Electronic Supplementary Material (ESI) for ChemComm.

One-Pot, Modular Approach to Functionalized Ketones *via* Nucleophilic Addition/Buchwald-Hartwig Amination Strategy

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Supplementary information

General methods

All reactions were carried out under a nitrogen atmosphere using oven dried glassware and using standard Schlenk techniques unless noted otherwise. THF and toluene were dried using an SPS-system. Palladium catalysts and ligands were purchased from Strem chemicals or Sigma Aldrich. All alkyllithium reagents and other reagents were purchased from Aldrich or TCI and used without further purification, unless noted otherwise. Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60, 0.25 mm, or Grace-Reveleris purification system with Grace cartridges. Components were visualized by UV and cerium/molybdenum or potassium permanganate staining. Progress of the reaction and conversion were determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Mass spectra were recorded on an AEI-MS-902 mass spectrometer (EI+) or a LTQ Orbitrap XL (ESI+). ^{1}H- and ^{13}C-NMR were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively) or a 600 MHz (600 and 125 MHz, respectively) using $CDCl_3$ as solvent, unless noted otherwise. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 for ^{1}H, δ 77.0 for ^{13}C) unless noted otherwise. Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration.

Procedures for the synthesis of organolithium reagents

4-methoxyphenyllithium, (3-(trifluoromethyl)phenyl)lithium, (4-(dimethylamino)phenyl)lithium and *2-tolyllithium* were synthesized *via* Li-halogen exchange according to the following general procedure

Method A : A solution of the corresponding aryl bromide (1 mmol, 1 eq.) in 1 mL dry THF was cooled down to -78 °C. 2.2 M *tert*-butyllithium (0.91 mL, 2 mmol, 2 eq.) was added dropwise and the resulting mixture was stirred for 1 h at -78 °C. Subsequently, the solution was allowed to reach room temperature. Before use, the solution was cooled down to 0 °C and used immediately.

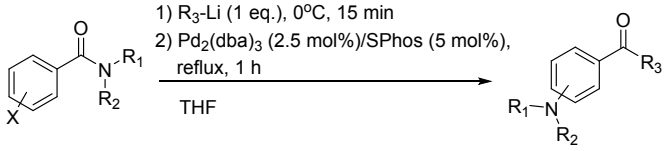
2-methoxymethoxy-phenyllithium

Method B : A solution of (methoxymethoxy)benzene (138 mg, 1 mmol, 1 eq.) in 1 mL dry THF was cooled down to -78 °C. 2.2 M *tert*-butyllithium (0.45 mL, 1 mmol, 1 eq.) was added dropwise and the resulting mixture was stirred for 1 h at -78 °C. Subsequently, the solution was allowed to reach room temperature. The solution was cooled down to 0 °C and used immediately.

2-furyllithium

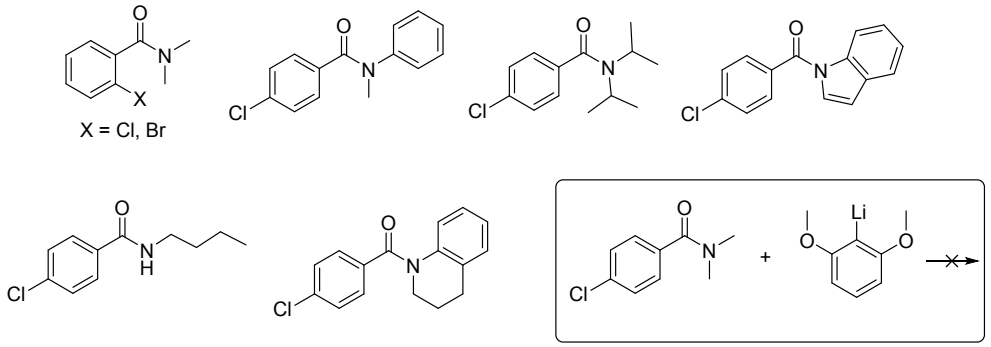
Method C : A solution of furan (0.07 mL, 1 mmol, 1 eq.) in 1.6 mL dry THF was cooled down to -40 °C. 1.6 M *n*-butyllithium (0.625 mL, 1 mmol, 1 eq.) was added dropwise. Then the resulting mixture was allowed to reach room temperature and stirred for 1 h. The solution was cooled down to 0 °C and used immediately.

General procedure for the one-pot 1,2-addition and Pd-catalyzed amination



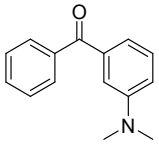
A solution of chloro- or bromo-benzamide substrate (1 mmol, 1 eq.) in 3.5 mL dry THF under nitrogen atmosphere was cooled down to 0 °C, after which the corresponding lithium reagent (1 mmol, 1 eq.) was added dropwise over the course of 15 min (unless otherwise noted). The resulting mixture was allowed to reach room temperature and a suspension of $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol, 2.5 mol%) and SPhos (20.5 mg, 0.05 mmol, 5.0 mol%) in 0.6 mL dry THF was added. The mixture was heated to reflux and stirred for 1 h (unless otherwise noted), after which the reaction was quenched with 3 mL methanol, and Celite was added to the reaction mixture. The solvent was evaporated under reduced pressure to afford the crude product on Celite which was purified by column chromatography.

Unsuccessful attempts



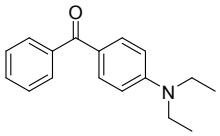
The substrates shown above failed to give the desired 1.2 addition-cross coupled product due to lack of reactivity in the Buchwald-Hartwig coupling under standard reaction conditions.

The following compounds were prepared according to the general procedure for the one-pot 1,2-addition and Pd-catalyzed amination

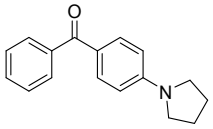


(3-(dimethylamino)phenyl)(phenyl)methanone (5a): Synthesized using 3-chloro-N,N-dimethylbenzamide (184 mg, 1 mmol, 1 eq.) and phenyllithium (0.53 mL, 1.9 M, 1 mmol, 1 eq.). The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc 90:10) as a yellow oil, 168 mg, 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.79 (m, 2H), 7.60 – 7.54 (m, 1H), 7.47 (m, 2H), 7.33 – 7.29 (m, 1H), 7.19 (dd, *J* = 2.5, 1.5 Hz, 1H), 7.06 (m, 1H), 6.95 (dd, *J* = 8.3, 2.4 Hz, 1H), 3.00 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.62, 150.56, 138.48, 138.15, 132.31, 130.20, 128.83, 128.24, 118.89, 116.51, 113.41, 40.68 ppm. HRMS (ESI+, *m/z*): calcd for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1232; found: 226.1229.
Spectral data are in agreement with those reported in the literature.[1]

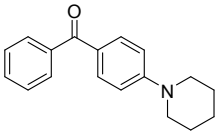
[1] Dong, Z.; Wang, J.; Ren, Z.; Dong, G. *Angew. Chem. Int. Ed.*, **2015**, 54, 12664–12668.



(4-(diethylamino)phenyl)(phenyl)methanone (5b): Synthesized using 4-chloro-N,N-diethylbenzamide (212 mg, 1 mmol, 1 eq.) and phenyllithium (0.53 mL, 1.9 M, 1 mmol, 1 eq.). The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc/TEA 89:10:1) as a yellow solid, 168 mg, 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 9.0 Hz, 2H), 7.72 (d, *J* = 7.1 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.3 Hz, 2H), 6.66 (d, *J* = 7.3 Hz, 2H), 3.44 (q, *J* = 7.1 Hz, 4H), 1.22 (t, *J* = 7.1 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.01, 150.88, 139.56, 133.22, 131.12, 129.51, 128.11, 125.38, 110.17, 44.76, 12.64 ppm. HRMS (ESI+, *m/z*): calcd for $C_{17}H_{20}NO$ $[M+H]^+$: 254.1545; found: 254.1544.

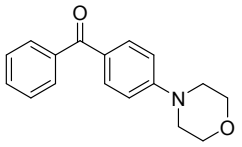


phenyl(4-(pyrrolidin-1-yl)phenyl)methanone (5c): Synthesized using (4-chlorophenyl)(pyrrolidin-1-yl)methanone (210 mg, 1 mmol, 1 eq.) and phenyllithium (0.53 mL, 1.9 M, 1 mmol, 1 eq.). The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc 95:5) as a gray solid, 178 mg, 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 7.1 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 6.55 (d, *J* = 8.8 Hz, 2H), 3.42 – 3.35 (m, 4H), 2.08 – 2.01 (m, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.28, 151.05, 139.64, 133.09, 131.10, 129.53, 128.11, 124.37, 110.75, 47.72, 25.59 ppm. HRMS (ESI+, *m/z*): calcd for $C_{17}H_{18}NO$ $[M+H]^+$: 252.1388; found: 252.1387.
Spectral data are in agreement with those reported in the literature.[2]

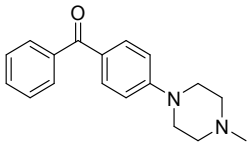


phenyl(4-(piperidin-1-yl)phenyl)methanone (5e): Synthesized using (4-chlorophenyl)(piperidin-1-yl)methanone (224 mg, 1 mmol, 1 eq.) and phenyllithium (0.53 mL, 1.9 M, 1 mmol, 1 eq.). After the phenyllithium addition, the mixture was stirred for 1 h at 0 °C. The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc 95:5) as a pink solid, 212 mg, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.9 Hz, 2H), 7.73 (d, *J* = 7.3 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 3.38 (m, 4H), 1.68 (br, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.20, 154.37, 139.20, 132.76, 131.36, 129.61, 128.14, 126.24, 113.23, 48.71, 25.49, 24.49 ppm. HRMS (ESI+, *m/z*): calcd for $C_{18}H_{20}NO$ $[M+H]^+$: 266.1545; found: 266.1546.
Spectral data are in agreement with those reported in the literature.[3]

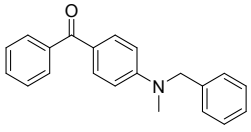
[2] Zhang, X.; Lu, G.; Cai, C. *Green Chem*., **2016**, 18, 5580-5585.
[3] Manolikakes, G.; Gavryushin, A.; Knochel, P. *J. Org. Chem.*, **2008**, 73, 1429–1434.



(4-morpholinophenyl)(phenyl)methanone (5f): Synthesized using (4-chlorophenyl)(morpholino)methanone (226 mg, 1 mmol, 1 eq.) and phenyllithium (0.53 mL, 1.9 M, 1 mmol, 1 eq.). After the phenyllithium addition, the mixture was stirred for 1 h at 0 °C. The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc 90:10 to 50:50) as an off-white solid, 228 mg, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.9 Hz, 2H), 7.74 (d, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 3.91 – 3.84 (m, 4H), 3.36 – 3.30 (m, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.41, 154.03, 138.82, 132.60, 131.73, 129.75, 128.26, 128.18, 113.49, 66.69, 47.86 ppm. HRMS (ESI+, *m/z*): calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$: 268.1338; found: 268.1338.
Spectral data are in agreement with those reported in the literature.[4]

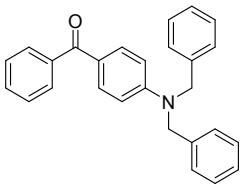


(4-(4-methylpiperazin-1-yl)phenyl)(phenyl)methanone (5g): Synthesized using (4-chlorophenyl)(4-methylpiperazin-1-yl)methanone (239 mg, 1 mmol, 1 eq.) and phenyllithium (0.53 mL, 1.9 M, 1 mmol, 1 eq.). After the phenyllithium addition, the mixture was stirred for 1 h at 0 °C. The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc 95:5 to 50:50) as a yellow solid, 202 mg, 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.9 Hz, 2H), 7.73 (d, *J* = 7.3 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 3.43 – 3.36 (m, 4H), 2.61 – 2.54 (m, 4H), 2.36 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.35, 154.01, 138.95, 132.62, 131.58, 129.68, 128.21, 127.40, 113.48, 54.81, 47.35, 46.16 ppm. HRMS (ESI+, *m/z*): calcd for $C_{18}H_{21}N_2O$ $[M+H]^+$: 281.1654; found: 281.1656.
Spectral data (^{1}H NMR) are in agreement with those reported in the literature.[5]

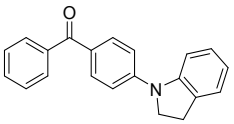


(4-(benzyl(methyl)amino)phenyl)(phenyl)methanone (5h): Synthesized using N-benzyl-4-chloro-N-methylbenzamide (260 mg, 1 mmol, 1 eq.) and phenyllithium (0.53 mL, 1.9 M, 1 mmol, 1 eq.). After the phenyllithium addition, the mixture was stirred for 1 h at 0 °C. The catalyst was added and the mixture was heated under reflux and stirred for 16h. The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc 95:5) as a yellow oil, 262 mg, 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.9 Hz, 2H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 7.4 Hz, 2H), 6.75 (d, *J* = 8.9 Hz, 2H), 4.66 (s, 2H), 3.16 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.20, 152.73, 139.30, 137.54, 132.97, 131.32, 129.60, 128.95, 128.16, 127.46, 126.68, 125.65, 111.14, 56.26, 38.98 ppm. HRMS (ESI+, *m/z*): calcd for $C_{21}H_{20}NO$ $[M+H]^+$: 302.1545; found: 302.1548.
Spectral data are in agreement with those reported in the literature.[6]

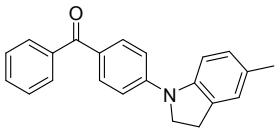
[4] Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.*, **1997**, 62, 1264–1267.
[5] Kamikawa, K.; Sugimoto, S.; Uemura, M. *J. Org. Chem*., **1998**, 63, 8407–8410.
[6] Bei, X.; Uno, T.; Norris, J.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Petersen, J. L. *Organometallics*, **1999**, 18, 1840–1853.



(4-(dibenzylamino)phenyl)(phenyl)methanone (5i): Synthesized using N,N-dibenzyl-4-chlorobenzamide (100 mg, 0.3 mmol, 1 eq.) and phenyllithium (0.16 mL, 1.9 M, 0.3 mmol, 1 eq.) in 1 mL dry THF. After the phenyllithium addition, the mixture was stirred for 2 h at 0 °C. After addition of $Pd_2(dba)_3$ (2.5 mol%, 0.0075 mmol, 6.8 mg) and SPhos (5.0 mol%, 0.015 mmol, 6.2 mg), the mixture was heated under reflux and stirred for 22 h, and quenched with 1 mL methanol. The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc 95:5) as an off-white solid, 26 mg, 23% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (m, 4H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.38 – 7.27 (m, 6H), 7.24 (d, *J* = 7.3 Hz, 4H), 6.76 (d, *J* = 9.0 Hz, 2H), 4.75 (s, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.11, 152.69, 139.20, 137.34, 133.04, 131.34, 129.58, 129.02, 128.15, 127.46, 126.61, 125.92, 111.37, 54.24 ppm. HRMS (ESI+, *m/z*): calcd for $C_{27}H_{24}NO$ $[M+H]^+$: 378.1858; found: 378.1861.
Spectral data are in agreement with those reported in the literature.[7]

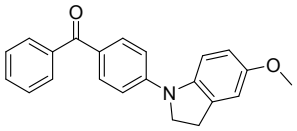


(4-(indolin-1-yl)phenyl)(phenyl)methanone (5j): Synthesized using (4-chlorophenyl)(indolin-1-yl)methanone (258 mg, 1 mmol, 1 eq.) and phenyllithium (0.53 mL, 1.9 M, 1 mmol, 1 eq.). The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc 95:5) as a brown solid, 254 mg, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.7 Hz, 2H), 7.78 (d, *J* = 7.3 Hz, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.28 – 7.21 (m, 3H), 7.15 (t, *J* = 7.7 Hz, 1H), 6.87 (t, *J* = 7.2 Hz, 1H), 4.05 (t, *J* = 8.4 Hz, 2H), 3.19 (t, *J* = 8.3 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.29, 147.88, 145.29, 138.81, 132.46, 132.24, 131.75, 129.78, 128.75, 128.28, 127.32, 125.51, 120.71, 115.27, 109.99, 51.97, 28.19 ppm. HRMS (ESI+, *m/z*): calcd for $C_{21}H_{18}NO$ $[M+H]^+$: 300.1388; found: 300.1386.

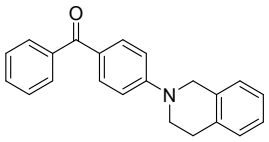


(4-(5-methylindolin-1-yl)phenyl)(phenyl)methanone (5k): Synthesized using (4-chlorophenyl)(5-methylindolin-1-yl)methanone (136 mg, 0.5 mmol, 1 eq.) and phenyllithium (0.26 mL, 1.9 M, 0.5 mmol, 1 eq.) in 2 mL dry THF. After the phenyllithium addition, the mixture was stirred for 1 h at 0 °C. After addition of $Pd_2(dba)_3$ (2.5 mol%, 0.013 mmol, 11.3 mg) and SPhos (5.0 mol%, 0.025 mmol, 10.3 mg), the mixture was heated under reflux and stirred for 1 h, and quenched with 1 mL methanol. The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc 95:5) as a yellow solid, 88 mg, 56% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.9 Hz, 2H), 7.78 (d, *J* = 6.8 Hz, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.49 (dd, *J* = 8.2, 6.8 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.9 Hz, 2H), 7.06 (s, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 4.02 (t, *J* = 8.3 Hz, 2H), 3.14 (t, *J* = 8.3 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.71, 150.57, 145.36, 141.43, 135.04, 135.02, 134.17, 132.84, 132.26, 130.77, 130.72, 130.04, 128.85, 117.31, 112.48, 54.50, 30.68, 23.46.

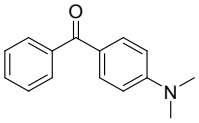
[7] Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed*., **2012**, 51, 3642–3645.



(4-(5-methoxyindolin-1-yl)phenyl)(phenyl)methanone (5l): Synthesized using (4-chlorophenyl)(5-methoxyindolin-1-yl)methanone (144 mg, 0.5 mmol, 1 eq.) and phenyllithium (0.26 mL, 1.9 M, 0.5 mmol, 1 eq.) in 2 mL dry THF. After the phenyllithium addition, the mixture was stirred for 1 h at 0 °C. After addition of $Pd_2(dba)_3$ (2.5 mol%, 0.013 mmol, 11.3 mg) and SPhos (5.0 mol%, 0.025 mmol, 10.3 mg), the mixture was heated under reflux and stirred for 1 h, and quenched with 1 mL methanol. The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc 90:10) as a yellow solid, 63 mg, 38% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.8 Hz, 2H), 7.76 (d, J = 7.0 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.47 (t, J = 7.4 Hz, 2H), 7.26 (d, J = 8.6 Hz, 1H), 7.17 (d, J = 8.9 Hz, 2H), 6.83 (d, J = 1.5 Hz, 1H), 6.68 (dd, J = 8.8, 2.6 Hz, 1H), 4.03 (t, J = 8.3 Hz, 2H), 3.78 (s, 3H), 3.15 (t, J = 8.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.65, 157.03, 150.63, 141.47, 141.44, 136.55, 135.09, 134.11, 132.22, 130.75, 130.38, 116.82, 114.93, 114.07, 113.18, 58.48, 54.59, 30.95.

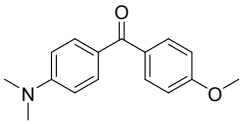


(4-(3,4-dihydroisoquinolin-2(1H)-yl)phenyl)(phenyl)methanone (5m): Synthesized using (4-chlorophenyl)(3,4-dihydroisoquinolin-2(1H)-yl)methanone (136 mg, 0.5 mmol, 1 eq.) and phenyllithium (0.26 mL, 1.9 M, 0.5 mmol, 1 eq.) in 2 mL dry THF. After the phenyllithium addition, the mixture was stirred for 1 h at 0 °C. After addition of $Pd_2(dba)_3$ (2.5 mol%, 0.013 mmol, 11.3 mg) and SPhos (5.0 mol%, 0.025 mmol, 10.3 mg), the mixture was heated under reflux and stirred for 1 h, and quenched with 1 mL methanol. The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc 95:5) as a yellow solid, 60 mg, 38% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 9.2 Hz, 2H), 7.74 (d, J = 7.0 Hz, 2H), 7.59 – 7.42 (m, 3H), 7.24 – 7.15 (m, 3H), 6.91 (d, J = 8.0 Hz, 2H), 4.56 (s, 2H), 3.69 (t, J = 5.8 Hz, 2H), 3.01 (t, J = 5.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.14, 152.91, 135.03, 133.69, 132.75, 131.26, 129.51, 128.20, 128.04, 126.81, 126.50, 126.44, 125.96, 111.82, 48.98, 44.74, 29.02.

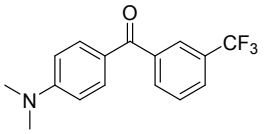


(4-(dimethylamino)phenyl)(phenyl)methanone (5n): Synthesized using 4-chloro-N,N-dimethylbenzamide (184 mg, 1 mmol, 1 eq.) and phenyllithium (0.53 mL, 1.9 M, 1 mmol, 1 eq.). The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc 90:10) as a yellow solid, 196 mg, 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.9 Hz, 2H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 6.69 (d, *J* = 8.9 Hz, 2H), 3.08 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.31, 153.27, 139.37, 132.87, 131.29, 129.59, 128.15, 120.71, 110.92, 40.33 ppm. HRMS (ESI+, *m/z*): calcd for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1232; found: 226.1229. Spectral data are in agreement with those reported in the literature.[8]

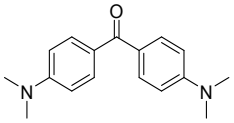
[8] Gooßen, L. J.; Rudolphi, F.; Oppel, C.; Rodríguez, N. *Angew. Chem. Int. Ed*., **2008**, 47, 3043–3045.



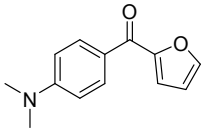
(4-(dimethylamino)phenyl)(4-methoxyphenyl)methanone (5o): Synthesized using 4-chloro-N,N-dimethylbenzamide (184 mg, 1 mmol, 1 eq.) and 4-methoxyphenyllithium (prepared according to method A, 1 mmol, 1 eq.). The reaction was quenched with 2 mL water and 2 mL sat. aq. NH_4Cl. Then the mixture was extracted three times with 10 mL diethyl ether and the combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc/TEA 89:10:1) as a yellow solid, 137 mg, 54% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (m, 4H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.69 (d, *J* = 9.0 Hz, 2H), 3.88 (s, 3H), 3.07 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.28, 162.39, 153.15, 132.60, 132.01, 131.84, 125.56, 113.41, 110.73, 55.55, 40.24 ppm. HRMS (ESI+, *m/z*): calcd for $C_{16}H_{18}NO_2$ $[M+H]^+$: 256.1338; found: 256.1335.
Spectral data are in agreement with those reported in the literature.[9]



(4-(dimethylamino)phenyl)(3-(trifluoromethyl)phenyl)methanone (5p): Synthesized using 4-chloro-N,N-dimethylbenzamide (184 mg, 1 mmol, 1 eq.) and (3-(trifluoromethyl)phenyl)lithium (prepared according to method A, 1 mmol, 1 eq.). The reaction was quenched with 2 mL water and 2 mL sat. aq. NH_4Cl. Then the mixture was extracted three times with 10 mL diethyl ether and the combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc/TEA 89:10:1) as a yellow solid, 145 mg, 49% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.77 (m, 3H), 7.59 (t, *J* = 7.7 Hz, 1H), 6.70 (d, *J* = 8.9 Hz, 2H), 3.09 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.57, 153.69, 140.18, 132.88, 132.69, 132.68, 128.79, 127.77, 127.73, 127.70, 127.66, 126.36, 126.33, 126.29, 126.25, 124.15, 110.89, 40.22 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.67 ppm. HRMS (ESI+, *m/z*): calcd for $C_{16}H_{15}F_3NO$ $[M+H]^+$: 294.1106; found: 294.1104.
Spectral data (^{1}H NMR) are in agreement with those reported in the literature.[10]

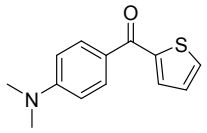


Bis(4-(dimethylamino)phenyl)methanone (5q): Synthesized using 4-chloro-N,N-dimethylbenzamide (184 mg, 1 mmol, 1 eq.) and (4-(dimethylamino)phenyl)lithium (prepared according to method A, 1 mmol, 1 eq.). The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc/TEA 94:5:1) as a green/gray solid, 110 mg, 41% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.9 Hz, 4H), 6.70 (d, *J* = 8.7 Hz, 4H), 3.06 (s, 12H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.13, 152.81, 132.31, 126.47, 110.68, 40.25 ppm. HRMS (ESI+, *m/z*): calcd for $C_{17}H_{21}N_2O$ $[M+H]^+$: 269.1654; found: 269.1652.
Spectral data are in agreement with those reported in the literature.[11]

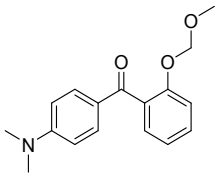


[9] Li, H.; Xu, Y.; Shi, E.; Wei, W.; Suo, X.; Wan, X. *Chem. Commun.*, **2011**, 47, 7880-7882.
[10] Muramatsu, H.; Okumura, A.; Shibata, K.; Matsui, M. *Chem. Ber.*, **1994**, 127, 1627-1632.
[11] Berini, C.; Winkelmann, O. H.; Otten, J.; Vicic, D. A.; Navarro, O. *Chem. Eur. J.*, **2010**, 16, 6857–6860.

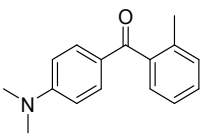
(4-(dimethylamino)phenyl)(furan-2-yl)methanone (5r): Synthesized using 4-chloro-N,N-dimethylbenzamide (184 mg, 1 mmol, 1 eq.) and 2-furyllithium (prepared according to method C, 1 mmol, 1 eq.). The reaction was quenched with 2 mL water and 2 mL sat. aq. NH_4Cl. Then the mixture was extracted three times with 10 mL diethyl ether and the combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc/TEA 89:10:1) as a brown solid, 107 mg, 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 9.0 Hz, 2H), 7.65 (m, 1H), 7.19 (d, *J* = 3.4 Hz, 1H), 6.71 (d, *J* = 9.0 Hz, 2H), 6.56 (dd, *J* = 3.4, 1.6 Hz, 1H), 3.08 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.77, 153.49, 153.37, 145.89, 131.99, 124.67, 118.56, 111.88, 110.85, 40.16 ppm. HRMS (ESI+, *m/z*): calcd for $C_{13}H_{14}NO_2$ $[M+H]^+$: 216.1025; found: 216.1020.



(4-(dimethylamino)phenyl)(thiophen-2-yl)methanone (5s): Synthesized using 4-chloro-N,N-dimethylbenzamide (184 mg, 1 mmol, 1 eq.) and 2-thienyllithium (1.00 mL, 1.0 M, 1 mmol, 1 eq.). The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc 90:10 to 50:50) as a green solid, 134 mg, 58% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.9 Hz, 2H), 7.63 (dd, *J* = 6.5, 4.8 Hz, 2H), 7.14 (t, 1H), 6.71 (d, *J* = 8.9 Hz, 2H), 3.08 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.33, 153.36, 144.58, 133.07, 132.34, 131.99, 127.59, 125.47, 110.89, 40.22 ppm. HRMS (ESI+, *m/z*): calcd for $C_{13}H_{14}NOS$ $[M+H]^+$: 232.0796; found: 232.0790.
Spectral data are in agreement with those reported in the literature.[12]



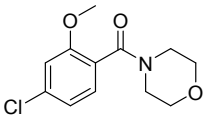
(4-(dimethylamino)phenyl)(2-(methoxymethoxy)phenyl)methanone (5t): Synthesized using 4-chloro-N,N-dimethylbenzamide (184 mg, 1 mmol, 1 eq.) and 2-methoxymethoxy-phenyllithium (prepared according to method B, 1 mmol, 1 eq.). The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc 90:10) as a yellow oil, 77 mg, 27% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 9.0 Hz, 2H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.65 (d, *J* = 8.9 Hz, 2H), 5.10 (s, 2H), 3.35 (s, 3H), 3.06 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.52, 154.45, 153.57, 132.53, 131.35, 130.76, 129.02, 125.83, 121.83, 115.41, 110.80, 94.87, 56.29, 40.30 ppm. HRMS (ESI+, *m/z*): calcd for $C_{17}H_{20}NO_3$ $[M+H]^+$: 286.1443; found: 286.1439.



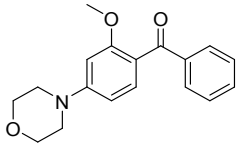
[12] Schmink, J. R.; Krska, S. W. *J. Am. Chem. Soc.*, **2011**, 133, 19574–19577.

(4-(dimethylamino)phenyl)(o-tolyl)methanone (5u): Synthesized using 4-chloro-N,N-dimethylbenzamide (184 mg, 1 mmol, 1 eq.) and 2-tolyllithium (prepared according to method A, 1 mmol, 1 eq.). The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc 95:5 to 90:10) as a yellow oil, 63 mg, 26% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 9.0 Hz, 2H), 7.37 – 7.18 (m, 4H), 6.66 (d, *J* = 9.0 Hz, 2H), 3.07 (s, 6H), 2.29 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.07, 153.63, 140.28, 135.86, 132.65, 130.69, 129.30, 127.71, 125.57, 125.22, 110.88, 40.27, 19.80 ppm. HRMS (ESI+, *m/z*): calcd for $C_{16}H_{18}NO$ $[M+H]^+$: 240.1388; found: 240.1385.

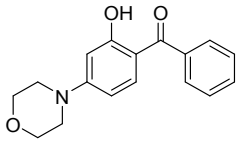
Procedures for the synthesis of AMA37



(4-chloro-2-methoxyphenyl)(morpholino)methanone (6): A solution of 4-chloro-2-methoxybenzoic acid (1 g, 5.4 mmol, 1 eq.) in 25 mL DCM was cooled down to 0°C. $SOCl_2$ (1.2 mL, 16 mmol, 3 eq.) was added slowly over the course of 10 min, after which the mixture was allowed to reach room temperature and stirred overnight. The mixture was concentrated under reduced pressure to remove the excess of $SOCl_2$. The residue was dissolved in 20 mL DCM and a solution of morpholine (1 mL, 11 mmol, 2 eq.) and triethylamine (3.5 mL, 25 mmol, 5 eq.) in 10 mL DCM was added dropwise at 0°C and stirred 3h at room temperature. The reaction was quenched by addition of 20 mL H_2O and the mixture was then extracted with 3x25 mL DCM. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc from 90:10 to 50:50), after which the product (**6**) was obtained as a yellow solid (1.28 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.0 Hz, 1H), 6.99 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.91 (d, *J* = 1.5 Hz, 1H), 3.84 (s, 3H), 3.77 (m, 4H), 3.66 – 3.52 (m, 2H), 3.30 – 3.17 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.01, 156.13, 136.36, 129.24, 123.98, 121.39, 111.93, 67.06, 66.96, 56.02, 47.44, 42.35 ppm. HRMS (ESI+, *m/z*): calcd for $C_{12}H_{15}ClNO_3$ $[M+H]^+$: 256.0740; found: 256.0743.



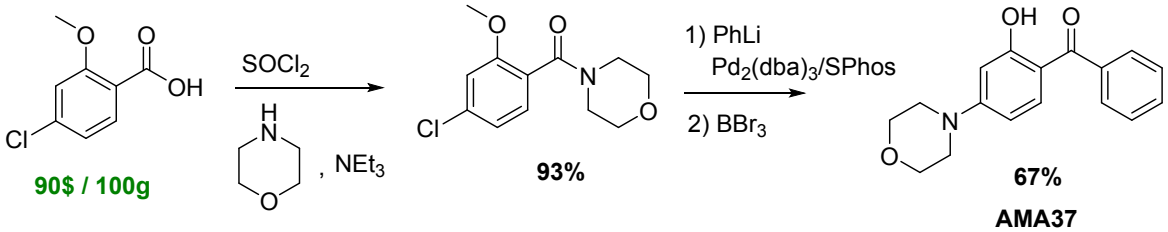
(2-methoxy-4-morpholinophenyl)(phenyl)methanone (7) : A solution of (4-chloro-2-methoxyphenyl)(morpholino)methanone (**6**) (128 mg, 0.5 mmol, 1 eq.) in 0.7 mL dry THF was cooled down to 0 °C, after which phenyllithium (0.26 mL, 1.9 M, 0.5 mmol, 1 eq.) was added dropwise over the course of 15 min. The resulting mixture was stirred for 1 h at 0 °C and then allowed to reach room temperature. A suspension of $Pd_2(dba)_3$ (2.5 mol%, 0.012 mmol, 11 mg) and SPhos (5.0 mol%, 0.025 mmol, 10 mg) in 0.1 mL dry THF was added. The mixture was heated under reflux and stirred for 2 h. The reaction was quenched with 2 mL sat. aq. NH_4Cl followed by 2 mL aq. sol. HCl (1M). Then the mixture was extracted with 3x10 mL of ethyl acetate and the combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The title compound was obtained after column chromatography (SiO_2, pentane/EtOAc from 90/10 to 10/90) as a yellow solid (135 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.5 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.46 – 7.36 (m, 3H), 6.52 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.44 (s, 1H), 3.88 (d, *J* = 4.9 Hz, 4H), 3.71 (s, 3H), 3.30 (t, *J* = 4.9 Hz, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ δ 195.38, 159.96, 154.95, 139.44, 132.67, 132.05, 129.62, 127.96, 119.62, 106.47, 98.03, 66.71, 55.55, 48.25. HRMS (ESI+, *m/z*): calcd for $C_{18}H_{20}NO_3$ $[M+H]^+$: 298.1443; found: 298.1446.



1-(2-Hydroxy-4-morpholin-4-yl-phenyl)-phenyl-methanone (8) : To a solution of (2-methoxy-4-morpholinophenyl)(phenyl)methanone (**7**) (21.5 mg, 0.072 mmol, 1 eq.) in 1 mL of DCM was added dropwise at 0°C a solution of BBr_3 (22µL, 0.22 mmol, 3 eq) in 0.2 mL of DCM**.** The reaction mixture was stirred for 2h at room temperature and then quenched with 2 mL sat. aq. $NaHCO_3$, diluted with 20 mL H_2O and extracted with 3x25 mL DCM. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude compound was purified by column chromatography (SiO_2, pentane/EtOAc 90:10), after which the product (**8**) was obtained as a yellow solid (15.1 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.0 Hz, 2H), 7.58 – 7.40 (m, 4H), 6.38 (d, *J* = 2.3 Hz, 1H), 6.33 (dd, *J* = 9.1, 2.4 Hz, 1H), 3.83 (m, 4H), 3.36 (m, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.58, 168.58, 159.08, 141.24, 137.89, 133.77, 131.42, 130.87, 113.80, 107.73, 103.04, 69.10, 49.55.

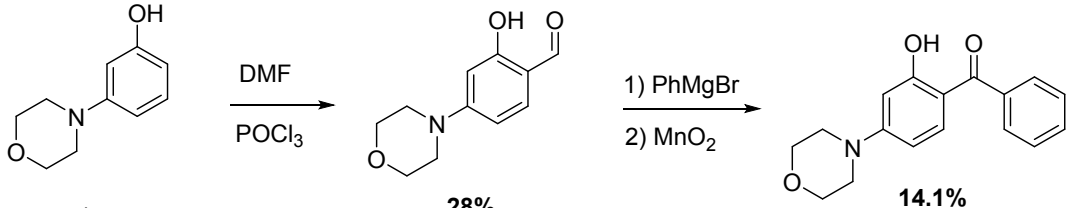
Comparison with the previously reported synthetic route

Our route for AMA37



Overall yield : 63%

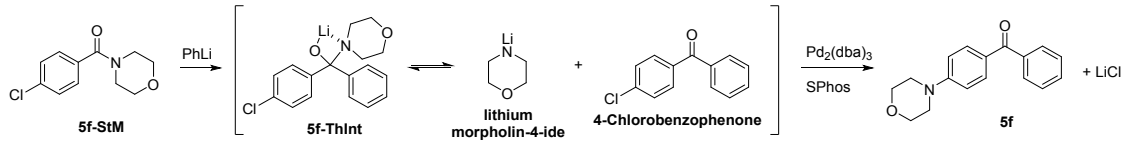
Previously reported synthesis for AMA37[13]

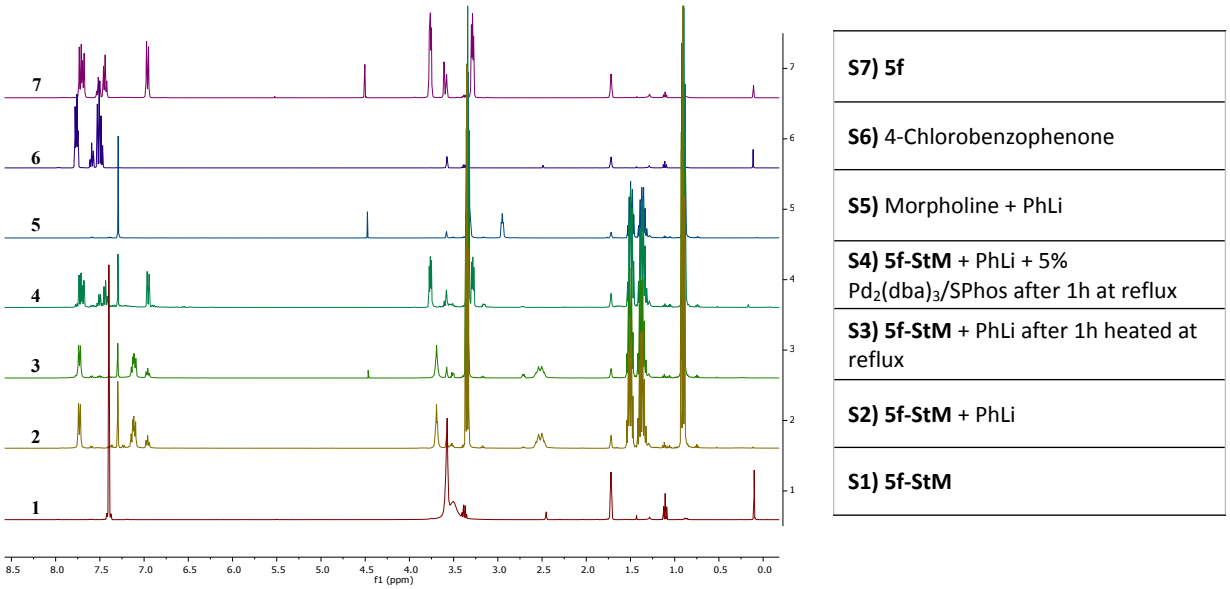


Overall yield : 4%

[13] Knight, Z. A.; Chiang, G. G.; Alaimo, P. J.; Kenski, D. M.; Ho, C. B.; Coan, K.; Abraham, R. T.; Shokat, K. M. *Bioorg. Med. Chem.* **2004**, 12 *(17)*, 4749–4759.

^{1}H-NMR study of the reaction with (4-chlorophenyl)(morpholino)methanone





S7) 5f
S6) 4-Chlorobenzophenone
S5) Morpholine + PhLi
S4) 5f-StM + PhLi + 5% $Pd_2(dba)_3$/SPhos after 1h at reflux
S3) 5f-StM + PhLi after 1h heated at reflux
S2) 5f-StM + PhLi
S1) 5f-StM

Figure 1 : ^{1}H-NMR analysis of the of the reactivity of (4-chlorophenyl)(morpholino)methanone

Note : 0.1 mmol in 0.7 mL of THF-d_8, solvent signal at 1.72 ppm used as a reference. Benzene signal (originating from commercially available phenyllithium) at 7.30 ppm.

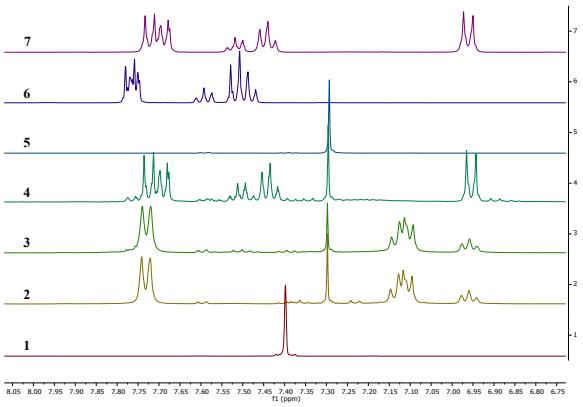


Figure 2: ^{1}H-NMR Expanded region from 6.75 ppm to 8 ppm

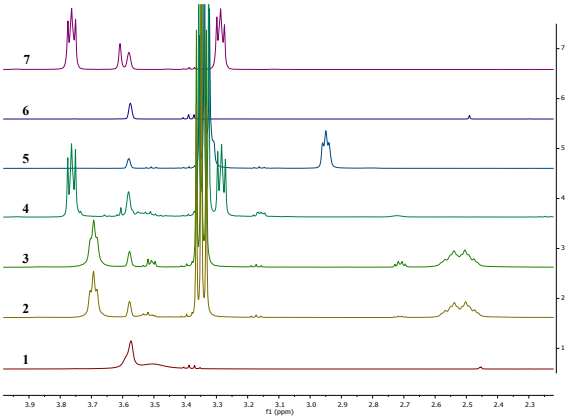
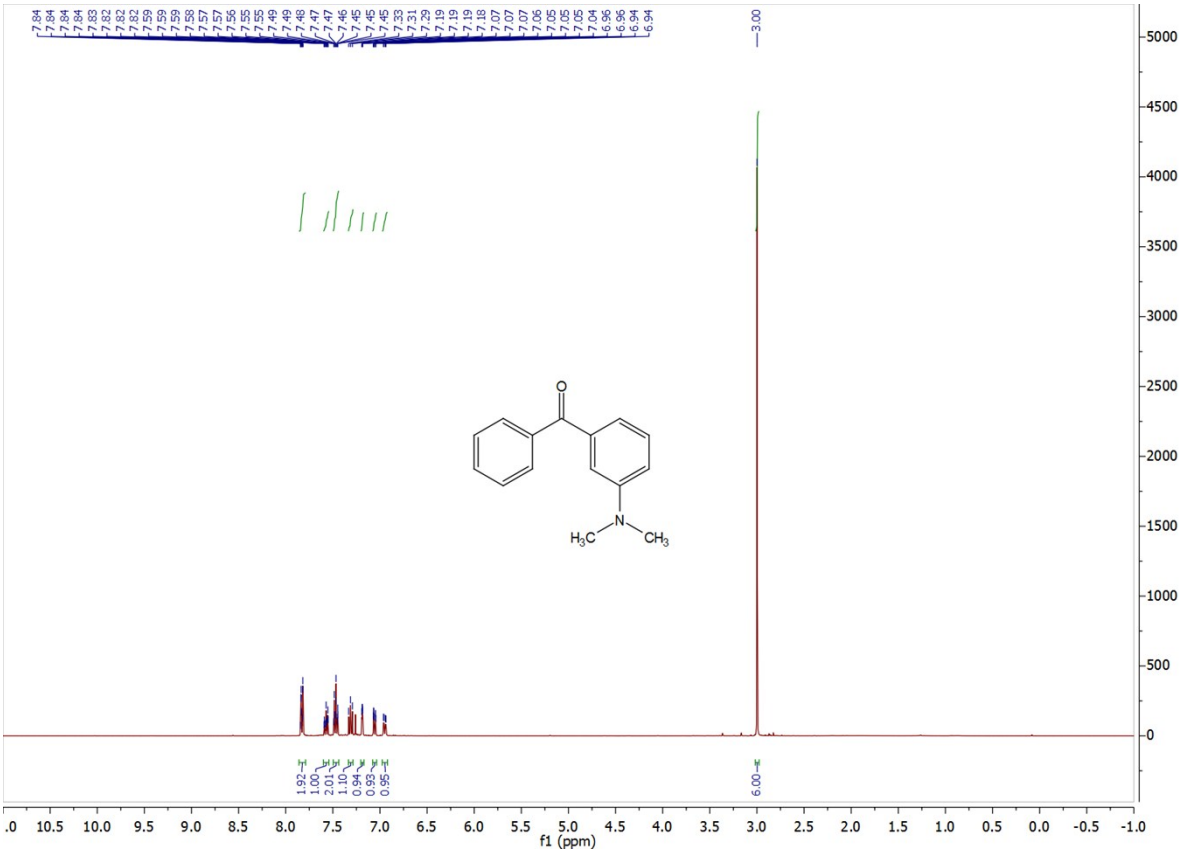
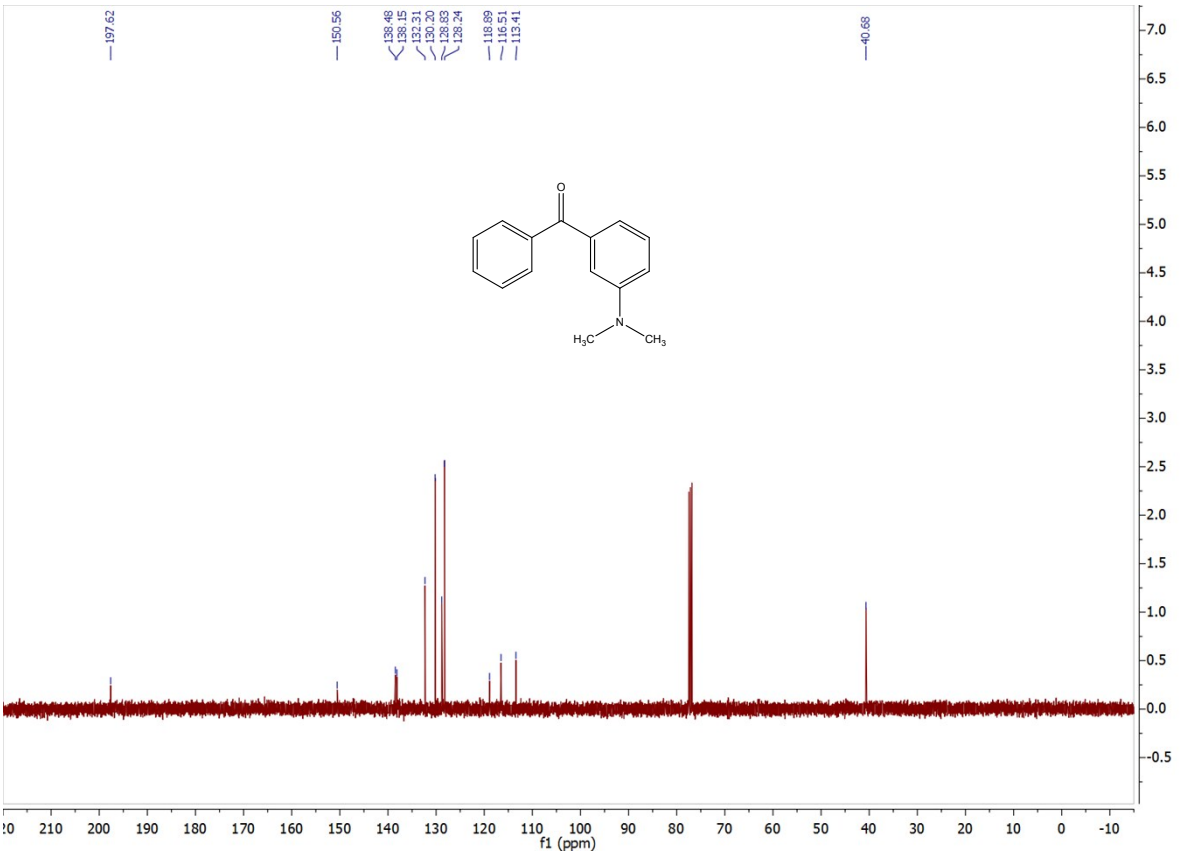


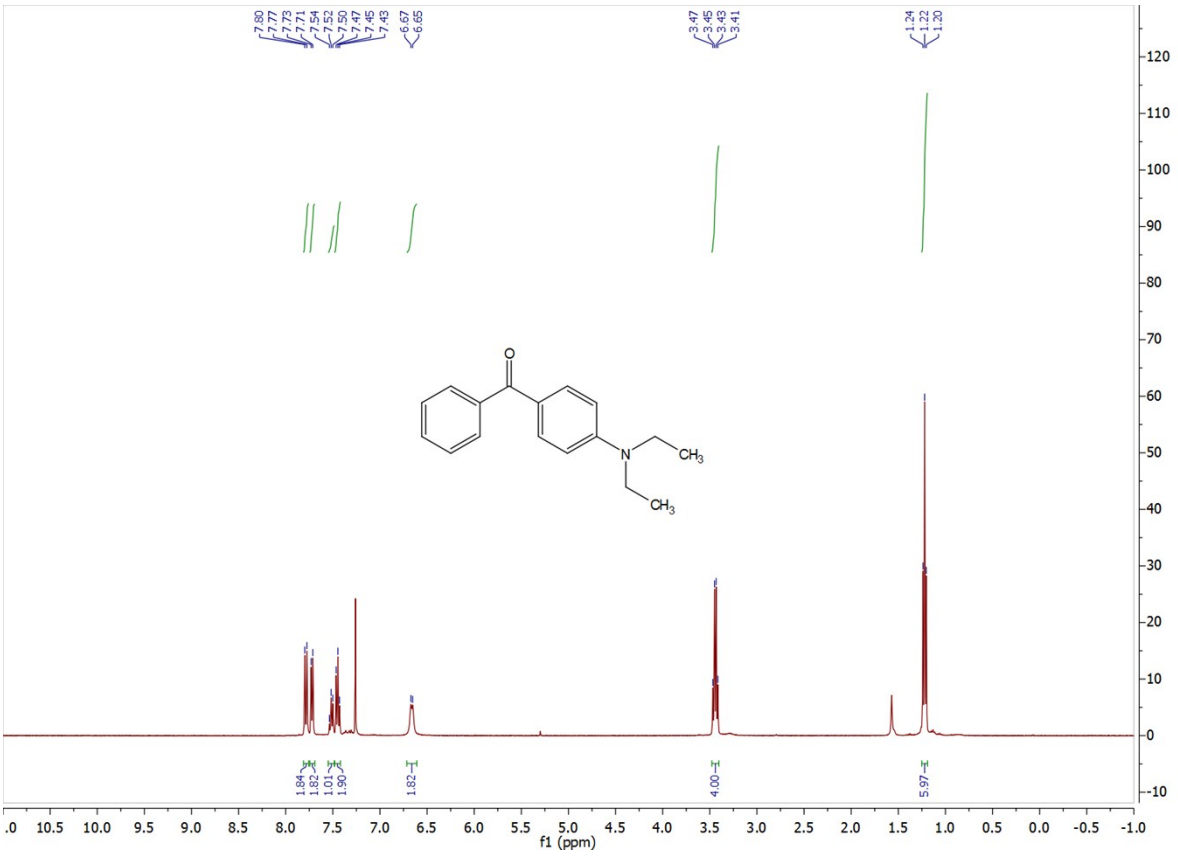
Figure 3: ^{1}H-NMR Expanded region from 2.2 ppm to 4.0 ppm

15 min. after the addition of 1 eq. of PhLi to (4-chlorophenyl)(morpholino)methanone (**5f-StM**) a new set of signals appears (δ 7.73 (d, *J* = 8.0 Hz, 4H), 7.12 (m, 4H), 6.96 (t, *J* = 7.0 Hz, 1H), 3.69 (t, *J* = 4.7 Hz, 4H), 2.62 – 2.45 (m, 4H)), indicating the complete consumption of the starting amide **5f-StM** (spectrum 1) to form a reaction intermediate (**5f-ThInt**). The equilibrium between the tetrahedral intermediate (**5f-ThInt**) and its products of 1,2-elimination (lithium morpholin-4-ide and 4-chlorobenzophenone) appears to be completely in favor of **5f-ThInt** as none of the characteristic signals of lithium morpholin-4-ide (spectrum 5) or of 4-chlorobenzophenone (spectrum 6) are observed. As shown in spectrum 3 the intermediate is stable when heated under reflux without catalyst. When **5f-ThInt** is heated at reflux for 1h in presence of 5% $Pd_2(dba)_3$/SPhos (spectrum 4), the signals are shifting to match with the set expected for the desired aminated product **5f** (spectrum 7).

^{1}H and ^{13}C-NMR spectra of isolated compounds



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3.45
3.43
3.41
1.24
1.22
1.20
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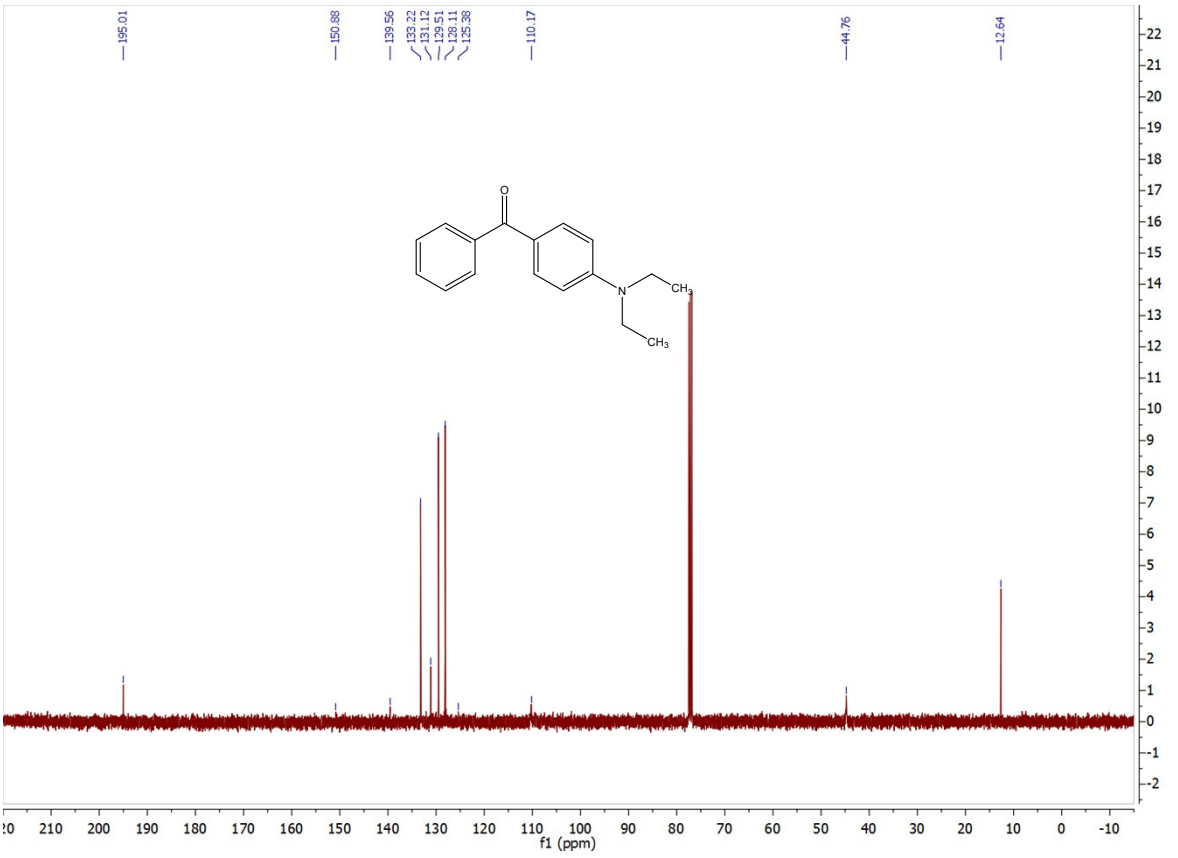
CH3
CH3
1.84
1.82
1.01
1.90
1.82
4.00
5.97
f1 (ppm)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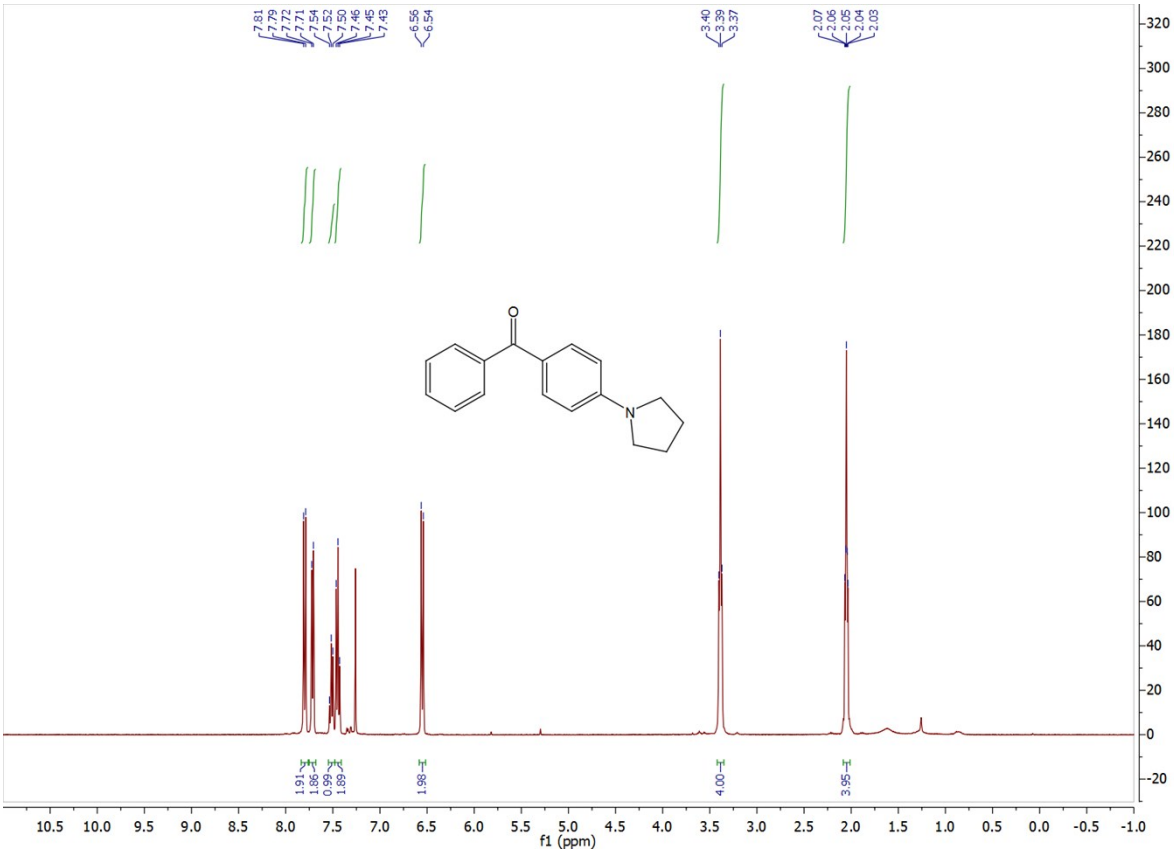
CH3
CH3
f1 (ppm)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3.39
3.37
2.07
2.06
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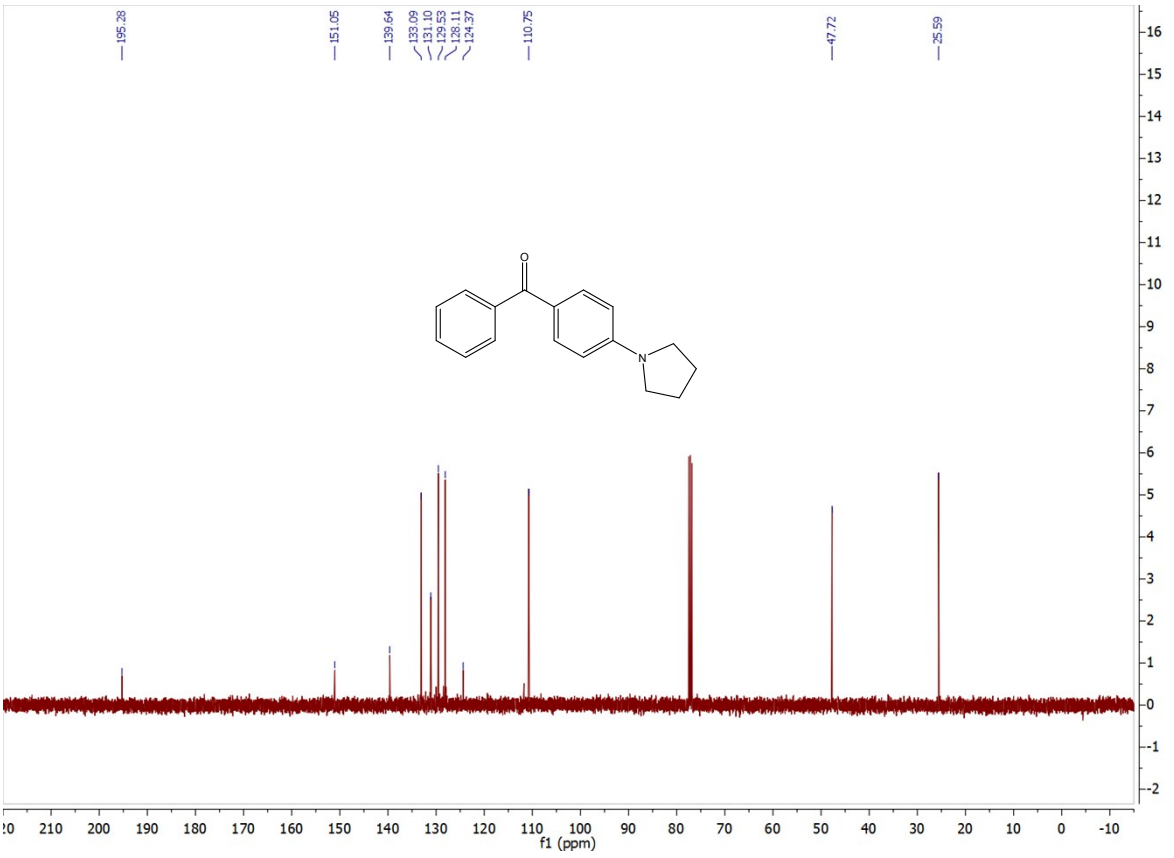
f1 (ppm)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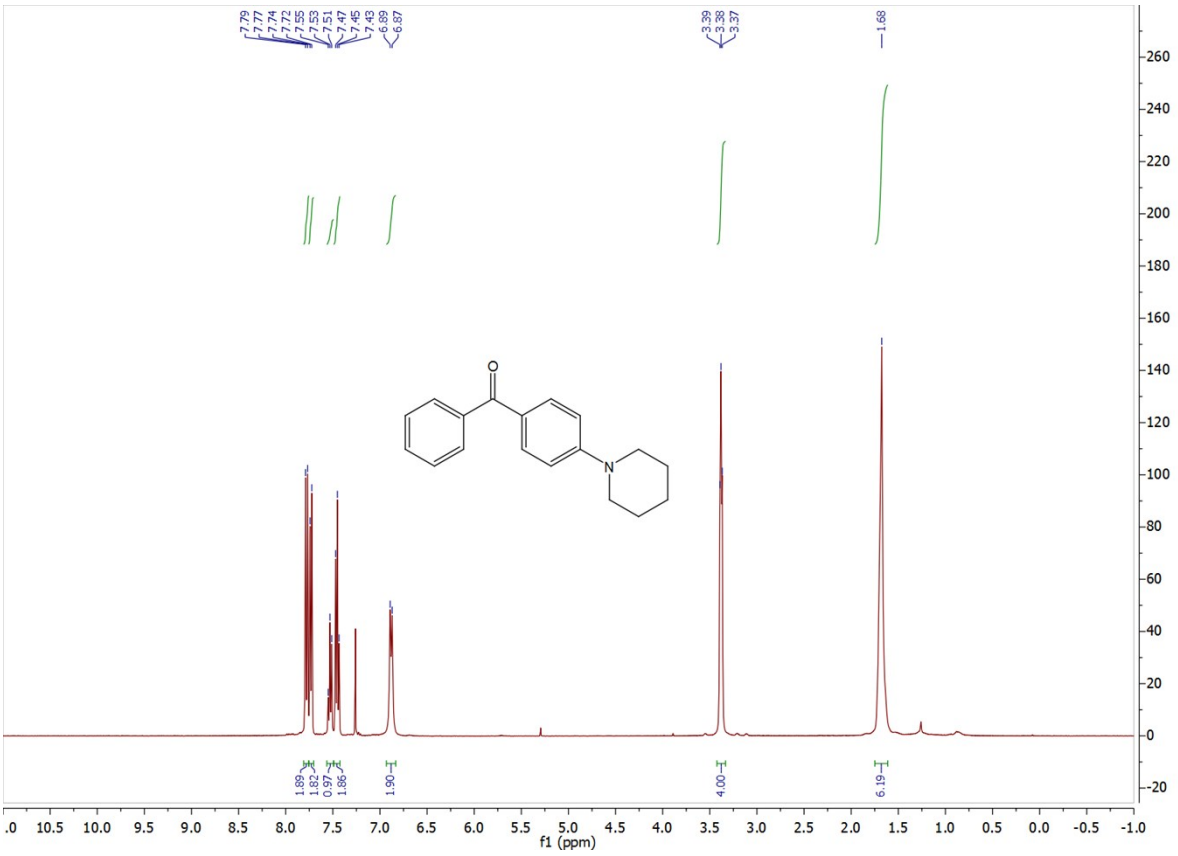
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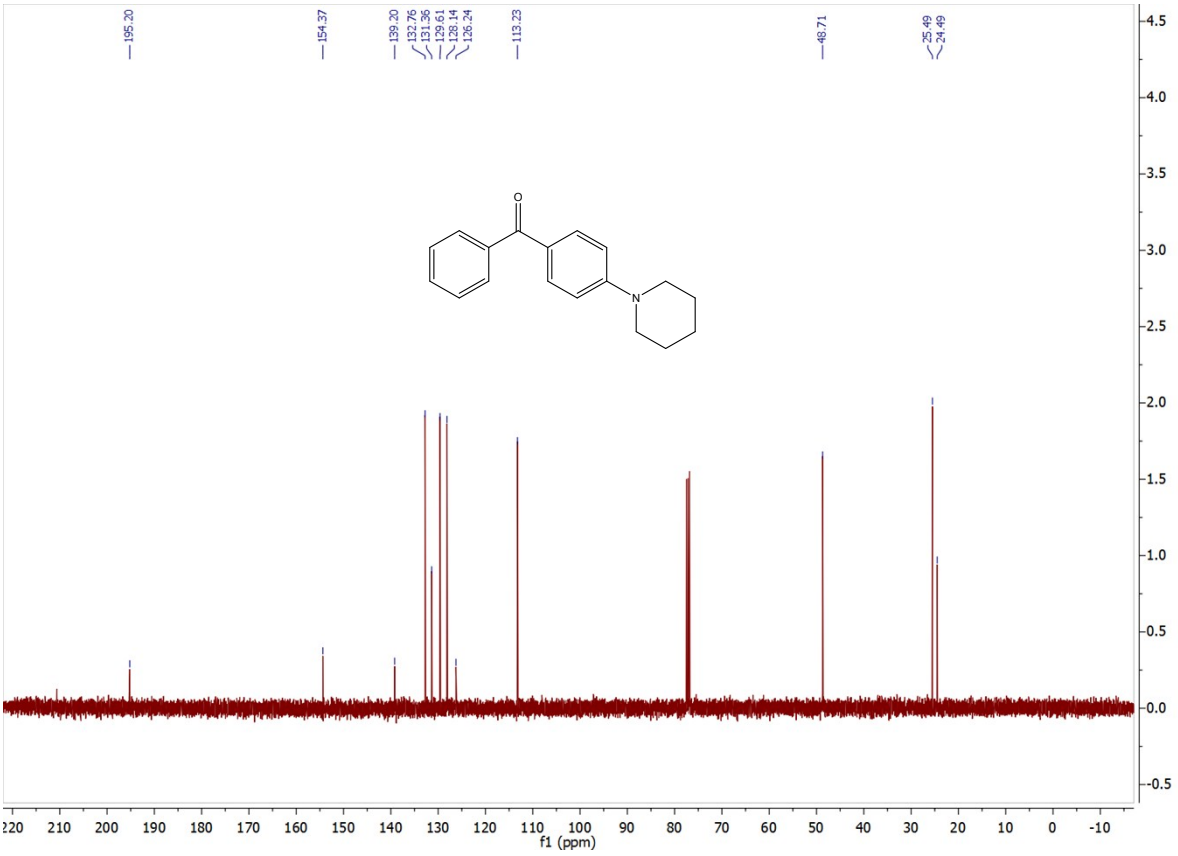
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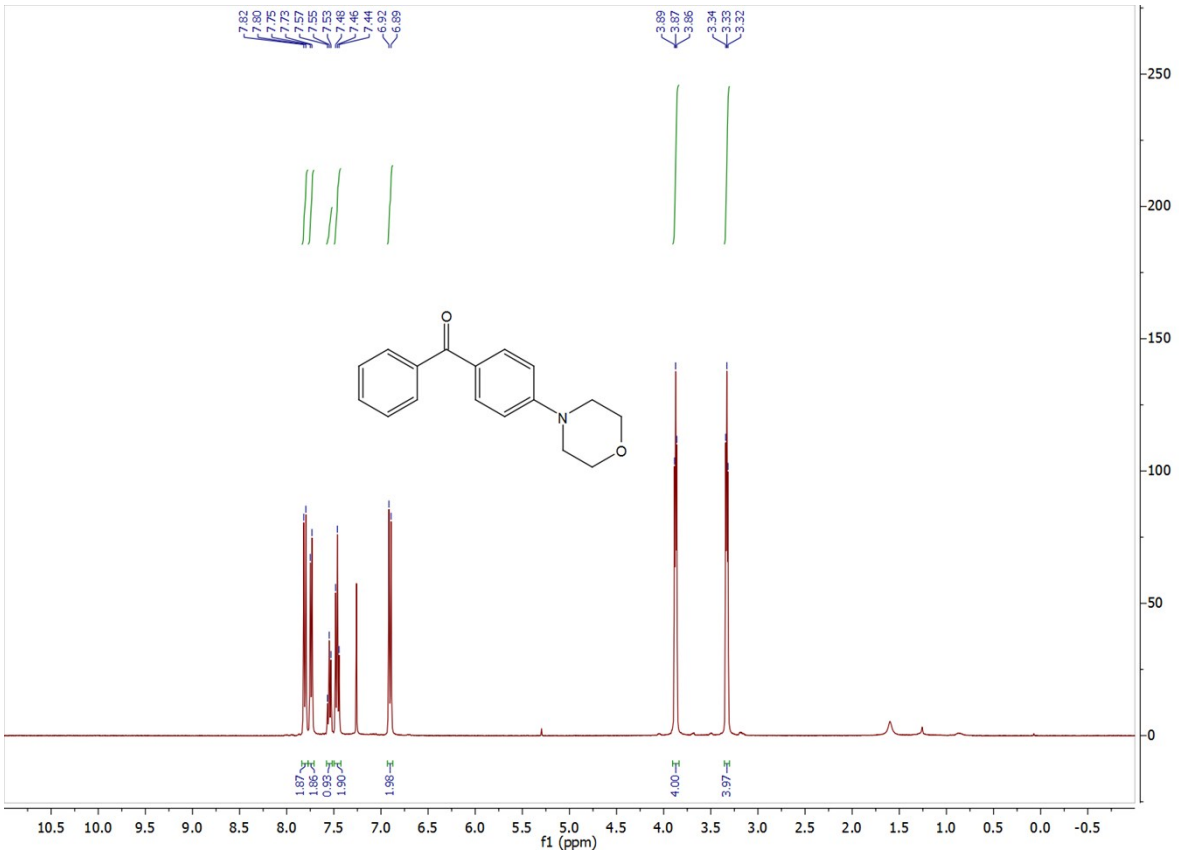
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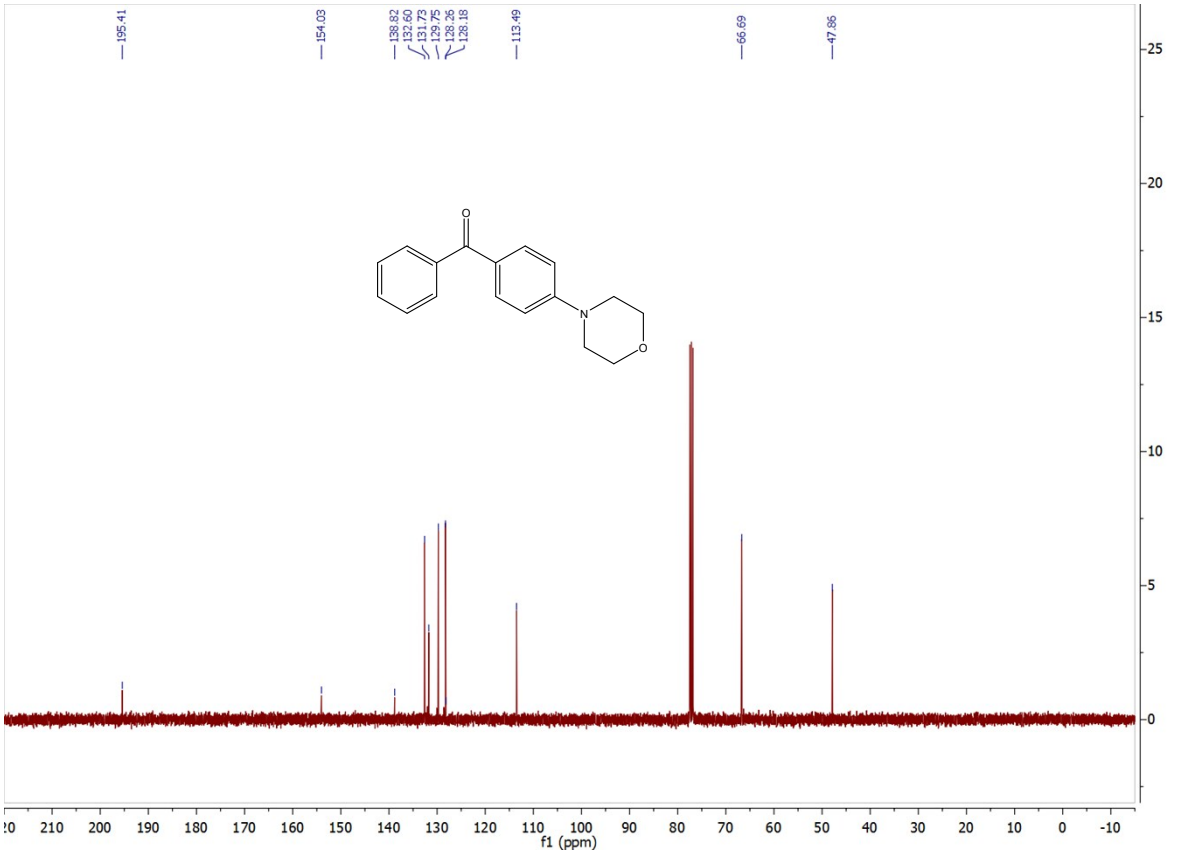
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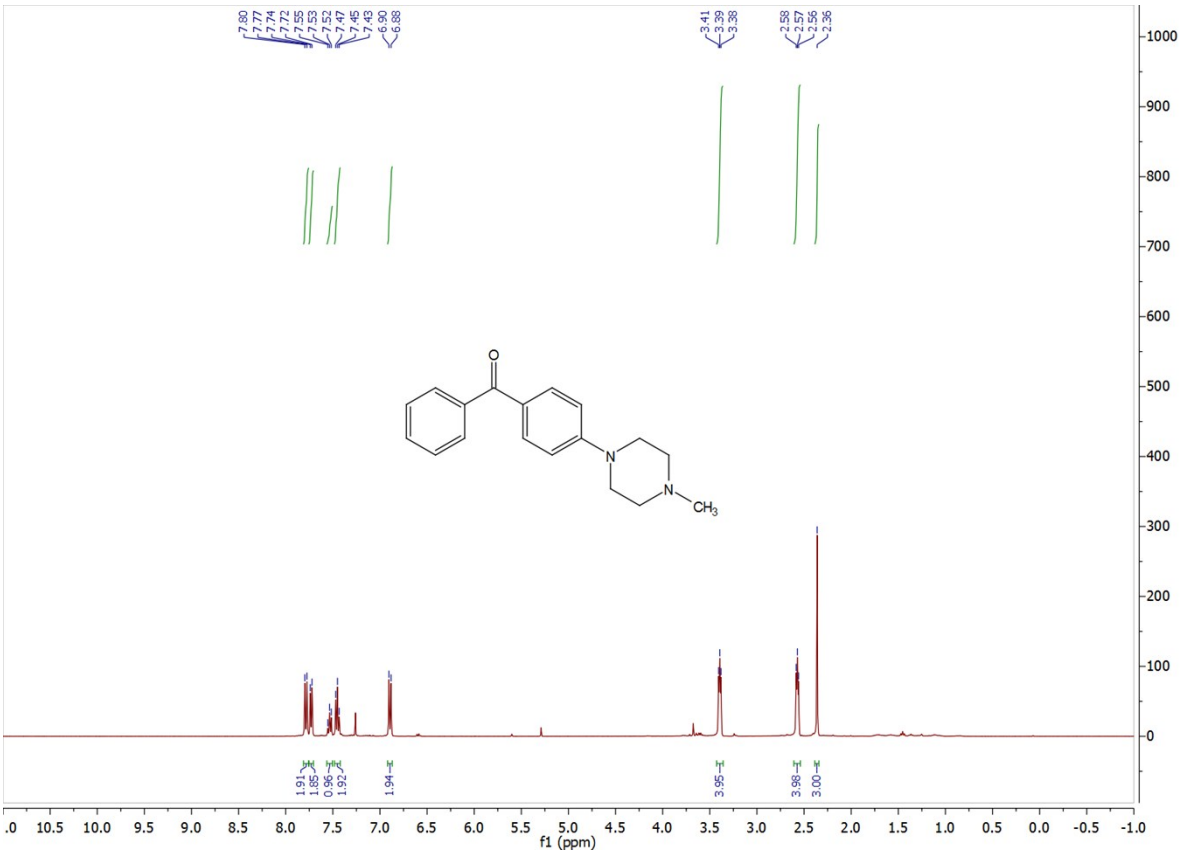
N
O
f1 (ppm)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3.38
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2.57
2.56
2.36
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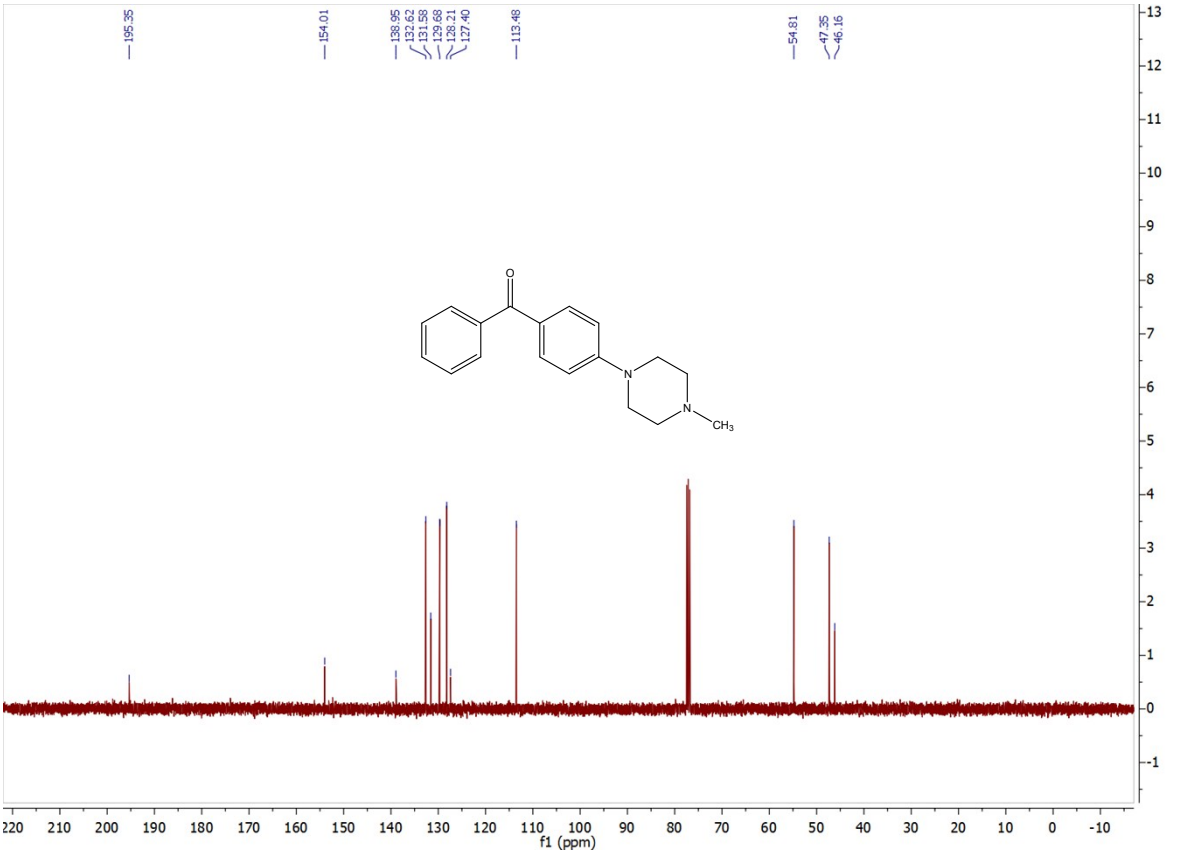
f1 (ppm)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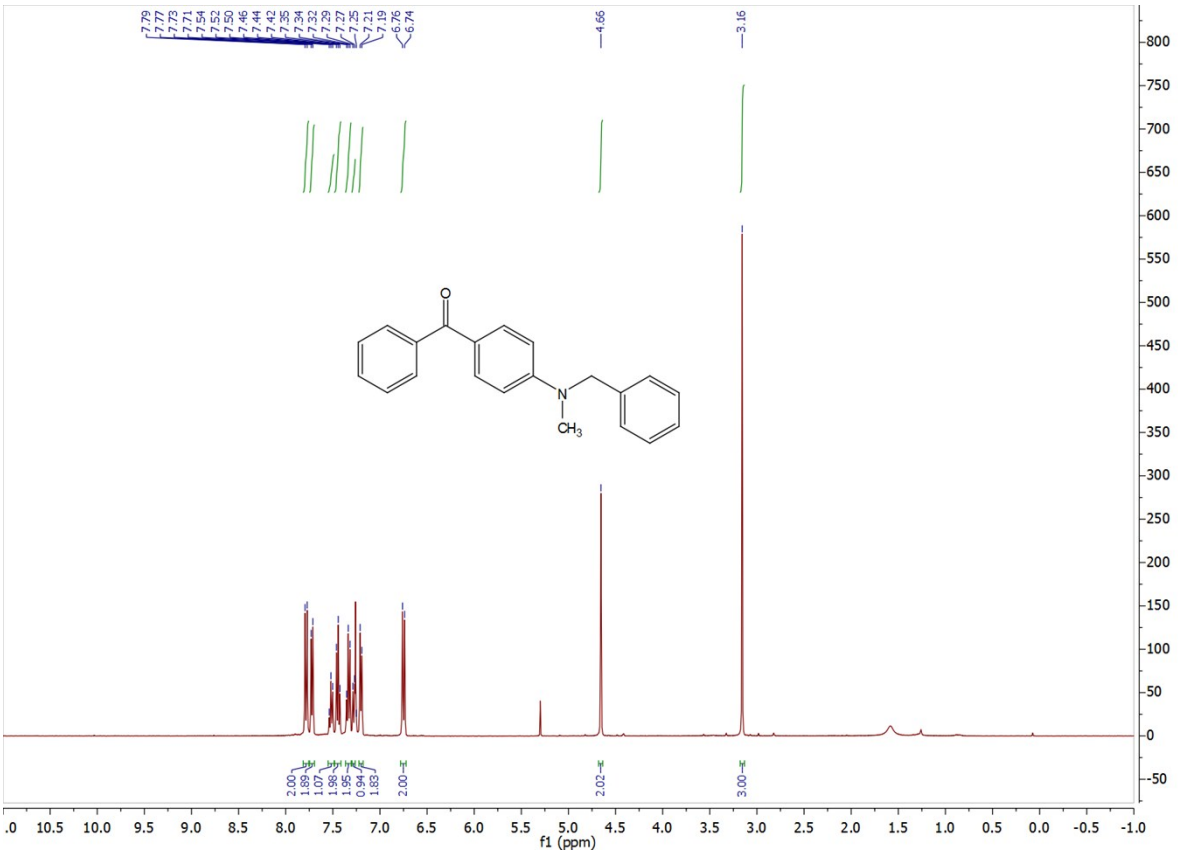
CH3
f1 (ppm)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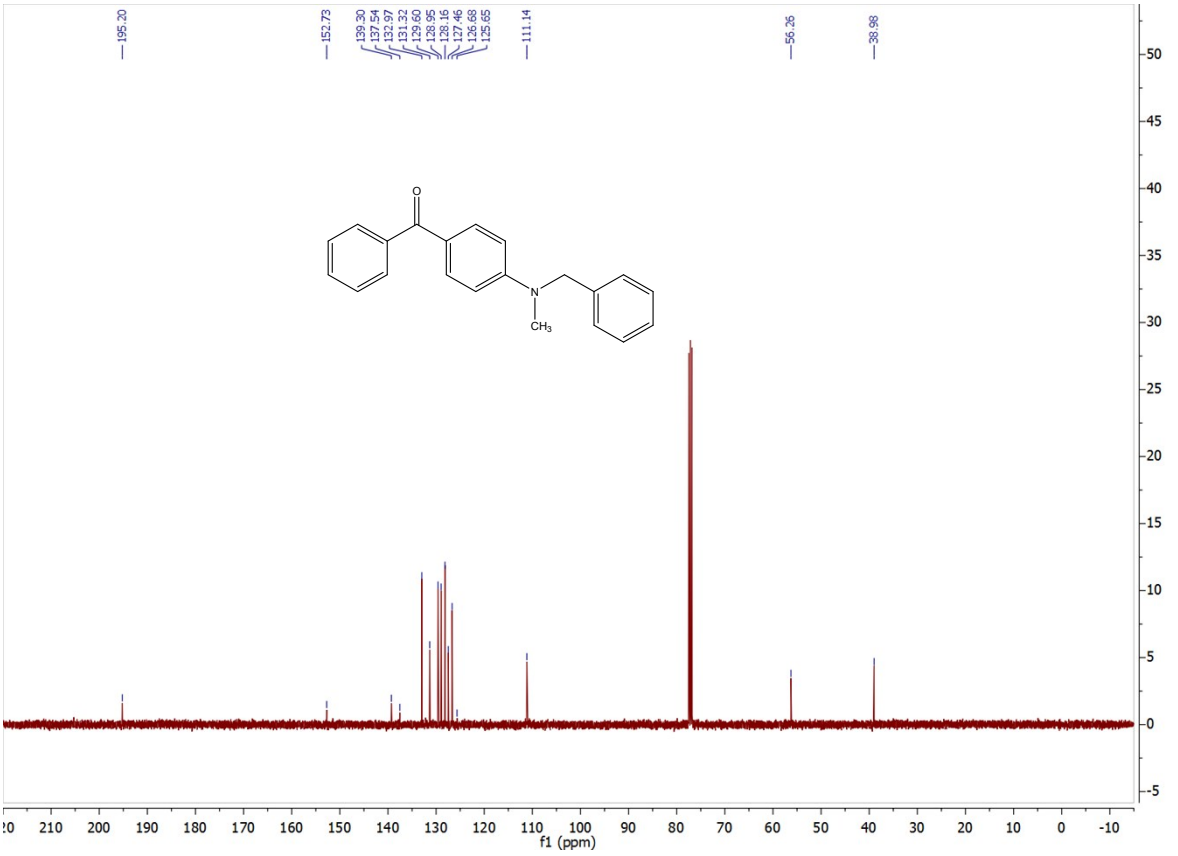
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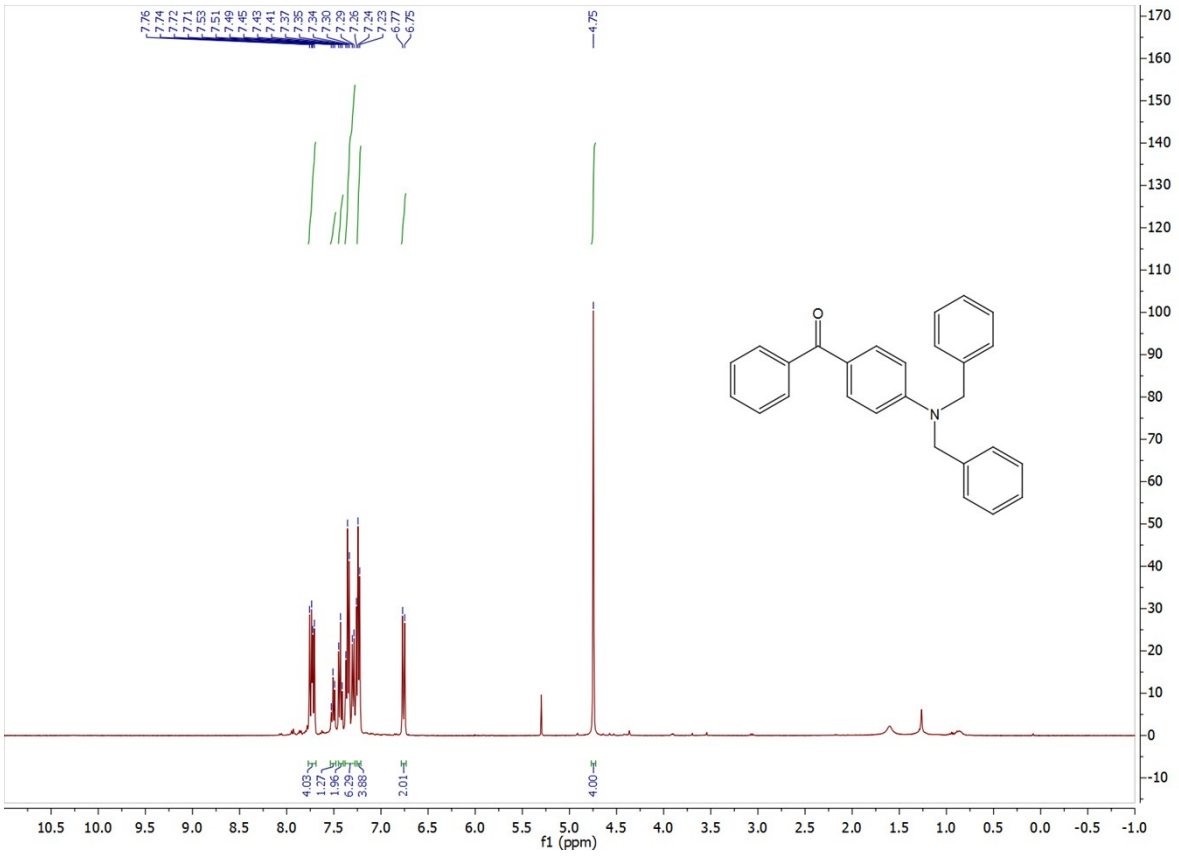
N
CH3
f1 (ppm)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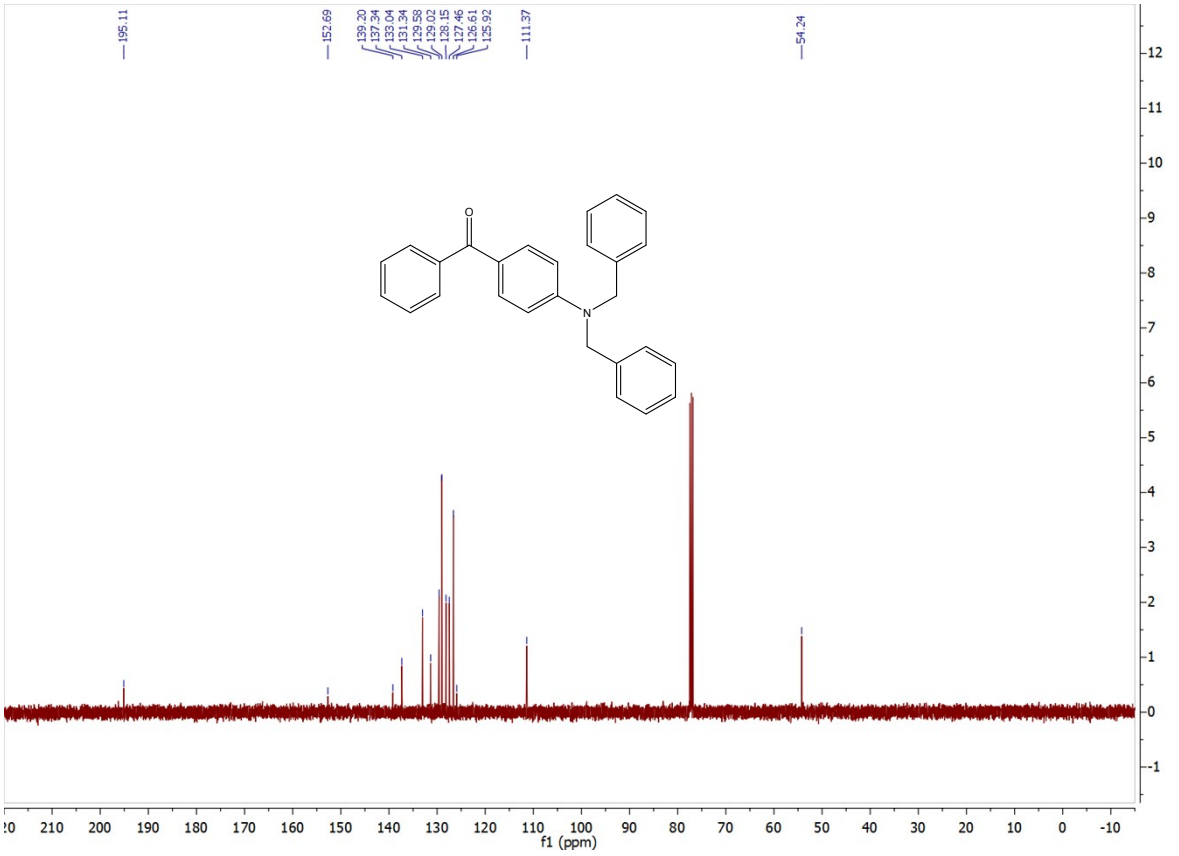
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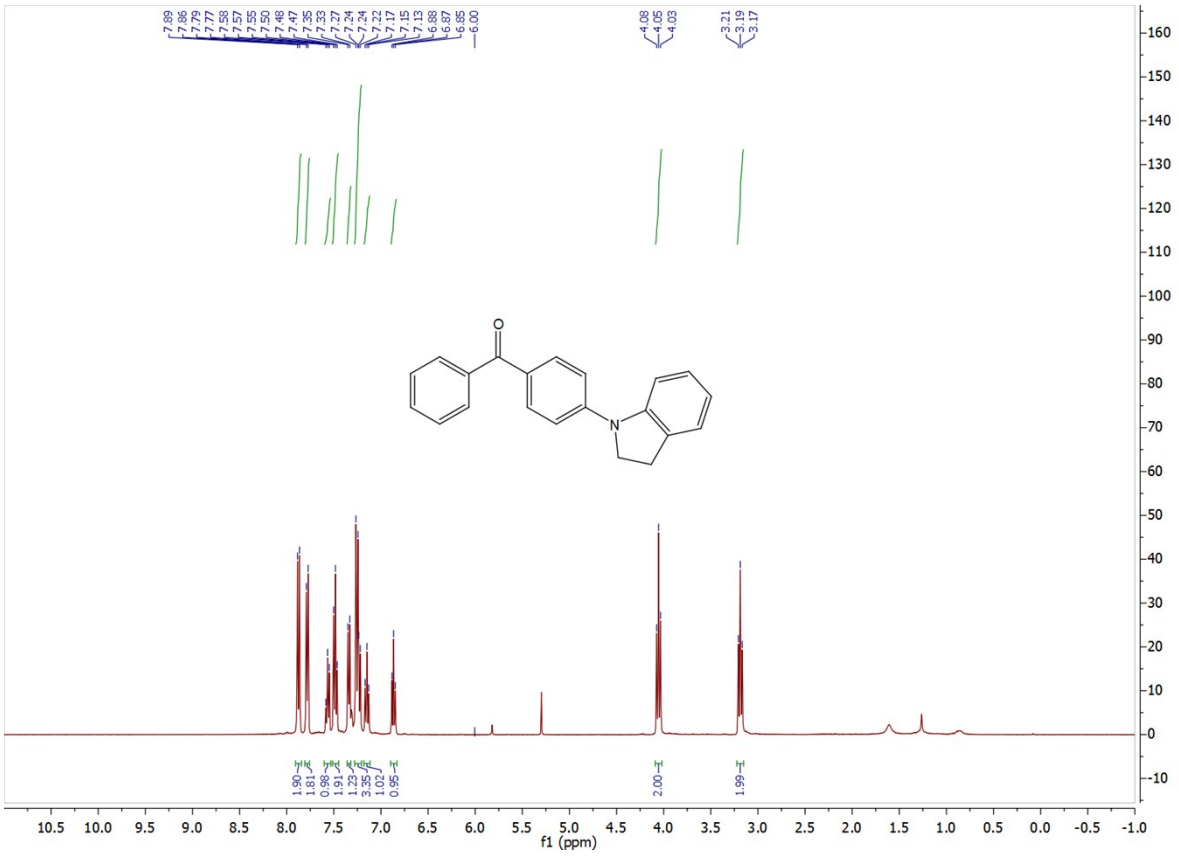
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4.05
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3.19
3.17
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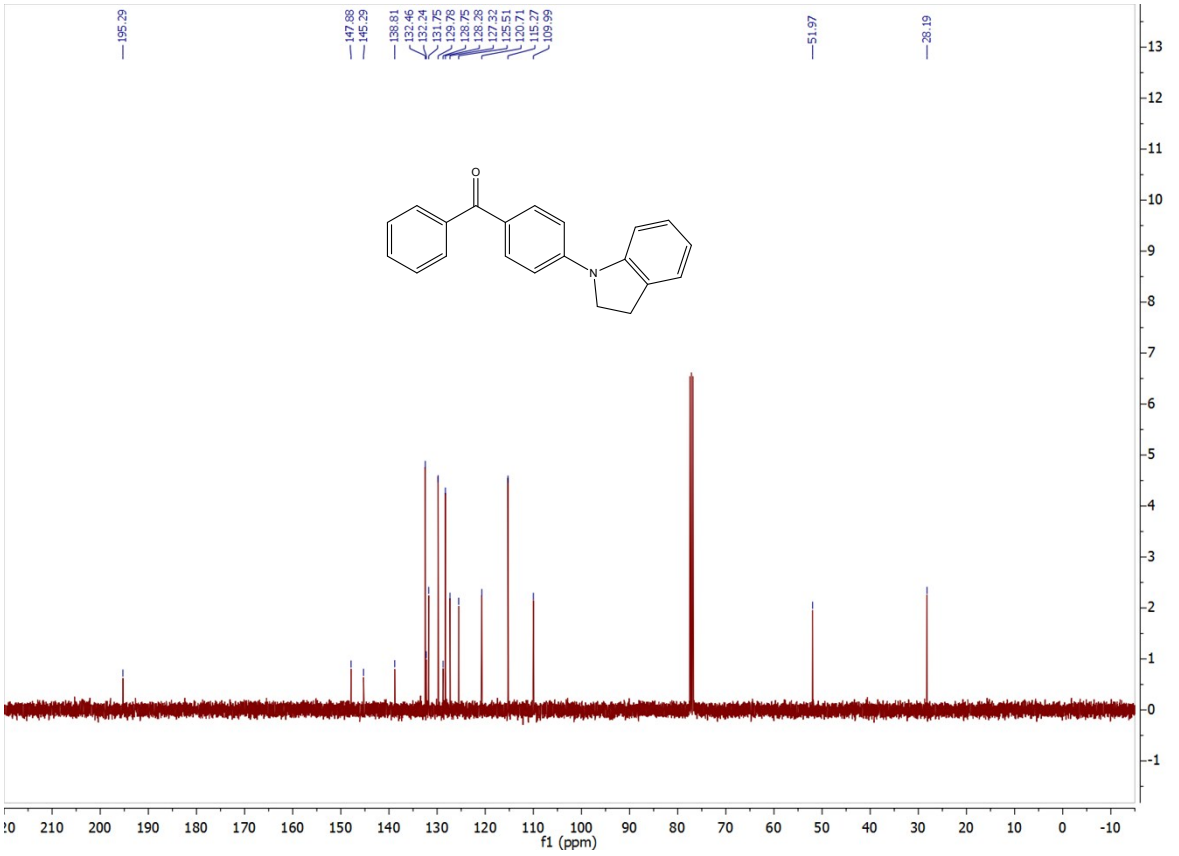
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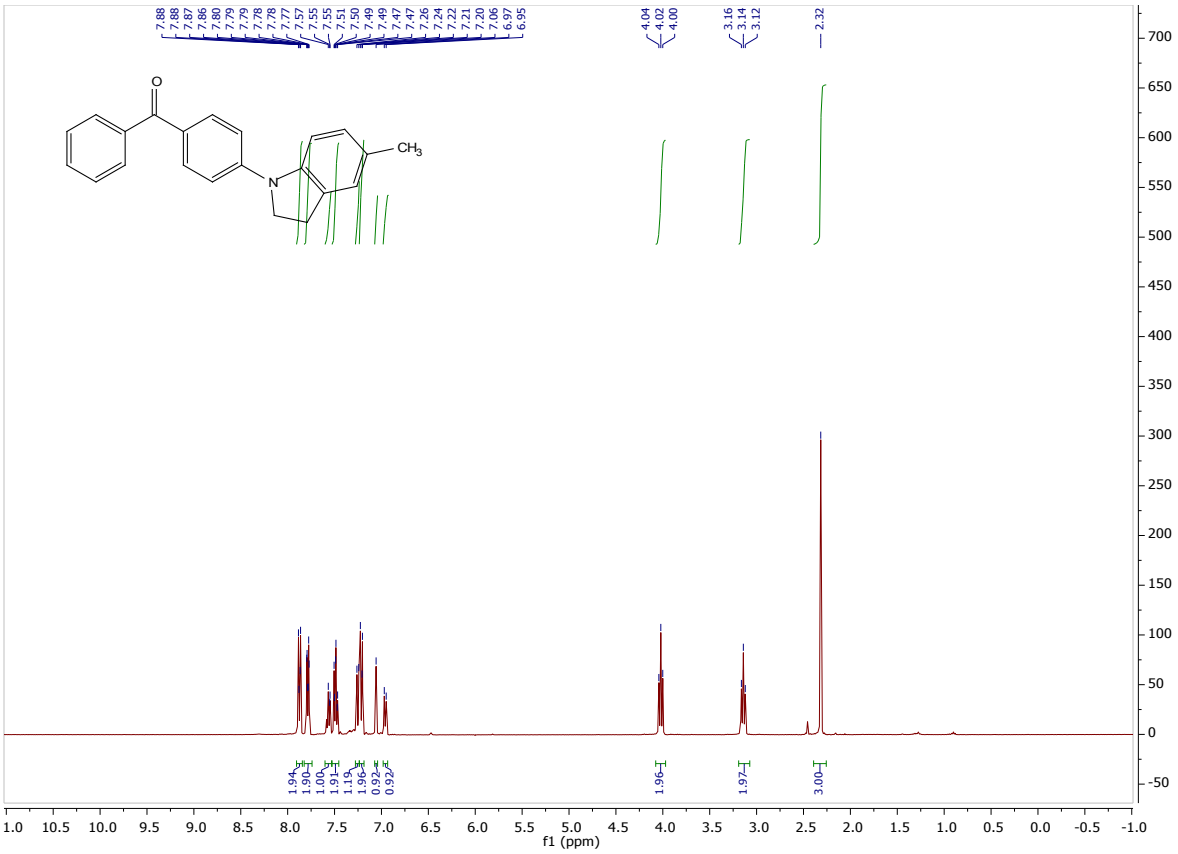
f1 (ppm)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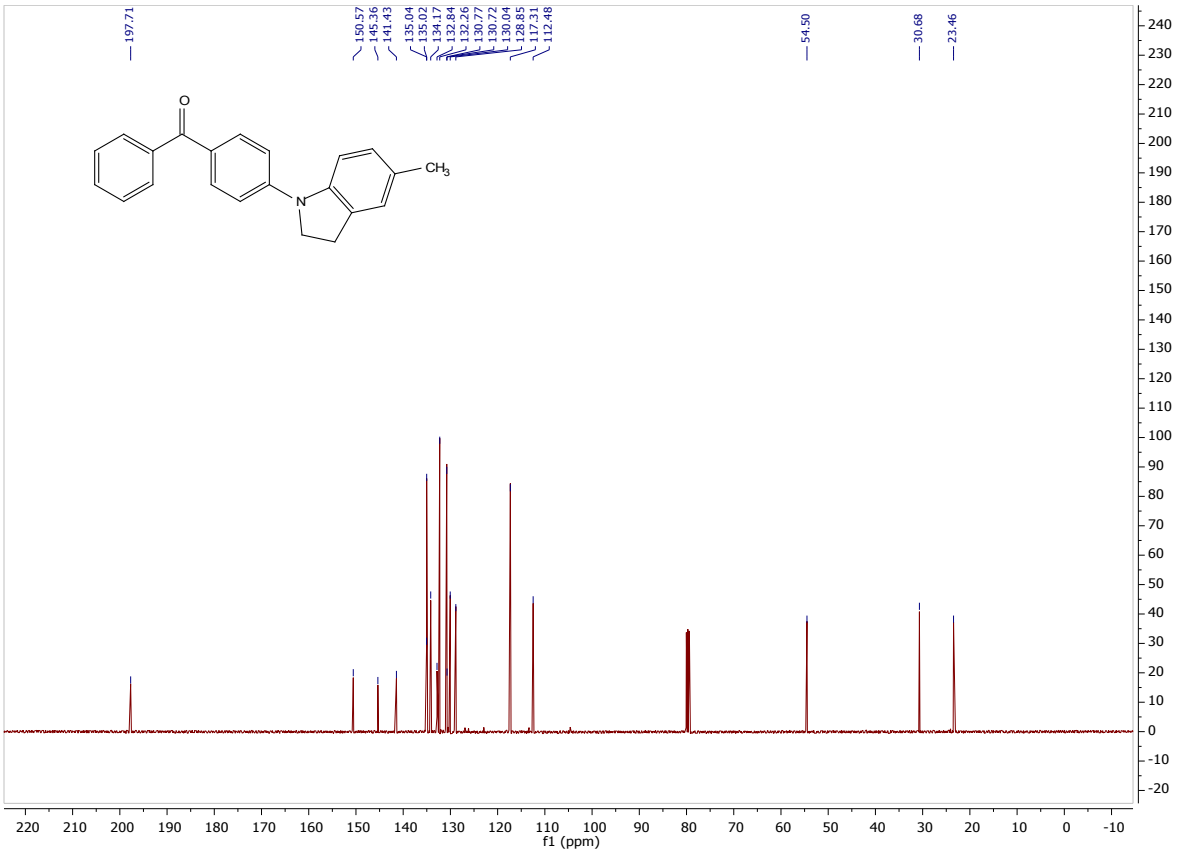
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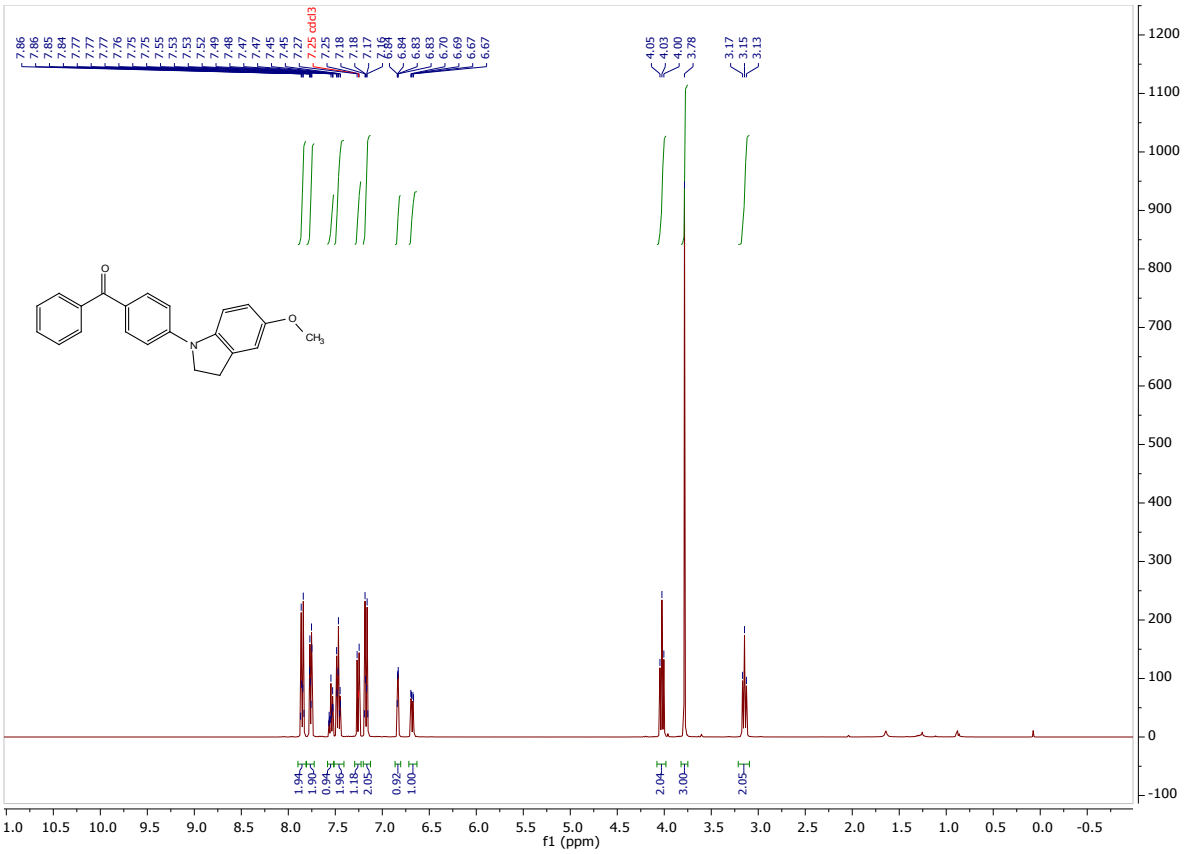
f1 (ppm)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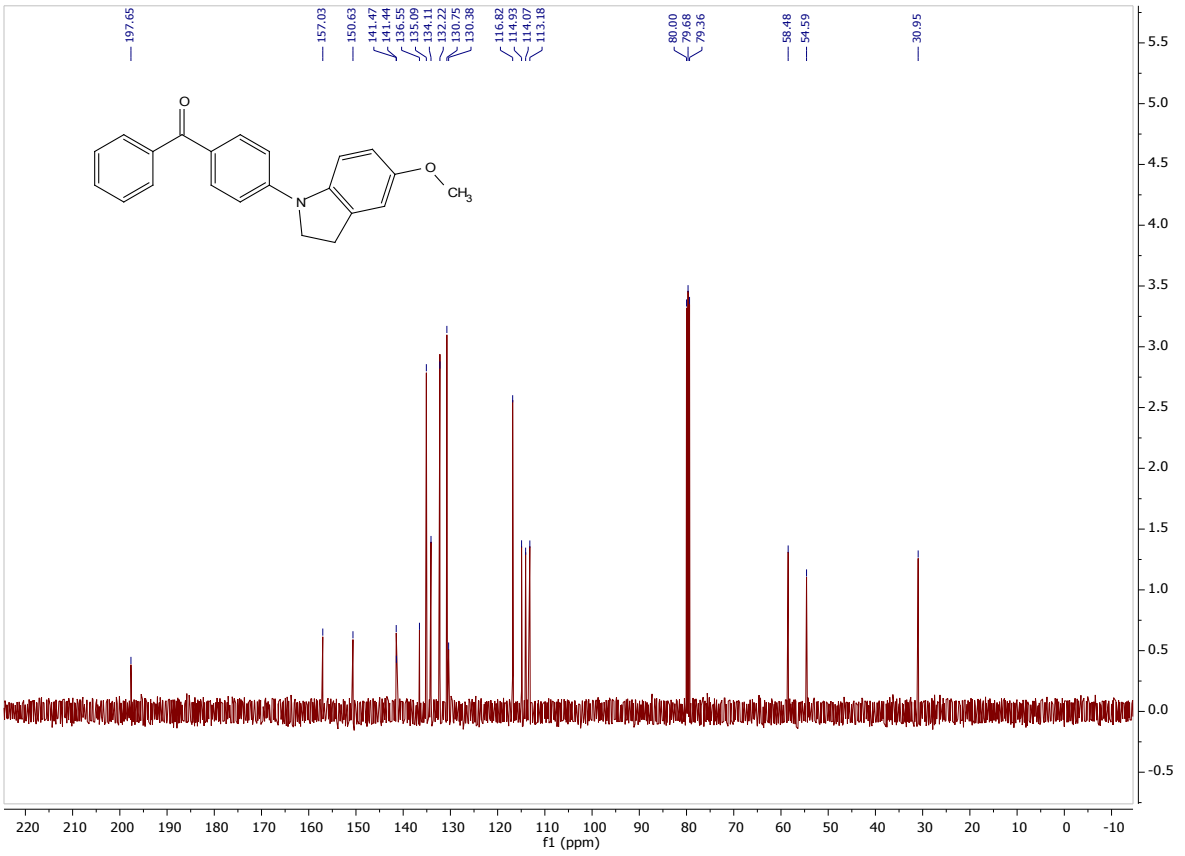
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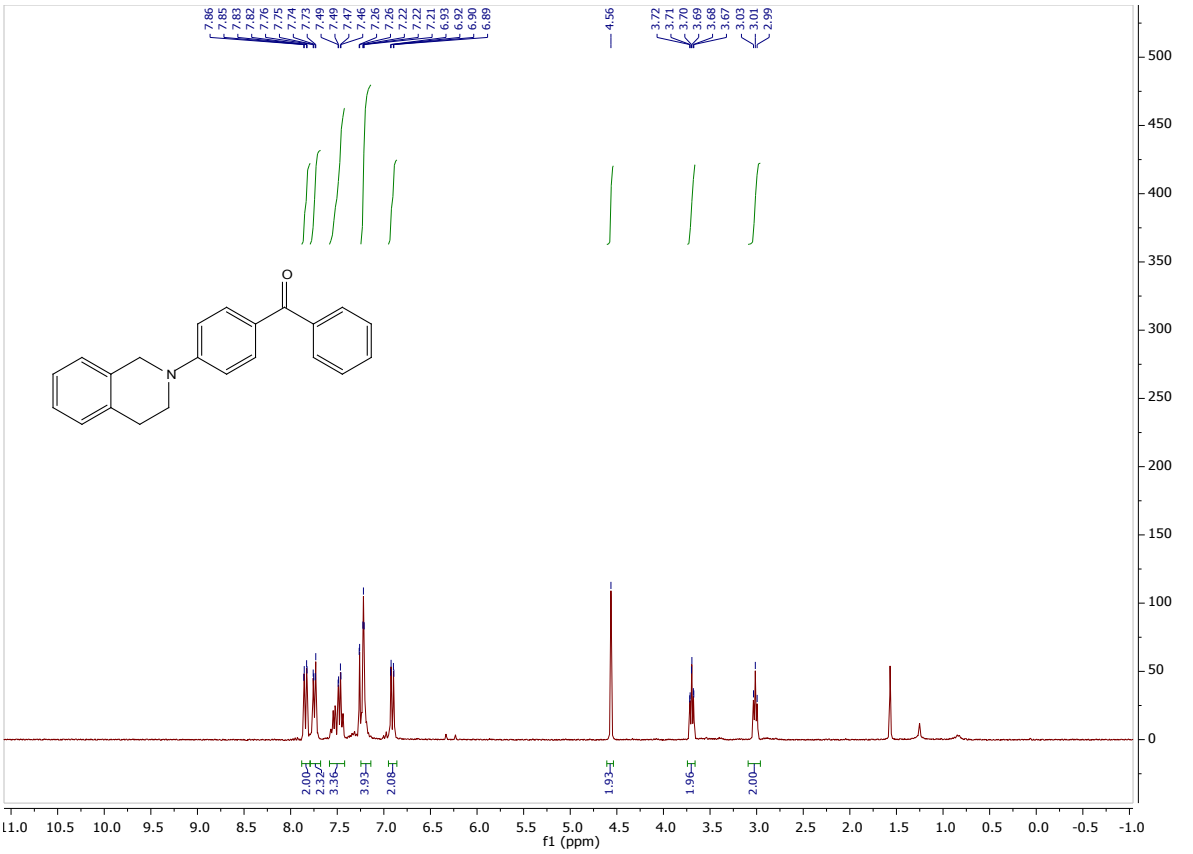
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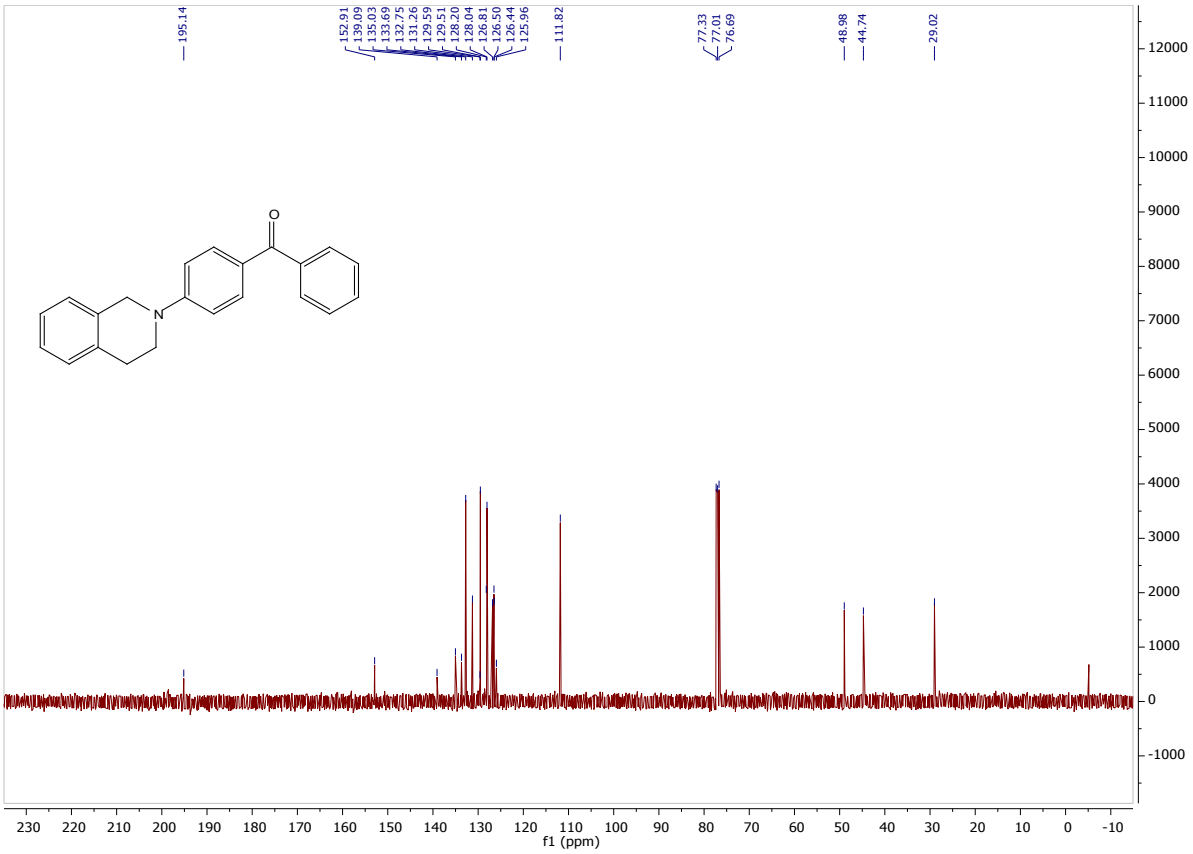
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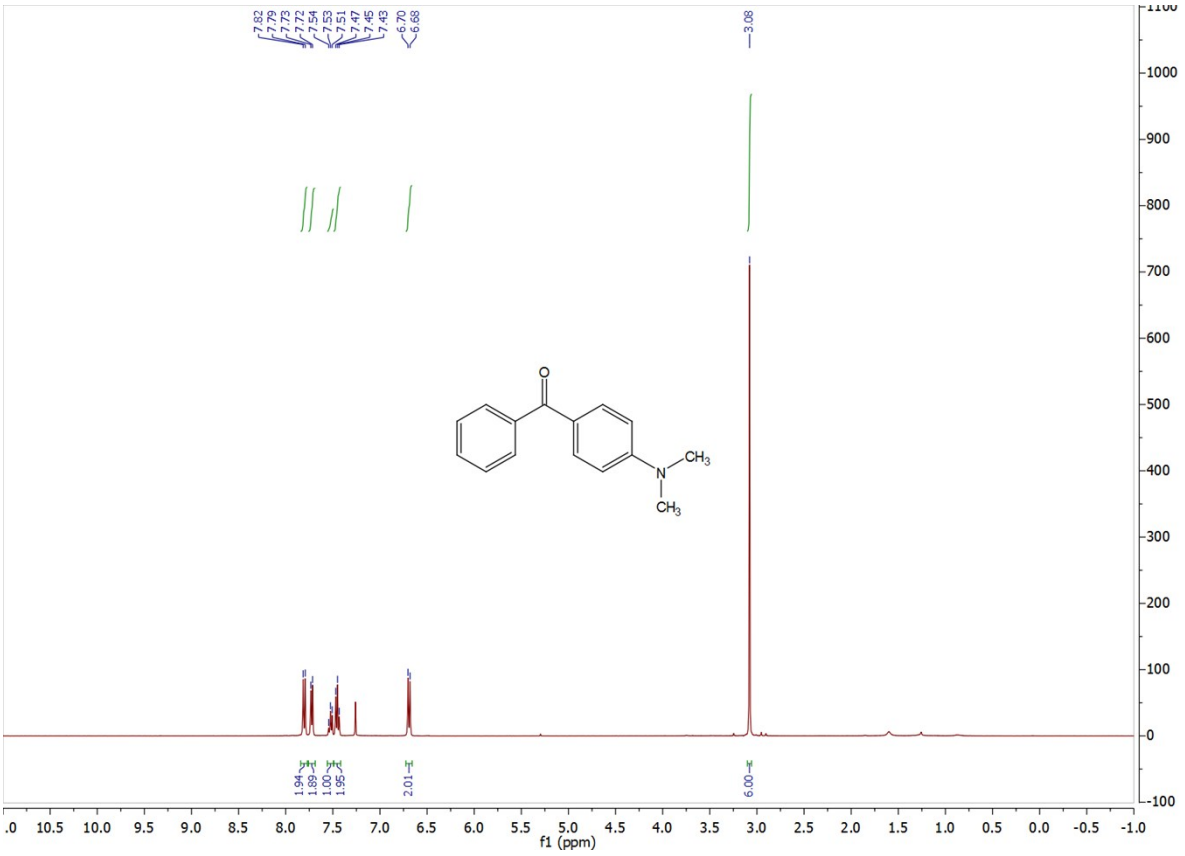
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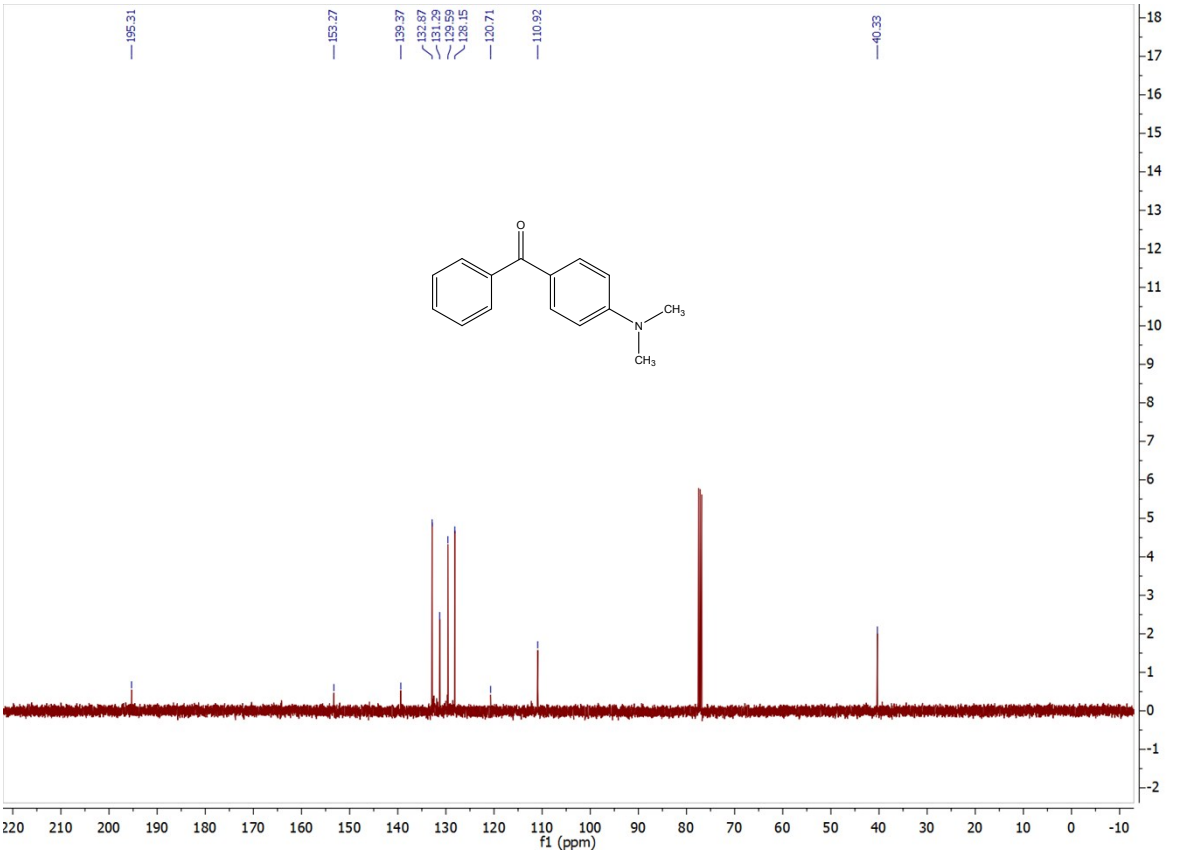
CH3
f1 (ppm)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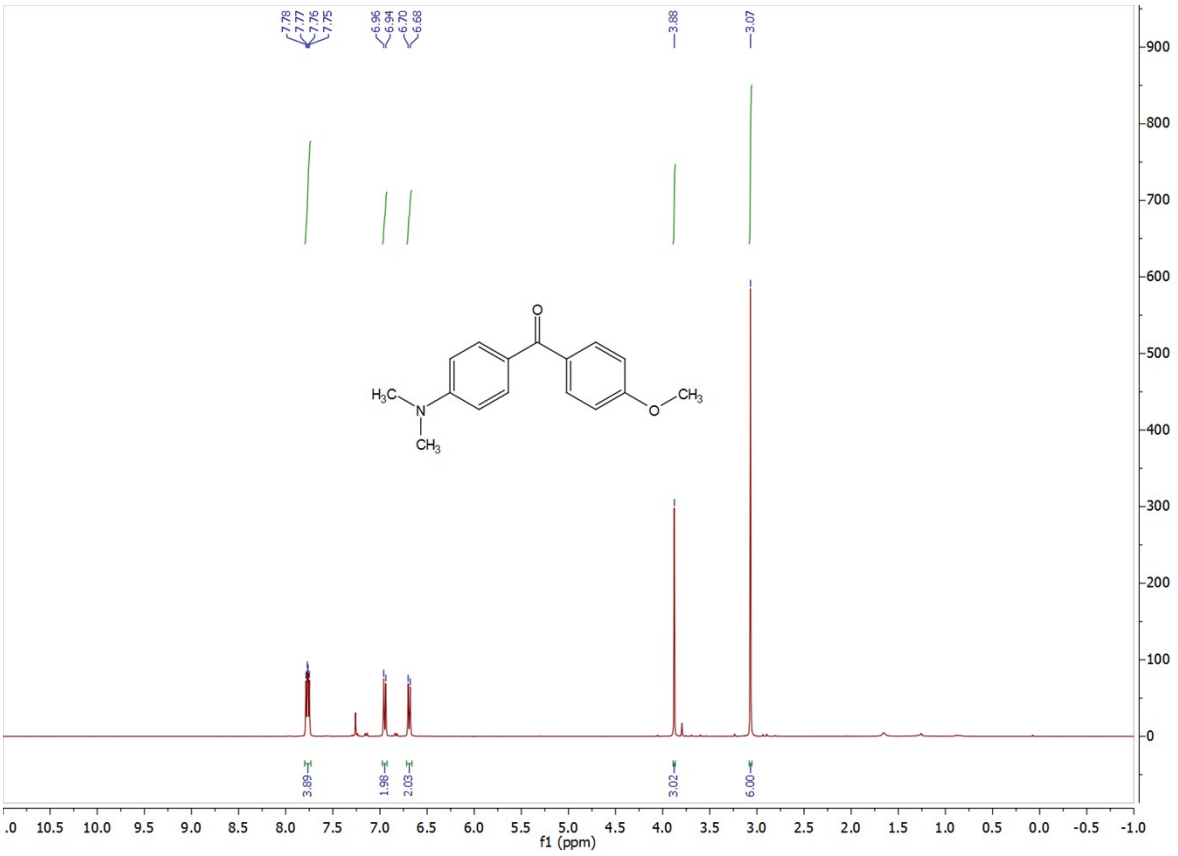
f1 (ppm)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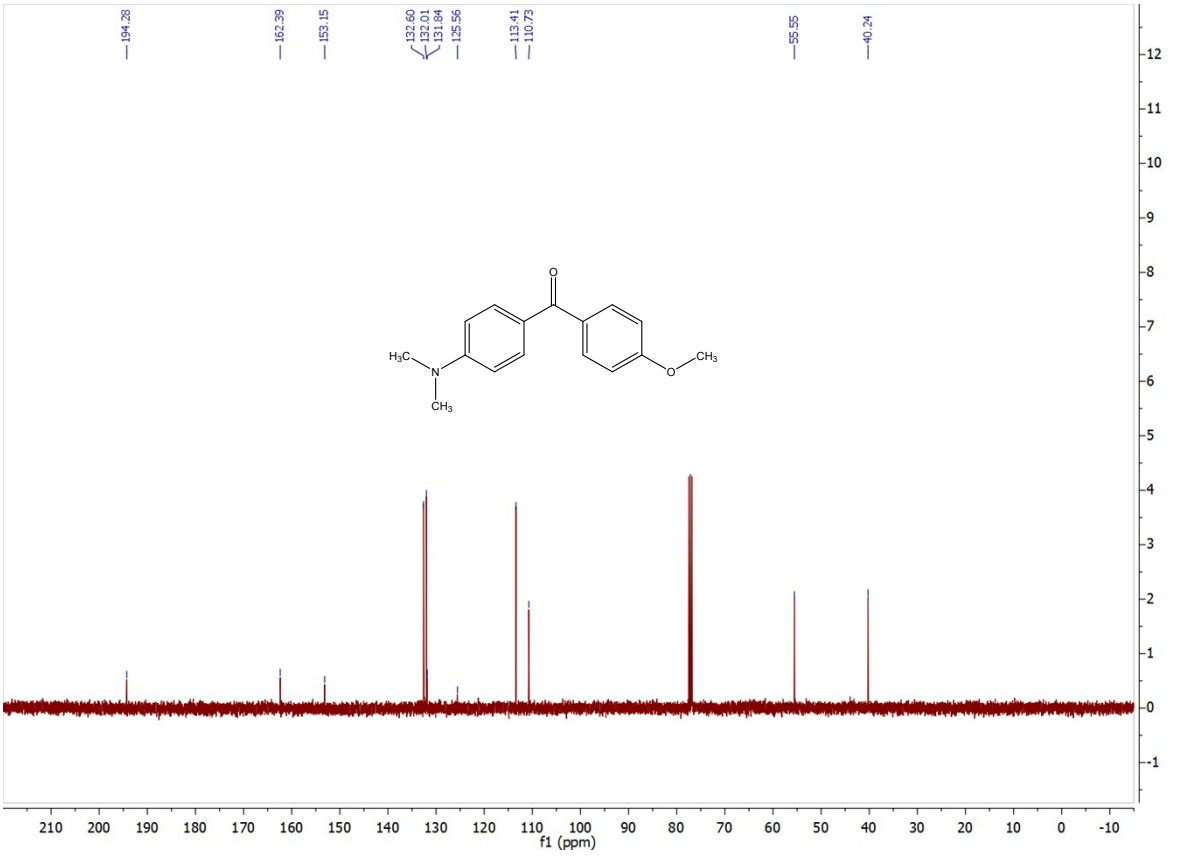
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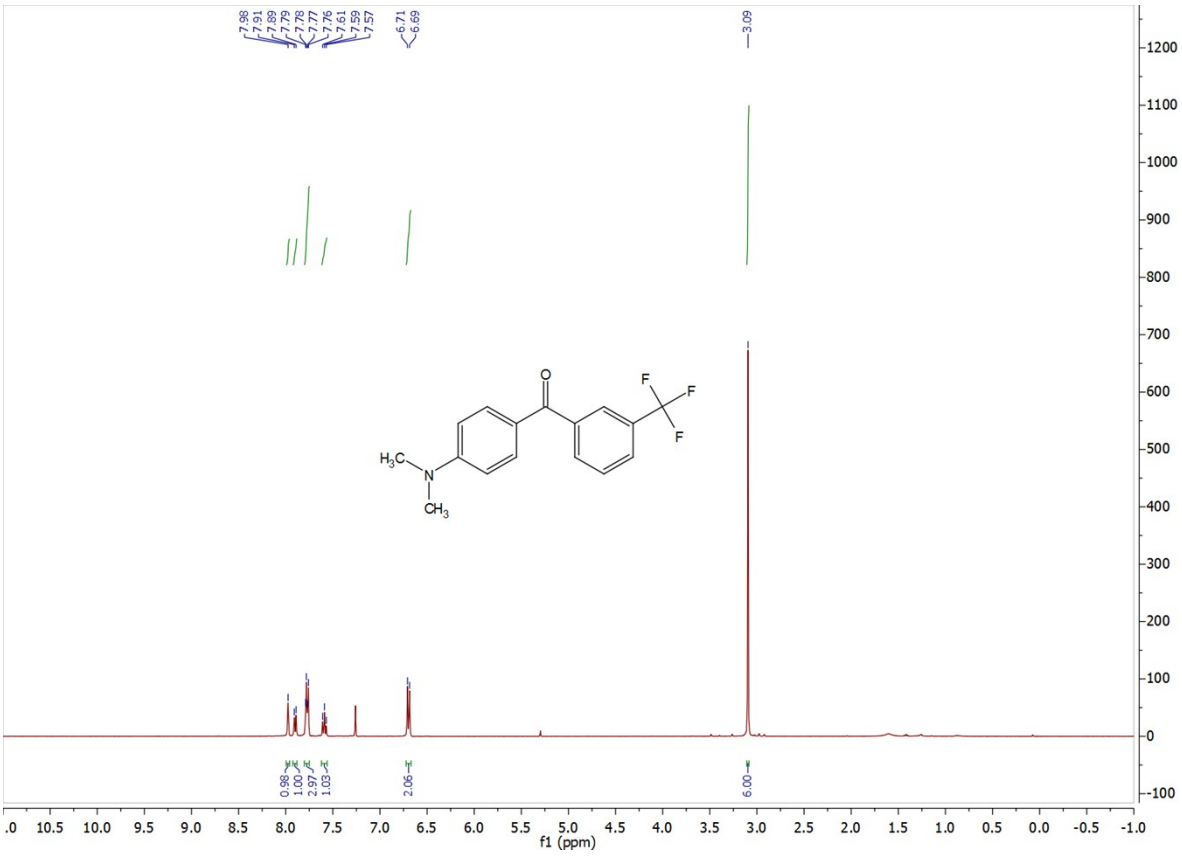
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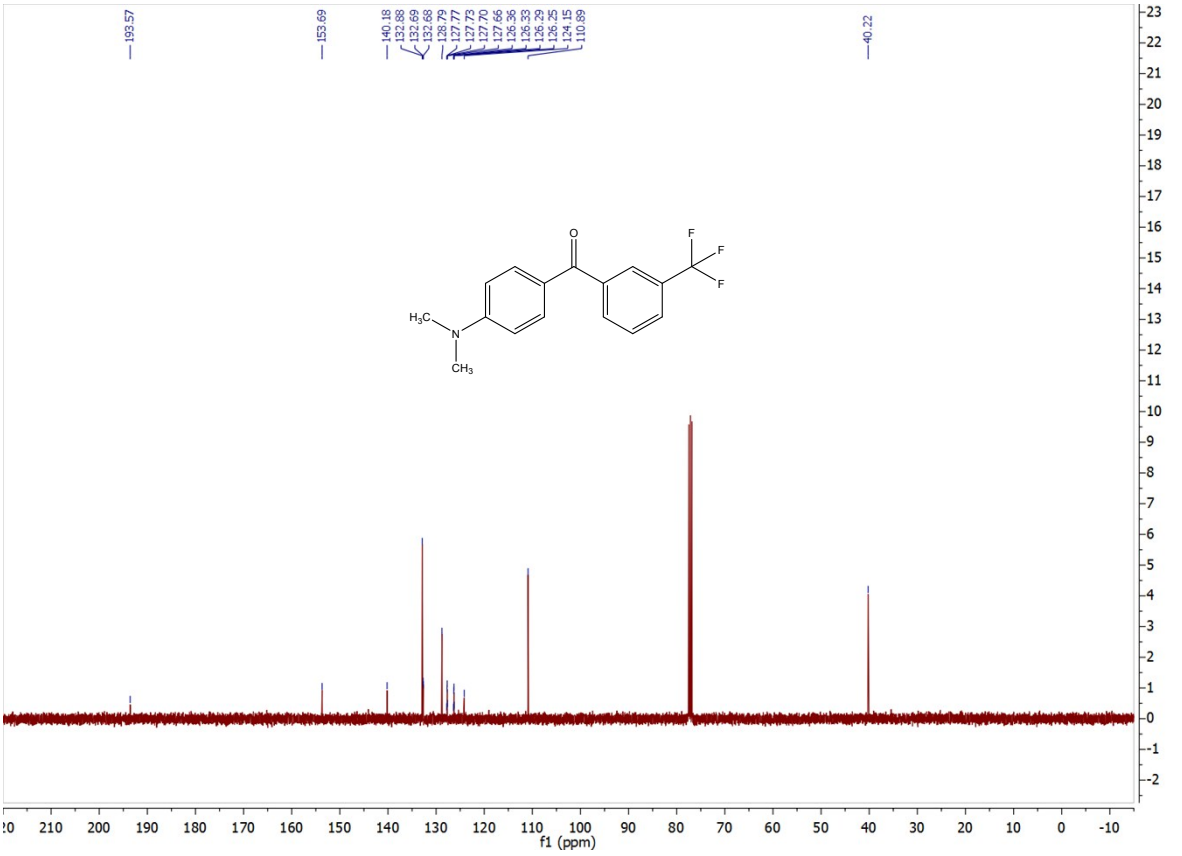
f1 (ppm)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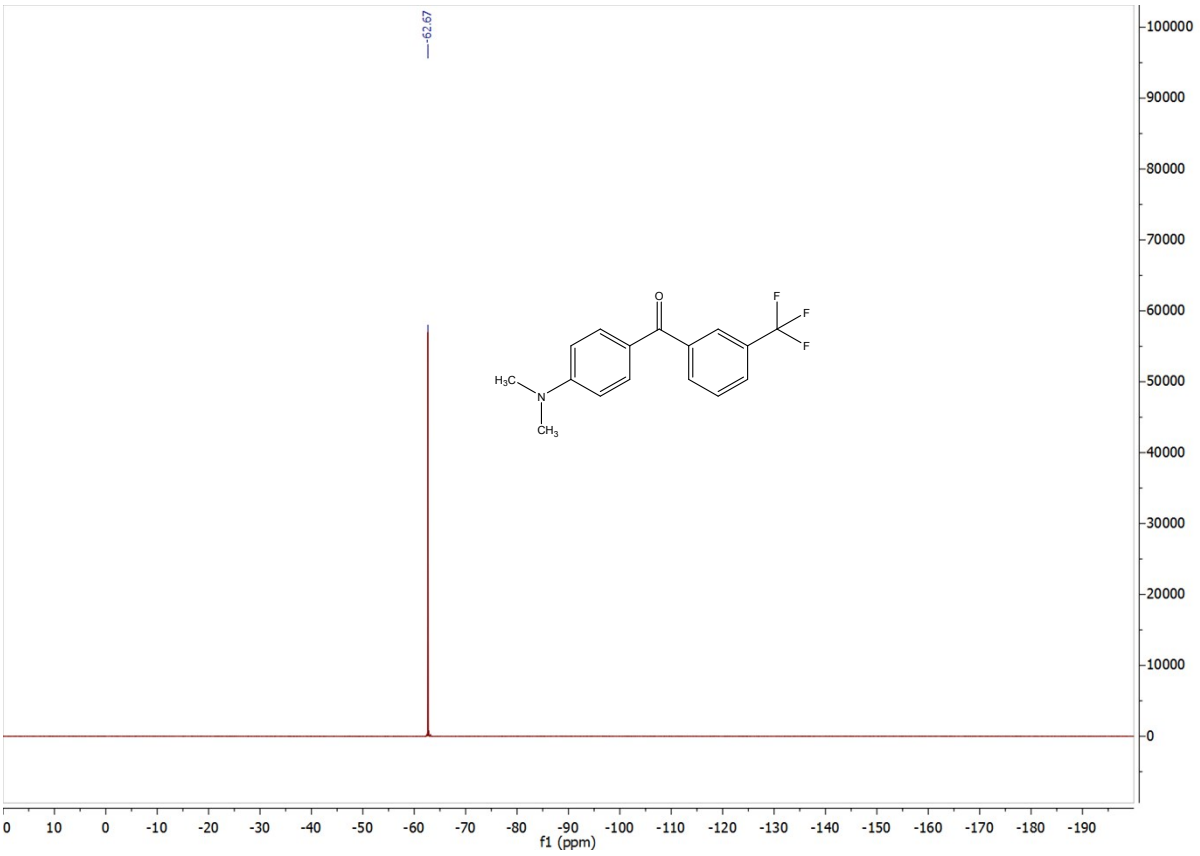
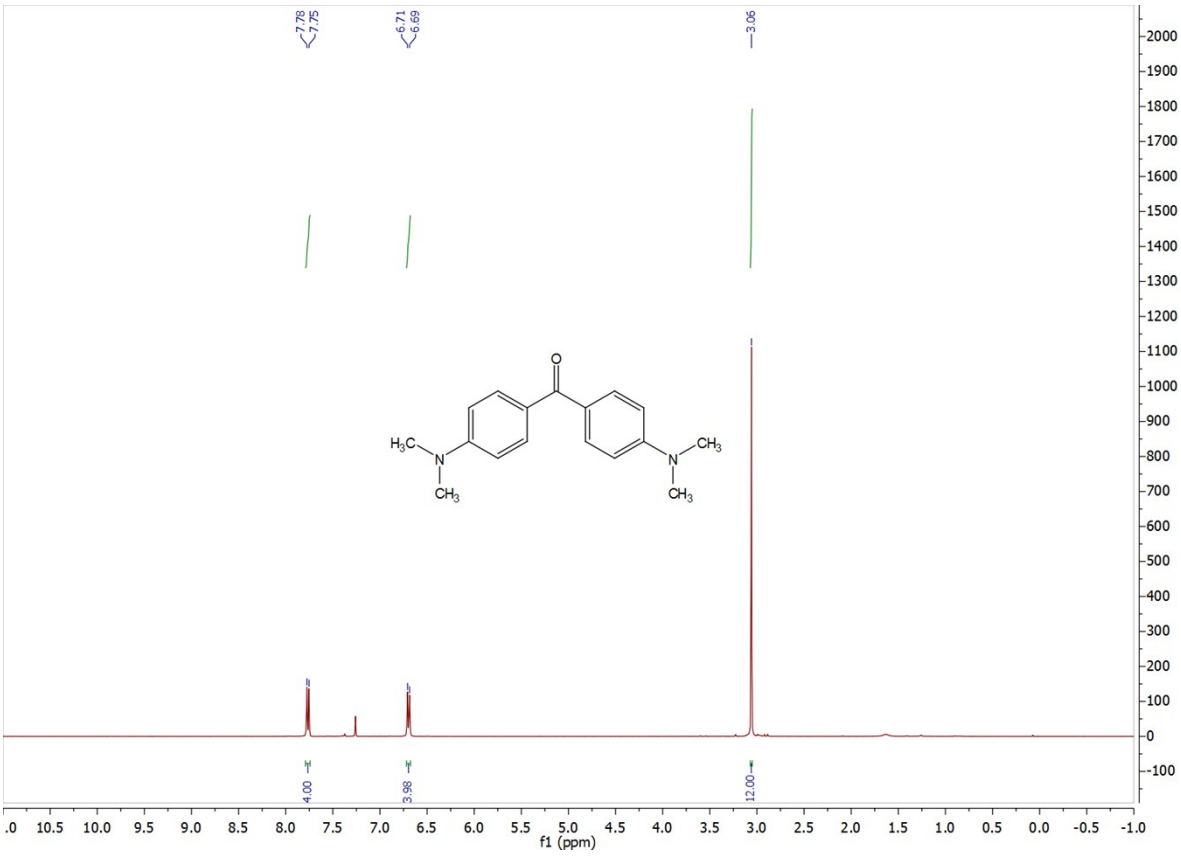
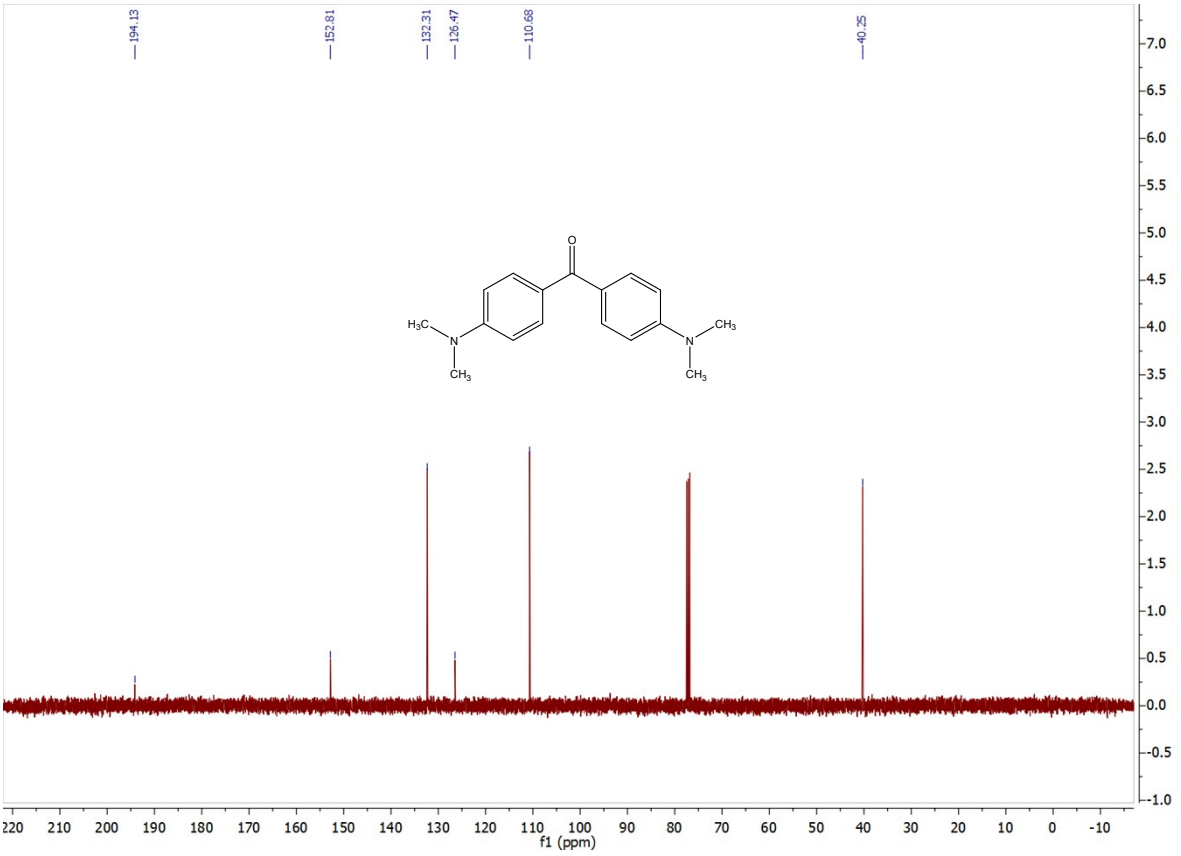
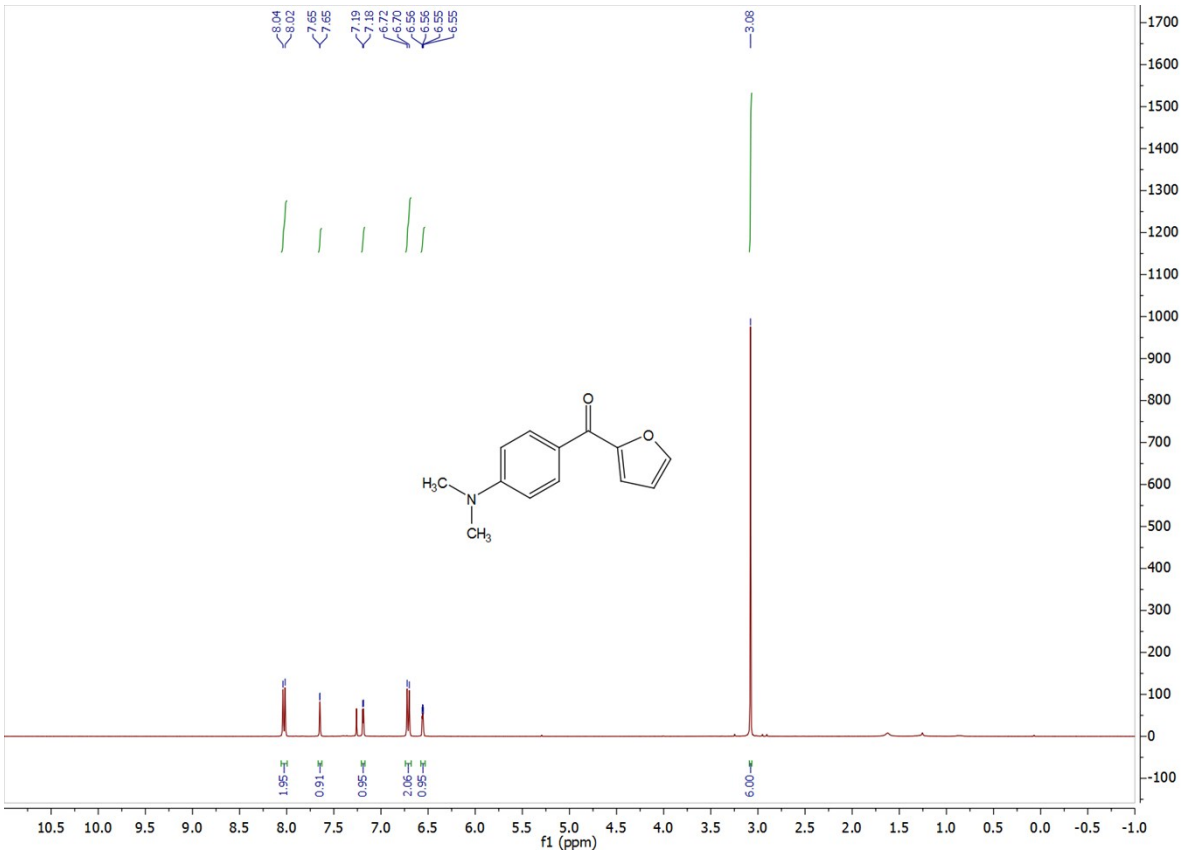
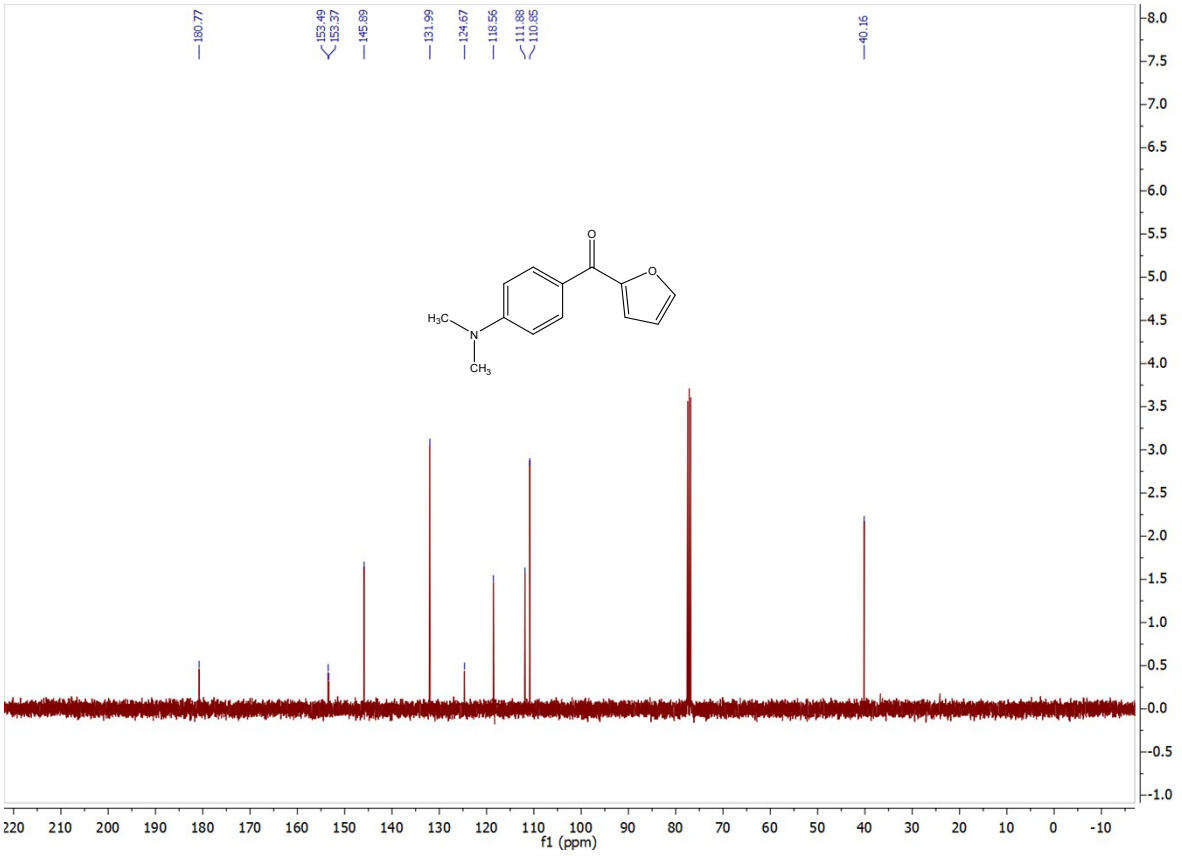
40.22
O
F
F
F
H3C
N
CH3
f1 (ppm)

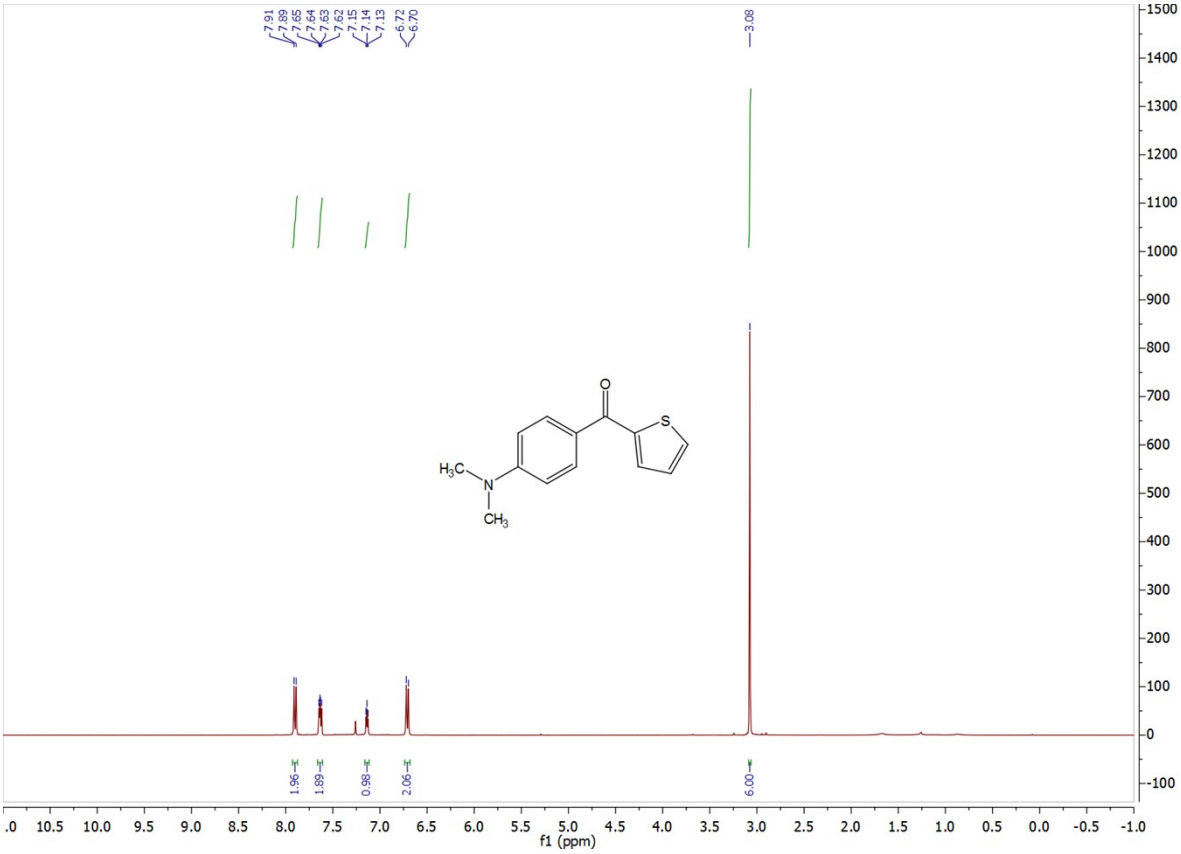

-62.67
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
O
F
F
F
H3C
N
CH3
0 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

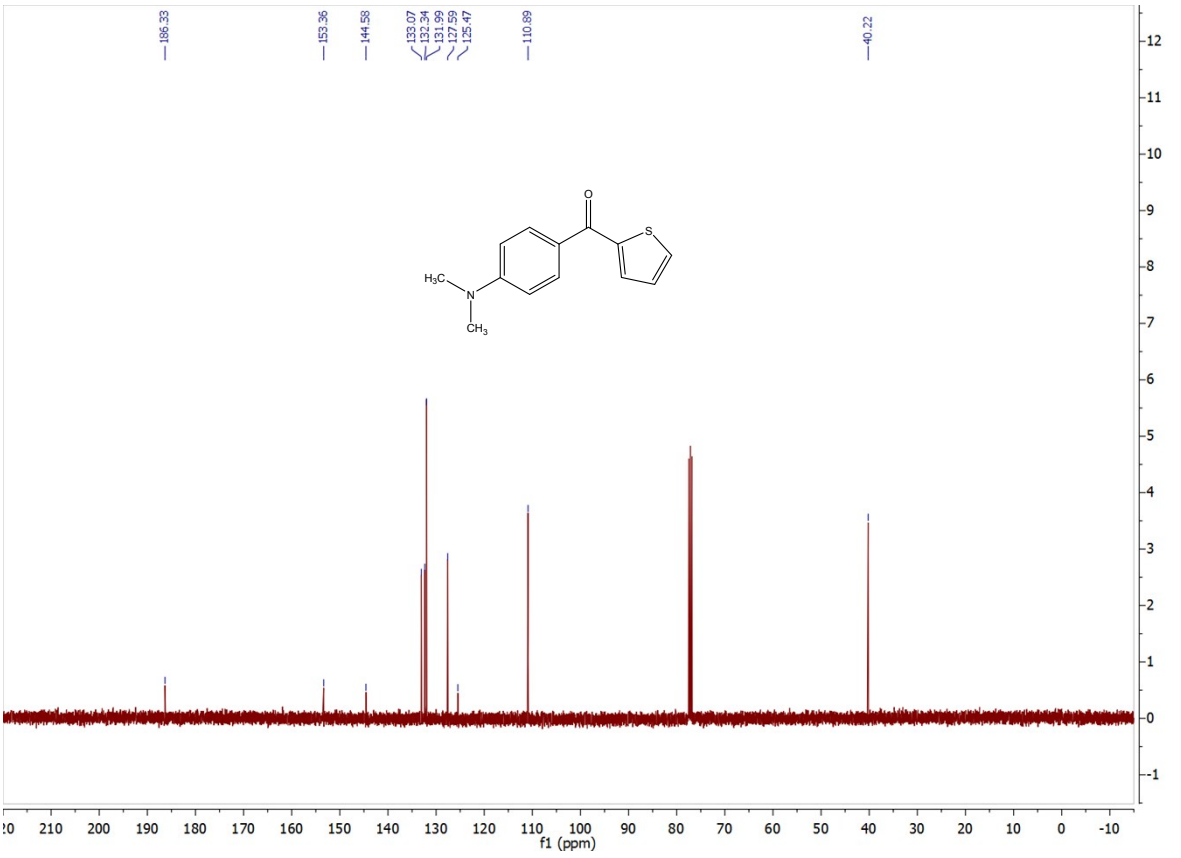

7.76
7.75
6.71
6.69
3.06
4.00
3.98
12.00
f1 (ppm)

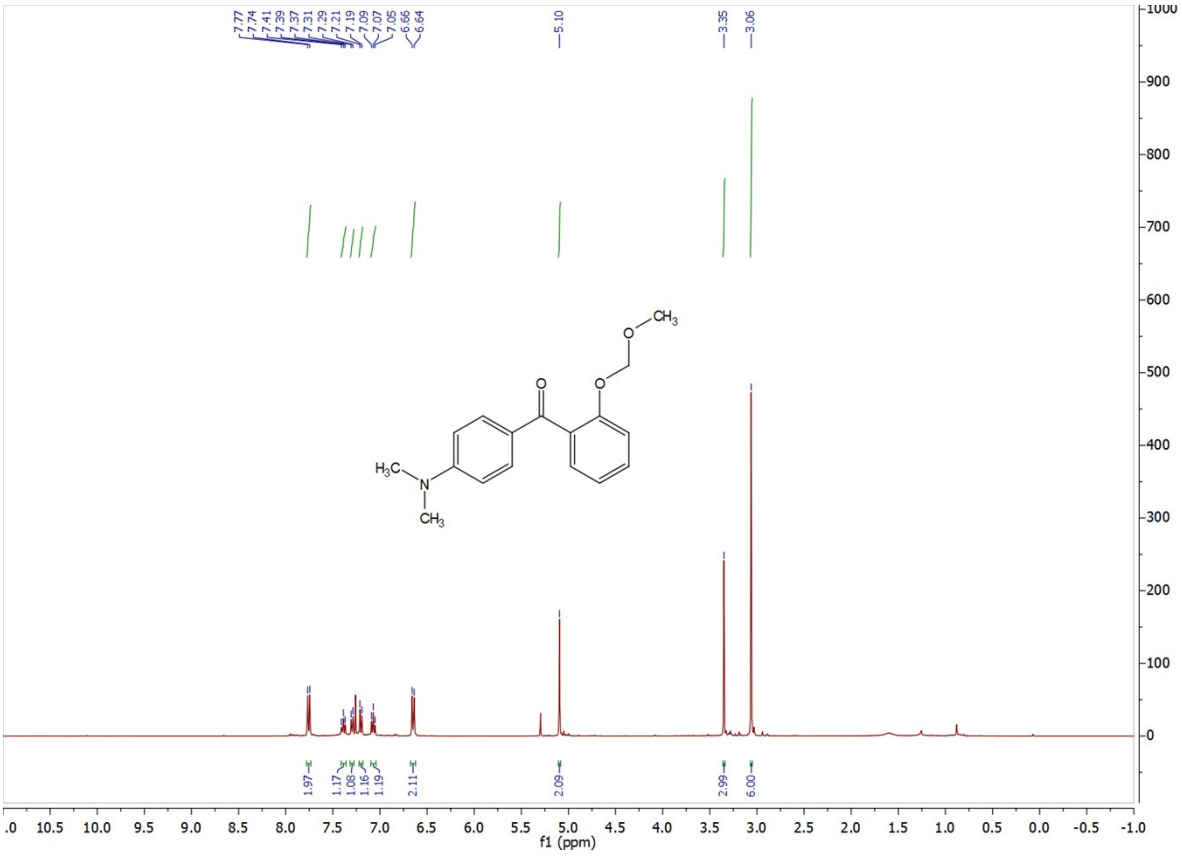

194.13
152.81
132.31
126.47
110.68
40.25
f1 (ppm)

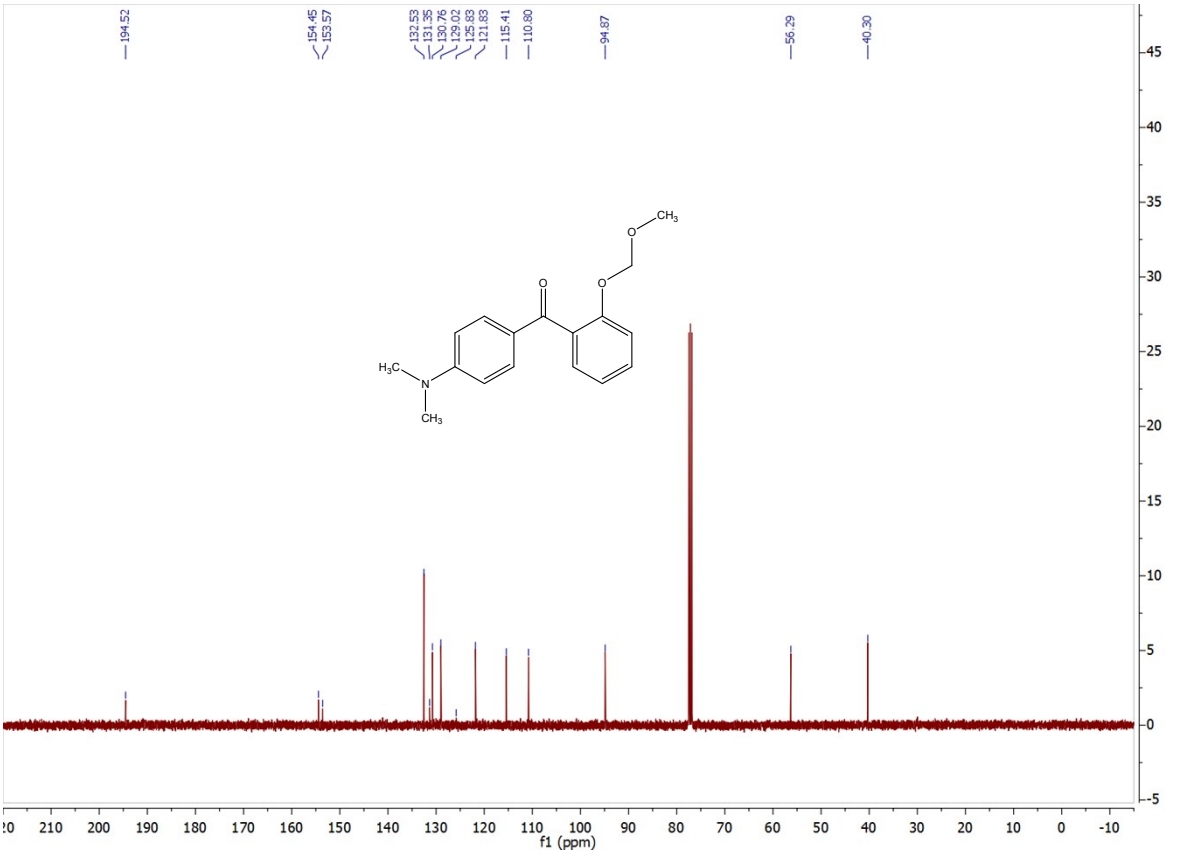

8.04
8.02
7.65
7.65
7.19
7.18
6.72
6.70
6.56
6.56
6.55
6.55
3.08
1.95
0.91
0.95
2.06
0.95
6.00
f1 (ppm)

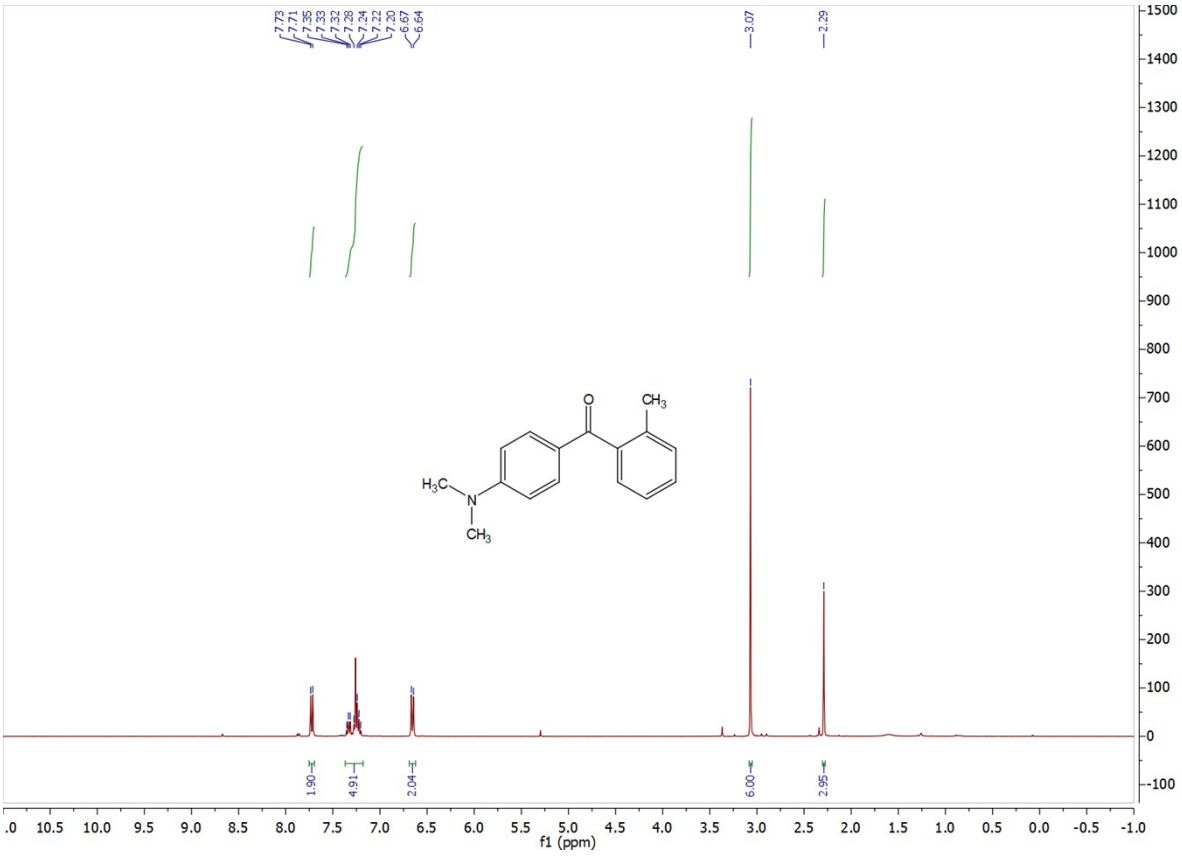

180.77
153.49
153.37
145.89
131.99
124.67
118.56
111.88
110.85
40.16
f1 (ppm)

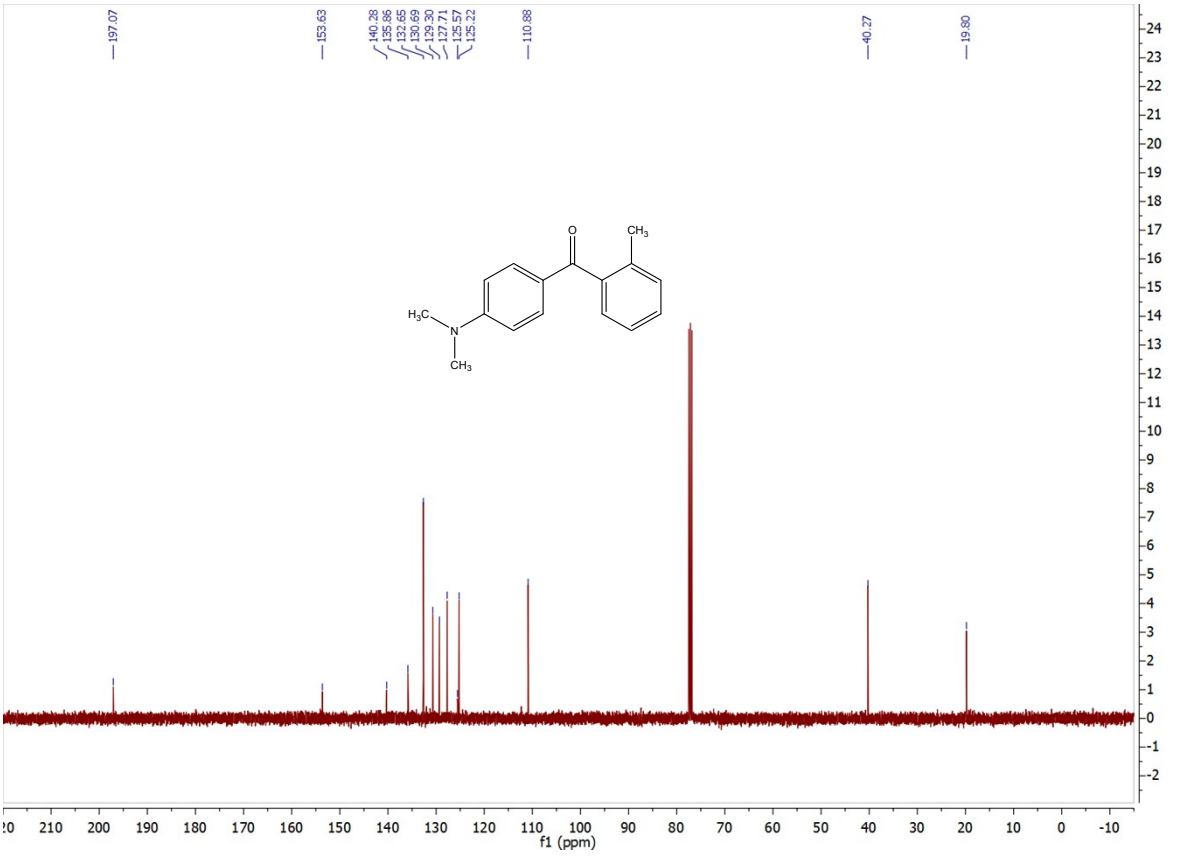

7.91
7.89
7.65
7.64
7.63
7.62
7.15
7.14
7.13
6.72
6.70
3.08
1.96
1.89
0.98
2.06
6.00
O
S
H3C
N
CH3
f1 (ppm)

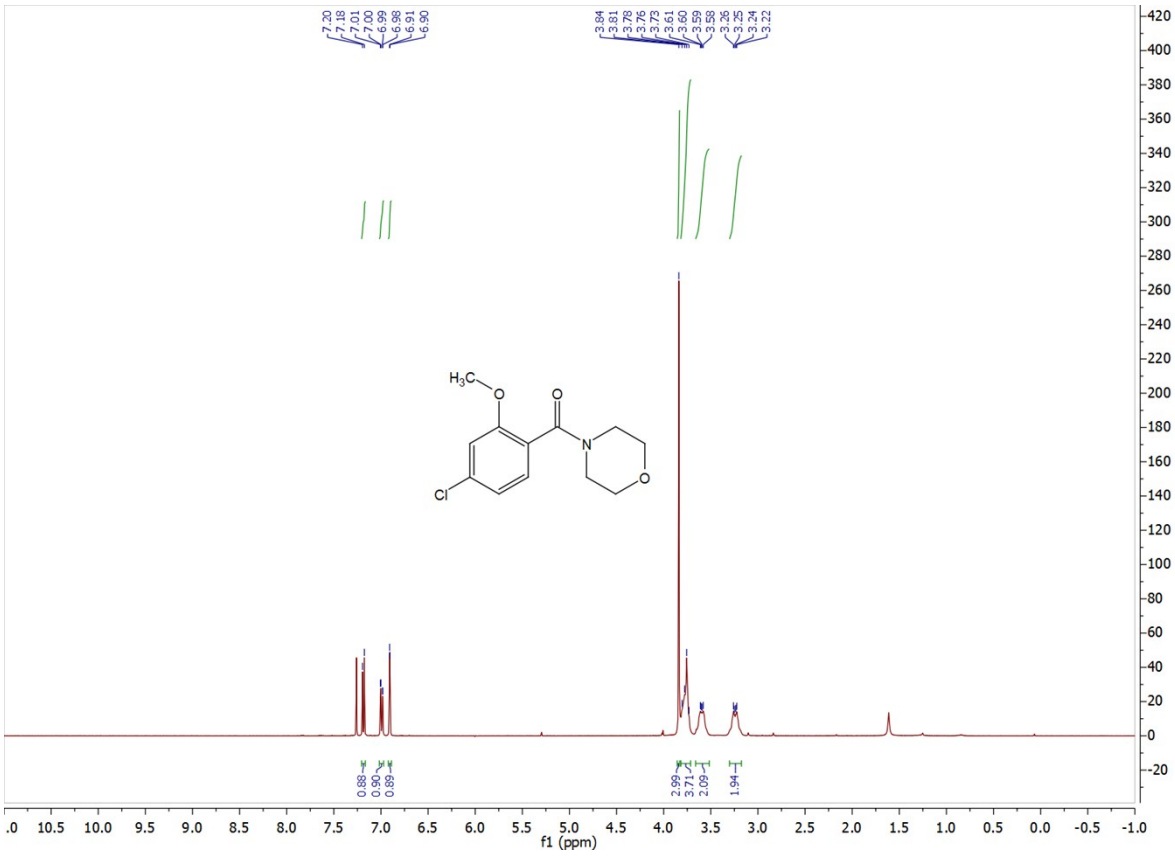

186.33
153.36
144.58
133.07
132.34
131.99
127.59
125.47
110.89
40.22
O
S
H3C
N
CH3
f1 (ppm)

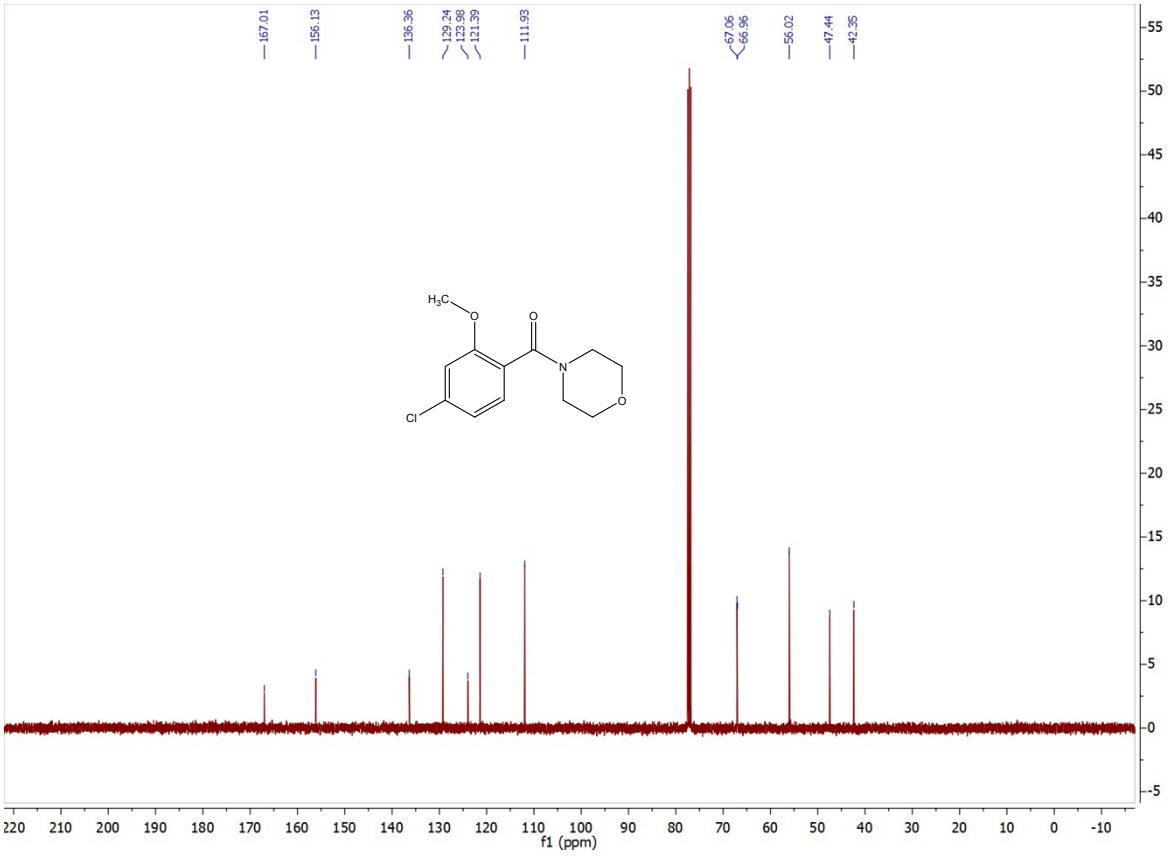

7.77
7.74
7.41
7.39
7.37
7.31
7.29
7.21
7.19
7.09
7.07
7.05
6.66
6.64
5.10
3.35
3.06
1.97
1.17
1.08
1.16
1.19
2.11
2.09
2.99
6.00
f1 (ppm)

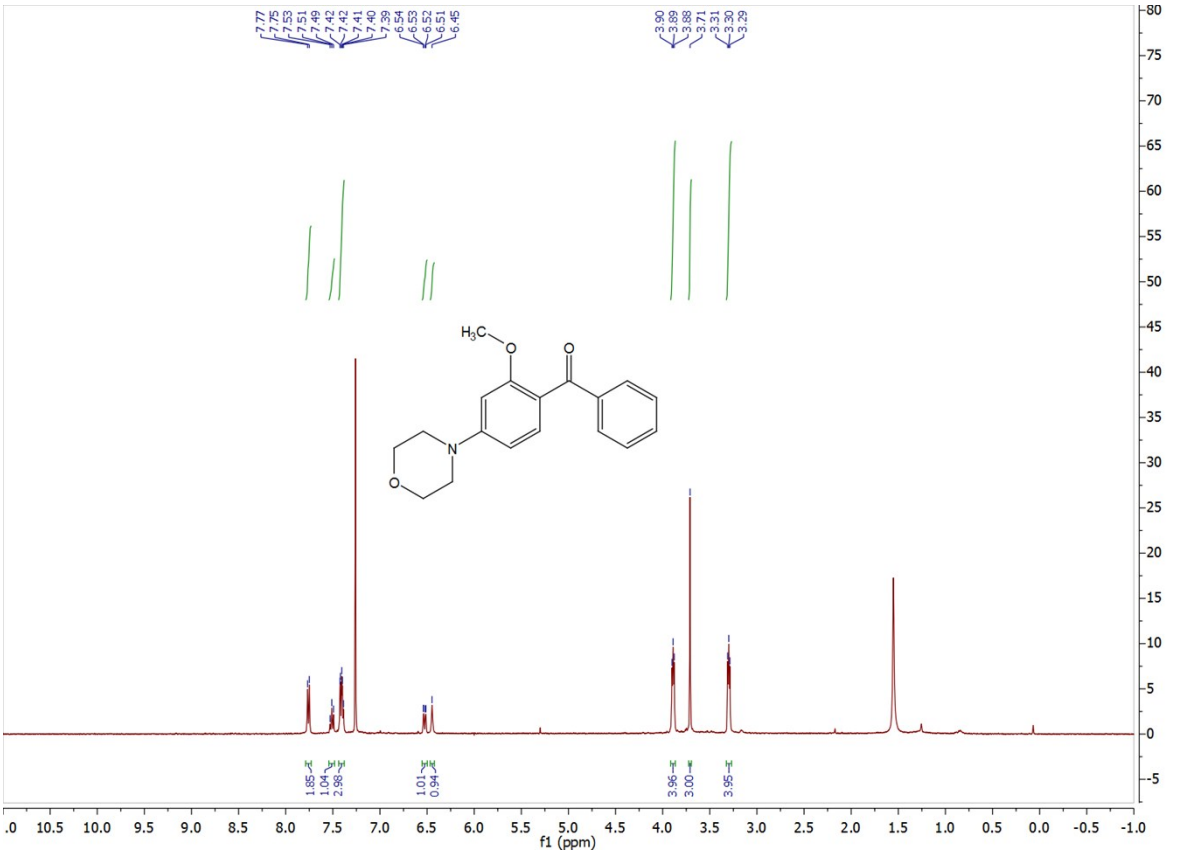

194.52
154.45
153.57
132.53
131.35
130.76
129.02
125.83
121.83
115.41
110.80
94.87
56.29
40.30
f1 (ppm)

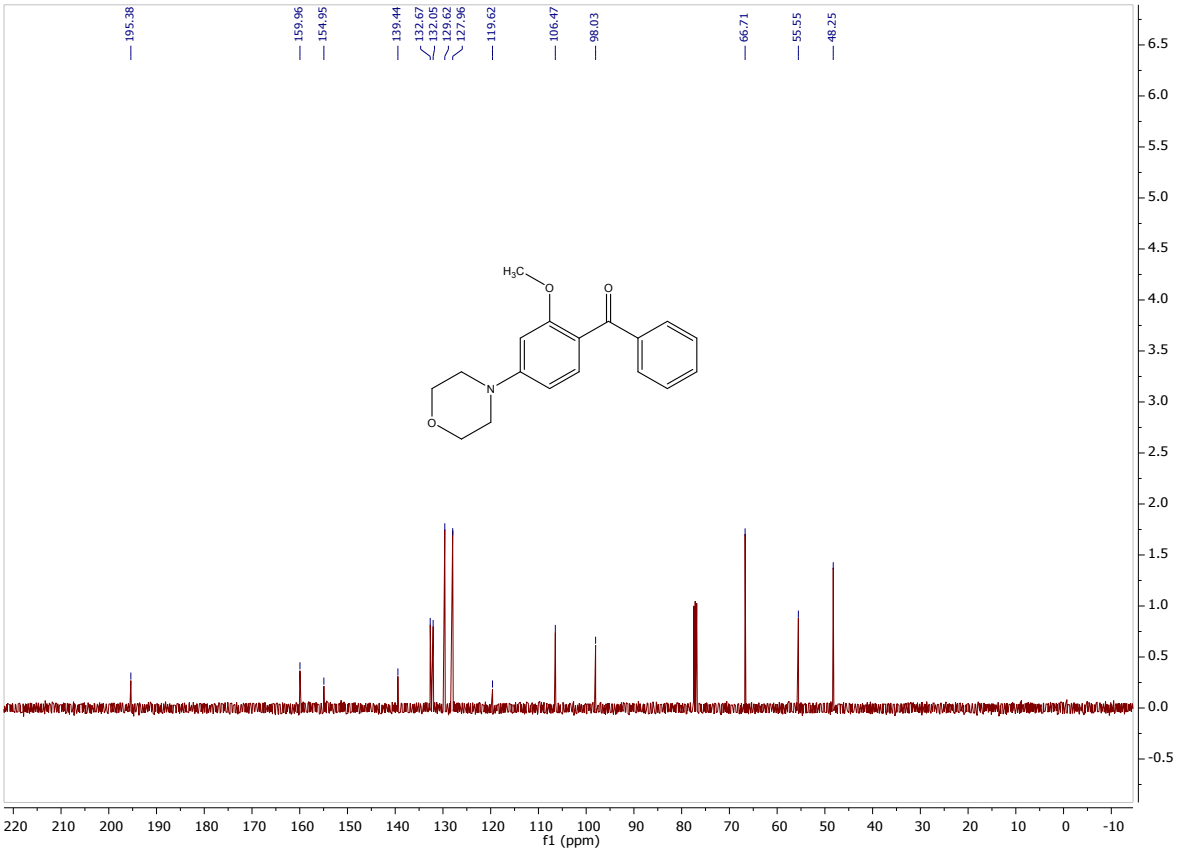

7.73
7.71
7.35
7.33
7.32
7.28
7.24
7.22
7.20
6.67
6.64
3.07
2.29
O
CH3
H3C
N
CH3
1.90
4.91
2.04
6.00
2.95
f1 (ppm)

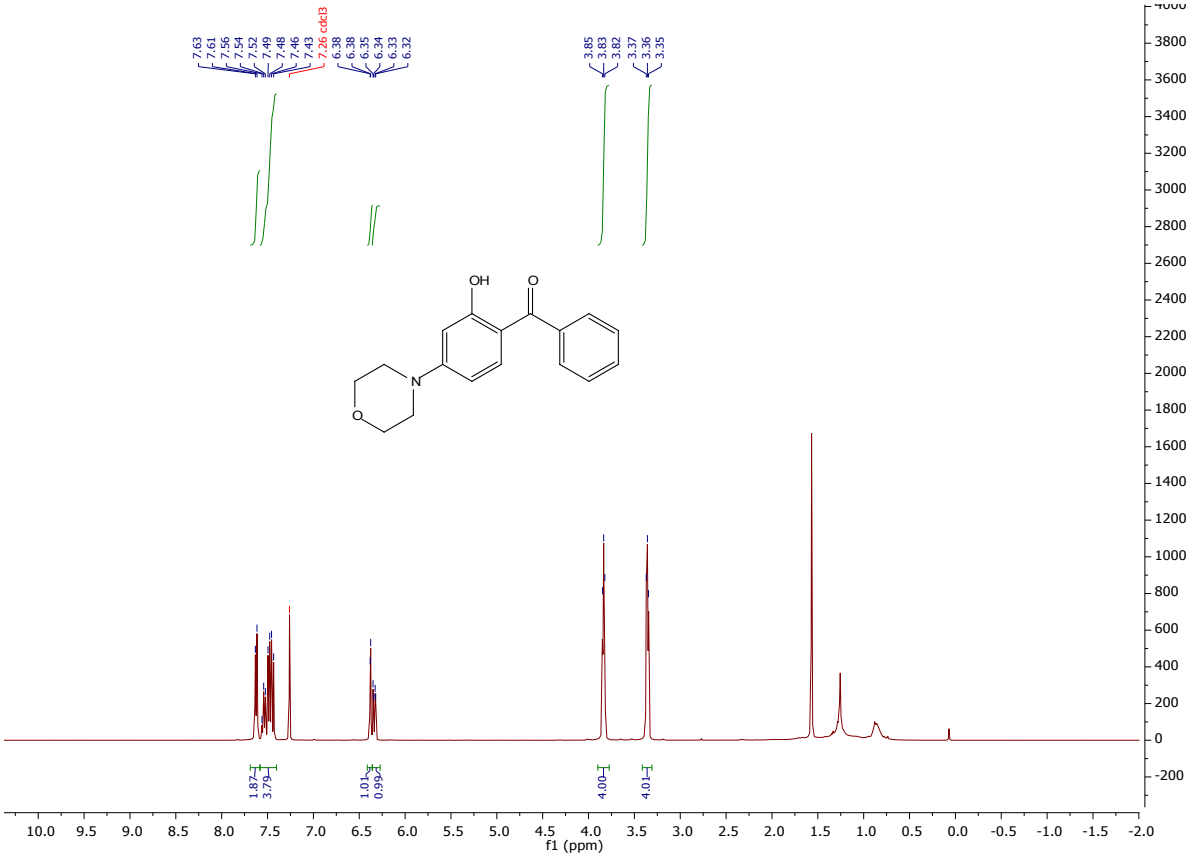

197.07
153.63
140.28
135.86
132.65
130.69
129.30
127.71
125.57
125.22
110.88
40.27
19.80
O
CH3
H3C
N
CH3
f1 (ppm)

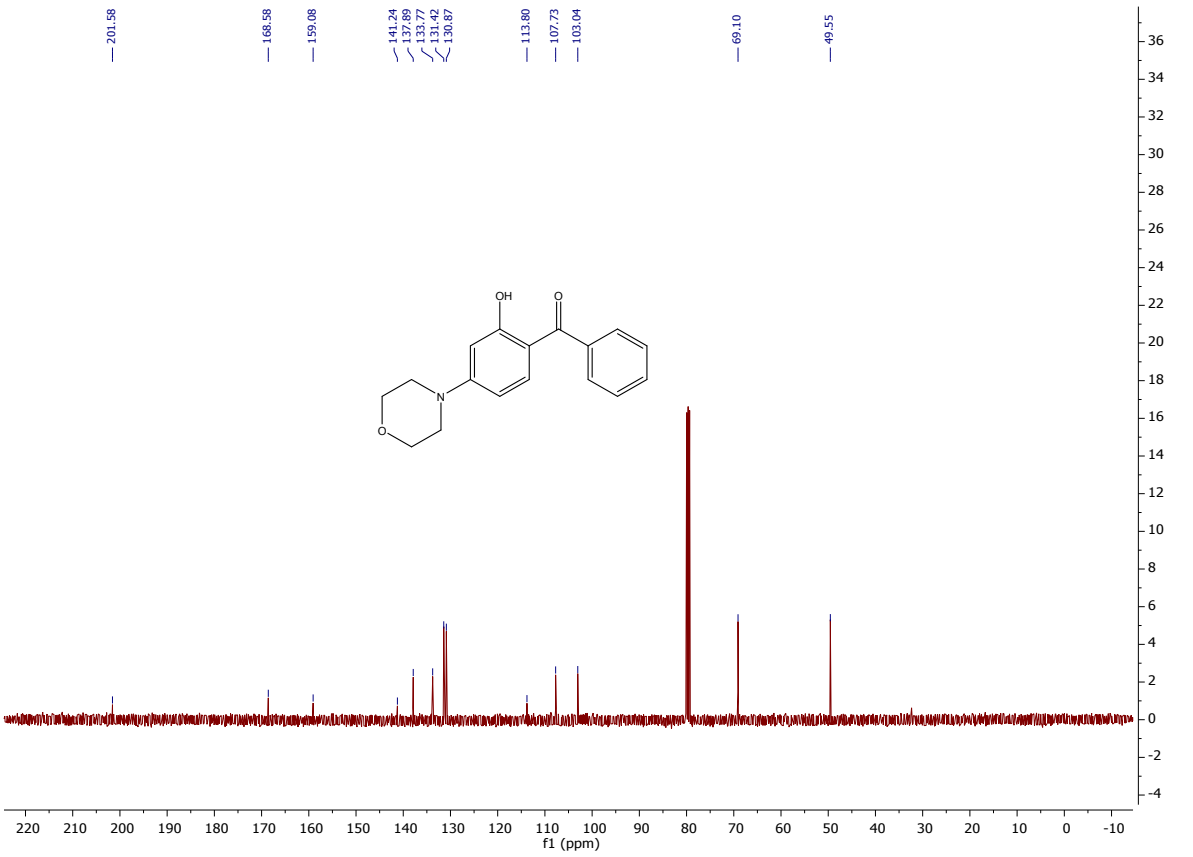

7.20
7.18
7.01
7.00
6.99
6.98
6.91
6.90
3.84
3.81
3.76
3.73
3.61
3.60
3.59
3.58
3.36
3.35
3.24
3.22
H3C
O
O
N
O
Cl
0.88
0.90
0.89
2.99
3.71
2.09
1.94
f1 (ppm)


167.01
156.13
136.36
129.24
123.98
121.39
111.93
67.06
66.96
56.02
47.44
42.35
H3C
O
O
N
O
Cl
f1 (ppm)


7.77
7.75
7.53
7.51
7.49
7.42
7.42
7.41
7.40
7.39
6.54
6.53
6.52
6.51
6.45
3.90
3.89
3.88
3.71
3.31
3.30
3.29
H3C
O
O
N
O
1.85
1.04
2.98
1.01
0.94
3.96
3.00
3.95
f1 (ppm)


195.38
159.96
154.95
139.44
132.67
132.05
129.62
127.96
119.62
106.47
98.03
66.71
55.55
48.25
H3C
O
O
N
O
f1 (ppm)


7.63
7.61
7.56
7.54
7.52
7.49
7.48
7.46
7.43
7.26 cdcl3
6.38
6.38
6.35
6.34
6.33
6.32
3.85
3.83
3.82
3.37
3.36
3.35
OH
O
N
O
1.87
3.79
1.01
0.99
4.00
4.01
f1 (ppm)


201.58
168.58
159.08
141.24
137.89
133.77
131.42
130.87
113.80
107.73
103.04
69.10
49.55
OH
O
N
O
f1 (ppm)