Highly Substituted Indole Library Synthesis by Palladium-Catalyzed Coupling Reactions in Solution and on a Solid Support

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Supporting Information

Contents

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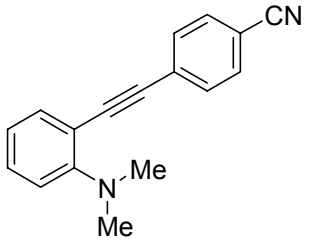
General. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Chemical shifts are reported in parts per million (ppm) downfield from TMS. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All reagents were used directly as obtained commercially unless otherwise noted. THF and CH_2Cl_2 were distilled from sodium/benzophenone or CaH_2 respectively, under an atmosphere of argon prior to use. All glassware and stirring bars were oven dried prior to use.

HPLC analysis was carried out using an XBridge MS C-18 column (5 μM, 4.6 × 150 mm) with gradient elution (5% CH_3CN to 100% CH_3CN) on a Waters Alliance 2795 Separation Module with a Waters 2996 Photodiode Array UV detector and a Waters/Micromass LCT Premier (TOF) detector. Purification was carried out using an XBridge MS C-18 column (5 μM, 19 × 150 mm) with a gradient elution (a narrow CH_3CN gradient was chosen based on the targets retention time from the LCMS analysis of the crude sample) on a Mass Directed Fractionation instrument with a Waters 2767 sample manager, a Waters 2525 HPLC pump, a Waters 2487 dual λ absorbance detector, and a Waters/Micromass ZQ (quadrupole) detector. Fractions were triggered using a MS and/or UV threshold determined by an LCMS analysis of the crude sample. One of three aqueous mobile phases were chosen for both analysis and purification to promote the targets neutral state (water, 0.05% formic acid or pH 9.8 1mM HCO_2NH_4). High resolution mass spectra (HRMS) were obtained using a Waters/Micromass LCT Premier (TOF instrument).

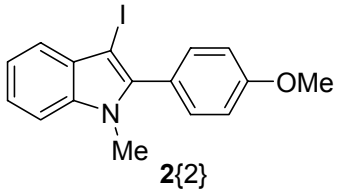
[2-(4-Methoxyphenylethynyl)phenyl]dimethylamine was prepared by a literature procedure.[1]

General procedure for the palladium/copper-catalyzed synthesis of the *N*,*N*-dialkyl-*o*-(1-alkynyl)anilines.[2] In a 100 ml round bottom flask, $PdCl_2(PPh_3)_2$ (0.2 mmol, 140.2 mg) and CuI (0.1 mmol, 19.0 mg) was added to a solution of *N*,*N*-dimethyl-*o*-iodoaniline (10.0 mmol, 2.47 g) in Et_3N (15 ml). The flask was then sealed and flushed with Ar. The reaction mixture was stirred for 20 min at room temperature. A solution of the corresponding alkyne (12.0 mmol) in Et_3N (10 mL) and DMF (10 ml) was then added dropwise and the reaction mixture was allowed to stir at 50 ^oC until completion of the reaction, which was monitored by TLC analysis. After the reaction was over, the resulting solution was diluted with H_2O (25 ml) and extracted with EtOAc (3 x 20 mL). The combined EtOAc fractions were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product. The crude product was purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent to afford the desired *N*,*N*-dialkyl-*o*-(1-alkynyl)aniline.



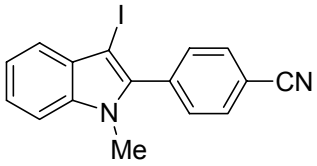
4-[2-(Dimethylamino)phenylethynyl]benzonitrile. Purification by flash chromatography (2:1 hexanes/EtOAc) afforded 1.67 g (68%) of the product: ^1H NMR ($CDCl_3$, 400 MHz) δ 2.99 (s, 6H), 6.88-6.95 (m, *2*H), 7.25-7.31 (m, 1H), 7.47-7.49 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.58-7.63 (m, 4H); ^{13}C NMR δ 43.72, 93.20, 93.83, 111.21, 113.94, 117.22, 118.83, 120.65, 128.98, 130.35, 131.81, 132.19, 134.72, 155.23; HRMS Calcd for $C_{17}H_{14}N_2$: 246.11570. Found: 246.11610.

General procedure for iodocyclization. To a solution of the *N*,*N*-dialkyl-*o*-(1-alkynyl)aniline (1.0 mmol) in CH_2Cl_2 (10 ml), I_2 (2 mmol, 508 mg) dissolved in CH_2Cl_2 (10 mL) was added gradually. The reaction mixture was allowed to stir at room temperature for the desired time. The reaction was monitored by TLC analysis. After completion of the reaction, the excess I_2 was removed by washing with satd aq $Na_2S_2O_3$. The mixture was then extracted by CH_2Cl_2 (3 x 10 mL). The combined CH_2Cl_2 layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using hexanes/ethyl acetate as the eluent to afford the desired 3-iodoindole.



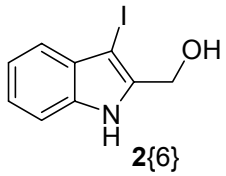
2{2}

3-Iodo-2-(4-methoxyphenyl)-1-methyl-1*H*-indole 2{2}. Purification by flash chromatography (10:1 hexanes/EtOAc) afforded 0.28 g (79%) of the product: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.65 (s, 3H), 3.87 (s, 3H), 7.01-7.04 (d, *J* = 8.6 Hz, 2H), 7.20-7.24 (m, 1H), 7.28-7.29 (d, *J* = 3.6 Hz, 2H), 7.36-7.39 (d, *J* = 8.7 Hz, 2H), 7.47-7.49 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 32.14, 55.53, 58.95, 109.96, 114.04, 120.79, 121.45, 122.88, 123.92, 130.47, 132.31, 137.81, 141.81, 160.05; HRMS Calcd for $C_{16}H_{14}ONI$: 363.01202. Found: 363.01253.



2{3}

4-(3-Iodo-1-methyl-1H-indol-2-yl)benzonitrile 2{3}. Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 0.17 g (48%) of the product: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.66 (s, 3H), 7.23-7.27 (m, 1H), 7.30-7.36 (m, 2H), 7.49-7.51 (d, *J* = 7.8 Hz, 1H), 7.56-7.59 (d, *J* = 8.2 Hz, 2H), 7.76-7.78 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR δ 32.40, 60.39, 110.20, 112.47, 118.65, 121.32, 121.96, 123.93, 130.44, 131.70, 132.32, 136.33, 138.23, 139.45; HRMS Calcd for $C_{16}H_{11}N_2I$: 357.99670. Found: 357.99728.



2{6}

Procedure for the preparation of (3-iodo-1*H*-indol-2-yl)methanol 2{6}. A modified literature procedure was used.[3] In a 100 mL flask to a solution of 3-iodo-1*H*-indole-2-carbaldehyde (3.0 mmol, 0.825 g) in anhydrous THF (20 ml), $NaBH_4$ (6.0 mmol) was added and the reaction mixture was refluxed for 5h. After completion of the reaction, which was monitored by TLC analysis, the reaction mixture was cooled to room temperature and the excess $NaBH_4$ was quenched by slow addition of water (20 ml). THF was removed under reduced pressure. The solid residue was filtered, washed with cold water and dried to afford 0.60 g (74%) of the desired (3-iodo-1*H*-indol-2-yl)methanol: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.82 (s, 2H), 7.15-7.28 (m, 4H), 7.39-7.41 (d, *J* = 7.5 Hz, 1H), 8.84 (s, 1H); ^{13}C NMR δ 57.75, 59.18, 111.53, 120.96, 121.03, 123.50, 130.42, 136.15, 137.95; HRMS Calcd for C_9H_9ONI: 273.96507. Found: 273.96562.

General procedure for the Sonogashira coupling in solution phase. To a 4-dram vial was added the appropriate 3-iodoindole (0.2 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol, 7.0 mg), CuI (0.005 mmol, 1.0 mg), Et_3N (1.5 mL), DMF (1.5 mL) and the acetylene (0.3 mmol). The reaction mixture was flushed with argon and stirred for 10 minutes at room temperature. The reaction was then heated to 65 ^oC until TLC analysis revealed complete conversion of the starting material. After the reaction was over, the resulting solution was diluted with H_2O (10 ml) and extracted with EtOAc (2 x 10 mL). The combined EtOAc fractions were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product. The residue was purified by preparative HPLC.

General procedure for the Suzuki-Miyaura cross-coupling in solution phase. To a 4-dram vial was added the appropriate 4-iodoindole (0.2 mmol), the arylboronic acid (0.3 mmol), $Pd(PPh_3)_4$ (0.02 mmol, 23.1 mg) and KOH (1.6 mmol, 89.6 mg) in 5:1 $PhCH_3$:EtOH (3.0 mL). A few drops of water were added to the reaction mixture, which was stirred at 90 ^oC until TLC analysis revealed complete conversion of the starting material. The reaction mixture was cooled, diluted with EtOAc (15 ml) and filtered through celite. The celite-bed was washed with EtOAc. The filtrate was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative HPLC.

General procedure for coupling the acid to the polymer-bound 4-(benzyloxy)benzyl chloride resin. Chlorinated Wang resin (3.73 g, 0.75 mmol/g) was placed in dry DMF (40 mL) for 10 min. After addition of 3-iodo-4-

[methyl(phenyl)amino]benzoic acid (1.25 g, 1.5 equiv), Cs_2CO_3 (2.8 g, 3.0 equiv) and KI (0.23 g, 0.5 equiv), the mixture was stirred at 80 °C for 2 d. The reaction mixture was allowed to cool to room temperature and the resin was then filtered, washed with water (4 x), DMF (4 x), methanol (4 x) and DCM (4 x), and dried under vacuum overnight.

General procedure for the palladium/copper-catalyzed synthesis of *N*,*N*-dialkyl-*o*-(1-alkynyl)anilines on a solid support. In a 100 mL round bottom flask were placed the acid coupled polymer-bound resin (1.0 g, 0.6 mmol), $PdCl_2(PPh_3)_2$ (23 mg, 5 mol %) and CuI (12.5 mg, 10 mol %). Toluene (13 mL) was added and the reaction mixture was shaken for 5 min. $HNEt_2$ (13 mL) and the terminal acetylene (5.0 equiv) were added and the mixture was shaken at room temperature for 2 d. The polymer was filtered, washed successively with DMF (4 x), MeOH (4 x) and DCM (4 x), and dried under vacuum overnight.

General procedure for iodocyclization on a solid support. The appropriate polymer bound *N*,*N*-dialkyl-*o*-(1-alkynyl)aniline (800 mg) was placed in DCM (20 mL) for 5 min. I_2 (0.52 g, 4.0 equiv) was added and the mixture was shaken at room temperature for 24 h. The polymer was filtered, washed successively with DMF (4 x), MeOH (4 x) and DCM (4 x), and dried under vacuum overnight.

General procedure for Sonogashira cross-coupling on a solid support. In a 100 mL round bottom flask were placed the appropriate polymer-bound 3-iodoindole (0.5 g, ~0.3 mmol), $PdCl_2(PPh_3)_2$ (12 mg, 5 mol %) and CuI (6.0 mg, 10 mol %). Toluene (7 mL) was added and the reaction mixture was shaken for 5 min. $HNEt_2$ (7 mL) and the terminal

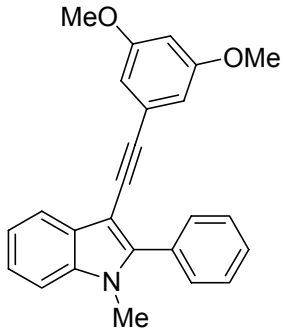
acetylene (5.0 equiv) were added and the mixture was stirred at 65 ^{o}C for 2 d. The polymer was filtered, washed successively with DMF (4 x), MeOH (4 x) and DCM (4 x), and dried under vacuum overnight.

General procedure for Suzuki-Miyaura cross-coupling on a solid support. In a 100 mL round bottom flask were placed the appropriate polymer-bound 3-iodoindole (0.5 g, ~0.3 mmol), $Pd(OAc)_2$ (7.3 mg, 10 mol %), PPh_3 (16.7 mg, 20 mol %), CsF (14.2 mg, 4.4 equiv) and the arylboronic acid (2.5 equiv). DME (15 mL) was added and the reaction mixture was heated at 90 °C for 48 h. The polymer was filtered, washed successively with DMF (4 x), MeOH (4 x) and DCM (4 x), and dried under vacuum overnight.

General procedure for cleavage by lithium aluminum hydride. A solution of LAH in THF (1.0 M, 2 mL) was added to a stirred suspension of the appropriate resin-bound indole (200 mg) in THF (4 mL) at 0 ^{o}C under an inert atmosphere. The mixture was stirred at 0 ^{o}C for 2 h, diluted with THF (2 mL), and quenched with a saturated solution of $Na^{+}K^{+}$ tartrate (8.0 mL). The reaction was warmed to room temperature and stirred vigorously for 2 h. The resulting mixture was filtered and the resin was washed with CH_2Cl_2. The biphasic filtrate was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified either by flash chromatography or by preparative HPLC to give the final isolated yield of product based upon the loading of resin.

General procedure for cleavage by an alkyl magnesium bromide. A solution of alkyl magnesium bromide in THF (2.0 M, 1 mL) was added to a stirred suspension of the appropriate resin bound indole (200 mg) in THF (4 mL) at 0 ^{o}C under an inert atmosphere. The mixture was gradually warmed to room temperature and stirred for 5 h. It was then quenched with a satd aq solution of NH_4Cl (10 mL). The resulting mixture was filtered and the resin was washed with CH_2Cl_2. The biphasic filtrate was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified either by flash chromatography or by preparative HPLC to give the final isolated yield of product based upon the loading of the resin.

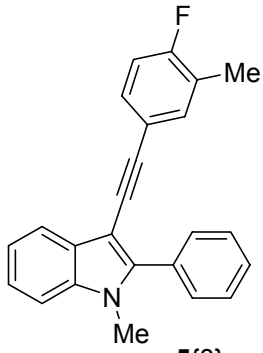
Characterization data for representative library compounds.



5{2}

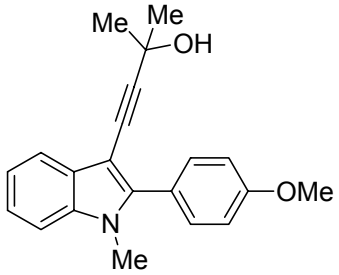
3-(3,5-Dimethoxyphenylethynyl)-1-methyl-2-phenyl-1*H*-indole 5{2}. Yield = 38%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.76 (s, 3H), 3.78 (s, 6H), 6.38-6.39 (t, *J* = 2.4 Hz, 1H), 6.59-6.596 (d, *J* = 2.4 Hz, 2H), 7.24-7.33 (m, 2H), 7.37-7.39 (m, 1H), 7.43-7.47 (m, 1H), 7.51-7.55 (m, 2H), 7.66-7.69 (m, 2H), 7.83-7.86 (m, 1H); ^{13}C NMR δ 31.89, 55.59, 84.22, 91.98, 96.83, 100.91, 109.10, 110.06, 120.27, 121.06, 123.14, 126.06, 128.58, 128.75, 128.94,

130.49, 130.96, 137.39, 144.27, 160.64; HRMS Calcd for $C_{25}H_{22}NO_2$: 368.1572 $[M + H]^+$. Found: 368.1666.



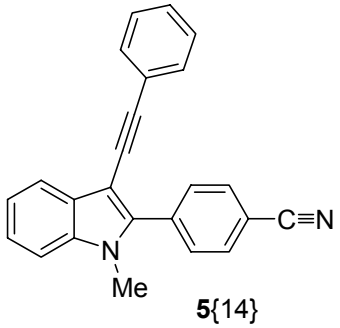
5{3}

3-(4-Fluoro-3-methylphenylethynyl)-1-methyl-2-phenyl-1*H*-indole 5{3}. Yield = 47%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (d, *J* = 2.0 Hz, 3H), 3.75 (s, 3H), 6.89-6.94 (t, *J* = 9.6 Hz, 1H), 7.19-7.20 (m, 1H), 7.24-7.27 (m, 2H), 7.29-7.33 (m, 1H), 7.36-7.38 (m, 1H), 7.43-7.47 (m, 1H), 7.51-7.55 (m, 2H), 7.66-7.68 (m, 2H), 7.81-7.83 (m, 1H); ^{13}C NMR δ 14.61, 14.64, 31.87, 83.52, 91.01, 96.92, 110.05, 115.12, 115.35, 120.22, 120.39, 120.43, 121.00, 123.12, 125.02, 125.20, 128.59, 128.72, 128.97, 130.39, 130.46, 131.03, 134.34, 134.39, 137.38, 143.92, 159.58, 162.03 (extra peaks due to C-F splitting); HRMS Calcd for $C_{24}H_{19}FN$: 340.1423 $[M + H]^+$. Found: 340.1522.



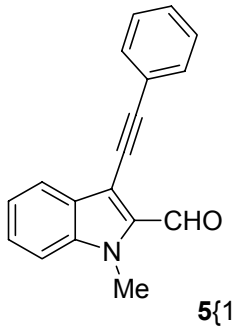
5{13}

4-[2-(4-Methoxyphenyl)-1-methyl-1*H*-indol-3-yl]-2-methylbut-3-yn-2-ol 5{13}. Yield = 33%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.59 (s, 6H), 3.71 (s, 3H), 3.88 (s, 3H), 7.01-7.04 (m, 2H), 7.18-7.29 (m, 3H), 7.32-7.34 (m, 1H), 7.52-7.55 (m, 2H), 7.69-7.71 (m, 1H); ^{13}C NMR δ 31.74, 31.93, 55.56, 66.16, 68.69, 95.61, 96.20, 109.86, 113.97, 119.85, 120.83, 122.76, 123.24, 129.01, 131.64, 137.15, 143.98, 159.94; HRMS Calcd for $C_{21}H_{22}NO_2$: 320.1572 $[M + H]^+$. Found: 320.1656.



5{14}

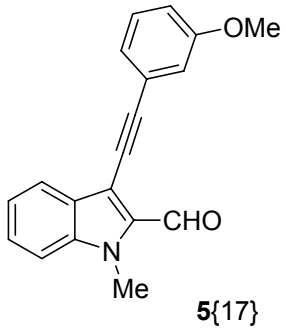
4-(1-Methyl-3-phenylethynyl-1*H*-indol-2-yl)benzonitrile 5{14}. Yield = 45%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.75 (s, 3H), 7.24-7.37 (m, 6H), 7.42-7.44 (m, 2H), 7.80 (s, 4H), 7.84-7.86 (dt, *J* = 7.6, 0.8 Hz, 1H); ^{13}C NMR δ 32.11, 83.38, 92.86, 98.73, 110.25, 112.03, 118.91, 120.65, 121.48, 124.10, 127.91, 128.56, 128.78, 130.85, 131.34, 132.34, 135.60, 137.91, 141.32; HRMS Calcd for $C_{24}H_{17}N_2$: 333.1313 $[M + H]^+$. Found: 333.1408.



5{15}

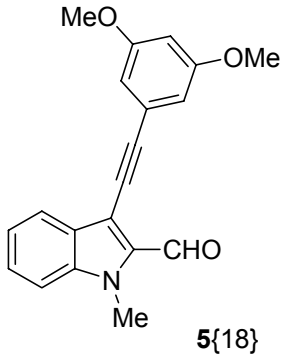
1-Methyl-3-phenylethynyl-1*H*-indole-2-carbaldehyde 5{15}. Yield = 89%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.06 (s, 3H), 7.23-7.26 (m, 1H), 7.34-7.39 (m, 4H), 7.43-7.46 (m,

1H), 7.57-7.59 (m, 2H), 7.87-7.89 (m, 1H), 10.25 (s, 1H); ^{13}C NMR δ 31.96, 80.48, 97.08, 110.69, 111.97, 121.82, 122.32, 123.17, 127.72, 127.92, 128.64, 128.71, 131.68, 135.47, 139.62, 182.44; HRMS Calcd for $C_{18}H_{14}NO$: 260.0997 $[M + H]^+$. Found: 260.1087.



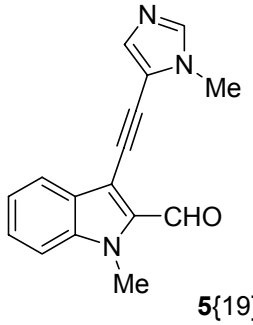
5{17}

3-(3-Methoxyphenylethynyl)-1-methyl-1*H*-indole-2-carbaldehyde 5{17}. Yield = 79%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.83 (s, 3H), 4.07 (s, 3H), 6.91-6.93 (m, 1H), 7.09-7.10 (m, 1H), 7.17-7.19 (m, 1H), 7.23-7.30 (m, 3H)(one extra proton due to overlap with the $CDCl_3$ peak), 7.35-7.37 (d, *J* = 6.8 Hz, 1H), 7.44-7.47 (m, 1H), 7.88-7.90 (m, 1H), 10.2 (s, 1H); ^{13}C NMR δ 31.98, 55.50, 80.32, 97.01, 100.93, 110.71, 111.89, 115.34, 116.32, 121.85, 122.34, 124.27, 127.74, 127.95, 129.73, 135.54, 139.64, 159.54, 182.46; HRMS Calcd for $C_{19}H_{16}NO_2$: 290.1102 $[M + H]^+$. Found: 290.1197.



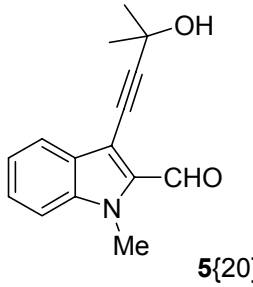
5{18}

3-(3,5-Dimethoxyphenylethynyl)-1-methyl-1*H*-indole-2-carbaldehyde 5{18}. Yield = 94%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.81 (s, 6H), 4.06 (s, 3H), 6.48-6.49 (t, *J* = 2.0 Hz, 1H), 6.71-6.73 (m, 2H), 7.23-7.26 (m, 2H)(one extra proton due to overlap with the $CDCl_3$ peak), 7.35-7.36 (d, *J* = 6.8 Hz, 1H), 7.43-7.46 (m, 1H), 7.88-7.89 (d, *J* = 6.8 Hz, 1H), 10.25 (s, 1H); ^{13}C NMR δ 31.95, 55.62, 80.08, 97.08, 102.13, 109.34, 110.70, 111.76, 121.84, 122.31, 124.43, 127.71, 127.93, 135.57, 139.61, 160.74, 182.42; HRMS Calcd for $C_{40}H_{38}N_3O_6$: 656.2416 $[2M + NH_4]^+$. Found: 656.2715.



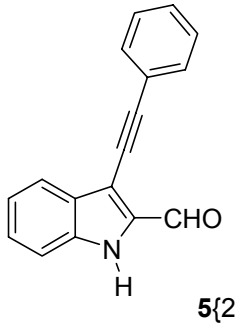
5{19}

1-Methyl-3-(3-methyl-3*H*-imidazol-4-ylethynyl)-1*H*-indole-2-carbaldehyde 5{19}. Yield = 82%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.77 (s, 3H), 4.06 (s, 3H), 7.25-7.28 (m, 1H), 7.37-7.41 (m, 2H), 7.45-7.49 (m, 1H), 7.53 (s, 1H), 7.81-7.83 (m, 1H), 10.20 (s, 1H); ^{13}C NMR δ 31.96, 32.33, 84.29, 87.55, 110.79, 116.27, 122.03, 127.43, 128.02, 128.57, 132.11, 134.71, 135.28, 138.73, 139.50, 181.84; HRMS Calcd for $C_{16}H_{14}N_3O$: 264.105862 $[M + H]^+$. Found: 264.1145.



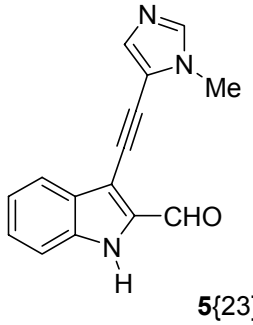
5{20}

3-(3-Hydroxy-3-methylbut-1-ynyl)-1-methyl-1*H*-indole-2-carbaldehyde 5{20}. Yield = 77%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70 (s, 6H), 3.21 (broad s, 1H), 3.93 (s, 3H), 7.16-7.19 (m, 1H), 7.22-7.24 (d, *J* = 6.8 Hz, 1H), 7.36-7.39 (m, 1H), 7.72-7.74 (m, 1H), 10.08 (s, 1H); ^{13}C NMR δ 31.70, 65.89, 72.93, 98.43, 101.94, 110.52, 111.49, 121.61, 122.02, 127.55, 127.80, 135.35, 139.35, 182.51; HRMS Calcd for $C_{30}H_{34}N_3O_4$: 500.2204 $[2M + NH_4]^+$. Found: 500.2557.



5{21}

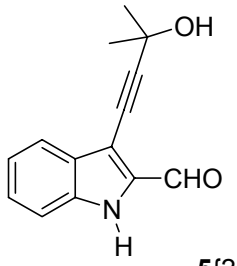
3-Phenylethynyl-1*H*-indole-2-carbaldehyde 5{21}. Yield = 52%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26-7.29 (m, 1H), 7.39-7.48 (m, 5H), 7.61-7.63 (m, 2H), 7.92-7.93 (dd, *J* = 6.4, 0.4 Hz, 1H), 9.43 (broad s, 1H), 10.16 (s, 1H); ^{13}C NMR δ 80.19, 96.88, 110.21, 112.90, 122.10, 122.48, 123.04, 128.39, 128.73, 128.80, 128.95, 131.87, 136.32, 137.17, 181.29; HRMS Calcd for $C_{17}H_{12}NO$: 246.0840 $[M + H]^+$. Found: 246.0935.



5{23}

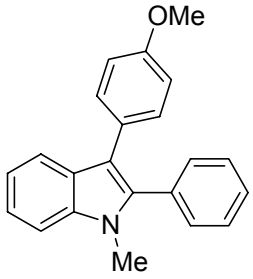
3-(3-Methyl-3*H*-imidazol-4-ylethynyl)-1*H*-indole-2-carbaldehyde 5{23}. Yield = 36%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.82 (s, 3H), 7.22-7.30 (m, 2H) (one extra proton due to

overlap with the $CDCl_3$ peak), 7.45-7.47 (m, 3H), 7.58 (s, 1H), 7.86-7.87 (d, J = 6.4 Hz, 1H), 9.27 (broad s, 1H), 10.12 (s, 1H); ^{13}C NMR δ 68.20, 84.16, 98.66, 108.16, 112.94, 122.27, 122.39, 128.52, 128.59, 130.44, 135.17, 136.26, 136.95, 138.95, 180.74; HRMS Calcd for $C_{15}H_{12}N_3O$: 250.0902 $[M + H]^+$. Found: 250.0982.



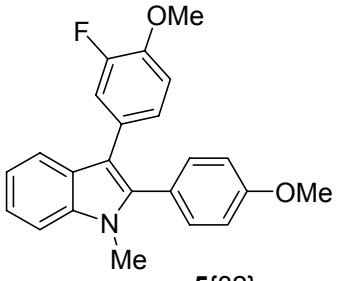
5{25}

3-(3-Hydroxy-3-methylbut-1-ynyl)-1*H*-indole-2-carbaldehyde 5{25}. Yield = 43%; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.71 (s, 6H), 7.41-7.55 (m, 3H), 7.65-7.69 (m, 1H), 7.79-7.81 (dd, J = 6.4, 0.8 Hz, 1H), 9.29 (broad s, 1H), 10.03 (s, 1H); ^{13}C NMR δ 31.79, 66.17, 101.44, 108.16, 109.43, 112.80, 122.04, 128.31, 128.68, 132.27, 136.41, 136.96, 181.21; HRMS Calcd for $C_{14}H_{17}N_2O_2$: 245.0946 $[M + NH_4]^+$. Found: 245.1307.



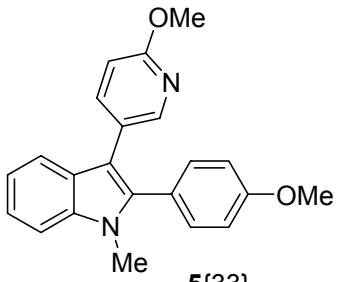
5{30}

3-(4-Methoxyphenyl)-1-methyl-2-phenyl-1*H*-indole 5{30}. Yield = 23%; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.67 (s, 3H), 3.79 (s, 3H), 6.81-6.83 (m, 2H), 7.16-7.24 (m, 3H), 7.27-7.41 (m, 7H), 7.74-7.76 (d, J = 8.0 Hz, 1H); ^{13}C NMR δ 31.37, 55.30, 109.72, 113.96, 114.94, 119.80, 120.21, 122.33, 127.35, 127.76, 128.12, 128.59, 131.12, 131.43, 132.26, 137.64, 157.80, 167.48; HRMS Calcd for $C_{22}H_{20}NO$: 314.1466 $[M + H]^+$. Found: 314.1535.



5{32}

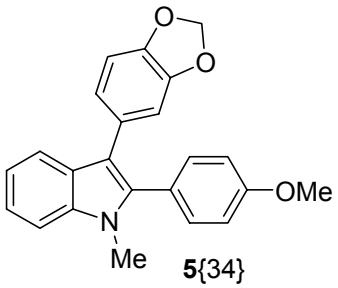
3-(3-Fluoro-4-methoxyphenyl)-2-(4-methoxyphenyl)-1-methyl-1*H*-indole 5{32}. Yield = 42%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.64 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 6.84-6.93 (m, 3H), 6.99-7.04 (m, 2H), 7.15-7.282 (m, 3H), 7.285-7.30 (m, 1H), 7.37-7.39 (d, *J* = 8.0 Hz, 1H), 7.72-7.74 (m, 1H); ^{13}C NMR δ 31.02, 55.46, 56.41, 109.76, 113.44, 113.46, 113.57, 114.20, 117.39, 117.57, 119.37, 120.40, 122.27, 123.98, 125.61, 125.64, 127.03, 128.87, 128.94, 132.45, 137.29, 137.80, 145.55, 145.66, 151.15, 153.58, 159.70 (extra peaks due to fluorine splitting); HRMS Calcd for $C_{23}H_{21}FNO_2$: 362.1478 $[M + H]^+$. Found: 362.1552.



5{33}

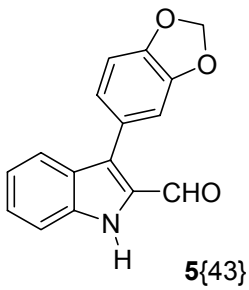
2-(4-Methoxyphenyl)-3-(6-methoxypyridin-3-yl)-1-methyl-1*H*-indole 5{33}. Yield = 50%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.66 (s, 3H), 3.83 (s, 3H), 3.93 (s, 3H), 6.66-6.68 (dd, *J* = 8.8, 0.8 Hz, 1H), 6.91-6.93 (m, 2H), 7.16-7.28 (m, 3H), 7.29-7.31 (m, 1H), 7.39-7.41 (d, *J* = 8.0 Hz, 1H), 7.45-7.47 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.70-7.72 (d, *J* = 8.0 Hz, 1H), 8.17 (dd, *J* = 2.4, 0.4 Hz, 1H); ^{13}C NMR δ 31.05, 53.61, 55.47, 109.82, 110.58, 111.17, 114.29,

119.21, 120.50, 122.37, 123.76, 124.67, 127.10, 132.44, 137.34, 138.10, 140.37, 147.23, 159.77, 162.24; HRMS Calcd for $C_{22}H_{21}N_2O_2$: 345.1524 $[M + H]^+$. Found: 345.1609.



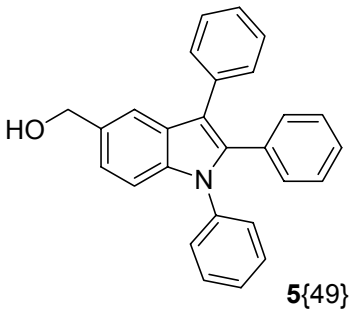
5{34}

3-Benzo[1,3]dioxol-5-yl-2-(4-methoxyphenyl)-1-methyl-1*H*-indole 5{34}. Yield = 39%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.64 (s, 3H), 3.84 (s, 3H), 5.92 (s, 2H), 6.75-6.77 (m, 3H), 6.91-6.93 (d, *J* = 8.8 Hz, 2H), 7.16-7.24 (m, 4H), 7.27-7.37 (m, 1H), 7.72-7.74 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR δ 31.05, 55.46, 100.91, 108.47, 109.68, 110.55, 114.12, 114.64, 119.57, 120.24, 122.16, 123.39, 124.19, 127.26, 129.45, 132.47, 137.25, 137.58, 145.60, 147.56, 159.58; HRMS Calcd for $C_{23}H_{20}NO_3$: 358.1364 $[M + H]^+$. Found: 358.1408.



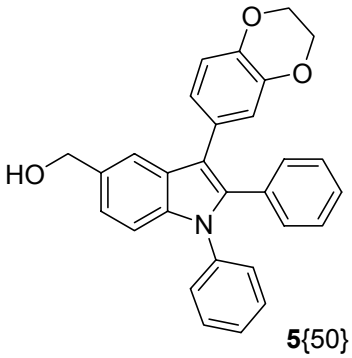
5{43}

3-Benzo[1,3]dioxol-5-yl-1*H*-indole-2-carbaldehyde 5{43}. Yield = 9%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.07 (s, 2H), 6.97-6.98 (d, *J* = 6.4 Hz, 1H), 7.04-7.09 (m, 2H), 7.18-7.22 (m, 1H), 7.41-7.48 (m, 2H), 7.79-7.81 (dd, *J* = 6.4, 0.8 Hz, 1H), 9.14 (broad s, 1H), 9.86 (s, 1H); ^{13}C NMR δ 101.62, 109.04, 110.77, 112.59, 121.61, 122.45, 124.55, 125.72, 127.01, 127.99, 129.46, 131.91, 137.30, 147.96, 148.37, 182.80; HRMS Calcd for $C_{16}H_{12}NO_3$: 266.0738 $[M + H]^+$. Found: 266.0845.



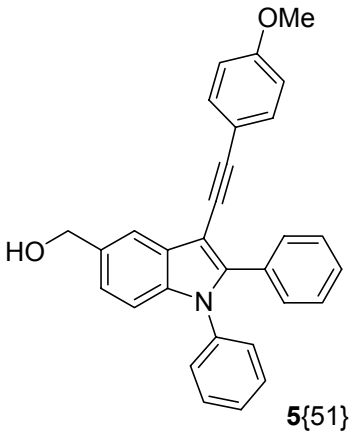
5{49}

(1,2,3-Triphenyl-1*H*-indol-5-yl)methanol 5{49}. Yield = 60%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.78 (s, 2H), 7.06-7.39 (m, 18H), 7.77 (s, 1H); ^{13}C NMR δ 66.47, 111.13, 117.00, 118.68, 122.79, 126.24, 127.43, 127.60, 127.86, 128.09, 128.39, 128.53, 129.30, 130.41, 131.32, 131.60, 133.89, 134.92, 137.76, 137.79, 138.23; HRMS Calcd for $C_{27}H_{21}NO$: 375.1623 $[M]^+$. Found: 375.1625.



5{50}

[3-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1,2-diphenyl-1*H*-indol-5-yl]methanol 5{50}. Yield = 54%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.24-4.27 (m, 4H), 4.76 (s, 2H), 6.74-6.80 (m, 2H), 6.941-6.945 (d, *J* = 1.6 Hz, 1H), 7.07-7.09 (m, 2H), 7.13-7.15 (m, 3H), 7.18-7.20 (m, 3H), 7.22-7.25 (dd, *J* = 7.2, 1.6 Hz, 2H) (one extra proton due to overlap with the $CDCl_3$ peak), 7.29-7.30 (m, 2H), 7.33-7.36 (m, 2H), 7.75-7.76 (d, *J* = 0.8 Hz, 1H); ^{13}C NMR δ 64.53, 66.33, 68.15, 108.10, 110.99, 116.36, 117.31, 118.67, 118.90, 122.72, 123.70, 127.32, 127.53, 127.90, 128.06, 128.33, 129.25, 131.25, 131.58, 133.79, 137.47, 137.56, 138.22, 142.14, 143.46; HRMS Calcd for $C_{29}H_{24}NO_3$: 434.1677 $[M + H]^+$. Found: 434.1767.

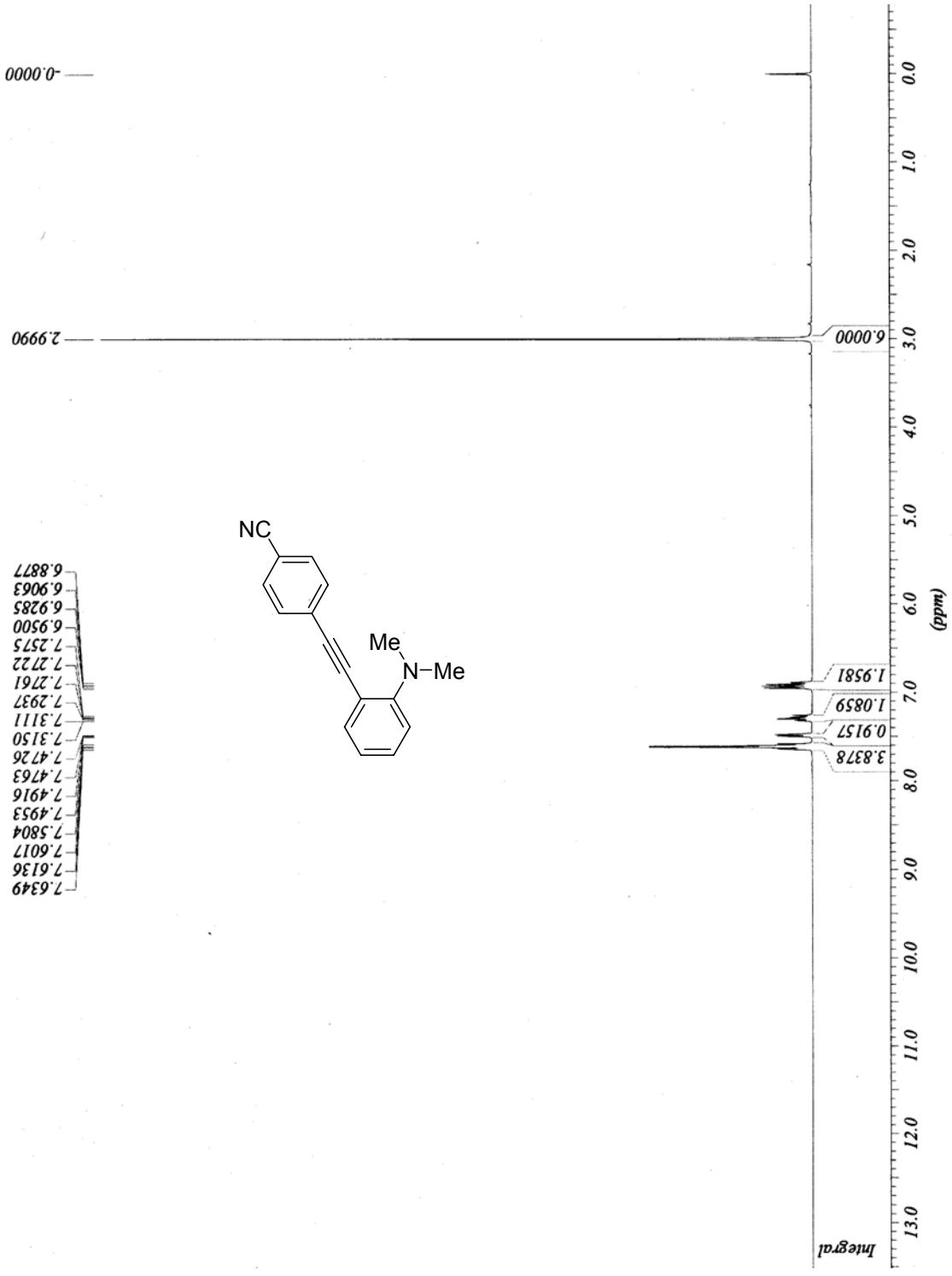


5{51}

[3-(4-Methoxyphenylethynyl)-1,2-diphenyl-1*H*-indol-5-yl]methanol 5{51}. Yield = 64%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.77 (s, 3H), 4.80 (s, 2H), 6.83-6.85 (m, 2H), 7.18-7.33 (m, 9H), 7.35-7.38 (m, 2H), 7.42-7.47 (m, 4H), 7.87 (s, 1H); ^{13}C NMR δ 55.44, 66.06, 82.26, 92.81, 99.18, 108.10, 111.14, 114.06, 116.52, 118.98, 123.39, 127.69, 128.01, 128.03, 128.07, 129.52, 130.20, 130.83, 132.81, 134.41, 137.43, 138.00, 142.75, 159.19; HRMS Calcd for $C_{30}H_{24}NO_2$: 430.1728 $[M + H]^+$. Found: 430.1826.

References

1. Koten, G.; ten Hoedt, R. W.; Noltes, J. G. *J. Org. Chem.* **1977**, *42*, 2705.
2. (a) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037. (b) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 62.
3. Bowyer, P. K.; Black, D. C.; Craig, D. C. *Tetrahedron* **2005**, *61*, 10781.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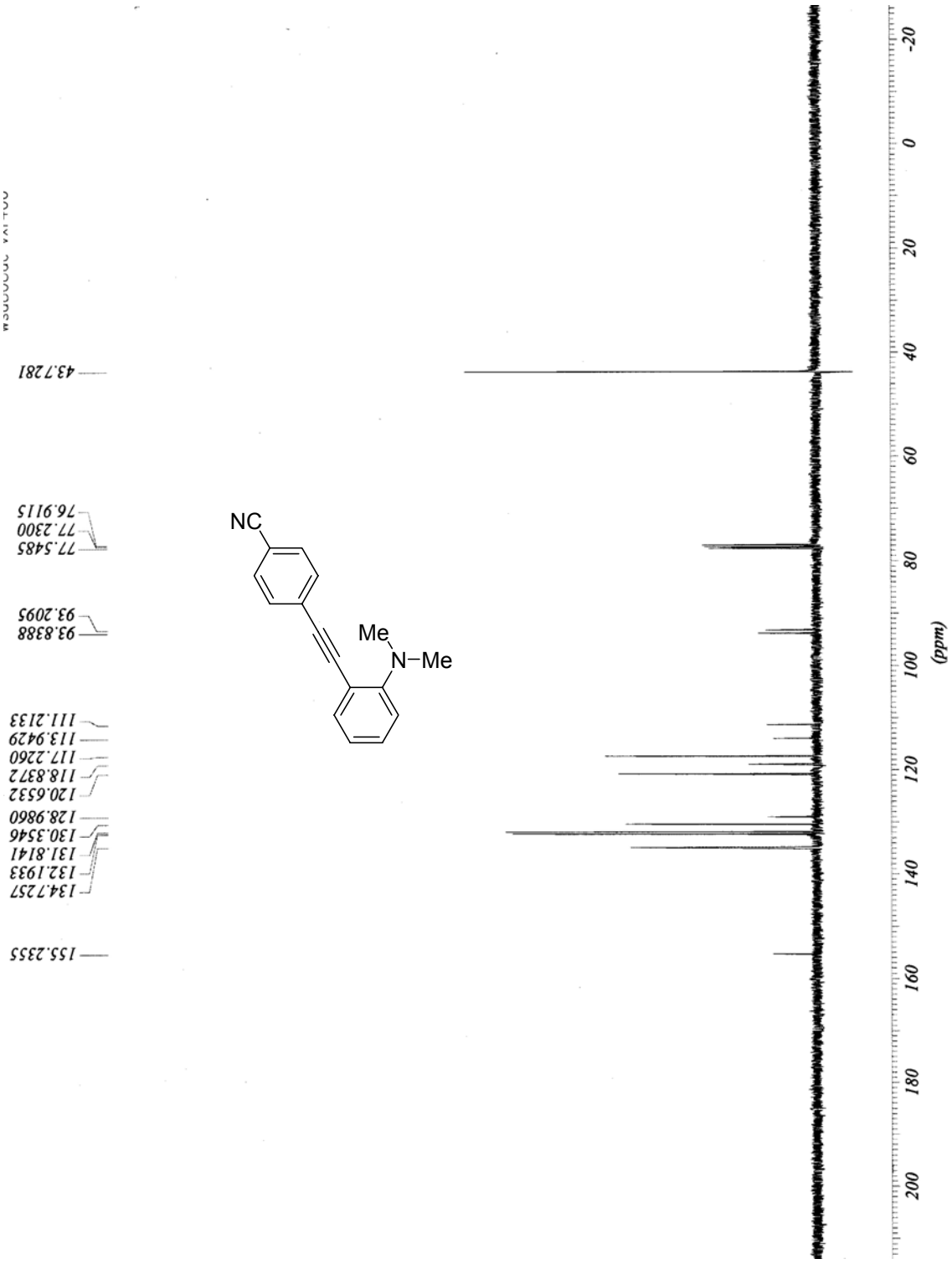
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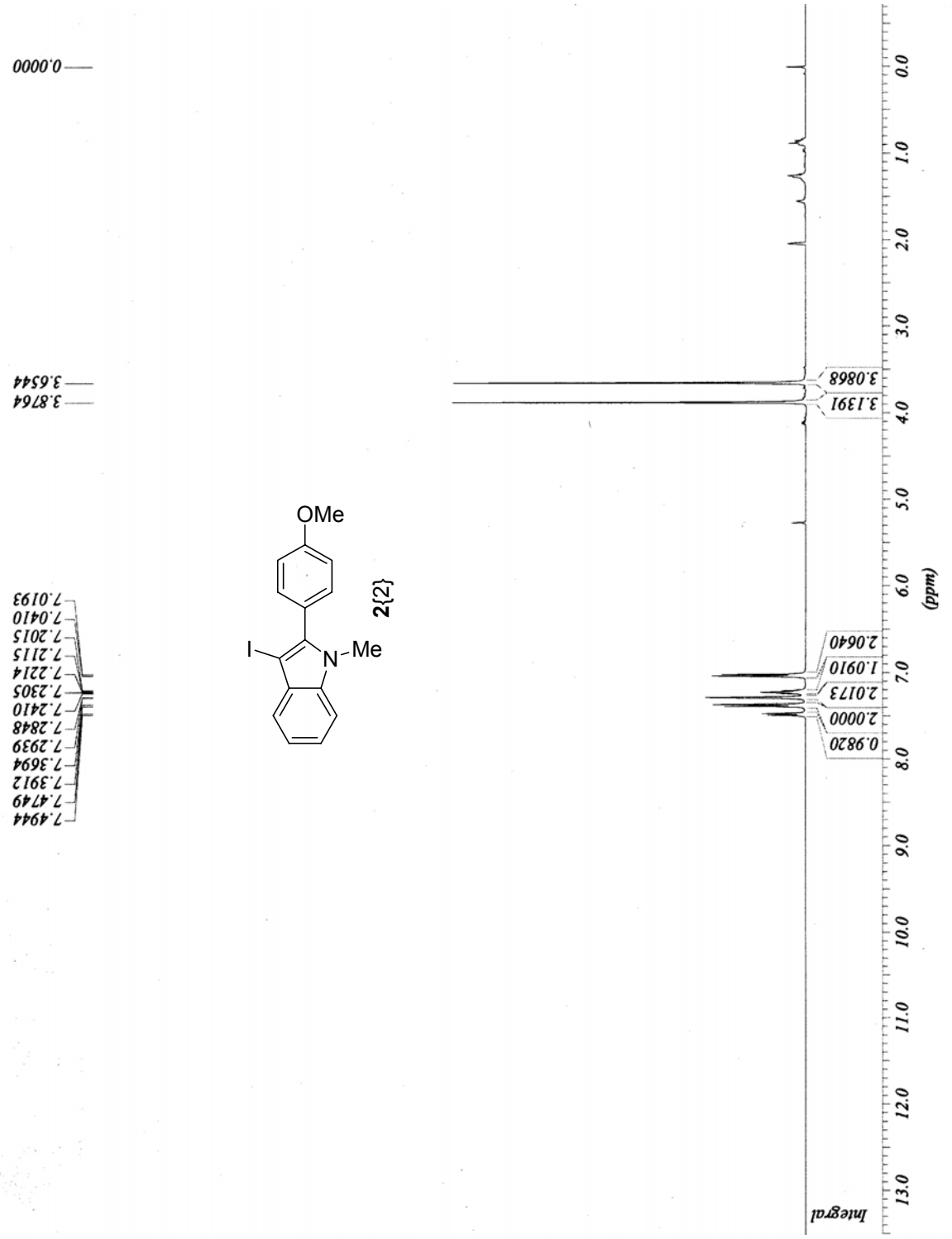
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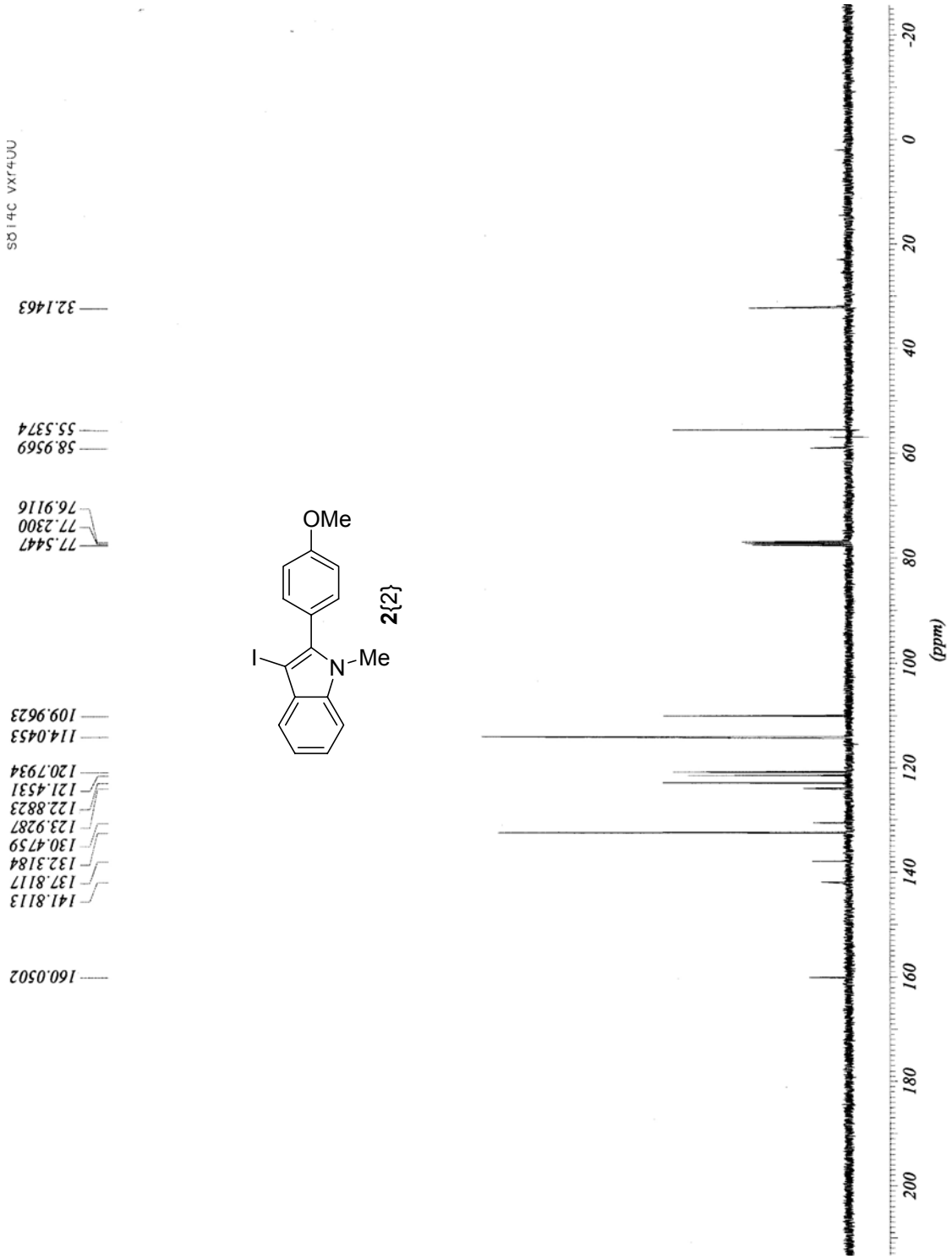
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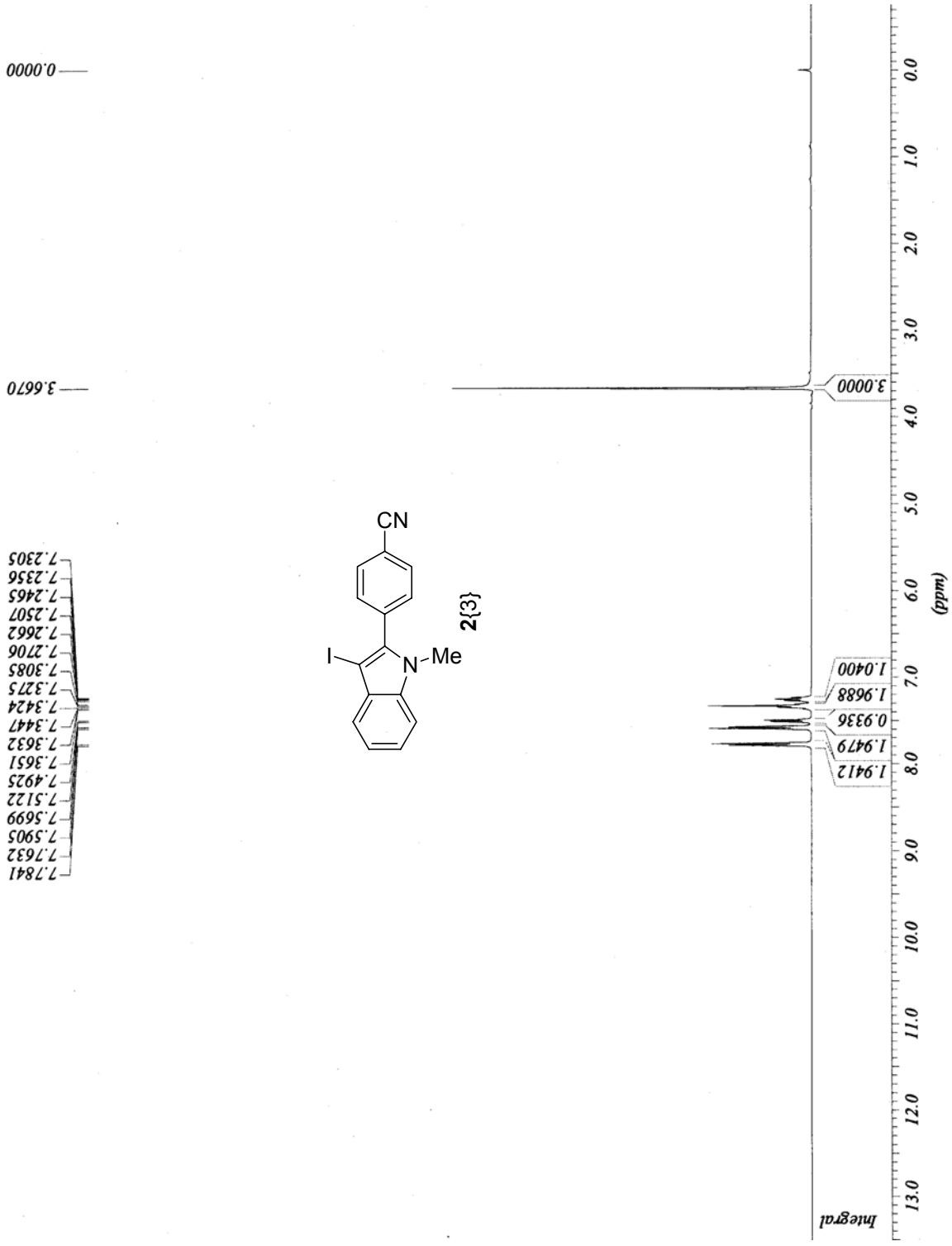
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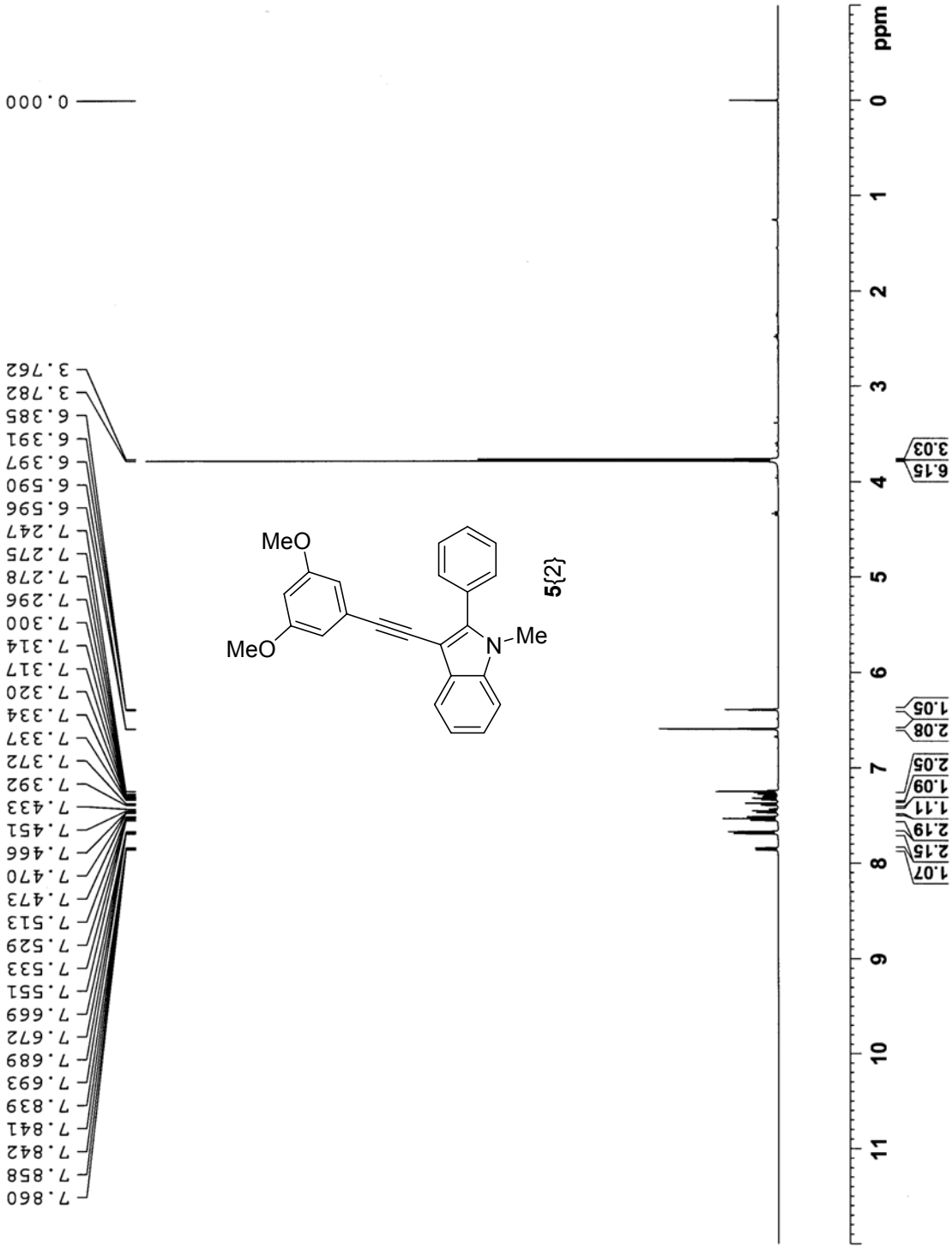
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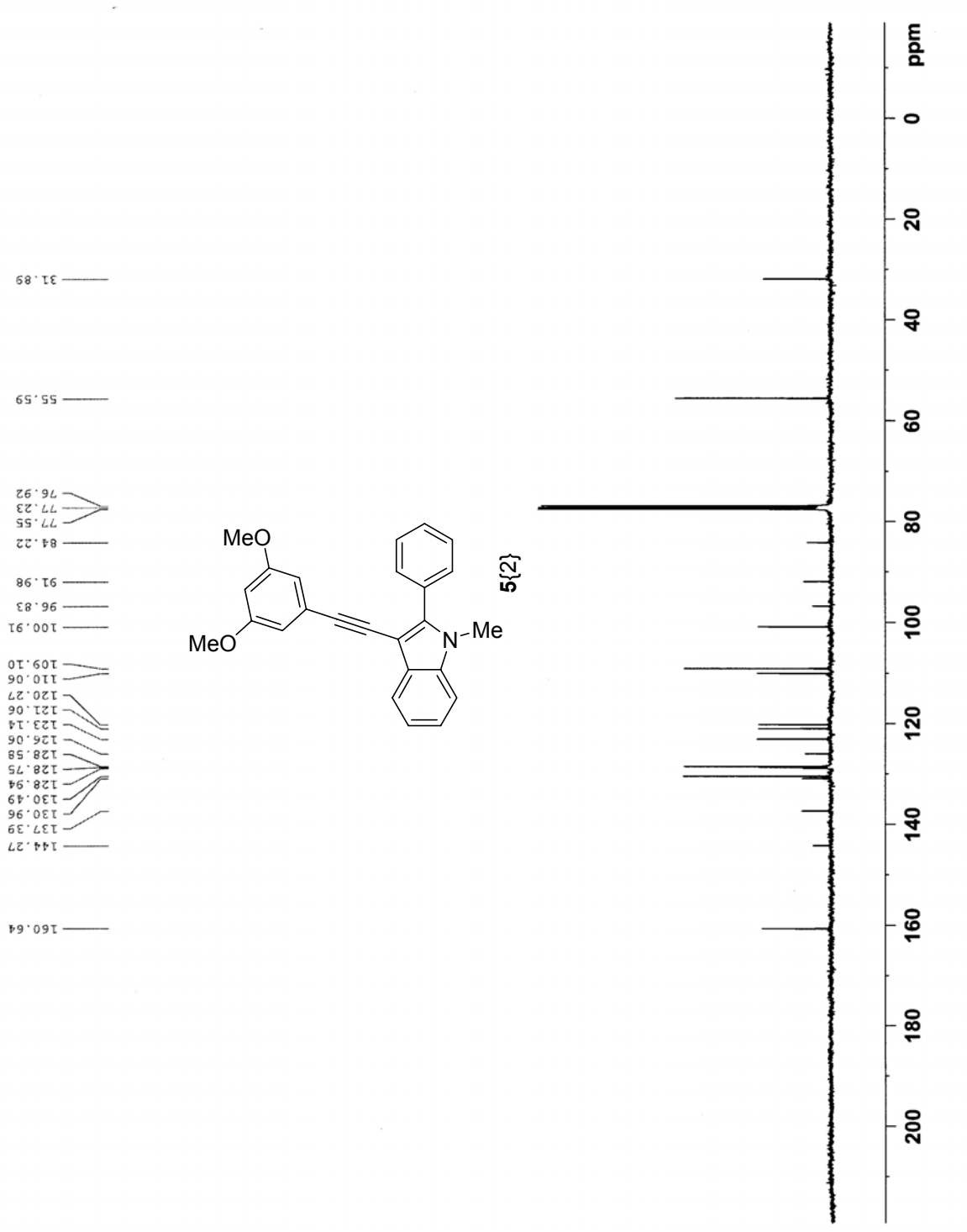
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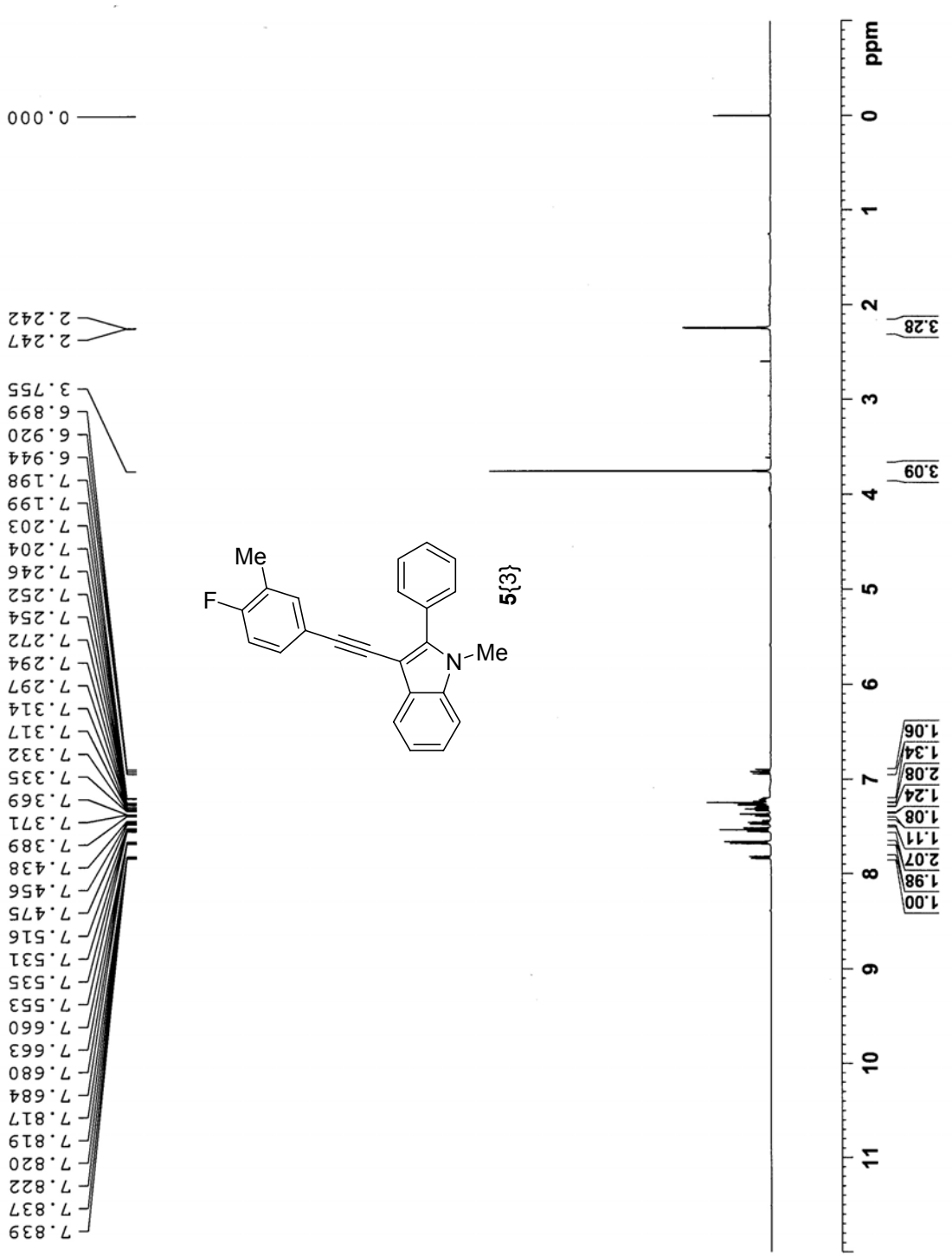
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7.297
7.314
7.317
7.332
7.335
7.369
7.371
7.389
7.438
7.456
7.475
7.516
7.531
7.535
7.553
7.660
7.663
7.680
7.684
7.817
7.819
7.820
7.822
7.837
7.839
Me
F
N
Me
5{3}
ppm
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2
3
4
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7
8
9
10
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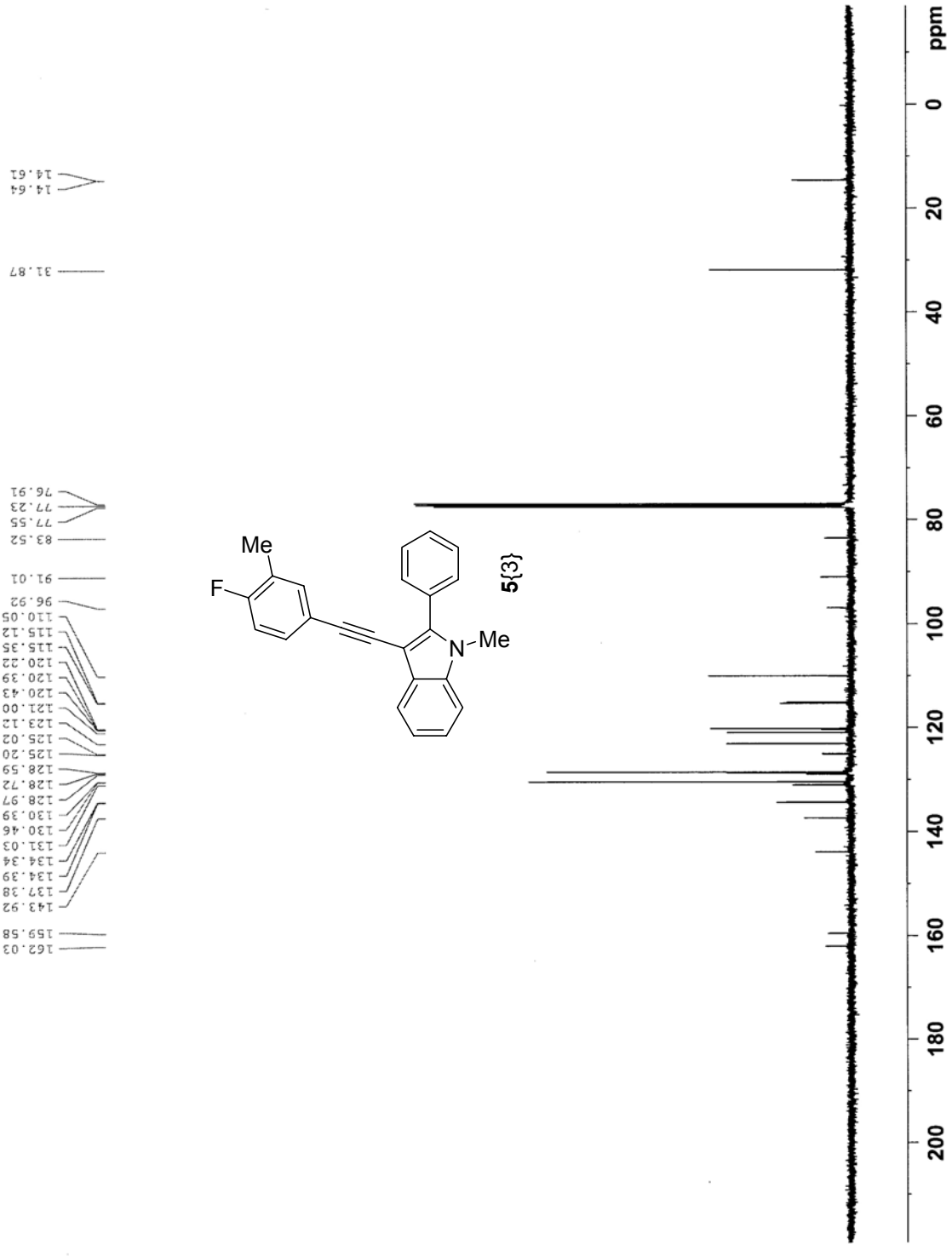
1.00
1.98
2.07
1.11
1.08
1.24
2.08
1.34
1.06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120.39
120.43
121.00
123.12
125.02
125.20
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128.97
130.39
130.46
131.03
134.34
134.39
137.38
143.92
159.58
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Me
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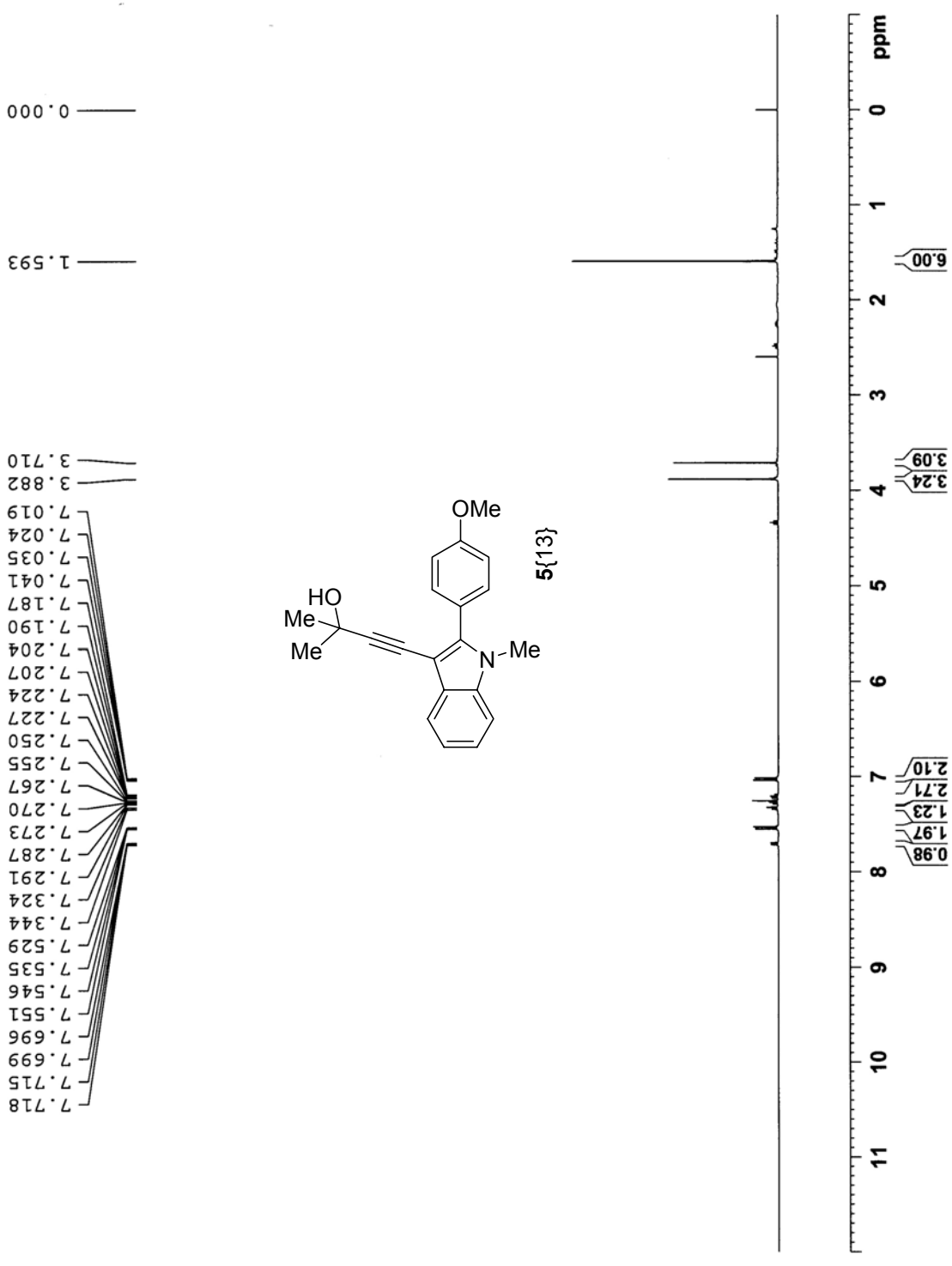
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3
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5
6
7
8
9
10
11
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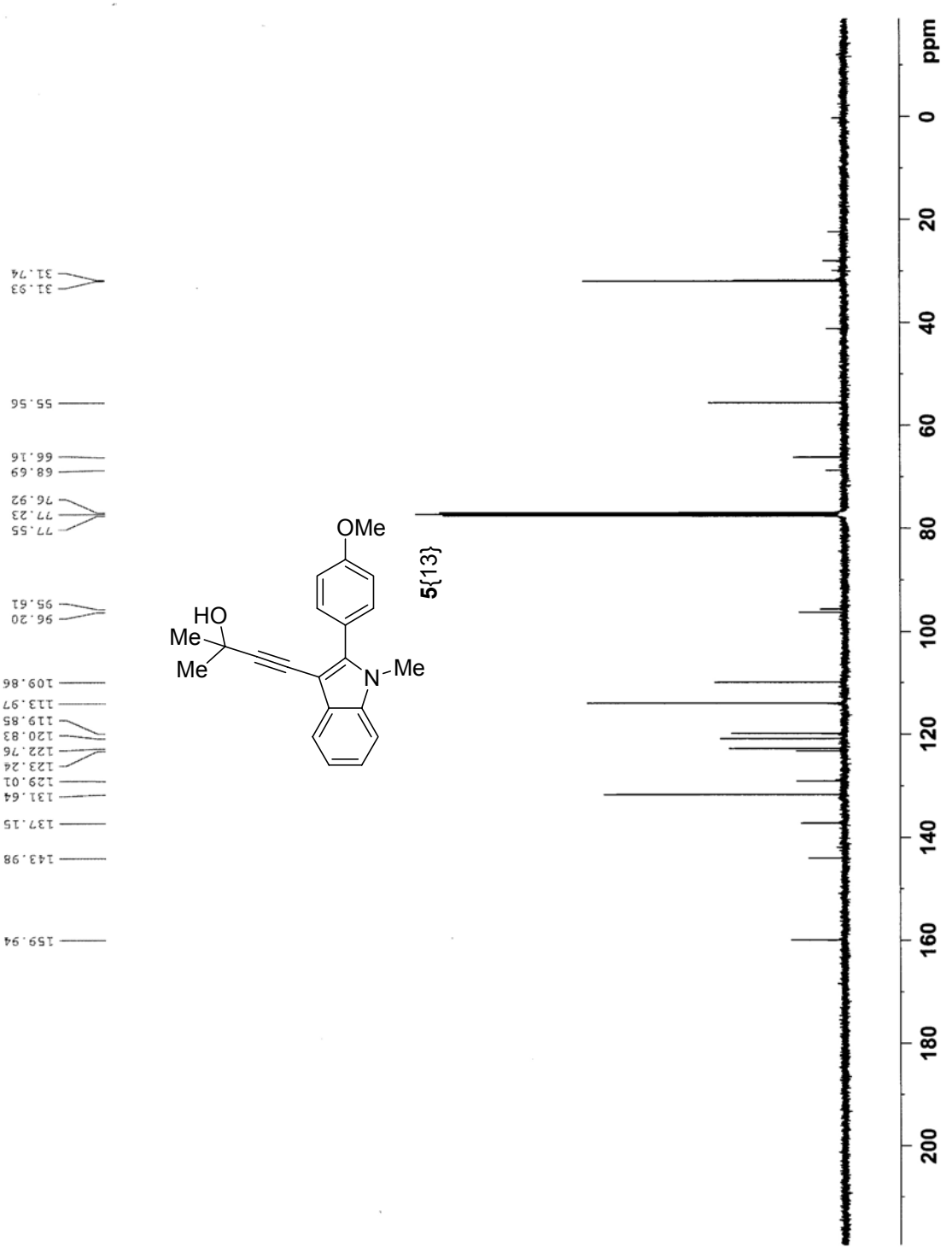
3.24
3.09
2.10
2.71
1.23
1.97
0.98
0.000
1.593
3.710
3.882
7.019
7.024
7.035
7.041
7.187
7.190
7.204
7.207
7.224
7.227
7.250
7.255
7.267
7.270
7.273
7.287
7.291
7.324
7.344
7.529
7.535
7.546
7.551
7.696
7.699
7.715
7.718
OMe
HO
Me
Me
N
Me
5{13}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77.23
77.55
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96.20
109.86
113.97
119.85
120.83
122.76
123.24
129.01
131.64
137.15
143.98
159.94
OMe
HO
Me
Me
N
Me
5{13}
ppm
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60
80
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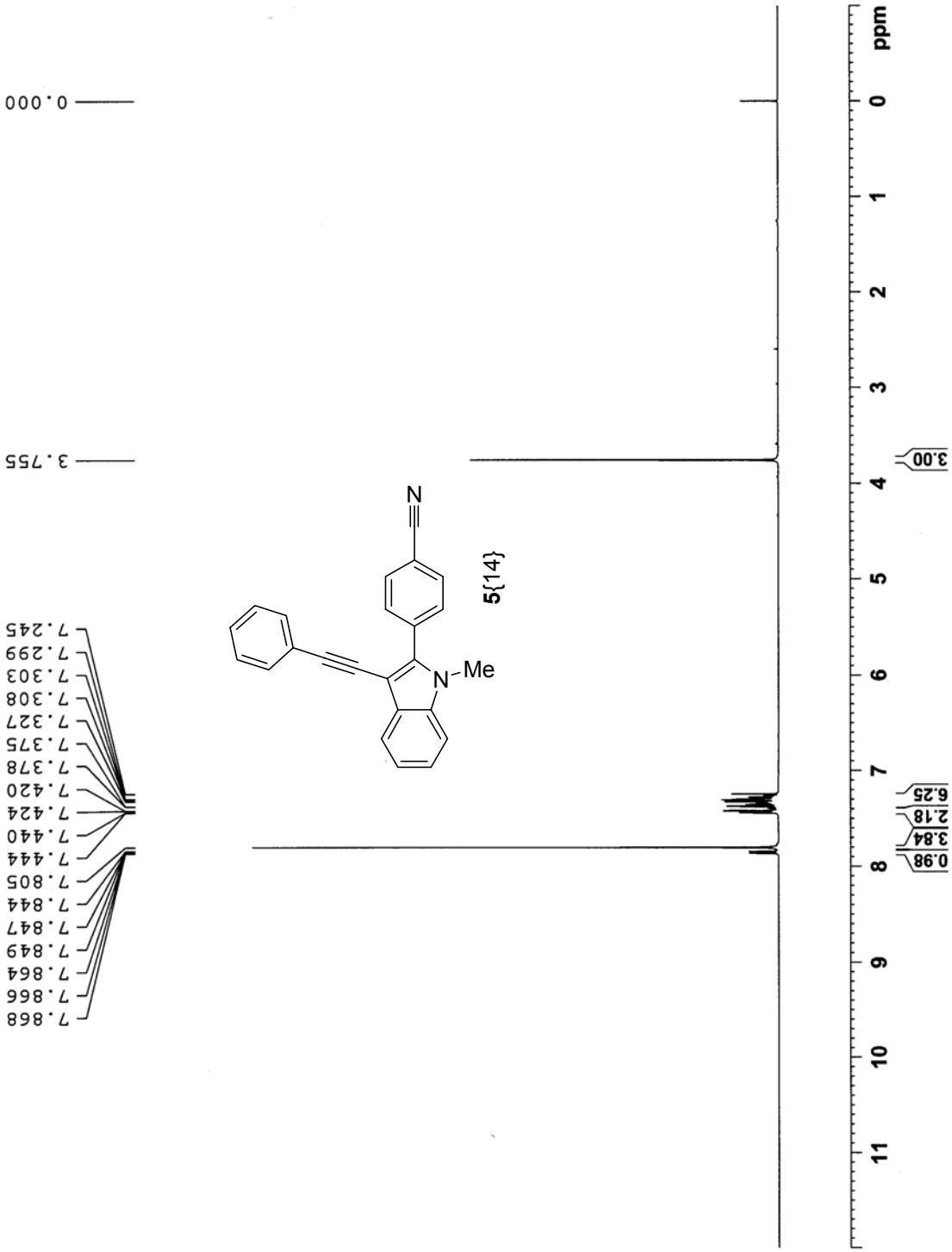
160
180
200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2
3
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5
6
7
8
9
10
11
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2.18
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0.000
3.755
7.245
7.299
7.303
7.308
7.327
7.375
7.378
7.420
7.424
7.440
7.444
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7.844
7.847
7.849
7.864
7.866
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N
Me
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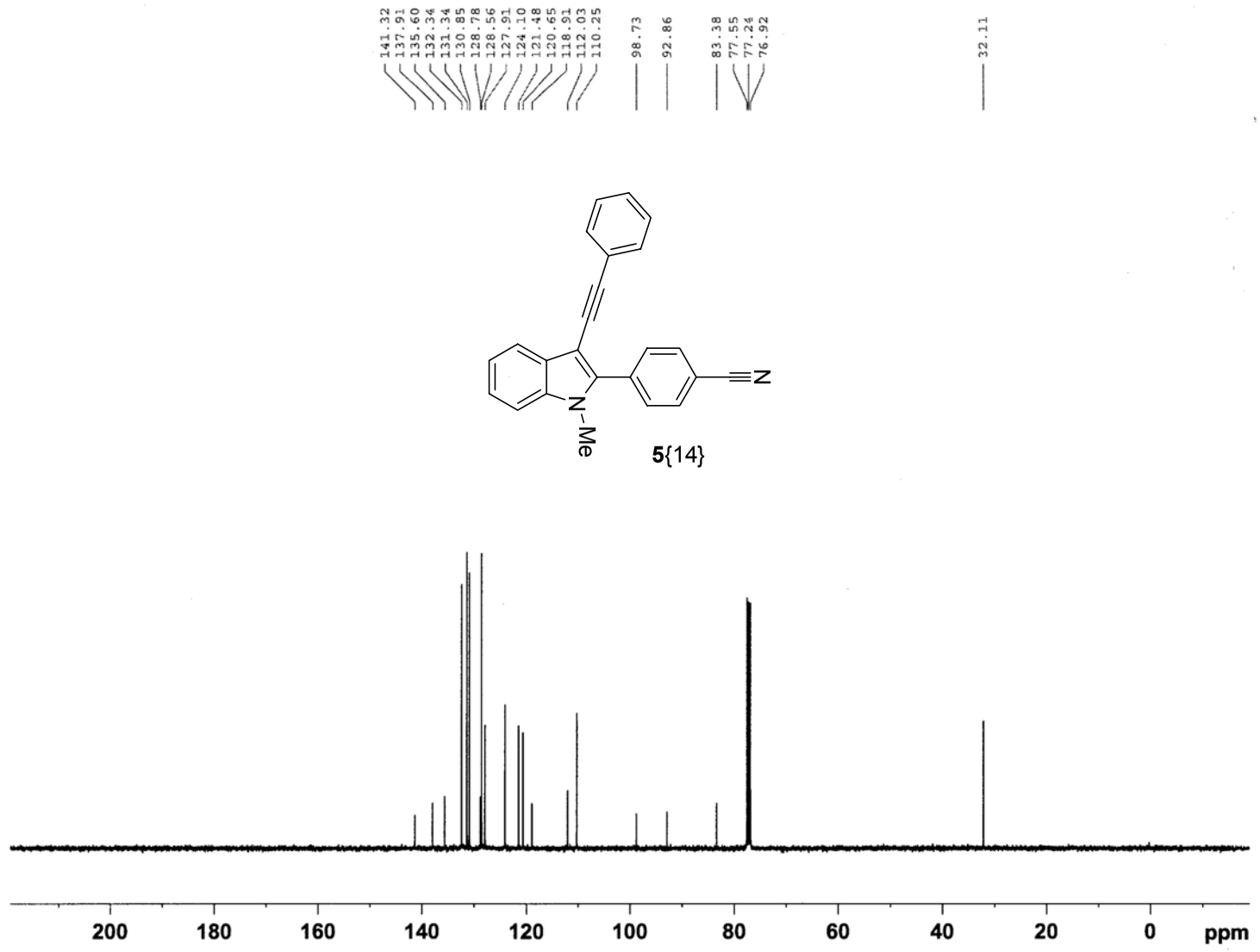
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128.56
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124.10
121.48
120.65
118.91
112.03
110.25
98.73
92.86
83.38
77.55
77.24
76.92
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N
N
Me
5{14}
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140
120
100
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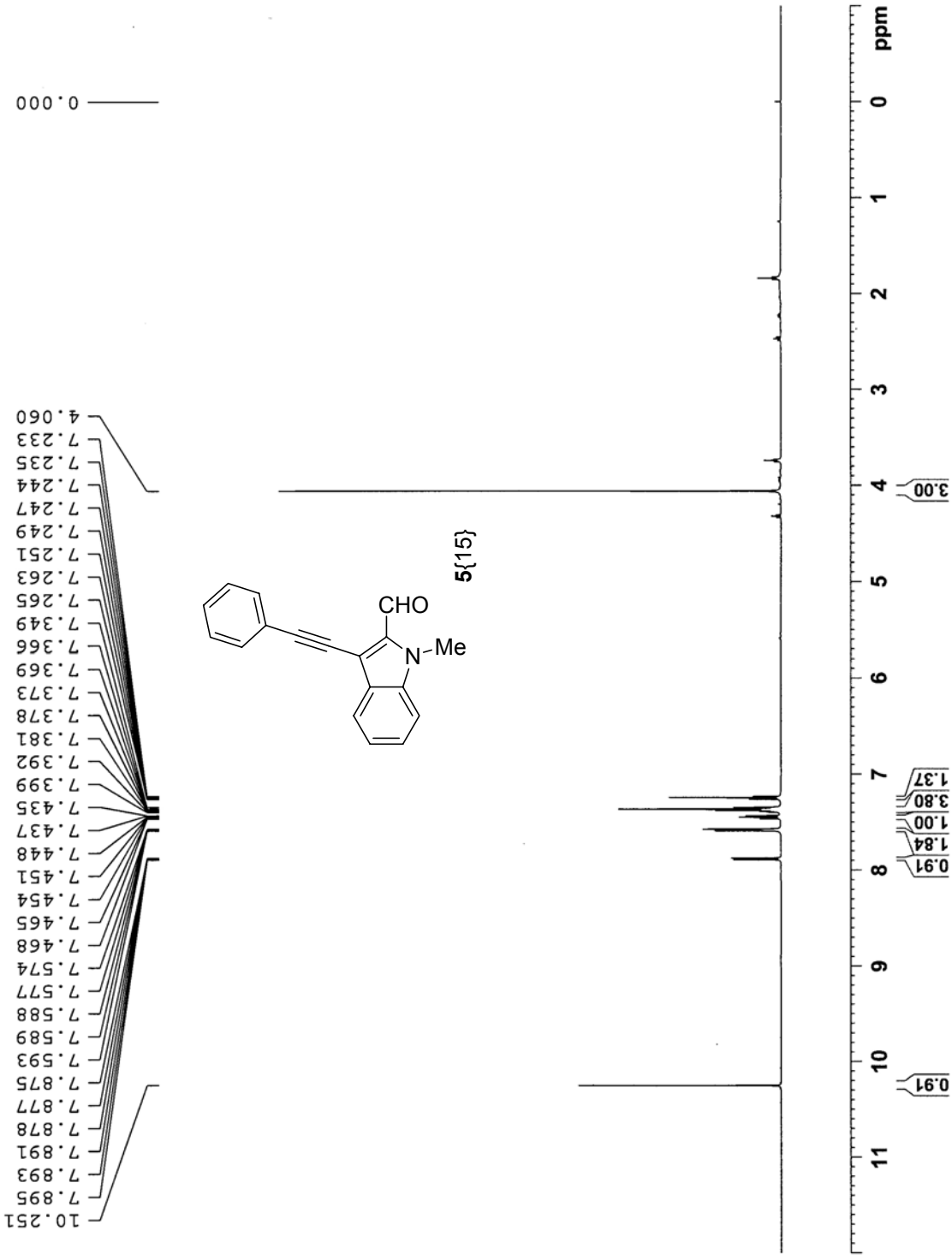
60
40
20
0
ppm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7.235
7.244
7.247
7.249
7.251
7.263
7.265
7.349
7.366
7.369
7.373
7.378
7.381
7.392
7.399
7.435
7.437
7.448
7.451
7.454
7.465
7.468
7.574
7.577
7.588
7.589
7.593
7.875
7.877
7.878
7.891
7.893
7.895
10.251
5{15}
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N-Me
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1.84
1.00
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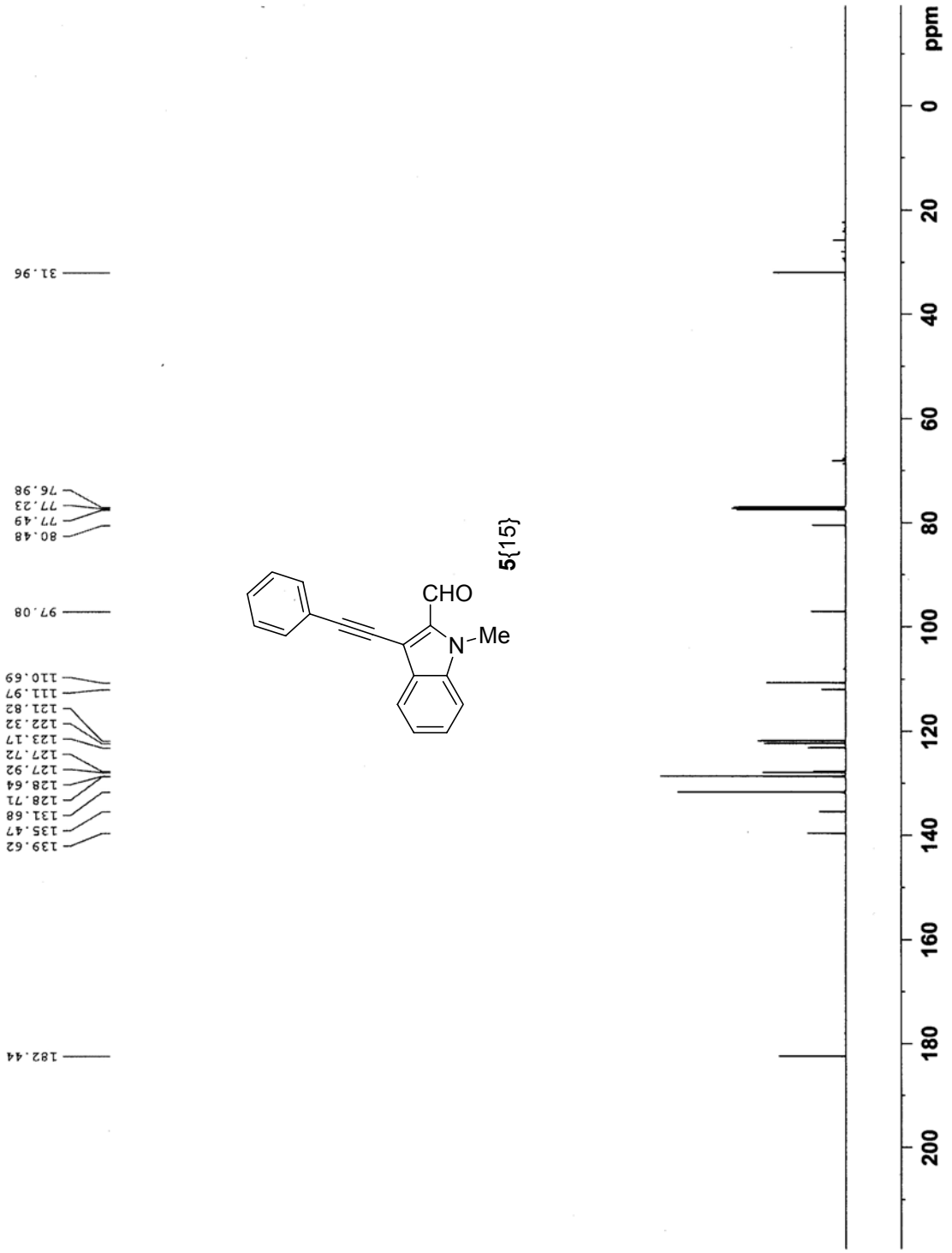
1.37
0.91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60
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100
120
140
160
180
200
31.96
76.98
77.23
77.49
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97.08
110.69
111.97
121.82
122.32
123.17
127.72
127.92
128.64
128.71
131.68
135.47
139.62
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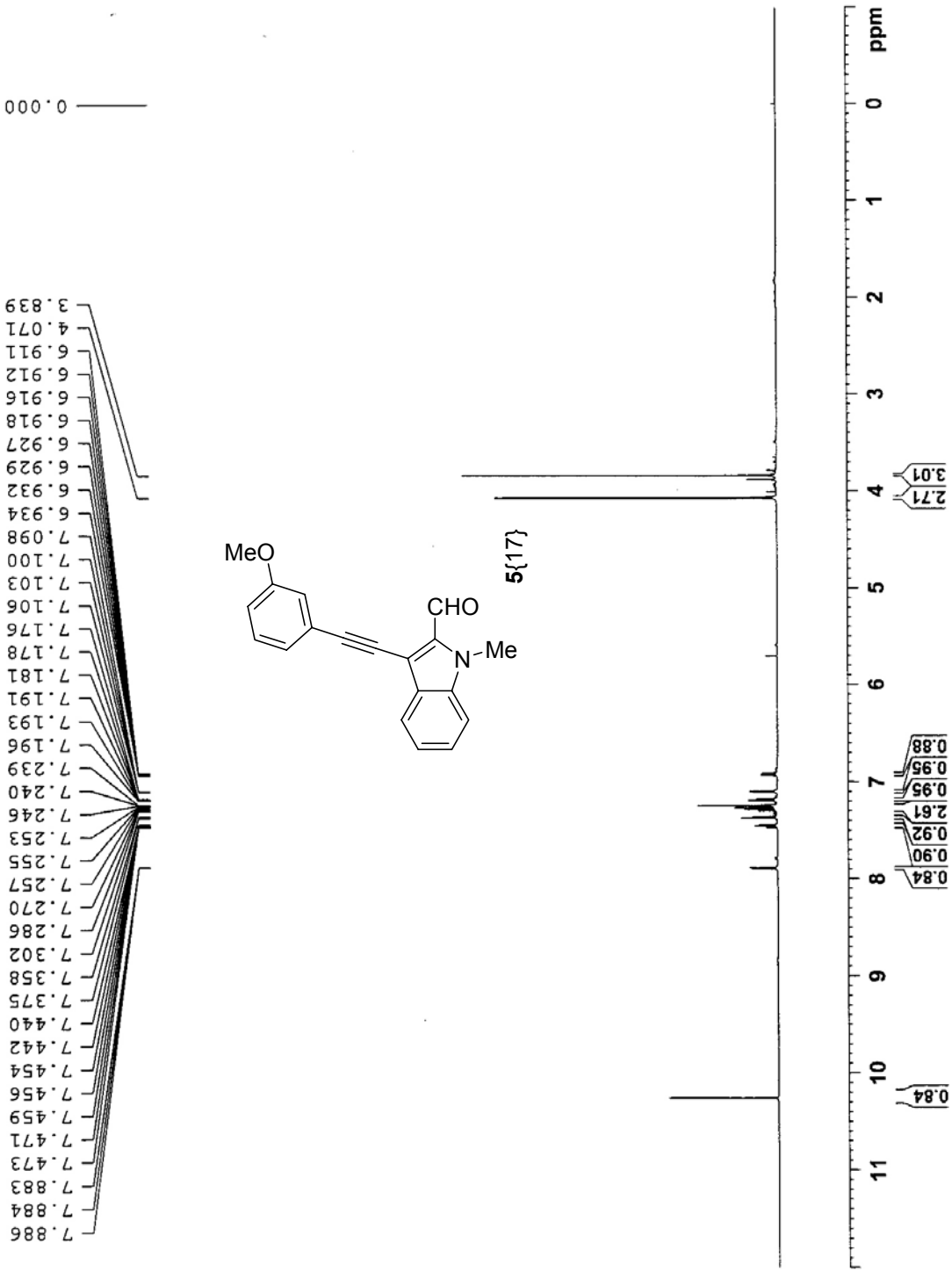
CHO
N
Me
5{15}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Me
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0.84
0.90
0.92
2.61
0.95
0.95
0.88
0.84
0.000
3.839
4.071
6.911
6.912
6.916
6.918
6.927
6.929
6.932
6.934
7.098
7.100
7.103
7.106
7.176
7.178
7.181
7.191
7.193
7.196
7.239
7.240
7.246
7.253
7.255
7.257
7.270
7.286
7.302
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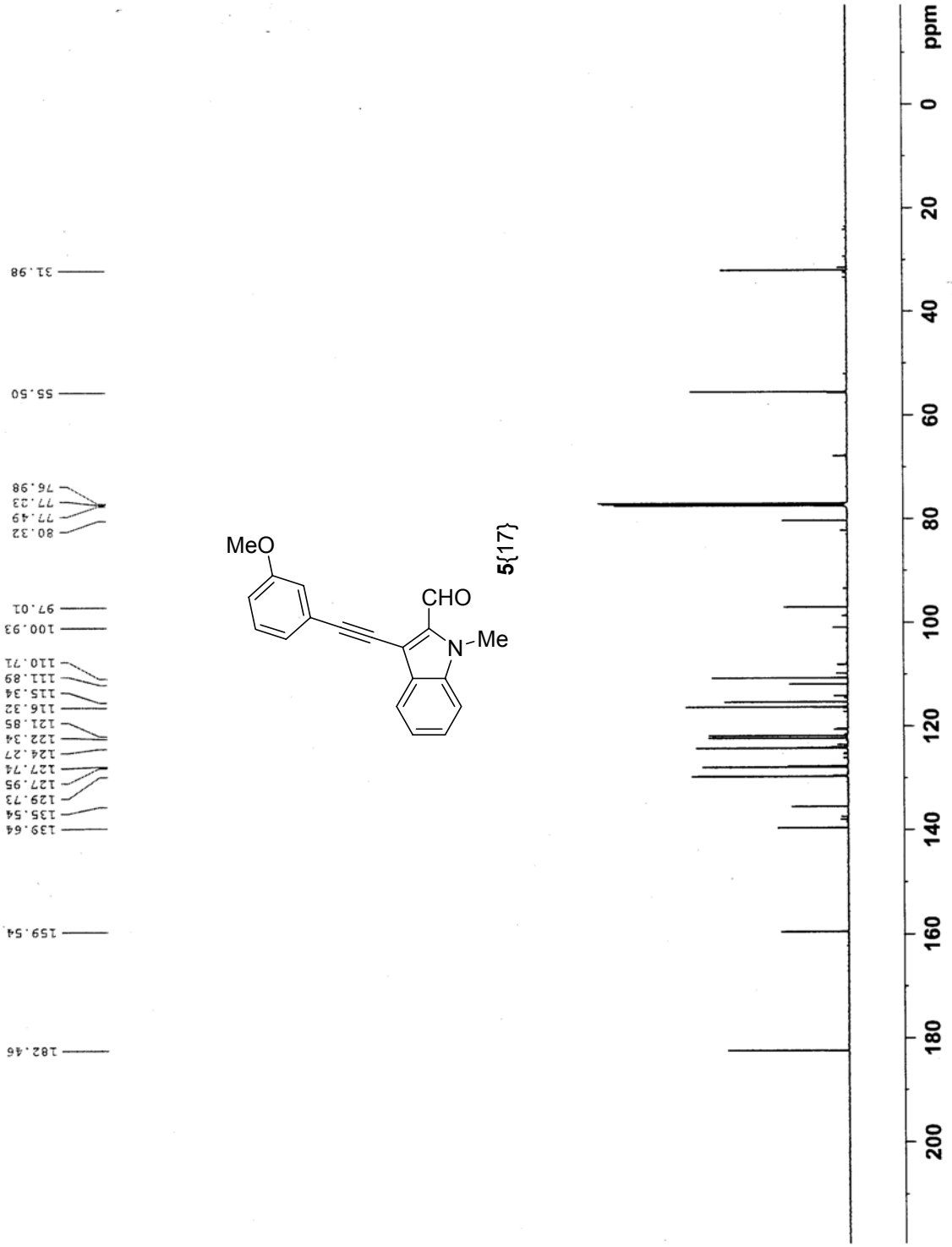
7.375
7.440
7.442
7.454
7.456
7.459
7.471
7.473
7.883
7.884
7.886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159.54
139.64
135.54
129.73
127.95
127.74
124.27
122.34
121.85
116.32
115.34
111.89
110.71
100.93
97.01
80.32
77.49
77.23
76.98
55.50
31.98
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CHO
N-Me
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ppm
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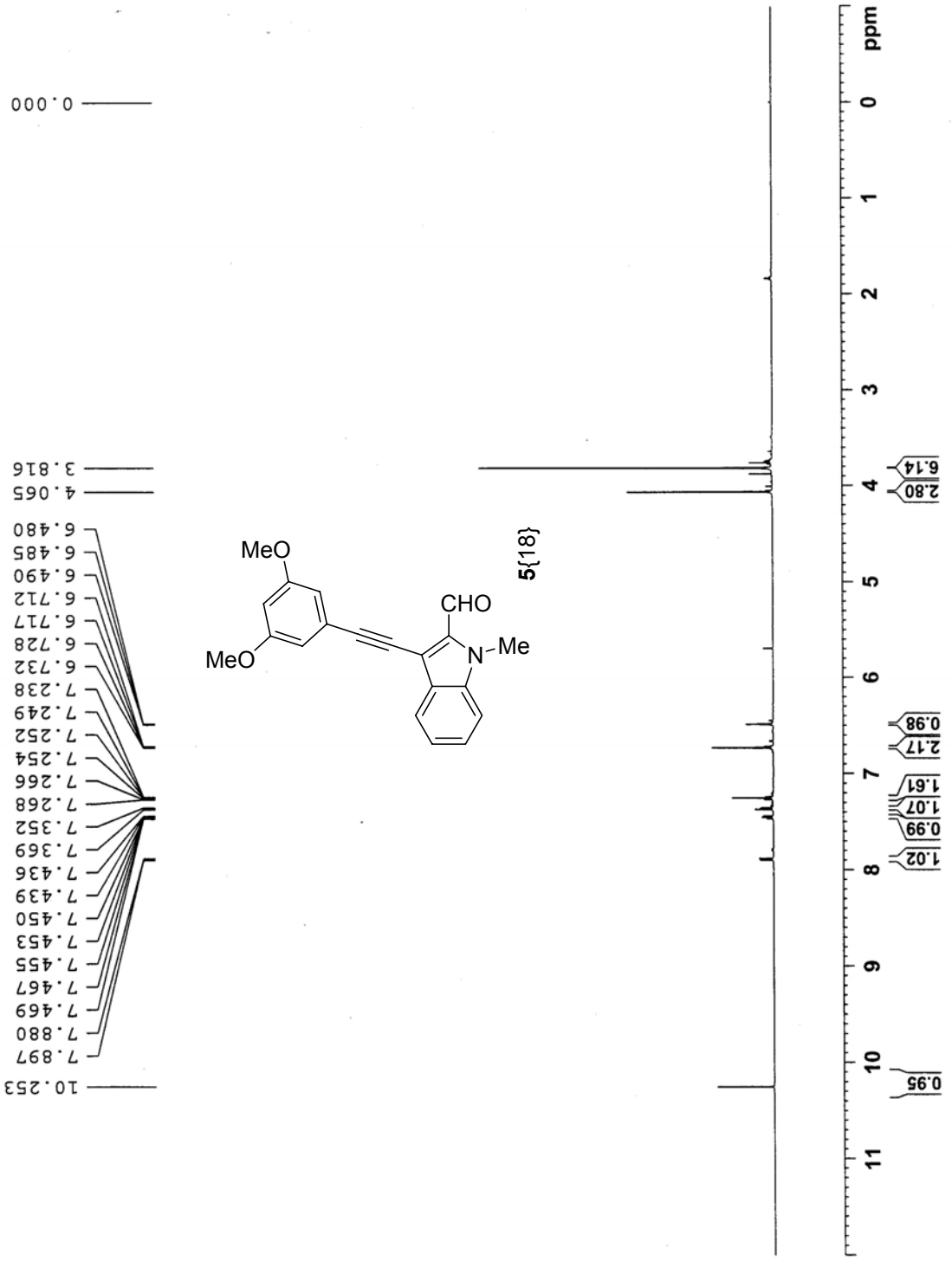
60
80
100
120
140
160
180
200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6.485
6.490
6.712
6.717
6.728
6.732
7.238
7.249
7.252
7.254
7.266
7.268
7.352
7.369
7.436
7.439
7.450
7.453
7.455
7.467
7.469
7.880
7.897
10.253
MeO
MeO
CHO
N
Me
5{18}
ppm
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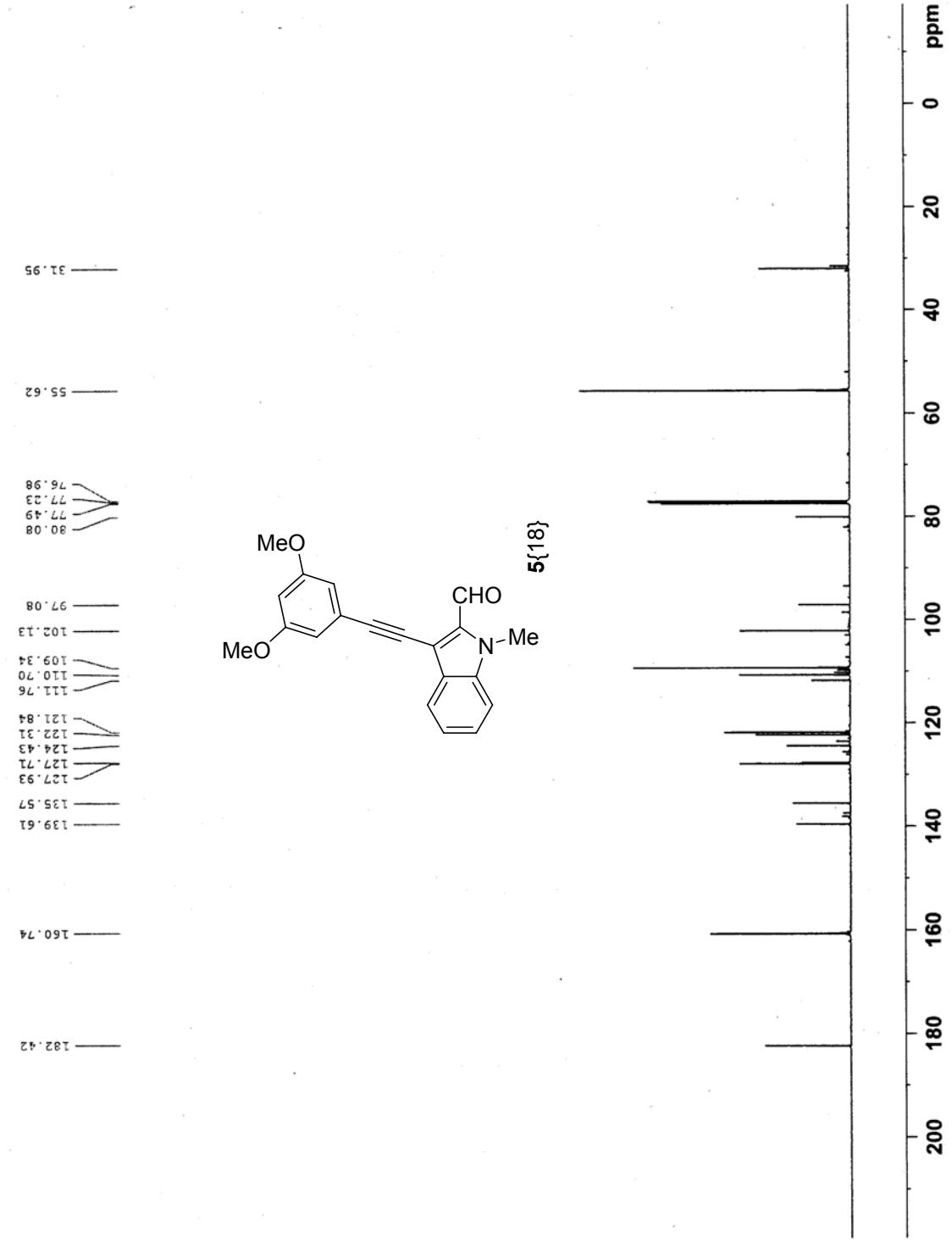
1
2
3
4
5
6
7
8
9
10
11
6.14
2.80
0.98
2.17
1.61
1.07
0.99
1.02
0.95


MeO
MeO
CHO
N
Me
5{18}
182.42
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135.57
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127.71
124.43
122.31
121.84
111.76
110.70
109.34
102.13
97.08
80.08
77.49
77.23
76.98
55.62
31.95
ppm
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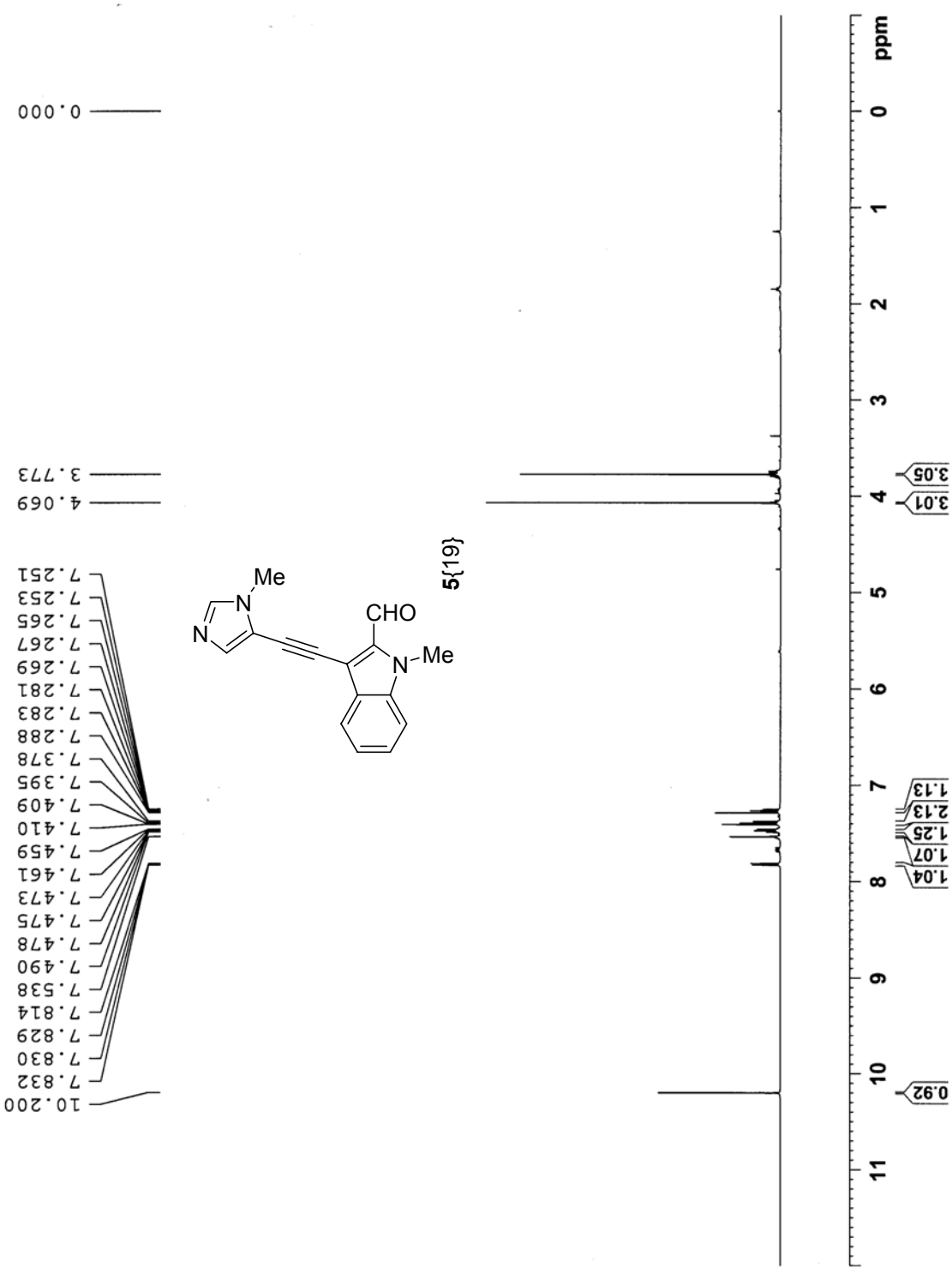
20
40
60
80
100
120
140
160
180
200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7.265
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7.269
7.281
7.283
7.288
7.378
7.395
7.409
7.410
7.459
7.461
7.473
7.475
7.478
7.490
7.538
7.814
7.829
7.830
7.832
10.200
Me
N
N
CHO
N
Me
5{19}
ppm
0
1
2
3
4
5
6
7
8
9
10
11
0.92
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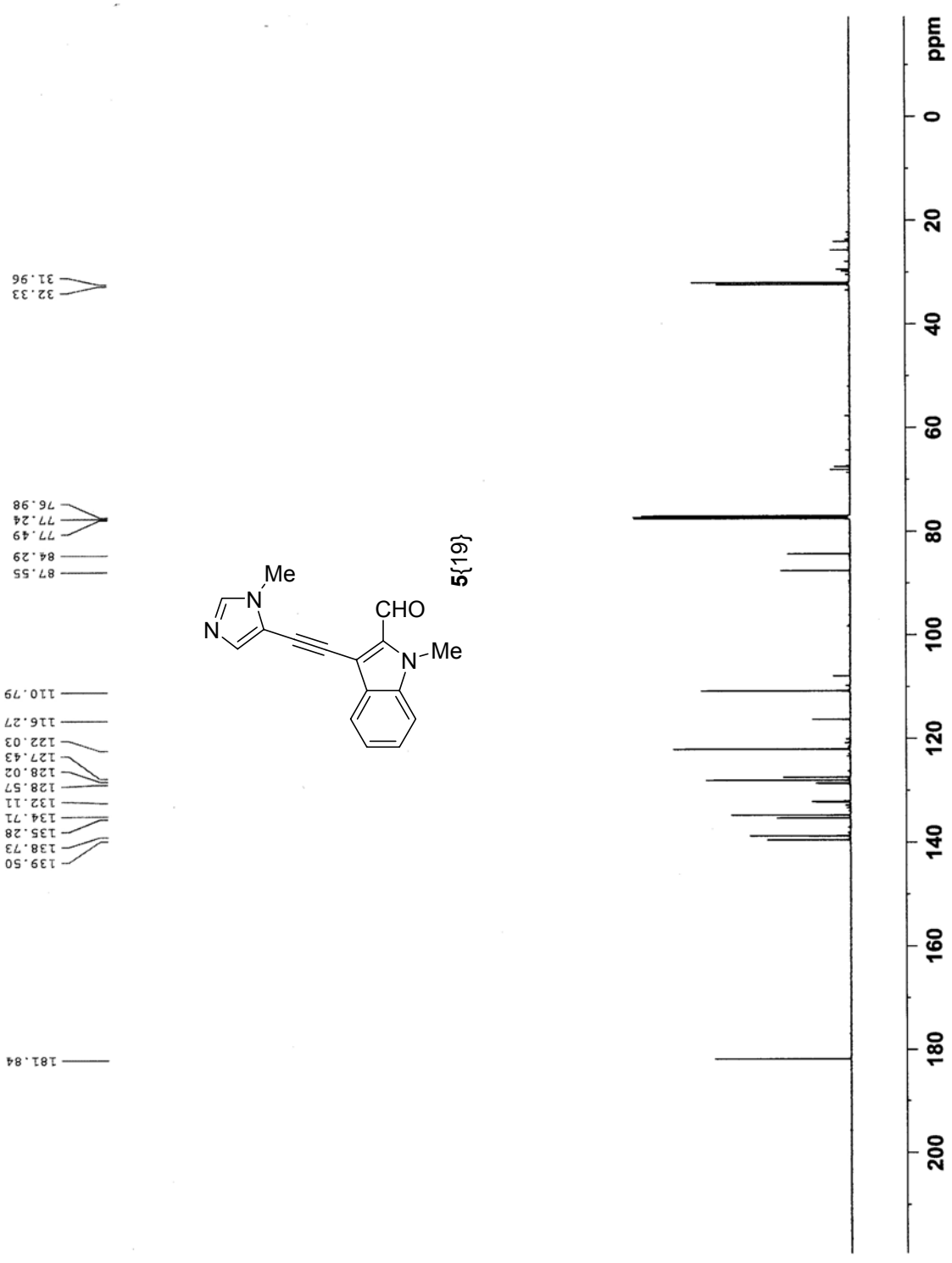
3.01
1.13
2.13
1.25
1.07
1.04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77.24
77.49
84.29
87.55
110.79
116.27
122.03
127.43
128.02
128.57
132.11
134.71
135.28
138.73
139.50
181.84
Me
N
N
CHO
N
Me
5{19}
ppm
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20
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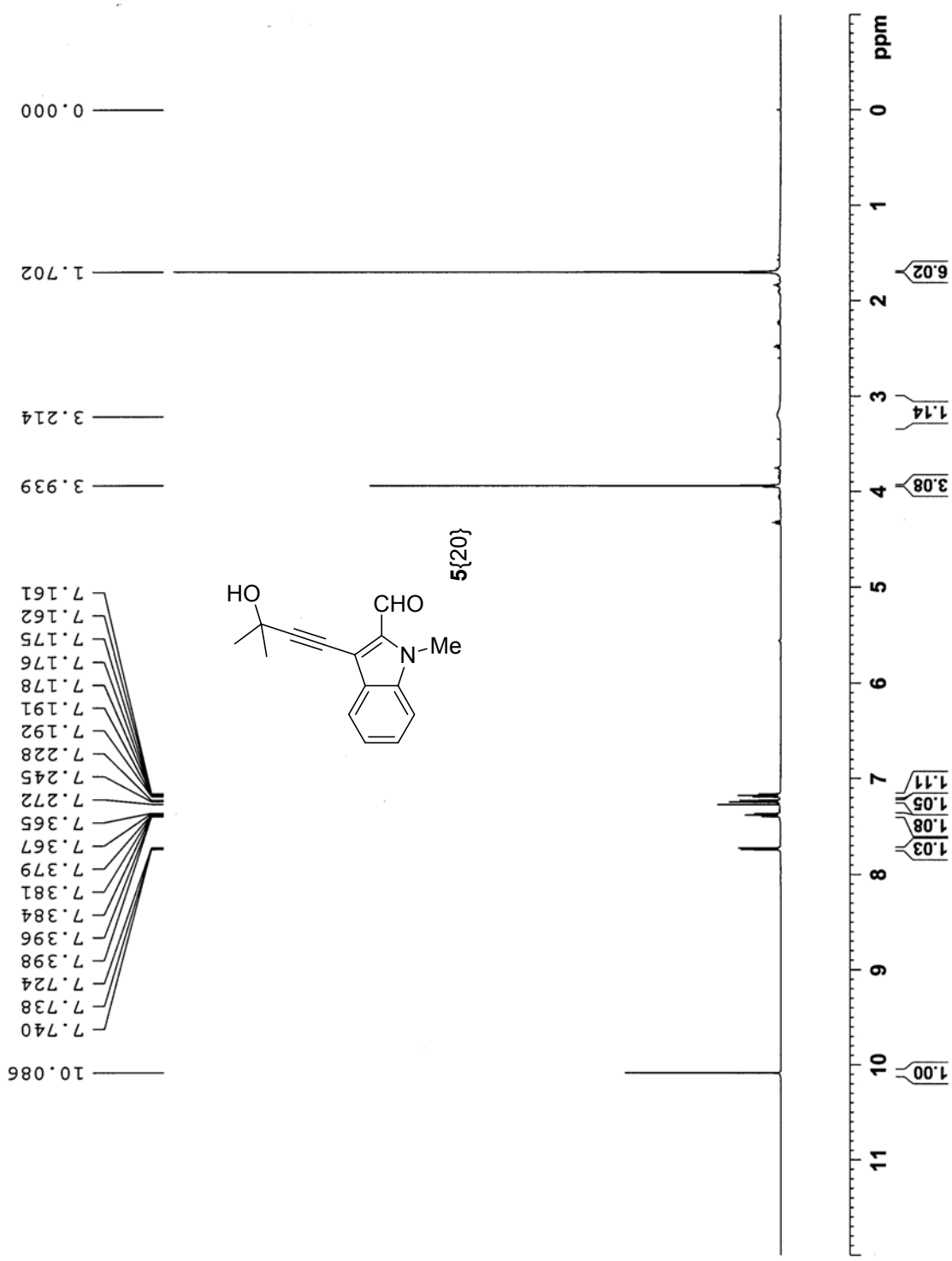
60
80
100
120
140
160
180
200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3.939
7.161
7.162
7.175
7.176
7.178
7.191
7.192
7.228
7.245
7.272
7.365
7.367
7.379
7.381
7.384
7.396
7.398
7.724
7.738
7.740
10.086
HO
CHO
N
Me
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ppm
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2
3
4
5
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10
11
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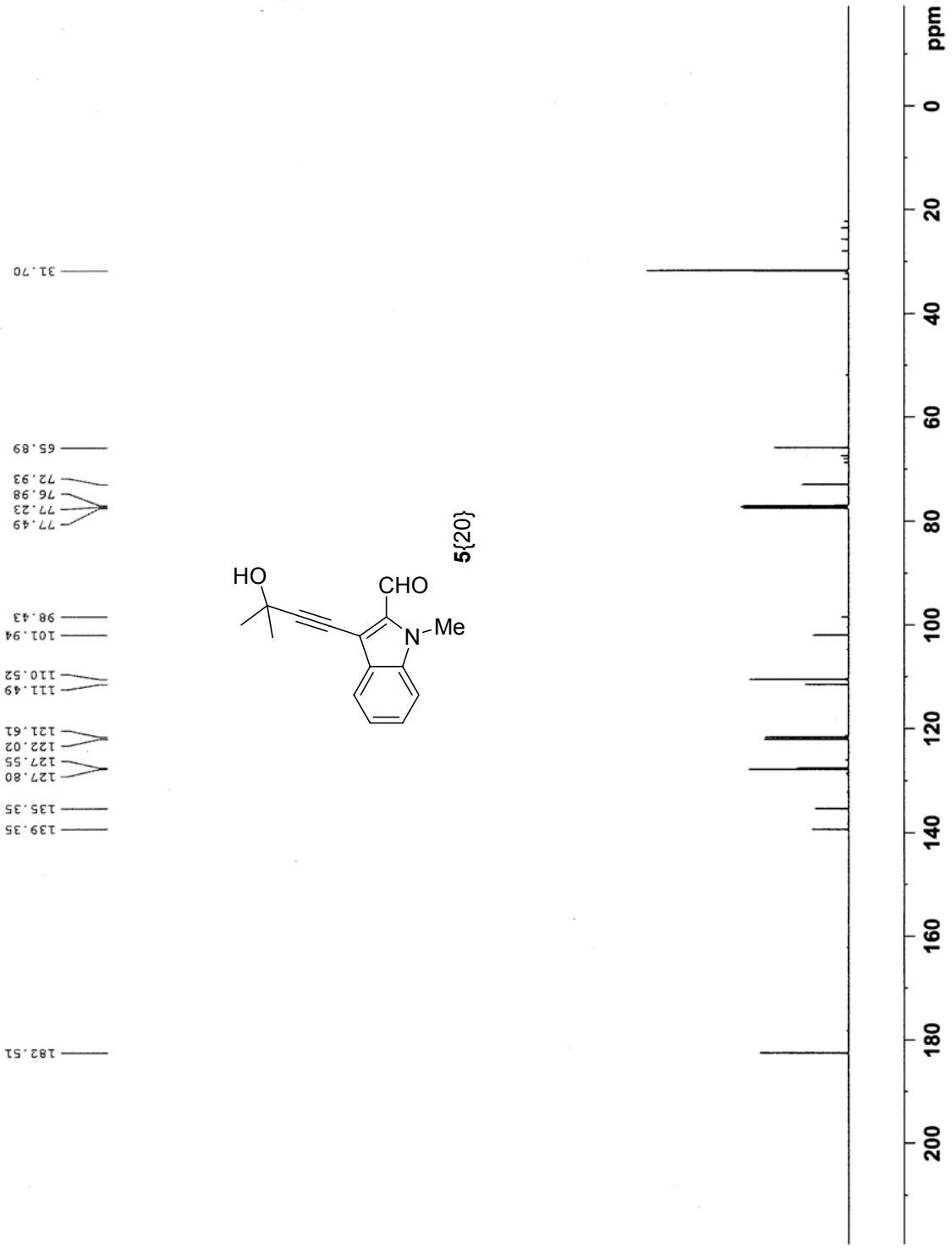
1.14
3.08
1.11
1.05
1.08
1.03
1.00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127.55
122.02
121.61
111.49
110.52
101.94
98.43
77.49
77.23
76.98
72.93
65.89
31.70
HO
CHO
N
Me
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ppm
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20
40
60
80
100
120
140
160
180
200

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7.262
7.275
7.278
7.287
7.291
7.399
7.402
7.413
7.454
7.456
7.467
7.469
7.471
7.473
7.474
7.487
7.488
7.615
7.619
7.629
7.635
7.921
7.922
7.937
7.938
9.433
10.166
5{21}
CHO
N
H
ppm
0
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2
3
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6
7
8
9
10
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0.99
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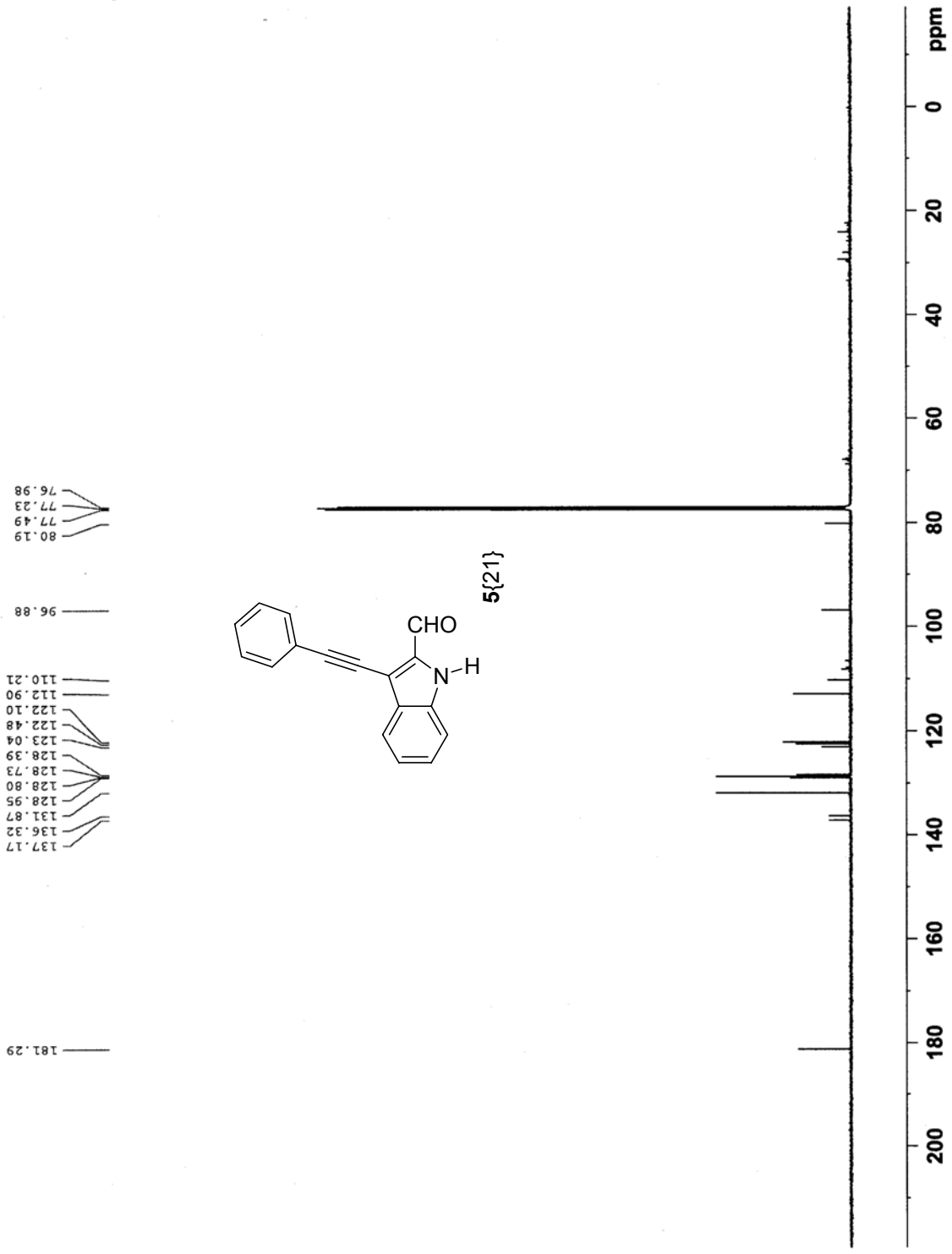
1.00


ppm
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60
80
100
120
140
160
180
200
CHO
N
H
5{21}
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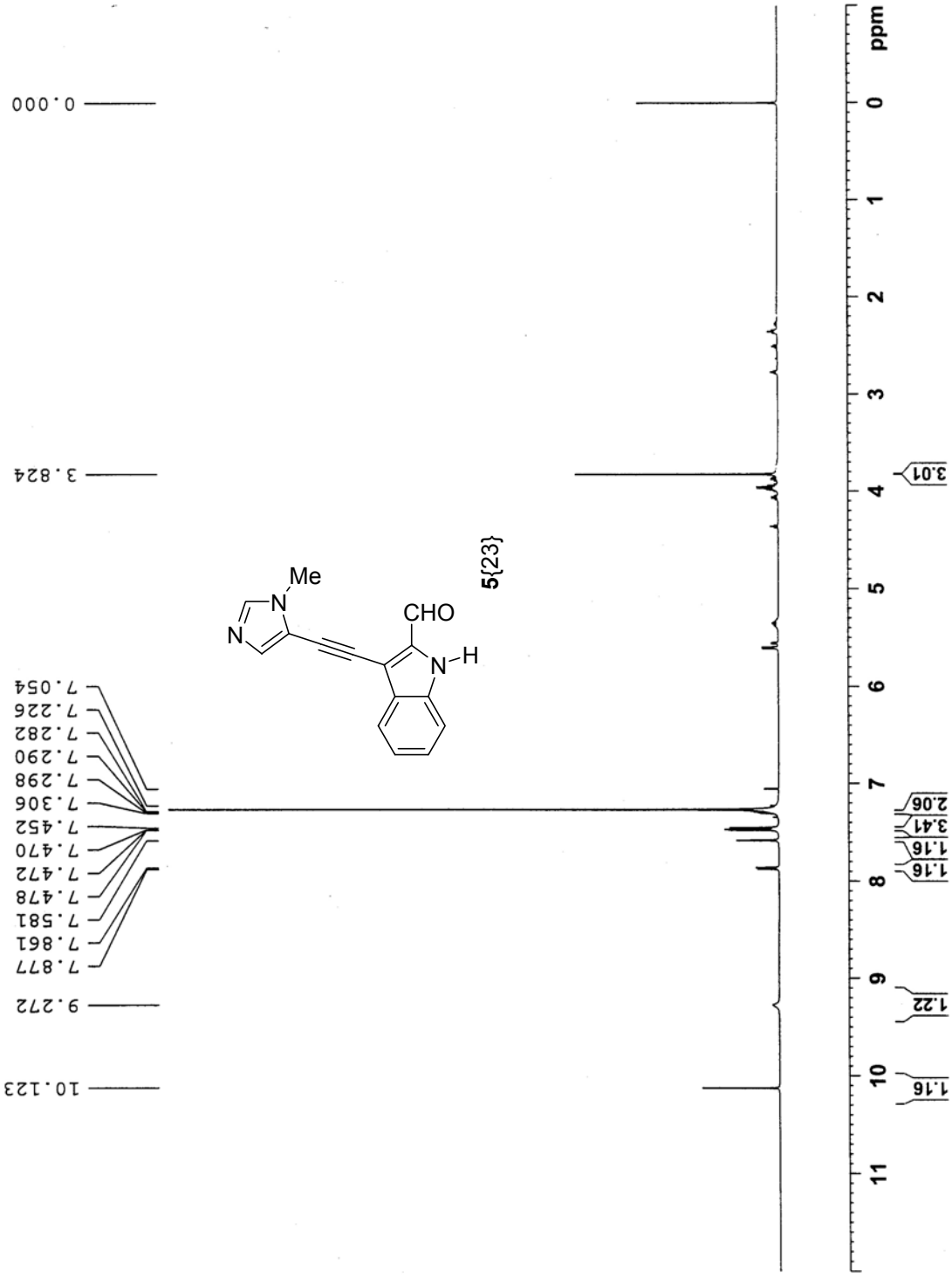
77.23
77.49
80.19
96.88
110.21
112.90
122.10
122.48
123.04
128.39
128.73
128.80
128.95
131.87
136.32
137.17
181.29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7.478
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7.470
7.452
7.306
7.298
7.290
7.282
7.226
7.054
Me
N
N
CHO
N
H
5{23}
ppm
0
1
2
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5
6
7
8
9
10
11
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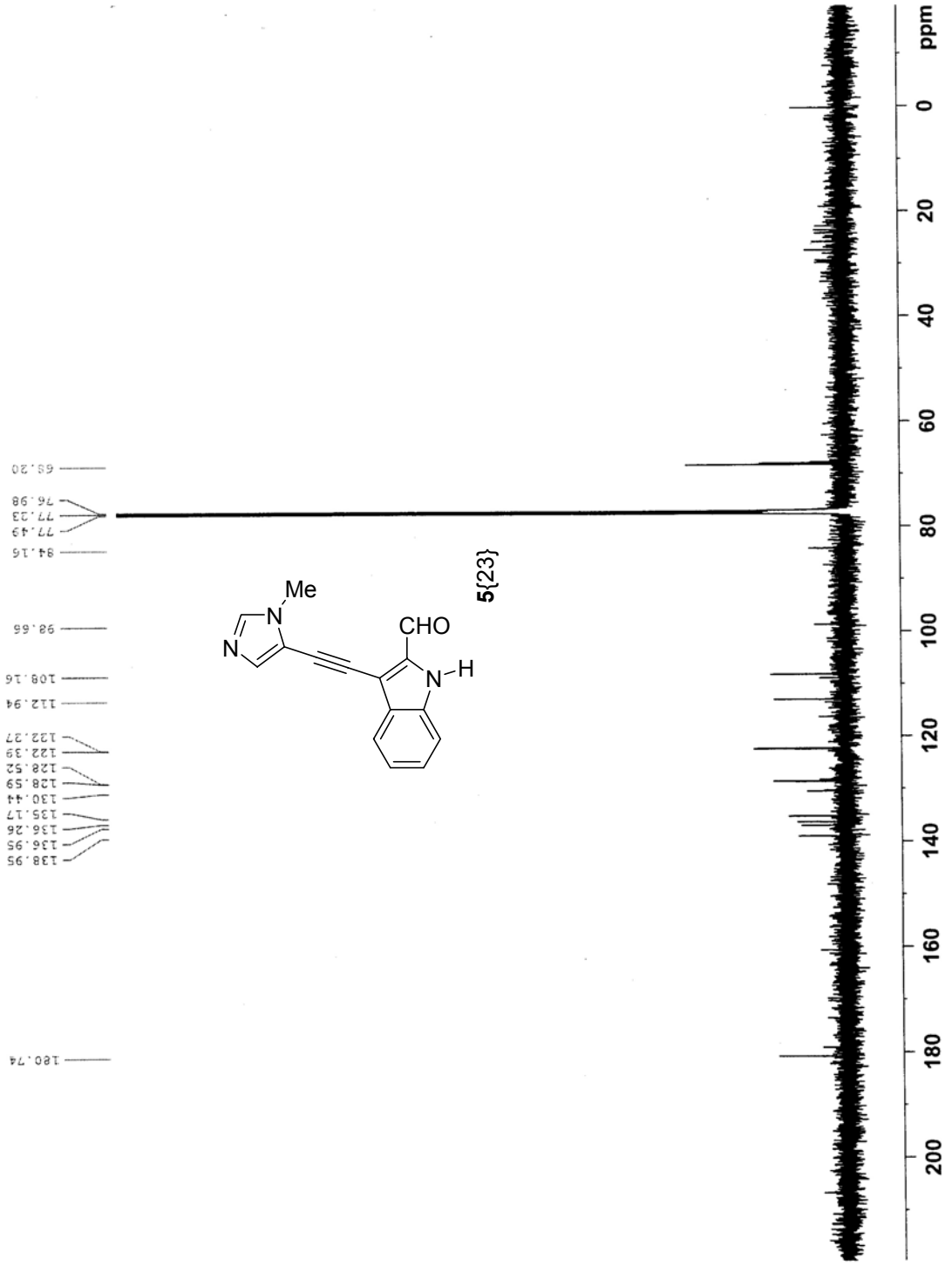
2.06
3.41
1.16
1.16
1.22
1.16


Me
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N
CHO
N
H
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ppm
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60
80
100
120
140
160
180
200
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76.98
77.23
77.49
84.16
98.66
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112.94
122.27
122.39
128.52
128.59
130.44
135.17
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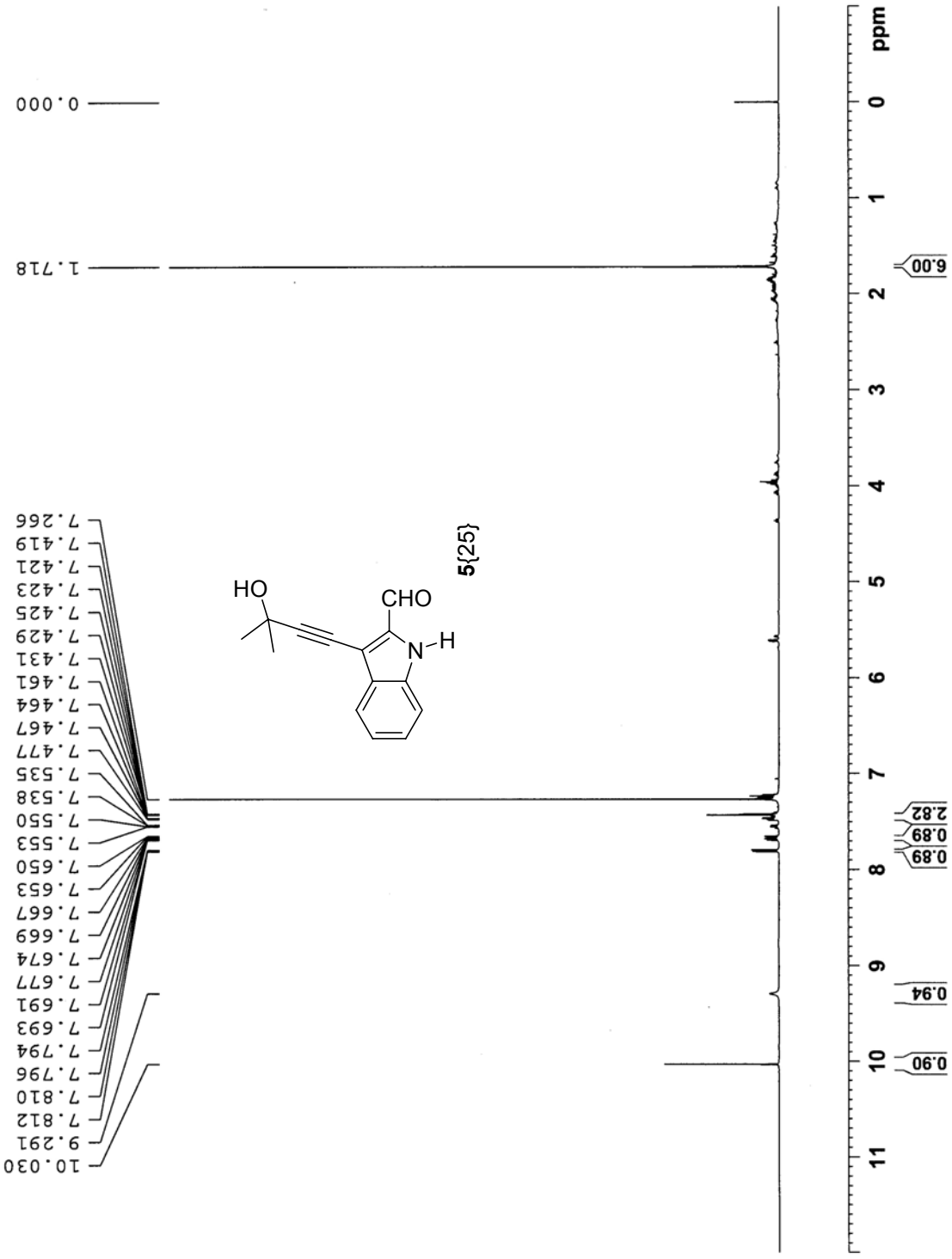
136.95
138.95
180.74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7.691
7.677
7.674
7.669
7.667
7.653
7.650
7.553
7.550
7.538
7.535
7.477
7.467
7.464
7.461
7.431
7.429
7.425
7.423
7.421
7.419
7.266
1.718
0.000
HO
CHO
N
H
5{25}
ppm
0
1
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6
7
8
9
10
11
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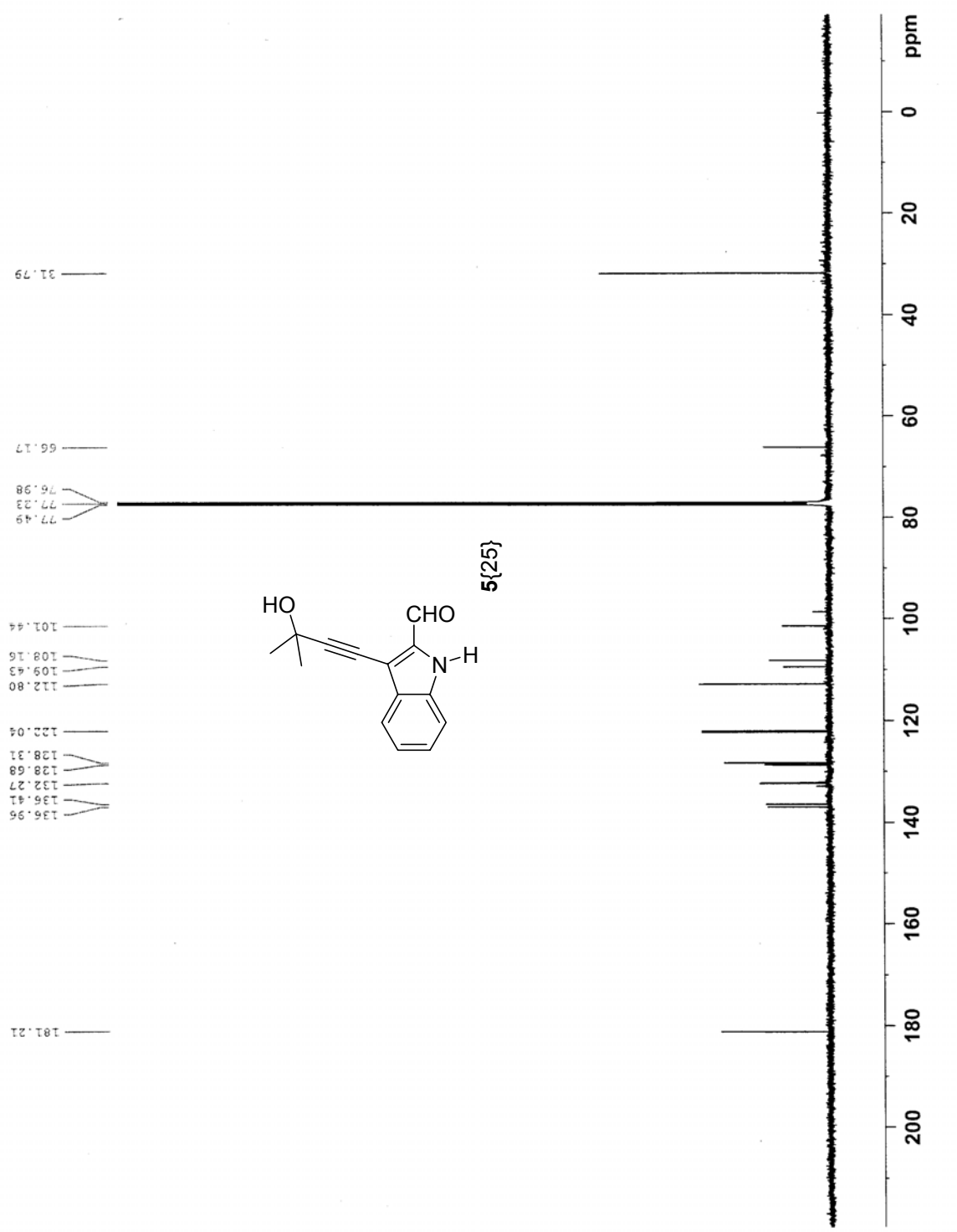
0.90


ppm
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60
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100
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140
160
180
200
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76.98
77.33
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101.44
108.16
109.43
112.80
122.04
128.31
128.68
132.27
136.41
136.96
181.21
HO
CHO
N
H
5{25}

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3.674
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6.816
6.821
6.832
6.838
7.161
7.176
7.178
7.196
7.198
7.208
7.213
7.225
7.230
7.248
7.276
7.279
7.293
7.296
7.299
7.311
7.316
7.320
7.322
7.323
7.329
7.335
7.353
7.356
7.364
7.369
7.374
7.383
7.387
7.394
7.415
7.747
7.767
MeO
N
Me
5{30}
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6
7
8
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3.08
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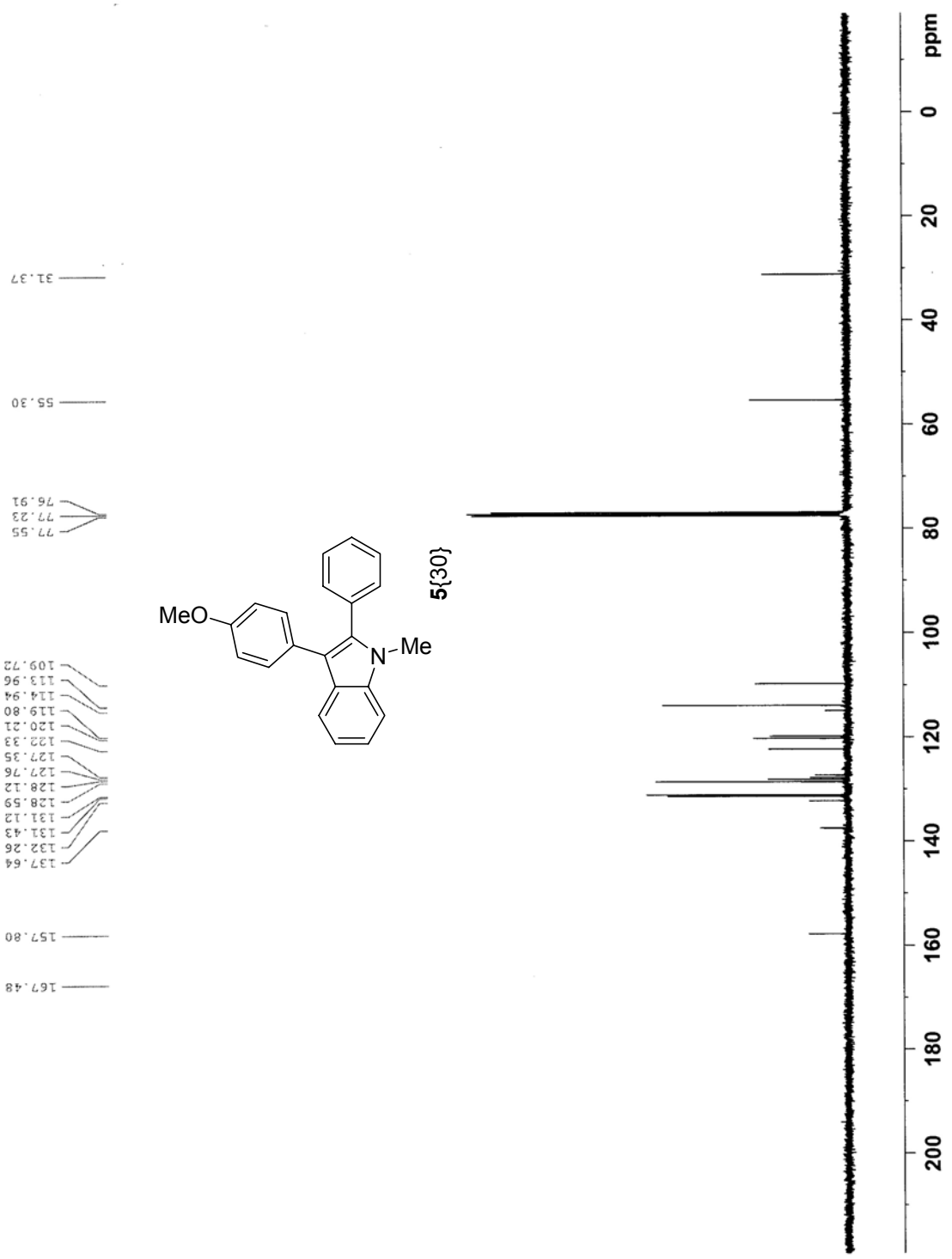
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N
Me
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ppm
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60
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140
160
180
200
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76.91
77.23
77.55
109.72
113.96
114.94
119.80
120.21
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127.76
128.12
128.59
131.12
131.43
132.26
137.64
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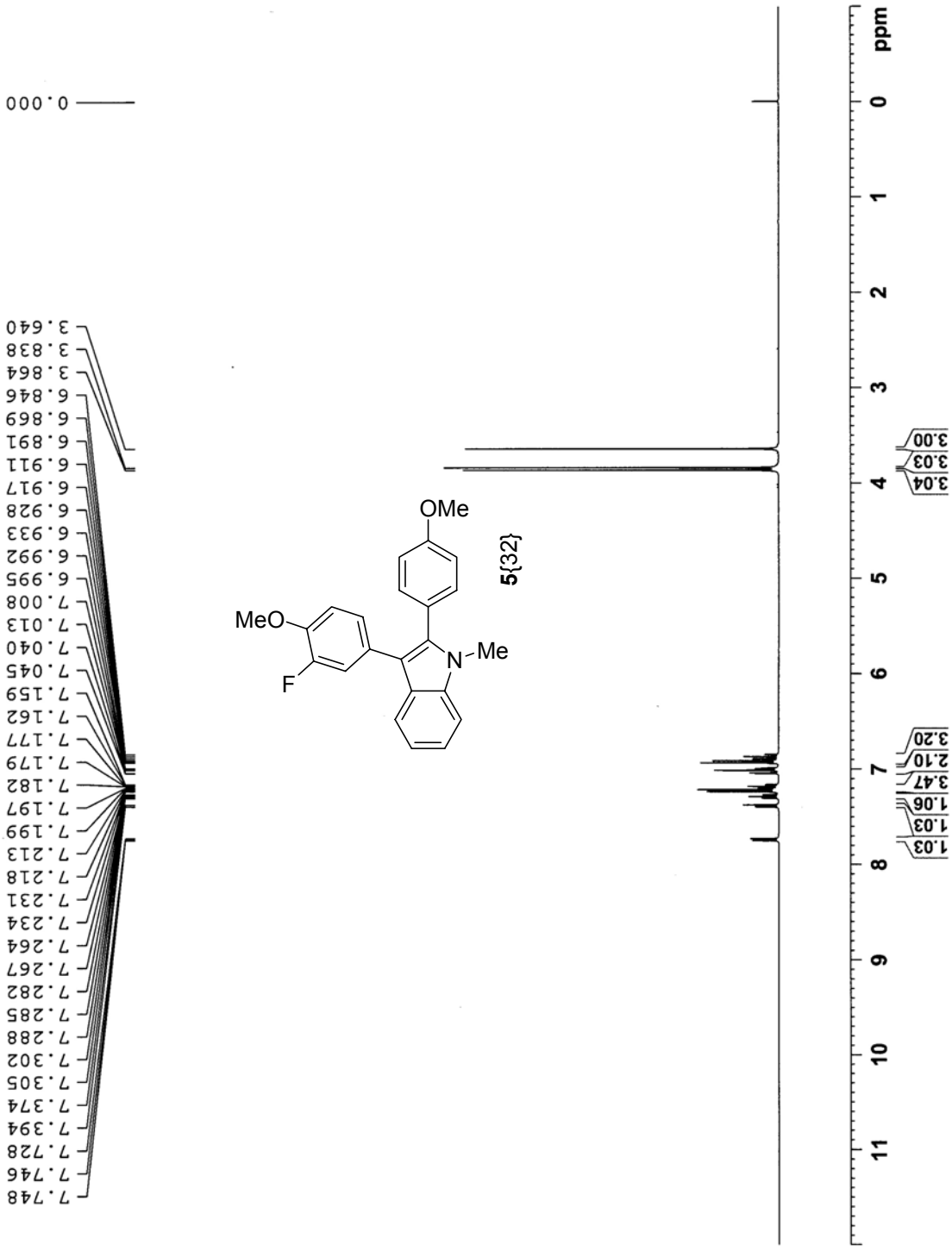
167.48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6.846
6.869
6.891
6.911
6.917
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6.933
6.992
6.995
7.008
7.013
7.040
7.045
7.159
7.162
7.177
7.179
7.182
7.197
7.199
7.213
7.218
7.231
7.234
7.264
7.267
7.282
7.285
7.288
7.302
7.305
7.374
7.394
7.728
7.746
7.748
OMe
MeO
F
N
Me
5{32}
ppm
0
1
2
3
4
5
6
7
8
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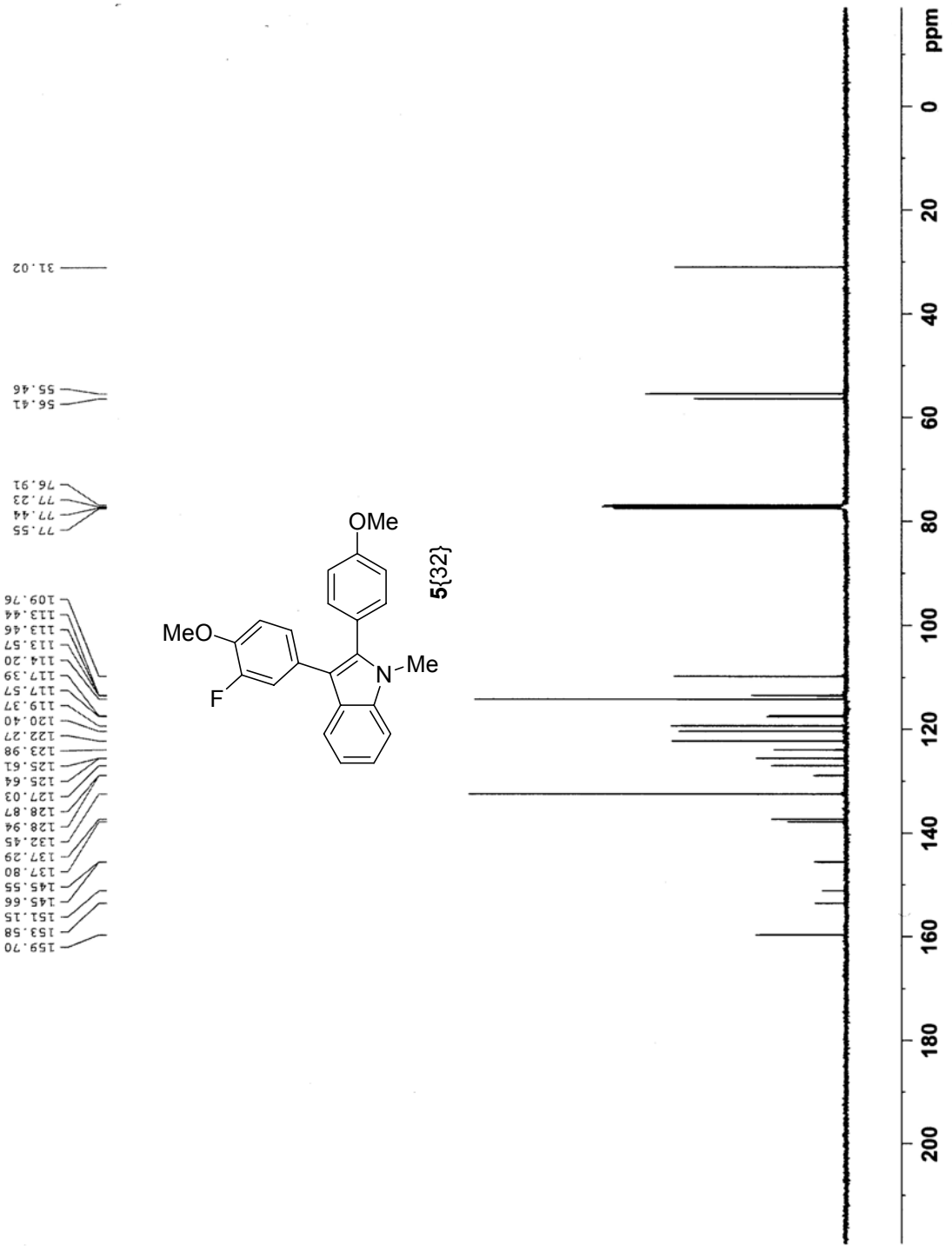
11
3.04
3.03
3.00
1.03
1.03
1.06
3.47
2.10
3.20


OMe
MeO
F
N
Me
5{32}
ppm
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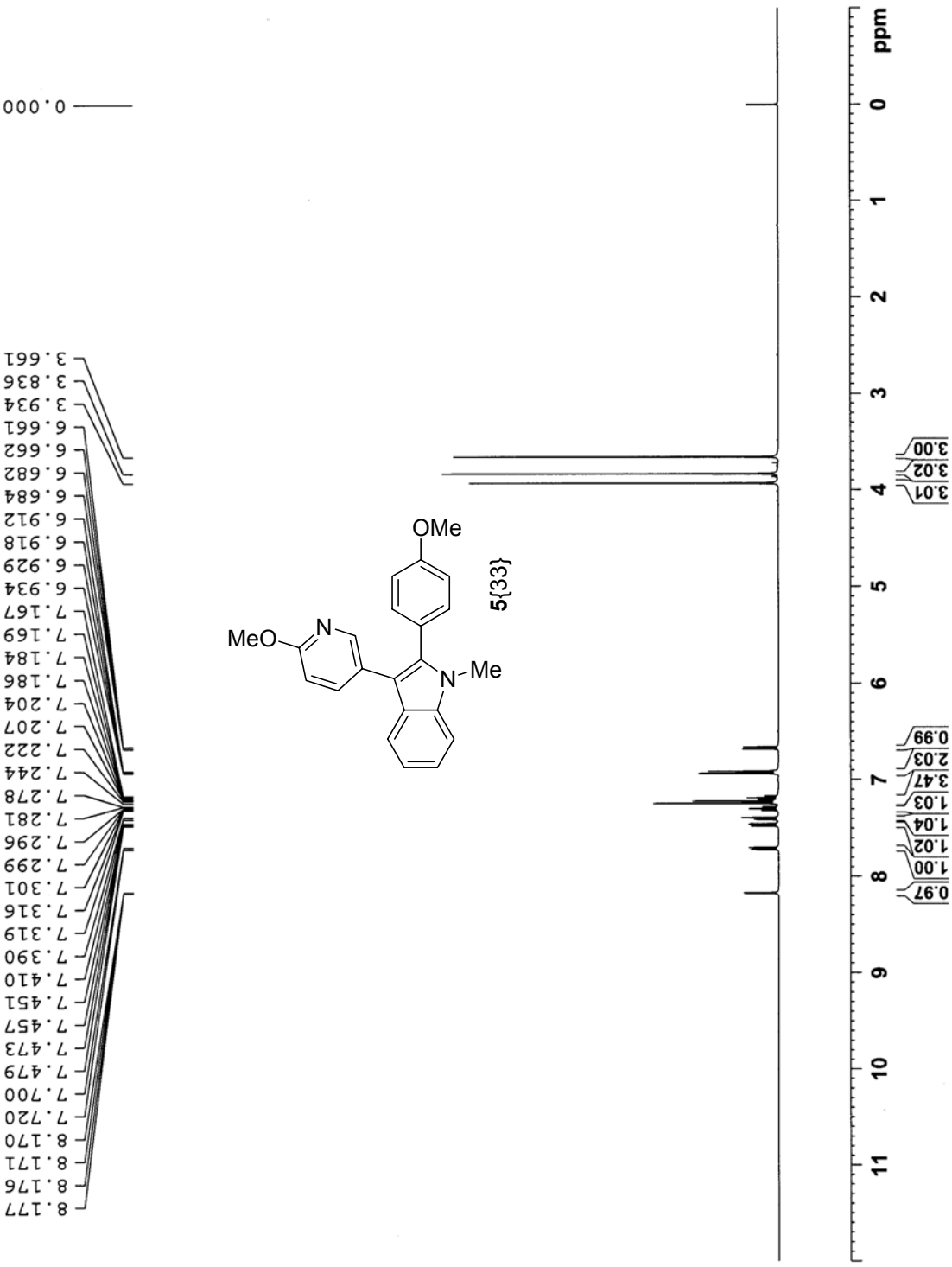
20
40
60
80
100
120
140
160
180
200
31.02
55.46
56.41
76.91
77.23
77.44
77.55
109.76
113.44
113.46
113.57
114.20
117.39
117.57
119.37
120.40
122.27
123.98
125.61
125.64
127.03
128.87
128.94
132.45
137.29
137.80
145.55
145.66
151.15
153.58
159.70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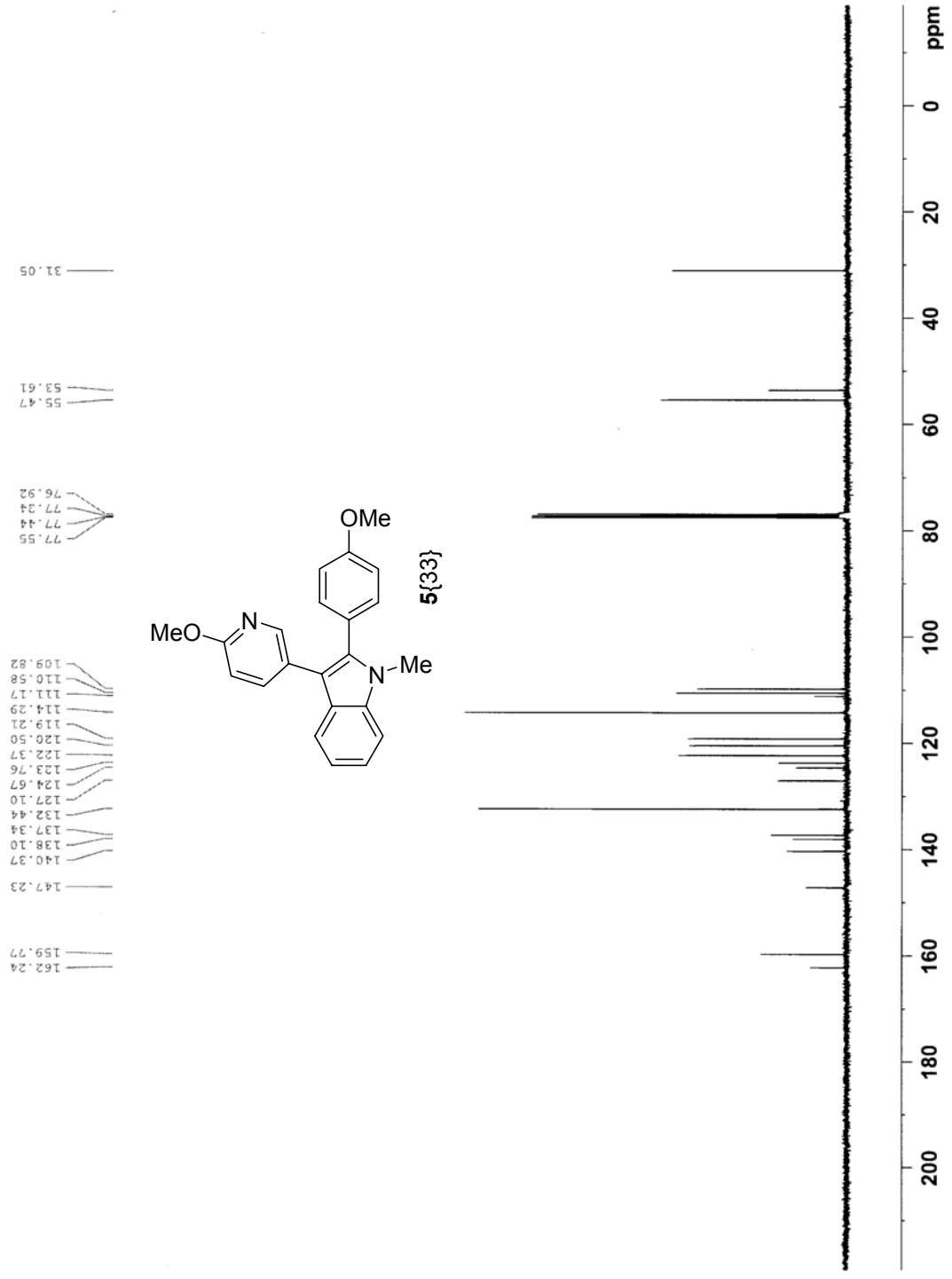
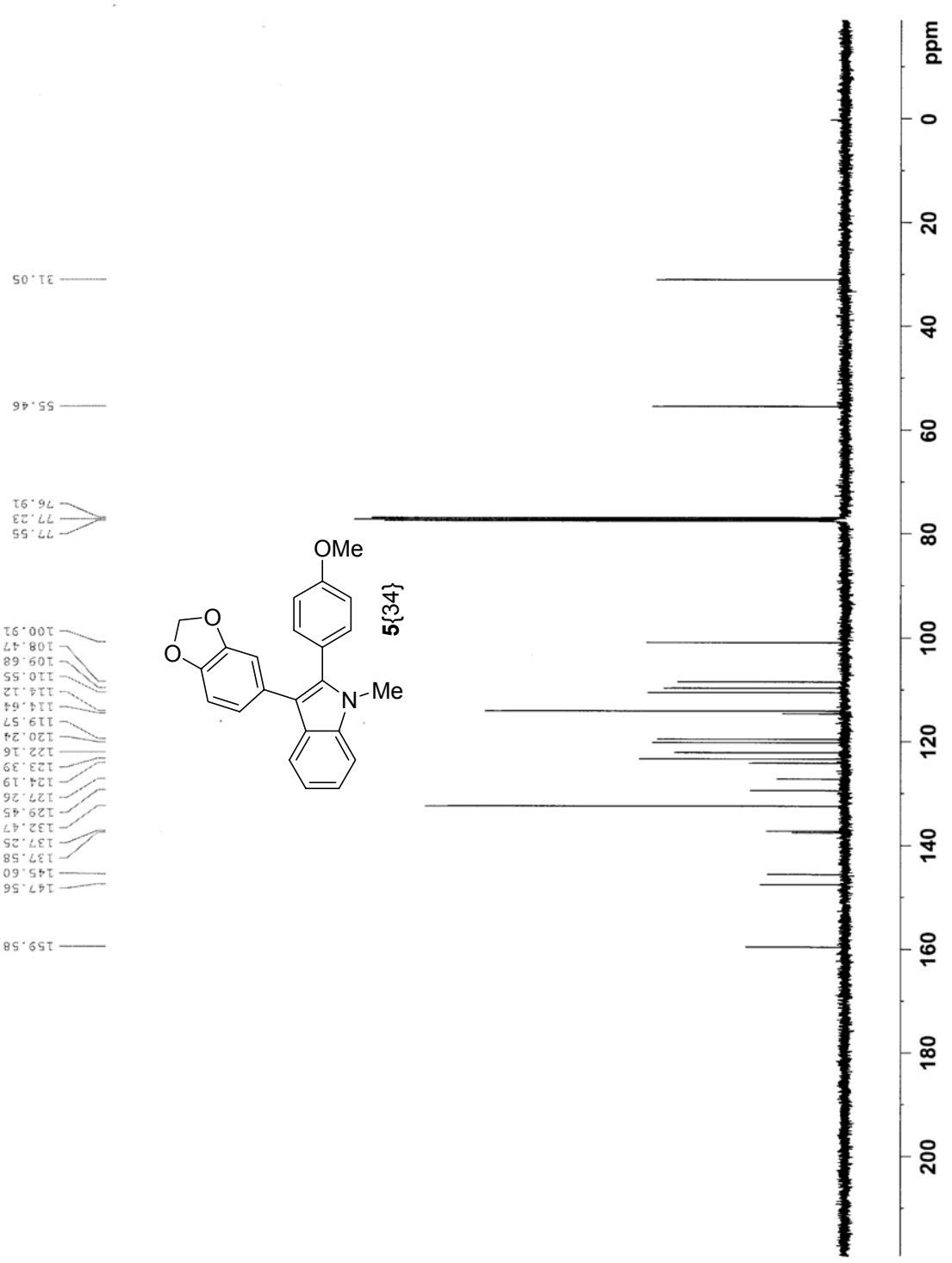
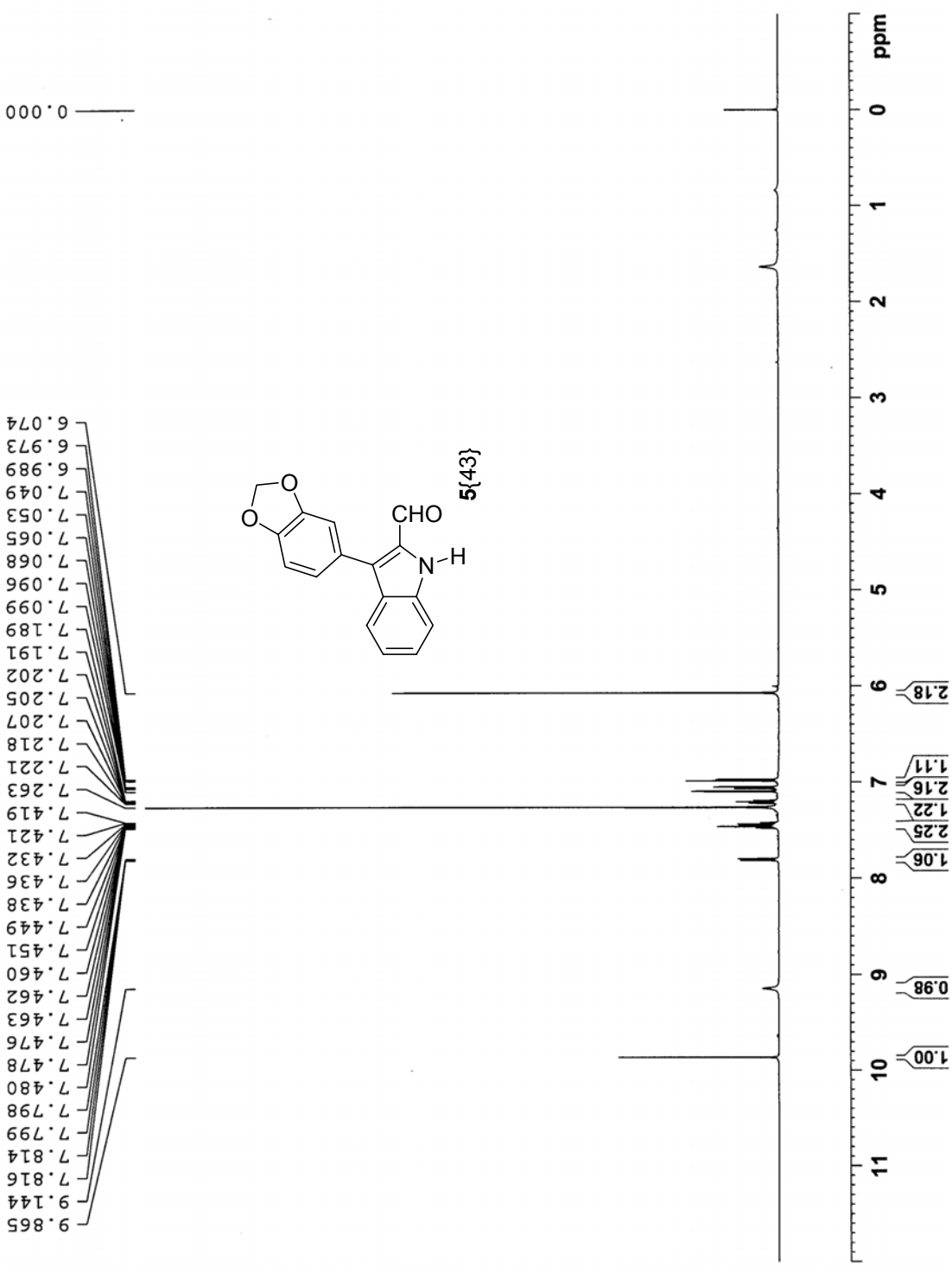
3.661
3.836
3.934
6.661
6.662
6.682
6.684
6.912
6.918
6.929
6.934
7.167
7.169
7.184
7.186
7.204
7.207
7.222
7.244
7.278
7.281
7.296
7.299
7.301
7.316
7.319
7.390
7.410
7.451
7.457
7.473
7.479
7.700
7.720
8.170
8.171
8.176
8.177
OMe
MeO
N
N
Me
5{33}
ppm
0 1 2 3 4 5 6 7 8 9 10 11
3.01
3.02
3.00
0.99
2.03
3.47
1.03
1.04
1.02
1.00
0.97


OMe
MeO
N
N
Me
5{33}
31.05
53.61
55.47
76.92
77.34
77.44
77.55
109.82
110.58
111.17
114.29
119.21
120.50
122.37
123.76
124.67
127.10
132.44
137.34
138.10
140.37
147.23
159.77
162.24
ppm
0
20
40
60
80
100
120
140
160
180
200

0.000
3.646
3.841
5.920
6.757
6.759
6.775
6.911
6.933
7.169
7.227
7.232
7.242
7.249
7.279
7.371
7.727
7.747
OMe
N
Me
O
O
5{34}
ppm
0
1
2
3
4
5
6
7
8
9
10
11
3.03
3.06
2.00
2.96
2.02
4.47
1.03
1.00


OMe
O
O
N
Me
5{34}
ppm
0
20
40
60
80
100
120
140
160
180
200
31.05
55.46
76.91
77.23
77.55
100.91
108.47
109.68
110.55
114.12
114.64
119.57
120.24
122.16
123.39
124.19
127.26
129.45
132.47
137.25
137.58
145.60
147.56
159.58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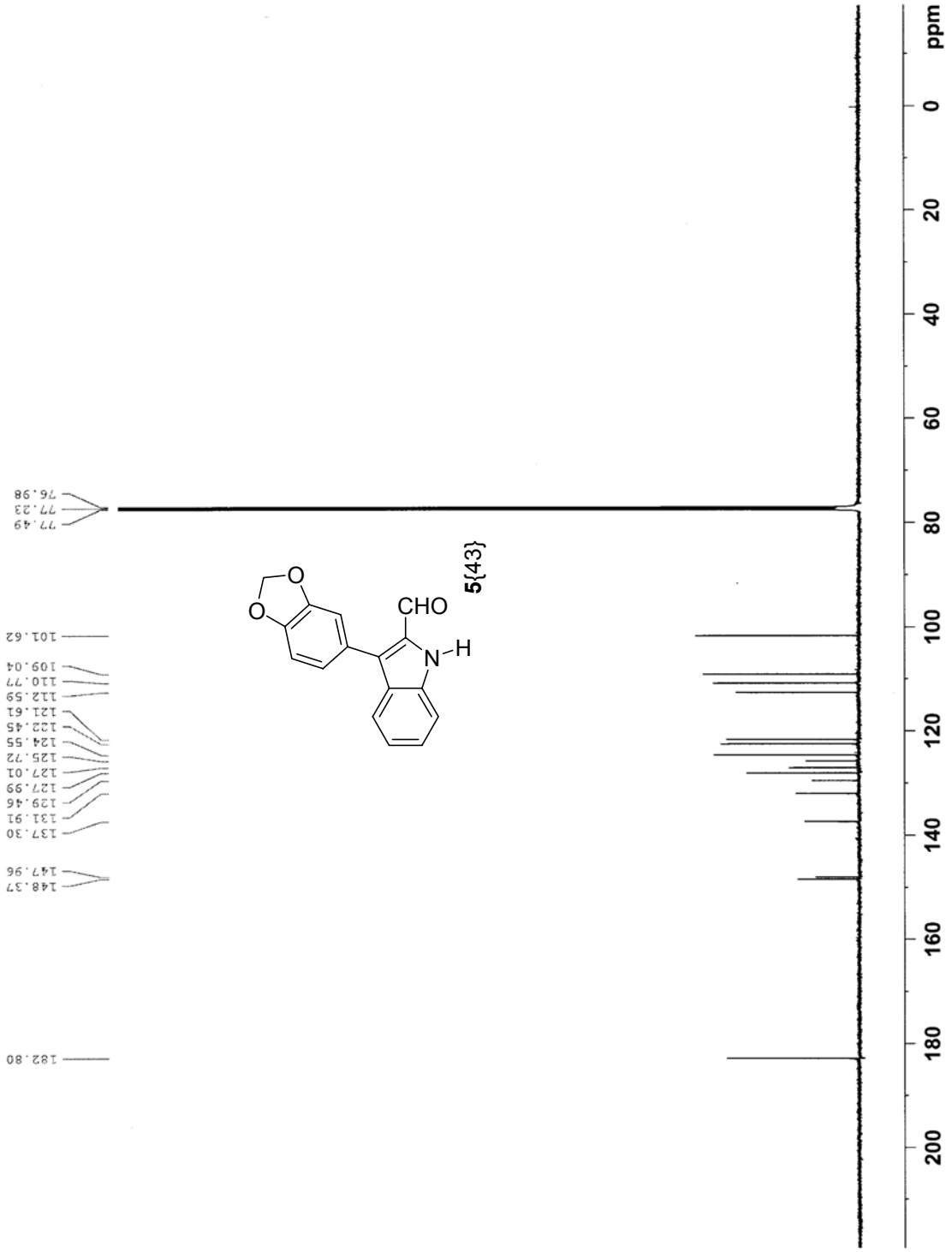
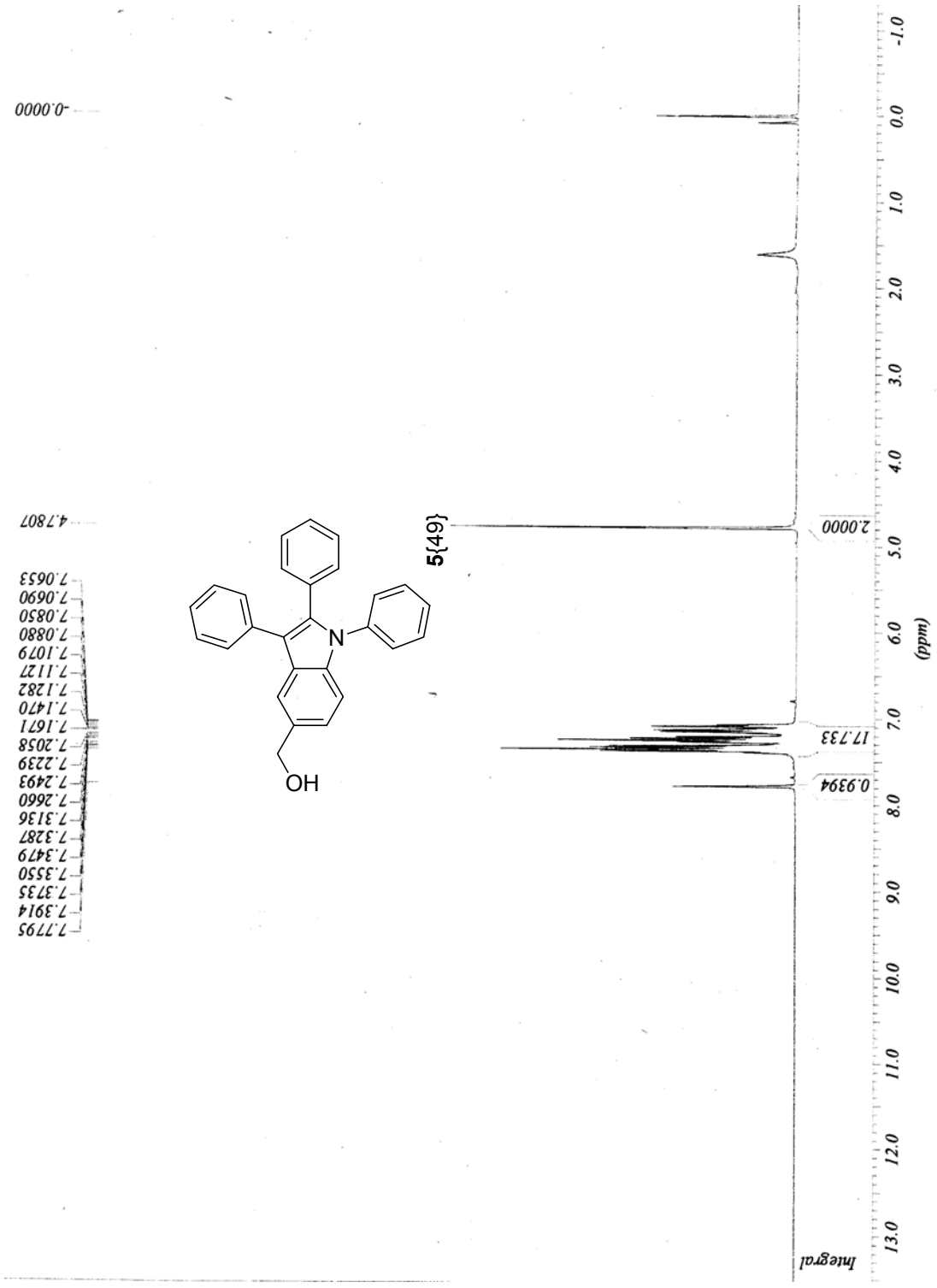
9.865
9.144
7.816
7.814
7.799
7.798
7.480
7.478
7.476
7.463
7.462
7.460
7.451
7.449
7.438
7.436
7.432
7.421
7.419
7.263
7.221
7.218
7.207
7.205
7.202
7.191
7.189
7.099
7.096
7.068
7.065
7.053
7.049
6.989
6.973
6.974
O
O
O
CHO
N–H
5{43}
ppm
0
1
2
3
4
5
6
7
8
9
10
11
2.18
1.11
2.16
1.22
2.25
1.06
0.98
1.00


ppm
0
20
40
60
80
100
120
140
160
180
200
77.49
77.23
76.98
101.62
109.04
110.77
112.59
121.61
122.45
124.55
125.72
127.01
127.99
129.46
131.91
137.30
147.96
148.37
182.80
CHO
N
H
O
O
5{43}


5{49}
N
OH
Integral
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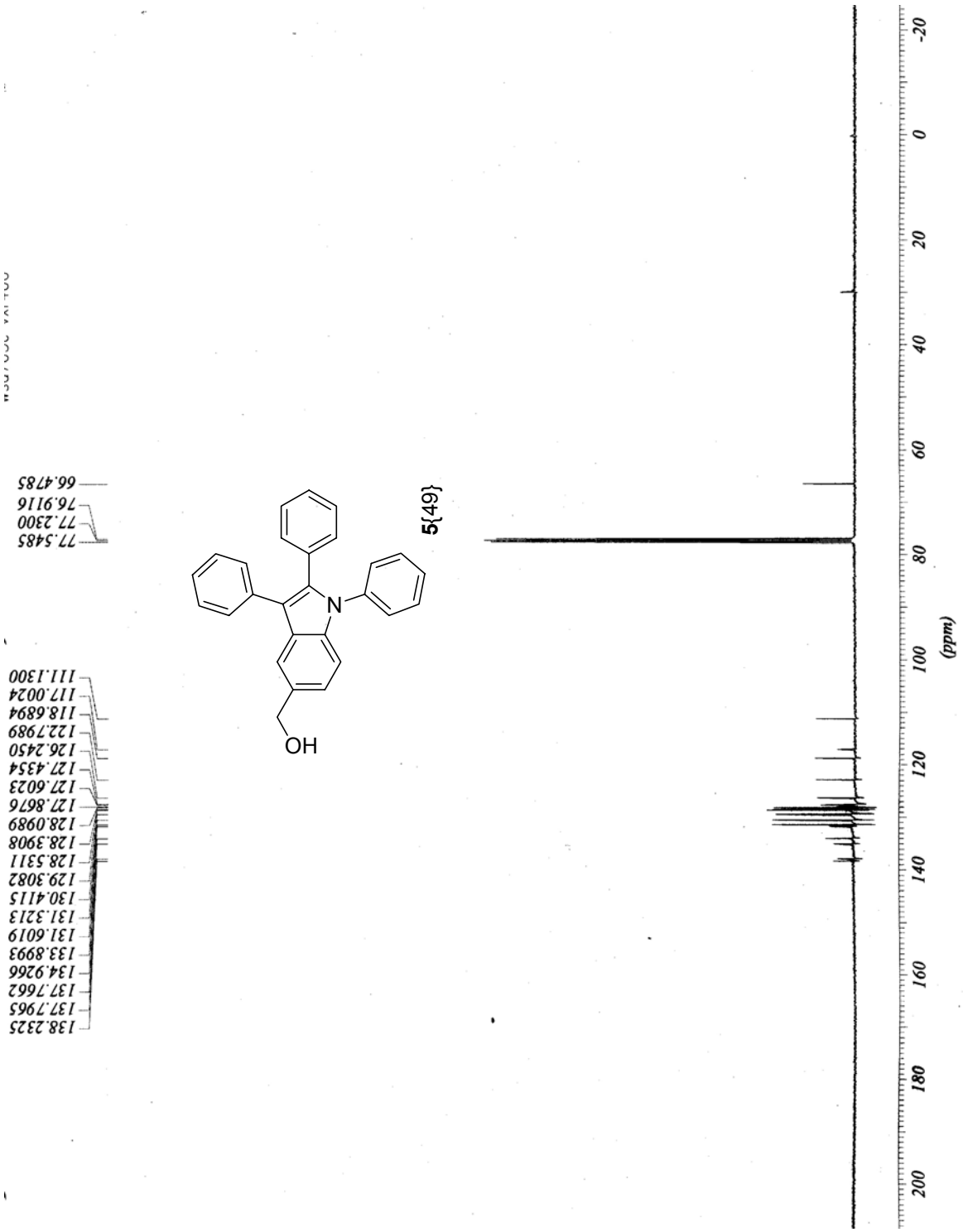
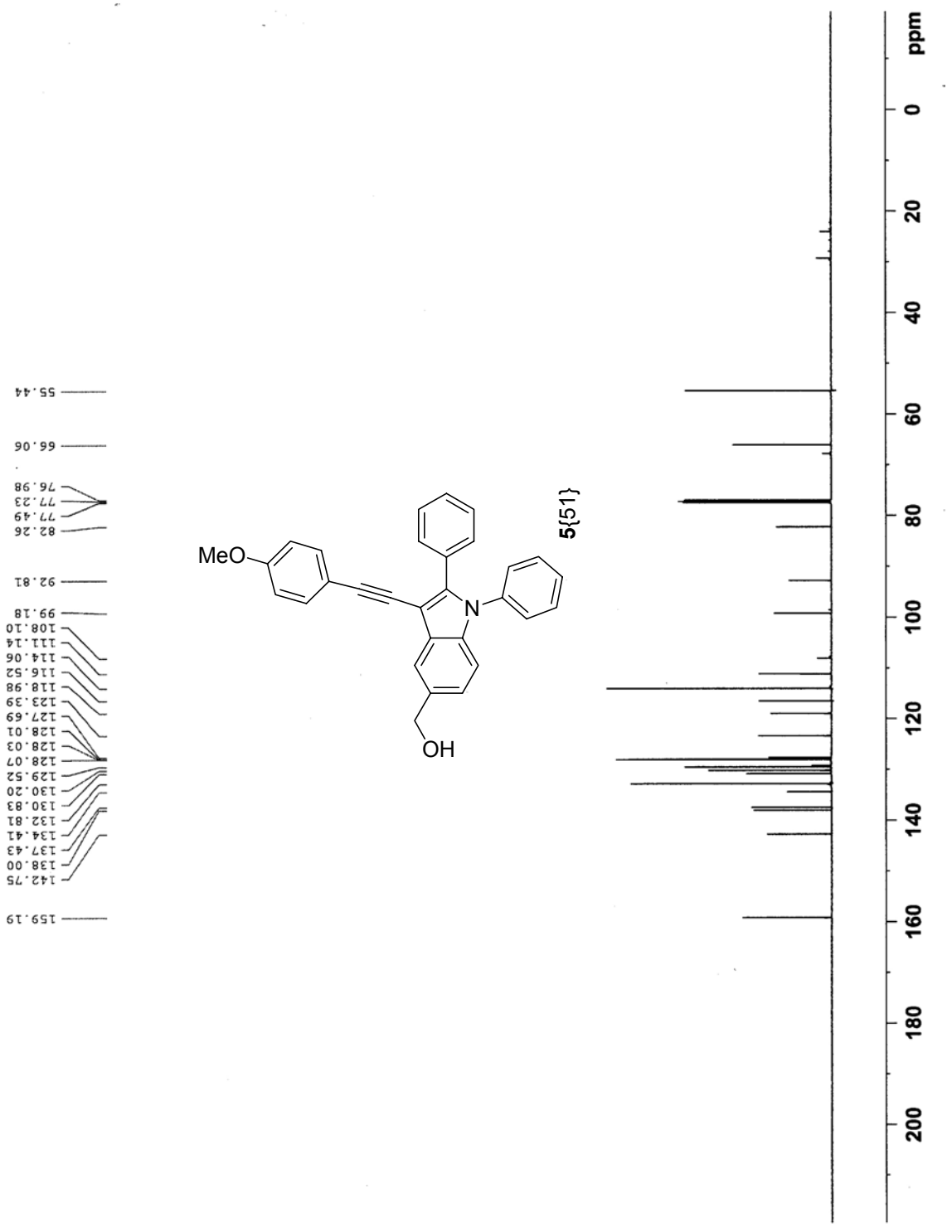
0.9394
4.7807
0.0000
7.7795
7.3914
7.3735
7.3550
7.3479
7.3287
7.3136
7.2660
7.2493
7.2239
7.2058
7.1671
7.1470
7.1282
7.1127
7.1079
7.0880
7.0850
7.0690
7.0653
(ppm)


5{49}
OH
N
66.4785
76.9116
77.2300
77.5485
111.1300
117.0024
118.6894
122.7989
126.2450
127.4354
127.6023
127.8676
128.0989
128.3908
128.5311
129.3082
130.4115
131.3213
131.6019
133.8993
134.9266
137.7662
137.7965
138.2325
(ppm)

ppm
0
1
2
3
4
5
6
7
8
9
10
11
4.00
2.00
0.95
2.06
2.07
1.77
2.71
3.02
1.97
0.92
2.02
5{50}
O
O
N
OH
0.001
7.761
7.759
7.369
7.355
7.352
7.339
7.309
7.306
7.292
7.250
7.246
7.232
7.229
7.204
7.201
7.187
7.152
7.149
7.145
7.137
7.134
7.095
7.092
7.079
7.075
6.945
6.941
6.806
6.789
6.761
6.757
6.745
6.740
4.767
4.274
4.272
4.262
4.261
4.251
4.248

64.53
66.33
68.15
76.98
77.23
77.49
108.10
110.99
116.36
117.31
118.67
118.90
122.72
123.70
127.32
127.53
127.90
128.06
128.33
129.25
131.25
131.58
133.79
137.47
137.56
138.22
142.14
143.46
O
O
N
OH
5{50}
200
180
160
140
120
100
80
60
40
20
0
ppm

0.000
3.779
4.806
6.834
6.839
6.848
6.852
7.186
7.200
7.203
7.219
7.231
7.233
7.239
7.251
7.256
7.269
7.271
7.316
7.330
7.355
7.358
7.368
7.371
7.385
7.423
7.427
7.437
7.441
7.460
7.462
7.465
7.475
7.479
7.875
MeO
N
OH
5{51}
ppm
0
1
2
3
4
5
6
7
8
9
10
11
3.00
2.03
1.94
9.20
2.14
4.10
0.95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76.98
77.23
77.49
82.26
92.81
99.18
108.10
111.14
114.06
116.52
118.98
123.39
127.69
128.01
128.03
128.07
129.52
130.20
130.83
132.81
134.41
137.43
138.00
142.75
159.19
MeO
N
OH
5{51}
ppm
0
20
40
60
80
100
120
140
160
180
200