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One pot three component synthesis of α-methylated ketones from secondary and primary aryl alcohols

Shaikh Samser, Priyabrata Biswal, Omkar Mohapatra, Sanu Siyad Pullarat, Sushanta Kumar Meher and Krishnan Venkatasubbaiah*

School of Chemical Sciences, National Institute of Science Education and Research (NISER), Bhubaneswar, an OCC of Homi Bhabha National Institute, Bhubaneswar-752050, Odisha, India. E-mail: krishv@niser.ac.in.

General information

Reagents and starting materials were purchased from Alfa-Aesar, Sigma-Aldrich and Spectrochem chemical companies and used as received unless otherwise noted. All 400 MHz ^{1}H and 100 MHz ^{13}C NMR, 377 MHz ^{19}F spectra and 161 MHz ^{31}P spectra were recorded on a Bruker ARX 400 spectrometer operating at 400 MHz and referenced internally to solvent signals. ^{19}F NMR spectra were externally referenced to α,α,α-trifluorotoluene in $CDCl_3$ (δ = -63.73 ppm). ^{31}P NMR (161 MHz) spectra were externally referenced to H_3PO_4 in D_2O (δ = 0). High-resolution mass spectra (HRMS) were recorded on a Bruker microTOF-QII mass spectrometer. The elemental composition of the synthesized catalysts were verified by using an inductively coupled plasma-optical emission spectrophotometer (iCAP 7000 ICP-OES). Unless mentioned, all reactions were carried out under aerobic condition and at 0.5 mmol scale.

General procedure for one-pot methylation reaction: Catalyst (1 mol% of Pd), KO^{t}Bu (2 mmol), primary alcohol (0.5 mmol) and secondary alcohol (0.75 mmol) were added to a pressure tube. Methanol (1 mL) was added to it and the tube was sealed. The reaction was stirred at 120 ^{o}C. After 24 hour, the reaction mixture was filtered using a filter paper. Aqueous layer was separated from the reaction mixture and the organic layer was collected using dichloromethane (3 x 10 mL). The organic layer was dried on Na_2SO_4 and concentrated under vacuum. Product was purified by column chromatography.

Procedure for recycling experiment: Catalyst (1 mol% Pd), KO^{t}Bu (6 mmol), primary alcohol (3 mmol) and secondary alcohol (4.5 mmol) were added to a pressure tube. Methanol (10 mL) was added to it. Then the tube was sealed and the reaction was stirred at 120 ^{o}C. After 24 hour, the reaction mixture was filtered using frit apparatus. Then the catalyst was washed with water to remove excess base followed by washing with dichloromethane, methanol and acetone three times each. The catalyst was then dried under high vacuum for 3 hour. The catalyst obtained was reused for the next cycle. This process was reiterated 5 times.

Characterisation data for all compounds:

2-Methyl-3-phenyl-1-(*p*-tolyl)propan-1-one (table 2, 1):[1] Prepared from 1-(*p*-tolyl)ethanol (0. 102 g, 0.75 mmol) and benzyl alcohol (0.054 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 93% (0.110 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.23 (dd, *J* = 7.7, 5.3 Hz, 4H), 7.20 – 7.14 (m, 3H), 3.71 (sextet, *J* = 7.0 Hz, 1H), 3.15 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.66 (dd, *J* = 13.7, 7.9 Hz, 1H), 2.38 (s, 3H), 1.17 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.47, 143.80, 140.18, 134.04, 129.43, 129.20, 128.54, 128.46, 126.26, 42.69, 39.52, 21.69, 17.56.

2-Methyl-1,3-di-*p*-tolylpropan-1-one (table 2, 2)[2]: Prepared from 1-(*p*-tolyl)ethanol (0. 102 g, 0.75 mmol) and 4-methylbenzyl alcohol (0.061 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 81% (0.102 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.25 – 7.20 (m, 2H), 7.11 – 7.03 (m, 4H), 3.70 (sextet, *J* = 8.0 Hz, 1H), 3.12 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.64 (dd, *J* = 13.7, 8.0 Hz, 1H), 2.39 (s, 3H), 2.29 (s, 3H), 1.18 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.50, 143.73, 136.99, 135.64, 133.95, 129.39, 129.36, 129.10, 129.03, 128.95, 128.50, 42.70, 38.99, 21.65, 21.07, 17.43.

2-Methyl-1,3-diphenylpropan-1-one (table 2, 3):[1] Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and benzyl alcohol (0.054g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 91% (0.101 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.0 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.30 – 7.23 (m, 2H), 7.23 – 7.15 (m, 3H), 3.76 (sextet, J = 6.9 Hz, 1H), 3.18 (dd, J = 13.7, 6.3 Hz, 1H), 2.70 (dd, J = 13.7, 7.8 Hz, 1H), 1.21 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.88, 140.08, 136.60, 133.04, 129.21, 128.76, 128.50, 128.41, 126.32, 42.90, 39.52, 17.54.

1-(4-Ethylphenyl)-2-methyl-3-phenylpropan-1-one (table 2, 4): Prepared from 1-(4-ethylphenyl)ethanol (0.112 g, 0.75 mmol) and benzyl alcohol (0.054 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 76% (0.095 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.2 Hz, 2H), 7.23 (dd, J = 7.9, 5.7 Hz, 4H), 7.19 – 7.11 (m, 3H), 3.70 (sextet, 6.9 Hz, 1H), 3.14 (dd, J = 13.7, 6.2 Hz, 1H), 2.70 – 2.63 (m, 3H), 1.22 (t, J = 7.6 Hz, 3H), 1.16 (d, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.53, 150.03, 140.23, 134.21, 129.24, 128.67, 128.49, 128.29, 126.28, 42.75, 39.49, 29.04, 17.59, 15.33. HRMS (ESI): calculated for $C_{18}H_{20}O$ ($[M+Na]^+$): 275.1406, found: 275.1409

2-Methyl-1,3-di-*o*-tolylpropan-1-one (table 2, 5): Prepared from 1-(*o*-tolyl)ethanol (0.102 g, 0.75 mmol) and 2-methylbenzyl alcohol (0.061g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 73% (0.092 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 6.0 Hz, 1H), 7.17 – 6.97 (m, 6H), 3.48 (sextet, *J* = 6.9 Hz, 1H), 3.07 (dd, *J* = 13.9, 6.4 Hz, 1H), 2.58 (dd, *J* = 13.9, 7.9 Hz, 1H), 2.33 (s, 3H), 2.24 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.49, 138.80, 138.22, 137.70, 136.23, 131.73, 130.88, 130.47, 129.97, 127.52, 126.45, 125.99, 125.65, 45.01, 36.25, 20.79, 19.68, 17.08. HRMS (ESI): calculated for $C_{18}H_{20}O$ ($[M+Na]^+$): 275.1406, found: 275.1420

3-(4-Methoxyphenyl)-2-methyl-1-(*p*-tolyl)propan-1-one (table 2, 6): Prepared from 1-(*p*-tolyl)ethanol (0. 102 g, 0.75 mmol) and 4-methoxybenzyl alcohol (0.069 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 76% (0.101 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 7.7 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 3.77 (s, 3H), 3.69 (sextet, *J* = 6.9 Hz, 1H), 3.11 (dd, *J* = 13.8, 6.3 Hz, 1H), 2.63 (dd, *J* = 13.8, 7.8 Hz, 1H), 2.40 (s, 3H), 1.18 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.64, 158.05, 143.78, 134.02, 132.16, 130.10, 129.41, 128.51, 113.82, 55.28, 42.87, 38.61, 21.69, 17.48. HRMS (ESI): calculated for $C_{18}H_{20}O_2$ ($[M+Na]^+$): 291.1356, found: 291.1371

1-(4-Methoxyphenyl)-2-methyl-3-phenylpropan-1-one (table 2, 7):[1] Prepared from 1-(4-methoxyphenyl)ethanol (0.114 g, 0.75 mmol) and benzyl alcohol (0.054 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 64% (0.081 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.9 Hz, 2H), 7.28 – 7.22 (m, 2H), 7.21 – 7.16 (m, 3H), 6.91 (d, *J* = 8.9 Hz, 2H), 3.84 (s, 3H), 3.74 – 3.65 (m, 1H), 3.15 (dd, *J* = 13.6, 6.3 Hz, 1H), 2.68 (dd, *J* = 13.7, 7.9 Hz, 1H), 1.18 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.40, 163.47, 140.23, 130.67, 129.45, 129.19, 128.45, 126.24, 113.87, 55.55, 42.42, 39.59, 17.67.

1-(2-Methoxyphenyl)-2-methyl-3-phenylpropan-1-one (table 2, 8)[2]: Prepared from 1-(2-methoxyphenyl)ethanol (0.114 g, 0.75 mmol) and benzyl alcohol (0.054 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 54% (0.068 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.40 (ddd, *J* = 8.8, 7.4, 1.8 Hz, 1H), 7.25 – 7.20 (m, 2H), 7.19 – 7.14 (m, 3H), 6.98 – 6.88 (m, 2H), 3.84 (s, 3H), 3.71 (dq, *J* = 13.9, 6.9 Hz, 1H), 3.15 (dd, *J* = 13.5, 5.7 Hz, 1H), 2.55 (dd, *J* = 13.5, 8.7 Hz, 1H), 1.09 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.33, 157.91, 140.44, 132.97, 130.26, 129.26, 129.05, 128.31, 126.05, 120.80, 111.44, 55.57, 47.34, 39.27, 16.40.

1-(Furan-2-yl)-2-methyl-3-phenylpropan-1-one (table 2, 9): Prepared from 1-(furan-2-yl)ethan-1-ol (0.084g, 0.75 mmol) and benzyl alcohol (0.054 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 71% (0.076g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 2.5 Hz, 1H), 7.23 (d, J = 7.3 Hz, 2H), 7.20 – 7.15 (m, 3H), 7.13 (d, J = 3.6 Hz, 1H), 6.48 (d, J = 3.6, 1H), 3.50 (sextet, 1H), 3.12 (dd, J = 13.6, 6.6 Hz, 1H), 2.66 (dd, J = 13.6, 7.8 Hz, 1H), 1.18 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.79, 152.43, 146.55, 139.83, 129.21, 128.46, 126.32, 117.55, 112.32, 43.75, 39.27, 17.03. HRMS (ESI): calculated for $C_{14}H_{14}O_2$ ($[M+Na]^+$): 237.0886, found: 237.0889.

2-Methyl-1-phenyl-3-(*p*-tolyl)propan-1-one (table 3, 10): [1] Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 4-methylbenzyl alcohol (0.061 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 84% (0.100 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.90 (m, 2H), 7.57 – 7.51 (m, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.08 (d, *J* = 1.8 Hz, 4H), 3.72 (sextet, *J* = 7.3 Hz, 1H), 3.13 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.64 (dd, *J* = 13.7, 7.9 Hz, 1H), 2.29 (s, 3H), 1.19 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.97, 136.95, 136.55, 135.79, 133.03, 129.18, 129.09, 128.76, 128.43, 42.94, 39.01, 21.14, 17.43.

2-methyl-1-phenyl-3-(*o*-tolyl)propan-1-one (table 3, 11)[3]: Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 2-methylbenzyl alcohol (0.061 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 78% (0.092 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.2 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 7.18 – 7.05 (m, 4H), 3.77 (sext, J = 7.0 Hz, 1H), 3.15 (dd, J = 14.0, 6.3 Hz, 1H), 2.74 (dd, J = 14.0, 7.9 Hz, 1H), 2.36 (s, 3H), 1.22 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.23, 138.22, 136.63, 136.31, 133.07, 130.45, 129.86, 128.75, 128.36, 126.43, 126.00, 41.40, 36.49, 19.81, 17.77.

2-Methyl-1-phenyl-3-(m-tolyl)propan-1-one (table 3, 12)[4]: Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 3-methylbenzyl alcohol (0.061 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 77% (0.091 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.61 – 7.51 (m, 1H), 7.51 – 7.41 (m, 2H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.07 – 6.98 (m, 3H), 3.76 (sextet, *J* = 8.0 Hz, 1H), 3.16 (dd, *J* = 13.6, 6.1 Hz, 1H), 2.67 (dd, *J* = 13.5, 7.9 Hz, 1H), 2.33 (s, 3H), 1.22 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.93, 139.96, 138.01, 136.53, 133.01, 130.01, 128.73, 128.40, 128.36, 127.04, 126.19, 42.83, 39.35, 21.50, 17.46.

3-(4-Methoxyphenyl)-2-methyl-1-phenylpropan-1-one (table 3, 13):[1] Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 4-methoxybenzyl alcohol (0.069 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 74% (0.094 g). ^{1}H NMR (400 MHz, $CDCl_3$) 7.93 (d, J = 7.7 Hz, 2H), 7.54 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.12 (d, J = 8.3 Hz, 2H), 6.81 (d, J = 8.3 Hz, 2H), 3.77 (s, 3H), 3.71 (sextet, 1H), 3.12 (dd, J = 13.8, 6.3 Hz, 1H), 2.65 (dd, J = 13.8, 7.7 Hz, 1H), 1.20 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.00, 158.11, 136.60, 133.00, 132.06, 130.12, 128.73, 128.38, 113.86, 55.31, 43.07, 38.61, 17.44.

3-(2-Methoxyphenyl)-2-methyl-1-phenylpropan-1-one (table 3, 14) [4]: Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 2-methoxybenzyl alcohol (0.069 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 67% (0.085 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 7.4 Hz, 1H), 6.85 (t, *J* = 8.7 Hz, 2H), 3.91 – 3.81 (m, 4H), 3.19 (dd, *J* = 13.3, 5.4 Hz, 1H), 2.61 (dd, *J* = 13.3, 8.6 Hz, 1H), 1.15 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.39, 157.61, 136.73, 132.89, 131.49, 128.60, 128.54, 128.18, 127.74, 120.44, 110.29, 55.27, 40.50, 35.25, 16.82.

3-(4-Chlorophenyl)-2-methyl-1-phenylpropan-1-one (table 3, 15)[5]: Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 4-chlorobenzyl alcohol (0.071 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 76% (0.098 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.4 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.1 Hz, 1H), 7.23 – 7.15 (m, 3H), 3.76 (sextet, *J* = 7.0 Hz, 1H), 3.18 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.70 (dd, *J* = 13.7, 7.8 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.87, 140.08, 136.61, 133.04, 129.22, 128.76, 128.66, 128.50, 128.41, 128.17, 126.32, 126.27, 42.88, 39.50, 17.52.

3-(2-Chlorophenyl)-2-methyl-1-phenylpropan-1-one (table 3, 16)[7]: Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 2-chlorobenzyl alcohol (0.071 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 81% (0.104 g). ^{1}H

NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.91 (m, 2H), 7.57 – 7.52 (m, 1H), 7.48 – 7.44 (m, 2H), 7.28 (dt, *J* = 6.8, 1.1 Hz, 1H), 7.25 (d, *J* = 1.0 Hz, 1H), 7.23 – 7.15 (m, 3H), 3.76 (sextet, *J* = 6.9 Hz, 1H), 3.18 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.70 (dd, *J* = 13.7, 7.9 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.92, 140.07, 136.54, 133.07, 129.22, 128.76, 128.50, 128.45, 128.41, 126.32, 42.87, 39.47, 17.52.

2-Methyl-1-phenyl-3-(4-(trifluoromethyl)phenyl)propan-1-one (table 3, 17) [4]: Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 4-(Trifluoromethyl)benzyl alcohol (0.088 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 71% (0.103 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.89 (m, 2H), 7.59 – 7.53 (m, 1H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.45 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 3.77 (sextet, *J* = 7.0 Hz, 1H), 3.24 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.78 (dd, *J* = 13.7, 7.3 Hz, 1H), 1.23 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (19F-decoupled) (101 MHz, $CDCl_3$) δ 203.18, 144.29, 136.37, 133.26, 129.54, 128.86, 128.72, 128.39, 125.43, 124.40, 42.63, 39.11, 17.90.^{19}F NMR (376 MHz, $CDCl_3$) δ -62.25.

3-(4-Fluorophenyl)-2-methyl-1-phenylpropan-1-one (table 3, 18)[5]: Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 4-Fluorobenzyl alcohol (0.063 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 79% (0.095 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.2 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.19 – 7.11 (m, 2H), 6.94 (t, J = 8.7 Hz, 2H), 3.72 (sextet, J = 7.0 Hz, 1H), 3.14 (dd, J = 13.8, 6.8 Hz, 1H), 2.68 (dd, J = 13.8, 7.4 Hz, 1H), 1.20 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.72, 161.5 (d, J_{C-F} = 245.4 Hz), 136.50, 135.70 (d, J_{C-F} = 3 Hz), 133.15, 130.58 (d, J_{C-F} = 8.08 Hz), 128.79, 128.36, 115.25, (d, J_{C-F} = 21 Hz), 42.96, 38.62, 17.66.^{19}F NMR (376 MHz, $CDCl_3$) δ -117.00, -117.03.

3-(2-Fluorophenyl)-2-methyl-1-phenylpropan-1-one (table 3, 19)[6]: Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 2-Fluorobenzyl alcohol (0.063 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 81% (0.098 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.92 (m, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.23 – 7.13 (m, 2H), 7.05 – 6.96 (m, 2H), 3.83 (sextet, *J* = 6.9 Hz, 1H), 3.17 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.76 (dd, *J* = 13.7, 8.1 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.59, 161.44 (J_{C-F} = 245.4 Hz), 136.41, 133.10, 131.95 (J_{C-F} = 5.0 Hz), 128.76, 128.44, 128.20 (J_{C-F} = 8.0 Hz), 126.82 (J_{C-F} = 15.1 Hz), 124.04 (J_{C-F} = 3.0 Hz), 115.46, 115.35 (J_{C-F} = 22 Hz), 41.14, 33.23, 17.34. ^{19}F NMR (377 MHz, $CDCl_3$) δ -117.76.

3-([1,1'-Biphenyl]-4-yl)-2-methyl-1-phenylpropan-1-one (table 3, 20): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 2-biphenylmethanol (0.092 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 64% (0.096 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 3H), 7.32 – 7.25 (m, 4H), 7.19 – 7.16 (m, 3H), 7.14 – 7.09 (m, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 3.34 – 3.24 (m, 1H), 3.19 (dd, *J* = 13.6, 5.4 Hz, 1H), 2.50 (dd, *J* = 13.6, 9.2 Hz, 1H), 2.29 (s, 3H), 0.85 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.65, 143.60, 142.21, 142.11, 137.19, 133.79, 130.94, 130.39, 129.36, 129.30, 128.58, 128.43, 127.43, 127.14, 126.44, 40.81, 37.36, 21.71, 16.39. HRMS (ESI): calcd for $C_{23}H_{22}O$ ($[M+Na]^+$): 337.1563, found: 337.1570

2-Methyl-3-(naphthalen-2-yl)-1-phenylpropan-1-one (table 3, 21)[4]: Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 2-naphthalenemethanol (0.079 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 82% (0.112 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.5 Hz, 2H), 7.84 – 7.75 (m, 3H), 7.68 (s, 1H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.1 Hz, 4H), 7.39 (d, *J* = 8.5 Hz, 1H), 3.88 (sextet, *J* = 6.9 Hz, 1H), 3.38 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.89 (dd, *J* = 13.7, 7.9 Hz, 1H), 1.27 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.76, 137.54, 136.42, 133.56, 133.05, 132.17, 128.73, 128.37, 128.07, 127.66, 127.64, 127.58, 126.05, 125.41, 77.46, 77.16, 76.84, 42.76, 39.48, 17.59.

2-Methyl-1-phenyl-3-(thiophen-2-yl)propan-1-one (table 3, 22) [4]: Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 2-thiophenemethanol (0. 057 g, 0.5 mmol). After purification by column chromatography

(silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 83% (0.095 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 7.8 Hz, 2H), 7.48 (t, J = 7.3 Hz, 1H), 7.39 (t, J = 7.5 Hz, 2H), 7.03 (d, J = 5.1 Hz, 1H), 6.84 – 6.78 (m, 1H), 6.73 (d, J = 2.9 Hz, 1H), 3.70 (sextet, J = 6.9 Hz, 1H), 3.31 (dd, J = 14.8, 6.7 Hz, 1H), 2.88 (dd, J = 14.8, 7.2 Hz, 1H), 1.18 (d, J = 6.8 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 203.36, 142.56, 136.37, 133.19, 128.82, 128.46, 126.93, 125.74, 123.73, 43.38, 33.37, 17.93.

3-(Furan-2-yl)-2-methyl-1-phenylpropan-1-one (table 3, 23)[7]: Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and furfuryl alcohol (0.049 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 86% (0.092 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.92 (m, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.29 – 7.23 (m, 1H), 6.23 (t, *J* = 2.4 Hz, 1H), 6.00 (d, *J* = 3.1 Hz, 1H), 3.85 (sextet, *J* = 7.0 Hz, 1H), 3.13 (dd, *J* = 15.1, 6.4 Hz, 1H), 2.75 (dd, *J* = 15.1, 7.6 Hz, 1H), 1.21 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.43, 153.75, 141.35, 136.25, 133.16, 128.79, 128.59, 128.46, 110.32, 106.63, 40.10, 31.72, 17.65.

3-(Benzo[d][1,3]dioxol-5-yl)-2-methyl-1-phenylpropan-1-one (table 3, 24)[8]: Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 3,4-(methylenedioxy)benzyl alcohol (0. 076 g, 0,5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 59% (0.079 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.8 Hz, 2H), 7.59 – 7.51 (m, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 6.70 (d, *J* = 7.6 Hz, 2H), 6.64 (d, *J* = 7.9 Hz, 1H), 5.90 (s, 2H), 3.70 (sextet, *J* = 7.0 Hz, 1H), 3.08 (dd, *J* = 13.8, 6.5 Hz, 1H), 2.62 (dd, *J* = 13.8, 7.6 Hz, 1H), 1.19 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.83, 147.64, 146.00, 136.55, 133.80, 133.06, 128.77, 128.39, 122.12, 109.55, 108.26, 100.91, 43.06, 39.18, 17.51.

Characterisation data for all deuterated compounds:

2-benzyl-1-phenylpropan-1-one-2,3,3,3-d4 (scheme 4, 28): Prepared from acetophenone (0.090 g, 0.75 mmol), benzyl alcohol (0.054 g, 0.5 mmol) and methanol-d4 (1 mL). After purification by column chromatography the compound was isolated in 93% (0.105 g).

Deuterium incorporation equation:

% D = 100-((peak integral/equivalent protons)*100)

Peak A: 100-((0.01/3)*100) = 99% D

Peak B: 100-((0.09/1)*100) = 91% D

2-**benzyl-1-phenylpropan-1-one-2,3,3-d3 (scheme 4, 29)**: Prepared from 1-phenylethanol (0.091 g, 0.75 mmol), benzyl alcohol (0.054 g, 0.5 mmol) and methanol-d4 (1 mL). After purification by column chromatography the compound was isolated in 89% (0.099 g, based on the molecular weight of the protonated compound). HRMS (ESI): calculated for $C_{16}H_{13}D_3O$ ($[M+Na]^+$): 250.1282, found: 250.1277 and HRMS (ESI): calculated for $C_{16}H_{12}D_4O$ ($[M+Na]^+$): 251.1344, found: 251.1327

Deuterium incorporation equation:

% D = 100-((peak integral/equivalent protons)*100)

Peak A: 100-((0.66/3)*100) = 78% D

Peak B: 100-((0.22/1)*100) = 93% D

Peak C: 100-((1.68/2)*100) = 24.5% D

2-(methyl-d2)-3-(4-methyl-1l5-phenyl)-1-phenyl-3l5-propan-1-one-2,3,3-d3 (scheme 4, 30): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol), 4-methylbenzyl alcohol (0.061 g, 0.5 mmol) and methanol-d4 (1 mL). After purification by column chromatography the compound was isolated in 79% (0.094 g, based on the

molecular weight of the protonated compound). HRMS (ESI): calculated for $C_{17}H_{15}D_3O$ ($[M+H]^+$): 242.1619, found: 242.1623 and HRMS (ESI): calculated for $C_{17}H_{14}D_4O$ ($[M+Na]^+$): 265.1501, found: 265.1485.

Deuterium incorporation equation:

% D = 100-((peak integral/equivalent protons)*100)

Peak A: 100-((0.86/3)*100) = 71% D

Peak B: 100-((0.21/1)*100) = 79% D

Peak C: 100-((1.87/2)*100) = 7% D

3-(4-chlorophenyl)-2-(methyl-d2)-1-phenylpropan-1-one-2,3,3-d3 (scheme 4, 31): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol), 4-chlorobenzyl alcohol (0.071 g, 0.5 mmol) and methanol-d4 (1 mL). After purification by column chromatography the compound was isolated in 81% (0.104 g, based on the molecular weight of the protonated compound). Calculated for $C_{16}H_{12}D_3ClO$ ($[M+K]^+$): 300.0631, found: 300.0630 and HRMS (ESI): calculated for $C_{16}H_{11}D_4ClO$ ($[M+K]^+$): 301.0694, found: 301.0607

Deuterium incorporation equation:

% D = 100-((peak integral/equivalent protons)*100)

Peak A: 100-((0.75/3)*100) = 75% D

Peak B: 100-((0.17/1)*100) = 83% D

Peak C: 100-((0.96/2)*100) = 52% D

3-(2-fluorophenyl)-2-(methyl-d2)-1-phenylpropan-1-one-2,3,3-d3 (scheme 4, 32): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol), 2-Fluorobenzyl alcohol (0.063 g, 0.5 mmol). and methanol-d4 (1 mL). After purification by column chromatography the compound was isolated in 76% (0.092 g, based on the molecular weight of the protonated compound). Calculated for $C_{16}H_{12}D_3FO$ ($[M+Na]^+$): 268.1187, found: 268.1191 and HRMS (ESI): calculated for $C_{16}H_{11}D_4FO$ ($[M+Na]^+$): 269.1250, found: 269.1246

Deuterium incorporation equation:

% D = 100-((peak integral/equivalent protons)*100)

Peak A: 100-((0.54/3)*100) = 82% D

Peak B: 100-((0.06/1)*100) = 94% D

Peak C: 100-((1.02/2)*100) = 49% D

3-(4-fluorophenyl)-2-(methyl-d2)-1-phenylpropan-1-one-2,3,3-d3 (scheme 4, 33): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol), 4-Fluorobenzyl alcohol (0.063 g, 0.5 mmol). and methanol-d4 (1 mL). After purification by column chromatography the compound was isolated in 76% (0.085 g, based on the molecular weight of the protonated compound). Calculated for $C_{16}H_{12}D_3FO$ ($[M+Na]^+$): 268.1187, found: 268.1188 and HRMS (ESI): calculated for $C_{16}H_{11}D_4FO$ ($[M+H]^+$): 247.1431, found: 247.1437

Deuterium incorporation equation:

% D = 100-((peak integral/equivalent protons)*100)

Peak A: 100-((0.63/3)*100) = 79% D

Peak B: 100-((0.2/1)*100) = 80% D

Peak C: 100-((1.3/2)*100) = 35% D

NMR spectra of all compounds:

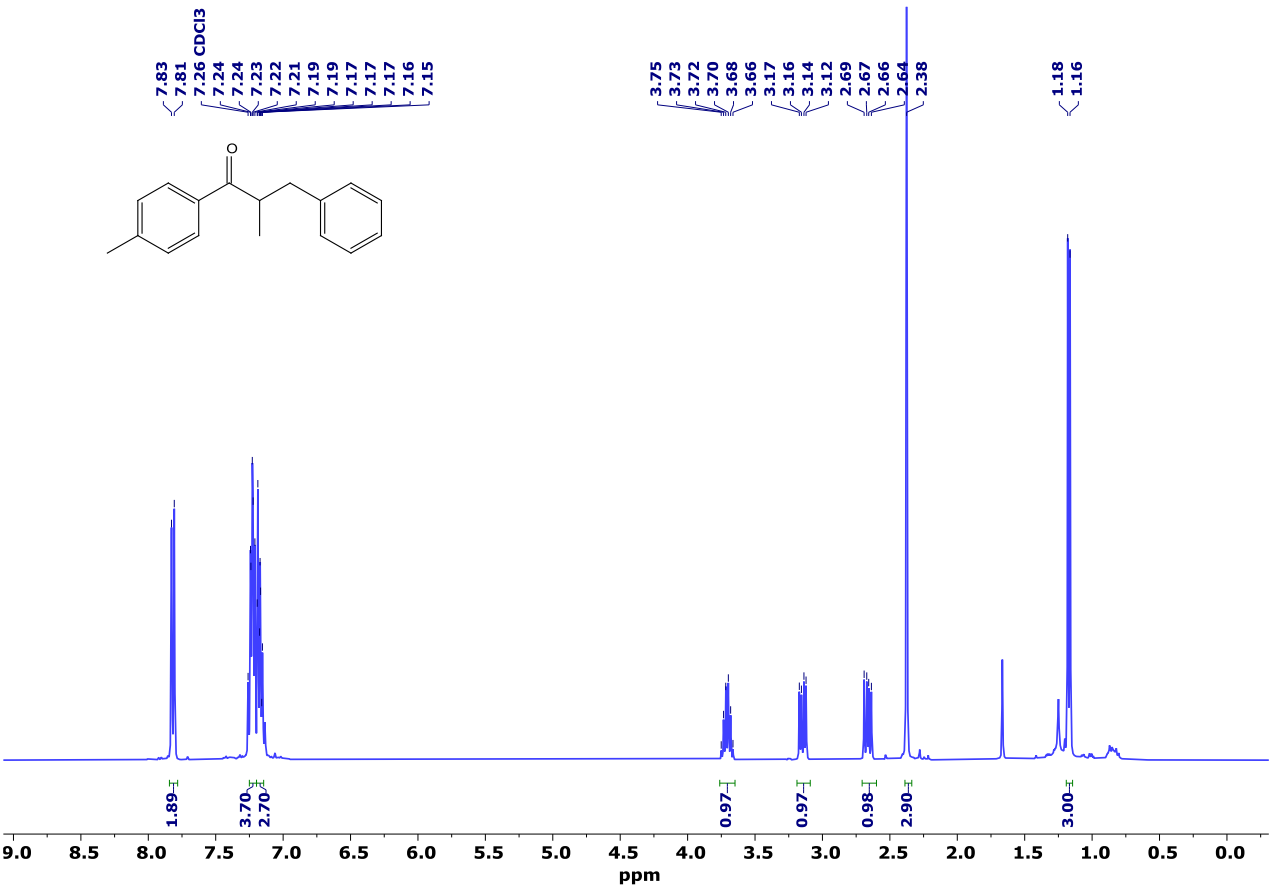

Figure S1: ^{1}H NMR spectrum of compound 1

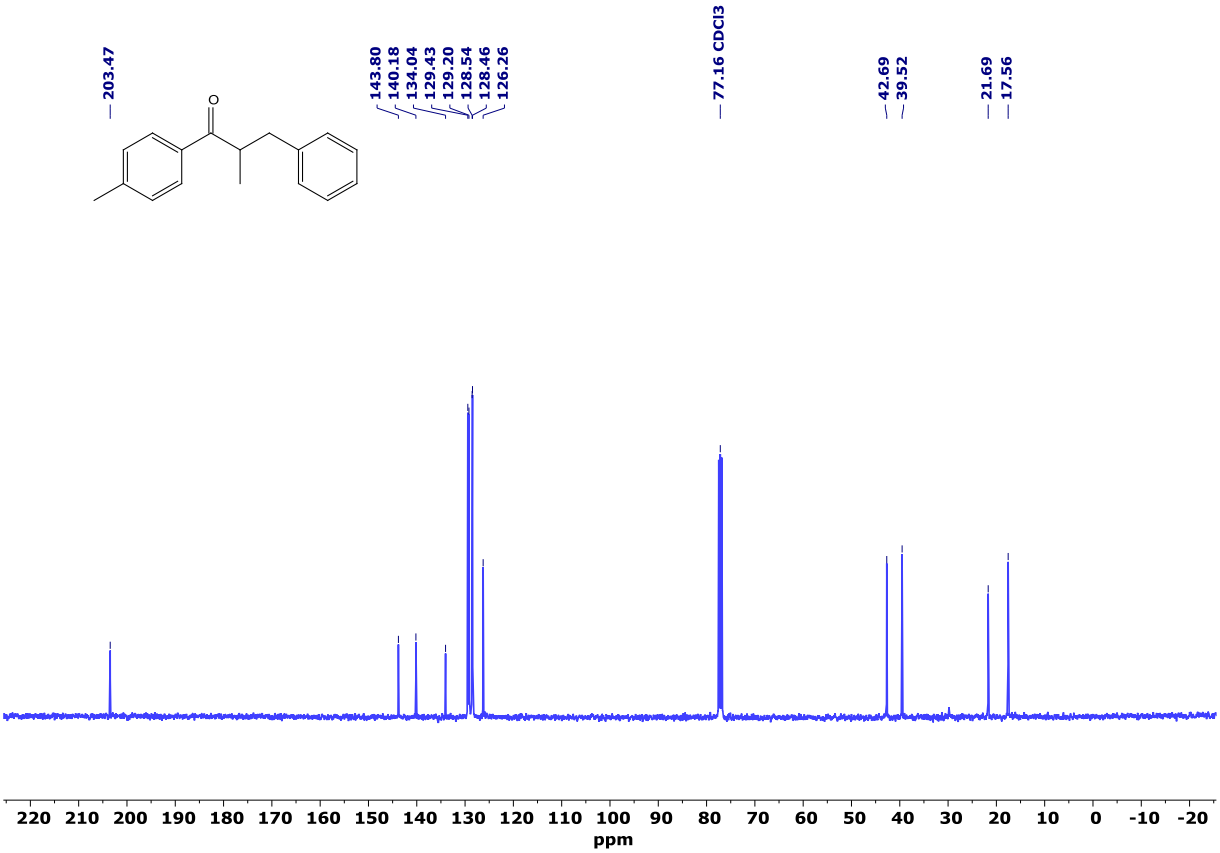

Figure S2: ^{13}C NMR spectrum of compound 1

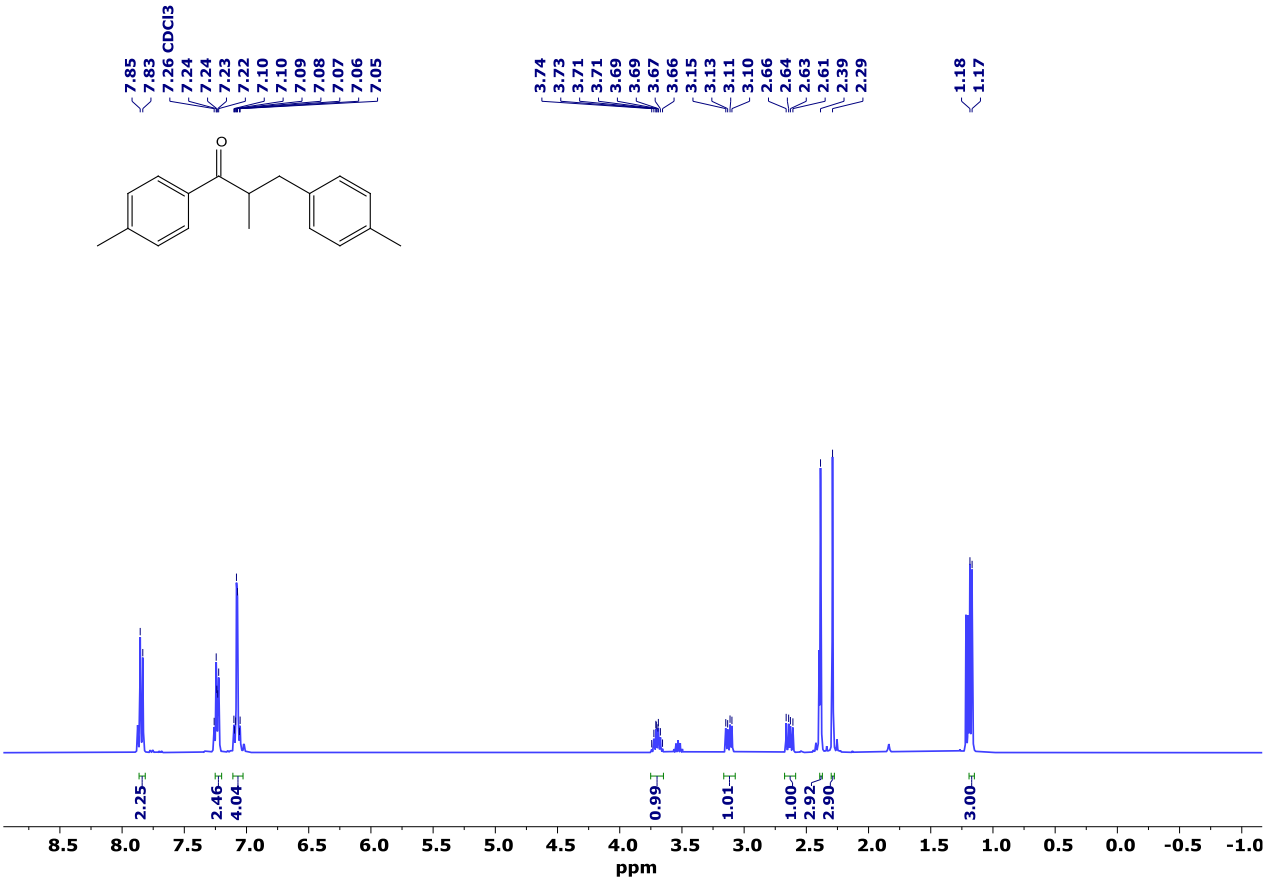

Figure S3: ^{1}H NMR spectrum of compound 2

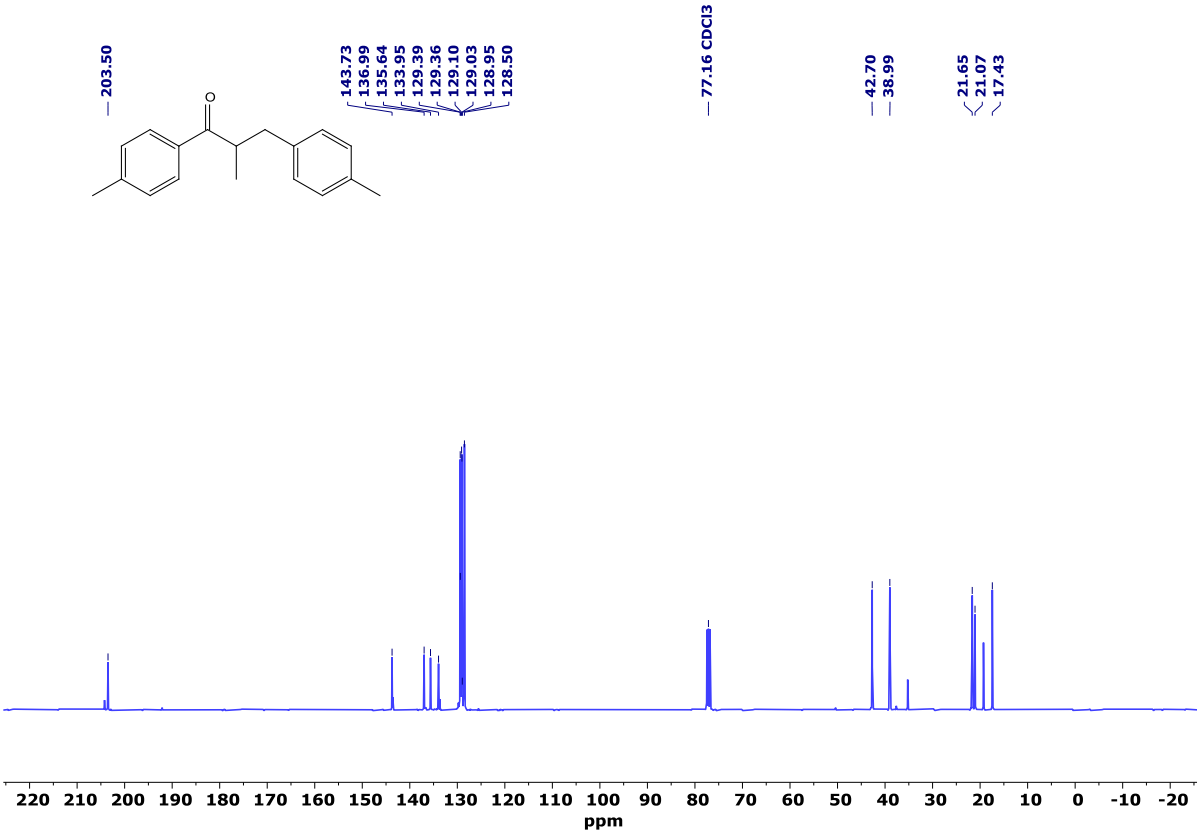

Figure S4: ^{13}C NMR spectrum of compound 2

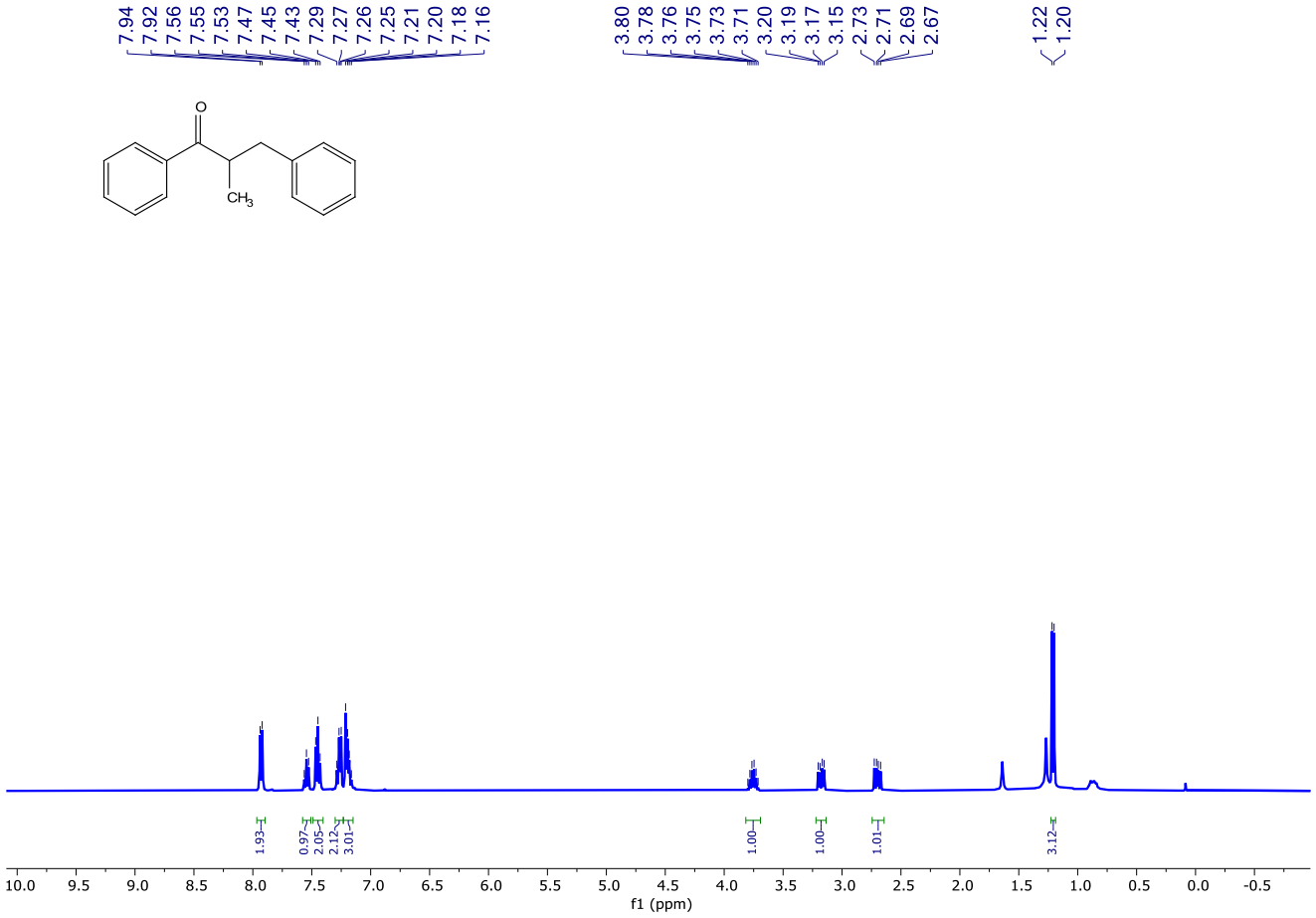

Figure S5: ^{1}H NMR spectrum of compound 3

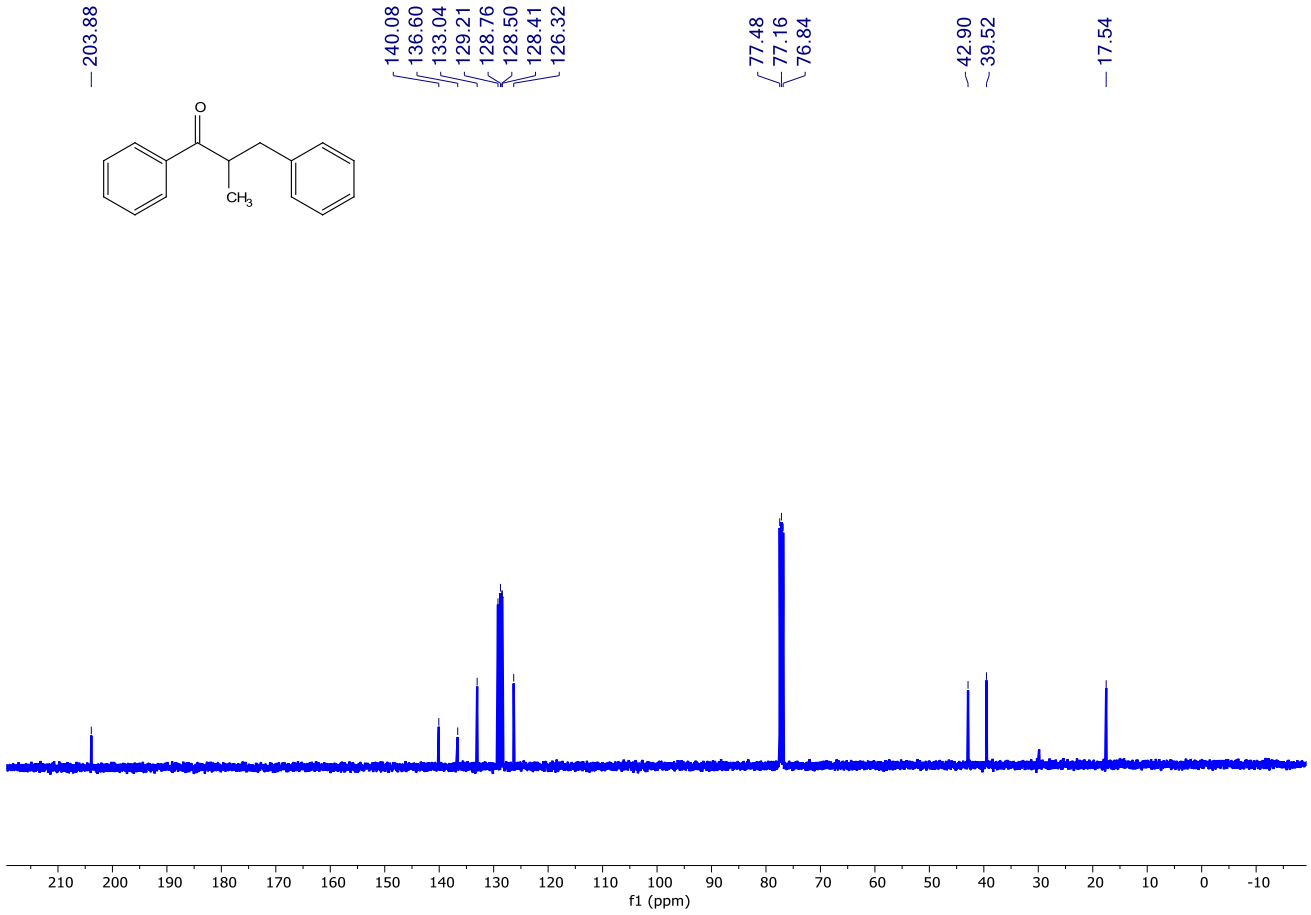

Figure S6: ^{13}C NMR spectrum of compound 3

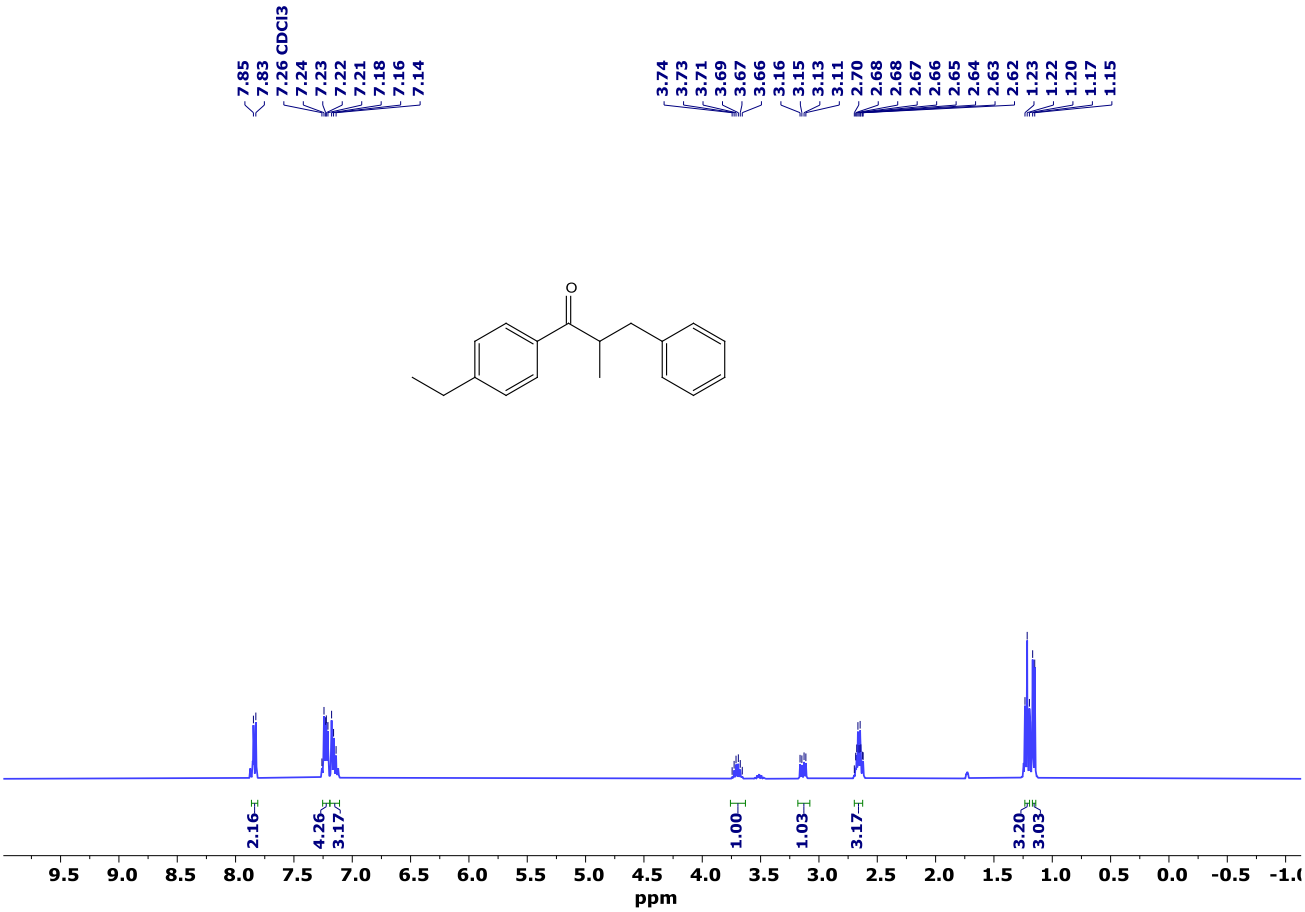

Figure S7: ^{1}H NMR spectrum of compound 4

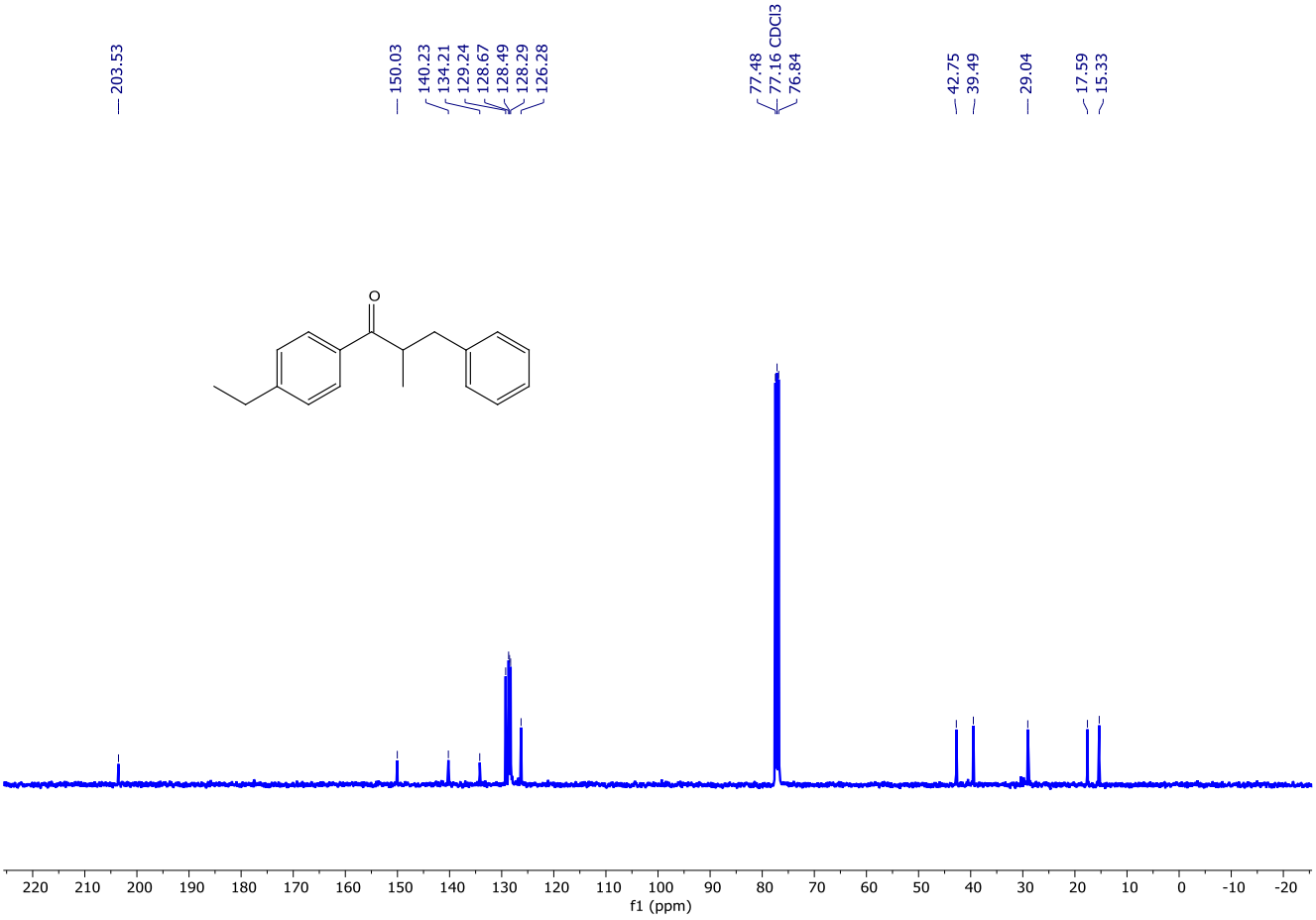

Figure S8: ^{13}C NMR spectrum of compound 4

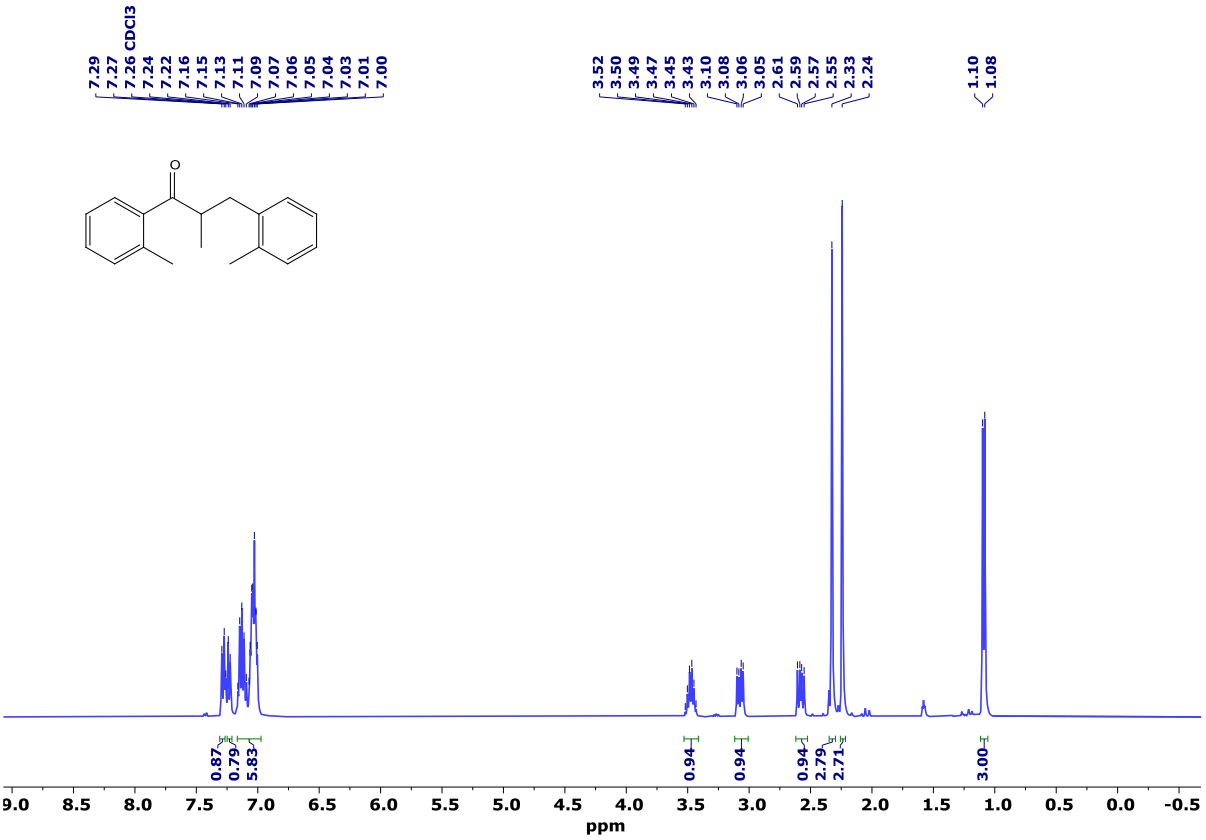

Figure S9: ^{1}H NMR spectrum of compound 5

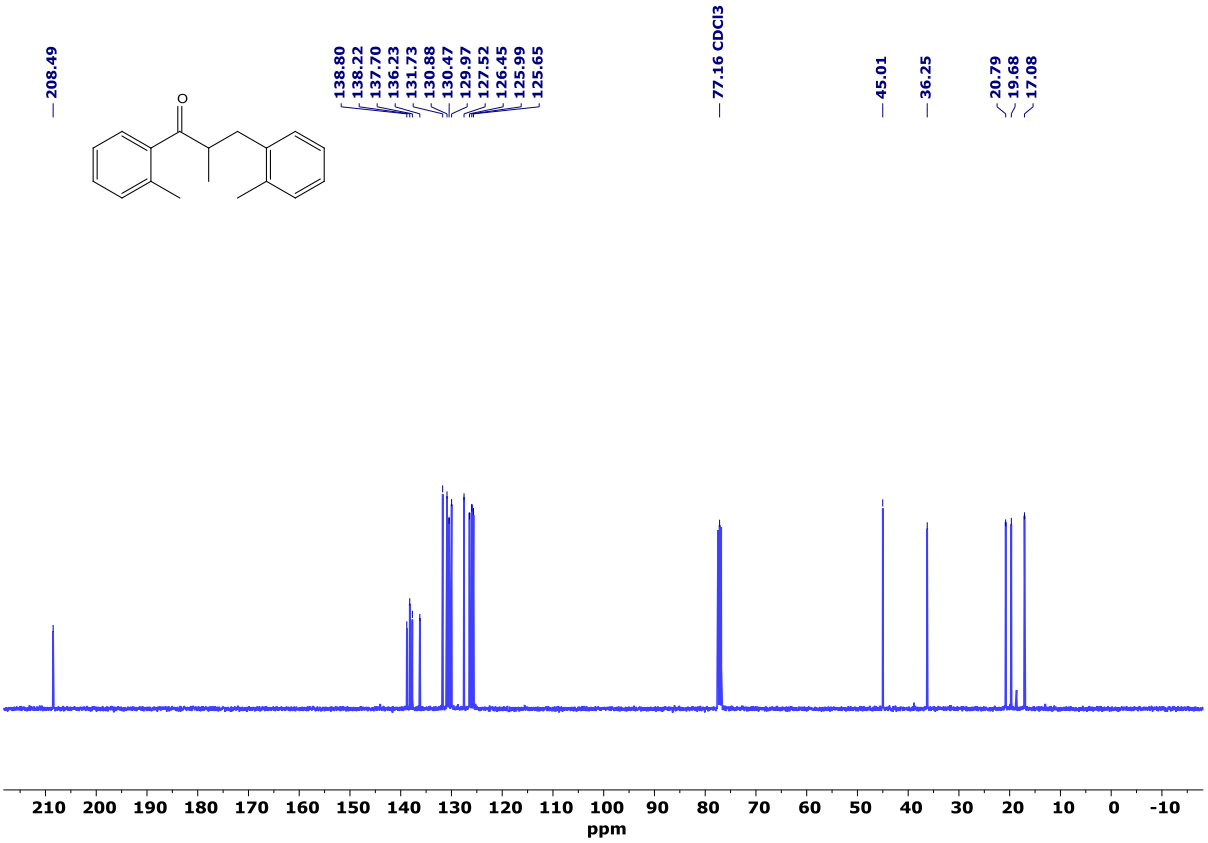

Figure S10: ^{13}C NMR spectrum of compound 5

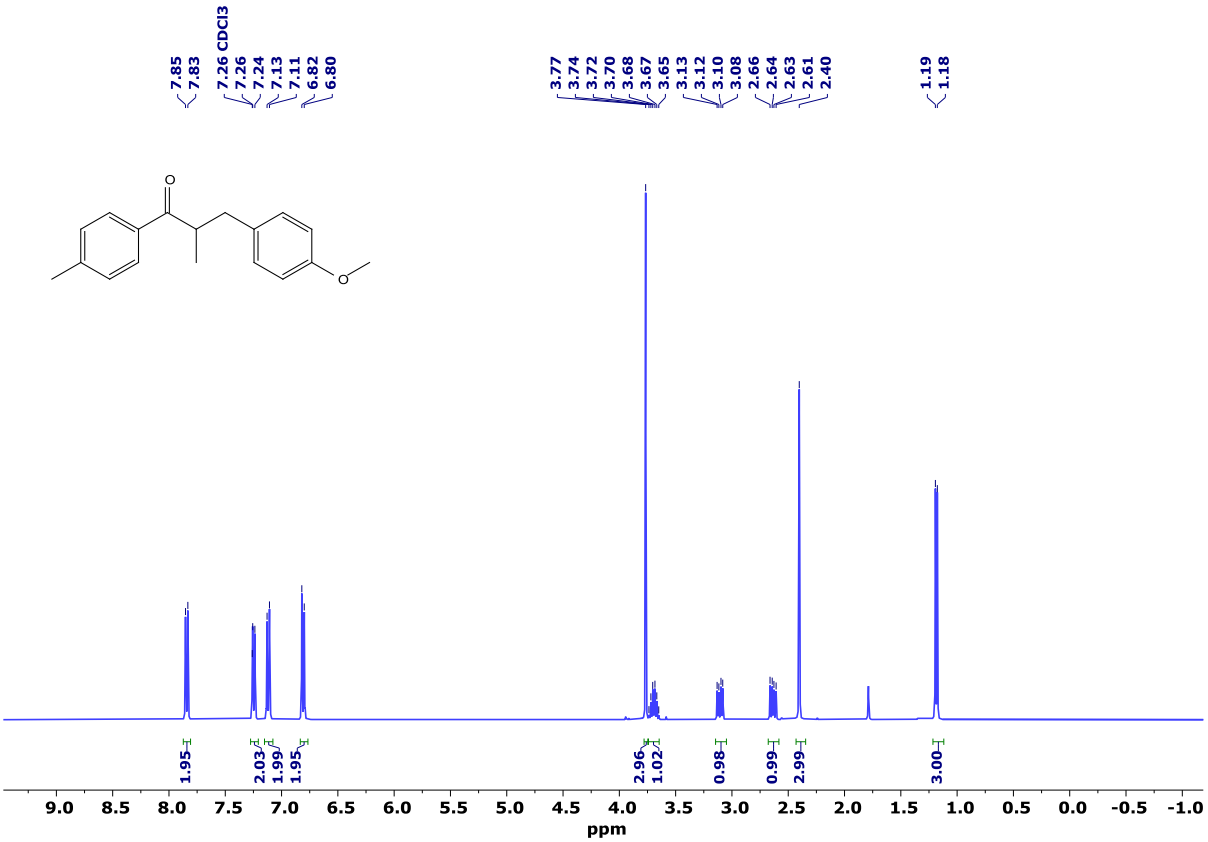

Figure S11: ^{1}H NMR spectrum of compound 6

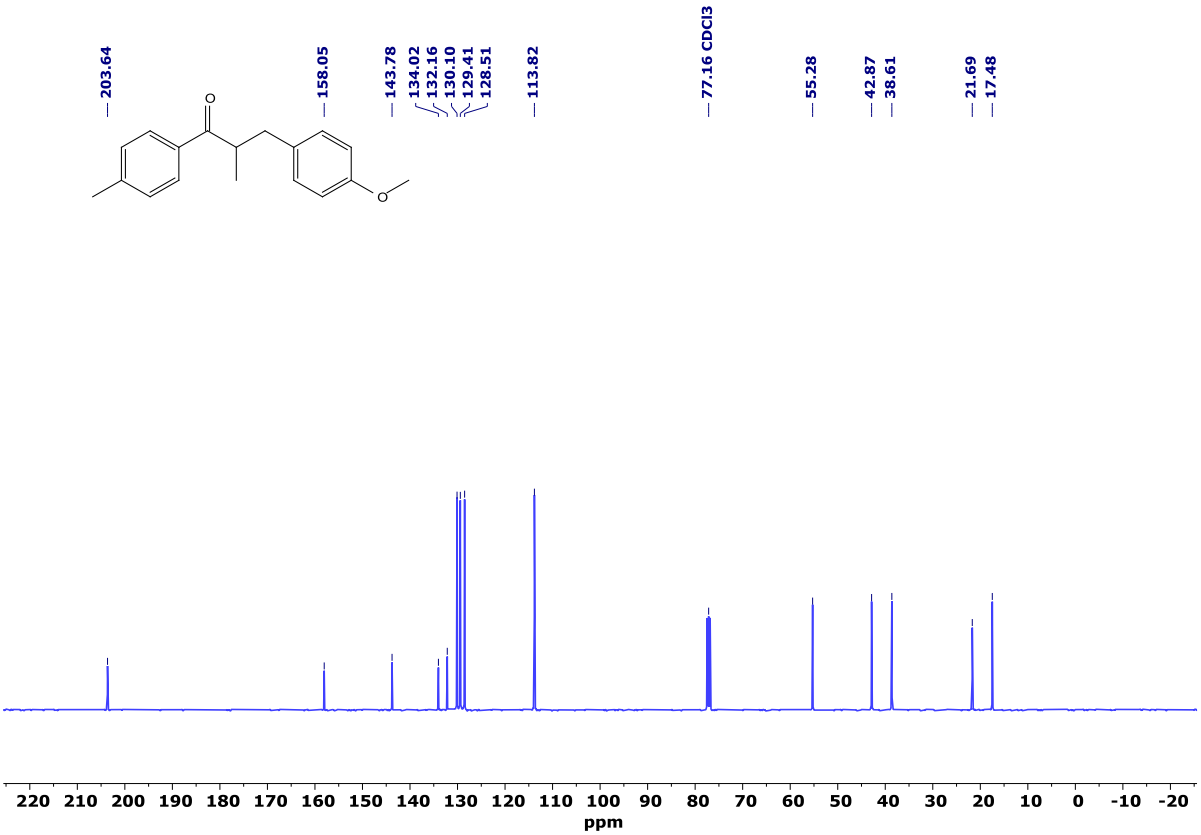

Figure S12: ^{13}C NMR spectrum of compound 6

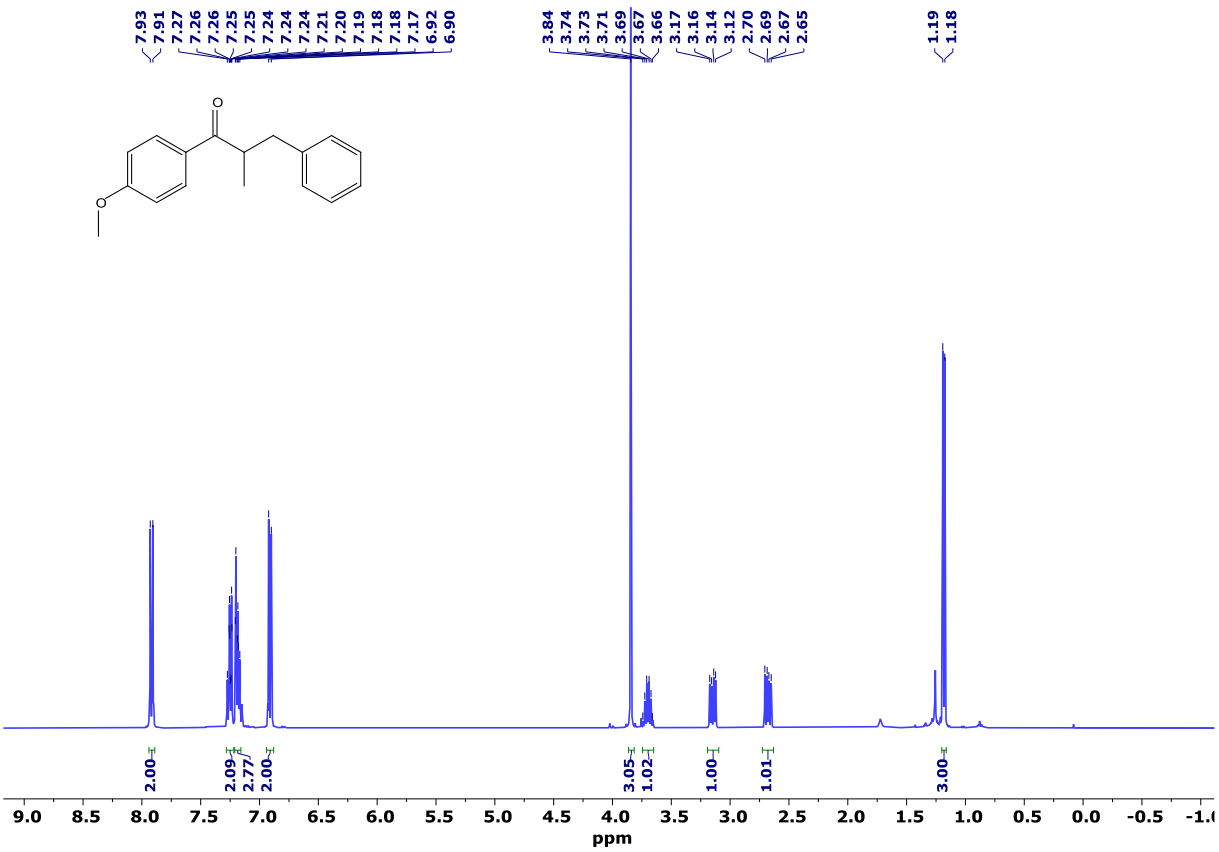

Figure S13: ^{1}H NMR spectrum of compound 7

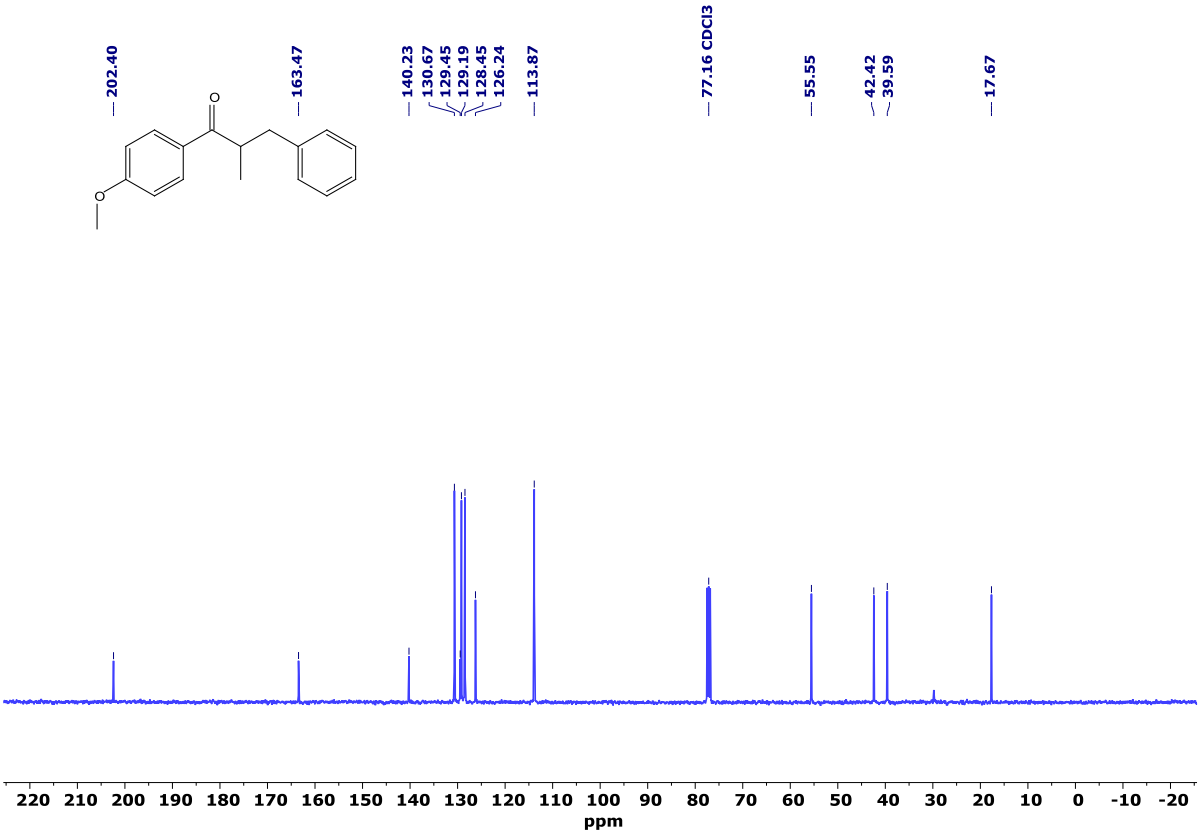

Figure S14: ^{13}C NMR spectrum of compound 7

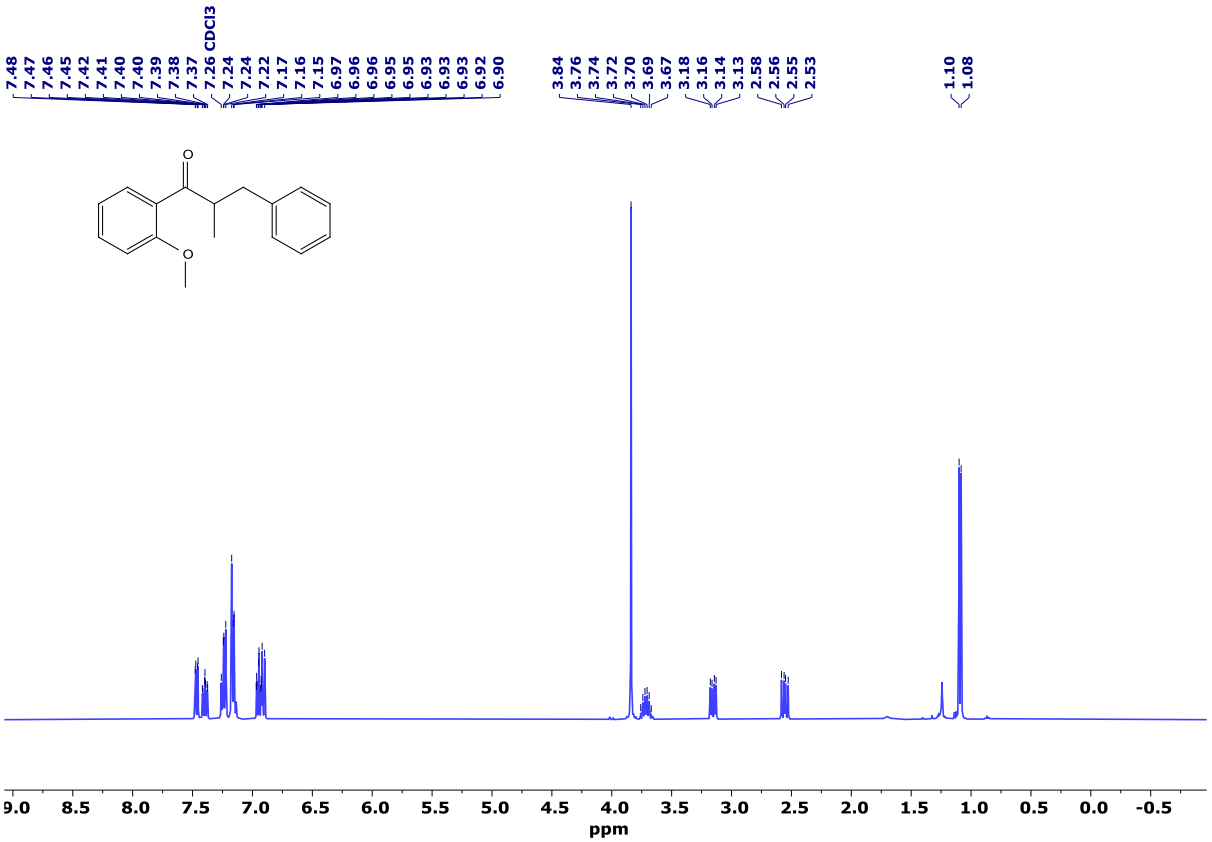

Figure S15: ^{1}H NMR spectrum of compound 8

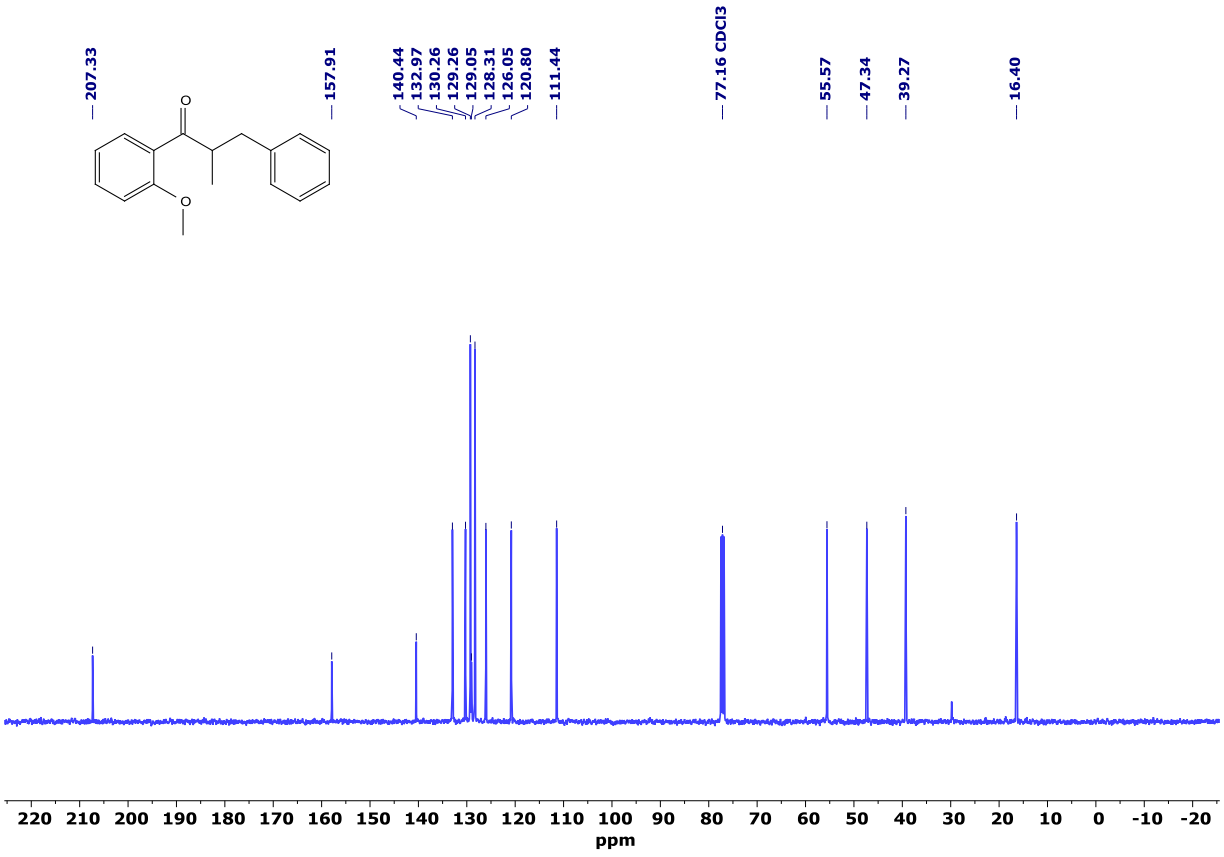

Figure S16: ^{13}C NMR spectrum of compound 8

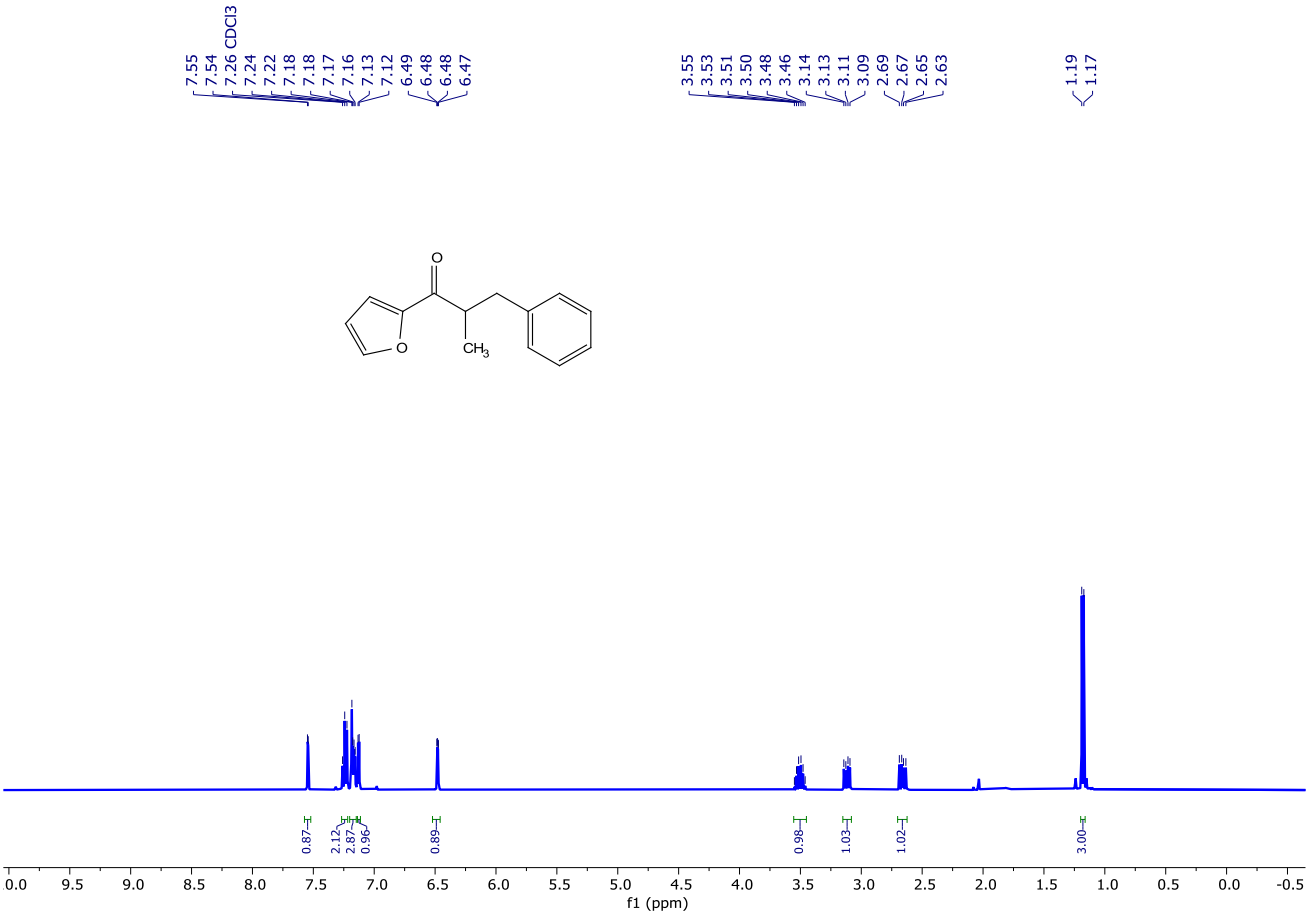

Figure S17: ^{1}H NMR spectrum of compound 9

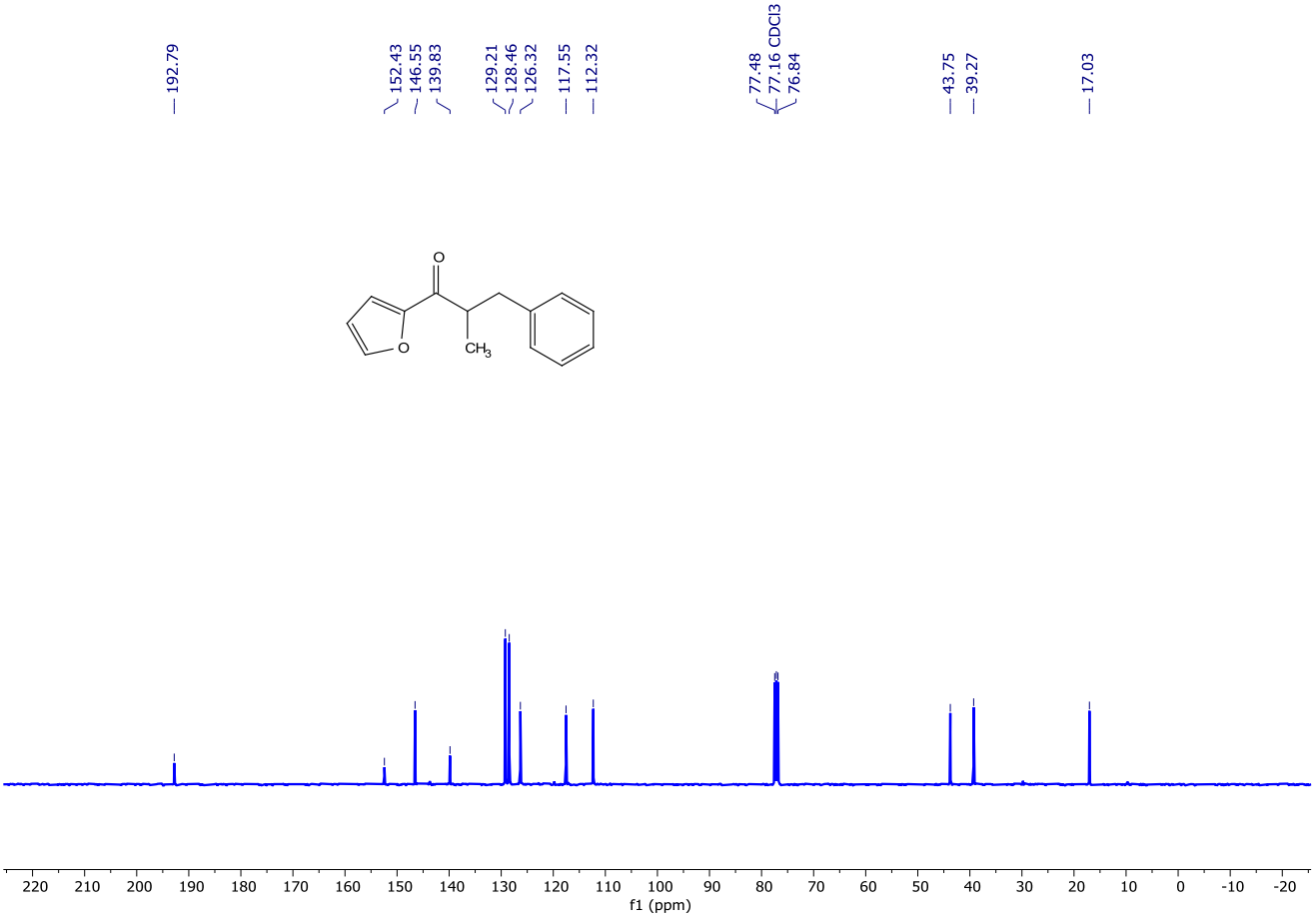

Figure S18: ^{13}C NMR spectrum of compound 9

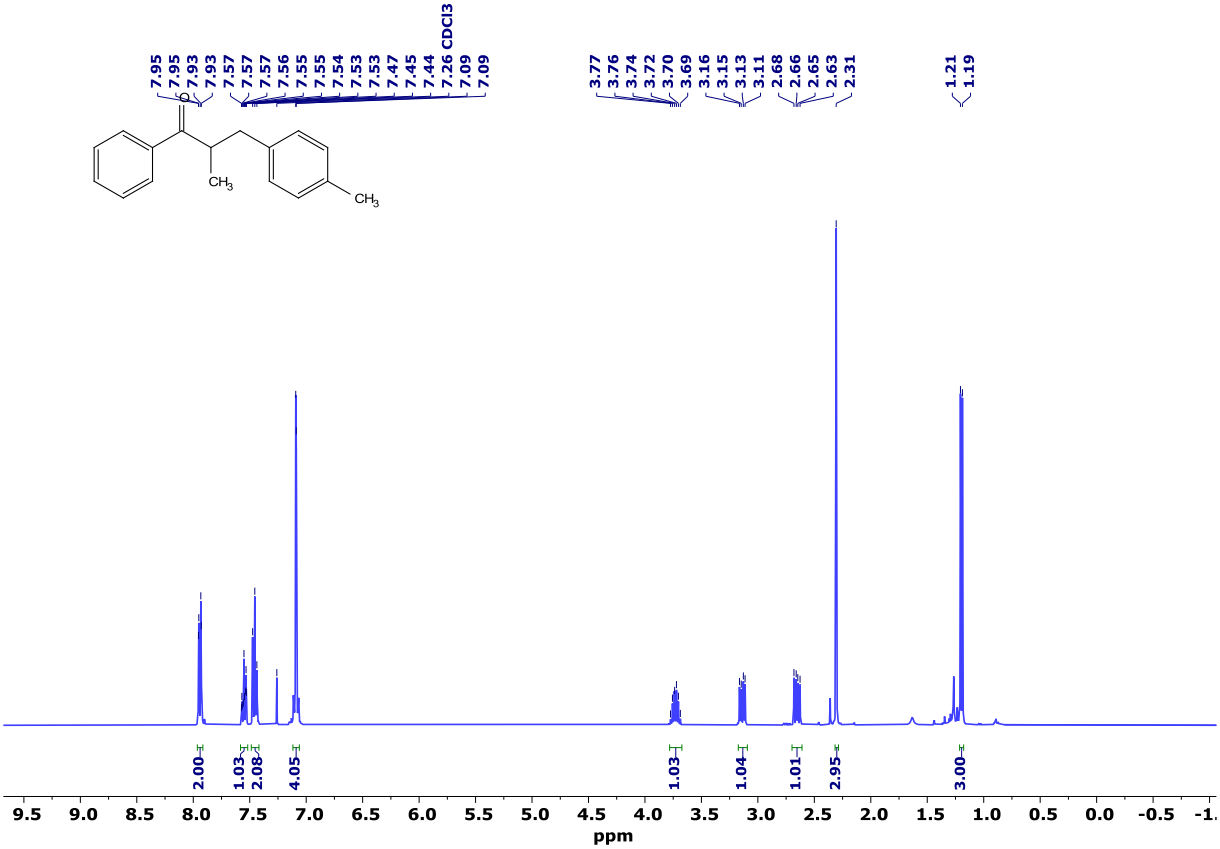

Figure S19: ^{1}H NMR spectrum of compound 10

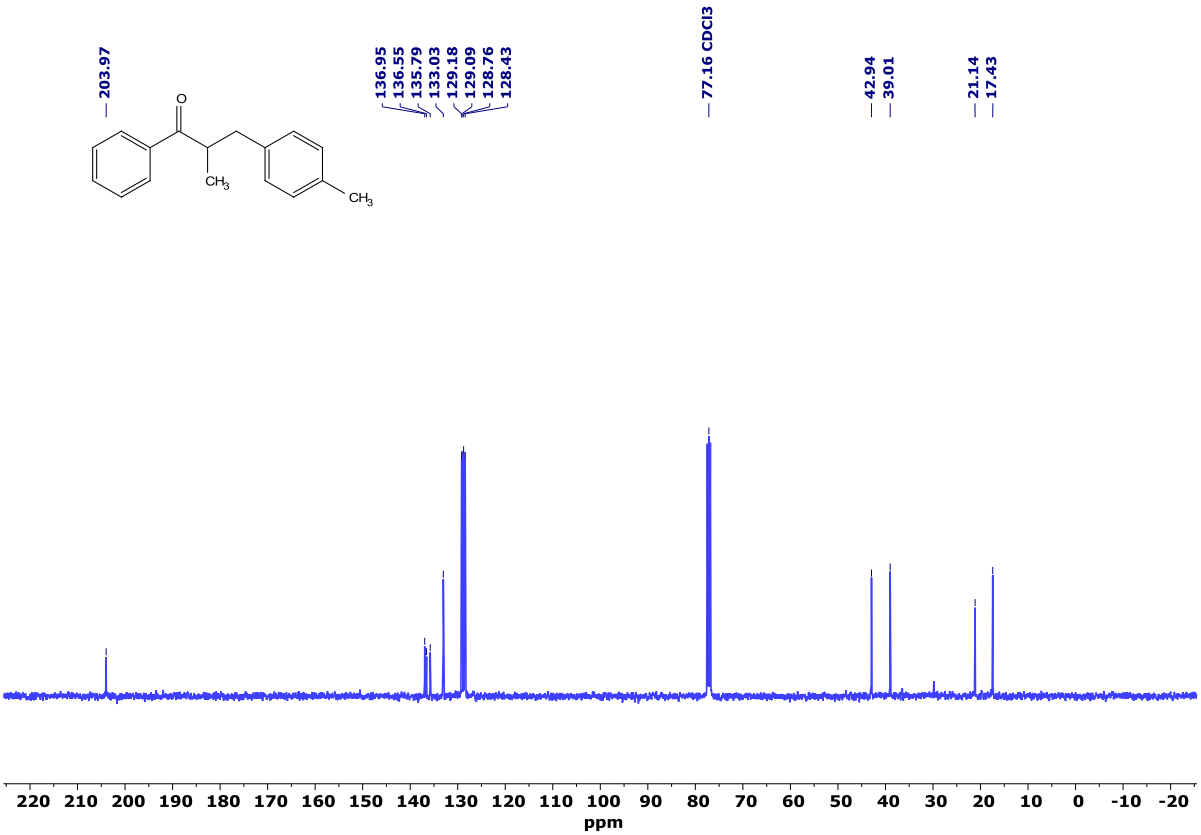

Figure S20: ^{13}C NMR spectrum of compound 10

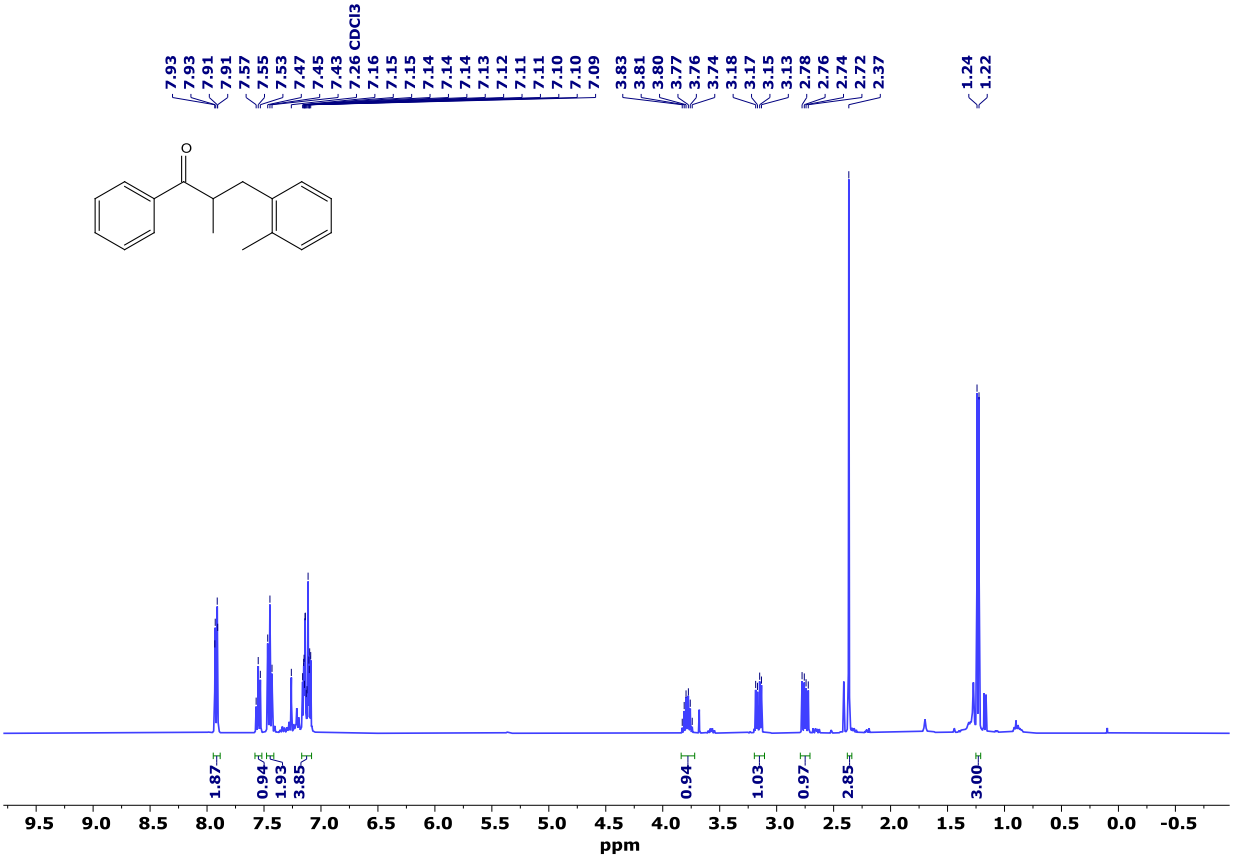

Figure S21: ^{1}H NMR spectrum of compound 11

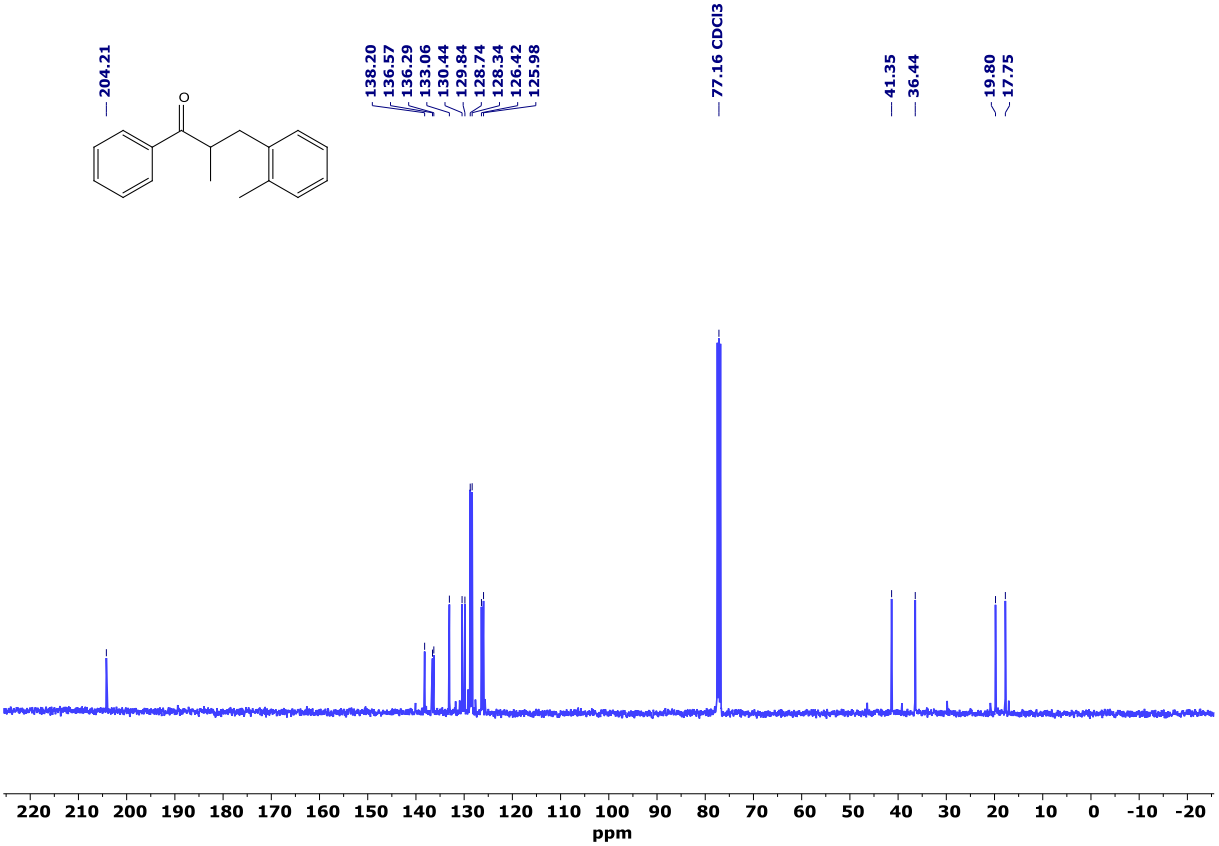

Figure S22: ^{13}C NMR spectrum of compound 11

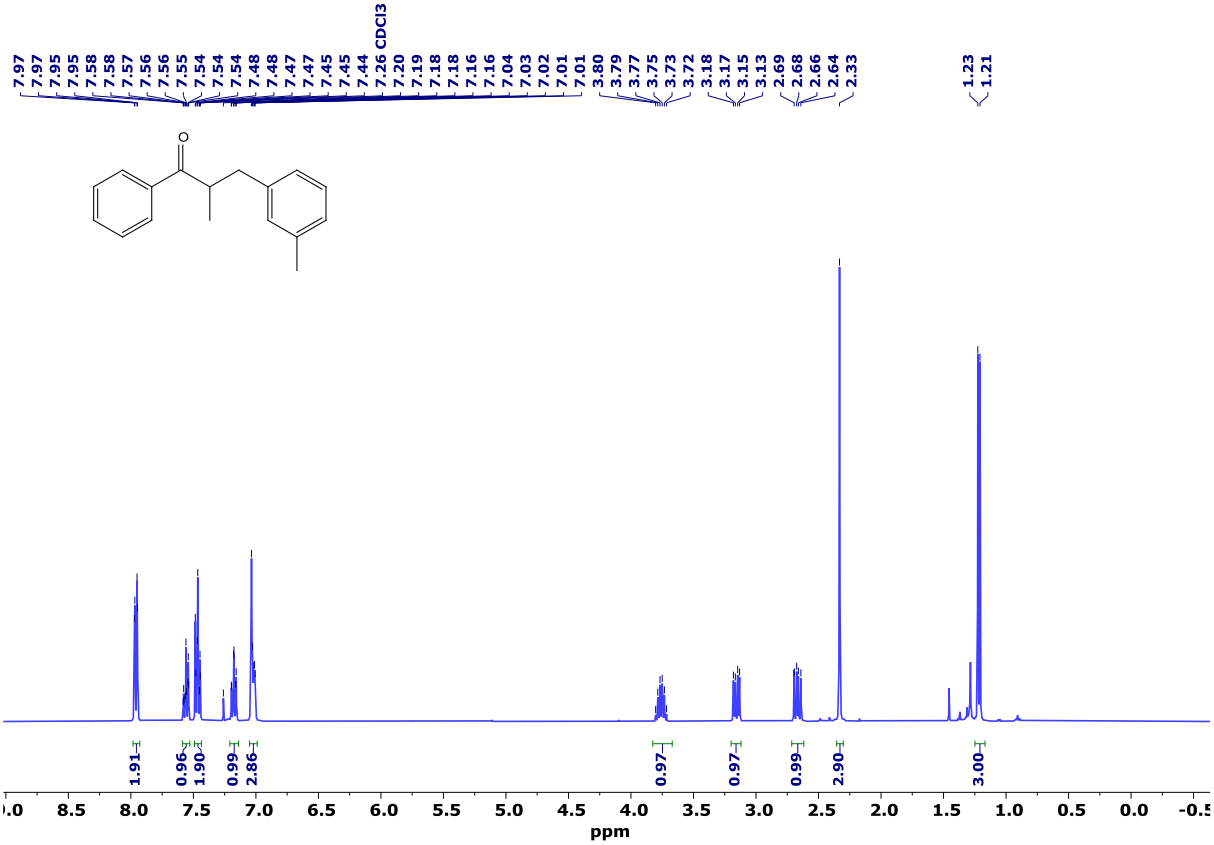

Figure S23: ^{1}H NMR spectrum of compound 12

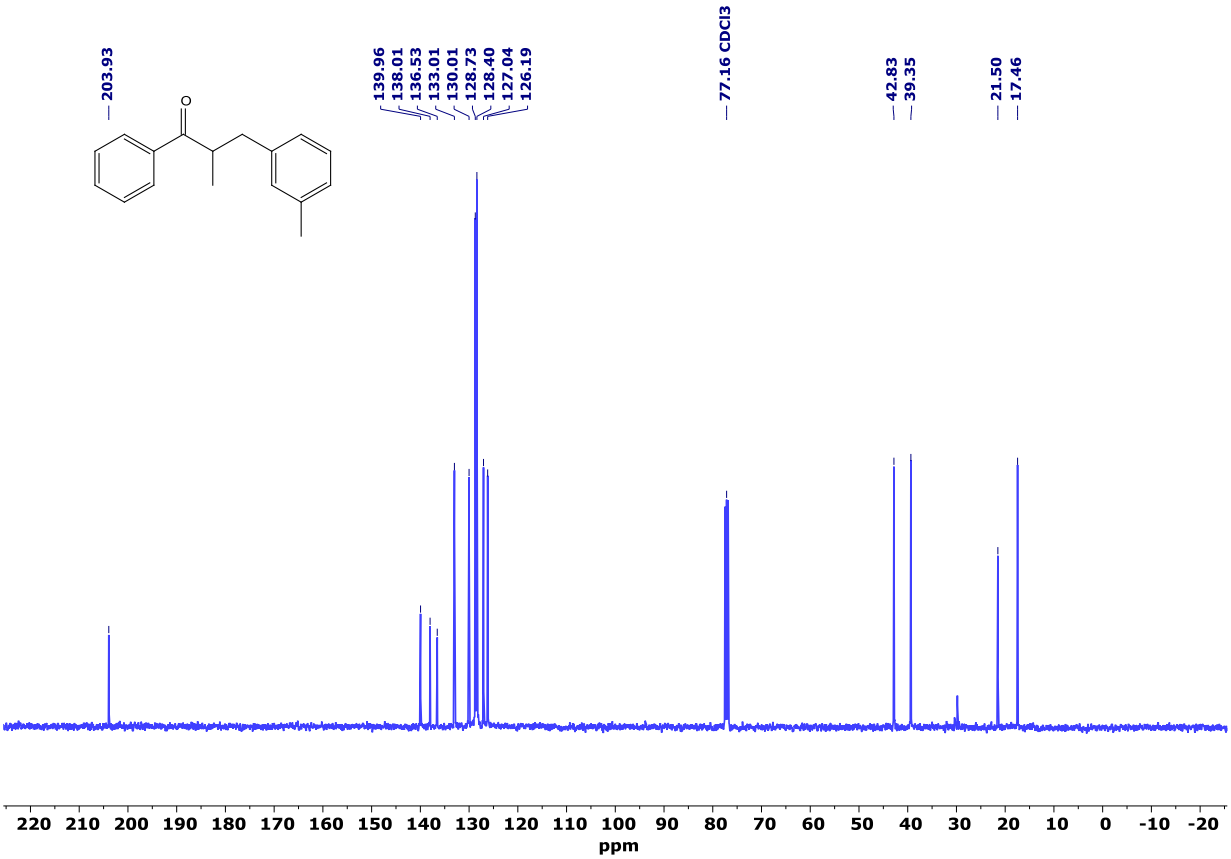

Figure S24: ^{13}C NMR spectrum of compound 12

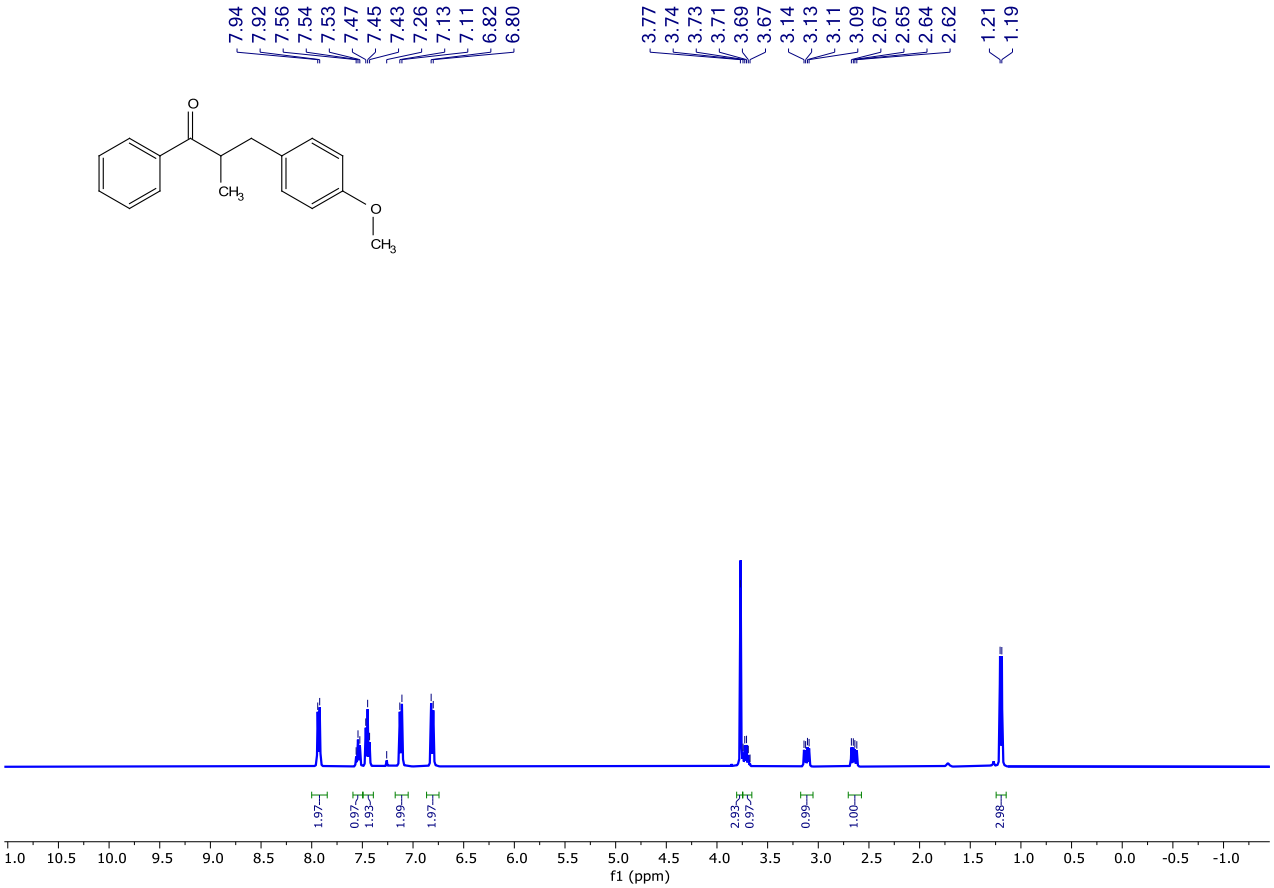

Figure S25: ^{1}H NMR spectrum of compound 13

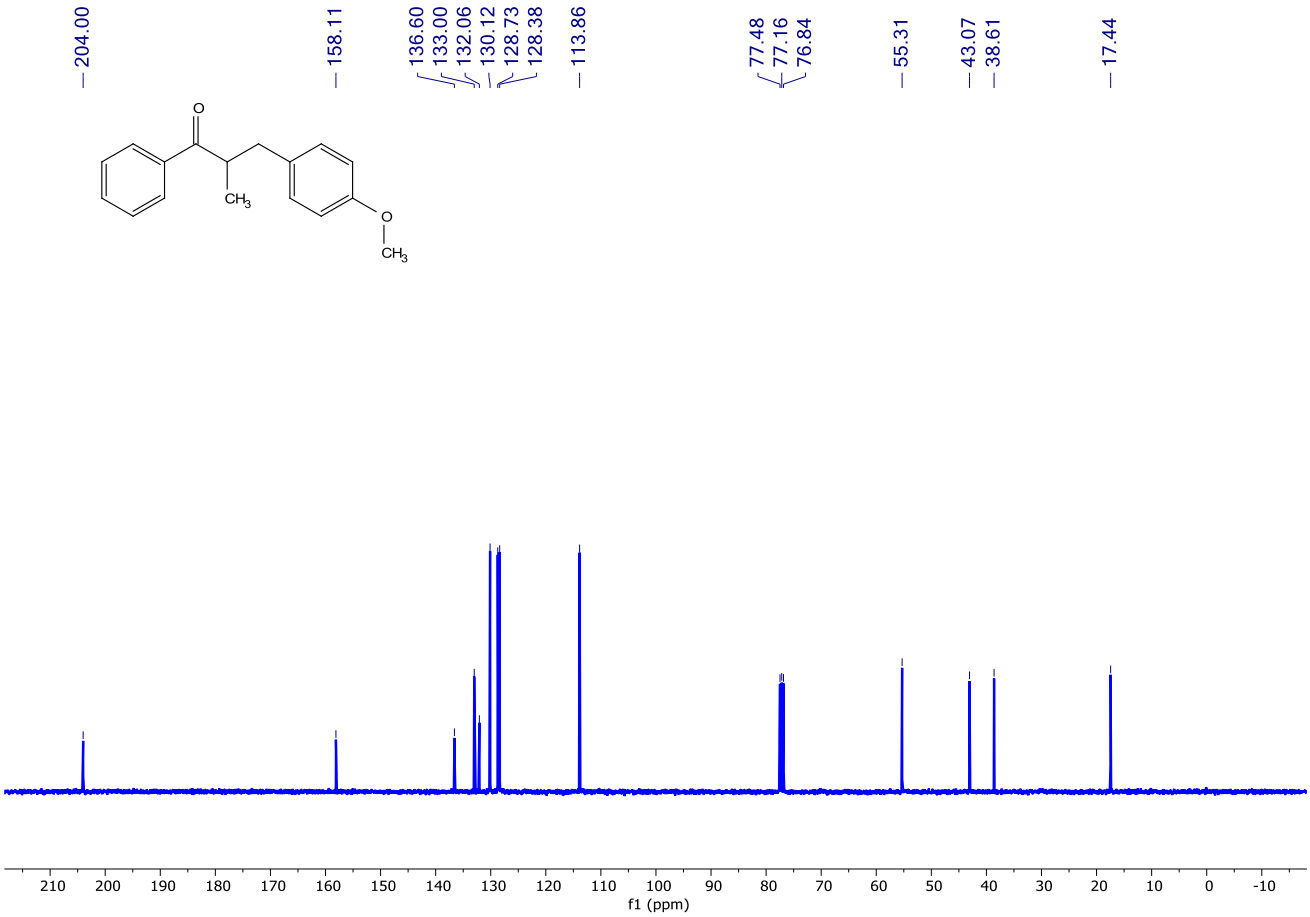

Figure S26: ^{13}C NMR spectrum of compound 13

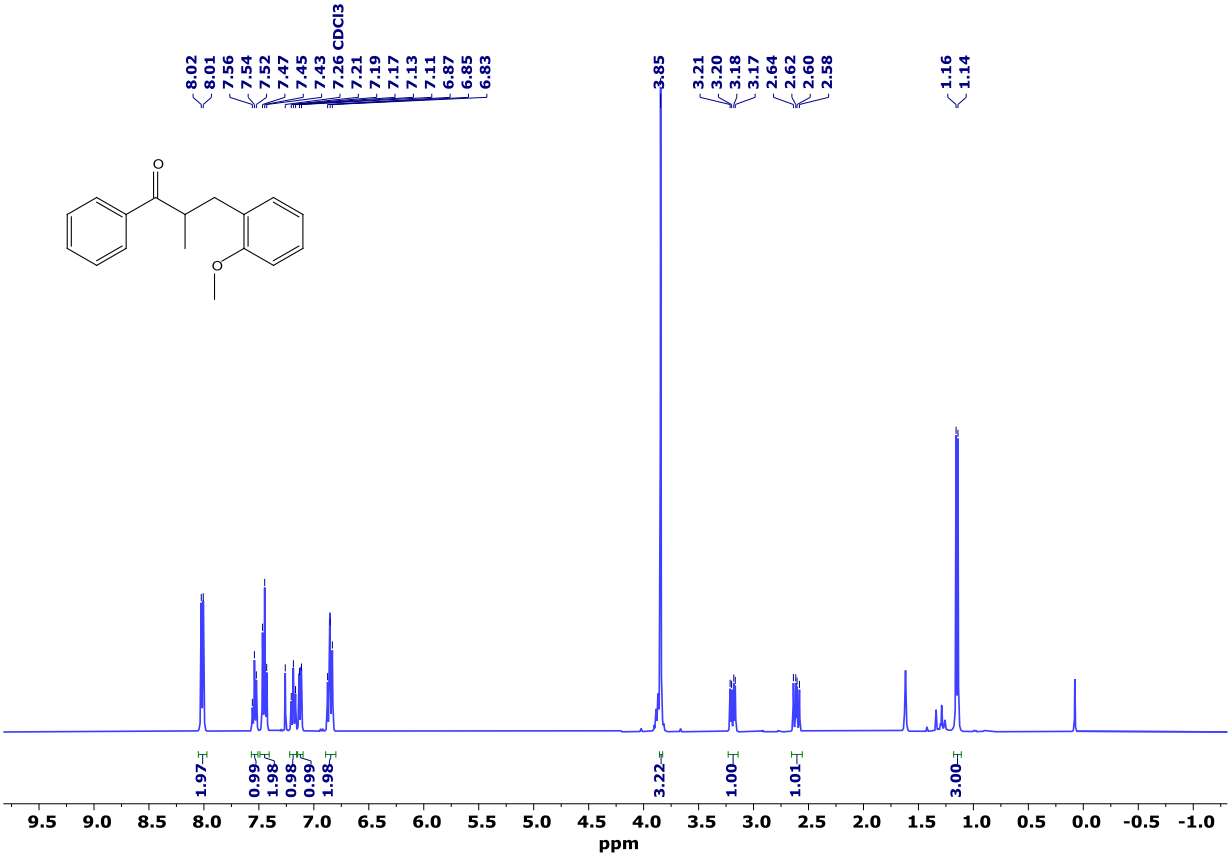

Figure S27: ^{1}H NMR spectrum of compound 14

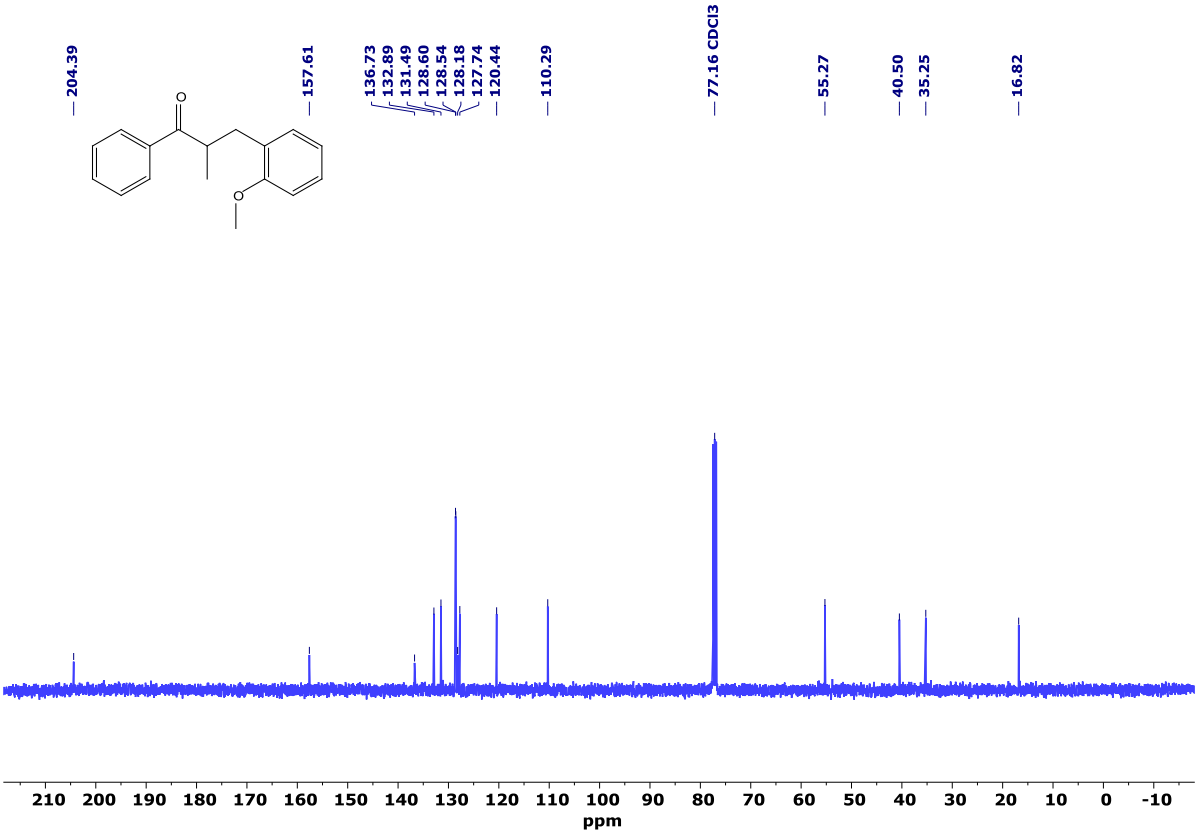

Figure S28: ^{13}C NMR spectrum of compound 14

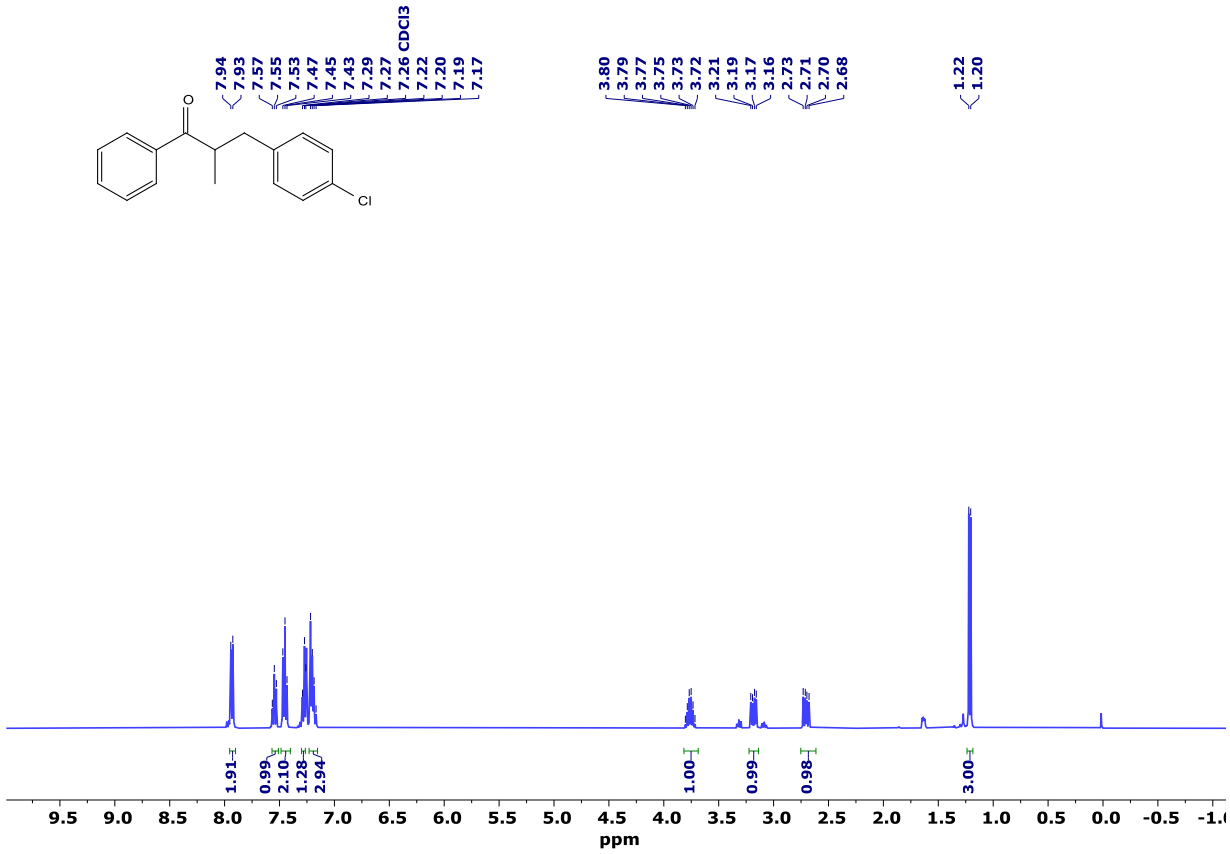

Figure S29: [1]HNMR spectrum of compound 15

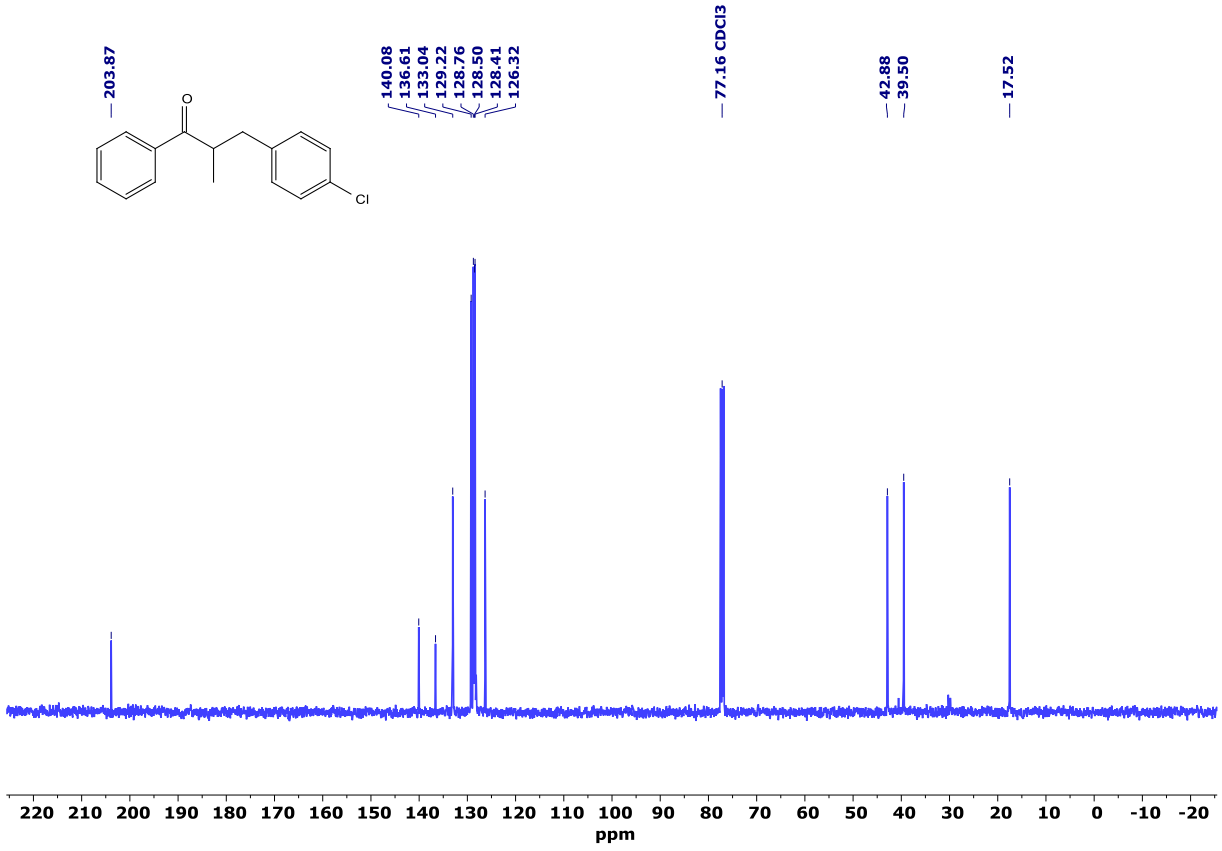

Figure S30: [13]C NMR spectrum of compound 15

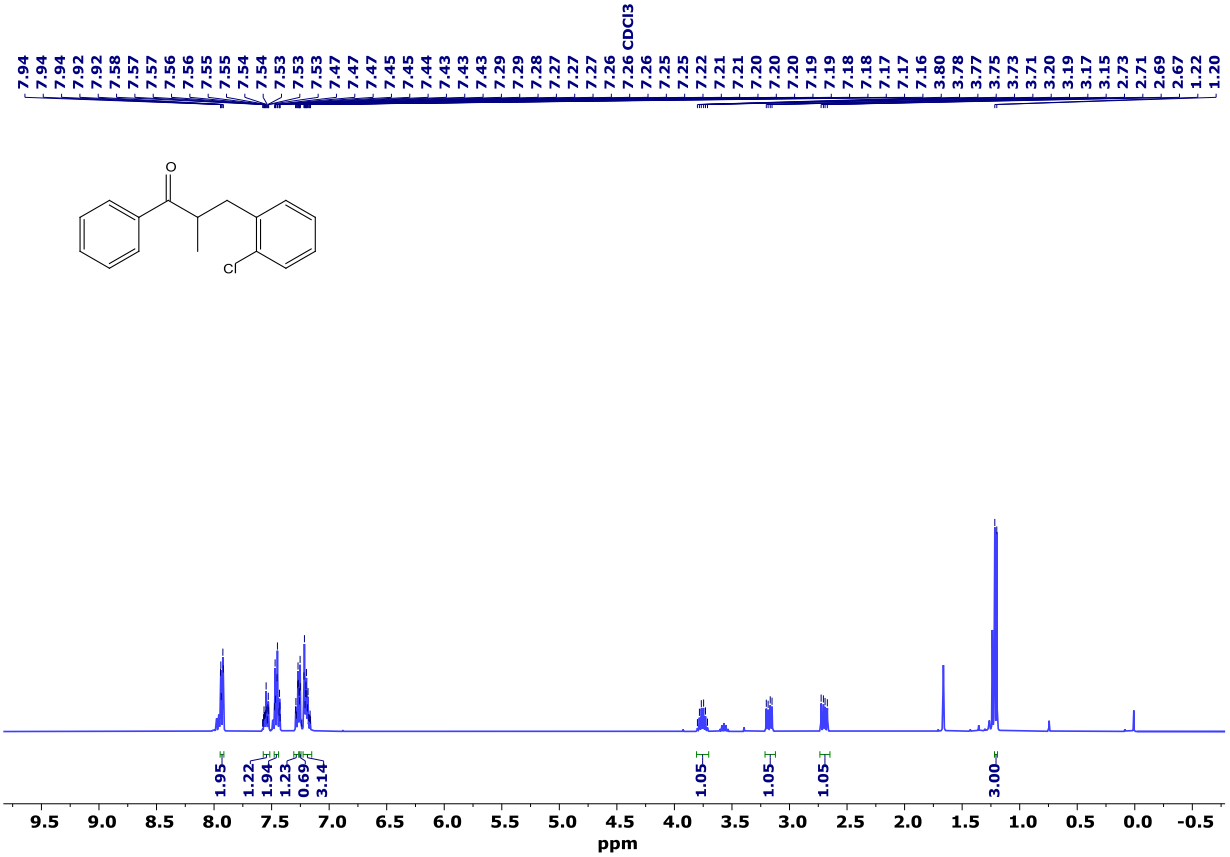

Figure S31: [1]HNMR spectrum of compound 16

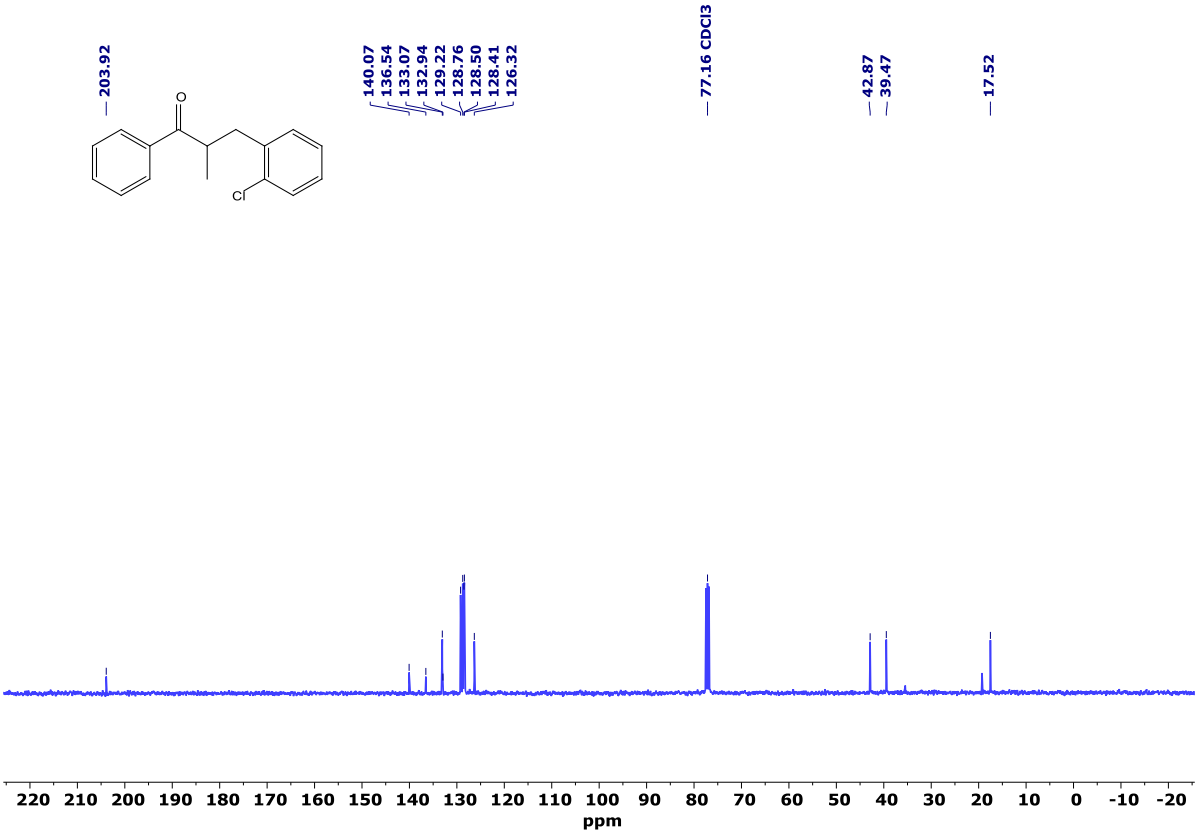

Figure S32: [13]C NMR spectrum of compound 16

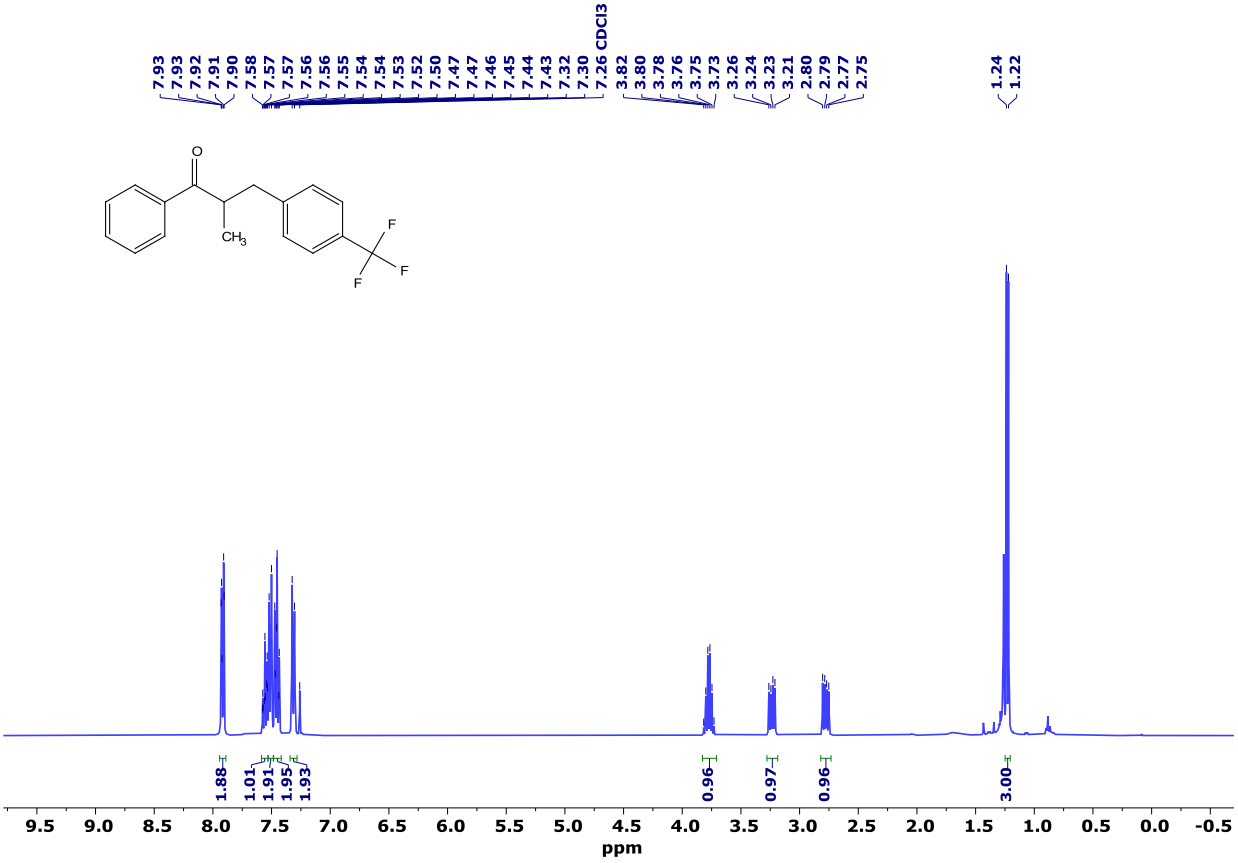

Figure S33: ^{1}HNMR spectrum of compound 17

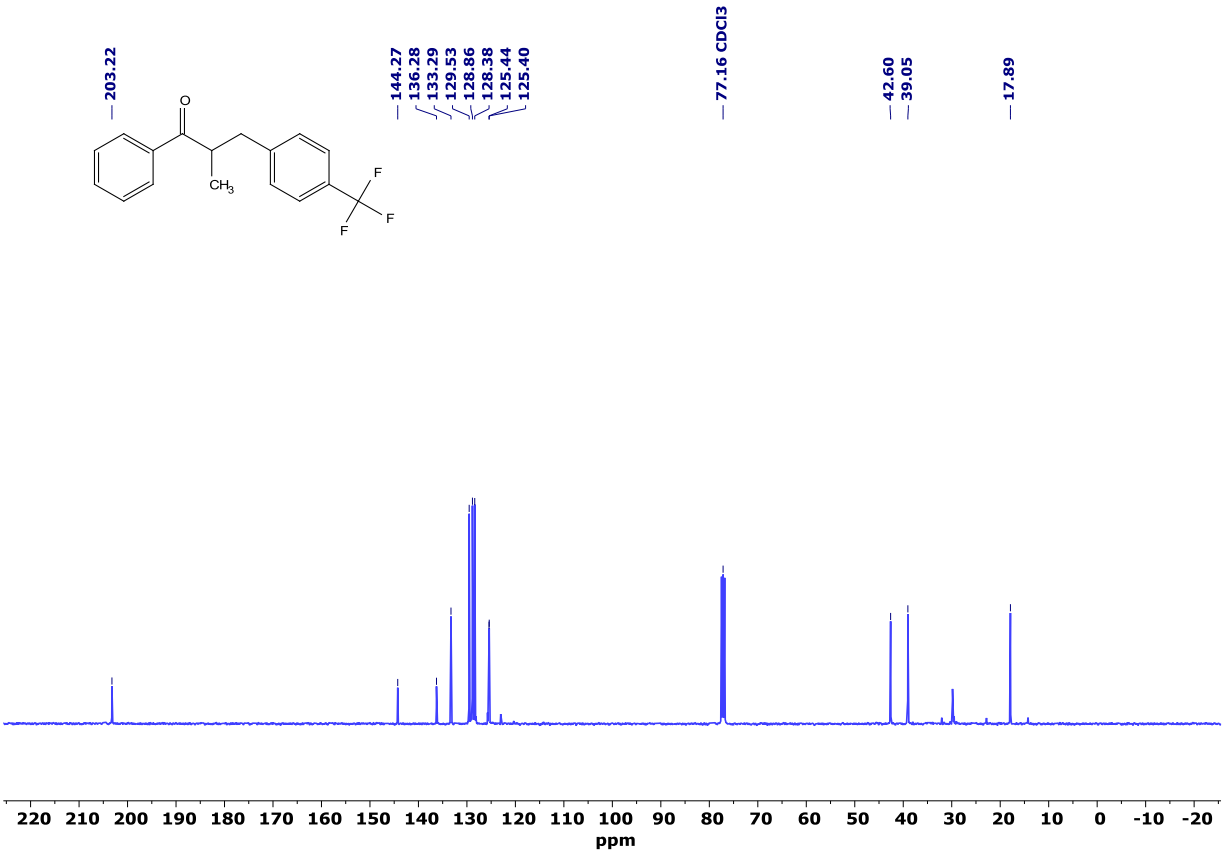

Figure S34: ^{13}C {^{1}H, ^{19}F} NMR spectrum of compound 17

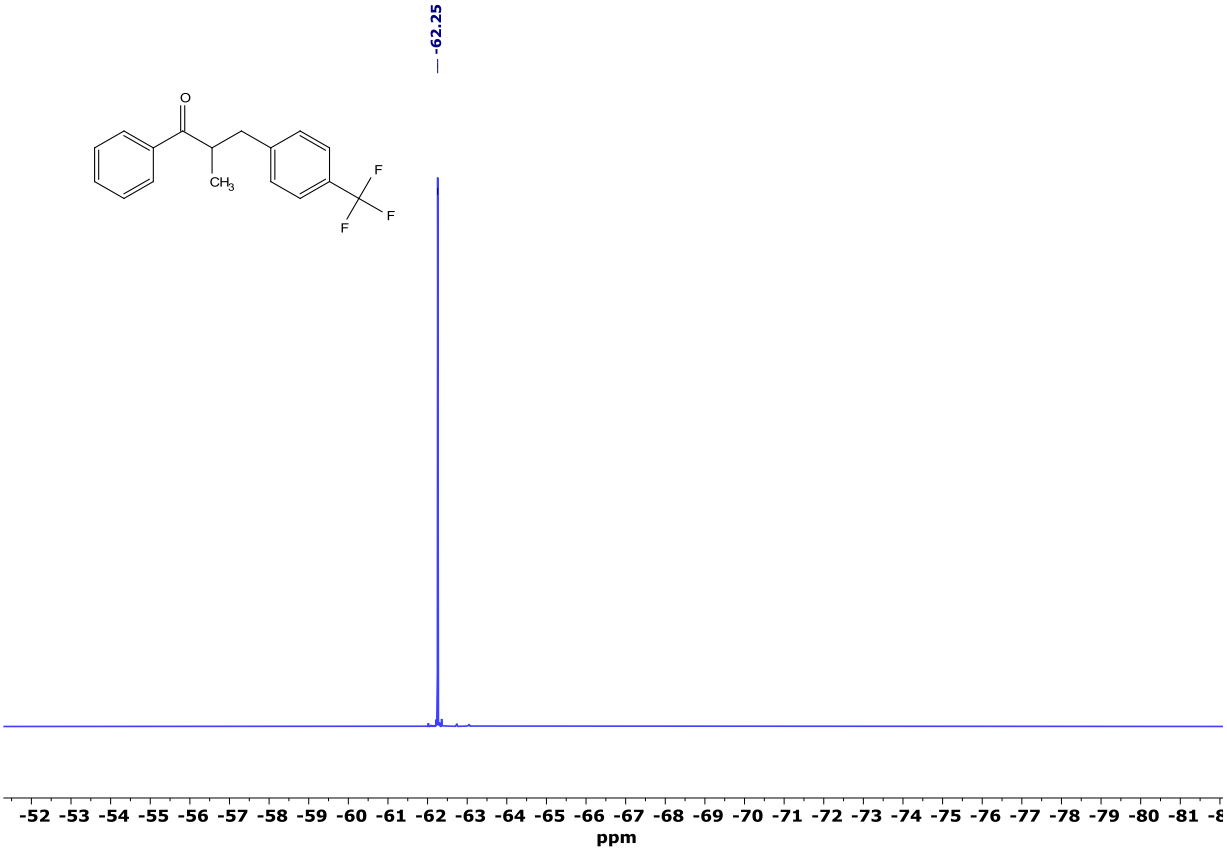

Figure S35: ^{19}F NMR spectrum of compound 17

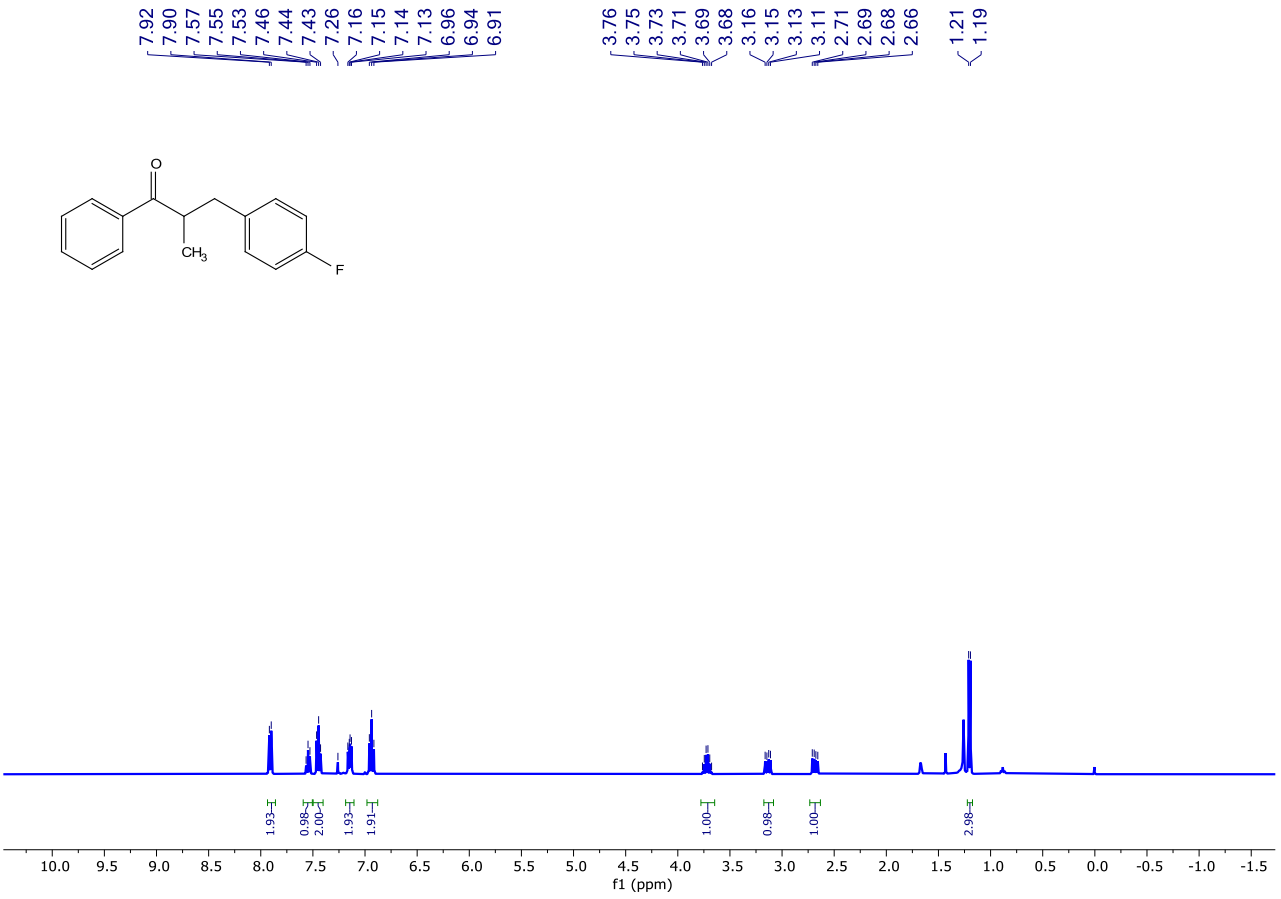

Figure S36: ^{1}H NMR spectrum of compound 18

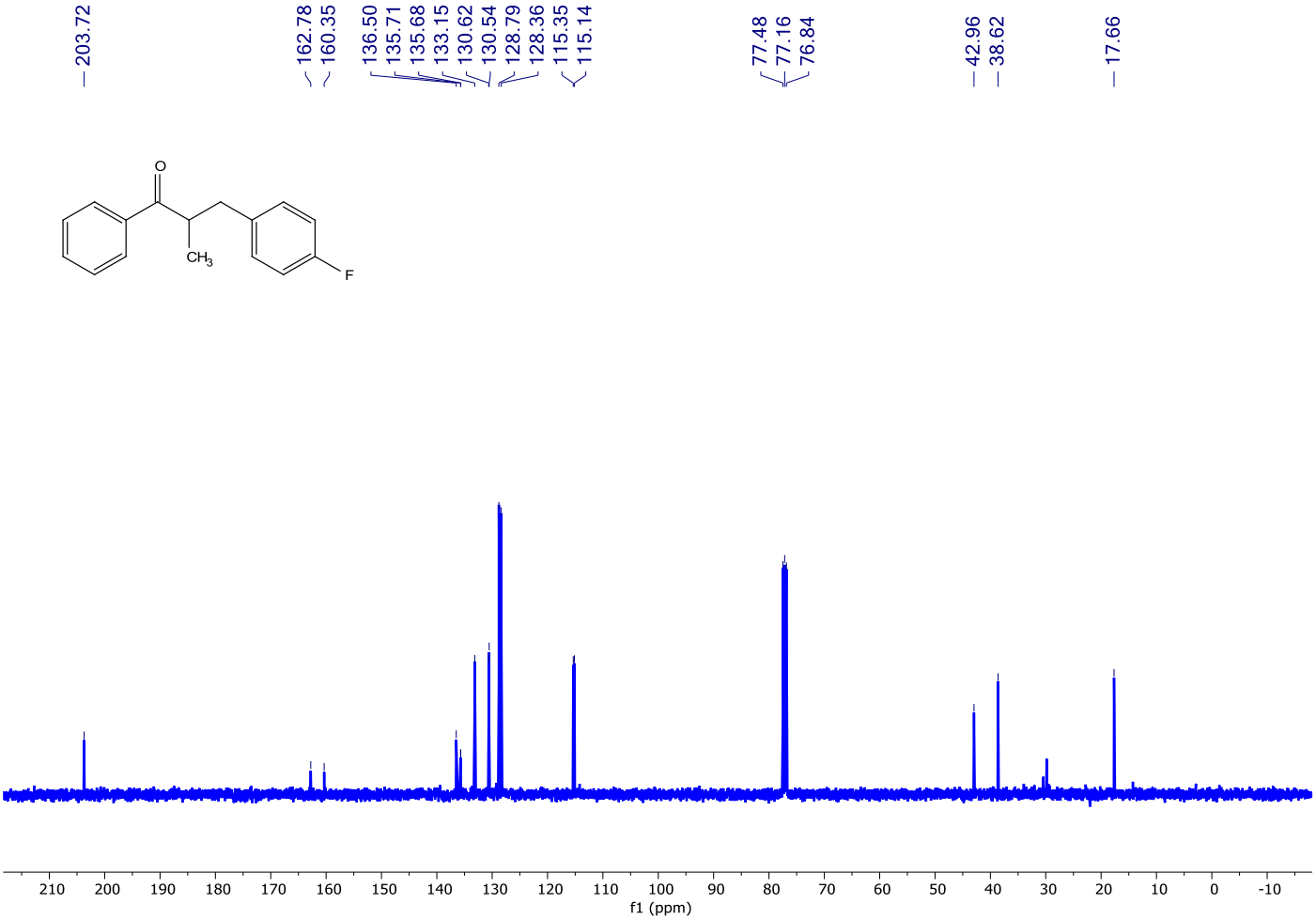

Figure S37: ^{13}C {^{1}H} NMR spectrum of compound 18

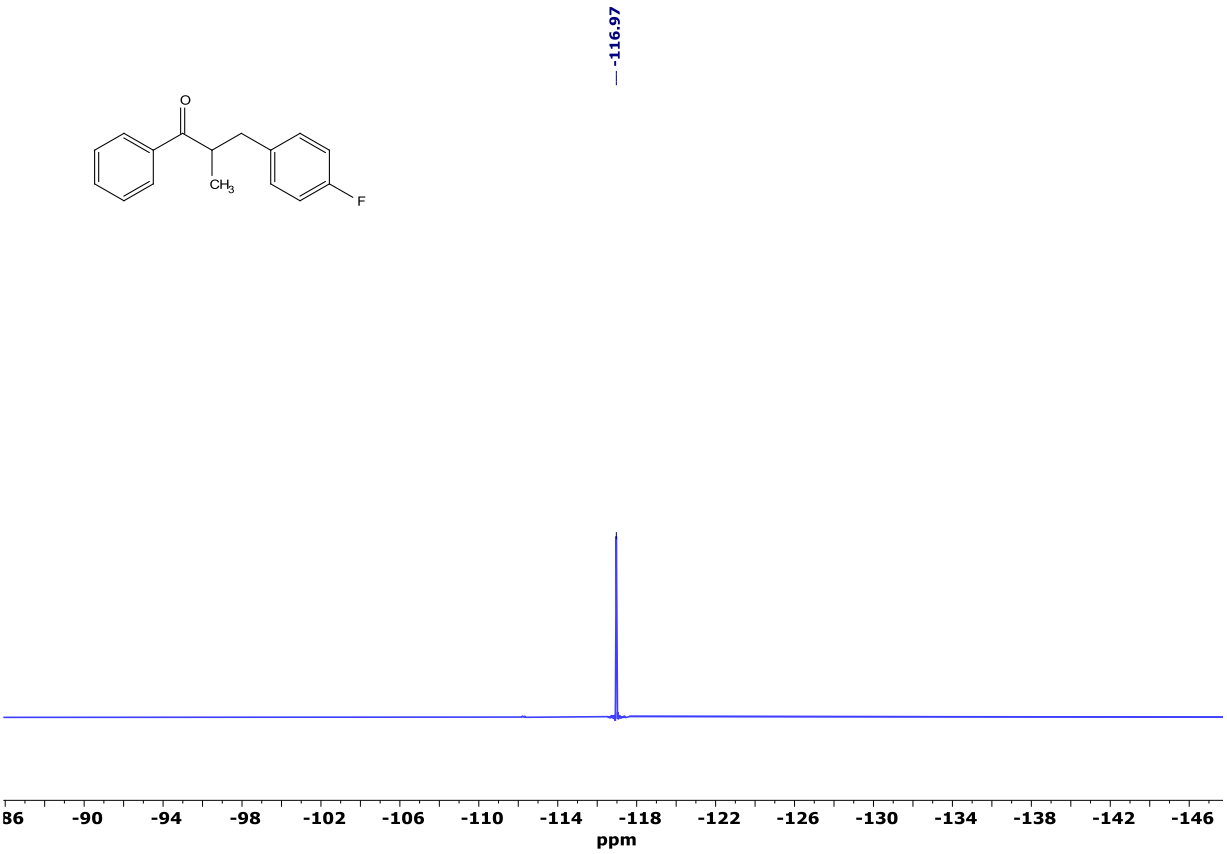

Figure S38: ^{19}F NMR spectrum of compound 18

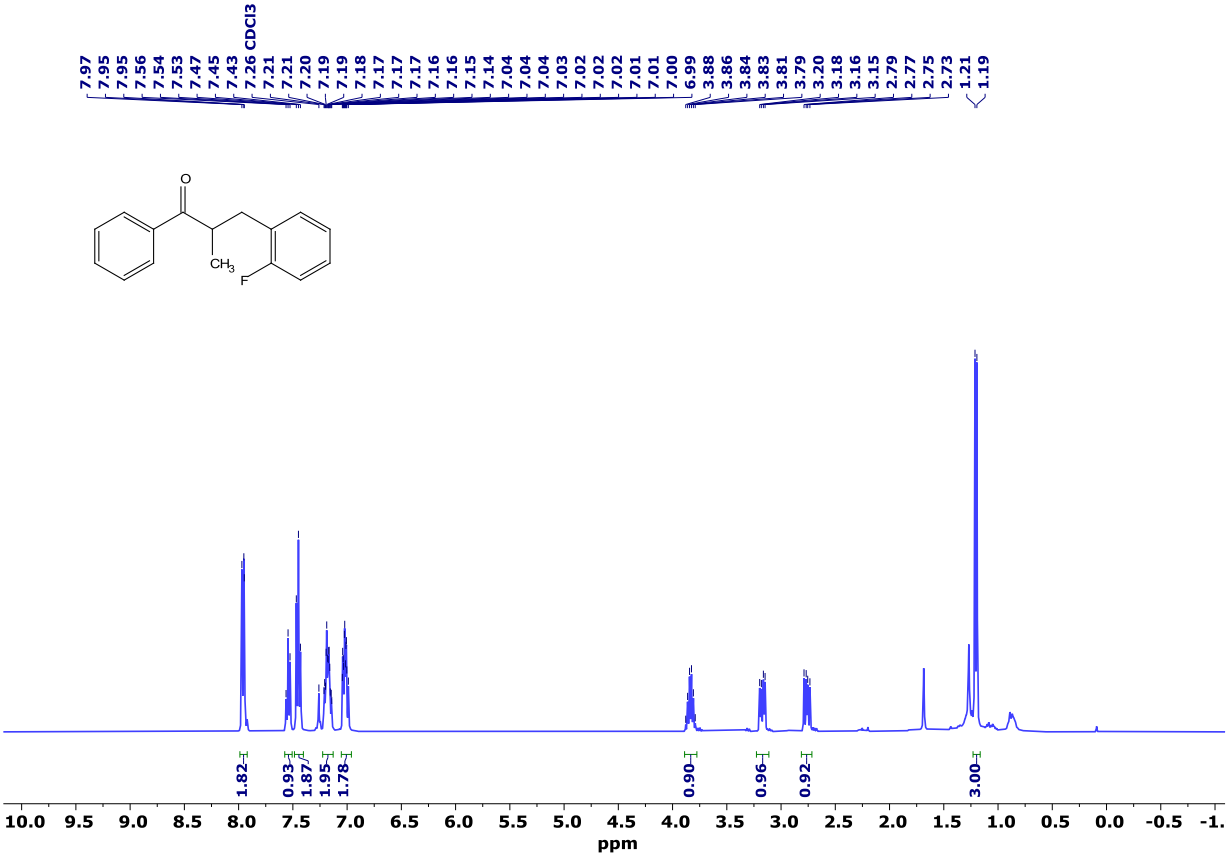

Figure S39: ^{1}H NMR spectrum of compound 19

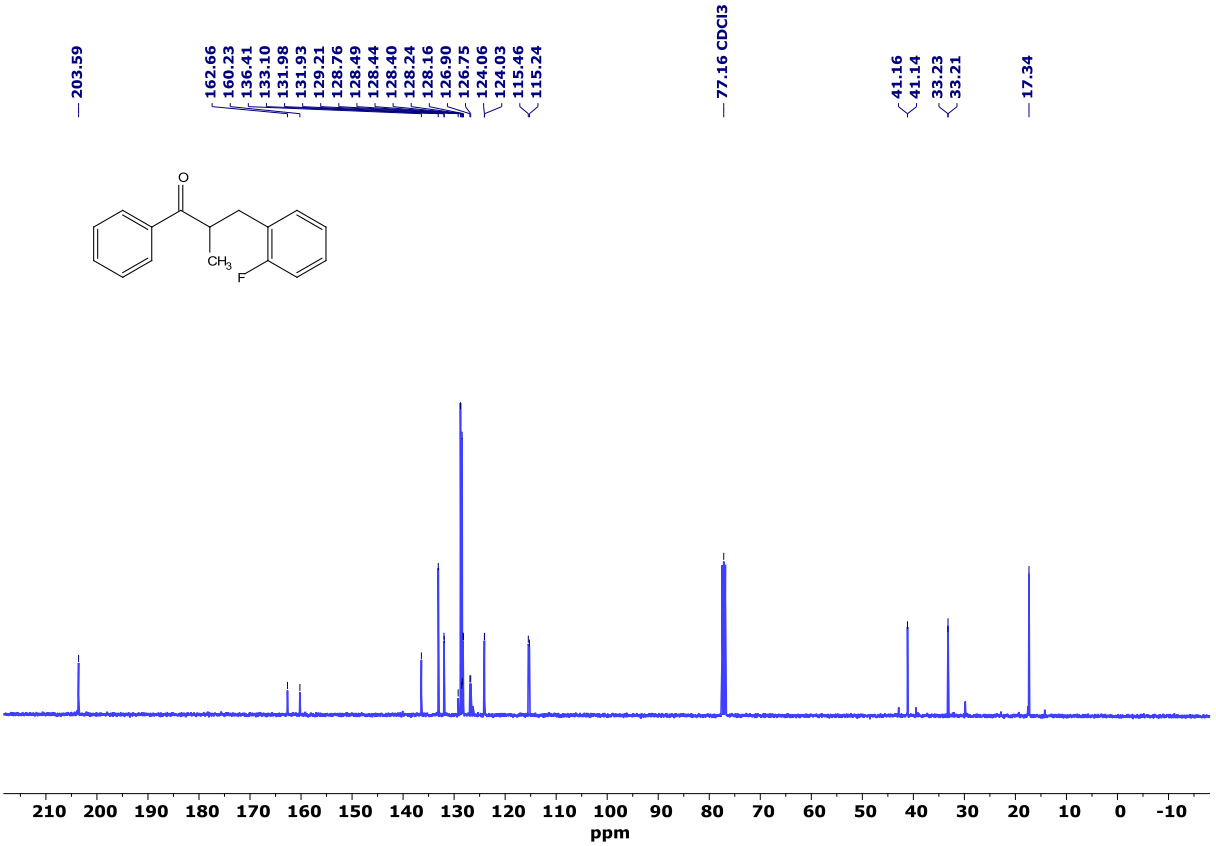

Figure S40: ^{13}C NMR spectrum of compound 19

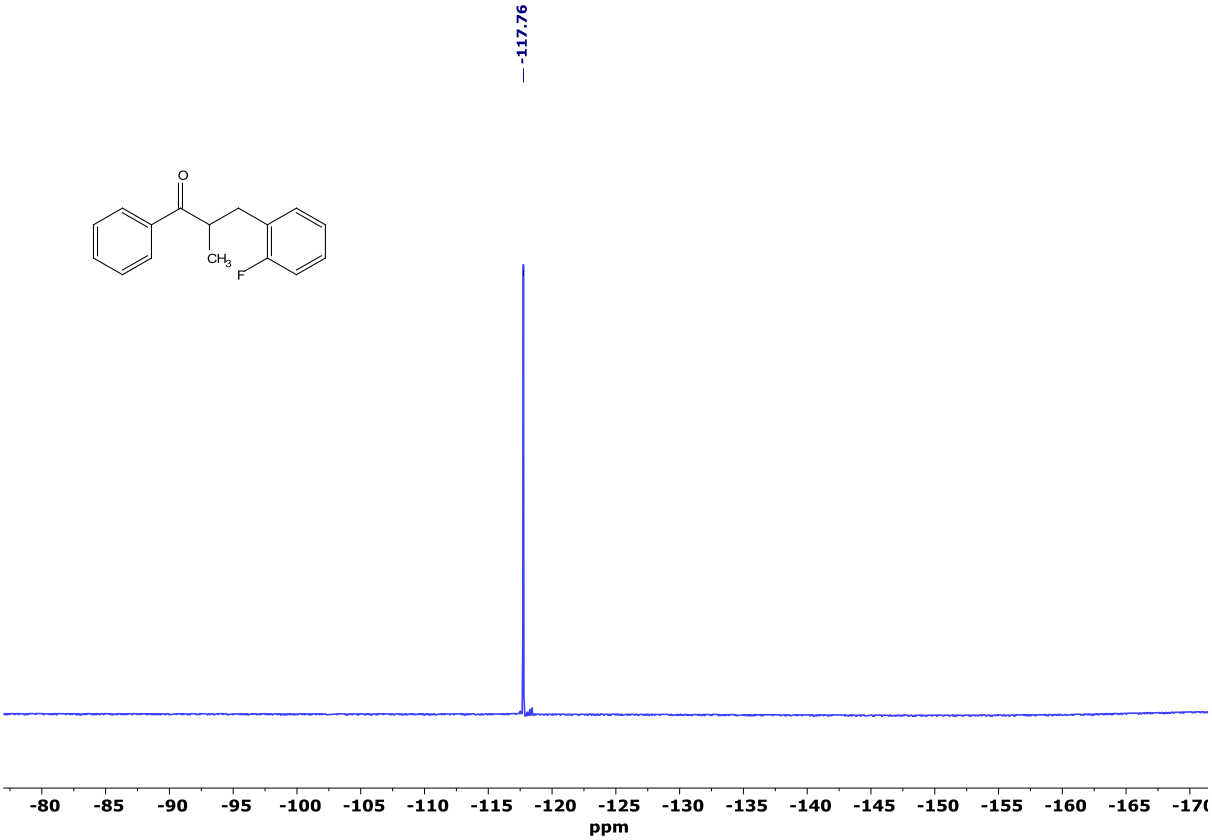

Figure S41: ^{19}F NMR spectrum of compound 19

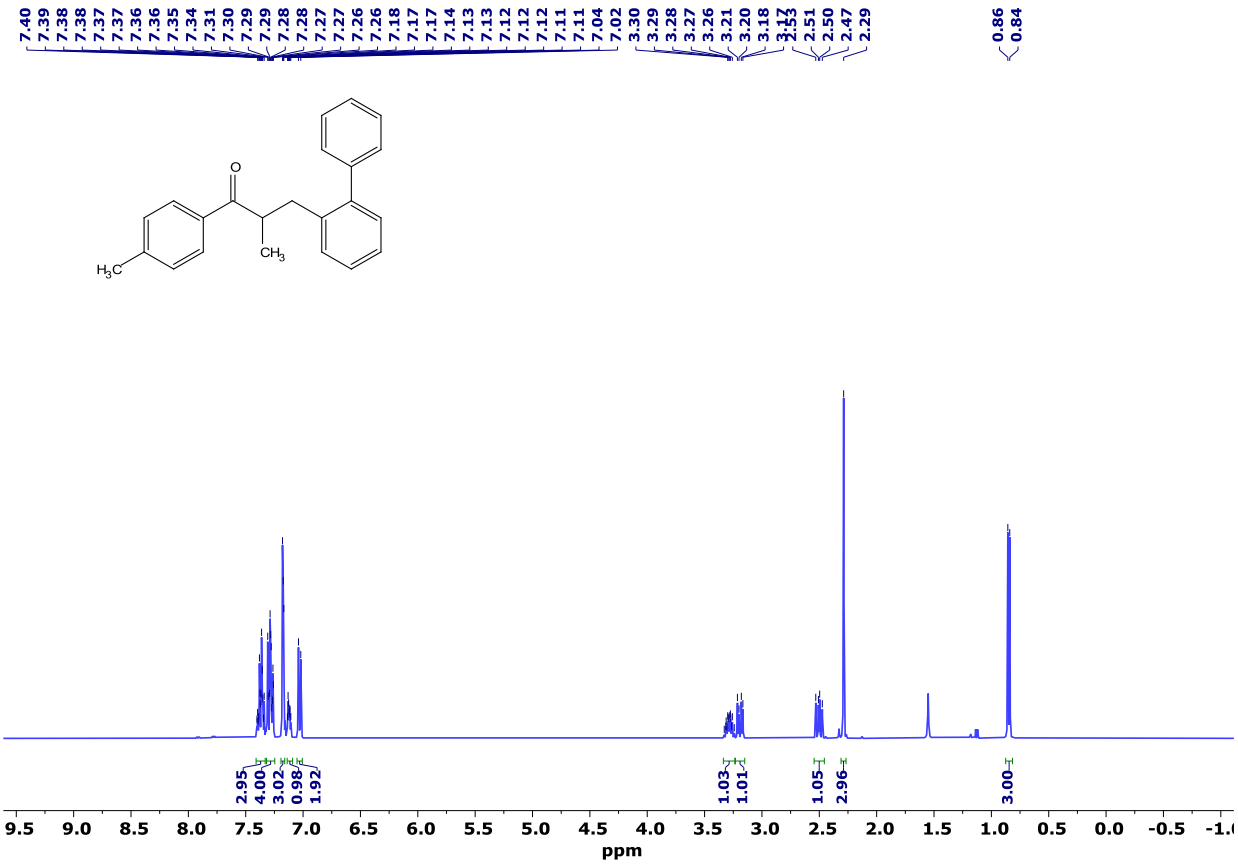

Figure S42: ^{1}H NMR spectrum of compound 20

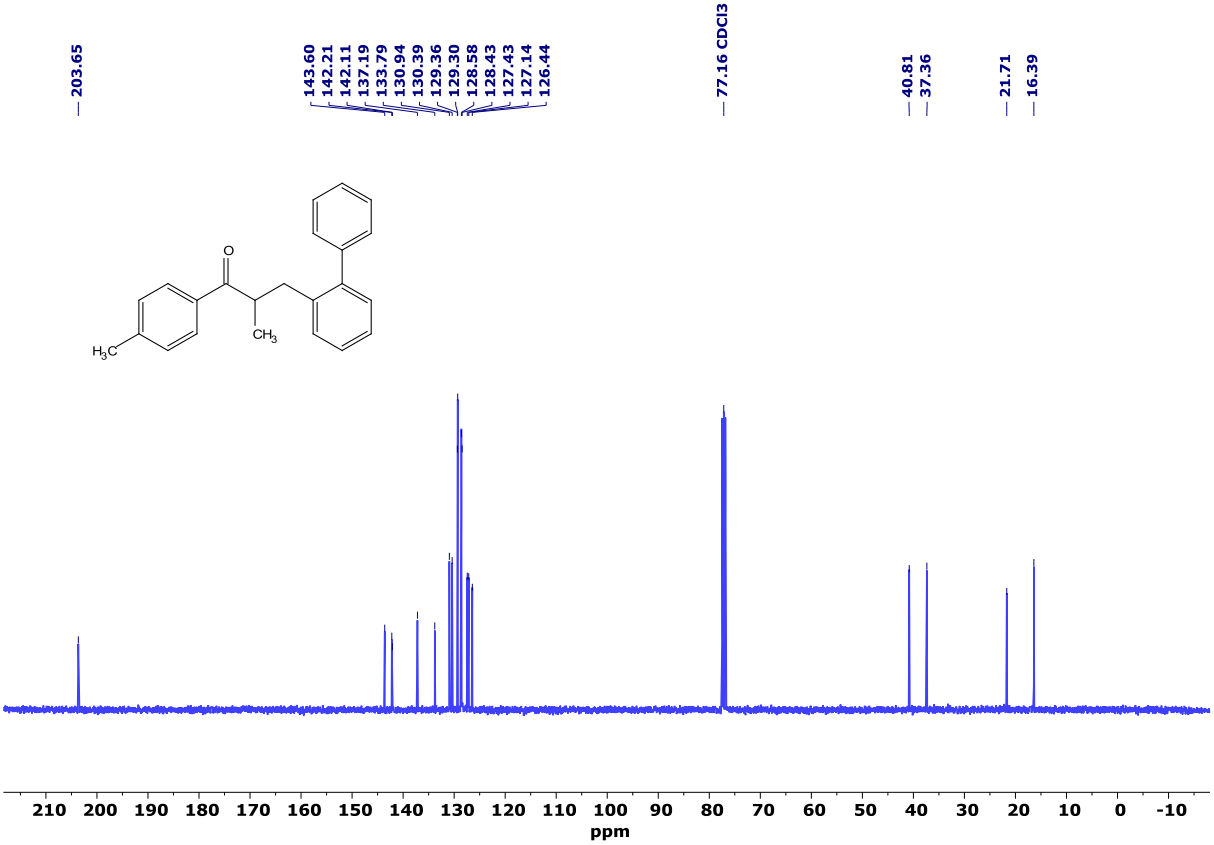

Figure S43: ^{13}C NMR spectrum of compound 20

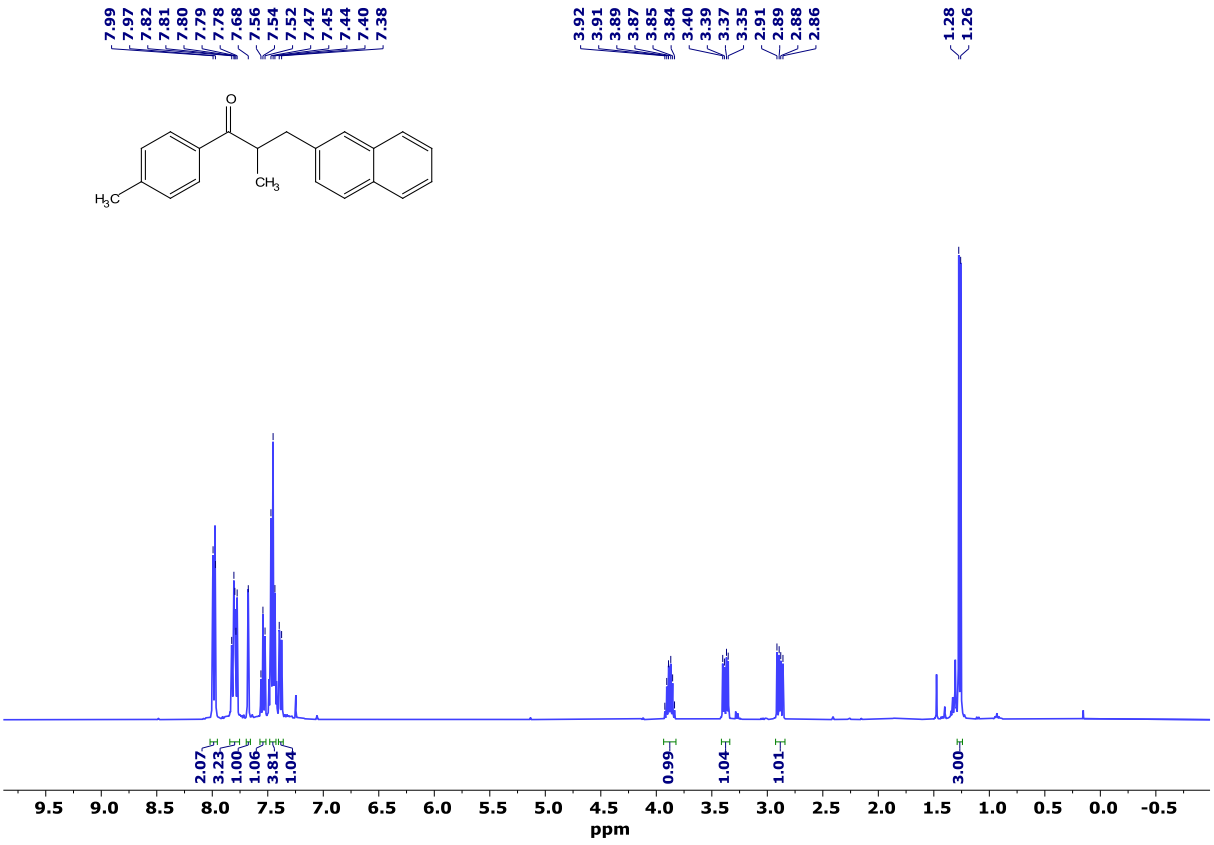

Figure S44: ^{1}H NMR spectrum of compound 21

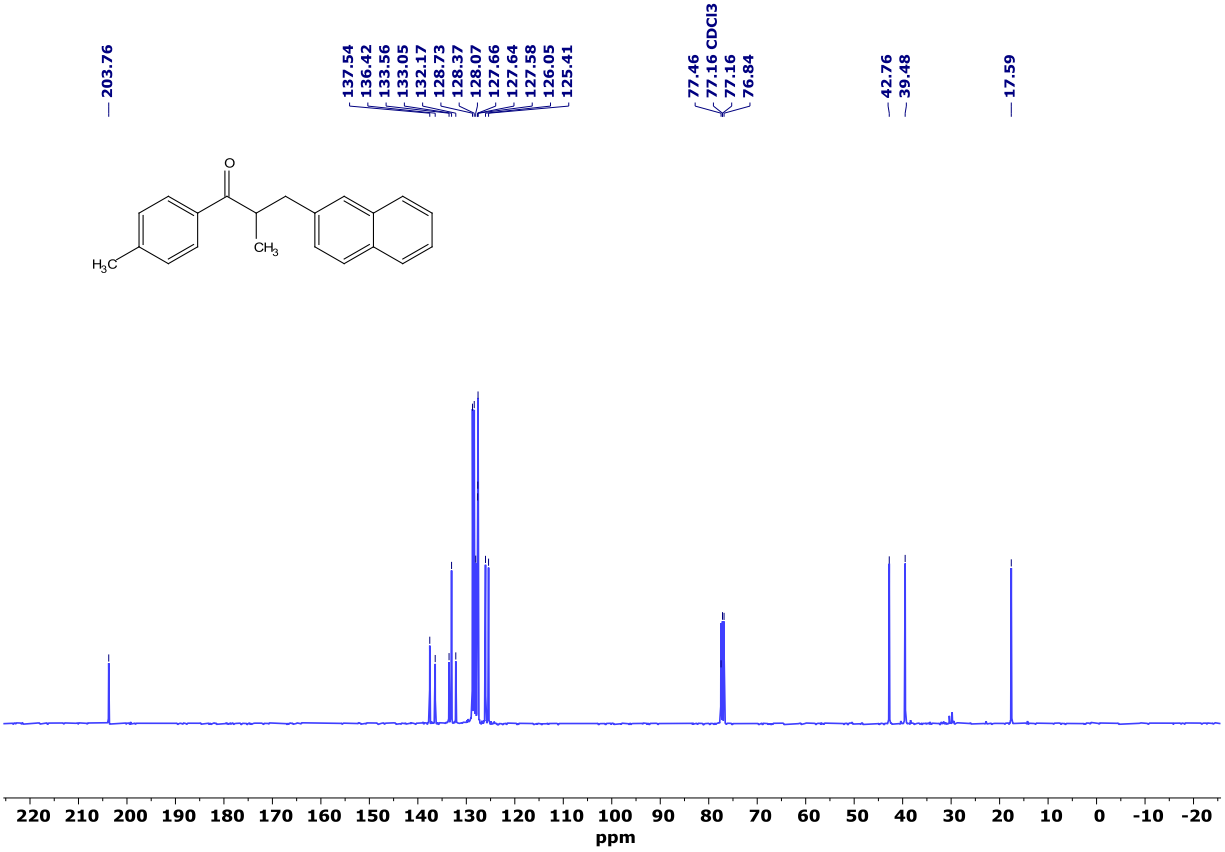

Figure S45: ^{13}C NMR spectrum of compound 21

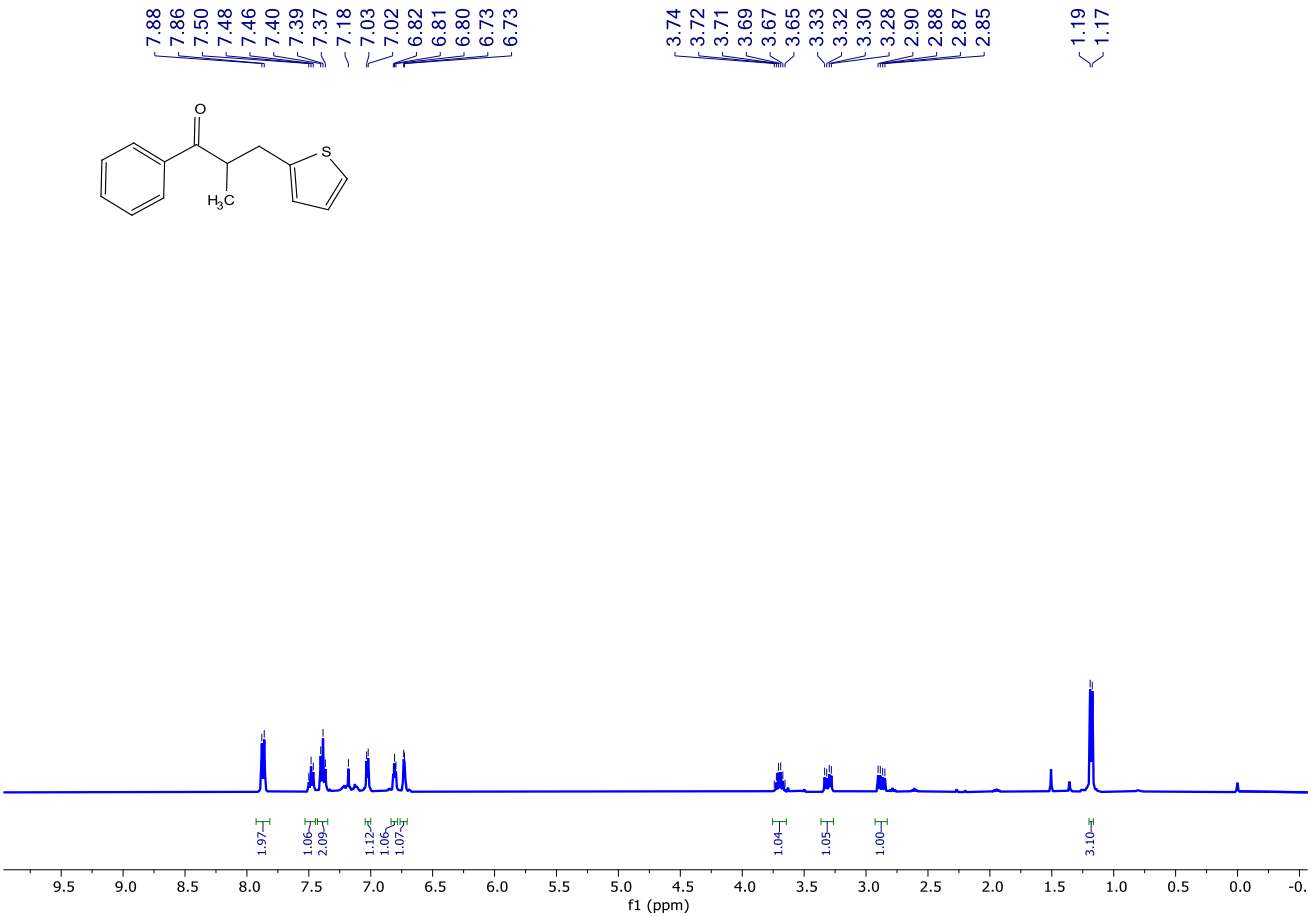

Figure S46: ^{1}H NMR spectrum of compound 22

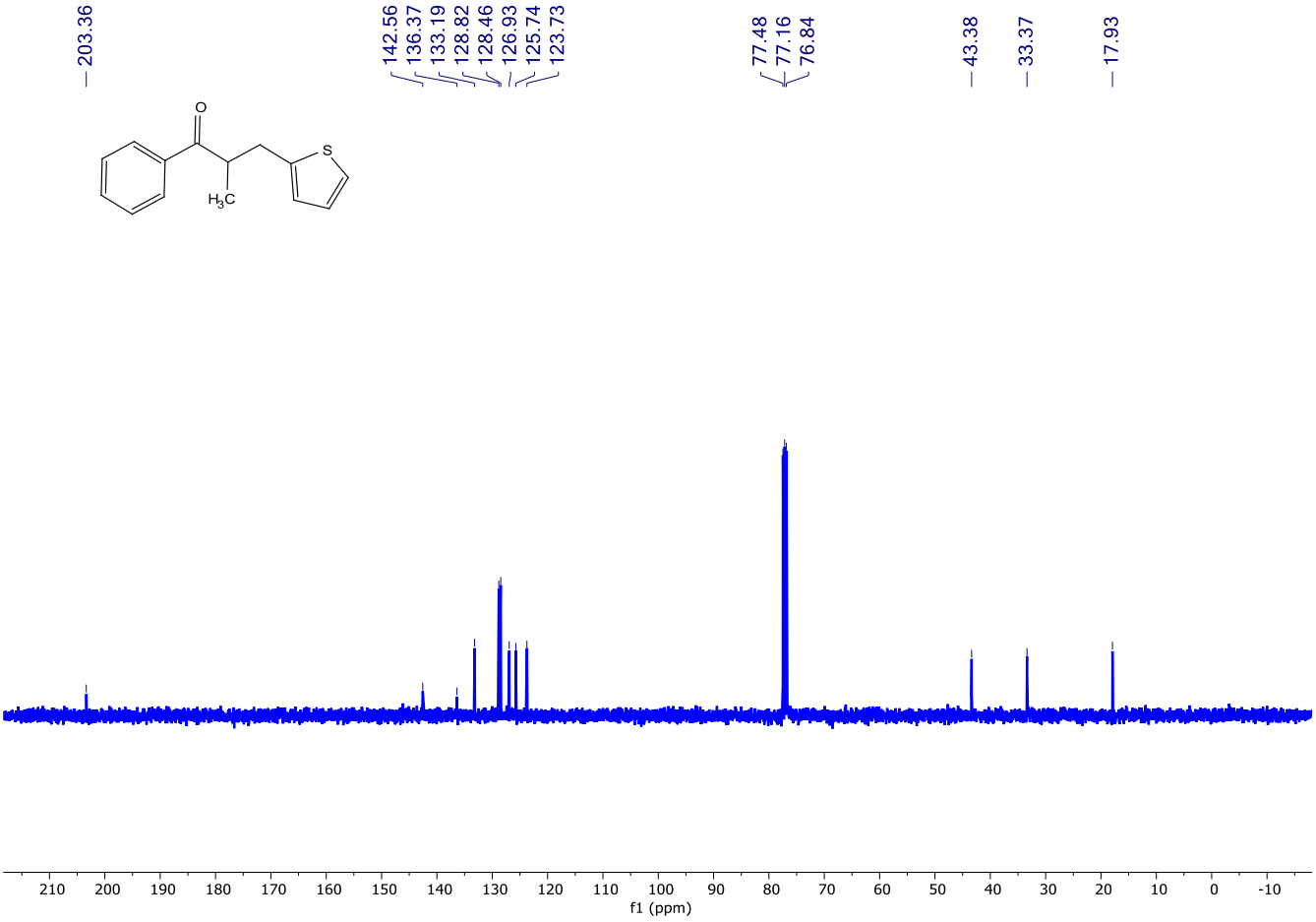

Figure S47: ^{13}C NMR spectrum of compound 22

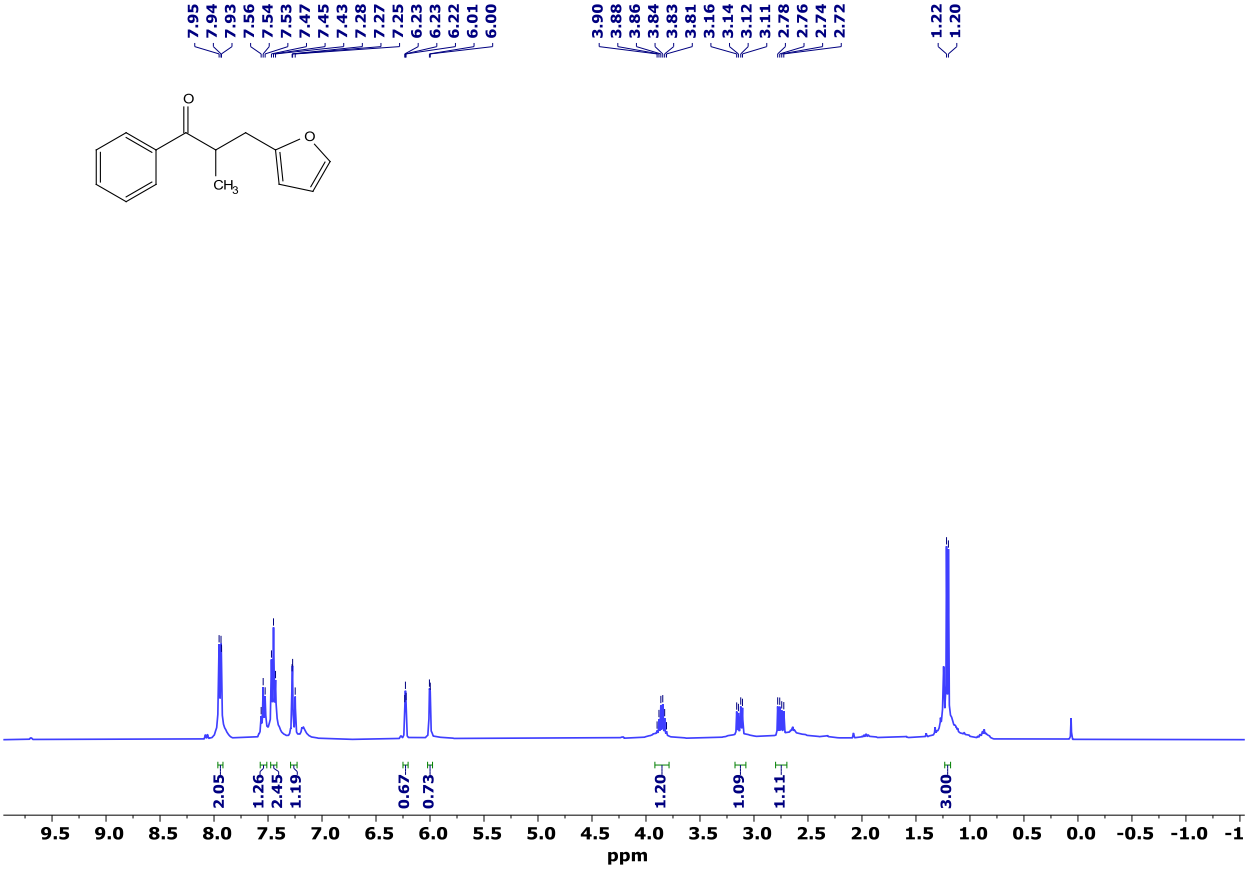

Figure S48: ^{1}H NMR spectrum of compound 23

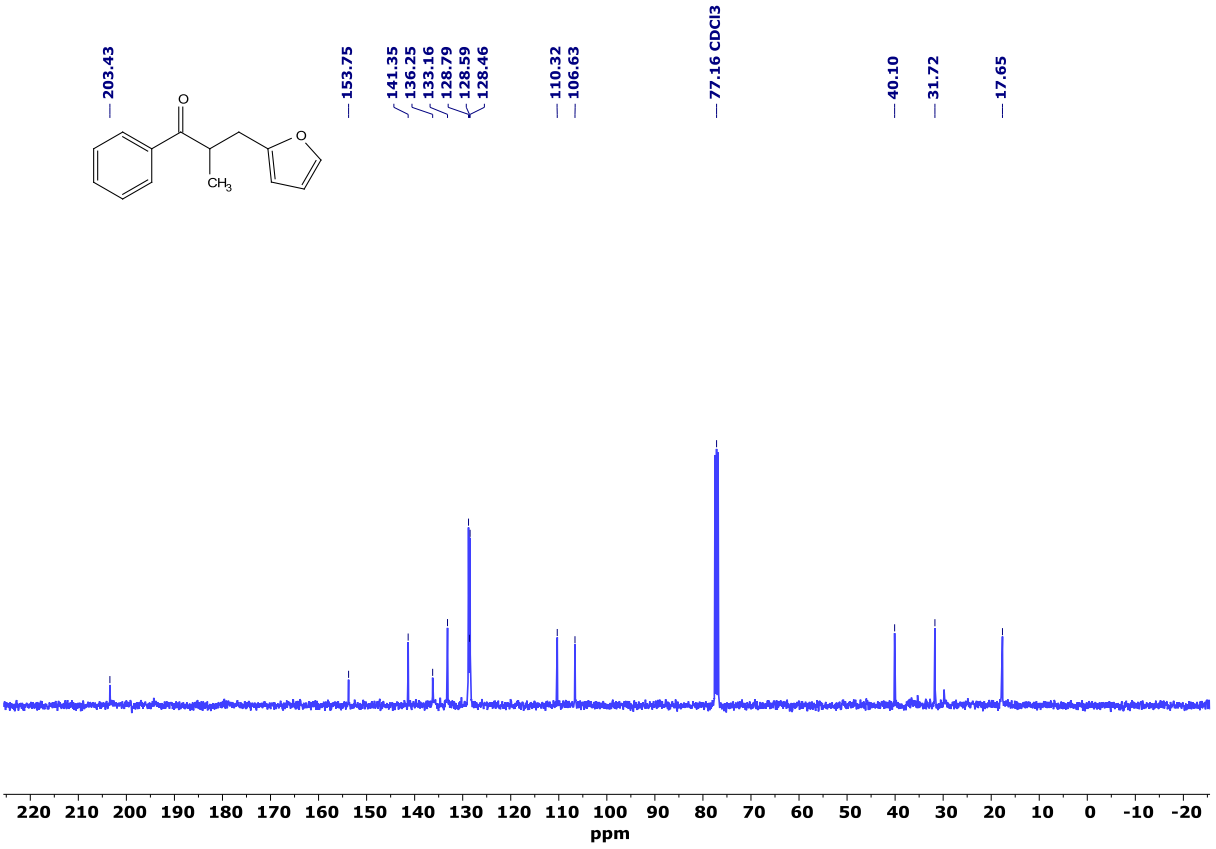

Figure S49: ^{13}C NMR spectrum of compound 23

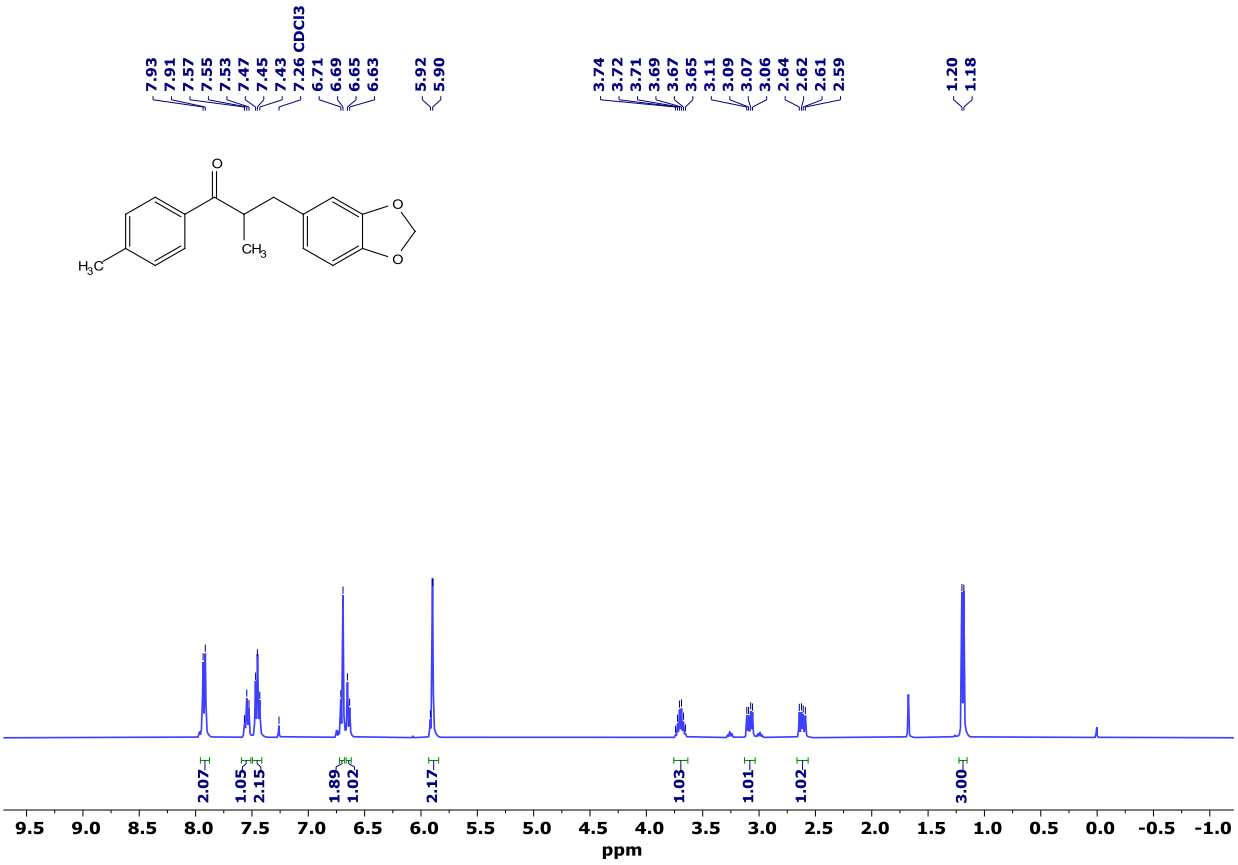

Figure S50: ^{1}H NMR spectrum of compound 24

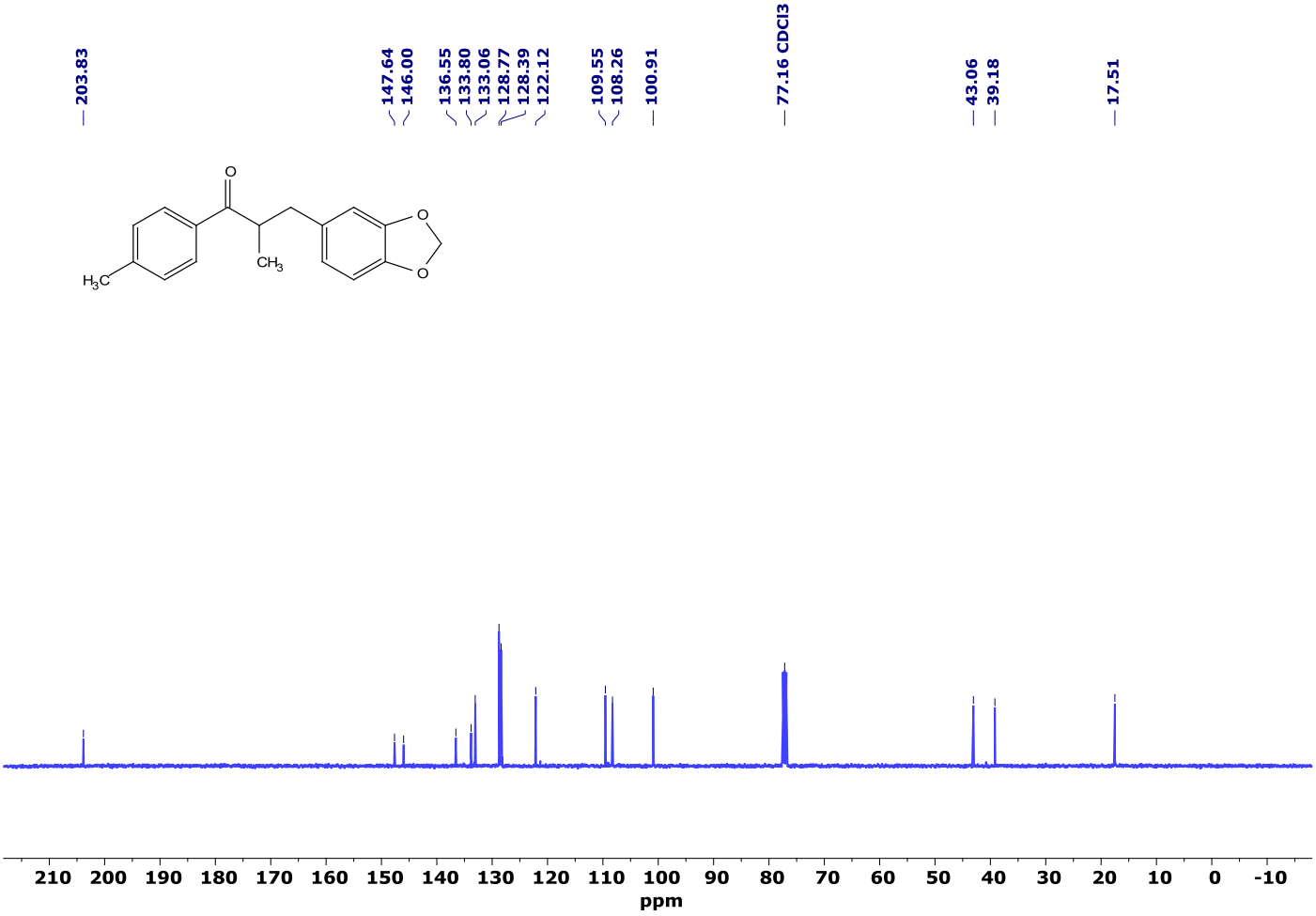

Figure S51: ^{13}C NMR spectrum of compound 24

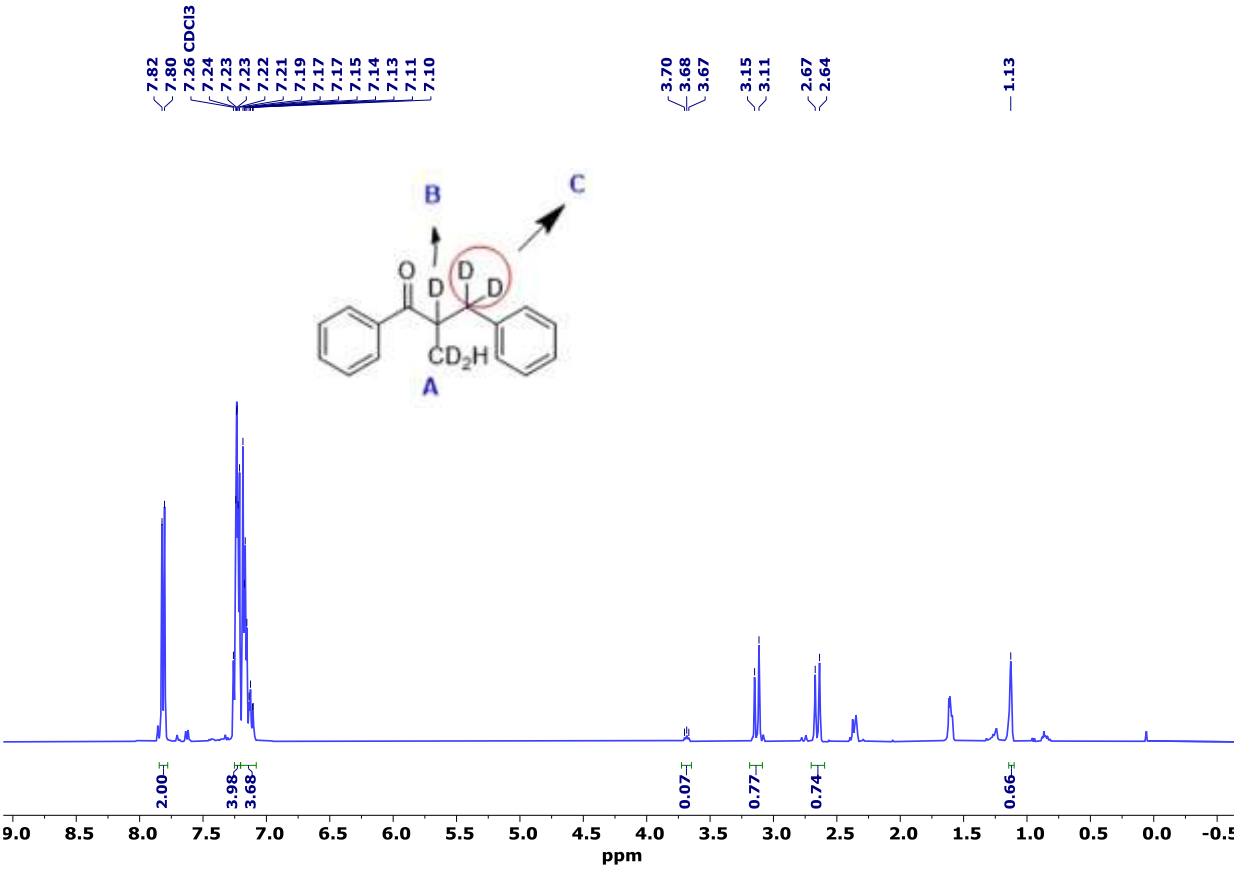

Figure S52: ^{1}H NMR spectrum of compound 29

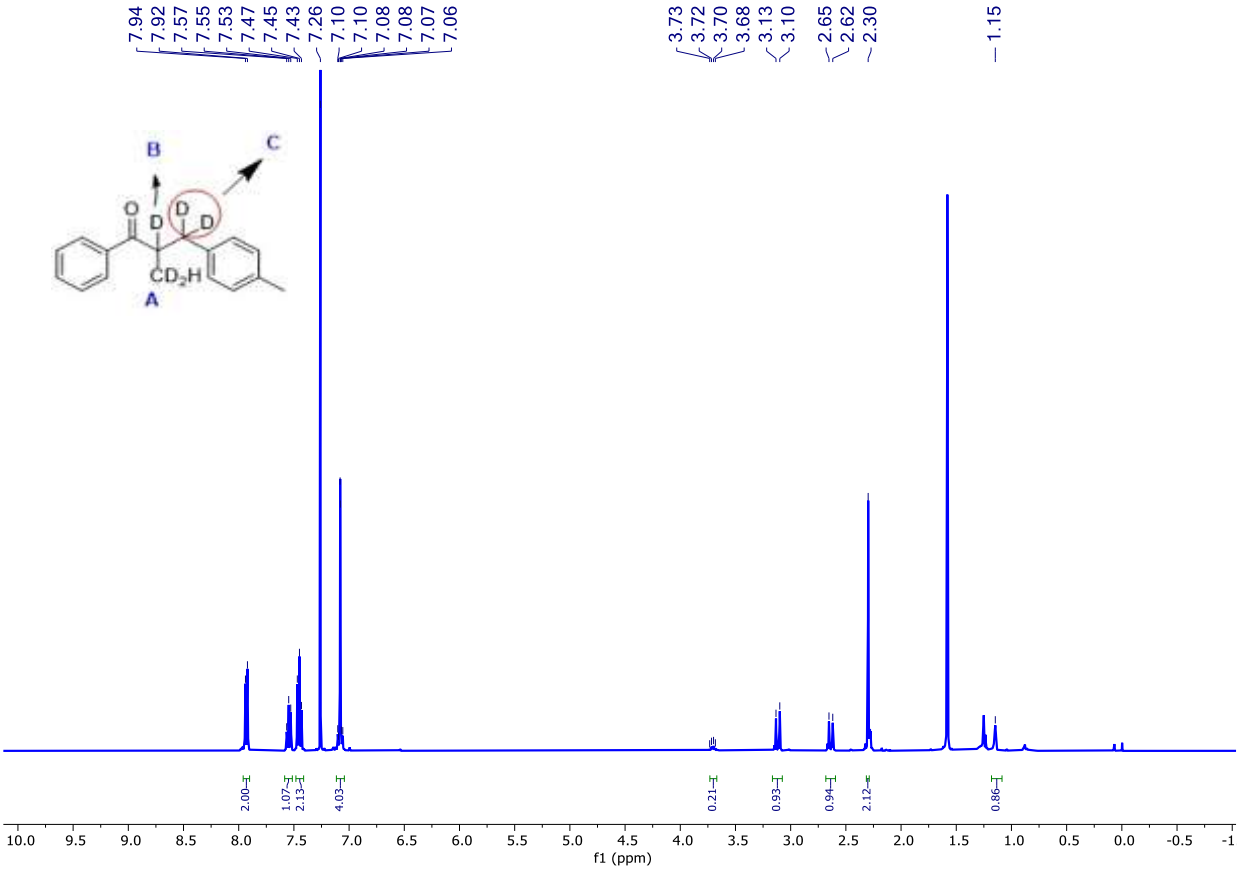

Figure S53: ^{1}H NMR spectrum of compound 30

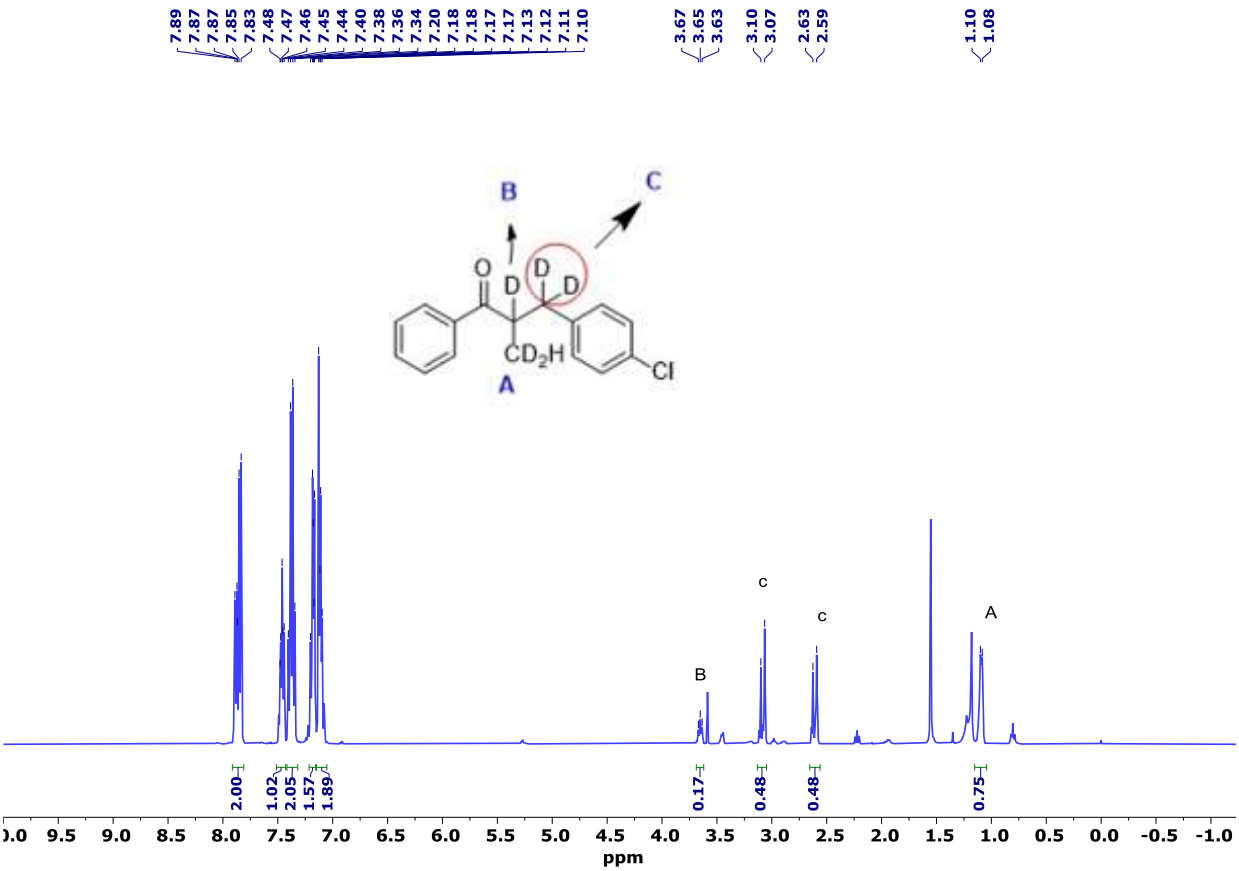

Figure S54: ^{1}H NMR spectrum of compound 31

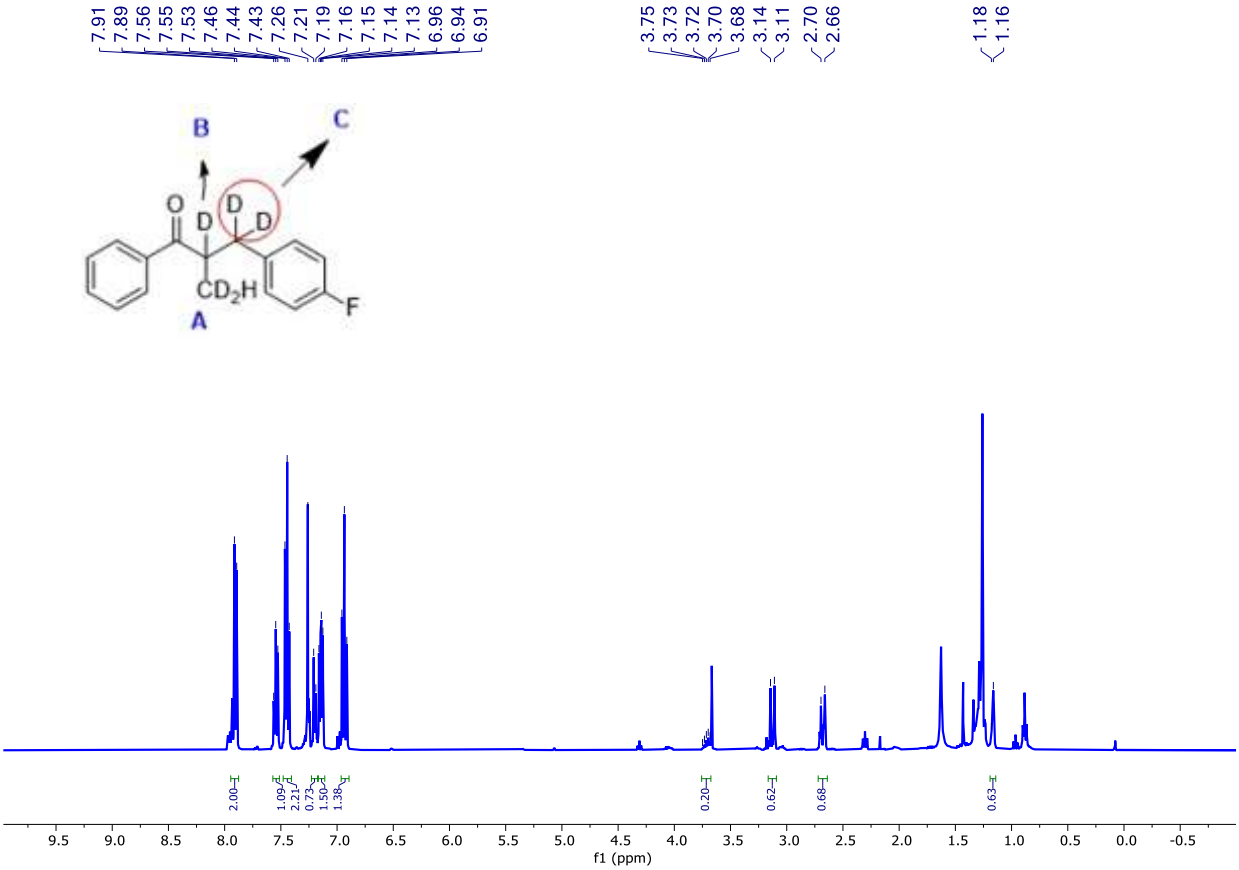

Figure S55: ^{1}H NMR spectrum of compound 32

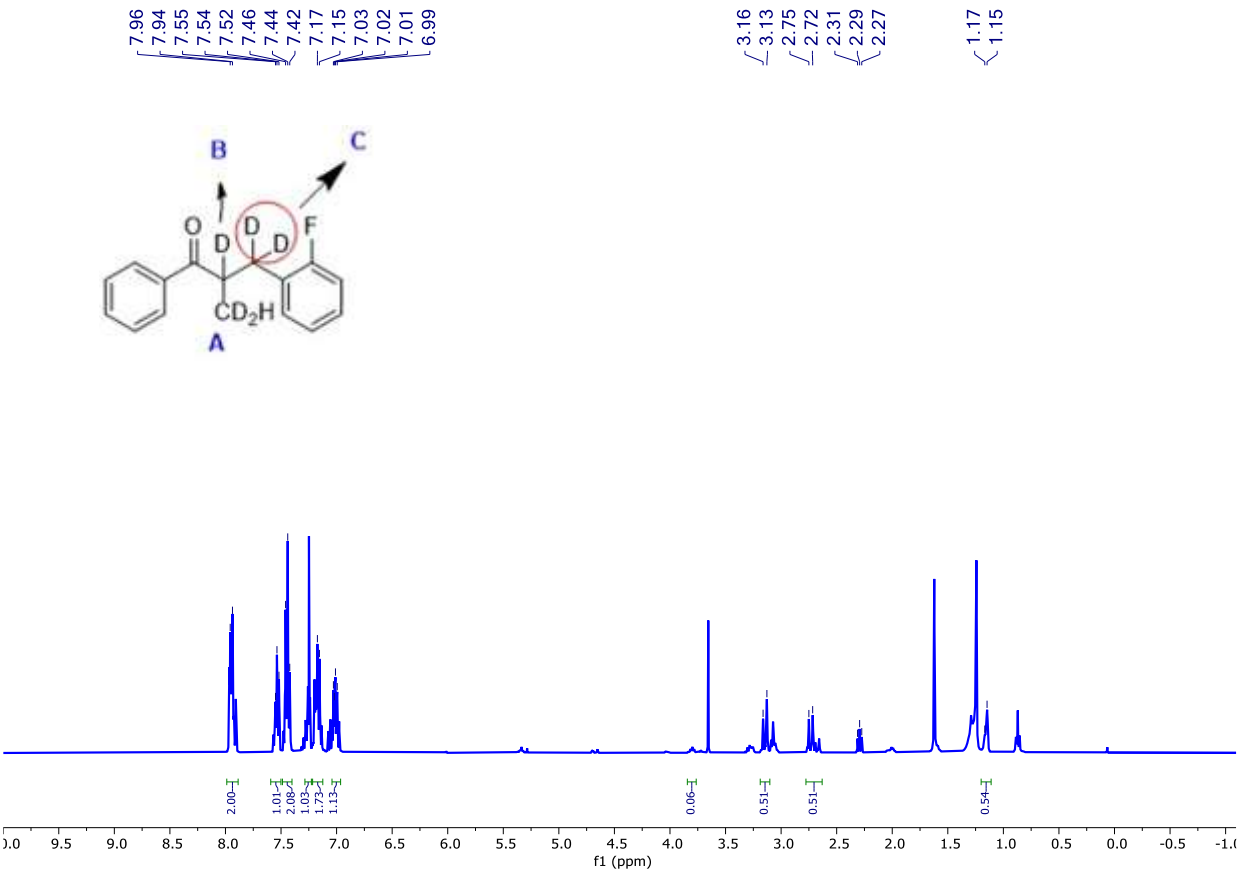

Figure S56: ^{1}H NMR spectrum of compound 33

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