SUPPORTING INFORMATION

Highly Chemoselective Metal-free Reduction of Tertiary Amides

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General Information. Unless otherwise stated, reactions were run under an argon atmosphere with rigid exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds.[1] All glassware was flame-dried prior to use. Dichloromethane, ether, THF and DMF were obtained by filtration through drying columns on a GlassContour system (Irvine, CA). Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Silicycle F_{254}). Visualization of the developed chromatogram was performed by UV and aqueous potassium permanganate. Flash column chromatography was performed using 230-400 mesh silica (EM Science or Silicycle). Melting points were obtained on a Buchi melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded either on Bruker AMX 300 (^{13}C) and AV 400 (^{1}H) spectrometers. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q =quartet, qn = quintet, s = sextet, h = heptet, m = multiplet and br = broad), coupling constant in Hz and integration. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (77.23 ppm) as the internal standard. All ^{13}C NMR spectra were obtained with complete proton decoupling. Infrared spectra were taken on a Perkin Elmer Spectrum One FTIR. High resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal. Combustion analyses were performed by the Laboratoire d'analyse élémentaire de l'Université de Montréal.

Reagents: Unless otherwise stated, commercial reagents were used without purification. Trifluoromethanesulfonic (triflic) anhydride was distilled over a small amount of phosphorous pentoxide and was stored for no more than five days before redistilling.

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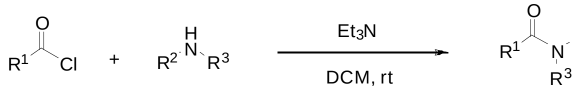
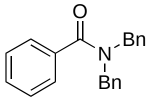
(1) Shriver, D. F.; Drezdzon, M. A. The manipulation of air-sensitive compounds; 2 nd Edition; Wiley: New York, 1986.



General procedure (1a-c, 1f-k). The acyl chloride (1 equiv) was added in one portion to a solution of the amine (1.1 equiv), Et_3N (1.25 equiv) and dichloromethane (0.5 M) at room temperature, resulting rapidly in a boiling solution. The reaction mixture was stirred for 20 min. at room temperature and then was diluted with dichloromethane. The solution was transferred to a separation funnel and was washed with 1N HCl. The organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure.

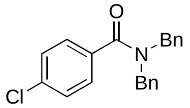
For amides 1a-c. Trituration of the resulting solid with hexane followed by filtration afforded the pure amides.

For amides 1f-k. Flash chromatography of the oily residue with EtOAc/hexane afforded the pure amides as colorless oils.

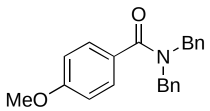


***N,N*-dibenzylbenzamide (1a).** 92 % yield; white solid, mp 107-108 °C (EtOH) (Lit. mp 112-113 °C); ^{1}**H NMR** ($CHCl_3$, 400 MHz) δ 7.52-7.56 (m, 2H), 7.32-7.45 (m, 10H), 7.18 (br d, J = 5.6 Hz, 2H), 4.75 (br s, 2H), 4.44 (br s, 2H).

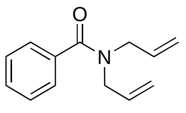
NMR: Moore, J. D.; Harned, A. W.; Henle, J.; Flynn, D. L.; Hanson, P. R. *Org. Lett.* **2002**, *4*, 1847-1849. MP: Kaiser, E. M.; Yun, H. H. *J. Org. Chem.* **1970**, *35*, 1348-1351.



***N,N*-dibenzyl-4-chlorobenzamide (1b).** 87 % yield; white solid, mp 103-104 °C (EtOH); ^{1}**H NMR** ($CHCl_3$, 400 MHz) δ 7.47 (d, J = 8.5 Hz, 1H), 7.28-7.41 (m, 10H), 7.17 (br s, 2H), 4.73 (br s, 2H), 4.42 (br s, 2H); ^{13}**C NMR** ($CHCl_3$, 75 MHz) δ 171.1, 136.7 (br s), 136.1(br s), 135.6, 134.4, 128.7 (2C), 128.2 (2C), 127.6 (br s, 4C), 126.8 (br s, 4C), 51.4 (br s), 47.0 (br s); **FTIR** (cm^{-1}) (neat) 3062, 3029, 1633, 1595, 1494; Anal. calcd for $C_{21}H_{18}ClN$: C, 75.11; H, 5.40; N, 4.17, found C, 75.10; H, 5.39; N, 4.22.

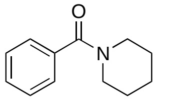


***N,N*-dibenzyl-4-methoxybenzamide (1c).** 87 % yield; white solid, mp 114-115 °C (EtOH); ^{1}**H NMR** ($CHCl_3$, 400 MHz) δ 7.54 (d, J = 8.8 Hz, 2H), 7.05-7.41 (m, 10H), 6.92 (d, J = 8.8 Hz, 2H), 4.73 (br s, 2H), 4.52 (br s, 2H), 3.82 (s, 3H); ^{13}**C NMR** ($CHCl_3$, 75 MHz) δ 172.0, 160.6, 136.7 (br s, 2C), 128.7 (2C), 128.3 (br s, 4C), 128.1 (2C), 127.4, 126.8 (br s, 4C), 113.7 (2C), 55.2, 51.6, 47.1; **FTIR** (cm^{-1}) (neat) 3062, 3029, 2933, 2836, 1628, 1606, 1512, 1494; Anal. calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23, found C, 79.58; H, 6.38; N, 4.30.



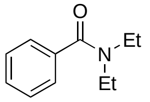
***N,N*-diallylbenzamide (1g).** 94 % yield. **R$_f$**: 0.52 (50% EtOAc/hexanes); ^{1}**H NMR** ($CHCl_3$, 400 MHz) δ 7.45-36 (m, 5H), 5.88 (br s, 1H), 5.75 (br s, 1H), 5.26-5.19 (m, 4H), 4.15 (br s, 2H), 3.85 (br s, 2H).

NMR: Moore, J. D.; Byrne, R. J.; Vedantham, P.; Flynn, D. L.; Hanson, P. R. *Org. Lett.* **2003**, *5*, 4241-4244.



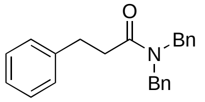
1-benzoylpiperidine (1h). 99 % yield. **R$_f$**: 0.38 (50% EtOAc/hexanes); ^{1}**H NMR** ($CHCl_3$, 400 MHz) δ 7.40 (s, 5H), 3.73 (br s, 2H), 3.36 (br s, 2H), 1.69 (br s, 4H), 1.53 (br s, 2H).

NMR: Aldrich (776-75-0)



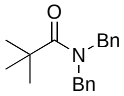
***N,N*-diethylbenzamide (1i).** 99 % yield. **R_f**: 0.40 (50% EtOAc/hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.40-7.35 (m, 5H), 3.54 (br s, 2H), 3.26 (br s, 2H), 1.23 (br s, 3H), 1.12 (br s, 3H).

NMR: Hans, J. J.; Driver, R. W.; Burke, S. D. *J. Org. Chem.* **2000**, *65*, 2114-2121.



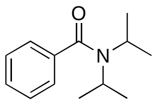
***N,N*-dibenzyl-3-phenylpropanamide (1j).** 62 % yield; white solid, mp 98-100 °C (EtOH) (Lit. mp 105-106 °C); **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.41-7.21 (m, 13H), 7.11 (d, *J* = 7.2 Hz, 2H), 4.64 (s, 2H), 4.40 (s, 2H), 3.09 (t, *J* = 7.6 Hz, 2H), 2.76 (t, *J* = 8.0 Hz, 2H).

NMR and MP: Aoyagi, Y.; Asakura, R.; Nobuko, K.; Yamamoto, R.; Kuromatsu, T.; Shimura, A.; Ohta, A. *Synthesis* **1996**, 970-974.



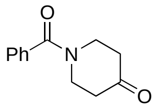
***N,N*-dibenzyl-2,2-dimethylpropanamide (1k).** 75 % yield; colorless crystals, mp 40-41 °C (from DCM evaporation) (Lit. mp 62.5-63.5 °C); **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.28-7.38 (m, 6H), 7.18 (d, *J* = 7.2 Hz, 4H), 4.63 (br s, 4H), 1.39 (s, 9H).

NMR and MP: Oki, M.; Ozaki, T.; Ikeda, H.; Matsusaka, M.; Mishima, H.; Koumura, M.; Toyota, S. *Russ. J. Org. Chem.* **1998**, *34*, 1538-1548.



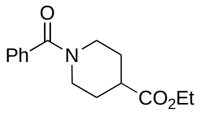
***N,N*-diisopropylbenzamide (1l).** 97 % yield; **R_f**: 0.52 (50% EtOAc/hexanes); white solid, mp 65-67 °C (from Hexane evaporation) (Lit. mp 68-69.5 °C); **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.30-7.42 (m, 5H), 3.72 (br s, 2H), 1.36 (br s, 12H).

NMR and MP: Huckin, S. N.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 1343-1351.



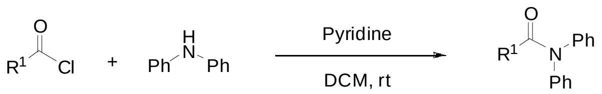
1-benzoylpiperidin-4-one (1m). 4-piperidone hydrochloride (1.10 equiv) was used with Et_3N (2.25 equiv); 70 % yield. **R_f**: 0.17 (50% EtOAc/hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.47 (s, 5H), 4.00 (br s, 2H), 3.79 (br s, 2H), 2.52 (br s, 4H).

NMR: Aldrich (24686-78-0)

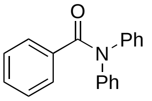


Ethyl 1-benzoylpiperidine-4-carboxylate (1n). 99 % yield. white solid, mp 70-72 °C (Lit. mp 73-75 °C); **R_f**: 0.49 (75% EtOAc/hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.41 (s, 5H), 4.55 (br s, 2H), 4.17 (d, *J* = 7.2 Hz, 2H), 3.75 (br s, 2H), 3.06 (br s, 4H), 2.55-2.62 (m, 4H), 2.04 (br s, 2H), 1.85 (br s, 2H), 1.74 (br s, 4H), 1.28 (d, *J* = 7.2 Hz, 3H).

NMR and MP: McCullough, K. J.; MacTavish, J.; Proctor, G. R.; Redpath, J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2353-2560.

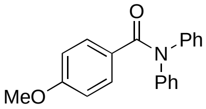


General procedure (1d-e). The acyl chloride (1.2 equiv) was added in one portion to a solution of the amine (1 equiv), pyridine (3 M) and dichloromethane (3 M), resulting rapidly in a boiling solution. The reaction mixture was stirred for 5 min. at room temperature and then was diluted with EtOAc. The solution was transferred to a separation funnel and was washed with 1N HCl. The organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure. Trituration of the resulting solid with hexane followed by filtration afforded the pure amide.

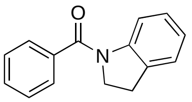


***N,N*-diphenylbenzamide (1d).** 92 % yield; white solid, mp 171-172 °C (EtOH) (Lit. mp 180-181 °C); **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.49 (d, *J* = 7.2 Hz, 2H), 7.18-7.34 (m, 13H).

NMR: Wei, P.; Bi, X.; Wu, Z.; Xu, Z. *Org. Lett.* **2005**, *7*, 3199-3202. MP: Gaylord, N. G. *J. Org. Chem.* **1960**, *25*, 1874-1876.

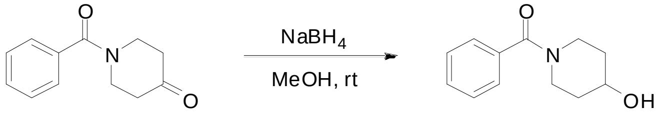


4-methoxy-*N,N*-diphenylbenzamide (1e). 99 % yield; off-white solid, mp 131-132 °C; **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.33-7.30 (m, 4H), 7.15-7.22 (m, 6H), 6.74 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H); **^{13}C NMR** ($CHCl_3$, 75 MHz) δ 170.2, 161.0, 144.3, 131.3, 129.0, 127.9, 127.4, 126.1, 113.1, 55.1; **FTIR** (cm^{-1}) (neat) 3038, 2935, 2838, 1650, 1603, 1590, 1509, 1489; Anal. calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62, found C, 79.00; H, 5.72; N, 4.65.



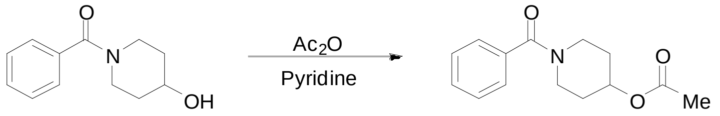
1-benzoylindoline (1f). 91 % yield; white solid, mp 111-112 °C (MeOH) (Lit. mp 116-117 °C); **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 8.13 (br s, 1H), 7.59-7.45 (m, 5H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.15 (br s, 1H), 7.08-6.99 (m, 1H), 4.10 (br s, 2H), 3.14 (t, *J* = 8.4 Hz, 2H).

NMR + MP: Ganton, M. D.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 4777-4779.



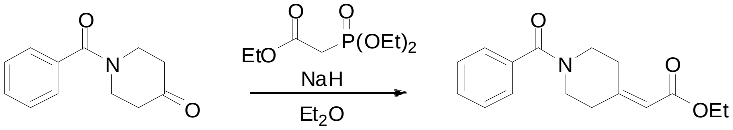
1-benzoylpiperidin-4-ol (6). $NaBH_4$ (1.1 g, 29 mmol) was added to a solution of ketone (**1j**) (5.9 g, 29 mmol) in MeOH (100 mL) and the reaction mixture was stirred for 3 h at room temperature. The solution was transferred to a separation funnel, diluted with 1N HCl and extracted with DCM (5X). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure yielding alcohol **6** as analytically pure off-white solid (mp 84-86 °C (Et_2O, precipitation from evaporation) (Lit. mp 89.6-90.5 °C)) (5.3 g) in 88 % yield . **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.41 (br s, 5H), 4.21 (br s, 1H), 3.96 (br s, 1H), 3.67 (br s, 1H), 3.38 (br s, 1H), 3.20 (br s, 1H), 2.04 (br s, 1H), 1.97 (br s, 1H), 1.83 (br s, 1H), 1.62 (br s, 1H), 1.50 (br s, 1H).

NMR and MP: Chang, D.; Feiten, H.; Engesser, K.; van Beilen, J. B.; Witholt, B.; Li, Z. *Org. Lett.* **2002**, *4*, 1859-1862.

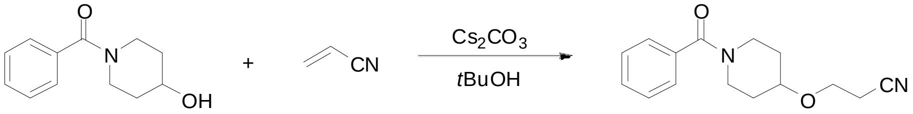


1-benzoylpiperidin-4-yl acetate (1o). Ac_2O (1.2 mL, 12 mmol) was added to a solution of alcohol **6** (1.0 g, 4.9 mmol) in pyridine (10 mL) and the reaction mixture was stirred for 20 h at room temperature. The solution was transferred to a separation funnel, diluted with Et_2O and washed with 1 N HCl (3X). The organic layer was concentrated under reduced pressure and the resulting oily residue was purified by flash chromatography with EtOAc/Hex (50/50) yielding **1l** as a colorless oil (671 mg) in 56 % yield. **R_f**: 0.41 (75% EtOAc/hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.35 (s, 5H), 4.93-4.99 (m, 1H), 4.02 (br s, 1H), 3.54 (br s, 2H), 3.26 (br s, 1H), 2.02 (s, 3H), 1.93 (br s, 1H), 1.80 (br s, 1H), 1.70 (br s, 1H), 1.57 (br s, 1H); **^{13}C NMR** ($CHCl_3$, 75 MHz) δ 170.2, 170.1, 135.7, 129.5, 128.3, 126.6, 69.2, 44.6, 39.2, 31.0, 30.3, 21.1;

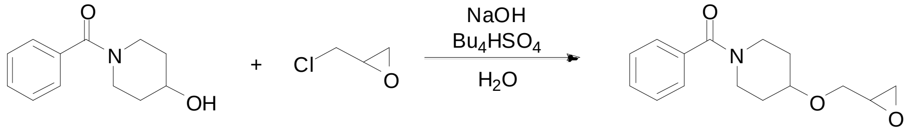
FTIR (cm^{-1}) (neat) 3058, 3002, 2955, 2865, 1731, 1627, 1577, 1496; **HRMS** (ESI, Pos) calcd for $C_{14}H_{17}NO_3$ $[M+H]^+$: 248.1281 *m/z*, found 248.1294 *m/z*.



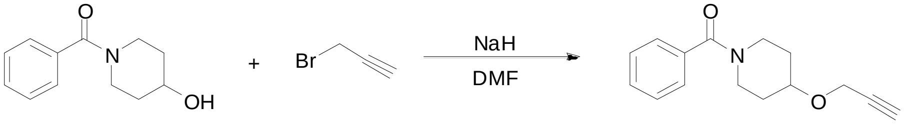
Ethyl (1-benzoylpiperidin-4-ylidene)acetate (1p). Diethylphosphonoacetate (0.52 mL, 2.6 mmol) was added to a suspension of NaH (60 % dispersion in oil, 108 mg, 2.7 mmol) in Et_2O (8.2 mL) and the reaction mixture was stirred for 5 min. at room temperature. A solution of ketone **1j** (500 mg, 2.5 mmol) was then added and the reaction mixture was stirred for 20 h at room temperature. The solution was transferred to a separation funnel, diluted with Et_2O and washed with water. The organic layer was concentrated under reduced pressure and the resulting oily residue was purified by flash chromatography with EtOAc/Hex (50/50) yielding **1m** as a white solid (mp 97-99 °C) (637 mg) in 95 % yield. **R_f**: 0.44 (50% EtOAc/hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.38 (s, 5H), 5.72 (br s, 1H), 4.11 (br q, *J* = 6.8 Hz, 2H), 3.78 (br s, 2H), 3.44 (br s, 2H), 3.04 (br s, 1H), 2.90 (br s, 1H), 2.39 (br s, 1H), 2.22 (br s, 1H), 1.23 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** ($CHCl_3$, 75 MHz) δ 170.3, 165.9, 156.4, 135.6, 129.6, 128.4, 136.7, 115.8, 59.7, 48.3, 47.4, 43.1, 42.5, 36.7, 35.8, 29.9, 29.0, 14.1; **FTIR** (cm^{-1}) (neat) 3059, 2980, 2939, 2903, 2869, 1707, 1630, 1602, 1577, 1495; Anal. calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12, found C, 70.45; H, 7.04; N, 5.20.



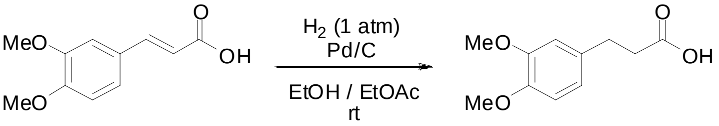
3-[(1-benzoylpiperidin-4-yl)oxy]propanenitrile (1q). Cs_2CO_3 (1.9 g, 5.9 mmol) and acrylonitrile (6.3 mL, 97 mmol) were added to a solution of alcohol **6** (1.0 g, 4.9 mmol) in *t*BuOH (24 mL) and the reaction mixture was stirred for 3 days at room temperature. The heterogeneous solution was diluted with DCM and absorbed on silica gel. The resulting powder was purified by flash chromatography with EtOAc/Hex (75/25) yielding **1n** as a colorless oil (1.2 g) in 95 % yield. **R_f**: 0.30 (75% EtOAc/hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.28-7.24 (m, 5H), 3.83 (br s, 1H), 3.53-3.50 (m, 2H), 3.43 (br s, 3H), 3.10 (br s, 1H), 2.45 (t, *J* = 6.4 Hz, 2H), 1.75 (br s, 1H), 1.65 (br s, 1H), 1.53 (br s, 1H), 1.46 (br s, 1H); **^{13}C NMR** ($CHCl_3$, 75 MHz) δ 170.1, 135.9, 129.4, 128.3, 126.6, 117.9, 77.6, 77.2, 76.7, 74.3, 62.6, 44.4, 38.8, 31.2, 30.3, 19.1; **FTIR** (cm^{-1}) (neat) 3059, 3002, 2930, 2871, 2249, 1622, 1577, 1495; Anal. calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84, found C, 69.50; H, 7.15; N, 11.11.



1-benzoyl-4-(oxiran-2-ylmethoxy)piperidine (1r). Alcohol **6** (1.0 g, 4.9 mmol) was added to a solution of Bu_4HSO_4 (83 mg, 0.24 mmol) in epichlorohydrine (2 mL) and 12 N NaOH aq (3.3 mL). The reaction mixture was stirred for 2 days at room temperature. The biphasic solution was transferred to a separation funnel, diluted with water and extracted with DCM (2X). The combined organic layers were concentrated under reduced pressure and the oily residue was purified by flash chromatography with EtOAc/Hex (75/25) yielding **1o** as a colorless oil (700 mg) in 55 % yield. **R$_f$**: 0.30 (75% EtOAc/hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.21 (s, 5H), 3.87 (br s, 1H), 3.60 (br d, J = 10.3 Hz, 1H), 3.36-3.51 (m, 2H), 3.30 (br s, 1H), 3.21 (br s, 1H), 3.03 (br s, 1H), 2.92-2.96 (m, 1H), 2.59 (t, J = 4.6 Hz, 1H), 2.42 (dd, J_1 = 5.0 Hz, J_2 = 2.6 Hz, 1H), 1.75 (br s, 1H), 1.61 (br s, 1H), 1.50 (br s, 1H), 1.37 (br s, 1H); **^{13}C NMR** ($CHCl_3$, 75 MHz) δ 169.9, 135.9, 129.2, 128.2, 126.5, 74.1, 68.6, 50.7, 44.5 (br s), 43.9, 38.9 (br s), 31.2 (br s), 30.5 (br s); **FTIR** (cm^{-1}) (neat) 3054, 2997, 2925, 2858, 1632, 1577, 1495; Anal. calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36, found C, 68.89; H, 7.38; N, 5.41.

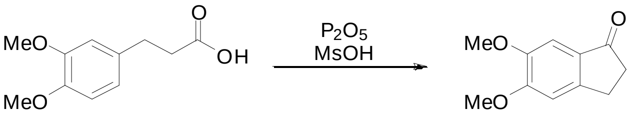


1-benzoyl-4-(prop-2-ynyloxy)piperidine (1s). NaH (60 % dispersion in oil, 244 mg, 6.1 mmol) was added to a solution of alcohol **6** (1.0 g, 4.9 mmol) DMF (20 mL) followed by the addition of propargyl bromide (80 % in toluene, 1.1 mL, 7.3 mmol). The reaction mixture was stirred for 3 h at room temperature. The solution was transferred to a separation funnel, diluted with EtOAc and washed with water (3X). The organic layer was adsorbed on silica gel and resulting powder was purified by flash chromatography with EtOAc/Hex (50/50) yielding **1p** as a brownish oil (741 mg) in 63 % yield. **R$_f$**: 0.38 (50% EtOAc/hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.38 (s, 5H), 4.19 (d, J = 2.4 Hz, 2H), 4.03 (br s, 1H), 3.84-3.78 (m, 1H), 3.61 (br s, 1H), 3.49 (br s, 1H), 3.24 (br s, 1H), 2.42 (t, J = 2.4 Hz, 1H), 1.87 (br s, 2H), 1.64 (br s, 2H); **^{13}C NMR** ($CHCl_3$, 75 MHz) δ 170.2, 135.9, 129.4, 128.3, 126.6, 79.8, 74.2, 73.0, 55.2, 44.6 (br s), 39.1 (br s), 31.4 (br s), 30.2 (br s); **FTIR** (cm^{-1}) (film) 3227, 3059, 3001, 2927, 2860, 1621, 1576, 1495; Anal. calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76, found C, 73.81; H, 7.05; N, 5.79.



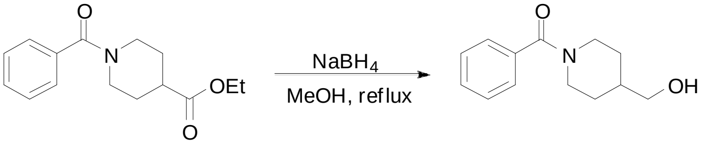
3-(3,4-dimethoxyphenyl)propanoic acid (7). The 3,4-dimethoxycinnamic acid (5.0 g, 24 mmol) was dissolved in MeOH (30 mL) and EtOAc (30 mL) and then Pd/C (400 mg, 5 % Pd/C, 0.19 mmol) was added. The reaction mixture was purged with hydrogen and was stirred at room temperature under a hydrogen atmosphere for 24 h. The solution was then diluted with EtOAc, filtered through celite (washing with EtOAc) and concentrated under reduced pressure. Trituration of the resulting solid with hexane with a small amount of EtOAc followed by filtration afforded the acid **7** as a white solid (mp 92-93 °C (Hexane / EtOAc) (Lit. mp 89-100 °C)) (5.3 g) in 98 % yield. **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 6.71-6.79 (m, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 2.88 (t, J = 10 Hz, 2H), 2.64 (t, J = 10 Hz, 2H).

NMR and MP: Maki, S.; Okawa, M.; Matsui, R.; Hirano, T.; Niwa, H. *Synlett* **2001**, 1590-1592.

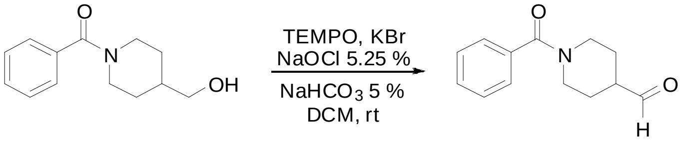


5,6-dimethoxyindan-1-one (8). A solution of P_2O_5 (2.16 g, 15.2 mmol) and MsOH (15 mL) was warmed to 80 °C and stirred for 30 min and at 100 °C for 15 minutes. To the clear homogeneous solution was added the acid **7** as a solid in one portion and the solution was stirred at 100 °C for 5 minutes. The deep purple solution was poured into ice water and extracted with DCM (3X). The combined organic layers were washed with aq. $NaHCO_3$, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The resulting brown solid was recrystallized from EtOAc/Hexane to give the indanone **8** as clear brown needles (mp 111-113 °C (EtOAc/ Hexane) (Lit. mp 116-118 °C)) (2.71 g) in 74 % yield. ^{1}**H NMR** ($CHCl_3$, 400 MHz) δ 7.12 (s, 1H), 6.85 (s, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 2.99-3.01 (m, 2H), 2.60-2.63 (m, 2H).

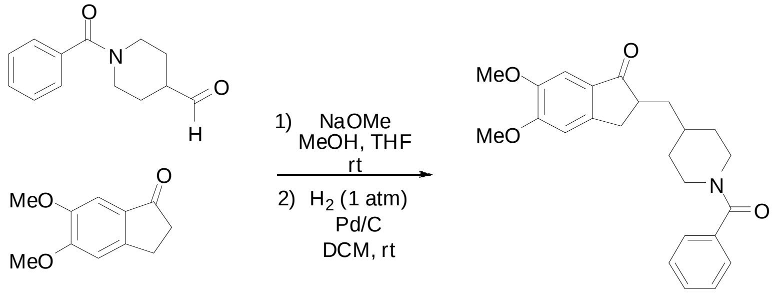
NMR and MP: Fillion, E.; Fishlock, D.; Wilsily, A.; Goll, J. M. *J. Org. Chem* **2005**, *70*, 1316-1327.



(1-benzoylpiperidin-4-yl)methanol (9). $NaBH_4$ (1.46 g, 38.6 mmol) was added to a solution of ester **1k** (10.1 g, 38.6 mmol) in THF (154 mL) and the reaction mixture was warmed to reflux. MeOH (48 mL) was added by portion (12 x 4 mL) over 1 h and the reaction mixture was refluxed over-night. At room temperature, the mixture is quenched with HCl 1N and concentrated under reduced pressure. The residue was transferred to a separation funnel and extracted with water and DCM (5X). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The oily residue was purified by flash chromatography with 100% EtOAc to MeOH/EtOAc (10/90) yielding **9** as a colorless oil that solidifies on standing to a white solid (mp 83-85 °C) (5.78 g) in 68 % yield. **R$_f$**: 0.28 (EtOAc); ^{1}**H NMR** ($CHCl_3$, 400 MHz) δ 7.41-7.30 (m, 5H), 4.68 (br s, 1H), 3.72 (br s, 1H), 3.42 (br s, 2H), 3.24 (br s, 1H), 2.94 (br s, 1H), 2.75 (br s, 1H), 1.88-1.57 (br m, 3H), 1.19 (br s, 2H); ^{13}**C NMR** ($CHCl_3$, 75 MHz) δ 170.3, 136.0, 129.4, 128.3, 126.6, 66.7, 47.6, 42.0, 38.6, 29.2, 28.3; **FTIR** (cm^{-1}) (neat) 3391, 3060, 3000, 2917, 2859, 1609, 1600, 1575, 1497, 1465, 1445; **HRMS** (ESI, Pos) calcd for $C_{13}H_{17}NO_2$ $[M+H]^+$: 220.1332 *m/z*, found 220.1338 *m/z*.



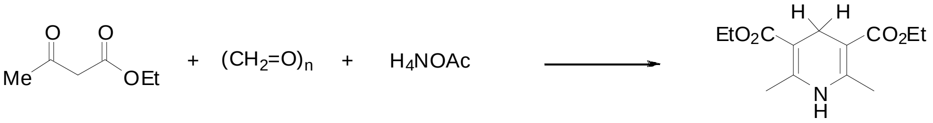
1-benzoylpiperidine-4-carbaldehyde (10). To a rapidly stirring solution of **9** (5.0 g, 23 mmol) in DCM (91 mL) and $NaHCO_3$ 5 % aq. (46 mL) was added KBr (43 mg, 0.37 mmol) and TEMPO (29 mg, 0.18 mmol). Bleach (5.25 % aq., 34 mL, 24 mmol) was then added and the reaction mixture was stirred at room temperature for 1 h. The solution was diluted with Et_2O and the organic phase was washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The oily residue was purified by flash chromatography with EtOAc yielding **10** as a colorless oil that solidifies in the fridge to a white solid (mp 77-78 °C) (4.3 g) in 87 % yield. **R$_f$**: 0.40 (EtOAc); ^{1}**H NMR** ($CHCl_3$, 400 MHz) δ 9.68 (s, 1H), 7.43-7.36 (m, 5H), 4.41 (br s, 1H), 3.72 (br s, 1H), 3.18-3.11 (m, 2H), 2.58-2.51 (m, 1H), 1.95 (br s, 2H), 1.65 (br s, 2H); ^{13}**C NMR** ($CHCl_3$, 75 MHz) δ 202.3, 170.3, 135.7, 129.5, 128.4, 126.6, 47.6, 46.5, 41.1, 25.5, 25.0; **FTIR** (cm^{-1}) (neat) 3057, 2999, 2923, 2855, 2716, 1720, 1622, 1577, 1493; **HRMS** (ESI, Pos) calcd for $C_{13}H_{15}NO_2$ $[M+H]^+$: 218.1181 *m/z*, found 218.1176 *m/z*.



2-[(1-benzoylpiperidin-4-yl)methyl]-5,6-dimethoxyindan-1-one (4). A suspension of NaOMe (747 mg, 13.8 mmol) in MeOH (2.7 mL) was added to a solution of aldehyde **10** (839 mg, 3.86 mmol) and indanone **8** (619 mg, 3.22 mmol) in THF (15 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The solution was diluted with EtOAc, washed with water, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The resulting solid was triturated with EtOAc/Hexane to give a beige solid (1.20 g) that was used directly in the next reaction without further purification.

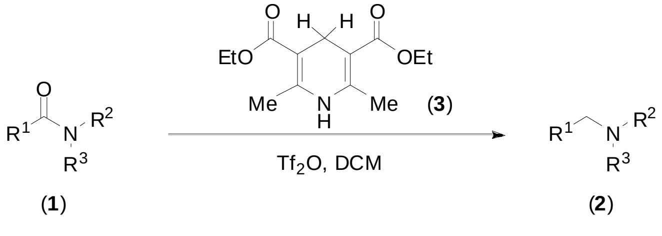
Pd/C (5 % wt, 540 mg, 0.255 mmol) was added to a solution of the beige solid (1.00 g) in DCM (15 mL). The reaction mixture was purged with hydrogen and was stirred at room temperature under a hydrogen atmosphere for 24 h. The solution was then filtered through celite (washing with DCM) and concentrated under reduced pressure. The resulting foam was recrystallized from EtOAc/Hexane, under agitation, to give the amide **4** as a white solid (mp 111-113 °C (EtOAc/ Hexane) (Lit. mp 151-152 °C)) (712 mg) in 71 % yield for the two steps. **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.36 (s, 5H), 7.13 (s, 1H), 6.83 (s, 1H), 4.69 (br s, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.74 (br s, 1H), 3.23 (dd, *J* = 17.2, 8.0 Hz, 1H), 2.97 (br s, 1H), 2.79 (br s, 1H), 2.67 (dd, *J* = 17.6, 3.2 Hz, 2H), 1.93-1.87 (m, 1H), 1.80 (br s, 2H), 1.70 (br s, 1H), 1.39-1.32 (m, 1H), 1.23 (br s, 2H); **^{13}C NMR** ($CHCl_3$, 75 MHz) δ 207.2, 170.1, 155.4, 149.3, 148.5, 136.2, 129.3, 129.0, 128.3, 126.6, 107.2, 104.1, 56.1, 55.9, 47.8, 44.9, 42.2, 38.3, 34.5, 33.2, 32.3, 31.3; **FTIR** (cm^{-1}) (neat) 3002, 2924, 2847, 2242, 1691, 1621, 1591, 1498; **HRMS** (ESI, Pos) calcd for $C_{24}H_{27}NO_4$ $[M+H]^+$: 394.2030 *m/z*, found 394.2013 *m/z*.

MP: Sugimoto, H.; Iimura, Y.; Yamanishi, Y.; Yamatsu, K. *J. Med. Chem.* **1995**, *38*, 4821-4829.



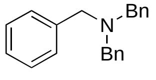
Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3). Ethyl acetoacetate (65 g, 500 mmol), paraformaldehyde (7.5 g, 250 mmol) and ammonium acetate (29 g, 375 mmol) were added to a 500 mL beaker equipped with a magnetic stirrer. The beaker was loosely covered with a plastic recipient and under slow agitation, the mixture was warmed to 70 °C in a water bath. *After around 10 min., the mixture becomes a thick pale yellow paste resulting in the lost of agitation. Within the next minute, a highly exothermic reaction occurs resulting in the formation of a yellow solid.* One minute after the appearance of the solid, the mixture was allowed to cool to room temperature, diluted with water (400 mL) and the yellow suspension was stirred for 10 minutes at room temperature. The solid was filtered, washed thoroughly with water and suspended in EtOH (250 mL). The suspension was refluxed for 5 minutes and allowed to slowly cool back to room temperature with agitation. The solid was filtered and washed thoroughly with EtOH yielding **3** as a bright yellow solid (45 g) in 72 % yield. mp 160-162 °C (EtOH) (Lit. mp 183-185 °C); **^{1}H NMR** (1:1 DMSO/$CHCl_3$, 400 MHz) δ 7.99 (s, 1H), 4.04 (q, *J* = 6.8 Hz, 2H), 3.09 (s, 2H), 2.09 (s, 6H), 1.20 (t, *J* = 7.2 Hz, 6H).

Synthesis: Zolfigol, M. A.; Safaiee, M. *Synlett* **2004**, *5*, 827-828. NMR + MP: Eynden, J. J. V.; Delfosse, F.; Mayence, A.; Haverbeke, Y. V. *Tetrahedron* **1995**, *51*, 6511-6516.



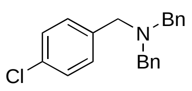
General procedure A (amides 1g-i, 1m-s). The amide (**1**) (1.0 mmol) was added to a flame-dried round bottom flask and put under an argon atmosphere. Dichloromethane (4.0 mL) was added followed by triflic anhydride (1.1 mmol) and the clear colorless solution was stirred at room temperature for 5 min. Hantzsch ester **3** (2.5 mmol) was added in one portion and the reaction mixture was stirred at room temperature for 1h, during which time the mixture went from a bright yellow suspension to a clear yellow-orange solution. The reaction mixture was transferred to a separation funnel, diluted with Et_2O (50 mL) and extracted with an aqueous 5 % $NaHSO_3$ solution (100 mL). The organic layer was extracted with additional H_2O (25 mL) (2X for amine **2g** et **2p**). The aqueous phases were combined and washed with EtOAc (50 mL). The organic layer was extracted with H_2O (25 mL) (2X for amine **2g** et **2p**). To the combined aqueous phases, aqueous 2.5 N NaOH (20 mL) was added and the resulting solution was extracted with Et_2O (100 mL). The organic layer was washed with brine (100 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure yielding the corresponding amine (**2**) as pure material.

General procedure B (amides 1a-f, 1j-k). The amide (**1**) (1.0 mmol) was added to a flame-dried round bottom flask and put under an argon atmosphere. Dichloromethane (4.0 mL) was added followed by triflic anhydride (1.1 mmol) and the clear colorless solution was stirred at room temperature for 5 min. Hantzsch ester **3** (2.5 mmol) was added in one portion and the reaction mixture was stirred at room temperature for 1h. MeOH (4 mL) and 12 N NaOH aq. (1 mL) were added and the solution was stirred at room temperature for 1 h. The reaction mixture was transferred to a separation funnel, diluted with hexane (50 mL) and extracted with water (50 mL). The organic layer was filtered on a short neutral alumina column and washed with hexane. The amine was eluted with 15 % EtOAc / hexane. The combined fractions were concentrated under reduced pressure yielding the corresponding amine (**2**) as pure material.

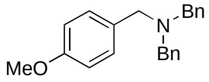


***N,N,N*-tribenzylamine (2a).** 73 % yield; white solid, mp 86-88 °C (Lit. mp 87-89 °C); **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.42 (d, *J* = 7.2 Hz, 6H), 7.32 (t, *J* = 7.2 Hz, 6H), 7.23 (t, *J* = 7.2 Hz, 3H), 3.57 (s, 6H).

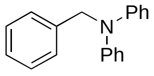
NMR: Loris, A.; Perosa, A.; Selva, M.; Tundo, P. *J. Org. Chem.* **2004**, *69*, 3953-3956. MP: Pollak, I. E.; Grillot, G. F. *J. Org. Chem.* **1967**, *32*, 2892-2893.



***N,N*-dibenzyl-*N*-(4-chlorobenzyl)amine (2b).** 70 % yield; **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.55 (d, *J* = 7.2 Hz, 4H), 7.37-7.54 (m, 10H), 3.69 (s, 4H), 3.66 (s, 2H); **^{13}C NMR** ($CHCl_3$, 75 MHz) δ 139.4, 138.2, 132.5, 130.0, 128.7, 128.4, 127.0, 57.9, 57.2; **FTIR** (cm^{-1}) (neat) 3084, 3062, 3027, 2924, 2882, 2797, 1598, 1490; **HRMS** (ESI, Pos) calcd for $C_{21}H_{21}NCl$ $[M+H]^+$: 322.1355 *m/z*, found 322.1357 *m/z*.

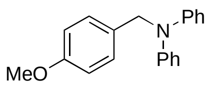


***N,N*-dibenzyl-*N*-(4-methoxybenzyl)amine (2c).** 72 % yield; **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.58 (d, *J* = 7.2 Hz, 4H), 7.48 (t, *J* = 7.6 Hz, 6H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 3.92 (s, 3H), 3.72 (s, 4H), 3.67 (s, 2H); **^{13}C NMR** ($CHCl_3$, 75 MHz) δ 158.6, 139.8, 131.6, 129.9, 128.8, 128.2, 126.9, 113.6, 57.8, 57.2, 55.2; **FTIR** (cm^{-1}) (neat) 3061, 3027, 2929, 2832, 2791, 1611, 1584, 1510, 1494; **HRMS** (ESI, Pos) calcd for $C_{22}H_{24}NO$ $[M+H]^+$: 318.1852 *m/z*, found 318.1849 *m/z*.



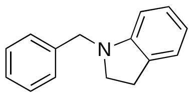
***N*-benzyl-*N,N*-diphenylamine (2d).** 48 % yield; colorless crystals, mp 83-84 °C (EtOH) (Lit. mp 88-90 °C); **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.23-7.39 (m, 9H), 7.10 (d, *J* = 8.4 Hz, 4H), 6.97 (t, *J* = 7.2 Hz, 2H), 5.04 (s, 2H).

NMR: Canè, F.; Brancaleoni, D.; Dembech, P.; Ricci, A.; Seconi, G. *Synthesis* **1997**, 545-548. mp: Paventi, M.; Hay, A. S. *J. Org. Chem.* **1991**, *56*, 5875-5882.



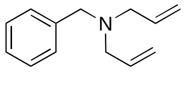
***N*-(4-methoxybenzyl)-*N,N*-diphenylamine (2e).** 50 % yield; **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.27-7.32 (m, 6H), 7.13 (d, *J* = 8.8 Hz, 4H), 6.99 (t, *J* = 7.6 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 5.00 (s, 2H), 3.82 (s, 3H).

NMR: Fox, M. A.; Dulay, M. T.; Krosley, K. *J. Am. Chem. Soc.* **1994**, *116*, 10992-10999.



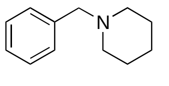
1-benzylindoline (1f). 53 % yield; **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.40-7.33 (m, 5H), 7.20-7.12 (m, 2H), 6.75 (t, *J* = 7.2 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 4.33 (s, 2H), 3.39 (t, *J* = 8.0 Hz, 2H), 3.05 (d, *J* = 8.4 Hz, 2H).

NMR: Zhang, M.; Moore, J. D.; Flynn, D. L.; Hanson, P. R. *Org. Lett.* **2004**, *6*, 2657-2660.



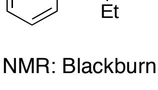
***N,N*-diallyl-*N*-benzylamine (2g).** 81 % yield. **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.44-7.28 (m, 5H), 6.03-5.93 (m, 2H), 5.31-5.22 (m, 4H), 3.68 (s, 2H), 3.18 (d, *J* = 6.4 Hz, 4H).

NMR: Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4085-4088.



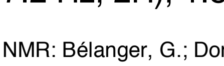
1-benzylpiperidine (2h). 86 % yield. **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.27-7.35 (m, 5H), 3.51 (s, 2H), 2.41 (br s, 4H), 1.58-1.64 (m, 4H), 1.42-1.55 (m, 2H).

NMR: Bull, S. D.; Davies, S. G., Fenton, G.; Mulvaney, A. W., Prasad, R. S.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3765-3774.



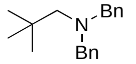
***N*-benzyl-*N,N*-diethylamine (2i).** 71 % yield. **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.41-7.26 (m, 5H), 3.63 (s, 2H), 2.59 (q, *J* = 7.2 Hz, 4H), 1.11 (t, *J* = 7.2 Hz, 6H).

NMR: Blackburn, L.; Taylor, R. J. K. *Org. Lett.* **2001**, *3*, 1637-1639.



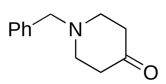
***N,N*-dibenzyl-3-phenylpropan-1-amine (2j).** 62 % yield. **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.42-7.12 (m, 15H), 3.61 (s, 4H), 2.63 (t, *J* = 7.2 Hz, 2H), 2.53 (t, *J* = 7.2 Hz, 2H), 1.87 (qi, *J* = 7.6 Hz, 2H).

NMR: Bélanger, G.; Doré, M.; Ménard, F.; Darsigny, V. *J. Org. Chem.* **2006**, *71*, 7481-7484.



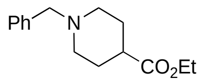
***N,N*-dibenzyl-2,2-dimethylpropan-1-amine (2k).** The resulting colorless oil was further purified by flash chromatography with EtOAc/Hex (2.5/97.5); 18 % yield. **R_f**: 0.77 (2.5% EtOAc/hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.44 (d, *J* = 7.2 Hz, 4H), 7.37 (t, *J* = 7.6 Hz, 4H), 7.28-7.31 (m, 2H), 3.66 (s, 4H), 2.39 (s, 2H), 0.86 (s, 9H).

NMR: Eisch, J. J.; McNulty, J. F.; Shi, X. *J. Org. Chem.* **1994**, *59*, 7-9.



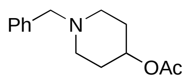
1-benzylpiperidin-4-one (2m). 86 % yield. **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.28-7.38 (m, 5H), 3.65 (s, 2H), 2.77 (t, *J* = 6.0 Hz, 2H), 2.48 (t, *J* = 6.0 Hz, 2H).

NMR: Aldrich (3612-20-2)



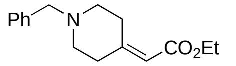
Ethyl 1-benzylpiperidine-4-carboxylate (2n). 81 % yield; **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.24-7.34 (m, 5H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.51 (s, 2H), 2.88 (br d, *J* = 11.6, 2H), 2.26-2.33 (m, 1H), 2.04 (td, *J* = 11.6, 2.0 Hz, 2H), 1.89 (dd, *J* = 9.6, 3.2 Hz, 2H), 1.79 (qd, *J* = 11.2, 4.0 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H).

NMR: Gilligan, P. J.; Cain, G. A.; Christos, T. E.; Cook, L.; Drummond, S.; Johnson, A. L.; Kergaye, A. A.; McElroy, J. F.; Rohrbach, K. W.; Schmidt, W. K.; Tam, S. W. *J. Med. Chem.* **1992**, *35*, 4344-4361.

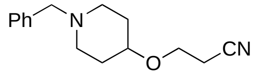


1-benzylpiperidin-4-yl acetate (2o). 82 % yield; **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.24-7.35 (m, 5H), 4.75-4.83 (m, 1H), 3.52 (s, 2H), 2.68-2.77 (m, 2H), 2.58 (br t, *J* = 10.4 Hz, 2H), 1.86-1.95 (m, 2H), 1.67-1.75 (m, 2H).

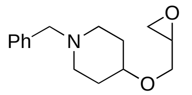
NMR: Banwell, M. G.; Coster, M. J.; Harvey, M. J.; Moraes, J. *J. Org. Chem.* **2003**, *68*, 613-616.



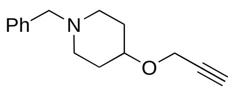
Ethyl (1-benzylpiperidin-4-ylidene)acetate (2p). 78 % yield; **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.26-7.35 (m, 5H), 5.66 (s, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.55 (s, 2H), 3.02 (t, *J* = 6.0 Hz, 2H), 2.55 (t, *J* = 5.6 Hz, 4H), 2.35 (t, *J* = 6.0 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CHCl_3$, 75 MHz) δ 166.5, 159.5, 138.1, 128.9, 128.1, 127.0, 113.9, 62.4, 59.5, 54.4, 53.9, 36.7, 29.3, 14.2; **FTIR** (cm^{-1}) (neat) 3027, 2978, 2942, 2903, 2799, 1713, 1652, 1495; **HRMS** (ESI, Pos) calcd for $C_{16}H_{22}NO_2$ $[M]^+$: 260.1645 *m/z*, found 260.1650 *m/z*.



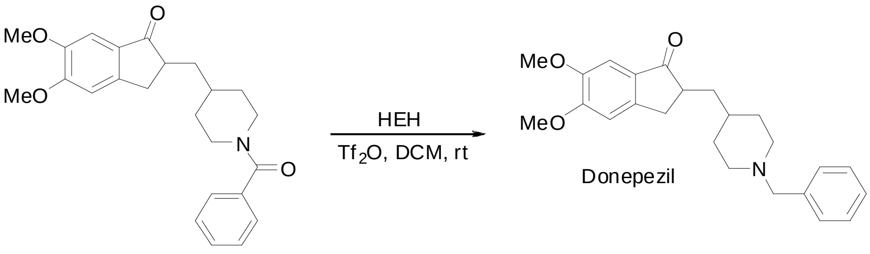
3-[(1-benzylpiperidin-4-yl)oxy]propanenitrile (2q). 91 % yield; **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.25-7.34 (m, 5H), 3.69 (t, *J* = 6.4 Hz, 2H), 3.51 (s, 2H), 3.39-3.43 (m, 1H), 2.70-2.80 (m, 2H), 2.59 (t, *J* = 6.4 Hz, 2H), 2.18 (br t, *J* = 9.2 Hz, 1H), 1.84-1.94 (m, 2H), 1.61-1.70 (m, 2H); **^{13}C NMR** ($CHCl_3$, 75 MHz) δ 138.4, 128.9, 128.1, 126.9, 118.0, 75.7, 62.8, 62.4, 50.7, 31.0, 19.2; **FTIR** (cm^{-1}) (neat) 3061, 3027, 2941, 2800, 2765, 2250, 1600, 1494; **HRMS** (ESI, Pos) calcd for $C_{15}H_{21}N_2O$ $[M+H]^+$: 245.1648 *m/z*, found 245.1650 *m/z*.



1-benzyl-4-(oxiran-2-ylmethoxy)piperidine (2r). 65 % yield; **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 7.33-7.25 (m, 5H), 3.72 (dd, *J* = 11.6, 3.2 Hz, 1H), 3.47 (s, 2H), 3.46-3.39 (m, 2H) (containing: 3.43 (dd, *J* = 11.6, 6.0 Hz, 1H)), 3.16-3.13 (m, 1H), 2.81-2.75 (m, 3H) (containing: 2.79 (dd, *J* = 9.2, 4.8 Hz, 1H)), 2.62 (dd, *J* = 4.8, 2.8 Hz, 1H), 2.16 (br t, *J* = 10.0 Hz, 2H), 1.93-1.88 (m, 2H), 1.68-1.61 (m, 2H); **^{13}C NMR** ($CHCl_3$, 75 MHz) δ 138.5, 128.9, 128.0, 126.8, 75.7, 68.5, 62.8, 51.0, 44.4, 31.3, 31.0; **FTIR** (cm^{-1}) (film) 3059, 3026, 2940, 2858, 2801, 2760, 1725, 1635, 1600, 1494; **HRMS** (ESI, Pos) calcd for $C_{15}H_{22}NO_2$ $[M+H]^+$: 248.1645 *m/z*, found 246.1648 *m/z*.



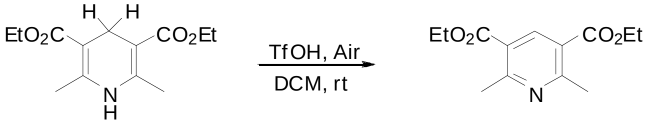
1-benzyl-4-(prop-2-ynyloxy)piperidine (2s). 75 % yield; ^{1}**H NMR** ($CHCl_3$, 400 MHz) δ 7.25-7.38 (m, 5H), 4.20 (s, 2H), 3.53-3.61 (m, 1H), 3.52 (s, 2H), 2.72-2.81 (m, 2H), 2.44 (t, 1H), 2.18 (br t, *J* = 9.8 Hz, 2H), 1.88-1.98 (m, 2H), 1.62-1.71 (m, 2H); ^{13}**C NMR** ($CHCl_3$, 75 MHz) δ 138.4, 129.0, 128.1, 126.9, 80.2, 77.5, 77.0, 76.6, 74.1, 73.8, 62.9, 54.8, 50.9, 30.9; **FTIR** (cm^{-1}) (neat) 3288, 3062, 3027, 2942, 2855, 2801, 2762, 1770, 1728, 1601, 1494; **HRMS** (ESI, Pos) calcd for $C_{15}H_{20}NO$ $[M+H]^+$: 230.1539 *m/z*, found 230.1546 *m/z*.



2-[(1-benzylpiperidin-4-yl)methyl]-5,6-dimethoxyindan-1-one (**5**). The amide **4** (100 mg, 0.254 mmol) was added to a flame-dried round bottom flask and put under an argon atmosphere. Dichloromethane (5.0 mL) was added followed by Hantzsch ester **3** (161 mg, 0.635 mmol). To the yellow suspension was added dropwise triflic anhydride (0.05 mL, 0.280 mmol) at room temperature and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was transferred to a separation funnel, diluted with Et_2O (50 mL) and extracted with an aqueous 5 % $NaHSO_3$ solution (25 mL). The organic layer was extracted with additional H_2O (10 mL). The aqueous phases were combined and washed with EtOAc (50 mL). The organic layer was extracted with H_2O (10 mL). To the combined aqueous phases, aqueous 2.5 N NaOH (10 mL) was added and the resulting solution was extracted with Et_2O (50 mL). The organic layer was washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure yielding the pure amine **5** as a colorless oil (47 mg) in 49 % yield. ^{1}**H NMR** ($CHCl_3$, 400 MHz) δ 7.39-7.22 (m, 5H), 7.18 (s, 1H), 6.86 (s, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 3.52 (s, 2H), 3.24 (dd, *J* = 17.2, 8.0, 1H), 2.92 (br s, 2H), 2.71 (br d, *J* = 14.0 Hz, 2H), 2.02-1.91 (m, 3H), 1.71 (dd, *J* = 25.2, 12.8, 1H), 1.51 (br s, 1H), 1.45-1.24 (m, 4H).

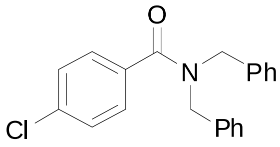
NMR: Fillion, E.; Fishlock, D.; Wilsily, A.; Goll, J. M. *J. Org. Chem* **2005**, *70*, 1316-1327.

Stability of 3 in the presence of acid and air :



Diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (11). HEH (**3**) (2.45 g, 9.70 mmol) was diluted with DCM (40 mL) in a 250 mL erlenmeyer equipped with a septum and a needle opened to air. Triflic anhydride (0.09 mL, 0.10 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. Silica gel was added and the mixture was concentrated under reduced pressure. The solid was purified by flash chromatography with EtOAc/Hex (50/50) yielding **11** as a white solid (1.28 g) in 53 % yield. $\mathbf{R_f}$: 0.30 (20% EtOAc/hexanes); mp 67-68 °C (EtOAc/Hex) (Lit. mp 71-72 °C); ^{1}**H NMR** ($CHCl_3$, 400 MHz) δ 8.67 (s, 1H), 4.40 (q, *J* = 6.4 Hz, 4H), 2.85 (s, 6H), 1.42 (t, *J* = 7.2 Hz, 6H).

NMR + MP: Nakamishi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett.* **2002**, *4*, 3955-3957.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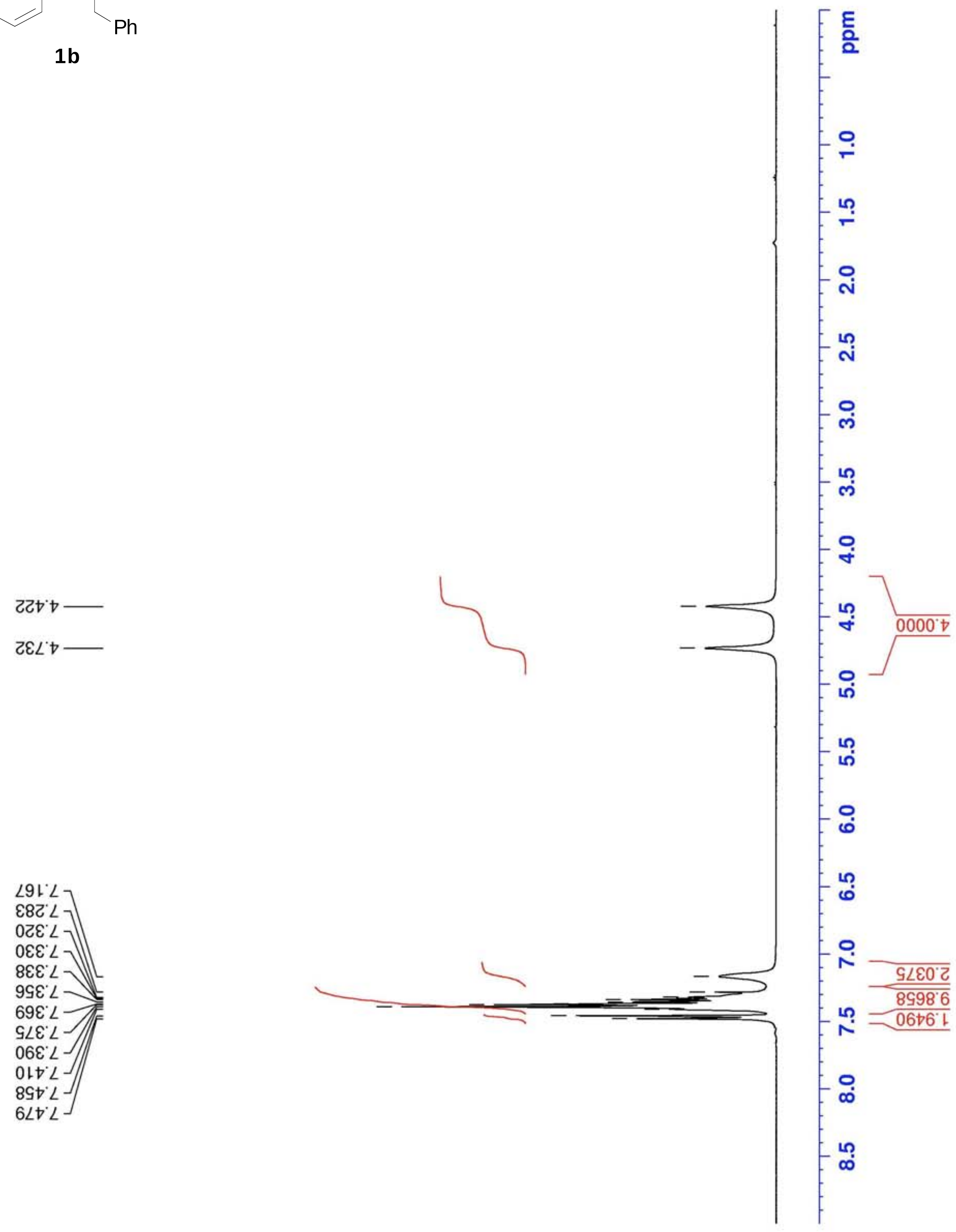
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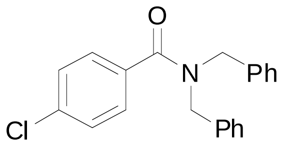
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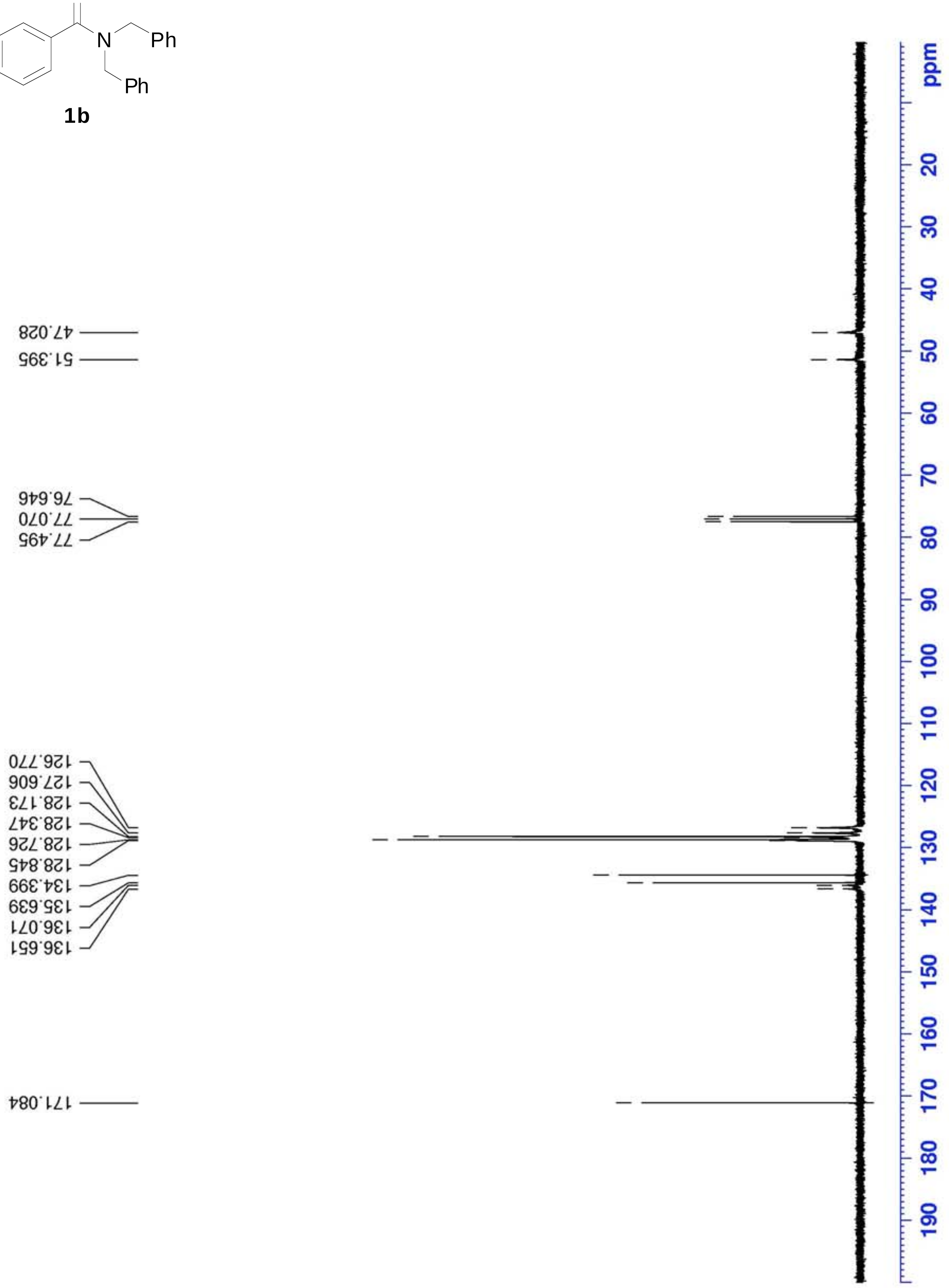
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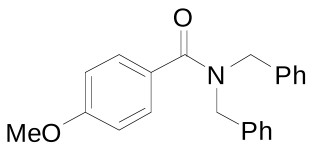
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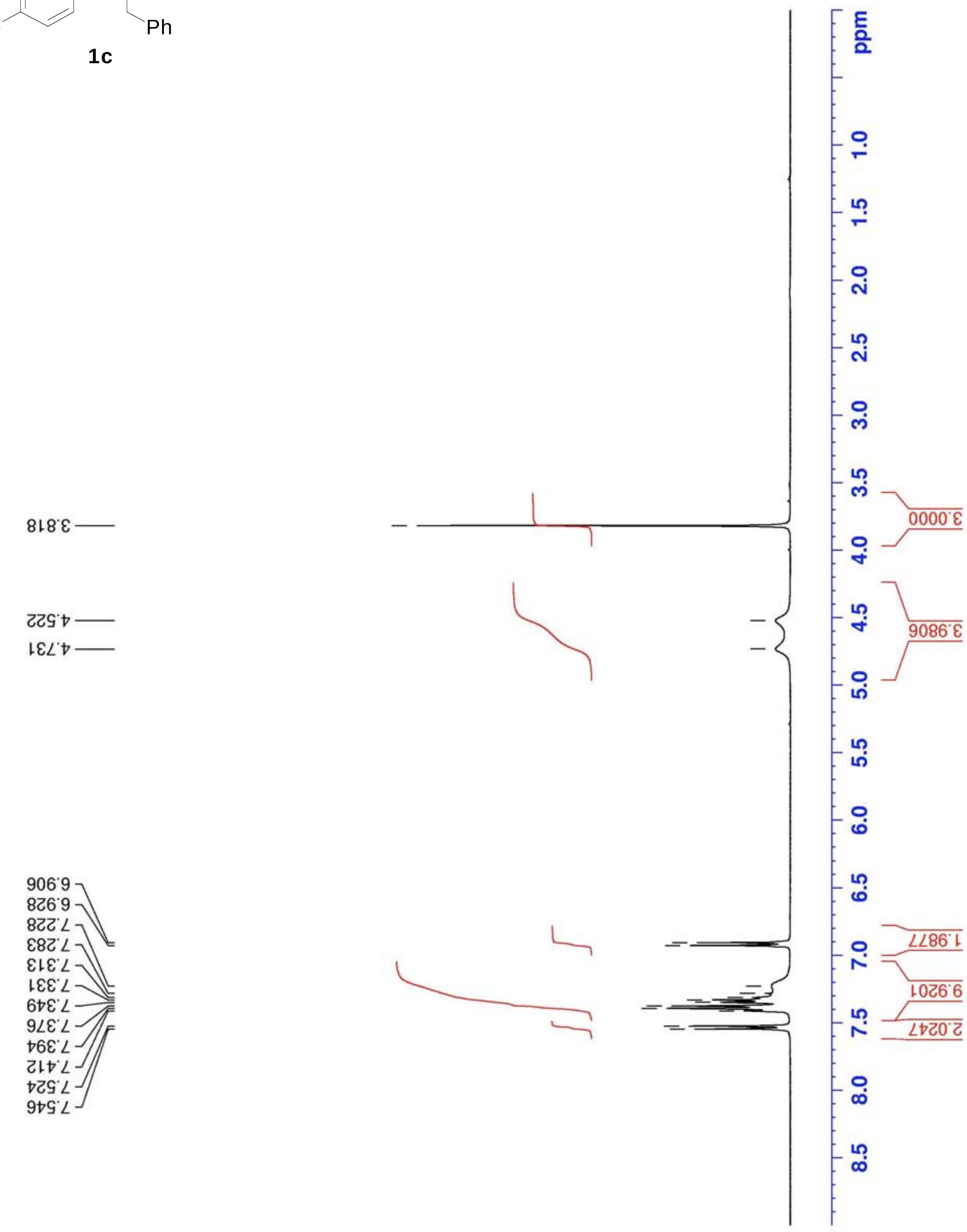
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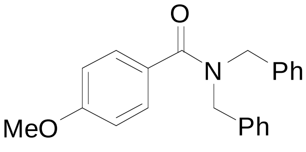
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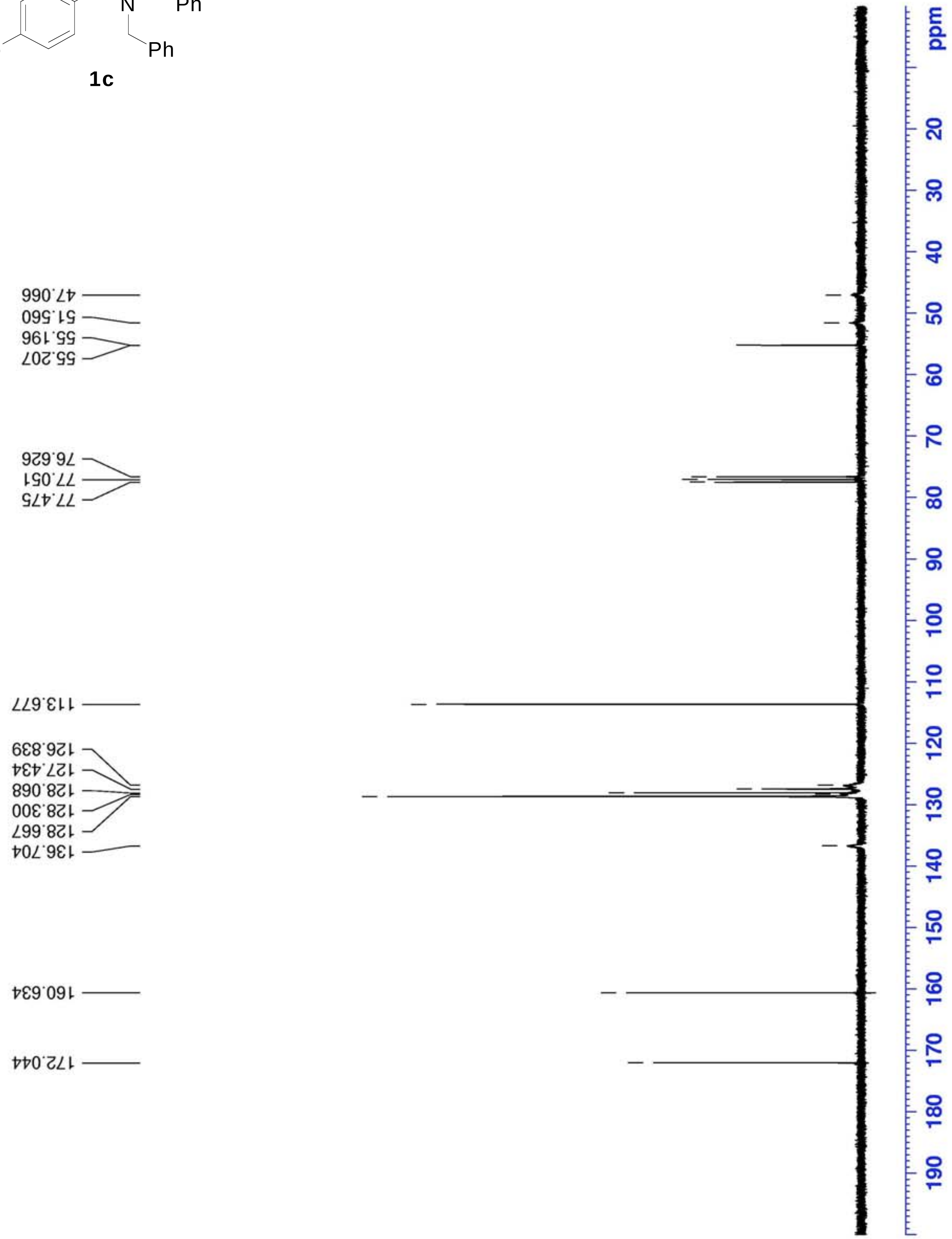
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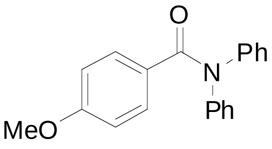
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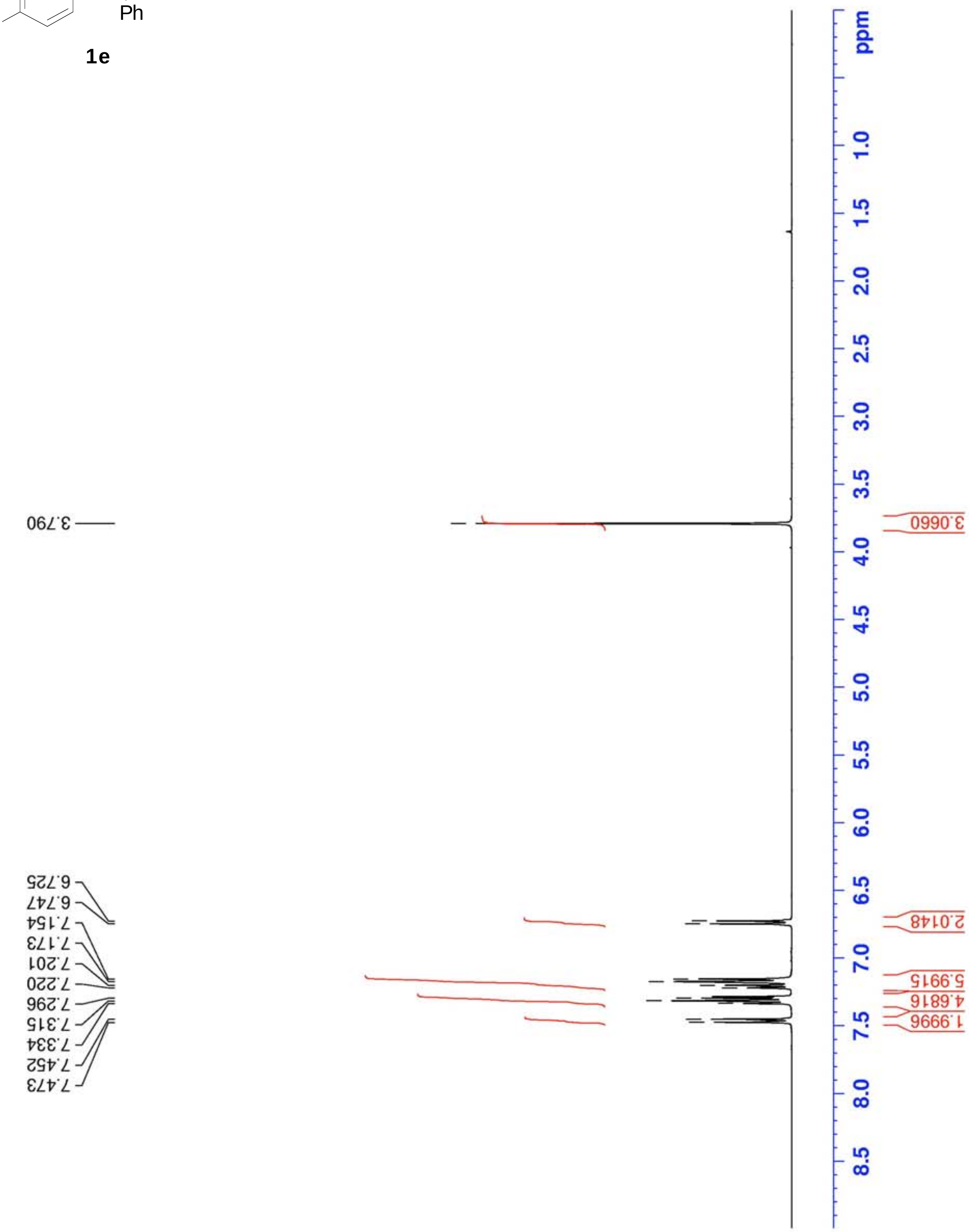
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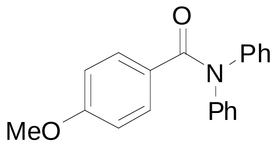
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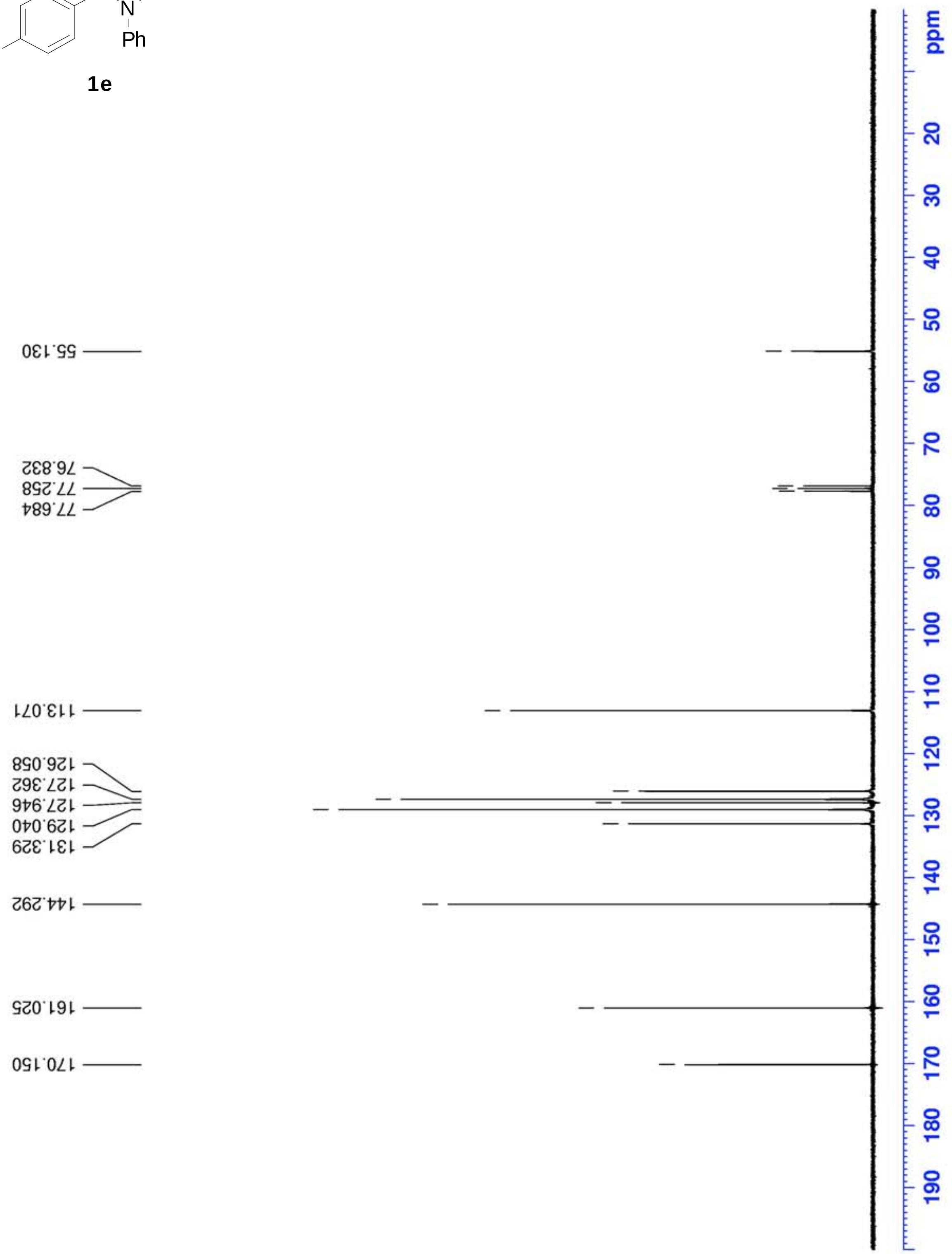
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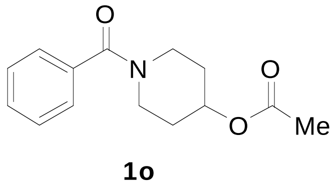
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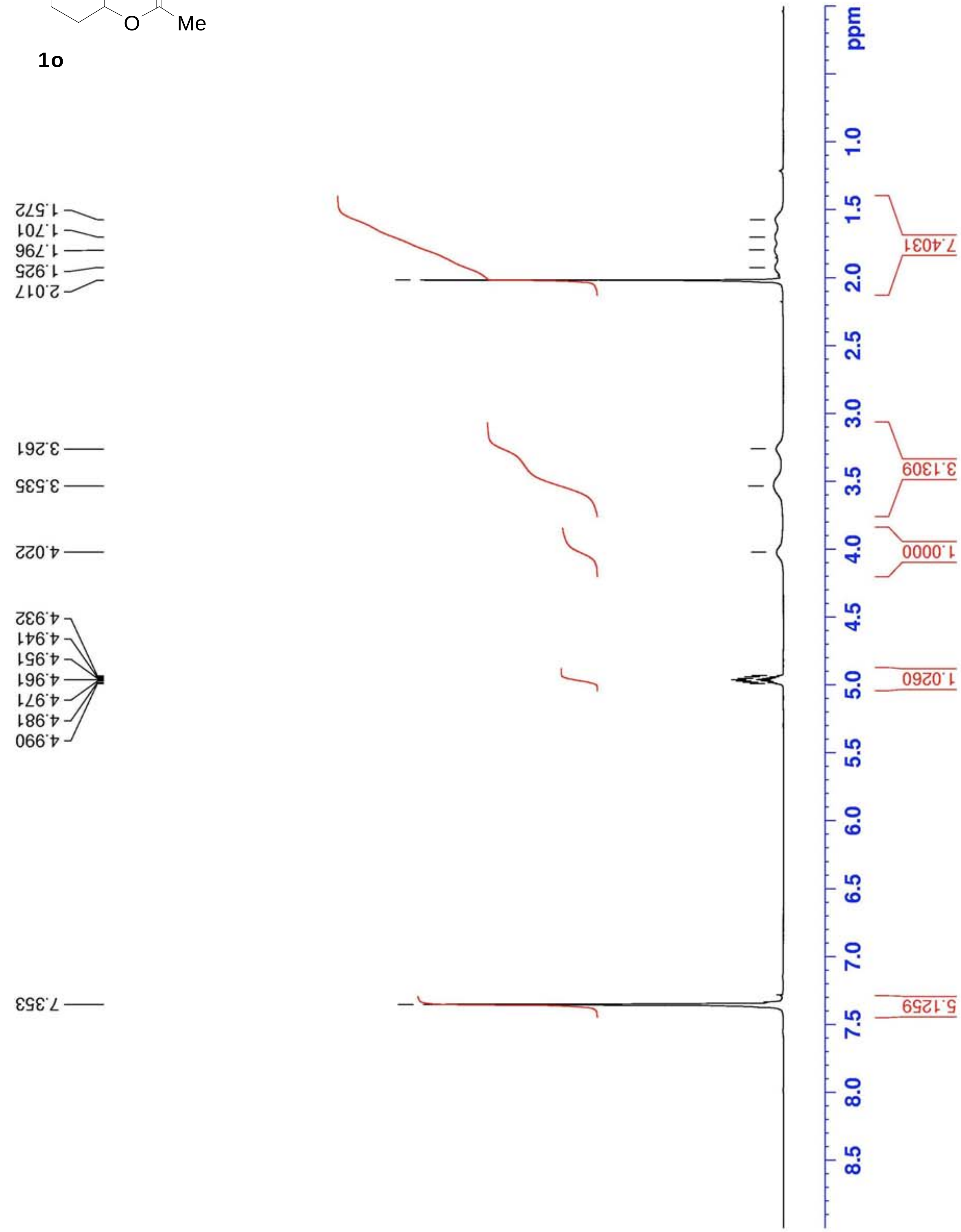
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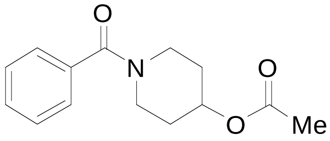

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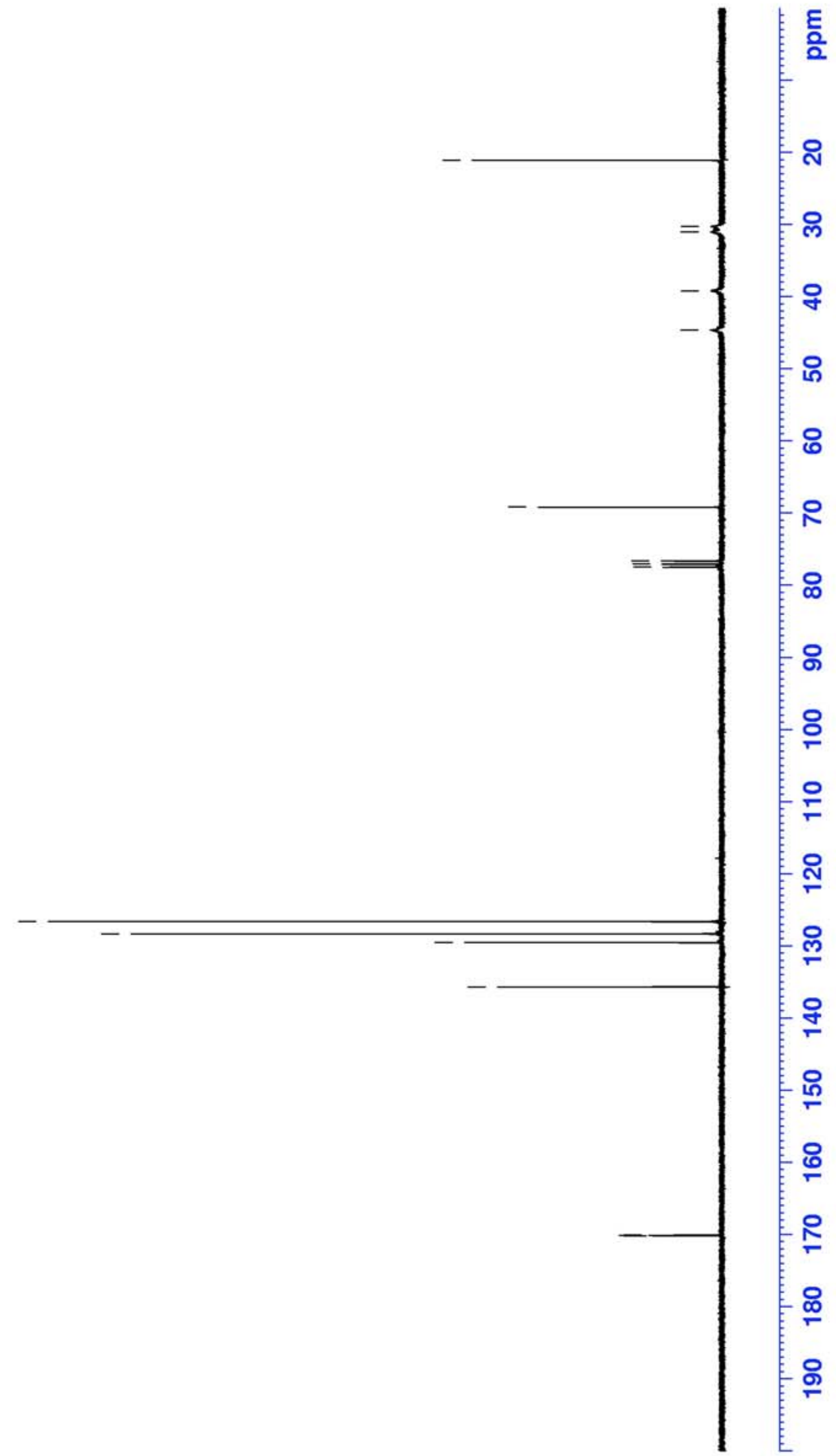
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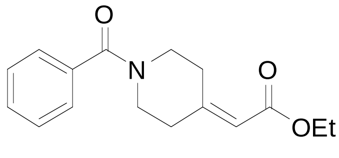
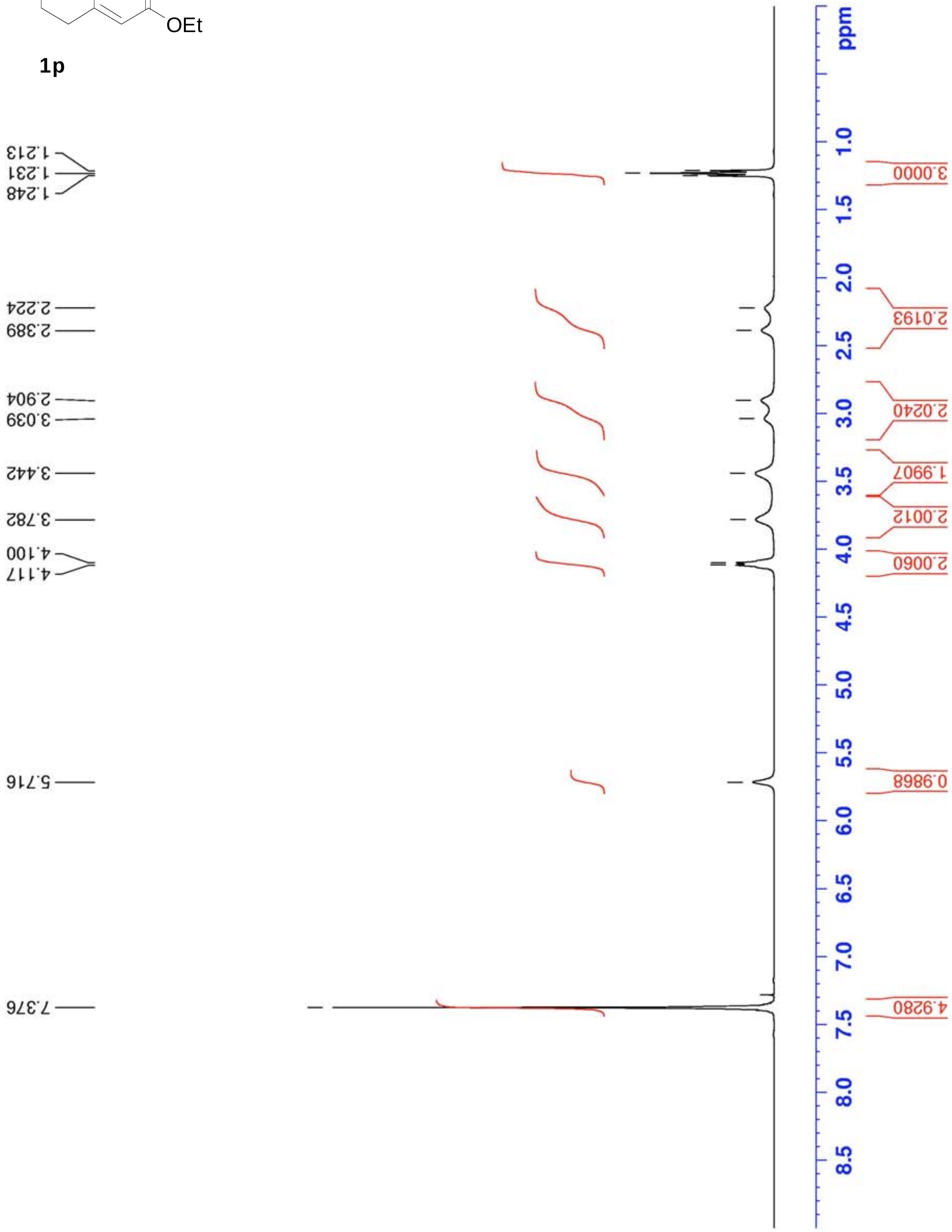

O
N
O
OEt

1p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7.376
ppm
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2.0
2.5
3.0
3.5
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4.5
5.0
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6.0
6.5
7.0
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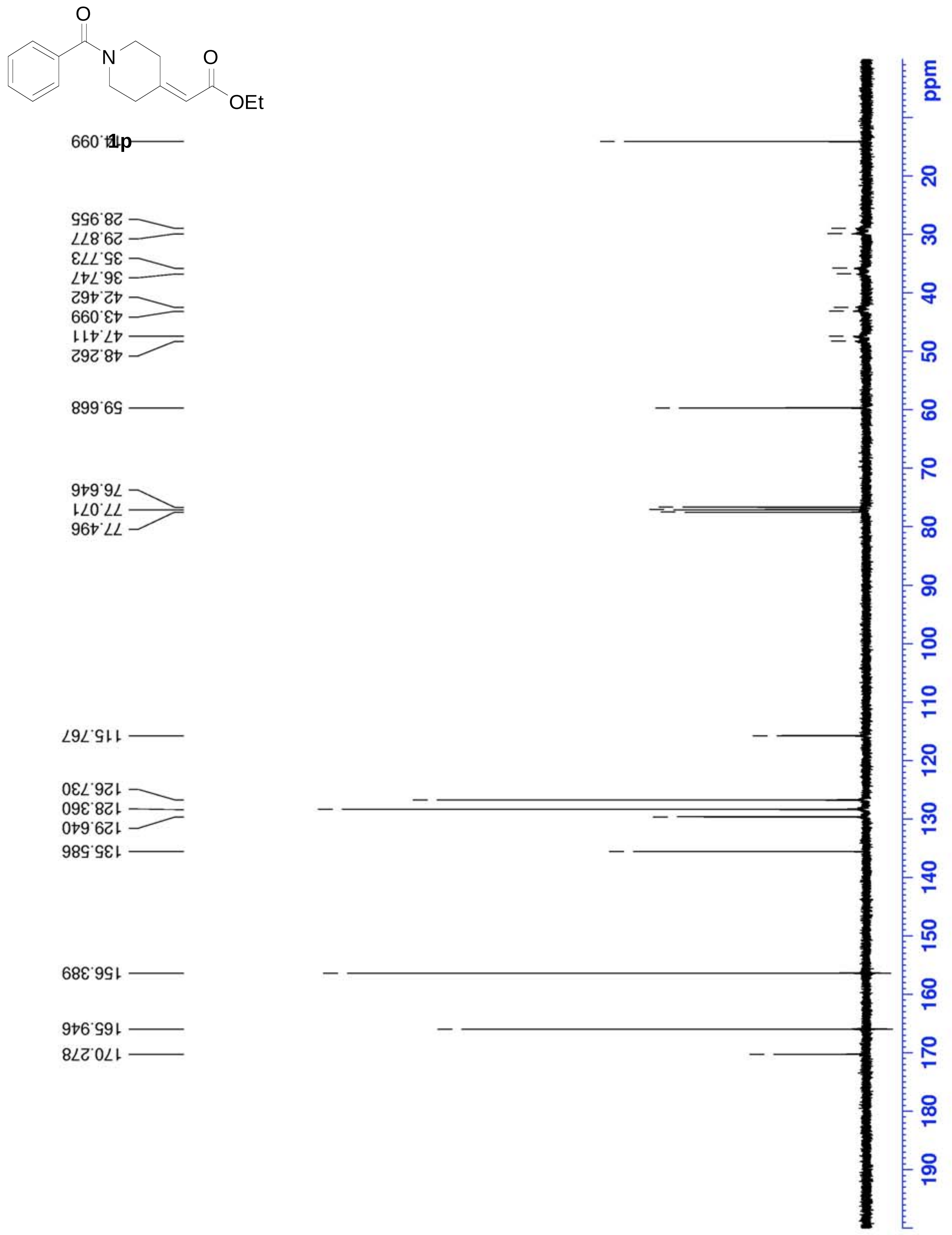
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O
OEt
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48.262
59.668
76.646
77.071
77.496
115.767
126.730
128.360
129.640
135.586
156.389
165.946
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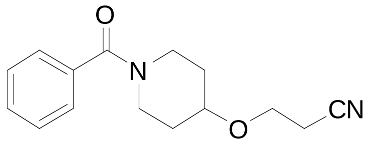
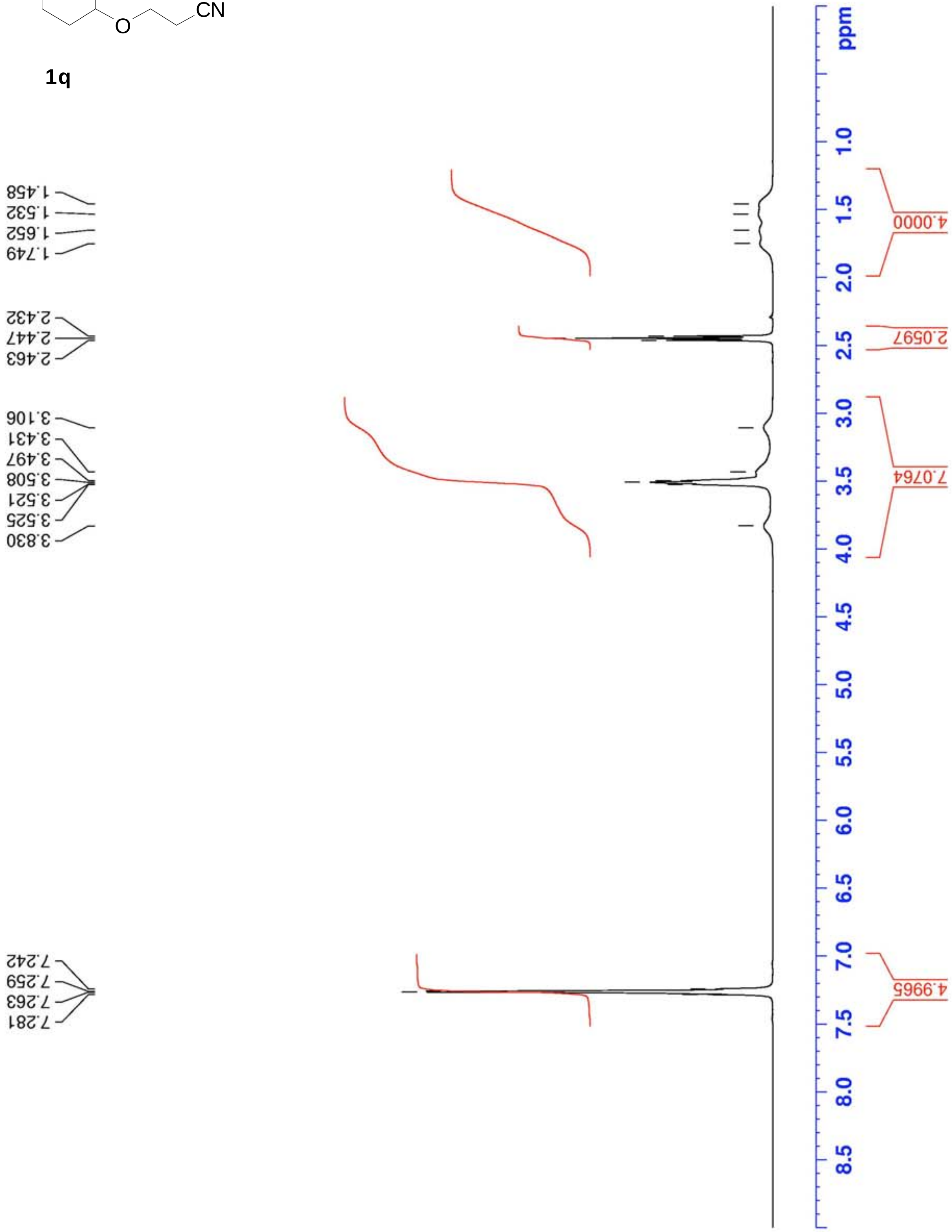


1q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3.106
3.431
3.497
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3.525
3.830
7.242
7.259
7.263
7.281
4.0000
2.0597
7.0764
4.9965
ppm
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1.5
2.0
2.5
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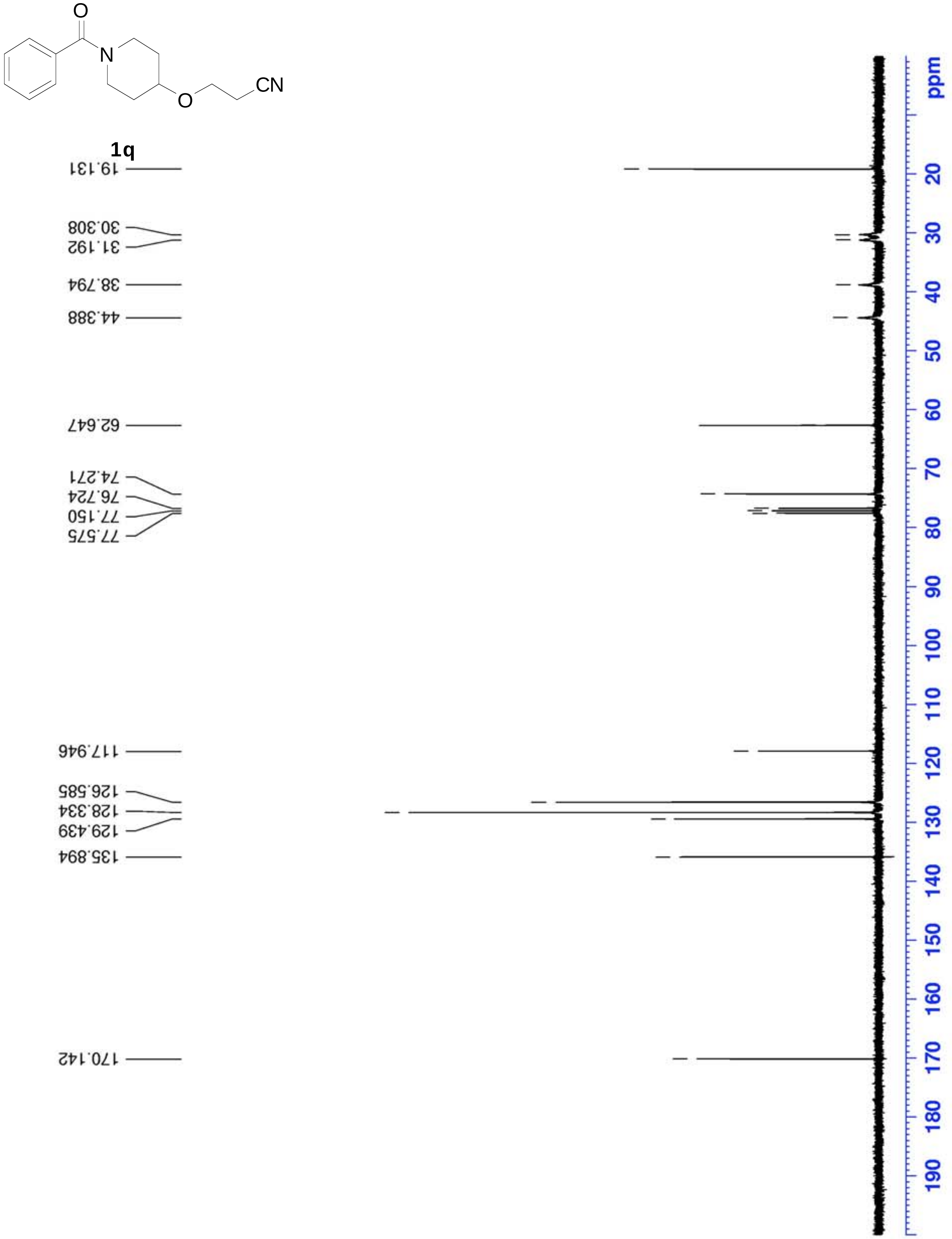
8.5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O
CN
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77.575
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126.585
128.334
129.439
135.894
170.142
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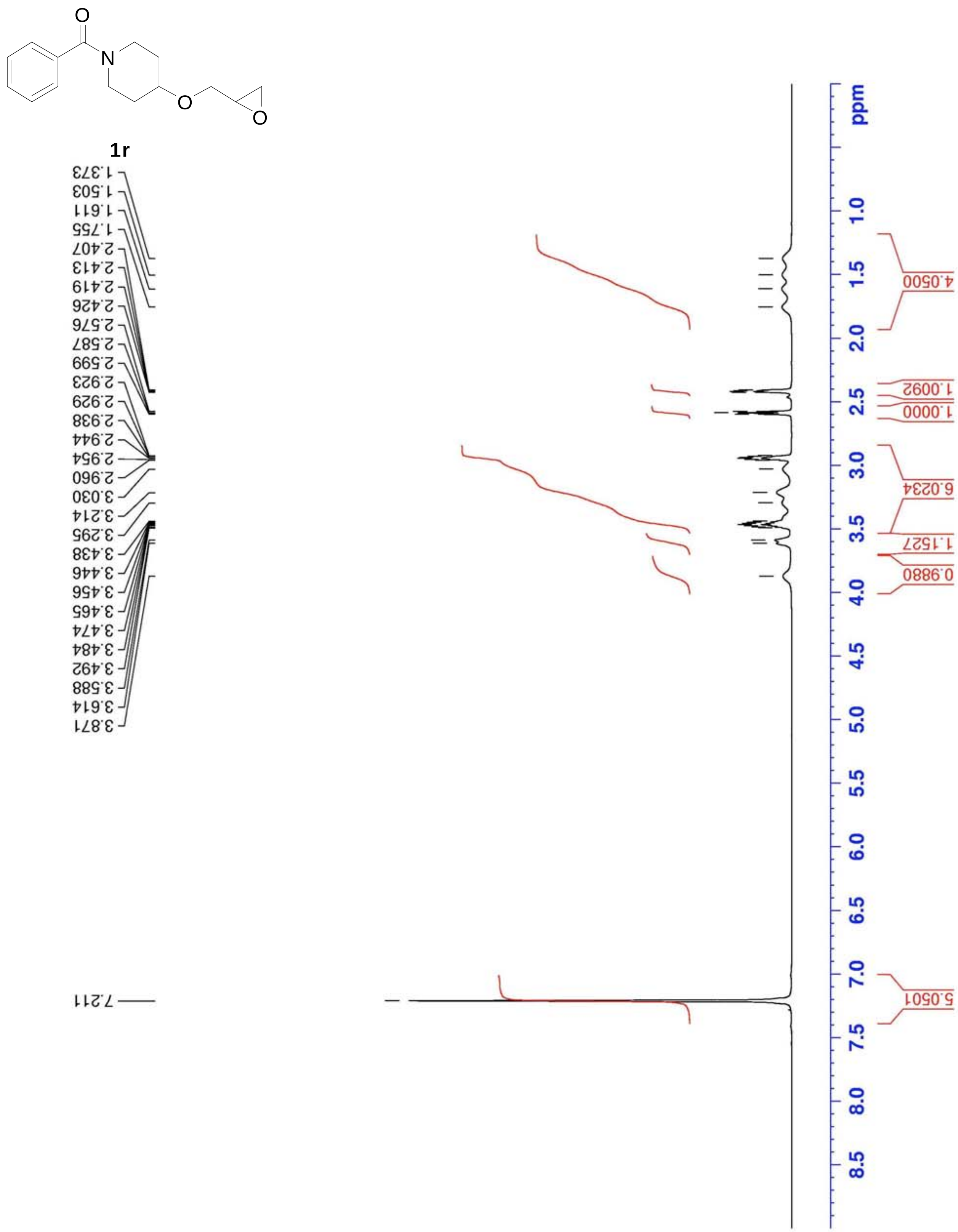
1q


1r

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2.413
2.419
2.426
2.576
2.587
2.599
2.923
2.929
2.938
2.944
2.954
2.960
3.030
3.214
3.295
3.438
3.446
3.456
3.465
3.474
3.484
3.492
3.588
3.614
3.871
7.211
4.0500
1.0092
1.0000
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1.1527
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5.0501
ppm
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1.5
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3.0
3.5
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6.0
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O
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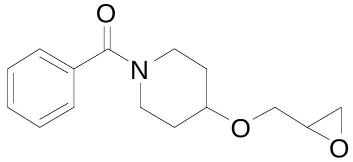
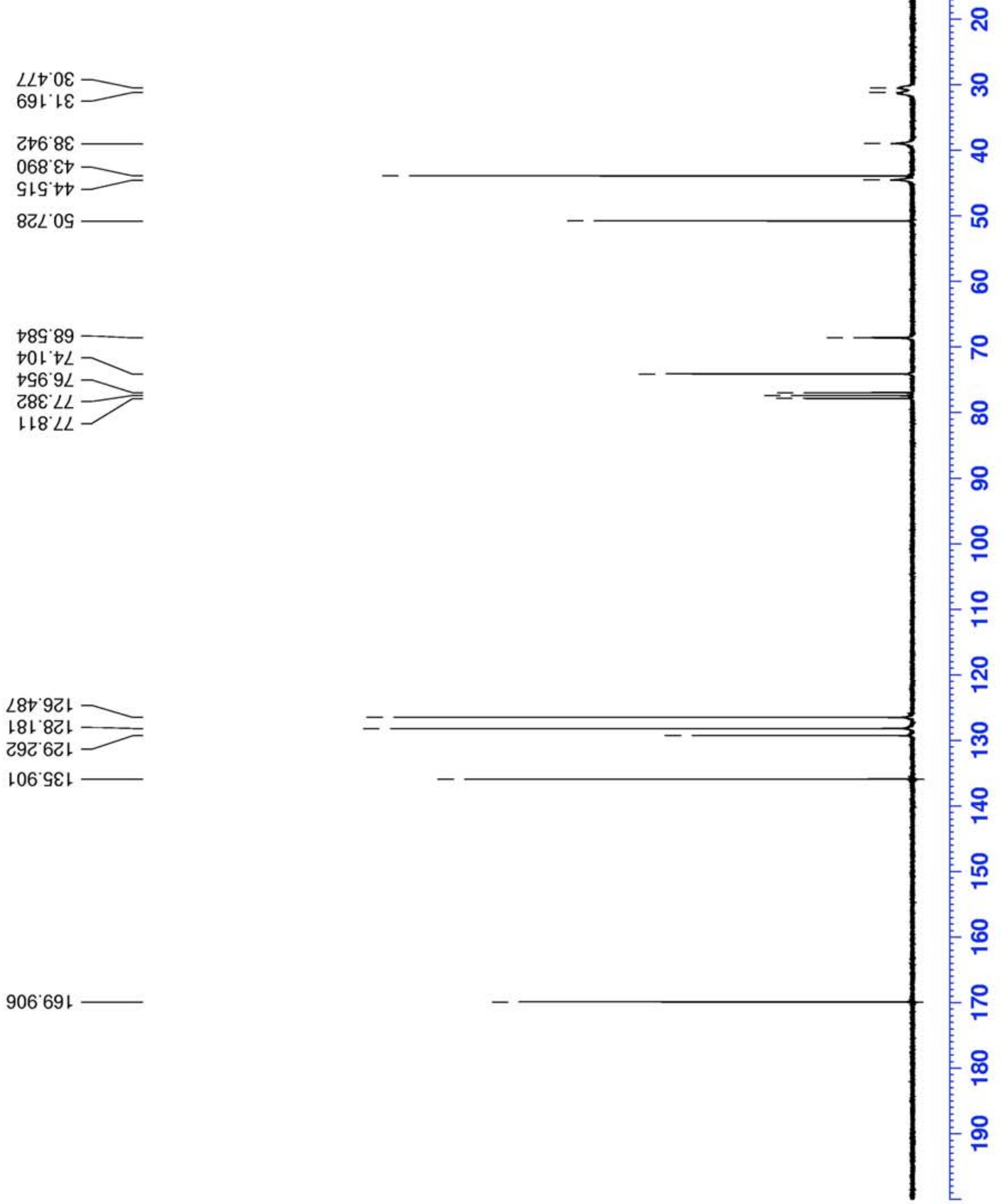
O
O



1r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76.954
77.382
77.811
126.487
128.181
129.262
135.901
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180
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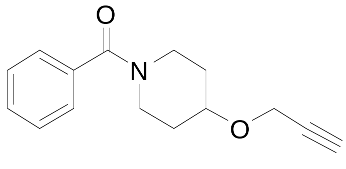
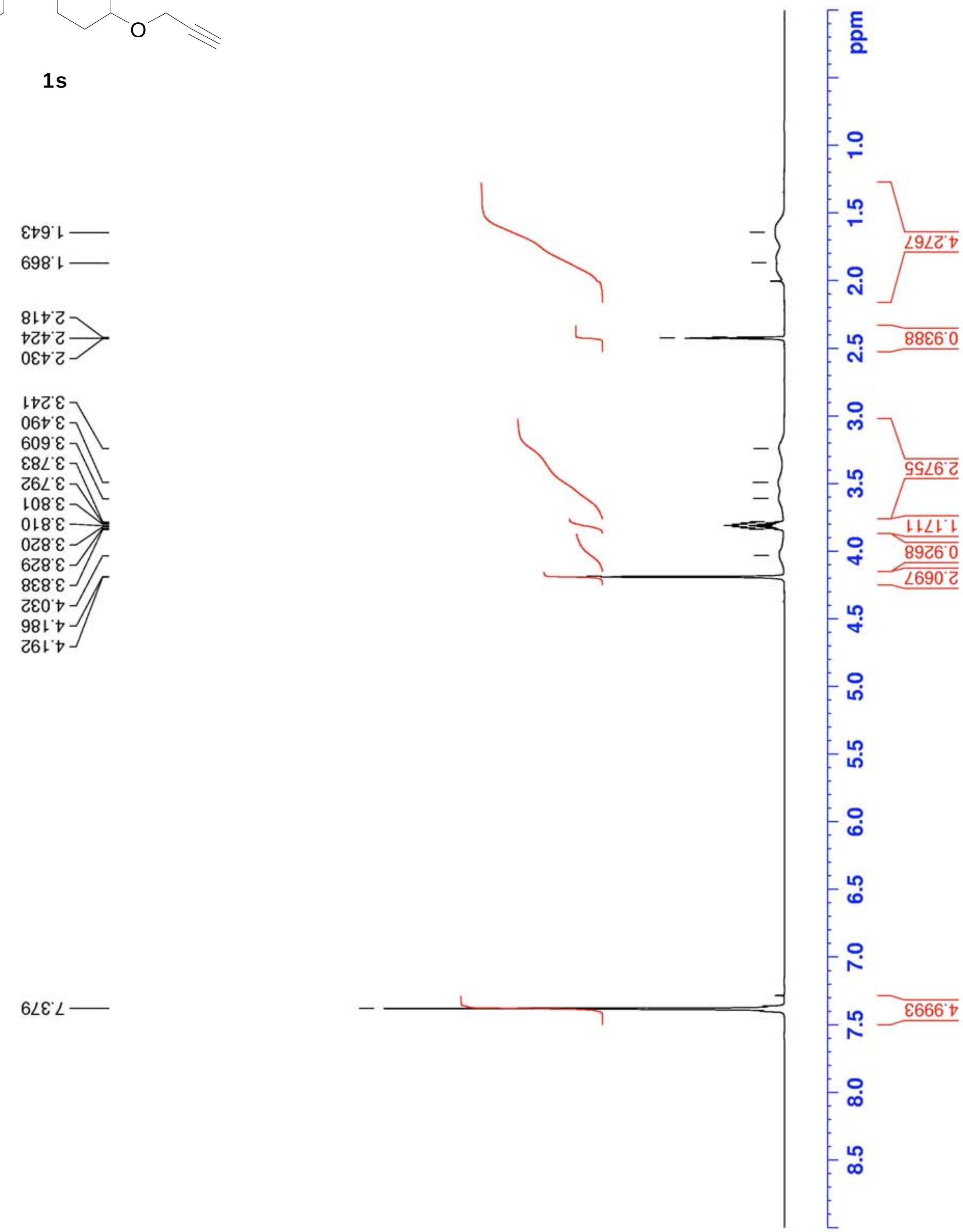


1s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3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
1.643
1.869
2.418
2.424
2.430
3.241
3.490
3.609
3.783
3.792
3.801
3.810
3.820
3.829
3.838
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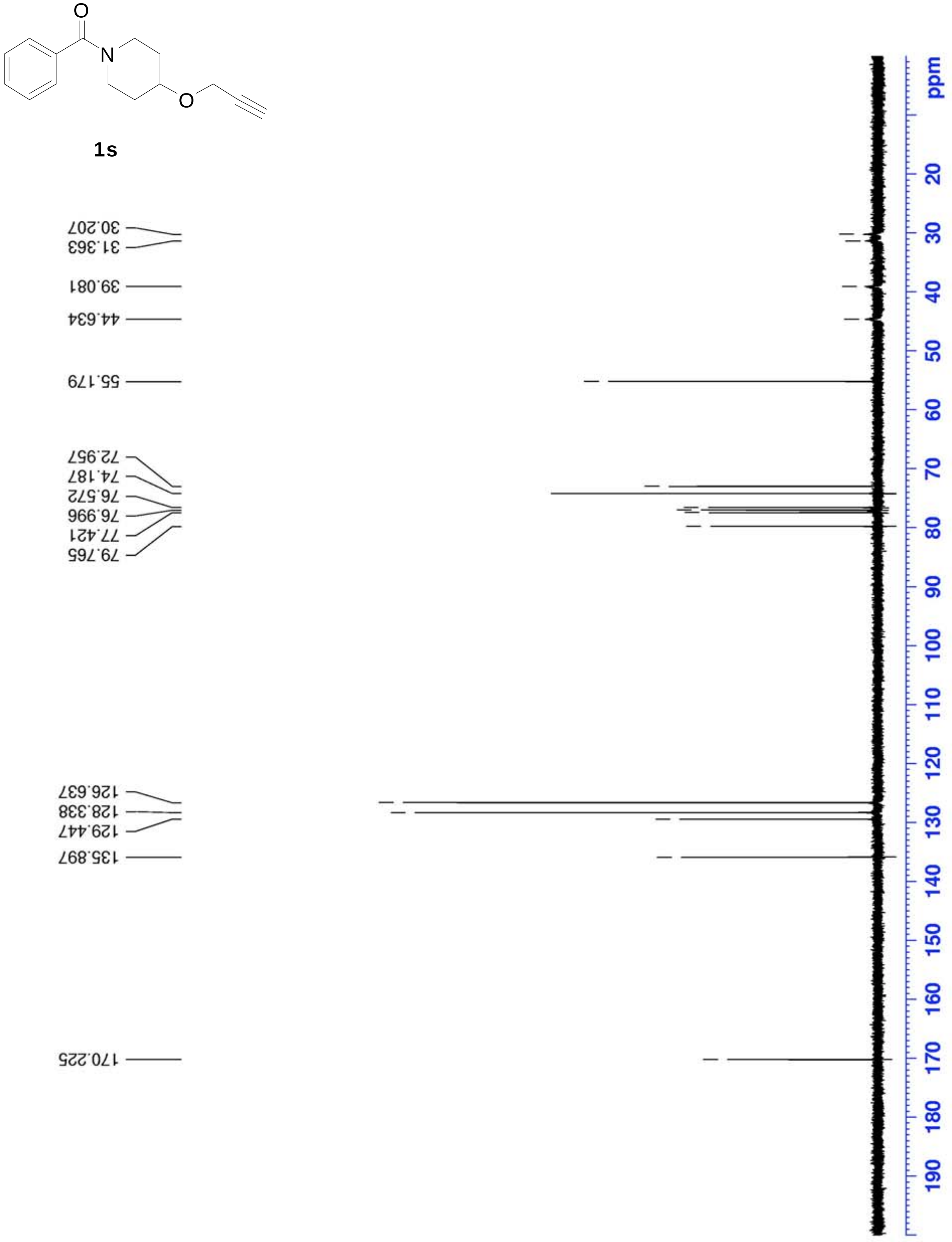
4.192
7.379
4.2767
0.9388
2.9755
1.1711
0.9268
2.0697
4.9993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N
O
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39.081
44.634
55.179
72.957
74.187
76.572
76.996
77.421
79.765
126.637
128.338
129.447
135.897
170.225
ppm
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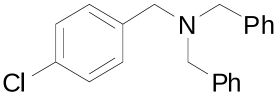
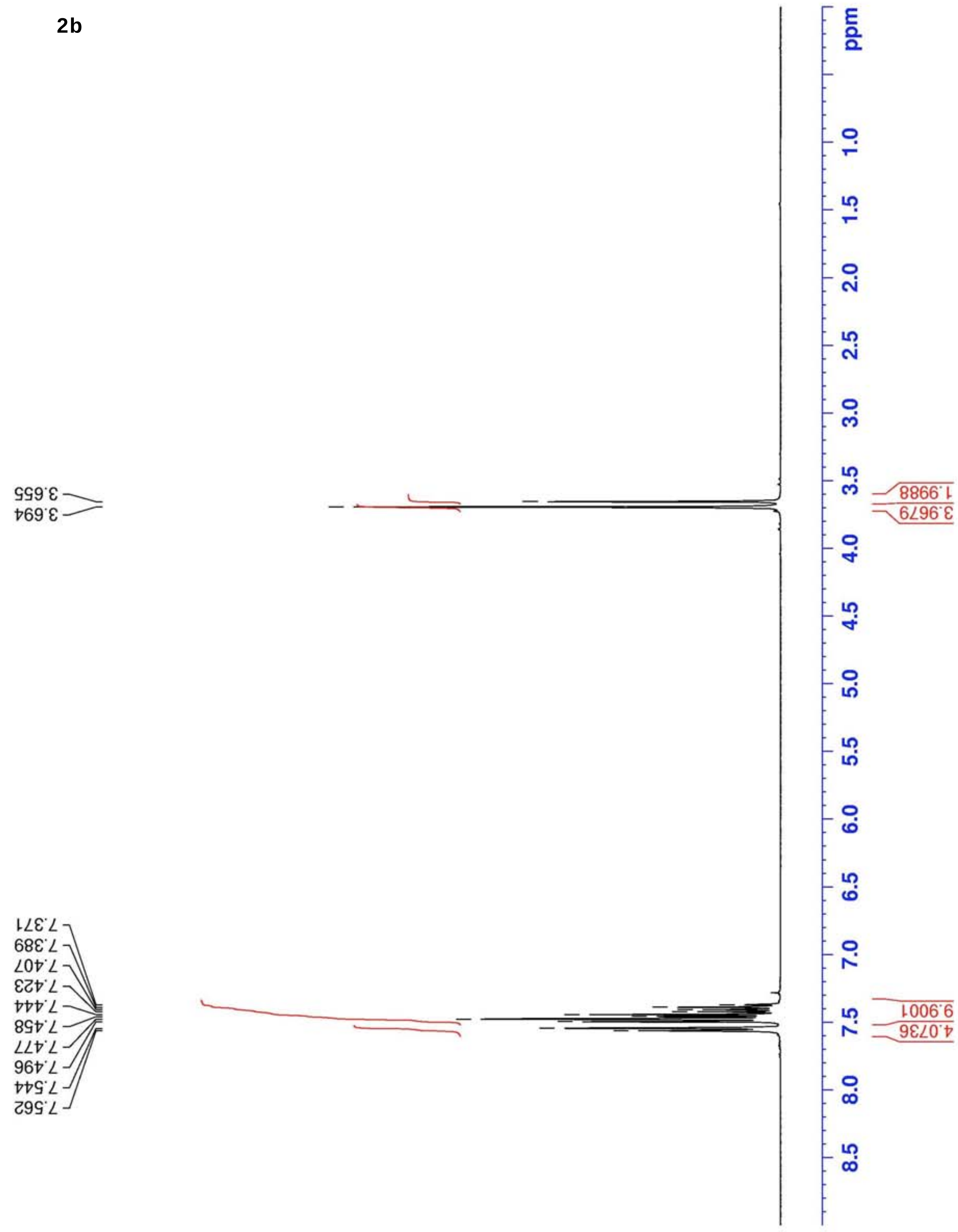
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

1s


N
Ph
Ph
Cl

2b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7.407
7.423
7.444
7.458
7.477
7.496
7.544
7.562
1.9988
3.9679
9.9001
4.0736
ppm
1.0
1.5
2.0
2.5
3.0
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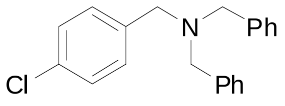
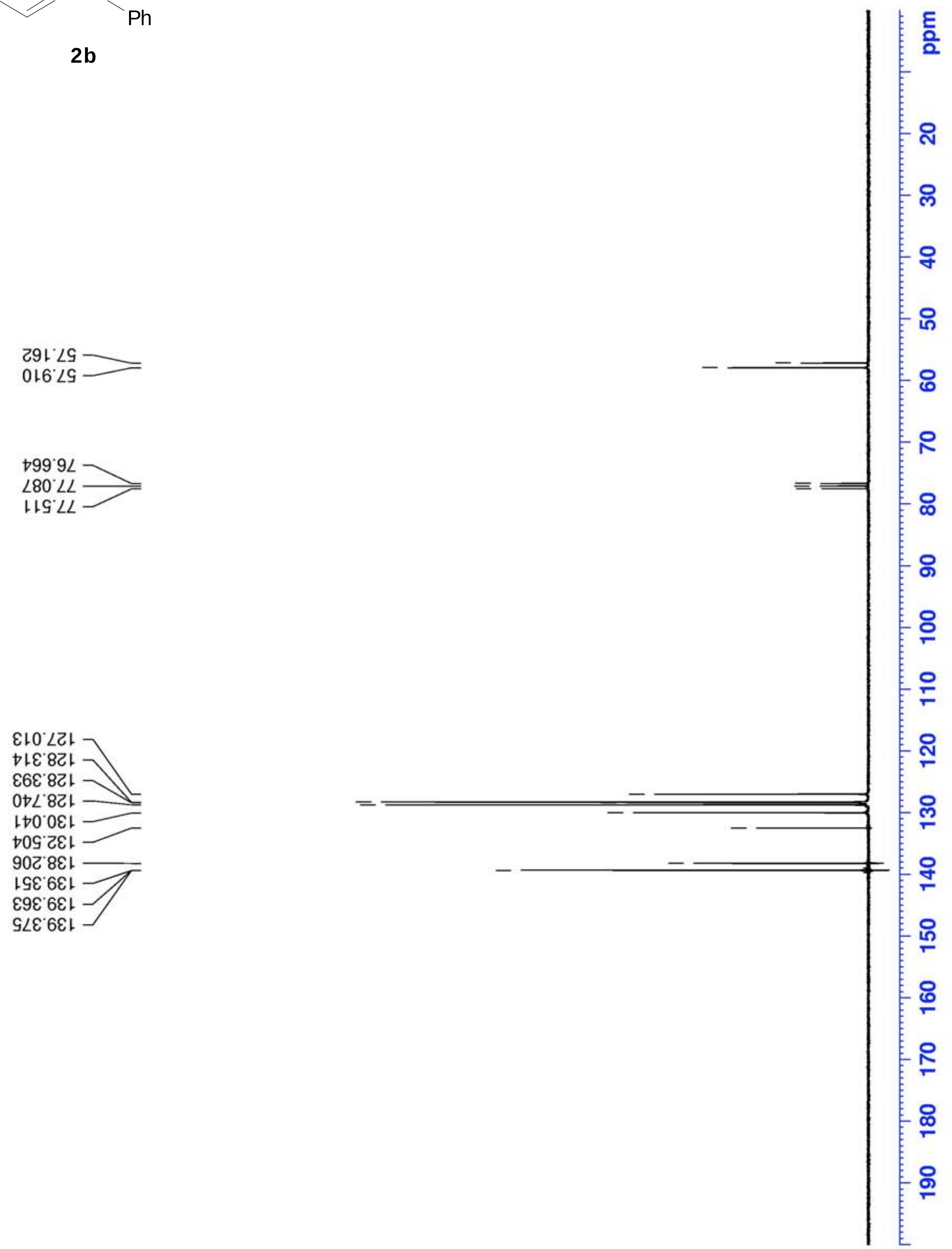
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5


Cl
N
Ph
Ph

2b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77.087
77.511
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128.314
128.393
128.740
130.041
132.504
138.206
139.351
139.363
139.375
ppm
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40
50
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70
80
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120
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160
170
180
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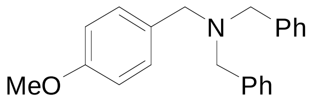
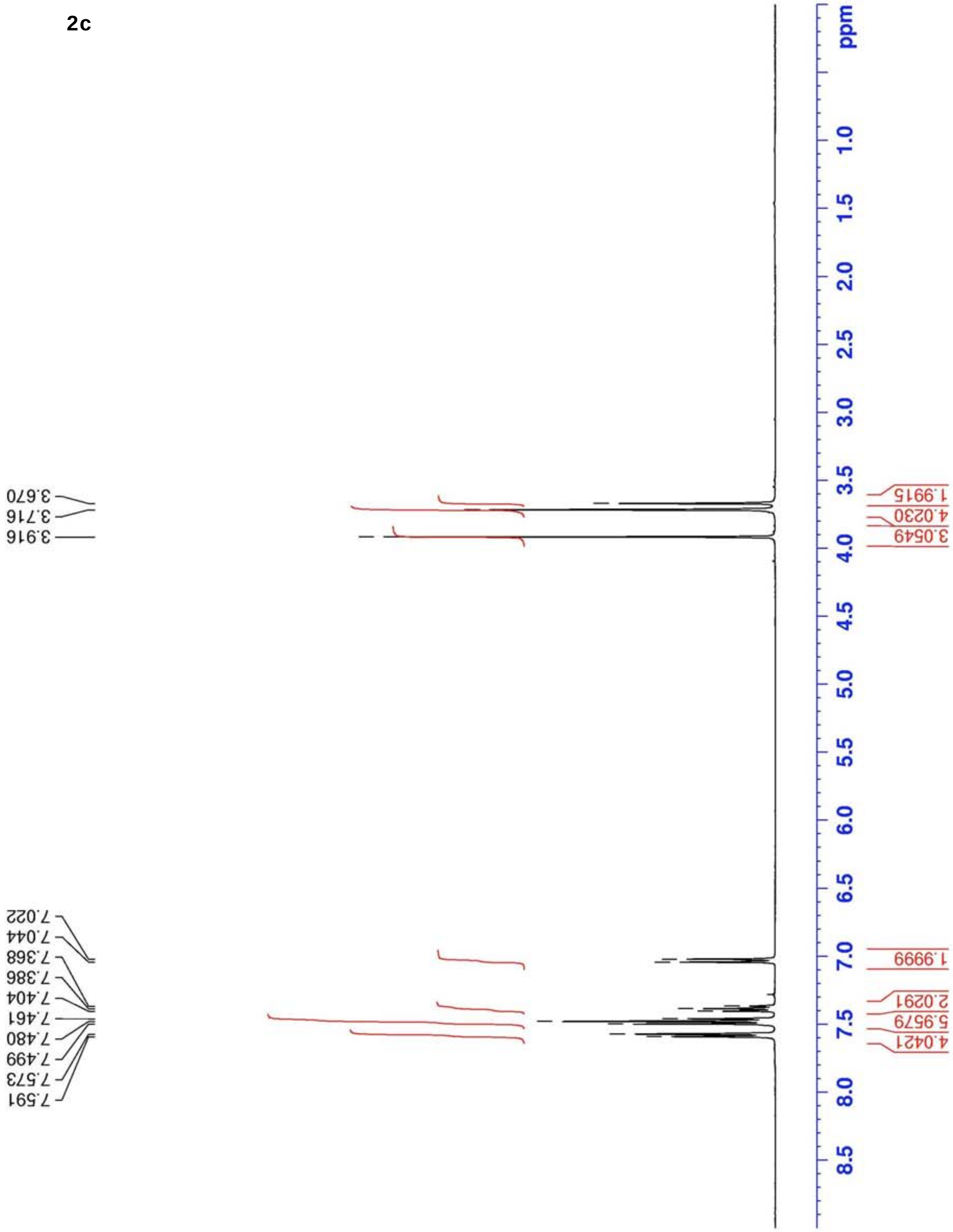

MeO
N
Ph
Ph

2c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7.404
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7.573
7.591
ppm
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1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
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7.5
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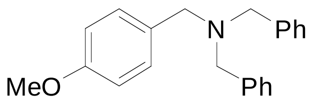
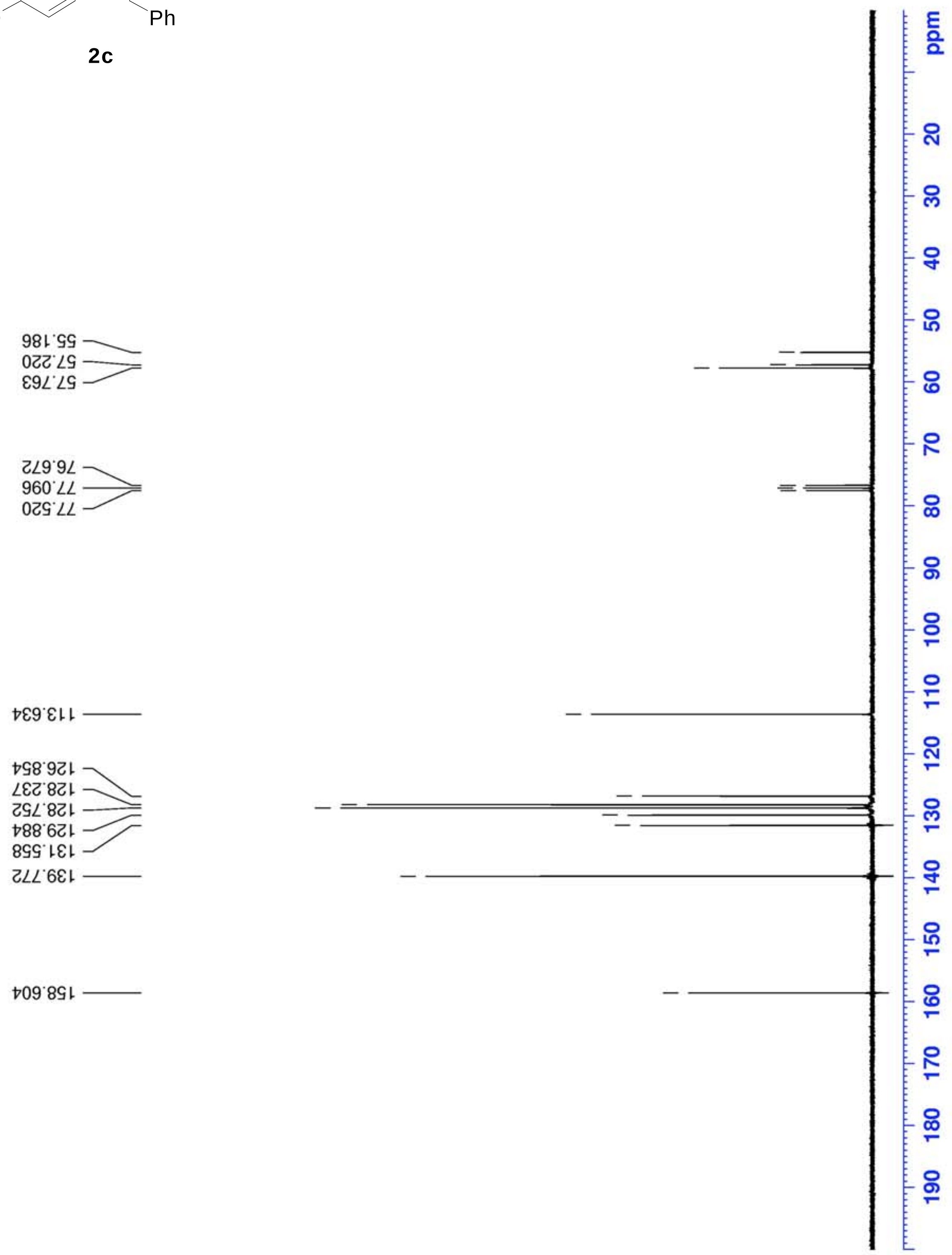
5.9579
4.0421


MeO
N
Ph
Ph

2c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77.520
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126.854
128.237
128.752
129.884
131.558
139.772
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70
80
90
100
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120
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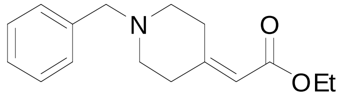
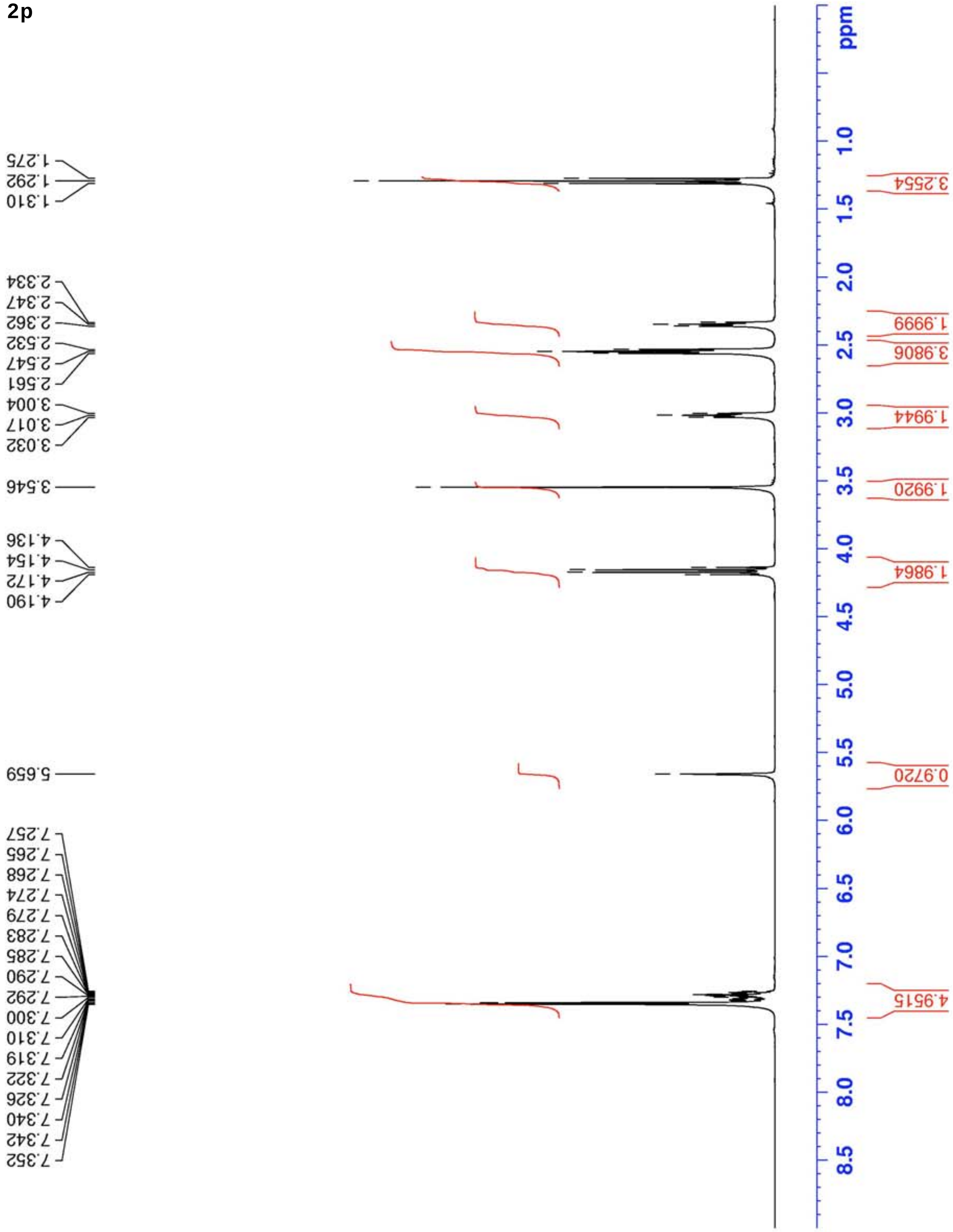
140
150
160
170
180
190


N
O
OEt

2p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2.547
2.561
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3.017
3.032
3.546
4.136
4.154
4.172
4.190
5.659
7.257
7.265
7.268
7.274
7.279
7.283
7.285
7.290
7.292
7.300
7.310
7.319
7.322
7.326
7.340
7.342
7.352
ppm
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1.5
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2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
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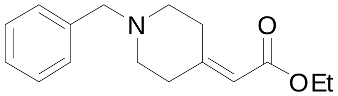
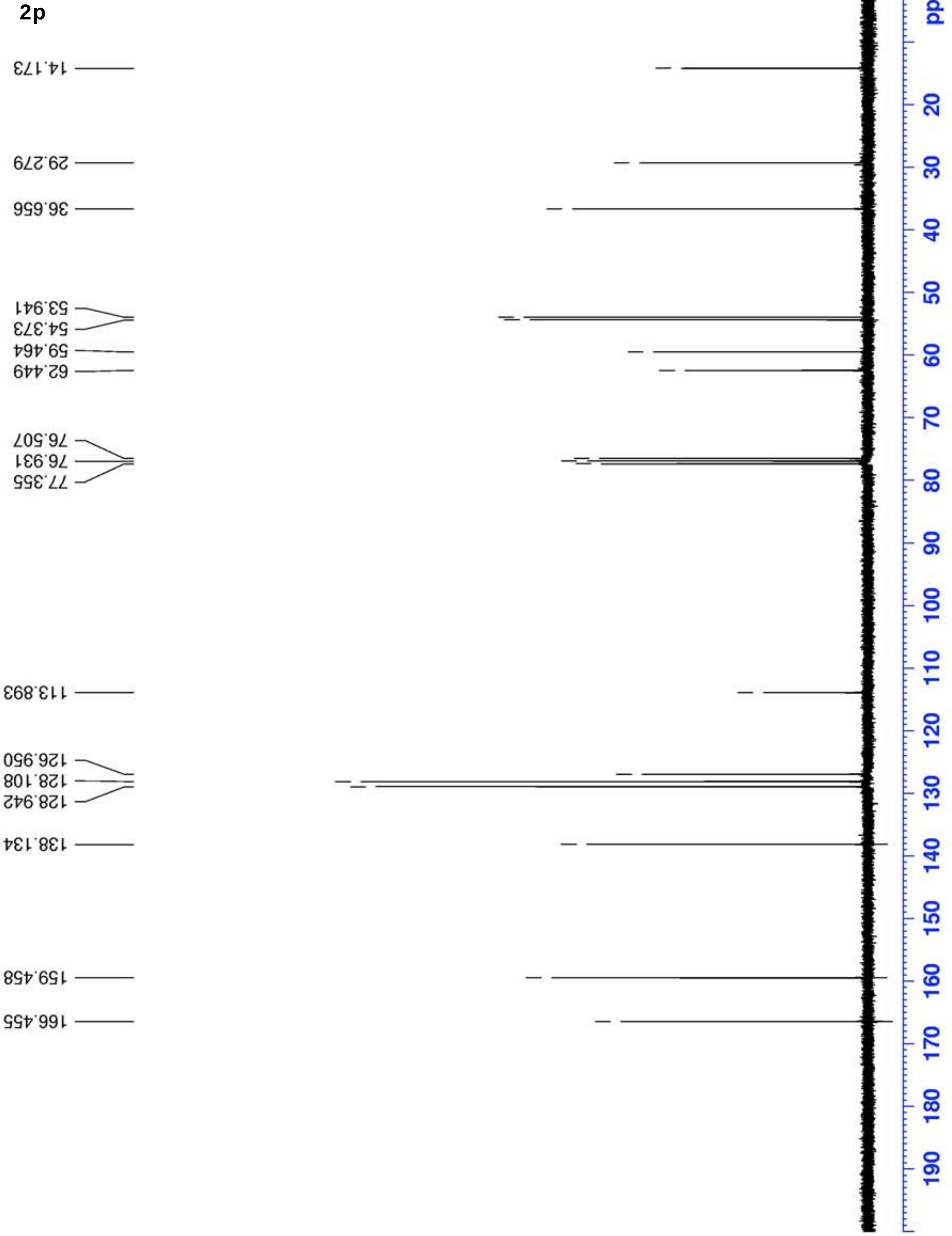

N
O
OEt

2p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62.449
76.507
76.931
77.355
113.893
126.950
128.108
128.942
138.134
159.458
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ppm
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80
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120
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180
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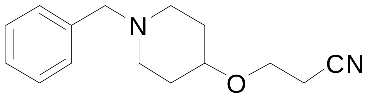
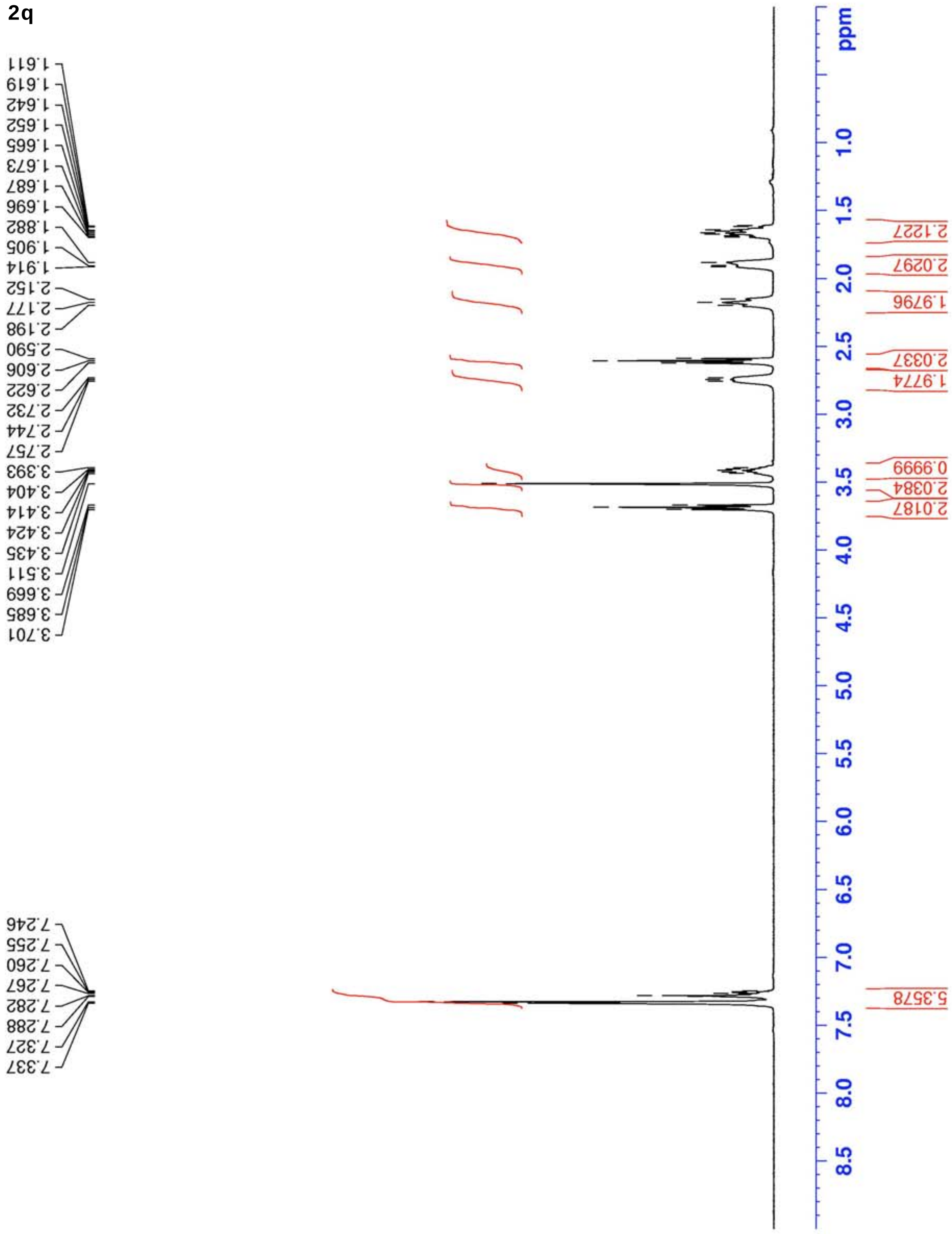

N
O
CN

2q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2.152
2.177
2.198
2.590
2.606
2.622
2.732
2.744
2.757
3.393
3.404
3.414
3.424
3.435
3.511
3.669
3.685
3.701
7.246
7.255
7.260
7.267
7.282
7.288
7.327
7.337
2.1227
2.0297
1.9796
2.0337
1.9774
0.9999
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2.0187
5.3578
ppm
1.0
1.5
2.0
2.5
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4.0
4.5
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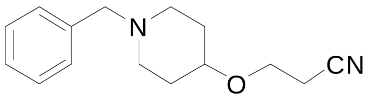
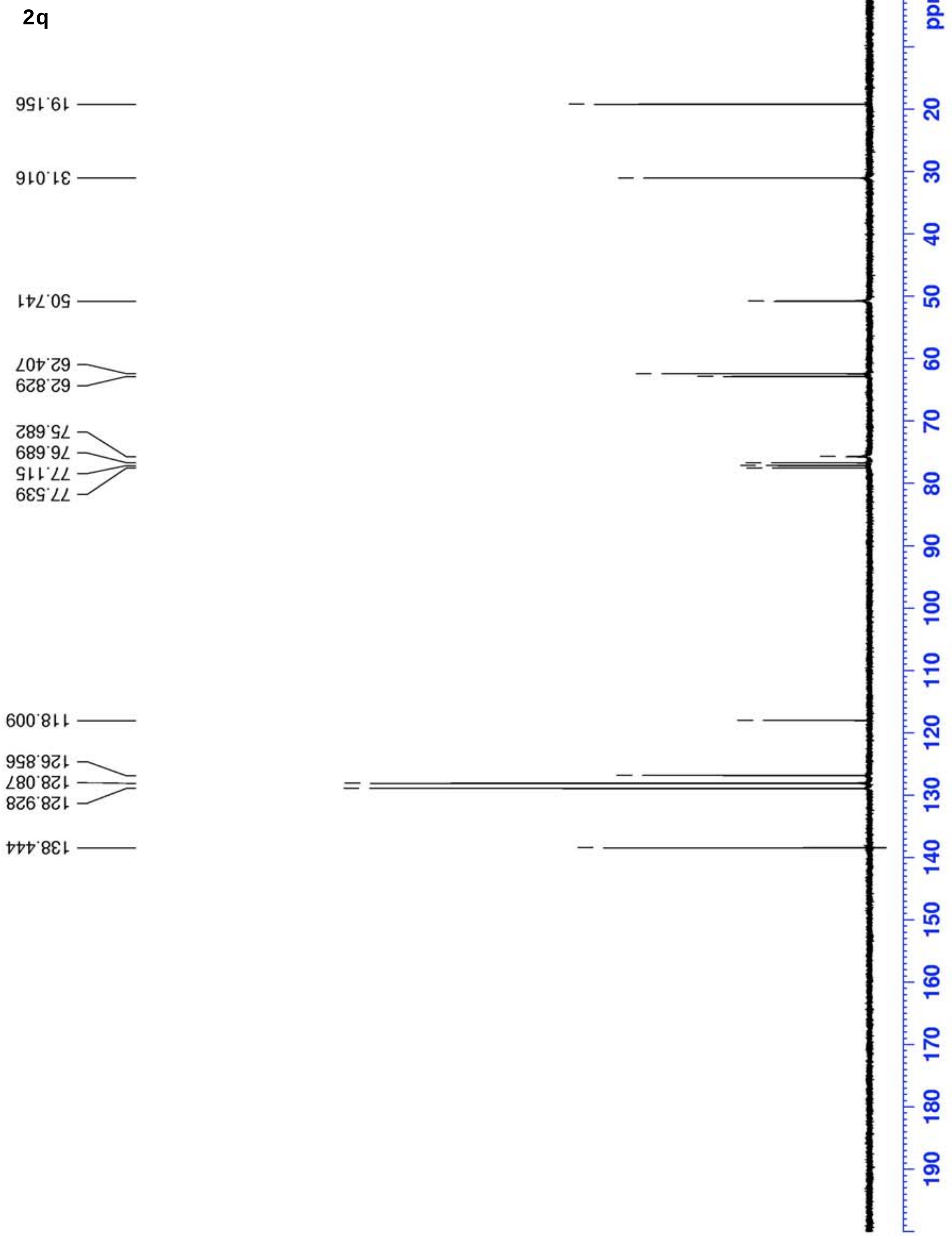
7.5
8.0
8.5


N
O
CN

2q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76.689
77.115
77.539
118.009
126.856
128.087
128.928
138.444
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40
50
60
70
80
90
100
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120
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180
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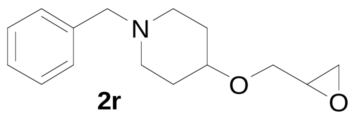
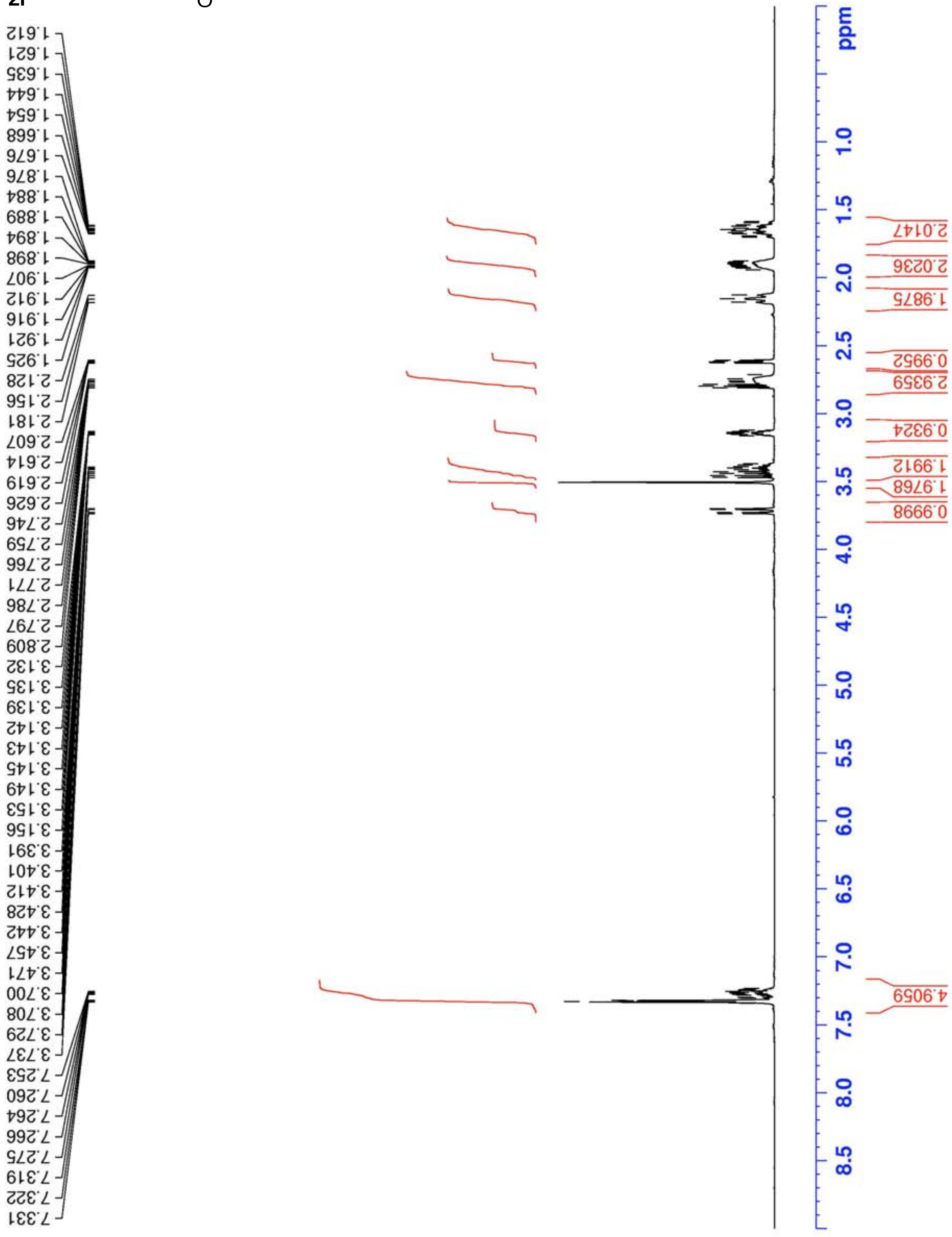


2r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1.676
1.876
1.884
1.889
1.894
1.898
1.907
1.912
1.916
1.921
1.925
2.128
2.156
2.181
2.607
2.614
2.619
2.626
2.746
2.759
2.766
2.771
2.786
2.797
2.809
3.132
3.135
3.139
3.142
3.143
3.145
3.149
3.153
3.156
3.391
3.401
3.412
3.428
3.442
3.457
3.471
3.700
3.708
3.729
3.737
7.253
7.260
7.264
7.266
7.275
7.319
7.322
7.331
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2.0236
1.9875
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2.9359
0.9324
1.9912
1.9768
0.9998
4.9059
ppm
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2.0
2.5
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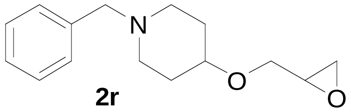
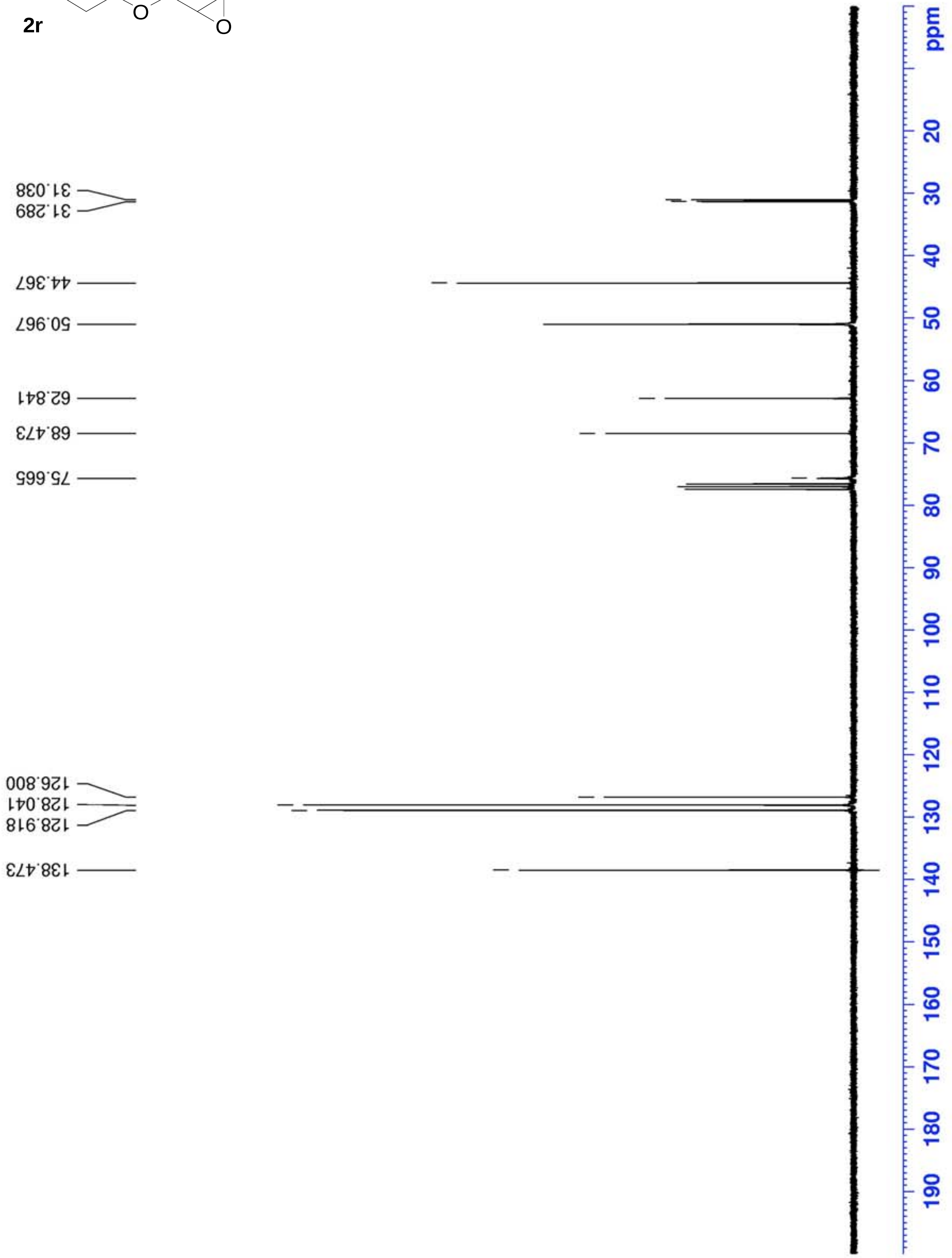
8.0
8.5


2r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68.473
75.665
126.800
128.041
128.918
138.473
ppm
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40
50
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120
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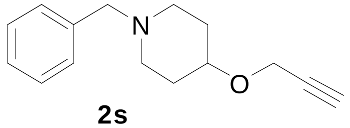
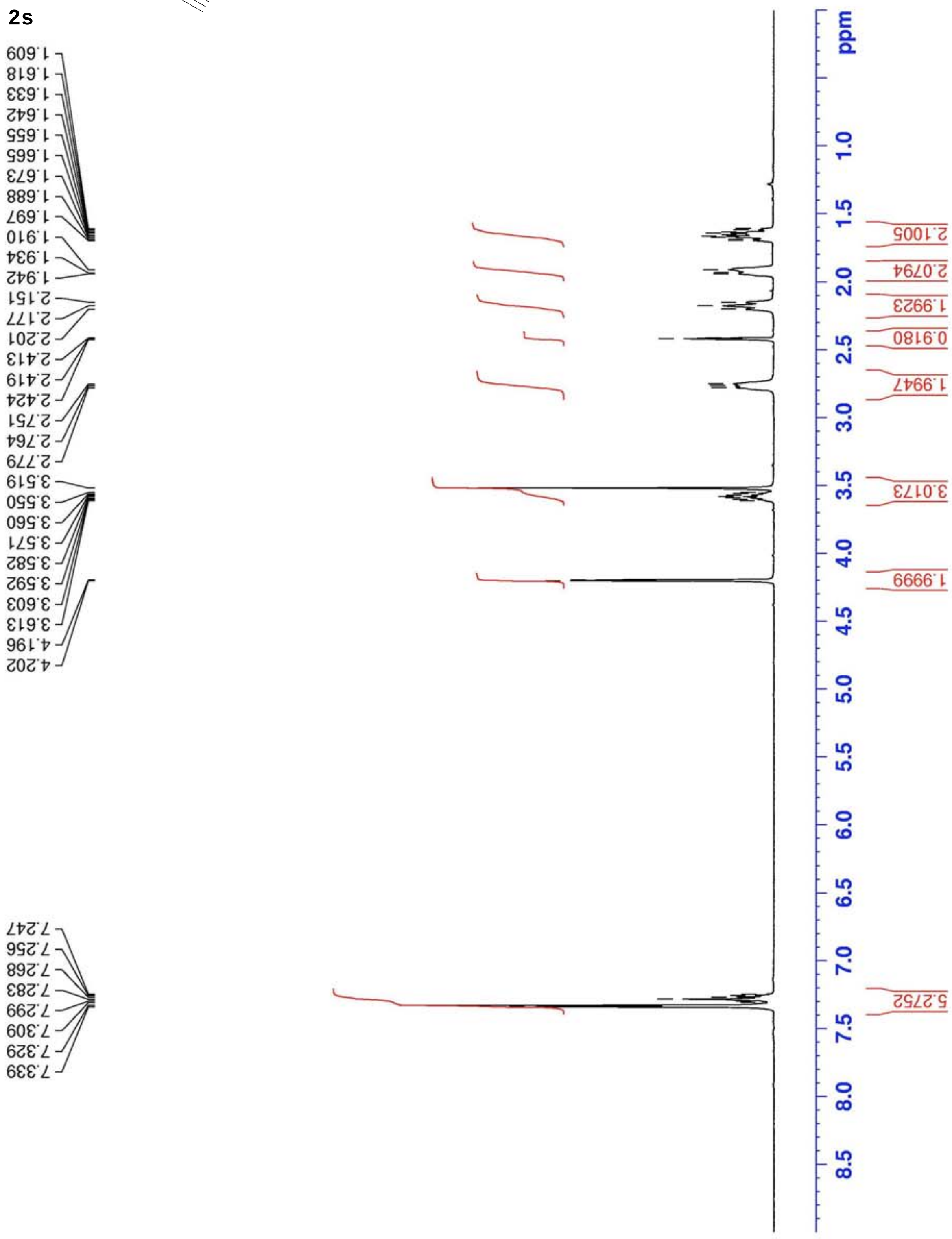

N
O

2s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1.633
1.642
1.655
1.665
1.673
1.688
1.697
1.910
1.934
1.942
2.151
2.177
2.201
2.413
2.419
2.424
2.751
2.764
2.779
3.519
3.550
3.560
3.571
3.582
3.592
3.603
3.613
4.196
4.202
7.247
7.256
7.268
7.283
7.299
7.309
7.329
7.339
2.1005
2.0794
1.9923
0.9180
1.9947
3.0173
1.9999
5.2752
ppm
1.0
1.5
2.0
2.5
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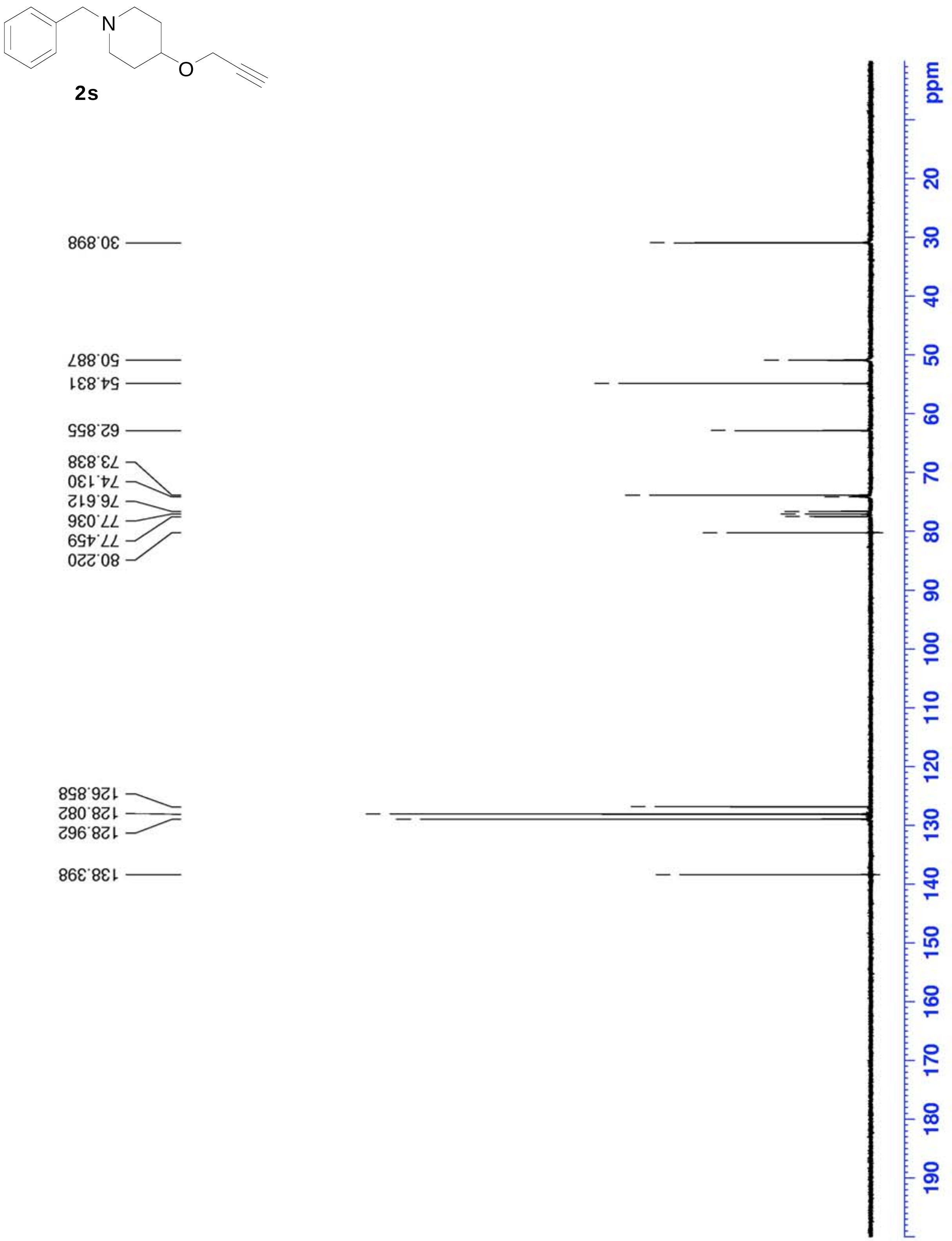
7.5
8.0
8.5



2s

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73.838
74.130
76.612
77.036
77.459
80.220
126.858
128.082
128.962
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100
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120
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180
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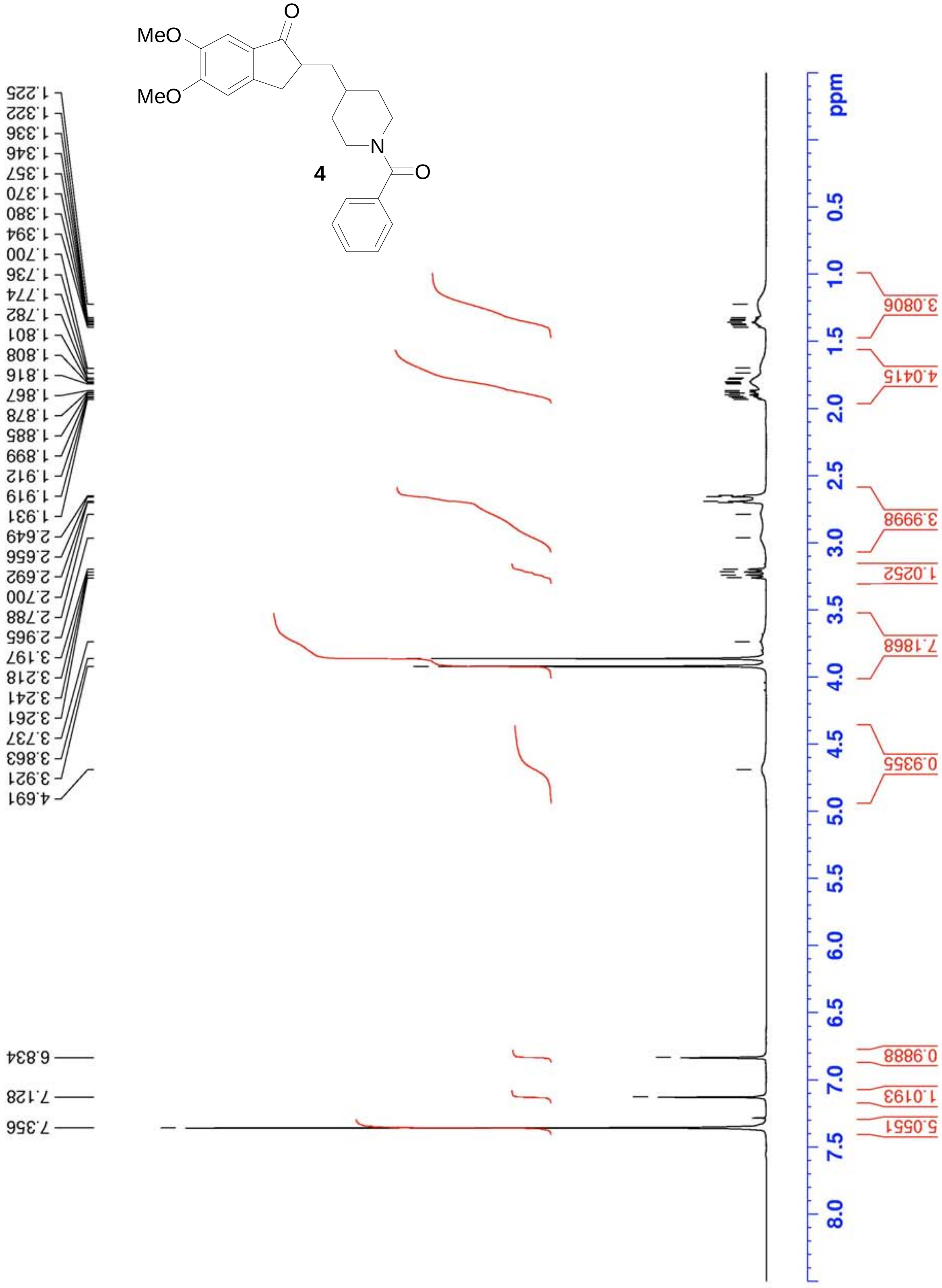
MeO
MeO
O
N
O
ppm
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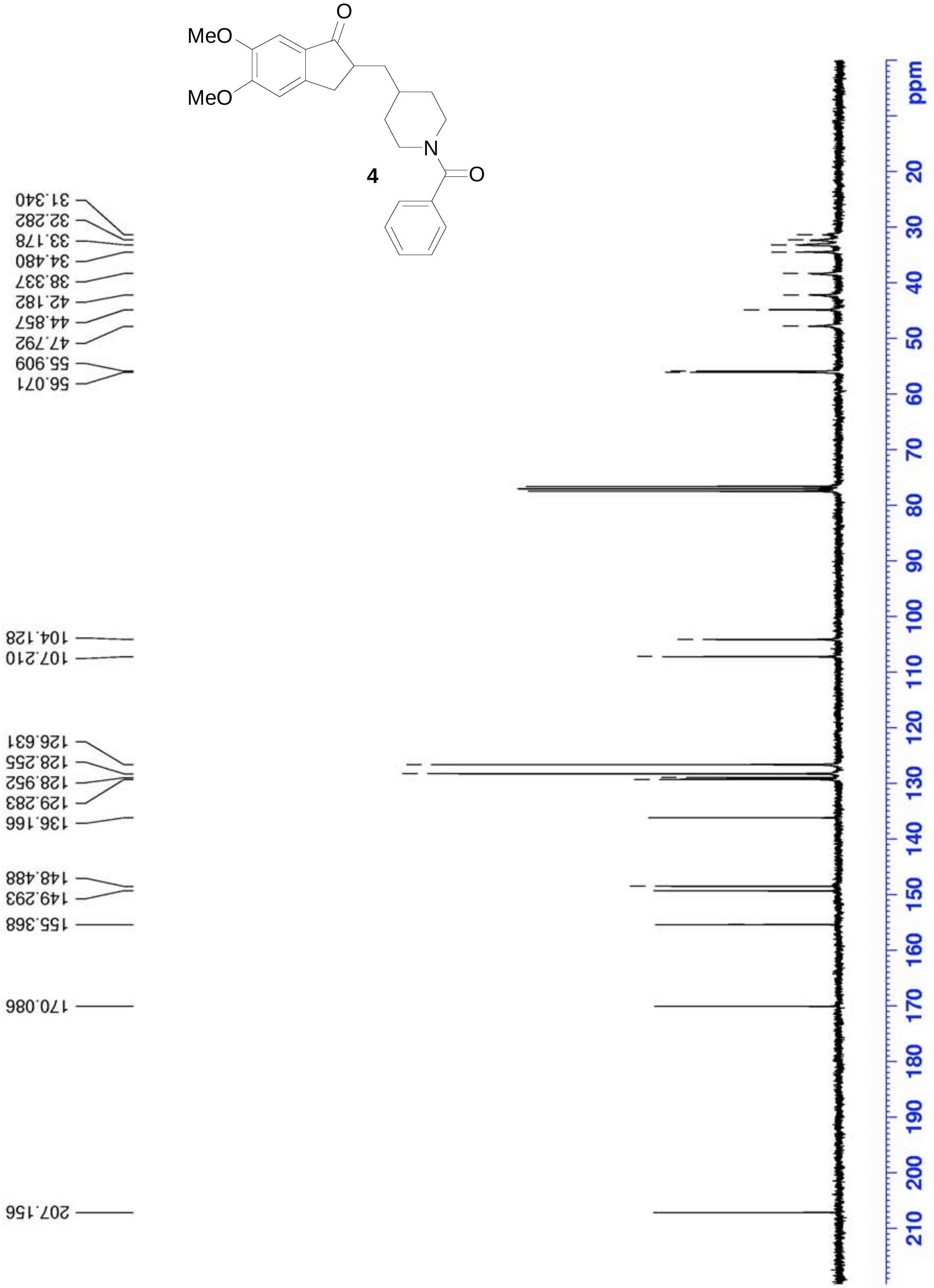
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
3.0806
4.0415
3.9998
1.0252
7.1868
0.9355
0.9888
1.0193
5.0551
1.225
1.322
1.336
1.346
1.357
1.370
1.380
1.394
1.700
1.736
1.774
1.782
1.801
1.808
1.816
1.867
1.878
1.885
1.899
1.912
1.919
1.931
2.649
2.656
2.692
2.700
2.788
2.965
3.197
3.218
3.241
3.261
3.737
3.863
3.921
4.691
6.834
7.128
7.356

4


4
MeO
MeO
O
N
O
31.340
32.282
33.178
34.480
38.337
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44.857
47.792
55.909
56.071
104.128
107.210
126.631
128.255
128.952
129.283
136.166
148.488
149.293
155.368
170.086
207.156
ppm
20
30
40
50
60
70
80
90
100
110
120
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140
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160
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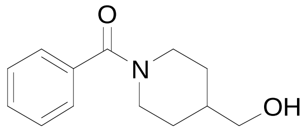
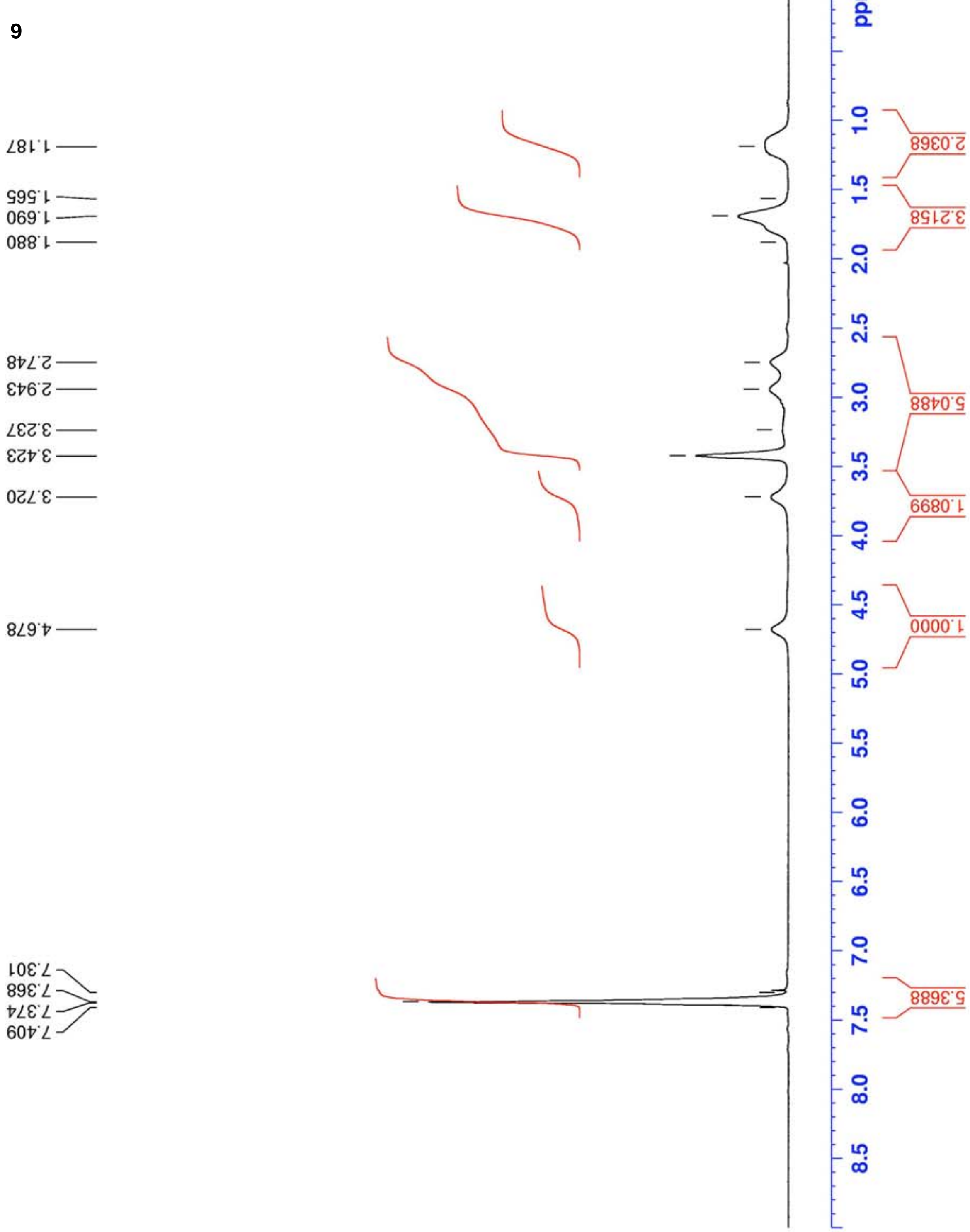
180
190
200
210


O
N
OH

9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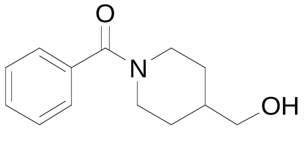
1.565
1.690
1.880
2.748
2.943
3.237
3.423
3.720
4.678
7.301
7.368
7.374
7.409
2.0368
3.2158
5.0488
1.0899
1.0000
5.3688
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5



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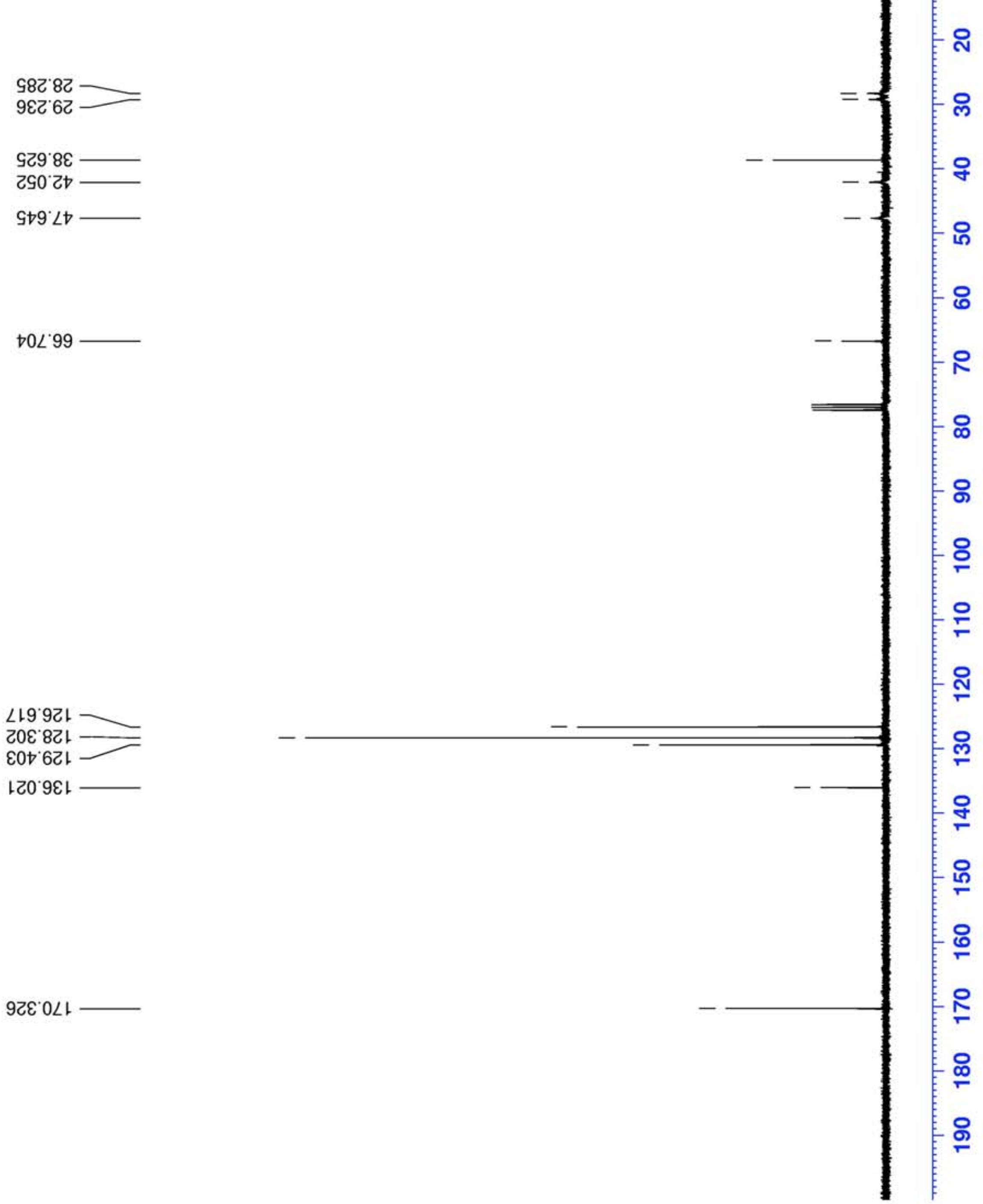

28.285
29.236
38.625
42.052
47.645
66.704
126.617
128.302
129.403
136.021
170.326
ppm
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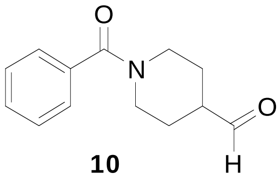
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190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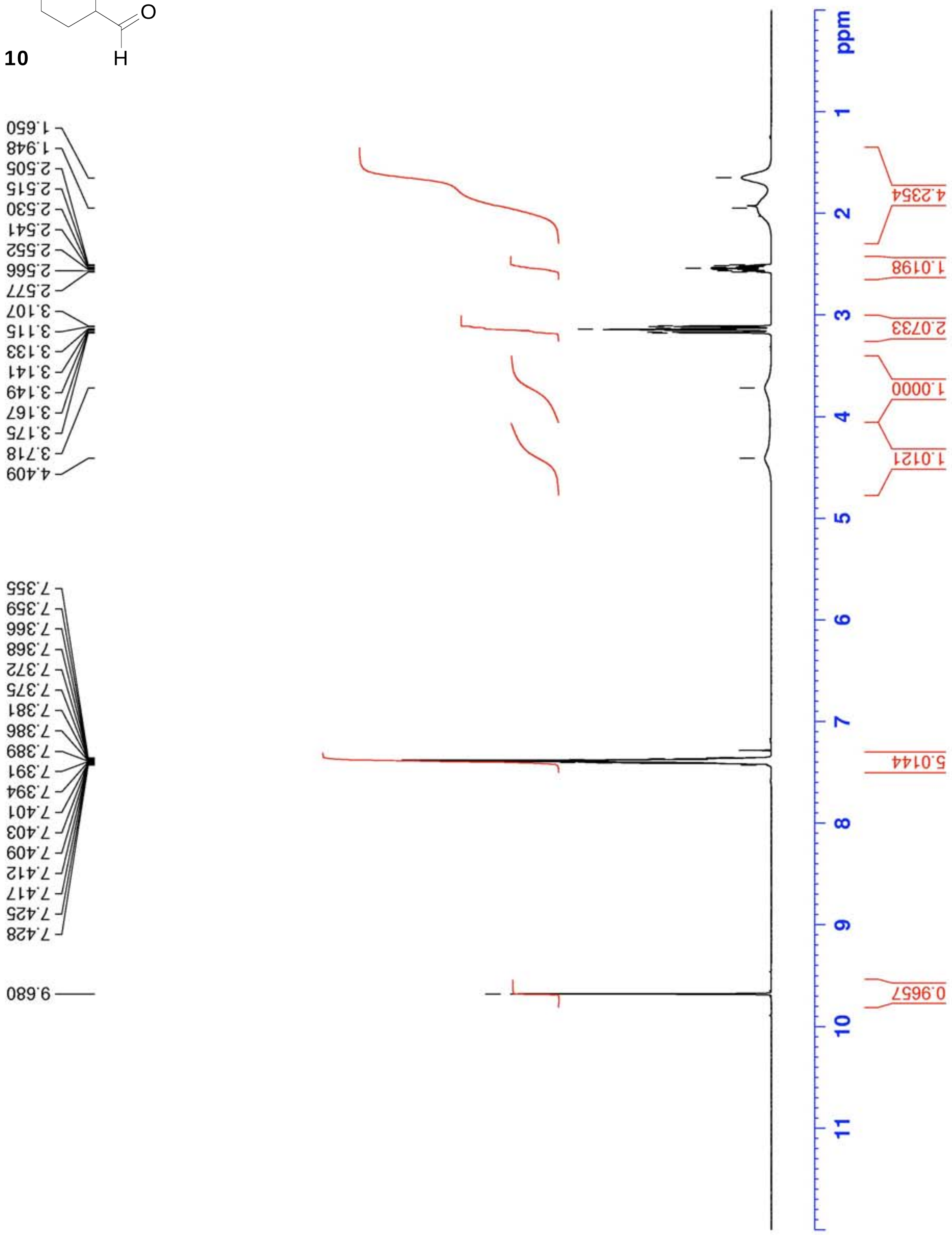
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1.948
2.505
2.515
2.530
2.541
2.552
2.566
2.577
3.107
3.115
3.133
3.141
3.149
3.167
3.175
3.718
4.409
7.355
7.359
7.366
7.368
7.372
7.375
7.381
7.386
7.389
7.391
7.394
7.401
7.403
7.409
7.412
7.417
7.425
7.428
9.680
4.2354
1.0198
2.0733
1.0000
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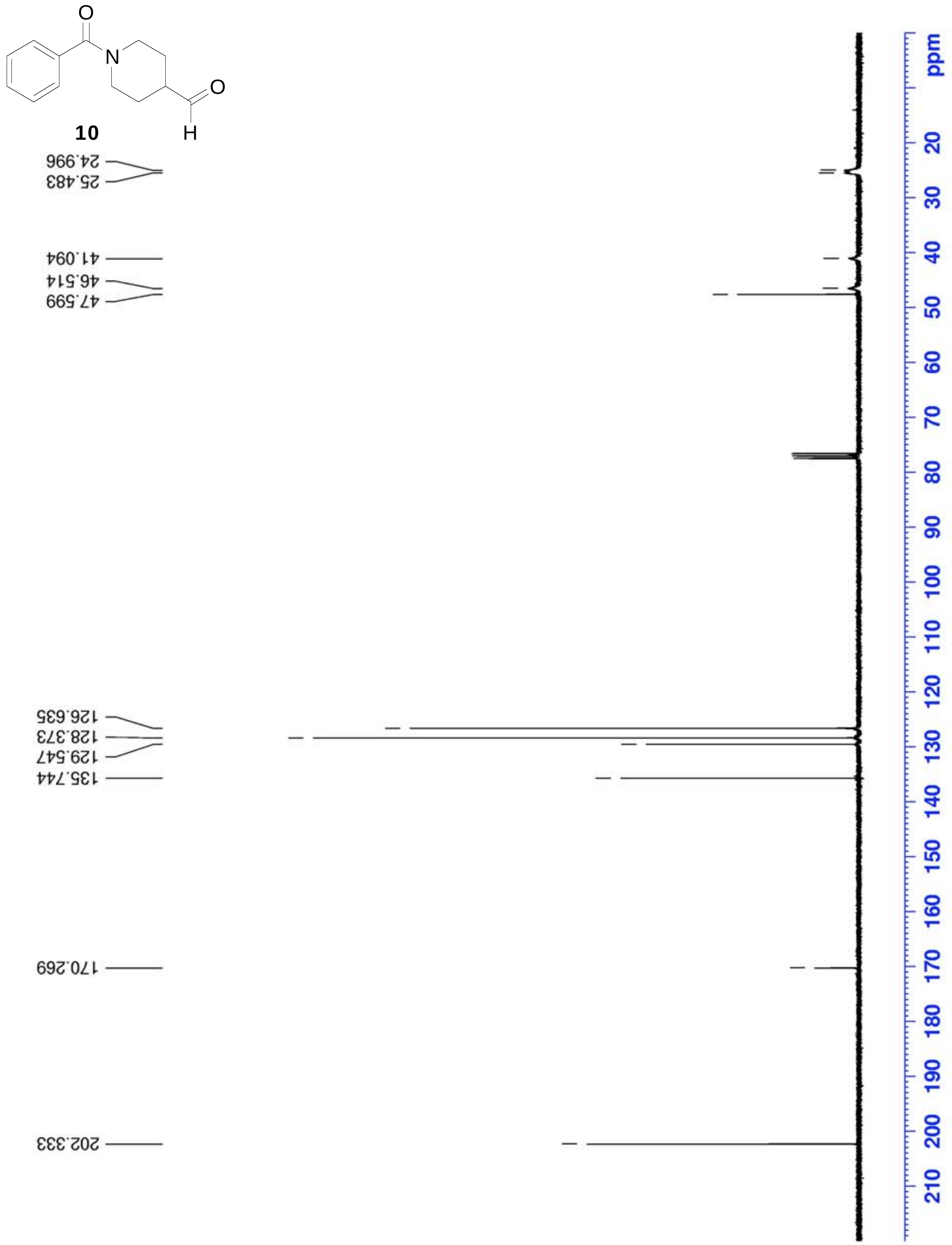
5.0144
0.9657
ppm
1
2
3
4
5
6
7
8
9
10
11


10
O
N
O
H
24.996
25.483
41.094
46.514
47.599
126.635
128.373
129.547
135.744
170.269
202.333
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210