Electronic Supplementary Material (ESI) for Green Chemistry.

Synthesis of Ureas in the Bio-alternative Solvent Cyrene

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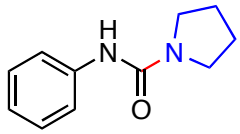
I. General Experimental Information

Unless otherwise indicated, all commercially available reagents and solvents were used directly from the supplier without further purification. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR were recorded at ambient temperature in $CDCl_3$ (7.27 ppm). Chemical shift values are expressed as parts per million (ppm) and J values are in Hertz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, q: quartet or combination, br.s broad singlet or m: multiplet. The melting points reported are uncorrected. All reactions were performed in 5 mL microwave vials with Teflon coated caps. In addition to the amines **5** outlined below, the following amines proved incompatible with the reaction conditions: aniline, benzylamine, proline·HCl, indole, imidazole, 2,5-dimethyl pyrrole, pyrrole and pipecolic acid.

II. Preparation of Ureas 6a-u

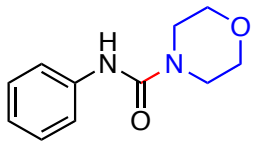


N-Phenylpyrrolidine-1-carboxamide (6a)[1]

M*ethod A:* To a stirred solution of pyrrolidine (42 µL, 0.5 mmol) in Cyrene (0.5 mL, 1 M) at 0 °C was added phenyl isocyanate (**4a**, 55 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 30 min. The solvent was removed by Buchner filtration and the filtrate was washed with water (60 mL). The residue was dissolved in EtOAc (20 mL), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give *N*-phenylpyrrolidine-1-carboxamide (**6a**, 76 mg, 80%), as a white solid.

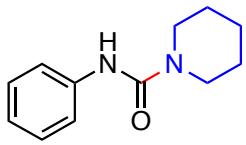
Method B: To a stirred solution of pyrrolidine (42 µL, 0.5 mmol) in Cyrene (0.5 mL, 1 M) at 0 °C was added phenyl isocyanate (**4a**, 55 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 30 min. Water (25 mL) and EtOAc (25 mL) were added. The organic layer was dried over $MgSO_4$ (10.0 g), filtered with the aid of EtOAc (10 mL). Silica gel (100 mg) was added and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (100 g; EtOAc:hexane, 9:1) to to give *N*-phenylpyrrolidine-1-carboxamide (**6a**, 92 mg, 97%), as a white solid.

mp. (^{o}C) 133-134 [Lit.[1] 133-134]; IR (neat): 3292, 2971, 2871, 1639, 1532, 1438, 1373, 1239, 759 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.92-1.94 (m, 4H), 3.42-3.45 (m, 4H), 6.29 (br. s, 1H), 6.98-7.01 (m, 1H), 7.24-2.28 (m, 2H), 7.40-7.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.5, 45.7, 119.5, 122.6, 128.7, 139.2, 153.9; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{15}N_2O]^+$ 191.1184; found 191.1179.



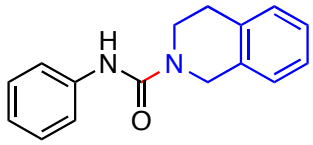
_N_-Phenylmorpholine-4-carboxamide (6b)

To a stirred solution of morpholine (43 µL, 0.50 mmol) in Cyrene (0.1 M) at 0 °C was added phenyl isocyanate (**4b**, 55 µL, 0.50 mmol). The resultant mixture was stirred at rt for 1 h. Water (5 mL) was added and the precipitate was filtered and washed with water. The residue was dried over anhydrous sodium sulphate to give *N*-phenylmorpholine-4-carboxamide (**6b**, 61 mg, 64%) as a white solid. mp. (°C) 157-158 [Lit.[2] 159-160] IR (ν /cm^{-1}): 3251, 3052, 2917, 2857, 1631, 1526; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 (t, *J* = 5.0 Hz, 4H), 3.70 (t, *J* = 4.7 Hz, 4H), 6.52 (bs, 1 H), 7.03-7.60 (m, 1H), 7.26-7.29 (m, 2 H), 7.33-7.35 (m, 2H): ^{13}C NMR (400 MHz, $CDCl_3$) 44.2, 66.4, 120.2, 123.3, 128.8, 138.6, 155.2; HRMS (ESI) m/z calculated for $[C_{11}H_{15}N_2O_2]$: 207.1134, Observed: 207.1131.



_N_-Phenylpiperidine-1-carboxamide (6c)

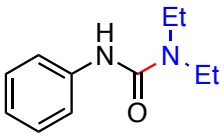
To a stirred solution of piperidine (49 µL, 0.50 mmol) in Cyrene (0.1 M) at 0 °C was added phenyl isocyanate (**4a**, 55 µL, 0.50 mmol). The resultant mixture was stirred at rt for 1 h. Water (5 mL) was added and the precipitate was filtered and washed with water. The residue was dried over anhydrous sodium sulphate to give *N*-phenylpiperidine-1-carboxamide (**6c**, 62 mg, 61%) as a white solid. MP (°C): 170-172 [Lit.[7] 171-172 °C]; IR (ν /cm^{-1}): 3284, 2924, 2854, 2359, 1626, 1533; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61-1.63 (m, 6H), 3.44-3.46 (m, 4H), 6.33 (bs, 1H), 6.99-7.03 (m, 1H), 7.25-7.29 (m, 2H), 7.34-7.36 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) 24.6, 25.9, 45.5, 119.9, 123.0, 129.1, 139.4, 155.2; HRMS (ESI) m/z calculated for $[C_{12}H_{17}N_2O]^+$: 205.1341, Observed: 205.1335.



_N_-Phenyl-3,4-dihydroisoquinoline-2(1H)-carboxamide (6d)

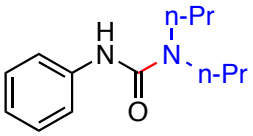
To a stirred solution of 1,2,3,4-tetrahydroisoquinoline (63 µL, 0.5 mmol) in Cyrene (0.5 mL, 1 M) at 0 °C was added phenyl isocyanate (**4a**, 55 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 30 min. The solvent was removed by Buchner filtration and the filtrate was washed with water (60 mL). The residue was dissolved in EtOAc (20 mL), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give *N*-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxamide (**6d**, 103 mg, 82 %) as a white solid. mp. (°C) 134–

135 [Lit.[3] 143-144]; IR (neat): 3316, 3030, 2917, 1627, 1594, 1525, 1444 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.91 (t, *J* = 5.9 Hz, 2 H), 3.72 (t, *J* = 5.9 Hz, 2H), 4.65 (s, 2H), 6.51 (bs, 1H), 7.01-7.04 (m, 1H), 7.12-7.21 (m, 4 H), 7.26-7.29 (m, 2H), 7.38-7.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.0, 41.5, 45.7,120.0, 123.1, 126.3, 126.5, 126.8, 128.3, 128.8, 133.0, 134.9, 138.9, 154.9; HRMS (ESI) *m/z* Calcd for $[C_{16}H_{17}N_2O]^+$ 253.1335; found 253.1335.



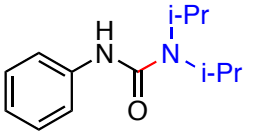
1,1-Diethyl-3-phenylurea (6e)

To a stirred solution of diethylamine (52 µL, 0.50 mmol) in Cyrene (0.1 M) at 0 °C was added phenyl isocyanate (**4a**, 55 µL, 0.50 mmol). The resultant mixture was stirred at rt for 1 h. Water (5 mL) was added and the precipitate was filtered and washed with water. The residue was dried over anhydrous sodium sulphate to give 1,1-diethyl-3-phenylurea (**6e**, 92 mg, 96%). as a white solid. mp. (°C)79-81 [Lit.[7] 84-85]; IR (neat): 2981, 2361, 1752, 1635, 1529 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.23 (t, *J* = 7.2 Hz, 6H), 3.37 (q, *J* = 7.2 Hz, 4H), 6.55 (bs, 1H), 7.07-7.11 (m, 1H), 7.29-7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.5, 42.0, 121.3, 124.1, 128.9, 137.8, 155.8; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{17}N_2O]^+$ 193.1335; found 193.1335.



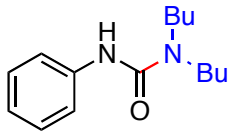
3-Phenyl-1,1-dipropylurea (6f)

To a stirred solution of dipropylamine (69 µL, 0.50 mmol) in Cyrene (0.1 M) at 0 °C was added phenyl isocyanate (**4a**, 55 µL, 0.50 mmol). The resultant mixture was stirred at rt for 1 h. Water (5 mL) was added and the precipitate was filtered and washed with water. The residue was dried over anhydrous sodium sulphate to give 1,1-dipropyl-3-phenylurea (**6f**, 49 mg, 44%). as a white solid. mp. (°C) 70-72 [Lit.[4] 71]; IR (neat): 3314, 2953, 2871, 2362, 1634 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.93 (t, *J* = 11.8 Hz, 6H), 1.64 (sex, *J* = 9.4 Hz, 4 H), 3.25 (t, *J* = 9.4 Hz, 4 H), 6.36 (bs, 1 H), 6.97-7.01 (m, 1 H), 7.23-7.27 (m, 2 H), 7.36-7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.4, 21.8, 49.4, 119.8, 122.7, 128.7, 139.3, 155.0; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{21}N_2O]^+$ 221.1648; found 221.648.



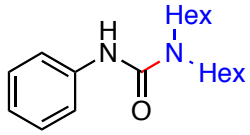
1,1-Diisopropyl-3-phenylurea (6g)

To a stirred solution of diisopropylamine (70 µL, 0.50 mmol) in Cyrene (0.1 M) at 0 °C was added phenyl isocyanate (**4a**, 55 µL, 0.50 mmol). The resultant mixture was stirred at rt for 1 h. Water (5 mL) was added and the precipitate was filtered and washed with water. The residue was dried over anhydrous sodium sulphate to give 1,1-diisopropyl-3-phenylurea (**6g**, 68 mg, 62%). as a white solid. mp. (°C) 119-121 [Lit.[5] 113-115]; IR (neat): 3313, 2954, 2871, 1634 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.29 (d, J = 8.6 Hz, 12 H), 3.94 (sept, J = 8.6 Hz, 2 H), 6.31 (bs, 1H), 6.96-6.99 (m, 1H), 7.23-7.26 (m, 2H), 7.35-7.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.5, 45.5, 119.7, 122.5, 128.7, 139.4, 154.6; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{21}N_2O]^+$ 221.1648; found 221.1648.



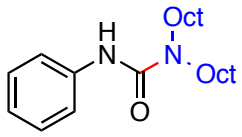
1,1-Dibutyl-3-phenylurea (6h)

To a stirred solution of dibutyl amine (84 µL, 0.5 mmol) in Cyrene (0.5 mL, 1 M) at 0 °C was added phenyl isocyanate (**4a**, 55 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 30 min. The solvent was removed by Buchner filtration and the filtrate was washed with water (60 mL). The residue was dissolved in EtOAc (20 mL), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give 1,1-dibutyl-3-phenylurea (**6h**, 112 mg, 90%) as a white solid. mp. (°C) 81–82 [Lit.[6] 81-82]; IR (neat): 3292, 2957, 2928, 2870, 1633, 1596, 1501, 1444, 1317, 1241, 1221 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.93 (t, J = 7.4 Hz, 6H), 1.33 (sext, J = 7.3 Hz, 4H), 1.53-1.59 (m, 4H), 3.24-3.27 (m, 4H), 6.50 (br. s, 1H), 6.96-6.99 (m, 1H), 7.22-7.25 (m, 2H) 7.37-7.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 20.0, 30.6, 47.2, 60.3, 119.7, 122.5, 128.5, 139.3, 154.9; HRMS (ESI) *m/z* Calcd for $[C_{15}H_{25}N_2O]^+$ 249.1961; found 249.1962.



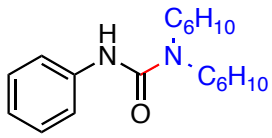
1,1-Dihexyl-3-phenylurea (6i)

To a stirred solution of dihexylamine (117 µL, 0.50 mmol) in Cyrene (0.1 M) at 0 °C was added phenyl isocyanate (**4a**, 55 µL, 0.50 mmol). The resultant mixture was stirred at rt for 1 h. Water (5 mL) was added and the precipitate was filtered and washed with water. The residue was dried over anhydrous sodium sulphate to give 1,1-dihexyl-3-phenylurea (**6i**, 136 mg, 89%). as a yellow solid. mp. (°C) 62-63; IR (neat): 3310, 2925, 2855, 1626, 1530 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.87-0.96 (m, 6 H), 1.30 (bs, 12 H), 1.56-1.60 (m, 4H), 3.26 (t, J = 9.5 Hz, 4H), 6.43 (bs, 1H), 6.96-7.00 (m, 1H), 7.22-7.26 (m, 2H), 7.36-7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 22.6, 26.6, 28.6, 31.6, 47.7, 119.8, 122.6, 128.7, 139.4, 154.9; HRMS (ESI) *m/z* Calcd for $[C_{19}H_{33}N_2O]^+$ 305.2587; found 305.2588.



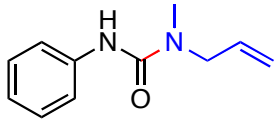
1,1-Dioctyl-3-phenylurea (6j)

To a stirred solution of dioctylamine (150 µL, 0.50 mmol) in Cyrene (0.1 M) at 0 °C was added phenyl isocyanate (**4a**, 55 µL, 0.50 mmol). The resultant mixture was stirred at rt for 1 h. Water (5 mL) was added and the precipitate was filtered and washed with water. The residue was dried over anhydrous sodium sulphate to give 1,1-dioctyl-3-phenylurea (**6j**, 108 mg, 56%). as a white solid. mp. (°C) 242-244; IR (neat): 3322, 2923, 2853, 1636, 1595, 1498 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86-0.89 (m, 6H), 1.26-1.31 (m, 20H), 1.58-1.61 (m, 4H), 3.26 (t, J = 7.6 Hz, 4H), 6.33 (bs, 1H), 6.98-7.01 (m, 1H), 7.24-7.27 (m, 2H), 7.36-7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 22.6, 27.0, 28.6, 29.2, 29.3, 31.7, 47.7, 119.7, 122.6, 128.7, 139.3, 154.8; HRMS (ESI) *m/z* Calcd for $[C_{23}H_{41}N_2O]^+$ 361.3213; found 361.3211.



1,1-Dicyclohexyl-3-phenylurea (6k)

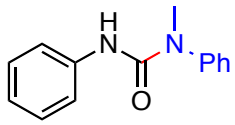
To a stirred solution of dicyclohexylamine (99 µL, 0.50 mmol) in Cyrene (0.1 M) at 0 °C was added phenyl isocyanate (**4a**, 55 µL, 0.50 mmol). The resultant mixture was stirred at rt for 1 h. Water (5 mL) was added and the precipitate was filtered and washed with water. The residue was dried over anhydrous sodium sulphate to give 1,1-dicyclohexyl-3-phenylurea (**6k**, 131 mg, 87%). as a white solid. mp. (°C) 173-175 [Lit.[7] 167-168]; IR (neat): 3321, 2924, 2850, 1627 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.07-1.17 (m, 2H), 1.24-1.38 (m, 4H), 1.64-1.84 (m, 14H), 3.43-3.50 (m, 2H), 6.33 (bs, 1 H), 6.96-6.99 (m, 1H), 7.23-7.27 (m, 2H), 7.34-7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.5, 26.4, 31.9, 55.4, 119.6, 122.4, 128.7, 139.4, 154.9; HRMS (ESI) *m/z* Calcd for $[C_{19}H_{29}N_2O]^+$ 301.2274; found 301.2275.



1-Allyl-1-methyl-3-phenylurea (6l)[3]

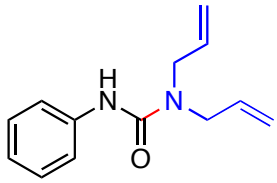
To a stirred solution of 1-allylmethylamine (48 µL, 0.5 mmol) in Cyrene (0.5 mL, 1 M) at 0 °C was added phenyl isocyanate (**4a**, 55 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 30 min. The solvent was removed by Buchner filtration and the filtrate was washed with water (60 mL). The residue was dissolved in EtOAc (20 mL), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give 1-allyl-1-methyl-3-phenylurea (**6l**, 68

mg, 71%), as a white solid. mp. (°C) 73-75 [Lit.[8] 73-76]; IR (neat): 3308, 1644, 1524, 1237, 1203, 991, 913, 747, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.01 (s, 3H), 3.97 (dt, J = 5.3 Hz, J = 1.6 Hz, 2H), 5.26 (t, J = 1.6 Hz, 1H), 5.27-5.29 (m, 1H), 5.83-5.91 (m, 1H), 6.38 (br. s, 1H) 7.00-7.03 (m, 1H), 7.25-7.29 (m, 2H), 7.34-7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.6, 51.6, 117.0, 120.0, 122.9, 128.8, 133.5, 139.2, 155.5; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{14}N_2ONa]^+$ 213.0998; found 213.0991.



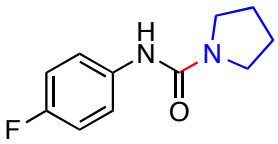
1-Methyl-1,3-diphenylurea (6m)[4]

To a stirred solution of *N*-methylaniline (54 µL, 0.5 mmol) in Cyrene (0.5 mL, 1 M) at 0 °C was added phenyl isocyanate (**4a**, 55 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 30 min. The solvent was removed by Buchner filtration and the filtrate was washed with water (60 mL). The residue was dissolved in EtOAc (20 mL), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give 1-methyl-1,3-diphenylurea (**6m**, 112 mg, 99%), as a white solid. mp. (°C) 100–101 [Lit.[5] 97-99]; IR (neat): 3364, 3039, 1646, 1594, 1523, 1494, 1436 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.34 (s, 3H), 6.26 (br. s, 1H), 6.97-7.00 (m, 1H), 7.21-7.24 (m, 2H), 7.27-7.29 (m, 2H), 7.32-7.34 (m, 2H), 7.36-7.39 (m, 2H), 7.46-7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.2, 119.2, 122.8, 127.4, 127.8, 128.7, 130.3, 138.8, 142.8, 154.3; HRMS (ESI) *m/z* Calcd for $[C_{14}H_{15}N_2O]^+$ 227.1179; found 227.1179.



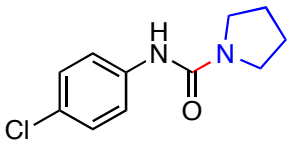
1,1-Diallyl-3-phenylurea (6n)[9]

To a stirred solution of diallyl amine (62 µL, 0.5 mmol) in Cyrene (0.5 mL, 1 M) at 0 °C was added phenyl isocyanate (**4a**, 55 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 30 min. The solvent was removed by Buchner filtration and the filtrate was washed with water (60 mL). The residue was dissolved in EtOAc (20 mL), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give 1,1-diallyl-3-phenylurea (**6n**, 108 mg, 99%) as a clear oil. IR (neat): 3351, 2980, 1639, 1597, 1532, 1443 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.95-3.97 (m, 4H), 5.25-5.31 (m, 4H), 5.85-5.92 (m, 2H), 6.51 (br. S, 1H), 6.99-7.02 (m, 1H), 7.24-7.28 (m, 2H), 7.31-7.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 49.8, 117.3, 119.6, 122.9, 128.8, 134.1, 139.2, 155.5; HRMS (ESI): *m/z* Calcd for $[C_{13}H_{17}N_2O]^+$ 217.1335; found 217.1344.



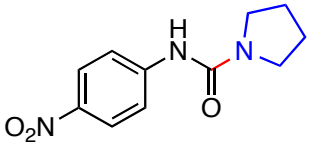
***N*-(4-Fluorophenyl)pyrrolidine-1-carboxamide (6o)**

To a stirred solution of pyrrolidine (43 µL, 0.5 mmol) in Cyrene (0.5 mL, 1 M) at 0 °C was added 4-fluorophenyl isocyanate (57 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 30 min. The solvent was removed by Buchner filtration and the filtrate was washed with water (60 mL). The residue was dissolved in EtOAc (20 mL), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give *N*-(4-fluorophenyl)pyrrolidine-1-carboxamide (**6o**, 89 mg, 86%) as a white solid. mp. (^{o}C) 137-138; IR (neat): 3278, 2966, 2871, 1631, 1506, 1414 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.96-1.99 (m, 4H), 3.44-3.47 (m, 4H), 6.09 (bs, 1H), 6.95-6.99 (m, 2H), 7.34-7.36 (m, 2H); HRMS (ESI) *m/z* Calcd for $[C_{11}H_{13}FN_2ONa]^+$ 231.0904; found 231.0902.



***N*-(4-Chlorophenyl)pyrrolidine-1-carboxamide (6p)**[1]

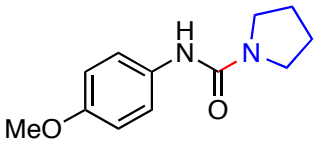
To a stirred solution of 4-chlorophenyl isocyanate (76.7 mg, 0.5 mmol) in Cyrene (0.5 mL, 1 M) at 0 °C was added pyrrolidine (42 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 30 min. The solvent was removed by Buchner filtration and the filtrate was washed with water (60 mL). The residue was dissolved in EtOAc (20 mL), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give *N*-(4-chlorophenyl)pyrrolidine-1-carboxamide (**6p**, 97 mg, 86%) as a white solid. mp. (^{o}C) 165-167; IR (neat): 3292, 2957, 2928, 2870, 1633, 1596, 1501, 1444, 1317, 1241, 1221 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) 1.96-1.98 (m, 4H), 3.44-3.46 (m, 4H), 6.18 (br. s, 1H), 7.21-7.24 (m, 2H), 7.35-7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.6, 45.8, 120.7, 127.6, 128.8, 137.8, 153.7; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{14}ClN_2O]^+$ 225.0789; found 225.0788.



***N*-(4-Nitrophenyl)pyrrolidine-1-carboxamide (6q)**

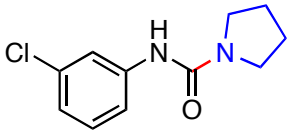
To a stirred solution of 4-nitrophenyl isocyanate (82 mg, 0.5 mmol) in Cyrene (0.5 mL, 1 M) at 0 °C was added pyrrolidine (42 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 30 min. The solvent was removed by Buchner filtration and the filtrate was washed with water (60 mL). The

residue was dissolved in EtOAc (20 mL), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give *N*-(4-nitrophenyl)pyrrolidine-1-carboxamide (**6q**, 83 mg, 70%) as a yellow solid. mp. (°C) 185-187 [Lit.[10] 185-186]; IR (neat): 3366, 3338, 2927, 2881, 17.32, 1657, 1596, cm^{-1}; ^{1}H NMR ($CDCl_3$, 500MHz) δ 1.99-2.20 (m, 4H), 3.48-3.51 (m, 4H), 6.51 (bs, 1H), 7.58-7.60 (m, 2H), 8.16-8.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.6, 46.0, 118.0, 125.2, 142.4, 145.4, 152.6; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{14}N_3O_3]^+$ 236.1030; found 236.1031.



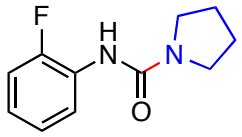
_N_-(4-Methoxyphenyl)pyrrolidine-1-carboxamide (6r)[1]

To a stirred solution of pyrrolidine (42 µL, 0.5 mmol) in Cyrene (0.5 mL, 1 M) at 0 °C was added 4-methoxyphenyl isocyanate (65 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 30 min. The solvent was removed by Buchner filtration and the filtrate was washed with water (60 mL). The residue was dissolved in EtOAc (20 mL), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give *N*-(4-methoxyphenyl)pyrrolidine-1-carboxamide (**6r**, 56 mg, 51%) as a white solid. mp. (°C) 111-112 [Lit.[1] 111-113]; IR (neat): 3329, 2965, 1639, 1597, 1509, 1411 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500MHz) δ 1.92-1.95 (m, 4H), 3.41-3.43 (m, 4H), 3.76 (s, 3H), 6.13 (bs, 1H), 6.80-6.83 (m, 2H), 7.28-7.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.5, 45.7, 55.4, 113.9, 121.8, 132.2, 154.4, 155.5; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{17}N_2O_2]^+$ 221.1285; found 221.1287.



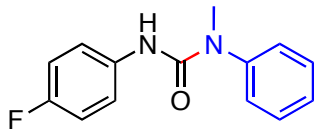
_N_-(3-Chlorophenyl)pyrrolidine-1-carboxamide (6s)

To a stirred solution of pyrrolidine (43 µL, 0.5 mmol) in Cyrene (0.5 mL, 1 M) at 0 °C was added 3-chlorophenyl isocyanate (65 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 30 min. The solvent was removed by Buchner filtration and the filtrate was washed with water (60 mL). The residue was dissolved in EtOAc (20 mL), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give *N*-(3-chlorophenyl)pyrrolidine-1-carboxamide (**6s**, 103 mg, 92%) as a white solid. mp. (°C) 138-140; IR (neat): 3305, 3275, 2980, 2878, 1651, 1586 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.95-1.98 (m, 4H), 3.43-3.46 (m, 4H), 6.22 (bs, 1H), 6.96-6.98 (m, 1H), 7.16-7.19 (m, 1H), 7.25-7.27 (m, 1H), 7.52-7.53 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.5, 45.8, 117.2, 119.3, 122.6, 129.7, 134.4, 140.4, 153.4; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{13}ClN_2ONa]^+$ 247.0609; found 224.0716.



_N_-(2-Fluorophenyl)pyrrolidine-1-carboxamide (6t)

To a stirred solution of pyrrolidine (43 µL, 0.5 mmol) in Cyrene (0.5 mL, 1 M) at 0 °C was added 2-fluorophenyl isocyanate (56 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 30 min. The solvent was removed by Buchner filtration and the filtrate was washed with water (60 mL). The residue was dissolved in EtOAc (20 mL), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give *N*-(2-fluorophenyl)pyrrolidine-1-carboxamide (**6t**, 43 mg, 41%) as a pale yellow solid. mp. (^{o}C) 61-62; IR (neat): 3269, 2965, 2870, 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.95-1.98 (m, 4H), 3.46-3.48 (m, 4H), 6.41 (bs, 1H), 6.89-6.94 (m, 1H), 7.00-7.09 (m, 2H), 8.18-8.28 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.5, 45.7, 114.4, 120.9, 122.2, 124.4, 127.8, 151.2, 153.3; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{13}FN_2ONa]^+$ 231.0904; found 231.0903.



3-(4-Fluorophenyl)-1-methyl-1-phenylurea (6u)[11]

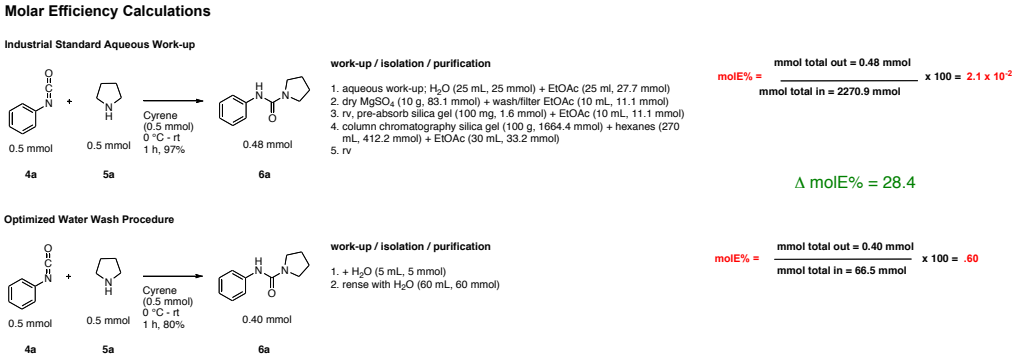
To a stirred solution of 1-methylaniline (54 µL, 0.5 mmol) in Cyrene (0.5 mL, 1 M) at 0 °C was added 4-fluorophenyl isocyanate (57 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 30 min. The solvent was removed by Buchner filtration and the filtrate was washed with water (60 mL). The residue was dissolved in EtOAc (20 mL), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give 3-(4-fluorophenyl)-1-methyl-1-phenylurea (**6u**, 79 mg, 65%) as a white solid. mp. (^{o}C) 109-110; IR (neat): 3352, 3045, 1644, 1595, 1525, 1491, 1442, 848 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.34 (s, 3H), 6.18 (br. s, 1H), 6.90-6.95 (m, 2H) 7.21-7.25 (m, 2H), 7.33-7.35 (m, 2H), 7.47-7.51 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.2, 115.2, 121.1, 127.4, 130.3, 134.7, 142.7, 154.4, 159.6; HRMS (ESI) *m/z* Calcd for $[C_{14}H_{13}FN_2ONa]^+$ 267.0904; found 267.0904.

III. Molar Efficiency Calculations

Molar efficiency calculations were calculated using the method of Watson *et al.*[12] in which:

molar efficiency (Mol. E%) = [moles product / moles starting material + additives + catalysts + solvents] x 100

The Mol. E% was calculated for each step of the process and the total molar efficiency ($molE_{total}$) is the multiplication of these values.



Thus, the approach presented in this report amounts to a 28-fold increase in molar efficiency *vs.* an industrial standard method of urea isolation and purification.

IV. References

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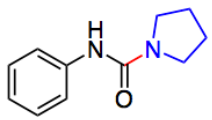

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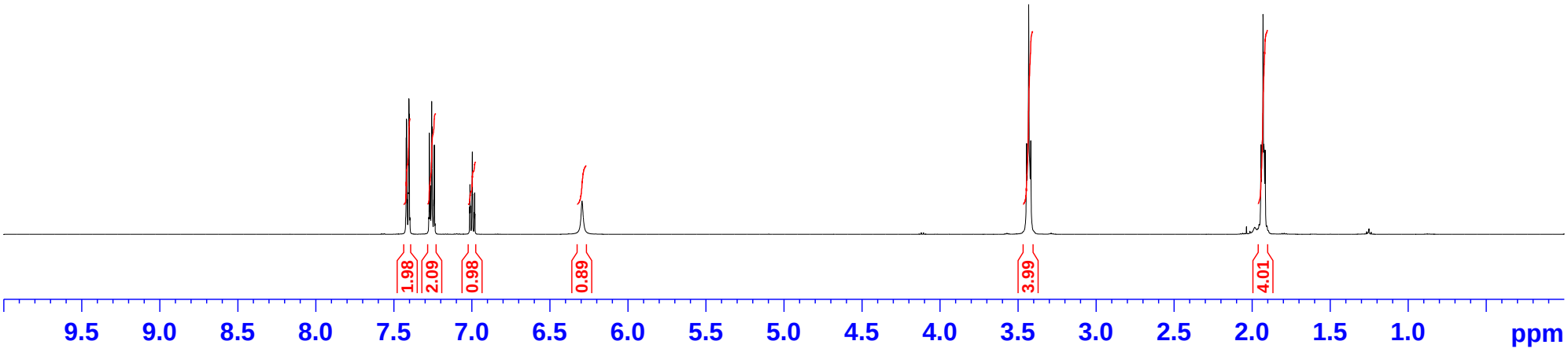
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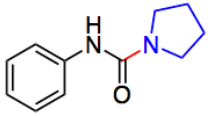

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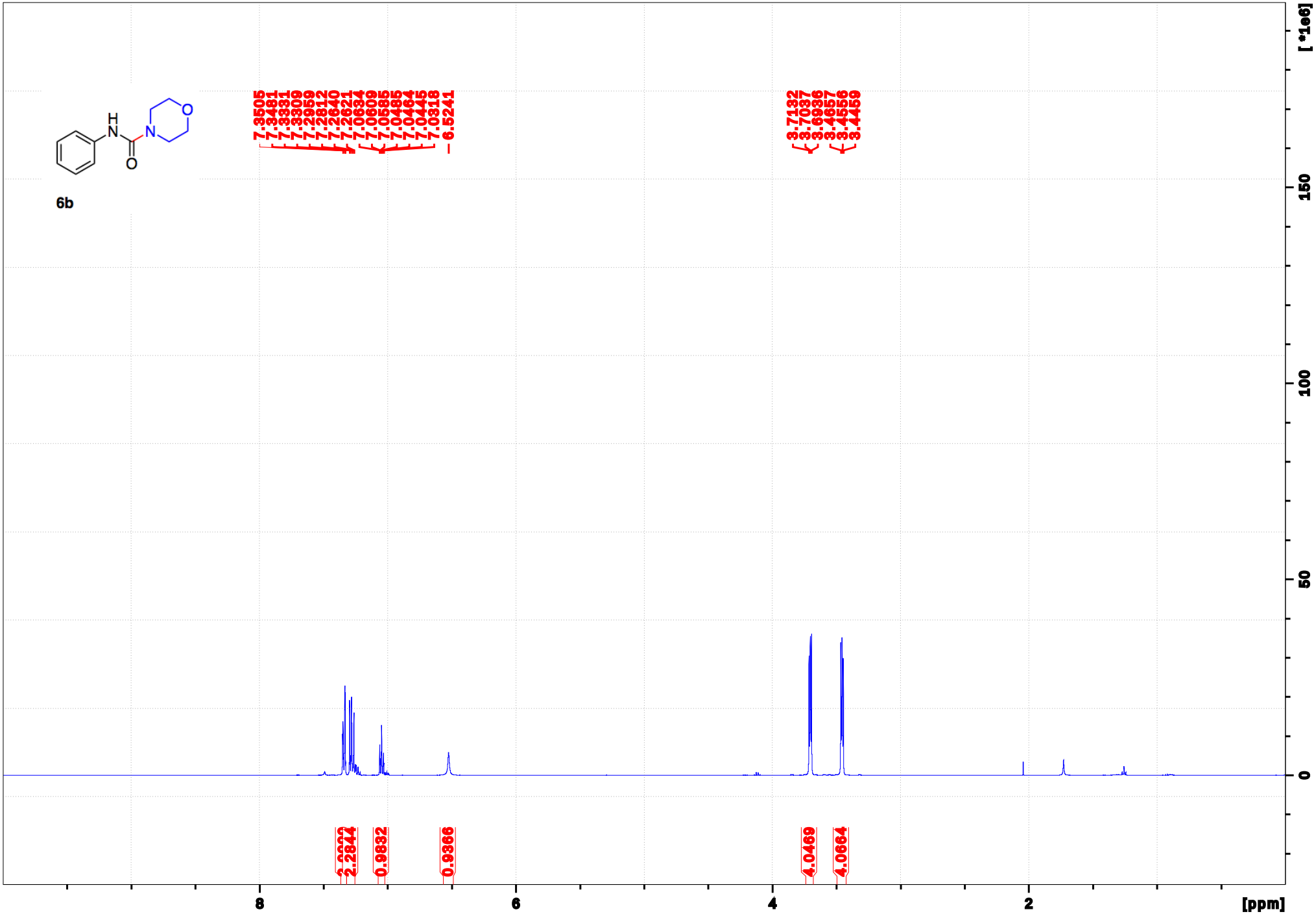
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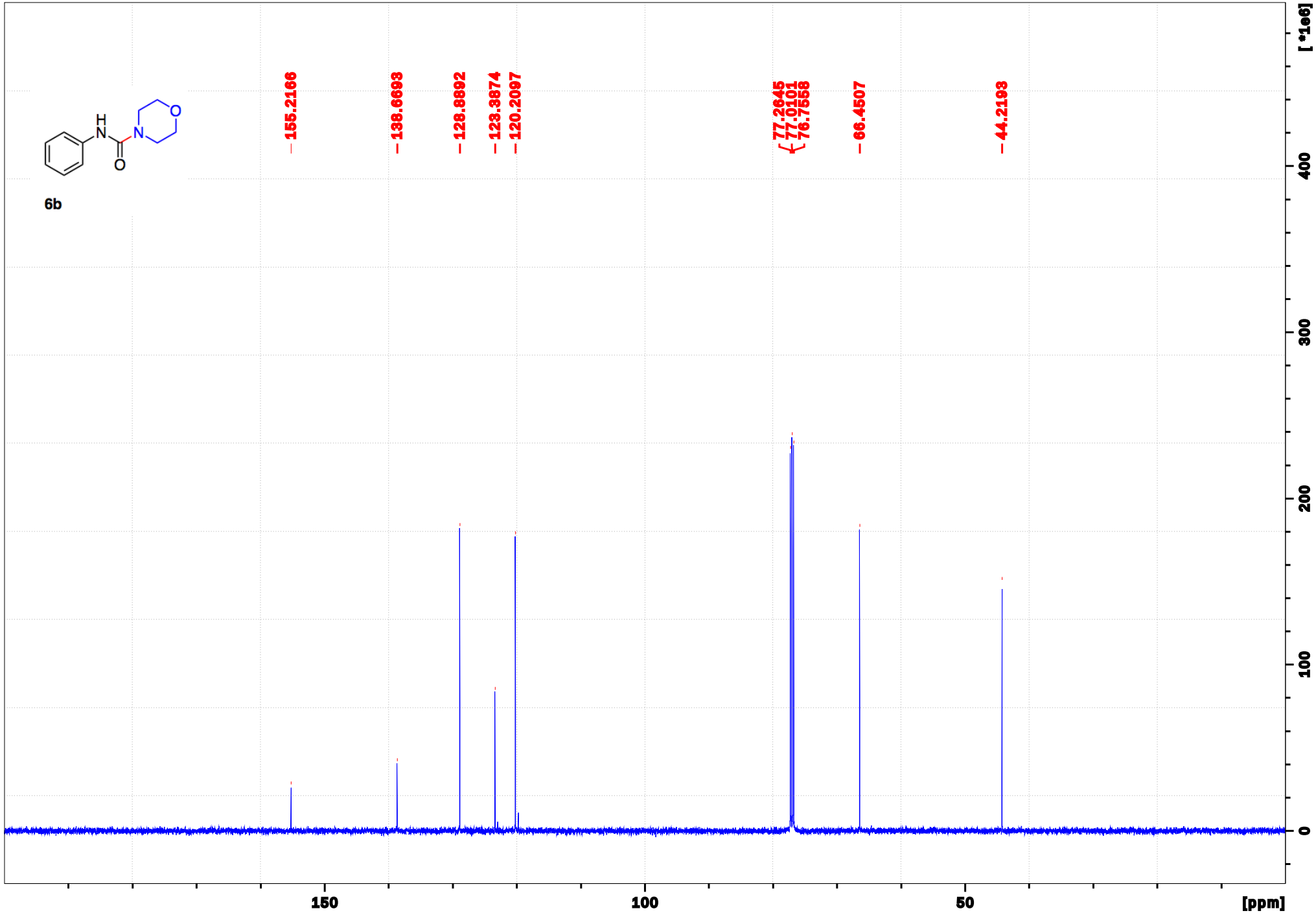
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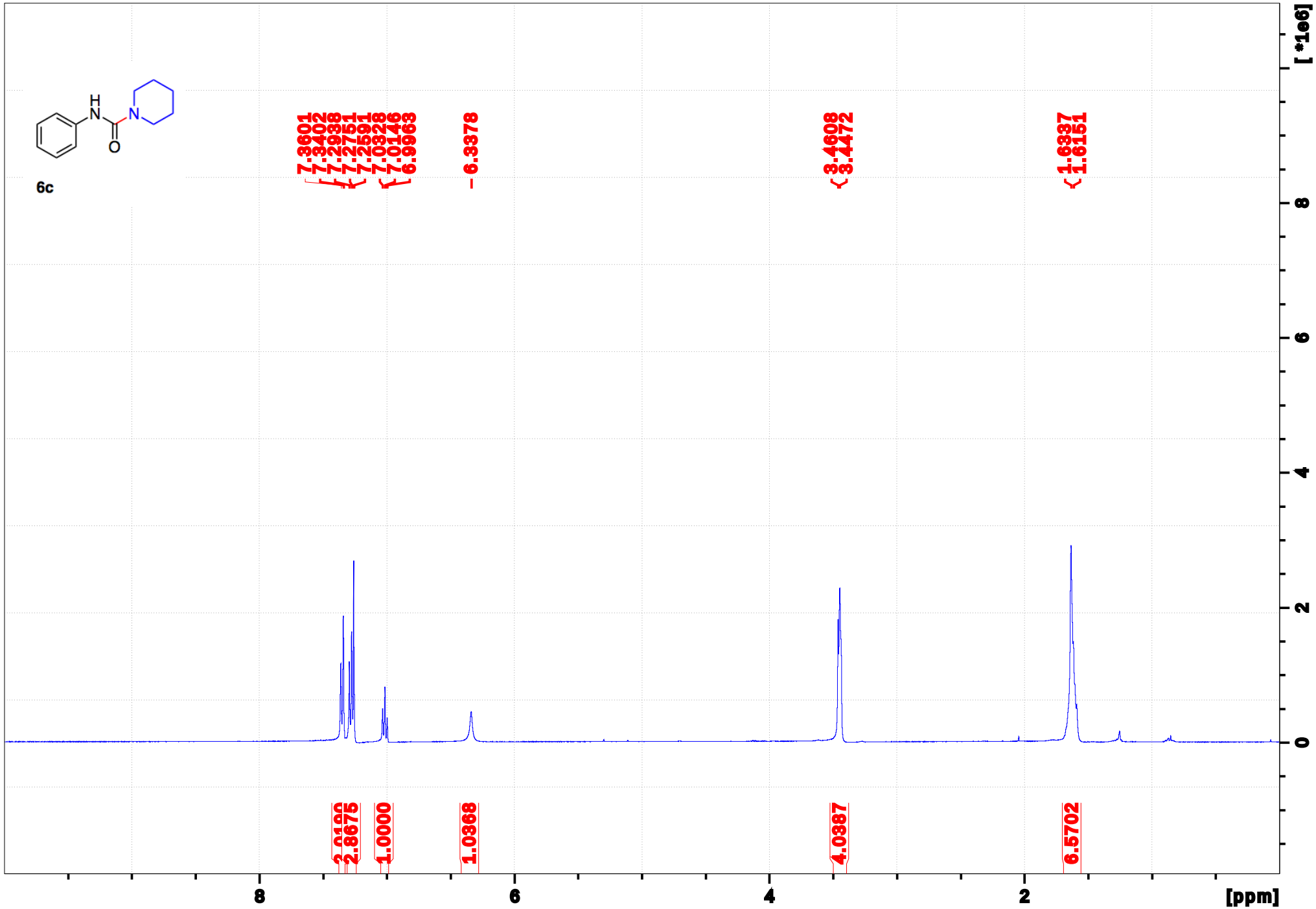
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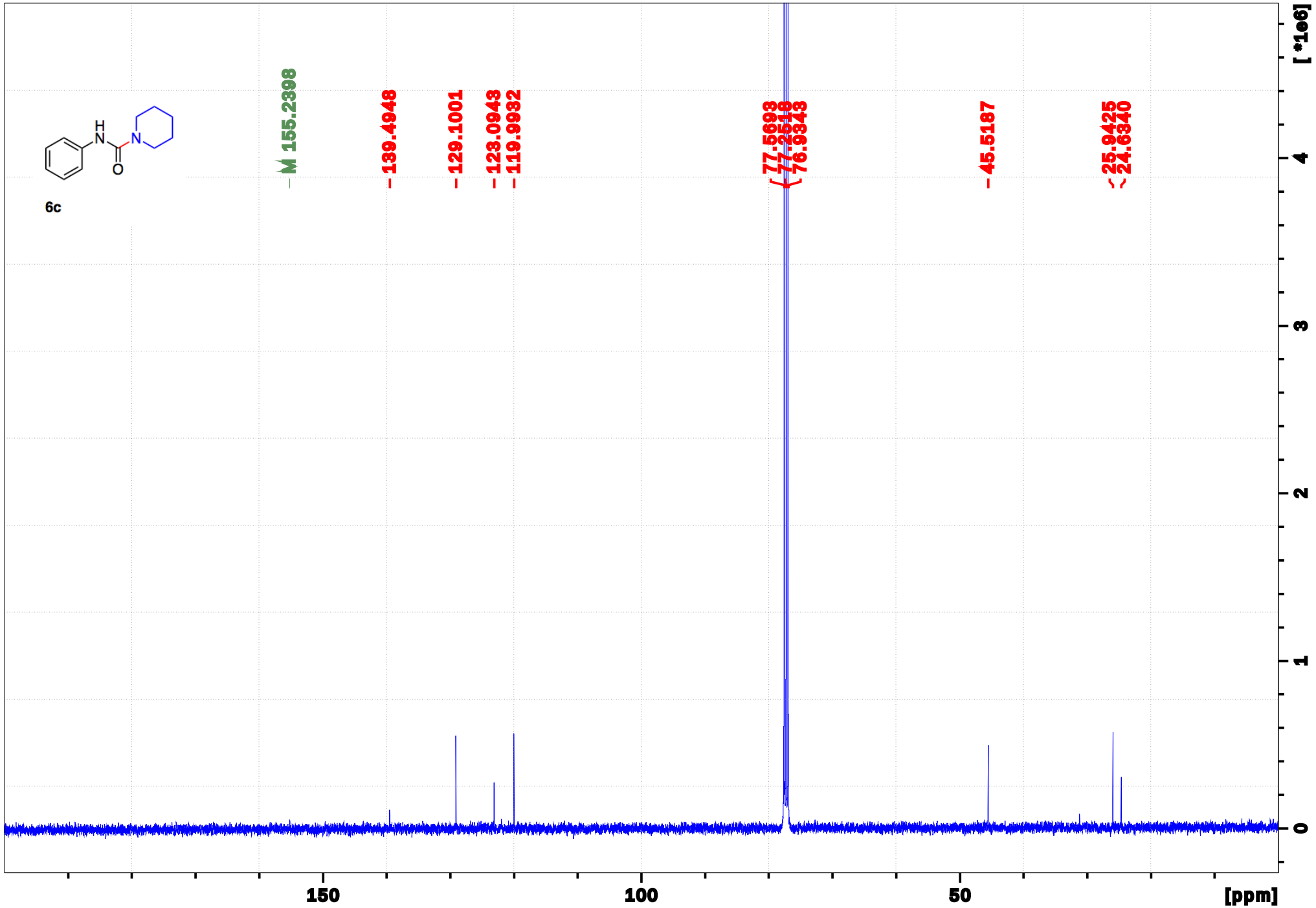
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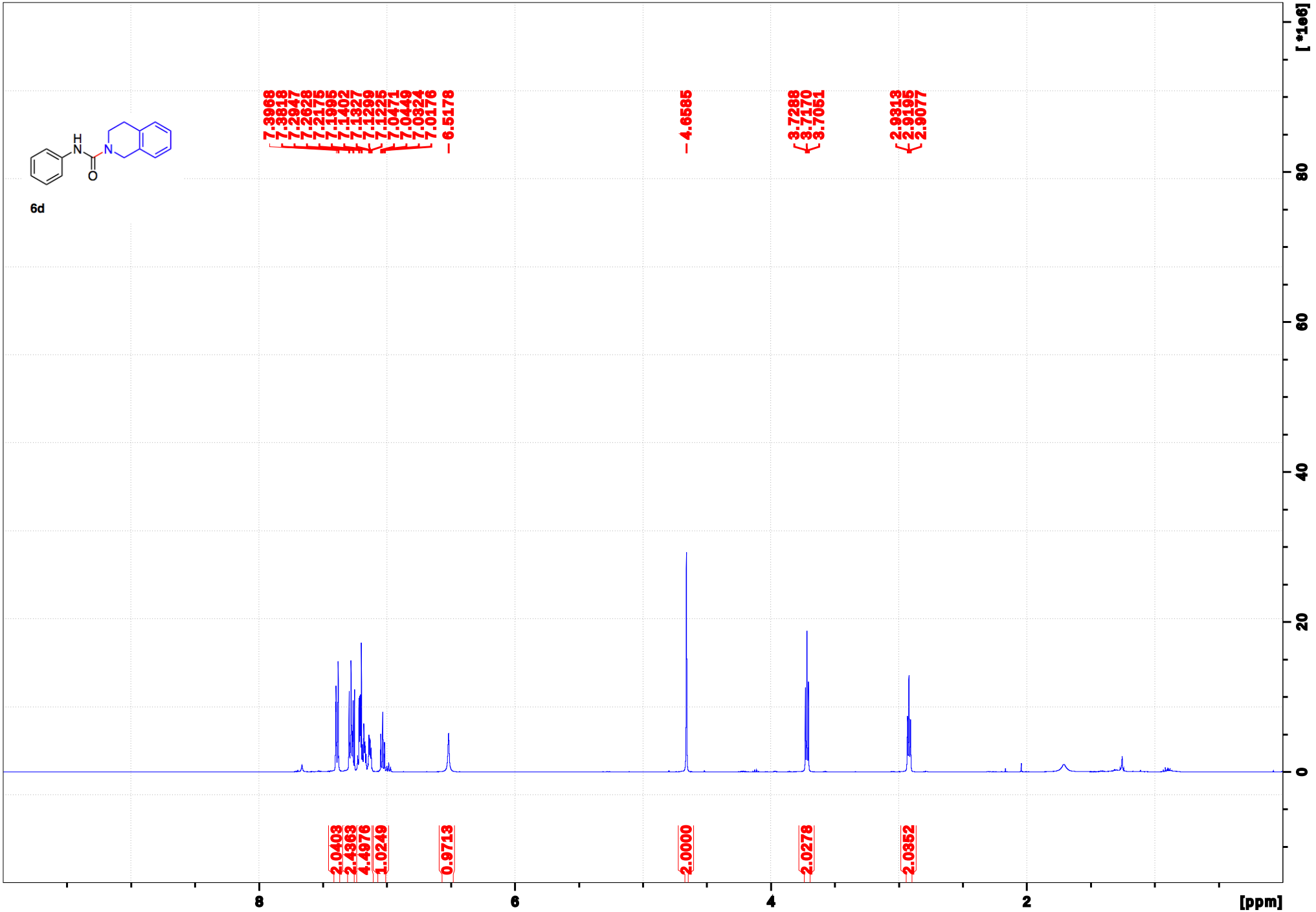
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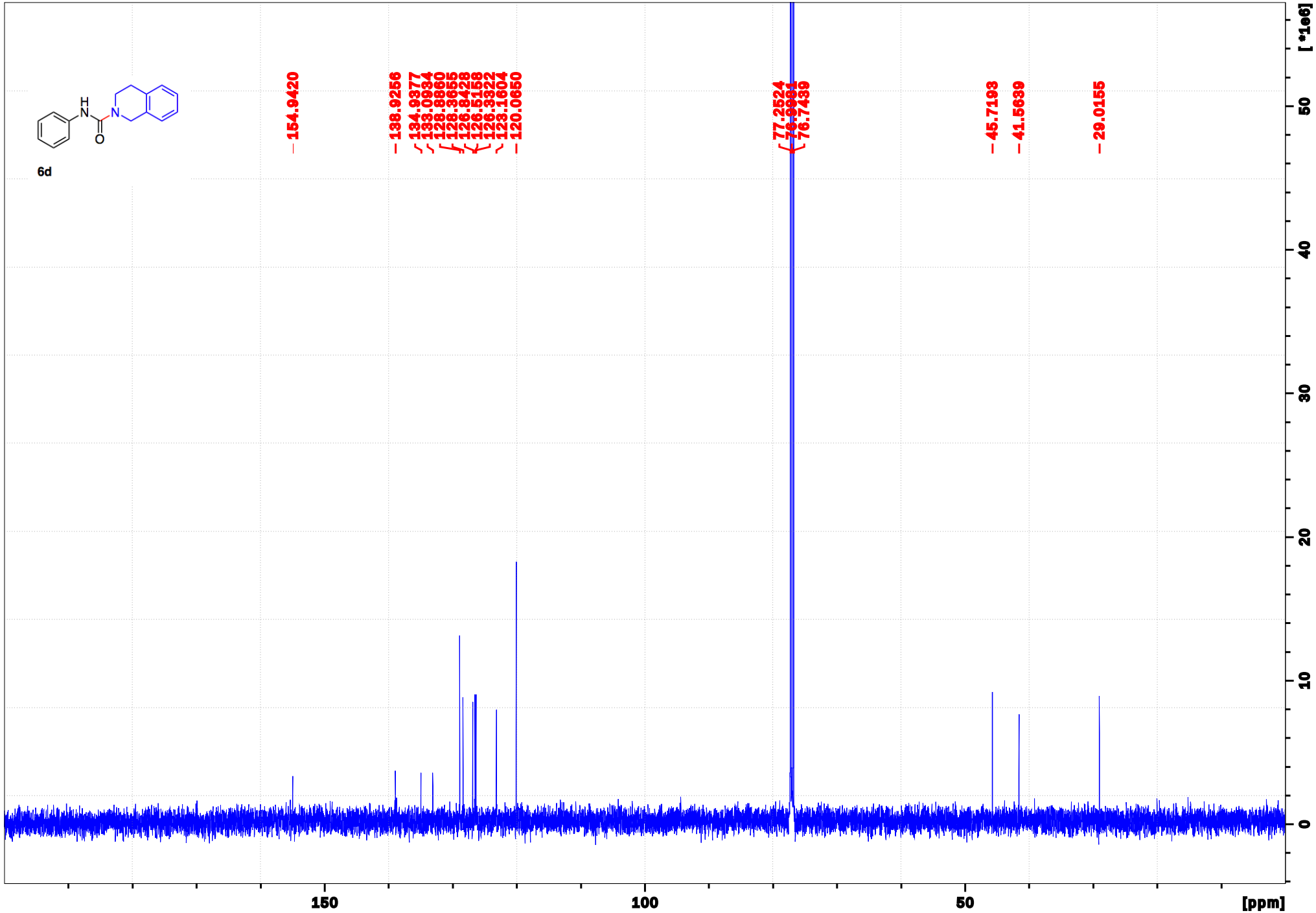
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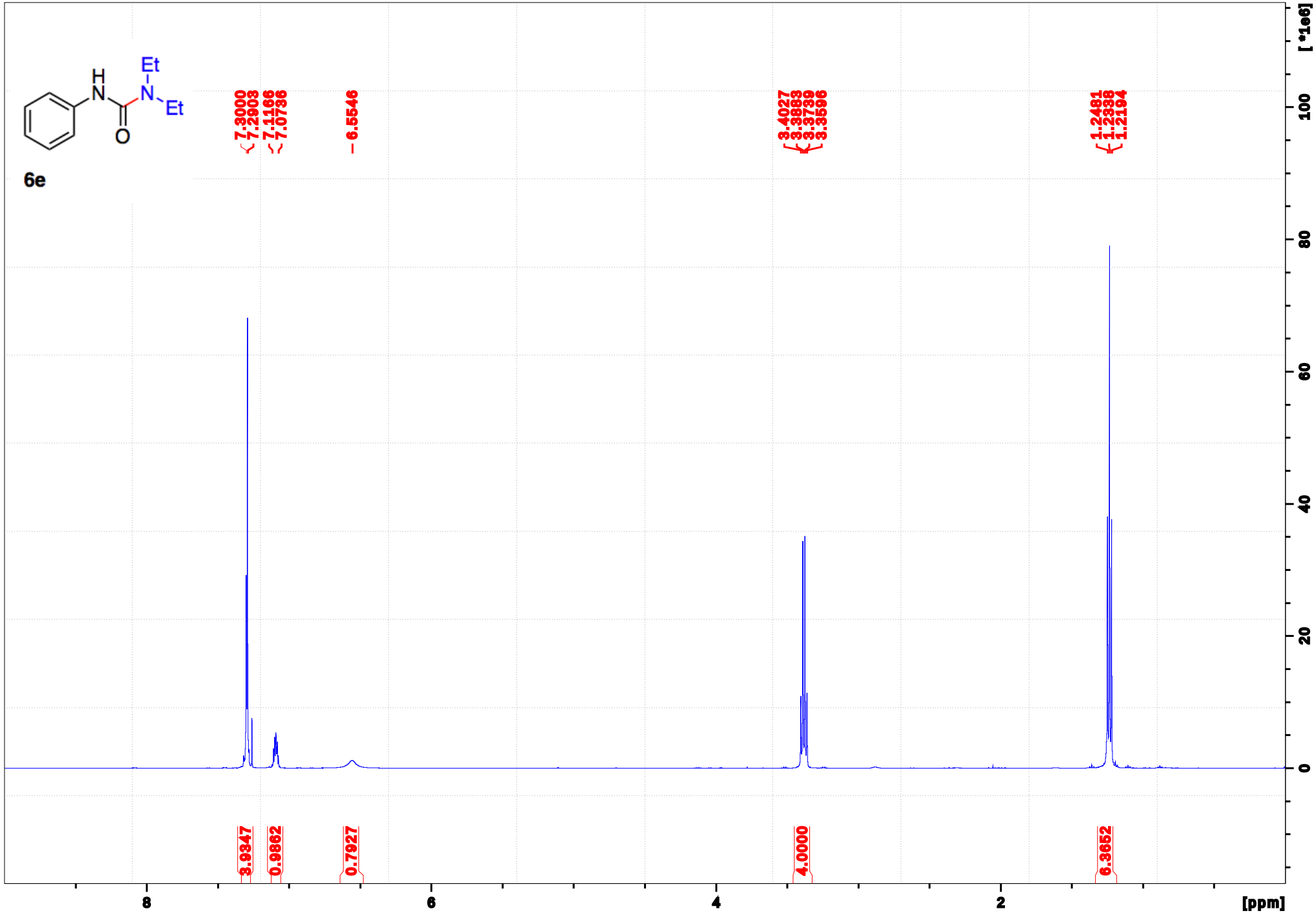
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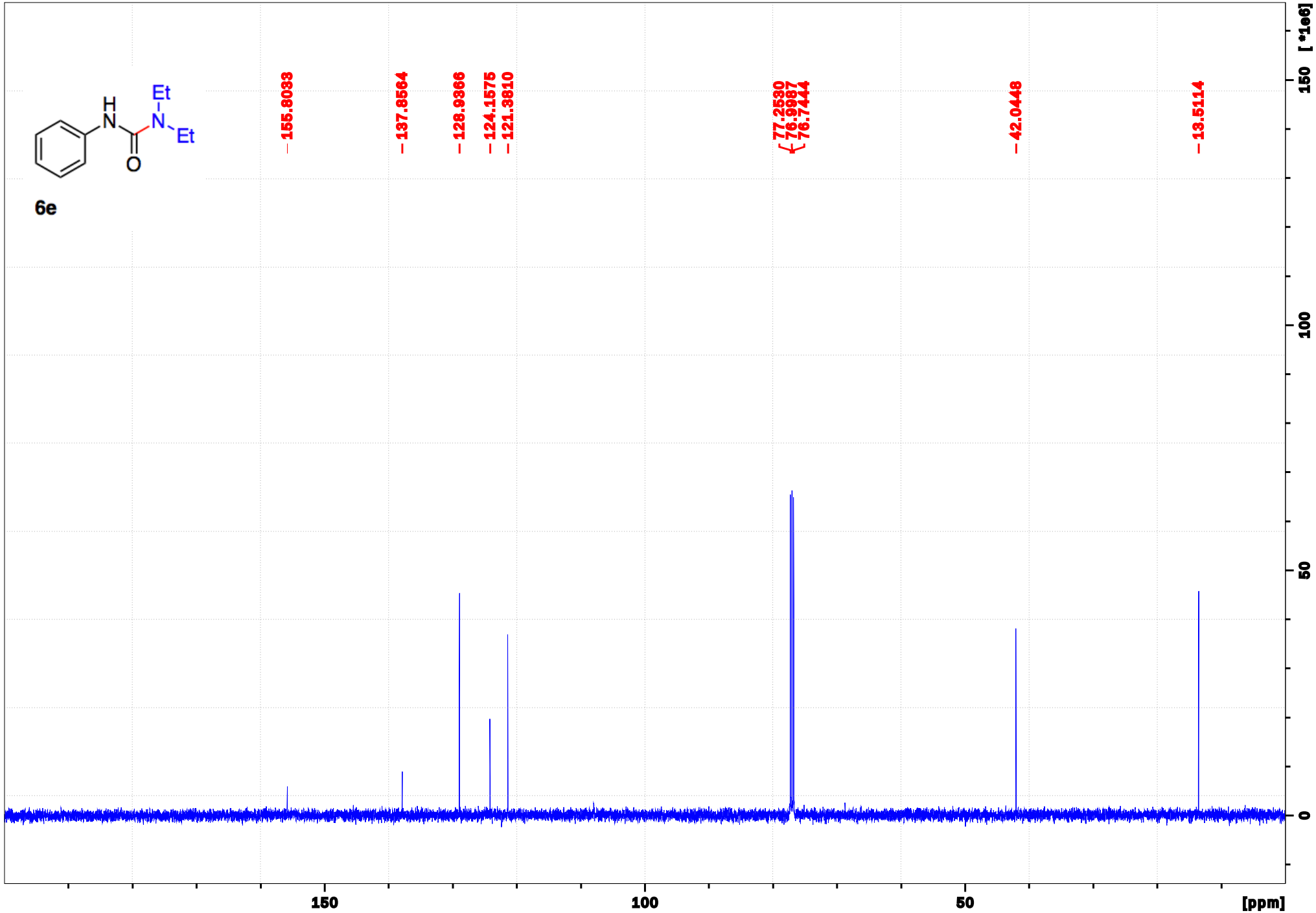
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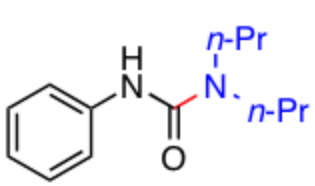
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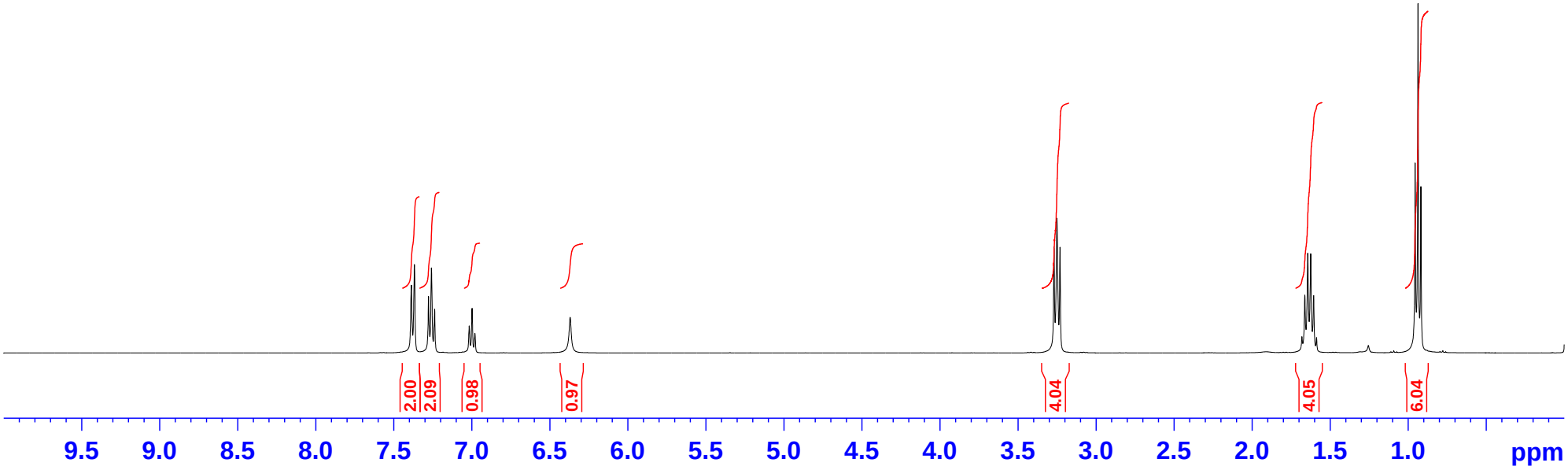
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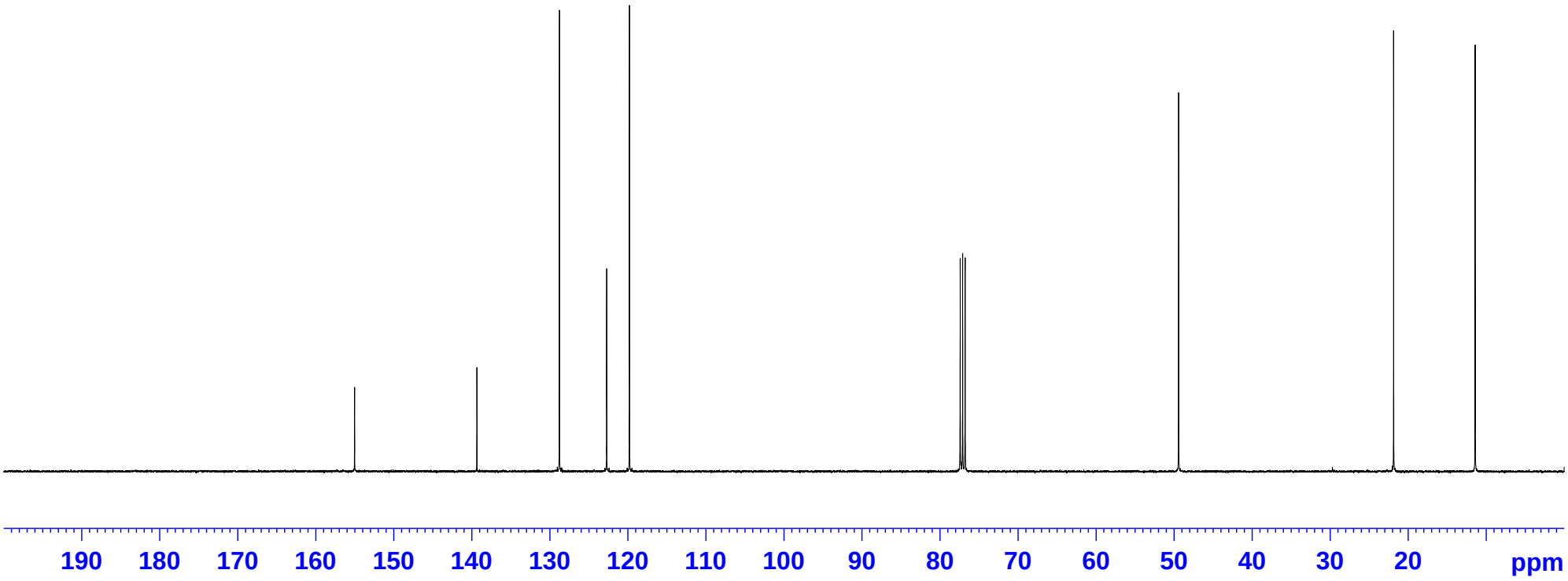
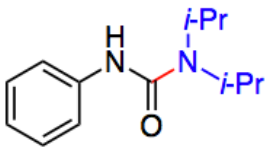
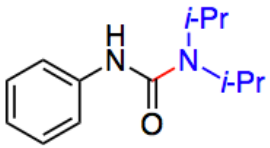



H
N
O
N
i-Pr
i-Pr

6g

7.3783
7.3755
7.3566
7.3545
7.2695
7.2620
7.2506
7.2301
6.9987
6.9803
6.9620
6.3110
3.9841
3.9670
3.9498
3.9327
3.9156
1.3065
1.2892
2.00
2.04
0.98
0.99
2.02
12.18
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm



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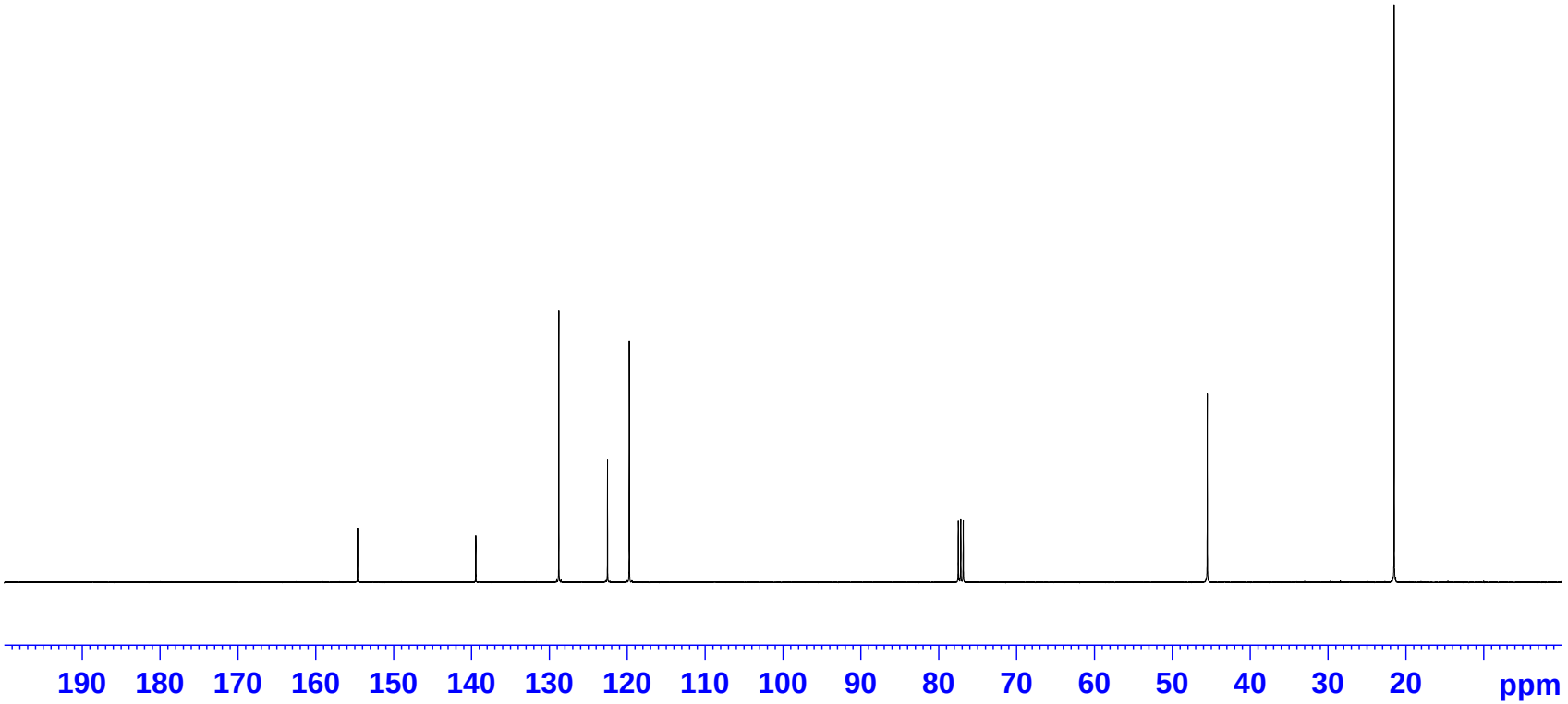
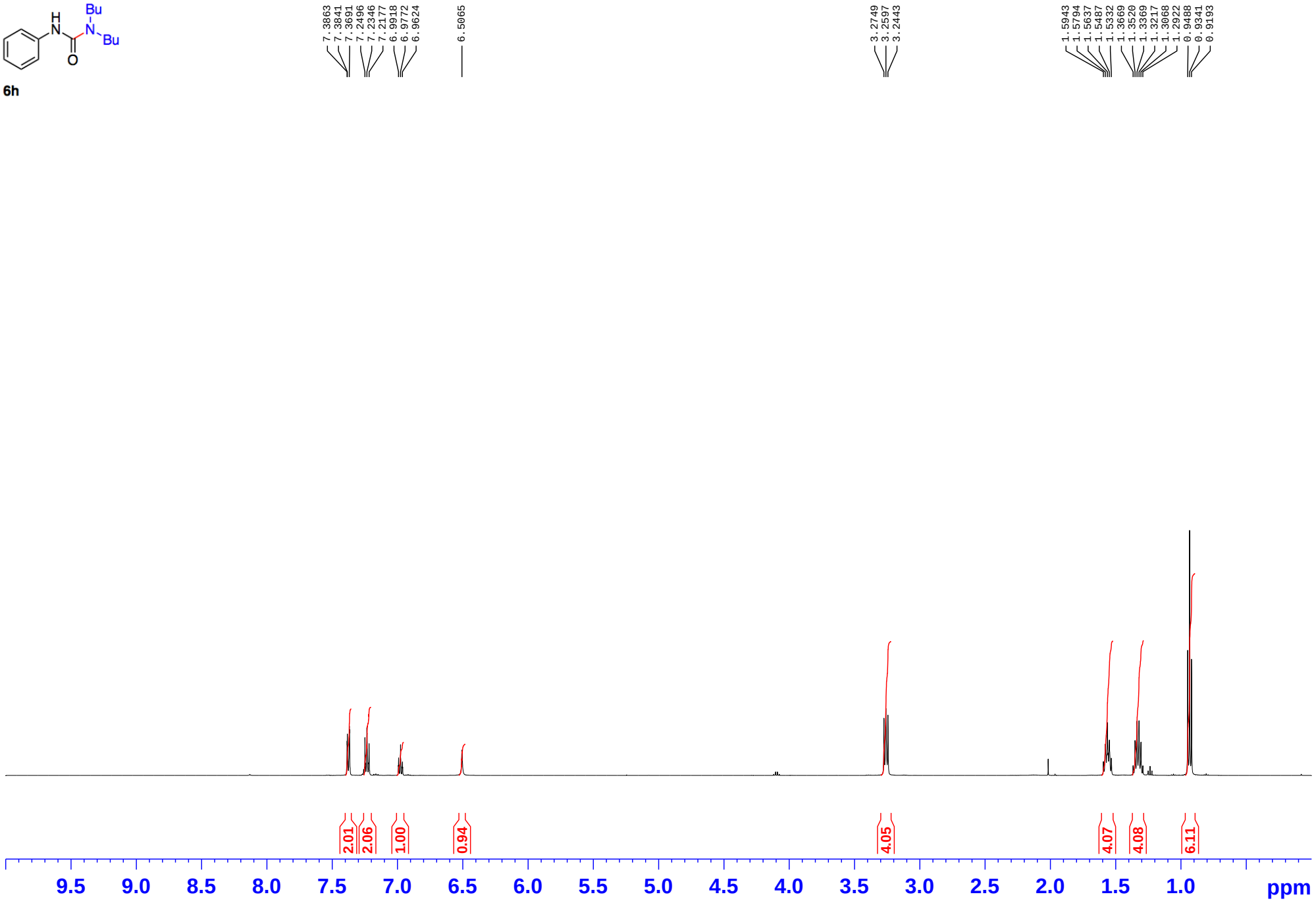
128.7973
122.5447
119.7473
45.5145
21.5155

6g




Bu
N
Bu
H
N
O
6h
7.3863
7.3841
7.3691
7.2496
7.2346
7.2177
6.9918
6.9772
6.9624
6.5065
3.2749
3.2597
3.2443
1.5943
1.5794
1.5637
1.5487
1.5332
1.3669
1.3520
1.3369
1.3217
1.3068
1.2922
0.9488
0.9341
0.9193
2.01
2.06
1.00
0.94
4.05
4.07
4.08
6.11
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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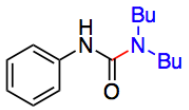
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm



6h

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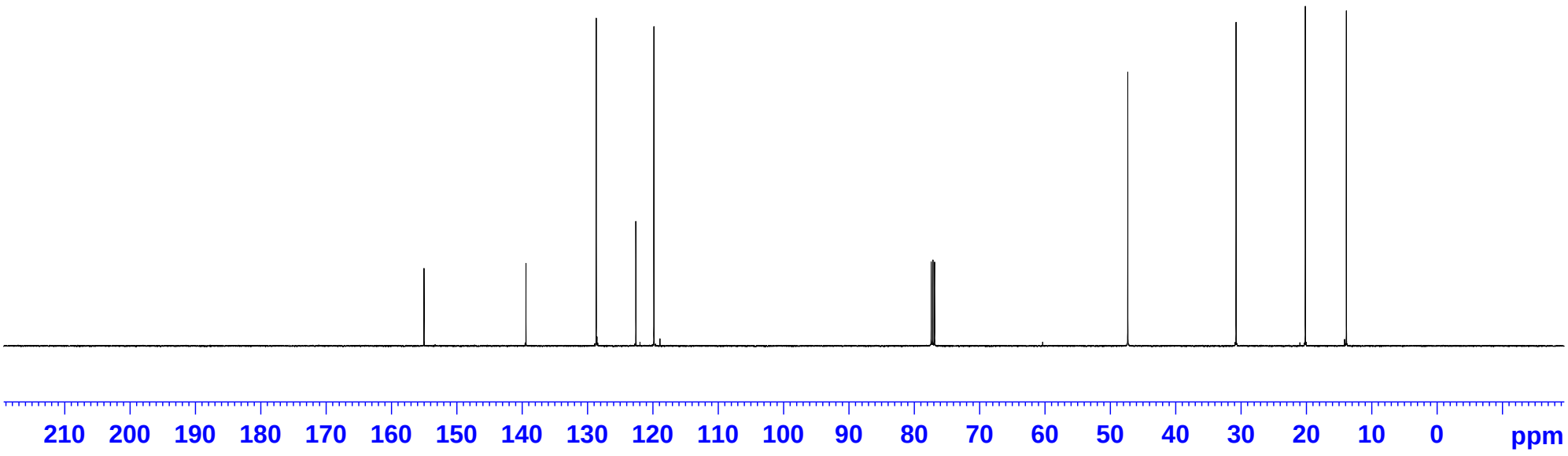
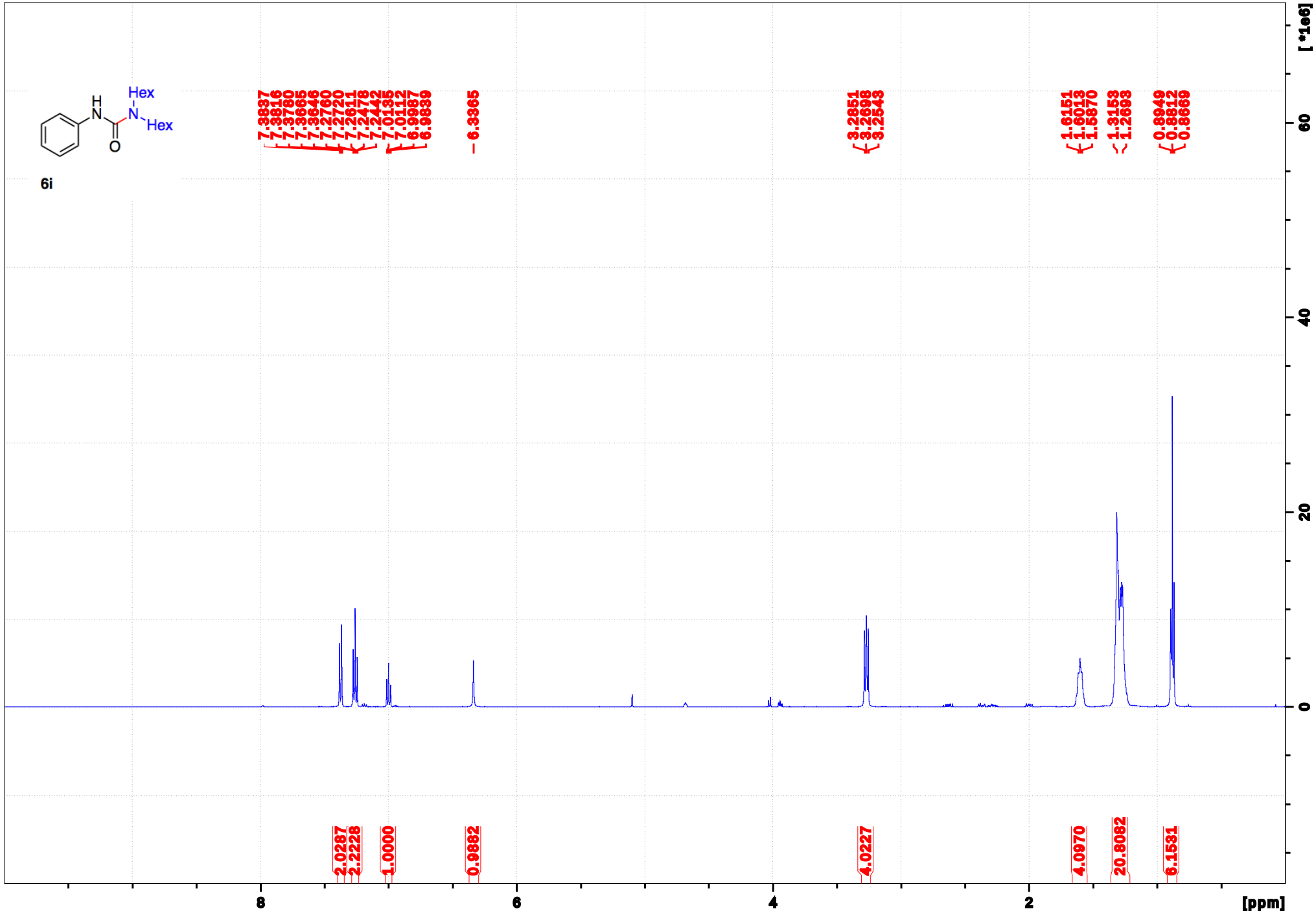
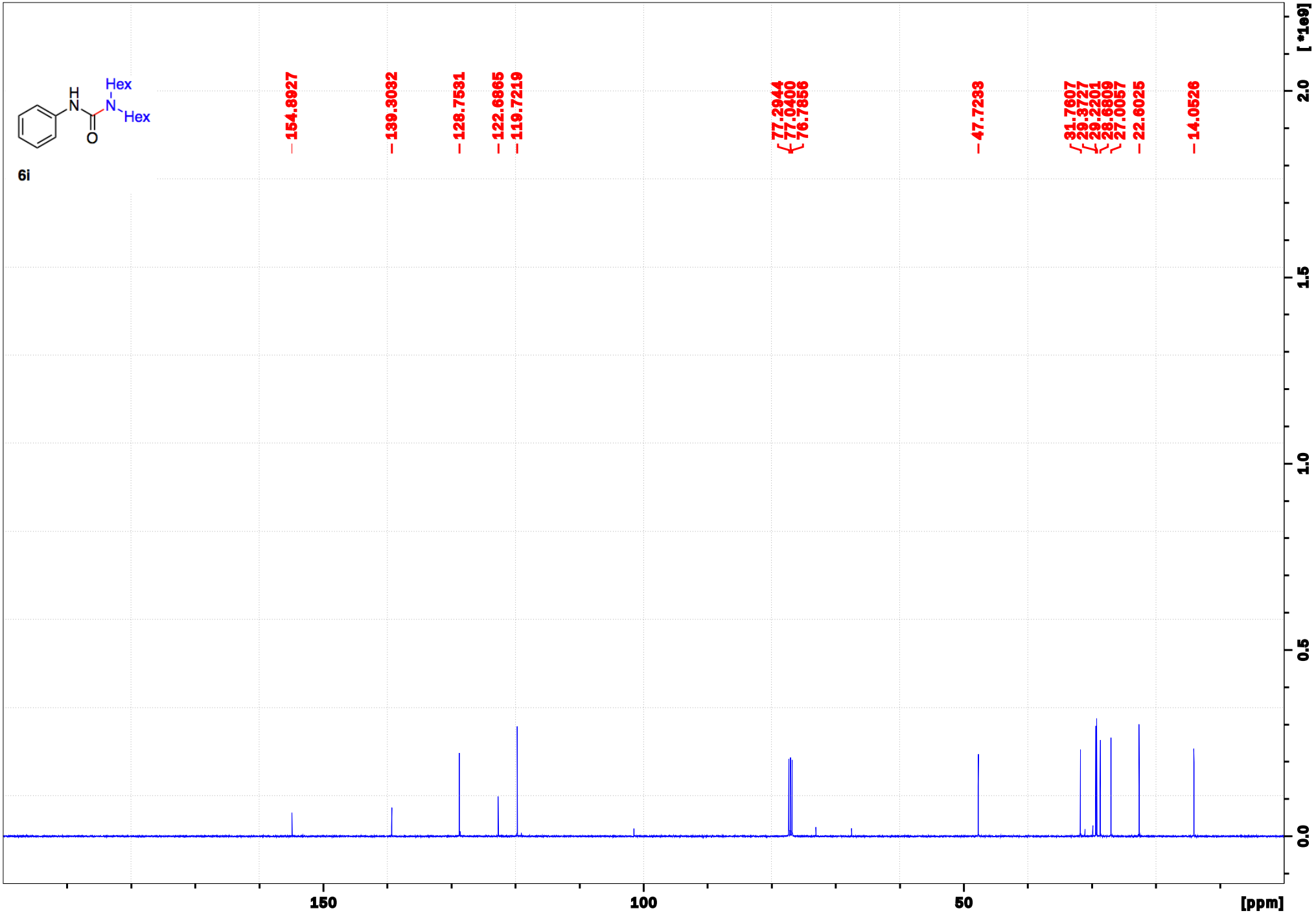
122.6063
119.8461
47.3284
30.7578
20.1612
13.8802




Hex
H
N
N
Hex
O
6i
7.3837
7.3816
7.3780
7.3665
7.3646
7.2760
7.2720
7.2611
7.2478
7.2442
7.0135
7.0112
6.9987
6.9839
6.3365
3.2851
3.2698
3.2543
1.6151
1.6013
1.5870
1.3153
1.2693
0.8949
0.8812
0.8669
2.0287
2.2228
1.0000
0.9882
4.0227
4.0970
20.8082
6.1531
[*1e6]
60
40
20
0
8
6
4
2
[ppm]


Hex
N
Hex
H
N
O
6i
154.8927
139.3032
128.7531
122.6865
119.7219
77.2944
77.0400
76.7856
47.7238
31.7607
29.3727
29.2201
28.6809
27.0057
22.6025
14.0526
[*1e9]
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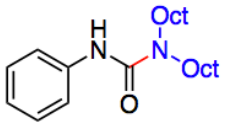
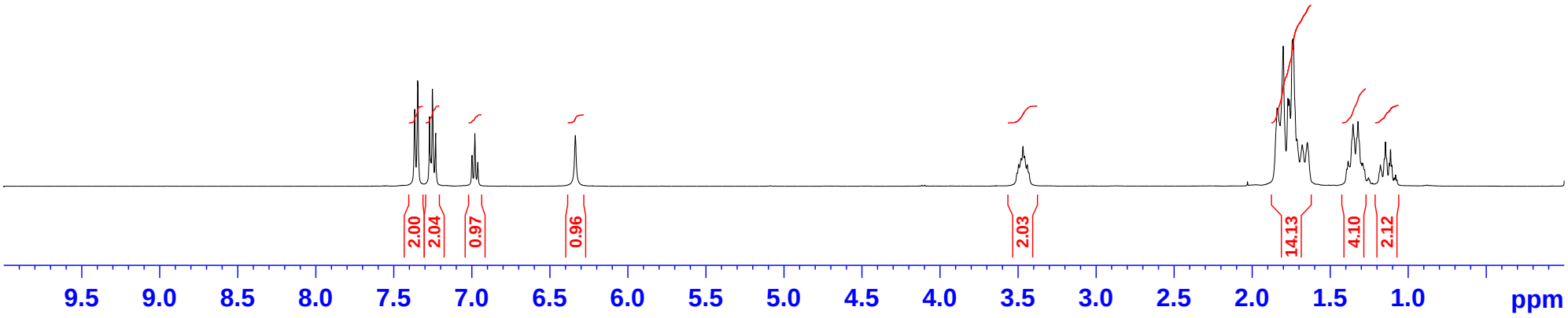
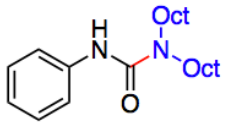
1.5
1.0
0.5
0.0
150
100
50
[ppm]



6j

7.3658
7.3467
7.2711
7.2620
7.2524
7.2316
6.9986
6.9803
6.9619
6.3366
3.5066
3.4963
3.4798
3.4687
3.4581
3.4411
3.4312
1.8401
1.8338
1.8009
1.7707
1.7623
1.7425
1.7359
1.7130
1.6789
1.6464
1.3851
1.3536
1.3217
1.3018
1.2923
1.2805
1.2644
1.2546
1.2471
1.1780
1.1531
1.1457
1.1216
1.1132
1.1051
1.0895
1.0806
1.0720




H
N
Oct
N
Oct
O

6j

154.9010
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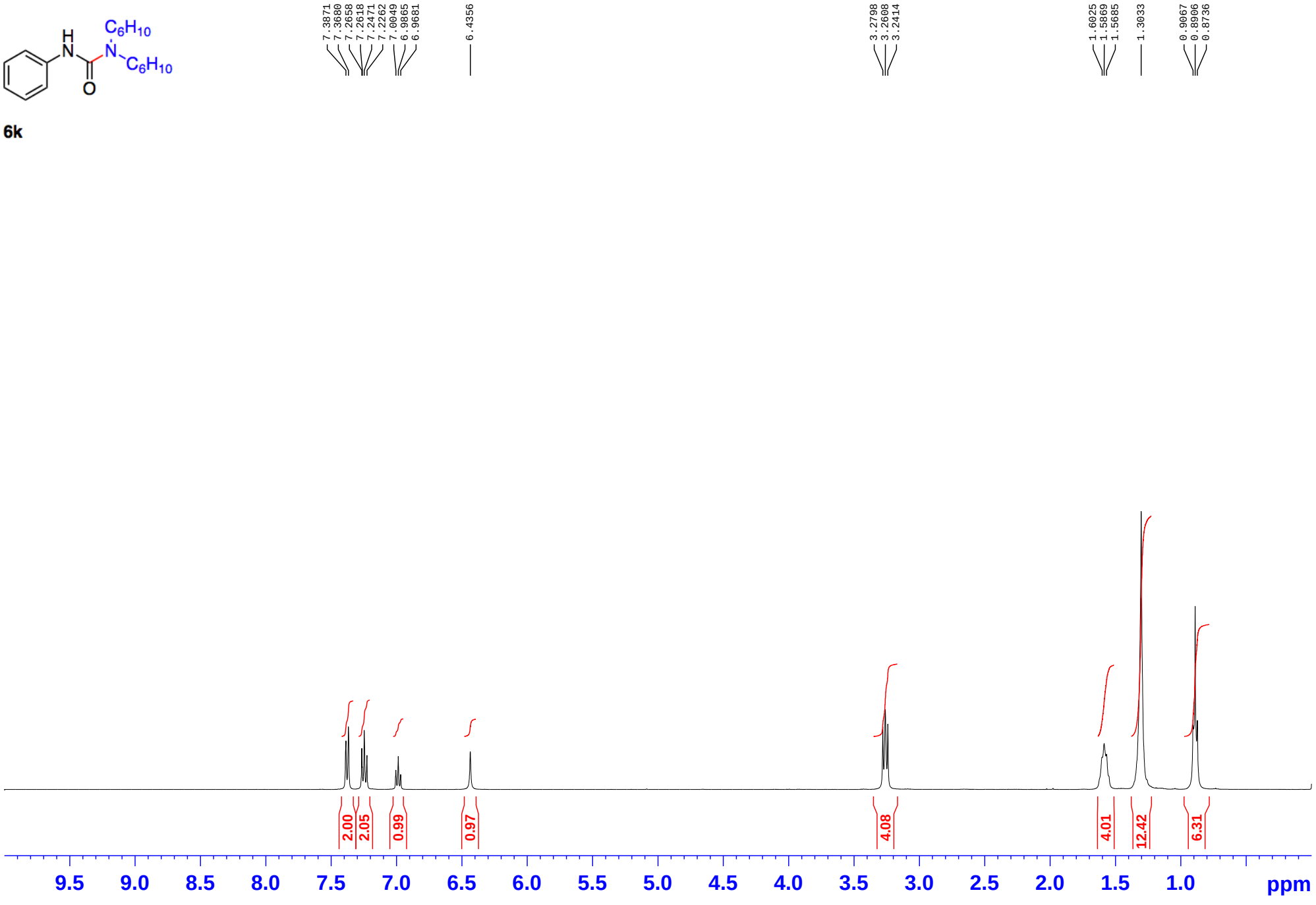
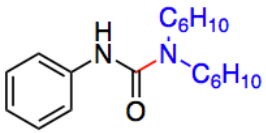
128.7716
122.4987
119.6742
55.4482
31.9084
26.4183
25.5530
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


C6H10
H
N
N
C6H10
O
7.3871
7.3680
7.2658
7.2618
7.2471
7.2262
7.0049
6.9865
6.9681
6.4356
3.2798
3.2608
3.2414
1.6025
1.5869
1.5685
1.3033
0.9067
0.8906
0.8736
2.00
2.05
0.99
0.97
4.08
4.01
12.42
6.31
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

6k


H
N
O
N
C6H10
C6H10

6k

154.9779
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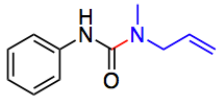
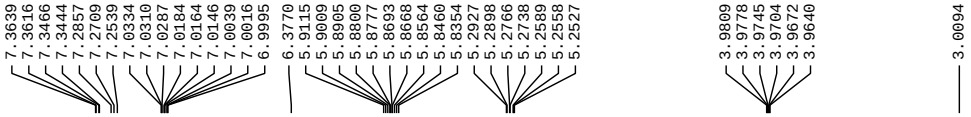
128.7409
122.6519
119.8151
47.7034
31.6426
28.6749
26.6990
22.6220
14.0366
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm



6l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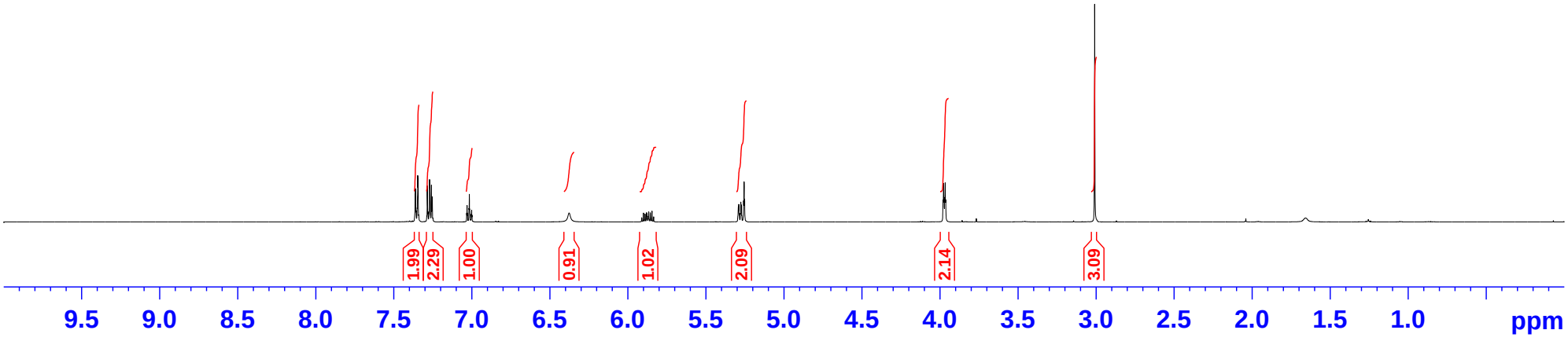
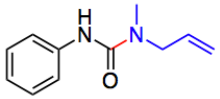
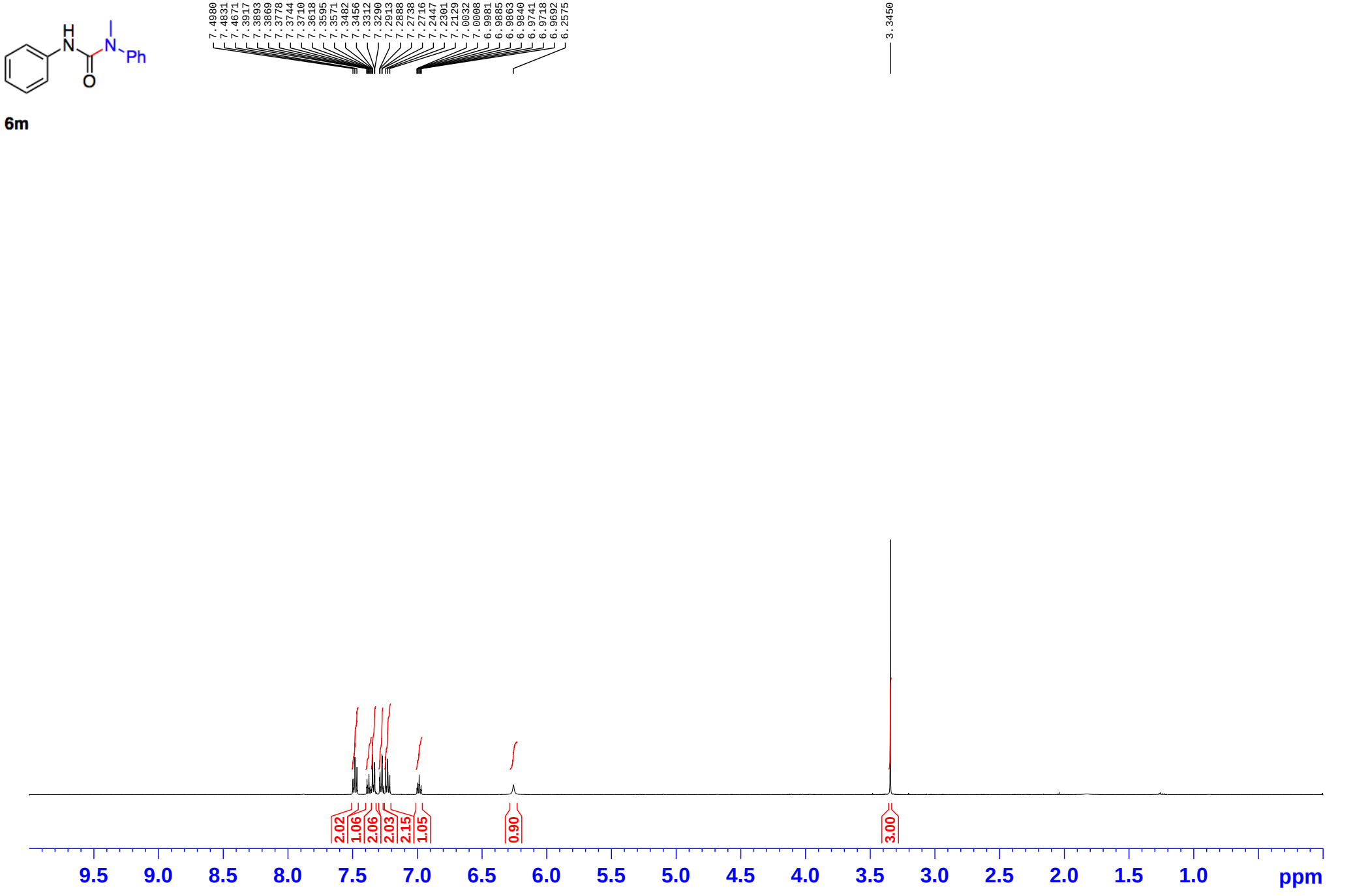
7.3466
7.3444
7.2857
7.2709
7.2539
7.0334
7.0310
7.0287
7.0184
7.0164
7.0146
7.0039
7.0016
6.9995
6.3770
5.9115
5.9009
5.8905
5.8800
5.8777
5.8693
5.8668
5.8564
5.8460
5.8354
5.2927
5.2898
5.2766
5.2738
5.2589
5.2558
5.2527
3.9809
3.9778
3.9745
3.9704
3.9672
3.9640
3.0094

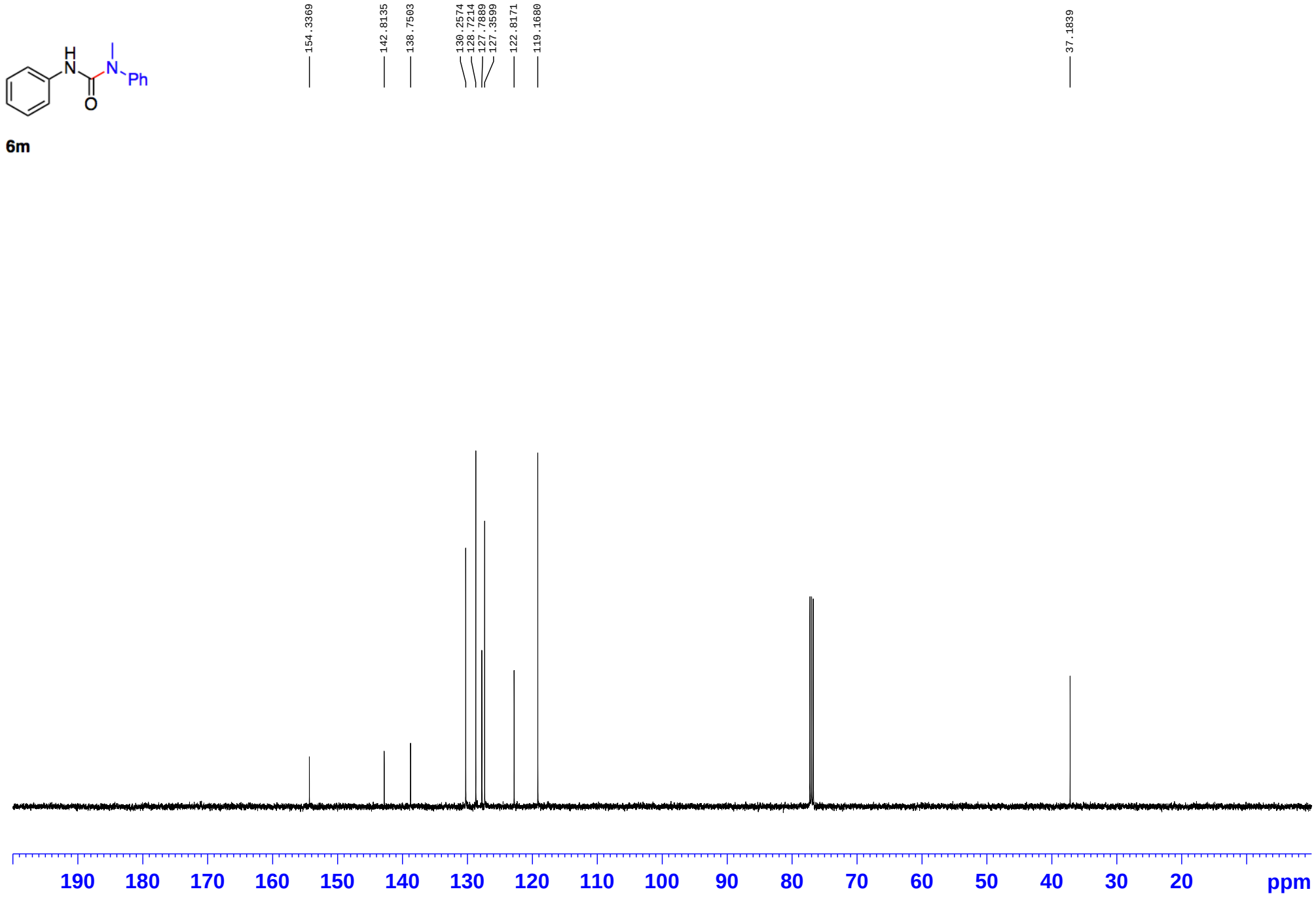

1.99
2.29
1.00
0.91
1.02
2.09
2.14
3.09
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm



6l

155.5368
139.1750
133.4821
128.8263
122.9387
119.7625
116.9699
51.5779
34.6097
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


7.4980
7.4831
7.4671
7.3917
7.3893
7.3869
7.3778
7.3744
7.3710
7.3618
7.3595
7.3571
7.3482
7.3456
7.3312
7.3290
7.2913
7.2888
7.2738
7.2716
7.2447
7.2301
7.2129
7.0032
7.0008
6.9981
6.9885
6.9863
6.9840
6.9741
6.9718
6.9692
6.2575
3.3450
H
N
N
Ph
O
6m
2.02
1.06
2.06
2.03
2.15
1.05
0.90
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm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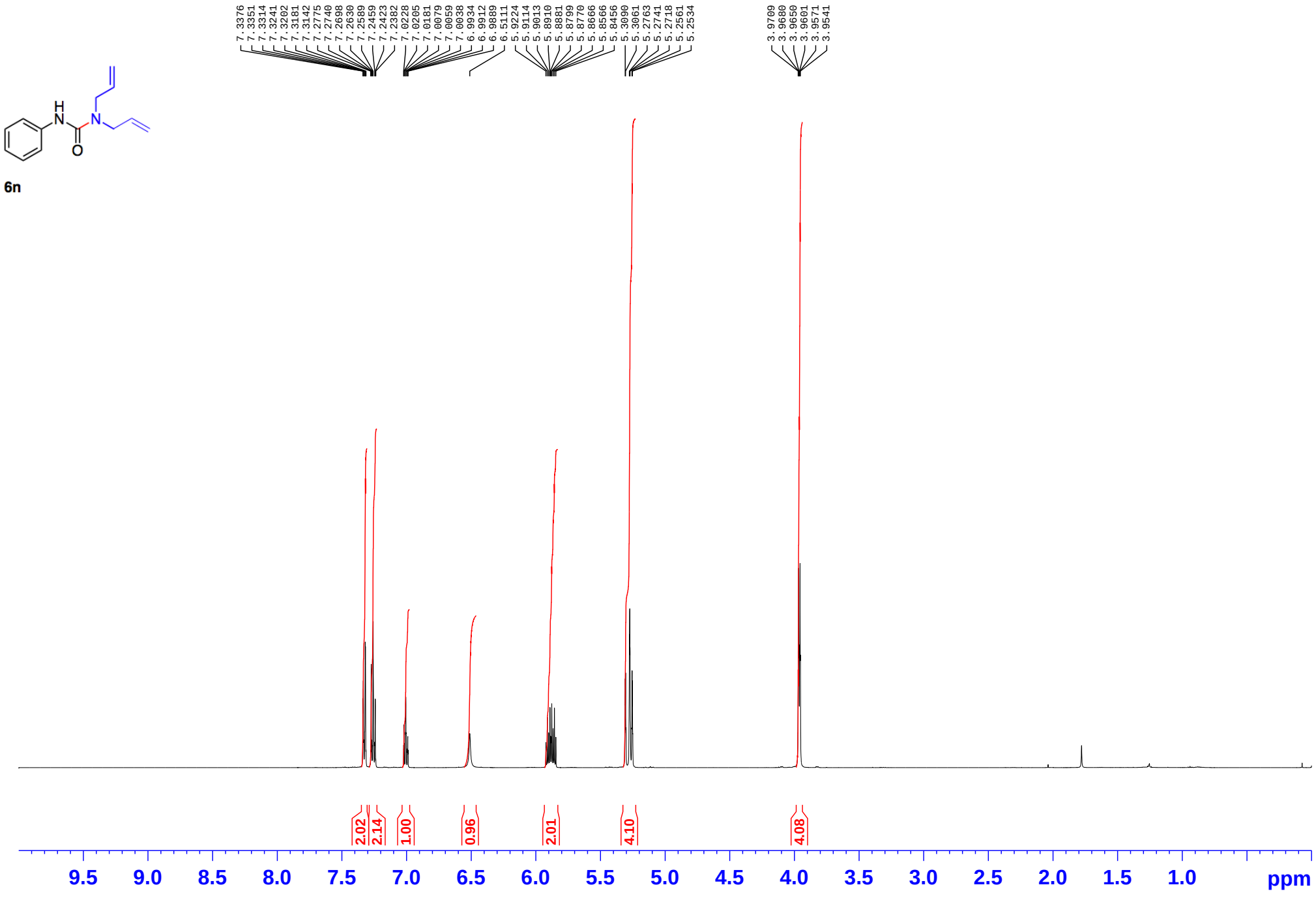
130.2574
128.7214
127.7889
127.3599
122.8171
119.1680
37.1839
H
N
O
N
Ph
6m
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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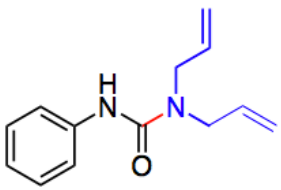
7.3241
7.3202
7.3181
7.3142
7.2775
7.2740
7.2698
7.2630
7.2589
7.2459
7.2423
7.2382
7.0228
7.0205
7.0181
7.0079
7.0059
7.0038
6.9934
6.9912
6.9889
6.5111
5.9224
5.9114
5.9013
5.8910
5.8881
5.8799
5.8770
5.8666
5.8566
5.8456
5.3090
5.3061
5.2763
5.2741
5.2718
5.2561
5.2534
3.9709
3.9680
3.9650
3.9601
3.9571
3.9541
H
N
N
O
6n
2.02
2.14
1.00
0.96
2.01
4.10
4.08
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm



6n

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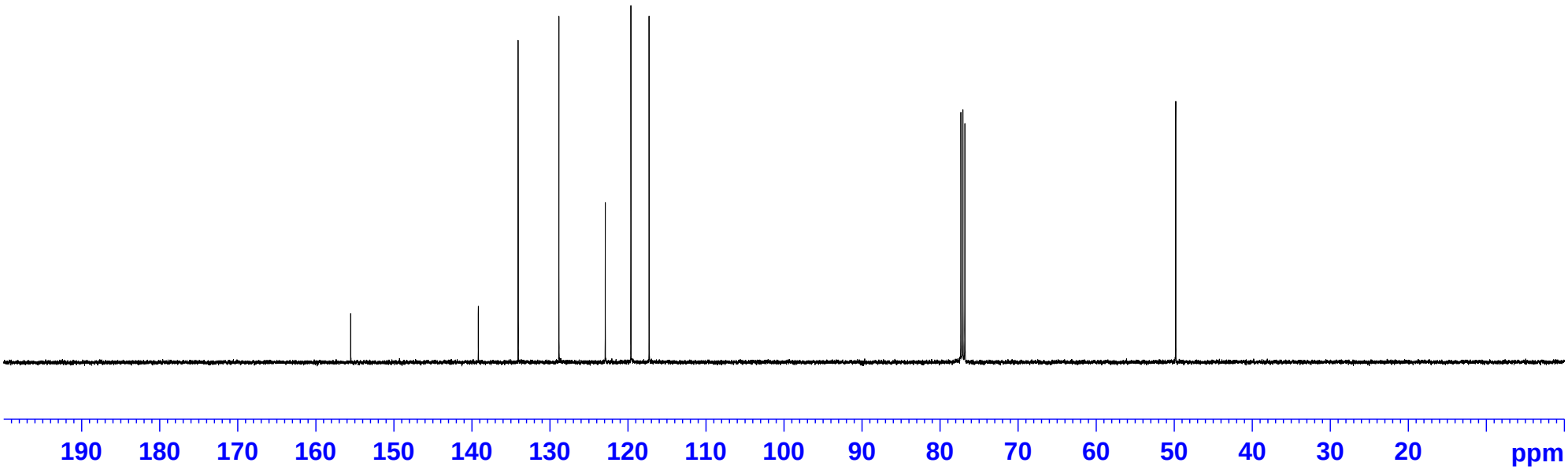
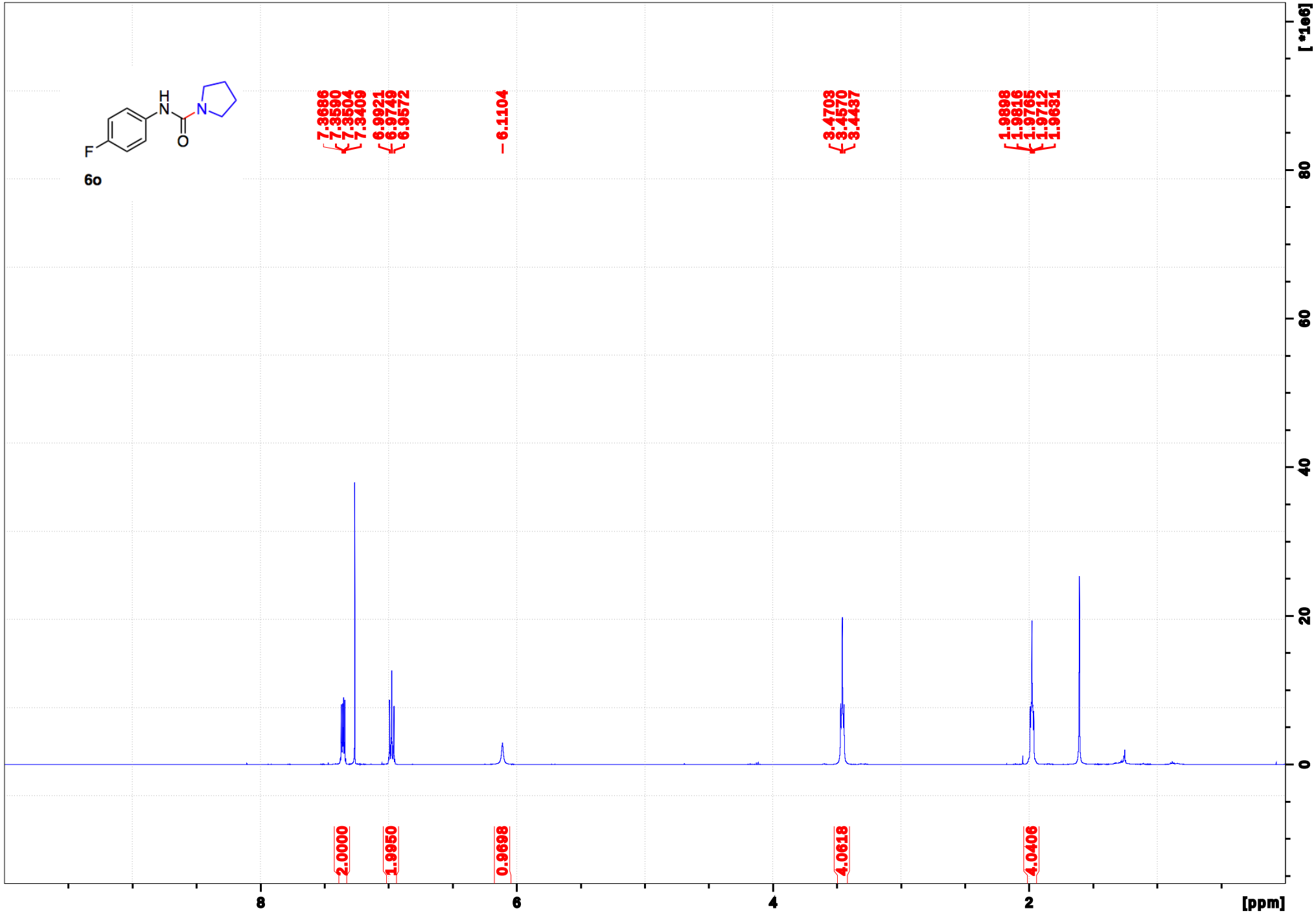
128.8424
122.9034
119.6165
117.2844
49.8061




6o
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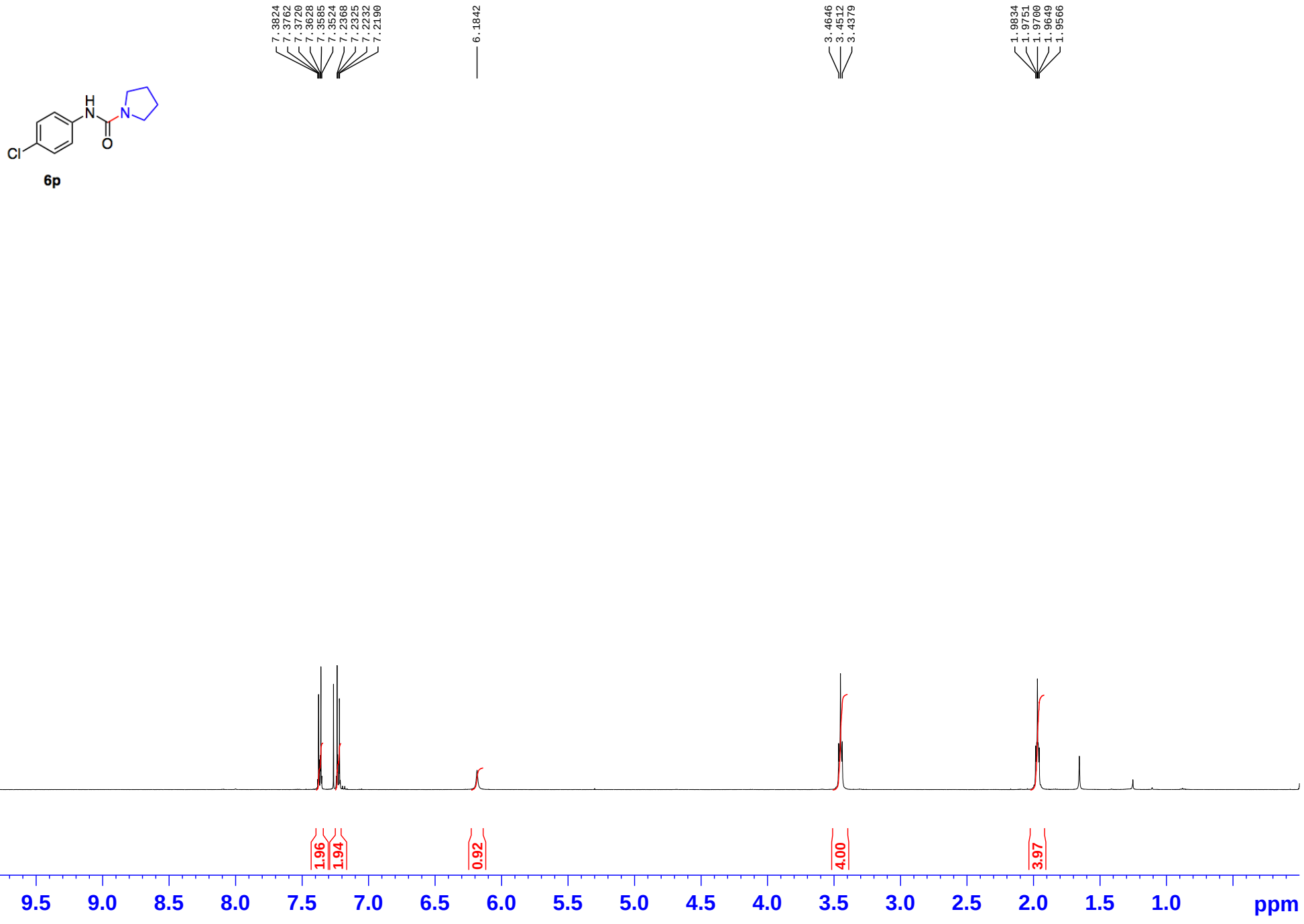
7.3504
7.3409
6.9921
6.9749
6.9572
6.1104
3.4703
3.4570
3.4437
1.9898
1.9816
1.9765
1.9712
1.9631
2.0000
1.9950
0.9698
4.0618
4.0406
[*1e6]
80
60
40
20
0
8
6
4
2
[ppm]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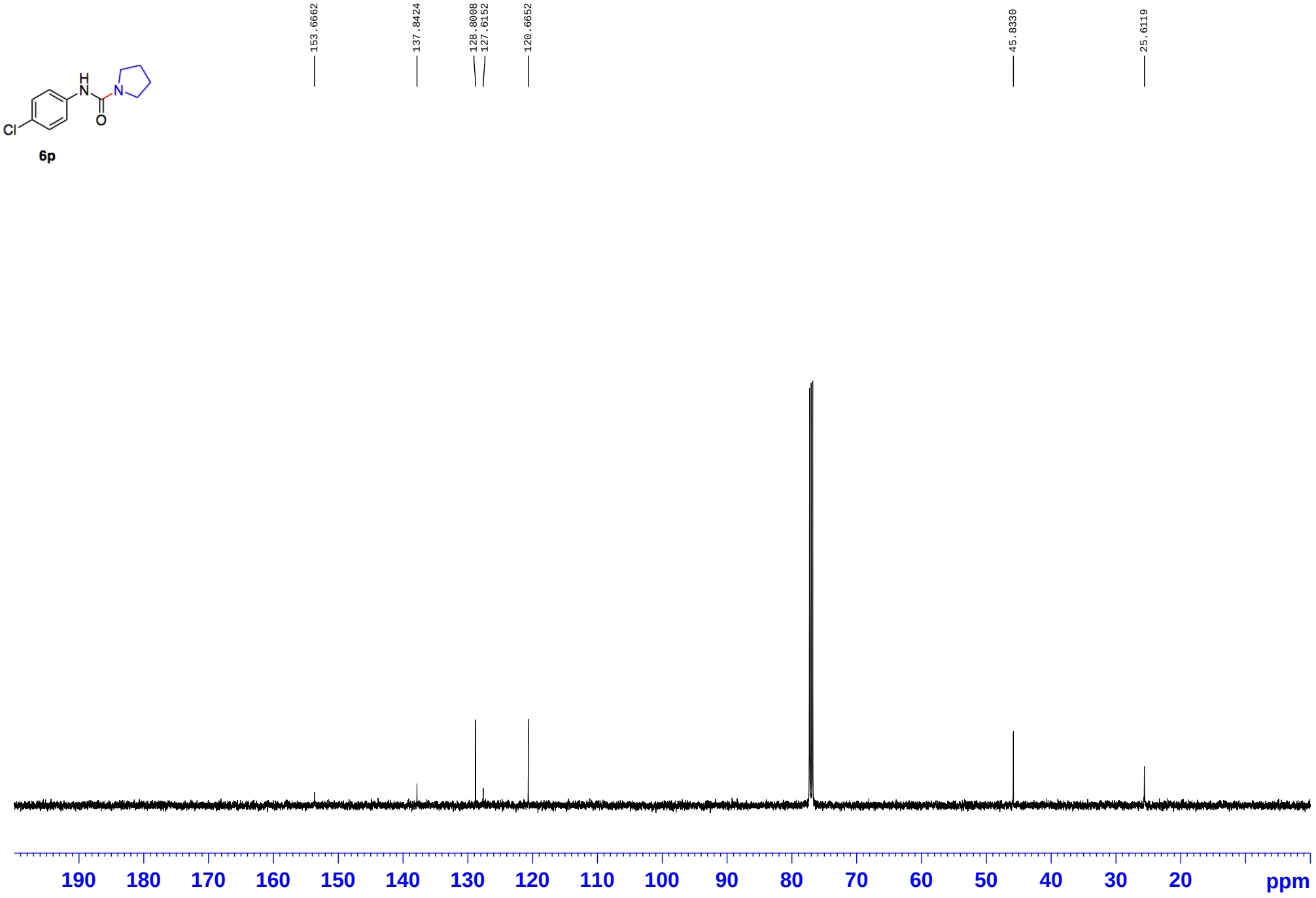
7.3585
7.3524
7.2368
7.2325
7.2232
7.2190
6.1842
3.4646
3.4512
3.4379
1.9834
1.9751
1.9700
1.9649
1.9566
H
N
N
O
Cl
6p
1.96
1.94
0.92
4.00
3.97
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm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128.8008
127.6152
120.6652
45.8330
25.6119
Cl
H
N
N
O
6p
190
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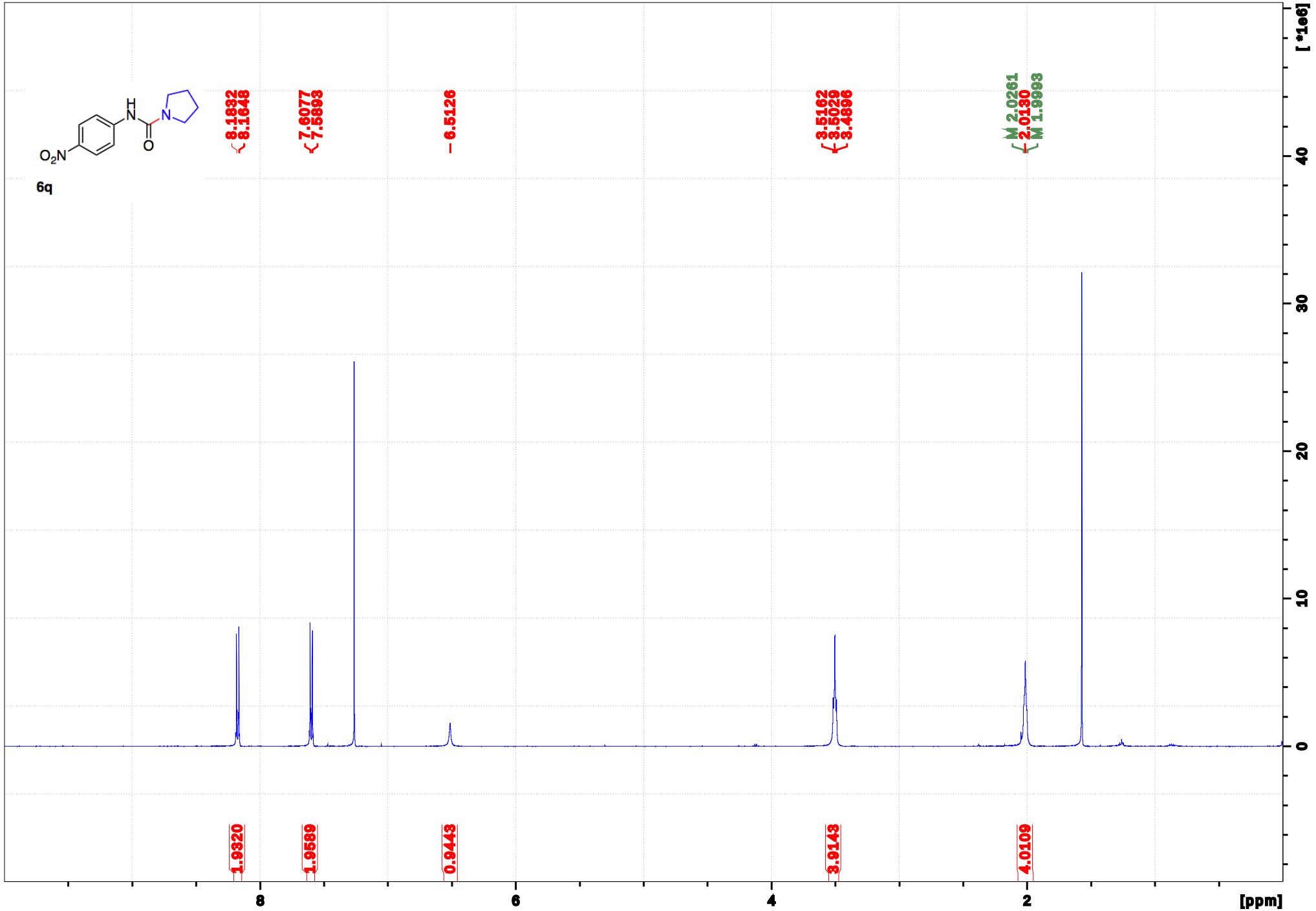
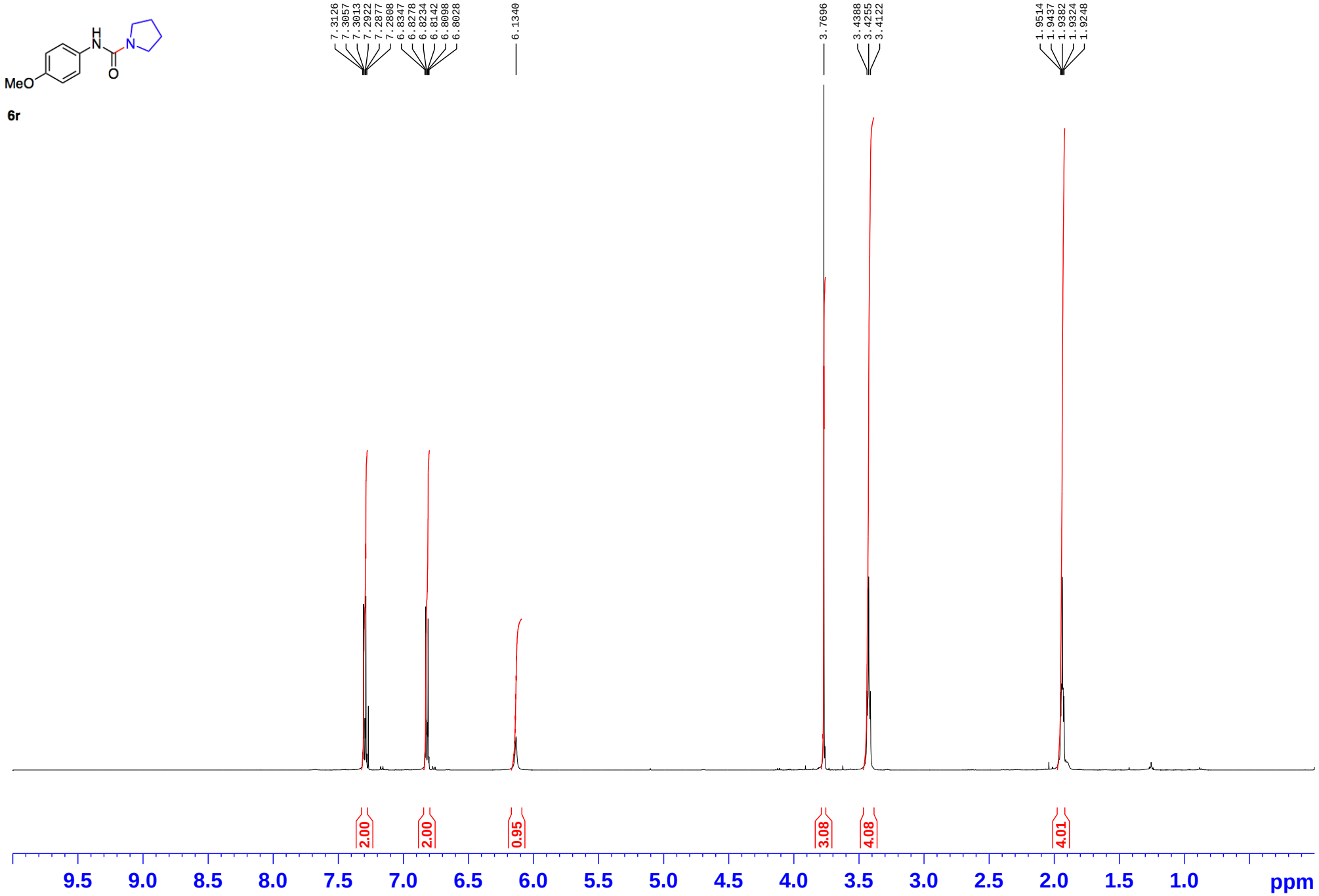
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


6q
8.1832
8.1648
7.6077
7.5893
6.5126
3.5162
3.5029
3.4896
M 2.0261
2.0130
M 1.9993
1.9320
1.9589
0.9443
3.9143
4.0109
[*1e6]
40
30
20
10
0
8
6
4
2
[ppm]


MeO
H
N
O
N
6r
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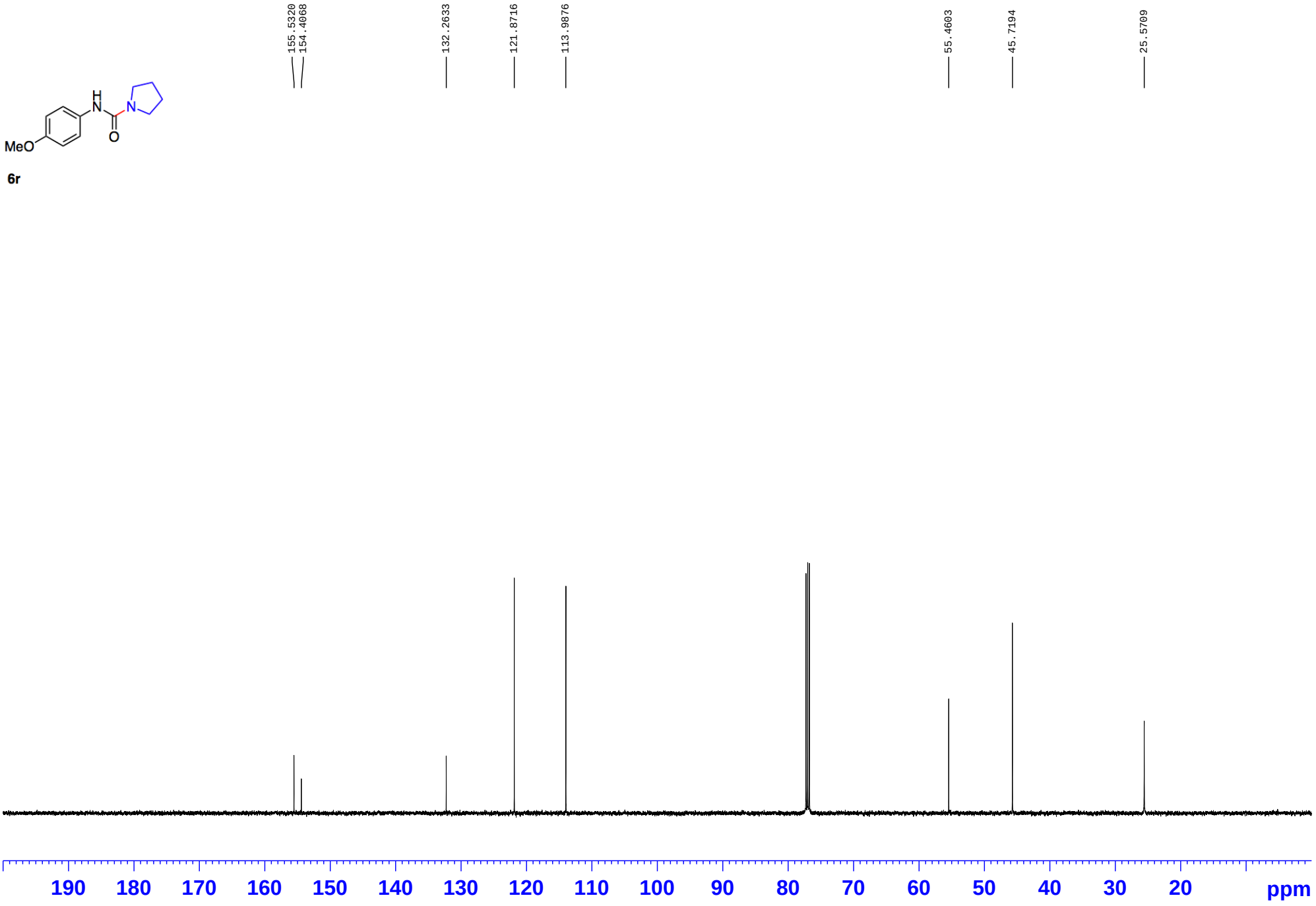
7.3057
7.3013
7.2922
7.2877
7.2808
6.8347
6.8278
6.8234
6.8142
6.8098
6.8028
6.1340
3.7696
3.4388
3.4255
3.4122
1.9514
1.9437
1.9382
1.9324
1.9248
2.00
2.00
0.95
3.08
4.08
4.01
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm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132.2633
121.8716
113.9876
55.4603
45.7194
25.5709
MeO
H
N
N
O
6r
190
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160
150
140
130
120
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80
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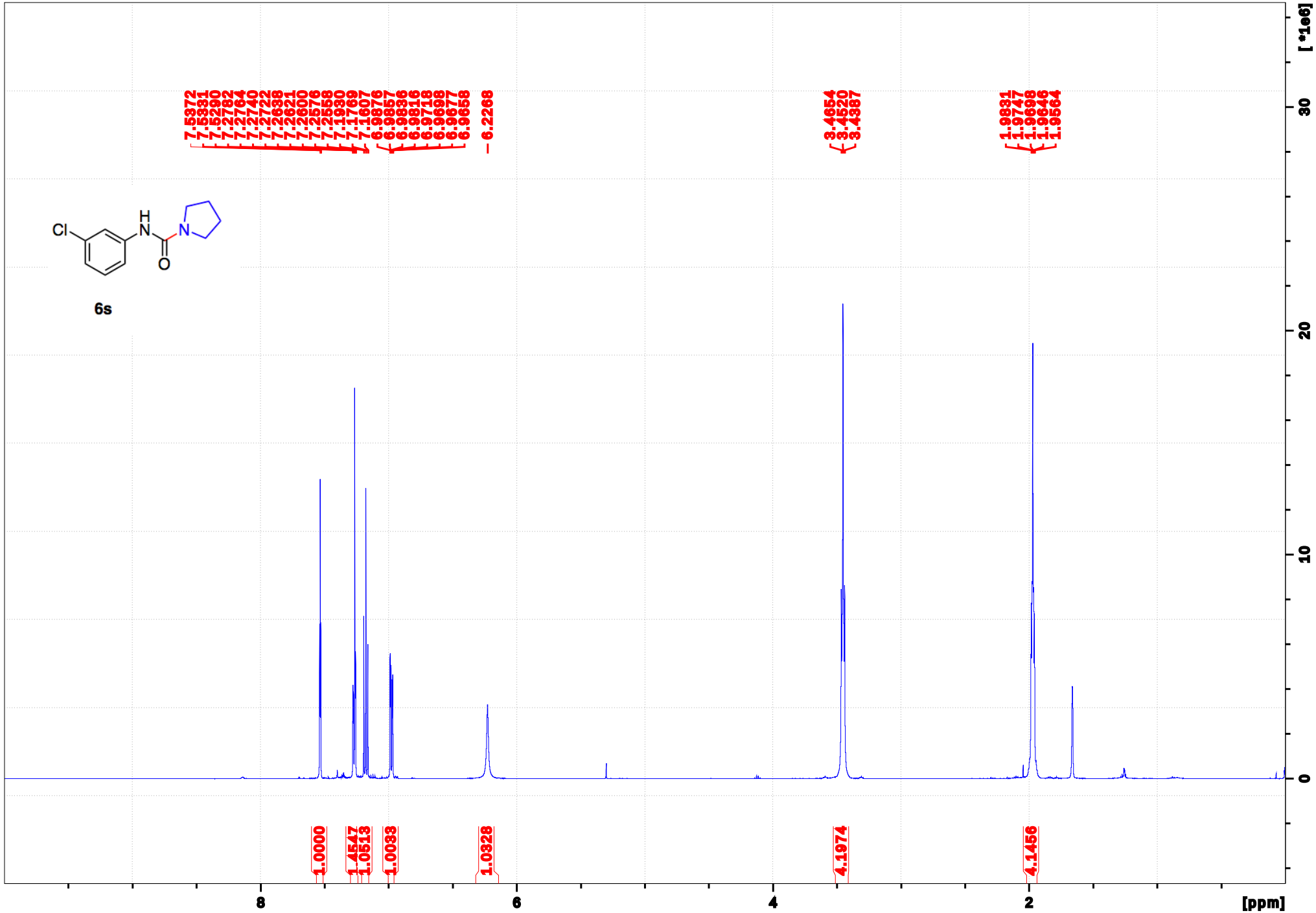
50
40
30
20
ppm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7.2621
7.2600
7.2576
7.2558
7.1930
7.1769
7.1607
6.9876
6.9857
6.9836
6.9816
6.9718
6.9698
6.9677
6.9658
6.2268
3.4654
3.4520
3.4387
1.9831
1.9747
1.9698
1.9646
1.9584
Cl
H
N
N
O
6s
1.0000
1.4547
1.0513
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4.1974
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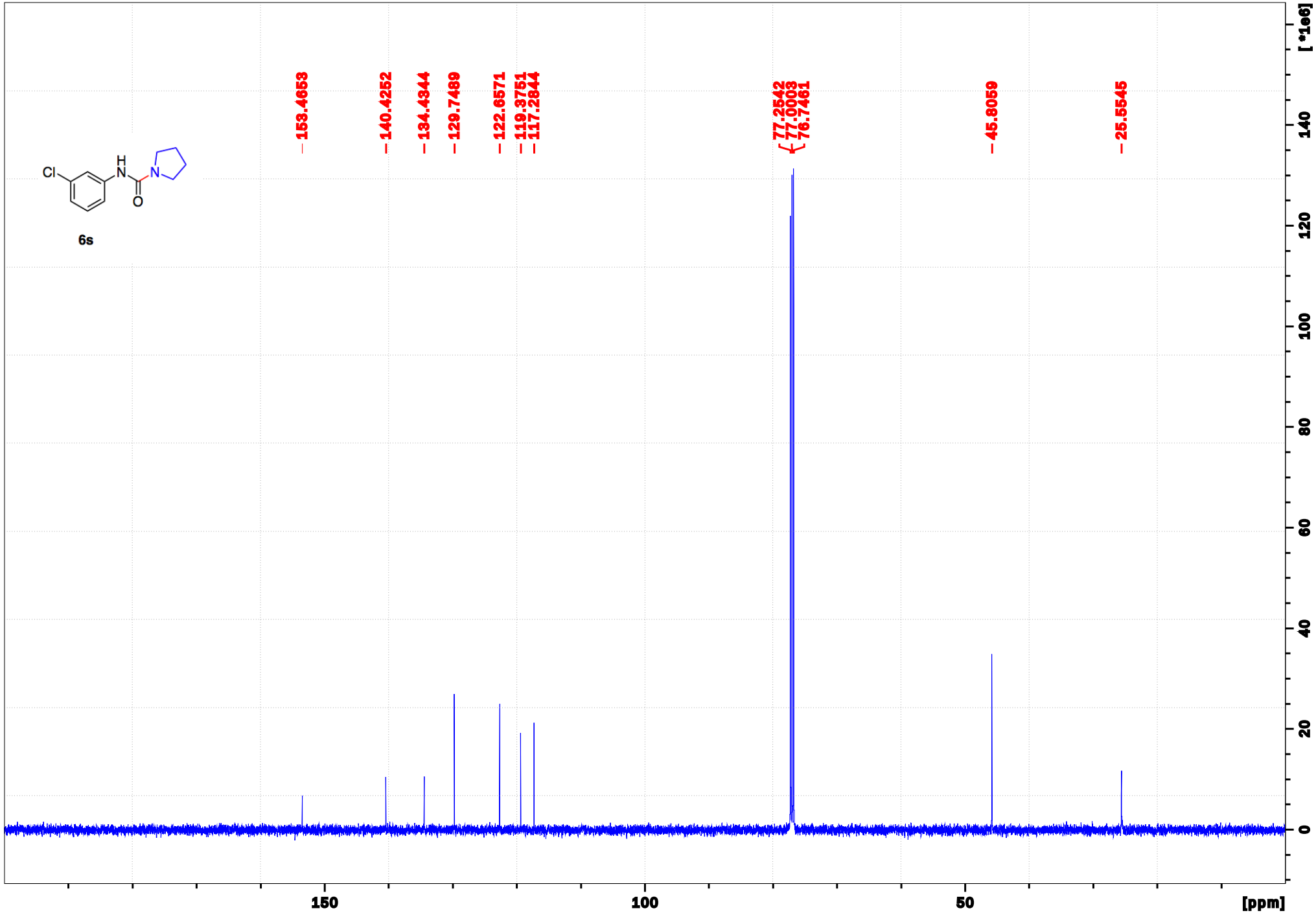
8
6
4
2
[ppm]
[*1e6]
30
20
10
0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140.4252
134.4344
129.7489
122.6571
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117.2844
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77.0003
76.7461
45.8059
25.5545
Cl
H
N
N
O
6s
150
100
50
[ppm]
[*1e6]
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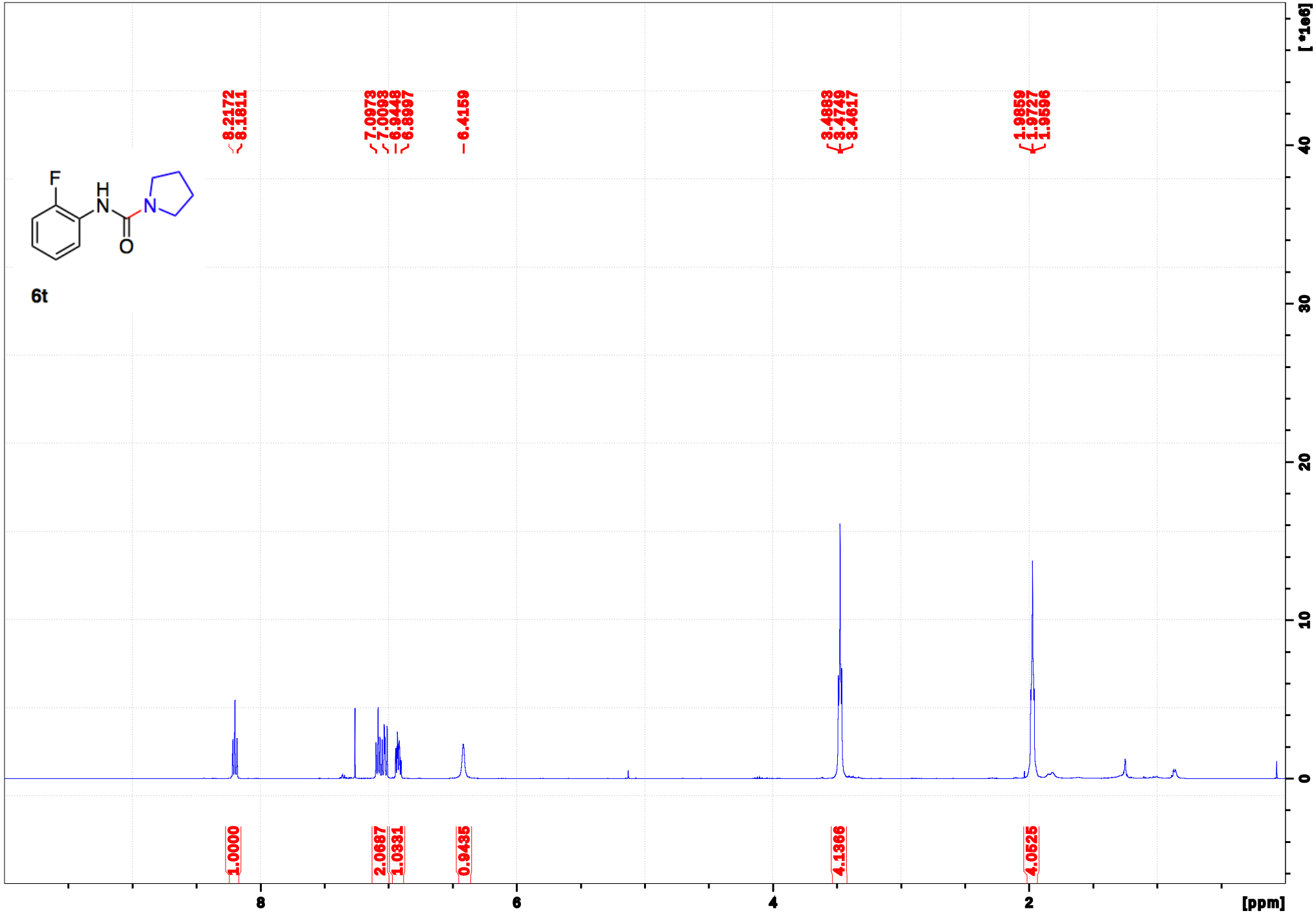
20
40
60
80
100
120
140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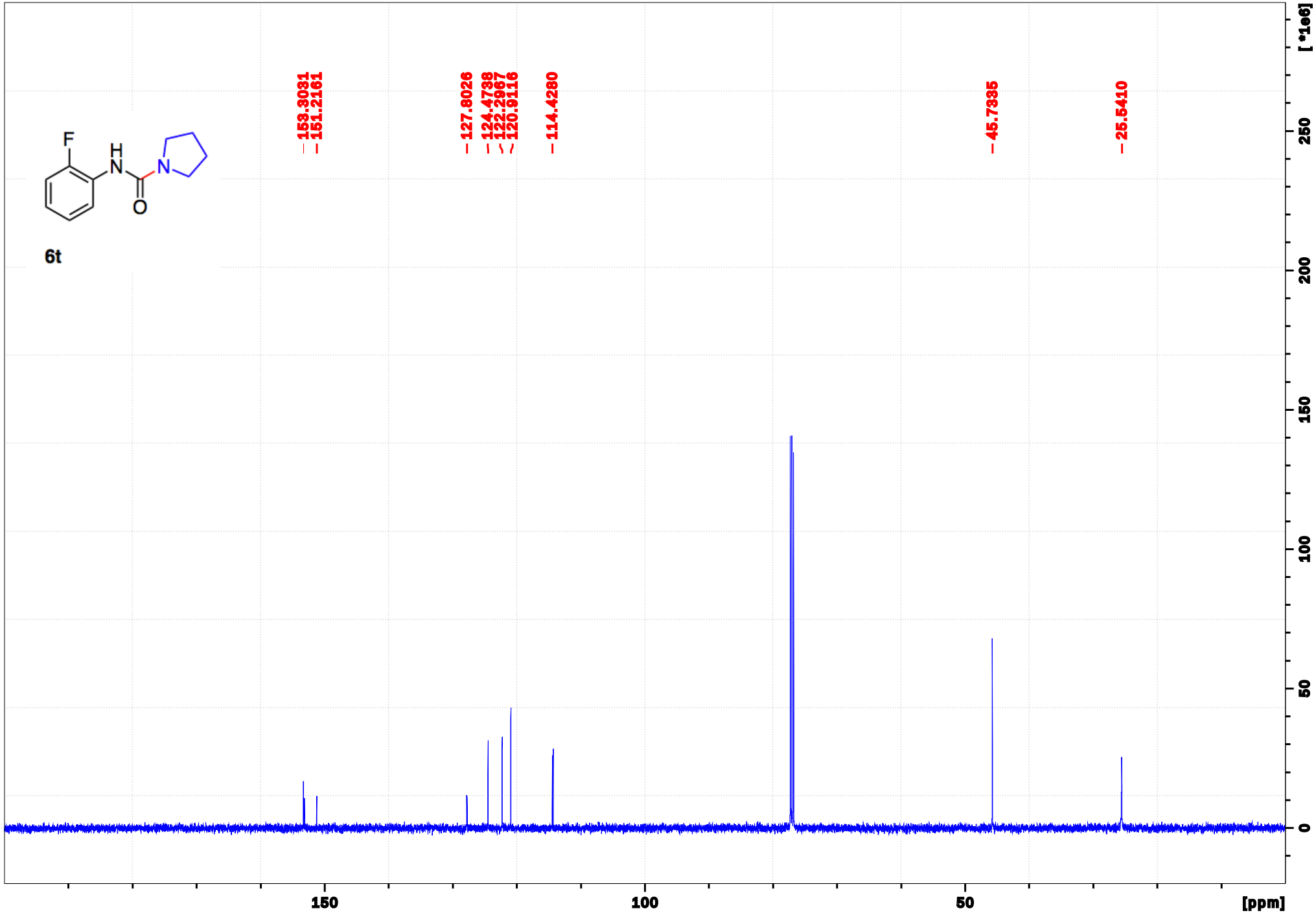
8.1811
7.0973
7.0093
6.9448
6.8997
6.4159
3.4883
3.4749
3.4617
1.9859
1.9727
1.9596
F
H
N
N
O
6t
1.0000
2.0687
1.0331
0.9435
4.1366
4.0525
8
6
4
2
[ppm]
0
10
20
30
40
[*1e6]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114.4280
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25.5410
F
H
N
N
O
6t
[*1e6]
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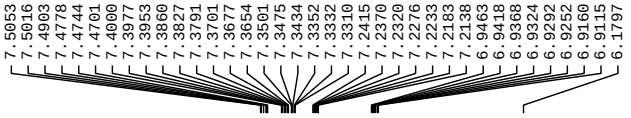
200
150
100
50
0
150
100
50
[ppm]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7.5016
7.4903
7.4778
7.4744
7.4701
7.4000
7.3977
7.3953
7.3860
7.3827
7.3791
7.3701
7.3677
7.3654
7.3501
7.3475
7.3434
7.3352
7.3332
7.3310
7.2415
7.2370
7.2320
7.2276
7.2233
7.2183
7.2138
6.9463
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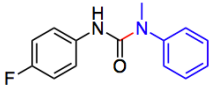
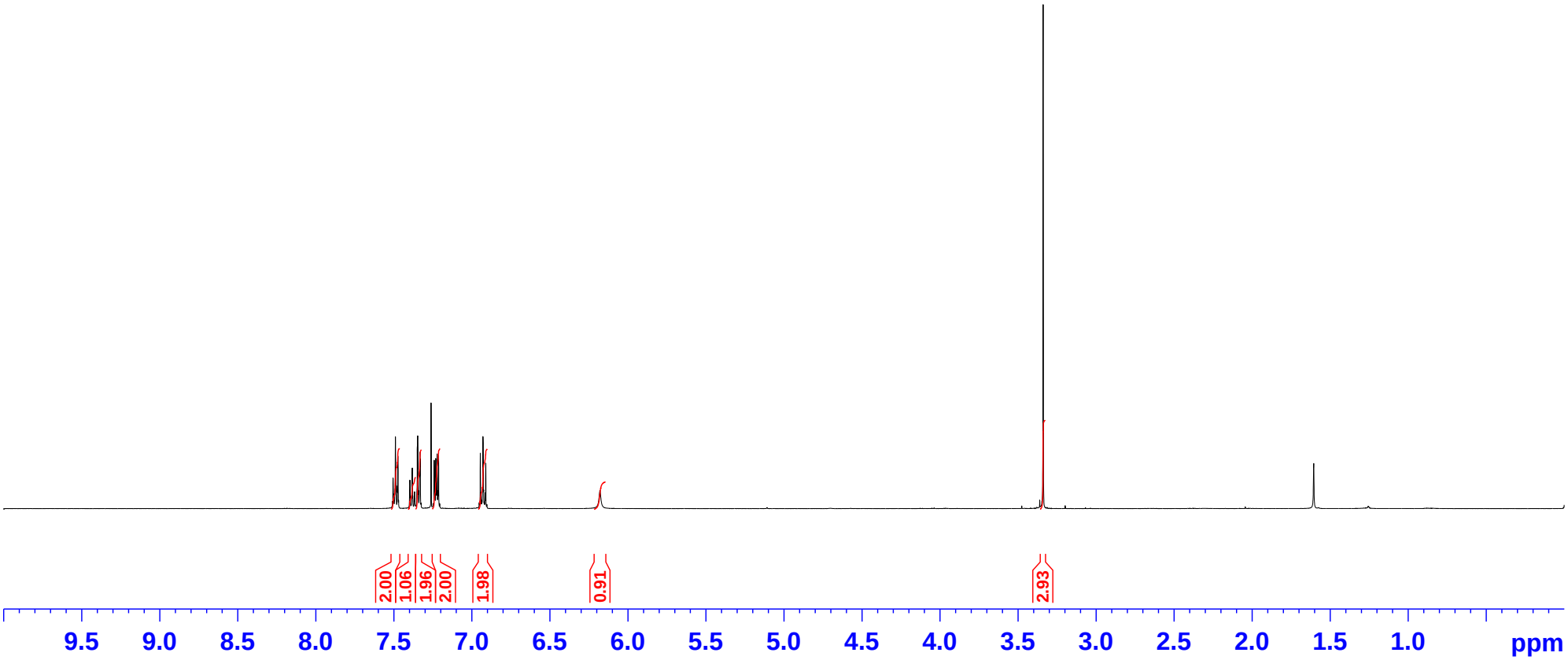
6.9368
6.9324
6.9292
6.9252
6.9160
6.9115
6.1797
3.3397


H
N
N
O
F

6u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1.96
2.00
1.98
0.91
2.93
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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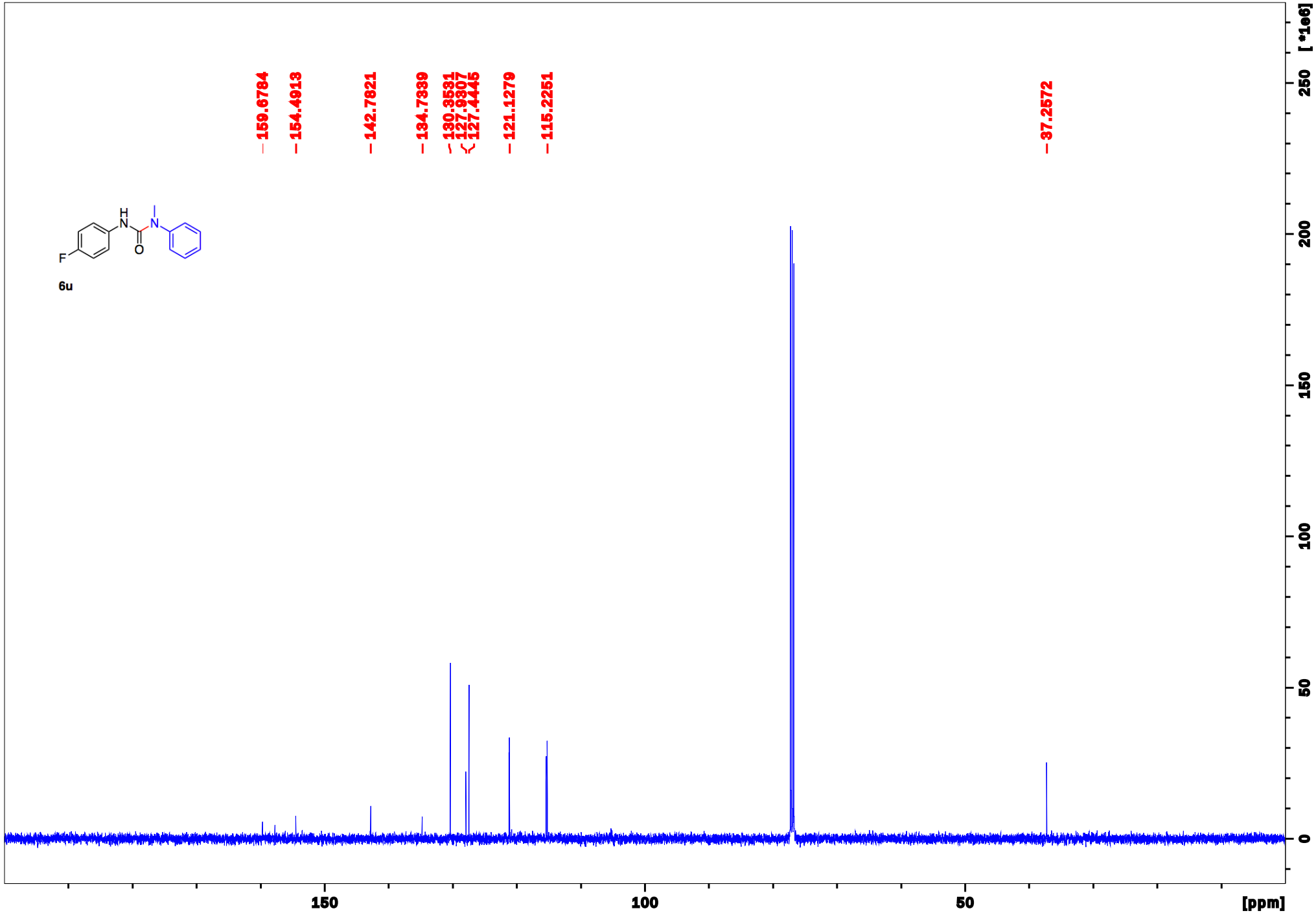
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


159.6784
154.4913
142.7821
134.7339
130.3531
127.9307
127.4445
121.1279
115.2251
37.2572
6u
150
100
50
[ppm]
0
50
100
150
200
250
[*1e6]