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Synthesis of 2,2-bis(pyridin-2-yl amino)cyclobutanols and their conversion into 5-(pyridin-2-ylamino)dihydrofuran-2(3H)-ones

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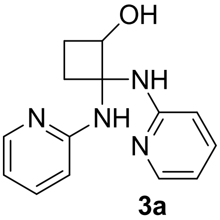
General Methods

^{1}H NMR spectra were recorded on a Varian 500 spectrometer at ambient temperature with $CDCl_3$ as solvent. Data are reported as follows: chemical shifts (δ), multiplicity, coupling constants and integration. ^{13}C NMR spectra were recorded operating at 126 MHz at 27 °C with $CDCl_3$ as solvent. Infrared spectra were recorded on a FT-IR spectrophotometer. High resolution mass spectra (HRMS) were recorded on a spectrometer using Positive Electro Ionization (ESI) mode. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash chromatography was performed using columns of 230-400 mesh silica gel 60 (0.040-0.063 mm).

General procedure for the two-step preparation of 5-(pyridin-2-ylamino)dihydrofuran-2(3H)-one 7 from 2-hydroxycyclobutanone 1 and 2-amino pyridines 2.

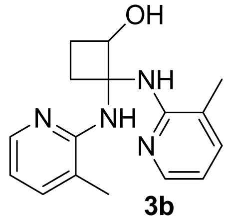
Step 1:

A solution of **1** (419 µmol) and **2** (837 µmol) in Toluene (0.4 mL) was stirred in a sealed tube reactor at room temperature for 24-72h. The resulting reaction mixture was concentrated in a vacuum and controlled by ^{1}H NMR. Conversions (based on **2**) and characteristic spectroscopic data of **3** are reported below. The crude products were used in the following step as obtained by evaporation of the solvent, contaminated with small amount of **1** and **2**.



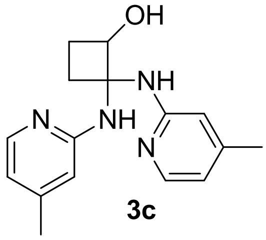
3a

Conversion 82%; purified by reprecipitation (CH_2Cl_2/Et_2O) to give the title compound as a white solid; m. p. = 107–111 °C. IR (neat): 3271, 3008, 2955, 2899, 1681, 1601, 1592, 1480, 1407, 1324, 1251, 1179, 1143, 1106, 1065 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.99 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.31 – 7.28 (m, 2H), 6.55 – 6.49 (m, 2H), 6.41 – 6-37 (m, 3H), 6.02 (s, 1H), 4.37 (t, *J* = 8.5 Hz, 1H), 2.47 (t, *J* = 10.2 Hz, 1H), 2.25 – 2.20 (m, 1H), 2.04 (dd, *J* = 19.8, 10.4 Hz, 1H), 1.96 (ddd, *J* = 18.8, 11.9, 7.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.1, 156.9, 147.4, 147.0, 137.6, 137.0, 113.3, 112.7, 110.9, 110.4, 70.7, 70.4, 26.1, 24.6. HRMS (ESI) Calcd. for $C_{14}H_{15}N_4$ (MH^+-H_2O) m/z 239.1291, found 239.1304.



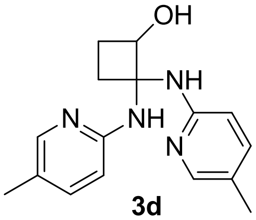
3b

Conversion 69%; the crude mixture, diluted with CH_2Cl_2, was purified by filtration through a pad of silica gel to give the title compound as a yellow oil. IR (neat): 3429, 3381, 2994, 2951, 1592, 1496, 1469, 1408, 1323, 1251, 1158 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.89 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.15 (dddd, *J* = 5.9, 4.2, 1.6, 0.7 Hz, 2H), 6.48 – 5.51 (m, 3H), 5.91 (s, 1H), 4.43 (t, *J* = 8.4 Hz, 1H), 2.48 (dd, *J* = 14.2, 5.1 Hz, 1H), 2.25 (ddd, *J* = 9.8, 6.4, 4.4 Hz, 1H), 2.10 – 2.04 (m, 2H), 2.03 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 155.5, 144.8, 144.5, 137.5, 137.0, 118.8, 118.2, 113.3, 112.7, 70.6, 70.5, 26.5, 24.7, 17.2, 17.0. HRMS (ESI) Calcd. for $C_{16}H_{19}N_4$ (MH^+-H_2O) m/z 267.1604, found 267.1600.



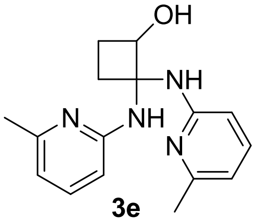
3c

Conversion 79%; purified by reprecipitation (CH_2Cl_2/Et_2O) to give the title compound as a white solid; m. p. = 124–128 °C. IR (neat): 3408, 3347, 2952, 2864, 1616, 1571, 1501, 1389, 1173, 1141 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 5.3 Hz, 1H), 7.86 (d, *J* = 5.4 Hz, 1H), 6.37 (dd, *J* = 11.0, 5.3 Hz, 2H), 6.28 (s, 1H), 6.22 (s, 1H), 6.19 (s, 1H), 5.89 (s, 1H), 4.34 (t, *J* = 8.5 Hz, 1H), 2.45 (dd, *J* = 14.1, 6.1 Hz, 1H), 2.21 (ddd, *J* = 7.8, 5.9, 3.0 Hz, 1H), 2.15 (s, 3H), 2.13 (s, 3H), 2.02 (dd, *J* = 19.8, 10.4 Hz, 1H), 1.99 – 1.90 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.4, 157.2, 148.6, 147.9, 147.2, 146.7, 115.1, 114.4, 111.0, 110.6, 70.7, 70.4, 26.2, 24.6, 21.0 (2C). HRMS (ESI) Calcd. for $C_{16}H_{19}N_4$ (MH^+-H_2O) m/z 267.1604, found 267.1596.



3d

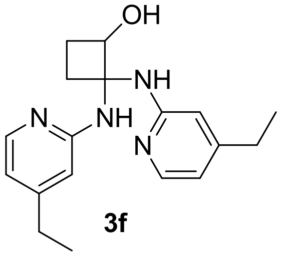
Conversion 70%; the crude mixture, diluted with CH_2Cl_2, was purified by filtration through a pad of silica gel to give the title compound as a yellow oil. IR (neat): 3404, 3235, 2989, 2952, 2900, 1611, 1566, 1506, 1431, 1320, 1260, 1168 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.82 (s, 1H), 7.15 – 7.12 (m, 2H), 6.33-6.30 (m, 2H), 6.27 (s, 1H), 5.86 (s, 1H), 4.35 (t, *J* = 8.5 Hz, 1H), 2.44 (t, *J* = 10.3 Hz, 1H), 2.24 – 2.20 (m, 1H), 2.12 (s, 3H), 2.11 (s, 3H), 2.02 (dt, *J* = 19.4, 9.8 Hz, 1H), 1.93 (td, *J* = 10.6, 8.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.3, 155.1, 146.9, 146.5, 138.7, 138.1, 122.1, 121.3, 110.5, 110.0, 70.9, 70.6, 26.1, 24.6, 17.48, 17.43. HRMS (ESI) Calcd. for $C_{16}H_{19}N_4$ (MH^+-H_2O) m/z 267.1604, found 267.1594.



3e

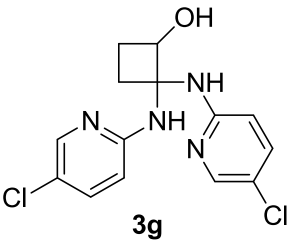
Conversion 61%; the crude mixture, diluted with CH_2Cl_2, was purified by filtration through a pad of silica gel to give the title compound as an orange oil. IR (neat): 3372, 2990, 2954, 1782, 1604, 1588, 1463, 1269, 1234, 1158 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.19 (m, 2H), 6.42 – 6.38 (m, 2H), 6.33 (br s, 1H), 6.23 – 6.19 (m, 2H), 5.97 (br s, 1H), 4.37 (t, *J* = 8.5 Hz, 1H), 2.48 – 2.44 (m, 1H), 2.37 (s, 3H), 2.36

(s, 3H), 2.22 (dtd, *J* = 9.6, 8.0, 1.6 Hz, 1H), 2.06 – 1.98 (m, 1H), 1.94 – 1.88 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.7, 156.4, 156.3, 155.6, 137.9, 137.3, 112.5, 111.8, 107.7, 106.7, 70.7, 70.6, 26.2, 24.68, 24.67, 24.3. HRMS (ESI) Calcd. for $C_{16}H_{19}N_4$ (MH^+-H_2O) m/z 267.1604, found 267.1602.



3f

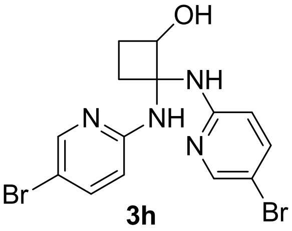
Conversion 67%; purified by reprecipitation (CH_2Cl_2/Et_2O) to give the title compound as a white solid. IR (neat): 3341, 2966, 2936, 2877, 1784, 1612, 1559, 1482, 1439, 1396, 1174 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 5.3 Hz, 1H), 7.88 (d, *J* = 5.6 Hz, 1H), 6.41 (dd, *J* = 5.4, 1.1 Hz, 1H), 6.39 (dd, *J* = 5.3, 1.0 Hz, 1H), 6.37 (s, 1H), 6.25 (s, 1H), 6.21 (s, 1H), 5.94 (s, 1H), 4.35 (t, *J* = 8.5 Hz, 1H), 2.49-2.41 (m, 5H), 2.22 – 2.20 (m, 1H), 2.04-1.97 (m, 1H), 1.95 – 1.91 (m, 1H), 1.17 – 1.12 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.4, 157.2, 154.6, 153.8, 147.1, 146.6, 113.8, 113.2, 109.7, 109.3, 70.7, 70.4, 28.2 (2C), 26.2, 24.6, 14.1, 14.0. HRMS (ESI) Calcd. for $C_{18}H_{23}N_4$ (MH^+-H_2O) m/z 295.1917, found 295.1920.



3g

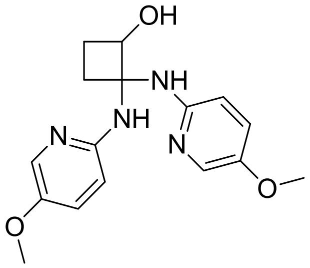
Conversion 76%; purified by reprecipitation (CH_2Cl_2/Et_2O) to give the title compound as a white solid; m. p. = 118–122°C. IR (neat): 3400, 2986, 2960, 1598, 1562, 1482, 1390, 1370, 1284, 1241, 1135, 1112 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 2.4 Hz, 1H), 7.97 (d, *J* = 2.5 Hz, 1H), 7.30 – 7.27 (m , 2H), 6.37 (dd, *J* = 8.9, 0.5 Hz, 1H), 6.35 – 6.33 (m, 1H), 6.23 (s, 1H), 5.99 (s, 1H), 4.35 (t, *J* = 8.5 Hz, 1H), 2.43 – 2.39 (m, 1H), 2.23 (ddd, *J* = 8.9, 5.8, 1.6 Hz, 1H), 2.02 – 1.98 (m, 1H), 1.93 (td, *J* =

10.4, 7.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.3, 155.1, 145.8, 145.5, 137.8, 137.1, 120.8, 120.1, 111.8, 111.3, 70.6, 70.5, 26.0, 24.5. HRMS (ESI) Calcd. for $C_{14}H_{13}Cl_2N_4$ (MH^+-H_2O) m/z 307.0512, found 307.0512.

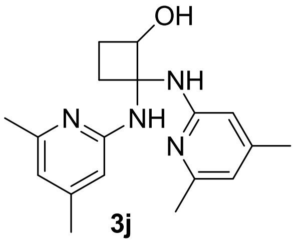


3h

Conversion 72%; purified by reprecipitation (CH_2Cl_2/Et_2O) to give the title compound as a yellow solid. IR (neat): 3387, 3307, 2953, 1625, 1588, 1496, 1476, 1386, 1367, 1300, 1284, 1237 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 2.3 Hz, 1H), 8.06 (d, *J* = 2.4 Hz, 1H), 7.41 (dd, *J* = 5.1, 2.5 Hz, 1H), 7.40 (dd, *J* = 5.1, 2.5 Hz, 1H), 6.34 (d, *J* = 8.8 Hz, 1H), 6.31 (d, *J* = 8.8 Hz, 1H), 6.26 (s, 1H), 6.01 (s, 1H), 4.35 (t, *J* = 8.4 Hz, 1H), 2.41 (dd, *J* = 14.0, 6.5 Hz, 1H), 2.27 – 2.21 (m, 1H), 2.00 (dd, *J* = 19.9, 10.5 Hz, 1H), 1.97 – 1.89 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 155.3, 148.1, 147.8, 140.3, 139.6, 112.4, 111.9, 108.1, 107.6, 70.6, 70.4, 25.9, 24.5. HRMS (ESI) Calcd. for $C_{14}H_{13}Br_2N_4$ (MH^+-H_2O) m/z 394.9507, found 394.9516.

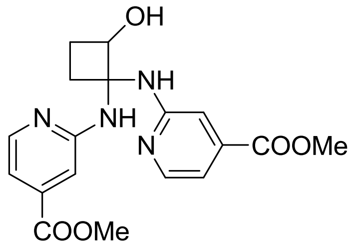


Conversion 73%. Orange oil. IR (neat): 3364, 2999, 2956, 2837, 1781, 1618, 1579, 1496, 1403, 1257, 1241, 1174, 1035 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 2.9 Hz, 1H), 7.71 (d, *J* = 2.6 Hz, 1H), 7.01 – 6.99 (m, *J* = 9.0, 3.0, 1.0 Hz, 2H), 6.37 – 6.33 (m, 2H), 6.16 (br s, 1H), 5.77 (br s, 1H), 4.35 (t, *J* = 8.5 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 2.43 – 2.38 (m, 1H), 2.23 – 2.21 (m, 1H), 2.06 – 1.98 (m, 1H), 1.95 – 1.89 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.1, 151.9, 149.0, 148.6, 132.6, 132.0, 126.4, 125.7, 111.5, 111.0, 71.1, 71.0, 56.4, 56.3, 26.2, 24.7. HRMS (ESI) Calcd. for $C_{16}H_{19}N_4O_2$ (MH^+-H_2O) m/z 299.1502, found 299.1499.



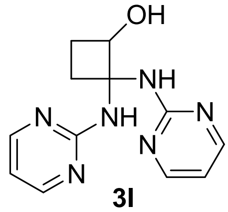
3j

Conversion 67%; the crude mixture, diluted with CH_2Cl_2, was purified by filtration through a pad of silica gel to give the title compound as an orange oil. IR (neat): 3364, 2983, 2953, 1787, 1615, 1572, 1502, 1456, 1267, 1234 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.29 (br s, 1H), 6.26 (s, 1H), 6.24 (s, 1H), 6.05 (s, 1H), 6.01 (s, 1H), 5.88 (br s, 1H), 4.34 (t, *J* = 8.6 Hz, 1H), 2.45 (t, *J* = 10.0 Hz, 1H), 2.32 (s, 6H), 2.21 (dd, *J* = 9.7, 7.5 Hz, 1H), 2.11 (s, 3H), 2.09 (s, 3H), 2.04 – 1.92 (m, 1H), 1.90 – 1.84 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.8, 156.6, 155.3, 155.1, 149.0, 148.2, 114.2, 113.5, 107.0, 106.4, 70.7, 70.6, 26.3, 24.6, 21.06 (2C), 21.00, 20.9. HRMS (ESI) Calcd. for $C_{18}H_{23}N_4$ (MH^+-H_2O) m/z 295.1917, found 295.1920.



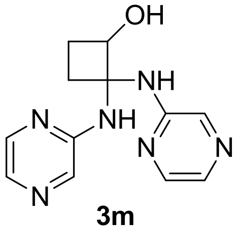
3k

Conversion 33%; purified by reprecipitation (CH_2Cl_2/Et_2O) to give the title compound as a white solid. IR (neat): 3380, 3205, 2983, 2956, 1784, 1724, 1612, 1562, 1502, 1486, 1439, 1390, 1297, 1251, 1112 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 5.2 Hz, 1H), 8.12 (d, *J* = 5.4 Hz, 1H), 7.06 – 7.05 (m, 2H), 7.02 – 6.99 (m, 2H), 6.57 (br s, 1H), 6.26 (br s, 1H), 4.38 (t, *J* = 8.2 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.49 – 2.44 (m, 1H), 2.26 – 2.23 (m, 1H), 2.06 – 1.98 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 165.8, 157.3, 157.2, 148.4, 148.0, 138.9, 138.5, 112.1, 111.7, 110.9, 110.3, 70.7, 70.3, 52.5, 52.4, 25.9, 24.5. HRMS (ESI) Calcd. for $C_{18}H_{19}N_4O_4$ (MH^+-H_2O) m/z 355.1409, found 355.1398.



3l

Conversion 95%; purified by reprecipitation (CH_2Cl_2/Et_2O) to give the title compound as a white solid; m. p. = 174–178 °C. IR (neat): 3377, 3231, 2983, 1588, 1562, 1532, 1496, 1453, 1416, 1393, 1277, 1174 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.28 – 8.26 (m, 4H), 6.83 (s, 1H), 6.70 (s, 1H), 6.59 – 6.54 (m, 2H), 4.42 (t, *J* = 8.3 Hz, 1H), 2.51 – 2.47 (m, 1H), 2.28 – 2.23 (m, 1H), 2.10 – 1.97 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.1, 160.9, 158.08, 158.03, 111.4, 111.3, 70.5, 69.2, 26.3, 24.5. HRMS (ESI) Calcd. for $C_{12}H_{13}N_6$ (MH^+-H_2O) m/z 241.1196, found 241.1194. A single crystal suitable for X-ray single-crystal structure determination was obtained by slow diffusion of hexane into a solution of **3l** in $CHCl_3$.

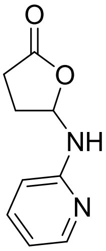


3m

Conversion 94%; purified by reprecipitation (CH_2Cl_2/Et_2O) to give the title compound as a white solid; m. p. = 144–149°C. IR (neat): 3334, 3244, 2983, 2897, 1588, 1519, 1423, 1396, 1290, 1204, 1148 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 – 7.96 (m, 1H), 7.93 (d, *J* = 1.4 Hz, 1H), 7.92 (dd, *J* = 2.8, 1.4 Hz, 1H), 7.90 (d, *J* = 1.3 Hz, 1H), 7.84 (d, *J* = 2.9 Hz, 1H), 7.81 (d, *J* = 2.8 Hz, 1H), 6.34 (s, 1H), 6.19 (s, 1H), 4.39 (t, *J* = 8.4 Hz, 1H), 2.47 – 2.42 (m, 1H), 2.32 – 2.27 (m, 1H), 2.09 – 1.97 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.9, 152.7, 141.3, 140.7, 135.3, 134.7, 133.6, 133.1, 70.3, 70.1, 25.7, 24.5. HRMS (ESI) Calcd. for $C_{12}H_{13}N_6$ (MH^+-H_2O) m/z 241.1196, found 241.1210.

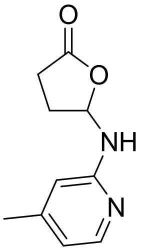
Step 2:

To a stirred solution of **3** (crude sample; 419 µmol) in CH_2Cl_2 (2 mL) at 0°C was added Dess-Martin periodinane (419 µmol, 0.178 g) and the reaction mixture was stirred at the same temperature for 6h. The precipitate was filtered and then the mixture was quenched with sat. $NaHCO_3$ aq. and extracted twice with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude mixture was purified by flash column chromatography (SiO_2, petroleum ether/ether = 5:1→1:1) to give compound **7**. Yields refer to chromatographically pure materials.



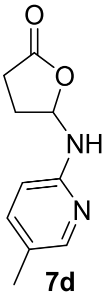
7a

Yield 65% (0.049 g) over two steps; yellow oil. IR (neat): 3450, 2974, 1708, 1590, 1573, 1474, 1435, 1394, 1304, 1215 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.32 – 8.31 (m, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 7.74 (ddd, *J* = 8.4, 7.4, 1.9 Hz, 1H), 7.08 (ddd, *J* = 7.3, 5.0, 0.9 Hz, 1H), 6.06 (dd, *J* = 6.7, 2.0 Hz, 1H), 2.92 – 2.84 (m, 1H), 2.58 – 2.52 (m, 1H), 2.39 – 2.31 (m, 1H), 2.12 (dddd, *J* = 13.5, 9.8, 3.6, 2.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 151.7, 147.2, 138.4, 120.1, 115.3, 83.8, 30.9, 25.4. HRMS (ESI) Calcd. for $C_9H_{11}N_2O_2$ $(M+H)^+$ m/z 179,081503, found 179,0815.



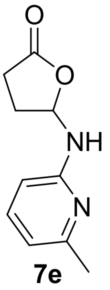
7c

Yield 72% (0.058 g) over two steps; yellow oil. IR (neat): 3431, 2974, 1704, 1607, 1563, 1479, 1413, 1295, 1217, 1065 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.16 (d, *J* = 5.1 Hz, 1H), 8.07 – 8.05 (m, 1H), 6.93 – 6.90 (m, 1H), 6.03 (dd, *J* = 6.7, 2.0 Hz, 1H), 2.88 (ddd, *J* = 17.7, 9.8, 8.7 Hz, 1H), 2.55 (ddd, *J* = 17.6, 9.9, 3.6 Hz, 1H), 2.38 (s, 3H), 2.36 – 2.30 (m, 1H), 2.11 (dddd, *J* = 13.6, 9.8, 3.6, 2.0 Hz, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 174.4, 151.7, 150.0, 146.8, 121.4, 115.8, 84.0, 31.0, 25.4, 21.5. HRMS (ESI) Calcd. for $C_{10}H_{13}N_2O_2$ (M+H)$^+$ m/z 193,097153, found 193,0975.



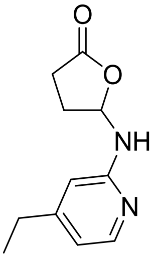
7d

Yield 67% (0.054 g) over two steps; yellow oil. IR (neat): 3429, 2976, 1708, 1604, 1573, 1486, 1382, 1304, 1210 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.12 – 8.11 (m, 2H), 7.57 – 7.54 (m, 1H), 6.02 (dd, *J* = 6.7, 2.0 Hz, 1H), 2.87 (ddd, *J* = 17.6, 9.7, 8.7 Hz, 1H), 2.54 (ddd, *J* = 17.5, 9.9, 3.6 Hz, 1H), 2.38 – 2.30 (m, 1H), 2.31 (s, 3H), 2.13 – 2.07 (m, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 174.2, 149.6, 147.1, 139.1, 129.5, 114.8, 84.0, 30.9, 25.5, 17.9. HRMS (ESI) Calcd. for $C_{10}H_{13}N_2O_2$ (M+H)$^+$ m/z 193,097153, found 193,0976.



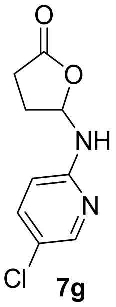
7e

Yield 50% (0.041 g) over two steps; yellow oil. IR (neat): 3450, 2976, 1708, 1578, 1454, 1389, 1309, 1277, 1159 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.01 (d, *J* = 8.3 Hz, 1H), 7.64 – 7.61 (m, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 6.04 (dd, *J* = 6.7, 2.0 Hz, 1H), 2.87 (ddd, *J* = 17.7, 9.8, 8.7 Hz, 1H), 2.55 (ddd, *J* = 17.5, 9.9, 3.6 Hz, 1H), 2.49 (s, 3H), 2.34 (dddd, *J* = 13.6, 9.9, 8.7, 6.7 Hz, 1H), 2.14 – 2.08 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 156.4, 151.1, 138.8, 119.5, 112.2, 84.0, 31.0, 25.4, 24.4. HRMS (ESI) Calcd. for $C_{10}H_{13}N_2O_2$ $(M+H)^+$ m/z 193,097153, found 193,0971.



7f

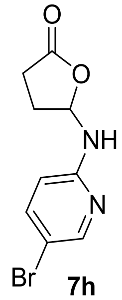
Yield 53% (0.046 g) over two steps; yellow oil. IR (neat): 3441, 2971, 2877, 1711, 1607, 1561, 1483, 1420, 1309, 1217 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 5.1 Hz, 1H), 8.09 (d, *J* = 0.5 Hz, 1H), 6.95 – 6.93 (m, 1H), 6.03 (dd, *J* = 6.7, 2.0 Hz, 1H), 2.91 – 2.84 (m, 1H), 2.68 (q, *J* = 7.6 Hz, 2H), 2.54 (ddd, *J* = 17.5, 9.9, 3.6 Hz, 1H), 2.33 (dddd, *J* = 13.7, 9.8, 8.7, 6.7 Hz, 1H), 2.11 (dddd, *J* = 13.5, 9.8, 3.6, 2.0 Hz, 1H), 1.26 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 156.0, 151.9, 146.9, 120.1, 114.6, 84.0, 31.0, 28.7, 25.4, 14.5. HRMS (ESI) Calcd. for $C_{11}H_{15}N_2O_2$ $(M+H)^+$ m/z 207,112803, found 207,1125.



7g

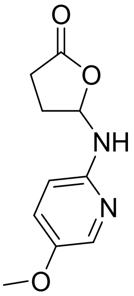
Yield 55% (0.049 g) over two steps; white solid; m. p. = 102–105 °C; IR (neat): 3279, 2962, 1684, 1578, 1466, 1372, 1297, 1212, 1108, 1065 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 – 8.26 (m, 2H), 7.71 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.04 (dd, *J* = 6.7, 1.9 Hz, 1H), 2.89 (ddd, *J* = 17.9, 9.7, 8.8 Hz, 1H), 2.56 (ddd, *J* = 17.6, 9.9, 3.6 Hz, 1H), 2.35

(dddd, J = 13.7, 9.8, 8.8, 6.7 Hz, 1H), 2.13 (dddd, J = 13.5, 9.8, 3.5, 2.0 Hz, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 174.3, 149.9, 146.0, 138.3, 127.5, 116.0, 83.7, 30.9, 25.5. HRMS (ESI) Calcd. for $C_9H_{10}ClN_2O_2$ $(M+H)^+$ m/z 213,042531, found 213,0429.

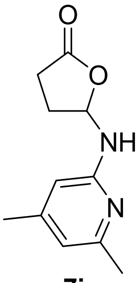


7h

Yield 57% (0.062 g) over two steps; yellow oil. IR (neat): 3409, 3061, 2959, 1687, 1575, 1471, 1372, 1300, 1210, 1072 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.38 – 8.36 (m, 1H), 8.22 (dd, J = 8.9, 0.5 Hz, 1H), 7.84 (dd, J = 8.9, 2.5 Hz, 1H), 6.03 (dd, J = 6.7, 2.0 Hz, 1H), 2.92 – 2.85 (m, 1H), 2.55 (ddd, J = 17.6, 9.8, 3.6 Hz, 1H), 2.39 – 2.31 (m, 1H), 2.12 (dddd, J = 13.6, 9.8, 3.6, 2.0 Hz, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 174.4, 150.3, 148.2, 141.0, 116.5, 115.4, 83.7, 30.9, 25.5. HRMS (ESI) Calcd. for $C_9H_{10}BrN_2O_2$ $(M+H)^+$ m/z 237,086983, found 237,0868.

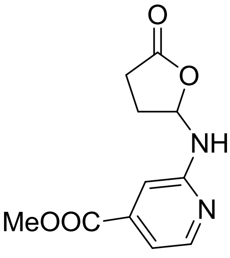


Yield 51% (0.043 g) over two steps; orange oil. IR (neat): 3440, 2950, 2840, 1694, 1575, 1482, 1446, 1396, 1274, 1244, 1241, 1214, 1032, 1012 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.16 (d, J = 9.1 Hz, 1H), 7.99 (d, J = 2.9 Hz, 1H), 7.31 (dd, J = 9.1, 3.1 Hz, 1H), 6.00 (dd, J = 6.6, 1.8 Hz, 1H), 3.85 (s, 3H), 2.91 – 2.83 (m, 1 H), 2.54 (ddd, J = 17.5, 9.9, 3.5 Hz, 1H), 2.34 (dddd, J = 13.7, 9.8, 8.7, 6.7 Hz, 1H), 2.11 (dddd, J = 11.7, 9.8, 3.4, 1.9 Hz, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 174.0, 153.1, 133.7, 124.0, 116.0, 84.1, 56.0, 30.8, 25.6. HRMS (ESI) Calcd. For $C_{10}H_{13}N_2O_3$ $(M+H)^+$ m/z 209.0921, found 209.0926.



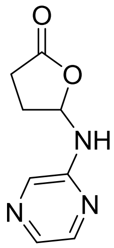
7j

Yield 43% (0.037 g) over two steps; yellow oil. IR (neat): 3448, 2981, 1711, 1612, 1575, 1420, 1387, 1338, 1234, 1164 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.83 (s, 1H), 6.78 (s, 1H), 6.00 (dd, *J* = 6.7, 2.0 Hz, 1H), 2.86 (ddd, *J* = 17.6, 9.8, 8.6 Hz, 1H), 2.54 (ddd, *J* = 17.5, 9.9, 3.7 Hz, 1H), 2.43 (s, 3H), 2.36 – 2.27 (m, 1H), 2.33 (s, 3H), 2.10 (dddd, *J* = 15.6, 9.9, 3.6, 2.0 Hz, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 174.3, 155.9, 151.1, 150.2, 120.7, 112.8, 84.2, 31.0, 25.4, 24.1, 21.4. HRMS (ESI) Calcd. for $C_{11}H_{15}N_2O_2$ $(M+H)^+$ m/z 207,112803, found 207,1128.



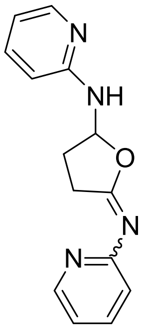
7k

Yield 20% (0.019 g) over two steps; white solid; m. p. = 144-147 °C; IR (neat): 3429, 2957, 1730, 1694, 1602, 1563, 1479, 1440, 1406, 1300, 1246, 1212 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.78 (s, 1H), 8.45 (d, *J* = 5.1 Hz, 1H), 7.65 (dd, *J* = 5.2, 1.4 Hz, 1H), 6.11 – 6.00 (m, 1H), 5.04 (br s, 1H), 3.96 (s, 3H), 2.95 – 2.87 (m, 1H), 2.63 – 2.55 (m, 1H), 2.40 – 2.33 (m, 1H), 2.19 – 2.10 (m, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 174.4, 165.4, 152.5, 148.0, 140.0, 119.4, 115.0, 83.9, 52.9, 30.9, 25.5. HRMS (ESI) Calcd. for $C_{11}H_{13}N_2O_4$ $(M+H)^+$ m/z 237,086983, found 237,0868.



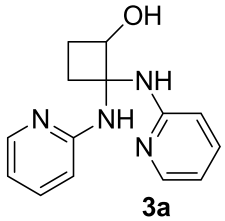
7m

Yield 56% (0.042 g) over two steps; white solid; m. p. = 107–109 °C; IR (neat): 3349, 2976, 1713, 1481, 1416, 1304, 1210, 1065 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.61 (d, *J* = 1.3 Hz, 1H), 8.40 (d, *J* = 2.6 Hz, 1H), 8.29 (dd, *J* = 2.5, 1.5 Hz, 1H), 6.06 (dd, *J* = 6.6, 1.9 Hz, 1H), 2.96 – 2.88 (m, 1H), 2.59 (ddd, *J* = 17.7, 9.8, 3.5 Hz, 1H), 2.44 – 2.36 (m, 1H), 2.18 (dddd, *J* = 13.5, 9.8, 3.4, 1.9 Hz, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 174.3, 148.2, 141.2, 140.3, 138.3, 83.2, 30.6, 26.0. HRMS (ESI) Calcd. for $C_8H_{10}N_3O_2$ (M+H)$^+$ m/z 180,076752, found 180,0763.



6

Yield 7% (0.007 g); brown resin; IR (neat): 3450, 3066, 2953, 1648, 1588, 1559, 1479, 1463, 1433, 1396, 1307, 1218, 1065 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.61 (d, *J* = 8.5 Hz, 1H), 8.38 (dd, *J* = 4.9, 1.1 Hz, 1H), 8.37 – 8.29 (m, 1H), 7.70 – 7.69 (m, 1H), 7.61 (td, *J* = 7.9, 1.9 Hz, 1H), 7.02 (ddd, *J* = 7.2, 5.0, 0.8 Hz, 1H), 6.95 (ddd, *J* = 7.3, 5.0, 0.9 Hz, 1H), 6.87 – 6.85 (m, 1H), 6.09 (dd, *J* = 5.6, 2.5 Hz, 1H), 5.43 (br s, 1H), 2.97– 2.90 (m, 1H), 2.86 – 2.79 (m, 1H), 2.29 – 2.20 (m, 1H), 2.09 – 2.03 (m, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 162.7, 161.4, 153.0, 148.7, 147.0, 138.0, 137.7, 119.0, 118.4, 117.1, 116.4, 85.1, 27.4, 27.1. HRMS (ESI) Calcd. for $C_{14}H_{14}N_4O$ (M+H)$^+$ m/z 255,124000, found 255,1249.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NH
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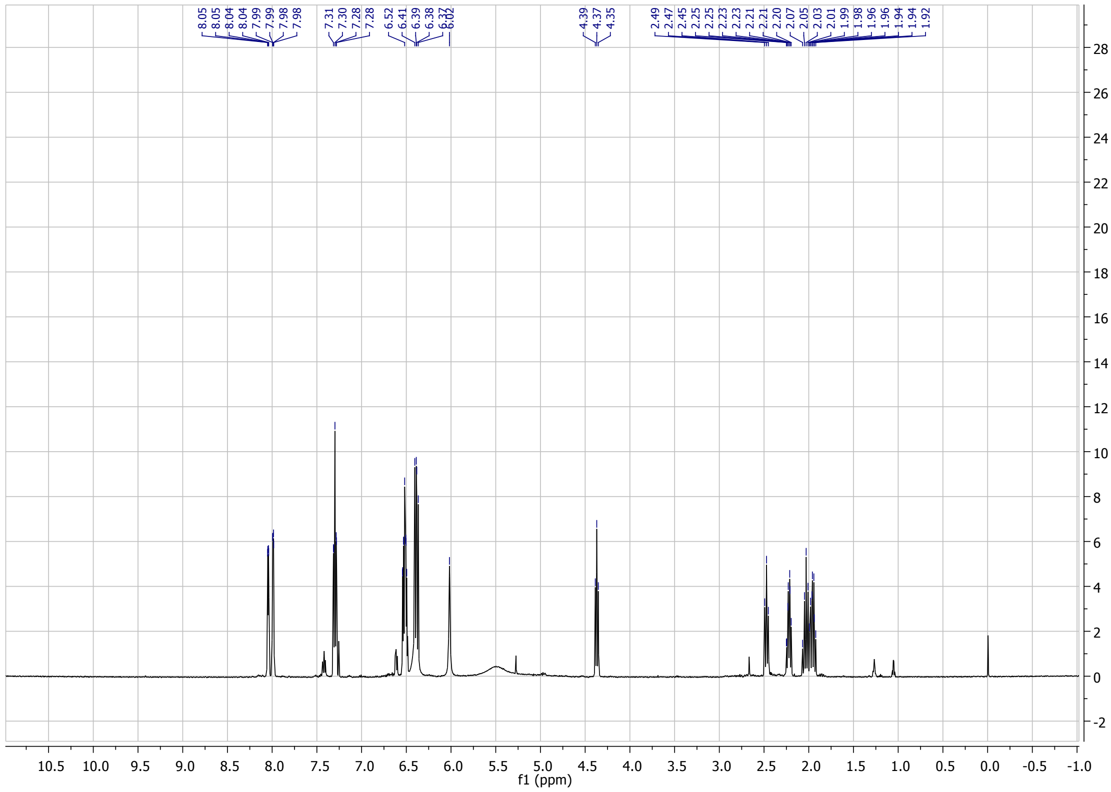
3a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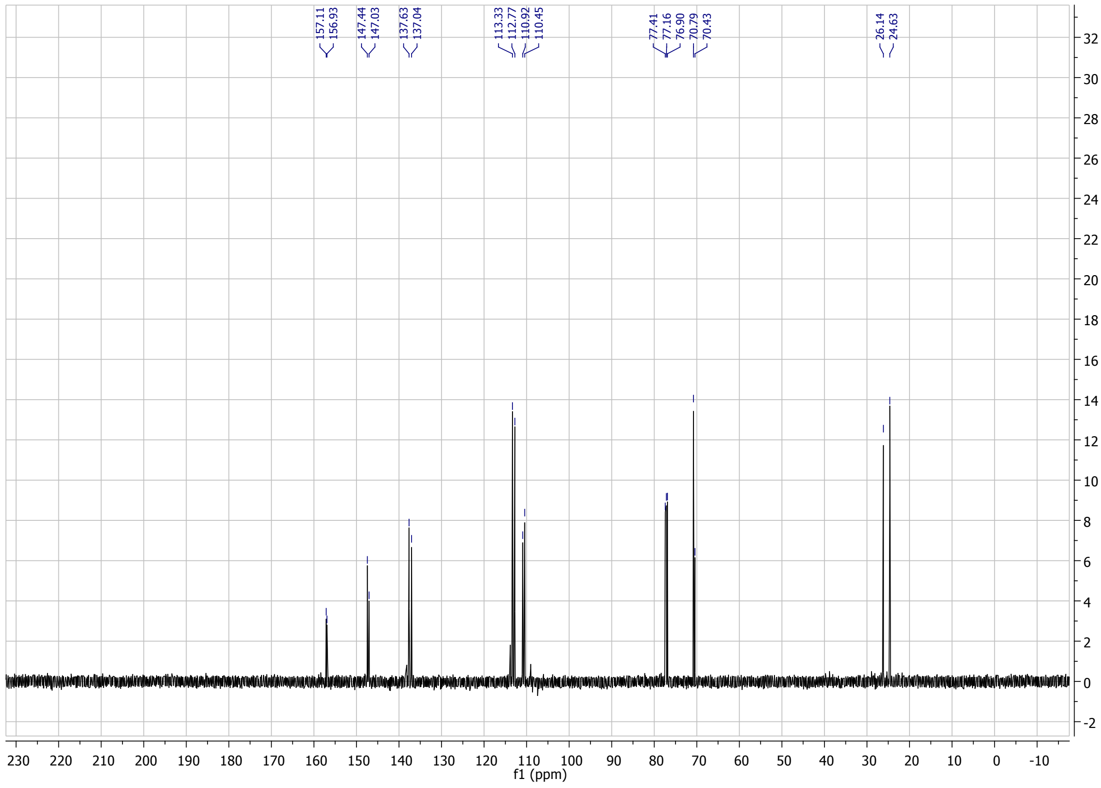
f1 (ppm)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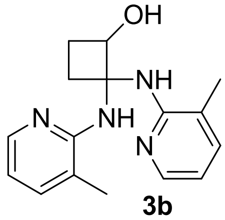
f1 (ppm)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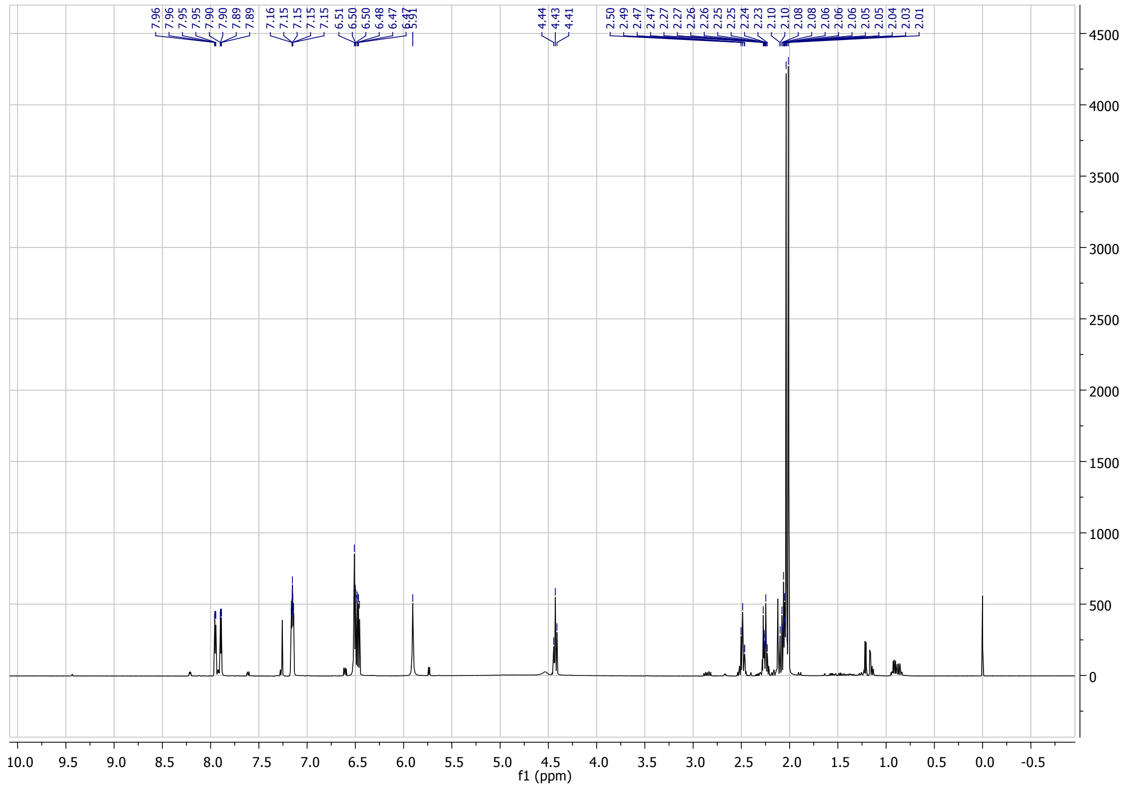
3b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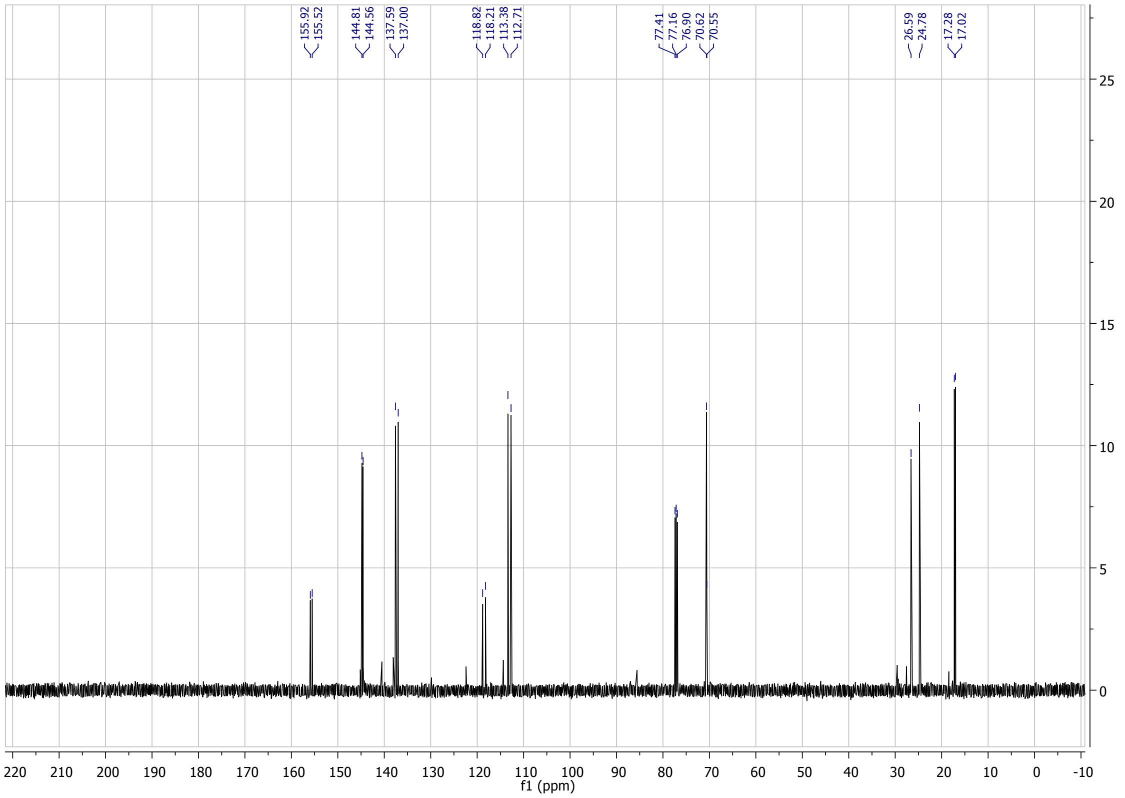
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70.55
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24.78
17.28
17.02
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15
10
5
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220
210
200
190
180
170
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100
90
80
70
60
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40
30
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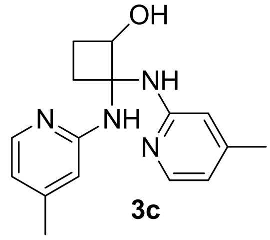
f1 (ppm)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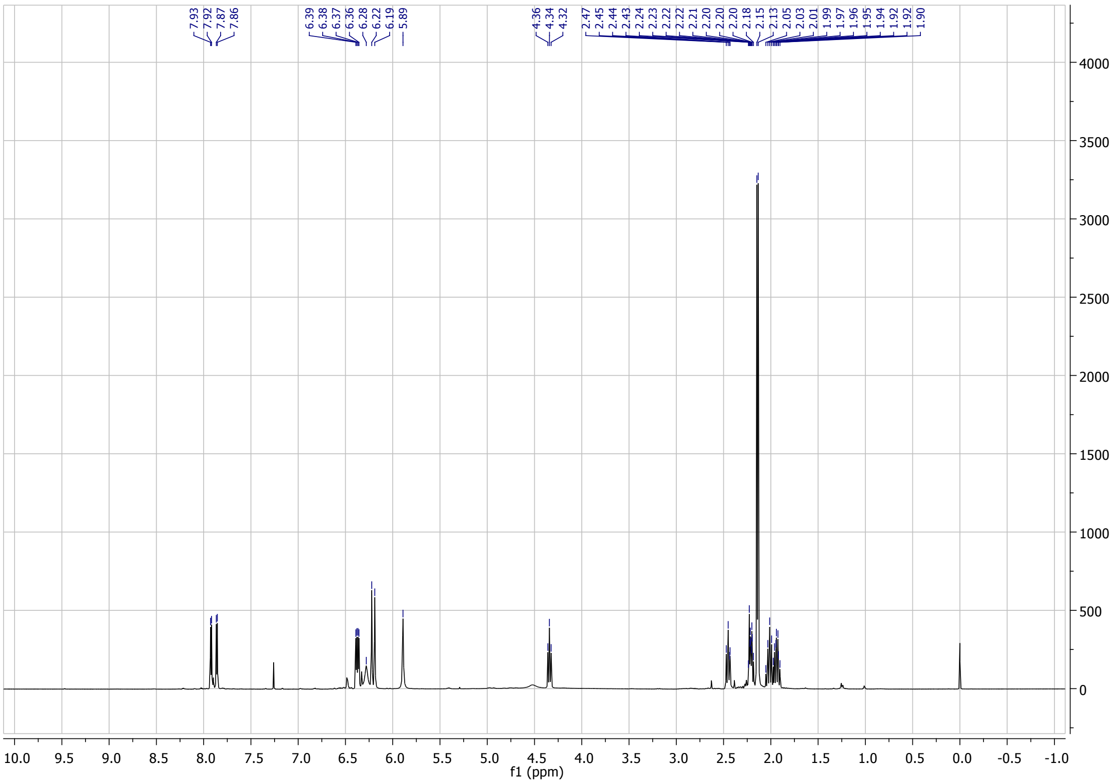
N
NH
N

3c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1.94
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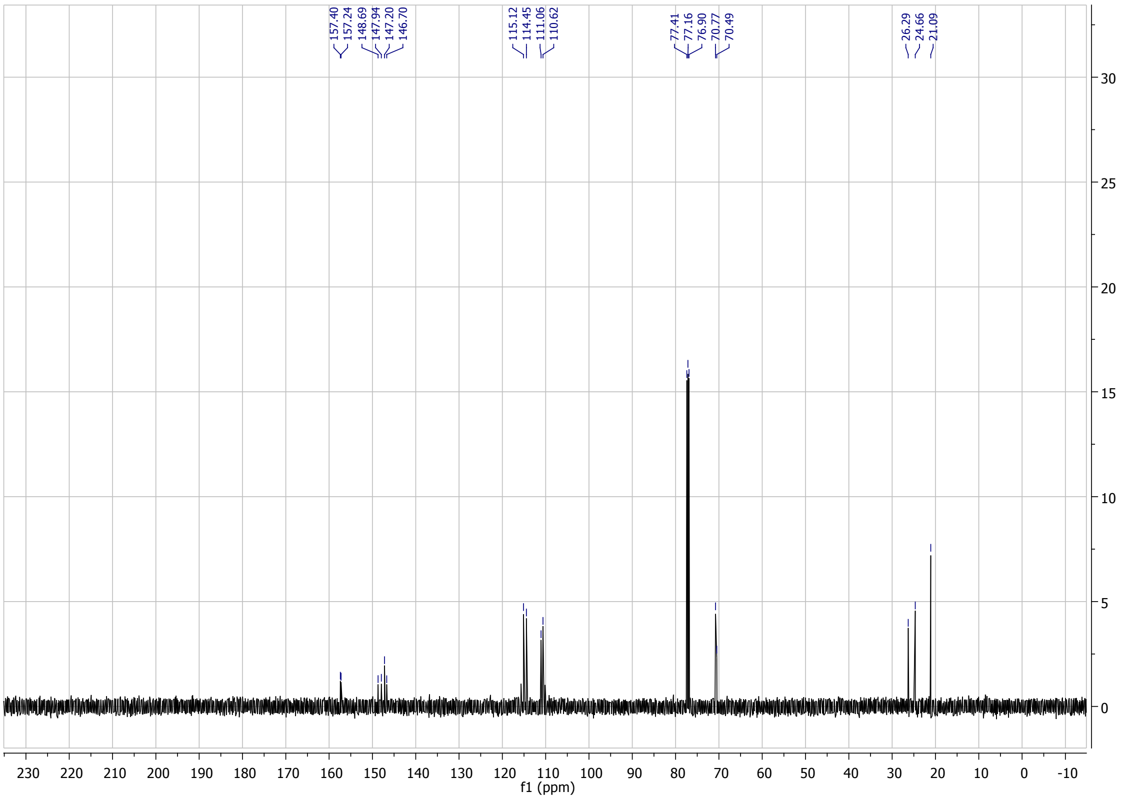
f1 (ppm)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70.49
26.29
24.66
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15
10
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0
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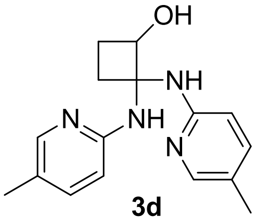
f1 (ppm)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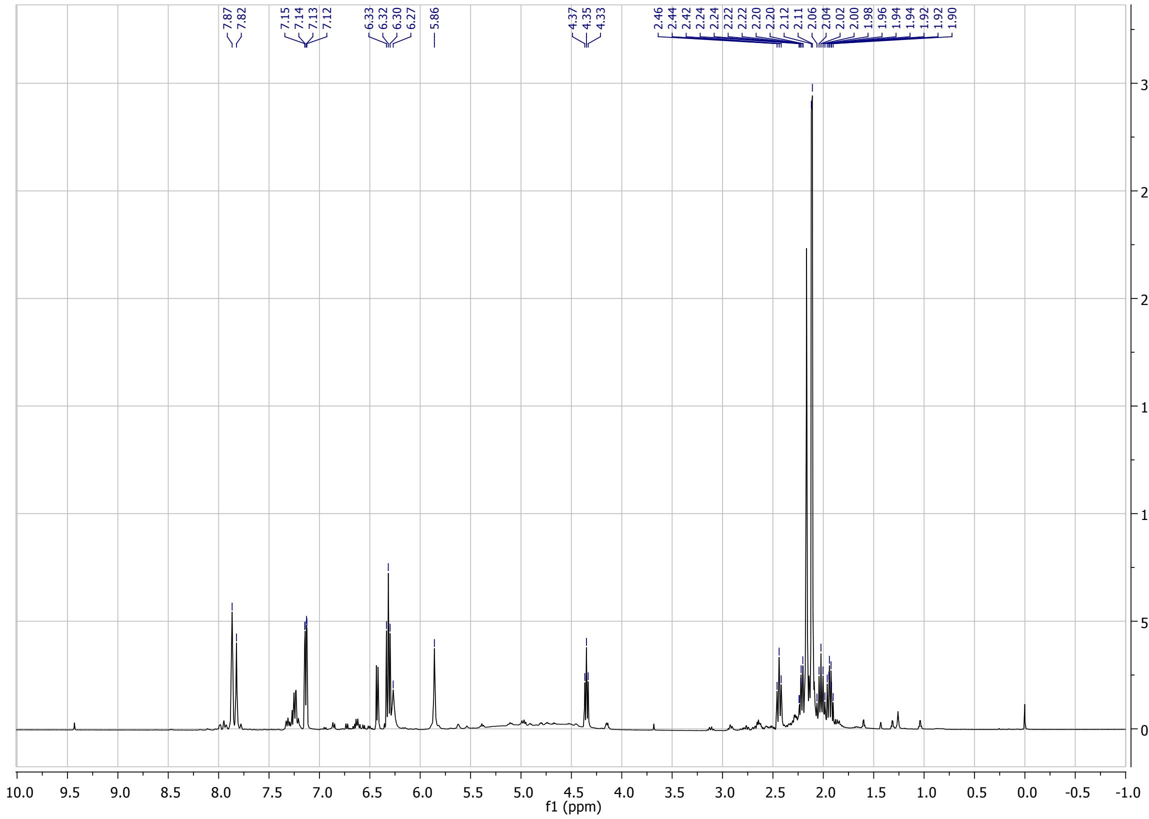
N

3d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2.44
2.42
2.24
2.24
2.22
2.22
2.20
2.20
2.12
2.11
2.06
2.04
2.02
2.00
1.98
1.96
1.94
1.94
1.92
1.92
1.90
3000
2500
2000
1500
1000
500
0
10.0
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
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0.0
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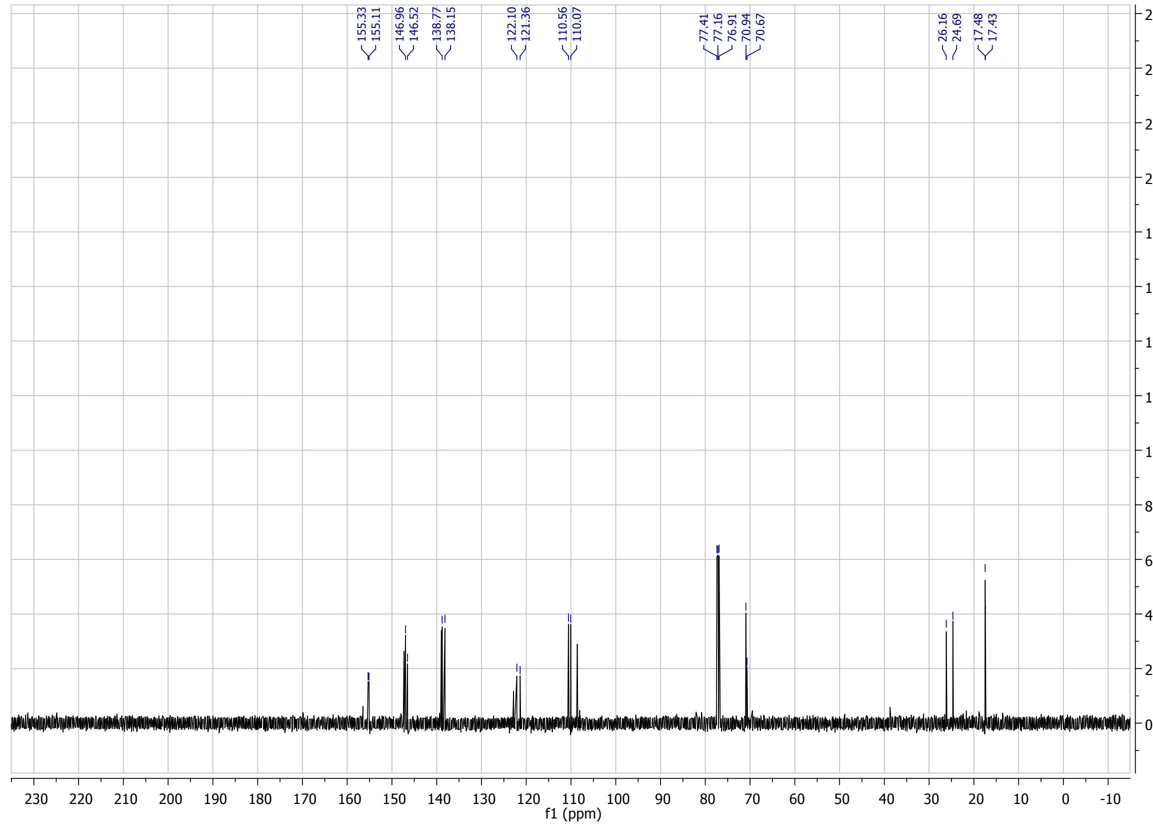
-1.0
f1 (ppm)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155.11
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146.52
138.77
138.15
122.10
121.36
110.56
110.07
77.41
77.16
76.91
70.94
70.67
26.16
24.69
17.48
17.43
26
24
22
20
18
16
14
12
10
8
6
4
2
0
230
220
210
200
190
180
170
160
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140
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120
110
100
90
80
70
60
50
40
30
20
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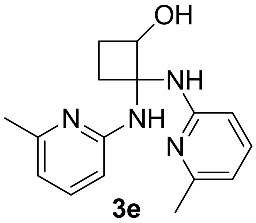
0
-10
f1 (ppm)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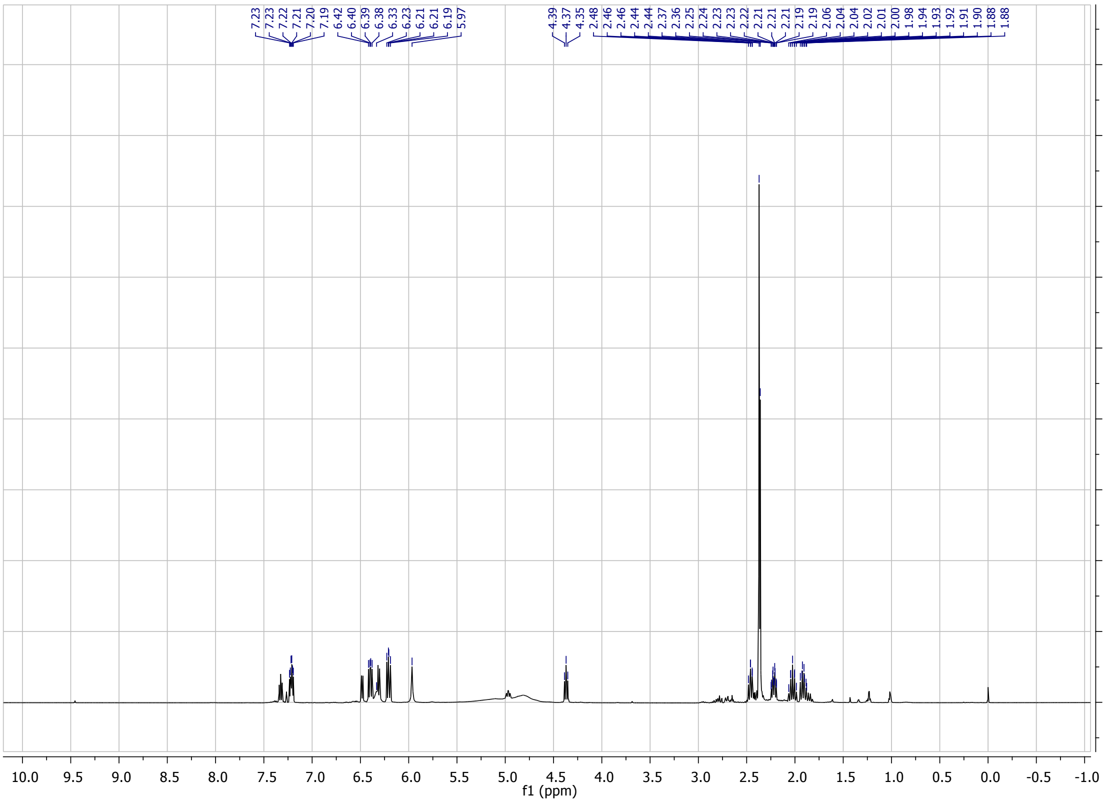
NH
N
NH
N

3e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7.23
7.22
7.21
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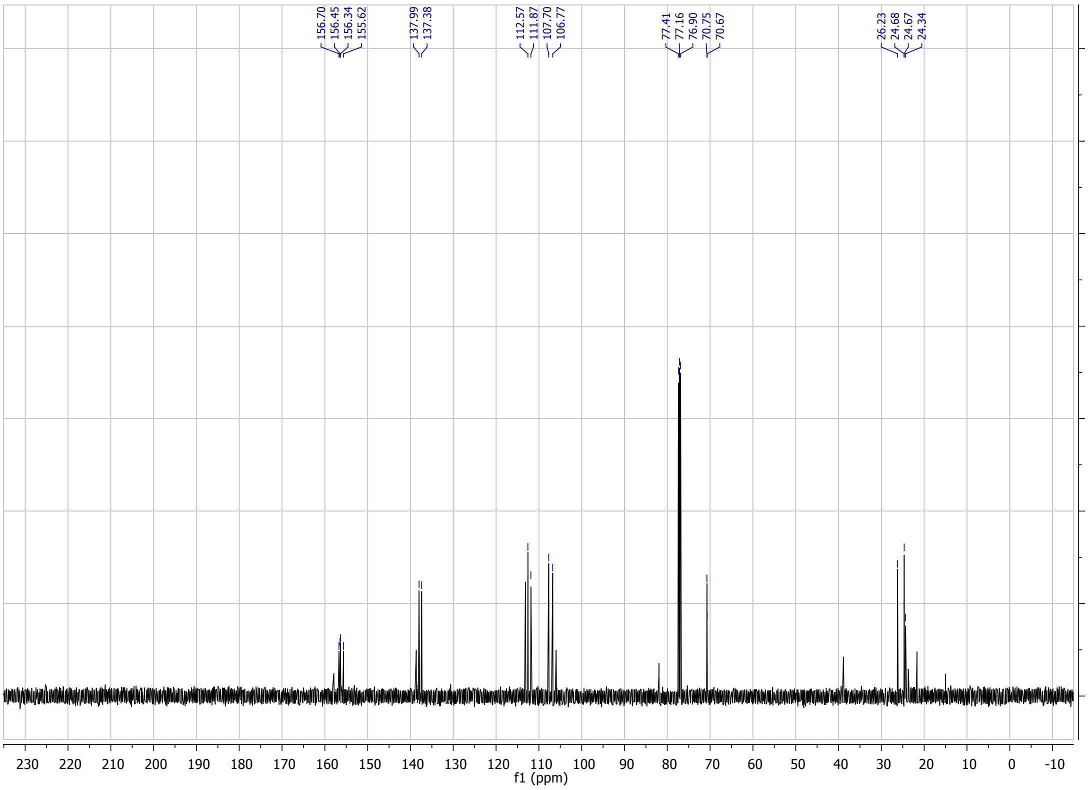
7.19
6.42
6.40
6.39
6.38
6.33
6.23
6.21
6.21
6.19
5.97
4.39
4.37
4.35
2.48
2.46
2.46
2.44
2.44
2.37
2.36
2.25
2.24
2.23
2.23
2.22
2.21
2.21
2.21
2.19
2.19
2.06
2.04
2.04
2.02
2.01
2.00
1.98
1.94
1.93
1.92
1.91
1.90
1.88
1.88
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
10.0
9.5
9.0
8.5
8.0
7.5
7.0
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
-0.5
-1.0
f1 (ppm)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156.45
156.34
155.62
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137.38
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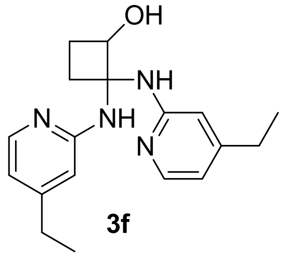
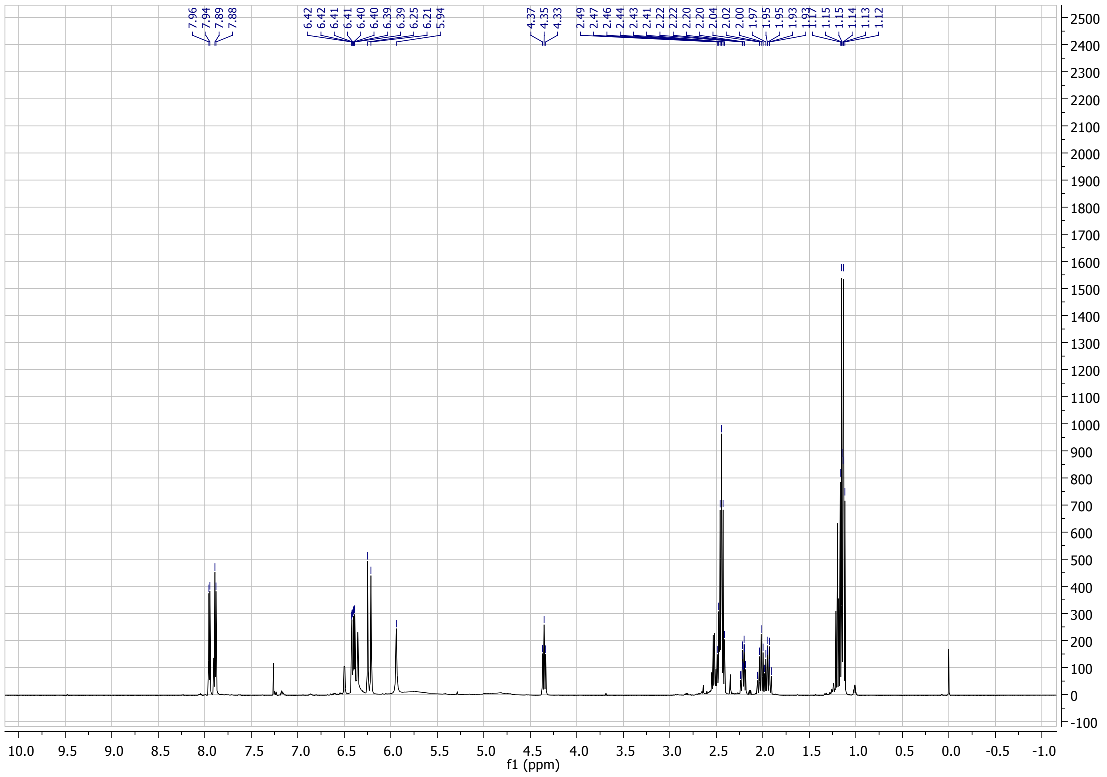
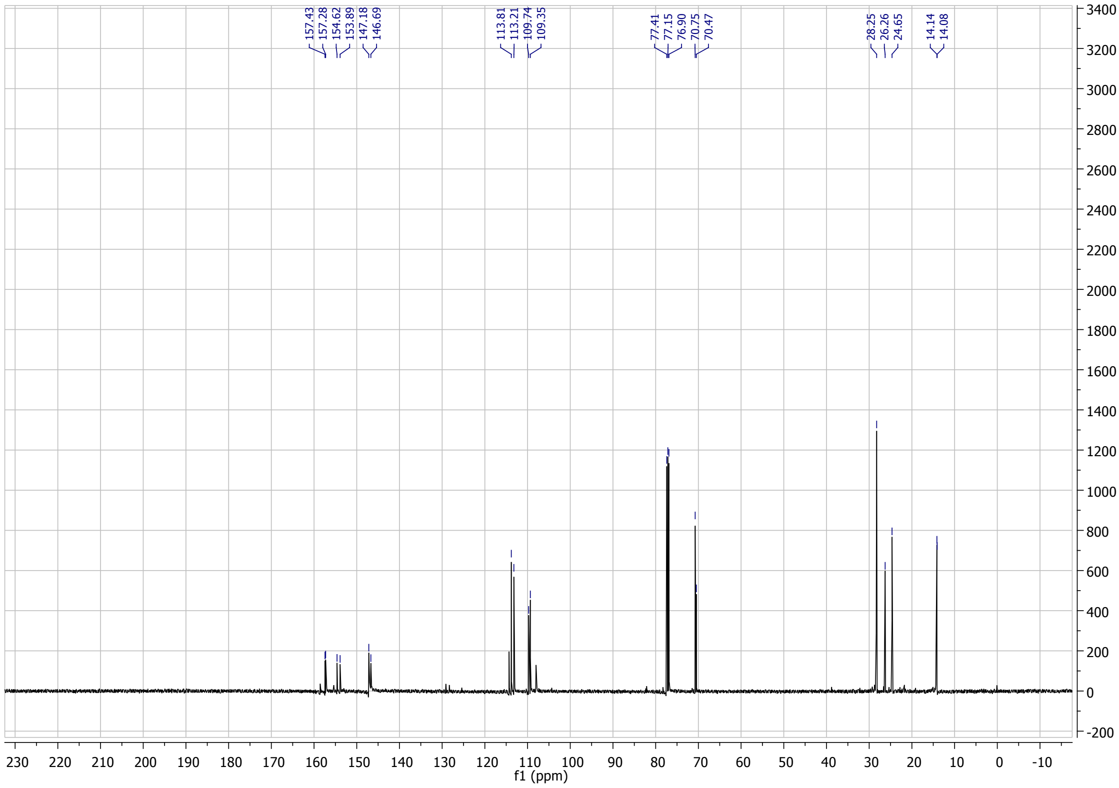
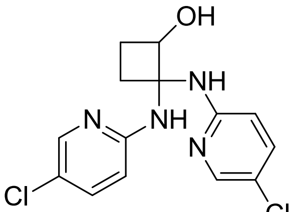
111.87
107.70
106.77
77.41
77.16
76.90
70.75
70.67
26.23
24.68
24.67
24.34
35
30
25
20
15
10
5
0
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
NH
N
NH
N

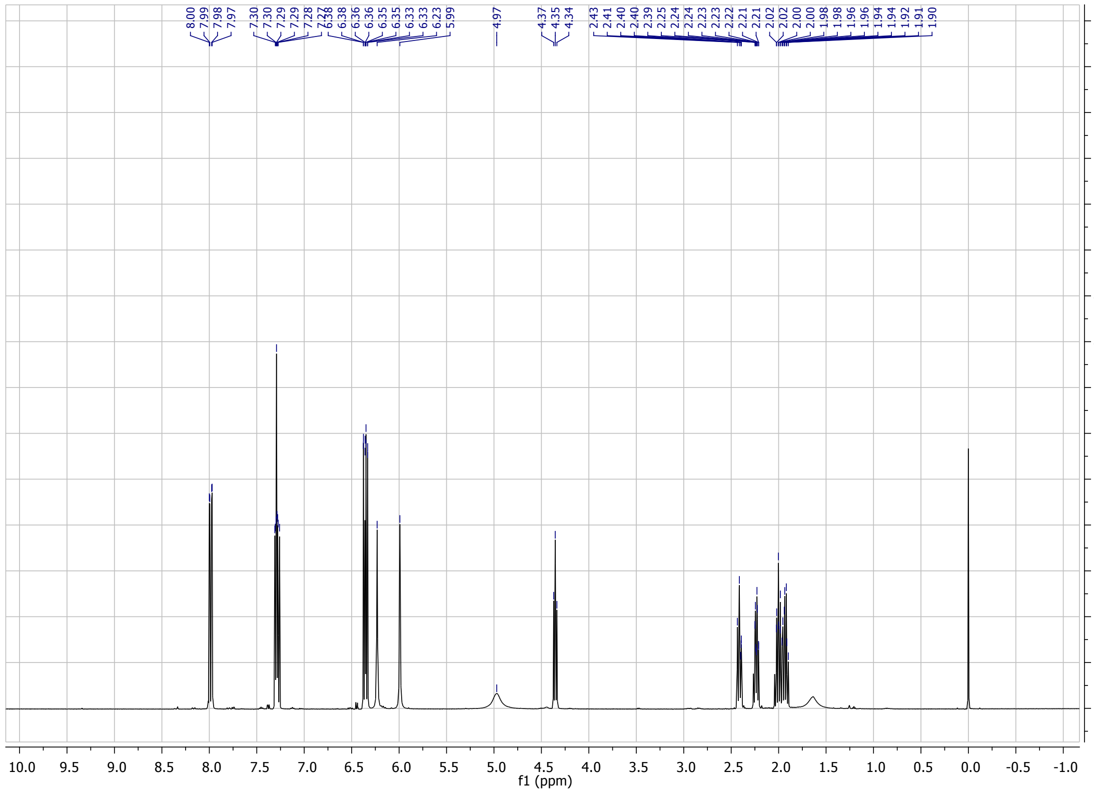
3f


7.96
7.94
7.89
7.88
6.42
6.42
6.41
6.41
6.40
6.40
6.39
6.39
6.25
6.21
5.94
4.37
4.35
4.33
2.49
2.47
2.46
2.44
2.43
2.41
2.22
2.22
2.20
2.20
2.04
2.02
2.00
1.97
1.95
1.95
1.93
1.93
1.17
1.15
1.15
1.14
1.13
1.12
f1 (ppm)


157.43
157.28
154.62
153.89
147.18
146.69
113.81
113.21
109.74
109.35
77.41
77.15
76.90
70.75
70.47
28.25
26.26
24.65
14.14
14.08
f1 (ppm)


OH
NH
NH
N
N
Cl
Cl

3g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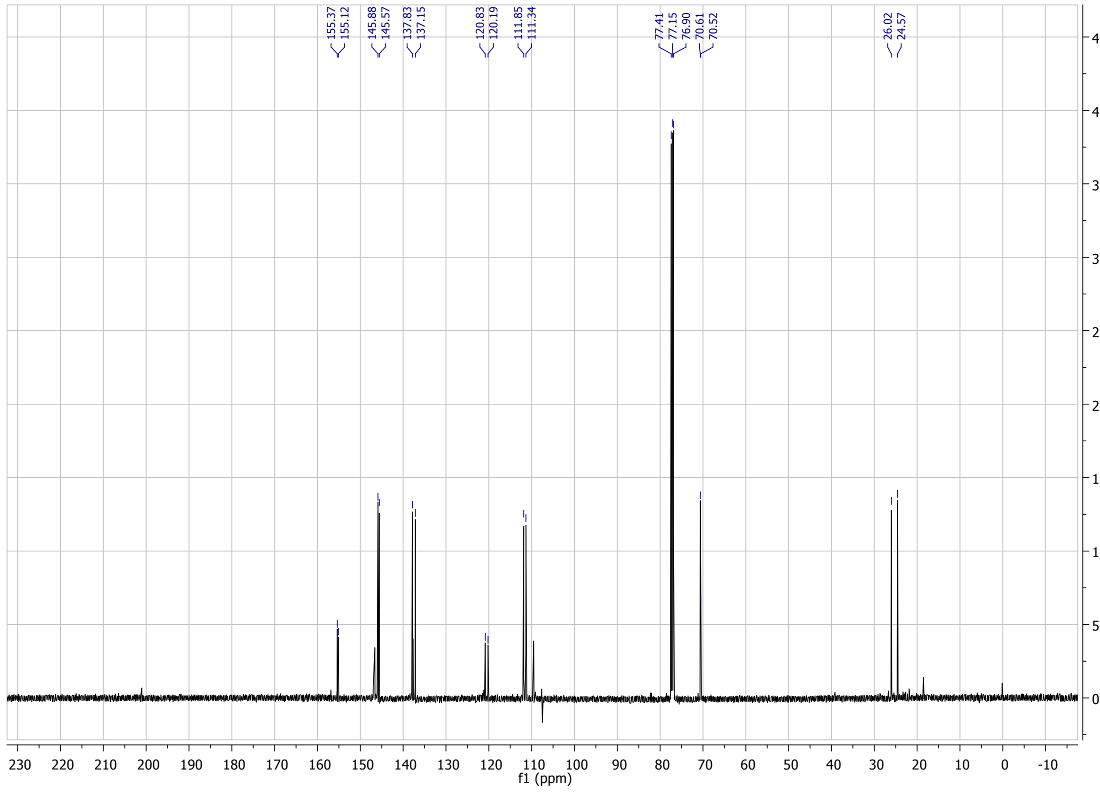
7.99
7.98
7.97
7.30
7.30
7.29
7.29
7.28
7.27
6.38
6.38
6.36
6.36
6.35
6.35
6.33
6.33
6.23
5.99
4.97
4.37
4.35
4.34
2.43
2.41
2.40
2.40
2.39
2.25
2.24
2.24
2.23
2.23
2.22
2.21
2.21
2.02
2.02
2.00
2.00
1.98
1.98
1.96
1.96
1.94
1.94
1.92
1.91
1.90
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10.0
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
-0.5
-1.0
f1 (ppm)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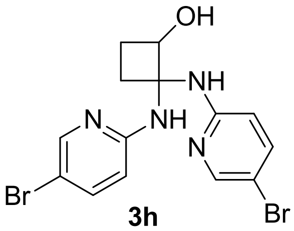
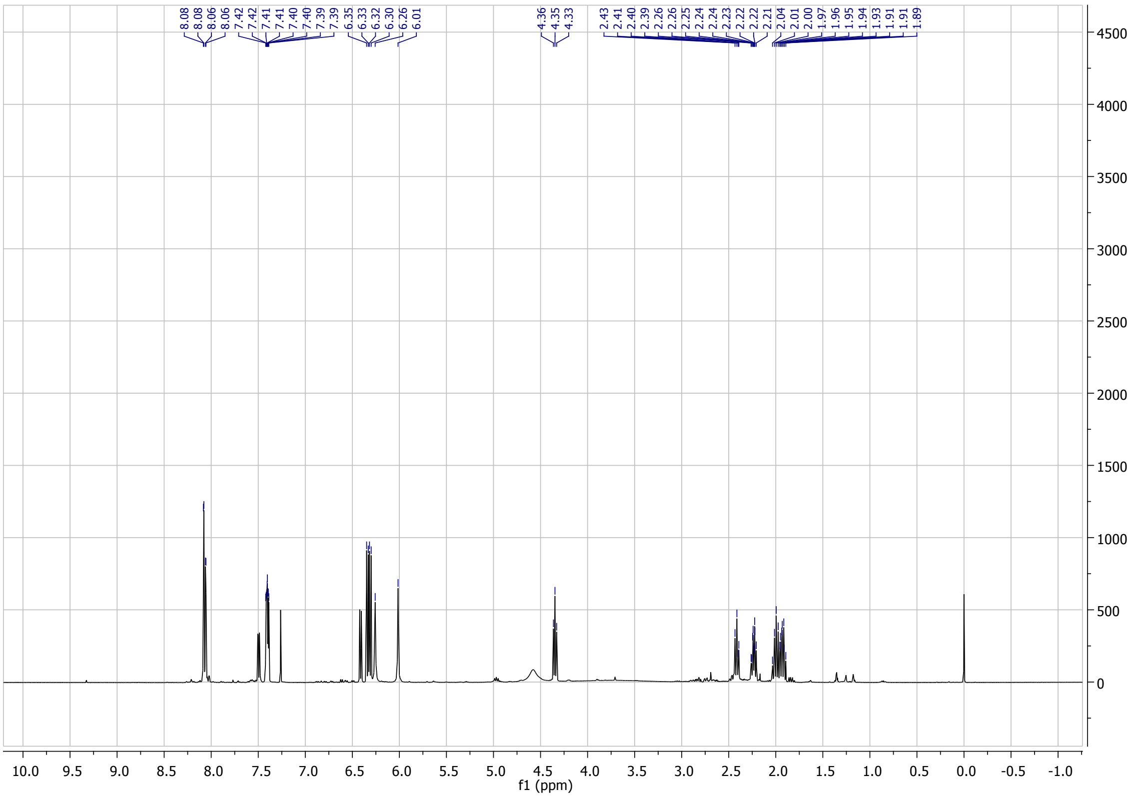
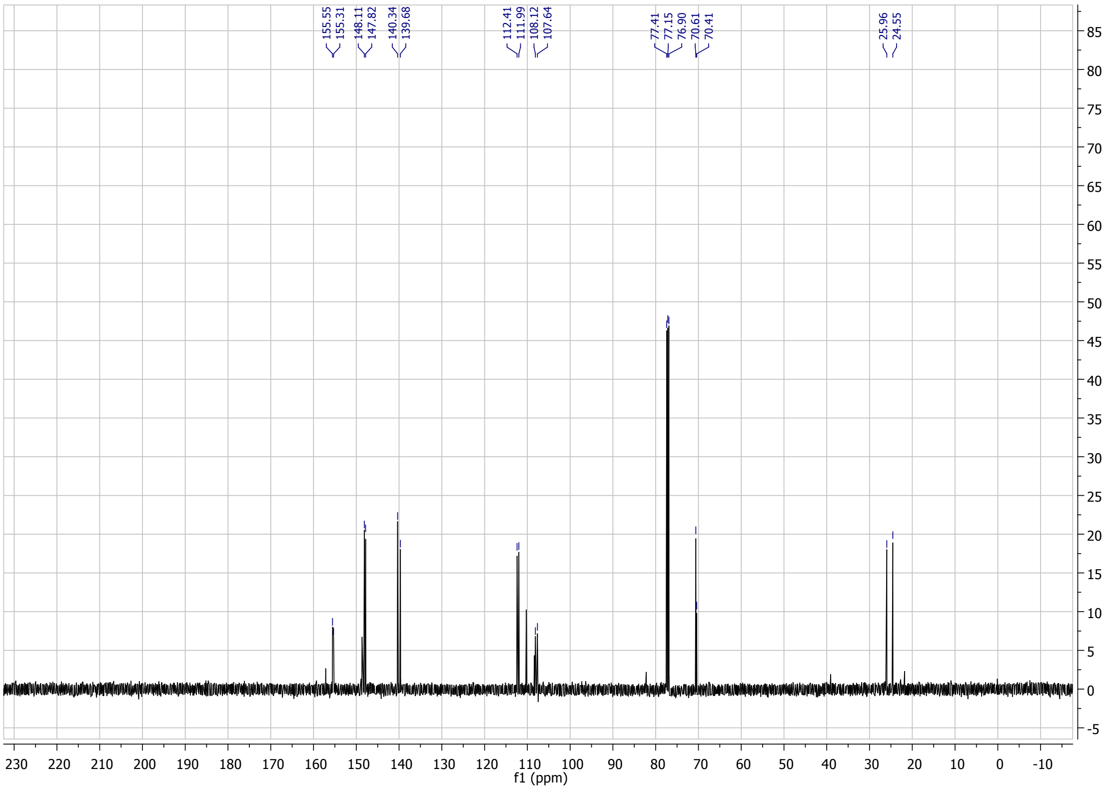
155.12
145.88
145.57
137.83
137.15
120.83
120.19
111.85
111.34
77.41
77.15
76.90
70.61
70.52
26.02
24.57
450
400
350
300
250
200
150
100
50
0
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
NH
NH
N
N
Br
Br

3h


8.08
8.08
8.06
8.06
7.42
7.42
7.41
7.41
7.40
7.40
7.39
7.39
6.35
6.33
6.32
6.30
6.26
6.01
4.36
4.35
4.33
2.43
2.41
2.40
2.39
2.26
2.25
2.24
2.24
2.23
2.22
2.22
2.21
2.04
2.01
2.00
1.97
1.96
1.95
1.94
1.93
1.91
1.91
1.89
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10.0
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
-0.5
-1.0
f1 (ppm)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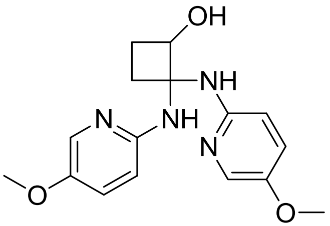
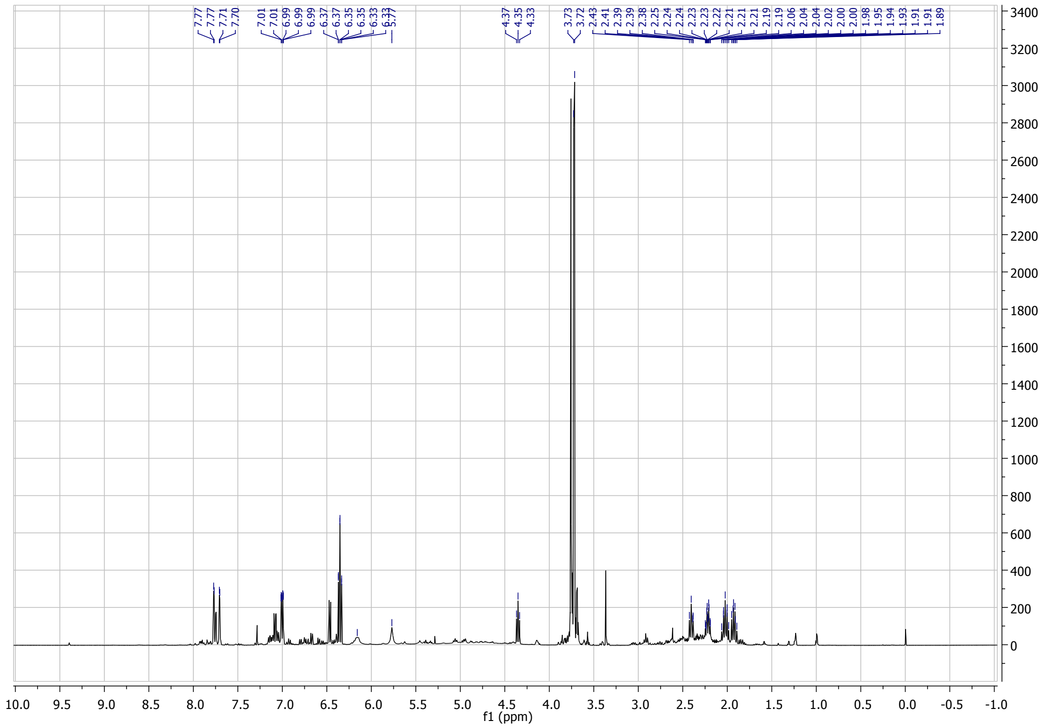
155.31
148.11
147.82
140.34
139.68
112.41
111.99
108.12
107.64
77.41
77.15
76.90
70.61
70.41
25.96
24.55
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
NH
N
NH
N
O
O

3i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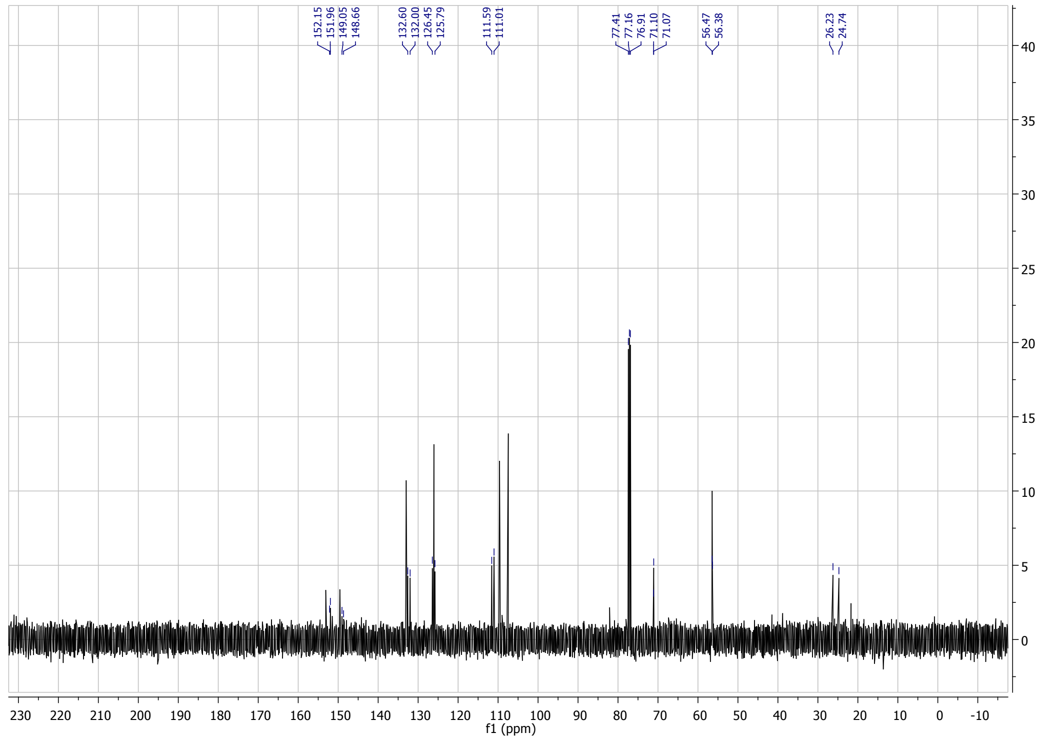
7.77
7.71
7.70
7.01
7.01
6.99
6.99
6.99
6.37
6.37
6.35
6.35
6.33
6.33
5.77
4.37
4.35
4.33
3.73
3.72
2.43
2.41
2.39
2.39
2.38
2.25
2.24
2.24
2.23
2.23
2.22
2.21
2.21
2.21
2.19
2.19
2.06
2.04
2.04
2.02
2.00
2.00
1.98
1.95
1.94
1.93
1.91
1.91
1.89
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
10.0
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
-0.5
-1.0
f1 (ppm)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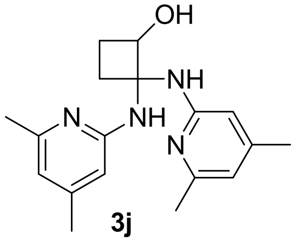
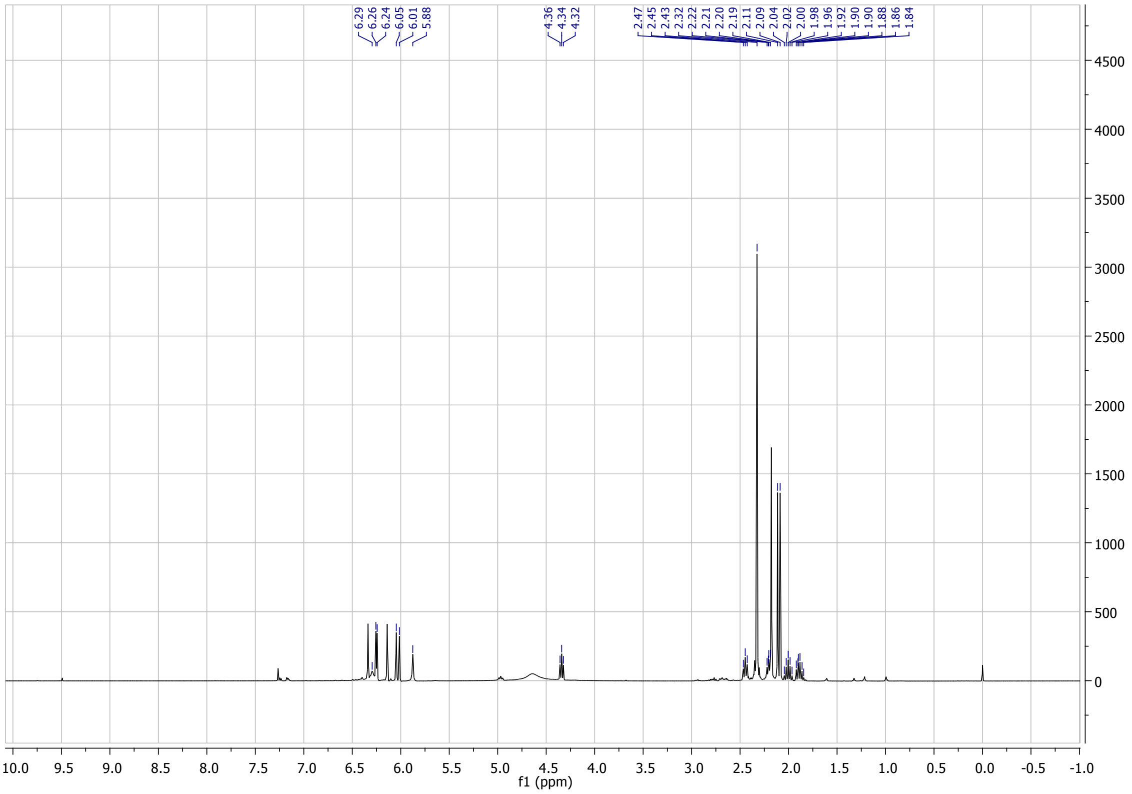
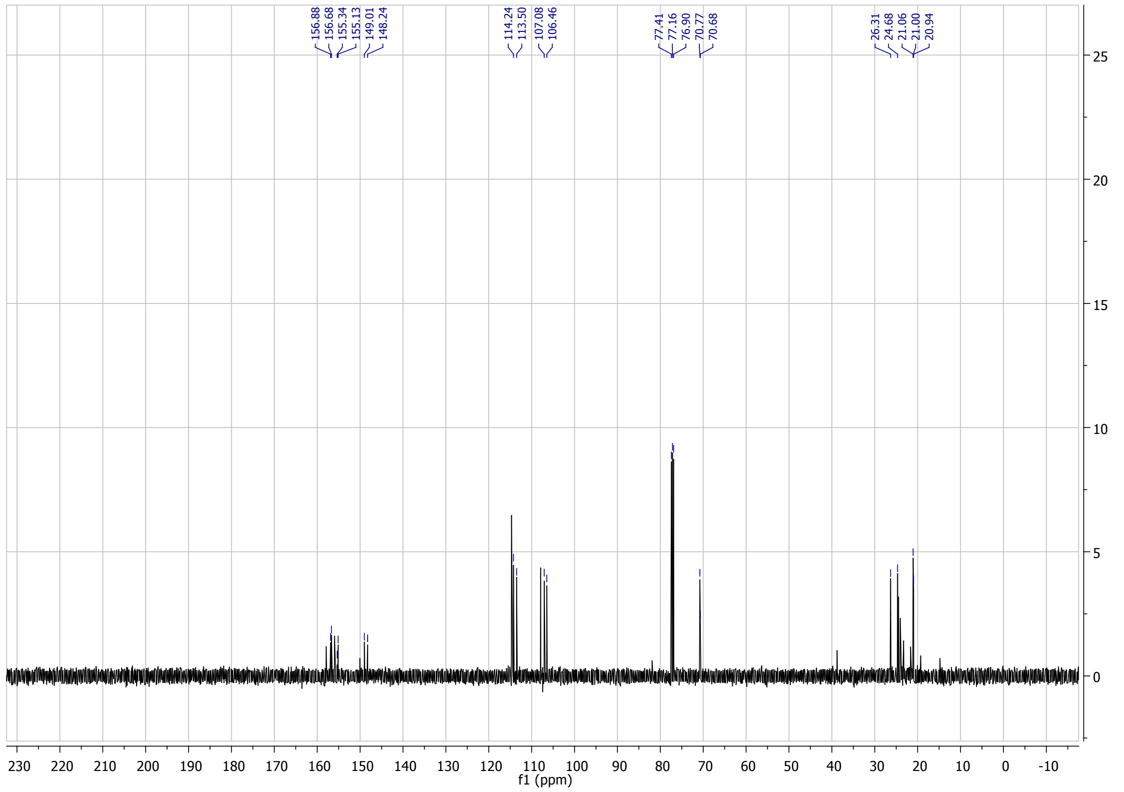
151.96
149.05
148.66
132.60
132.00
126.45
125.79
111.59
111.01
77.41
77.16
76.91
71.10
71.07
56.47
56.38
26.23
24.74
40
35
30
25
20
15
10
5
0
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
NH
NH
N
N

3j


6.29
6.26
6.24
6.05
6.01
5.88
4.36
4.34
4.32
2.47
2.45
2.43
2.32
2.22
2.21
2.20
2.19
2.11
2.09
2.04
2.02
2.00
1.98
1.96
1.92
1.90
1.90
1.88
1.86
1.84
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10.0
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
-0.5
-1.0
f1 (ppm)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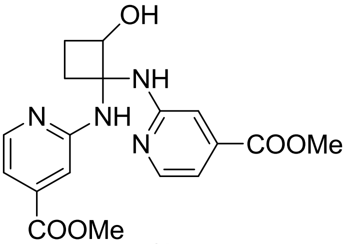
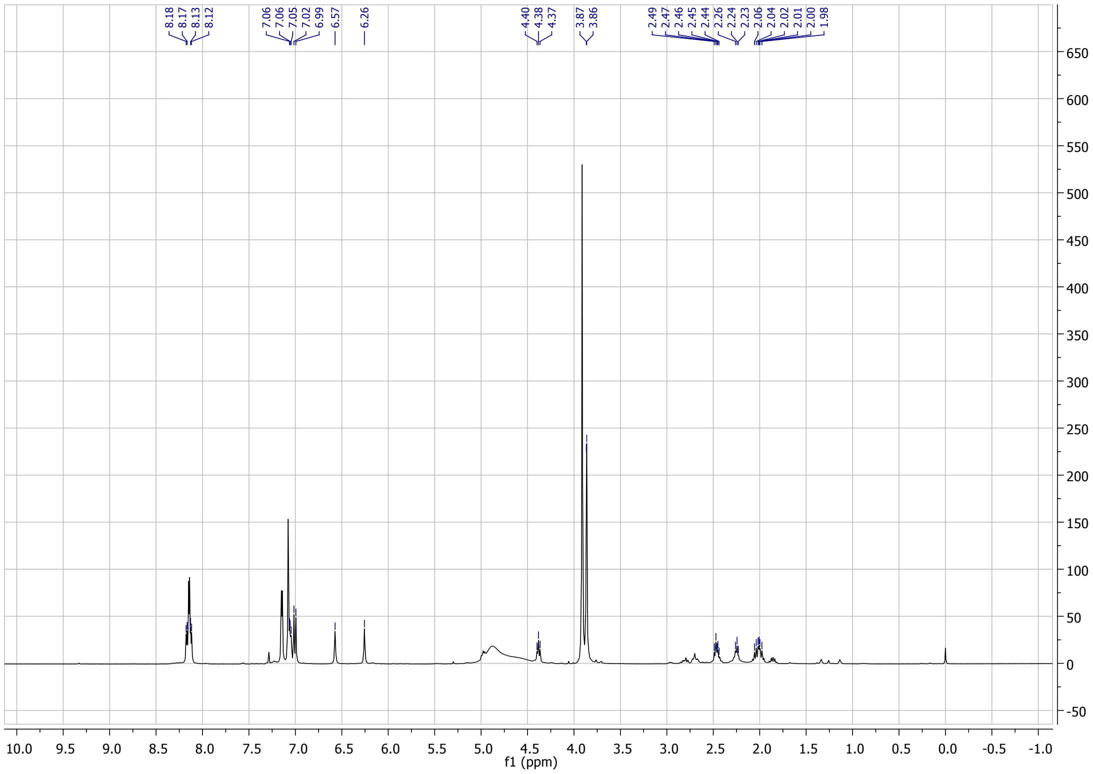
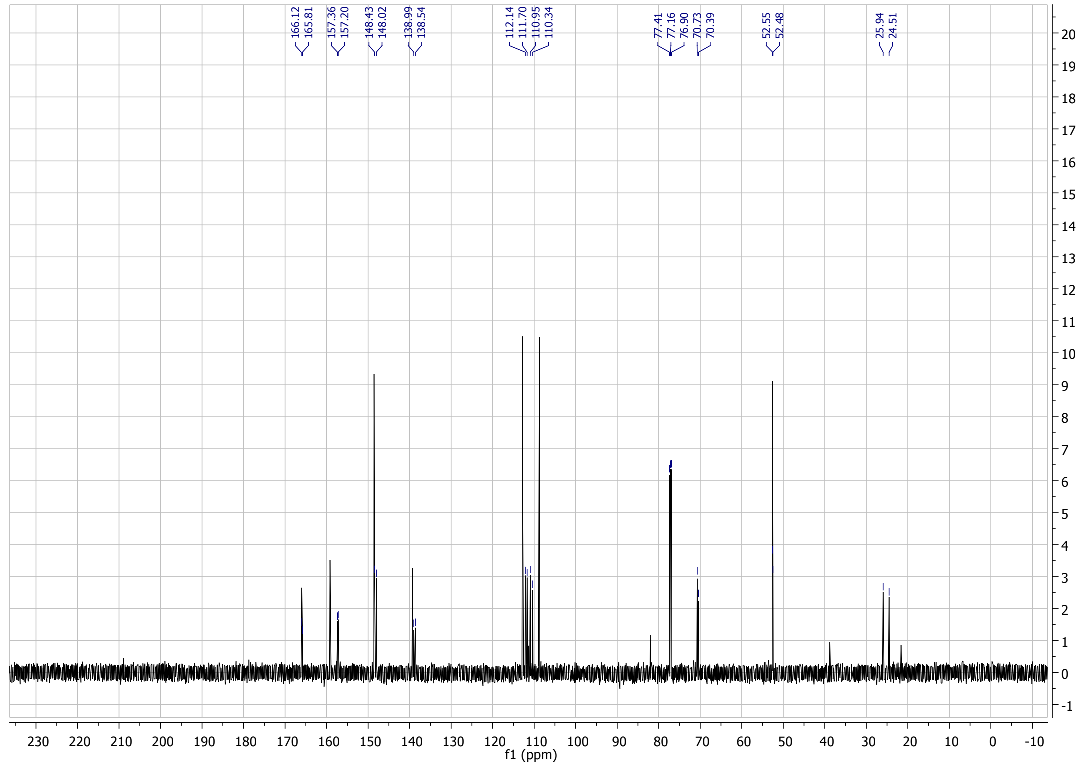
156.68
155.34
155.13
149.01
148.24
114.24
113.50
107.08
106.46
77.41
77.16
76.90
70.77
70.68
26.31
24.68
21.06
21.00
20.94
25
20
15
10
5
0
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
NH
NH
N
N
COOMe
COOMe

3k


8.18
8.17
8.13
8.12
7.06
7.06
7.05
7.02
6.99
6.57
6.26
4.40
4.38
4.37
3.87
3.86
2.49
2.47
2.46
2.45
2.44
2.26
2.24
2.23
2.06
2.04
2.02
2.01
2.00
1.98
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
10.0
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
-0.5
-1.0
f1 (ppm)


166.12
165.81
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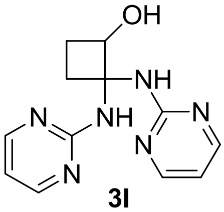
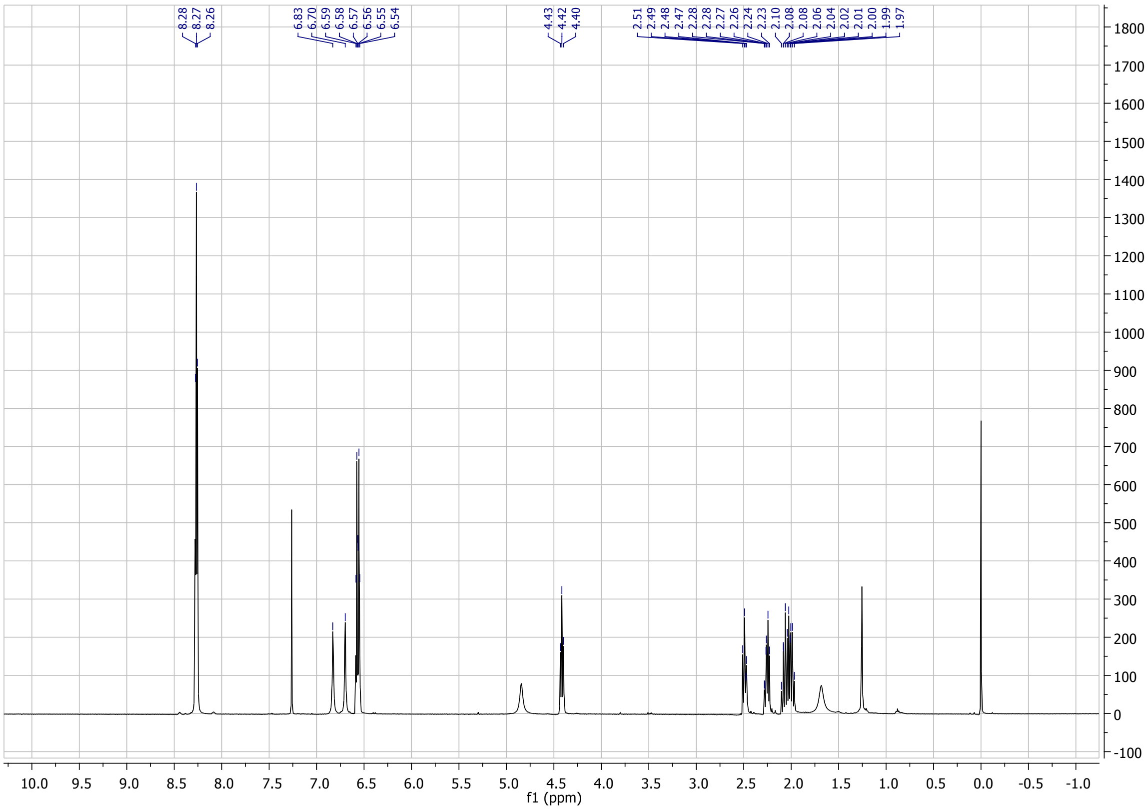
148.02
138.99
138.54
112.14
111.70
110.95
110.34
77.41
77.16
76.90
70.73
70.39
52.55
52.48
25.94
24.51
20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
NH
NH
N
N
N
N

3l


8.28
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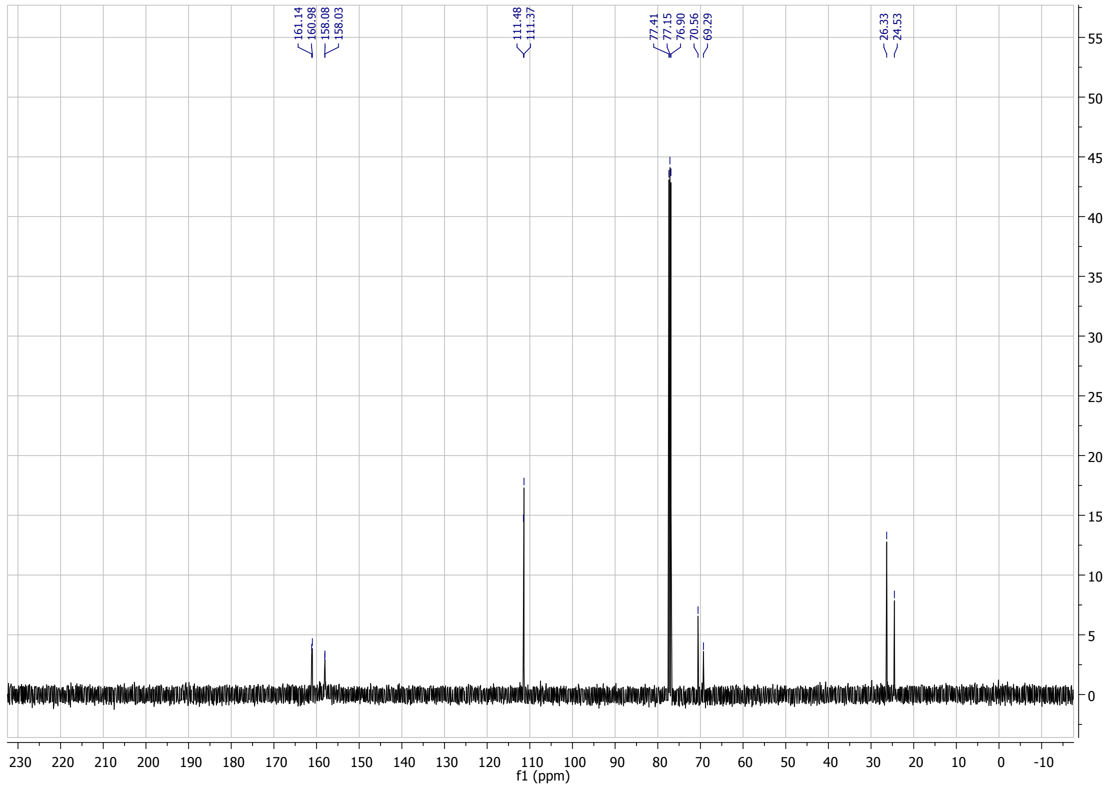
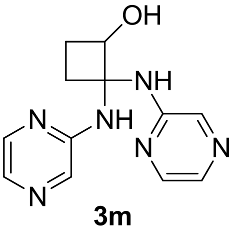
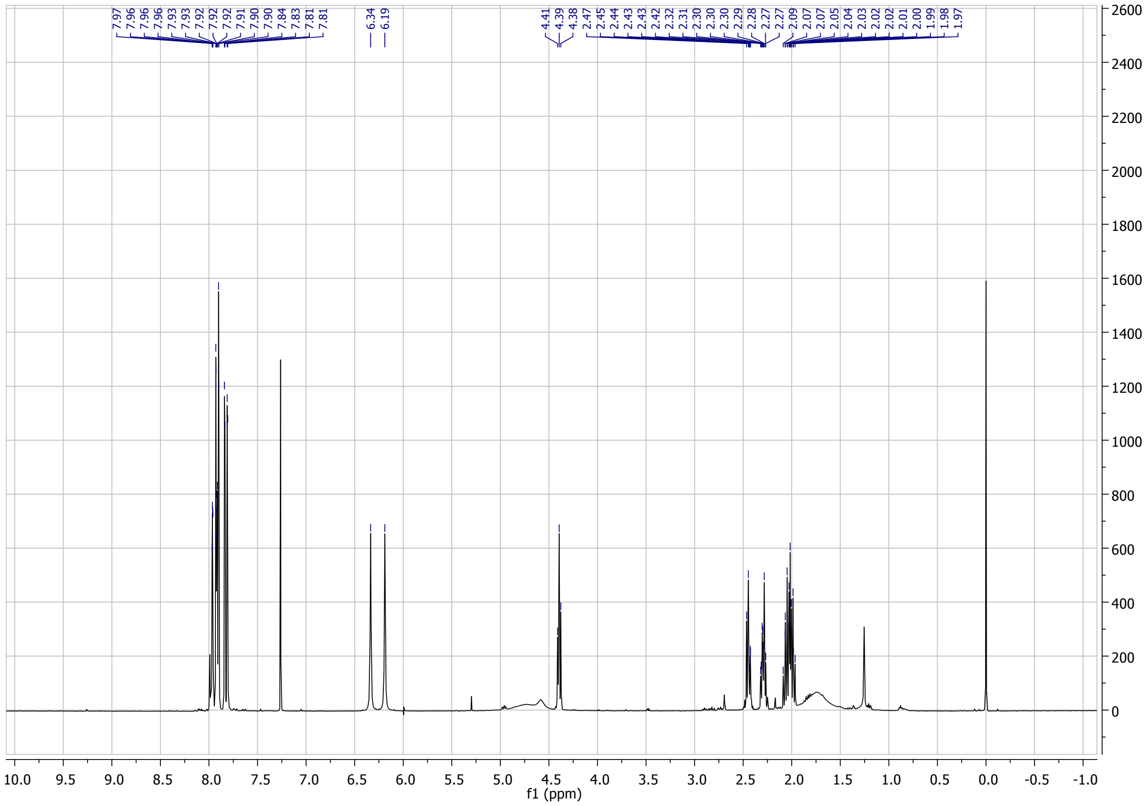
6.70
6.59
6.58
6.57
6.56
6.55
6.54
4.43
4.42
4.40
2.51
2.49
2.48
2.47
2.28
2.28
2.27
2.26
2.24
2.23
2.10
2.08
2.08
2.06
2.04
2.02
2.01
2.00
1.99
1.97
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


161.14
160.98
158.08
158.03
111.48
111.37
77.41
77.15
76.90
70.56
69.29
26.33
24.53
55
50
45
40
35
30
25
20
15
10
5
0
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
NH
NH
N
N
N
N

3m


7.97
7.96
7.96
7.93
7.93
7.92
7.92
7.92
7.91
7.90
7.90
7.84
7.83
7.81
7.81
6.34
6.19
4.41
4.39
4.38
2.47
2.45
2.44
2.43
2.43
2.42
2.32
2.31
2.30
2.30
2.30
2.29
2.28
2.27
2.27
2.09
2.07
2.07
2.05
2.04
2.03
2.02
2.02
2.01
2.00
1.99
1.98
1.97
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
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9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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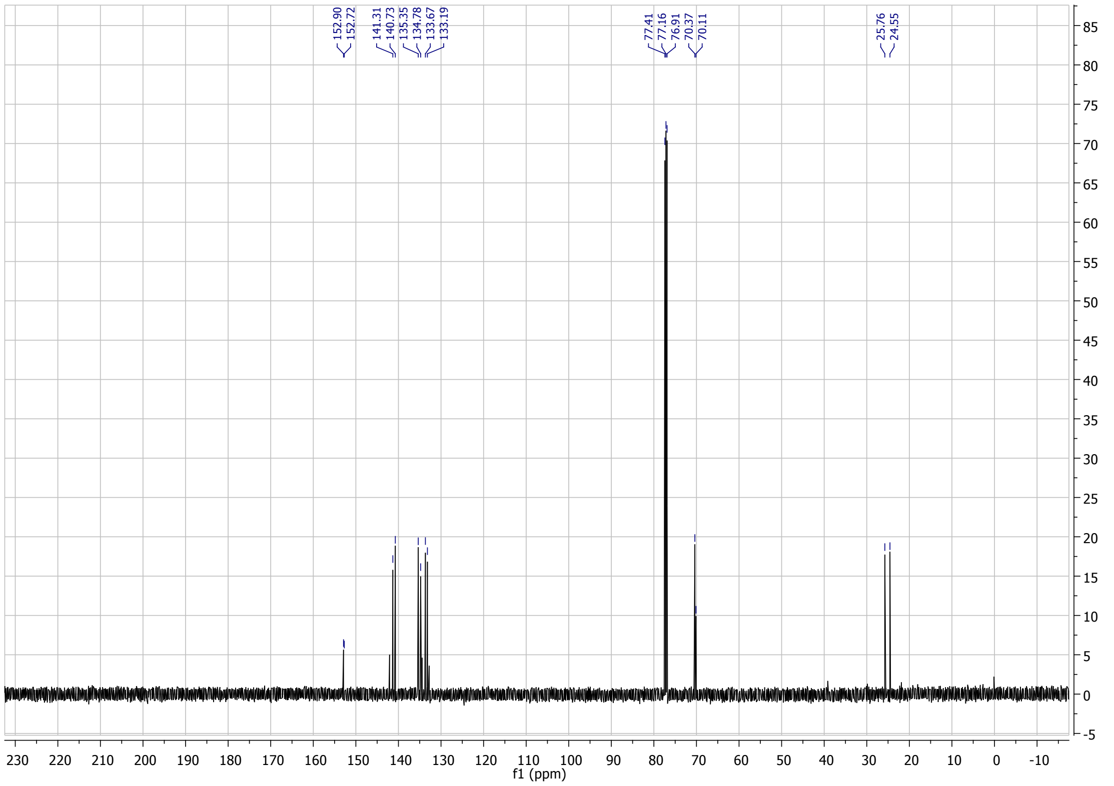
-1.0
f1 (ppm)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133.19
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77.16
76.91
70.37
70.11
25.76
24.55
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
230
220
210
200
190
180
170
160
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110
100
90
80
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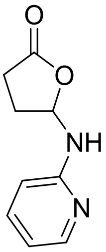
30
20
10
0
-10
f1 (ppm)



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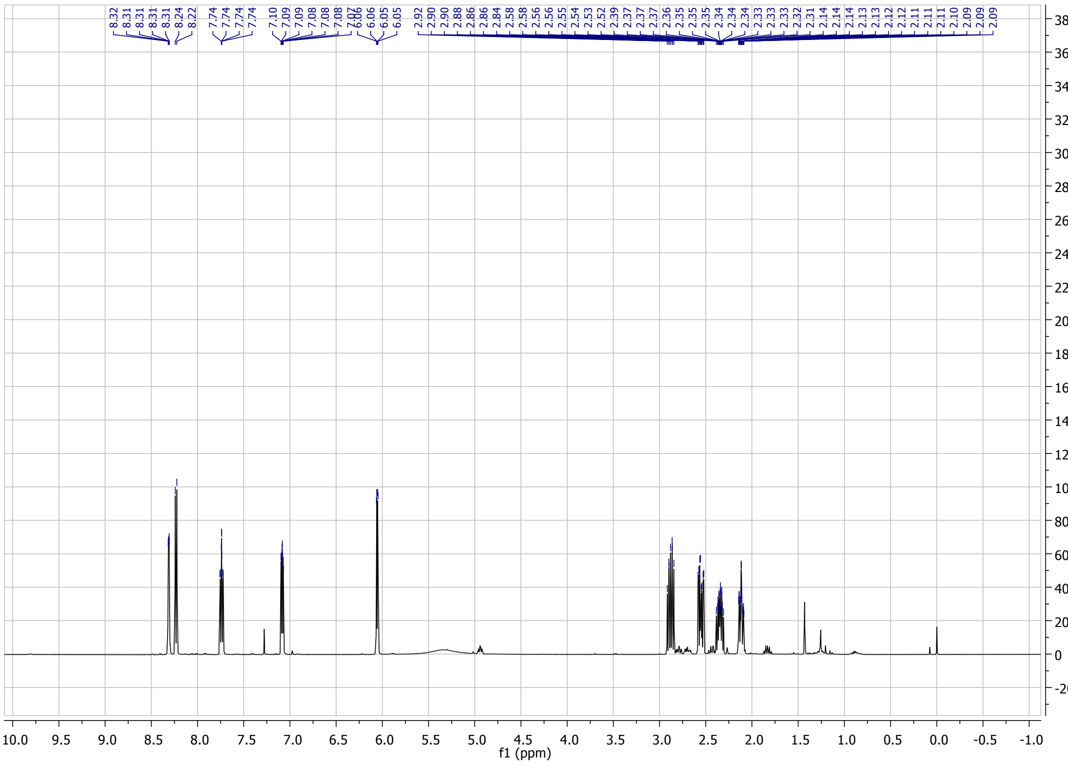
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7.74
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7.09
7.08
7.08
7.08
7.07
7.06
6.06
6.06
6.05
6.05
2.92
2.90
2.90
2.88
2.86
2.86
2.84
2.58
2.58
2.56
2.56
2.55
2.54
2.53
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2.37
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2.36
2.35
2.35
2.35
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2.34
2.33
2.33
2.33
2.32
2.31
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2.14
2.14
2.13
2.13
2.12
2.12
2.11
2.11
2.11
2.10
2.09
2.09
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3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
10.0
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9.0
8.5
8.0
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7.0
6.5
6.0
5.5
5.0
4.5
4.0
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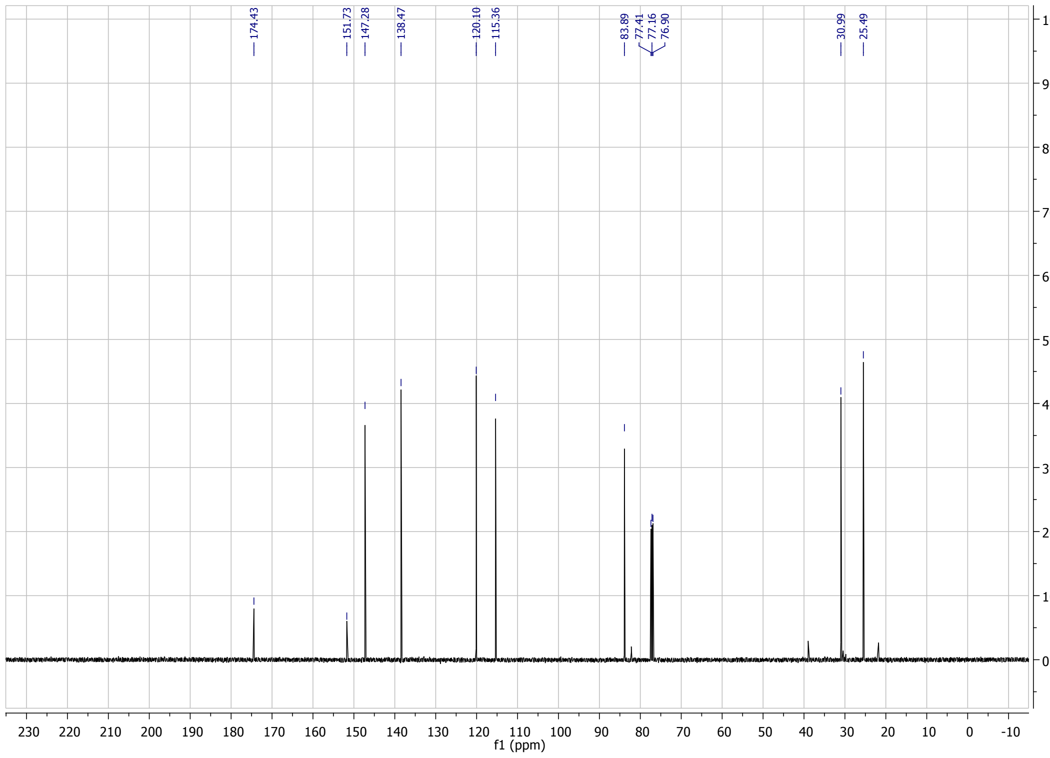
-1.0
f1 (ppm)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151.73
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138.47
120.10
115.36
83.89
77.41
77.16
76.90
30.99
25.49
1000
900
800
700
600
500
400
300
200
100
0
230
220
210
200
190
180
170
160
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140
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120
110
100
90
80
70
60
50
40
30
20
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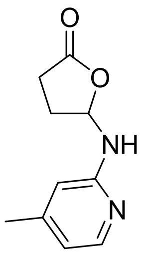
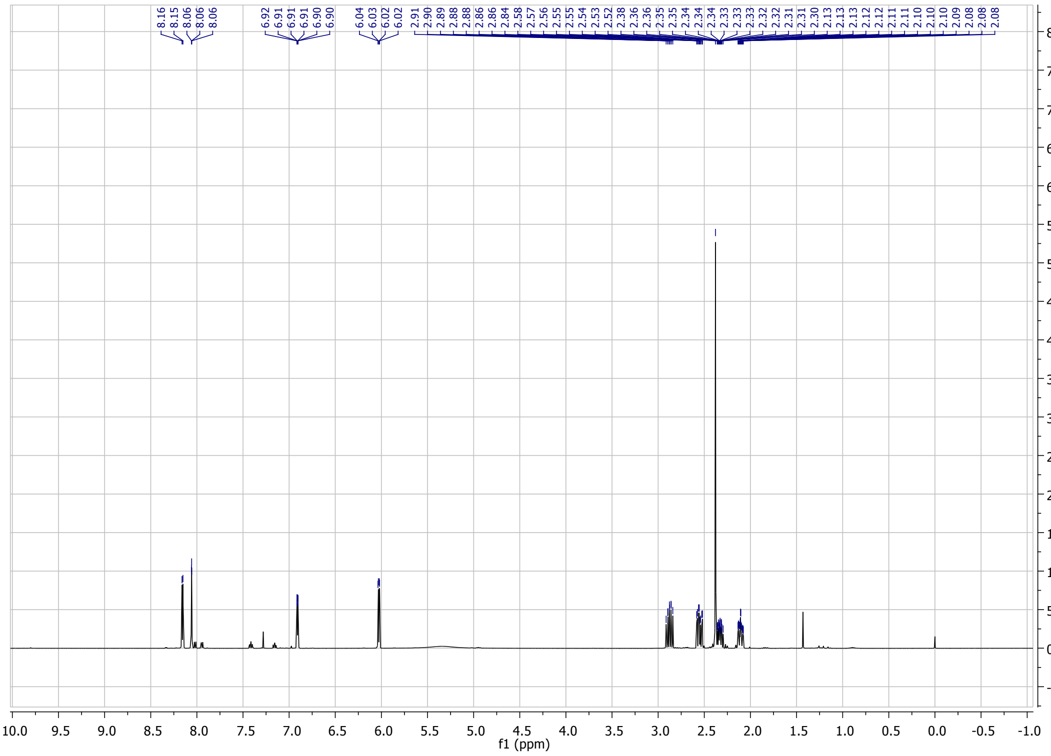
0
-10
f1 (ppm)


O
O
NH
N

7c


8.16
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6.91
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6.90
6.90
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6.03
6.02
6.02
2.91
2.90
2.89
2.88
2.88
2.86
2.86
2.84
2.58
2.57
2.56
2.55
2.55
2.54
2.53
2.52
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2.36
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2.35
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2.34
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2.33
2.32
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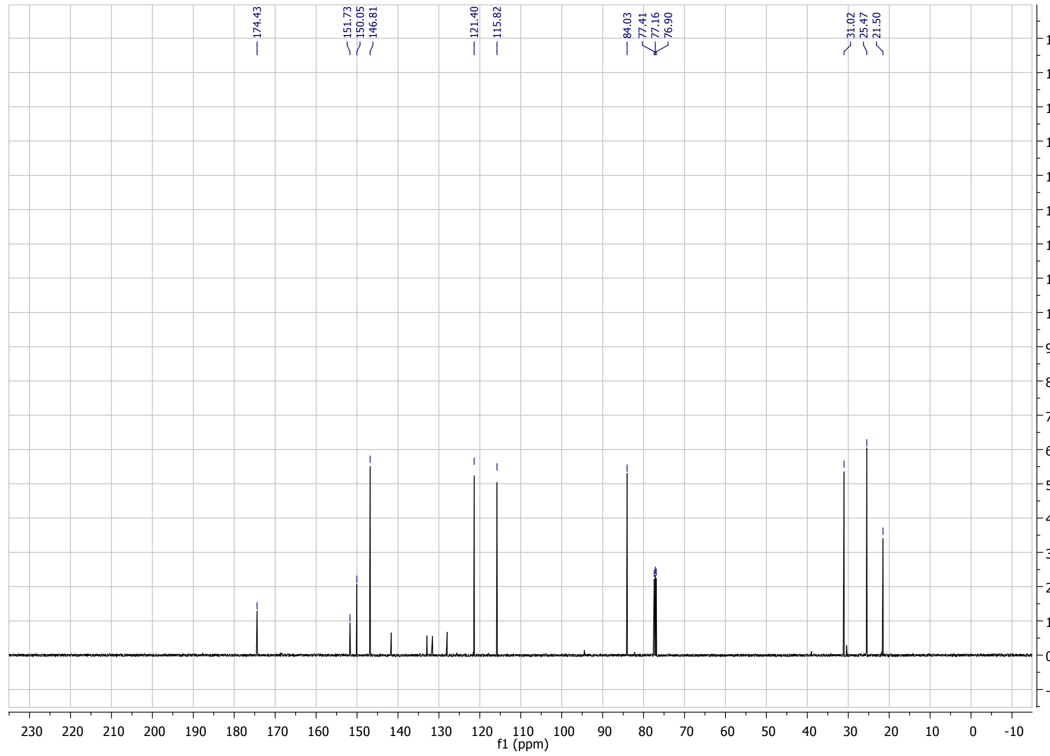
2.13
2.13
2.12
2.12
2.11
2.11
2.10
2.10
2.10
2.09
2.08
2.08
2.08
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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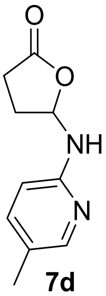
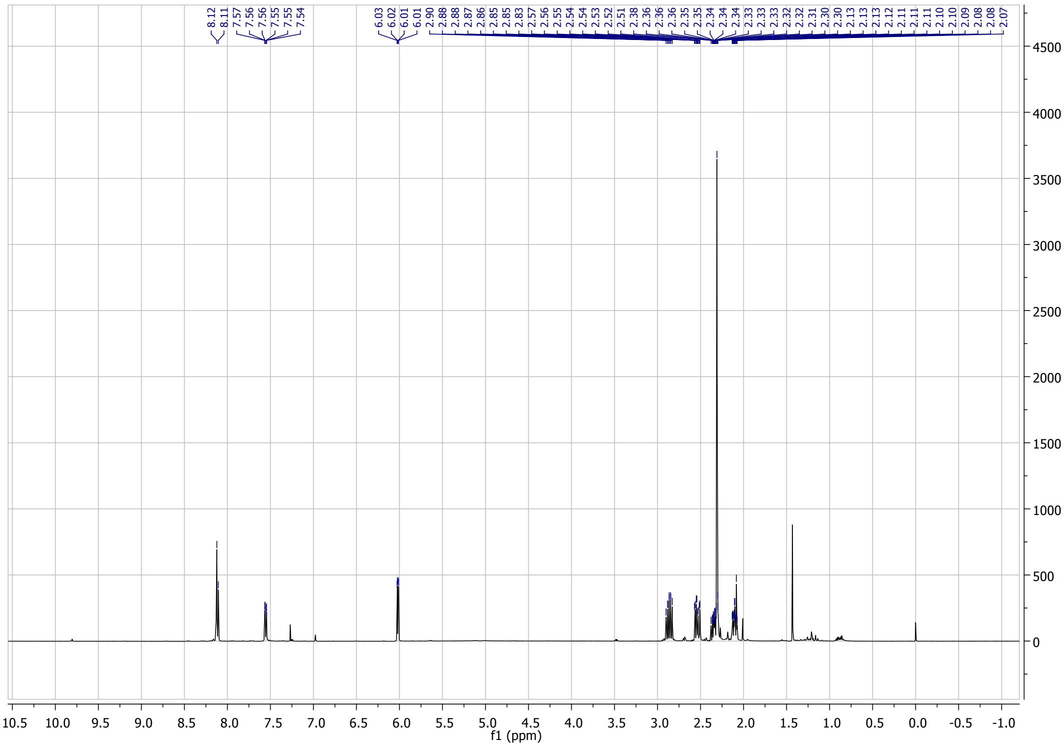
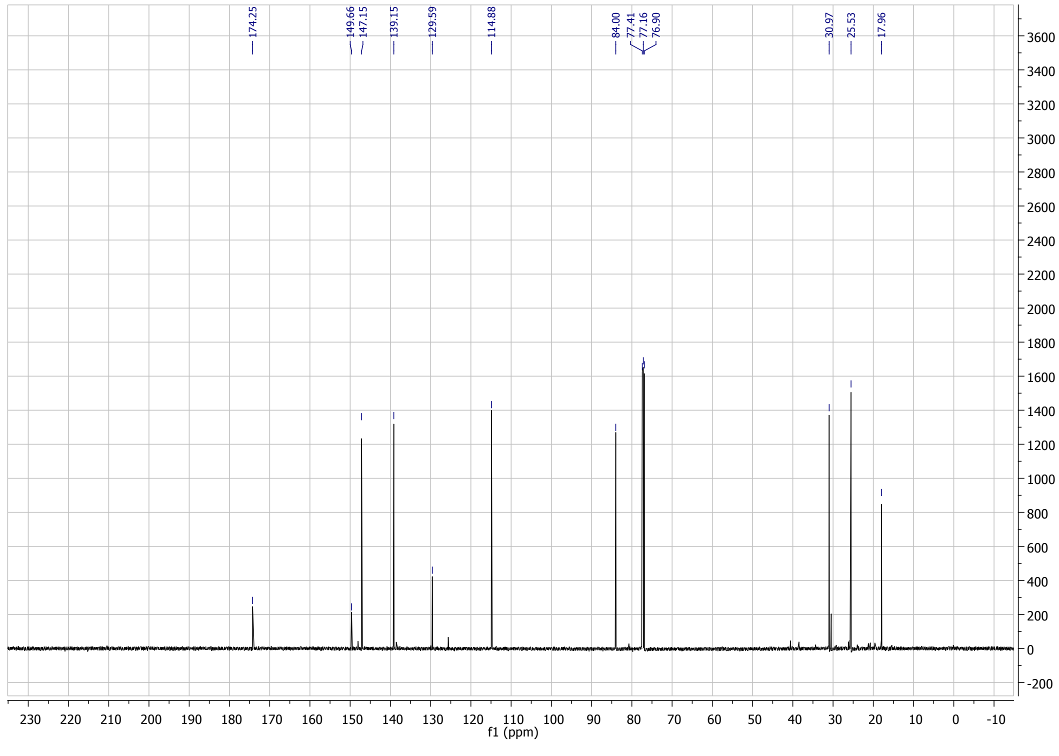
121.40
115.82
84.03
77.41
77.16
76.90
31.02
25.47
21.50
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



7d


8.12
8.11
7.57
7.56
7.56
7.55
7.55
7.54
6.03
6.02
6.01
6.01
2.90
2.88
2.88
2.87
2.86
2.85
2.85
2.83
2.57
2.56
2.55
2.54
2.54
2.53
2.52
2.51
2.38
2.36
2.36
2.36
2.35
2.35
2.34
2.34
2.34
2.33
2.33
2.33
2.32
2.32
2.31
2.30
2.30
2.13
2.13
2.13
2.12
2.11
2.11
2.11
2.10
2.09
2.08
2.08
2.07
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10.5
10.0
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
-0.5
-1.0
f1 (ppm)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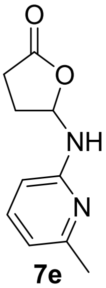
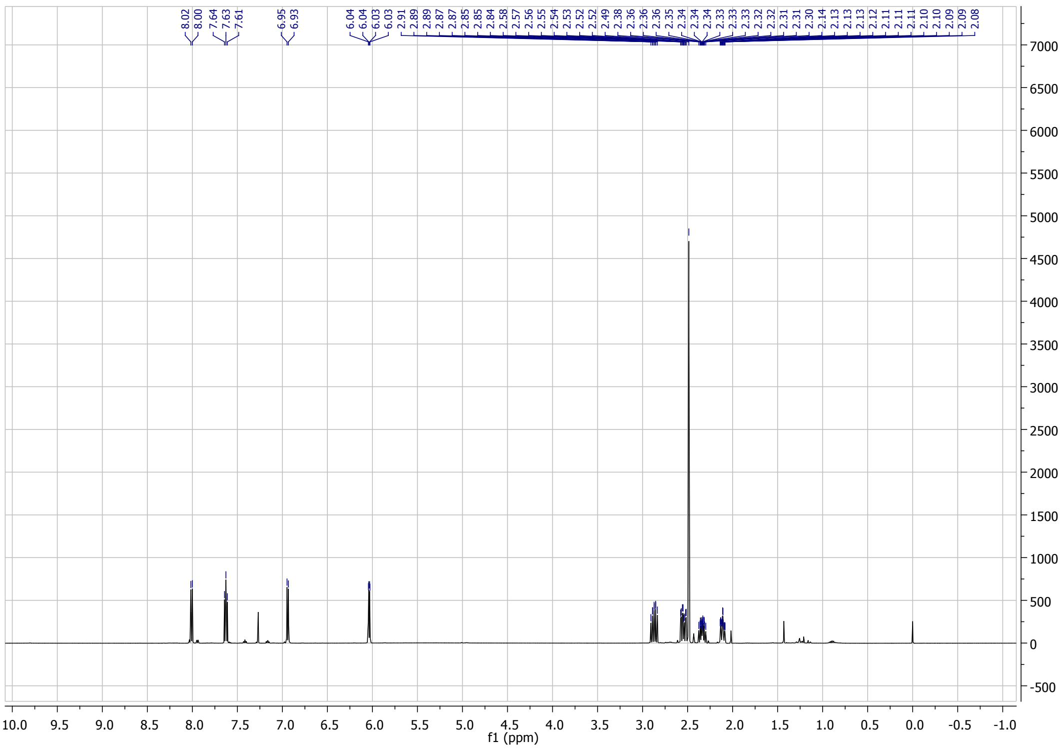
147.15
139.15
129.59
114.88
84.00
77.41
77.16
76.90
30.97
25.53
17.96
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
O
NH
N

7e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6.04
6.04
6.03
6.03
2.91
2.89
2.89
2.87
2.87
2.85
2.85
2.84
2.58
2.57
2.56
2.55
2.54
2.53
2.52
2.52
2.49
2.38
2.36
2.36
2.36
2.35
2.34
2.34
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2.33
2.33
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2.32
2.31
2.31
2.30
2.14
2.13
2.13
2.13
2.12
2.11
2.11
2.11
2.10
2.10
2.09
2.09
2.08
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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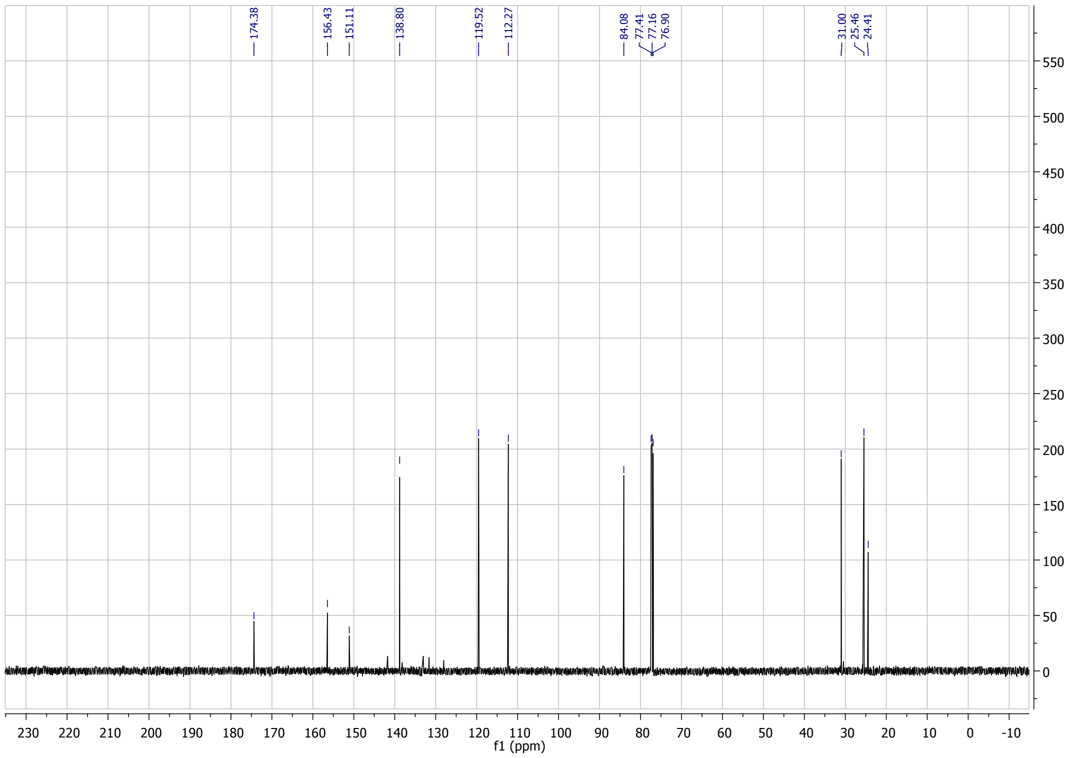
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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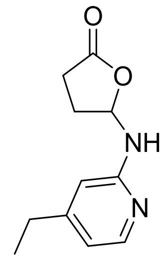
119.52
112.27
84.08
77.41
77.16
76.90
31.00
25.46
24.41
550
500
450
400
350
300
250
200
150
100
50
0
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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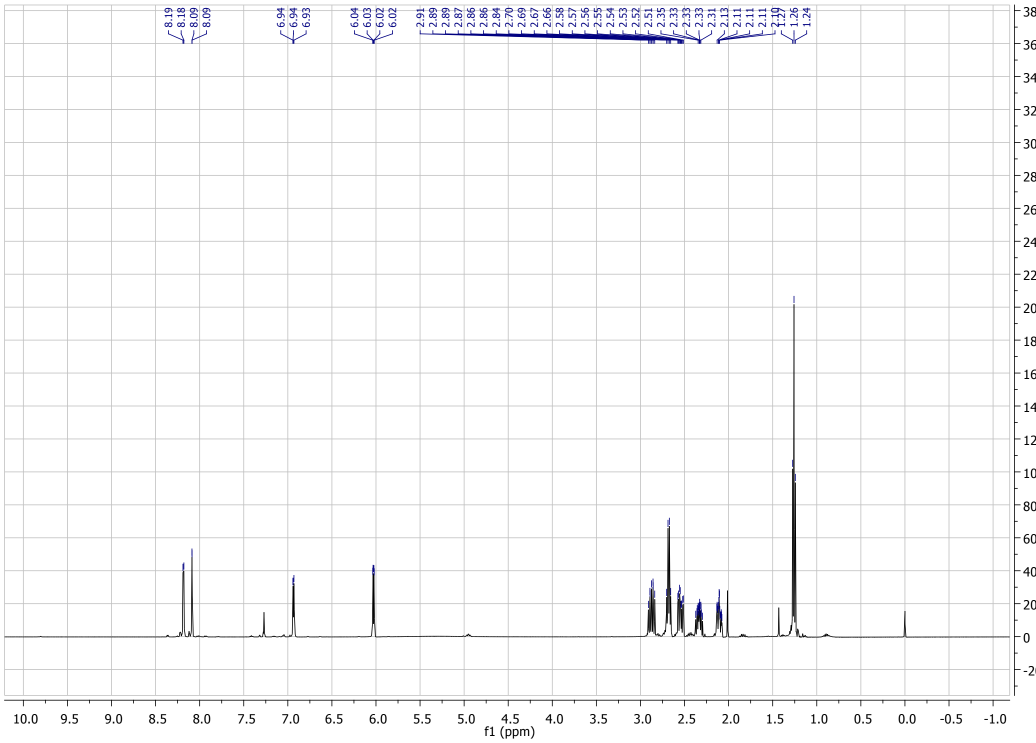
O
NH
N

7f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8.09
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6.04
6.03
6.02
6.02
2.91
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2.87
2.86
2.86
2.84
2.70
2.69
2.67
2.66
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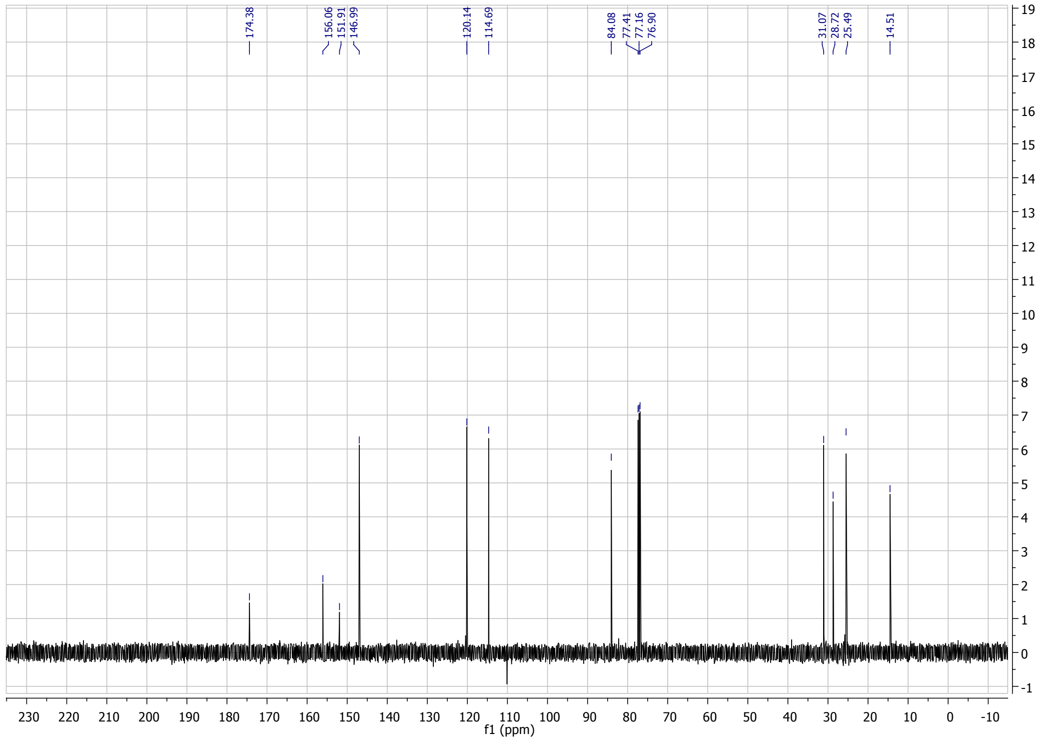
2.57
2.56
2.55
2.54
2.53
2.52
2.51
2.35
2.33
2.33
2.33
2.31
2.13
2.11
2.11
2.11
2.10
1.27
1.26
1.24
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200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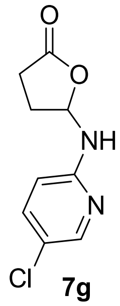
114.69
84.08
77.41
77.16
76.90
31.07
28.72
25.49
14.51
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1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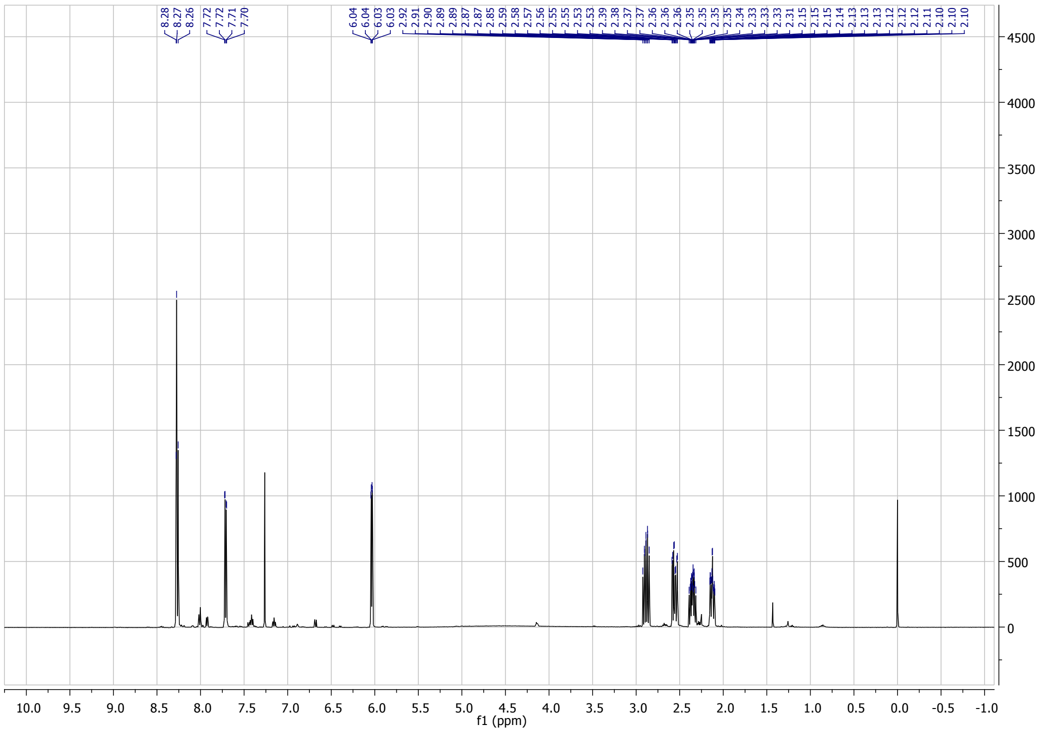
O
NH
N
Cl

7g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8.27
8.26
7.72
7.72
7.71
7.70
6.04
6.04
6.03
6.03
2.92
2.91
2.90
2.89
2.89
2.87
2.87
2.85
2.59
2.58
2.57
2.56
2.55
2.55
2.53
2.53
2.39
2.38
2.37
2.37
2.36
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2.33
2.33
2.33
2.31
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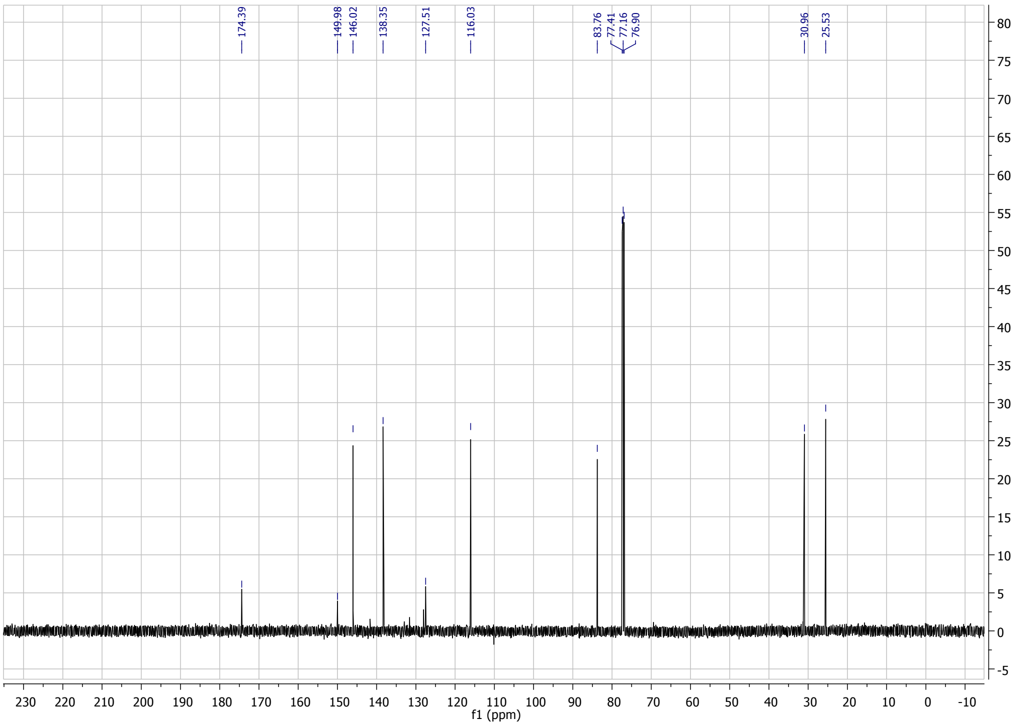
2.15
2.15
2.14
2.13
2.13
2.13
2.12
2.12
2.12
2.11
2.10
2.10
2.10
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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77.16
76.90
30.96
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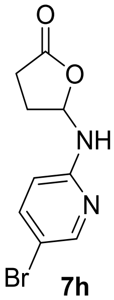
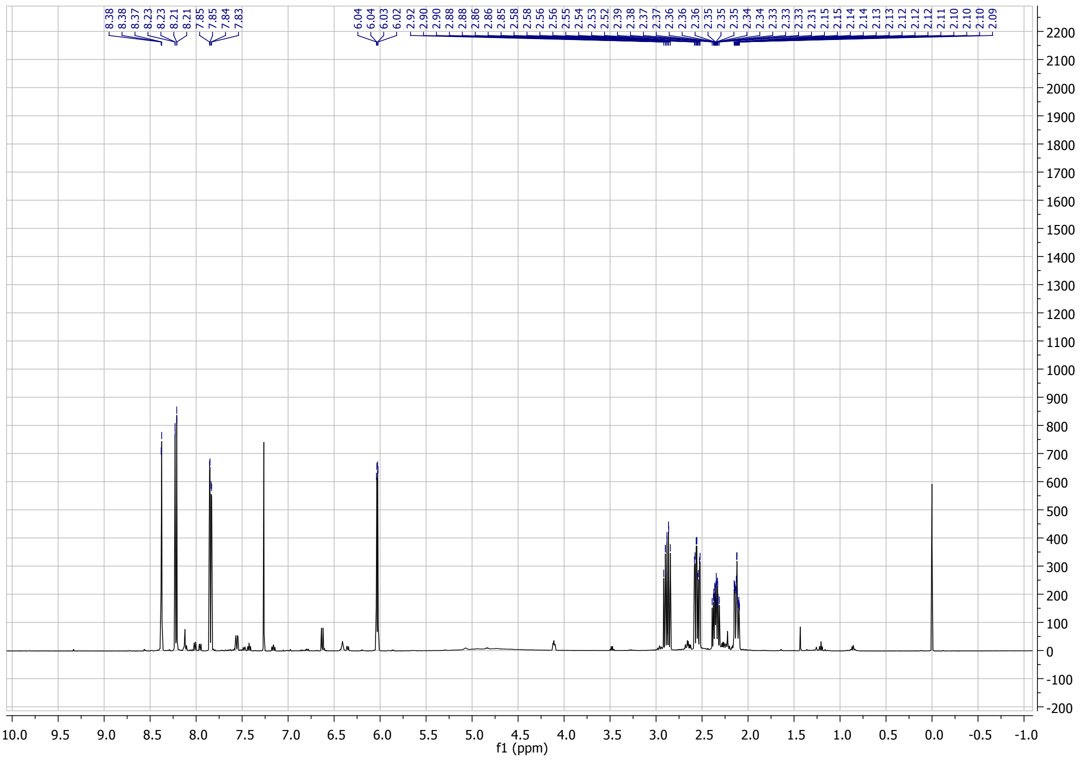
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
O
NH
N
Br

7h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8.37
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8.23
8.21
8.21
7.85
7.85
7.84
7.83
6.04
6.04
6.03
6.02
2.92
2.90
2.88
2.88
2.86
2.86
2.85
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2.58
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2.55
2.54
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2.11
2.10
2.10
2.09
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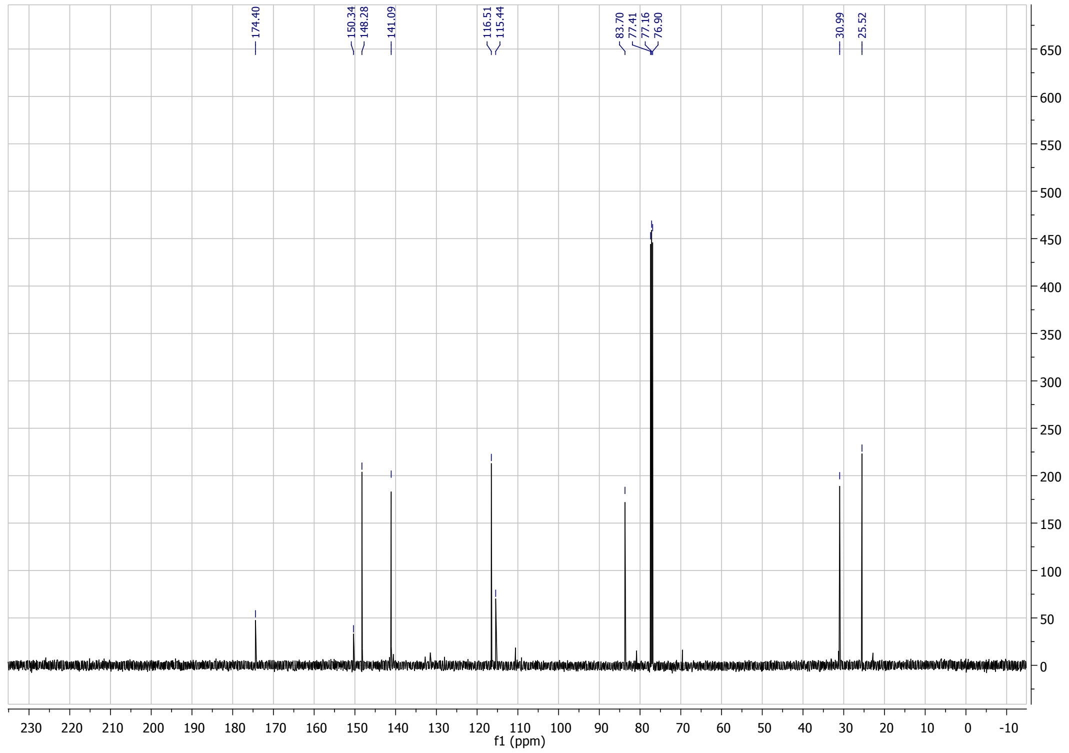
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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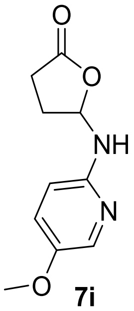
115.44
83.70
77.41
77.16
76.90
30.99
25.52
650
600
550
500
450
400
350
300
250
200
150
100
50
0
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
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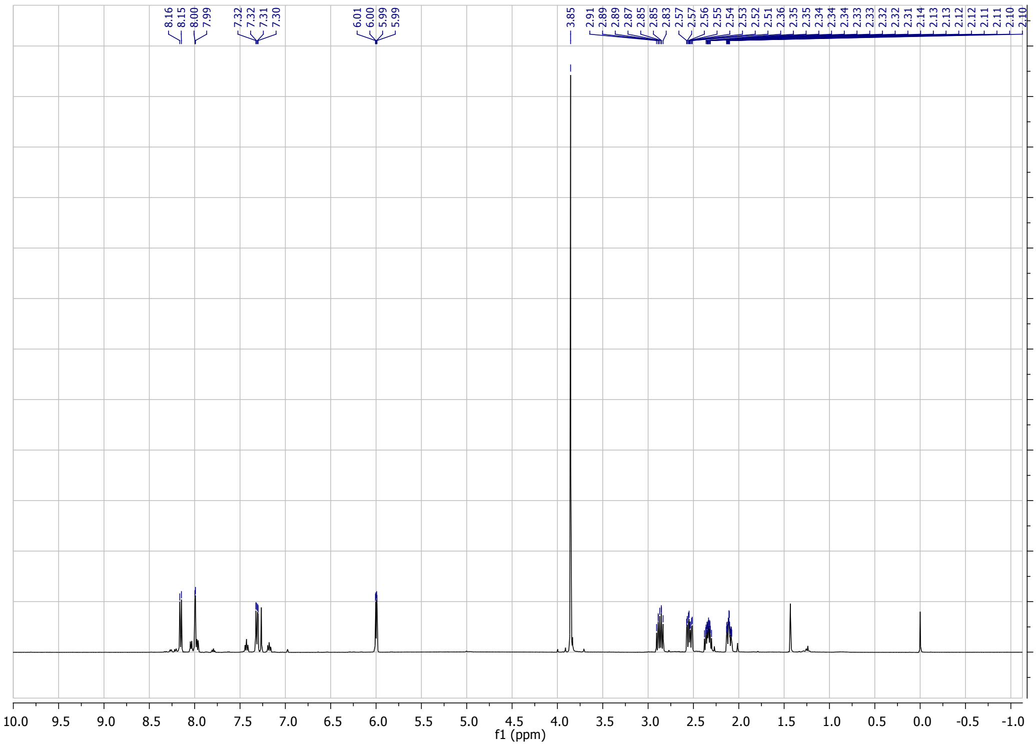
NH
N
O

7i


8.16
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7.31
7.30
6.01
6.00
5.99
5.99
3.85
2.91
2.89
2.89
2.87
2.85
2.85
2.83
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2.57
2.56
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2.33
2.33
2.32
2.32
2.31
2.14
2.13
2.13
2.12
2.12
2.11
2.11
2.10
2.10
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10.0
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
-0.5
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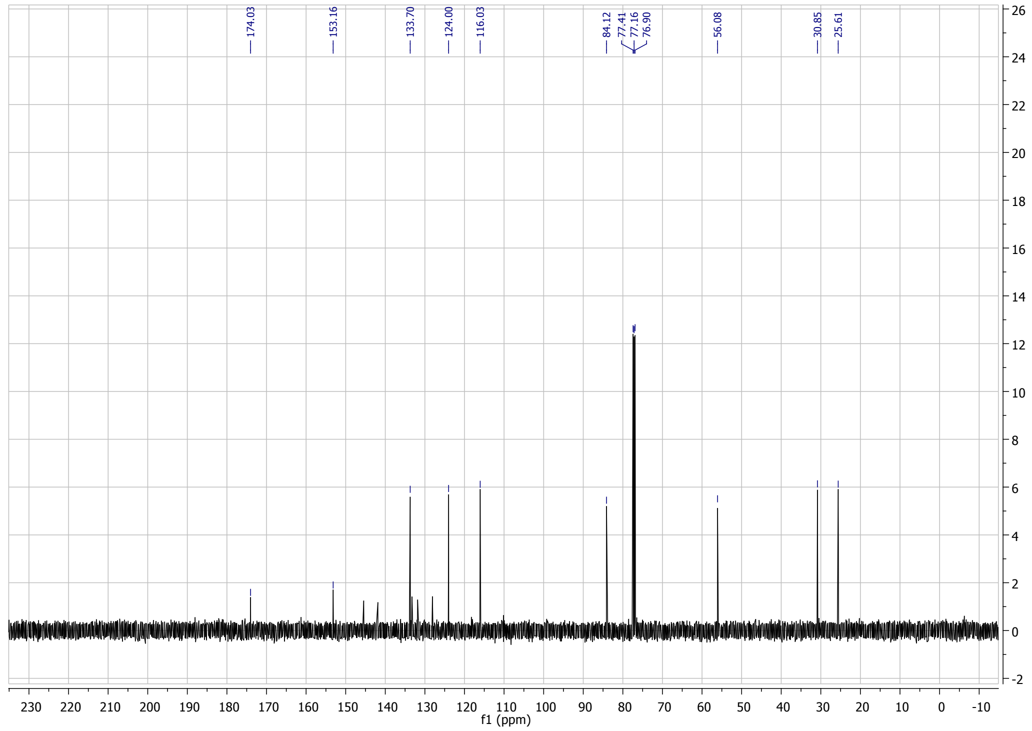
f1 (ppm)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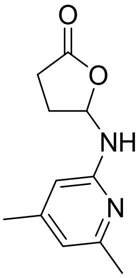
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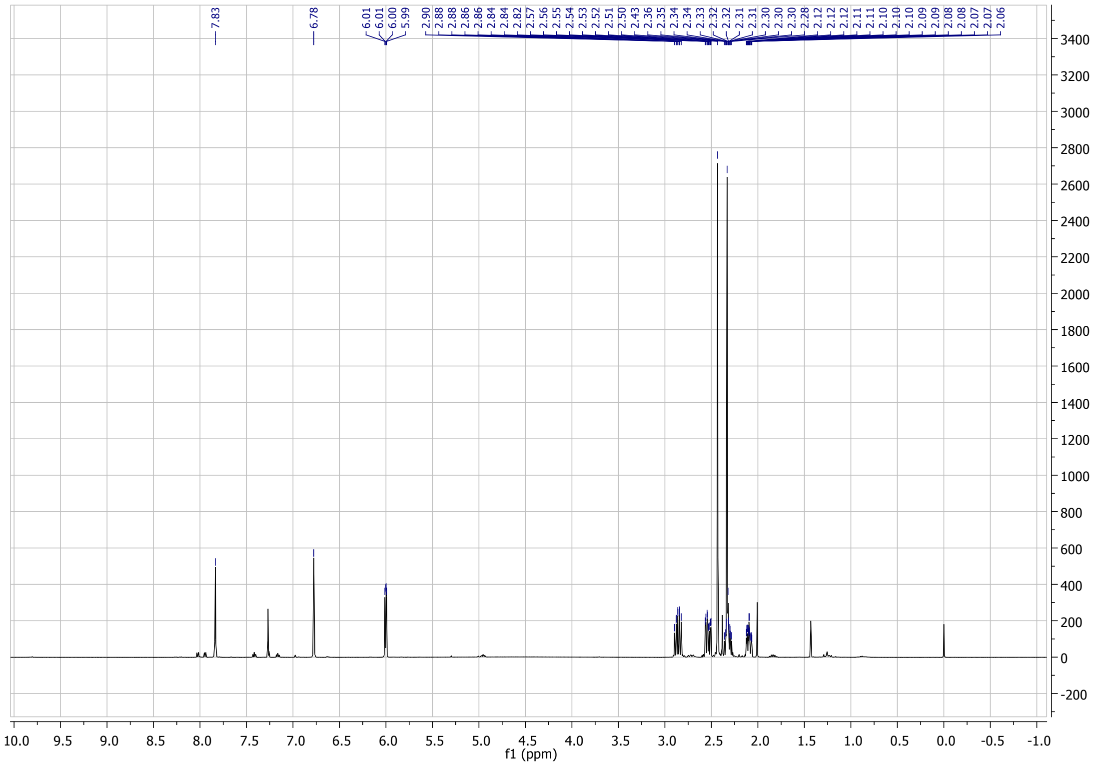
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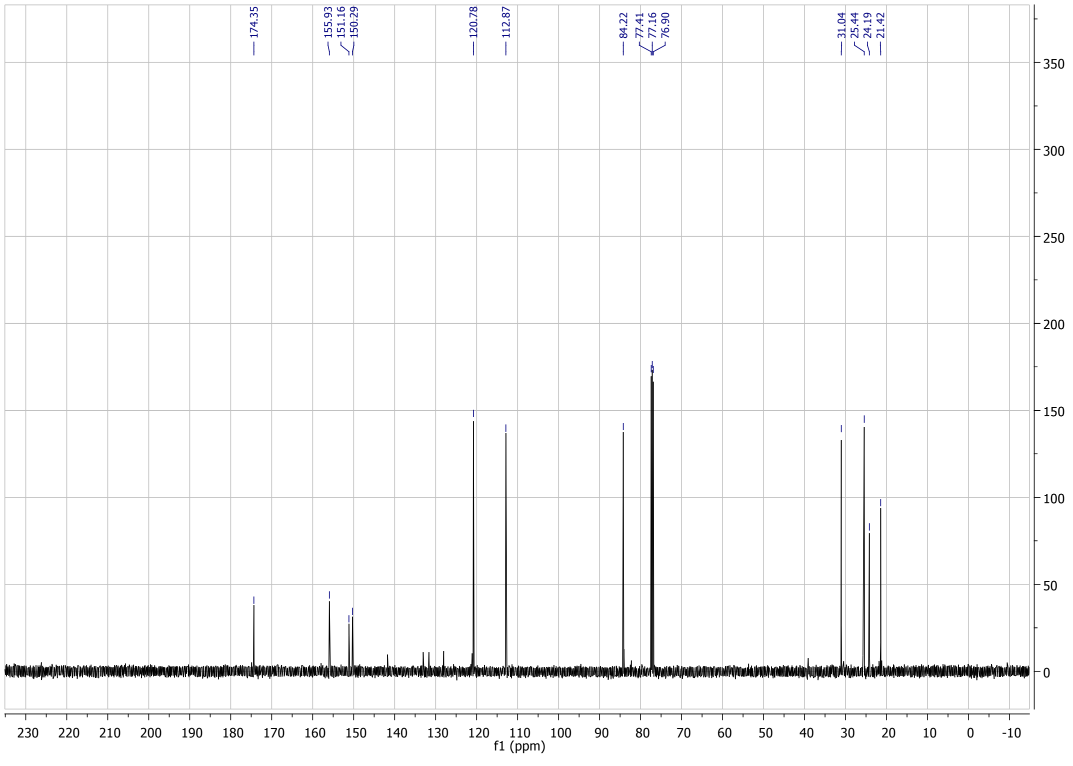
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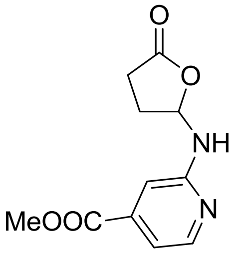
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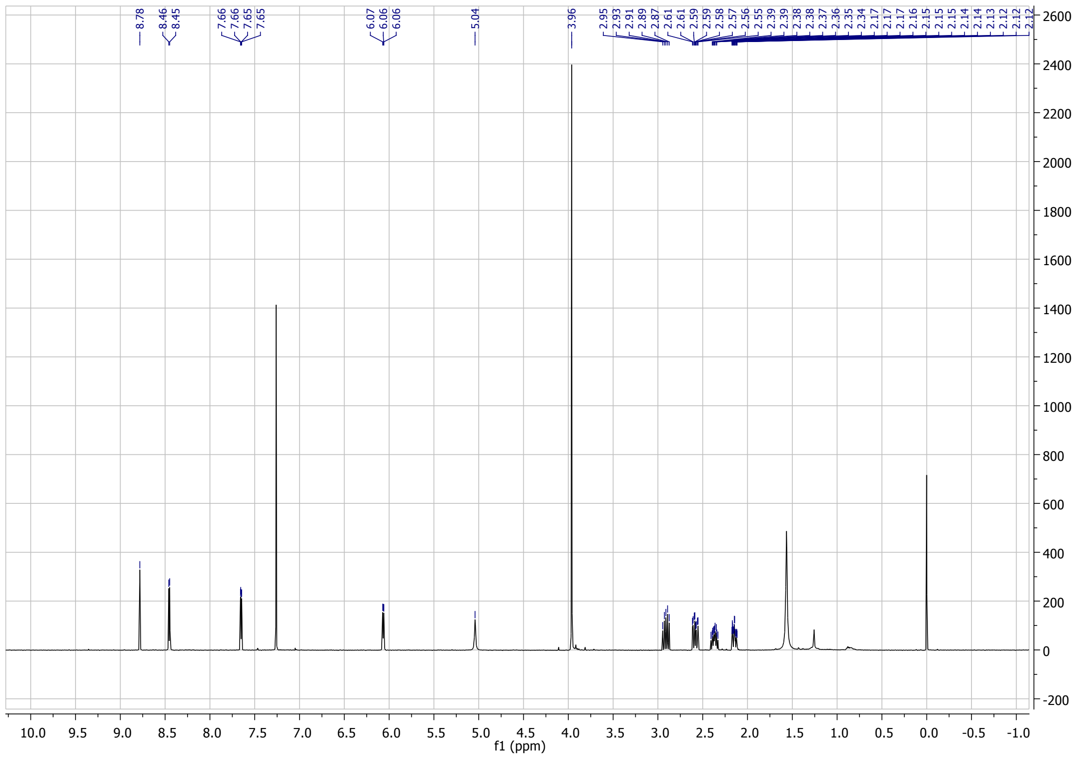
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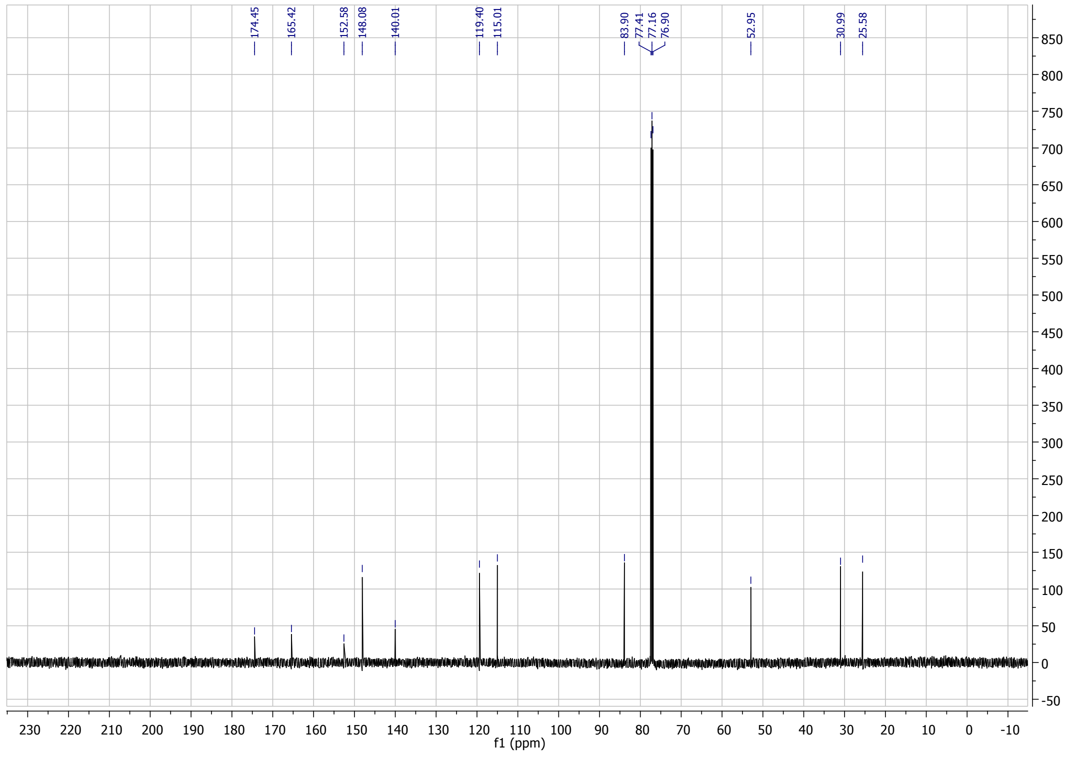
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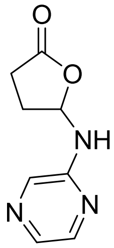

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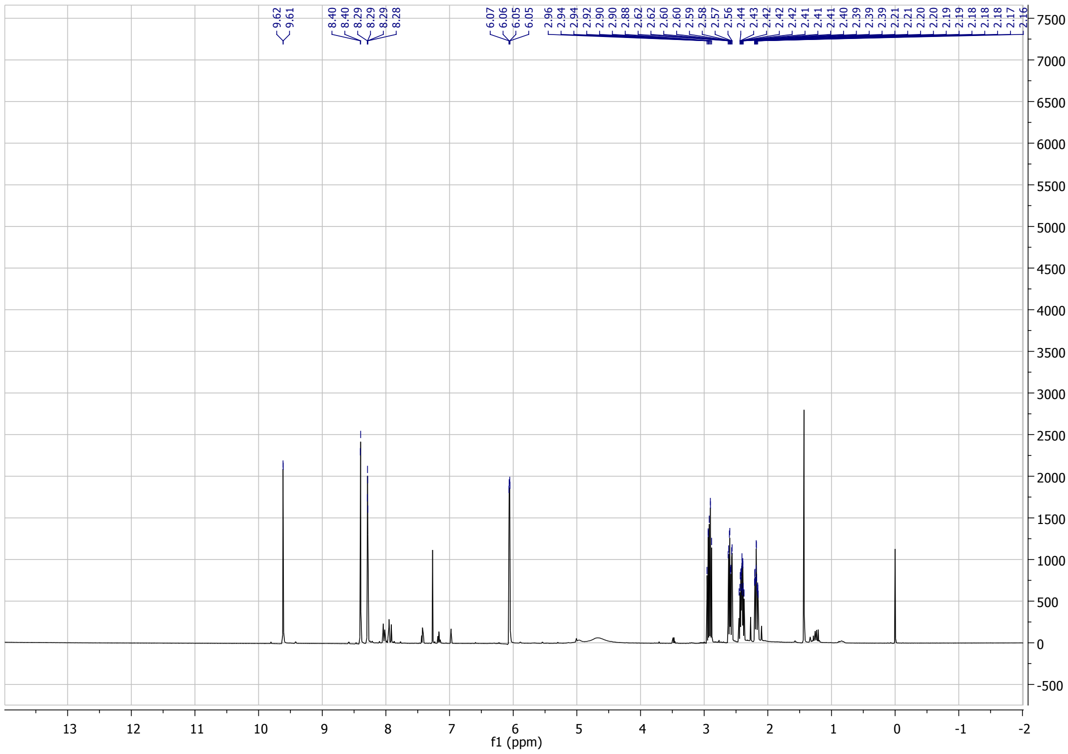
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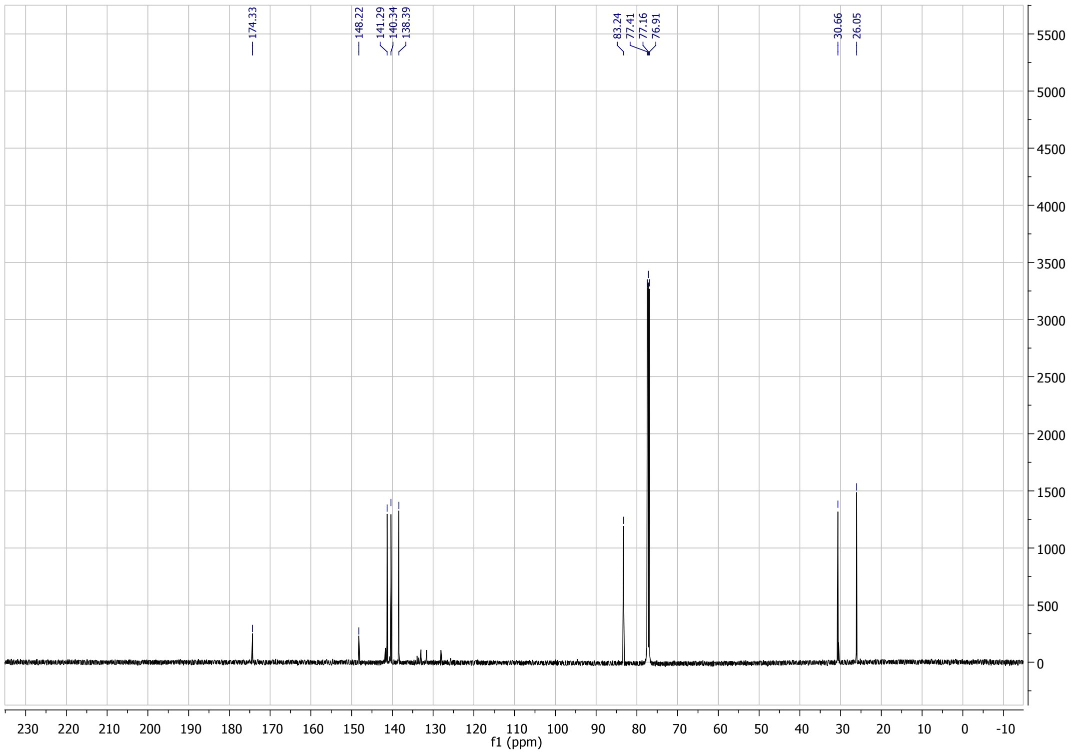
f1 (ppm)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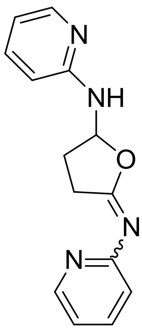
f1 (ppm)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N

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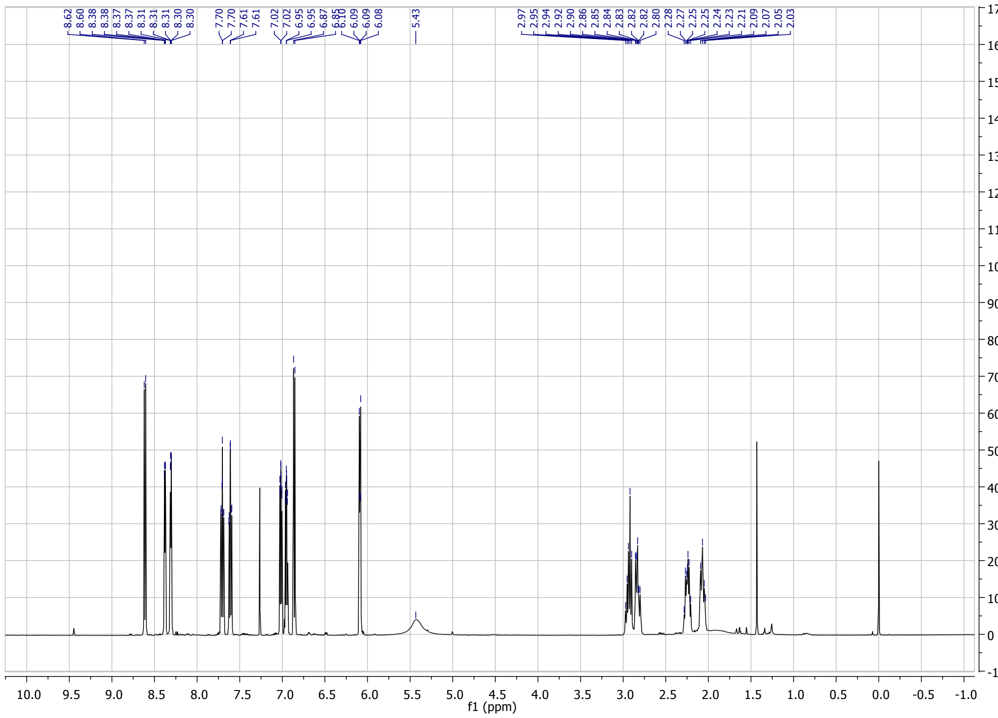
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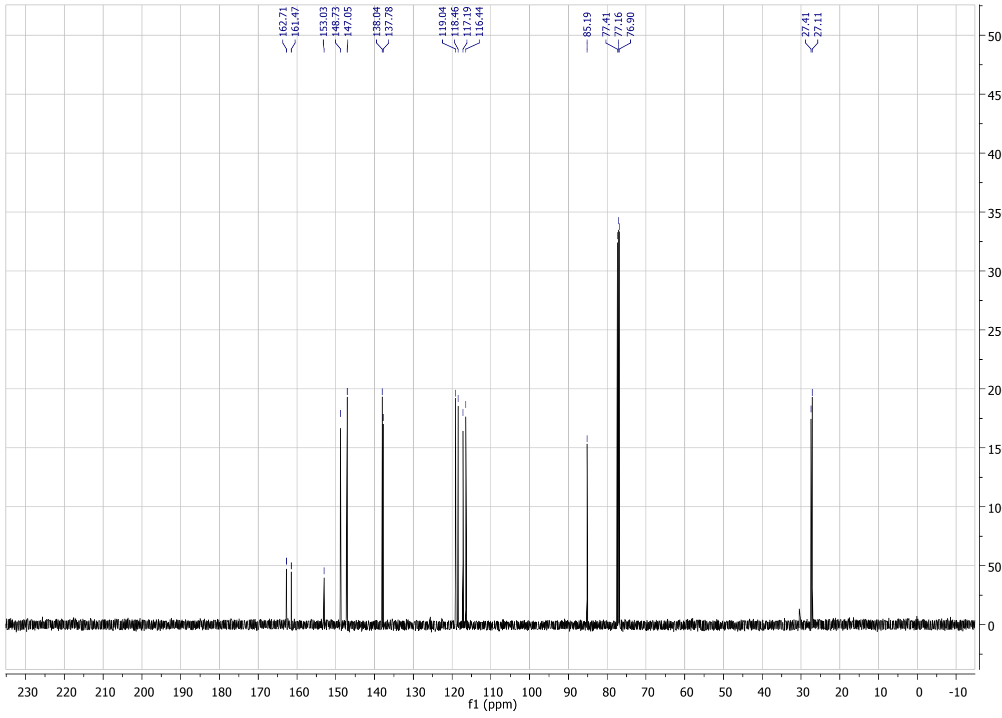
f1 (ppm)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76.90
27.41
27.11
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160
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140
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120
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100
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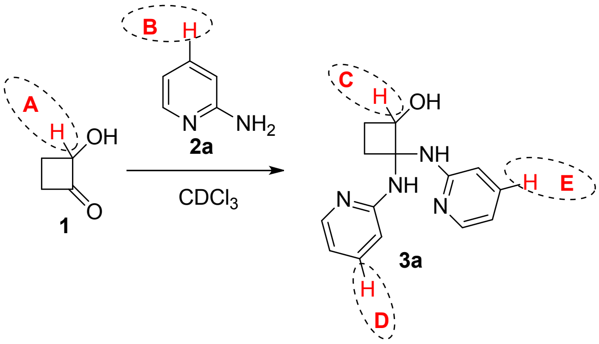
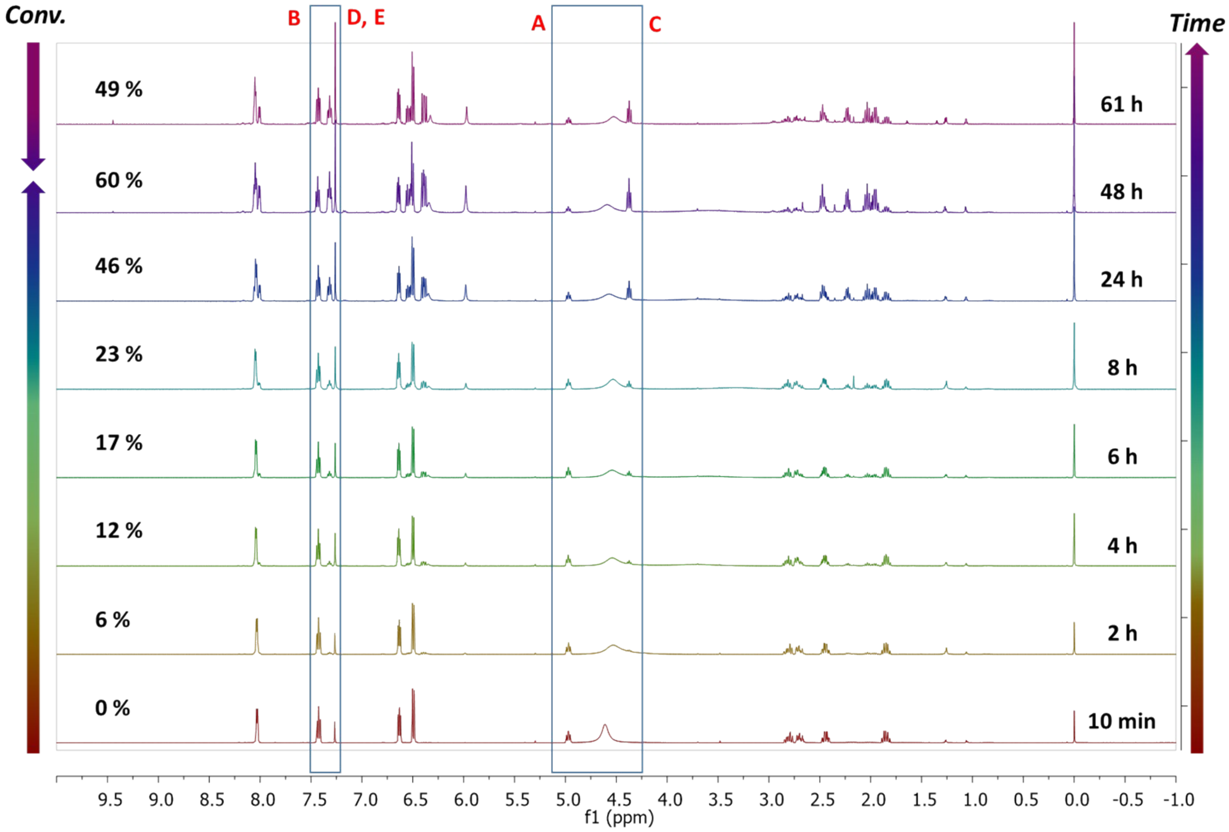
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

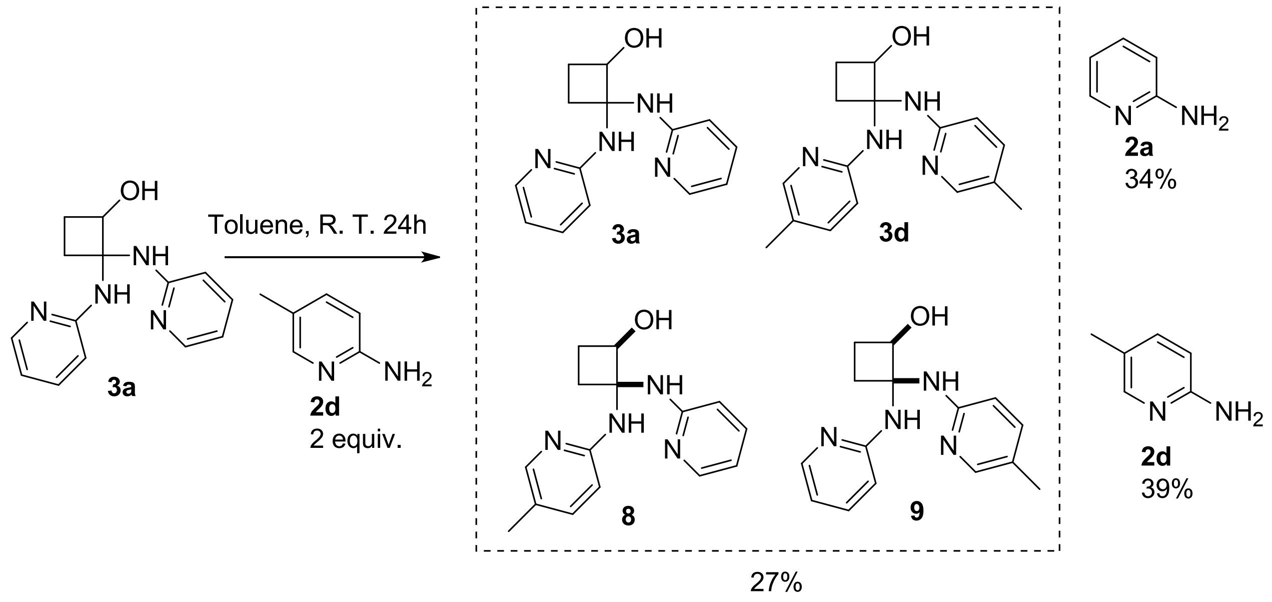
Preliminary characterization of the dynamic covalent reaction for the synthesis of 2,2-bis(aza-heteroaryl amino)cyclobutanols 3.

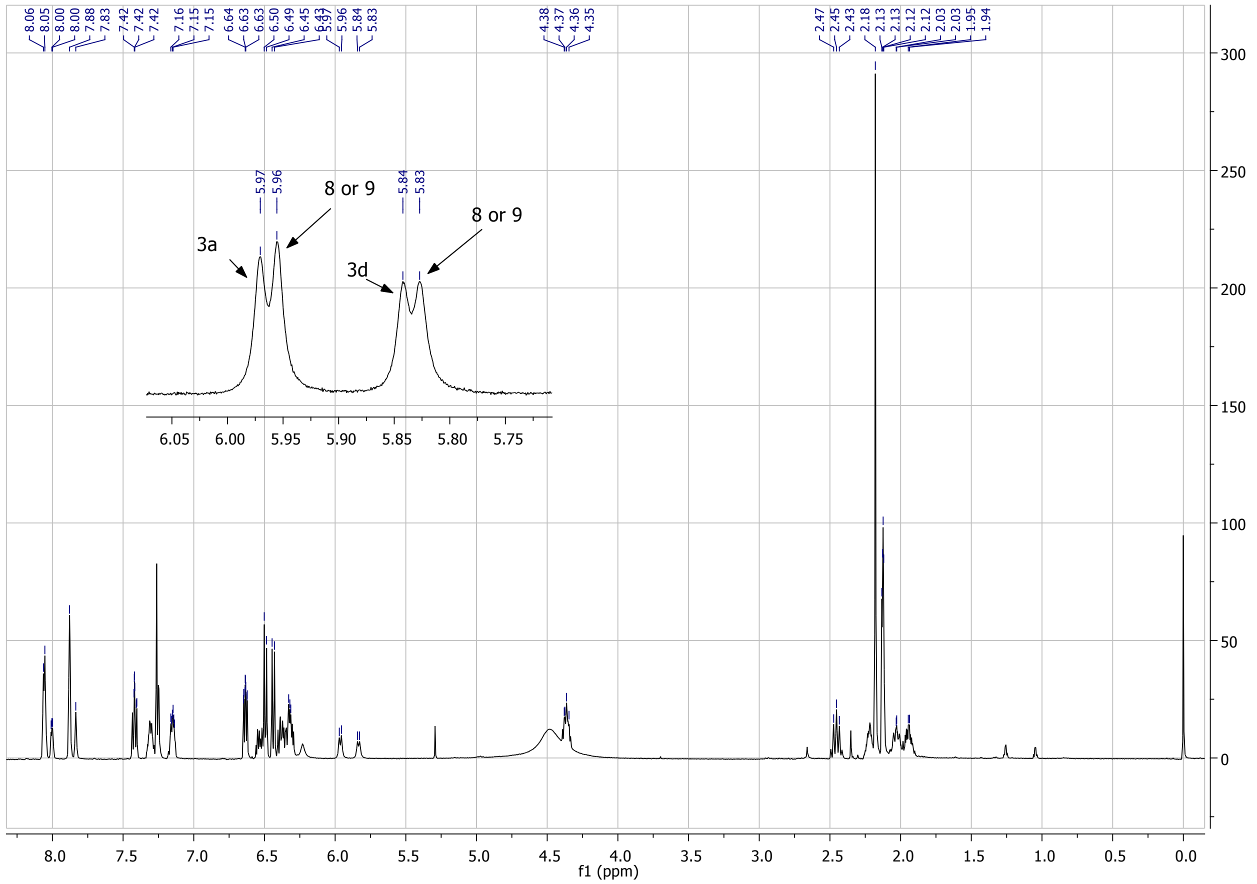
To follow the course of the reaction, the mixture was stirred in $CDCl_3$ and studied by ^{1}H NMR. The consumption of **1** was monitored by the integration of the peaks at 4.97 ppm with the consumption of **2a** again being monitored by disappearance of the signal at 7.41 ppm. The formation of **3a** was monitored by integration of the signals at 7.31-7.28 ppm and 4.37 ppm. The equilibrium was reached around 48h (~60 % conversion). The ^{1}H NMR spectrum showed the expected mixture of **1**, **2a** and **3a**; no other products and/or intermediates were detected.





In a strategy of proving the reversibility and to examine the dynamic nature of the system, component exchange was conducted. Aminal **3a**, isolated and purified by reprecipitation was treated with 2 equivalents of **2d** and after 24h, ^{1}H NMR revealed the formation of all the four possible aminals (^{1}H NMR overall yield 27%; aminals ratio = ~26:28:23:23).





X-ray diffraction data for compound 3l

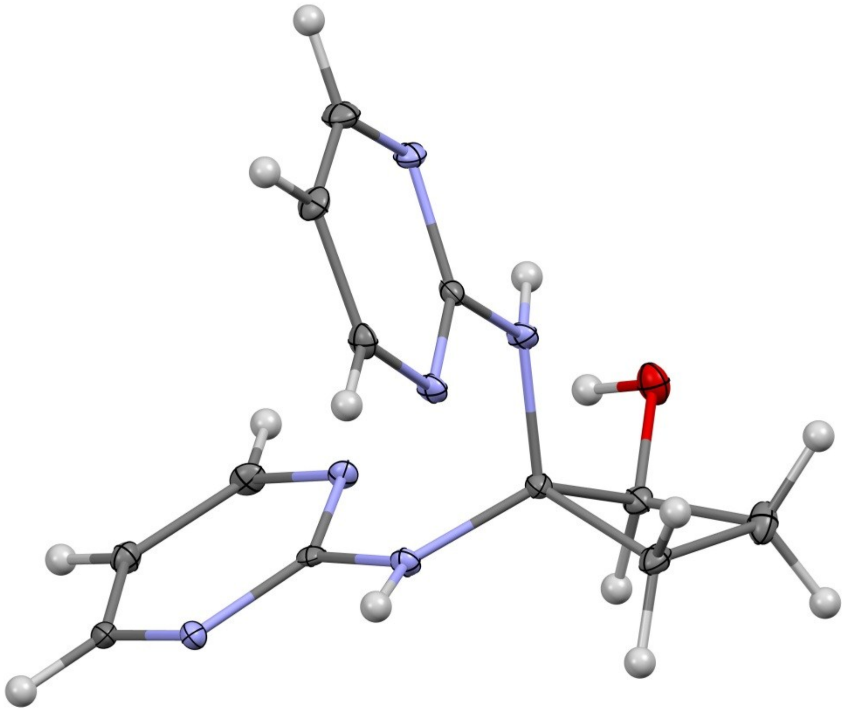


Fig. 1. ORTEP diagram of compound **3l**, showing 30% probability ellipsoids.

X-ray diffraction data for compound were collected by using a VENTURE PHOTON100 CMOS Bruker diffractometer with Micro-focus IuS source Mo $_{K\square}$ radiation. Crystals were mounted on a CryoLoop (Hampton Research) with Paratone-N (Hampton Research) as cryoprotectant and then flashfrozen in a nitrogen-gas stream at 100 K. For compounds, the temperature of the crystal was maintained at the selected value by means of a 700 series Cryostream cooling device to within an accuracy of ±1 K. The data were corrected for Lorentz polarization, and absorption effects. The structures were solved by direct methods using SHELXS-97[1] and refined against F^2 by full-matrix least-squares techniques using SHELXL-2016[2] with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were located on a difference Fourier map and introduced into the calculations as a riding model with

---

1) Sheldrick, G. M. SHELXS-97, Program for Crystal Structure Solution, University of Göttingen, Göttingen, Germany, 1997.

2) G. M. Sheldrick, Acta Crystallogr., Sect. A: Found. Crystallogr., 2008, **64**, 112-122

isotropic thermal parameters. All calculations were performed by using the Crystal Structure crystallographic software package WINGX.[3]

The crystal data collection and refinement parameters are given in Table X1.

Table X1. Crystallographic data and structure refinement details.

Compounds	**3l**
Recrystallization method	slow evaporation of $CHCl_3$
Empirical Formula	C_{12} H_{14} N_6 O
M_r	258.29
Crystal size, mm^3	0.11 x 0.05 x 0.03
Crystal system	triclinic
Space group	*P -1*
a, Å	8.3805(7)
b, Å	8.9419(8)
c, Å	9.0849(7)
α, °	103.317(3)
β, °	107.305(3)
γ, °	98.863(4)
Cell volume, $Å^3$	614.08(9)
Z ; Z'	2 ; 1
T, K	100(1)
Radiation type ; wavelength Å	MoKα ; 0.71073
F_{000}	272
μ, mm^{-1}	0.097
θ range, °	2.411 - 24.997
Reflection collected	13 706
Reflections unique	2 165
R_{int}	0.2330
GOF	0.869
Refl. obs. ($I > 2\sigma(I)$)	2 165
Parameters	182
wR_2 (all data)	0.0770
R value ($I > 2\sigma(I)$)	0.0458
Largest diff. peak and hole ($e^-.Å^{-3}$)	0.239 ; -0.277

Details of theoretical calculations

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3) Farrugia, L. J. *J. Appl. Cryst.*, 1999, **32**, 837.

Quantum Mechanics (QM) calculations were carried out at the Density Functional Theory (DFT) level on compounds **1**, **2a**, **A**/**A'**, **B**, and **3a** (Scheme 1). All calculations were performed with the Gaussian 09 commercial suite of computational software.[4] The mPW1PW hybrid functional[5] and the Def2SVP full-electron split valence basis sets with polarization functions (pVDZ) for all atomic species[6,7] were adopted throughout. For all compounds the geometries were optimized (opt keyword) until a stationary point on the potential surface was found. Analytic gradients were used. The default Berny algorithm was used with a geometry optimization method using an Energy-represented Direct Inversion in the Iterative Subspace algorithm (GEDIIS)[8] in redundant internal coordinates. The converged optimized geometries were verified by a calculation of harmonic frequencies (freq=raman keyword), computed by determining the second derivatives of the electronic energy with respect to the nuclear coordinates. Natural Bonding Orbital (NBO) populations[9-11] and Wiberg bond indices (bndidx keywork in nboread keyword subsection)[12] were calculated at the optimized geometries using the NBO 3.1 module. NPA results were exploited through a Second Order Perturbation Theory Analysis of Fock Matrix in NBO Basis, which allowed defining the donor-acceptor electron transfers between NBOs responsible for the H-bond formation. The results of the calculations were examined with GaussView 5.0.9[13] and Molden 5.3[14] programs. All calculations were carried out on a IBM x3755 server with 4 12-core AMD Opteron processors (48 cores) equipped with 64GB of RAM memory.

Figure S1. Relative total electronic energy profile (red) calculated at DFT level (mPW1PW functional; Def2SVP basis set) for the reactions leading from **1** + 2 **2a** to **3a** or **4** (See Scheme 1). The energy of the intermediates **A/A'** and **B** are also reported. The Zero Point Energy (ZPE) corrected values are depicted in a green color.

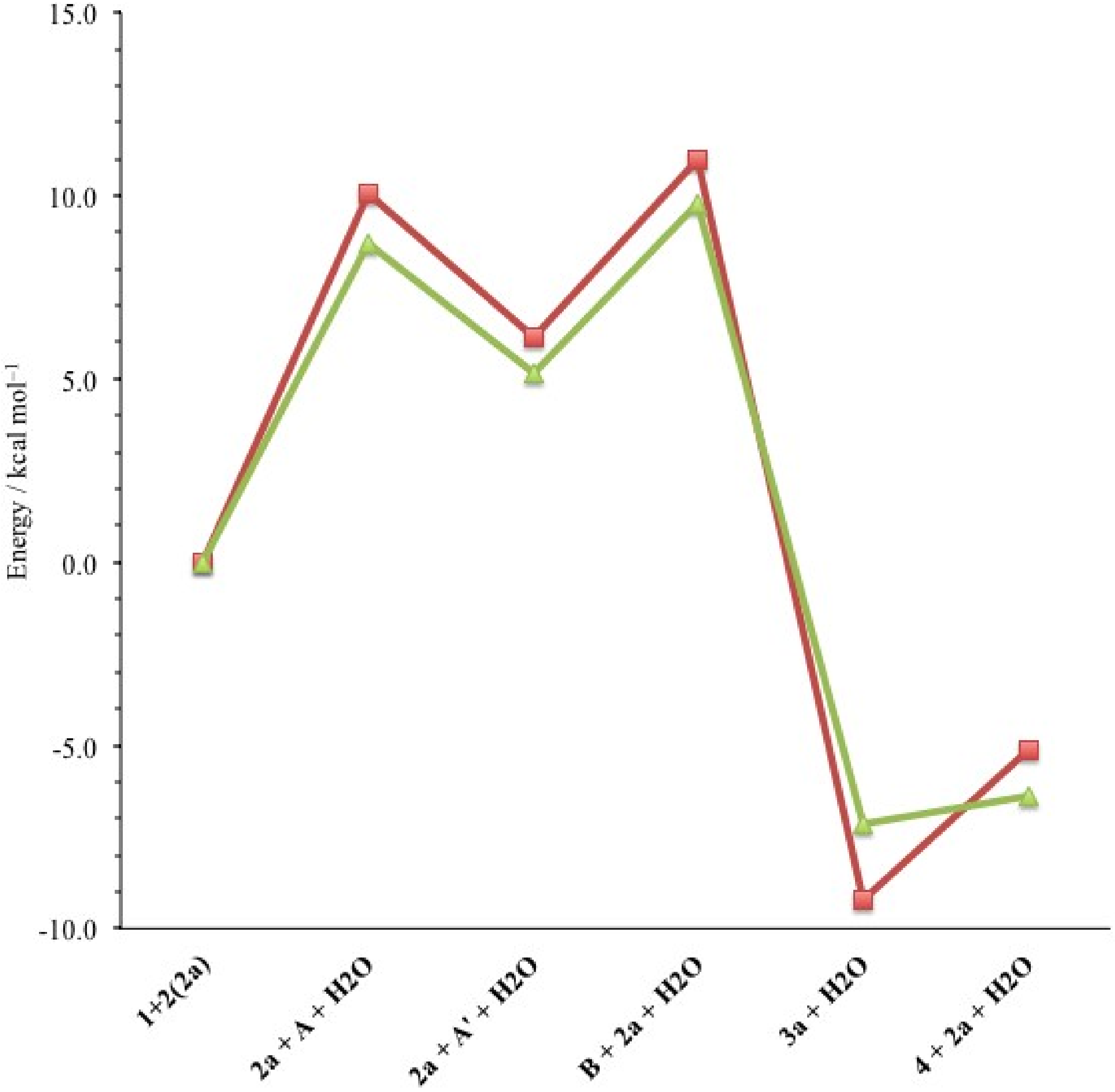

Table S1. Total electronic energies (Hartree) calculated at the optimized geometries for water, **1**, **2a**, **3a**, **4** and the intermediates **A**, **A'**, and **B** in the gas phase at DFT level (mPW1PW functional; Def2SVP basis set). ZPE-corrected values (E_0+ZPE) are also reported.

	E_0	E_0+ZPE
H_2O	-76.3389	-76.3173
1	-306.1412	-306.0449
2a	-303.3626	-303.2562
3a	-836.5423	-836.2514
A	-533.1489	-532.9700
A'	-533.1552	-532.9756
B	-533.1474	-532.9682
4	-533.1732	-532.9940

4) Gaussian 09, rev. D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.
5) C. Adamo, V. Barone, *J. Chem. Phys.* 1998, **108**, 664–675.
6) F. Weigend and R. Ahlrichs, *Phys. Chem. Chem. Phys.* 2005, **7**, 3297–3305.
7) F. Weigend, "Accurate Coulomb-fitting basis sets for H to Rn," *Phys. Chem. Chem. Phys.*, 2006, **8**, 1057–1065.
8) X. Li, M. J. Frisch, *J. Chem. Theory Comput.* 2006, **2**, 835-839.
9) A. E. Reed, F. Weinhold, *J. Chem. Phys.* 1983, **78**, 4066–4073.
10) A. E. Reed, R.B. Weinstock, F. Weinhold, *J. Chem. Phys.* 1985, **83**, 735–746.
11) A. E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev.* 1988, **88**, 899–926.
12) K. B. Wiberg, *Tetrahedron* 1968, **24**, 1083–1096.
13) R. Dennington, T. Keith, J. Millam, *GaussView*, Version 5.0.9, Gaussian, Inc.: Wallingford, CT, USA, 2009.
14) G. Schaftenaar, J.H. Noordik, *J. Comput. Aided Mol. Des.* 2000, **14**, 123–134.