

Supporting Information

Design, synthesis, and evaluation of trisubstituted bicyclo[2.2.2]oct-2-enes as non-classical isosteres of trisubstituted benzenes

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Contents

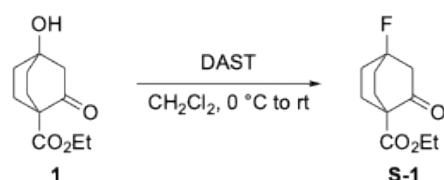
Part I: Synthesis of BCOene-Derived Analogs of Fungicidal and Anticancer Agents	S-2
Part II: Computational Studies and Exit Vector Analysis	S-12
Part III: Determination of Aqueous Solubility.....	S-23
Part IV: Measurement of Partition Coefficient (LogP).....	S-24
Part V: Assessment of Metabolic Stability in Human Liver Microsomes.....	S-25
Part VI: Bioactivity	S-29
Part VII: References	S-34
Part VIII: Copies of NMR Spectral Data.....	S-36

General Information: ^1H , ^{13}C , and ^{19}F NMR spectra were recorded on Bruker AVIII HD 400 spectrometer in CDCl_3 . Chemical shifts were reported in parts per million (ppm) from chloroform using the solvent resonance as the internal standard (CHCl_3 : δ 7.26 ppm) for ^1H NMR and (CDCl_3 : δ 77.0 ppm) for ^{13}C NMR. For ^{19}F NMR, trifluoroacetic acid was used as an external standard (δ -76.55 ppm). High-resolution mass spectroscopic data were collected at the Instrumentation Center of National Taiwan Normal University using a Waters Xevo G2-S ToF and JEOL JMS-700. Column chromatography was carried out using either silica gel (Silica gel 60, 40-63 μm) or aluminium oxide (Aluminium oxide 90 active neutral, 63-200 μm) from Merck.

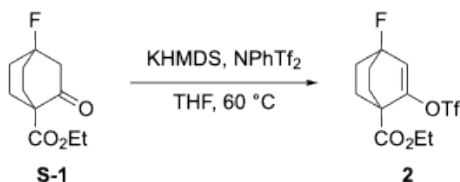
Reagents: Unless stated otherwise, commercial reagents were used without purification. Solvents were either purified by distillation under dry nitrogen from CaH_2 or purchased as anhydrous solvent.

Part I: Synthesis of BCOene-Derived Analogs of Fungicidal and Anticancer Agents

Synthesis of bixafen analog **5**

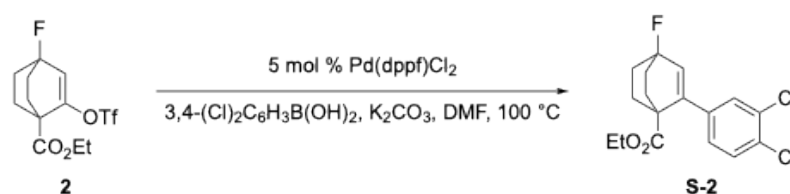


Ethyl 4-fluoro-2-oxobicyclo[2.2.2]octane-1-carboxylate (S-1).^[1] In a flame-dried round bottom flask under a balloon of dry nitrogen with **1** (2.806 g, 13.23 mmol) in dry CH_2Cl_2 (20 mL) was added DAST (4.36 mL, 33.0 mmol) at -78 °C. After stirring at room temperature for 3 hours, the reaction mixture was slowly added into ice water. The organic layer was washed with extracted with CH_2Cl_2 , dried over Na_2SO_4 , and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel) using (10:90 EtOAc:hexane) as the eluent to afford **S1** as a white solid (1.700 g, 60%). R_f = 1.6/4.0 (20% EtOAc in hexane). ^1H NMR (CDCl_3 , 400 MHz) δ 4.20 (q, J = 7.16 Hz, 2H), 2.67 (dt, J = 5.03, 1.48 Hz, 2H), 2.33-2.20 (m, 2H), 2.12-2.01 (m, 3H), 2.01-1.88 (m, 3H), 1.26 (t, J = 7.14 Hz, 3H); ^{13}C NMR (CDCl_3 , 101 MHz) δ 204.8 (d, J = 11.7 Hz), 170.5 (d, J = 1.7 Hz), 91.8 (d, J = 190.8 Hz), 61.2, 53.7, 49.2 (d, J = 19.4 Hz), 30.0 (d, J = 20.0 Hz), 24.6 (d, J = 11.3 Hz), 14.0; ^{19}F NMR (CDCl_3 , 376 MHz) δ -152.2.

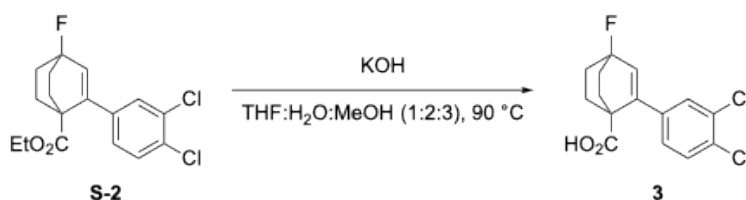


Ethyl 4-fluoro-2-(((trifluoromethyl)sulfonyl)oxy)bicyclo[2.2.2]oct-2-ene-1-carboxylate (2). In a flame-dried round bottom flask under a balloon of dry nitrogen with **S-1** (0.6426 g, 2.999 mmol) in dry THF (30 mL) was added KHMDS (3.6 mL, 1.0 M in THF, 3.6 mmol) at 0

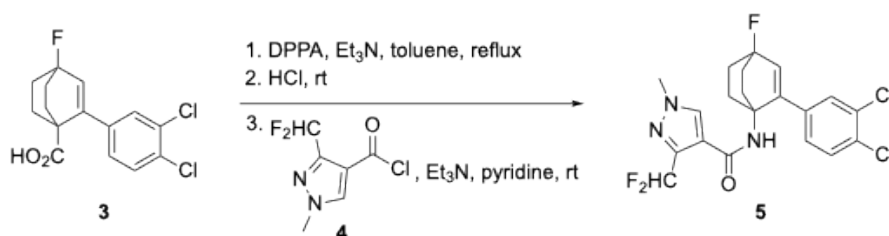
°C. After stirring for 10 min, a solution of NPhTf₂ (1.3932 g, 3.8998 mmol) in THF (6 mL) was added to the reaction mixture, and then the temperature was raised to 60 °C and stirred for 1 h. The reaction was quenched with a saturated solution of NH₄Cl, extracted with EtOAc, dried over Na₂SO₄, and then concentrated under reduced pressure. The crude mixture was purified by column chromatography (silica gel) using hexane as the eluent to afford **2** as a colorless liquid (0.6138 g, 59%). R_f = 2.2/4.0 (20% EtOAc in hexane). ¹H NMR (CDCl₃, 400 MHz) δ 6.23 (d, *J* = 12.79 Hz, 1H), 4.23 (q, *J* = 7.21 Hz, 2H), 2.04-1.95 (m, 2H), 1.95-1.87 (m, 4H), 1.80-1.71 (m, 2H), 1.29 (t, *J* = 7.20 Hz, 3H); ¹³C NMR (CDCl₃, 101 MHz) δ 170.1, 144.7 (d, *J* = 12.7 Hz), 121.9 (d, *J* = 30.5 Hz), 118.4 (q, *J* = 321.2 Hz), 94.5 (d, *J* = 191.6 Hz), 61.9, 47.3, 30.6 (d, *J* = 19.9 Hz), 28.9 (d, *J* = 10.2 Hz), 13.8; ¹⁹F NMR (CDCl₃, 376 MHz) δ -74.2, -160.6; IR (neat, ZnSe, cm⁻¹) 3095, 2985, 2965, 2881, 1741, 1645, 1479, 1458, 1425, 1369, 1344, 1330, 1281, 1250, 1213, 1158, 1141, 1089, 1044, 1016, 994, 978, 942, 878, 841, 788, 758, 681; HRMS (ESI) *m/z*: [M+Na]⁺ calcd for C₁₂H₁₄F₄O₅Na⁺ 369.0396; found 369.0388.



Ethyl 2-(3,4-dichlorophenyl)-4-fluorobicyclo[2.2.2]oct-2-ene-1-carboxylate (S-2). In a nitrogen filled glove box, a screw-cap vial was charged with **2** (0.3463 g, 1.000 mmol), K₂CO₃ (0.3816 g, 2.761 mmol), 3,4-dichlorophenylboronic acid (0.2764 g, 1.448 mmol), and 1,1'-bis(diphenylphosphino)ferrocene palladium(II) dichloride (0.0366 g, 0.050 mmol) in degassed DMF (2 mL). The vial was then sealed with a cap, removed from the glove box, and the mixture was stirred at 100 °C (preheat oil bath). After stirring for 1 h, the reaction was cooled to room temperature, quenched with a saturated solution of NH₄Cl, extracted with diethyl ether, dried over Na₂SO₄, and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel) using EtOAc:hexane (5:95) as the eluent to afford **S-2** as a yellow solid (0.3056 g, 89%). R_f = 1.8/4.0 (20% EtOAc in hexane). ¹H NMR (CDCl₃, 400 MHz) δ 7.34 (d, *J* = 8.29 Hz, 1H), 7.23 (d, *J* = 2.10 Hz, 1H), 6.95 (dd, *J* = 8.32, 2.09 Hz, 1H), 6.36 (d, *J* = 13.33 Hz, 1H), 3.92 (q, *J* = 7.14 Hz, 2H), 2.04-1.91 (m, 6H), 1.80-1.70 (m, 2H), 0.94 (t, *J* = 7.17 Hz, 3H); ¹³C NMR (CDCl₃, 101 MHz) δ 173.9, 141.3 (d, *J* = 9.3 Hz), 138.7, 133.2 (d, *J* = 27.8 Hz), 132.2, 131.3, 130.0, 128.6, 126.0, 95.5 (d, *J* = 187.3), 60.8, 48.1, 30.5 (d, *J* = 19.9 Hz), 29.6 (d, *J* = 10.3 Hz), 13.7; ¹⁹F NMR (CDCl₃, 376 MHz) δ -163.2; IR (neat, ZnSe, cm⁻¹) 2975, 2874, 1730, 1623, 1587, 1550, 1469, 1367, 1326, 1300, 1284, 1251, 1228, 1186, 1133, 1093, 1031, 1019, 990, 979, 916, 888, 856, 811, 750, 736, 704, 684; HRMS (ESI) *m/z*: [M+H]⁺ calcd for C₁₇H₁₈Cl₂FO₂⁺ 342.0668; found 342.0666.



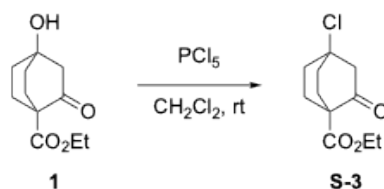
2-(3,4-Dichlorophenyl)-4-fluorobicyclo[2.2.2]oct-2-ene-1-carboxylic acid (3). In a seal tube, **S-2** (0.1716 g, 0.5000 mmol) was dissolved in THF (0.5 mL), methanol (1 mL), and water (1.5 mL). Potassium hydroxide (0.0842 g, 1.50 mmol) was added at ambient temperature, and the mixture was heated to 90 °C. After stirring overnight, the reaction mixture was cooled to room temperature, diluted with water and washed with CH₂Cl₂. The aqueous layer was acidified (pH = 2) with concentrated HCl, and subsequently extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and then concentrated under reduced pressure to afford **3** as a white solid (0.1575 g, quant.). *R_f* = 0.4/4.0 (20% EtOAc in hexane). ¹H NMR (CDCl₃, 400 MHz) δ 8.74 (br, 1H), 7.34 (d, *J* = 8.25 Hz, 1H), 7.27 (d, *J* = 2.02 Hz, 1H), 6.97 (dd, *J* = 8.29, 2.10 Hz, 1H), 6.39 (d, *J* = 13.25 Hz, 1H), 2.06-1.89 (m, 6H), 1.84-1.69 (m, 2H); ¹³C NMR (CDCl₃, 101 MHz) δ 180.1, 140.7 (d, *J* = 9.2 Hz), 138.2, 133.6 (d, *J* = 27.3 Hz), 132.3, 131.6, 130.1, 128.6, 125.9, 95.4 (d, *J* = 187.5), 48.1, 30.5 (d, *J* = 20.0 Hz), 29.6 (d, *J* = 10.0 Hz); ¹⁹F NMR (CDCl₃, 376 MHz) δ -163.1; IR (neat, ZnSe, cm⁻¹) 3074, 2969, 2875, 2647, 2562, 1701, 1617, 1550, 1468, 1458, 1419, 1380, 1327, 1269, 1183, 1135, 1101, 1068, 1030, 981, 909, 884, 810, 735; HRMS (EI) *m/z*: [*M*]⁺ calcd for C₁₅H₁₃Cl₂FO₂⁺ 314.0277; found 314.0269.



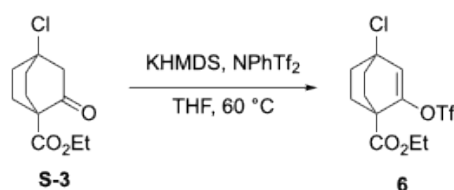
N-(2-(3,4-Dichlorophenyl)-4-fluorobicyclo[2.2.2]oct-2-en-1-yl)-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide (5). In an oven-dried round bottom flask under a balloon of dry nitrogen with **3** (0.0935 mg, 0.297 mmol) in toluene (3.6 mL) was added Et₃N (128 μL, 0.919 mmol) and diphenylphosphoryl azide (99 μL, 0.46 mmol). The reaction temperature was then raised to 110 °C and stirred for 3 h. Upon cooling to room temperature, 3N HCl (7.5 mL) was added and the mixture was stirred for overnight. The reaction was concentrated under reduced pressure, and the residue was triturated with diethyl ether. The resulting solid was collected, washed with ether, dissolved in CH₂Cl₂, and concentrated again under reduced pressure. The crude product was then dissolved with pyridine (5 mL) followed by addition of 3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carbonyl chloride (**4**) (0.1198 g, 0.6157 mmol). After stirring overnight, the reaction was quenched with a solution of 1N HCl, extracted with CH₂Cl₂, dried over Na₂SO₄, and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel) using EtOAc:hexane (40:60) as the eluent to afford **5** as a white solid (0.0603 g, 46% over three steps). *R_f* = 1.2/4.0 (50% EtOAc in hexane). ¹H NMR (CDCl₃, 400 MHz) δ 7.57 (s, 1H), 7.31 (d, *J* = 2.03 Hz, 1H), 7.28 (d, *J* = 8.31 Hz, 1H), 7.11 (dd, *J* = 8.27, 2.02 Hz, 1H), 6.87 (t, *J* = 54.31 Hz, 1H), 6.55 (d, *J* = 4.88 Hz, 1H), 6.31 (d, *J* = 12.78 Hz, 1H), 3.81 (s, 3H), 2.33-2.21 (m, 2H), 2.10-1.91 (m, 4H), 1.88-1.80 (m, 2H); ¹³C NMR (CDCl₃, 101 MHz) δ 160.2, 142.7 (d, *J* = 10.2 Hz), 142.0 (t, *J* = 28.8 Hz), 138.1, 135.5, 132.0, 131.8 (d, *J* = 5.1 Hz), 131.0, 129.8, 128.8, 126.5, 116.8, 112.0 (t, *J* = 231.4

Hz), 94.1 (d, $J = 188.1$ Hz), 56.2 (d, $J = 3.1$ Hz), 39.3, 31.4 (d, $J = 10.5$ Hz), 30.8 (d, $J = 20.1$ Hz); ^{19}F NMR (CDCl_3 , 376 MHz) δ -107.9, -162.8; IR (neat, ZnSe, cm^{-1}) 3425, 3270, 3133, 3069, 3001, 2957, 2921, 1652, 1617, 1590, 1550, 1521, 1470, 1416, 1374, 1336, 1284, 1255, 1185, 1132, 1111, 1078, 1030, 1014, 919, 873, 820, 796, 764, 7366, 681; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{19}\text{Cl}_2\text{F}_3\text{N}_3\text{O}^+$ 444.0857; found 444.0862.

Synthesis of miconazole analog **9**

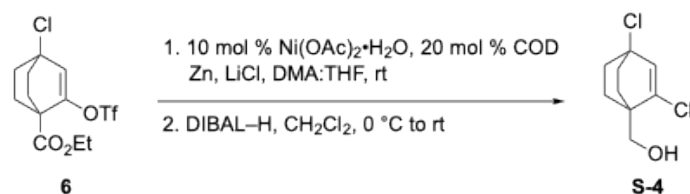


Ethyl 4-chloro-2-oxobicyclo[2.2.2]octane-1-carboxylate (S-3). In an oven-dried round bottom flask under a balloon of dry nitrogen containing **1** (6.363 g, 30.00 mmol) in CH_2Cl_2 (300 mL) was carefully added PCl_5 (12.50 g, 60.03 mmol) at 0 °C. After stirring overnight, the reaction was quenched with water at 0 °C, extracted with CH_2Cl_2 , dried over Na_2SO_4 , and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel) using EtOAc:hexane (5:95) as the eluent to afford **S-3** as a white solid (3.98 g, 58%). $R_f = 1.9/4.0$ (20% EtOAc in hexane). ^1H NMR (CDCl_3 , 400 MHz) δ 4.20 (q, $J = 6.81$ Hz, 2H), 2.79 (s, 2H), 2.39-2.18 (m, 4H), 2.18-1.96 (m, 4H), 1.26 (t, $J = 7.12$ Hz, 3H); ^{13}C NMR (CDCl_3 , 101 MHz) δ 205.4, 170.5, 62.5, 61.3, 53.3, 53.2, 34.9, 26.5, 14.1; IR (neat, ZnSe, cm^{-1}) 2977, 2962, 2917, 2878, 1733, 1718, 1685, 1475, 1457, 1402, 1368, 1329, 1294, 1256, 1185, 1126, 1059, 1040, 962, 892, 820, 747; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{16}\text{ClO}_3^+$ 231.0788; found 231.0779.



Ethyl 4-chloro-2-(((trifluoromethyl)sulfonyl)oxy)bicyclo[2.2.2]oct-2-ene-1-carboxylate (6). In a flame-dried round bottom flask under a balloon of dry nitrogen containing **S-3** (1.154 g, 5.002 mmol) in dry THF (50 mL) was added KHMDS (6.0 mL, 1.0 M in THF, 6.0 mmol) at 0 °C. After stirring for 10 min, a solution of NPhTf_2 (2.322 g, 6.504 mmol) in THF (10 mL) was added to the reaction mixture, and then the temperature was raised to 60 °C and stirred for 1 h. The reaction was quenched with a saturated solution of NH_4Cl , extracted with EtOAc, dried over Na_2SO_4 , and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel) using hexane as the eluent to afford **6** as a colorless liquid (1.265 g, 70%). $R_f = 2.1/4.0$ (20% EtOAc in hexane). ^1H NMR (CDCl_3 , 400 MHz) δ 6.22 (s, 1H), 4.24 (q, $J = 7.20$ Hz, 2H), 2.12-1.99 (m, 4H), 1.98-1.85 (m, 4H), 1.30 (t, $J = 7.19$ Hz, 3H); ^{13}C NMR (CDCl_3 , 101 MHz) δ 170.0, 146.3, 125.0, 118.4 (q, $J = 320.9$ Hz), 63.5, 61.9, 46.9, 36.2, 30.9, 13.8; ^{19}F NMR (CDCl_3 , 376 MHz) δ -74.2; IR (neat, ZnSe, cm^{-1}) 3091, 2984, 2918, 2878, 1741, 1637, 1477, 1456, 1427, 1369, 1342, 1317, 1280, 1255, 1205,

1143, 1113, 1081, 1030, 1010, 956, 907, 865, 839, 784, 754, 741, 669; HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{12}H_{15}ClF_3O_5S^+$ 363.0821; found 363.0829.



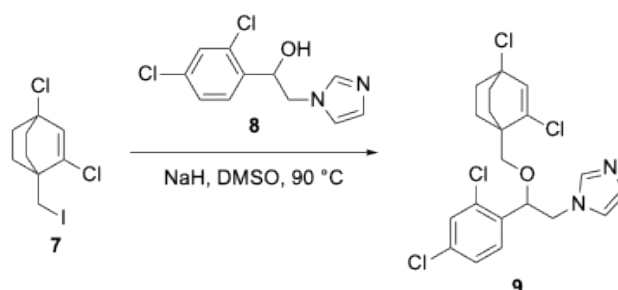
(2,4-Dichlorobicyclo[2.2.2]oct-2-en-1-yl)methanol (S-4). In a nitrogen filled glove box, a screw-cap vial was charged with $Ni(OAc)_2 \cdot 4H_2O$ (0.0074 g, 0.030 mmol), Zn powder (0.0040 g, 0.061 mmol), 1,5-cyclooctadiene (7 μ L, 0.06 mmol), LiCl (0.0383 g, 0.903 mmol) in degassed DMA (0.3 mL) and THF (0.9 mL). After stirring for 10 min, the preformed nickel catalyst solution was added to a separate vial containing enol triflate **6** (0.1088 g, 0.2999 mmol), and the mixture was stirred overnight at room temperature. The reaction was quenched with water, extracted with diethyl ether, dried over Na_2SO_4 , and then concentrated under reduced pressure. The crude product was used without further purification for the next step.

In a flame-dried round bottom flask under a balloon of dry nitrogen containing the crude intermediate in CH_2Cl_2 (3 mL) was added DIBAL-H (0.9 mL, 1.0 M in hexane, 0.9 mmol) at 0 °C. After stirring for 2 h at room temperature, the reaction was quenched with saturated NH_4Cl at 0 °C, extracted with CH_2Cl_2 , dried over Na_2SO_4 , and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel) using EtOAc:hexane (10:90) as the eluent to afford **S-4** as a colorless liquid (0.0398 g, 64% over two steps). $R_f = 0.7/4.0$ (20% EtOAc in hexane). 1H NMR ($CDCl_3$, 400 MHz) δ 6.33 (s, 1H), 3.72 (s, 2H), 2.07-1.97 (m, 2H), 1.93-1.78 (m, 3H), 1.64-1.54 (m, 4H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 134.0, 133.8, 66.5, 65.8, 43.6, 36.9, 30.0; IR (neat, ZnSe, cm^{-1}) 3420, 2943, 2872, 1717, 1604, 1473, 1456, 1387, 1331, 1308, 1232, 1140, 1053, 1025, 1005, 989, 964, 949, 895, 859, 841, 804, 758; HRMS (ESI) m/z : molecular weight peak not found despite extensive efforts.



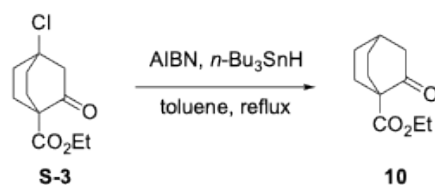
2,4-Dichloro-1-(iodomethyl)bicyclo[2.2.2]oct-2-ene (7). In an oven-dried round bottom flask under a balloon of dry nitrogen with **S-4** (0.1035 g, 0.4998 mmol) in THF (5 mL) was added imidazole (0.1021 g, 1.500 mmol), PPh_3 (0.3934 g, 1.500 mmol), and I_2 (0.3808 g, 1.500 mmol). After stirring for 2 d at room temperature, the reaction was quenched with 10% $Na_2S_2O_3$, extracted with EtOAc, dried over Na_2SO_4 , and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel) using hexane as the eluent to afford **7** as a colorless liquid (0.1066 g, 67%). $R_f = 2.5/4.0$ (20% EtOAc in hexane). 1H NMR ($CDCl_3$, 400 MHz) δ 6.35 (s, 1H), 3.46 (s, 2H), 2.10-1.99 (m, 2H), 1.92-1.79 (m, 4H), 1.57-1.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 133.8, 132.5, 65.5, 40.5, 37.1,

34.1, 13.4; IR (neat, ZnSe, cm^{-1}) 3071, 2961, 2907, 2869, 1602, 1507, 1482, 1453, 1435, 1418, 1337, 1307, 1263, 1198, 1153, 1135, 1118, 1038, 1006, 962, 940, 862, 843, 805, 794, 755, 720, 695; HRMS (EI) m/z : $[M]^+$ calcd for $\text{C}_9\text{H}_{11}\text{Cl}_2\text{I}^+$ 315.9283; found 315.9278.



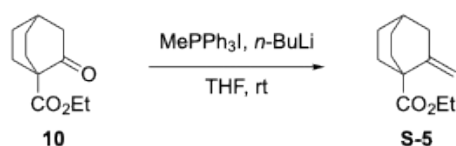
1-(2-((2,4-Dichlorobicyclo[2.2.2]oct-2-en-1-yl)methoxy)-2-(2,4-dichlorophenyl) ethyl)-1H-imidazole (9). In a nitrogen filled glove box, a round bottom flask was charged with **8** (0.0772 g, 0.300 mmol) and NaH (0.0136 g, 60% dispersion in mineral oil, 0.3400 mmol) in anhydrous DMSO (1 mL). After stirring for 10 min, to the mixture was added **7** (0.0634 g, 0.2000 mmol) in anhydrous DMSO (1 mL), and the resulting solution was removed from the glove box and stirred for 2 d at 70 °C. The reaction was quenched with water, extracted with CH_2Cl_2 , dried over Na_2SO_4 , and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel) using EtOAc:hexane (50:50) as the eluent to afford **9** as a yellow viscous liquid (0.0570 g, 66%). $R_f = 1.2/4.0$ (50% EtOAc in hexane). ^1H NMR (CDCl_3 , 400 MHz) δ 7.43 (s, 2H), 7.24 (dd, $J = 8.36, 1.86$ Hz, 1H), 7.16 (d, $J = 8.36$ Hz, 1H), 7.00 (s, 1H), 6.86 (s, 1H), 6.30 (s, 1H), 4.96 (dd, $J = 6.87, 2.77$ Hz, 1H), 4.23 (dd, $J = 14.46, 2.65$ Hz, 1H), 4.05 (dd, $J = 14.35, 6.96$ Hz, 1H), 3.39 (d, $J = 9.61$ Hz, 1H), 3.33 (d, $J = 9.61$ Hz, 1H), 2.08-1.93 (m, 2H), 1.91-1.74 (m, 2H), 1.73-1.58 (m, 2H), 1.57-1.45 (m, 1H), 1.43-1.21 (m, 1H); ^{13}C NMR (CDCl_3 , 101 MHz) δ 137.8, 134.9, 133.8, 133.7, 133.6, 133.1, 129.6, 128.8, 128.6, 127.8, 119.9, 78.5, 73.4, 65.5, 51.3, 42.4, 36.6, 30.4; IR (neat, ZnSe, cm^{-1}) 3110, 3086, 2929, 2870, 1734, 1717, 1654, 1603, 1588, 1559, 1506, 1471, 1435, 1381, 1344, 1308, 1285, 1231, 1185, 1108, 1098, 1074, 1043, 1029, 1006, 968, 905, 862, 843, 822, 789, 754, 735, 658; HRMS (ESI) m/z : $[M+H]^+$ calcd for $\text{C}_{20}\text{H}_{21}\text{Cl}_4\text{N}_2\text{O}^+$ 445.0408; found 445.0407.

Synthesis of sonidegib analog **14**

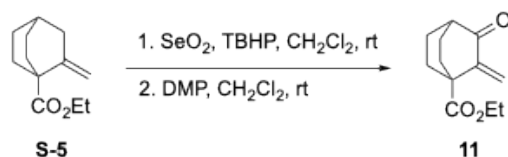


Ethyl 2-oxobicyclo[2.2.2]octane-1-carboxylate (10). In an oven-dried round bottom flask under a balloon of dry nitrogen with **S-3** (0.4614 g, 2.000 mmol) in toluene (20 mL) was added tributyltin hydride (1.08 mL, 4.02 mmol) and AIBN (0.0492 g, 0.300 mmol), and I_2 (0.1904 g, 1.500 mmol). After the reaction was heated to reflux for 5 h, the mixture was quenched with I_2 and 2N NaOH, extracted with EtOAc, dried over Na_2SO_4 , and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel) using

EtOAc:hexane (10:90) as the eluent to afford **10** as a white solid (0.3389 g, 86%). $R_f = 1.6/4.0$ (20% EtOAc in hexane). $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 4.17 (q, $J = 7.08$ Hz, 2H), 2.32-2.29 (m, 2H), 2.29-2.15 (m, 3H), 1.90 (ddd, $J = 16.14, 10.92, 5.21$ Hz, 2H), 1.81-1.61 (m, 4H), 1.24 (t, $J = 7.09$ Hz, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 101 MHz) δ 211.0, 171.7, 60.8, 54.0, 44.3, 27.8, 25.8, 24.6, 14.1; IR (neat, ZnSe, cm^{-1}) 2938, 2873, 1738, 1476, 1454, 1403, 1390, 1366, 1346, 1251, 1192, 1172, 1130, 1101, 1056, 1035, 960, 911, 857, 823, 808, 761, 702; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{17}\text{O}_3^+$ 197.1178; found 197.1181.

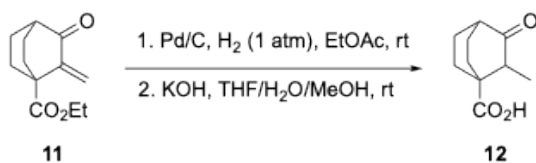


Ethyl 2-methylenebicyclo[2.2.2]octane-1-carboxylate (S-5). In a flame-dried round bottom flask under a balloon of dry nitrogen was added methyltriphenylphosphonium iodide (13.74 g, 33.99 mmol) and THF (78 mL). After the reaction vessel was cooled to 0 °C with an ice bath, *n*-butyllithium (26.1 mL, 1.6 M in hexane, 41.8 mmol) was carefully added and then the reaction mixture was stirred for 30 min. Then a solution of **10** (5.129 g, 26.14 mmol) dissolved in THF (52 ml) was added dropwise. Next, the reaction mixture was allowed to warm to room temperature and then was stirred overnight. After the completion of the reaction (determined by TLC), the reaction mixture was cooled to 0 °C, and then quenched with 10% $\text{Na}_2\text{S}_2\text{O}_3$. The resulting biphasic mixture was extracted with CH_2Cl_2 and the combined organic fractions were washed with brine, dried over Na_2SO_4 , and then concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel) using EtOAc:hexane (2:98) as the eluent to afford **S-5** as a colorless oil (3.000 g, 59%). $R_f = 2.5/4.0$ (20% EtOAc in hexane). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 4.73 (t, $J = 2.02$ Hz, 1H), 4.60 (t, $J = 2.37$ Hz, 1H), 4.15 (q, $J = 7.11$ Hz, 2H), 2.32 (q, $J = 2.76$ Hz, 2H), 2.01-1.96 (m, 2H), 1.84-1.77 (m, 1H), 1.75-1.64 (m, 2H), 1.64-1.52 (m, 4H), 1.24 (t, $J = 1.24$ Hz, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 101 MHz) δ 175.3, 149.6, 106.1, 60.2, 46.4, 35.6, 28.5, 26.2, 25.4, 14.2; IR (neat, ZnSe, cm^{-1}) 2931, 2866, 1730, 1644, 1456, 1365, 1331, 1252, 1232, 1189, 1067, 1041, 878; HRMS (ESI/Q-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{19}\text{O}_2^+$ 195.1385; found 195.1388.



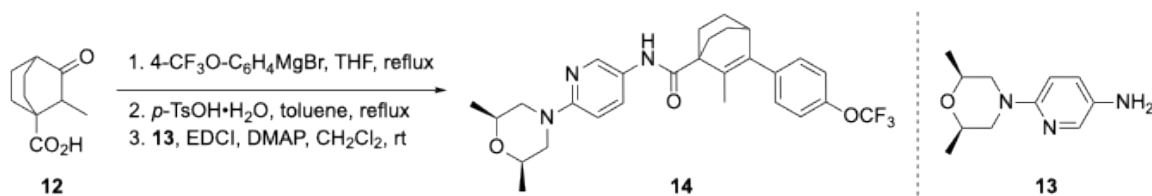
Ethyl 2-methylene-3-oxobicyclo[2.2.2]octane-1-carboxylate (11). In a flame-dried round bottom flask under a balloon of dry nitrogen with bicyclic olefin **S-5** (3.000 g, 15.29 mmol) and SeO_2 (5.091 g, 45.88 mmol) in CH_2Cl_2 (122 mL) was added TBHP (27.8 mL, 5.5 M in nonane, 156 mmol) at 0 °C. After stirring for 3 h at room temperature, the reaction was quenched with water at 0 °C, extracted with CH_2Cl_2 , dried over Na_2SO_4 , and then concentrated under reduced pressure to afford the crude intermediate. This was dissolved in CH_2Cl_2 (122 mL) and DMP (7.781 g, 18.35 mmol) was added. After stirring for 3 h at room temperature, the reaction was quenched with 10% $\text{Na}_2\text{S}_2\text{O}_3$ and NaHCO_3 at 0 °C, extracted with CH_2Cl_2 ,

dried over Na₂SO₄, and then concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel) using EtOAc:hexane (10:90) as the eluent to afford **11** as a colorless oil (2.2601 g, 71% over two steps). R_f = 1.6/4.0 (20% EtOAc in hexane). ¹H NMR (CDCl₃, 400 MHz) δ 6.05 (d, *J* = 0.56 Hz, 1H), 5.15 (t, *J* = 0.68 Hz, 1H), 4.20 (q, *J* = 7.07 Hz, 2H), 2.46-2.41 (m, 1H), 2.13-2.02 (m, 2H), 1.95-1.80 (m, 6H), 1.26 (t, *J* = 7.15 Hz, 3H); ¹³C NMR (CDCl₃, 101 MHz) δ 201.9, 172.9, 145.8, 117.0, 60.8, 48.0, 41.3, 27.9, 22.5, 14.1; IR (neat, ZnSe, cm⁻¹) 2958, 2926, 2854, 1734, 1717, 1623, 1457, 1364, 1265, 1241, 1171, 1094, 1049, 1029, 941, 869, 805; HRMS (ESI) *m/z*: [M+H]⁺ calcd for C₁₂H₁₇O₃⁺ 209.1178; found 209.1177.



2-Methyl-3-oxobicyclo[2.2.2]octane-1-carboxylic acid (12). In an oven-dried round bottom flask under a balloon of hydrogen with compound **11** (2.2601 g, 10.852 mmol) in EtOAc (222 mL) was added palladium on carbon [232.0 mg, 10 wt % on carbon (wetted with ca. 55% water), 2.0 mol %]. After stirring for 2 h at room temperature, the reaction mixture was filtered through celite and the filter cake was washed with ethyl acetate. The filtrate was then concentrated under reduced pressure. The crude product was used without further purification for the next step.

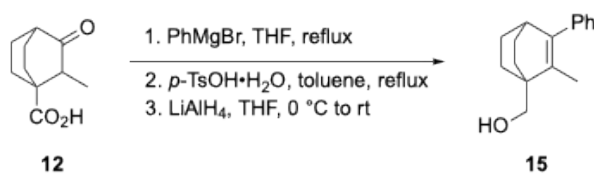
In an oven-dried round bottom flask under a balloon of dry nitrogen containing the crude intermediate in THF (20 mL), methanol (40 mL), and water (60 mL) was added potassium hydroxide (1.830 g, 32.62 mmol). After stirring overnight, the reaction mixture was cooled to room temperature, diluted with water and washed with CH₂Cl₂. The aqueous layer was acidified (pH = 2) with concentrated HCl, and subsequently extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and then concentrated under reduced pressure to afford **12** as a white solid (1.751 g, 89% over two steps). R_f = 2.3/4.0 (EtOAc). ¹H NMR (CDCl₃, 400 MHz) δ 9.51 (br, 1H), 2.53 (qd, *J* = 7.49, 1.34 Hz, 1H), 2.33-2.28 (m, 1H), 2.04-1.92 (m, 3H), 1.92-1.70 (m, 5H), 1.13 (d, *J* = 7.35 Hz, 3H); ¹³C NMR (CDCl₃, 101 MHz) δ 217.5, 180.7, 48.6, 46.2, 41.6, 30.1, 22.8, 22.1, 20.9, 11.8; IR (neat, ZnSe, cm⁻¹) 3145, 2967, 2879, 2602, 2576, 1729, 1690, 1457, 1394, 1371, 1344, 1318, 1287, 1223, 1192, 1078, 1017, 943, 906, 870, 835, 731, 697; HRMS (ESI) *m/z*: [M+H]⁺ calcd for C₁₀H₁₅O₃⁺ 183.1021; found 183.1024.



***N*-(6-(*cis*-2,6-Dimethylmorpholino)pyridin-3-yl)-2-methyl-3-(4-(trifluoromethoxy)phenyl)bicyclo[2.2.2]oct-2-ene-1-carboxamide (**14**).** In a flame-dried round bottom flask under a balloon of dry nitrogen was added **12** (0.1822 g, 0.9999 mmol) and THF (2 mL). After the reaction vessel was cooled to 0 °C with an ice bath, a solution of the 4-(trifluoromethoxy)phenylmagnesium bromide solution (10 mL, 1.0 M in THF, 10 mmol) was added dropwise. After the addition of the organometallic reagent was completed, the reaction mixture was heated to reflux and stirred overnight. The mixture was cooled to 0 °C and then a saturated NH₄Cl solution was added. The resulting biphasic mixture was diluted with water and washed with CH₂Cl₂. The aqueous layer was acidified (pH = 2) with concentrated HCl, and subsequently extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and then concentrated under reduced pressure. Next, the crude product was dissolved in toluene (20 mL), and then *p*-TsOH·H₂O (0.1902 g, 0.9999 mmol) was added. After the reaction was heated to reflux for 1 h, the mixture was quenched with water, extracted with CH₂Cl₂, dried over Na₂SO₄, and then concentrated under reduced pressure. The crude product was used directly in the next step without further purification.

To the solution of the crude intermediate in CH₂Cl₂ (4 mL) was added amine **13** (0.0829 g, 0.400 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.0373 g, 0.240 mmol), and DMAP (0.0293 g, 0.240 mmol). After stirring overnight at room temperature, the reaction was quenched with water, extracted with CH₂Cl₂, dried over Na₂SO₄, and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel) using EtOAc:hexane (30:70) as the eluent to afford **14** as a purplish solid (0.2302 g, 45% over three steps). *R*_f = 2.0/4.0 (50% EtOAc in hexane). ¹H NMR (CDCl₃, 400 MHz) δ 8.14 (d, *J* = 2.61 Hz, 1H), 7.94 (dd, *J* = 9.06, 2.69 Hz, 1H), 7.31 (s, 1H), 7.24-7.14 (m, 4H), 6.64 (d, *J* = 8.96 Hz, 1H), 4.00 (d, *J* = 2.13 Hz, 1H), 3.97 (d, *J* = 2.13 Hz, 1H), 3.73 (qd, *J* = 6.25, 2.52 Hz, 2H), 2.85-2.82 (m, 1H), 2.52 (d, *J* = 10.59 Hz, 1H), 2.49 (d, *J* = 10.59 Hz, 1H), 1.99-1.81 (m, 7H), 1.81-1.69 (m, 2H), 1.69-1.56 (m, 2H), 1.27 (s, 3H), 1.26 (s, 3H); ¹³C NMR (CDCl₃, 101 MHz) δ 173.8, 156.8, 147.5, 140.5, 139.2 (*J* = 14.4 Hz), 135.0, 131.9, 129.4, 125.4, 120.6, 106.9, 71.5, 51.2, 49.9, 37.1, 29.0, 26.4, 19.0, 15.1; ¹⁹F NMR (CDCl₃, 376 MHz) δ -58.9; IR (neat, ZnSe, cm⁻¹) 3306, 2974, 2935, 2864, 1645, 1610, 1580, 1495, 1451, 1388, 1377, 1313, 1260, 1165, 1107, 1086, 1001, 920, 906, 852, 808, 738; HRMS (ESI) *m/z*: [M+H]⁺ calcd for C₂₈H₃₃F₃N₃O₃⁺ 516.2474; found 516.2471.

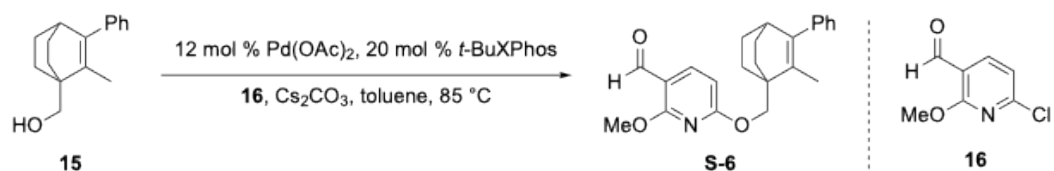
Synthesis of BMS-202 analog **18**



(2-Methyl-3-phenylbicyclo[2.2.2]oct-2-en-1-yl)methanol (15**).** In a flame-dried round bottom flask under a balloon of dry nitrogen was added **12** (0.1822 g, 0.9999 mmol) and THF (2 mL). After the reaction vessel was cooled to 0 °C with an ice bath, a solution of the phenylmagnesium bromide (10 mL, 1.0 M in THF, 10 mmol) was added dropwise. After the

addition of the organometallic reagent was finished, the reaction was heated to reflux and stirred overnight. The mixture was cooled to 0 °C and then a saturated NH₄Cl solution was added. The resulting biphasic mixture was diluted with water and washed with CH₂Cl₂. The aqueous layer was acidified (pH = 2) with concentrated HCl, and subsequently extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and then concentrated under reduced pressure. Next, the crude product was dissolved in toluene (20 mL), and then *p*-TsOH•H₂O (0.1902 g, 0.9999 mmol) was added. After the reaction was heated to reflux for 1 h, the mixture was quenched with water, extracted with CH₂Cl₂, dried over Na₂SO₄, and then concentrated under reduced pressure. The crude product was used directly in the next step without further purification.

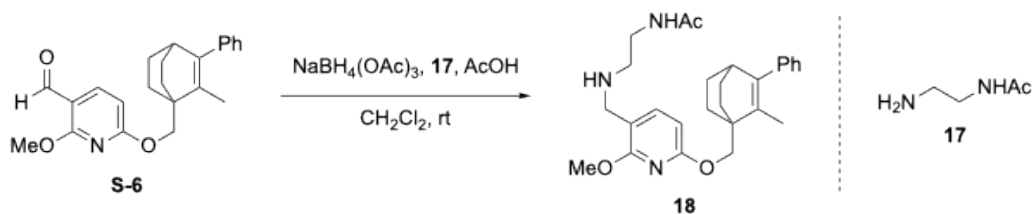
In an oven-dried round bottom flask with the crude intermediate in dry THF (10 mL) was slowly added LiAlH₄ (0.2272 g, 0.5987 mmol) in dry THF (10 mL) at 0 °C. The reaction was allowed to warm to room temperature and was stirred for 2 h. The reaction mixture was cooled to 0 °C and then quenched with water (0.4 mL) and KOH (0.2 mL, 6.0 N). The reaction mixture was filtered, washed with ethyl acetate, dried over Na₂SO₄, and then concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel) using EtOAc:hexane (10:90) as the eluent to afford **15** as a white solid (0.1333 g, 58% over three steps). *R*_f = 1.3/4.0 (20% EtOAc in hexane). ¹H NMR (CDCl₃, 400 MHz) δ 7.39-7.31 (m, 2H), 7.28-7.19 (m, 3H), 3.80 (s, 2H), 2.85-2.78 (m, 1H), 1.96 (br, 1H), 1.95 (s, 3H), 1.77-1.64 (m, 2H), 1.63-1.45 (m, 4H), 1.44-1.30 (m, 2H); ¹³C NMR (CDCl₃, 101 MHz) δ 141.4, 139.9, 135.7, 128.1, 127.8, 125.7, 68.2, 41.8, 37.4, 28.2, 26.4, 13.3; IR (neat, ZnSe, cm⁻¹) 3245, 2940, 2921, 2899, 2861, 2845, 1489, 1456, 1447, 1439, 1376, 1265, 1176, 1148, 1121, 1037, 1022, 759, 706; HRMS (EI) *m/z*: [M]⁺ calcd for C₁₆H₂₀O⁺ 228.1514; found 228.1506.



2-Methoxy-6-((2-methyl-3-phenylbicyclo[2.2.2]oct-2-en-1-yl)methoxy)nicotinaldehyde

(S-6). In a nitrogen filled glove box, a screw-cap vial was charged with **15** (0.1143 g, 0.5006 mmol), **16** (0.1288 g, 0.7507 mmol), Cs₂CO₃ (0.3258 g, 0.9999 mmol), *t*-BuXPhos (0.0850 mg, 0.200 mmol), and palladium(II) acetate (0.0293 mg, 0.131 mmol) in degassed toluene (2 mL). The vial was then sealed with a cap, removed from the glove box, and the mixture was stirred at 85 °C (preheat oil bath). After stirring overnight, the reaction was cooled to room temperature. The reaction mixture was filtered through celite and the filter cake was washed with ethyl acetate. The filtrate was then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel) using EtOAc:hexane (5:95) as the eluent to afford **S-6** as a colorless liquid (0.0432 g, 24%). *R*_f = 2.0/4.0 (20% EtOAc in hexane). ¹H NMR (CDCl₃, 400 MHz) δ 10.2 (d, *J* = 0.75 Hz, 1H), 8.05 (d, *J* = 8.36 Hz, 1H), 7.37-7.29 (m, 2H), 7.26-7.18 (m, 3H), 6.42 (dd, *J* = 8.36, 0.74 Hz, 1H), 4.48 (s, 2H), 4.07 (s, 3H), 2.83-2.79 (m, 1H), 1.88 (s, 3H), 1.77-1.66 (m, 2H), 1.63-1.49 (m, 6H); ¹³C NMR (CDCl₃, 101 MHz) δ 187.5, 166.9, 165.1, 141.2, 140.1, 135.2, 128.2, 127.9, 125.9, 112.0, 103.7, 71.6, 53.7, 40.7,

37.4, 28.9, 26.4, 13.6; IR (neat, ZnSe, cm^{-1}) 3053, 3020,, 2951, 2857, 2754, 1739, 1682, 1645, 1598, 1574, 1481, 1455, 1398, 1386, 1330, 1277, 1242, 1210, 1175, 1153, 1093, 1066, 1007, 977, 944, 909, 868, 822, 760, 737, 702; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{26}\text{NO}_3^+$ 364.1913; found 364.1920.



***N*-(2-(((2-Methoxy-6-((2-methyl-3-phenylbicyclo[2.2.2]oct-2-en-1-yl)methoxy)pyridine-3-yl)methyl)amino)ethyl)acetamide (18)**. Into a round bottom flask was added **S-6** (0.0727 g, 0.200 mmol), *N*-(2-aminoethyl)acetamide (0.0409 g, 0.400 mmol), acetic acid (one drop) and CH_2Cl_2 (20 mL). After the reaction mixture was stirred for 5 min, sodium triacetoxyborohydride (0.1272 g, 0.6002 mmol) was added and then stirred overnight. After the completion of the reaction (determined by TLC), the reaction mixture was quenched with NaHCO_3 , extracted with CH_2Cl_2 , and concentrated under reduced pressure. Then the crude product was acidified with 1N HCl and the mixture was stirred for 10 minutes. The mixture was concentrated under reduced pressure, and the residue was triturated with diethyl ether. The resulting solid was collected, washed with ether, dissolved in CH_2Cl_2 . The solution was basified with 2 N NaOH (pH = 12), extracted with CH_2Cl_2 , dried over Na_2SO_4 , and concentrated under reduced pressure to afford **18** as white solid (0.1469 g, 56%). $R_f = 0.3/4.0$ (5% MeOH in CH_2Cl_2). ^1H NMR (CDCl_3 , 400 MHz) δ 7.39 (d, $J = 7.95$ Hz, 1H), 7.36-7.28 (m, 2H), 7.25-7.16 (m, 3H), 6.29 (d, $J = 7.83$ Hz, 1H), 6.14 (br, 1H), 4.36 (s, 2H), 3.97 (s, 3H), 3.66 (s, 2H), 3.34 (q, $J = 5.54$ Hz, 2H), 2.82-2.77 (m, 1H), 2.74-2.69 (t, $J = 5.96$ Hz, 2H), 1.97 (s, 3H), 1.88 (s, 4H), 1.76-1.64 (m, 2H), 1.63-1.44 (m, 6H); ^{13}C NMR (CDCl_3 , 101 MHz) δ 170.2, 162.2, 160.4, 121.4, 121.1, 139.7, 135.9, 128.2, 127.8, 125.8, 112.2, 101.0, 70.8, 53.3, 47.6, 47.5, 40.8, 38.9, 37.4, 28.9, 26.4, 23.2, 13.6; IR (neat, ZnSe, cm^{-1}) 3304, 3077, 3060, 2923, 2859, 1673, 1586, 1556, 1444, 1394, 1373, 1320, 1243, 1199, 1173, 1116, 1097, 1020, 976, 909, 808, 733, 701; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{27}\text{H}_{36}\text{N}_3\text{O}_3^+$ 450.2757; found 450.2754.

Part II: Computational Studies and Exit Vector Analysis

All density functional theory (DFT) calculations were performed using ORCA 6.0.^[2] Geometry optimizations were carried out at the B3LYP-D4^[3-5] level in the gas phase with the def2-TZVP^[6] basis set, employing tight convergence criteria for both geometry optimization and SCF iterations.

Bixafen

F	0.96000447813438	0.17052544721348	-1.39499516897629
C	2.30293651079811	0.13852023987505	-1.50689805811393
C	2.95647439551298	1.21625848525819	-2.07645433359823

C	4.33589581268081	1.16003003985956	-2.19009621861833
C	5.05365251063445	0.05890724809382	-1.72431965912318
N	6.46834473156403	0.07648510558149	-1.78165996425102
C	7.31241250193075	1.06724202529259	-1.33613385513605
C	6.78774184250868	2.04255985007558	-0.36409684050885
C	5.81828611513400	1.89701065996224	0.61176776957602
N	5.78195265918007	3.05180170178651	1.30291559075972
C	4.95728330018478	3.38103524718344	2.44728699852123
N	6.66120824637647	3.95681003284112	0.83803563807766
C	7.27940365096391	3.35481181895184	-0.16374245288408
C	8.31530270704525	4.05581806953415	-0.98627418566973
F	8.68376711654840	5.22948002674240	-0.40903650152095
F	7.77898719744372	4.35775792909514	-2.22004090859469
O	8.47379570932446	1.10254358760385	-1.70999546058963
C	4.37199151820507	-1.03244643816807	-1.16322234306895
C	5.09188324793396	-2.22111650539741	-0.65098549949018
C	5.91721810683815	-2.98849017016957	-1.47405136656042
C	6.57453042077371	-4.10080386702302	-0.97802942770170
C	6.42393893117317	-4.47205242030676	0.35347578310786
Cl	7.26449011340146	-5.86554273913664	0.94127900565700
C	5.59630029834192	-3.71783641998644	1.18364099704918
Cl	5.37001534063973	-4.13508125754645	2.84949934616049
C	4.93673271673133	-2.60480577484449	0.67777063414738
C	2.98068320380998	-0.97870069893414	-1.06081708107723
H	2.39280146751463	2.06780544949357	-2.43153196636316
H	4.87556421884065	1.98777318869662	-2.62905774670208
H	6.94655160598711	-0.62663750488442	-2.32357080636265
H	5.17859865196148	1.06827073337149	0.85978376794806
H	4.26411858752444	2.56229130031629	2.62785246040655
H	4.39950468064850	4.29418377915913	2.24499319594646
H	5.58241465959254	3.53206108297099	3.32718046054023
H	9.20048840482086	3.44564053144271	-1.15820184166471
H	6.02329444838019	-2.73755208599256	-2.52175260026855
H	7.20760462034545	-4.69768621069387	-1.61950941933924
H	4.30406372424722	-2.03033282133591	1.34013606489926
H	2.42639154632286	-1.80869866598152	-0.64416400661327

Bixafen analog 5

F	0.49452501547047	-0.62798275588665	0.89374877003147
C	1.69003984146519	-0.12167044205534	0.37887079277075
C	1.55518915271844	1.39411259158564	0.15076819948938
C	2.91832558097426	1.93466771602023	-0.33184920378872
C	2.80945281641048	-0.33123597224600	1.34288404720738
C	3.99955580205419	0.17011951996152	0.98186344114274
C	5.10013013738053	0.32852336398643	1.95723023988071
C	4.77355801495371	0.55240028761195	3.30440715400236
C	5.74808548340619	0.68150372188988	4.27556264234458
C	7.09436285472929	0.60780299430979	3.93745155311878
Cl	8.29192314095823	0.78100882085493	5.17416874267589

C	7.44178392529756	0.41152404974461	2.60392262210720
Cl	9.10038606472922	0.31720624880695	2.10972198559681
C	6.45709860486194	0.28117798000474	1.63343047321328
C	3.95861864522807	0.77551546127799	-0.43142281152702
N	5.20147487713517	1.36675463416250	-0.90709991364551
C	6.22555688037106	0.91778254261418	-1.70209026732128
C	6.48288850299617	-0.52320012864698	-1.90154781379275
C	6.25877676051986	-1.62546526695612	-1.09313061772043
N	6.79448021194237	-2.69023268817964	-1.71813991754984
C	6.86278939031788	-4.05813135123686	-1.24573241777716
N	7.35622187932600	-2.36490602366536	-2.89445093429901
C	7.18185488803629	-1.06048757566867	-3.01296199538840
C	7.63834920971159	-0.32308360228428	-4.23530004563365
F	6.53569691365260	0.04183936367315	-4.97568755539245
F	8.40486185018380	-1.12372364579307	-5.02287454637008
O	6.97843819328018	1.73604423331889	-2.21601992129745
C	3.35706563981363	-0.23174239448923	-1.45349153338264
C	2.01492897333530	-0.79621779432766	-0.94888771777251
H	1.24769366815848	1.86393717905610	1.08451440600995
H	0.77007185739018	1.57363001855357	-0.58552851458498
H	3.30267697403593	2.69309354421502	0.35308470489705
H	2.83156896002387	2.39396829000997	-1.31791741624065
H	2.59914089669561	-0.78118462357056	2.30364305749686
H	3.73689361570454	0.65286726363994	3.59235995652509
H	5.47458975064612	0.85774698923135	5.30661508329957
H	6.79168466431476	0.13269103013399	0.62477407224165
H	5.25497620262339	2.37220634384114	-0.82466695732309
H	5.77601031841972	-1.72726740018820	-0.13733098124806
H	6.26990078133815	-4.14583581993605	-0.33786213721821
H	7.89692408746802	-4.32989425237937	-1.03422080563668
H	6.46669602883161	-4.72603858643199	-2.00892664466670
H	8.18967617008224	0.58484945361788	-4.00028325442050
H	4.04754094523302	-1.04015722212398	-1.65013745485327
H	3.23022445220329	0.30657578129457	-2.39377596484621
H	2.07023146495813	-1.87355690180759	-0.79313130096543
H	1.20593991061291	-0.60379497554329	-1.65538329938877

Miconazole

Cl	3.51044214159758	3.89620747672981	0.84637242349765
C	4.48209156674448	2.45864616479291	0.72804657893492
C	5.61845692685512	2.33115612675509	1.51685357158247
C	6.40191585590233	1.20214656569646	1.37145262528498
C	6.09788313207646	0.19692069910497	0.45145203735680
C	7.10487035715267	-0.89738763002480	0.20685531815487
O	8.29184211511234	-0.40396557360590	-0.42911092053497
C	8.06643167094225	0.31059632377918	-1.64090744575591
C	9.20028433475771	-0.04301744215129	-2.60413109811329
N	9.14684631051999	-1.42410624716738	-3.03031978017925
C	9.54126653031212	-2.53234206636177	-2.31412415782839

C	9.21184910325478	-3.60937550116356	-3.09031301016638
N	8.62196912502329	-3.19569191522952	-4.25989596542399
C	8.59555888491811	-1.88798021130756	-4.18964069468834
C	8.00854681681376	1.80119507454543	-1.38049509725617
C	7.10322249907350	2.64882632800444	-2.01231731508422
Cl	6.04087089929431	2.04151309962314	-3.25744410428747
C	6.99972956542663	3.99349752779885	-1.68153045440628
C	7.84971549579723	4.50918989606021	-0.71799756947265
Cl	7.71303332892883	6.18602428298052	-0.27405493371472
C	8.80211026338709	3.70823862977146	-0.10222004727182
C	8.86538536789445	2.36710295382260	-0.43804396123523
C	4.92414454531261	0.34284573434039	-0.28582686067550
Cl	4.42896932939089	-0.86963712510132	-1.44065963812567
C	4.11281090226099	1.46387807151253	-0.15990242684601
H	5.88693290752545	3.11131972611721	2.21430876702618
H	7.30789675371753	1.10756523814850	1.95638117615143
H	6.67642880686092	-1.70008873076806	-0.39406698729139
H	7.45034405050977	-1.31824963763806	1.15100669897078
H	7.13204011506200	-0.01607629999230	-2.09847998373664
H	10.16023310608405	0.15657079520752	-2.12464194258690
H	9.12905821543613	0.59097155138123	-3.48828320199074
H	9.99536523495489	-2.44446109899646	-1.34386033824371
H	9.36995961614833	-4.65378776699121	-2.87655323074423
H	8.20254237684530	-1.21864496142751	-4.93947365100570
H	6.26619289106243	4.62101361493081	-2.16492128560104
H	9.46717653759790	4.12807663527710	0.63902094823800
H	9.56672326388930	1.72070298244433	0.07207607417309
H	3.22232905555552	1.56314670910197	-0.76177011710441

Miconazole analog 9

Cl	1.55295307754216	1.31120481554086	1.47771381848843
C	3.03352584052811	0.71699178533783	0.62043516702538
C	2.65253610490852	0.21185153220789	-0.78463232277345
C	3.94415273046770	-0.20517346150388	-1.52791994613377
C	4.04452178245494	1.81973858068806	0.47253827541600
C	5.14619245229918	1.43383124671137	-0.16129613350487
Cl	6.44250660533835	2.53275471944644	-0.52397792913510
C	5.17903008596815	-0.01527254584474	-0.60512552725258
C	6.43918082224786	-0.45171539195476	-1.33590492574587
O	7.55722612092207	-0.35232473737270	-0.47006894833994
C	8.50605657480276	-1.38598843508464	-0.54371231354868
C	9.42807127698185	-1.20709047394775	0.67023454232479
N	8.68197783416172	-1.23898811356143	1.90889713654792
C	8.26243277321515	-2.36383865830394	2.58498382031134
C	7.45567264507251	-1.91133444579946	3.59232997905547
N	7.35823714467872	-0.54197772948206	3.54662929622794
C	8.09580809156047	-0.17451071853037	2.52640207699581
C	9.27552361821245	-1.43882699995837	-1.84952988956188
C	9.91147379606289	-0.34392172899884	-2.44148440467565

Cl	9.87387314223196	1.24057715685972	-1.71750262411482
C	10.60345420122427	-0.46501989132192	-3.63963889832218
C	10.67336013530760	-1.70150996593569	-4.26184479840584
Cl	11.54144340102857	-1.85011576217577	-5.76169563207705
C	10.05938245619077	-2.81333933602122	-3.70589864700123
C	9.36829749558057	-2.66140709802940	-2.51421301781493
C	4.94537635058298	-0.88901640473369	0.65677274033992
C	3.67261296040021	-0.43760044311602	1.40727192796303
H	2.12948152628750	1.00313302034046	-1.31913024501009
H	1.96299273620995	-0.62753373785865	-0.68378997611377
H	4.07433573749161	0.38622257864746	-2.43554363938048
H	3.89080225309808	-1.25440572563160	-1.82785351163759
H	3.85952253515504	2.81745480041203	0.83946083889729
H	6.30507437463388	-1.48951848505113	-1.66275204124998
H	6.60593267767224	0.16164214375921	-2.22750911495337
H	7.99444003816163	-2.35259467281275	-0.43408248828862
H	9.94396014757566	-0.25191965536369	0.59900314971171
H	10.17630513989979	-1.99993717745601	0.67809168288611
H	8.58883462107964	-3.35099373261185	2.30595789430225
H	6.95208210088678	-2.48897612020516	4.35008834586422
H	8.23258244862702	0.83382036962235	2.17043453022691
H	11.08300748822863	0.39821004616824	-4.07657386982092
H	10.11458439313243	-3.77283150182088	-4.19981465366959
H	8.87515499629365	-3.52363668155513	-2.08123760742868
H	5.81015289164367	-0.82515778608420	1.30981913314518
H	4.85173911962379	-1.92913928539026	0.33341819924832
H	3.91635965055895	-0.09820531654368	2.41250882830359
H	2.95067560376721	-1.25072057568025	1.49633172267934

Sonidegib

C	1.54194213505827	-0.27200589233553	-1.04954231655355
C	2.36270938235915	-0.42700096499776	0.20516911005751
C	2.84007887751380	0.68641324316065	0.91889295858919
C	2.51194171550931	2.07867645381943	0.52486775858028
C	1.18896149618049	2.51029472405897	0.40127657112813
C	0.89208982905971	3.82077231287036	0.06860950462694
C	1.92413655762453	4.72184920550701	-0.14988372113023
O	1.50057879814758	6.00556905065487	-0.50008559588096
C	2.35659370071213	7.04088179996170	-0.58128991696403
F	3.02740035164351	7.25660946918037	0.56556864864414
F	3.27768425396066	6.88510978293606	-1.55377214524761
F	1.64524767501625	8.12979093986084	-0.86067136560661
C	3.24848890315047	4.32978812777997	-0.03324106499260
C	3.52526063863372	3.01085166480090	0.30753571066227
C	3.64867569970862	0.49515687824332	2.04232444329229
C	3.98446358905498	-0.77557520065414	2.47968316722440
C	3.51548063659408	-1.87779929280646	1.78455585104792
C	2.71194427291748	-1.70497591495829	0.66206934945369
C	2.16008537084050	-2.92242180950710	-0.01827763971138

N	3.06343994904217	-3.85143799299735	-0.46564793958111
C	4.46922244981289	-3.72962289854190	-0.57182846444686
C	5.09110736914738	-2.62243383196998	-1.14659130088946
C	6.46594400999477	-2.56540751687520	-1.21539587472300
C	7.22529286526056	-3.65608793724636	-0.74012116974613
N	8.60049650872838	-3.70527955635581	-0.83724465296891
C	9.34219312373513	-4.63230153041301	0.01100515134870
C	10.67246253428135	-4.99968493093966	-0.62768398841599
H	10.46826275067642	-5.54459137515278	-1.56172551204015
C	11.53422841234799	-5.84574796735575	0.28591702111345
O	11.41172700114436	-3.82152822846227	-0.94634461213115
C	10.71150746644922	-2.97650485281670	-1.84721529148625
H	10.50767625914943	-3.54091922989529	-2.77021600788405
C	11.60233453482615	-1.79008675096894	-2.15388314139536
C	9.36821990919720	-2.54802676954825	-1.25892271806124
N	6.62056651214028	-4.71559546911790	-0.18705955130319
C	5.29746724382851	-4.73962704739779	-0.10204073896695
O	0.96103671800467	-3.10553572310597	-0.13950634473005
H	1.72359318527650	0.68955940227958	-1.52558442793625
H	0.47386340793133	-0.35131484214759	-0.83847470082081
H	1.76824225105845	-1.05996556615588	-1.76759758178690
H	0.38013285827302	1.81559569166460	0.58378521969716
H	-0.13130594764527	4.15941824808365	-0.01896891484621
H	4.05990829890821	5.01943293443640	-0.20570584744482
H	4.55873930732018	2.69982065513916	0.39138728509633
H	3.99802531677325	1.36285441918829	2.58767619675900
H	4.60228881251359	-0.90512639878959	3.35882296189409
H	3.77073240240967	-2.87720943640523	2.11117760743780
H	2.63115941849529	-4.69475207482541	-0.81609774561178
H	4.49879738984203	-1.80078251080299	-1.52558899144180
H	6.93347240876094	-1.68895221571664	-1.63481346318584
H	8.73549391382486	-5.51943836461851	0.16380034225687
H	9.53205991610807	-4.17578975701178	0.99433956125445
H	11.02744191703171	-6.77965475984927	0.53553310373316
H	11.75211715441639	-5.30885337057400	1.21108053058432
H	12.47948721503737	-6.08346538800588	-0.20239283107541
H	12.54697891676240	-2.13056383120977	-2.57779480886020
H	11.81825771666193	-1.22952604874930	-1.24248857790964
H	11.12223101476151	-1.12102419135673	-2.87075106521346
H	8.82741166815320	-2.00508853544742	-2.03106469029675
H	9.54318430549321	-1.86053666302864	-0.41662669838030
H	4.86071765037957	-5.61639236451125	0.36910336518490

Sonidegib analog 14

C	2.50085820770072	1.26824624245432	2.40883950946942
C	3.10560939515599	0.34139531097286	1.39597755601987
C	3.88584388717941	-0.71750555911450	1.66750440553739
C	4.23971336046107	-1.21950516508106	3.00778676532518
C	4.09751145187467	-2.57916424569986	3.30853303070653

C	4.43635608729159	-3.08042276190402	4.55267514350698
C	4.94240647166413	-2.22356866260982	5.51988188959321
O	5.25377709792842	-2.84774132734707	6.73025496178124
C	5.72375362290698	-2.16210603547879	7.78762512461036
F	6.90382229213636	-1.55999086396985	7.54122995369285
F	4.87517005500889	-1.20655820368461	8.21330840039974
F	5.90268402395698	-3.03001685674858	8.78087136372921
C	5.11560749734000	-0.87474924256479	5.25437678786092
C	4.76196118709255	-0.38961687650649	4.00007528478390
C	4.49369375115869	-1.37548402055396	0.44949284151673
C	3.36861782715134	-1.80928752600635	-0.50299922845771
C	2.60356816288820	-0.55662022669841	-0.96242955636728
C	3.02754081764240	0.66877409836044	-0.09591634197059
C	2.15789755256529	1.88786361062570	-0.37890639045624
N	0.77866203624263	1.80985199536138	-0.34906370331828
C	-0.19574768064299	0.82243633006196	-0.08866911154311
C	-0.06284671310644	-0.25491040784161	0.78390440193972
N	-1.01934668606822	-1.15139528704964	0.99776597462920
C	-2.19885717442571	-1.04103048622626	0.37998049222379
N	-3.12528846560643	-2.04046252714012	0.61186689284008
C	-4.49013733617129	-1.91219251593476	0.13554073003947
C	-5.15248609852023	-3.28355921997711	0.01783132693594
H	-4.62431152568926	-3.84351624170207	-0.76937573075974
C	-6.62460500983108	-3.17796973505220	-0.32395395217816
O	-5.04295927244880	-4.00510270115114	1.23575511487068
C	-3.68426225479169	-4.20192357874893	1.62441225070811
H	-3.16991957792893	-4.74966127032418	0.82033208695707
C	-3.68769008295135	-5.02836933626242	2.89338712320584
C	-2.98916171087915	-2.86241556911460	1.80986651520925
C	-2.44870125218051	0.04833448486986	-0.47852269982419
C	-1.43980476410422	0.95635052493627	-0.71078148898977
O	2.65218896720932	2.97064455852650	-0.64765576108819
C	4.49850436551420	0.96566041981469	-0.50831847489927
C	5.34933517525216	-0.30265691032110	-0.26677355240911
H	2.51320122076038	0.83420813428311	3.40647193614358
H	1.47094099859284	1.53178303235042	2.16808916830730
H	3.05723750616435	2.21082646436789	2.44248319664685
H	3.70133808129808	-3.25339615262033	2.55994838068141
H	4.31452019840735	-4.12884979853880	4.78904056678380
H	5.52390661429819	-0.20081967159929	5.99128010289736
H	4.91823765199871	0.65910844534890	3.78780371374453
H	5.11192859984005	-2.22769452599806	0.73102210055811
H	2.69896411263445	-2.49905240572229	0.01426958408416
H	3.78659448934698	-2.34386213651902	-1.35933989872874
H	1.53450483665196	-0.73276844884567	-0.93377815074296
H	2.84935230860571	-0.31071782401676	-1.99794802169024
H	0.39472921214276	2.70397749508141	-0.62376089921864
H	0.85546420685339	-0.42402159785510	1.32705968590572
H	-4.49438653745032	-1.45754666675342	-0.85331948034054
H	-5.08830060949736	-1.27542492418330	0.80651261601750

H	-6.76553608336221	-2.66004911596892	-1.27474849779886
H	-7.15915891313413	-2.63083527987669	0.45479687352346
H	-7.06230782613414	-4.17297790460789	-0.40428789370585
H	-4.20496228712908	-5.97318323316661	2.72541625292129
H	-4.20038528024378	-4.49444628439998	3.69563785756582
H	-2.66675108885514	-5.24283351754680	3.21442231132426
H	-1.93169755168038	-3.00650414874269	2.00953313673332
H	-3.43086340358796	-2.34725429655668	2.67662502370003
H	-3.40582051170856	0.19330769145387	-0.95388742798806
H	-1.61568484169542	1.78946964478265	-1.38209434131961
H	4.86682937759812	1.81068491337535	0.06942702288994
H	4.52224351090823	1.26866941455276	-1.55548098671478
H	6.22632089284330	-0.06869161286427	0.33820972970231
H	5.71646342755792	-0.71067990438345	-1.21204359771355

BMS-202

C	0.67052886780169	0.45031200728173	-1.17858586363553
C	1.73941284912808	0.32326587944285	-0.12402253523330
C	2.70025378120439	1.33059008236033	0.06497992202055
C	2.76116467487247	2.53855276146086	-0.79671461391031
C	2.94678459032817	2.43393851044796	-2.17700680712321
C	3.04009525586765	3.56936731648953	-2.97033333346092
C	2.94642634228920	4.83285473759455	-2.39733398319195
C	2.76420304983442	4.95071716285193	-1.02484130870275
C	2.67591510023734	3.81291220327383	-0.23232862520633
C	3.64009492433264	1.20997693450106	1.09241309456157
C	3.65855224261430	0.09951001440111	1.91821313248383
C	2.72905613458943	-0.91015641503016	1.71674218504254
C	1.77265221530711	-0.80572767962056	0.71280065780448
C	0.77271541208565	-1.91197885334788	0.55538722442361
O	0.98473904953106	-2.53176785346784	-0.72624335504281
C	0.09315536849194	-3.45597570550436	-1.13407033262710
C	0.28402527537928	-4.02418637685673	-2.39095982955423
C	-0.64298018032951	-4.96869876694871	-2.80093003266546
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H	3.01675050548981	5.71843928521097	-3.01612343057142
H	2.68804023727008	5.93017829288733	-0.56923505514561
H	2.52671114276855	3.90877544898616	0.83605938873057
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H	-0.25520776321855	-1.54760078272530	0.60741367360200
H	0.89272967248371	-2.66001044482060	1.34053530377592
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H	-3.00022188978588	-3.31264582281469	1.21839615844935
H	-1.98334446416476	-4.57806190981926	1.93336632799228

BMS-202 analog 18

C	1.51054560251634	0.86682430151418	-0.52806657231627
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C	2.67315438376476	-2.67460449384608	1.48759057932432
C	1.90137118029204	-3.44991062815833	2.34124321516295
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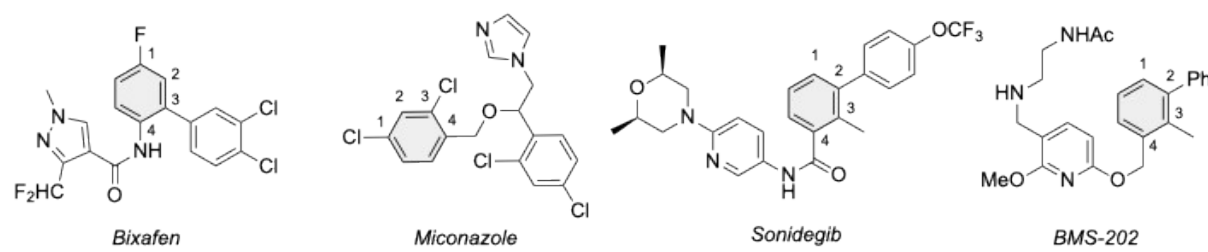
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O	1.86712550662245	10.38505984895292	-11.19417175765423
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H	0.37406114985119	-3.45304944578884	3.85518025909912
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H	1.49766132677473	0.38303814519136	2.31898193356225
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H	3.97380430346623	9.90458442423918	-8.99512447989177
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H	4.02172129304484	6.10221507258711	-3.40716219524080
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H	4.53463579606870	2.55522558294060	0.54434625921857
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H	5.25514788446839	0.88071337971369	1.98505587132919
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Exit vector analysis of bixafen, miconazole, sonidegib, BMS-202, and their BCOene analogs

The geometric parameters of bixafen, miconazole, sonidegib, BMS-202, and their analogs **5**, **9**, **14**, and **18** were compared by exit vector analysis (**Table S1**). The relative spatial orientation of the substituents was quantified using four geometric parameters. The parameter r represents the distance between the carbon atoms bearing the substituent vectors n_x and n_y , while d represents the distance between the two substituents. The angles $\phi_{x,y}$ and $\phi_{y,x}$ correspond to the angles between each substituent vectors (n_x and n_y) and the C_x-C_y bond. The dihedral angle θ is defined by the vectors n_x , C_x-C_y , and n_y .

Exit vector analyses and visualizations were performed using a custom Python 3.13.2 script with NumPy and Matplotlib. The script reads XYZ coordinates, calculates vectors from ring atoms to substituents (specified by the user), computes angles ($\phi_{x,y}$, $\phi_{y,x}$, θ) and distances (d , r), aligns molecules based on ring atoms using the Kabsch algorithm, and visualizes ring atoms, substituents, and exit vectors in 3D.

Table S1. Geometric parameters of calculated optimized geometry of bixafen, miconazole, sonidegib, BMS-202 and their analogs **5**, **9**, **14**, and **18**



	Bixafen	5	Miconazole	9	Sonidegib	14	BMS-202	18	
$d_{1,3}$ (Å)	4.832	4.823	5.365	5.423	$d_{2,3}$ (Å)	2.991	3.094	2.980	3.091
$d_{1,4}$ (Å)	5.523	5.420	6.026	5.908	$d_{2,4}$ (Å)	5.043	5.046	5.059	5.078
$d_{3,4}$ (Å)	2.907	3.048	3.143	3.093	$d_{3,4}$ (Å)	2.910	2.876	2.932	2.947
$r_{1,3}$ (Å)	2.402	2.405	2.388	2.364	$r_{2,3}$ (Å)	1.406	1.343	1.405	1.344
$r_{1,4}$ (Å)	2.760	2.571	2.793	2.577	$r_{2,4}$ (Å)	2.409	2.402	2.417	2.401
$r_{3,4}$ (Å)	1.404	1.538	1.394	1.516	$r_{3,4}$ (Å)	1.401	1.529	1.406	1.526
$\phi_{1,3}$ (°)	30.9	39.3	30.1	38.0	$\phi_{2,3}$ (°)	57.8	53.7	57.8	53.6
$\phi_{3,1}$ (°)	30.8	26.8	32.5	22.0	$\phi_{3,2}$ (°)	58.3	54.2	58.8	54.5
$\phi_{1,4}$ (°)	0.4	3.5	2.3	2.7	$\phi_{2,4}$ (°)	26.9	18.2	27.1	18.0
$\phi_{4,1}$ (°)	3.2	3.7	7.9	0.4	$\phi_{4,2}$ (°)	29.1	36.7	28.4	34.0
$\phi_{3,4}$ (°)	58.3	54.3	58.9	58.2	$\phi_{3,4}$ (°)	59.9	59.6	59.9	58.9
$\phi_{4,3}$ (°)	59.3	64.1	56.4	64.3	$\phi_{4,3}$ (°)	60.0	67.6	59.1	64.9
$\theta_{1,3}$ (°)	2.3	25.1	2.6	5.4	$\theta_{2,3}$ (°)	3.1	3.6	3.0	2.8
$\theta_{1,4}$ (°)	97.2	122.7	22.2	122.4	$\theta_{2,4}$ (°)	5.0	10.7	3.0	1.0
$\theta_{3,4}$ (°)	2.0	10.4	7.7	2.3	$\theta_{3,4}$ (°)	6.0	6.8	1.4	3.5

Definition of vectors and geometric parameters



Analysis of the data revealed that, in general, there is good geometric correlation between trisubstituted benzenes and the corresponding trisubstituted BCOenes. Compared to benzene, the BCOene framework exhibits a flattened geometry at the bridgehead positions. Consequently, the C1–C4 ($r_{1,4}$) and C2–C3 ($r_{2,3}$) distances in BCOene are shorter by

approximately 0.2 Å and 0.06 Å, respectively, relative to the corresponding substituted benzenes, while the C3–C4 ($r_{3,4}$) distance is longer by about 0.12 Å. For the distances between substituents ($d_{x,y}$), no clear trend was observed. However, the differences were minor, with an average deviation of 0.06 Å and a maximum difference of 0.14 Å. For the φ angles, the average deviation was 4.8° and the largest difference was 9.1°. With respect to θ , the average deviation for *ortho*-substitution was 2.5°, with the largest difference being 8.4°. For *meta*-substitution, the average deviation was 8.3°, and the maximum difference reached 22.8° (observed for bixafen and **5**). When the outlier data is excluded, a good correlation in θ is observed. In contrast, *para*-substitution exhibited widely varied θ values (22.2° to 122.4°). However, because the exit vector lies along a symmetry axis of the benzene ring, rotation of the molecule about the ring normal does not alter the structure, rendering θ ill-defined for *para*-substituted benzene. Consequently, the reported θ values are arbitrary and depend on the software-defined in-plane coordinate system. Nevertheless, the $\varphi_{1,4}$ and $\varphi_{4,1}$ angles remain close to 0° (average 3°), consistent with a largely planar orientation of the substituents.^[7] The exit vector analysis reveals that, despite minor distortions in bond distances and angles, BCOene generally serve as effective isosteric replacements for trisubstituted benzenes.

Part III: Determination of Aqueous Solubility

Kinetic solubility assays were conducted to determine the aqueous solubility of the test compounds, following a procedure adapted from Enamine's standard protocol.^[8] Stock solutions (20 mM) of each compound were prepared in DMSO, and aliquots were diluted with phosphate-buffered saline (PBS, pH 7.4) to a final theoretical concentration of 400 µM with 2% DMSO. Samples were prepared in duplicate and equilibrated at 25 °C for 2 h on a thermostatic shaker. After equilibration, suspensions were filtered through 0.22 µm nylon filter. The filtrates were then diluted two-fold with acetonitrile containing 2% DMSO prior to analysis.

For calibration, a series of reference solutions (0, 10, 25, 50, 100, and 200 µM) were prepared in acetonitrile/PBS (1:1) with 2% DMSO. Each sample (800 µL) was transferred into a quartz cuvette and UV–Vis absorbance spectra were measured from 200 to 550 nm with a 5 nm step interval.

Compound concentrations in the filtrates were determined using calibration curves constructed from the reference standards. The absorbance maximum of each compound was selected within a linear range (0-3 OD) to ensure accurate quantification. Data processing and curve fitting were carried out in a spreadsheet (Microsoft Excel) and each calibration curve was assessed for linearity based on the coefficient of determination (R^2).

Table S2. The solubility data of bixafen, miconazole, sonidegib, BMS-202 and their analogs **5, 9, 14, and 18**

Compound	Solubility pH 7.4 (μM)			SE
	Incubation 1	Incubation 2	Mean	
<i>Bixafen</i>	2.88	2.33	2.60	0.27
5	4.96	4.68	4.82	0.14
<i>Miconazole</i>	23.2	31.2	27.2	4.01
9	38.8	44.4	41.6	2.84
<i>Sonidegib</i>	1.96	1.01	1.49	0.48
14	2.04	2.48	2.26	0.22
<i>BMS-202</i>	55.3	62.0	58.6	3.39
18	28.3	26.2	27.3	1.03

Part IV: Measurement of Partition Coefficient (LogP)

The lipophilicity of the compounds was determined by a reverse-phase high-performance liquid chromatography (RP-HPLC) method.^[9] Each compound was prepared as a 20 mM stock solution in DMSO and further diluted to approximately 2 mM in acetonitrile prior to analysis. Three calibration ranges were established based on reference standards with known LogP values (uracil was used to determine the column dead time):

1. For the low lipophilicity range (-0.07 to 2.13), a standard mixture containing urea, caffeine, 4-acetylpyridine, phenol, and benzene was employed with a 55:45 acetonitrile/water mobile phase.
2. For the medium lipophilicity range (0.48 to 3.30), a standard mixture containing 4-acetylpyridine, phenol, benzene, toluene, and naphthalene were employed with a 75:25 acetonitrile/water mobile phase.
3. For the high lipophilicity range (2.73 to 5.74), a standard mixture containing naphthalene, fluorene, pyrene, and triphenylamine was employed with a 95:5 acetonitrile/water mobile phase.

All HPLC analyses were performed on an Agilent 1260 Infinity Quaternary LC system or a Waters 1525 binary pump. Samples ($10 \mu\text{L}$) were injected onto an YMC-Triart C18 column ($5 \mu\text{m}$, $4.6 \times 150 \text{ mm}$) and eluted under isocratic conditions with acetonitrile/water as the mobile phase at a flow rate of 1.0 mL/min . The LogP values of reference standards were plotted against their corresponding $\text{Log}k$ values, which were calculated from the retention time (t_r) and the dead time (t_0) using the equation $k = (t_r - t_0) / t_0$. The resulting LogP– $\text{Log}k$ calibration curve was then used to determine the LogP values of the test compounds based on their measured retention times.

Table S3. The lipophilicity data of bixafen, miconazole, sonidegib, BMS-202 and their analogs **5**, **9**, **14**, and **18**

Compound	Retention time (min)	Dead time (min)	<i>k</i>	Log <i>k</i>	LogP
<i>Bixafen</i>	6.432	2.538	1.534	0.186	2.66
5	7.002	2.538	1.759	0.245	2.82
<i>Miconazole</i>	3.085	2.500	0.234	-0.631	0.47
9	3.260	2.500	0.304	-0.517	0.78
<i>Sonidegib</i>	4.206	2.849	0.476	-0.322	2.90
14	5.899	2.849	1.071	0.030	4.98
<i>BMS-202</i>	4.837	2.985	0.620	-0.207	0.91
18	7.844	2.985	1.628	0.212	1.72

Part V: Assessment of Metabolic Stability in Human Liver Microsomes

Test compounds were prepared as 20 mM stock solutions in DMSO and diluted to 200 μ M working solution (1% DMSO, v/v) in acetonitrile. Human liver microsomes (20 mg/mL, ThermoFisher, SKU# HMMCPL) were diluted to 0.56 mg/mL in 100 mM phosphate buffer (pH 7.4). NADPH (Merck, N1630) was prepared as a 30 mM stock solution in 10 mM MgCl₂.

Control (NCF, no co-factor added), positive control (propranolol), and test compounds were incubated with human liver microsomes. Empty incubation Eppendorf tubes were pre-warm at 37 °C for 5 min. Separately, the microsome solution and test compound were pre-warm at 37 °C for 5 min. The incubation was initiated by the addition of 4 μ L of the compound working solution to the microsome solution, followed by addition of the NADPH solution. For control experiments, a 10 mM MgCl₂ solution was added in place of NADPH. All components were pre-warmed prior to mixing.

The reaction was initiated by the addition of 40 μ L of NADPH. For control experiments, a 10 mM MgCl₂ solution was added in place of NADPH. An aliquot (40 μ L) was collected at 30 s as the initial time point (T₀) and immediately quenched with 48 μ L of ice-cold acetonitrile containing caffeine (98 ng/mL) as an internal standard. Additional aliquots were collected at 7, 15, 25, and 40 min after initiation and quenched with 48 μ L of ice-cold acetonitrile containing the same internal standard.

All samples were vortex-mixed, centrifuged (12,000 rpm, 10 min, 4 °C), and filtered through 0.22 μ m nylon syringe filters prior to solid-phase extraction (SPE) using C18 cartridges (Oasis HLB, 1 cc Vac Cartridge, 30 mg sorbent, 30 μ m; Waters). The SPE cartridges were conditioned with 1 mL of acetonitrile and equilibrated with 1 mL of deionized water containing 0.1% formic acid. The quenched samples were diluted to 1 mL with deionized water and loaded onto the cartridges, followed by washing with 1 mL of deionized water. Analytes

were eluted with 200 μL of acetonitrile containing 0.1% formic acid and analyzed by LC-MS/MS

Relative quantification of the target analytes was performed by liquid chromatography–tandem mass spectrometry (LC-MS/MS). Chromatographic separation was achieved using an Agilent 1200 HPLC system equipped with a Waters Atlantis dC18 column (2.1×100 mm, 3 μm , 100 \AA), maintained at 40 $^{\circ}\text{C}$. The mobile phase consisted of (A) 98:2 water/acetonitrile + 0.1% formic acid and (B) 98:2 acetonitrile/water + 0.1% formic acid. Isocratic elution with 60% B was applied for 10 min at a flow rate of 0.2 mL min^{-1} , and the injection volume was 5 μL .

Mass spectrometric detection was conducted using a triple quadrupole mass spectrometer (API 4000TM System, AB Sciex, Canada) equipped with an electrospray ionization source operated in positive ion mode (ESI⁺). Data acquisition was performed in multiple reaction monitoring (MRM) mode. The optimized source parameters were as follows: ion spray voltage (ISV), +5500 V; nebulizer gas (GS1), 30 psi; heating gas (GS2), 30 psi; curtain gas (CUR), 20 psi; collision gas (CAD), 4 (instrument units) and source temperature (TEM), 400 $^{\circ}\text{C}$. MRM transitions and compound-specific parameters are summarized in **Table S4**. Data acquisition and processing were performed using Analyst[®] software (version 1.6.2).

Table S4. Mass Spectrometry Parameters for MRM Transitions for the analytes

Compounds	M.W. (g/mol)	Precursor ion (m/z)	DP (V)	EP	Product ion (m/z)	CE (V)	CXP (V)
<i>Propranolol</i>	259.16	260	64	5	110	27	5
					129	46	10
					155	34	13
<i>Caffeine</i>	194.08	195	65	11	138	25	9
					110	35	4
<i>Bixafen</i>	413.03	414	80	4	394	20	11
					373	35	20
5	443.08	444	84	9	424	25	11
					159	27	13
<i>Miconazole</i>	413.99	415	99	11	159	41	9
					123	95	10
					133	95	10
9	444.03	445	90	5	189	36	15
					341	27	7
					117	52	9
<i>Sonidegib</i>	485.19	486	150	6	428	41	23
					468	46	22
14	515.24	516	166	12	458	43	12
					151	56	11
					178	67	4
<i>BMS-202</i>	419.22	420	60	11	318	15	8
					181	27	13
18	449.27	450	50	5	211	29	19
					348	15	9

Peak area ratios relative to the internal standard were used as proportional measures of analyte abundance, and the resulting semi-quantitative responses were used to construct clearance profiles for evaluation of relative pharmacokinetic behavior. The elimination rate constant (k_{el}), half-life ($t_{1/2}$), and intrinsic clearance (CL_{int}) were determined by linear regression analysis of $\ln(\text{peak area ratio})$ over time.

$$k_{el} = -\text{slope}$$

$$t_{1/2} = \frac{0.693}{k_{el}}$$

$$CL_{int} = \frac{0.693}{t_{1/2}} \times \frac{\mu L_{incubation}}{mg_{microsomes}}$$

Table S5. The metabolic stability data of propranolol, bixafen, miconazole, sonidegib, BMS-202 and their analogs **5**, **9**, **14**, and **18**

Compound	Time (min)	Peak Area Ratio		Mean	Remaining (%)	R ²	K _{el} (min ⁻¹)	t _{1/2} (min)	CL _{int} (μL/min/mg)	NCF (%)
		Incubation 1	Incubation 2							
<i>Propranolol</i>	0	0.74	0.53	0.63	100	0.9416	0.023	29.7	47	100
	7	0.63	0.55	0.59	92					
	15	0.45	0.41	0.43	67					
	25	0.33	0.30	0.31	49					
	40	0.32	0.22	0.27	42					
<i>Bixafen</i>	0	5.96	4.73	5.34	100	0.1802	0.003*	203.8*	7*	100
	7	5.46	3.49	4.48	84					
	15	3.02	5.88	4.45	83					
	25	5.57	4.04	4.80	90					
	40	5.03	2.55	3.79	71					
5	0	5.14	3.97	4.55	100	0.9176	0.402	1.7	804	100
	7	0.03	0.06	0.05	1					
	15	0.00	0.01	0.01	0					
	25	0.00	0.02	0.01	0					
	40	0.03	0.04	0.03	1					
<i>Miconazole</i>	0	7.91	5.52	6.71	100	0.9869	0.084	8.3	168	100
	7	5.22	2.79	4.00	60					
	15	2.70	2.58	2.64	39					
	25	0.91	0.89	0.90	13					
	40	0.22	0.18	0.20	3					
9	0	1.26	1.16	1.21	100	0.9958	0.090	7.7	179	100
	7	0.70	0.75	0.72	60					
	15	0.28	0.31	0.29	24					
	25	0.06	0.18	0.12	10					
	40	0.00	0.07	0.04	3					

*This parameter is only an estimate because of the high metabolic stability of the compound.

Compound	Time (min)	Peak Area Ratio		Mean	Remaining (%)	R ²	K _{el} (min ⁻¹)	t _{1/2} (min)	CL _{int} (μL/min/mg)	NCF (%)
		Incubation 1	Incubation 2							
<i>Sonidegib</i>	0	4.06	3.20	3.63	100	0.6129	0.013	53.7	26	100
	7	3.40	1.35	2.38	65					
	15	2.83	1.62	2.23	61					
	25	2.28	1.47	1.87	52					
	40	2.69	1.35	2.02	56					
14	0	0.86	0.71	0.78	100	0.0915	0.003*	256.7*	5*	100
	7	0.88	0.51	0.69	89					
	15	0.60	0.51	0.56	71					
	25	0.94	0.59	0.76	97					
	40	0.71	0.57	0.64	82					
<i>BMS-202</i>	0	20.48	15.23	17.86	100	0.4335	0.008*	88.8*	16*	100
	7	16.69	9.33	13.01	73					
	15	9.38	13.95	11.66	65					
	25	17.71	11.20	14.45	81					
	40	14.33	8.23	11.28	63					
18	0	20.63	11.26	15.94	100	0.6628	0.004*	161.2*	9*	100
	7	20.02	10.57	15.30	96					
	15	18.62	8.18	13.40	84					
	25	16.95	10.02	13.49	85					
	40	17.57	9.35	13.46	84					

*This parameter is only an estimate because of the high metabolic stability of the compound.

Part VI: Bioactivity

Antifungal assays

Sclerotinia sclerotiorum BCRC 34830 and *Cryptococcus neoformans* ATCC 90113 were purchased from Bioresource Collection and Research Center (Taiwan). Premixed powder of potato dextrose agar (PDA) was purchased from HiMedia (India) and Mueller-Hinton agar (MHA) was prepared by powders of beef extract (2.0 g/L), casein hydrolysate (17.5 g/L), starch (1.5 g/L) and agar (17.0 g/L) as stock solutions (12.8 mg/mL). The standard broth microdilution method was not applicable due to poor water solubility of our compounds. We instead

performed assays based on the disk diffusion assay and agar dilution assays reported by Denisenko et al. and in protocols published by the Clinical and Laboratory Standards Institute (M44) with slight modifications.^[10,11] All assays were performed in triplicates.

Agar dilution method. A four-fold dilution series for each compound was prepared in DMSO 1.6, 0.4, 0.1, 0.025, 0.0063, 0.0016 mg/mL of isostere **5**, 1.6, 0.4, 0.1, 0.025, 0.0063, 0.0016, 0.00039, 0.000098, 0.000024, 0.0000061 mg/mL of bixafen and then diluted 1/100× into molten PDA, so that the final concentrations of test compounds range from 16 to 0.0016 µg/mL or 16 to 0.0000061 µg/mL. The mixture was mixed, poured into petri dishes, and allowed to cool down and solidify in a sterilized hood. PDA containing 1% (w/v) DMSO was used as the negative control. Mycelial plugs ($d = 5$ mm) were taken from the edge of a *S. sclerotiorum* grown on PDA at 25 °C for 2 days to inoculate the compound-infused PDA plates. The diameters (d , unit: mm) of colonies were measured after incubation at 25 °C for 24 hours. The inhibition rate (%)^[12] at 16 µg/mL was calculated as follows:

$$\text{Inhibition rate (\%)} = \frac{d_{\text{control}} - d_{\text{treatment}}}{d_{\text{control}} - 5} \times 100 \%$$

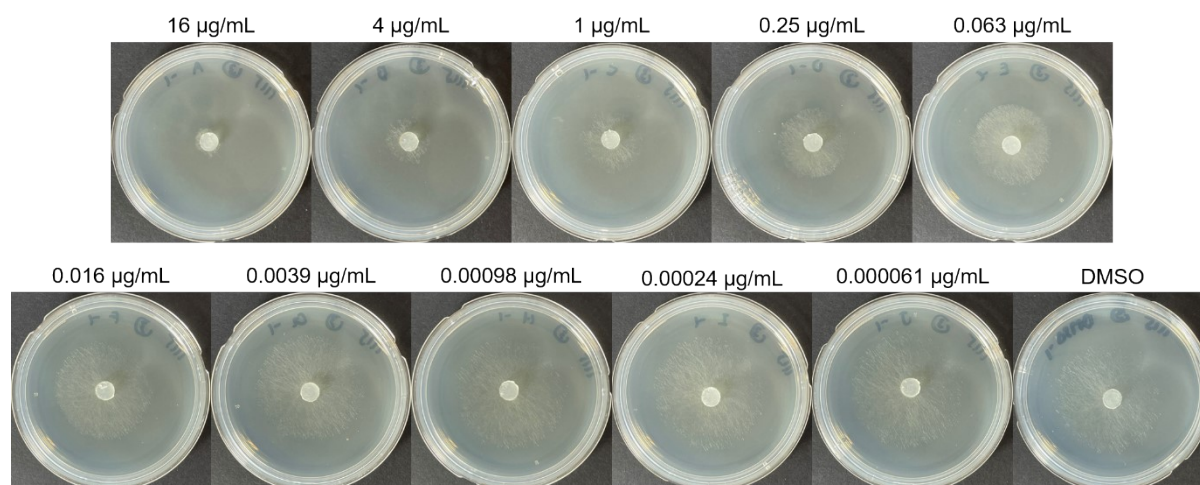


Figure S1. Representative image showing growth inhibition of *Sclerotinia sclerotiorum* by bixafen at different concentrations (16, 4, 1, 0.25, 0.063, 0.016, 0.0039, 0.00098, 0.00024, 0.000061 µg/mL)

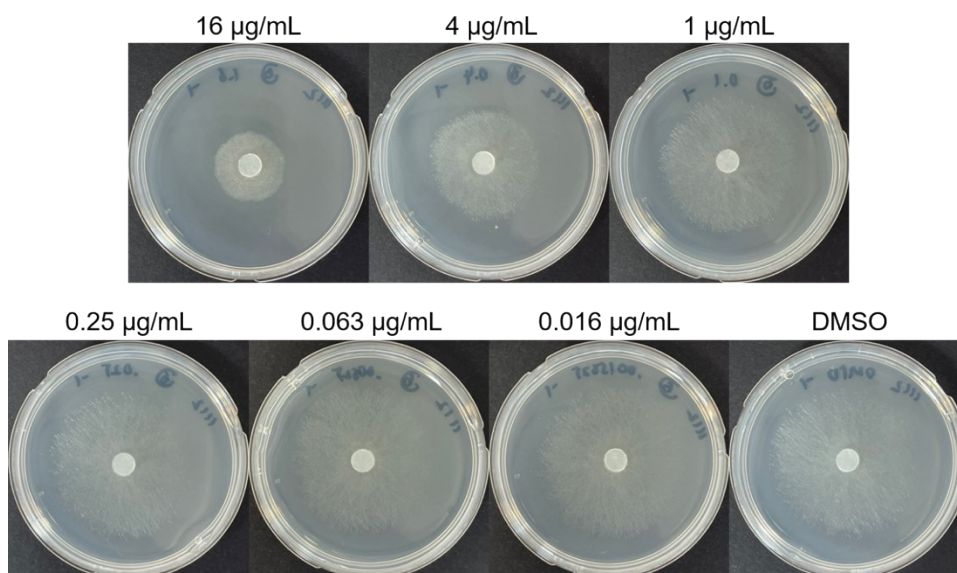


Figure S2. Representative image showing growth inhibition of *Sclerotinia sclerotiorum* by bixafen isostere **5** at different concentrations (16, 4, 1, 0.25, 0.063, 0.016 µg/mL)

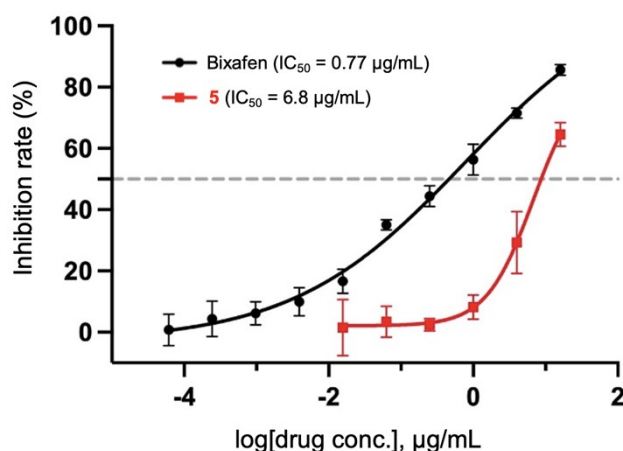


Figure S3. Dose–response curves for the growth inhibition of *Sclerotinia sclerotiorum* by bixafen and isostere **5** determined using the agar dilution method.

Disk diffusion assay. Our assay was based on CLSI M44-A with slight modifications. A two-fold dilution series for each compound was prepared in DMSO (1.6, 0.8, 0.4, 0.2, 0.1, 0.05, 0.025, 0.0125, 0.00625, and 0.003125 mg/mL), and 10 µL of each solution was added onto filter paper disks ($d = 6$ mm). *C. neoformans* was grown on PDA at 35 °C for 2 days, and single colonies were suspended in NaCl solution (8.5 g/L) to an OD_{530} of 0.1 ± 0.01 . The suspension was spread evenly on MHA supplemented with glucose (2% w/v), and methylene blue (0.5 µg/mL). After the inoculated plate has dried, the aforementioned disks were placed at the center of the plates. The diameter of the growth inhibition zones at each concentration was measured after incubating the plates at 35 °C for 72 hours.



Figure S4. Representative image showing growth inhibition of *Cryptococcus neoformans* by miconazole and isostere **9** at different concentrations (1.6, 0.8, 0.4, 0.2, 0.1, 0.05, 0.025, 0.0125, 0.00625, 0.003125 mg/mL)

Antitumor assays

Cell Lines and Culture Conditions. HeLa cells were cultured in DMEM (Dulbecco's Modified Eagle Medium) containing 10% (v/v) fetal bovine serum (FBS) and 1% (v/v) of Antibiotic-Antimycotic (100×) solution (ThermoFisher, USA), and supplemented with test compounds as described below.

MTT assay.^[13] HeLa cells were seeded in 96-well microtiter plates (5×10^3 cells per well) and incubated at 37 °C for 12 h in a humidified incubator with 5% (v/v) CO₂. Cells were washed with fresh media and then supplemented with 0.5, 1.0, 2.0, 4.0, 8.0, 16.0, 32.0, and 64 μM (DMSO ≤ 0.2% (v/v)). Media containing 0.1% (v/v) of DMSO was used as the negative control. After 48 h, MTT was added to each well to a final concentration of 0.5 mg/mL and incubated for another 3 h. The media was removed and 100 μL of DMSO was added to dissolve the formazan crystals. Absorbance was then measured at 570 nm. Cell viability (%) was calculated based on Abs₅₇₀ relative to the negative control.

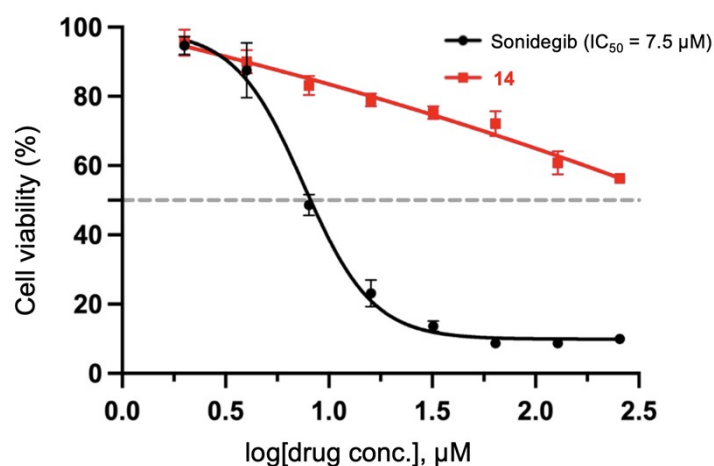


Figure S5. Dose-response curves showing the effect of sonidegib and sonidegib isostere **14** on cell viability in an MTT assay

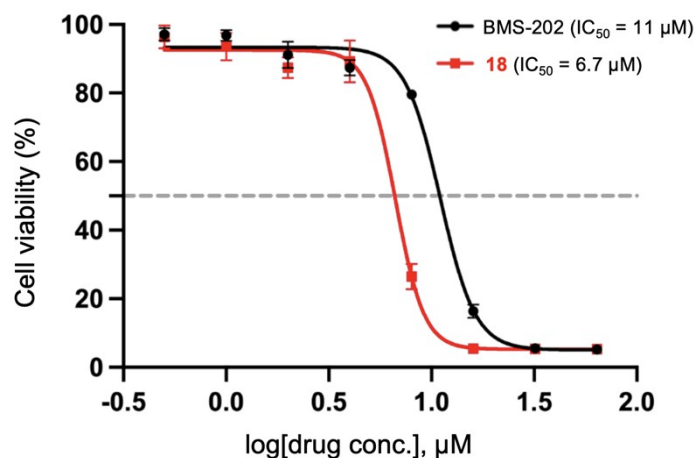


Figure S6. Dose-response curves showing the effect of BMS-202 and BMS-202 isostere **18** on cell viability in an MTT assay

Colony formation assay.^[9] HeLa cells were seeded in 6-well microtiter plates (2×10^4 cells per well) and incubated at 37 °C for 12 h in a humidified incubator with 5% (v/v) CO₂. The cells were then treated with the test compounds at 0.5, 1.0, and 2.0 μM (DMSO ≤ 0.1% (v/v)) and incubated for another 5 days. After treatment, the cells were fixed with 500 μL of ice-cold methanol for 20 min, stained with crystal violet for 30 min at room temperature, air-dried, and photographed.

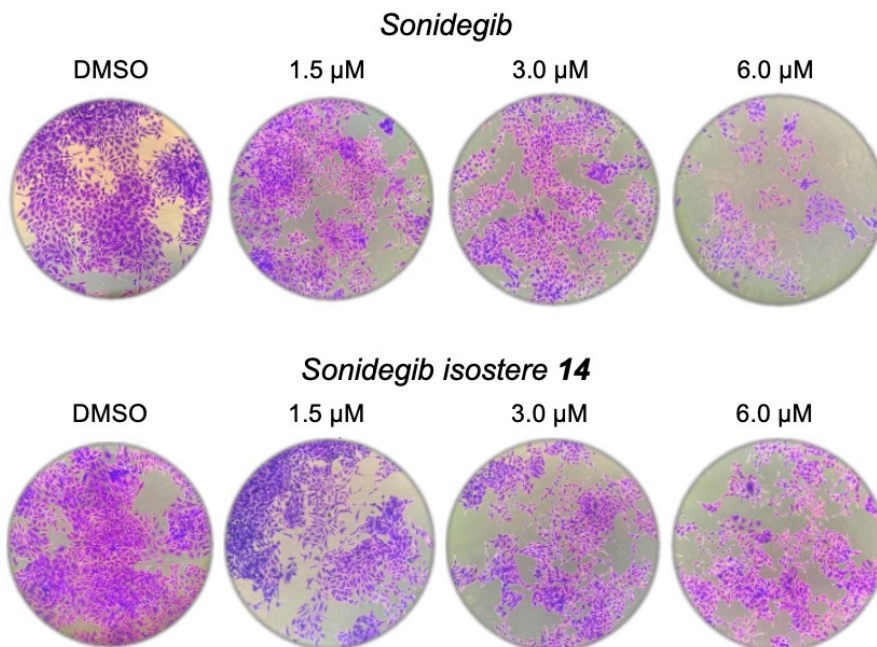


Figure S7. Representative images of colonies formed by HeLa cells in a colony formation assay following treatment with sonidegib and sonidegib isostere **14**

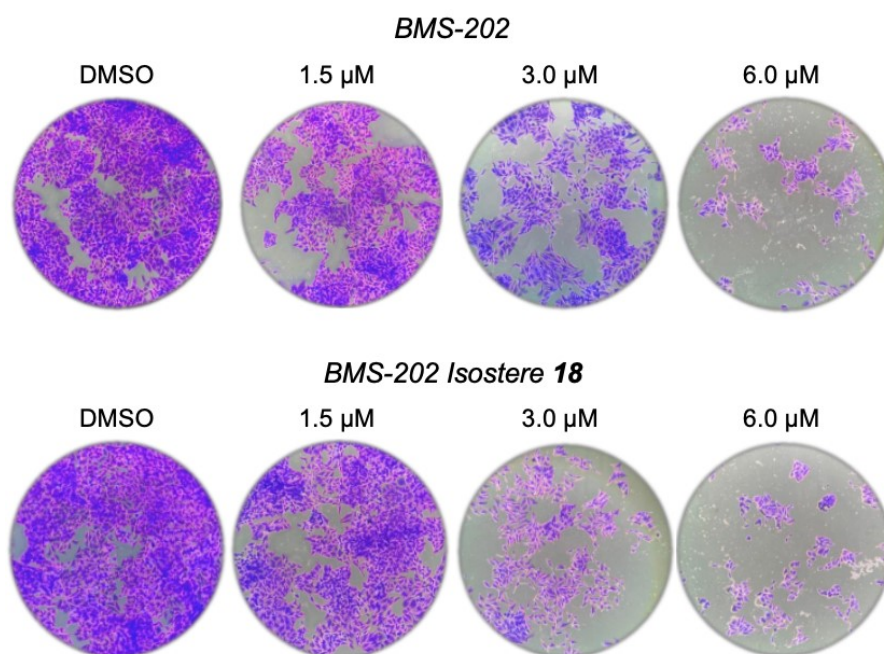
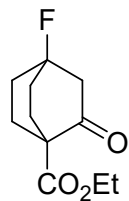


Figure S8. Representative images of colonies formed by HeLa cells in a colony formation assay following treatment with BMS-202 and BMS-202 isostere **18**

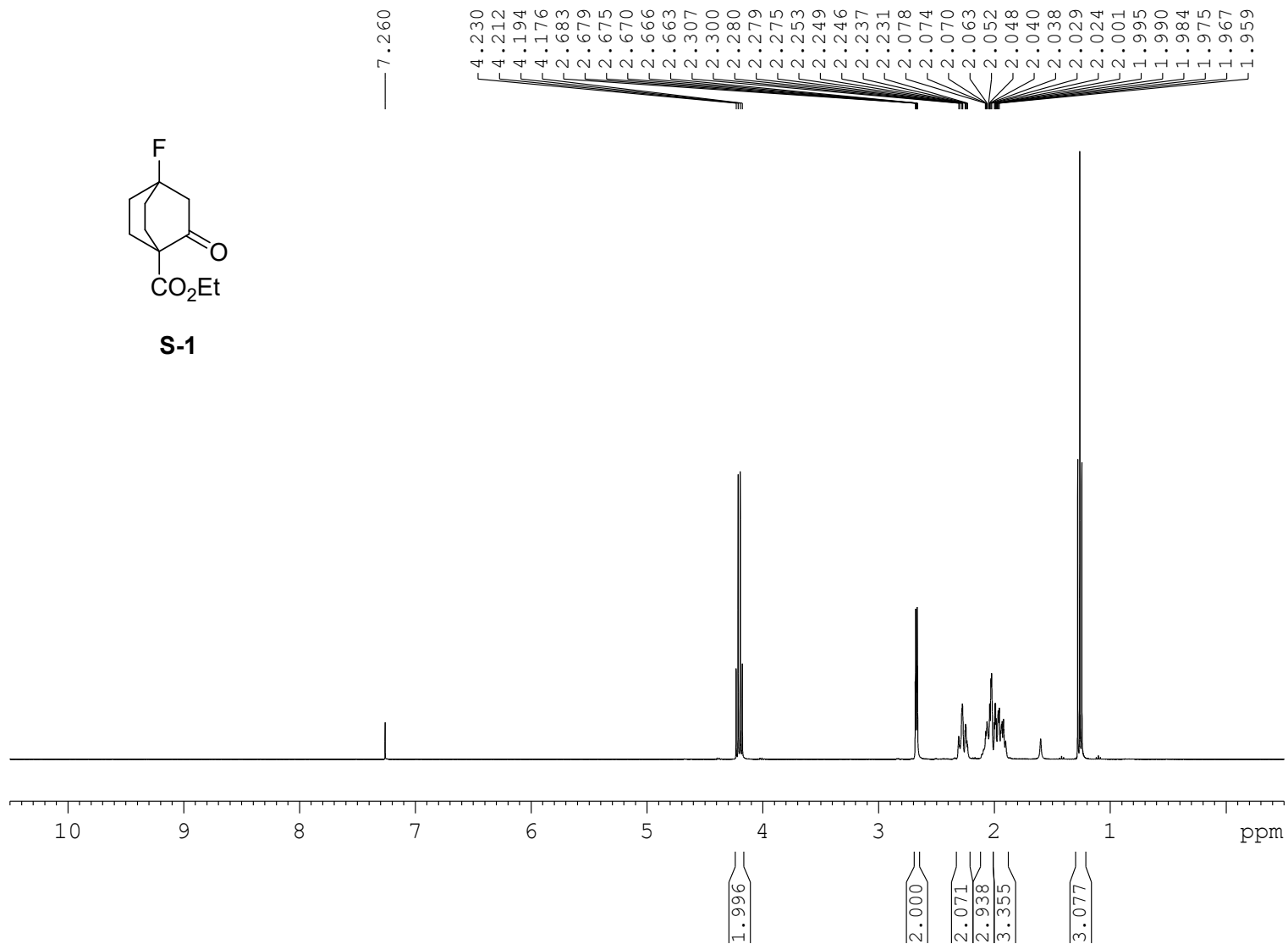
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3. C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785–789.
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11. Clinical and Laboratory Standards Institute, *Method for Antifungal Disk Diffusion Susceptibility Testing of Yeasts*, CLSI Document M44-A, CLSI, Wayne, PA, 2004.
12. Y.-J. Chen, M.-H. Lee, H. Sang and H.-X. Chang, *iScience*, 2025, **28**, 112756.

Part VIII: Copies of NMR Spectra Data



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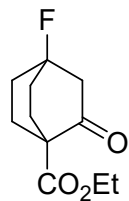
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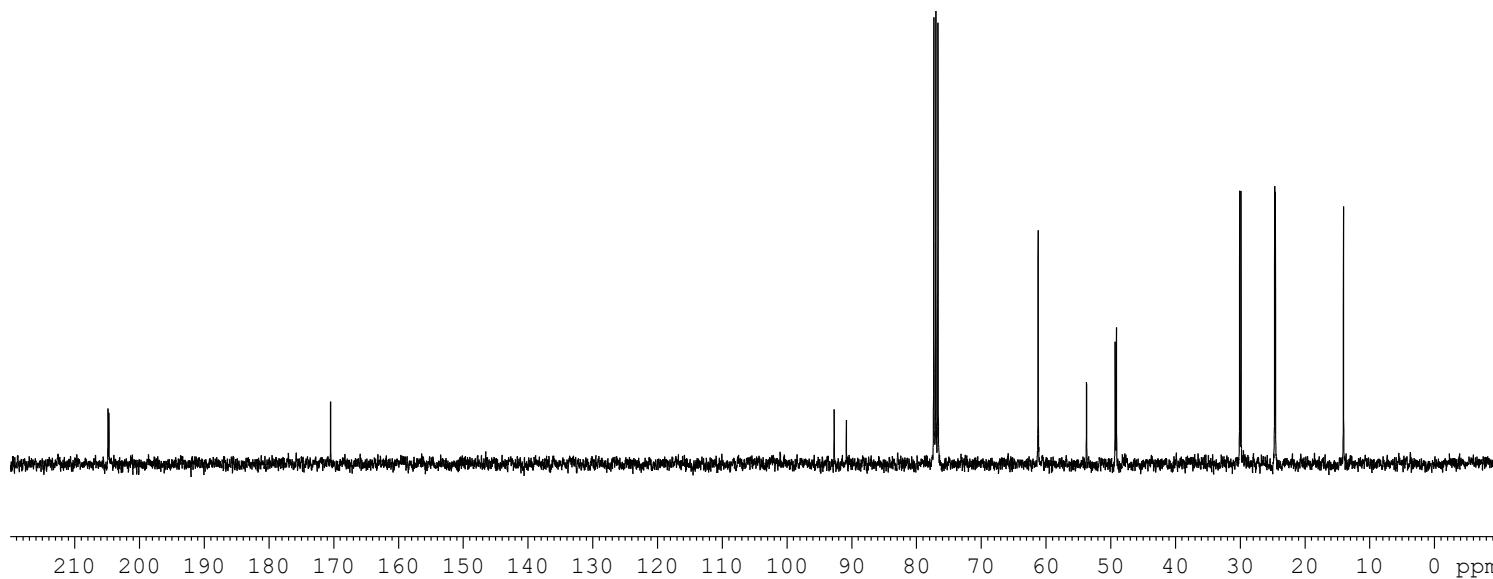
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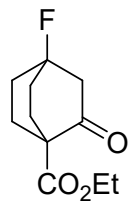
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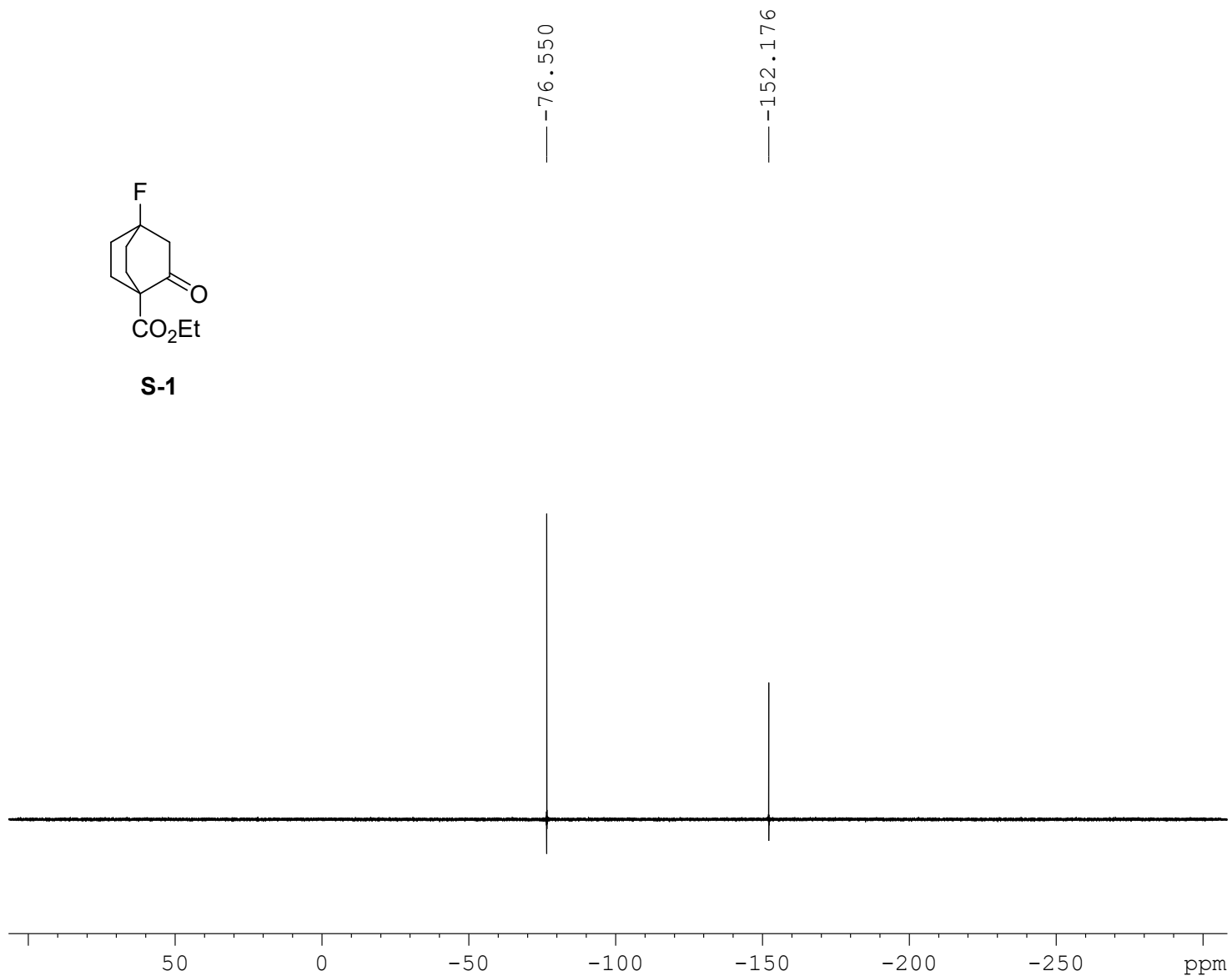
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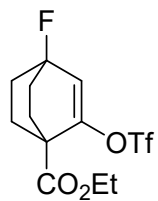
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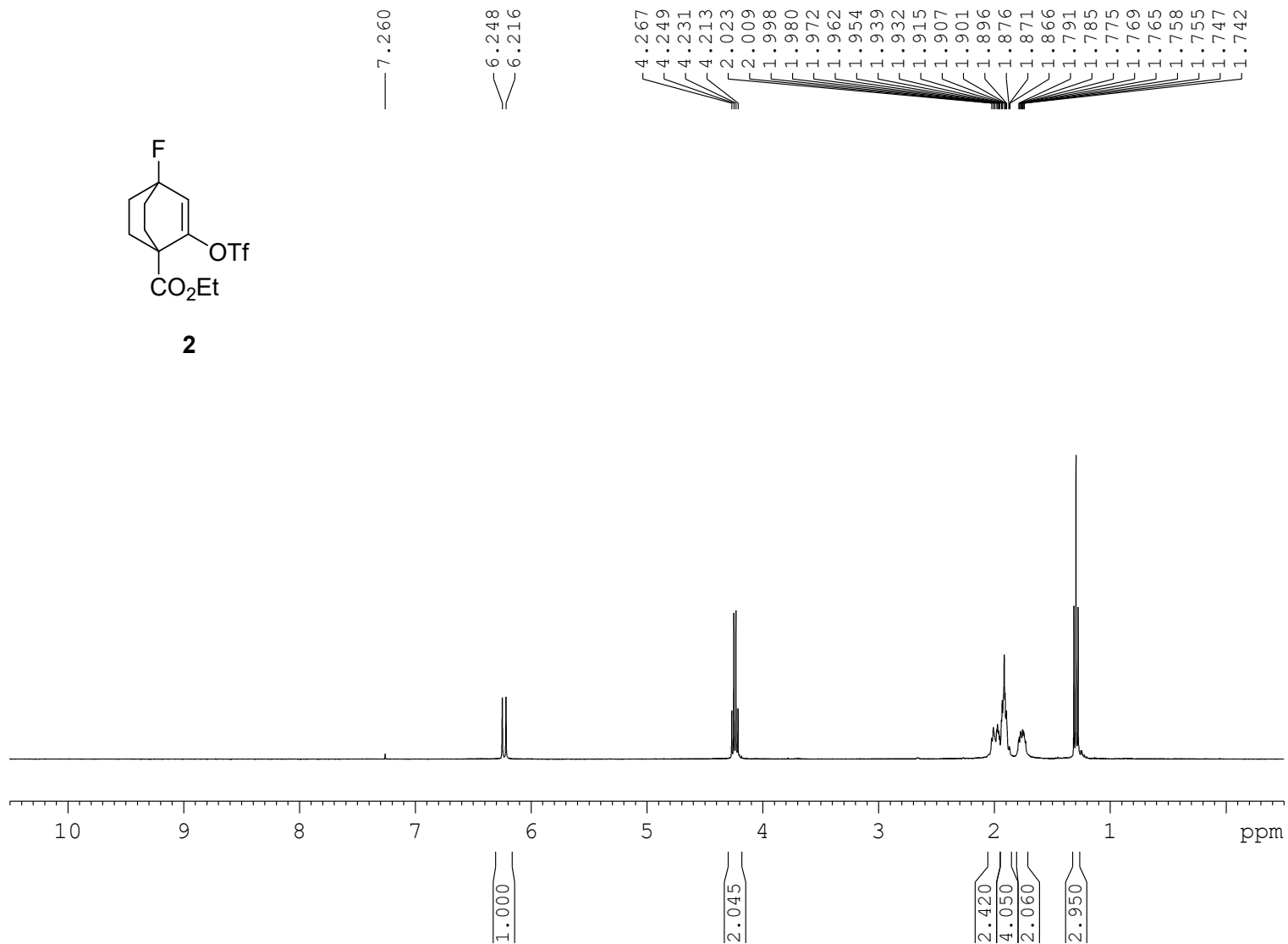
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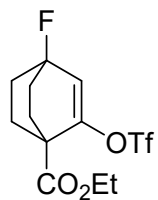
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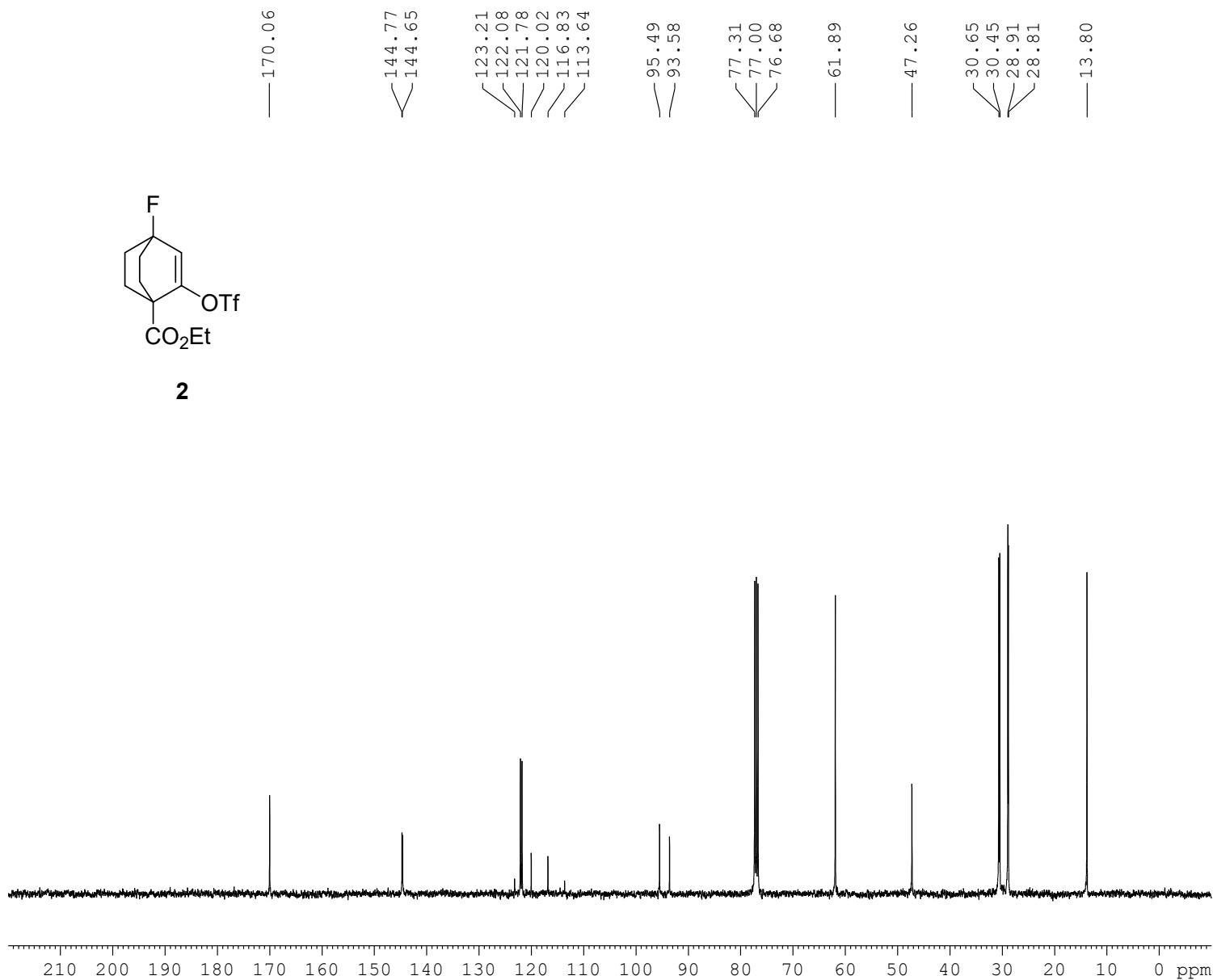
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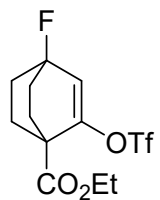
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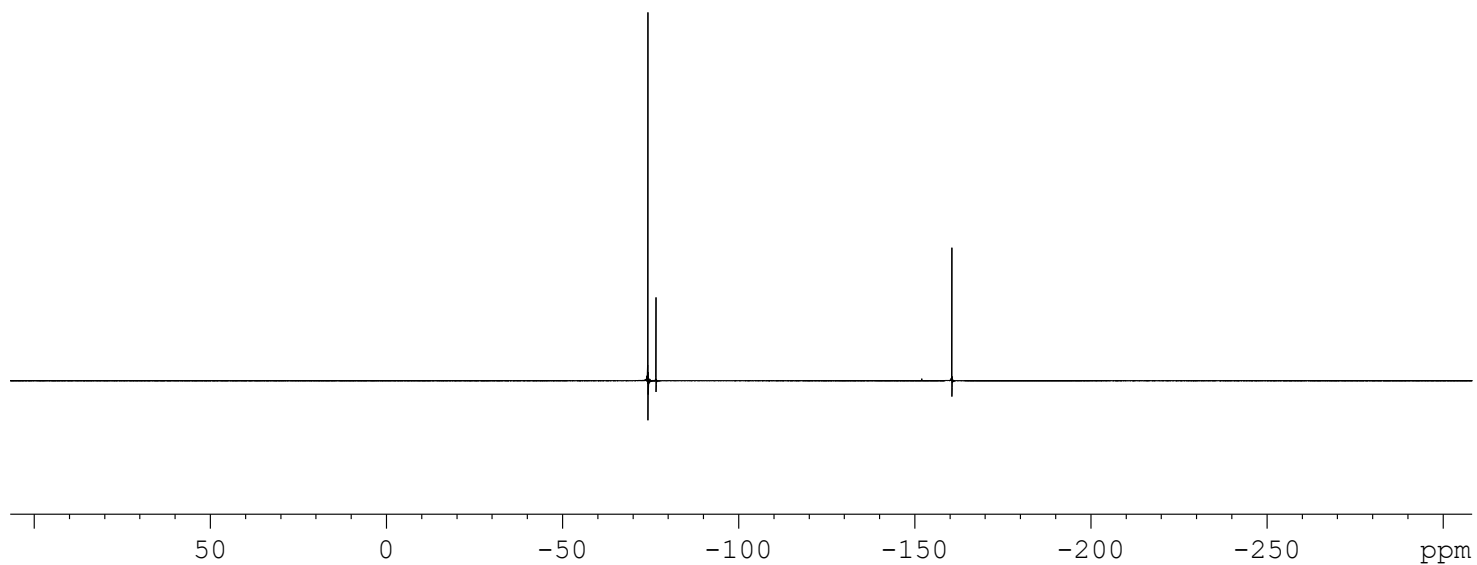
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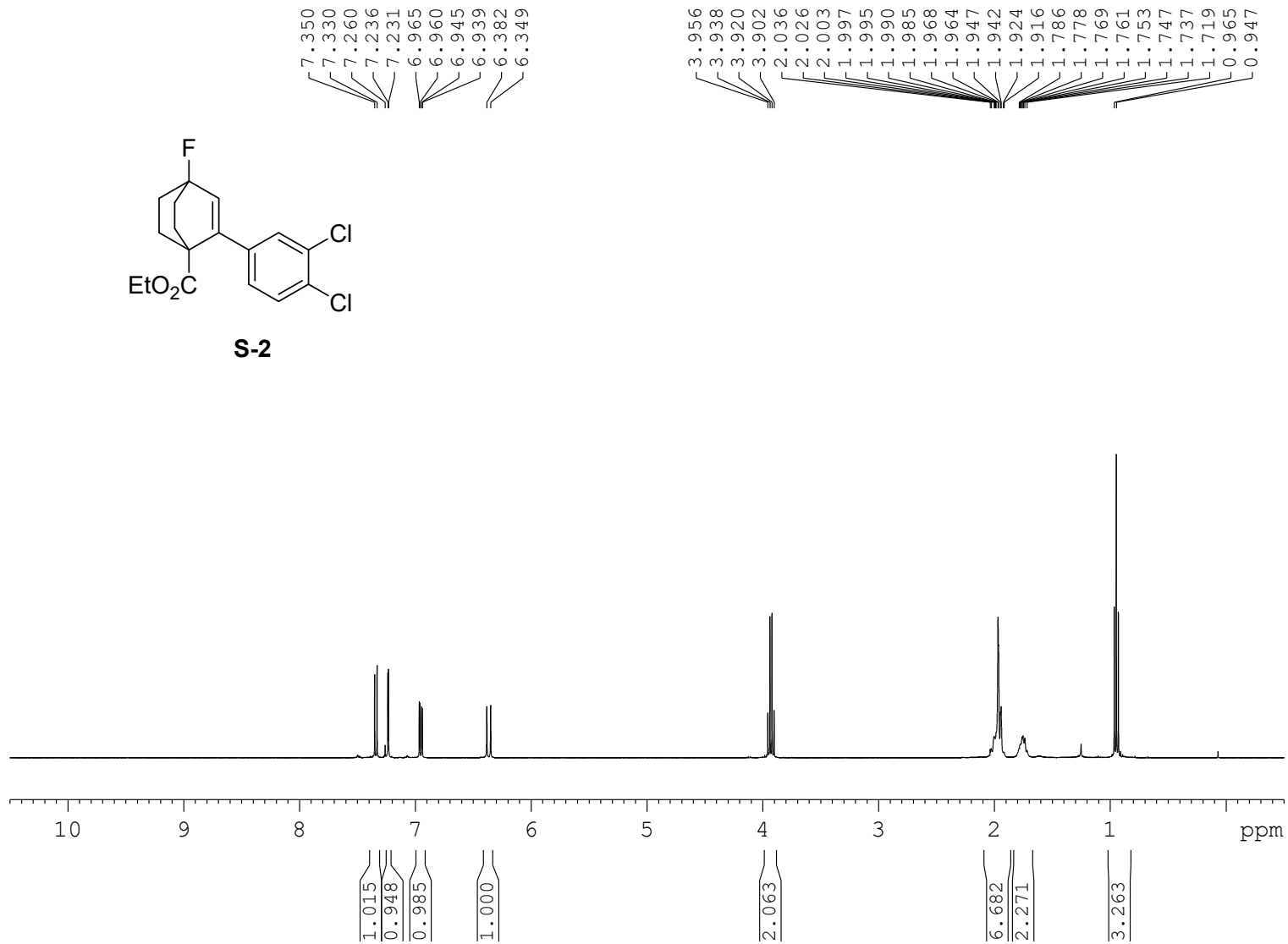
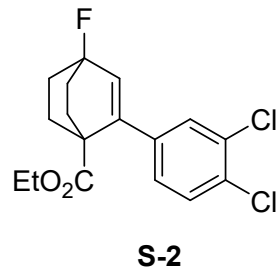
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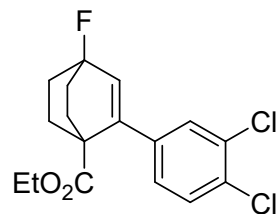
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S-2

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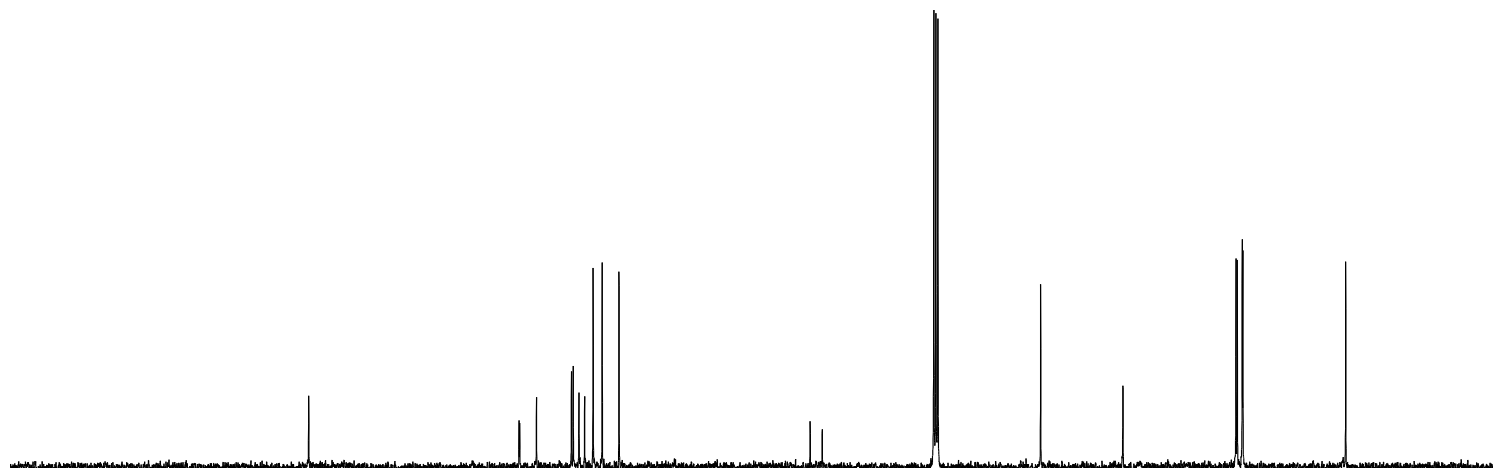
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29.57

— 13.69

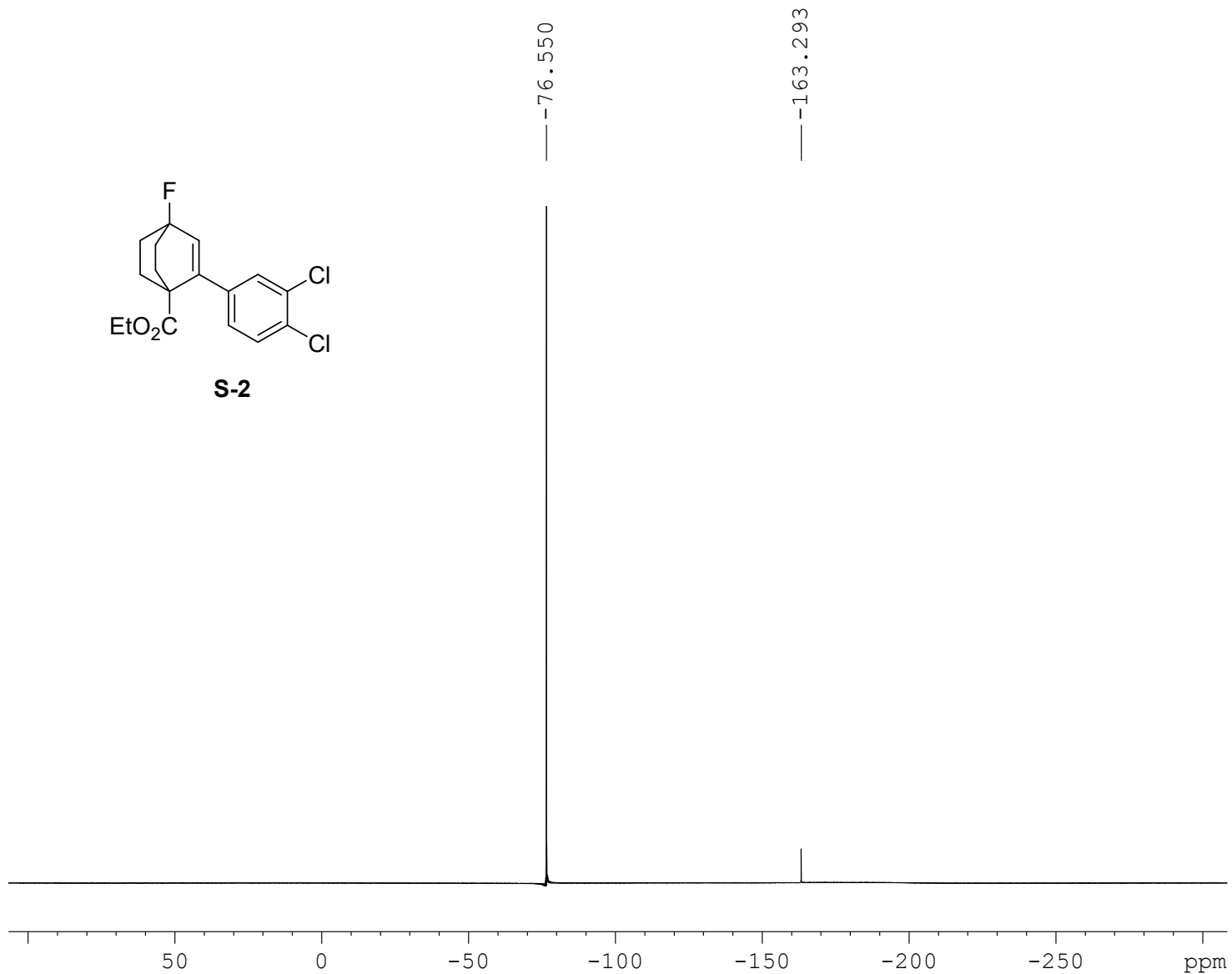
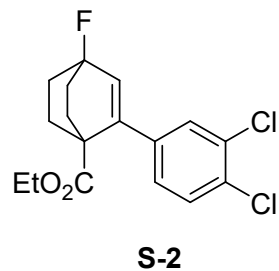


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

Current Data Parameters
NAME CW446
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20250306
Time_ 20.17 h
INSTRUM spect
PROBHD Z108618_0411 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 120
DS 0
SWH 28409.092 Hz
FIDRES 0.866977 Hz
AQ 1.1534336 sec
RG 212.49
DW 17.600 usec
DE 6.50 usec
TE 297.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6258487 MHz
NUC1 13C
P1 10.50 usec
PLW1 42.50000000 W
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2] waltz16
PCPD2 90.00 usec
PLW2 9.89999962 W
PLW12 0.29363999 W
PLW13 0.14747000 W

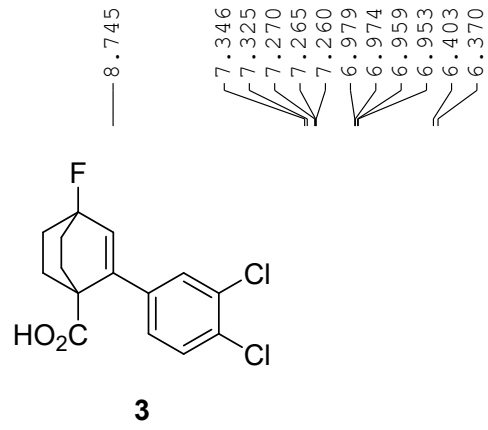
F2 - Processing parameters
SI 32768
SF 100.6127723 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40



Current Data Parameters
 NAME 222 check 5F
 EXPNO 10
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20250615
 Time_ 19.26 h
 INSTRUM spect
 PROBHD Z108618_0411 (
 PULPROG zgpg30
 TD 65536
 SOLVENT CDCl3
 NS 4
 DS 0
 SWH 156250.000 Hz
 FIDRES 4.768372 Hz
 AQ 0.2097152 sec
 RG 212.49
 DW 3.200 usec
 DE 6.73 usec
 TE 300.4 K
 D1 1.50000000 sec
 D11 0.03000000 sec
 TD0 1
 SFO1 376.4607162 MHz
 NUC1 19F
 P0 5.17 usec
 P1 15.50 usec
 PLW1 11.89999962 W
 SFO2 400.1316005 MHz
 NUC2 1H
 CPDPRG[2] garp4
 PCPD2 90.00 usec
 PLW2 9.89999962 W
 PLW12 0.29363999 W
 PLW13 0.14770000 W

F2 - Processing parameters
 SI 131072
 SF 376.4987007 MHz
 WDW EM
 SSB 0
 LB 0 Hz
 GB 0
 PC 1.00



Chemical shifts (ppm) indicated above the spectrum:

- 1.982
- 1.975
- 1.942
- 1.816
- 1.780
- 1.763
- 1.736

Current Data Parameters

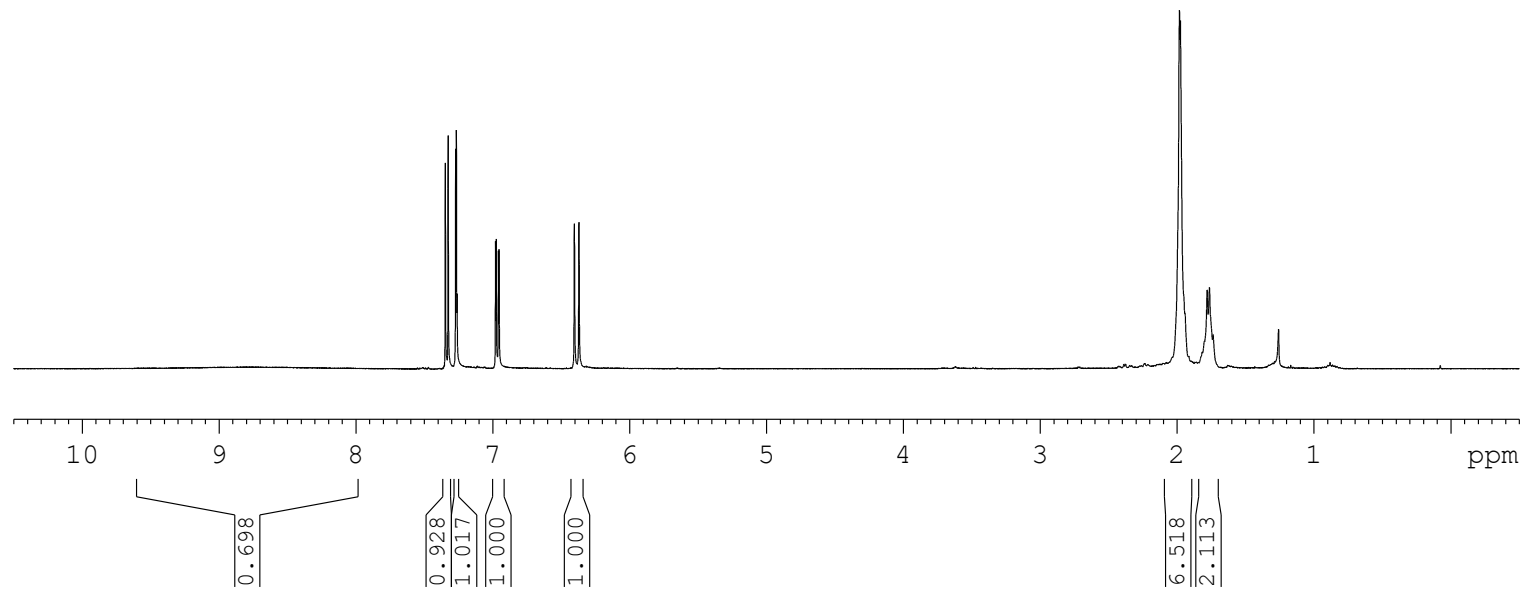
NAME	CW448
EXPNO	9
PROCNO	1

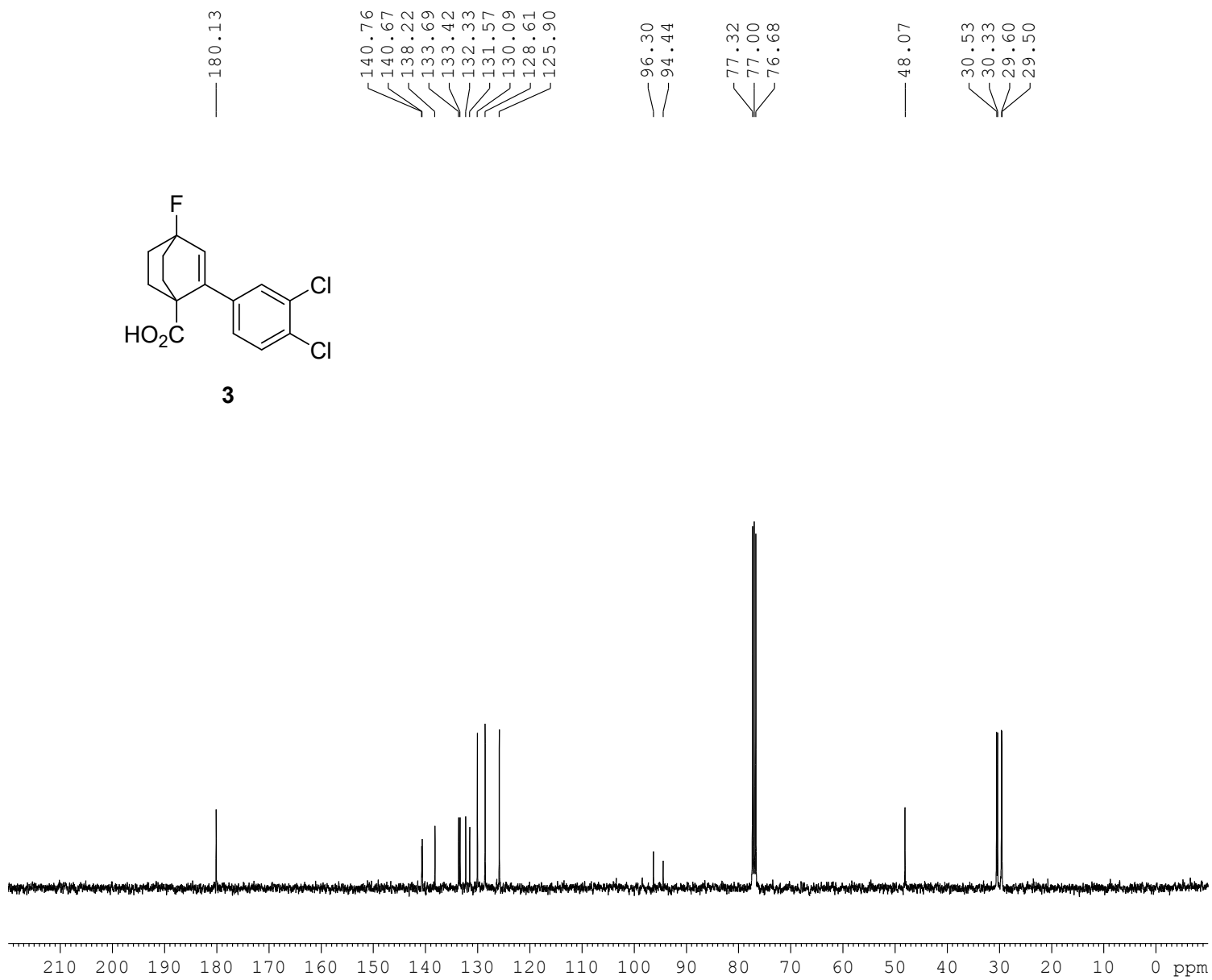
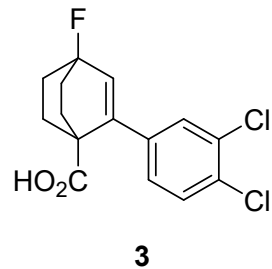
F2 - Acquisition Parameters

Date_	20250407
Time_	17.46 h
INSTRUM	spect
PROBHD	Z108618_0411 (
PULPROG	zg30
TD	32768
SOLVENT	CDC13
NS	8
DS	0
SWH	8802.817 Hz
FIDRES	0.537281 Hz
AQ	1.8612224 sec
RG	143.54
DW	56.800 usec
DE	14.47 usec
TE	298.0 K
D1	1.00000000 sec
TD0	1
SFO1	400.1328009 MHz
NUC1	1H
P1	15.50 usec
PLW1	9.89999962 W

F2 - Processing parameters

SI	131072
SF	400.1300098 MHz
WDW	EM
SSB	0
LB	0 Hz
GB	0
PC	1.00

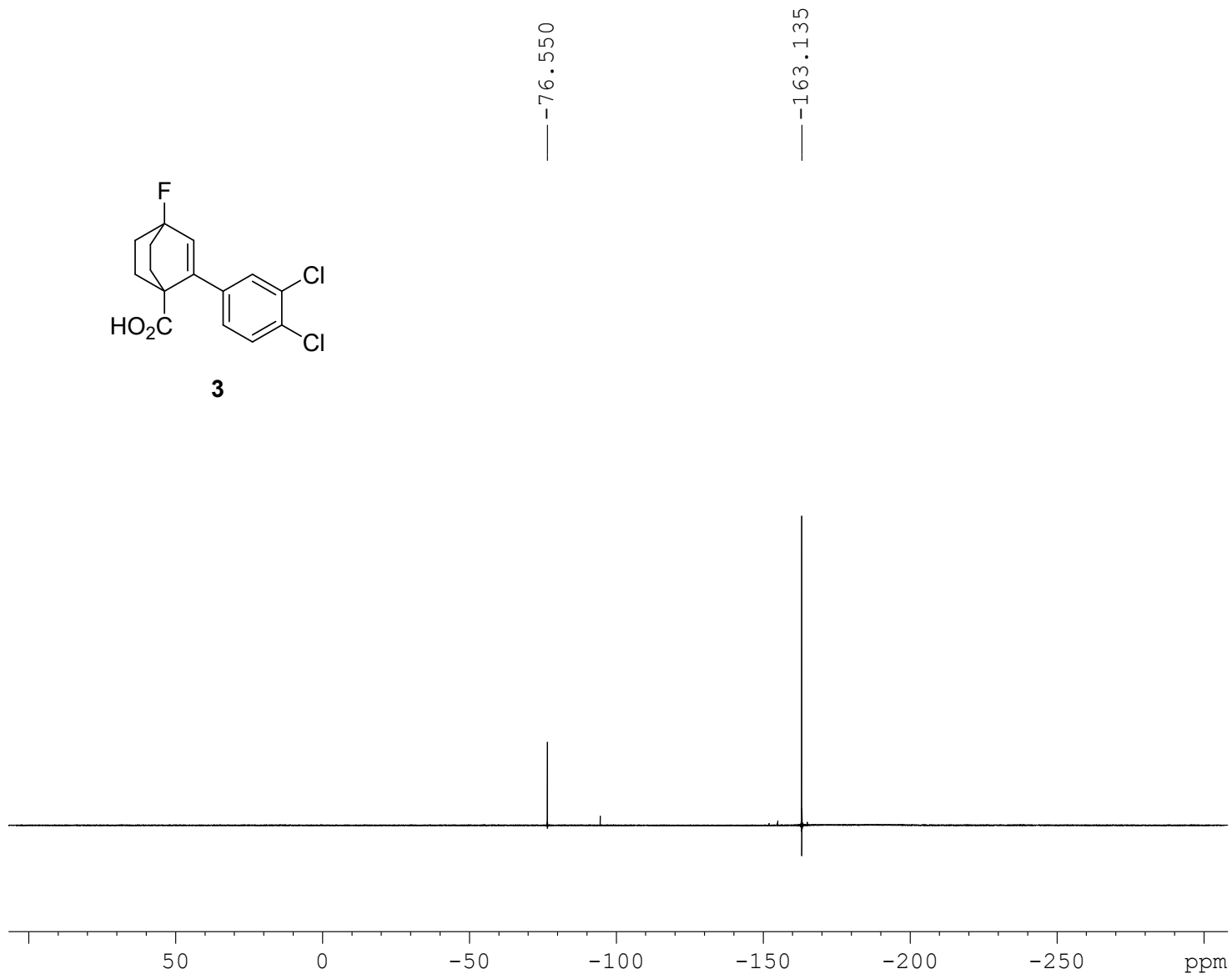
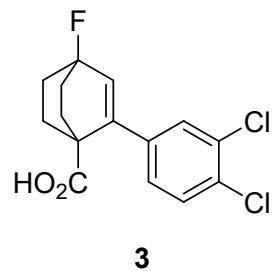




Current Data Parameters
 NAME CW448
 EXPNO 2
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20250312
 Time 14.53 h
 INSTRUM spect
 PROBHD Z108618_0411 (
 PULPROG zgpg30
 TD 65536
 SOLVENT CDCl3
 NS 60
 DS 0
 SWH 28409.092 Hz
 FIDRES 0.866977 Hz
 AQ 1.1534336 sec
 RG 212.49
 DW 17.600 usec
 DE 6.50 usec
 TE 298.1 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TD0 1
 SFO1 100.6258487 MHz
 NUC1 13C
 P1 10.50 usec
 PLW1 42.50000000 W
 SFO2 400.1316005 MHz
 NUC2 1H
 CPDPRG[2] waltz16
 PCPD2 90.00 usec
 PLW2 9.89999962 W
 PLW12 0.29363999 W
 PLW13 0.14747000 W

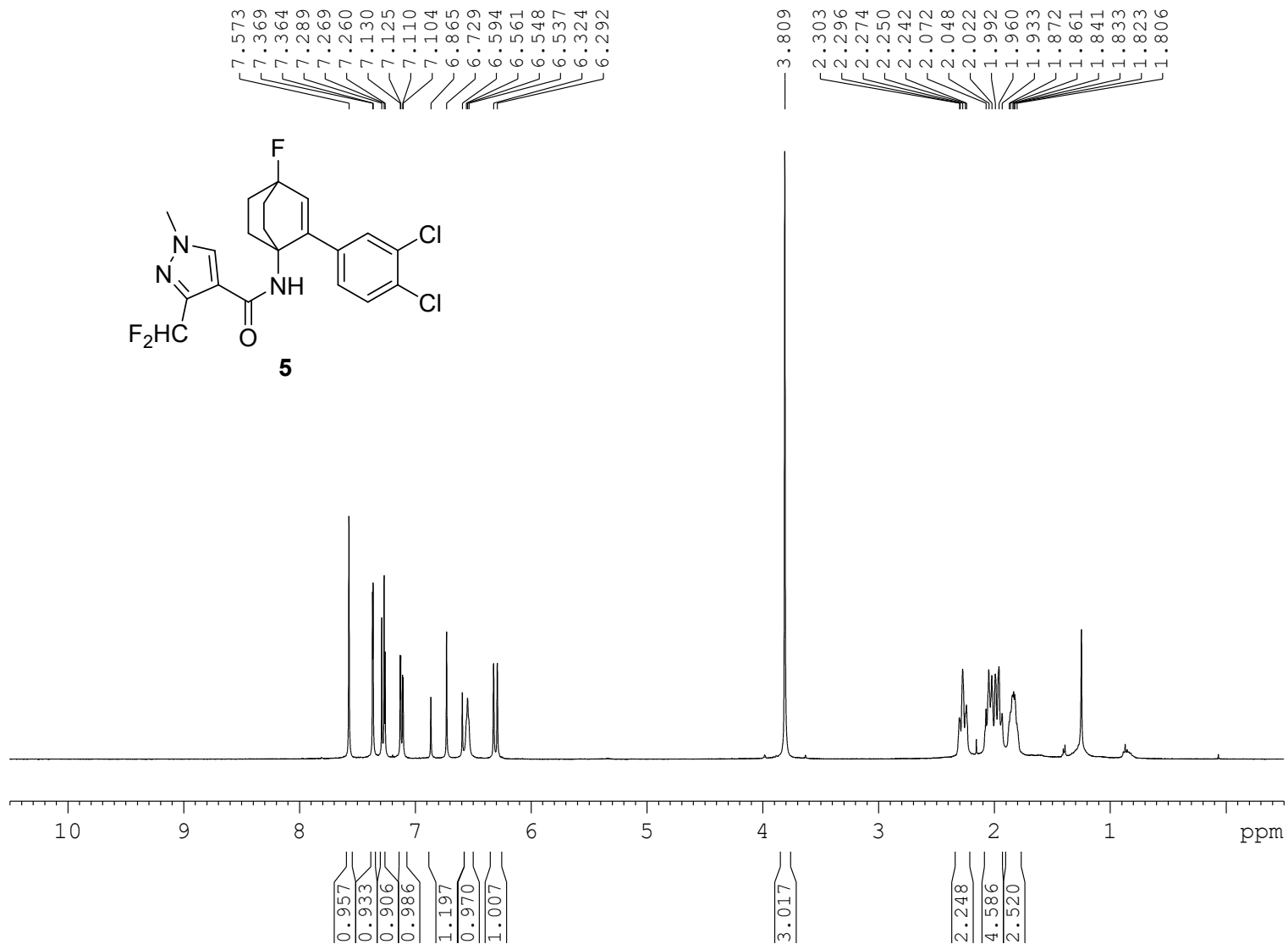
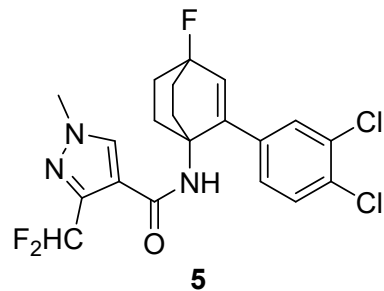
F2 - Processing parameters
 SI 32768
 SF 100.6127721 MHz
 WDW EM
 SSB 0
 LB 3.00 Hz
 GB 0
 PC 1.40



Current Data Parameters
 NAME CW448
 EXPNO 8
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20250407
 Time 17.41 h
 INSTRUM spect
 PROBHD Z108618_0411 (
 PULPROG zgpg30
 TD 65536
 SOLVENT CDCl3
 NS 4
 DS 0
 SWH 156250.000 Hz
 FIDRES 4.768372 Hz
 AQ 0.2097152 sec
 RG 212.49
 DW 3.200 usec
 DE 6.92 usec
 TE 298.1 K
 D1 1.50000000 sec
 D11 0.03000000 sec
 TD0 1
 SFO1 376.4607162 MHz
 NUC1 19F
 P1 15.50 usec
 PLW1 11.89999962 W
 SFO2 400.1316005 MHz
 NUC2 1H
 CPDPRG[2] garp4
 PCPD2 90.00 usec
 PLW2 9.89999962 W
 PLW12 0.29363999 W
 PLW13 0.14747000 W

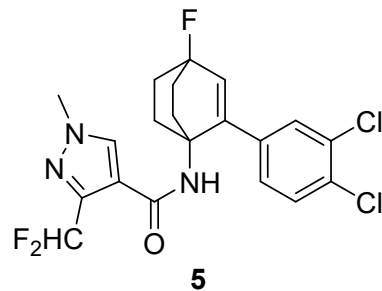
F2 - Processing parameters
 SI 131072
 SF 376.4986146 MHz
 WDW EM
 SSB 0
 LB 0 Hz
 GB 0
 PC 1.00



Current Data Parameters
 NAME CW451
 EXPNO 10
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20250411
 Time_ 20.16 h
 INSTRUM spect
 PROBHD z108618_0411 (
 PULPROG zg30
 TD 32768
 SOLVENT CDCl3
 NS 8
 DS 0
 SWH 8802.817 Hz
 FIDRES 0.537281 Hz
 AQ 1.8612224 sec
 RG 94.01
 DW 56.800 usec
 DE 14.47 usec
 TE 298.0 K
 D1 1.00000000 sec
 TD0 1
 SFO1 400.1328009 MHz
 NUC1 1H
 P1 15.50 usec
 PLW1 9.89999962 W

F2 - Processing parameters
 SI 131072
 SF 400.1300100 MHz
 WDW EM
 SSB 0
 LB 0 Hz
 GB 0
 PC 1.00

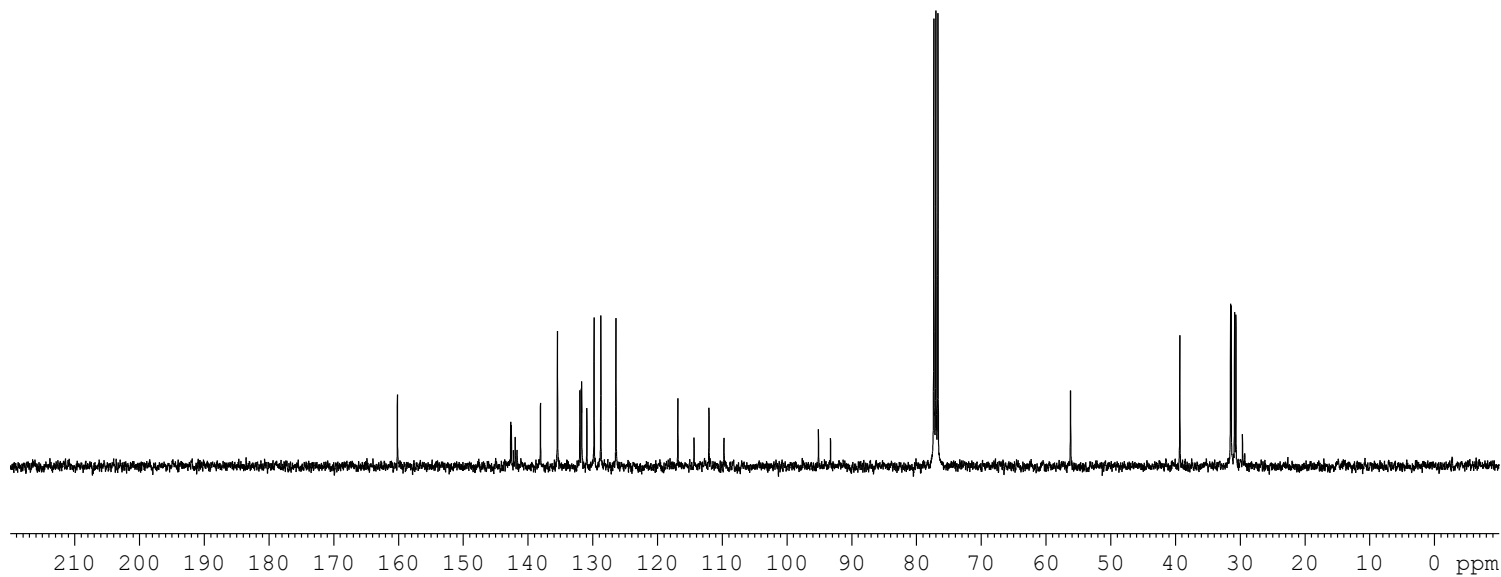


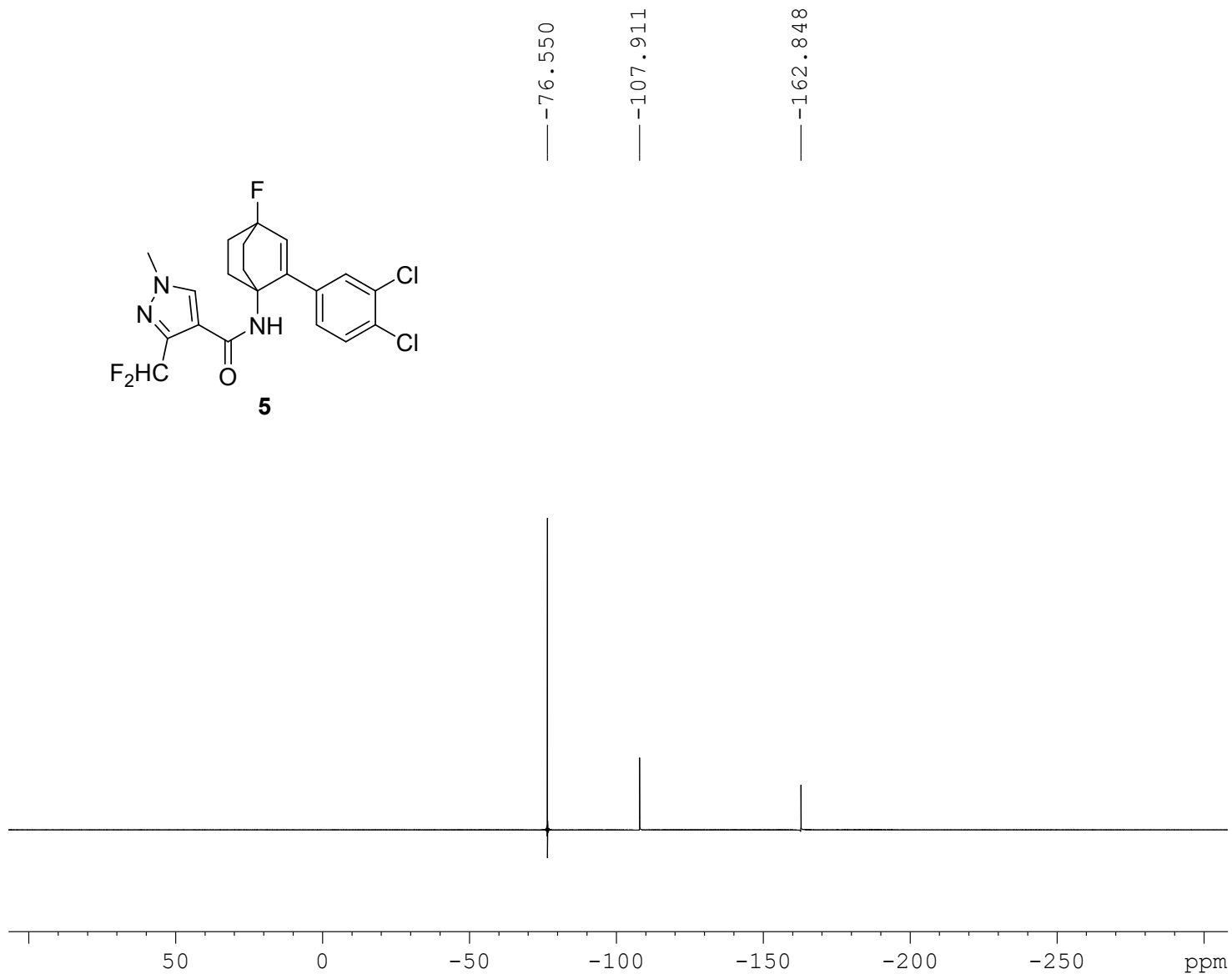
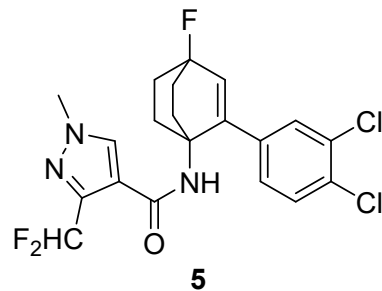
160.21
142.71
142.61
142.32
142.02
141.74
138.12
135.49
132.03
131.81
131.76
130.95
129.83
128.80
126.45
116.85
114.35
112.04
109.73
95.13
93.27
77.31
77.00
76.68
56.21
56.18
39.32
31.48
31.37
30.86
30.65

Current Data Parameters
NAME CW451
EXPNO 11
PROCNO 1

F2 - Acquisition Parameters
Date_ 20250411
Time 20.26 h
INSTRUM spect
PROBHD Z108618_0411 (
PULPROG zgpg30
TD 65536
SOLVENT CDC13
NS 160
DS 0
SWH 28409.092 Hz
FIDRES 0.866977 Hz
AQ 1.1534336 sec
RG 212.49
DW 17.600 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6258487 MHz
NUC1 13C
P1 10.50 usec
PLW1 42.50000000 W
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2] waltz16
PCPD2 90.00 usec
PLW2 9.89999962 W
PLW12 0.29363999 W
PLW13 0.14747000 W

F2 - Processing parameters
SI 32768
SF 100.6127737 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40

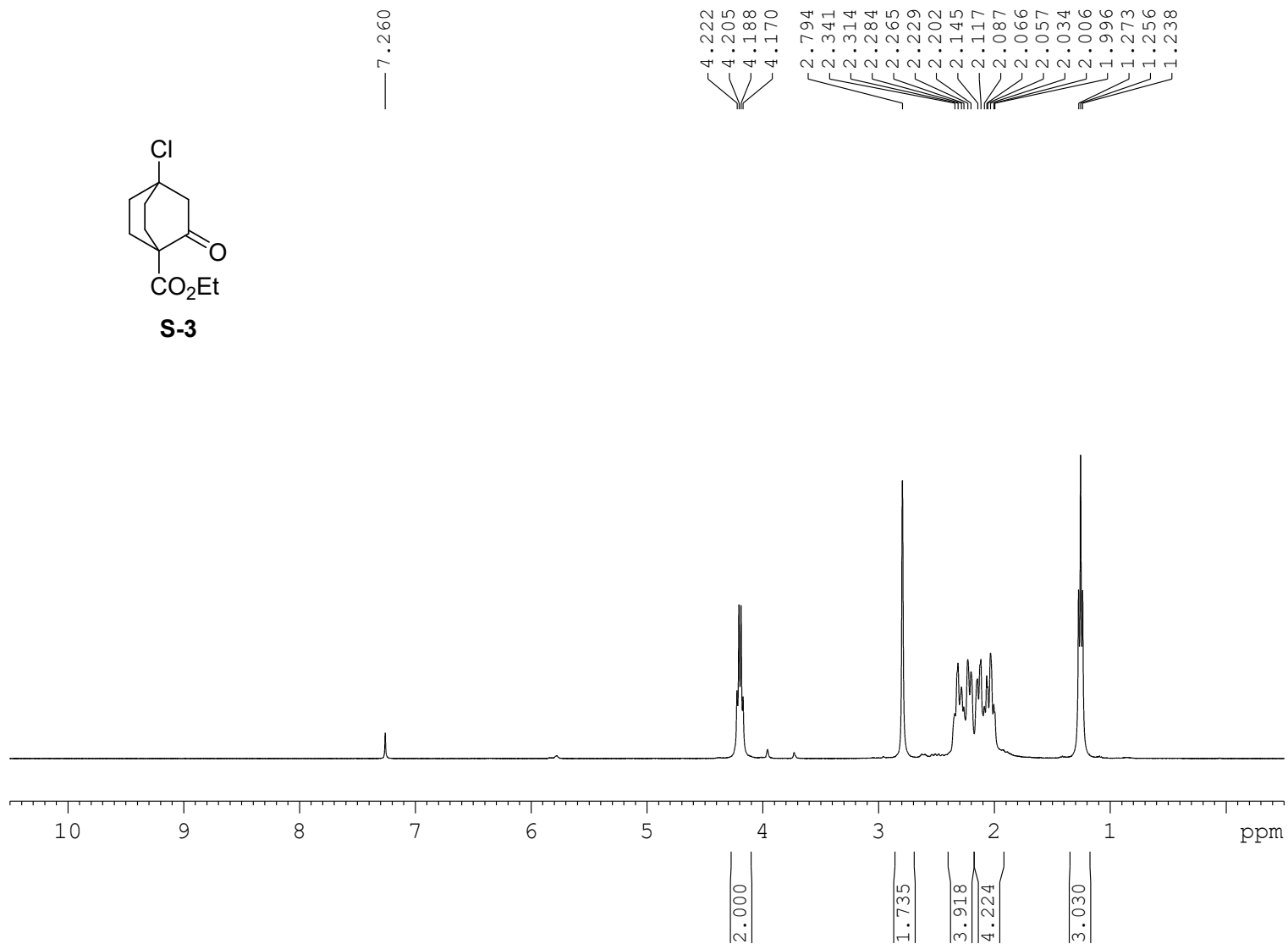
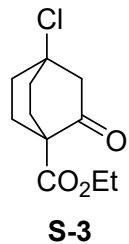




Current Data Parameters
NAME CW451
EXPNO 14
PROCNO 1

F2 - Acquisition Parameters
Date_ 20250412
Time 14.03 h
INSTRUM spect
PROBHD Z108618_0411 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 4
DS 0
SWH 156250.000 Hz
FIDRES 4.768372 Hz
AQ 0.2097152 sec
RG 212.49
DW 3.200 usec
DE 6.92 usec
TE 298.1 K
D1 1.50000000 sec
D11 0.03000000 sec
TD0 1
SFO1 376.4607162 MHz
NUC1 19F
P1 15.50 usec
PLW1 11.89999962 W
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2] garp4
PCPD2 90.00 usec
PLW2 9.89999962 W
PLW12 0.29363999 W
PLW13 0.14747000 W

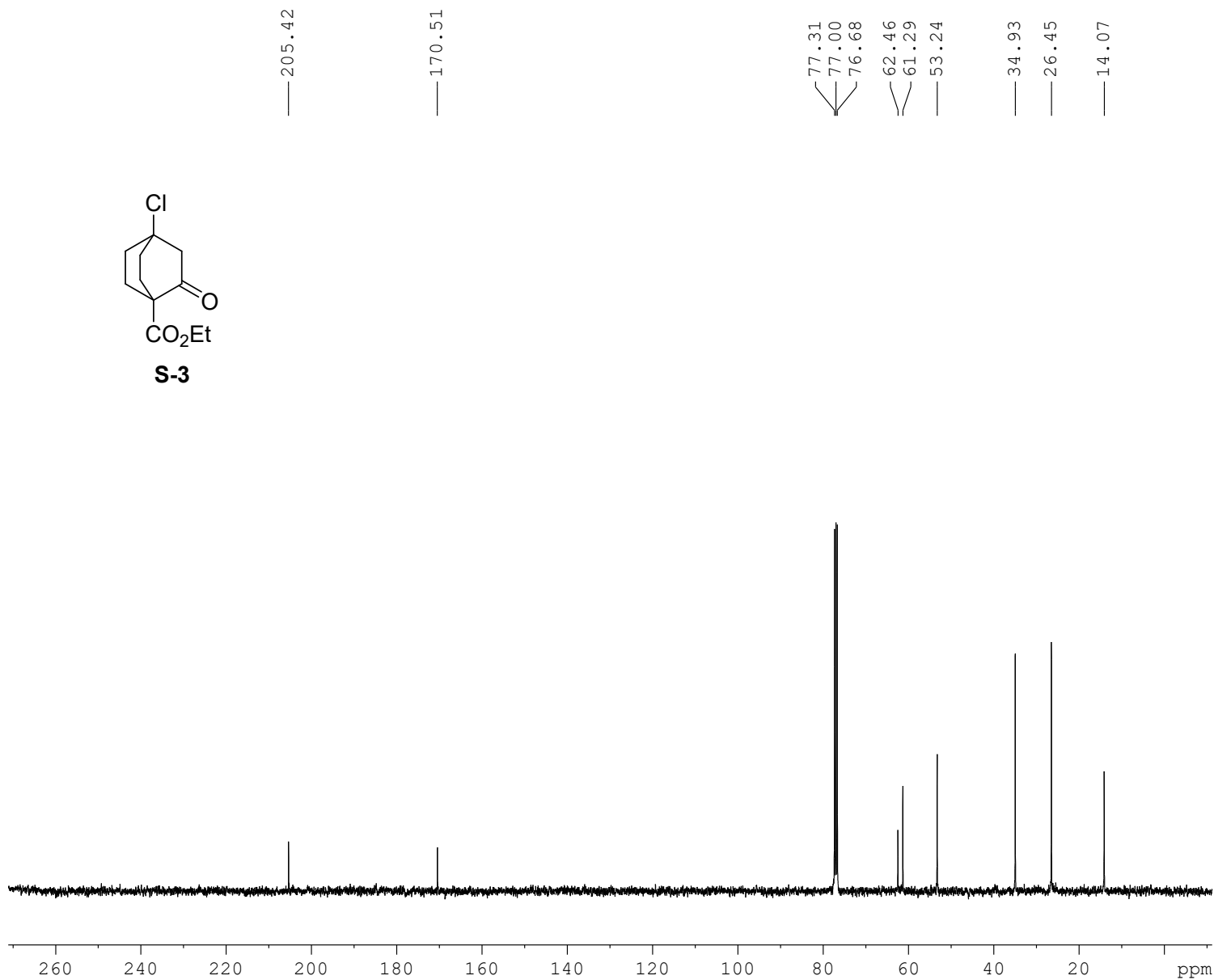
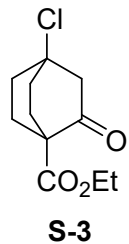
F2 - Processing parameters
SI 131072
SF 376.4986122 MHz
WDW EM
SSB 0
LB 0 Hz
GB 0
PC 1.00



Current Data Parameters
 NAME CW432
 EXPNO 2
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20241213
 Time_ 18.52 h
 INSTRUM spect
 PROBHD z108618_0411 (
 PULPROG zg30
 TD 32768
 SOLVENT CDCl3
 NS 8
 DS 0
 SWH 8802.817 Hz
 FIDRES 0.537281 Hz
 AQ 1.8612224 sec
 RG 118.08
 DW 56.800 usec
 DE 14.47 usec
 TE 298.0 K
 D1 1.00000000 sec
 TD0 1
 SFO1 400.1328009 MHz
 NUC1 1H
 P1 15.50 usec
 PLW1 9.89999962 W

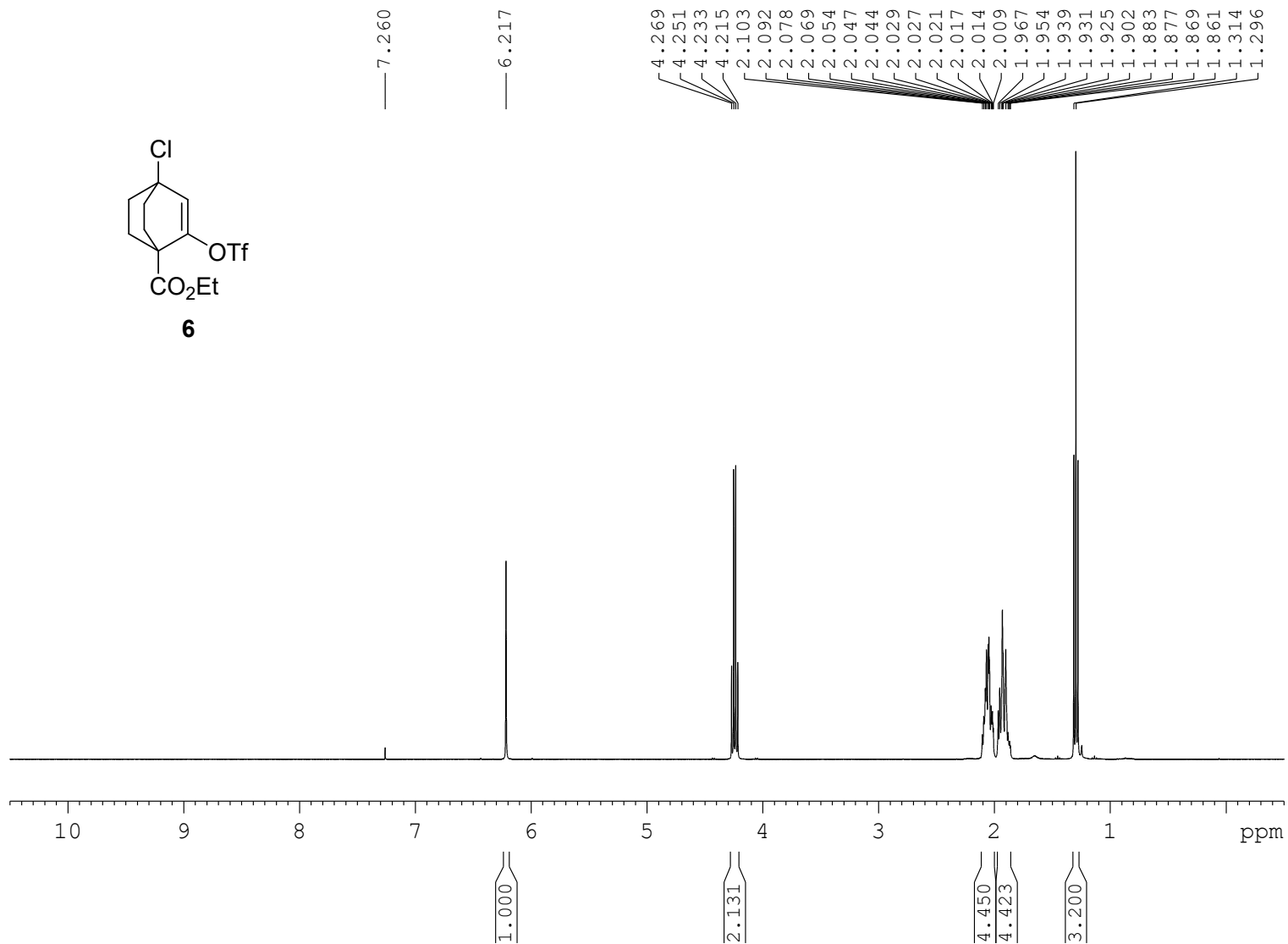
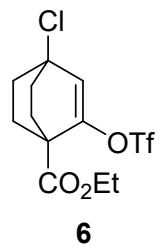
F2 - Processing parameters
 SI 131072
 SF 400.1300098 MHz
 WDW EM
 SSB 0
 LB 0 Hz
 GB 0
 PC 1.00



Current Data Parameters
 NAME CW432
 EXPNO 3
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20241213
 Time_ 19.00 h
 INSTRUM spect
 PROBHD Z108618_0411 (
 PULPROG zgpg30
 TD 65536
 SOLVENT CDCl3
 NS 120
 DS 0
 SWH 28409.092 Hz
 FIDRES 0.866977 Hz
 AQ 1.1534336 sec
 RG 212.49
 DW 17.600 usec
 DE 6.50 usec
 TE 298.0 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TD0 1
 SFO1 100.6258487 MHz
 NUC1 13C
 P1 10.50 usec
 PLW1 42.50000000 W
 SFO2 400.1316005 MHz
 NUC2 1H
 CPDPRG[2] waltz16
 PCPD2 90.00 usec
 PLW2 9.89999962 W
 PLW12 0.29363999 W
 PLW13 0.14747000 W

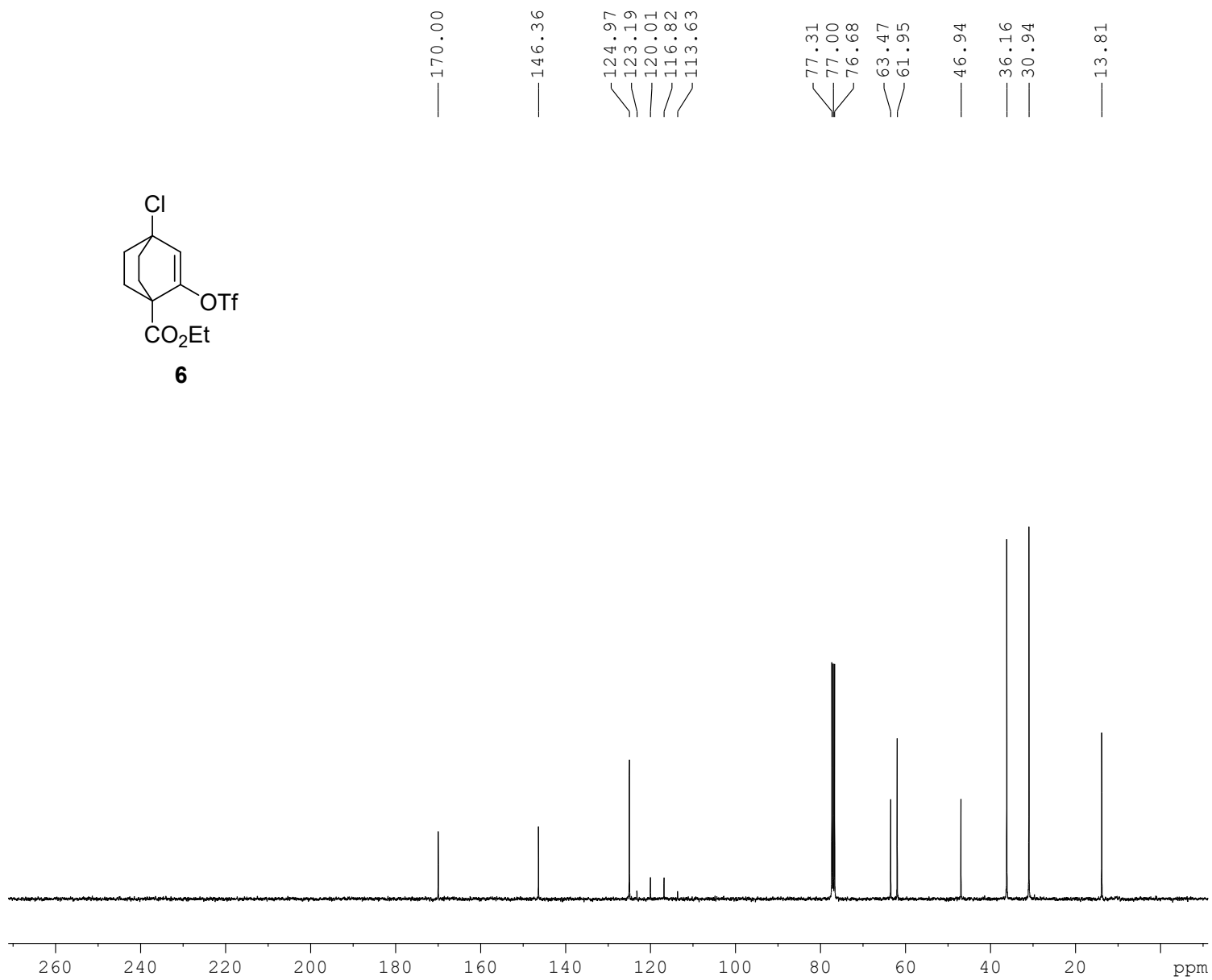
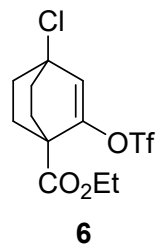
F2 - Processing parameters
 SI 32768
 SF 100.6127726 MHz
 WDW EM
 SSB 0
 LB 3.00 Hz
 GB 0
 PC 1.40



Current Data Parameters
NAME CW439
EXPNO 8
PROCNO 1

F2 - Acquisition Parameters
Date_ 20250226
Time_ 17.33 h
INSTRUM spect
PROBHD z108618_0411 (
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 0
SWH 8802.817 Hz
FIDRES 0.537281 Hz
AQ 1.8612224 sec
RG 62.98
DW 56.800 usec
DE 14.47 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
SF01 400.1328009 MHz
NUC1 1H
P1 15.50 usec
PLW1 9.89999962 W

F2 - Processing parameters
SI 131072
SF 400.1300095 MHz
WDW EM
SSB 0
LB 0 Hz
GB 0
PC 1.00



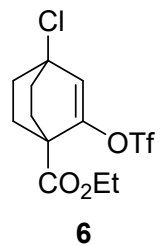
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Current Data Parameters
NAME          CW439
EXPNO         9
PROCNO        1

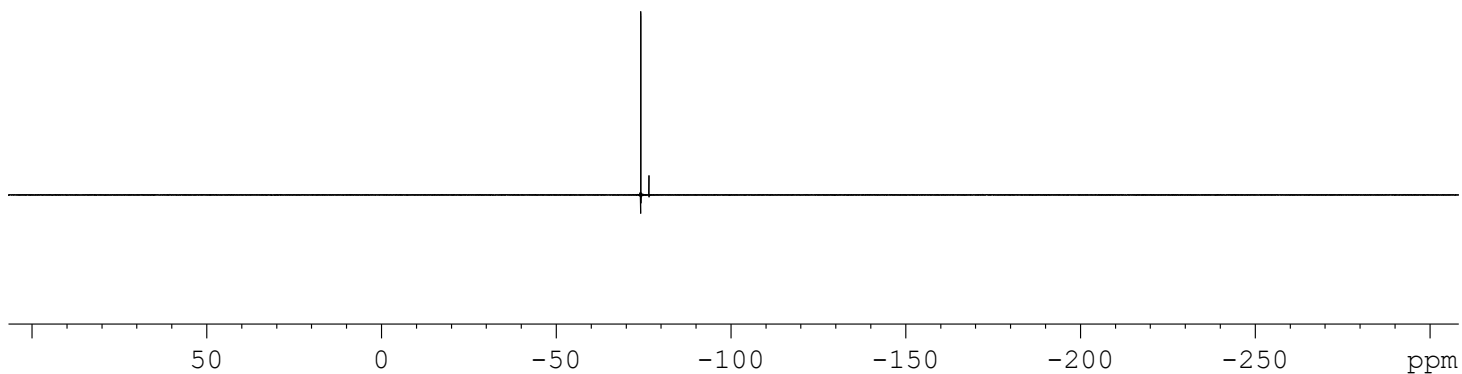
F2 - Acquisition Parameters
Date_         20250226
Time          17.45 h
INSTRUM       spect
PROBHD        Z108618_0411 (
PULPROG       zgpg30
TD            65536
SOLVENT       CDCl3
NS            200
DS            0
SWH           28409.092 Hz
FIDRES        0.866977 Hz
AQ            1.1534336 sec
RG            212.49
DW            17.600 usec
DE            6.50 usec
TE            298.0 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0           1
SFO1          100.6258487 MHz
NUC1          13C
P1            10.50 usec
PLW1          42.50000000 W
SFO2          400.1316005 MHz
NUC2          1H
CPDPRG[2]    waltz16
PCPD2         90.00 usec
PLW2          9.89999962 W
PLW12         0.29363999 W
PLW13         0.14747000 W

F2 - Processing parameters
SI            32768
SF            100.6127708 MHz
WDW           EM
SSB           0
LB            3.00 Hz
GB            0
PC            1.40

```



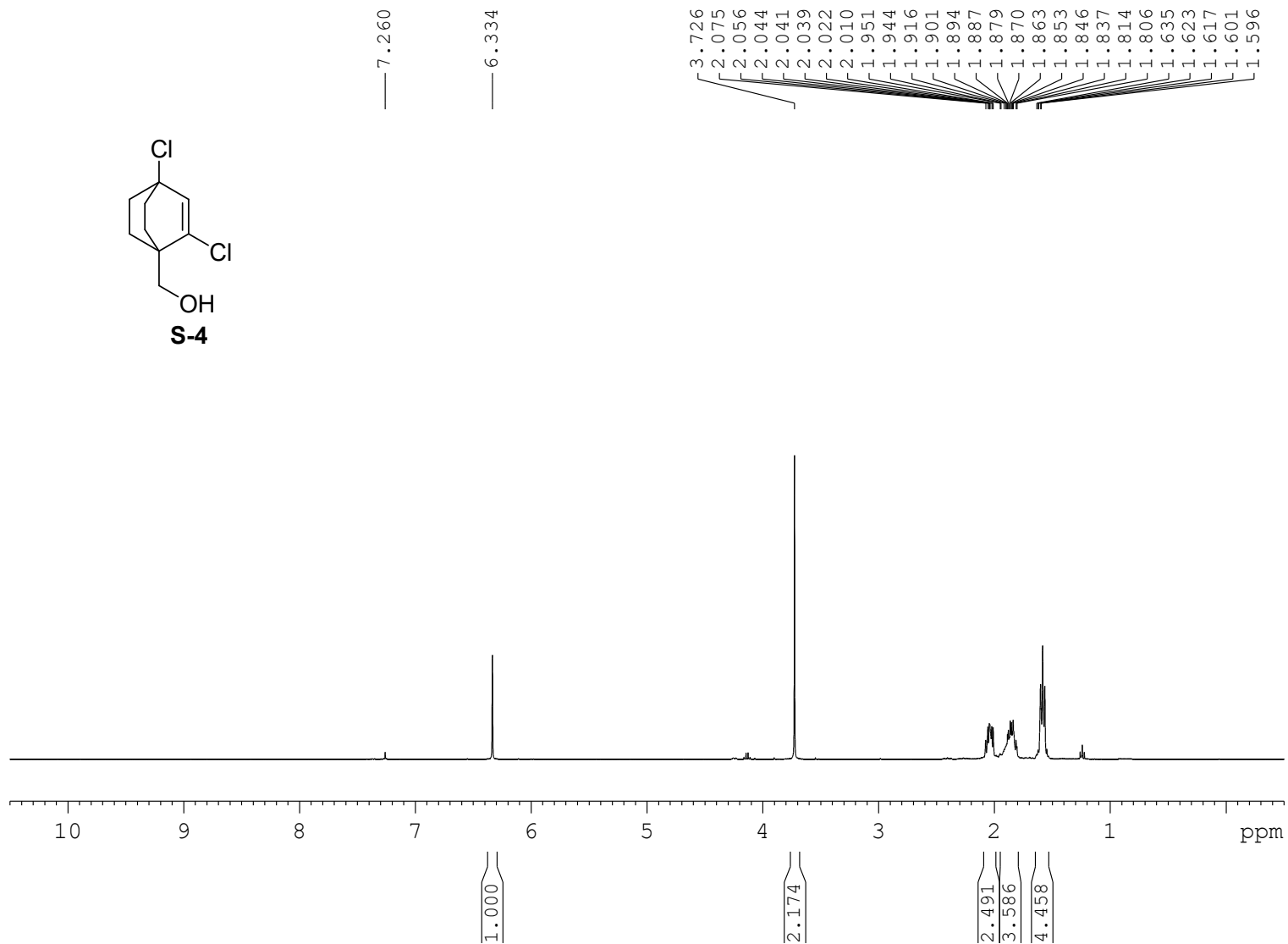
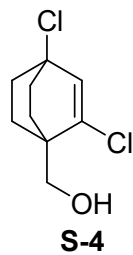
-74.203
 -76.549



Current Data Parameters
 NAME CW439
 EXPNO 10
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20250226
 Time_ 18.02 h
 INSTRUM spect
 PROBHD Z108618_0411 (
 PULPROG zgpg30
 TD 65536
 SOLVENT CDCl3
 NS 8
 DS 0
 SWH 156250.000 Hz
 FIDRES 4.768372 Hz
 AQ 0.2097152 sec
 RG 212.49
 DW 3.200 usec
 DE 6.92 usec
 TE 298.0 K
 D1 1.50000000 sec
 D11 0.03000000 sec
 TD0 1
 SFO1 376.4607162 MHz
 NUC1 19F
 P1 15.50 usec
 PLW1 11.89999962 W
 SFO2 400.1316005 MHz
 NUC2 1H
 CPDPRG[2] garp4
 PCPD2 90.00 usec
 PLW2 9.89999962 W
 PLW12 0.29363999 W
 PLW13 0.14747000 W

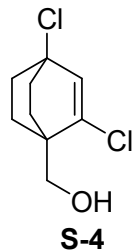
F2 - Processing parameters
 SI 131072
 SF 376.4986386 MHz
 WDW EM
 SSB 0
 LB 0 Hz
 GB 0
 PC 1.00



Current Data Parameters
 NAME CW462
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20250428
 Time_ 17.33 h
 INSTRUM spect
 PROBHD z108618_0411 (
 PULPROG zg30
 TD 32768
 SOLVENT CDCl3
 NS 8
 DS 0
 SWH 8802.817 Hz
 FIDRES 0.537281 Hz
 AQ 1.8612224 sec
 RG 94.01
 DW 56.800 usec
 DE 14.47 usec
 TE 301.2 K
 D1 1.00000000 sec
 TD0 1
 SFO1 400.1328009 MHz
 NUC1 1H
 P1 15.50 usec
 PLW1 9.89999962 W

F2 - Processing parameters
 SI 131072
 SF 400.1300098 MHz
 WDW EM
 SSB 0
 LB 0 Hz
 GB 0
 PC 1.00



133.97
133.82

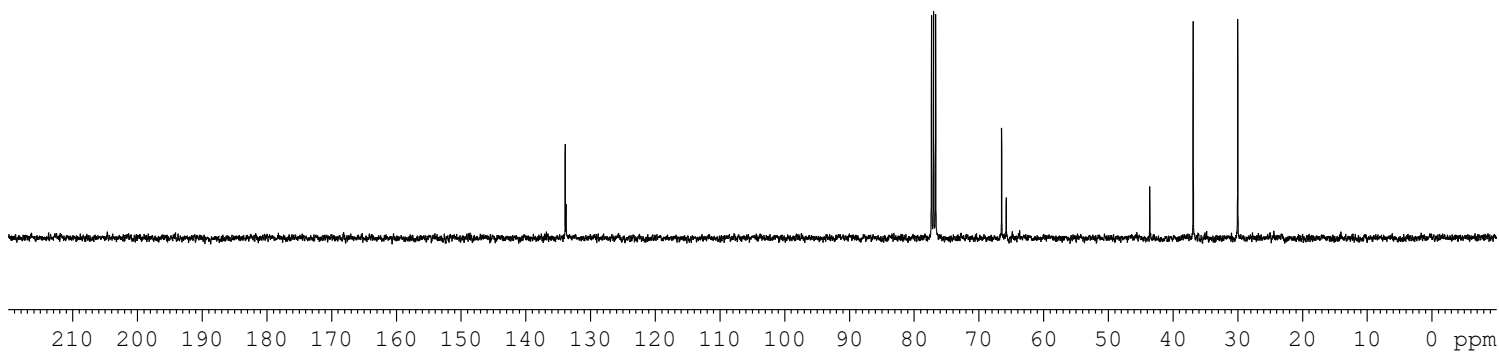
77.31
77.00
76.68
66.47
65.76

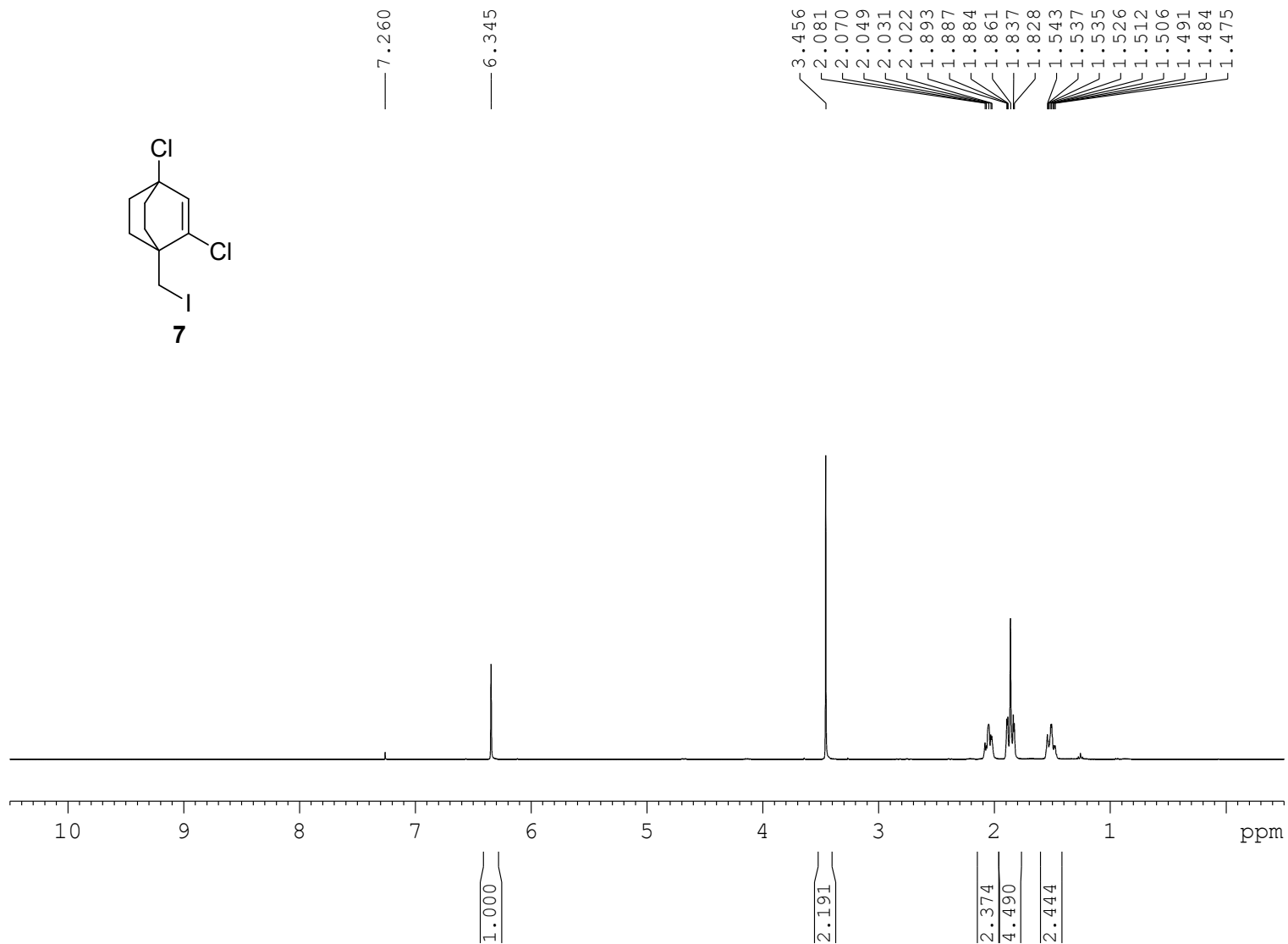
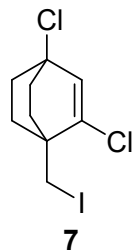
43.59
36.87
29.99

Current Data Parameters
NAME CW462
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20250428
Time_ 17.37 h
INSTRUM spect
PROBHD Z108618_0411 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 36
DS 0
SWH 28409.092 Hz
FIDRES 0.866977 Hz
AQ 1.1534336 sec
RG 212.49
DW 17.600 usec
DE 6.50 usec
TE 301.4 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6258487 MHz
NUC1 13C
P1 10.50 usec
PLW1 42.50000000 W
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2] waltz16
PCPD2 90.00 usec
PLW2 9.89999962 W
PLW12 0.29363999 W
PLW13 0.14747000 W

F2 - Processing parameters
SI 32768
SF 100.6127722 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40

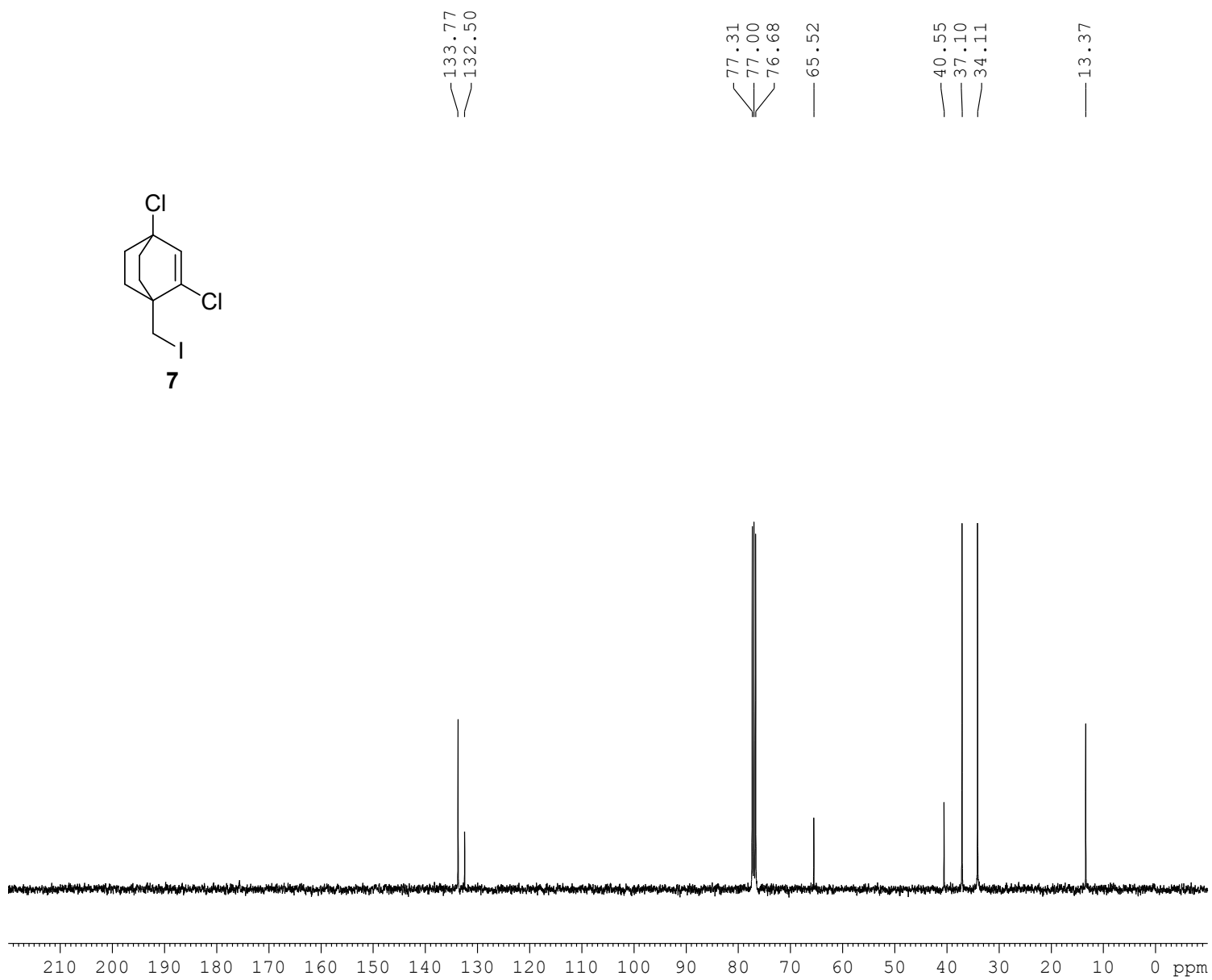
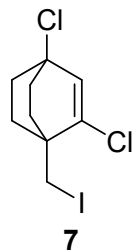




Current Data Parameters
 NAME CW459
 EXPNO 7
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20250429
 Time_ 16.22 h
 INSTRUM spect
 PROBHD z108618_0411 (
 PULPROG zg30
 TD 32768
 SOLVENT CDCl3
 NS 8
 DS 0
 SWH 8802.817 Hz
 FIDRES 0.537281 Hz
 AQ 1.8612224 sec
 RG 103.36
 DW 56.800 usec
 DE 14.47 usec
 TE 301.2 K
 D1 1.00000000 sec
 TD0 1
 SFO1 400.1328009 MHz
 NUC1 1H
 P1 15.50 usec
 PLW1 9.89999962 W

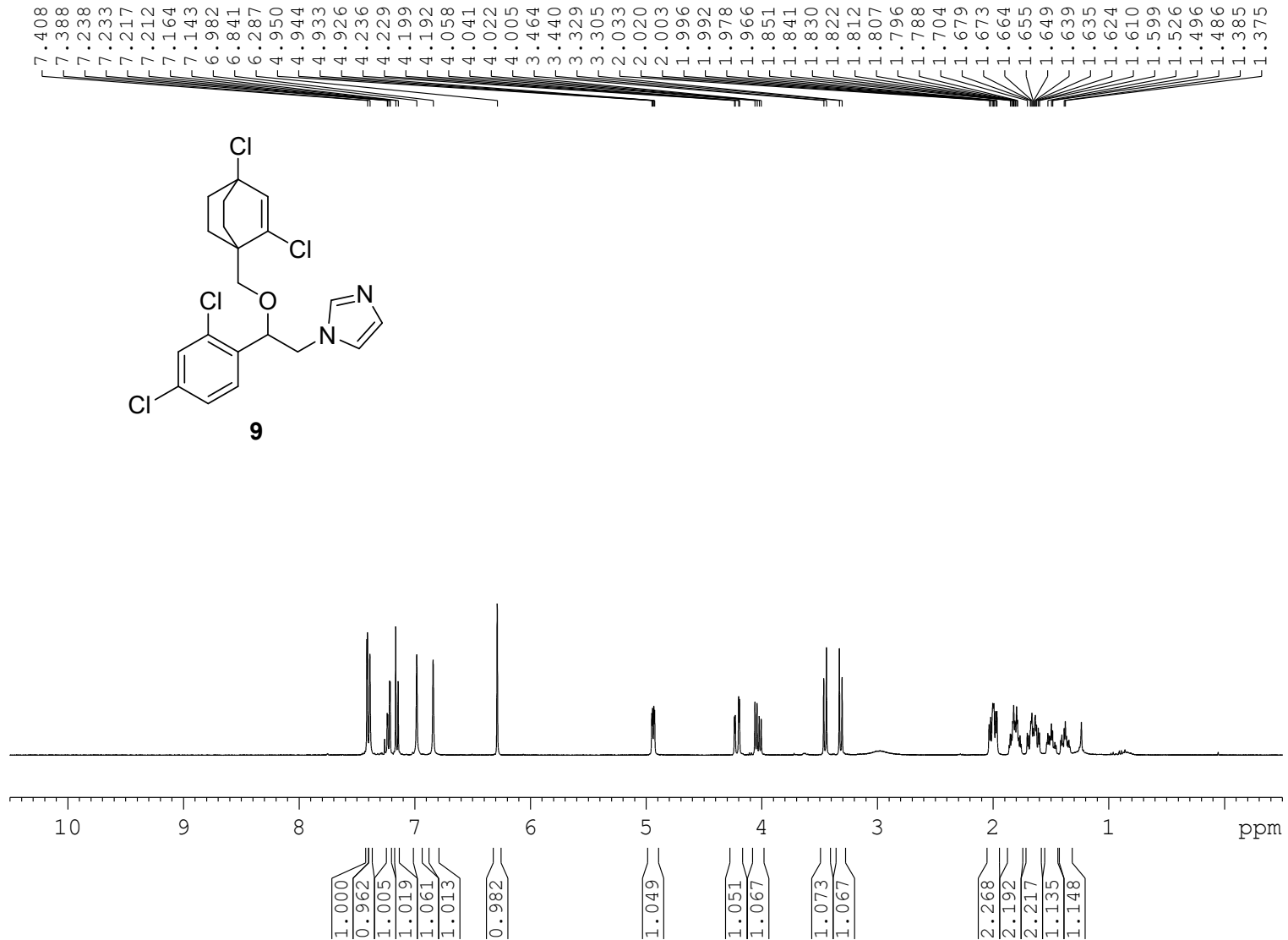
F2 - Processing parameters
 SI 131072
 SF 400.1300097 MHz
 WDW EM
 SSB 0
 LB 0 Hz
 GB 0
 PC 1.00



Current Data Parameters
 NAME CW459
 EXPNO 8
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20250429
 Time_ 16.26 h
 INSTRUM spect
 PROBHD Z108618_0411 (
 PULPROG zgpg30
 TD 65536
 SOLVENT CDCl3
 NS 60
 DS 0
 SWH 28409.092 Hz
 FIDRES 0.866977 Hz
 AQ 1.1534336 sec
 RG 212.49
 DW 17.600 usec
 DE 6.50 usec
 TE 301.4 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TD0 1
 SFO1 100.6258487 MHz
 NUC1 13C
 P1 10.50 usec
 PLW1 42.50000000 W
 SFO2 400.1316005 MHz
 NUC2 1H
 CPDPRG[2] waltz16
 PCPD2 90.00 usec
 PLW2 9.89999962 W
 PLW12 0.29363999 W
 PLW13 0.14747000 W

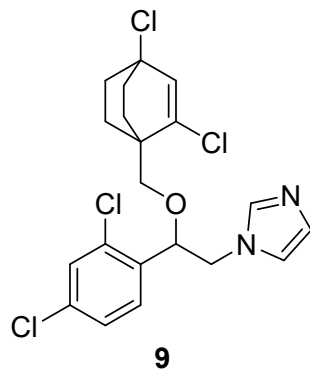
F2 - Processing parameters
 SI 32768
 SF 100.6127725 MHz
 WDW EM
 SSB 0
 LB 3.00 Hz
 GB 0
 PC 1.40



Current Data Parameters
NAME CW468
EXPNO 19
PROCNO 1

F2 - Acquisition Parameters
Date_ 20250710
Time_ 9.39 h
INSTRUM spect
PROBHD z108618_0411 (
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 0
SWH 8802.817 Hz
FIDRES 0.537281 Hz
AQ 1.8612224 sec
RG 83.88
DW 56.800 usec
DE 15.08 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
SF01 400.1328009 MHz
NUC1 1H
P0 5.17 usec
P1 15.50 usec
PLW1 9.89999962 W

F2 - Processing parameters
SI 131072
SF 400.1300098 MHz
WDW EM
SSB 0
LB 0 Hz
GB 0
PC 1.00



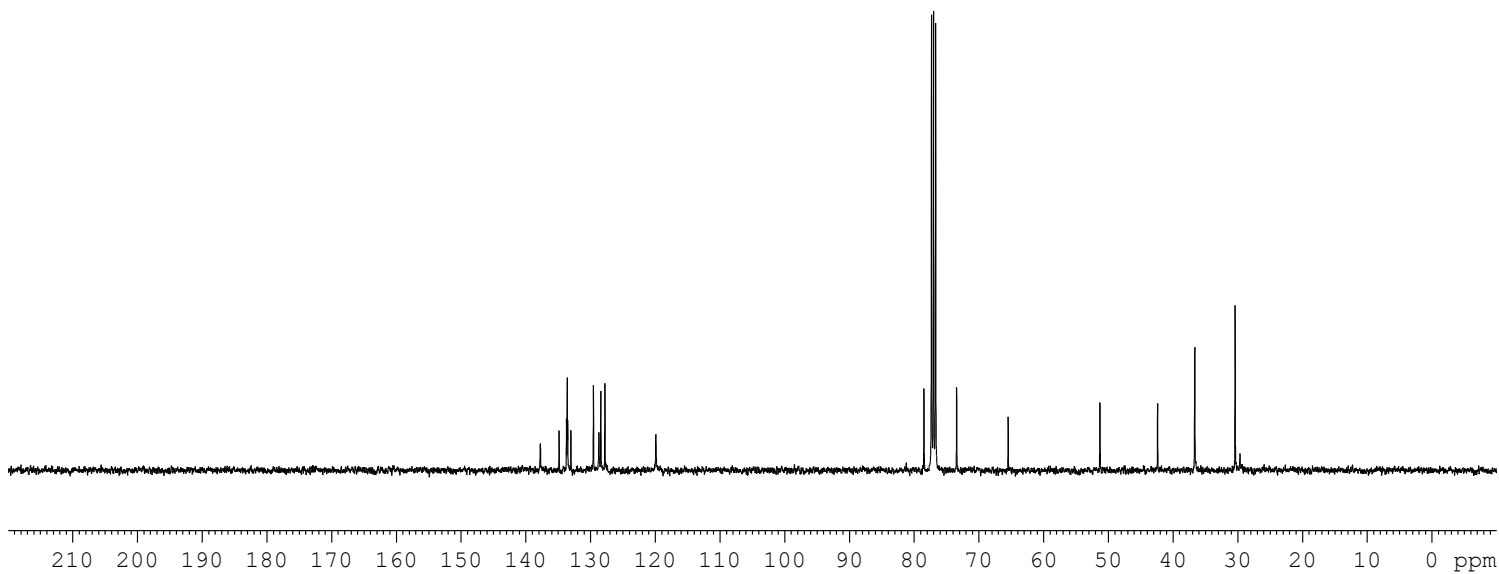
137.80
134.91
133.76
133.64
133.57
133.08
129.60
128.75
128.45
127.83
119.90

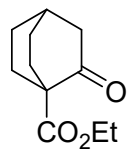
78.48
77.32
77.00
76.68
73.43
65.46
51.29
42.38
36.63
30.40

Current Data Parameters
NAME CW468
EXPNO 13
PROCNO 1

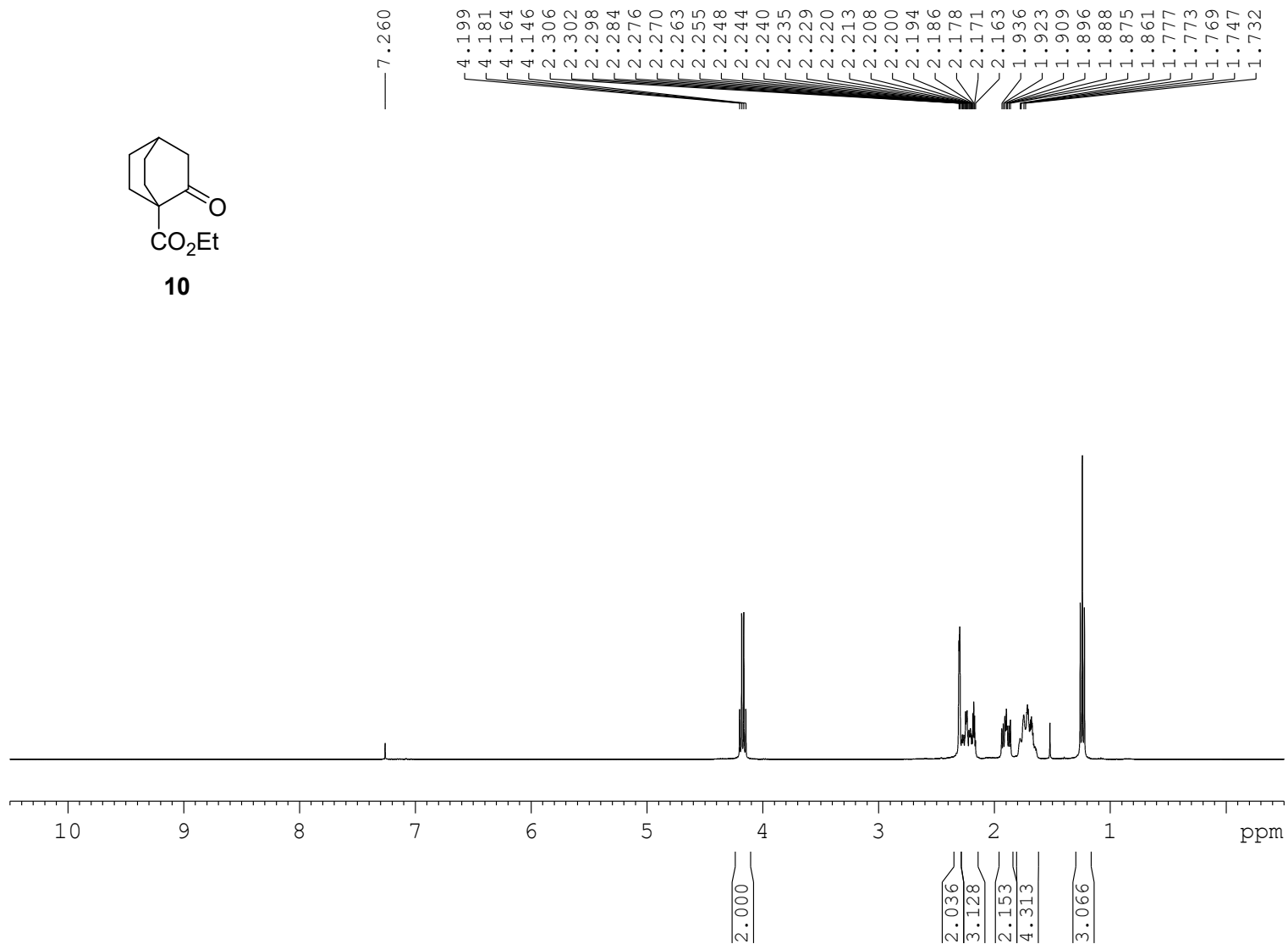
F2 - Acquisition Parameters
Date_ 20250613
Time 12.18 h
INSTRUM spect
PROBHD Z108618_0411 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 360
DS 0
SWH 28409.092 Hz
FIDRES 0.866977 Hz
AQ 1.1534336 sec
RG 212.49
DW 17.600 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6258487 MHz
NUC1 13C
P0 3.50 usec
P1 10.50 usec
PLW1 42.50000000 W
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2] waltz16
PCPD2 90.00 usec
PLW2 9.89999962 W
PLW12 0.29363999 W
PLW13 0.14770000 W

F2 - Processing parameters
SI 32768
SF 100.6127721 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40





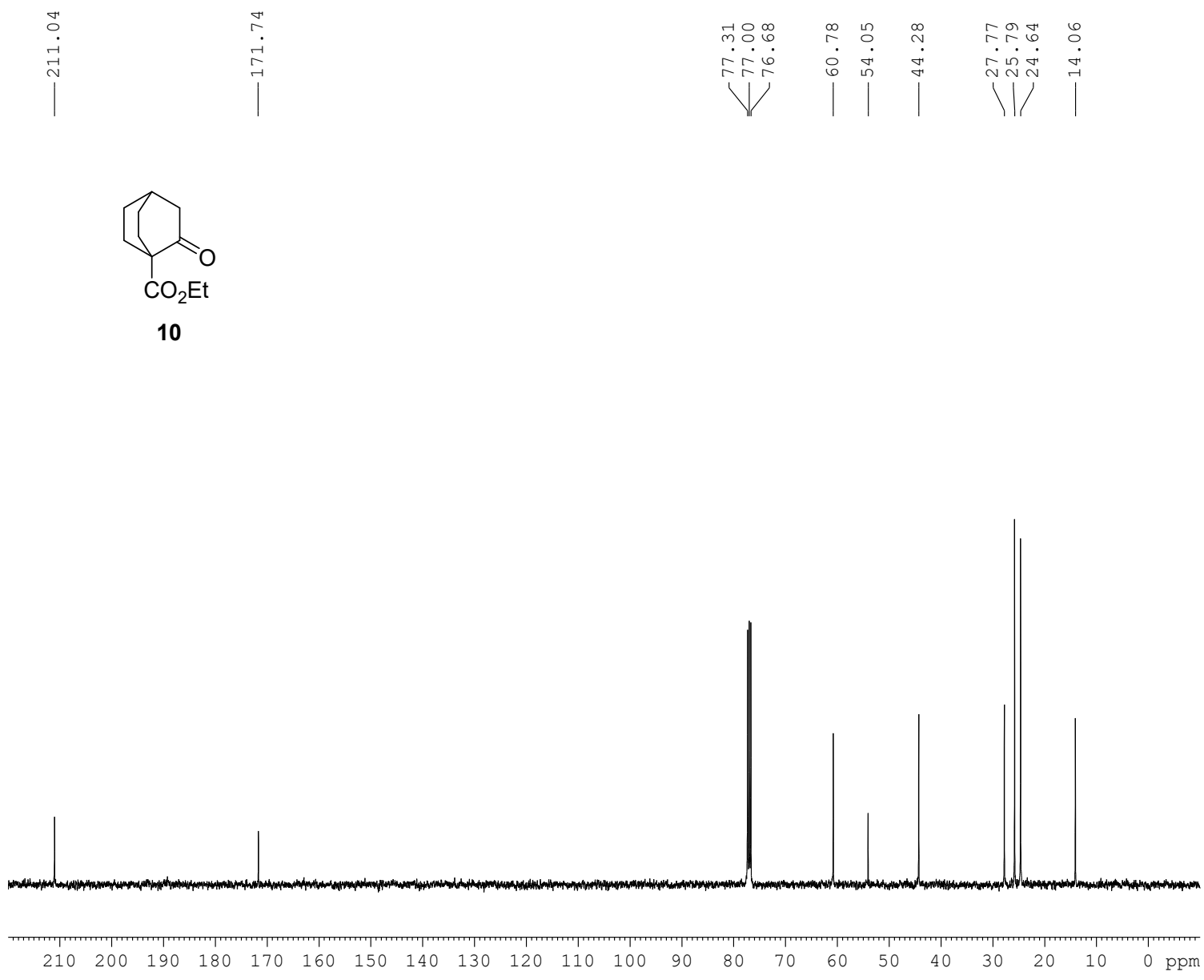
10



Current Data Parameters
 NAME CW413
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20240827
 Time_ 9.44 h
 INSTRUM spect
 PROBHD z108618_0411 (
 PULPROG zg30
 TD 32768
 SOLVENT CDCl3
 NS 8
 DS 0
 SWH 8802.817 Hz
 FIDRES 0.537281 Hz
 AQ 1.8612224 sec
 RG 62.98
 DW 56.800 usec
 DE 14.47 usec
 TE 298.0 K
 D1 1.00000000 sec
 TD0 1
 SFO1 400.1328009 MHz
 NUC1 1H
 P1 15.50 usec
 PLW1 9.89999962 W

F2 - Processing parameters
 SI 131072
 SF 400.1300097 MHz
 WDW EM
 SSB 0
 LB 0 Hz
 GB 0
 PC 1.00



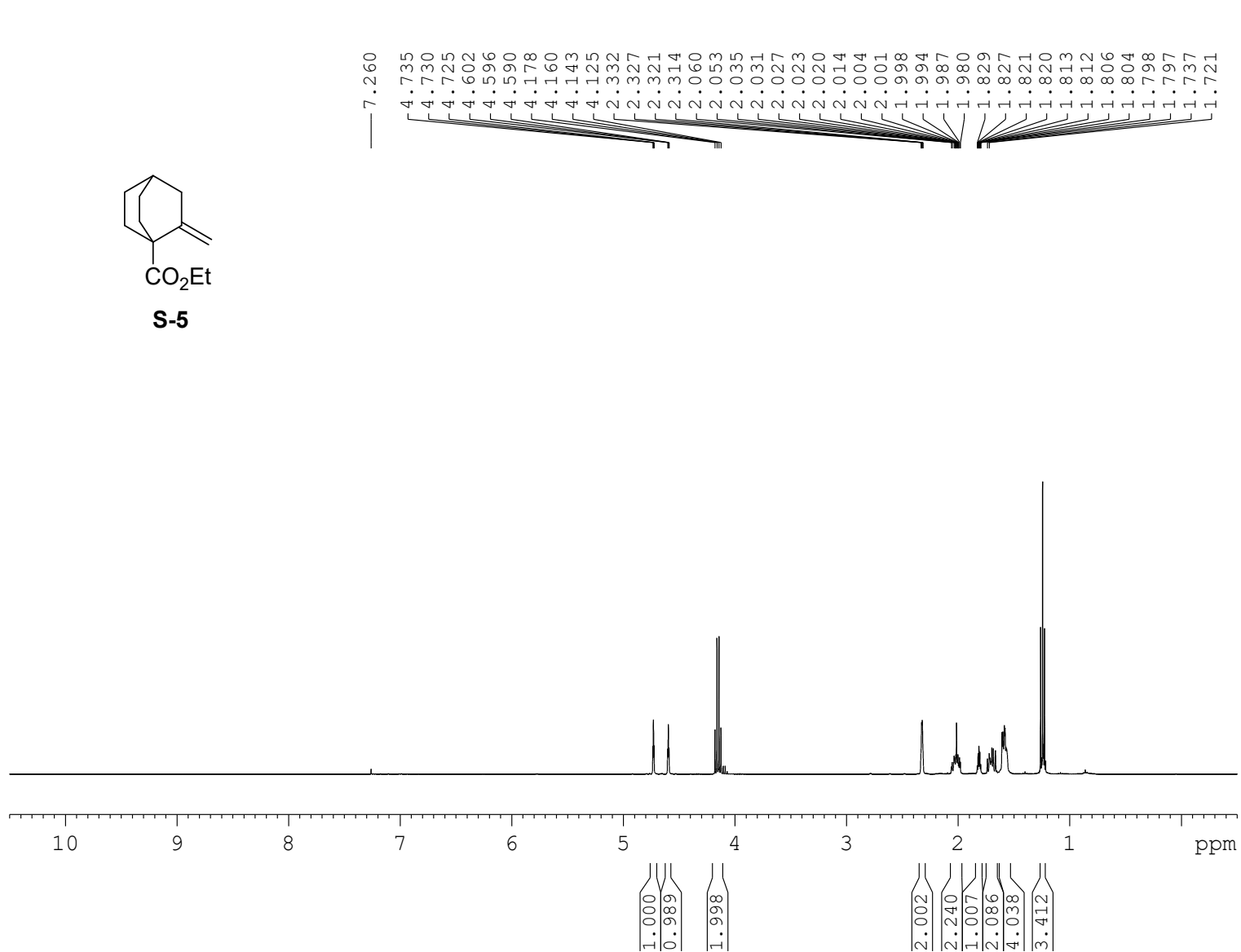
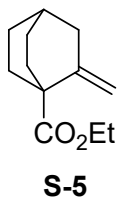
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Current Data Parameters
NAME          CW413
EXPNO         2
PROCNO        1

F2 - Acquisition Parameters
Date_         20240827
Time          9.48 h
INSTRUM       spect
PROBHD        Z108618_0411 (
PULPROG       zgpg30
TD            65536
SOLVENT       CDCl3
NS            60
DS            0
SWH           28409.092 Hz
FIDRES        0.866977 Hz
AQ            1.1534336 sec
RG            212.49
DW            17.600 usec
DE            6.50 usec
TE            298.0 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0           1
SFO1          100.6258487 MHz
NUC1          13C
P1            10.50 usec
PLW1          42.50000000 W
SFO2          400.1316005 MHz
NUC2          1H
CPDPRG[2]    waltz16
PCPD2         90.00 usec
PLW2          9.89999962 W
PLW12         0.29363999 W
PLW13         0.14747000 W

F2 - Processing parameters
SI            32768
SF            100.6127755 MHz
WDW           EM
SSB           0
LB            3.00 Hz
GB            0
PC            1.40

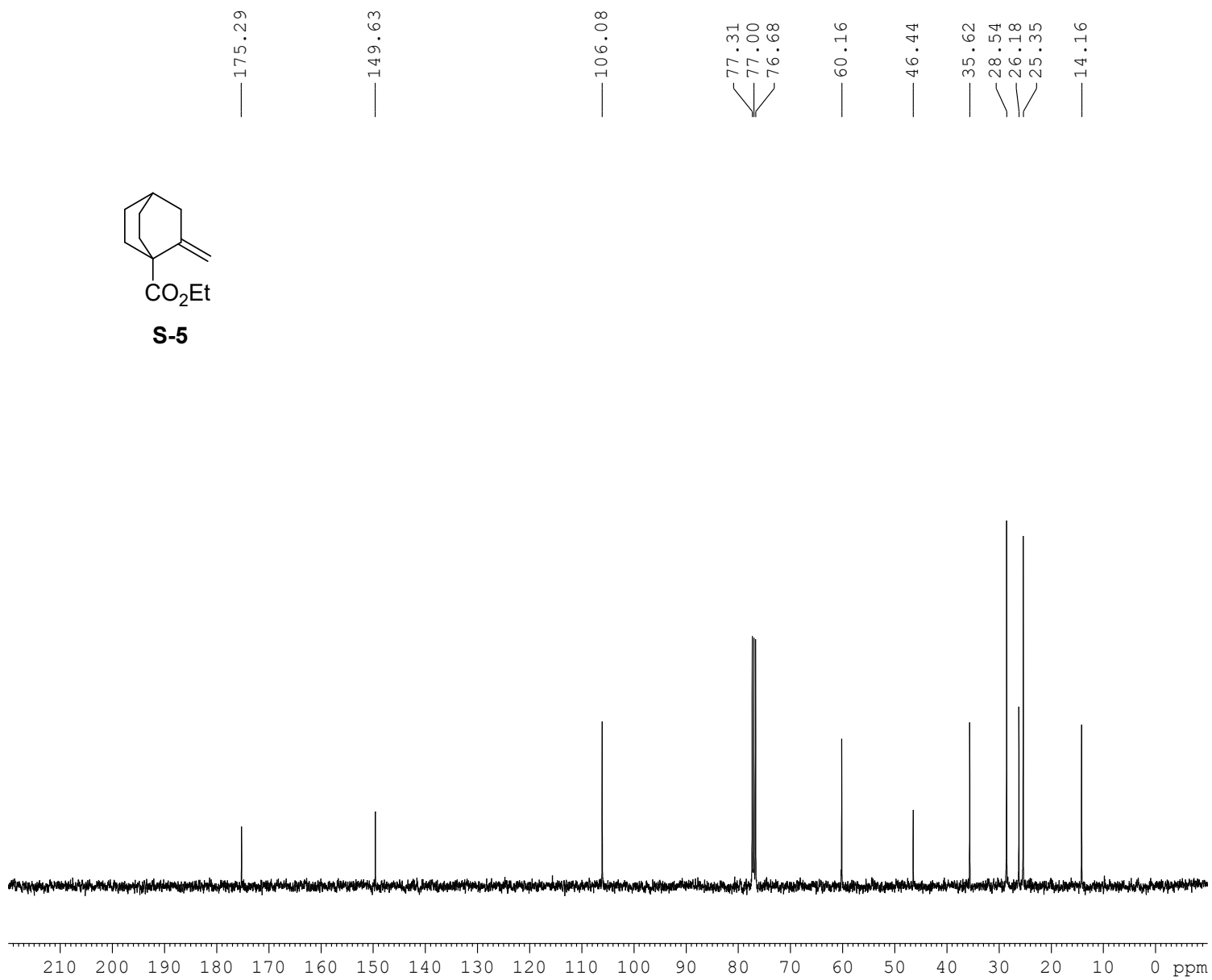
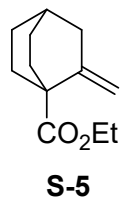
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Current Data Parameters
 NAME CW474
 EXPNO 4
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20250626
 Time_ 14.44 h
 INSTRUM spect
 PROBHD z108618_0411 (
 PULPROG zg30
 TD 32768
 SOLVENT CDCl3
 NS 8
 DS 0
 SWH 8802.817 Hz
 FIDRES 0.537281 Hz
 AQ 1.8612224 sec
 RG 31.38
 DW 56.800 usec
 DE 15.08 usec
 TE 301.6 K
 D1 1.00000000 sec
 TD0 1
 SFO1 400.1328009 MHz
 NUC1 1H
 P0 5.17 usec
 P1 15.50 usec
 PLW1 9.89999962 W

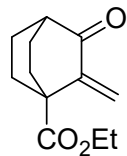
F2 - Processing parameters
 SI 131072
 SF 400.1300094 MHz
 WDW EM
 SSB 0
 LB 0 Hz
 GB 0
 PC 1.00



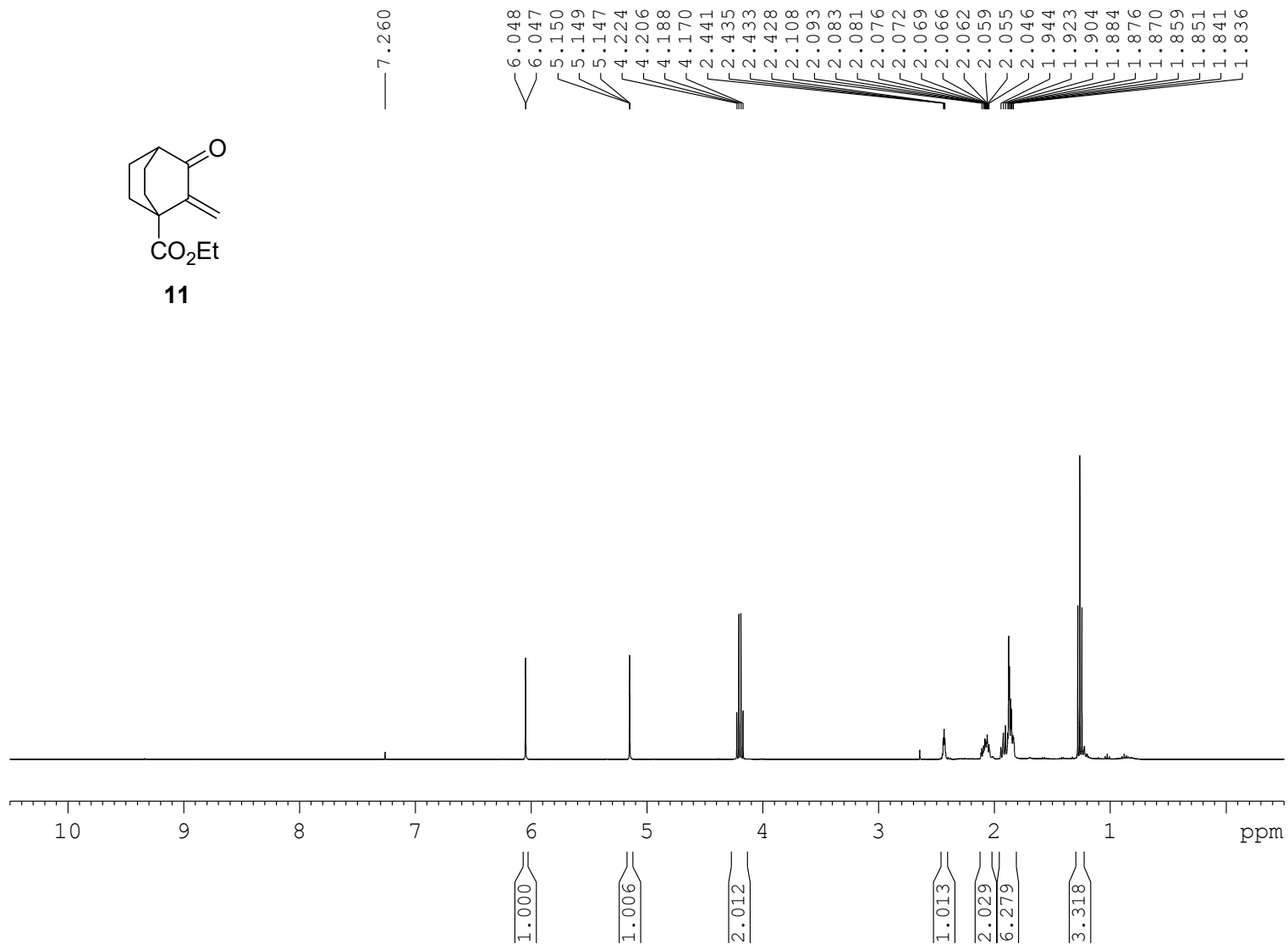
Current Data Parameters
 NAME CW474
 EXPNO 5
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20250626
 Time_ 14.46 h
 INSTRUM spect
 PROBHD Z108618_0411 (
 PULPROG zgpg30
 TD 65536
 SOLVENT CDCl3
 NS 12
 DS 0
 SWH 28409.092 Hz
 FIDRES 0.866977 Hz
 AQ 1.1534336 sec
 RG 212.49
 DW 17.600 usec
 DE 6.50 usec
 TE 301.6 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TD0 1
 SFO1 100.6258487 MHz
 NUC1 13C
 P0 3.50 usec
 P1 10.50 usec
 PLW1 42.50000000 W
 SFO2 400.1316005 MHz
 NUC2 1H
 CPDPRG[2] waltz16
 PCPD2 90.00 usec
 PLW2 9.89999962 W
 PLW12 0.29363999 W
 PLW13 0.14770000 W

F2 - Processing parameters
 SI 32768
 SF 100.6127737 MHz
 WDW EM
 SSB 0
 LB 3.00 Hz
 GB 0
 PC 1.40



11



Current Data Parameters
 NAME CW476
 EXPNO 5
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20250627
 Time_ 17.32 h
 INSTRUM spect
 PROBHD z108618_0411 (
 PULPROG zg30
 TD 32768
 SOLVENT CDCl3
 NS 8
 DS 0
 SWH 8802.817 Hz
 FIDRES 0.537281 Hz
 AQ 1.8612224 sec
 RG 57.72
 DW 56.800 usec
 DE 15.08 usec
 TE 301.6 K
 D1 1.00000000 sec
 TD0 1
 SF01 400.1328009 MHz
 NUC1 1H
 P0 5.17 usec
 P1 15.50 usec
 PLW1 9.89999962 W

F2 - Processing parameters
 SI 131072
 SF 400.1300094 MHz
 WDW EM
 SSB 0
 LB 0 Hz
 GB 0
 PC 1.00

— 201.91

— 172.90

— 145.84

— 117.01

77.32
77.00
76.68

— 60.76

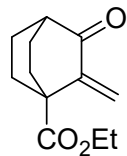
— 47.99

— 41.33

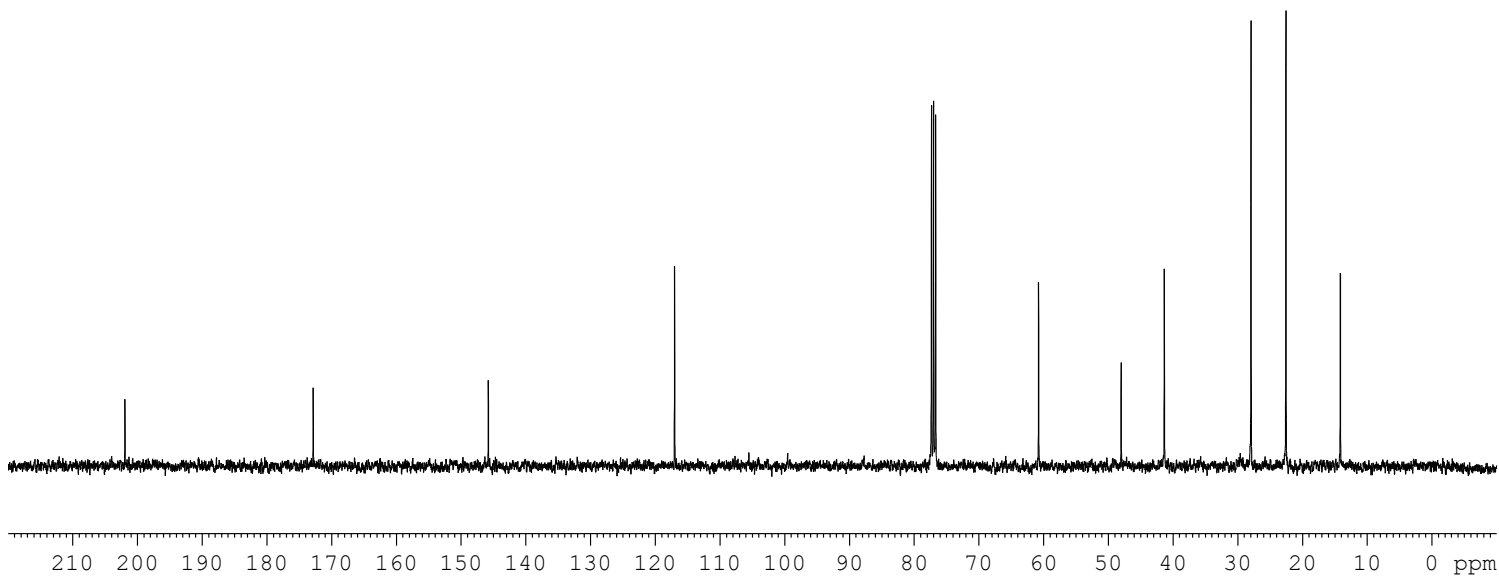
— 27.93

— 22.54

— 14.13



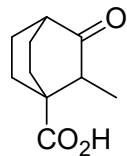
11



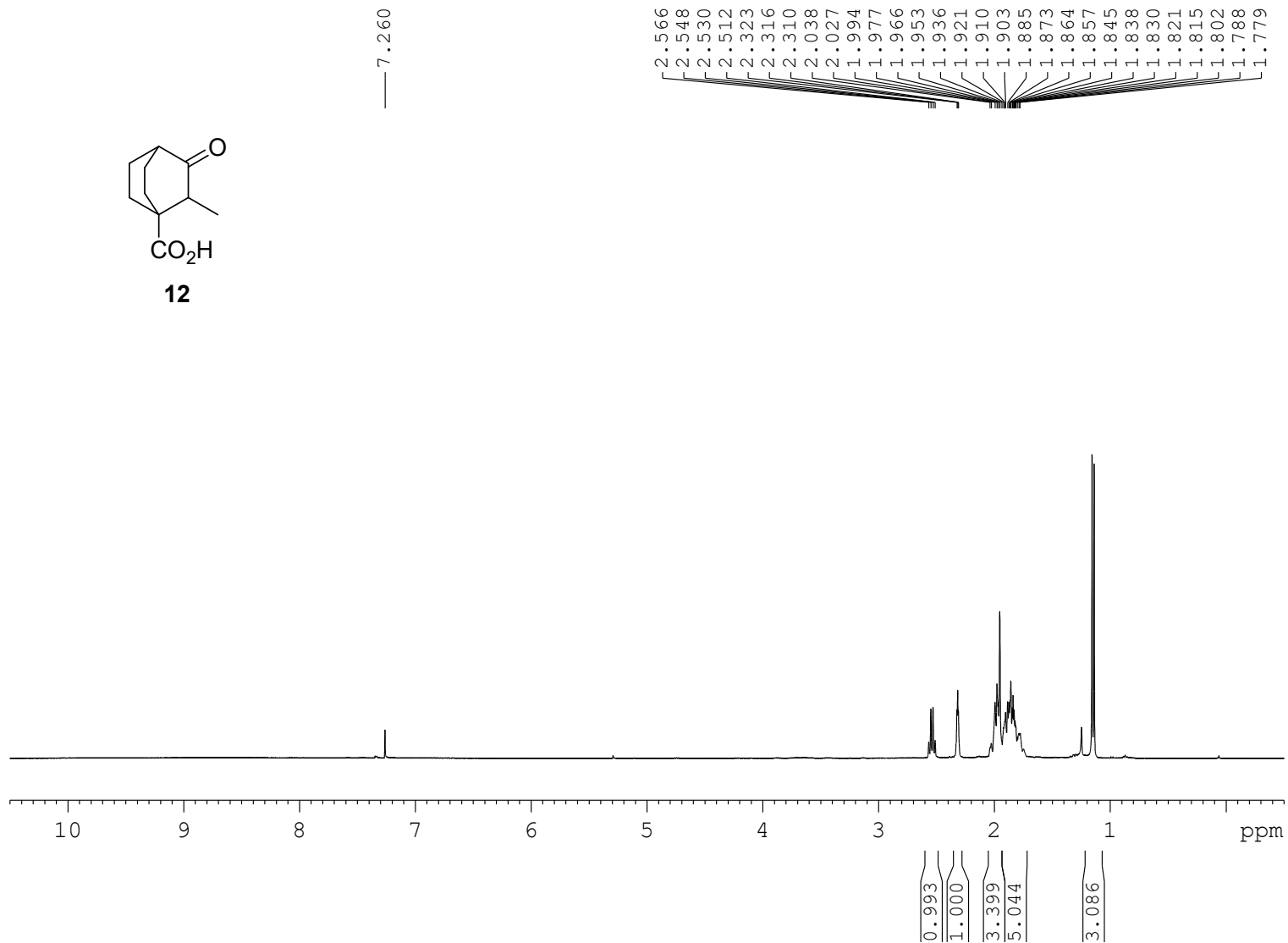
Current Data Parameters
 NAME CW476
 EXPNO 6
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20250627
 Time_ 17.35 h
 INSTRUM spect
 PROBHD Z108618_0411 (
 PULPROG zgpg30
 TD 65536
 SOLVENT CDCl3
 NS 32
 DS 0
 SWH 28409.092 Hz
 FIDRES 0.866977 Hz
 AQ 1.1534336 sec
 RG 212.49
 DW 17.600 usec
 DE 6.50 usec
 TE 301.7 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TD0 1
 SFO1 100.6258487 MHz
 NUC1 13C
 P0 3.50 usec
 P1 10.50 usec
 PLW1 42.50000000 W
 SFO2 400.1316005 MHz
 NUC2 1H
 CPDPRG[2] waltz16
 PCPD2 90.00 usec
 PLW2 9.89999962 W
 PLW12 0.29363999 W
 PLW13 0.14770000 W

F2 - Processing parameters
 SI 32768
 SF 100.6127741 MHz
 WDW EM
 SSB 0
 LB 3.00 Hz
 GB 0
 PC 1.40



12

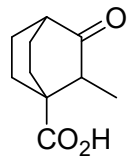


Current Data Parameters
 NAME CW498
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date 20250812
 Time 13.36
 INSTRUM Avance NEO 400
 PROBHD Z104450_0301
 PULPROG zg30
 TD 32768
 SOLVENT CDCl3
 NS 8
 DS 0
 SWH 8196.721
 FIDRES 0.500288
 AQ 1.9988480
 RG 101
 DW 61.000
 DE 6.50 usec
 TE 303.8 K
 D1 1.00000000
 TD0 1
 SFO1 400.1528010 MHz
 NUC1 1H
 P0 5.00
 P1 15.00
 PLW1 8.71049976

F2 - Processing parameters
 SI 32768
 SF 400.1500093 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

—217.46
—180.70



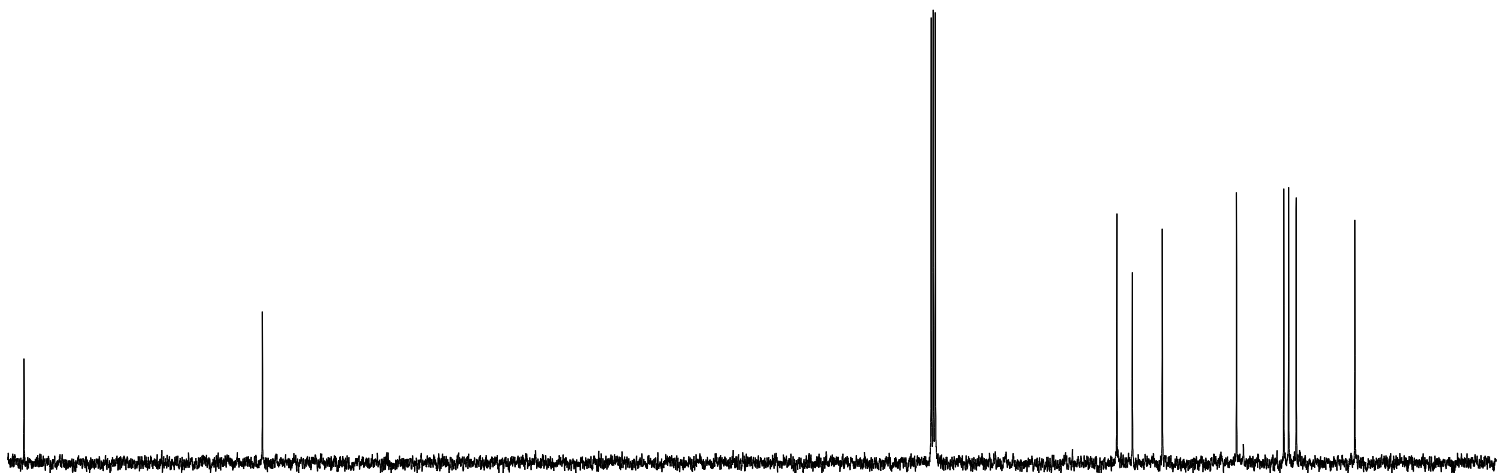
12

77.32
77.00
76.68
48.61
46.23
41.60
30.12
22.82
22.07
20.90
11.85

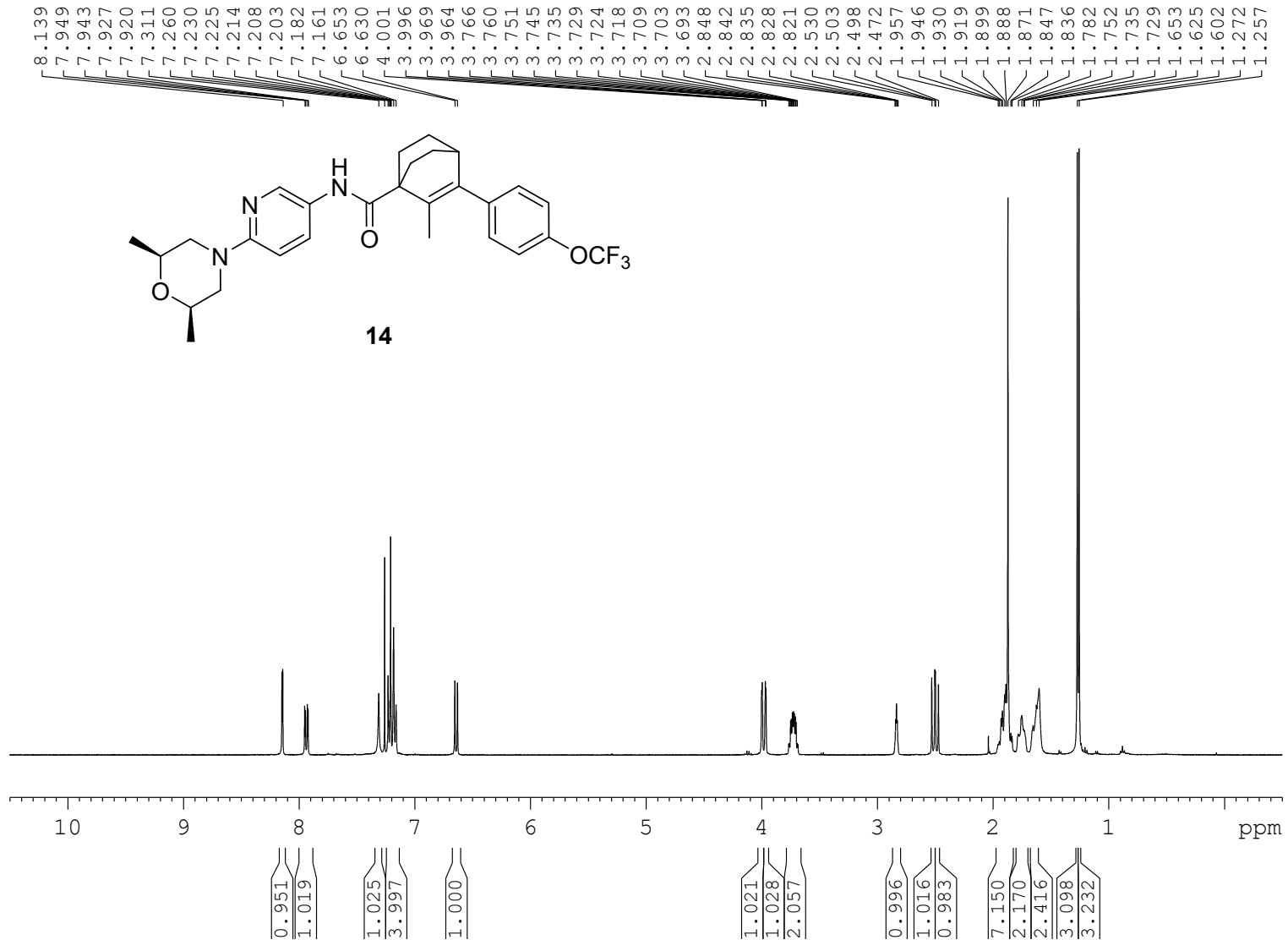
Current Data Parameters
NAME CW477
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
Date 20250628
Time 21.12 h
INSTRUM spect
PROBHD Z108618_0411 (
PULPROG zgpg30
TD 65536
SOLVENT CDC13
NS 36
DS 0
SWH 28409.092 Hz
FIDRES 0.866977 Hz
AQ 1.1534336 sec
RG 212.49
DW 17.600 usec
DE 6.50 usec
TE 301.6 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6258487 MHz
NUC1 13C
P0 3.50 usec
P1 10.50 usec
PLW1 42.50000000 W
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2] waltz16
PCPD2 90.00 usec
PLW2 9.89999962 W
PLW12 0.29363999 W
PLW13 0.14770000 W

F2 - Processing parameters
SI 32768
SF 100.6127730 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40



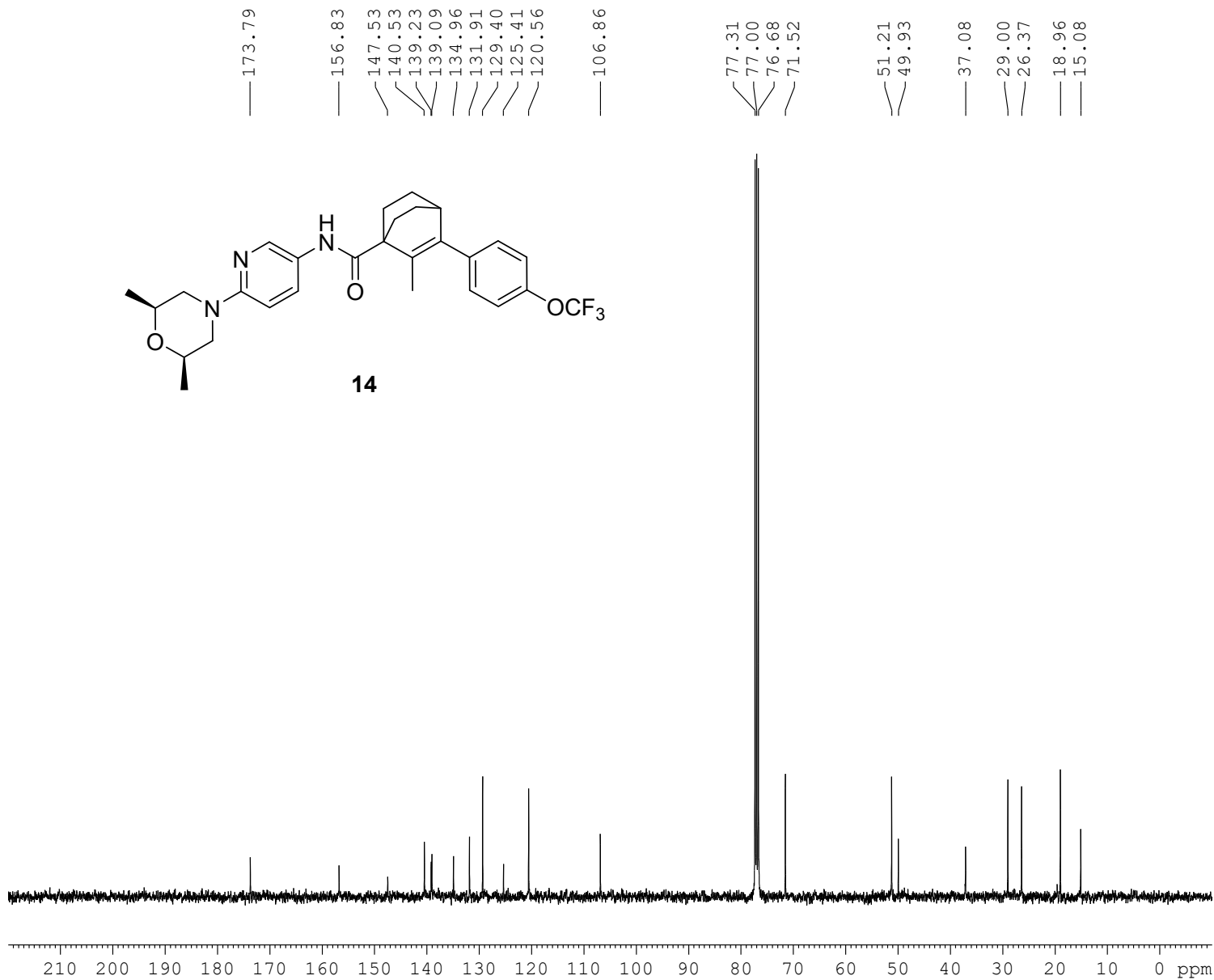
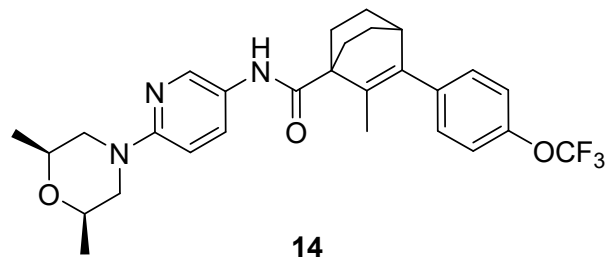
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



Current Data Parameters
NAME CW487
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20250824
Time_ 15.47 h
INSTRUM spect
PROBHD z108618_0411 (
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 0
SWH 8802.817 Hz
FIDRES 0.537281 Hz
AQ 1.8612224 sec
RG 188.2
DW 56.800 usec
DE 15.08 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
SF01 400.1328009 MHz
NUC1 1H
P0 5.17 usec
P1 15.50 usec
PLW1 9.89999962 W

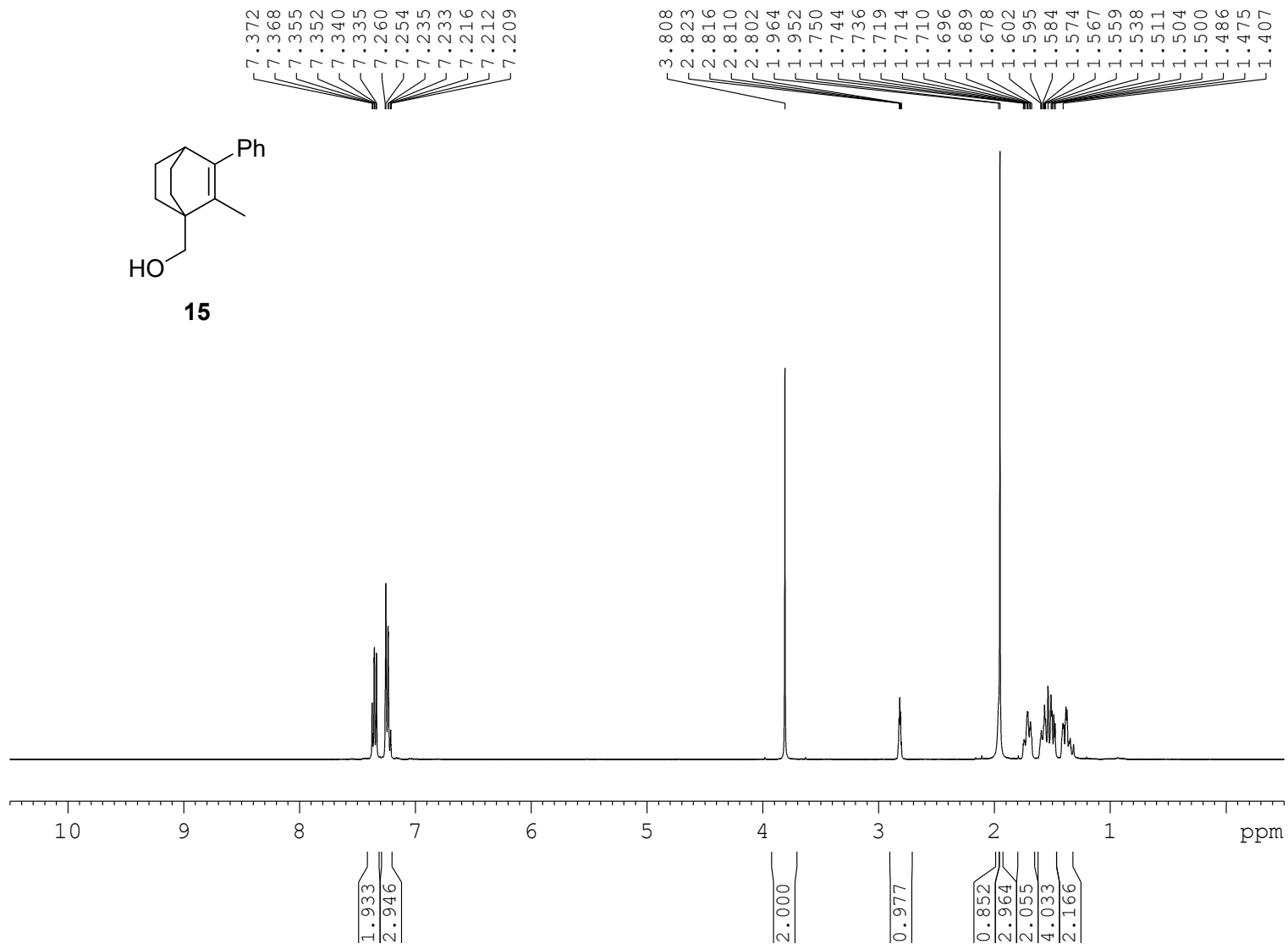
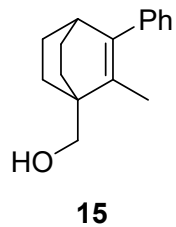
F2 - Processing parameters
SI 131072
SF 400.1300097 MHz
WDW EM
SSB 0
LB 0 Hz
GB 0
PC 1.00



Current Data Parameters
 NAME CW487
 EXPNO 6
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20250824
 Time_ 17.07 h
 INSTRUM spect
 PROBHD Z108618_0411 (
 PULPROG zgpg30
 TD 65536
 SOLVENT CDCl3
 NS 220
 DS 0
 SWH 28409.092 Hz
 FIDRES 0.866977 Hz
 AQ 1.1534336 sec
 RG 212.49
 DW 17.600 usec
 DE 6.50 usec
 TE 298.1 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TD0 1
 SFO1 100.6258487 MHz
 NUC1 13C
 P0 3.50 usec
 P1 10.50 usec
 PLW1 42.50000000 W
 SFO2 400.1316005 MHz
 NUC2 1H
 CPDPRG[2] waltz16
 PCPD2 90.00 usec
 PLW2 9.89999962 W
 PLW12 0.29363999 W
 PLW13 0.14770000 W

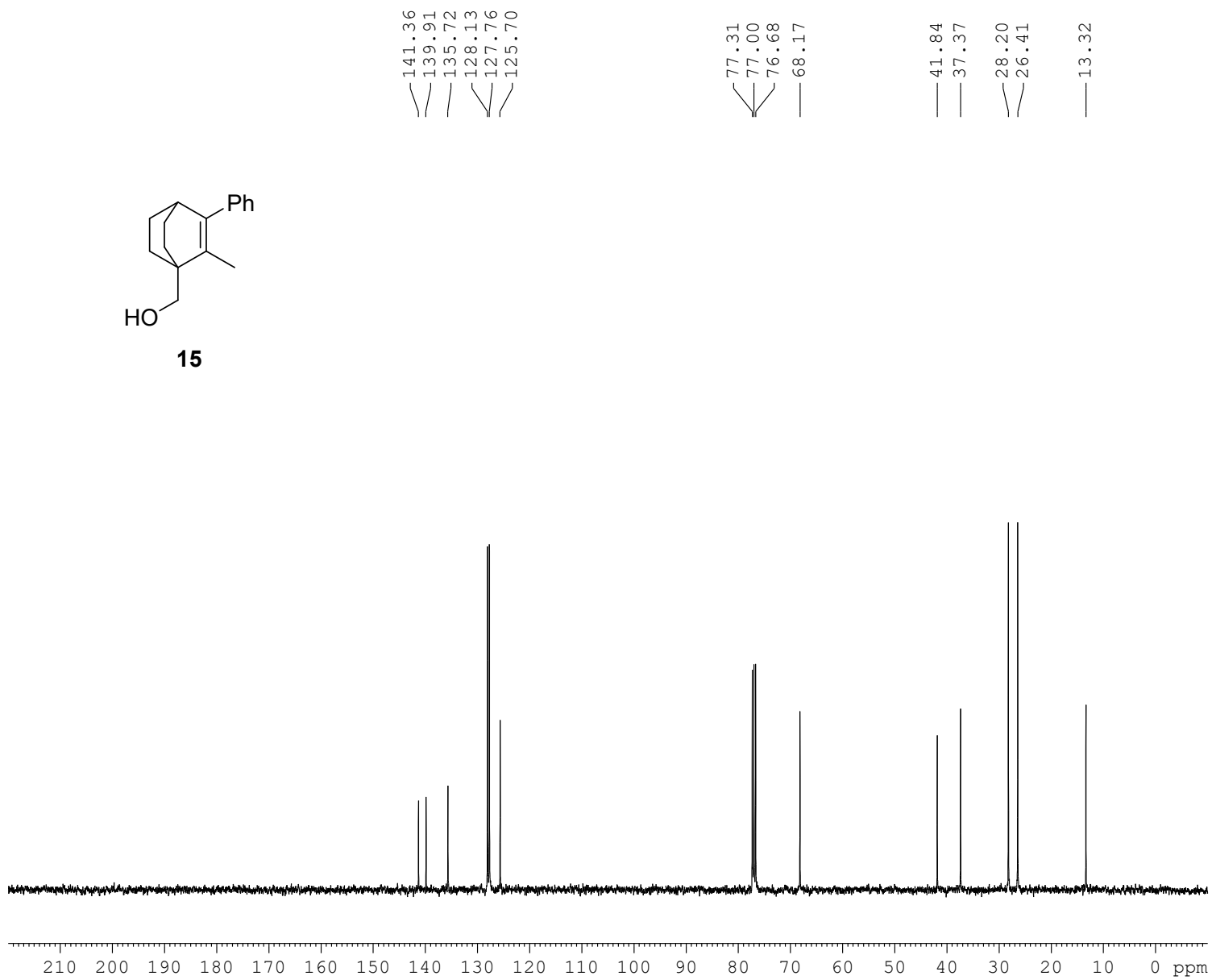
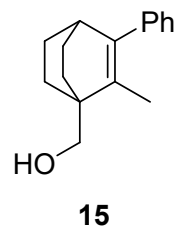
F2 - Processing parameters
 SI 32768
 SF 100.6127722 MHz
 WDW EM
 SSB 0
 LB 3.00 Hz
 GB 0
 PC 1.40



Current Data Parameters
 NAME CW483
 EXPNO 6
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20250813
 Time_ 18.18 h
 INSTRUM spect
 PROBHD z108618_0411 (
 PULPROG zg30
 TD 32768
 SOLVENT CDCl3
 NS 8
 DS 0
 SWH 8802.817 Hz
 FIDRES 0.537281 Hz
 AQ 1.8612224 sec
 RG 22.56
 DW 56.800 usec
 DE 15.08 usec
 TE 298.0 K
 D1 1.00000000 sec
 TD0 1
 SFO1 400.1328009 MHz
 NUC1 1H
 P0 5.17 usec
 P1 15.50 usec
 PLW1 9.89999962 W

F2 - Processing parameters
 SI 131072
 SF 400.1300092 MHz
 WDW EM
 SSB 0
 LB 0 Hz
 GB 0
 PC 1.00

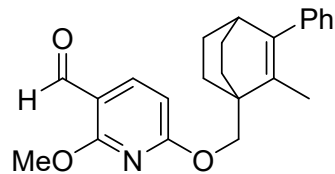


Current Data Parameters
 NAME CW483
 EXPNO 7
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20250813
 Time_ 18.21 h
 INSTRUM spect
 PROBHD Z108618_0411 (
 PULPROG zgpg30
 TD 65536
 SOLVENT CDCl3
 NS 36
 DS 0
 SWH 28409.092 Hz
 FIDRES 0.866977 Hz
 AQ 1.1534336 sec
 RG 212.49
 DW 17.600 usec
 DE 6.50 usec
 TE 298.0 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TD0 1
 SFO1 100.6258487 MHz
 NUC1 13C
 P0 3.50 usec
 P1 10.50 usec
 PLW1 42.50000000 W
 SFO2 400.1316005 MHz
 NUC2 1H
 CPDPRG[2] waltz16
 PCPD2 90.00 usec
 PLW2 9.89999962 W
 PLW12 0.29363999 W
 PLW13 0.14770000 W

F2 - Processing parameters
 SI 32768
 SF 100.6127851 MHz
 WDW EM
 SSB 0
 LB 3.00 Hz
 GB 0
 PC 1.40

< 10.212
10.210



S-6

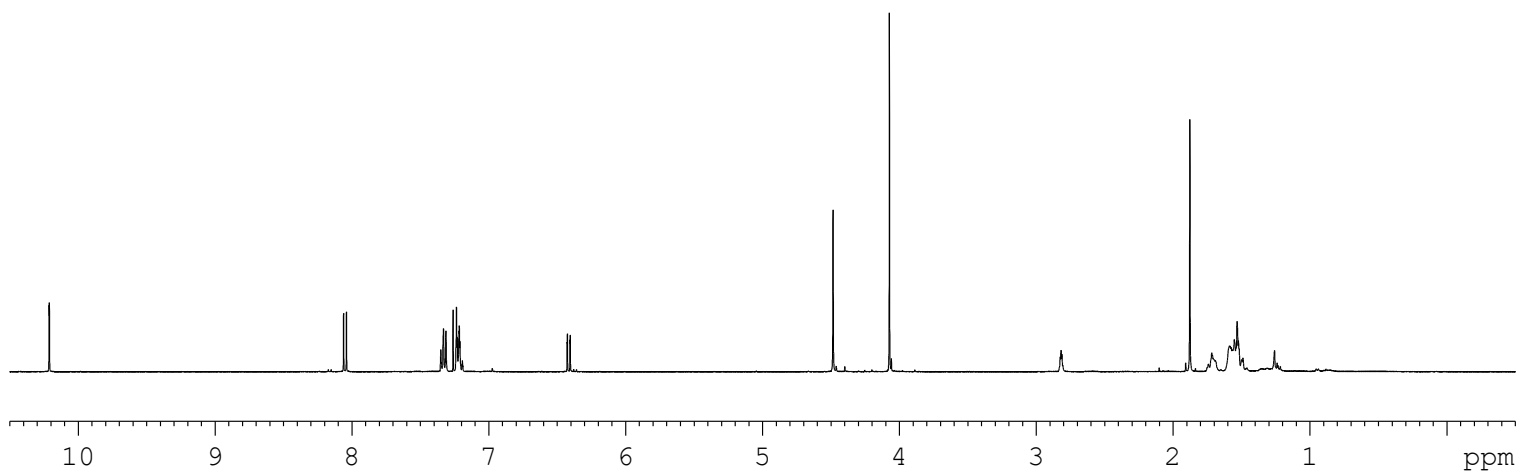
8.060
8.039
7.350
7.346
7.333
7.330
7.318
7.313
7.260
7.236
7.230
7.218
7.215
7.210
7.205
7.195
7.192
7.189
6.427
6.425
6.406
6.404

4.484
4.072
2.824
2.818
2.812
2.804
1.877
1.750
1.742
1.736
1.717
1.712
1.705
1.690
1.588
1.581
1.575
1.565
1.552
1.540
1.532
1.522
1.517
1.500
1.489

Current Data Parameters
NAME CW484
EXPNO 22
PROCNO 1

F2 - Acquisition Parameters
Date_ 20250825
Time_ 17.33 h
INSTRUM spect
PROBHD z108618_0411 (
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 0
SWH 8802.817 Hz
FIDRES 0.537281 Hz
AQ 1.8612224 sec
RG 165.3
DW 56.800 usec
DE 15.08 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1
SF01 400.1328009 MHz
NUC1 1H
P0 5.17 usec
P1 15.50 usec
PLW1 9.89999962 W

F2 - Processing parameters
SI 131072
SF 400.1300097 MHz
WDW EM
SSB 0
LB 0 Hz
GB 0
PC 1.00



0.844

0.893

1.976

2.942

0.911

1.899

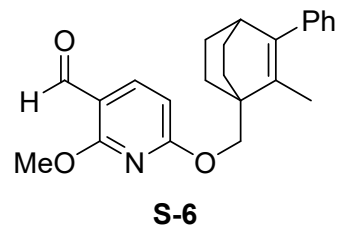
2.833

1.000

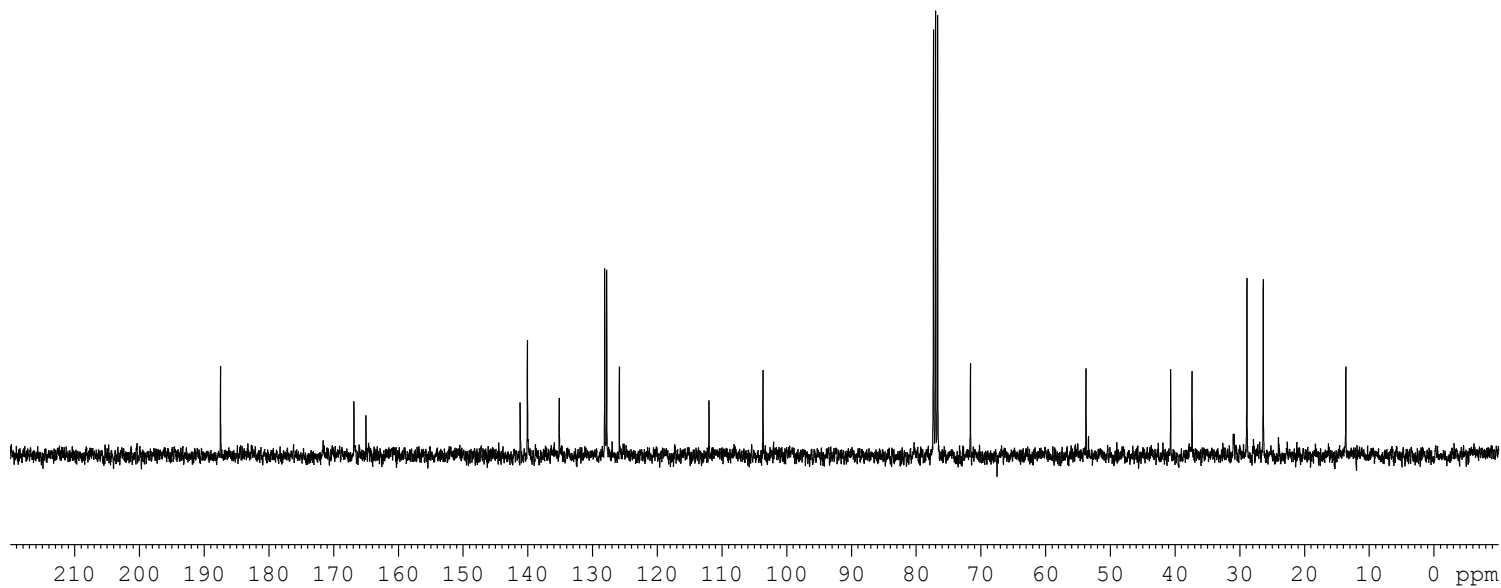
3.030

2.190

6.458



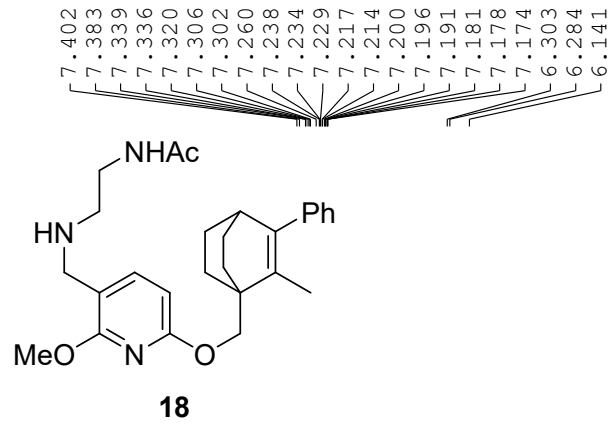
— 187.53
 — 166.91
 — 165.06
 — 141.24
 — 140.10
 — 135.19
 — 128.17
 — 127.86
 — 125.90
 — 112.00
 — 103.65
 — 77.31
 — 77.00
 — 76.68
 — 71.60
 — 53.74
 — 40.67
 — 37.36
 — 28.87
 — 26.35
 — 13.60



Current Data Parameters
 NAME CW484
 EXPNO 19
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20250819
 Time_ 17.20 h
 INSTRUM spect
 PROBHD Z108618_0411 (
 PULPROG zgpg30
 TD 65536
 SOLVENT CDCl3
 NS 36
 DS 0
 SWH 28409.092 Hz
 FIDRES 0.866977 Hz
 AQ 1.1534336 sec
 RG 212.49
 DW 17.600 usec
 DE 6.50 usec
 TE 298.0 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TD0 1
 SFO1 100.6258487 MHz
 NUC1 13C
 P0 3.50 usec
 P1 10.50 usec
 PLW1 42.50000000 W
 SFO2 400.1316005 MHz
 NUC2 1H
 CPDPRG[2] waltz16
 PCPD2 90.00 usec
 PLW2 9.89999962 W
 PLW12 0.29363999 W
 PLW13 0.14770000 W

F2 - Processing parameters
 SI 32768
 SF 100.6127754 MHz
 WDW EM
 SSB 0
 LB 3.00 Hz
 GB 0
 PC 1.40



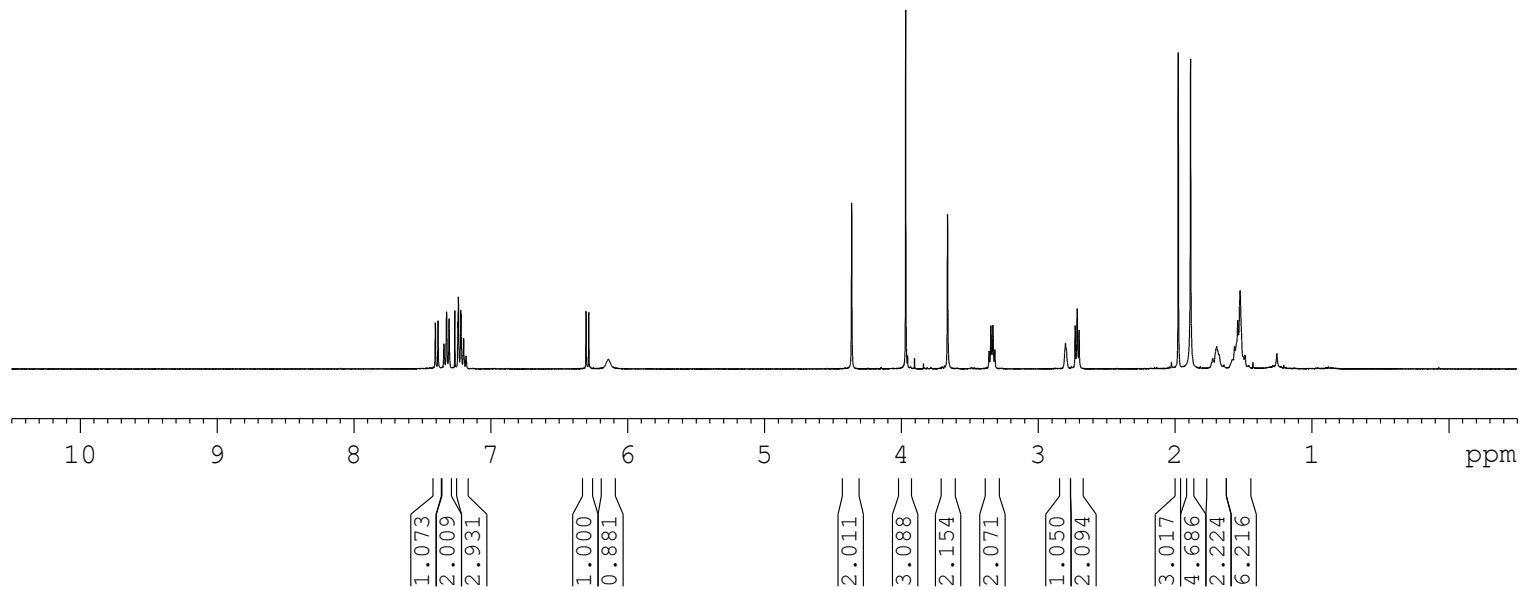
7.402
7.383
7.339
7.336
7.320
7.306
7.302
7.260
7.238
7.234
7.229
7.217
7.214
7.200
7.196
7.191
7.181
7.178
7.174
6.303
6.284
6.141

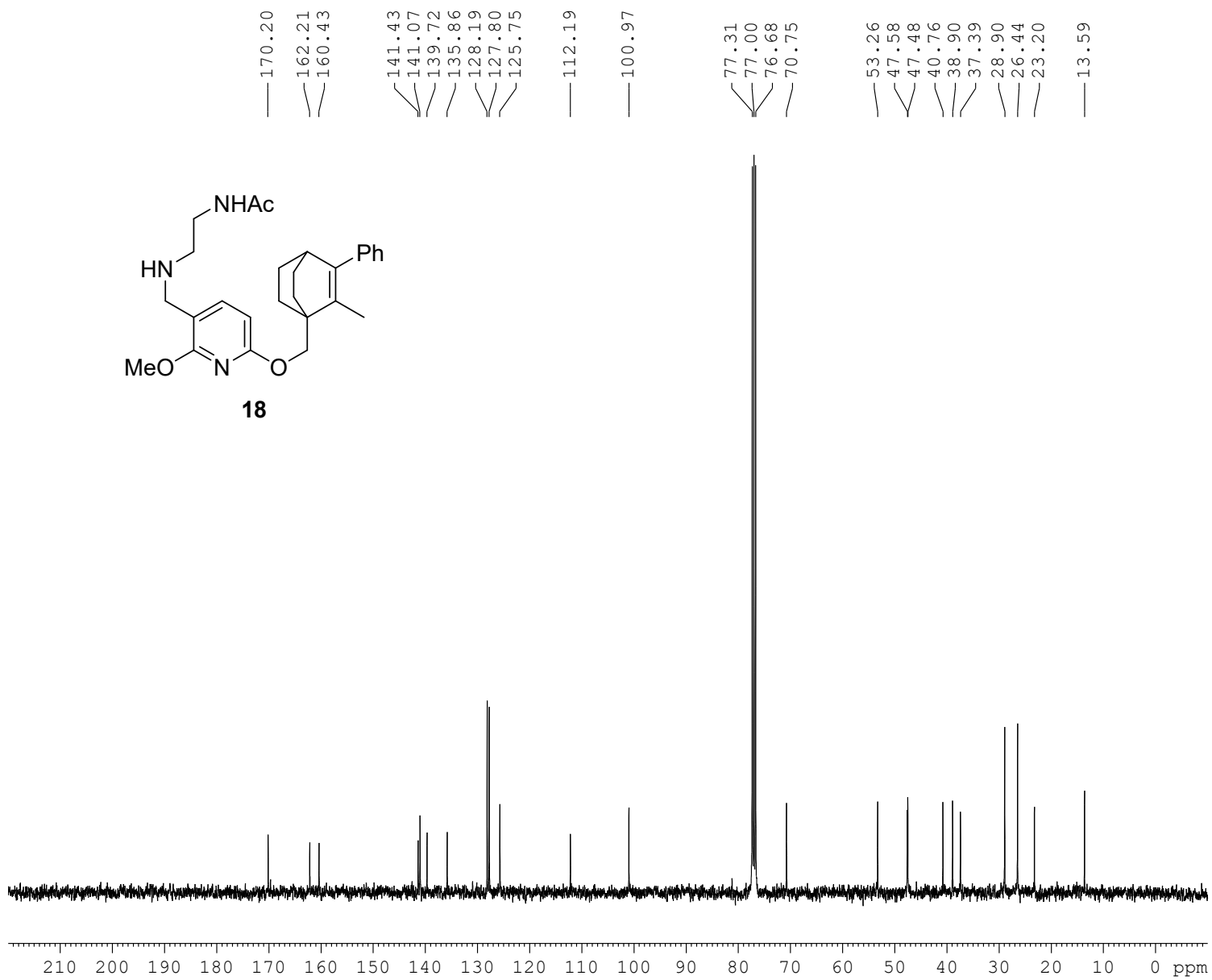
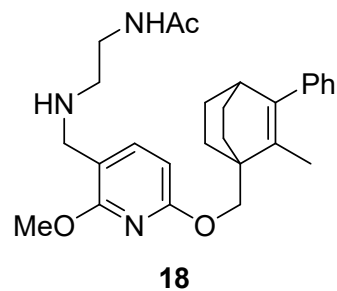
4.363
3.968
3.662
3.359
3.345
3.331
3.317
2.800
2.794
2.730
2.715
2.701
1.976
1.886
1.725
1.695
1.689
1.677
1.582
1.565
1.550
1.541
1.524
1.502
1.488

Current Data Parameters
NAME CW486
EXPNO 16
PROCNO 1

F2 - Acquisition Parameters
Date_ 20250823
Time_ 12.30 h
INSTRUM spect
PROBHD Z108618_0411 (
PULPROG zg30
TD 32768
SOLVENT CDC13
NS 8
DS 0
SWH 8802.817 Hz
FIDRES 0.537281 Hz
AQ 1.8612224 sec
RG 118.08
DW 56.800 usec
DE 15.08 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
SFO1 400.1328009 MHz
NUC1 1H
P0 5.17 usec
P1 15.50 usec
PLW1 9.89999962 W

F2 - Processing parameters
SI 131072
SF 400.1300098 MHz
WDW EM
SSB 0
LB 0 Hz
GB 0
PC 1.00





Current Data Parameters
 NAME CW486
 EXPNO 12
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20250822
 Time_ 21.32 h
 INSTRUM spect
 PROBHD Z108618_0411 (
 PULPROG zgpg30
 TD 65536
 SOLVENT CDCl3
 NS 120
 DS 0
 SWH 28409.092 Hz
 FIDRES 0.866977 Hz
 AQ 1.1534336 sec
 RG 212.49
 DW 17.600 usec
 DE 6.50 usec
 TE 297.9 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TD0 1
 SFO1 100.6258487 MHz
 NUC1 13C
 P0 3.50 usec
 P1 10.50 usec
 PLW1 42.50000000 W
 SFO2 400.1316005 MHz
 NUC2 1H
 CPDPRG[2] waltz16
 PCPD2 90.00 usec
 PLW2 9.89999962 W
 PLW12 0.29363999 W
 PLW13 0.14770000 W

F2 - Processing parameters
 SI 32768
 SF 100.6127756 MHz
 WDW EM
 SSB 0
 LB 3.00 Hz
 GB 0
 PC 1.40