Mild Intramolecular Ring Opening of Oxetanes

Lindsey G. DeRatt, Edward C. Lawson, Chao-Yuan Wang, Scott D. Kuduk

Janssen R&D, 1400 McKean Road, Spring House, PA 19477, United States

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1. General Considerations

DriSolv solvents were purchased from EMD Millipore corporation. Analytical thin layer chromatography (TLC) was performed using 250 μm Silica Gel 60 F254 pre-coated plates. Flash column chromatography was performed using an Isco with RediSep silica columns. Proton nuclear magnetic resonance (1H NMR) spectra were recorded using a Bruker AVANCE III HD NanoBay 400 NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS, 0.0 ppm), CDCl3 (7.26 ppm), MeOD (3.31 ppm), or $(CD_3)_2SO$ (2.50 ppm). Coupling constants (J) are reported in Hz. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; b, broad; Carbon-13 nuclear magnetic resonance (13C NMR) spectra were recorded using a Bruker AVANCE III HD NanoBay 400 NMR spectrometer at 101 MHz. Chemical shifts are reported in ppm relative to the carbon resonance of CDCl3 (77.23 ppm), MeOD (49.01 ppm), or $(CD_3)_2SO$ (39.58 ppm). High resolution mass spectra (HRMS) are reported as m/z (relative ratio). The Instrument Agilent 1260 Infinity Series was used for ESI-TOF analysis (Agilent model 6230). Accurate m/z are reported for the molecular ion [M+H]+. All carboxylic acid and oxetanylamine reagents were purchased from commercial vendors and used without further purification. When heating is indicated in procedure, the reaction was performed using a IKA hot plate with an aluminum block and a thermocouple.

2. Optimization

General procedure for cyclization under basic conditions: To a solution of **14** in DMF (0.3 M) was added base (2.0 equiv.) The mixture was heated at the noted temperature for 1-16 h. The % conversion to **15** was determined by crude NMR.

entry	(°C)	base (2.0 equiv.)	conversion to **15** (%)
1	70	Cs_2CO_3	>99
2	70	K_2CO_3	>99
3	70	DBU	>99
4	70	Et_3N	<10
5	70	Pyridine	<10
6	50	DBU	>99

Procedure for cyclization under acidic conditions: To a solution of **14** in THF at 0 °C was added BF_3•OEt_2 (1.0 equiv.). The reaction was complete upon addition to form **44** and trace **15** was observed by crude NMR.

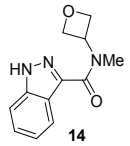
General conditions for optimization of one-pot reaction:

For HATU: To a solution of indazole-3-carboxylic acid (1.0 equiv.) and HATU (1.2 equiv.) in solvent (0.3 M) was added N-methyloxetan-3-amine (1.2 equiv) followed by Et_3N (2.5 equiv.) The mixture was stirred overnight then DBU (3.0 equiv.) was added. The mixture was heated at 70 °C then concentrated in vacuo and purified by column chromatography (0-10% MeOH/DCM).

For CDI: A solution of indazole-3-carboxylic acid (1.0 equiv.) and CDI (1.2 equiv.) in DMF (0.3 M) was stirred for 1 h at 70 °C then N-methyloxetan-3-amine (1.2 equiv) was added. The mixture was stirred overnight then DBU (3.0 equiv.) was added. The mixture was heated at 70 °C then concentrated in vacuo and purified by column chromatography (0-10% MeOH/DCM).

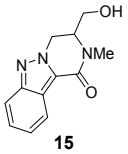
entry	coupling agent	solvent	isolated yield (%)
1	HATU	DCE	<5
2	HATU	1,4-dioxane	97
3	HATU	MeCN	71
4	HATU	DMF	97
5	CDI	DMF	78

3. Product Characterization



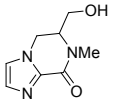
14

N-methyl-N-(oxetan-3-yl)-1H-indazole-3-carboxamide. To a solution of 1H-indazole-3-carboxylic acid (338 mg, 2.1 mmol) and HATU (951 mg, 2.5 mmol) in DMF (3.0 mL) was added Et_3N (0.58 mL, 0.728 g/mL, 4.17 mmol) followed by N-methyloxetan-3-amine (0.22 mL, 0.979 g/mL, 2.50 mmol). The mixture was stirred at room temperature for 24 h then diluted with EtOAc and water. The organics were extracted with EtOAc, washed with brine, and dried over sodium sulfate. Purification by column chromatography (70-80% EtOAc/heptane) afforded the title compound as a white solid (454 mg, 94% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.95 (br s, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.43 (t, J = 7.7 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 5.97 – 5.30 (m, 1H), 4.89 – 4.80 (m, 4H), 3.41 (s, 3H). 13C NMR peaks not assigned due to ambiguous spectra (*vide infra*). HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{12}H_{13}N_3O_2H^+$ 232.1086; found 232.1093.



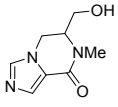
15

3-(hydroxymethyl)-2-methyl-3,4-dihydropyrazino[1,2-b]indazol-1(2H)-one. To a solution of indazole-3-carboxylic acid (100 mg, 0.62 mmol) and HATU (281 mg, 0.74 mmol) in DMF (2.0 mL) was added N-methyloxetan-3-amine (66 µL, 0.979 g/mL, 0.74 mmol) followed by Et_3N (0.21 mL, 0.728 g/mL, 1.5 mmol). The mixture was stirred overnight then DBU (0.28 mL, 1.019 g/mL, 1.9 mmol) was added. The mixture was heated at 70 °C for 5 h. The mixture was concentrated in vacuo then purified by column chromatography (0-10% MeOH/DCM) to afford the title compound as a white solid (139 mg, 97% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.05 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.7 Hz, 1H), 7.44 – 7.32 (m, 1H), 7.30 – 7.21 (m, 1H), 4.83 (d, J = 3.3 Hz, 2H), 3.98 (m, 1H), 3.72 (dd, J = 11.3, 4.9 Hz, 1H), 3.47 (dd, J = 11.2, 7.9 Hz, 1H), 3.23 (s, 3H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 158.2, 148.2, 126.5, 124.7, 124.2, 121.1, 120.3, 117.1, 59.5, 58.9, 47.4, 32.2. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{12}H_{13}N_3O_2H^+$ 232.1086; found 232.1094.



17

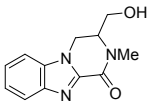
6-(hydroxymethyl)-7-methyl-6,7-dihydroimidazo[1,2-a]pyrazin-8(5H)-one. A mixture of 1H-imidazole-2-carboxylic acid (143 mg, 1.276 mmol) and CDI (248 mg, 1.53 mmol) in DMF was stirred at 70 °C for 2 h then N-methyloxetan-3-amine (136 µL, 0.979 g/mL, 1.53 mmol) was added. The mixture was stirred for an additional 2 h then DBU (0.572 mL, 1.019 g/mL, 3.827 mmol) was added to the reaction. The mixture was heated at 70 °C for 6 h then concentrated and purified by column chromatography (0-15% MeOH/DCM) to afford the product as a white solid (129 mg, yield 56%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.23 (s, 1H), 7.15 (s, 1H), 4.51 – 4.39 (m, 2H), 3.88 – 3.80 (m, 1H), 3.69 (dd, J = 11.3, 5.0 Hz, 1H), 3.43 (dd, J = 11.3, 8.0 Hz, 1H), 3.18 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.3, 138.1, 130.1, 121.8, 59.5, 58.9, 43.0, 33.6. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_8H_{11}N_3O_2H^+$ 182.0930; found 182.0936.



18

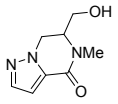
6-(hydroxymethyl)-7-methyl-6,7-dihydroimidazo[1,5-a]pyrazin-8(5H)-one. 1H-imidazole-4-carboxylic acid (134 mg, 1.2 mmol), CDI (232.6 mg, 1.4 mmol) in DMF was stirred at 70 °C for 2 h then N-methyloxetan-3-amine (128 µL, 0.979 g/mL, 1.4 mmol) was added. The mixture was stirred an

additional 2 h then DBU (0.54 mL, 1.019 g/mL, 3.6 mmol) was added and the mixture heated at 70 °C for 6 h. The mixture was concentrated then purified by column chromatography (0-15% MeOH/DCM) to afford the product as a white solid (112 mg, yield 52%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.79 (s, 1H), 7.55 (s, 1H), 4.57 (dd, *J* = 13.3, 1.5 Hz, 1H), 4.31 (dd, *J* = 13.3, 4.8 Hz, 1H), 3.88 – 3.77 (m, 1H), 3.66 (dd, *J* = 11.2, 5.1 Hz, 1H), 3.39 (dd, *J* = 11.2, 8.2 Hz, 1H), 3.17 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.6, 138.5, 131.4, 124.1, 59.2, 59.1, 41.9, 33.2. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_8H_{11}N_3O_2H^+$ 182.0930; found 182.0938.



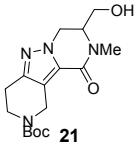
19

3-(hydroxymethyl)-2-methyl-3,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrazin-1(2H)-one. To a solution of 1H-benzimidazole-2-carboxylic acid (200 mg, 1.2 mmol) and HATU (562.8 mg, 1.5 mmol) in DMF (4 mL) was added N-methyloxetan-3-amine (0.13 mL, 0.979 g/mL, 1.5 mmol) followed by Et_3N (0.43 mL, 0.728 g/mL, 3.1 mmol). The mixture was stirred overnight then DBU (0.55 mL, 1.019 g/mL, 3.7 mmol) was added and heated to 70 °C. Upon full conversion to the cyclized product, the mixture was concentrated in vacuo then purified by column chromatography (0-10% MeOH/DCM) to afford the product as a pale yellow solid (208 mg, 73% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.77 (d, *J* = 8.1 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.50 – 7.42 (m, 1H), 7.40 – 7.31 (m, 1H), 4.72 (dd, *J* = 13.2, 1.4 Hz, 1H), 4.52 (dd, *J* = 13.1, 5.2 Hz, 1H), 4.11 – 3.96 (m, 1H), 3.74 (dd, *J* = 11.5, 4.6 Hz, 1H), 3.54 (dd, *J* = 11.5, 7.4 Hz, 1H), 3.28 (s, 3H).^{13}C NMR (101 MHz, Methanol-d_4) δ 157.0, 142.1, 141.7, 133.8, 124.9, 123.5, 120.0, 110.5, 60.0, 59.3, 40.7, 33.0. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{12}H_{13}N_3O_2H^+$ 232.1086; found 232.1096.



20

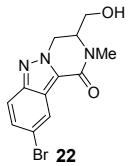
6-(hydroxymethyl)-5-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one. To a solution of 1H-pyrazole-5-carboxylic acid (200 mg, 1.8 mmol) and HATU (814.1 mg, 2.1 mmol) in DMF (5.8 mL) was added N-methyloxetan-3-amine (0.19 mL, 0.979 g/mL, 2.1 mmol) followed by Et_3N (0.62 mL, 0.728 g/mL, 4.5 mmol). The mixture was stirred overnight then DBU (0.8 mL, 1.019 g/mL, 5.4 mmol) was added and heated to 70 °C for 5 h. The mixture was concentrated in vacuo then purified by column chromatography (0-10% MeOH/DCM) to afford the product as a colorless oil (318 mg, 98% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.53 (d, *J* = 2.0 Hz, 1H), 6.75 (d, *J* = 2.0 Hz, 1H), 4.55 (dd, *J* = 13.4, 1.4 Hz, 1H), 4.43 (dd, *J* = 13.4, 5.1 Hz, 1H), 3.90 – 3.81 (m, 1H), 3.65 (dd, *J* = 11.2, 5.1 Hz, 1H), 3.40 (dd, *J* = 11.2, 8.1 Hz, 1H), 3.16 (s, 3H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 158.0, 139.1, 133.4, 106.7, 59.4, 59.3, 45.7, 32.6. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_8H_{11}N_3O_2H^+$ 182.0930; found 182.0925.



21

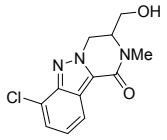
tert-butyl 8-(hydroxymethyl)-9-methyl-10-oxo-3,4,7,8,9,10-hexahydropyrido[4',3':3,4]pyrazolo[1,5-a]pyrazine-2(1H)-carboxylate. To a solution of 5-(tert-butoxycarbonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-3-carboxylic acid[1] (200 mg, 0.75 mmol) and HATU (341.4 mg, 0.90 mmol) in DMF (2.4 mL) was added N-methyloxetan-3-amine (80 µL, 0.979 g/mL, 0.90 mmol) followed by Et_3N (0.26 mL, 0.728 g/mL, 1.9 mmol). The mixture was stirred overnight then DBU (0.8 mL, 1.019 g/mL, 5.4 mmol) was added and heated to 70 °C. Upon full conversion to the cyclized product, the mixture was concentrated in vacuo then purified by column chromatography (0-10% MeOH/DCM) to afford the product as a pale yellow solid (236 mg, 94% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 4.63 (m, 2H), 4.49 (dd, *J* = 13.4, 1.6 Hz, 1H), 4.39 (dd, *J* = 13.3, 5.0 Hz, 1H), 3.84 (m, 1H), 3.79 – 3.61 (m, 3H), 3.46 (dd, *J* = 11.2, 8.0 Hz, 1H), 3.16 (s, 3H),

2.72 (t, *J* = 5.9 Hz, 2H), 1.48 (s, 9H). 13C NMR peaks not assigned due to ambiguous spectra. . HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{16}H_{24}N_4O_4H^+$ 337.1876; found 337.1880.



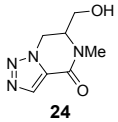
22

9-bromo-3-(hydroxymethyl)-2-methyl-3,4-dihydropyrazino[1,2-b]indazol-1(2H)-one. To a solution of 5-bromo-1H-indazole-3-carboxylic acid (159 mg, 0.66 mmol) and HATU (301 mg, 0.79 mmol) in DMF (2.3 mL) was added Et_3N (0.18 mL, 0.728 g/mL, 1.3 mmol) followed by N-methyloxetan-3-amine (70 µL, 0.979 g/mL, 0.79 mmol). The mixture was stirred overnight then DBU (0.30 mL, 1.019 g/mL, 2.0 mmol) was added and the mixture heated at 70 °C for 4 h. The mixture was concentrated in vacuo and dissolved in EtOAc. Water was added and the organics were extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (0-10% MeOH/DCM) afforded the title compound as an off-white solid (166 mg, 81% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 (d, *J* = 1.7 Hz, 1H), 7.61 (d, *J* = 9.1 Hz, 1H), 7.42 (dd, *J* = 9.1, 1.7 Hz, 1H), 4.91 (dd, *J* = 14.0, 1.3 Hz, 1H), 4.75 (dd, *J* = 14.0, 5.0 Hz, 1H), 3.96 – 3.80 (m, 2H), 3.65 – 3.54 (m, 1H), 3.27 (s, 3H), 2.06 (t, *J* = 4.7 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.5, 146.9, 130.5, 124.5, 123.1, 122.5, 119.3, 118.6, 60.1, 58.8, 47.9, 33.4. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{12}H_{12}BrN_3O_2H^+$ 310.0191; found 310.0197.



23

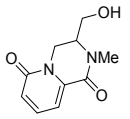
7-chloro-3-(hydroxymethyl)-2-methyl-3,4-dihydropyrazino[1,2-b]indazol-1(2H)-one. To a solution of 7-chloro-1H-indazole-3-carboxylic acid (160 mg, 0.8 mmol) and HATU (371 mg, 0.98 mmol) in DMF (2.7 mL) was added Et_3N (0.23 mL, 0.728 g/mL, 1.63 mmol) followed by N-methyloxetan-3-amine (87 µL, 0.979 g/mL, 0.98 mmol). The mixture was stirred at room temperature overnight then DBU (0.45 mL, 1.019 g/mL, 3.0 mmol) was added. The reaction was heated to 70 °C and stirred 5 h then concentrated. The crude material was dissolved in water and EtOAc. The organics were extracted with EtOAc (3x), washed with brine, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (60-80% EtOAc/heptane) provided the title compound as an off-white solid (163 mg, 76% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 7.3 Hz, 1H), 7.22 – 7.16 (m, 1H), 5.01 (dd, *J* = 14.1, 1.3 Hz, 1H), 4.78 (dd, *J* = 14.1, 5.1 Hz, 1H), 3.98 – 3.79 (m, 2H), 3.69 – 3.54 (m, 1H), 3.28 (s, 3H), 2.03 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.2, 145.1, 126.5, 126.0, 125.0, 122.5, 122.3, 120.2, 59.9, 58.5, 48.5, 33.0. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{12}H_{12}ClN_3O_2H^+$ 266.0516; found 266.0703.



24

6-(hydroxymethyl)-5-methyl-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-4(5H)-one. To a mixture of 1H-1,2,3-triazole-4-carboxylic acid (130 mg, 1.2 mmol) and HATU (525 mg, 1.4 mmol) in DMF (3.7 mL) was added Et_3N (0.4 mL, 0.728 g/mL, 2.9 mmol) followed by N-methyloxetan-3-amine (123 µL, 0.979 g/mL, 1.4 mmol). The mixture was stirred at room temperature overnight then DBU (0.52 mL, 1.019 g/mL, 3.5 mmol) was added and heated at 70 °C for 5 h. The mixture was then concentrated and purified by column chromatography (0-20% MeOH/DCM) to afford the title compound as a tan solid (154 mg, 74% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.13 (s, 1H), 4.98 (dd, *J* = 13.8, 1.3 Hz, 1H), 4.72 (dd, *J* = 13.8, 5.5 Hz, 1H), 4.08 – 3.97 (m, 1H), 3.70 (dd, *J* = 11.6, 4.5 Hz, 1H), 3.52 (dd, *J* = 11.5, 6.9 Hz, 1H), 3.22 (s, 3H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 156.6,

133.1, 129.3, 59.8, 59.2, 45.1, 32.3. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_7H_{10}N_4O_2H^+$ 183.0882; found 183.0885.



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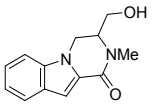
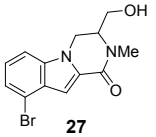
3-(hydroxymethyl)-2-methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione. To a mixture of 6-hydroxypicolinic acid (161 mg, 1.2 mmol) and HATU (528 mg, 1.4 mmol) in DMF (3.9 mL) was added Et_3N (0.32 mL, 0.728 g/mL, 2.3 mmol) followed by N-methyloxetan-3-amine (0.12 mL, 0.979 g/mL, 1.4 mmol). The mixture was stirred at room temperature overnight then DBU (0.52 mL, 1.019 g/mL, 3.5 mmol) was added. The reaction was heated to 70 °C for 24 h then concentrated. Purification by column chromatography (0-5% MeOH/DCM) afforded the title compound as a yellow solid (185 mg, 77% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 (dd, *J* = 9.2, 6.9 Hz, 1H), 6.90 (dd, *J* = 6.9, 1.2 Hz, 1H), 6.61 (dd, *J* = 9.2, 1.2 Hz, 1H), 5.10 (t, *J* = 5.2 Hz, 1H), 4.68 (dd, *J* = 13.9, 1.2 Hz, 1H), 3.80 – 3.66 (m, 2H), 3.56 – 3.44 (m, 1H), 3.38 – 3.25 (m, 1H), 3.07 (s, 3H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 161.9, 158.4, 139.5, 137.0, 122.7, 108.6, 60.1, 57.1, 40.2, 33.6. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{10}H_{12}N_2O_3H^+$ 209.0926; found 209.0930.



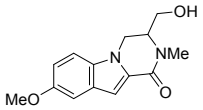
26

3-(hydroxymethyl)-2-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one. To a mixture of 1H-indole-2-carboxylic acid (200 mg, 1.24 mmol) and HATU (566 mg, 1.49 mmol) in DMF (4.0 mL) was added Et_3N (0.0.43 mL, 0.728 g/mL, 3.1 mmol) followed by N-methyloxetan-3-amine (0.13 mL, 0.979 g/mL, 1.49 mmol). The mixture was stirred at room temperature overnight then DBU (0.56 mL, 1.019 g/mL, 3.72 mmol) was added. The reaction was heated to 70 °C for 24 h then concentrated. Purification by column chromatography (0-10% MeOH/DCM) afforded the title compound as a white solid (281 mg, 98% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.65 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.16 – 7.08 (m, 2H), 4.71 – 4.61 (m, 1H), 4.22 (dd, *J* = 12.7, 4.5 Hz, 1H), 3.95 – 3.84 (m, 1H), 3.70 (dd, *J* = 11.0, 5.2 Hz, 1H), 3.43 (dd, *J* = 11.0, 8.6 Hz, 1H), 3.24 (s, 3H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 160.3, 137.1, 128.0, 127.3, 124.3, 121.9, 120.4, 109.6, 105.0, 60.0, 59.5, 39.8, 33.0. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{13}H_{14}N_2O_2H^+$ 231.1134; found 231.1142.



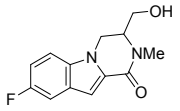
27

9-bromo-3-(hydroxymethyl)-2-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one. To a solution of 4-bromo-1H-indole-2-carboxylic acid (181 mg, 0.75 mmol) and HATU (344 mg, 0.91 mmol) in DMF (2.5 mL) was added Et_3N (0.21 mL, 0.728 g/mL, 1.51 mmol) followed by N-methyloxetan-3-amine (81 µL, 0.979 g/mL, 0.91 mmol). The mixture was stirred at room temperature overnight then DBU (0.338 mL, 1.019 g/mL, 2.262 mmol) was added. The reaction was heated to 70 °C for 5 h then concentrated and purified by column chromatography (0-10% MeOH/DCM) to provide the title compound as a white solid (213 mg, 91% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.50 (d, *J* = 8.3 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 7.9 Hz, 1H), 7.15 (s, 1H), 4.69 (dd, *J* = 12.8, 1.5 Hz, 1H), 4.30 (dd, *J* = 12.8, 4.7 Hz, 1H), 3.99 – 3.89 (m, 1H), 3.73 (dd, *J* = 11.2, 5.2 Hz, 1H), 3.45 (dd, *J* = 11.1, 8.4 Hz, 1H), 3.27 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.3, 137.0, 130.3, 127.6, 125.3, 123.5, 115.2, 111.0, 103.5, 59.7, 59.3, 41.0, 33.8. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{13}H_{13}BrN_2O_2H^+$ 309.0239; found 309.0245.



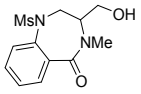
28

3-(hydroxymethyl)-8-methoxy-2-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one. To a mixture of 5-methoxyindole-2-carboxylic acid (182 mg, 0.95 mmol) and HATU (434 mg, 1.14 mmol) in DMF (3.2 mL) was added Et_3N (0.27 mL, 0.728 g/mL, 1.9 mmol) followed by N-methyloxetan-3-amine (0.10 mL, 0.979 g/mL, 1.14 mmol). The mixture was stirred at room temperature overnight then DBU (0.43 mL, 1.019 g/mL, 2.86 mmol) was added. The reaction was heated to 70 °C for 24 h then concentrated and purified by column chromatography (0-8% MeOH/DCM) to afford the title compound as a white solid (227 mg, 92% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.37 (dd, *J* = 9.0 Hz, 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 7.08 (s, 1H), 7.00 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.67 – 4.59 (m, 1H), 4.26 – 4.16 (m, 1H), 3.94 – 3.86 (m, 1H), 3.84 (s, 3H), 3.72 (dd, *J* = 11.0, 5.3 Hz, 1H), 3.45 (dd, *J* = 11.0, 8.6 Hz, 1H), 3.25 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.3, 154.1, 131.7, 129.3, 127.1, 115.0, 111.5, 103.5, 102.4, 59.1, 59.0, 55.3, 40.1, 33.3. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{14}H_{16}N_2O_3H^+$ 261.1239; found 261.1247.



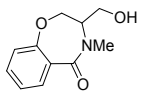
29

8-fluoro-3-(hydroxymethyl)-2-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one. To a mixture of 5-fluoroindole-2-carboxylic acid (180 mg, 1.0 mmol) and HATU (458 mg, 1.2 mmol) in DMF (3.4 mL) was added Et_3N (0.28 mL, 0.728 g/mL, 2.0 mmol) followed by N-methyloxetan-3-amine (0.11 mL, 0.979 g/mL, 1.2 mmol). The mixture was stirred at room temperature overnight then DBU (0.45 mL, 1.019 g/mL, 3.0 mmol) was added. The reaction was heated to 70 °C for 5 h then concentrated and purified by column chromatography (0-10% MeOH/DCM) to afford the title compound as a white solid (246 mg, 98%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.44 (dd, *J* = 9.0, 4.3 Hz, 1H), 7.33 (dd, *J* = 9.5, 2.5 Hz, 1H), 7.15 – 7.07 (m, 2H), 4.64 (dd, *J* = 12.8, 1.5 Hz, 1H), 4.22 (dd, *J* = 12.8, 4.6 Hz, 1H), 3.94 – 3.85 (m, 1H), 3.69 (dd, *J* = 11.1, 5.2 Hz, 1H), 3.42 (dd, *J* = 11.1, 8.5 Hz, 1H), 3.23 (s, 3H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 159.9, 159.4, 157.1, 133.7, 129.7, 127.5, 127.4, 113.1, 112.9, 111.0, 110.9, 106.1, 105.9, 104.8, 104.7, 59.9, 59.5, 40.0, 33.0. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{13}H_{13}FN_2O_2H^+$ 249.1039; found 249.1047.



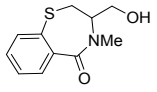
30

3-(hydroxymethyl)-4-methyl-1-(methylsulfonyl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one. To a mixture of 2-(methylsulfonamido)benzoic acid (155 mg, 0.72 mmol) and HATU (329 mg, 0.86 mmol) in DMF (2.4 mL) was added Et_3N (0.2 mL, 0.728 g/mL, 1.44 mmol) followed by N-methyloxetan-3-amine (77 µL, 0.979 g/mL, 0.86 mmol). The mixture was stirred at room temperature overnight then DBU (0.323 mL, 1.019 g/mL, 2.16 mmol) was added. The reaction was heated to 70 °C for 24 h then concentrated and purified by column chromatography (0-5% MeOH/DCM) to afford the title compound as a colorless oil (153 mg, 75% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75 – 7.68 (m, 1H), 7.59 – 7.46 (m, 3H), 4.23 (dd, *J* = 13.1, 11.4 Hz, 1H), 3.99 – 3.73 (m, 3H), 3.69 (dd, *J* = 13.1, 3.9 Hz, 1H), 3.25 (s, 3H), 2.78 (s, 3H), 1.66 (t, *J* = 5.1 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.5, 135.4, 133.8, 132.3, 131.2, 129.8, 129.6, 59.8, 58.1, 52.8, 38.9, 28.7. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{12}H_{16}N_2O_4SH^+$ 285.0909; found 285.0916.



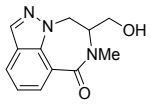
31

3-(hydroxymethyl)-4-methyl-3,4-dihydrobenzo[f][1,4]oxazepin-5(2H)-one. A mixture of salicylic acid (228 mg, 1.65 mmol) and CDI (321 mg, 1.98 mmol) in DMF (5.3 mL) was stirred at 70 °C for 2 h then N-methyloxetan-3-amine (176 µL, 0.979 g/mL, 1.98 mmol) was added and the mixture stirred overnight. DBU (0.74 mL, 1.019 g/mL, 4.952 mmol) was then added and the reaction was stirred at 70 °C for 48 h. The mixture was concentrated and purified by column chromatography (0-10% MeOH/DCM) to afford the title compound as a colorless oil (264 mg, yield 77% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.29 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 8.2, 1H), 4.72 (dd, *J* = 12.6, 5.1 Hz, 1H), 4.20 (d, *J* = 12.6 Hz, 1H), 3.88 – 3.67 (m, 3H), 3.26 (s, 3H), 1.95 (bs, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.0, 155.9, 134.0, 132.9, 121.9, 120.9, 119.6, 69.8, 62.0, 60.2, 37.8. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{11}H_{13}NO_3H^+$ 208.0974; found 208.0978.



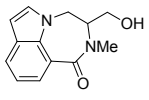
32

3-(hydroxymethyl)-4-methyl-3,4-dihydrobenzo[f][1,4]thiazepin-5(2H)-one. To a mixture of 2-mercaptobenzoic acid (200 mg, 1.30 mmol) and HATU (592 mg, 1.56 mmol) in DMF (4.2 mL) was added Et_3N (0.45 mL, 0.728 g/mL, 3.24 mmol) followed by N-methyloxetan-3-amine (139 µL, 0.979 g/mL, 1.56 mmol). The mixture was stirred at room temperature overnight then DBU (0.58 mL, 1.019 g/mL, 3.89 mmol) was added. The reaction was heated to 70 °C for 24 h then concentrated and purified by column chromatography (0-10% MeOH/DCM) to afford the title compound as an off-white solid (204 mg, 70% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 (dd, 7.4, 1.4 Hz,, 1H), 7.50 – 7.35 (m, 3H), 4.01 – 3.89 (m, 1H), 3.85 – 3.69 (m, 2H), 3.22 – 3.13 (m, 4H), 3.20-2.90 (m, 1H), 1.82 (s, 1H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 171.7, 141.1, 133.6, 131.1, 129.1, 128.9, 128.7, 60.2, 58.8, 34.6, 26.1. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{11}H_{13}NO_2SH^+$ 224.0745; found 224.0751.



33

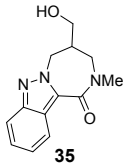
8-(hydroxymethyl)-7-methyl-8,9-dihydro-[1,4]diazepino[6,7,1-hi]indazol-6(7H)-one. To a solution of 1H-indazole-7-carboxylic acid (173 mg, 1.1 mmol) and HATU (487 mg, 1.3 mmol) in DMF (3.6 mL) was added Et_3N (0.30 mL, 0.728 g/mL, 2.1 mmol) followed by N-methyloxetan-3-amine (0.13 mL, 0.979 g/mL, 1.5 mmol). The mixture was stirred overnight then Cs_2CO_3 (1043 mg, 3.2 mmol) was added to and the mixture heated at 70 °C for 5 h. The mixture was diluted with EtOAc and water. The organics were extracted with EtOAc (5x), dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (60-80% EtOAc/heptane) afforded the title compound as a white solid (223 mg, 90% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.33 (dd, *J* = 7.5, 1.2 Hz, 1H), 8.05 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.33 – 7.26 (m, 1H), 5.06 (dd, *J* = 14.1, 4.7 Hz, 1H), 4.66 (dd, *J* = 14.1, 1.8 Hz, 1H), 4.17 – 4.06 (m, 1H), 3.66 – 3.53 (m, 1H), 3.50-3.35 (m, 4H), 1.92 (s, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.8, 135.3, 134.0, 131.9, 125.4, 124.9, 121.2, 115.9, 61.6, 60.8, 51.6, 39.9. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{12}H_{13}N_3O_2H^+$ 232.1086; found 232.1090.



34

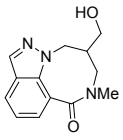
3-(hydroxymethyl)-2-methyl-3,4-dihydro-[1,4]diazepino[6,7,1-hi]indol-1(2H)-one. To a mixture of 1H-indole-7-carboxylic acid (198 mg, 1.23 mmol) and HATU (561 mg, 1.47 mmol) in DMF (4.1 mL) was added Et_3N (0.34 mL, 0.728 g/mL, 2.5 mmol) followed by N-methyloxetan-3-amine (0.13 mL, 0.979 g/mL, 1.47 mmol). The mixture was stirred at room temperature overnight then Cs_2CO_3 (1201 mg, 3.69 mmol) was added. The reaction was heated to 70 °C for 24 h then filtered over a plug of celite. Purification by column chromatography (0-10% MeOH/DCM) then washing the solid with ether provided the title compound as a white solid (240 mg, 85% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.16 (d, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.06 (d, *J*

= 3.0 Hz, 1H), 6.59 (d, *J* = 3.0 Hz, 1H), 4.64 (dd, *J* = 13.7, 4.9 Hz, 1H), 4.45 (d, *J* = 13.7 Hz, 1H), 4.08 – 3.98 (m, 1H), 3.64 – 3.54 (m, 1H), 3.45 – 3.35 (m, 4H), 1.65 – 1.59 (m, 1H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 167.6, 132.1, 129.9, 129.1, 126.0, 124.8, 118.8, 116.7, 101.6, 62.4, 59.5, 49.0, 38.8. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{13}H_{14}N_2O_2H^+$ 231.1134; found 231.1142.



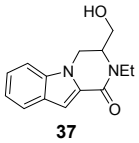
35

4-(hydroxymethyl)-2-methyl-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-b]indazol-1-one. To a solution of indazole-3-carboxylic acid (135 mg, 0.83 mmol) and HATU (380 mg, 1.0 mmol) in DMF (2.9 mL) was added Et_3N (0.23 mL, 0.728 g/mL, 1.67 mmol) followed by N-methyl-1-(oxetan-3-yl)methanamine (126 mg, 1.25 mmol). The mixture was stirred overnight then Cs_2CO_3 (814 mg, 2.5 mmol) was added and the mixture stirred at 70 °C for 24 h. The reaction was then diluted with EtOAc and water and transferred to a separatory funnel. The organics were extracted (3x), dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (70-100% EtOAc/heptane) afforded P1 as a colorless oil (178 mg, 87% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.94 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.7 Hz, 1H), 7.35 (dd, *J* = 8.3, 7.0 Hz, 1H), 7.26 – 7.19 (m, 1H), 4.74 (dd, *J* = 14.0, 6.8 Hz, 1H), 4.60 (dd, *J* = 14.1, 5.0 Hz, 1H), 3.76 – 3.65 (m, 2H), 3.44 (dd, *J* = 15.0, 5.9 Hz, 1H), 3.35 – 3.22 (m, 4H), 2.97 – 2.77 (m, 1H), 2.14 (t, *J* = 4.8 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.0, 147.6, 129.3, 126.8, 124.1, 123.0, 120.5, 117.3, 61.9, 51.6, 49.9, 43.6, 35.7. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{13}H_{15}N_3O_2H^+$ 246.1243; found 246.1253.



36

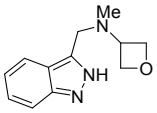
9-(hydroxymethyl)-7-methyl-7,8,9,10-tetrahydro-6H-[1,5]diazocino[3,2,1-hi]indazol-6-one. To a solution of 1H-indazole-7-carboxylic acid (190 mg, 1.17 mmol) and HATU (535 mg, 1.41 mmol) in DMF (3.9 mL) was added Et_3N (0.33 mL, 0.728 g/mL, 2.34 mmol) followed by N-methyl-1-(oxetan-3-yl)methanamine (142 mg, 1.406 mmol). The mixture was stirred overnight then Cs_2CO_3 (1145 mg, 3.52 mmol) was added and the mixture heated to 100 °C for 24 h. The crude mixture was filtered, concentrated and purified by column chromatography (2-8% MeOH/DCM) to afford the title compound as a white solid (209 mg, 72% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.07 (s, 1H), 7.92 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.72 (dd, *J* = 7.2, 1.0 Hz, 1H), 7.30 – 7.21 (m, 1H), 4.72 (d, *J* = 15.0 Hz, 1H), 4.48 (dd, *J* = 15.1, 3.4 Hz, 1H), 3.49 – 3.36 (m, 2H), 3.27 – 3.17 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.2, 137.3, 133.2, 129.8, 124.5, 124.0, 121.2, 118.6, 61.1, 49.8, 47.6, 38.2, 34.2. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{13}H_{15}N_3O_2H^+$ 246.1243; found 246.1249.



37

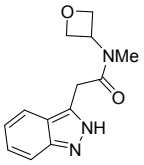
2-ethyl-3-(hydroxymethyl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one. 1H-indole-2-carboxylic acid (173 mg, 1.07 mmol) and HATU (490 mg, 1.29 mmol) in DMF (3.6 mL) was added Et_3N (0.30 mL, 0.728 g/mL, 2.15 mmol) followed by N-ethyloxetan-3-amine (130 mg, 1.289 mmol). The mixture was stirred at room temperature overnight then DBU (0.48 mL, 1.019 g/mL, 3.22 mmol) was added and the mixture heated to 70 °C for 24 h. The reaction mixture was diluted with EtOAc and water. The organics were extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (0-10% MeOH/DCM) afforded the title compound as a white solid (210 mg, 80% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.68 (d, *J* = 8.1 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.17 – 7.11 (m, 2H), 4.75 (d, *J* = 12.7 Hz, 1H), 4.23 – 4.06 (m, 2H), 3.96 (m, 1H), 3.68 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.40 (dd, *J* = 10.9, 9.2 Hz, 1H), 3.27 (m, 1H), 1.32 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz,

Chloroform-*d*) δ 159.0, 136.8, 128.8, 127.5, 124.4, 122.6, 120.6, 109.6, 105.9, 60.6, 56.9, 40.8, 40.6, 13.9. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{14}H_{16}N_2O_2H^+$ 245.1290; found 245.1299.



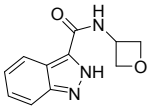
38

N-((2H-indazol-3-yl)methyl)-N-methyloxetan-3-amine. A mixture of 1H-indazole-3-carbaldehyde (215 mg, 1.47 mmol) and N-methyloxetan-3-amine (154 mg, 1.77 mmol) in DCM was stirred for 15 minutes at room temperature then Et_3N (0.61 mL, 0.728 g/mL, 4.41 mmol) and sodium triacetoxylborohydride (935 mg, 4.41 mmol) were added. The mixture was stirred for 3 h then quenched with water. The organics were extracted with DCM, washed with brine, dried over sodium sulfate, filtered and concentrated. The crude material was purified by column chromatography (0-10% MeOH/EtOAc) to provide the title compound as a pale yellow solid (202 mg, 63% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.89 (s, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.56 – 7.32 (m, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 4.73 – 4.55 (m, 4H), 3.81 (s, 2H), 3.75 (p, *J* = 6.6 Hz, 1H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.3, 141.1, 126.9, 122.5, 120.8, 120.7, 109.8, 76.2, 59.2, 51.2, 38.7. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{12}H_{15}N_3OH^+$ 218.1293; found 218.1308.



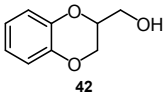
39

2-(2H-indazol-3-yl)-N-methyl-N-(oxetan-3-yl)acetamide. To a mixture of 2-(1H-indazol-3-yl)acetic acid (150 mg, 0.85 mmol) and HATU (356 mg, 0.94 mmol) in DMF (1.0 mL) was added N-methyloxetan-3-amine 0.91 µL, 0.979 g/mL, 1.02 mmol) and Et_3N (0.24 mL, 0.728 g/mL, 1.70 mmol). The mixture was stirred at room temperature overnight then concentrated to an orange oil. Purification of the crude residue by column chromatography (0-10% MeOH/DCM) yielded the title compound as an orange oil (208 mg, 99% yield). Mixture of rotamers. 1H and 13C NMR peaks not assigned due to ambiguous spectra (*vide infra*). HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{13}H_{15}N_3O_2H^+$ 246.1243; found 246.1249.



40

N-(oxetan-3-yl)-2H-indazole-3-carboxamide. To a solution of indazole-3-carboxylic acid (51 mg, 0.32 mmol) and HATU (145 mg, 0.38 mmol) in DMF was added Et_3N (87 µL, 0.728 g/mL, 0.63 mmol) followed by 3-oxetaneamine (26 µL, 1.042 g/mL, 0.38 mmol). The mixture was stirred at room temperature overnight then DBU (0.14 mL, 1.019 g/mL, 0.94 mmol) was added. The reaction was heated to 70 °C for 24 h then concentrated. Trace cyclized product observed. The title compound was purified by column chromatography (0-10% MeOH/DCM) to yield a white solid (51 mg, 74% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.18 (d, *J* = 8.2 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.47 – 7.37 (t, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 5.23 (p, *J* = 7.0 Hz, 1H), 4.95 (t, *J* = 7.0 Hz, 2H), 4.79 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 163.6, 141.5, 137.6, 126.5, 122.1, 121.7, 121.2, 110.1, 77.9, 44.3. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{11}H_{11}N_3O_2H^+$ 218.0930; found 218.0934.



42

(2,3-dihydrobenzo[b][1,4]dioxin-2-yl)methanol. A mixture of catechol (110 mg, 1 mmol), 3-iodooxetane (0.1 mL, 2.09 g/mL, 1.1 mmol) and Cs_2CO_3 (977 mg, 3 mmol) were stirred in DMF (2 mL) at 80 °C for 16 h then concentrated. Purification by column chromatography (5-20%

EtOAc/heptane) afforded the title compound (125 mg, 75% yield). Spectroscopic data matched that previously reported in literature.[2]

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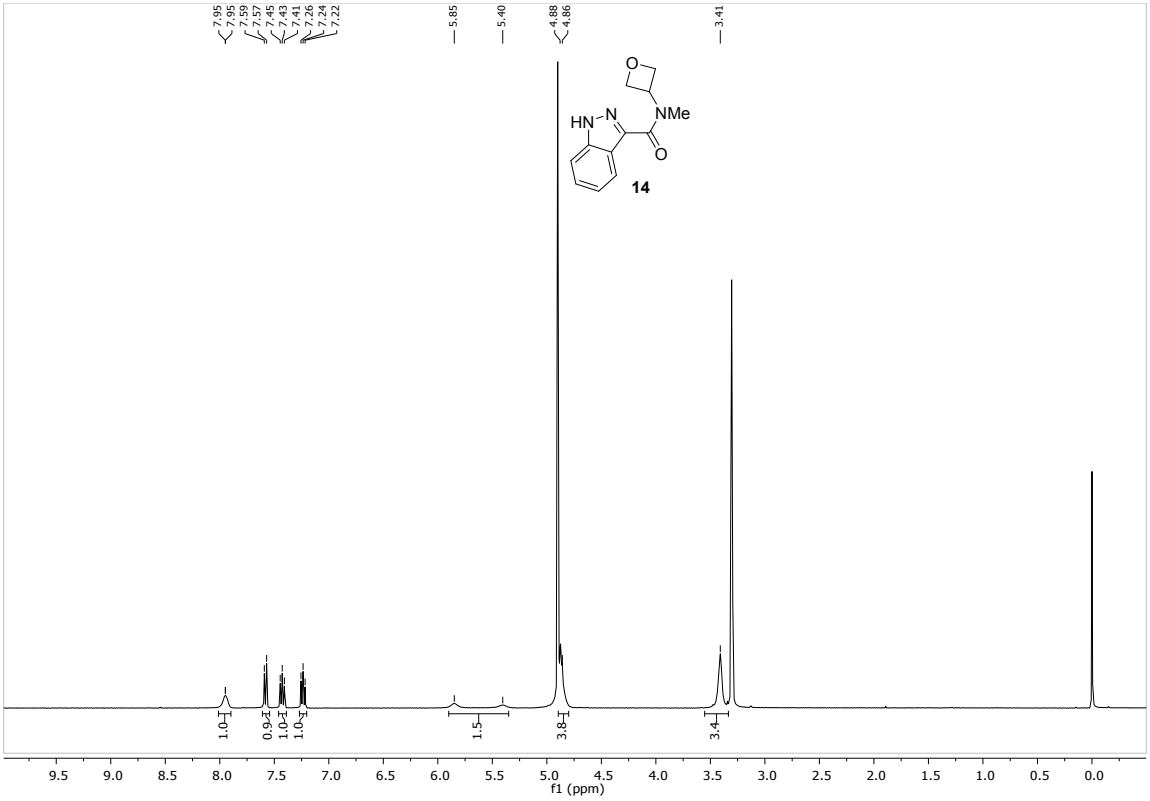
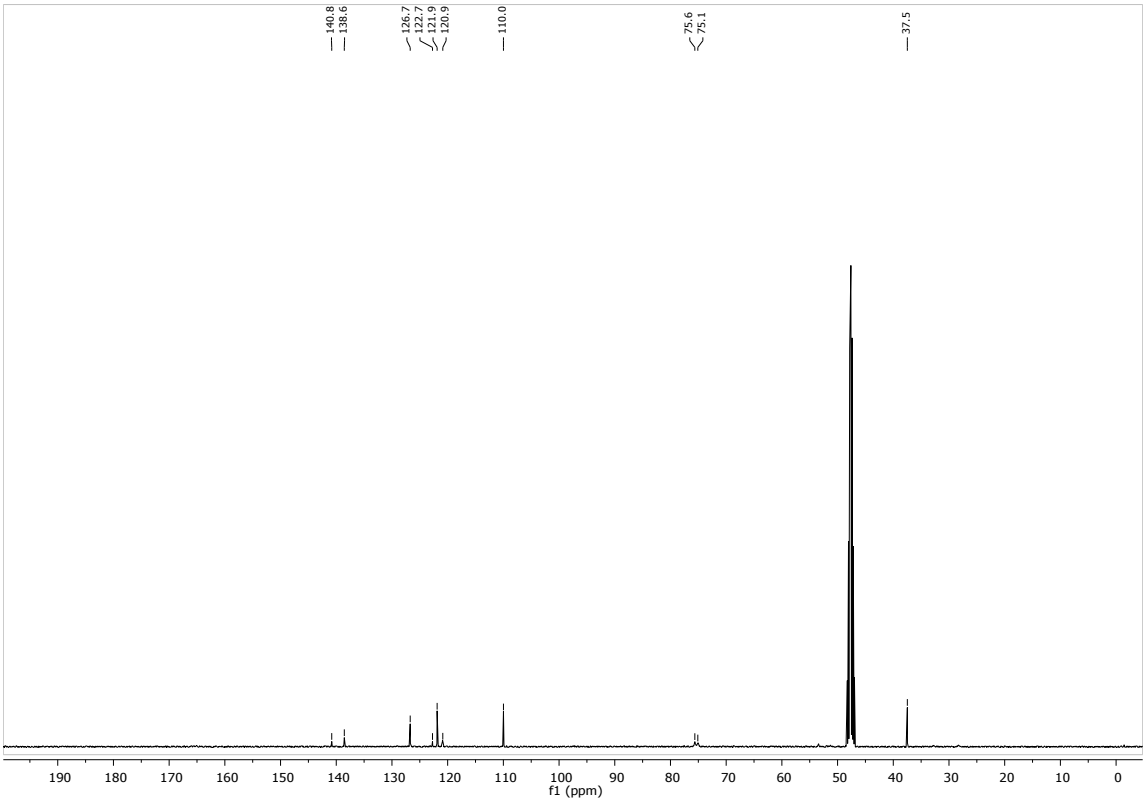
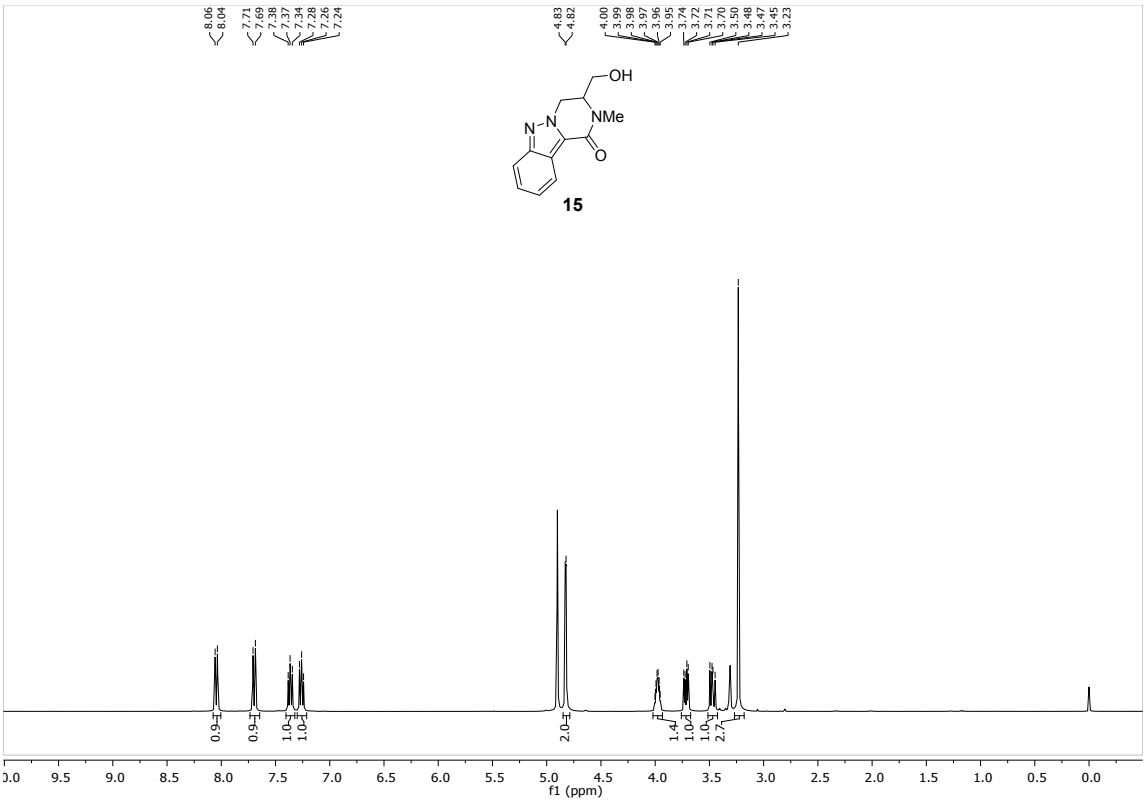
[1] Kuduk, S.; Hartman, G. D. Oxadiazepinone derivatives and their use in the treatment of hepatitis B infections. WO 2018/005881 A1, January 4th, 2018.
[2] Wang, S.; Chen, Y.; Zhao, S.; Xu, X.; Liu, X.; Liu, B.-F.; Zhang, G. *Bioorganic and Medicinal Chemistry Letters,* **2014**, *7*, 1766-1770.

4. NMR Spectra



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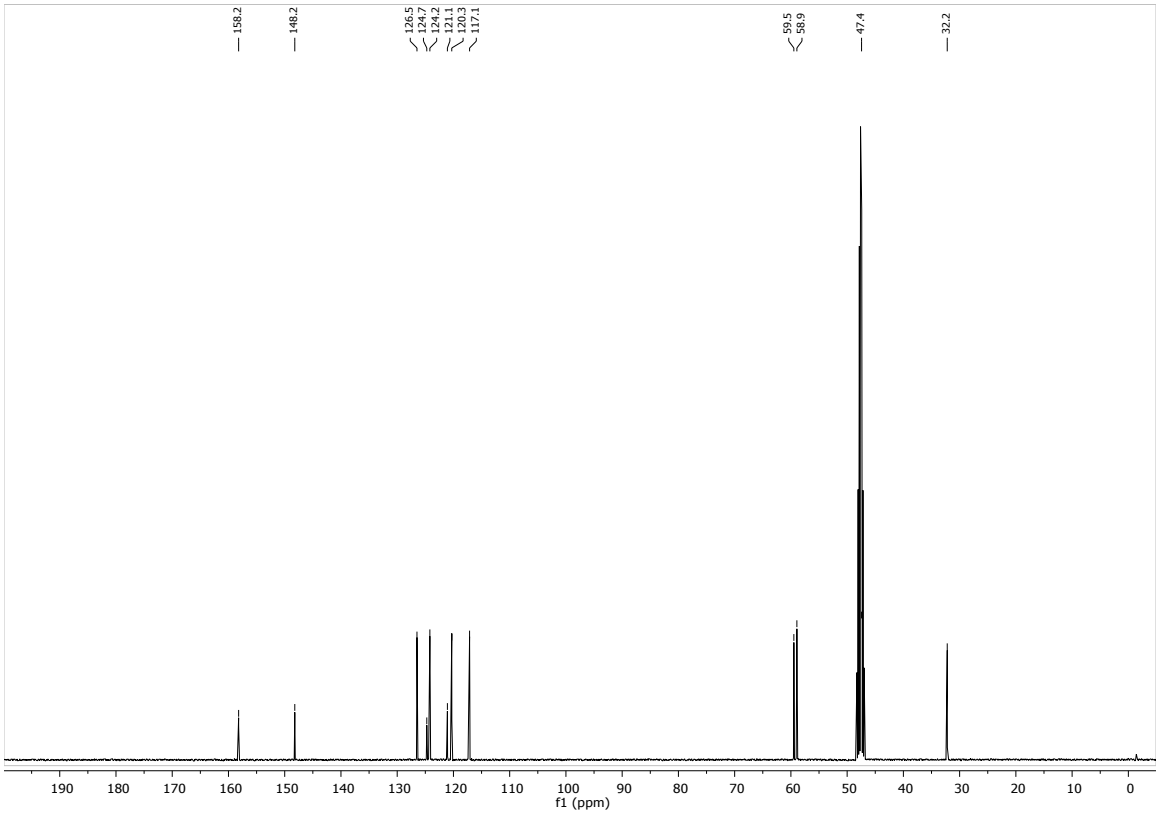
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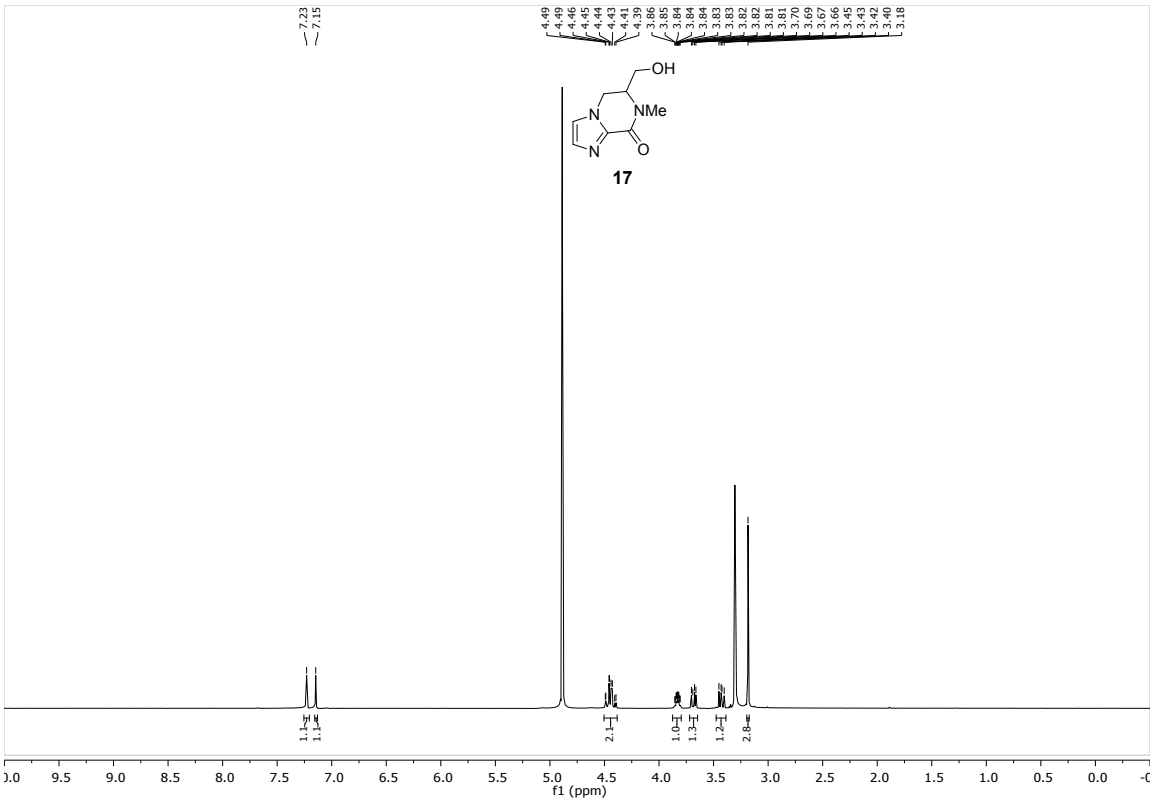
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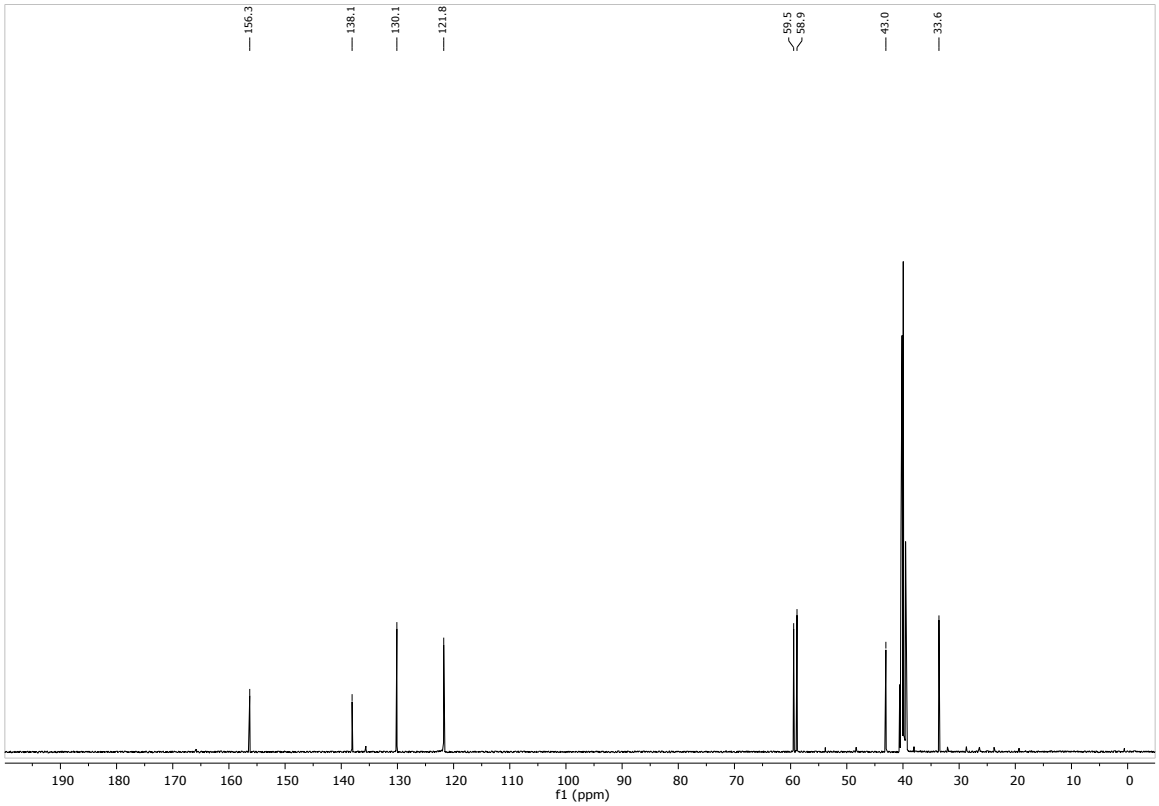
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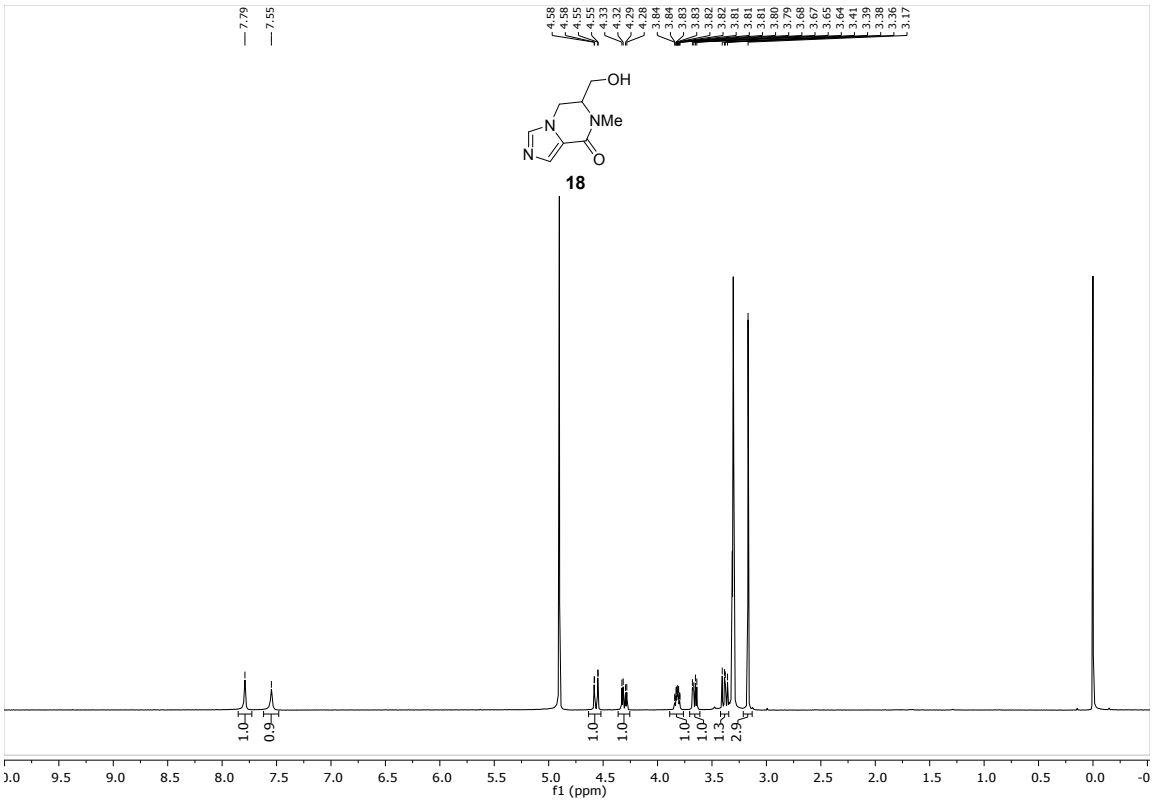
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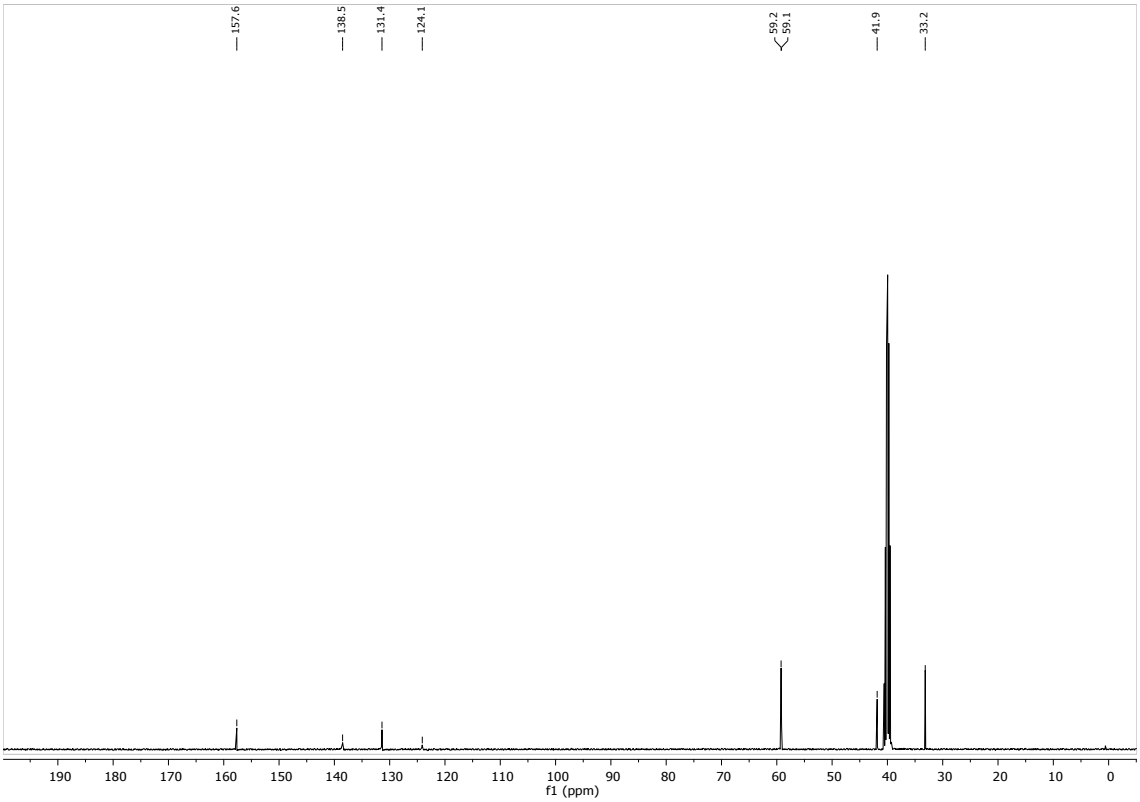
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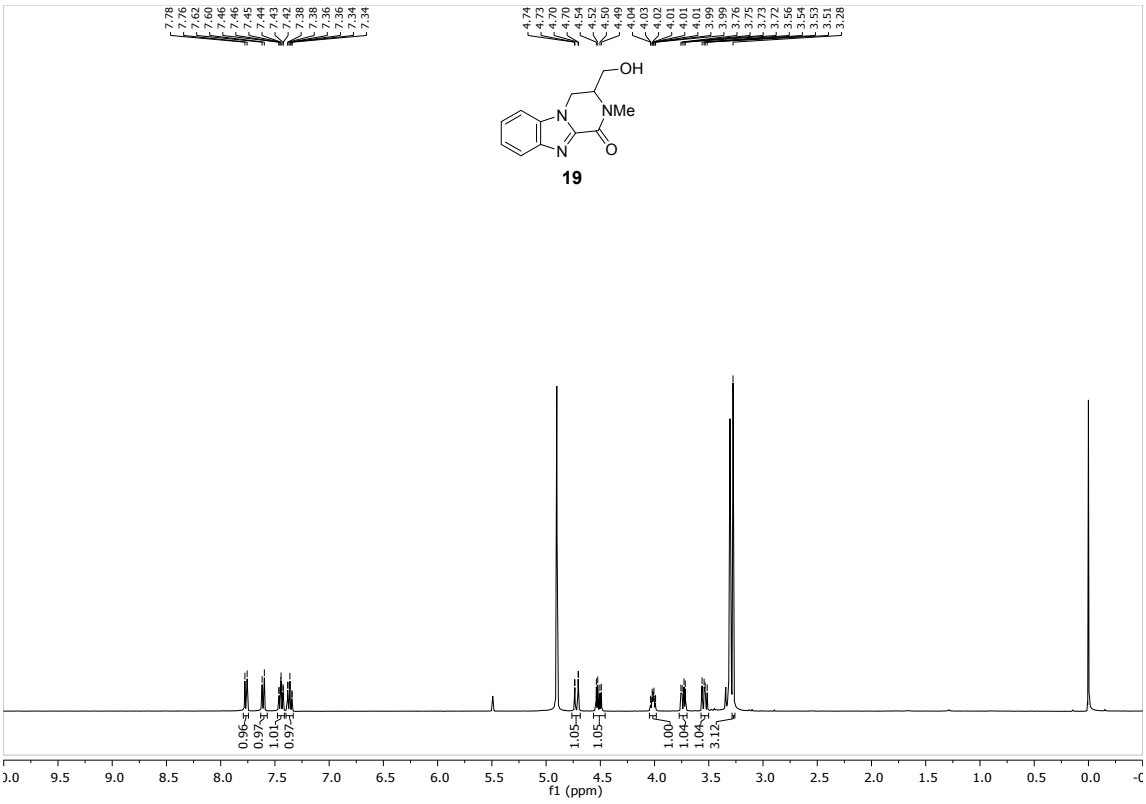
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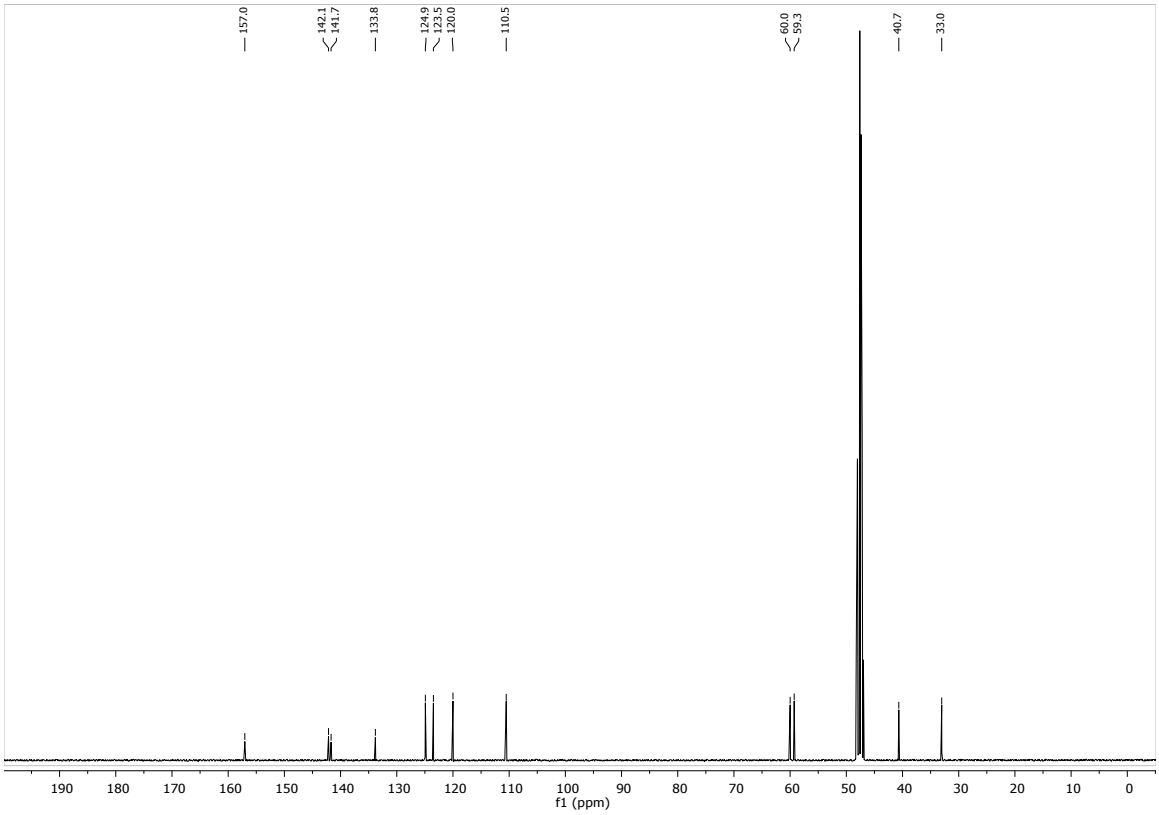
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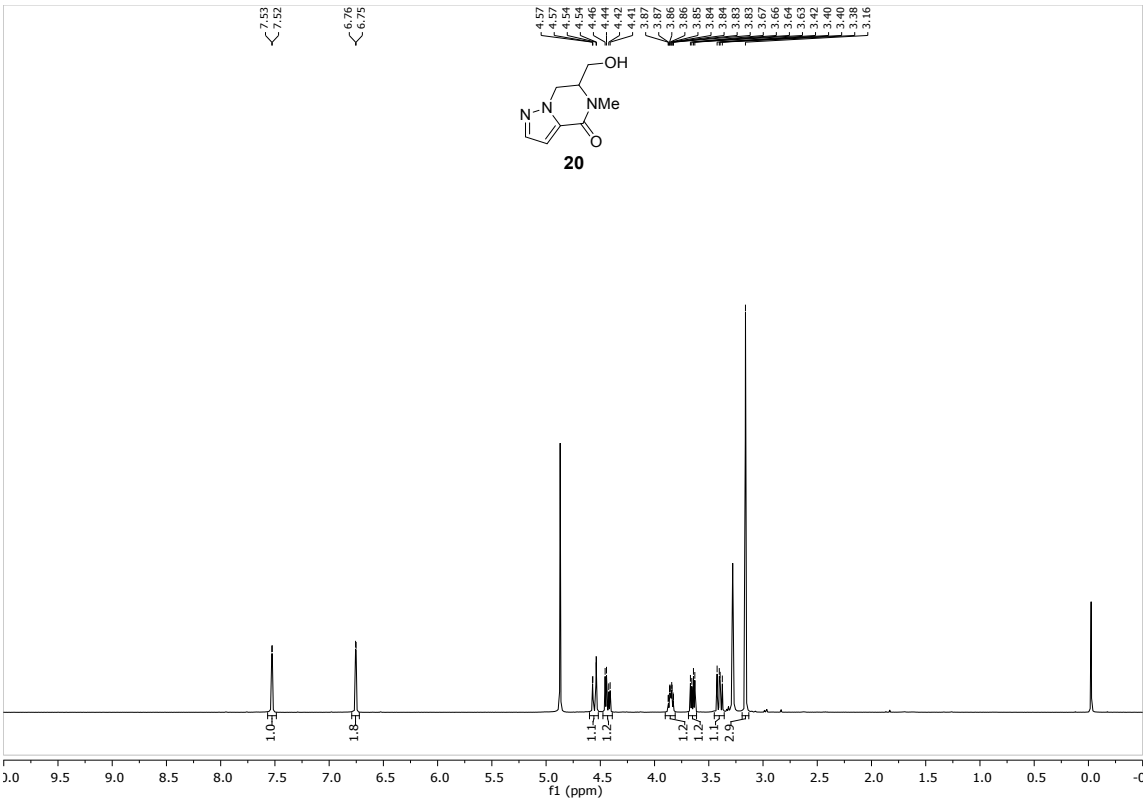
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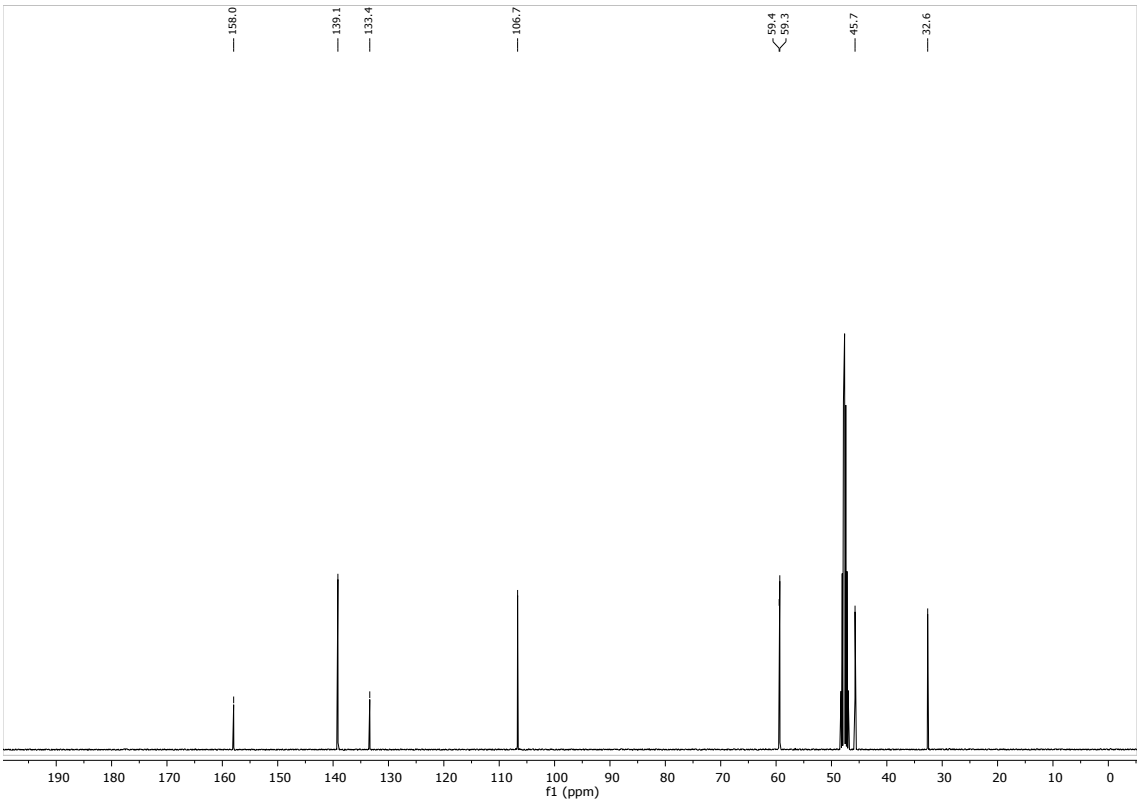
20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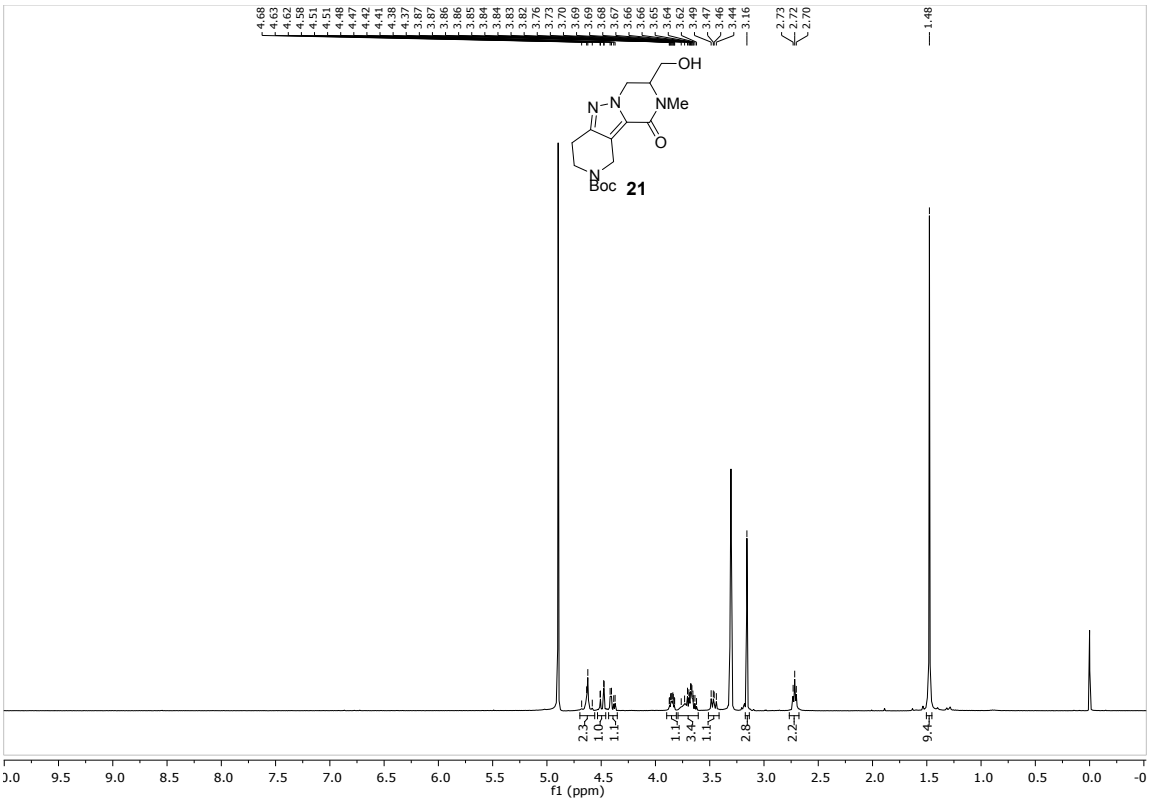
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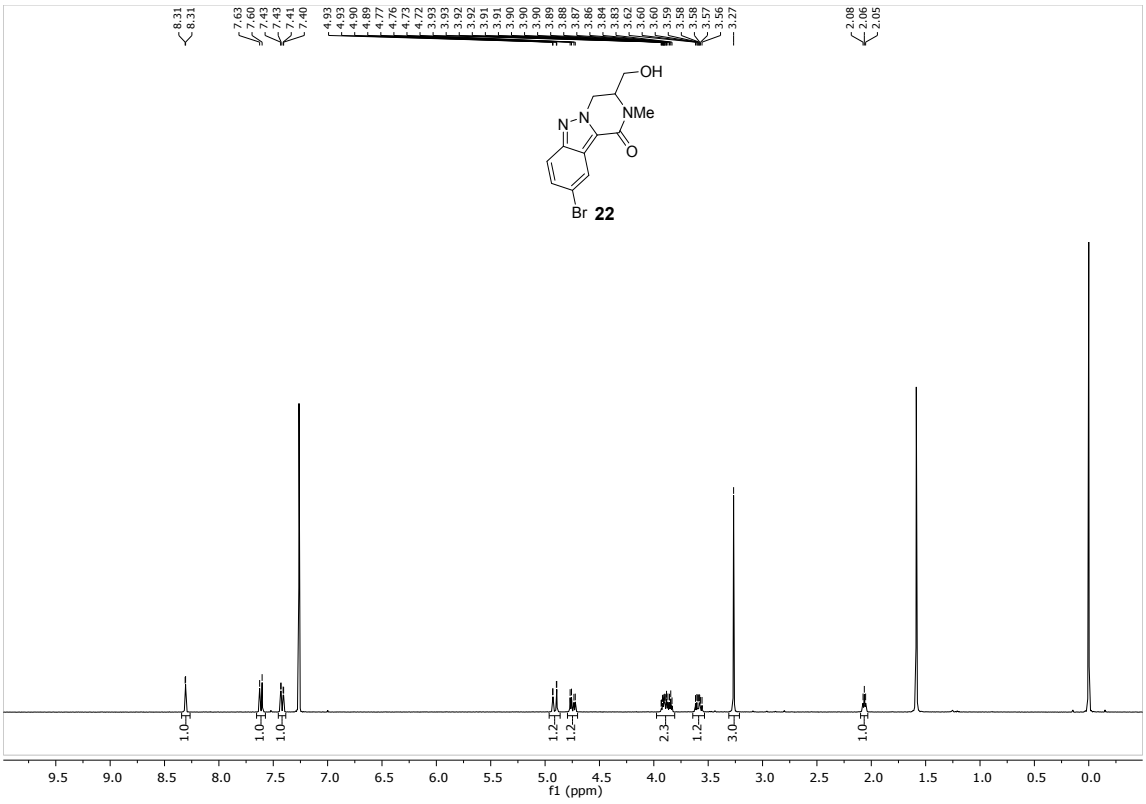
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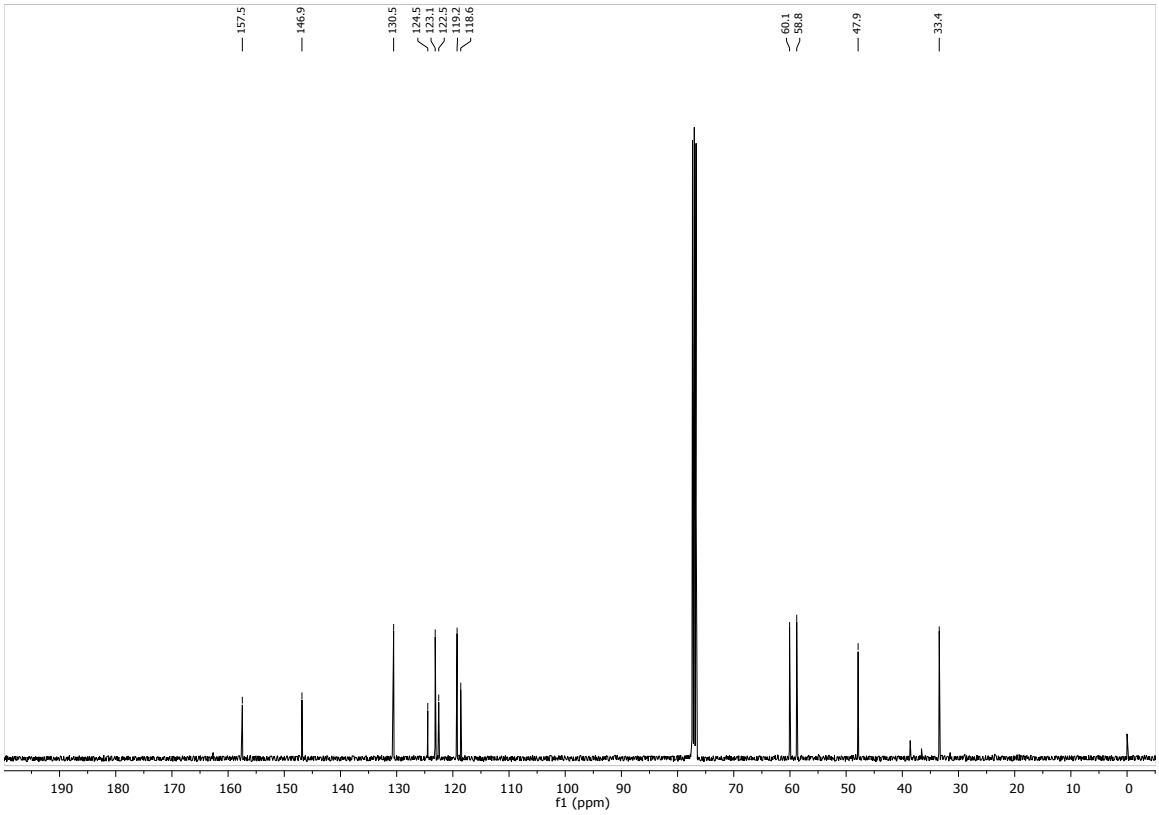
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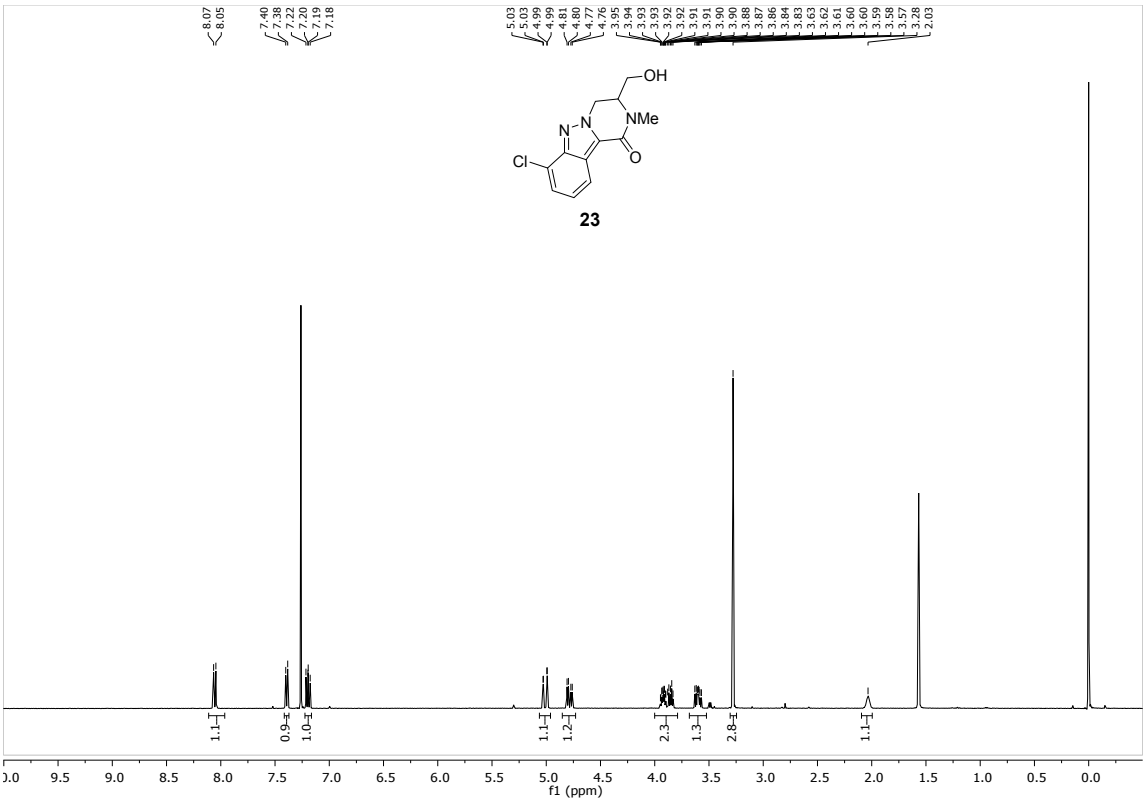
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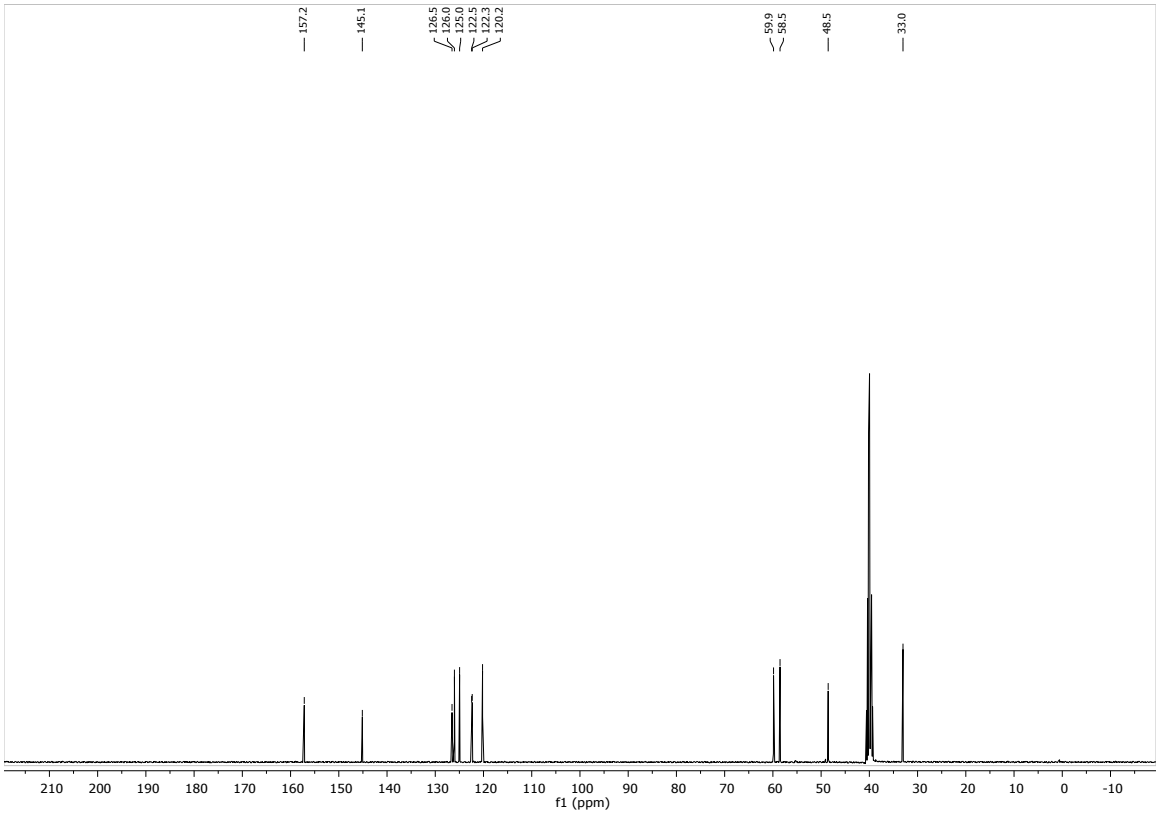
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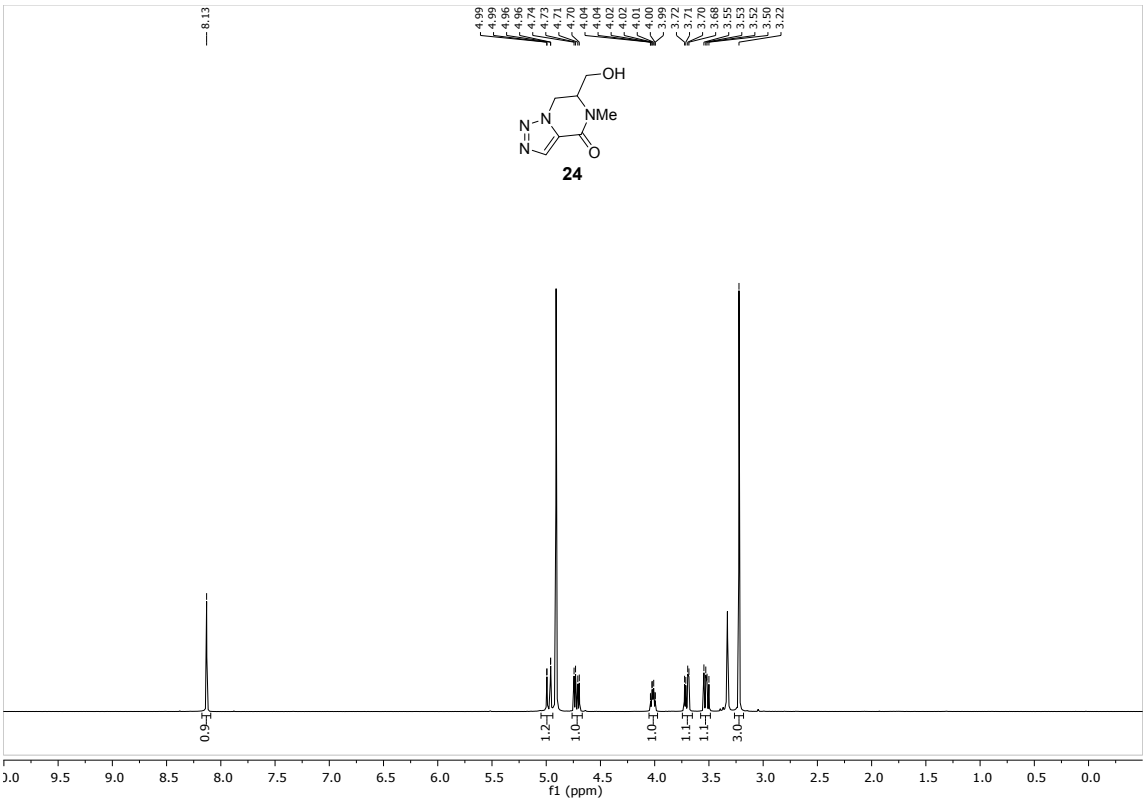
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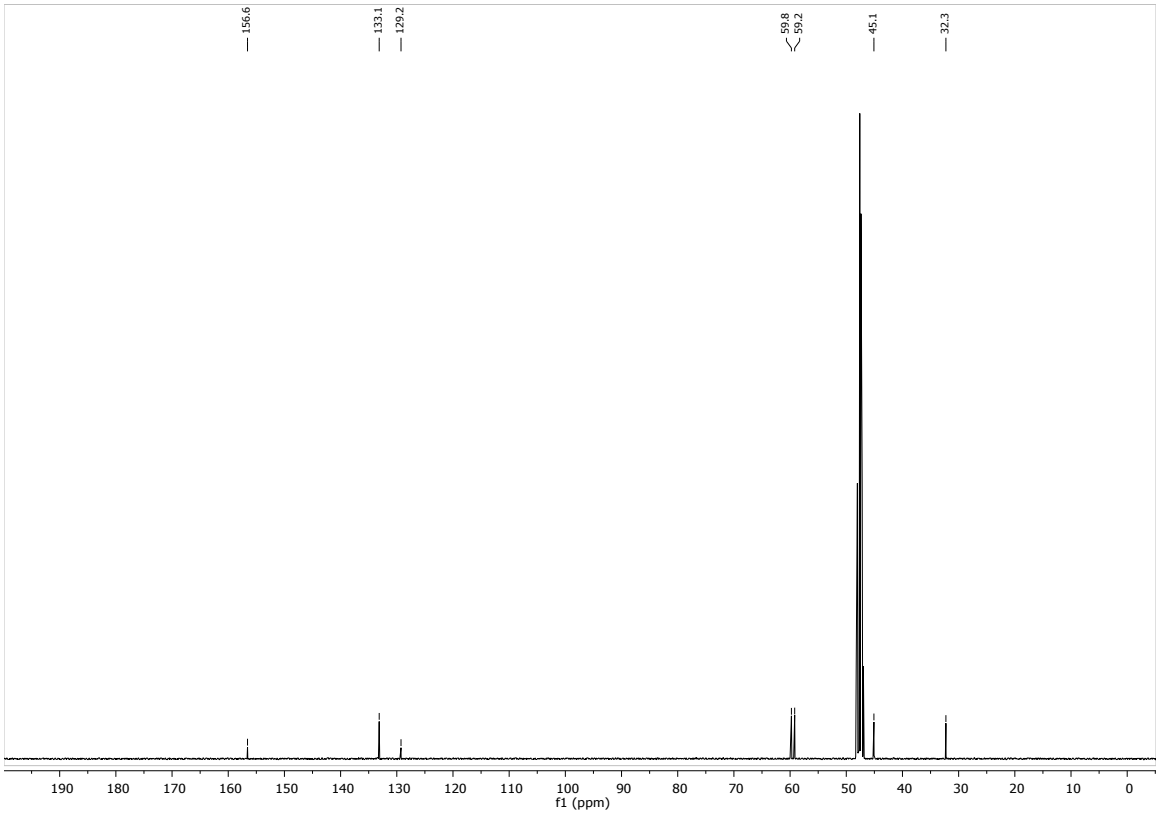
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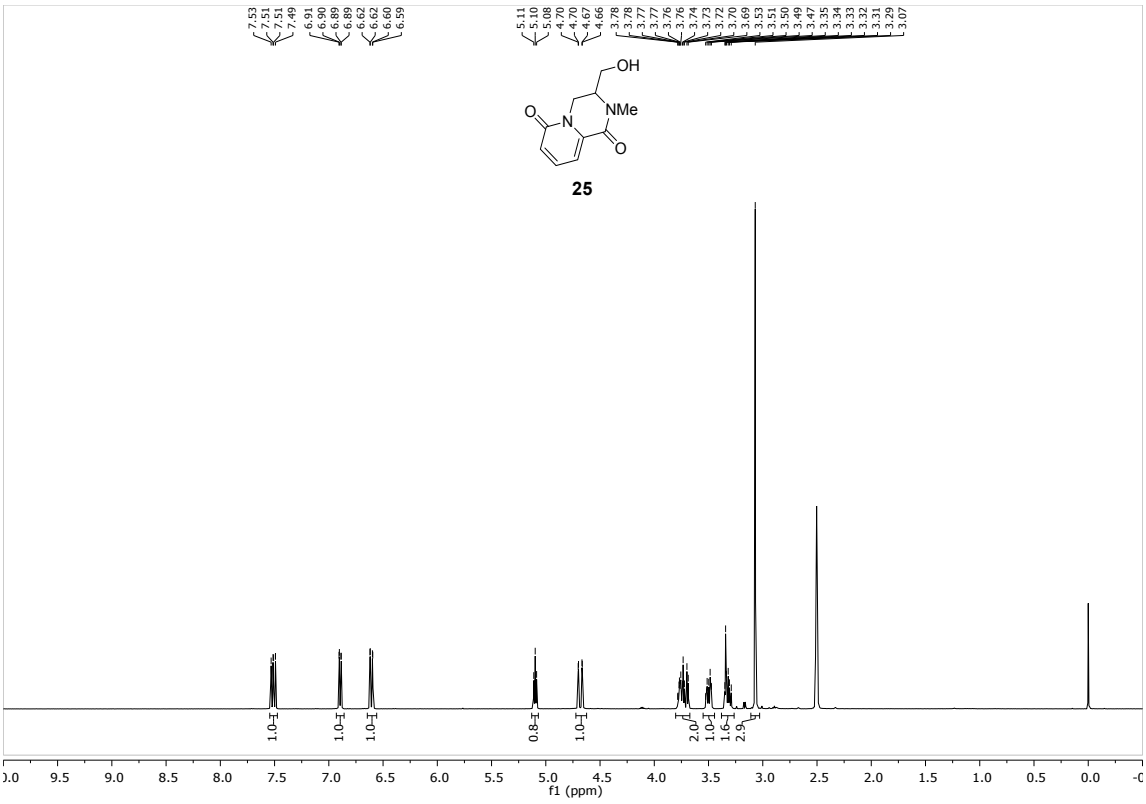
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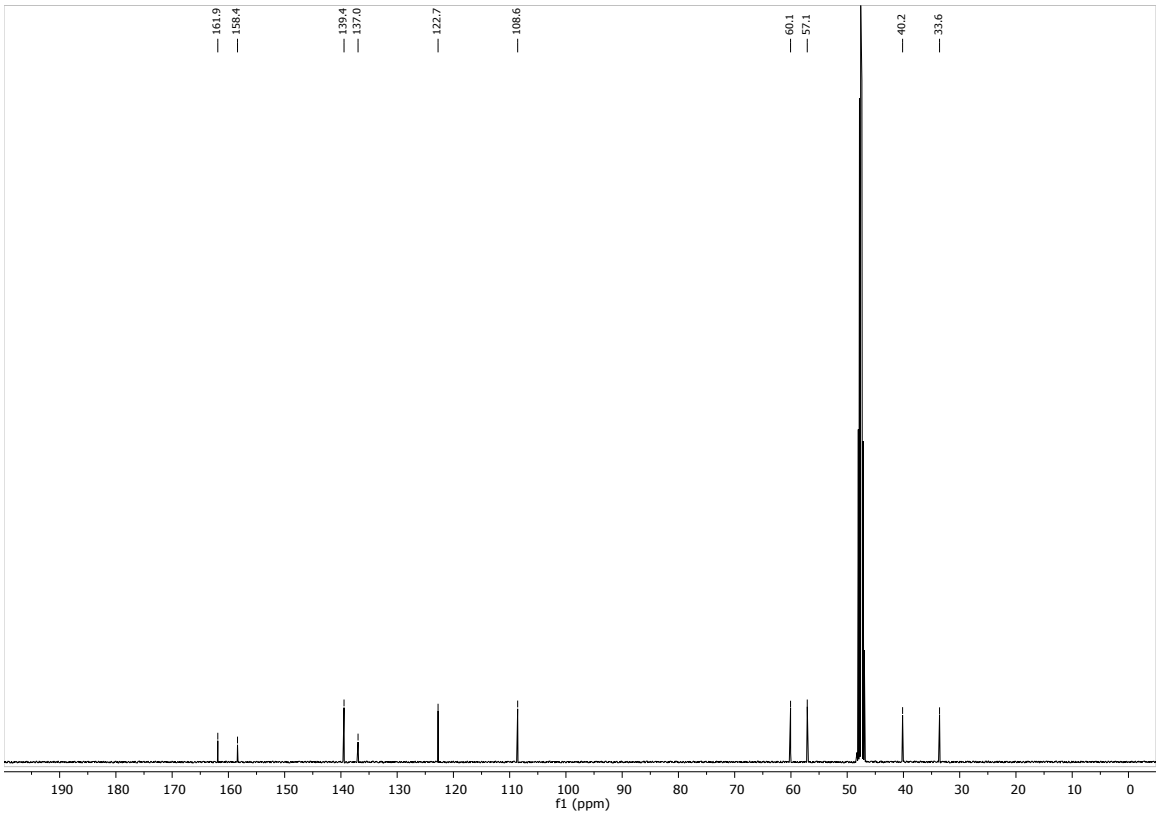
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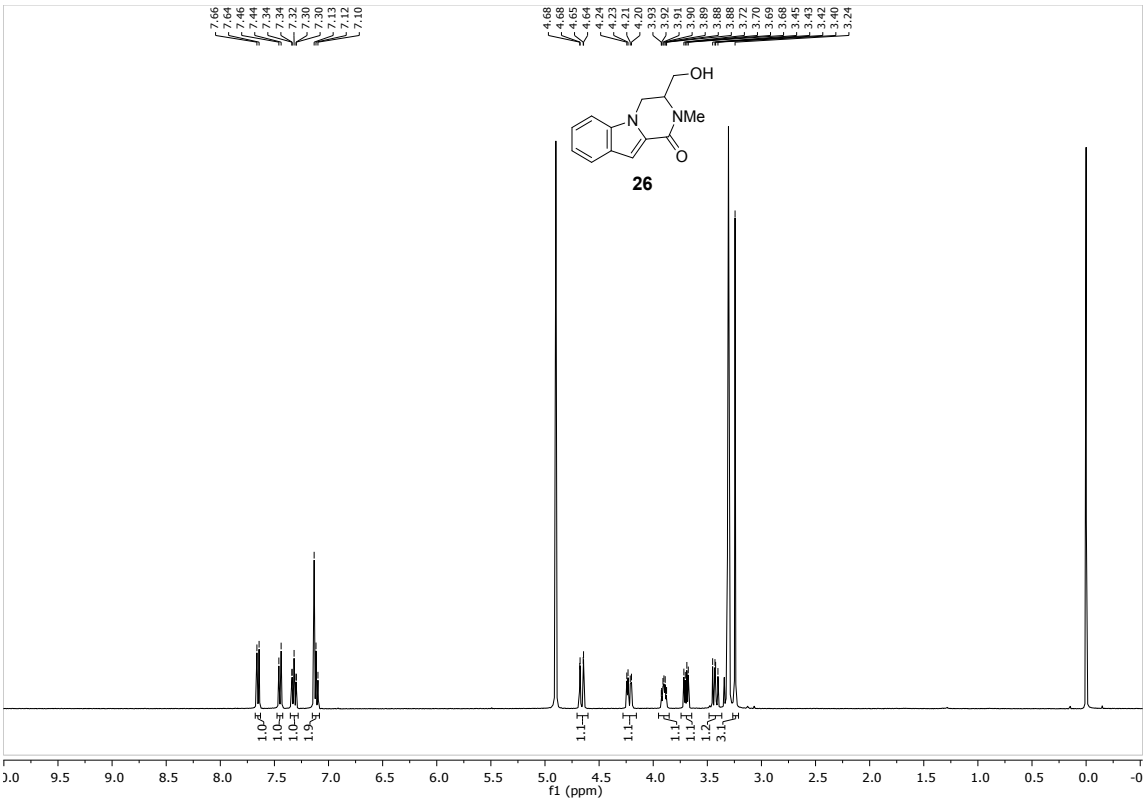
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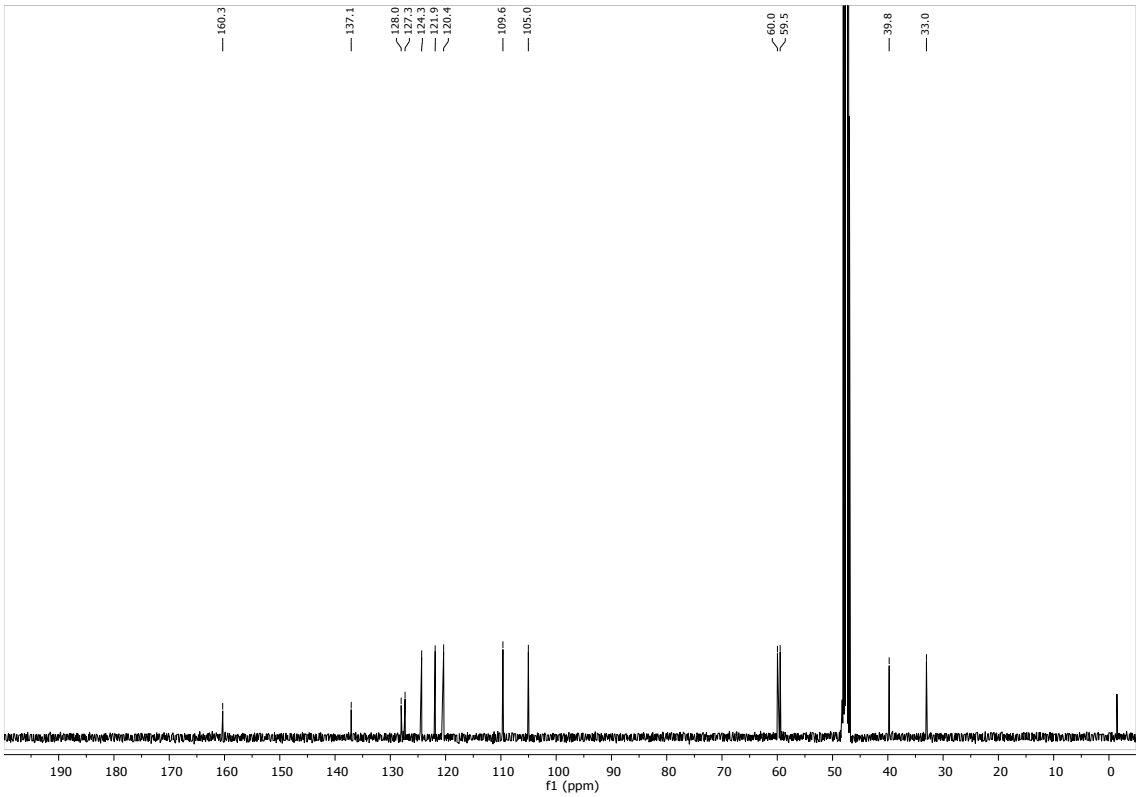
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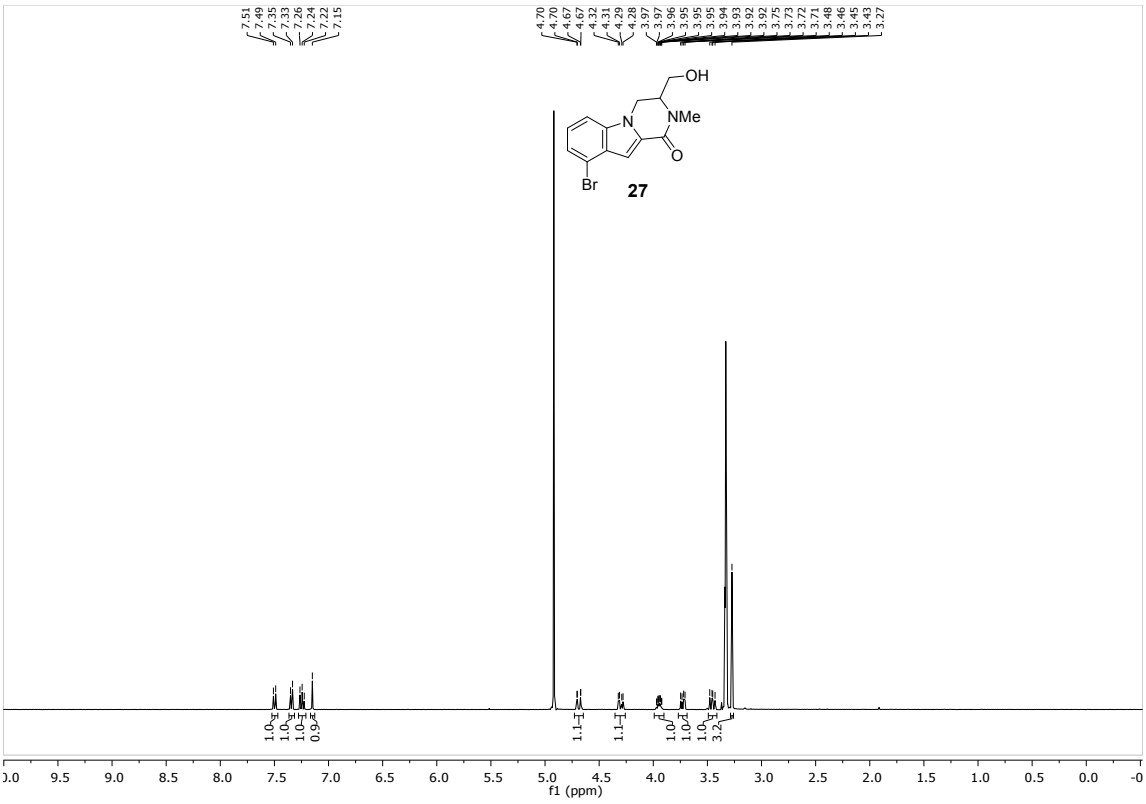
33.0
f1 (ppm)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7.26
7.24
7.22
7.15
4.70
4.70
4.67
4.67
4.32
4.31
4.29
4.28
3.97
3.97
3.96
3.95
3.95
3.95
3.94
3.93
3.92
3.92
3.75
3.73
3.72
3.71
3.48
3.46
3.45
3.43
3.27
OH
N
NMe
O
Br
27
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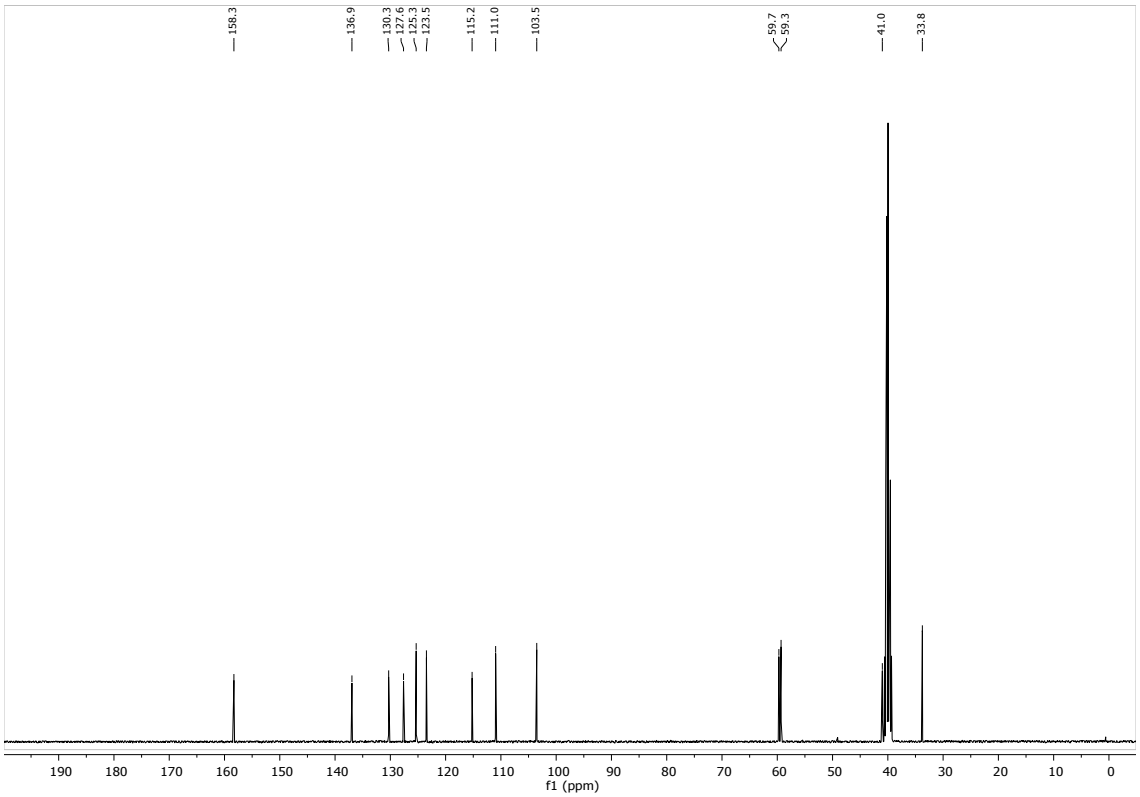
1.0
0.9
1.1
1.1
1.0
1.0
1.0
3.2
f1 (ppm)


158.3
136.9
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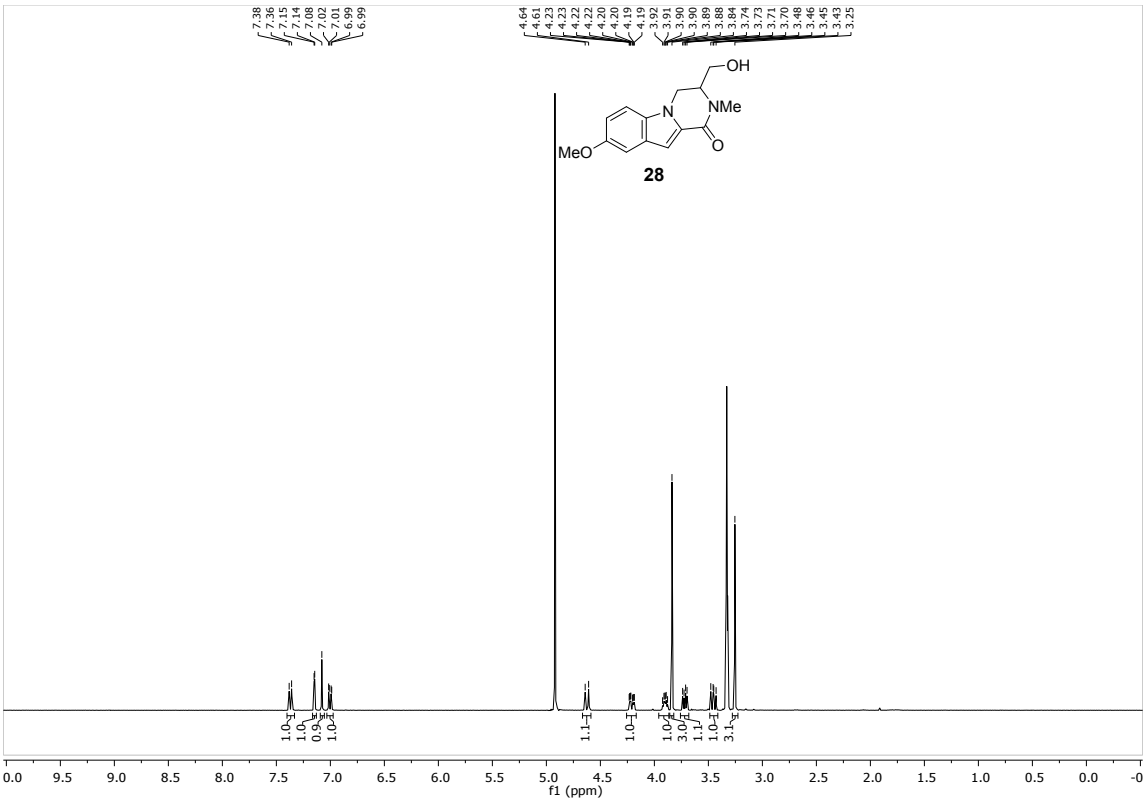
125.3
123.5
115.2
111.0
103.5
59.7
59.3
41.0
33.8
f1 (ppm)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7.01
6.99
6.99
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4.61
4.23
4.23
4.23
4.22
4.22
4.20
4.20
4.19
4.19
3.92
3.91
3.90
3.90
3.89
3.88
3.84
3.74
3.73
3.71
3.70
3.48
3.46
3.45
3.43
3.25
OH
N
NMe
O
MeO
28
1.0
1.0
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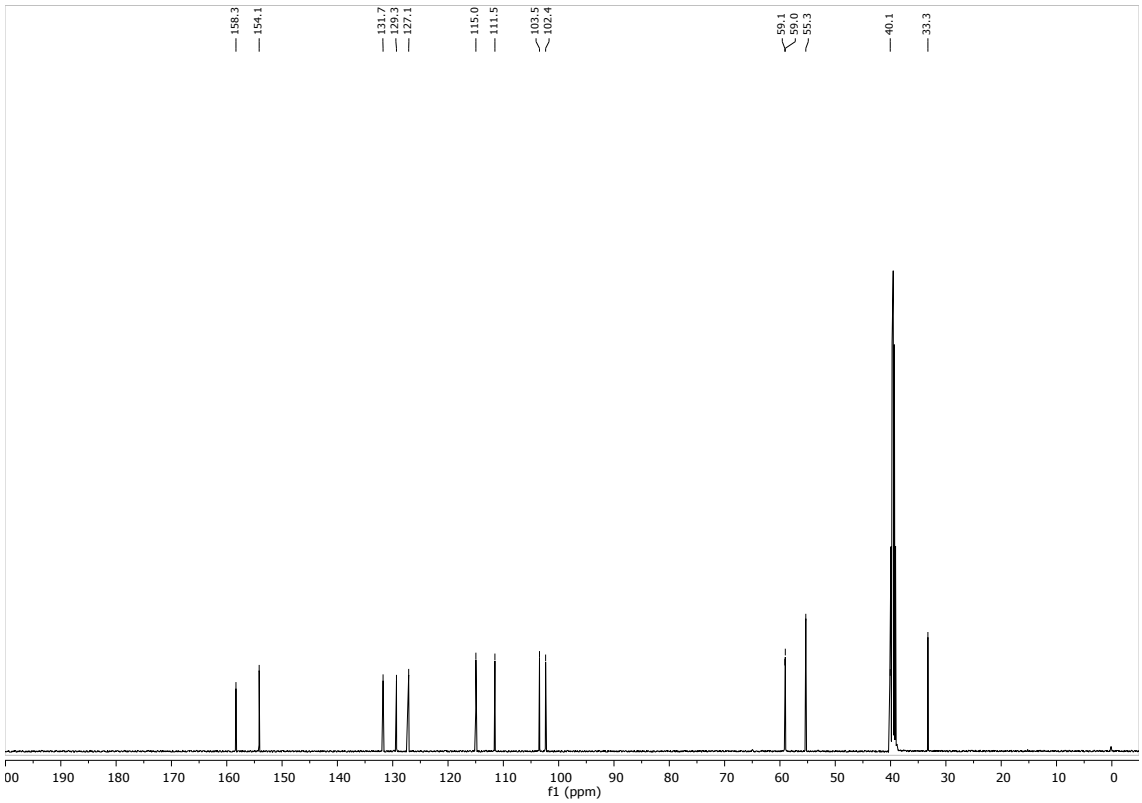
1.0
1.1
1.0
1.0
3.0
1.1
1.0
3.1
f1 (ppm)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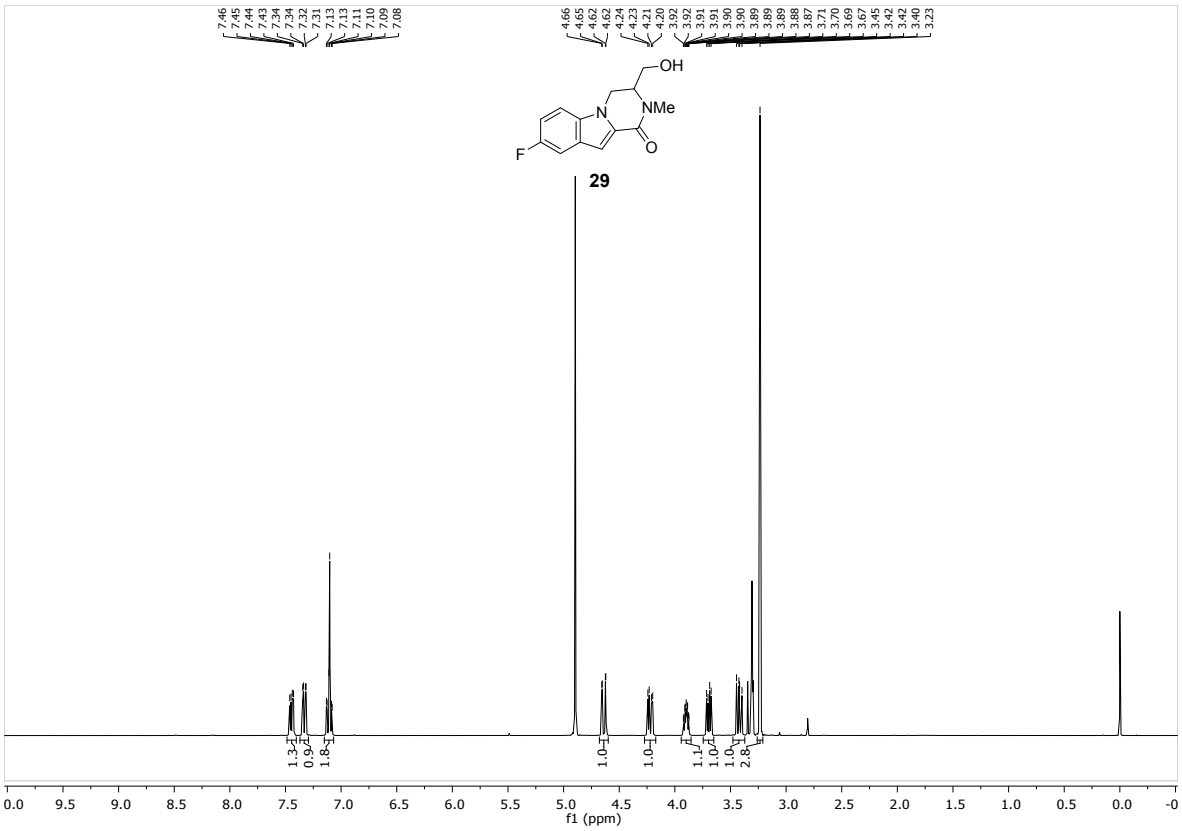
154.1
131.7
129.3
127.1
115.0
111.5
103.5
102.4
59.1
59.0
55.3
40.1
33.3
f1 (ppm)


7.46
7.45
7.44
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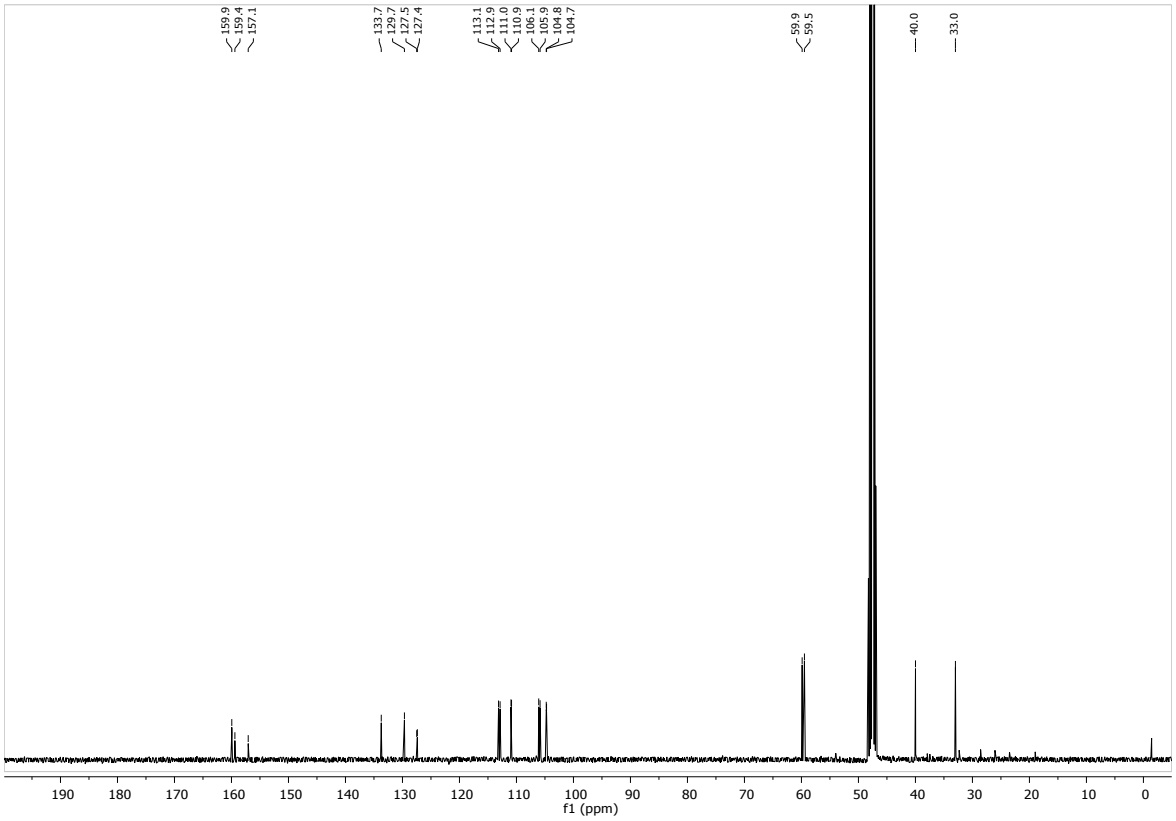
7.32
7.31
7.13
7.13
7.11
7.10
7.09
7.08
4.66
4.65
4.62
4.62
4.24
4.23
4.21
4.20
3.92
3.92
3.91
3.91
3.90
3.90
3.89
3.89
3.89
3.88
3.87
3.71
3.70
3.69
3.67
3.45
3.42
3.42
3.40
3.23
OH
N
NMe
O
F
29
1.3
0.9
1.8
1.0
1.0
1.1
1.0
1.0
2.8
f1 (ppm)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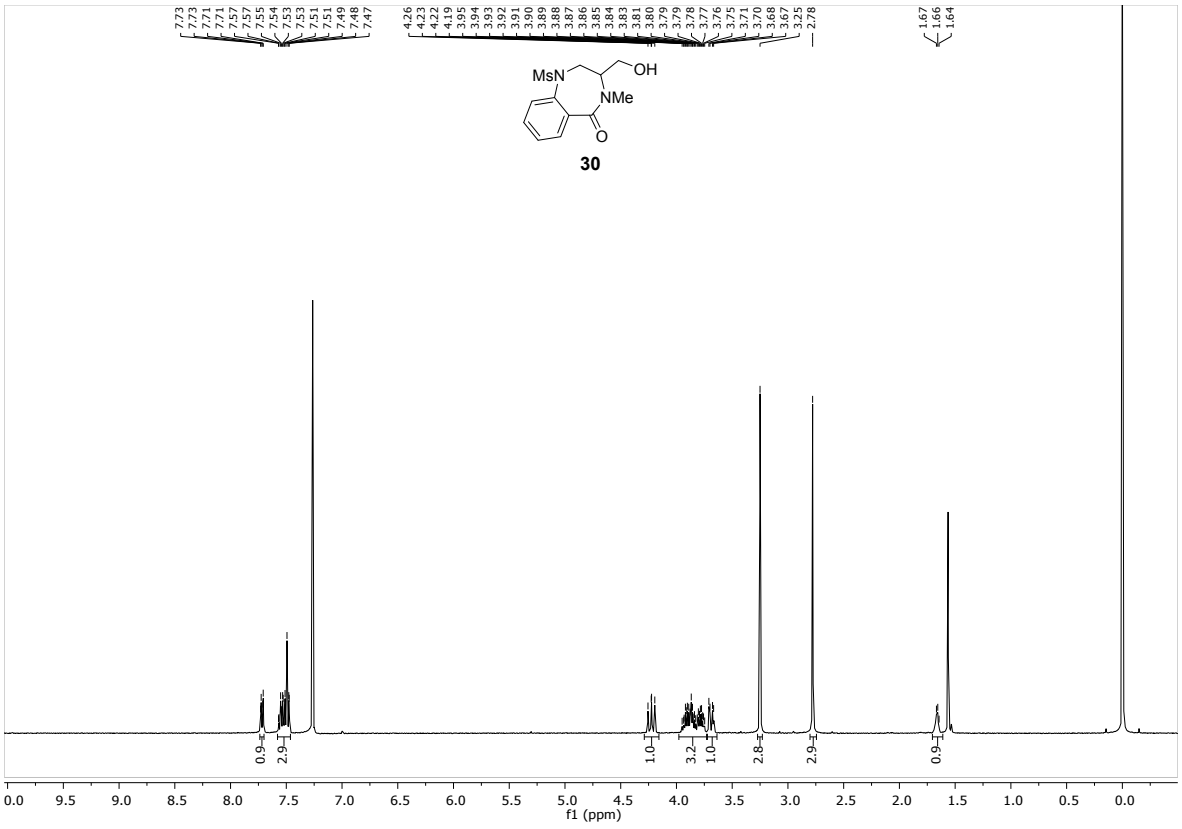
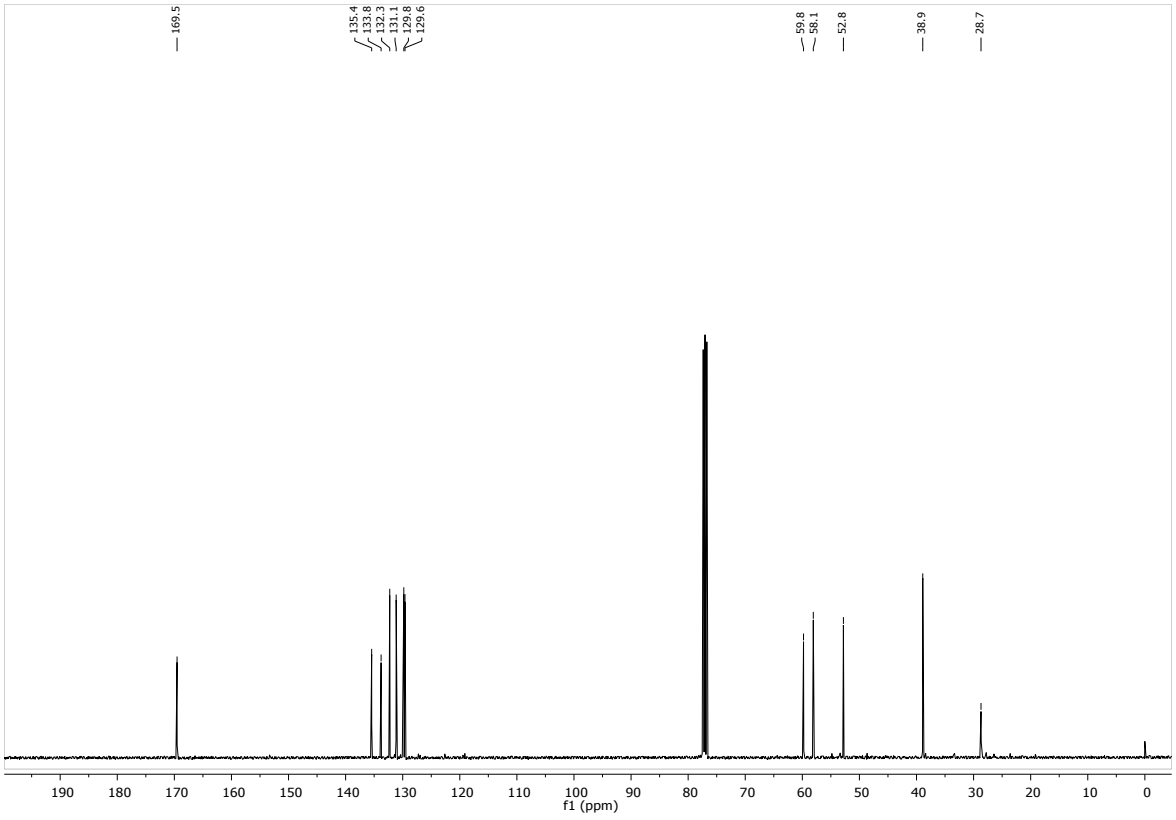
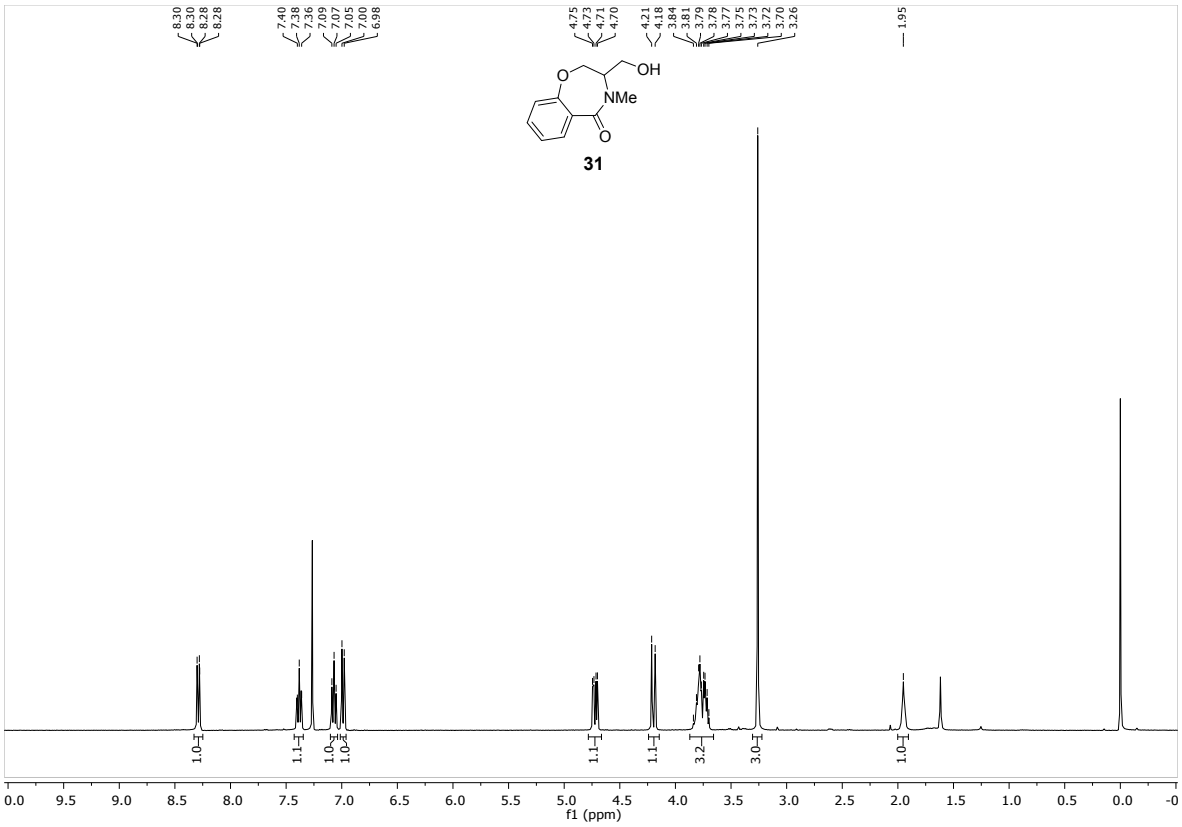
159.4
157.1
133.7
129.7
127.5
127.4
113.1
112.9
111.0
110.9
106.1
105.9
104.8
104.7
59.9
59.5
40.0
33.0
f1 (ppm)


MsN
OH
NMe
O
f1 (ppm)

30


169.5
135.4
133.8
132.3
131.1
129.8
129.6
59.8
58.1
52.8
38.9
28.7
f1 (ppm)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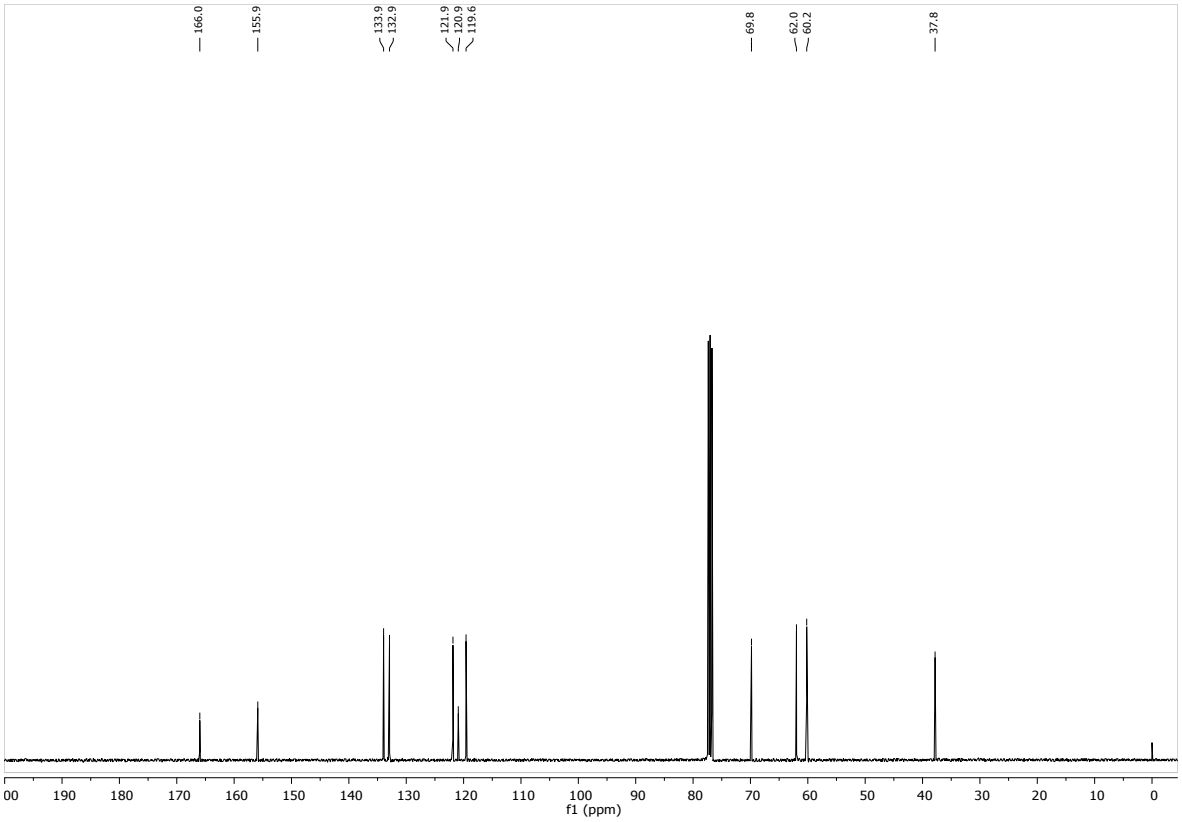
8.30
8.28
8.28
7.40
7.38
7.36
7.09
7.07
7.05
7.00
6.98
4.75
4.73
4.71
4.70
4.21
4.18
3.84
3.81
3.79
3.78
3.77
3.75
3.73
3.72
3.70
3.26
1.95
OH
O
NMe
O
31
1.0
1.1
1.0
1.0
1.1
1.1
3.2
3.0
1.0
f1 (ppm)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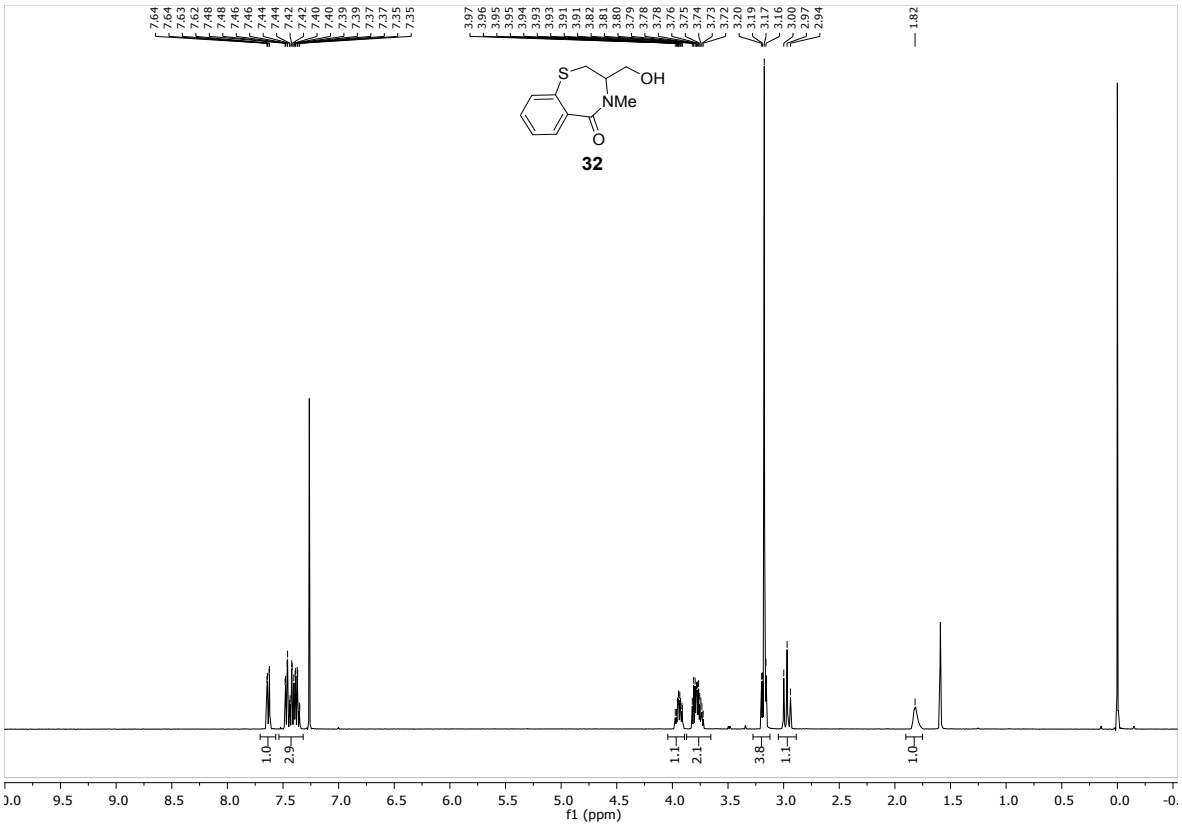
155.9
133.9
132.9
121.9
120.9
119.6
69.8
62.0
60.2
37.8
f1 (ppm)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7.64
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7.62
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7.48
7.46
7.46
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7.44
7.42
7.42
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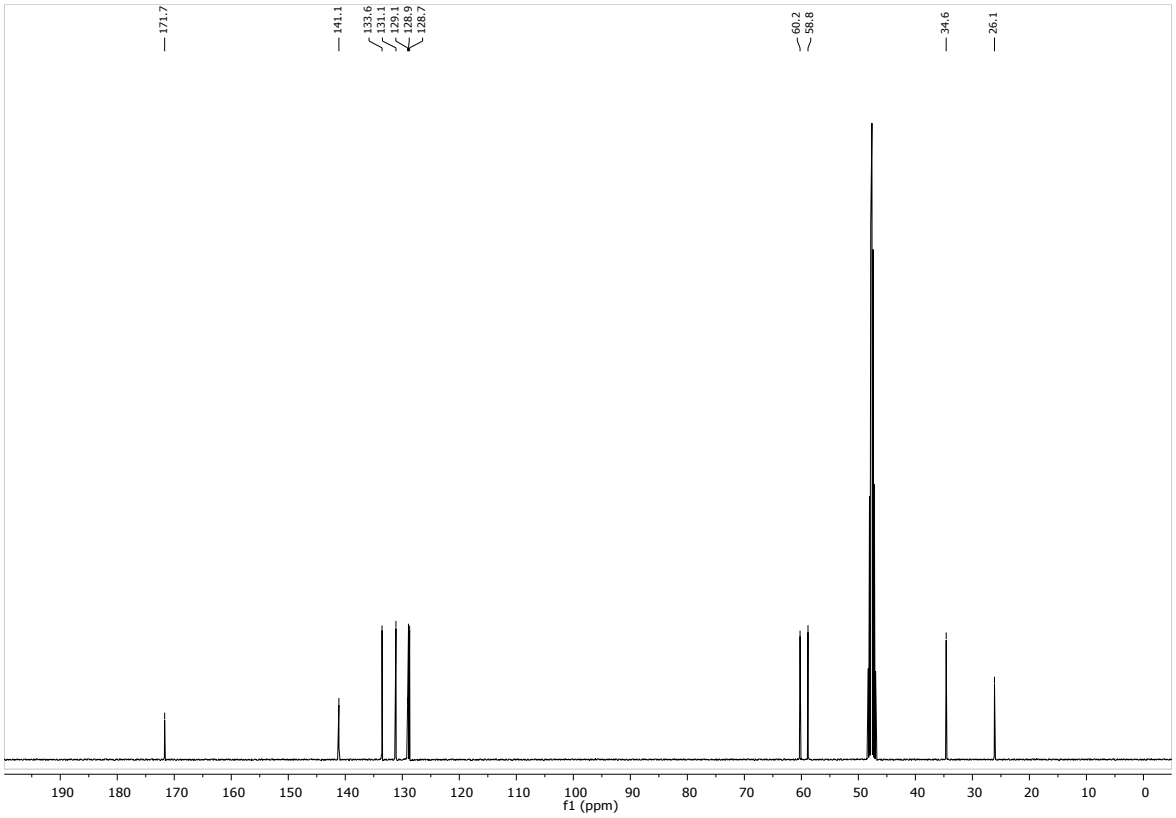
7.40
7.39
7.39
7.37
7.37
7.35
7.35
3.97
3.96
3.95
3.95
3.94
3.93
3.93
3.91
3.91
3.82
3.81
3.80
3.79
3.78
3.78
3.76
3.75
3.74
3.73
3.72
3.20
3.19
3.17
3.16
3.00
2.97
2.94
1.82
S
OH
NMe
O
32
1.0
2.9
1.1
2.1
3.8
1.1
1.0
f1 (ppm)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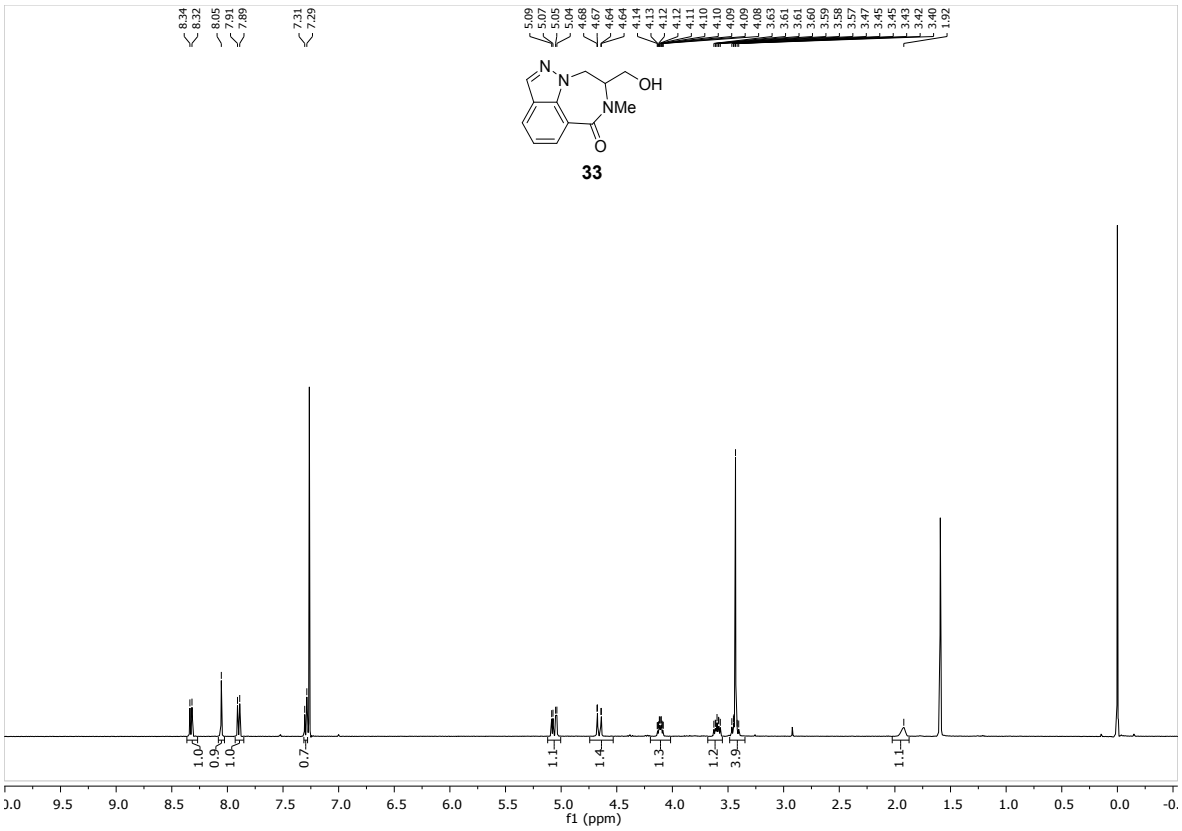
141.1
133.6
131.1
129.1
128.9
128.7
60.2
58.8
34.6
26.1
f1 (ppm)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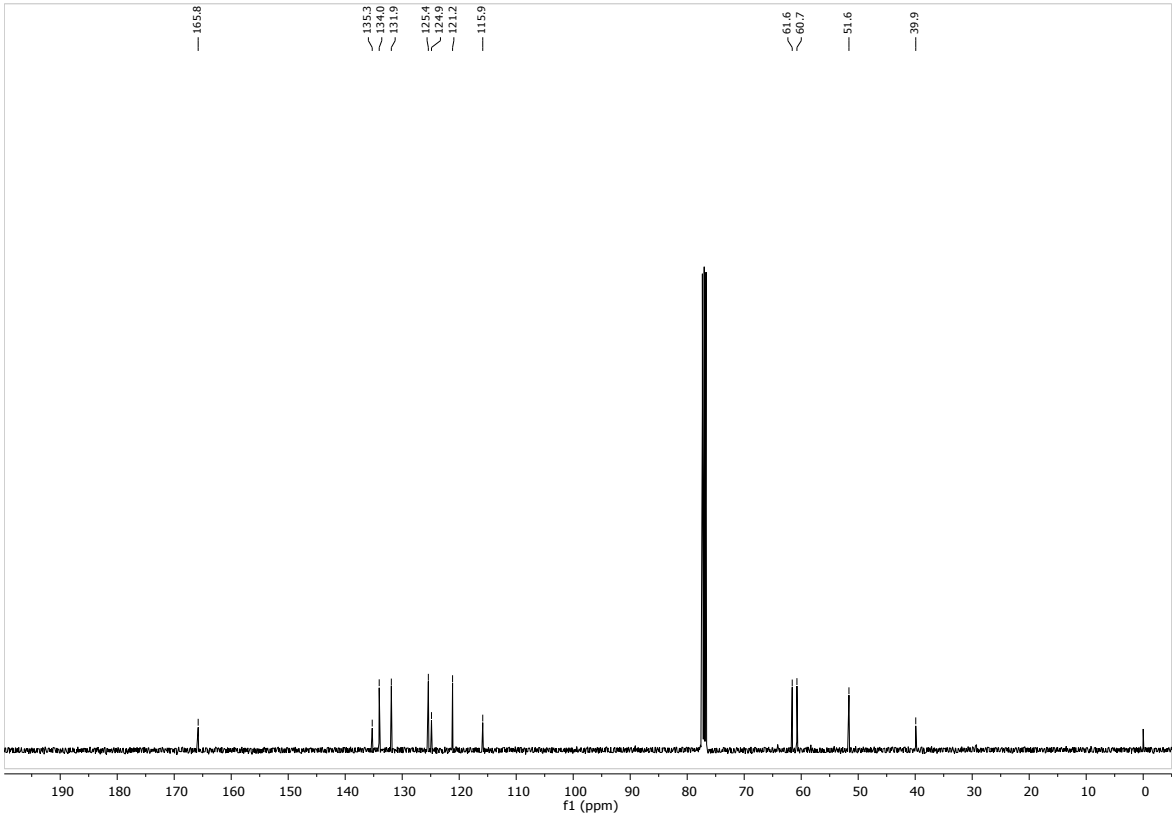
8.32
8.05
7.91
7.89
7.31
7.29
5.09
5.07
5.05
5.04
4.68
4.67
4.64
4.64
4.14
4.13
4.12
4.12
4.11
4.10
4.10
4.09
4.09
4.08
3.63
3.61
3.61
3.60
3.59
3.58
3.57
3.47
3.45
3.45
3.43
3.42
3.40
1.92
N
N
OH
NMe
O
1.0
0.9
1.0
0.7
1.1
1.4
1.3
1.2
3.9
1.1
f1 (ppm)

33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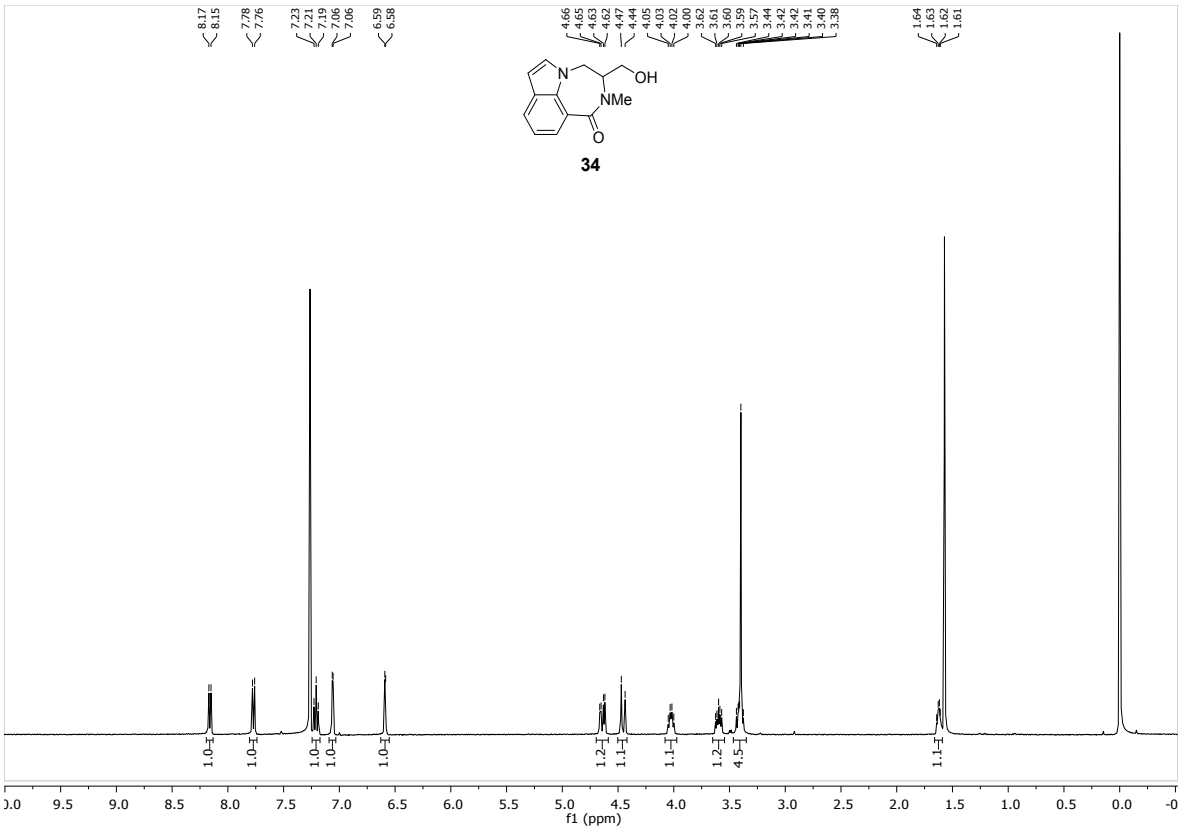
135.3
134.0
131.9
125.4
124.9
121.2
115.9
61.6
60.7
51.6
39.9
f1 (ppm)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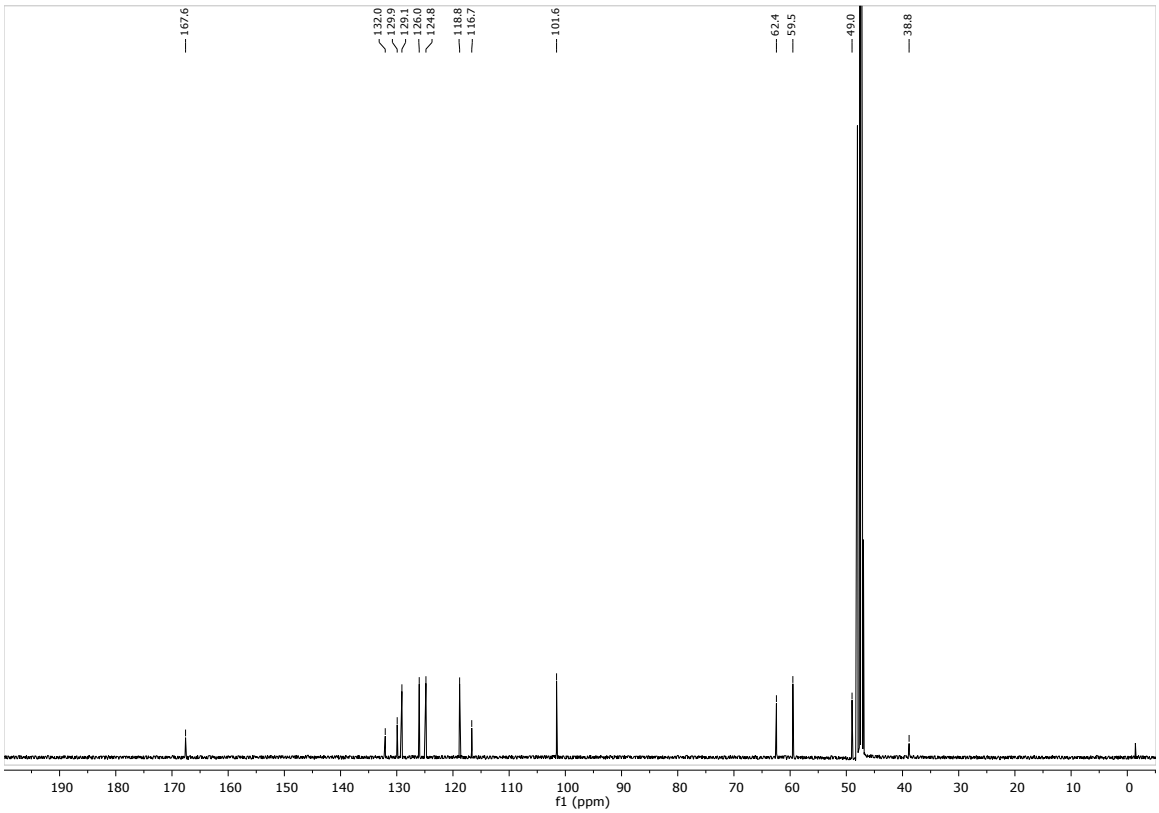
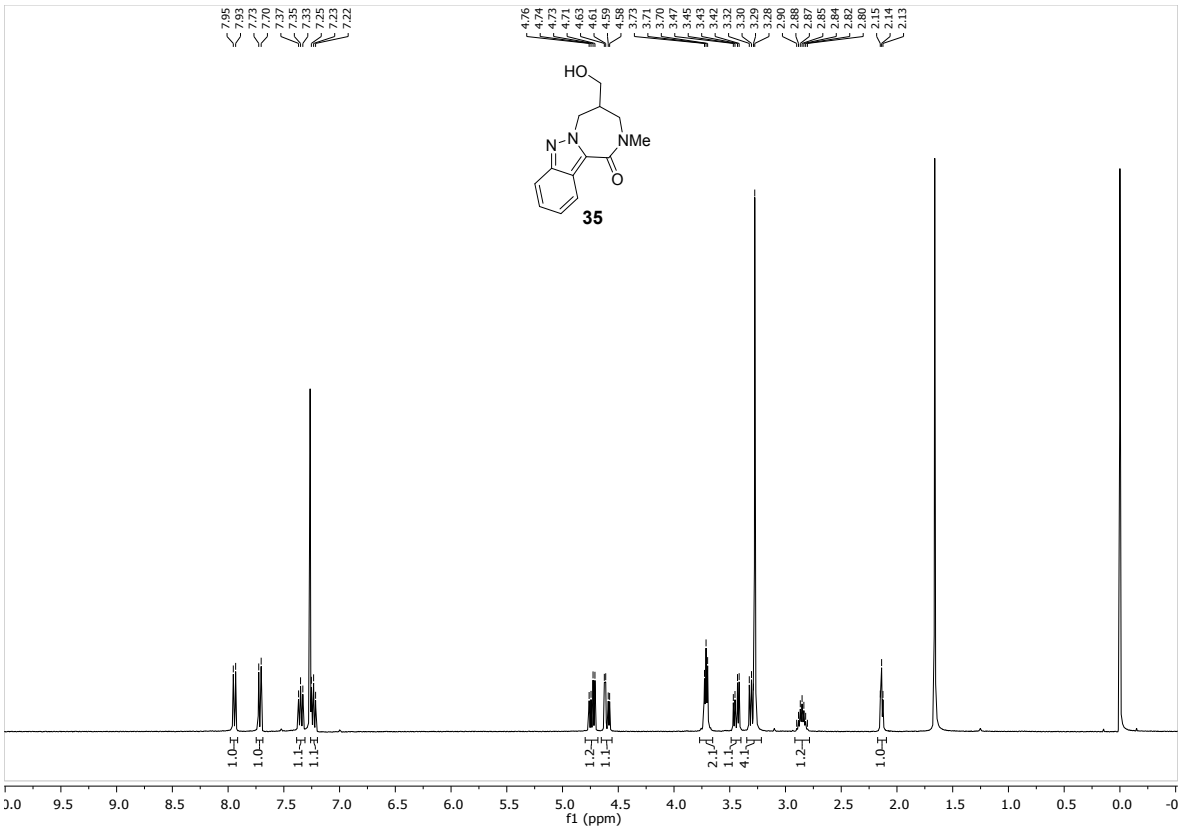
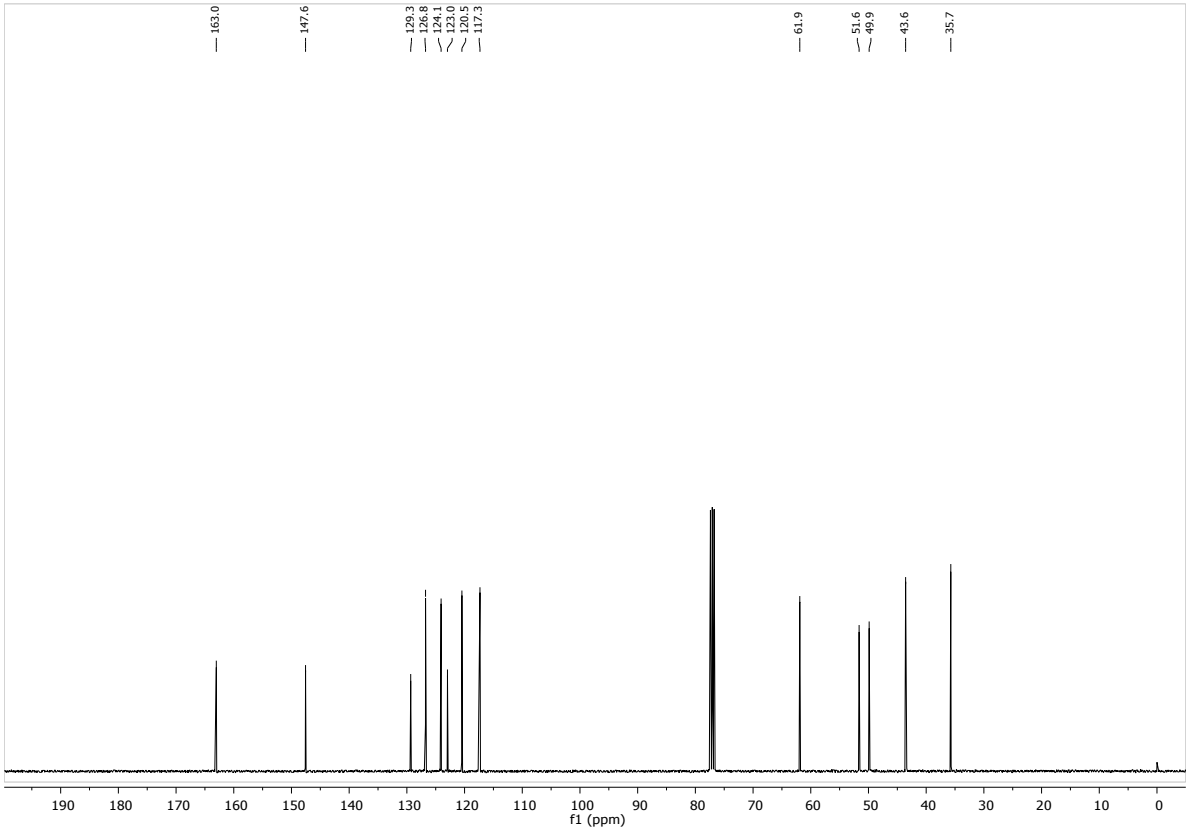
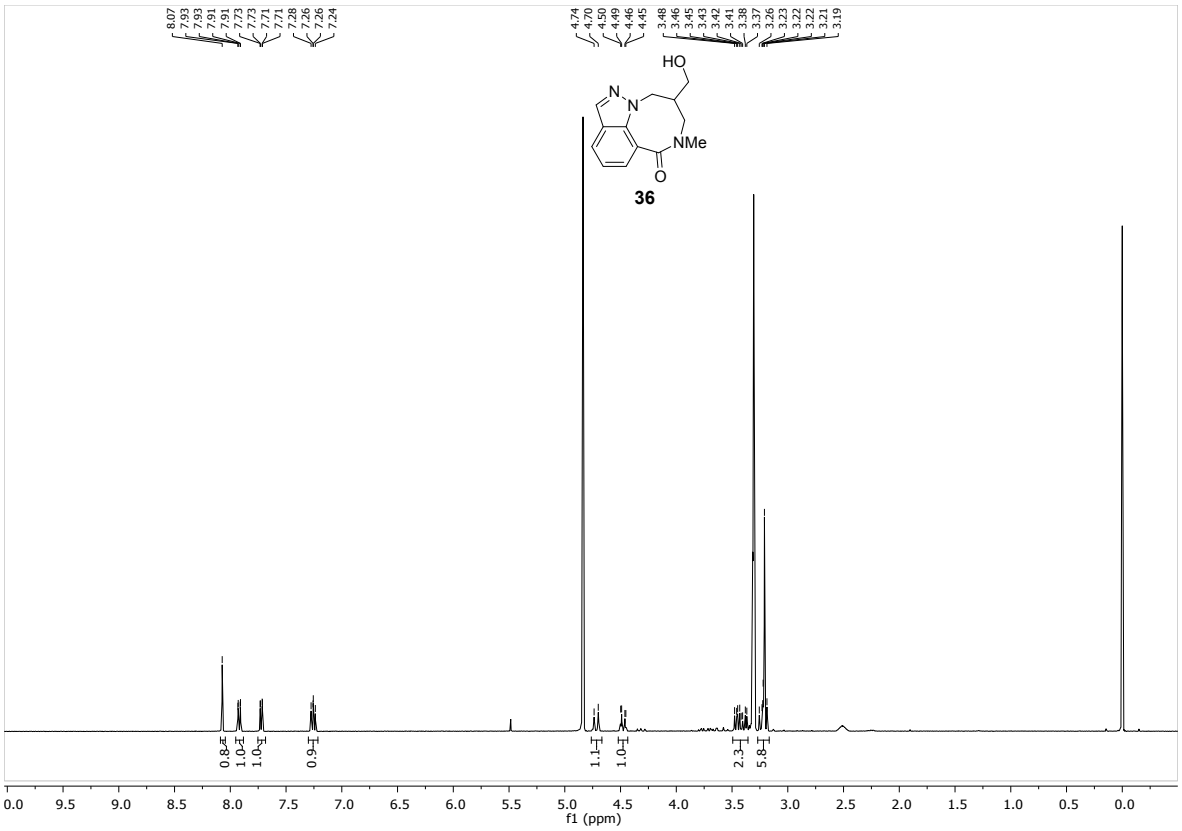
8.15
7.78
7.76
7.23
7.21
7.19
7.06
7.06
6.59
6.58
4.66
4.65
4.63
4.62
4.47
4.44
4.05
4.03
4.02
4.00
3.62
3.61
3.60
3.59
3.57
3.44
3.42
3.41
3.40
3.38
1.64
1.63
1.62
1.61
N
OH
NMe
O
34
1.0
1.0
1.0
1.0
1.0
1.2
1.1
1.1
1.2
4.5
1.1
f1 (ppm)


167.6
132.0
129.9
129.1
126.0
124.8
118.8
116.7
101.6
62.4
59.5
49.0
38.8
f1 (ppm)


HO
N
N
NMe
O
35
f1 (ppm)


163.0
147.6
129.3
126.8
124.1
123.0
120.5
117.3
61.9
51.6
49.9
43.6
35.7
f1 (ppm)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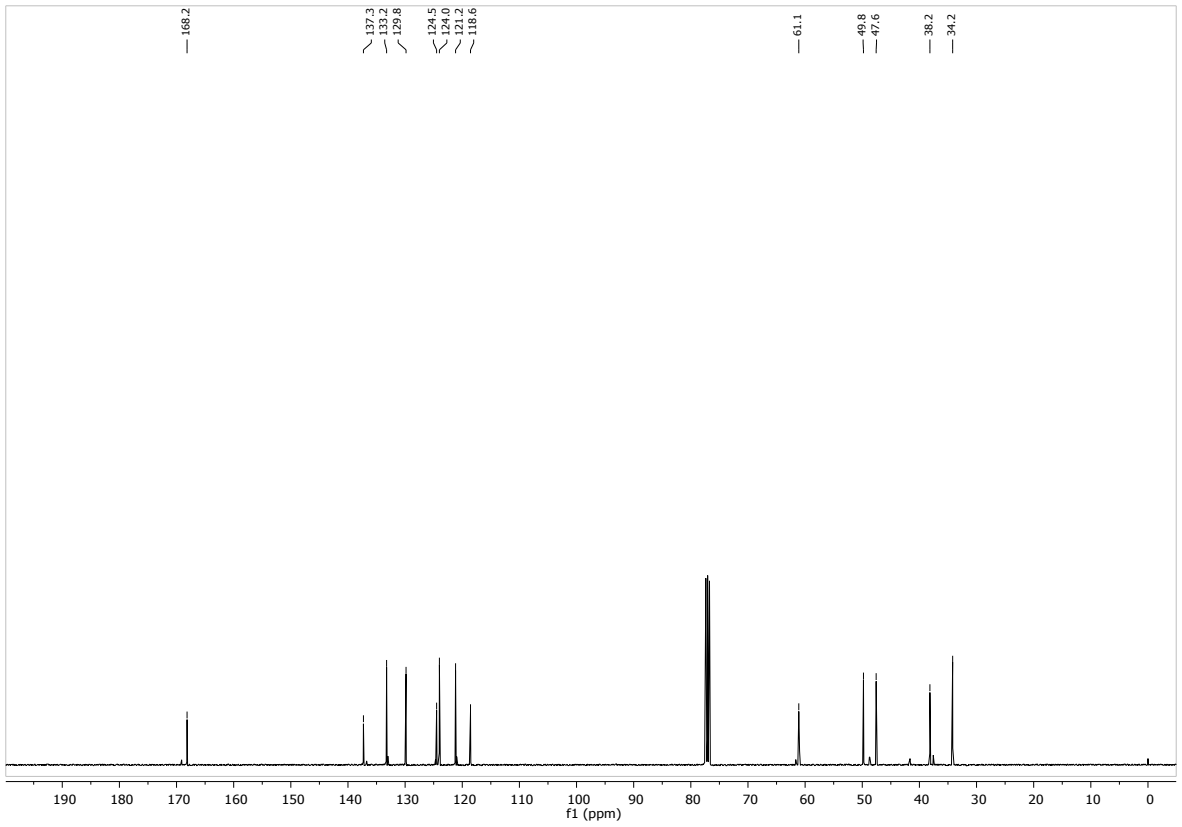
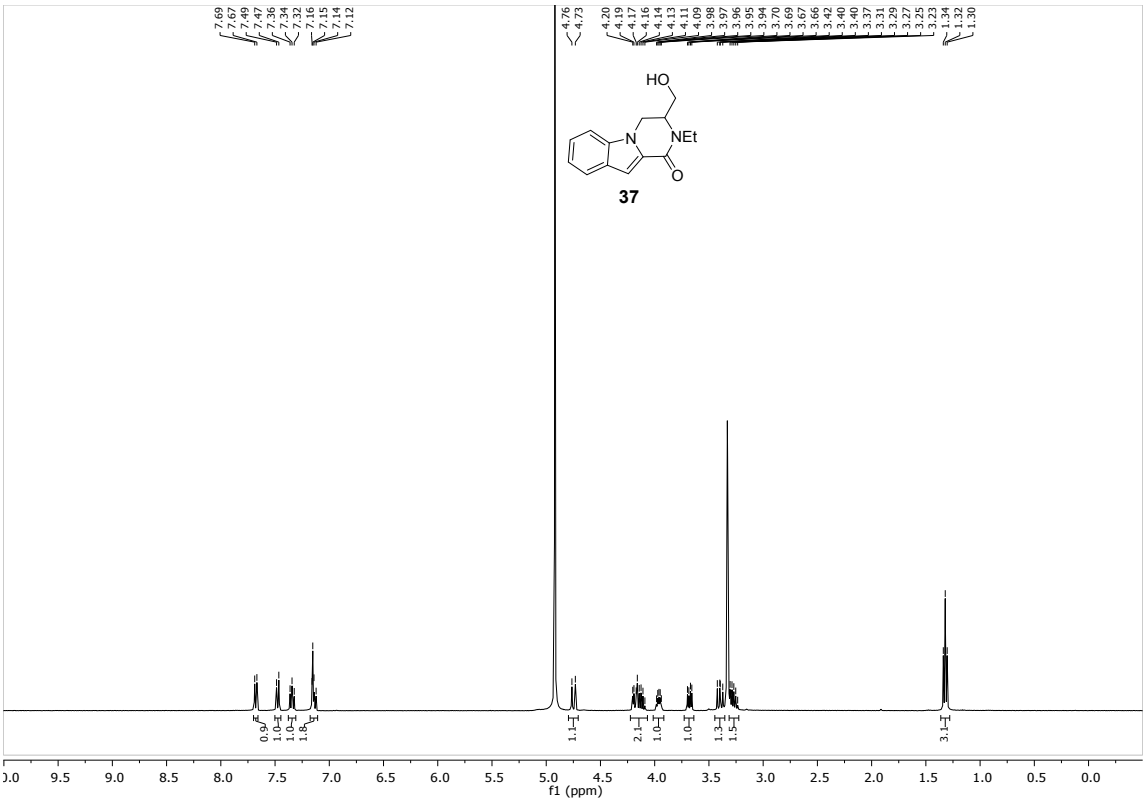
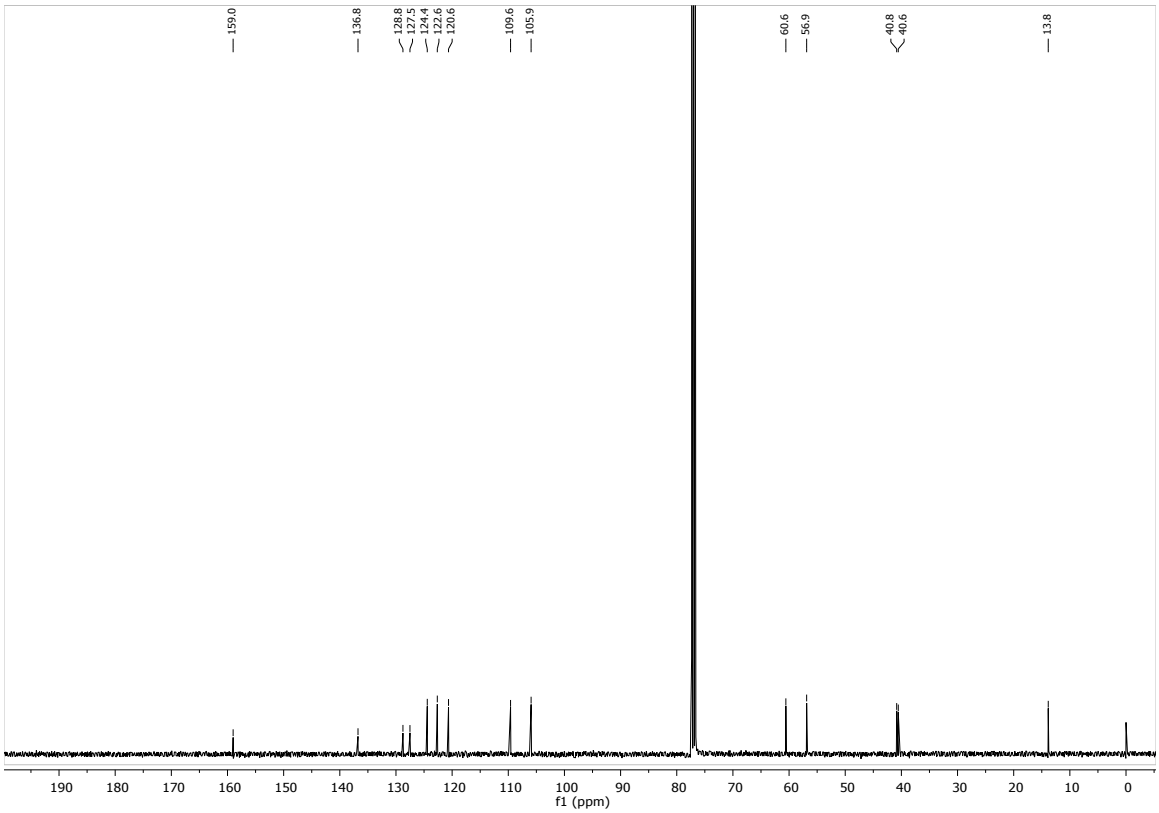
7.73
7.73
7.71
7.71
7.28
7.26
7.26
7.24
4.74
4.70
4.50
4.49
4.46
4.45
3.48
3.46
3.45
3.43
3.42
3.41
3.38
3.37
3.26
3.23
3.22
3.21
3.19
HO
N
N
NMe
O
36
0.8
1.0
1.0
0.9
1.1
1.0
2.3
5.8
f1 (ppm)


168.2
137.3
133.2
129.8
124.5
124.0
121.2
118.6
61.1
49.8
47.6
38.2
34.2
f1 (ppm)


HO
N
NEt
O
37
f1 (ppm)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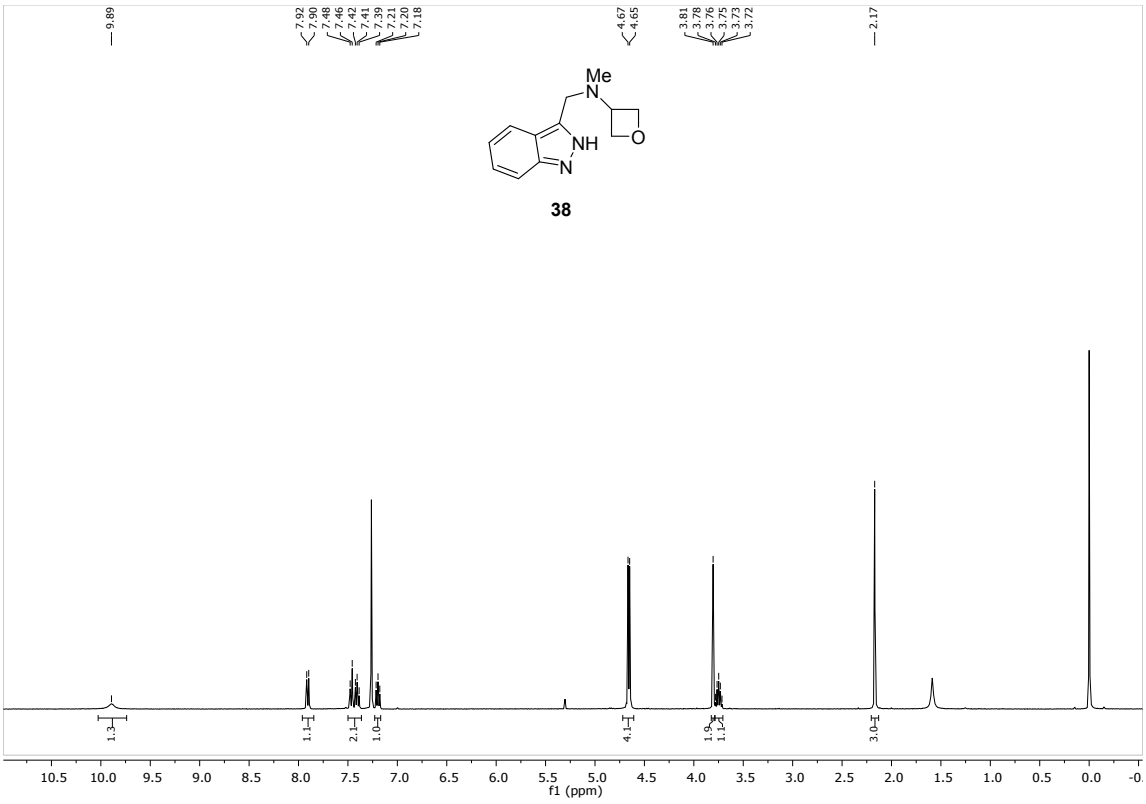
136.8
128.8
127.5
124.4
122.6
120.6
109.6
105.9
60.6
56.9
40.8
40.6
13.8
f1 (ppm)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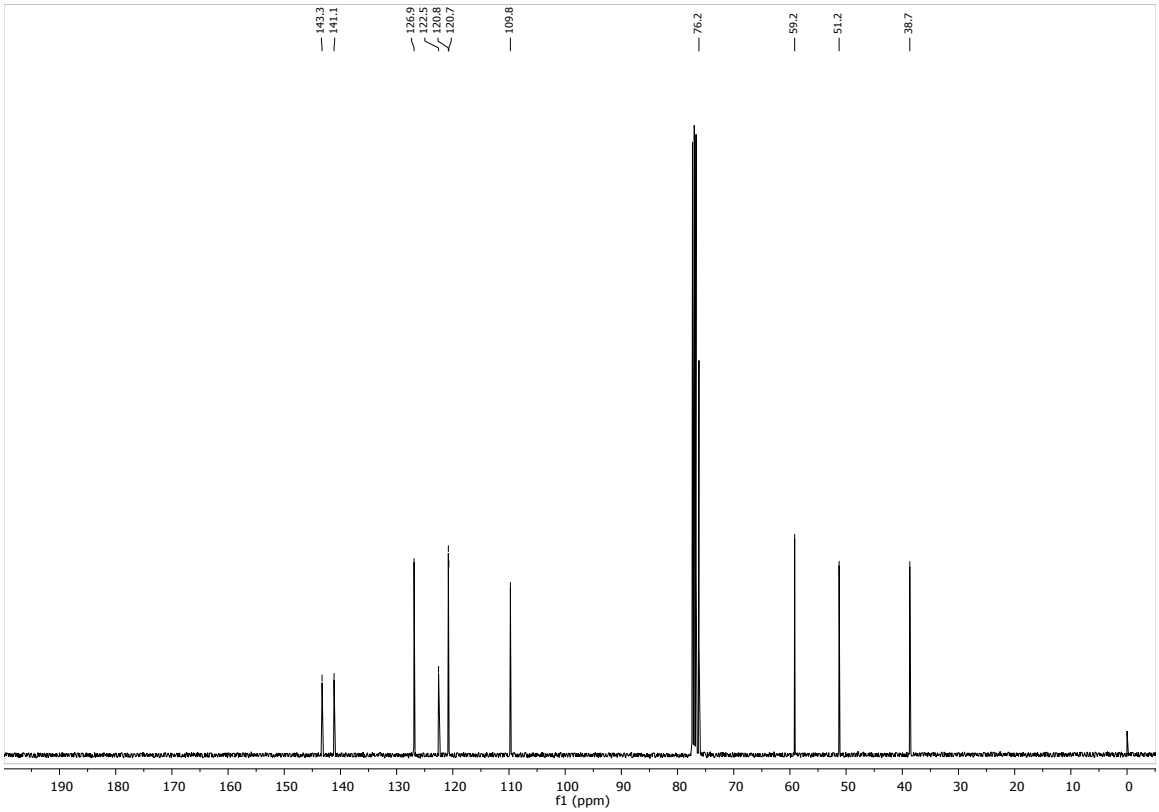
7.46
7.42
7.41
7.39
7.21
7.20
7.18
4.67
4.65
3.81
3.78
3.76
3.75
3.73
3.72
2.17
Me
N
NH
N
O
38
1.3
1.1
2.1
1.0
4.1
1.9
1.1
3.0
f1 (ppm)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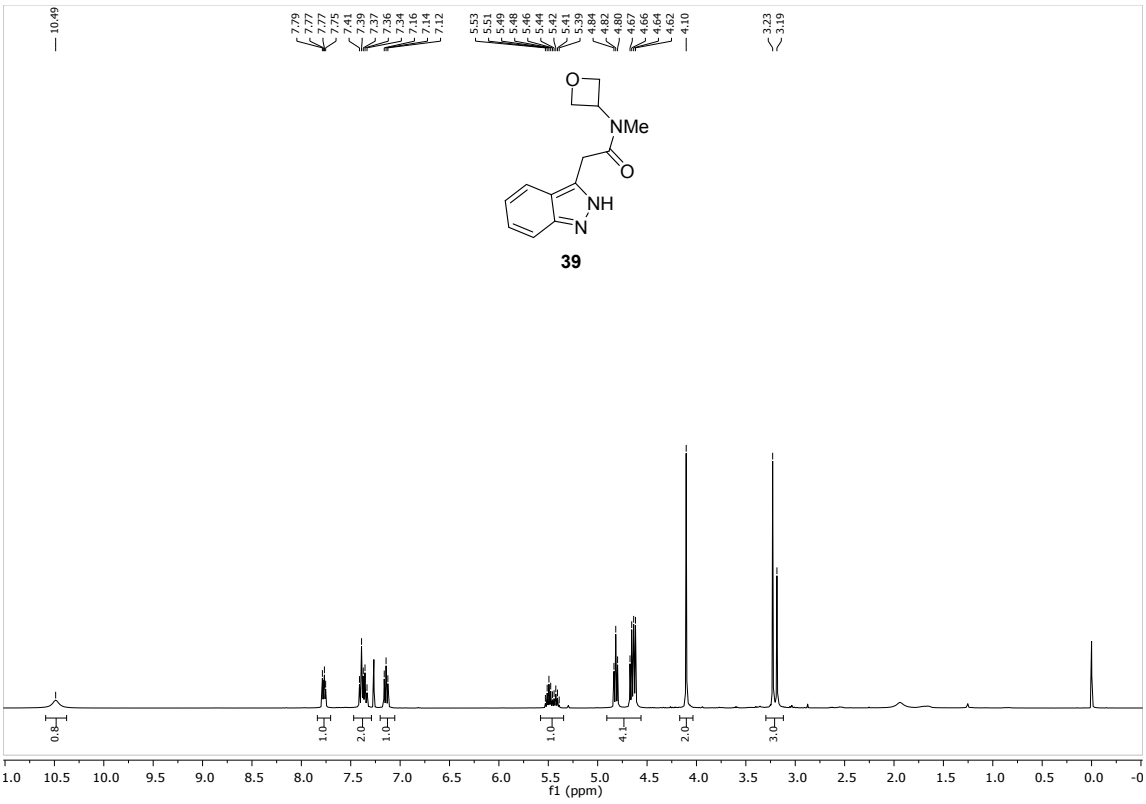
122.5
120.8
120.7
109.8
76.2
59.2
51.2
38.7
f1 (ppm)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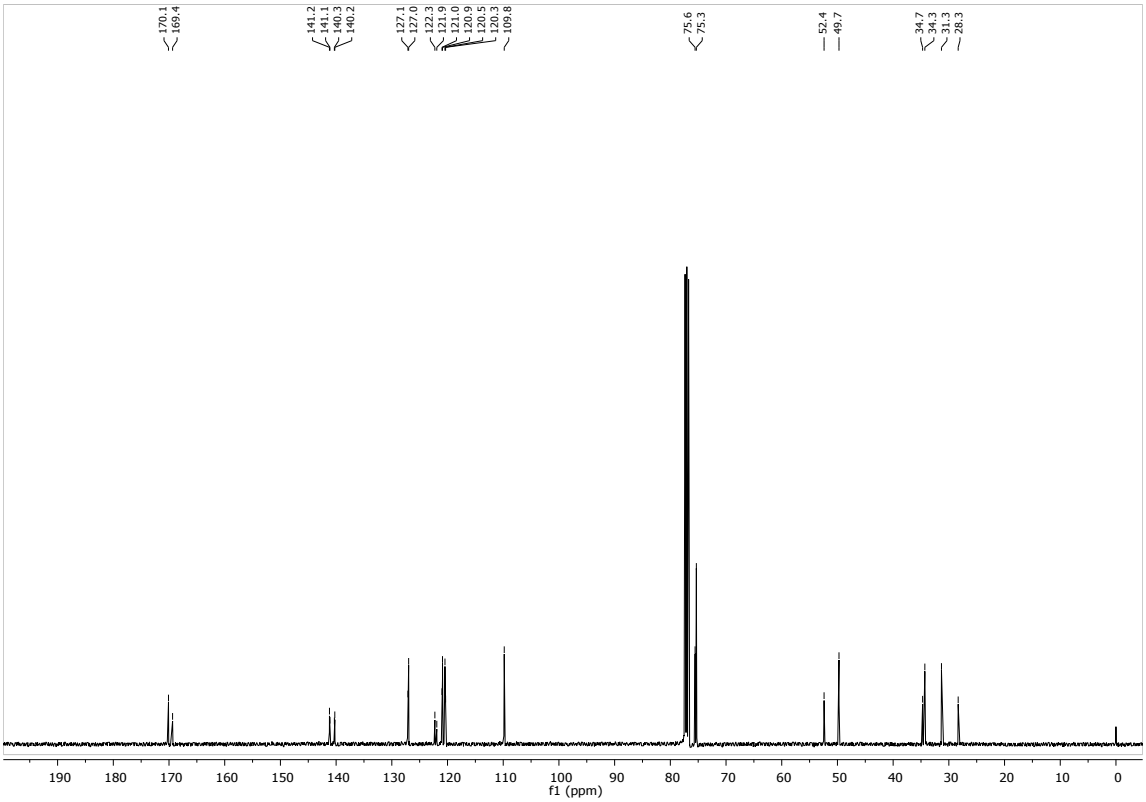
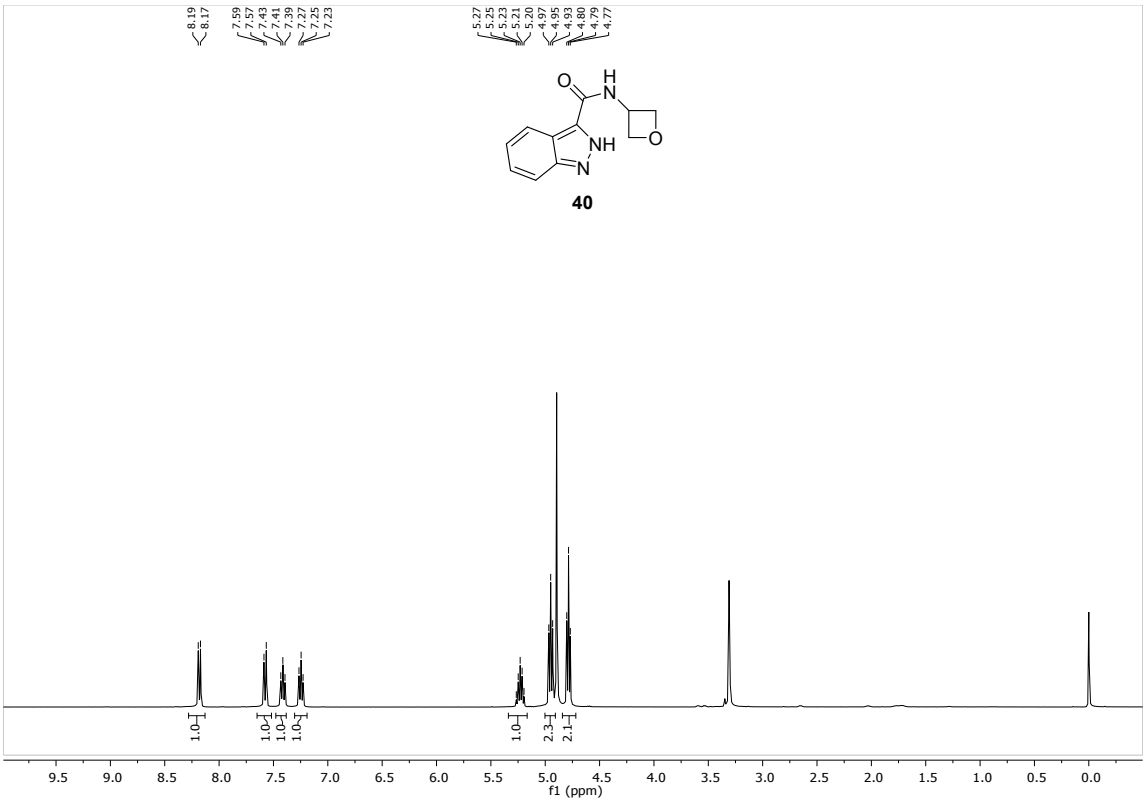
7.34
7.16
7.14
7.12
5.53
5.51
5.49
5.48
5.46
5.44
5.42
5.41
5.39
4.84
4.82
4.80
4.67
4.66
4.64
4.62
4.10
3.23
3.19
O
NMe
O
NH
N
39
0.8
1.0
2.0
1.0
1.0
4.1
2.0
3.0
f1 (ppm)


170.1
169.4
141.2
141.1
140.3
140.2
127.1
127.0
122.3
121.9
121.0
120.9
120.5
120.3
109.8
75.6
75.3
52.4
49.7
34.7
34.3
31.3
28.3
f1 (ppm)


8.19
8.17
7.59
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7.41
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7.27
7.25
7.23
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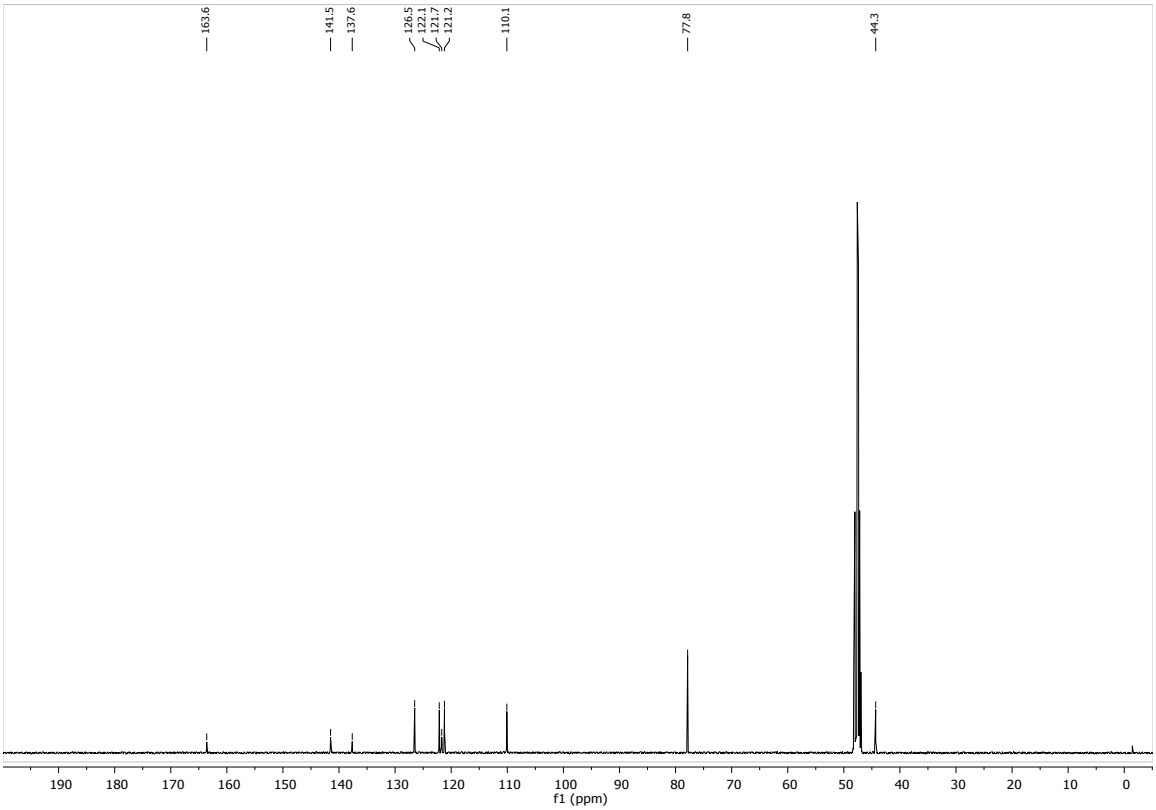
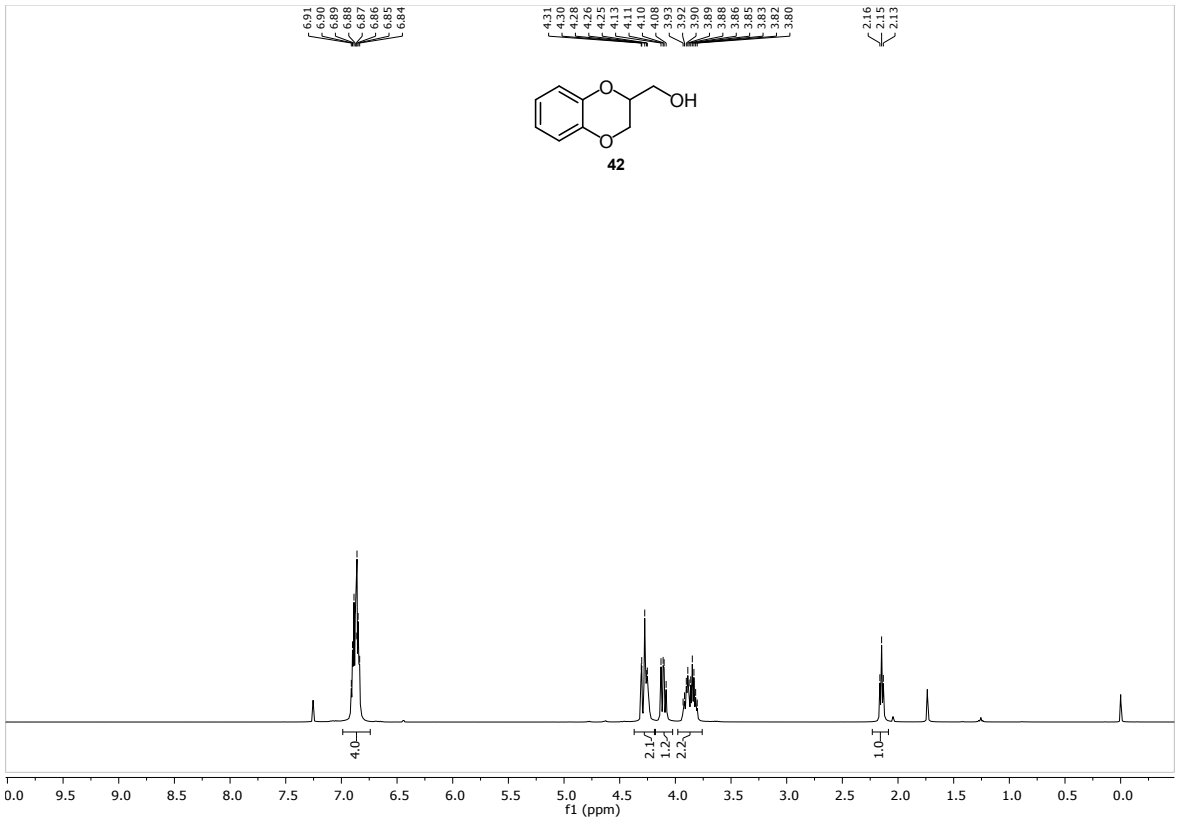
5.25
5.23
5.21
5.20
4.97
4.95
4.93
4.80
4.79
4.77
O
H
N
NH
N
O
40
1.0
1.0
1.0
1.0
1.0
2.3
2.1
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


163.6
141.5
137.6
126.5
122.1
121.7
121.2
110.1
77.8
44.3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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6.90
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6.84
4.31
4.30
4.28
4.26
4.25
4.13
4.11
4.10
4.08
3.93
3.92
3.90
3.89
3.88
3.86
3.85
3.83
3.82
3.80
2.16
2.15
2.13
O
OH
O
42
4.0
2.1
1.2
2.2
1.0
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)