

SUPPLEMENTARY MATERIAL TO

Synthetic route towards potential bivalent ligands possessing opioid and D₂/D₃

pharmacophores

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Isolated yields and spectroscopic data of synthesized compounds

N-Phenyl-*N*-(piperidin-4-yl) propionamide (norfentanyl) (**4**). Obtained from **5** via three step synthesis already known from literature.¹⁻³ Overall yield: 2.00 g (88.1 %); off-white solid; m.p. 83-84 °C. ¹H NMR (500 MHz, CDCl₃): δ = 7.46 – 7.36 (3H, m, Ar -H), 7.13 – 7.00 (2H, m, Ar-H), 4.79 – 4.68 (1H, m, CH-H), 3.07 (2H, d, *J* = 12.3 Hz, CH₂-H), 2.78 (1H, br. s, NH-H, partially overlapped), 2.76 – 2.67 (2H, m, CH₂-H), 1.92 (2H, q, *J* = 7.4 Hz, CH₂-H), 1.84 – 1.74 (2H, m, CH₂-H), 1.37 – 1.21 (2H, m, CH₂-H), 1.01 (3H, t, *J* = 7.5 Hz, CH₃-H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 173.3, 138.9, 130.3, 129.3, 128.3, 52.1, 45.8, 31.5, 28.5, 9.6 ppm. The spectra were in accordance with the previously reported data.

N-(1-(3-Chloropropyl) piperidin-4-yl)-*N*-phenylpropionamide (**8a**). Yield: 0.28 g (69.9 %); pale yellow oil. ¹H NMR (500 MHz, CDCl₃): δ = 7.55 – 7.29 (3H, m, Ar-H), 7.19 – 7.00 (2H, m, Ar-H), 4.79 – 4.51 (1H, m, CH-H), 3.51 (2H, t, *J* = 6.5 Hz, CH₂-H), 2.88 (2H, br. d, *J* = 12.0 Hz, CH₂-H), 2.41 (2H, t, *J* = 7.2 Hz, CH₂-H), 2.21 – 2.04 (2H, m, CH₂-H), 2.00 – 1.70 (6H, m, CH₂-H), 1.59 – 1.28 (2H, m, CH₂-H), 1.01 (3H, t, *J* = 7.4 Hz, CH₃-H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 173.5, 138.9, 130.4, 129.3, 128.2, 55.3, 53.2, 52.1, 43.2, 30.5, 30.0, 28.4, 9.4 ppm.

8-(*N*-Phenylpropionamido)-5-azaspiro [4.5] decan-5-ium chloride (**8b**). Yield: 0.27 g (64.5%); yellow oil. IR (ATR, cm⁻¹): 2977.3 (C-H aliphatic), 1645.1 (C=O), 1272.8 (C-N amine). ¹H NMR (500 MHz, CDCl₃): δ = 7.53 – 7.40 (3H, m, Ar-H), 7.14 (2H, d, *J* = 7.1 Hz, Ar-H), 4.82 – 4.59 (1H, m, CH-H), 4.02 – 3.74 (6H, m, CH₂-H), 3.66 – 3.51 (2H, m, CH₂-H), 2.23 (br. s, 4H), 2.12 (2H, d, *J* = 13.5 Hz, CH₂-2), 2.05 – 1.86 (4H, m, CH₂-H), 0.98 (3H, t, *J* = 7.4 Hz, CH₃-3) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 174.1, 139.1, 130.3, 129.7, 129.2, 67.1, 59.3, 57.7, 51.0, 41.2, 28.7, 26.0, 21.8, 21.2, 9.6 ppm. HRMS-HESI-Orbitrap: calcd. for C₁₈H₂₇N₂O⁺ [M]⁺ 287.21179; found 287.21169.

3-(*N*-Phenylpropionamido)-6-azaspiro [5.5] undecan-6-ium chloride (**8c**). Yield: 0.29 g (66.2 %); yellow oil. IR (ATR, cm⁻¹): 2943.0 (C-H aliphatic), 1647.4 (C=O), 1269.7 (C-N amine). ¹H NMR (500 MHz, CDCl₃): δ = 7.53 – 7.37 (3H, m, Ar-H,) 7.15 (2H, dd, *J* = 7.3, 1.9 Hz, Ar-H), 4.61 – 4.49 (1H, m, CH-H), 4.03 (2H, d, *J* = 12.6 Hz, CH₂-H), 3.90 – 3.82 (2H, m, CH₂-H), 3.78 (2H, t, *J* = 12.2 Hz, CH₂-H), 3.59 (2H, br. s, CH₂-H), 2.29 – 2.10 (2H, m, CH₂-H), 2.07 (2H, d, *J* = 13.1 Hz, CH₂-H), 1.98 – 1.87 (4H, m, CH₂-H), 1.79 (4H, br. s, CH₂-H), 0.98 (3H, t, *J* = 7.4 Hz, CH₃-H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 174.2, 139.8, 130.3, 129.3, 129.1, 64.2, 58.2, 53.7, 52.4, 28.8, 23.4, 21.3, 20.2, 19.7, 9.5 ppm. HRMS-HESI-Orbitrap: calcd. for C₁₉H₂₉N₂O⁺ [M]⁺ 301.22744; found 301.22694.

N-(1-(6-bromohexyl) piperidin-4-yl)-*N*-phenylpropionamide (**8d**). Yield: 0.36 g (71.2 %); pale yellow oil. ¹H NMR (500 MHz, CDCl₃): δ = 7.44 – 7.31 (3H, m, Ar-H), 7.14 – 6.98 (2H, m, Ar-H), 4.73 – 4.56 (1H, m, CH-H), 3.50 (2H, t, *J* = 6.7 Hz, CH₂-H), 2.91 (2H, d, *J* = 11.7 Hz, CH₂-H), 2.36 – 2.18 (2H, m, CH₂-H), 2.09 – 1.98 (2H, m, CH₂-H), 1.92 (2H, q, *J* = 7.4 Hz, CH₂-H), 1.86 – 1.66 (4H, m, CH₂-H), 1.47 – 1.34 (6H, m, CH₂-H), 1.35 – 1.20 (2H, m, CH₂-H), 1.01 (3H, t, *J* = 7.4 Hz, CH₃-H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 173.70, 139.07, 130.61, 129.44, 128.41, 58.71, 53.38, 52.44, 45.19, 32.67, 30.73, 28.69, 27.17, 27.08, 26.95, 9.80 ppm.

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72 *N*-phenylpiperidin-4-amine (**12**) Obtained from **9** via three step procedure already known from
73 literature.^{4,5} Overall yield: 8.00 g (84.5 %); pale yellow oil. ¹H NMR (500 MHz, CDCl₃): δ = 7.21
74 – 7.09 (2H, m, Ar-H), 6.67 (1H, t, *J* = 7.3 Hz, Ar-H), 6.60 (2H, d, *J* = 7.7 Hz, Ar-H), 3.52 (1H, br.
75 s, NH-H), 3.36 (1H, br. s, CH-H), 3.11 (2H, dt, *J* = 12.8, 3.5 Hz, CH₂-H), 2.71 (2H, td, *J* = 12.5,
76 2.5 Hz, CH₂-H), 2.07 (2H, d, *J* = 12.5 Hz, CH₂-H), 1.78 (1H, br. s, NH-H), 1.40 – 1.21 (2H, m,
77 CH₂-H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 146.92, 129.26, 117.15, 113.21, 50.32, 45.50,
78 33.96 ppm.

79 4-chloro-1-(4-phenylpiperazin-1-yl) butan-1-one (**13a**). Yield: 0.90 g (97.3 %); pale yellow oil.
80 IR (ATR, cm⁻¹): 2916.3 (C-H aliphatic), 1644.4 (C=O), 869.9 (C-Cl). ¹H NMR (500 MHz, CDCl₃):
81 δ = 7.28 – 7.17 (2H, m, Ar-H), 6.97 – 6.77 (3H, m, Ar-H), 3.76 – 3.67 (2H, m, CH₂-H), 3.64 –
82 3.54 (4H, m, CH₂-H), 3.11 (4H, dt, *J* = 16.4, 5.2 Hz, CH₂-H), 2.49 (2H, t, *J* = 7.1 Hz, CH₂-H), 2.13
83 – 2.05 (2H, m, CH₂-H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 170.3, 151.0, 129.4, 120.7, 116.7,
84 49.8, 49.5, 45.5, 45.0, 41.7, 29.8, 28.0 ppm.

85 4-chloro-1-(4-(3-methoxyphenyl) piperazin-1-yl) butan-1-one (**13b**). Yield: 0.99 g (95.9 %); pale
86 yellow oil. IR (ATR, cm⁻¹): 2919.8 (C-H aliphatic), 1590.8 (C=O), 746.9 (C-Cl). ¹H NMR (500
87 MHz, CDCl₃): δ = 7.05 – 6.97 (1H, m, Ar-H), 6.94 – 6.82 (3H, m, Ar-H), 3.86 (3H, s, OCH₃-H),
88 3.81 – 3.75 (2H, m, CH₂-H), 3.69 – 3.60 (4H, m, CH₂-H), 3.02 (4H, dt, *J* = 18.4, 5.1 Hz, CH₂-H),
89 2.53 (2H, t, *J* = 7.1 Hz, CH₂-H), 2.14 (2H, q, *J* = 6.5 Hz, CH₂-H). ppm. ¹³C NMR (126 MHz,
90 CDCl₃): δ = 170.3, 152.4, 140.7, 123.7, 121.2, 118.5, 111.5, 55.5, 51.1, 50.7, 45.8, 45.0, 42.0,
91 29.9, 28.0 ppm.

92 4-chloro-1-(4-(2,3-dichlorophenyl) piperazin-1-yl) butan-1-one (**13c**). Yield: 1.14 g (97.9 %); pale
93 yellow oil. IR (ATR, cm⁻¹): 2921.7 (C-H aliphatic), 1644.6 (C=O), 784.2 (C-Cl), 715.0 (C-Cl). ¹H
94 NMR (500 MHz, CDCl₃): δ = 7.24 – 7.13 (2H, m, Ar-H), 6.93 (1H, dd, *J* = 7.7, 1.9 Hz, Ar-H),
95 3.84 – 3.77 (2H, m, CH₂-H), 3.69 – 3.65 (4H, m, CH₂-H), 3.07 – 2.98 (4H, m, CH₂-H), 2.56 (2H,
96 t, *J* = 7.1 Hz, CH₂-H), 2.20 – 2.12 (2H, m, CH₂-H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 13C
97 NMR (126 MHz, CDCl₃) δ 170.4, 150.7, 134.2, 127.7, 125.3, 118.9, 51.7, 45.9, 45.8, 44.9, 41.9,
98 29.8, 28.0 ppm.

99 4-(4-(phenylamino) piperidin-1-yl)-1-(4-phenylpiperazin-1-yl) butan-1-one (**14a**). Yield: 0.34 g
100 (49.2 %); pale yellow oil. IR (ATR, cm⁻¹): 3340.7 (N-H amine), 3048.8 (C-H aromatic), 2939.2
101 (C-H aliphatic), 1637.7 (C=O), 1232.1 (C-N amine). ¹H NMR (500 MHz, CDCl₃): δ = 7.34 – 7.20
102 (2H, m, Ar-H), 7.22 – 7.07 (2H, m, Ar-H), 6.97 – 6.79 (3H, m, Ar-H), 6.76 – 6.63 (1H, m, Ar-H),
103 6.64 – 6.56 (2H, m, Ar-H), 3.86 – 3.73 (2H, m, CH₂-H), 3.70 – 3.60 (2H, m, CH₂-H), 3.51 (1H,
104 br. s, NH-H), 3.37 – 3.24 (1H, m, CH-H), 3.21 – 3.11 (4H, m, CH₂-H), 2.89 (2H, d, *J* = 11.4 Hz,
105 CH₂-H), 2.51 – 2.34 (4H m, CH₂-H), 2.25 – 2.10 (2H, m, CH₂-H), 2.06 (2H, d, *J* = 12.0 Hz, CH₂-
106 H), 1.95 – 1.81 (2H, m, CH₂-H), 1.60 – 1.37 (2H, m, CH₂-H) ppm. ¹³C NMR (126 MHz, CDCl₃):
107 δ = 171.5, 151.1, 147.2, 129.4, 129.4, 120.7, 117.3, 116.7, 113.4, 58.0, 52.5, 50.0, 49.9, 49.5, 45.6,
108 41.6, 32.6, 31.1, 22.8 ppm.

109 *1-(4-(3-methoxyphenyl) piperazin-1-yl)-4-(4-(phenylamino) piperidin-1-yl) butan-1-one (14b)*.
110 Yield: 0.33 g (45.1%); pale yellow oil. IR (ATR, cm^{-1}): 3340.4 (N-H amine), 3050.8 (C-H
111 aromatic), 2936.6 (C-H aliphatic), 1636.4 (C=O), 1241.5 (C-N amine). ^1H NMR (500 MHz,
112 CDCl_3): δ = 7.21 – 7.11 (2H, m, Ar-H), 7.11 – 6.99 (1H, m, Ar-H), 6.96 – 6.87 (3H, m, Ar-H),
113 6.73 – 6.63 (1H, m, Ar-H), 6.62 – 6.56 (2H, m, Ar-H), 3.87 (3H, s, OCH_3 -H), 3.83 – 3.77 (2H, m,
114 CH_2 -H), 3.73 – 3.61 (2H, m, CH_2 -H), 3.52 (1H, br. s, NH-H), 3.34 – 3.24 (1H, m, CH-H), 3.01 –
115 2.96 (4H, m, CH_2 -H), 2.88 (2H, d, J = 11.0 Hz, 2H), 2.47 – 2.36 (4H, m, CH_2 -H), 2.14 (2H, t, J =
11.0 Hz, CH_2 -H), 2.05 (2H, d, J = 11.8 Hz, CH_2 -H), 1.94 – 1.78 (2H, m, CH_2 -H), 1.58 – 1.35 (2H,
117 m, CH_2 -H) ppm. ^{13}C NMR (126 MHz, CDCl_3): δ = 171.4, 152.3, 147.1, 140.7, 129.3, 123.6, 121.1,
118 118.4, 117.2, 113.3, 111.4, 57.9, 55.5, 52.4, 51.1, 50.6, 49.9, 45.9, 41.8, 32.5, 31.0, 22.7 ppm.

119 *1-(4-(2,3-dichlorophenyl) piperazin-1-yl)-4-(4-(phenylamino) piperidin-1-yl) butan-1-one (14c)*.
120 Yield: 0.45 g (55 %); pale yellow oil. IR (ATR, cm^{-1}): 3341.4 (N-H amine), 3049.9 (C-H aromatic),
121 2940.6 (C-H aliphatic), 1638.1 (C=O), 1237.8 (C-N amine). ^1H NMR (500 MHz, CDCl_3): δ = 1H
122 NMR (500 MHz, Chloroform-d) δ 7.21 – 7.11 (3H, m, Ar-H), 7.01 – 6.88 (2H, m, Ar-H), 6.71 –
123 6.64 (1H, m, Ar-H), 6.62 – 6.56 (2H, m, Ar-H), 3.84 – 3.77 (2H, m, CH_2 -H), 3.71 – 3.62 (2H, m,
124 CH_2 -H), 3.52 (1H, br. s, NH-H), 3.36 – 3.28 (1H, m, CH-H), 3.05 – 2.97 (4H, m, CH_2 -H), 2.94 –
125 2.85 (2H, m, CH_2 -H), 2.46 – 2.36 (4H, m, CH_2 -H), 2.22 – 2.11 (2H, m, CH_2 -H), 2.10 – 2.02 (2H,
126 m, CH_2 -H), 1.93 – 1.80 (2H, m, CH_2 -H), 1.60 – 1.41 (2H, m, CH_2 -H) ppm. ^{13}C NMR (126 MHz,
127 CDCl_3): δ = 171.5, 150.7, 147.2, 134.3, 129.4, 127.8, 127.7, 125.3, 118.8, 117.3, 113.3, 57.9, 52.5,
128 51.8, 51.2, 50.1, 45.9, 41.9, 32.6, 31.0, 22.7 ppm.

129 *N-phenyl-1-(4-(4-phenylpiperazin-1-yl) butyl) piperidin-4-amine (16a)*. Yield: 0.33 g (84.8 %);
130 pale yellow oil. IR (ATR, cm^{-1}): 3397.6 (N-H amine), 3053.4 (C-H aromatic), 2938.4 (C-H
131 aliphatic), 1601.4 (C=O), 1235.7 (C-N amine). ^1H NMR (500 MHz, CDCl_3): δ = 7.32 – 7.24 (2H,
132 m, Ar-H), 7.21 – 7.14 (2H, m, Ar-H), 6.98 – 6.91 (2H, m, Ar-H), 6.91 – 6.83 (1H, m, Ar-H), 6.73
133 – 6.65 (1H, m, Ar-H), 6.65 – 6.57 (2H, m, Ar-H), 3.46 (1H, br. s, NH-H), 3.39 – 3.28 (1H, m, CH-
134 H), 3.27 – 3.18 (4H, m, CH_2 -H), 2.92 (2H d, J = 11.0 Hz, CH_2 -H), 2.65 – 2.57 (4H, m, CH_2 -H),
135 2.46 – 2.35 (4H, m, CH_2 -H), 2.15 (2H, t, J = 11.1 Hz, CH_2 -H), 2.08 (2H, d, J = 12.1 Hz, CH_2 -H),
136 1.62 – 1.44 (6H, m, CH_2 -H) ppm. ^{13}C NMR (126 MHz, CDCl_3): δ = 151.3, 147.0, 129.3, 129.1,
137 119.6, 117.2, 116.0, 113.2, 58.5, 58.4, 53.2, 52.4, 49.1, 32.4, 25.0, 24.9 ppm.

138 *1-(4-(4-(3-methoxyphenyl) piperazin-1-yl) butyl)-N-phenylpiperidin-4-amine (16b)*. Yield: 0.42 g
139 (84.2 %); pale yellow oil. IR (ATR, cm^{-1}): 3307.5 (N-H amine), 3052.1 (C-H aromatic), 2939.0 (C-
140 H aliphatic), 1601.1 (C=O), 1241.2 (C-N amine). ^1H NMR (500 MHz, CDCl_3): δ = 7.19 – 7.12
141 (2H, m, Ar-H), 7.03 – 6.94 (1H, m, Ar-H), 6.97 – 6.89 (2H, m, Ar-H), 6.88 – 6.82 (1H, m, Ar-H),
142 6.72 – 6.64 (1H, m, Ar-H), 6.63 – 6.55 (2H, m, Ar-H), 3.85 (3H, s, OCH_3 -H), 3.53 (1H, br. s, NH-
143 H), 3.40 – 3.24 (1H, m, CH-H), 3.10 (4H, br. s, CH_2 -H), 2.91 (2H, d, J = 11.2 Hz, CH_2 -H), 2.66
144 (4H, br. s, CH_2 -H), 2.47 – 2.35 (4H, m, CH_2 -H), 2.15 (2H, t, J = 11.0 Hz, CH_2 -H), 2.07 (2H, d, J =
145 11.8 Hz, CH_2 -H), 1.56 (4H, br. s, CH_2 -H), 1.55 – 1.44 (2H, m, CH_2 -H) ppm. ^{13}C NMR (126
146 MHz, CDCl_3): δ = 153.8, 148.6, 142.9, 130.9, 124.5, 122.6, 119.8, 118.8, 114.8, 112.8, 60.1, 56.9,
147 55.0, 54.0, 52.2, 51.4, 33.9, 26.6 ppm.

148 *1-(4-(4-(2,3-dichlorophenyl) piperazin-1-yl) butyl)-N-phenylpiperidin-4-amine (16c)*. Yield: 0.46
149 g (83.1 %); pale yellow oil. IR (ATR, cm^{-1}): 3399.9 (N-H amine), 3051.9 (C-H aromatic), 2936.4

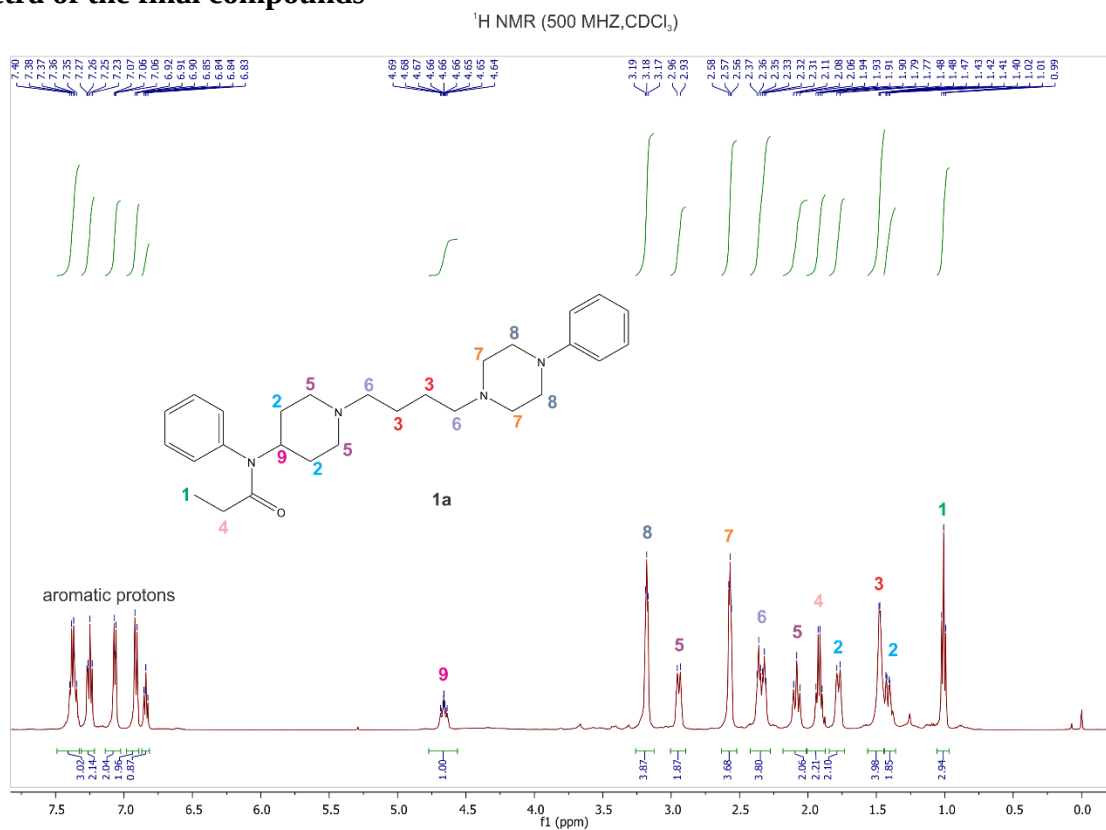
(C-H aliphatic), 1602.2 (C=O), 1242.3 (C-N amine), 781.3 (C-Cl). ¹H NMR (500 MHz, CDCl₃): δ = 7.19 – 7.05 (4H, m, Ar-H), 6.70 – 6.63 (1H, m, Ar-H), 6.62 – 6.56 (3H, m, Ar-H), 3.50 (1H, br. s, NH-H), 3.34 – 3.21 (1H, m, CH-H), 3.12 – 2.93 (4H, m, CH₂-H), 2.86 (4H, d, *J* = 10.7 Hz, CH₂-H), 2.39 – 2.29 (4H, m, CH₂-H), 2.15 – 1.99 (6H, m, CH₂-H), 1.55 – 1.47 (4H, m, CH₂-H), 1.50 – 1.41 (2H, m, CH₂-H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 13C NMR (126 MHz, CDCl₃) δ 151.8, 147.2, 134.1, 129.4, 127.5, 124.7, 124.6, 118.8, 117.3, 113.3, 58.7, 52.6, 51.4, 50.1, 46.4, 32.7, 25.4 ppm.

N-Phenyl-*N*-(1-(4-(4-phenylpiperazin-1-yl) butyl) piperidin-4-yl) propionamide (**1a**). Yield: 0.22 g (83 %); pale yellow oil. IR (ATR, cm⁻¹): 3058.6 (C-H aromatic); 2939.1 (C-H aliphatic); 1655.8 (C=O); 1238.4 (C-N-amine). ¹H NMR (500 MHz, CDCl₃): δ = 7.49 – 7.32 (3H, m, Ar-H), 7.29 – 7.20 (2H, m, Ar-H), 7.11 – 7.00 (2H, m, Ar-H), 6.94 – 6.88 (2H, m, Ar-H), 6.89 – 6.81 (1H, m, Ar-H), 4.73 – 4.58 (1H, m, CH-H), 3.22 – 3.15 (4H, m, CH₂-H), 2.94 (2H, d, *J* = 11.4 Hz, CH₂-H), 2.62 – 2.53 (4H, m, CH₂-H), 2.34 (4H, dt, *J* = 20.1, 6.2 Hz, CH₂-H), 2.08 (2H, t, *J* = 11.5 Hz, CH₂-H), 1.92 (2H, q, *J* = 7.3 Hz, CH₂-H), 1.78 (2H, d, *J* = 11.6 Hz, CH₂-H), 1.53 – 1.44 (4H, m, CH₂-H, partially overlapped), 1.44 – 1.35 (2H, m, CH₂-H, partially overlapped), 1.01 (3H, t, *J* = 7.4 Hz, CH₃-H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 173.6, 151.4, 138.9, 130.5, 129.4, 129.2, 129.2, 128.4, 119.7, 116.1, 58.5, 58.4, 53.3, 53.2, 52.2, 49.1, 30.5, 28.6, 25.1, 24.9, 9.7 ppm. HRMS-HESI-Orbitrap: calcd. for C₂₈H₄₀N₄O [M+H]⁺ 449.32749; found 449.32844.

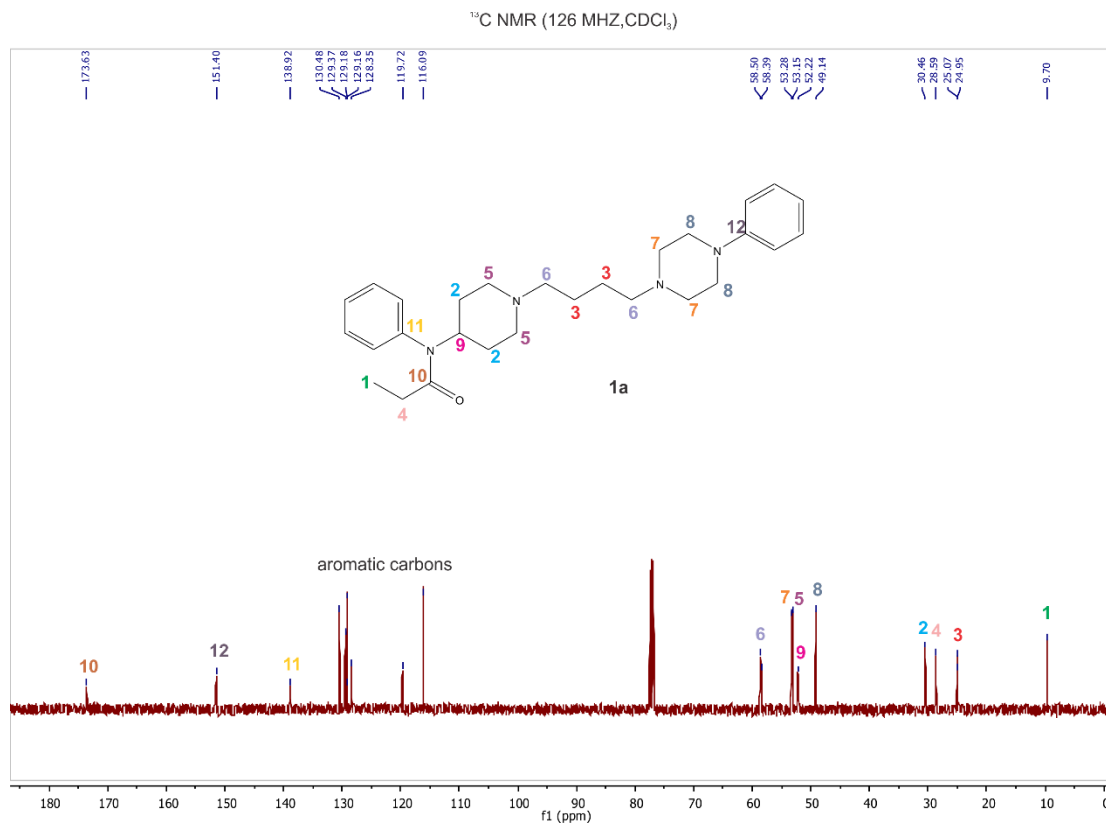
N-(1-(4-(4-(3-methoxyphenyl) piperazin-1-yl) butyl) piperidin-4-yl)-*N*-phenylpropionamide (**1b**). Yield: 0.25 g (85.6 %); pale yellow oil. IR (ATR, cm⁻¹): 3058.2 (C-H aromatic); 2939.1 (C-H alkane); 1655.5 (C=O); 1241.4 (C-N amine). ¹H NMR (500 MHz, CDCl₃): δ = 7.44 – 7.34 (3H, m, Ar-H), 7.11 – 7.04 (2H, m, Ar-H), 7.03 – 6.97 (1H, m, Ar-H), 6.96 – 6.90 (2H, m, Ar-H), 6.89 – 6.83 (1H, m, Ar-H), 4.78 – 4.54 (1H, m, CH-H), 3.86 (3H, s, OCH₃-H), 3.09 (4H s, CH₂-H), 2.95 (2H, d, *J* = 11.4 Hz, CH₂-H), 2.64 (4H, s, CH₂-H), 2.44 – 2.36 (2H, m, CH₂-H), 2.37 – 2.28 (2H, m, CH₂-H), 2.08 (2H, t, *J* = 11.3 Hz, CH₂-H), 1.93 (2H, q, *J* = 7.3 Hz, CH₂-H), 1.79 (2H, d, *J* = 11.5 Hz, CH₂-H), 1.58 – 1.44 (4H, m, CH₂-H, partially overlapped), 1.46 – 1.34 (2H, m, CH₂-H, partially overlapped), 1.02 (3H, t, *J* = 7.4 Hz, CH₃-H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 173.6, 152.3, 141.4, 138.9, 130.5, 129.4, 128.3, 123.0, 121.1, 118.3, 111.3, 58.6, 58.5, 55.4, 53.5, 53.2, 52.3, 50.6, 30.5, 28.6, 25.2, 24.9, 9.7 ppm. HRMS-HESI-Orbitrap: calcd. for C₂₉H₄₂N₄O₂ [M+H]⁺ 479.33805; found 479.33886.

N-(1-(4-(4-(2,3-dichlorophenyl) piperazin-1-yl) butyl) piperidin-4-yl)-*N*-phenylpropionamide (**1c**). Yield: 0.26 g (84.2 %); pale yellow oil. IR (ATR, cm⁻¹): 3057.9 (C-H aromatic); 2940.2 (C-H aliphatic); 1653.8 (C=O); 1242.7 (C-N amine), 735.7 (C-Cl). ¹H NMR (500 MHz, CDCl₃): δ = 7.45 – 7.33 (3H, m, Ar-H), 7.16 – 7.10 (2H, m, Ar-H), 7.10 – 7.02 (2H, m, Ar-H), 6.99 – 6.89 (1H, m, Ar-H), 4.71 – 4.60 (1H, m, CH-H), 3.05 (4H s, CH₂-H), 2.96 (2H, d, *J* = 11.5 Hz, CH₂-H), 2.62 (4H s, CH₂-H), 2.47 – 2.37 (2H, m, CH₂-H), 2.37 – 2.30 (2H, m, CH₂-H), 2.10 (2H, t, *J* = 11.6 Hz, CH₂-H), 1.97 – 1.88 (2H, m, CH₂-H), 1.78 (2H, d, *J* = 12.6 Hz, CH₂-H), 1.53 – 1.46 (4H, m, CH₂-H, partially overlapped), 1.46 – 1.35 (2H, m, CH₂-H, partially overlapped), 1.01 (3H, t, *J* = 7.4 Hz, CH₃-H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 173.6, 151.3, 138.9, 134.1, 130.4, 129.4, 128.4, 127.5, 124.6, 118.7, 58.4, 58.3, 53.3, 53.1, 52.2, 51.2, 30.4, 28.6, 24.9, 24.8, 9.7 ppm. HRMS-Heated ESI-Orbitrap: calcd. for C₂₈H₃₈Cl₂N₄O [M+H]⁺ 517.24954; found 517.25082.

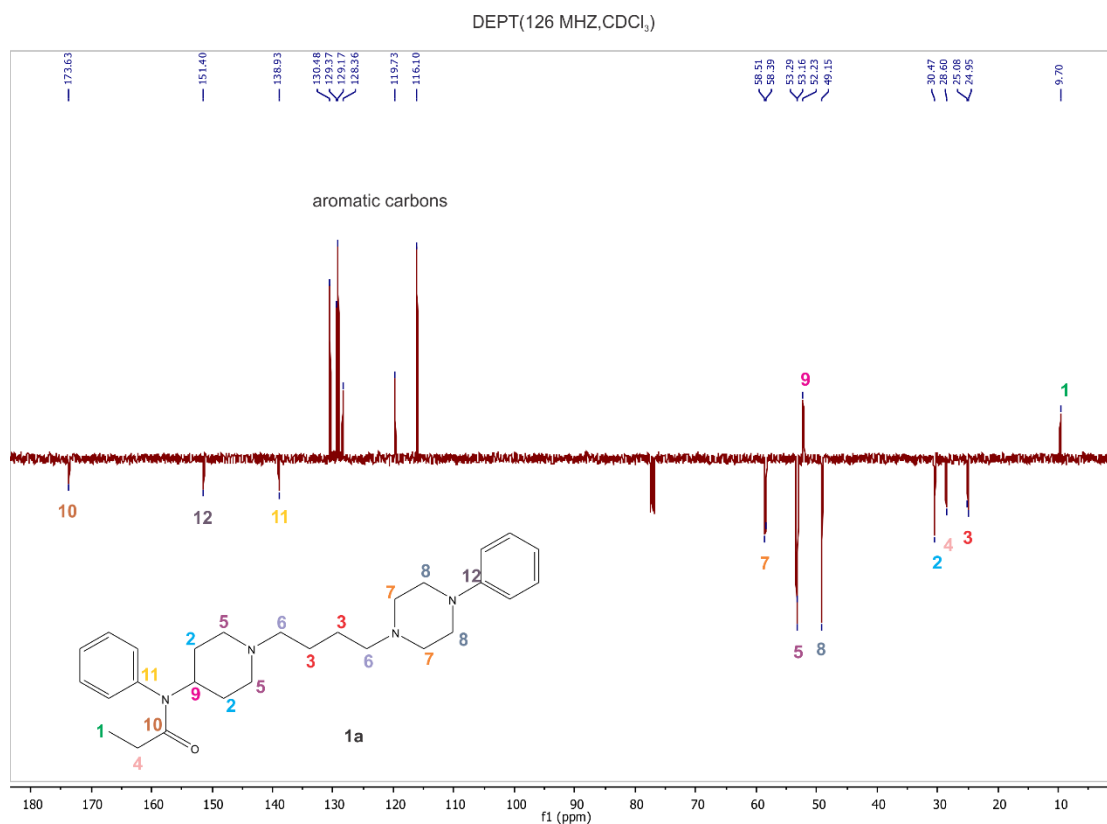
191 Spectra of the final compounds



192

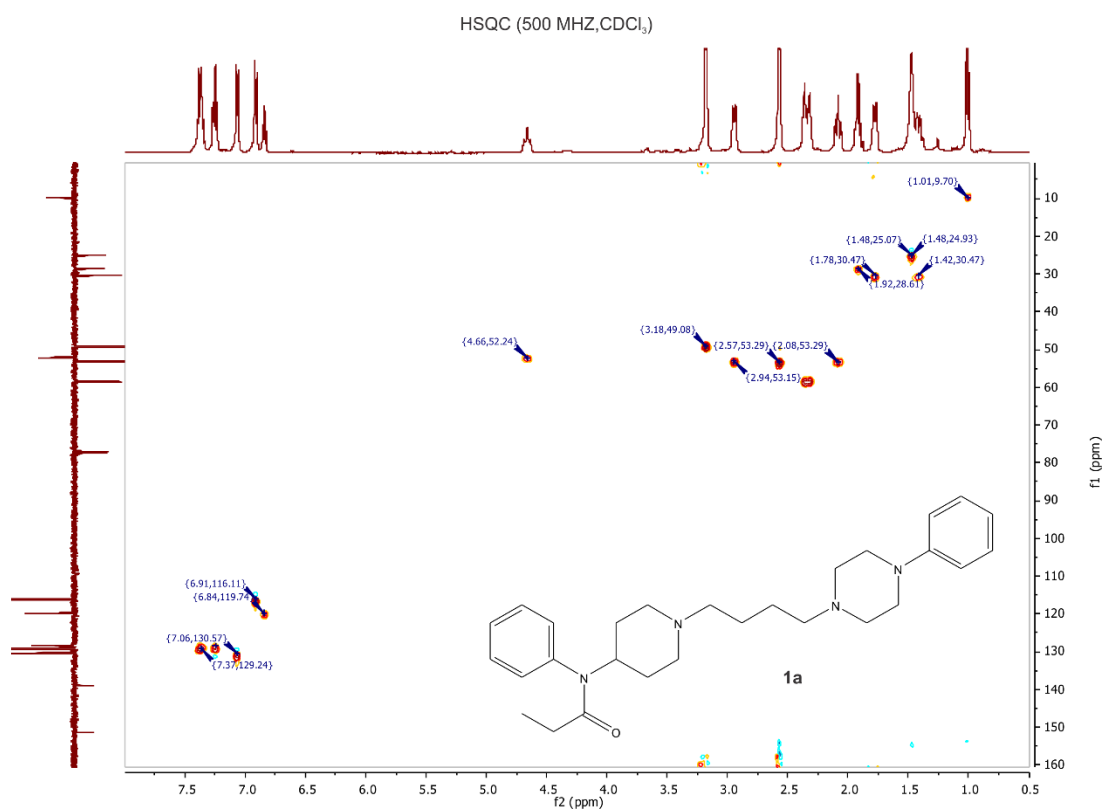


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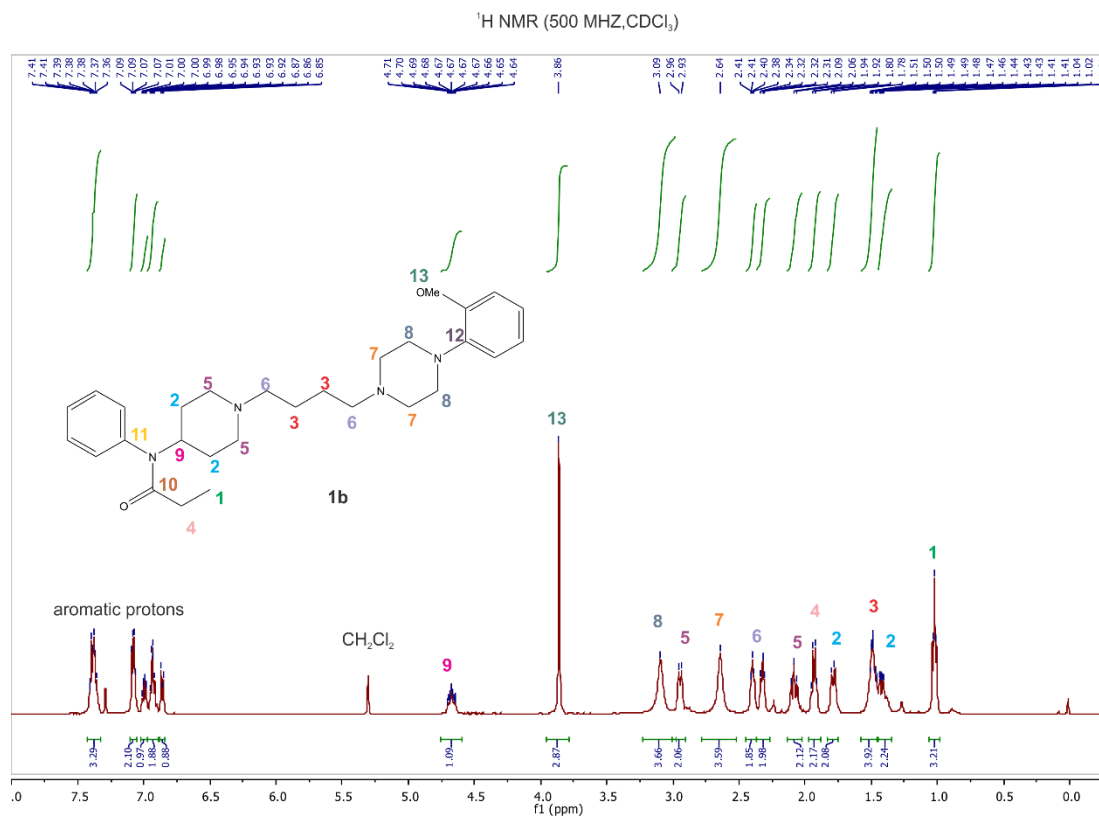
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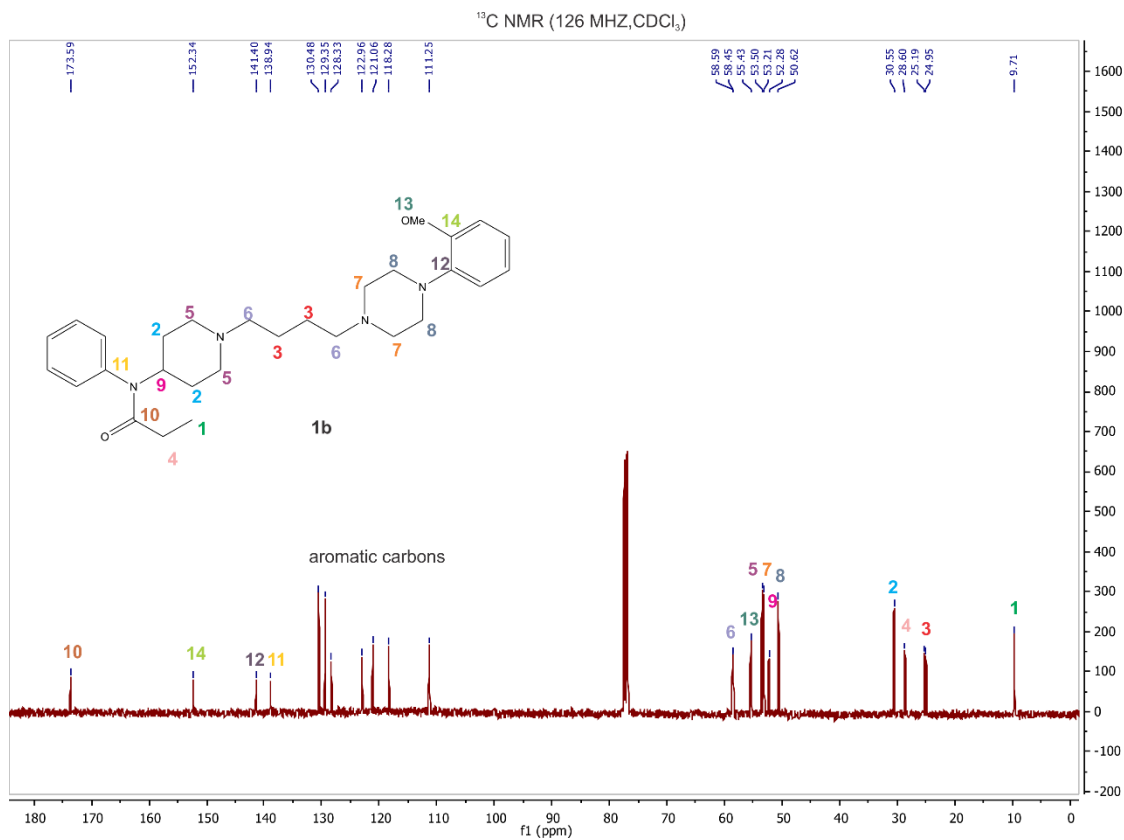


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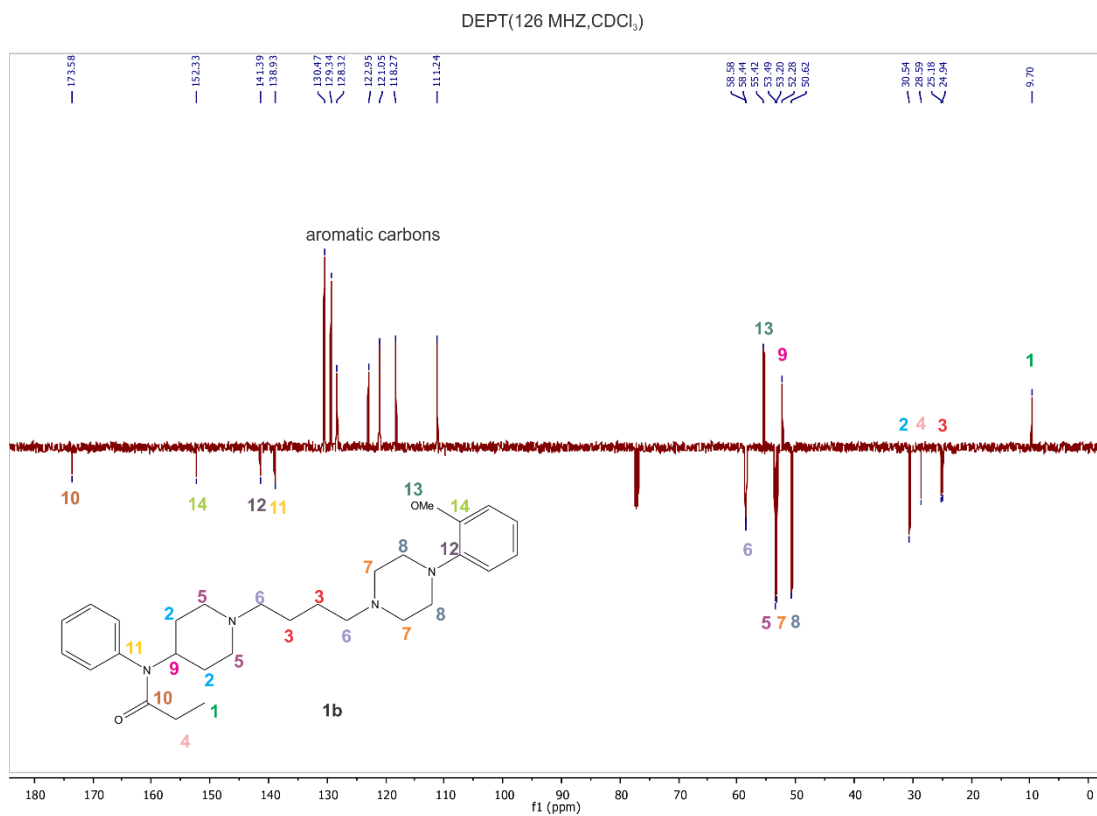


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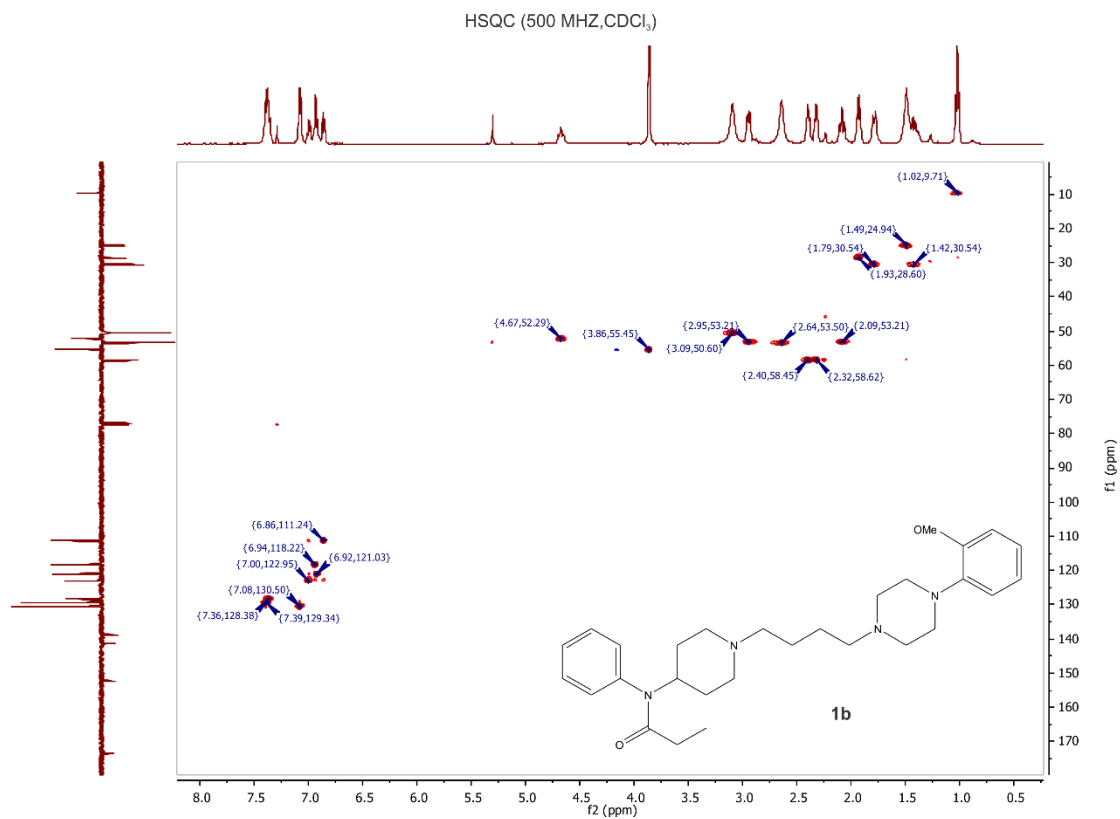


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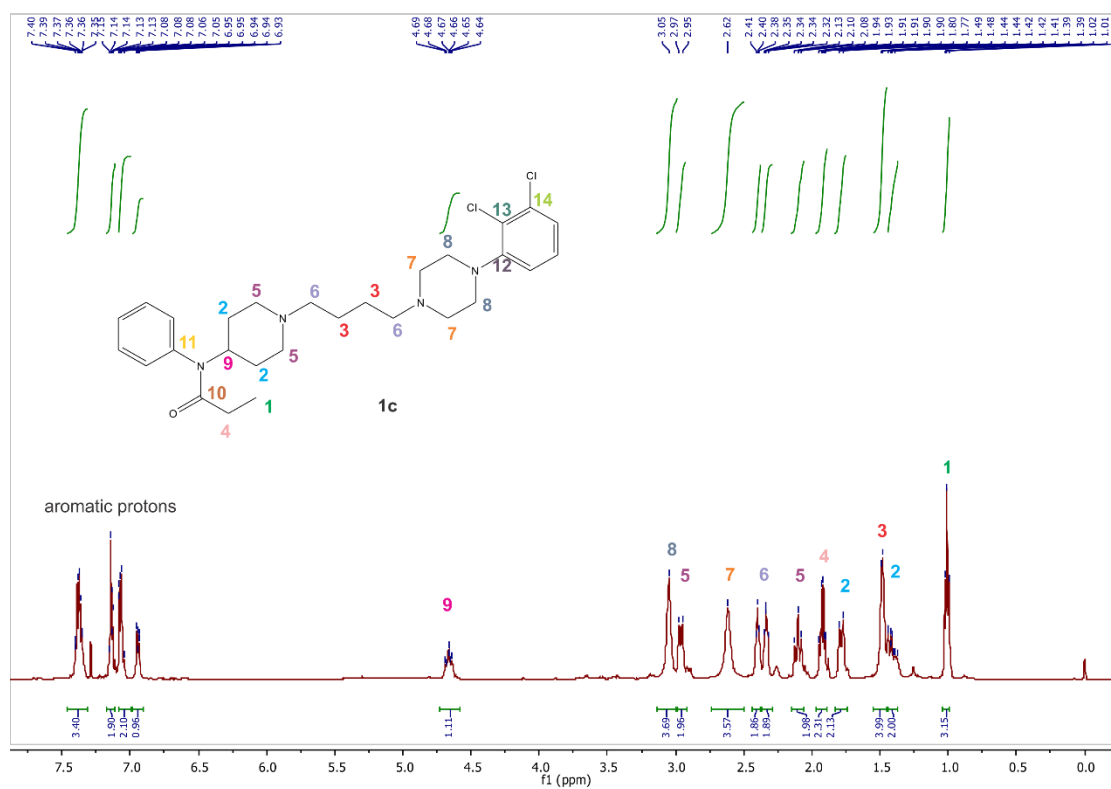
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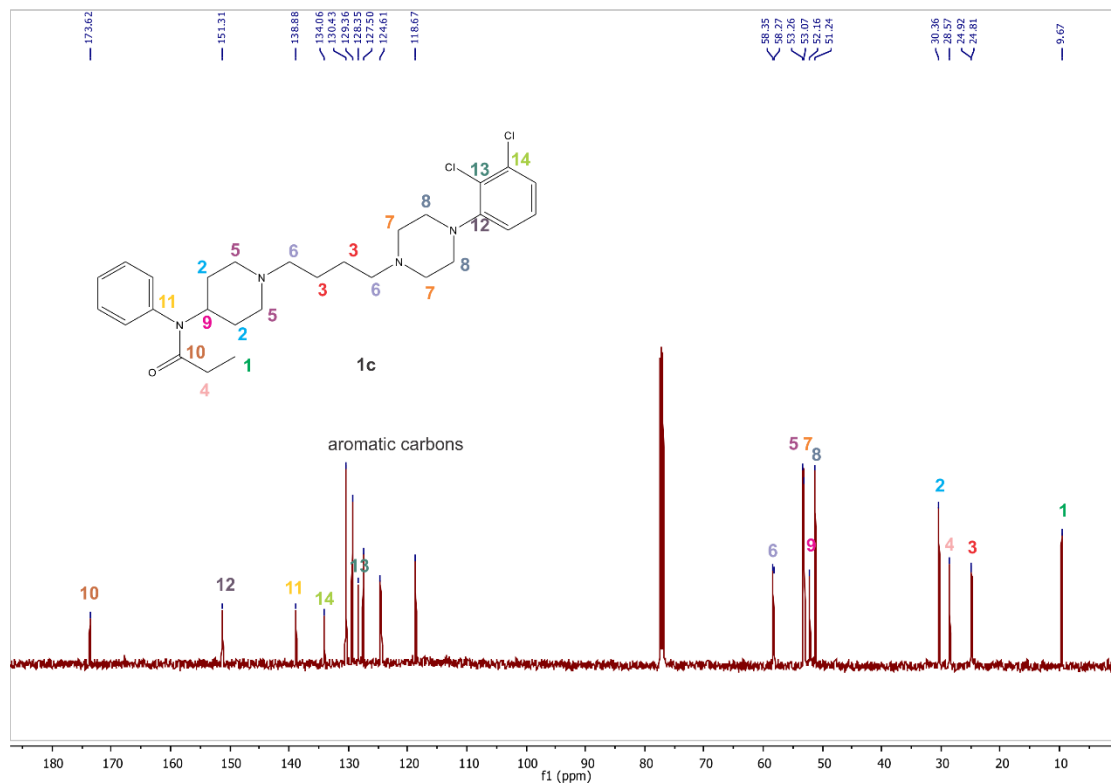


¹H NMR (500 MHz, CDCl₃)



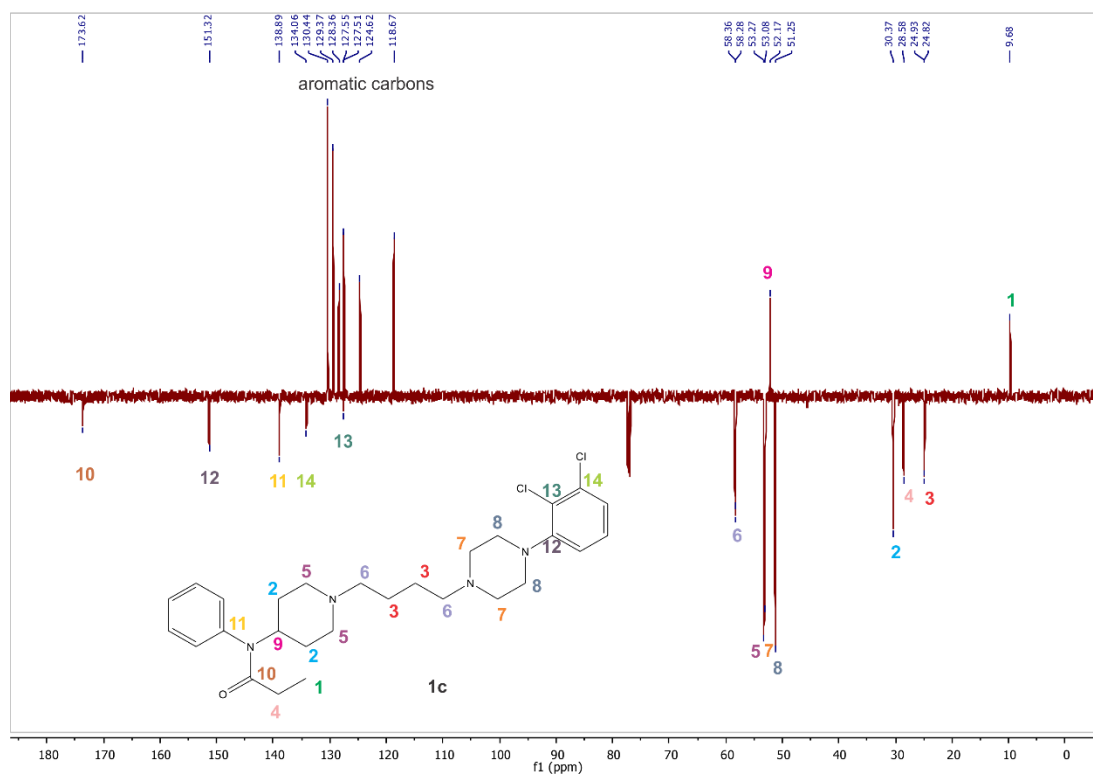
202

¹³C NMR (126 MHz, CDCl₃)

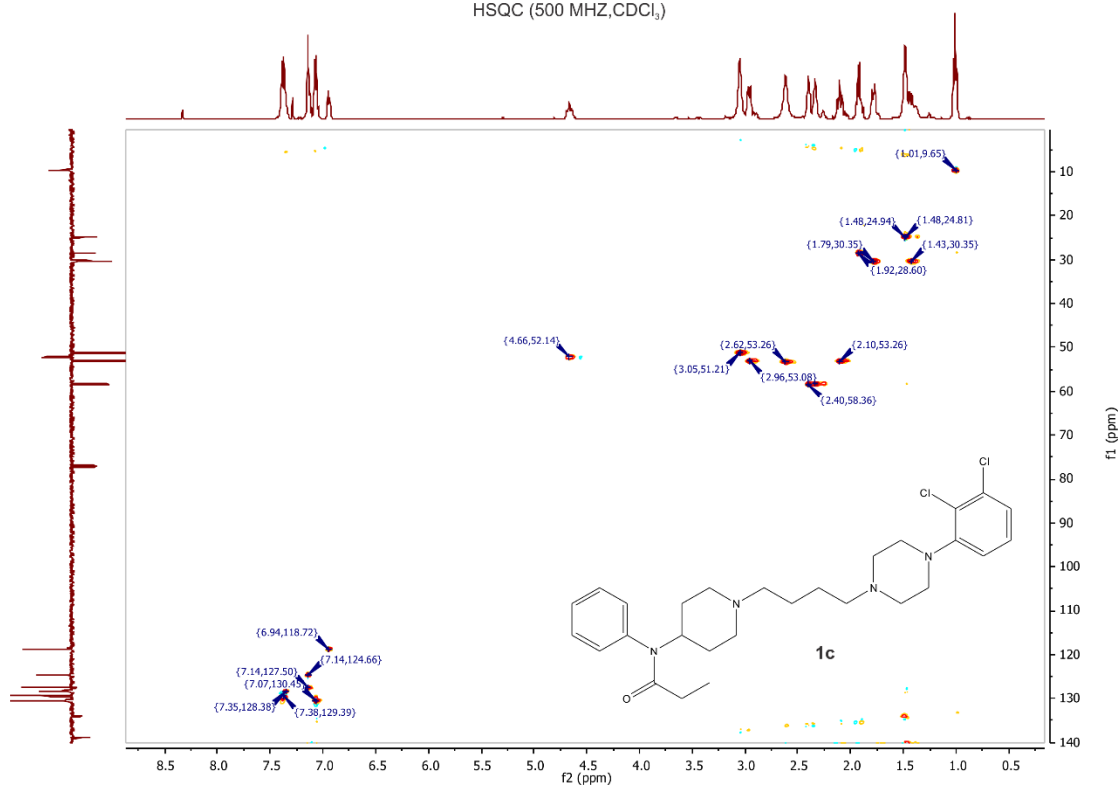


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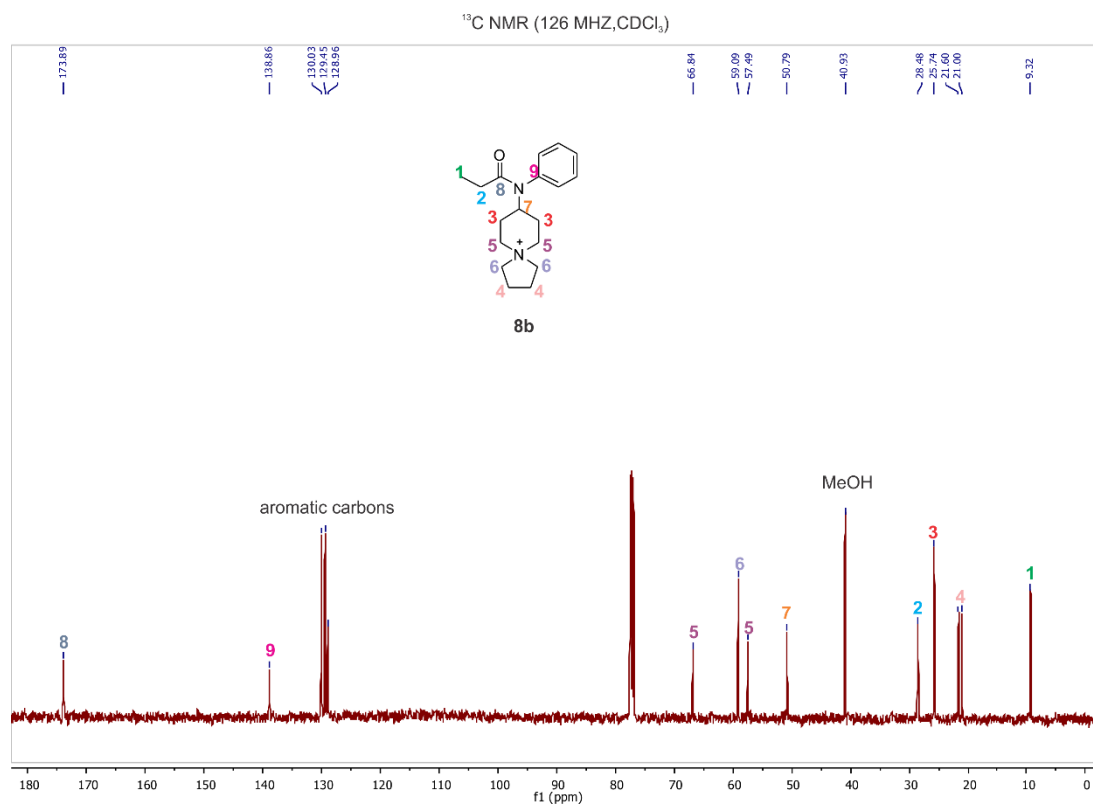
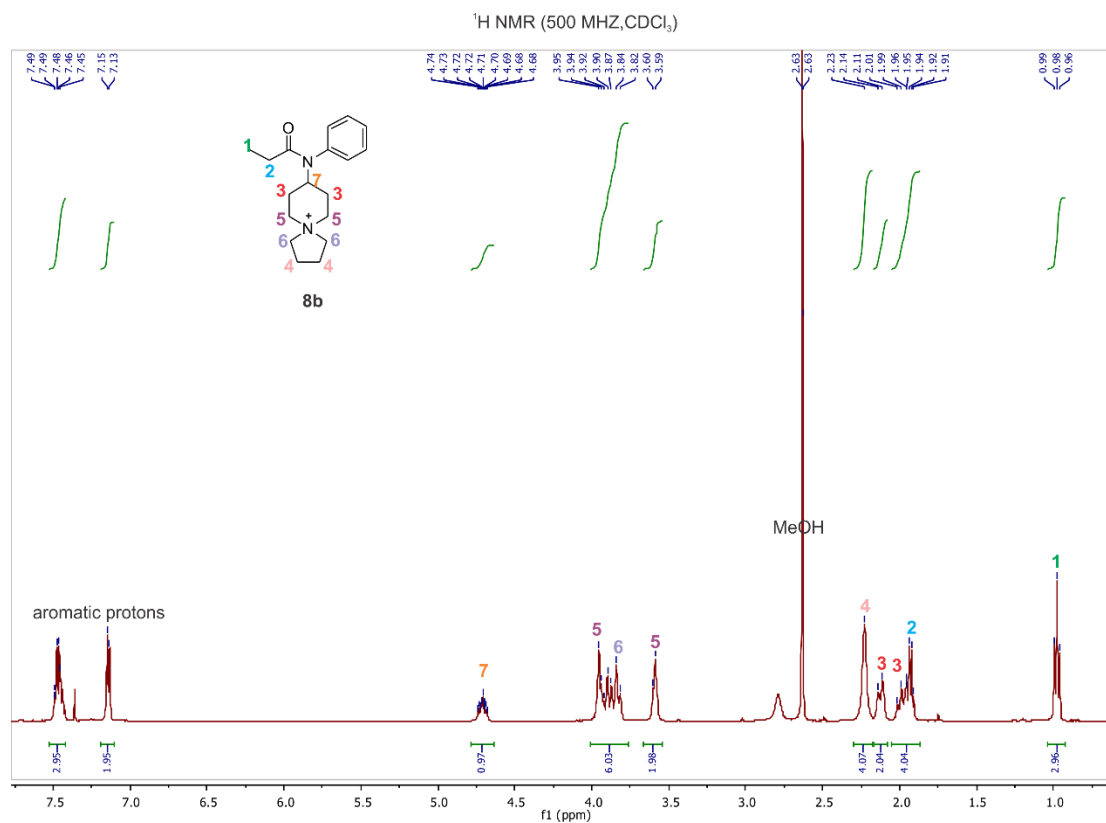
DEPT(126 MHz,CDCl₃)



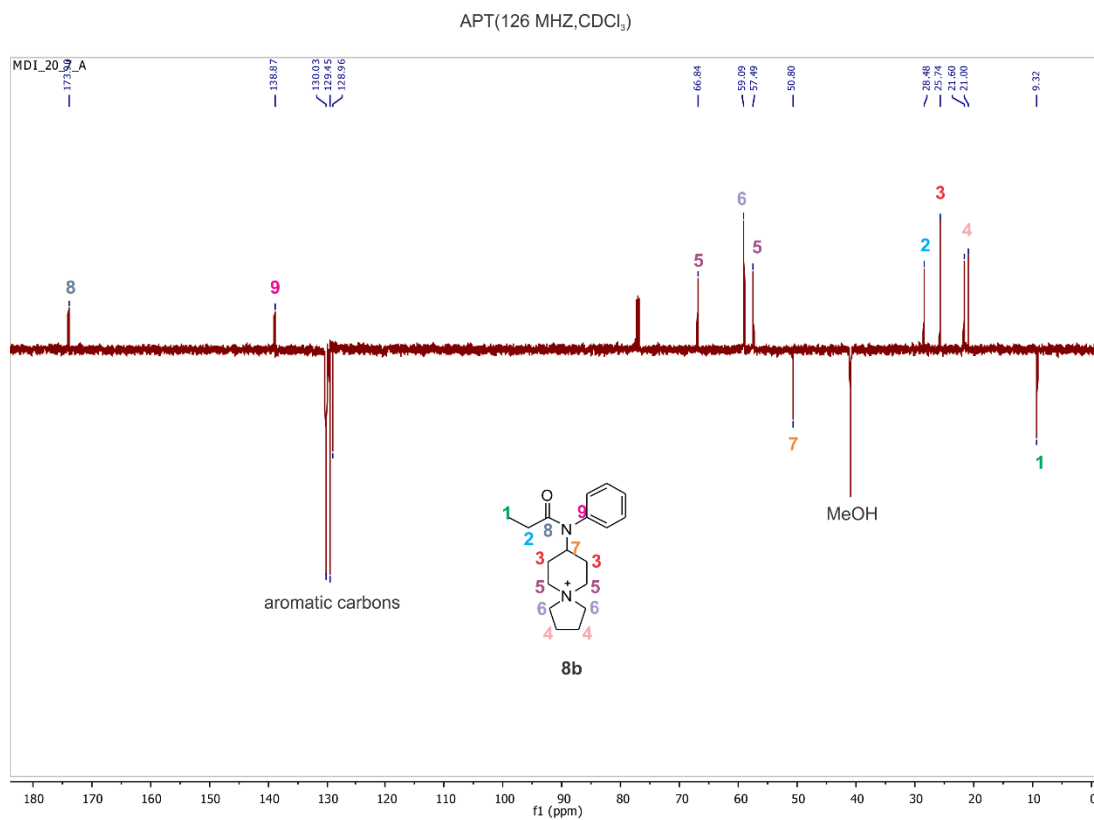
HSQC (500 MHz,CDCl₃)



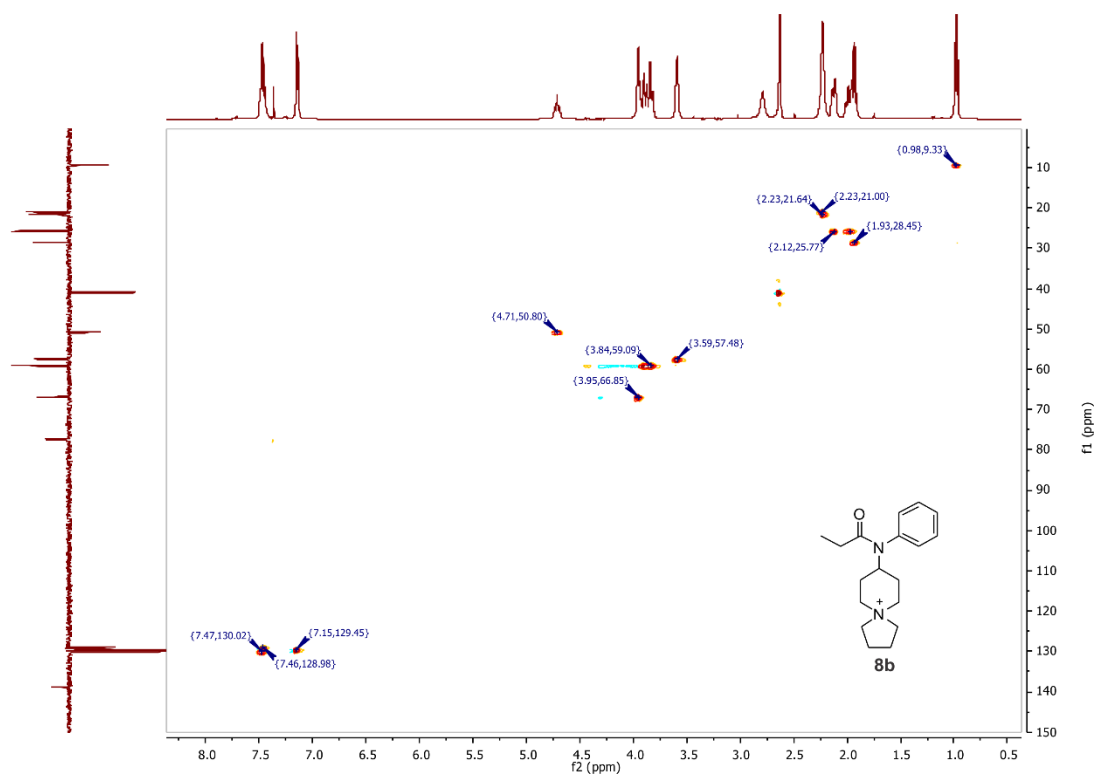
207 Spectra of the undesired products
208



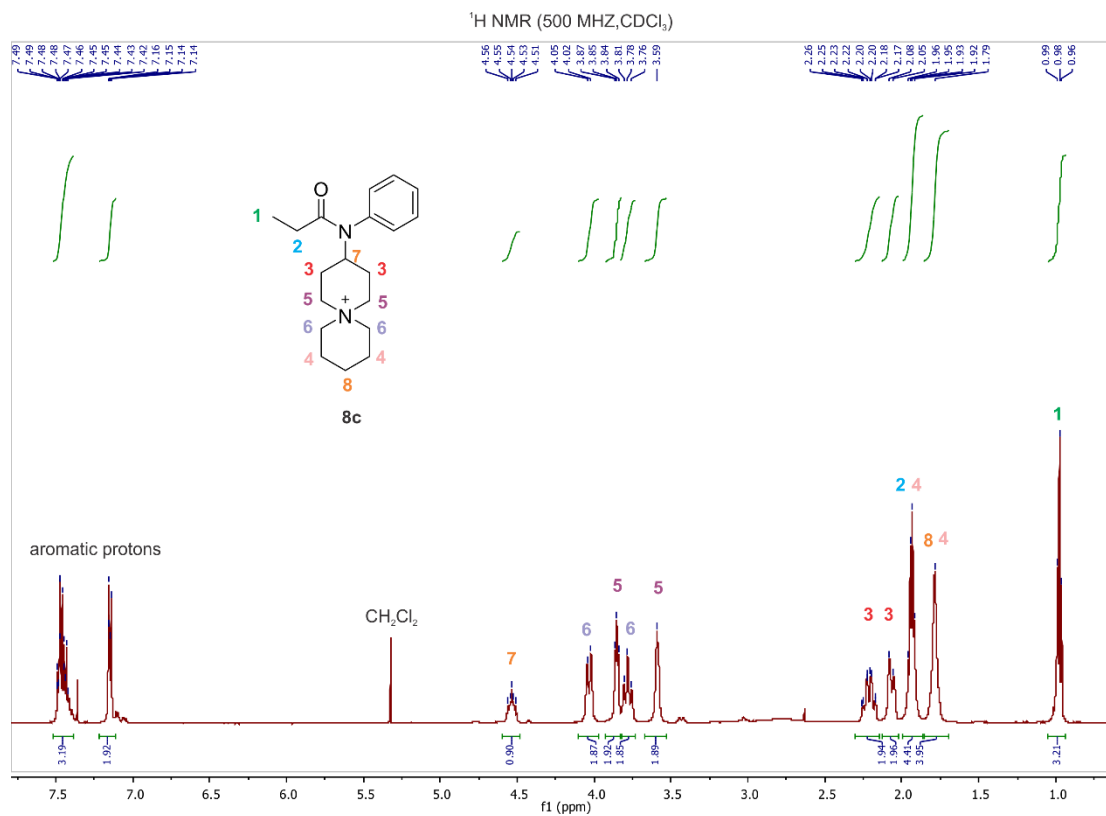
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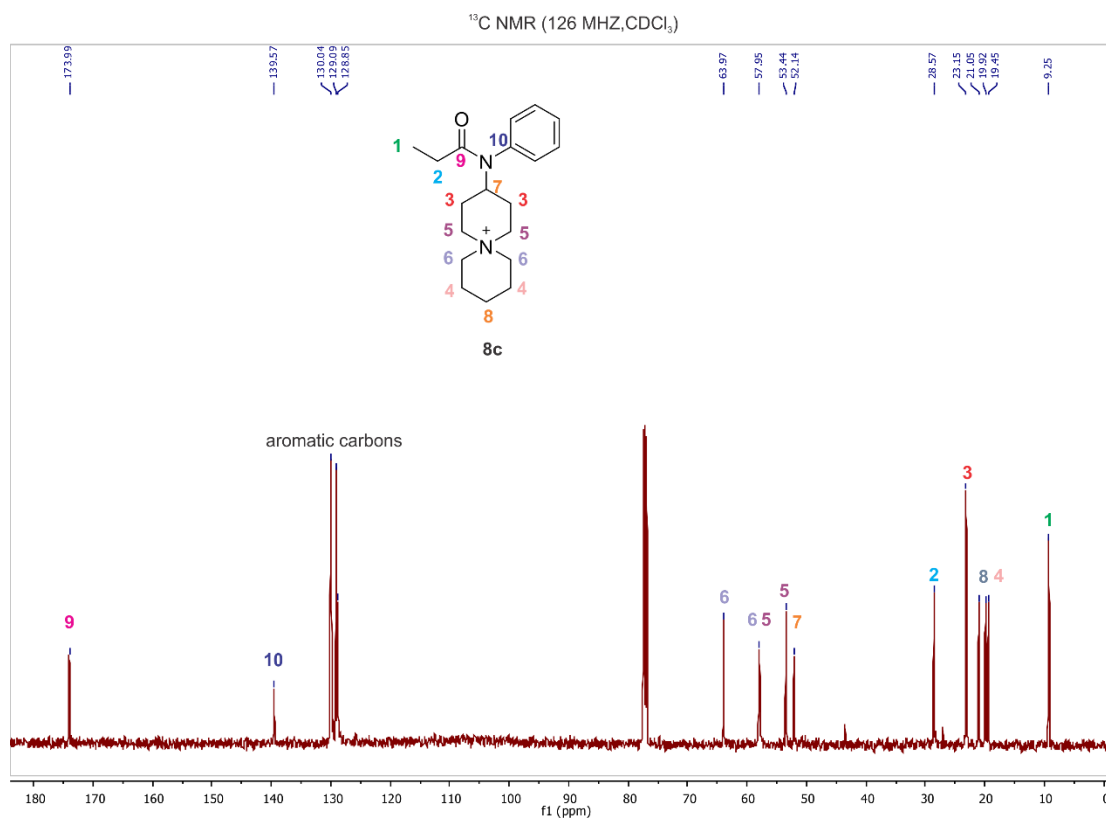
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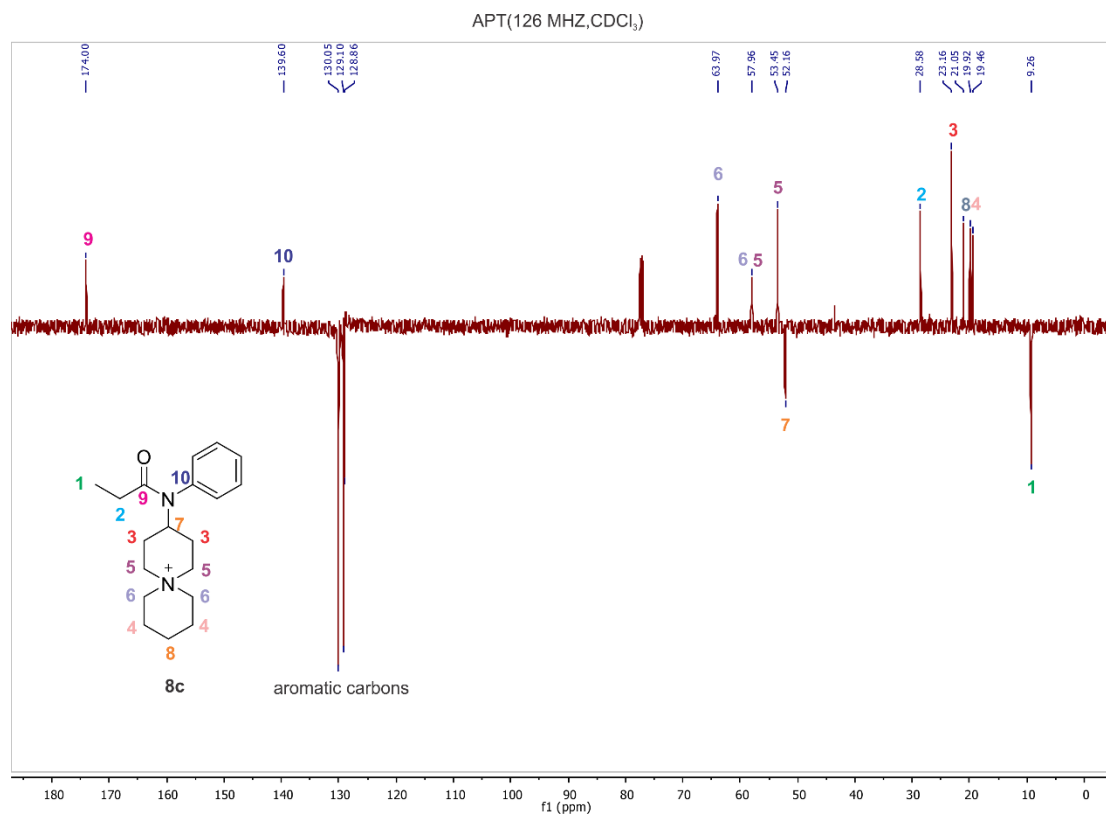


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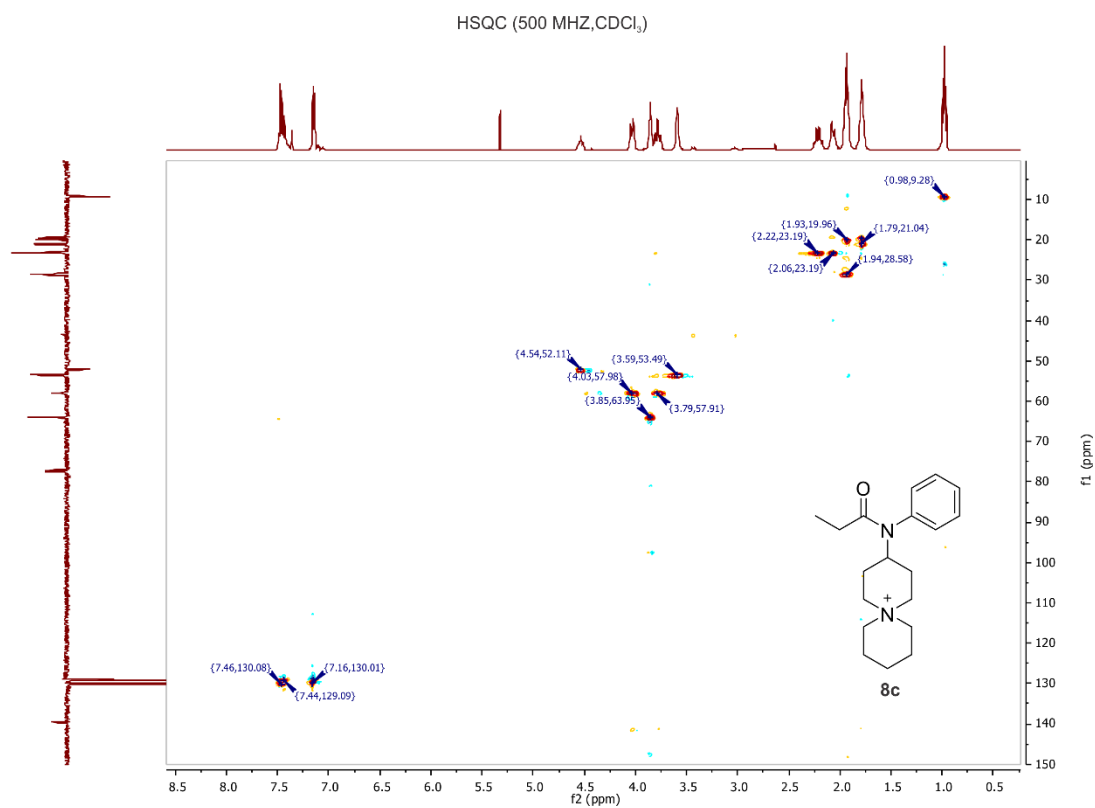


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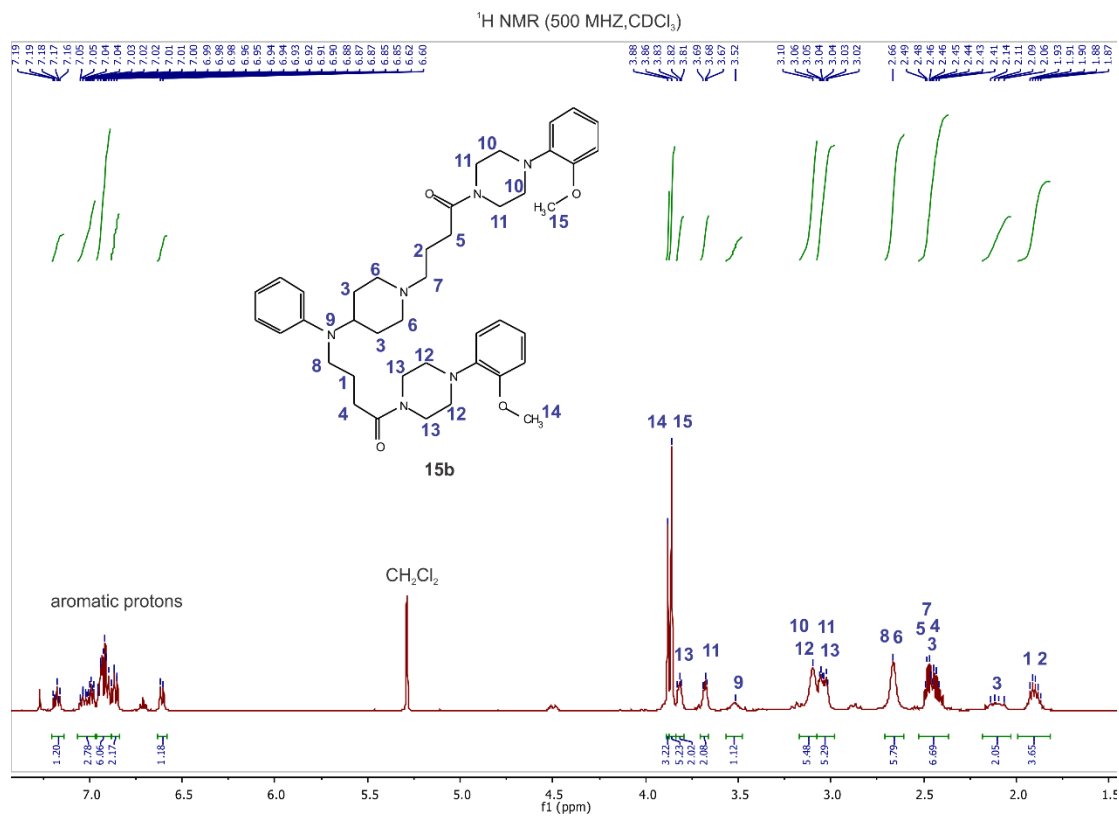
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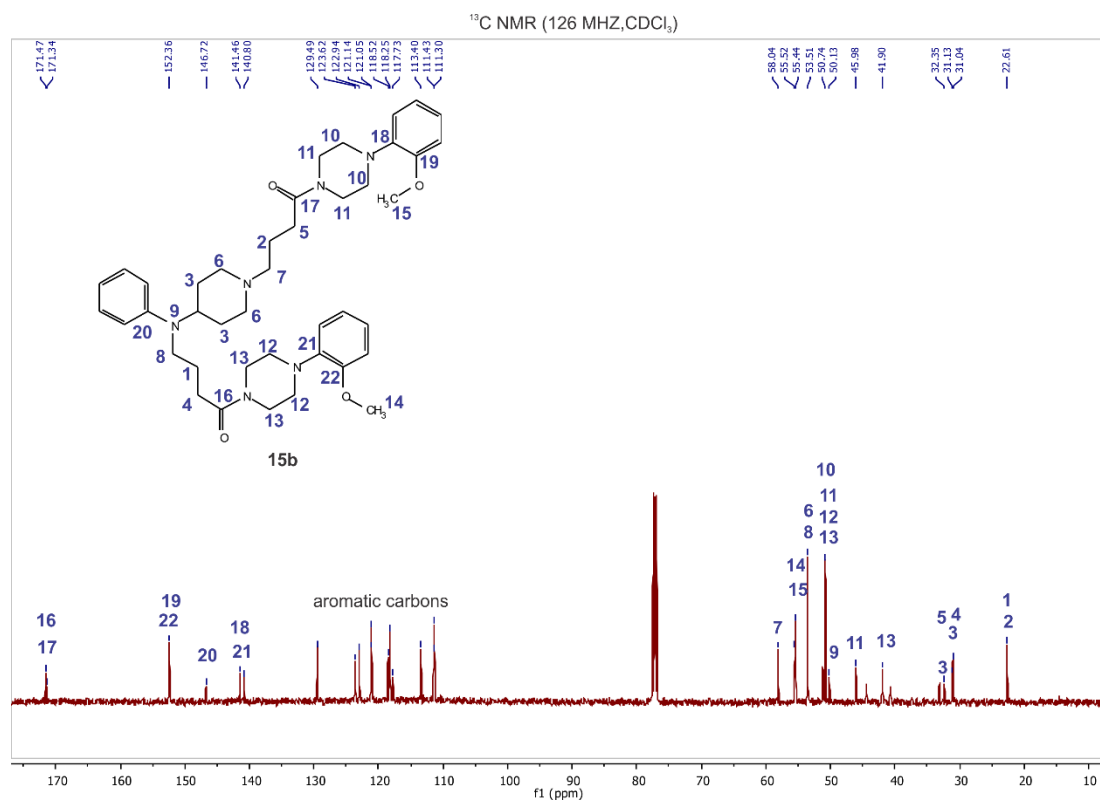
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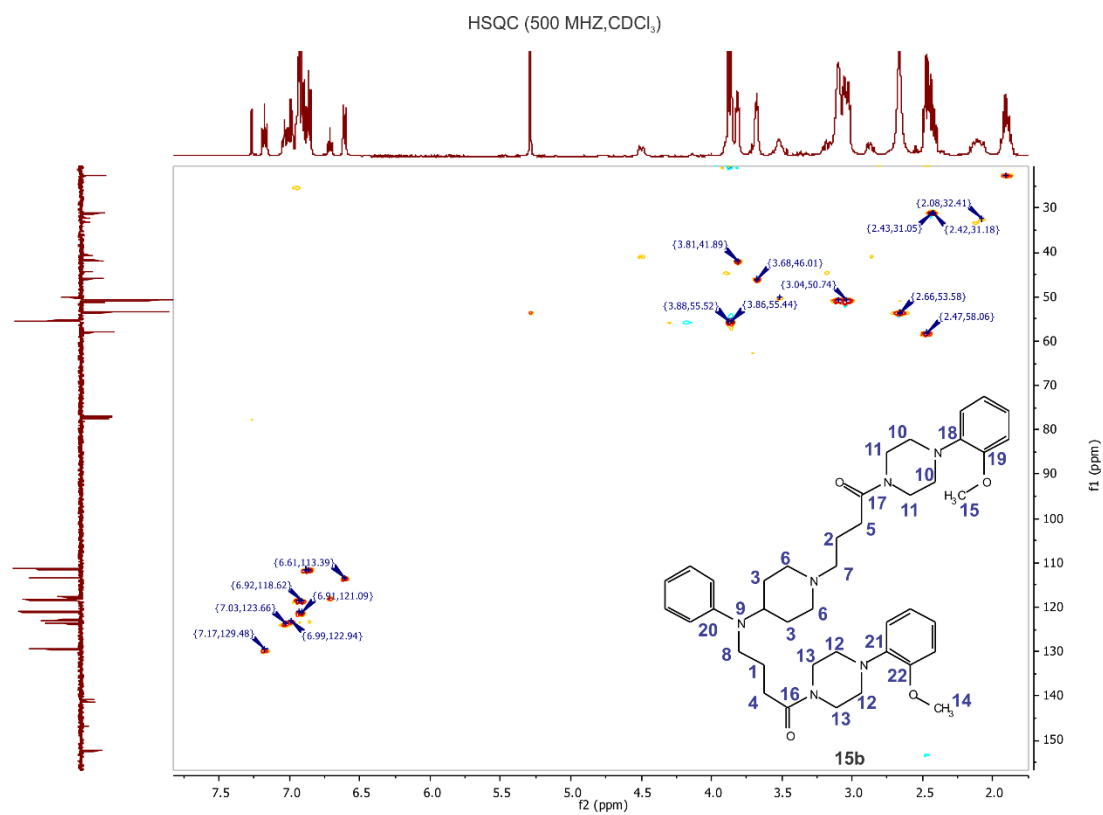
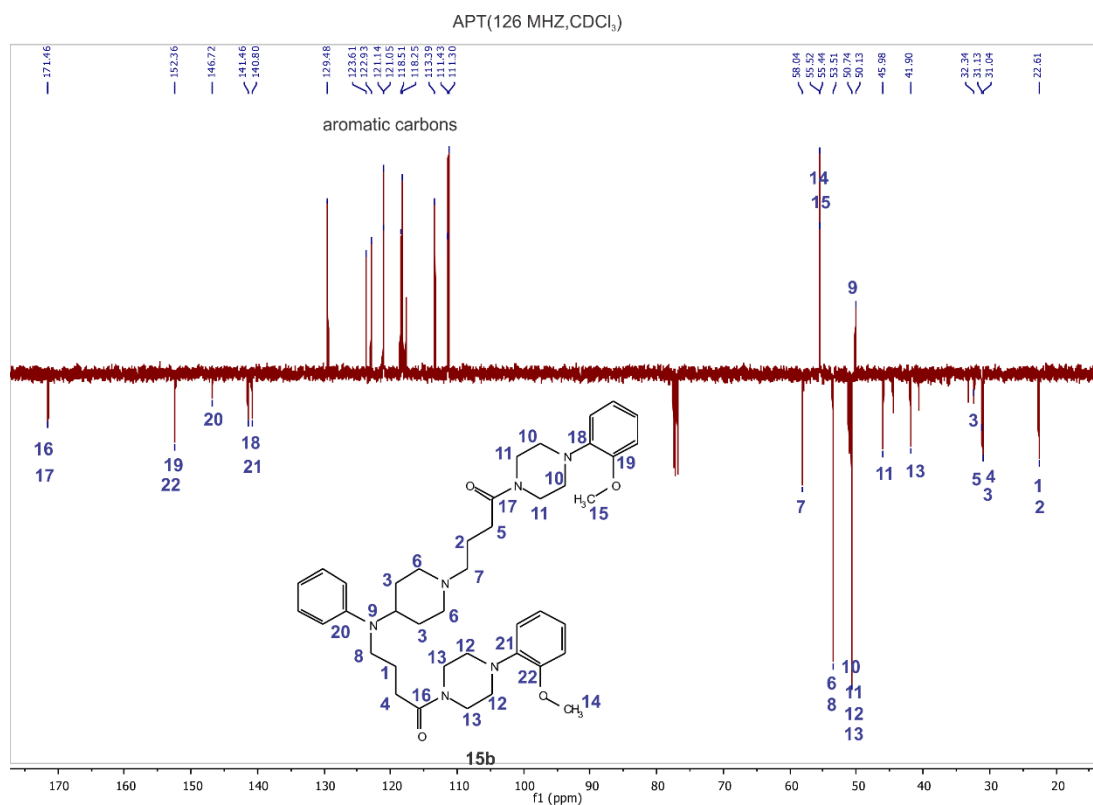
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