Supporting Information

An uncharged oxetanyl sulfoxide as a covalent modifier for improving aqueous solubility

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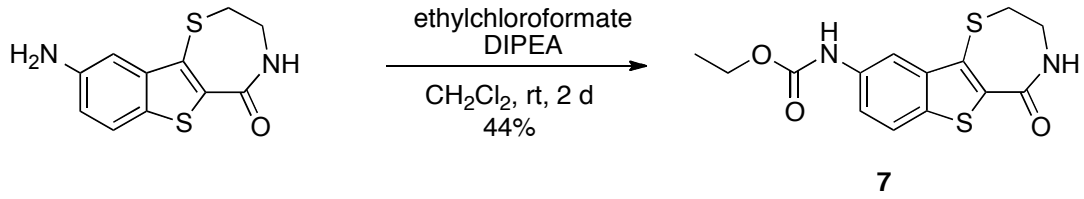
Contents

General Methods

All non-aqueous reactions were carried out under a nitrogen atmosphere in oven- or flame-dried glassware unless otherwise noted. Anhydrous tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl; anhydrous dichloromethane and toluene were distilled from CaH_2; alternatively, the same solvents were obtained from a solvent purification system using alumina columns. All other solvents and reagents were used as obtained from commercial sources without further purification unless noted. Reactions were monitored via TLC using 250 μm pre-coated silica gel 60 F_{254} plates, which were visualized with 254 nm and/or 365 nm UV light and by staining with $KMnO_4$ (1.5 g $KMnO_4$, 10 g K_2CO_3, and 1.25 mL 10% NaOH in 200 mL water), cerium molybdate (0.5 g $Ce(NH_4)_2(NO_3)_6$, 12 g $(NH_4)_6Mo_7O_{24}•4H_2O$, and 28 mL conc. H_2SO_4 in 235 mL water), or vanillin (6 g vanillin and 1.5 mL conc. H_2SO_4 in 100 mL EtOH). Flash chromatography was performed with SiliCycle silica gel 60 (230-400 mesh) or with ISCO MPLC. ^1H and

^{13}C NMR spectra were recorded on Bruker Avance 300, 400, or 500 MHz spectrometers, using the residual solvent as an internal standard. IR spectra were obtained on a Smiths IdentifyIR or PerkinElmer Spectrum 100. HRMS data were obtained on a Thermo Scientific Exactive HRMS coupled to a Thermo Scientific Accela HPLC system using a 2.1 x 50 mm 3.5 μm Waters XTerra C_{18} column eluting with MeCN/H_2O containing 0.1% formic acid. Purity of compounds was assessed using the same HPLC system with either the PDA or an Agilent 385 ELSD. Compounds **2**, **3**, **4**,[1] **5**, and **6** were purchased and were used without purification (following QC by LC/MS/ELS and ^1H NMR analyses). Compound **8**[2] was synthesized following published procedures and was also assessed for purity prior to solubility testing (LC/MS/ELS and ^1H NMR analyses).

Synthetic Experimental Procedures



7

Ethyl (5-oxo-2,3,4,5-tetrahydrobenzo[4,5]thieno[2,3-*f*][1,4]thiazepin-9-yl)-carbamate (7). A solution of amine[3] (51 mg, 0.20 mmol) in THF (2.1 mL, 0.1 M) was treated with ethyl chloroformate (40 μL, 0.4 mmol, 2 equiv) and NEt_3 (60 μL, 0.4 mmol, 2 equiv), stirred overnight, concentrated in vacuo, and dried overnight. The solid residue was purified by suspension in water (1 mL) followed by centrifugation at 4,400 rpm for 5 min. This procedure was repeated twice more with water, then once with CH_2Cl_2, and once with Et_2O. The resulting solid was

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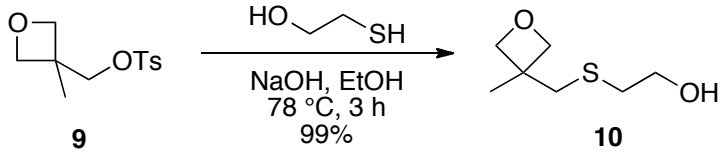
1 The carboxylic acid was formed from the sodium salt of this compound by reaction with HCl.

2 Frantz, M.-C.; Pierce, J. G.; Pierce, J. M.; Kangying, L.; Qingwei, W.; Johnson, M.; Wipf, P. *Org. Lett.* **2011**, *13,* 2318.

3 Bravo-Altamirano, K.; George, K. M.; Frantz, M.-C. l.; LaValle, C. R.; Tandon, M.; Leimgruber, S.; Sharlow, E. R.; Lazo, J. S.; Wang, Q. J.; Wipf, P. *ACS Med. Chem. Lett.* **2011**, *2,* 154.

dried in vacuo overnight to yield a dark yellow solid (29 mg, 44%): mp 310 °C (dec); ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.85 (s, 1H), 8.45 (bs, 1H), 8.10 (s, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.64-3.60 (m, 2H), 3.41-3.36 (m, 2H), 1.26 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 165.1, 153.6, 138.9, 136.8, 132.7, 132.4, 128.1, 122.9, 119.2, 110.8, 60.3, 42.5, 33.2, 14.5; IR (ATR, neat) 3331, 3268, 3151, 3017, 2919, 1689, 1633, 1576, 1527, 1499, 1466, 1405, 1281, 1232, 1061, 808, 768 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd for $C_{14}H_{15}O_3N_2S_2$ 323.0519, found 323.0514.



9 **10**

2-(((3-Methyloxetan-3-yl)methyl)thio)ethanol (10). To a solution of (3-methyloxetan-3-yl)methyl *p*-toluenesulfonate[4] (**9**) (5.00 g, 19.5 mmol) and sodium hydroxide (875 mg, 21.4 mmol) in EtOH (50 mL) was added 2-mercaptoethanol (1.65 mL, 23.3 mmol). The reaction mixture was stirred at reflux for 3 h, during which a white precipitate formed. The mixture was cooled to rt, and the EtOH was evaporated. The residue was diluted with EtOAc (100 mL) and washed with 1 M NaOH (30 mL) and brine (30 mL). The combined aqueous layers were back extracted with EtOAc, and the combined organic portion was dried ($MgSO_4$), and evaporated. Removal of residual solvent and mercaptoethanol under vacuum at rt overnight gave thioether alcohol **10** (3.12 g, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46, 4.37 (ABq, *J* = 6.0 Hz, 4H), 3.74 (t, *J* = 6.0 Hz, 2H), 2.89 (s, 2H), 2.76 (t, *J* = 6.0 Hz, 2H), 2.12 (br s, 1H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.0, 60.7, 41.8, 40.2, 36.9, 23.2; IR (neat) 3390, 1450, 1377, 1045, 973 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd for $C_7H_{15}O_2S$ 163.0787, found 163.0786.

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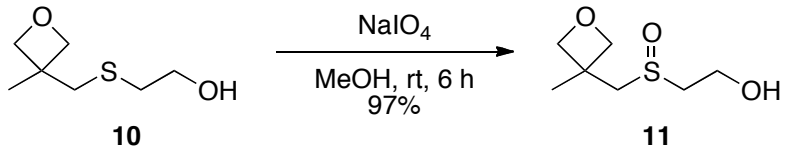
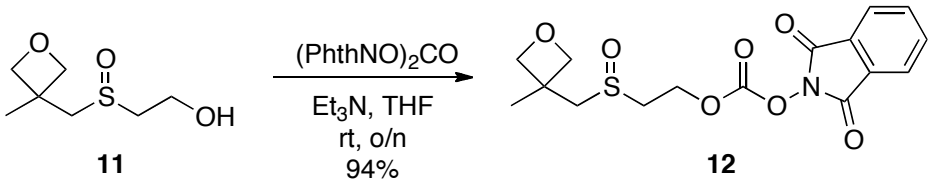
[4] Rose, N. G.; Blaskovich, M. A.; Evindar, G.; Wilkinson, S.; Luo, Y.; Fishlock, D.; Reid, C.; Lajoie, G. A. *Org. Synth.* **2002**, *79*, 216



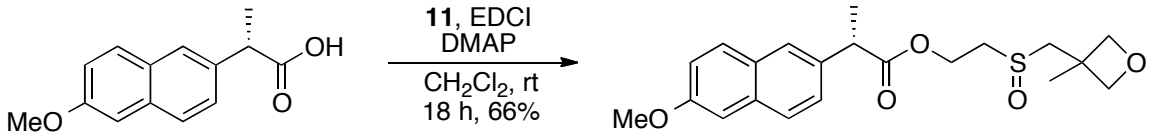
2-(((3-Methyloxetan-3-yl)methyl)sulfinyl)ethanol (11). To a solution of thioether **10** (1.00 g, 6.163 mmol) in MeOH (12 mL) at 0 °C was added dropwise a solution of sodium metaperiodate (1.320 g, 6.171 mmol) in water (6 mL). The resulting heterogeneous mixture was allowed to warm to rt and stirred for 8 h. The reaction mixture was filtered through a plug of Celite® eluting with MeOH, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2, dried ($MgSO_4$), and evaporated to give sulfoxide **11** (1.068 g, 97%) as a colorless oil that solidified on standing: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (dd, *J* = 6.3, 2.9 Hz, 1H), 4.52 (d, *J* = 6.0 Hz, 1 H), 4.38 (dd, *J* = 6.0, 2.4 Hz, 1H), 4.34 (dd, *J* = 6.2, 4.3 Hz, 1H), 4.27 (bs s, 1H), 4.02-3.90 (br m, 2H), 3.24 (dd, *J* = 13.2, 2.4 Hz, 1H), 2.95-2.80 (m, 2H), 2.79 (d, *J* = 13.2 Hz, 1H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.3, 81.8, 61.0, 55.5, 55.2, 38.3, 23.4; IR (ATR, neat) 3309, 2958, 2937, 2869, 1451, 1383, 1329, 1068, 1027, 992, 978, 841 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd for $C_7H_{15}O_3S$ 179.0736, found 179.0740.



1,3-Dioxoisoindolin-2-yl (2-(((3-methyloxetan-3-yl)methyl)sulfinyl)ethyl) carbonate (12). To a suspension of diphthalimidyl carbonate[5] (370 mg, 1.05 mmol) and sulfoxide **11** (185 mg, 1.04 mmol) in THF (14 mL) was added triethylamine (150 µL, 1.07 mmol). Upon addition of base, the suspension turned yellow, eventually progressing to a clear orange solution after ~30 min. The reaction mixture was stirred for 4 h, and the solvent was evaporated. The residue was dissolved in EtOAc (25 mL) and washed with saturated aqueous $NaHCO_3$ (5 x 3

[5] Kurita, K.; Imajo, H. *J. Org. Chem.* **1982**, *47*, 4584

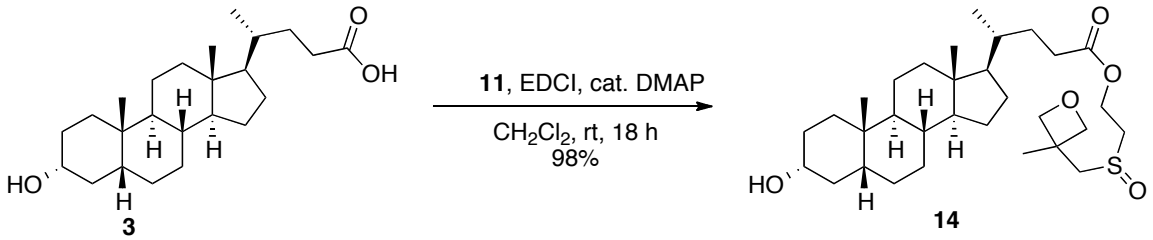
mL) until the organic layer became clear. The combined aqueous washings were extracted with EtOAc (2 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to give the mixed carbonate **12** (357 mg, 94%) as a pale yellow solid, which is somewhat unstable: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.87 (m, 2H), 7.85-7.80 (m, 2H), 4.88-4.75 (m, 2H), 4.79 (d, *J* = 6.4 Hz, 1H), 4.62 (d, *J* = 6.0 Hz, 1H), 4.49 (d, *J* = 6.0 Hz, 1H), 4.45 (d, *J* = 6.4 Hz, 1H), 3.36 (d, *J* = 13.2 Hz, 1H), 3.25–3.16 (m, 1H), 3.14-3.08 (m, 1H), 2.86 (d, *J* = 13.2 Hz, 1H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 152.2, 135.2, 128.6, 124.3, 82.4, 81.9, 63.3, 61.6, 51.6, 38.5, 23.5; IR (ATR, neat) 2963, 2924, 2869, 1814, 1787, 1741, 1467, 1374, 1221, 1185 cm^{-1}.



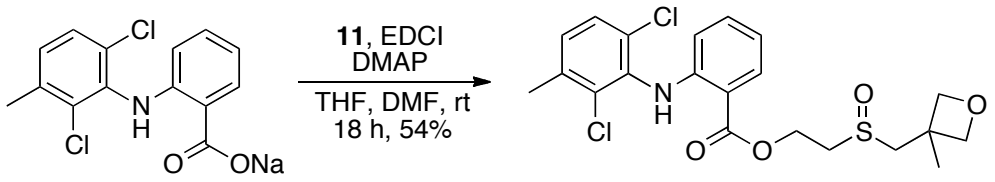
2 **13**

(2*S*)-2-(((3-Methyloxetan-3-yl)methyl)sulfinyl)ethyl 2-(6-methoxynaphthalen-2-yl)propanoate (13). A solution of (*S*)-naproxen (**2**, 112 mg, 0.487 mmol) in CH_2Cl_2 (4 mL) was treated with **11** (100 mg, 0.56 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (83 mg, 0.53 mmol), and DMAP (6 mg) and stirred at rt for 18 h. The reaction mixture was concentrated, and the crude material was purified by chromatography on SiO_2 (100% EtOAc followed by 5-10% MeOH/EtOAc) to give **13** (126 mg, 66%) as a white solid mixture of diastereomers: mp 123-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ δ 7.65 (dd, *J* = 8.6, 3.0 Hz, 2H), 7.61 (s, 1H), 7.33 (ddd, *J* = 8.0, 6.0, 2.0 Hz, 1H), 7.11(dd, *J* = 8.8, 2.4 Hz, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 4.59 (d, *J* = 6.4 Hz, 0.5H), 4.54 (d, *J* = 6.4 Hz, 0.5H), 4.59-4.51 (m, 0.5H), 4.50-4.45 (m, 1H), 4.41-4.34 (m, 0.5H), 4.26 (dt, *J* = 10.4, 6.0 Hz, 2.5H), 4.16 (d, *J* = 6.0 Hz, 0.5H), 3.86 (s, 3H), 3.86-3.82 (m, 1H), 3.02 (d, *J* = 13.0 Hz, 0.5H), 2.94 (d, *J* = 13.0 Hz, 0.5H), 3.00-2.90 (m, 0.5H), 2.87-2.80 (m, 1H), 2.40 (d, *J* = 13.0 Hz, 0.5H), 2.31 (d, *J* = 13.0 Hz, 0.5H), 1.56 (s, 1.5H), 1.54 (s, 1.5H), 1.31 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 157.7, 135.1, 133.7, 129.1, 128.8, 125.9, 119.2, 105.5, 82.2, 82.1, 81.7, 81.6, 61.0, 60.8, 57.0, 56.9, 55.3, 52.3, 52.0, 45.3, 45.1, 38.0, 21.1, 23.0, 18.4, 18.2; IR (ATR, neat) 2958, 2870, 1731, 1632, 1605, 1506,

1484, 1449, 1392, 1378, 1326, 1256, 1215, 1150, 1162, 1096, 1028, 980, 924, 891, 836, 818, 745, 666 cm^{-1}; HRMS (ESI) $(M+H)^+$ calcd for $C_{21}H_{27}O_5S$ 391.1574, found 391.1559.

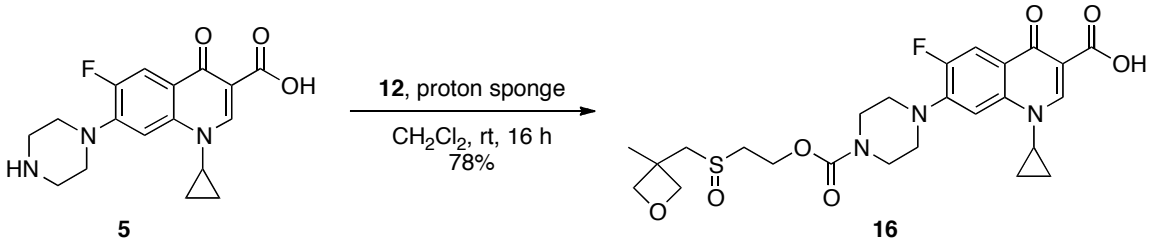


2-(((3-Methyloxetan-3-yl)methyl)sulfinyl)ethyl (4*R*)-4-((3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-Hydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pentanoate (14). A suspension of lithocholic acid (**3**) (375 mg, 0.996 mmol) in CH_2Cl_2 (5 mL) was treated with a solution of sulfoxide **11** (200 mg, 1.12 mmol) in CH_2Cl_2 (5 mL), followed by DMAP (12 mg, 0.98 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (210 mg, 1.10 mmol). The reaction mixture, which became clear after ~15 min, was stirred for 18 h and then concentrated. The residue was purified by chromatography on SiO_2 (5% MeOH/CH_2Cl_2) to provide ester **14** (279 mg, 98%) as a waxy, white solid: mp 49–52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (d, *J* = 6.4 Hz, 1H), 4.50 (d, *J* = 6.0 Hz, 1H), 4.45-4.41 (m, 1H), 4.39 (d, *J* = 6.0 Hz, 1H), 4.37-4.32 (m, 1H), 4.33 (d, *J* = 7.6 Hz, 1H), 3.49 (sept., *J* = 4.8 Hz, 1H), 3.20 (d, *J* = 12.8 Hz, 1H), 2.96 (t, *J* = 5.8 Hz, 2H), 2.74 (d, *J* = 12.8 Hz, 1H), 2.64 (br s, 1H), 2.33–2.23 (m, 1H), 2.21–2.11 (m, 1H), 1.85 (d, *J* = 11.2 Hz, 1H), 1.79–1.54 (m, 6H), 1.51 (s, 3H), 1.50–0.85 (m, 19H), 0.82 (s, 6H), 0.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 82.2, 81.8, 71.3, 61.1, 56.7, 56.4, 55.8, 52.4, 42.6, 42.0, 40.3, 40.0, 38.2, 36.3, 35.7, 35.3, 35.2, 34.4, 30.9, 30.7, 30.4, 28.1, 27.1, 26.3, 24.1, 23.3, 23.3, 20.7, 18.2, 11.9; IR (ATR, neat) 3402, 2928, 2864, 1735, 1449, 1382, 1246, 1160 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd for $C_{31}H_{53}O_5S$ 537.3608, found 537.3595.



15

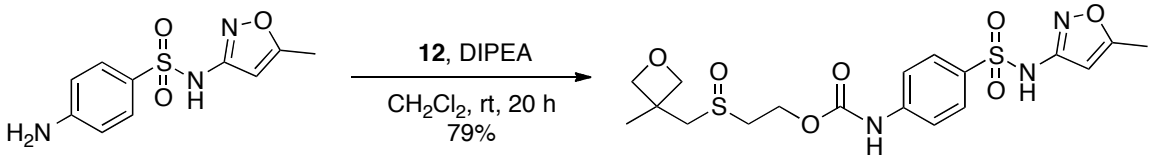
2-(((3-Methyloxetan-3-yl)methyl)sulfinyl)ethyl 2-((2,6-dichloro-3-methylphenyl)amino)benzoate (15). A solution of meclofenamate sodium salt (215 mg, 0.675 mmol) in THF (5.6 mL) and 0.10 mL DMF was treated with **11** (138 mg, 0.777 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (142 mg, 0.743 mmol), and DMAP (8.0 mg, 0.065 mmol) and stirred at rt for 18 h. The reaction mixture was concentrated, and the crude material was purified by chromatography on SiO_2 (50-100% EtOAc-Hexanes followed by 5-10% CH_3OH-EtOAc) to give **15** (165 mg, 54%) as a colorless viscous oil: ^1H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1 H), 7.98 (d, *J* = 8.2 Hz, 1 H), 7.31-7.26 (m, 2 H), 7.11 (d, *J* = 8.2 Hz, 1 H), 6.76 (t, *J* = 7.6 Hz, 1 H), 6.32 (d, *J* = 8.4 Hz, 1 H), 4.87-4.67 (m, 3 H), 4.60 (d, *J* = 6.0 Hz, 1 H), 4.46 (dd, *J* = 10.8, 6.1 Hz, 2 H), 3.33 (d, *J* = 13.0 Hz, 1 H), 3.24-3.12 (m, 2 H), 2.85 (d, *J* = 12.9 Hz, 1 H), 2.39 (s, 3 H), 1.60 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 147.9, 136.6, 134.9, 134.6, 134.3, 131.4, 131.3, 128.8, 127.8, 117.5, 113.9, 110.7, 82.5, 82.0, 61.4, 57.2, 52.8, 38.4, 23.5, 20.7; IR (neat) 3309, 2962, 2869, 2240, 1685, 1582, 1505, 1451, 1380, 1313, 1246, 1233, 1143, 1083, 1035, 977, 908, 808, 726, 700 cm^{-1}; HRMS (ESI) $(M+H)^+$ calcd for $C_{21}H_{24}O_4Cl_2S$ 456.0798, found 456.0780.



5 **16**

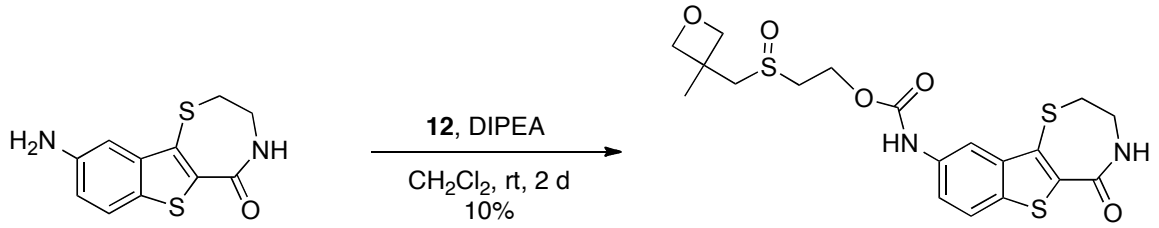
1-Cyclopropyl-6-fluoro-7-(4-((2-(((3-methyloxetan-3-yl)methyl)sulfinyl)-ethoxy)carbonyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (16). A suspension of ciprofloxacin (**5**, 100 mg, 0.30 mmol), mixed carbonate

12 (120 mg, 0.33 mmol), and proton sponge (68 mg, 0.32 mmol) in CH_2Cl_2 (6 mL) was stirred at rt for 16 h (reaction mixture became homogeneous after ~2 h). The solvent was evaporated, and the residue was purified by chromatography on SiO_2 (1–10% MeOH/CH_2Cl_2, eluted ~7%) to provide **16** (125 mg, 78%) as a white solid: mp 193–195 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.89 (br s, 1H), 8.71 (s, 1H), 7.97 (d, *J* = 12.8 Hz, 1H), 7.35 (d, *J* = 7.2 Hz, 1H), 4.77 (d, *J* = 6.4 Hz, 1H), 4.68-4.62 (m, 1H), 4.61 (d, *J* = 6.4 Hz, 1H), 4.55 (app q, *J* = 6.1 Hz, 1H), 4.50 (d, *J* = 6.0 Hz, 1H), 4.46 (d, *J* = 6.4 Hz, 1H), 3.73 (br s, 4H), 3.55 (sept, *J* = 3.6 Hz, 1H), 3.31 (br s, 3H), 3.30 (d, *J* = 12.8 Hz, 1H), 3.09 (t, *J* = 5.6 Hz, 2H), 2.83 (d, *J* = 13.2 Hz, 1H), 1.61 (s, 3H), 1.40 (q, *J* = 6.7 Hz, 2H), 1.22-1.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 166.9, 155.0, 154.6, 152.5, 147.7, 145.7, 145.6, 139.1, 120.4, 120.3, 112.8, 112.5, 108.3, 105.3, 82.5, 82.1, 61.6, 58.6, 53.3, 49.7, 43.9, 38.6, 35.5, 23.6, 8.4; IR (ATR, neat) 3433, 2957, 2873, 1701, 1627, 1492, 1467, 1336, 1243, 1030 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd for $C_{25}H_{31}O_7N_3FS$ 536.1861, found 536.1858.



2-(((3-Methyloxetan-3-yl)methyl)sulfinyl)ethyl (4-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)carbamate (17). To a solution of sulfamethoxazole (**6**, 40 mg, 0.158 mmol) and activated carbonate **12** (75 mg, 0.204 mmol) in CH_2Cl_2 (1 mL) was added *N*,*N*-diisopropylethylamine (40 μL, 0.23 mmol). The reaction mixture was stirred for 20 h and concentrated. The residue was purified by chromatography on SiO_2 (5% MeOH/CH_2Cl_2 +1% AcOH) to provide carbamate **17** (56.9 mg, 79%) as a white solid: mp 163-165 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 9.34 (br. s, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.8 Hz, 2H), 6.23 (s, 1H), 4.71 (d, *J* = 6.0 Hz, 1H), 4.69-4.64 (m, 1H), 4.57 (d, *J* = 5.6 Hz, 1H), 4.51 (td, *J* = 9.0, 3.4 Hz, 1H), 3.29 (d, *J* = 13.2 Hz, 1H), 3.26-3.18 (m, 1H), 3.13-3.07 (m, 1H), 3.04 (d, *J* = 13.2 Hz, 1H), 2.33 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 171.4, 158.7, 153.7, 144.6, 134.1, 129.4, 118.8,

96.3, 82.6, 82.0, 61.5, 58.8, 53.0, 39.1, 23.8, 12.4; IR (ATR, neat) 3055, 2966, 2873, 1733, 1615, 1594, 1536, 1464, 1407, 1320, 1220, 1163, 1071, 1035, 1009, 833, 699 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{24}O_7N_3S_2$ 458.1050, found 458.1045.



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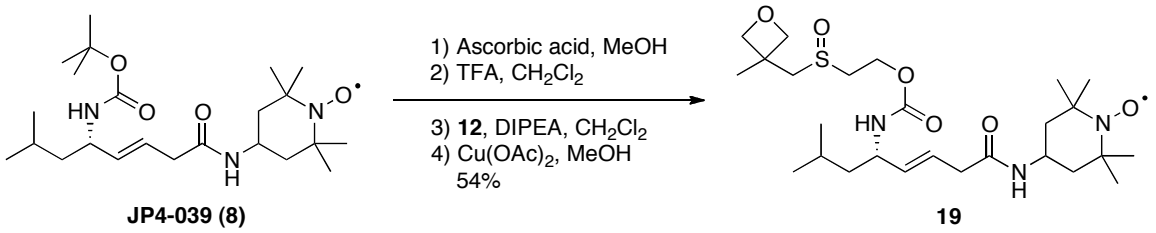
2-(((3-Methyloxetan-3-yl)methyl)sulfinyl)ethyl (5-oxo-2,3,4,5-tetrahydro-benzo[4,5]thieno[2,3-*f*][1,4]thiazepin-9-yl)carbamate (18). A solution of amine[3] (87 mg, 0.35 mmol) in $CHCl_3$ (3 mL) was treated with phthalimidyl carbonate **12** (210 mg, 0.43 mmol), followed by *N,N*-diisopropylethylamine (120 µL, 0.66 mmol). The solution was stirred at rt for 2 d and the solvent was evaporated in vacuo. The crude residue was purified by chromatography on SiO_2 ($MeOH/CH_2Cl_2$, 5:95) to give impure **18**. The impure product was purified by chromatography on reverse phase SiO_2 (ISCO, 4 g C18 column, H_2O/MeCN gradient 5-95% MeCN, eluted at 80%) to give **18** as an off-white solid (14 mg, 10%): R_f 0.3 (5:95 CH_3OH/CH_2Cl_2); mp 236-237 °C; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 10.03 (br. s, 1 H), 8.46 (t, *J* = 5.8 Hz, 1 H), 8.11 (br. s, 1 H), 7.89 (d, *J* = 8.8 Hz, 1 H), 7.54 (dd, *J* = 1.8, 8.8 Hz, 1 H), 4.64 (d, *J* = 6.0 Hz, 1 H), 4.59-4.52 (m, 2 H), 4.43-4.35 (m, 1 H), 4.32 (d, *J* = 5.8 Hz, 1 H), 4.24 (d, *J* = 6.0 Hz, 1 H), 3.66-3.61 (m, 2 H), 3.41-3.38 (m, 2 H), 3.28 (d, *J* = 13.3 Hz, 1H), 3.27-3.17 (m, 1 H), 3.16-3.09 (m, 1 H), 3.06 (d, *J* = 13.2 Hz, 1 H), 1.49 (s, 3 H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 165.0, 153.1, 138.9, 136.5, 132.8, 132.6, 128.1, 123.0, 119.2, 111.1, 81.4, 80.8, 59.6, 57.4, 51.4, 42.4, 37.7, 33.2, 23.3; IR (neat) 3264, 2933, 1717, 1627, 1494, 1450, 1340, 1232 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{23}O_5N_2S_3$ 455.0769, found 455.0753.



JP4-039 (8) 19

2-(((3-Methyloxetan-3-yl)methyl)sulfinyl)ethyl ((*S*,*E*)-8-((1-oxyl-2,2,6,6-tetramethyl-piperidin-4-yl)amino)-2-methyl-8-oxooct-5-en-4-yl)carbamate (19). A solution of JP4-039 (**8**, 100 mg, 0.235 mmol) in MeOH (2 mL) was treated with ascorbic acid (50 mg, 0.28 mmol). The orange mixture became colorless in less than 1 min. Stirring was continued for 20 min, and the solvent was evaporated. The residue was diluted with CH_2Cl_2 (5 mL) and water (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic portion was dried ($MgSO_4$), evaporated, and the crude hydroxylamine was carried on to the deprotection step.

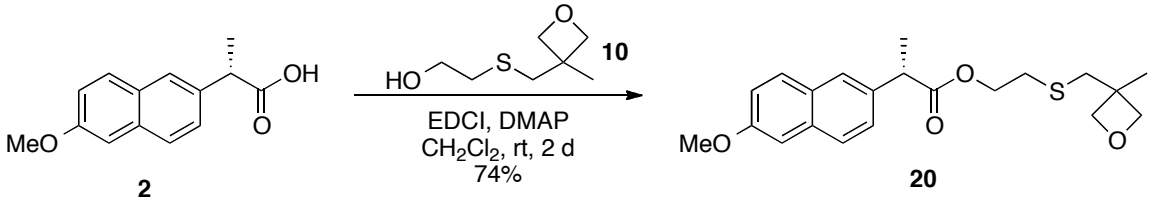
To a solution of the crude hydroxylamine in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (350 µL, 4.69 mmol), and the mixture was stirred 3 h. The solvent and excess acid were evaporated, and the residue was dissolved in EtOAc (10 mL). The organic portion was washed with 5% Na_2CO_3 (2 x 10 mL) and brine (10 mL), dried (Na_2CO_3), and evaporated to give the free amine as an off-white solid.

To the above amine was added a solution of carbonate **12** (60 mg, 0.16 mmol) in CH_2Cl_2 (2 mL), followed by *N*,*N*-diisopropylethylamine (60 µL, 0.35 mmol) upon which there was an immediate color change to dark orange. The mixture was stirred at rt for 18 h, and saturated aqueous $NaHCO_3$ was added. The layers were separated, and the aqueous portion was extracted with EtOAc. The combined organic portion was dried ($MgSO_4$) and evaporated.

The crude residue was dissolved in MeOH (1 mL), and catalytic copper (II) acetate hydrate (~5 mg) was added. The mixture was stirred open to air for 1 h, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 and purified by chromatography on SiO_2 (1% to 10% MeOH in CH_2Cl_2, eluted at 10%) to give nitroxide **19** (46.6 mg, 54%) as a pale orange solid mixture of diastereomers: IR (ATR, neat) 3460, 3285, 2957, 2938, 2869, 1708, 1648, 1537, 1456, 1243, 1178,

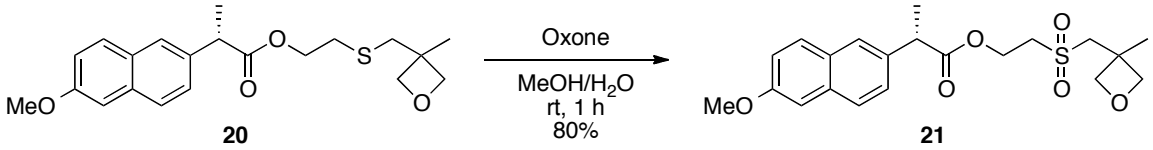
1116, 1035, 973 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd for $C_{26}H_{48}N_3O_6S$ 530.3258, found 530.3255.

A small sample was reduced (ascorbic acid, MeOH) for NMR analysis, and spectra were taken in $CDCl_3$ layered with 5% ascorbic acid in D_2O. Solubility of the hydroxylamine is greater in D_2O than in $CDCl_3$, allowing for the characterization of **19-H**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.80-5.65 (m, 1H), 5.50-5.38 (m, 1H), 4.76 (d, *J* = 5.1 Hz, 1H), 4.70–4.40 (m, 2H), 4.60 (d, *J* = 6.0 Hz, 1H), 4.52 (d, *J* = 6.0 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 1H), 4.23–4.16 (m, 1H), 4.12–4.00 (m, 1H), 3.38-3.28 (m, 1H), 3.07 (br s, 2H), 2.95 (d, *J* = 6.3 Hz, 2H), 2.86 (dd, *J* = 12.0, 7.1 Hz, 1H), 1.96-1.86 (m, 1H), 1.70-1.50 (m, 1H), 1.60 (s, 3H), 1.45–1.10 (m, 12H), 0.94 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$,) δ 168.8, 153.7, 134.9, 81.2, 80.7, 60.3, 52.0, 50.5, 50.4, 42.2, 41.2, 37.0, 28.1, 23.1, 22.4, 21.0; HRMS (ESI) $[M+H]^+$ calcd for $C_{26}H_{48}N_3O_6S$ 530.3258, found 530.3261.

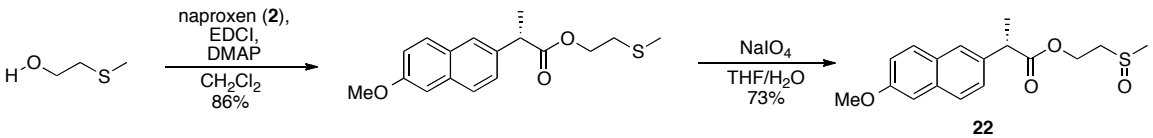


2-(((3-Methyloxetan-3-yl)methyl)thio)ethyl (*S*)-2-(6-methoxynaphthalen-2-yl)propanoate (20). To a solution of (*S*)-naproxen (**2**). (460 mg, 2.00 mmol) in CH_2Cl_2 (20 mL) were added thioether **10** (375 mg, 2.31 mmol), EDCI (425 mg, 2.22 mmol) and DMAP (25 mg, 0.20 mmol). The mixture was stirred at rt for 2 d, and the solvent was evaporated. The residue was purified by chromatography on SiO_2 (10–50% EtOAc/hexanes, eluted ~25–30%) to provide ester **20** (555 mg, 74%) as a colorless, waxy solid: mp 37-38 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 1.5 Hz, 1H), 7.40 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.14 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.11 (d, *J* = 2 Hz, 1H), 4.34 (dd, *J* = 7.5, 6.0 Hz, 2H), 4.28–4.22 (m, 4H), 3.91 (s, 3H), 3.87 (q, *J* = 7.0 Hz, 1H), 2.75 (app q, *J* = 11.7 Hz, 2H), 2.70 (td, *J* = 5.4, 1.8 Hz, 2H), 1.58 (d, *J* = 7.5 Hz, 3H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 157.8, 135.6, 133.8, 129.4, 129.0, 127.3, 126.3, 126.1, 119.2, 105.4, 81.9, 81.9, 64.2, 55.4,

45.6, 42.3, 40.0, 32.0, 23.0, 18.7; IR (ATR, neat) 2959, 2934, 2866, 1730, 1633, 1606, 1264, 1231, 1175, 1156, 1031, 977, 854 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd for $C_{21}H_{27}O_4S$ 375.1625, found 375.1610.



2-(((3-Methyloxetan-3-yl)methyl)sulfonyl)ethyl (*S*)-2-(6-methoxynaphthalen-2-yl)propanoate (21). To a suspension of Oxone® (330 mg, 0.537 mmol) in water (1 mL) at ~10 °C was added a solution of thioether **20** (100 mg, 0.267 mmol) in MeOH (1 mL). The mixture was warmed to rt and stirred 1 h. The methanol was evaporated, and the mixture was diluted with water (~5 mL) and extracted with CH_2Cl_2 (5 x 5 mL). The combined organic portion was dried ($MgSO_4$) and evaporated, and the residue was purified by chromatography on SiO_2 (30–70% EtOAc/hexanes) to provide sulfone **21** (86.4 mg, 80%) as a colorless oil, which solidified on standing: mp 105-107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 10.4, 9.2 Hz, 2H), 7.62 (s, 1H), 7.33 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.17 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.10 (d, *J* = 2 Hz, 1H), 4.62 (ddd, *J* = 14.8, 6.8, 4.0 Hz, 1H), 4.43 (ddd, *J* = 14.8, 6.1, 3.6 Hz, 1H), 4.29 (d, *J* = 6.4 Hz, 2H), 4.11 (d, *J* = 7.2 Hz, 2H), 3,94 (d, *J* = 6.4 Hz, 1H), 3.91 (s, 3H), 3.88 (q, *J* = 7.2 Hz, 1H), 3.23–3.09 (m, 2H), 2.92, 2.59 (ABq, *J* = 14 Hz, 2H), 1.58 (d, *J* = 6.8 Hz, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 158.2, 135.3, 133.9, 129.3, 129.0, 127.8, 126.1, 125.9, 119.8, 105.7, 82.2, 81.9, 61.0, 58.7, 55.5, 55.3, 45.6, 37.4, 23.1, 18.8; IR (ATR, neat) 2969, 2936, 2875, 1735, 1606, 1317, 1265, 1176, 1126 ,945, 855, 829 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd for $C_{21}H_{27}O_6S$ 407.1523, found 407.1509.



(2*S*)-2-(Methylsulfinyl)ethyl 2-(6-methoxynaphthalen-2-yl)propanoate (22). A solution of 2-(methylthio)ethanol (110 mg, 1.19 mmol) and naproxen (250 mg, 1.09 mmol) in CH_2Cl_2 at 0 °C was treated with EDCI (229 mg, 1.19 mmol) and DMAP (13 mg, 0.11 mmol), warmed to room temperature, and stirred overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with sat. NH_4Cl, sat. $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated to give a yellow oil. The compound was purified by chromatography on SiO_2 (ISCO, 24 g column, liquid load in CH_2Cl_2, 0-20% MeOH/ CH_2Cl_2) to give the product as a white solid (285 mg, 86%): mp 102-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.68 (s, 1H), 7.41 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.12 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.12 (d, *J* = 2.0 Hz, 1H), 4.31-4.20 (ddd, *J* = 3.2, 6.4, 13 Hz, 2H), 3.91 (s, 3H), 3.89 (ap dd, *J* = 13, 6.6 Hz, 1H), 2.66 (t, *J* = 6.8 Hz, 2H), 2.06 (s, 3H), 1.59 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 156.6, 134.5, 132.7, 128.2, 127.9, 126.1, 125.2, 124.9, 118.0, 104.5, 62.5, 54.3, 44.4, 31.3, 17.5, 14.7; IR (ATR, neat) 2976, 2937, 2839, 1731, 1606, 1506, 1484, 1392, 1325, 1264, 1175, 1157 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd for $C_{17}H_{20}O_3NaS$ 327.1024, found 327.1025.

A solution of the thioether (129 mg, 0.424 mmol) in THF (1 mL) at 0 °C was treated with $NaIO_4$ (92 mg, 0.43 mmol) in H_2O (0.5 mL). The reaction was allowed to warm to rt as it stirred overnight. The reaction mixture was passed through Celite and eluted with THF and MeOH and concentrated to give a white solid (147 mg). The crude material was adsorbed onto SiO_2 and purified by chromatography on SiO_2 (ISCO, 4 g gold column, 0-20% MeOH/CH_2Cl_2) to give the product as a white solid (99 mg, 73%): mp 100-103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 1.5 Hz, 1H), 7.69 (d, *J* = 2.5 Hz, 1H), 7.65 (br s, 1H), 7.37 (ddd, *J* = 6.8, 2.0, 2.0, 1H), 7.14 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.11 (d, *J* = 2.0 Hz, 1H), 4.55 (ddd, *J* = 9.6, 9.6, 4.0 Hz, 1 H), 4.50-4.42 (m, 1H), 3.91 (s, 3H), 3.87 (dd, *J* = 15, 7.3 Hz, 1H), 2.99-2.93 (m, 0.5H), 2.89-2.83 (m, 1.5H), 2.41 (s, 1.5H), 2.40 (s, 1.5H), 1.59 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 156.7, 134.0, 133.9, 132.7, 128.2, 127.9, 126.3, 125.04, 125.02, 118.1, 104.6, 56.3, 56.2, 54.3, 52.4, 52.2, 44.3, 44.2, 37.9, 17.3, 17.2; IR (ATR, neat) 3455,

2977, 1732, 1632, 1606, 1485, 1392, 1326, 1265, 1176, 1158, 1031, 856, 815, 688 cm^{-1}; HRMS (ESI) [M+H]+ calcd for $C_{17}H_{21}O_4S$ 321.1155, found 321.1151.

Stability of MMS-350

A sample of MMS-350 (**1**, 4 mg) was dissolved in H_2O (HPLC grade, 1 mL) and vortexed for 10 s. The sample was monitored by LC/MS/ELS at the following time points: 1 d, 3 d, 4 d, 7 d, 2 weeks, 1 month, 2 months, 3 months, and 6 months. After 6 months, the sample was 99% pure by ELS, and it was deemed stable as an aqueous solution.

Solubility Measurements

General solubility procedure A. A > 5 mg sample of a test compound was added to a plastic Eppendorf tube, diluted with H_2O (1 mL), vortexed for 10 s, and rotated in an end-over-end rotator for 24 h at 30 °C. The tubes were then centrifuged at 4200 rpm for 20 min, and the solution was removed with a 1 mL syringe, filtered through a 0.45 μm filter into a high-recovery vial, and then 2 x 400 μL aliquots were transferred into 2 tared LCMS vials. The vials were dried in a Genevac evaporator for 24 h, weighed, and the mass difference was used to calculate the solubility.

General solubility procedure B. This solubility procedure follows procedure A, except that the compounds were added to a glass autosampler vial for testing rather than a plastic Eppendorf tube. This was a necessary change for the more lipophilic compounds to improve reproducibility.

Solubility of 2. This compound was tested using *general solubility procedure B* with the following changes: The sample was dissolved in 10 mL of H_2O and 4 mL aliquots were used.

Trial	Amount in 10 mL H_2O (mg)	Solubility A (mg/mL)	Solubility B (mg/mL)	Avg. (mg/mL)
1	10.2	0.065	0.020	0.043
Avg (mM)				**0.17 mM**

Solubility of 3. This compound was tested using *general solubility procedure A*, and the mass recovery was undetectable. This is consistent with the reported solubility of 0.05 μM.

Solubility of 4. This compound was tested using *general solubility procedure A*.

Trial	Amount in 1 mL H_2O (mg)	Solubility A (mg/mL)	Solubility B (mg/mL)	Avg. (mg/mL)
1	6.0	0.58	0.68	0.63
2	5.8	0.45	0.45	0.45
3	5.5	0.58	0.60	0.59
Avg. (mg/mL)				0.55
Std. Dev.				0.08
Avg (mM)				**1.9 mM**

Solubility of 5. This compound was tested using *general solubility procedure B* with the following modification: the compound was dissolved in 10 mL water and 3 mL aliquots were used in the measurements.

Trial	Amount in 10 mL H_2O (mg)	Solubility A (mg/mL)	Solubility B (mg/mL)	Avg. (mg/mL)
1	13	0.079	0.013	0.05

Avg (mM)				**0.09 mM**

Solubility of 6. This compound was tested using *general solubility procedure B* with the following modification: the compound was dissolved in 10 mL water and 3 mL aliquots were used in the measurements.

Trial	**Amount in 1 mL H_2O (mg)**	**Solubility A (mg/mL)**	**Solubility B (mg/mL)**	**Avg. (mg/mL)**
1	51	0.53	0.57	0.55
Avg (mM)				**1.0 mM**

Solubility of 7. This compound was tested using *general solubility procedure A*.

Trial	**Amount in 1 mL H_2O (mg)**	**Solubility A (mg/mL)**	**Solubility B (mg/mL)**	**Avg. (mg/mL)**
1	5.0	0	0.18	0.088
2	6.2	0.050	0.13	0.088
3	5.2	0.025	0.025	0.025
Avg. (mg/mL)				0.067
Std. Dev.				0.03
Avg (mM)				**0.21 mM**

Solubility of 8. This compound was tested using *general solubility procedure B*.

Trial	**Amount in 1 mL H_2O (mg)**	**Solubility A (mg/mL)**	**Solubility B (mg/mL)**	**Avg. (mg/mL)**

1	5.8	0.30	0.30	0.30
2	5.7	0.28	0.25	0.26
3	5.5	0.18	0.19	0.18
Avg. (mg/mL)				0.25
Std. Dev.				0.07
Avg (mM)				**0.58 mM**

Solubility of 13 by mass recovery & UV. These samples were tested using *general solubility procedure A* for mass recovery, and they were compared to the results of the UV analysis. For the UV analysis, the same sample was used (i.e., trial 3, solubility B). The molar absorptivity of **13** used in the UV analysis was calculated from a known sample concentration, and was ε=62.833 $mM^{-1}cm^{-1}$

Trial	**Amount in 1 mL H_2O (mg)**	**Solubility A (mg/mL)**	**Solubility B (mg/mL)**	**Avg. (mg/mL)**
1	10.5	0.88	0.93	0.90
2	7.21	0.65	0.75	0.70
3	10.3	0.85	0.88[a]	0.87
Avg. (mg/mL)				0.82
Std. Dev.				0.09
Avg (mM)				**2.1 mM**

[a]This value was calculated via UV analysis.

Solubility of 14. This compound was tested using *general solubility procedure B* with the addition of a 1 h sonication prior to subjecting to the end-over-end rotator to break up the detergent–like emulsion.

Trial	**Amount in 1**	**Solubility A**	**Solubility B**	**Avg.**

	mL H_2O (mg)	**(mg/mL)**	**(mg/mL)**	**(mg/mL)**
1	5.0	0.22	0.10	0.16
2	7.1	0.36	0.33	0.34
3	8.6	0.35	n/a[a]	0.35
4	8.9	0.2	0.23	0.21
Avg. (mg/mL)				0.28
Std. Dev.				0.09
Avg (mM)				**0.48 mM**

[a]This sample was lost due to a clogged filter. Sample A was solely used for trial 3.

Solubility of 15. This compound was tested using *general solubility procedure B.*

Trial	**Amount in 1 mL H_2O (mg)**	**Solubility A (mg/mL)**	**Solubility B (mg/mL)**	**Avg. (mg/mL)**
1	6.6	0.20	0.30	0.25
2	5.2	0.38	0.13	0.25
3	6.7	0.25	0.23	0.24
Avg. (mg/mL)				0.26
Std. Dev.				0.006
Avg (mM)				**0.54 mM**

Solubility of 16. This compound was tested using *general solubility procedure B*.

Trial	**Amount in 1 mL H_2O (mg)**	**Solubility A (mg/mL)**	**Solubility B (mg/mL)**	**Avg. (mg/mL)**

1	5.0	0.13	0.13	0.13
2	5.0	0.20	0.30	0.25
3	5.5	0.18	0.20	0.19
Avg. (mg/mL)				0.19
Std. Dev.				0.05
Avg (mM)				**0.35 mM**

Solubility of 17. This compound was tested using *general solubility procedure B*.

Trial	**Amount in 1 mL H_2O (mg)**	**Solubility A (mg/mL)**	**Solubility B (mg/mL)**	**Avg. (mg/mL)**
1	6.7	1.18	1.10	1.14
2	5.5	0.93	n/a[a]	0.93
3	6.4	0.95	0.93	0.94
Avg. (mg/mL)				1.0
Std. Dev.				0.098
Avg (mM)				**2.2 mM**

[a]This sample was lost due to a handling error, and sample A was solely used for this trial.

Solubility of 18. This compound was tested using *general solubility procedure A*.

Trial	**Amount in 1**	**Solubility A**	**Solubility B**	**Avg.**

	mL H_2O (mg)	**(mg/mL)**	**(mg/mL)**	**(mg/mL)**
1	5.0	0.30	0.40	0.35
2	5.1	0.43	0.63	0.53
Avg. (mg/mL)				0.44
Std. Dev.				0.09
Avg (mM)				**0.96 mM**

Solubility of 19. This compound was tested using *general solubility procedure A*.

Trial	**Amount in 1 mL H_2O (mg)**	**Solubility A (mg/mL)**	**Solubility B (mg/mL)**	**Avg. (mg/mL)**
1	30.3	24.8	24.4	24.6
2	29.9	24.9	24.4	24.7
3	24.2	21.2	21.0	21.1
Avg. (mg/mL)				23.5
Std. Dev.				1.7
Avg (mM)				**44.4 mM**

Solubility of 20. This compound was tested using *general solubility procedure A*.

Trial	**Amount in 1**	**Solubility A**	**Solubility B**	**Avg.**

	mL H_2O (mg)	**(mg/mL)**	**(mg/mL)**	**(mg/mL)**
1	11.2	0.025	0.10	0.063
2	5.8	0	0.13	0.063
Avg. (mg/mL)				0.063
Std. Dev.				0
Avg (mM)				**0.17 mM**

Solubility of 21. This compound was tested using *general solubility procedure A*.

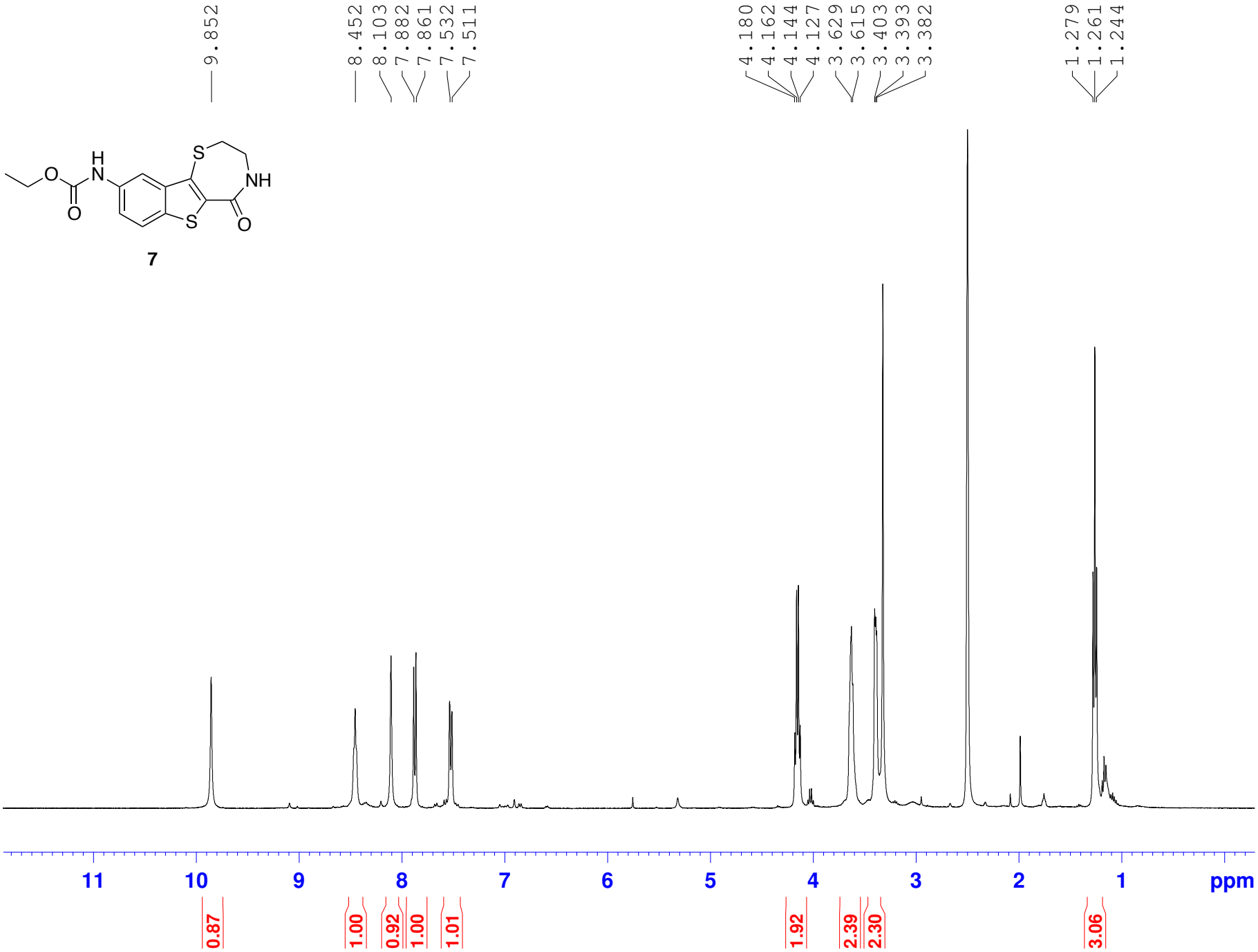
Trial	**Amount in 1 mL H_2O (mg)**	**Solubility A (mg/mL)**	**Solubility B (mg/mL)**	**Avg. (mg/mL)**
1	5.1	0.23	0.23	0.23
2	6.9	0.025	0.025	0.025
Avg. (mg/mL)				0.13
Std. Dev.				0.1
Avg (mM)				**0.31 mM**

Solubility of 22. This compound was tested using *general solubility procedure A*.

Trial	**Amount in 1**	**Solubility A**	**Solubility B**	**Avg.**

	mL H_2O (mg)	**(mg/mL)**	**(mg/mL)**	**(mg/mL)**
1	5.70	0.17	0.18	**0.18**
2	5.19	0.30	0.30	**0.30**
3	5.35	0.27	0.38	**0.32**
Avg. (mg/mL)				0.27
Std. Dev.				0.06
Avg (mM)				**0.83 mM**

NMR Spectra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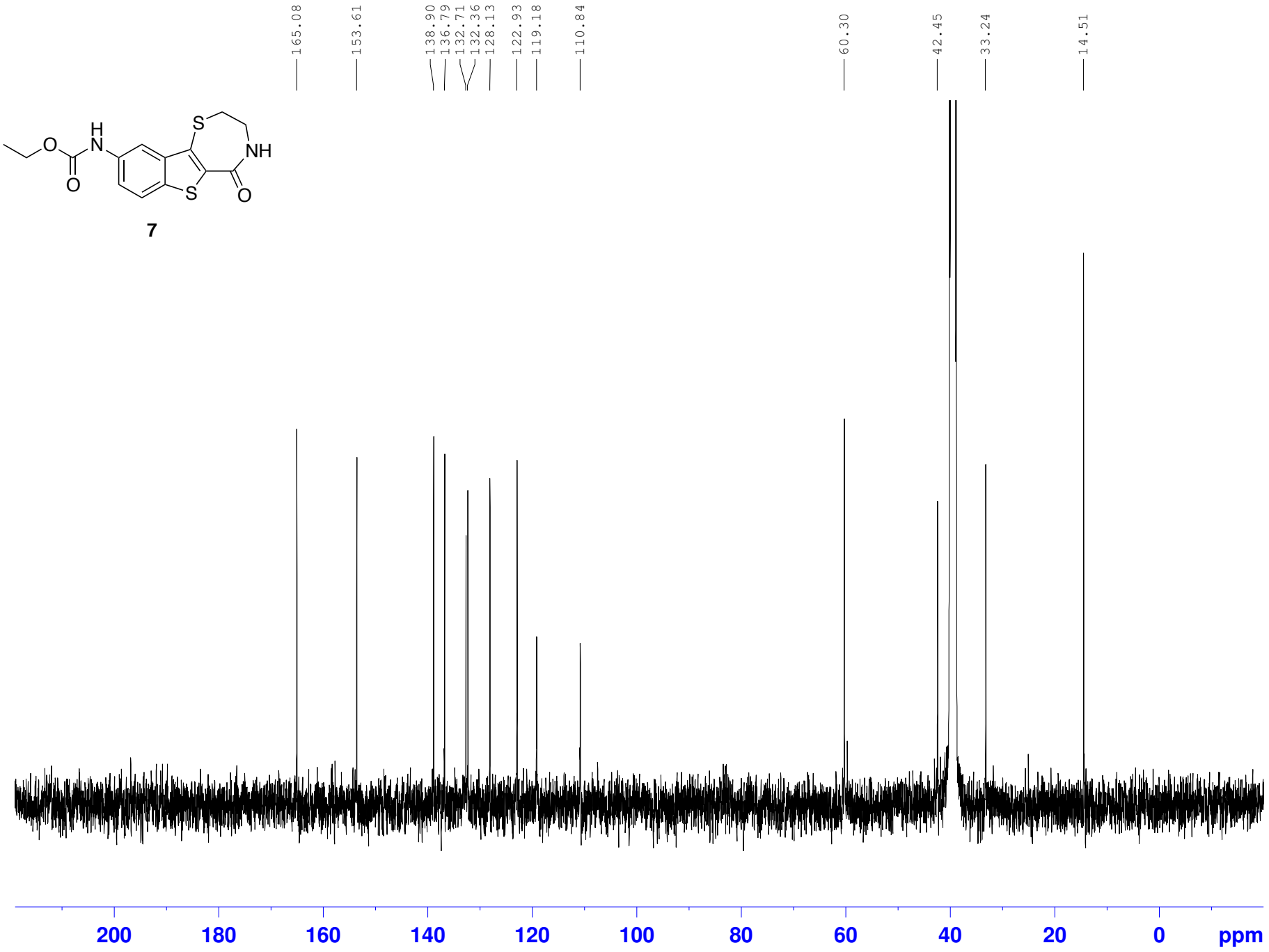
8.103
7.882
7.861
7.532
7.511
4.180
4.162
4.144
4.127
3.629
3.615
3.403
3.393
3.382
1.279
1.261
1.244
O
H
N
O
S
NH
O
S
11
10
9
8
7
6
5
4
3
2
1
ppm
0.87
1.00
0.92
1.00
1.01
1.92
2.39
2.30
3.06

7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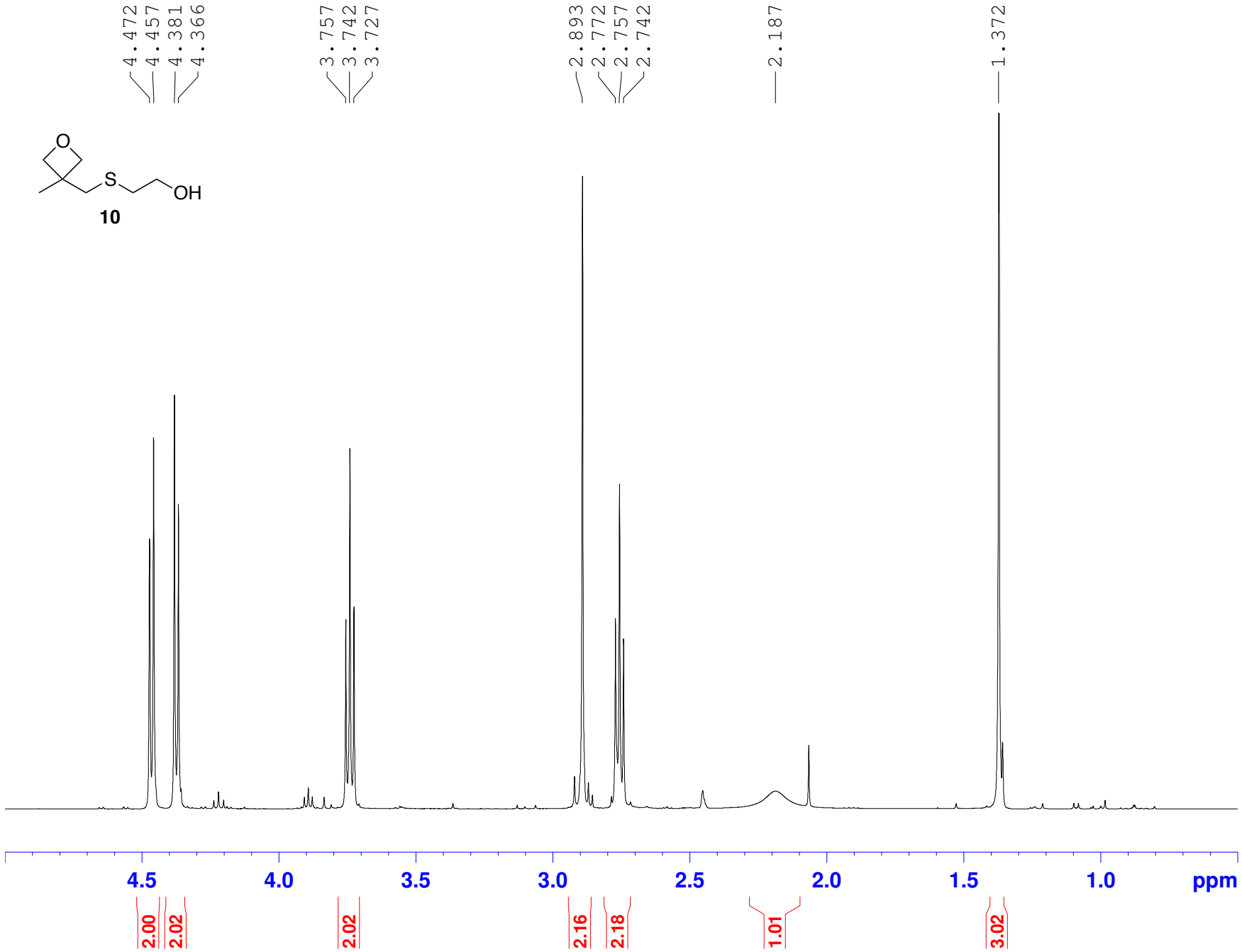
138.90
136.79
132.71
132.36
128.13
122.93
119.18
110.84
60.30
42.45
33.24
14.51
H
N
O
O
S
NH
S
O
200
180
160
140
120
100
80
60
40
20
0
ppm

7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4.381
4.366
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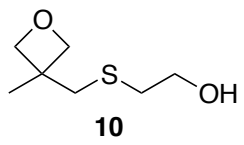
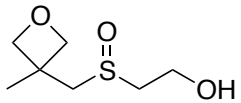
3.742
3.727
2.893
2.772
2.757
2.742
2.187
1.372
O
S
OH
10
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.00
2.02
2.02
2.16
2.18
1.01
3.02


O
S
OH

10

82.02
60.73
41.79
40.22
36.88
23.19
200
180
160
140
120
100
80
60
40
20
0
ppm


O
O
S
OH

11

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4.684
4.670
4.532
4.512
4.398
4.390
4.378
4.370
4.356
4.348
4.335
4.328
4.274
3.961
3.267
3.259
3.223
3.215
2.908
2.902
2.884
2.876
2.868
2.861
2.808
2.764
1.504
9
8
7
6
5
4
3
2
1
ppm
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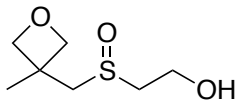
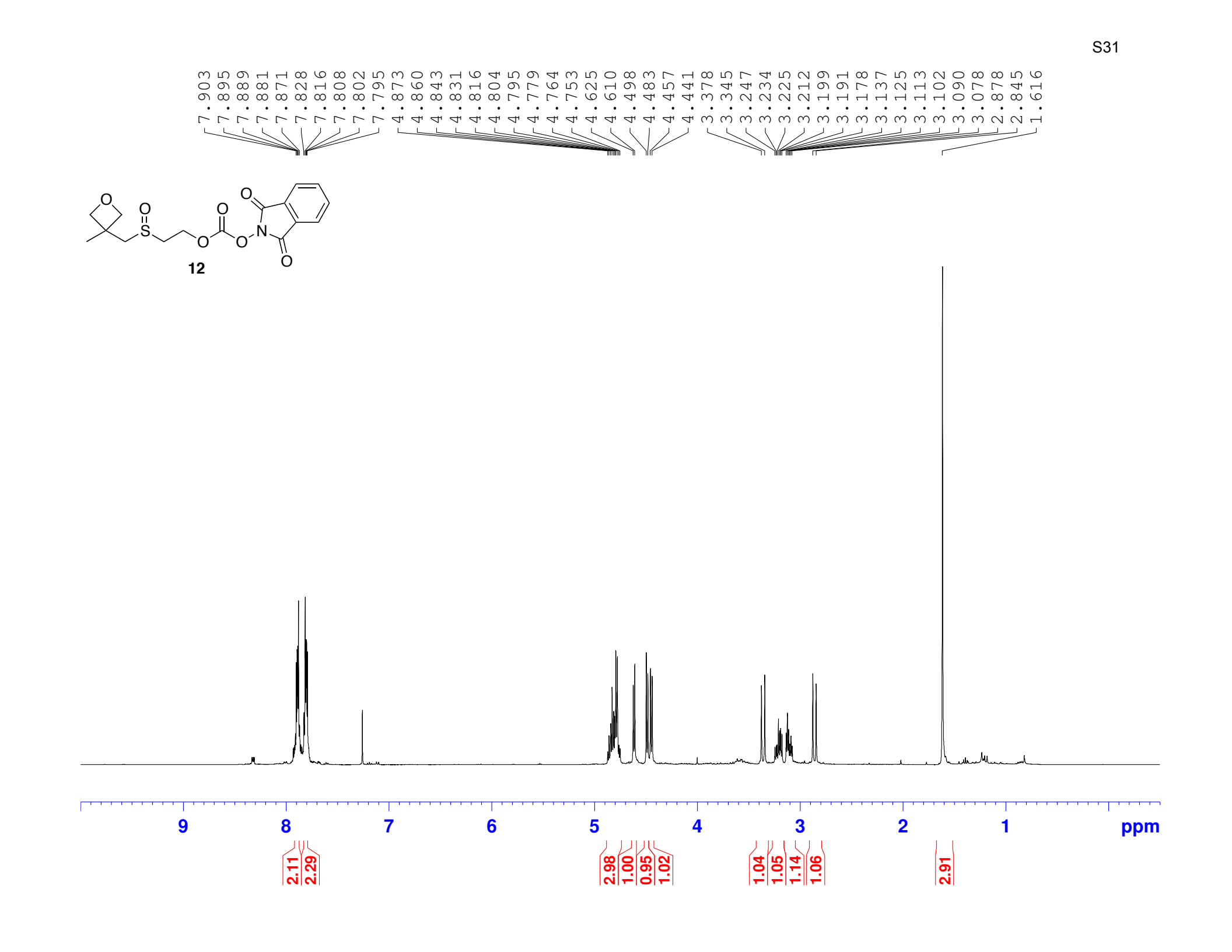
1.00
1.01
1.05
0.95
2.16
1.09
2.09
1.05
3.00


O
O
S
OH

11

82.30
81.82
61.00
55.49
55.24
55.21
38.29
23.42
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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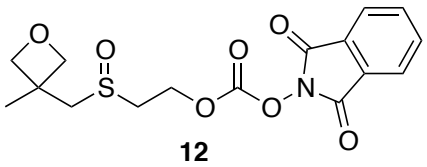
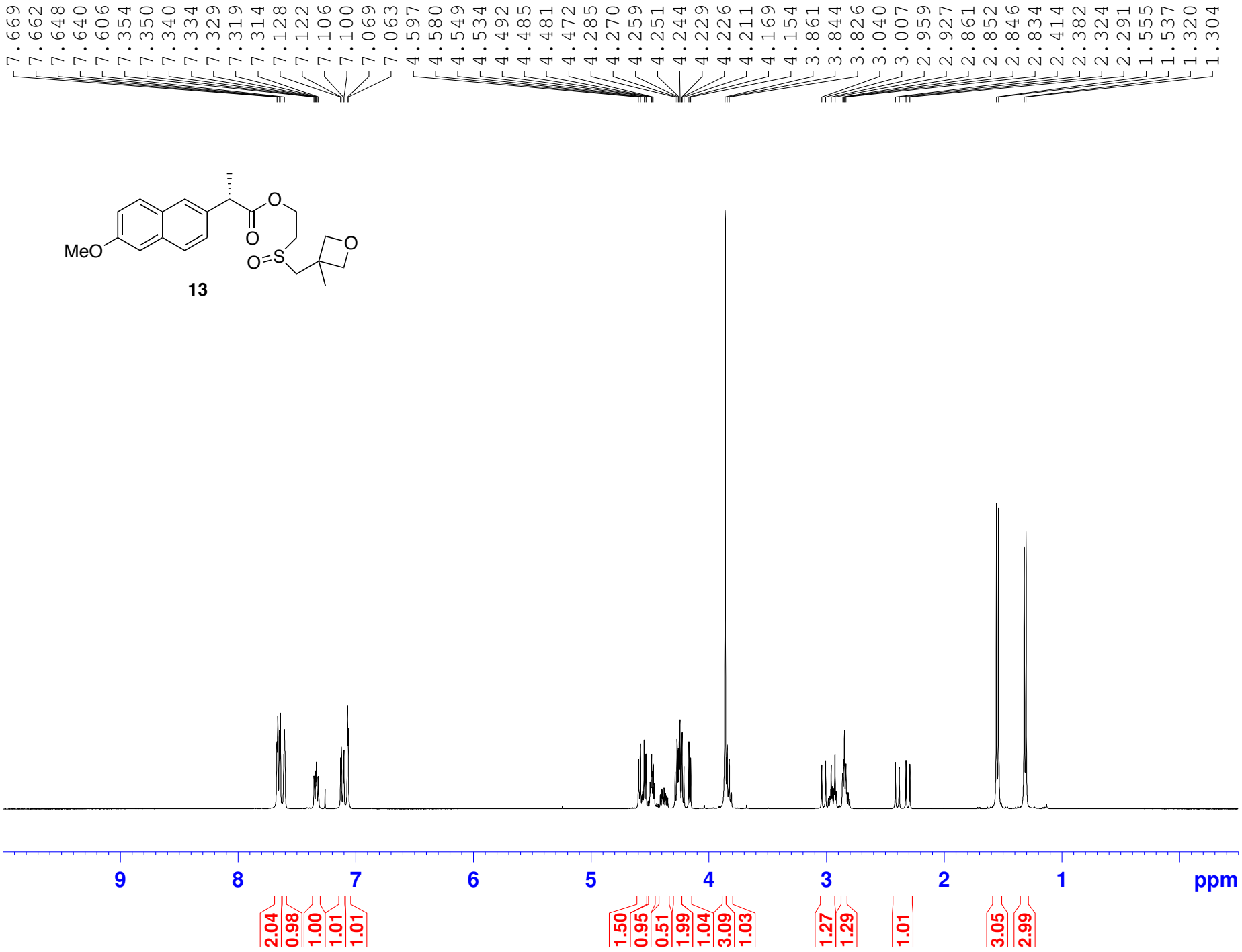
7.881
7.871
7.828
7.816
7.808
7.802
7.795
4.873
4.860
4.843
4.831
4.816
4.804
4.795
4.779
4.764
4.753
4.625
4.610
4.498
4.483
4.457
4.441
3.378
3.345
3.247
3.234
3.225
3.212
3.199
3.191
3.178
3.137
3.125
3.113
3.102
3.090
3.078
2.878
2.845
1.616
12
9
8
7
6
5
4
3
2
1
ppm
2.11
2.29
2.98
1.00
0.95
1.02
1.04
1.05
1.14
1.06
2.91



12

161.29
152.18
135.17
128.62
124.28
82.43
81.93
63.33
61.57
51.62
38.50
23.48
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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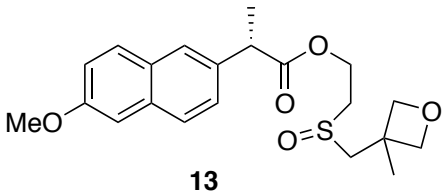
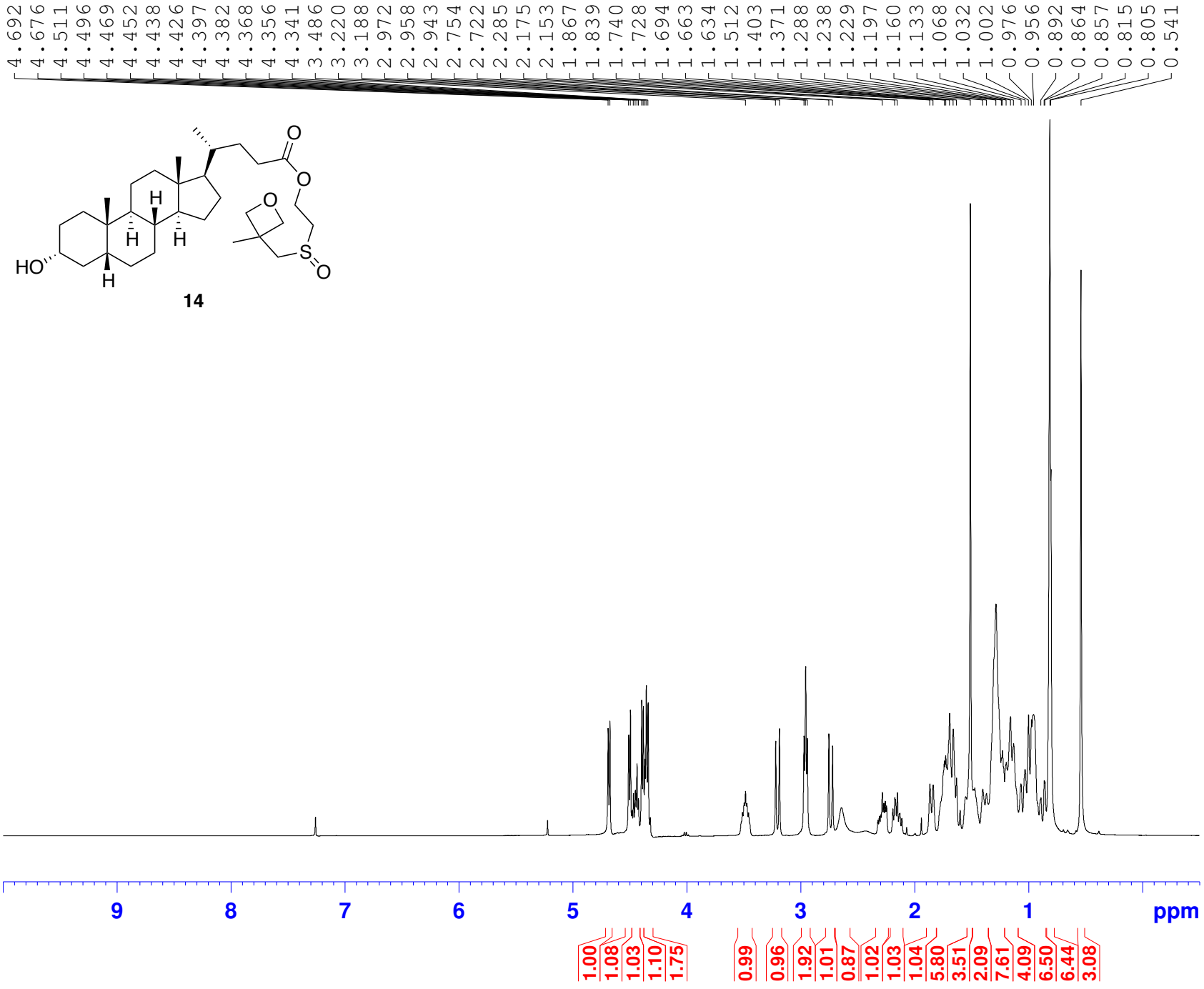
7.606
7.354
7.350
7.340
7.334
7.329
7.319
7.314
7.128
7.122
7.106
7.100
7.069
7.063
4.597
4.580
4.549
4.534
4.492
4.485
4.481
4.472
4.285
4.270
4.259
4.251
4.244
4.229
4.226
4.211
4.169
4.154
3.861
3.844
3.826
3.040
3.007
2.959
2.927
2.861
2.852
2.846
2.834
2.414
2.382
2.324
2.291
1.555
1.537
1.320
1.304
MeO
O
O
O=S
O
13
9
8
7
6
5
4
3
2
1
ppm
2.04
0.98
1.00
1.01
1.01
1.50
0.95
0.51
1.99
1.04
3.09
1.03
1.27
1.29
1.01
3.05
2.99


MeO
O
O
O=S
O

13

174.02
157.73
135.08
133.66
129.14
128.76
127.27
125.92
119.17
105.50
82.16
82.05
81.70
81.62
60.96
60.78
57.03
56.87
55.25
52.33
52.03
45.28
45.14
38.01
37.96
23.10
23.02
18.37
18.22
200
180
160
140
120
100
80
60
40
20
0
ppm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4.452
4.438
4.426
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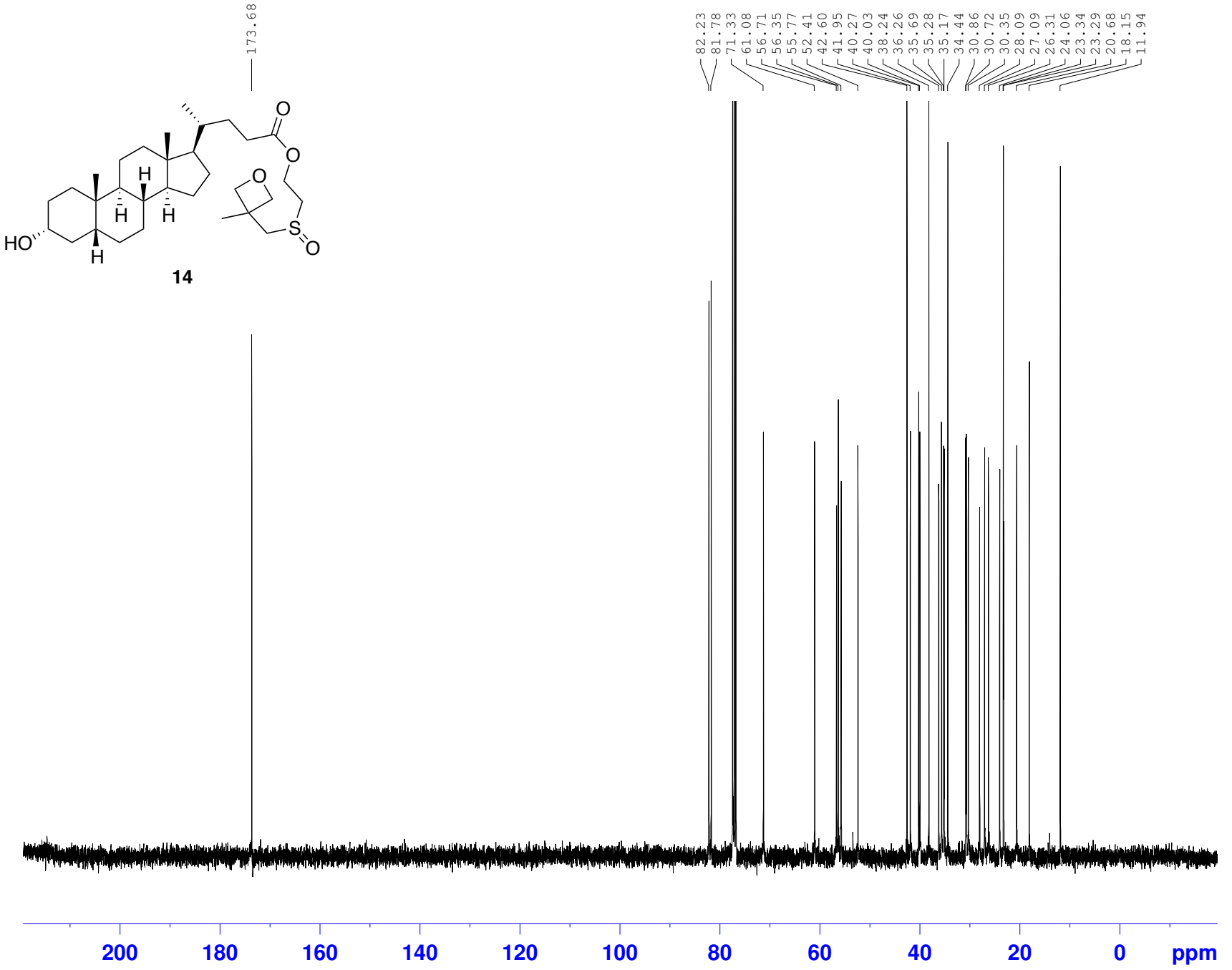
4.368
4.356
4.341
3.486
3.220
3.188
2.972
2.958
2.943
2.754
2.722
2.285
2.175
2.153
1.867
1.839
1.740
1.728
1.694
1.663
1.634
1.512
1.403
1.371
1.288
1.238
1.229
1.197
1.160
1.133
1.068
1.032
1.002
0.976
0.956
0.892
0.864
0.857
0.815
0.805
0.541
HO
H
H
H
H
O
O
O
S
O
9
8
7
6
5
4
3
2
1
ppm
1.00
1.08
1.03
1.10
1.75
0.99
0.96
1.92
1.01
0.87
1.02
1.03
1.04
5.80
3.51
2.09
7.61
4.09
6.50
6.44
3.08

14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71.33
61.08
56.71
56.35
55.77
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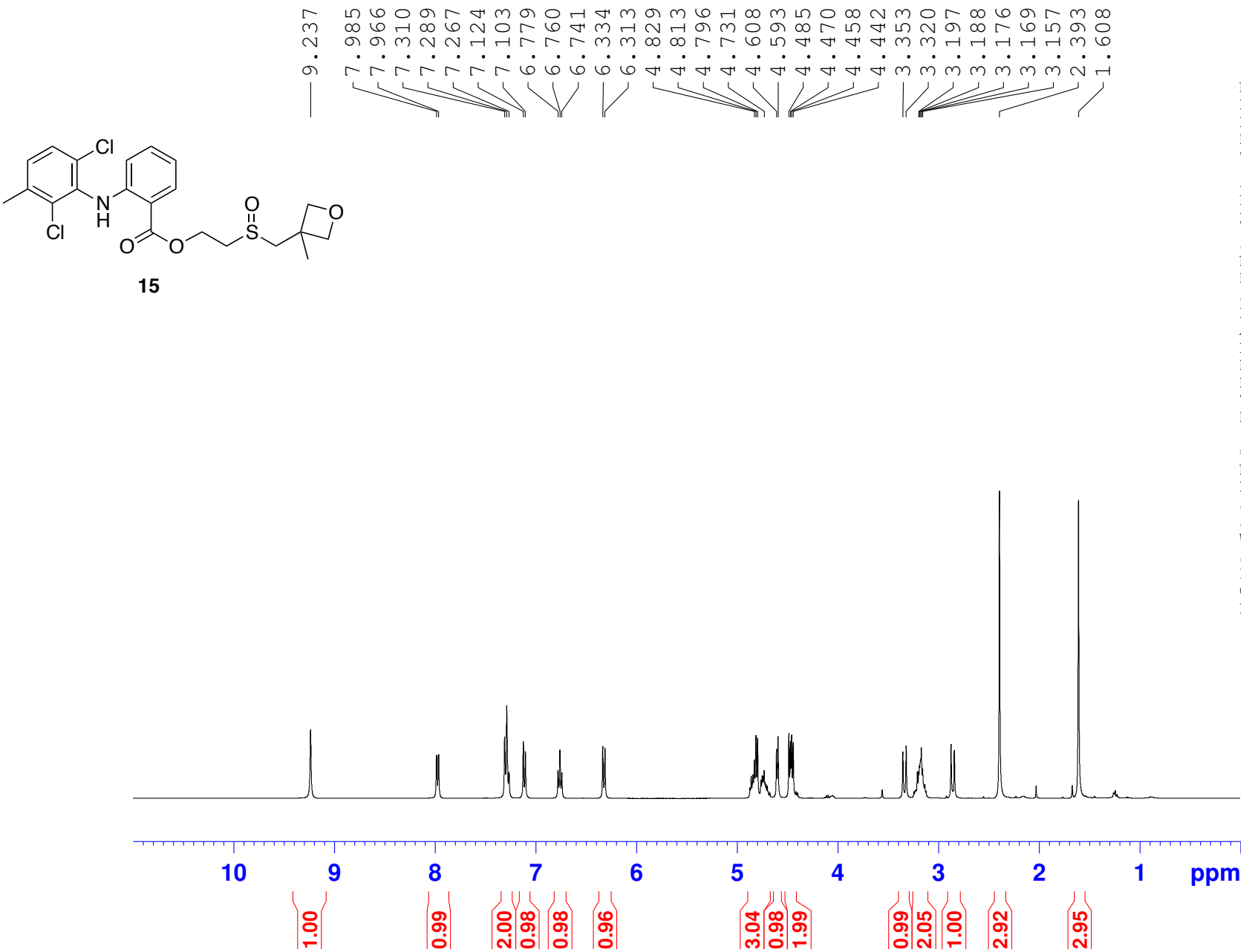
42.60
41.95
40.27
40.03
38.24
36.26
35.69
35.28
35.17
34.44
30.86
30.72
30.35
28.09
27.09
26.31
24.06
23.34
23.29
20.68
18.15
11.94
HO
H
H
H
H
O
O
O
S
O
200
180
160
140
120
100
80
60
40
20
0
ppm

14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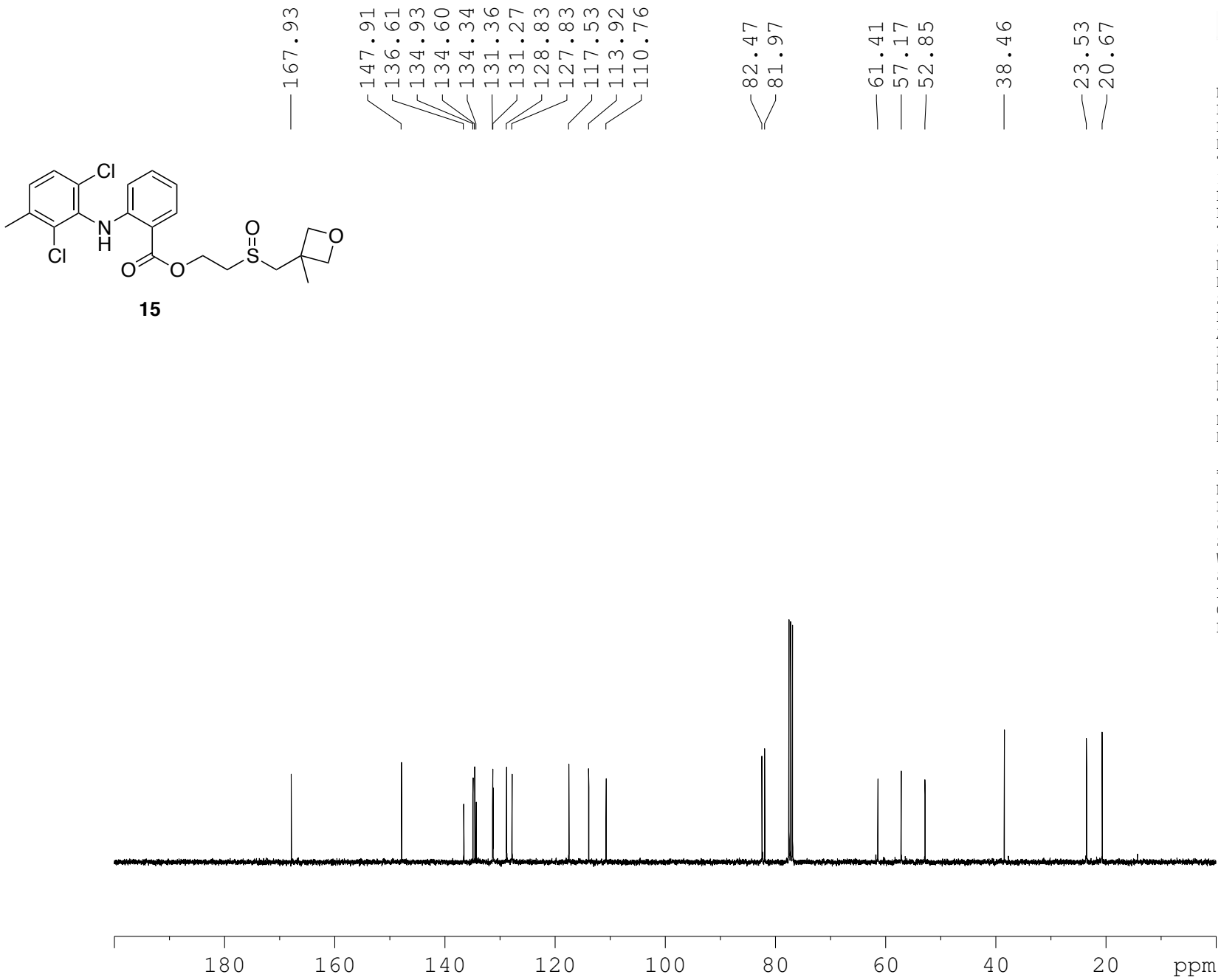
7.289
7.267
7.124
7.103
6.779
6.760
6.741
6.334
6.313
4.829
4.813
4.796
4.731
4.608
4.593
4.485
4.470
4.458
4.442
3.353
3.320
3.197
3.188
3.176
3.169
3.157
2.393
1.608
Cl
N
H
Cl
O
O
O
S
O
10
9
8
7
6
5
4
3
2
1
ppm
1.00
0.99
2.00
0.98
0.98
0.96
3.04
0.98
1.99
0.99
2.05
1.00
2.92
2.95

15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134.34
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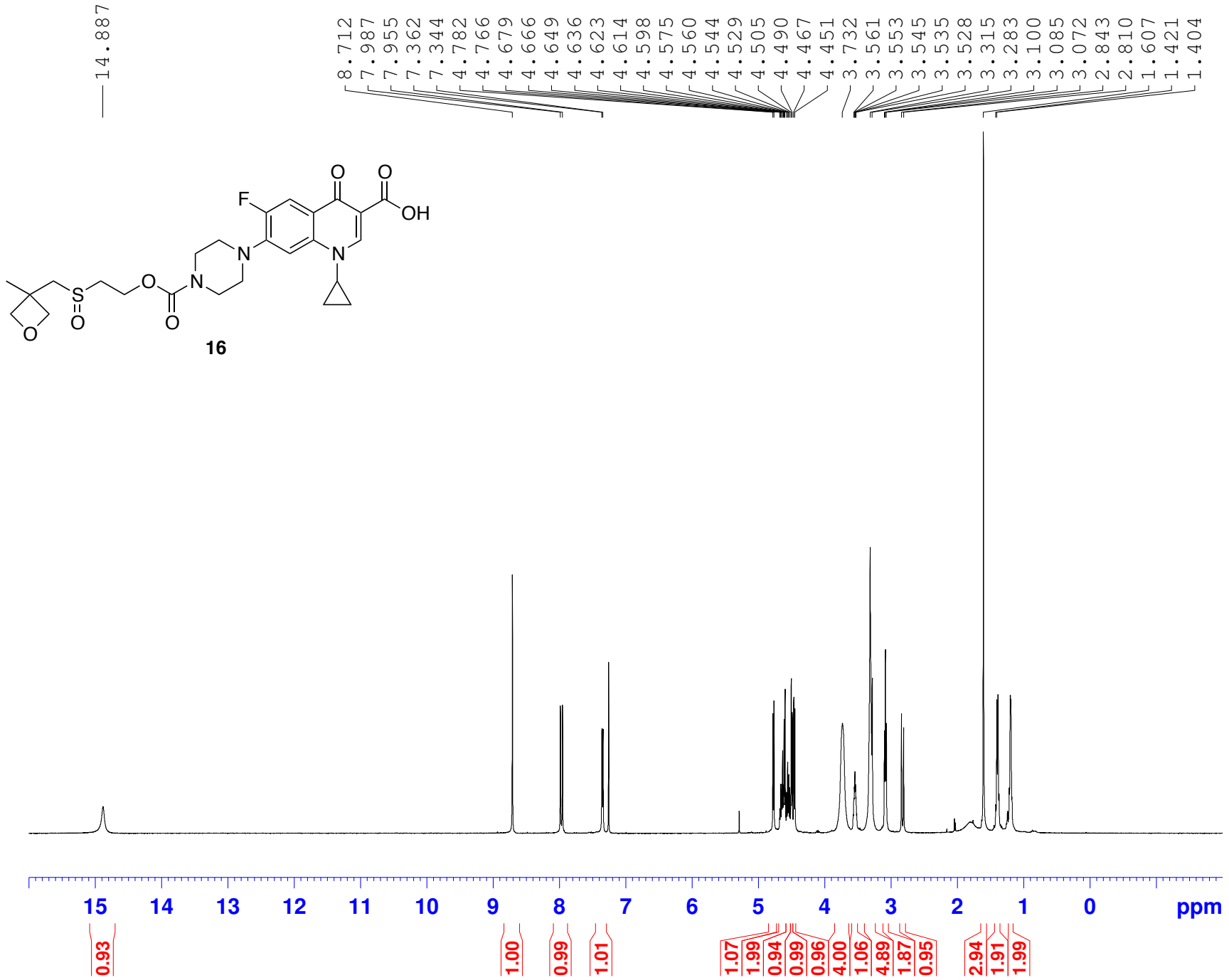
131.27
128.83
127.83
117.53
113.92
110.76
82.47
81.97
61.41
57.17
52.85
38.46
23.53
20.67
Cl
N
H
Cl
O
O
O
S
O
180
160
140
120
100
80
60
40
20
ppm

15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7.344
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4.766
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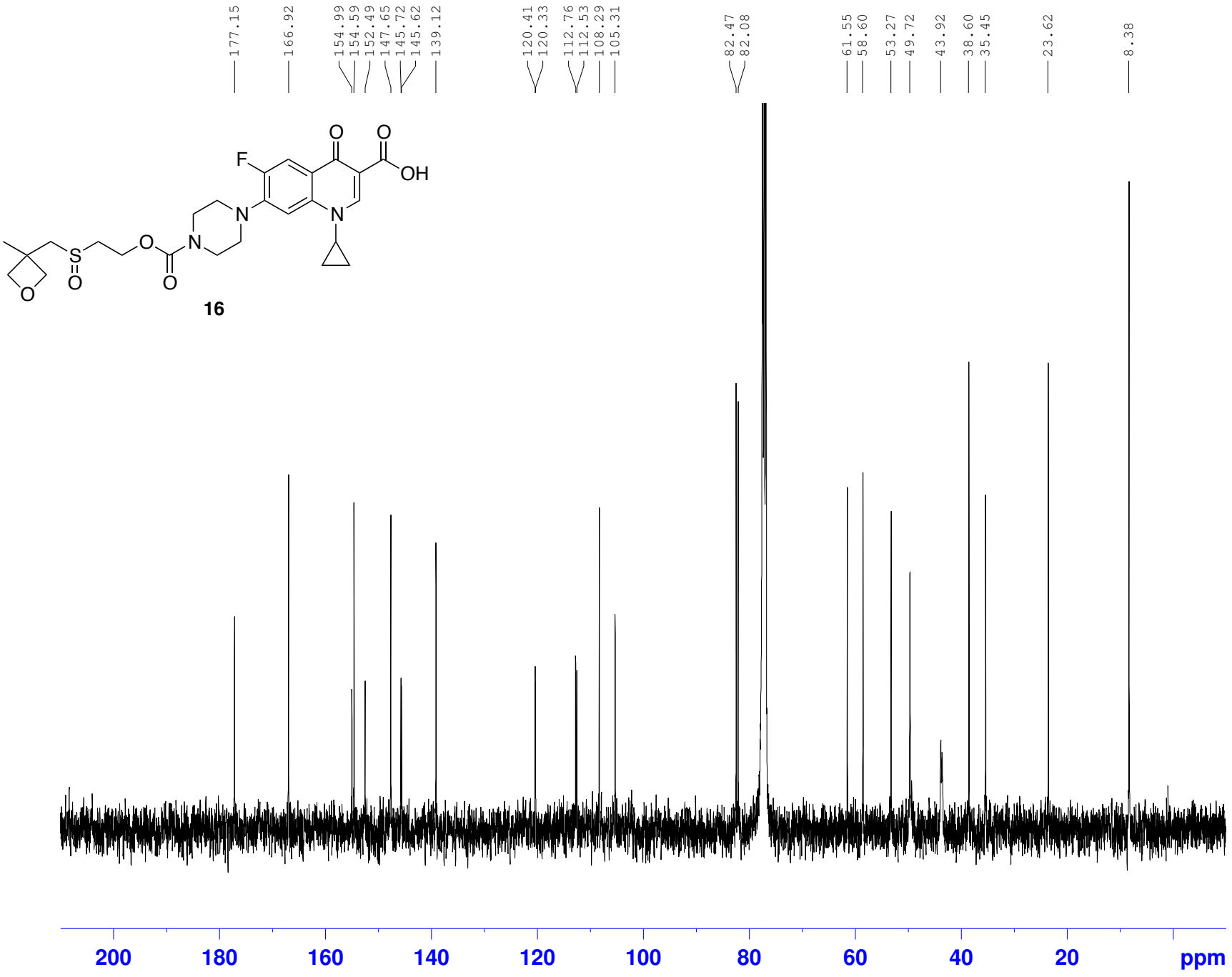
4.649
4.636
4.623
4.614
4.598
4.575
4.560
4.544
4.529
4.505
4.490
4.467
4.451
3.732
3.561
3.553
3.545
3.535
3.528
3.315
3.283
3.100
3.085
3.072
2.843
2.810
1.607
1.421
1.404
F
O
O
OH
N
N
N
O
S
O
O
O
O
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.93
1.00
0.99
1.01
1.07
1.99
0.94
0.99
0.96
4.00
1.06
4.89
1.87
0.95
2.94
1.91
1.99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154.99
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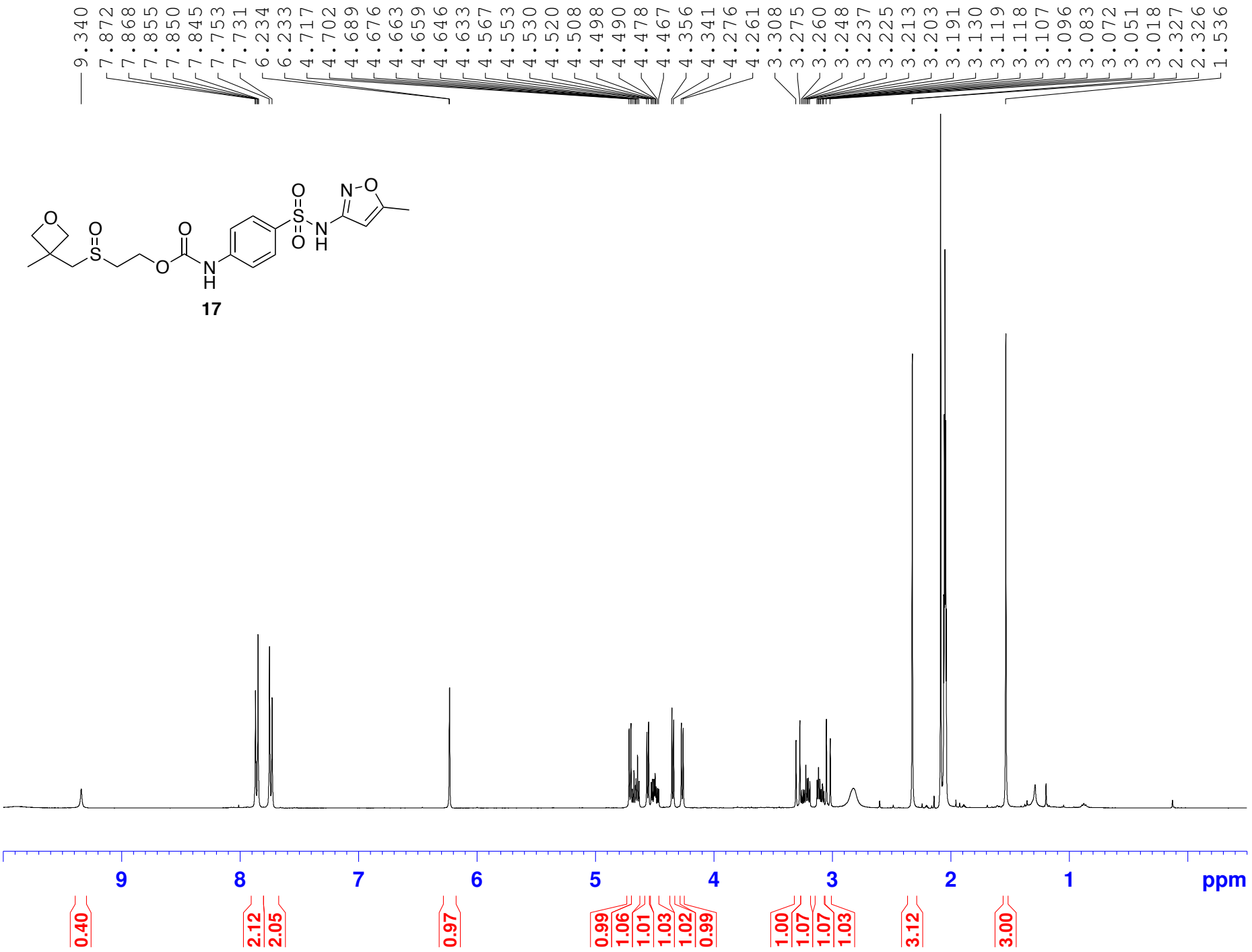
152.49
147.65
145.72
145.62
139.12
120.41
120.33
112.76
112.53
108.29
105.31
82.47
82.08
61.55
58.60
53.27
49.72
43.92
38.60
35.45
23.62
8.38
F
O
O
OH
N
N
N
O
S
O
O
O
O
16
200
180
160
140
120
100
80
60
40
20
ppm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7.855
7.850
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7.731
6.234
6.233
4.717
4.702
4.689
4.676
4.663
4.659
4.646
4.633
4.567
4.553
4.530
4.520
4.508
4.498
4.490
4.478
4.467
4.356
4.341
4.276
4.261
3.308
3.275
3.260
3.248
3.237
3.225
3.213
3.203
3.191
3.130
3.119
3.118
3.107
3.096
3.083
3.072
3.051
3.018
2.327
2.326
1.536
17
9
8
7
6
5
4
3
2
1
ppm
0.40
2.12
2.05
0.97
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1.03
1.02
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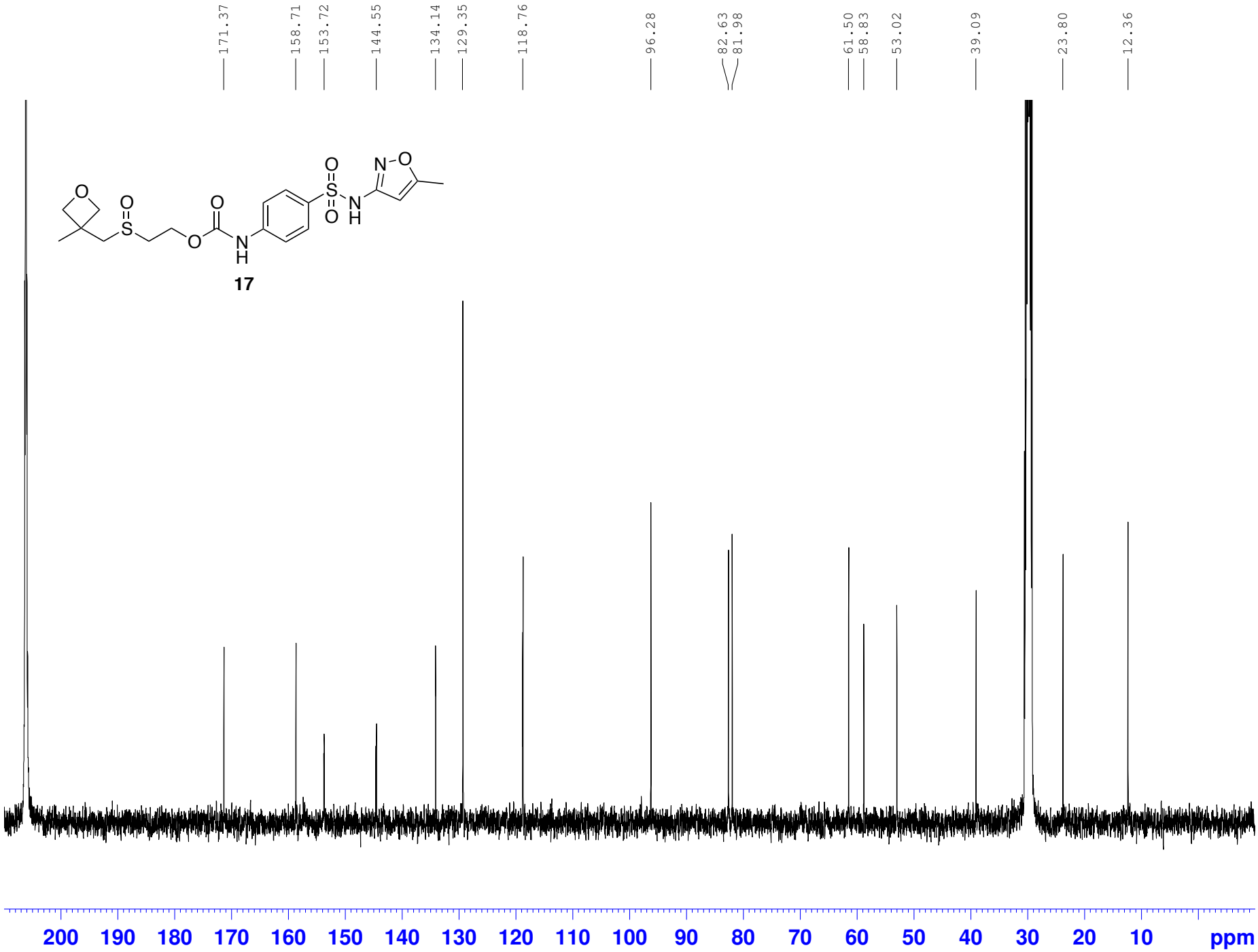
1.07
1.07
1.03
3.12
3.00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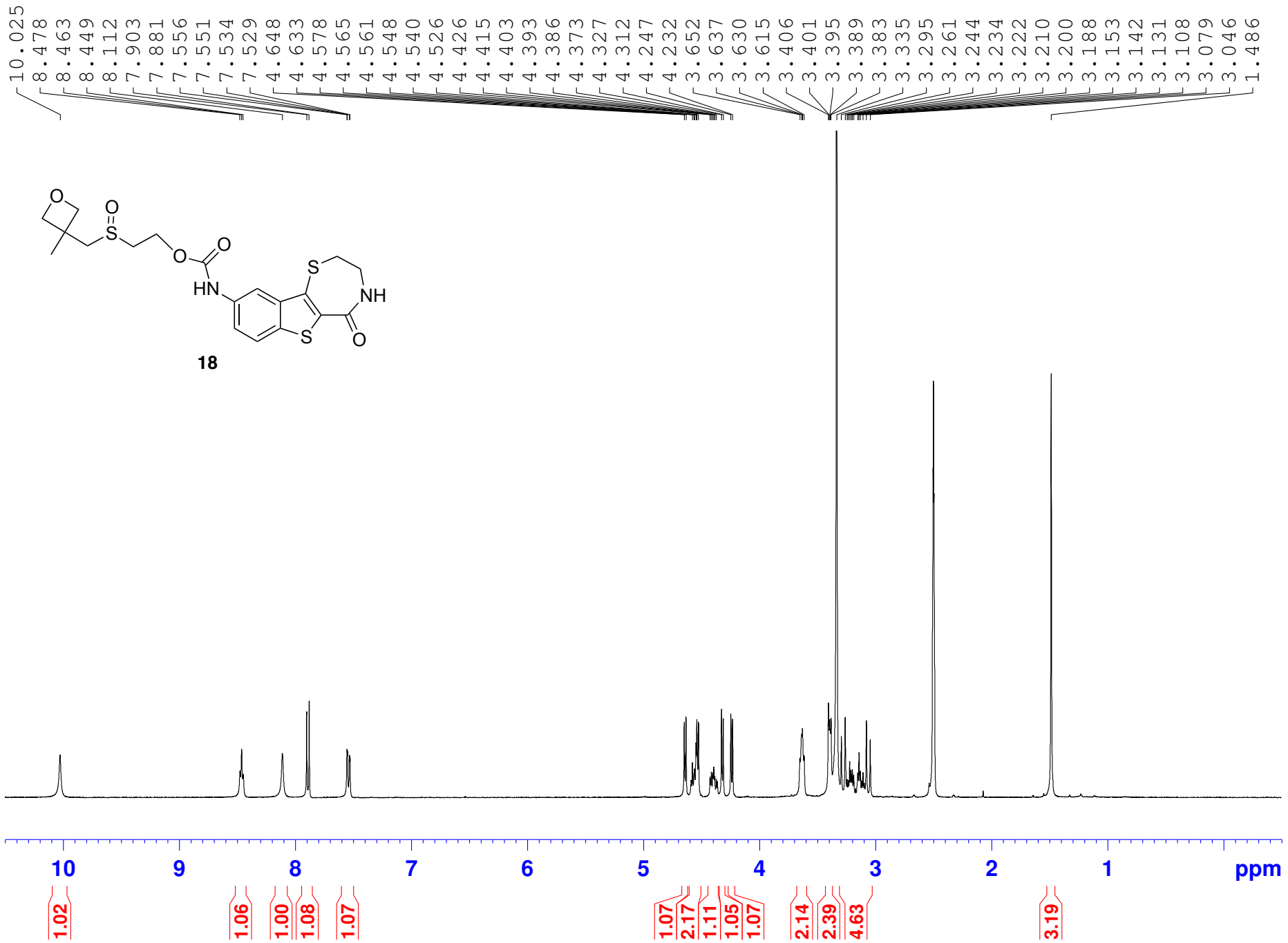
158.71
153.72
144.55
134.14
129.35
118.76
96.28
82.63
81.98
61.50
58.83
53.02
39.09
23.80
12.36
17
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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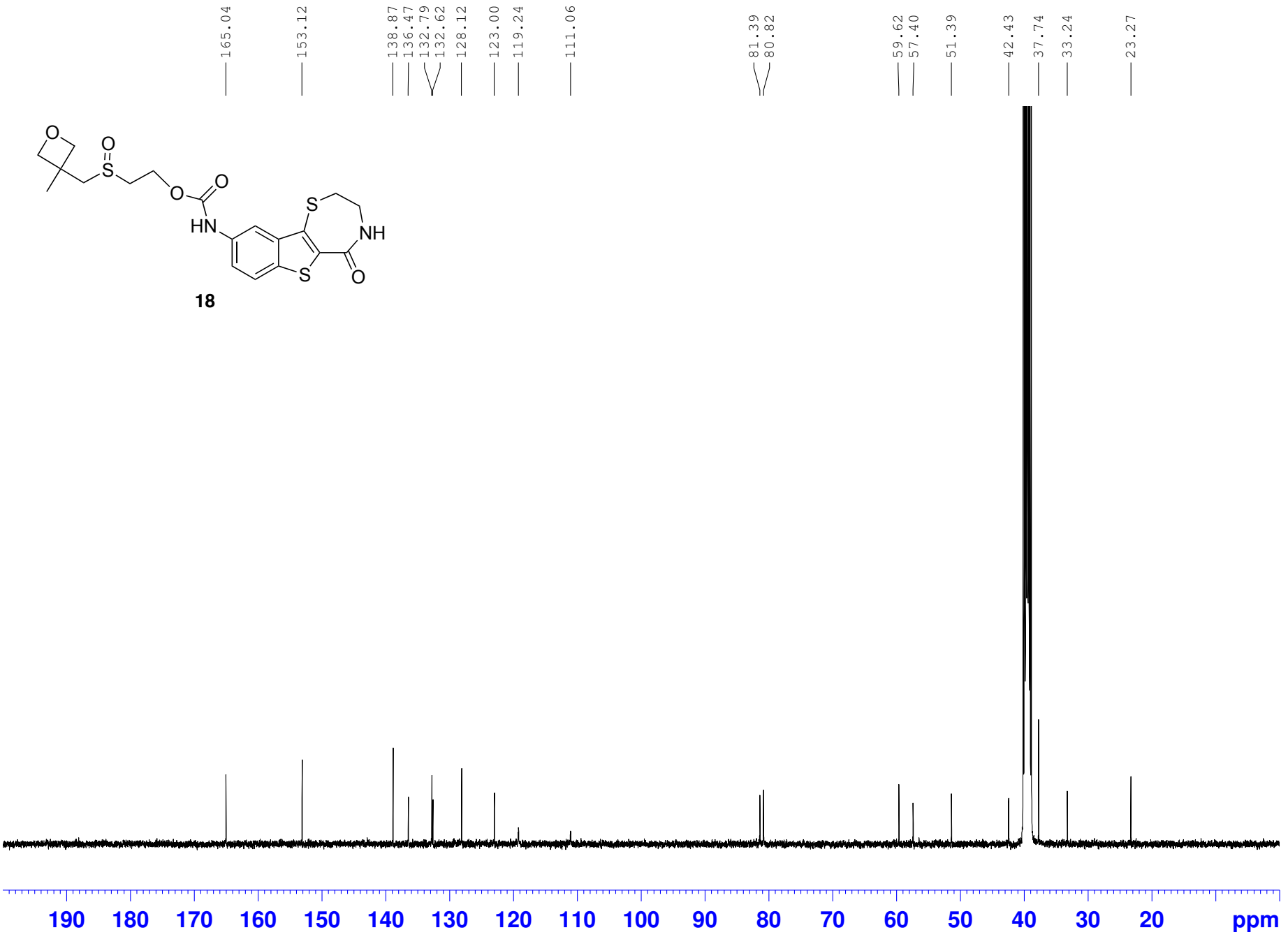
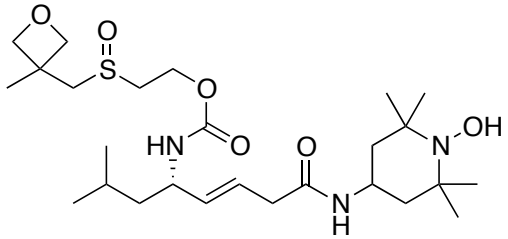
7.903
7.881
7.556
7.551
7.534
7.529
4.648
4.633
4.578
4.565
4.561
4.548
4.540
4.526
4.426
4.415
4.403
4.393
4.386
4.373
4.327
4.312
4.247
4.232
3.652
3.637
3.630
3.615
3.406
3.401
3.395
3.389
3.383
3.335
3.295
3.261
3.244
3.234
3.222
3.210
3.200
3.188
3.153
3.142
3.131
3.108
3.079
3.046
1.486
O
O
S
O
O
HN
S
NH
S
O
18
10
9
8
7
6
5
4
3
2
1
ppm
1.02
1.06
1.00
1.08
1.07
1.07
2.17
1.11
1.05
1.07
2.14
2.39
4.63
3.19

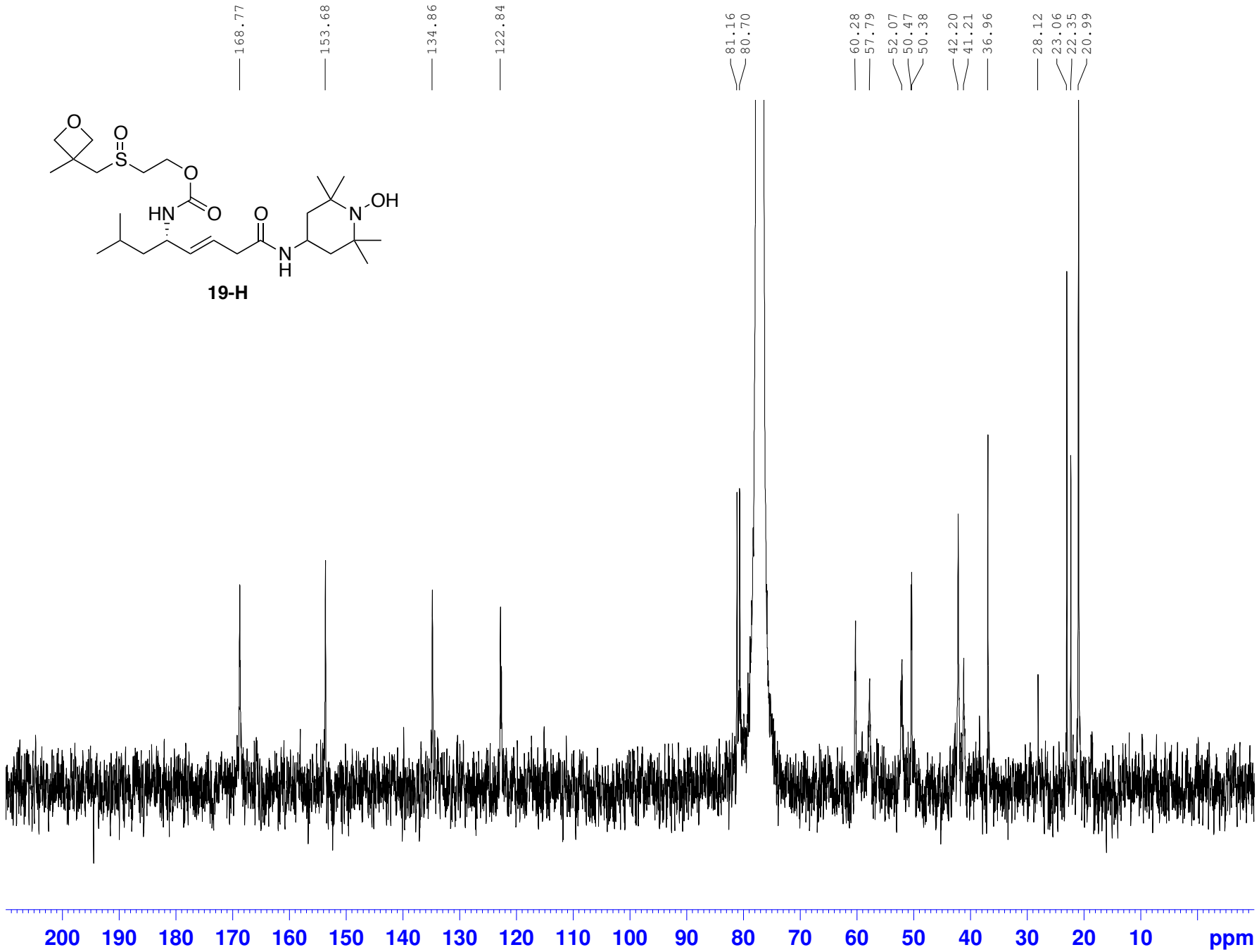

165.04
153.12
138.87
136.47
132.79
132.62
128.12
123.00
119.24
111.06
81.39
80.82
59.62
57.40
51.39
42.43
37.74
33.24
23.27
O
O
S
O
O
HN
S
NH
S
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

18



19-H

5.708
5.689
5.670
5.426
4.755
4.741
4.592
4.578
4.514
4.500
4.472
4.457
4.166
4.139
4.121
4.103
4.085
4.037
3.498
3.480
3.463
3.445
3.346
3.315
3.075
2.940
2.924
2.885
2.867
2.853
2.836
2.037
1.841
1.813
1.631
1.581
1.368
1.268
1.250
1.233
1.210
1.200
1.188
0.917
0.909
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
1.03
1.13
5.22
2.56
1.12
1.01
1.06
2.20
2.14
1.42
2.26
2.11
1.10
3.34
3.57
3.99
12.21
6.27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134.86
122.84
81.16
80.70
60.28
57.79
52.07
50.47
50.38
42.20
41.21
36.96
28.12
23.06
22.35
20.99
O
O
S
O
HN
O
O
N
OH
N
H
200
190
180
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100
90
80
70
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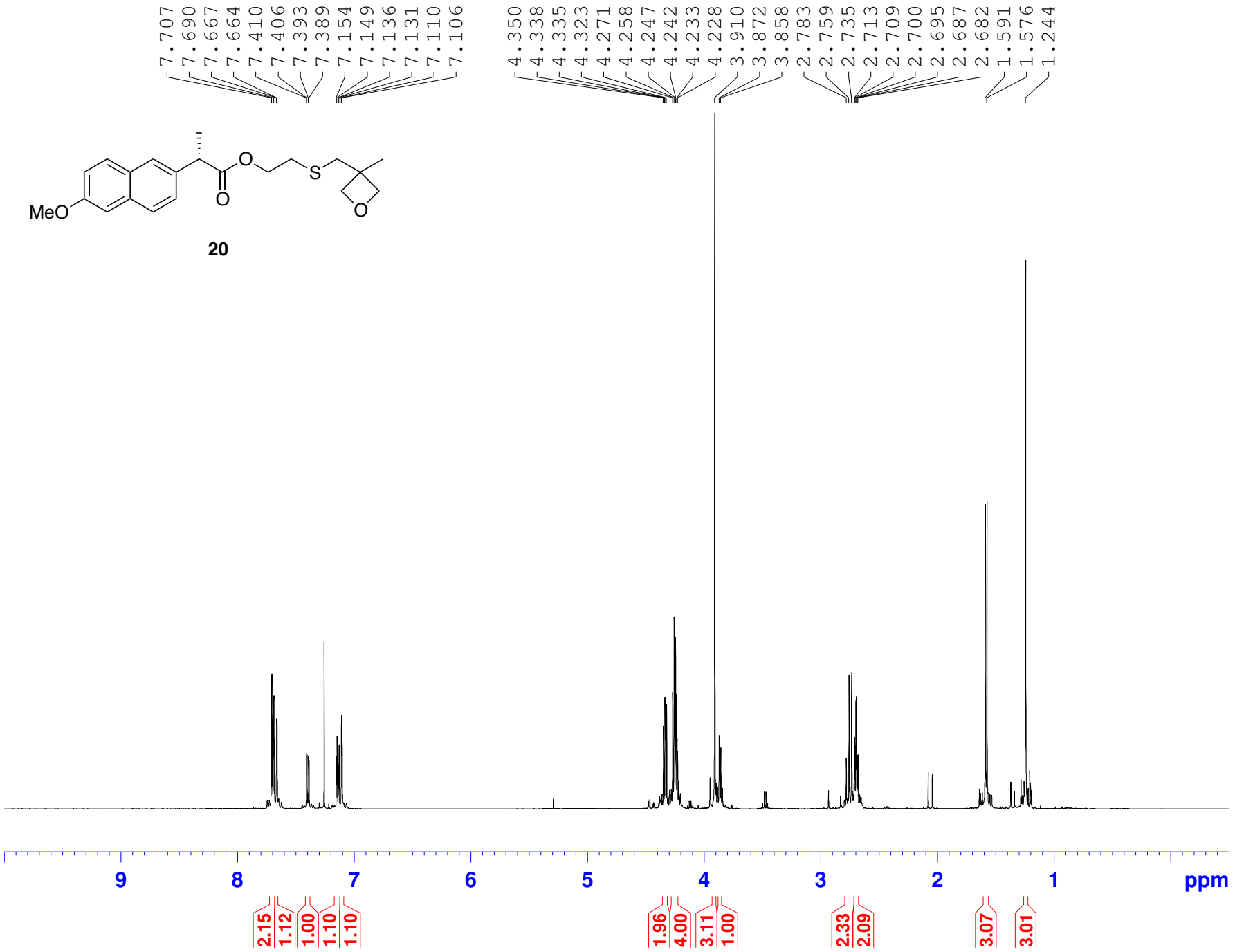
50
40
30
20
10
ppm

19-H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4.323
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4.258
4.247
4.242
4.233
4.228
3.910
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3.858
2.783
2.759
2.735
2.713
2.709
2.700
2.695
2.687
2.682
1.591
1.576
1.244
MeO
O
O
S
O
9
8
7
6
5
4
3
2
1
ppm
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2.33
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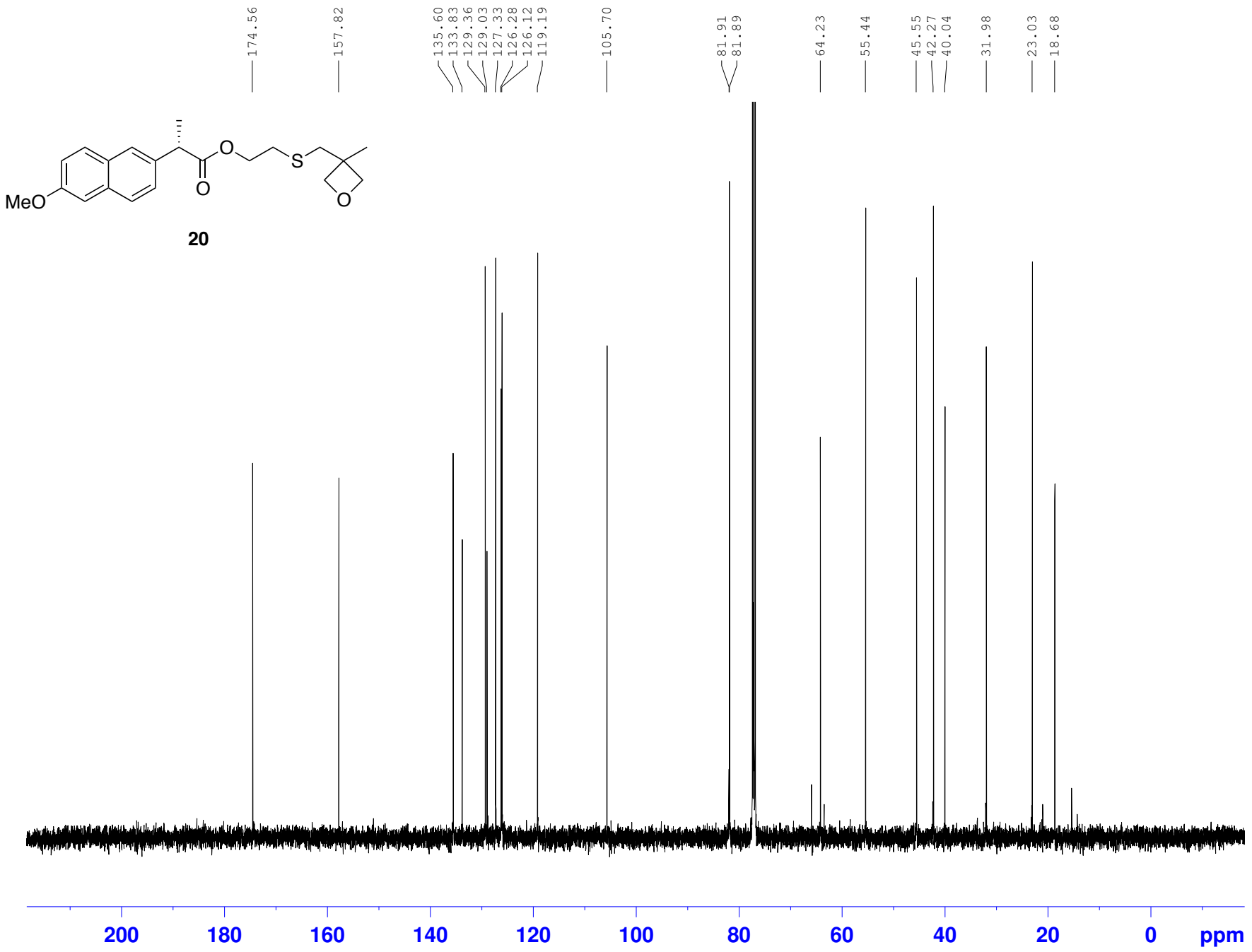
3.07
3.01

20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129.03
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126.28
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105.70
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81.89
64.23
55.44
45.55
42.27
40.04
31.98
23.03
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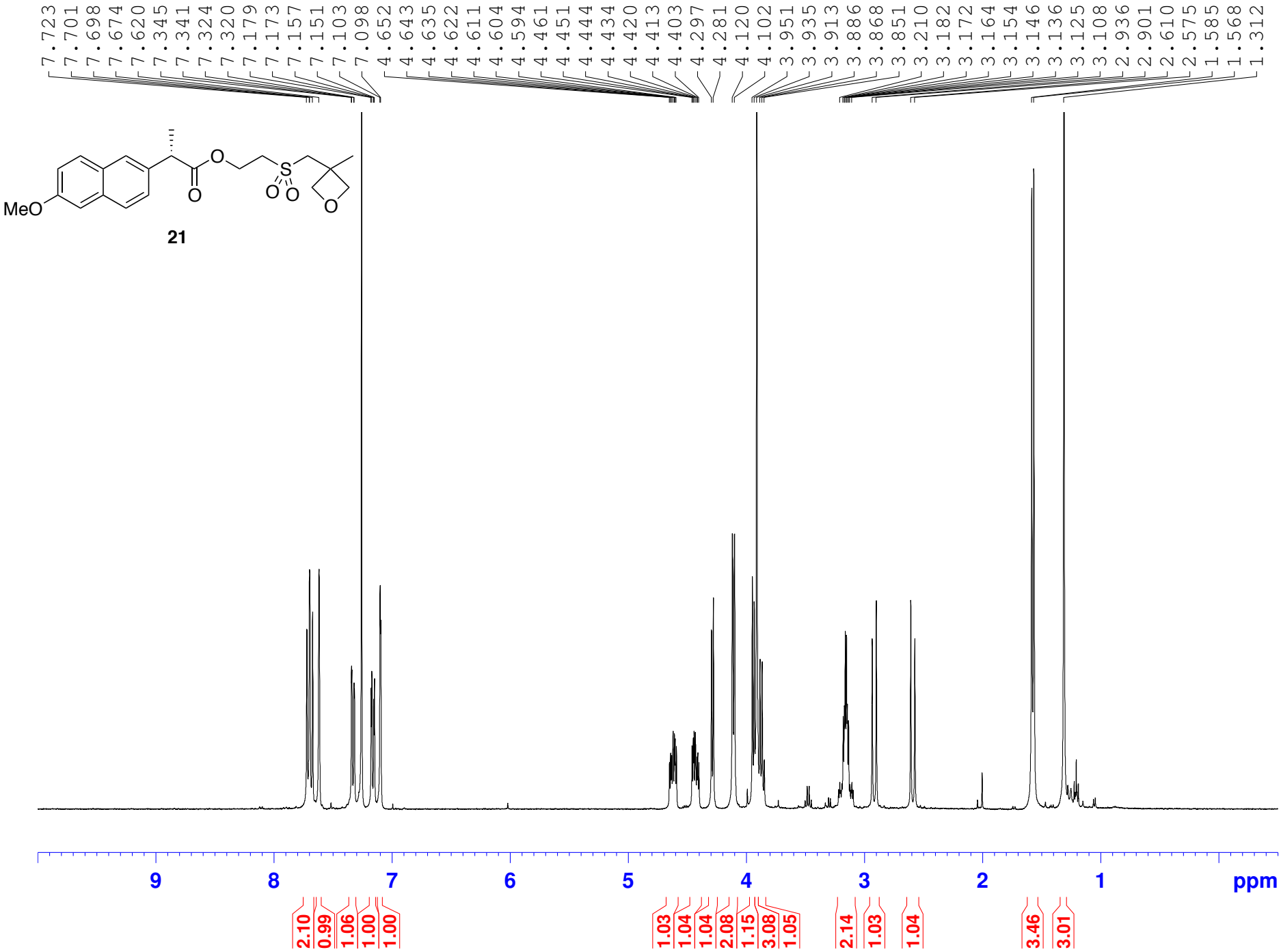
O
S
O
200
180
160
140
120
100
80
60
40
20
0
ppm

20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7.103
7.098
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4.643
4.635
4.622
4.611
4.604
4.594
4.461
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4.444
4.434
4.420
4.413
4.403
4.297
4.281
4.120
4.102
3.951
3.935
3.913
3.886
3.868
3.851
3.210
3.182
3.172
3.164
3.154
3.146
3.136
3.125
3.108
2.936
2.901
2.610
2.575
1.585
1.568
1.312
MeO
O
O
S
O
O
O
9
8
7
6
5
4
3
2
1
ppm
2.10
0.99
1.06
1.00
1.00
1.03
1.04
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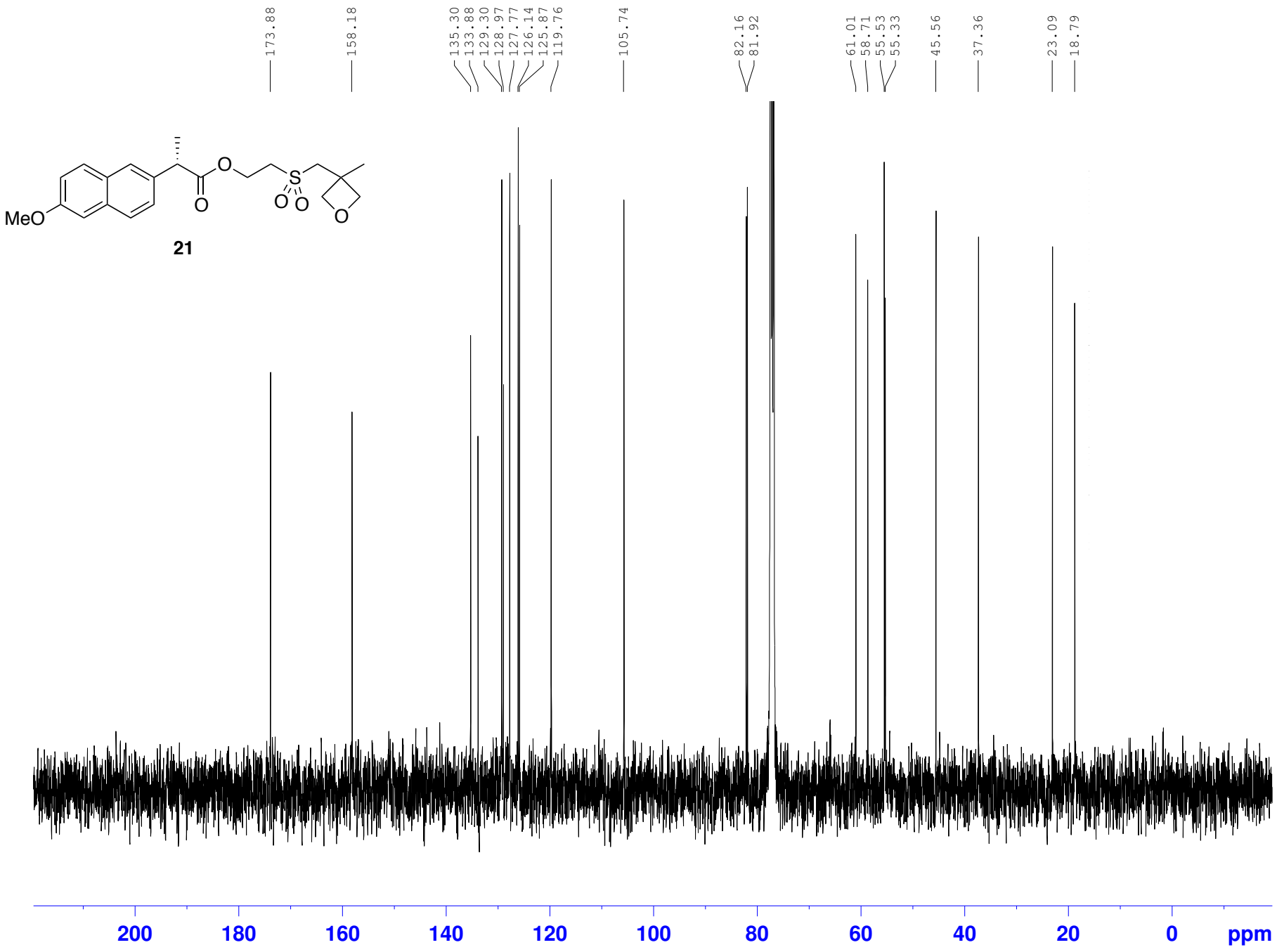
2.08
1.15
3.08
1.05
2.14
1.03
1.04
3.46
3.01

21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82.16
81.92
61.01
58.71
55.53
55.33
45.56
37.36
23.09
18.79
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S
O
O
O
200
180
160
140
120
100
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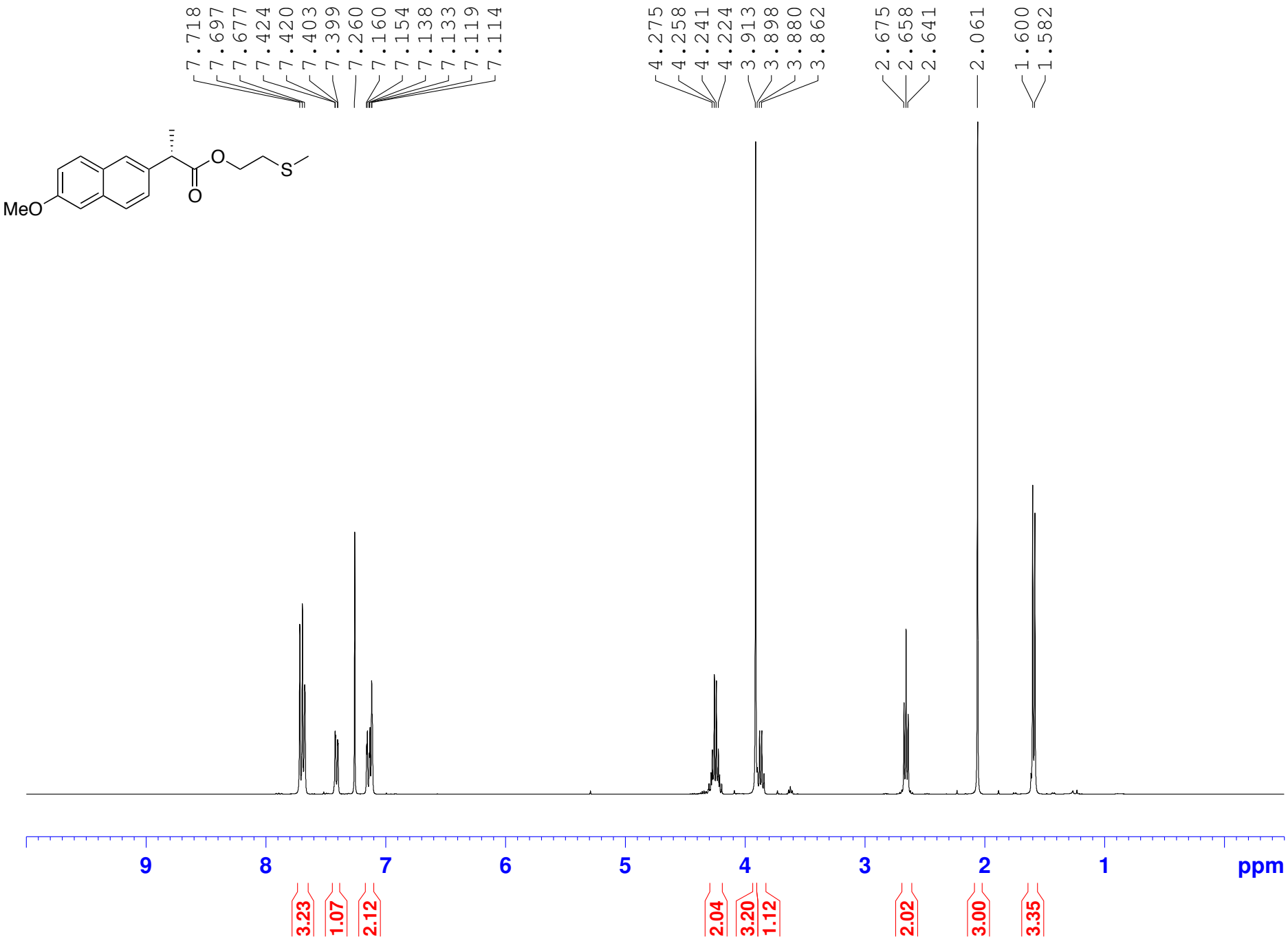
60
40
20
0
ppm

21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7.154
7.138
7.133
7.119
7.114
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4.258
4.241
4.224
3.913
3.898
3.880
3.862
2.675
2.658
2.641
2.061
1.600
1.582
MeO
O
O
S
9
8
7
6
5
4
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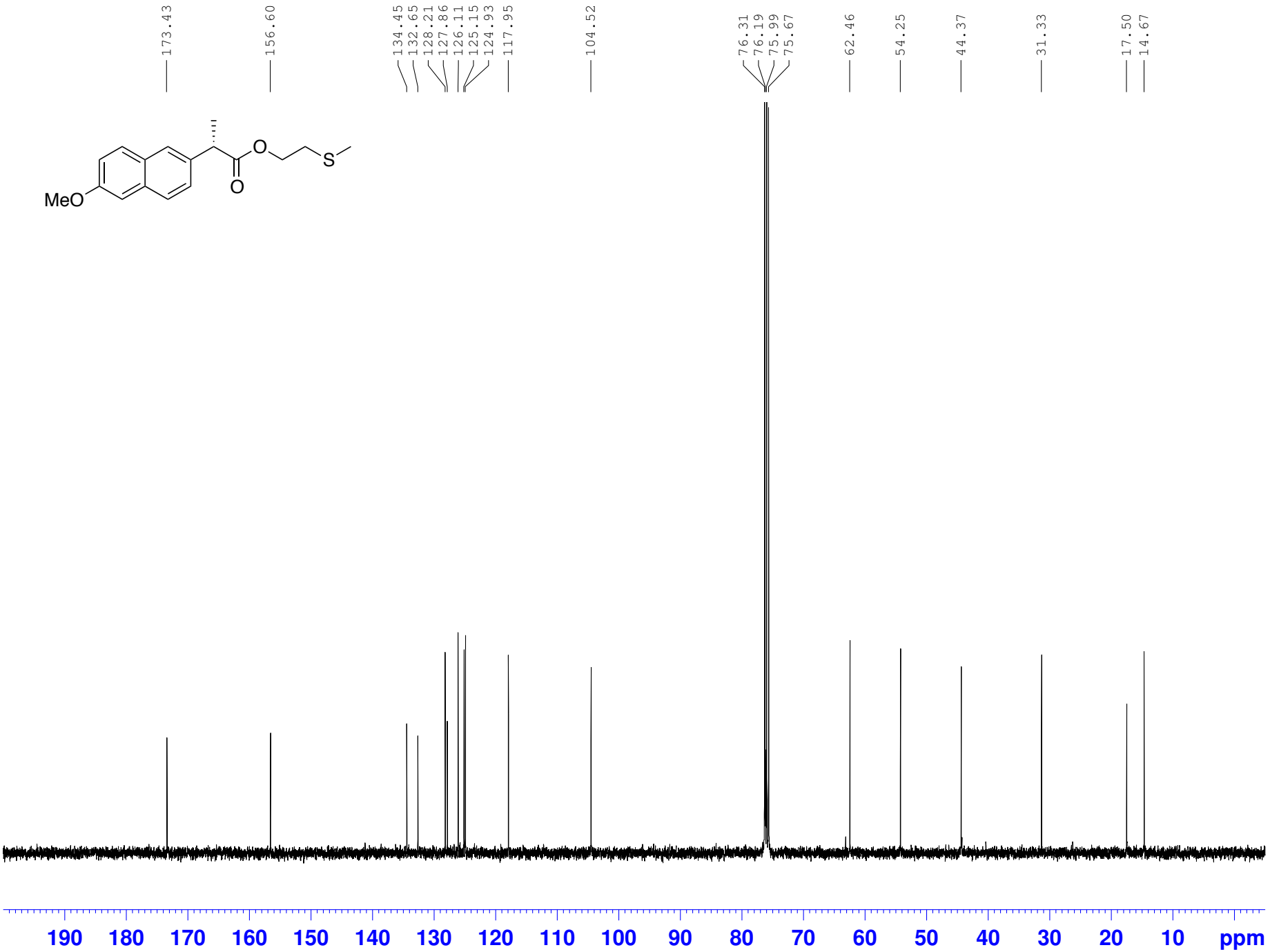
1
ppm
3.23
1.07
2.12
2.04
3.20
1.12
2.02
3.00
3.35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125.15
124.93
117.95
104.52
76.31
76.19
75.99
75.67
62.46
54.25
44.37
31.33
17.50
14.67
MeO
O
O
S
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150
140
130
120
110
100
90
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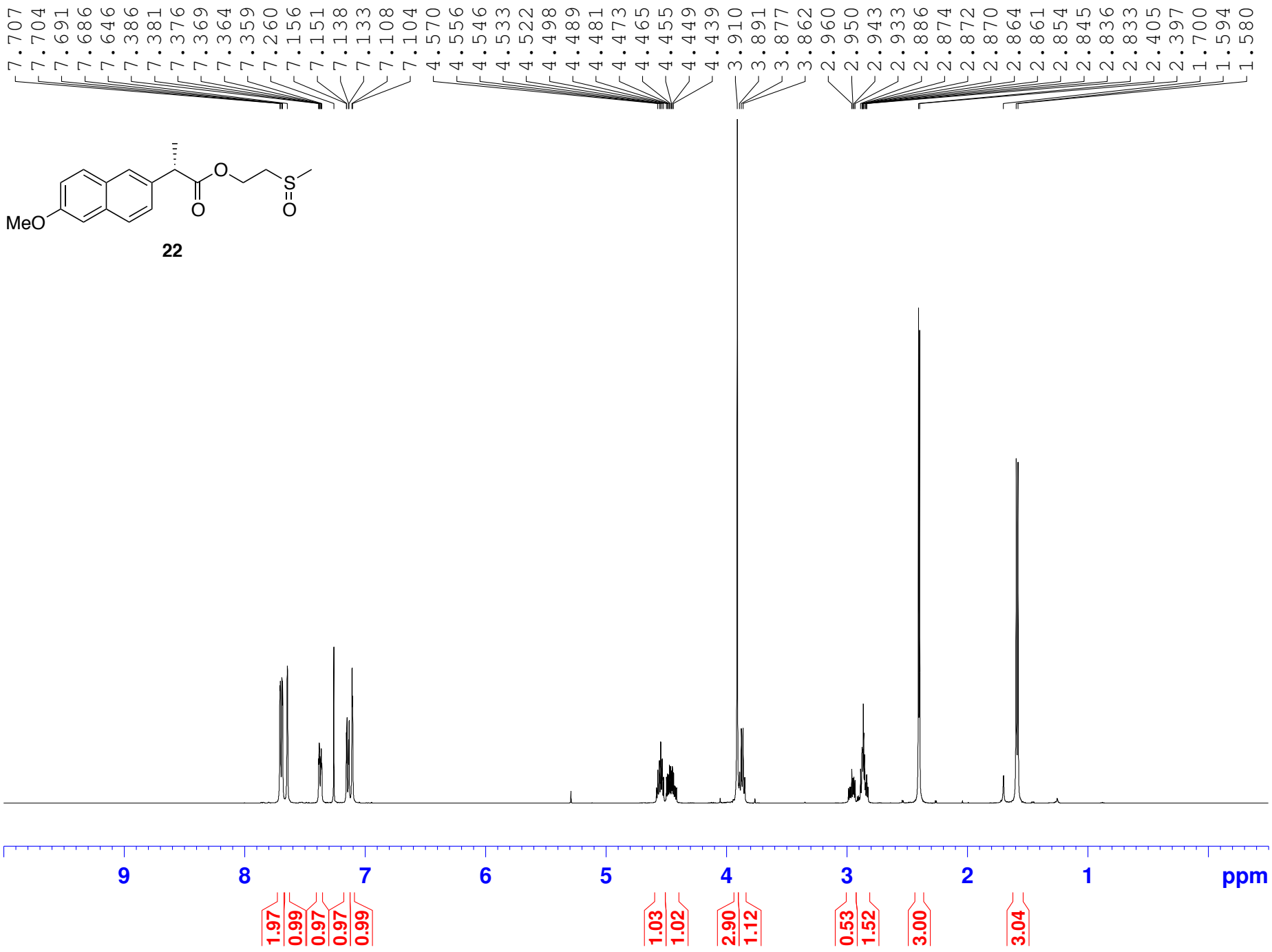
70
60
50
40
30
20
10
ppm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7.138
7.133
7.108
7.104
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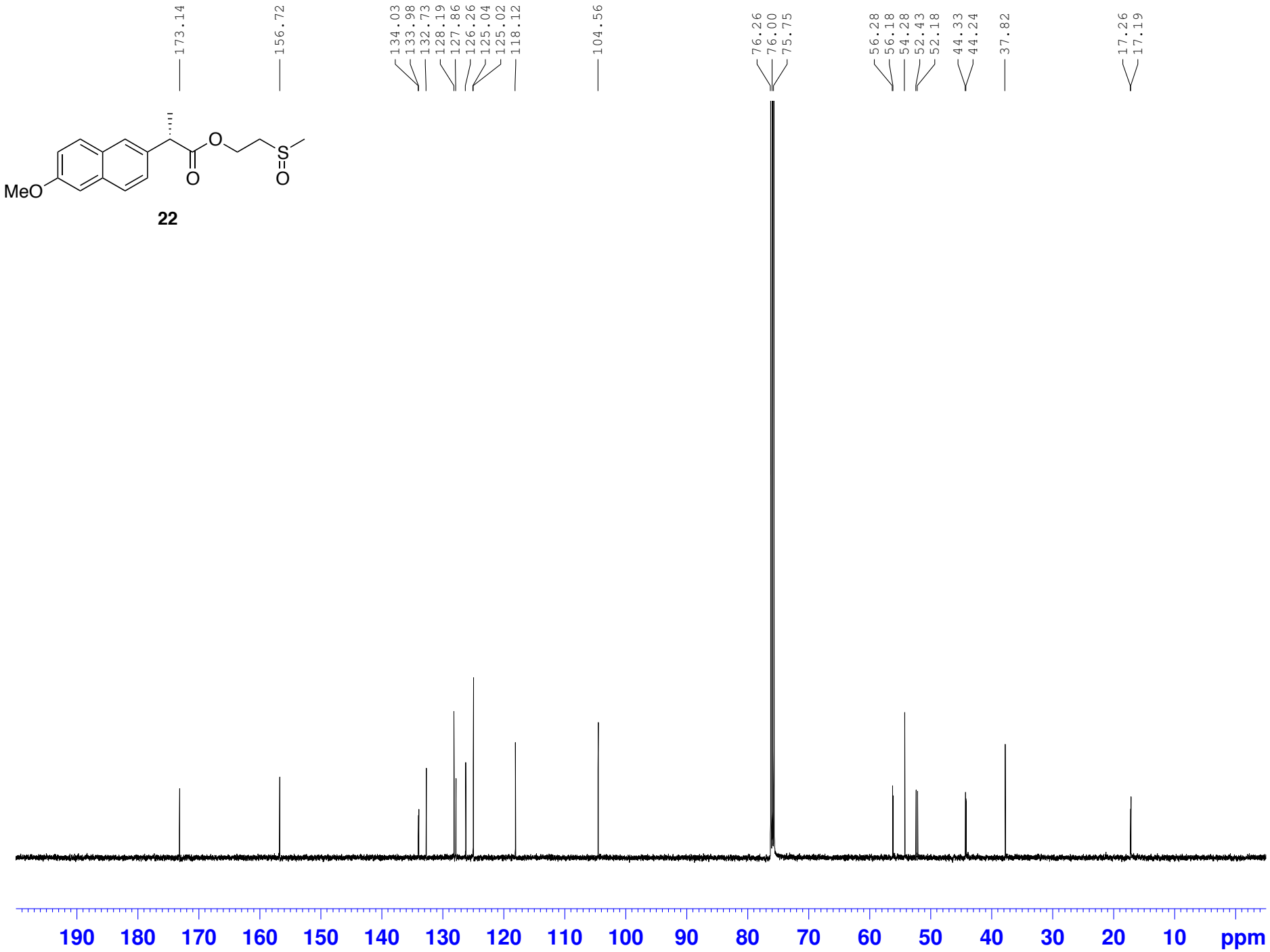
4.556
4.546
4.533
4.522
4.498
4.489
4.481
4.473
4.465
4.455
4.449
4.439
3.910
3.891
3.877
3.862
2.960
2.950
2.943
2.933
2.886
2.874
2.872
2.870
2.864
2.861
2.854
2.845
2.836
2.833
2.405
2.397
1.700
1.594
1.580
MeO
O
O
S
O
9
8
7
6
5
4
3
2
1
ppm
1.97
0.99
0.97
0.97
0.99
1.03
1.02
2.90
1.12
0.53
1.52
3.00
3.04

22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126.26
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125.02
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104.56
76.26
76.00
75.75
56.28
56.18
54.28
52.43
52.18
44.33
44.24
37.82
17.26
17.19
MeO
O
O
S
O
22
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm