Electronic Supplementary Material (ESI) for ChemComm.

Supplementary Information

Triphenylphosphine-catalysed amide bond formation between carboxylic acids and amines

Danny C. Lenstra, Floris P. J. T. Rutjes and Jasmin Mecinović*

Institute for Molecules and Materials, Radboud University Nijmegen, Heyendaalseweg 135, 6525 AJ Nijmegen, The Netherlands. Fax: +31 24 3653393; Tel: +31 24 3652381; E-mail: j.mecinovic@science.ru.nl

Contents

1. Materials and methods

Solvents were dried by purging over activated alumina columns in an MBraun MB SPS800 and and stored under nitrogen. Chemicals were purchased from commercial sources and were used without further purification. Reactions were carried out under an inert atmosphere of dry nitrogen or argon. Standard syringe techniques were applied for the transfer of dry solvents and air- or moisture-sensitive reagents.

Gas chromatography (GC) was performed on a Shimadzu GC2010+, containing an Agilent DB-1 column (30 m, 0.32 mm ID, 0.25 Am DF) using FID detection.

The chiral HPLC measurements were performed on a Shimadzu LC2010C Analytical HPLC system equipped with a 250 x 4.6 ID mm Diacel Chiralpak AD-H column with Heptane/Isopropanol (90:10 v/v).

NMR spectra were recorded on a Bruker DMX 300 (300 MHz), and a Varian 400 (400 MHz) spectrometer in $CDCl_3$ solutions). ^1H NMR chemical shifts are given in ppm with respect to tetramethylsilane (TMS, δ 0.00 ppm) as internal standard, ^{13}C NMR shift are given in ppm with respect to $CHCl_3$ (δ 77.4 ppm). Coupling constants are reported as *J*-values in Hz.

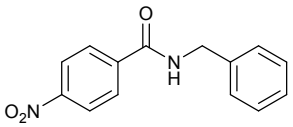
2. General procedures

Catalytic reaction
Amine (1.30 mmol) and acid (1.00 mmol) were suspended in 5 mL of anhydrous toluene. While stirring, triphenylphosphine (52.7 mg, 0.20 mmol), tetrachloromethane (307.6 mg, 2.00 mmol), diethoxymethylsilane (201.4 mg, 1.5 mmol) and bis(4-nitrophenyl) phosphate (17 mg, 0.05 mmol) were added. The reaction was stirred at 110°C for 20 hours under intert atmosphere. The solvent was then removed under reduced pressure, and the crude mixture redissolved in ethyl acetate and a saturated NaHCO3 solution was added. The organic layer was separated, dried (Na_2SO_4), filtered and evaporated. Silica gel purification (0 - 40%, EtOAc in n-heptane) was performed to isolate the desired amide.

Uncatalytic reaction
Amine (1.30 mmol) and acid (1.00 mmol) were suspended in 5 mL of anhydrous toluene. While stirring, triphenylphosphine (52.7 mg, 0.20 mmol) and tetrachloromethane (307.6 mg, 2.00 mmol) were added. The reaction was stirred at 110°C for 20 hours under inert atmosphere. The solvent was then removed under reduced pressure, and the crude mixture was redissolved in ethyl acetate and a saturated $NaHCO_3$ solution was added. The organic layer was separated, dried (Na_2SO_4), filtered and evaporated. Silica gel purification (0 - 40%, EtOAc in n-heptane) was performed to isolate the desired amide.

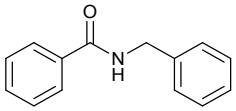
3. Characterisations of products

N-benzyl-4-nitrobenzamide



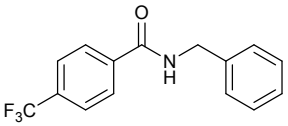
^{1}H NMR (300 MHz, $CDCl_3$):[1] δ 4.67 (d, 2H, J = 6 Hz), δ 6.62 (bs, 1H), δ 7.36 (m, 5H), δ 7.96 (d, *J* = 9.0 Hz, 2H), δ 8.28 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 149.9, 140.3, 137.8, 129.3, 128.5, 128.3, 128.3, 124.2, 44.8.

N-benzylbenzamide



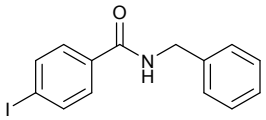
^{1}H NMR (300 MHz, $CDCl_3$):[1] δ 4.65 (d, 2H, J = 6 Hz), 6.44 (bs, 1H), δ 7.28-7,36 (m, 5H), δ 7.40-7.45 (m, 2H), δ 7.48-7.52 (m,1H), δ 7.78-7.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 138.5, 134.7, 131.8, 129.0, 128.9, 128.2, 127.9, 127.3, 44.4.

N-benzyl-4-(trifluoromethyl)benzamide



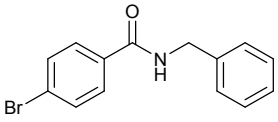
^{1}H NMR (300 MHz, $CDCl_3$):[2] δ 4.66 (d, 2H, J = 3 Hz), δ 6.58 (bs, 1H), δ 7.28-7,36 (m, 5H), δ 7.70 (d, 2H, J = 9 Hz), δ 7.91 (d, 2H, J = 6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 138.1, 137.9, 129.2, 128.3, 128.2, 127.8, 126.0, 125.9, 122.2, 44.7.

N-benzyl-4-iodobenzamide



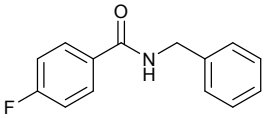
^{1}H NMR (300 MHz, $CDCl_3$):[3] δ 4.63 (d, 2H, J = 3 Hz), δ 6.48 (bs, 1H), δ 7.28-7.38 (m, 5H), δ 7.52 (d, *J* = 9.0 Hz, 2H), δ 7.78 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 138.1, 134.1, 129.2, 128.9, 128.3, 128.1, 98.8, 44.6.

N-benzyl-4-bromobenzamide



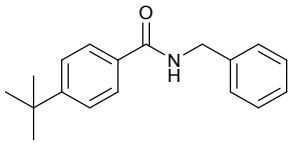
^{1}H NMR (300 MHz, $CDCl_3$):[3] δ 4.64 (d, 2H, J = 6 Hz), δ 6.47 (bs, 1H), δ 7.28-7.41 (m, 5H), δ 7.57 (d, *J* = 9.0 Hz, 2H), 7.67 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 138.2, 133.5, 132.2, 129.2, 128.9, 128.2, 128.1, 126.6, 44.6.

N-benzyl-4-fluorobenzamide



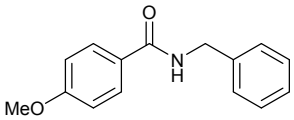
^{1}H NMR (400 MHz, $CDCl_3$):[3] δ 4.65 (d, 2H, J = 6 Hz), δ 6.48 (bs, 1H), δ 7.07-7.14 (m, 2H), δ 7.28-7.36 (m, 5H), δ 7.78 – 7.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 163.4, 138.4, 129.7, 129.2, 128.25, 128.0, 116.1, 115.8, 44.6.

N-benzyl-4-(*tert*-butyl)benzamide



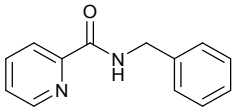
^{1}H NMR (400 MHz, $CDCl_3$):[4] δ 1.33 (s, 9H), δ 4.55 (d, 2H, J = 2 Hz), δ 6.43 (bs, 1H), δ 7.25-7.35 (m, 5H), δ 7.44 (dt, 2H, J = 4 Hz, J = 8 Hz), δ 7.73 (dt, 2H, J = 4 Hz, J = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 155.0, 138.3, 131.44, 128.7, 127.9, 127.5, 126.8, 125.5, 44.0, 34.9, 33.1.

N-benzyl-4-methoxybenzamide



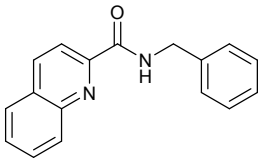
^{1}H NMR (300 MHz, $CDCl_3$):[1] δ 3.86 (s, 3H), δ 4.64 (d, 2H, J = 6 Hz), δ 6.41 (bs, 1H), δ 6.92 (d, *J* = 9.0 Hz, 2H), δ 7.28-7.38 (m, 5H), 7.78 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 162.6, 138.7, 129.1, 129.0, 128.2, 127.9, 126.9, 114.1, 55.7, 44.4.

N-benzyl-picolinamide



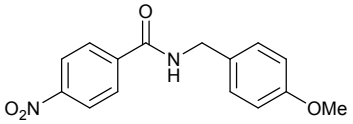
^{1}H NMR (300 MHz, $CDCl_3$):[5] δ 4.70 (d, 2H, J = 6 Hz), δ 7.28-7.44 (m, 5H), δ 7.85 (td, 1H, J = 6 Hz, 7.5 J = Hz), 8.26 (dt, 1H, J = 1 Hz, J = 7.5 Hz), 8.40 (bs, 1H), 8.53-8.56 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6, 150.2, 148.4, 138.6, 137.7, 129.0, 127.8, 126.5, 122.7, 118.5, 48.8.

N-benzylquinoline-2-carboxamide



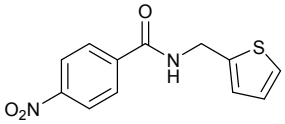
^{1}H NMR (400 MHz, $CDCl_3$):[6] δ 4.74 (d, 2H, J = 6 Hz), δ 7.23-7.43 (m, 5H), δ 7.58-7.61 (m, 1H), δ 7.70-7.74 (m, 1H), δ 7.88 (dd, 1H, J = 6 Hz, J = 2 Hz), δ 8.06 (dd, 1H, J = 6 Hz, J = 2 Hz), δ 8.32 (q, 2H, J = 9 Hz), δ 8.62 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.8, 150.0, 146.8, 138.7, 137.8, 130.4, 129.1, 128.1, 127.6, 119.3, 50.7, 43.9.

N-(4-methoxybenzyl)-4-nitrobenzamide



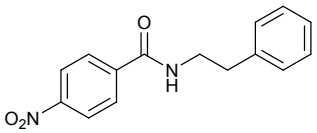
^{1}H NMR (300 MHz, $CDCl_3$):[7] δ 3.82 (s, 3H), δ 4.60 (d, 2H, J = 3 Hz), δ 6.52 (bs, 1H), δ 6.88-6.93 (m, 2H), δ 7.27-7.32 (m, 2H), δ 7.95 (d, *J* = 9.0 Hz, 2H), δ 8.28 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 159.7, 149.9, 140.3, 129.8, 128.5, 124.2, 114.6, 55.7, 44.3.

4-nitro-N-(thiophen-2-ylmethyl)benzamide



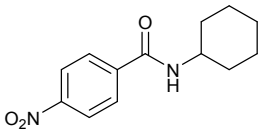
^{1}H NMR (300 MHz, $CDCl_3$):[8] δ 4.85 (dd, 2H, J = 1 Hz, J = 6 Hz), δ 6.64 (bs, 1H), δ 6.94-7.02 (m, 1H), δ 7.07-7.08 (m, 1H), δ 7.28-7.30 (m, 1H), δ 7.96 (d, *J* = 9.0 Hz, 2H), δ 8.29 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 150.0, 140.1, 128.6, 127.4, 127.0, 126.1, 124.2, 39.4.

4-nitro-N-phenethylbenzamide



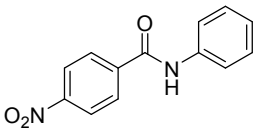
^{1}H NMR (300 MHz, $CDCl_3$):[9] δ 2.98 (t, 2H, J = 6 Hz), δ 3.77 (q, 2H, J = 6 Hz, J = 9 Hz), δ 6.25 (bs, 1H), δ 7.24-7.38 (m, 5H), δ 7.85 (d, *J* = 9.0 Hz, 2H), δ 8.26 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8, 149.9, 140.5, 138.8, 129.1, 128.3, 128.2, 127.2, 124.2, 41.7, 35.8.

N-cyclohexyl-4-nitrobenzamide



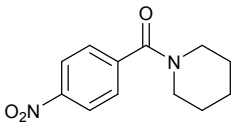
^{1}H NMR (400 MHz, $CDCl_3$):[10] δ 1.17-1.31 (m, 4H), δ 1.38-1.49 (m, 2H), δ 1.65-1.70 (m, 2H), δ 1.75-1.81 (m, 2H), δ 2.03-2.07 (m, 2H), δ 3.94-4,01 (m, 1H), δ 6.06 (bs, 1H), δ 7.91 (d, *J* = 9.0 Hz, 2H), δ 8.28 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 149.4, 140.6, 128.2, 123.7, 49.2, 33.1, 25.4, 24.8.

4-nitro-N-phenylbenzamide



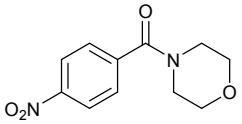
^{1}H NMR (400 MHz, DMSO-d_6):[11] δ 7.09-7.13 (m, 1H), δ 7.32-7.37 (m, 2H), δ 7.73-7.76 (m, 2H), δ 8.15 (d, *J* = 9.0 Hz, 2H), δ 8.34 (d, *J* = 9.0 Hz, 2H), δ 10.54 (bs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3, 149.5, 141.0, 139.1, 129.6, 129.1, 124.6, 124.0, 120.9.

(4-nitrophenyl)-N-(piperidin-1-yl)methanone



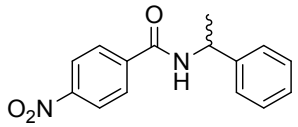
^{1}H NMR (300 MHz, $CDCl_3$):[12] δ 1.43 (bs, 2H), δ 1.71 (bs, 4H), δ 3.30 (bs, 2H), δ 3.74 (bs, 2H), 7.57 (d, *J* = 9.0 Hz, 2H), 8.28 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 148.5, 143.0, 128.1, 124.2, 48.9, 43.5, 26.9, 25.8, 24.7.

morpholino(4-nitrophenyl)methanon



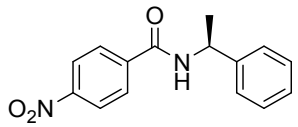
^{1}H NMR (300 MHz, $CDCl_3$):[13] δ 3.41-3.81 (m, 8H), δ 7.60 (d, *J* = 9.0 Hz, 2H), δ 8.30 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4, 141.7, 128.5, 124.3, 67.1, 48.3, 42.9.

(*R,S*)-N-(1-phenylethyl)-4-nitrobenzamide



^{1}H NMR (300 MHz, $CDCl_3$):[14] δ 1.65 (d, 3H, J = 12 Hz), δ 5.34 (m, 1H), δ 6.54 (d, 2H, J = 6 Hz), δ 7.28-7.40 (m, 5H), δ 7.92 (d, *J* = 9.0 Hz, 2H), δ 8.26 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): δ ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.9, 149.9, 142.8, 140.5, 129.2, 128.5, 128.1, 126.6, 124.1, 50.1, 21.9

***(S)*-N-(1-phenylethyl)-4-nitrobenzamide**



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.66 (d, 3H, J = 12 Hz), δ 5.36 (m, 1H), δ 6.42 (d, 2H, J = 6 Hz), δ 7.28-7.41 (m, 5H), δ 7.94 (d, *J* = 9.0 Hz, 2H), δ 8.28 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.9, 149.9, 142.8, 140.5, 129.2, 128.5, 128.1, 126.6, 124.1, 50.1, 21.9.

4. Solvent effect

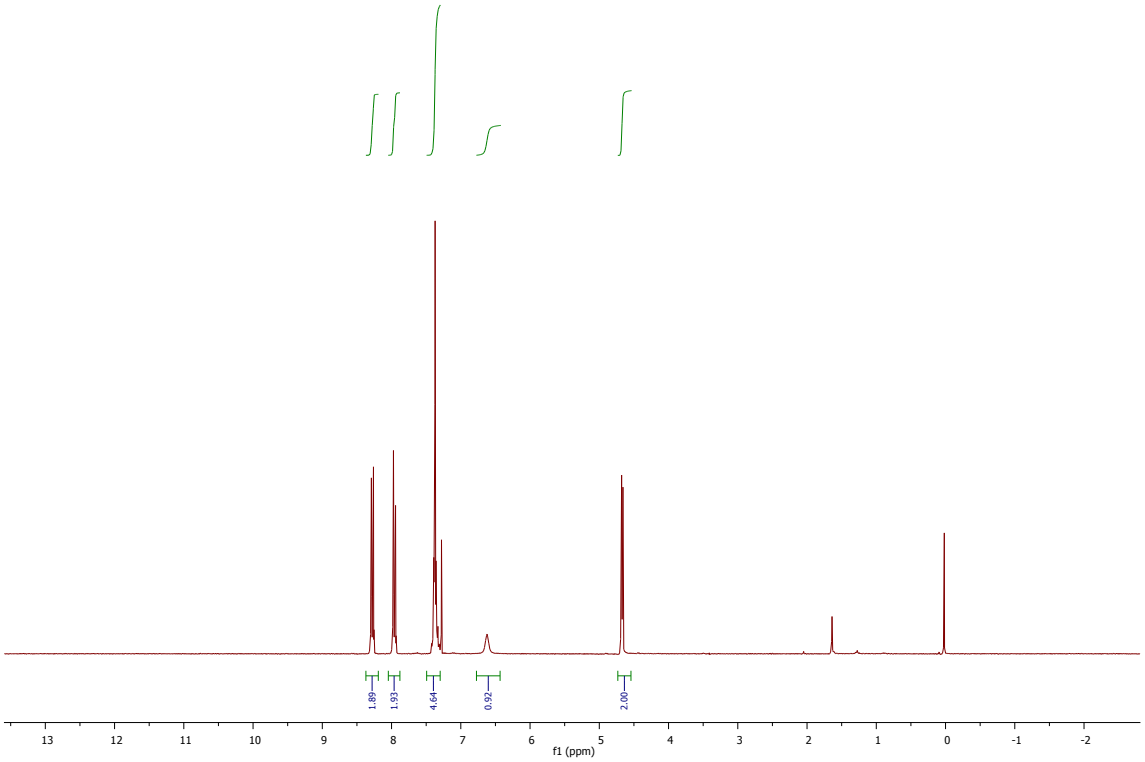
Table S1: Effect of the solvent on the amide bond formation[a]

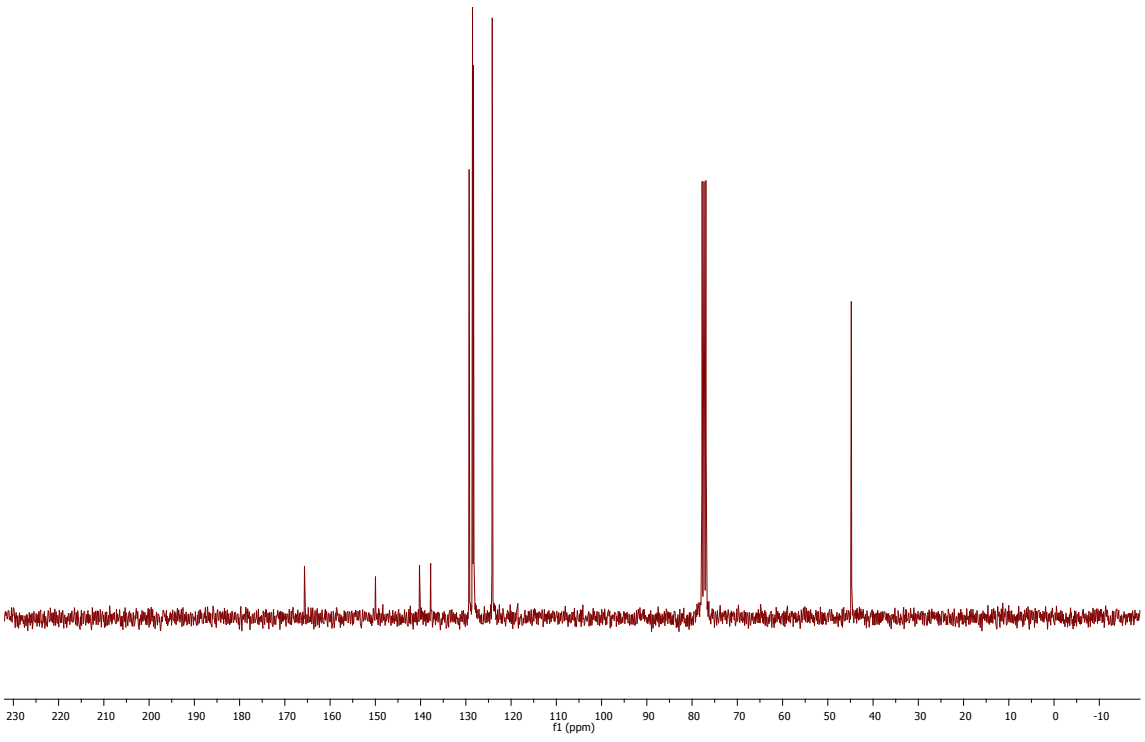
Entry	Solvent	Catalytic conversion (%)	Uncatalytic conversion (%)
1	acetonitrile	36	55
2	dioxane	17	60
3	THF	7	30
4	o-xylene	59	79

[a]Conditions: 4-nitrobenzoic acid (1 mmol), benzylamine (1.3 mmol), Ph_3P (0.25 mmol), CCl_4 (2.00 mmol), $(EtO)_2MeSiH$ (1.5 mmol), bis(4-nitrophenyl) phosphate (0.05 mmol), anhydrous solvent (5 mL), reflux, 20 h.

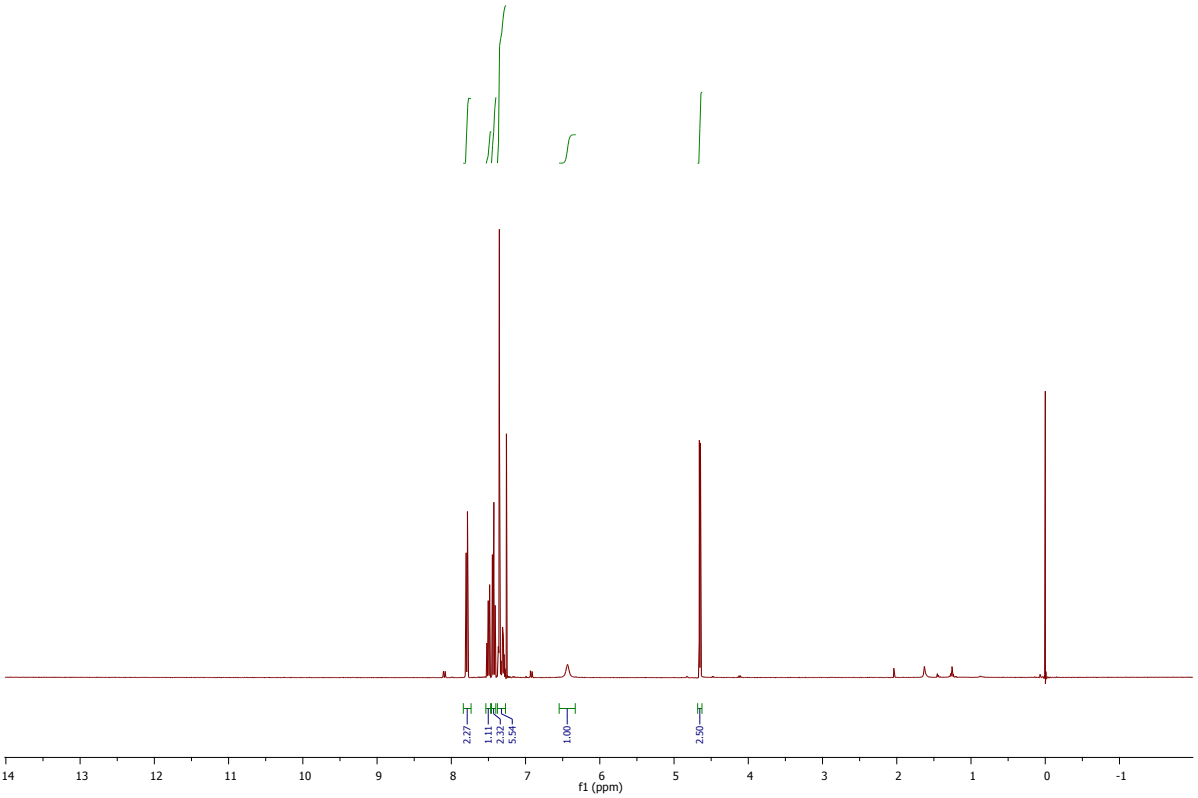
5. ^{1}H and ^{13}C NMR spectra

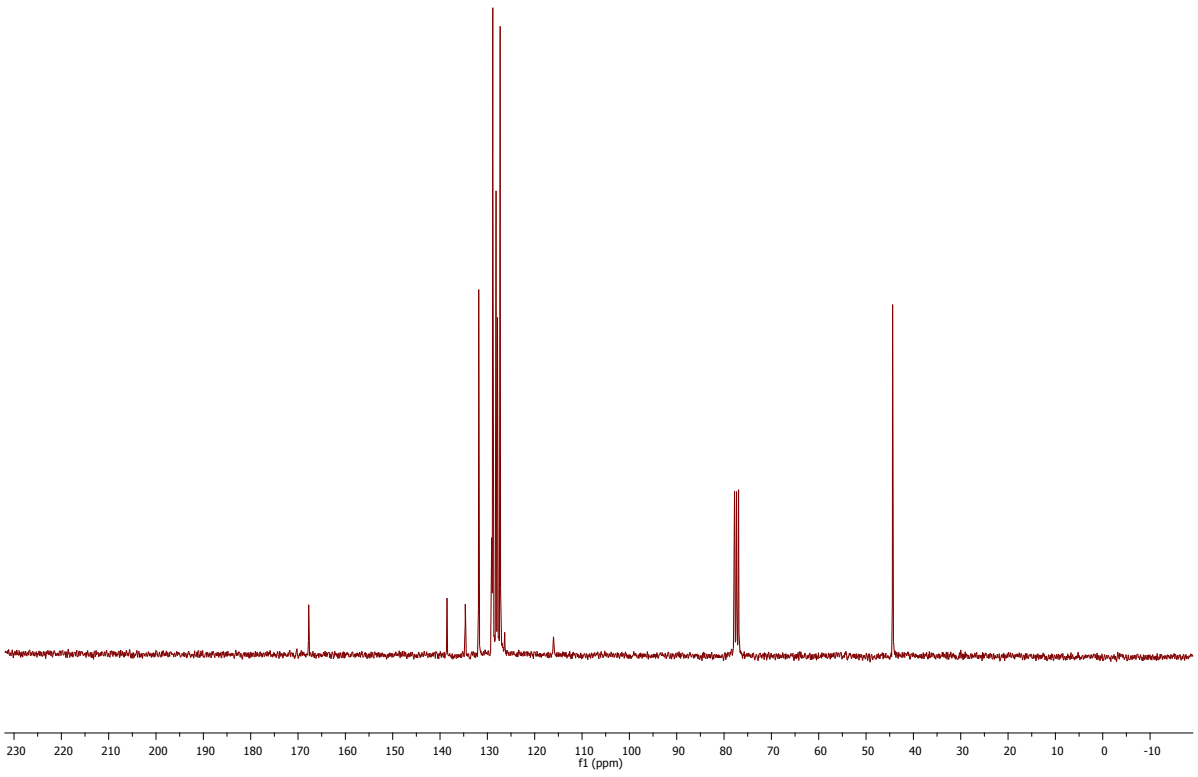
N-benzyl-4-nitrobenzamide



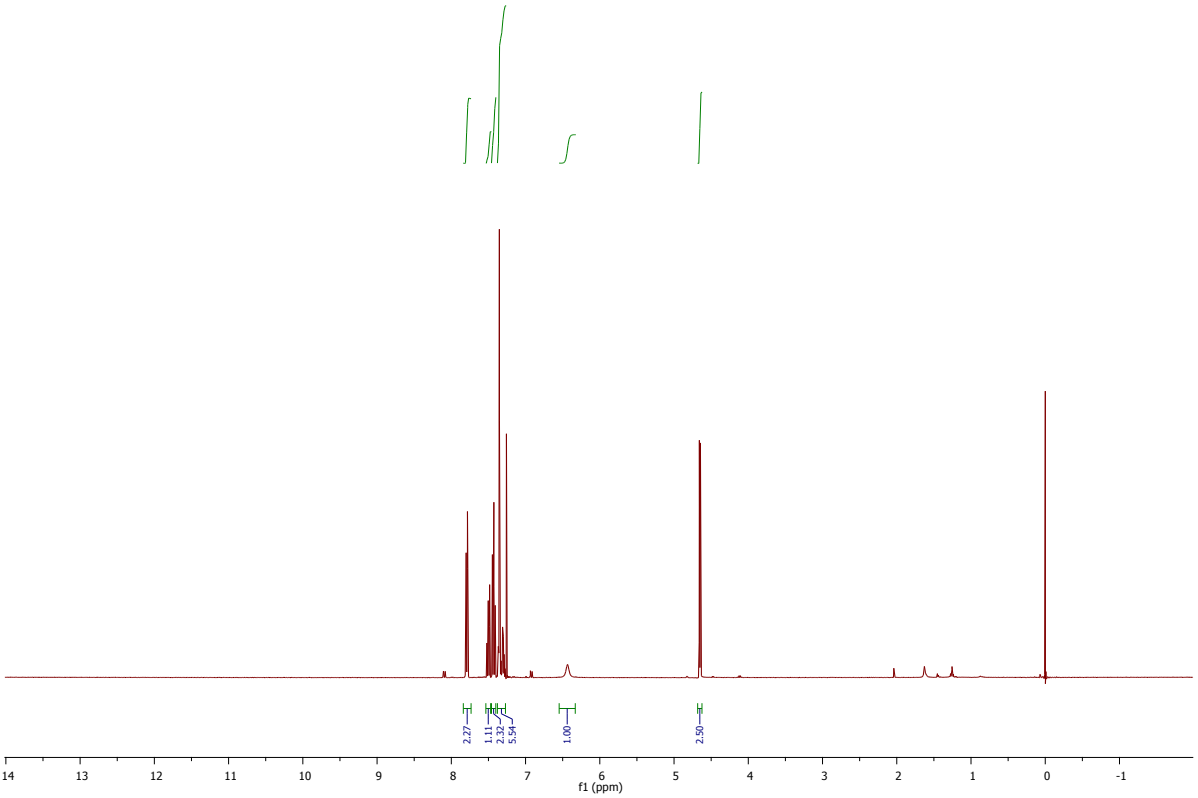


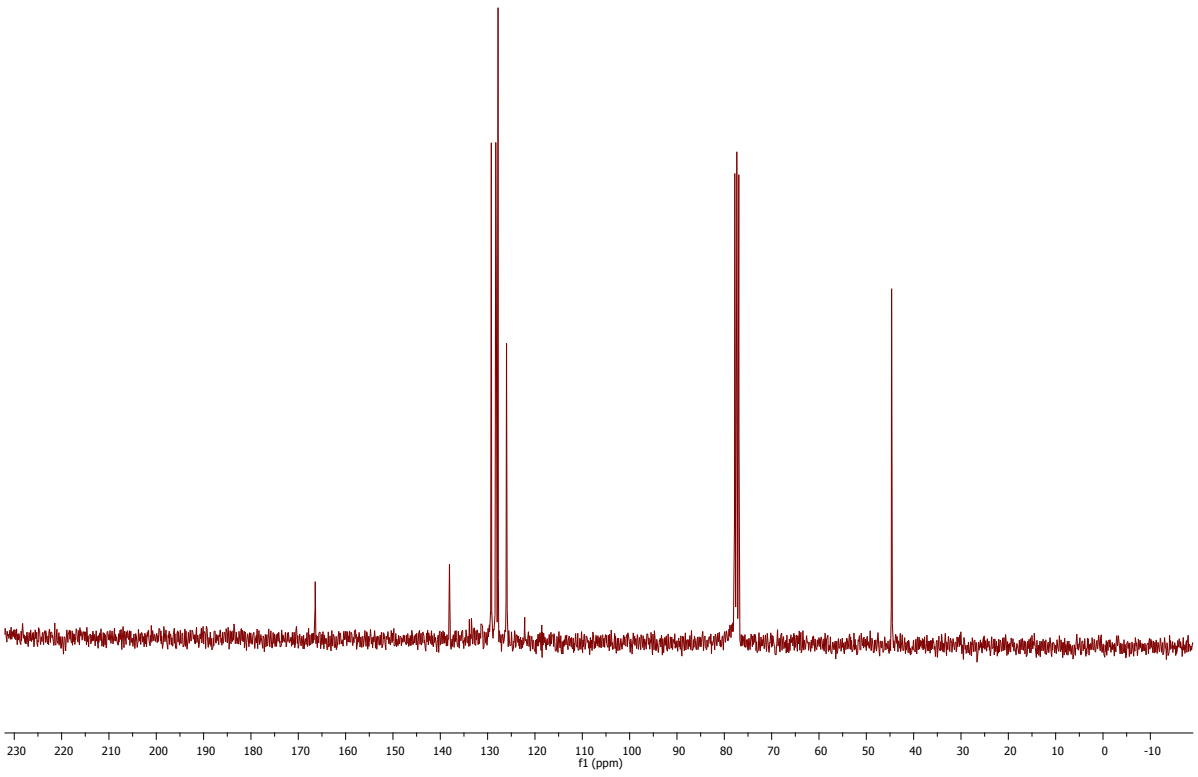
N-benzylbenzamide



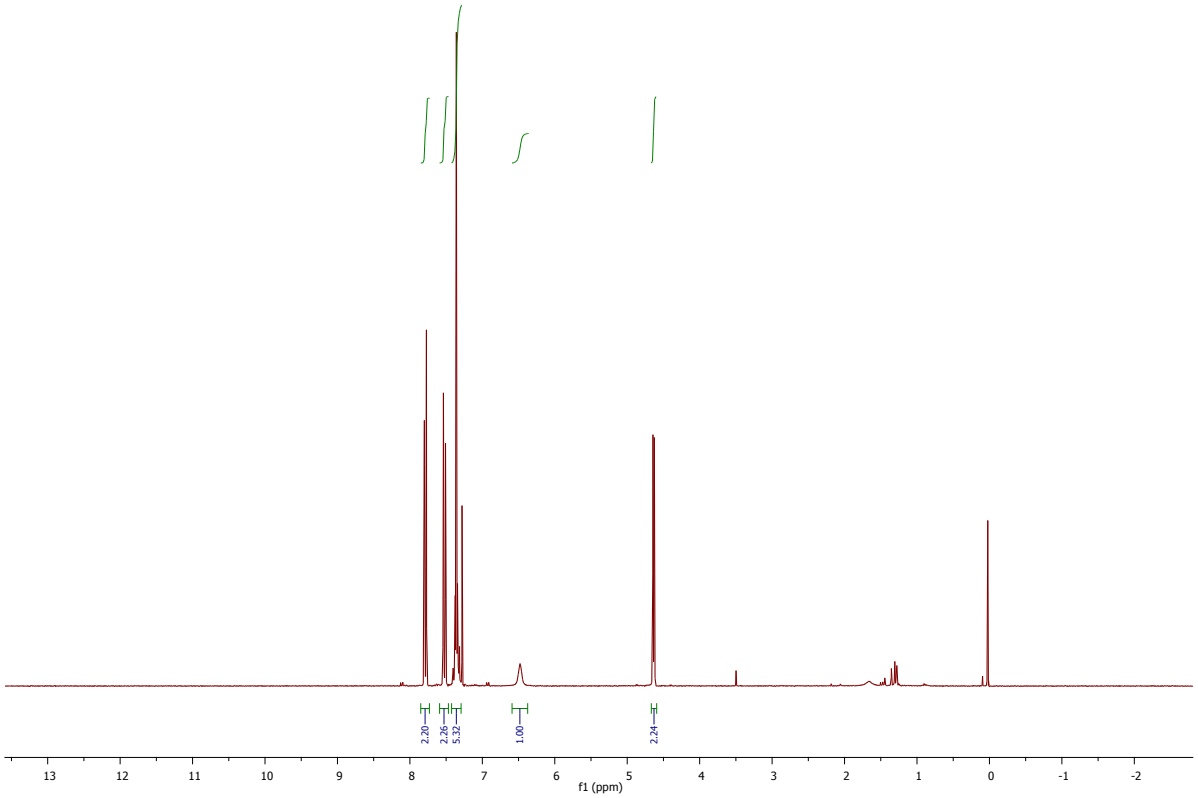


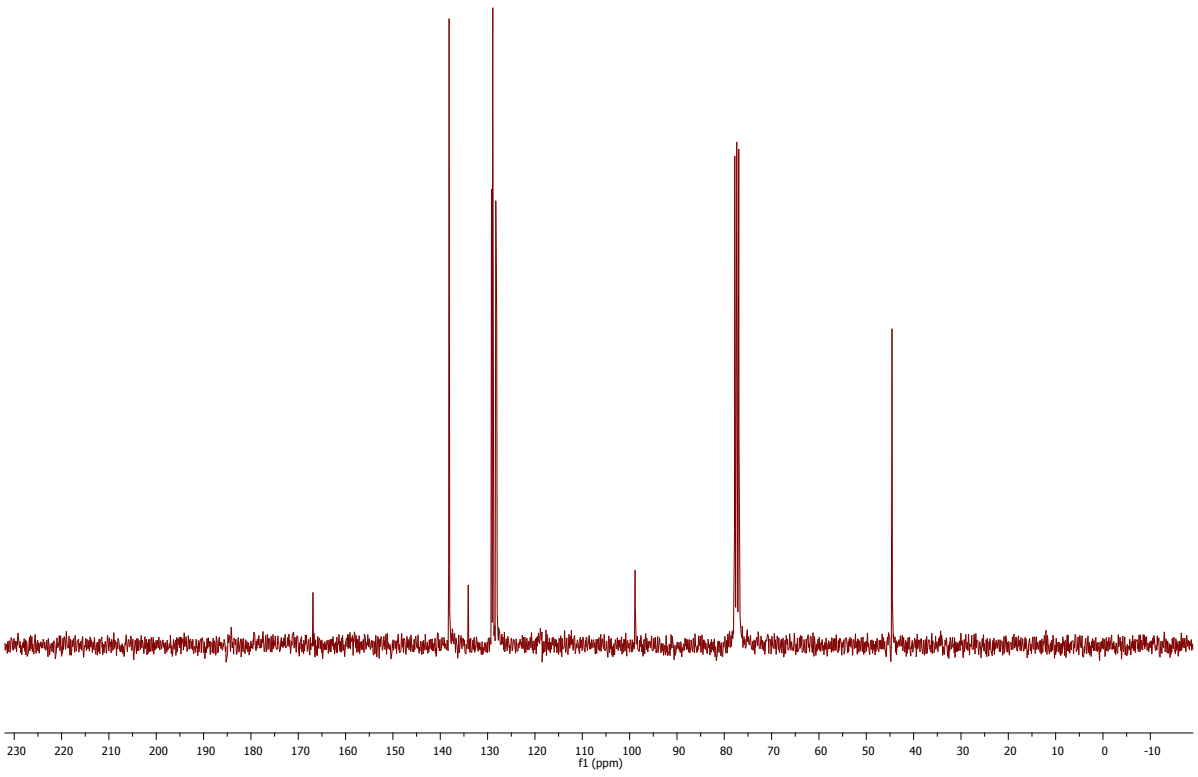
N-benzyl-4-(trifluoromethyl)benzamide



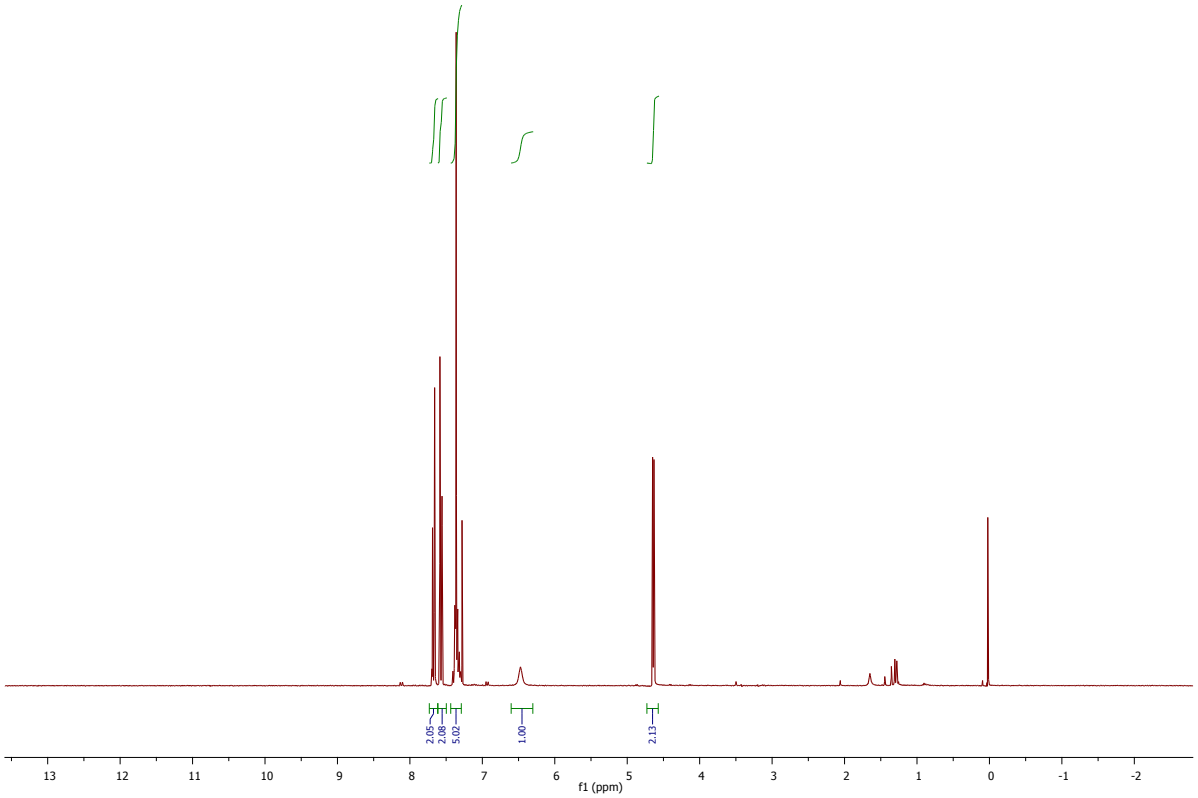


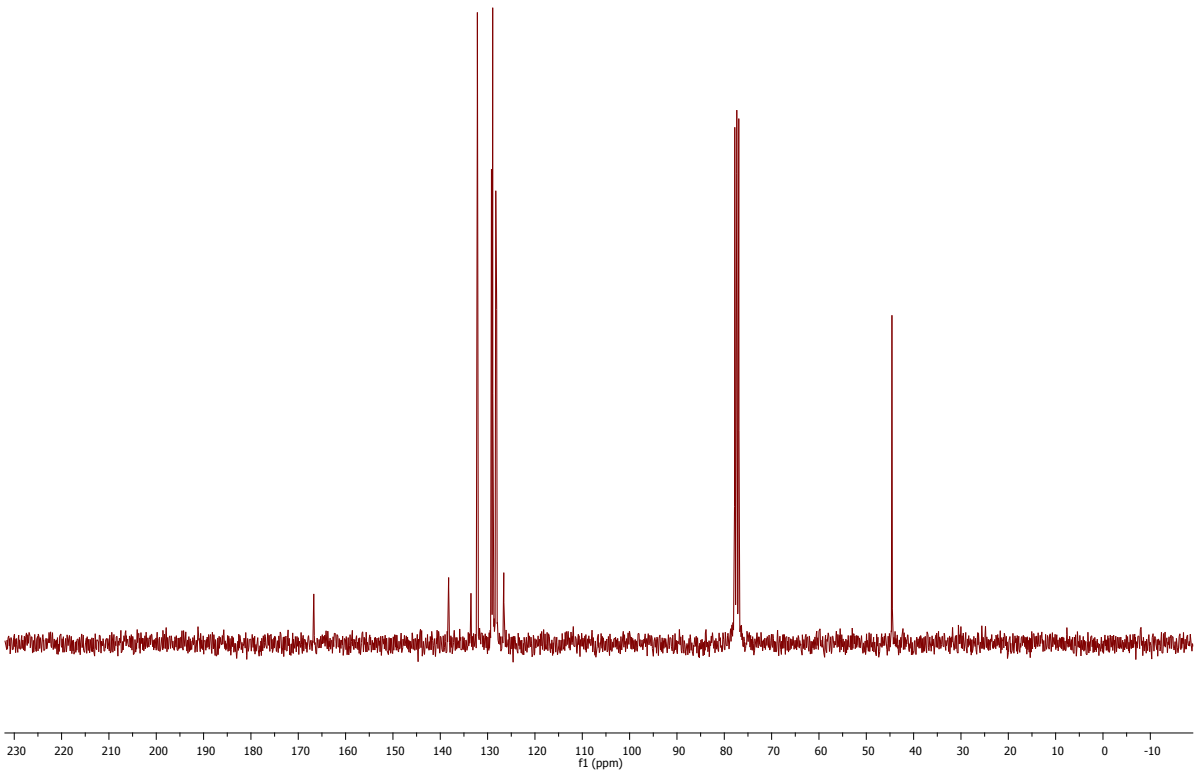
N-benzyl-4-iodobenzamide





N-benzyl-4-bromobenzamide





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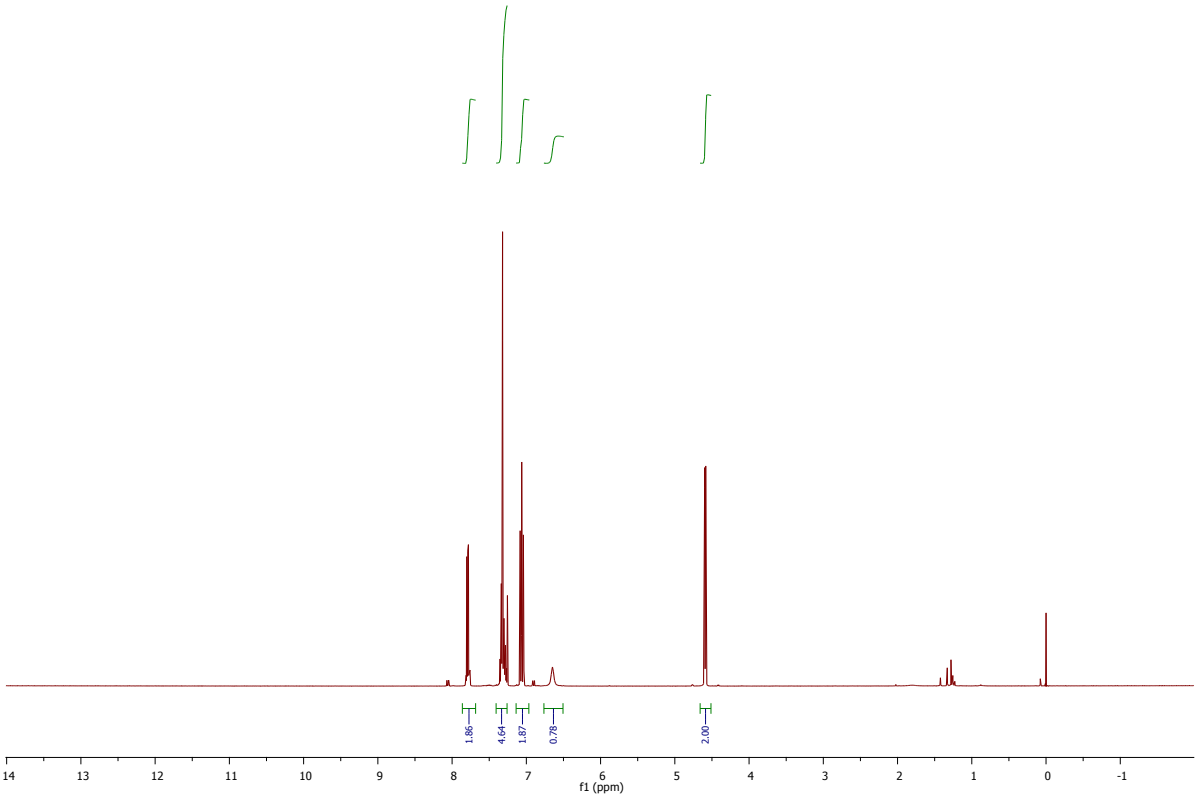

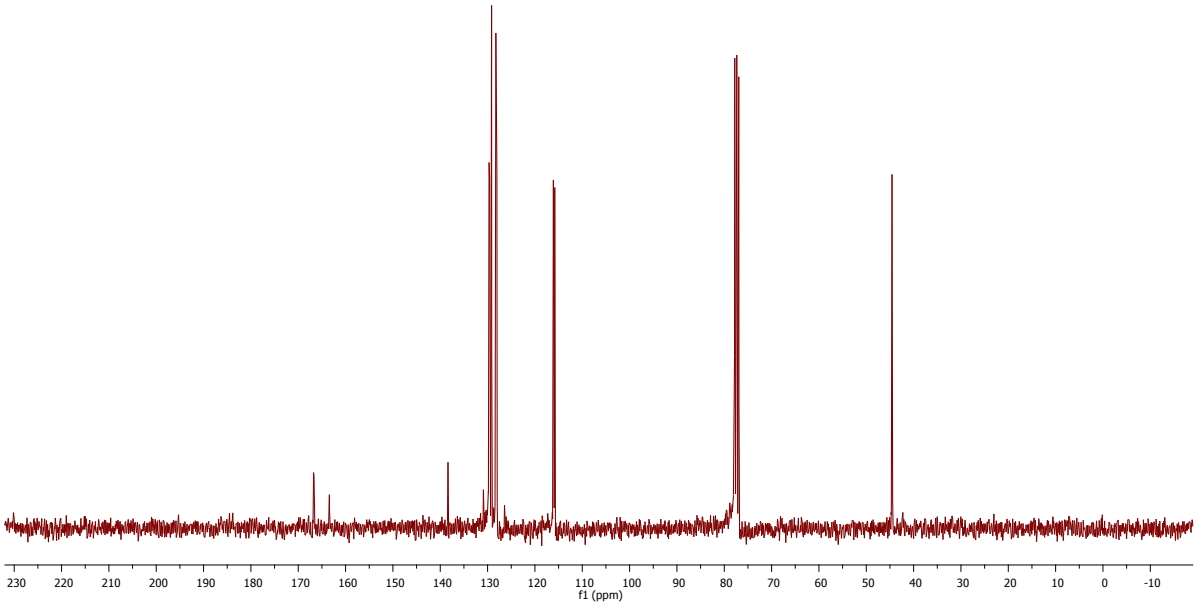

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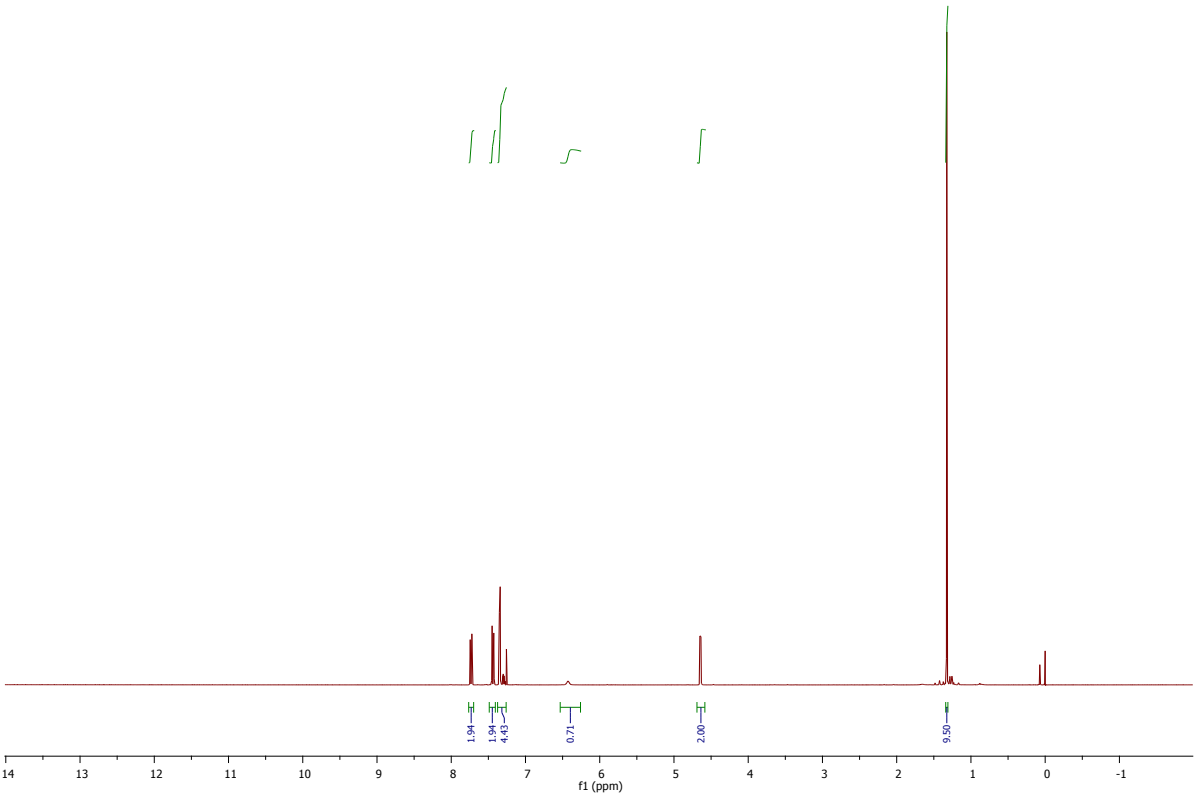

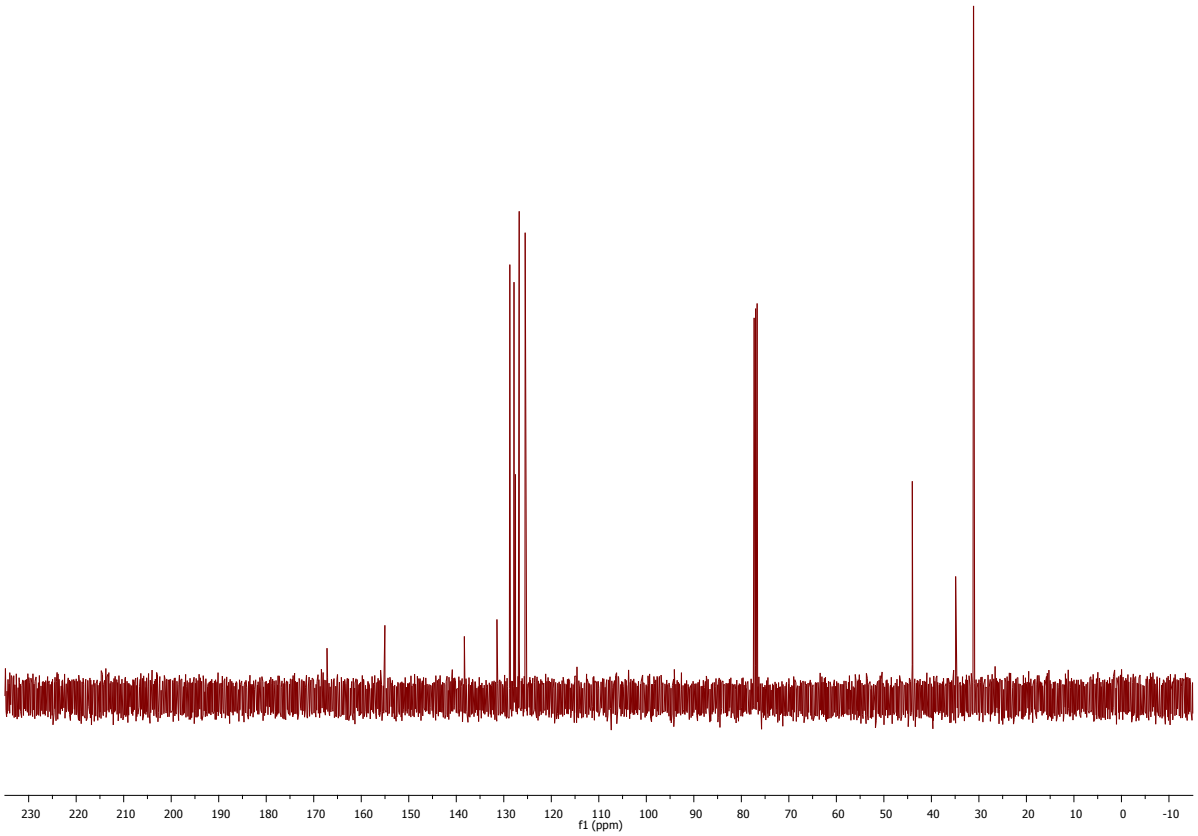

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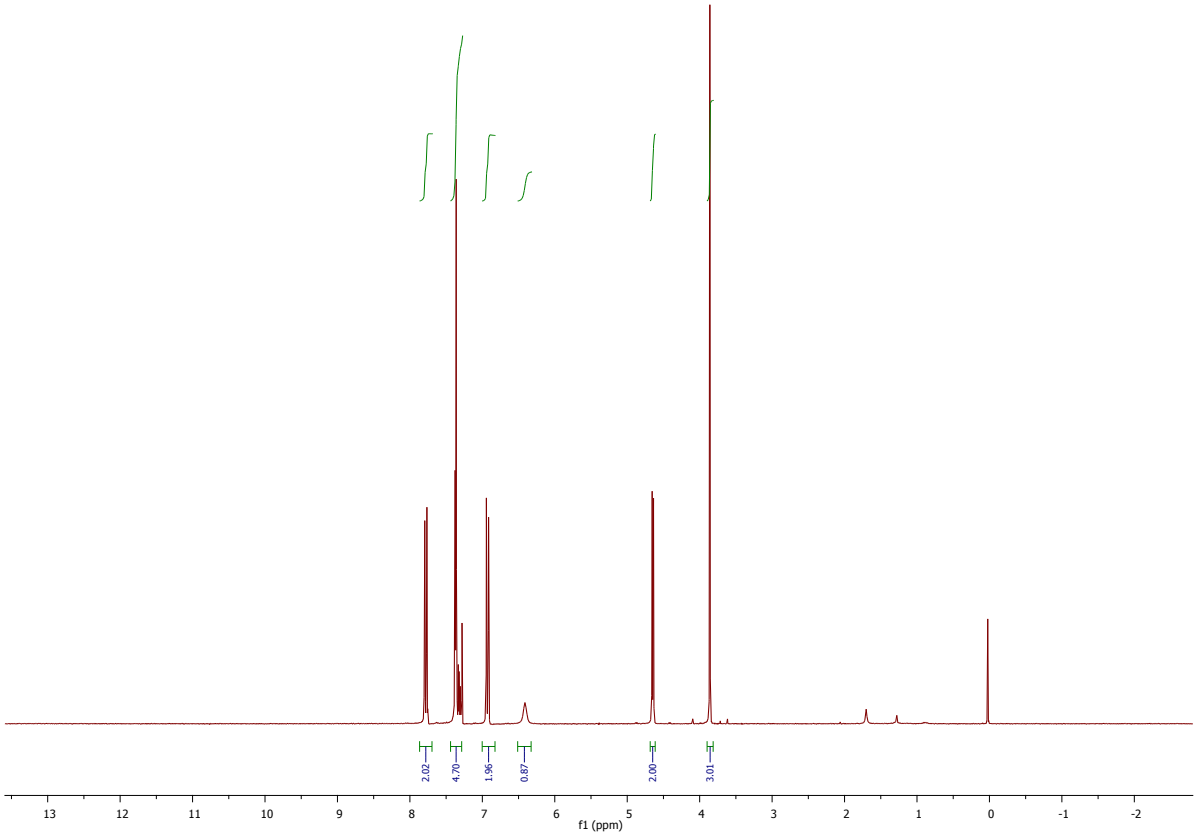
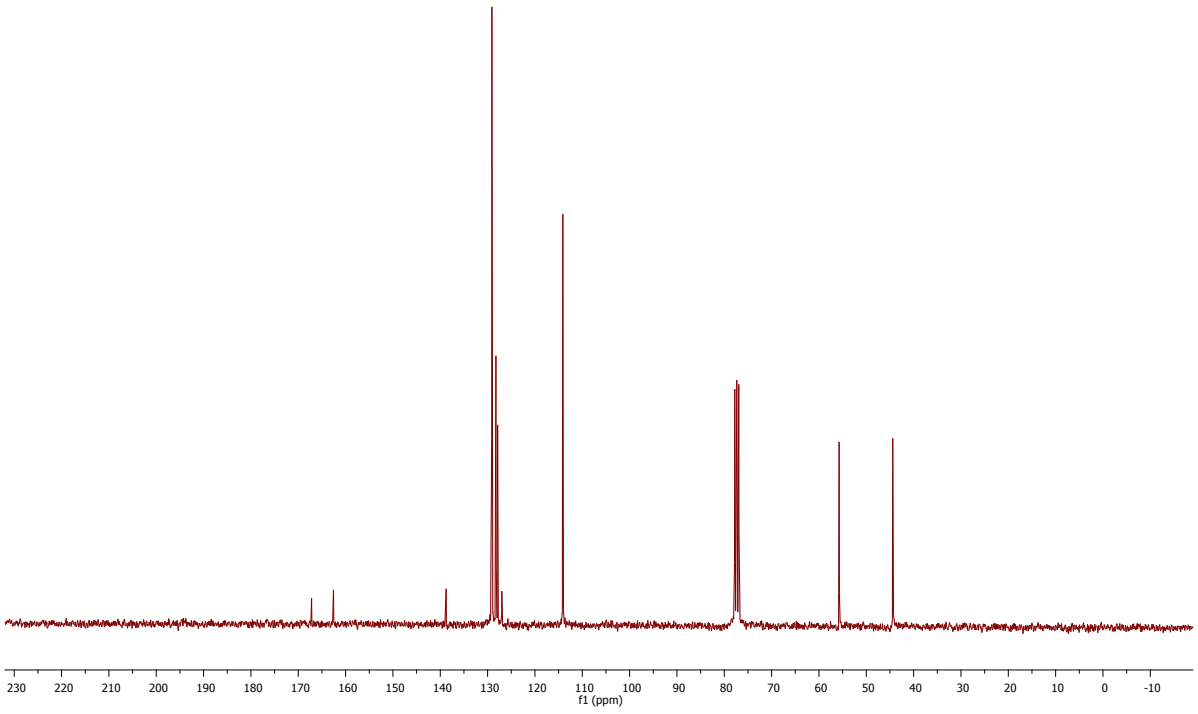
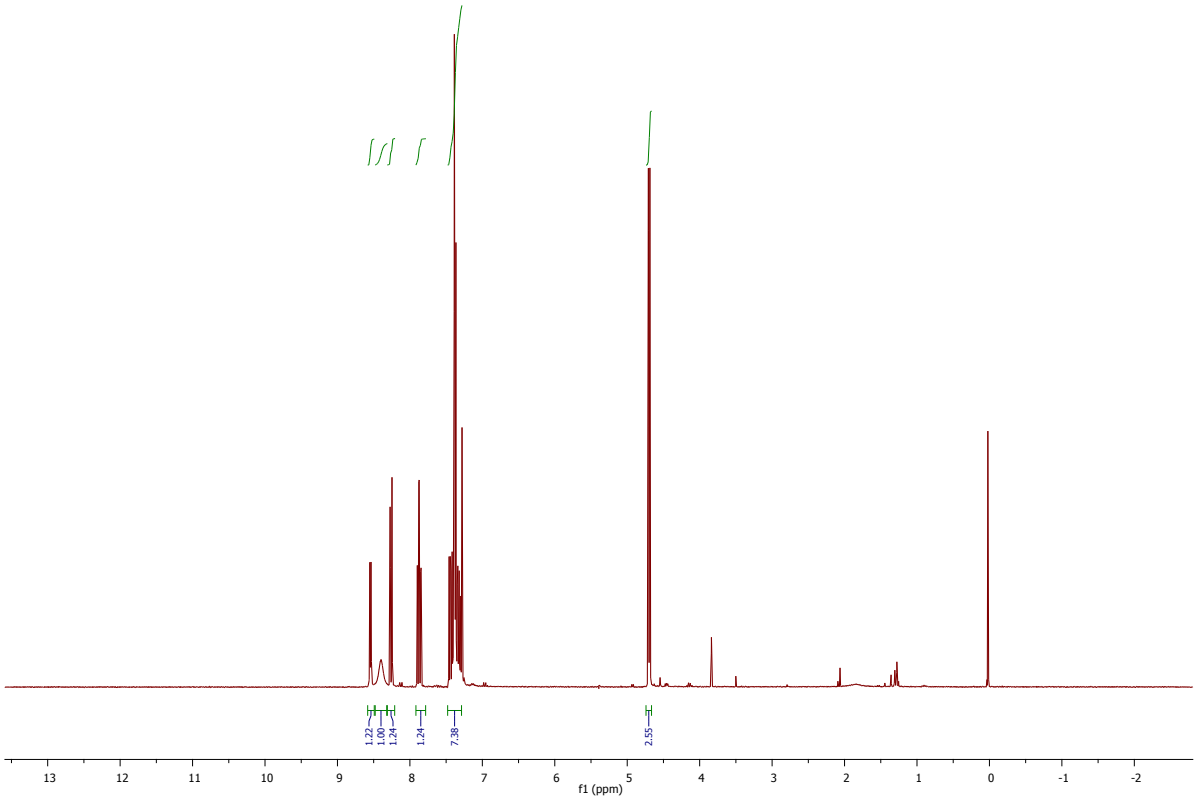
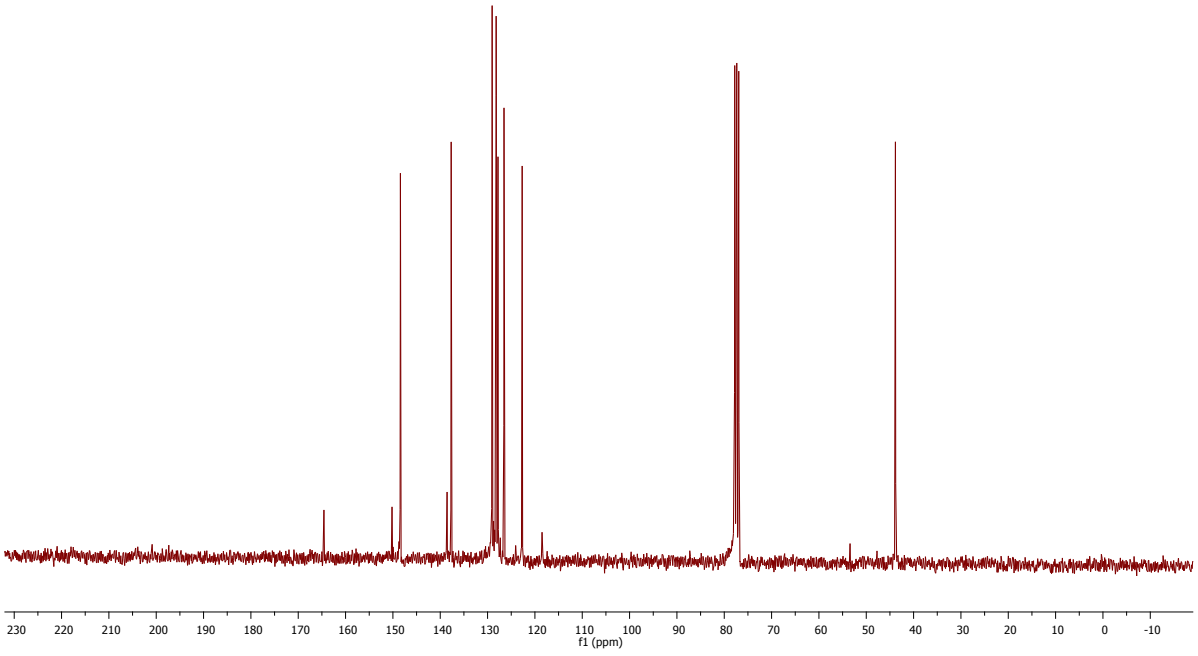


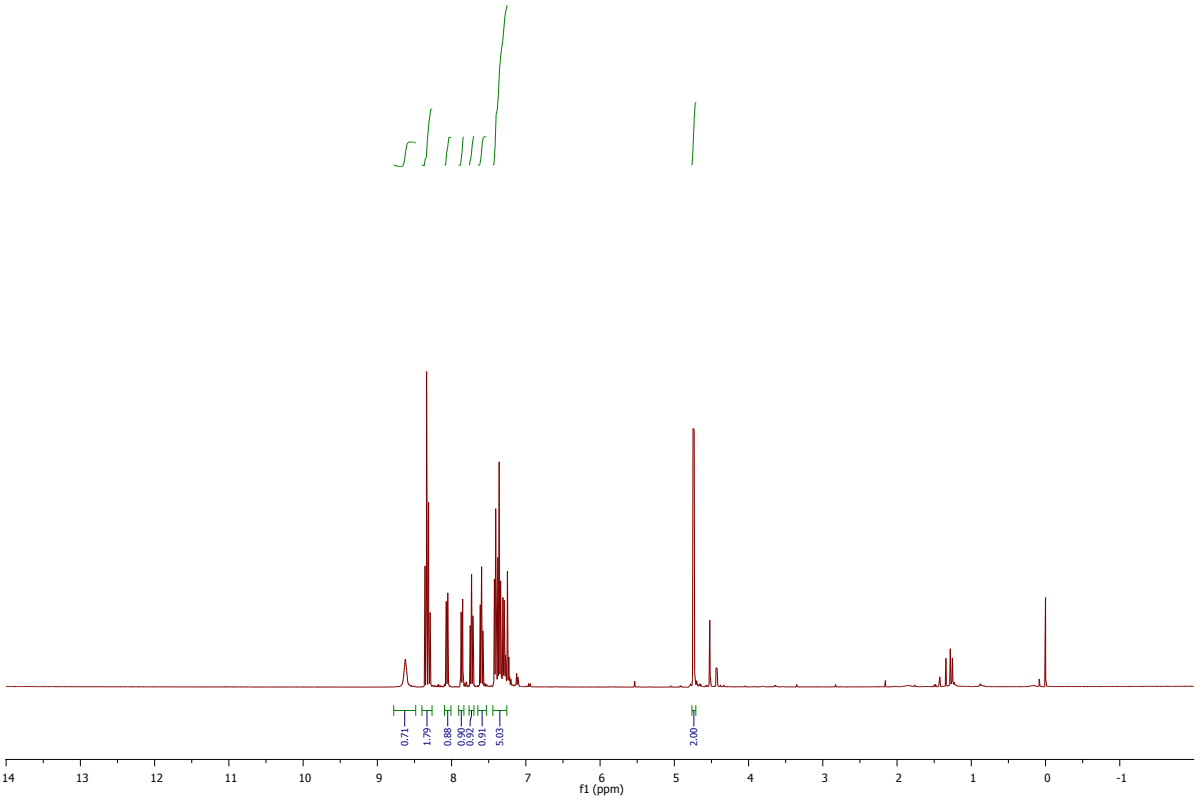


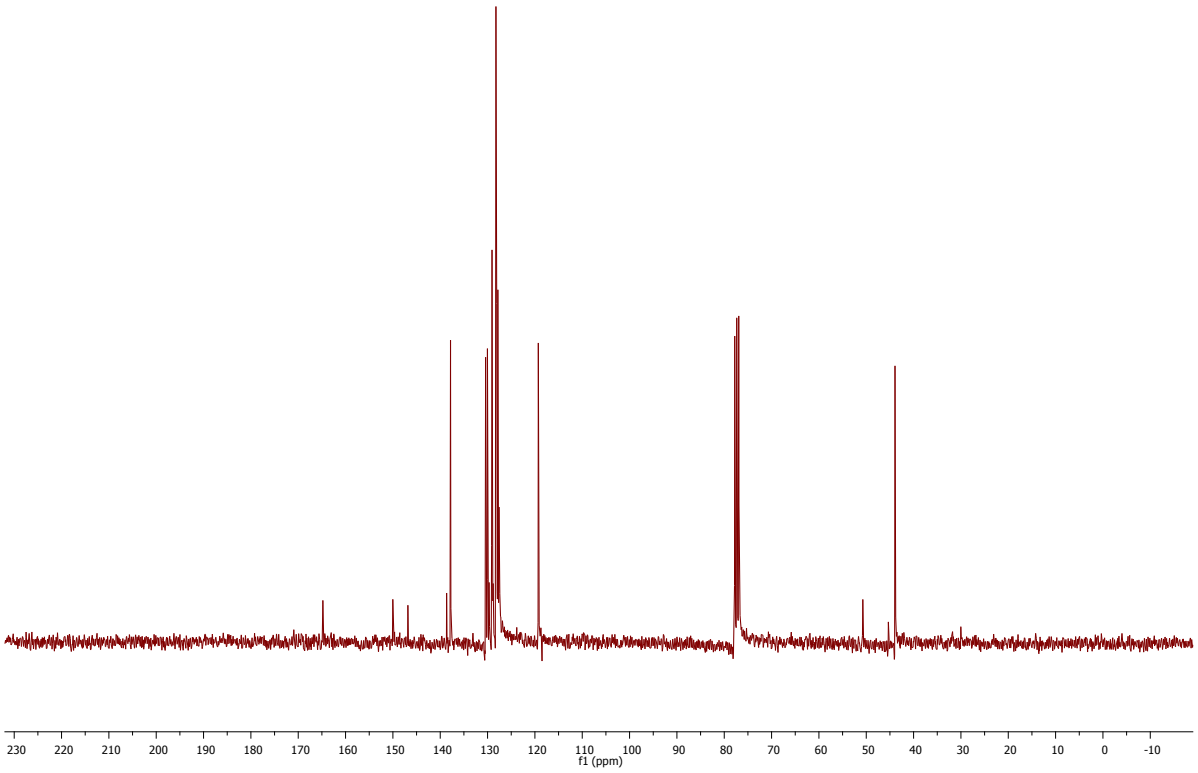
N-benzyl-picolinamide



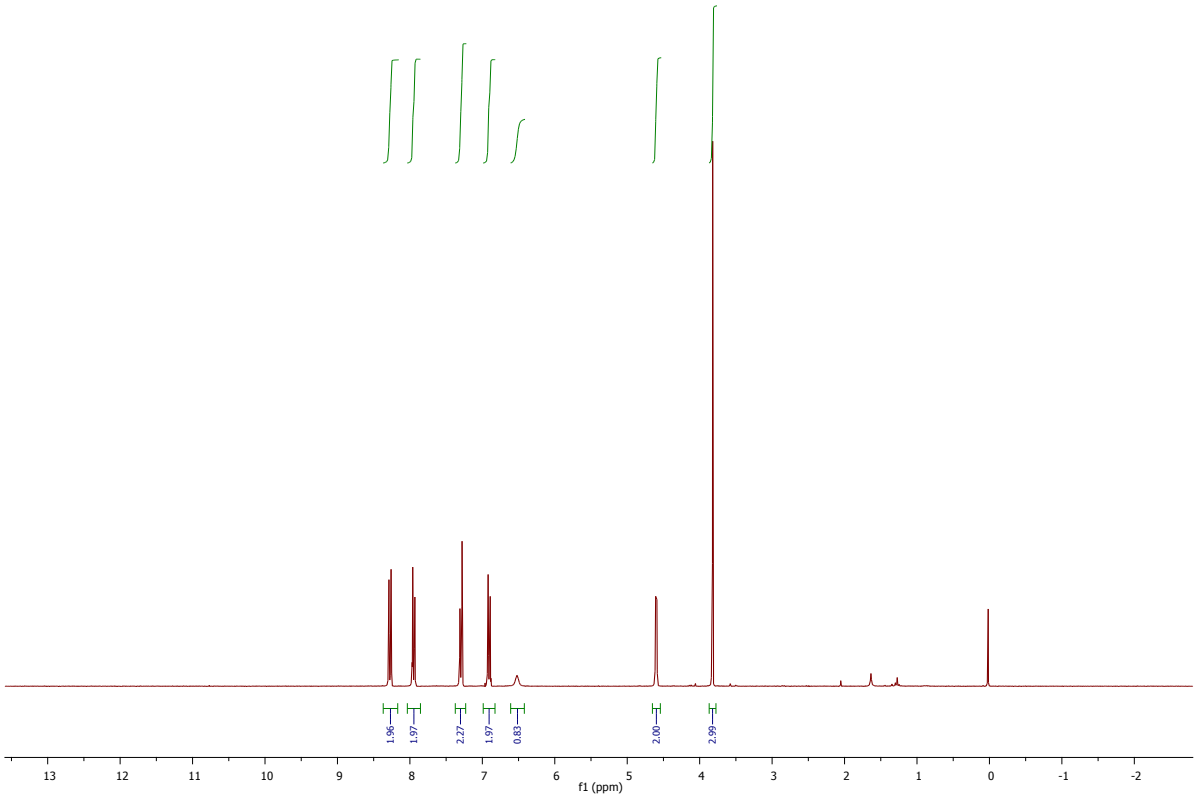


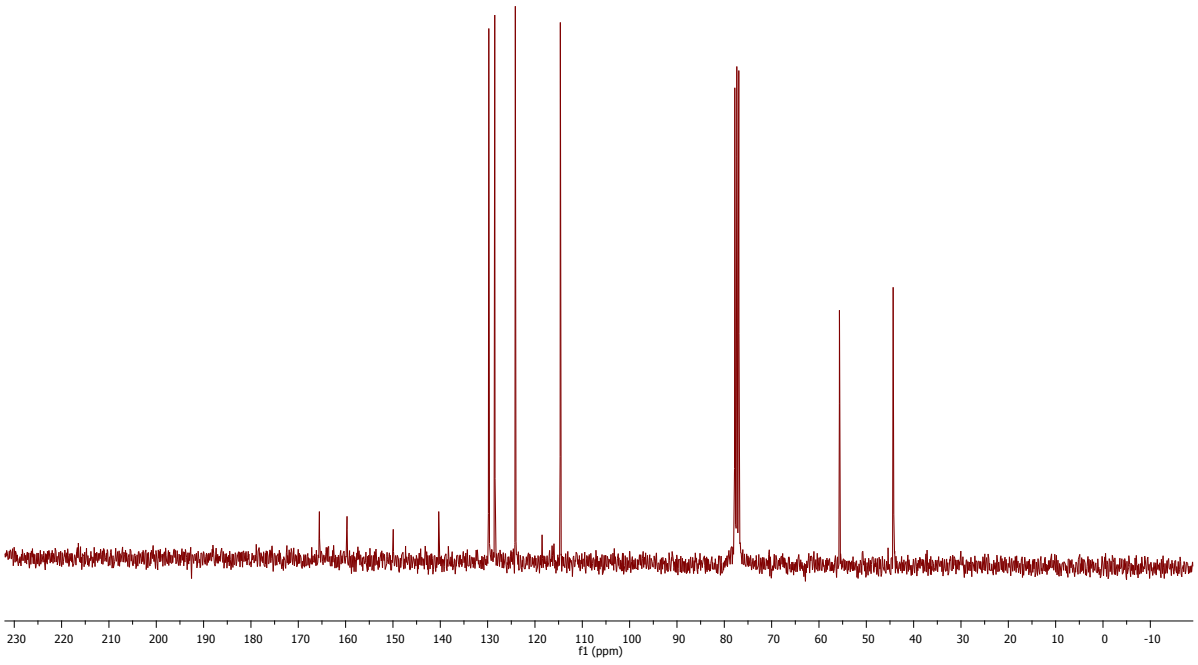
N-benzylquinoline-2-carboxamide



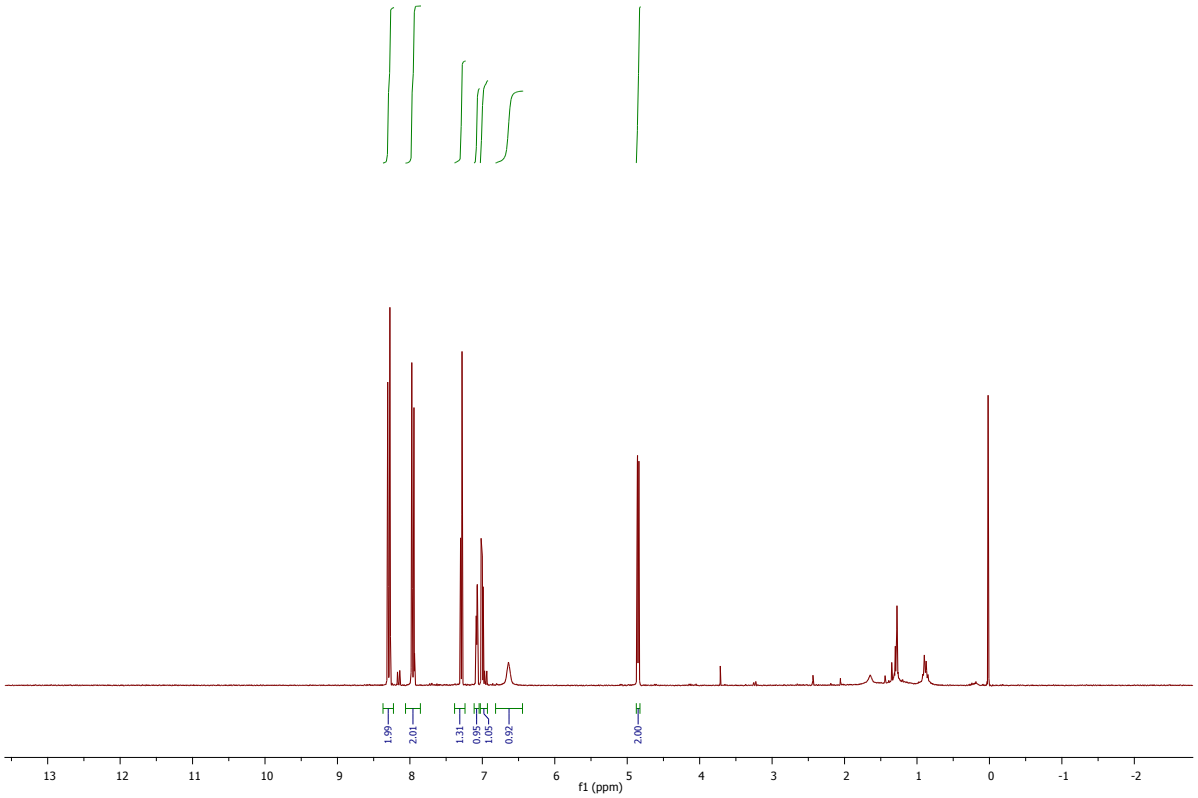


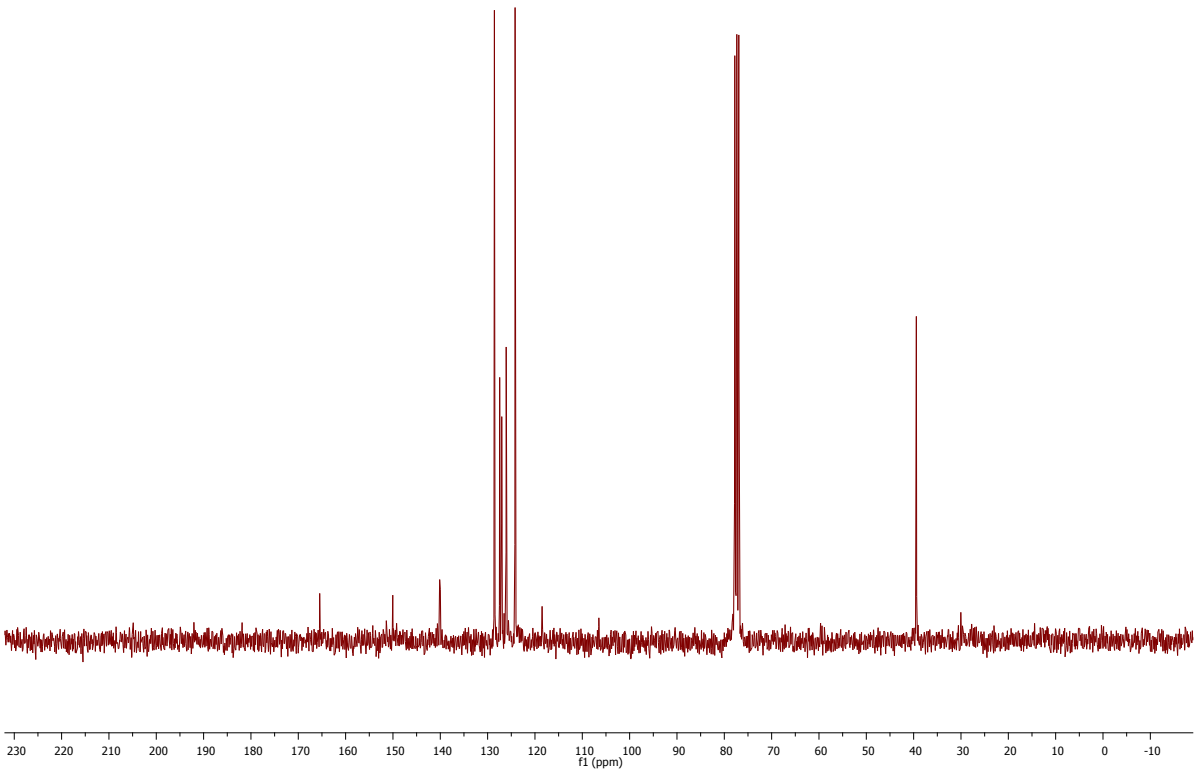
N-(4-methoxybenzyl)-4-nitrobenzamide



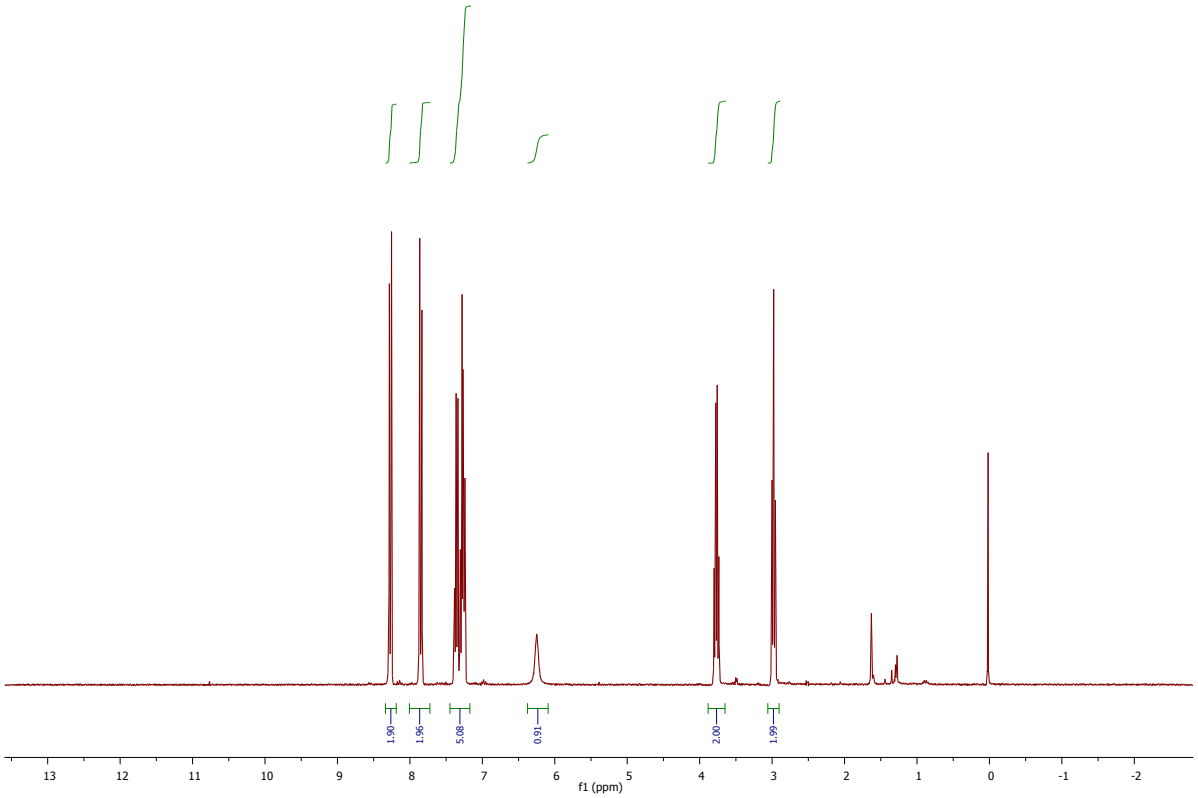


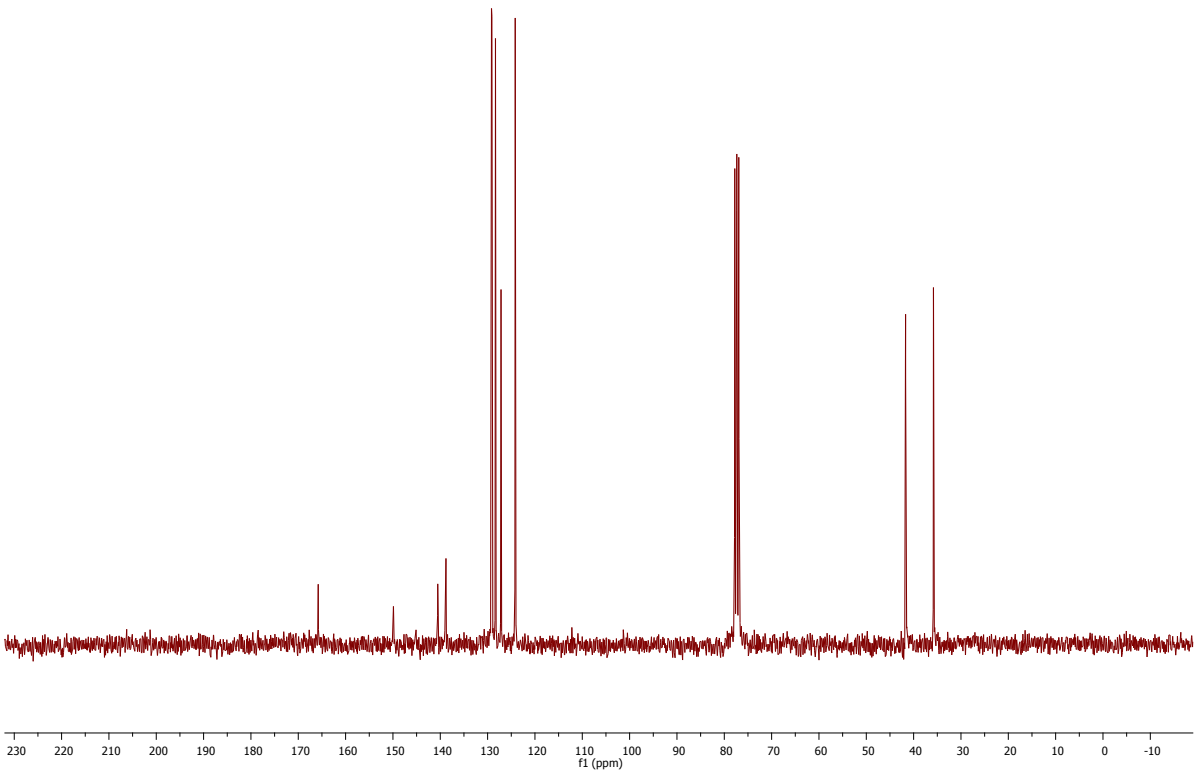
4-nitro-N-(thiophen-2-ylmethyl)benzamide



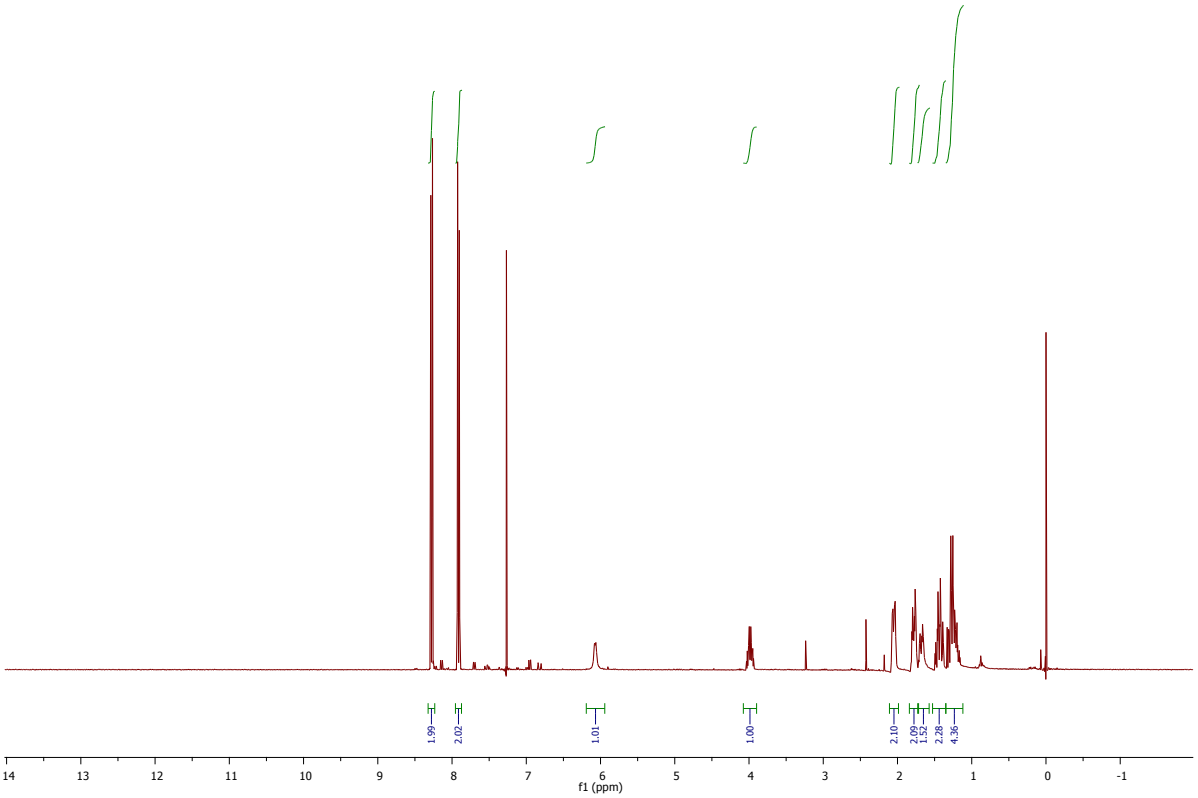


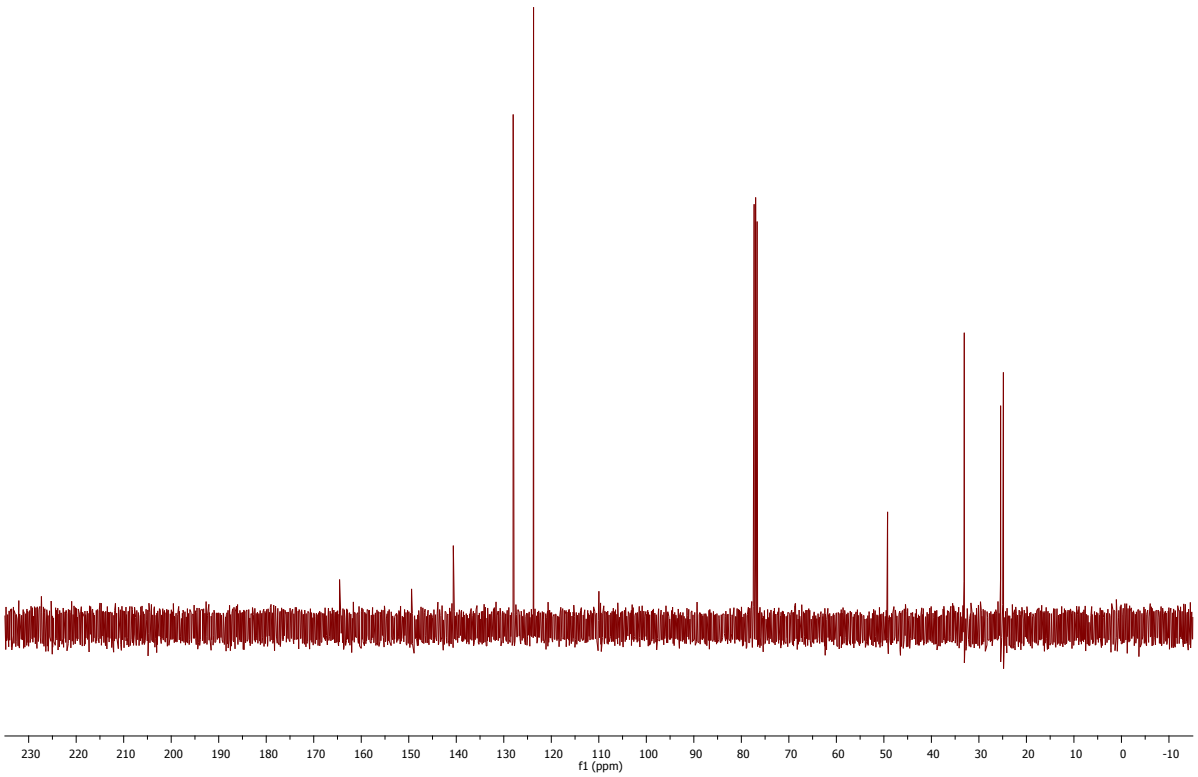
4-nitro-N-phenethylbenzamide



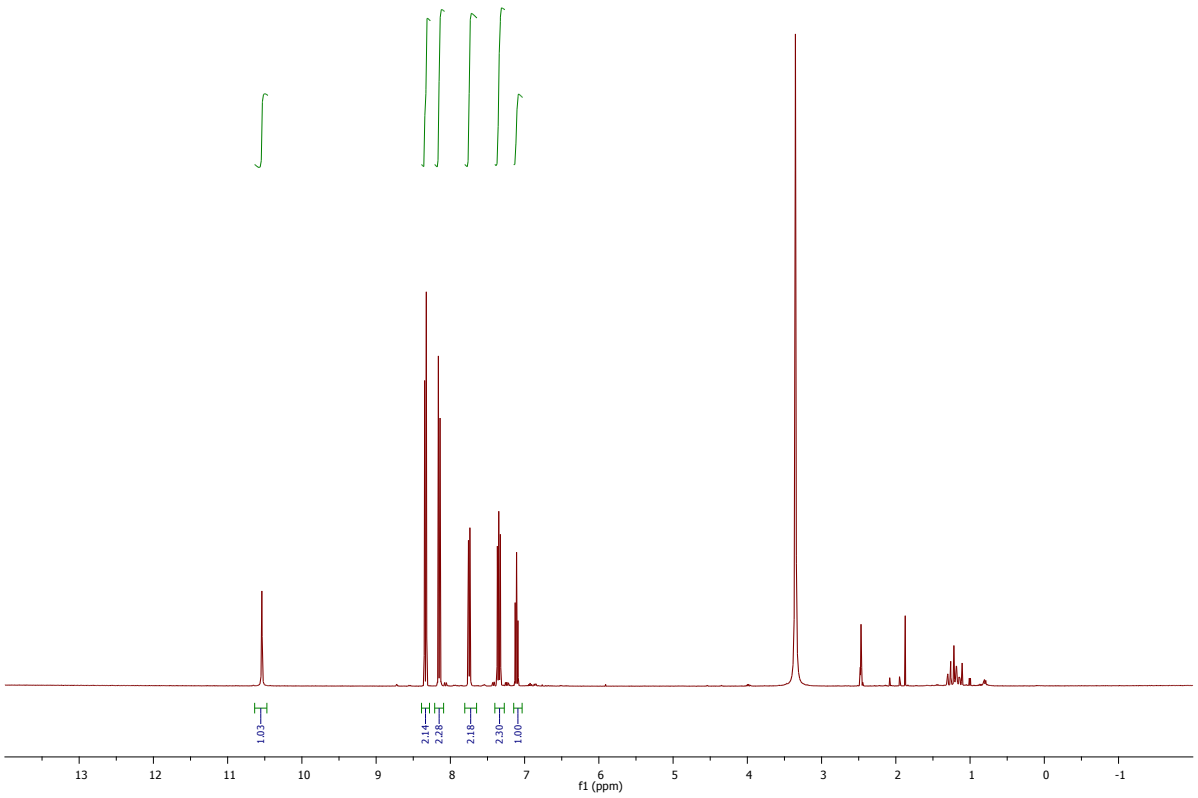


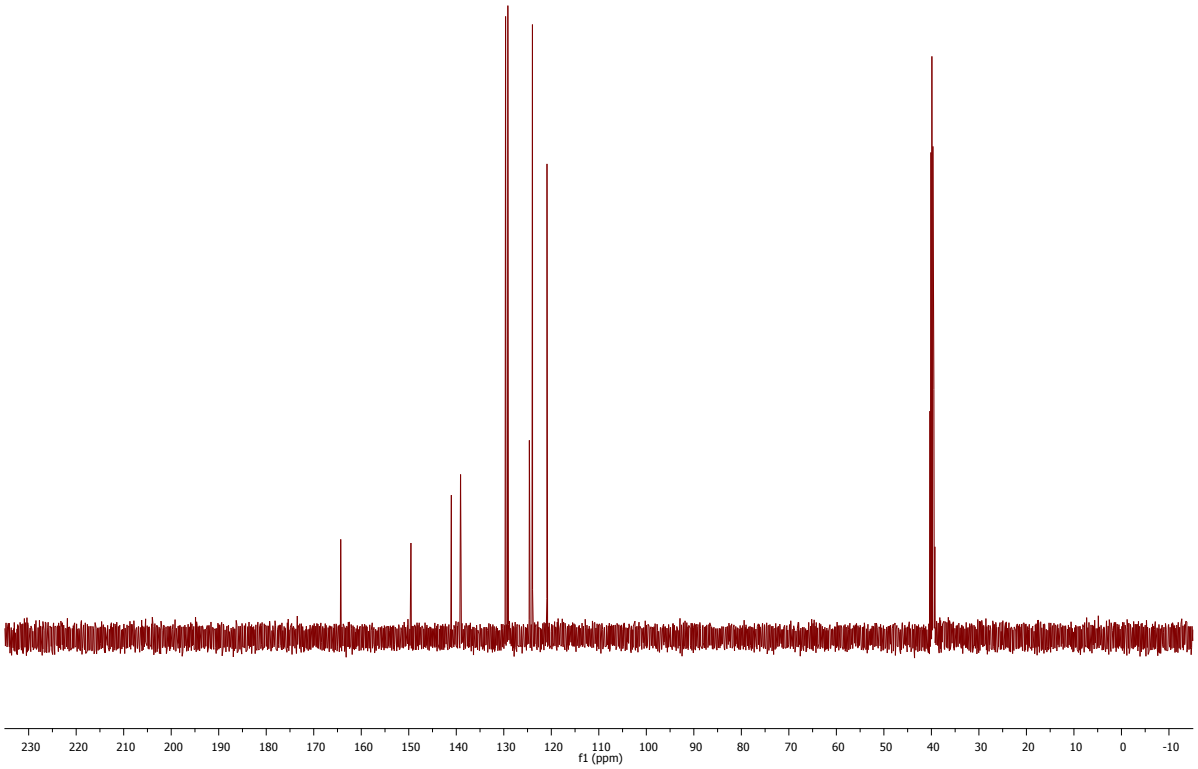
N-cyclohexyl-4-nitrobenzamide



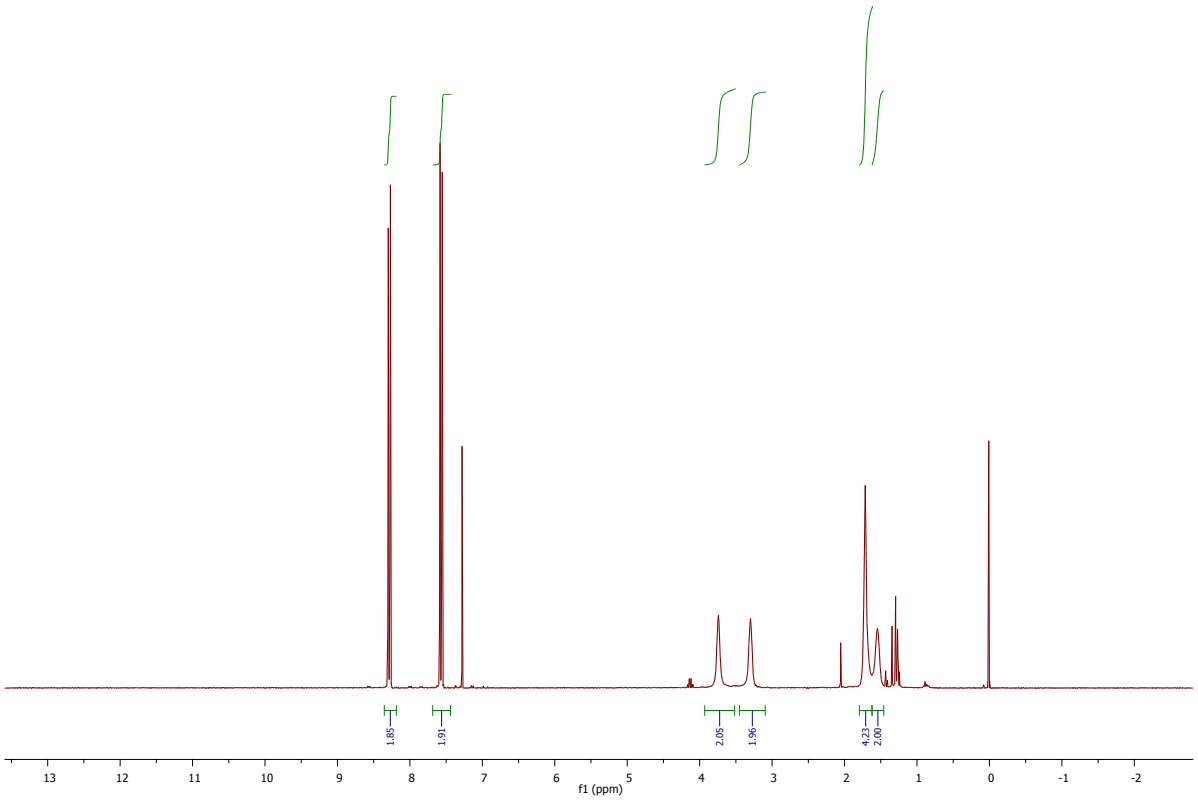


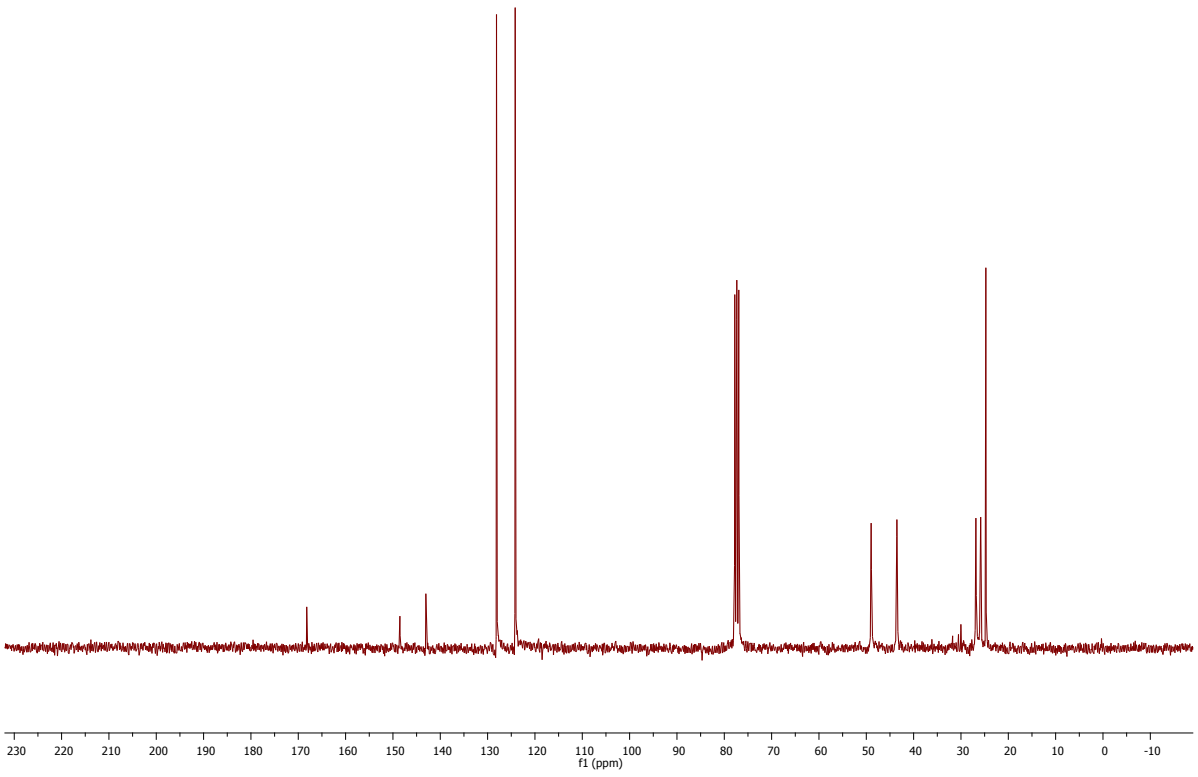
4-nitro-N-phenylbenzamide



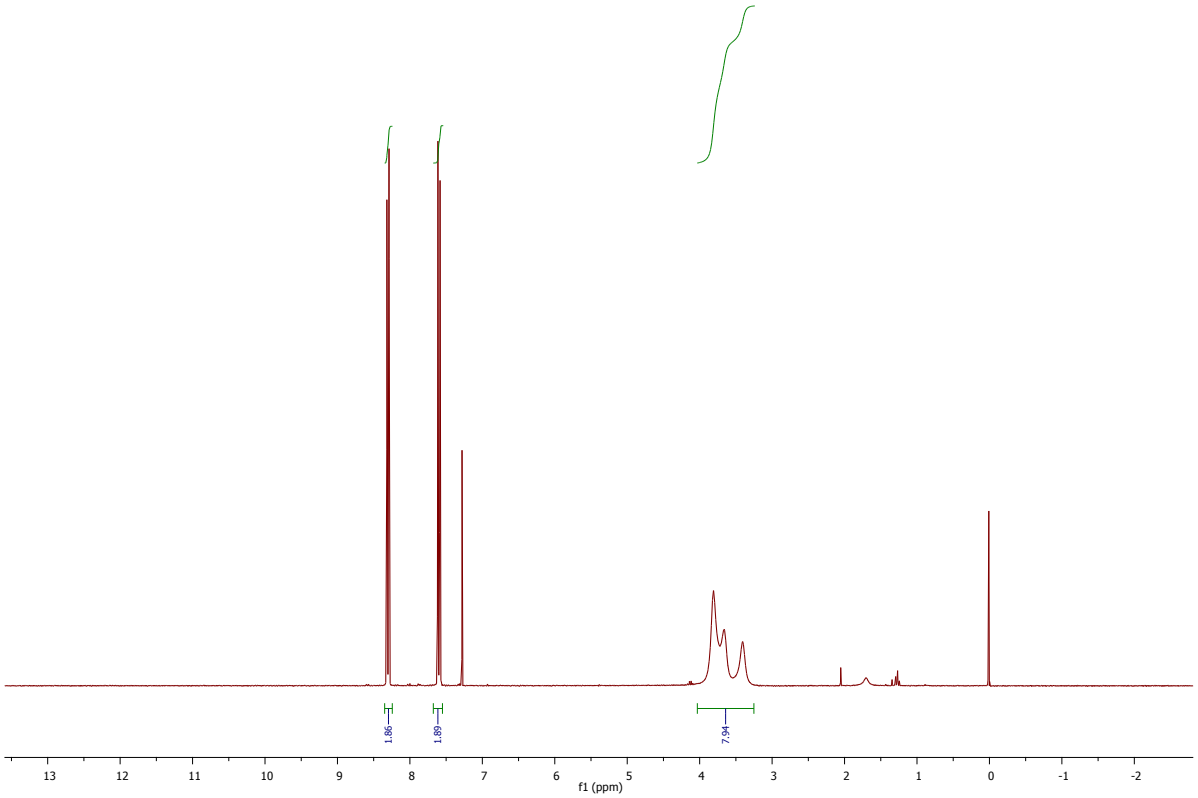


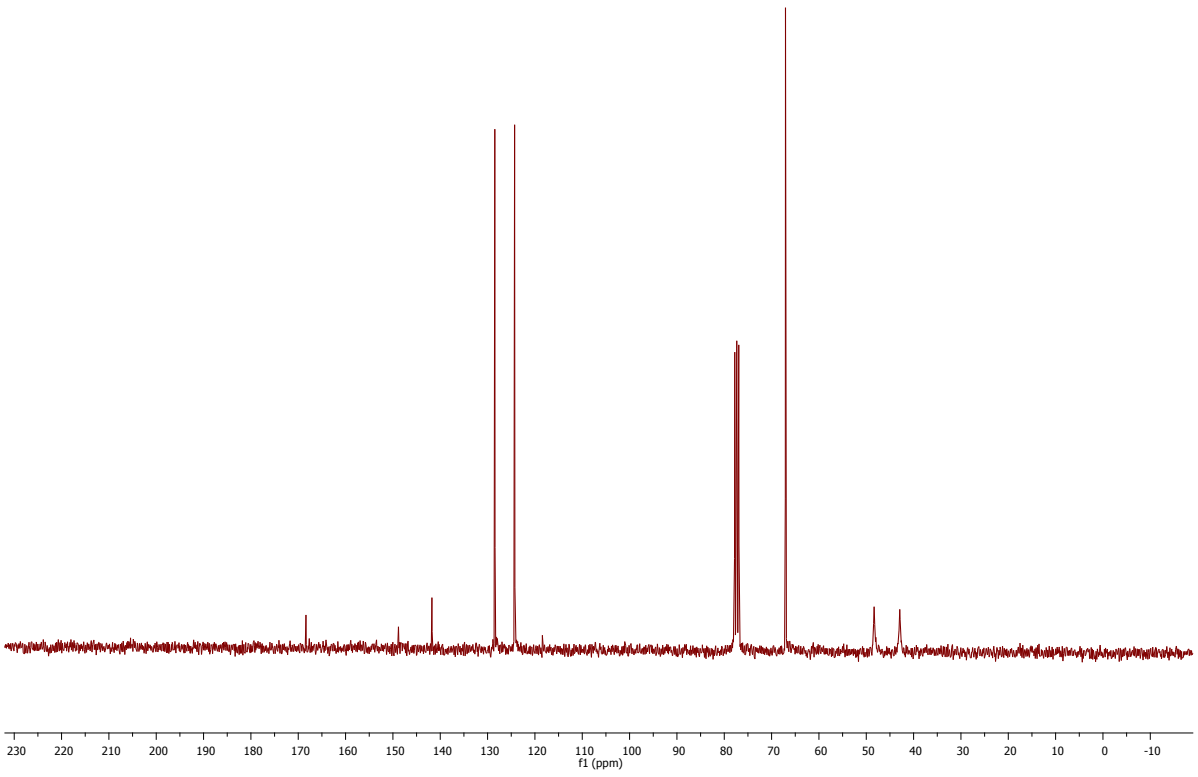
(4-nitrophenyl)-N-(piperidin-1-yl)methanone



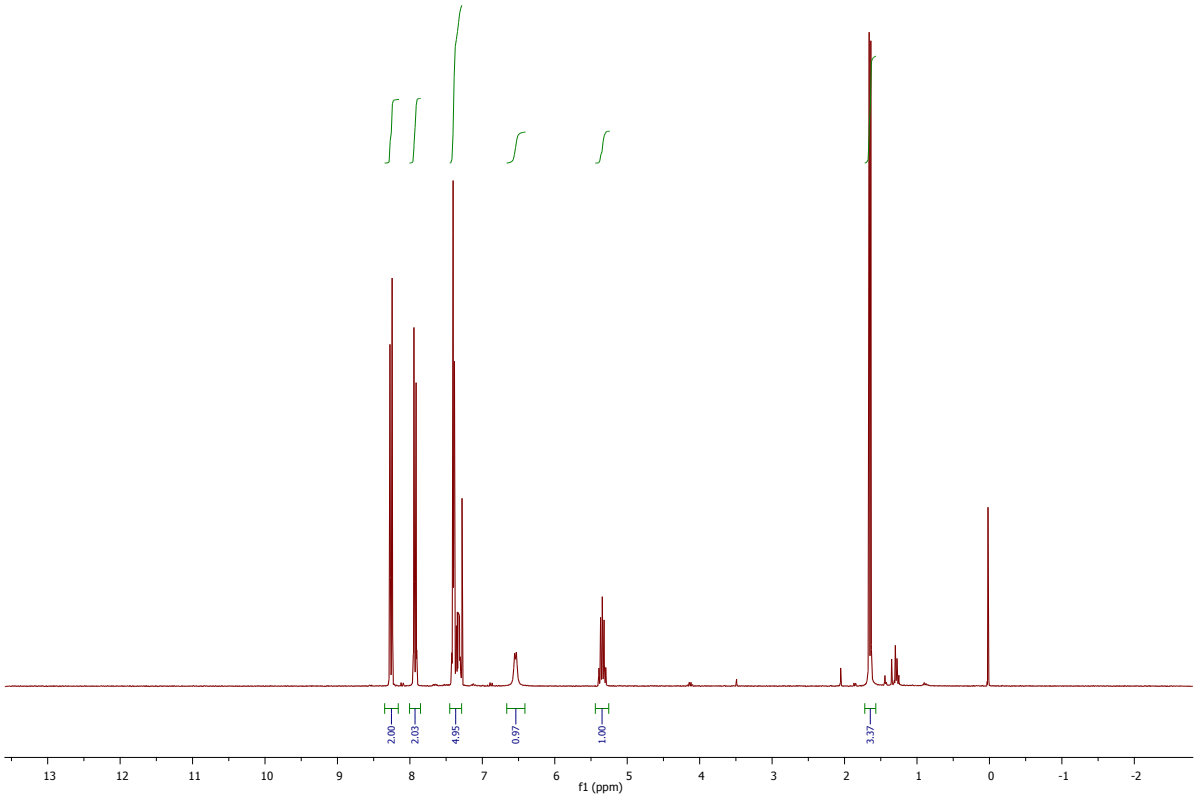


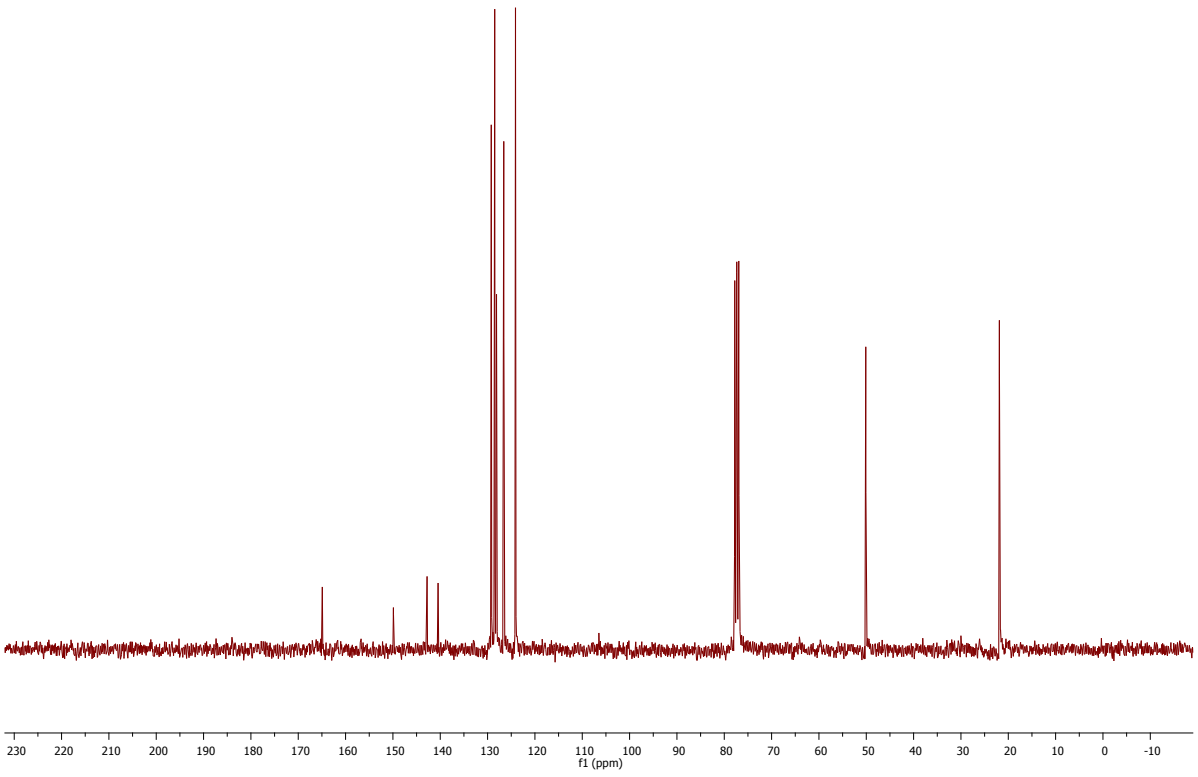
morpholino(4-nitrophenyl)methanon



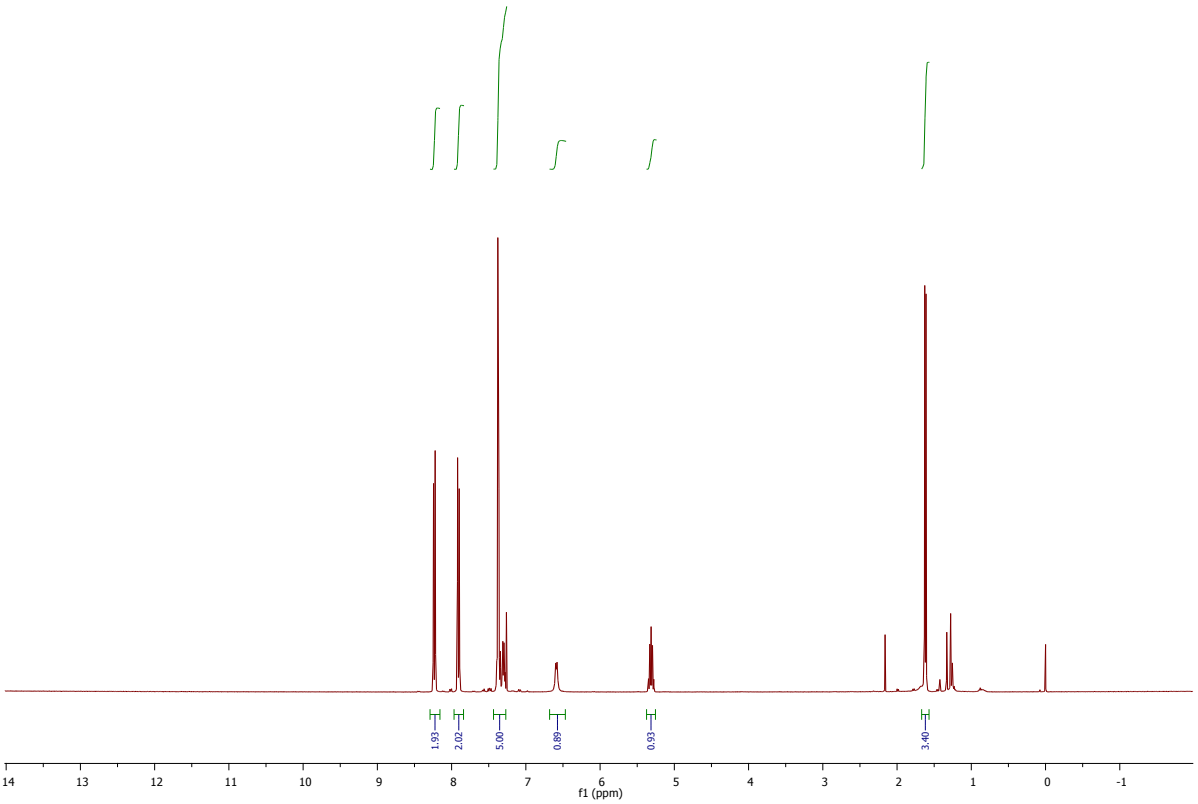


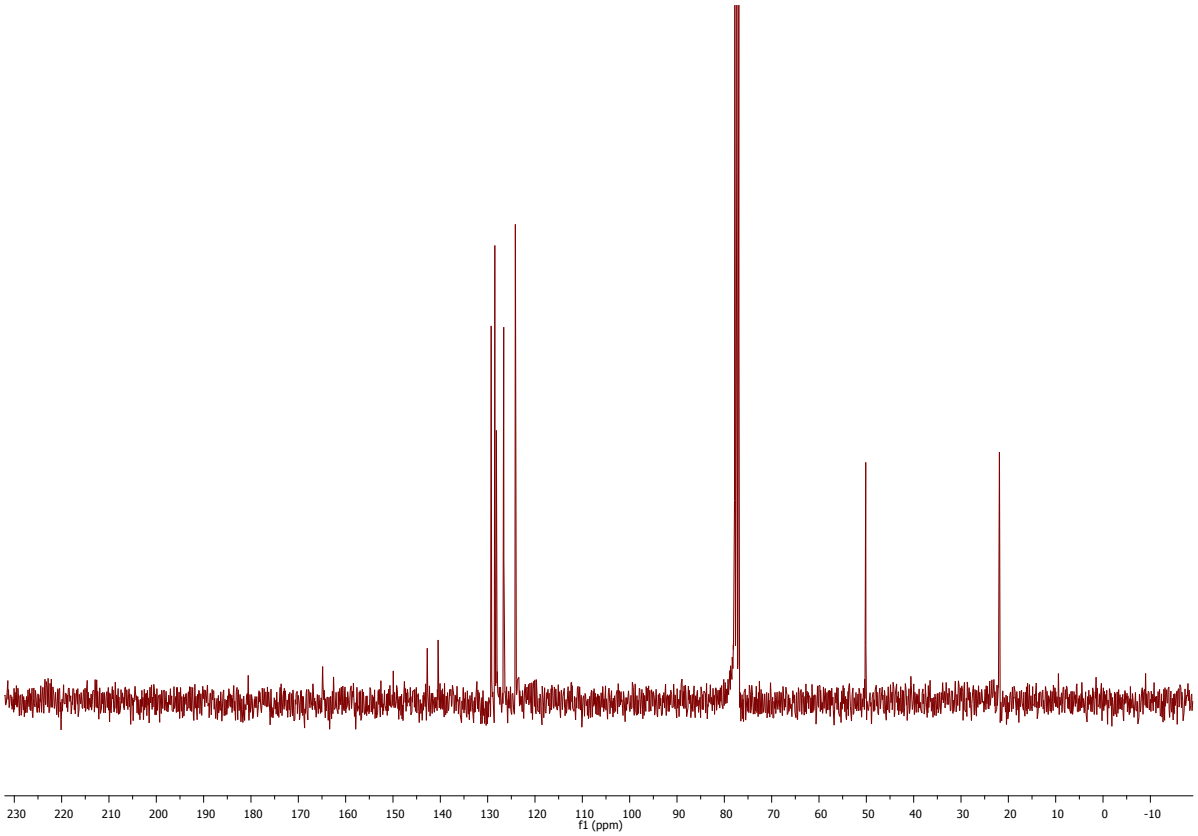
(*R*,*S*)-N-(1-phenylethyl)-4-nitrobenzamide



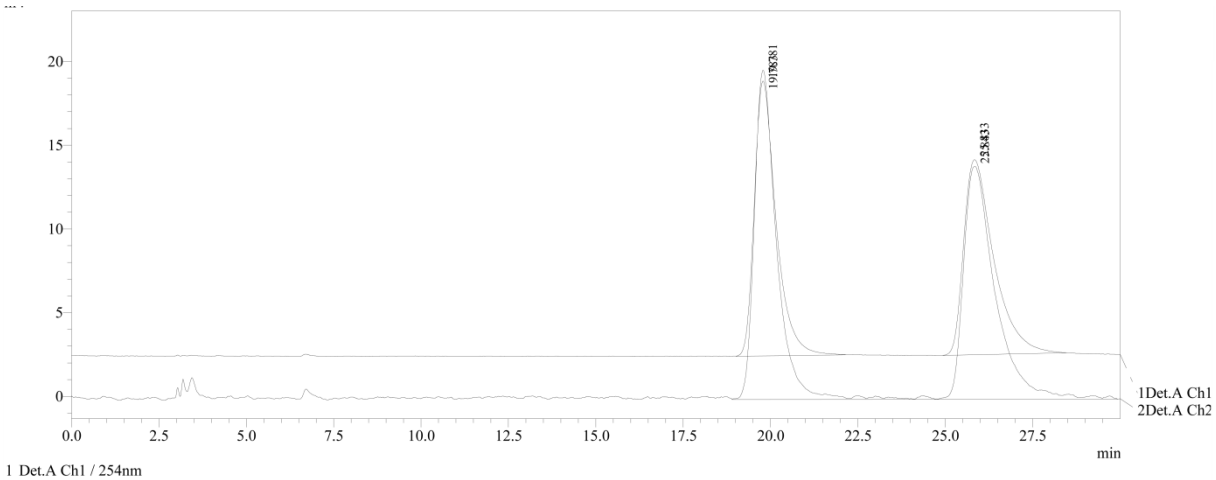


***(S)*-N-(1-phenylethyl)-4-nitrobenzamide**





6. Chiral HPLC data



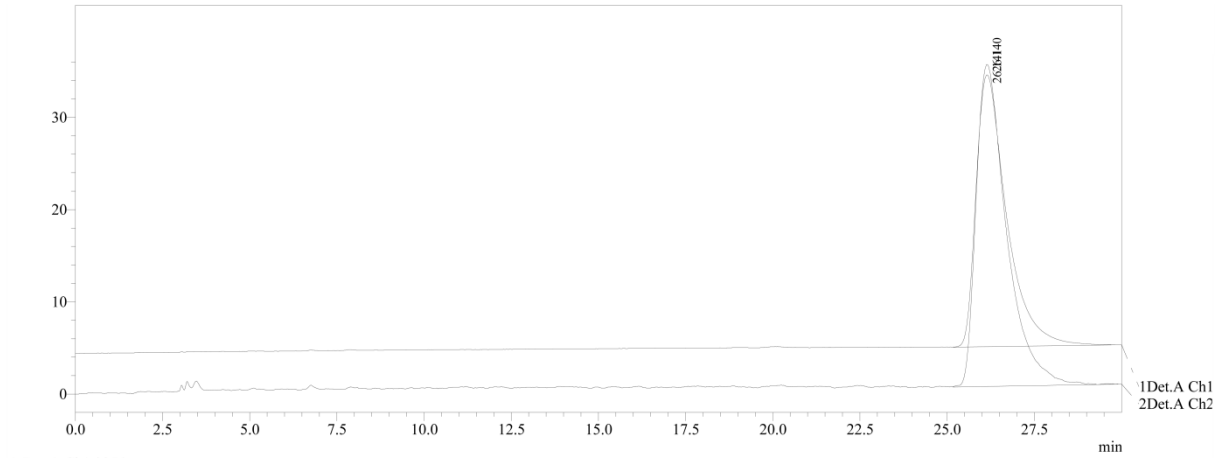
1 Det.A Ch1 / 254nm
2 Det.A Ch2 / 215nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.781	710402	16415	50.430	58.489
2	25.833	698274	11650	49.570	41.511
Total		1408676	28065	100.000	100.000

PeakTable

Detector A Ch2 215nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.783	869790	19673	50.060	58.587
2	25.843	867698	13906	49.940	41.413
Total		1737489	33580	100.000	100.000



1 Det.A Ch1 / 254nm
2 Det.A Ch2 / 215nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	26.140	1795880	29467	100.000	100.000
Total		1795880	29467	100.000	100.000

PeakTable

Detector A Ch2 215nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	26.141	2121244	34909	100.000	100.000
Total		2121244	34909	100.000	100.000

7. References

1. H. Lundberg, F. Tinnis and H. Adolfsson, *Chem. Eur. J.*, 2012, **18**, 3822-3826.
2. J. Wannberg and M. Larhed, *J. Org. Chem*., 2003, **68**, 5750-5753.
3. Y. Kawagoe, K. Moriyama and H. Togo, *Tetrahedron*, 2013, **69**, 3971-3977.
4. M. Kunishima, K. Yoshimura, H. Morigaki, R. Kawamata, K. Terao and S. Tani*, J. Am. Chem. Soc.,* 2001, **123**, 10760-10761.
5. J. F. Soulé, H. Miyamura and S. Kobayashi**,** *J. Am. Chem. Soc.*, 2011, **133** , 18550–1855.
6. N. Mamidi and D. Manna, *J. Org. Chem.*, 2013, **78**, 2386–2396.
7. U. M. V. Basavanag, A. Dos Santos, L. El Kaim, R. Gámez-Montano, L. Grimaud, *Angew. Chem. Int. Ed.,* 2013, **52**, 7194-7197.
8. J. E. Banning, J. Gentillon, P. G. Ryabchuk, A. R. Prosser, A. Rogers, A. Edwards, A. Holtzen, I. A. Babkov, M. Rubina and M. Rubin., *J. Org. Chem.*, 2013, **78**, 7601–7616.
9. V. Prasad, R. R. Kale, B. B. Mishra, D. Kumar and V. K. Tiwari, *Org. Lett.*, 2012, **14**, 2936–2939.
10. G. Pelletier, W. S. Bechara and A. B. Charette, *J. Am. Chem. Soc.*, 2010, **132**, 12817–12819.
11. Z. Guo, Q. Liu, X. Wei, Y. Zhang, H. Tong, J. Chao, J. Guo, D. Liu, *Organometallics*, 2013, **32**, 4677-4683.
12. N. Mamidi and D. Manna, *J. Org. Chem.*, 2013, **78**, 2386–2396.
13. T. T. Dang, Y. Zhu, S. C. Ghosh, A. Chen, C. L. L. Chai and A. M. Seayad., *Chem. Commun.***,** 2012, **48**, 1805-1807.
14. Y. Zhang, B. Feng and C. Zhu, *Org. Biomol. Chem.***,** 2012,**10**, 9137-9141.