Supporting Information

Small Molecule Antagonists of the Nuclear Androgen Receptor for the Treatment of Castration-Resistant Prostate Cancer

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Contents:

1. Biological Materials and Methods

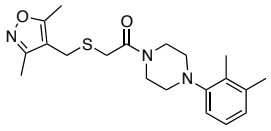
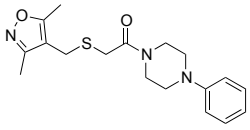
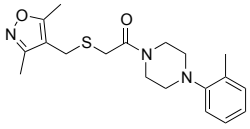
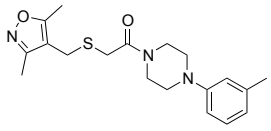
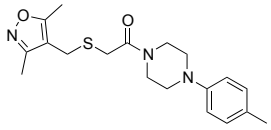
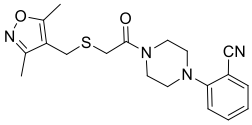
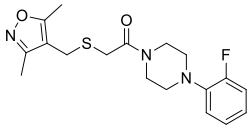
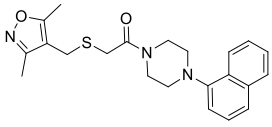
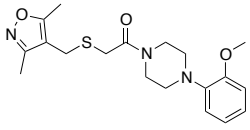
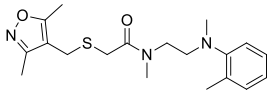
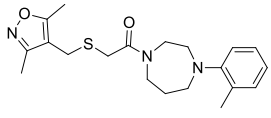
Materials

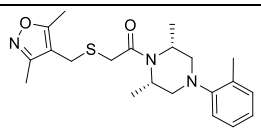
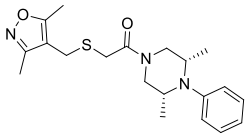
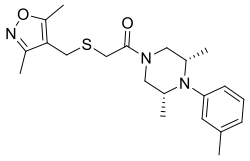
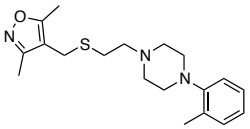
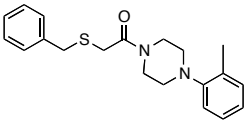
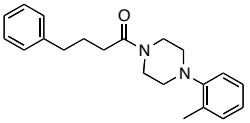
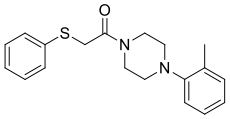
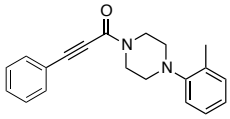
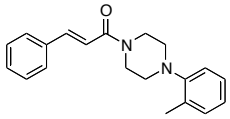
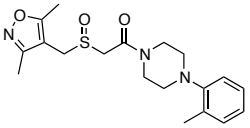
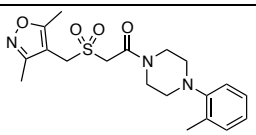
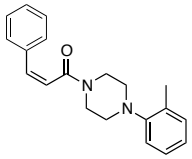
Phosphate buffered saline (PBS) solution was purchased from Fisher Scientific (MA, USA). Trypsin-EDTA solution, dimethyl sulfoxide (DMSO), Roswell Park Memorial Institute (RPMI) 1640 medium, ethanol (200 proof), puromycin powder, and G418 powder were purchased from Sigma-Aldrich (MO, USA). Fetal bovine Serum (FBS), penicillin-streptomycin solution were purchased from Invitrogen (NY, USA). Dual-Luciferase® Reporter Assay System was purchased from Promega (WI, USA). PSA6.1--luc plasmid was a gift from Dr. Marianne Sadar at the University of British Columbia (BC, CA) and pRL-TK Renilla luciferase reporter plasmid was purchased from Promega (WI, USA). The C4-2 castration-resistant prostate cancer cell line was kindly provided by Dr. Leland W. K. Chung (Cedars-Sinai Medical Center).

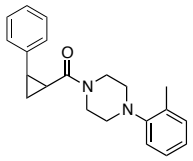
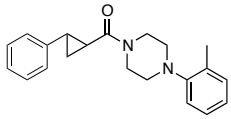
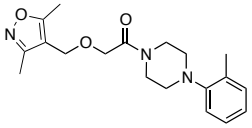
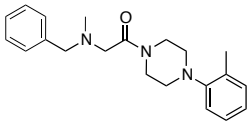
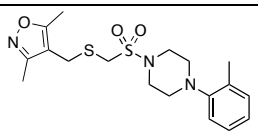
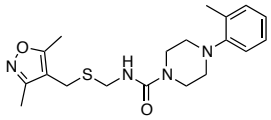
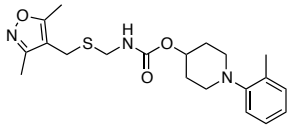
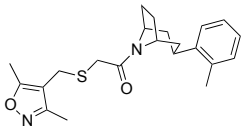
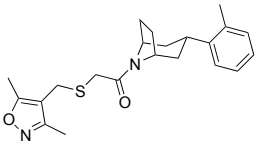
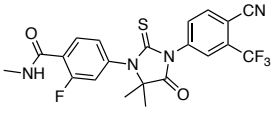
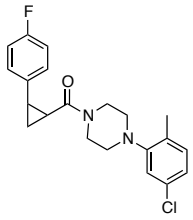
Luciferase Assay

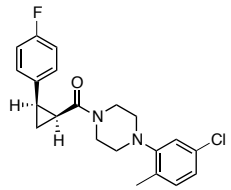
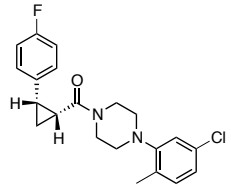
The C4-2-PSA-rl stable cell line was generated by transfection with PSA6.1--luc and pRL-TK followed by stable selection using G418 and puromycin. C4-2-PSA-rl stable cells were cultured in RPMI 1640 medium with 10% FBS, 1% penicillin-streptomycin, 1% L-glutamine, 10 mg/mL puromycin, and 50 mg/mL G418. C4-2-PSA-rl cells were seeded in 24-well plates such that they reached 75-80% cell monolayer density after 24 h. C4-2-PSA-rl cells were then treated for 24 h with 0, 0.2, 0.8, 3.2, 12.8, or 25 μM of each compound dissolved in DMSO (0.8% DMSO/well) in the presence of 1 nM synthetic androgen R1881, with each experimental condition in triplicate. The cells were also treated in parallel with 12.8 μM compound **1** and 12.8 μM MDV3100 as positive controls. Each compound was tested in at least two independent experiments. Luciferase activity was assayed using the Dual-Luciferase® Reporter Assay System (Promega) using LMax II Microplate Reader (Molecular Devices). The luciferase assay results were acquired using SoftMax Pro5.45 software (Molecular Devices) and analyzed using GraphPad Prism. PSA6.1-luc activity was normalized to the Renilla luciferase activity.

Table S1. Overview of analog structures and biochemical activities.

Entry	Analog	Structure	EC_{50} [μM]
1	1		7.3±2.5[c]
2	5a		>25[a]
3	5b		14.5±3.2[b]
4	5c		>25[a]
5	5d		>25[a]
6	5e		12.0±1.6[b]
7	5f		12.6±7.7[b]
8	5g		11.1±5.3[b]
9	5h		>25[a]
10	5i		18.4±9.2[b]
11	5j		11.1±3.3[a]

12	5k		3.1±1.1[a]
13	5l		14.7±4.4[a]
14	5m		16.6±4.8[b]
15	6		10.8±5.7[b]
16	7		13.7±0.8[b]
17	8		14.4±3.7[b]
18	9		>25[a]
19	10		20.3±11.6[a]
20	11		>25[a]
21	12		>25[b]
22	13		16.1±3.3[b]
23	14		12.7±0.8[a]

24	15		2.9±1.0[b]
25	16		>25[b]
26	18a		>25[b]
27	18b		>25[b]
28	18c		7.2±2.7[c]
29	20a		>25[a]
30	20b		>25[c]
31	26a		7.7±1.6[b]
32	26b		7.9±2.8[a]
33	Enzalutamide		1.1±0.5[e]
34	27		2.7±1.1[d]

35	**(1*S*,2*R*)-27**		**1.7+0.2[a]**
36	**(1*R*,2*S*)-27**		**15.2±3.3[a]**

Assay repeats: [a]n=2; [b]n=3; [c]n=4; [d]n=5; [e]n=6;

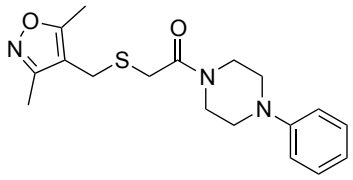
2. Chemistry

2.1 General

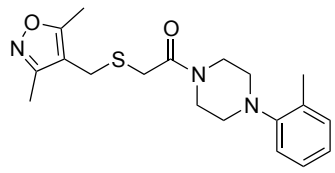
Moisture and air-sensitive reactions were performed under N_2 or Ar atmosphere and glassware used for these reactions was flamed dried and cooled under N_2 or Ar prior to use. THF and Et_2O were distilled from sodium/benzophenone ketyl. DMF and CH_2Cl_2 were distilled from CaH_2. 1,4-Dioxane was purchased from Acros (Sure/Seal bottle) and used as received. Et_3N was distilled from CaH_2 and stored over KOH. Toluene was purified by passage through an activated alumina filtration system. Melting points were determined using a Mel-Temp II instrument and are not corrected. Infrared spectra were determined using a Smiths Detection IdentifyIR FT-IR spectrometer. High-resolution mass spectra were obtained on a Micromass UK Limited, Q-TOF Ultima API, Thermo Scientific Exactive Orbitrap LC-MS. Automated column chromatography was done using an Isco Combiflash Rf. ^1H and ^{13}C NMR spectra were obtained on Bruker Advance 300 MHz, 400 MHz, or 500 MHz instruments. Chemical shifts (δ) were reported in parts per million with the residual solvent peak used as an internal standard, δ $^1H/^{13}C$ (Solvent): 7.26/77.00 ($CDCl_3$); 2.05/29.84 (acetone-d6); 2.50/39.52 (DMSO-d6), 3.31/49.00 (CD_3OD); and are tabulated as follows: chemical shift, multiplicity (s = singlet, brs = broad singlet, d = doublet, brd = broad doublet, t = triplet, app t = apparent triplet, q = quartet, m = multiplet), number of protons, and coupling constant(s). ^{13}C NMR spectra were obtained at 75 MHz, 100 MHz, or 125 MHz using a proton-decoupled pulse sequence and are tabulated by observed peak. $CDCl_3$ was filtered through dried basic alumina prior to use. Thin-layer chromatography was performed using pre-coated silica gel 60 F_{254} plates (EMD, 250 μm thickness) and visualization was accomplished with a 254 nm UV light and by staining with a PMA solution (5 g of phosphomolybdic acid in 100 mL of 95% EtOH), Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}•4H_2O$ and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 N H_2SO_4 solution) or a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution). Chromatography on SiO_2 (Silicycle, Silia-P Flash Silica Gel or SiliaFlash® P60, 40-63 μm) was used to purify crude reaction mixtures. Final products were of >95% purity as analyzed by RP HPLC (Alltech Prevail C-18, 100 × 4.6 mm, 1 mL/min, CH_3CN, H_2O and 0.1% TFA) with UV (210, 220 and 254 nm), ELS (nebulizer 45 ^oC, evaporator 45 ^oC, N_2 flow 1.25 SLM), and

MS detection using a Thermo Scientific Exactive Orbitrap LC-MS (ESI positive). All other materials were obtained from commercial sources and used as received.

2.2 Experimental Part:

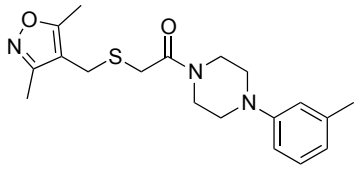


2-(((3,5-Dimethylisoxazol-4-yl)methyl)thio)-1-(4-phenylpiperazin-1-yl)ethanone (**5a**). To a solution of 2-(((3,5-dimethylisoxazol-4-yl)methyl)thio)acetic acid **3a** (0.0200 g, 0.0994 mmol) in CH_2Cl_2 (1.25 mL) was added 1-phenylpiperazine **4a** (0.0190 g, 0.119 mmol) and Et_3N (41 µL, 0.298 mmol). The reaction mixture was cooled to 0 °C, treated with T3P (50 wt. % solution in EtOAc, 105 µL, 0.149 mmol), allowed to warm to room temperature, stirred for 2 d, diluted with CH_2Cl_2 and washed with satd. aqueous NH_4Cl, satd. aqueous $NaHCO_3$, brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (ISCO, 12 g column, liquid load in CH_2Cl_2, EtOAc/hexanes gradient (10-100%), product eluted at 60%) to give product **5a** (0.0330 g, 0.0955 mmol, 96%, 100% pure by ELSD) as a colorless solid: Mp 74-75 °C; IR (ATR) 2856, 2802, 1627, 1599, 1496, 1440, 1416, 1229, 1141, 1034, 909, 765, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.21 (m, 1 H), 6.89-6.83 (m, 3 H), 3.72 (app t, 2 H, J = 5.2 Hz), 3.56 (s, 2 H), 3.56-3.54 (m, 2 H), 3.18 (s, 2 H), 3.15-3.10 (m, 2 H), 2.34 (s, 3 H), 2.23 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 165.8, 158.6, 149.8, 128.2, 119.6, 115.6, 108.7, 48.5, 48.3, 45.3, 40.7, 31.0, 22.7, 10.0, 9.1; HRMS (ESI) *m/z* calcd for $C_{18}H_{24}N_3O_2S$ ($[M+H]^+$) 346.1584, found: 346.1571.



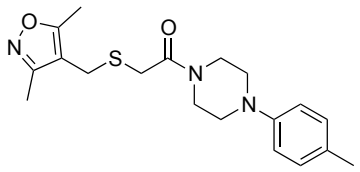
2-(((3,5-Dimethylisoxazol-4-yl)methyl)thio)-1-(4-(*o*-tolyl)piperazin-1-yl)ethanone (**5b**). To a solution of 2-(((3,5-dimethylisoxazol-4-yl)methyl)thio)acetic acid (**3a**, 0.0200

g, 0.0994 mmol) in CH_2Cl_2 (1.25 mL) was added 1-(*o*-tolyl)piperazine **4b** (0.0210 g, 0.119 mmol) and Et_3N (41 μL, 0.298 mmol). The reaction mixture was cooled to 0 °C, treated with T3P (50 wt.% solution in EtOAc, 105 μL, 0.149 mmol), allowed to warm to room temperature, stirred for 2 d, diluted with CH_2Cl_2 and washed with satd. aqueous NH_4Cl, satd. aqueous $NaHCO_3$, brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by chromatography on SiO_2 (ISCO, 12 g column, liquid load in CH_2Cl_2, EtOAc/hexanes gradient (10-100%), product eluted at 40%) to give **5b** (0.0348 g, 0.0968 mmol, 97%, 100% pure by ELSD) as a colorless solid: Mp 89-91 °C; IR (ATR) 2959, 2828, 1631, 1492, 1430, 1261, 1226, 1138, 1036, 979, 959, 776, 726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (dd, 2 H, *J* = 9.0, 7.5 Hz), 7.01 (dd, 2 H, *J* = 14.1, 9.0 Hz), 3.76 (app t, 2 H, *J* = 4.9 Hz), 3.63 (s, 2 H), 3.59 (app t, 2 H, *J* = 4.9 Hz), 3.24 (s, 2 H), 2.93 (app t, 2 H, *J* = 4.9 Hz), 2.88 (app t, 2 H, *J* = 4.9 Hz), 2.43 (s, 3 H), 2.32 (s, 3 H), 2.30 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 165.8, 158.7, 149.6, 131.7, 130.2, 125.7, 122.8, 118.1, 108.7, 50.8, 50.6, 46.0, 41.3, 31.1, 22.7, 16.7, 10.0, 9.1; HRMS (ESI) *m/z* calcd for $C_{19}H_{26}N_3O_2S$ ($[M+H]^+$) 360.1740, found 360.1725.

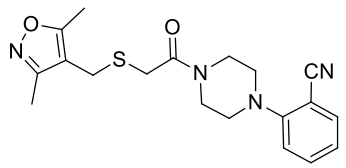


2-(((3,5-Dimethylisoxazol-4-yl)methyl)thio)-1-(4-(*m*-tolyl)piperazin-1-yl)ethanone (**5c**). A solution of 2-(((3,5-dimethylisoxazol-4-yl)methyl)thio)acetic acid (**3a**, 0.0200 g, 0.0994 mmol) in CH_2Cl_2 (1.25 mL) was added 1-(*m*-tolyl)piperazine (**4c**, 21 μL, 0.119 mmol), Et_3N (41 μL, 0.298 mmol). The reaction mixture was cooled to 0 °C, treated with T3P (50 wt.% solution in EtOAc, 105 μL, 0.149 mmol), allowed to warm to room temperature, stirred for 2 d, diluted with CH_2Cl_2 and washed with satd. aqueous NH_4Cl, satd. aqueous $NaHCO_3$, brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (ISCO, 12 g column, liquid load in CH_2Cl_2, EtOAc/hexanes gradient (10-100%), eluted at 60%) to give **5c** (0.0343 g, 0.954 mmol, 96%, 99.5% pure by ELSD) as a yellow oil: IR (ATR) 2918, 2819, 1635, 1600, 1493, 1424, 1244, 1192, 1145, 995, 957, 775, 729, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (app t, 1 H, *J* = 7.8 Hz), 6.75-6.72 (m, 3 H), 3.76 (app t, 2 H, *J* = 5.2 Hz),

3.61 (s, 2 H), 3.60-3.58 (m, 2 H), 3.23 (s, 2 H), 3.17 (ddd, 4 H, J = 5.5, 5.2, 5.0 Hz), 2.41 (s, 3 H), 2.32 (s, 3 H), 2.28 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 165.8, 158.6, 149.8, 138.0, 128.1, 120.5, 116.5, 112.8, 108.7, 48.6, 48.5, 45.3, 40.8, 31.0, 22.7, 20.7, 10.0, 9.1; HRMS (ESI) *m/z* calcd for $C_{19}H_{26}N_3O_2S$ ($[M+H]^+$) 360.1740, found: 360.1725.

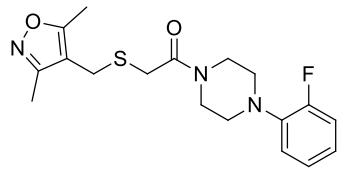


2-(((3,5-Dimethylisoxazol-4-yl)methyl)thio)-1-(4-(*p*-tolyl)piperazin-1-yl)ethanone (**5d**). A solution of 2-(((3,5-dimethylisoxazol-4-yl)methyl)thio)acetic acid (**3a**, 0.0200 g, 0.0994 mmol) in CH_2Cl_2 (1.25 mL) was added 1-(*p*-tolyl)piperazine (**4d**, 21 μL, 0.119 mmol), Et_3N (41 μL, 0.298 mmol). The reaction mixture was cooled to 0 °C, treated with T3P (50 wt.% solution in EtOAc, 105 μL, 0.149 mmol), allowed to warm to room temperature, stirred for 2 d, diluted with CH_2Cl_2, washed with satd. aqueous NH_4Cl, satd. aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (ISCO, 12 g column, liquid load in CH_2Cl_2, EtOAc/hexanes gradient ((10-100%), eluted at 60%) to give **5d** (0.0266 g, 0.0740 mmol, 74%, 100% pure by ELSD) as a red solid: Mp 83-85 °C; IR (ATR) 2855, 2801, 1627, 1514, 1440, 1416, 1261, 1230, 1142, 1043, 960, 815, 724 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, 2 H, J = 8.1 Hz), 6.85 (d, 2 H, J = 8.1 Hz), 3.77 (app t, 2 H, J = 4.7 Hz), 3.61-3.58 (m, 4 H), 3.23 (s, 2 H), 3.13 (ddd, 4 H, J = 5.6, 5.5, 4.7 Hz), 2.41 (s, 3 H), 2.28, (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 166.8, 159.7, 148.7, 130.3, 129.8, 117.0, 109.7, 50.1, 49.9, 46.4, 41.8, 32.1, 23.7, 20.4, 11.0, 10.1; HRMS (ESI) *m/z* calcd for $C_{19}H_{26}N_3O_2S$ ($[M+H]^+$) 360.1740, found 360.1725.



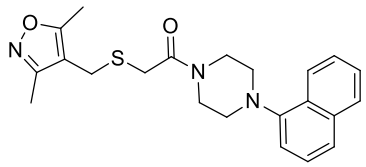
2-(4-(2-(((3,5-Dimethylisoxazol-4-yl)methyl)thio)acetyl)piperazin-1-yl)benzonitrile (**5e**). To a solution of ([(3,5-dimethylisoxazol-4-yl)methyl]thio)acetic acid (**3a**, 0.0280 g,

0.132 mmol) in CH_2Cl_2 (1.3 mL) was added 2-(piperazin-1-yl)benzonitrile (**4e**, 0.0253 g, 0.132 mmol) and Et_3N (56 μL, 0.400 mmol). The reaction mixture was cooled to 0 °C, treated with T3P (50 wt.% solution in EtOAc, 140 μL, 0.200 mmol), allowed to warm to room temperature, stirred for 20 h, diluted with CH_2Cl_2 and washed with satd. aqueous NH_4Cl, satd. aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (95:5, CH_2Cl_2/MeOH) to give **5e** (0.0390 g, 0.105 mmol, 80%, 99.9% pure by ELSD) as a yellow solid: Mp 142-143 °C; IR (neat) 2919, 2216, 1637, 1593, 1420, 1232 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, 1 H, J = 7.6, 1.6 Hz), 7.51 (ddd, 1 H, J = 8.4, 7.6, 1.6 Hz), 7.09 (dt, 1 H, J = 7.6, 0.9 Hz), 7.02 (d, 1 H, J = 8.4 Hz), 3.82 (app t, 2 H, J = 4.8 Hz), 3.67 (app t, 2 H, J = 4.8 Hz), 3.62 (s, 2 H), 3.24 (s, 2 H), 3.24-3.21 (m, 2 H) 3.15 (app t, 2 H, J = 5.4 Hz), 2.41 (s, 3 H), 2.28 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 166.7, 159.6, 154.9, 134.3, 133.9, 122.7, 118.9, 118.0, 109.7, 106.7, 51.9, 51.1, 46.6, 41.8, 32.1, 23.7, 11.0, 10.1; HRMS (ESI) *m/z* calcd for $C_{19}H_{23}N_4O_2S$ ($[M+H]^+$) 371.1542, found 371.1536.



2-(((3,5-Dimethylisoxazol-4-yl)methyl)thio)-1-(4-(2-fluorophenyl)piperazin-1-yl)ethan-1-one (**5f**). To a solution of 2-(((3,5-dimethylisoxazol-4-yl)methyl)thio)acetic acid (**3a**, 0.0758 g, 0.377 mmol) in CH_2Cl_2 (3.8 mL) was added 1-(2-fluorophenyl)-piperazine (**4f**, 0.0814 g, 0.452 mmol) and Et_3N (262 μL, 1.88 mmol). The reaction mixture was cooled to 0 °C, treated with T3P (50 wt. % solution in EtOAc, 399 μL, 0.565 mmol), allowed to warm to room temperature, stirred for 20 h, diluted with CH_2Cl_2, and washed with satd. aqueous NH_4Cl solution, satd. aqueous $NaHCO_3$ solution, and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (3:2, EtOAc/hexanes, base washed with 0.1% Et_3N prior to use) to give **5f** (0.134 g, 0.369 mmol, 98%, 100% pure by ELSD) as a light yellow oil: IR (ATR) 2918, 2827, 1636, 1613, 1500, 1439, 1237, 1195, 1147, 1031, 909, 811, 753, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10-6.90 (m, 4 H), 3.79 (app t, 2 H, J = 5.2 Hz),

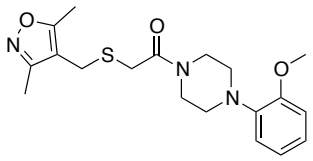
3.63-3.59 (m, 4 H), 3.23 (s, 2 H), 3.10 (app t, 2 H, J = 4.8 Hz), 3.05 (app t, 2 H, J = 5.2 Hz), 2.28 (s, 3 H), 2.42 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 166.8, 159.7, 155.7 (d, $J_{C\text{-}F}$ = 245.0 Hz), 139.4 (d, $J_{C\text{-}F}$ = 8.8 Hz), 124.5 (d, $J_{C\text{-}F}$ = 3.8 Hz), 123.3 (d, $J_{C\text{-}F}$ = 8.8 Hz), 119.2 (d, $J_{C\text{-}F}$ = 2.5 Hz), 116.3 (d, $J_{C\text{-}F}$ = 20.0 Hz), 109.7, 50.7 (d, $J_{C\text{-}F}$ = 2.5 Hz), 50.3 (d, $J_{C\text{-}F}$ = 2.5 Hz), 46.6, 41.9, 32.1, 23.7, 11.1, 10.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{23}N_3O_2FS$ ($[M+H]^+$) 364.1490, found 364.1474.



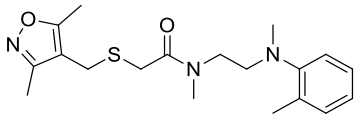
2-(((3,5-Dimethylisoxazol-4-yl)methyl)thio)-1-(4-(naphthalen-1-yl)piperazin-1-yl)ethanone (**5g**). A Schlenk flask was charged under N_2 with piperazine (0.0500 g, 0.580 mmol), NaO-*t*-Bu (0.100 g, 1.06 mmol), (*rac*)-BINAP (0.0051 g, 0.0079 mmol), $Pd_2(dba)_3$ (0.0050 g, 0.0053 mmol), and degassed toluene (5 mL). After addition of 1-bromonaphthalene (75 µL, 0.530 mmol), the reaction mixture was heated at 110 °C for 24 h, cooled to room temperature, diluted with CH_2Cl_2, filtered through Celite, and concentrated *in vacuo*. The resulting 1-(naphthalen-1-yl)piperazine (**4g**) was used without further purification for the next reaction.

To a solution of (((3,5-dimethylisoxazol-4-yl)methyl)thio)acetic acid (**3a**, 0.0580 g, 0.272 mmol) in CH_2Cl_2 (4 mL) was added 1-(naphthalen-1-yl)piperazine **4g** (0.0750 g, 0.353 mmol) and Et_3N (114 µL, 0.815 mmol). The reaction mixture was cooled to 0 °C, treated with T3P (50 wt.% solution in EtOAc, 288 µL, 0.408 mmol), allowed to warm to room temperature, stirred for 20 h, diluted with CH_2Cl_2, and washed with satd. aqueous NH_4Cl, satd. aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (95:5 CH_2Cl_2/MeOH) to give **5g** (0.0700 g, 0.177 mmol, 65% 2 steps, 99.9% pure by ELSD) as a yellow oil: IR (neat) 2919, 1637, 1435, 1398, 1215, 1192 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, 1 H, J = 7.5 Hz), 7.85 (d, 1 H, J = 7.5 Hz), 7.61 (d, 1 H, J = 8.0 Hz), 7.54-7.49 (m, 2 H), 7.42 (d, 1 H, J = 8.0 Hz), 7.08 (d, 1 H, J = 7.5 Hz), 3.73-3.66 (m, 4 H), 3.64 (s, 2 H), 3.28 (s, 2 H), 3.27-2.85 (m, 4 H), 2.45 (s, 3 H), 2.32 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 166.8, 159.7, 148.7, 134.7, 128.7, 128.5, 126.0, 125.7 (2 C), 124.2, 123.0, 115.0, 109.7,

52.9, 52.7, 47.0, 42.4, 32.1, 23.7, 11.1, 10.2; HRMS (ESI) *m/z* calcd for $C_{22}H_{26}N_3O_2S$ ($[M+H]^+$) 396.1746, found 396.1740.

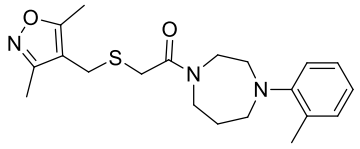


2-(((3,5-Dimethylisoxazol-4-yl)methyl)thio)-1-(4-(2-methoxyphenyl)piperazin-1-yl)ethanone (**5h**). To a solution of 2-(((3,5-dimethylisoxazol-4-yl)methyl)thio)acetic acid (**3a**, 0.0200 g, 0.0994 mmol) in CH_2Cl_2 (1.25 mL) was added 1-(*o*-methoxyphenyl)piperazine (**4h**, 0.0230 g, 0.119 mmol) and Et_3N (41 μL, 0.298 mmol). The reaction mixture was cooled to 0 °C, treated with T3P (50 wt.% solution in EtOAc, 105 μL, 0.149 mmol), warmed to room temperature, stirred for 2 d, diluted with CH_2Cl_2 and washed with satd. aqueous NH_4Cl, satd. aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (ISCO, 12 g column, liquid load in CH_2Cl_2, EtOAc/hexanes gradient (10-100%, eluted at 50-70%) to give **5h** (0.0195 g, 0.0519 mmol, 52%, 100% pure by ELSD) as a colorless solid: Mp 91-93 °C; IR (ATR) 2997, 2926, 2812, 1626, 1500, 1447, 1243, 1223, 1143, 1023, 979, 751, 741, 726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.06-7.01 (m, 1 H), 6.95-6.87 (m, 3 H), 3.87 (s, 3 H), 3.80 (app t, 2 H, J = 5.0 Hz), 3.64-3.62 (m, 4 H), 3.23 (s, 2 H), 3.07 (app t, 2 H, J = 5.0 Hz), 3.03 (app t, 2 H, J = 5.0 Hz), 2.41 (s, 3 H), 2.28 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 166.7, 159.8, 152.2, 140.4, 123.6, 121.0, 118.4, 111.3, 109.7, 55.4, 50.7, 50.5, 46.7, 42.0, 32.1, 23.7, 11.0, 10.1; HRMS (ESI) *m/z* calcd for $C_{19}H_{26}N_3O_{23}S$ ($[M+H]^+$) 376.1689, found 376.1673.



2-(((3,5-Dimethylisoxazol-4-yl)methyl)thio)-N-methyl-N-(2-(methyl(*o*-tolyl)amino)ethyl) acetamide (**5i**). To a solution of 2-(((3,5-dimethylisoxazol-4-yl)methyl)thio)acetic acid (**3a**, 0.0608 g, 0.302 mmol) in CH_2Cl_2 (3.0 mL) was added

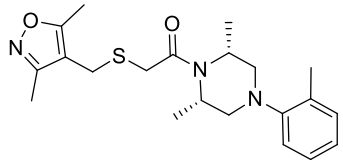
N,*N'*-dimethyl-*N*-(*o*-tolyl)ethane-1,2-diamine (**4i**, 0.0500 g, 0.275 mmol) and Et_3N (115 µL, 0.825 mmol). The reaction mixture was cooled to 0 °C, treated with T3P (50 wt.% solution in EtOAc, 292 µL, 0.412 mmol), warmed to room temperature, stirred for 20 h, diluted with CH_2Cl_2, and washed with satd. aqueous NH_4Cl solution, satd. aqueous $NaHCO_3$ solution, and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (3:2, EtOAc/hexanes, base washed with 0.1% Et_3N prior to use) to give **5i** (0.0752 g, 0.207 mmol, 75%, 99.6% pure by ELSD) as a light yellow oil: IR (ATR) 2932, 2795, 1640, 1598, 1493, 1451, 1421, 1393, 1196, 1108, 1047, 766, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, room temperature, mixture of rotamers coalescing in DMSO-d_6 at 357 K) δ 7.20-7.12 (m, 2 H), 7.07-6.95 (m, 2 H), 3.59, 3.58 (2s, 2 H), 3.54 (t, 1 H, *J* = 6.6 Hz), 3.39 (t, 1 H, *J* = 6.6 Hz), 3.16-3.08 (m, 3 H), 2.97, 2.95 (2s, 4 H), 2.71, 2.67 (2s, 3 H), 2.38 (s, 3 H), 2.30 (s, 2 H), 2.27, 2.26 (3s, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$, room temperature, mixture of rotamers coalescing in DMSO-d_6 at 357 K) δ 169.2, 168.8, 166.7 (2 C), 159.7, 151.7, 150.8, 133.8, 132.9, 131.4, 131.2, 126.7, 126.5, 124.0, 123.2, 120.2, 119.9, 109.8, 53.9, 53.2, 48.4, 46.4, 43.3, 42.3, 36.7, 33.8, 32.4, 31.6, 23.7, 23.4, 18.2, 18.0, 11.0 (2 C), 10.1; HRMS (ESI) *m/z* calcd for $C_{19}H_{28}N_3O_2S$ ($[M+H]^+$) 362.1897, found 362.1890.



2-(((3,5-Dimethylisoxazol-4-yl)methyl)thio)-1-(4-(*o*-tolyl)-1,4-diazepan-1-yl)ethan-1-one (**5j**). A solution of *tert*-butyl 4-(*o*-tolyl)-1,4-diazepane-1-carboxylate (**30a**, 0.0750 g, 0.258 mmol) in THF (0.3 mL) was cooled to 0 ºC, treated with 4 M HCl in dioxane (1.6 mL) and stirred at 0 ºC for 2 h. The reaction mixture was concentrated *in vacuo* and the yellow solid **4j** was precipitated in Et_2O, filtered off from the solution, washed with Et_2O, dried under high vacuum, and used without further purification for the next step.

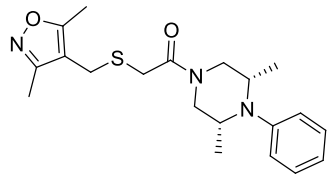
To a solution of 2-(((3,5-dimethylisoxazol-4-yl)methyl)thio)acetic acid (**3a**, 0.0460 g, 0.229 mmol) in CH_2Cl_2 (2.3 mL) was added 4-(*o*-tolyl)-1,4-diazepane hydrochloride (**4j**, 0.258 mmol) and Et_3N (159 µL, 1.14 mmol). The reaction mixture was cooled to 0 °C, treated with T3P (50 wt.% solution in EtOAc, 242 µL, 0.343 mmol), warmed to room

temperature, stirred for 20 h, diluted with CH_2Cl_2, and washed with satd. aqueous NH_4Cl solution, satd. aqueous $NaHCO_3$ solution, and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (3:2, EtOAc/hexanes, base washed with 0.1% Et_3N) to give **5j** (0.0854 g, 0.229 mmol, quant. 100% pure by ELSD) as a clear colorless oil: IR (ATR) 2945, 2825, 1634, 1598, 1491, 1447, 1423, 1215, 1194, 1136, 915, 762, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, room temperature, mixture of rotamers) δ 7.20 (app d, 1 H, J = 7.6 Hz), 7.17 (app t, 1 H, J = 7.6 Hz), 7.05 (app d, 1 H, J = 7.6 Hz), 7.01 (app dt, 1 H, J = 7.2, 2.0 Hz), 3.82-3.78 (m, 2 H), 3.71-3.65 (m, 4 H), 3.24-3.20 (m, 3 H), 3.15 (t, 1 H, J = 5.2 Hz), 3.12-3.07 (m, 2 H), 2.46 (app s, 3 H), 2.32 (2s, 6 H), 2.04 (sept, 2 H, J = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, room temperature, mixture of rotamers) δ 168.9, 168.8, 166.9, 166.8, 159.8 (2 C), 153.4, 153.3, 132.9 (2 C), 131.1 (2 C), 126.7, 126.6, 123.6, 123.4, 120.8, 120.7, 109.9, 56.4, 55.8, 55.5, 54.9, 50.1, 47.6, 47.2, 44.9, 32.2, 32.0, 29.5, 28.2, 23.7, 18.5 (2 C), 11.1, 10.2 (2 C); HRMS (ESI) *m/z* calcd for $C_{20}H_{28}N_3O_2S$ ($[M+H]^+$) 374.1897, found 374.1883.



1-(2,6-Dimethyl-4-(*o*-tolyl)piperazin-1-yl)-2-(((3,5-dimethylisoxazol-4-yl)methyl)thio)ethanone (**5k**). A solution of (((3,5-dimethylisoxazol-4-yl)methyl)thio)acetic acid (**3a**, 0.0300 g, 0.142 mmol) in CH_2Cl_2 (2 mL) was treated with 3,5-dimethyl-1-(*o*-tolyl)piperazine (**4k**, 0.0350 g, 0.170 mmol) and Et_3N (59 μL, 0.425 mmol). The reaction mixture was cooled to 0 °C, treated with T3P (50 wt.% solution in EtOAc, 150 μL, 0.212 mmol), warmed to room temperature, stirred for 20 h, diluted with CH_2Cl_2, and washed with satd. aqueous NH_4Cl, satd. aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (95:5 CH_2Cl_2/MeOH) to give **5k** (0.0450 g, 0.116 mmol, 82%, 99.8% pure by ELSD) as a light yellow oil: IR (neat) 2975, 1629, 1491, 1422, 1327, 1127 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22-7.19 (m, 2 H), 7.06-7.02 (m, 2 H), 4.68 (brs, 1 H), 4.05 (brs, 1 H), 3.73-3.70 (m, 1 H), 3.66-3.61 (m, 1 H), 3.30-3.19 (m, 2 H), 2.98-2.96

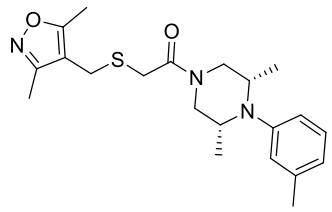
(m, 2 H), 2.94-2.89 (m, 1 H), 2.81-2.78 (m, 1 H), 2.44 (s, 3 H), 2.41 (s, 3 H), 2.31 (s, 3 H), 1.55 (d, 3 H, J = 6.0 Hz), 1.48 (d, 3 H, J = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 166.7, 151.2, 133.3, 131.2, 126.8, 124.1, 119.6, 109.8, 57.0, 56.8, 49.8, 45.8, 32.0, 23.6, 21.6, 20.3, 18.2, 11.0, 10.1; HRMS (ESI) *m/z* calcd for $C_{21}H_{30}N_3O_2S$ ($[M+H]^+$) 388.2059, found 388.2053.



1-(3,5-Dimethyl-4-phenylpiperazin-1-yl)-2-(((3,5-dimethylisoxazol-4-yl)methyl)thio)ethan-1-one (**5l**). A solution of *tert*-butyl 3,5-dimethyl-4-phenylpiperazine-1-carboxylate (**30b**, 0.0330 g, 0.114 mmol) in THF (0.1 mL) at 0 ºC was treated with 4 M HCl in dioxane (0.70 mL) and stirred at 0 ºC for 1.5 h and at room temperature for 1.5 h. The yellow solid was filtered off, washed with Et_2O, dried under high vacuum and the resulting crude **4l** was directly used for the next step.

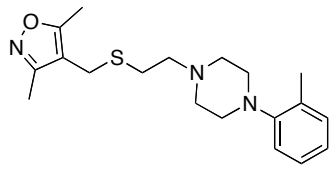
To a solution of 2-(((3,5-dimethylisoxazol-4-yl)methyl)thio)acetic acid **3a** (0.0229 g, 0.114 mmol) in CH_2Cl_2 (1.1 mL) was added 2,6-dimethyl-1-phenylpiperazine hydrochloride (**4l**, 0.0258 g, 0.114 mmol) and Et_3N (79 μL, 0.569 mmol). The reaction mixture was cooled to 0 °C, treated with T3P (50 wt.% solution in EtOAc, 121 μL, 0.171 mmol), warmed to room temperature, stirred for 20 h, diluted with CH_2Cl_2, and washed with satd. aqueous NH_4Cl solution, satd. aqueous $NaHCO_3$ solution, and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (1:1, acetone/hexanes, base washed with 0.1% Et_3N prior to use) to give **5l** (0.0322 g, 0.0862 mmol, 76%, 100% pure by ELSD) as a colorless oil: IR (ATR) 2967, 2931, 1639, 1597, 1493, 1449, 1377, 1319, 1272, 1238, 1151, 1091, 886, 771, 731, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, 2 H, J = 7.6 Hz), 7.18 (t, 1 H, J = 7.2 Hz), 7.10 (d, 2 H, J = 7.6 Hz), 4.42 (ddd, 1 H, J = 12.8, 4.0, 2.4 Hz), 3.70-3.60 (m, 3 H), 3.29-3.18 (m, 2 H), 3.10-2.93 (m, 3 H), 2.67 (dd, 1 H, J = 13.2, 10.4 Hz), 2.43 (s, 3 H), 2.30 (s, 3 H), 0.77 (d, 3 H, J = 6.4 Hz), 0.76 (d, 3 H, J = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 166.8, 159.7, 148.5, 128.9, 126.4, 125.6, 109.8, 56.0, 55.6, 53.4,

48.7, 31.9, 23.7, 18.2, 18.2, 11.1, 10.2; HRMS (ESI) *m/z* calcd for $C_{20}H_{28}N_3O_2S$ ($[M+H]^+$) 374.1897, found 374.1887.

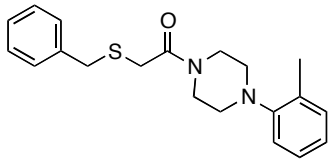


1-(3,5-Dimethyl-4-(*m*-tolyl)piperazin-1-yl)-2-(((3,5-dimethylisoxazol-4-yl)methyl)thio)ethan-1-one (**5m**). A solution of *tert*-butyl 3,5-dimethyl-4-(*m*-tolyl)piperazine-1-carboxylate **(30c**, 0.0400 g, 0.131 mmol) in THF (0.1 mL) at 0 ºC was treated with 4 M HCl in dioxane (0.80 mL), and stirred at 0 ºC for 1.5 h and at room temperature for 1.5 h. A yellow precipitate formed and the solid was filtered off, washed with Et_2O, and dried under high vacuum and the resulting crude **4m** was used directly for the next step.

To a solution of 2-(((3,5-dimethylisoxazol-4-yl)methyl)thio)acetic acid (**3a**, 0.0264 g, 0.131 mmol) in CH_2Cl_2 (1.3 mL) was added 2,6-dimethyl-1-(*m*-tolyl)piperazine hydrochloride (**4m**, 0.0316 g, 0.131 mmol) and Et_3N (91 µL, 0.656 mmol). The reaction mixture was cooled to 0 °C, treated with T3P (50 wt. % solution in EtOAc, 139 µL, 0.197 mmol), warmed to room temperature, stirred for 20 h, diluted with CH_2Cl_2, washed with satd. aqueous NH_4Cl solution, satd. aqueous $NaHCO_3$ solution, and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (3:2, EtOAc/hexanes, base washed with 0.1% Et_3N prior to use) to give **5m** (0.0400 g, 0.103 mmol, 79%, 100% pure by ELSD) as a clear colorless oil: IR (ATR) 2966, 2929, 1637, 1602, 1451, 1376, 1319, 1271, 1194, 1149, 1108, 1088, 911, 889, 788, 730, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, 1 H, *J* = 7.6 Hz), 6.97 (d, 1 H, *J* = 7.6 Hz), 6.90-6.88 (m, 2 H), 4.41 (app d, 1 H, *J* = 12.8 Hz), 3.64 (brs, 3 H), 3.27-3.19 (m, 2 H), 3.15-2.91 (m, 3 H), 2.67 (t, 1 H, *J* = 9.2 Hz), 2.43 (s, 3 H), 2.32 (s, 3 H), 2.30, (s, 3 H), 0.77 (br app s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 166.8, 159.7, 148.4, 138.7, 128.7, 127.1, 126.4, 123.4, 109.8, 56.0, 55.6, 53.4, 48.7, 32.0, 23.7, 21.4, 18.3, 18.2, 11.1, 10.2; HRMS (ESI) *m/z* calcd for $C_{21}H_{30}N_3O_2S$ ($[M+H]^+$) 388.2053, found 388.2046.

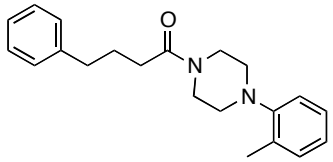


3,5-Dimethyl-4-(((2-(4-(*o*-tolyl)piperazin-1-yl)ethyl)thio)methyl)isoxazole (6). A solution of 2-(((3,5-dimethylisoxazol-4-yl)methyl)thio)-1-(4-(*o*-tolyl)piperazin-1-yl)ethanone (**5b**, 0.0387 g, 0.108 mmol) in THF (1 mL) at 0 °C was treated with $LiAlH_4$ (1 M solution in Et_2O, 120 μL, 0.118 mmol), stirred at 0 °C for 1 h, and then quenched with Rochelle's salt ($NaKC_4H_4O_6$, satd. aqueous solution, 1 mL). The mixture was stirred for an additional 1 h at 0 °C, diluted with EtOAc, extracted with EtOAc (2 x 15 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by chromatography on SiO_2 (ISCO, 4 g column, liquid load in CH_2Cl_2, 0-20% MeOH/CH_2Cl_2, product eluted at 5% MeOH) to give a colorless oil. This oil was further purified by chromatography on SiO_2 (CH_2Cl_2 to 5:95, MeOH/CH_2Cl_2) on a pipette column to give **6** (0.0155 g, 0.0449 mmol, 42%, 100% pure by ELSD) as a colorless oil: IR (neat) 3393, 2925, 2814, 1637, 1599, 1493, 1448, 1424, 1372, 1227, 1195, 1130, 1041, 1006, 931, 763, 723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (app t, 2 H, J = 7.4 Hz), 7.03-6.95 (m, 2 H), 3.75 (t, 1 H, J = 5.7 Hz), 3.50 (s, 2 H), 2.93 (app t, 4 H, J = 4.5 Hz), 2.63 (brs, 8 H), 2.38 (s, 3 H), 2.30 (s, 3 H), 2.29 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 159.6, 151.4, 132.6, 131.0, 126.6, 123.2, 119.0, 110.5, 77.2, 58.1, 53.6, 51.6, 29.1, 24.0, 23.5, 17.8, 11.1, 10.2; HRMS (ESI) *m/z* calcd for $C_{19}H_{28}ON_3S$ ($[M+H]^+$) 346.1948, found 346.1946.

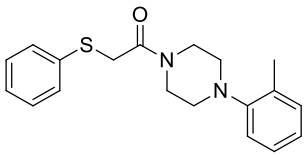


2-(Benzylthio)-1-(4-(*o*-tolyl)piperazin-1-yl)ethanone (**7**). A solution of 2-(benzylthio)acetic acid **3b** (0.0440 g, 0.241 mmol) in CH_2Cl_2 (3.05 mL) was treated with 1-(*o*-tolyl)piperazine **4b** (0.0521 g, 0.290 mmol) and Et_3N (101 μL, 0.724 mmol). The reaction mixture was cooled to 0 °C, treated with T3P (50 wt.% solution in EtOAc, 256

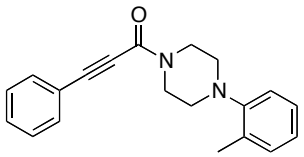
μL, 0.362 mmol), warmed to room temperature and stirred for 2 d. The solution was diluted with CH_2Cl_2 and washed with satd. aqueous NH_4Cl, satd. aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (ISCO, 12 g column, liquid load in CH_2Cl_2, EtOAc/hexanes gradient (10-100%)) to give **7** (0.0635 g, 0.187 mmol, 77%, 100% pure by ELSD) as a yellow oil: IR (ATR) 2917, 1815, 1634, 1598, 1492, 1437, 1223, 1150, 1031, 975, 761, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.23 (m, 7 H), 7.06-7.01 (m, 2 H), 3.89 (s, 2 H), 3.79 (app t, 2 H, J = 4.9 Hz), 3.59 (app t, 2 H, J = 4.9 Hz), 3.30 (s, 2 H), 2.95-2.90 (m, 4 H), 2.37 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 150.9, 137.7, 132.8, 131.2, 129.3, 128.5, 127.2, 126.7, 123.8, 119.3, 51.9, 51.7, 46.9, 42.4, 36.3, 32.4, 17.8; HRMS (ESI) *m/z* calcd for $C_{20}H_{25}N_2OS$ ($[M+H]^+$) 341.1682, found: 341.1674.



4-Phenyl-1-(4-(*o*-tolyl)piperazin-1-yl)butan-1-one (**8**). To a solution of phenyl butanoic acid (**3c**, 0.0500 g, 0.305 mmol) in CH_2Cl_2 (3.05 mL) was added 1-(*o*-tolyl)piperazine (**4b**, 0.0657 g, 0.365 mmol) and Et_3N (85 μL, 0.609 mmol). The reaction mixture was cooled to 0 °C, treated with T3P (50 wt. % solution in EtOAc, 322 μL, 0.457 mmol), warmed to room temperature, stirred overnight, diluted with CH_2Cl_2 and washed with satd. aqueous NH_4Cl, satd. aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (ISCO, 12 g column, liquid load in CH_2Cl_2, EtOAc/hexanes gradient (10-100%), eluted at 30%) to give **8** (0.0863 g, 0.268 mmol, 88%, 100% pure by ELSD) as a colorless oil: IR (ATR) 3024, 2917, 2813, 1641, 1492, 1432, 1223, 1150, 1025, 761, 722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.31 (m, 2 H), 7.27-7.18 (m, 5 H), 7.07-6.99 (m, 2 H), 3.80 (app t, 2 H, J = 4.8 Hz), 3.55 (app t, 2 H, J = 4.8 Hz), 2.88 (app t, 4 H, J = 4.8 Hz), 2.75 (t, 2 H, J =7.5 Hz), 2.41 (t, 2 H, J = 7.5 Hz), 2.36 (s, 3 H), 2.06 (ddd, 2 H, J = 7.9, 7.7, 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 150.8, 141.6, 132.6, 131.0, 128.4, 128.3, 126.6, 125.8, 123.6, 119.0, 51.9, 51.6, 45.9, 41.9, 35.2, 32.3, 26.6, 17.7; HRMS (ESI) *m/z* calcd for $C_{21}H_{27}N_2O$ ($[M+H]^+$) 323.2118, found: 323.2110.

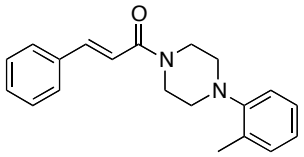


2-(Phenylthio)-1-(4-(o-tolyl)piperazin-1-yl)ethan-1-one (**9**). To a solution of 2-(phenylthio)acetic acid (**3d**, 0.0500 g, 0.297 mmol) in CH_2Cl_2 (3.0 mL) was added 1-(o-tolyl)piperazine (**4b**, 0.0642 g, 0.357 mmol) and Et_3N (83 µL, 0.594 mmol). The mixture was cooled to 0 °C, treated with T3P (50 wt.% solution in EtOAc, 315 µL, 0.446 mmol), warmed to room temperature, stirred for 3 d, diluted with CH_2Cl_2 and washed with satd. aqueous NH_4Cl, satd. aqueous $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (ISCO, 4 g column, liquid load in CH_2Cl_2, EtOAc/hexanes gradient (0-30%), eluted at 20-30%) to give **9** (0.0746 g, 0.229 mmol, 77%, 100% pure by ELSD) as a clear colorless oil: IR (ATR) 3057, 2947, 2911, 2856, 2815, 1639, 1598, 1492, 1482, 1382, 1275, 1223, 1203, 1149, 1115, 1032, 974, 950, 909, 762, 738, 723, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, 2 H, *J* = 7.6, 1.2 Hz), 7.34 (app t, 2 H, *J* = 7.6 Hz), 7.26-7.17 (m, 3 H), 7.02 (app t, 1 H, *J* = 7.6 Hz), 6.98 (app d, 1 H, *J* = 7.6 Hz), 3.81 (s, 2 H), 3.76 (app t, 2 H, *J* = 4.8 Hz), 3.63 (app t, 2 H, *J* = 4.8 Hz), 2.91 (app t, 2 H, *J* = 4.8 Hz), 2.86 (t, 2 H, *J* = 4.8 Hz), 2.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 150.7, 134.9, 132.7, 131.2, 130.3, 129.1, 127.0, 126.7, 123.8, 119.2, 51.9, 51.6, 47.0, 42.5, 36.7, 17.8; HRMS (ESI) *m/z* calcd for $C_{19}H_{23}N_2OS$ ($[M+H]^+$) 327.1526, found 327.1514.



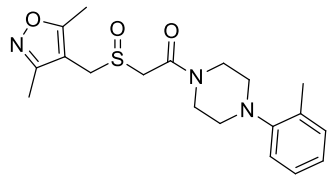
3-Phenyl-1-(4-(*o*-tolyl)piperazin-1-yl)prop-2-yn-1-one (**10**). To a solution of phenyl propiolic acid (**3e**, 0.200 g, 1.37 mmol) in CH_2Cl_2 (12 mL) was added 1-(*o*-tolyl)piperazine (**4b**, 0.290 g, 1.6 mmol) and Et_3N (570 µL, 4.1 mmol). The reaction mixture was cooled to 0 °C, treated with T3P (50 wt. % solution in EtOAc, 1.4 mL, 2.0 mmol), warmed to room temperature, stirred for 3 d, diluted with CH_2Cl_2 (30 mL), and

washed with satd. aqueous NH_4Cl (5 mL), satd. aqueous $NaHCO_3$ (5 mL), and brine (5 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (ISCO, 24 g column, liquid load in CH_2Cl_2, EtOAc/hexanes gradient (10-100%), product eluted at 40% EtOAc/hexanes) to give **10** (0.401 g, 96%, >99.9% pure by ELSD) as a colorless solid: Mp 127-129 °C; IR (neat) 3037, 2907, 2857, 2206, 1616, 1491, 1424, 1279, 1226, 1207, 1035, 923, 758, 726, 686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59-7.56 (m, 2 H), 7.43-7.34 (m, 3 H), 7.22-7.16 (m, 2 H), 7.05-6.99 (m, 2 H), 3.99 (app t, 2 H, J = 5.0 Hz), 3.85 (app t, 2 H, J = 5.0 Hz), 2.99 (app t, 2 H, J = 5.0 Hz), 2.92 (app t, 2 H, J = 5.0 Hz), 2.35 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 150.8, 132.8, 132.4, 131.2, 130.1, 128.6, 126.8, 123.9, 120.5, 119.3, 90.9, 81.2, 52.2, 51.5, 47.7, 42.1, 17.8; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}ON_2$ ($[M+H]^+$) 305.1648, found 305.1643.

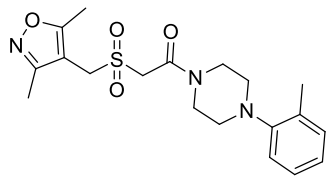


(*E*)-3-Phenyl-1-(4-(*o*-tolyl)piperazin-1-yl)prop-2-en-1-one (**11**). A solution of *trans*-cinnamic acid (**3f**, 0.0400 g, 0.270 mmol) in CH_2Cl_2 (2.5 mL) was treated with 1-(*o*-tolyl)piperazine (**4b**, 0.0570 g, 0.320 mmol), Et_3N (113 µL, 0.810 mmol). The reaction mixture was cooled to 0 °C, treated with T3P (50 wt.% solution in EtOAc, 290 µL, 0.405 mmol),warmed to room temperature, stirred for 3 d, diluted with CH_2Cl_2 (10 mL), and washed with satd. aqueous NH_4Cl (2 mL), satd. aqueous $NaHCO_3$ (2 mL), and brine (2 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (ISCO, 12 g column, liquid load in CH_2Cl_2, EtOAc/hexanes gradient (10-100%), product eluted at 35%) to give **11** (0.0520 g, 0.168 mmol, 62%, >99% purity by ELSD) as a yellow solid: Mp 110-111 °C; IR (neat) 3045, 2920, 2840, 1643, 1595, 1423, 1327, 1225, 1152, 986, 765, 710, 682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, 1 H, J = 11.4 Hz), 7.55 (dd, 2 H, J = 6.8, 1.4 Hz), 7.41-7.36 (m, 3 H), 7.20 (dd, 2 H, J = 14.6, 7.4 Hz), 7.02 (ddd, 2 H, J = 14.6, 7.4, 0.6 Hz), 6.95 (d, 1 H, J = 15.6 Hz), 3.90 (brs, 2 H), 3.81 (brs, 2 H), 2.96 (brs, 4 H), 2.36 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 150.8, 142.8, 135.2, 132.7, 131.1, 129.6, 128.8, 127.7, 126.6,

123.7, 119.2, 117.1, 52.1, 51.6, 46.4, 42.6, 17.8; HRMS (ESI) *m/z* calcd for $C_{20}H_{23}ON_2$ ($[M+H]^+$) 307.1805, found 307.1796.

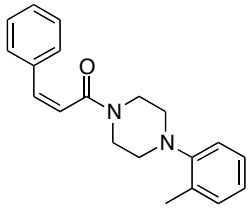


2-(((3,5-Dimethylisoxazol-4-yl)methyl)sulfinyl)-1-(4-(*o*-tolyl)piperazin-1-yl)ethan-1-one (**12**). To a solution of 2-(((3,5-dimethylisoxazol-4-yl)methyl)thio)-1-(4-(*o*-tolyl)piperazin-1-yl)ethanone (**5b**, 0.0500 g, 0.139 mmol) in MeOH (0.30 mL) at 0 °C was added dropwise a solution of sodium metaperiodate (0.0301 g, 0.139 mmol) in water (0.14 mL). The resulting heterogeneous mixture was allowed to warm to room temperature and stirred for 15 h. The reaction mixture was filtered through a plug of Celite (MeOH), concentrated, dissolved in CH_2Cl_2, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (100% EtOAc) to give **12** (0.0356 g, 0.0948 mmol, 68%, 100% pure by ELSD) as a colorless foam: IR (ATR) 2917, 2818, 1631, 1599, 1493, 1441, 1384, 1275, 1224, 1195, 1151, 1053, 1028, 911, 764, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21-7.15 (m, 2 H), 7.02 (app t, 1 H, *J* = 7.2 Hz), 6.97 (app d, 1 H, *J* = 8.0 Hz), 4.18 (d, 1 H, *J* = 14.0 Hz), 3.90-3.84 (m, 5 H), 3.64 (app t, 2 H, *J* = 4.4 Hz), 2.95 (app t, 2 H, *J* = 4.4 Hz), 2.85 (brs, 2 H), 2.45 (s, 3 H), 2.32 (s, 3 H), 2.31 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 162.9, 159.9, 150.4, 132.7, 131.2, 126.7, 124.0, 119.2, 104.5, 53.7, 52.0, 51.5, 47.0, 46.8, 42.5, 17.7, 11.6, 10.3; HRMS (ESI) *m/z* calcd for $C_{19}H_{26}N_3O_3S$ ($[M+H]^+$) 376.1689, found 376.1684.



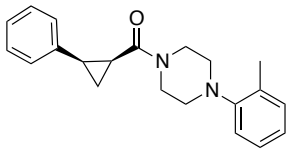
2-(((3,5-Dimethylisoxazol-4-yl)methyl)sulfonyl)-1-(4-(*o*-tolyl)piperazin-1-yl)ethan-1-one (**13**). A solution of 2-(((3,5-dimethylisoxazol-4-yl)methyl)thio)-1-(4-(*o*-tolyl)piperazin-1-yl)ethanone (**5b**, 0.0429 g, 0.117 mmol) in CH_2Cl_2 (0.65 mL) was

treated with 3-chloroperoxybenzoic acid (70 wt.%, 0.0576 g, 0.234 mmol) in 2 portions. The reaction mixture was stirred at room temperature for 15 h, quenched with 10% aqueous sodium metabisulfite solution (2 mL), diluted with aqueous 1 M NaOH (10 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with 1 M NaOH (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (70-100% EtOAc/hexanes) to give **13** (0.0203 g, 0.0519 mmol, 44%, 100% pure by ELSD) as a colorless foam: IR (ATR) 2919, 2819, 1641, 1599, 1493, 1445, 1318, 1225, 1150, 1126, 1030, 911, 765, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21-7.16 (m, 2 H), 7.05-6.98 (m, 2 H), 4.36 (s, 2 H), 4.09 (s, 2 H), 3.85 (app brs, 2 H), 3.72 (brt, 2 H, J = 4.0 Hz), 3.00 (brt, 2 H, J = 4.0 Hz), 2.93 (brt, 2 H, J = 4.4 Hz), 2.50 (s, 3 H), 2.35 (s, 3 H), 2.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 160.7, 160.3, 150.3, 132.7, 131.2, 126.7, 124.0, 119.2, 101.8, 54.9, 51.7, 51.4, 48.3, 47.8, 43.0, 17.8, 11.5, 10.2; HRMS (ESI) *m/z* calcd for $C_{19}H_{26}N_3O_4S$ ($[M+H]^+$) 392.1639, found 392.1633.

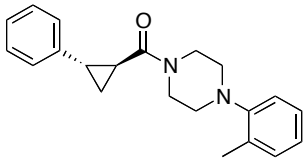


(*Z*)-3-Phenyl-1-(4-(*o*-tolyl)piperazin-1-yl)prop-2-en-1-one (**14**). To a solution of 3-phenyl-1-(4-(*o*-tolyl)piperazin-1-yl)prop-2-yn-1-one (**10**, 0.103 g, 0.337 mmol) in MeOH (2 mL) and EtOAc (1 mL) was added Lindlar's catalyst (5% Pd on $CaCO_3$, lead poisoned, 0.120 g) and quinoline (15 μL, 0.130 mmol). The reaction mixture was purged and backfilled with H_2 (balloon, 2 x), allowed to stir for 45 min, filtered through SiO_2, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (ISCO, modified dry load in CH_2Cl_2, 0-90% EtOAc/hexanes gradient, product eluted at 25% EtOAc/hexanes) to give **14** (0.104 g, 0.339 mmol, quant., 99.6% purity by ELSD) as a yellow oil: IR (neat) 3022, 2914, 2815, 1513, 1597, 1493, 1434, 1364, 1223, 1149, 1115, 1034, 973, 913, 855, 762, 722, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.30 (m, 5 H), 7.17-7.11 (m, 2 H), 6.98 (t, 1 H, J = 7.1 Hz), 6.81 (d, 1 H, J = 7.8 Hz), 6.71 (d, 1 H, J = 12.6 Hz), 6.07 (d, 1 H, J = 12.6 Hz), 3.81 (app brt, 2 H, J = 4.8 Hz), 3.48 (app t,

2 H, *J* = 4.8 Hz), 2.81 (app t, 2 H, *J* = 4.8 Hz), 2.44 (app t, 2 H, *J* = 4.8 Hz), 2.25 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 150.9, 135.6, 133.5, 132.7, 131.1, 128.7, 128.6, 128.5, 126.6, 123.7, 123.2, 119.1, 51.5, 51.3, 46.8, 41.7, 17.7; HRMS (ESI) *m/z* calcd for $C_{20}H_{23}ON_2$ ($[M+H]^+$) 307.1805, found 307.1800.

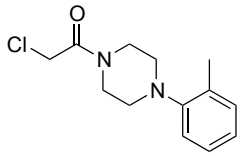


((1*SR*,2*RS*)-2-Phenylcyclopropyl)(4-(*o*-tolyl)piperazin-1-yl)methanone (**15**). A solution of anhydrous $CrCl_2$ (0.0486 g, 0.392 mmol) in THF (0.6 mL) at room temperature under N_2 was treated with a solution of (*Z*)-3-phenyl-1-(4-(*o*-tolyl)piperazin-1-yl)prop-2-en-1-one (**14**, 0.0200 g, 0.0653 mmol) in THF (0.5 mL) and CH_2ICl (20 μL, 0.261 mmol). The reaction mixture was stirred for 18 h at reflux, quenched by addition of 1 M aqueous HCl (6 mL) and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (4:1, EtOAc/hexanes) to give **15** (0.0120 g, 0.0375 mmol, 57%, 100% pure by ELSD) as a brown oil: IR (neat) 2920, 1638, 1491, 1457, 1340, 1223, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2 H), 7.22-7.11 (m, 5 H), 6.98 (dt, 1 H, *J* = 7.2, 1.2 Hz), 6.72 (dd, 1 H, *J* = 7.9, 0.8 Hz), 3.93-3.90 (m, 1 H), 3.77-3.73 (m, 1 H), 3.60-3.53 (m, 1 H), 3.30-3.22 (m, 1 H), 2.75-2.72 (m, 2 H), 2.50-2.41 (m, 1 H), 2.26 (s, 3 H), 2.24-2.16 (m, 1 H), 2.10-2.00 (m, 1 H), 1.87 (dd, 1 H, *J* = 12.4, 5.8 Hz), 1.40-1.33 (m, 1 H), 0.92-0.80 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 150.9, 137.6, 132.7, 131.0, 128.2, 127.4, 126.5, 126.4, 123.6, 119.2, 51.9, 51.6, 45.7, 42.3, 24.4, 24.1, 17.7, 10.6; HRMS (ESI) *m/z* calcd for $C_{21}H_{25}ON_2$ ($[M+H]^+$) 321.1967, found 321.1961.

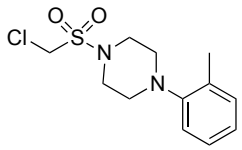


((1*SR*,2*SR*)-2-Phenylcyclopropyl)(4-(*o*-tolyl)piperazin-1-yl)methanone (**16**). To a solution of *trans*-2-phenylcyclopropanecarboxylic acid (**3g**, 0.0400 g, 0.247 mmol) in CH_2Cl_2 (2.5 mL) was treated with 1-(*o*-tolyl)piperazine (**4b**, 0.0540 g, 0.296 mmol), Et_3N

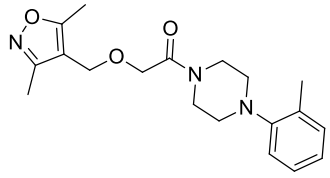
(100 μL, 0.740 mmol). The reaction mixture was cooled to 0 °C, treated with T3P (50 wt.% solution in EtOAc, 260 μL, 0.370 mmol, 1.5 equiv), warmed to room temperature, stirred for 3 d, diluted with EtOAc (10 mL), and washed with satd. aqueous NH_4Cl (2 mL), satd. aqueous $NaHCO_3$ (2 mL), and brine (2 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (ISCO, 12 g column, liquid load in CH_2Cl_2, EtOAc/hexanes gradient (10-90%), product eluted at 20%) to give **16** (0.0676 g, 0.211 mmol, 86%, >99.9% pure by ELSD) as a yellow oil: IR (neat) 3026, 2912, 2814, 1631, 1600, 1493, 1440, 1381, 1223, 1150, 1033, 919, 910, 760, 723, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.26 (m, 2 H), 7.23-7.12 (m, 5 H), 7.01 (dd, 2 H, *J* = 11.1, 7.5 Hz), 3.79 (brs, 4 H), 2.90 (brs, 4 H), 2.52 (brpent, 1 H, *J* = 4.6 Hz), 2.33 (s, 3 H), 2.02 (pent, 1 H, *J* = 4.6 Hz), 1.71 (pent, 1 H, *J* = 4.6 Hz), 1.34-1.26 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 150.9, 141.0, 132.7, 131.2, 128.6, 126.7, 126.3, 126.1, 123.8, 119.2, 52.2, 51.7, 46.2, 25.6, 23.3, 17.9, 16.2; HRMS (ESI) *m/z* calcd for $C_{21}H_{25}ON_2$ ($[M+H]^+$) 321.1961, found 321.1957.



2-Chloro-1-(4-(*o*-tolyl)piperazin-1-yl)ethanone (**17a**).[1,2] To a solution of chloroacetyl chloride (0.698 g, 6.05 mmol) and potassium carbonate (1.14 g, 8.25 mmol) in THF (7.0 mL) was added 1-(*o*-tolyl)piperazine (**4b**, 1.00 g, 5.50 mmol) in THF (12.6 mL) at 0 °C. The reaction mixture was gradually warmed to room temperature, stirred for 16 h, diluted with water, and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed sequentially with satd. aqueous $NaHCO_3$, 0.1 M aqueous HCl, and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude solid was filtered through a plug of SiO_2 (3:7, EtOAc/hexanes v/v 1% Et_3N) and washed thoroughly with EtOAc/hexanes (3:7) to give **17a** (1.37 g, 5.42 mmol, 99%) as an off white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.22-7.16 (m, 2 H), 7.05-6.99 (m, 2 H), 4.12 (s, 2 H), 3.78 (app t, 2 H, *J* = 4.8 Hz), 3.67 (app t, 2 H, *J* = 4.8 Hz), 2.97 (app t, 2 H, *J* = 4.8 Hz), 2.91 (app t, 2 H, *J* = 4.8 Hz), 2.33 (s, 3 H).

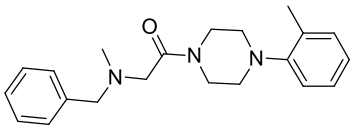


1-((Chloromethyl)sulfonyl)-4-(*o*-tolyl)piperazine (**17b**).[3] To a solution of 1-(*o*-tolyl)piperazine (**4b**, 0.500 g, 2.75 mmol) in CH_2Cl_2 (9.8 mL) and Et_3N (0.390 mL, 2.75 mmol) at 0 °C was added chloromethanesulfonyl chloride (0.460 g, 3.03 mmol). The reaction mixture was stirred at 0 °C, gradually warmed to room temperature quenched after 14 h with satd. aqueous NH_4Cl solution (3 mL), and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed water (2 x 10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude solid was filtered through a plug of SiO_2 (3:7, EtOAc/hexanes containing 1% Et_3N) and washed thoroughly with EtOAc/hexanes (3:7). The combined filtrates were concentrated *in vacuo* to give **17b** (0.676 g, 2.34 mmol, 85%) as an orange solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (t, 2 H, J = 8.1 Hz), 7.03 (t, 2 H, J = 8.1 Hz), 4.56 (s, 2 H), 3.63 (app t, 4 H, J = 5.0 Hz), 2.99 (app t, 4 H, J = 5.0 Hz), 2.32 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 132.7, 131.2, 126.8, 124.1, 119.4, 54.5, 51.9, 47.1, 17.7.

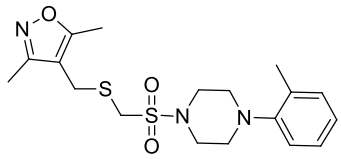


2-((3,5-Dimethylisoxazol-4-yl)methoxy)-1-(4-(*o*-tolyl)piperazin-1-yl)ethan-1-one (**18a**). A solution of (3,5-dimethylisoxazol-4-yl)methanol (**28**, 0.0302 g, 0.237 mmol) in THF (0.48 mL) was cooled to 0 ºC and NaH (60% dispersion in mineral oil, 0.0190 g, 0.475 mmol) was added. The reaction mixture was stirred at 0 ºC for 30 min, treated with 2-chloro-1-(4-(*o*-tolyl)piperazin-1-yl)ethanone (**17a**, 0.0600 g, 0.237 mmol), warmed to room temperature, stirred for 20 h, quenched with brine (1 mL), diluted with EtOAc (15 mL) and brine (5 mL), and extracted with EtOAc (2 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (3:2, EtOAc/hexanes) to give **18a** (0.0735 g, 0.214 mmol, 90%, 100% pure by ELSD) as a light yellow oil: IR (ATR) 2918, 2817, 1645, 1599, 1493, 1443, 1369, 1273, 1225, 1116, 1030, 977, 764, 725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.21-7.16 (m, 2 H), 7.02 (dt, 1 H, J = 7.6, 1.2 Hz), 6.97 (app d, 1 H, J = 8.0 Hz), 4.41 (s, 2 H), 4.17 (s, 2 H), 3.77 (brs, 2 H), 3.59 (app t, 2 H, J = 4.8 Hz), 2.89 (app t, 4 H, J = 3.6 Hz), 2.41 (s, 3 H), 2.32 (s, 3 H), 2.30 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 167.5, 159.8, 150.7, 132.7, 131.2, 126.7, 123.9, 119.2, 110.5, 68.7, 61.7, 52.1, 51.7, 45.6, 42.3, 17.8, 11.1, 10.1; HRMS (ESI) *m/z* calcd for $C_{19}H_{26}N_3O_3$ ($[M+H]^+$) 344.1969, found 344.1960.

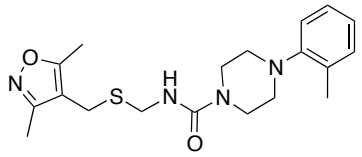


2-(Benzyl(methyl)amino)-1-(4-(*o*-tolyl)piperazin-1-yl)ethanone (**18b**). To a solution of 2-chloro-1-(4-(*o*-tolyl)piperazin-1-yl)ethanone (**17a**, 0.0534 g, 0.211 mmol), in CH_3CN (4 mL) was added *N*-methylbenzylamine (23 μL, 0.176 mmol) and K_2CO_3 (0.730 g, 0.528 mmol). The reaction mixture was heated at reflux for 5 h, cooled to room temperature, filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (2:3, EtOAc/hexanes) to give **18b** (0.0590 g, 0.175 mmol, 99%, >95% pure by LCMS) as a light yellow oil: IR (neat) 2933, 2816, 1640, 1450, 1491, 1222 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.33 (m, 4 H), 7.31-7.27 (m, 1 H), 7.23-7.19 (m, 2 H), 7.04 (t, 1 H, J = 7.5 Hz), 7.01 (d, 1 H, J = 8.0 Hz), 3.77 (brs, 2 H), 3.71-3.69 (m, 2 H), 3.61 (s, 2 H), 3.27 (s, 2 H), 2.91-2.87 (m, 4 H), 2.35 (s, 3 H) 2.34 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 138.1, 132.6, 131.1, 129.1, 128.2, 127.2, 126.6, 123.6, 119.1, 62.0, 60.3, 52.1, 51.7, 46.1, 42.4, 42.2, 17.8; HRMS (ESI) *m/z* calcd for $C_{21}H_{28}N_3O$ ($[M+H]^+$) 338.2238, found 338.2211.



3,5-Dimethyl-4-(((((4-(*o*-tolyl)piperazin-1-yl)sulfonyl)methyl)thio)methyl)isoxazole (**18c**). A suspension of NaH (60% dispersion in mineral oil, 0.0200 g, 0.499 mmol) in THF (0.6 mL) was treated under an atmosphere of N_2 at 0 °C with a solution of (3,5-dimethylisoxazol-4-yl)methanethiol (**25**, 0.0536 g, 0.374 mmol) in THF (0.4 mL). The

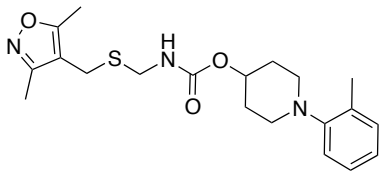
reaction mixture was stirred for 10 min, treated with 1-((chloromethyl)sulfonyl)-4-(*o*-tolyl)piperazine (**17b**, 0.0360 g, 0.125 mmol), stirred for 2 d at room temperature, quenched (water) and extracted (EtOAc). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (1:4, EtOAc/hexanes) to give crude **18c** that was further purified by preparative TLC (2:3, Et_2O/hexanes) to give **18c** (2.0 mg, 0.00506 mmol, 4%, 100% pure by ELSD) as a colorless oil: IR (neat) 2924, 1636, 1450, 1420, 1320, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, 2 H, J = 7.7 Hz), 7.06-7.00 (m, 2 H), 3.87 (s, 2 H), 3.76 (s, 2 H), 3.58 (app t, 4 H, J = 4.8 Hz), 2.99 (app t, 4 H, J = 4.8 Hz), 2.44 (s, 3 H), 2.32 (s, 3 H), 2.31 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 159.7, 150.6, 132.7, 131.2, 126.8, 124.0, 119.4, 108.7, 51.8, 48.6, 47.0, 24.1, 17.8, 11.1, 10.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{26}O_3N_3S_2$ ($[M+H]^+$) 396.1416, found 396.1410.



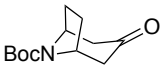
***N*-((((3,5-Dimethylisoxazol-4-yl)methyl)thio)methyl)-4-(*o*-tolyl)piperazine-1-carboxamide** (**20a**). To a solution of 2-(((3,5-dimethylisoxazol-4-yl)methyl)thio)acetic acid (**3a**, 0.0500 g, 0.248 mmol) in toluene (4.0 mL) was added DPPA (57 µL, 0.261 mmol) and Et_3N (37 µL, 0.261 mmol). The reaction mixture was heated at 110 °C for 60 min, cooled and washed with satd. aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated to give the isocyanate **19** as a pink oil that was used without further purification.

A solution of 1-(o-tolyl)piperazine (**4b**, 0.460 g, 0.261 mmol) and Et_3N (37 µL, 0.261 mmol) in CH_2Cl_2 (0.5 mL) was cooled to 0 °C and treated with a solution of the isocyanate **19** in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred overnight at room temperature, then diluted with EtOAc and satd. aqueous NH_4Cl. The organic layer was washed with satd. aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (ISCO, 4 g column, gradient hexanes to 1:1, EtOAc/hexanes, with an initial base wash of the column using hexanes containing 1% Et_3N) to give **20a** (0.0606 g, 0.162 mmol, 65%, 98% pure by

ELSD) as a clear oil that turns to a red oil upon standing: IR (CH_2Cl_2) 3336, 2941, 2891, 2850, 1629, 1523, 1491, 1495, 1420, 1254, 1223, 1193, 997, 907, 761, 731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (dd, 2 H, *J* = 8.7, 7.5 Hz), 7.04-6.98 (m, 2 H), 4.88 (brt, 1 H, *J* = 6.0 Hz), 4.44 (d, 2 H, *J* = 6.0 Hz), 3.67 (s, 2 H), 3.50 (app t, 4 H, *J* = 5.0 Hz), 2.89 (app t, 4 H, *J* = 5.0 Hz), 2.39 (s, 3 H), 2.32 (s, 3 H), 2.29 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 159.5, 156.9, 150.9, 132.7, 131.2, 126.7, 123.7, 119.1, 110.8, 51.6, 44.4, 43.9, 23.6, 17.8, 11.0, 10.2; HRMS (ESI) *m/z* calcd for $C_{19}H_{27}N_4O_2S$ ($[M+H]^+$) 375.1849, found 375.1845.

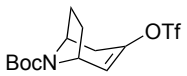


1-(*o*-Tolyl)piperidin-4-yl((((3,5-dimethylisoxazol-4-yl)methyl)thio)methyl)carbamate (**20b**). To a solution of 2-(((3,5-dimethylisoxazol-4-yl)methyl)thio)acetic acid (**3a**, 0.0500 g, 0.248 mmol) in toluene (4.0 mL) was added DPPA (0.06 mL, 0.261 mmol) and Et_3N (37 µL, 0.261 mmol). The reaction mixture was heated at 110 °C for 60 min, cooled to room temperature and treated with a solution of 1-(o-tolyl)piperidin-4-ol (**4n**, 0.0427 g, 0.224 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred overnight at 80 °C, and diluted with EtOAc and satd. aqueous NH_4Cl. The organic layer was washed with satd. aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (ISCO, 4 g column, gradient hexanes to 3:7, EtOAc/hexanes, with an initial base wash of the column with hexanes w/ 1% Et_3N) to give **20b** (0.0168 g, 0.0431 mmol, 17%, 100% pure by ELSD) as a clear oil that eventually turned to a light yellow oil upon standing: IR (CH_2Cl_2) 3323, 2947, 2924, 2848, 2811, 1711, 1491, 1450, 1422, 1228, 1195, 1027, 762, 723 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6) δ 7.98 (t, 1 H, *J* = 6.4 Hz), 7.16-7.11 (m, 2 H), 7.02 (d, 1 H, *J* = 7.2 Hz), 6.94 (dt, 1 H, *J* = 7.2, 1.2 Hz), 4.72-4.69 (m, 1 H), 4.15 (d, 2 H, *J* = 6.4 Hz), 3.66 (s, 2 H), 3.01-2.98 (m, 2 H), 2.78-2.72 (m, 2 H), 2.36 (s, 3 H), 2.24 (s, 3 H), 2.18 (s, 3 H), 2.04-1.94 (m, 2 H), 1.77-1.67 (m, 2 H); ^{13}C NMR (100 MHz, DMSO-d6) δ 165.7, 159.2, 155.5, 151.5, 131.8, 130.7, 126.5, 122.8, 118.9, 110.9, 69.9, 49.2, 42.9, 31.6, 21.9, 17.4, 10.5, 9.7; HRMS (ESI) *m/z* calcd for $C_{20}H_{28}N_3O_3S$ ($[M+H]^+$) 390.1846, found 390.1846.



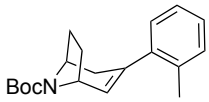
(*tert*-Butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (21a).[4] A solution of nortropinone•HCl (**21**, 2.00 g, 12.4 mmol) in a minimum amount of water (6.0 mL) was cooled to 0 °C, treated dropwise with 1 M NaOH (14.8 mL, 14.8 mmol, 1.2 equiv), warmed to room temperature over 20 min, extracted with CH_2Cl_2 (3 x 40 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* (water bath at 23 °C) to give nortropinone **21** as the free base (1.54 g, quant.). The colorless oil was used without further purification

To a solution of nortropinone **21** (1.54 g, 12.3 mmol) in CH_2Cl_2 (50 mL) cooled to 0 °C was added Boc anhydride (4.26 mL, 18.6 mmol), DMAP (0.302 g, 2.47 mmol), and Et_3N (7.0 mL, 50.2 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. After 19 h, the solvent was removed under reduced pressure, and the residue was diluted with water, extracted with EtOAc (3x), washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a red sticky solid which was purified by chromatography on SiO_2 (CH_2Cl_2) to give **21a** (2.18 g, 9.68 mmol, 78% over two steps) as a pale yellow oil that solidified to an off-white solid upon standing at room temperature: ^{1}H NMR (300 MHz, DMSO-d6) δ 4.34-4.30 (m, 2 H), 2.55 (dt, 2 H, J = 15.6, 4.2 Hz), 2.23 (d, 2 H, J = 15.6 Hz), 2.20 (app s, 1 H), 2.03-1.94 (m, 2 H), 1.60-1.52 (m, 2 H), 1.44 (s, 9 H); ^{13}C NMR (75 MHz, DMSO-d6) δ 207.4, 152.6, 79.2, 52.7, 48.1, 28.0 (2 C).

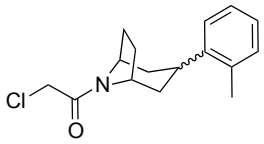


***tert*-Butyl 3-(((trifluoromethyl)sulfonyl)oxy)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (22).**[4] A solution of NaHMDS (0.895 g, 4.88 mmol) in THF (12 mL) was added dropwise (over 10 min) at -78 °C to a solution of *tert*-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (**21a**, 1.00 g, 4.44 mmol) in THF (12 mL). The reaction mixture was stirred at -78 °C for 2 h, treated dropwise (over 20 min) with a solution of $PhN(Tf)_2$ (1.90 g, 5.33 mmol) in THF (12 mL), stirred for an additional 30 min at -78 °C and then allowed to warm to room temperature and stirred for 2 h. After

addition of 10% w/v Na_2CO_3 (50 mL), the solution was extracted with Et_2O (2 x 75 mL). The combined organic layers were washed with 10% Na_2CO_3 solution, dried ($MgSO_4$), and concentrated *in vacuo* to give the crude residue as a yellow oil that was purified by chromatography on SiO_2 (1:19, EtOAc/hexanes w/ 1% Et_3N) to give **22** (1.24 g, 3.47 mmol, 78%) as a clear oil that solidified to a wax upon storage at -20 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (brs, 1 H), 4.54-4.38 (m, 2 H), 3.07-3.02 (m, 1 H), 2.30-2.20 (m, 1 H), 2.11-1.99 (m, 3 H), 2.00-1.97 (m, 2 H), 1.79-1.70 (m, 1 H), 1.45 (s, 9 H).



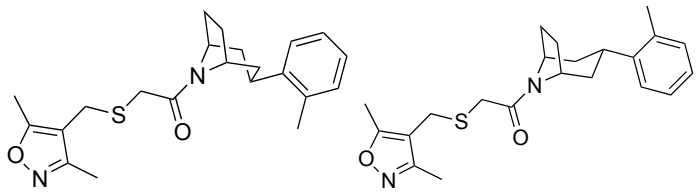
***tert*-Butyl 3-(o-tolyl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate** (**23a**). A solution of Na_2CO_3 (0.330 g, 3.11 mmol), lithium chloride (0.0600 g, 1.41 mmol), *tert*-butyl 3-(((trifluoromethyl)sulfonyl)oxy)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (**22**, 0.460 g, 1.41 mmol) and o-tolylboronic acid (0.235 g, 1.70 mmol) in DME (11 mL) and H_2O (3 mL) was sparged with N_2 for 1 h, and treated with $Pd(PPh_3)_4$ (0.0376 g, 0.0325 mmol). The flask was evacuated and backfilled with nitrogen (3x) and the mixture was heated at 60 °C for 3 h. The mixture was allowed to cool to room temperature, diluted with brine, extracted with EtOAc (3x), dried (Na_2SO_4), and concentrated *in vacuo* to give a a brown oil which was dry loaded onto SiO_2 and purified by chromatography on SiO_2 (hexanes to 15:1, hexanes/EtOAc) to give **23a** (0.330 g, 1.10 mmol, 78%) as a colorless solid: Mp 67.5-68.4 °C; IR (neat) 2975, 2934, 1685, 1420, 1364, 1329, 1169, 1094 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.20-7.12 (m, 3 H), 7.02-7.00 (m, 1 H), 5.94-5.86 (m, 1 H), 4.50-4.30 (m, 2 H), 3.11-2.91 (m, 1 H), 2.27 (app s, 4 H), 2.10-1.90 (m, 3 H), 1.90-1.80 (m, 1 H), 1.50 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 154.4, 141.6, 136.2, 135.5, 134.9, 131.3, 130.8, 130.7, 130.1, 129.3, 128.1, 126.9, 126.8, 125.6, 123.5, 120.0, 114.8, 79.3, 53.6, 52.9, 52.7, 52.0, 39.2, 38.4, 34.9, 34.3, 30.4, 29.6, 28.4, 19.5, 15.8; HRMS (ESI) *m/z* calcd for $C_{14}H_{17}N$ ($[M+H-C_5H_9O_2]^+$) 200.1439, found 200.1435.



2-Chloro-1-(3-(o-tolyl)-8-azabicyclo[3.2.1]octan-8-yl)ethan-1-one (**24**). A solution of *tert*-butyl 3-(*o*-tolyl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (**23a**, 0.196 g, 0.655 mmol) in EtOH (5.0 mL) was treated with Pd/C (5%, 0.0480 g). The flask was evacuated and flushed with H_2 (balloon, 3x). The reaction mixture was stirred under H_2 (1 atm, balloon) overnight, filtered through Celite, rinsed with EtOH and concentrated *in vacuo* to give (**23**, 0.160 g, 0.531 mmol, 81%) as a yellow liquid that was used without further purification.

A solution of **23** (0.200 g, 0.664 mmol) in CH_2Cl_2 (5 mL) was treated at room temperature with TFA (0.30 mL, 3.98 mmol). After 16 h, the solution was concentrated *in vacuo*. The oily residue was extracted with CH_2Cl_2, washed with satd. aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 3-(*o*-tolyl)-8-azabicyclo[3.2.1]octane (**23b**, 0.133 g, 0.661 quant) as a light yellow oil that was used without further purification.

A solution of **23b** (0.130 g, 0.646 mmol) and Et_3N (0.10 mL, 0.710 mmol) in THF (3 mL) was cooled to 0 °C and treated with chloroacetyl chloride (60 µL, 0.710 mmol) dropwise over 1 min. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 20 h. The solution was filtered, concentrated *in vacuo* and the residue was dissolved in EtOAc, washed with water, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (1:1, hexanes/EtOAc) to give **24** (0.141 g, 0.508 mmol, 79%) as a brown oil. ^{1}H NMR analysis indicated an approximately 4:3 ratio of *endo*/*exo* isomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.09 (m, 6.8 H), 4.85-4.80 (m, 1 H), 4.80-4.74 (m, 0.7 H), 4.38-4.30 (m, 1.7 H), 4.14-4.04 (m, 3.6 H), 3.49-3.39 (m, 1 H), 2.99-2.88 (m, 0.7 H), 2.58-2.49 (m, 1 H), 2.38 (s, 3 H), 2.32 (s, 2 H), 2.22-1.70 (m, 11 H), 1.55-1.48 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 162.1, 141.8, 141.7, 135.9, 135.0, 130.4 (2 C), 126.5, 126.4, 126.2, 126.1 (2 C), 126.0, 55.7, 55.4, 52.6, 49.6, 41.5, 41.4, 39.5, 39.1, 37.9, 37.5, 32.8, 30.9, 30.3, 29.7, 28.9, 27.1, 19.4, 19.3; HRMS (ESI) *m/z* calcd for $C_{16}H_{21}ClNO$ ($[M+H]^+$), 298.1312, found 298.1301



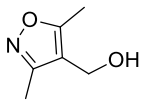
26a **26b**

2-(((3,5-Dimethylisoxazol-4-yl)methyl)thio)-1-(3-(*o*-tolyl)-8-azabicyclo[3.2.1]octan-8-yl)ethanone (**26a**) and **2-(((3,5-dimethylisoxazol-4-yl)methyl)thio)-1-(3-(*o*-tolyl)-8-azabicyclo[3.2.1]octan-8-yl)ethanone** (**26b**). A solution of (3,5-dimethylisoxazol-4-yl)methanethiol (**25**, 0.0247 g, 0.172 mmol) in THF (0.4 mL) was added to a suspension of NaH (60% dispersion in mineral oil, 0.0115 g, 0. mmol) in THF (1.0 mL) at 0 °C. The resultant slurry was stirred at 0 °C for 30 min and a solution of 2-chloro-1-(3-(*o*-tolyl)-8-azabicyclo[3.2.1]octan-8-yl)ethanone (**24**, 0.0400 g, 0.144 mmol) in THF (0.4 mL) was added. The reaction mixture was allowed to warm to room temperature, stirred for 24 h, quenched with brine (1 mL), diluted with EtOAc (15 mL) and brine (5 mL), and extracted with EtOAc (2 x 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (3:7, EtOAc/hexanes) to give **26**a (16.2 mg, 0.0421 mmol, 29%, 99.8% pure by ELSD) and **26b** (16.6 mg, 0.0432 mmol, 30%, 100% pure by ELSD) as light yellow oils.

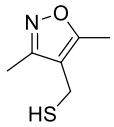
26a (*dr* 82:18 by ^{1}HNMR): IR (neat) 2952, 2933, 1629, 1446, 1424, 1195 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.11 (m, 4 H), 4.81-4.80 (m, 1 H), 4.25-4.24 (m, 1 H), 3.72 (s, 2 H), 3.46-3.40 (m, 1 H), 3.19 (s, 2 H), 2.44 (brs, 4 H), 2.37 (s, 3 H), 2.31 (s, 3 H), 2.19-2.09 (m, 1 H), 2.08-1.84 (m, 5 H), 1.80-1.66 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) d 166.8, 164.8, 159.8, 141.9, 135.1, 130.5, 126.5, 126.2, 126.0, 109.9, 55.8, 52.2, 39.2, 37.6, 32.5, 30.4, 28.9, 27.3, 23.8, 19.3, 11.0, 10.1; HRMS (ESI) *m/z* calcd for $C_{22}H_{29}O_2N_2S$ ($[M+H]^+$) 385.1950, found 385.1946.

26b (*dr* 92:8 by ^{1}HNMR): IR (neat) 2952, 2934, 1629, 1489, 1446, 1193, 1163 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.12 (m, 4 H), 4.76 (t, 1 H, J = 7.6 Hz), 4.20 (t, 1 H, J = 7.6 Hz), 3.80 (d, 1 H, J = 14.0 Hz), 3.62 (d, 1 H, J = 14.0 Hz), 3.20 (d, 1 H, J = 12.8 Hz), 3.10 (d, 1 H, J = 13.6 Hz), 3.01-2.90 (m, 1 H), 2.60-2.45 (m, 5 H), 2.40 (s, 6 H), 2.22-2.11 (m, 1 H), 2.10-2.00 (m, 1 H), 1.85-1.69 (m, 2 H), 1.55-1.40 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 166.3, 159.8, 142.0, 135.7, 130.4, 126.5, 126.2, 126.0, 109.9,

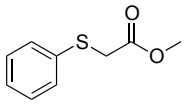
53.3, 49.3, 39.0, 38.0, 32.8, 31.9, 31.1, 29.9, 23.9, 19.5, 11.1, 10.2; HRMS (ESI) *m/z* calcd for $C_{22}H_{29}O_2N_2S$ ($[M+H]^+$) 385.1950, found 385.1944.



(3,5-Dimethylisoxazol-4-yl)methanol (**28**).[5] To a solution of 3,5-dimethylisoxazole-4-carboxylic acid (1.60 g, 11.3 mmol) in THF (69 mL) at 0 ºC was added dropwise a 2 M solution of $LiAlH_4$ in THF (5.6 mL, 11.2 mmol). The reaction mixture was allowed to warm to room temperature, stirred overnight, transferred to a 500-mL Erlenmeyer flask and treated with sodium sulfate decahydrate until the foaming subsided. Celite (2.3 g) was added and the slurry was filtered and washed with CH_2Cl_2 (75 mL). The filtrate was concentrated *in vacuo* to give **28** (1.14 g, 8.97 mmol, 79%) as a clear colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (s, 2 H), 2.38 (s, 3 H), 2.29 (s, 3 H).

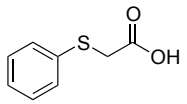


(3,5-Dimethylisoxazol-4-yl)methanethiol (**25**).[6] A solution of (3,5-dimethylisoxazol-4-yl)methanol (**28**, 0.500 g, 3.90 mmol) in toluene (13 mL) was treated with Lawesson's reagent (0.890 g, 2.15 mmol) at room temperature, heated to 80 °C and stirred for 1 d. The crude mixture was loaded directly onto SiO_2 and purified by chromatography on SiO_2 (4:1, hexanes/EtOAc) to give **25** (0.115 g, 0.803 mmol, 21%) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.49 (d, 2 H, J = 6.6 Hz), 2.36 (s, 3 H), 2.30 (s, 3 H), 1.64 (t, 1 H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 159.0, 113.3, 15.9, 10.9, 10.0.

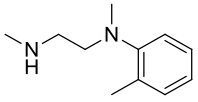


Methyl 2-(phenylthio)acetate (**29**).[7] A solution of thiophenol (0.10 mL, 0.977 mmol), and methyl bromoacetate (0.164 g, 1.07 mmol) in THF (13 mL) was treated with Et_3N (0.17 mL, 1.17 mmol), stirred at room temperature for 4 h, and diluted with Et_2O and satd. aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O (2 x 5 mL). The

combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **29** (0.176 g, 0.966 mmol, 99%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.38 (m, 2 H), 7.33-7.20 (m, 3 H), 3.71 (s, 3 H), 3.65 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 134.9, 129.9, 129.0, 127.0, 52.5, 36.5.

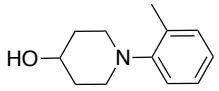


2-(Phenylthio)acetic acid (**3d**).[7,8] To a solution of methyl 2-(phenylthio)acetate (**29**, 0.176 g, 0.966 mmol) in MeOH (2 mL) was added 2 M LiOH (1 mL). The reaction mixture was stirred at room temperature for 1 h and TLC analysis (4:1, hexanes/EtOAc) indicated that **29** had been consumed. The solution was concentrated *in vacuo*, diluted with water (3 mL) and acidified to pH 2 with 1 M HCl at 0 °C. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **3d** (0.144 g, 0.857 mmol, 89%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.27 (brs, 1 H), 7.43 (d, 2 H, J = 7.6 Hz), 7.36-7.24 (m, 3 H), 3.69 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 134.4, 130.1, 129.2, 127.2, 36.6.

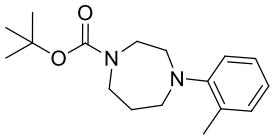


***N*,*N'*-Dimethyl-*N*-(*o*-tolyl)ethane-1,2-diamine** (**4i**).[9] A microwave vial was flushed with argon and charged with the *N*,*N'*-dimethylethylenediamine (0.180 g, 2.04 mmol), NaO-*t*-Bu (0.202 g, 2.04 mmol), (*rac*)-BINAP (0.0162 g, 0.0260 mmol), $Pd_2(dba)_3$ (0.0078 g, 0.0085 mmol), degassed toluene (10.2 mL), and 2-bromotoluene (0.297 g, 1.70 mmol). The reaction mixture was heated in the sealed vial under argon at 110 °C for 24 h, cooled to room temperature, diluted with CH_2Cl_2, filtered through Celite, and concentrated *in vacuo*. The residue was purified by chromatography on basic Al_2O_3 (95:5, CH_2Cl_2/MeOH) to give **4i** (0.0508 g, 0.285 mmol, 17%) as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, 2 H, J = 7.6 Hz), 7.08 (d, 1 H, J = 7.6 Hz), 6.98 (d, 1 H, J = 7.2 Hz), 3.05 (t, 2 H, J = 6.4 Hz), 2.71 (t, 2 H, J = 6.4 Hz), 2.65 (s, 3 H), 2.43 (s, 3 H), 2.32

(s, 3 H), 1.36 (brs, 1 H); HRMS (ESI) *m/z* calcd for $C_{11}H_{19}N_2$ ($[M+H]^+$) 179.1543, found 179.1541.

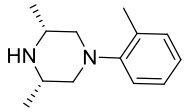


1-(*o*-Tolyl)piperidin-4-ol (**4n**).[10] An oven-dried microwave tube was charged with $Pd_2(dba)_3$ (0.0606 g, 0.0653 mmol), CyJohnphos (0.0292 g, 0.0816 mmol), and 4-piperidinol (0.330 g, 3.26 mmol). The microwave tube was evacuated and back-filled with argon. A 1 M solution of $LiN(TMS)_2$ (1.21 g, 7.17 mmol) in degassed THF (7.2 mL) was added via syringe along with 2-bromotoluene (0.600 g, 3.26 mmol). The reaction vessel was sealed and heated at 65 °C with stirring for 22 h. The reaction mixture was cooled to room temperature, quenched with 1 M HCl (10 mL), stirred at room temperature for 5 min, neutralized with a satd. aqueous $NaHCO_3$ solution, and diluted with EtOAc. The organic layer was dried ($MgSO_4$), filtered through Celite, and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (ISCO, 12 g column, gradient hexanes to 3:7, EtOAc/hexanes) to give **4n** (0.372 g, 1.94 mmol, 60%) as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (dd, 2 H, J = 9.3, 7.2 Hz), 7.04-6.96 (m, 2 H), 3.87-3.81 (m, 1 H), 3.15-3.08 (m, 2 H), 2.74 (dt, 2 H, J = 9.6, 2.7 Hz), 2.32 (s, 3 H), 2.06-2.00 (m, 2 H), 1.80-1.69 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 132.7, 130.9, 126.4, 123.0, 119.0, 68.0, 49.8, 35.2, 17.7; HRMS (ESI) *m/z* calcd for $C_{12}H_{18}NO$ ($[M+H]^+$) 192.1383, found 192.1307.

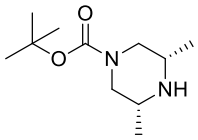


***tert*-Butyl 4-(*o*-tolyl)-1,4-diazepane-1-carboxylate** (**30a**). A microwave vial was flushed with argon and charged with Boc-homopiperazine (0.223 g, 1.10 mmol), NaO-*t*-Bu (0.116 g, 1.20 mmol), (*rac*)-BINAP (0.0478 g, 0.0752 mmol, 7.5 mol%), $Pd_2(dba)_3$ (0.0233 g, 0.0251 mmol), degassed toluene (2.8 mL), and 2-bromotoluene (0.175 g, 1.00 mmol). The reaction mixture was heated in the sealed vial under argon at 80 °C for 19 h, cooled to room temperature, diluted with CH_2Cl_2, filtered through Celite, and

concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (1:9, EtOAc/hexanes) to give **30a** (0.139 g, 0.479 mmol, 48%) as a yellow oil: IR (ATR) 2973, 2828, 1689, 1598, 1491, 1457, 1411, 1364, 1233, 1215, 1156, 1122, 878, 761, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, room temperature, mixture of rotamers) δ 7.16 (d, 1 H, J = 6.0 Hz), 7.12 (d, 1 H, J = 6.0 Hz), 7.04 (d, 1 H, J = 7.5 Hz), 6.95 (t, 1 H, J = 7.0 Hz), 3.61-3.56 (m, 4 H), 3.11-3.04 (m, 4 H), 2.31 (s, 3 H), 1.96-1.91 (m, 2 H), 1.49 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers) δ 155.6, 155.5, 153.9, 153.8, 132.9, 130.9, 126.5, 123.1, 120.8 (2 C), 79.3, 56.2, 56.0, 55.5, 55.2, 48.4, 48.0, 46.2, 45.4, 29.0, 28.9, 28.5, 18.5; HRMS (ESI) *m/z* calcd for $C_{17}H_{27}N_2O_2$ ($[M+H]^+$) 291.2067, found 291.2062.

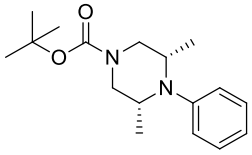


(3*S*,5*R*)-3,5-Dimethyl-1-(*o*-tolyl)piperazine (**4k**).[11] A Schlenk flask was flushed with N_2 and charged with *cis*-2,6-dimethylpiperazine (0.110 g, 0.963 mmol), NaO-*t*-Bu (0.170 g, 1.75 mmol), (*rac*)-BINAP (0.0084 g, 0.0130 mmol), $Pd_2(dba)_3$ (0.0083 g, 0.0087 mmol), degassed toluene (4 mL), and 2-bromotoluene (0.150 g, 0.880 mmol). The reaction mixture was heated under N_2 at 110 °C for 24 h, cooled to room temperature, diluted with CH_2Cl_2, filtered through Celite, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (1:19, MeOH/CH_2Cl_2) to give **4k** (0.140 g, 0.685 mmol, 78%) as clear, yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.19-7.15 (m, 2 H), 7.02-6.98 (m, 2 H), 3.13-3.10 (m, 2 H), 3.01 (app d, 2 H, J = 10.5 Hz), 2.35-2.31 (m, 5 H), 1.12 (d, 6 H, J = 6.5 Hz).

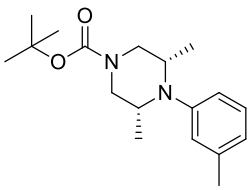


***tert*-Butyl 3,5-dimethylpiperazine-1-carboxylate** (**31**).[12] To a solution of *cis*-2,6-dimethylpiperazine (0.500 g, 4.38 mmol) in CH_2Cl_2 (11 mL) at 0 °C was added dropwise a solution of Boc-anhydride (0.946 g, 4.33 mmol) in CH_2Cl_2 (2.6 mL). The reaction mixture was allowed to warm to room temperature, stirred overnight, diluted with CH_2Cl_2

and washed with satd. aqueous Na_2CO_3 solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give **31** (0.813 g, 3.79 mmol, 87%) as an off-white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10-3.80 (m, 2 H), 2.85-2.70 (m, 2 H), 2.40-2.20 (m, 2 H), 1.46 (s, 9 H), 1.05 (d, 6 H, J = 6.3 Hz).

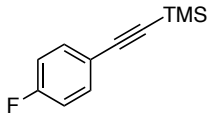


***tert*-Butyl 3,5-dimethyl-4-phenylpiperazine-1-carboxylate** (**30b**). To a sealed tube under an argon atmosphere was added a solution of KHMDS (0.241 g, 1.15 mmol) in dry 1,4-dioxane (2.0 mL), a solution of *tert*-butyl 3,5-dimethylpiperazine-1-carboxylate (**31**, 0.246 g, 1.15 mmol) in dry 1,4-dioxane (0.9 mL) and bromobenzene (100 μL, 0.955 mmol). The reaction mixture was stirred at 100 °C for 18 h, cooled to room temperature, quenched with water (5 mL), diluted with Et_2O (15 mL) and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (1:9, EtOAc/hexanes) to give **30b** (0.0970 g, 0.334 mmol, 35%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.27 (m, 2 H), 7.15-7.09 (m, 3 H), 4.00-3.80 (m, 2 H), 3.07-3.03 (m, 2 H), 2.82 (brt, 2 H, J = 11.7 Hz), 1.50 (s, 9 H), 0.77 (d, 6 H, J = 6.3 Hz).

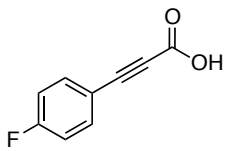


***tert*-Butyl 3,5-dimethyl-4-(*m*-tolyl)piperazine-1-carboxylate** (**30c**). A sealed tube under an argon atmosphere was treated with KHMDS (0.221 g, 1.05 mmol) in dry 1,4-dioxane (2.0 mL), a solution of *tert*-butyl 3,5-dimethylpiperazine-1-carboxylate (**31**, 0.226 g, 1.05 mmol) in dry 1,4-dioxane (0.7 mL) and bromotoluene (105 μL, 0.877 mmol). The reaction mixture was stirred at 100 °C for 18 h, cooled to room temperature, quenched

with water (5 mL), diluted with Et_2O (15 mL) and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (1:9, EtOAc/hexanes) to give **30c** (0.0441 g, 0.145 mmol, 17%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (t, 1 H, J = 7.5 Hz), 6.96-6.89 (m, 3 H), 4.00-3.80 (m, 2 H), 3.06-3.00 (m, 2 H), 2.81 (brt, 2 H, J = 11.7 Hz), 2.32 (s, 3 H), 1.50 (s, 9 H), 0.77 (d, 6 H, J = 6.3 Hz).

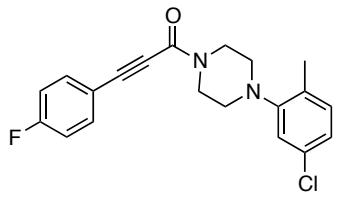


((4-Fluorophenyl)ethynyl)trimethylsilane (**32**).[13,14] A flame-dried flask under Ar was charged with $Pd(PPh)_2Cl_2$ (0.361 g, 0.514 mmol), CuI (0.0979 g, 0.514 mmol), and 4-fluorobromobenzene (5.66 mL, 51.4 mmol). Et_3N (110 mL) and (trimethylsilyl)acetylene (10.9 mL, 77.1 mmol) were added via syringe and the solution was sparged with Ar for 30 min. The reaction mixture was heated to 80 °C overnight and analysis by TLC (4:1, hexanes/EtOAc) indicated that 4-fluorobromobenzene had been consumed. The solution was cooled to room temperature and filtered through celite. The celite was washed (Et_2O) until the washes appeared colorless. The combined filtrates were concentrated in vacuo. The crude residue was purified by chromatography on SiO_2 (hexanes) to afford **32** (9.03 g, 47.0 mmol, 91%) as a pale orange oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.42 (m, 2 H), 6.99 (t, 2 H, J = 8.7 Hz), 0.25 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6 (d, $J_{C\text{-}F}$ = 248 Hz), 133.9 (d, $J_{C\text{-}F}$ = 8 Hz), 119.3 (d, $J_{C\text{-}F}$ = 4 Hz), 115.5 (d, $J_{C\text{-}F}$ = 22 Hz), 104.0, 93.8, -0.07.

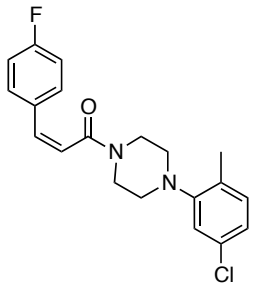


3-(4-Fluorophenyl)propiolic acid (**33**).[14] CsF (4.74 g, 31.2 mmol) was loaded into an oven-dried 250-mL round bottom flask in a glovebox. The flask was removed from the glovebox, attached to a CO_2 balloon, equipped with a magnetic stirrer and a septum, and

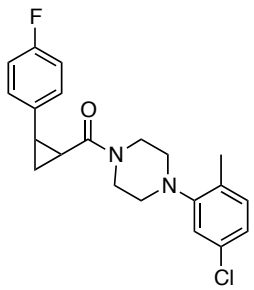
filled with anhydrous DMSO (60 mL). Neat **32** (5.00 g, 26.0 mmol) was added dropwise. The reaction mixture was stirred under CO_2 at room temperature overnight, diluted with water (600 mL) and washed with CH_2Cl_2 (2 × 150 mL). The aqueous layer was acidified at 0 °C to pH 1 with 6 M HCl and then extracted with Et_2O (3 × 200 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford **33** (3.02 g, 18.4 mmol, 71%) as an orange solid: ^{1}H NMR (400 MHz, Acetone-d_6) δ 11.74 (brs, 1 H), 7.71 (dd, 2 H, J = 8.6, 5.6 Hz), 7.26 (t, 2 H, J = 8.6 Hz); ^{13}C NMR (100 MHz, Acetone-d_6) δ 164.8 (d, $J_{C\text{-}F}$ = 249 Hz), 154.7, 136.1 (d, $J_{C\text{-}F}$ = 9 Hz), 117.1 (d, $J_{C\text{-}F}$ = 23 Hz), 84.6, 81.8.



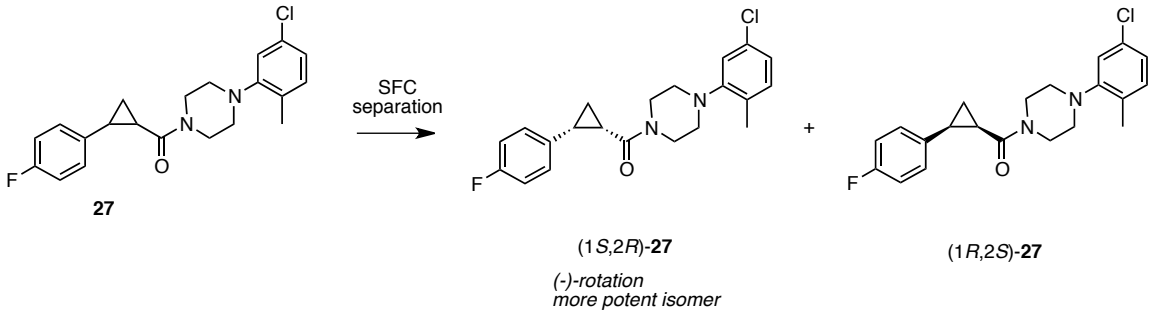
1-(4-(5-Chloro-2-methylphenyl)piperazin-1-yl)-3-(4-fluorophenyl)prop-2-yn-1-one (**34**). To a solution of **33** (3.00 g, 18.3 mmol) in anhydrous CH_2Cl_2 (180 mL) at 0 °C was added 1-(5-chloro-2-methylphenyl)piperazine (4.62 g, 21.9 mmol), and Et_3N (6.35 mL, 45.7 mmol), followed by dropwise addition of T3P (50 wt.% solution in EtOAc, 19.4 mL, 27.4 mmol). The reaction mixture was stirred at 0 °C for 30 min, warmed to room temperature overnight, diluted with CH_2Cl_2 (200 mL), washed with 1 M HCl (150 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by chromatography on SiO_2 (2:1, hexanes/EtOAc) to give **34** (5.22 g, 14.6 mmol, 80%) as an off white solid: Mp 138.7-140.4 °C; IR (neat) 2924, 2216, 1625, 1596, 1504, 1443, 1431, 1219, 1038, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, 2 H, J = 7.5, 5.4 Hz), 7.12-6.94 (m, 5 H), 3.96 (app t, 2 H, J = 4.8 Hz), 3.82 (app t, 2 H, J = 4.8 Hz), 2.95 (app t, 2 H, J = 4.8 Hz), 2.87 (app t, 2 H, J = 4.8 Hz), 2.28 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (d, $J_{C\text{-}F}$ = 251 Hz), 153.0, 151.7, 134.5 (d, $J_{C\text{-}F}$ = 9 Hz), 132.1, 131.8, 130.9, 123.7, 119.8, 116.4 (d, $J_{C\text{-}F}$ = 4 Hz), 116.0 (d, $J_{C\text{-}F}$ = 23 Hz), 89.9, 80.9, 51.9, 51.3, 47.4, 41.8, 17.3; HRMS (ESI) *m/z* calcd for $C_{20}H_{19}ClFON_2$ ($[M+H]^+$) 357.1164, found 357.1165



(*Z*)-1-(4-(5-Chloro-2-methylphenyl)piperazin-1-yl)-3-(4-fluorophenyl)prop-2-en-1-one (**35**). To a solution of **34** (5.00 g, 14.0 mmol) in dry EtOAc (140 mL) was added Lindlar's catalyst (5% Pd on $CaCO_3$, lead poisoned, 0.298 g, equivalent to 1 mol% Pd) and quinoline (0.83 mL, 7.01 mmol). The reaction vessel was placed under vacuum, backfilled with H_2 (balloon, 2x) and allowed to stir at room temperature for 6 h. Analysis by TLC (2:1, hexanes/EtOAc) indicated that **34** had been mostly consumed. The reaction mixture was filtered through Celite, washed with EtOAc, and concentrated under vacuum. The combined organic layers were washed with 1 M HCl, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude material was purified by chromatography on SiO_2 (1:1, hexanes/EtOAc) to afford **35** (3.15 g, 8.78 mmol, 63%, 87% brsm) as a colorless solid: IR (neat) 2913, 2239, 1616, 1506, 1437, 1223, 837, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.36 (m, 2 H), 7.08-7.02 (m, 3 H), 6.96 (dd, 1 H, J = 8.1, 2.1 Hz), 6.80 (d, 1 H, J = 2.1 Hz), 6.66 (d, 1 H J = 12.5 Hz), 6.05 (d, 1 H, J = 12.5 Hz), 3.80 (m, 2 H, J = 5.0 Hz), 3.49 (t, 2 H, J = 5.0 Hz), 2.80 (t, 2 H, J = 5.0 Hz), 2.53 (t, 2 H, J = 5.0 Hz), 2.21 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 162.7 (d, $J_{C\text{-}F}$ = 248 Hz), 151.7, 132.6, 132.0, 131.8, 131.5 (d, $J_{C\text{-}F}$ = 3 Hz), 132.1, 131.8, 130.9, 130.2 (d, $J_{C\text{-}F}$ = 8 Hz), 123.6, 122.7, 119.6, 115.6 (d, $J_{C\text{-}F}$ = 21 Hz), 51.4, 51.2, 46.5, 41.5, 17.3; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}ClFON_2$ ($[M+H]^+$) 359.1321, found 359.1329.



(4-(5-Chloro-2-methylphenyl)piperazin-1-yl)((1*RS*,2*SR*)-2-(4-fluorophenyl)cyclopropyl)-methanone (27). THF (90 mL) was degassed by sparging with Ar for 60 min and treated at room temperature under Ar atmosphere with anhydrous $CrCl_2$ (6.43 g, 51.8 mmol) followed by **35** (3.10 g, 8.64 mmol) and CH_2ICl (3.36 mL, 43.2 mmol). The reaction mixture was stirred for 20 h at 80 °C, cooled to room temperature, quenched by the addition of 1.0 M aqueous HCl (300 mL) and extracted with EtOAc (3 x 300 mL). The combined organic layers were filtered through a plug of basic Al_2O_3, and concentrated in vacuo. The residue was purified by chromatography on SiO_2 (1:1, hexanes/EtOAc) to afford an oil that was further purified twice by chromatography on basic Al_2O_3 (1:1, hexanes/EtOAc) to give **27** (2.76 g, 7.41 mmol, 86%) as a clear oil that solidified after storage on high vacuum overnight: Mp 78.2-80.4 °C (hexanes); IR (CH_2Cl_2) 2936, 1637, 1592, 1510, 1487, 1435, 1223, 1033, 837, 815 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16-7.11 (m, 2 H), 7.07 (dd, 1 H, J = 8.1, 0.5 Hz), 7.00-6.94 (m, 3 H), 6.73 (d, 1 H, J = 2.1 Hz), 3.81-3.76 (m, 1 H), 3.71-3.60 (m, 2 H), 3.36 (ddd, 1 H, J = 12.4, 8.8, 3.1 Hz), 2.79-2.71 (m, 2 H), 2.45 (td, 1 H, J = 8.8, 7.0 Hz), 2.35-2.29 (m, 1 H), 2.26-2.16 (m, 5 H), 1.83 (dt, 1 H, J = 7.0, 5.6 Hz), 1.35 (td, 1 H, J = 8.8, 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 161.7 (d, $J_{C\text{-}F}$ = 244 Hz), 151.9, 133.1 (d, $J_{C\text{-}F}$ = 3 Hz), 131.9 (d, $J_{C\text{-}F}$ = 14 Hz), 130.9, 129.1 (d, $J_{C\text{-}F}$ = 8 Hz), 123.6, 119.7, 115.0 (d, $J_{C\text{-}F}$ = 21 Hz), 51.8, 51.6, 45.6, 42.2, 23.8, 23.5, 17.3, 10.7; HRMS (ESI) *m/z* calcd for $C_{21}H_{23}ClFON_2$ ($[M+H]^+$) 373.1477, found 373.1478.

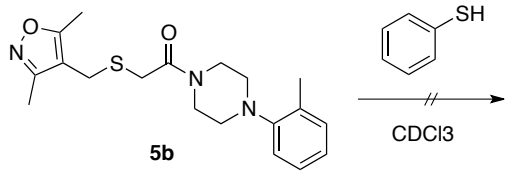


Racemic **27** was separated on a SFC Chiralpak-IC semiprep (250 x 10 mm) column (20% MeOH, 6 mL/min, 220 nM, P=100) to afford (4-(5-chloro-2-methylphenyl)piperazin-1-yl)((1*S*,2*R*)-2-(4-fluorophenyl)cyclopropyl)methanone ((1*S*,2*R*)-**27**, retention time 13.1 min) as a colorless viscous oil (100% purity by ELSD): $[a]^{20}_D$ -118.7 (*c* 0.39, $CHCl_3$); ^1H

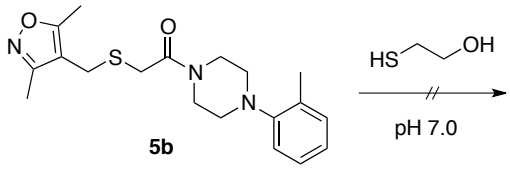
NMR (300 MHz, $CDCl_3$) δ 7.17-7.10 (m, 2 H), 7.07 (d, 1 H, *J* = 8.1 Hz), 7.02-6.94 (m, 3 H), 6.72 (d, 1 H *J* = 2.1 Hz), 3.83-3.75 (m, 1 H), 3.72-3.58 (m, 2 H), 3.39-3.31 (m, 1 H), 2.81-2.69 (m, 2 H), 2.45 (td, 1 H, *J* = 8.7, 6.9 Hz), 2.36-2.25 (m, 1 H), 2.25-2.15 (m, 5 H), 1.83 (dt, 1 H, *J* = 6.9, 5.5 Hz), 1.35 (td, 1 H, *J* = 8.7, 5.5 Hz); HRMS (ESI) *m/z* calcd for $C_{21}H_{23}ClFON_2$ ($[M+H]^+$) 373.1477, found 373.1476. The enantiomeric excess was 100% ee (SFC Chiralpak-IC (250 x 4.6 mm); 20% MeOH, 220 nM, 2 mL/min; retention time: 9.8 min).

(4-(5-Chloro-2-methylphenyl)piperazin-1-yl)((1*R*,2*S*)-2-(4-fluorophenyl)cyclopropyl)-methanone ((1*R*,2*S*)-**27**, retention time 16.5 min) was obtained as a colorless viscous oil (100% purity by ELSD): $[a]^{20}_D$ +117.4 (*c* 0.38, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.17-7.10 (m, 2 H), 7.07 (d, 1 H, *J* = 8.1Hz), 7.01-6.94 (m, 3 H), 6.72 (d, 1 H, *J* = 2.1 Hz), 3.82-3.74 (m, 1 H), 3.71-3.60 (m, 2 H), 3.39-3.30 (m, 1 H), 2.81-2.68 (m, 2 H), 2.45 (td, 1 H, *J* = 8.6, 7.0 Hz), 2.35-2.26 (m, 1 H), 2.25-2.15 (m, 5 H), 1.83 (dt, 1 H, *J* = 7.0, 5.6 Hz), 1.35 (td, 1 H, *J* = 8.6, 5.6 Hz); HRMS (ESI) *m/z* calcd for $C_{21}H_{23}ClFON_2$ ($[M+H]^+$) 373.1477, found 373.1476. The enantiomeric excess was 100% ee (SFC Chiralpak-IC (250 x 4.6 mm); 20% MeOH, 220 nM, 2 mL/min; retention time: 12 min).

Stability testing of **5b**:



Stability Testing of 5b monitored by ^{1}H NMR. To a solution of **5b** (5.3 mg, 0.015 mmol) in $CDCl_3$ (400 μL) in an NMR tube was added a solution of thiophenol (140 μL of a solution of of thiophenol (100 μL, 10.78 mg) in $CDCl_3$ (1 mL). NMR spectra were recorded at 0, 1 h, 4.5 h, 24 h, 48 h, 1 week, and 2 weeks. The spectra remained unchanged over this time period. After 2 weeks, the sample was analyzed by LCMS and showed starting material and another other compound tentatively assigned as thiophenol.



Stability Testing of 5b monitored by LCMS. To a solution of **5b** (1.6 mg, 0.0045 mmol) in MeOH (150 μL) was added pH 7 buffer (1.35 mL) and mercaptoethanol (1 drop). After 1.5 h, 3 h, 24 h, and 1 week, a sample of the cloudy solution was filtered (filter diameter 0.45 μm) into an LCMS vial and monitored by LCMS. Chromatograms did not change during this time period.

3. References

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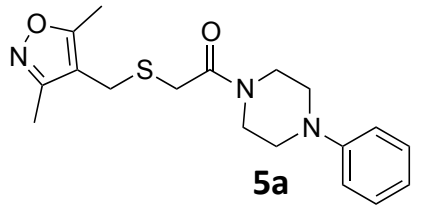

5a

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7.211
6.890
6.862
6.836

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3.133
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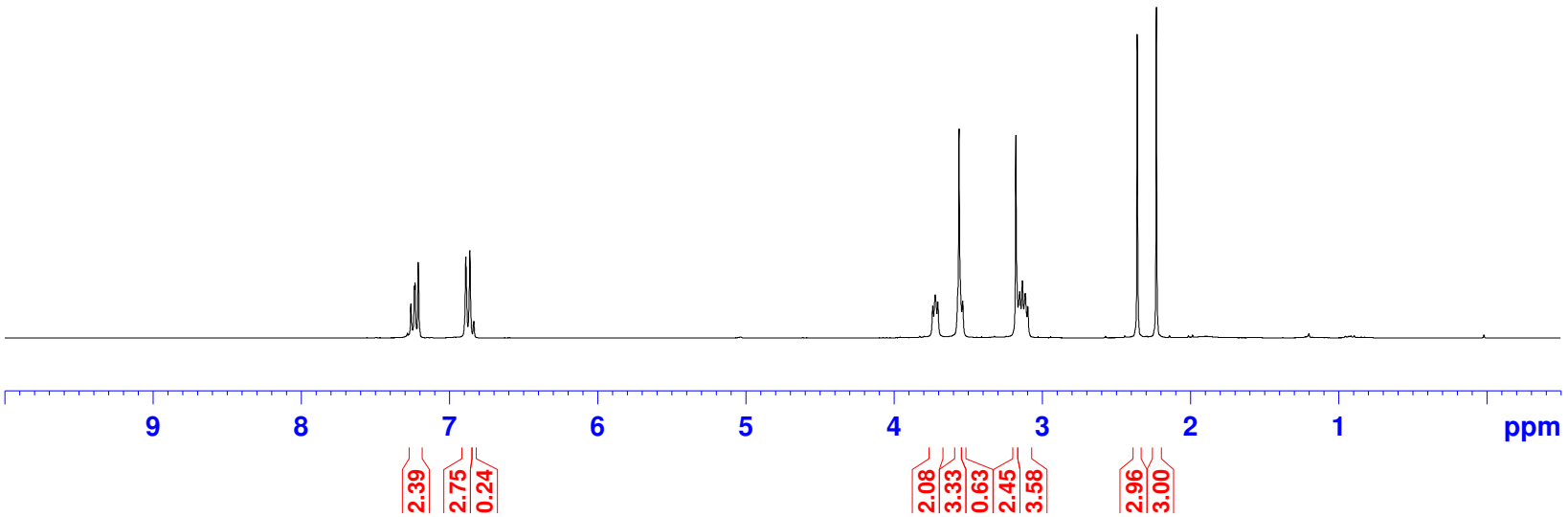
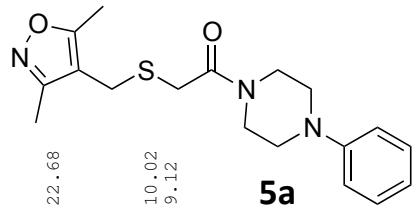
2.229




O
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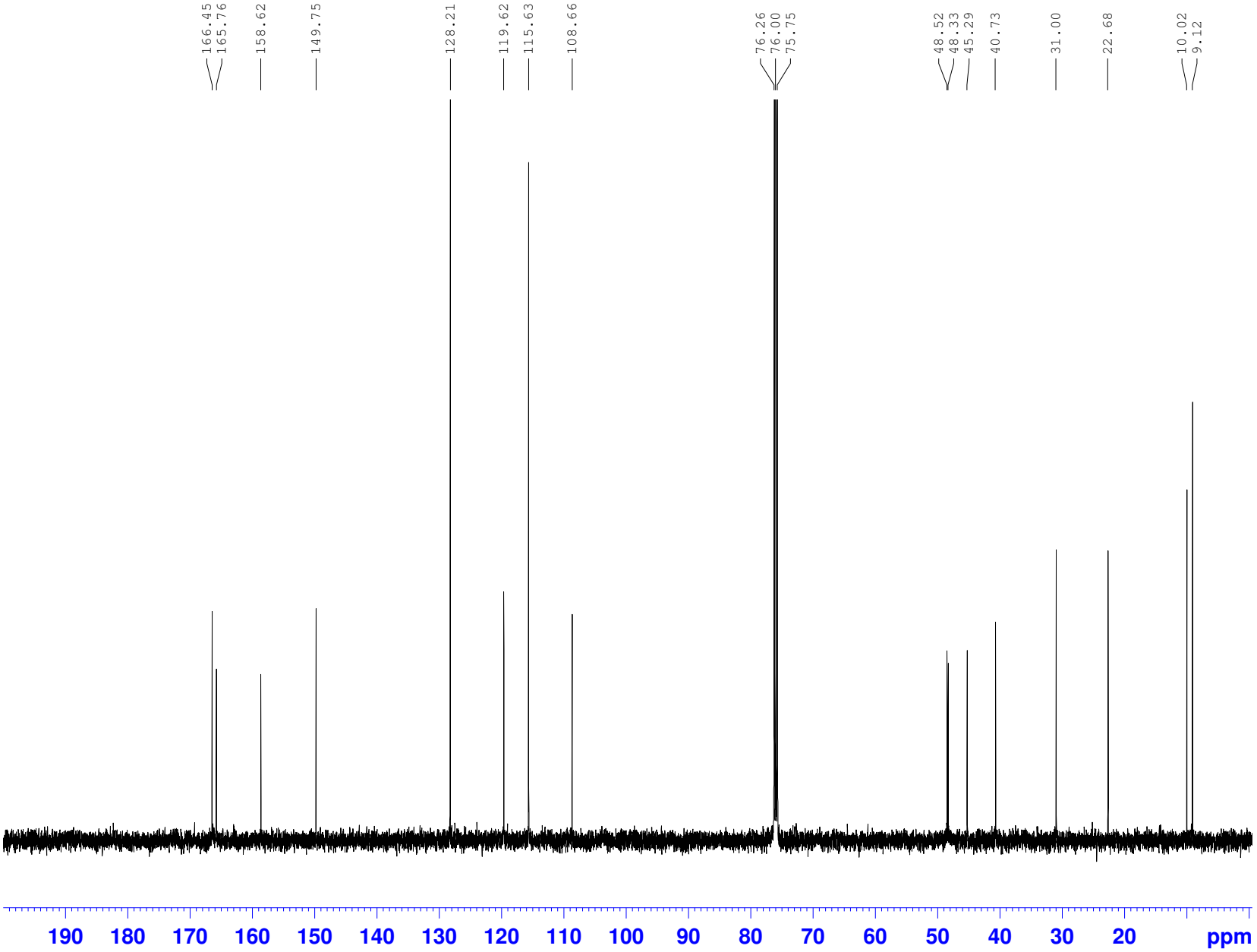
S
O
N
N

5a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10.02
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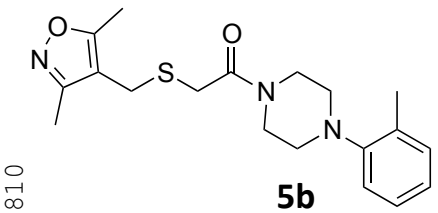
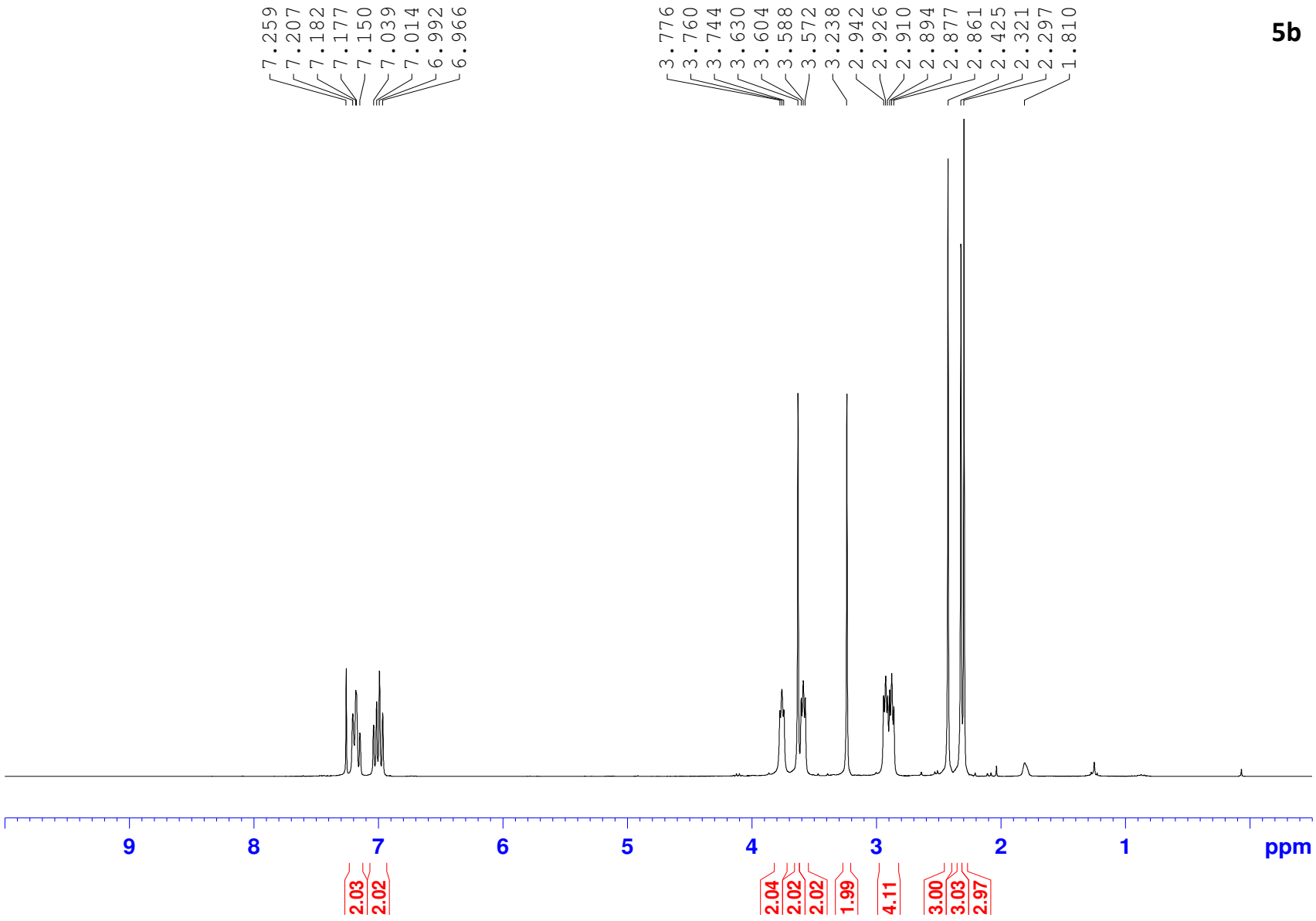


5b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3.630
3.604
3.588
3.572
3.238
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2.910
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2.861
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6
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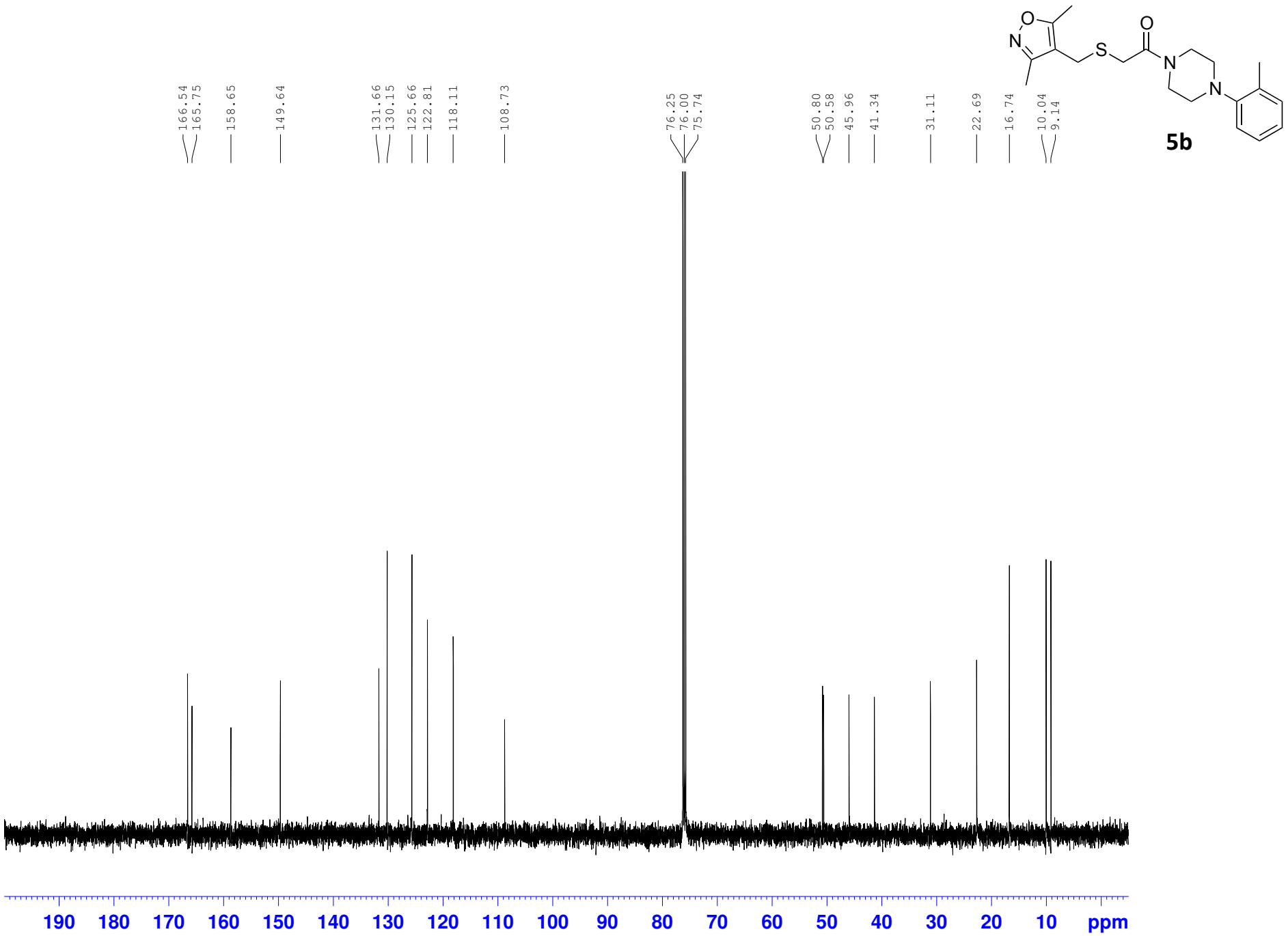
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5b
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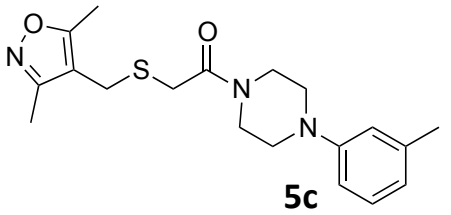

5c

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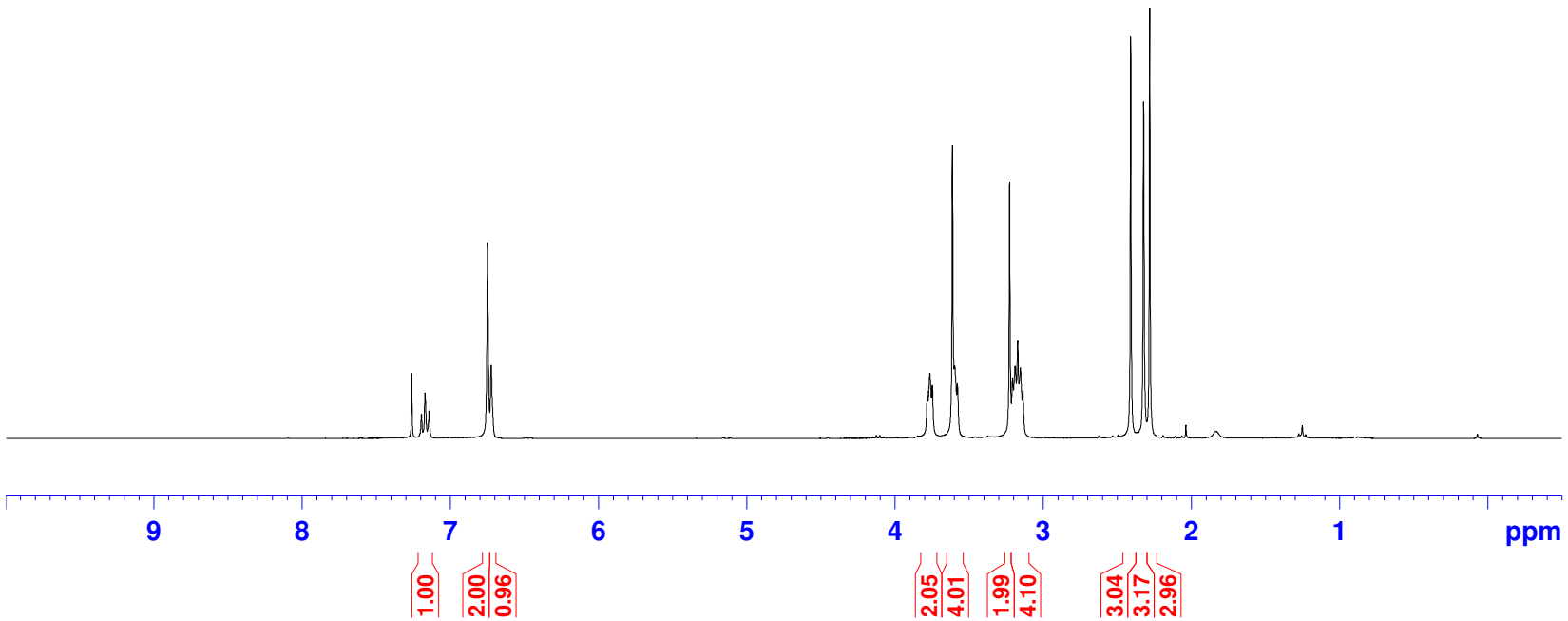

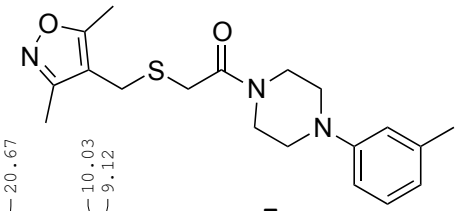

5c

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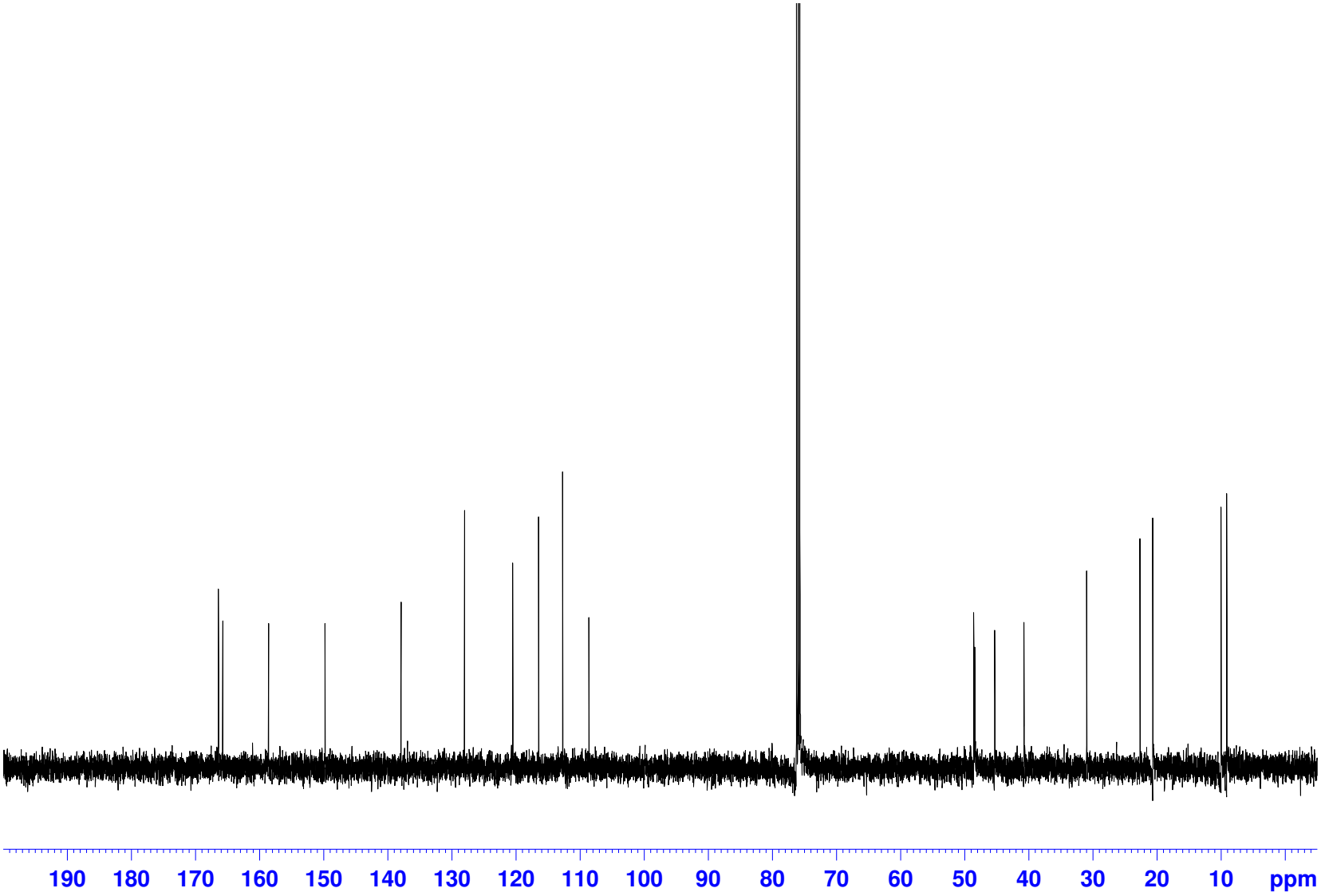

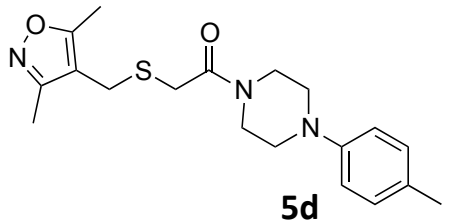
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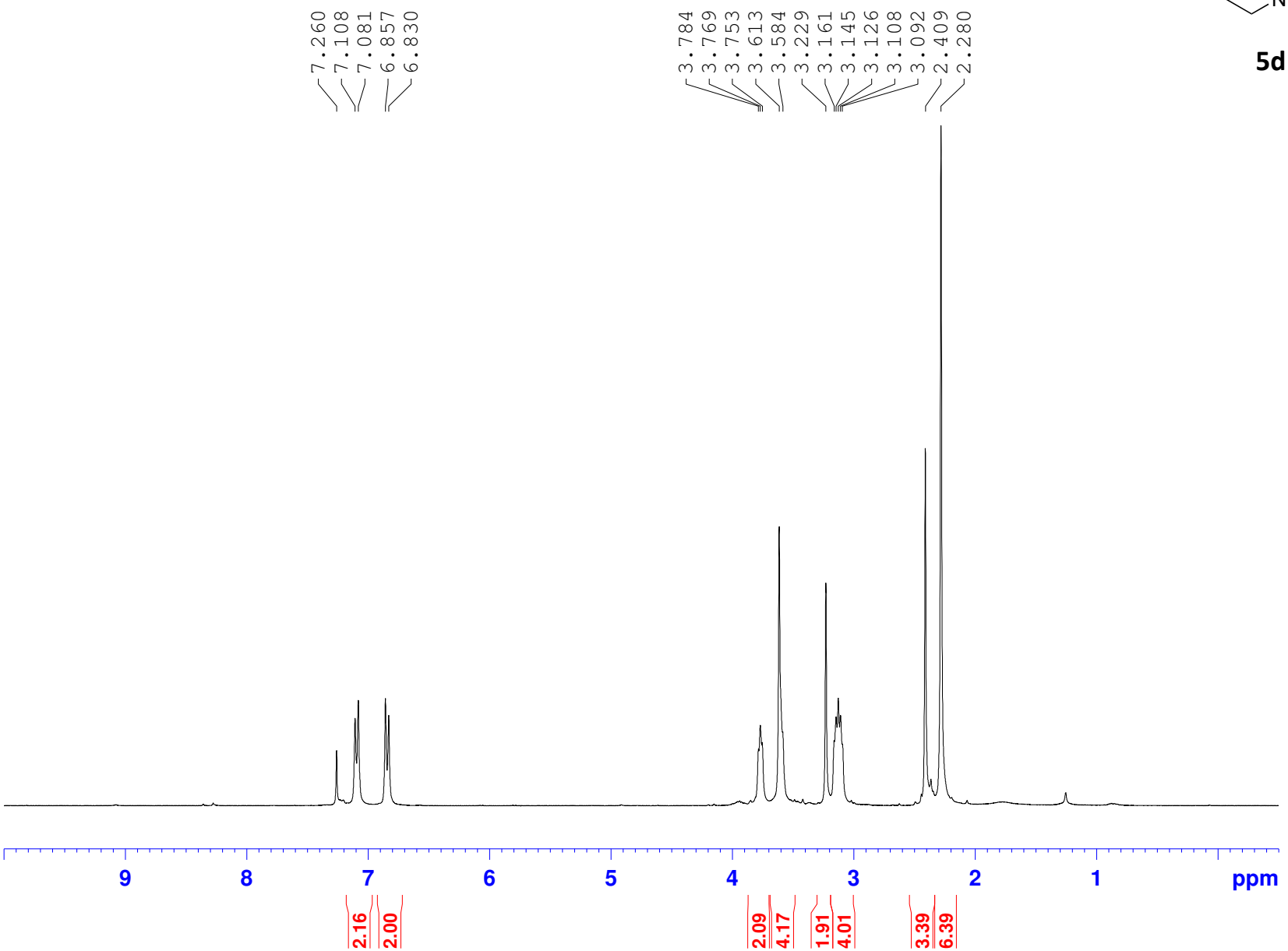
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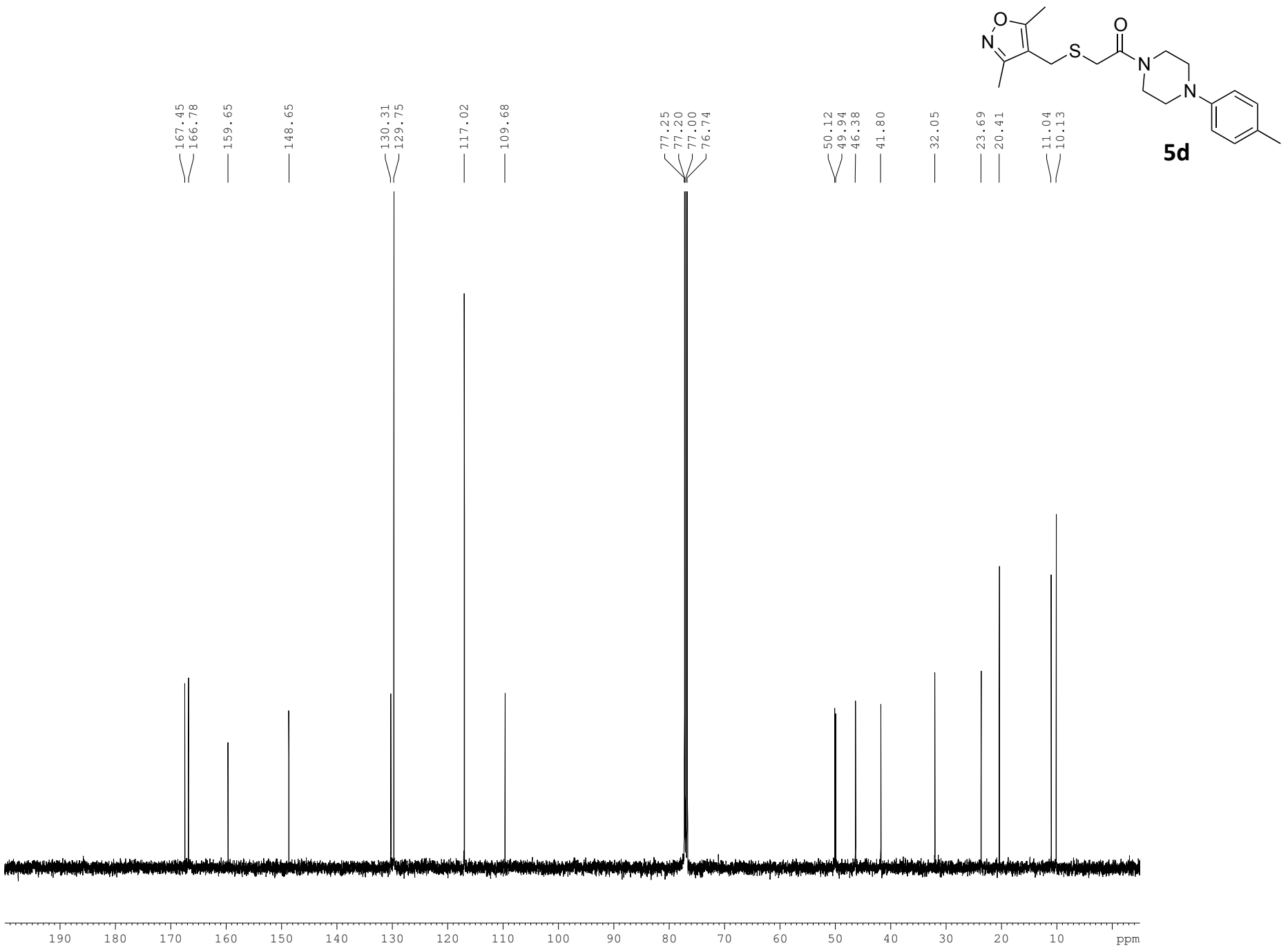
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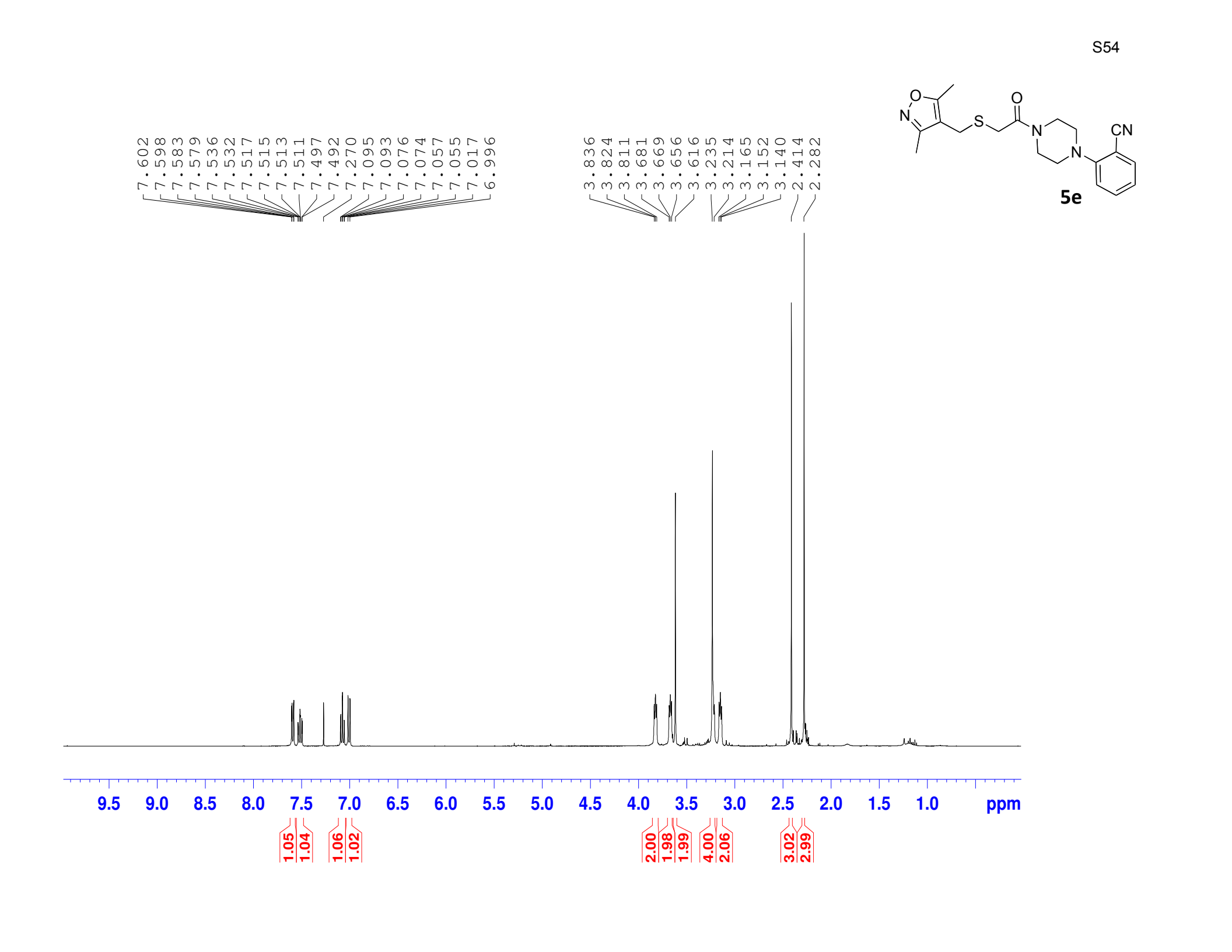
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N
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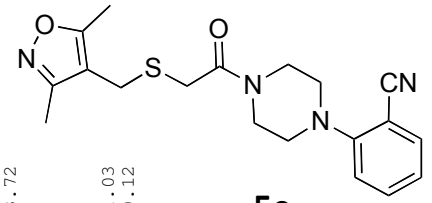
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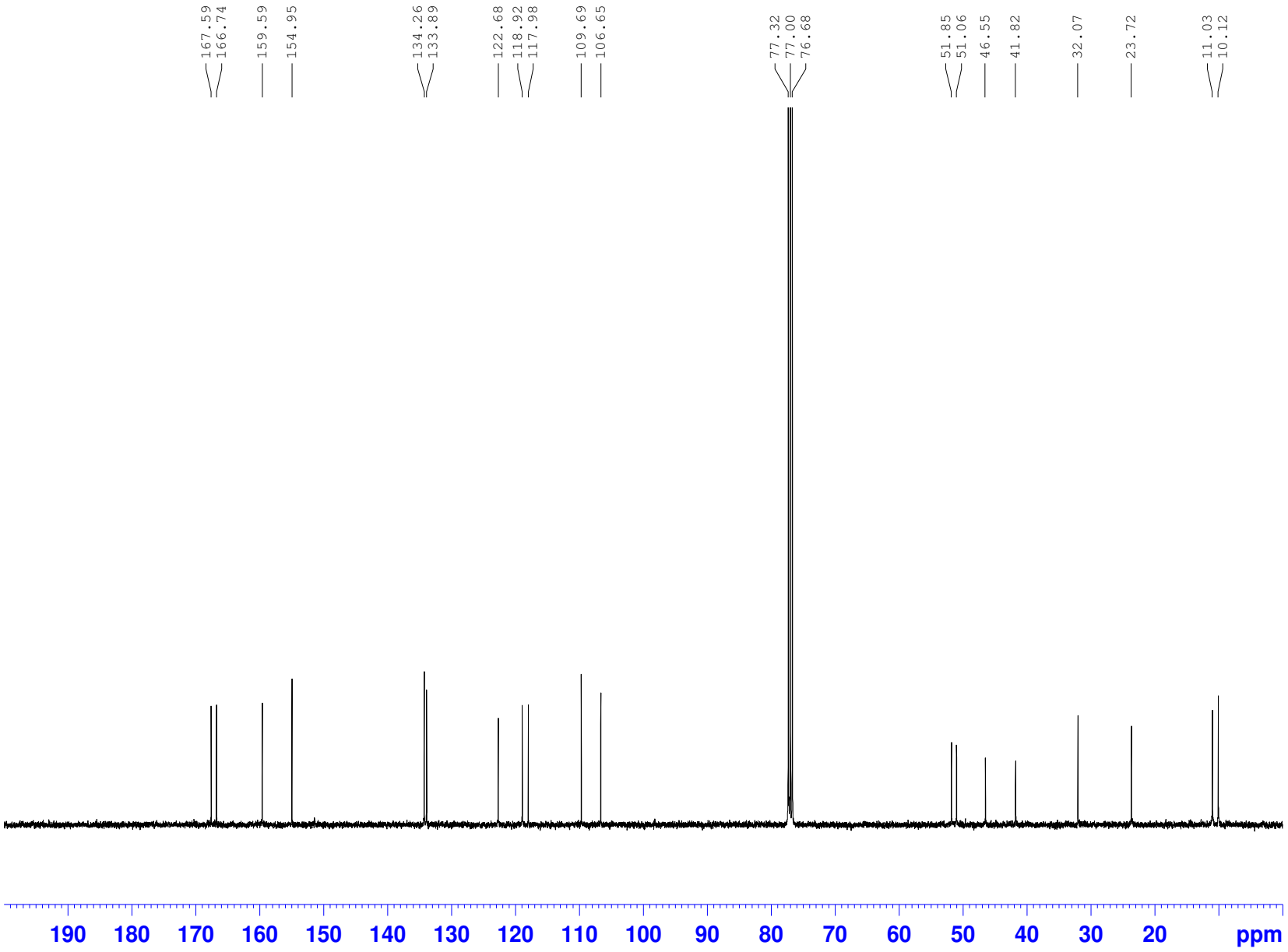
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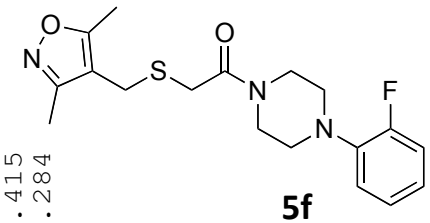
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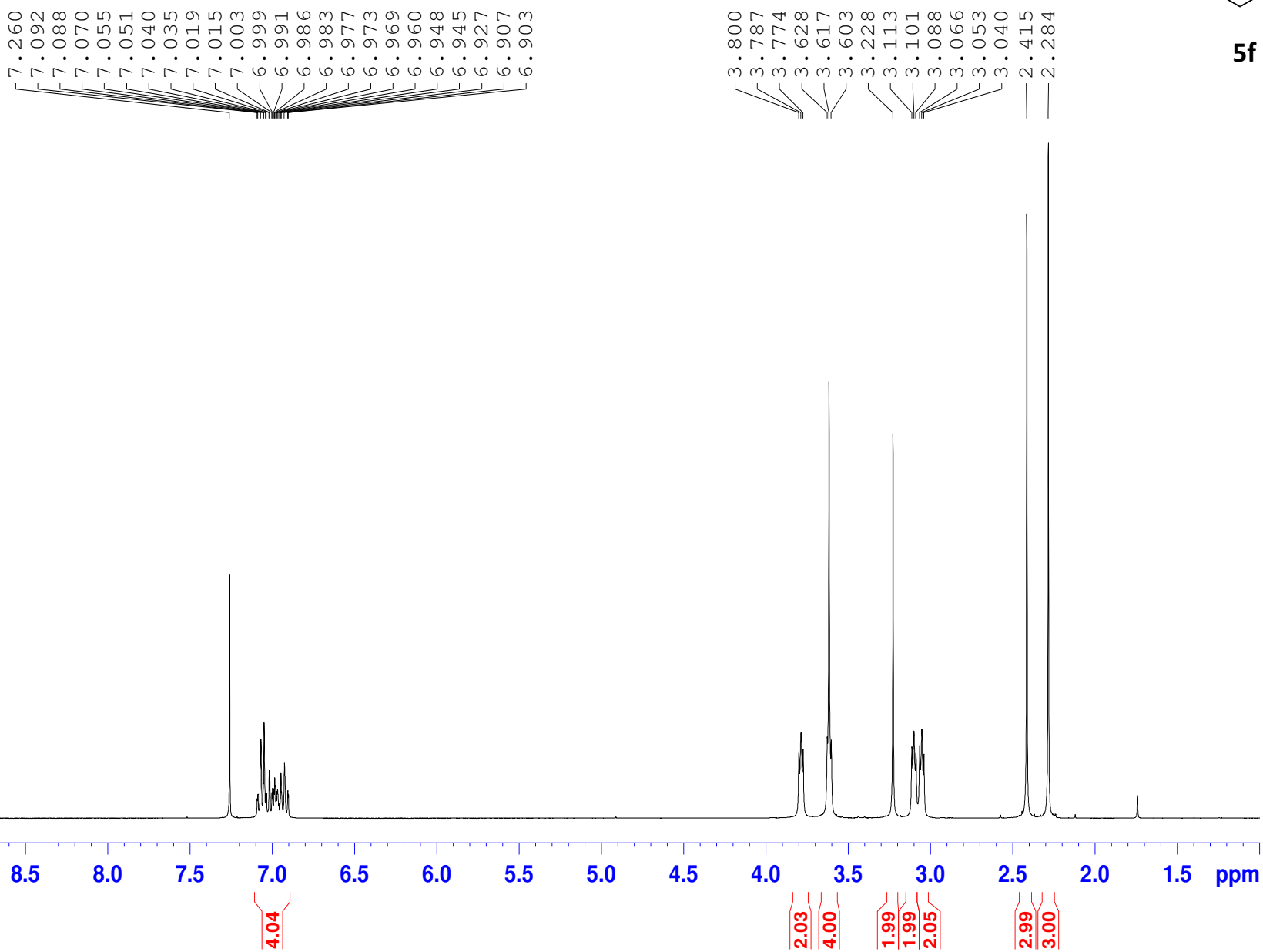
5f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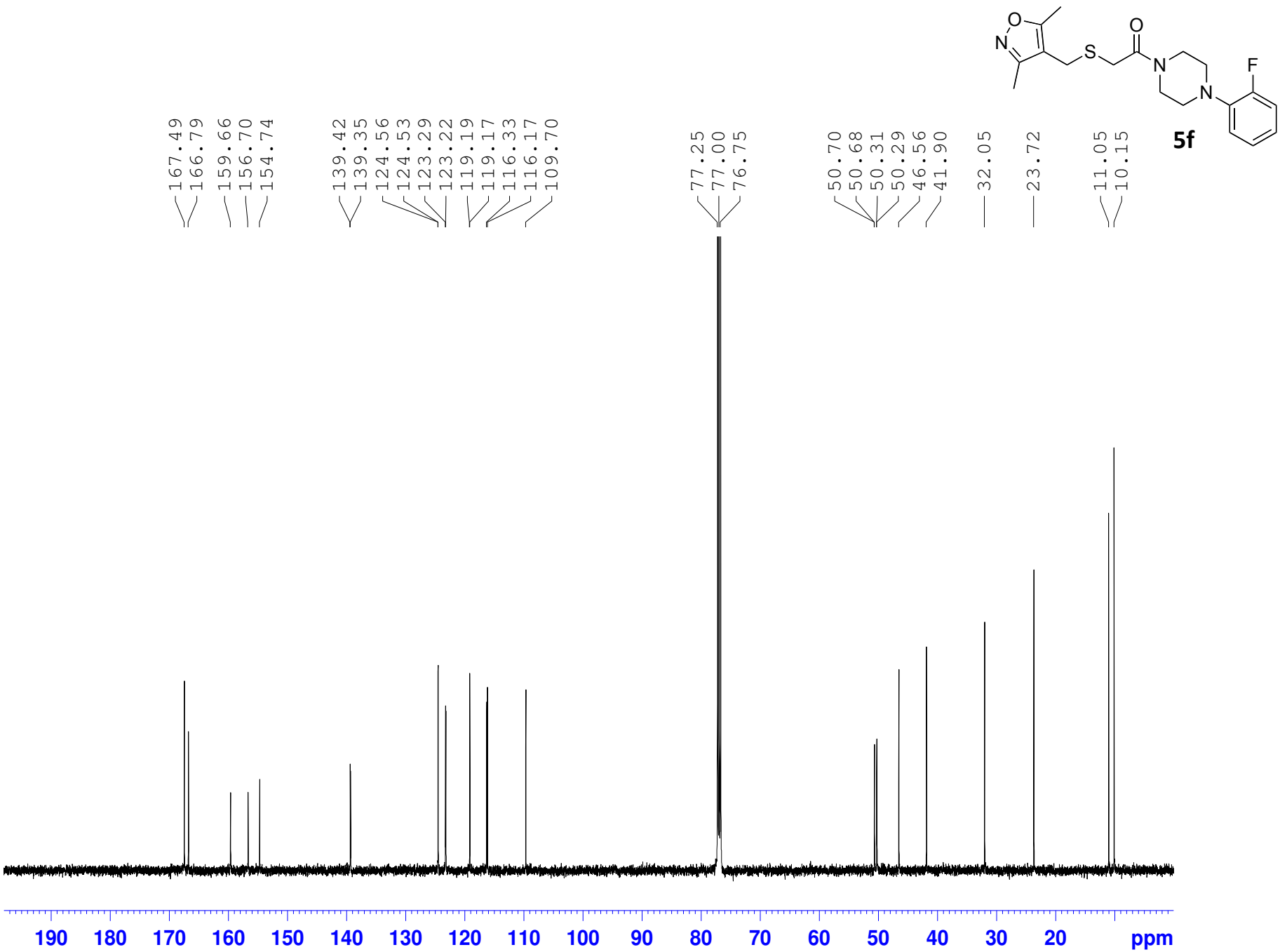
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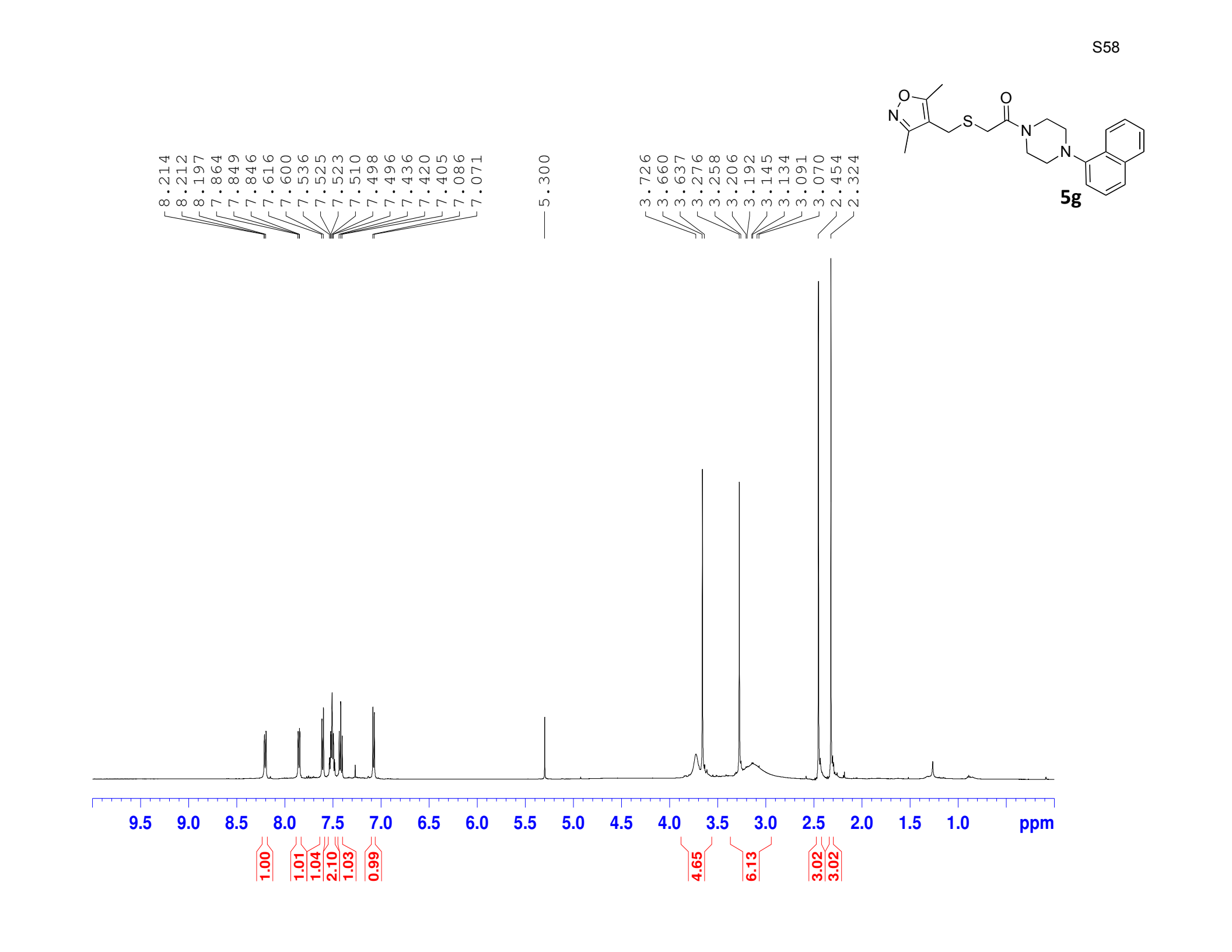
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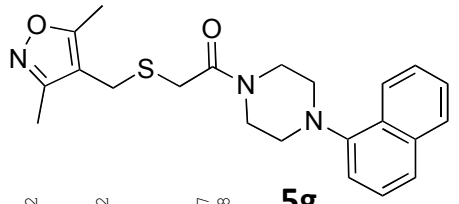

5g

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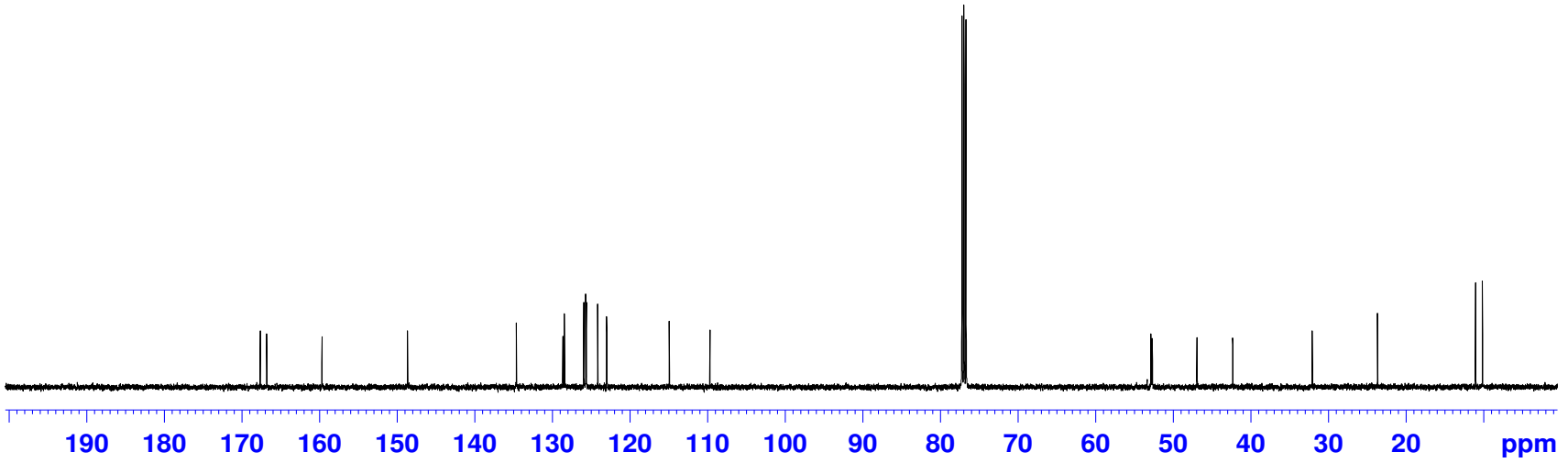
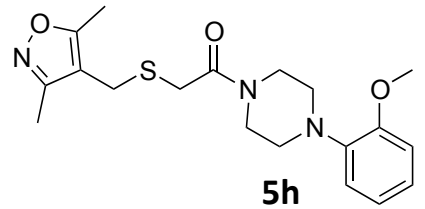
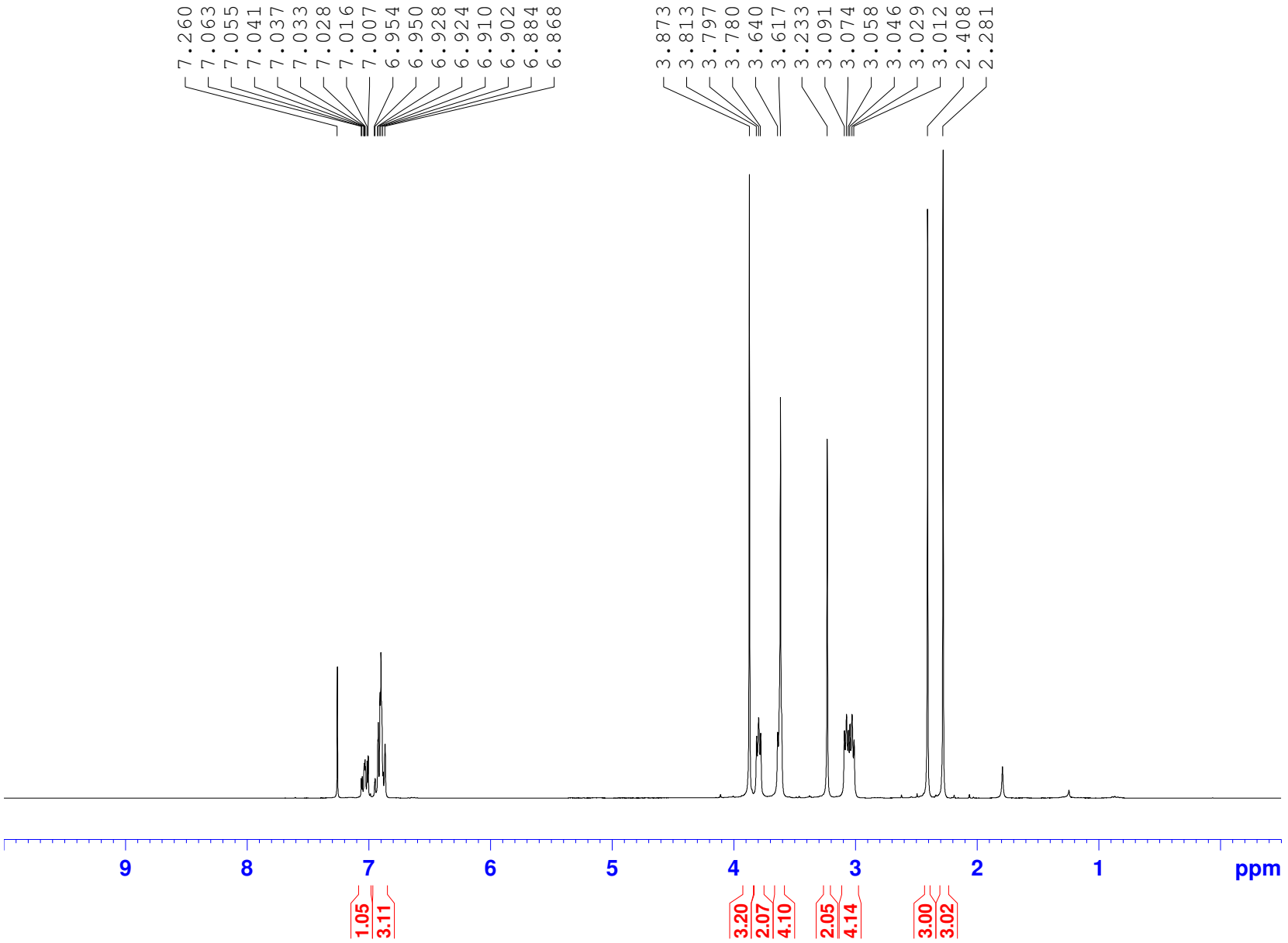



O
N
S
O
N
N
O

5h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7.016
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6.928
6.924
6.910
6.902
6.884
6.868
3.873
3.813
3.797
3.780
3.640
3.617
3.233
3.091
3.074
3.058
3.046
3.029
3.012
2.408
2.281
9
8
7
6
5
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ppm
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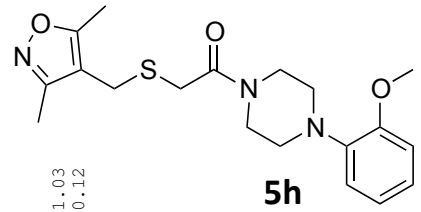
3.20
2.07
4.10
2.05
4.14
3.00
3.02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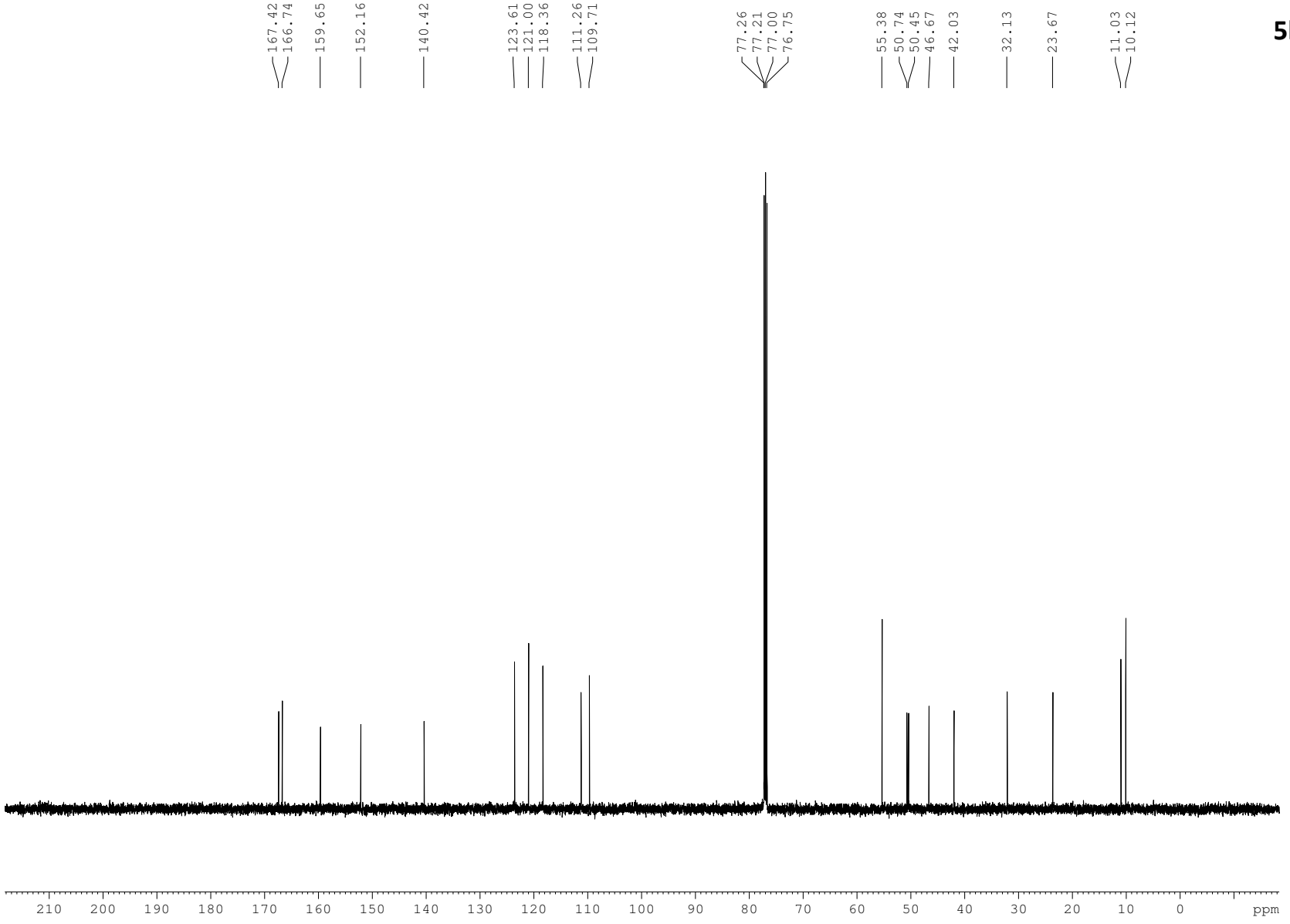
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118.36
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77.21
77.00
76.75
55.38
50.74
50.45
46.67
42.03
32.13
23.67
11.03
10.12
210
200
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170
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140
130
120
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100
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80
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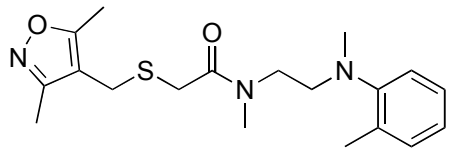
20
10
0
ppm



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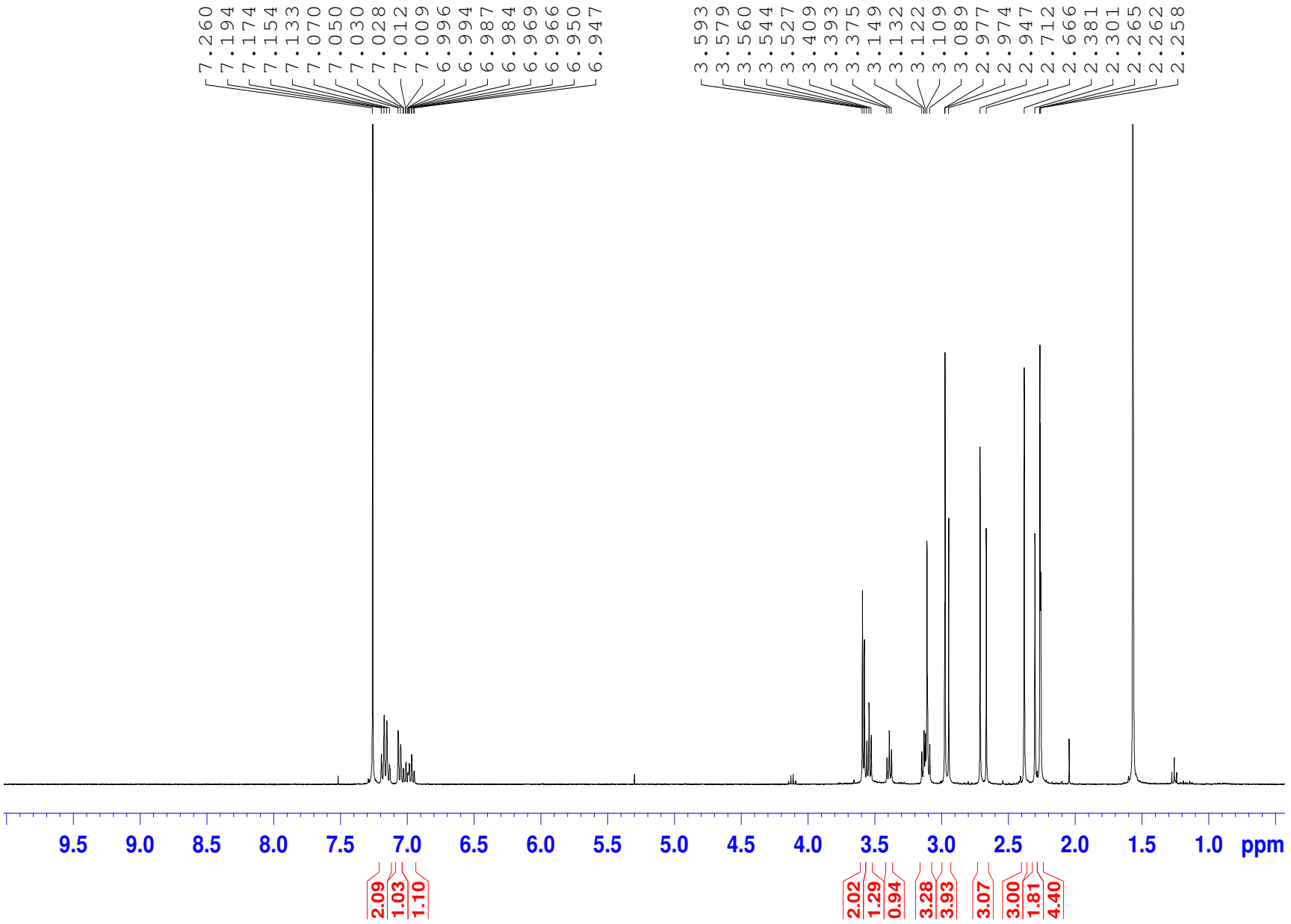
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7.070
7.050
7.030
7.028
7.012
7.009
6.996
6.994
6.987
6.984
6.969
6.966
6.950
6.947
3.593
3.579
3.560
3.544
3.527
3.409
3.393
3.375
3.149
3.132
3.122
3.109
3.089
2.977
2.974
2.947
2.712
2.666
2.381
2.301
2.265
2.262
2.258
9.5
9.0
8.5
8.0
7.5
7.0
6.5
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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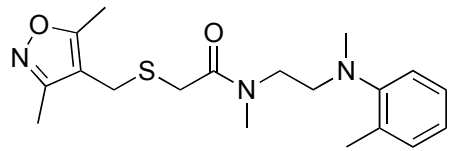
1.10
2.02
1.29
0.94
3.28
3.93
3.07
3.00
1.81
4.40



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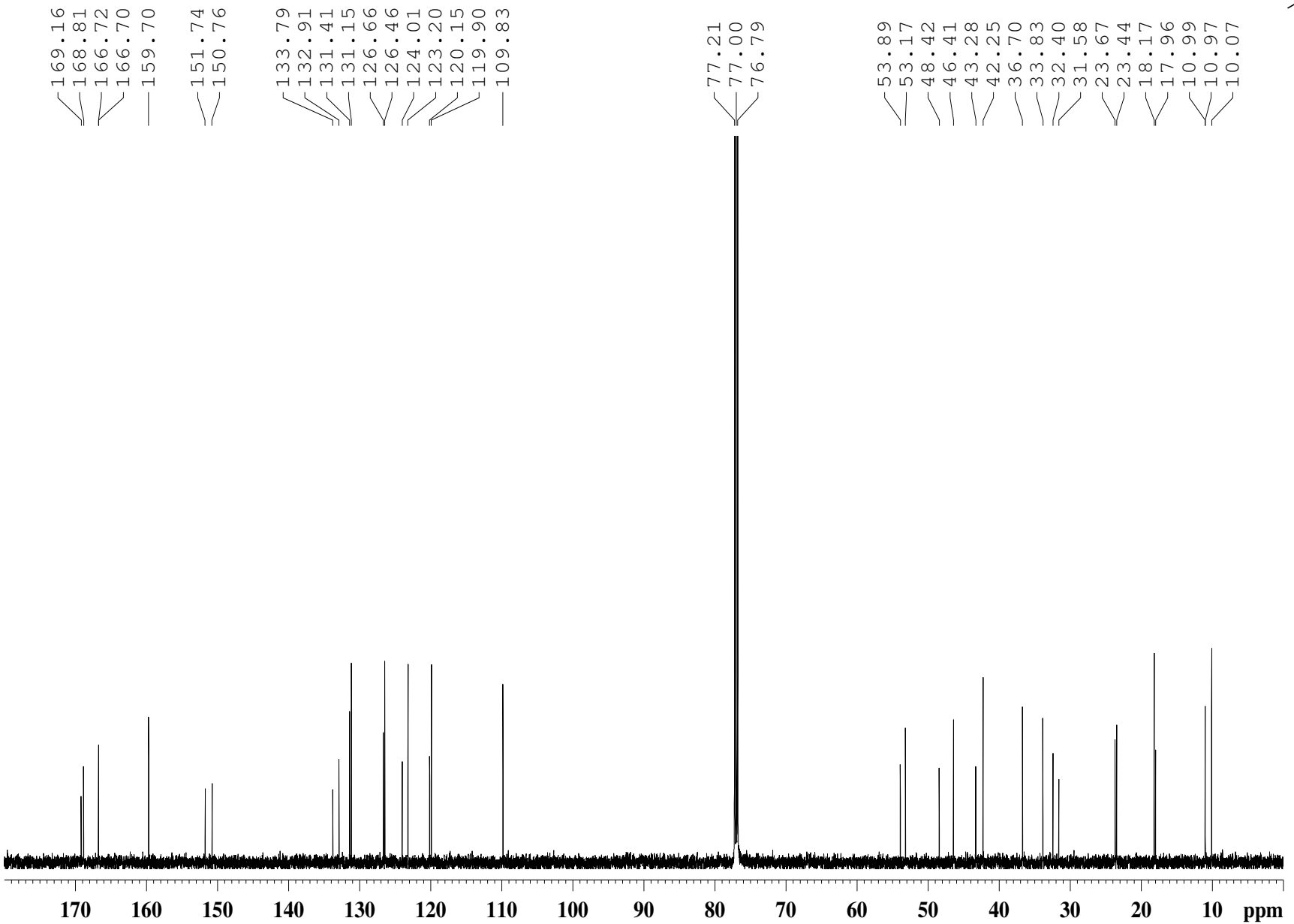
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150.76
133.79
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131.41
131.15
126.66
126.46
124.01
123.20
120.15
119.90
109.83
77.21
77.00
76.79
53.89
53.17
48.42
46.41
43.28
42.25
36.70
33.83
32.40
31.58
23.67
23.44
18.17
17.96
10.99
10.97
10.07
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150
140
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120
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100
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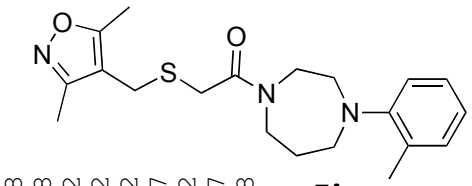
80
70
60
50
40
30
20
10
ppm



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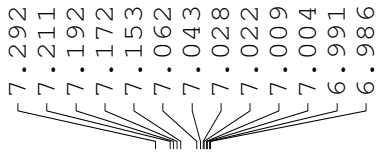
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7.192
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7.062
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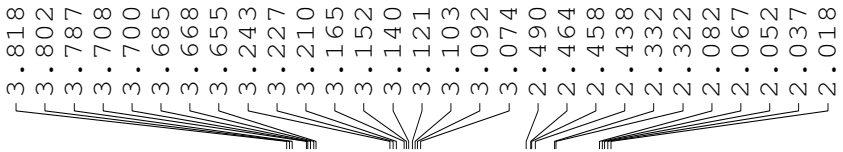
7.028
7.022
7.009
7.004
6.991
6.986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3.802
3.787
3.708
3.700
3.685
3.668
3.655
3.243
3.227
3.210
3.165
3.152
3.140
3.121
3.103
3.092
3.074
2.490
2.464
2.458
2.438
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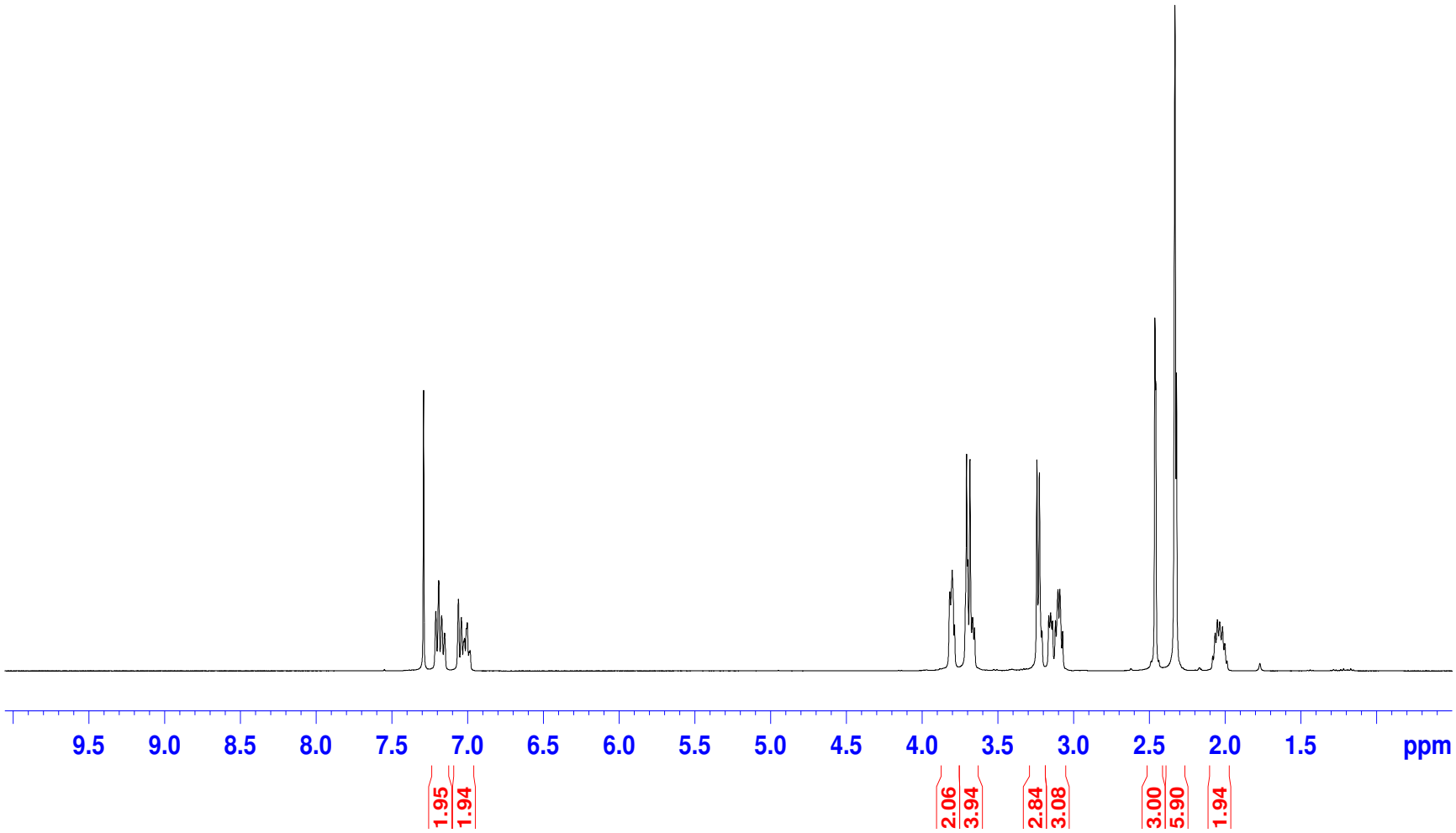
2.322
2.082
2.067
2.052
2.037
2.018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7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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ppm
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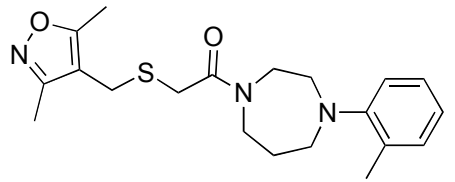
1.94
2.06
3.94
2.84
3.08
3.00
5.90
1.94



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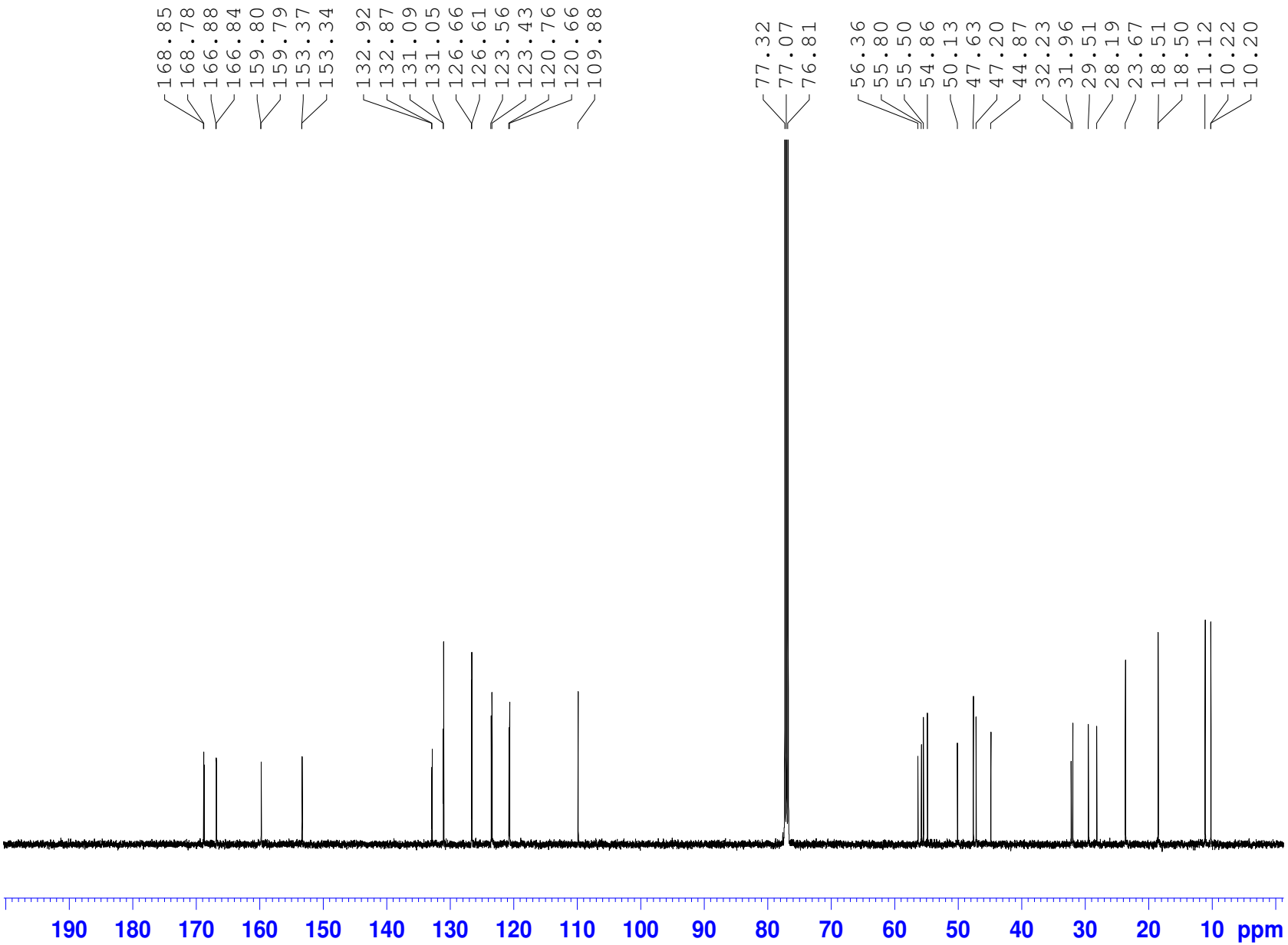
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166.84
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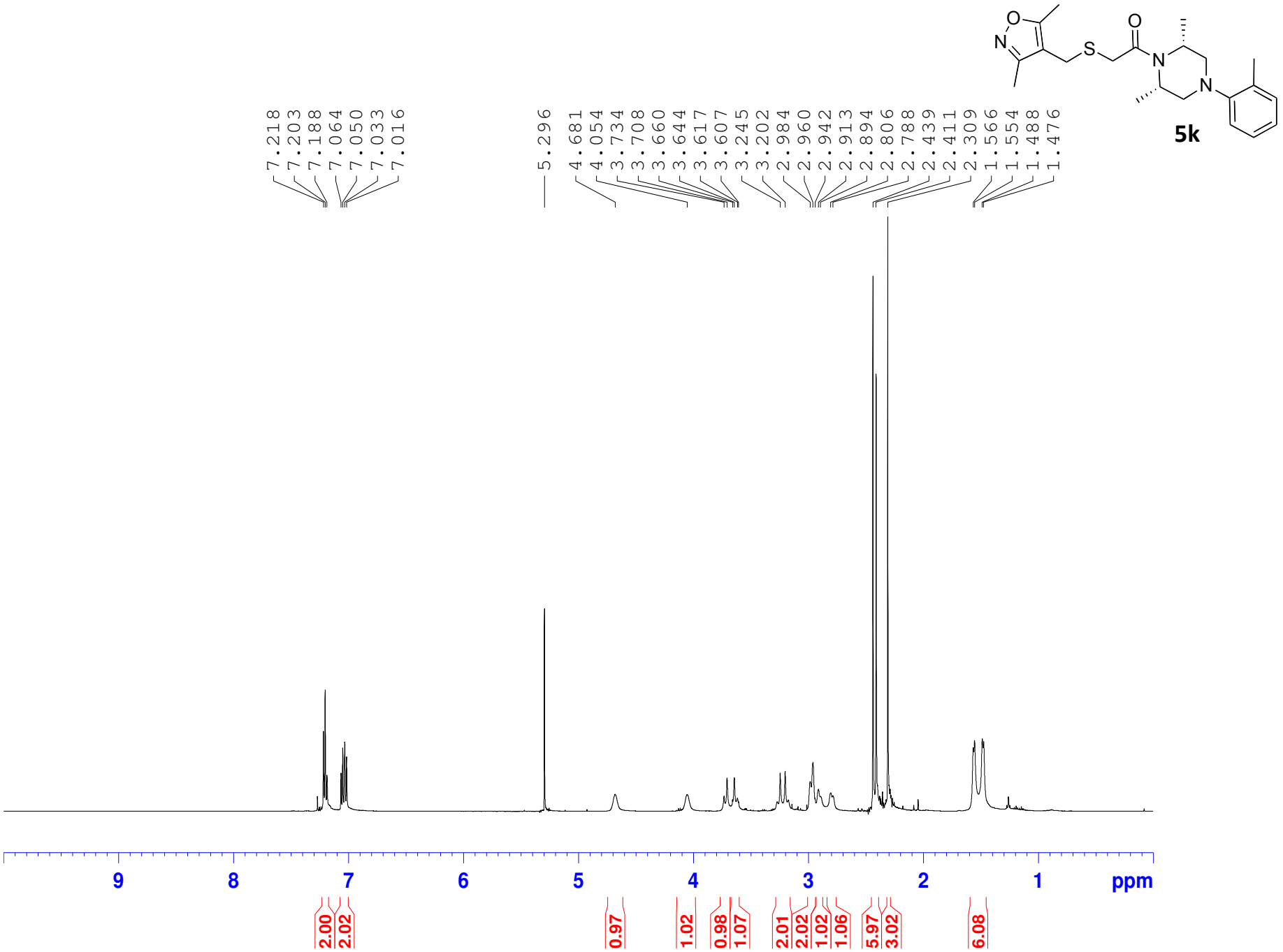
159.79
153.37
153.34
132.92
132.87
131.09
131.05
126.66
126.61
123.56
123.43
120.76
120.66
109.88
77.32
77.07
76.81
56.36
55.80
55.50
54.86
50.13
47.63
47.20
44.87
32.23
31.96
29.51
28.19
23.67
18.51
18.50
11.12
10.22
10.20
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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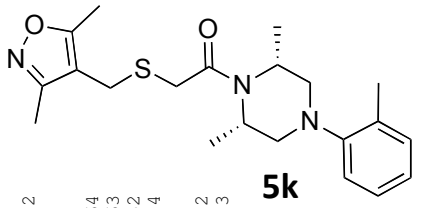
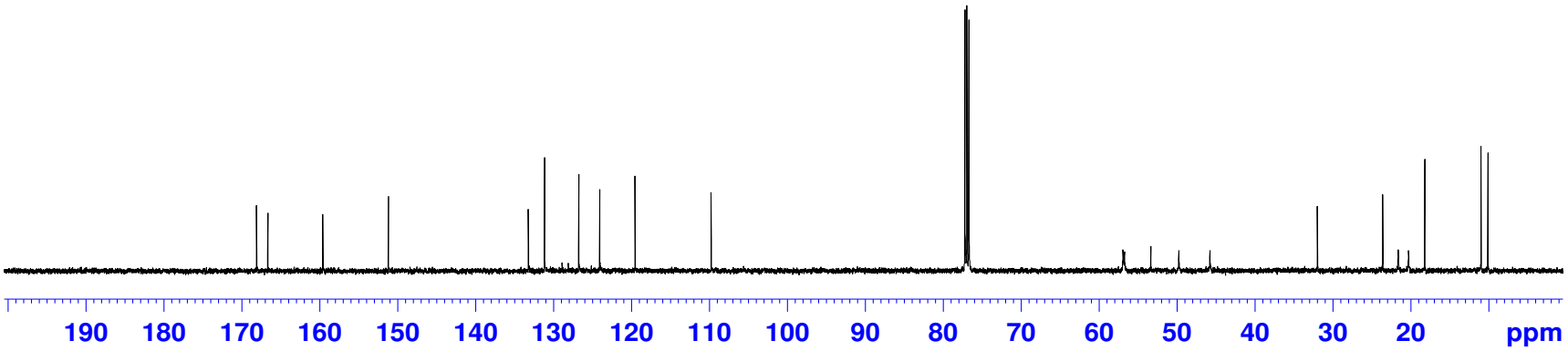
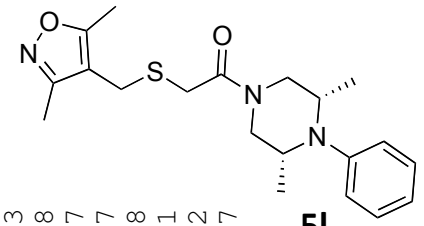
4.054
3.734
3.708
3.660
3.644
3.617
3.607
3.245
3.202
2.984
2.960
2.942
2.913
2.894
2.806
2.788
2.439
2.411
2.309
1.566
1.554
1.488
1.476
5k
9
8
7
6
5
4
3
2
1
ppm
2.00
2.02
0.97
1.02
0.98
1.07
2.01
2.02
1.02
1.06
5.97
3.02
6.08



5k

168.16
166.71
159.67
151.23
133.27
131.19
126.80
124.12
119.58
109.81
56.97
56.77
53.38
49.80
45.80
32.02
23.64
21.63
20.32
18.24
11.02
10.13





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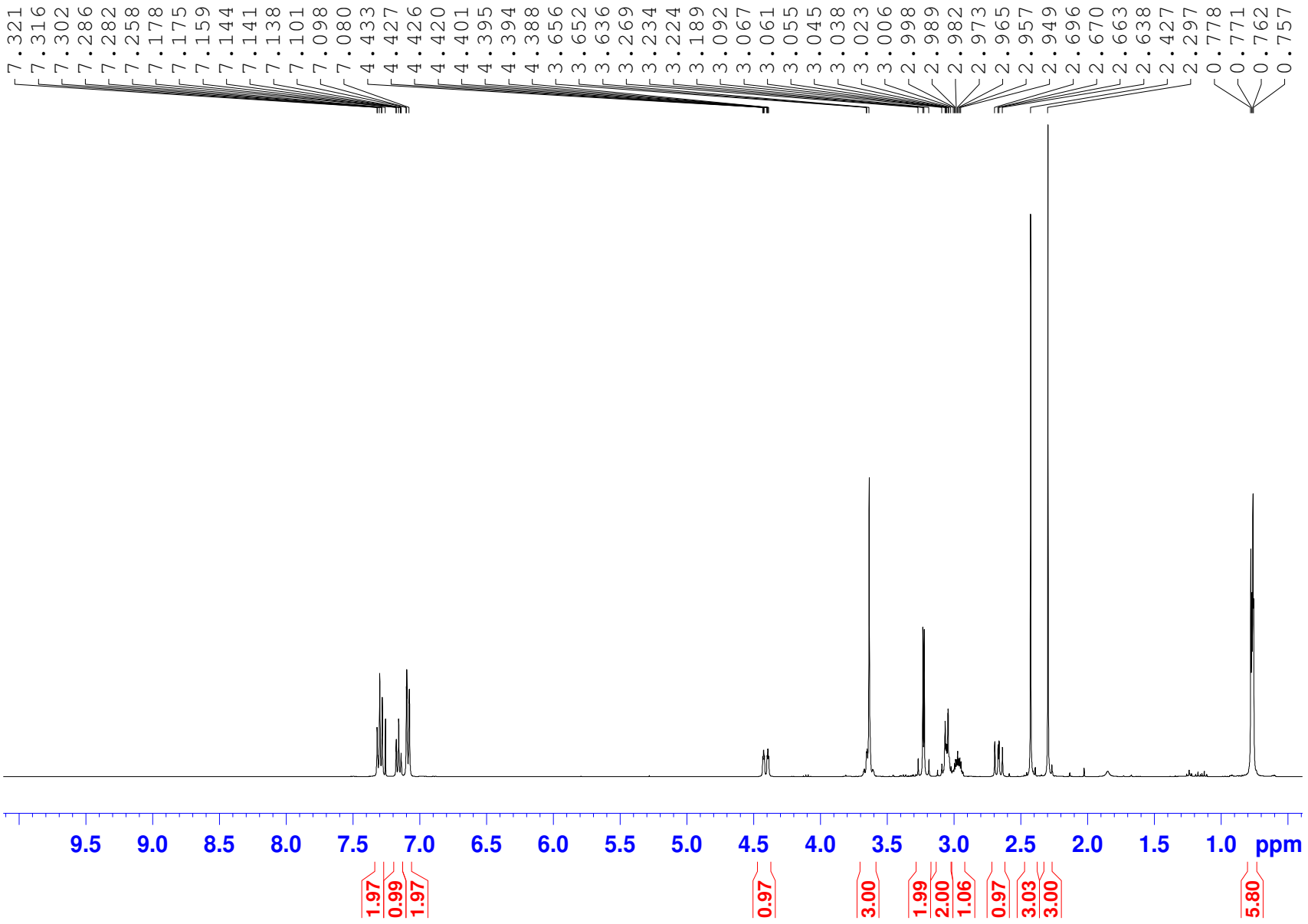
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7.175
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7.138
7.101
7.098
7.080
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4.420
4.401
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4.388
3.656
3.652
3.636
3.269
3.234
3.224
3.189
3.092
3.067
3.061
3.055
3.045
3.038
3.023
3.006
2.998
2.989
2.982
2.973
2.965
2.957
2.949
2.696
2.670
2.663
2.638
2.427
2.297
0.778
0.771
0.762
0.757
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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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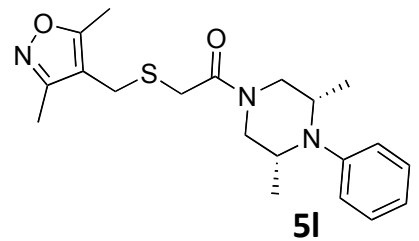
0.99
1.97
0.97
3.00
1.99
2.00
1.06
0.97
3.03
3.00
5.80



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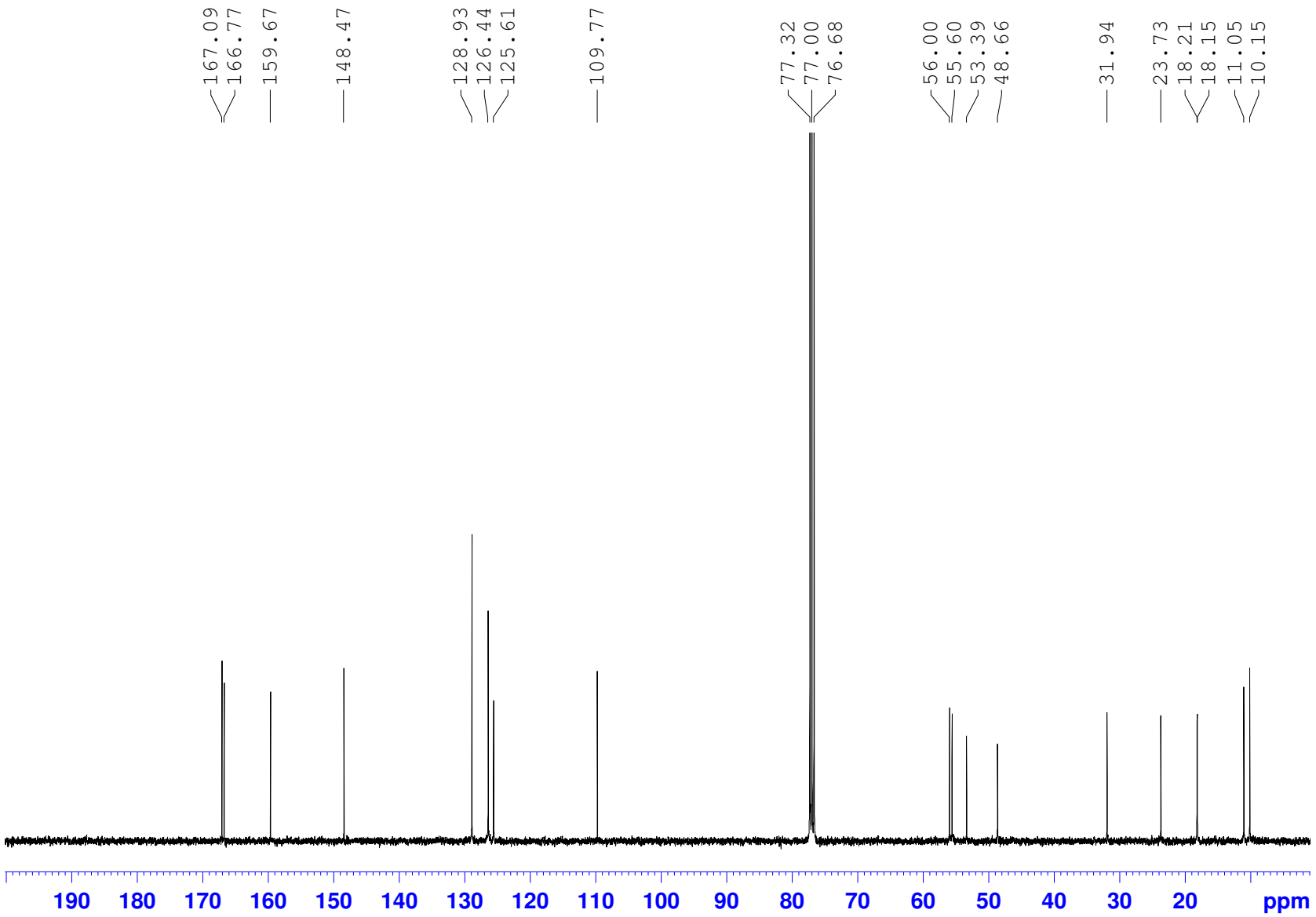
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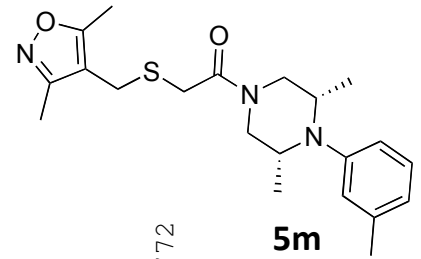
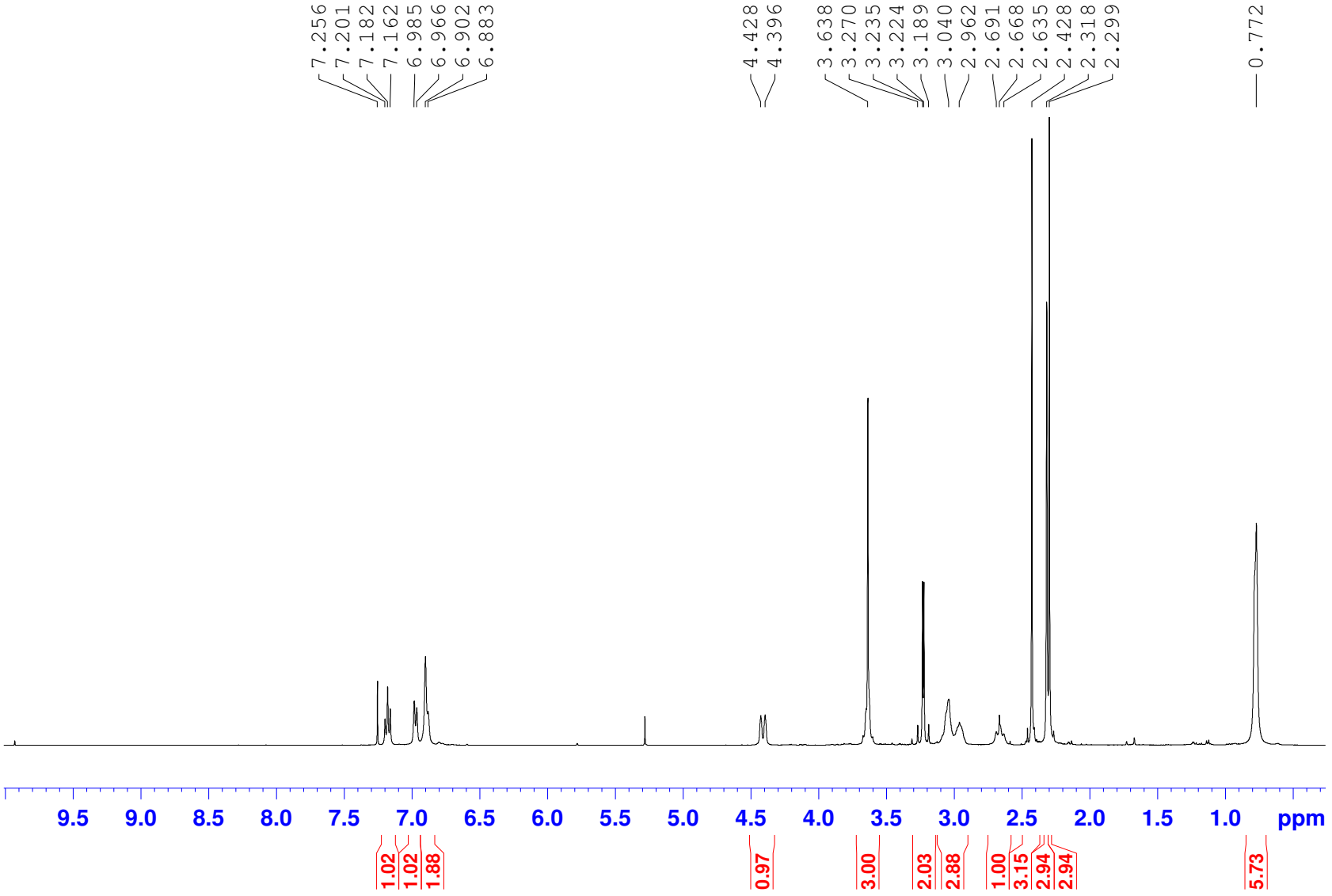
125.61
109.77
77.32
77.00
76.68
56.00
55.60
53.39
48.66
31.94
23.73
18.21
18.15
11.05
10.15
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm



5m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7.162
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6.966
6.902
6.883
4.428
4.396
3.638
3.270
3.235
3.224
3.189
3.040
2.962
2.691
2.668
2.635
2.428
2.318
2.299
0.772
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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0.97
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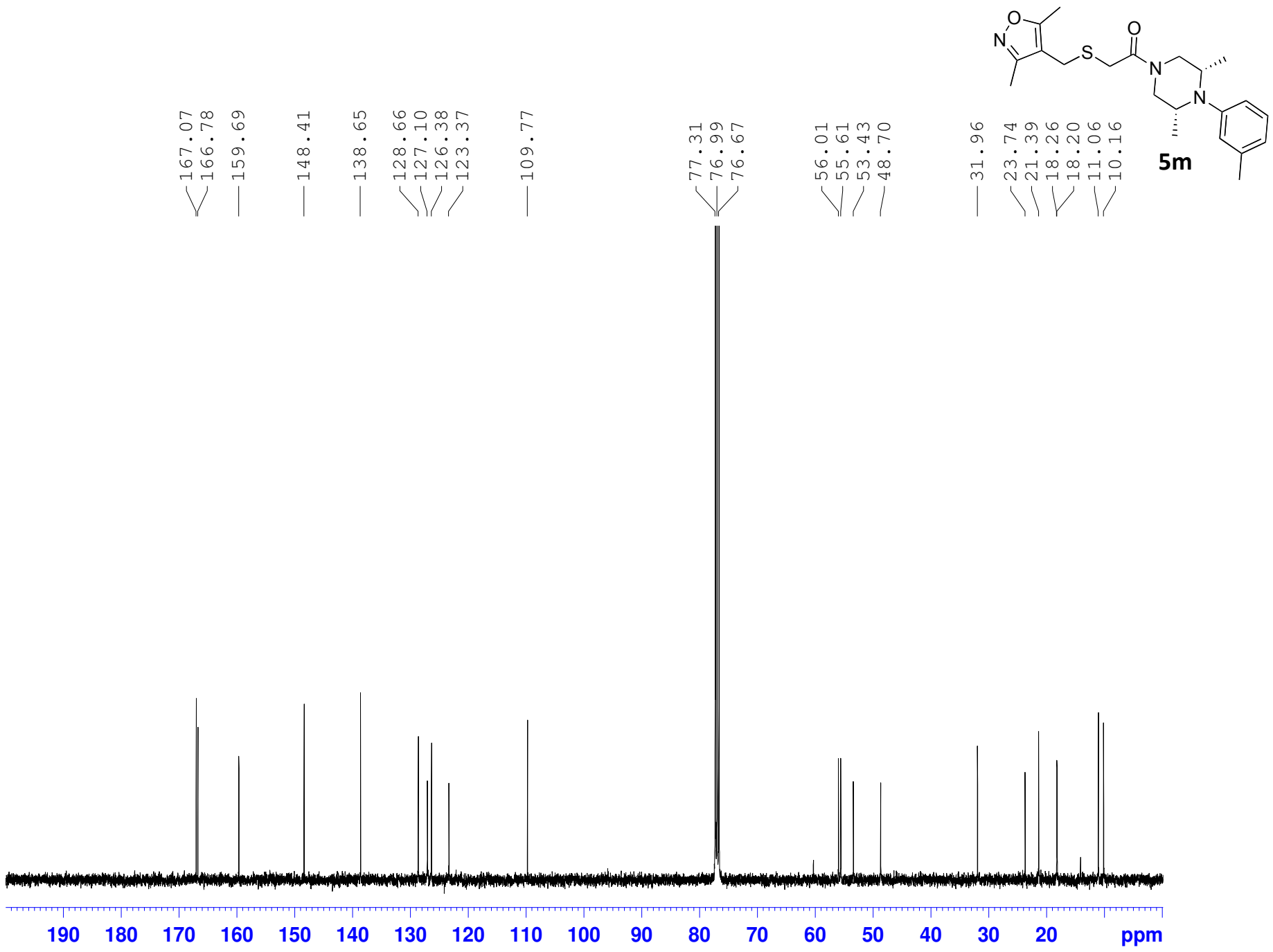
2.03
2.88
1.00
3.15
2.94
2.94
5.73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109.77
77.31
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76.67
56.01
55.61
53.43
48.70
31.96
23.74
21.39
18.26
18.20
11.06
10.16
5m
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180
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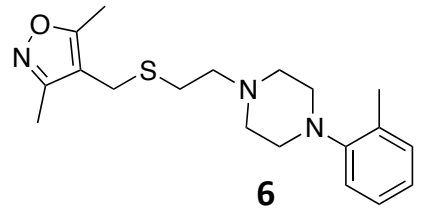
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm



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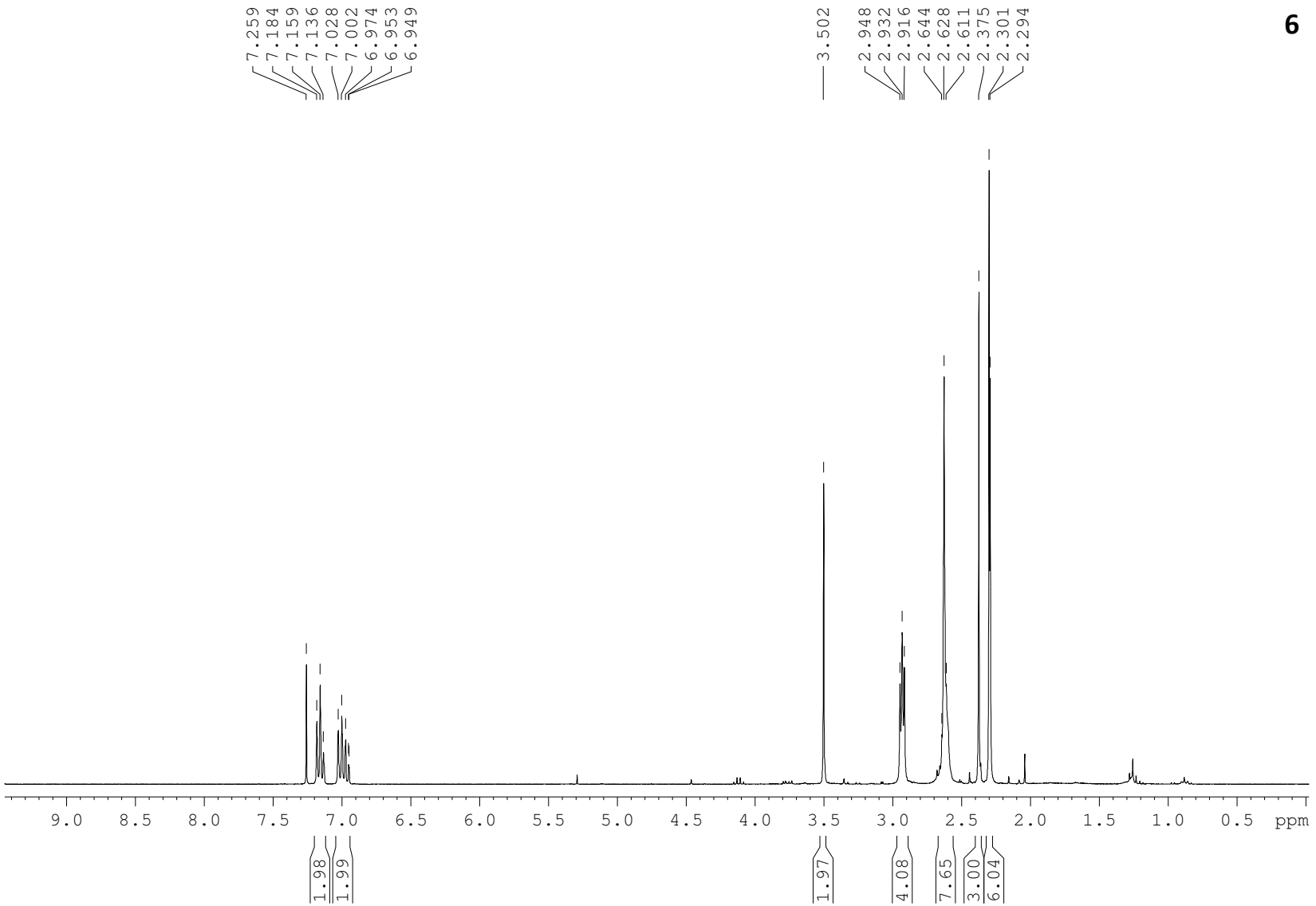
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7.159
7.136
7.028
7.002
6.974
6.953
6.949
3.502
2.948
2.932
2.916
2.644
2.628
2.611
2.375
2.301
2.294
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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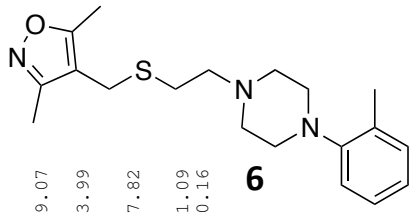
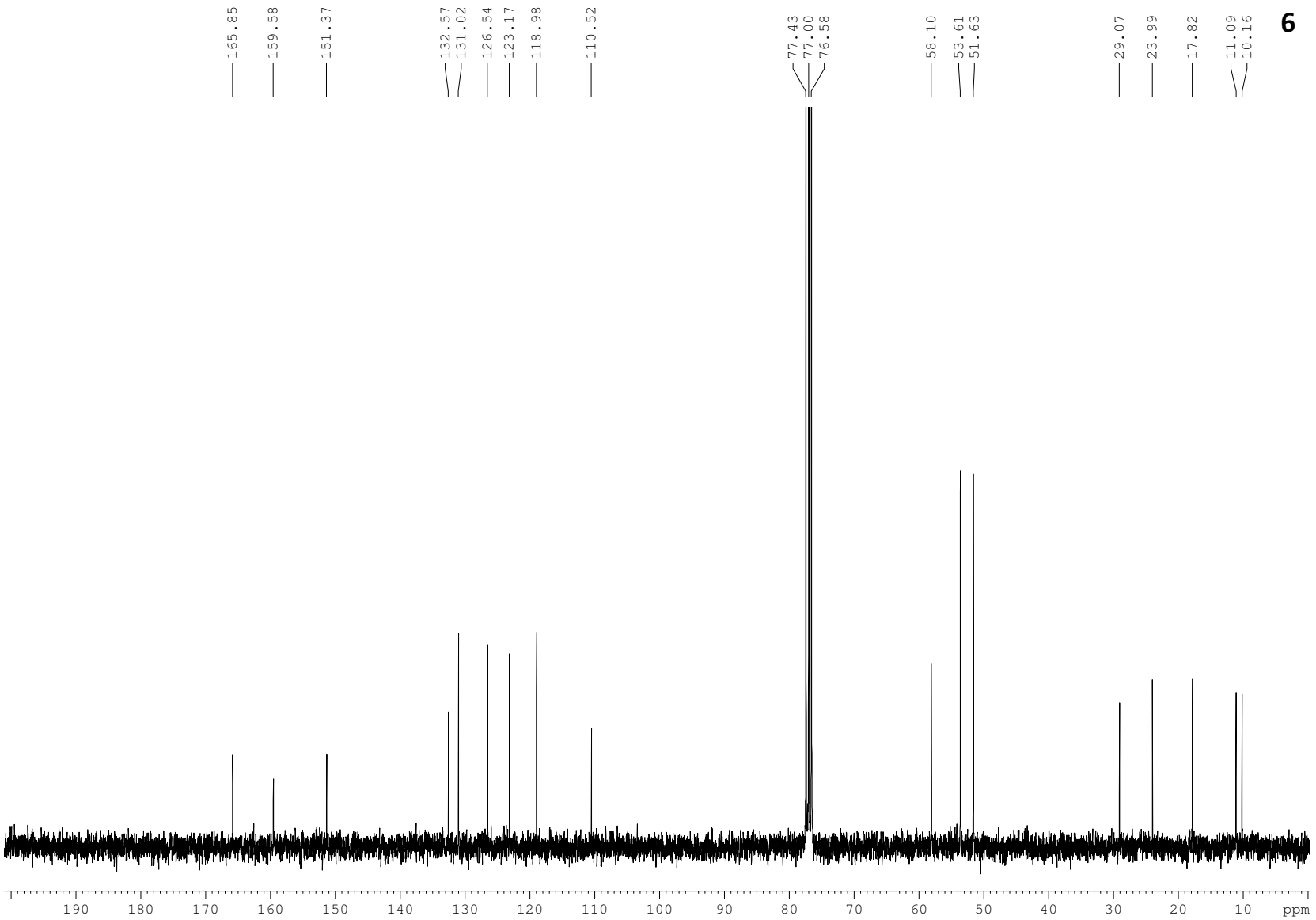
1.99
1.97
4.08
7.65
3.00
6.04


O
N
S
N
N

6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77.43
77.00
76.58
58.10
53.61
51.63
29.07
23.99
17.82
11.09
10.16
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150
140
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120
110
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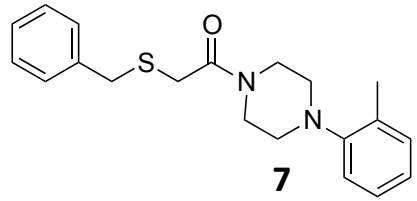
80
70
60
50
40
30
20
10
ppm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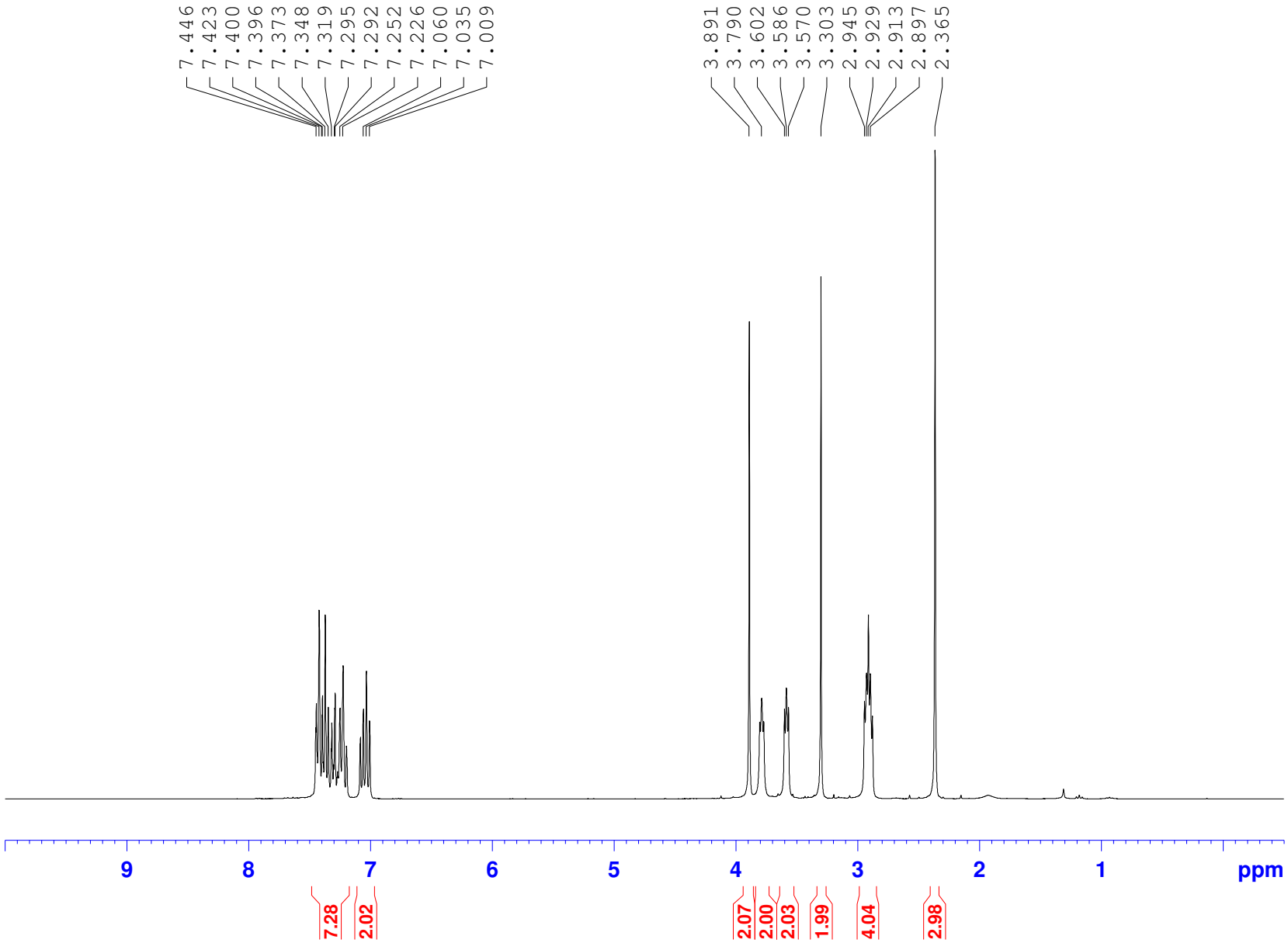
N

7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3.602
3.586
3.570
3.303
2.945
2.929
2.913
2.897
2.365
9
8
7
6
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ppm
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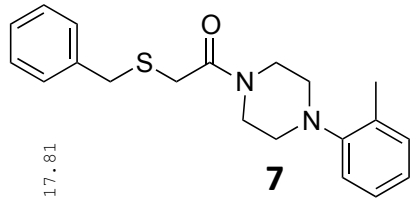
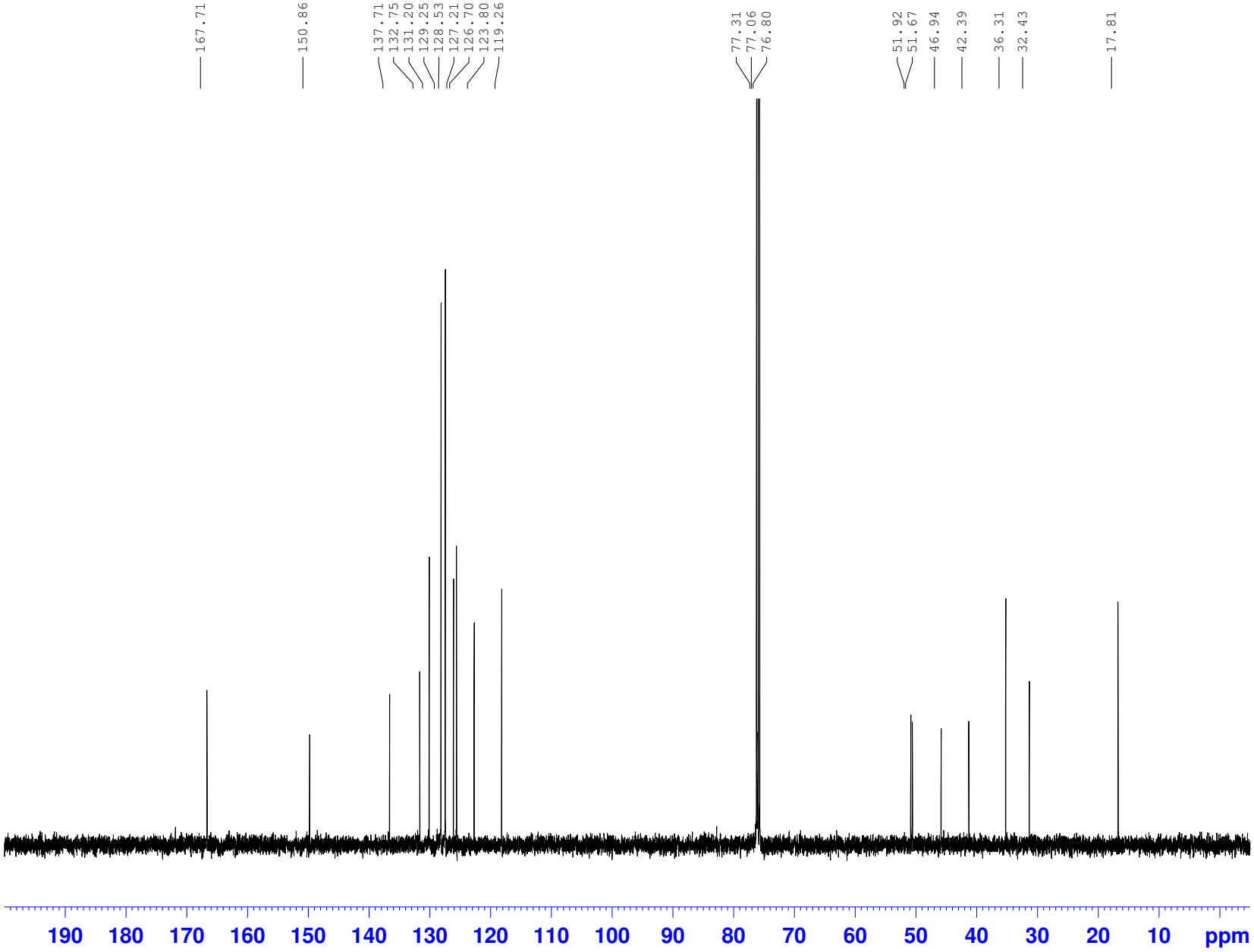
2.02
2.07
2.00
2.03
1.99
4.04
2.98


O
S
N
N

7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119.26
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76.80
51.92
51.67
46.94
42.39
36.31
32.43
17.81
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180
170
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130
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100
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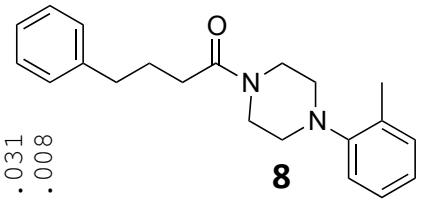
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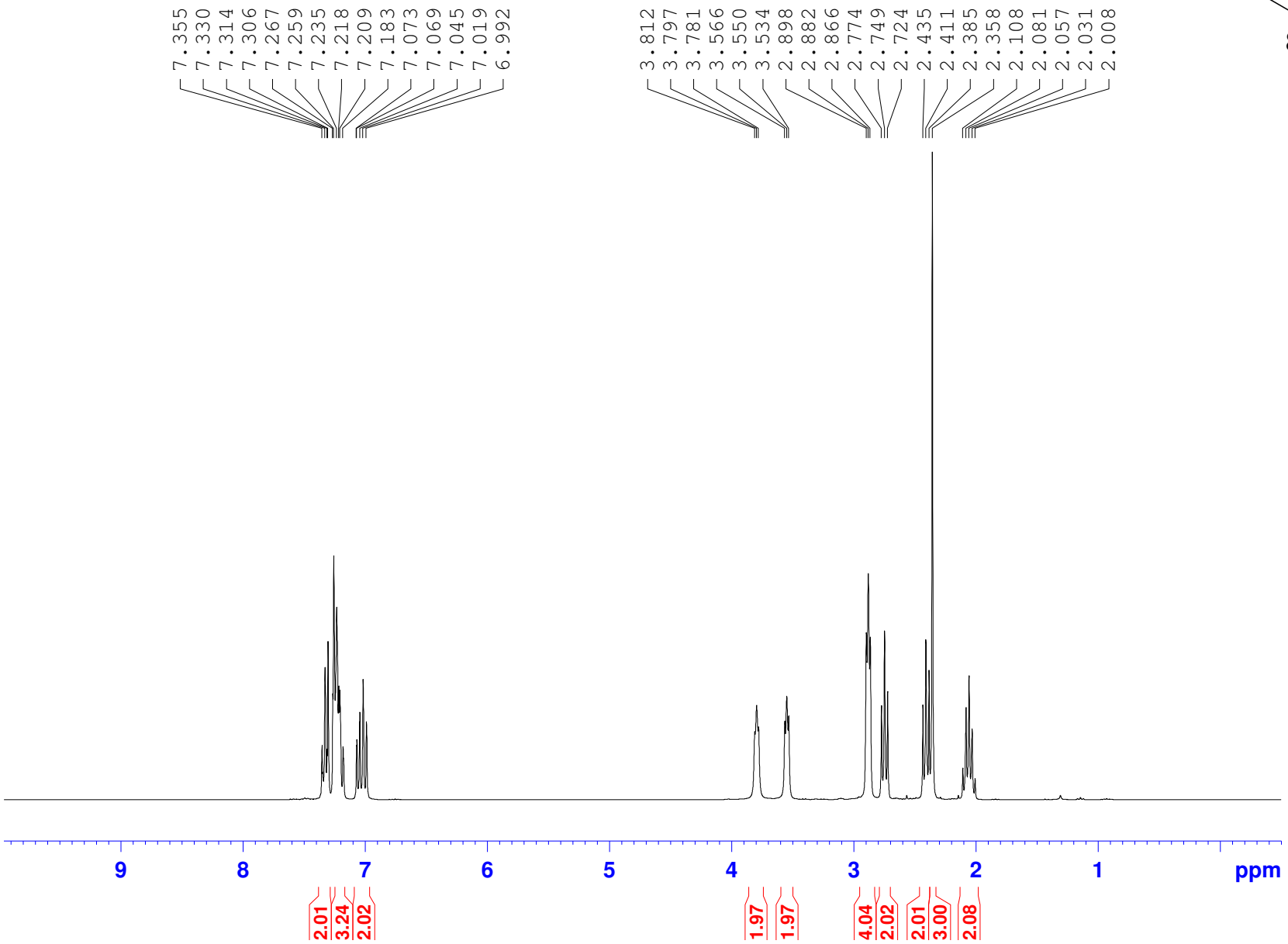
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7.045
7.019
6.992
3.812
3.797
3.781
3.566
3.550
3.534
2.898
2.882
2.866
2.774
2.749
2.724
2.435
2.411
2.385
2.358
2.108
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2.057
2.031
2.008
9
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7
6
5
4
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2.01
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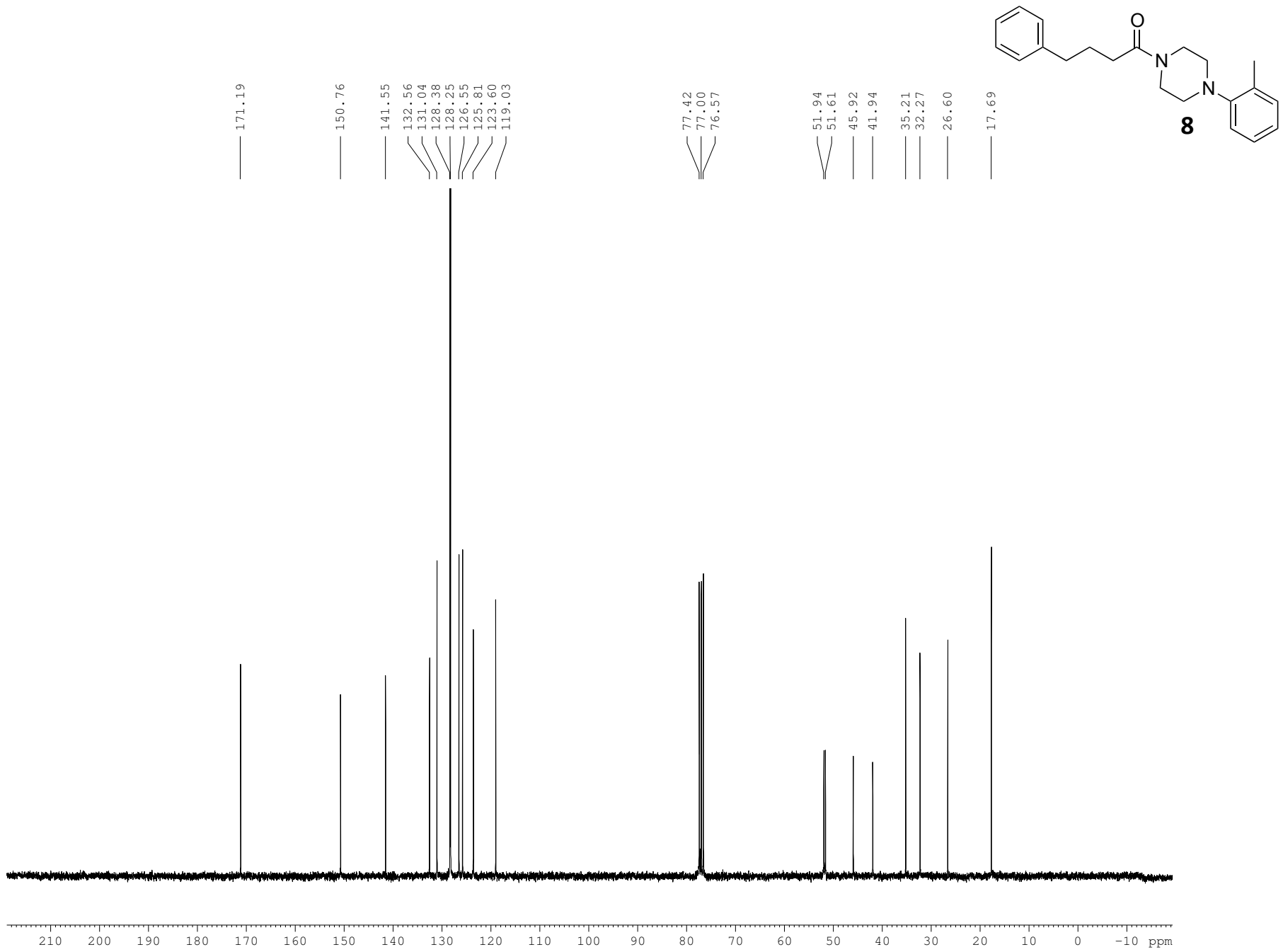
2.08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77.42
77.00
76.57
51.94
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26.60
17.69
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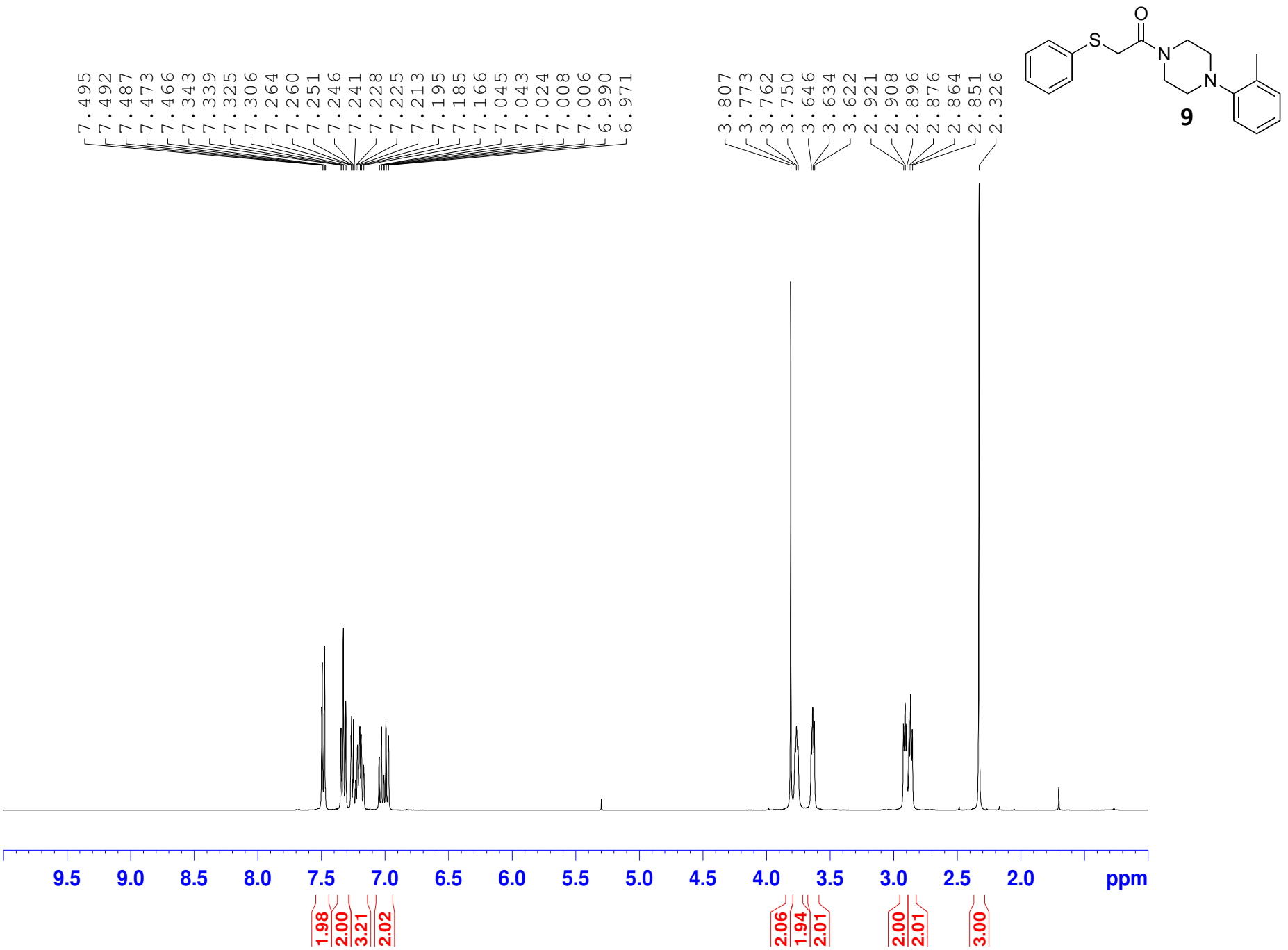
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7.225
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7.185
7.166
7.045
7.043
7.024
7.008
7.006
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3.773
3.762
3.750
3.646
3.634
3.622
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2.908
2.896
2.876
2.864
2.851
2.326
O
S
N
N
9
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8.0
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6.0
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5.0
4.5
4.0
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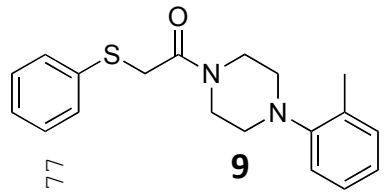
2.01
3.00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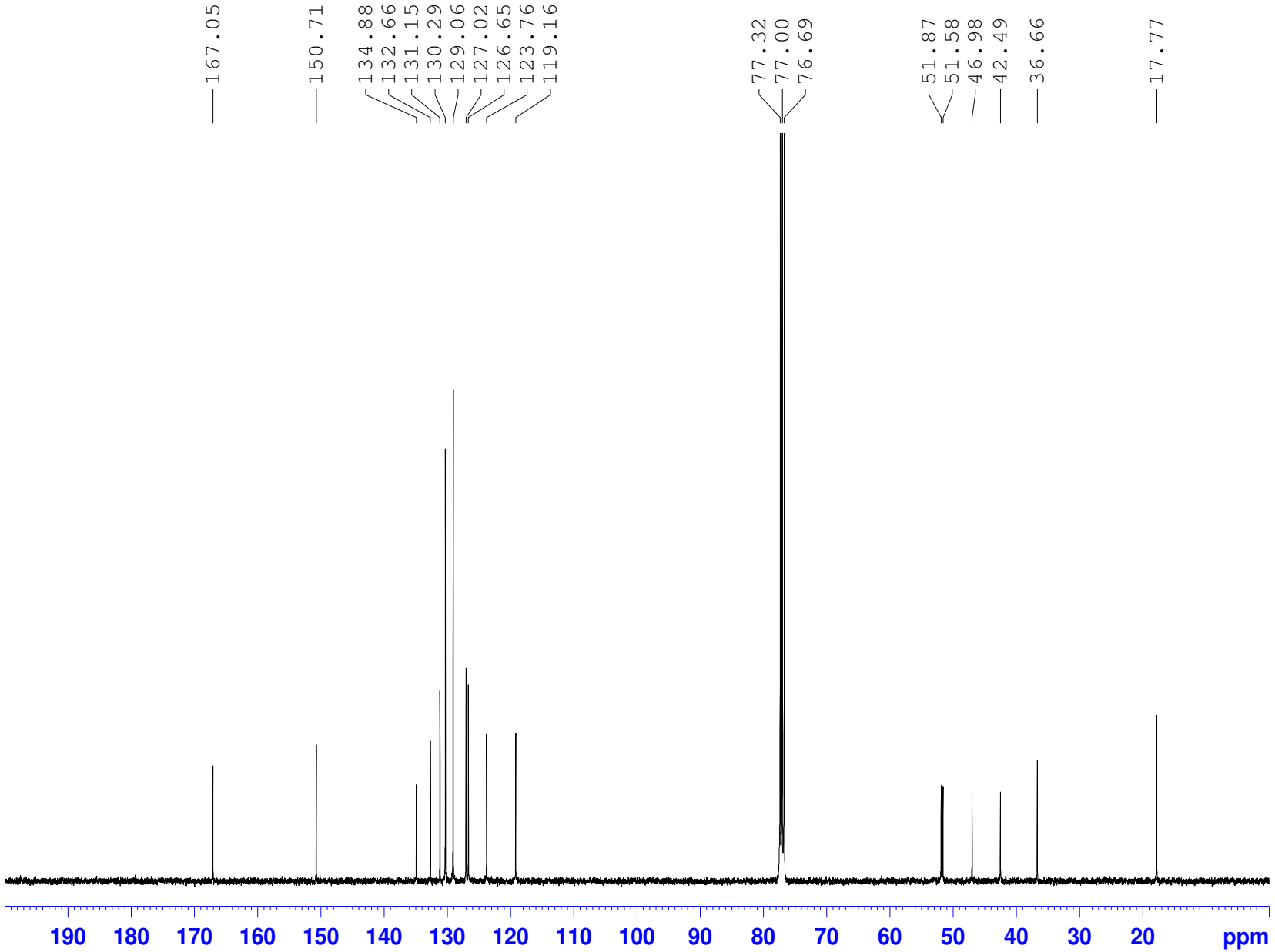
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51.58
46.98
42.49
36.66
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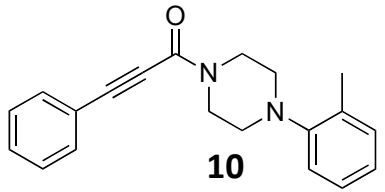
ppm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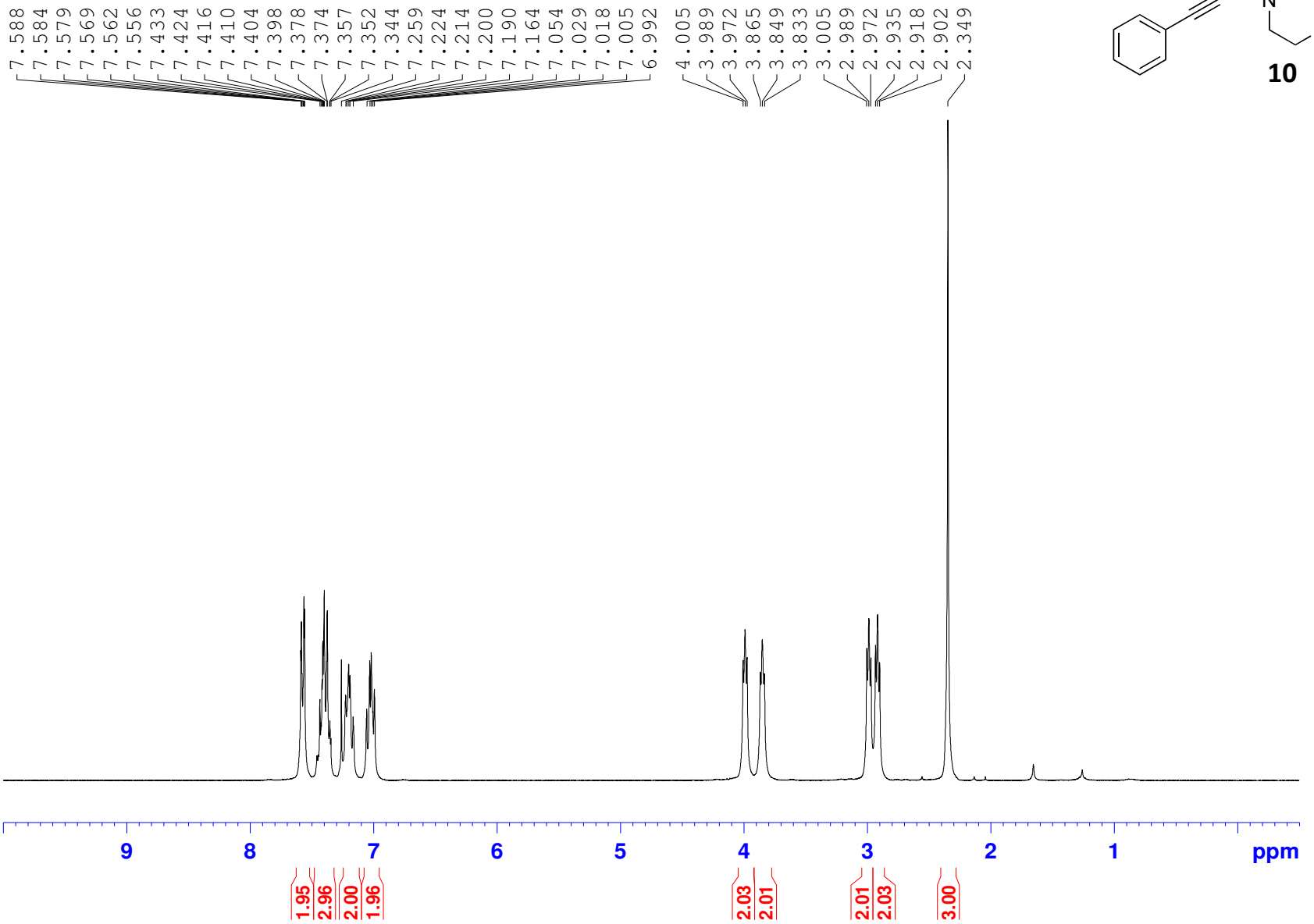
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7.398
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7.374
7.357
7.352
7.344
7.259
7.224
7.214
7.200
7.190
7.164
7.054
7.029
7.018
7.005
6.992
4.005
3.989
3.972
3.865
3.849
3.833
3.005
2.989
2.972
2.935
2.918
2.902
2.349
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8
7
6
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1.96
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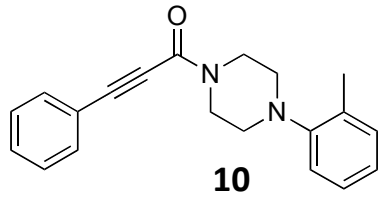
2.01
2.01
2.03
3.00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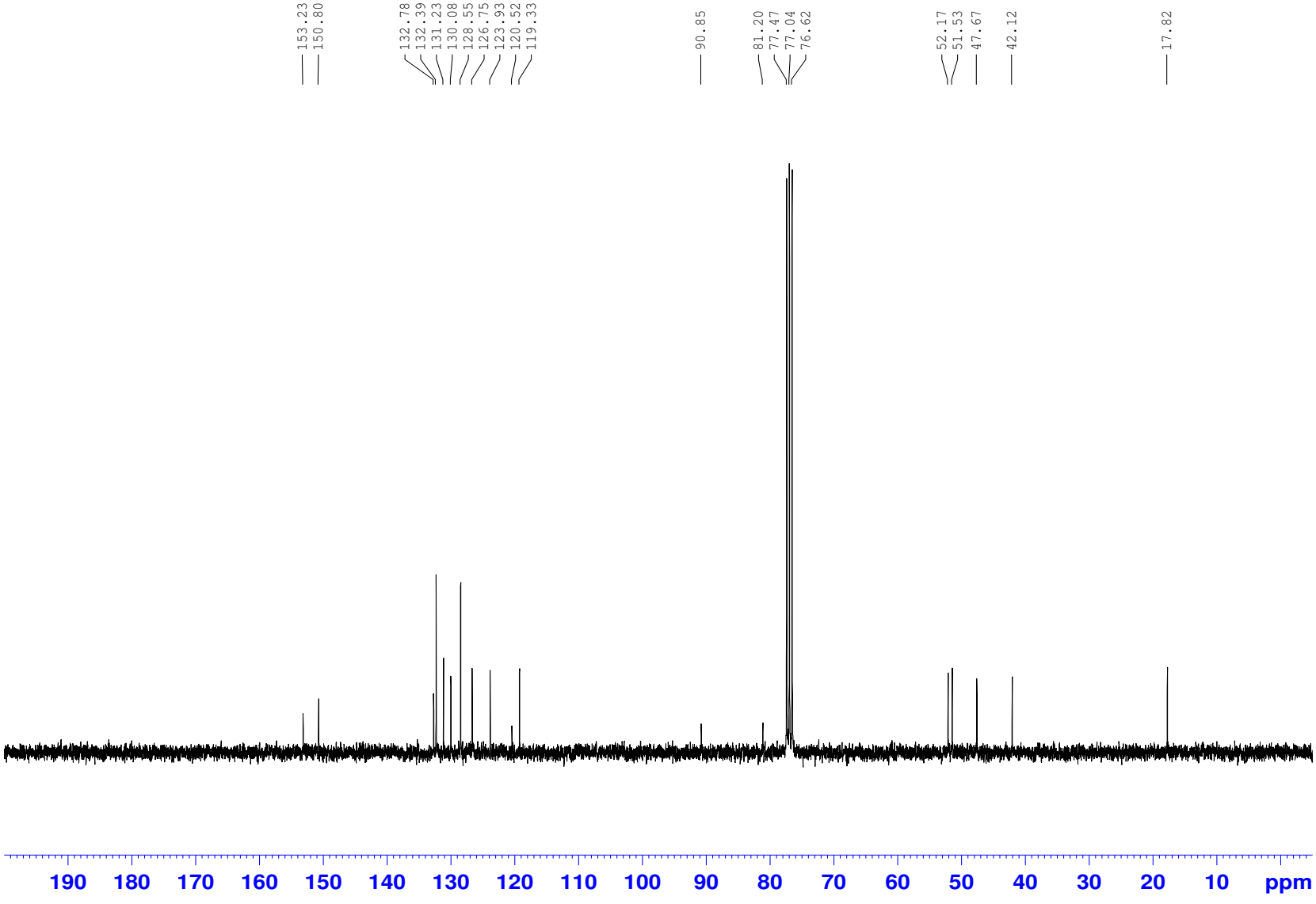
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130.08
128.55
126.75
123.93
120.52
119.33
90.85
81.20
77.47
77.04
76.62
52.17
51.53
47.67
42.12
17.82
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150
140
130
120
110
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70
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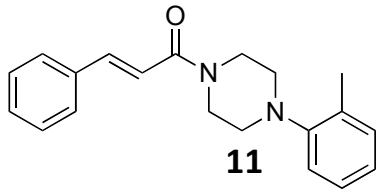
30
20
10
ppm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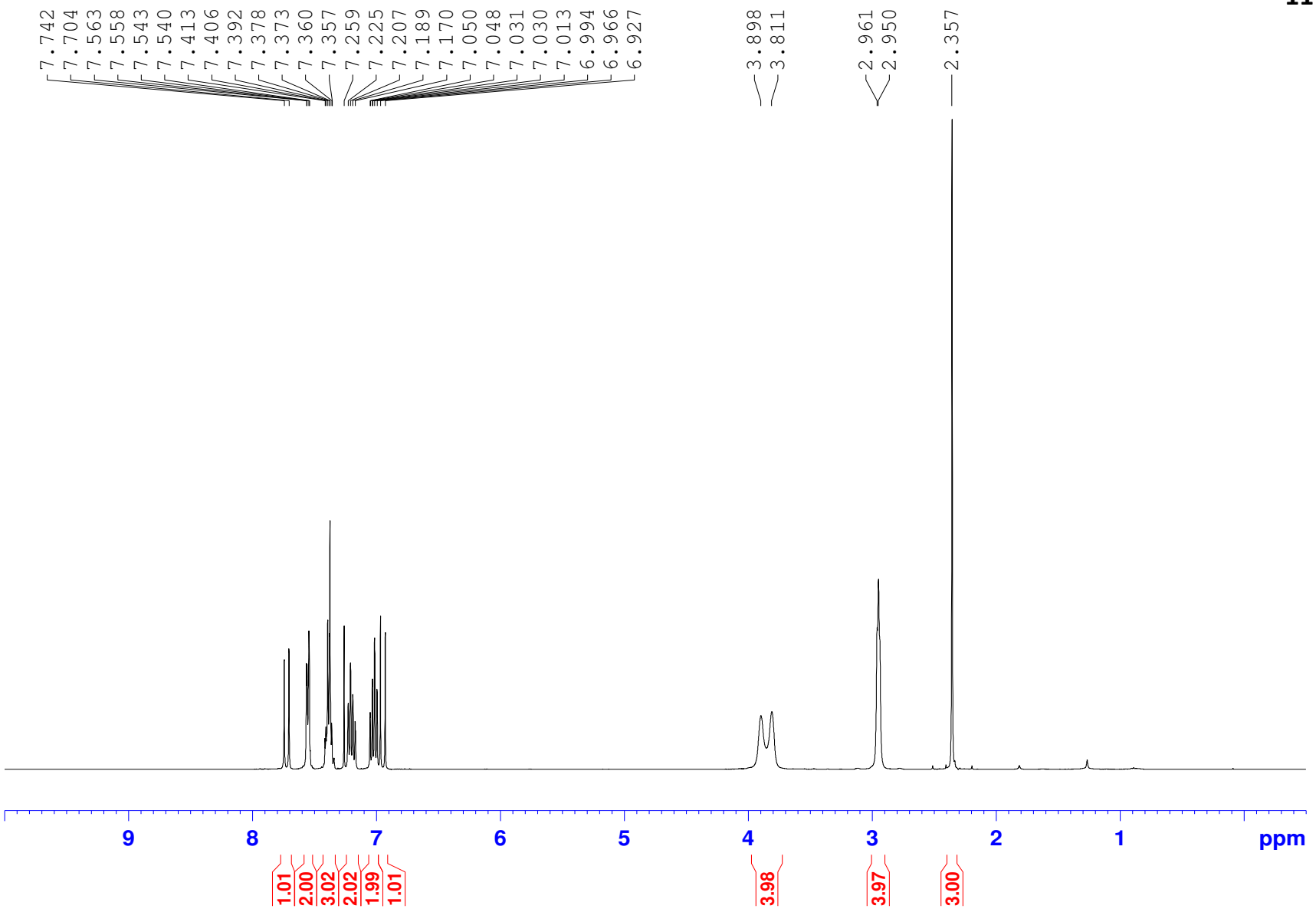
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7.406
7.392
7.378
7.373
7.360
7.357
7.259
7.225
7.207
7.189
7.170
7.050
7.048
7.031
7.030
7.013
6.994
6.966
6.927
3.898
3.811
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2.357
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7
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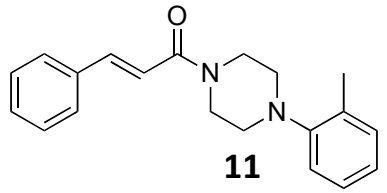
2.02
1.99
1.01
3.98
3.97
3.00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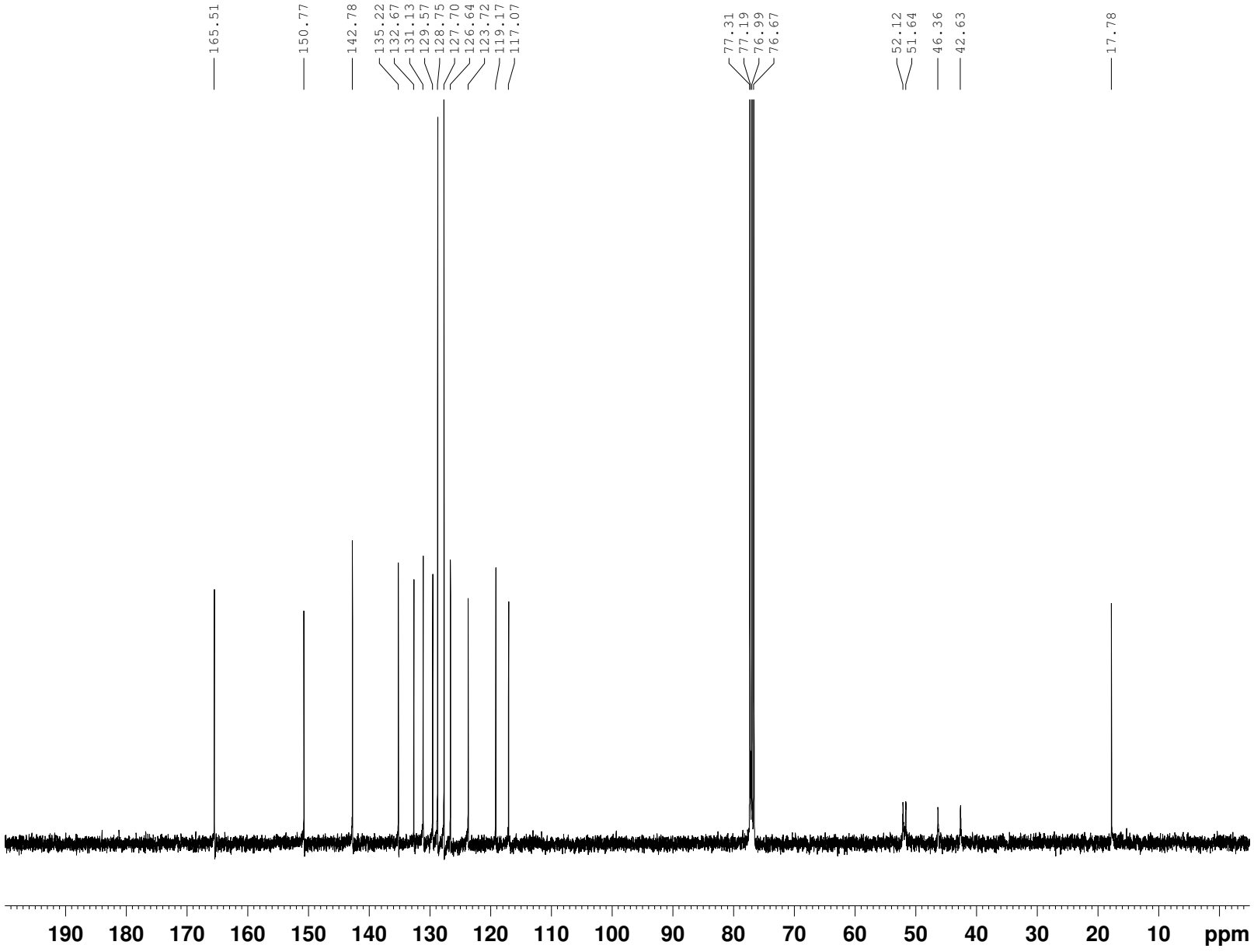
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123.72
119.17
117.07
77.31
77.19
76.99
76.67
52.12
51.64
46.36
42.63
17.78
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150
140
130
120
110
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80
70
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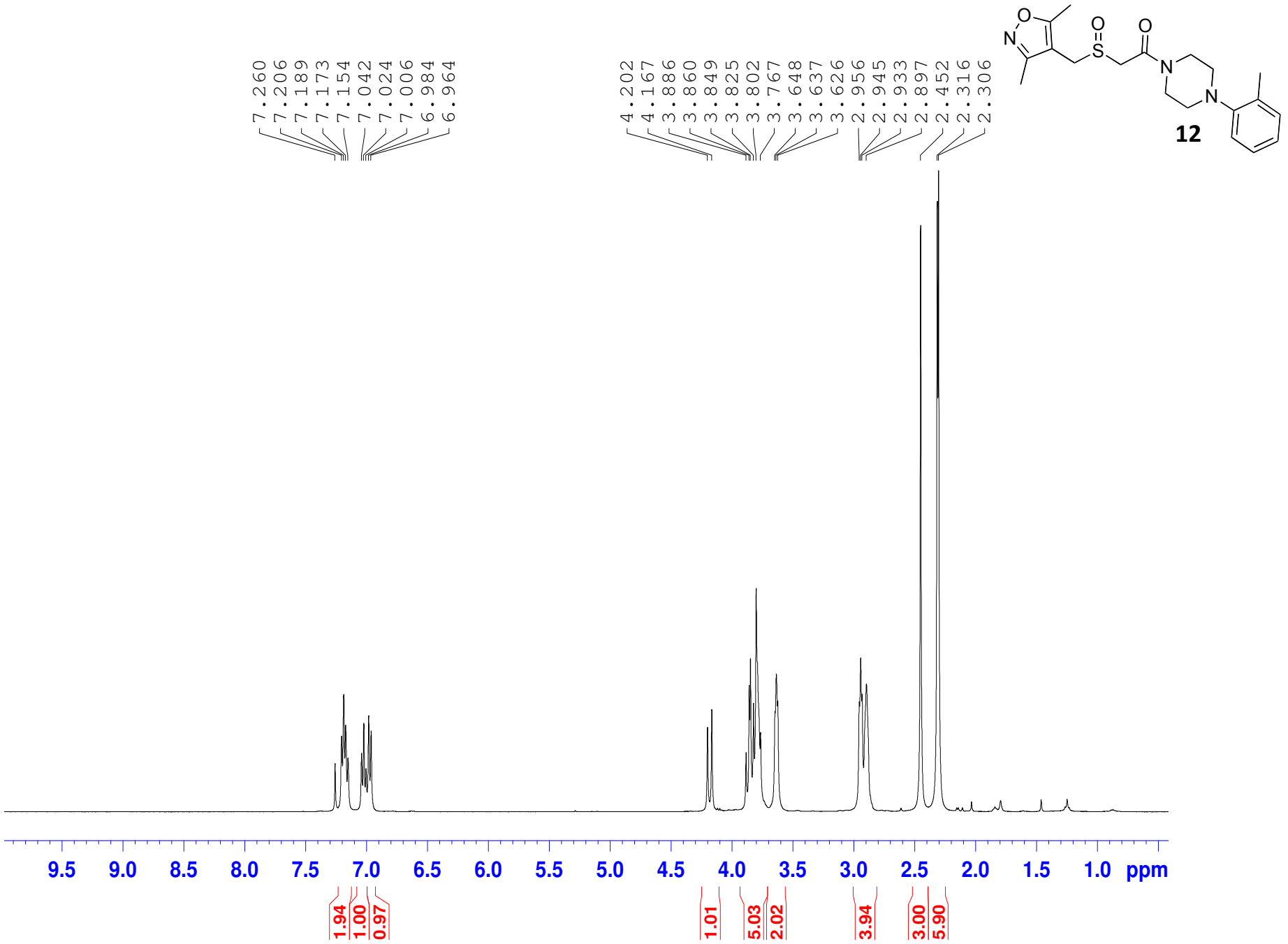
30
20
10
ppm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7.154
7.042
7.024
7.006
6.984
6.964
4.202
4.167
3.886
3.860
3.849
3.825
3.802
3.767
3.648
3.637
3.626
2.956
2.945
2.933
2.897
2.452
2.316
2.306
12
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
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ppm
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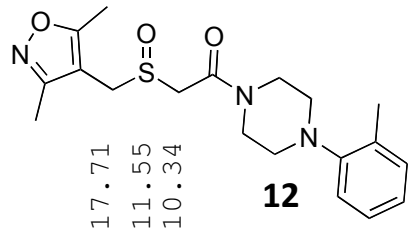
1.00
0.97
1.01
5.03
2.02
3.94
3.00
5.90



12

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159.93
150.35
132.65
131.19
126.70
124.01
119.17
104.50
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76.67
53.68
51.99
51.52
47.00
46.84
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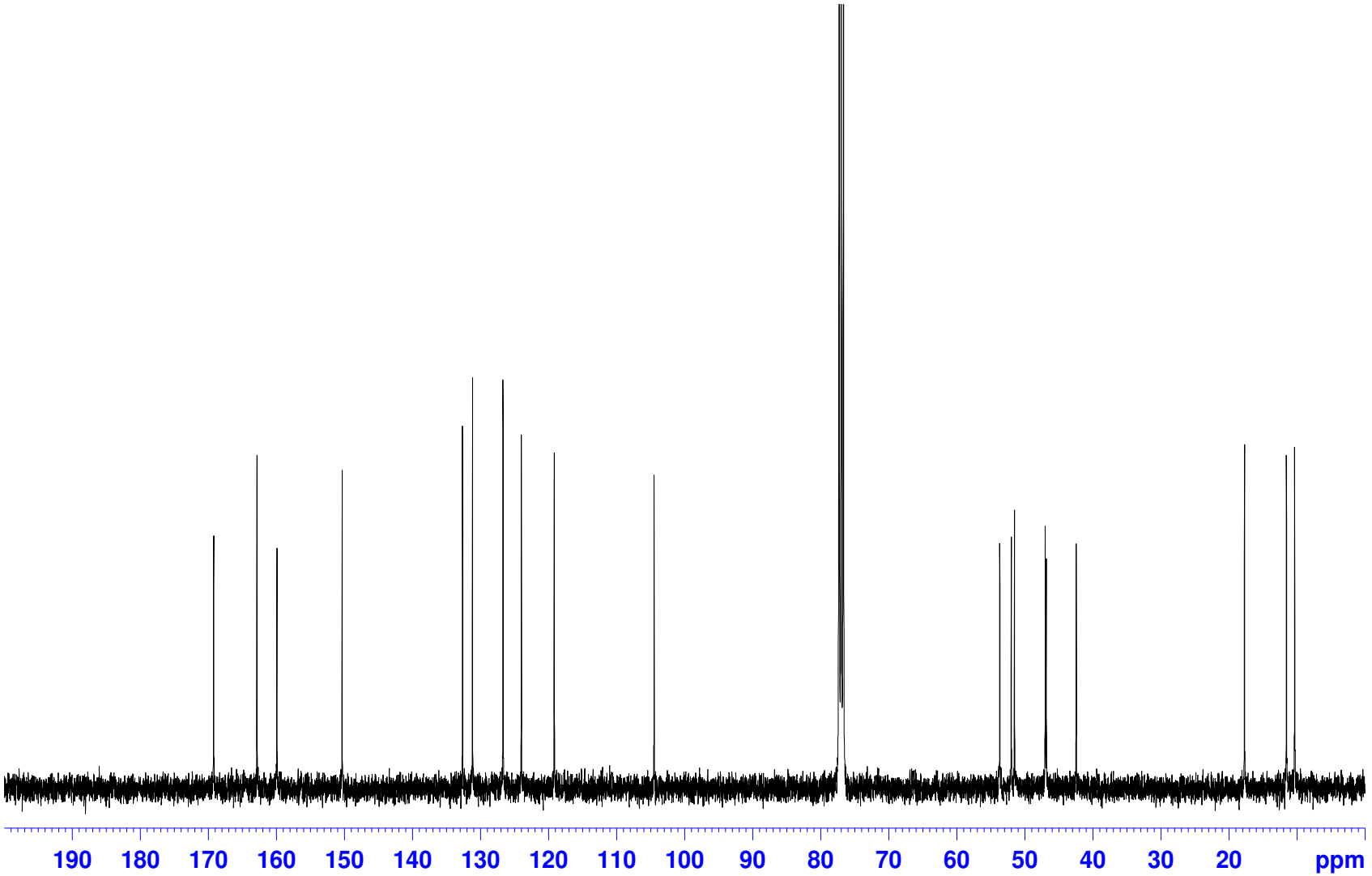
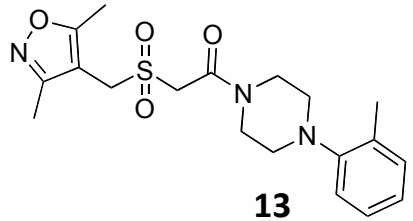
11.55
10.34





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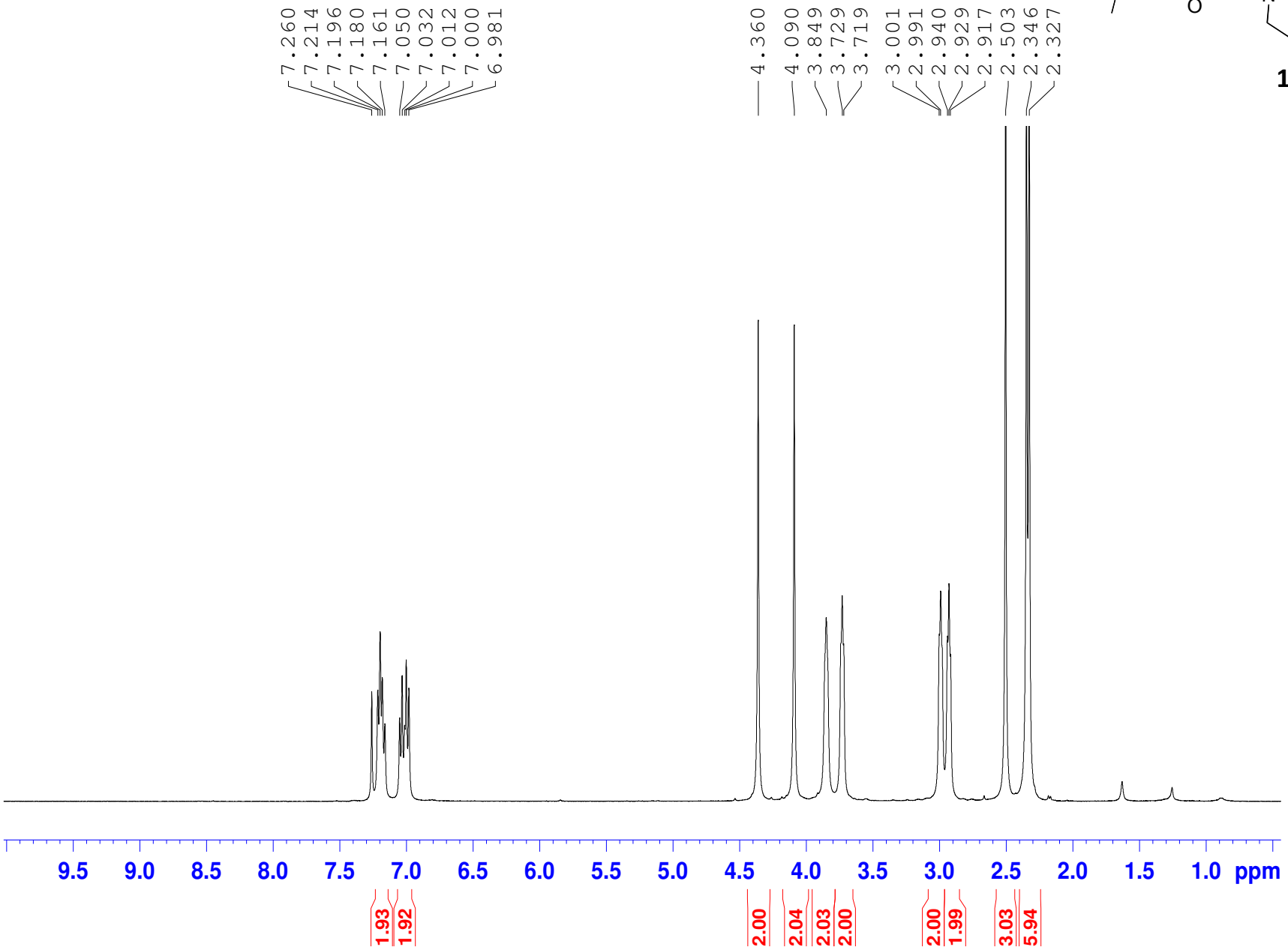
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7.012
7.000
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4.090
3.849
3.729
3.719
3.001
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2.940
2.929
2.917
2.503
2.346
2.327
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9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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1.0
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2.03
2.00
2.00
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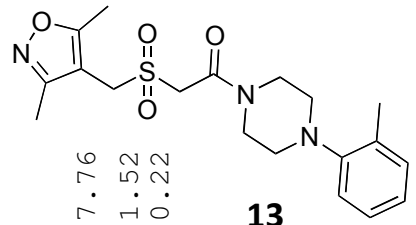
3.03
5.94



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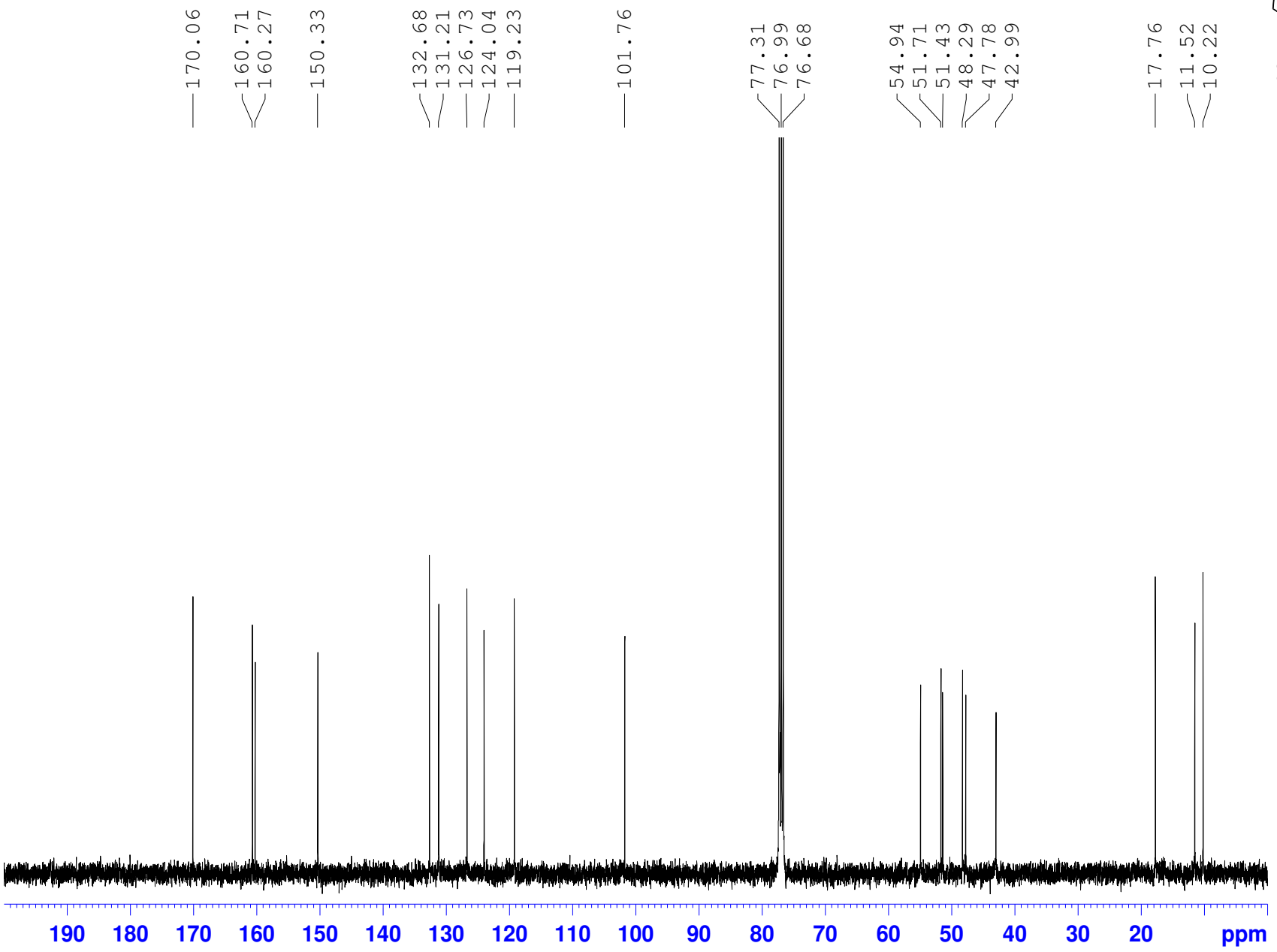
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124.04
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101.76
77.31
76.99
76.68
54.94
51.71
51.43
48.29
47.78
42.99
17.76
11.52
10.22
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160
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140
130
120
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80
70
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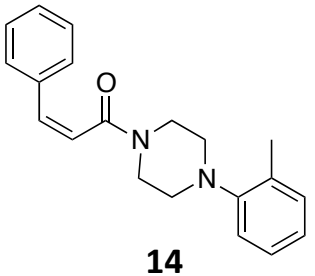
50
40
30
20
ppm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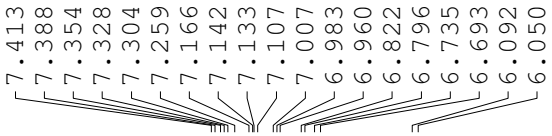
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6.796
6.735
6.693
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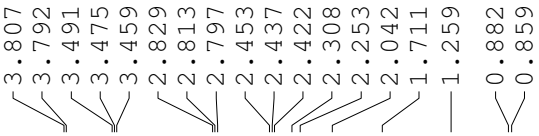
6.050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1.259
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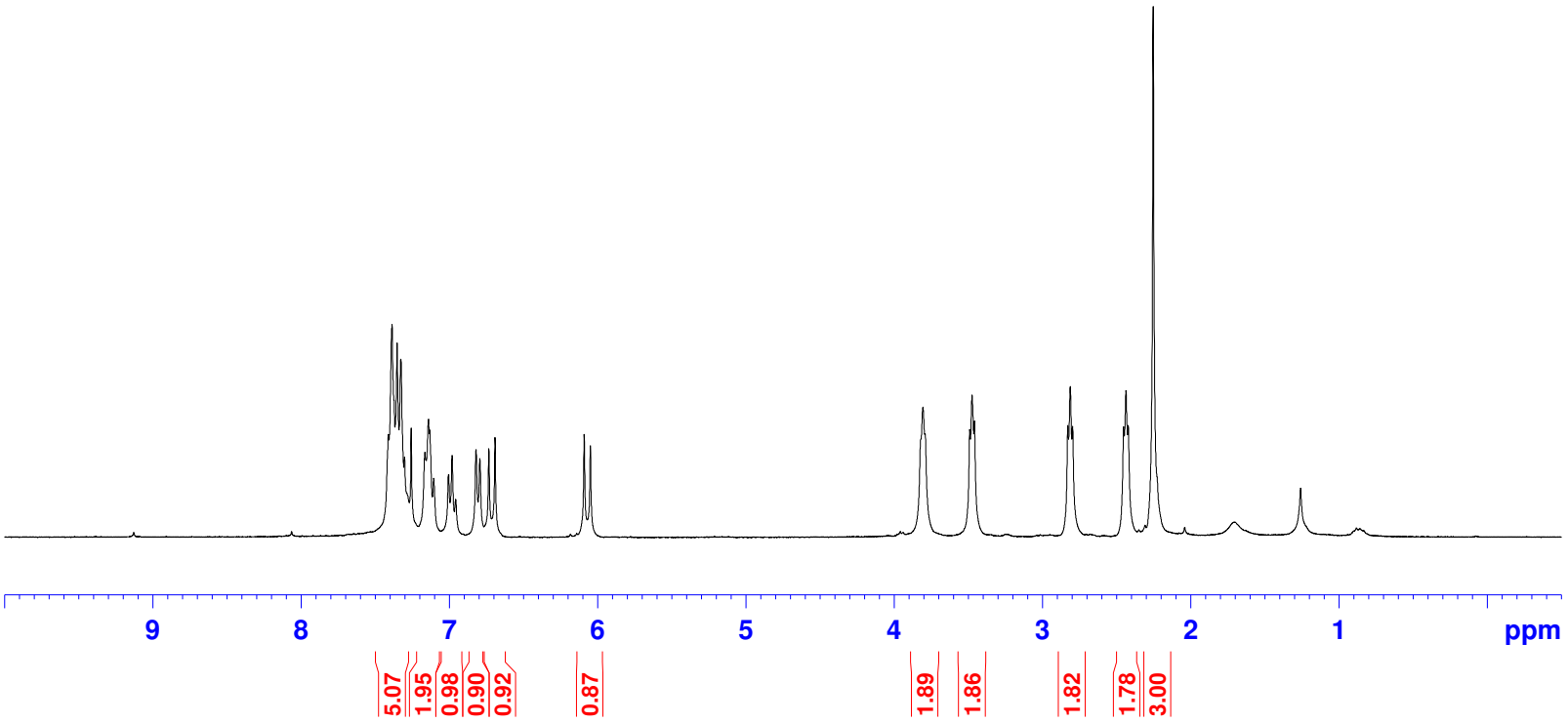
0.859


9
8
7
6
5
4
3
2
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ppm
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0.87
1.89
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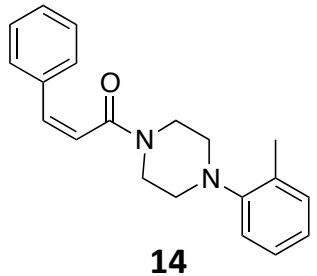
1.78
3.00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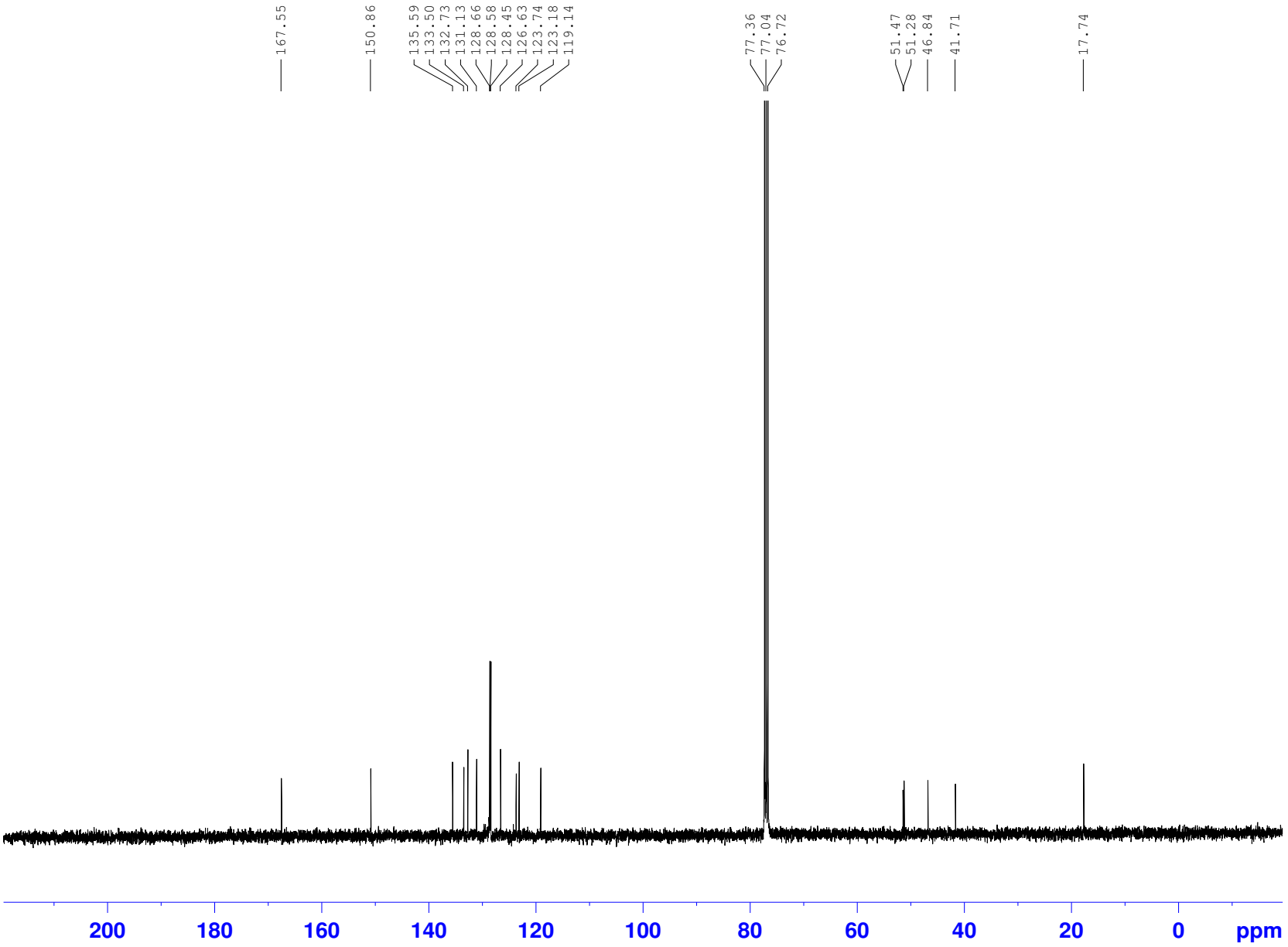
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128.58
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126.63
123.74
123.18
119.14
77.36
77.04
76.72
51.47
51.28
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41.71
17.74
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160
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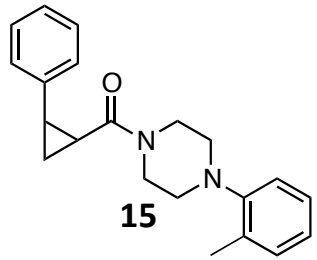
120
100
80
60
40
20
0
ppm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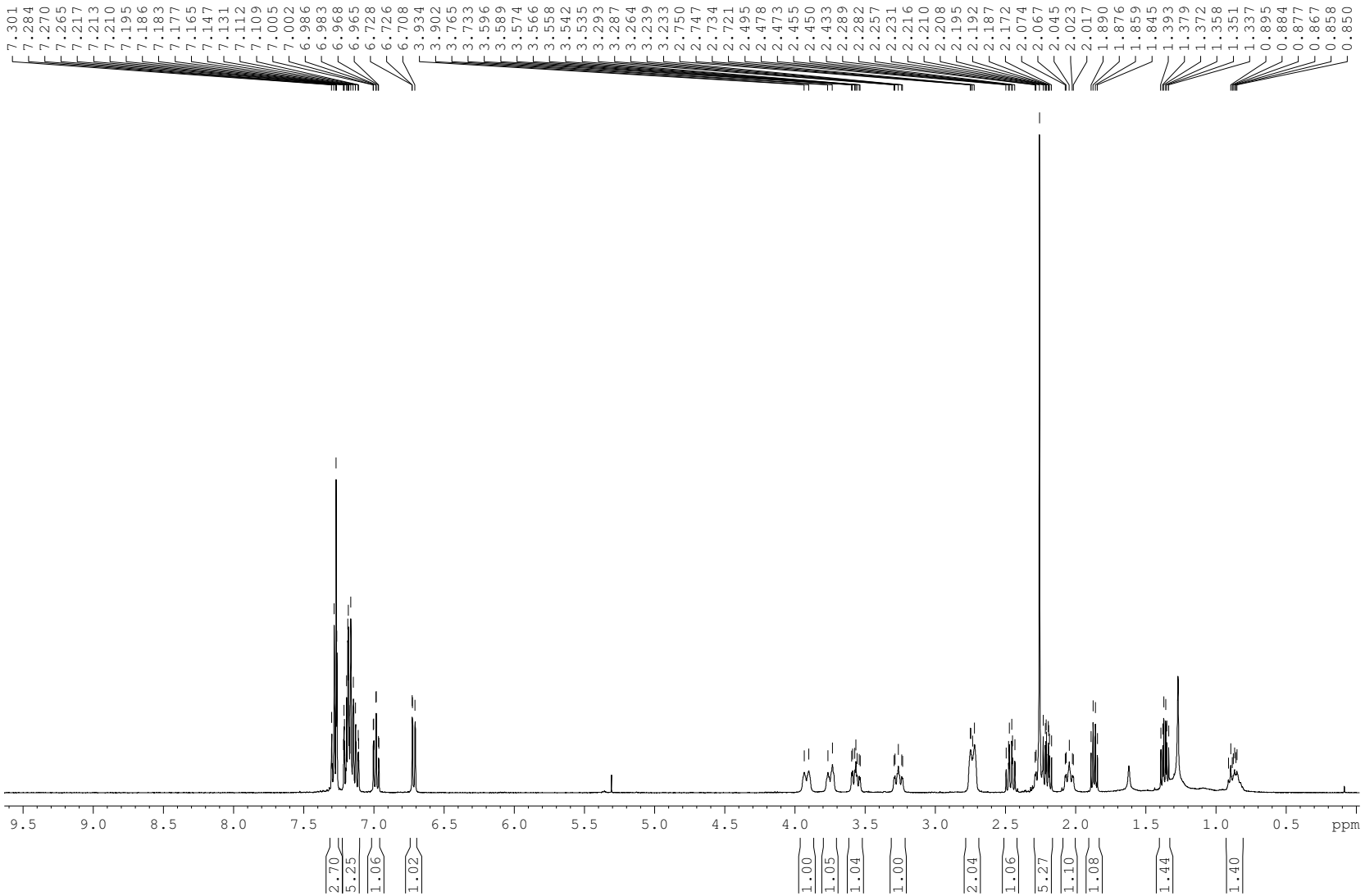
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7.147
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7.109
7.005
7.002
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6.983
6.968
6.965
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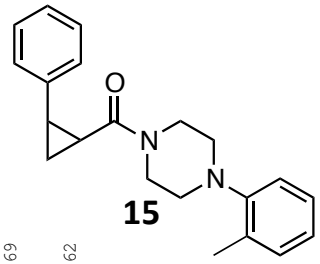
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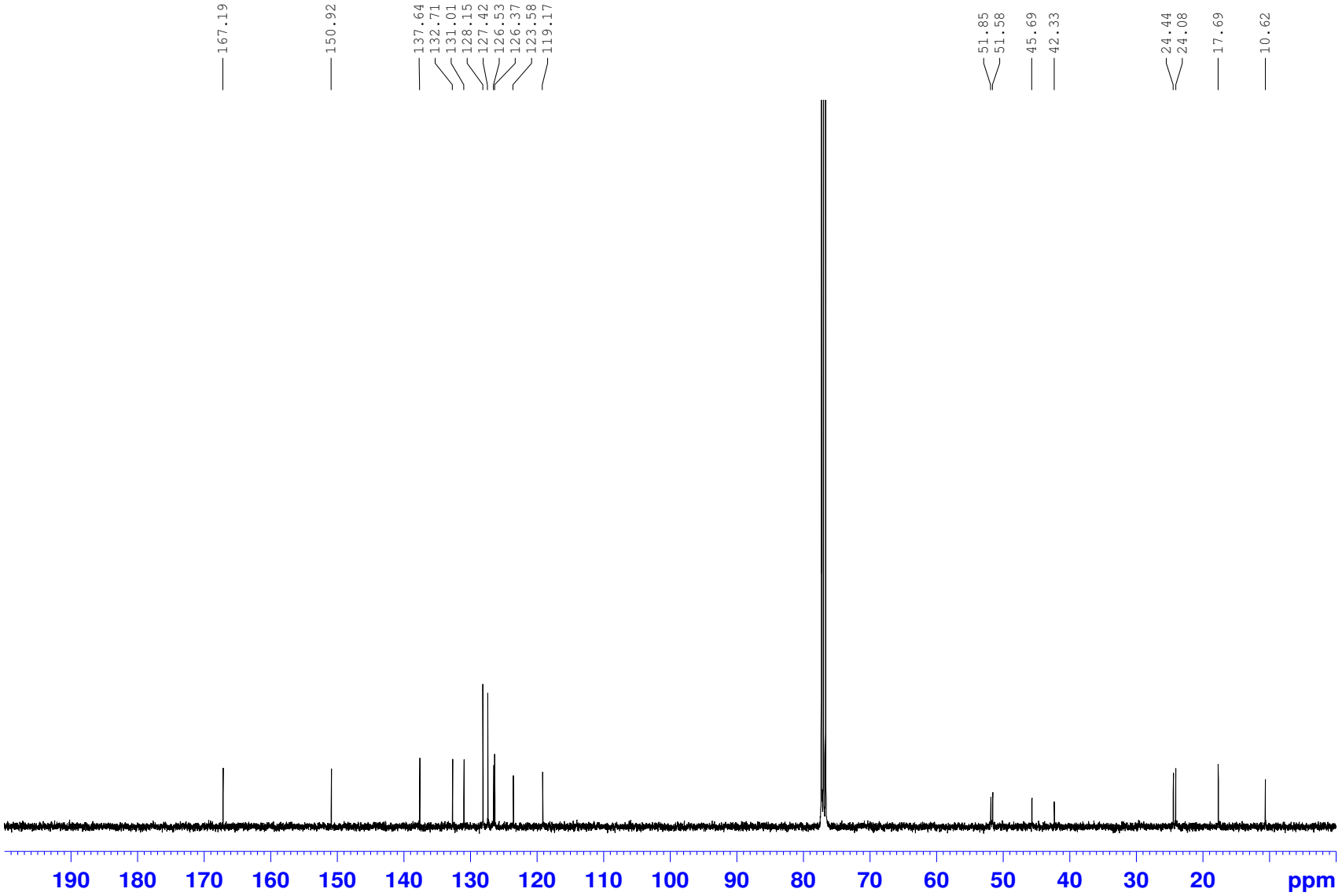
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51.58
45.69
42.33
24.44
24.08
17.69
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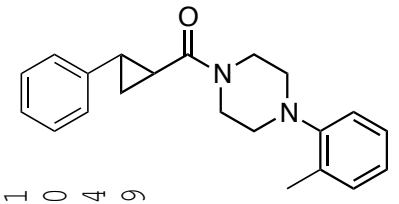
20
ppm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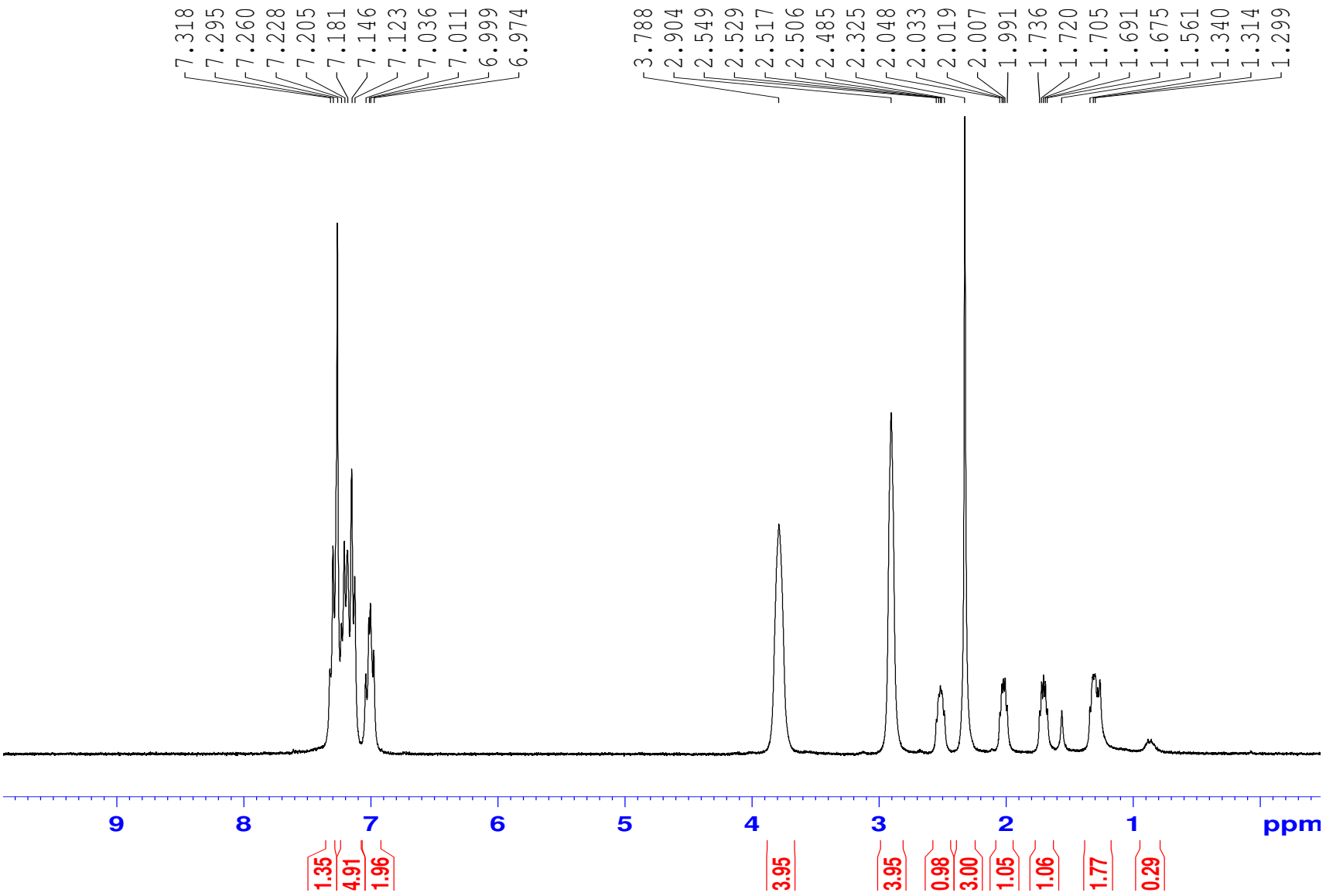
N

16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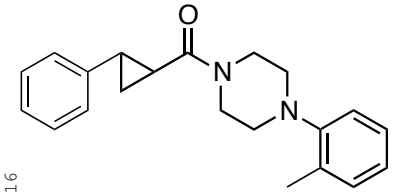
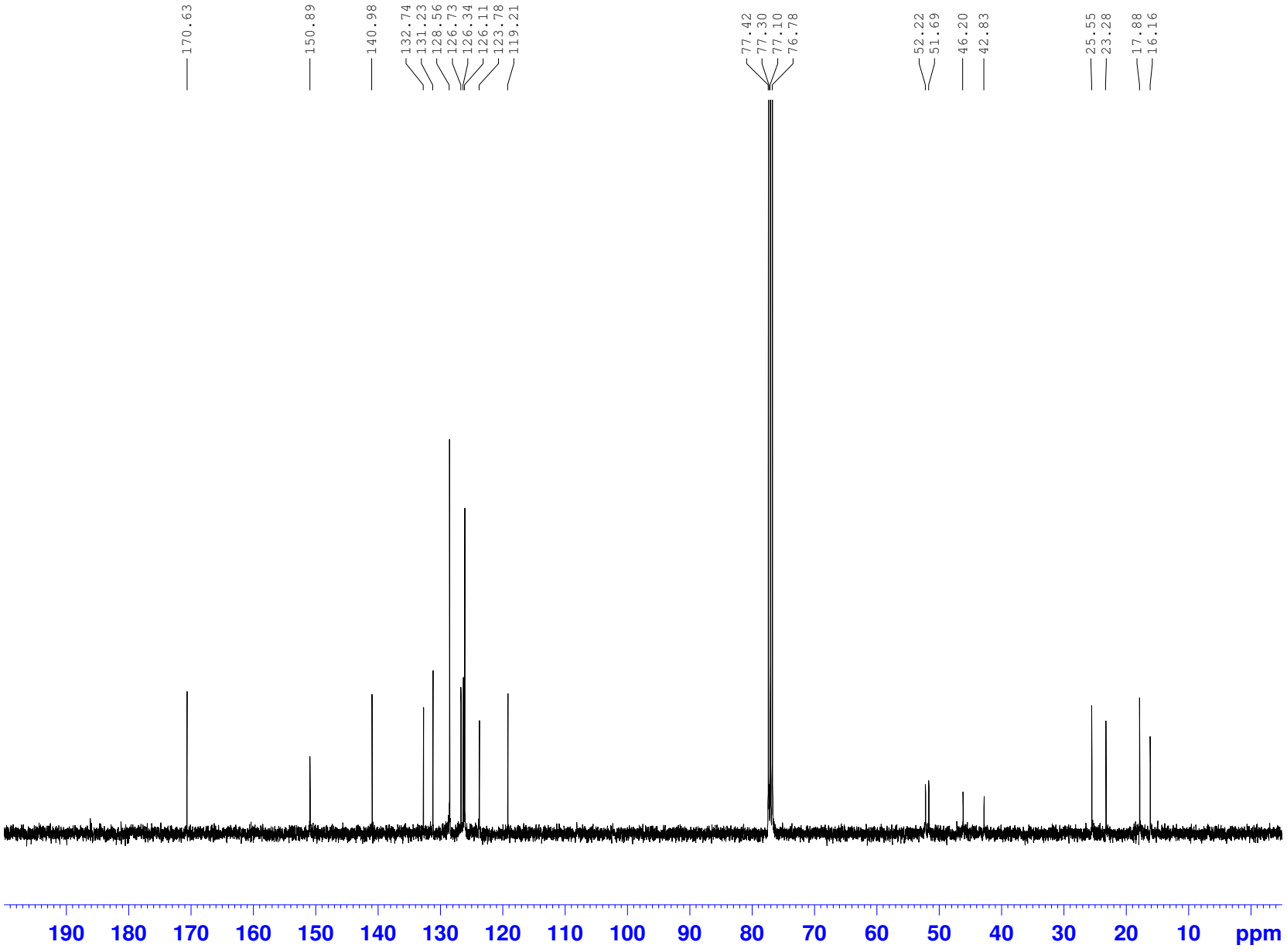
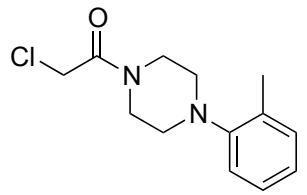
7.295
7.260
7.228
7.205
7.181
7.146
7.123
7.036
7.011
6.999
6.974
3.788
2.904
2.549
2.529
2.517
2.506
2.485
2.325
2.048
2.033
2.019
2.007
1.991
1.736
1.720
1.705
1.691
1.675
1.561
1.340
1.314
1.299
9
8
7
6
5
4
3
2
1
ppm
1.35
4.91
1.96
3.95
3.95
0.98
3.00
1.05
1.06
1.77
0.29

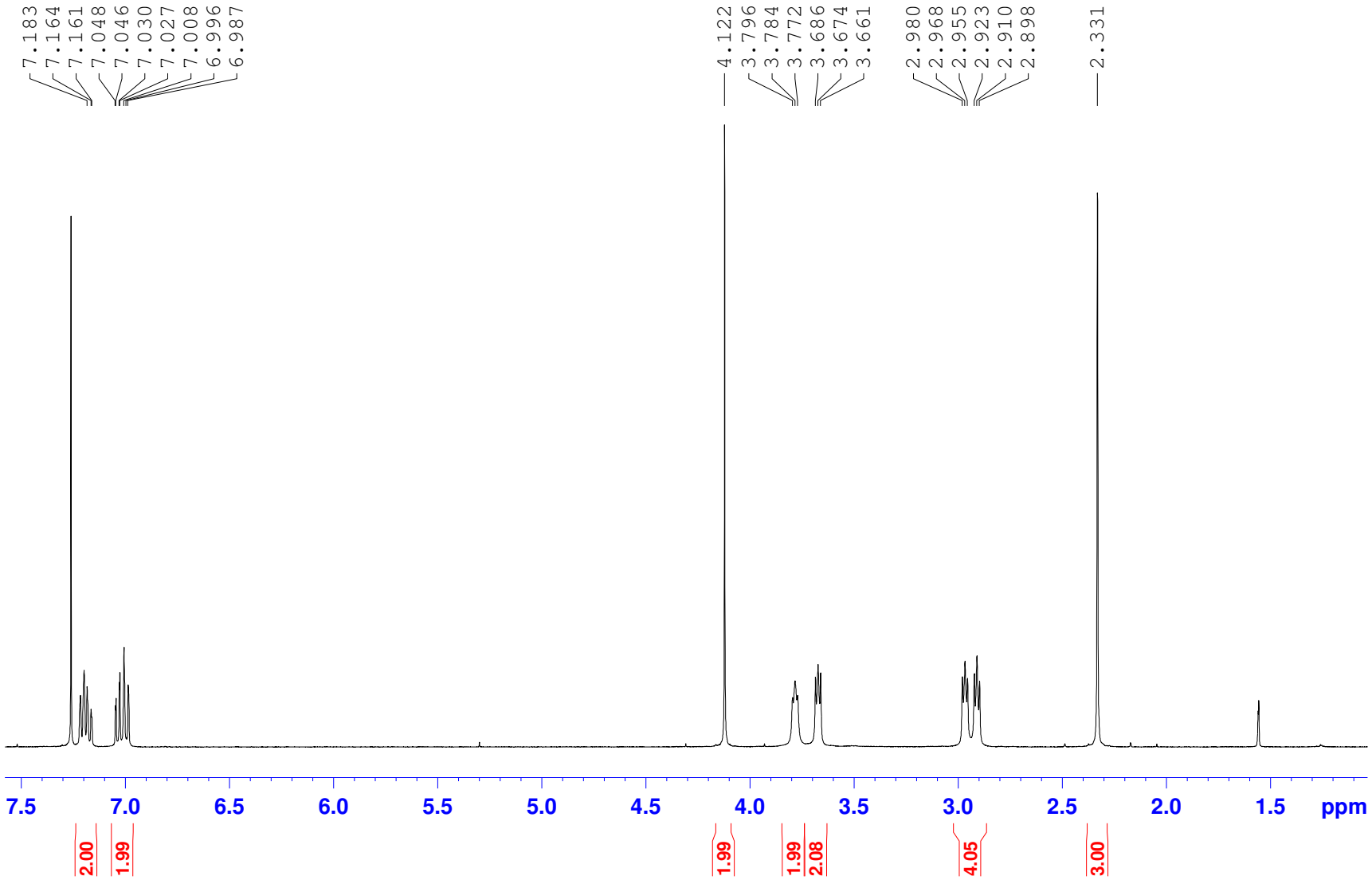

O
N
N

16


170.63
150.89
140.98
132.74
131.23
128.56
126.73
126.34
126.11
123.78
119.21
77.42
77.30
77.10
76.78
52.22
51.69
46.20
42.83
25.55
23.28
17.88
16.16
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


O
Cl
N
N

17a


7.183
7.164
7.161
7.048
7.046
7.030
7.027
7.008
6.996
6.987
4.122
3.796
3.784
3.772
3.686
3.674
3.661
2.980
2.968
2.955
2.923
2.910
2.898
2.331
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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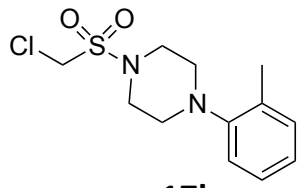
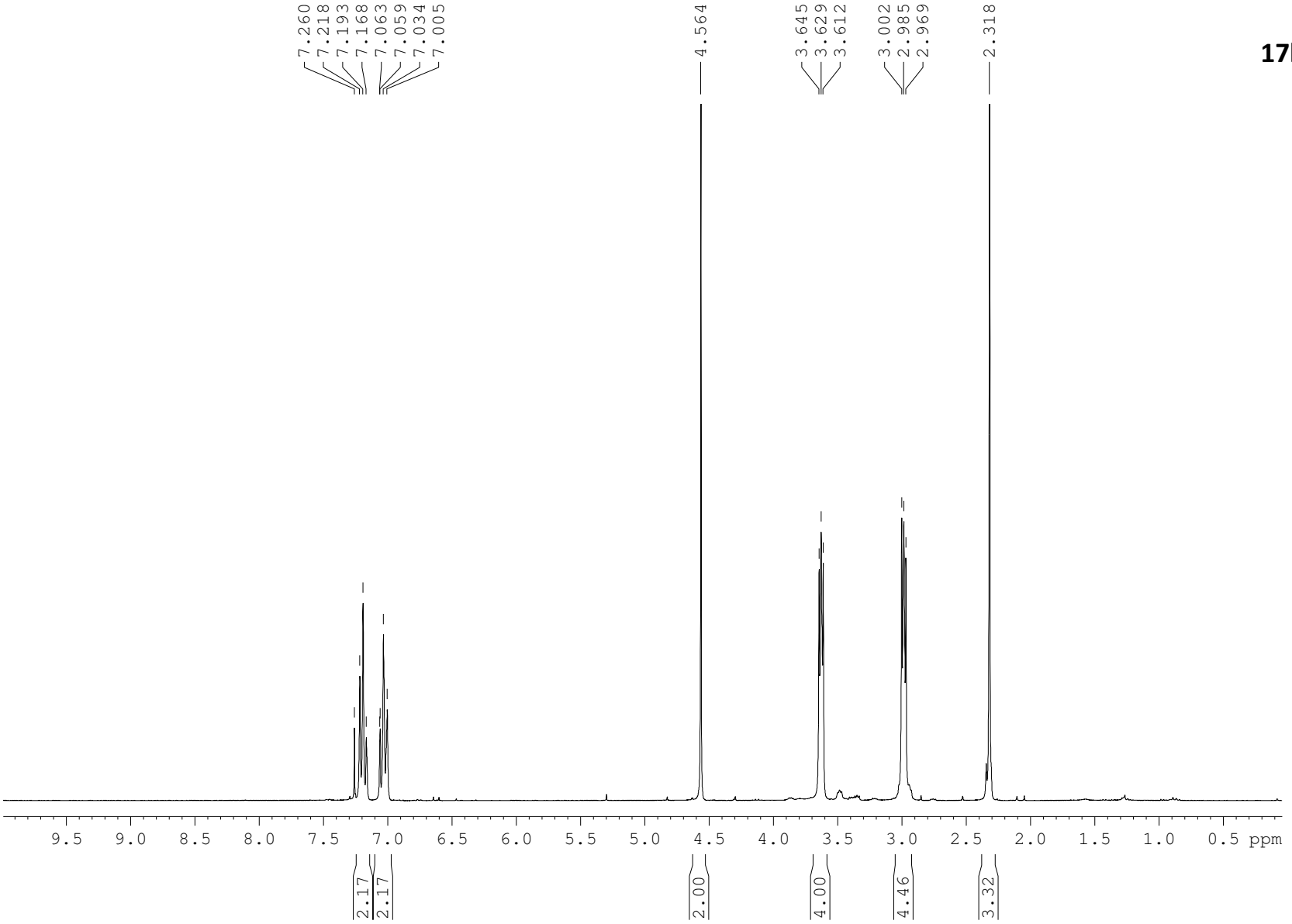
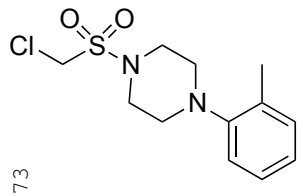
2.0
1.5
ppm
2.00
1.99
1.99
1.99
2.08
4.05
3.00



17b

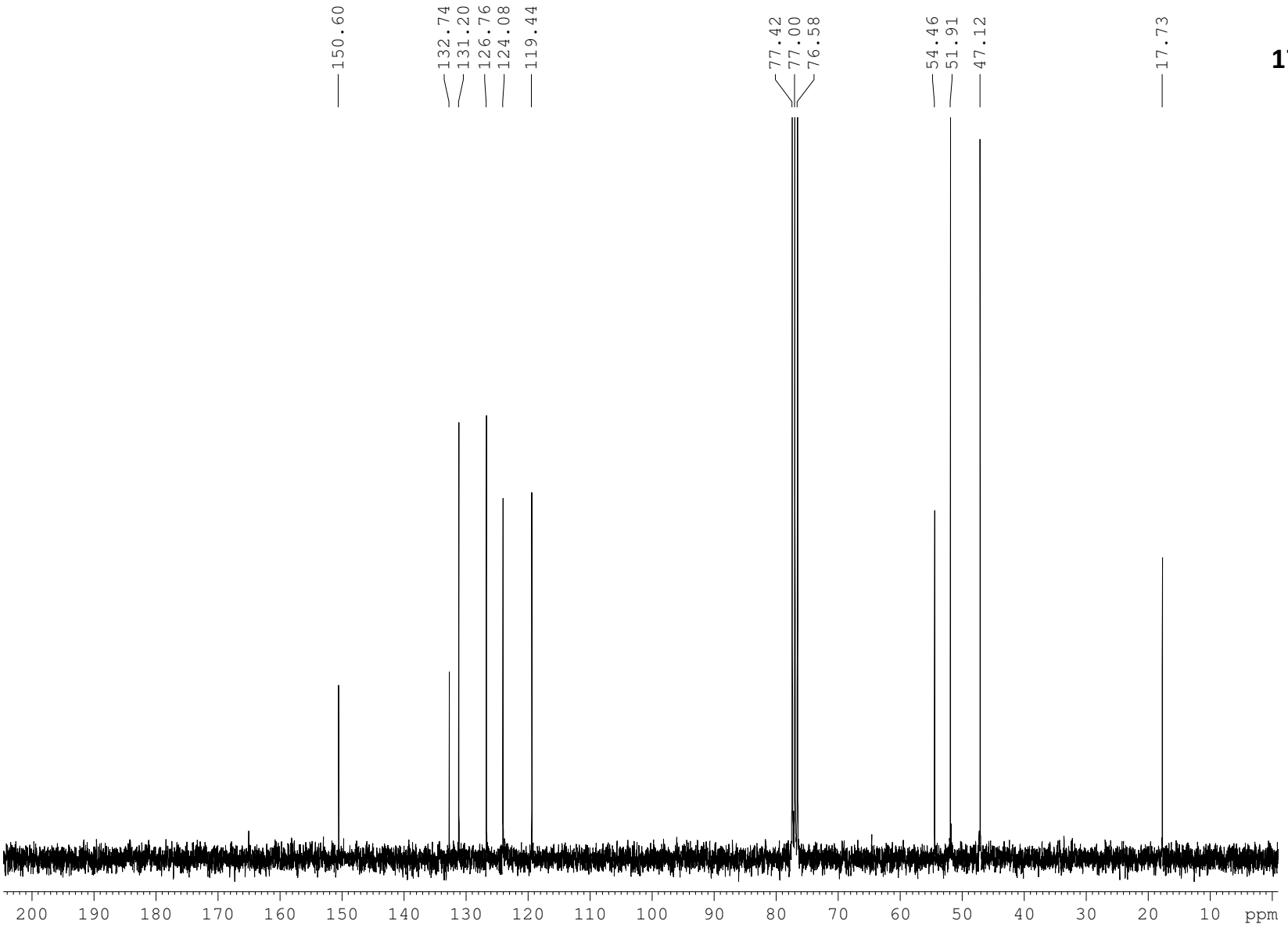
71-548-1-CDCl3-300Mhz

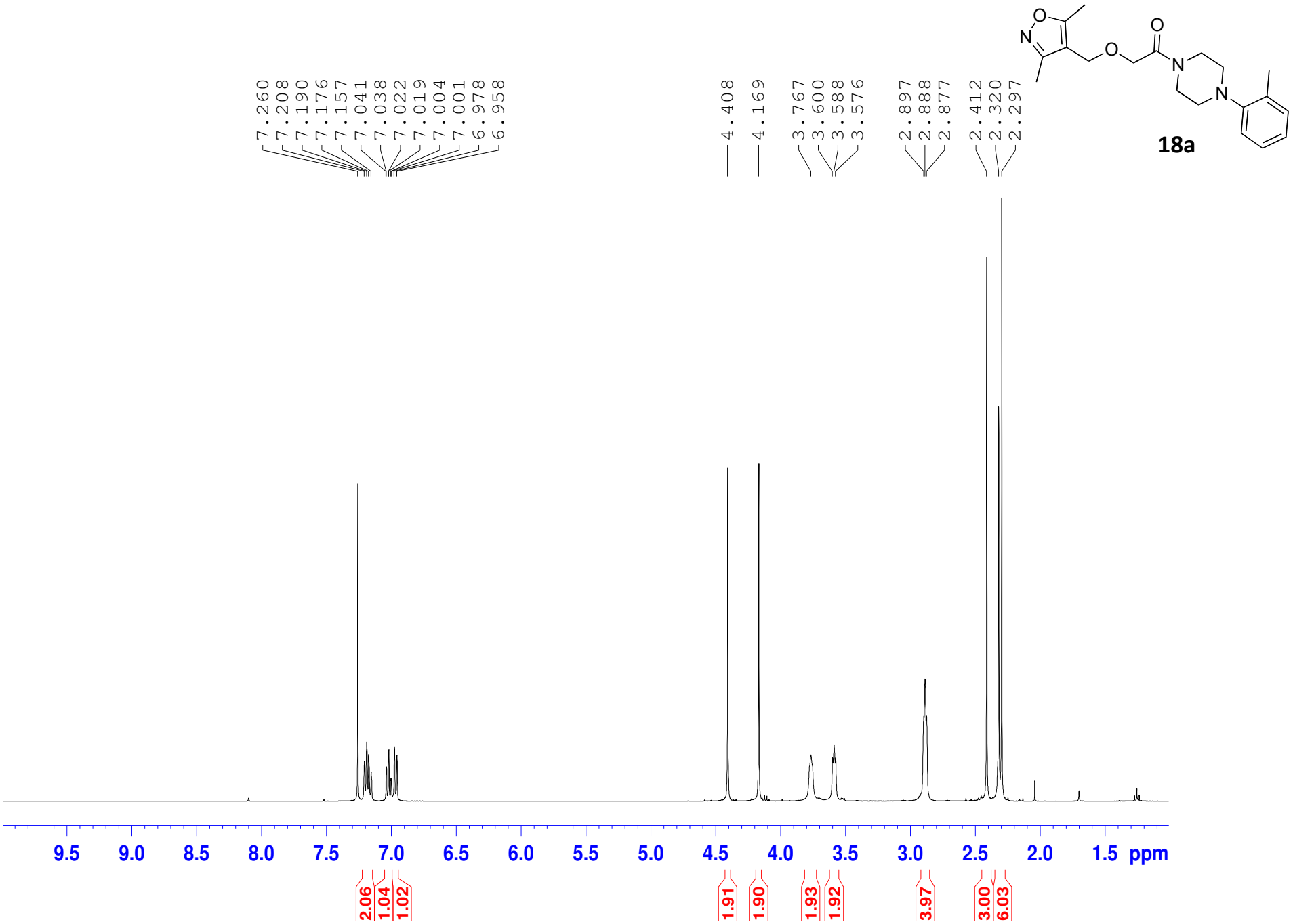




17b

71-548-1-CDCl3-300Mhz

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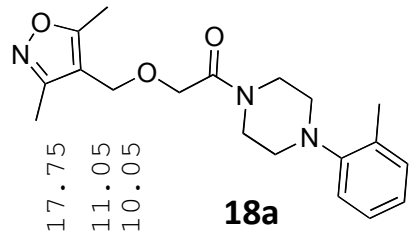
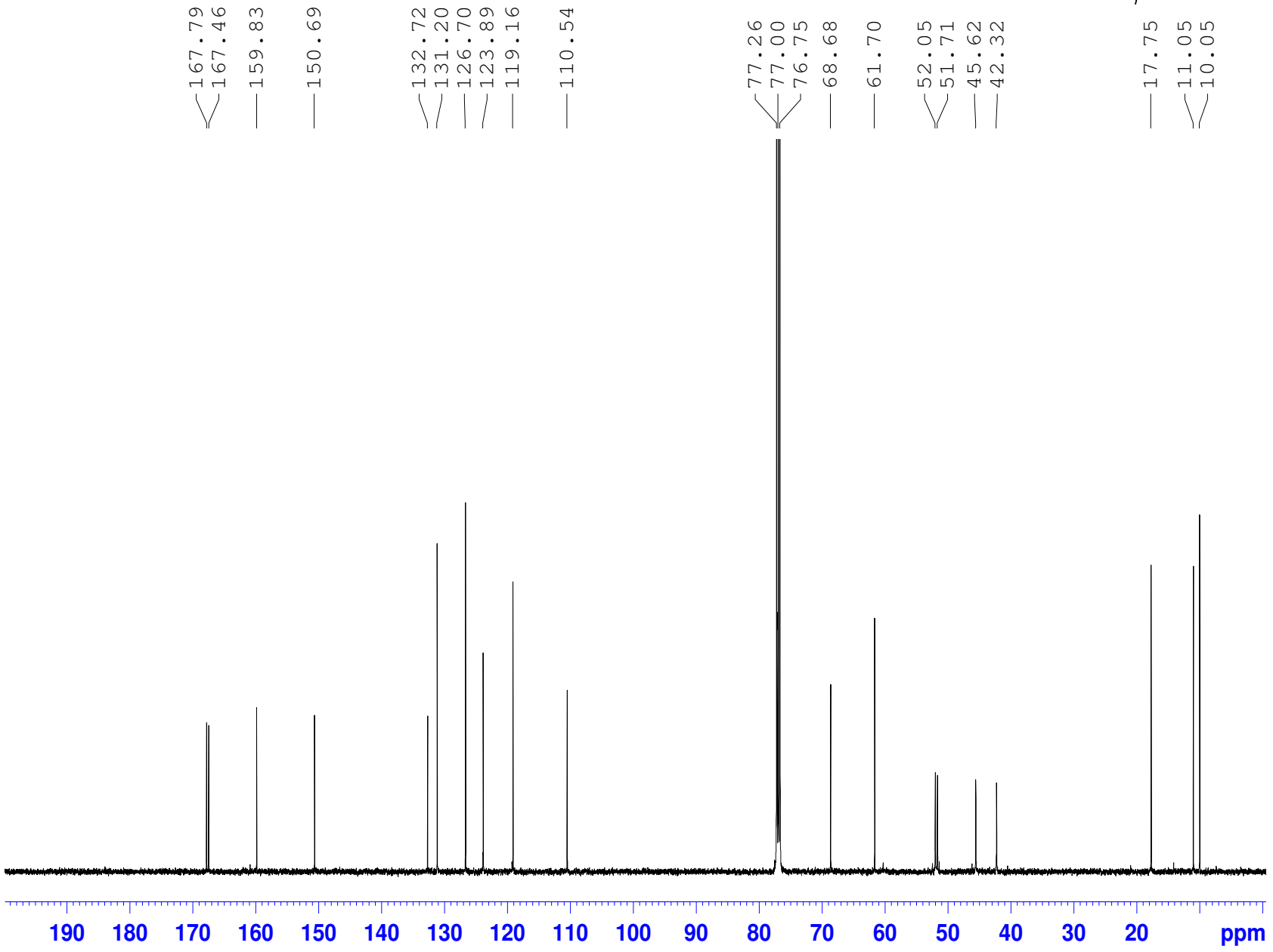
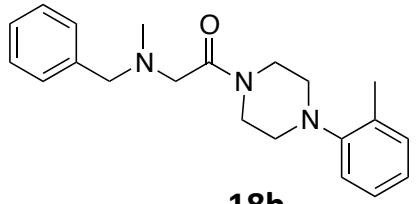
7.208
7.190
7.176
7.157
7.041
7.038
7.022
7.019
7.004
7.001
6.978
6.958
4.408
4.169
3.767
3.600
3.588
3.576
2.897
2.888
2.877
2.412
2.320
2.297
18a
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
2.06
1.04
1.02
1.91
1.90
1.93
1.92
3.97
3.00
6.03

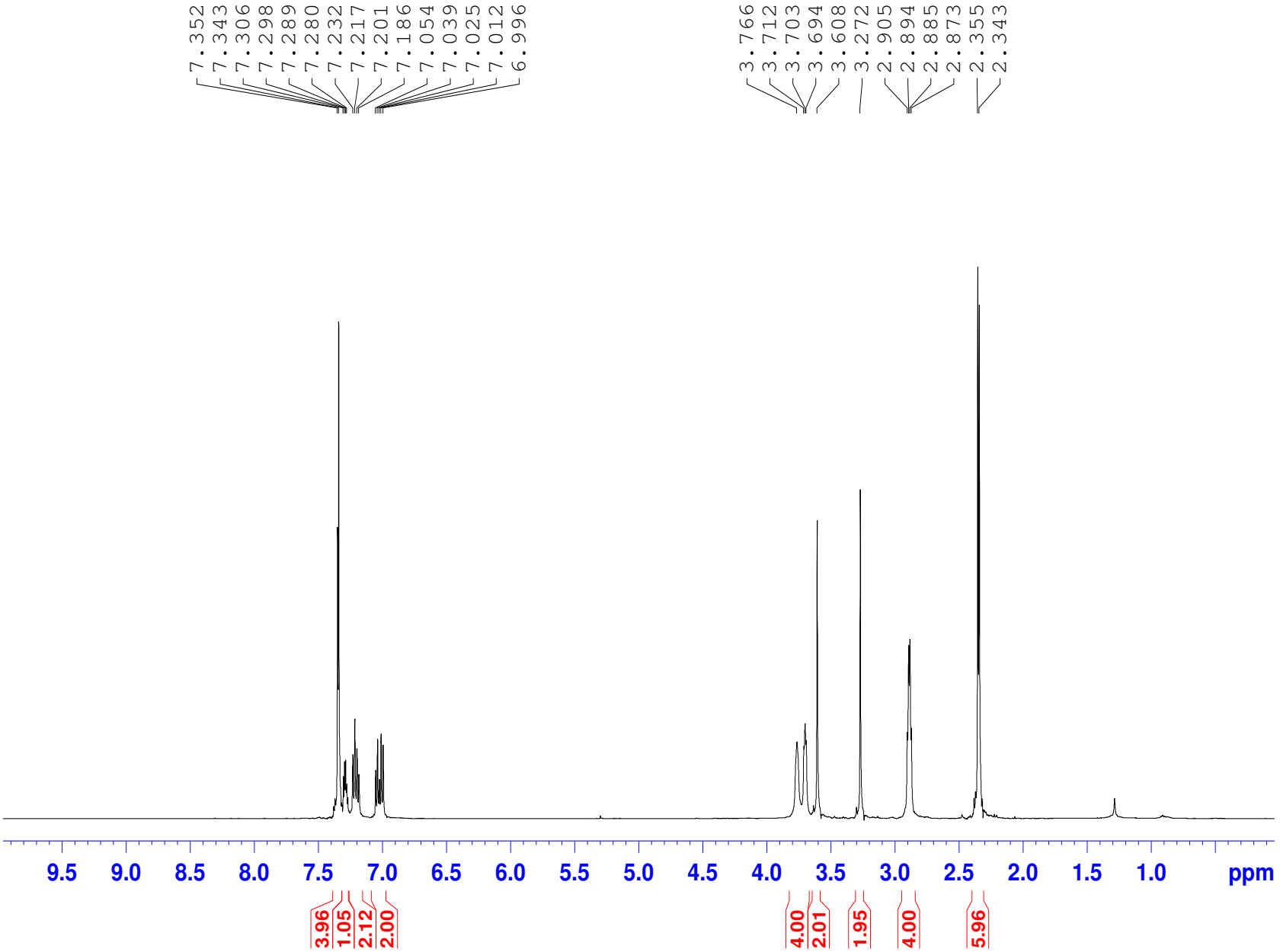


18a


167.79
167.46
159.83
150.69
132.72
131.20
126.70
123.89
119.16
110.54
77.26
77.00
76.75
68.68
61.70
52.05
51.71
45.62
42.32
17.75
11.05
10.05
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm



18b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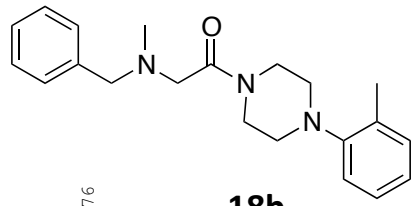
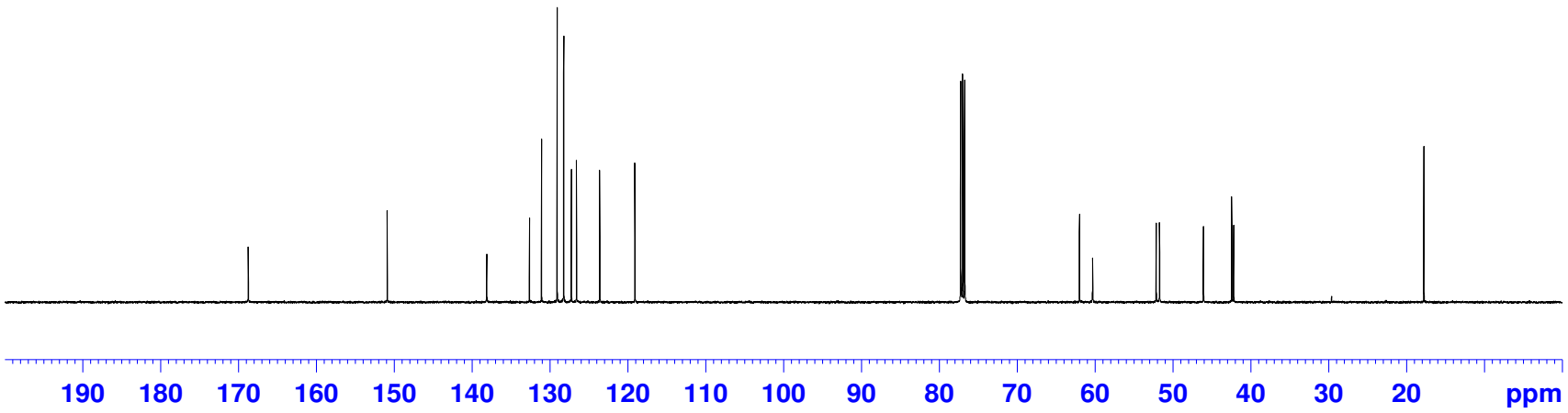
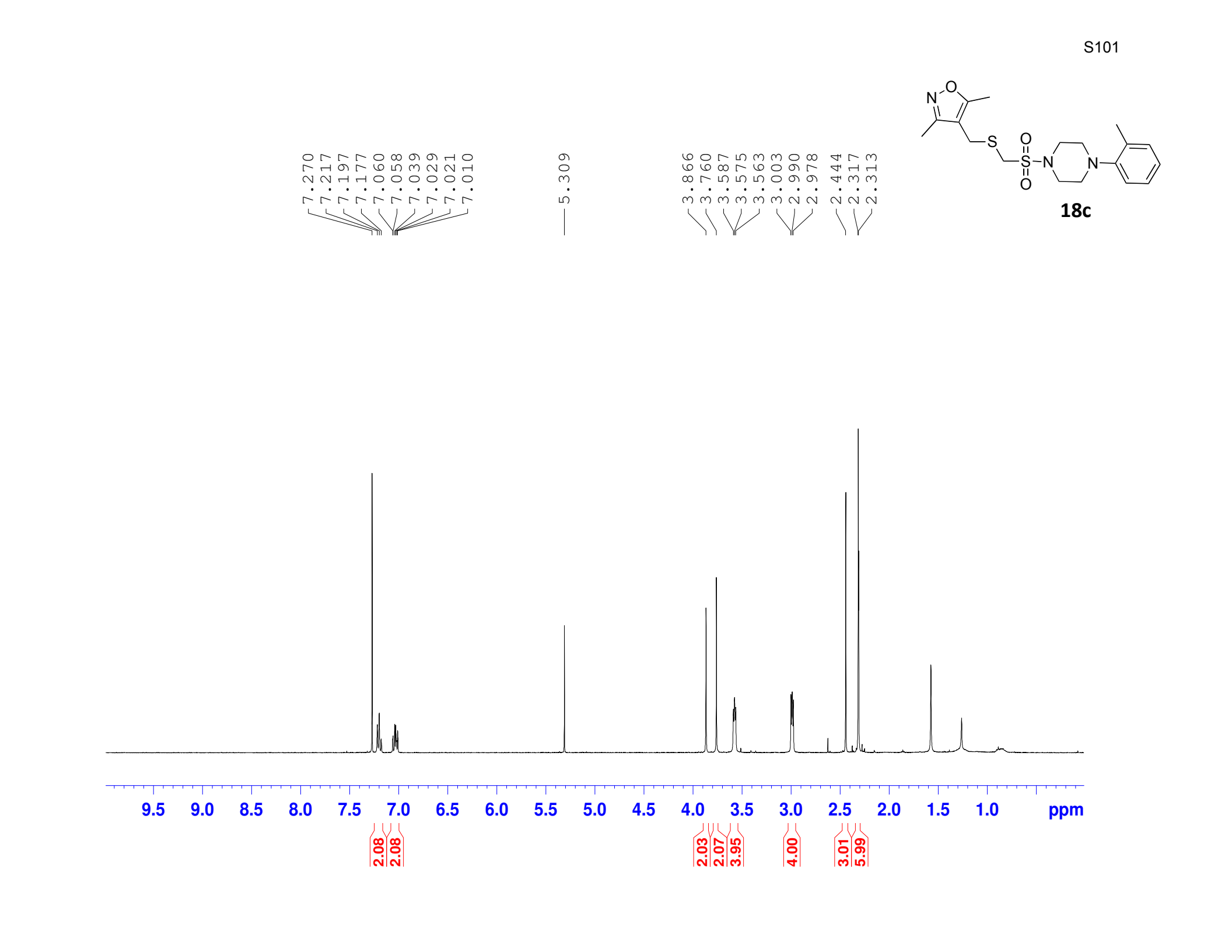
7.343
7.306
7.298
7.289
7.280
7.232
7.217
7.201
7.186
7.054
7.039
7.025
7.012
6.996
3.766
3.712
3.703
3.694
3.608
3.272
2.905
2.894
2.885
2.873
2.355
2.343
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
3.96
1.05
2.12
2.00
4.00
2.01
1.95
4.00
5.96

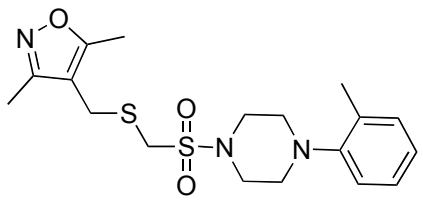


18b

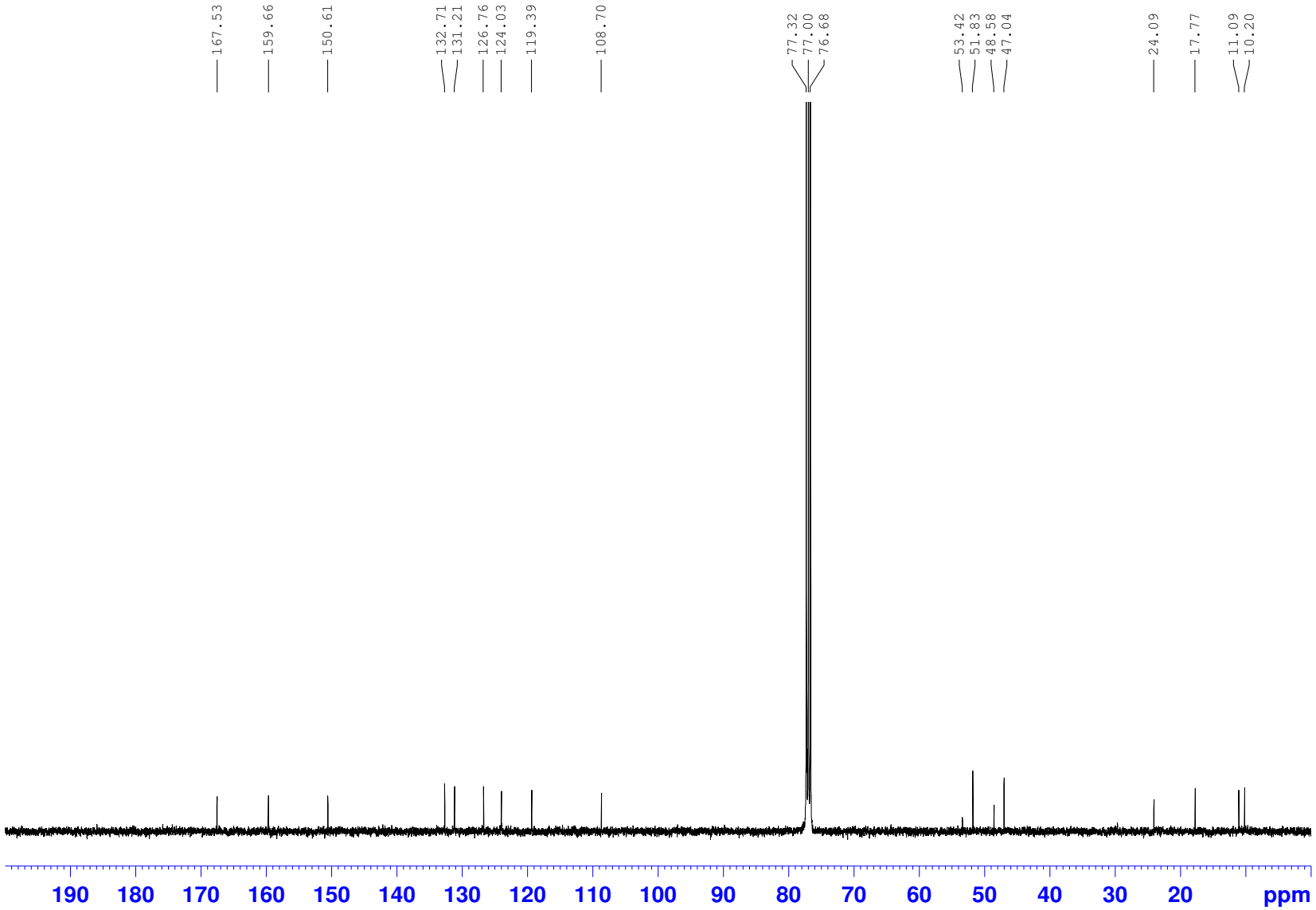
168.73
150.89
138.11
132.63
131.08
129.08
128.23
127.24
126.58
123.60
119.08
61.99
60.30
52.14
51.70
46.07
42.43
42.20
17.76

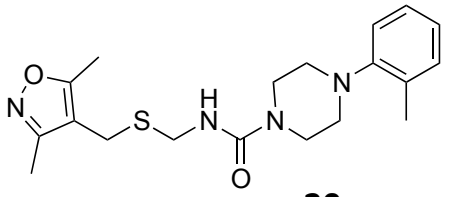



7.270
7.217
7.197
7.177
7.060
7.058
7.039
7.029
7.021
7.010
5.309
3.866
3.760
3.587
3.575
3.563
3.003
2.990
2.978
2.444
2.317
2.313
18c
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.08
2.08
2.03
2.07
3.95
4.00
3.01
5.99

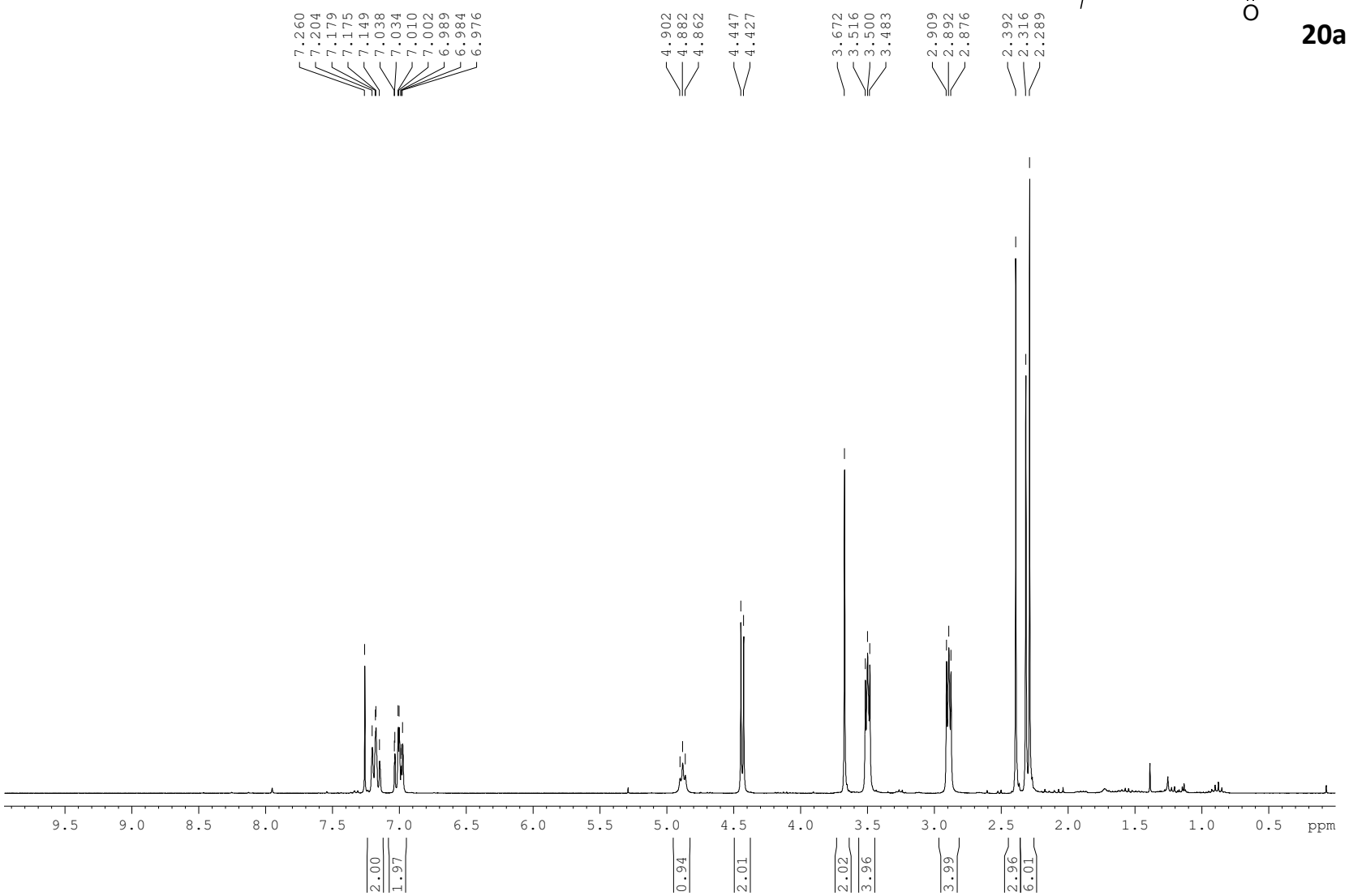


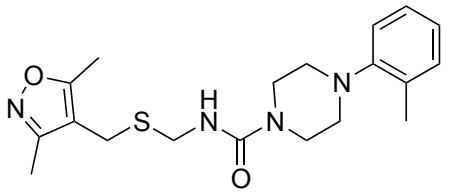
18c


167.53
159.66
150.61
132.71
131.21
126.76
124.03
119.39
108.70
77.32
77.00
76.68
53.42
51.83
48.58
47.04
24.09
17.77
11.09
10.20
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

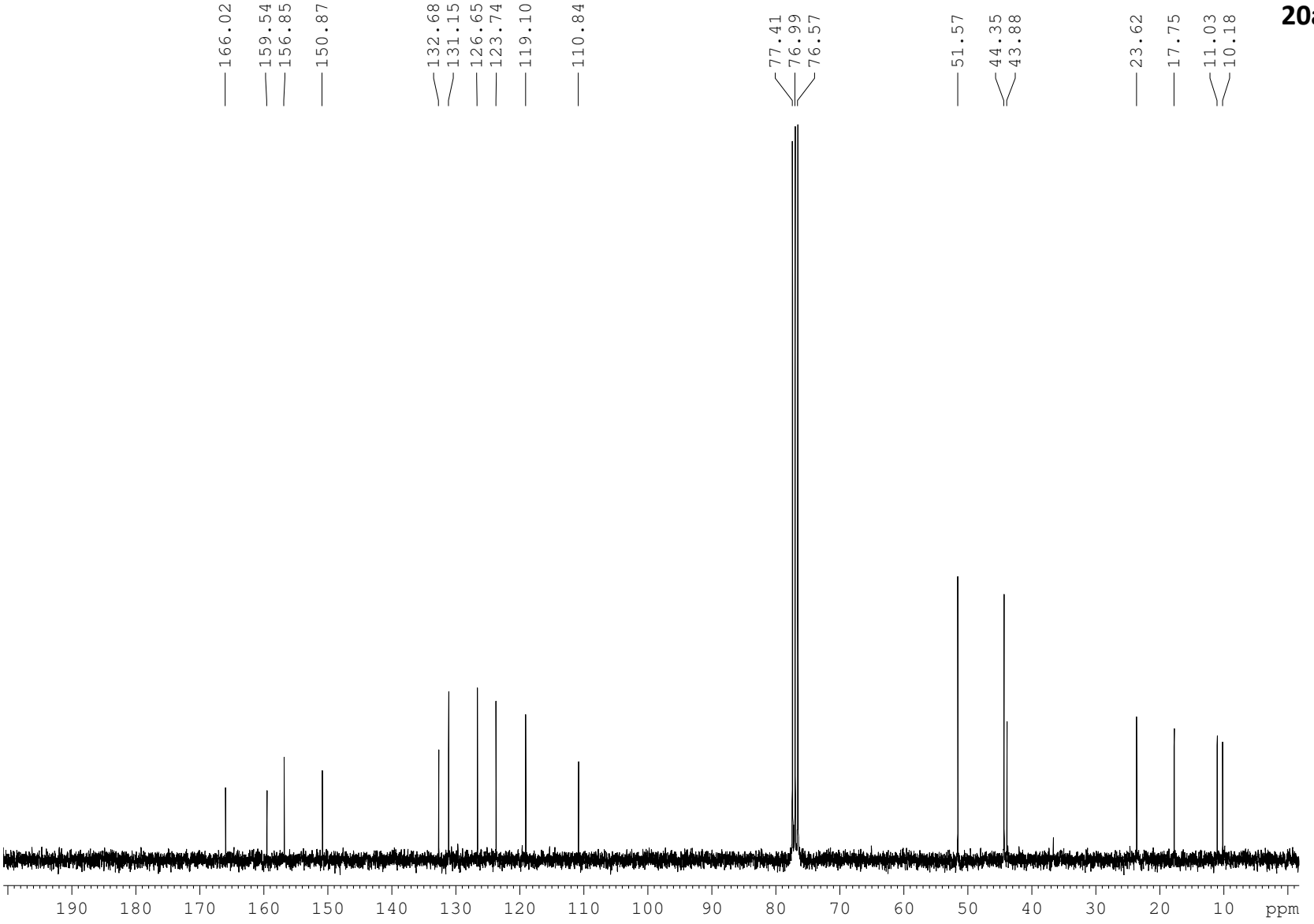


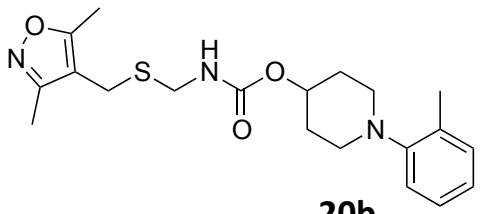
20a


7.260
7.204
7.179
7.175
7.149
7.038
7.034
7.010
7.002
6.989
6.984
6.976
4.902
4.882
4.862
4.447
4.427
3.672
3.516
3.500
3.483
2.909
2.892
2.876
2.392
2.316
2.289
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
0.5
ppm
2.00
1.97
0.94
2.01
2.02
3.96
3.99
2.96
6.01

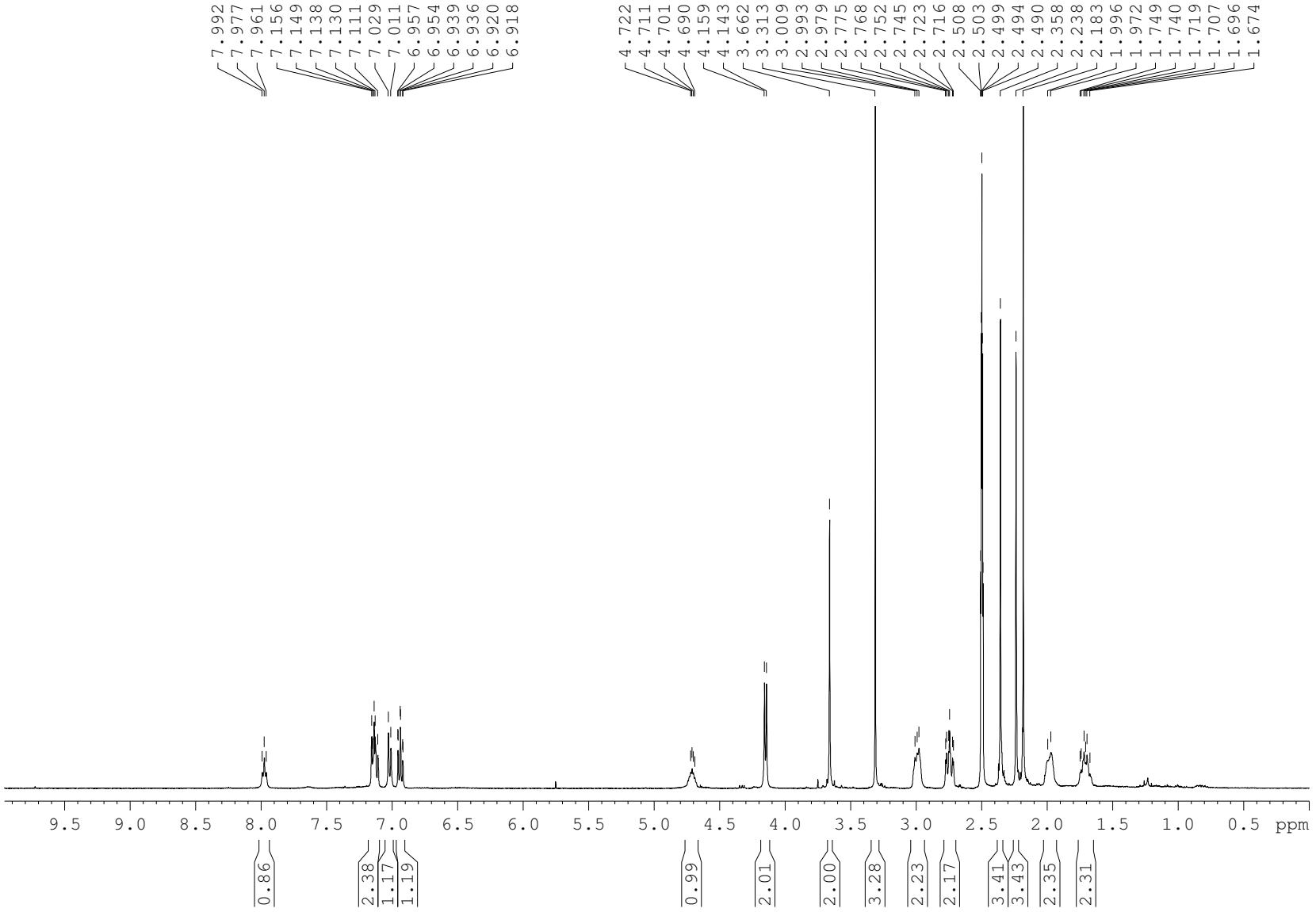


20a


166.02
159.54
156.85
150.87
132.68
131.15
126.65
123.74
119.10
110.84
77.41
76.99
76.57
51.57
44.35
43.88
23.62
17.75
11.03
10.18
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



20b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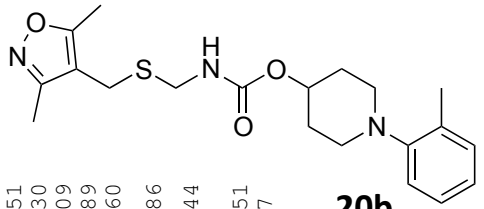
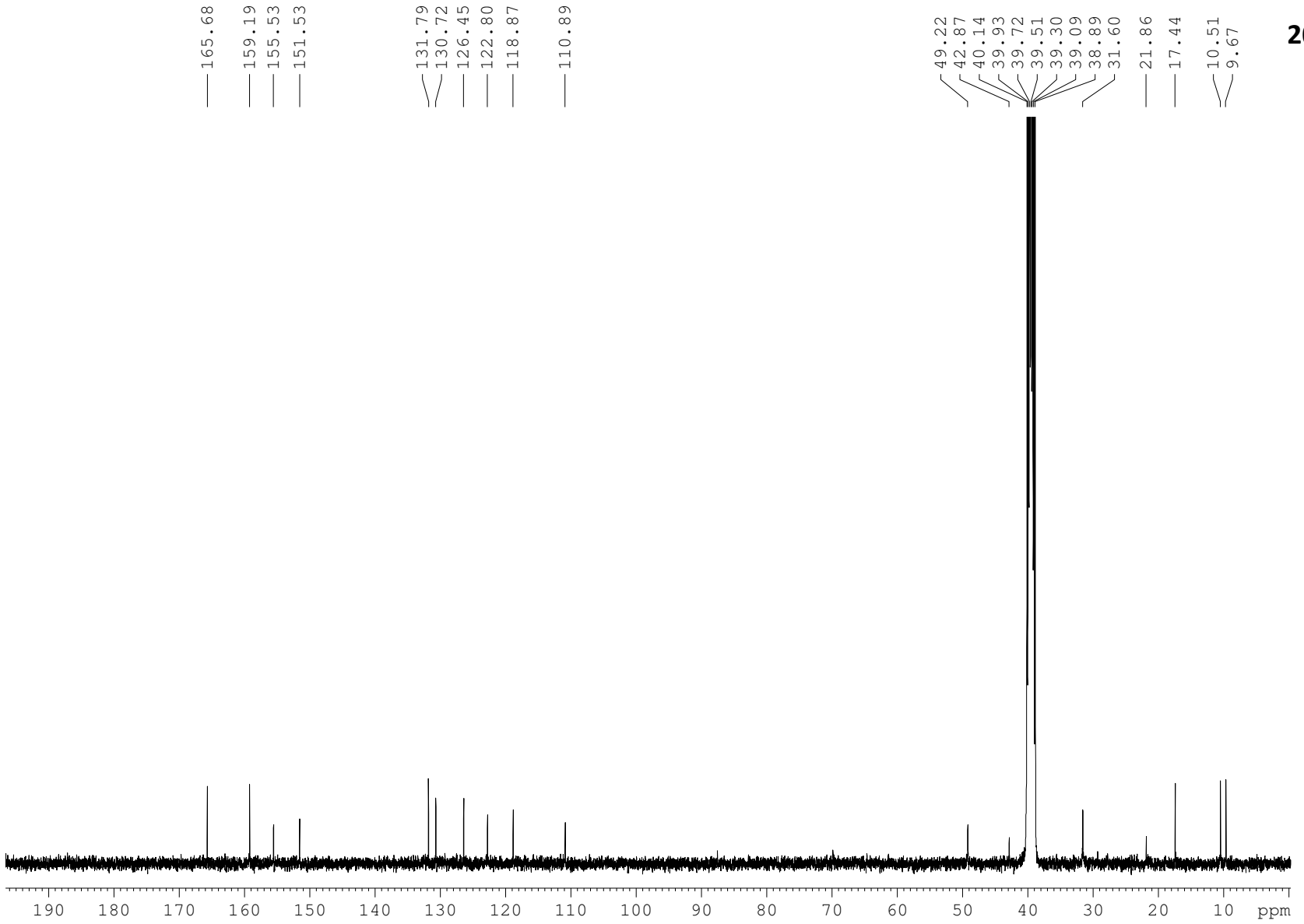
7.977
7.961
7.156
7.149
7.138
7.130
7.111
7.029
7.011
6.957
6.954
6.939
6.936
6.920
6.918
4.722
4.711
4.701
4.690
4.159
4.143
3.662
3.313
3.009
2.993
2.979
2.775
2.768
2.752
2.745
2.723
2.716
2.508
2.503
2.499
2.494
2.490
2.358
2.238
2.183
1.996
1.972
1.749
1.740
1.719
1.707
1.696
1.674
9.5 9.0 8.5 8.0 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 0.5 ppm
0.86
2.38
1.17
1.19
0.99
2.01
2.00
3.28
2.23
2.17
3.41
3.43
2.35
2.31



20b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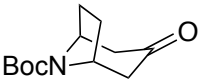
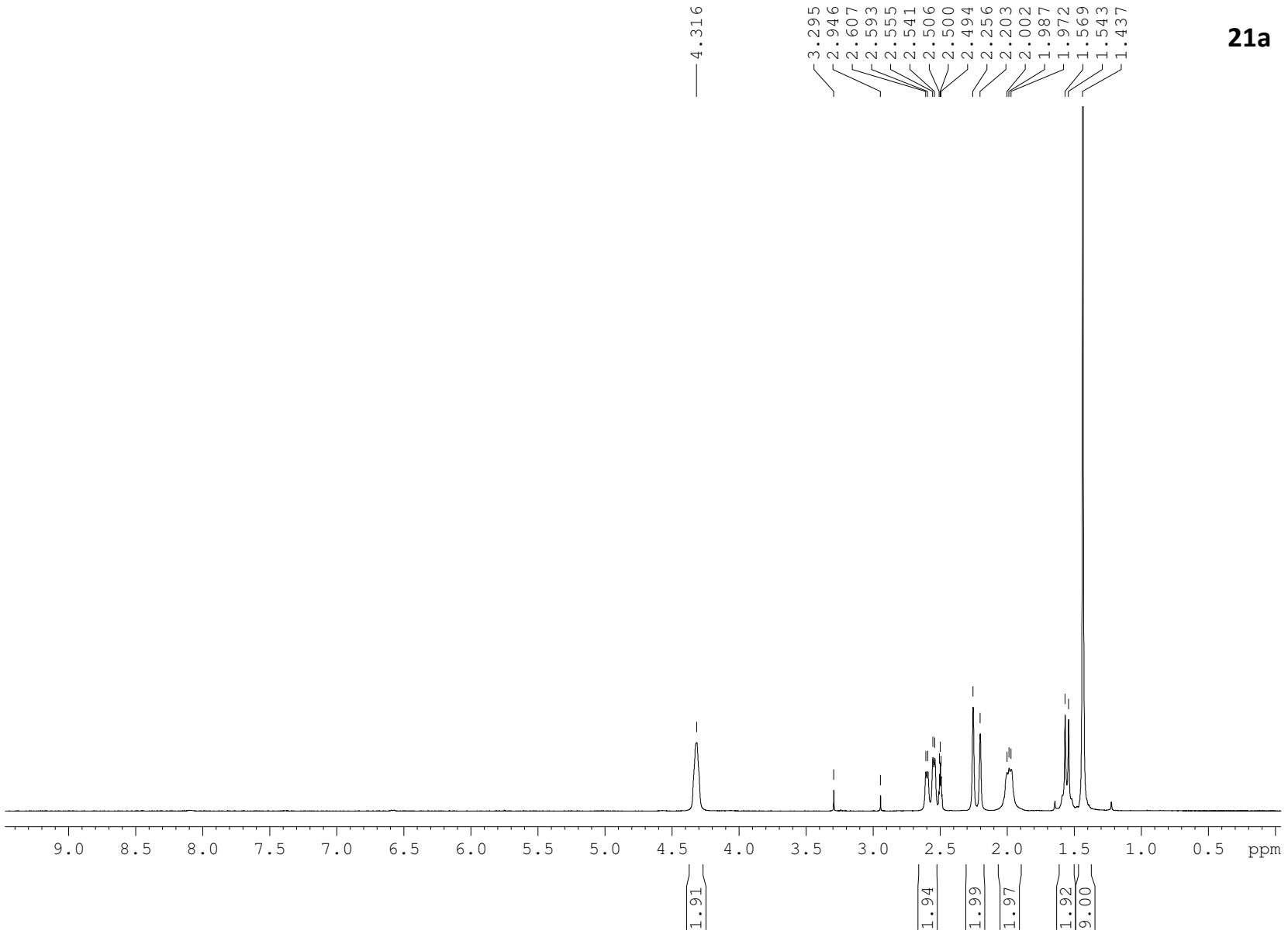
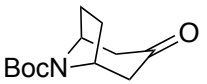
159.19
155.53
151.53
131.79
130.72
126.45
122.80
118.87
110.89
49.22
42.87
40.14
39.93
39.72
39.51
39.30
39.09
38.89
31.60
21.86
17.44
10.51
9.67
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

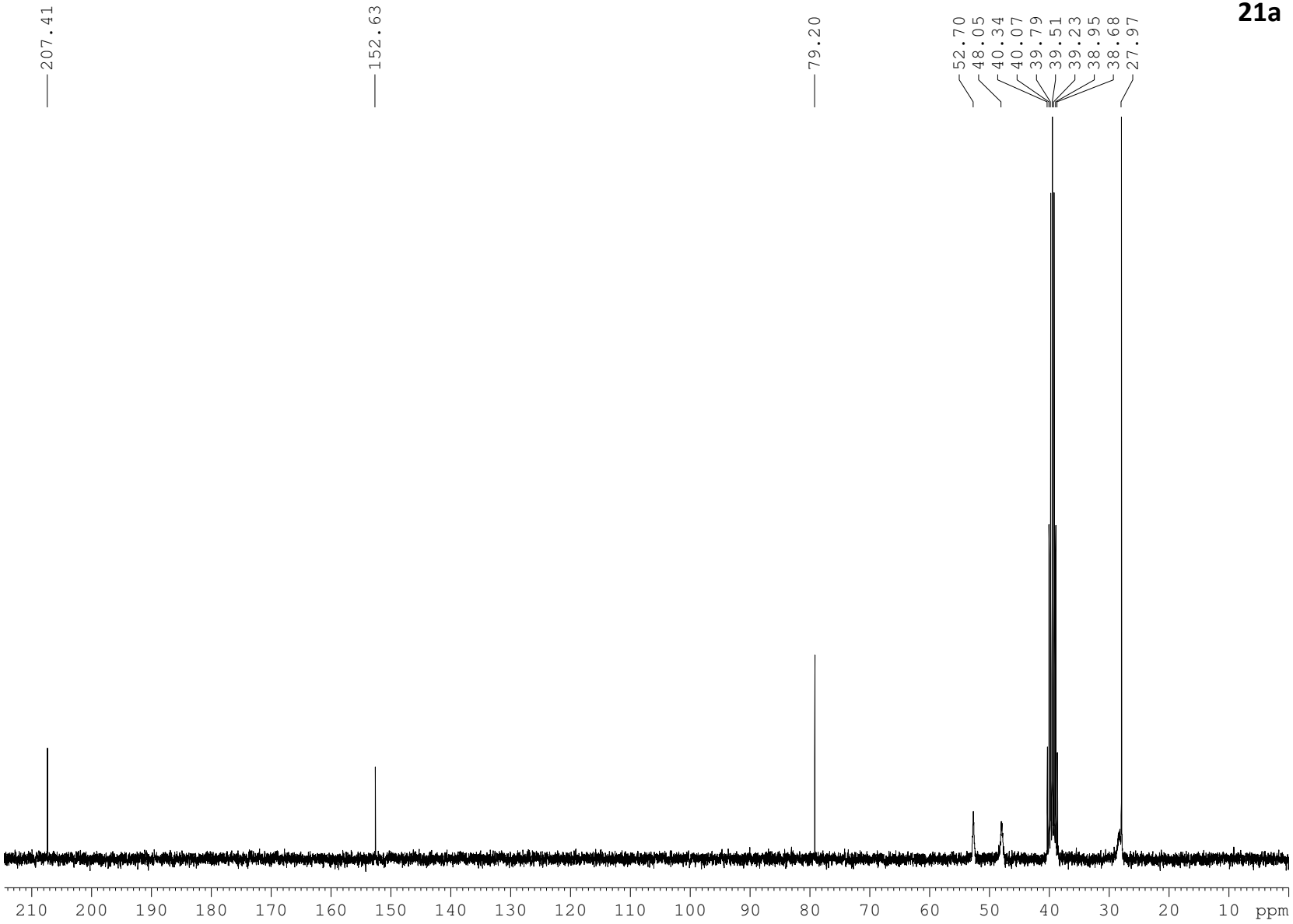

BocN
O

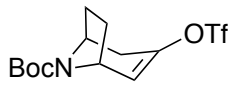
21a


4.316
3.295
2.946
2.607
2.593
2.555
2.541
2.506
2.500
2.494
2.256
2.203
2.002
1.987
1.972
1.569
1.543
1.437
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
0.5
ppm
1.91
1.94
1.99
1.97
1.92
9.00

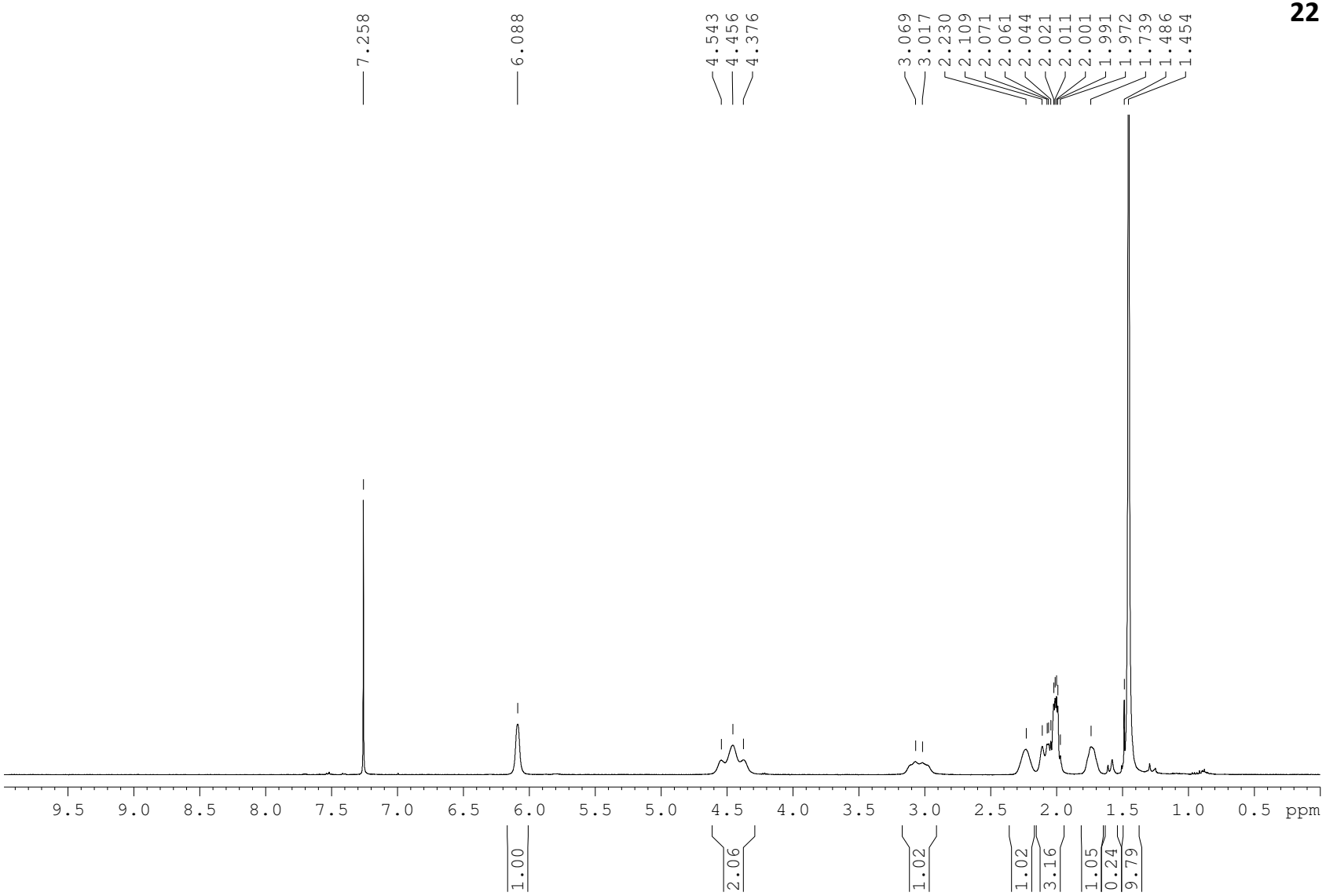

BocN
O

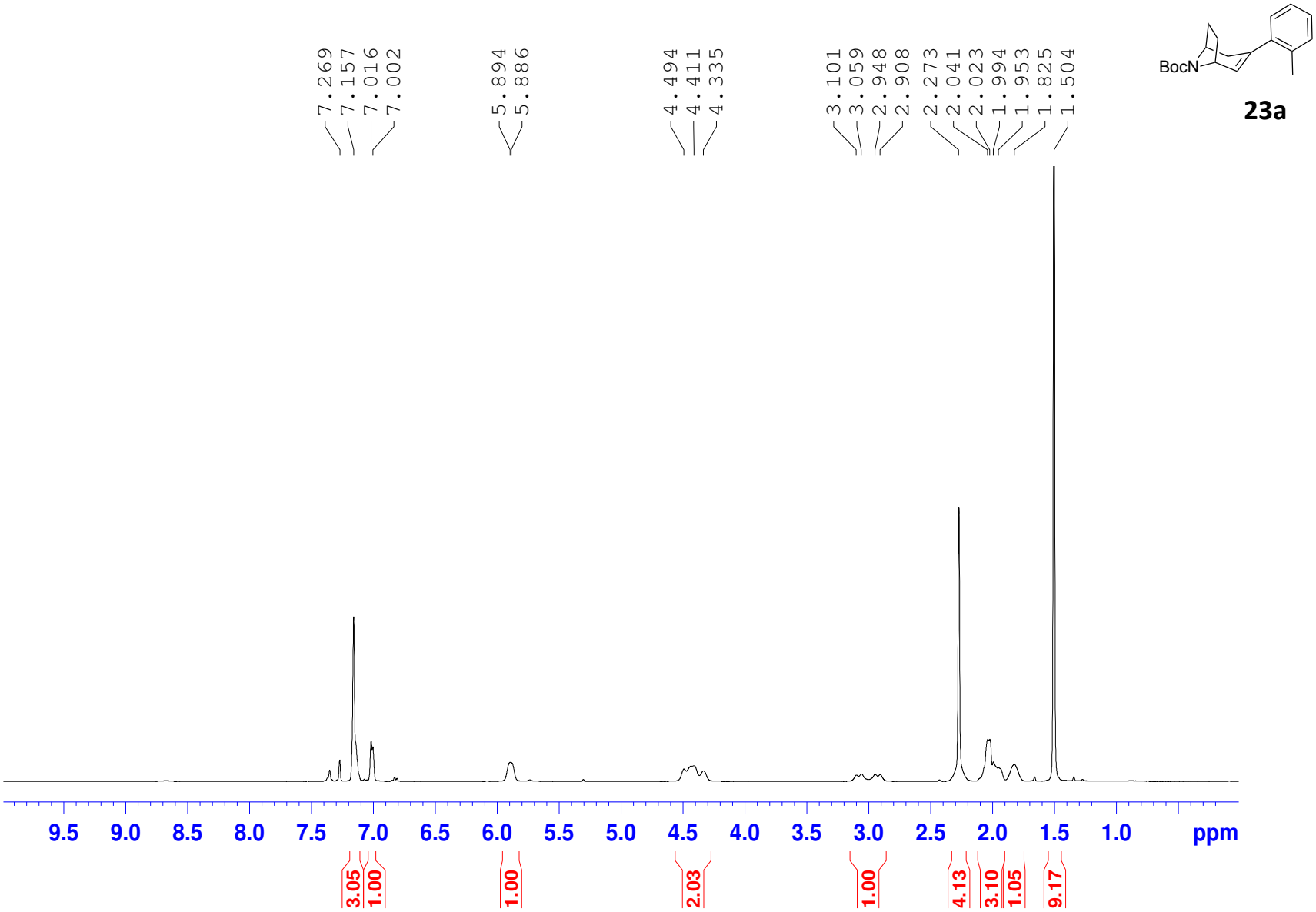
21a


207.41
152.63
79.20
52.70
48.05
40.34
40.07
39.79
39.51
39.23
38.95
38.68
27.97
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


BocN
OTf

22


7.258
6.088
4.543
4.456
4.376
3.069
3.017
2.230
2.109
2.071
2.061
2.044
2.021
2.011
2.001
1.991
1.972
1.739
1.486
1.454
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 0.5 ppm
1.00
2.06
1.02
1.02
3.16
1.05
0.24
9.79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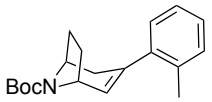
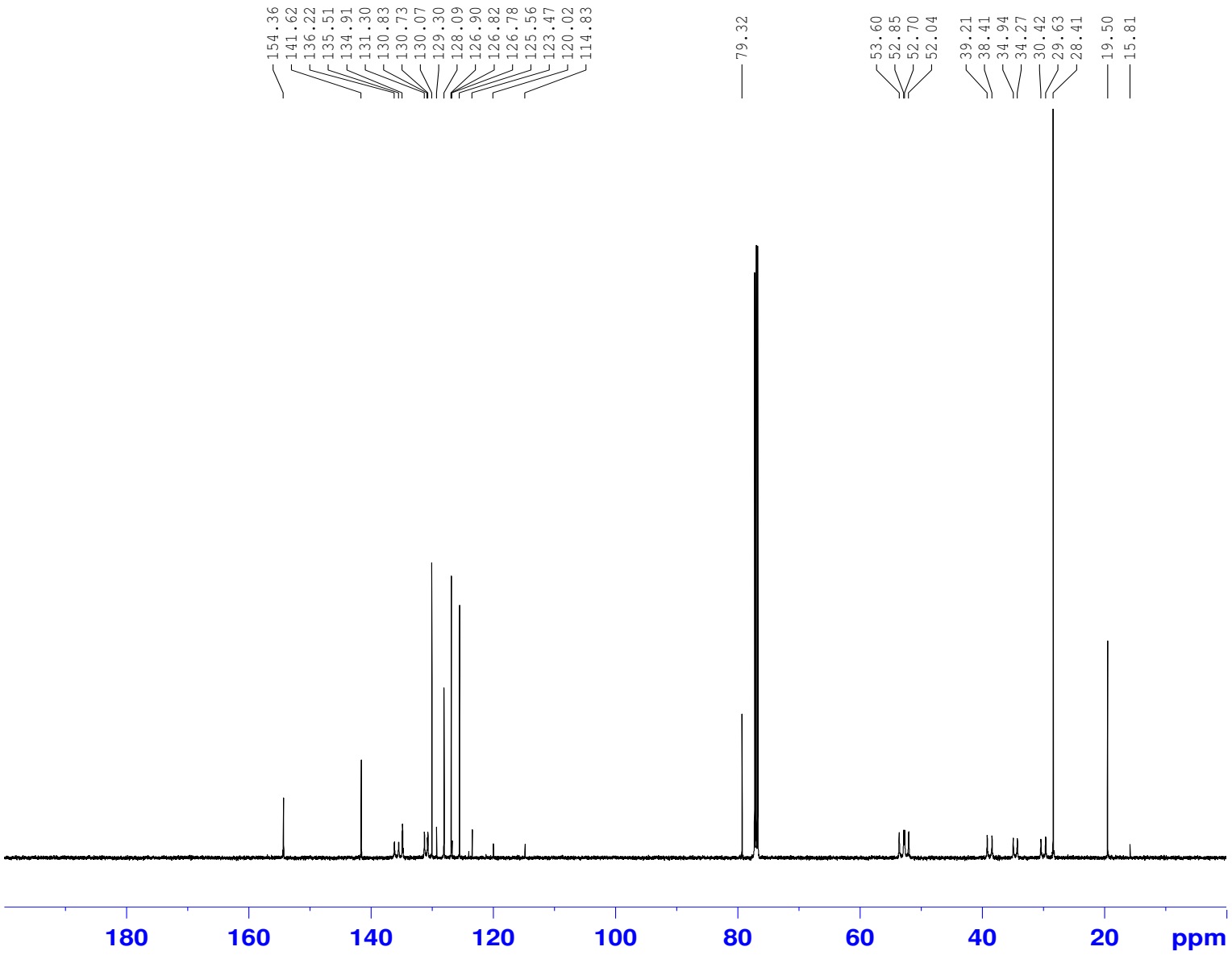
7.157
7.016
7.002
5.894
5.886
4.494
4.411
4.335
3.101
3.059
2.948
2.908
2.273
2.041
2.023
1.994
1.953
1.825
1.504
BocN
23a
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
3.05
1.00
1.00
2.03
1.00
4.13
3.10
1.05
9.17


BocN

23a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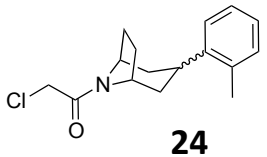
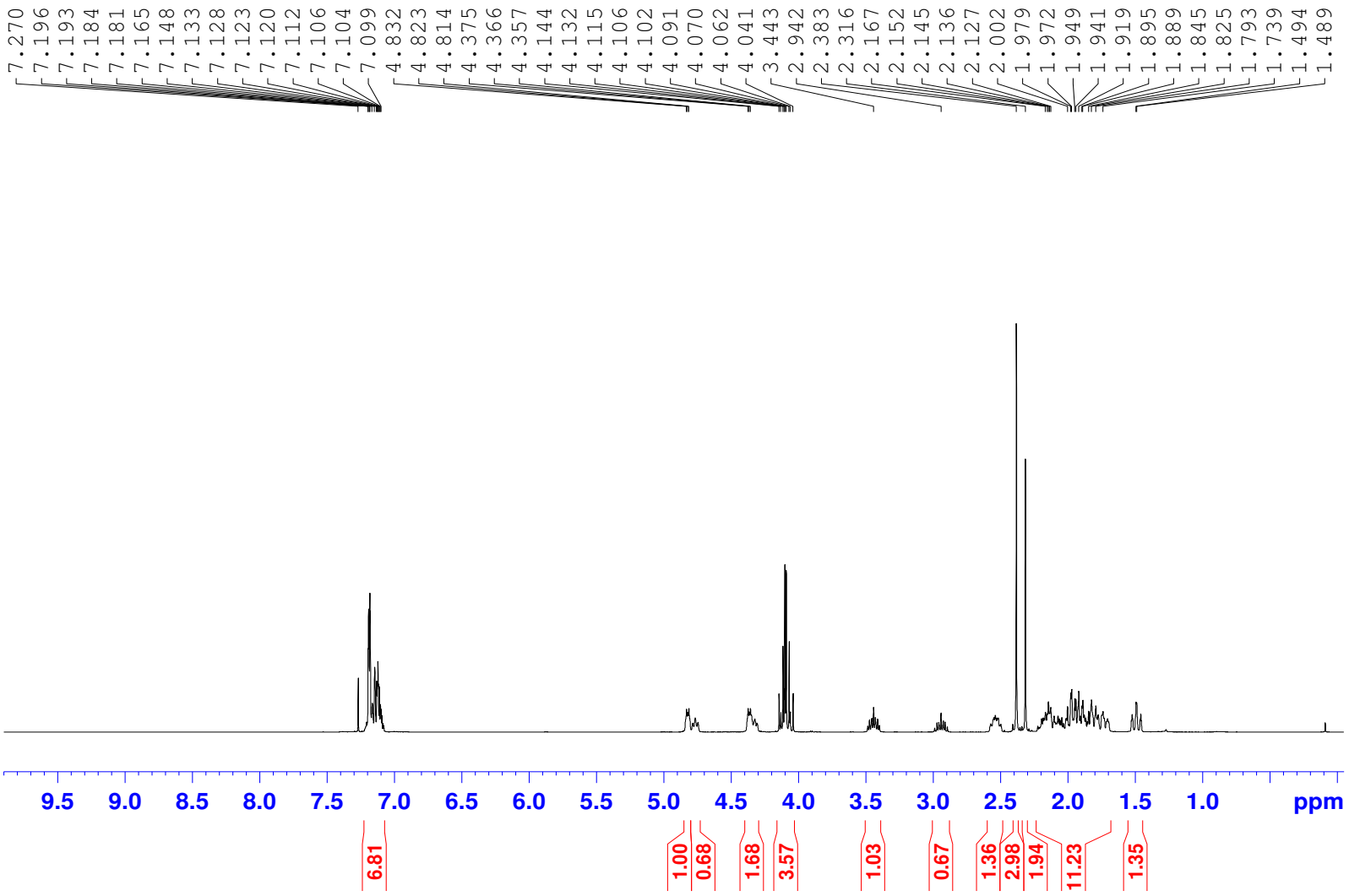
136.22
135.51
134.91
131.30
130.83
130.73
130.07
129.30
128.09
126.90
126.82
126.78
125.56
123.47
120.02
114.83
79.32
53.60
52.85
52.70
52.04
39.21
38.41
34.94
34.27
30.42
29.63
28.41
19.50
15.81
180
160
140
120
100
80
60
40
20
ppm


Cl
N
O

24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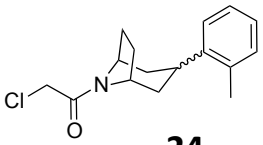
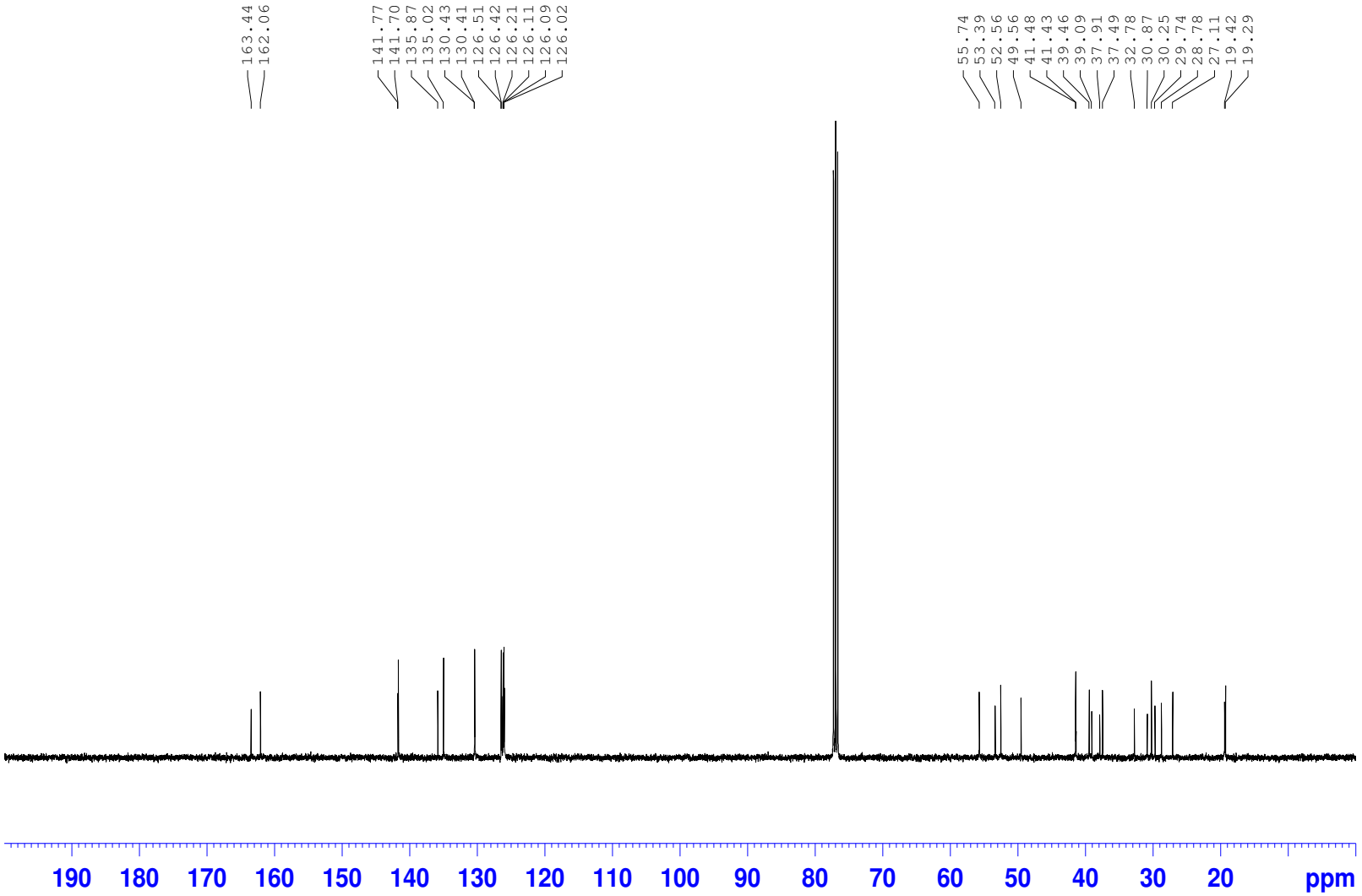
7.196
7.193
7.184
7.181
7.165
7.148
7.133
7.128
7.123
7.120
7.112
7.106
7.104
7.099
4.832
4.823
4.814
4.375
4.366
4.357
4.144
4.132
4.115
4.106
4.102
4.091
4.070
4.062
4.041
3.443
2.942
2.383
2.316
2.167
2.152
2.145
2.136
2.127
2.002
1.979
1.972
1.949
1.941
1.919
1.895
1.889
1.845
1.825
1.793
1.739
1.494
1.489
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
6.81
1.00
0.68
1.68
3.57
1.03
0.67
1.36
2.98
1.94
11.23
1.35


Cl
N
O

24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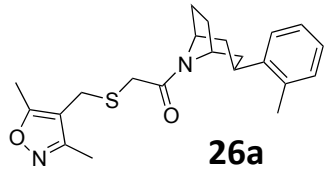
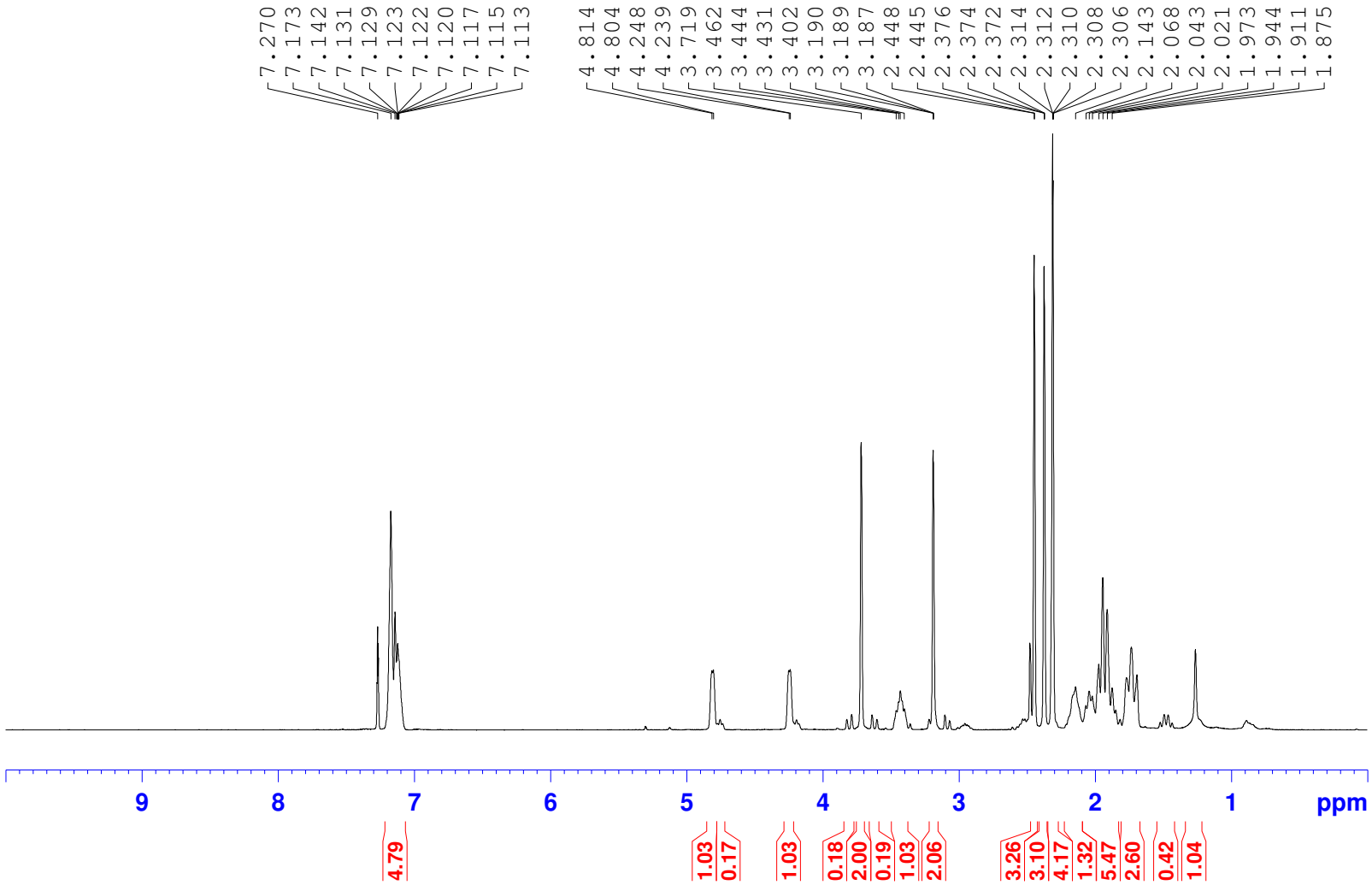
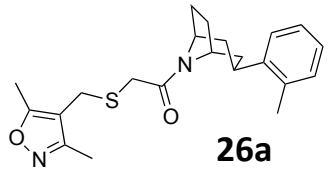
162.06
141.77
141.70
135.87
135.02
130.43
130.41
126.51
126.42
126.21
126.11
126.09
126.02
55.74
53.39
52.56
49.56
41.48
41.43
39.46
39.09
37.91
37.49
32.78
30.87
30.25
29.74
28.78
27.11
19.42
19.29
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

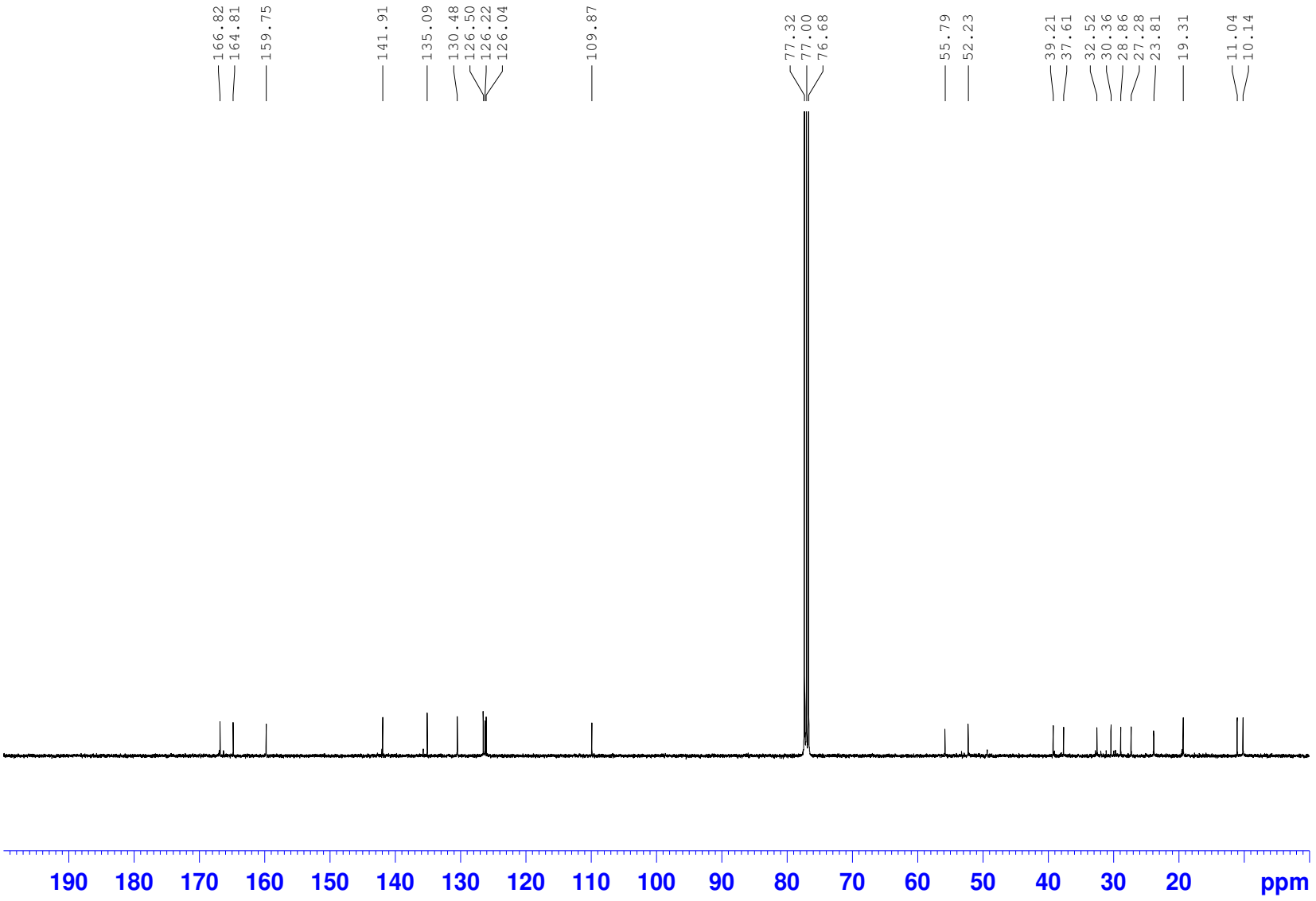

O
N
S
N
O

26a


7.270
7.173
7.142
7.131
7.129
7.123
7.122
7.120
7.117
7.115
7.113
4.814
4.804
4.248
4.239
3.719
3.462
3.444
3.431
3.402
3.190
3.189
3.187
2.448
2.445
2.376
2.374
2.372
2.314
2.312
2.310
2.308
2.306
2.143
2.068
2.043
2.021
1.973
1.944
1.911
1.875
9
8
7
6
5
4
3
2
1
ppm
4.79
1.03
0.17
1.03
0.18
2.00
0.19
1.03
2.06
3.26
3.10
4.17
1.32
5.47
2.60
0.42
1.04


O
N
S
O
N

26a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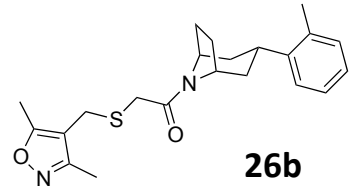
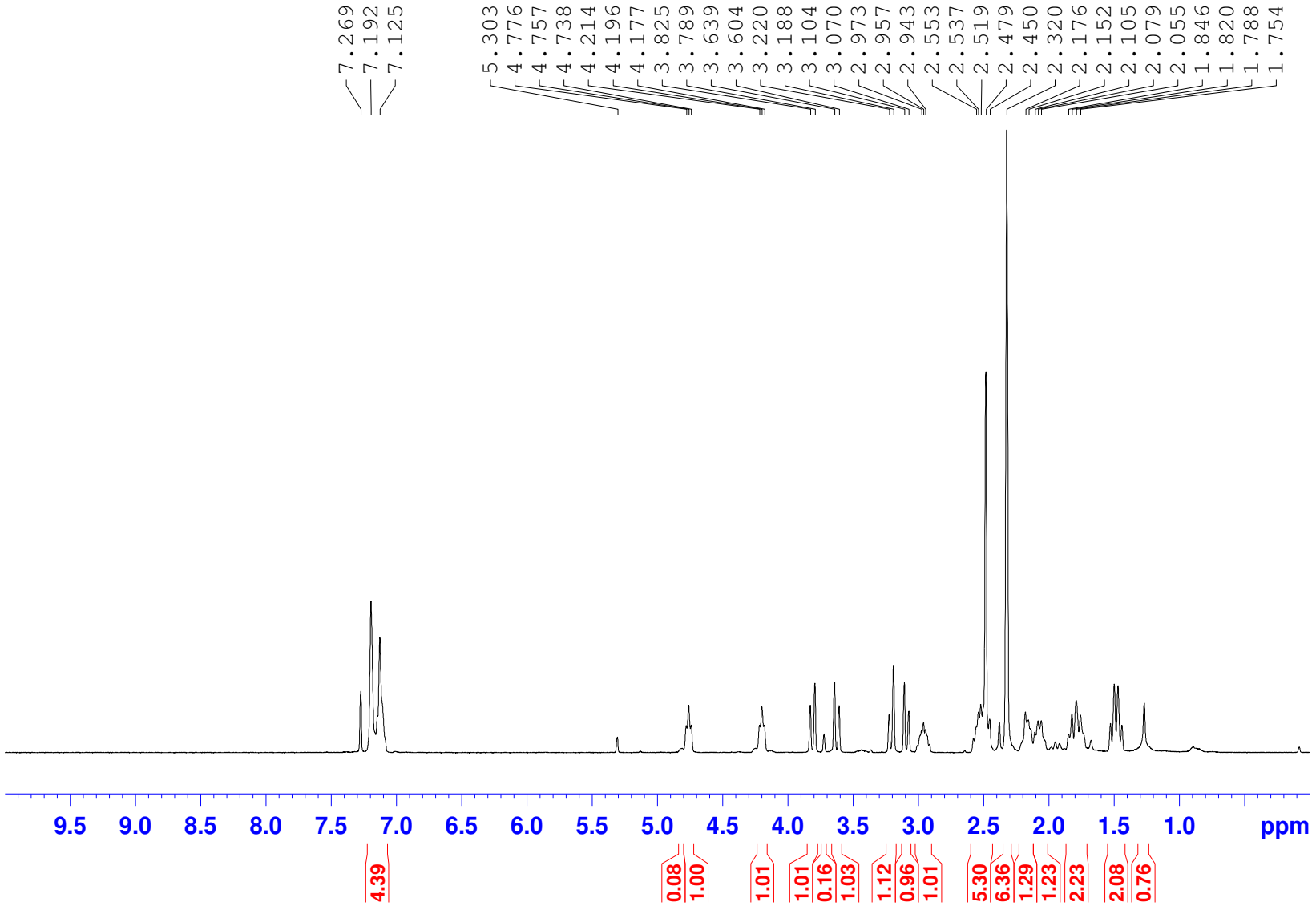
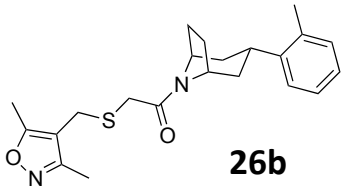
164.81
159.75
141.91
135.09
130.48
126.50
126.22
126.04
109.87
77.32
77.00
76.68
55.79
52.23
39.21
37.61
32.52
30.36
28.86
27.28
23.81
19.31
11.04
10.14
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

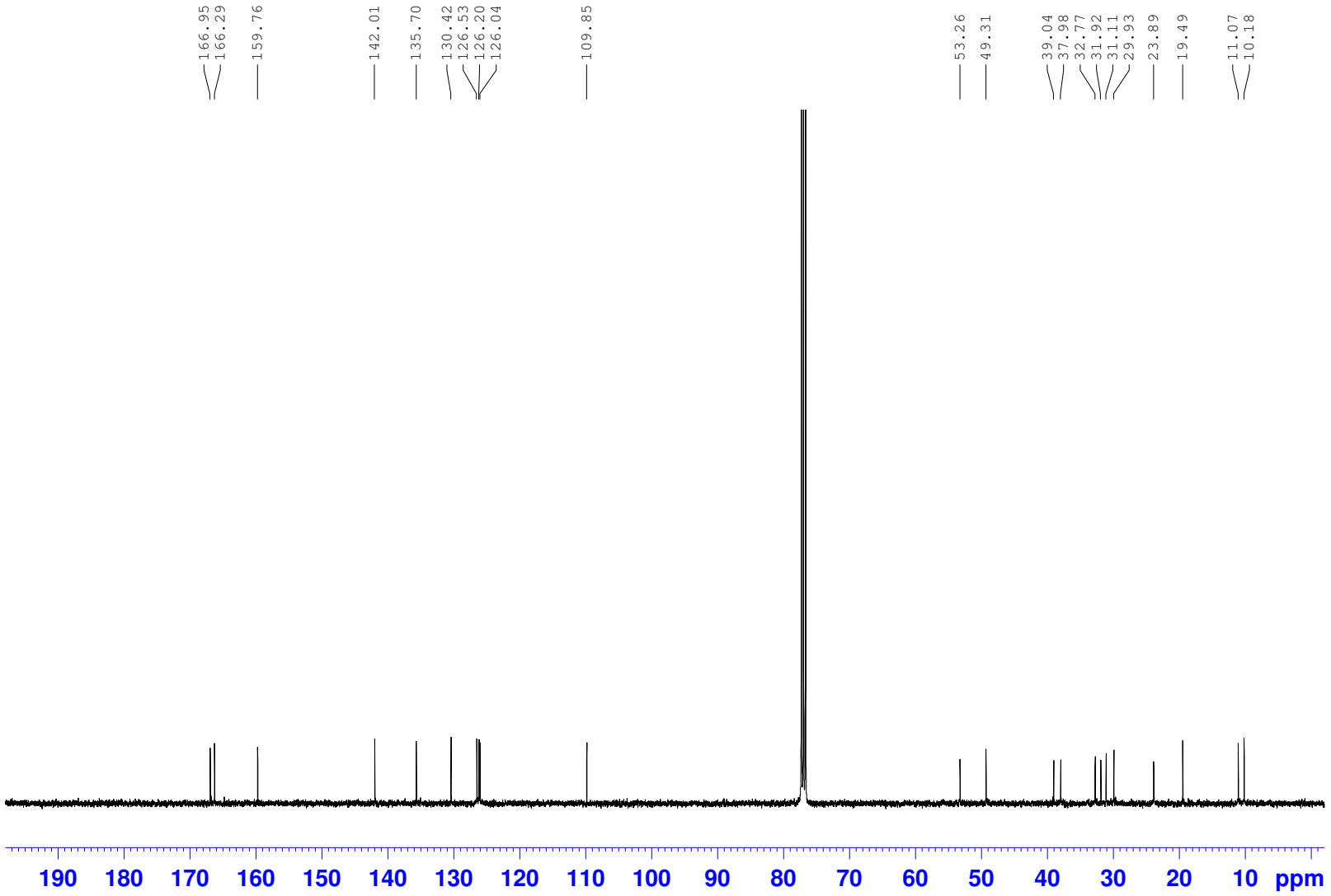

O
N
S
N
O

26b


7.269
7.192
7.125
5.303
4.776
4.757
4.738
4.214
4.196
4.177
3.825
3.789
3.639
3.604
3.220
3.188
3.104
3.070
2.973
2.957
2.943
2.553
2.537
2.519
2.479
2.450
2.320
2.176
2.152
2.105
2.079
2.055
1.846
1.820
1.788
1.754
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
4.39
0.08
1.00
1.01
1.01
0.16
1.03
1.12
0.96
1.01
5.30
6.36
1.29
1.23
2.23
2.08
0.76


N
S
O
O
N

26b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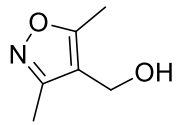
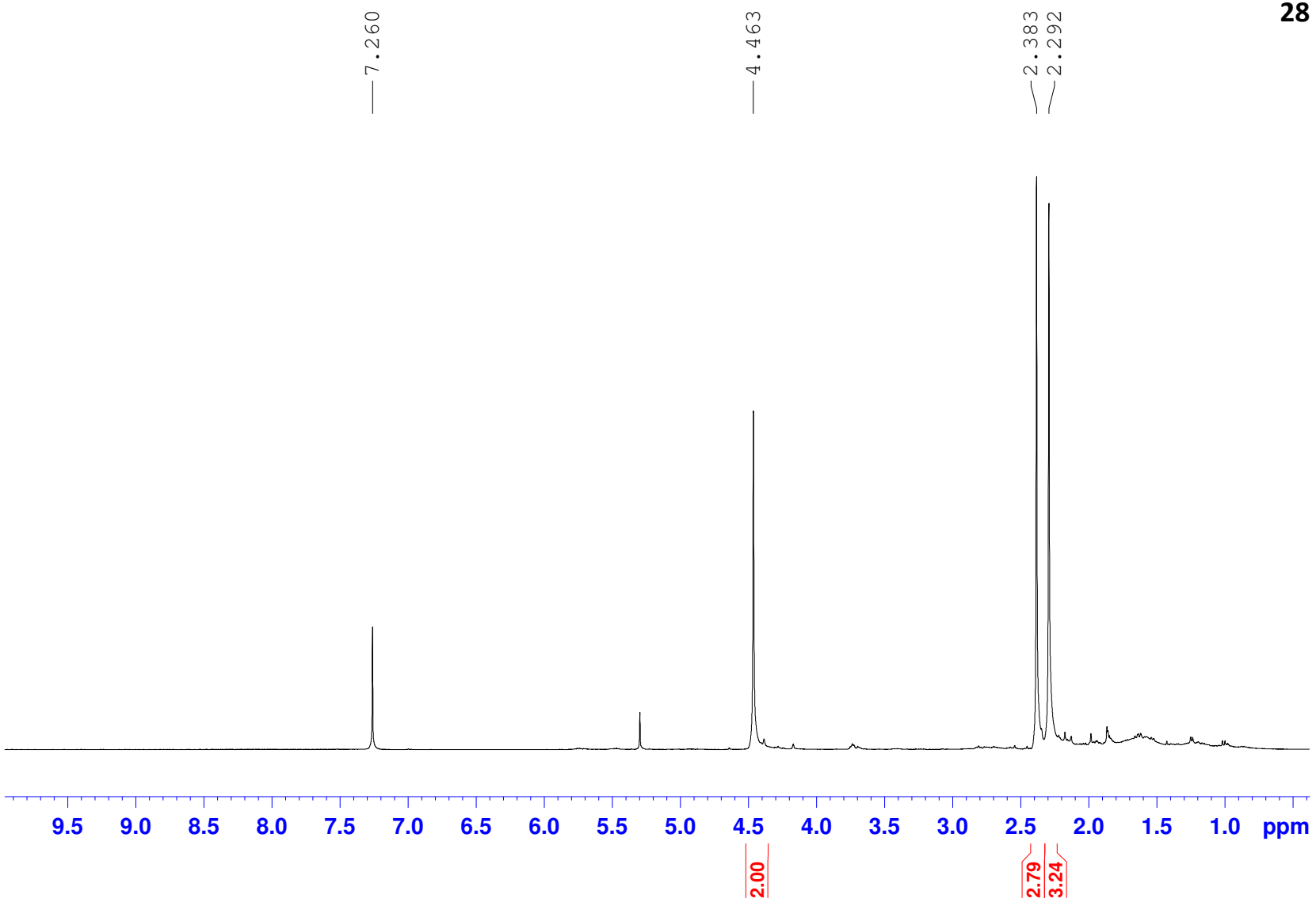
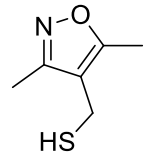
166.29
159.76
142.01
135.70
130.42
126.53
126.20
126.04
109.85
53.26
49.31
39.04
37.98
32.77
31.92
31.11
29.93
23.89
19.49
11.07
10.18
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

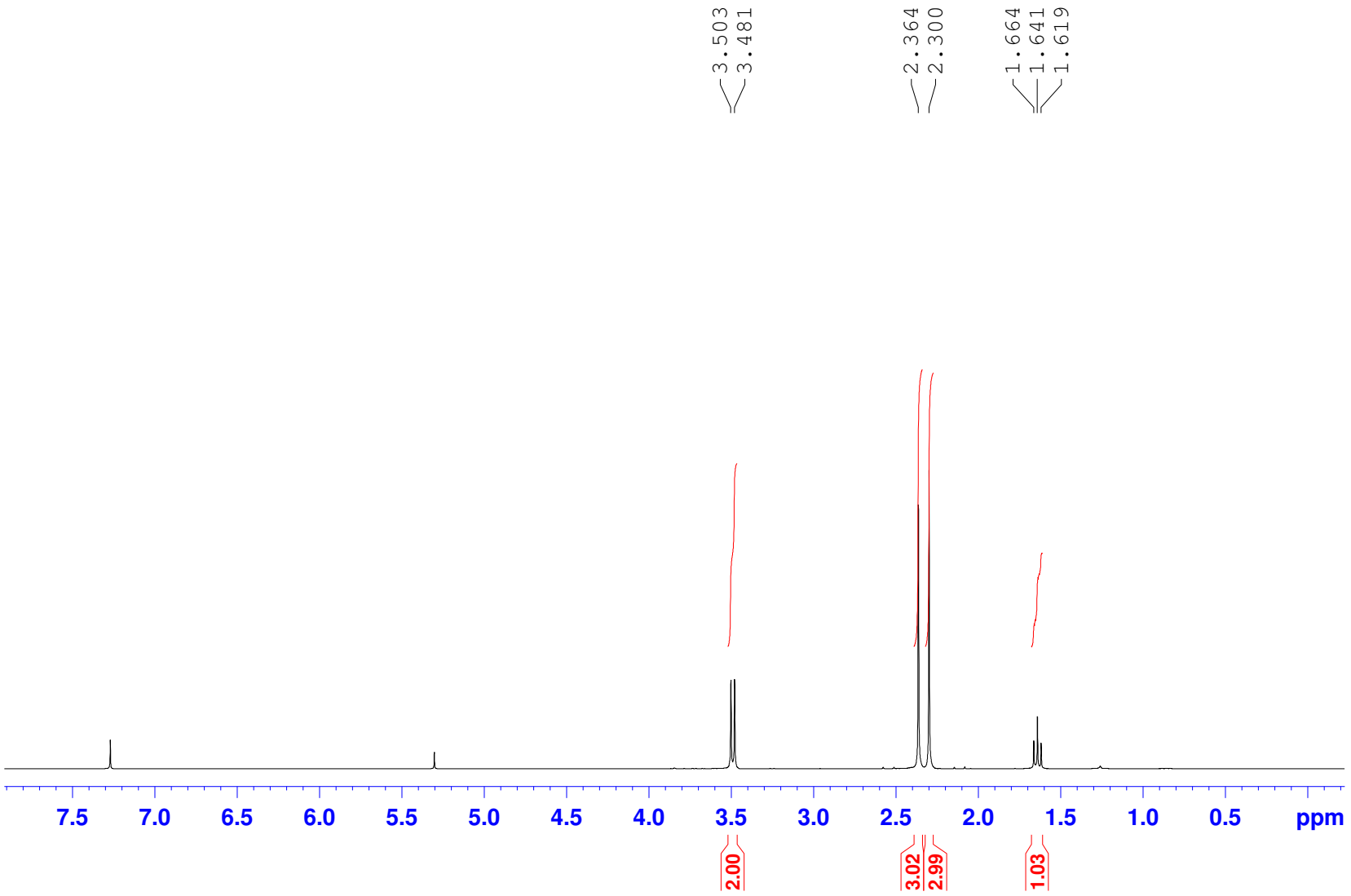

O
N
OH

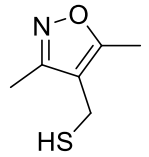
28


7.260
4.463
2.383
2.292
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
2.00
2.79
3.24

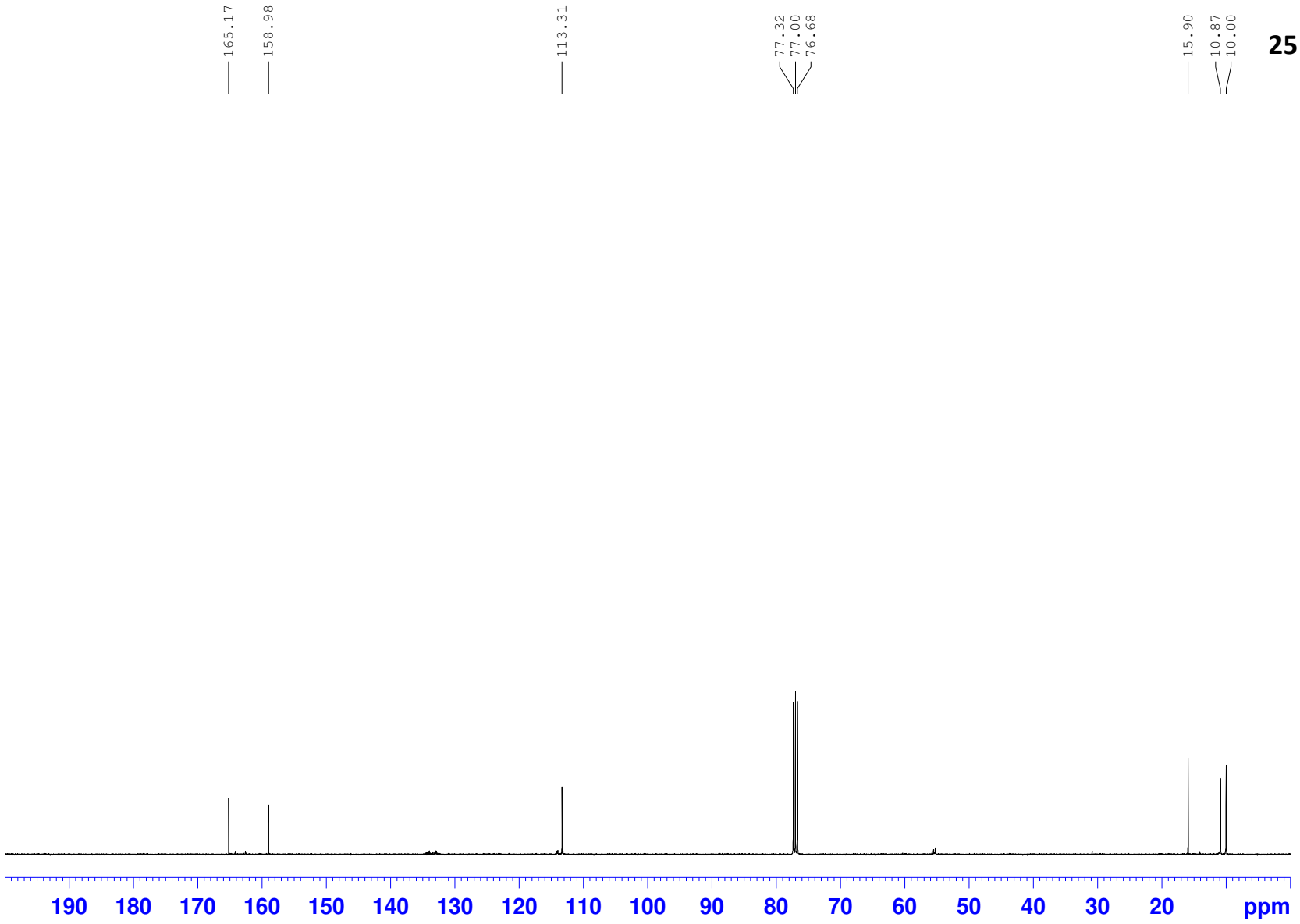

N
O
HS

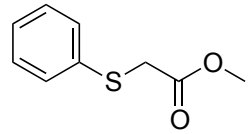
25


3.503
3.481
2.364
2.300
1.664
1.641
1.619
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
0.5
ppm
2.00
3.02
2.99
1.03

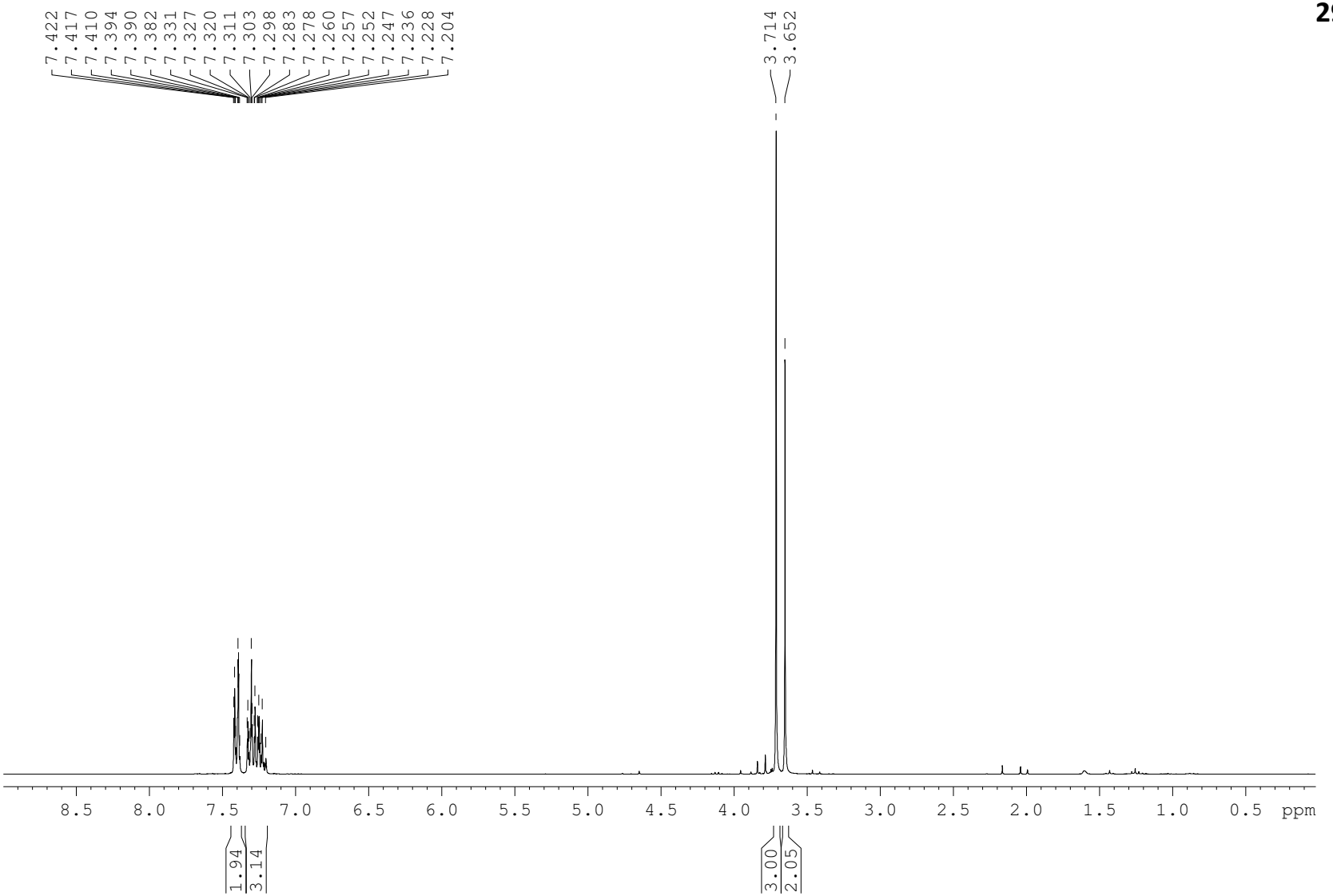

N
O
HS

25


165.17
158.98
113.31
77.32
77.00
76.68
15.90
10.87
10.00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


S
O
O

29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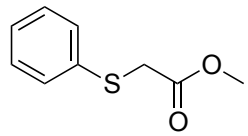
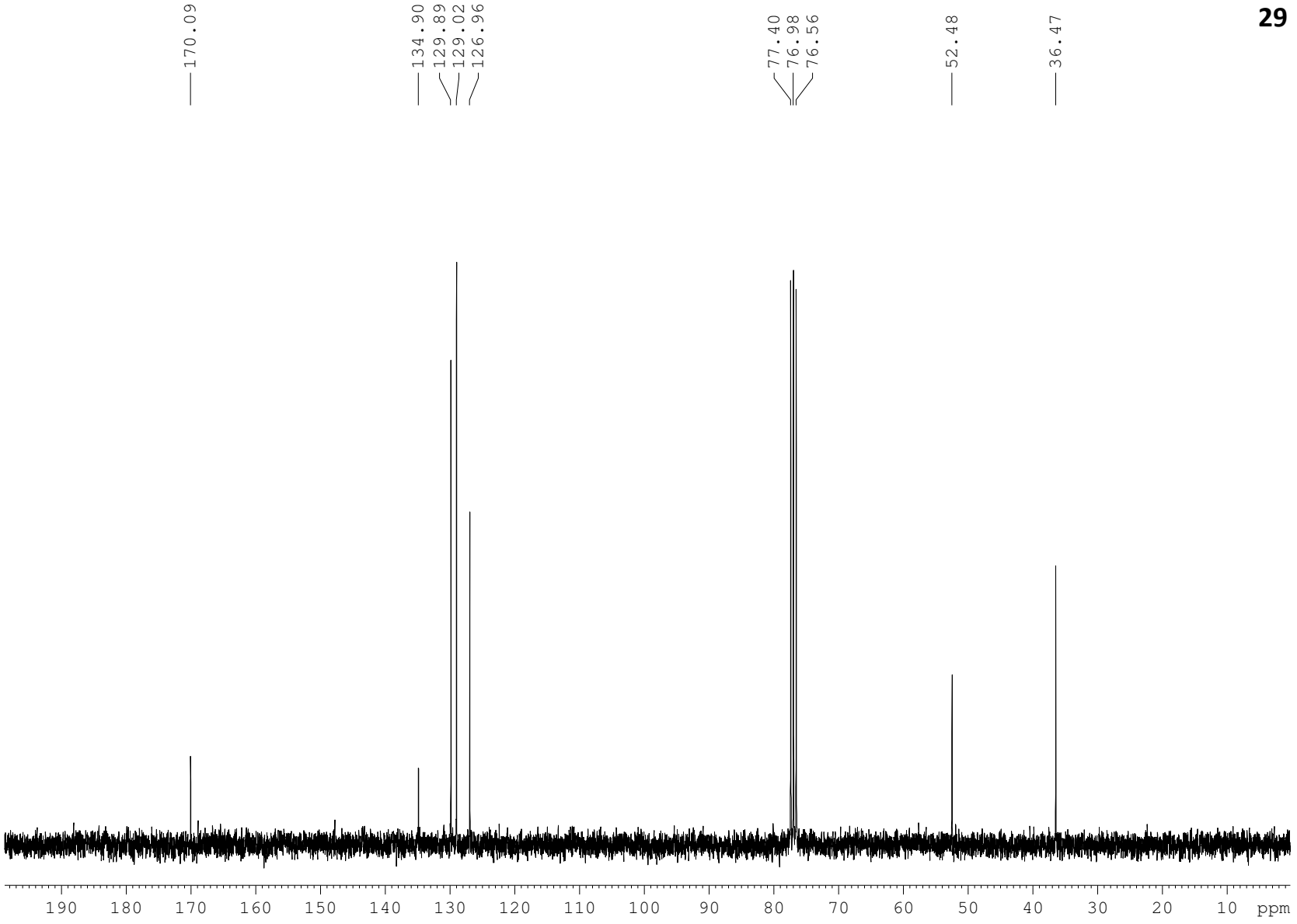
7.417
7.410
7.394
7.390
7.382
7.331
7.327
7.320
7.311
7.303
7.298
7.283
7.278
7.260
7.257
7.252
7.247
7.236
7.228
7.204
3.714
3.652
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.94
3.14
3.00
2.05


S
O
O

29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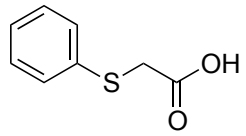
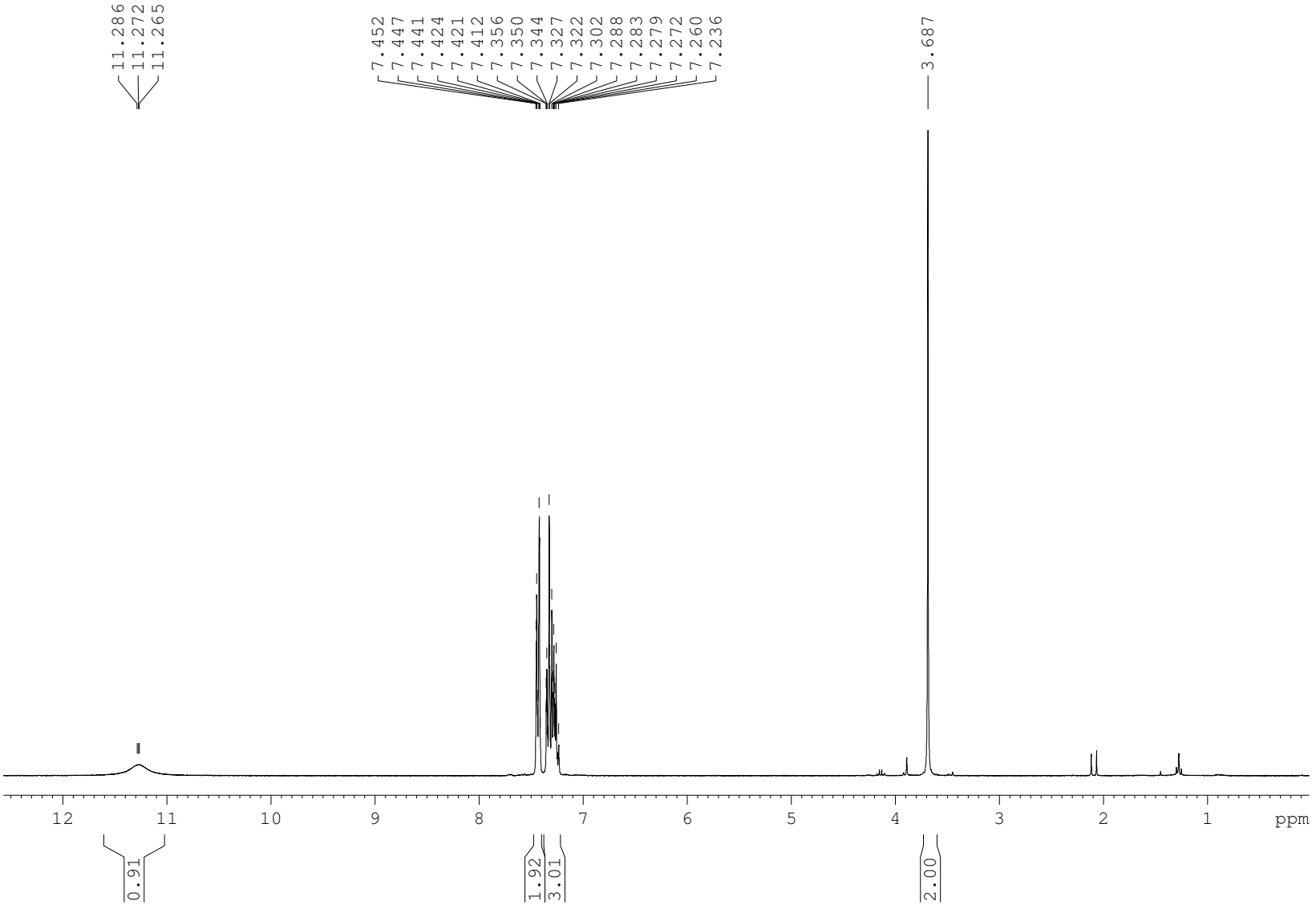
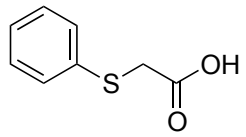
134.90
129.89
129.02
126.96
77.40
76.98
76.56
52.48
36.47
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

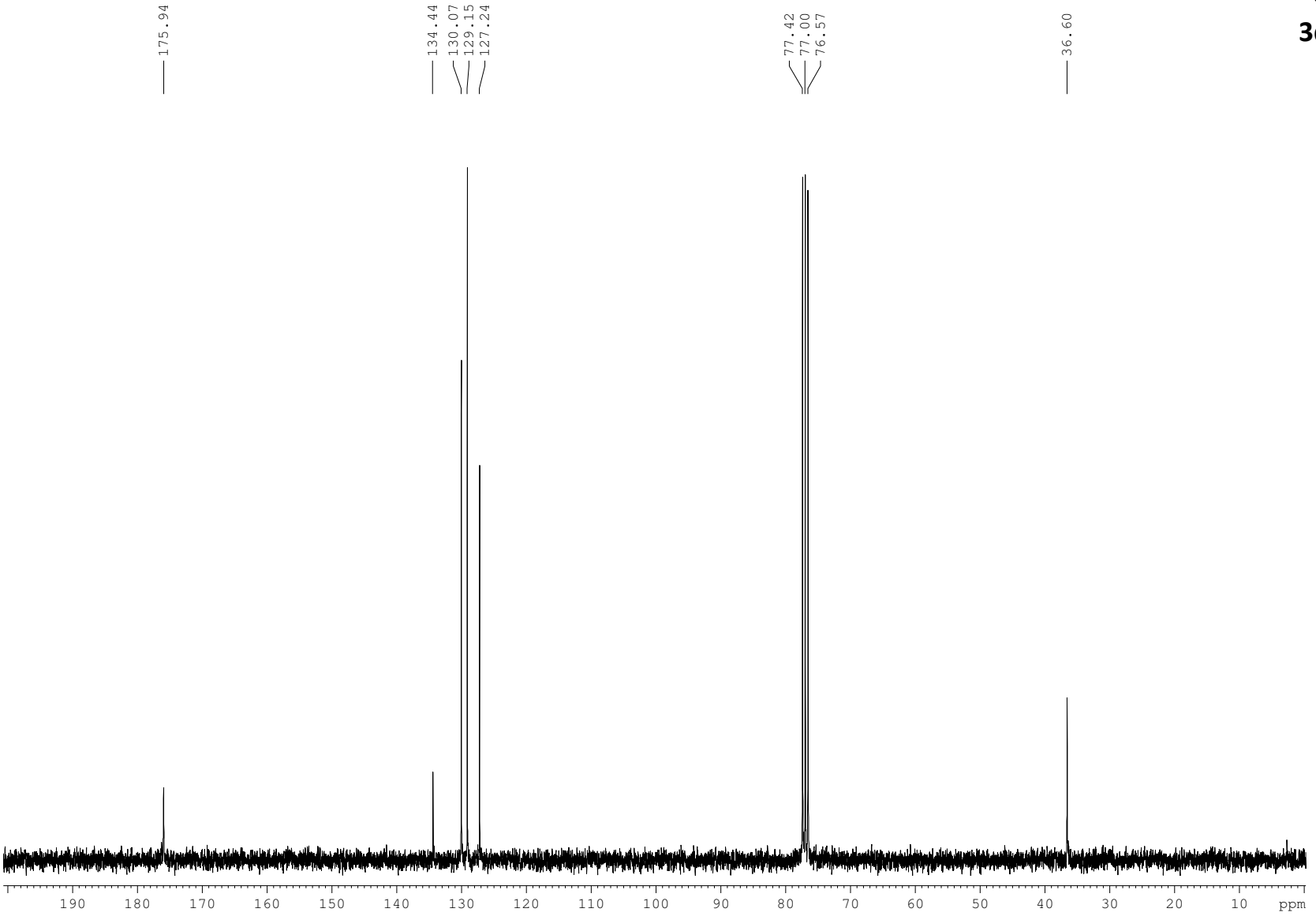

S
OH
O

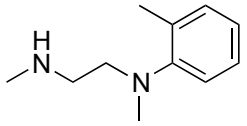
3d


11.286
11.272
11.265
7.452
7.447
7.441
7.424
7.421
7.412
7.356
7.350
7.344
7.327
7.322
7.302
7.288
7.283
7.279
7.272
7.260
7.236
3.687
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.91
1.92
3.01
2.00

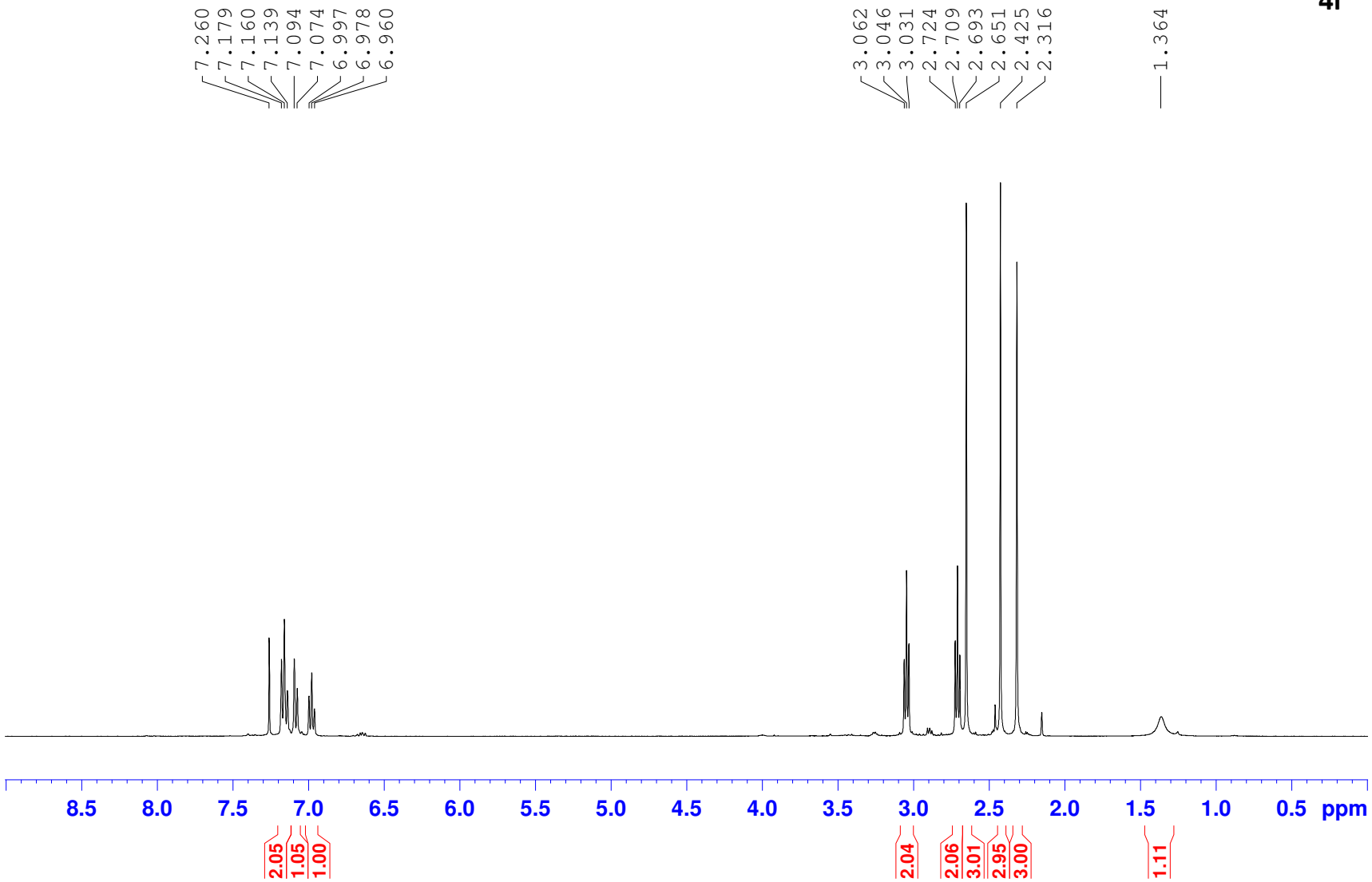

S
OH
O

3d


175.94
134.44
130.07
129.15
127.24
77.42
77.00
76.57
36.60
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



4i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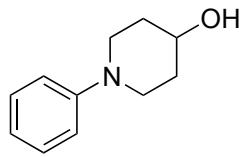
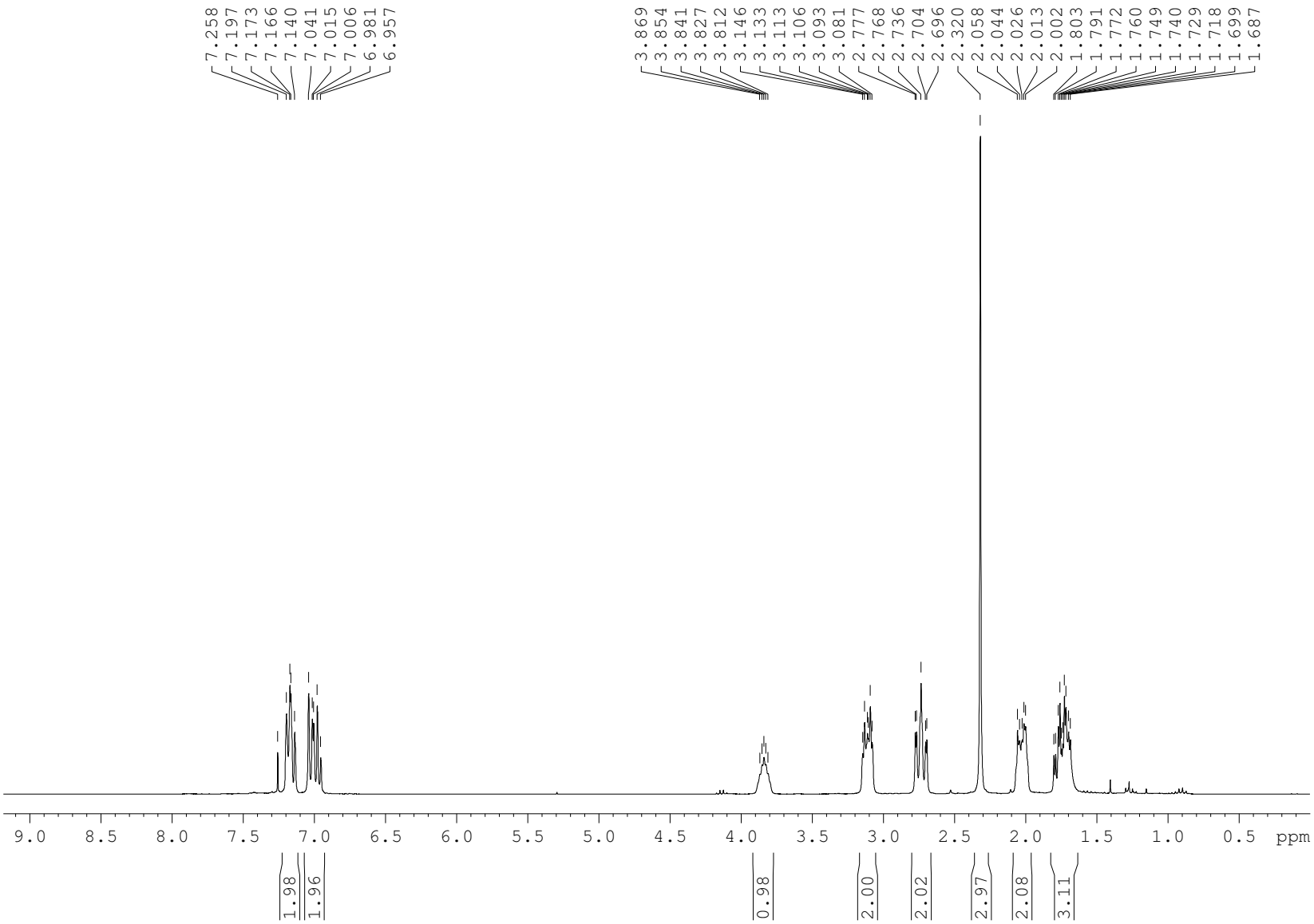
7.179
7.160
7.139
7.094
7.074
6.997
6.978
6.960
3.062
3.046
3.031
2.724
2.709
2.693
2.651
2.425
2.316
1.364
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.05
1.05
1.00
2.04
2.06
3.01
2.95
3.00
1.11


OH
N

4n


7.258
7.197
7.173
7.166
7.140
7.041
7.015
7.006
6.981
6.957
3.869
3.854
3.841
3.827
3.812
3.146
3.133
3.113
3.106
3.093
3.081
2.777
2.768
2.736
2.704
2.696
2.320
2.058
2.044
2.026
2.013
2.002
1.803
1.791
1.772
1.760
1.749
1.740
1.729
1.718
1.699
1.687
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
0.5
ppm
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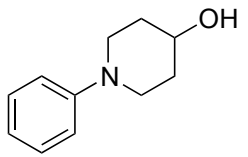
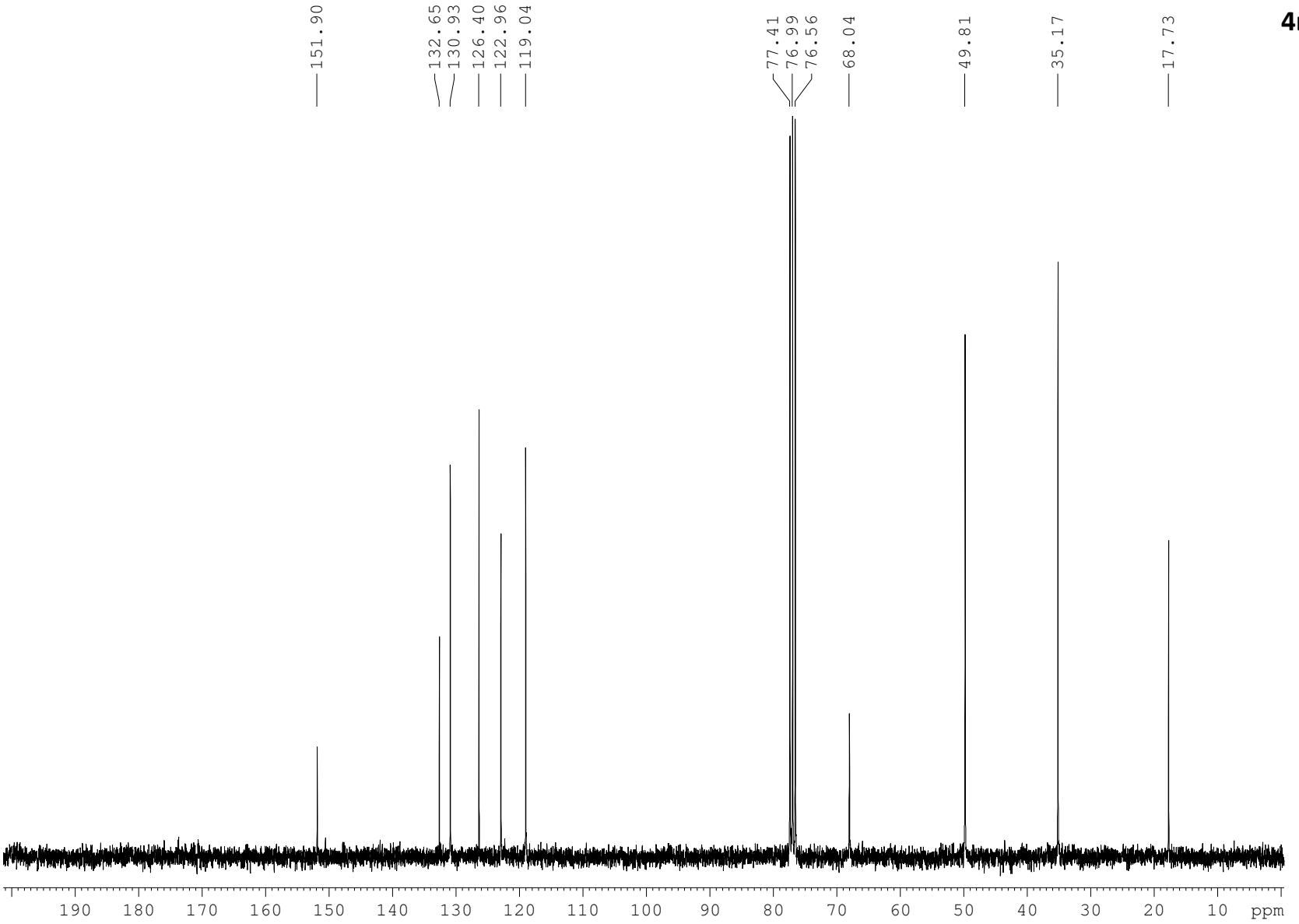
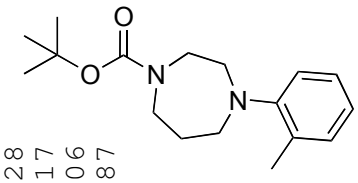
2.00
2.02
2.97
2.08
3.11

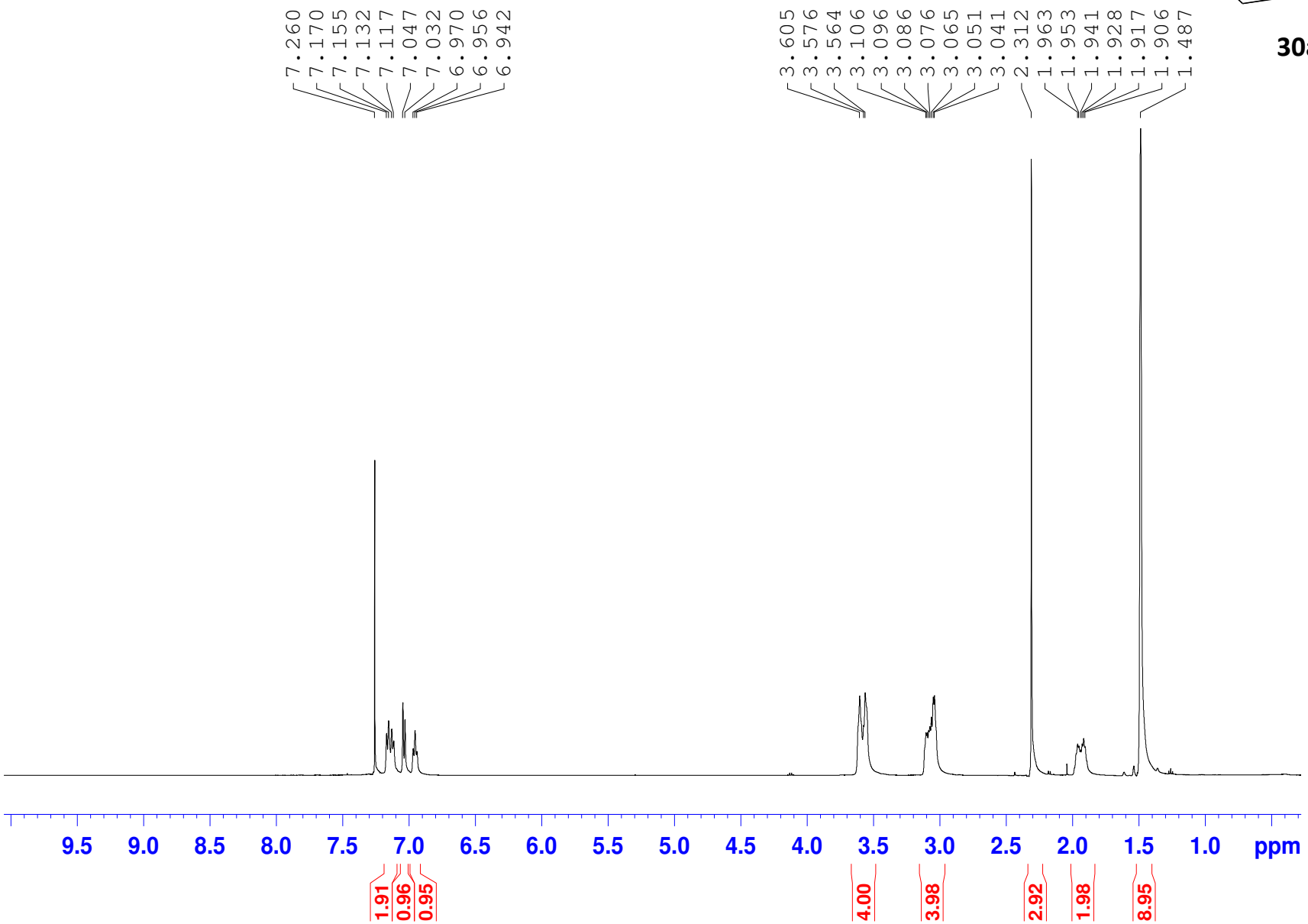

OH
N

4n


151.90
132.65
130.93
126.40
122.96
119.04
77.41
76.99
76.56
68.04
49.81
35.17
17.73
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
O
N
N

30a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7.170
7.155
7.132
7.117
7.047
7.032
6.970
6.956
6.942
3.605
3.576
3.564
3.106
3.096
3.086
3.076
3.065
3.051
3.041
2.312
1.963
1.953
1.941
1.928
1.917
1.906
1.487
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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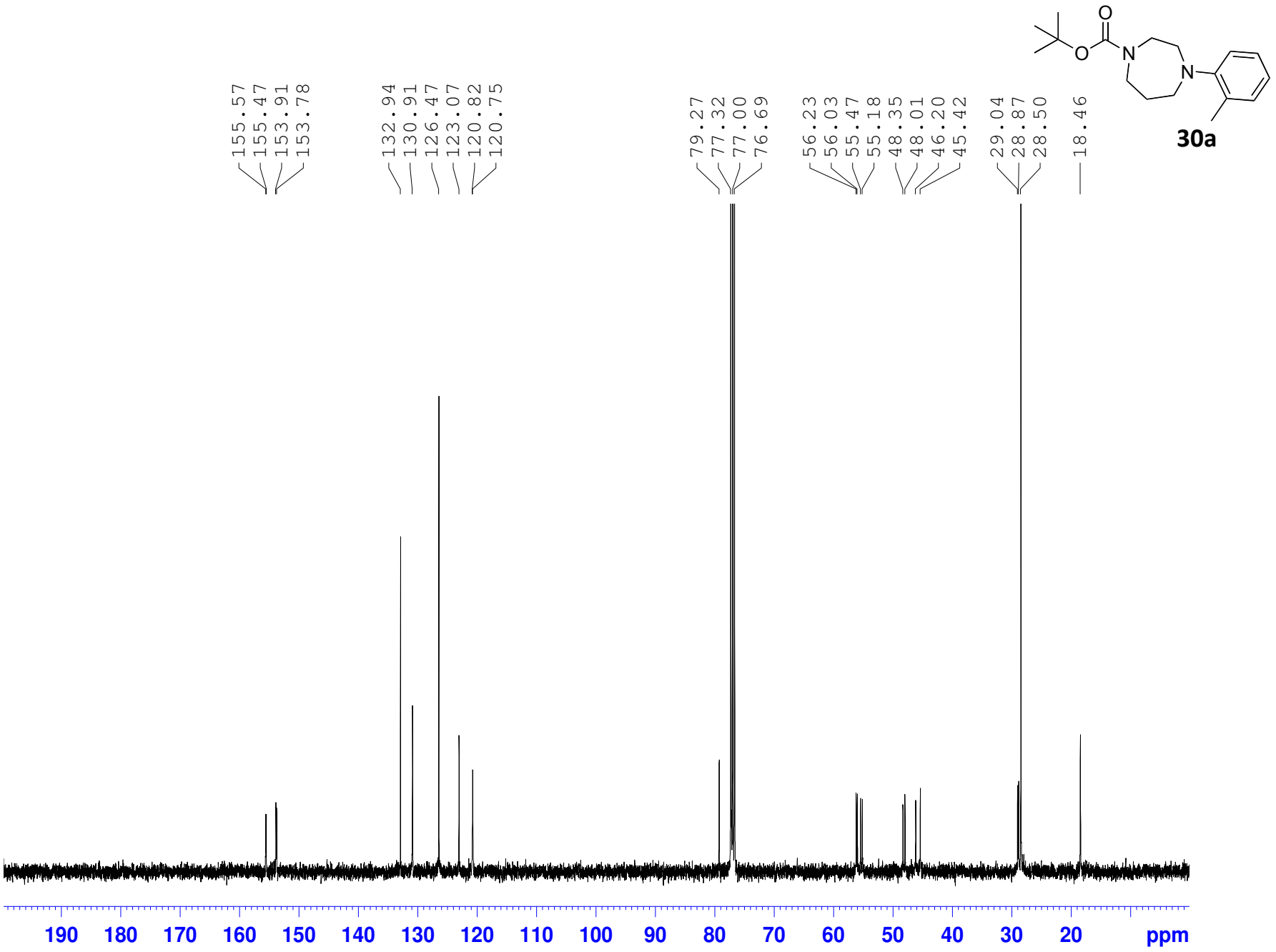
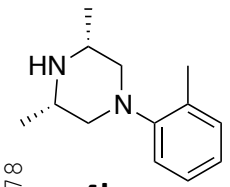
0.96
0.95
4.00
3.98
2.92
1.98
8.95


155.57
155.47
153.91
153.78
132.94
130.91
126.47
123.07
120.82
120.75
79.27
77.32
77.00
76.69
56.23
56.03
55.47
55.18
48.35
48.01
46.20
45.42
29.04
28.87
28.50
18.46
O
O
N
N
30a
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

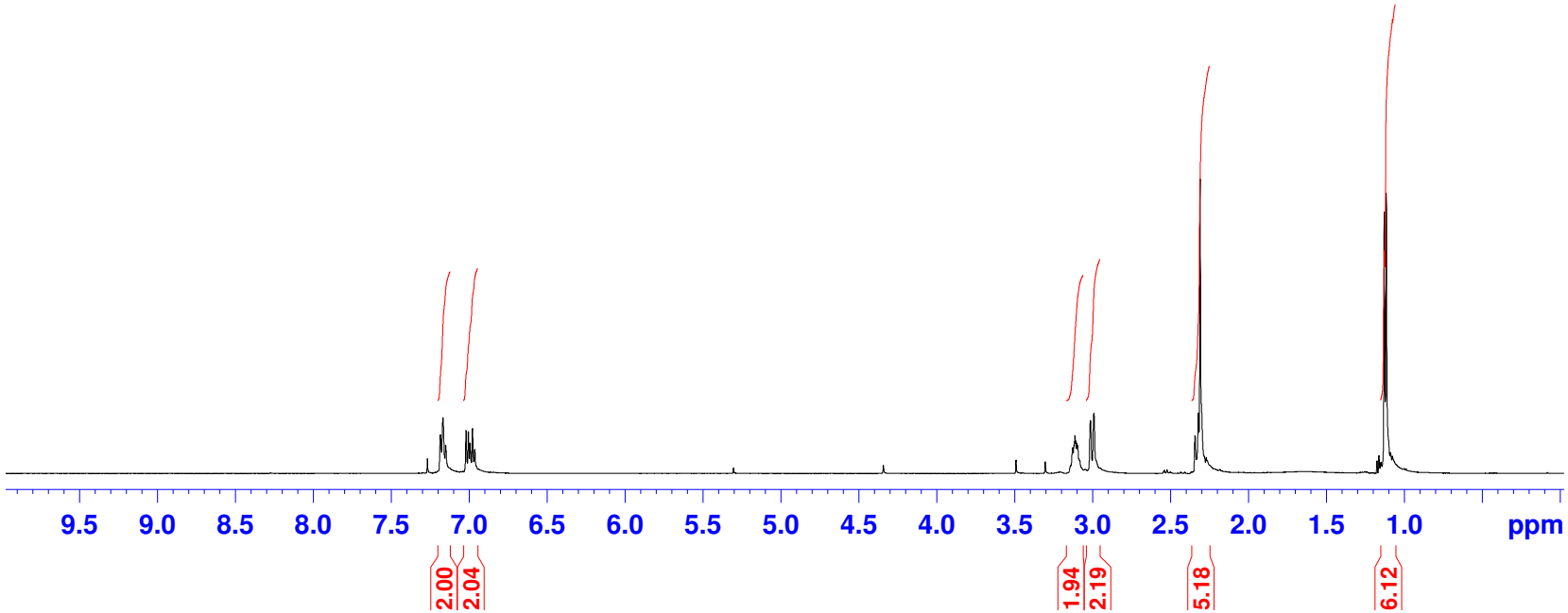


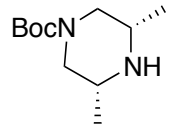
4k

7.186
7.170
7.153
7.022
7.006
6.995
6.981

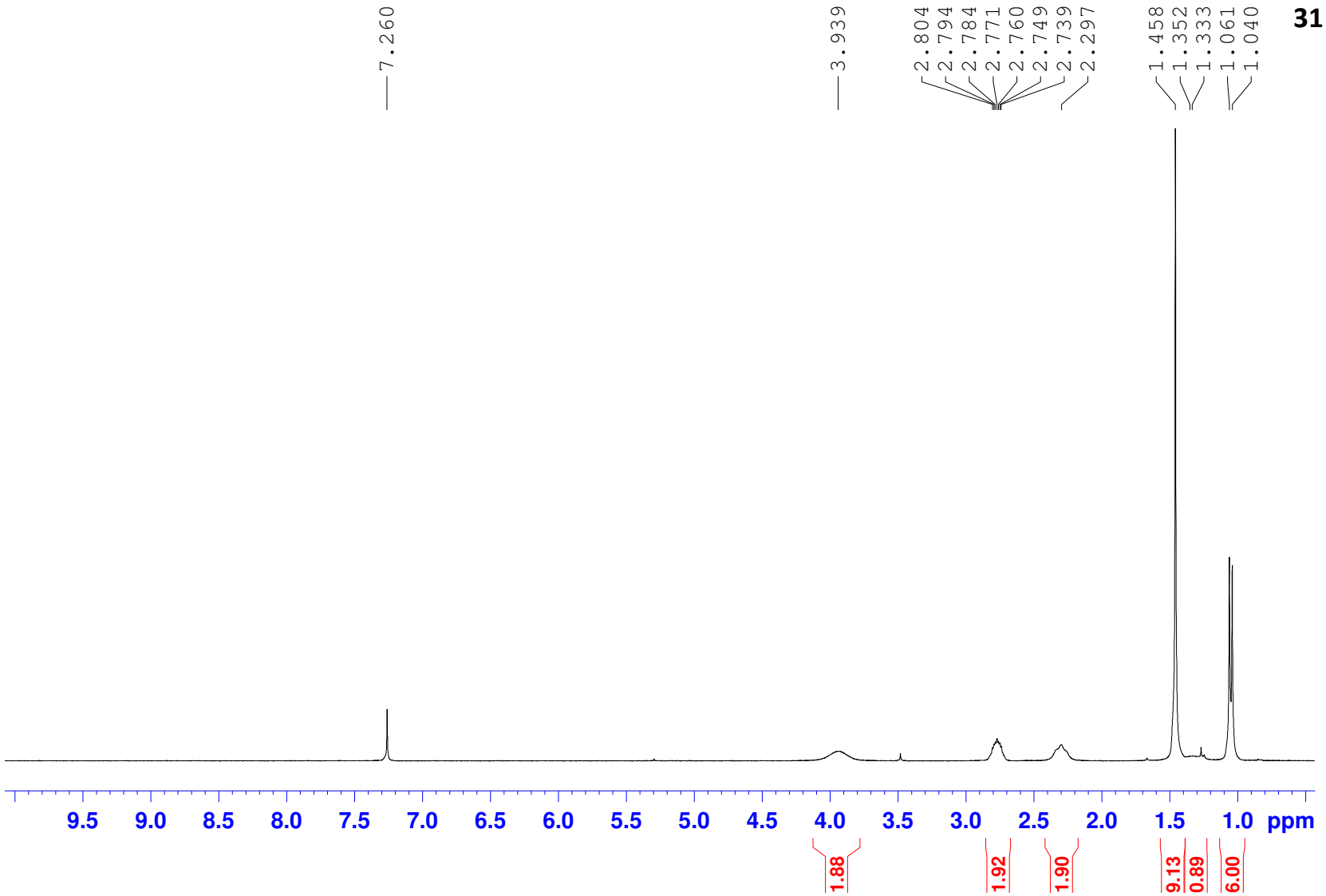
3.128
3.121
3.115
3.109
3.102
3.097
3.015
2.994
2.345
2.323
2.311

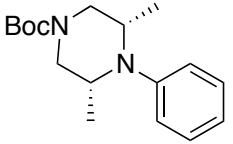
1.176
1.164
1.152
1.130
1.117
1.091
1.078



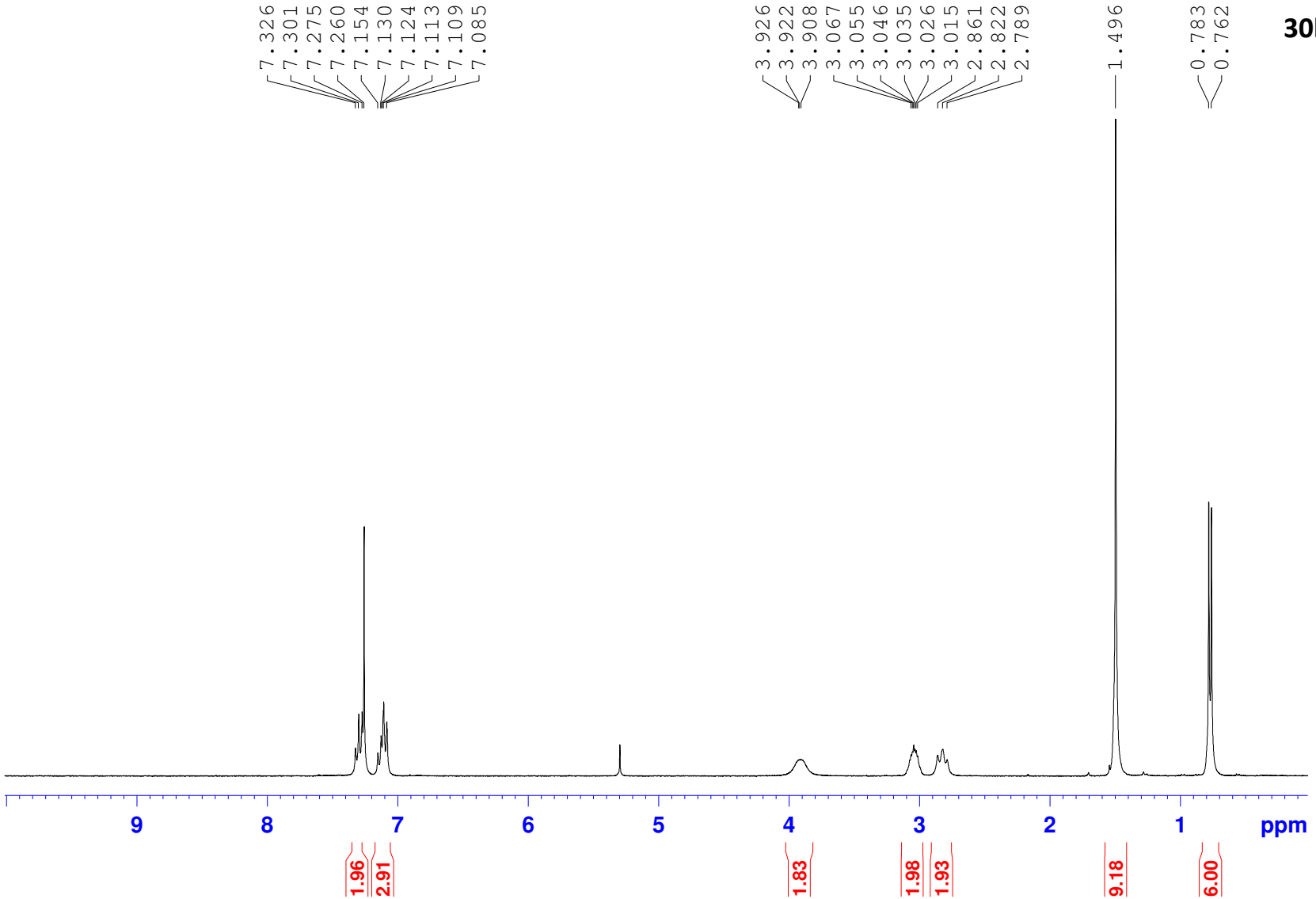

BocN
NH

31


7.260
3.939
2.804
2.794
2.784
2.771
2.760
2.749
2.739
2.297
1.458
1.352
1.333
1.061
1.040
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
1.88
1.92
1.90
9.13
0.89
6.00


BocN
N

30b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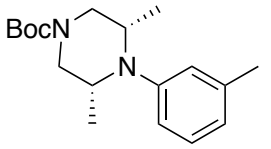
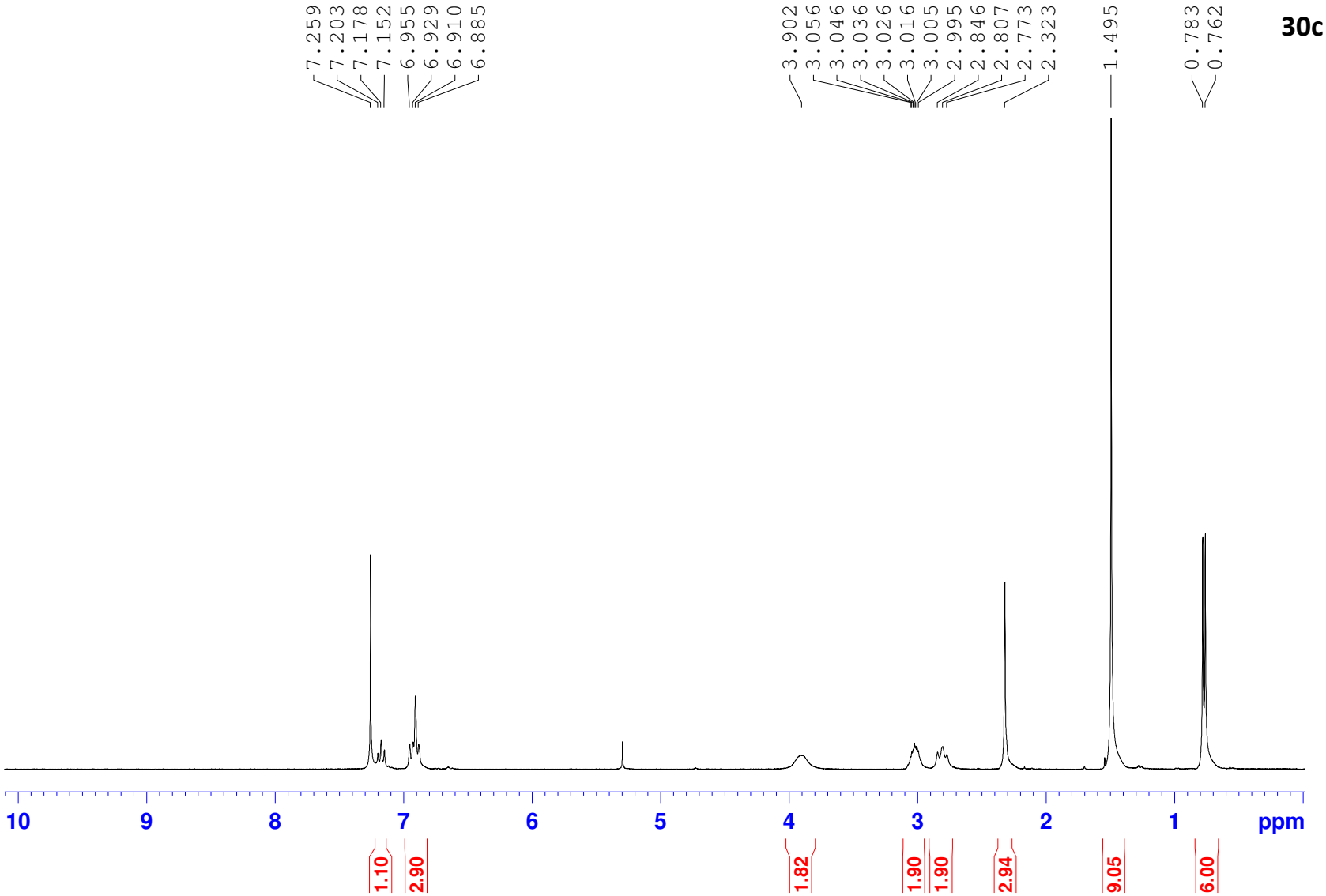
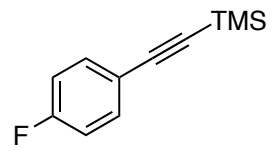
7.301
7.275
7.260
7.154
7.130
7.124
7.113
7.109
7.085
3.926
3.922
3.908
3.067
3.055
3.046
3.035
3.026
3.015
2.861
2.822
2.789
1.496
0.783
0.762
9
8
7
6
5
4
3
2
1
ppm
1.96
2.91
1.83
1.98
1.93
9.18
6.00

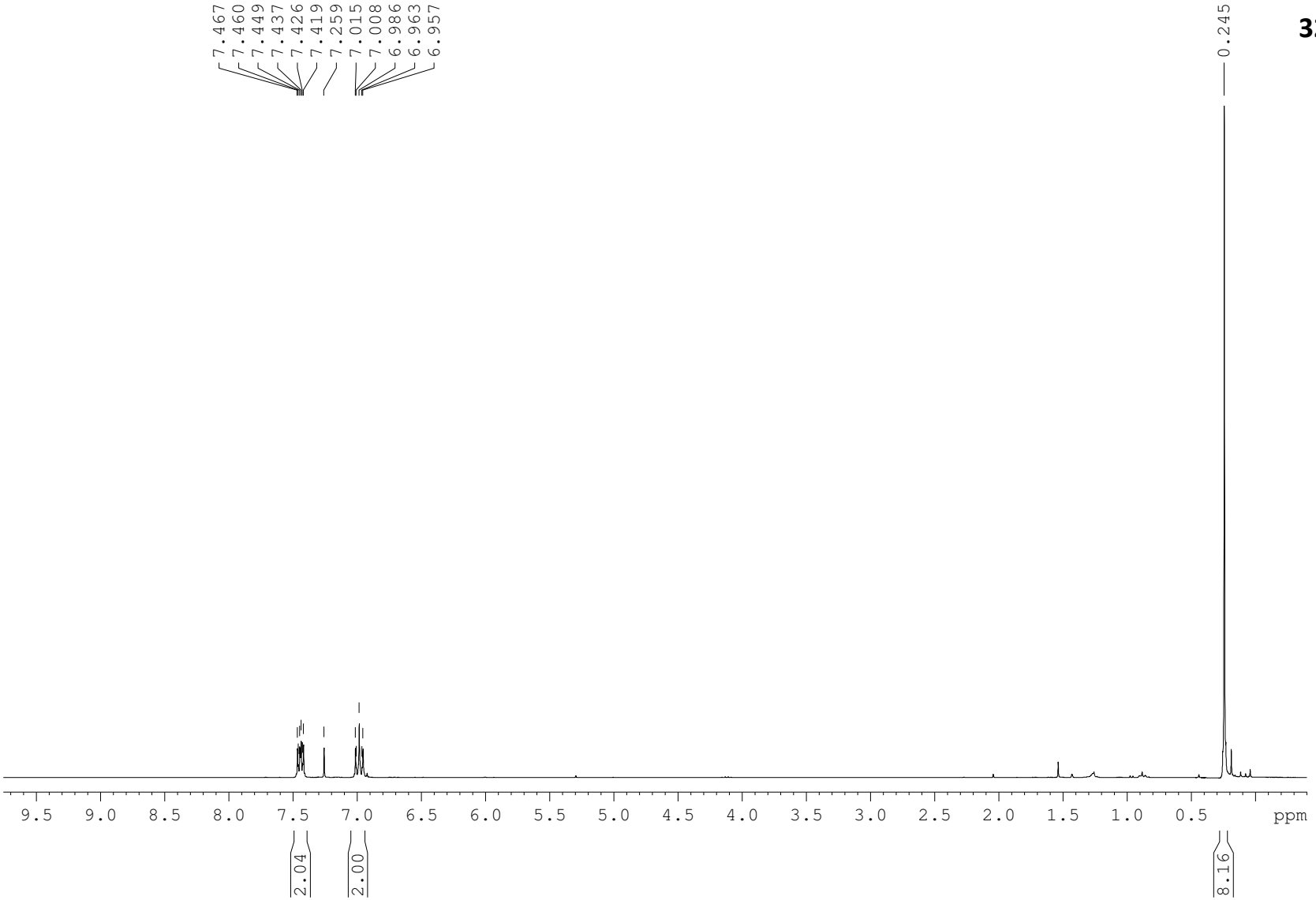

BocN
N

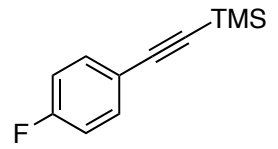
30c


7.259
7.203
7.178
7.152
6.955
6.929
6.910
6.885
3.902
3.056
3.046
3.036
3.026
3.016
3.005
2.995
2.846
2.807
2.773
2.323
1.495
0.783
0.762
10
9
8
7
6
5
4
3
2
1
ppm
1.10
2.90
1.82
1.90
1.90
2.94
9.05
6.00

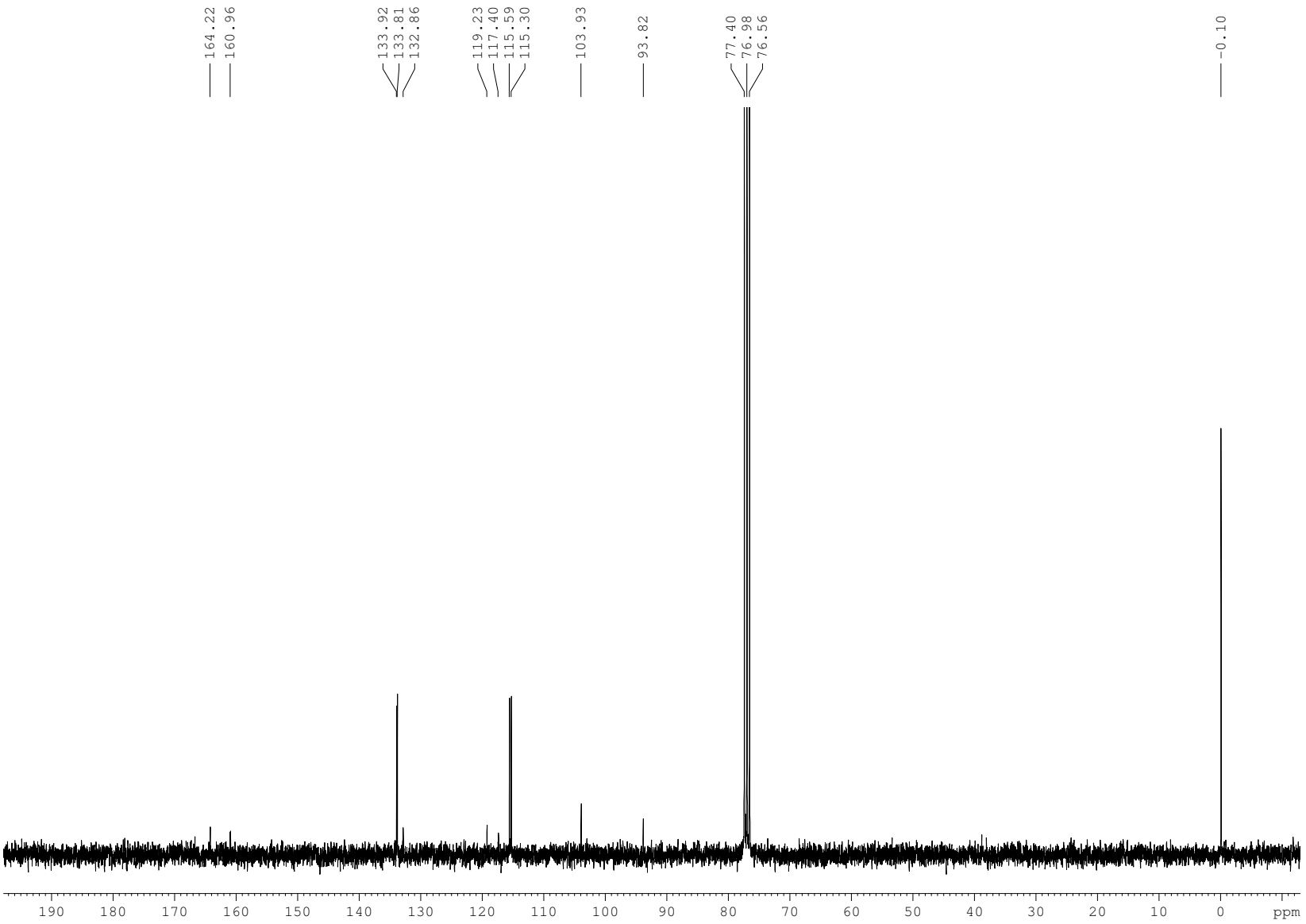

TMS
F

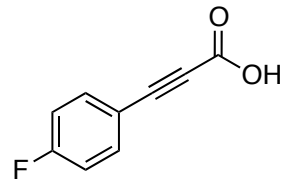
32


7.467
7.460
7.449
7.437
7.426
7.419
7.259
7.015
7.008
6.986
6.963
6.957
0.245
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
0.5
ppm
2.04
2.00
8.16

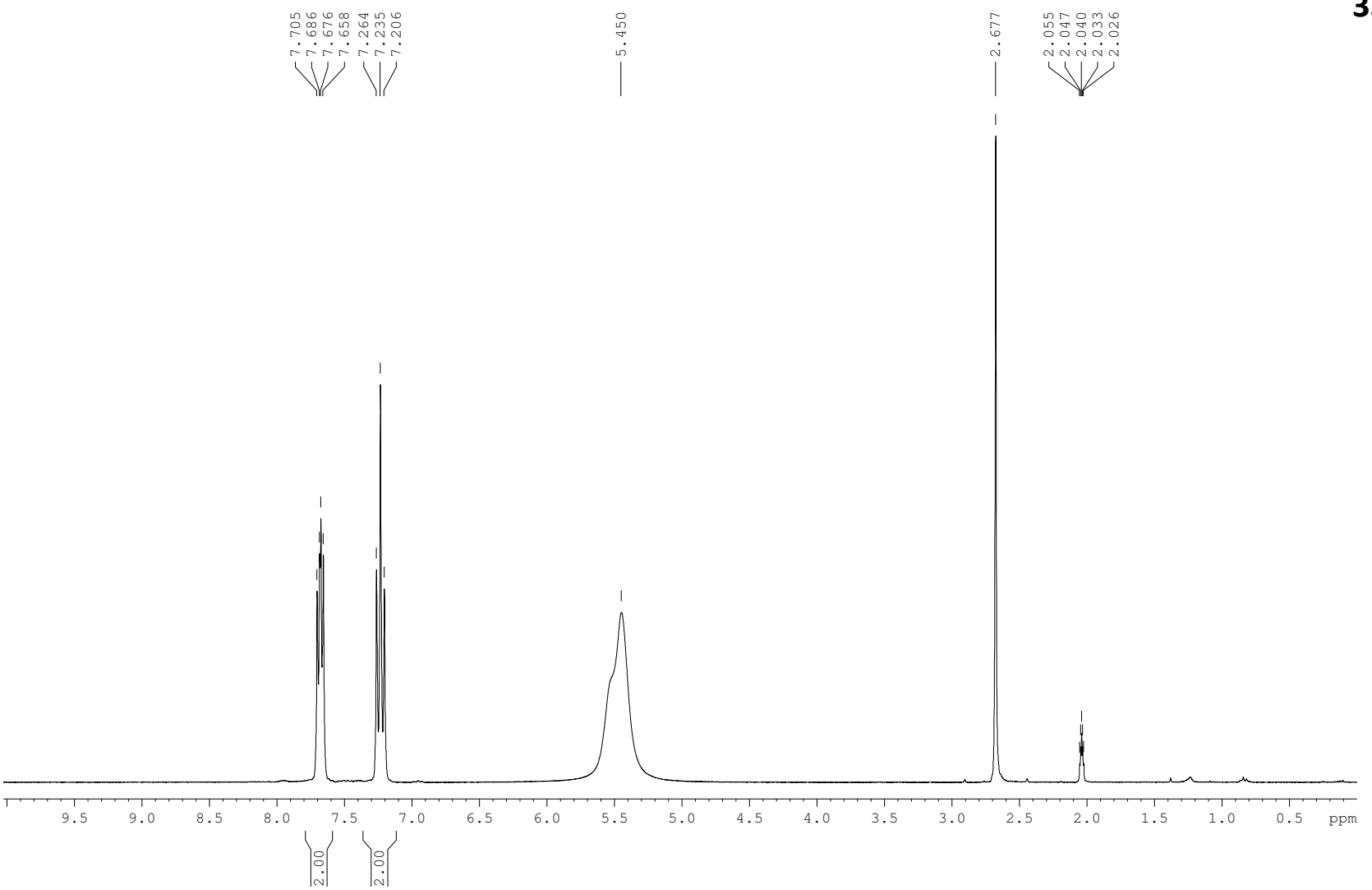

TMS
F

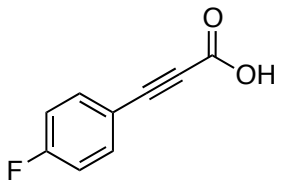
32


164.22
160.96
133.92
133.81
132.86
119.23
117.40
115.59
115.30
103.93
93.82
77.40
76.98
76.56
-0.10
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

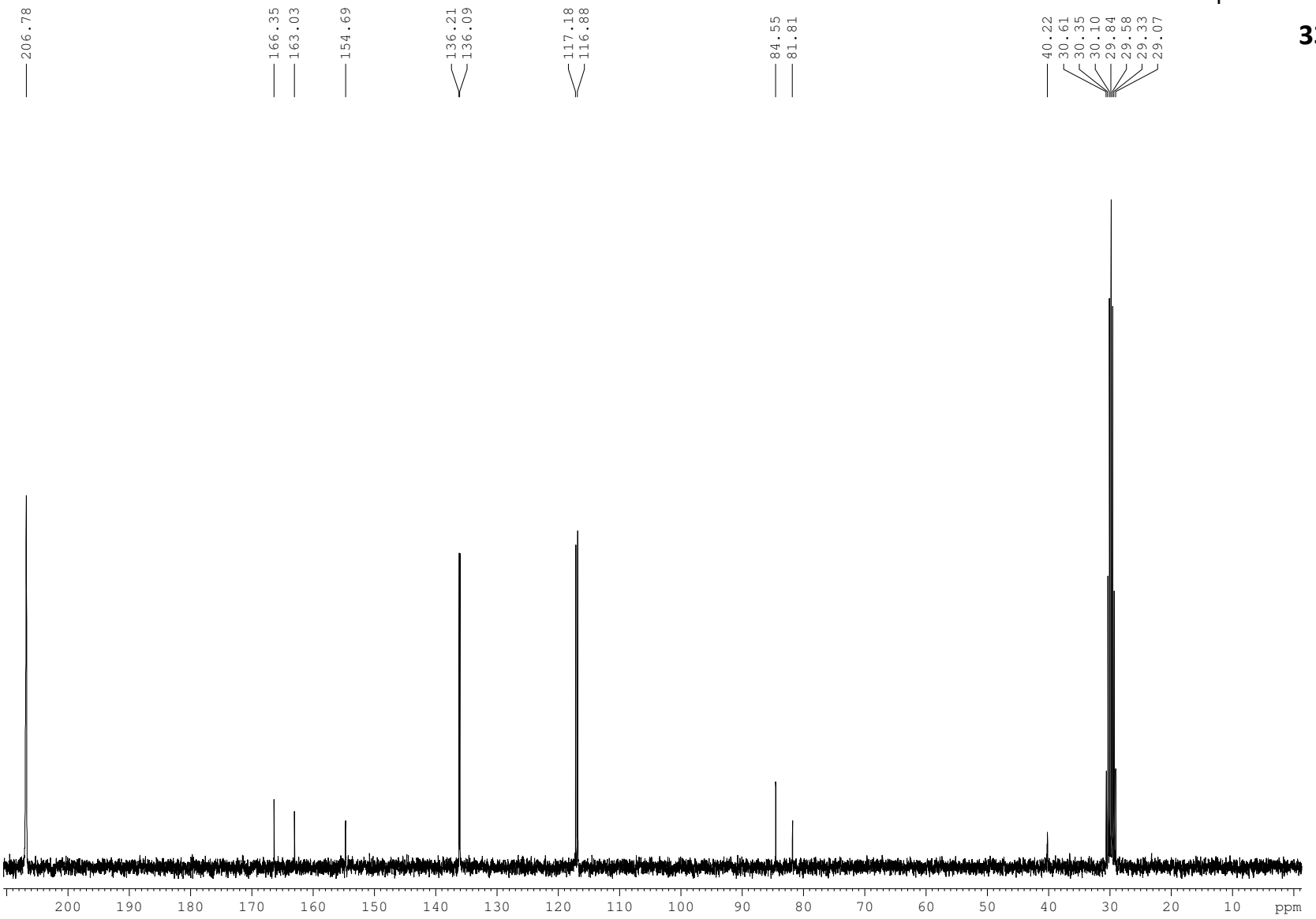

O
OH
F

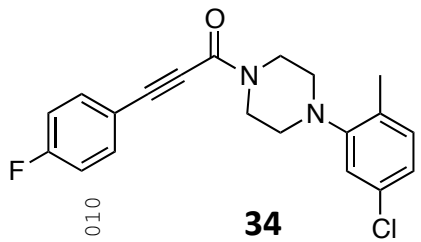
33


7.705
7.686
7.676
7.658
7.264
7.235
7.206
5.450
2.677
2.055
2.047
2.040
2.033
2.026
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
0.5
ppm
2.00
2.00

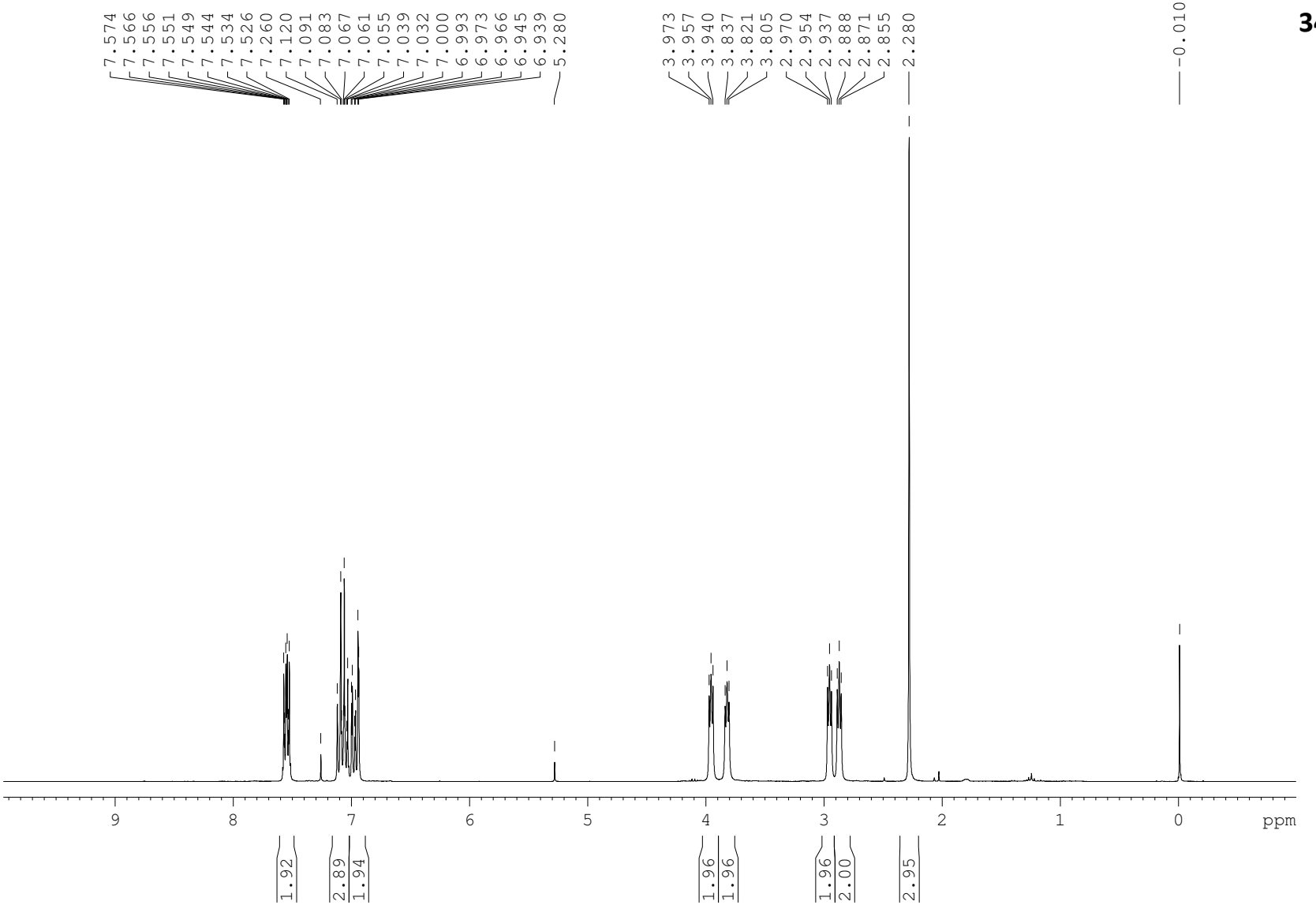

O
OH
F

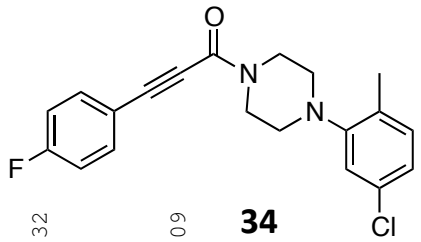
33


206.78
166.35
163.03
154.69
136.21
136.09
117.18
116.88
84.55
81.81
40.22
30.61
30.35
30.10
29.84
29.58
29.33
29.07
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
N
N
F
Cl

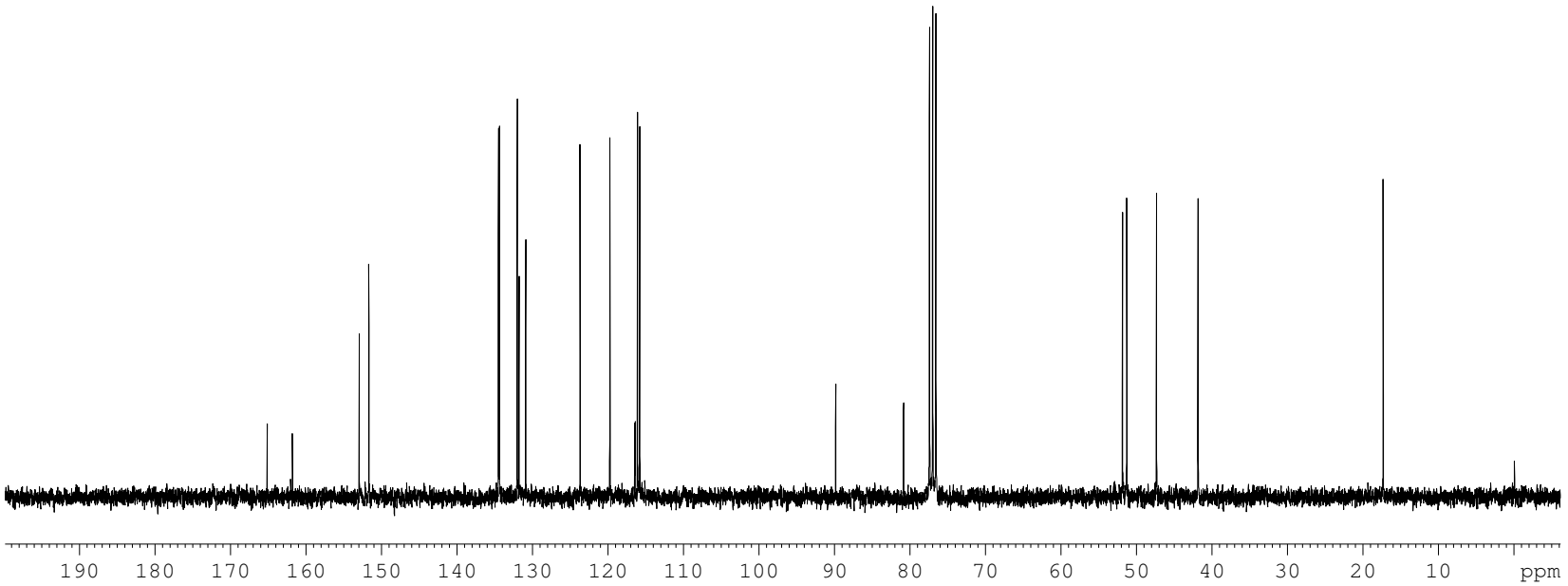
34

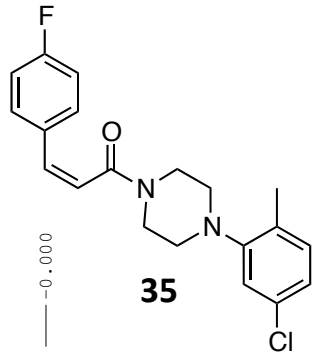

7.574
7.566
7.556
7.551
7.549
7.544
7.534
7.526
7.260
7.120
7.091
7.083
7.067
7.061
7.055
7.039
7.032
7.000
6.993
6.973
6.966
6.945
6.939
5.280
3.973
3.957
3.940
3.837
3.821
3.805
2.970
2.954
2.937
2.888
2.871
2.855
2.280
-0.010
9
8
7
6
5
4
3
2
1
0
ppm
1.92
2.89
1.94
1.96
1.96
1.96
2.00
2.95



34

165.17
161.83
152.98
151.70
134.54
134.42
132.05
131.81
130.92
123.72
119.78
116.47
116.42
116.11
115.81
89.85
80.85
77.42
77.00
76.57
51.85
51.28
47.35
41.84
17.32
-0.09





35

7.414
7.409
7.401
7.393
7.384
7.379
7.255
7.172
7.164
7.154
7.145
7.125
7.067
7.060
7.055
7.038
7.021
7.016
7.012
7.009
7.000
6.993
6.991
6.975
6.973
6.857
6.837
6.673
6.641
6.077
6.046

3.819
3.808
3.797
3.508
3.495
3.483

2.843
2.831
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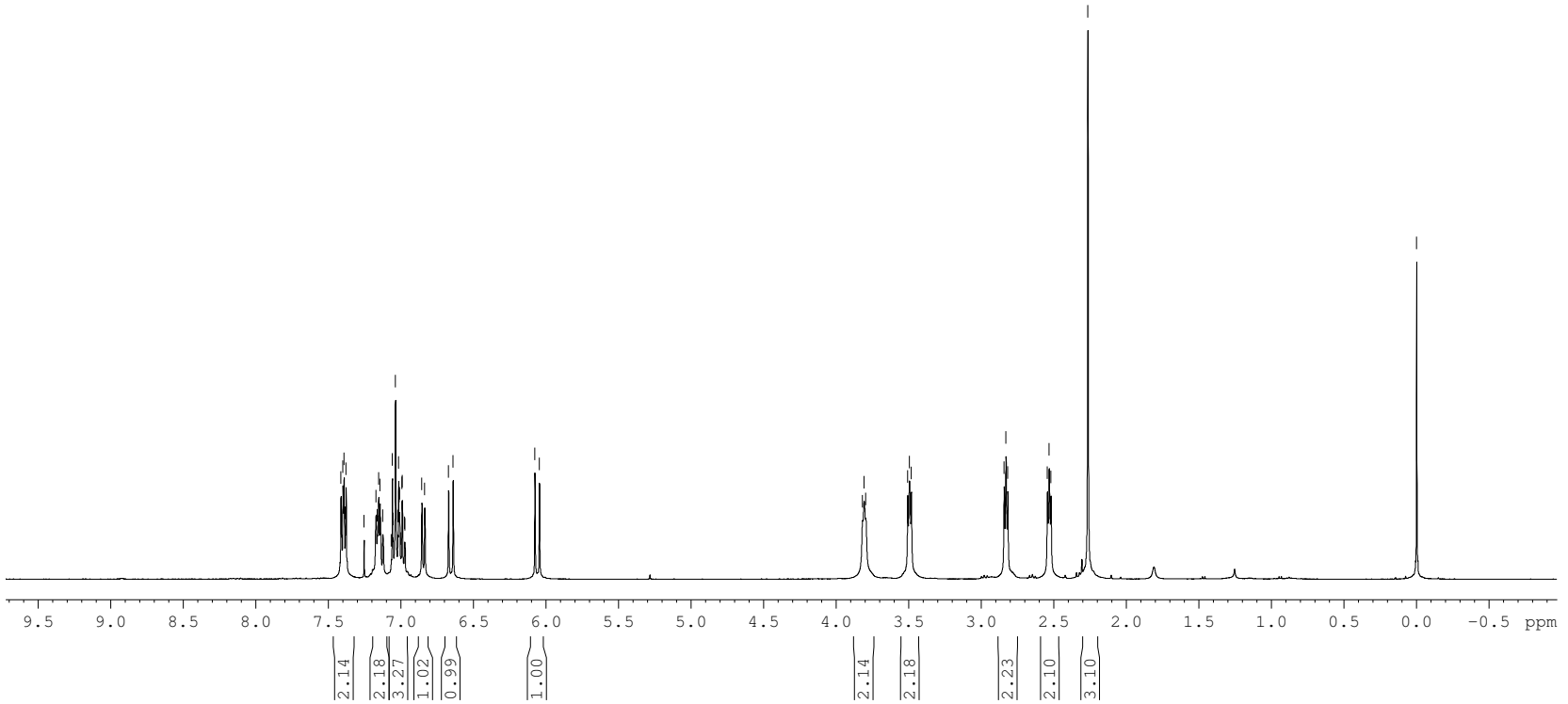
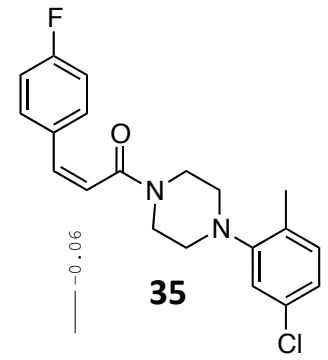
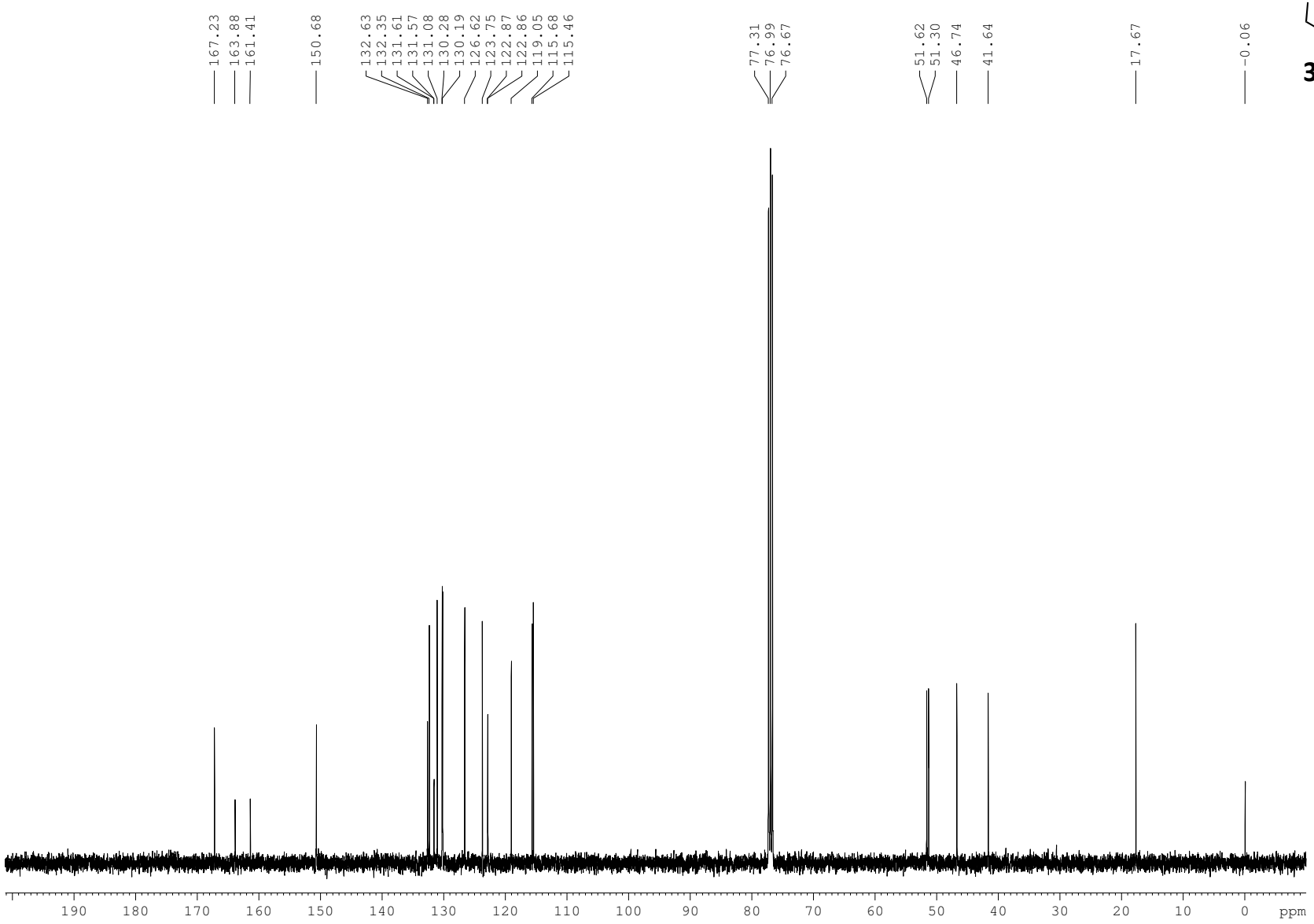
2.545
2.533
2.520
2.266

-0.000




F
O
N
N
Cl

35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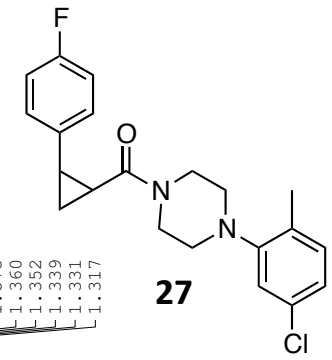
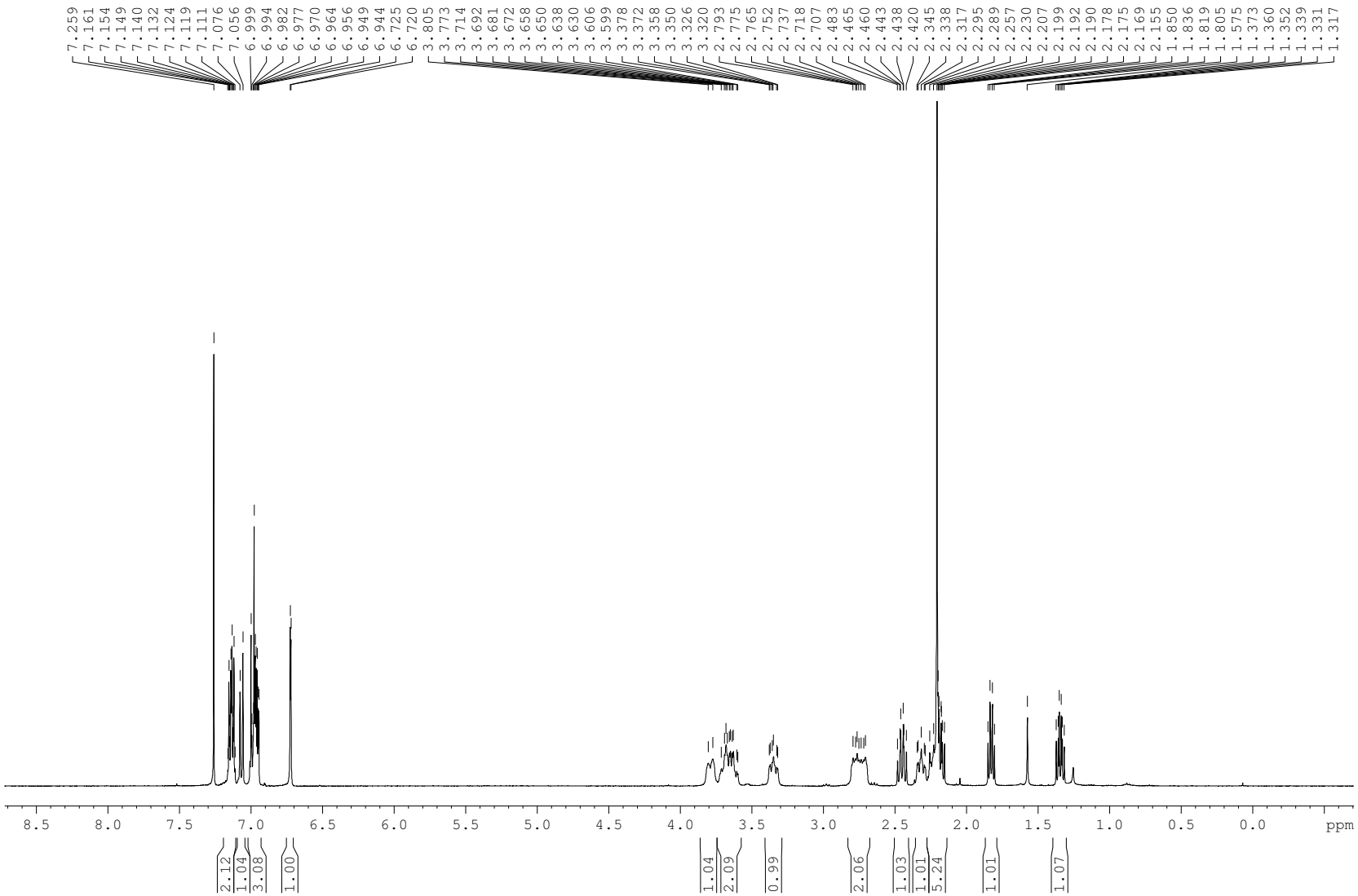
161.41
150.68
132.63
132.35
131.61
131.57
131.08
130.28
130.19
126.62
123.75
122.87
122.86
119.05
115.68
115.46
77.31
76.99
76.67
51.62
51.30
46.74
41.64
17.67
-0.06
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


F
O
N
N
Cl

27


7.259
7.161
7.154
7.149
7.140
7.132
7.124
7.119
7.111
7.076
7.056
6.999
6.994
6.982
6.977
6.970
6.964
6.956
6.949
6.944
6.725
6.720
3.805
3.773
3.714
3.692
3.681
3.672
3.658
3.650
3.638
3.630
3.606
3.599
3.378
3.372
3.358
3.350
3.326
3.320
2.793
2.775
2.765
2.752
2.737
2.718
2.707
2.483
2.465
2.460
2.443
2.438
2.420
2.345
2.338
2.317
2.295
2.289
2.257
2.230
2.207
2.199
2.192
2.190
2.178
2.175
2.169
2.155
1.850
1.836
1.819
1.805
1.575
1.373
1.360
1.352
1.339
1.331
1.317
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
0.5
0.0
ppm
2.12
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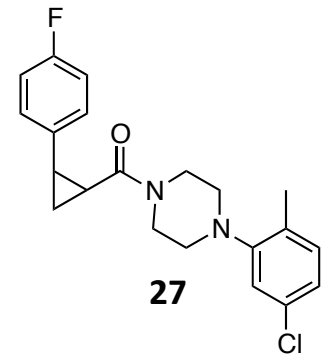
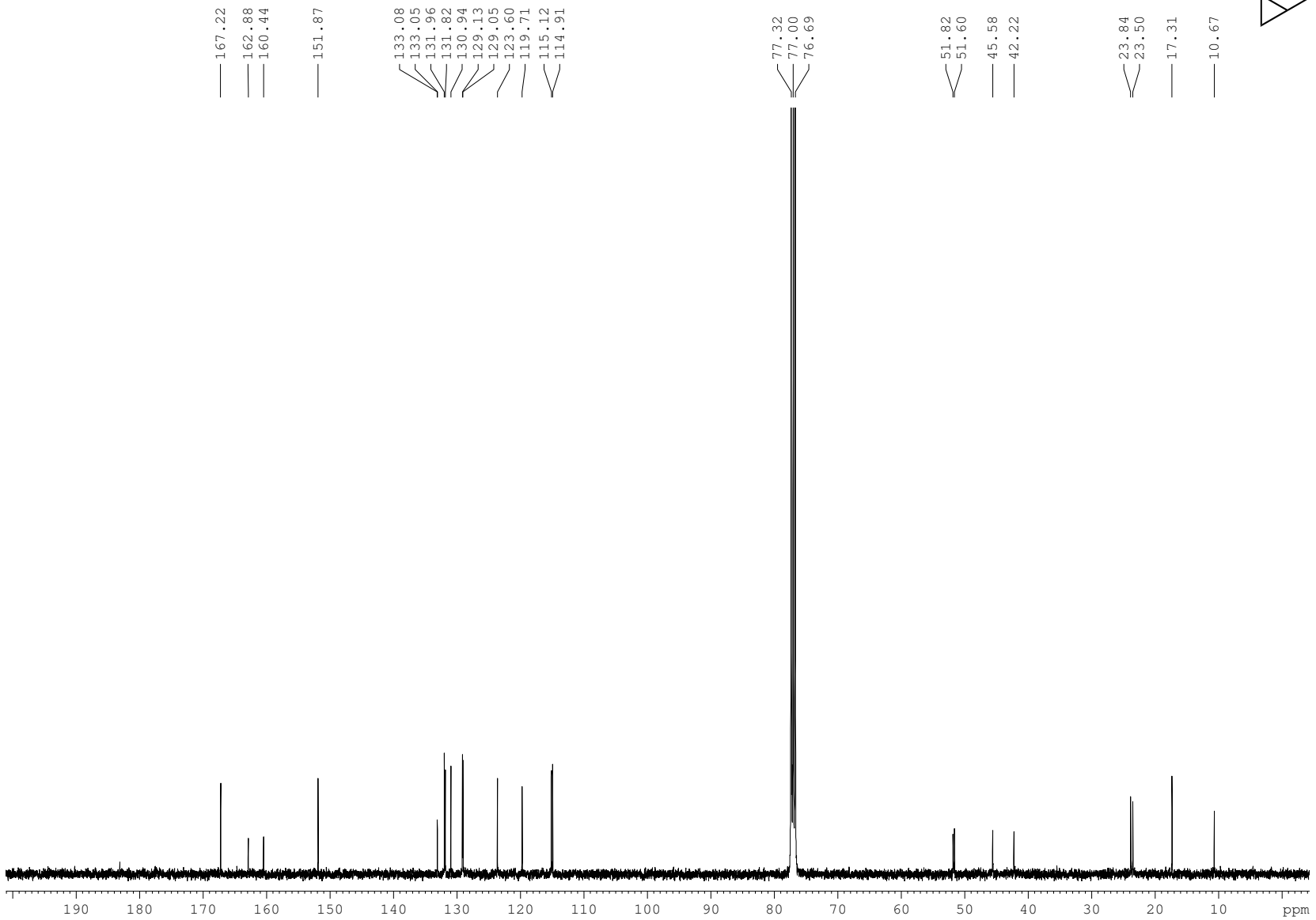
3.08
1.00
1.04
2.09
0.99
2.06
1.03
1.01
5.24
1.01
1.07


F
O
N
N
Cl

27


167.22
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151.87
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133.05
131.96
131.82
130.94
129.13
129.05
123.60
119.71
115.12
114.91
77.32
77.00
76.69
51.82
51.60
45.58
42.22
23.84
23.50
17.31
10.67
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150
140
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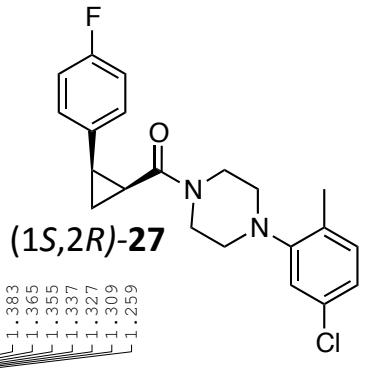
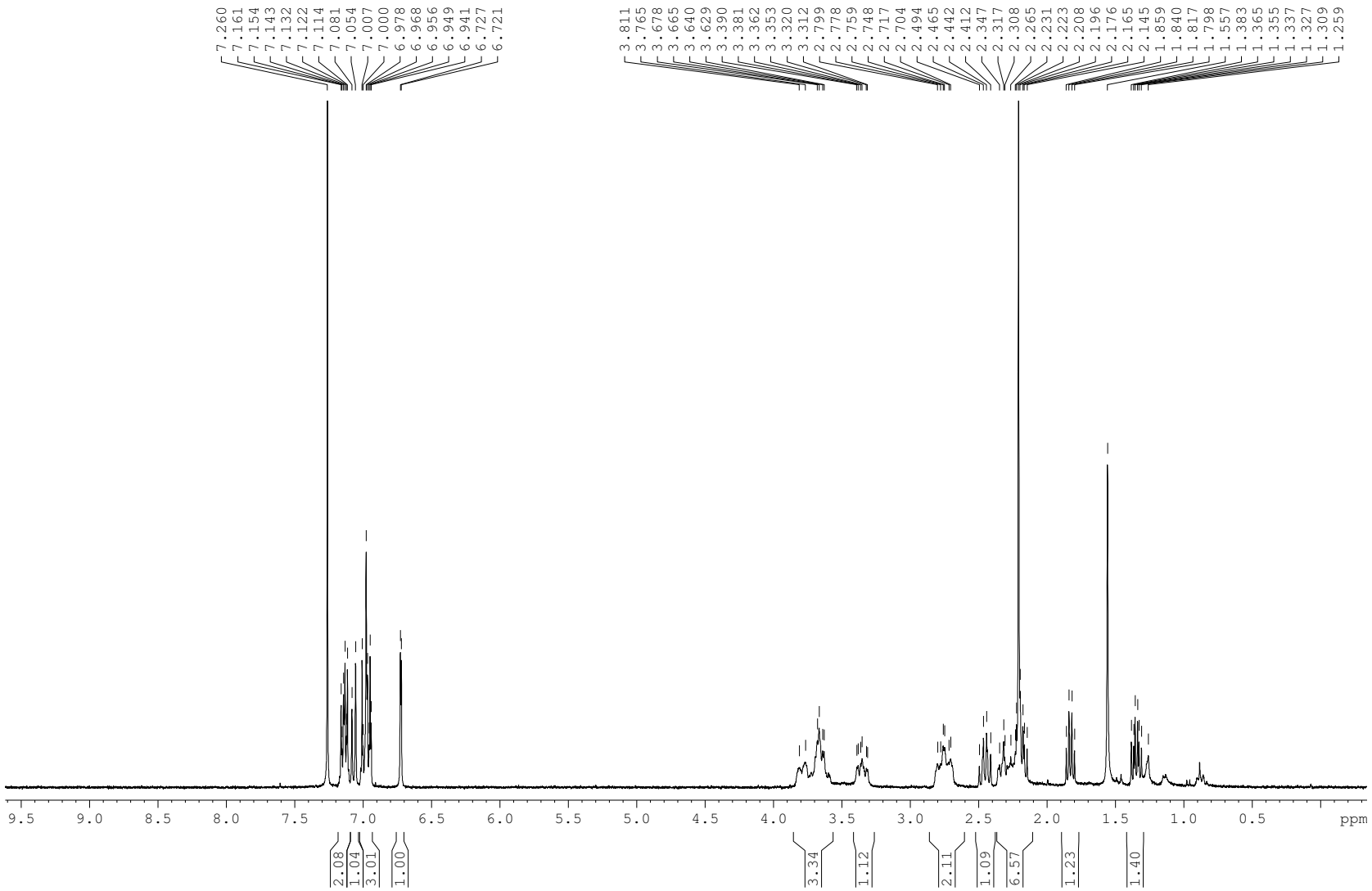
120
110
100
90
80
70
60
50
40
30
20
10
ppm


F
O
N
N
Cl

(1*S*,2*R*)-**27**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7.161
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7.143
7.132
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7.114
7.081
7.054
7.007
7.000
6.978
6.968
6.956
6.949
6.941
6.727
6.721
3.811
3.765
3.678
3.665
3.640
3.629
3.390
3.381
3.362
3.353
3.320
3.312
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2.778
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2.748
2.717
2.704
2.494
2.465
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2.412
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2.208
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2.176
2.165
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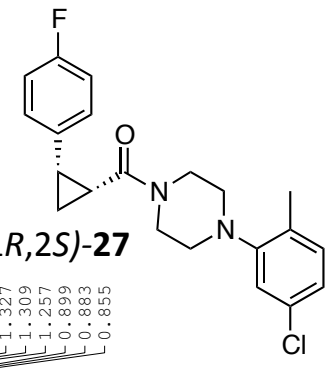
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N
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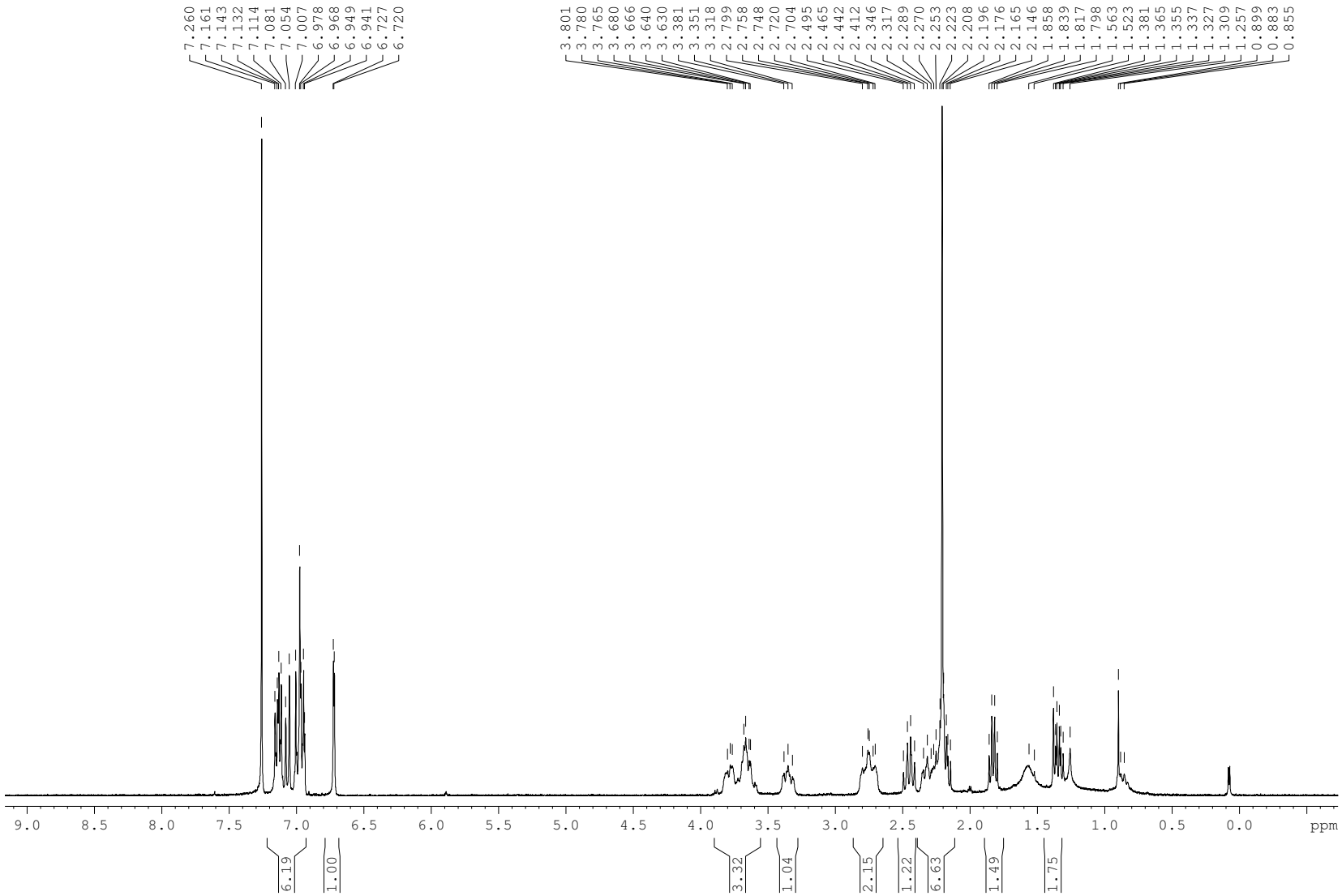
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