref. see S2))

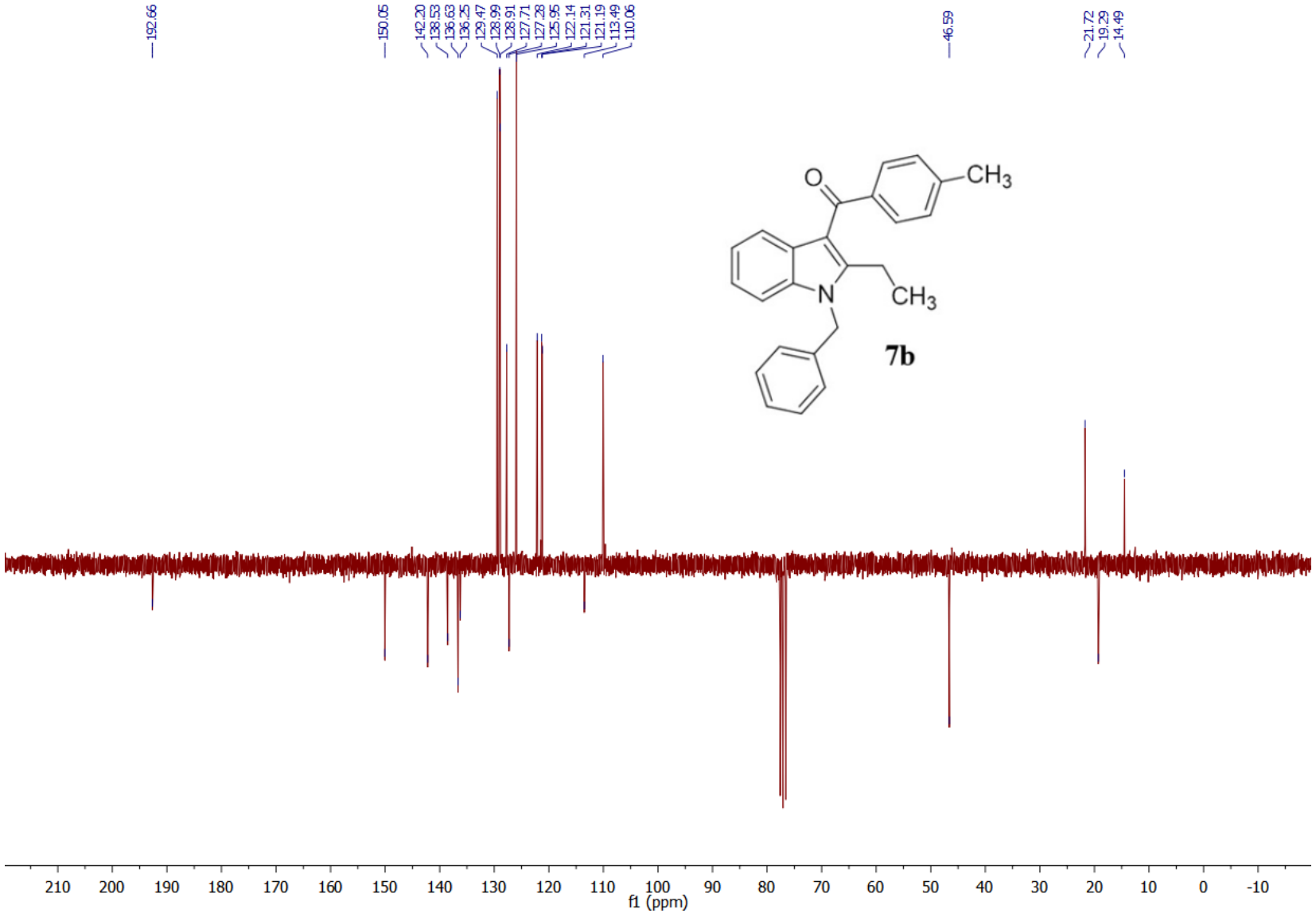


**Figure S4** $^{13}C$ NMR of **7b**, $CDCl_3$, 63 MHz

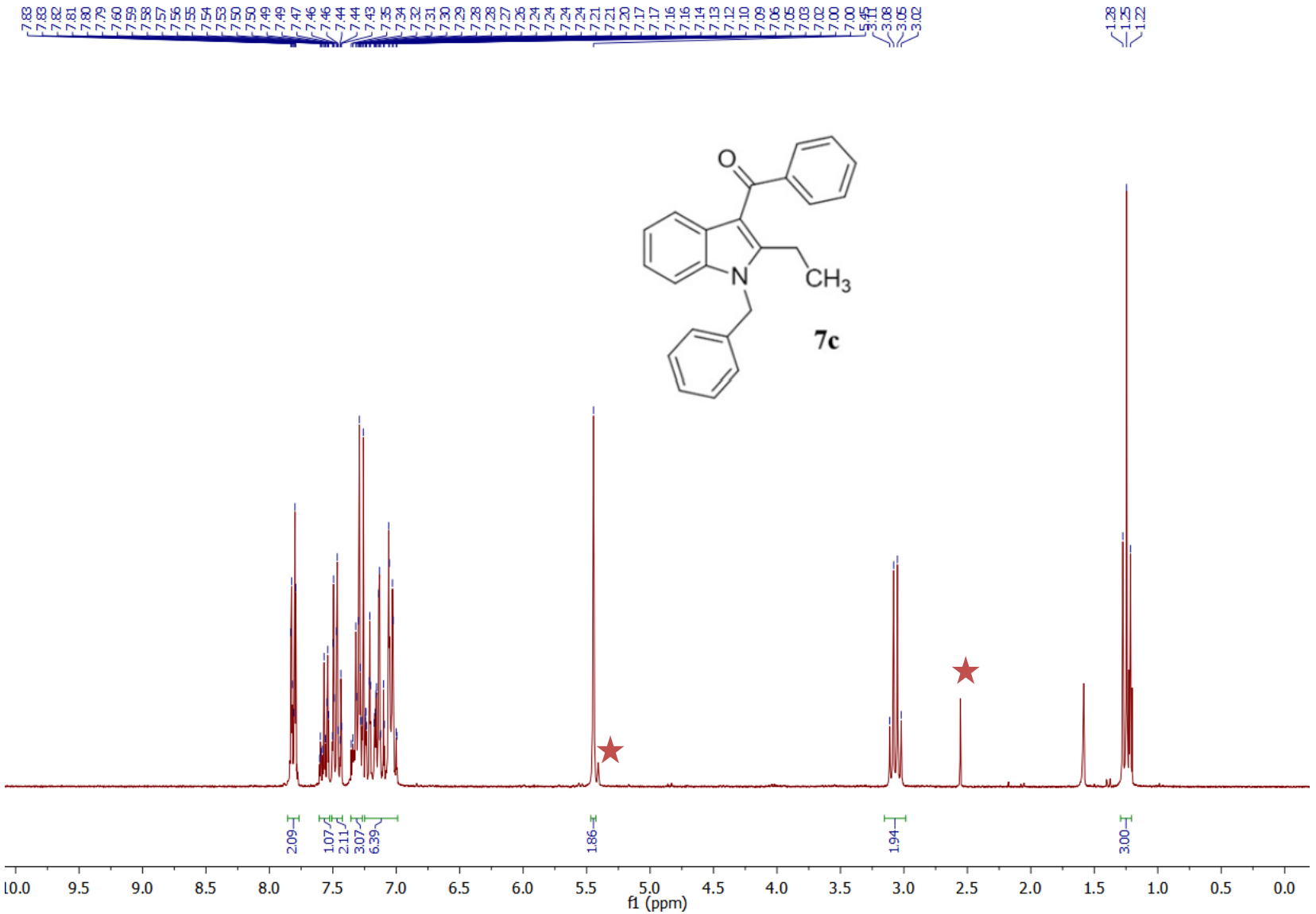


**Figure S5** $^{1}$H NMR of **7c**, $CDCl_3$, 250 MHz (Signals from starting compound **1c** are marked by red asterisk (for ref. see S2))

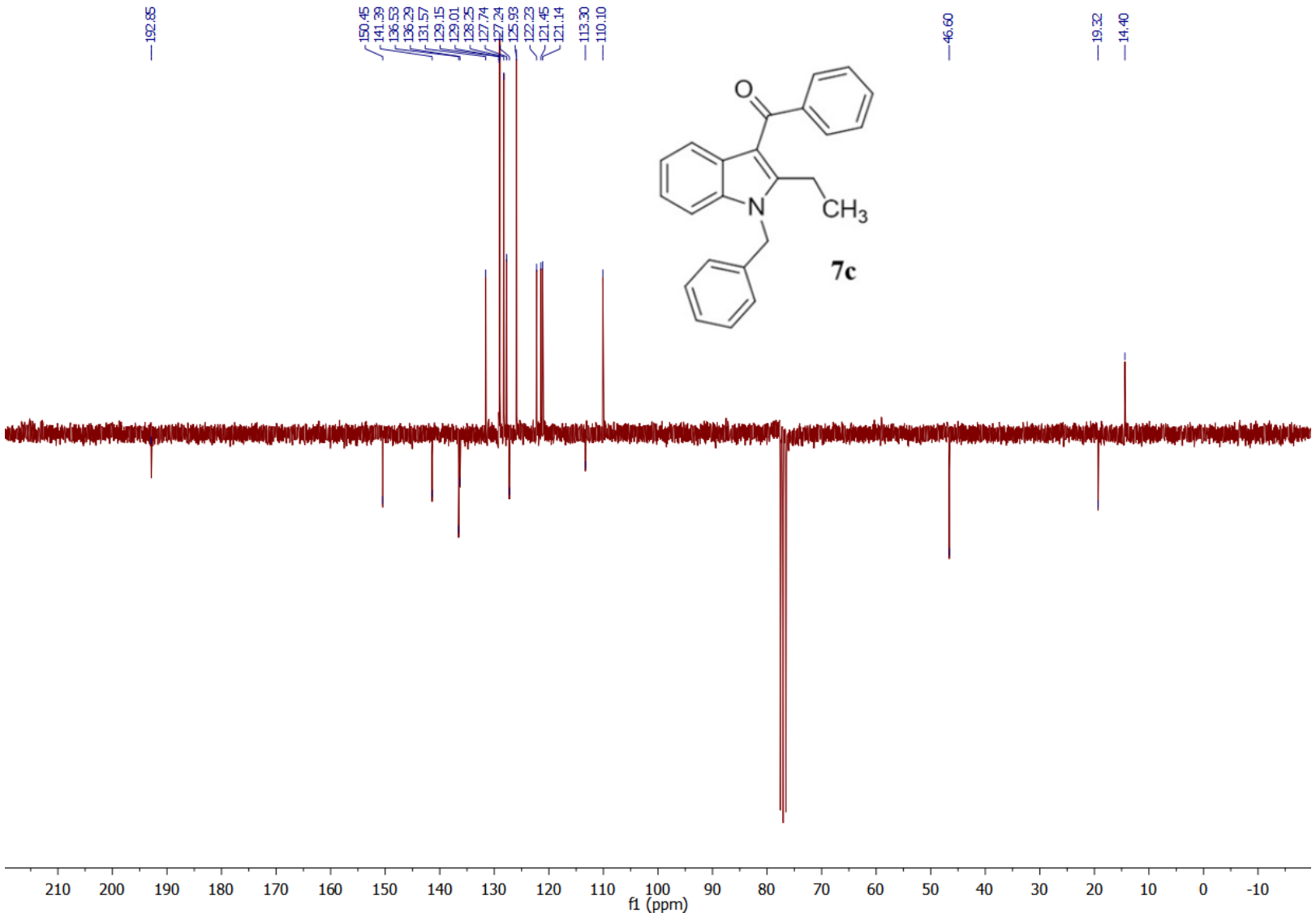


**Figure S6** $^{13}C$ NMR of **7c**, $CDCl_3$, 63 MHz

**General procedure for the synthesis of 3-acyl-2-(2-phenylethyl)indoles 10a-h (GP2)**. All reactions were carried out in dried glassware under a slightly positive pressure of dry, pre-purified argon. Compound **1a-h** (1 equiv.) was dissolved in THF, cooled down to −32 °C, and treated with lithium diisopropylamide (2 equiv., 2 M sol in THF/*n*-heptane/ethylbenzene). The reaction mixture was kept for 3 h. Benzyl chloride (1.5 equiv) was added, and the reaction mixture was left overnight at room temperature. The reaction was quenched with water (30-50 mL), and product **10a-h** was precipitated and purified by recrystallization.

*4.3.1. [1-Methyl-2-(2-phenylethyl)-1H-indol-3-yl](phenyl)methanone* (**10a**) was obtained according to **GP2** using (1,2-dimethyl-1*H*-indol-3-yl)(phenyl)methanone **1a** (0.50 g, 2.00 mmol), LDA (2.00 mL of 2 M sol., 4.00 mmol) and BnCl (0.35 mL, 3.00 mmol). White solid, 69% isolated yield (0.47 g); mp 136−138°C (PrOH). $^{1}$H NMR (250 MHz, $CDCl_3$) δ: 2.99-3.05 (m, 2H, $CH_2$, J=6.6, 8,9), 3.34-3.41 (m, 2H, $CH_2$, J=6.5, 9,0), 3.54 (s, 3H, $CH_3$), 6.97-7.08 (m, 2H, $CH_{arom}$), 7.14-7.29 (m, 7H, $CH_{arom}$), 7.40-7.57 (m, 3H, $CH_{arom}$), 7.71-7.74 (m, 2H, $CH_{arom}$, J=1.3, 8,2). $^{13}$C{$^{1}$H} NMR (63 MHz, CDCl3) δ: 28.33; 29.56; 36.09; 109.50; 113.26; 121.08; 121.38; 122.06; 126.35; 126.98; 128.25; 128.57; 128.63; 129.03; 131.45; 136.55; 140.95; 141.57; 148.28; 192.84.

*4.3.2. [1-Benzyl-2-(2-phenylethyl)-1H-indol-3-yl](p-tolyl)methanone* (**10b**) was obtained according to **GP2** using (1-benzyl-2-methyl-1*H*-indol-3-yl)(*p*-tolyl)methanone **1b** (0.50 g, 1.47 mmol), LDA (1.47 mL of 2 M sol., 2.94 mmol) and BnCl (0.25 mL, 2.21 mmol). White solid, 63% isolated yield (0.40 g); mp 124−126 °C (PrOH). $^{1}$H NMR (250 MHz, $CDCl_3$) δ: 2.47 (s, 3H, $CH_3$), 2.88-2.94 (m, 2H, $CH_2$, J=6.6, 9,4), 3.30-3.36 (m, 2H, $CH_2$, J=6.7, 9,3), 5.25(s, 2H, $CH_2$), 7.00-7.05 (m, 2H, $CH_{arom}$), 7.08-7.12 (m, 2H, $CH_{arom}$), 7.15-7.23 (m, 7H, $CH_{arom}$), 7.29-7.32 (m, 5H, $CH_{arom}$, J=6.8), 7.73 (d, 2H, $CH_{arom}$, J=8.1). $^{13}$C{$^{1}$H} NMR (63 MHz, CDCl3) δ: 21.76; 28.56; 36.32; 46.55; 110.12; 113.91; 121.30; 121.44; 122.32; 126.05; 126.32; 127.23; 127.84; 128.54; 128.59; 128.98; 129.08; 129.42; 136.36; 136.65; 138.65; 141.08; 142.20; 147.89; 192.81.

*4.3.3. [1-Benzyl-2-(2-phenylethyl)-1H-indol-3-yl](phenyl)methanone* (**10c**) was obtained according to **GP2** using (1-benzyl-2-methyl-1*H*-indol-3-yl)(phenyl)methanonee **1c** (0.50 g, 1.90 mmol), LDA (1.90 mL of 2 M sol., 3.80 mmol) and BnCl (0.33 mL, 2.85 mmol). White solid, 90% isolated yield (0.58 g); mp 128−131 °C (PrOH). $^{1}$H NMR (250 MHz, $CDCl_3$) δ: 2.91-2.97 (m, 2H, $CH_2$), 3.34-3.41 (m, 2H, $CH_2$), 5.28 (s, 2H, $CH_2$), 7.00-7.05 (m, 2H, $CH_{arom}$), 7.04-7.25 (m, 9H, $CH_{arom}$), 7.26-7.35 (m, 5H, $CH_{arom}$), 7.47-7.64 (m, 3H, $CH_{arom}$), 7.81-7.84 (m, 2H, $CH_{arom}$). $^{13}$C{$^{1}$H} NMR (63 MHz, CDCl3) δ: 28.51; 36.24; 46.57; 110.16; 113.81; 121.23; 121.58; 122.42; 126.04; 126.34; 127.19; 127.88; 128.32; 128.57; 129.10; 131.59; 136.42; 136.57; 141.01; 141.49; 148.25; 193.00.

*4.3.4. [1-Methyl-2-(2-phenylethyl)-1H-indol-3-yl](p-tolyl)methanone* (**10d**) was obtained according to **GP2** using (1,2-dimethyl-1*H*-indol-3-yl)(*p*-tolyl)methanone **1d** (0.50 g, 1.90 mmol), LDA (1.90 mL of 2 M sol., 3.80 mmol) and BnCl (0.33 mL, 2.85 mmol). White solid, 70% isolated yield (0.47 g); mp 137−140 °C (PrOH). $^{1}$H NMR (250 MHz, $CDCl_3$) δ: 2.45 (s, 3H, $CH_3$), 3.00-3.07 (m, 2H, $CH_2$, J=6.4, 9,0), 3.35-3.42 (m, 2H, $CH_2$, J=6.5, 9,0), 3.56 (s, 3H, $CH_3$), 7.00-7.06 (m, 1H, $CH_{arom}$), 7.15-7.23 (m, 7H, $CH_{arom}$), 7.25 (s, 1H, $CH_{arom}$), 7.29 (s, 1H, $CH_{arom}$, J=8.1), 7.67 (d, 2H, $CH_{arom}$). $^{13}$C{$^{1}$H} NMR (63 MHz, CDCl3) δ: 21.70; 28.26; 29.52; 36.16; 109.43; 113.46; 121.15; 121.23; 121.95; 126.31; 127.02; 128.54; 128.63; 128.89; 129.33; 136.36; 136.50; 138.71; 141.01; 142.01; 147.89; 192.64.

*4.3.5. 2,2-Dimethyl-1-[1-methyl-2-(2-phenylethyl)-1H-indol-3-yl]propan-1-one* (**10e**) was obtained according to **GP2** using 1-(1,2-dimethyl-1*H*-indol-3-yl)-2,2-dimethylpropan-1-one **1e** (0.50 g, 2.18 mmol), LDA (2.20 mL of 2 M sol., 4.36 mmol) and BnCl (0.25 mL, 3.27 mmol). White solid, 42% isolated yield (0.29 g); mp 102−105 °C (i-PrOH). $^{1}$H NMR (250 MHz, $CDCl_3$) δ: 1.40 (s, 3H, $CH_3$), 2.95-3.01 (m, 2H, $CH_2$), 3.14-3.23 (m, 2H, $CH_2$), 3.52 (s, 3H, $CH_3$), 7.17-7.21 (m, 3H, $CH_{arom}$), 7.22-7.25 (m, 3H, $CH_{arom}$), 7.27-7.31 (m, 2H, $CH_{arom}$), 7.75-7.78 (m, 1H, $CH_{arom}$). $^{13}$C{$^{1}$H} NMR (63 MHz, CDCl3) δ: 27.64; 28.35; 29.56; 36.53; 44.14;

109.54; 115.14; 120.69; 121.51; 121.75; 125.03; 126.32; 128.59 (2C); 136.36; 141.17; 144.74; 208.57.

*4.3.6. [1-Ethyl-2-(2-phenylethyl)-1H-indol-3-yl](phenyl)methanone* (**10f**) was obtained according to **GP2** using (1-ethyl-2-methyl-1*H*-indol-3-yl)(phenyl)methanone **1f** (0.50 g, 1.54 mmol), LDA (1.55 mL of 2 M sol., 3.10 mmol) and BnCl (0.26 mL, 2.30 mmol). White solid, 64% isolated yield (0.43 g); mp 98−100 °C (PrOH). $^{1}$H NMR (250 MHz, $CDCl_3$) δ: 1.32 (t, 3H, $CH_3$, J=7.2), 2.92-2.99 (m, 2H, $CH_2$, J=6.5, 9,5), 3.26-3.33 (m, 2H, $CH_2$, J=6.5, 9,4), 4.03 (q, 2H, $CH_2$, J=7.2), 6.90-7.01 (m, 2H, $CH_{arom}$), 7.07-7.23 (m, 7H, $CH_{arom}$), 7.33-7.50 (m, 3H, $CH_{arom}$), 7.65-7.68 (m, 2H, $CH_{arom}$). $^{13}$C{$^{1}$H} NMR (63 MHz, CDCl3) δ: 15.22; 28.33; 36.41; 37.97; 109.72; 113.27; 121.24; 121.31; 122.04; 126.37; 127.35; 128.27; 128.59; 129.01; 131.42; 135.40; 141.07; 141.67; 147.71; 192.88.

*4.3.7. (4-Chlorophenyl)[1-ethyl-2-(2-phenylethyl)-1H-indol-3-yl]methanone* (**10g**) was obtained according to **GP2** using (4-chlorophenyl)(1-ethyl-2-methyl-1*H*-indol-3-yl)methanone **1g** (0.50 g, 1.68 mmol), LDA (1.70 mL of 2 M sol., 3.36 mmol) and BnCl (0.29 mL, 2.52 mmol). White solid, 43% isolated yield (0.30 g); mp 115−117°C (iPrOH). $^{1}$H NMR (250 MHz, $CDCl_3$) δ: 1.43 (t, 3H, $CH_3$, J=7.2), 3.03-3.09 (m, 2H, $CH_2$, J=6.5, 9,3), 3.38-3.44 (m, 2H, $CH_2$, J=6.4, 9,4), 4.14 (q, 2H, $CH_2$, J=7.2), 7.06-7.25 (m, 6H, $CH_{arom}$, J=3.7), 7.28-7.38 (m, 3H, $CH_{arom}$), 7.45 (d, 2H, $CH_{arom}$, J=8.4), 7.73 (d, 2H, $CH_{arom}$, J=8.4). $^{13}$C{$^{1}$H} NMR (63 MHz, CDCl3) δ: 15.19; 28.24; 36.34; 38.01; 109.86; 112.95; 121.03; 121.47; 122.17; 126.42; 127.10; 128.59; 130.60; 135.41; 137.63; 139.86; 140.93; 147.96; 191.35.

*4.3.8. (4-Chlorophenyl)[1-methyl-2-(2-phenylethyl)-1H-indol-3-yl]methanone* (**10h**) was obtained according to **GP2** using (4-chlorophenyl)(1,2-dimethyl-1*H*-indol-3-yl)methanone **1h** (0.50 g, 1.76 mmol), LDA (1.80 mL of 2 M sol., 3.60 mmol) and BnCl (0.30 mL, 2.64 mmol). White solid, 56% isolated yield (0.37 g); mp 141−143 °C (i-PrOH). $^{1}$H NMR (250 MHz, $CDCl_3$) δ: 3.09-3.15 (m, 2H, $CH_2$), 3.44-3.51 (m, 2H, $CH_2$), 3.63 (s, 3H, $CH_3$), 7.12-7.14 (m, 2H, $CH_{arom}$), 7.23-7.26 (m, 2H, $CH_{arom}$), 7.26-7.39 (m, 5H, $CH_{arom}$), 7.50 (d, 2H, $CH_{arom}$), 7.76 (d, 2H, $CH_{arom}$).

$^{13}C\{^{1}H\}$ NMR (63 MHz, CDCl3) δ: 28.27; 29.60; 36.04; 109.69; 112.96; 120.87; 121.57; 122.22; 126.42; 126.75; 128.55; 128.62; 128.65; 130.63; 136.58; 137.67; 139.79; 140.83; 148.52; 191.31.

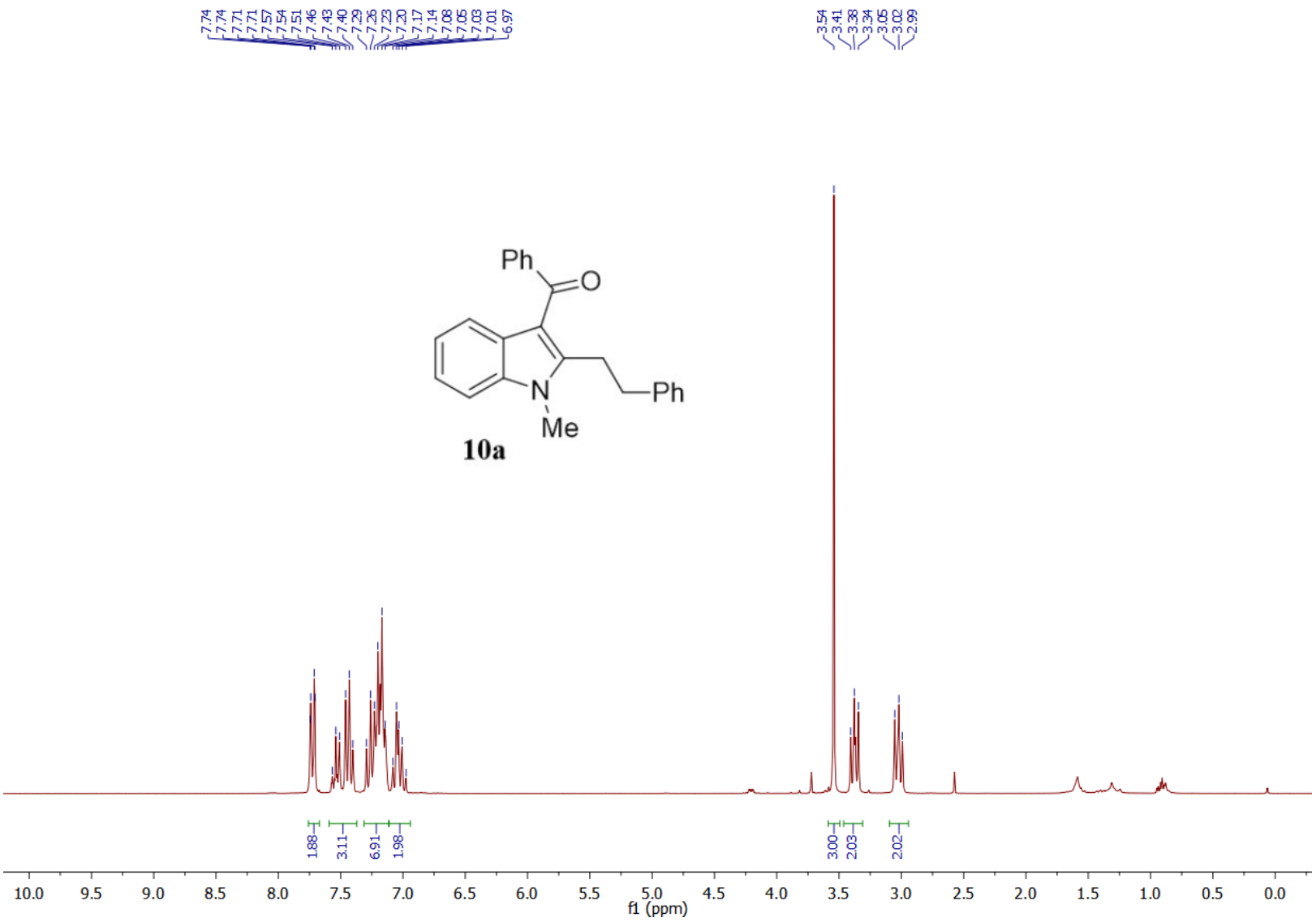


**Figure S7** $^{1}$H NMR of **10a**, $CDCl_3$, 250 MHz

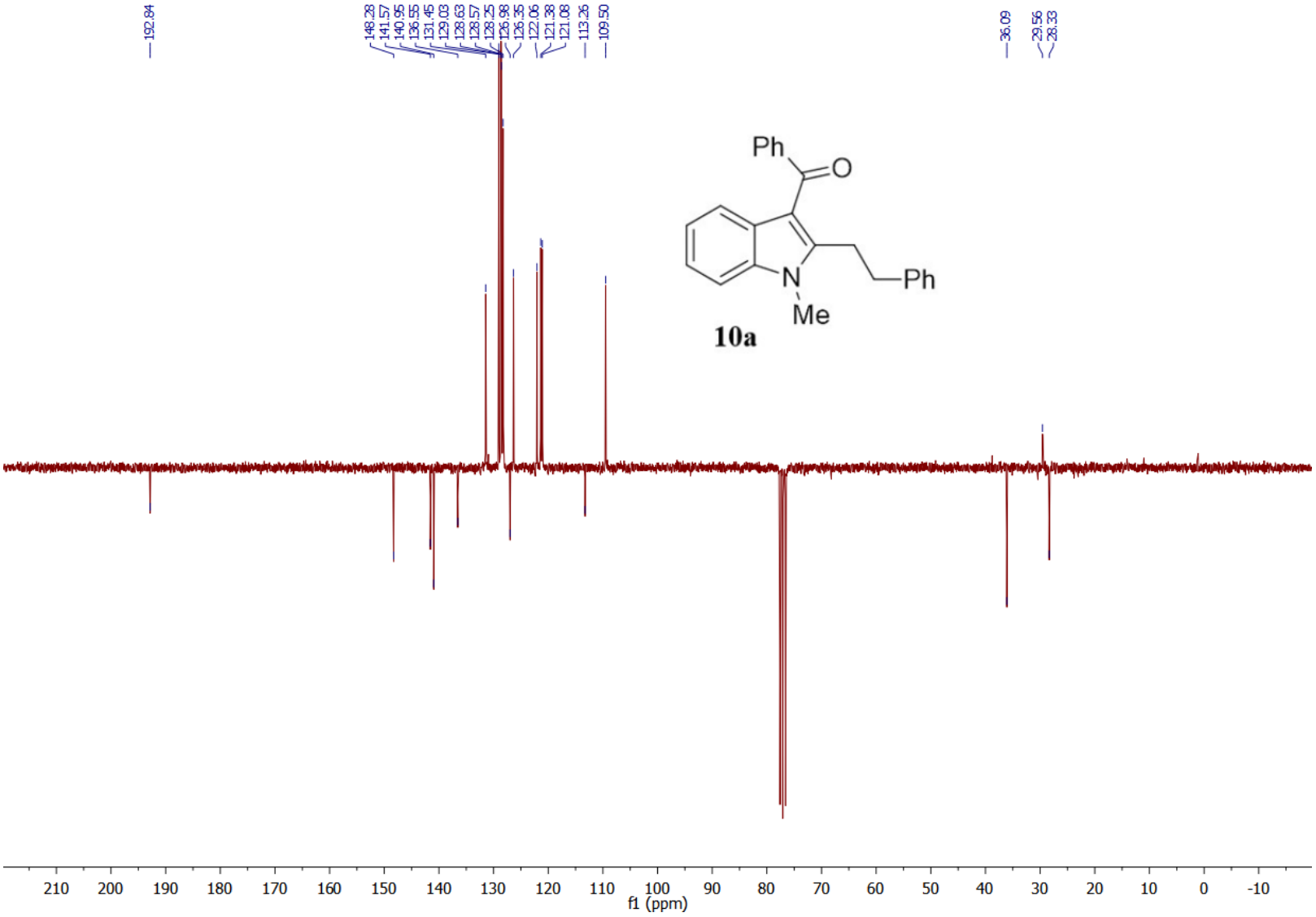


**Figure S8** $^{13}C$ NMR of **10a**, $CDCl_3$, 63 MHz

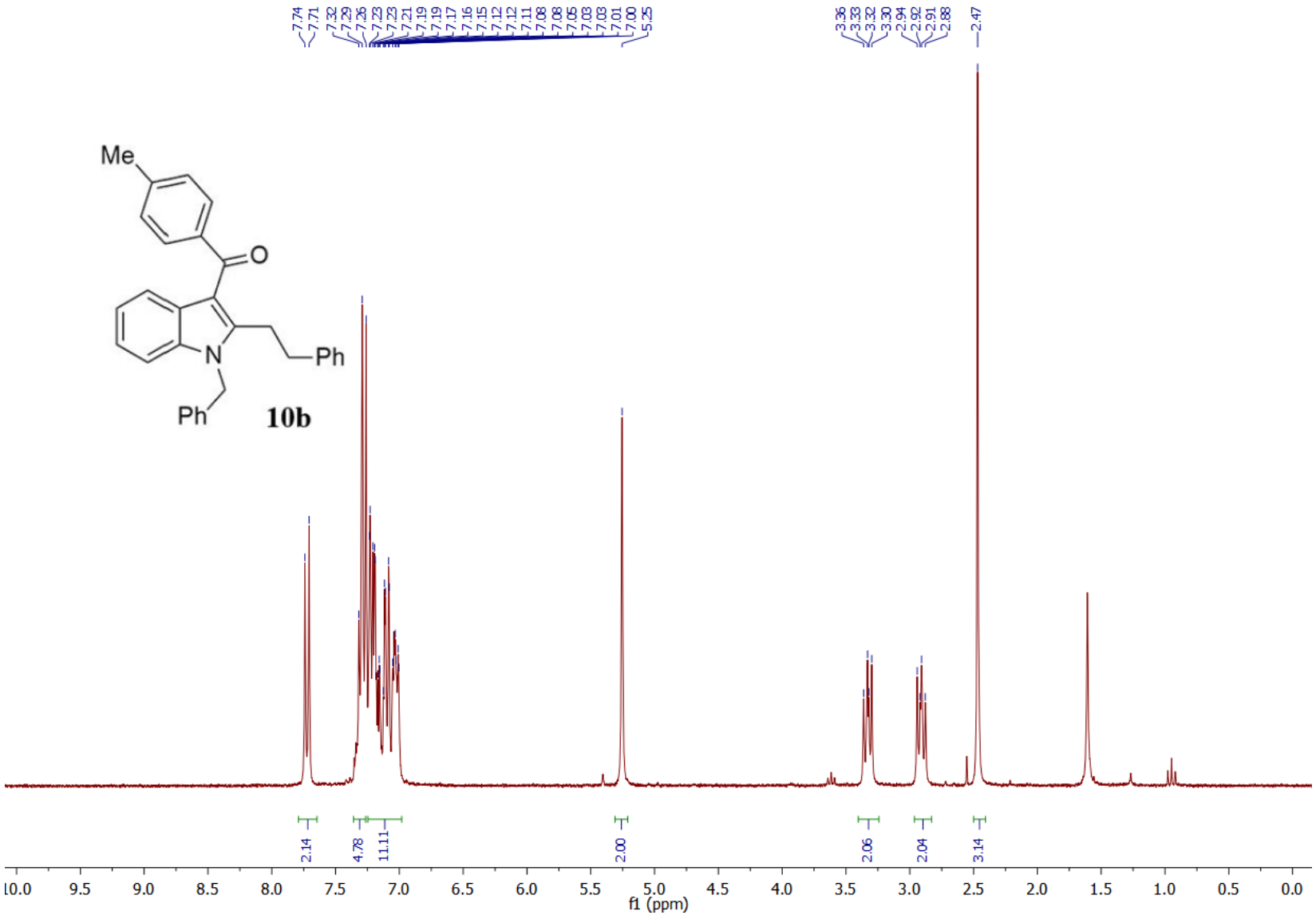


**Figure S9** $^{1}$H NMR of **10b**, $CDCl_3$, 250 MHz

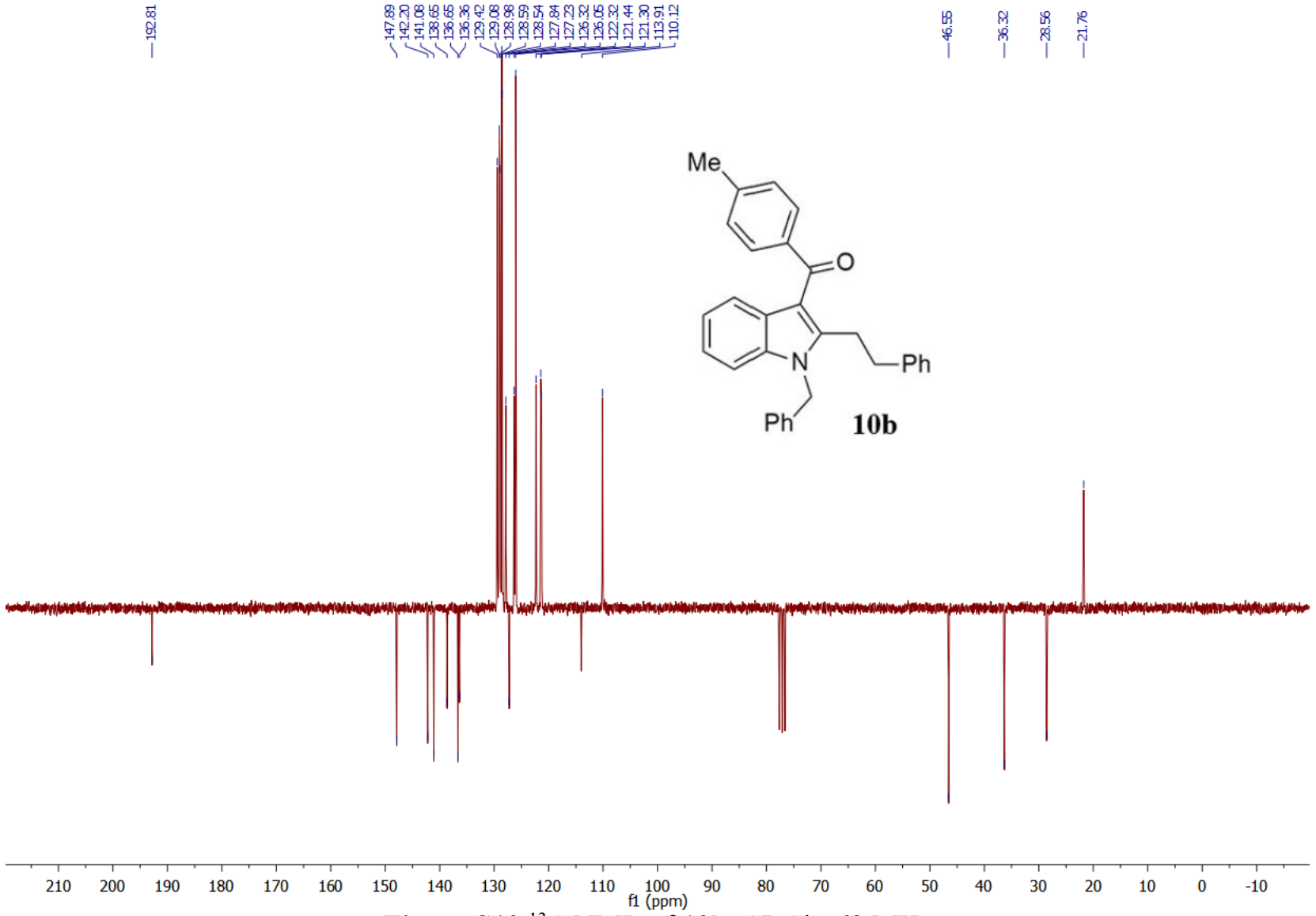


**Figure S10** $^{13}C$ NMR of **10b**, $CDCl_3$, 63 MHz

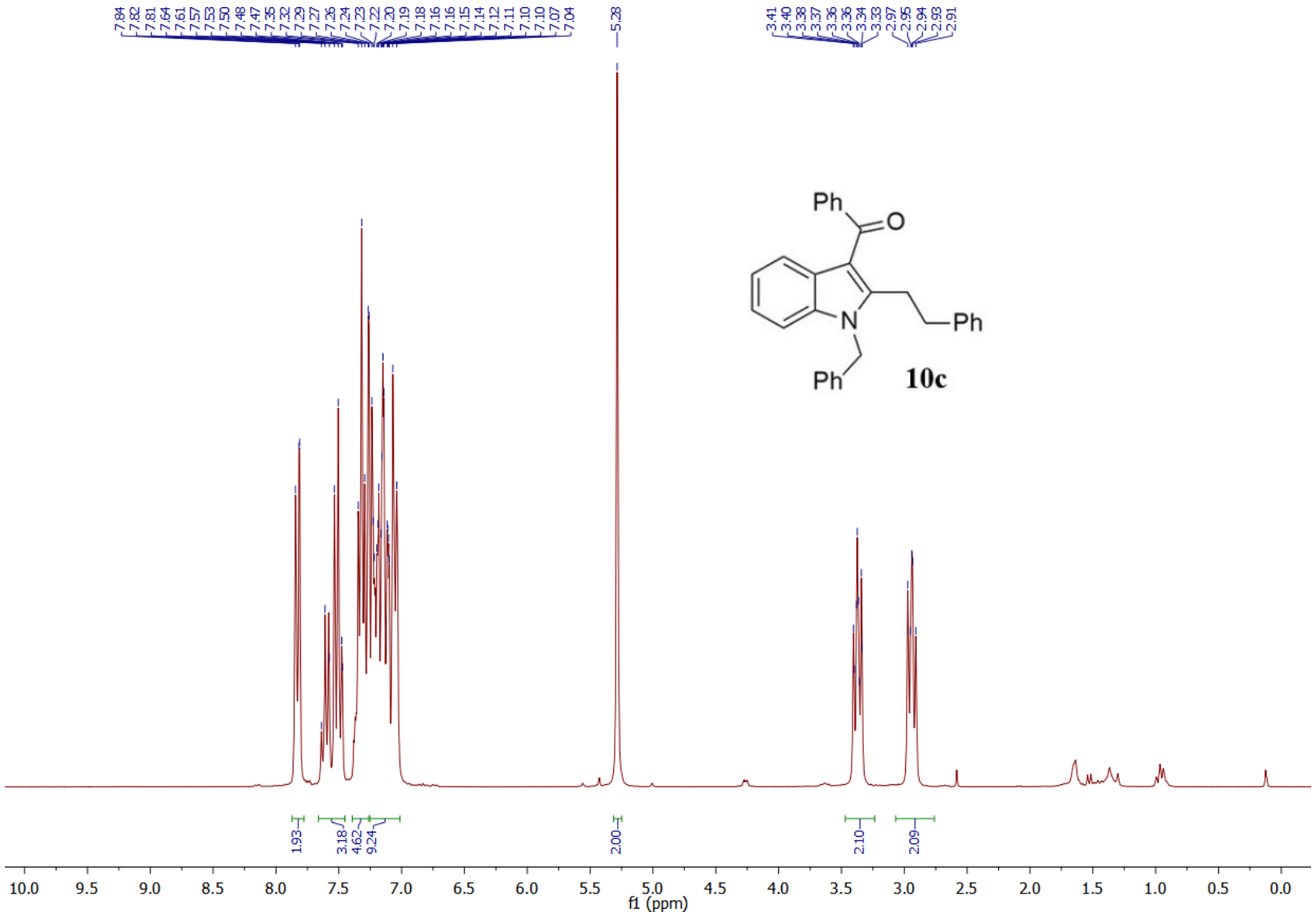


**Figure S11** $^{1}$H NMR of **10c**, $CDCl_3$, 250 MHz

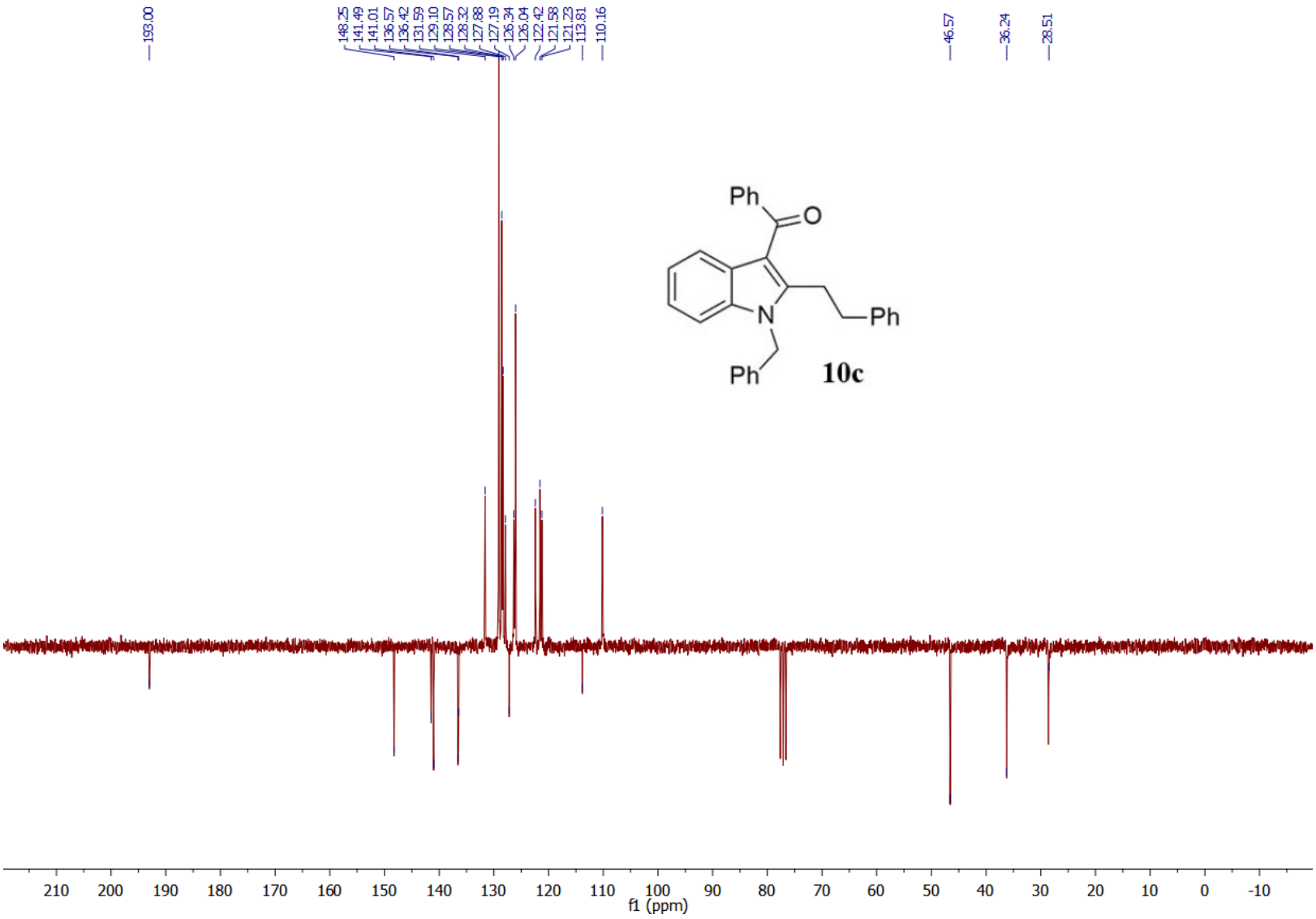


**Figure S12** $^{13}C$ NMR of **10c**, $CDCl_3$, 63 MHz

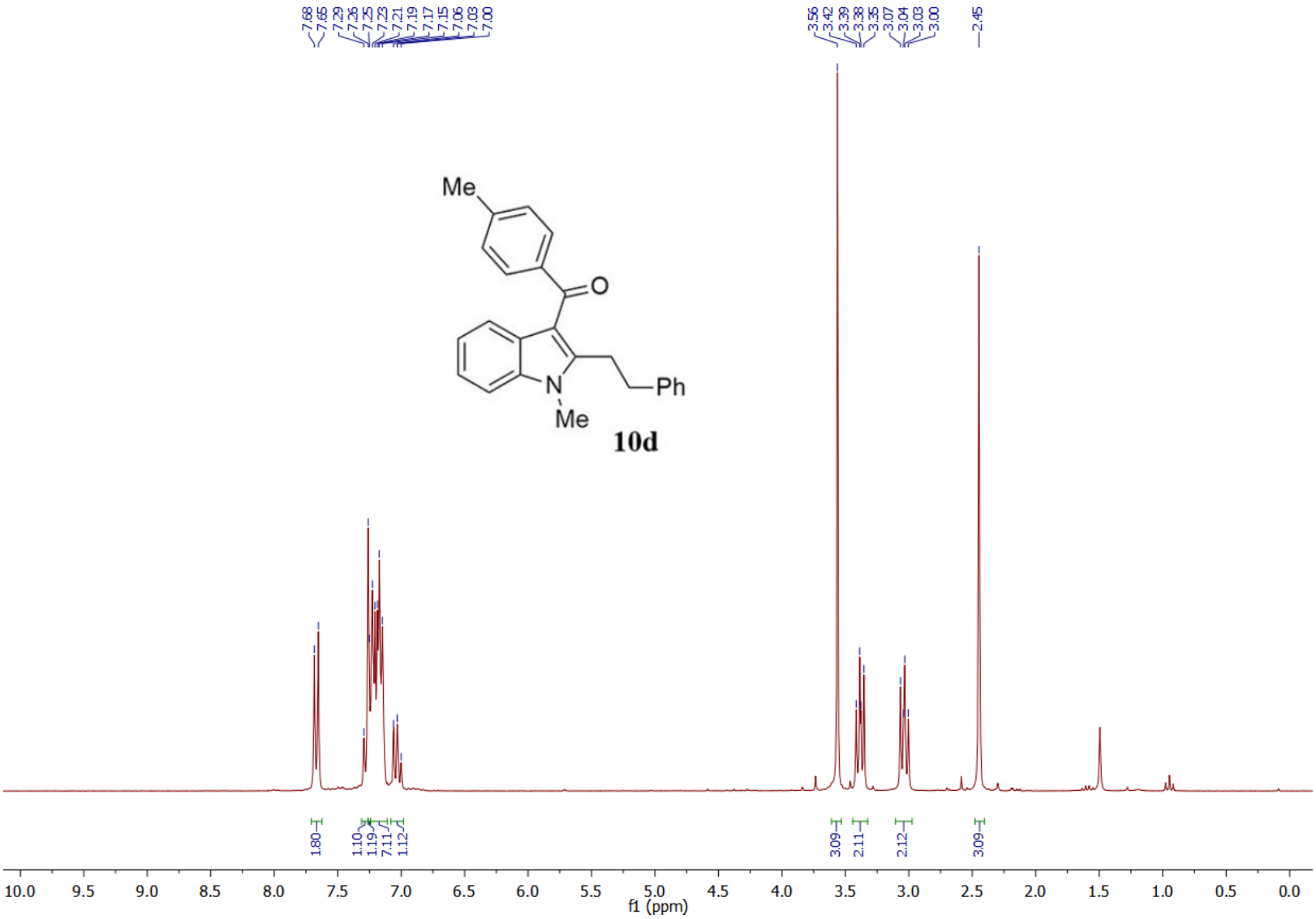


**Figure S13** $^{1}$H NMR of **10d**, $CDCl_3$, 250 MHz

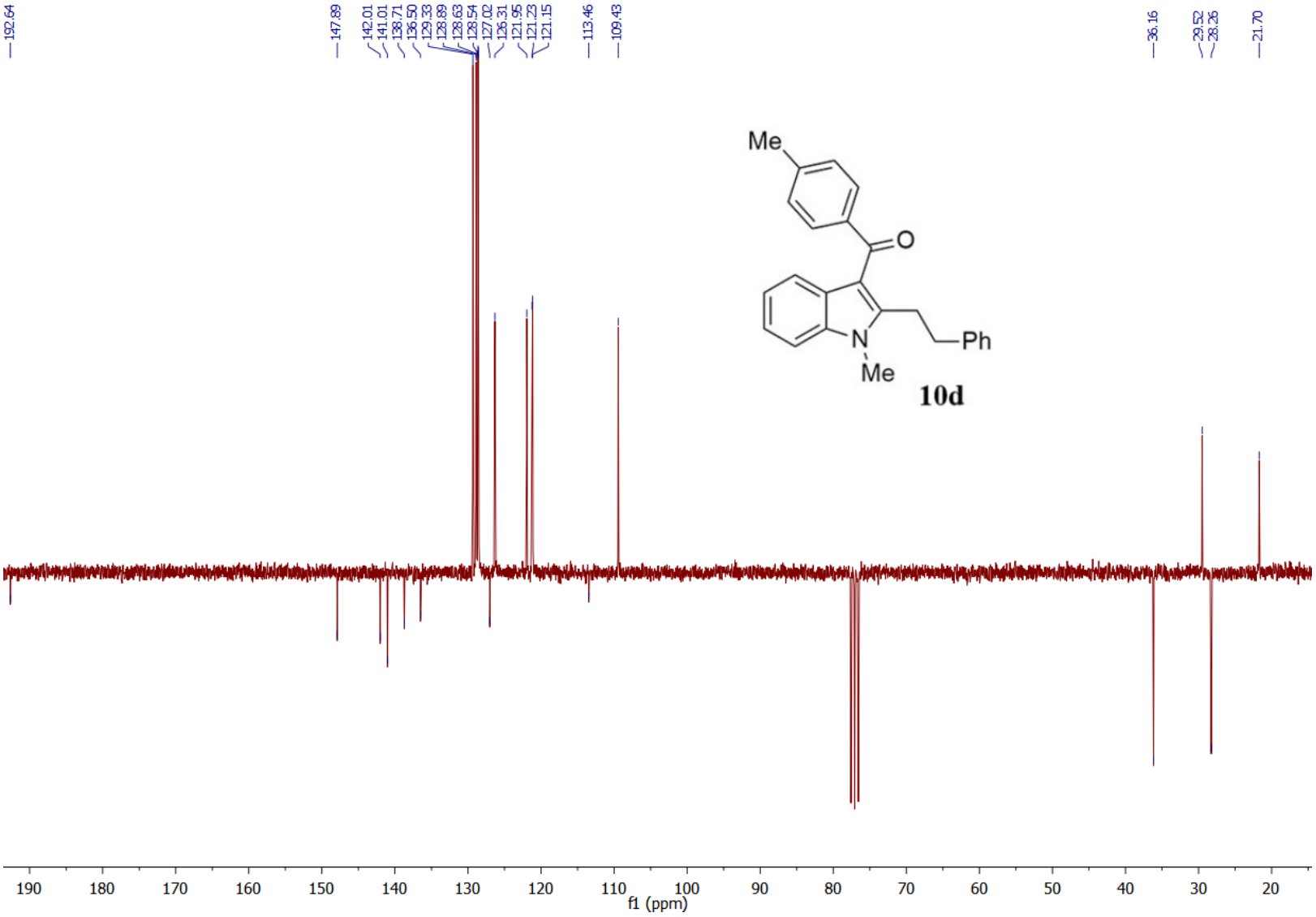


**Figure S14** $^{13}C$ NMR of **10d**, $CDCl_3$, 63 MHz

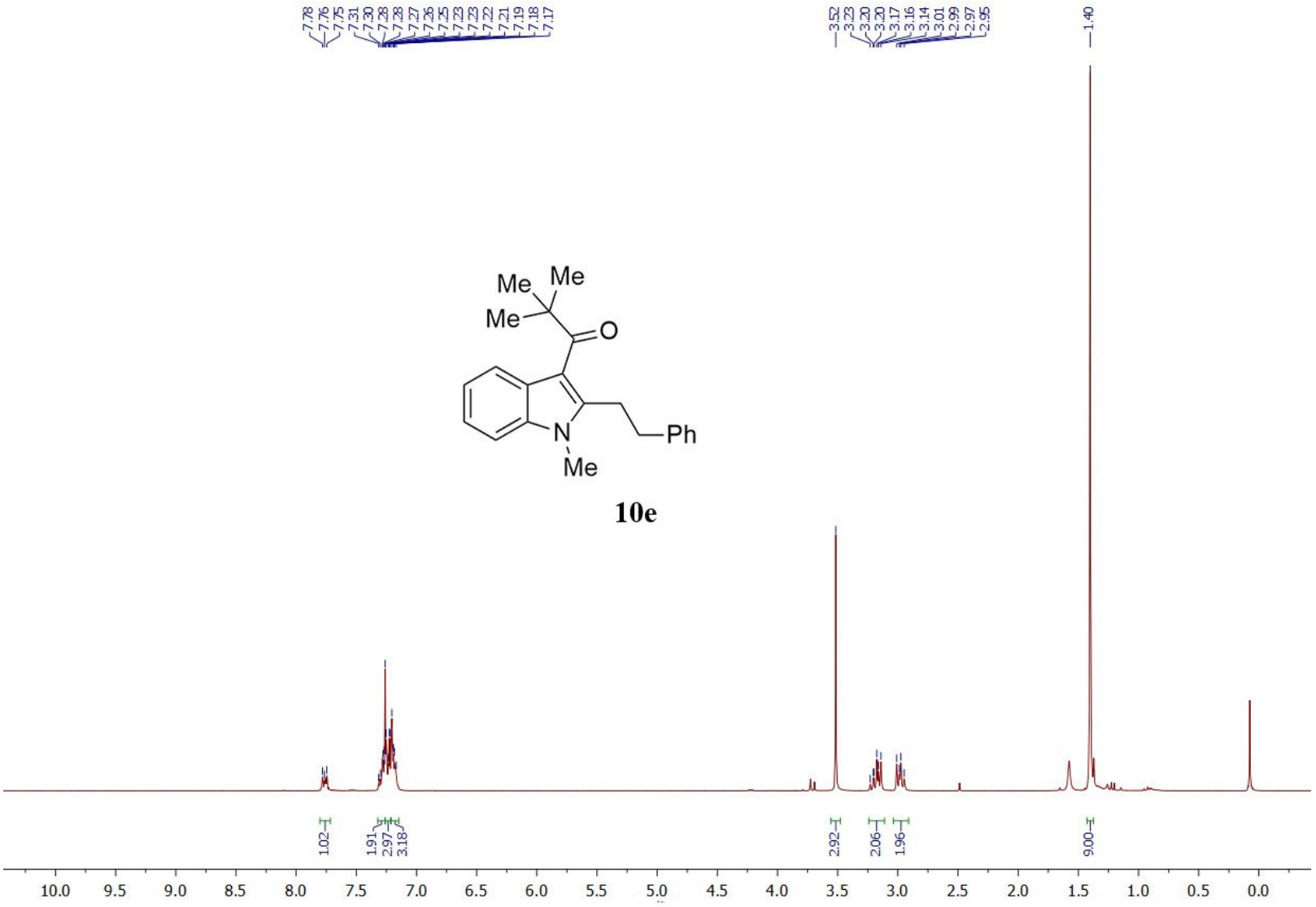


**Figure S15** $^{1}$H NMR of **10e**, $CDCl_3$, 250 MHz

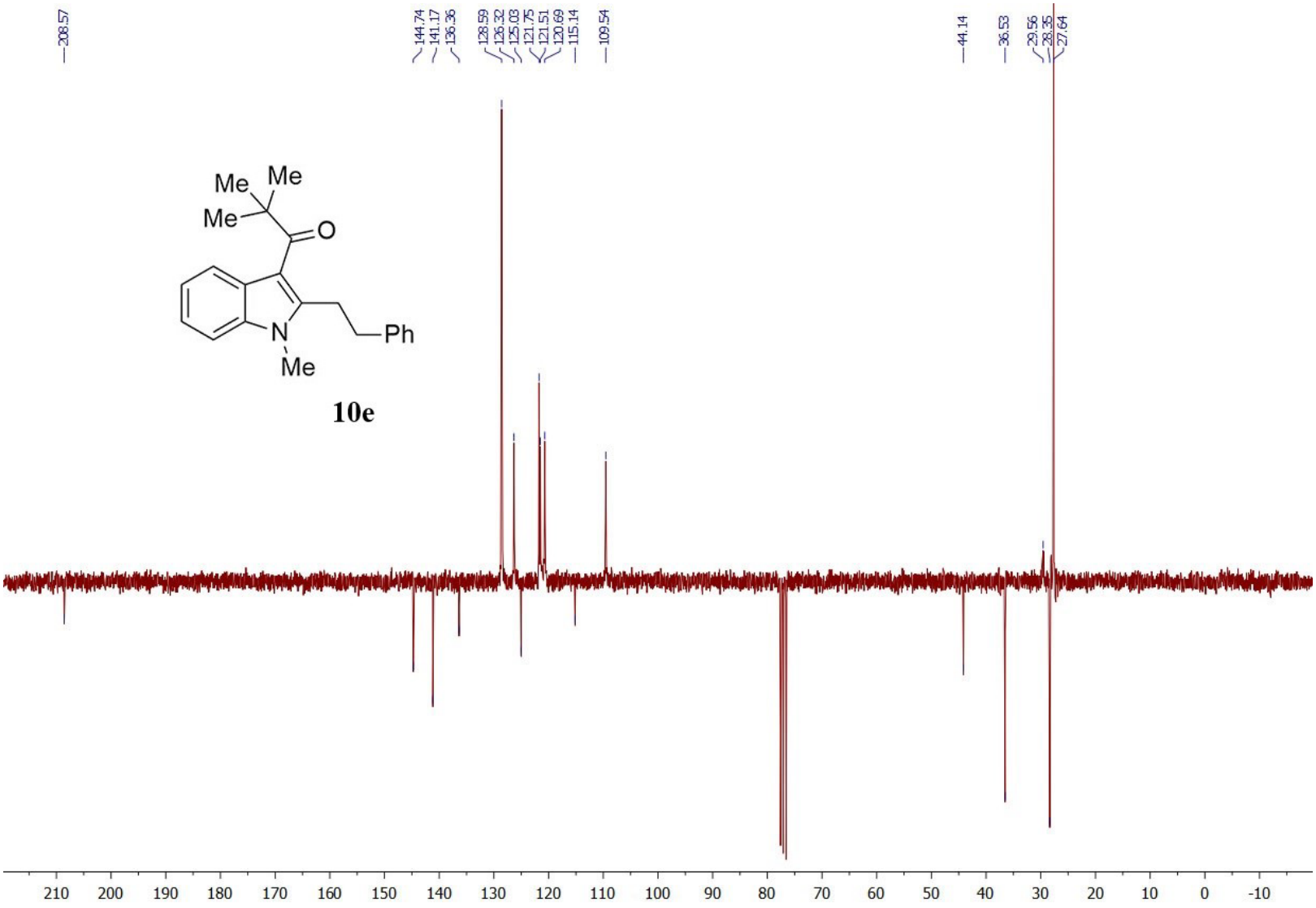


**Figure S16** $^{13}C$ NMR of **10e**, $CDCl_3$, 63 MHz

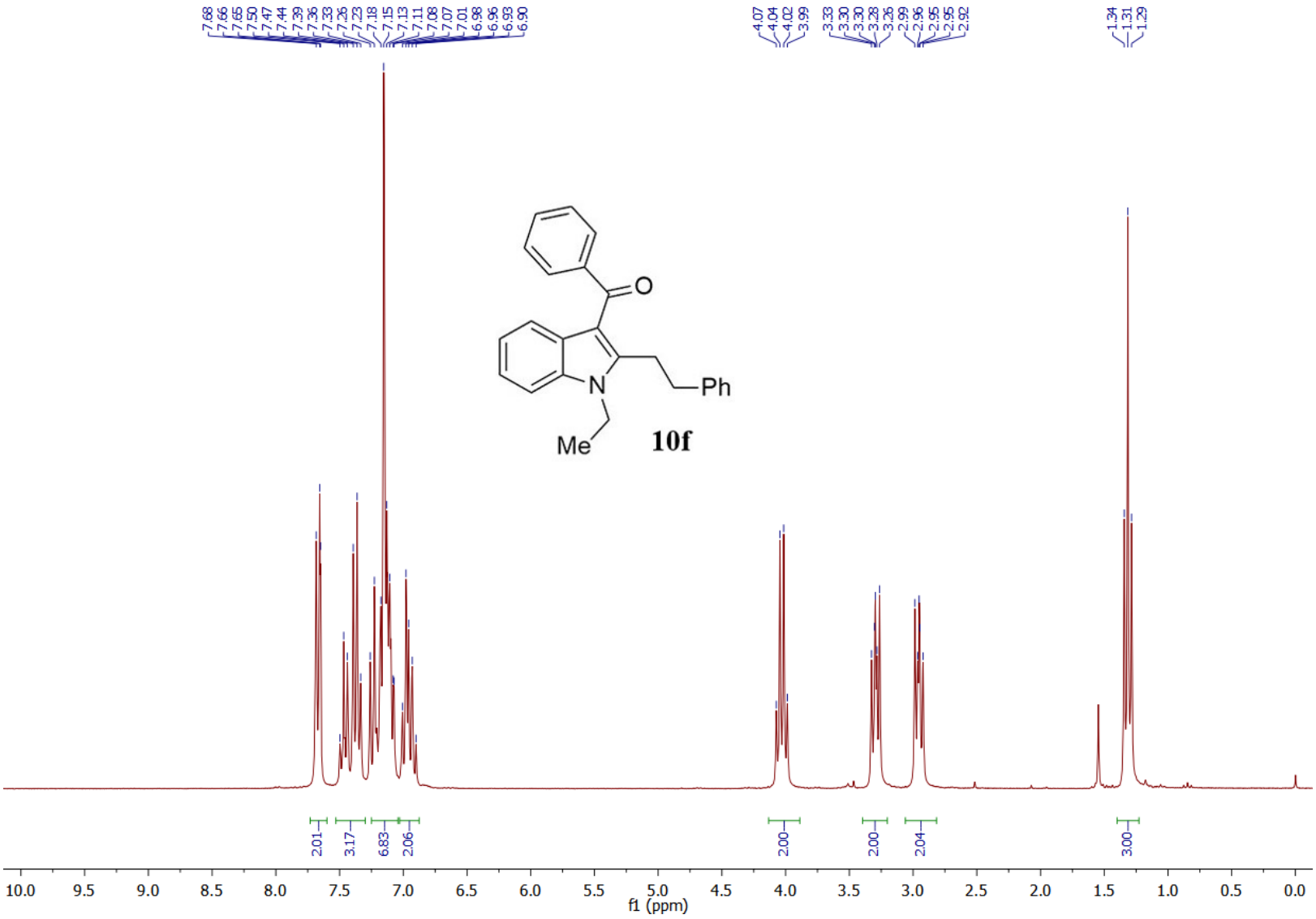


**Figure S17** $^{1}$H NMR of **10f**, $CDCl_3$, 250 MHz

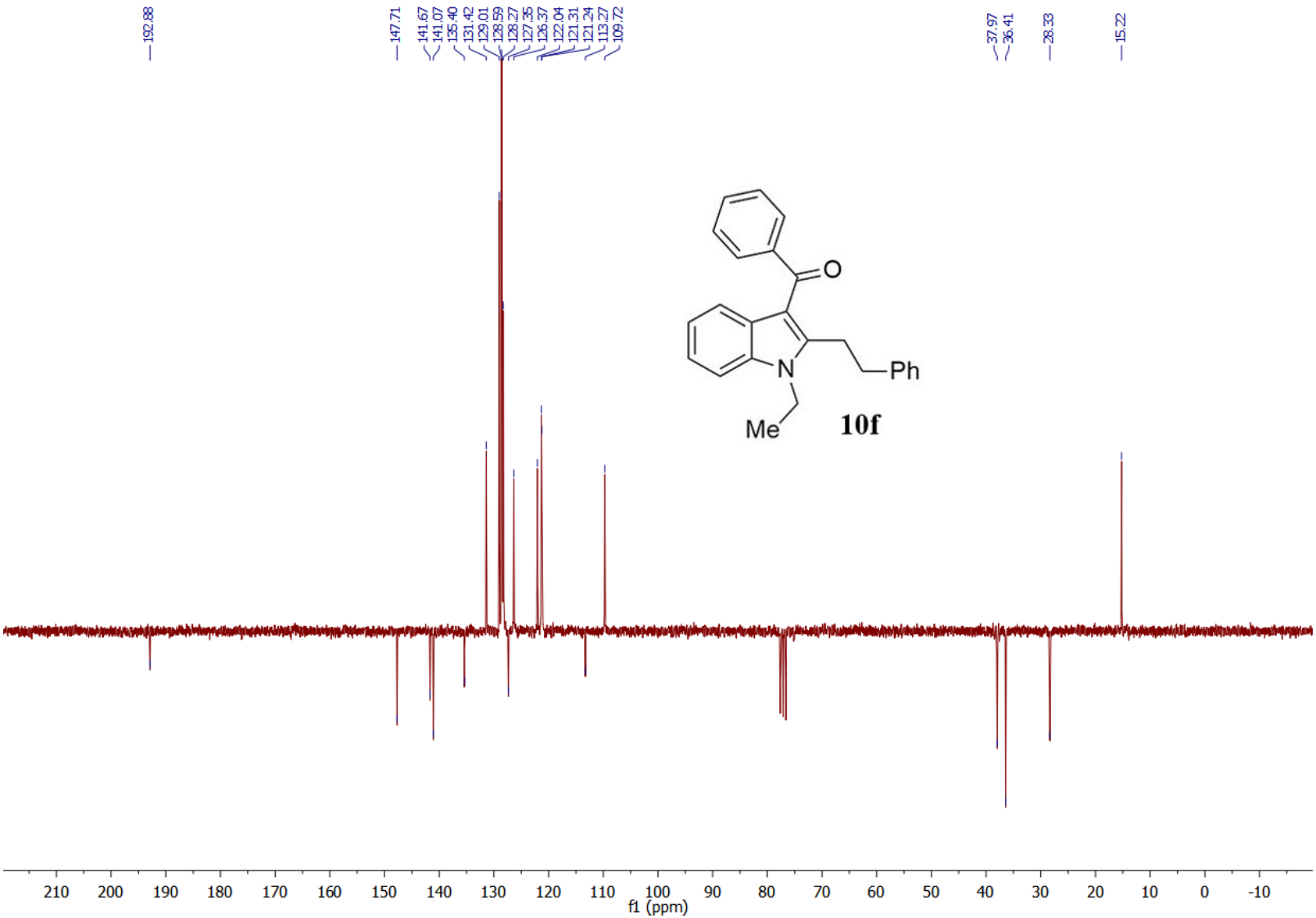


**Figure S18** $^{13}C$ NMR of **10f**, $CDCl_3$, 63 MHz

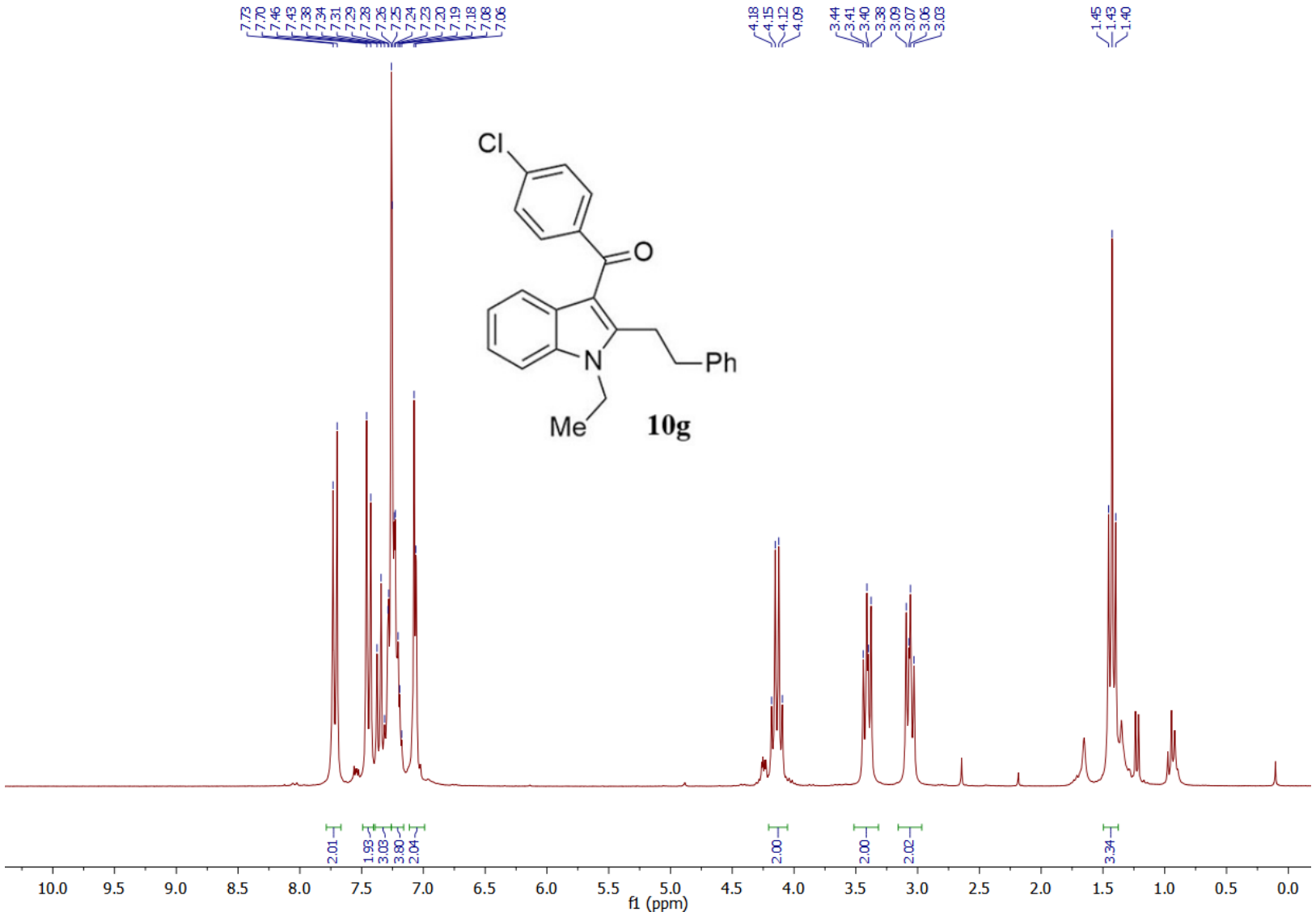


**Figure S19** $^{1}$H NMR of **10g**, $CDCl_3$, 250 MHz

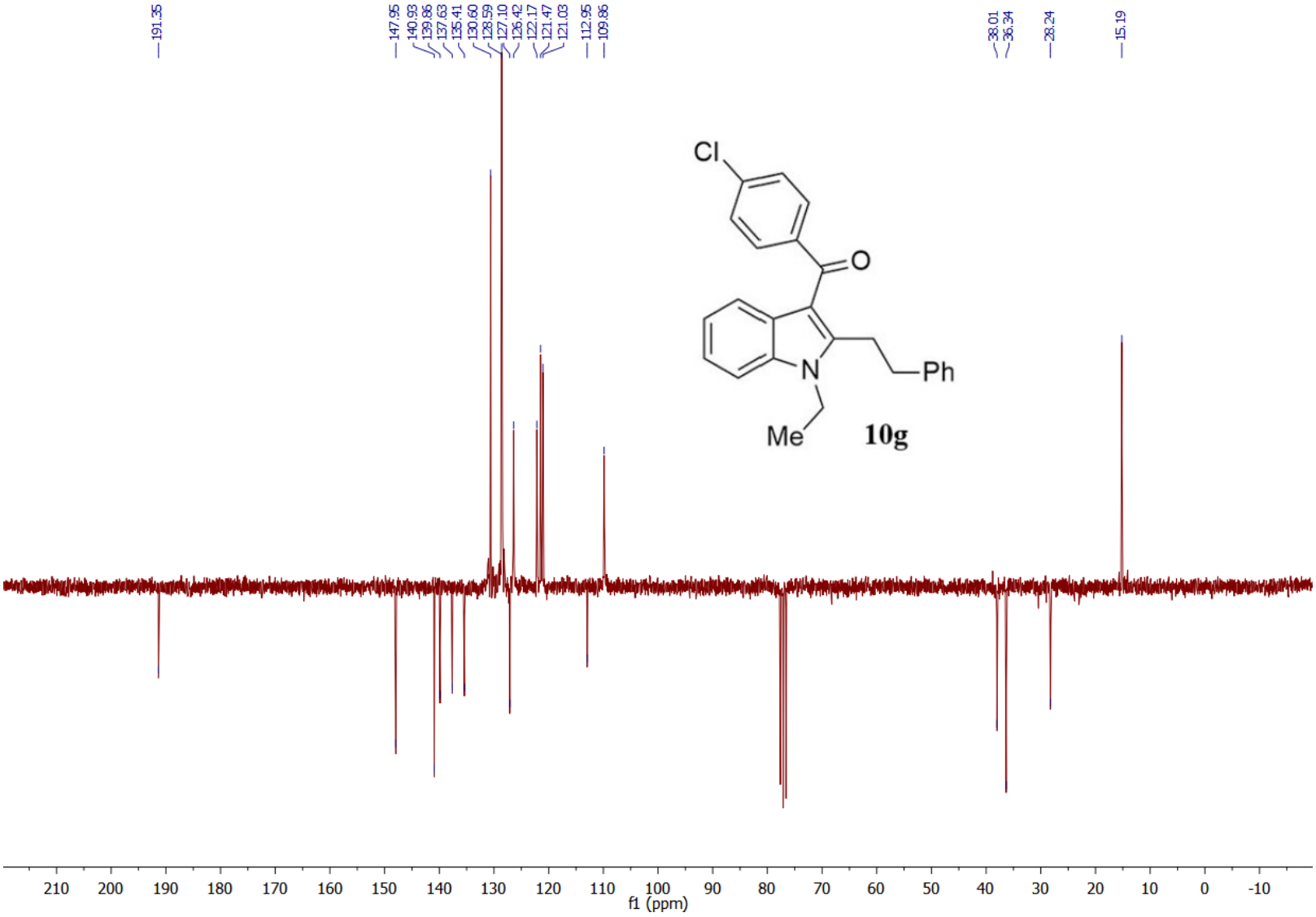


**Figure S20** $^{13}C$ NMR of **10g**, $CDCl_3$, 63 MHz

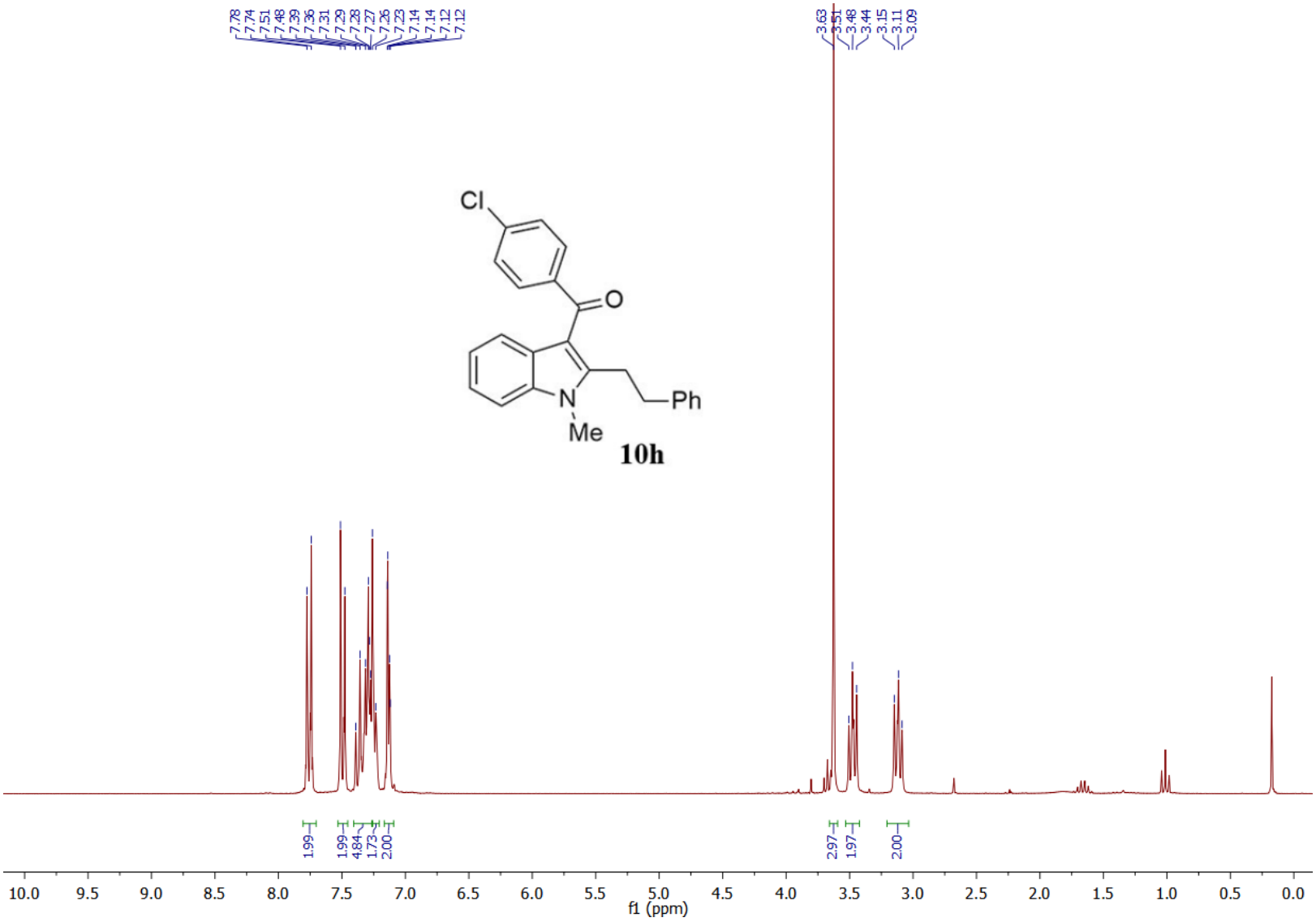


**Figure S21** $^{1}$H NMR of **10h**, $CDCl_3$, 250 MHz

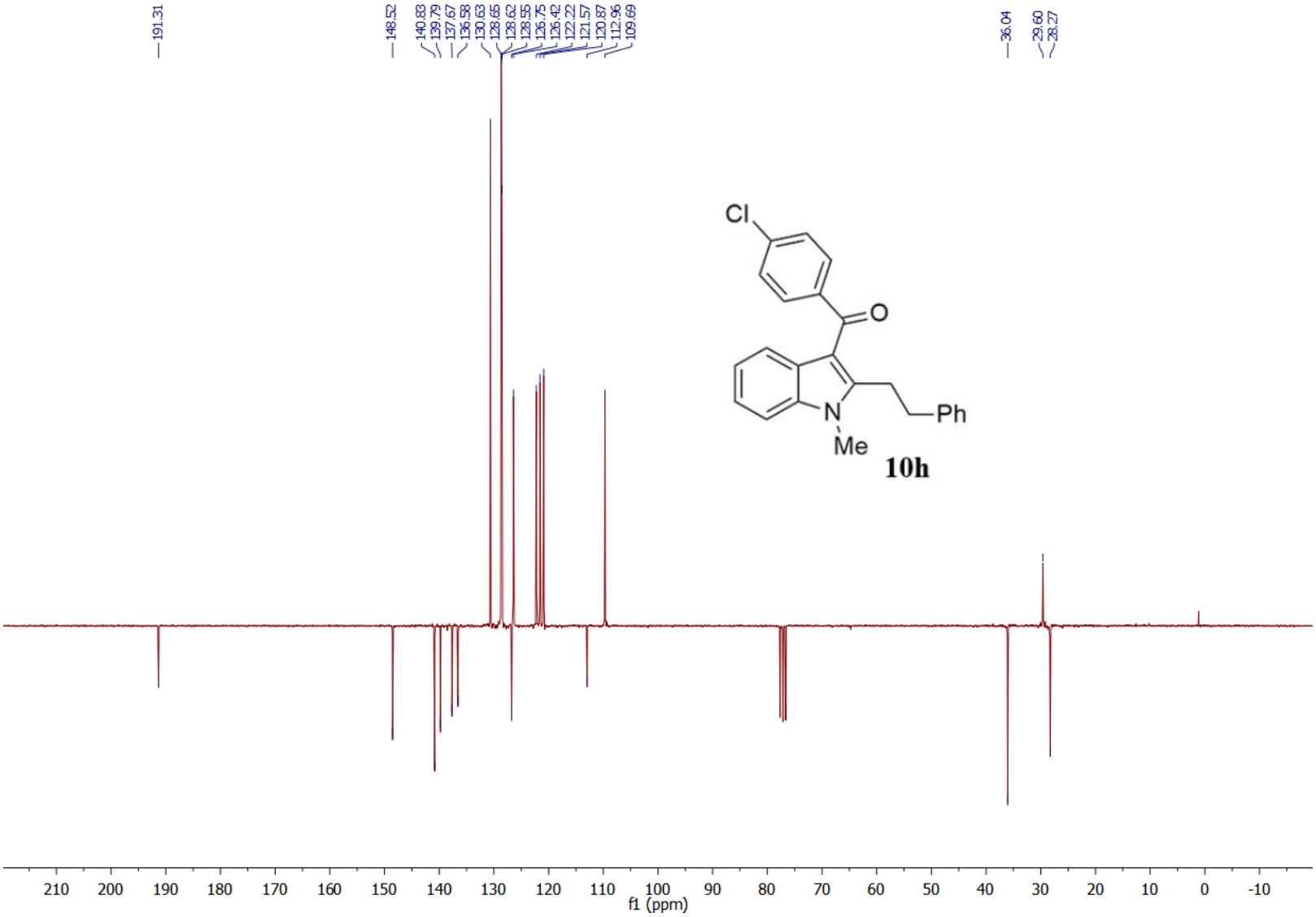


**Figure S22** $^{13}C$ NMR of **10h**, $CDCl_3$, 63 MHz

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S1 U. Pindur and C. Flo, *Monatsh. Chem.*, 1986, **117**, 375; https://doi.org/10.1007/BF00816532.

S2 K. F. Suzdalev, J. V. Vyalyh, V. V. Tkachev, E. A. Lysenko, O. N. Burov, A. V. Lisovin, M. E. Kletskii and S. V. Kurbatov, *J. Org. Chem.*, 2021, **86**, 11698; https://doi.org/10.1021/acs.joc.1c01200.