Synthesis of 2-oxazolidinones from β-lactams: Stereospecific total synthesis of (-)-Cytoxazone and all of its stereoisomers.

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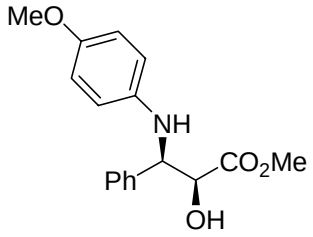
Supporting Information

General: THF was distilled from sodium/benzophenone. CH_2Cl_2, Et_3N and diisopropylamine were freshly distilled from CaH_2. All other solvents and reagents were obtained from commercial sources and used without further purification. Organic extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated by rotary evaporation. Non-volatile oils and solids were vacuum dried prior to characterization. Optical rotations were measured on a digital polarimeter. Melting points are uncorrected. Flash column chromatography was performed using commercial grades of silica gel finer than 220 mesh. Analytical thin layer chromatography was performed on precoated Merck silica gel 60 F_{254} plates, and compounds were visualized by UV illumination (254 nm).

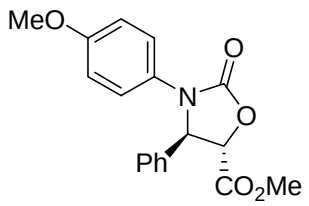
(±)-(2*S*, 3*R*)-Methyl 2-hydroxy-3-(4-methoxyphenylamino)-3-phenylpropanoate (2):



2

Chlorotrimethylsilane (11.6 mL, 93 mmol) was added dropwise at 0 ^oC to a stirred solution of hydroxy β-lactam **1** (5 g, 18.6 mmol) in anhydrous methanol (100 mL). The reaction mixture was refluxed for 5 hours, cooled to room temperature and the solvent was removed under vacuum. The crude residue was dissolved in water and neutralized with 5% aqueous $NaHCO_3$, followed by extraction with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4, concentrated under vacuum and purified by flash column chromatography to afford the title compound **2** (5.3 g, 95 %) as a white solid; mp 69-71 ^oC; ^1H NMR (250 MHz, $CDCl_3$) δ: 7.38-7.28 (5H, m), 6.71 (2H, d, J = 8.8 Hz),6.55 (2H, d, J = 8.8 Hz), 4.88 (1H, d, J = 2.5 Hz), 4.52 (1H, d, J = 2.8 Hz), 3.81 (3H, s), 3.71 (3H, s); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 173.4, 152.3, 140.4, 139.4, 128.5, 127.5, 127.0, 115.4,114.7, 74.7, 60.0, 55.6, 53.0.

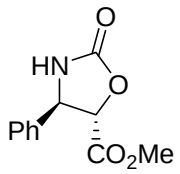
(±)-(4*R*, 5*S*)-Methyl 3-(4-methoxyphenyl)-2-oxo-4-phenyloxazolidine-5-carboxylate (3):



3

To a stirred solution of amino ester **2** (4 g, 13. 2 mmol) in anhydrous CH_2Cl_2 (100 mL) at 0 ^oC was added Hunig's base (5.6 mL, 39.8 mmol) dropwise and the reaction mixture was stirred for 15 minutes at 0 ^oC. A solution of triphosgene (4.7 g, 15.8 mmol) in anhydrous CH_2Cl_2 (50 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred for 3 hours. The mixture was diluted with CH_2Cl_2, washed with water, brine, dried over Na_2SO_4 and the solvent was removed by rotary evaporation. The residue was purified by flash column chromatography to yield oxazolidinone **3** (3.4 g, 80%) as a white solid; mp 109-111 ^oC. ^1H NMR (250 MHz, $CDCl_3$) δ: 7.40-7.27 (7H, m), 6.81 (2H, dd, *J* = 7.0, 2.3 Hz), 5.38 (1H, d, *J*= 4.5 Hz), 4.80 (1H, d, *J*= 4.3 Hz), 3.92 (3H, s), 3.75 (3H, s); ^{13}C NMR (62.5 Hz MHz, $CDCl_3$) δ: 168.8, 157.1, 154.4, 137.6, 129.4, 129.3, 129.2, 126.3, 123.1, 114.3, 76.5, 64.1, 55.4, 53.2.

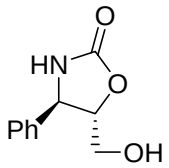
(±)-(4*R*, 5*S*)-Methyl 2-oxo-4-phenyloxazolidine-5-carboxylate:



4

To a stirred solution of oxazolidinone **3** (2.0 g, 6.1 mmol) in CH_3CN and water (50 mL, 7:3) at 0^oC was added drop wise a solution of ceric ammonium nitrate (10.0 g, 18.2 mmol) in CH_3CN and water (50 mL, 1:10 v:v) over a period of 30 minutes. The mixture was allowed to warm to room temperature and stirred for another two hours. The reaction mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organic extracts were washed with 10 % aqueous $NaHCO_3$ solution (3 x 100 mL), brine, dried over Na_2SO_4 and concentrated by rotary evaporation. The crude product was purified by flash column chromatography to afford the compound **4** (946 mg, 70%) as a white solid; mp 112-115 ^oC. ^1H NMR (250 MHz, $CDCl_3$) δ: 7.45-7.41 (5H, m), 6.00 (1H, br s), 5.02 (1H, d, *J* = 5.3 Hz), 4.80 (1H, d, *J*= 5.3 Hz), 3.90 (3H, s);^{13}C NMR (62.5 Hz MHz, $CDCl_3$) δ: 168.8, 158.3, 138.9, 129.2, 129.0, 125.8, 80.2, 59.1, 53.13.

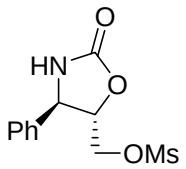
(±)-(4R, 5S)-5-(Hydroxymethyl)-4-phenyloxazolidin-2-one (5):



5

To a stirred solution of methyl ester **4** (0.8 g, 3.6 mmol) in aqueous THF (25 mL) at 0 ^{o}C was added $NaBH_4$ (0.4 g, 10.8 mmol) in one portion and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred for six hours and quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated by rotary evaporation. The crude product was purified by flash column chromatography to afford alcohol **5** (0.64 g, 92%) as a white solid; mp 106-108 ^{o}C .^{1}H NMR (250 MHz, acetone-d_6) δ: 7.44-7.35 (5H, m), 7.09 (1H, br s), 4.87 (1H, d, *J*=6.3 Hz), 4.45 (1H, br s), 4.29 (1H, dt, *J*= 2.5, 6.3 Hz), 3.80 (2H, ddd, *J*= 4.0, 6.3, 12.5 Hz); ^{13}C NMR (62.5 MHz, acetone-d_6) δ: 159.0, 142.2, 129.7, 128.9, 127.1, 85.4, 62.5, 58.1.

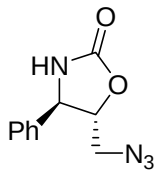
(±)-((4R, 5S)-2-Oxo-4-phenyloxazolidin-5-yl)methyl methanesulfonate (6):



6

To a solution of alcohol **5** (0.50 g, 2.5 mmol) in freshly distilled CH_2Cl_2 (50 mL) at 0 ^oC was added triethylamine (1.0 mL, 7.7 mmol) under the atmosphere of nitrogen. The reaction was stirred for 30 minutes, followed by addition of methanesulfonyl chloride (300 μL 3.8 mmol). The reaction mixture was stirred for six hours at room temperature. It was diluted with CH_2Cl_2, washed with water, brine, dried over Na_2SO_4 and concentrated by rotary evaporation. The crude product was purified by flash column chromatography to afford mesylate **6** (0.68 g, 98%) as a yellow oil. ^1H NMR (250 MHz, $CDCl_3$) δ: 7.34-7.24 (5H, m), 7.04 (1H, br s), 4.71 (1H, d, *J*= 6.5 Hz), 4.47-4.35 (3H, m), 3.06 (3H, s).

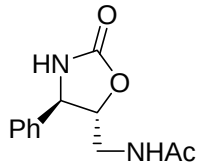
(±)-(4R, 5S)-5-(Azidomethyl)-4-phenyloxazolidin-2-one (7):



7

A mixture of mesylate **6** (0.5 g, 1.8 mmol) and NaN_3 (0.14 g, 2.2 mmol) in anhydrous DMF (10 mL) was refluxed for 12 hours under the atmosphere of nitrogen. The reaction mixture was cooled to room temperature and dilute with ice cold water. The solution was extracted with ethyl acetate (3 x 50 mL) and the combine organic extracts were dried over Na_2SO_4. The solvent was removed under vacuum and the crude product was purified by flash column chromatography to afford azide **7** (0. 29 g, 72%) as a white solid; mp 82-85 ^oC; ^1H NMR (250 MHz, $CDCl_3$) δ: 7.49-7.29 (5H, m), 6.29(1H, br s), 4.65 (1H, d, *J*= 6.0 Hz), 4.52-4.46 (1H, m), 3.75-3.52 (2H, m); ^{13}C NMR (62.5 Hz MHz, $CDCl_3$) δ: 158.4, 138.6, 129.3, 129.0, 126.1, 82.7, 58.8, 51.9.

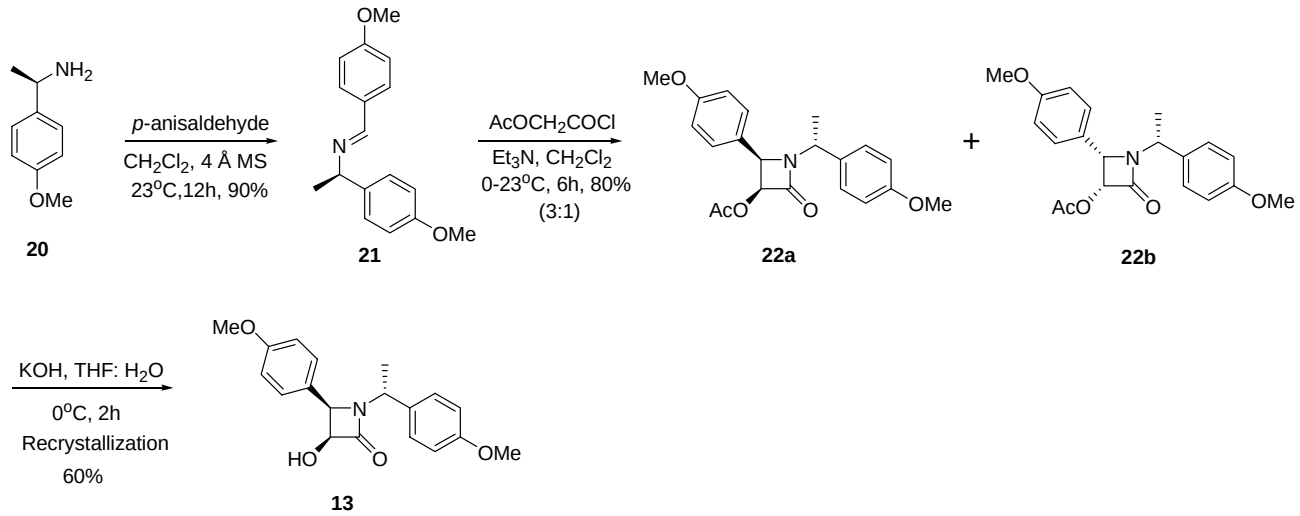
(±)- ((4R, 5R)-2-Oxo-4-phenyloxazolidin-5-yl)methyl)acetamide (8):



8

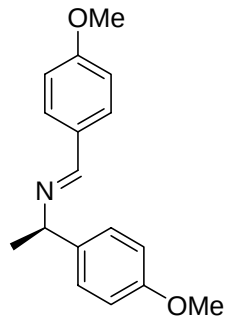
To a solution of azide **7** (0.1 g, 0.4 mmol) in ethyl acetate (10 mL) was added a catalytic amount of 10% Pd/C. The reaction mixture was stirred at room temperature for 12 hours under the atmosphere of hydrogen. The reaction mixture was evacuated and flushed with nitrogen. The mixture was cooled to 0^{o}C and pyridine (147 µL, 1.8 mmol) and acetic anhydride (173 µL, 1.8 mmol) were added sequentially and further stirred for 6 hours. The solution was diluted with ethyl acetate and washed with water, brine, dried over Na_2SO_4 and concentrated by rotary evaporation. The crude product was purified by flash column chromatography to afford **8** (0.08 g, 75%) as a white solid; mp 118-120 ^{o}C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40-7.31 (5H, m), 6.23 (1H, br s), 5.60 (1H, br s), 4.64 (1H, d, *J*= 7.3 Hz), 4.44-4.38 (1H, m), 3.67-3.57 (2H, m), 2.01 (3H, s); ^{13}C NMR (62.5 Hz, $CDCl_3$): δ 171.1, 158.6, 138.4, 129.2, 128.9, 128.7, 128.6, 126.0, 83.7, 58.6, 40.2, 23.1.

Synthesis of Optically Pure Hydroxy β-Lactam 13:



The above reaction scheme was used to prepare enantiomerically-pure lactam **13** in a manner similar to that previously reported (see Brown, S.; Jordan, A. M.; Lawrence, N. J.; Pritchard, R. G.; McGown, A. T. *Tetrahedron Lett*. **1998**, *39*, 3559; Bourzat, J.D.; Commercon, A.; *Tetrahedron Lett.* **1993**, *34*, 6042; Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron*. **1992**, *48*, 6985). *p*-Anisaldehyde was combined with an equimolar amount of amine **20** to afford chiral imine **21**, which was immediately subjected to Staudinger reaction with acetoxyacetyl chloride (one molar equivalent) and Et_3N (3 molar equivalents) in methylene chloride to afford azetidinones **22** in 80% yield as a 3:1 diastereomeric mixture. Although the minor diastereomer could in principle be removed at this stage, it was easier to do the separation after the next step. Thus, the acetate functionality was hydrolyzed with one equivalent of KOH in THF: H_2O (7:3) and the resultant diastereomeric mixture of hydroxy β-lactams was recrystallized with EtOAc: hexane (7:3) to afford a 60% yield of hydroxy β-lactam **13** as a single diastereomer.

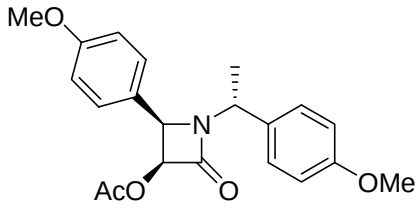
(*E*)-(*R*)-N-(4-Methoxybenzylidene)-1-(4-methoxyphenyl)ethanamine (21):



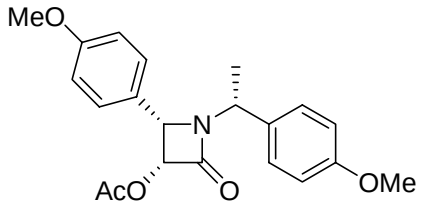
21

To a solution of 4-methoxybenzaldehyde (10.0 g, 73.4 mmol) in CH_2Cl_2 (250 mL) was added amine **20** (11.0 g, 73.4 mmol) and powdered 4Å molecular sieves (5 g). The reaction mixture was stirred for 12 hours at room temperature and then filtered through a sintered glass vacuum filtration funnel containing a ½" pad of Celite. The pad was washed three times with CH_2Cl_2 and the filtrate was concentrated to dryness by rotary evaporation to give imine **21** (17.7 g, 90%) as an opalescent oil. This imine was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.33 (1H, s), 7.78-7.74(2H, m), 7.41-7.36 (2H, m), 6.97-6.90 (4H, m), 4.52 (1H, q, *J*= 6.5 Hz), 3.86 (3H, s), 3.83 (3H, s), 1.61 (3H, d, *J*= 6.5 Hz); ^{13}C NMR (62.5 Hz, $CDCl_3$): δ 161.5, 158.5, 158.4, 137.6, 129.7, 129.4, 127.6, 113.9, 113.8, 58.9, 55.3, 55.2, 24.8.

3-Acetoxy-4-(4-methoxypheny)-1-[(R)-1-(4-methoxyphenyl)ethyl] azetidin-2-ones (22a and 22b):



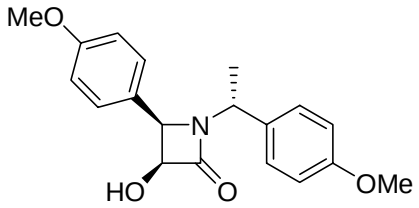
22a



22b

To a solution of imine **21** (10 g, 37.1 mmol) in CH_2Cl_2 (250 mL) was added triethylamine (15.6 mL, 111.3 mmol) under a nitrogen atmosphere at room temperature. The reaction mixture was cooled to 0^oC and a solution of acetoxyacetyl chloride (5.1 mL, 44.5 mmol) in CH_2Cl_2 (100 mL) was added dropwise over a period of one hour. The reaction mixture was stirred at room temperature for 12 hours and then diluted with CH_2Cl_2, washed with water, brine, dried over Na_2SO_4 and then concentrated by rotary evaporation to afford a brownish yellow oil. This oil was purified by flash column chromatography to afford a 3:1 diastereomeric mixture of β-lactams **22a** and **22b** (10.9 g, 80 %). This mixture was carried forward to the next step without any further purification.

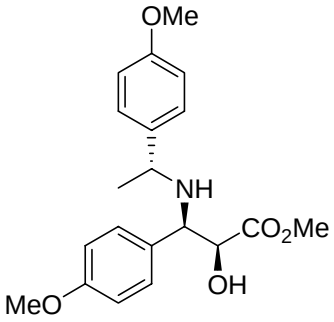
(3*S*, 4*R*)-3-Hydroxy-4(methoxyphenyl)-1-[(*R*)-1-(4-methoxyphenyl) ethyl] azetidin-2-one (13):



13

To a solution of solid KOH (2.7 g, 48.7 mmol) in THF: H_2O (50 mL, 7:3 v:v) at 0^oC was added dropwise a solution of a mixture (3: 1 molar ratio) of the two diastereomers **22a** and **22b** (6 g, 16.2 mmol) in THF (25 mL). The reaction mixture was stirred at 0^oC for two hours and then diluted with water and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and then concentrated to dryness by rotary evaporation to give a white solid, which was recrystallized from 40 mL of a 3:1 mixture of ethyl acetate: hexane to give compound **13** (3.0 g, 58%) as a single diastereomer; mp 128-130 ^oC; $[\alpha]_D^{23}$ -227.0 (c=0.5 M, $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.32-7.17 (4H, m), 6.98-6.88 (4H, m), 5.06 (1H, q, *J* = 7.5 Hz), 4.90 (1H, dd, *J* = 5.0, 7.5 Hz), 4.53 (1H, d, *J* = 5.0 Hz), 3.88 (3H, s), 3.83 (3H, s), 2.50 (1H, br s), 1.40 (3H, d, *J* = 7.3 Hz); ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 169.1, 159.9, 159.1, 131.6, 129.7, 128.5, 126.8, 113.9, 76.5, 61.3, 55.3, 51.3, 19.4.

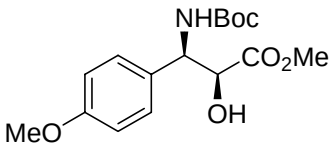
(2*S*, 3*R*)-methyl 2-hydroxy-3-(4-methoxyphenyl)-3-(*R*)-(4-methoxyphenyl) ethyl amino) propionate (14):



14

Compound **14** was synthesized from compound **13** employing the same procedure as described for compound **2**. mp 88-90 ^{o}C; $[\alpha]_D^{23}$ -28.1 (c=0.5 M, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.24 (2H, d, *J*= 8.5 Hz), 7.17 (2H, d, *J*= 8.5 Hz), 6.90 (2H, d, *J*=8.5 Hz), 6.85 (2H, d, *J*= 8.5 Hz), 4.26 (1H, d, *J* = 3.3 Hz), 4.14 (1H, d, *J*= 3.5 Hz), 3.85 (3H, s), 3.81 (3H, s), 3.79 (3H,s), 3.77 (3H, s), 3.63 (1H, q, *J*= 5.5 Hz), 1.29 (3H, d, *J*= 6.8 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 174.0, 159.0, 158.6, 137.9, 132.3, 128.5, 127.5, 113.9, 113.8, 76.6, 74.5, 61.0, 55.2, 54.0, 53.8, 52.3, 22.4.

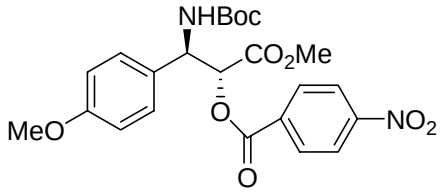
(2*S*, 3*R*)-methyl 3-(tert-butoxycarbonylamino-2-hydroxy-3-(4-methoxyphenyl)propanoate (15):



15

To a solution of compound **14** (1.0 g, 2.7 mmol) in anhydrous methanol (25 mL) was added a catalytic amount of Pearlman´s catalyst [$Pd(OH)_2$/C] and the reaction mixture was stirred at room temperature for 12 hours under an atmosphere of hydrogen (balloon). The flask was evacuated and flushed with nitrogen. It was then charged with powdered $NaHCO_3$ (0.7 g, 8.3 mmol) and Boc_2O (0.72 g, 3.3 mmol). The resultant reaction mixture was sonicated at room temperature for six hours, then filtered through a sintered funnel containing a pad of Celite. The pad was washed three times with methanol and the filtrate was concentrated to dryness by rotary evaporation. The crude product was partitioned between water and CH_2Cl_2.and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The crude product was purified by flash chromatography to afford the compound **15** (0.72 g, 80%) as a white solid; mp 110-112^oC; $[\alpha]_D^{23}$ -3.8 (c=0.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ: 7.21 (2H, d, *J* = 8.8 Hz), 6.81 (2H, d, *J*= 8.8 Hz), 5.30 (1H d, *J*= 9.5 Hz), 5.07 (1H, d, *J*= 9.5 Hz), 4.35 (1H, d, *J*= 1.8 Hz), 3.74 (3H, s), 3.71 (3H, s), 3.16 (1H, d, *J*= 4.3 Hz), 1.37 (9H, s); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 173.4, 159.1, 155.1, 131.3, 127.9, 113.9, 79.8, 76.5, 73.6, 55.2, 52.9, 28.3.

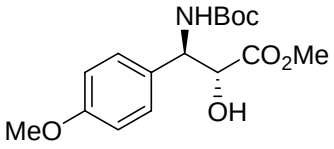
(1*R*, 2*R*)-1-(tert-Butoxycarbonylamino)-3-methoxy-1-(4-methoxyphenyl)-3-oxopropan-2yl-4-nitrobenzoate (15a):



15a

To a stirred solution of compound **15** (0.5 g, 1.5 mmol) in anhydrous THF (25 mL) were added PPh_3 (1.2 g, 4.6 mmol) and 4-nitrobenzoic acid (0.77 g, 4.6 mmol). The solution was cooled to 0 ^oC and DIAD (932 µL, 4.6 mmol) was slowly added. The reaction mixture was allowed to stir at room temperature for six hours under a nitrogen atmosphere. THF was removed by rotary evaporation and the crude product was partitioned between water and ethyl acetate. The combine organic extracts were washed with brine, dried over Na_2SO_4 and concentrated by rotary evaporation. The residue was purified by flash column chromatography to give compound **15a** (0.5 g, 70%) as a yellowish syrup. ^1H NMR (250 MHz, $CDCl_3$): δ 8.22 (2H, d, *J*= 8.8 Hz), 8.10 (2H, d, *J*= 8.8 Hz), 7.21 (2H, d, *J*=8.8 Hz), 6.82 (2H, d, *J*= 8.8 Hz). 5.58 (1H, d, *J*= 4.3 Hz), 5.25 (1H, br s), 5.23 (1H, d, *J*= 7.0 Hz), 3.73 (3H, s), 3.61 (3H, s), 1.35 (9H, s); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 167.7, 163.8, 159.6, 154.8, 150.8, 134.5, 131.0, 128.6, 128.3, 123.6, 114.1, 80.4, 76.5, 75.3, 55.2, 54.5, 52.6, 28.2.

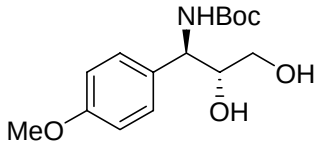
(2*R*, 3*R*)-Methyl 3-tert-butoxycarbonylamino-2-hydroxy-3-(4-methoxyphenyl)propanoate (16) :



16

Triethylamine (446 µL, 3.1 mmol) was added dropwise to a stirred solution of compound **15a** (0.5 g, 1.0 mmol) in anhydrous THF (20 mL) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for one hour and concentrated to dryness by rotary evaporation. The crude product was partitioned between water and ethyl acetate then extracted with ethyl acetate, dried over Na_2SO_4 and concentrated by rotary evaporation. The crude product was purified by flash column chromatography to afford compound **16** (0.33 g, 98%) as a pale yellow solid; mp 150-152 ^oC; $[\alpha]_D^{23}$ -1.8 (c= 0.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ: 7.09 (2H, d, *J*= 8.5 Hz), 6.76 (2H, d, *J*= 8.8 Hz), 5.49 (1H, d, *J* = 8.3 Hz), 4.97 (1H, d, *J* = 6.3 Hz), 4.50 (1H, dd, *J* = 3.3, 6.5 Hz), 3.70 (3H, s), 3.65 (3H, s), 2.85 (1H, d, *J*= 6.5 Hz), 1.37 (9H, s); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 172.4, 159.3, 154.9, 128.9, 128.4, 113.8, 79.8, 76.5, 73.3, 56.1, 55.1, 52.5, 28.3.

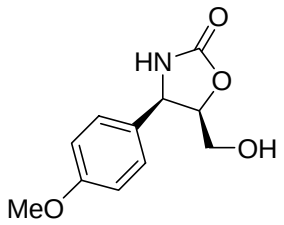
***tert*-Butyl (1*R*, 2*R*)-2,3-dihydroxy-1-(4-methoxphenyl)propylcarbamate (17):**



17

To an ice-cooled solution of $NaBH_4$ (0.08 g, 2.3 mmol) in anhydrous methanol (10 mL) was added dropwise a solution of compound **16** (0.25 g, 0.7 mmol) in anhydrous methanol (5 mL). The reaction mixture was stirred at room temperature for four hours and the solvent was removed by rotary evaporation. The crude product was partitioned between water and ethyl acetate then extracted with ethyl acetate, washed with saturated NH_4Cl solution, brine, dried over Na_2SO_4 and concentrated by rotary evaporation. The crude product was purified by flash column chromatography to give compound **17** (0.21 g, 92%) as a white solid; mp 116-118 ^oC (Lit, mp 118 ^oC); $[\alpha]_D^{23}$ -50.2 (c= 0.5 M, $CHCl_3$) [Lit, $[\alpha]_D^{23}$ -51.2 (c=1 M, $CHCl_3$)]. ^1H NMR (250 MHz, $CDCl_3$) δ: 7.17 (2H, d, *J*= 8.8 Hz), 6.82 (2H, dd, *J*= 2.8, 5.0 Hz), 5.18 (1H, br s), 4.55 (1H, m), 3.76-3.70 (1H, m), 3.72 (3H, s), 3.59 (2H, d, *J*= 2.5 Hz), 2.52 (2H, d, *J*= 2.5 Hz), 1.39 (9H, s); ^{13}C NMR (62.5 MHz, acetone-d_6) δ: 160.6, 158.9, 133.9, 128.4, 115.0, 85.8, 62.4, 57.6, 55.6, 28.9.

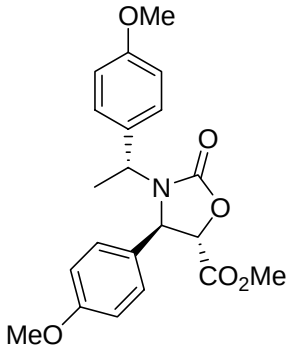
(4*R*, 5*R*)-5-(Hydroxymethyl)-4-(4-methoxyphenyl)oxazolidin-2one (9):



9

To a solution of compound **17** (0.1 g, 0.3 mmol) in anhydrous THF (10 mL) was added sodium hydride [0.04 g, 1.0 mmol (60% w/w in mineral)] at room temperature and the mixture was stirred under a nitrogen atmosphere for two hours. The reaction mixture was concentrated, CH_2Cl_2 was added, washed with aqueous saturated NH_4Cl solution, brine and dried over Na_2SO_4. The organic layer was concentrated by rotary evaporation and the residue was purified by flash column chromatography to give compound **9** (0.07 g, 92%) as a white solid; mp 117-118 ^oC; $[\alpha]_D^{23}$ -68.2 (c= 0.5 M, MeOH) [Lit: $[\alpha]_D^{23}$ -69.7 (c=0.5 M in MeOH)]; ^1H NMR (250 MHz, acetone-d_6) δ: 7.26 (2H, d, *J*= 8.8 Hz), 6.96 (2H, dd, *J*= 2.8, 6.8 Hz), 5.04(1H, d, *J*= 8.3 Hz), 4.83 (1H, ddd, *J*= 4.4, 7.3, 8.1 Hz), 3.87-3.80 (1H, m), 3.82 (3H, s), 3.19-3.26 (2H, m), 2.88 (1H, s); ^{13}C NMR (62.5 MHz, acetone-d_6) δ: 160.6, 159.5, 130.2, 129.0, 114.6, 81.5, 62.6, 57.8, 55.5.

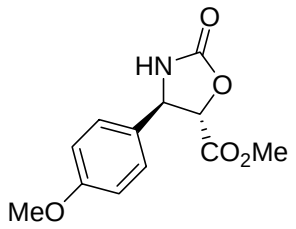
(4*R*, 5*S*)-Methyl 4-(4-methoxyphenyl)-3-((R)-1-(4-methoxyphenyl)ethyl)-2-oxazolidine-5-carboxylate (18):



18

Compound **18** was synthesized from compound **14** employing a similar procedure as described for the synthesis of compound **3**. mp 140-142 ^{o}C; $[\alpha]_D^{23}$ +42.8 (c=0.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.04-7.00 (4H, m), 6.82-6.76 (4H, m), 5.10 (1H, q, *J* = 8.7 Hz), 4.51 (1H, d, *J*= 4.3 Hz), 4.14 (1H, d, *J*= 4.3 Hz), 3.73 (6H, s), 3.61(3H, s), 1.07 (3H, d, *J*= 7.3 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 168.9, 160.2, 159.2, 156.5, 131.4, 130.6, 128.7, 128.2, 114.4, 113.8, 78.3, 60.4, 55.3, 55.2, 52.7, 52.6, 17.9.

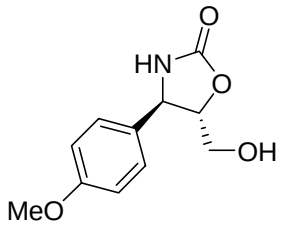
(4*R*, 5*S*)-Methyl 4-(4-methoxyphenyl)oxazolidin-2-one-5-carboxylate (19):



19

Compound **19** was synthesized from compound **18** employing a similar procedure as described for the synthesis of compound **4**. mp 88-90^{o}C; $[\alpha]_D^{23}$ +87.4 (c=0.5,MeOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.26 (2H, d, *J*= 8.3 Hz), 6.88 (2H, d, *J*= 8.3 Hz), 6.50 (1H, s), 4.85 (1H, d, *J*= 4.3 Hz), 4.65 (1H, d, *J*= 4.3 Hz), 3.82 (3H, s), 3.72(3H, s).^{13}C-NMR (250 MHz, $CDCl_3$) δ: 167.8, 159.1, 157.0, 129.8, 126.2, 113.6, 79.4, 57.7, 54.3, 52.0.

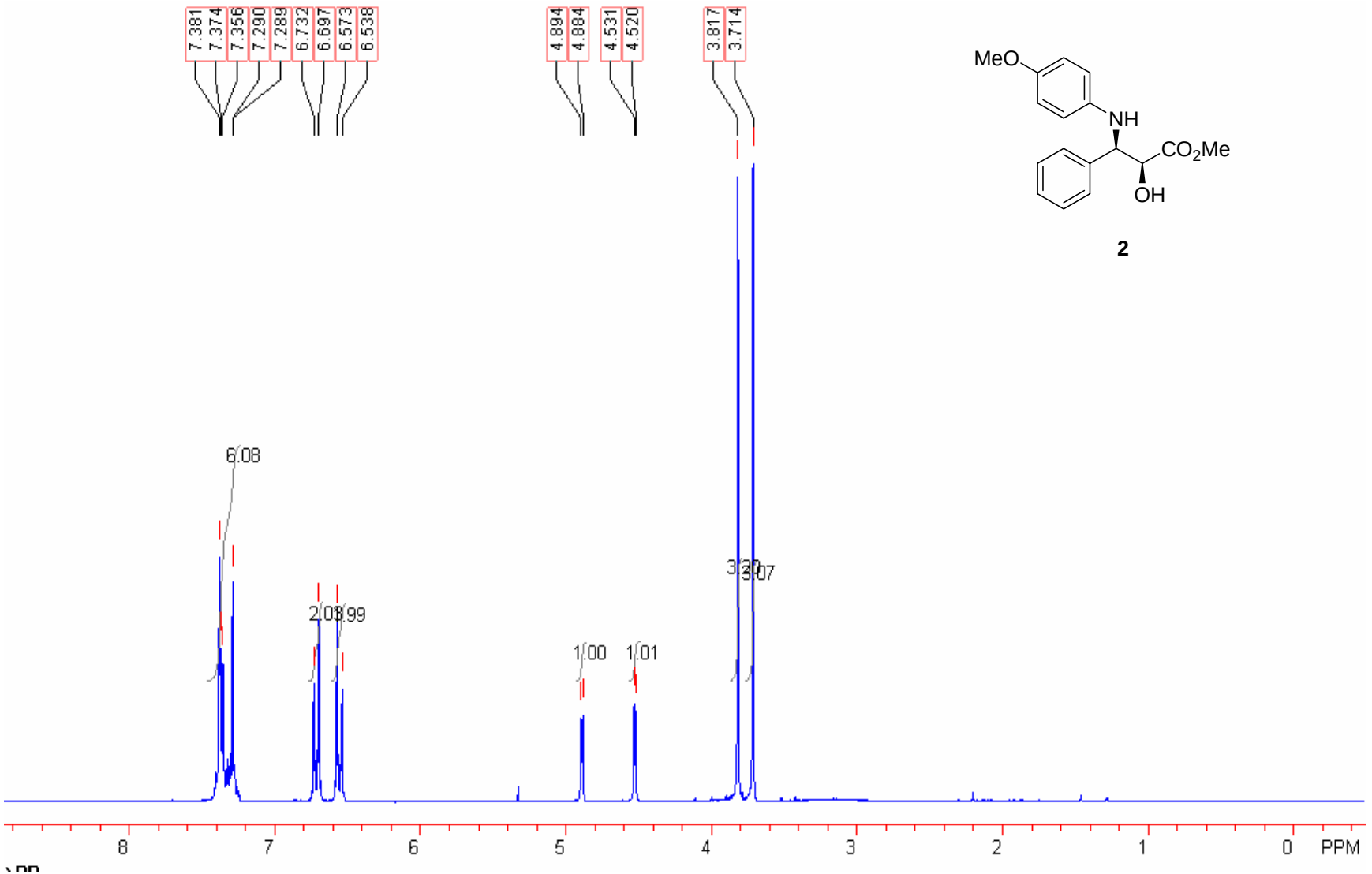
(4*R*, 5*S*)-5-(Hydroxymethyl)-4-(4-methoxyphenyl)oxazolidin-2-one (10):



10

Compound **10** was synthesized from compound **19** employing the similar procedure as described for the synthesis of compound **5**. mp 159-160 ^{o}C; $[\alpha]_D^{23}$ +30 (c=0.5, MeOH); ^{1}H NMR (250 MHz, CD_3OH) δ: 7.20 (2H, d, *J*= 8.5 Hz), 6.80 (2H, d, *J* = 8.5 Hz), 4.65 (1H, d, *J*= 6.5 Hz), 4.09-4.20 (2H, m), 3.78-3.52 (2H, m), 3.75 (3H, s), 2.72 (1H, s); ^{13}C NMR (250 MHz, CD_3OH) δ: 161.5, 161.3, 133.6, 128.6, 115.4, 86.8, 62.5, 58.5, 55.8.

^{1}H NMR and ^{13}C NMR Spectra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6.08
2.08
2.99
1.00
1.01
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6
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4
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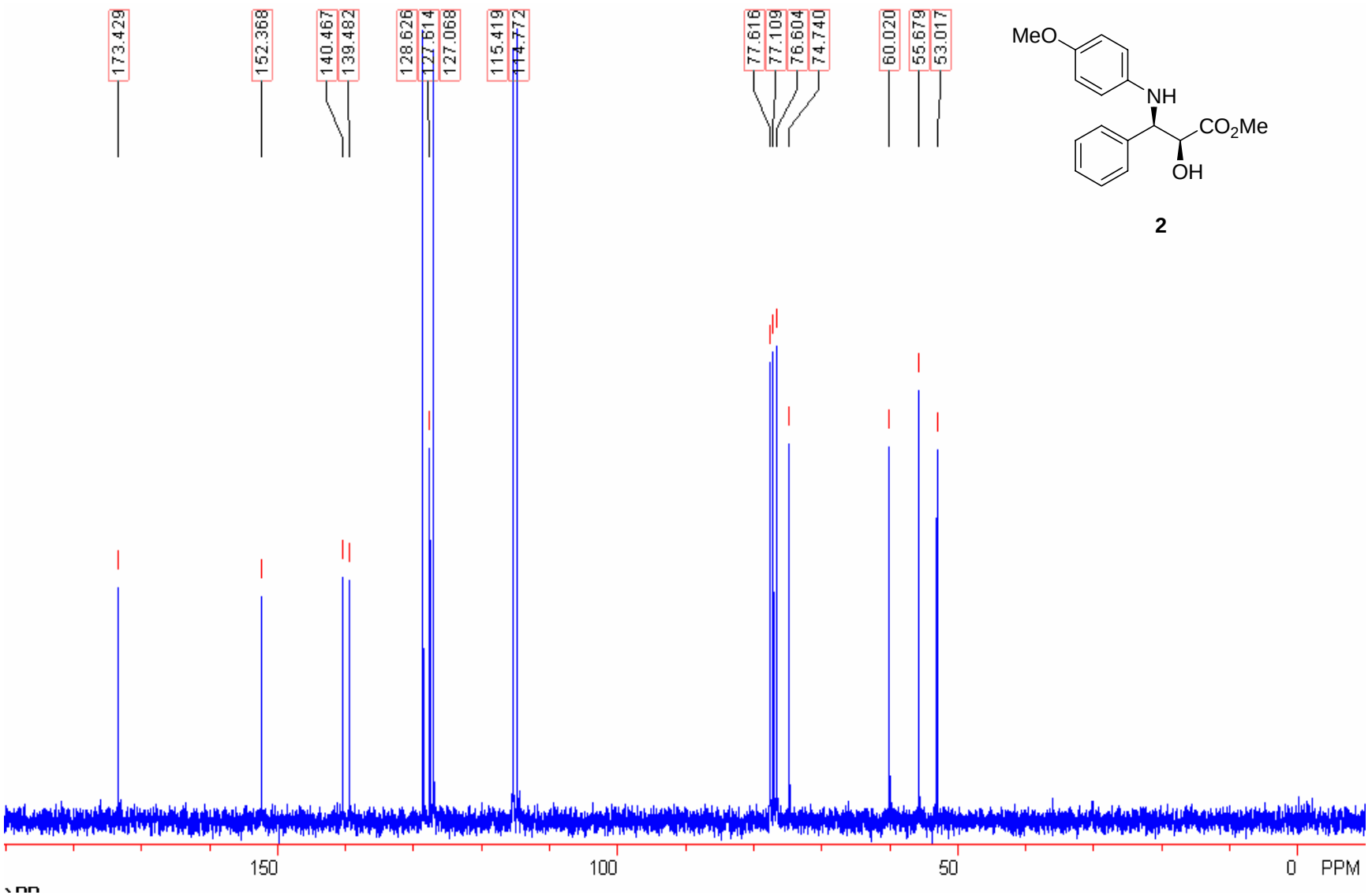
CO2Me
OH

2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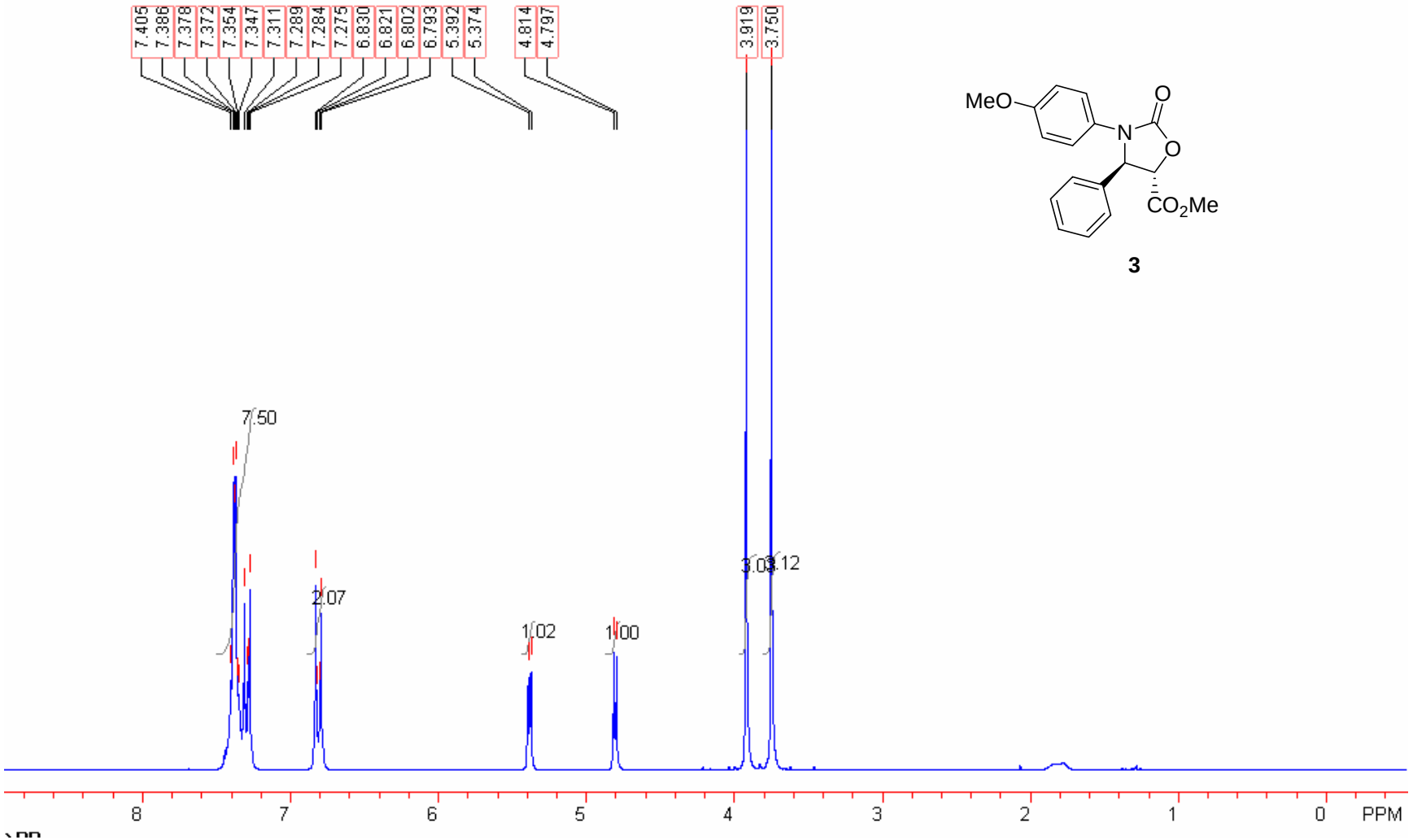
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5.392
5.374
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5
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PPM

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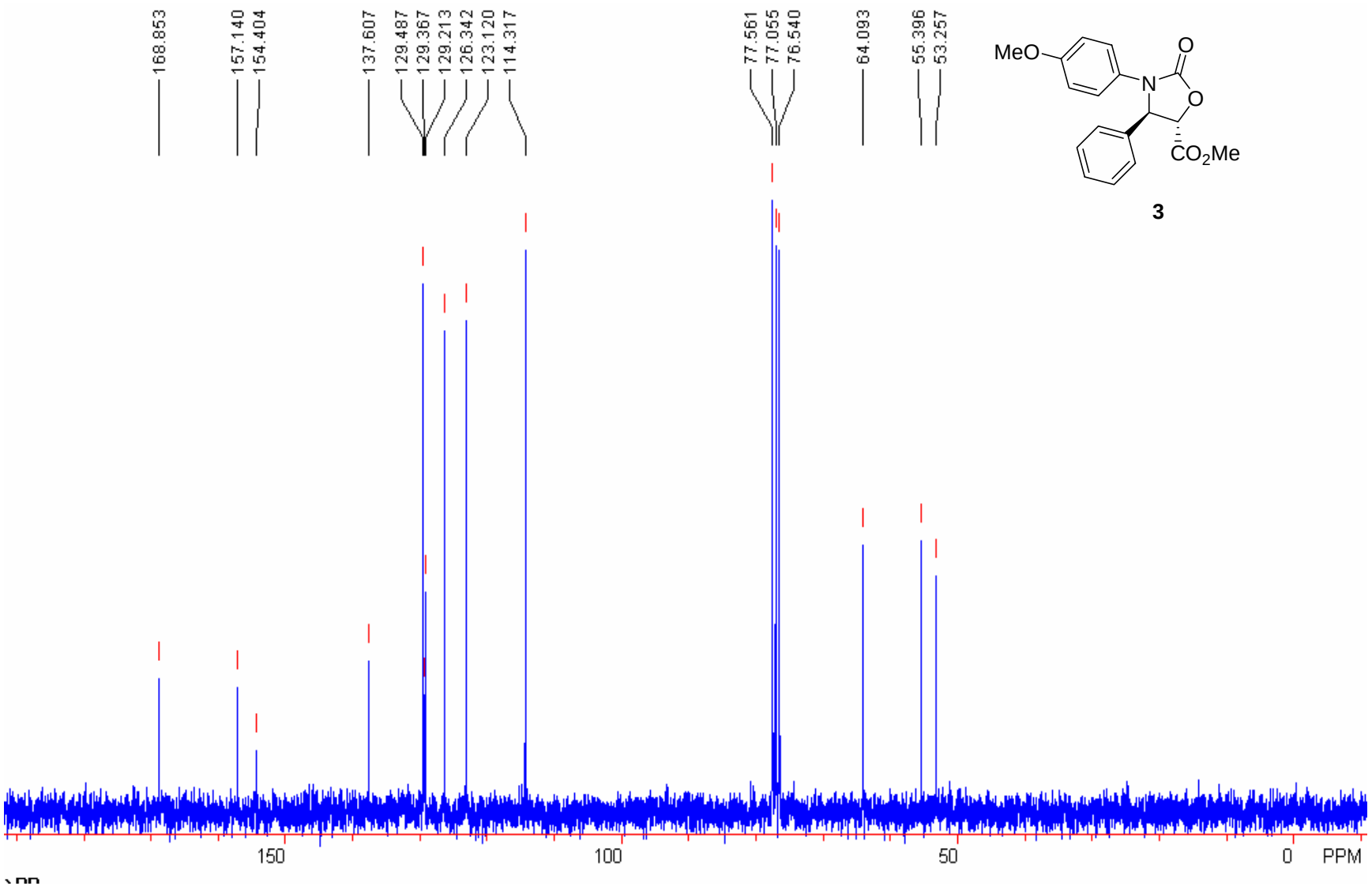
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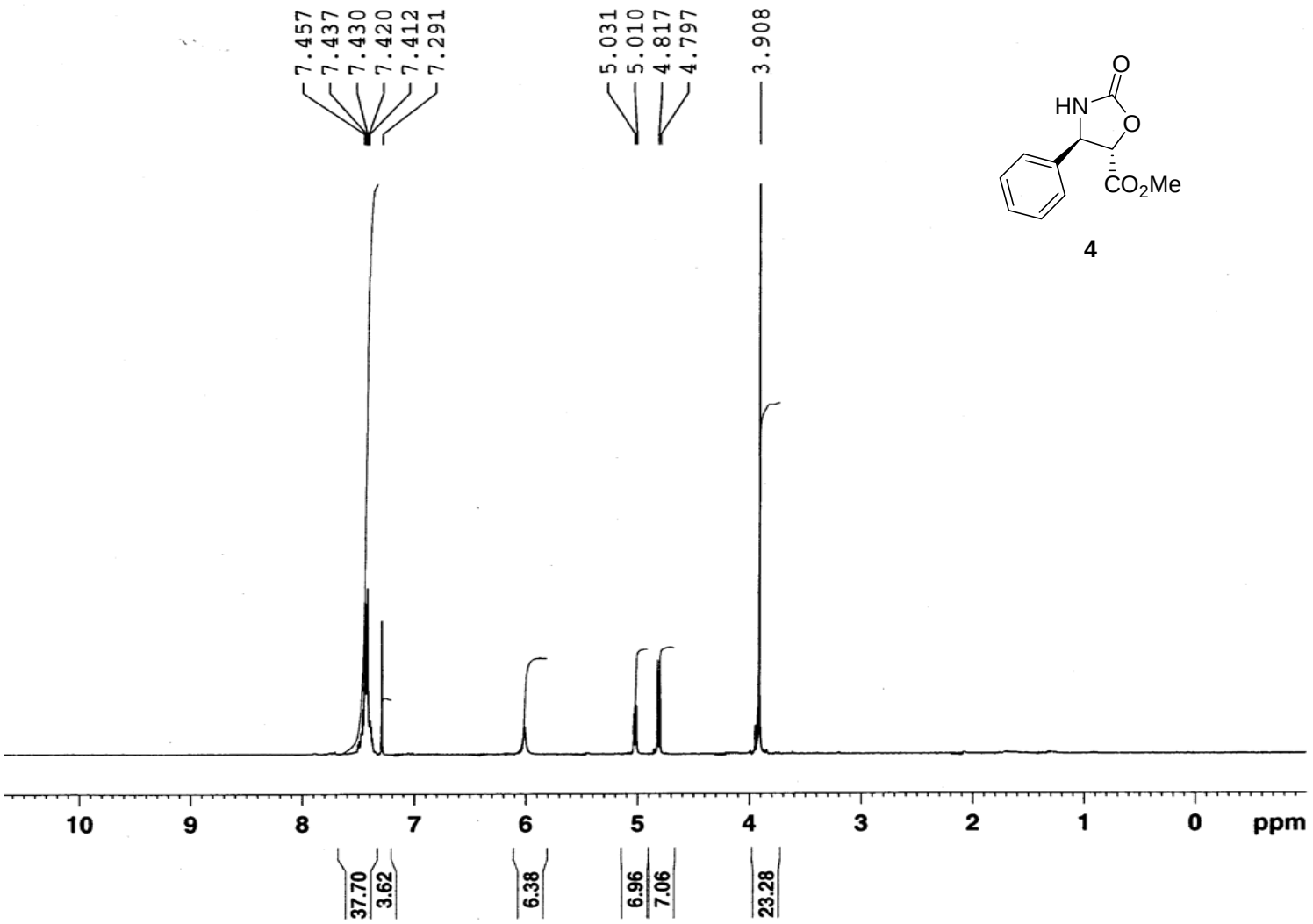

4

NH Ester
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PROCNO 1

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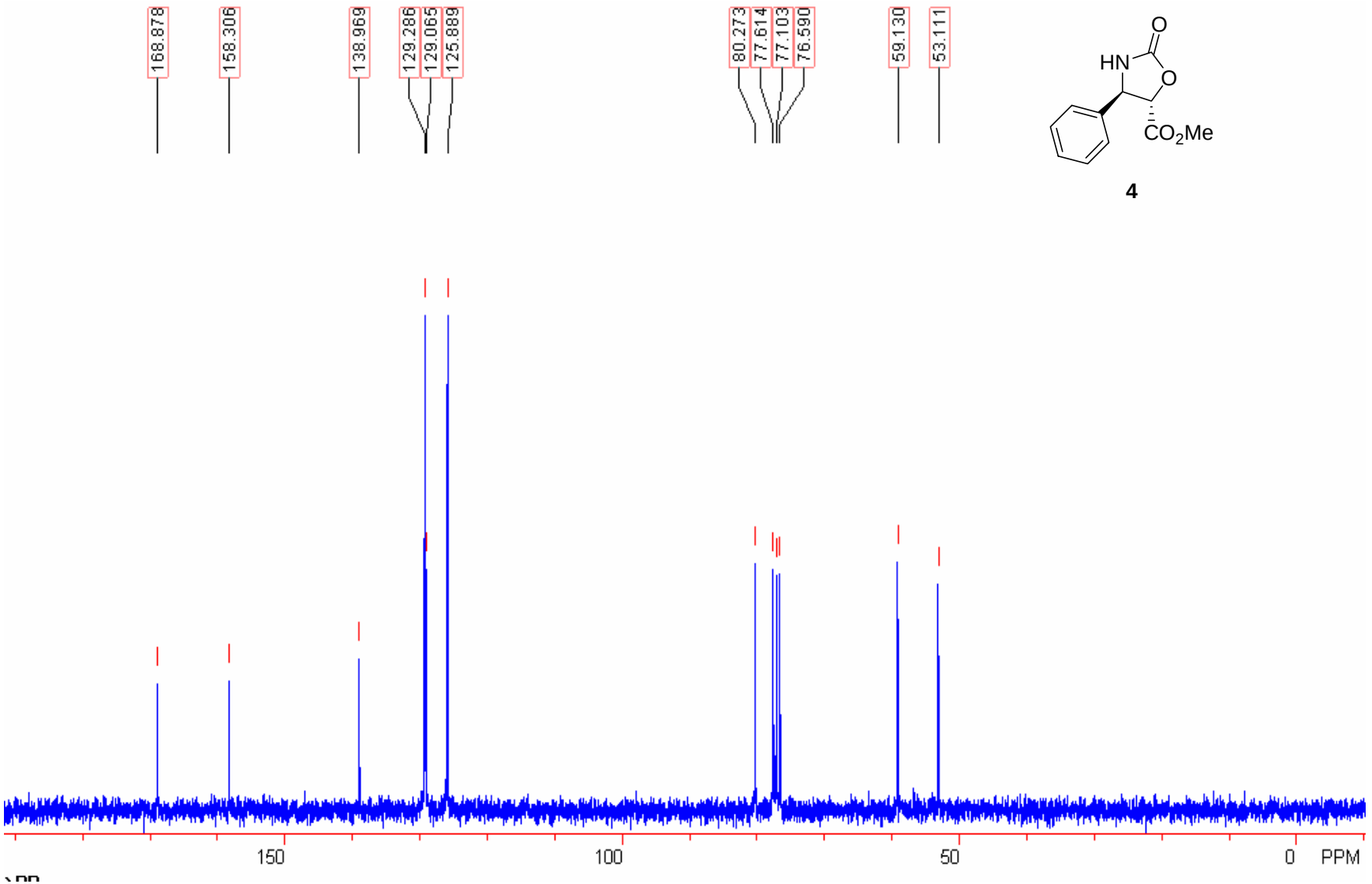
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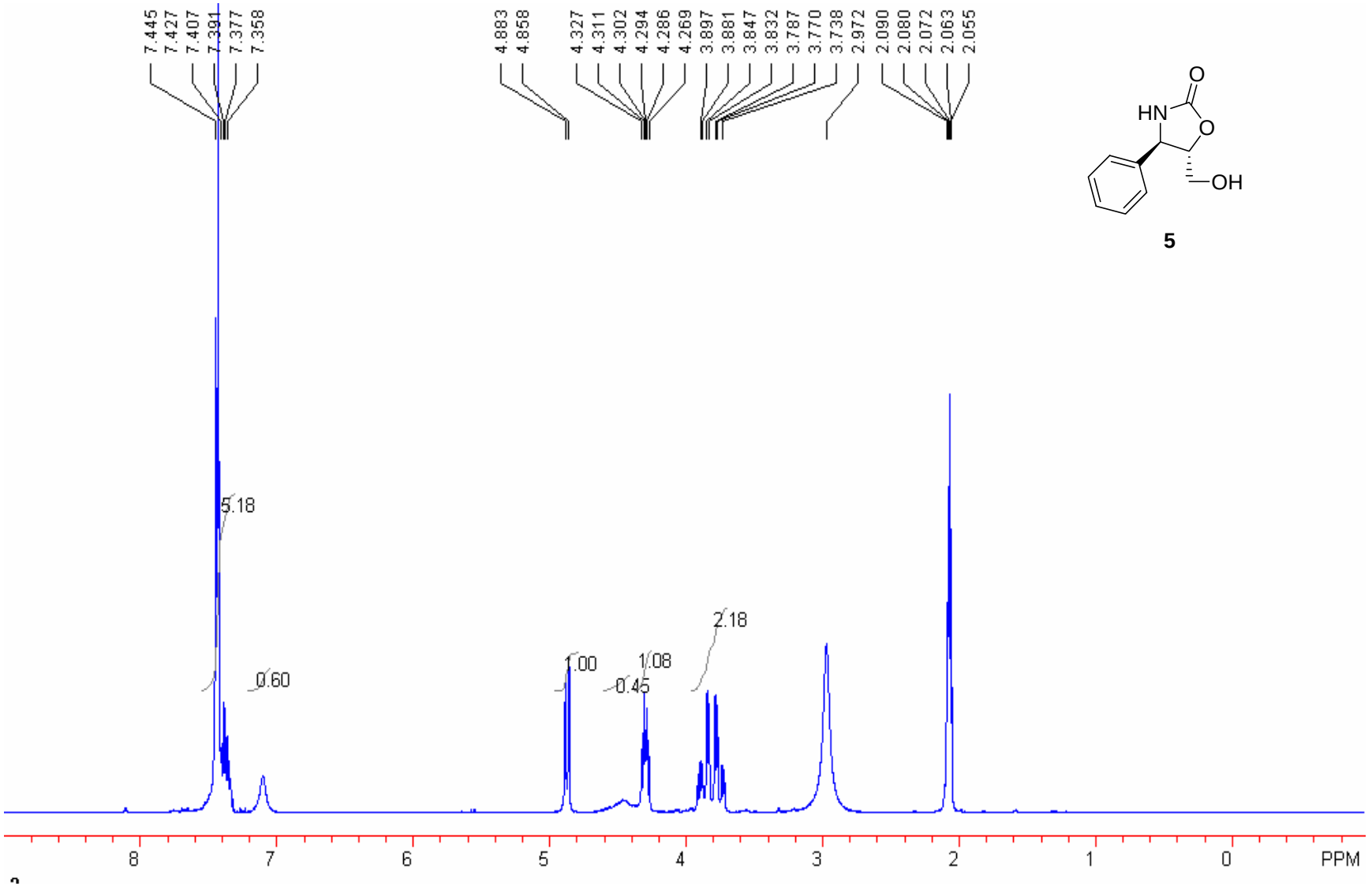
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O
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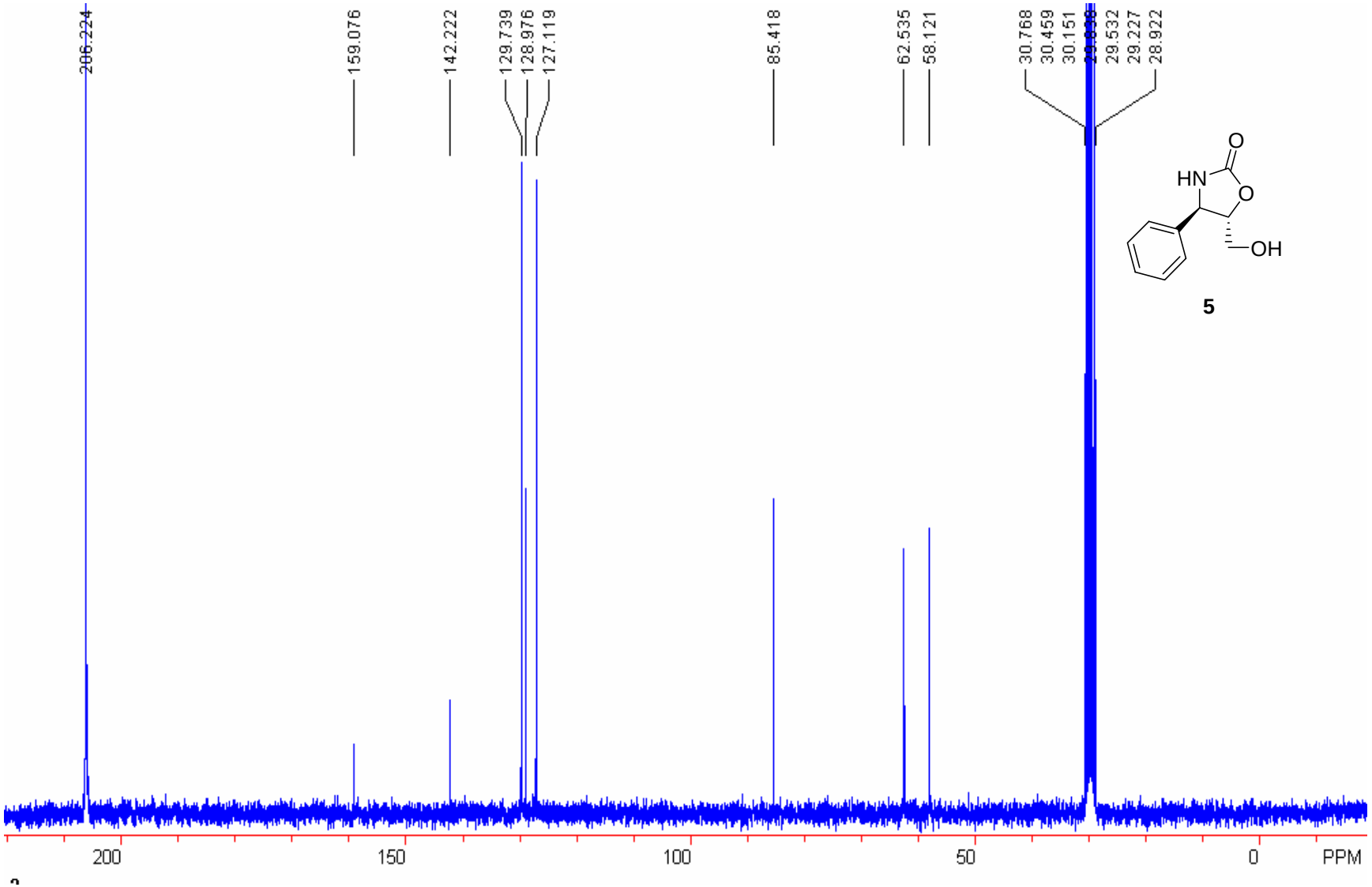
5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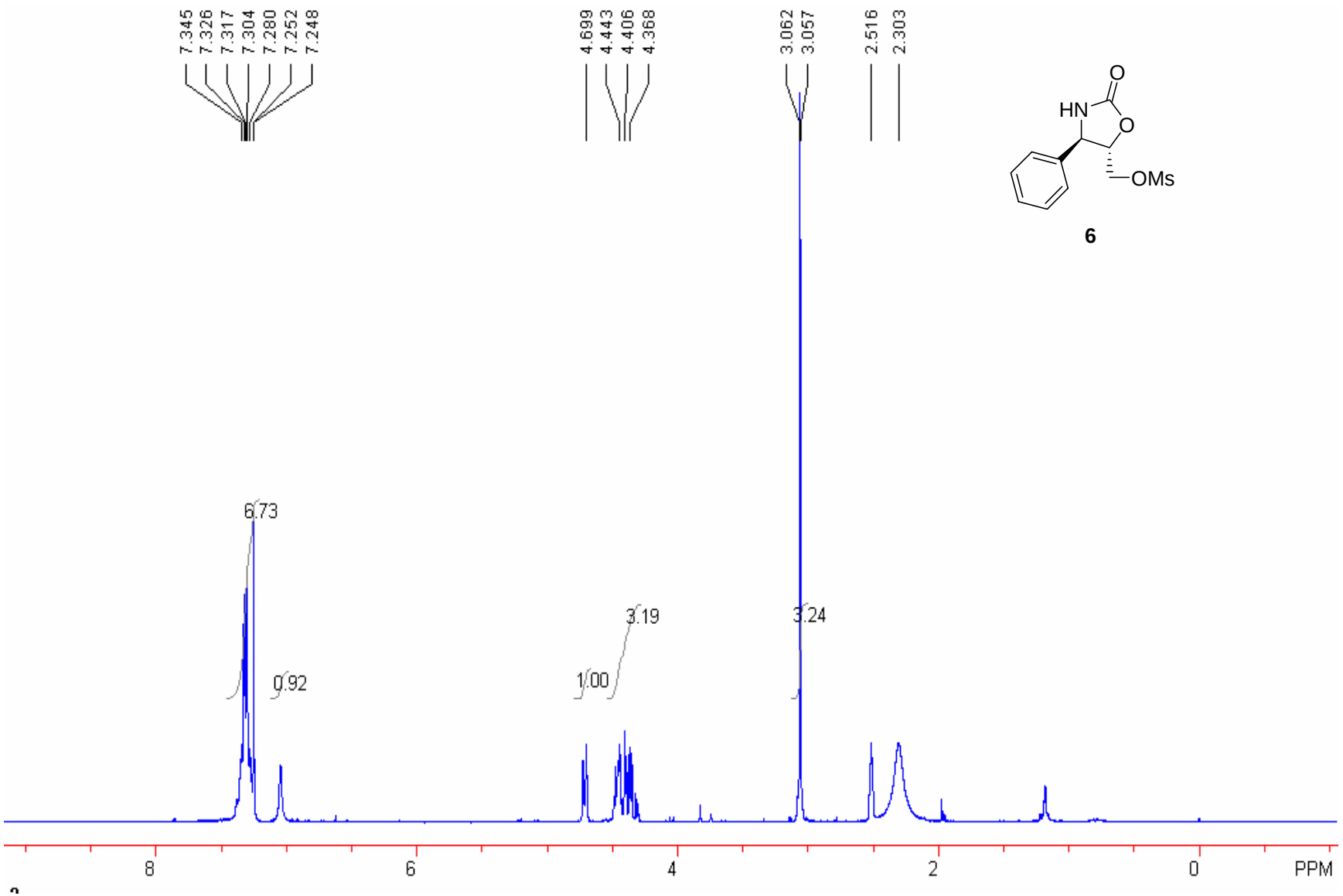
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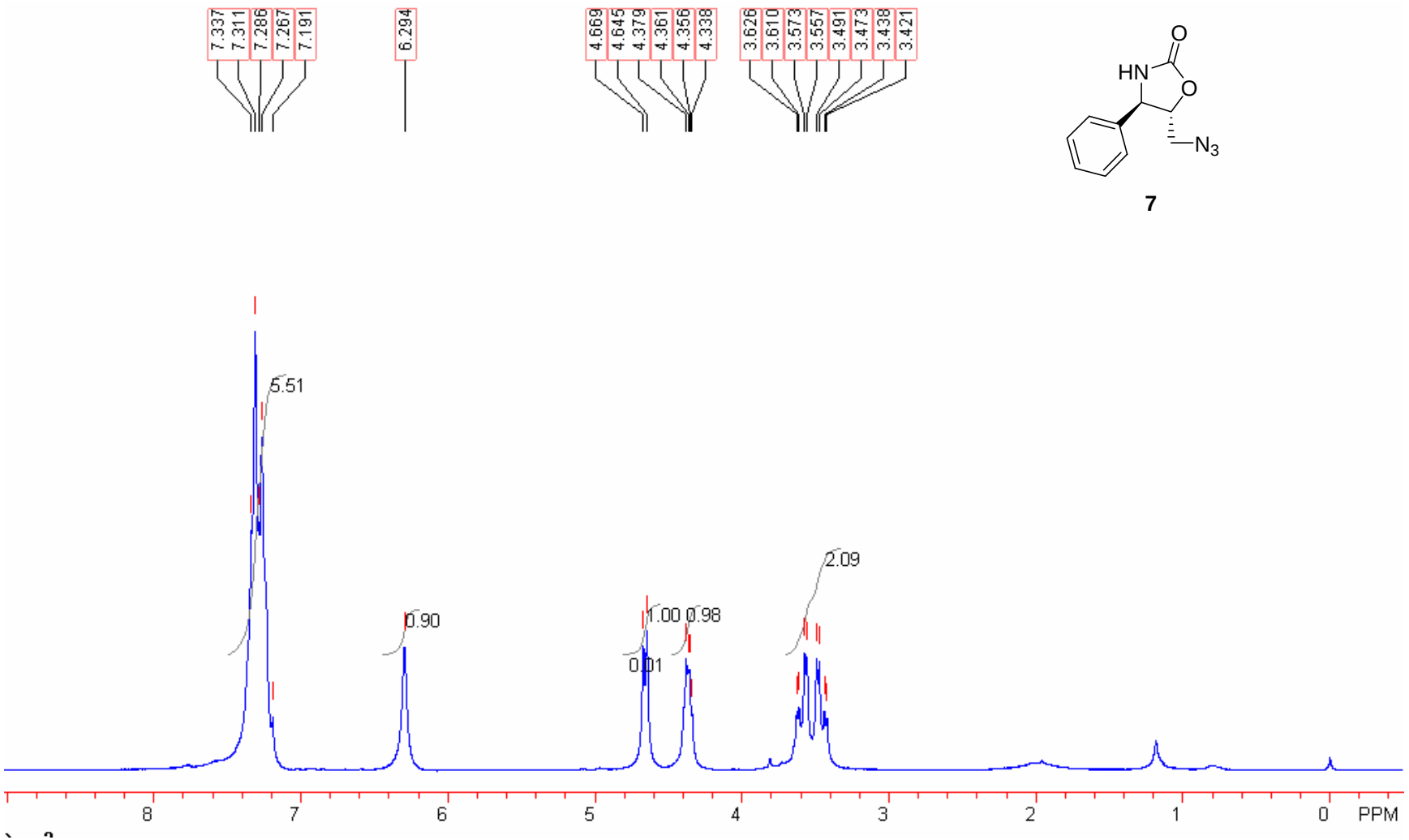
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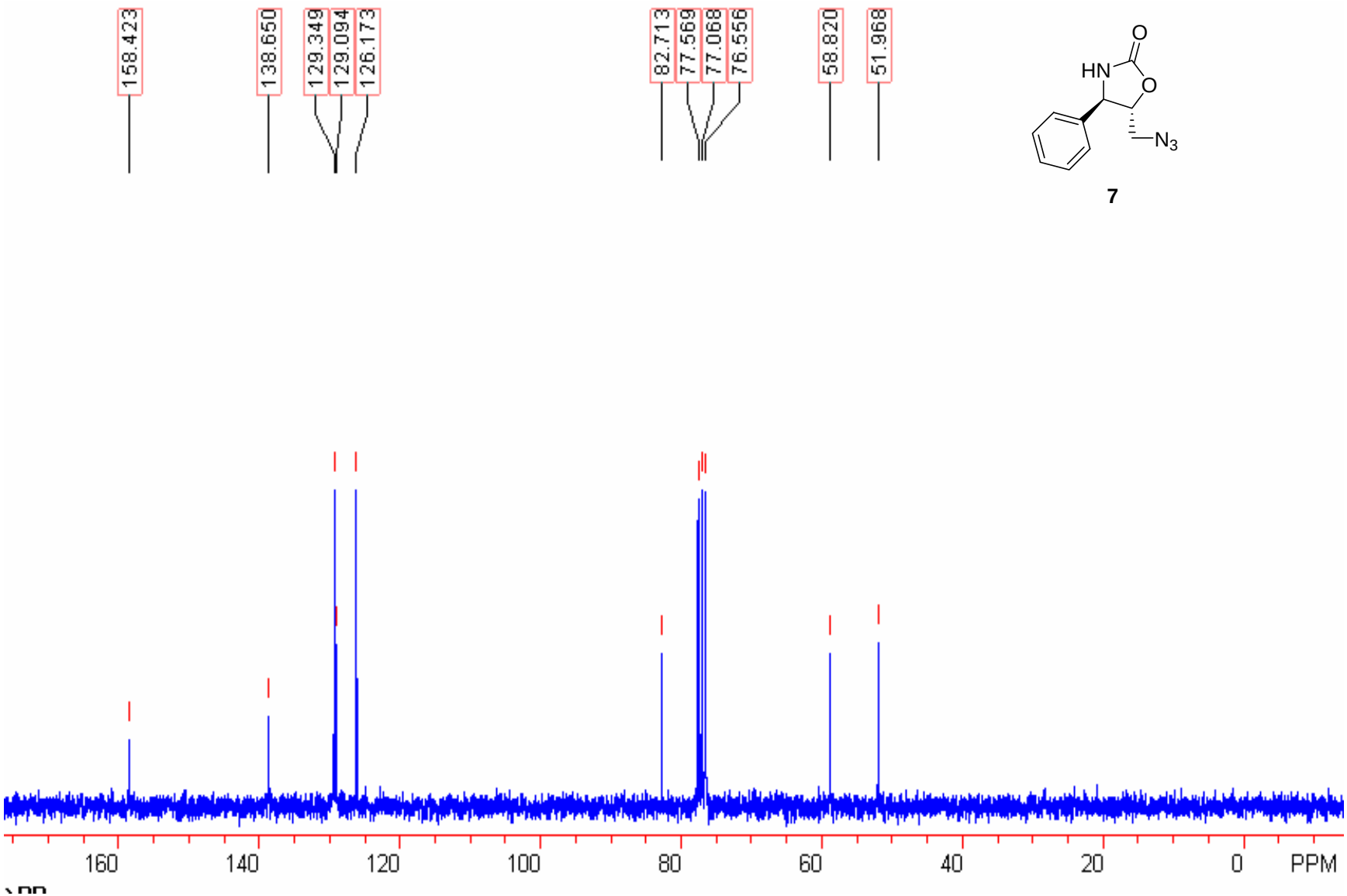
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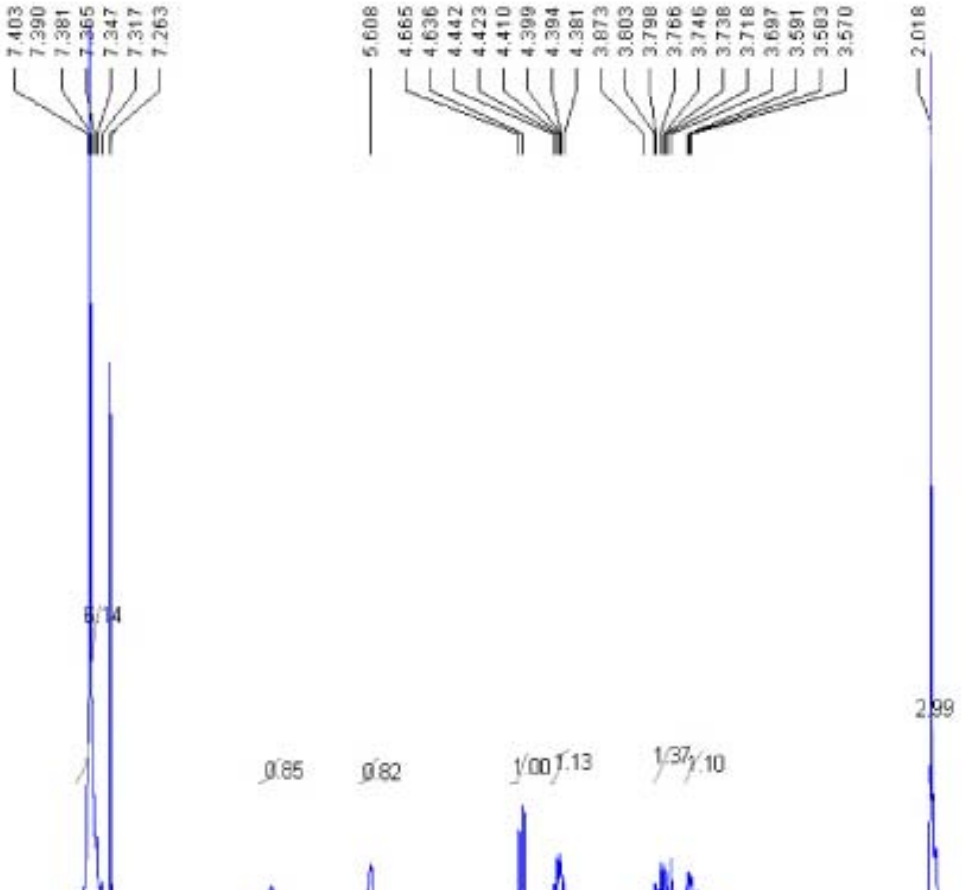
7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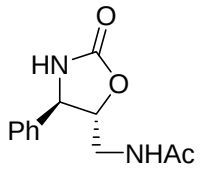
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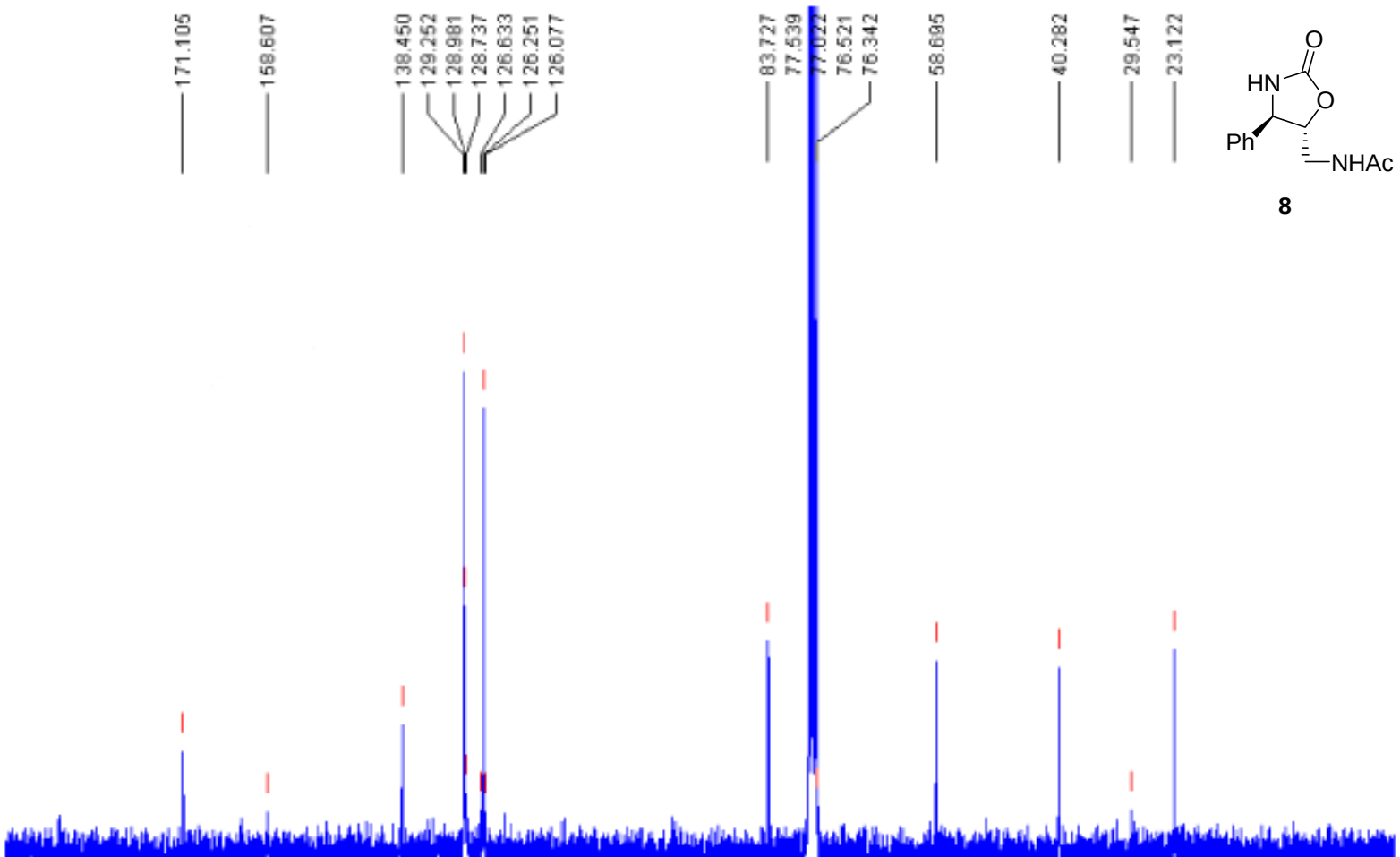
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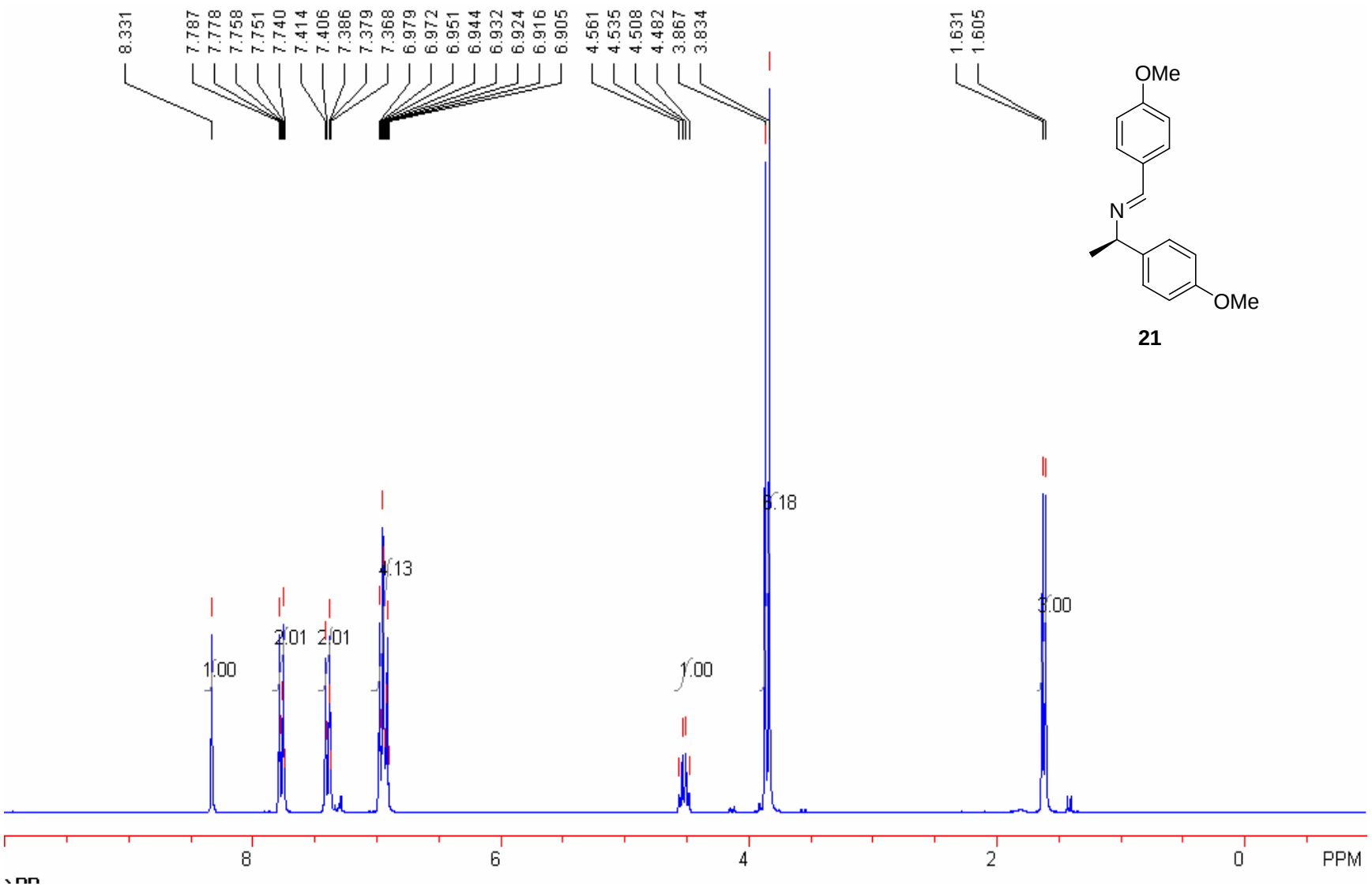
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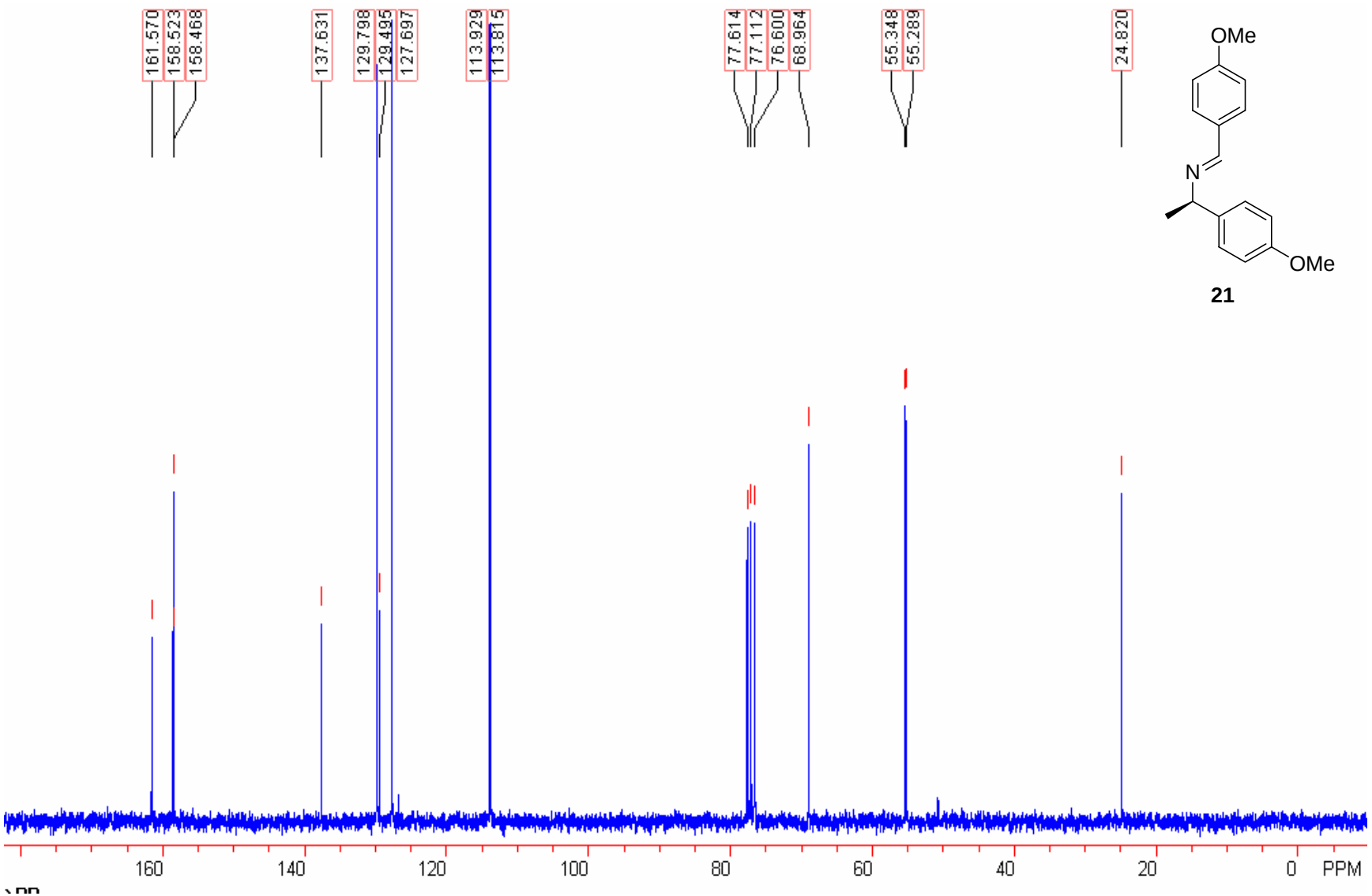
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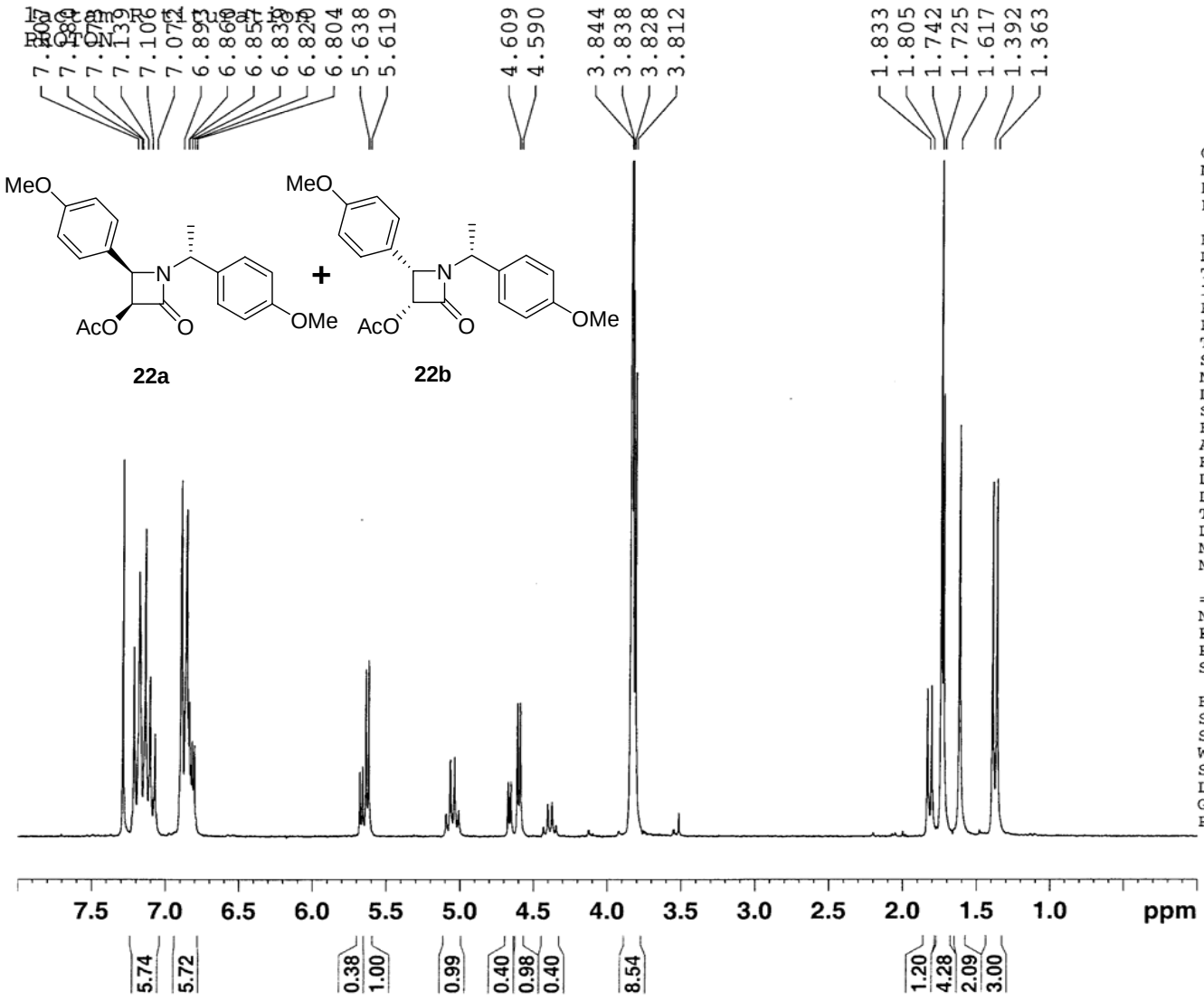

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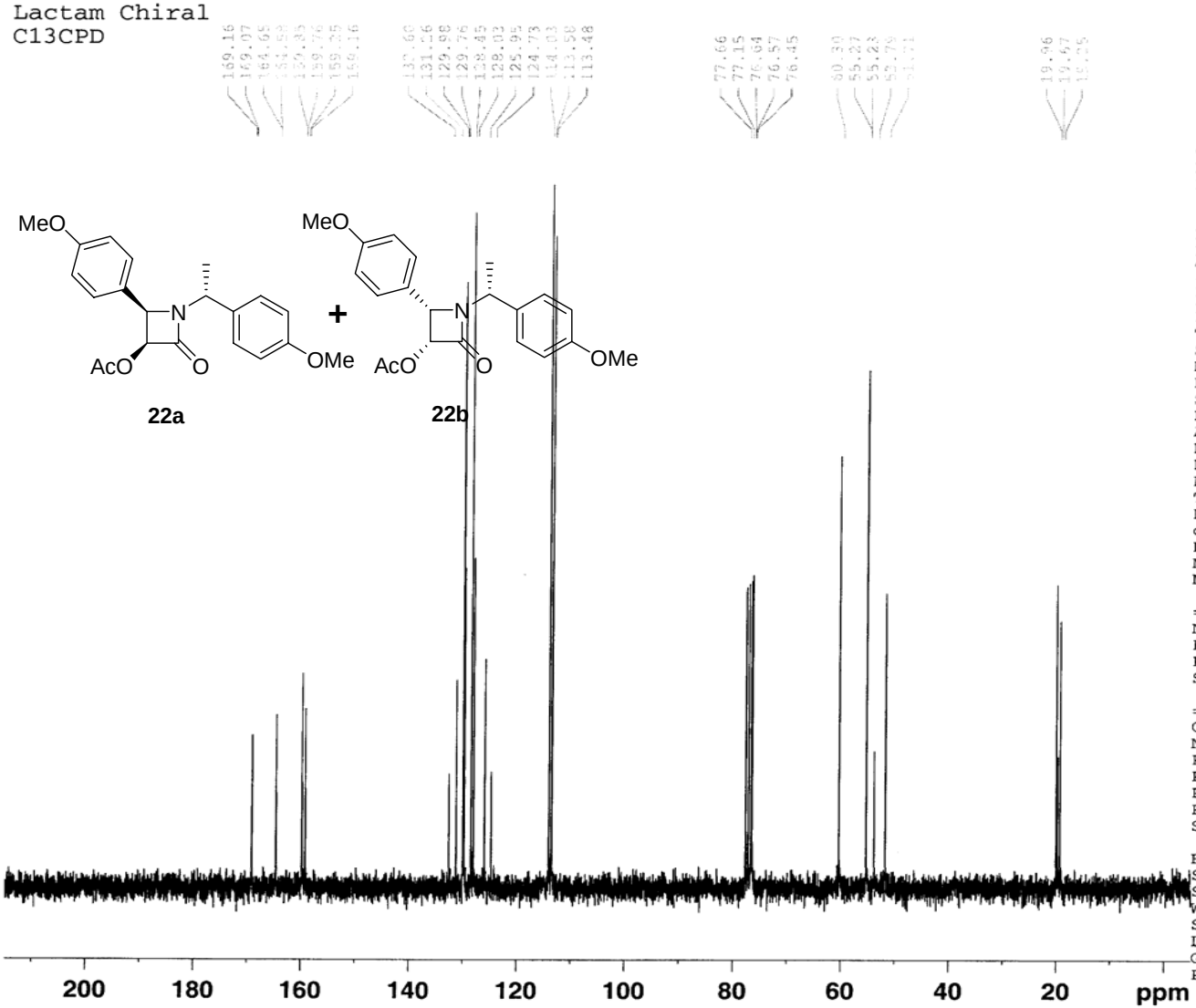

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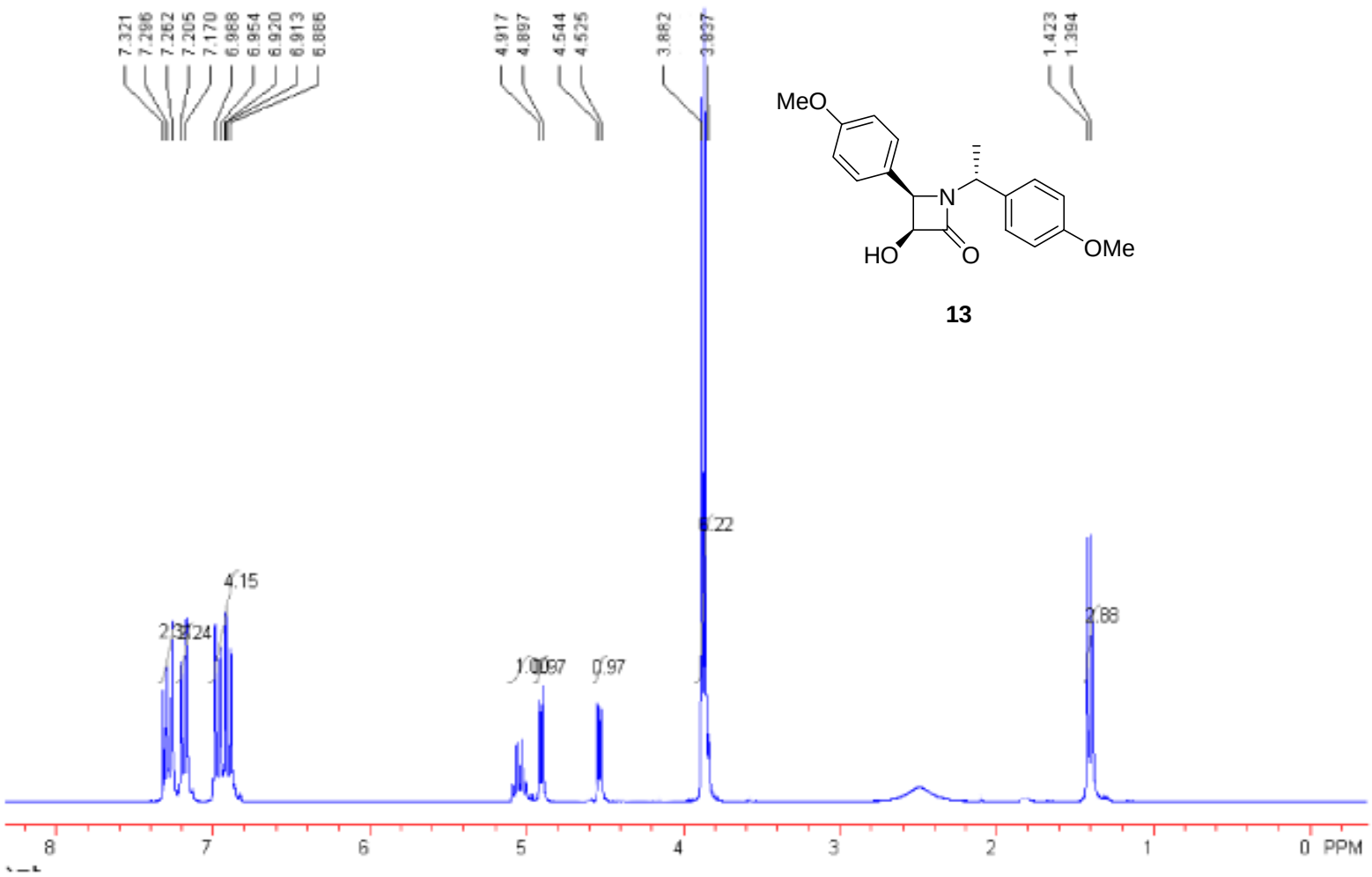
TE                298.2 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

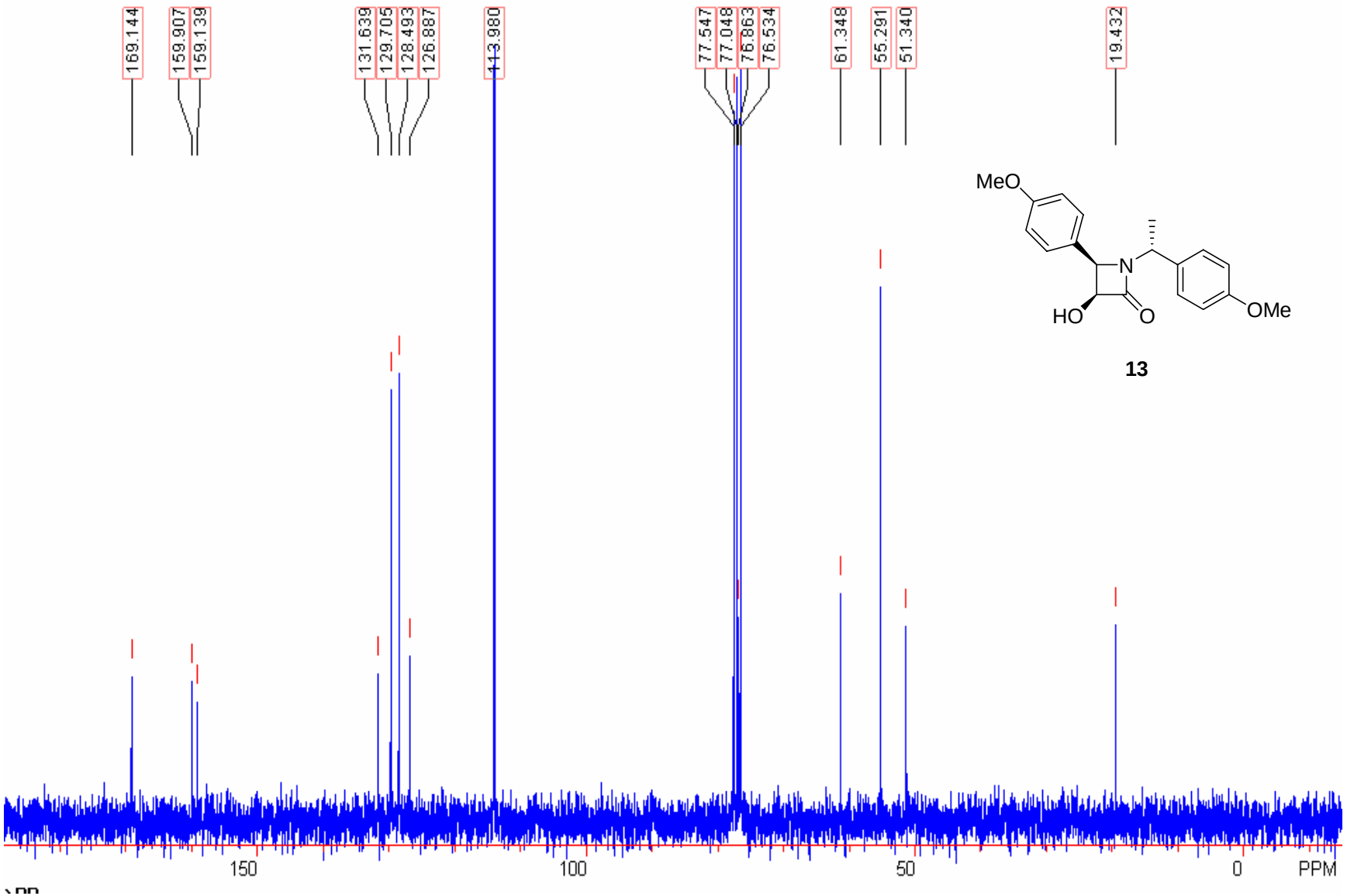
======== CHANNEL f1 ========
NUC1                13C
P1               15.50 usec
PL1              -6.00 dB
SFO1         62.9015280 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2           100.00 usec
PL2               0.00 dB
PL12             25.10 dB
PL13             25.10 dB
SFO2        250.1310005 MHz

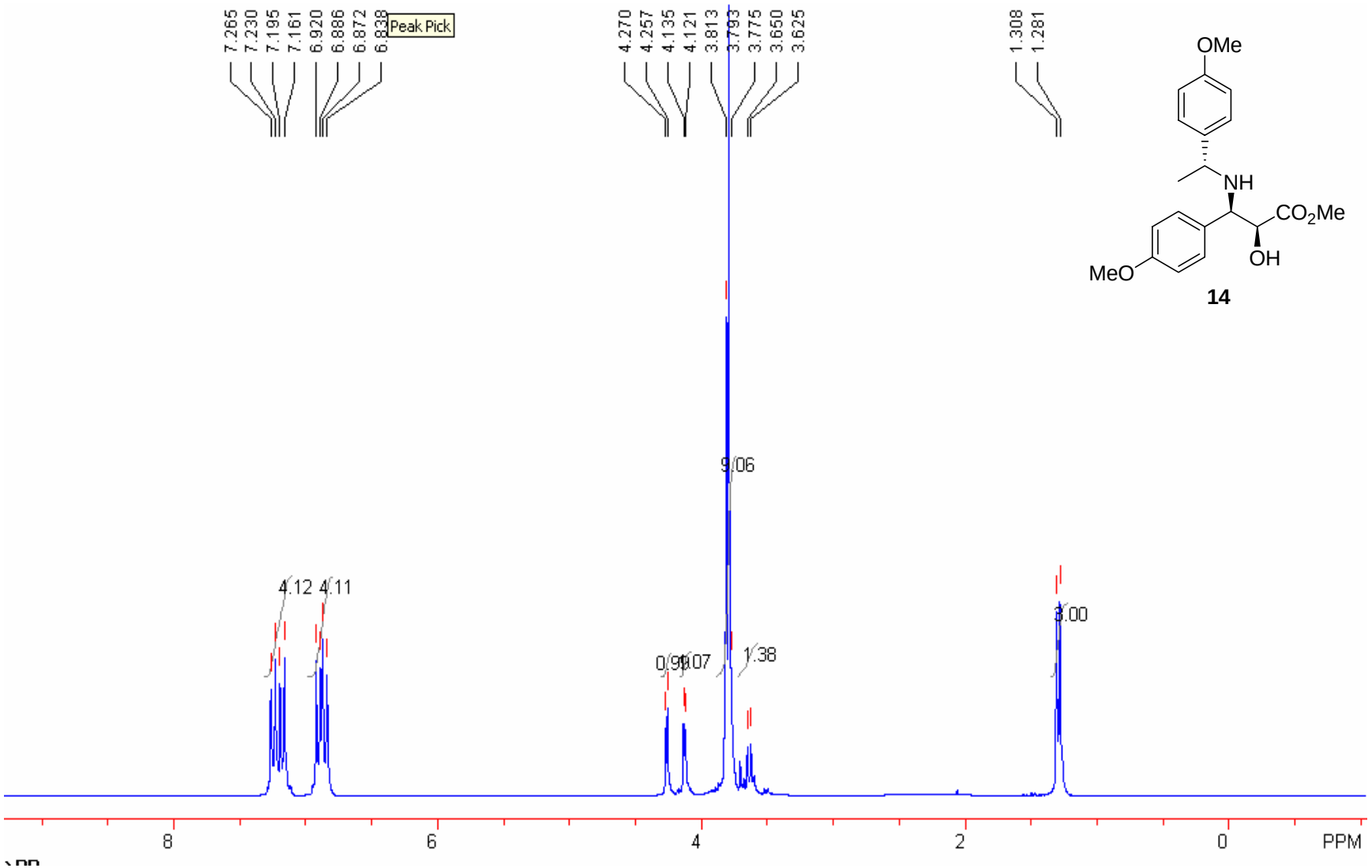
F2 - Processing parameters
SI                32768
SF           62.8952390 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

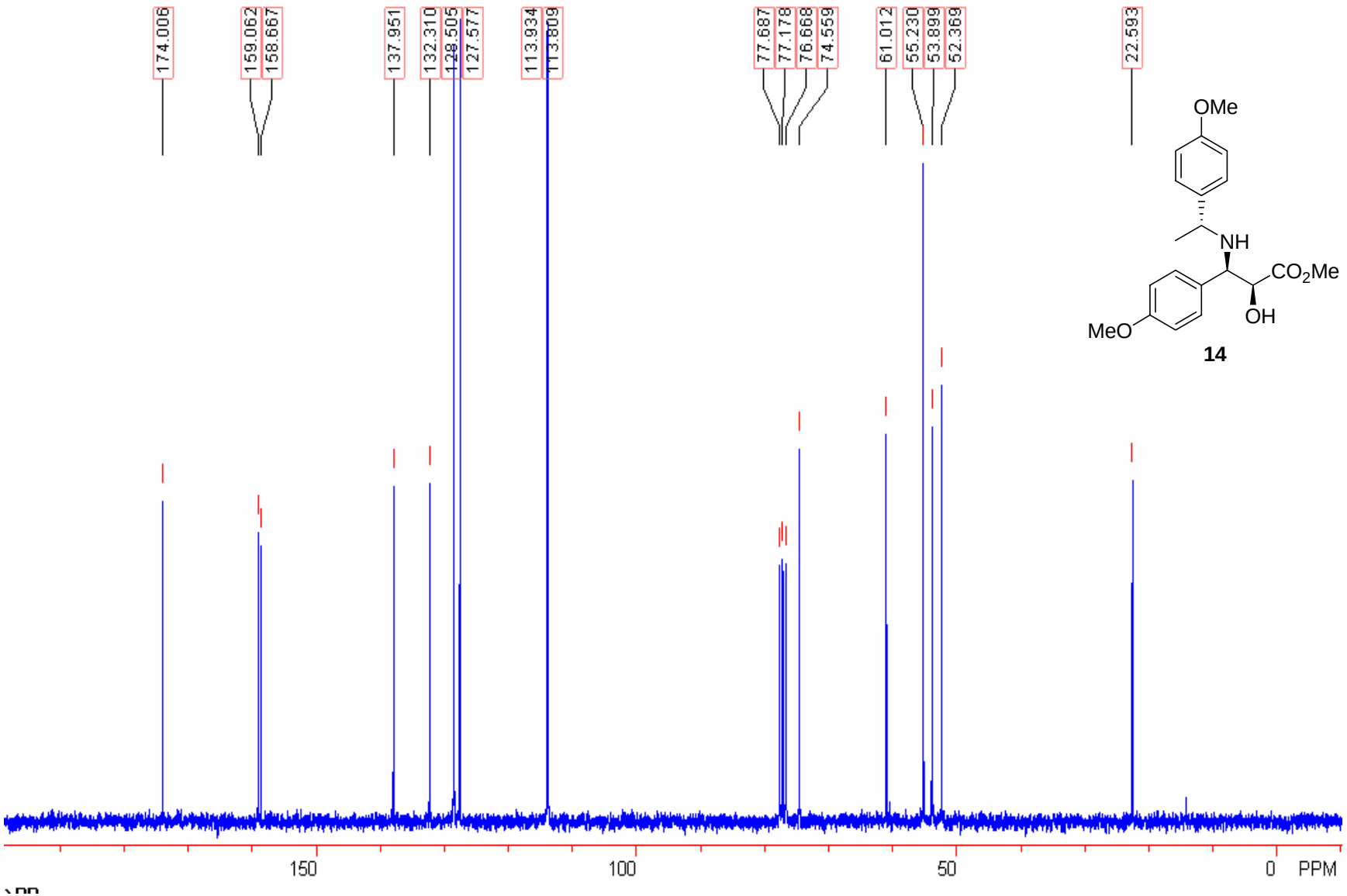

7.321
7.296
7.262
7.205
7.170
6.988
6.954
6.920
6.913
6.866
4.917
4.897
4.544
4.525
3.882
3.857
1.423
1.394
MeO
N
HO
O
OMe
4.15
2.24
1.00
0.97
6.22
2.88
8
7
6
5
4
3
2
1
0 PPM

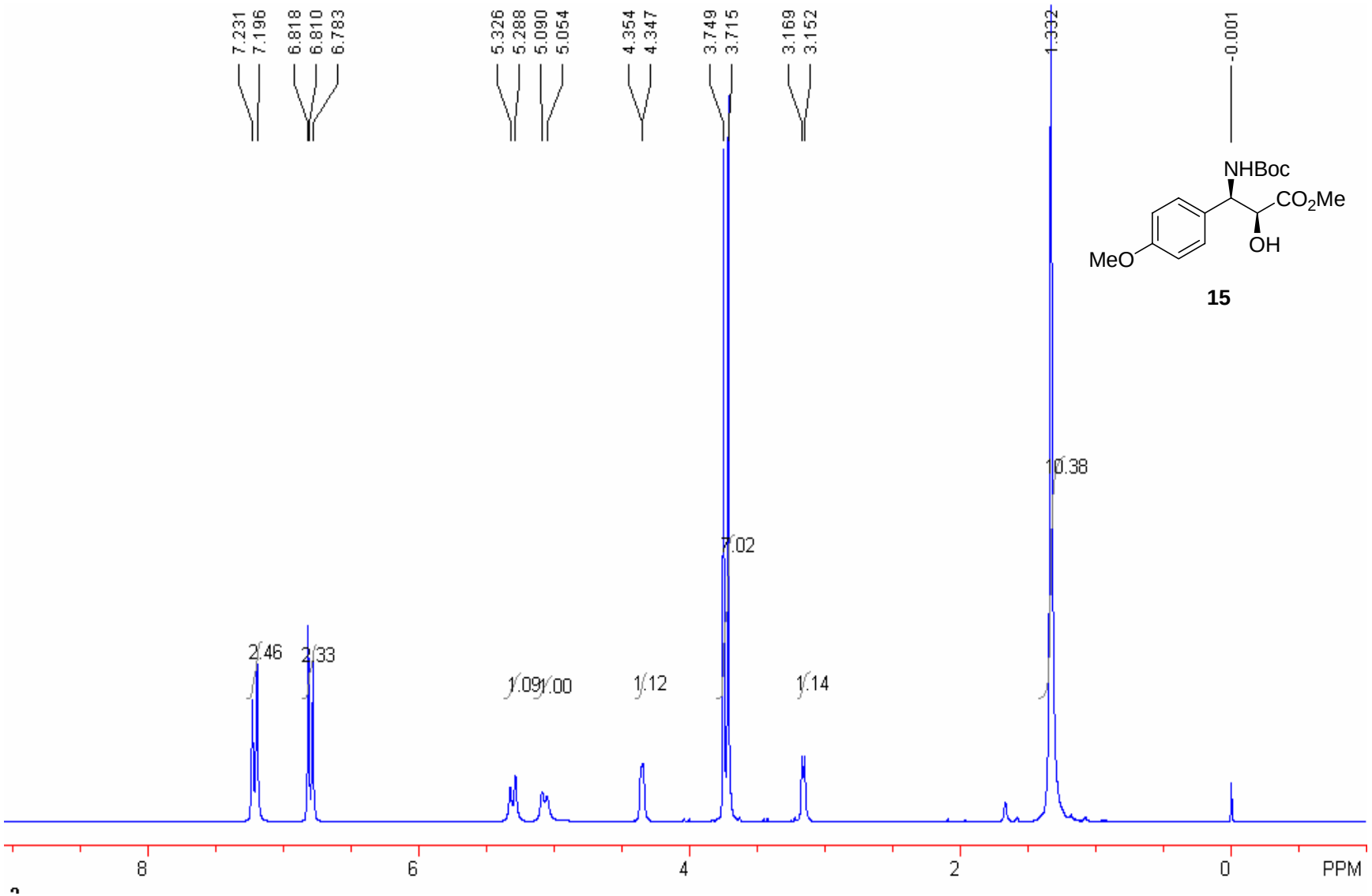
13

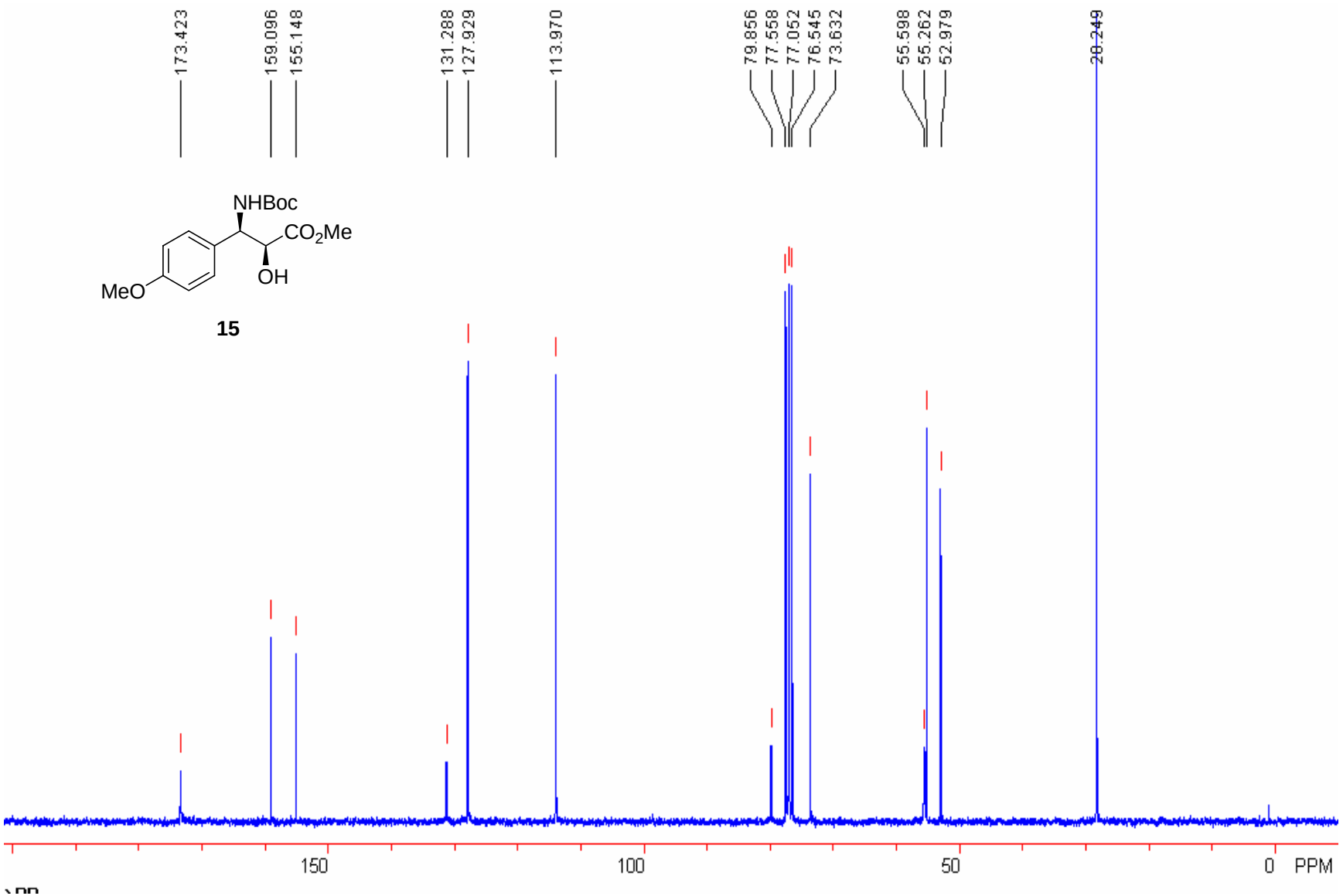

169.144
159.907
159.139
131.639
129.705
128.493
126.887
113.980
77.547
77.048
76.863
76.534
61.348
55.291
51.340
19.432
MeO
N
HO
O
OMe
150
100
50
0
PPM

13

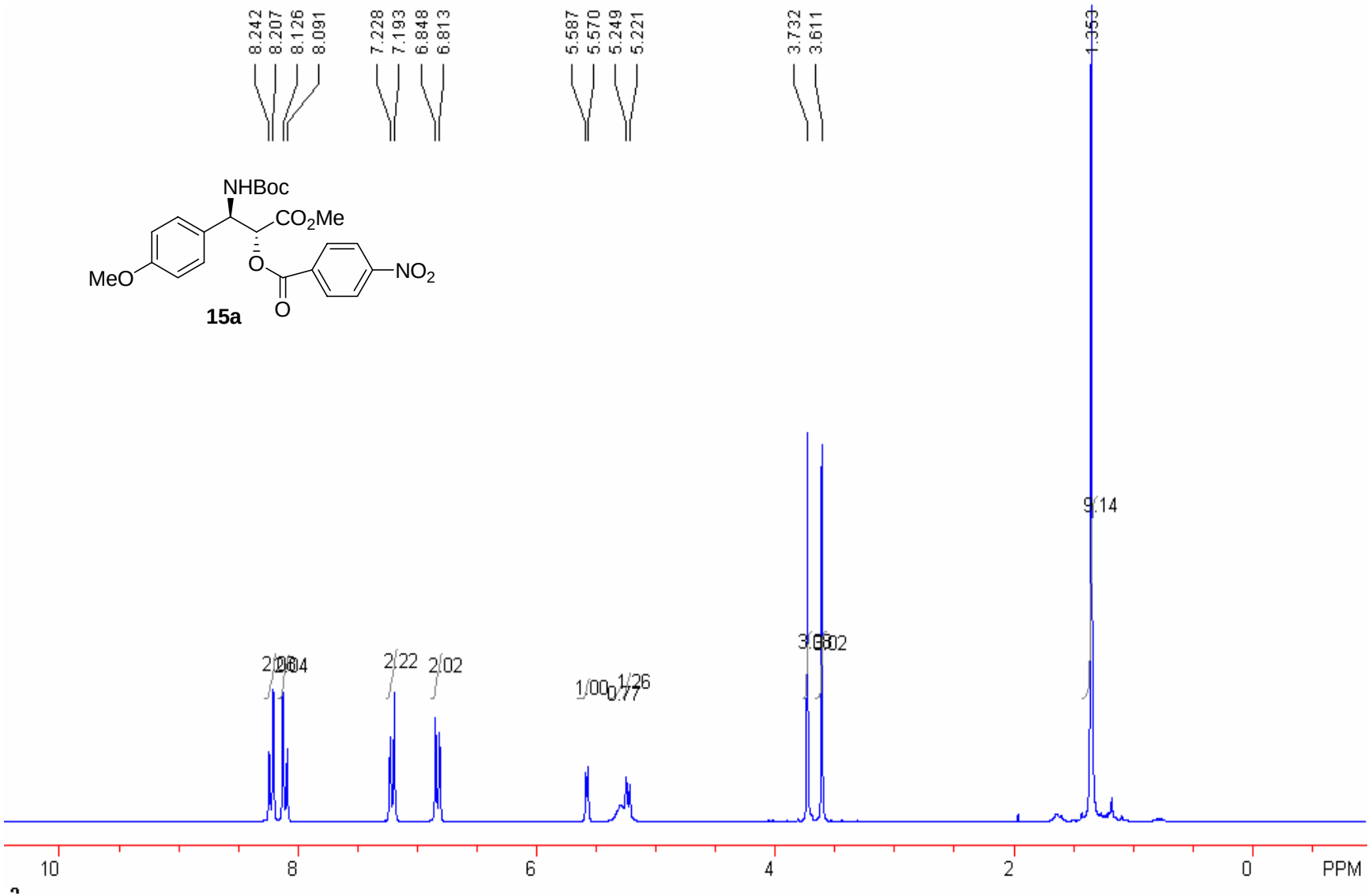

7.265
7.230
7.195
7.161
6.920
6.886
6.872
6.838
Peak Pick
4.270
4.257
4.135
4.121
3.813
3.793
3.775
3.650
3.625
1.308
1.281
OMe
NH
CO2Me
OH
MeO
14
9.06
4.12
4.11
0.99
1.07
1.38
3.00
8
6
4
2
0
PPM

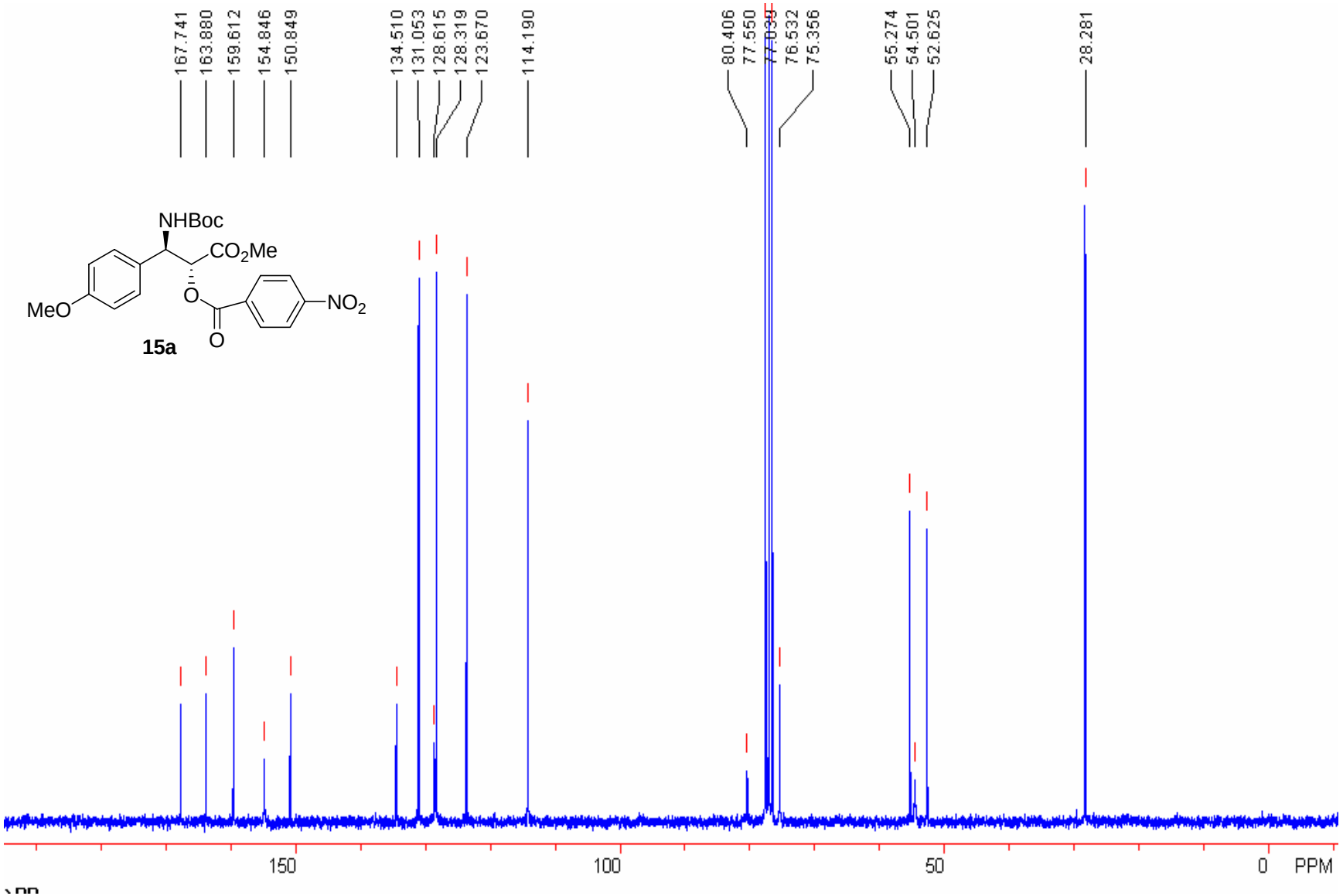

174.006
159.062
158.667
137.951
132.310
129.505
127.577
113.934
113.809
77.687
77.178
76.668
74.559
61.012
55.230
53.899
52.369
22.593
OMe
NH
CO2Me
OH
MeO
14
150
100
50
0
PPM

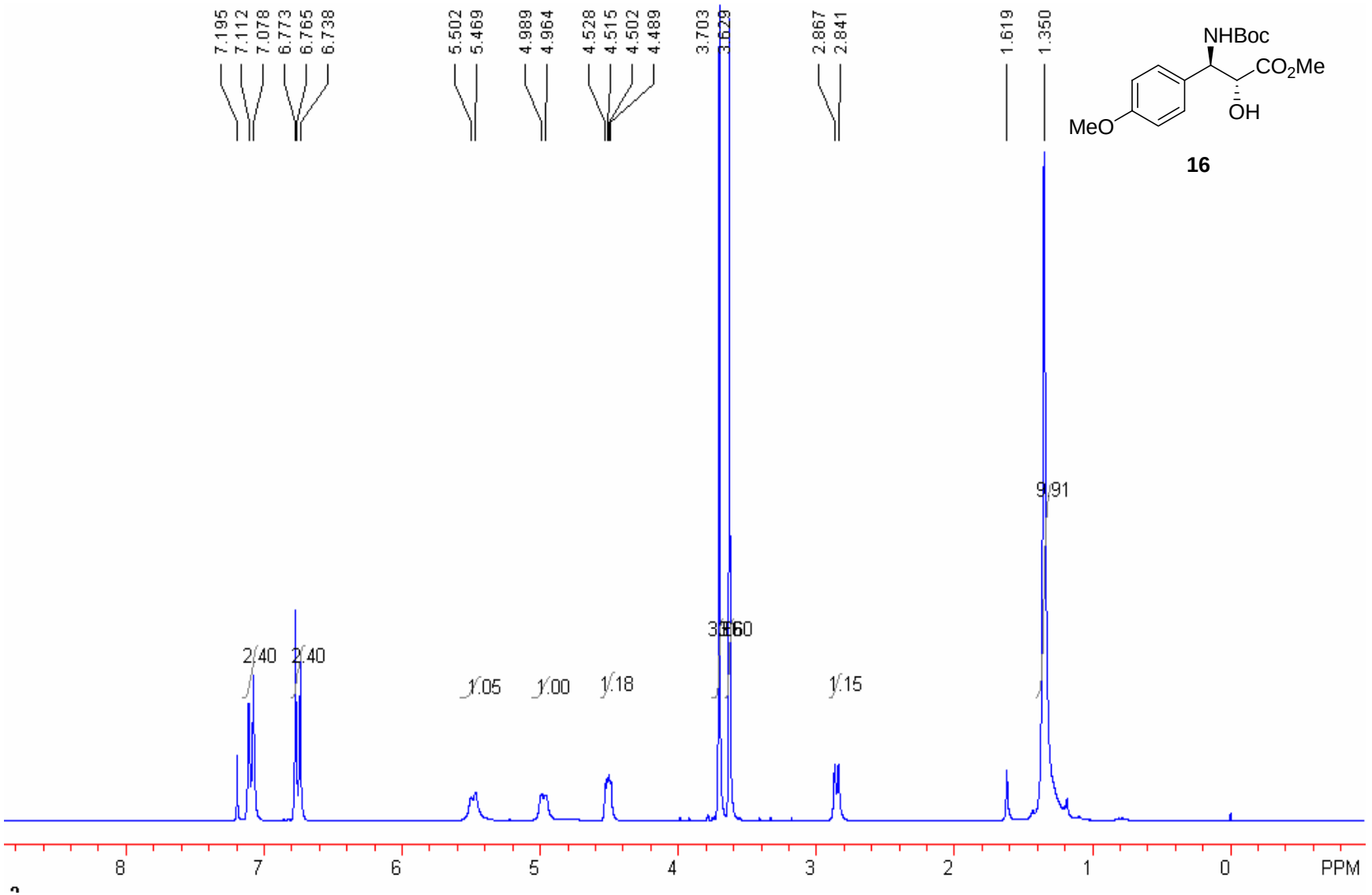

7.231
7.196
6.818
6.810
6.783
5.326
5.288
5.090
5.054
4.354
4.347
3.749
3.715
3.169
3.152
1.332
-0.001
2.46
2.33
1.09
1.00
1.12
7.02
1.14
10.38
NHBoc
CO2Me
OH
MeO
15
8
6
4
2
0
PPM


173.423
159.096
155.148
131.288
127.929
113.970
79.856
77.558
77.052
76.545
73.632
55.598
55.262
52.979
28.249
NHBoc
CO2Me
OH
MeO
150
100
50
0
PPM

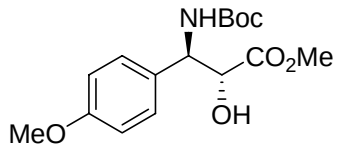
15


8.242
8.207
8.126
8.091
7.228
7.193
6.848
6.813
5.587
5.570
5.249
5.221
3.732
3.611
1.353
NHBoc
CO2Me
MeO
O
NO2
O
15a
9.14
2.22
2.02
1.00
0.77
1.26
10
8
6
4
2
0
PPM


167.741
163.880
159.612
154.846
150.849
134.510
131.053
128.615
128.319
123.670
114.190
80.406
77.550
77.039
76.532
75.356
55.274
54.501
52.625
28.281
NHBoc
CO2Me
MeO
O
NO2
O
15a
150
100
50
0
PPM


7.195
7.112
7.078
6.773
6.765
6.738
5.502
5.469
4.989
4.964
4.528
4.515
4.502
4.489
3.703
3.629
2.867
2.841
1.619
1.350
NHBoc
CO2Me
OH
MeO
16
2.40
2.40
1.05
1.00
1.18
3.60
1.15
9.91
8
7
6
5
4
3
2
1
0
PPM

AntiAminolR
C13CPD



16

BRUKER

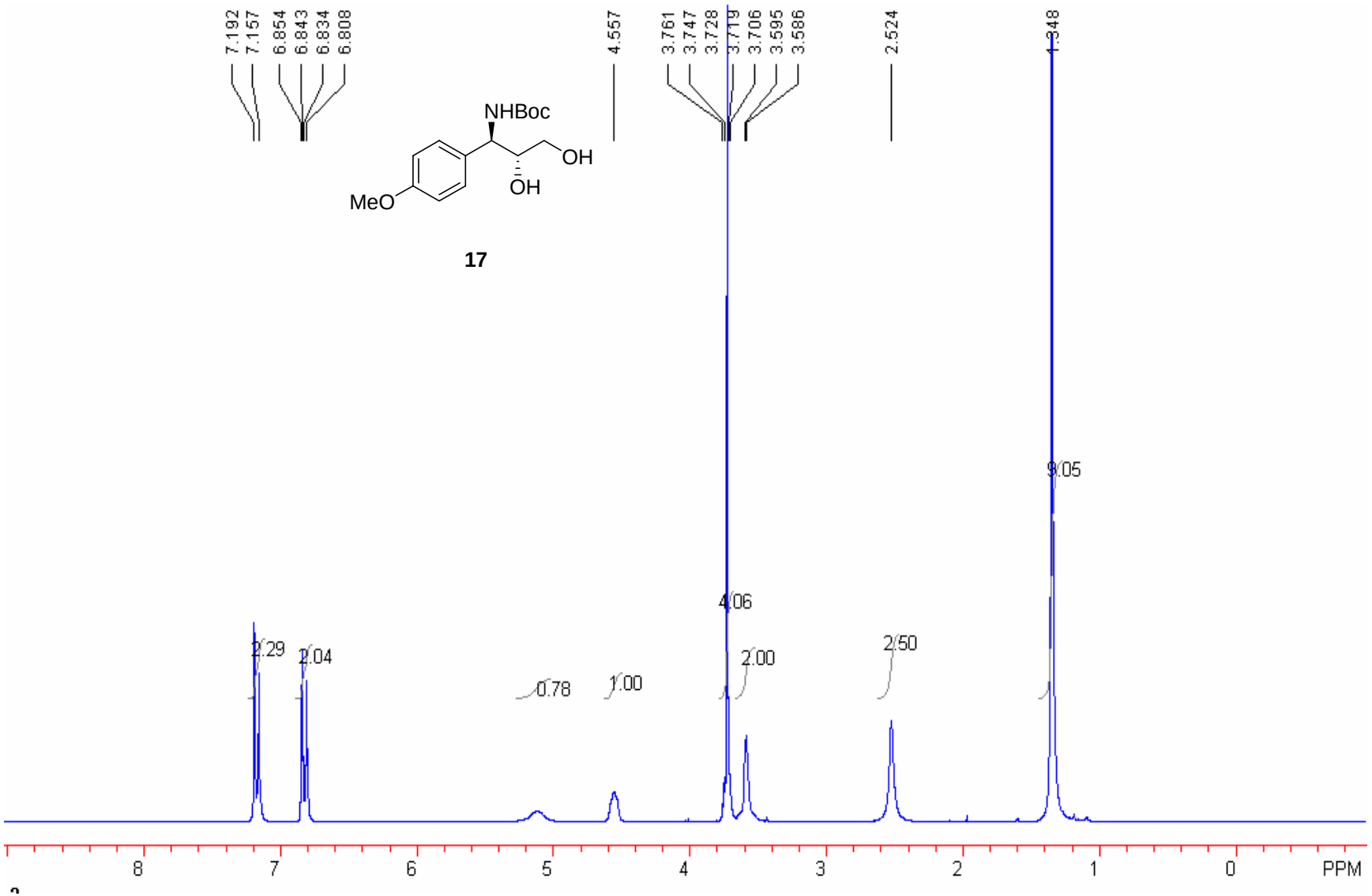
```
Current Data Parameters
NAME          May08-2006
EXPNO                  9
PROCNO                 1

F2 - Acquisition Parameters
Date_           20060509
Time                9.09
INSTRUM            spect
PROBHD   5 mm Multinucl
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 8500
DS                    0
SWH           15060.241 Hz
FIDRES         0.229801 Hz
AQ            2.1758451 sec
RG                574.7
DW               33.200 usec
DE                6.00 usec
TE                298.2 K
D1           2.00000000 sec
d11          0.03000000 sec
DELTA        1.89999998 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

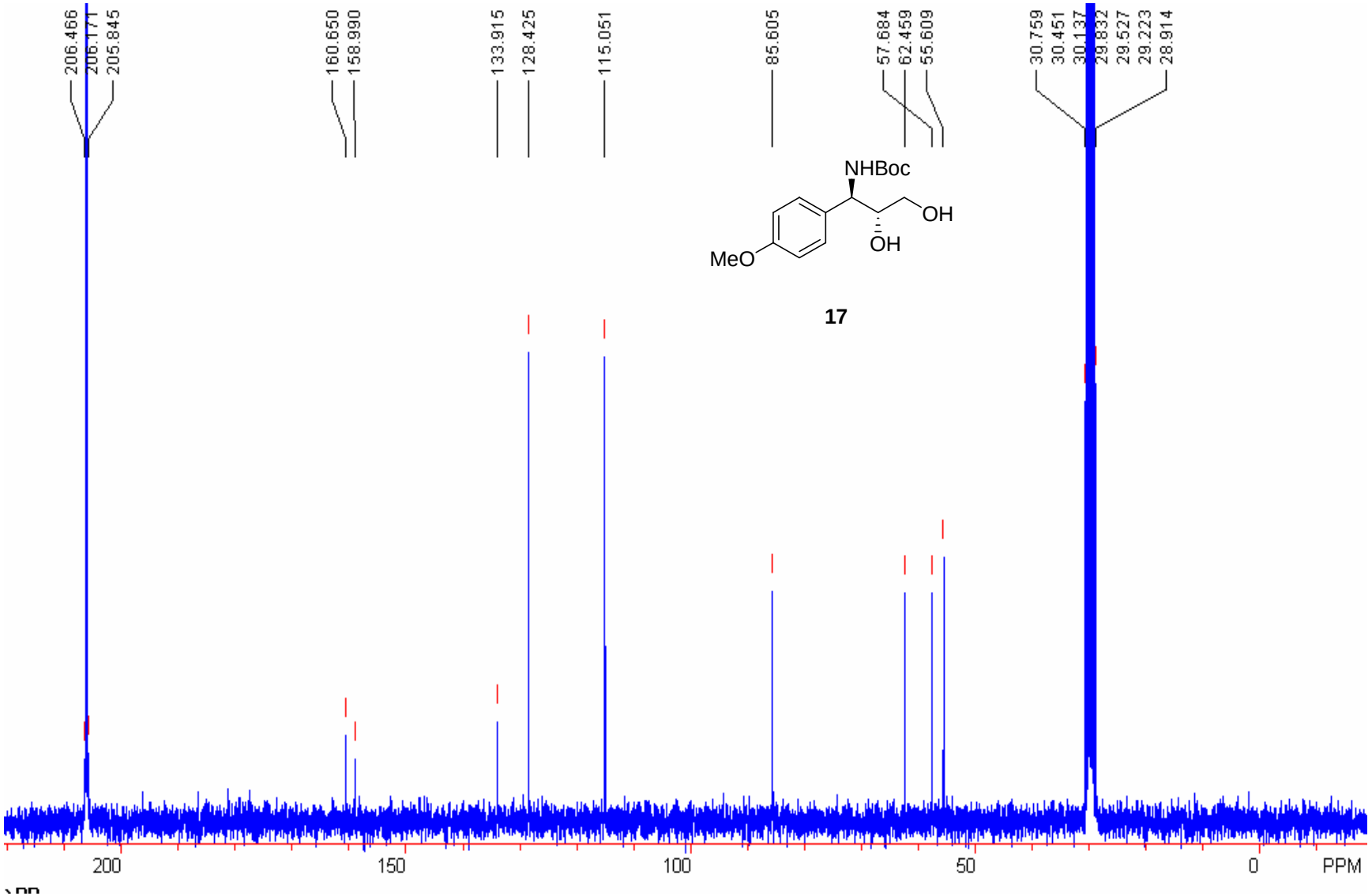
======== CHANNEL f1 ========
NUC1                13C
P1                15.50 usec
PL1               -6.00 dB
SFO1         62.9015280 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2           100.00 usec
PL2               0.00 dB
PL12             25.10 dB
PL13             25.10 dB
SFO2        250.1310005 MHz

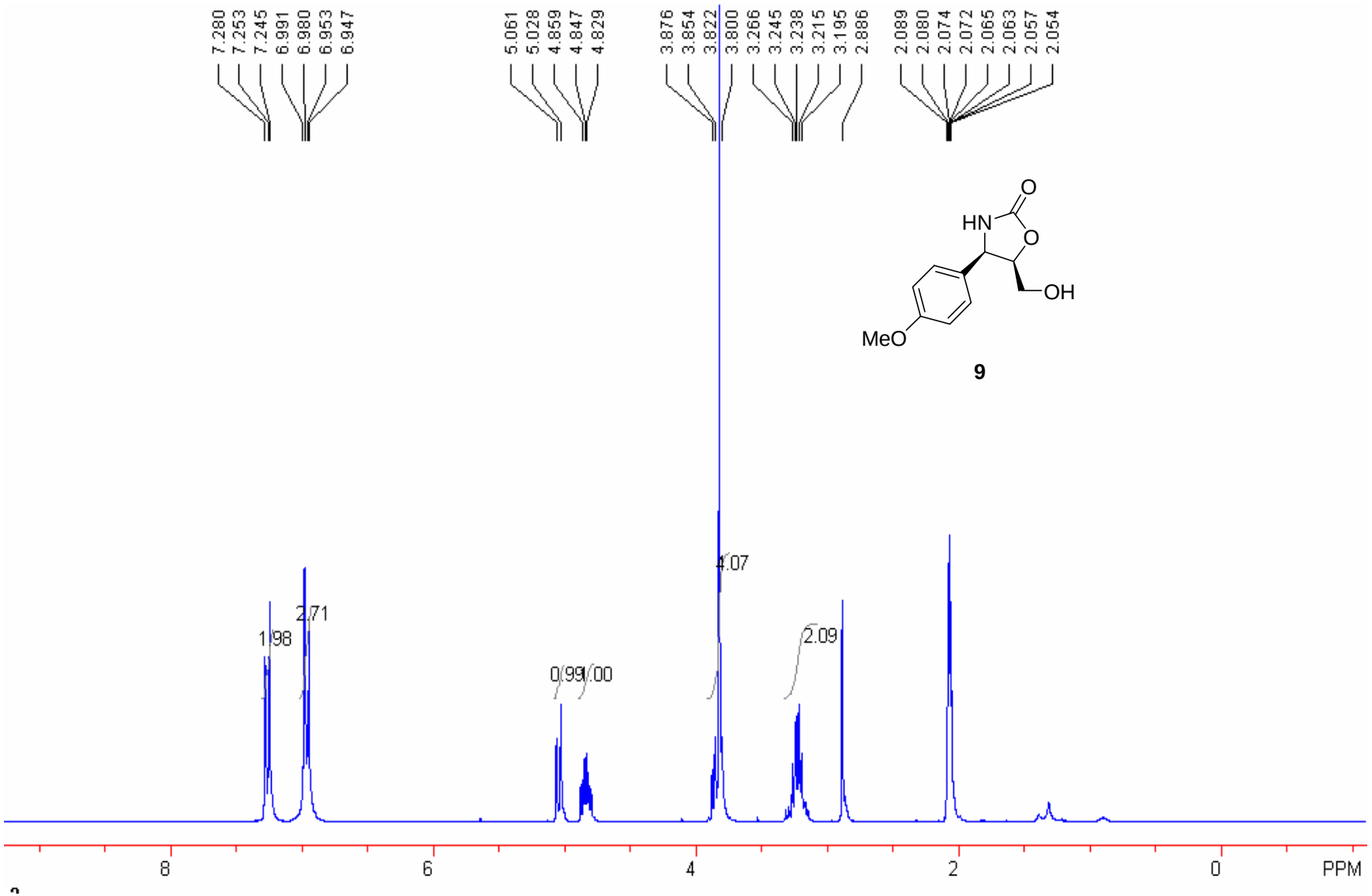
F2 - Processing parameters
SI                 32768
SF           62.8952390 MHz
WDW                   EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```


7.192
7.157
6.854
6.843
6.834
6.808
4.557
3.761
3.747
3.728
3.719
3.706
3.595
3.586
2.524
1.348
NHBoc
OH
OH
MeO
2.29
2.04
0.78
1.00
4.06
2.00
2.50
9.05
8
7
6
5
4
3
2
1
0
PPM

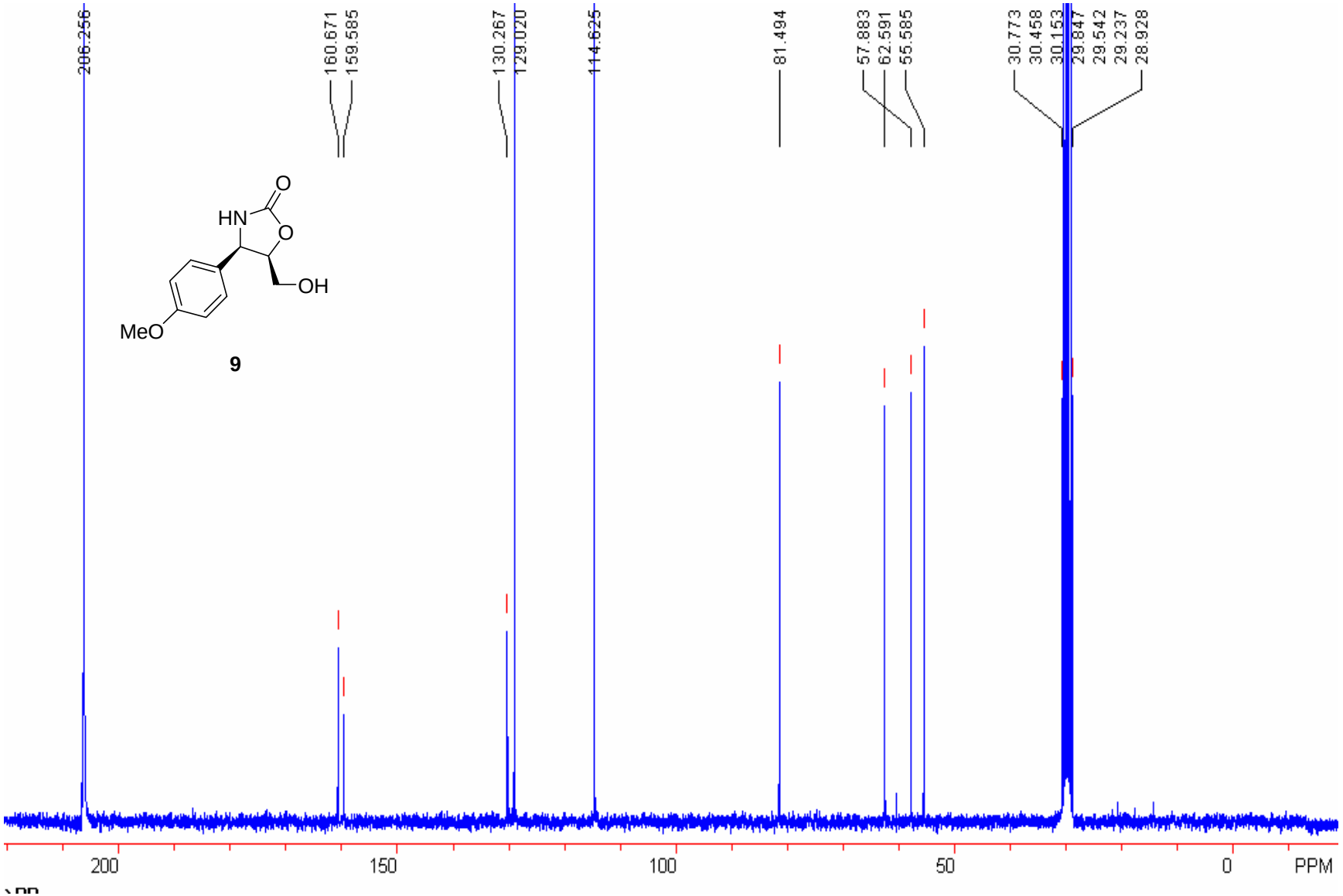
17


206.466
206.171
205.845
160.650
158.990
133.915
128.425
115.051
85.605
57.684
62.459
55.609
30.759
30.451
30.137
29.832
29.527
29.223
28.914
NHBoc
OH
OH
MeO
200
150
100
50
0
PPM

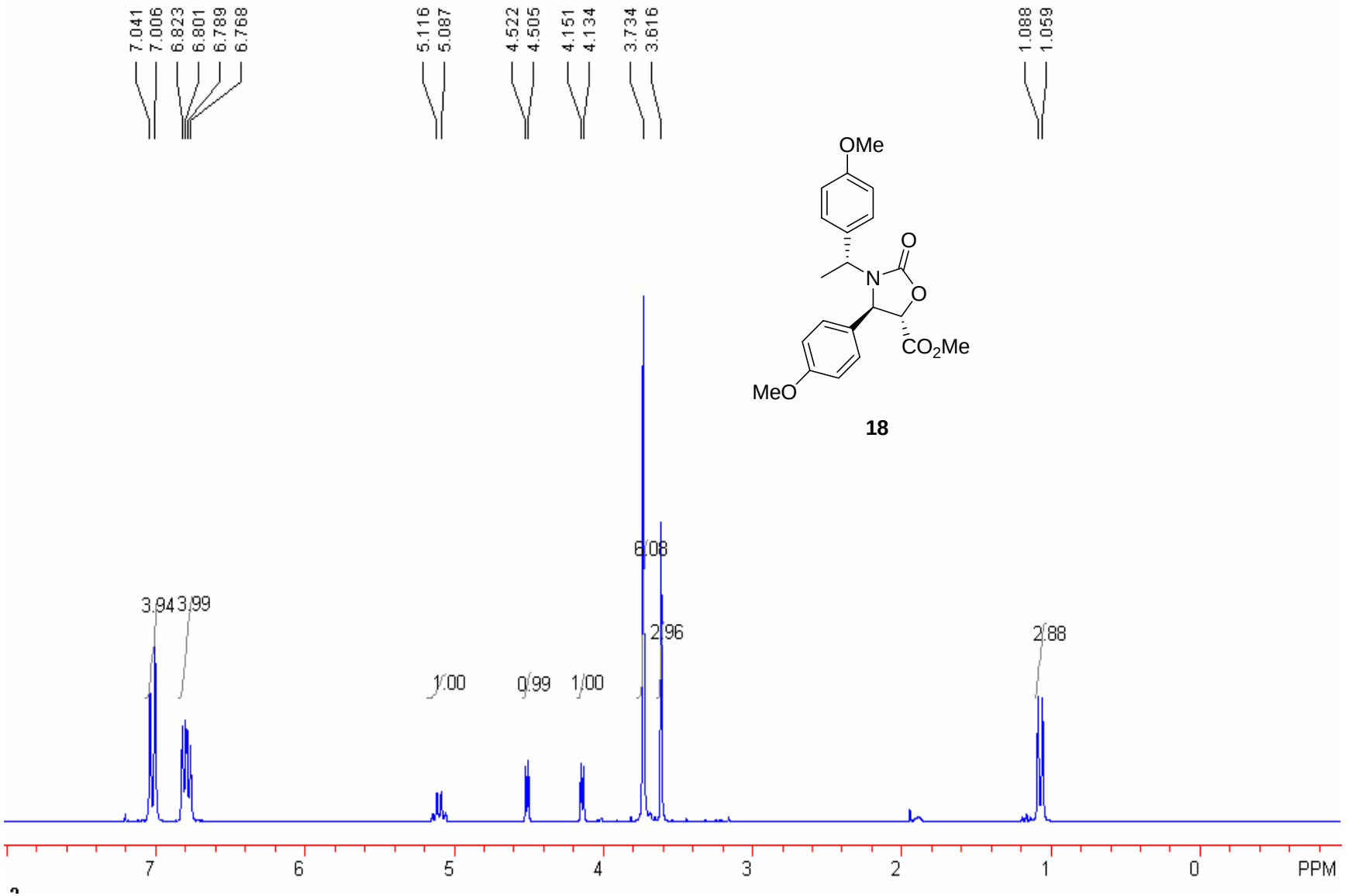
17

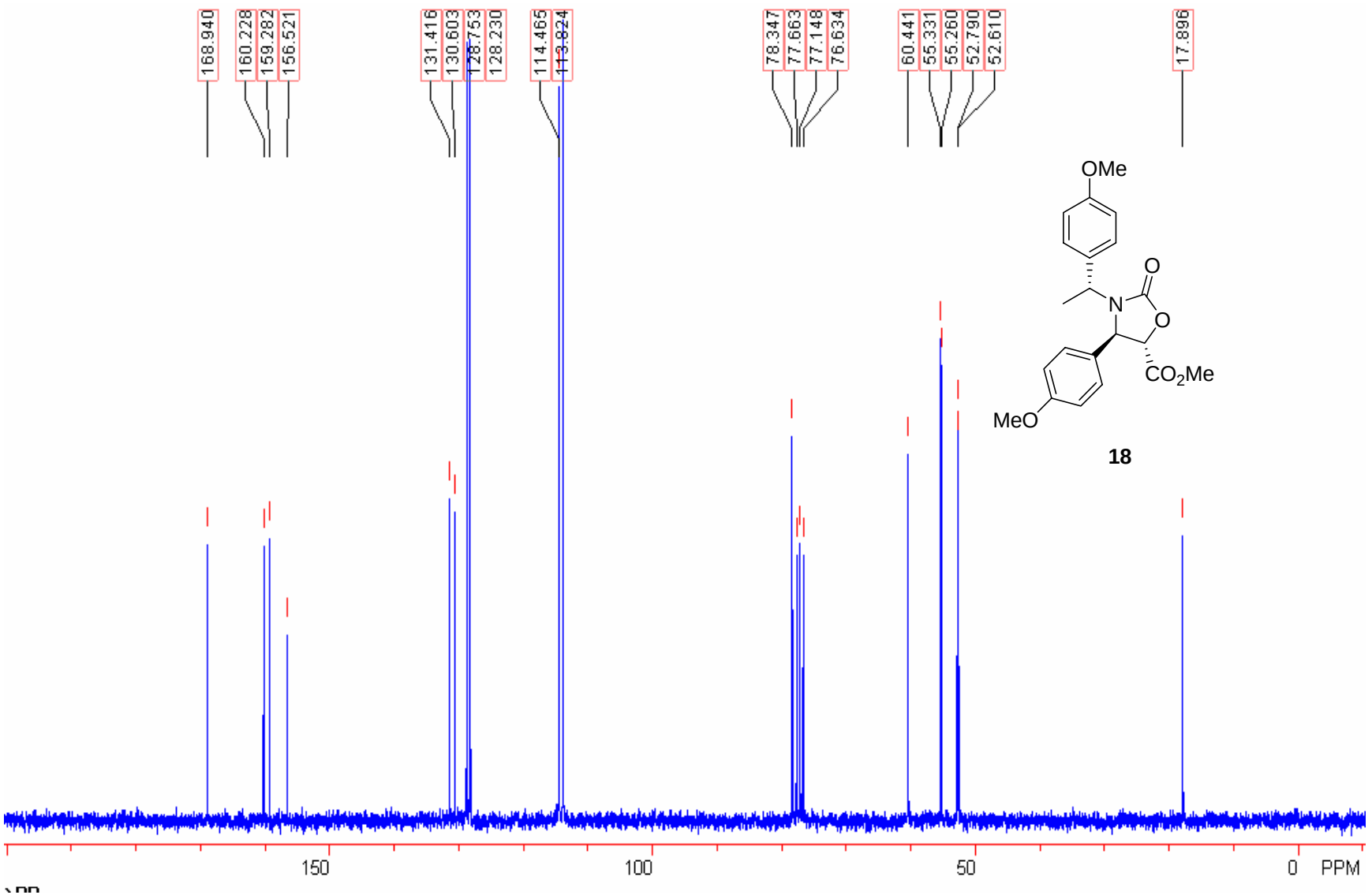

7.280
7.253
7.245
6.991
6.980
6.953
6.947
5.061
5.028
4.859
4.847
4.829
3.876
3.854
3.822
3.800
3.266
3.245
3.238
3.215
3.195
2.886
2.089
2.080
2.074
2.072
2.065
2.063
2.057
2.054
HN
O
O
OH
MeO
1.98
2.71
0.99
1.00
4.07
2.09
8
6
4
2
0
PPM

9

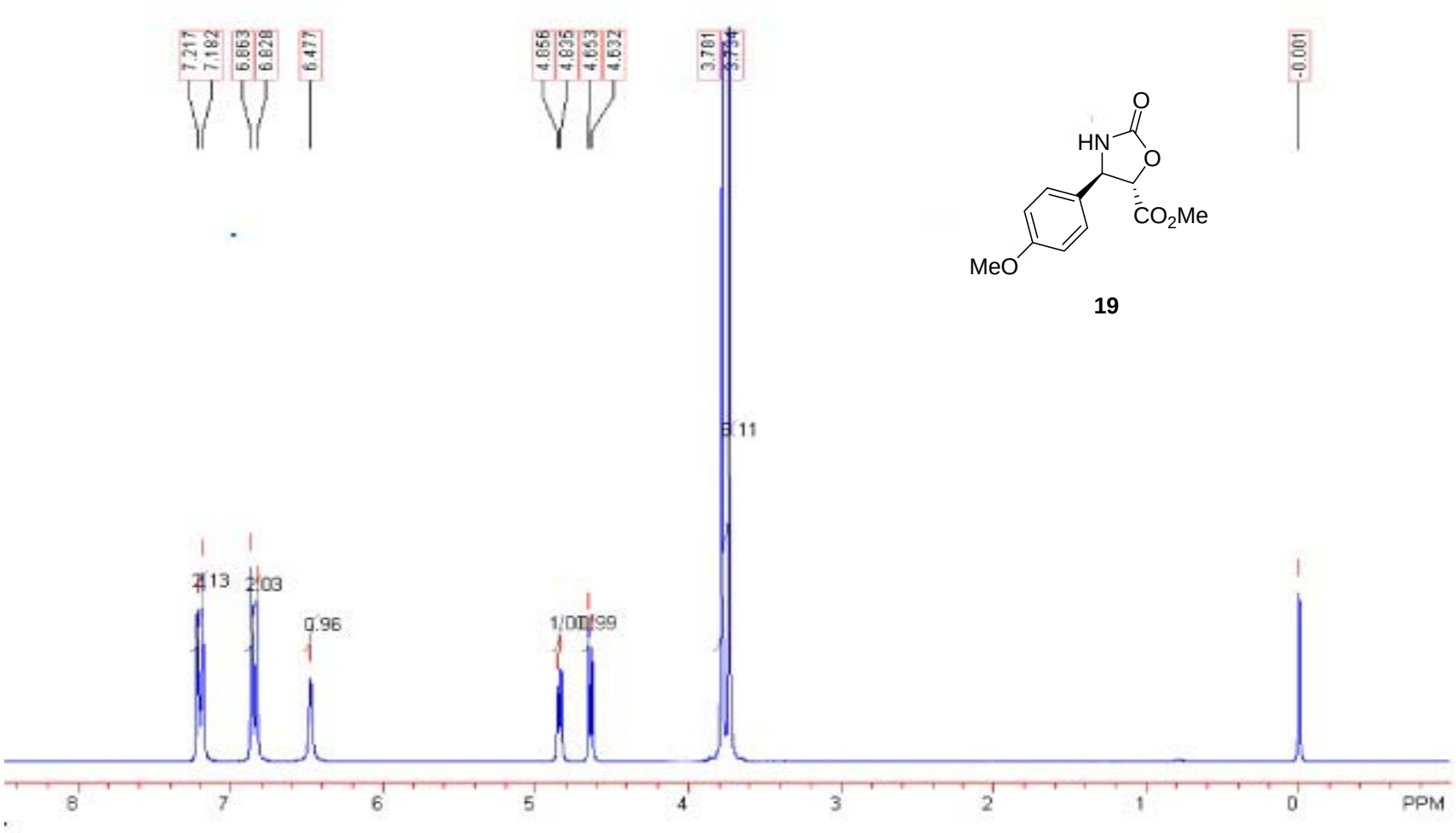

206.256
160.671
159.585
130.267
129.020
114.625
81.494
57.883
62.591
55.585
30.773
30.458
30.153
29.847
29.542
29.237
28.928
HN
O
O
OH
MeO
200
150
100
50
0
PPM

9

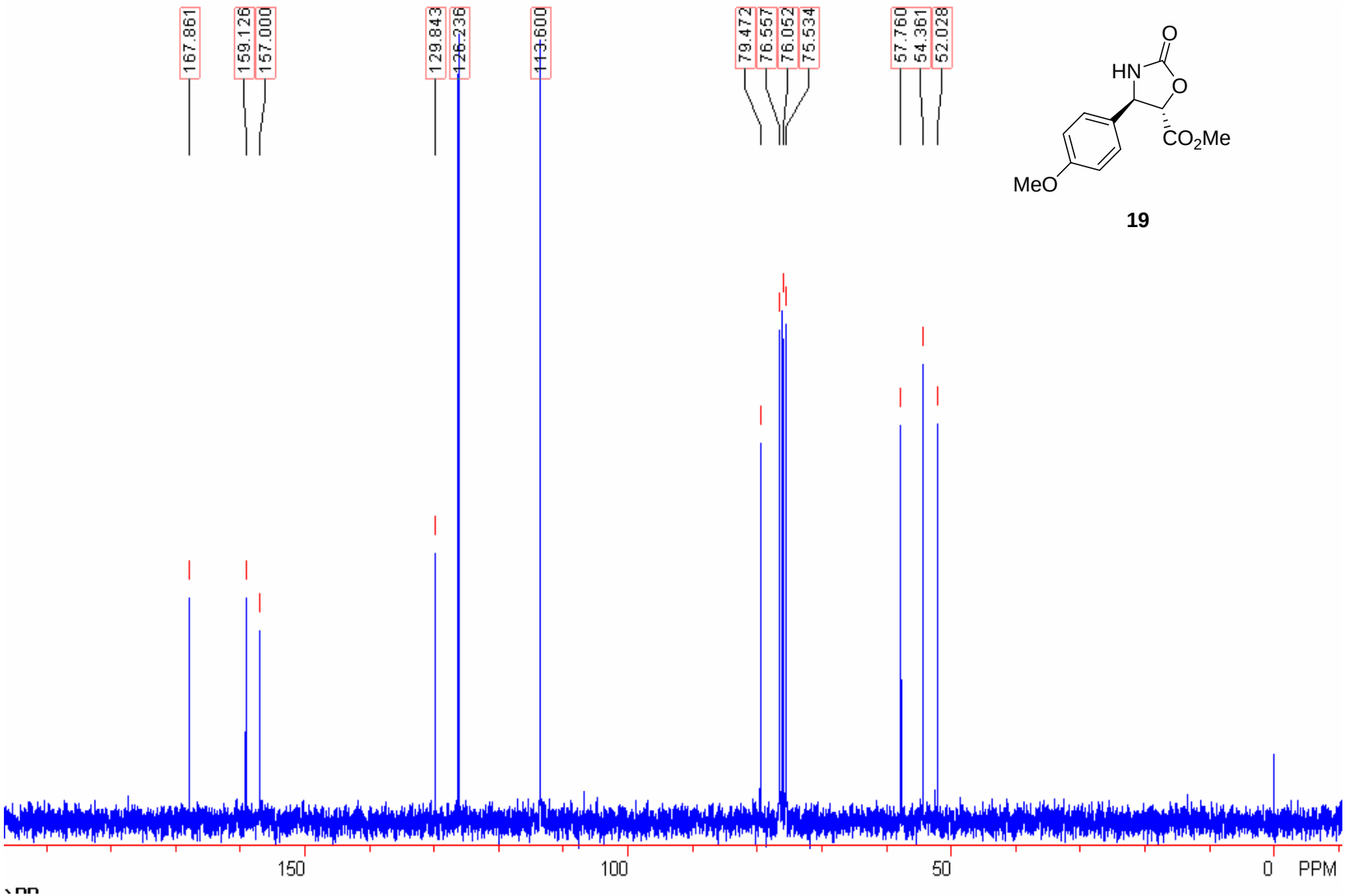

7.041
7.006
6.823
6.801
6.789
6.768
5.116
5.087
4.522
4.505
4.151
4.134
3.734
3.616
1.088
1.059
OMe
O
N
O
CO2Me
MeO
18
3.94
3.99
1.00
0.99
1.00
6.08
2.96
2.88
7
6
5
4
3
2
1
0
PPM


168.940
160.228
159.282
156.521
131.416
130.603
128.753
128.230
114.465
113.824
78.347
77.663
77.148
76.634
60.441
55.331
55.260
52.790
52.610
17.896
OMe
O
N
O
CO2Me
MeO
150
100
50
0
PPM

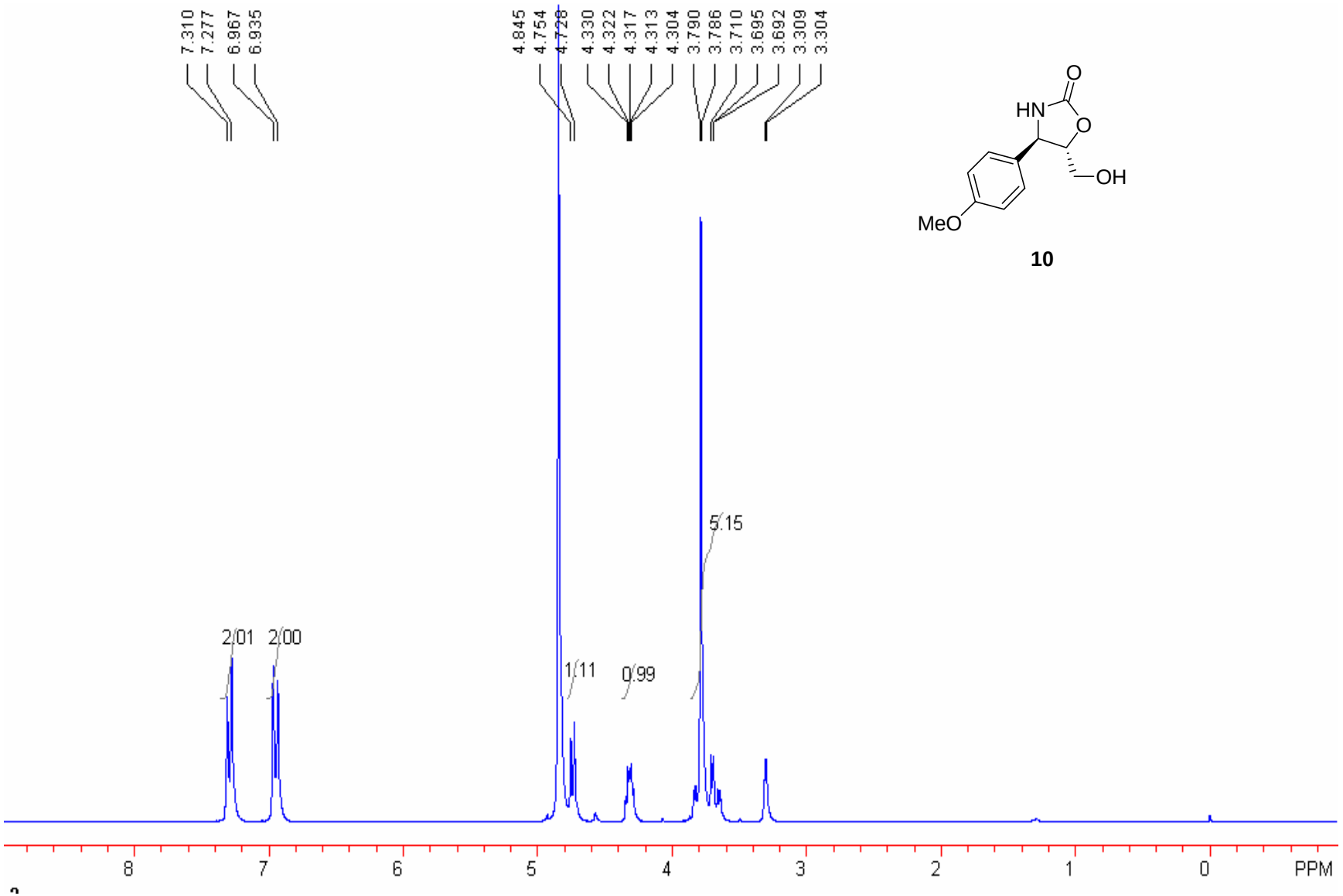
18


7.217
7.182
6.863
6.828
6.477
4.656
4.635
4.653
4.632
3.761
-0.001
3.11
2.13
2.03
0.96
1.00
0.99
8
7
6
5
4
3
2
1
0
PPM
HN
O
O
CO2Me
MeO

19

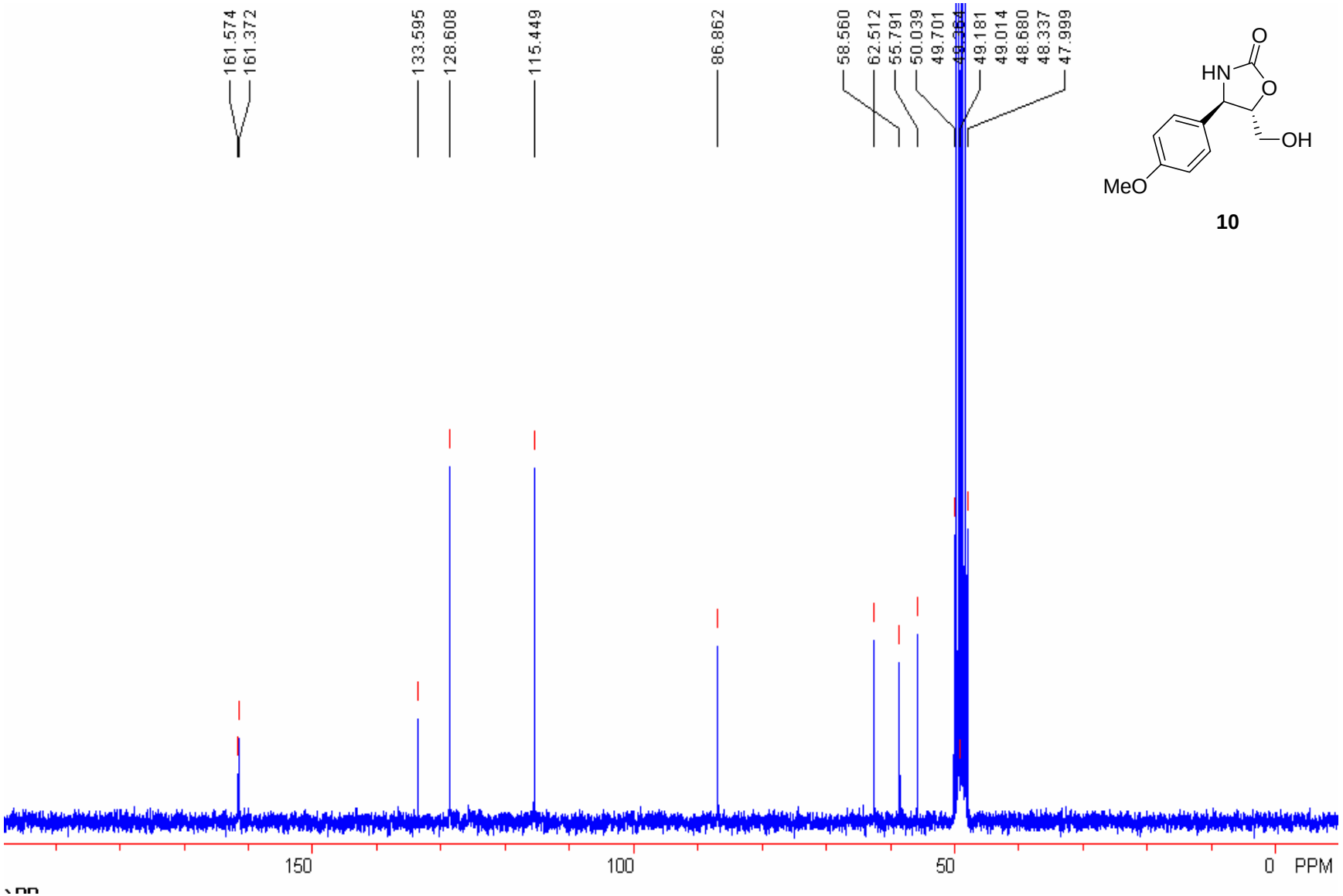

167.861
159.126
157.000
129.843
126.236
113.600
79.472
76.557
76.052
75.534
57.760
54.361
52.028
HN
O
O
O
CO2Me
MeO
150
100
50
0
PPM

19


7.310
7.277
6.967
6.935
4.845
4.754
4.728
4.330
4.322
4.317
4.313
4.304
3.790
3.786
3.710
3.695
3.692
3.309
3.304
2.01
2.00
1.11
0.99
5.15
8
7
6
5
4
3
2
1
0
PPM

O
HN
O
OH
MeO

10


161.574
161.372
133.595
128.608
115.449
86.862
58.560
62.512
55.791
50.039
49.701
49.181
49.014
48.680
48.337
47.999
O
HN
O
OH
MeO
150
100
50
0
PPM

10