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Prekinamycin and an Isosteric-Isoelectronic Analogue Exhibit Comparable Cytotoxicity Towards K562 Human Leukemia Cells

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Supplementary Information

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1. Theoretical calculations

All computations were performed at the DFT level of theory employing the hybrid density functional B3LYP[1, 2] (Becke three-parameter Lee-Yang-Parr exchange-correlation functional) and the 6-31G(d) basis set[3] (a valence double-zeta polarized basis set) using the suite of programs accessible in the commercially available software package Gaussian 03 by Gaussian Inc. (Copyright © 1994-2003, Gaussian, Inc)[4] installed on a desktop computer running the Linux operating system (Redhat Enterprise Linux 4). Unless otherwise stated, all calculations were carried out in the gas phase at T = 298.15 K and P = 1 atm.

2. Cell culture and growth inhibition assays

Human leukemia K562 cells, obtained from the American Type Culture Collection, were maintained as suspension cultures in Dulbecco's modified Eagle's medium (Invitrogen, Burlington, Canada) containing 4 mM L-glutamine and supplemented with 20 mM Hepes, 10% fetal calf serum (Invitrogen), 100 units/ml penicillin G, and 100 μg/ml streptomycin in an atmosphere of 5% CO2 and 95% air at 37 °C (pH 7.4).

For the measurement of growth inhibition, K562 cells in exponential growth were harvested and seeded at 6000 cells/well in 96-well plates (100 μl/well). At 24 h later cells were treated with vehicle or various concentrations of kinamycin F and allowed to grow an additional 72 h. Kinamycin F was dissolved in DMSO and the final concentration of DMSO did not exceed 0.5% (v/v), which was an amount that was shown not to affect cytotoxicity. After treatment cells were assayed with the MTS CellTiter 96 Aqueous One Solution Cell Proliferation assay (Promega, Madison, WI). The spectrophotometric 96-well plate cell growth inhibition assay measures the ability of the cells to enzymatically reduce MTS. Three replicates were measured at each drug concentration and the IC_{50}-values for growth inhibition were measured by fitting the absorbance–drug concentration data to a three-or four-parameter logistic equation as described.[5] The IC_{50} data reported are the results of three such experiments carried out on three separate days.

3. General procedures

Materials and Methods. All reactions were carried out under an atmosphere of nitrogen and/or argon in flame-dried and/or oven-dried glassware with magnetic stirring unless otherwise stated. Where required, the purification of solvents and reagents was accomplished according to standard procedures.[6] All solvents were reagent grade unless otherwise stated. Dichloromethane and triethylamine were distilled from calcium hydride. DMSO was distilled from calcium hydride under reduced pressure. Toluene was distilled from sodium benzophenone ketyl. Dimethylformamide was pre-dried with calcium hydride and distilled under reduced pressure from 3Å molecular sieves and stored over 3Å molecular sieves. Alternatively, solvents were purified using the M. Braun Solvent Purification System.
All commercial reagents used were purchased from the Aldrich Chemical Co. or VWR Canada (EMD, BDH, Alfa Aesar and J.T. Baker) and were used as received unless otherwise stated. Reactions were monitored by analytical thin layer chromatography (TLC) with silica coated aluminum sheets (EMD TLC Silica gel 60 F_{254}). Visualization was accomplished using UV light (254 nm) or basic $KMnO_4$ stain. Unless otherwise stated, purification of crude reaction products was carried out using flash silica gel chromatography (Silicycle SiliaFlash® P60 40-63 μm, 230-400 mesh) according to established procedures.[7] All reported yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated.

Characterization Methods. In some instances, compounds previously reported in the literature in which the characterization data was insufficient are reported here with a more complete characterization data set. Melting points were obtained on a MEL-TEMP® apparatus (Laboratory Devices Inc., Holliston MA, USA) and are uncorrected. ^{1}H NMR NMR spectra were acquired on a Brüker AC300 (300 MHz), Brüker AVANCE300 (300 MHz) or Brüker AVANCE500 (500 MHz) spectrometer and are reported in parts per million (ppm) in either CD_2Cl_2 or $CDCl_3$ using the solvent residual peak as the internal standard. For $CDCl_3$ this was 7.24 and 77.0 ppm for ^{1}H NMR and ^{13}C NMR, respectively. Data are reported as chemical shift in ppm, integrated intensity; peak multiplicities; coupling constants *J* (Hz) and assignment. The following abbreviations are used for reporting peak multiplicities: br = broad, w = weak, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet. ^{13}C NMR spectra were broadband decoupled and acquired on Brüker AC300 (75.5 MHz), Brüker AVANCE300 (75.5 MHz) or Brüker AVANCE500 (125.8 MHz) spectrometers and are reported in ppm in CD_2Cl_2 or $CDCl_3$, using the carbon signal of the deuterated solvent as the internal standard. Infrared spectra (IR) were recorded on a Perkin Elmer Spectrum RX I FT-IR System spectrometer either as thin films on a NaCl plate, or as a KBr pellet or as a solution in $CDCl_3$ using an IR solution cell with 0.1 mm path length and CaF_2 windows. Low and high resolution mass spectra were recorded in electron impact (EI) mode, chemical ionization (CI) mode and/or electrospray ionization (ESI) mode obtained at the WATSPEC mass spectrometry facilities, University of Waterloo, Waterloo, Ontario, Canada.

4. Experimental procedures

1,5-Dimethoxynaphthalene. From a modification of a known procedure,[8] a solution of 1,5-dihydroxynaphthalene (**14**) (10.155 g, 0.0596 mol) was dissolved in acetone (850 mL) by vigorous stirring to which was added anhydrous K_2CO_3 (101.186 g, 0.732 mol) followed by dimethyl sulfate (84 mL, 0.888 mol). The mixture was heated at reflux (60 °C oil bath) for 22 h. The solution was cooled to room temperature and filtered through a sintered glass funnel. Triethylamine (50 mL) was added to the filtrate and the mixture was evaporated to dryness on a rotary evaporator. The residue was taken up in dichloromethane (400 mL) and triethylamine (100 mL) and the mixture was stirred at room temperature for 15 min. This solution was then washed twice with 1 M HCl, once with brine, dried over Na_2SO_4, filtered and the solvent evaporated in vacuo to afford 11.07 g (99%) of the title compound as a brown solid. The crude naphthalene was typically taken to the next step without further purification: mp 174-176 °C (lit. value[9] 180-181 °C); IR (KBr, cm^{-1}) ν_{max} 3073, 3007, 2960, 2936, 2830, 1592, 1509, 1469, 1453, 1401, 1342, 1267, 1083, 865, 775; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.37 (2H, dd, *J* = 7.9, 8.3 Hz, Ar*H*), 6.84 (2H, d, *J* = 7.9 Hz, Ar*H*), 3.98 (6H, s, ArOCH_3); ^{13}C NMR (75.5 Hz, $CDCl_3$) δ 155.2, 126.6, 125.1, 114.2, 104.5, 55.5; MS *m/z* (rel. intensity) (EI) 188 (M^+, 100), 173 (57), 158 (3), 143 (7), 127 (4), 115 (38), 102 (8), 94 (3); HRMS (EI) calc. for $C_{12}H_{12}O_2$: 188.0837, found: 188.0836.

4,8-Dimethoxy-1-naphthaldehyde. Following a known procedure,[10] 1,5-dimethoxynaphthalene (18.77 g, 0.0997 mol), toluene (20 mL) and DMF (12 mL, 0.155 mol) were mixed together and cooled to 0 ºC. To this was added $POCl_3$ (12 mL, 0.129 mol) and stirring was continued for another hour. The mixture was then heated at 110 ºC for two hours, cooled to room temperature and poured into 300 mL of 10% NaOH containing 100 mL ice. The mixture was then extracted with benzene three times. The extracts were pooled, washed twice with 1 M HCl, twice with water, once with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to furnish 19.73 g (92%) of the title compound as a light orange solid that was of satisfactory purity for the next step. A small amount (0.1462 g) was purified by column chromatography (silica, 1:1 hexanes:ether) and recrystallized from ethanol to furnish fine white needles: mp 127-128 °C (lit. value[10] 125-126 °C); IR (KBr, cm^{-1}) ν_{max} 3073, 3025, 2971, 2908, 2838, 1663, 1587, 1517, 1465, 1412, 1330, 1270, 1225, 1064, 868, 828, 801, 765; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.03 (1H, s, C*H*O), 8.05 (1H, d, *J* = 8.3 Hz, Ar*H*), 7.93 (1H, dd, *J* = 0.7, 8.3 Hz, Ar*H*), 7.42 (1H, dd, *J* = 7.9, 8.3 Hz, Ar*H*), 7.01 (1H, d, *J* = 7.9 Hz, Ar*H*), 6.87 (1H, d, *J* = 8.3 Hz, Ar*H*), 4.03 (3H, s, OCH_3), 3.99 (3H, s, OCH_3); ^{13}C NMR (75.5 Hz, $CDCl_3$) δ 194.6, 159.5, 156.4, 129.3, 127.7, 127.1, 125.8, 124.7, 115.3, 107.8, 103.9, 55.9, 55.6; MS *m/z* (rel. intensity) (EI) 216 (M^+, 100), 215 (30), 201 (19), 185 (17), 173 (10), 143 (3), 115 (17), 102 (5); HRMS (EI) calc. for $C_{13}H_{12}O_3$: 216.0786, found: 216.0783.

4,8-Dimethoxynaphthalen-1-yl formate (15). Following a published procedure,[10] to a solution of naphthaldehyde (19.61 g, 0.0906 mol) in dichloromethane (900 mL) was added *m*CPBA (39.305 g at 75.7% assay, 0.172 mol). The solution was stirred vigorously at room temperature for 2 h 40 min. This solution was then poured into 10% $Na_2S_2O_3$ (700 mL) and stirred for 25 min. The aqueous layer was removed and water (900 mL) was added. The mixture was stirred

for 5 min and the aqueous layer removed. This sequence was repeated once more. The solution was then transferred to a separatory funnel and washed with a 10% solution of $Na_2S_2O_3$ twice with water washings between and three washings with saturated $NaHCO_3$ solution with water washings between, brine once, dried over Na_2SO_4, filtered and the solvent evaporated in vacuo producing 19.44 g (92%) of the crude formate as a brown solid. The crude material was employed in the next step without further purification. A small portion (0.587 g) was purified by column chromatography (silica, 2:1 hexanes:ether) to afford 0.224 g of the title compound as fine colourless needles: mp 136 °C (lit. value[11] 137-138.5 °C); IR (NaCl, film, cm^{-1}) ν_{max} 2938, 1737, 1599, 1516, 1449, 1411, 1378, 1267, 1148, 1125, 1061, 846, 789, 746; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (1H, s, C*H*O), 7.88 (1H, dd, *J* = 0.7, 8.3 Hz, Ar*H*), 7.39 (1H, dd, *J* = 8.0, 8.3 Hz, Ar*H*), 7.03 (1H, d, *J* = 8.3 Hz, Ar*H*), 6.89 (1H, d, *J* = 8.0 Hz, Ar*H*), 6.75 (1H, d, *J* = 8.3 Hz, Ar*H*), 3.97 (3H, s, ArOCH_3), 3.89 (3H, s, ArOCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.9, 154.9, 153.7, 138.9, 128.3, 126.2, 119.2, 118.8, 115.0, 107.1, 103.7, 55.82, 55.78; MS *m/z* (rel. intensity) (EI) 232 (M^+, 32), 204 (54), 189 (100), 174 (18), 161 (5), 146 (3), 118 (3), 102 (6); HRMS (EI) calc. for $C_{13}H_{12}O_4$: 232.0736, found: 232.0739.

4,8-Dimethoxynaphthalen-1-ol. Following a known procedure,[10] the crude formate **15** (24.39 g, 0.105 mol) obtained from the previous reaction was dissolved in a 1:1 mixture of degassed methanol/THF (750 mL) and stirred on ice at 0 ºC. Potassium hydroxide (17.186 g, 0.3063 mol) was dissolved in methanol (150 ml), extensively degassed, cooled to 0 ºC and added to the formate solution that was then stirred for 1 h. The reaction was quenched with 5% aq. HCl (130 mL) to obtain a pH ~2, poured into water (3 L) and extracted three times with dichloromethane. The organic extracts were pooled, washed twice with water and dried over sodium sulfate, filtered through a sintered funnel and the solvent evaporated in vacuo to yield 20.60 g of a dark brown solid. The crude naphthenol was purified by flash column chromatography (silica, $CHCl_3$) furnishing 13.646 g (64%) of the title compound as a pale yellow solid: mp 153-154 °C (lit. value[10] 155-156 °C); IR (NaCl, film, cm^{-1}) ν_{max} 3419, 2942, 1631, 1514, 1446, 1412, 1288, 1071, 815, 752; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (1H, s, ArO*H*), 7.84 (1H, dd, *J* = 0.8, 8.3 Hz, Ar*H*), 7.32 (1H, dd, *J* = 7.9, 8.3 Hz, Ar*H*), 6.82 (1H, d, *J* = 7.9 Hz, Ar*H*), 6.77, 6.75 (2H, AB_q, *J* = 8.5 Hz, *H*2, *H*3), 4.03 (3H, s, ArOCH_3), 3.92 (3H, s, ArOCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.9, 148.1, 147.9, 127.8, 125.1, 115.9, 115.5, 109.0, 106.3, 104.9, 56.1, 55.9; MS *m/z* (rel. intensity) (EI) 204 (M^+, 82), 189 (100), 174 (19), 161 (5), 146 (3), 131 (2), 118 (4), 102 (5); HRMS (EI) calc. for $C_{12}H_{12}O_3$: 204.0786, found: 204.0780.

2-Bromo-4,8-dimethoxynaphthalen-1-ol. Following a published procedure,[10] the naphthenol (12.157 g, 0.0595 mol) obtained from the previous reaction was dissolved in CCl_4 (600 mL) and was stirred vigorously at room temperature. A separate flask was charged with bromine (9.746 g, 0.0609 mol) dissolved in CCl_4 (100 mL) which was immediately transferred to a dropping funnel. The flask was rinsed with two separate washings of CCl_4 (25 mL each) and these rinses were added to the dropping funnel to ensure quantitative transfer of bromine. The bromine solution was then added drop-wise to the stirred solution of naphthenol over the course of 2 h, after which stirring continued for another hour at which time a 20% solution of $Na_2S_2O_3$ (800 mL) was added and stirred for 10 min. This solution was transferred to a separatory funnel and the aqueous and organic layers separated. The aqueous layer was extracted three times with

CH_2Cl_2 and the extracts were pooled, washed twice with a 10% solution of $Na_2S_2O_3$, once with water, once with brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The same workup procedure was also applied to the CCl_4 layer. The crude products were pooled together to give 16.728 g (99%) of the title compound as a brown solid which was judged by ^{1}H NMR to be sufficiently pure for the following step. A small portion (0.1814 g) was by purified by column chromatography (silica, 2:1 hexanes:ether) to afford 0.1519 g of a white solid as fine needles: mp 138-139 °C (lit. value[10] 141-142 °C); IR (NaCl, film, cm^{-1}) ν_{max} 3358, 1609, 1509, 1398, 1294, 1238, 1068, 872, 820, 798, 771, 750; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (1H, s, ArO*H*), 7.79 (1H, d, *J* = 8.3 Hz, Ar*H*), 7.33 (1H, dd, *J* = 8.0, 8.3 Hz, Ar*H*), 6.92 (1H, s, Ar*H*), 6.86 (1H, d, *J* = 8.0 Hz, Ar*H*), 4.03 (3H, s, ArOCH_3), 3.90 (3H, s, ArOCH_3); ^{13}C NMR (75.5 Hz, $CDCl_3$) δ 155.1, 148.1, 144.4, 127.2, 125.6, 116.2, 115.6, 110.1, 106.1, 102.8, 56.4, 56.0; MS *m/z* (rel. intensity) (EI) 284 (M^+ for $C_{12}H_{11}{}^{81}BrO_3$, 99), 282 (M^+ for $C_{12}H_{11}{}^{79}BrO_3$, 100), 269 (83), 267 (85), 254 (5), 252 (6), 241 (4), 239 (5), 226 (2), 224 (2), 187 (7), 173 (9), 159 (3), 145 (10), 129 (4), 101 (3), 89 (3); HRMS (EI) calc. for $C_{12}H_{11}{}^{79}BrO_3$: 281.9892, found: 281.9888.

2-Bromo-1,4,8-trimethoxynaphthalene (16). To a stirred solution of 2-Bromo-4,8-dimethoxynaphthalen-1-ol (0.906 g, 3.2 mmol) in acetone (100 mL) was added K_2CO_3 (3.187 g, 23.1 mmol) and dimethyl sulfate (1.8 mL, 19 mmol). The mixture was heated at reflux (60 °C oil bath) for 21 h. The solution was cooled to ambient temperature, filtered through Celite 545 and the solvent evaporated on a rotary evaporator. The residue was dissolved in ether (50 mL) and triethylamine (5 mL) and the solution was stirred for 25 min. The solution was then washed with 10% HCl twice, water once, brine once and dried over $MgSO_4$, filtered and concentrated in vacuo to yield 1.155 g of dark orange brown solid that was purified by column chromatography (silica, 12:1 hexanes:ethyl acetate) affording 0.878 g (92%) of the title compound as a white solid: mp 81-82 °C (lit. value[12] 85-87 °C); IR (NaCl, film, cm^{-1}) ν_{max} 2934, 1576, 1508, 1450, 1413, 1337, 1326, 1267, 1071, 1006, 970, 874; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (1H, d, *J* = 8.3 Hz, Ar*H*), 7.37 (1H, dd, *J* = 8.0, 8.3 Hz, Ar*H*), 6.94 (1H, d, *J* = 8.0 Hz, Ar*H*) overlapping with 6.93 (1H, s, Ar*H*), 3.97 (3H, s, ArOCH_3), 3.93 (3H, s, ArOCH_3), 3.83 (3H, s, ArOCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.4, 151.7, 146.7, 128.1, 126.0, 121.2, 114.9, 114.1, 108.9, 107.9, 61.6, 56.4, 55.9; MS *m/z* (rel. intensity) (EI) 298 (M^+ for $C_{13}H_{13}{}^{81}BrO_3$, 98), 296 (M^+ for $C_{13}H_{13}{}^{79}BrO_3$, 100), 283 (23), 281 (24), 253 (4), 251 (3), 225 (3), 223 (4), 202 (57), 187 (32), 159 (11), 149 (4), 129 (8), 116 (6), 113 (4), 101 (4); HRMS (EI) for $C_{13}H_{13}{}^{79}BrO_3$: 296.0048, found: 296.0058.

***N*-(Diphenylmethylene)-1,4,8-trimethoxynaphthalen-2-amine.** Following a known procedure,[13] a 25 mL two-neck flask was charged with bromonaphthalene **16** (0.202 g, 0.68 mmol), benzophenone imine (0.164 g, 0.91 mmol), sodium *tert*-butoxide (0.082 g, 0.86 mmol) and toluene (4 mL) under argon environment and the mixture was degassed with two freeze–thawing cycles under high vacuum with argon purges. To the frozen mixture was added $Pd_2(dba)_3$ (0.002 g, 0.64 mol%) and (±) BINAP (0.007 g, 1.7 mol%) and the mixture was freeze–thawed twice again and then heated at 85 °C for 14 h. The mixture was allowed to cool, diluted with ether, filtered through Celite 545 and concentrated in vacuo to yield a yellow oil that was purified using flash silica column chromatography (4:1 than 2:1 hexanes:ether) producing 0.251 g (93%) of a bright yellow solid as the title compound: mp 160-162 °C; IR (NaCl, film, cm^{-1})

ν_{max} 3058, 2931, 2832, 1616, 1596, 1576, 1507, 1447, 1412, 1364, 1337, 1316, 1290, 1264, 1202, 1076, 1017; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 to 7.83 (2H, m, Ar*H*), 7.70 (1H, dd, *J* = 0.6, 8.4 Hz, Ar*H*), 7.51 to 7.40 (3H, m, Ar*H*), 7.27 to 7.17 (6H, m, Ar*H*), 6.84 (1H, d, *J* = 7.6 Hz, Ar*H*), 6.17 (1H, s, Ar*H*), 3.90 (3H, s, ArOCH_3), 3.83 (3H, s, ArOCH_3), 3.69 (3H, s, ArOCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.6, 156.2, 151.1, 141.6, 139.5, 137.7, 136.7, 130.6, 129.4, 128.8, 128.5, 128.1, 127.8, 125.4, 123.7, 121.4, 114.7, 107.7, 101.1, 60.1, 56.7, 55.6; MS *m/z* (mass intensity) (EI) 397 (M^+, 84), 382 (100), 367 (11), 352 (15), 290 (3), 280 (2), 230 (2), 191 (3), 165 (18), 160 (3), 105 (2); HRMS (EI) calc. for $C_{26}H_{23}NO_3$: 397.1678, found: 397.1668.

1,4,8-Trimethoxynaphthalen-2-amine (18). Following a known procedure,[13] a mixture of the imine (0.251 g, 0.63 mmol) obtained from the previous reaction, 5% palladium on carbon (0.162 g, 12 mol%) and ammonium formate (0.681 g, 10.9 mmol) in methanol (5 mL) was heated at reflux for 1 h 40 min. The mixture was cooled to room temperature and diluted ten-fold with dichloromethane. The mixture was filtered through a bed of Celite 545, washed once with 0.1 M NaOH, dried over sodium sulfate, filtered and concentrated in vacuo to give 0.232 g of a light brown solid that was further purified by flash silica gel chromatography (1:12 hexanes:ether) to afford 0.123 g (84%) of the title compound as a light tan solid: mp 118-119 °C (lit. value[14] 125 °C); IR (NaCl, film, cm^{-1}) ν_{max} 3482, 3368, 2960, 1623, 1603, 1512, 1448, 1421, 1388, 1341, 1258, 1211, 1163, 1070; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (1H, dd, *J* = 0.6, 8.3 Hz, Ar*H*), 7.11 (1H, dd, *J* = 7.8, 8.3 Hz, Ar*H*), 6.83 Hz (1H, d, *J* = 7.8 Hz, Ar*H*), 6.40 (1H, s, Ar*H*), 3.98 (2H, br s, ArNH_2) overlapping with 3.96 (3H, s, ArOCH_3), 3.90 (3H, s, ArOCH_3), 3.78 (3H, s, ArOCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 154.4, 152.2, 136.6, 133.6, 122.5, 121.7, 121.2, 114.9, 107.2, 97.8, 60.9, 56.1, 55.6; MS *m/z* (rel. intensity) (EI) 233 (M^+, 74), 218 (100), 201 (8), 173 (13), 159 (3), 145 (6), 130 (3), 116 (5), 102 (3) 101 (2), 89 (2), 76 (2), 63 (1) 51 (1); HRMS (EI) calc. for $C_{13}H_{15}NO_3$: 233.1052, found: 233.1059.

5-Methyl-3-(1,4,8-trimethoxynaphthalen-2-ylamino)cyclohex-2-enone (20). A mixture of naphthylamine **18** (0.099 g, 0.42 mmol), 5-methylcyclohexane-1,3-dione (0.055 g, 0.43 mmol), *p*-TsOH hydrate (0.011 g, 0.055 mmol) in toluene (4 mL) was heated at reflux for 6 h. The solution was cooled and the solvent evaporated in vacuo. The residue was purified by flash silica gel chromatography (ethyl acetate) providing the title compound as a white solid (0.125 g, 86%): mp 169-170 °C; IR (NaCl, film, cm^{-1}) ν_{max} 3226, 2954, 1581, 1529, 1502, 1450, 1417, 1378, 1338, 1262, 1142, 1075, 1016; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (1H, d, *J* = 8.4 Hz, Ar*H*), 7.31 (1H, dd, *J* = 7.7, 8.4 Hz, Ar*H*), 6.89 (1H, d, *J* = 7.7 Hz, Ar*H*), 6.83 (1H, s, Ar*H*), 6.43 (1H, br s, N*H*), 5.71 (1H, s, *H*2), 3.96 (3H, s, ArOCH_3), 3.91 (3H, s, ArOCH_3), 3.72 (3H, s, ArOCH_3), 2.49 to 2.29 (4H, m, *H*4, *H*6), 2.12 to 2.04 (1H, m, *H*5), 1.12 (3H, d, *J* = 5.4 Hz, CHCH_3); ^{13}C NMR (75.5 Hz, $CDCl_3$) δ 198.1, 160.7, 155.4, 151.8, 141.1, 128.4, 126.1, 125.2, 120.4, 114.9, 107.4, 101.4, 99.9, 62.4, 56.1, 55.9, 44.9, 38.3, 29.3, 21.0; MS *m/z* (rel. intensity) (EI) 341 (M^+, 66), 326 (100), 310 (4), 294 (4), 278 (3), 240 (5), 217 (5), 204 (3), 189 (2), 141 (2), 120 (6), 103 (2), 69 (3), 57 (1); HRMS (EI) calc. for $C_{20}H_{23}NO_4$: 341.1627, found: 341.1628.

6,7,11-Trimethoxy-3-methyl-3,4-dihydro-2*H*-benzo[*b*]carbazol-1(5*H*)-one (21). From a modification of procedures described by Akermark,[15] a mixture of the anilinoketone **20** (0.032

g, 0.09 mmol), palladium acetate (0.043 g, 0.189 mmol) in glacial acetic acid (5 mL) was heated at 95 °C for 90 min. The mixture was cooled to ambient temperature, filtered through a small pad of Celite 545 and the residue concentrated under reduced pressure and purified by column chromatography (silica, 1:7 hexanes:ethyl acetate) to furnish 0.015 g (51%) of a light brown solid as the title compound: m.p. > 260 °C decomposition; IR (NaCl, film, cm^{-1}) ν_{max} 3231, 3072, 2996, 2956, 2929, 2840, 1620, 1543, 1505, 1479, 1465, 1445, 1428, 1395, 1357, 1263, 1247, 1215, 1134, 1100, 1058, 1004; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (1H, br s, N*H*), 7.96 (1H, d, *J* = 8.7 Hz, Ar*H*), 7.27 (1H, dd, *J* = 7.5, 8.7 Hz, Ar*H*), 6.79 (1H, d, *J* = 7.5 Hz, Ar*H*), 4.03 (3H, s, ArOCH_3), 4.00 (3H, s, ArOCH_3), 3.99 (3H, s, ArOCH_3), 3.05 (1H, dd, *J* = 4.3, 16.5 Hz, *H*4), 2.69 to 2.63 (2H, m, *H*2, *H*4), 2.50 to 2.44 (1H, m, *H*3), 2.36 (1H, dd, *J* = 11.7, 15.8 Hz, *H*2), 1.16 (3H, d, *J* = 6.5 Hz, CHCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 191.1, 155.5, 154.9, 145.4, 135.7, 130.7, 127.4, 123.2, 118.2, 117.0, 115.9, 112.6, 103.8, 63.7, 63.0, 55.9, 47.2, 32.2, 30.8, 21.2; MS *m/z* (rel. intensity) (EI) 339 (M^+, 66), 324 (100), 310 (4), 267 (5), 239 (3), 218 (6), 186 (7), 170 (9), 142 (13), 129 (41), 104 (33), 91 (10), 57 (5); HRMS (EI) calc. for $C_{20}H_{21}NO_4$: 339.1471, found: 339.1480.

6,7,11-Trimethoxy-3-methyl-1-oxo-3,4-dihydro-1*H*-benzo[*b*]carbazole-5(2*H*)-carbonitrile. A solution of the carbazole **21** (0.017 g, 0.051 mmol), phenyl cyanate[16] (0.040 mL, 0.37 mmol) and triethylamine (0.030 mL, 0.21 mmol) in dry DMSO (0.8 mL) was stirred at room temperature for 4 h after which another 2 drops of triethylamine (~0.012 g, 0.12 mmol) was added and stirring was continued overnight. The solution was then diluted with water (10 mL) and extracted with ethyl acetate three times and the organic extracts were pooled. The pooled extracts were washed three times with water, brine once and dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the title compound as a light tan solid (0.019 g, 99%): mp 183-184 °C; IR (NaCl, film, cm^{-1}) ν_{max} 2930, 2841, 2244, 1752, 1680, 1613, 1570, 1508, 1452, 1408, 1391, 1356, 1342, 1266, 1099, 1066, 1044, 997, 967, 912, 882, 810, 761, 729; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92 (1H, d, *J* = 8.6 Hz, Ar*H*), 7.39 (1H, dd, *J* = 7.6, 8.6 Hz, Ar*H*), 6.89 (1H, d, *J* = 7.6 Hz, Ar*H*), 4.024 (3H, s, ArOCH_3), 4.019 (3H, s, ArOCH_3), 3.95 (3H, s, ArOCH_3), 3.23 (1H, dd, *J* = 4.2, 17.5 Hz, *H*4), 2.81 to 2.71 (2H, m, *H*2, *H*4), 2.66 to 2.49 (1H, m, *H*3), 2.42 (1H, dd, *J* = 11.6, 15.5 Hz, *H*2), 1.26 (3H, d, *J* = 6.3 Hz, CHCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 190.7, 155.9, 154.3, 146.2, 138.3, 129.6, 128.4, 125.4, 118.8, 117.3, 116.6, 115.7, 106.3, 105.7, 64.7, 64.1, 56.1, 47.1, 30.7, 30.2, 21.0; MS *m/z* (rel. intensity) (EI) 364 (M^+, 99), 349 (100), 335 (4), 322 (2), 292 (3), 264 (3), 237 (3), 182 (4), 149 (2), 126 (3), 111 (1), 69 (11), 57 (1); HRMS (EI) calc. for $C_{21}H_{20}N_2O_4$: 364.1423, found: 364.1414.

7-Methoxy-3-methyl-1,6,11-trioxo-3,4,6,11-tetrahydro-1*H*-benzo[*b*]carbazole-5(2*H*)-carbonitrile (22). The cyanamide (0.012 g, 0.033 mmol) obtained from the previous reaction was dissolved in acetonitrile (1 mL) and the solution cooled to 0 °C. To this solution was added ceric ammonium nitrate (0.048 g, 0.087 mmol) dissolved in distilled water (0.3 mL), in 0.04 mL aliquots over a 5 min period. The solution was then allowed to come to room temperature over a period of 10 minutes and water (20 mL) was added. This mixture was extracted with CH_2Cl_2 four times and the extracts were pooled, washed with water, a saturated solution of $NaHCO_3$, water, brine and dried over Na_2SO_4. The solution was then filtered and concentrated in vacuo to give the crude product as an orange solid which was purified chromatographically (silica, 2:5

then 1:5 hexanes:ethyl acetate) to afford the title compound as an orange solid (0.011 g, 95%): mp > 240 °C decomposition; IR ($CDCl_3$, cm^{-1}) ν_{max} 3693, 2259, 1701, 1662, 1586, 1528, 1472, 1454, 1440, 1408, 1298, 1272, 1240, 1168, 1041, 1005, 929; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (1H, d, *J* = 7.7 Hz, Ar*H*), 7.71 (1H, dd, *J* = 7.7, 8.4 Hz, Ar*H*), 7.31 (1H, d, *J* = 8.4 Hz, Ar*H*), 4.03 (3H, s, ArOCH_3), 3.18 (1H, dd, *J* = 4.4, 17.3 Hz, *H*4), 2.77 to 2.66 (2H, m, *H*2, *H*4), 2.60 to 2.49 (1H, m, *H*3) 2.40 (1H, dd, *J* = 11.4, 15.7 Hz, *H*2), 1.24 (3H, d, *J* = 6.4 Hz, CHCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 190.0, 177.2, 174.0, 160.7, 152.7, 136.1, 136.0, 135.7, 124.1, 120.9, 120.5, 118.4, 118.0, 103.3, 56.6, 47.1, 30.3, 29.9, 20.9; MS *m/z* (rel. intensity) (EI) 334 (M^+, 100), 321 (19), 307 (11), 292 (37), 279 (19), 264 (41), 237 (63), 221 (5), 206 (6), 178 (4), 151 (4), 105 (6), 76 (6), 51 (2); HRMS calc. for $C_{19}H_{14}N_2O_4$: 334.0954, found: 334.0951.

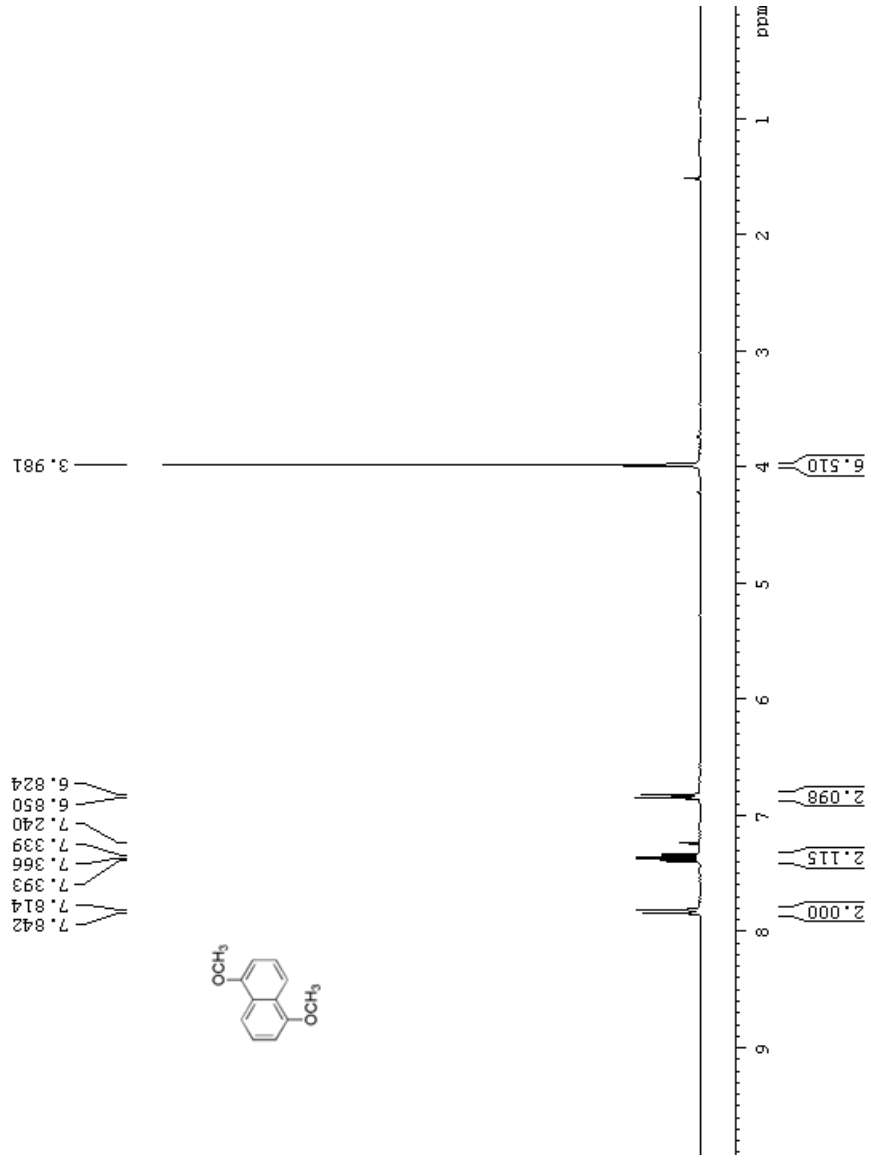
1-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-3-methyl-6,11-dioxo-6,11-dihydro-3*H*-benzo[*b*]carbazole-5(4*H*)-carbonitrile (23). Following a procedure described by Mander and Sethi,[17] *N*-cyanocarbazoloquinone **22** (0.216 g, 0.65 mmol) was dissolved in dichloromethane (12 mL) and the solution was cooled to 0 °C. To this was added TBSOTf (0.24 mL, 1.05 mmol) and the mixture was stirred for 2 min. Triethylamine (0.25 mL, 1.79 mmol) was added and was stirring continued at room temperature for 1 h. Dichloromethane was then added and the reaction was quenched with an excess of an ice cold solution of saturated sodium bicarbonate. The organic phase was dried over sodium sulfate, evaporated in vacuo and purified by flash silica column chromatography (2:3 hexanes:ether) to afford 0.103 g (35%) of the title compound as an orange solid: IR ($CDCl_3$, cm^{-1}) ν_{max} 2961, 2932, 2860, 1679, 1652, 1619, 1586, 1509, 1471, 1439, 1418, 1365, 1339, 1279, 1253, 1235, 1186, 1165, 1141, 1026, 1012, 994, 974, 944; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (1H, d, *J* = 7.5 Hz, Ar*H*), 7.65 (1H, dd, *J* = 7.5, 8.2 Hz, Ar*H*), 7.26 overlapping with $CHCl_3$ peak (1H, d, *J* = 8.2 Hz, Ar*H*), 4.96 (1H, d, *J* = 3.9 Hz, *H*2), 4.01 (3H, s, ArOCH_3), 2.95 (1H, dd, *J* = 7.3, 16.1 Hz, *H*4), 2.88 to 2.76 (1H, m, *H*3), 2.55 (1H, dd, *J* = 9.6, 16.1 Hz, *H*4), 1.14 (3H, d, *J* = 6.8 Hz, CHCH_3), 0.98 (9H, s, SiC(CH_3)$_3$), 0.21 (3H, s, Si(CH_3)), 0.19 (3H, s, Si(CH_3)); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.7, 173.7, 160.5, 144.5, 141.9, 136.6, 135.2, 134.4, 123.4, 120.3, 119.9, 119.0, 117.5, 110.6, 104.2, 56.5, 29.3, 28.2, 26.0, 20.7, 18.7, -4.26, -4.31; MS *m/z* (rel. intensity) (EI) 448 (M^+, 1), 433 (3), 391 (100), 364 (20), 349 (12), 320 (8), 319 (4), 292 (3), 279 (2), 262 (1), 174 (3), 149 (3), 111(1), 73 (5), 57 (3); HRMS (EI) calc. for $C_{21}H_{19}O_4N_2Si$ (M^+ - *t*Bu): 391.1114, found: 391.1110.

1-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-3-methyl-6,11-dioxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-5-carbonitrile. Silyl enol ether **23** (0.005 g, 0.011 mmol) was dissolved in benzene (1 mL) and DDQ (0.003 g, 0.013 mmol) was added and stirring was continued for 3.5 h at room temperature. The reaction mixture was diluted with dichloromethane (10 mL), concentrated under reduced pressure and the residue purified by column chromatography (silica, 1:3 hexanes:ether) to yield a yellow solid (0.005 g, 88%) as the title compound: IR ($CDCl_3$, cm^{-1}) ν_{max} 2932, 2860, 1675, 1657, 1615, 1587, 1576, 1549, 1500, 1471, 1437, 1415, 1373, 1352, 1321, 1280, 1253, 1232, 1183, 1133, 1106, 1070, 1032, 1014; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (1H, d, *J* = 7.8 Hz, Ar*H*), 7.69 (1H, dd, *J* = 7.8, 8.4 Hz, Ar*H*), 7.29 (1H, d, *J* = 8.4 Hz, Ar*H*), 7.12 (1H, s, Ar*H*), 6.72 (1H, s, Ar*H*), 4.03 (3H, s, ArOCH_3), 2.47 (3H, s, ArCH_3), 1.05 (9H, s, SiC(CH_3)$_3$), 0.32 (6H, s, Si(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.5, 175.3, 160.4, 152.3, 142.0, 141.1, 136.5, 136.3, 135.7, 122.4, 120.4, 118.9, 118.1, 117.5, 114.5, 105.0, 104.8,

56.5, 26.1, 22.1, 18.9, -3.8; MS *m/z* (rel. intensity) (EI) 431 (2), 405 (4), 389 (100), 374 (13), 362 (36), 346 (11), 334 (14), 332 (5), 304 (3), 288 (2), 261 (1), 181 (3), 173 (2), 152 (1), 97(1), 73 (1), 57 (2); HRMS (EI) calc. for $C_{21}H_{17}O_4N_2Si$ (M^+ - *t*Bu): 389.0958, found: 389.0959.

1,7-Dihydroxy-3-methyl-6,11-dioxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-5-carbonitrile (4). *N*-Cyanocarbazoloquinone (0.075 g, 0.168 mmol) obtained from the previous reaction was dissolved in dichloromethane (7 mL) and the solution was cooled to -78 °C. To this was added BBr_3 (1.2 mL of a 1 M solution in CH_2Cl_2, 1.2 mmol) and the mixture was stirred for 40 min, allowed to come to room temperature over a 15 min period and then quenched with an ice cold solution of saturated sodium bicarbonate. The mixture was diluted with dichloromethane, washed with water, dried over Na_2SO_4, filtered and the solvent evaporated in vacuo. The crude material was purified by flash silica gel chromatography (1:1 then 2:3 hexanes:ether) to afford the target compound as a blackish-purple solid (0.018 g, 34%): IR ($CDCl_3$, cm^{-1}) ν_{max} 3692, 3208, 3123, 2927, 2247, 1627, 1593, 1553, 1455, 1430, 1408, 1300, 1250, 1219, 1184, 1164, 1089; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.81 (1H, s, ArO*H*), 10.17 (1H, s, ArO*H*), 7.82 (1H, d, *J* = 7.5 Hz, Ar*H*), 7.67 (1H, dd, *J* = 7.5, 8.1 Hz, Ar*H*), 7.34 (1H, d, *J* = 8.1 Hz, Ar*H*), 7.01 (1H, s, Ar*H*), 6.79 (1H, s, Ar*H*), 2.49 (3H, s, ArCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 182.2, 179.4, 162.9, 153.1, 145.5, 140.8, 136.9, 133.2, 132.0, 126.8, 124.9, 121.4, 114.6, 113.7, 111.1, 104.4, 103.1, 22.5; MS *m/z* (rel. intensity) (EI) 318 (M^+, 100), 293 (6), 289 (3), 261 (2), 219 (3), 190 (3), 159 (3), 115 (1), 87 (2); HRMS (EI) calc. for $C_{18}H_{10}N_2O_4$: 318.0641, found: 318.0645.

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



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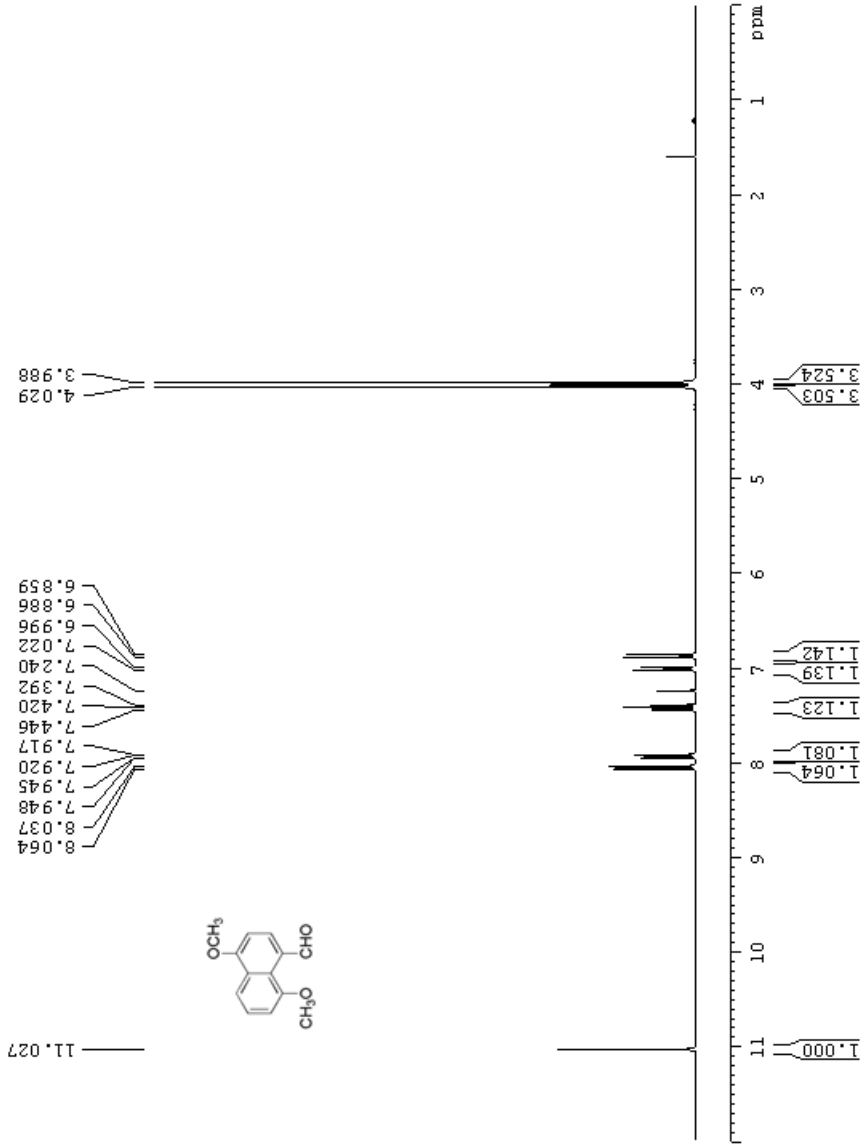
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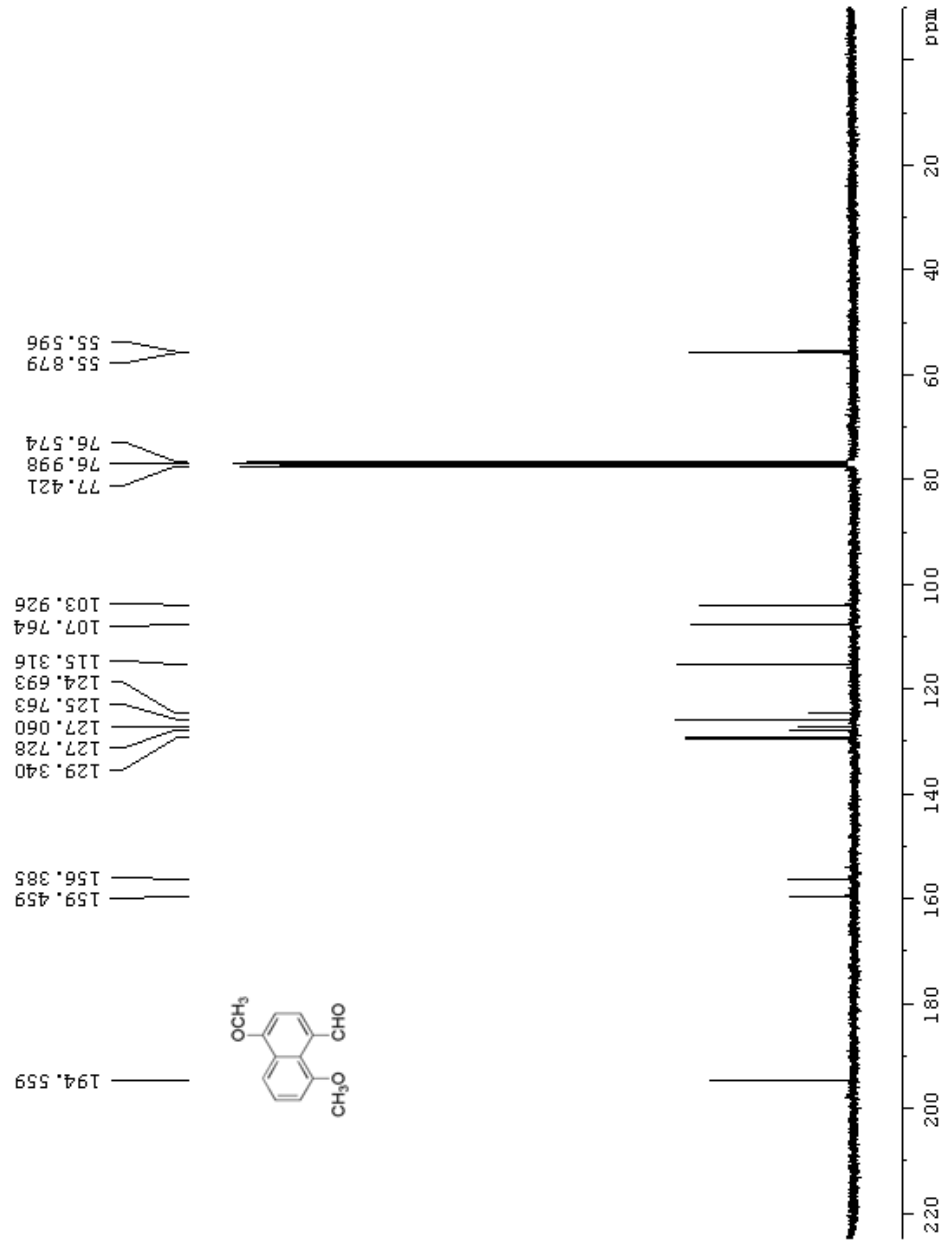
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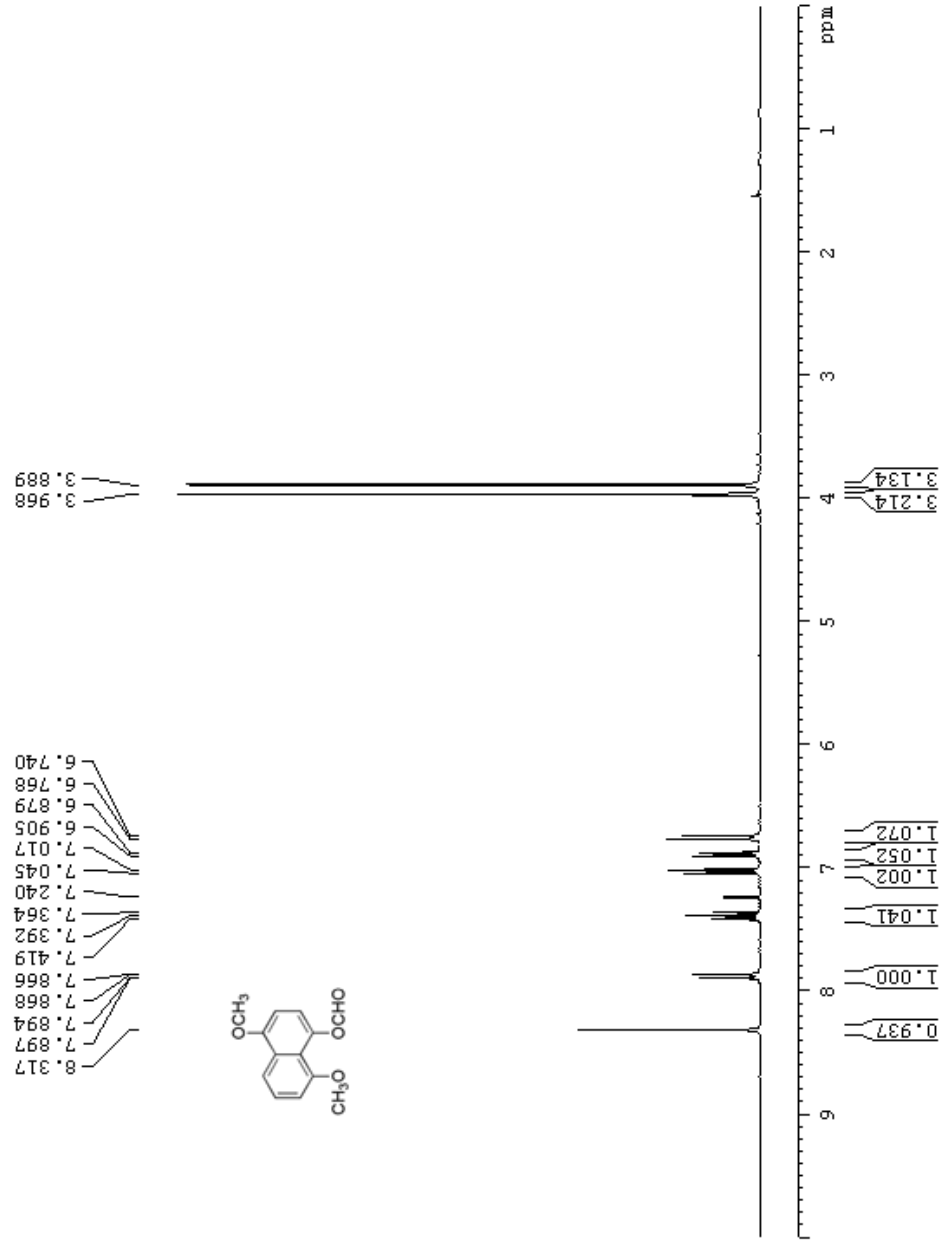
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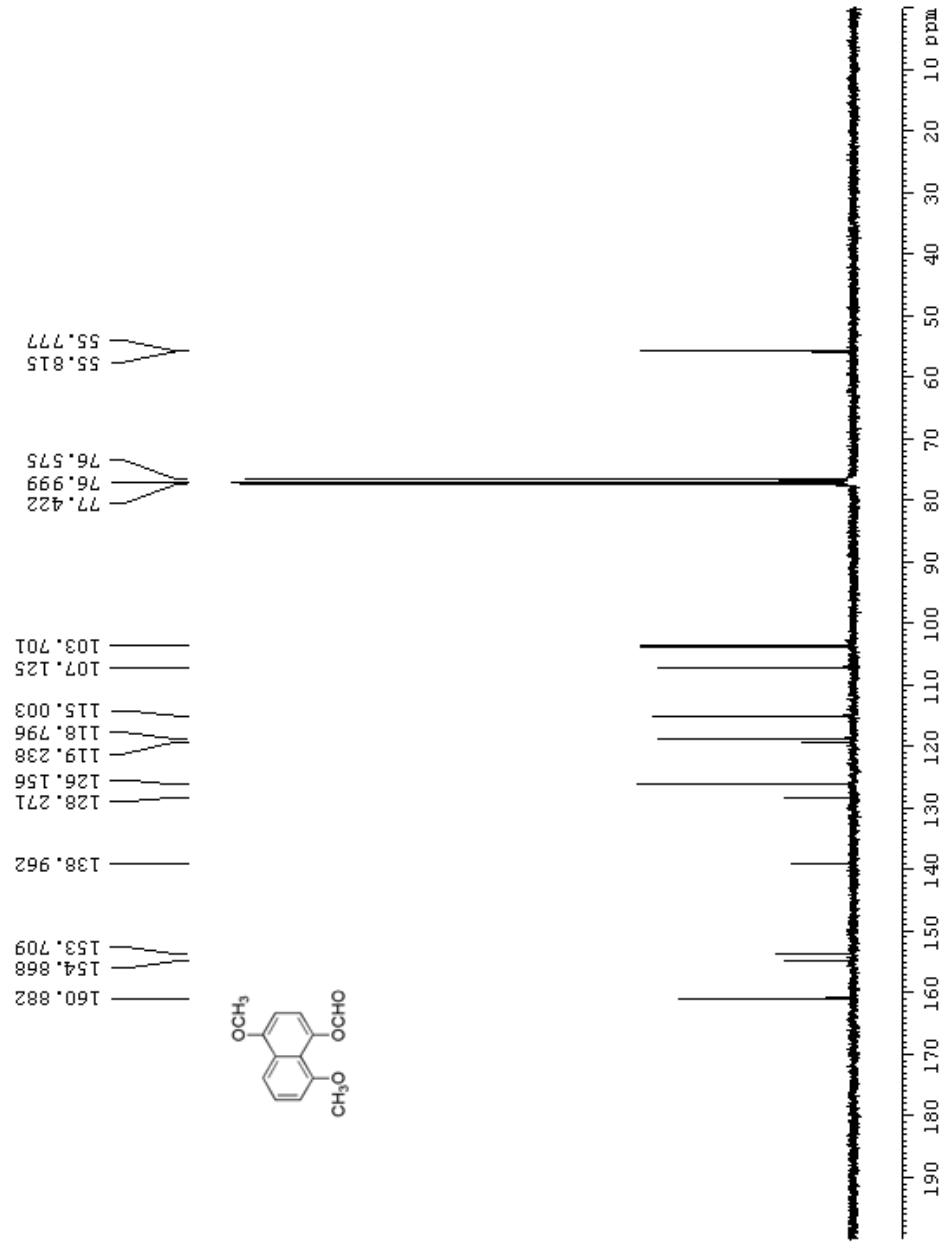
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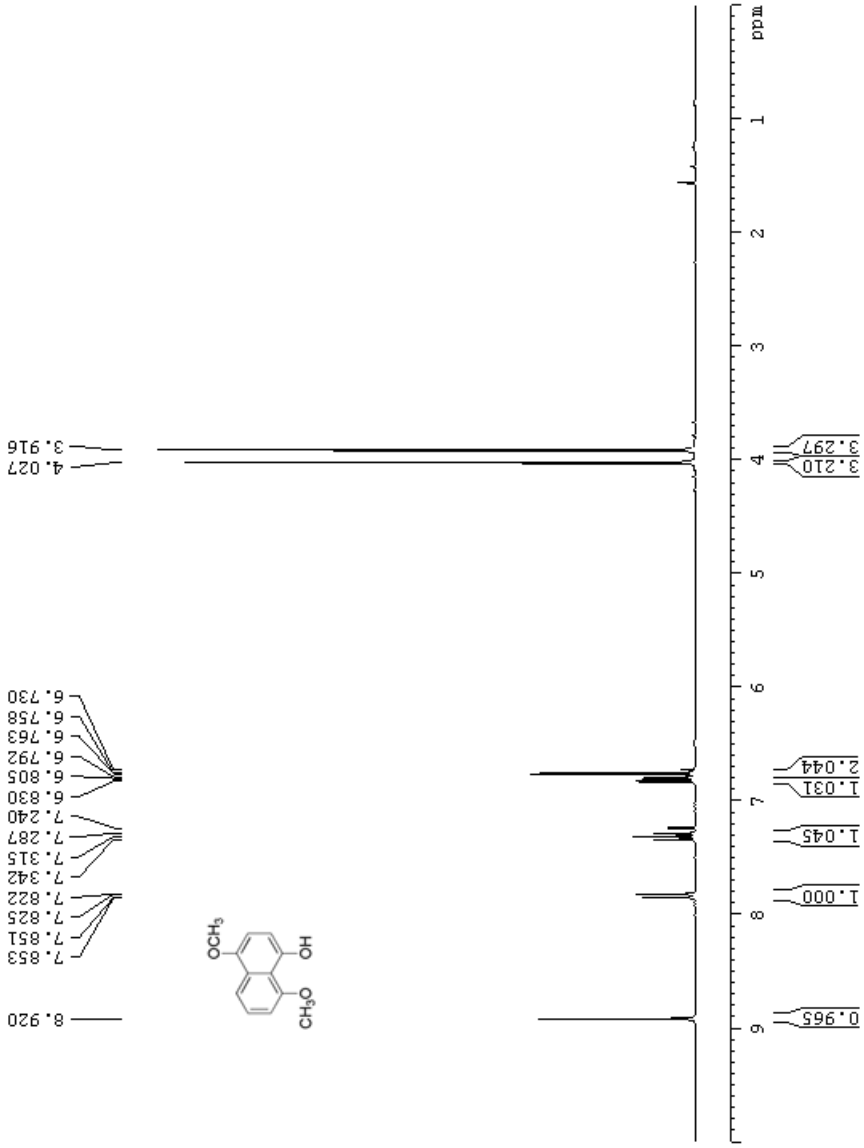
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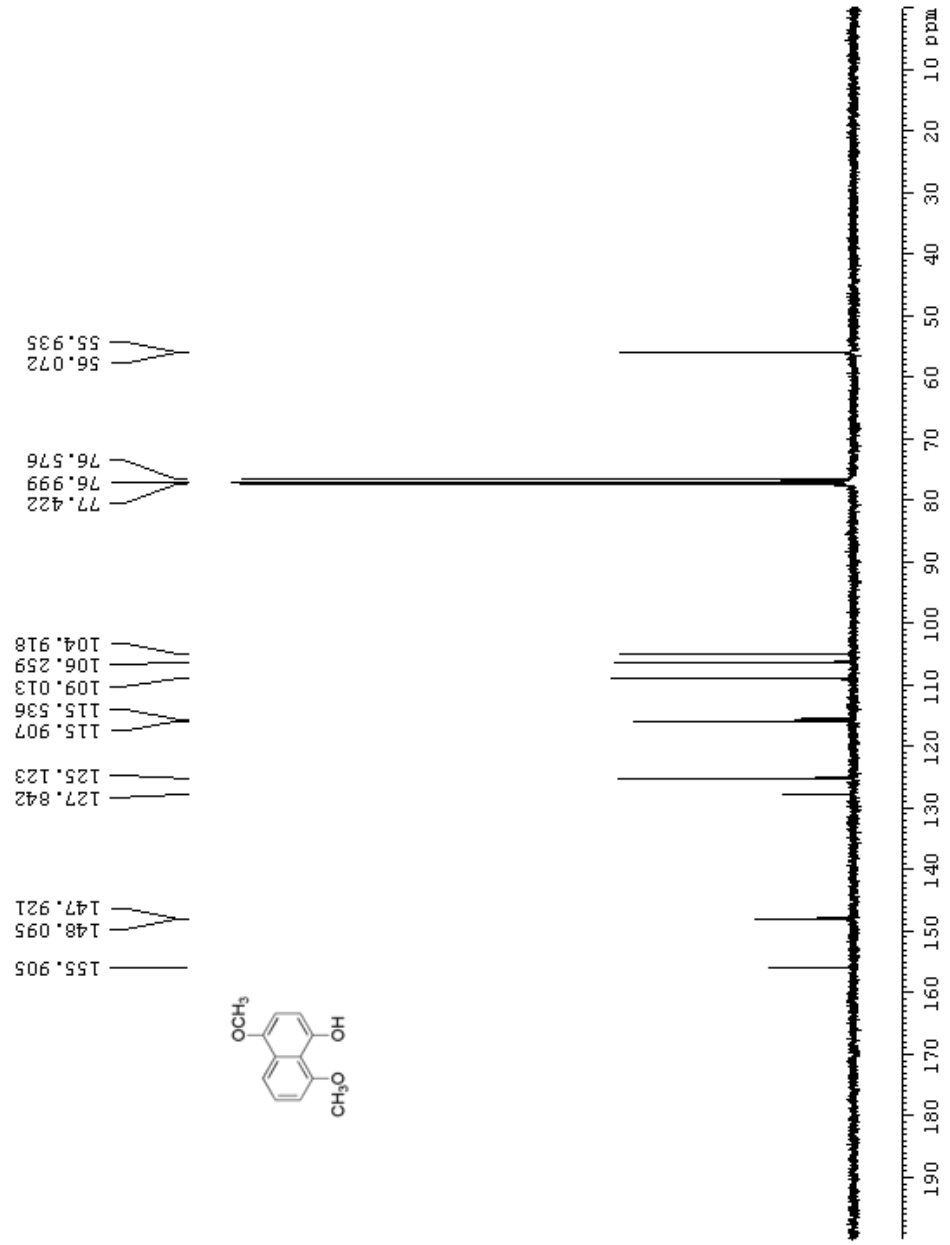
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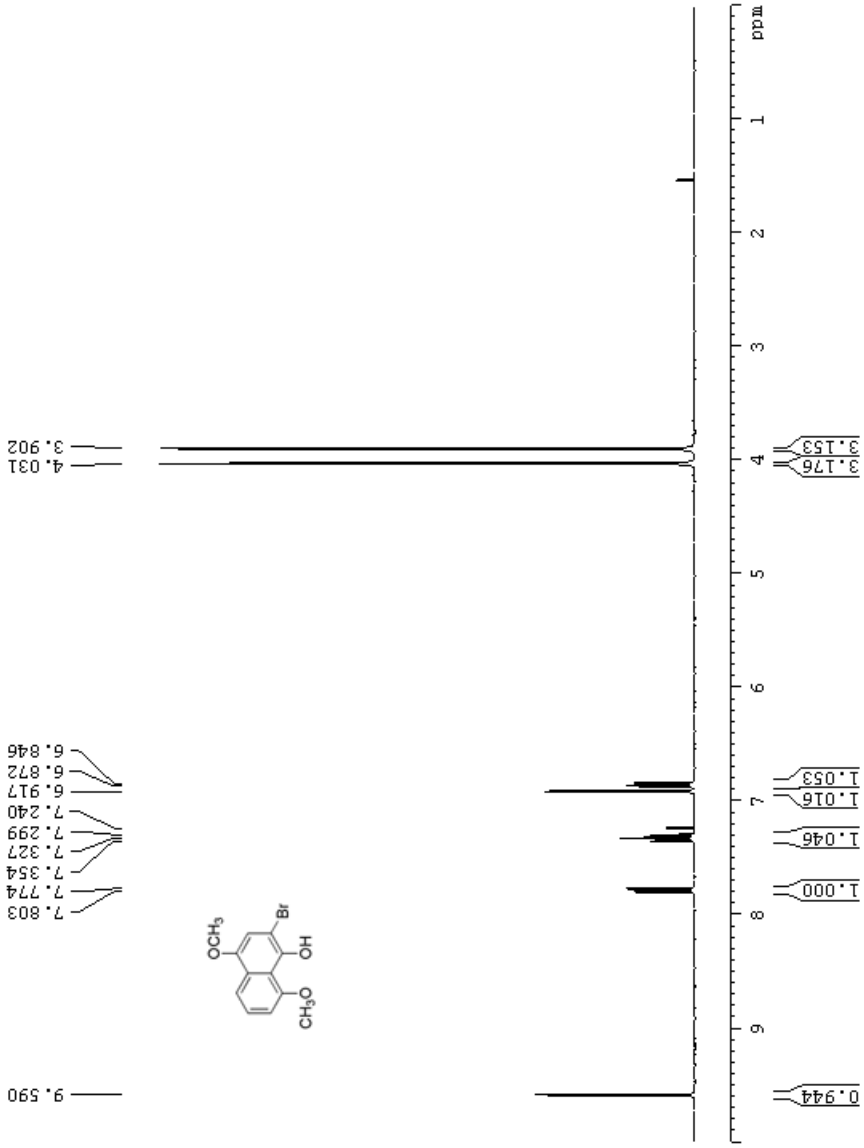
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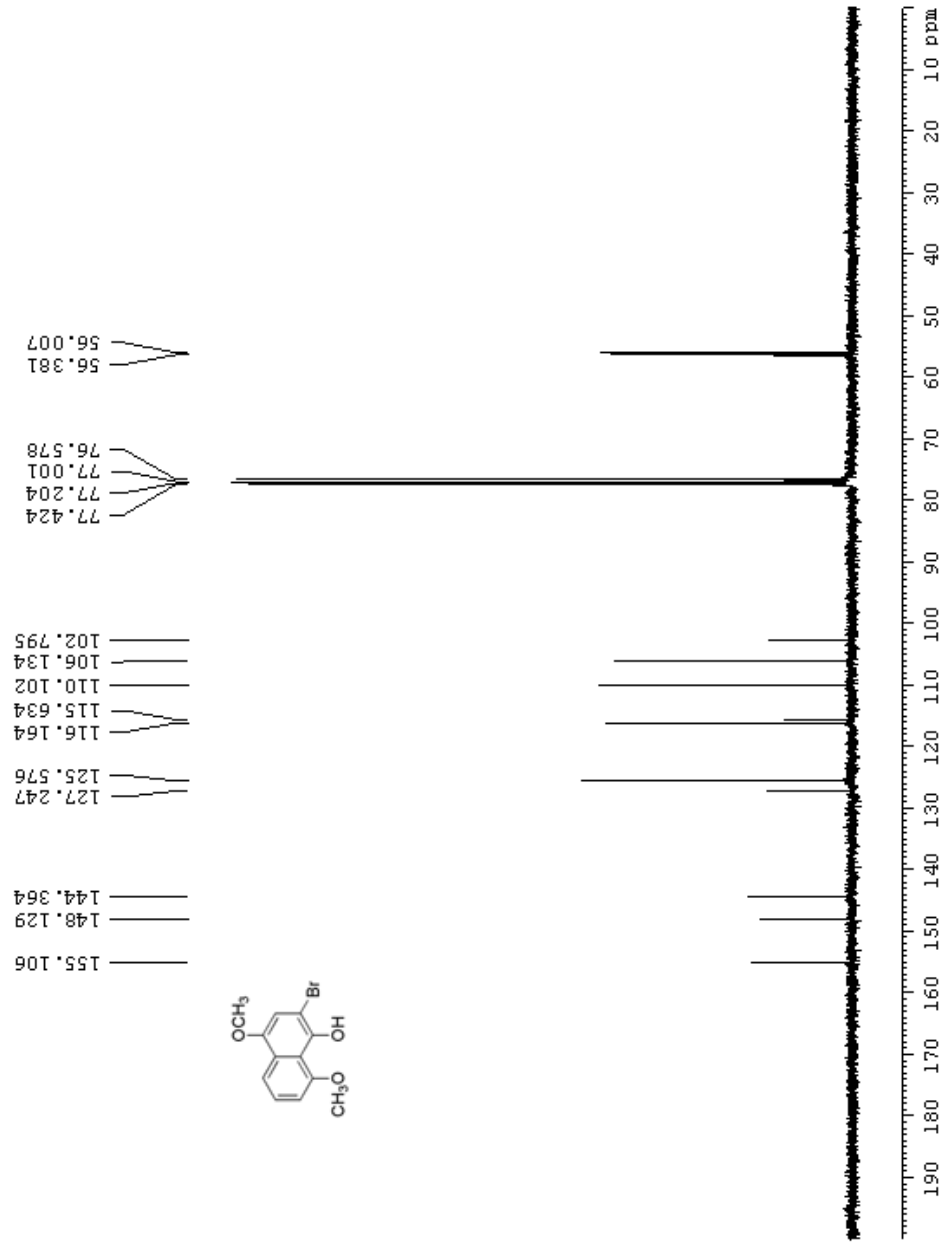
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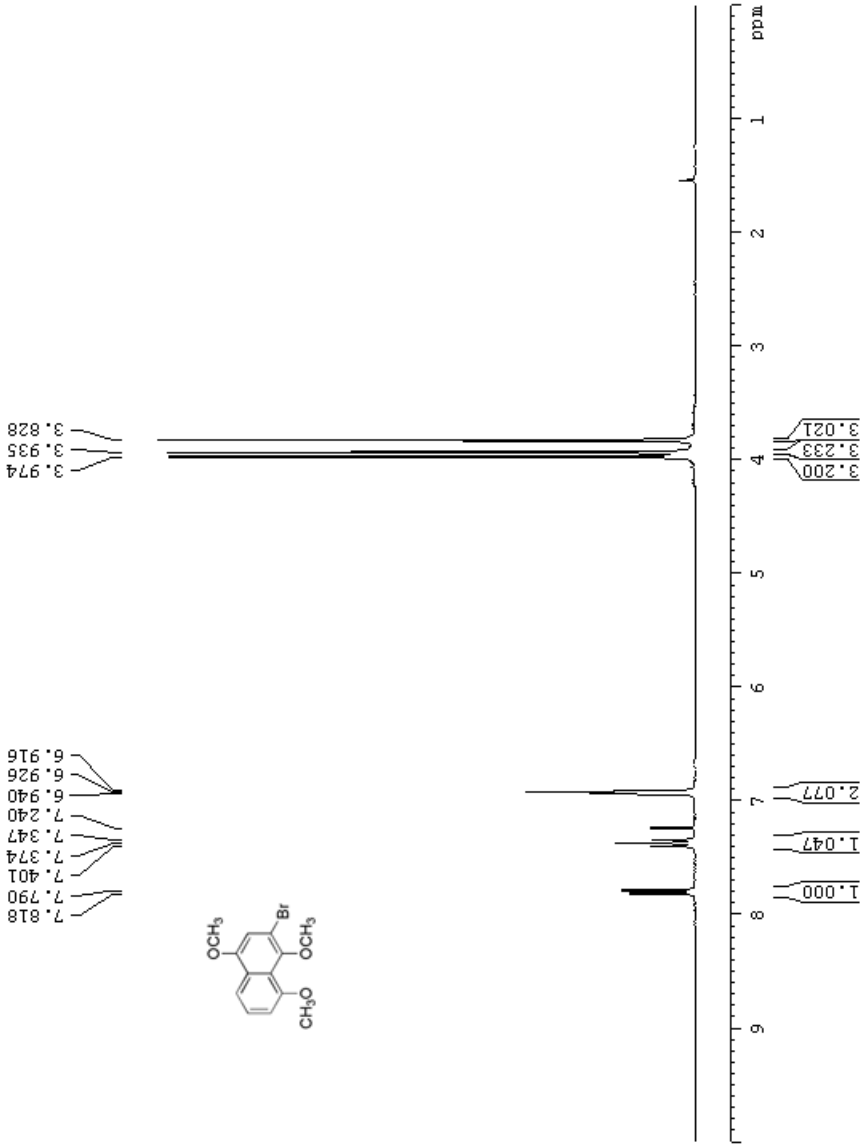
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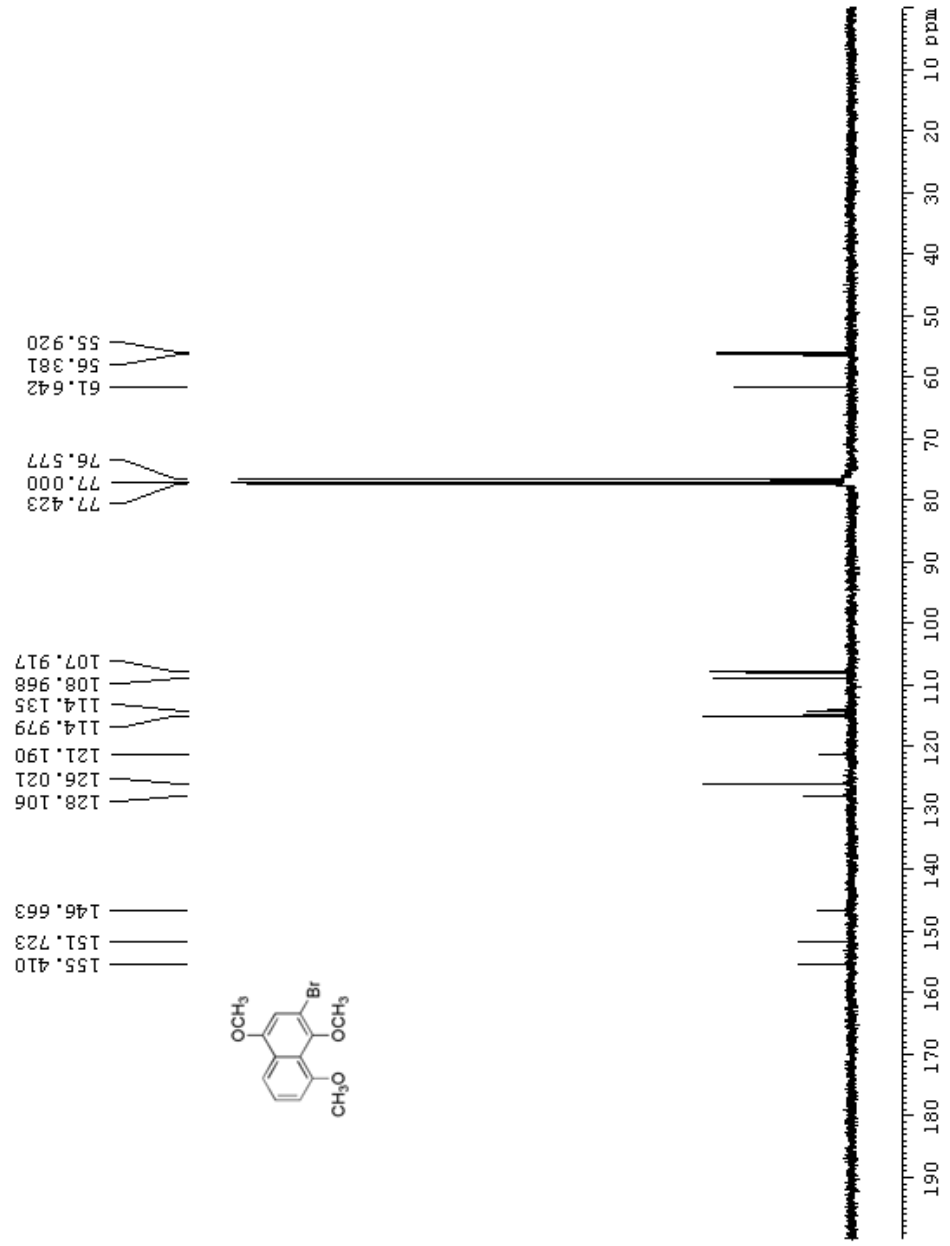
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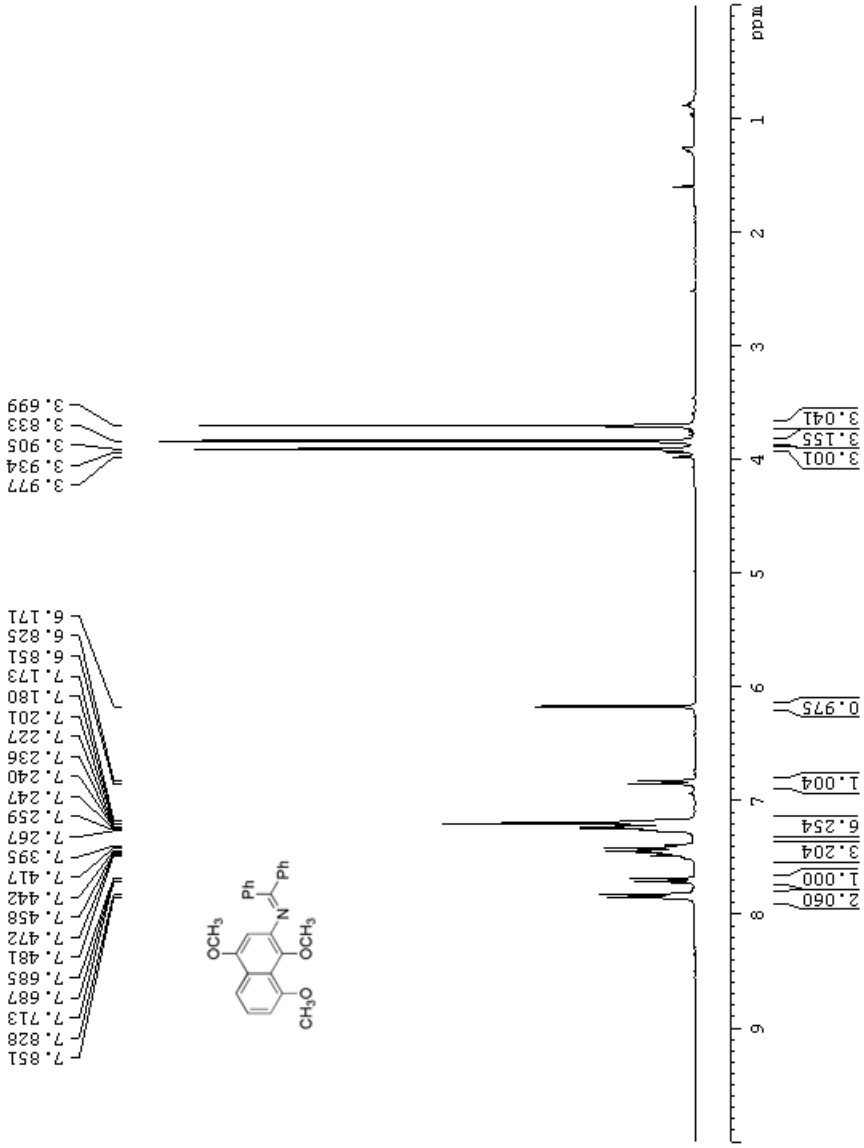
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6.171
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7.247
7.259
7.267
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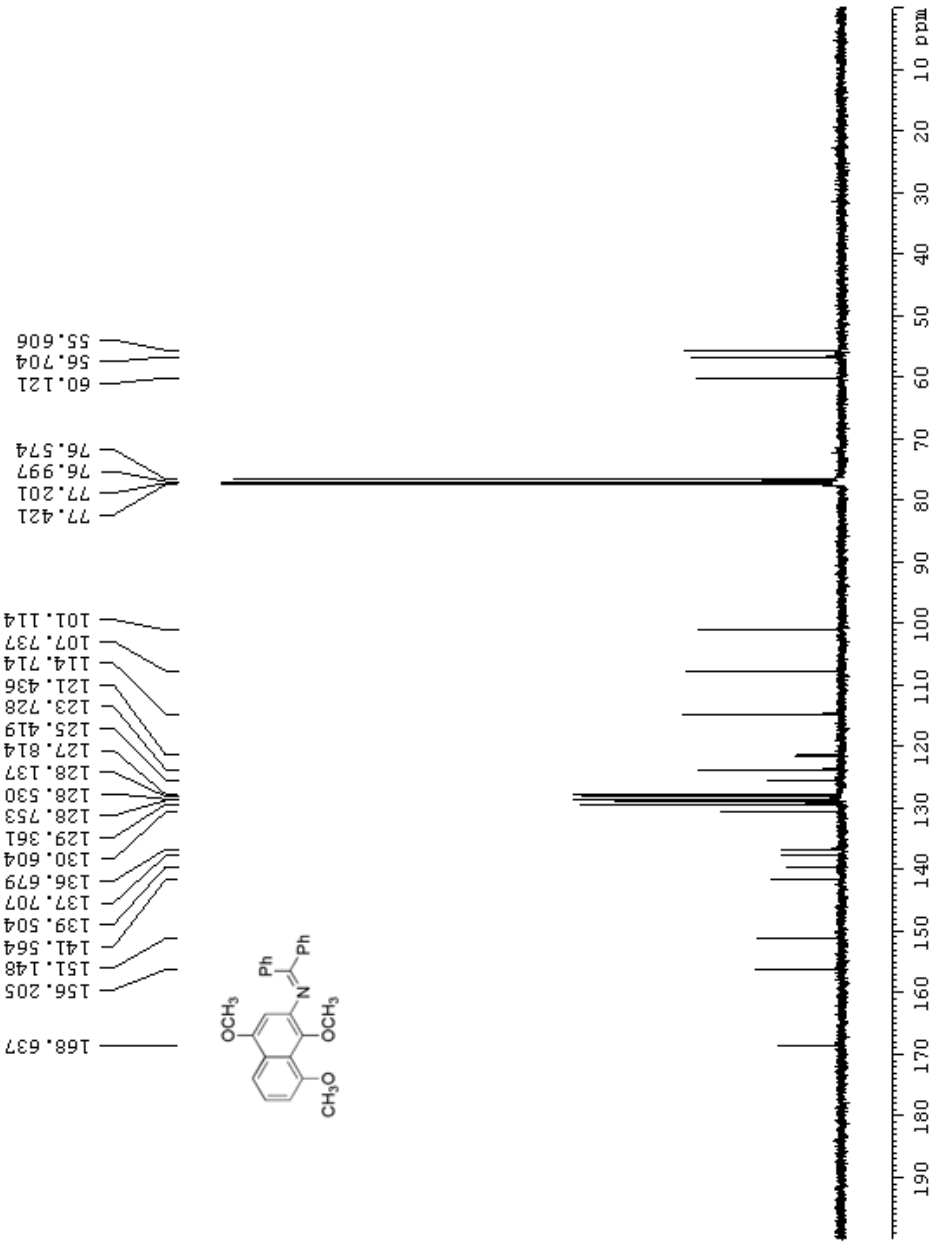
7.685
7.687
7.713
7.828
7.851
Ph
Ph
N
OCH3
OCH3
CH3O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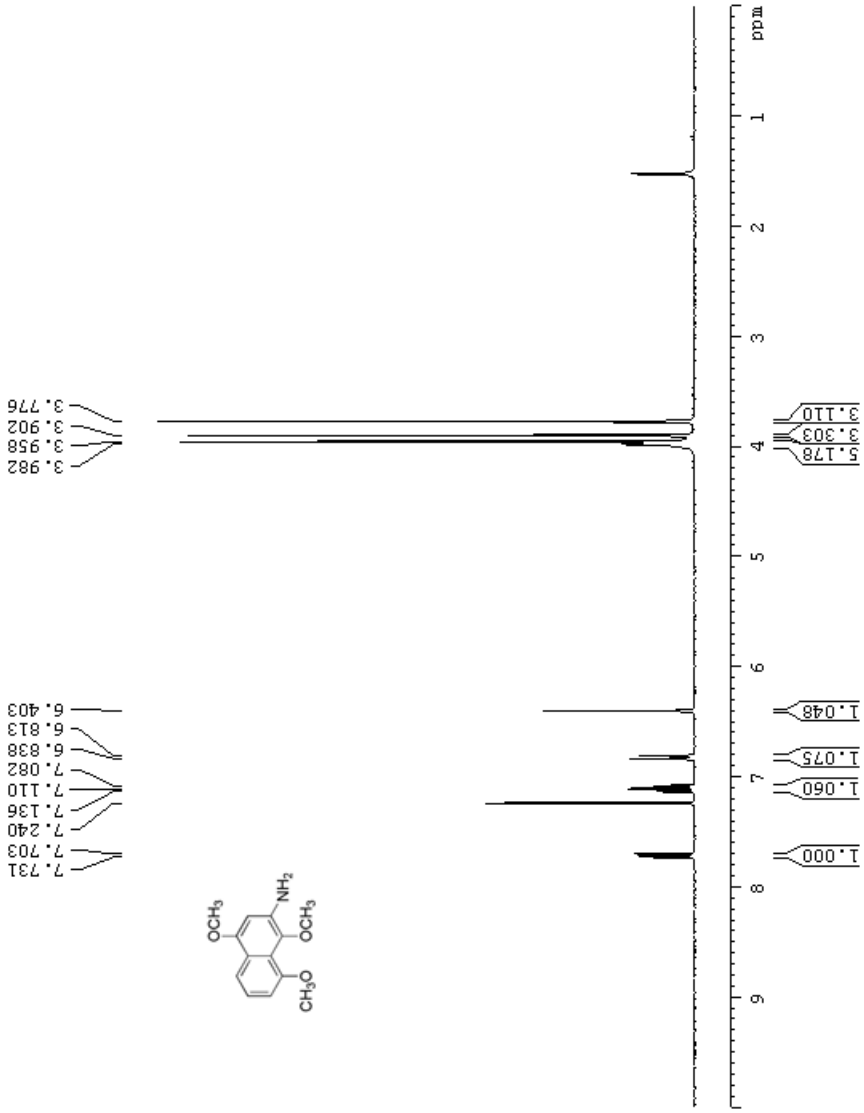
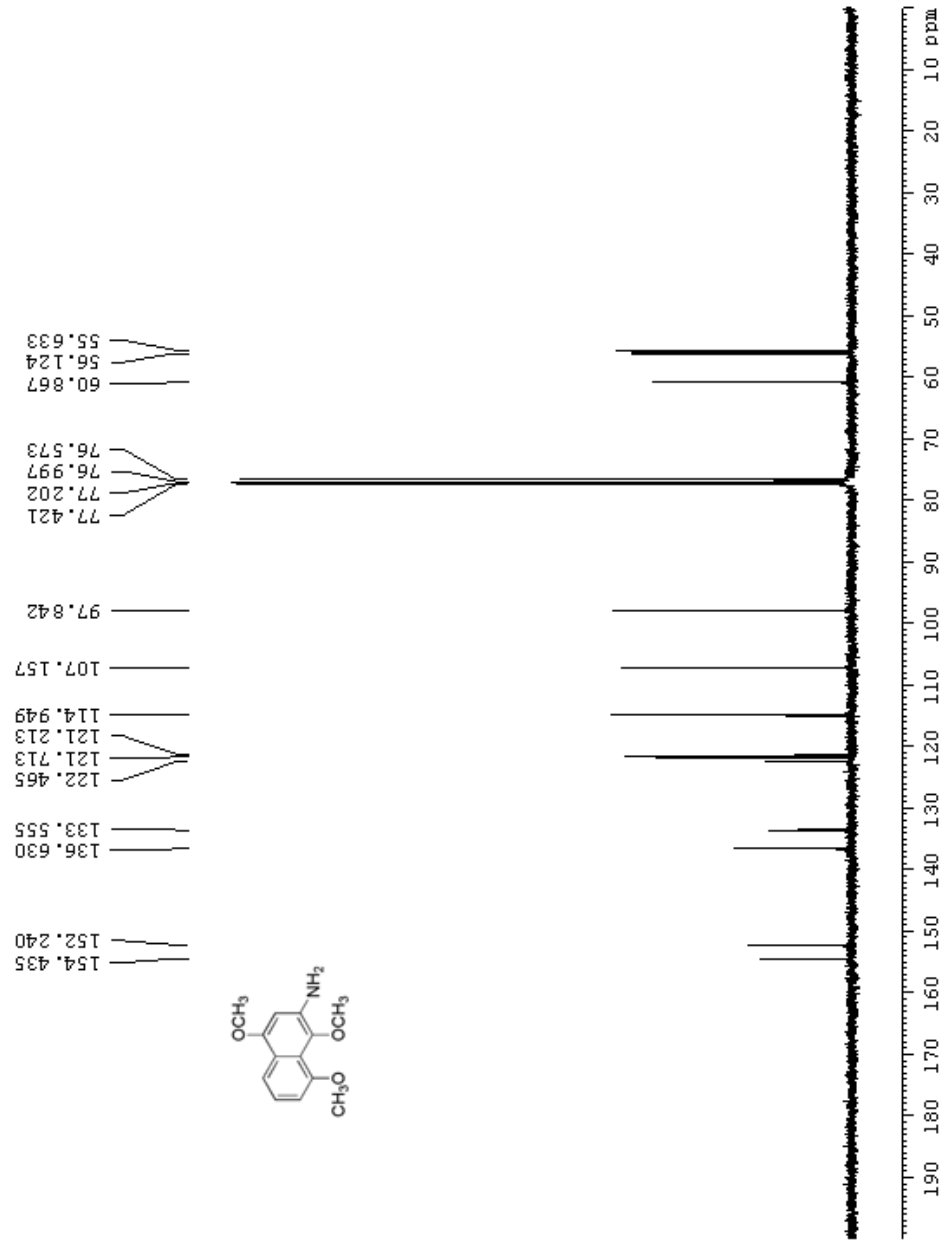
60.121
76.574
76.997
77.201
77.421
101.114
107.737
114.714
121.436
123.728
125.419
127.814
128.137
128.530
128.753
129.361
130.604
136.679
137.707
139.504
141.564
151.148
156.205
168.637
OCH3
OCH3
CH3O
N
Ph
Ph
10 ppm


7.731
7.703
7.240
7.136
7.110
7.082
6.838
6.813
6.403
3.982
3.958
3.902
3.776
1.000
1.060
1.075
1.048
5.178
3.303
3.110
ppm
NH2
OCH3
OCH3
CH3O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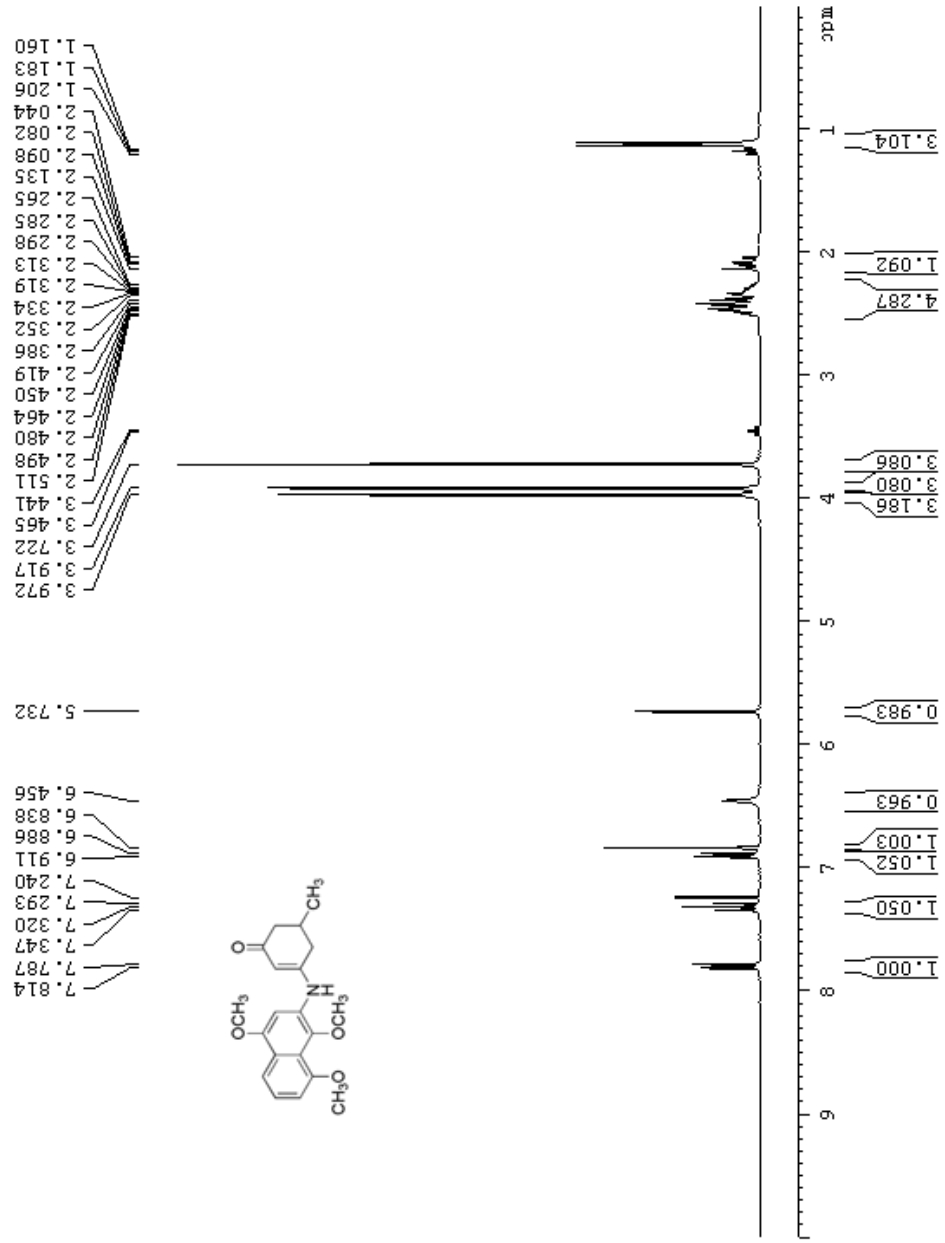
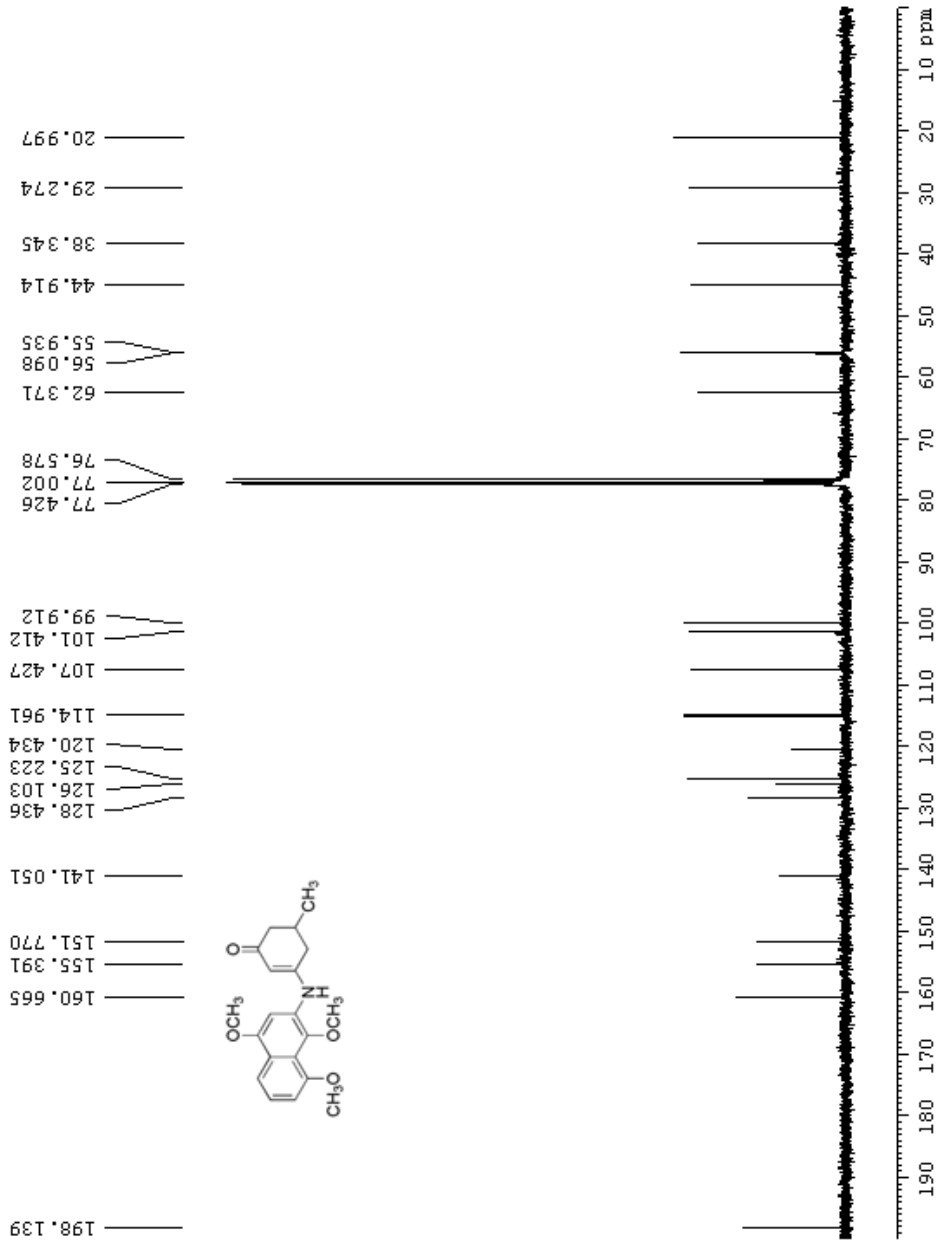
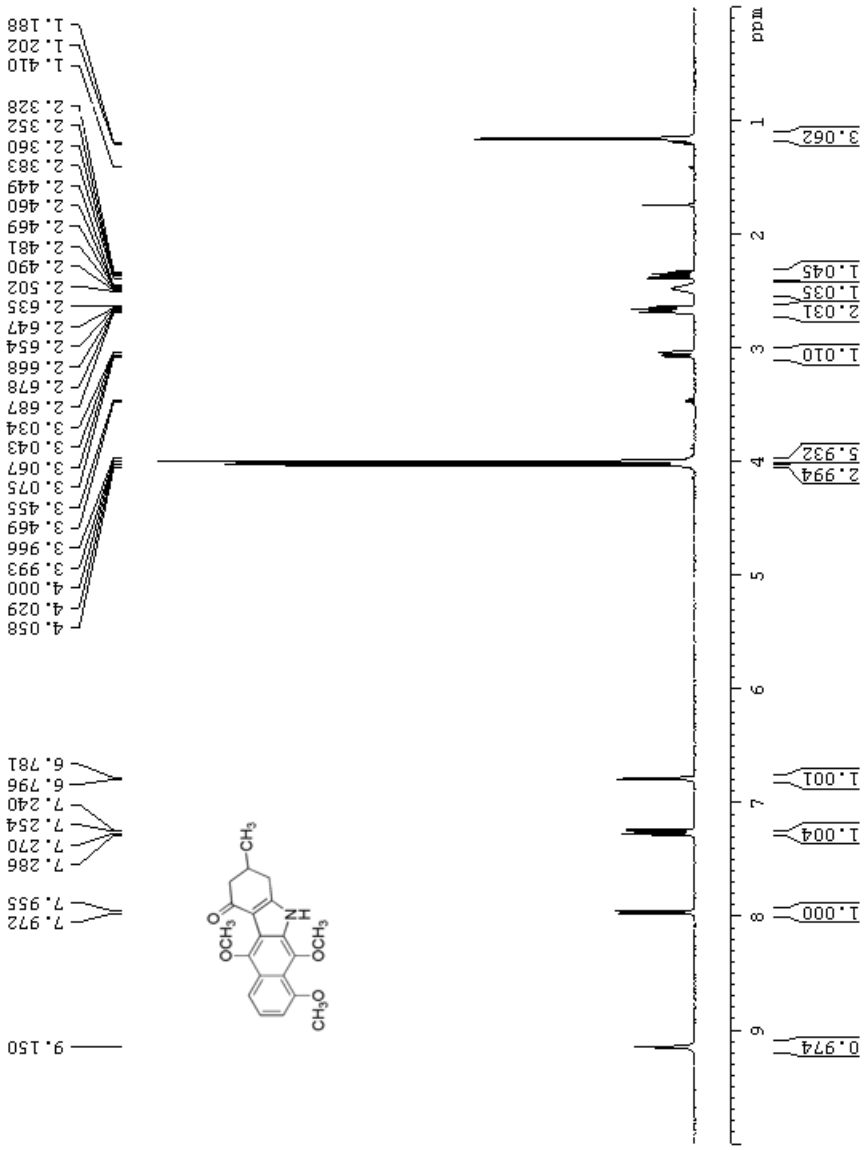
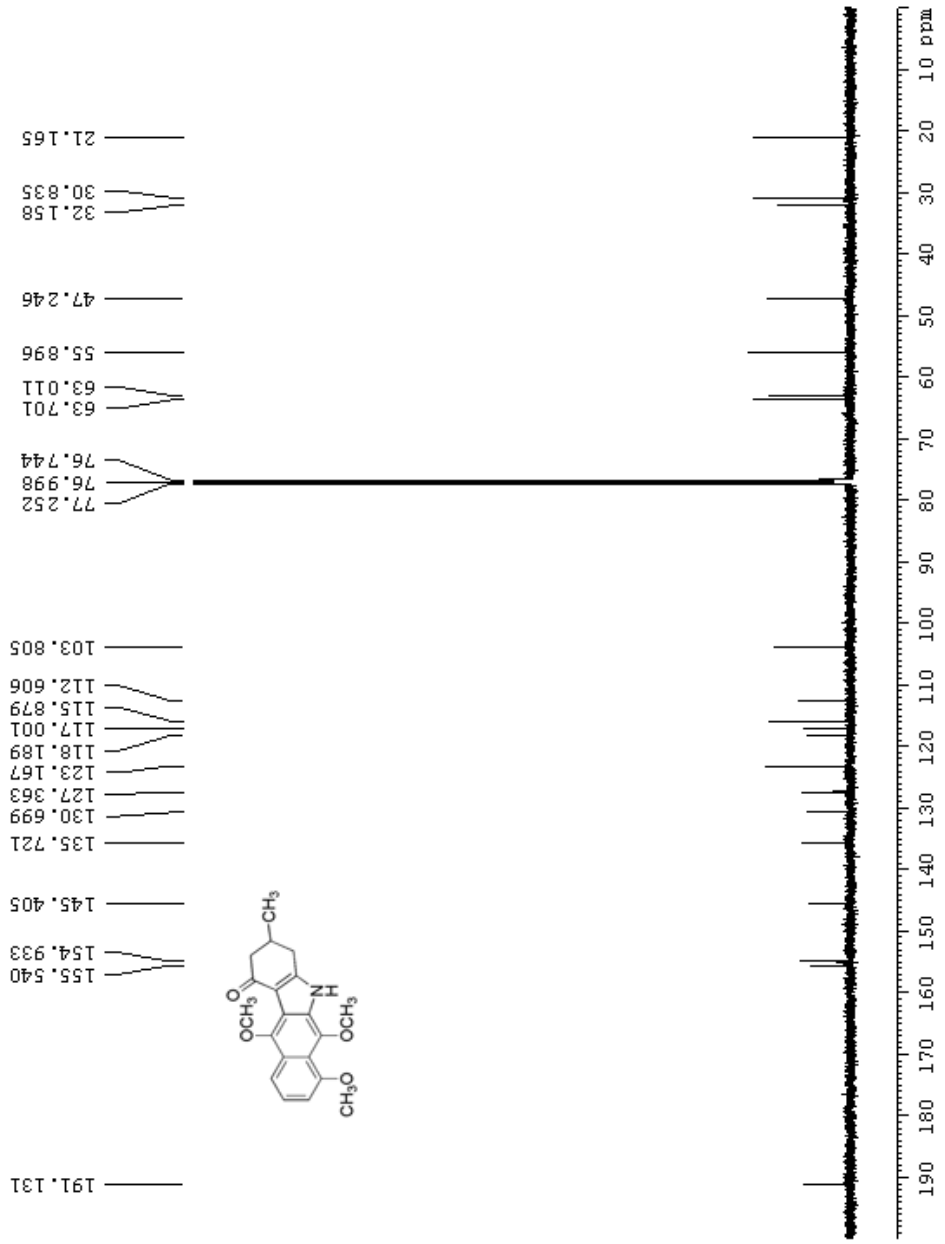
56.124
60.867
76.573
76.997
77.202
77.421
97.842
107.157
114.949
121.213
121.713
122.465
133.555
136.630
152.240
154.435
OCH3
NH2
OCH3
CH3O
10 ppm


7.814
7.787
7.347
7.320
7.293
7.240
6.911
6.886
6.838
6.456
5.732
3.972
3.917
3.722
3.465
3.441
2.511
2.498
2.480
2.464
2.450
2.419
2.386
2.352
2.334
2.319
2.313
2.298
2.285
2.265
2.135
2.098
2.082
2.044
1.206
1.183
1.160
3.104
1.092
4.287
3.086
3.080
3.186
0.983
0.963
1.003
1.052
1.050
1.000
ppm
1
2
3
4
5
6
7
8
9
O
CH3
N
H
OCH3
OCH3
CH3O


198.139
160.665
155.391
151.770
141.051
128.436
126.103
125.223
120.434
114.961
107.427
101.412
99.912
77.426
77.002
76.578
62.371
56.098
55.935
44.914
38.345
29.274
20.997
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
O
CH3
N
H
OCH3
OCH3
CH3O


ppm
1
2
3
4
5
6
7
8
9
3.062
1.045
1.035
2.031
1.010
2.994
5.932
1.001
1.004
1.000
0.974
1.188
1.202
1.410
2.328
2.352
2.360
2.383
2.449
2.460
2.469
2.481
2.490
2.502
2.635
2.647
2.654
2.668
2.678
2.687
3.034
3.043
3.067
3.075
3.455
3.469
3.966
3.993
4.000
4.029
4.058
6.781
6.796
7.240
7.254
7.270
7.286
7.955
7.972
9.150
CH3
O
OCH3
NH
OCH3
CH3O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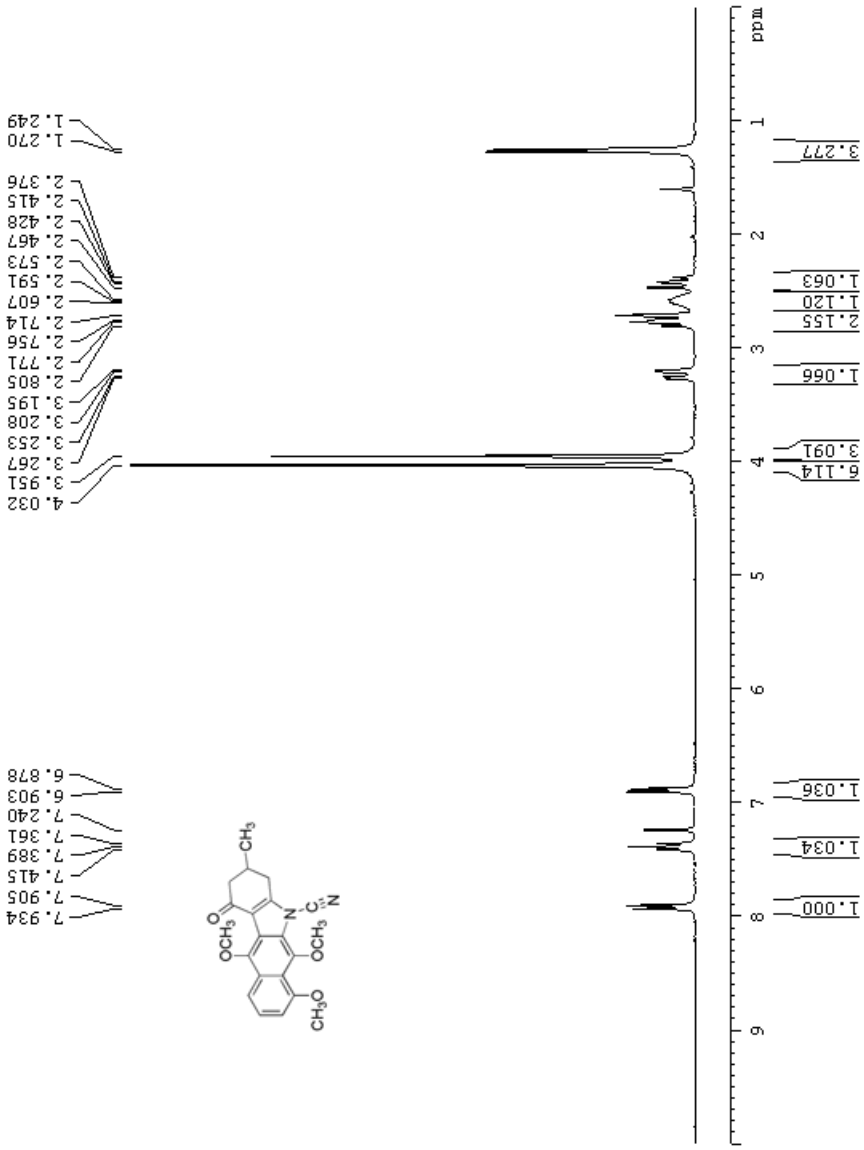
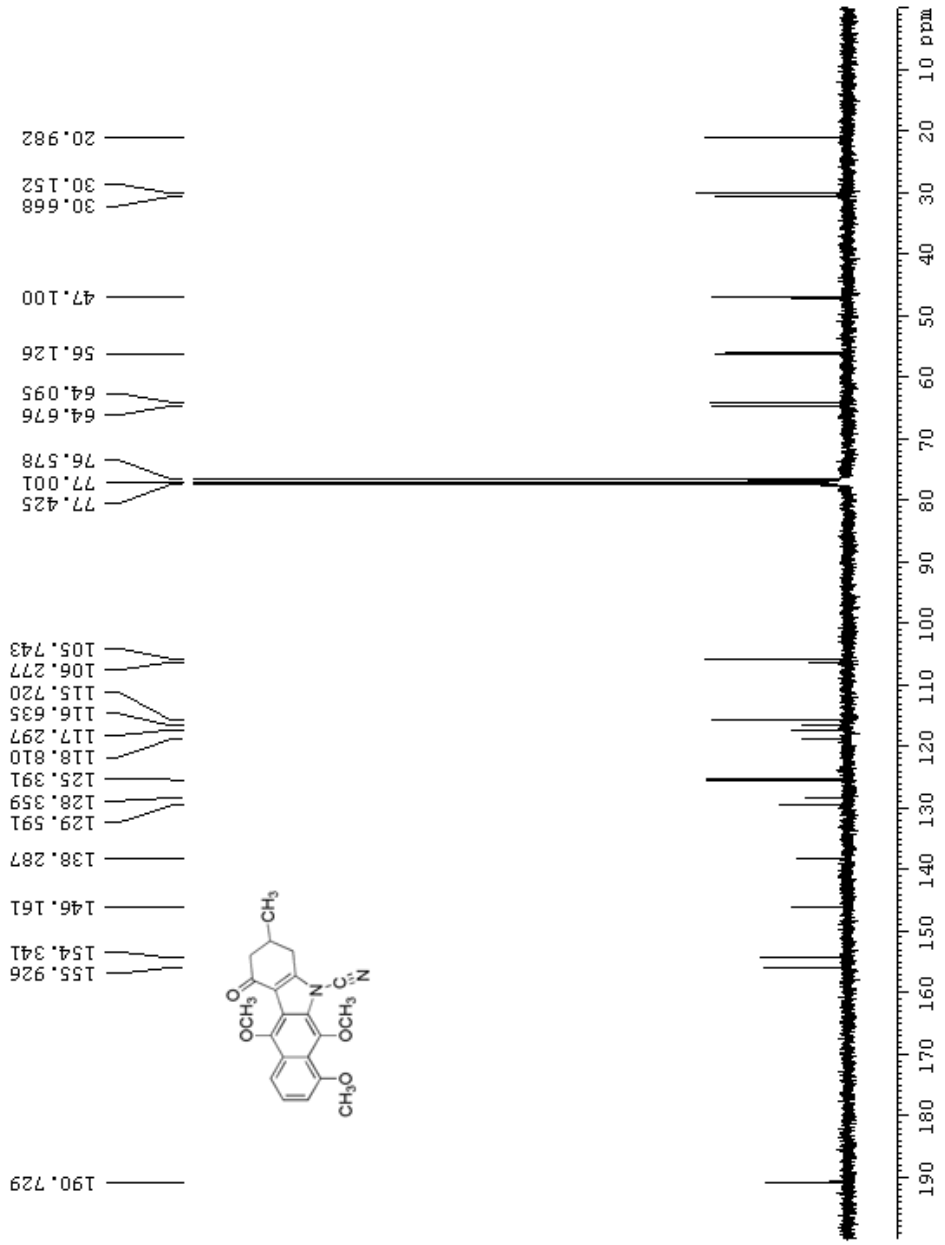
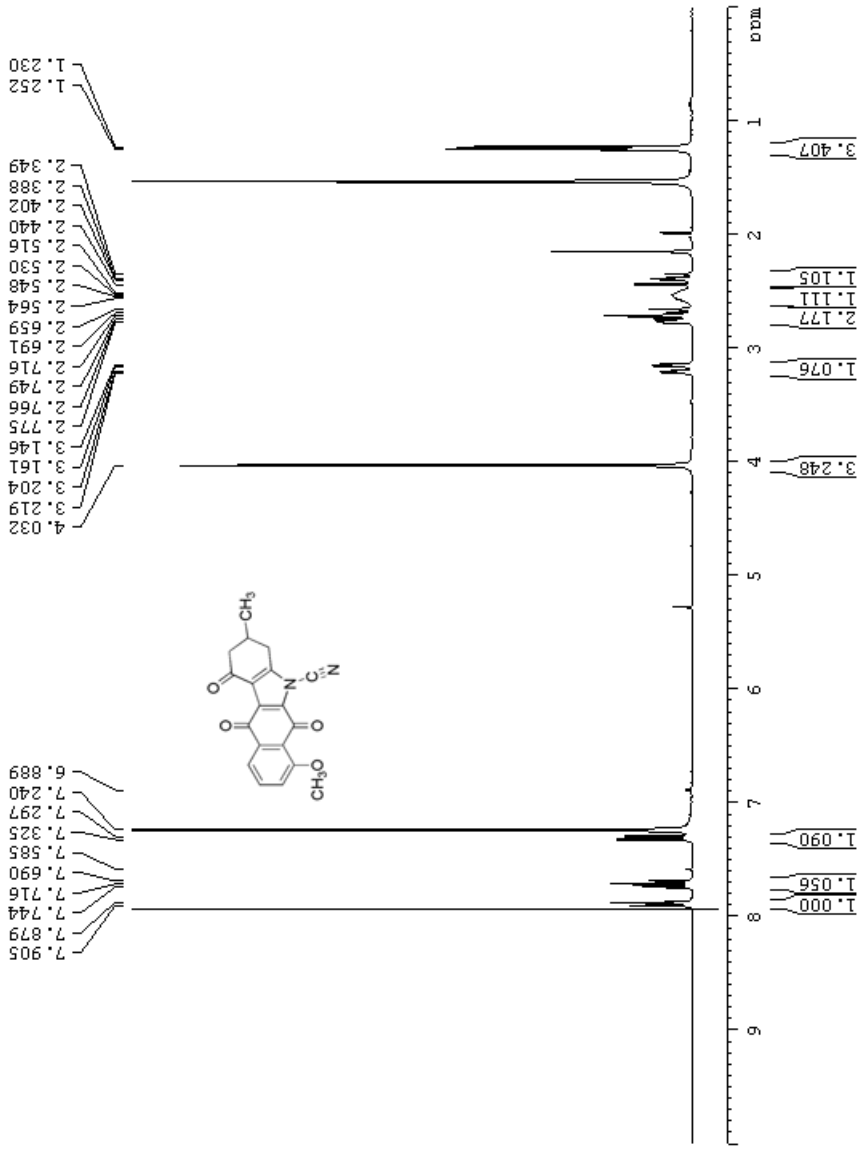
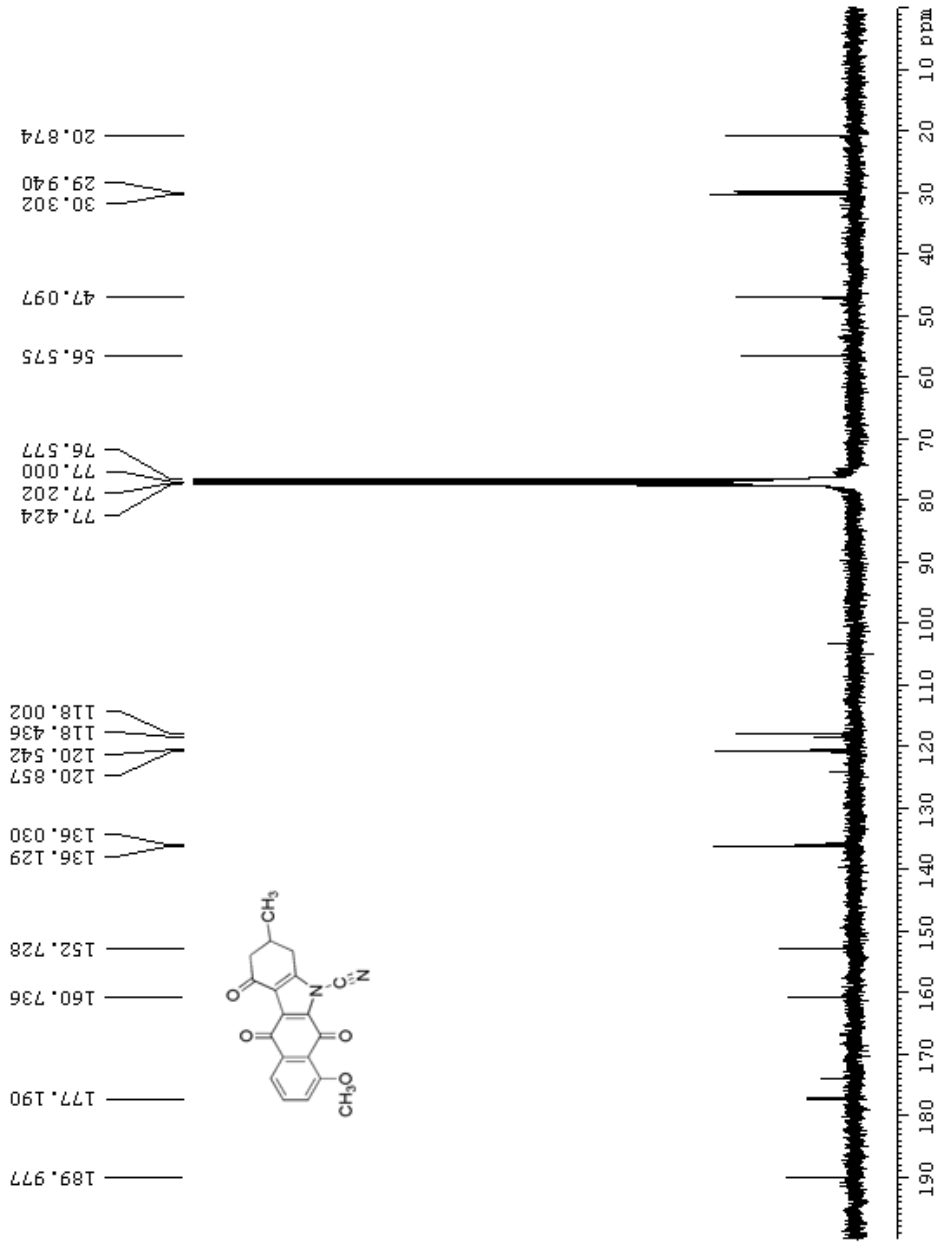
30.835
32.158
47.246
55.896
63.011
63.701
76.744
76.998
77.252
103.805
112.606
115.879
117.001
118.189
123.167
127.363
130.699
135.721
145.405
154.933
155.540
191.131
CH3
O
OCH3
N
H
OCH3
CH3O
10 ppm


ppm
1
2
3
4
5
6
7
8
9
3.277
1.063
1.120
2.155
1.066
6.114
3.091
1.036
1.034
1.000
1.249
1.270
2.376
2.415
2.428
2.467
2.573
2.591
2.607
2.714
2.756
2.771
2.805
3.195
3.208
3.253
3.267
3.951
4.032
6.878
6.903
7.240
7.361
7.389
7.415
7.905
7.934
CH3
O
OCH3
N
C
N
OCH3
CH3O


190.729
155.926
154.341
146.161
138.287
129.591
128.359
125.391
118.810
117.297
116.635
115.720
106.277
105.743
77.425
77.001
76.578
64.676
64.095
56.126
47.100
30.668
30.152
20.982
ppm


1.230
1.252
2.349
2.388
2.402
2.440
2.516
2.530
2.548
2.564
2.659
2.691
2.716
2.749
2.766
2.775
3.146
3.161
3.204
3.219
4.032
6.889
7.240
7.297
7.325
7.585
7.690
7.716
7.744
7.879
7.905
3.407
1.105
1.111
2.177
1.076
3.248
1.090
1.056
1.000
ppm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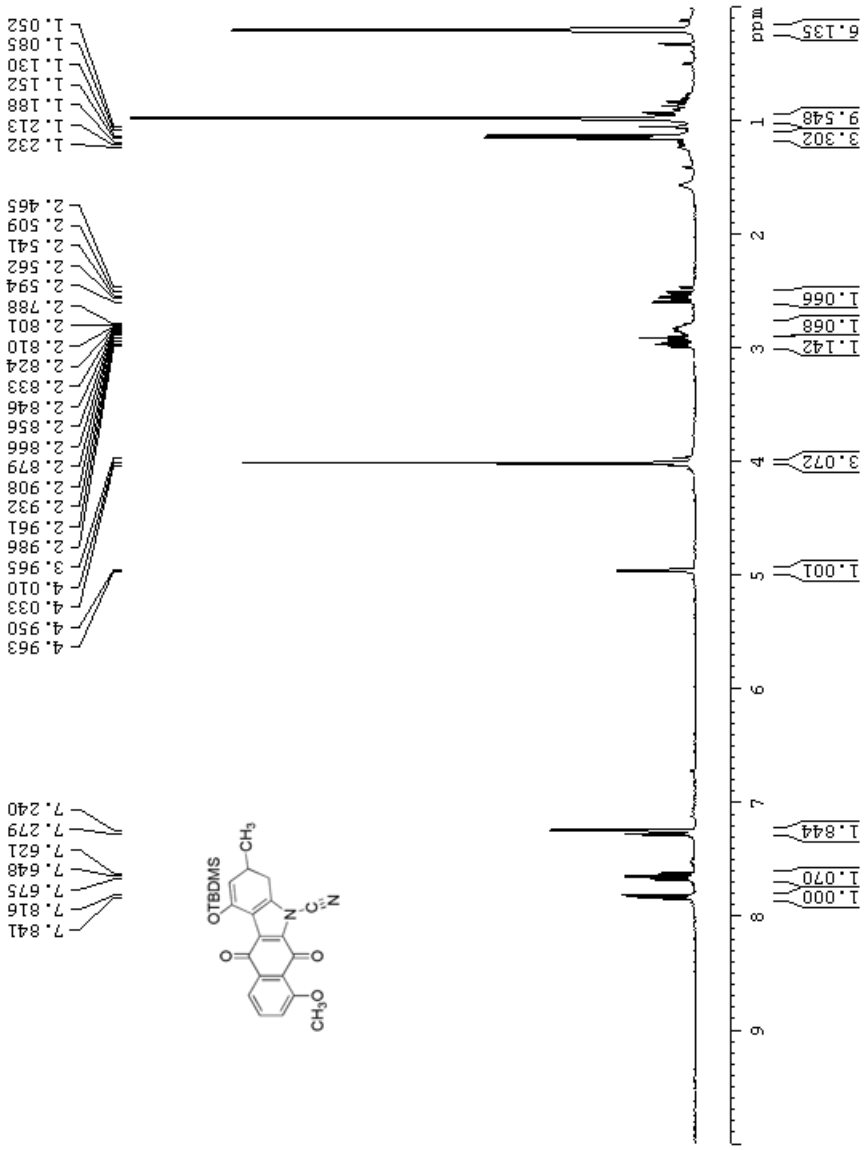
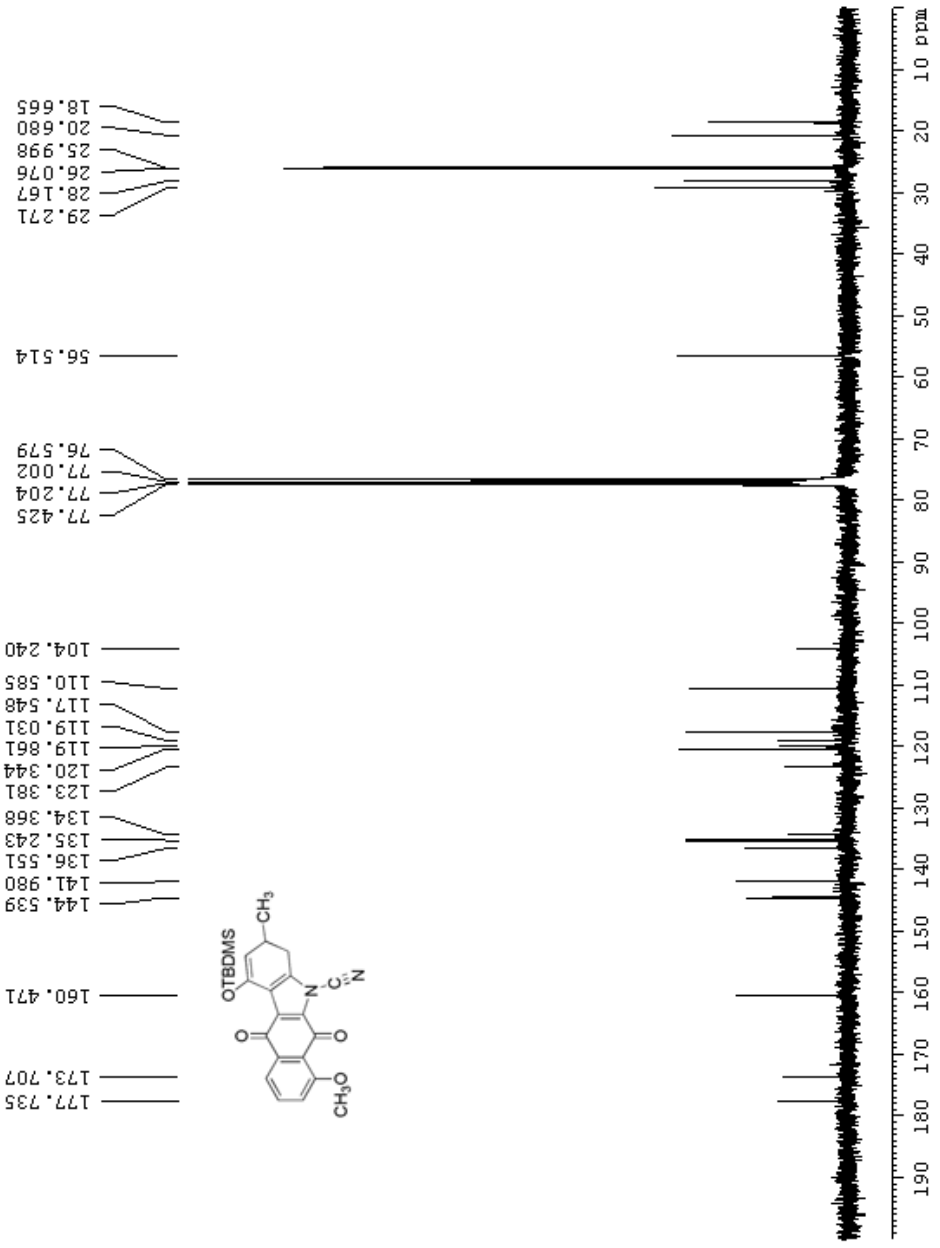
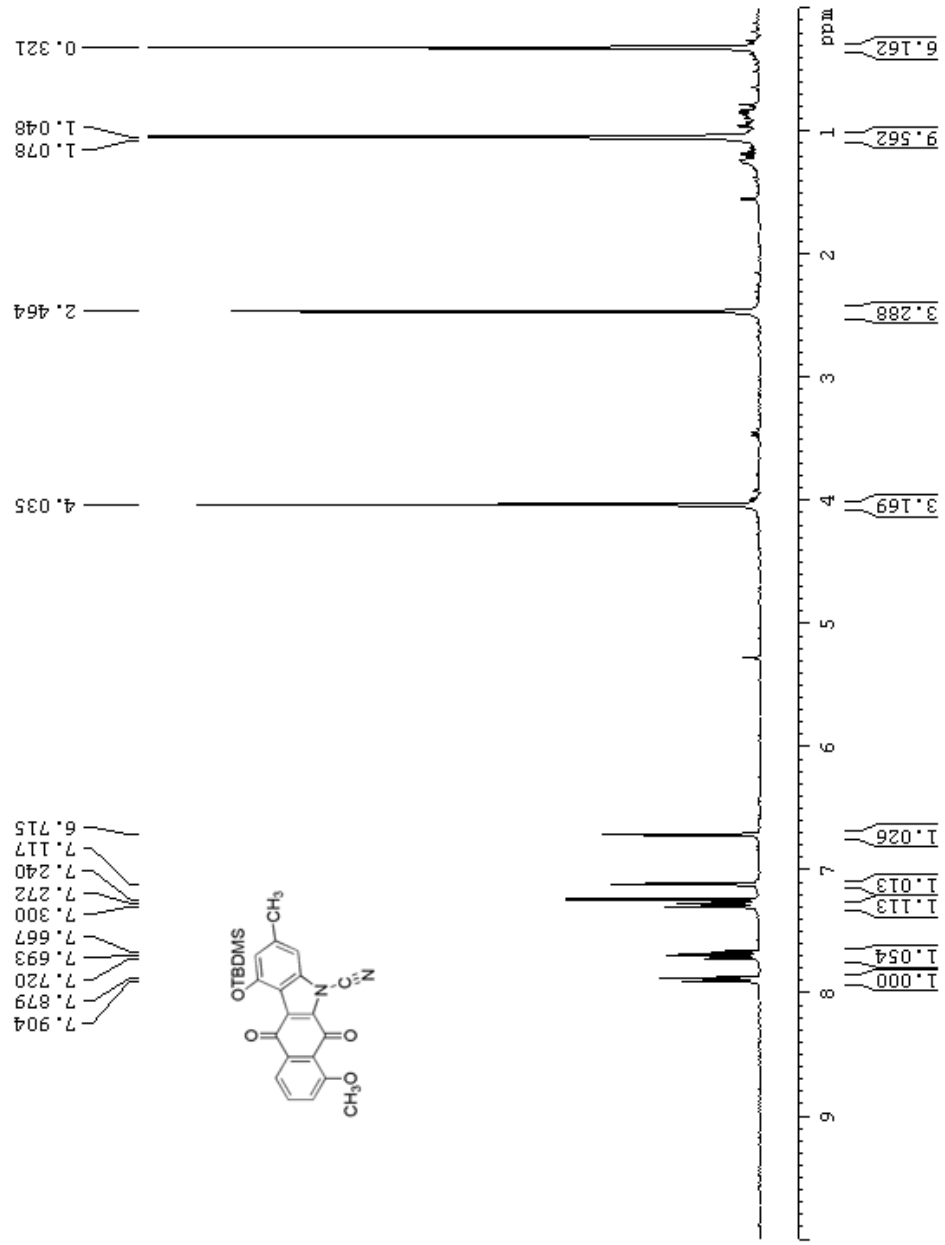
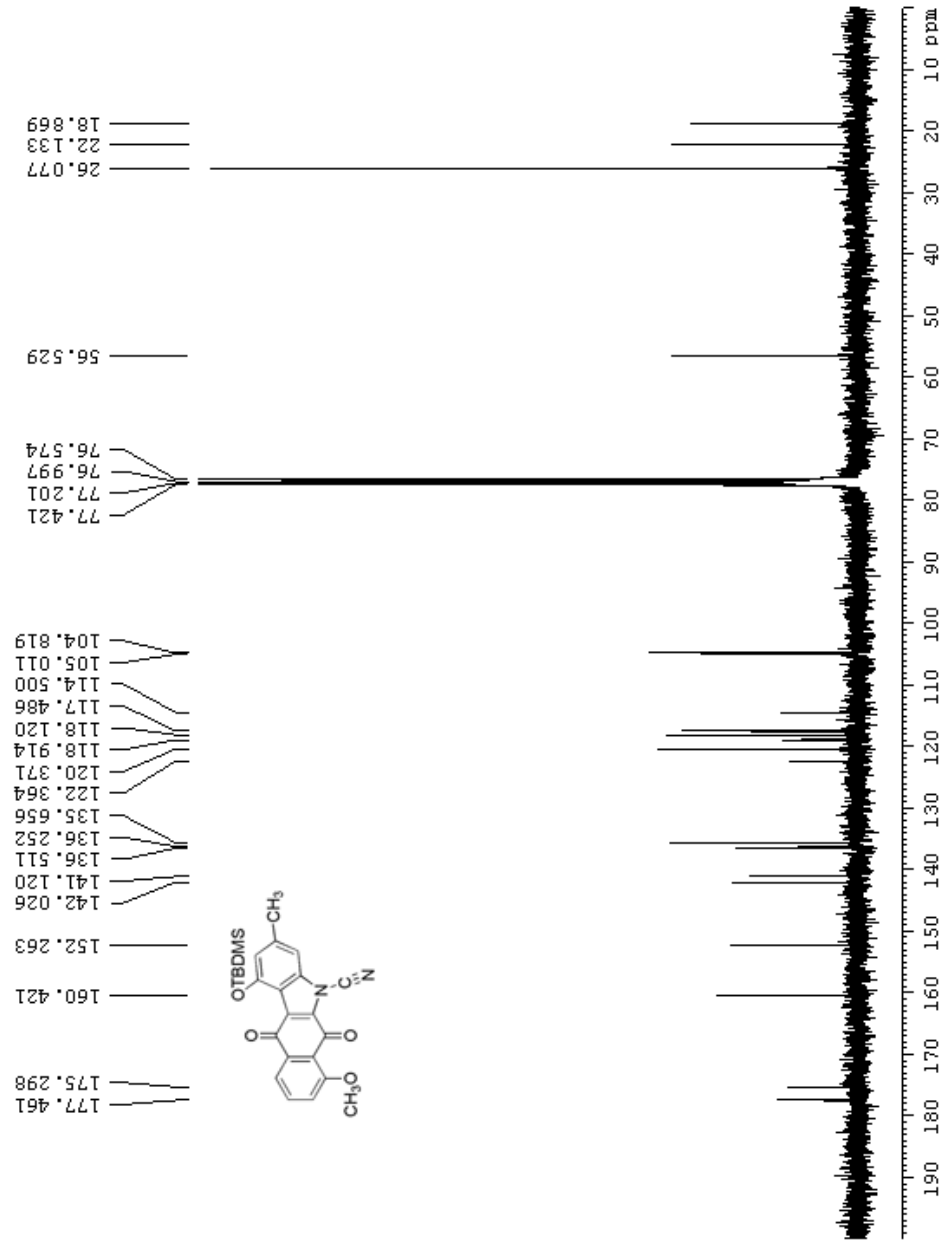
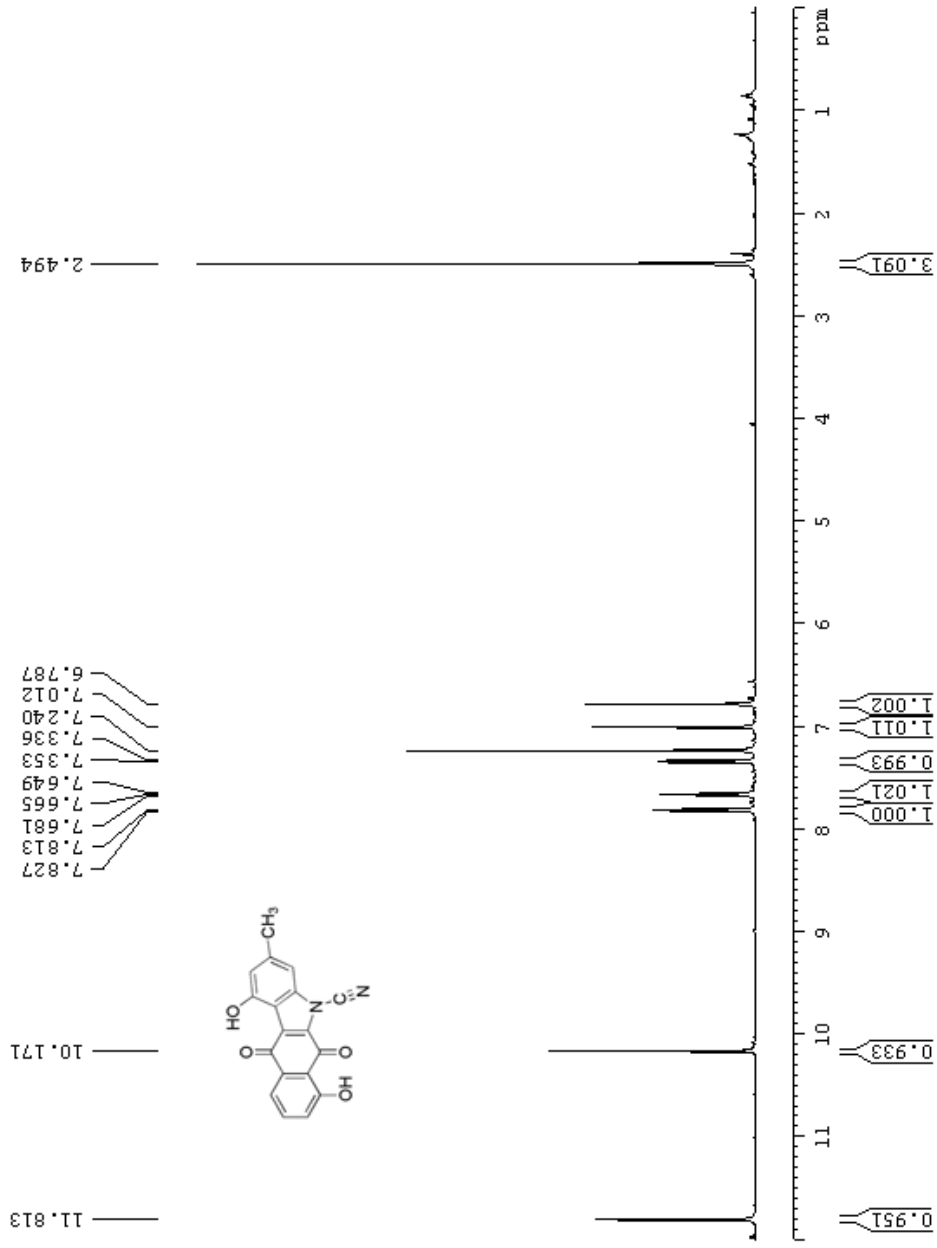
29.940
30.302
47.097
56.575
76.577
77.000
77.202
77.424
118.002
118.436
120.542
120.857
136.030
136.129
152.728
160.736
177.190
189.977
CH3
CH3O
N
C
N
O
O
O
10 ppm

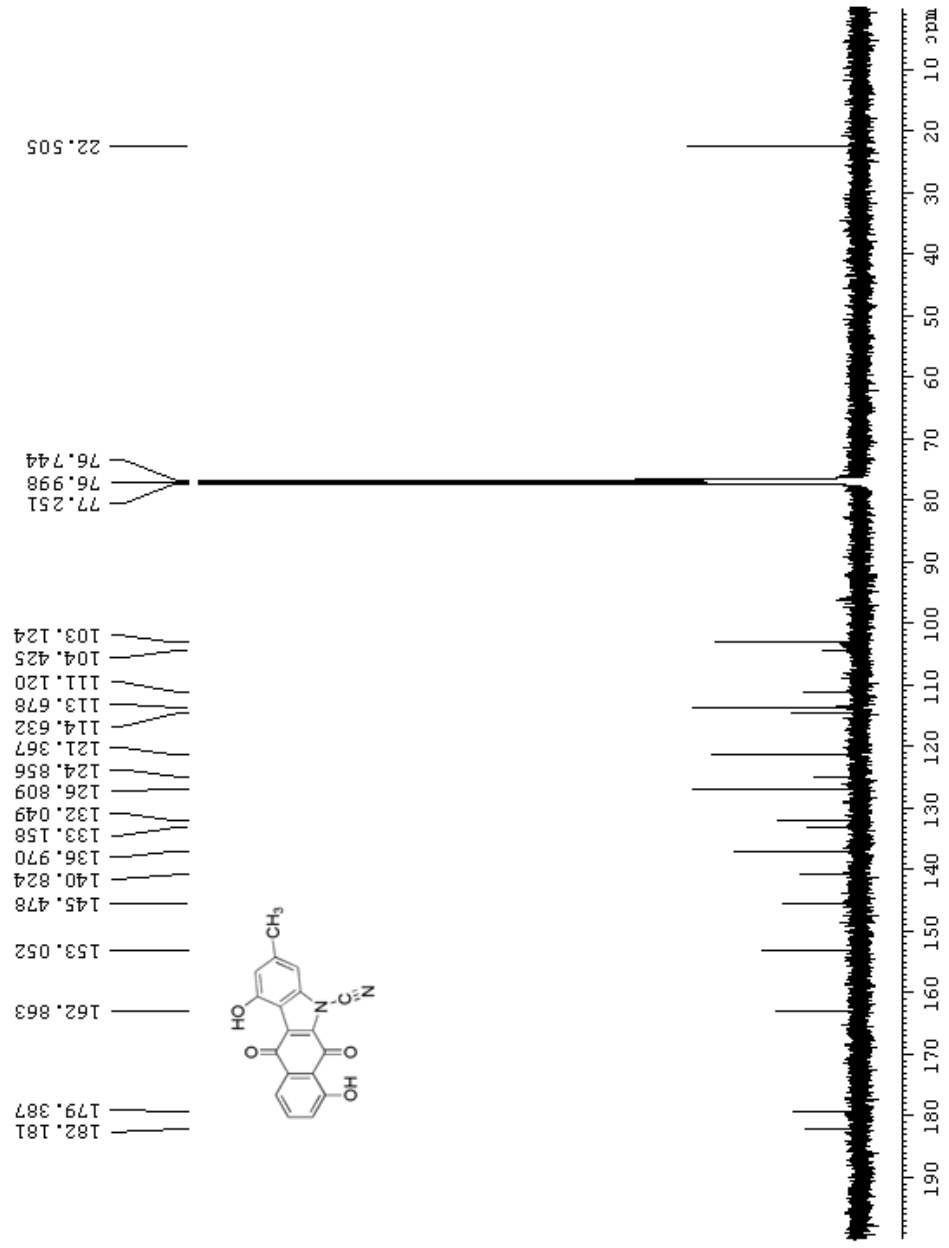

ppm
6.135
9.548
3.302
1.066
1.068
1.142
3.072
1.001
1.844
1.000
1.070
1.052
1.085
1.130
1.152
1.188
1.213
1.232
2.465
2.509
2.541
2.562
2.594
2.788
2.801
2.810
2.824
2.833
2.846
2.856
2.866
2.879
2.908
2.932
2.961
2.986
3.965
4.010
4.033
4.950
4.963
7.240
7.279
7.621
7.648
7.675
7.816
7.841
OTBDMS
CH3
N
O
O
O
CH3O


18.665
20.680
25.998
26.076
28.167
29.271
56.514
76.579
77.002
77.204
77.425
104.240
110.585
117.548
119.031
119.861
120.344
123.381
134.368
135.243
136.551
141.980
144.539
160.471
173.707
177.735
OTBDMS
CH3
N
C
N
O
O
CH3O
10 ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190


0.321
1.048
1.078
2.464
4.035
6.715
7.117
7.240
7.272
7.300
7.667
7.693
7.720
7.879
7.904
OTBDMS
CH3
N
C
N
O
O
CH3O
ppm
1
2
3
4
5
6
7
8
9
6.162
9.562
3.288
3.169
1.026
1.013
1.113
1.054
1.000


18.869
22.133
26.077
56.529
76.574
76.997
77.201
77.421
104.819
105.011
114.500
117.486
118.120
118.914
120.371
122.364
135.656
136.252
136.511
141.120
142.026
152.263
160.421
175.298
177.461
OTBDMS
CH3
CH3O
N
C
N
O
O
10 ppm


11.813
10.171
7.827
7.813
7.681
7.665
7.649
7.353
7.336
7.240
7.012
6.787
2.494
0.951
0.933
1.000
1.021
0.993
1.011
1.002
3.091
ppm


22.505
76.744
76.998
77.251
103.124
104.425
111.120
113.678
114.632
121.367
124.856
126.809
132.049
133.158
136.970
140.824
145.478
153.052
162.863
179.387
182.181
HO
O
O
OH
N
C
N
CH3
ppm

6. References

1. C. T. Lee, W. T. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785-789.
2. A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648-5652.
3. P. v. R. Schleyer, ed., *Encyclopedia of Computational Chemistry*, John Wiley, New York, 1998.
4. *Gaussian 03, Revision C.02*, M. J. T. Frisch, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.
5. B. B. Hasinoff, A. M. Creighton, H. Kozlowska, P. Thampatty, W. P. Allan and J. C. Yalowich, *Mol. Pharmacol.*, 1997, **52**, 839-845.
6. W. L. F. Armarego and D. D. Perrin, *Purification of laboratory chemicals*, Butterworth-Heinemann; Elsevier Science, Oxford, Boston, 1996, p. 1-529.
7. W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923-2925.
8. T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley, New York, 1999, p. 23.
9. O. Cakmak, I. Demirtas and H. T. Balaydin, *Tetrahedron*, 2002, **58**, 5603-5609.
10. R. L. Hannan, R. B. Barber and H. Rapoport, *J. Org. Chem,*. 1979, **44**, 2153-2158.
11. Y. Tanoue, A. Terada and Y. Matsumoto, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 2736-2738.
12. W. Williams, X. Sun and D. Jebaratnam, *J. Org. Chem.*, 1997, **62**, 4364-4369.
13. J. P. Wolfe, J. Ahman, J. P. Sadighi, R. A. Singer and S. L. Buchwald, *Tetrahedron Lett.*, 1997, **38**, 6367-6370.
14. G. Malesani and M. G. Ferlin, *J. Heterocycl. Chem.*, 1987, **24**, 513-517.
15. B. Akermark, L. Eberson, E. Jonsson and E. Pettersson, *J. Org. Chem.*, 1975, **40**, 1365-1367.
16. R. E. Murray and G. Zweifel, *Synthesis*, 1980, 150-151.
17. L. N. Mander and S. P. Sethi, *Tetrahedron Lett.*, 1984, **25**, 5953-5956.