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Supporting Information

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Synthesis of Diverse Lactam Carboxamides Leading to the Discovery of an New Transcription Factor Inhibitor

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Ia. General Methods.

^{1}H NMR spectra were obtained on a Varian UNITY INOVA500 spectrometer (500 MHz) or Bruker Avance 300 spectrometer (300 MHz). Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent ($CHCl_3$, s, δ 7.26). Multiplicities are given as: s (singlet), d (doublet), t (triplet), q (quartet), dt (doublet of triplets), m (multiplet). Proton-decoupled ^{13}C NMR spectra were obtained on a Varian UNITY INOVA 500 spectrometer (125 MHz) or Bruker Avance 300 spectrometer (300 MHz). ^{13}C chemical shifts are reported relative to $CDCl_3$ (t, δ 77.2). IR frequencies are given in cm^{-1} and spectra were obtained on a Nicolet Avatar 370 FT-IR spectrometer equipped with a DTGS detector and Smart Orbit single bounce diamond ATR accessory. Tandem high performance liquid chromatography/mass spectral (LCMS) analyses were performed on a

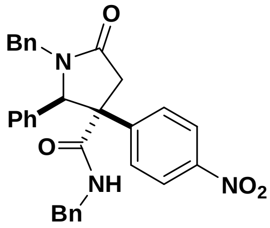
Micromass Platform LCZ mass spectrometer or a Micromass Platform LCT mass spectrometer in atmospheric pressure chemical ionization (APCI) mode after separation performed on a Waters Alliance 2690 separations module. The actual separations were performed on a Waters Symmetry® C_{18} 3.5 μm, 2.1 x 50 mm column with a flow rate of 0.4 mL/min and a 12 min gradient of 15-100% CH_3CN in H_2O, with a constant 0.1% formic acid buffer using a Waters 996 photodiode array detector.

Silica gel chromatographic purifications were performed by flash chromatography with silica gel (EMD, 40–63 μm) packed in glass columns; the eluting solvent for each purification was determined by thin layer chromatography (TLC). Analytical TLC was performed on glass plates coated with 0.25 mm silica gel using UV for visualization.

Manipulations under an inert atmosphere were carried out using standard Schlenk line techniques. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and toluene ($PhCH_3$) were dried by passage through a column of activated alumina (as described in *Organometallics* **1996**, *15*, 1518–1520). All other reagents and solvents were reagent grade and were used without further purification unless otherwise specified.

The following abbreviations are used throughout: isopropanol (IPA), 4-*N,N*-dimethylaminopyridine (DMAP), bromotripyrrolidinophosphonium hexafluorophosphate (PyBrOP), trimethylsilylmethoxide (TMSOMe), trifluoromethanesulfonic acid (TfOH), trifluoromethanesulfonic anhydride (Tf_2O), *N,N*-dimethylformamide (DMF), O-(7-azabenzotriazol-1-yl)-*N,N,N',N*-tetramethyl-uronium hexafluorophosphate (HATU), dimethyl sulfoxide (DMSO), cesium acetate (CsOAc), copper (I) iodide (CuI).

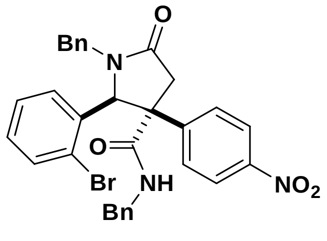
Ib. Pathway development



(+/-) (2S, 3S)-N,1-dibenzyl-3-(4-nitrophenyl)-5-oxo-2-phenylpyrrolidine-3-carboxamide (1a). To the solution of the *p*-nitrophenylthiosuccinic anhydride in CH_2Cl_2 was added imine (98 mg, 0.5 mmol). The solution was heated at 90 ^{o}C oil bath under stirring for a period of 10 hours and subsequently concentrated *in vacuo* to yield 1-benzyl-3-(4-nitrophenyl)-5-oxo-2-phenylpyrrolidine-3-carboxylic acid as a pale yellow oil.

The acid was utilized without further purification in the subsequent amidation. To the solution of carboxylic acid and HATU (209 mg, 0.55 mmol) in anhydrous DMF (5 mL) was added diisopropylethylamine (174 μL, 1.0 mmol). To the mixture was added benzyl amine (65 μL, 0.6 mmol) and the reaction mixture was stirred at room temperature over a period of 3 hours and subsequently diluted with EtOAc. The reaction solution was washed with brine solution and water. The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo.* Purification on SiO_2 (30% EtOAc/hexanes) afforded 102 mg of amide **(1a)** (40% yield from diacid) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.5 Hz, 2H), 7.44-7.36 (m, 6H), 7.22 - 7.16 (m, 7H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 5.20 (d, *J* = 1.4 Hz, 1H), 5.08 (t, *J* = 5.5 Hz, 1H), 4.86 (s, 1H), 4.10 (dd, *J* = 14.5, 6.0 Hz, 1H), 4.03 (d, *J* = 17.5 Hz, 1H), 3.78 (dd, *J* = 14.5, 5.0 Hz, 1H), 3.37 (d, *J* = 14 Hz, 1H), 2.50 (d, *J* = 17.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 169.2, 150.1, 147.2, 137.0, 135.5, 135.0, 129.7, 129.5, 129.2, 129.1, 129.0, 128.6, 128.5, 128.0, 127.8, 127.7, 124.1, 66.8, 58.0, 44.9, 44.4, 42.4; IR (thin film): 3313, 3032, 1670, 1604, 1521, 728, 703 cm^{-1}; LCMS: mass calcd $(M+H)^{+}$ *m/z* 506.21, found: *m/z* 506.00.

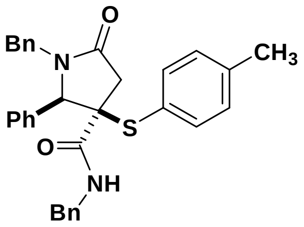


(+/-) (2S, 3S)-N,1-dibenzyl-2-(2-bromophenyl)-3-(4-nitrophenyl)-5-oxopyrrolidine-3-carboxamide (1b). *p*-Nitrophenylthiosuccinic acid^{2} (72 mg, 0.3 mmol) was suspended in trifluoacetic anhydride (10 mL) and reaction mixture was stirred for a period of 4 hours. The mixture was extracted with benzene three times and the extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give *p*-nitrophenylthiosuccinic anhydride as a brown oil.

To the solution of the *p*-nitrophenylthiosuccinic anhydride in CH_2Cl_2 was added imine (96 mg, 0.3 mmol). The solution was heated at 90 °C oil bath under stirring for a period of 10 hours and subsequently concentrated *in vacuo* to yield 1-benzyl-2-(2-bromophenyl)-3-(4-nitrophenyl)-5-oxopyrrolidine-3-carboxylic acid as a pale yellow oil .

The acid was utilized without further purification in the subsequent amidation. To the solution of carboxylic acid and HATU (125 mg, 0.33 mmol) in anhydrous DMF (2 mL) was added diisopropylethylamine (115 µL, 0.66 mmol). To the mixture was added benzyl amine (44 µL, 0.40 mmol) and the reaction mixture was stirred at room temperature over a period of 3 hours and subsequently diluted with EtOAc. The reaction solution was washed with brine solution and water. The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification on SiO_2 (30% EtOAc/hexanes) afforded 60 mg of amide **(1b)** (34% yield from diacid) as a white solid.

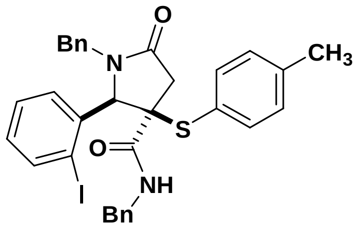
Mp = 210-212 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.5 Hz, 2H), 7.45 (m, 5H), 7.30 – 7.18 (m, 8H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.88 (dd, *J* = 7.0, 1.5 Hz, 1H), 5.59 (s, 1H), 5.33 (t, *J* = 5.5 Hz, 1H), 5.22 (d, *J* = 14.0 Hz, 1H), 4.26 (d, *J* = 18.0 Hz, 1H), 4.07 (dd, *J* = 14.5, 6.5 Hz, 1H), 3.73 (dd, *J* = 14.5, 5.0 Hz, 1H), 3.28(d, *J* = 14.0 Hz, 1H), 2.46 (d, *J* = 14.5 Hz, 1H);^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 168.9, 149.9, 147.4, 136.9, 135.4, 134.5, 133.4, 131.0, 130.0, 129.2, 129.1, 128.9, 128.83, 128.82, 128.19, 127.85, 127.48, 125.23, 124.47, 64.0, 57.8, 45.2, 44.4, 43.2; IR (thin film): 3338, 3064, 3031, 2927, 1677, 1519, 1348 cm^{-1}; LCMS: mass calcd $(M+H)^+$ *m/z* 584.12, found: *m/z* 584.27.



(+/-) (2R,3R)-N,1-dibenzyl-2-(2-iodophenyl)-5-oxo-3-(p-tolylthio)pyrrolidine-3-carboxamide (2a). To a solution of benzaldehyde (5.06 mL, 50 mmol) in CH_2Cl_2, was added benzyl amine (5.72 mL, 52.5 mmol) and Na_2SO_4 (20 g). The suspension was stirred at room temperature for a period of 3 hours. The reaction was filtered through Celite, washed with anhydrous CH_2Cl_2, and concentrated *in vacuo* to give 9.53 g of the imine (98% yield) as a waxy solid. To the solution of the imine (59 mg, 0.30 mmol) in CH_2Cl_2, was added *p*-tolythiosuccinic anhydride (67 mg, 0.30 mmol).[3] The solution was heated at 90°C oil bath under stirring for a period of 10 hours and subsequently concentrated *in vacuo* to yield of 1-benzyl-5-oxo-2-phenyl-3-(p-tolylthio)pyrrolidine-3-carboxylic acid as a yellow solid.

The acid was utilized without further purification in the subsequent amidation. To the solution of carboxylic acid and HATU (125 mg, 0.33 mmol) in anhydrous DMF (2 mL) was added diisopropylethylamine (115 μL, 0.66 mmol). To the mixture was added benzyl amine (36 μL, 0.33 mmol) and the reaction mixture was stirred at room temperature over a period of 3 hours and subsequently diluted with CH_2Cl_2. The reaction solution was washed with brine solution and water. The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification on SiO_2 (30% EtOAc/hexanes) afforded 111 mg of amide **(2a)** (73% yield) as a white solid.

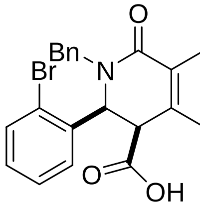
Mp = 188-190 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.77 (m, 13H), 7.00-6.94 (m, 7H), 5.23 (d, J = 15.0 Hz, 1H), 4.65 (s, 1H), 4.41 (d, J = 5.0 Hz, 2H), 3.63 (d, J = 15.5 Hz, 1H), 3.56 (d, *J* = 17.5 Hz, 1H), 2.74 (d, *J* = 17.5 Hz, 1H), 2.29 (s, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 170.9, 139.4, 137.7, 135.5, 133.8, 133.0, 130.4, 129.64, 129.60, 129.0, 128.8, 128.7, 128.5, 128.0, 127.9, 126.9, 110.0, 69.2, 60.1, 45.0, 44.8, 40.8, 21.3; IR (thin film): 3325, 3030, 2919, 1683, 1494 cm^{-1}; LCMS: mass calcd $(M+H)^+$ *m/z* 507.21, found: *m/z* 507.17.



2b **(+/-) (2R,3R)-N,1-dibenzyl-2-(2-iodophenyl)-5-oxo-3-(p-tolylthio)pyrrolidine-3-carboxamide (2b)[3].** To a solution of the imine (7.76 mmol) in toluene (40 mL, 0.2 M) over Na_2SO_4 (16.5 g) was added *p*-tolylthiosuccinic anhydride (1.72 g, 7.76 mmol, 1.0 equiv). The reaction was heated to reflux under stirring for a period of 16 hours and subsequently concentrated *in vacuo* to afford carboxylic acid.

To a cooled solution of carboxylic acid (7.76 mmol) at 0 °C in anhydrous DMF (26 mL, 0.3 M) was added diisopropylethylamine (2.97 mL, 17.1 mmol, 2.2 equiv) and HATU (3.25 g, 8.54 mmol, 1.1 equiv). To the cooled mixture was added benzylamine (0.93 mL, 8.54 mmol, 1.1 equiv) and the mixture was stirred at 0°C for 2 hours. The reaction mixture was allowed to warm to room temperature over a period of 12 hours and subsequently diluted with CH_2Cl_2 (100 mL). The reaction solution was washed with water (2 x 400 mL) and then with a brine solution. The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification on SiO_2 (30% EtOAc/hexanes) afforded 3.58 g of amide **(2b)** (73% yield from aldehyde) as a white solid.

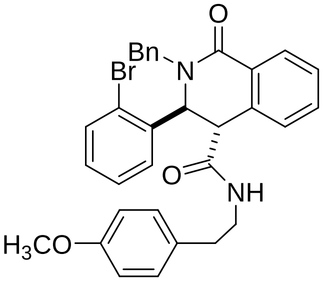
^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.47 (dt, *J* = 8.0, 7.8, 1.1 Hz, 1H), 6.97-7.37 (m, 17H), 5.20 (d, *J* = 14.6 Hz, 1H), 5.01 (s, 1H), 4.35 (dd, *J* = 8.4, 5.7 Hz, 2H), 3.51 (d, *J* = 16.8 Hz, 1H), 3.39 (d, *J* = 14.6 Hz, 1H), 2.85 (d, *J* = 16.8 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 170.6, 140.3, 139.5, 137.5, 136.6, 135.1, 134.0, 131.10, 130.2, 129.4, 129.0, 128.9, 128.9, 128.8, 128.6, 128.0, 127.8, 126.6, 101.4, 71.8, 59.0, 45.0, 44.9, 41.5, 21.3; IR (thin film): 3387, 1690, 1667, 1507, 1491, 1420, 1264 cm-1; LCMS: mass calcd for $(M+H)^+$ *m/z* 633.11, found: *m/z* 633.11.



(+/-) (3S, 4R) 2-benzyl-3-(2-bromophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid. To a solution of 2-bromobenzaldehyde (3.70g, 20 mmol) in CH_2Cl_2 (10 mL), was added benzyl amine (2.18mL, 20 mmol) and Na_2SO_4 (10 g). The suspension was stirred at room temperature for a period of 3 hours. The reaction was filtered through Celite, washed with anhydrous CH_2Cl_2, and concentrated *in vacuo* to give the imine (5.45 g, 99%) as a waxy solid.

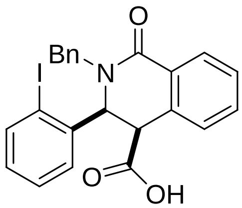
To the solution of the imine (822 mg, 3.0 mmol) in CH_2Cl_2, was added methyl homophthalic anhydride (486 mg, 3.0 mmol). The reaction mixture was stirred at rt for a period of 3 hours. The precipitated was filtered, washed with CH_2Cl_2, and dried under reduced pressure to afford 1.10 g of 2-benzyl-3-(2-bromophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (87% yield) as a colorless powder.

^{1}H NMR (500 MHz,$CDCl_3$) δ 8.27 (d, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.51-7.41 (m, 2H), 7.30 (m, 1H), 7.26 (m, 2H), 7.15- 6.99 (m, 5H), 6.80 (dd, *J* = 7.5, 1.5 Hz, 1H), 5.53 (s, 1H), 5.44 (d, *J* = 14.5 Hz, 1H), 3.95 (s, 1H), 3.82 (d, *J* = 14.0 Hz, 1H)
LCMS: mass calcd $(M+H)^+$ *m/z* 436.05, found: *m/z* 436.30.



(+/-) (3S, 4S)-2-benzyl-3-(2-bromophenyl)-N-(4-methoxyphenethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide (3a). To the solution of carboxylic acid (84 mg, 0.2 mmol) and HATU (84 mg, 0.22 mmol) in anhydrous DMF (2 mL) was added diisopropylethylamine (76 μL, 0.22 mmol). To the mixture was added 2-(4-methoxyphenyl)ethanamine (32 μL, 0.22 mmol) and the reaction mixture was stirred at room temperature over a period of 3 hours and subsequently diluted with EtOAc. The reaction solution was washed with water and the with a brine solution. The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo.* Purification on SiO_2 (33% EtOAc/hexanes) afforded 95 mg of amide **(3a)** (85% yield) as a white solid.

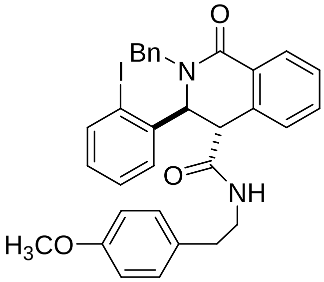
Mp = 160-161 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.52 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.45 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.38 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.39 – 7.23 (m, 7H) , 7.03 (m, 2H), 6.96 (d, *J* = 7.0 Hz, 1H), 6.81 (d, = 9.0 Hz, 2H), 6.74 (m, 2H), 5.72 (s, 1H), 5.33 (d, *J* = 14.5 Hz, 1H), 5.11 (t, *J* = 5.0 Hz, 1H), 3.86 (d, *J* = 14.5 Hz), 3.80 (s, 1H), 3.78 (m, 3H), 3.20 (m, 2H), 2.45 (m ,2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 164.1, 158.4, 137.3, 136.6, 133.7, 132.8, 132.6, 130.5, 129.7, 129.6, 129.4, 129.24, 129.18, 129.0, 128.8, 128.7, 128.0, 127.74, 127.69, 123.0, 114.3, 61.2, 55.5, 50.6, 50.2, 41.3, 34.4; IR (thin film): 1654, 1511 cm^{-1}; LCMS: mass calcd $(M+H)^+$ *m/z* 569.14, found: *m/z* 569.41.



(+/-) (3S, 4R) 2-benzyl-3-(2-iodophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid. Homophthalic acid (1.80 g , 10 mmol) was suspended in trifluoacetic anhydride (10 mL) and reaction mixture was stirred for a period of 4 hours. The mixture was extracted with benzene three times and extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 1.40 g of homophthalic anhydride (87% yield) as a colorless powder .

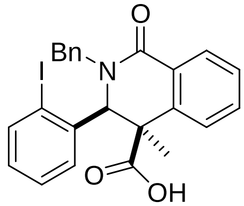
To the solution of the imine (963 mg, 3.0 mmol) in CH_2Cl_2, was added homophthalic anhydride (486 mg, 3.0 mmol). The reaction mixture was stirred at rt for a period of 3 hours. The precipitated was filtered, washed with CH_2Cl_2, and dried under reduced pressure to afford 1.35 g of 2-benzyl-3-(2-iodophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (93% yield) a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.26 (m, 2H), 7.46 (m, 2H), 7.15-7.05 (m, 5H), 6.90 (t, *J* = 7.5Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 5.42 (d, *J* = 14.5 Hz, 1H), 5.37 (s, 1H), 3.89 (s, 1H), 3.84 (d, *J* = 14.5 Hz, 1H); LCMS: mass calcd $(M+H)^+$ *m/z* 484.28, found: *m/z* 484.04.



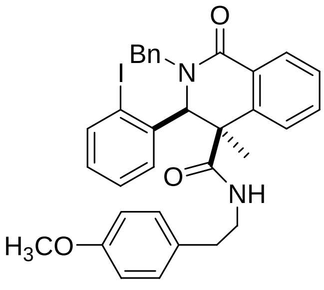
(+/-) (3S, 4S) 2-benzyl-3-(2-iodophenyl)-N-(4-methoxyphenethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide (3b). To the solution of carboxylic acid (97 mg, 0.20 mmol) and HATU (84 mg, 0.22 mmol) in anhydrous DMF (2 mL) was added diisopropylethylamine (76 μL, 0.44 mmol). To the mixture was added 2-(4-methoxyphenyl)ethanamine (32 μL, 0.22 mmol) and the reaction mixture was stirred at room temperature over a period of 3 hours and subsequently diluted with CH_2Cl_2. The reaction solution was washed with water and the with a brine solution. The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo.* Purification on SiO_2 (30% EtOAc/hexanes) afforded 100 mg of amide **(3b)** (81% yield) as a white solid.

Mp= 166-167 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.46 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.38 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.31-7.24 (m, 5H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.87 (dt, *J* = 7.5, 1.5 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 2H), 6.75 (m, 2H), 6.72 (dd, *J* = 8.0, 1.5 Hz, 1H), 5.51 (s, 1H), 5.34 (d, *J* = 14.5Hz, 1H), 5.16 (m, 1H), 3.82 (d, *J* = 14.5 Hz, 1H), 3.79 (s, 3H), 3.72 (m, 1H), 3.20 (m, 2H), 2.46 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 164.0, 158.3, 140.5, 139.7, 136.5,132.8, 132.4, 130.5, 129.8, 129.7, 129.4, 129.3, 129.1, 128.9, 128.73, 128.68, 128.5, 127.9, 127.2, 114.2, 98.3, 65.2, 55.4, 50.6, 49.9, 41.2, 34.3; IR (thin film): 3315, 2932, 1649, 1512 cm^{-1}; LCMS: mass calcd $(M+H)^+$ *m/z* 617.13, found: *m/z* 617.39.



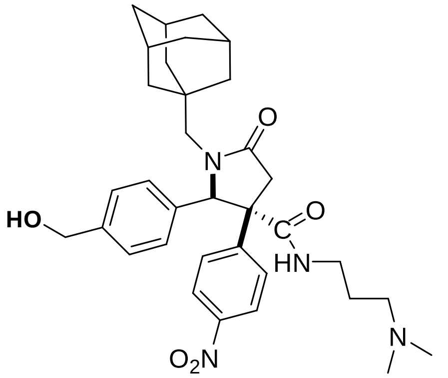
(+/-) (3S,4R)-2-benzyl-3-(2-iodophenyl)-4-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid. To a solution of 2-iodobenzaldehyde (1.88 g, 8.08 mmol) in CH_2Cl_2, was added benzyl amine (0.88 mL, 8.08 mmol) and Na_2SO_4 (2.0 g). The suspension was stirred at room temperature for a period of 3 hours. The reaction was filtered through Celite, washed with anhydrous CH_2Cl_2, and concentrated *in vacuo* to give the imine (2.50 g, 97%) as a waxy solid. To the solution of the imine (1.64 g, 5.1 mmol) in CH_2Cl_2, was added 2'-methyl homophthalic anhydride[1] (853 mg, 4.85 mmol). The reaction mixture was stirred at rt for a period of 3 hours. The precipitate was filtered, washed with CH_2Cl_2, and dried under reduced pressure to give 2.08 g of 2-benzyl-3-(2-iodophenyl)-4-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (86% yield) as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (m, 1H), 7.79 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.54 (m, 2H), 7.34 (m, 3H), 7.13 (m, 3H), 6.98 (m, 1H), 6.86 (m, 1H), 6.60 (dd, *J* = 8.0, 1.5 Hz, 1H), 5.60 (s, 1H), 5.23 (d, *J* = 15.0 Hz, 1H), 3.75 (d, *J* = 14.5 Hz, 1H), 1.43 (s, 3H); LCMS: mass calcd $(M+H)^+$ *m/z* 498.75, found: *m/z* 498.66.



(+/-) (3S, 4R)-2-benzyl-3-(2-iodophenyl)-N-(4-methoxyphenethyl)-4-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide (4). To the solution of carboxylic acid (50 mg, 0.10 mmol) and HATU (42 mg, 0.11mmol) in anhydrous DMF (1 mL) was added diisopropylethylamine (38 µL, 0.22 mmol). To the mixture was added 2-(4-methoxyphenyl)ethanamine (16 µL, 0.11 mmol) and the reaction mixture was stirred at room temperature over a period of 3 hours and subsequently diluted with EtOAc. The reaction solution was washed with water and then with a brine solution. The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification on SiO_2 (30% EtOAc/hexanes) afforded 54 mg of amide **(4)** (86% yield) as a white solid.

Mp = 60-70 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 7.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.53 - 6.72 (m, 13H), 6.55 (d, *J* = 8.0 Hz, 1H), 5.95 (s, 1H), 5.02 (d, *J* = 14.5 Hz, 1H), 4.83 (t, *J* = 5.0 Hz, 1H), 4.02 (d, *J* = 14.5 Hz, 1H), 3.78 (s, 3H), 3.24 (m, 1H), 3.11 (m, 1H), 2.77 (m, 1H), 2.49 (m, 1H), 2.38 (m, 1H), 1.32 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 162.9, 158.3, 140.2, 139.6, 157.5, 136.9, 133.0, 130.5, 130.1, 130.05, 129.7, 129.2, 128.9, 128.7, 128.3, 127.7, 127.6, 126.3, 114.21, 114.17, 103.1, 69.5, 55.4, 51.5, 50.5, 41.5, 34.4, 20.3; IR (thin film): 3421, 2931, 1649, 1510 cm^{-1}; LCMS: mass calcd $(M+H)^+$ *m/z* 631.15, found: *m/z* 631.42.



(+/-) (2S, 3S)-N-(3-(dimethylamino)propyl)-2-(4-(hydroxymethyl)phenyl)-1-methyladamantyl-3-(4-nitrophenyl)-5-oxopyrrolidine-3-carboxamide (31). To a solution of 4-(hydroxymethyl)benzaldehyde[2] (529 mg, 1.81 mmol in CH_2Cl_2, was added 1-adamantyl methyl amine (299 mg, 1.81 mmol) and Na_2SO_4 (1.0 g). The suspension was stirred at room temperature for a period of 3 hours. The reaction was filtered through Celite, washed with anhydrous CH_2Cl_2, and concentrated *in vacuo* to give the imine (780 mg, 99% yield) as colorless oil. To the solution of the imine (220 mg, 0.50 mmol) in CH_2Cl_2, was added *p*-nitrophenylthiosuccinic anhydride (110 mg, 0.50 mmol). The solution was heated at 90 ^{o}C oil bath under stirring for a period of 10 hours and subsequently concentrated *in vacuo* to yield the carboxylic acid as a pale yellow oil.

The acid was utilized without further purification in the subsequent amidation. To the solution of carboxylic acid and HATU (87 mg, 0.23 mmol) in anhydrous DMF (1 mL) was added diisopropylethylamine (73 µL, 0.42 mmol). To the mixture was added benzyl amine (32 µL, 0.25 mmol) and the reaction mixture was stirred at room temperature over a period of 3 hours and subsequently diluted with CH_2Cl_2. The reaction solution was washed with brine solution and water. The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo.*

To the EtOH solution of the crude amid was added 2.0 M HCl (100 µL) and the reaction was refluxed for 2h, the solvent was removed under reduced pressure. Purification on silica gel (20% EtOH + 0.2% Et_3N in CH_2Cl_2) afforded 27 mg of N-(3-(dimethylamino)propyl)-2-(4-(hydroxymethyl)phenyl)-1-methyladamantyl-3-(4-

nitrophenyl)-5-oxopyrrolidine-3-carboxamide **(31)** (22% yield from diacid) as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 9.0 Hz, 1H), 8.02 (d, *J* = 9.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.24 (m, 2H), 5.18 (s, 1H), 4.66 (s, 1H), 3.48 (d, *J* = 16.5 Hz, 1H), 3.36 (d, *J* = 14.0 Hz, 1H), 3.01-2.79 (m, 5H), 2.14 (s, 6H), 2.10 (m, 1H), 1.98 (m, 1H), 1.81 (m, 3H), 1.58 (m, 3H), 1.34 (d, *J* = 11.5 Hz, 3H), 1.28-1.21 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 173.6, 169.5, 149.6, 147.5, 142.6, 134.8, 128.3, 127.6, 123.8, 123.4, 73.9, 64.9, 57.7, 53.7, 45.7, 44.5, 41.1, 38.2, 36.9, 36.8, 36.1, 29.9, 28.31, 28.26, 24.4, 9.3; IR (thin film): 3307, 2903, 2848, 1668, 1603, 1520, 1450 cm^{-1}; LCMS: mass calcd $(M+H)^+$ *m/z* 589.34, found: *m/z* 589.27.

References and Notes:

1. Kita, Y.; Akai, S.; Ajimura, N.; Yoshigi, M.; Tsugoshi, T.; Yasuda, H; and Tamura, Y. *J. Org. Chem.* **1986**, *51,* 4150-4158.
2. Masse, C. E.; Ng, P. Y.; Fukase, Y.; Sanchez-Rosello, M; Shaw, J. T. *J. Comb. Chem. J. Comb. Chem.* **2006,** *8*(3); 293-296.
3. Ng, P. Y.; Masse, C. E.; Shaw, J. T. *Org. Lett.* **2006,** *8*(18), 3999 – 4002.

II. Library production

A library of 510 compounds was produced using split/pool chemistry according to the scheme provided on pages S14 and S16. Micro X-Kans (Discovery Partners International, XK-C096 XMicrokans™) were filled with 35 mg of silyl-functionalized 500-600 μm polystyrene macrobeads,[1] with a loading level of 1.13 mmol/g. Irori Accutag™ equipment and X-Kan manager software were used to track the chemical

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[1] Blackwell, H. E.; Perez, L.; Stavenger, R. A.; Tallarico, J. A.; Cope Eatough, E.; Foley, M. A.; Schreiber, S. L., *Chem. Biol.* **2001,** *8*, 1167-1182. (b) Tallarico, J. A.; Depew, K. M.; Pelish, H. E.; Westwood, N. J.; Lindsley, C. W.; Shair, M. D.; Schreiber, S. L.; Foley, M. A., *J. Comb. Chem.* **2001,** *3*, 312-318.

history of the X-Kans using optical encoding techniques.[2] After synthesis, the Kans were arrayed into a cleavage block (Accucleave 192), treated with 1.00 mL of cleavage cocktail consisting of 5% HF-pyridine (30% w/w HF) and 5% pyridine in THF, placed in a vacuum chamber and evacuated briefly to remove air from the Kans, and incubated at room temperature for 2h. The HF was quenched by the addition of 0.500 mL of TMSOMe and incubation for 30 minutes. The resultant solution was transferred into two 2.2 mL ("deep" well) 96-well plates (96WP#1). Fresh THF (1.5 mL) was added to the wells of the cleavage block, and the block was again placed in a vacuum chamber and evacuated briefly to remove air. After 30 minutes at room temperature, the THF was transferred into a second pair of 2.2 mL 96-well plates (96WP#2). This step was repeated to yield a third pair of 96-well plates (96WP#3). All of the 96 well plates were dried *in vacuo* using a Genevac^{TM} HT-12 centrifugating vacuum chamber. DMSO (1 mL) was added to 96WP#3, and the resultant solution was transferred to 96WP#2. The resultant solution was then transferred to the first pair of 96-well plates (96WP#1) to produce the "mother" plate of DMSO stock solutions of the library compounds, estimated to be at a concentration of 0.5 mM. 20 μL aliquots of these 96 well plates were removed and arrayed into standard 384-well plates which were employed in screening experiments. The "mother" plate was dried *in vacuo* using the Genevac, sealed, and stored at -20 °C between screening plate productions.

The aryl amidation pathway (final step, shown below) is not described in this communication, but will be included in a subsequent full disclosure of this study.

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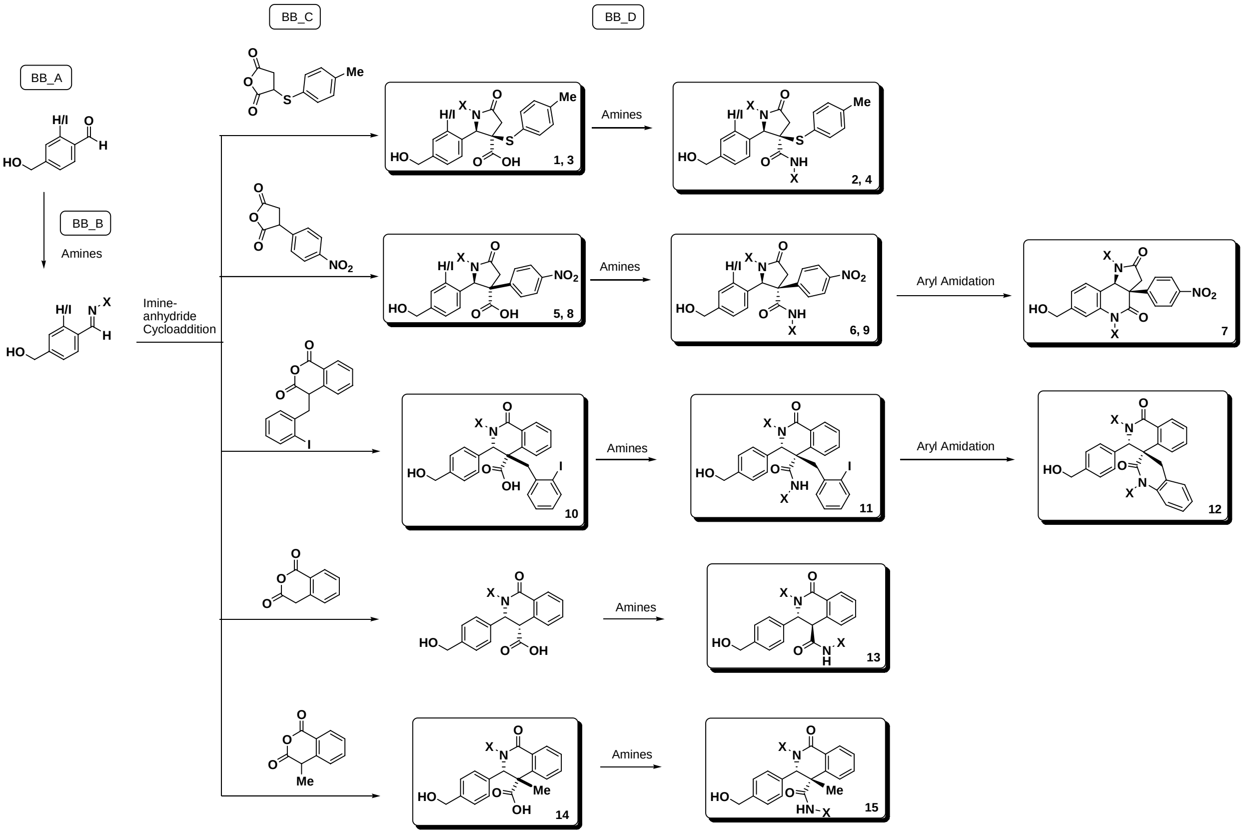
[2] Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker, A. J.; Barluenga, S.; Cao, G. Q.; Affleck, R. L.; Lillig, J. E., *J. Am. Chem. Soc.* **2000,** *122*, 9954-9967.

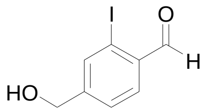
Summary of Library Synthesis:



Precursor	***BB_A***	***BB_B***	***BB_C***	***BB_D***	***Products***	***Notes***
Precursor	A01	B01-04, 09-11	C03	---	*7*	**Acids with iodine, from thiosuccinic anhydride**
Precursor	A01	B01-04, 09-11	C03	D01-	*70*	**Amides with iodine, from thiosuccinic anhydride**
Precursor	A02	B01-04, 09-11	C03	---	*7*	**Acids without iodine, from thiosuccinic**
Precursor	A02	B01-04, 09-11	C03	D01-	*70*	**Amides without iodine, from thiosuccinic**
Precursor	A01	B11-12	C01	---	*2*	**Acids with iodine, from *p*-NO_2 phenylsuccinic**
Precursor	A01	B11-12	C01	D01-	*20*	**Amides with iodine, from *p*-NO_2 phenylsuccinic**
Precursor	A01	B11-12	C01	D01-	*20*	**Aryl amidation products, from *p*-NO_2**
Precursor	A02	B10-12	C01	---	*3*	**Acids without iodine, from *p*-NO_2 phenylsuccinic**
Precursor	A02	B10-12	C01	D01-	*30*	**Amides without iodine, from *p*-NO_2**
Precursor	A02	B01, 03-04,	C02	---	*5*	**Acids without iodine, from *o*-iodobenzyl**
Precursor	A02	B01, 03-04,	C02	D02-	*45*	**Amides without iodine, from *o*-iodobenzyl**
Precursor	A02	B01, 03-04,	C02	D02-	*45*	**Aryl amidation products, from *o*-iodobenzyl**
Precursor	A02	B01-12	C04	D01-	*120*	**Amides without iodine, from homophthalic**
Precursor	A02	B01-2, 5-6, 8,	C05	---	*6*	**Acids without iodine, from methyl-homophthalic**
Precursor	A02	B01-2, 5-6, 8,	C05	D01-	*60*	**Amides without iodine, from methyl-**
					510	

Building Blocks

BB_A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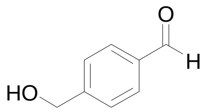
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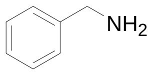
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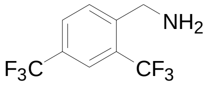
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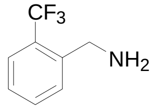
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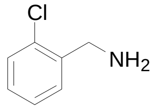
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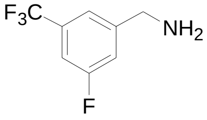
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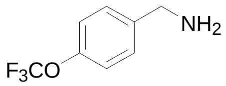
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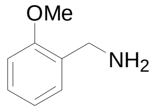
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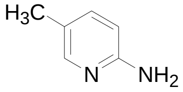
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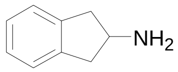
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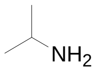
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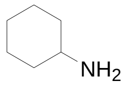
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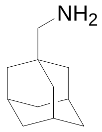
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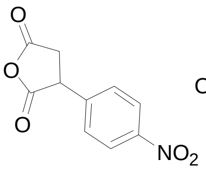
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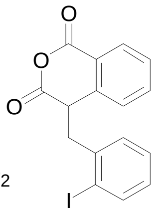
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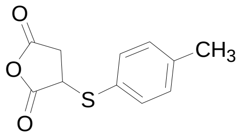
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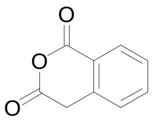
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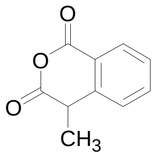
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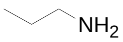
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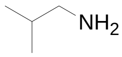
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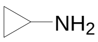
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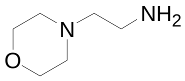
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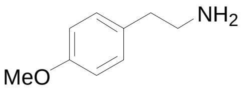
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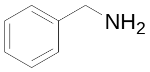
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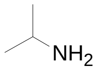
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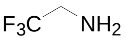
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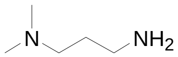
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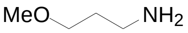
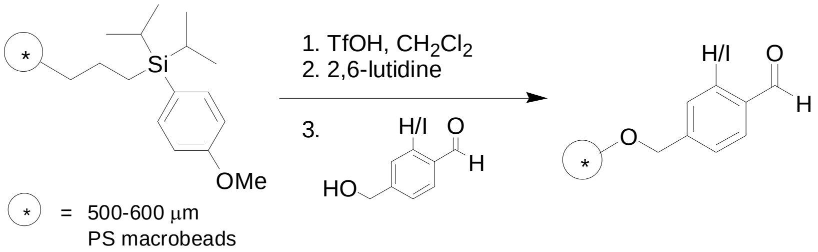
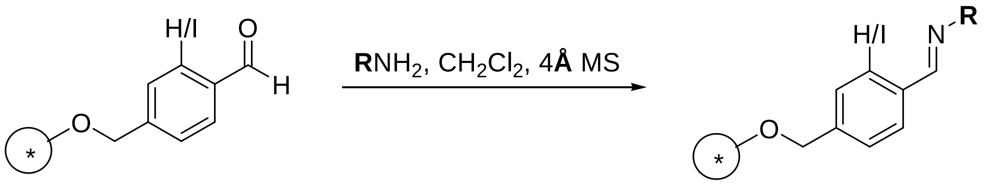

D10

General procedures for synthesis in Kans. All reactions were performed using standard lab glassware that had been oven-dried. The Kans were dried on the lyophilizer overnight before each reaction. After each addition of solvent or reagent, the reaction vessel was evacuted and backfilled with Argon twice to help the solvent or reagent to fully permeate into the Kans. Mixing of reagents/solvents and Kans during reaction and washing was accomplished by agitation on a Burrell #75 Wrist Action™ Shaker.

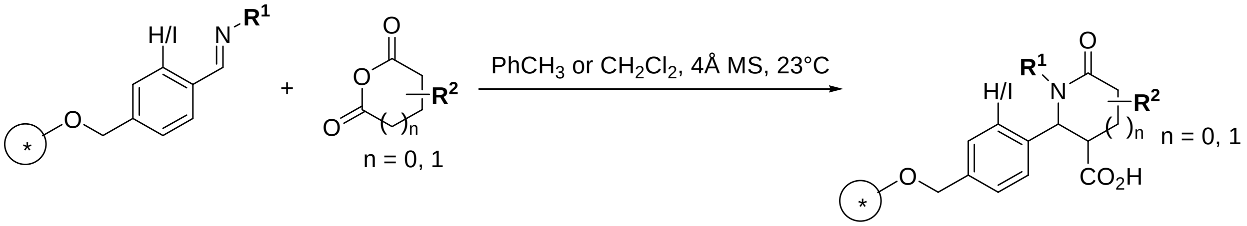
Standard wash procedure: After the reaction solvents were drained, the Kans were rinsed with fresh reaction solvent and agitated for 30 minutes. The Kans were washed sequentially in this manner with the following solvents: THF (2x), THF/IPA (3:1, 2x), THF/H_2O (3:1, 2x), THF/IPA (3:1, 2x), THF (2x).



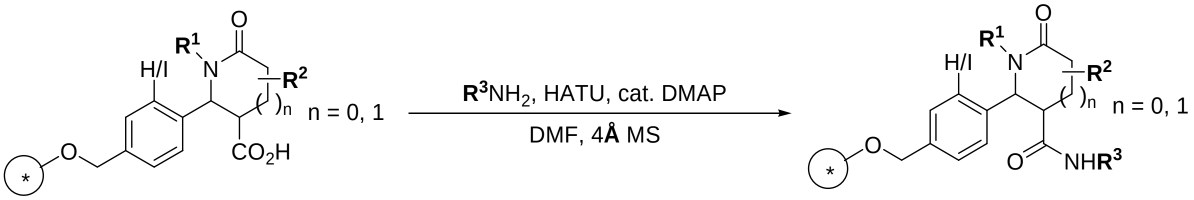
General loading procedure. The macrobead-filled Kans (1 equiv) were swelled in CH_2Cl_2 (enough to cover Kans, ~1 mL/Kan) for 30 minutes. About half of the solvent was removed, followed by the addition of a Tf_2O solution (0.31 M, 0.5 equiv). After 15 minutes, a TfOH solution (0.47 M, 6 equiv) was added and the beads became an orange color. The Kans were agitated occasionally over a period of 20 minutes. The reaction mixture was drained *via* cannulation and rinsed twice with CH_2Cl_2. The Kans were swelled in fresh CH_2Cl_2 and residual TfOH was quenched with 2,6-lutidine (8 equiv). The beads became colorless once more. A solution of aldehyde (1-2 equiv) in a minimum amount of CH_2Cl_2 (with some 2,6-lutidine to help solubilize the aldehyde) was added. The reaction vessel was gently agitated overnight. The Kans were then subjected to the standard wash procedure.



General imine formation procedure. The macrobead-filled Kans (1 equiv) were swelled in CH_2Cl_2 (enough to cover Kans, ~1 mL/Kan) for 30 minutes. To the reaction vessel was added activated 4Å molecular sieves (~80 mg/mL solvent) and amine (5 equiv). The reaction vessel was gently agitated overnight. The Kans were then subjected to an abbreviated wash procedure of just CH_2Cl_2 washes (2x) and THF washes (1x).

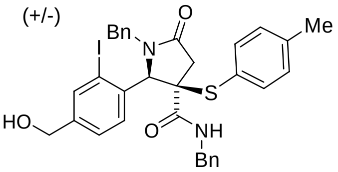


General imine-anhydride cycloaddition procedure. The macrobead-filled Kans (1 equiv) were swelled in the reaction solvent (enough to cover Kans, ~1 mL/Kan) for 30 minutes. For anhydride BB_C01, 03-05, the reaction was performed in $PhCH_3$. For anhydride BB_C02, the reaction was performed in CH_2Cl_2. To the reaction vessel was added a solution of anhydride (5 equiv) in the reaction solvent and 4Å molecular sieves (~80 mg/mL solvent). The reaction vessel was gently agitated overnight. The Kans were then subjected to the standard wash procedure.

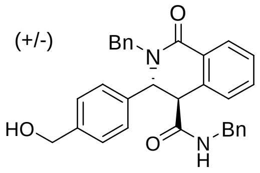


General amide coupling procedure. The macrobead-filled Kans (1 equiv) were swelled in CH_2Cl_2/DMF (1:3, ~1 mL/Kan) for 30 minutes. To the reaction vessel was added PyBrOP (4 equiv), amine (5 equiv), DMAP (5 equiv), and 4Å molecular sieves (~80 mg/mL solvent). The reaction vessel was gently agitated for 4.5 hours, at which time a second batch of PyBrOP (4 equiv) was added. The reaction vessel was gently agitated overnight. The Kans were then subjected to the standard wash procedure.

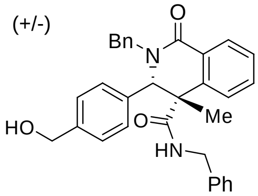
Representative Library Members (prepared in solution phase for LCMS comparison):



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.13-7.39 (m, 9H), 6.89-7.03 (m, 8H), 5.11 (d, *J* = 14.6 Hz, 1H), 4.92 (s, 1H), 4.65 (s, 2H), 4.21-4.33 (m, 2H), 3.43 (d, *J* = 16.8 Hz, 1H), 3.29 (d, *J* = 14.6 Hz, 1H), 2.78 (d, *J* = 16.8 Hz, 1H), 2.37 (s, 1H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 170.5, 144.2, 139.4, 138.2, 137.3, 134.9, 133.8, 130.1, 129.0, 128.9, 128.7, 128.5, 127.9, 127.7, 126.9, 126.5, 71.5, 63.6, 58.9, 44.9, 41.4, 21.2; IR (thin film): 3520, 3379, 1669, 1509, 1490, 1398, 1261 cm^{-1}; LCMS: mass calcd for $(C_{33}H_{31}IN_2O_3S+H)^+$ *m/z* 663.12 found: *m/z* 663.04.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.1 Hz, 1H), 7.47-7.50 (m, 2H), 7.22-7.29 (m, 10H), 6.98-7.10 (m, 5H), 5.51 (d, *J* = 14.5 Hz, 1H), 5.45 (s, 1H), 5.42 (s, 1H), 4.62 (s, 2H), 4.33 (dd, *J* = 15.0, 6.1 Hz, 1H), 4.07 (dd, *J* = 15.1, 5.2 Hz, 1H), 3.82 (s, 1H), 3.76 (d, *J* = 14.6 Hz, 1H), 1.96 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 163.7, 140.8, 138.1, 137.4, 136.6, 132.9, 132.3, 129.37, 129.2, 129.0, 128.9, 128.7, 128.5, 127.7, 127.5, 127.4, 127.1, 126.4, 64.7, 61.6, 53.7, 49.8, 43.8; IR (thin film): 3420, 3296, 1631, 1603, 1576, 1468, 1450, 1410, 1260 cm^{-1}; LCMS: mass calcd for $(C_{31}H_{28}N_2O_3+H)^+$ *m/z* 477.22 found: *m/z* 477.16.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38-8.41 (m, 1H), 7.44-7.47 (m, 2H), 7.17-7.37 (m, 11H), 6.99-7.05 (m, 2H), 6.80-6.87 (m, 2H), 5.73 (d, *J* = 14.4 Hz, 1H), 4.93 (br t, *J* = 4.4, 4.4 Hz, 1H), 4.61 (s, 2H), 4.45 (s, 1H), 4.21 (dd, *J* = 14.4, 5.8 Hz, 1H), 3.52 (dd, *J* = 14.5, 4.2 Hz, 1H), 3.40 (d, *J* = 14.4 Hz, 1H), 1.85 (s, 1H), 1.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 162.9, 141.5, 139.6, 137.2, 136.9, 136.1, 132.7, 129.5, 129.2, 128.9, 128.7, 128.5, 128.1, 128.0, 127.9, 127.8, 127.5, 127.3, 127.2, 67.1, 64.6, 53.3, 48.6, 44.6, 28.7; IR (thin film): 3427, 3370, 1635, 1598, 1513, 1466, 1452, 1251 cm^{-1}; LCMS: mass calcd for $(C_{32}H_{30}N_2O_3+H)^+$ *m/z* 491.23 found: *m/z* 491.17.

III. Screen for small molecule disruptors of HOXA13-DNA interaction

A small molecule screen was performed at the Harvard/MIT Broad Institute Chemical Biology Facility. The screen used a fluorescence polarization assay (FP) to detect small molecules capable of disrupting the HOXA13-DNA complex. A Hoxa13 DNA binding domain peptide (A13-DBD) was synthesized, purified, and ascertained for proper folding as previously described (ref 16). 384 well microtiter plates (Nunc) were used for the screen. Each well contained 50 microliters of ice-cold binding buffer consisting of 20mM Tris.HCl (pH 7.8), 80mM KCl, 10mM $MgCl_2$, 0.2mM EDTA, 1mM DTT and 10nM A13-DBD combined with 1 nM of a self-annealing, fluorescein-labeled Hoxa13 consensus binding site oligonucleotide. The FP of the A13-DBD DNA complex was measured in the 384 well plates using a Perkin Elmer Envision multiplate reader as described by the manufacturer (PE Biosystems). Each compound was screened in duplicate. A 384 pin robotic system (CyBio) was used to introduce 100 nl of each compound (42,000 total screened) to individual well containing the A13-DBD DNA complex. After the compounds were introduced to the individual wells, the plates were chilled at 4 degrees Celsius for 15 minutes to maintain maximal A13-DBD stability, briefly centrifuged, and assayed for FP. Changes in FP relative to controls containing DNA only were used to ascertain the effect of individual compounds on A13-DBD DNA binding.

Hit in HOXA13 DNA Binding assay (31):

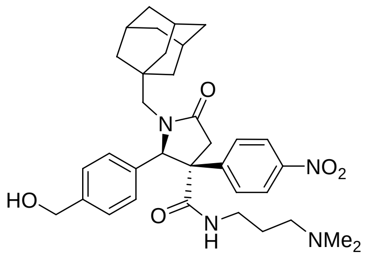
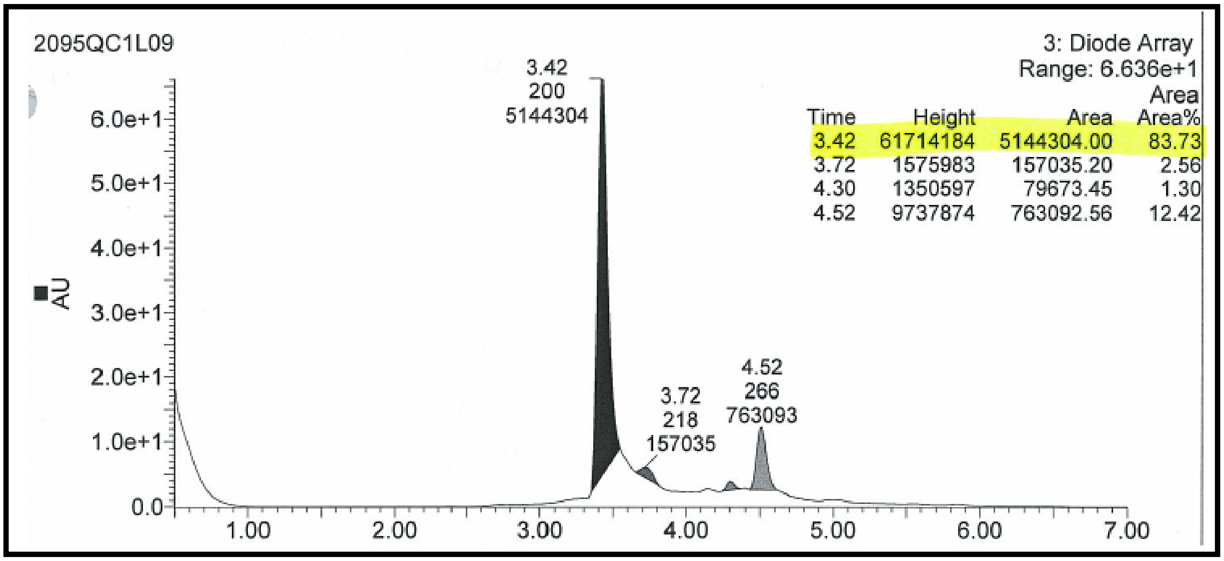


Plate 2095, Well L09. Isolated 1.2 mg from ~0.5 mL of library stock solution using preparative LCMS. LCMS trace of screening well 2095L09 (**31**):



Time	Height	Area	Area Area%
3.42	61714184	5144304.00	83.73
3.72	1575983	157035.20	2.56
4.30	1350597	79673.45	1.30
4.52	9737874	763092.56	12.42

Assessment of compound efficacy (31)

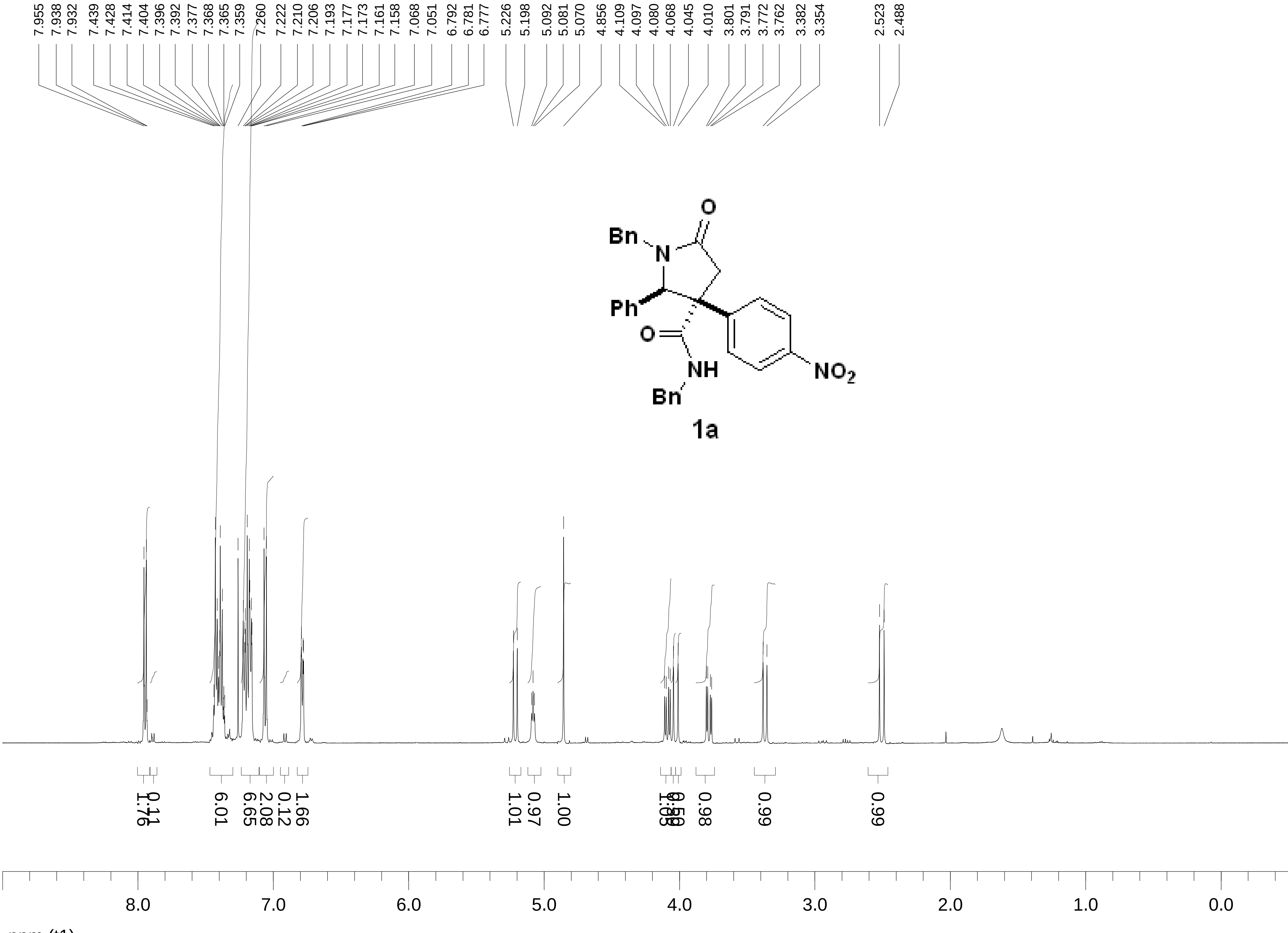
Compounds exhibiting reproducible disruption of the A13-DBD DNA complex were assessed for efficacy by examining their capacity to disrupt the A13-DBD DNA complex in a dosage-dependent manner. Binding buffer used in the small molecule screen containing 10 nM of A13-DBD and 1 nM A13 consensus binding site oligonucleotide was assessed for dosage sensitivity to Compound 31 at 0-40 μM. Disruption of the protein-DNA complex was measured as a change in FP using a Pan Vera Beacon 2000 fluorescence polarization anisometer set to read each sample at 15 degrees Celsius as described by the manufacturer (InVitrogen). Each concentration of compound **31** was tested in triplicate and the mean FP was plotted using Sigma Plot 9.0. The specificity of compound **31** to disrupt A13-DBD DNA complexes was ascertained using the same concentrations of Compound **31** and a Trp repressor DNA binding kit in parallel assays as described by the manufacturer (#p2202, Pan Vera InVitrogen).

The HOXA13 binding site was a fluoroscein tagged self annealing oligonucleotide containing the following sequence: 5' 56-FAM-CAAATAAAATCCCCCATTTTATTTG 3' as described by Knosp et al. (*J. Biol. Chem.* **2007**, 282, 6843-6853). The Trp repressor protein was used at a concentration 0.3 nM which was obtained from a Trp repressor DNA binding Kit #P2202 from PanVera which has been bought by InVitrogen. The trp repressor binding site was described by LeTilly and Royer (*Biochemistry* **1993**, 32, 7753-7758). It was created by annealing two complementary oligonucleotides containing the following sequence: TRP F: 5' 56-FAM-ATCGAACTAGTT AACTAGTACGCAA 3' and TRP R: 5'TTGCGTACTAGTTAAC

TAGTTCGAT 3'. The Trp Repressor binding site concentration was adjusted to 0.2 nM to accommodate the higher affinity of the Trp repressor protein for its consensus sequence versus HOXA13 (Kd Trp Repressor=0.1-0.3 nM vs Kd HOXA13 = 3.7 nM) (LeTilly and Royer, 1993; Knosp et al., 2007).

***In vitro* assessment of Compound 31**:

A HOXA13-controlled gene regulatory element present in the promoter region of Sostdc1 (NCBI M35 mouse assembly; ENSMUSG00000036169) was cloned into the pGL4 luciferase vector as described (Knosp et al., 2007). NG108-15 cells (ATCC#HB-12317) were maintained and transfected as previously described (Knosp et al., 2004). Transfections were performed in 12 well plates (Costar) using 2 μg pGL4 plasmid, 0.25 μg pRL-CMV Renilla, and 0.5 μg pCAGGS-*Hoxa13* or empty pCAGGS control plasmid per well. Cell lysates were processed to detect luciferase activity using the Dual-Glo Luciferase Assay System (Promega) in OptiPlate-96F black plates (Packard) as described (Promega) (Knosp et al., 2004). Luciferase activity was detected using a Packard Fusion Microplate Analyzer (Perkin Elmer), wells were read 3 times for 1 second each and averaged. Two replicates of each transfection were performed and each transfection assay was repeated 3 times. Results were normalized for Renilla Luciferase expression and control transfections and plotted using SigmaPlot 9.0 (Systat).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7.222
7.210
7.206
7.193
7.177
7.173
7.161
7.158
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7.051
6.792
6.781
6.777
5.226
5.198
5.092
5.081
5.070
4.856
4.109
4.097
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2.08
0.12
1.66
1.01
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1.00
1.05
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0.50
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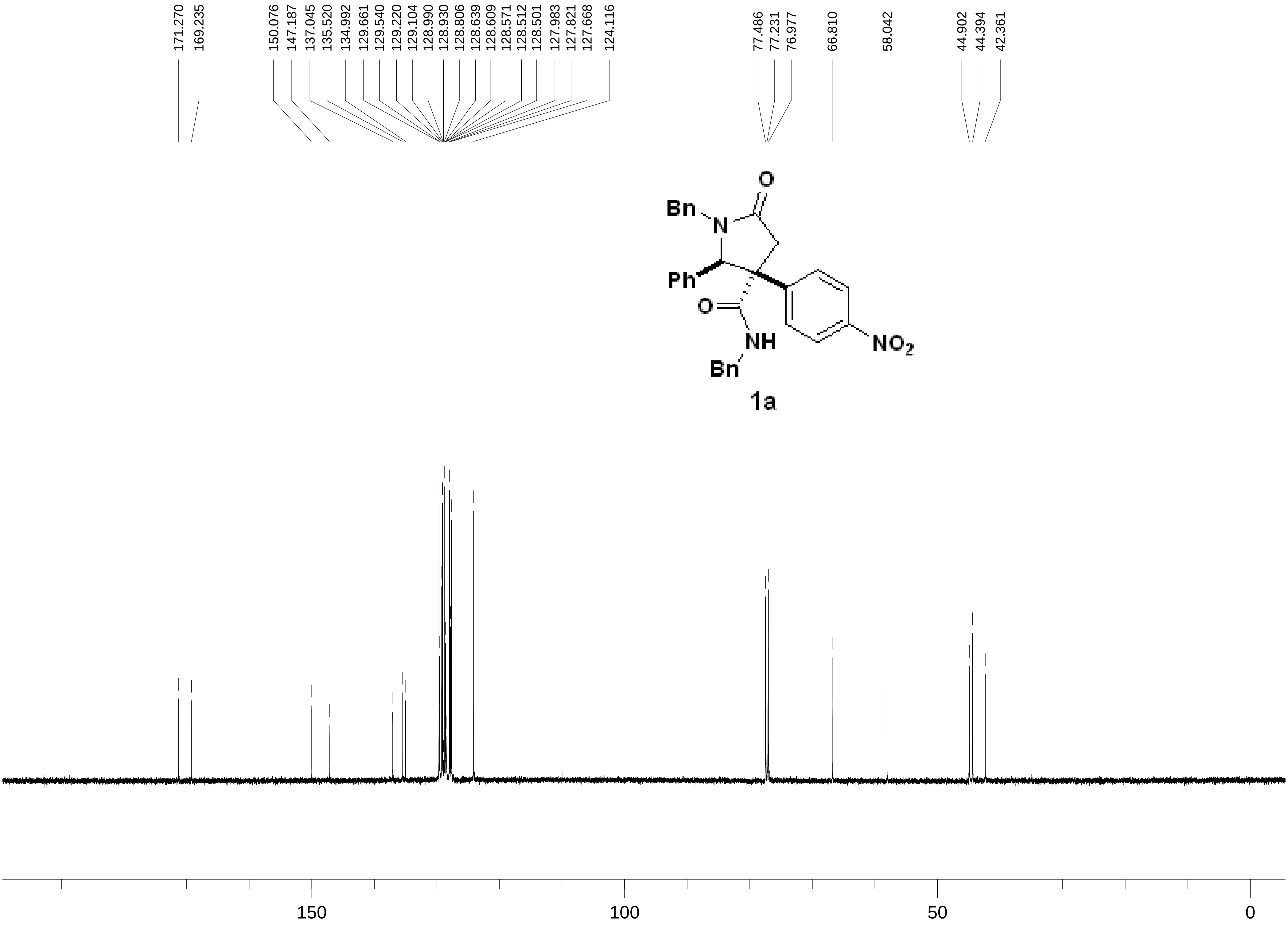
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128.512
128.501
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127.821
127.668
124.116
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77.231
76.977
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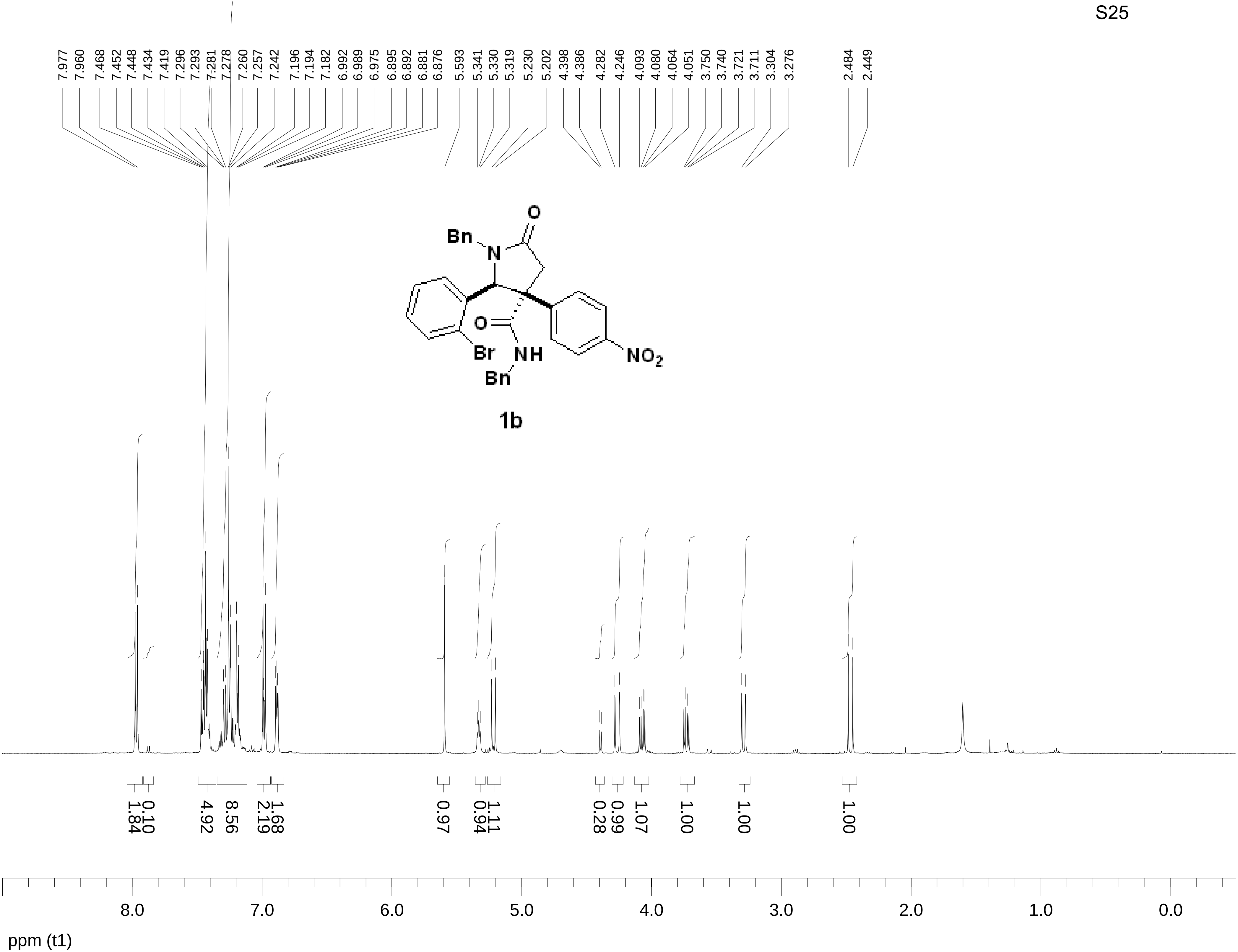
ppm (t1)

1a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7.242
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6.989
6.975
6.895
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6.881
6.876
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5.319
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Br
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0.99
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4.0
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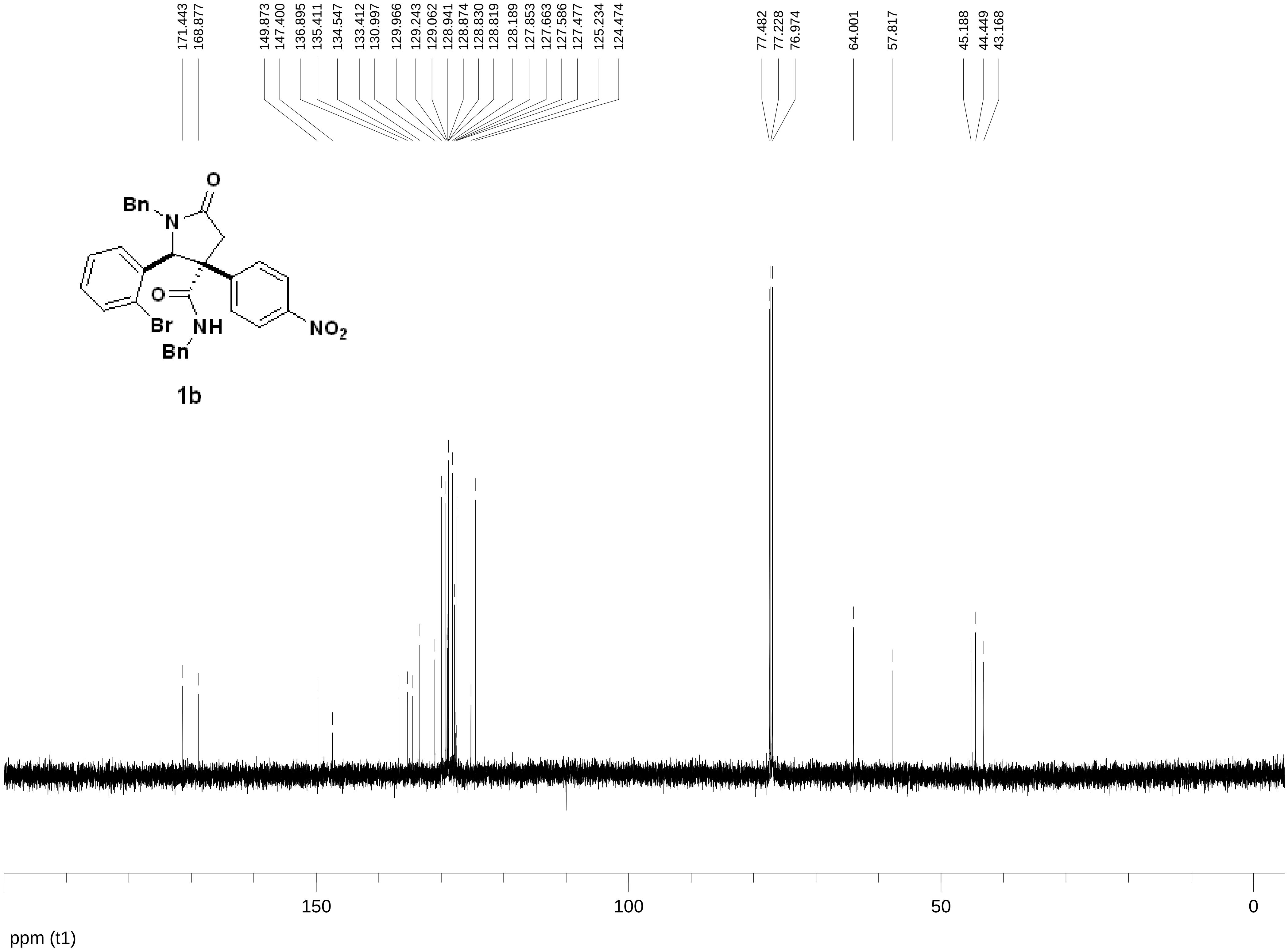
ppm (t1)

1b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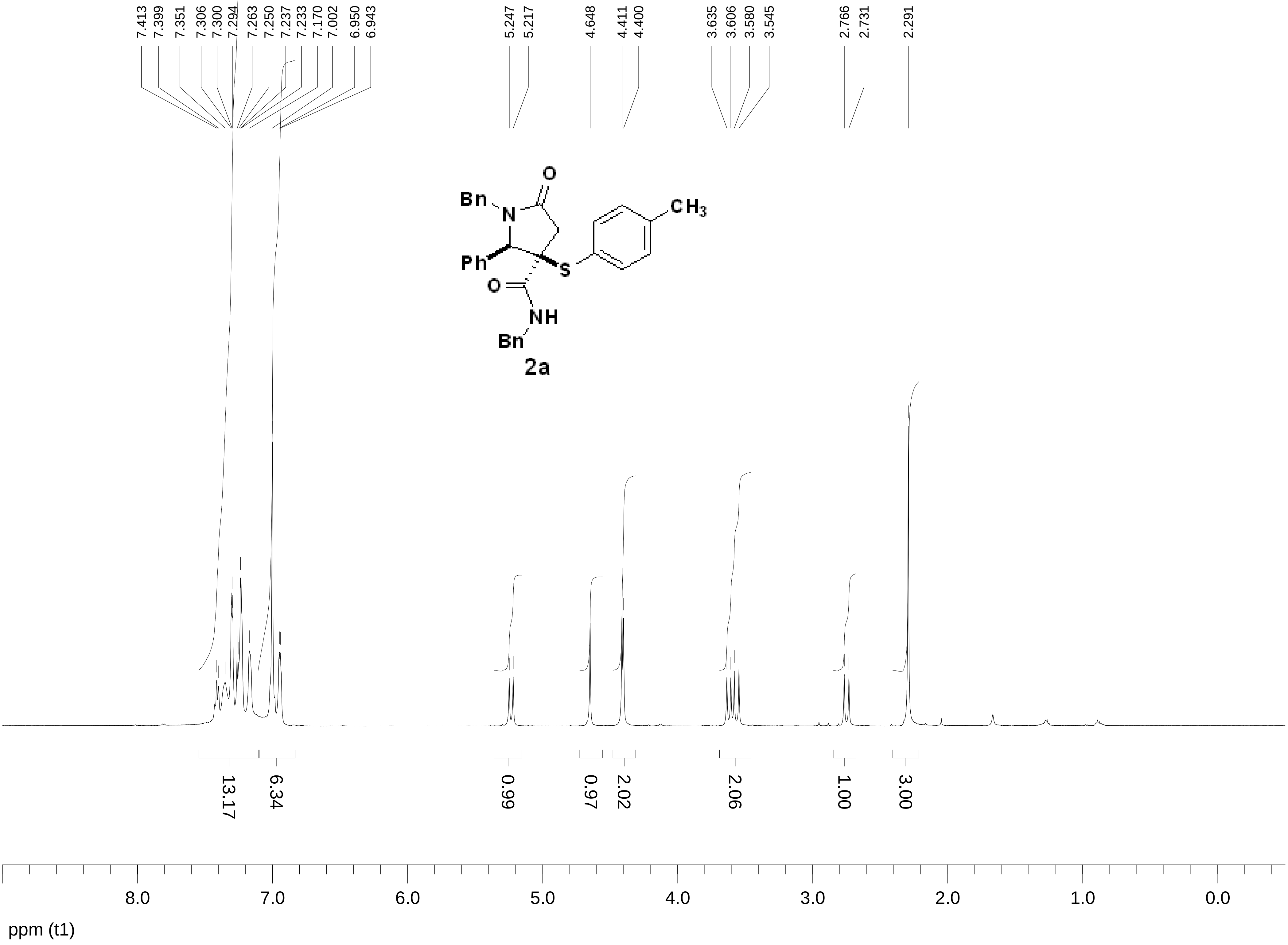
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6.943
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4.400
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2.731
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Ph
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Bn
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2.06
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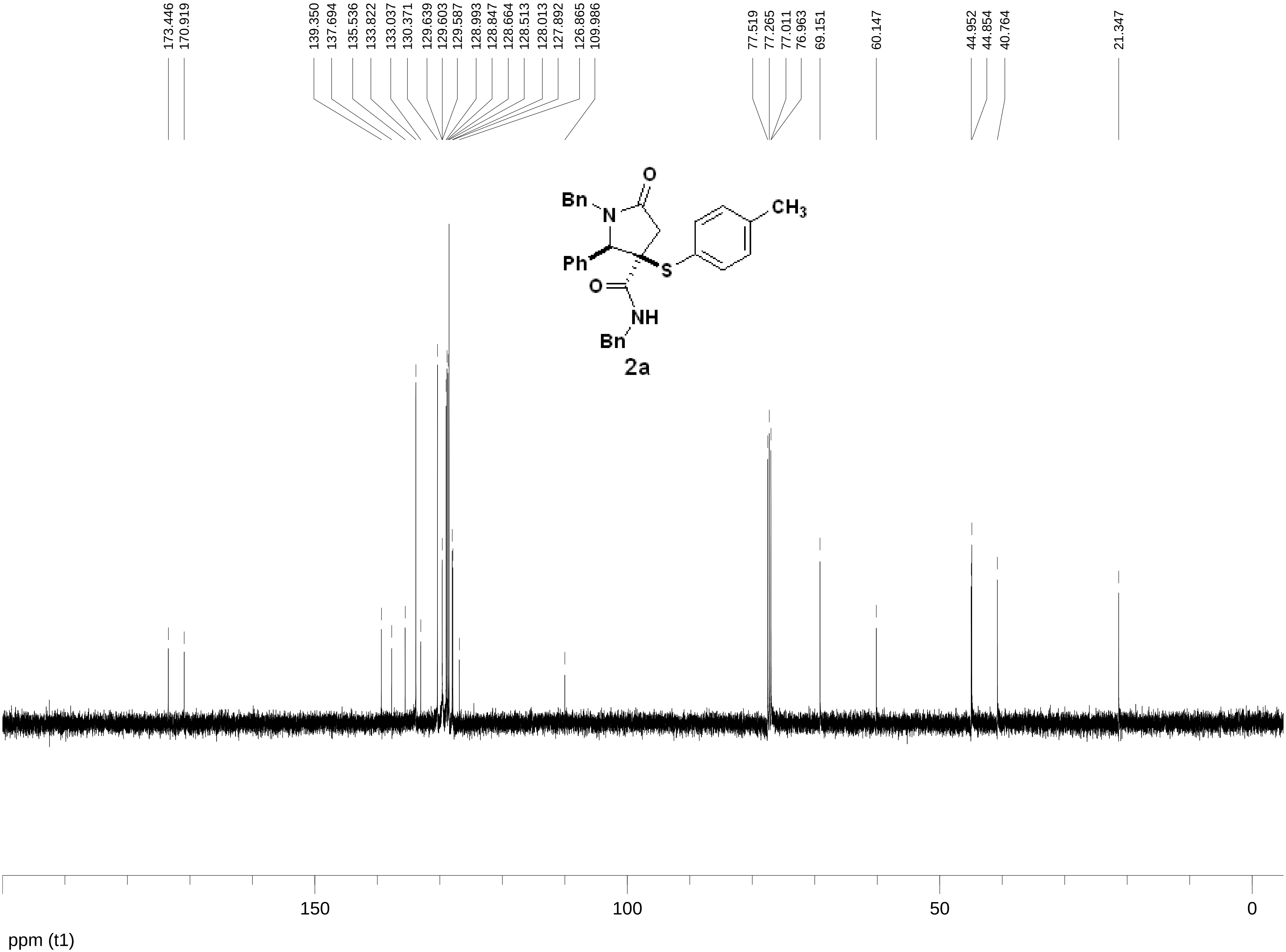
ppm (t1)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128.013
127.892
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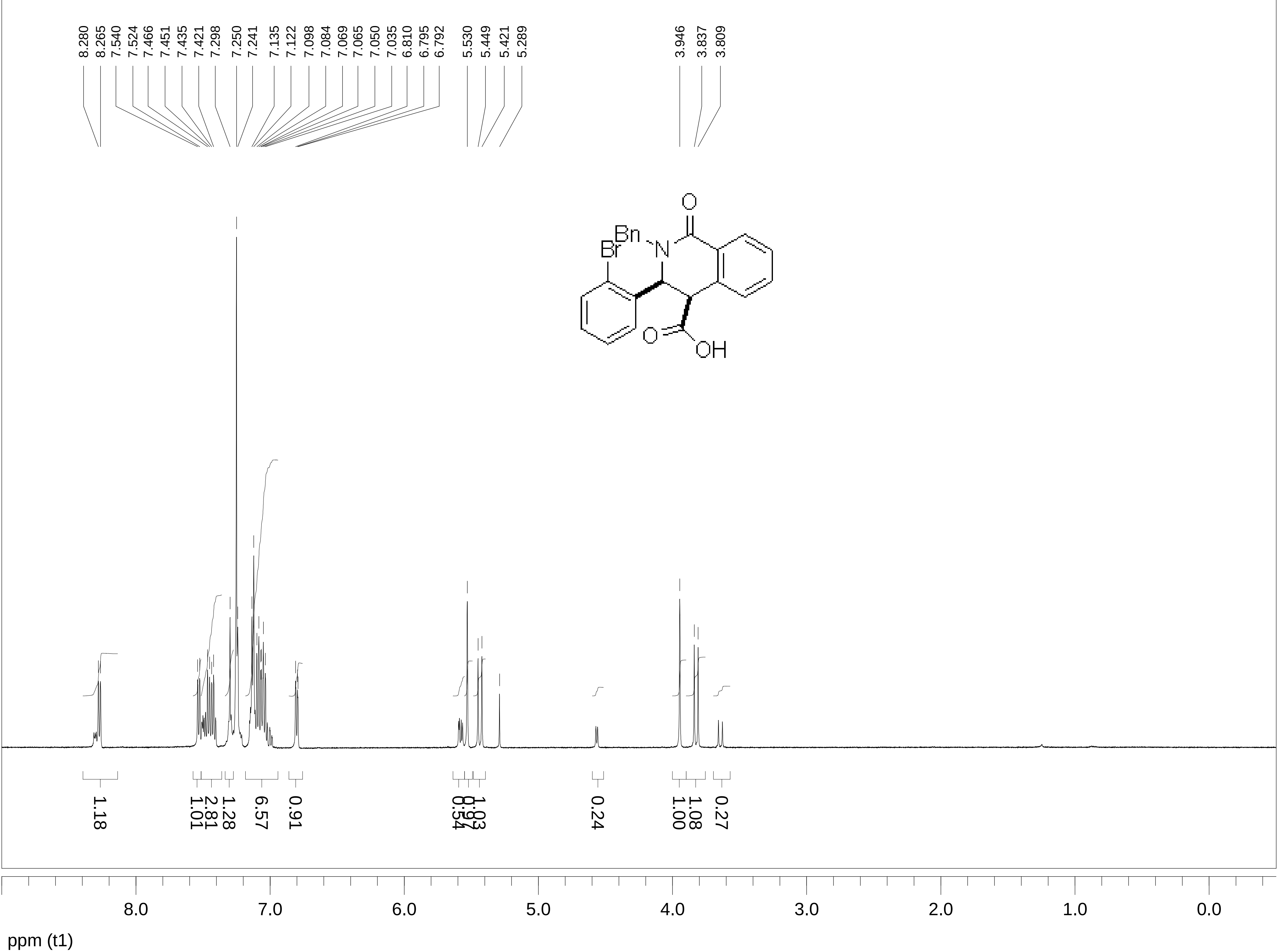
ppm (t1)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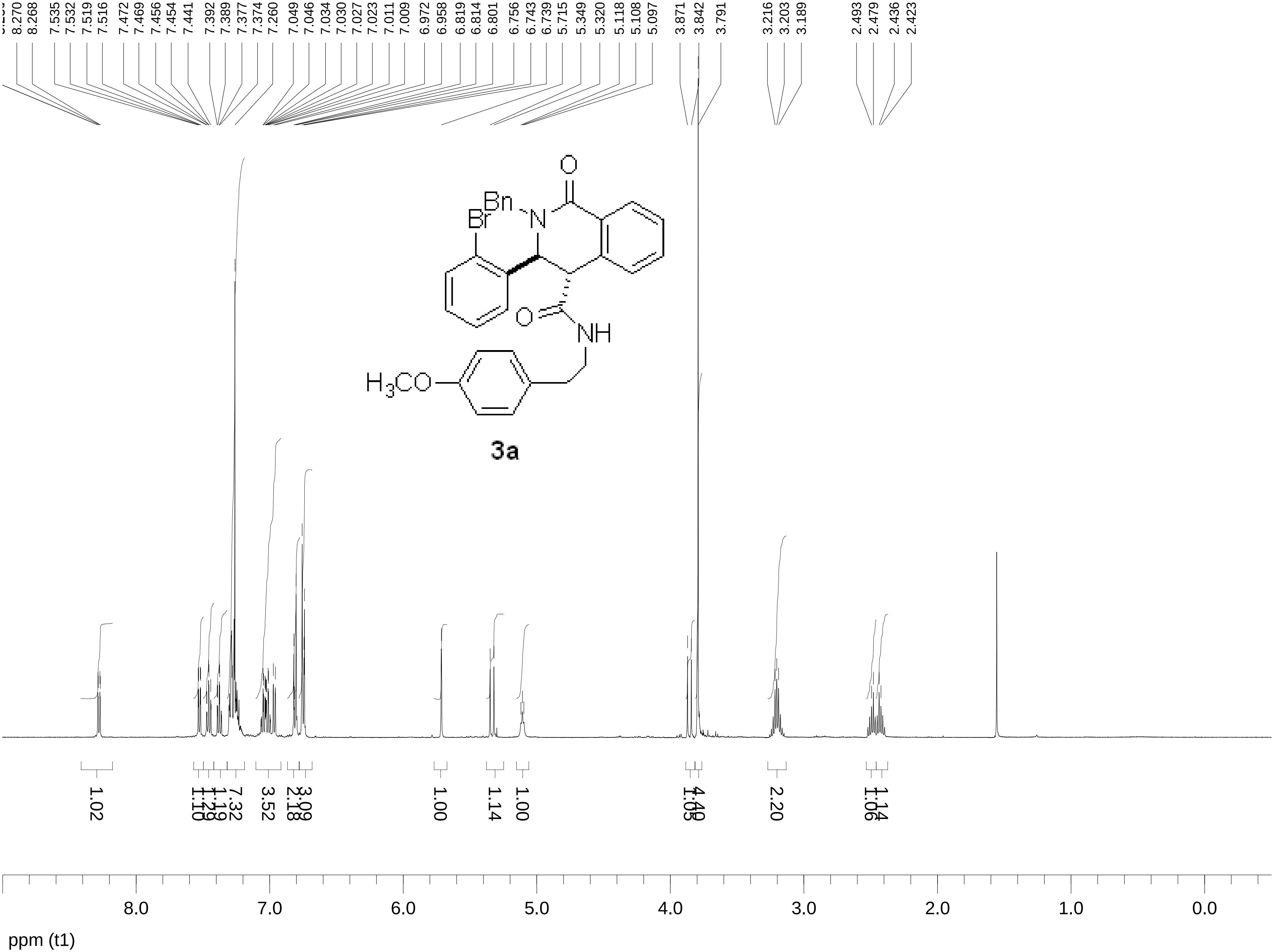
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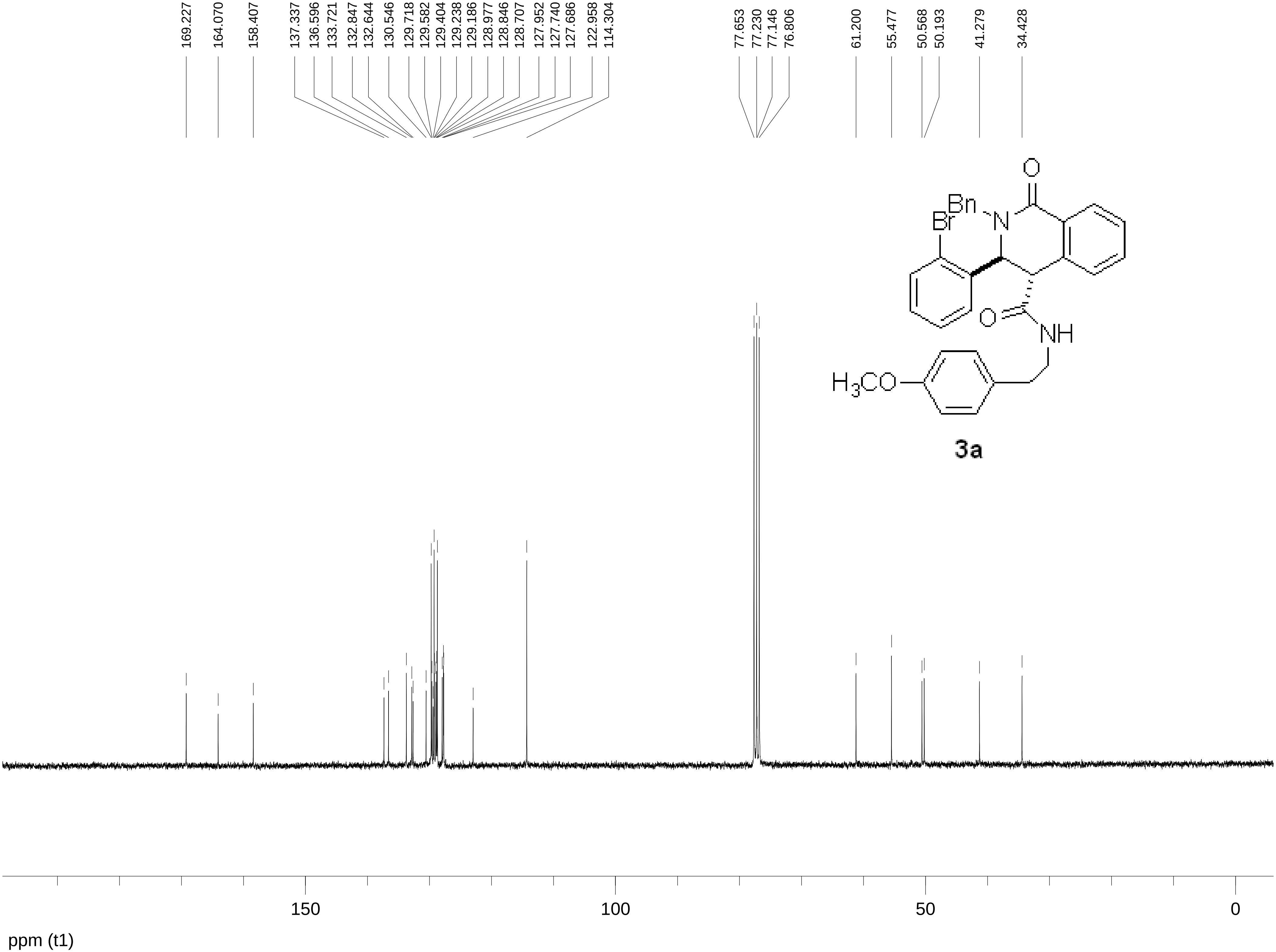
3a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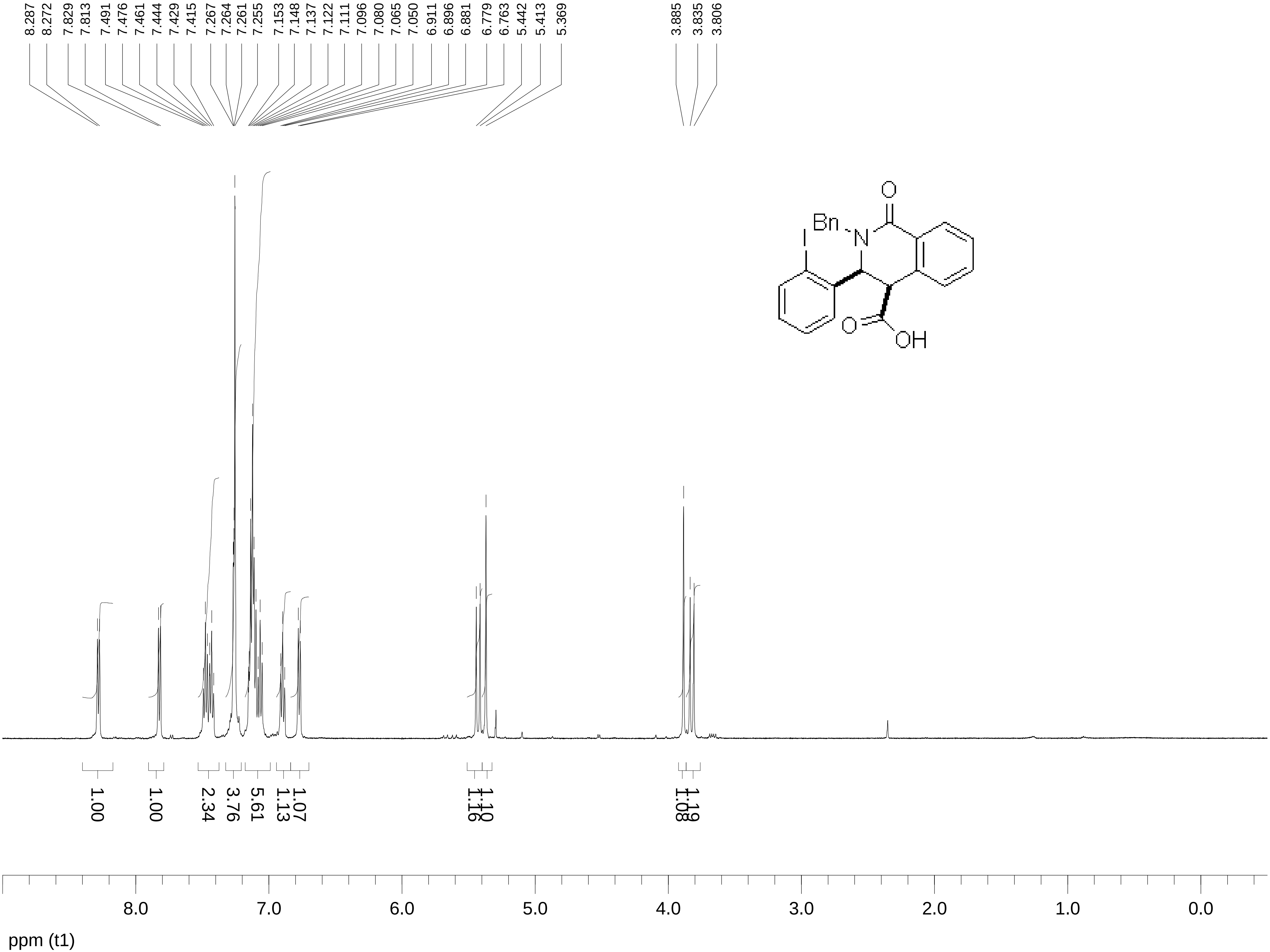
3a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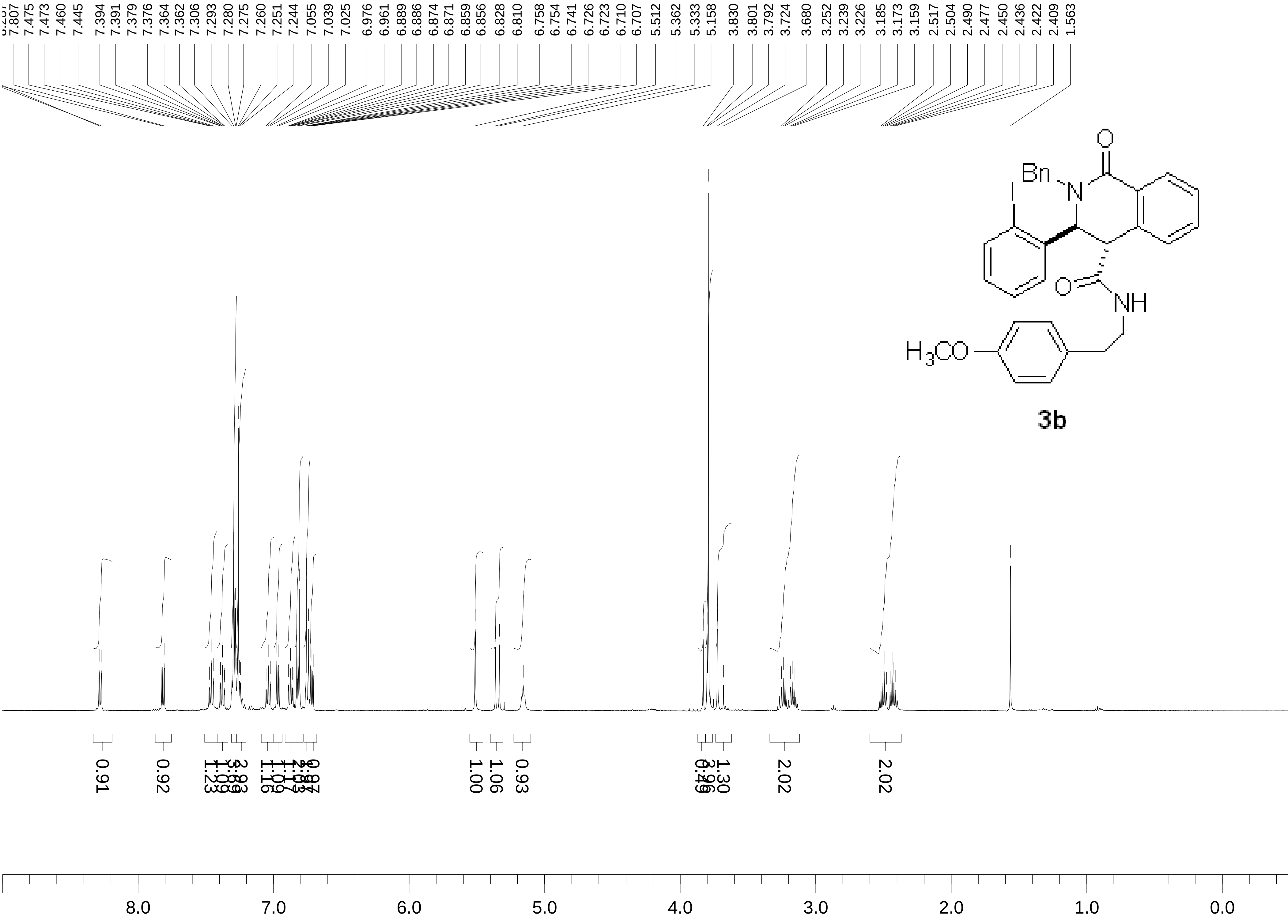
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0.92
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1.09
3.89
2.83
1.16
1.09
1.17
2.03
2.97
0.87
1.00
1.06
0.93
0.49
3.96
1.30
2.02
2.02
8.0
7.0
6.0
5.0
4.0
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1.0
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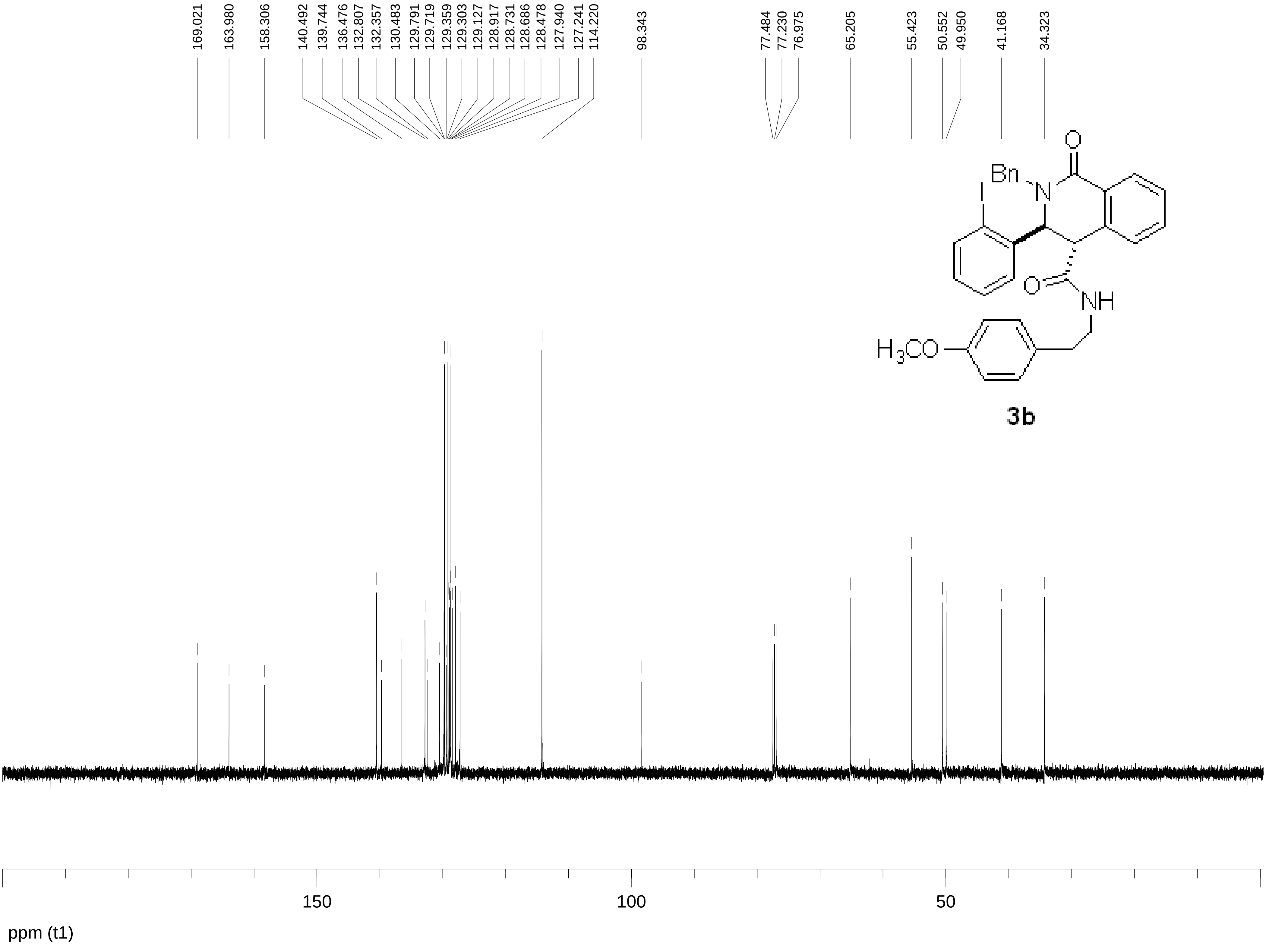
I
O
NH
H3CO

3b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76.975
65.205
55.423
50.552
49.950
41.168
34.323
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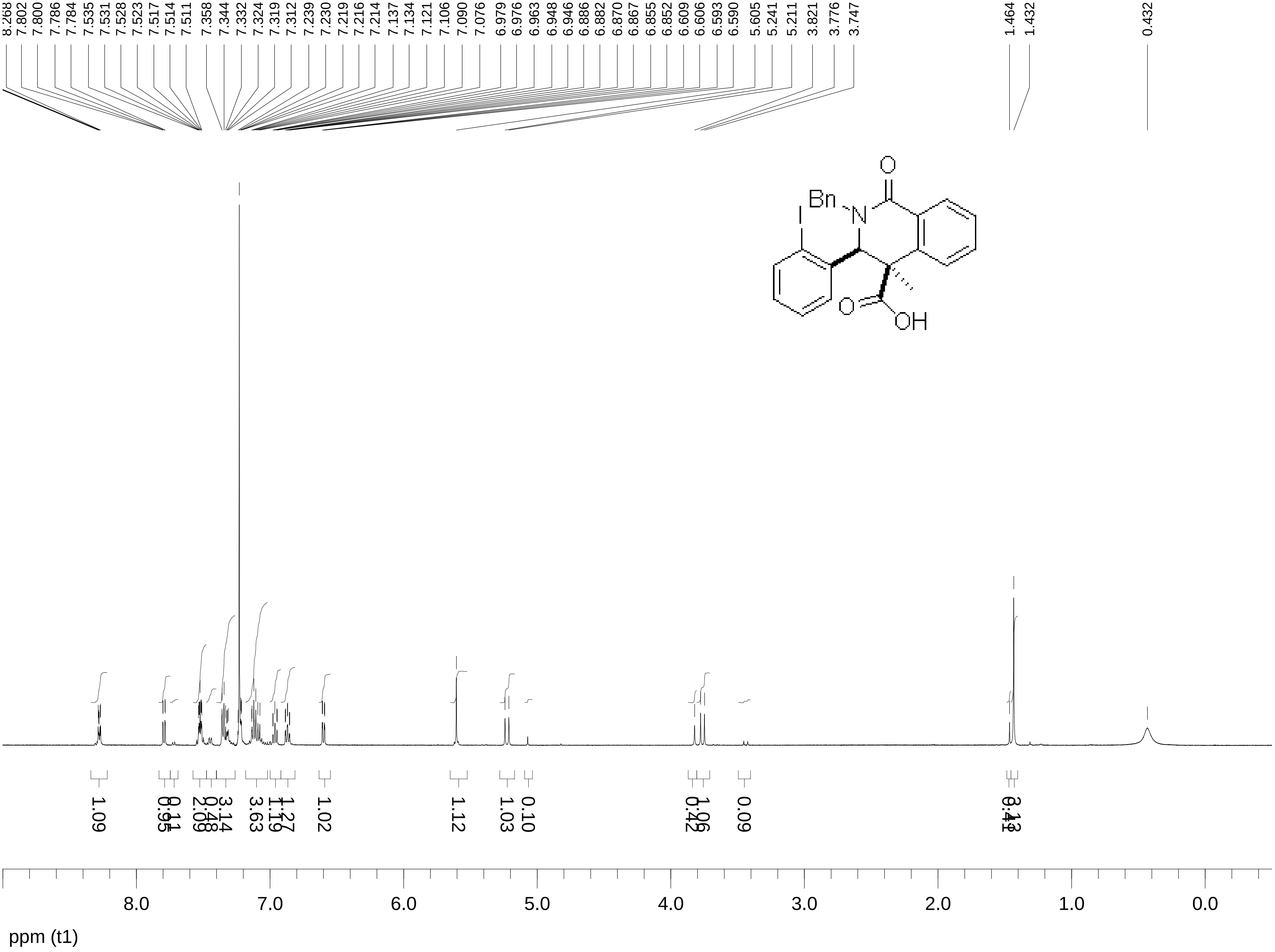
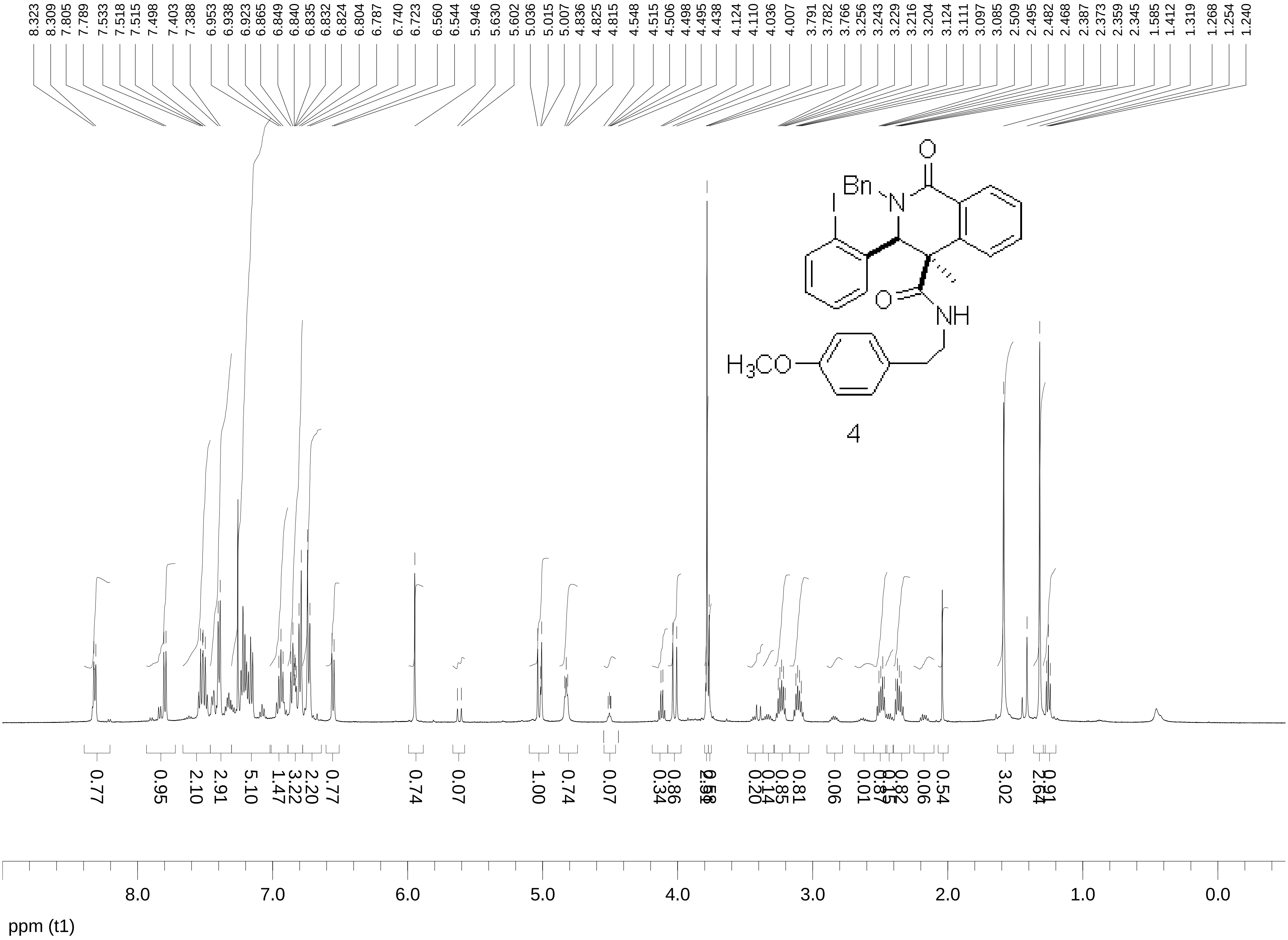
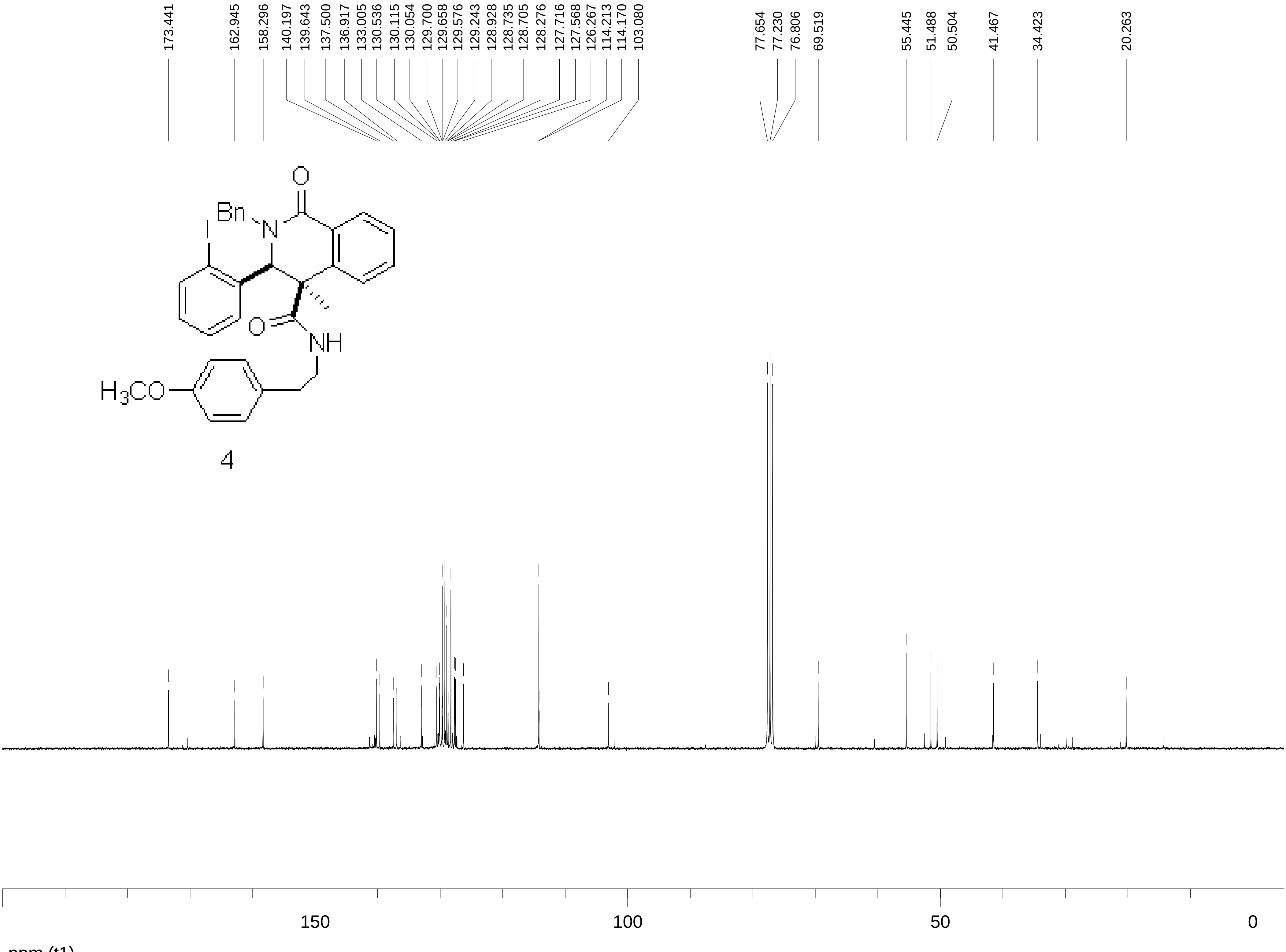
N
I
O
NH
H_3CO
150
100
50
ppm (t1)

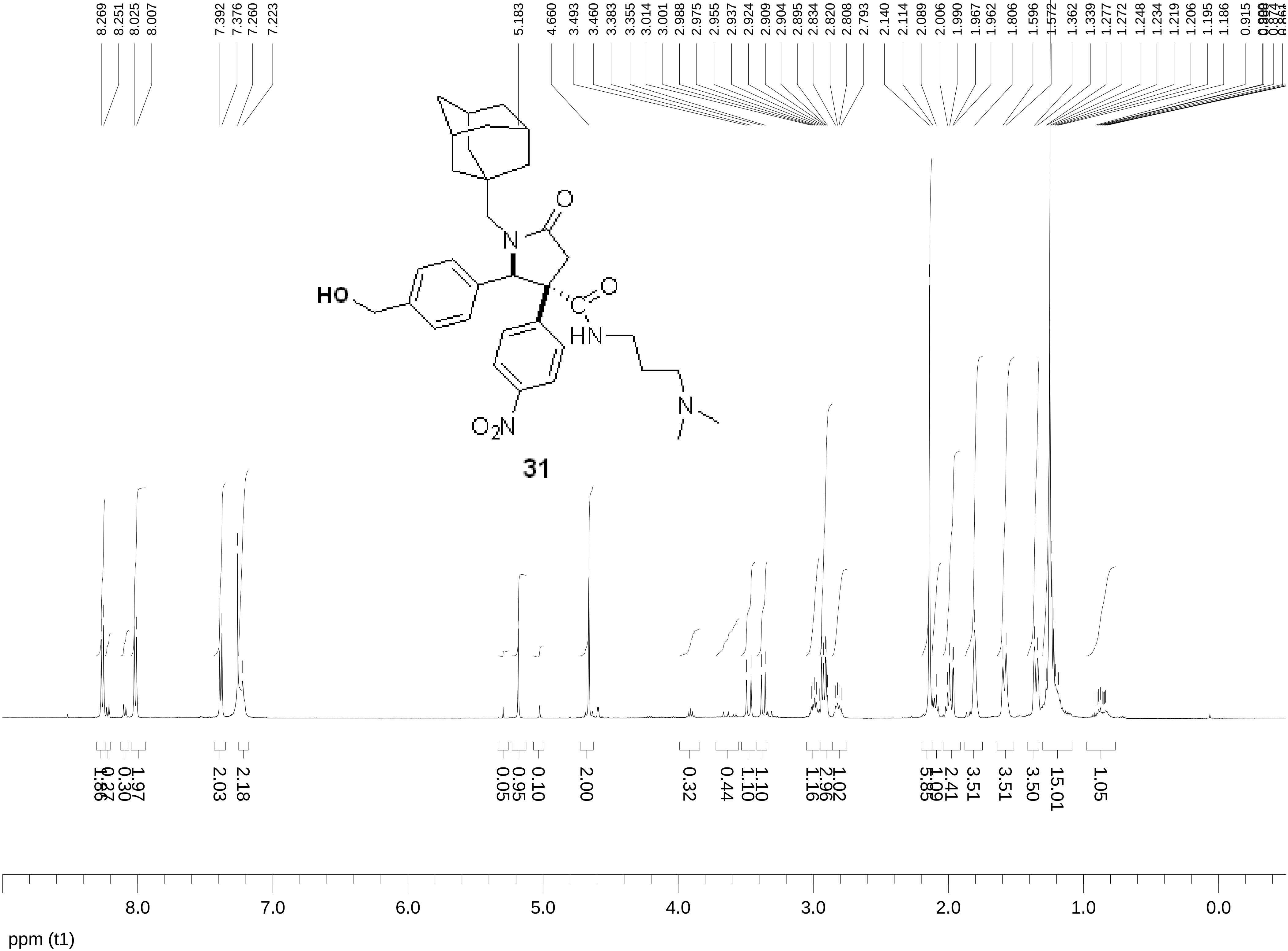
3b


8.268
7.802
7.800
7.786
7.784
7.535
7.531
7.528
7.523
7.517
7.514
7.511
7.358
7.344
7.332
7.324
7.319
7.312
7.239
7.230
7.219
7.216
7.214
7.137
7.134
7.121
7.106
7.090
7.076
6.979
6.976
6.963
6.948
6.946
6.886
6.882
6.870
6.867
6.855
6.852
6.609
6.606
6.593
6.590
5.605
5.241
5.211
3.821
3.776
3.747
1.464
1.432
0.432
Bn
N
O
I
O
OH
1.09
0.95
0.11
2.09
0.48
3.14
3.63
1.19
1.27
1.02
1.12
1.03
0.10
0.42
1.06
0.09
0.41
3.13
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


8.323
8.309
7.805
7.789
7.533
7.518
7.515
7.498
7.403
7.388
6.953
6.938
6.923
6.865
6.849
6.840
6.835
6.832
6.824
6.804
6.787
6.740
6.723
6.560
6.544
5.946
5.630
5.602
5.036
5.015
5.007
4.836
4.825
4.815
4.548
4.515
4.506
4.498
4.495
4.438
4.124
4.110
4.036
4.007
3.791
3.782
3.766
3.256
3.243
3.229
3.216
3.204
3.124
3.111
3.097
3.085
2.509
2.495
2.482
2.468
2.387
2.373
2.359
2.345
1.585
1.412
1.319
1.268
1.254
1.240
Bn
N
O
I
NH
H$_3$CO
4
0.77
0.95
2.10
2.91
5.10
1.47
3.22
2.20
0.77
0.74
0.07
1.00
0.74
0.07
0.34
0.86
2.58
1.91
0.20
0.14
0.85
0.81
0.06
0.01
0.87
0.15
0.82
0.06
0.54
3.02
2.64
0.91
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

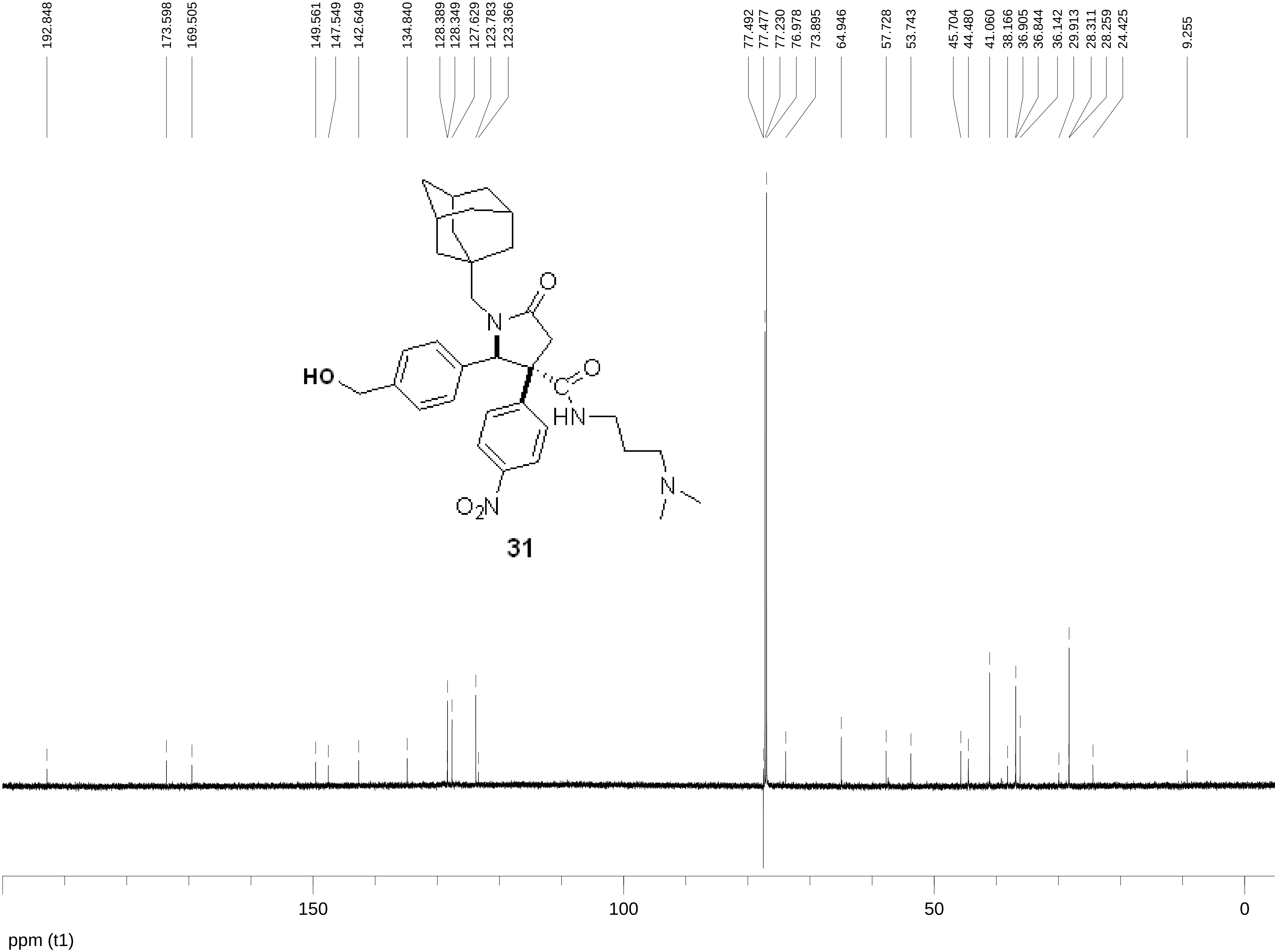

173.441
162.945
158.296
140.197
139.643
137.500
136.917
133.005
130.536
130.115
130.054
129.700
129.658
129.576
129.243
128.928
128.735
128.705
128.276
127.716
127.568
126.267
114.213
114.170
103.080
77.654
77.230
76.806
69.519
55.445
51.488
50.504
41.467
34.423
20.263
O
Bn
N
I
O
NH
H3CO
150
100
50
0
ppm (t1)

4



31

8.269
8.251
8.025
8.007
7.392
7.376
7.260
7.223
5.183
4.660
3.493
3.460
3.383
3.355
3.014
3.001
2.988
2.975
2.955
2.937
2.924
2.909
2.904
2.895
2.834
2.820
2.808
2.793
2.140
2.114
2.089
2.006
1.990
1.967
1.962
1.806
1.596
1.572
1.362
1.339
1.277
1.272
1.248
1.234
1.219
1.206
1.195
1.186
0.915
0.874
0.861
HO
O
N
O
C
HN
N
O_2N
1.86
0.27
0.30
1.97
2.03
2.18
0.05
0.95
0.10
2.00
0.32
0.44
1.10
1.10
1.16
2.96
1.02
5.85
1.09
2.41
3.51
3.51
3.50
15.01
1.05
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


192.848
173.598
169.505
149.561
147.549
142.649
134.840
128.389
128.349
127.629
123.783
123.366
77.492
77.477
77.230
76.978
73.895
64.946
57.728
53.743
45.704
44.480
41.060
38.166
36.905
36.844
36.142
29.913
28.311
28.259
24.425
9.255
HO
N
O
O
C
HN
N
O_2N
31
150
100
50
0
ppm (t1)