10.1071/CH15475_AC

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Supplementary Material

Thiol-reactive analogues of galanthamine, codeine and morphine as potential probes to interrogate allosteric binding within nAChRs

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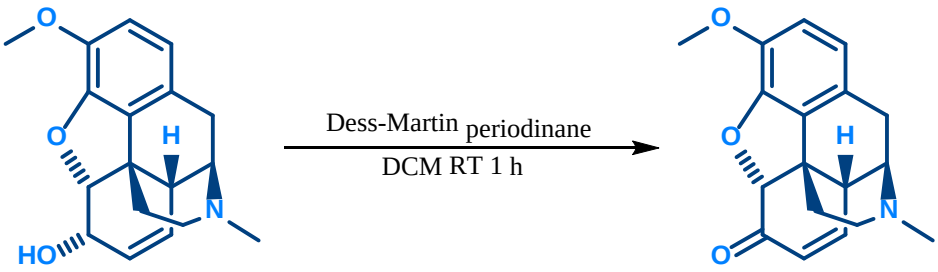
Contents

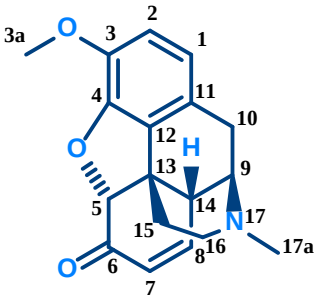
1. Synthesis and Characterisation:

Synthesis of Ketones:

codeinone [1, 2]**:**



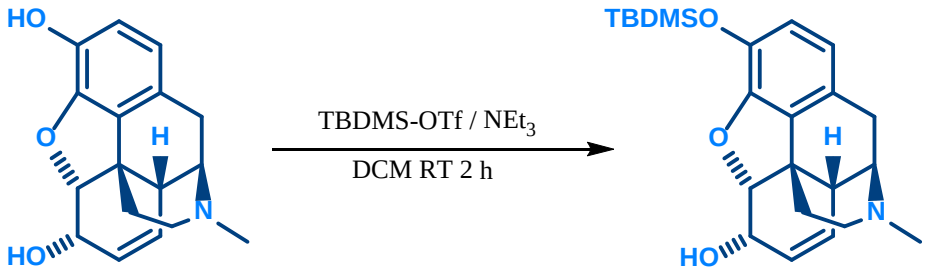
Dess-Martin periodinane (100 mg, 234 µmol) was added to a stirred solution of codeine (**2**, 50 mg, 166 µmol) in dichloromethane (2 mL). The resulting solution was stirred at room temperature for 1 hour, turning orange over time. After 1 hour 2 M aq NaOH (2 mL) was added and the resulting two phase mixture stirred vigorously for a further hour. After this time the two phases were separated and the organic phase was dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to yield the title compound **5** as a pale yellow solid (40 mg, 81 %).



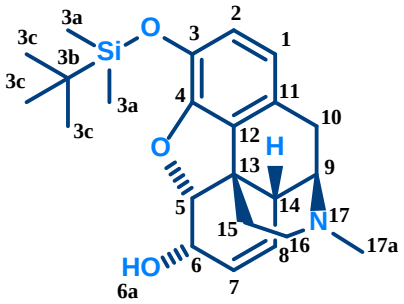
mp: 163 °C (decomposes, literature [2] 182-183 °C) $[\alpha]_D^{20}$ –207° (*c* 1.0, $CHCl_3$) literature [1] –218° (*c* 1.0, $CHCl_3$) **IR** (NaCl) 1675 (C=O), 1637, 1609 (C=C), 1279 (C–O) **^{1}H-NMR** (δ, 400 MHz, $CDCl_3$): 6.58-6.69 (3H, m, H_1, H_2, H_8), 6.07 (1H, dd, J = 10.4 Hz, 2.8 Hz, H_7), 4.69 (1H, s, H_5), 3.83 (3H, s, H_{3a}), 3.44 (1H, m, H_9), 3.24 (1H, s, br, H_{14}), 3.10 (1H, d, J = 18.4 Hz, $H_{10\alpha}$), 2.63 (1H, dd, J = 12.4 Hz, 4.4 Hz, H_{16eq}), 2.46 (3H, s, H_{17a}), 2.26-2.36 (2H, m, $H_{10\beta}$, H_{16ax}), 2.08 (1H, td, J = 12.4 Hz, 4.8 Hz, H_{15ax}), 1.84 (1H, dd, J = 12.4 Hz, 2.0 Hz, H_{15eq}), **^{13}C-NMR** (δ, 100MHz, $CDCl_3$): 194.6 (C_6), 149.0 (C_8), 145.0 (C_4), 142.7 (C_3), 132.7 (C_7), 129.1 (C_{12}), 126.0 (C_{11}), 120.1 (C_1), 115.0 (C_2), 88.2 (C_5), 59.2 (C_9), 57.0 (C_{3a}), 47.0 (C_{16}), 43.2 (C_{13}), 43.0 (C_{17a}), 41.5 (C_9), 34.0 (C_{15}), 20.6 (C_{10})

morphinone:

3-(*tert-butyldimethylsilyl*)*morphine* [3, 4]*:*

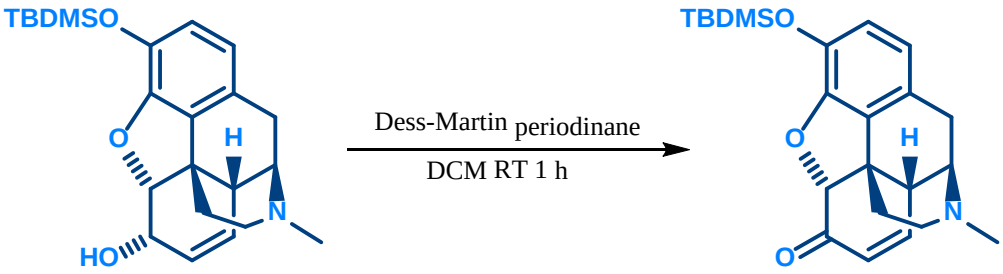


tert-Butyldimethylsilyl triflate (160 µL, 699 µmol) was added to a solution of morphine (**3**, 100 mg, 352 µmol) and triethylamine (140 µL, 1.00 mmol) in dichloromethane (4 mL) and the resulting solution was stirred at room temperature for 2 hours. After 2 hours the reaction mixture was diluted with dichloromethane to a total volume of 10 mL and washed with saturated aq $NaHCO_3$ (10 mL). The remaining solution was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo* to yield a yellow oil, purified by flash chromatography (17:3 chloroform : methanol) to give the title compound **9** as a yellow solid (42 mg, 30%).

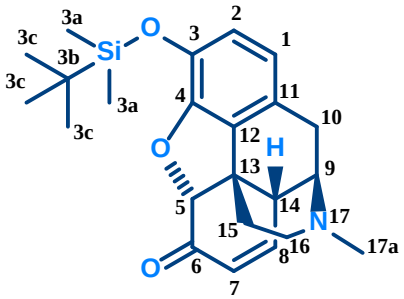


mp: 118-121 °C (literature [4] 122-123 °C) $[\alpha]_D^{20}$ –77° (*c* 1.0, $CHCl_3$) **IR** (NaCl) 3369 (O–H), 1631, 1603 (C=C), 1273, 1254 (C–O) **^{1}H-NMR** (δ, 400 MHz, $CDCl_3$): 6.57 (1H, d, J = 8.0 Hz, H_2), 6.48 (1H, d, J = 8.0 Hz, H_1), 5.67 (1H, dm, J = 10.0 Hz, H_7), 5.28 (1H, dt, J = 10.0 Hz, 2.8 Hz, H_8), 4.85 (1H, dd, J = 6.4 Hz, 1.2 Hz, H_5), 4.16 (1H, m, H_6), 3.34 (1H, dd, J = 6.0 Hz, 3.2 Hz, H_9), 3.02 (1H, d, J = 18.8 Hz, $H_{10\alpha}$), 2.78 (1H, s, br, H_{6a}), 2.65 (1H, m, H_{14}), 2.58 (1H, dd, J = 12.4 Hz, 4.8 Hz, H_{16eq}), 2.44 (3H, s, H_{17a}) 2.41 (1H, td, J = 12.4 Hz, 3.6 Hz, H_{16ax}) 2.29 (1H, dd, 18.8 Hz, 6.0 Hz, $H_{10\beta}$), 2.05 (1H, td, J = 12.4 Hz, 5.2 Hz, H_{15ax}), 1.85 (1H, dm, J = 12.4 Hz, H_{15eq}), 0.99 (9H, s, H_{3c}), 0.19 (3H, s, H_{3a}), 0.16 (3H, s, H_{3a}), **^{13}C-NMR** (δ, 100MHz, $CDCl_3$): 148.4 (C_4), 137.4 (C_3), 133.4 (C_7), 131.4 (C_{12}), 128.6 (C_8), 127.8 (C_{11}), 121.1 (C_2), 119.8 (C_1), 91.1 (C_5), 66.5 (C_6), 59.0 (C_9), 46.6 (C_{16}), 43.3 (C_{17a}), 43.1 (C_{13}), 40.9 (C_{14}), 36.0 (C_{15}), 25.8 (C_{3c}), 20.7 (C_{10}), 18.4 (C_{3b}), -4.22 (C_{3a}), -4.48 (C_{3a})

3-(tert-butyldimethylsilyl)morphinone [3, 4]*:*

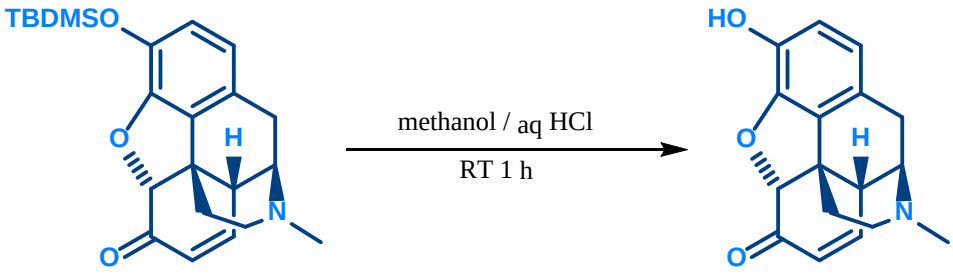


Dess-Martin periodinane (60 mg, 140 µmol) was added to a stirred solution of compound **9** (40 mg, 100 µmol) in dichloromethane (4 mL). The resulting solution was stirred at room temperature for 1 hour, turning yellow over time. After 1 hour 2 M aq NaOH (4 mL) was added and the resulting two phase mixture stirred vigorously for a further hour. After this time the two phases were separated and the organic phase was dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to yield the title compound **10** as a yellow solid (35 mg, 88 %).

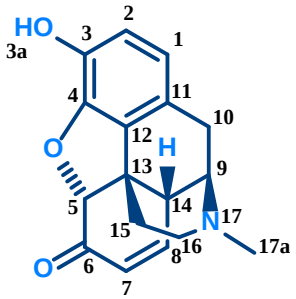


mp: 99 °C (decomposes) $[\alpha]_D^{20}$ –176° (*c* 1.0, $CHCl_3$) **IR** (NaCl) 1677 (C=O), 1634, 1606 (C=C), 1269 (C–O) **^{1}H-NMR** (δ, 400 MHz, $CDCl_3$): 6.59-6.65 (2H, m, H_8, H_2), 6.54 (1H, d, J = 8.0 Hz, H_1), 6.07 (1H, dd, J = 10.0 Hz, 2.8 Hz, H_7), 4.66 (1H, s, H_5), 3.40 (1H, m, H_9), 3.17 (1H, m, H_{14}), 3.09 (1H, d, J = 18.4 Hz, $H_{10\alpha}$), 2.60 (1H, dd, J = 12.0 Hz, 4.8 Hz, H_{16eq}), 2.45 (3H, s, H_{17a}), 2.26-2.35 (2H, m, $H_{10\beta}$, H_{16ax}), 2.04 (1H, td, J = 12.4 Hz, 4.8 Hz, H_{15ax}), 1.82 (1H, dm, J = 12.4 Hz, H_{15eq}), 0.97 (9H, s, H_{3c}), 0.18 (3H, s, H_{3a}), 0.12 (3H, s, H_{3a}) **^{13}C-NMR** (δ, 100MHz, $CDCl_3$): 194.4 (C_6), 149.3 (C_8), 147.0 (C_4), 137.8 (C_3), 132.7 (C_7), 129.2 (C_{12}), 126.7 (C_{11}), 122.3 (C_2), 120.0 (C_1), 88.1 (C_5), 59.2 (C_9), 46.9 (C_{16}), 43.3 (C_{13}), 43.1 (C_{17a}), 41.7 (C_{14}), 34.3 (C_{15}), 25.8 (C_{3c}), 20.7 (C_{10}), 18.4 (C_{3b}), -4.46, -4.61 (C_{3a})

morphinone [4]*:*



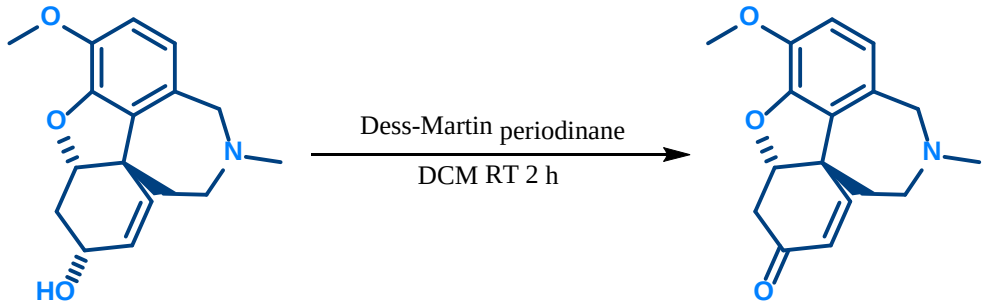
Compound **10** (10 mg, 25 µmol) was dissolved in methanol (1 mL) and 1 M aq HCl (1 mL) was added. The resulting solution was stirred at room temperature for 1 hour. After this time the solvent was removed *in vacuo* and the residue was redissolved in water (5 mL). The solution was basified to pH 9 using 2 M aq NaOH and the product was extracted with a 3:1 mixture of chloroform and isopropanol (3 × 5 mL). The combined extracts were dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo* to yield the title compound **6** as a pale yellow oil (5 mg, 70%).



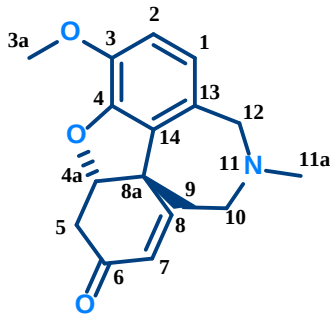
$[\alpha]_D^{20}$ –173° (*c* 0.5, $CHCl_3$) **IR** (NaCl) 3600-2400 (O–H) 1672 (C=O), 1638, 1612 (C=C), 1246 (C–O) **^{1}H-NMR** (δ, 400 MHz, $CDCl_3$): 6.65-6.71 (2H, m, H_8, H_2), 6.54 (1H, d, J = 8.0 Hz, H_1), 6.08 (1H, dd, J = 10.4 Hz, 2.8 Hz, H_7), 4.72 (1H, s, H_5), 3.49 (1H, m, H_9), 3.27 (1H, s, br, H_{14}), 3.11 (1H, d, J = 18.4 Hz, $H_{10\alpha}$), 2.67 (1H, dd, J = 12.4 Hz, 4.8 Hz, H_{16eq}), 2.47 (3H, s, H_{17a}), 2.29-2.37 (2H, m, $H_{10\beta}$, H_{16ax}), 2.12 (1H, td, J = 12.4 Hz, 4.8 Hz, H_{15ax}), 1.85 (1H, dm, J = 12.4 Hz, H_{15eq}), H_{3a} not observed **^{13}C-NMR** (δ, 100MHz, $CDCl_3$): 195.2 (C_6), 149.8 (C_8), 143.5 (C_4), 138.6 (C_3), 132.5 (C_7), 128.6 (C_{12}), 125.4 (C_{11}), 120.6 (C_2), 117.7 (C_1), 88.6 (C_5), 59.1 (C_9), 47.0 (C_{16}), 43.5 (C_{13}), 43.0 (C_{17a}), 41.6 (C_{14}), 33.9 (C_{15}), 20.7 (C_{10})

narwedine [5, 6]**:**

Method A:

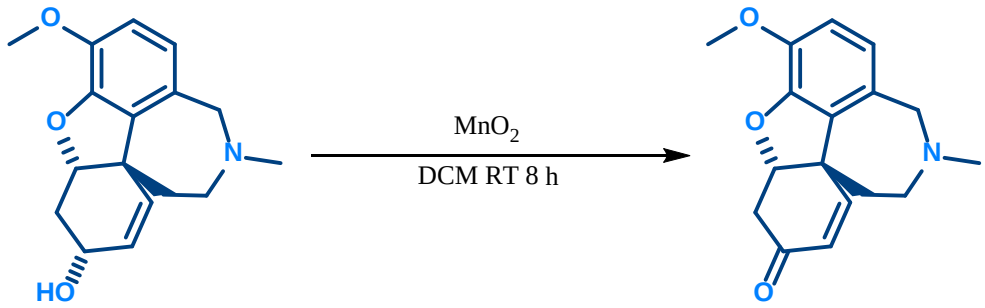


Galanthamine hydrobromide (100 mg, 272 µmol) was dissolved in dichloromethane (40 mL) and the resulting solution was washed with 2 M aq, NaOH (40 mL), dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The residue was redissolved in dichloromethane (4 mL) and Dess-Martin periodinane (160 mg, 376 µmol) was added. The resulting solution was stirred for 1 hour before an additional 160 mg of Dess-Martin periodinane was added and the solution left to stir for a further hour. After this time 2 M aq NaOH (4 mL) was added and the resulting two phase mixture was stirred vigorously for 1 hour. The phases were then separated and the organic phase was dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to yield the title compound **4** as a pale yellow oil (55 mg, 71 %).



$[\alpha]_D^{20}$ –7° (*c* 1.0, $CHCl_3$) literature [6] –408° (*c* 1.0, $CHCl_3$) **IR** (NaCl) 1684 (C=O), 1623 (C=C), 1284 (C–O) **^{1}H-NMR** (δ, 400 MHz, $CDCl_3$): 6.95 (1H, d, J = 10.4 Hz, H_8), 6.69 (1H, d, J = 8.0 Hz, H_2), 6.64 (1H, d, J = 8.0 Hz, H_1), 6.03 (1H, d, J = 10.4 Hz, H_7), 4.72 (1H, m, H_{4a}), 4.08 (1H, d, J = 15.6 Hz, $H_{12\beta}$), 3.83 (3H, s, H_{3a}), 3.73 (1H, d, J = 15.6 Hz, $H_{12\alpha}$), 3.09-3.28 (3H, m, $H_{5\beta}$, $H_{10\alpha}$, $H_{10\beta}$), 2.74 (1H, dd, J = 17.6 Hz, 3.6 Hz, $H_{5\alpha}$), 2.43 (3H, s, H_{11a}), 2.26 (1H, td, J = 13.6 Hz, 3.6 Hz, $H_{9\beta}$), 1.84 (1H, dm, J = 13.6 Hz, $H_{9\alpha}$) **^{13}C-NMR** (δ, 100MHz, $CDCl_3$): 194.6 (C_6), 147.1 (C_4) 144.5 (C_8), 144.1 (C_3), 130.7 (C_{14}), 129.5 (C_{13}), 127.3 (C_7), 122.2 (C_1), 112.0 (C_2), 88.1 (C_{4a}), 60.8 (C_{12}), 56.1 (C_{3a}), 54.2 (C_{10}), 49.1 (C_{8a}), 42.6 (C_{11a}), 37.4 (C_5), 33.4 (C_9)

Method B:

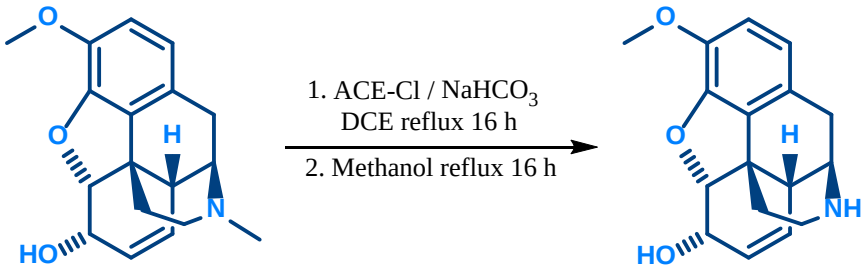


Galanthamine hydrobromide (50 mg, 136 µmol) was dissolved in dichloromethane (20 mL) and the resulting solution was washed with 2 M aq, NaOH (20 mL), dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The residue was redissolved in dichloromethane (5 mL) and MnO_2 (250 mg, 2.88 mmol) was added. The resulting solution was stirred vigorously for 8 hours before the suspension was filtered to remove MnO_2. The solvent was removed *in vacuo* to yield the title compound **4** as a white solid (30 mg, 77 %).

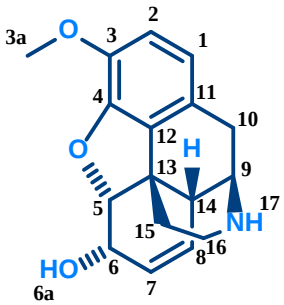
mp: 188 °C (decomposes, literature [7] 184-190 °C) $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ –237° (*c* 1.0, $CHCl_3$) literature [6] –408° (*c* 1.0, $CHCl_3$). Spectral data were identical to those obtained for the product from method A.

Synthesis of Codeine Mustard:

norcodeine [8]**:**

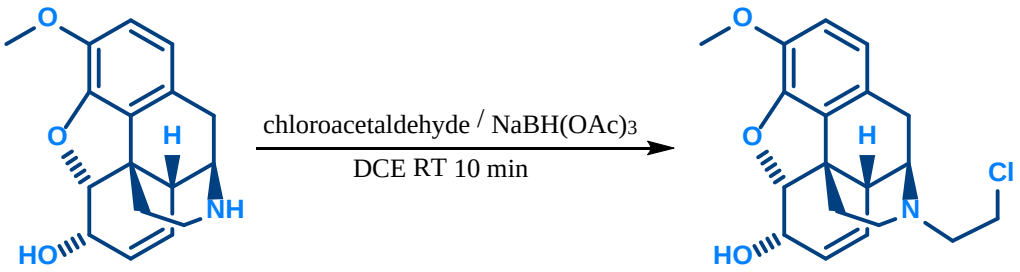


α-Chloroethyl chloroformate (250 µL, 1.32 mmol) was added to a stirred solution of codeine (**2**, 50 mg, 166 µmol) and $NaHCO_3$ (100 mg, 595 µmol) in dichloromethane (5 mL) and the resulting mixture was stirred at reflux overnight, turning yellow over time. The following morning the mixture was cooled and washed with water (2 × 5 mL). The solution was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The residue was redissolved in methanol (5 mL) and stirred at reflux overnight. The following morning the solvent was removed *in vacuo* to yield a brown solid, purified by flash chromatography (90:10:1 chloroform : methanol : ammonia) to give the title compound **13** as a pale yellow solid (39 mg, 82%).

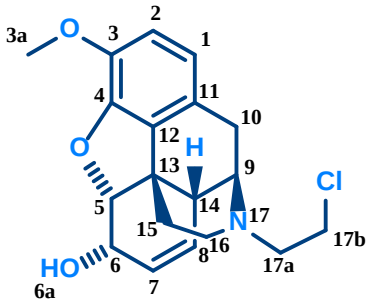


mp: 181-183 °C (literature [8] 182-183 °C) $[\alpha]_D^{20}$ –110° (*c* 1.0, $CHCl_3$) literature [8] –91° (*c* 0.22, $CHCl_3$) **IR** (NaCl) 3311 (O–H, N–H), 1634, 1603 (C=C), 1282, 1261 (C–O) **^{1}H-NMR** (δ, 400 MHz, $CDCl_3$): 6.67 (1H, d, J = 8.0 Hz, H_2), 6.58 (1H, d, J = 8.0 Hz, H_1), 5.72 (1H, d, br, J = 10.0 Hz, H_7), 5.25 (1H, dt, J = 10.0 Hz, 2.4 Hz, H_8), 4.87 (1H, d, J = 6.4 Hz, H_5), 4.18 (1H, m, H_6), 3.84 (3H, s, H_{3a}), 3.66 (1H, s, br, H_9), 2.78-3.01 (4H, m, $H_{10\alpha}$, $H_{10\beta}$, H_{16ax}, H_{16eq}), 2.61 (1H, m, H_{14}), 2.54 (2H, s, br, H_{6a}, H_{17}), 1.86-1.99 (2H, m, H_{15ax}, H_{15eq}) **^{13}C-NMR** (δ, 100MHz, $CDCl_3$): 146.5 (C_4), 142.4 (C_3), 133.9 (C_7), 131.2 (C_{12}), 128.1 (C_8), 127.4 (C_{11}), 119.7 (C_1), 113.1 (C_2), 92.0 (C_5), 66.4 (C_6), 56.5 (C_{3a}), 52.1 (C_9), 43.9 (C_{13}), 41.2 (C_{14}), 38.6 (C_{16}), 36.6 (C_{15}), 31.3 (C_{10})

N-(2-chloroethyl) codeine:



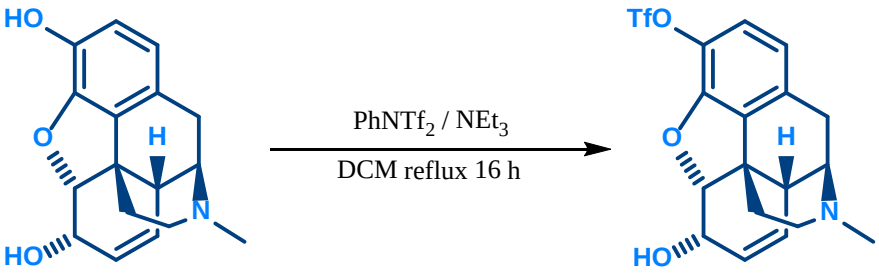
Sodium triacetoxyborohydride (120 mg, 566 µmol) was added to a solution of norcodeine **13** (30 mg, 106 µmol) and chloroacetaldehyde (20 µL, 286 µmol) in dichloromethane (2 mL) and the resulting mixture was stirred at room temperature for 10 minutes. After this time, the mixture was diluted with dichloromethane (5 mL) and washed with water (2 × 5 mL). The solution was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo* to yield the title compound **7** as a yellow oil (31 mg, 85%).



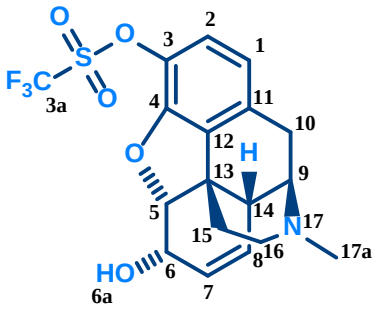
$[\alpha]_D^{20}$ –103° (*c* 1.0, $CHCl_3$) **IR** (NaCl) 3386 (O–H), 1635, 1604 (C=C), 1283, 1258 (C–O) **^{1}H-NMR** (δ, 400 MHz, $CDCl_3$): 6.66 (1H, d, J = 8.0 Hz, H_2), 6.56 (1H, d, J = 8.0 Hz, H_1), 5.71 (1H, dm, J = 10.0 Hz, H_7), 5.27 (1H, dt, J = 10.0 Hz, 2.8 Hz, H_8), 4.89 (1H, dd, J = 6.4 Hz, 1.2 Hz, H_5), 4.17 (1H, s, br, H_6), 3.84 (3H, s, H_{3a}), 3.58 (2H, t, J = 6.8 Hz, H_{17b}), 3.43 (1H, m, H_9), 2.77-2.97 (4H, m, $H_{10\alpha}$, H_{17a}, H_{6a}), 2.64-2.71 (2H, m, H_{14}, H_{16eq}), 2.53 (1H, td, J = 12.0 Hz, 3.6 Hz, H_{16ax}), 2.42 (1H, dd, J = 18.4 Hz, 6.4 Hz, $H_{10\beta}$), 2.05 (1H, td, J = 12.4 Hz, 5.2 Hz, H_{15ax}), 1.86 (1H, dm, J = 12.4 Hz, H_{15eq}) **^{13}C-NMR** (δ, 100MHz, $CDCl_3$): 146.4 (C_4), 142.4 (C_3), 133.6 (C_7), 131.2 (C_{12}), 128.3 (C_8), 127.0 (C_{11}), 119.7 (C_1), 113.0 (C_2), 91.5 (C_5), 66.6 (C_6), 58.1 (C_9), 57.3 (C_{17a}), 56.5 (C_{3a}), 45.1 (C_{16}), 43.4 (C_{13}), 42.3 (C_{17b}), 40.7 (C_{14}), 35.9 (C_{15}), 22.9 (C_{10}) **LRMS (EI):** m/z = 349 ($M^{+\cdot}$, 20), 347 ($M^{+\cdot}$, 50), 299 (20), 298 ($[M–CH_2Cl]^+$, 50) **HRMS (EI):** 349.1257 ($M^{+\cdot}$, $C_{19}H_{22}NO_3{}^{37}Cl$ gives 349.1259), 347.1289 ($M^{+\cdot}$, $C_{19}H_{22}NO_3{}^{35}Cl$ gives 347.1288)

Synthesis of 3-chloromethyl-3-deoxymorphine:

3-(trifluoromethanesulfonyl)morphine [9, 10]**:**

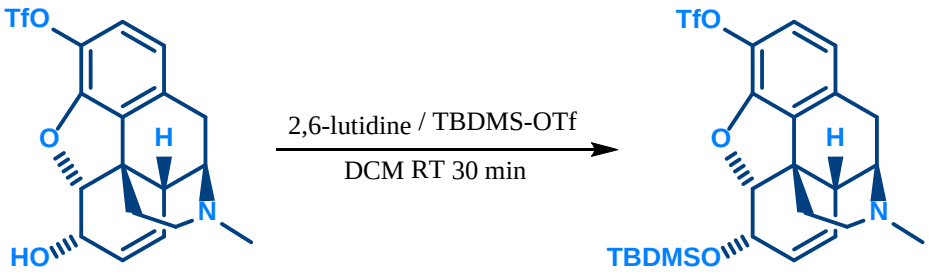


Triethylamine (700 µL, 5.02 mmol) was added to a solution of morphine (**3**, 500 mg, 1.76 mmol) and *N*-phenyltriflimide (700 mg, 1.96 mmol) in dichloromethane (20 mL) and the resulting solution was stirred at reflux overnight. The following morning the mixture was cooled and the solvent was removed *in vacuo* to yield a yellow oil, purified by flash chromatography (9:1 chloroform : methanol) to give the title compound **16** as a pale yellow solid (598 mg, 82%).

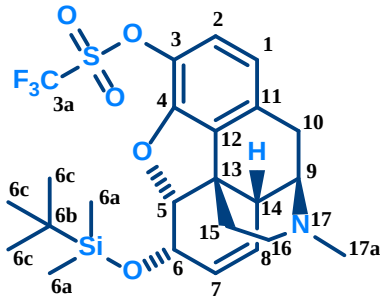


mp: 113-115 °C (literature [9] 123-124 °C) $[\alpha]_D^{20}$ –145° (*c* 1.0, $CHCl_3$), –70° (*c* 1.0, CH_3OH), literature [9] –78° (*c* 1.0, CH_3OH) **IR** (NaCl) 3551 (O–H), 1623 (C=C), 1218 (C–O) **^{1}H-NMR** (δ, 400 MHz, $CDCl_3$): 6.89 (1H, d, J = 8.4 Hz, H_2), 6.64 (1H, d, J = 8.4 Hz, H_1), 5.70 (1H, dm, J = 10.0 Hz, H_7), 5.27 (1H, dt, J = 10.0 Hz, 2.8 Hz, H_8), 5.01 (1H, d, J = 6.4 Hz, H_5), 4.21 (1H, m, H_6), 3.40 (1H, m, H_9), 3.08 (1H, d, J = 19.2 Hz, $H_{10\alpha}$), 3.02 (1H, s, br, H_{6a}), 2.74 (1H, s, br, H_{14}), 2.64 (1H, dd, J = 12.4 Hz, 4.4 Hz, H_{16eq}), 2.45 (3H, s, H_{17a}), 2.30-2.40 (2H, m, $H_{10\beta}$, H_{16ax}), 2.13 (1H, td, J = 12.4 Hz, 4.8 Hz, H_{15ax}), 1.89 (1H, dm, J = 12.8 Hz, H_{15eq}) **^{13}C-NMR** (δ, 100MHz, $CDCl_3$): 149.7 (C_4), 135.7 (C_{11}), 133.9 (C_7), 133.8 (C_{12}), 130.8 (C_3), 128.2 (C_8), 121.3 (C_2), 120.4 (C_1), 118.8 (q, J = 319 Hz, C_{3a}), 93.7 (C_5), 66.6 (C_6), 58.7 (C_9), 46.2 (C_{16}), 43.4 (C_{13}), 43.1 (C_{17a}), 40.5 (C_{14}), 35.3 (C_{15}), 21.2 (C_{10})

3-(trifluoromethanesulfonyl)-6-(tert-butyldimethylsilyl)morphine [11]**:**

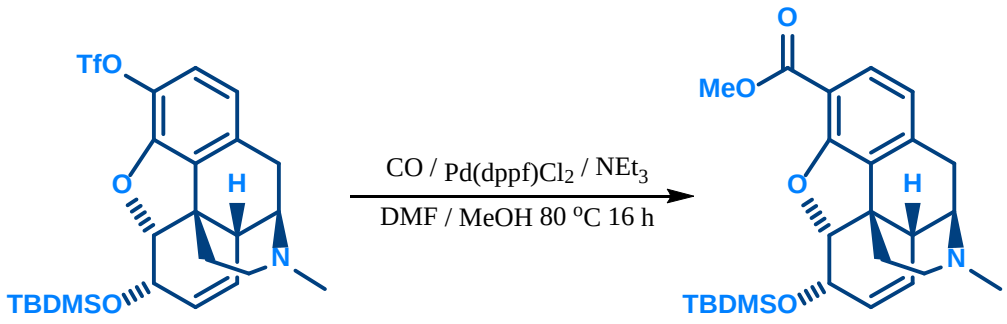


tert-Butyldimethylsilyl triflate (550 µL, 2.40 mmol) was added to a solution of compound **16** (500 mg, 1.20 mmol) and 2,6-lutidine (400 µL, 3.73 mmol) in dichloromethane (10 mL) and the resulting solution was stirred at room temperature for 30 minutes. After this time, the mixture was diluted with dichloromethane (40 mL) and washed with saturated aq $NaHCO_3$ (50 mL). The solution was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo* to yield a pale yellow oil, purified by flash chromatography (9:1 chloroform : methanol) to give the title compound **17** as a white solid (570 mg, 90%).

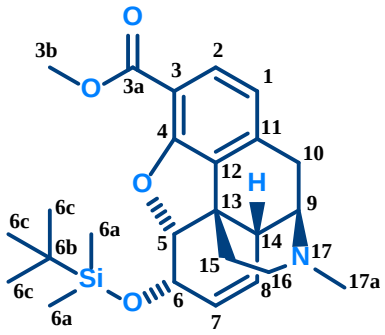


mp: 76-77 °C (literature [11] 75 °C) $[\alpha]_D^{20}$ –111° (*c* 1.0, $CHCl_3$), literature [11] –128° (*c* 1.0, $CHCl_3$) **IR** (NaCl) 1623 (C=C), 1207, 1249 (C–O) **^{1}H-NMR** (δ, 400 MHz, $CDCl_3$): 6.90 (1H, d, J = 8.4 Hz, H_2), 6.56 (1H, d, J = 8.4 Hz, H_1), 5.62 (1H, d, br, J = 9.6 Hz, H_7), 5.24 (1H, dt, J = 9.6 Hz, 2.8 Hz, H_8), 4.81 (1H, d, J = 5.6 Hz, H_5), 4.27 (1H, m, H_6), 3.39 (1H, m, H_9), 3.07 (1H, d, J = 19.2 Hz, $H_{10\alpha}$), 2.71 (1H, s, br, H_{14}), 2.63 (1H, dd, J = 12.0 Hz, 4.4 Hz, H_{16eq}), 2.45 (3H, s, H_{17a}), 2.30-2.43 (2H, m, $H_{10\beta}$, H_{16ax}), 2.08 (1H, td, J = 12.4 Hz, 4.8 Hz, H_{15ax}), 1.86 (1H, dm, J = 12.8 Hz, H_{15eq}), 0.93 (9H, s, H_{6c}), 0.14 (3H, s, H_{6a}), 0.11 (3H, s, H_{6a}) **^{13}C-NMR** (δ, 100MHz, $CDCl_3$): 150.7 (C_4), 135.1 (C_{11}), 134.4 (C_7), 133.5 (C_{12}), 130.8 (C_3), 127.7 (C_8), 121.8 (C_2), 119.3 (C_1), 118.9 (q, J = 319 Hz, C_{3a}) 94.2 (C_5), 68.5 (C_6), 58.8 (C_9), 46.3 (C_{16}), 43.9 (C_{13}), 43.1 (C_{17a}), 40.8 (C_{14}), 35.6 (C_{15}), 25.8 (C_{6c}), 21.2 (C_{10}), 18.3 (C_{6b}), -4.60 (C_{6a}), -4.72 (C_{6a})

3-(methoxycarbonyl)-3-deoxy-6-(tert-butyldimethylsilyl)morphine:

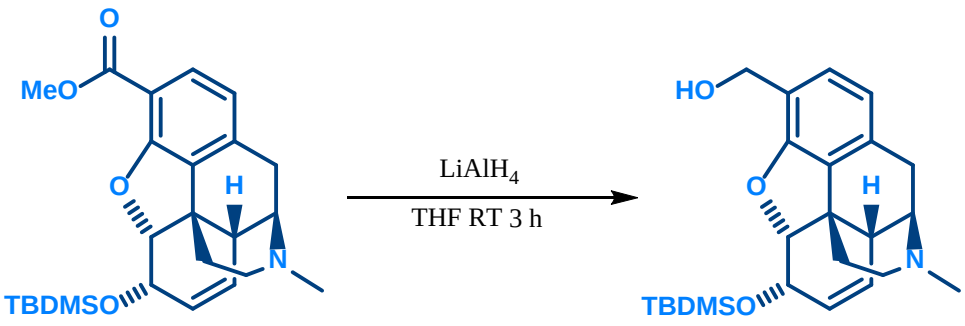


Carbon monoxide was bubbled through a solution of compound **17** (100 mg, 188 µmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (50 mg, 61 µmol) and triethylamine (60 µL, 430 µmol) in a mixture of deoxygenated DMF (3 mL) and deoxygenated methanol (2 mL) for 10 minutes. The mixture was then sealed under an atmosphere of carbon monoxide and heated to 80 °C overnight, darkening over time. The following morning the mixture was vented for 30 minutes, then diluted with dichloromethane (50 mL). The resulting solution was washed with water (50 mL), then washed with brine (50 mL) and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to yield a brown oil, purified by flash chromatography (19:1 chloroform : methanol) to give the title compound **18** as a brown oil (60 mg, 72%).

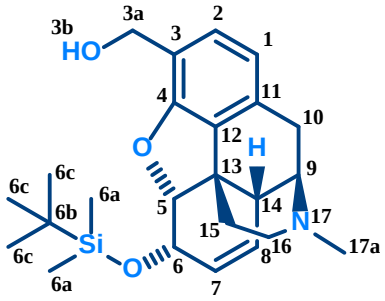


$[\alpha]_D^{20}$ –70° (*c* 1.0, $CHCl_3$) **IR** (NaCl) 1709 (C=O), 1630 (C=C), 1256, 1287 (C–O) **^{1}H-NMR** (δ, 400 MHz, $CDCl_3$): 7.63 (1H, d, J = 8.0 Hz, H_2), 6.61 (1H, d, J = 8.0 Hz, H_1), 5.63 (1H, dm, J = 10.0 Hz, H_7), 5.27 (1H, dt, J = 10.0 Hz, 2.8 Hz, H_8), 4.84 (1H, d, J = 6.0 Hz, H_5), 4.30 (1H, m, H_6), 3.87 (3H, s, H_{3b}), 3.35 (1H, m, H_9), 3.08 (1H, d, 19.2 Hz, $H_{10\alpha}$), 2.68 (1H, m, H_{14}), 2.58 (1H, dd, J = 12.0 Hz, 4.0 Hz, H_{16eq}), 2.44 (3H, s, H_{17a}), 2.29-2.39 (2H, m, $H_{10\beta}$, H_{16ax}), 2.03 (1H, td, J = 12.4 Hz, 5.2 Hz, H_{15ax}), 1.85 (1H, dm, 12.4 Hz, H_{15eq}), 0.95 (9H, s, H_{6c}), 0.16 (3H, s, H_{6a}), 0.13 (3H, s, H_{6a}) **^{13}C-NMR** (δ, 100MHz, $CDCl_3$): 166.6 (C_{3a}), 160.6 (C_4), 140.6 (C_{11}) 134.5 (C_7), 131.5 (C_{12}), 130.3 (C_2), 128.0 (C_8), 118.6 (C_1), 110.4 (C_3), 92.9 (C_5), 68.6 (C_6), 58.6 (C_9), 51.9 (C_{3b}), 46.3 (C_{16}), 43.2 (C_{17a}), 42.5 (C_{13}), 41.0 (C_{14}), 35.9 (C_{15}), 25.9 (C_{6c}), 21.8 (C_{10}), 18.4 (C_{6b}), -4.52 (C_{6a}), -4.57 (C_{6a}) **LRMS (EI):** m/z = 441 ($M^{+\cdot}$, < 1), 385 (40), 384 ($[M–C_4H_9]^+$, 100), 342 (35), 341 (85), 73 (30) **HRMS (ESI):** 442.2416 ($[M+H]^+$, $C_{25}H_{36}NO_4Si$ gives 442.2414)

3-(hydroxymethyl)-3-deoxy-6-(tert-butyldimethylsilyl)morphine:

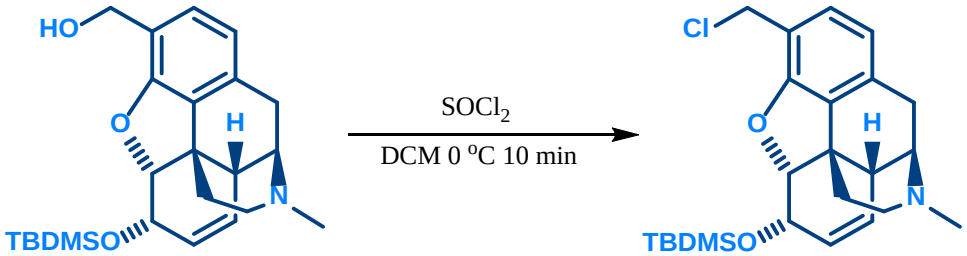


Lithium aluminium hydride (15 mg, 395 µmol) was added to a solution of compound **18** (60 mg, 136 µmol) in dry THF (5 mL) and the resulting mixture was stirred at room temperature for 3 hours. After this time the reaction is quenched by adding a 10% aq solution of sodium potassium tartrate (5 mL) and the mixture is stirred for a further hour. Then, the product was extracted with ethyl acetate (2 × 5 mL) and the combined extracts were dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to yield a brown oil, purified by flash chromatography (19:1 chloroform : methanol) to give the title compound **19** as a pale brown solid (47 mg, 84%).

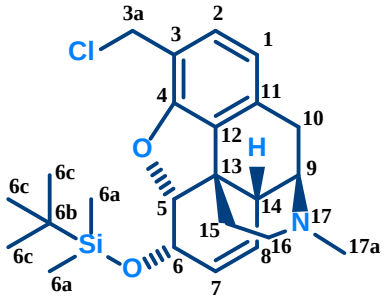


IR (NaCl) 3363 (O–H), 1604 (C=C), 1251 (C–O) **^{1}H-NMR** (δ, 400 MHz, $CDCl_3$): 6.94 (1H, d, J = 7.6 Hz, H_2) 6.55 (1H, d, J = 7.6 Hz, H_1) 5.56 (1H, dm, 10.0 Hz, H_7) 5.22 (1H, dt, J = 10.0 Hz, 2.4 Hz, H_8) 4.70-4.75 (2H, m, H_{3a}, H_5) 4.49 (1H, d, J = 12.4 Hz, H_{3a}) 4.25 (1H, m, H_6) 3.34 (1H, m, H_9) 3.05 (1H, d, J = 18.8 Hz, $H_{10\alpha}$) 2.66 (1H, m, H_{14}) 2.58 (1H, dd, J = 12.0 Hz, 3.6 Hz, H_{16eq}) 2.35-2.44 (4H, m, H_{16ax}, H_{17a}) 2.37 (1H, s, br, H_{3b}) 2.30 (1H, dd, J = 18.8 Hz, 6.4 Hz, $H_{10\beta}$) 2.04 (1H, td, J = 12.4 Hz, 5.2 Hz, H_{15ax}) 1.86 (1H, dm, J = 12.4 Hz, H_{15eq}) 0.93 (9H, s, H_{6c}) 0.15 (3H, s, H_{6a}) 0.11 (3H, s, H_{6a}) **^{13}C-NMR** (δ, 100MHz, $CDCl_3$): 157.9 (C_4), 134.8 (C_{11}), 133.9 (C_7), 129.8 (C_{12}), 128.1 (C_8), 127.7 (C_2), 120.2 (C_3), 118.8 (C_1), 92.3 (C_5), 68.3 (C_6), 61.2 (C_{3a}), 59.0 (C_9), 46.6 (C_{16}), 43.2 (C_{17a}), 42.8 (C_{13}), 41.0 (C_{14}), 35.7 (C_{15}), 25.9 (C_{6c}), 21.2 (C_{10}), 18.4 (C_{6b}), -4.51 (C_{6a}), -4.71 (C_{6a}) **LRMS (EI):** m/z = 413 ($M^{+\cdot}$, < 1), 357 (40), 356 ($[M–C_4H_9]^+$, 100), 299 (35), 238 (20), 75 (20), 73 (30) **HRMS (EI):** 413.2386 ($M^{+\cdot}$, $C_{24}H_{35}NO_3Si$ gives 413.2386)

3-(chloromethyl)-3-deoxy-6-(tert-butyldimethylsilyl)morphine:

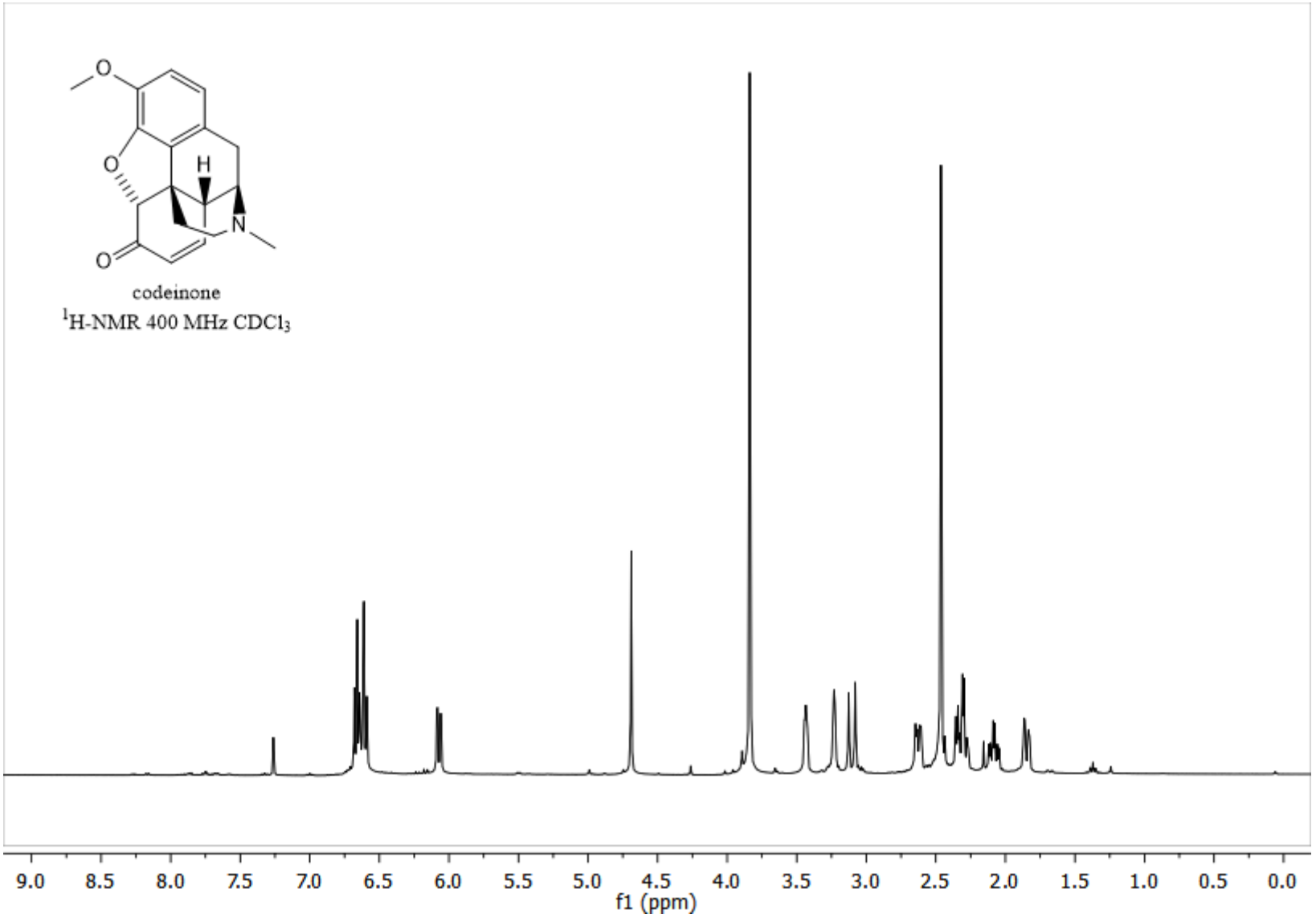


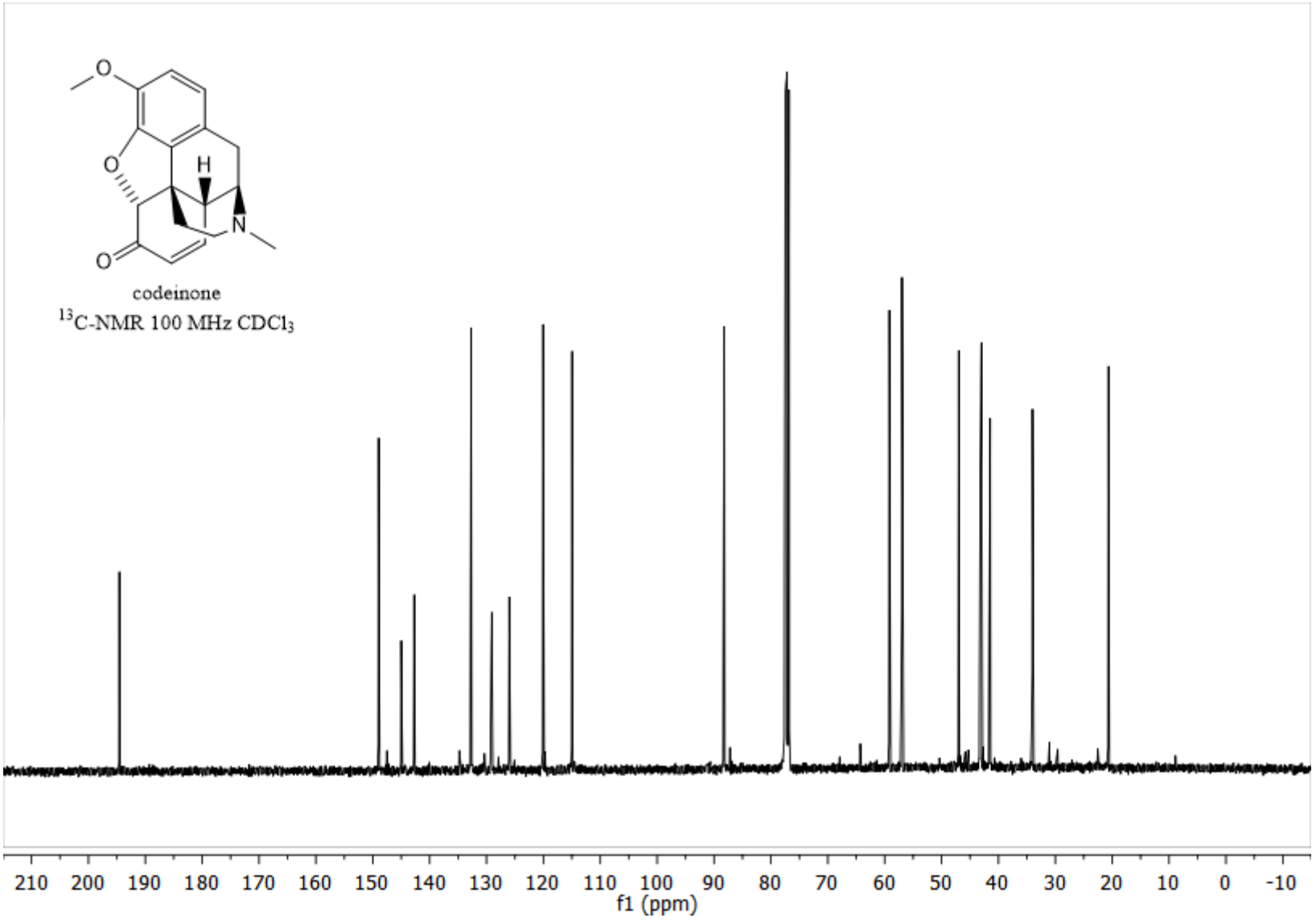
Thionyl chloride (4 µL, 55 µmol) was added to a solution of compound **19** (10 mg, 24 µmol), and triethylamine (7 µL, 50 µmol) in dichloromethane (500 µL) at 0 °C and the resulting solution was stirred at 0 °C for 10 minutes. After this time the mixture was diluted with dichloromethane (5 mL) and washed with saturated aq $NaHCO_3$ (5 mL). The solution was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo* to yield the title compound **15** as a brown oil (9 mg, 86%).



IR (NaCl) 1604, 1639 (C=C), 1251 (C–O) **^{1}H-NMR** (δ, 400 MHz, $CDCl_3$): 7.01 (1H, d, J = 8.0 Hz, H_2), 6.55 (1H, d, J = 8.0 Hz, H_1), 5.60 (1H, dm, J = 10.0 Hz, H_7), 5.24 (1H, dt, J = 10.0 Hz, 2.4 Hz, H_8), 4.74 (1H, dd, J = 6.0 Hz, 1.2 Hz, H_5), 4.66 (1H, d, J = 11.2 Hz, H_{3a}), 4.49 (1H, d, J = 11.2 Hz, H_{3a}), 4.25 (1H, m, H_6), 3.34 (1H, m, H_9), 3.06 (1H, d, J = 19.2 Hz, $H_{10\alpha}$), 2.65 (1H, m, H_{14}), 2.58 (1H, dd, J = 12.4 Hz, 4.4 Hz, H_{16eq}), 2.43 (3H, s, H_{17a}), 2.38 (1H, td, J = 12.4 Hz, 3.6 Hz, H_{16ax}), 2.29 (1H, dd, J = 19.2 Hz, 6.0 Hz $H_{10\beta}$), 2.02 (1H, td, J = 12.4 Hz, 5.2 Hz, H_{15ax}), 1.86 (1H, dm, J = 12.4 Hz, H_{15eq}), 0.94 (9H, s, H_{6c}), 0.16 (3H, s, H_{6a}), 0.11 (3H, s, H_{6a}), **^{13}C-NMR** (δ, 100MHz, $CDCl_3$): 158.2 (C_4), 135.9 (C_{11}), 134.3 (C_7), 130.2 (C_{12}), 129.0 (C_8), 128.0 (C_2), 118.8 (C_1), 116.1 (C_3), 92.4 (C_5), 68.4 (C_6), 58.9 (C_9), 46.5 (C_{16}), 43.3 (C_{17a}), 43.1 (C_{13}), 41.2 (C_{3a}), 41.0 (C_{14}), 35.9 (C_{15}), 25.9 (C_{6c}), 21.3 (C_{10}), 18.4 (C_{6b}), -4.35 (C_{6a}), -4.63 (C_{6a}) **LRMS (EI):** m/z = 431 ($M^{+\cdot}$, < 1), 396 ($[M–Cl]^+$, 20), 376 ($[M–C_4H_9]^+$, 40), 374 ($[M–C_4H_9]^+$, 100), 332 (30), 331 (45), 330 (30), 238 (25), 75 (20), 73 (45) **HRMS (EI):** 433.2018 ($M^{+\cdot}$, $C_{24}H_{34}NO_2Si^{37}Cl$ gives 433.2018) 431.2049 ($M^{+\cdot}$, $C_{24}H_{34}NO_2Si^{35}Cl$ gives 431.2047)

2. Spectral Data:




codeinone
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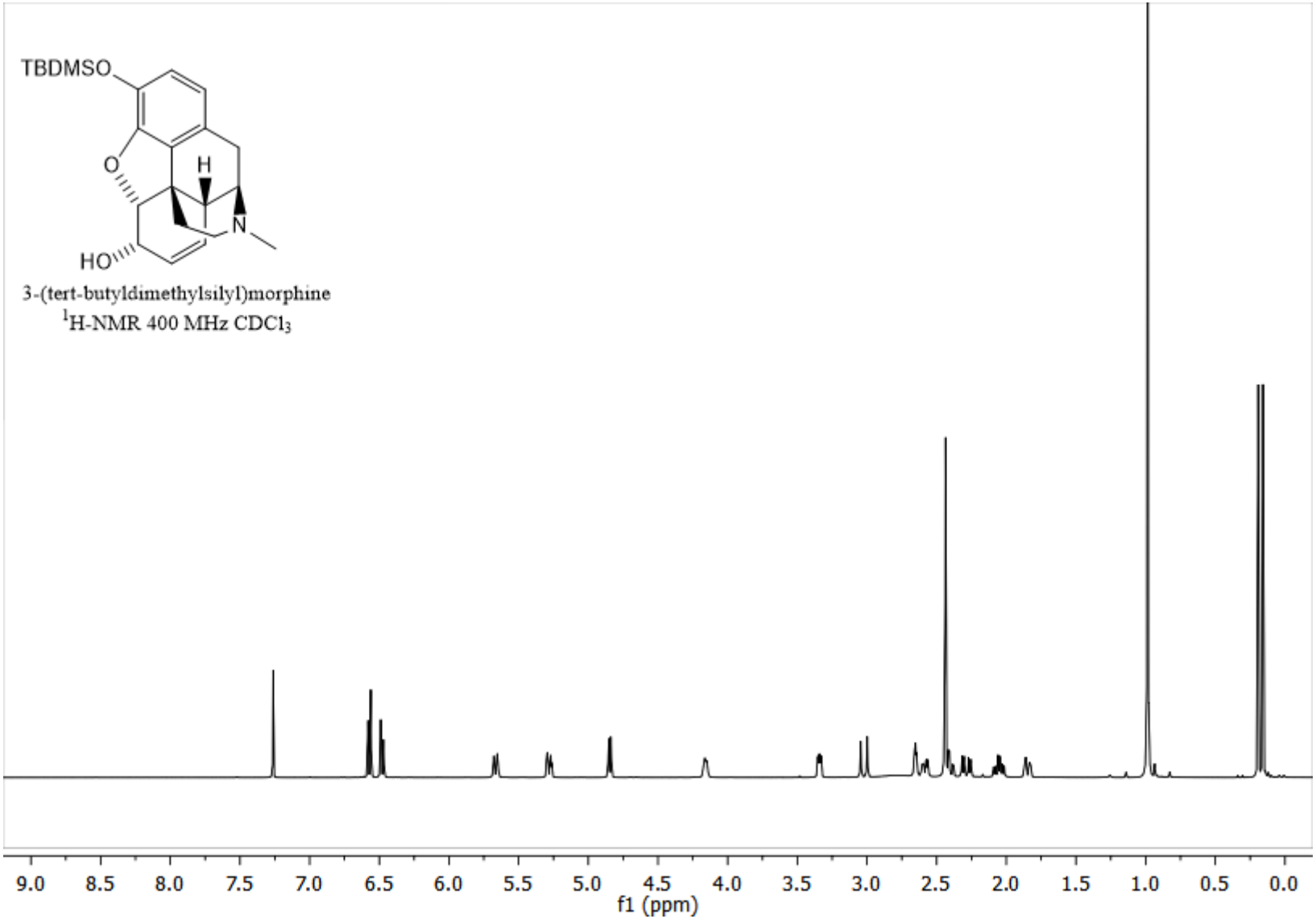
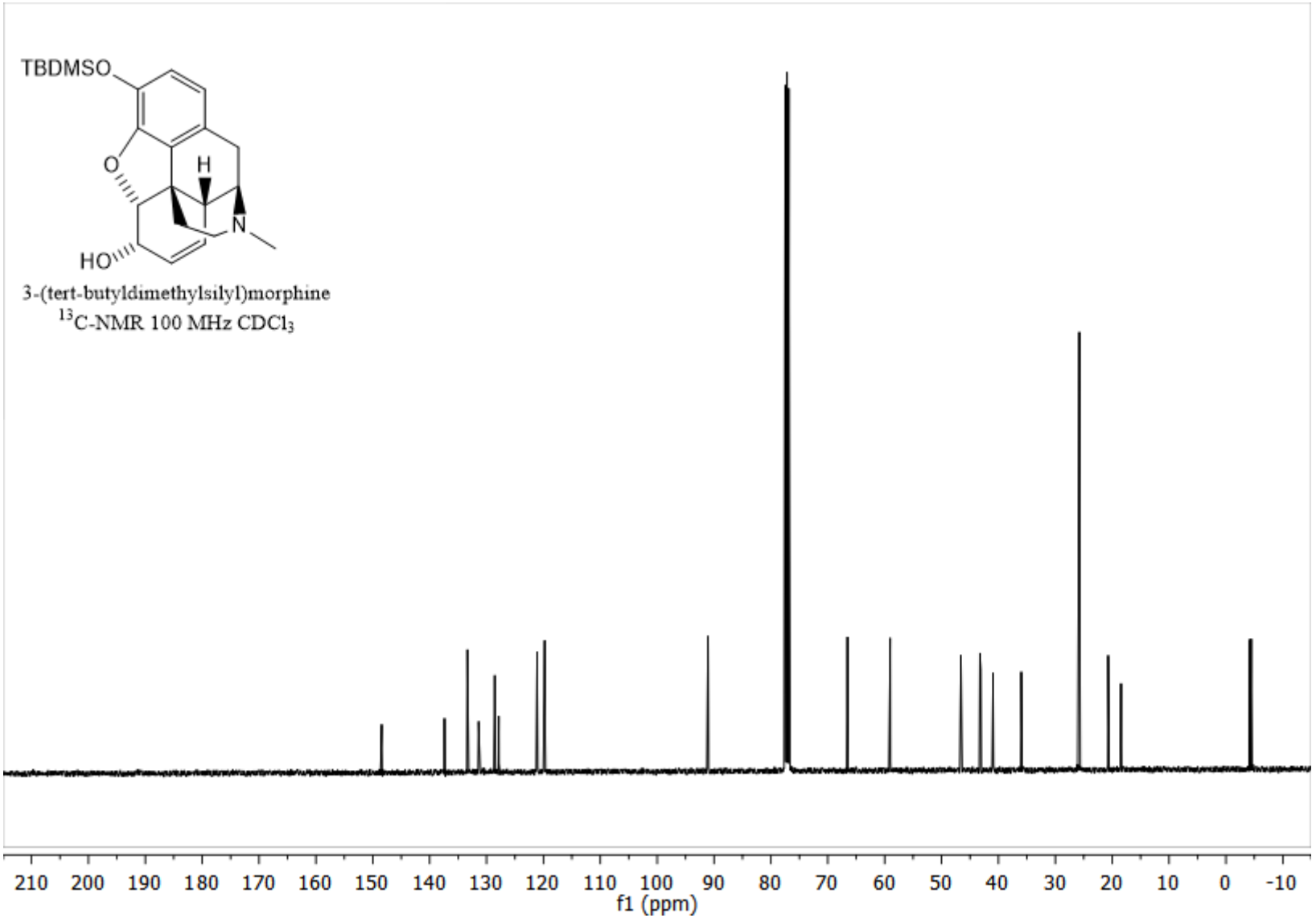
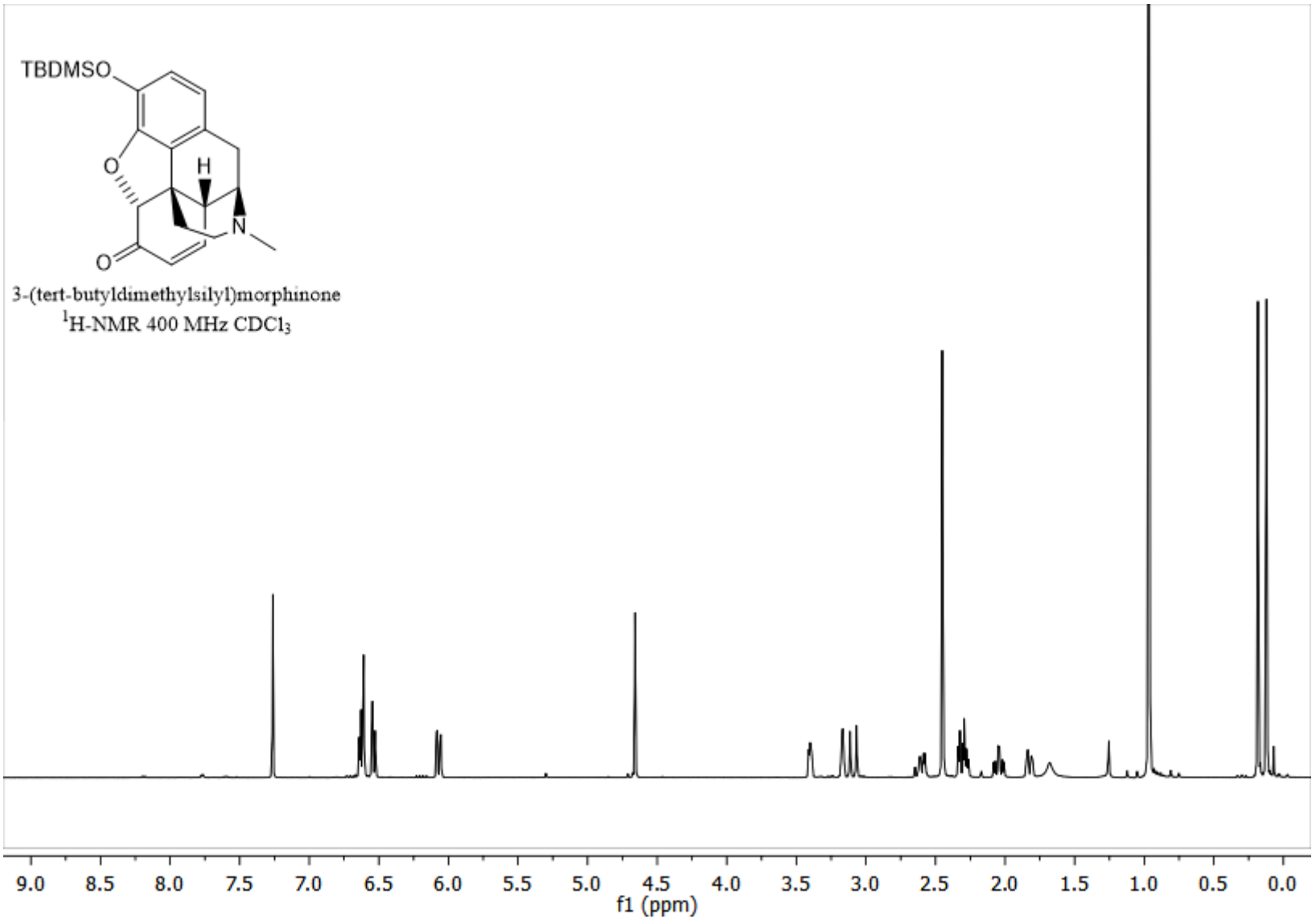
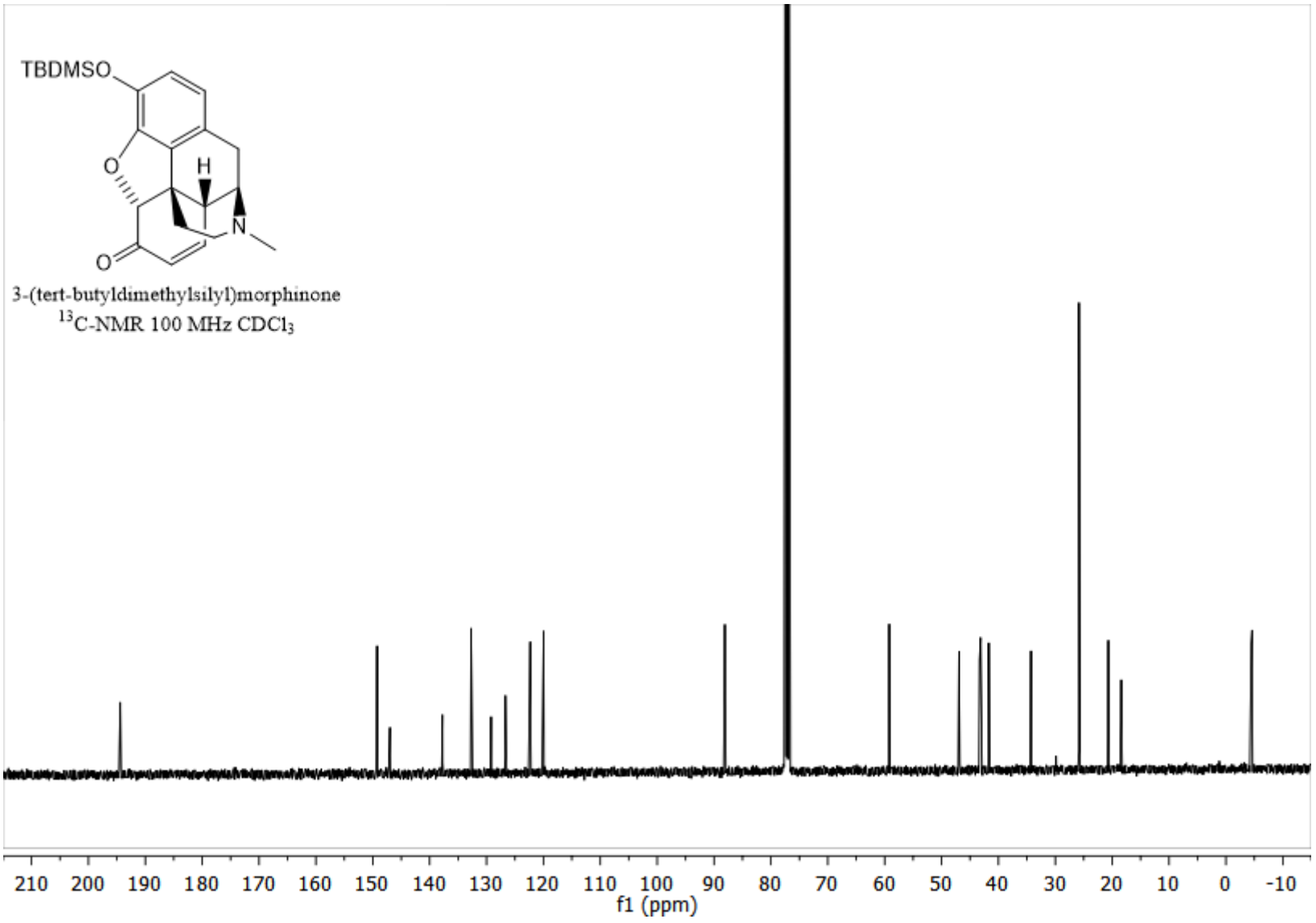
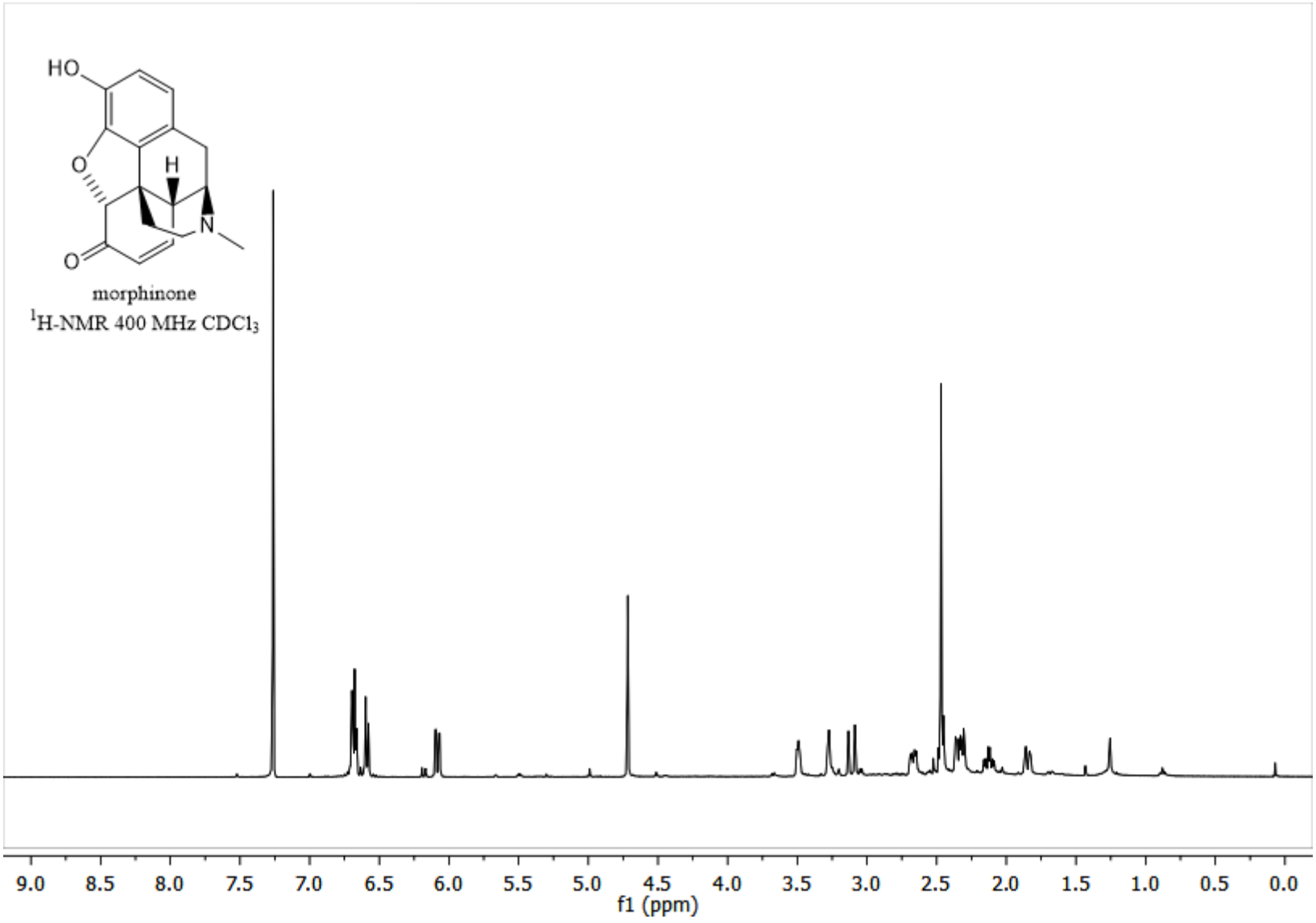
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

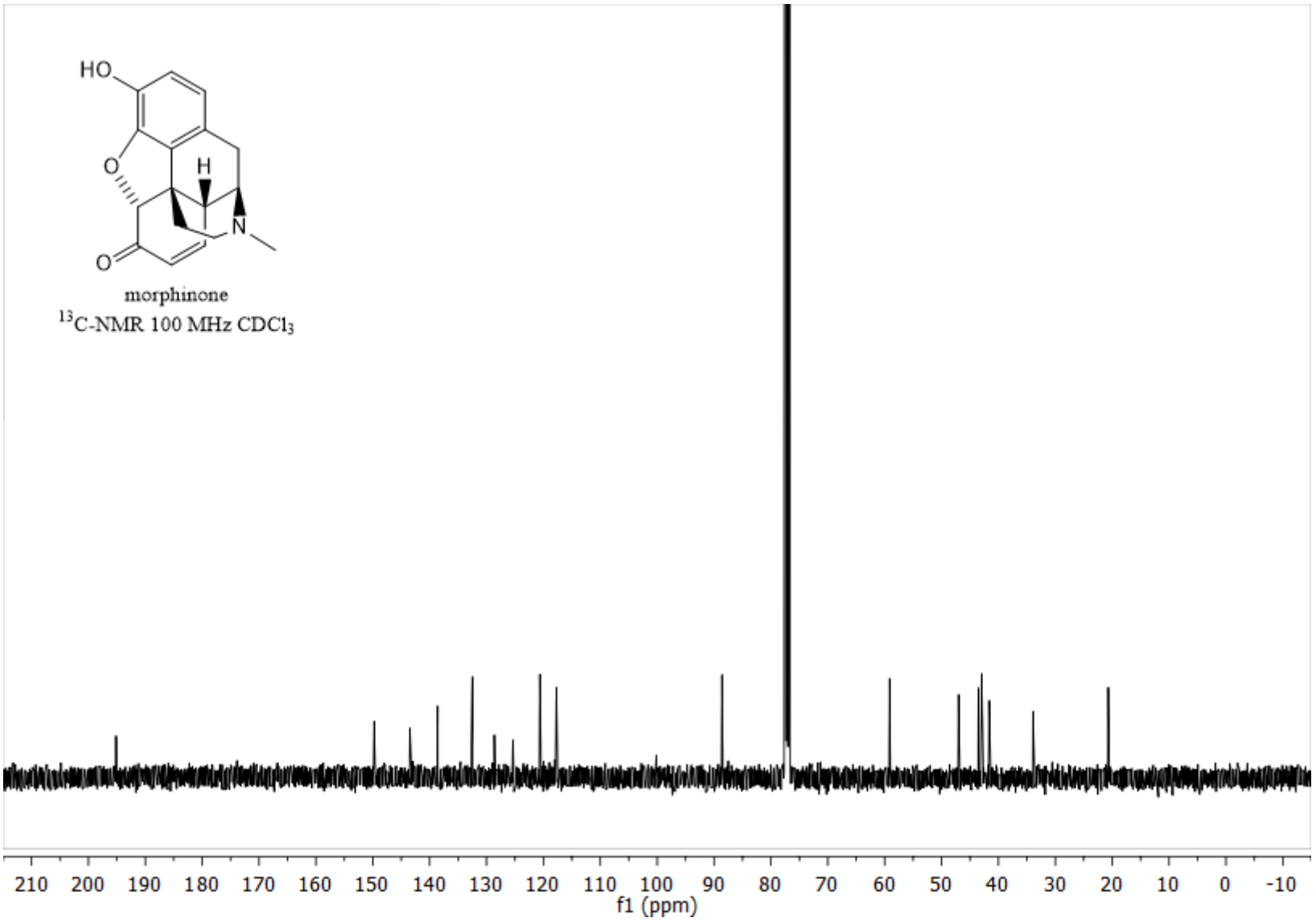

TBDMSO
O
H
N
HO
3-(tert-butyldimethylsilyl)morphine
^{1}H-NMR 400 MHz $CDCl_3$
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

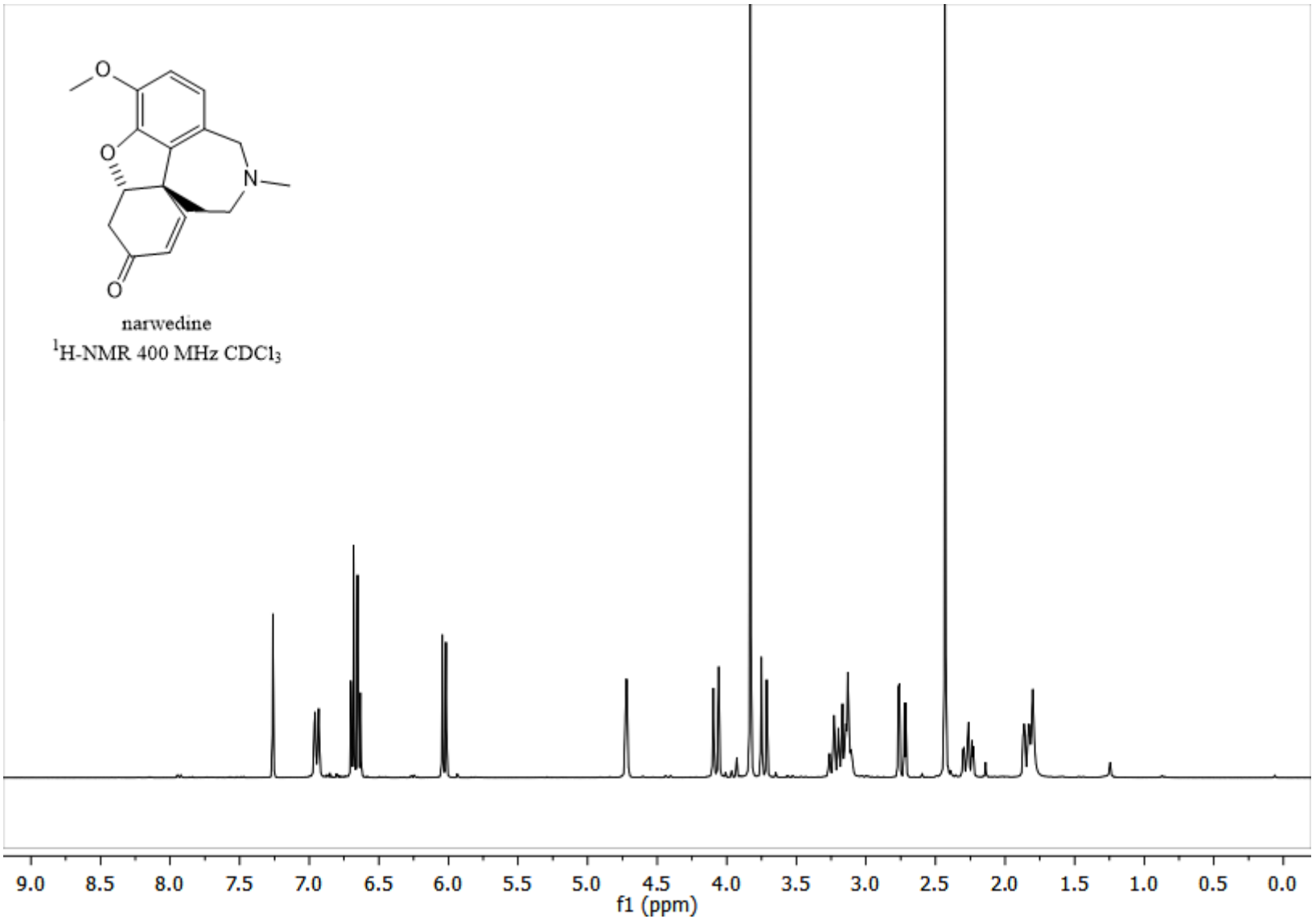

TBDMSO
O
H
N
HO
3-(tert-butyldimethylsilyl)morphine
13C-NMR 100 MHz CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

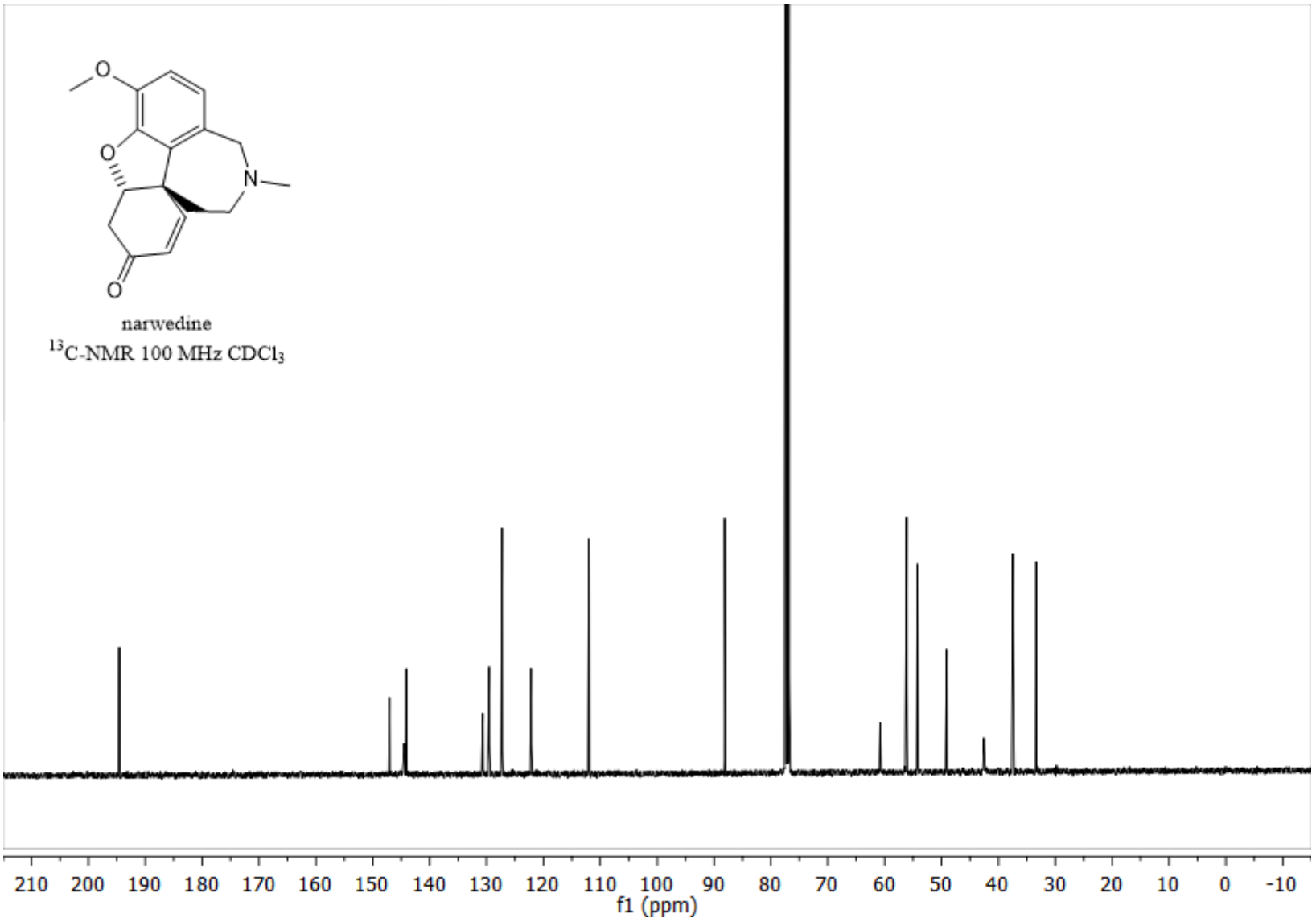

TBDMSO
O
H
N
O
3-(tert-butyldimethylsilyl)morphinone
1H-NMR 400 MHz CDCl3
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

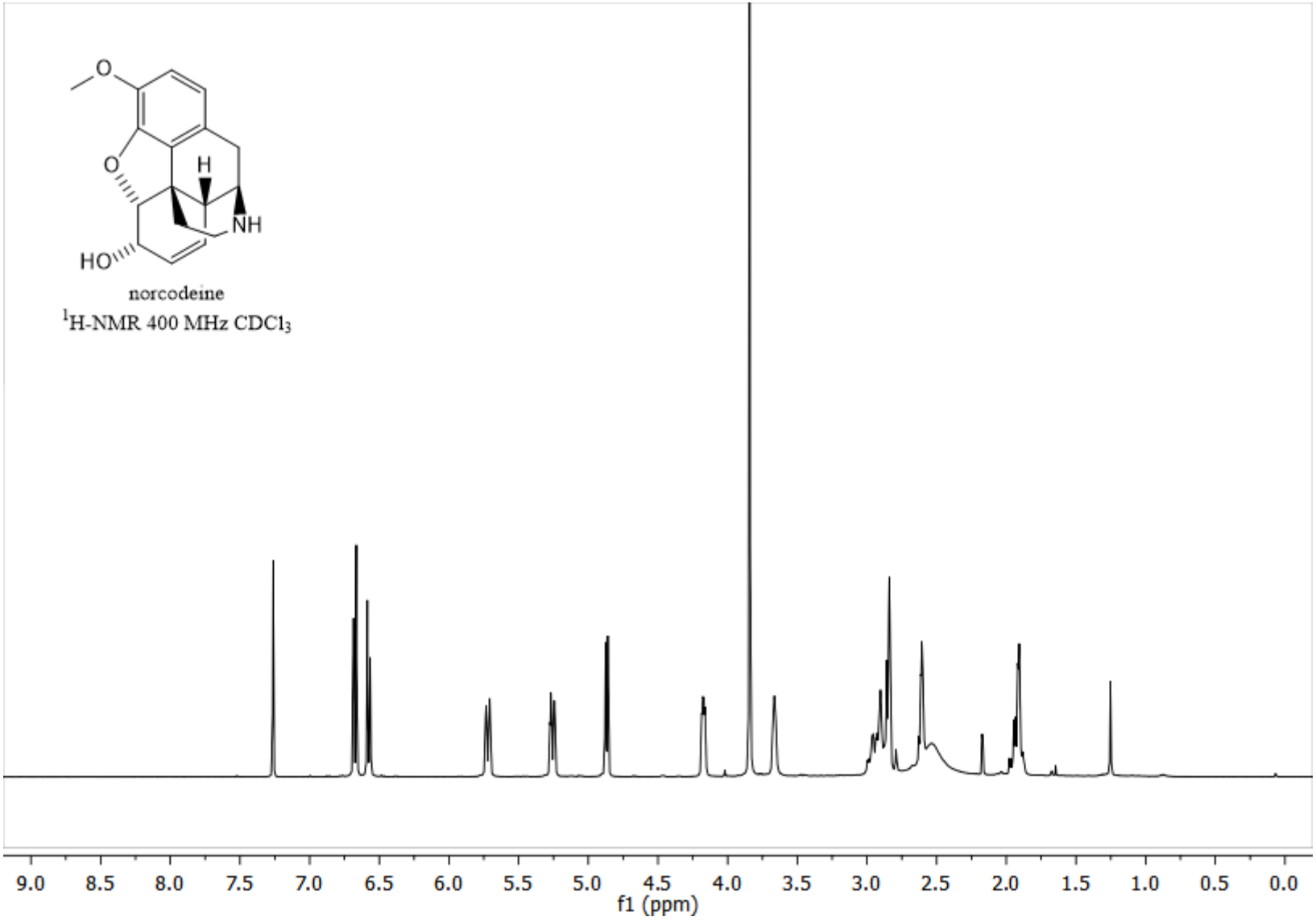

TBDMSO
O
H
N
O
3-(tert-butyldimethylsilyl)morphinone
13C-NMR 100 MHz CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

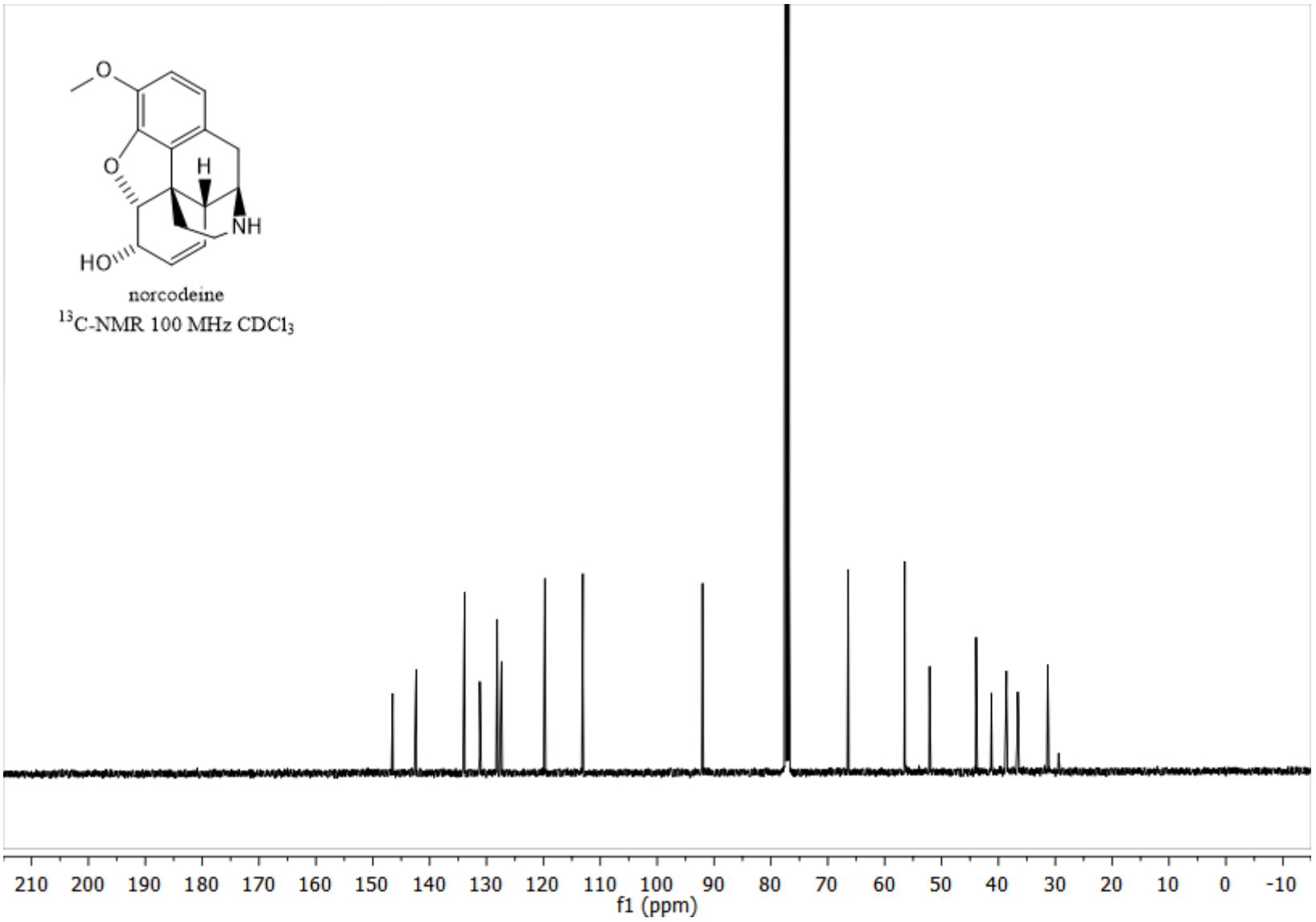

HO
O
H
N
O
morphinone
^{1}H-NMR 400 MHz $CDCl_3$
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

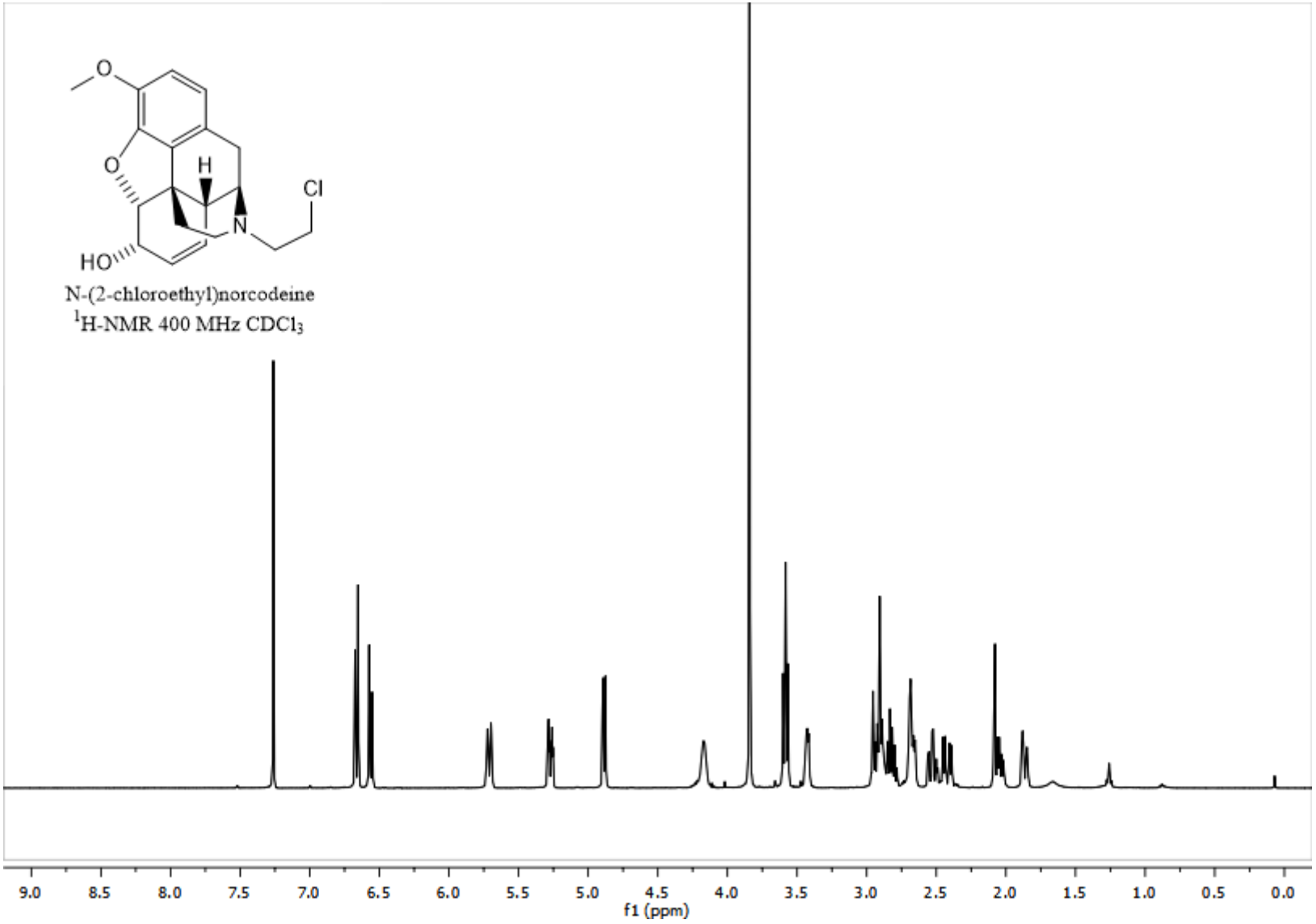

HO
O
H
N
O
morphinone
^{13}C-NMR 100 MHz $CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

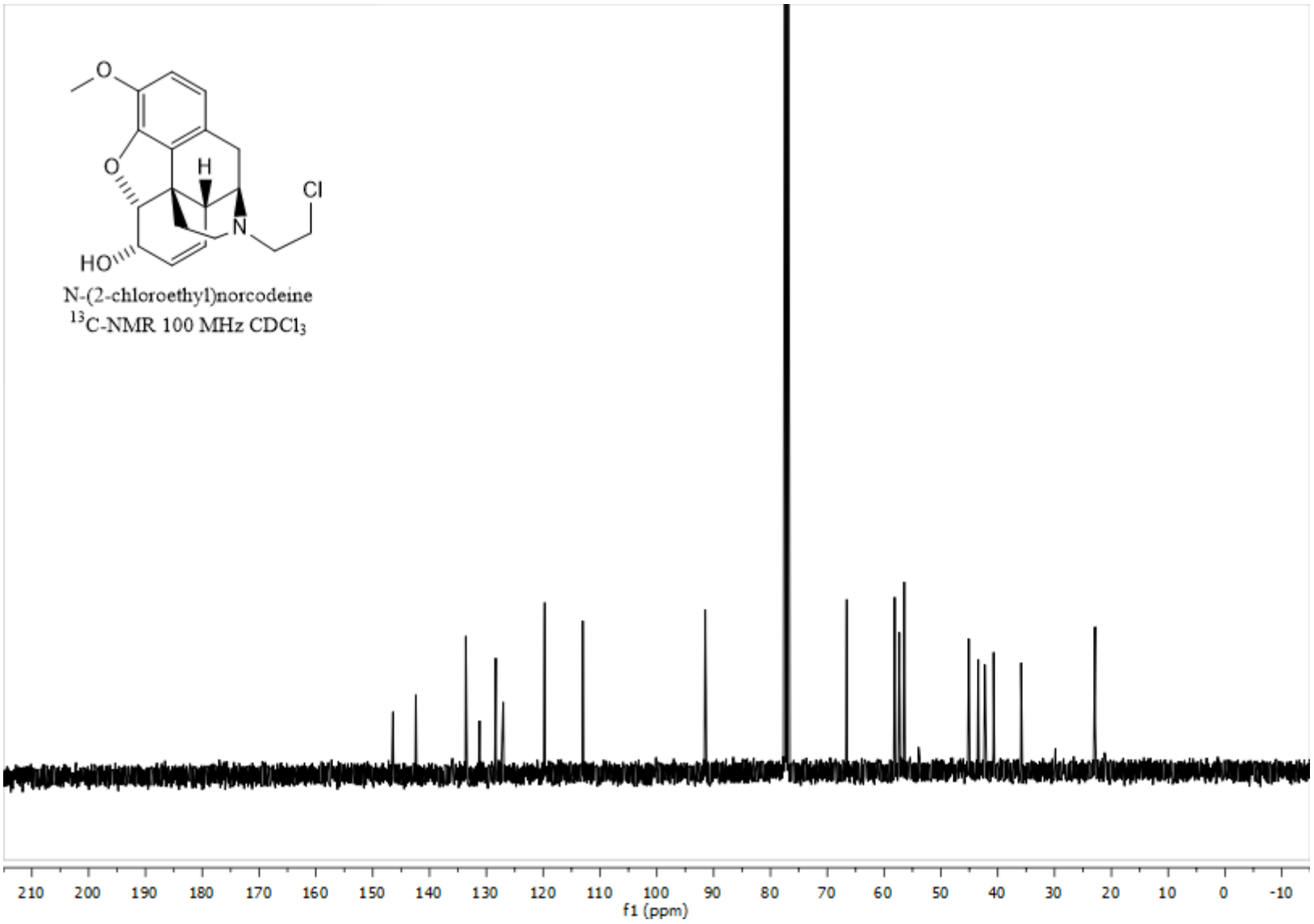

O
O
N
O
narwedine
^{1}H-NMR 400 MHz $CDCl_3$
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
O
N
O
narwedine
13C-NMR 100 MHz CDCl3
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
H
NH
HO
norcodeine
1H-NMR 400 MHz CDCl3
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)

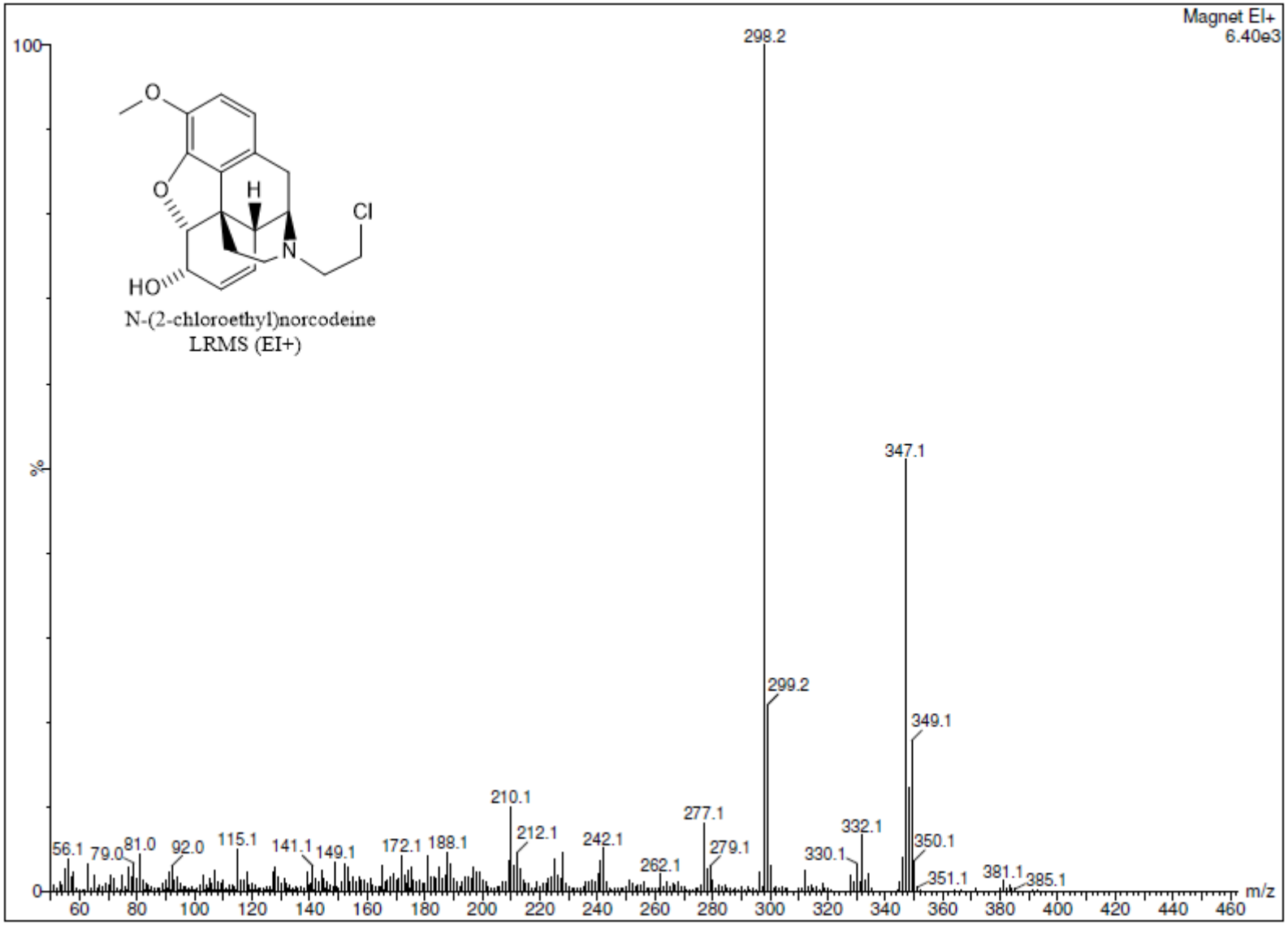

O
O
H
NH
HO
norcodeine
^{13}C-NMR 100 MHz $CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

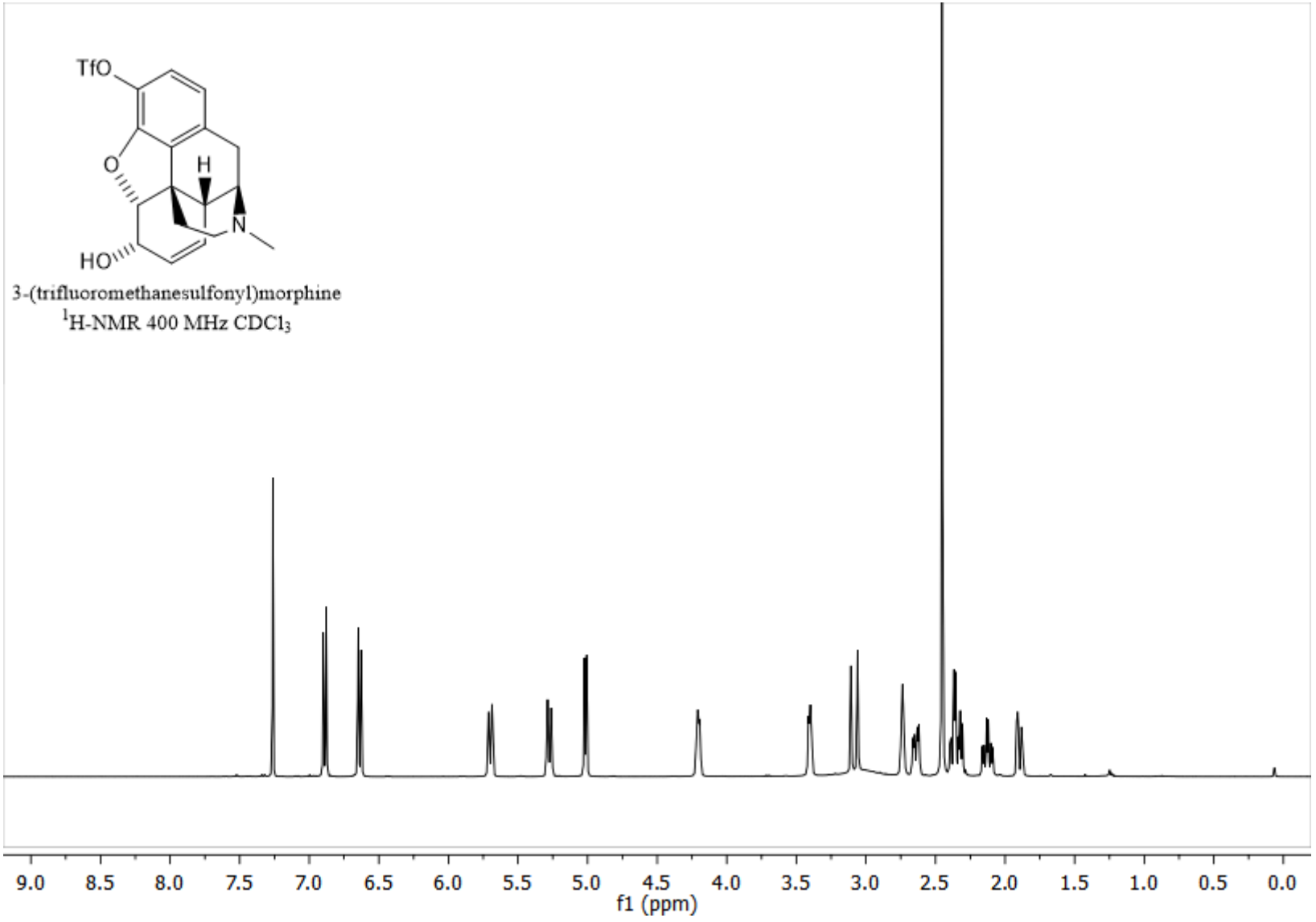

O
O
H
Cl
N
HO
N-(2-chloroethyl)norcodeine
1H-NMR 400 MHz CDCl3
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

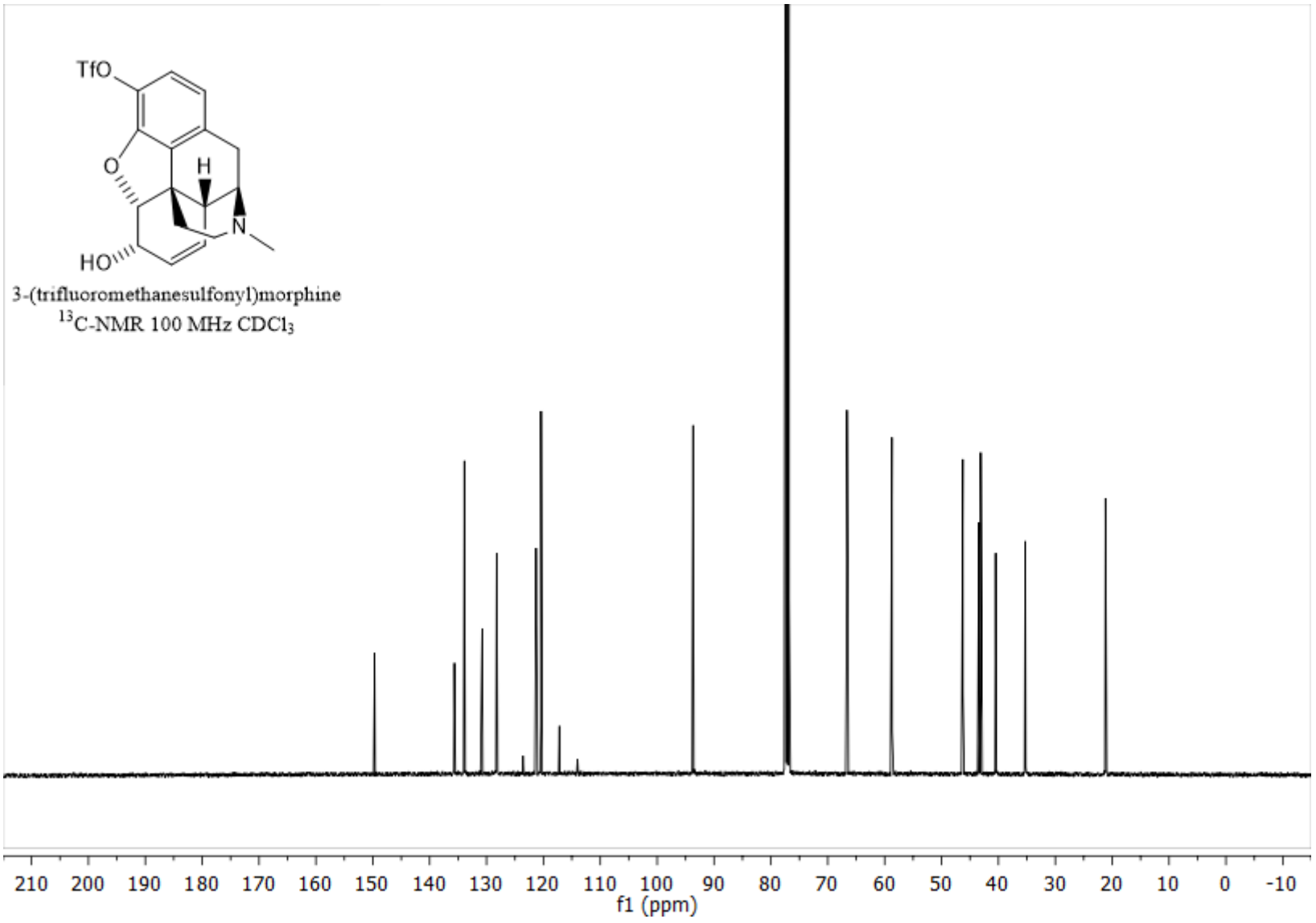


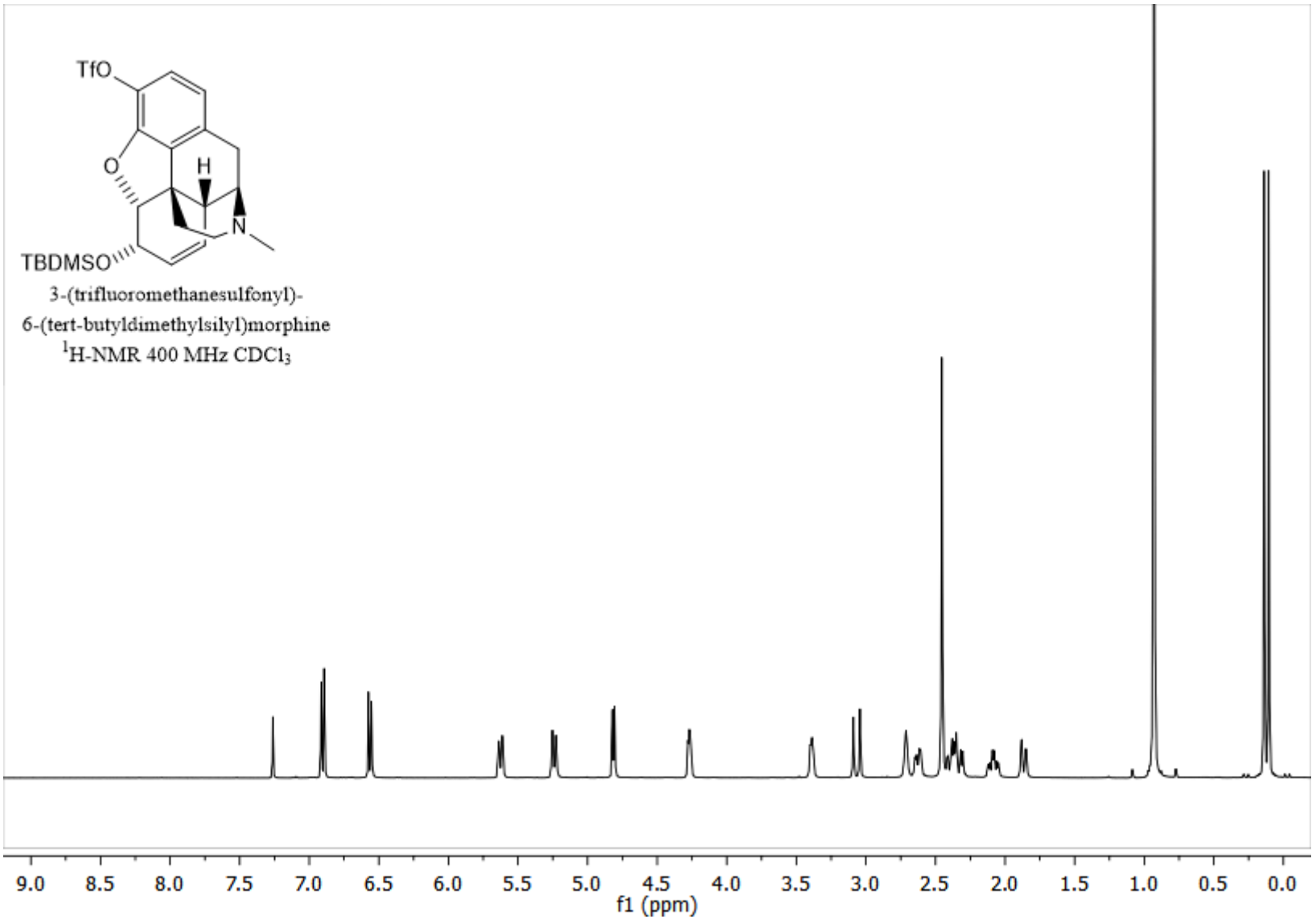
N-(2-chloroethyl)norcodeine

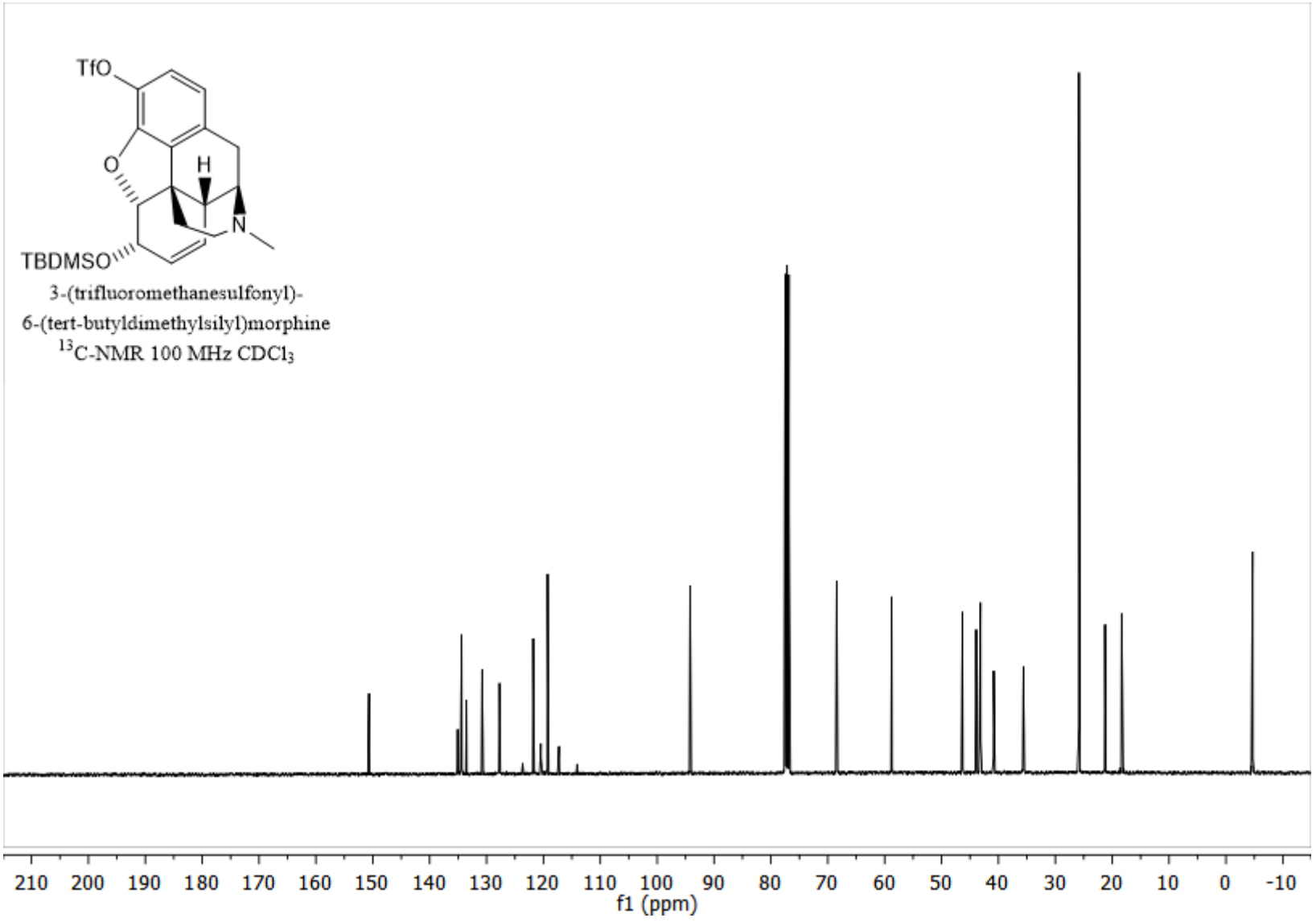
^{13}C-NMR 100 MHz $CDCl_3$

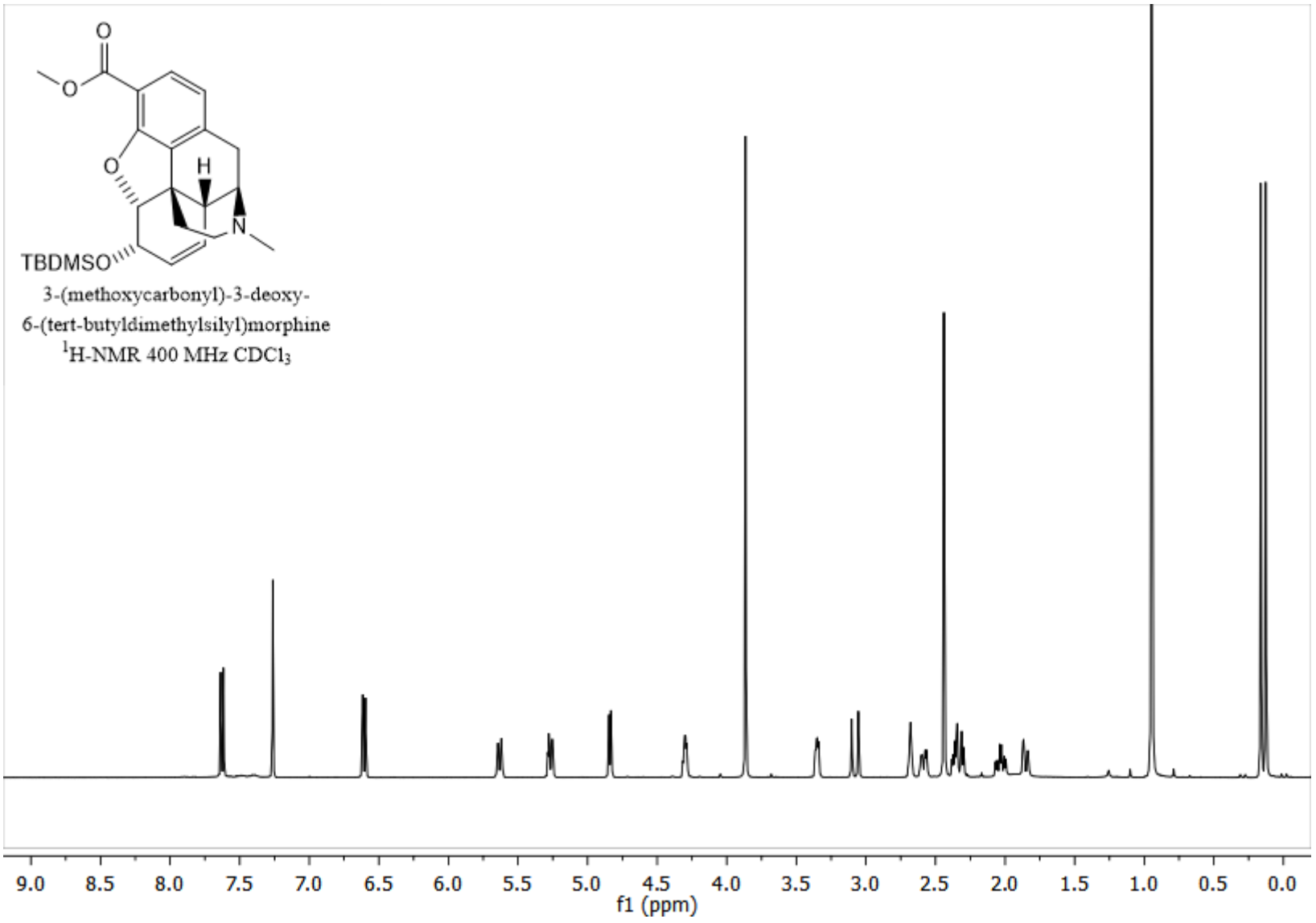

Magnet EI+
6.40e3
100
%
0
298.2
347.1
299.2
349.1
210.1
277.1
212.1
242.1
332.1
350.1
56.1
79.0
81.0
92.0
115.1
141.1
149.1
172.1
188.1
262.1
279.1
330.1
351.1
381.1
385.1
m/z
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440
460
O
O
H
N
Cl
HO
N-(2-chloroethyl)norcodeine
LRMS (EI+)

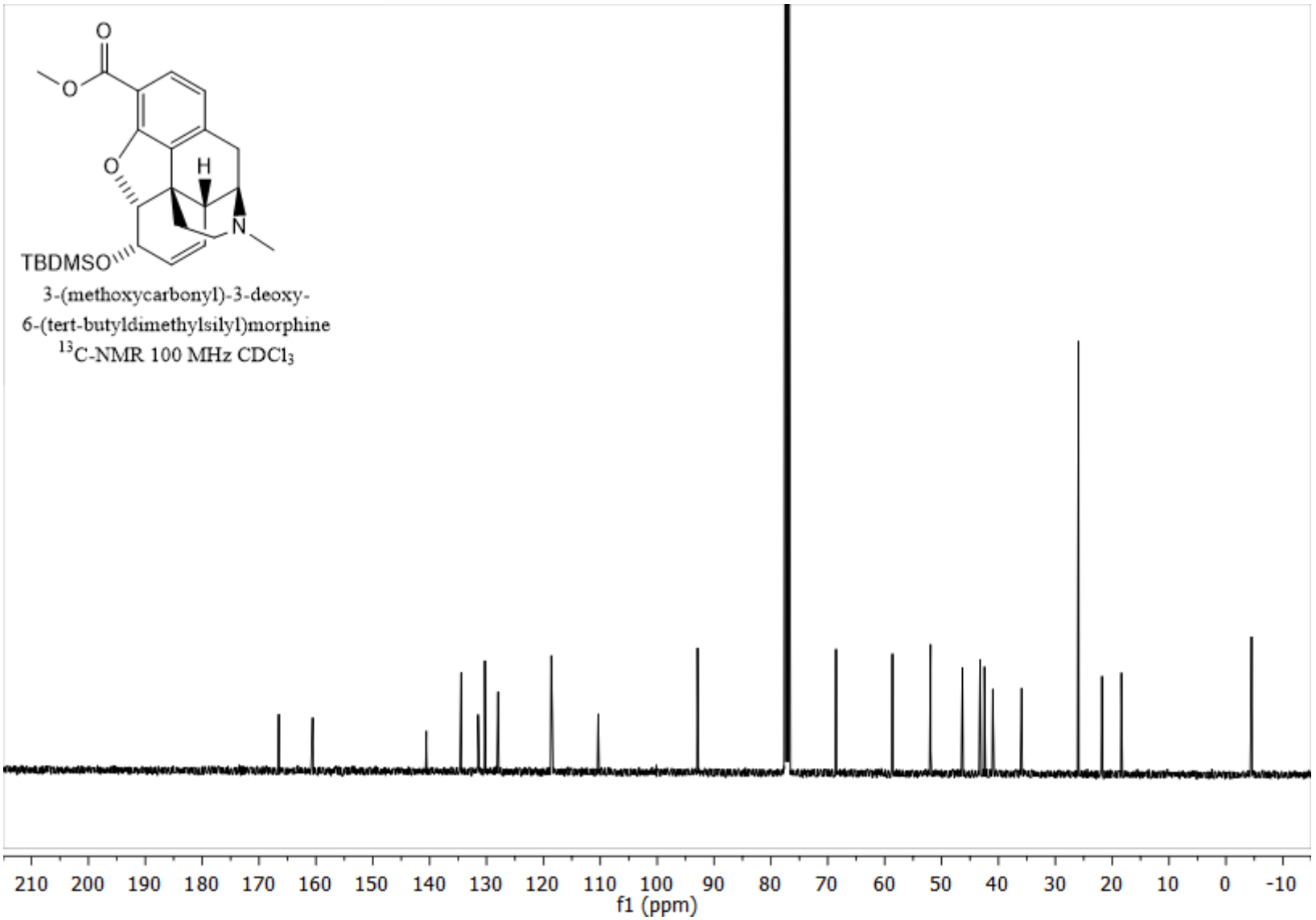

TfO
O
H
N
HO
3-(trifluoromethanesulfonyl)morphine
1H-NMR 400 MHz CDCl3
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

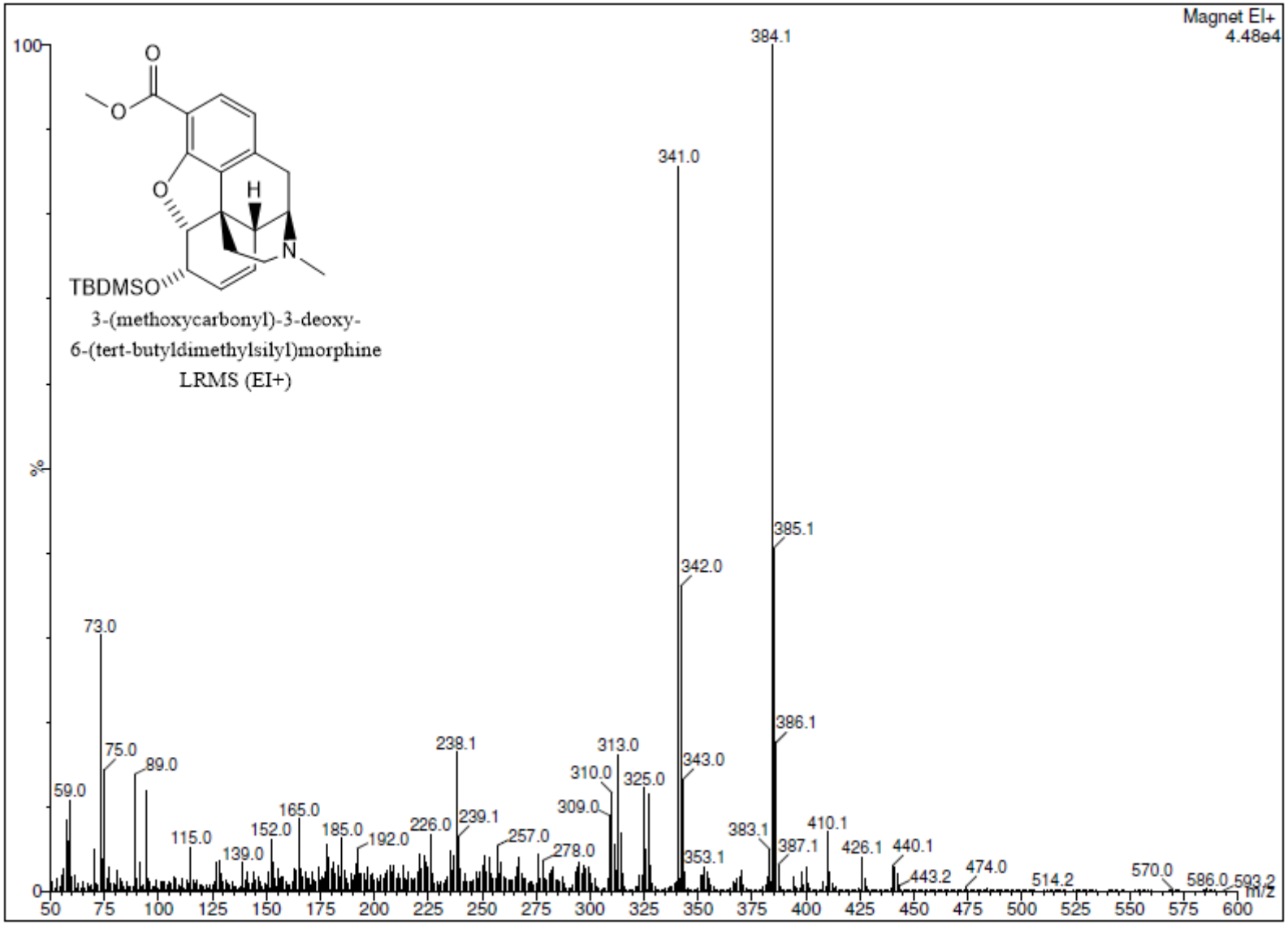

TfO
O
H
N
HO
3-(trifluoromethanesulfonyl)morphine
13C-NMR 100 MHz CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

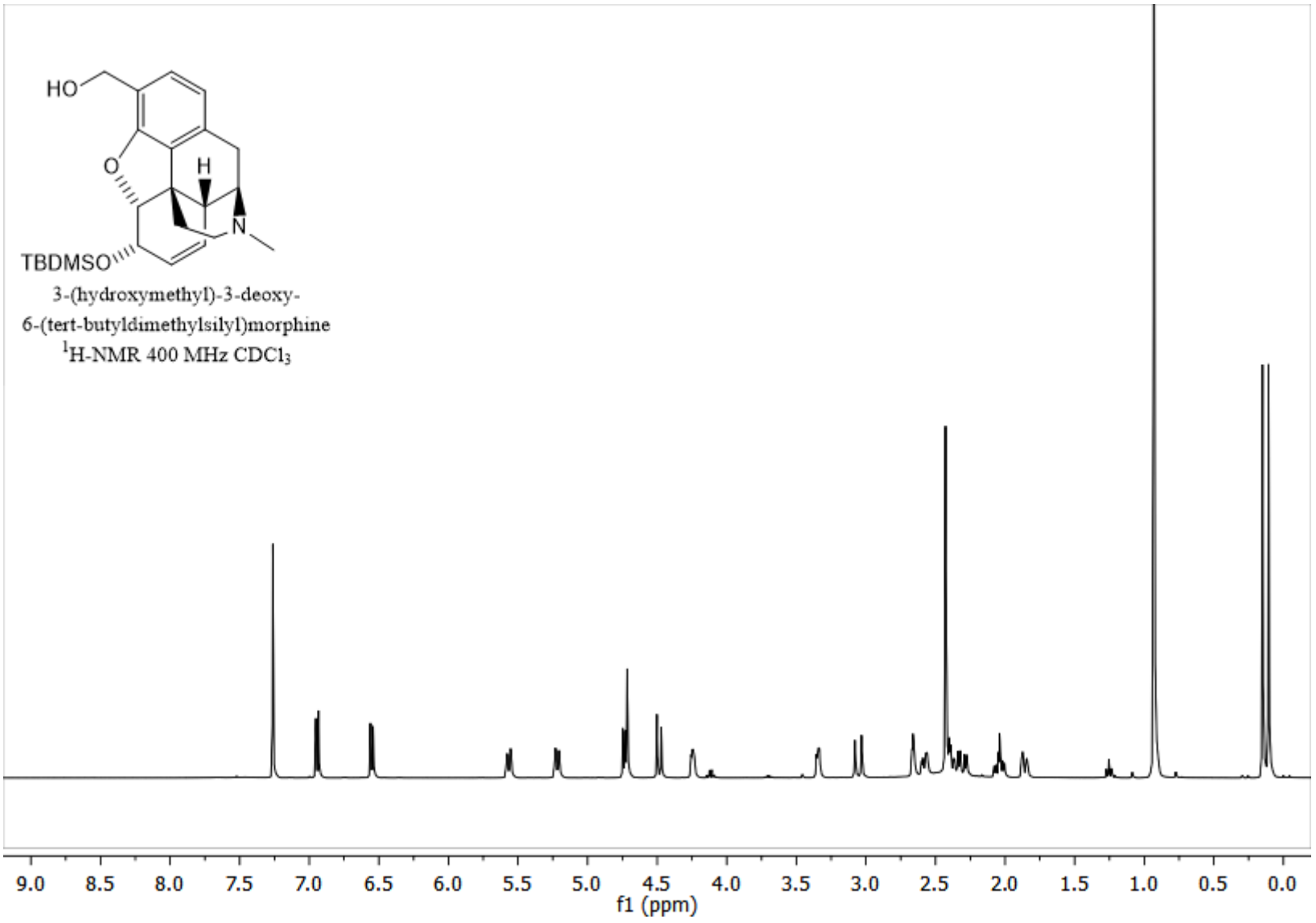

TfO
O
H
N
TBDMSO
3-(trifluoromethanesulfonyl)-
6-(tert-butyldimethylsilyl)morphine
^{1}H-NMR 400 MHz $CDCl_3$
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

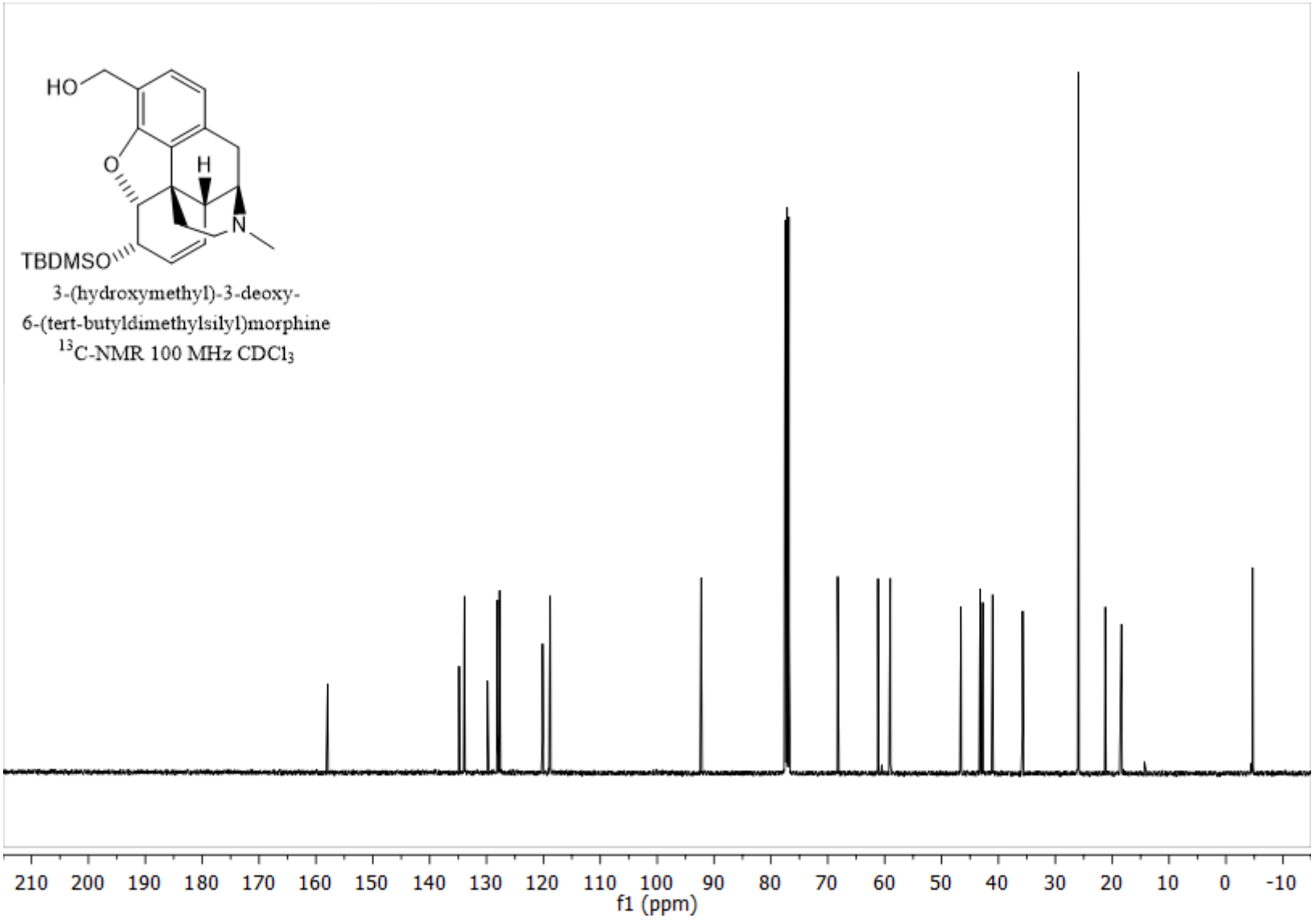

TfO
O
H
N
TBDMSO
3-(trifluoromethanesulfonyl)-
6-(tert-butyldimethylsilyl)morphine
^{13}C-NMR 100 MHz $CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

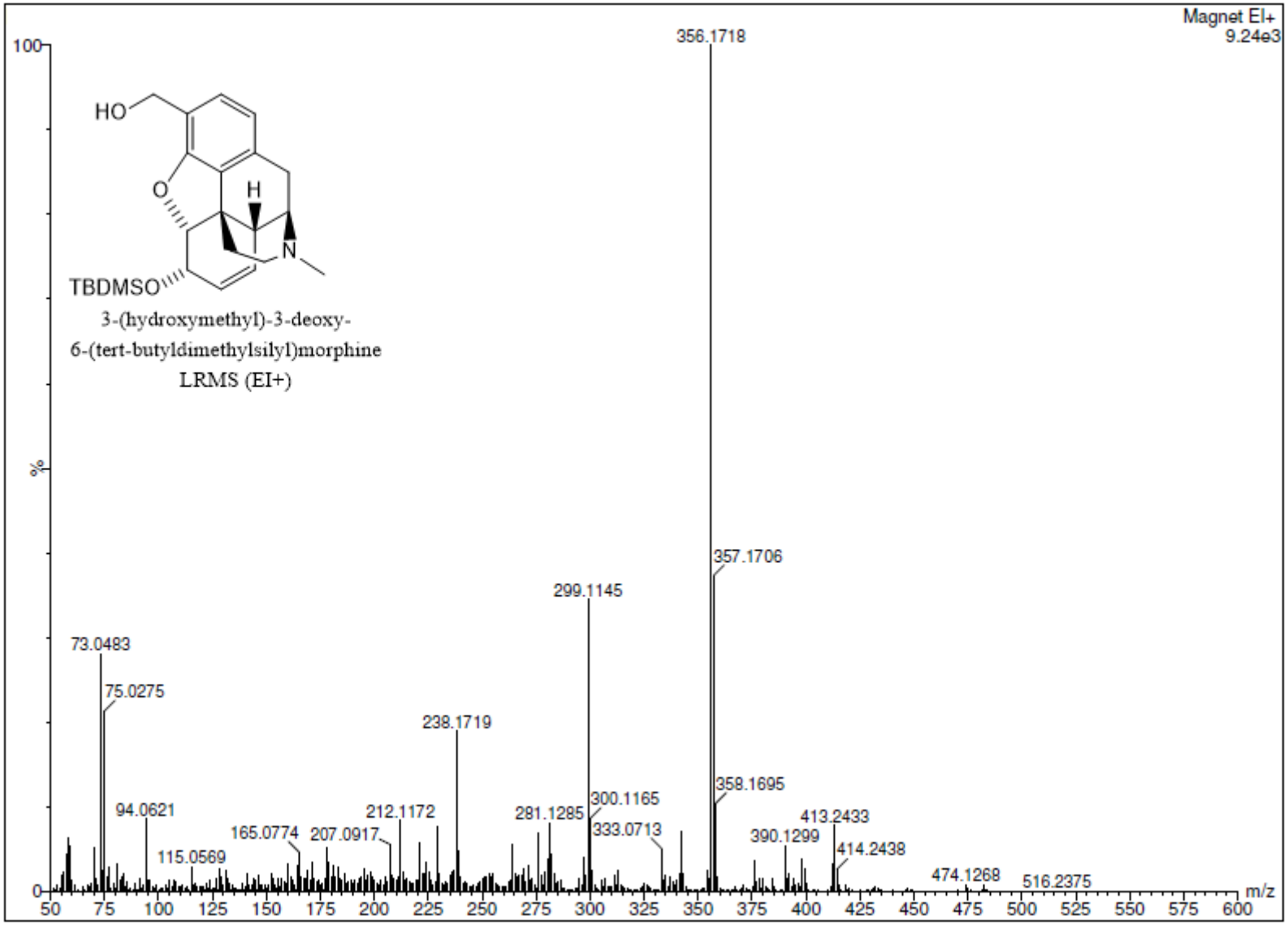

O
O
O
H
N
TBDMSO
3-(methoxycarbonyl)-3-deoxy-
6-(tert-butyldimethylsilyl)morphine
1H-NMR 400 MHz CDCl3
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

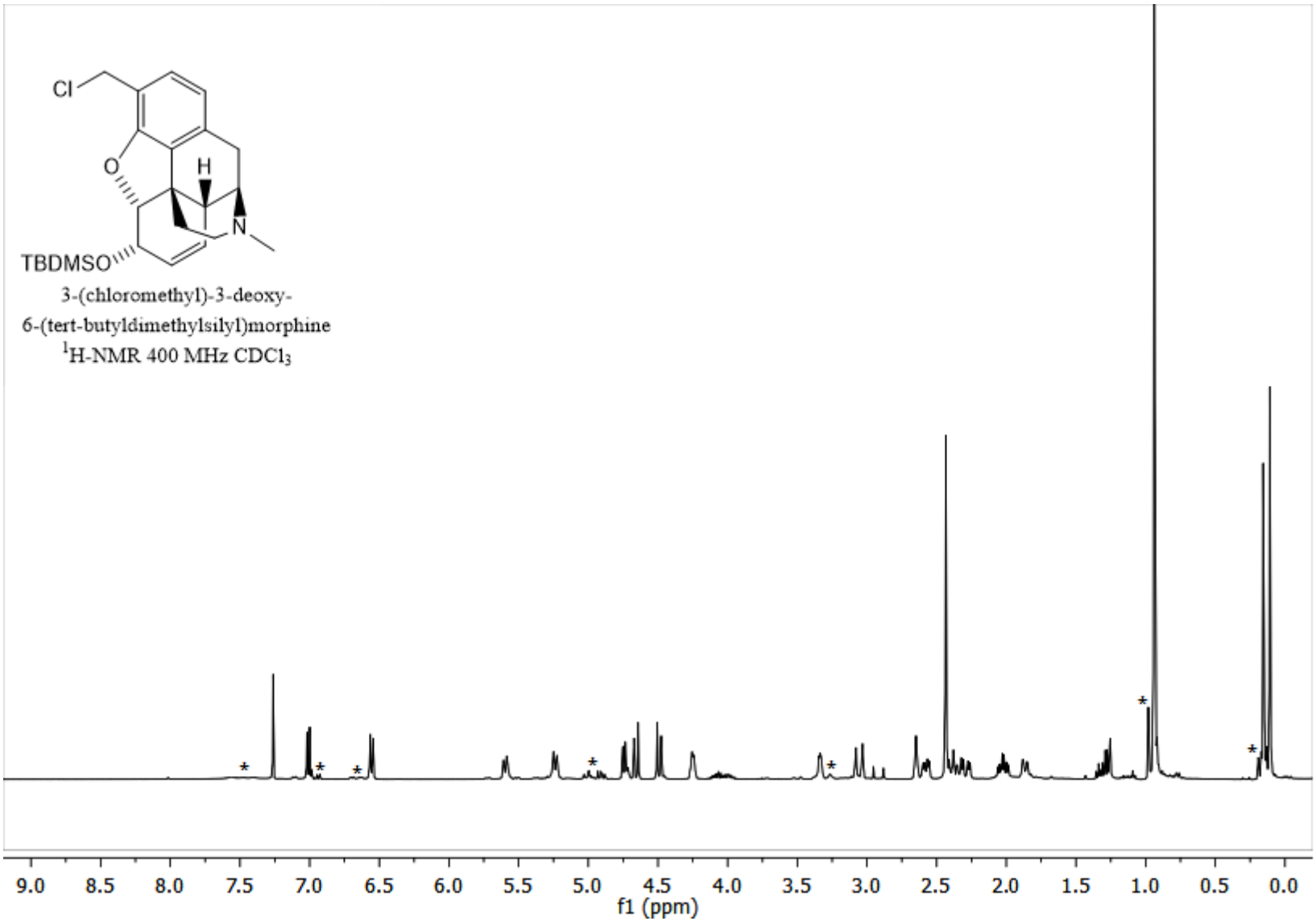

O
O
O
H
N
TBDMSO
3-(methoxycarbonyl)-3-deoxy-
6-(tert-butyldimethylsilyl)morphine
13C-NMR 100 MHz CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Magnet EI+
4.48e4
100
%
0
O
O
O
H
N
TBDMSO
3-(methoxycarbonyl)-3-deoxy-
6-(tert-butyldimethylsilyl)morphine
LRMS (EI+)
384.1
341.0
385.1
342.0
73.0
386.1
238.1
313.0
75.0
89.0
310.0
343.0
325.0
59.0
309.0
165.0
410.1
383.1
115.0
152.0
185.0
192.0
226.0
239.1
257.0
387.1
426.1
440.1
139.0
278.0
353.1
443.2
474.0
514.2
570.0
586.0
593.2
m/z
50
75
100
125
150
175
200
225
250
275
300
325
350
375
400
425
450
475
500
525
550
575
600


HO
O
H
N
TBDMSO
3-(hydroxymethyl)-3-deoxy-
6-(tert-butyldimethylsilyl)morphine
1H-NMR 400 MHz CDCl3
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)

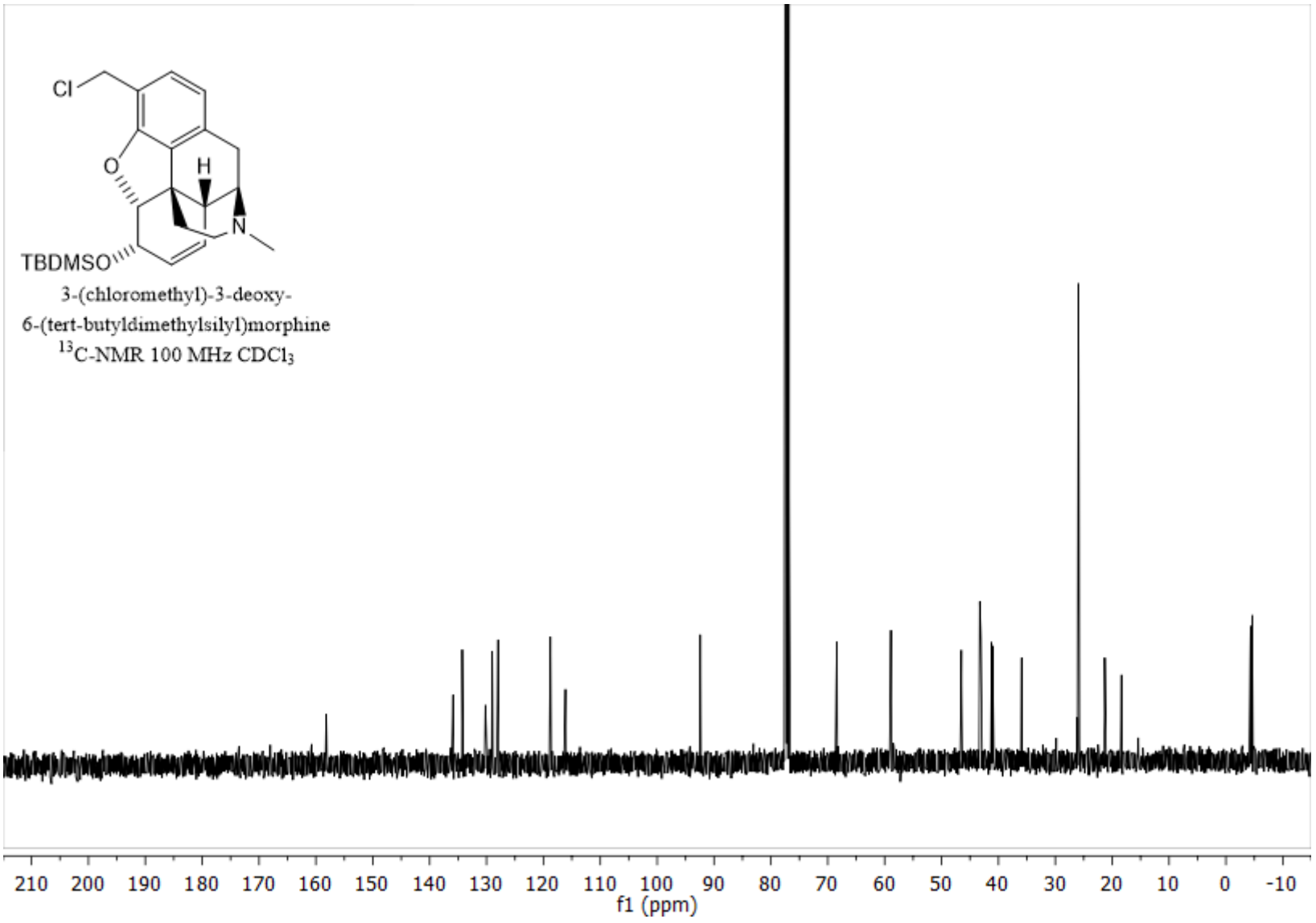

HO
O
H
N
TBDMSO
3-(hydroxymethyl)-3-deoxy-
6-(tert-butyldimethylsilyl)morphine
13C-NMR 100 MHz CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

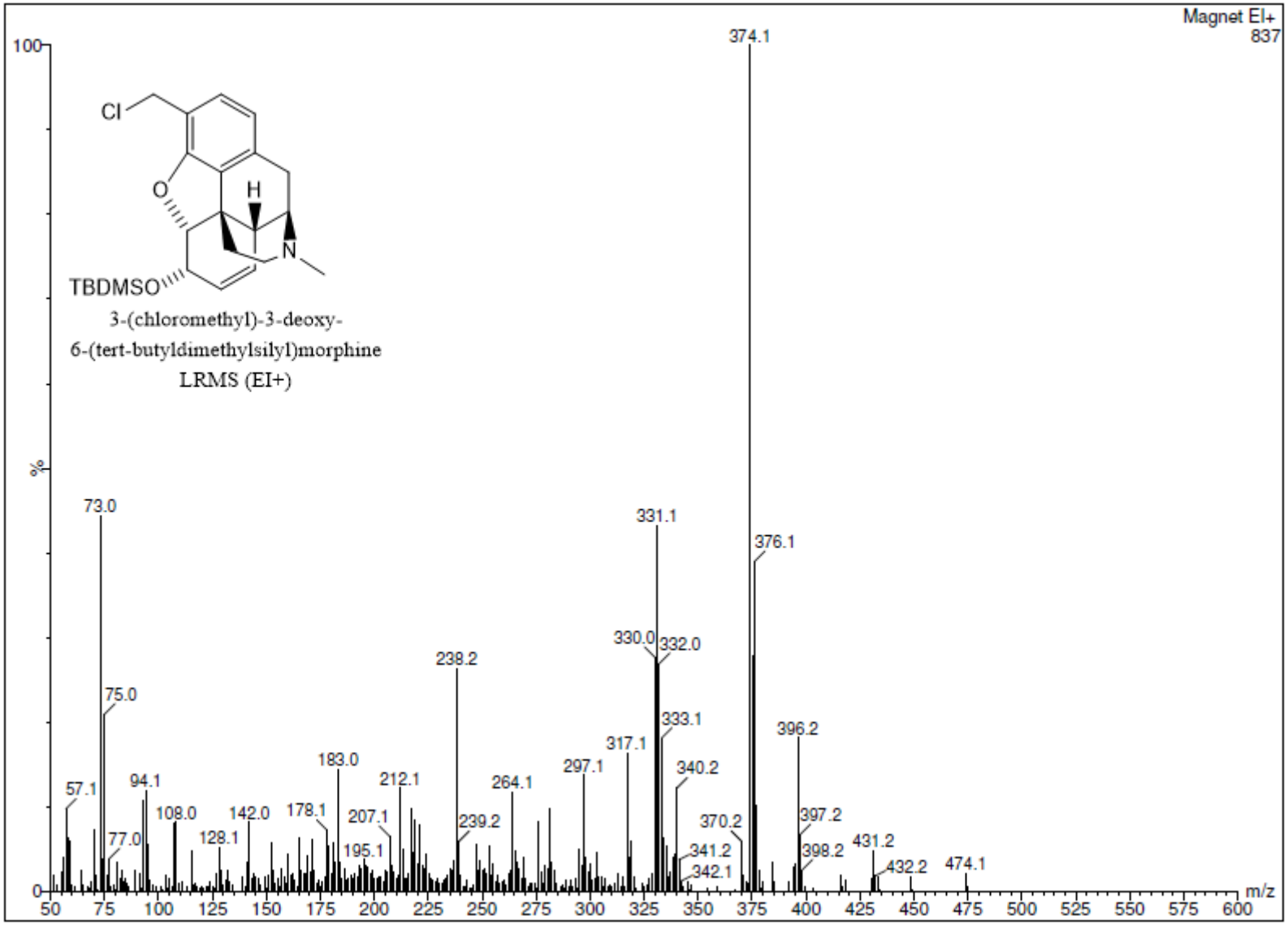

Magnet EI+
9.24e3
356.1718
100
%
0
HO
O
H
N
TBDMSO
3-(hydroxymethyl)-3-deoxy-
6-(tert-butyldimethylsilyl)morphine
LRMS (EI+)
357.1706
299.1145
73.0483
75.0275
238.1719
358.1695
300.1165
94.0621
212.1172
281.1285
413.2433
333.0713
165.0774
207.0917
390.1299
414.2438
115.0569
474.1268
516.2375
m/z
50 75 100 125 150 175 200 225 250 275 300 325 350 375 400 425 450 475 500 525 550 575 600

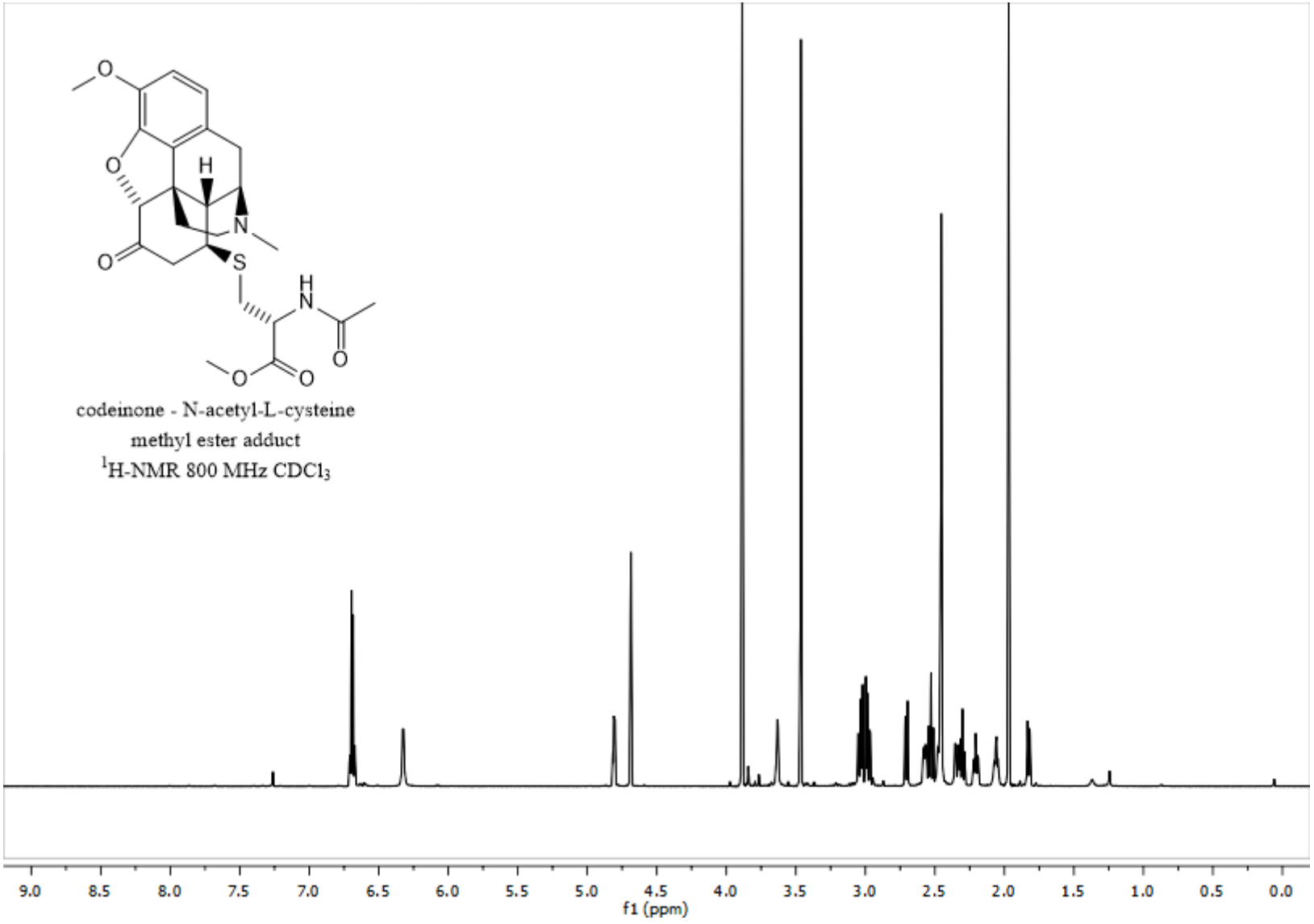


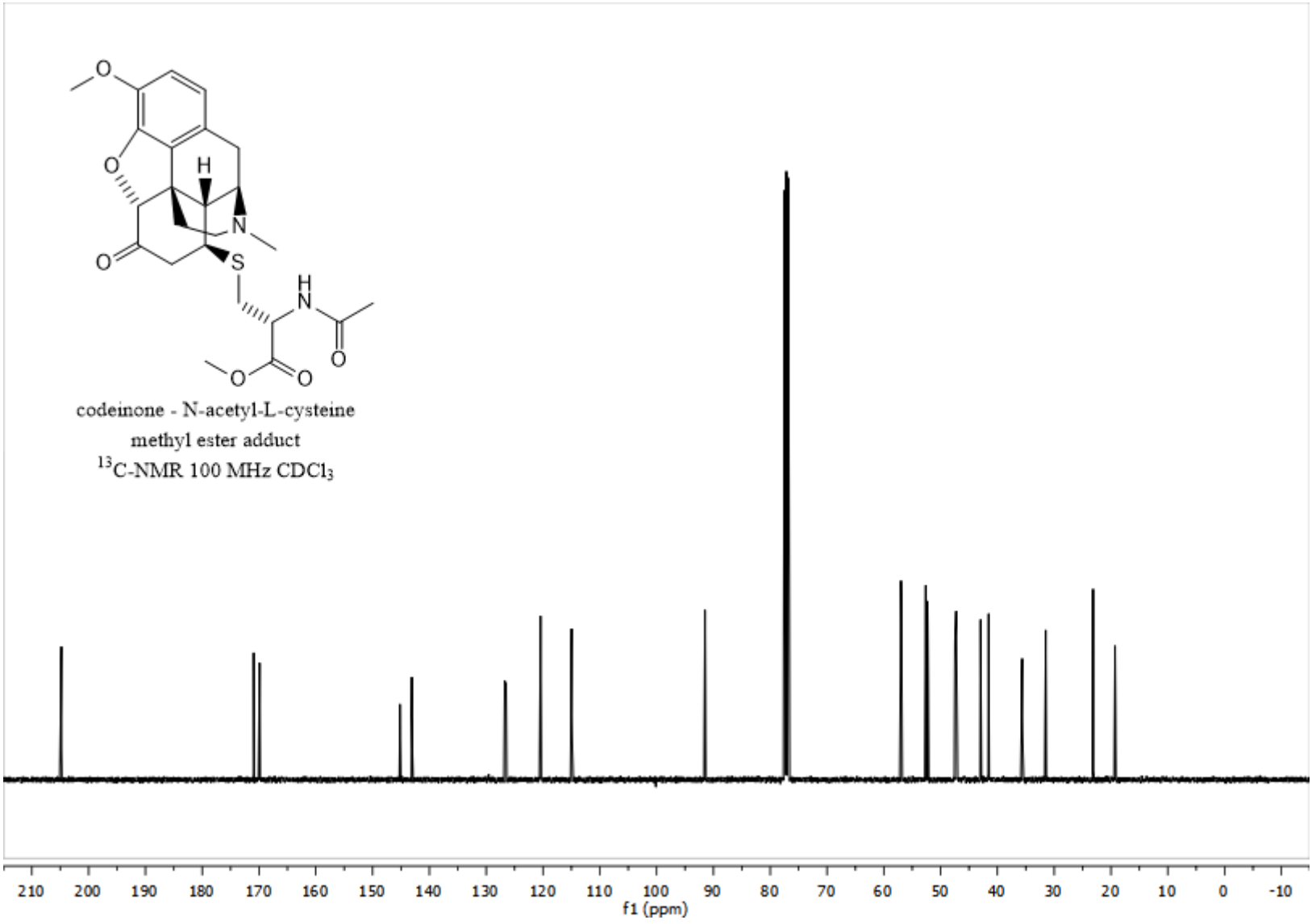
3-(chloromethyl)-3-deoxy-
6-(tert-butyldimethylsilyl)morphine
^{1}H-NMR 400 MHz $CDCl_3$

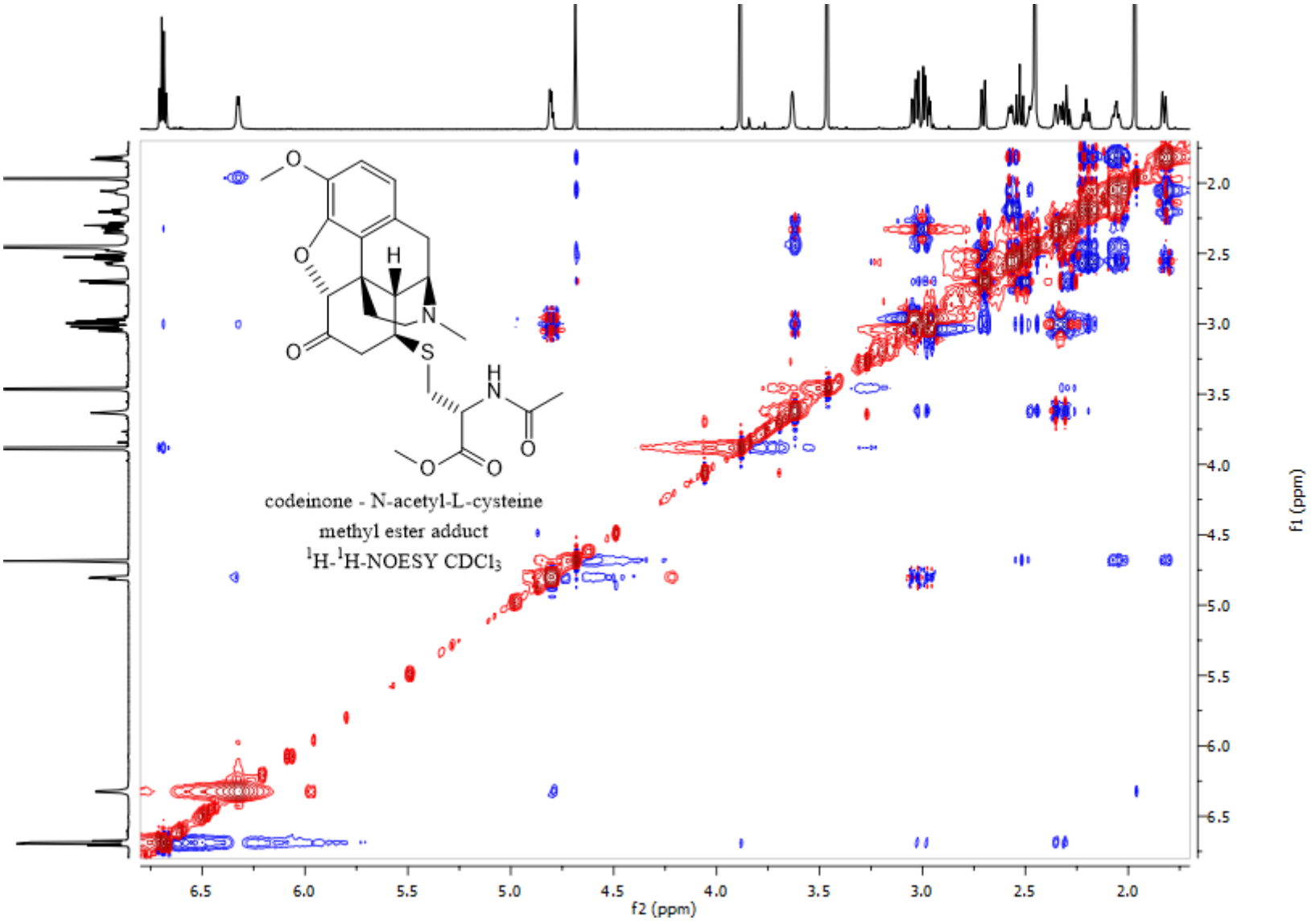
* Denotes peaks arising from intermolecular reaction between the benzyl chloride of one molecule and the amine of another

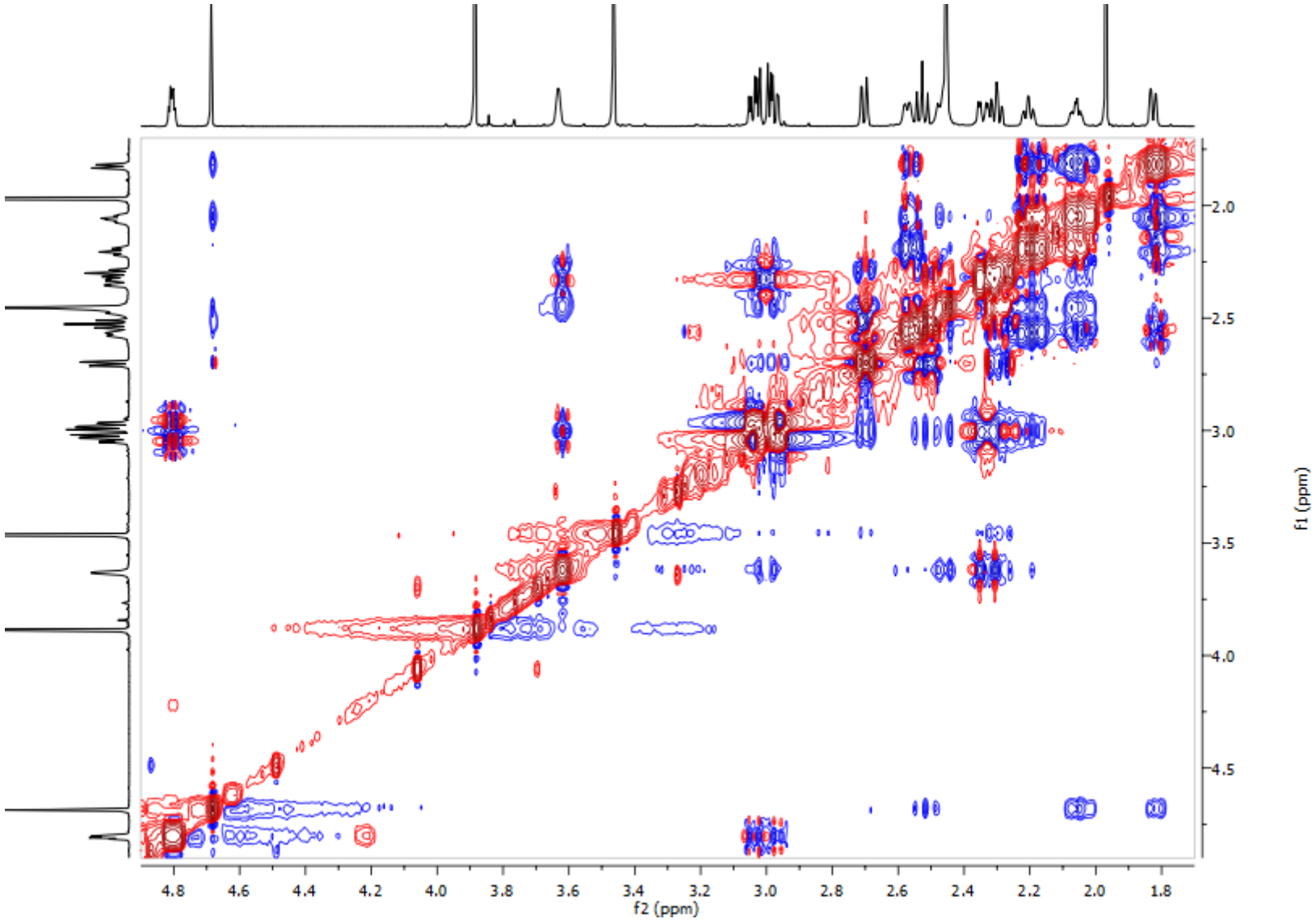

Cl
O
H
N
TBDMSO
3-(chloromethyl)-3-deoxy-
6-(tert-butyldimethylsilyl)morphine
13C-NMR 100 MHz CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

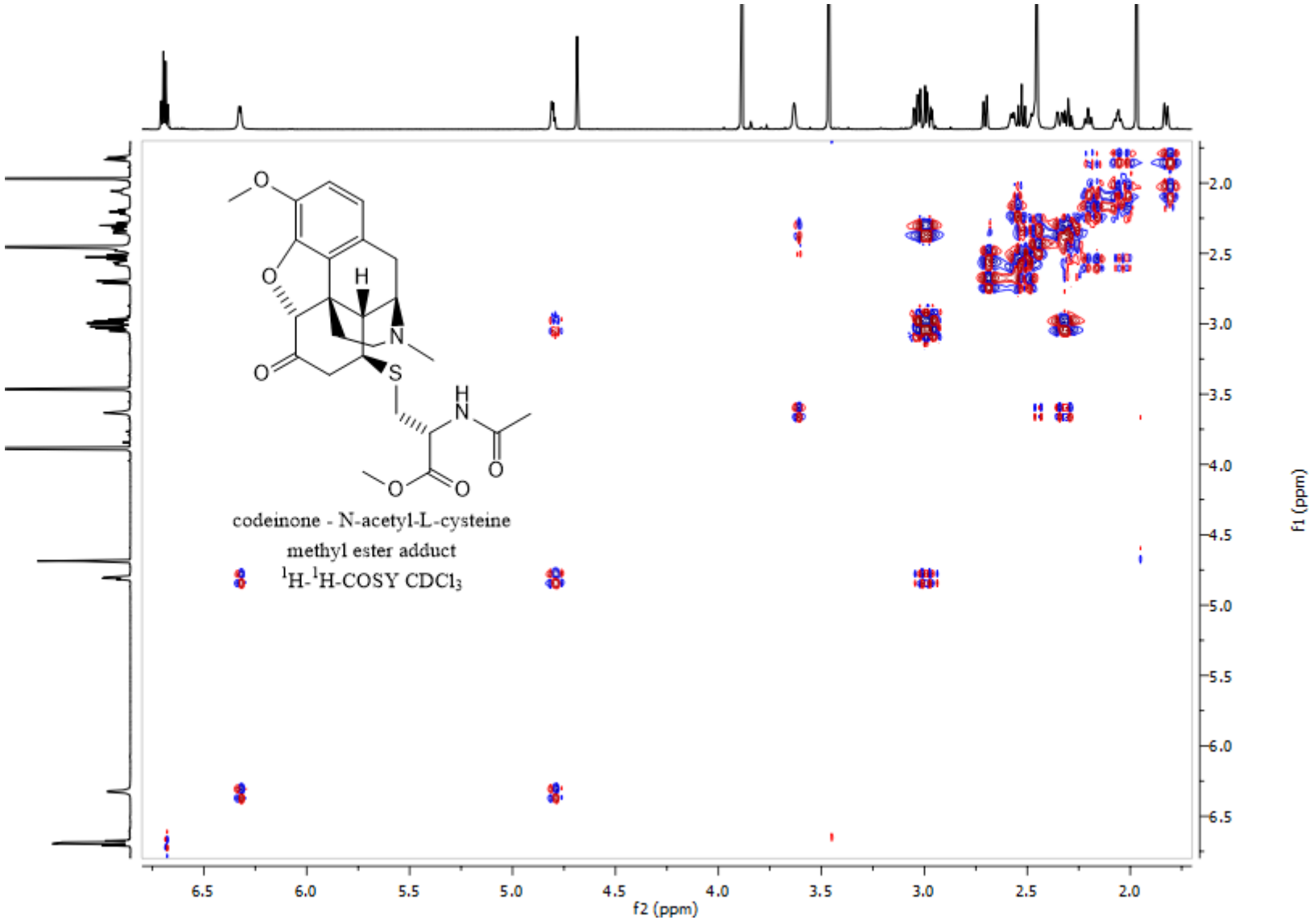

Magnet EI+
837
100
%
0
374.1
Cl
O
H
N
TBDMSO
3-(chloromethyl)-3-deoxy-
6-(tert-butyldimethylsilyl)morphine
LRMS (EI+)
73.0
331.1
376.1
330.0
332.0
238.2
75.0
333.1
396.2
317.1
183.0
297.1
340.2
212.1
264.1
57.1
94.1
108.0
142.0
178.1
207.1
239.2
370.2
397.2
77.0
128.1
195.1
341.2
398.2
431.2
342.1
432.2
474.1
m/z
50 75 100 125 150 175 200 225 250 275 300 325 350 375 400 425 450 475 500 525 550 575 600

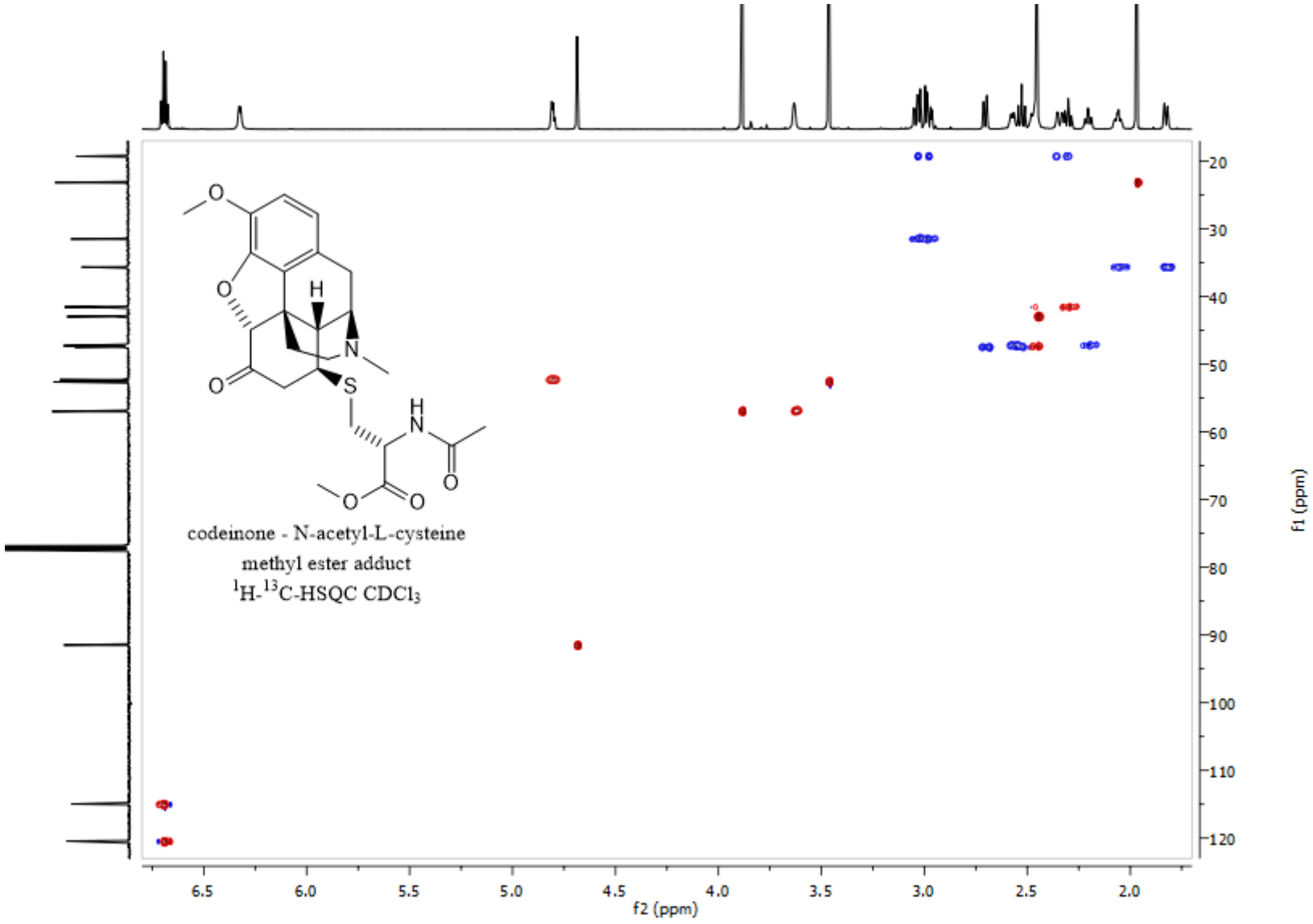

codeinone - N-acetyl-L-cysteine
methyl ester adduct
^{1}H-NMR 800 MHz $CDCl_3$
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

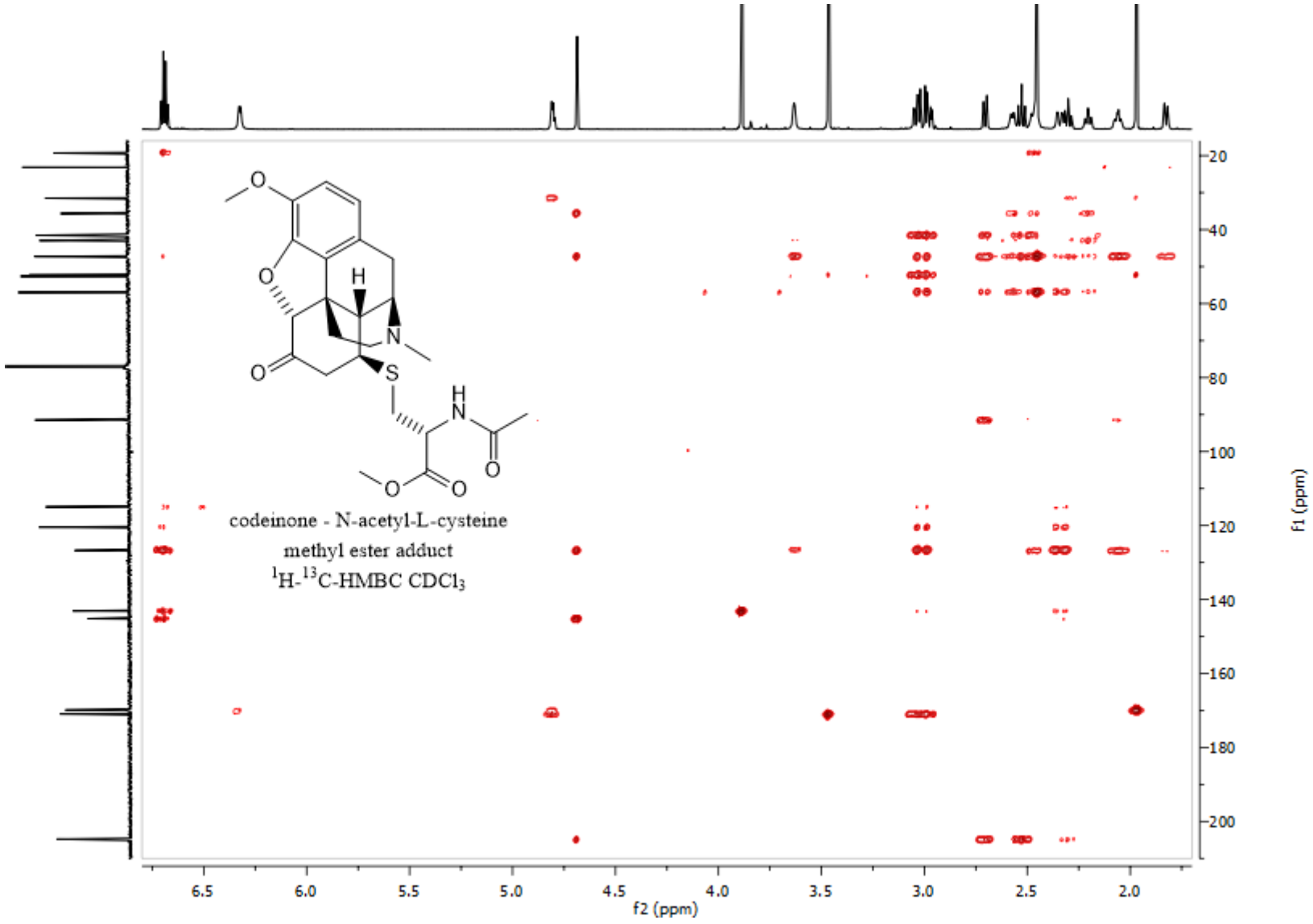

codeinone - N-acetyl-L-cysteine
methyl ester adduct
^{13}C-NMR 100 MHz $CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

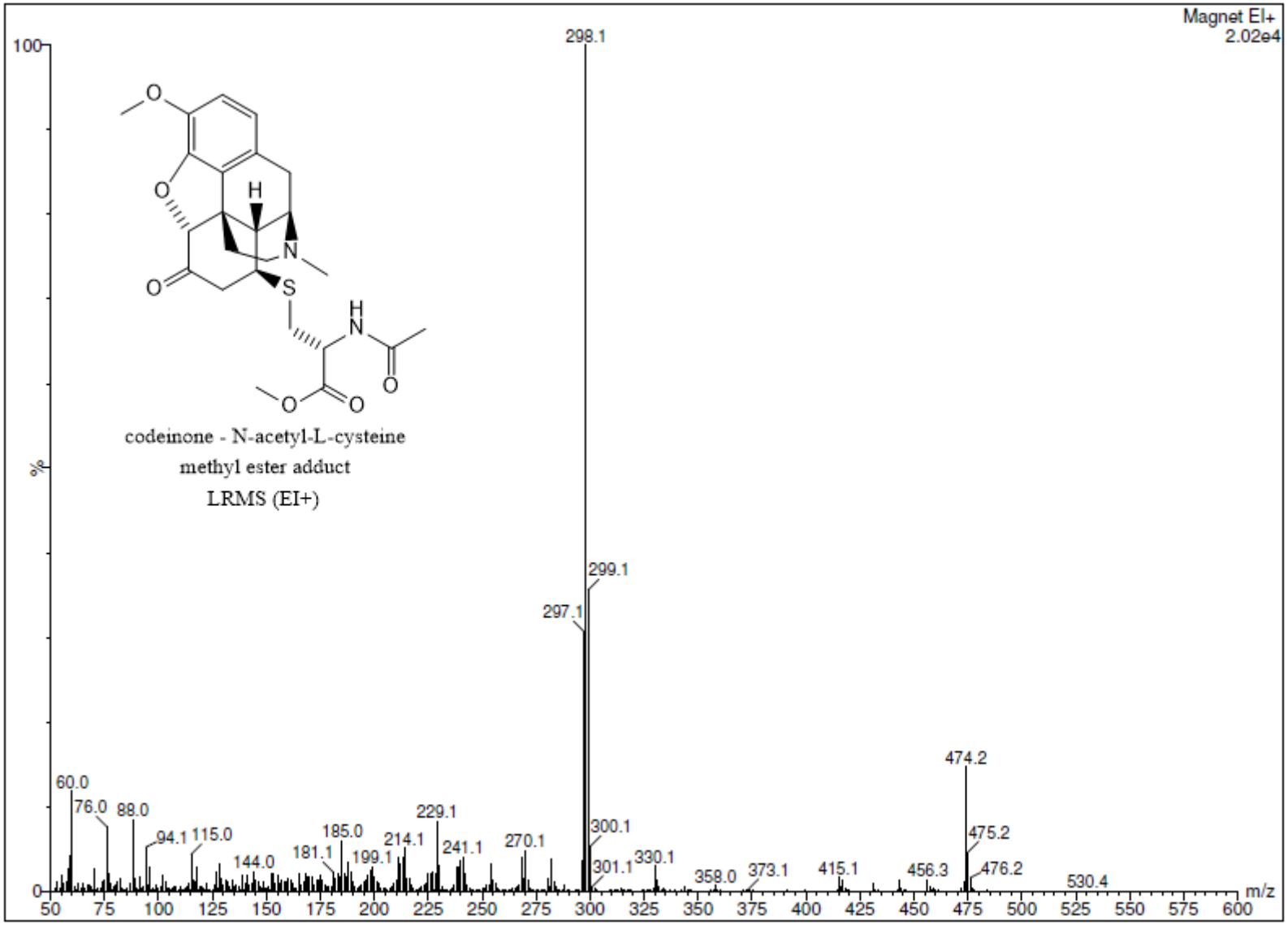

codeinone - N-acetyl-L-cysteine
methyl ester adduct
^{1}H-^{1}H-NOESY CDCl$_3$
f2 (ppm)
f1 (ppm)

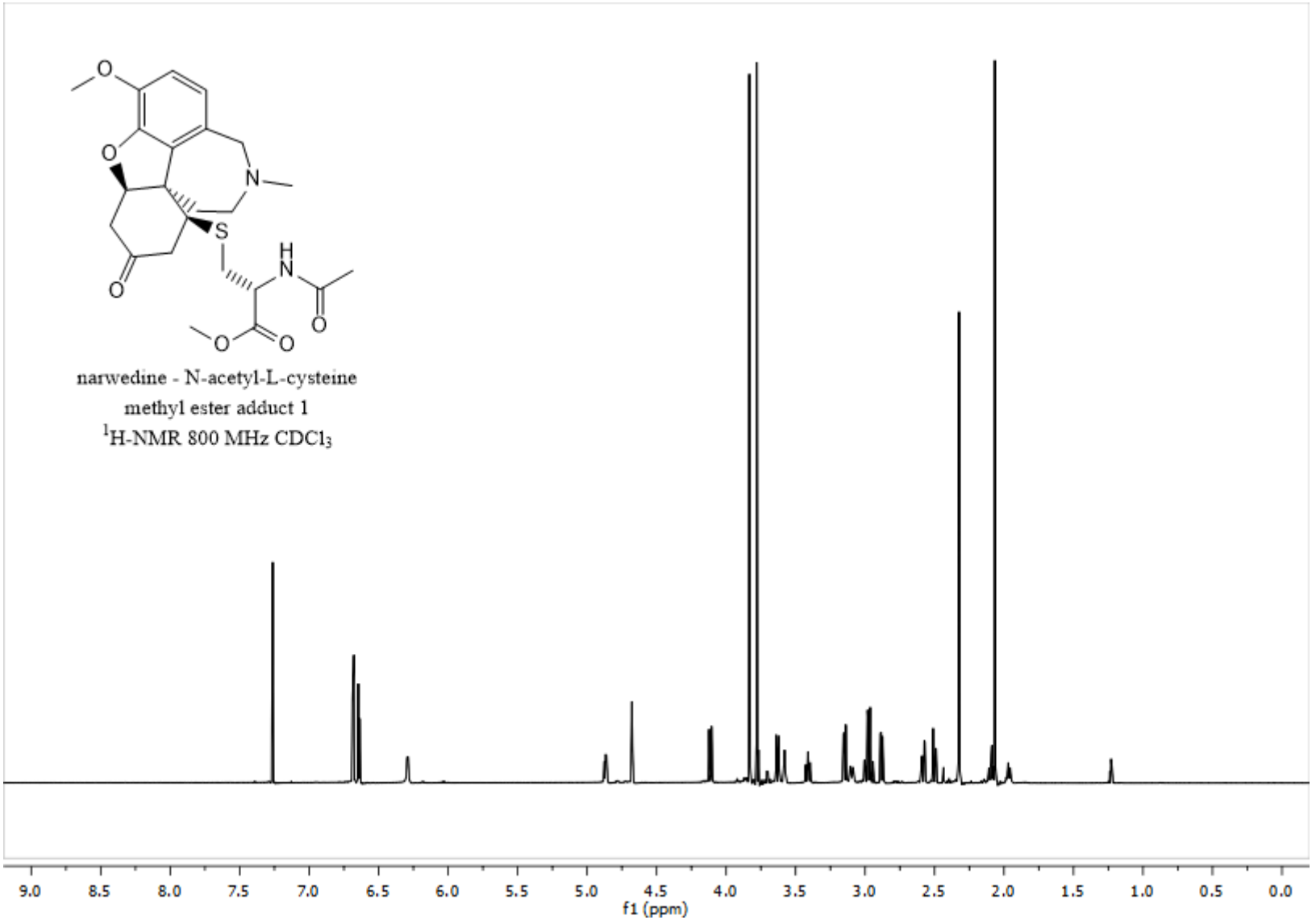

4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
f2 (ppm)
2.0
2.5
3.0
3.5
4.0
4.5
f1 (ppm)

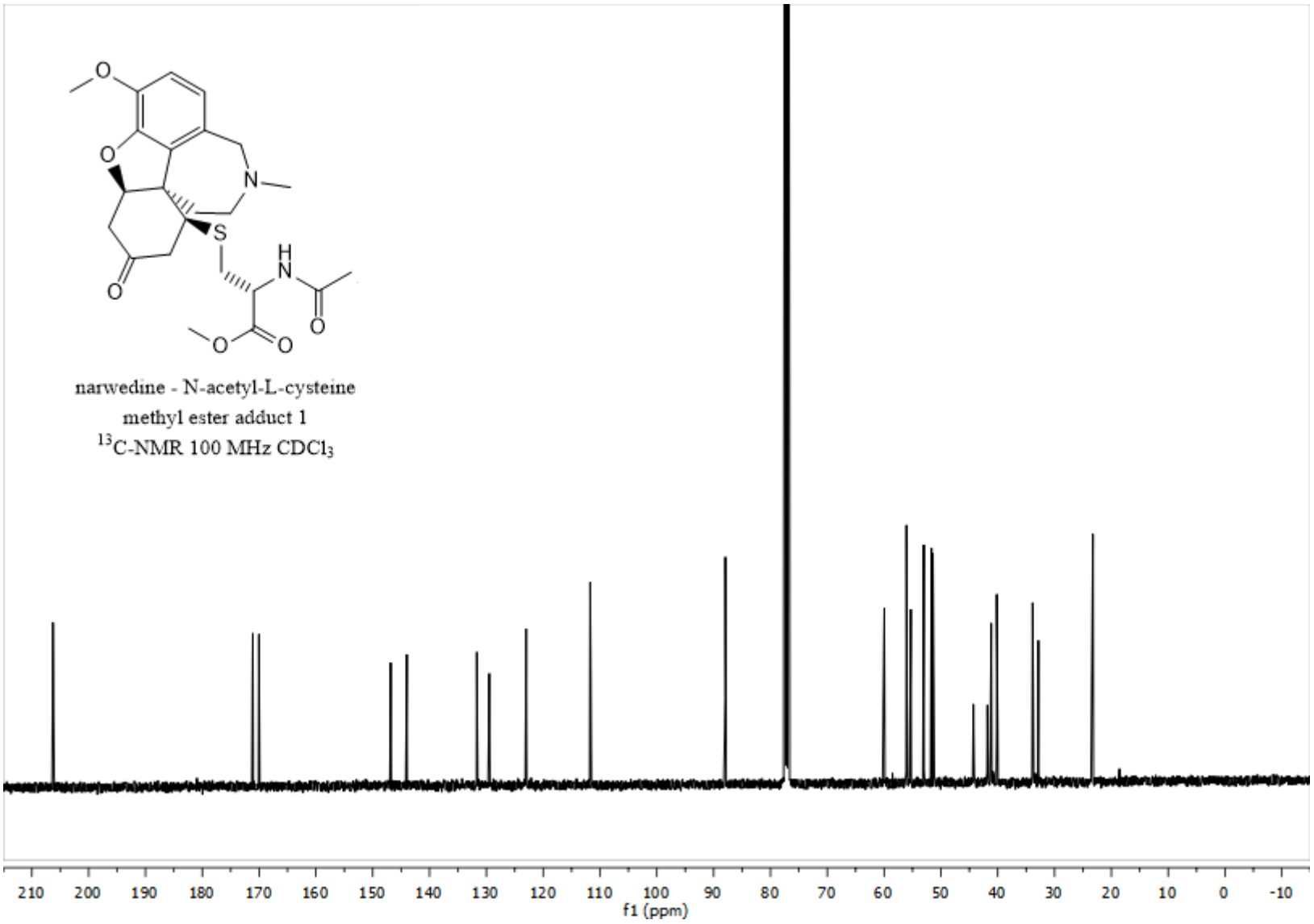

codeinone - N-acetyl-L-cysteine
methyl ester adduct
^{1}H-^{1}H-COSY CDCl$_3$
f2 (ppm)
f1 (ppm)

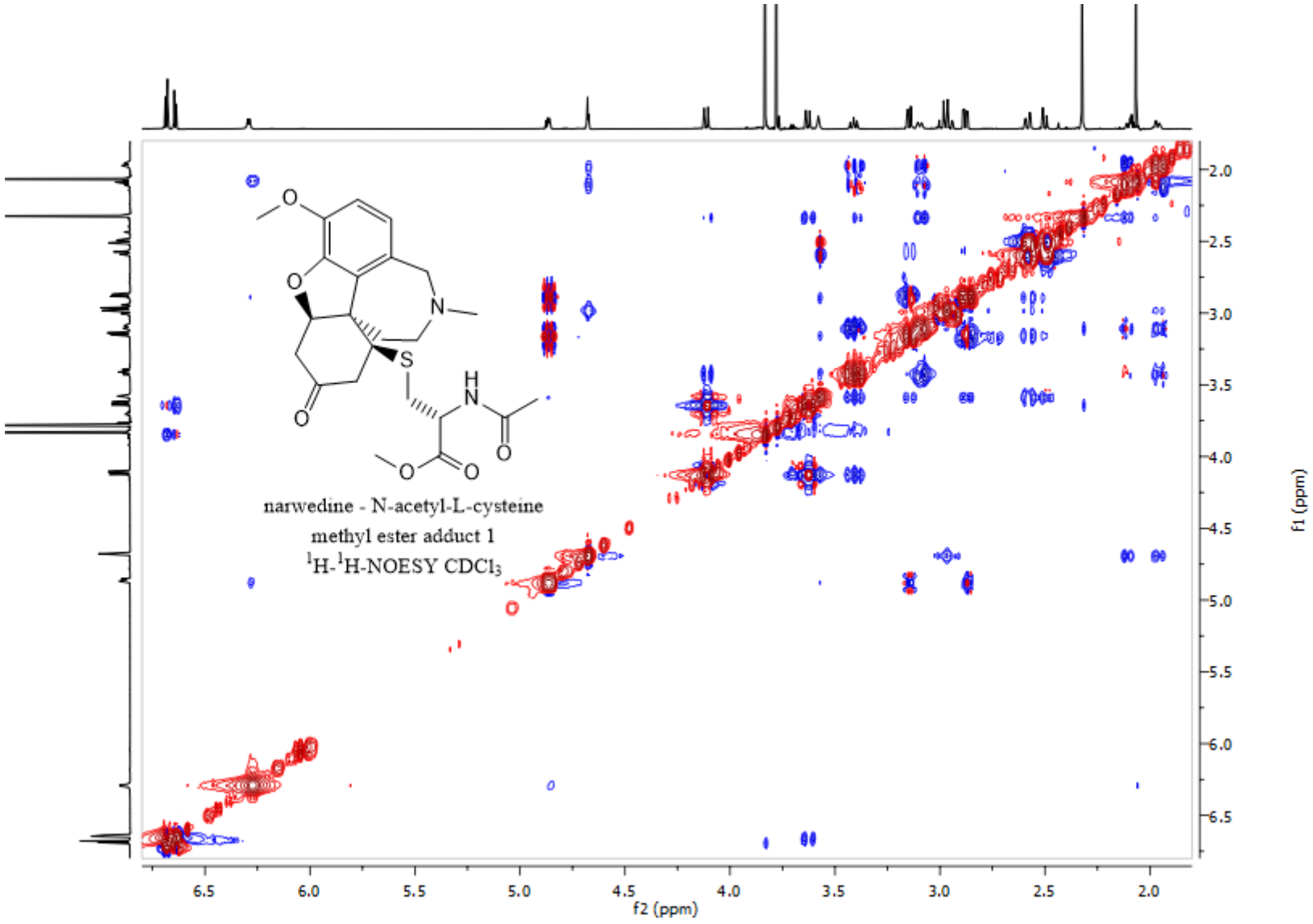

codeinone - N-acetyl-L-cysteine
methyl ester adduct
^{1}H-^{13}C-HSQC $CDCl_3$
f2 (ppm)
f1 (ppm)

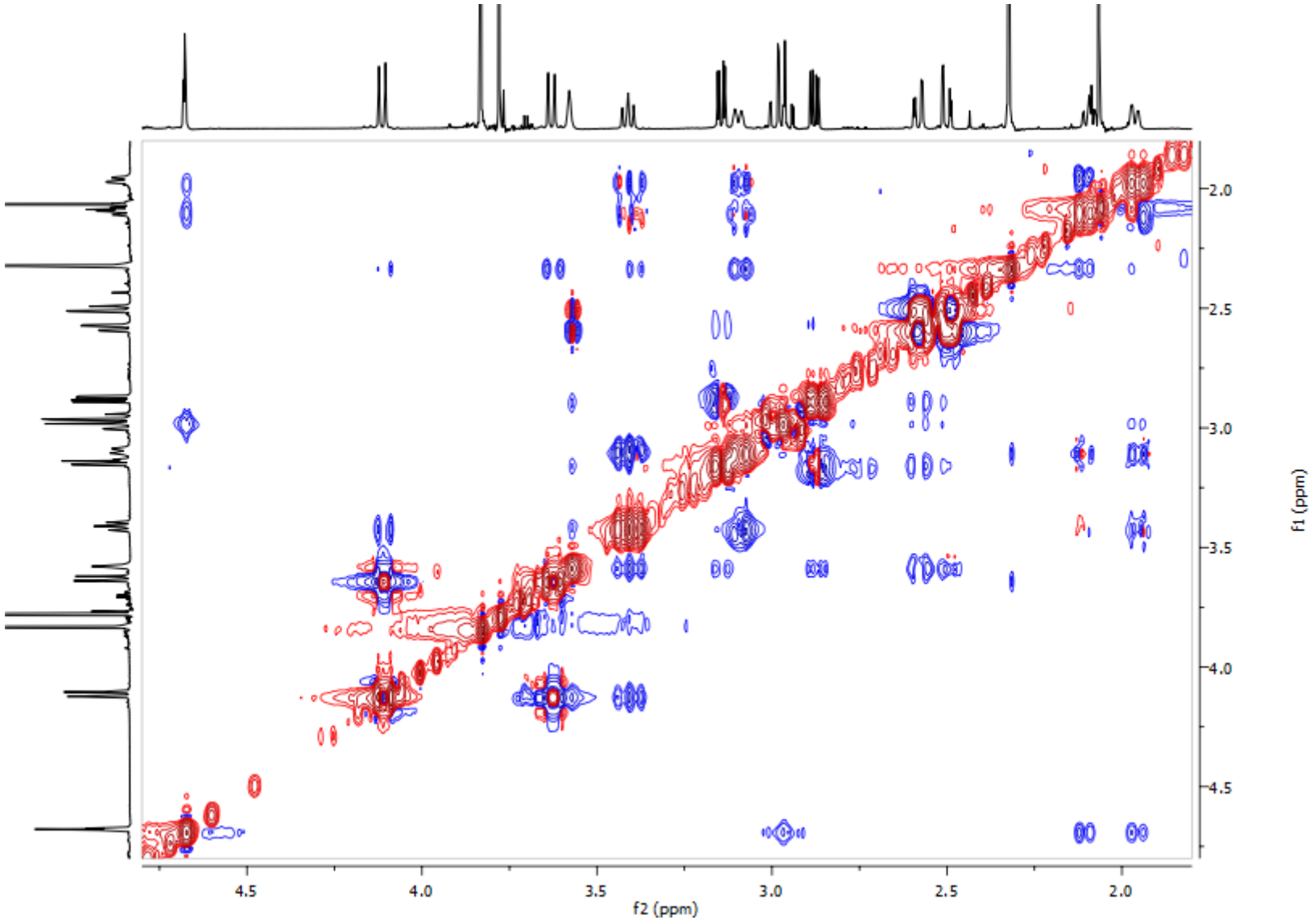

codeinone - N-acetyl-L-cysteine
methyl ester adduct
^{1}H-^{13}C-HMBC $CDCl_3$
f2 (ppm)
f1 (ppm)

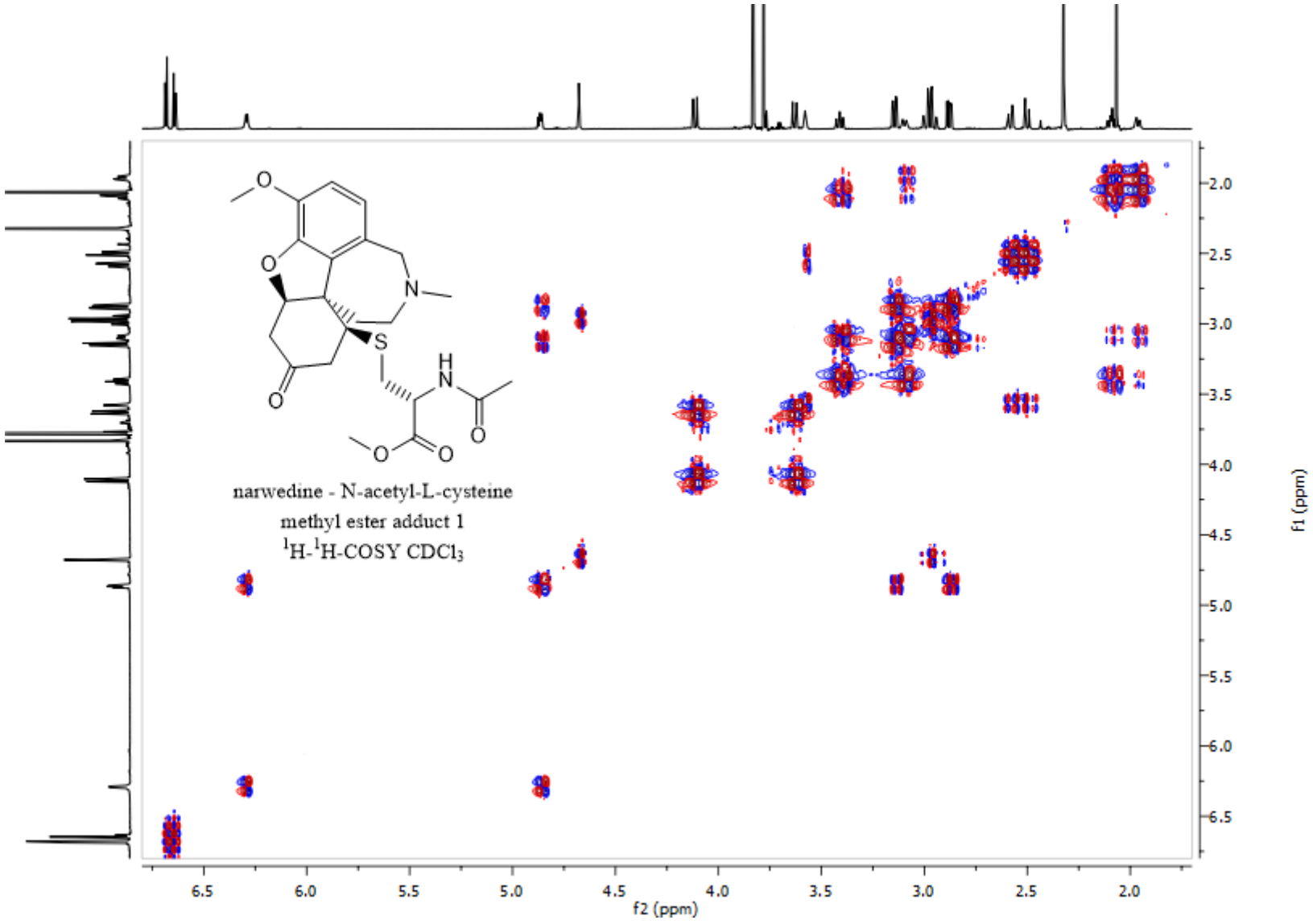

Magnet EI+
2.02e4
100
%
0
298.1
299.1
297.1
474.2
475.2
476.2
60.0
76.0
88.0
94.1
115.0
144.0
181.1
185.0
199.1
214.1
229.1
241.1
270.1
300.1
301.1
330.1
358.0
373.1
415.1
456.3
530.4
50 75 100 125 150 175 200 225 250 275 300 325 350 375 400 425 450 475 500 525 550 575 600
m/z
codeinone - N-acetyl-L-cysteine
methyl ester adduct
LRMS (EI+)

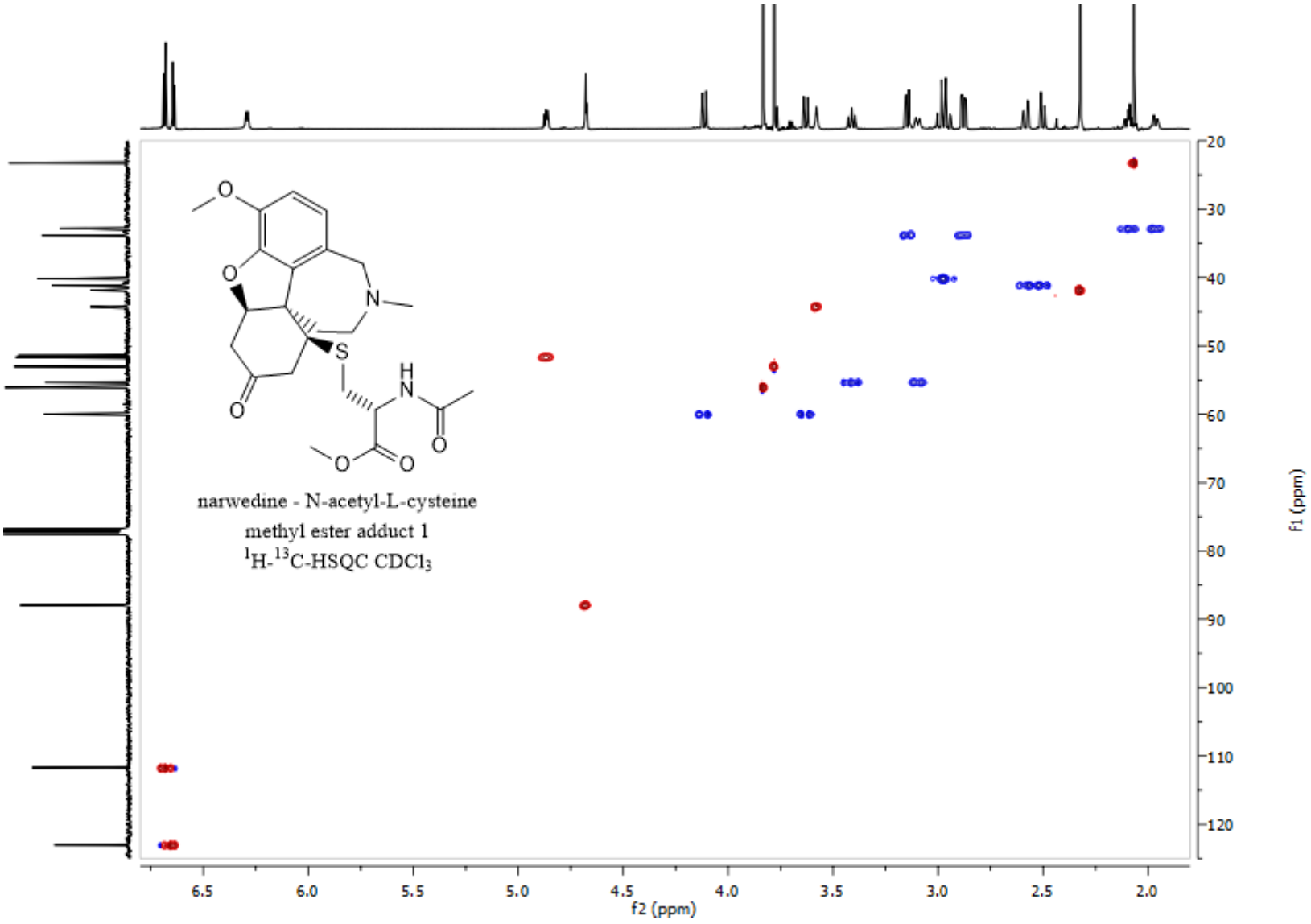

narwedine - N-acetyl-L-cysteine
methyl ester adduct 1
^{1}H-NMR 800 MHz $CDCl_3$
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

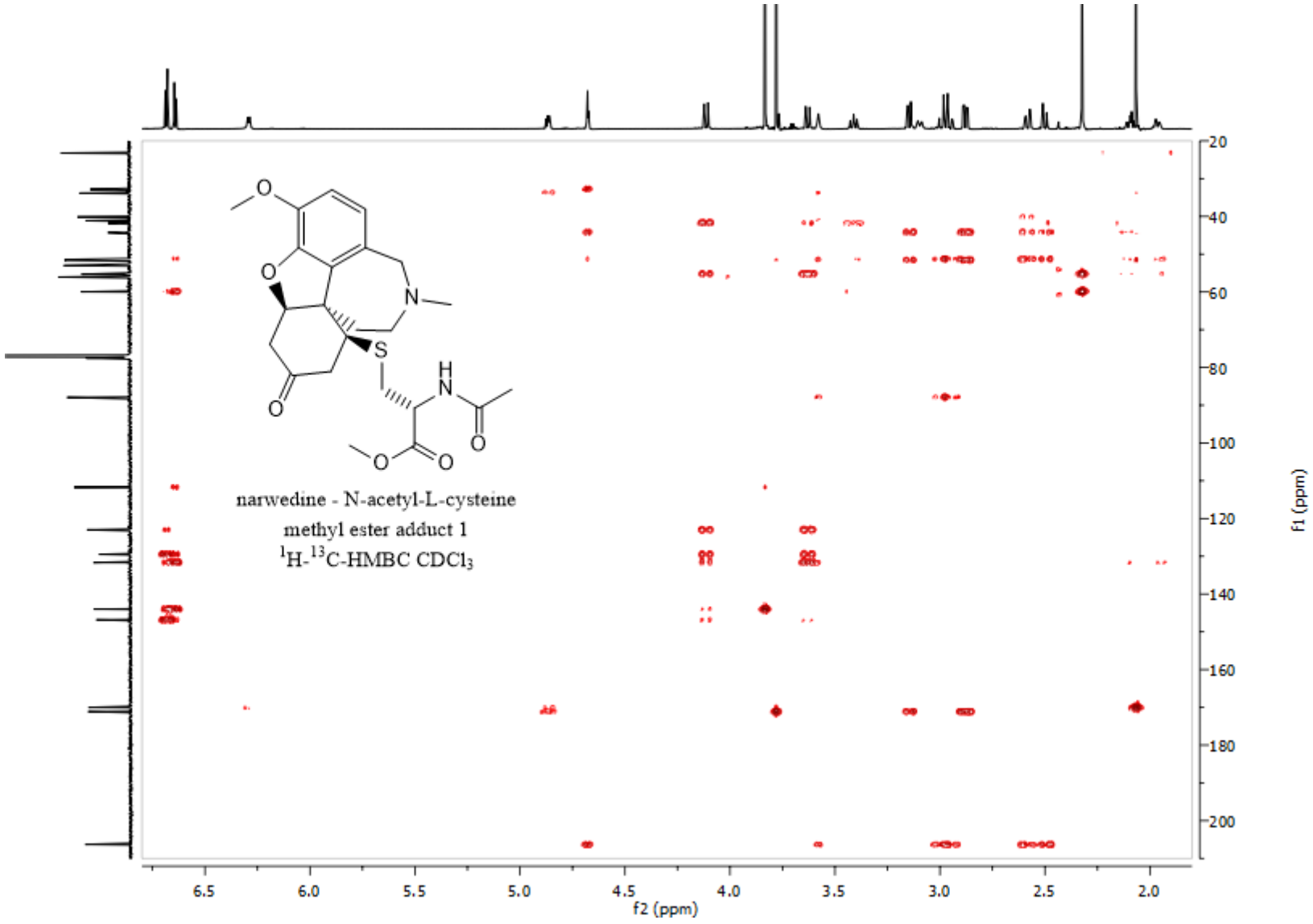

narwedine - N-acetyl-L-cysteine
methyl ester adduct 1
^{13}C-NMR 100 MHz $CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

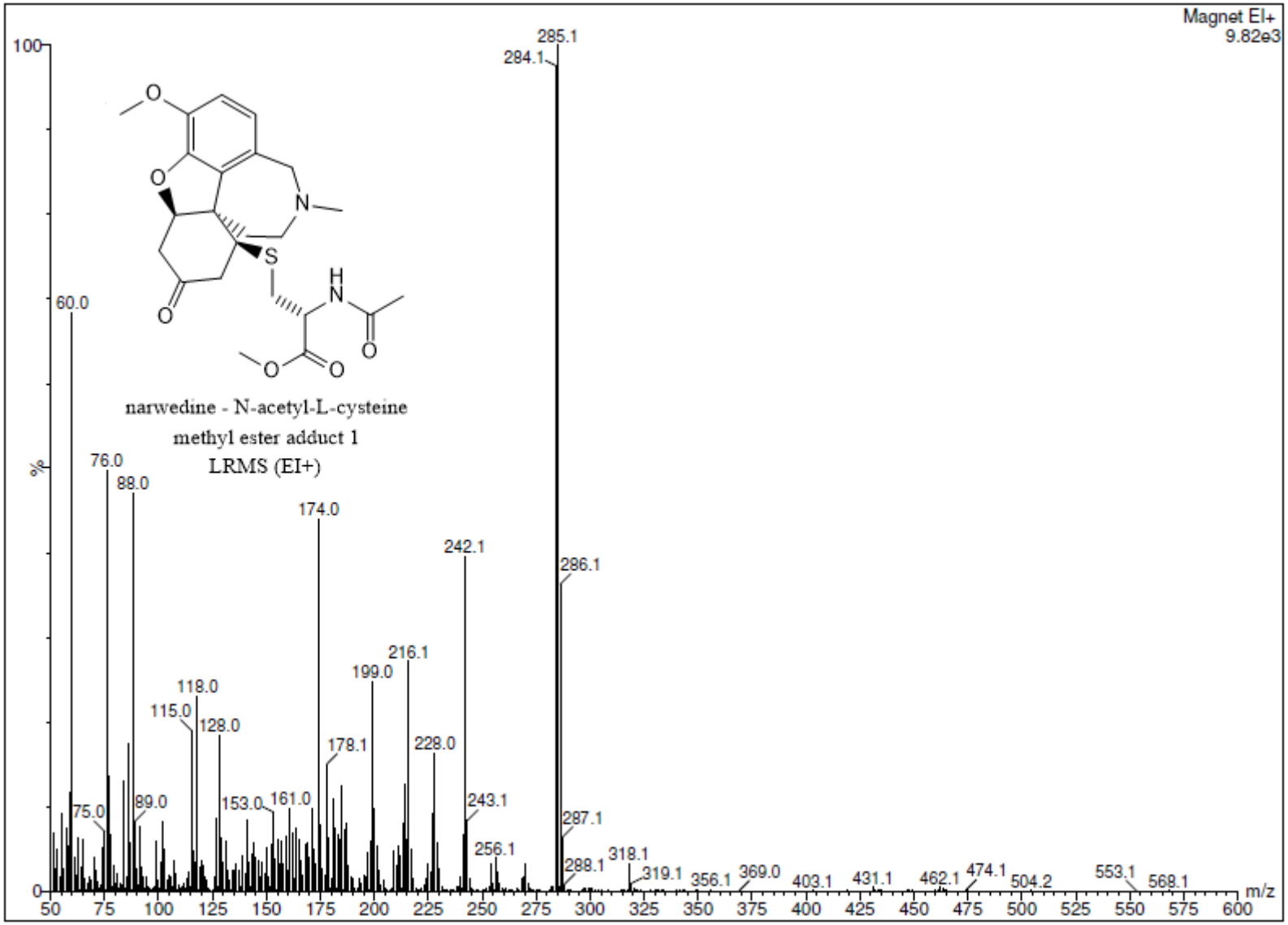

narwedine - N-acetyl-L-cysteine
methyl ester adduct 1
^{1}H-^{1}H-NOESY CDCl$_3$
f2 (ppm)
f1 (ppm)

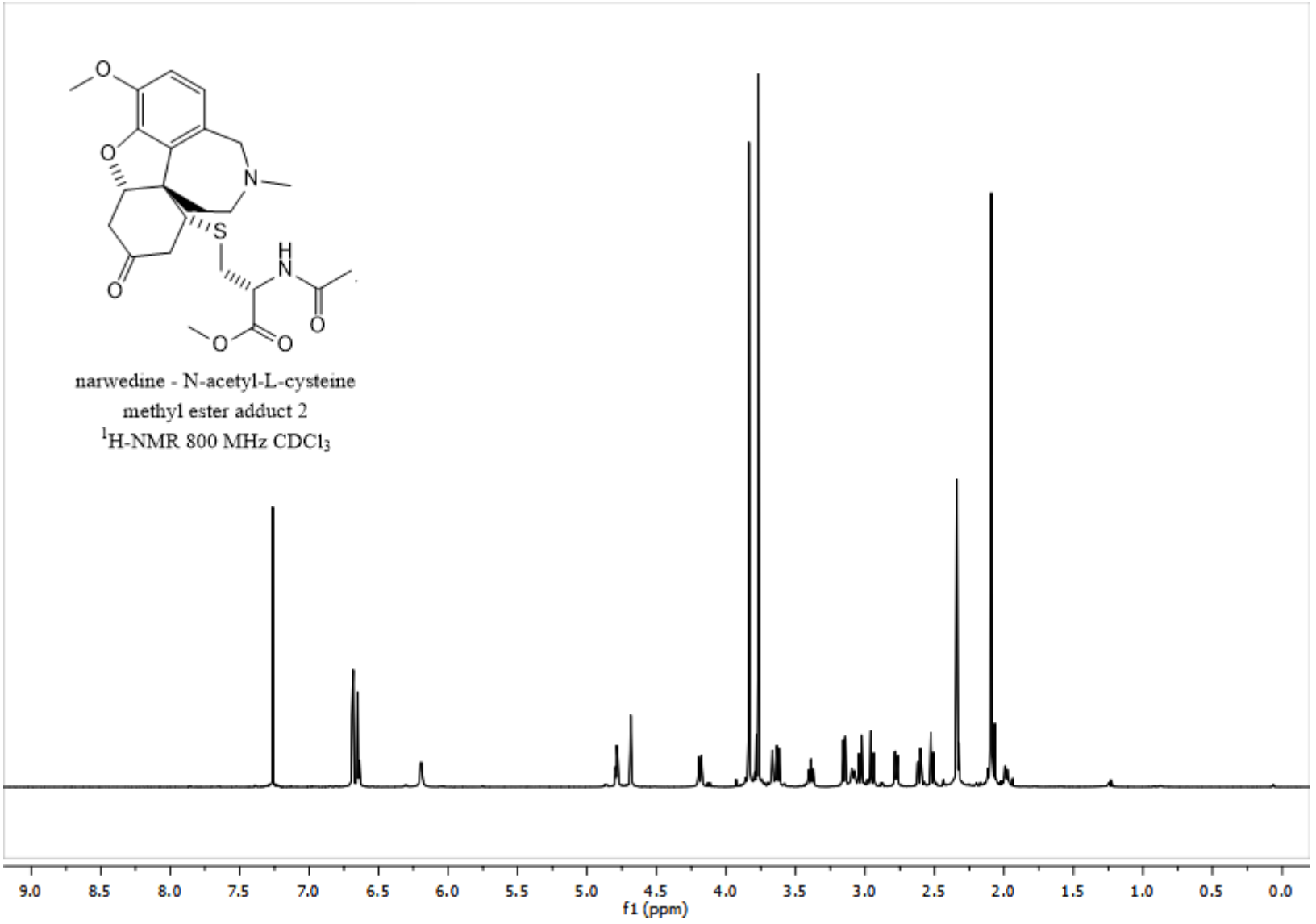

4.5
4.0
3.5
3.0
2.5
2.0
f2 (ppm)
2.0
2.5
3.0
3.5
4.0
4.5
f1 (ppm)

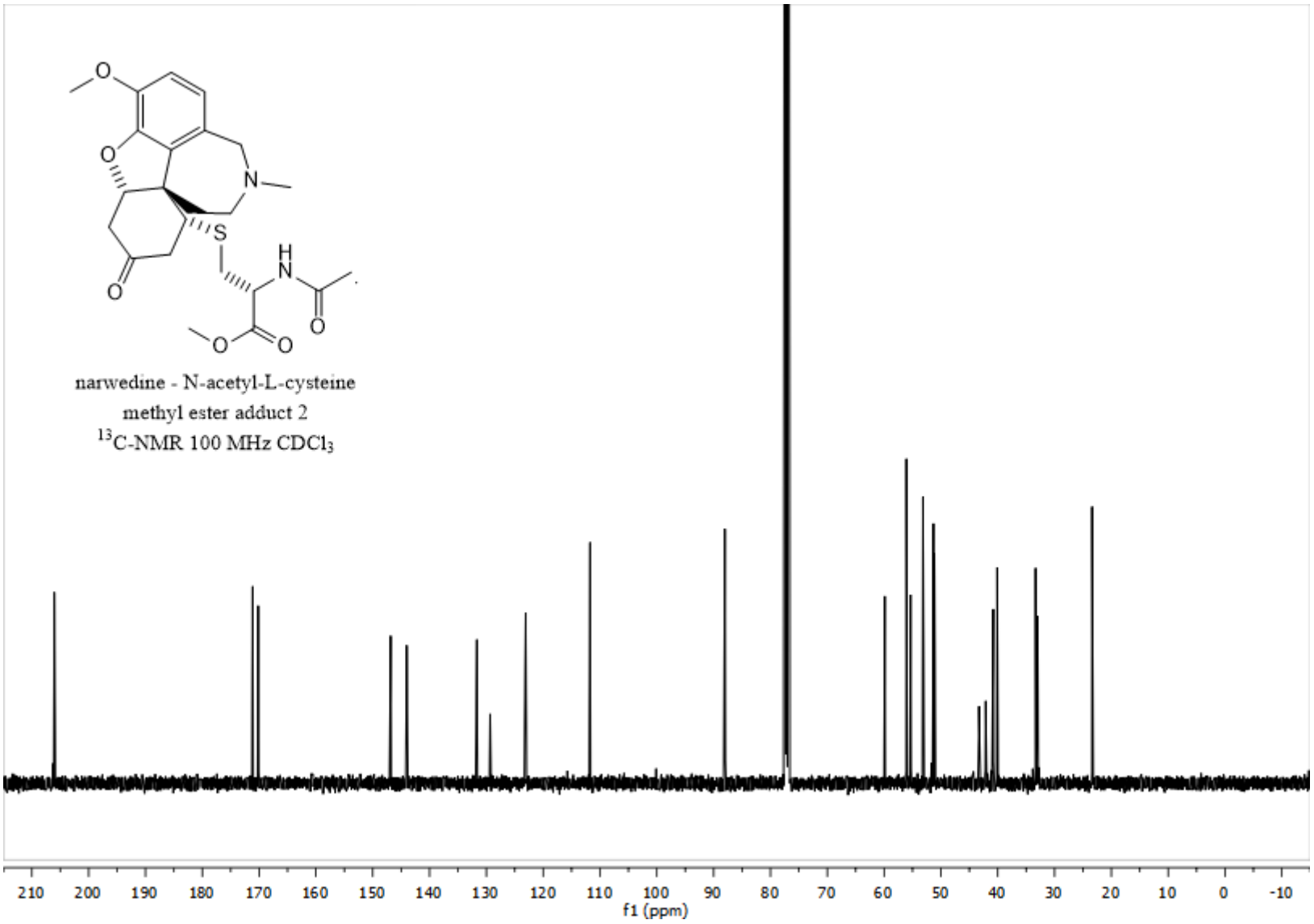

narwedine - N-acetyl-L-cysteine
methyl ester adduct 1
^{1}H-^{1}H-COSY CDCl$_3$
f2 (ppm)
f1 (ppm)

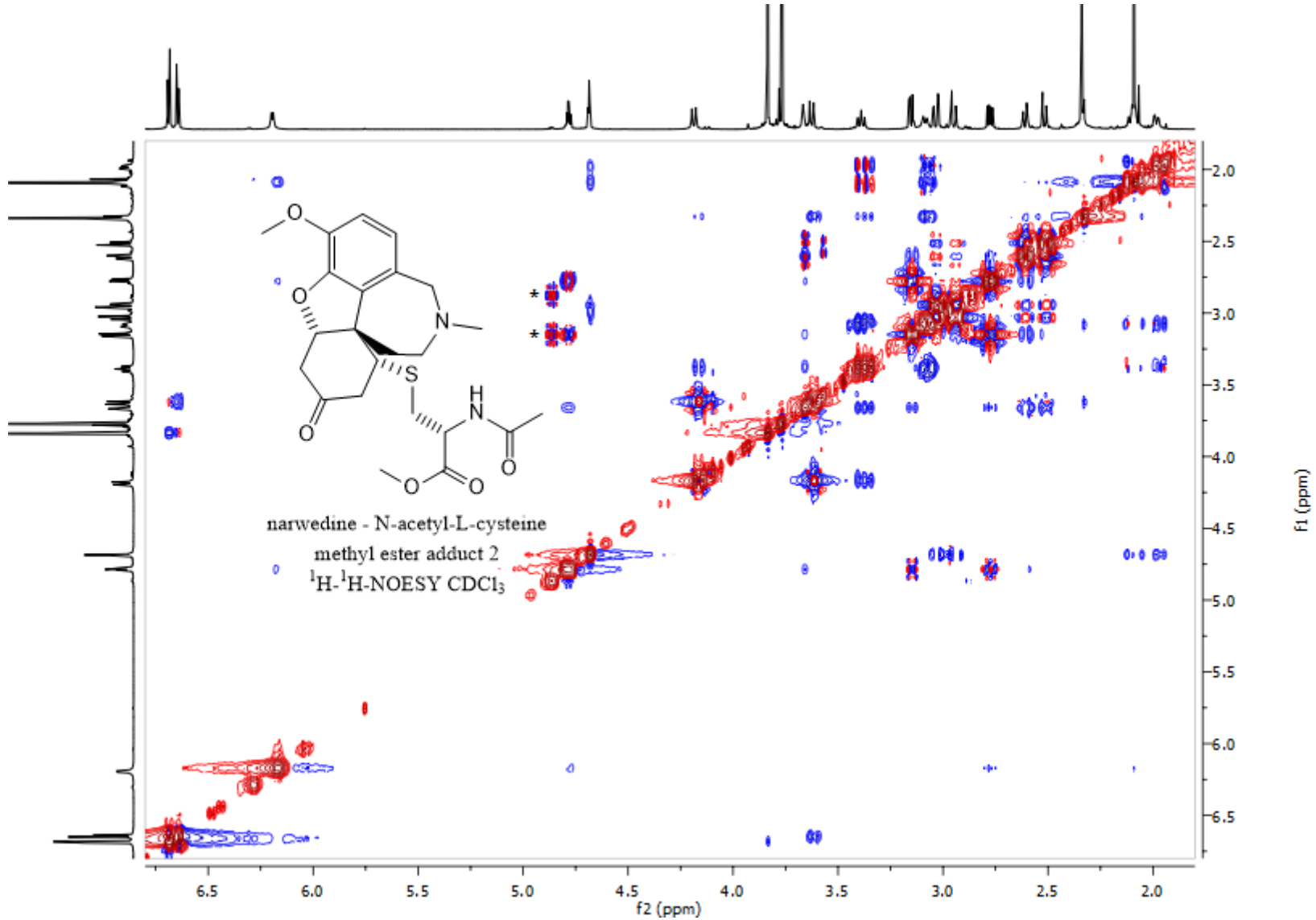

narwedine - N-acetyl-L-cysteine
methyl ester adduct 1
^{1}H-^{13}C-HSQC $CDCl_3$
f2 (ppm)
f1 (ppm)


narwedine - N-acetyl-L-cysteine
methyl ester adduct 1
^{1}H-^{13}C-HMBC $CDCl_3$
f2 (ppm)
f1 (ppm)

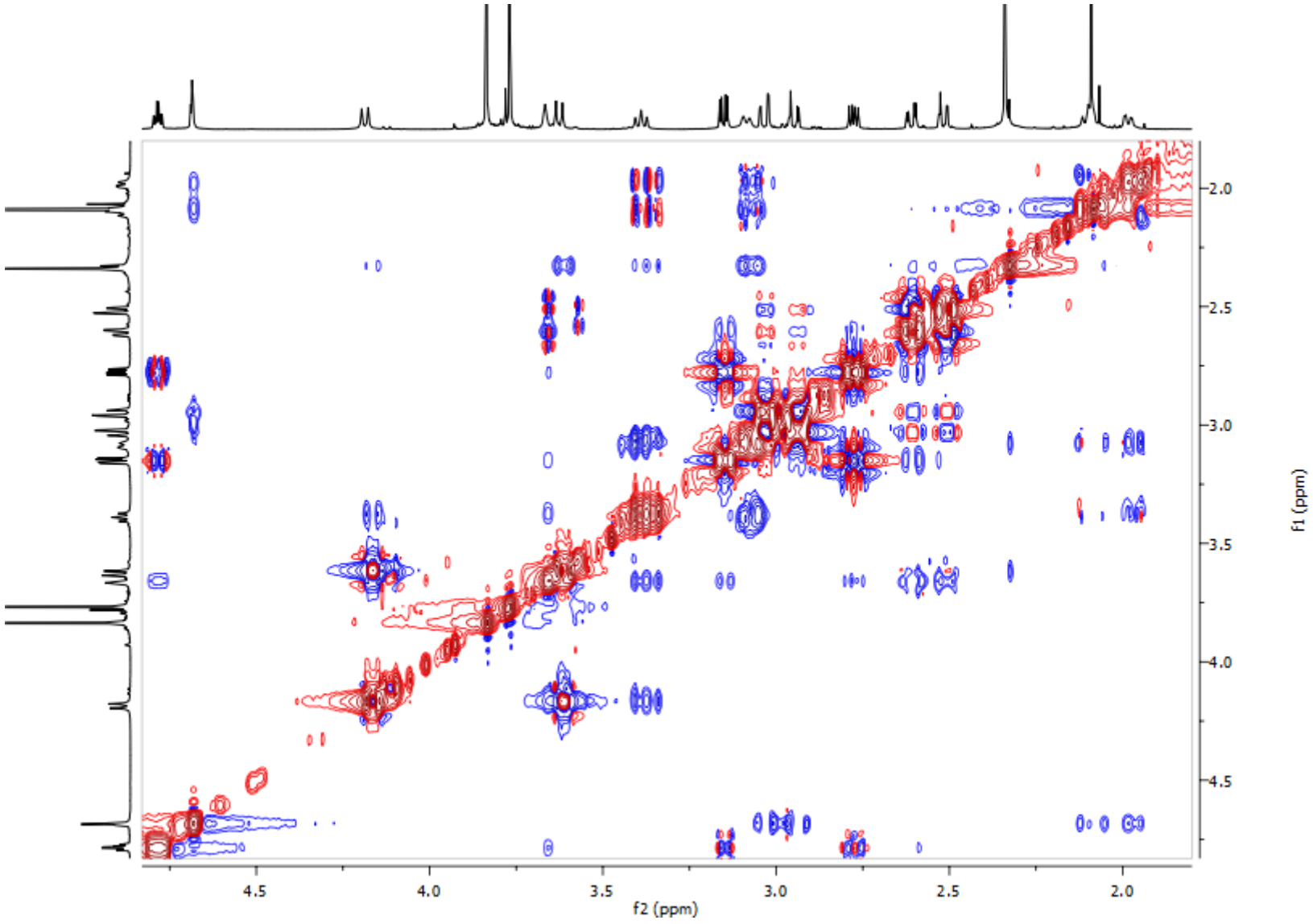

Magnet EI+
9.82e3
100
%
0
285.1
284.1
60.0
76.0
88.0
174.0
242.1
286.1
216.1
199.0
118.0
115.0
128.0
178.1
228.0
75.0
89.0
153.0
161.0
243.1
256.1
287.1
288.1
318.1
319.1
356.1
369.0
403.1
431.1
462.1
474.1
504.2
553.1
568.1
m/z
50 75 100 125 150 175 200 225 250 275 300 325 350 375 400 425 450 475 500 525 550 575 600
narwedine - N-acetyl-L-cysteine
methyl ester adduct 1
LRMS (EI+)

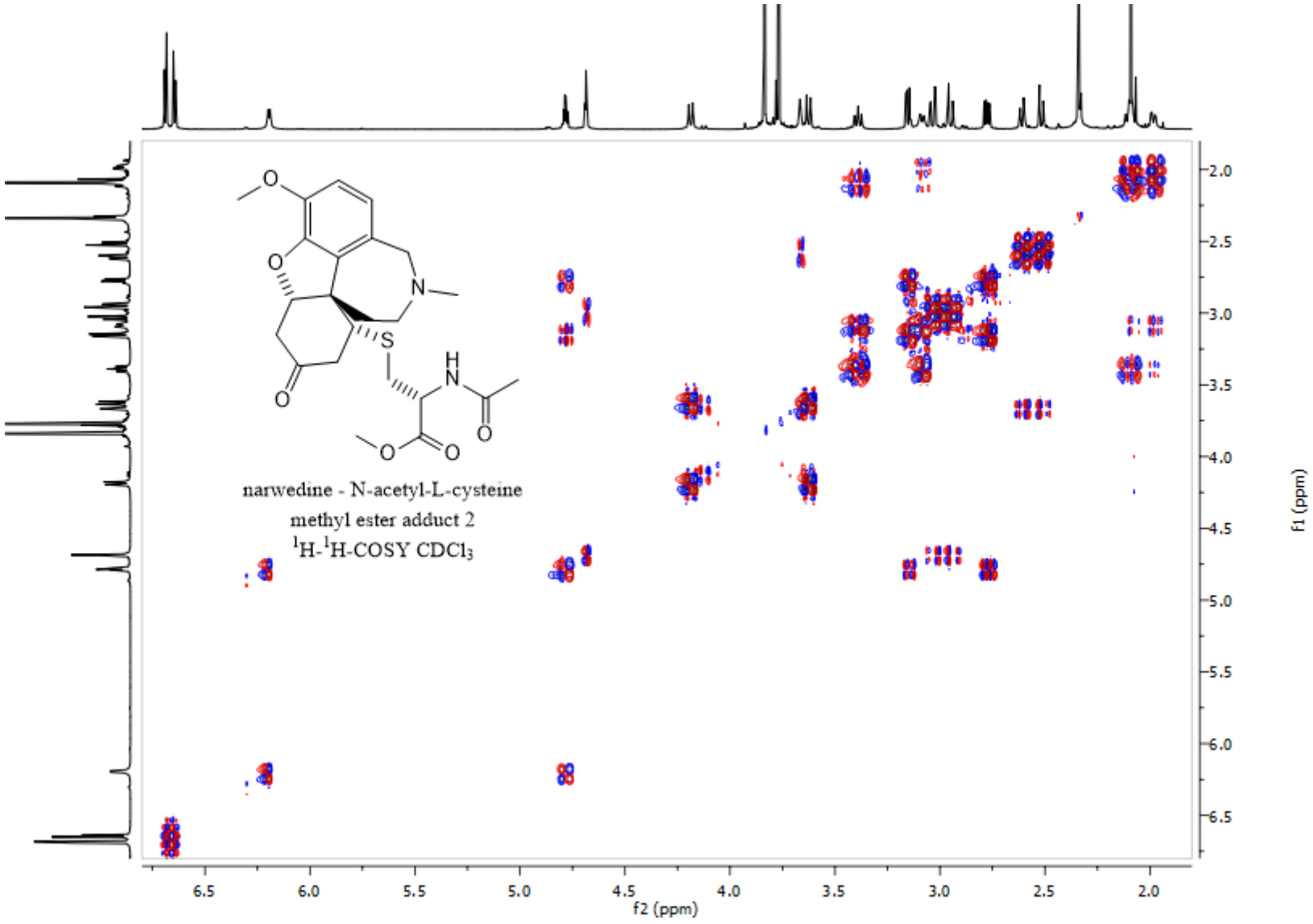

narwedine - N-acetyl-L-cysteine
methyl ester adduct 2
^{1}H-NMR 800 MHz $CDCl_3$
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

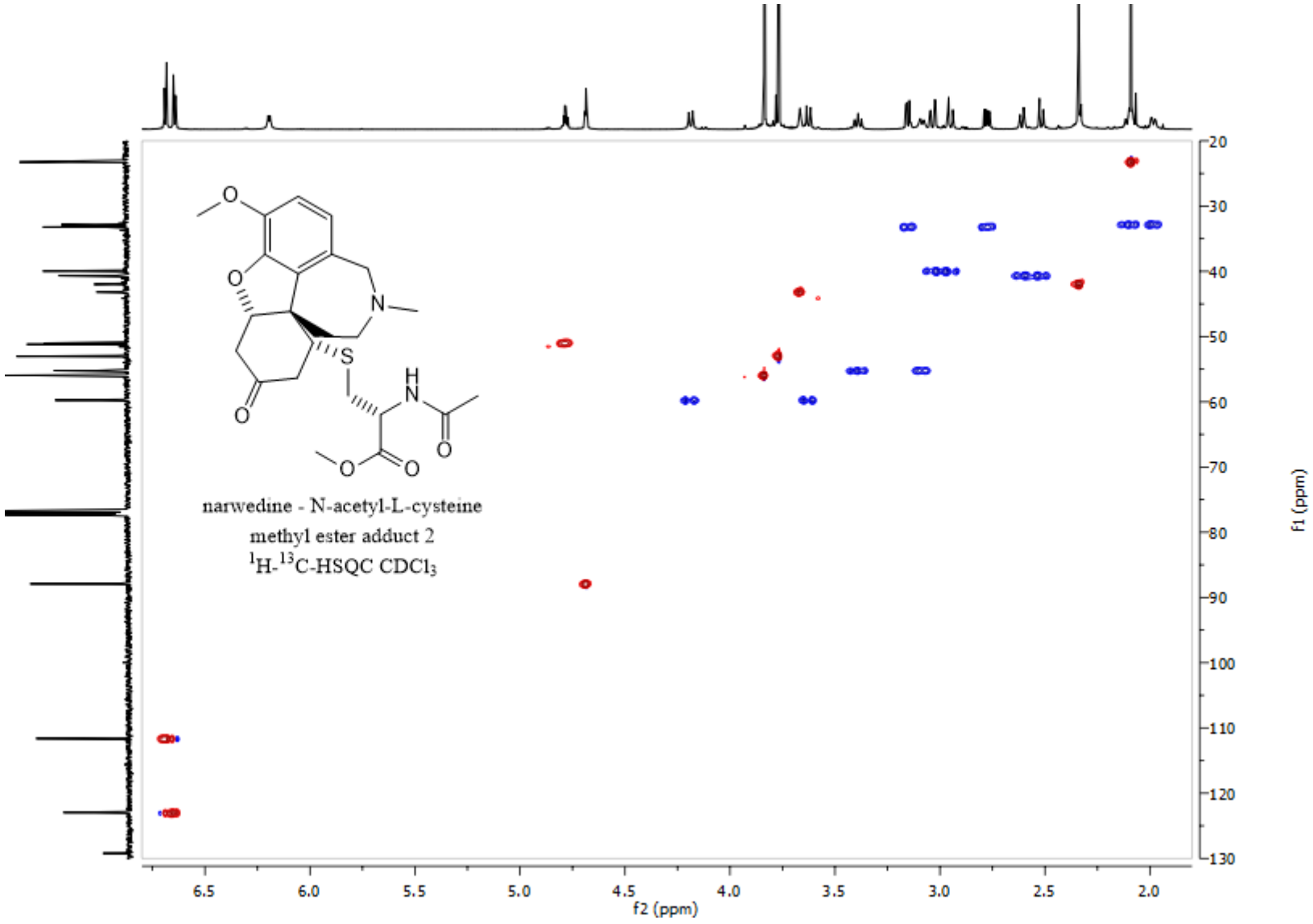

narwedine - N-acetyl-L-cysteine
methyl ester adduct 2
^{13}C-NMR 100 MHz $CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

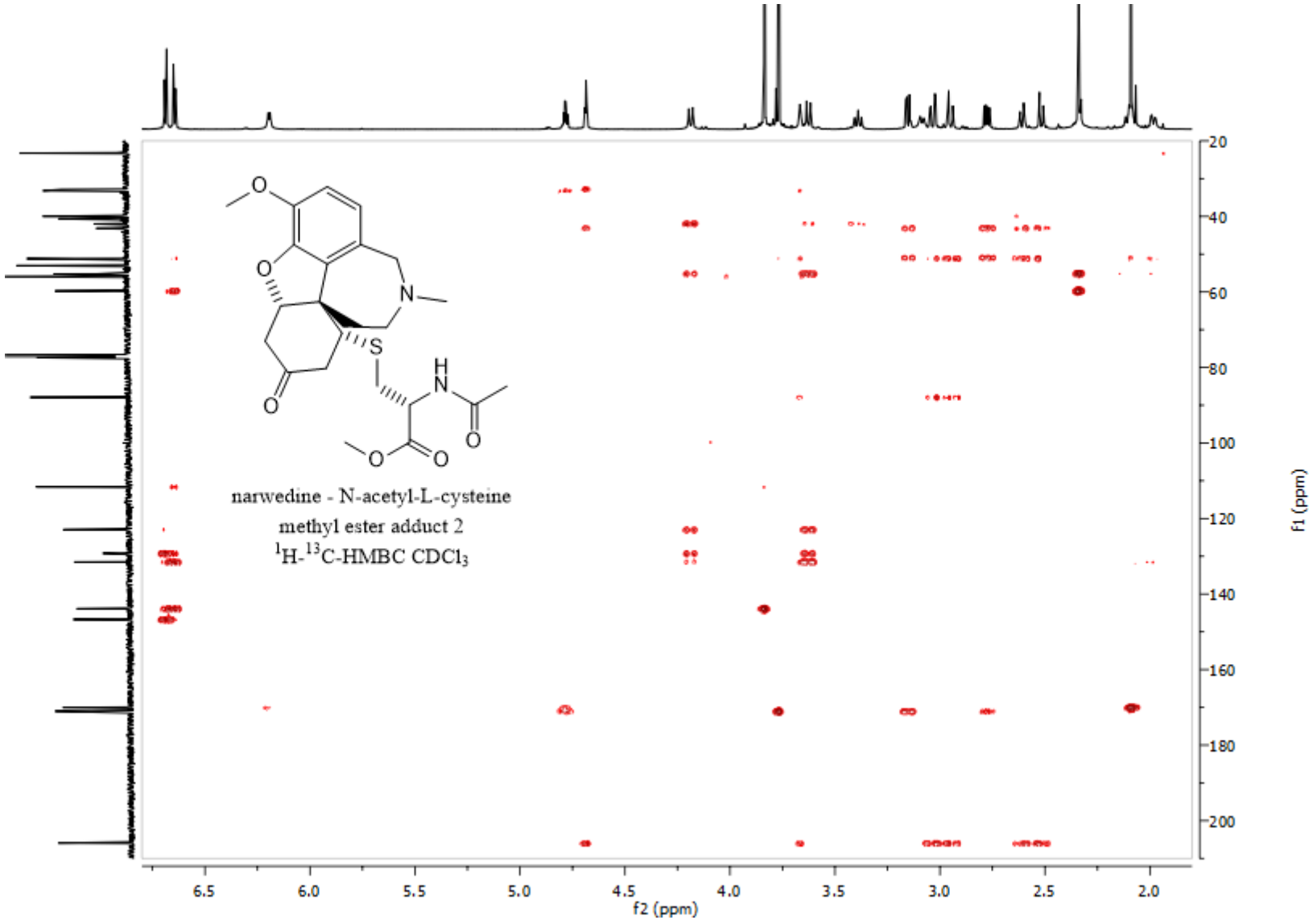


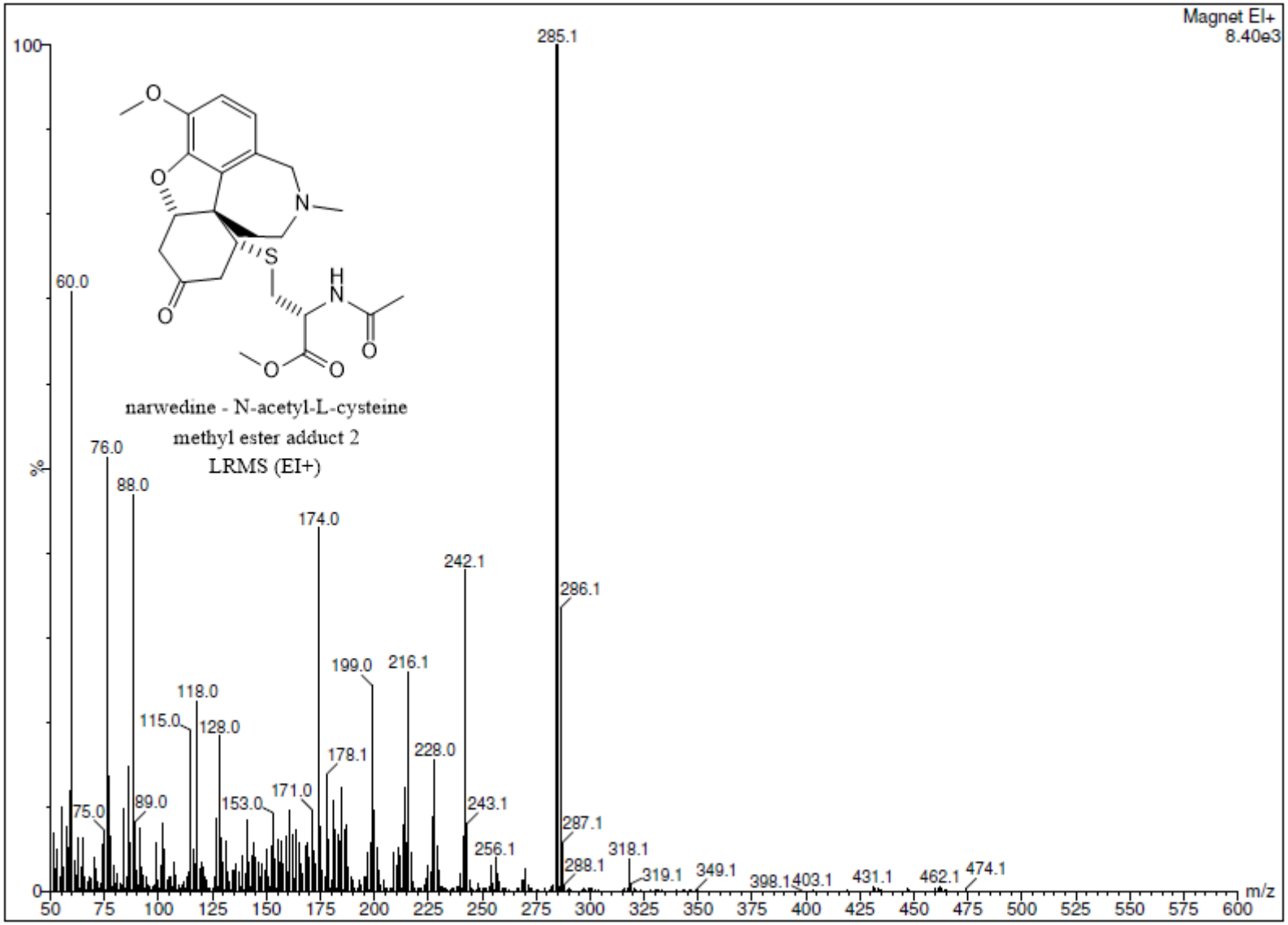
* Denotes cross-peaks resulting from traces of the other isomer in the sample


4.5
4.0
3.5
3.0
2.5
2.0
f2 (ppm)
2.0
2.5
3.0
3.5
4.0
4.5
f1 (ppm)

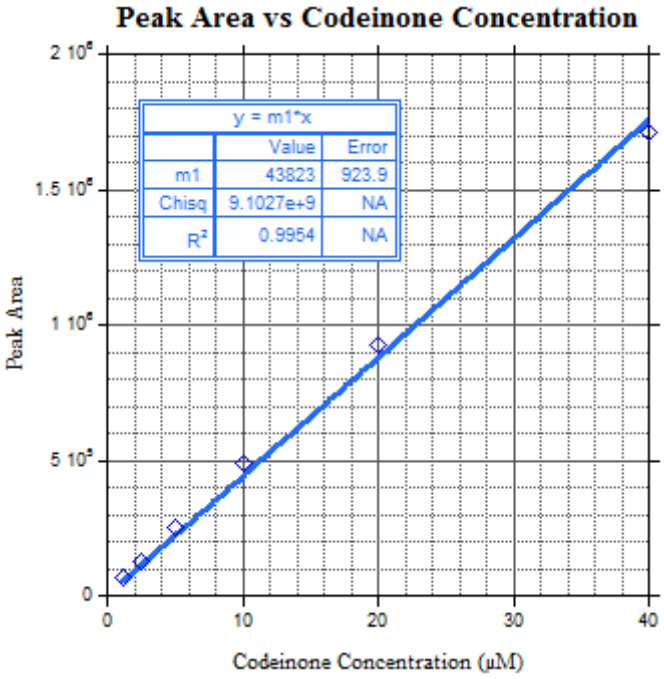

narwedine - N-acetyl-L-cysteine
methyl ester adduct 2
^{1}H-^{1}H-COSY CDCl$_3$
f2 (ppm)
f1 (ppm)

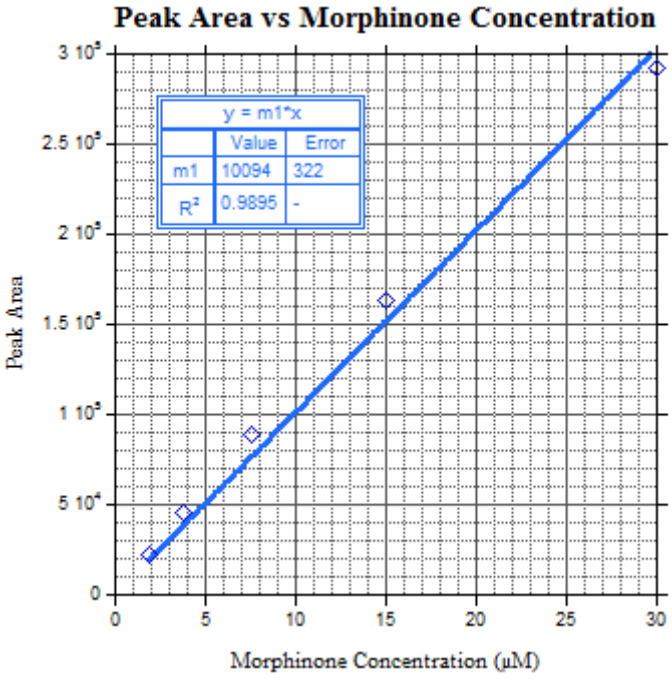

narwedine - N-acetyl-L-cysteine
methyl ester adduct 2
^{1}H-^{13}C-HSQC $CDCl_3$
f2 (ppm)
f1 (ppm)

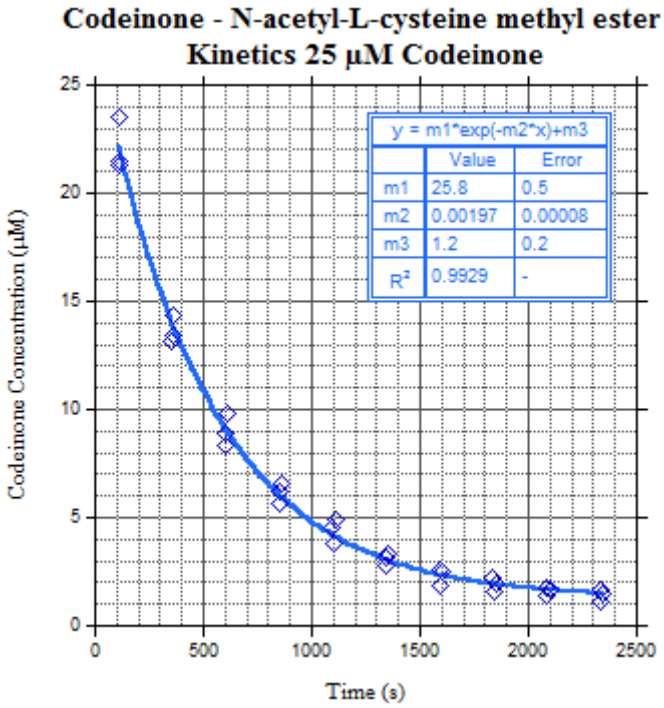

narwedine - N-acetyl-L-cysteine
methyl ester adduct 2
^{1}H-^{13}C-HMBC $CDCl_3$
f2 (ppm)
f1 (ppm)

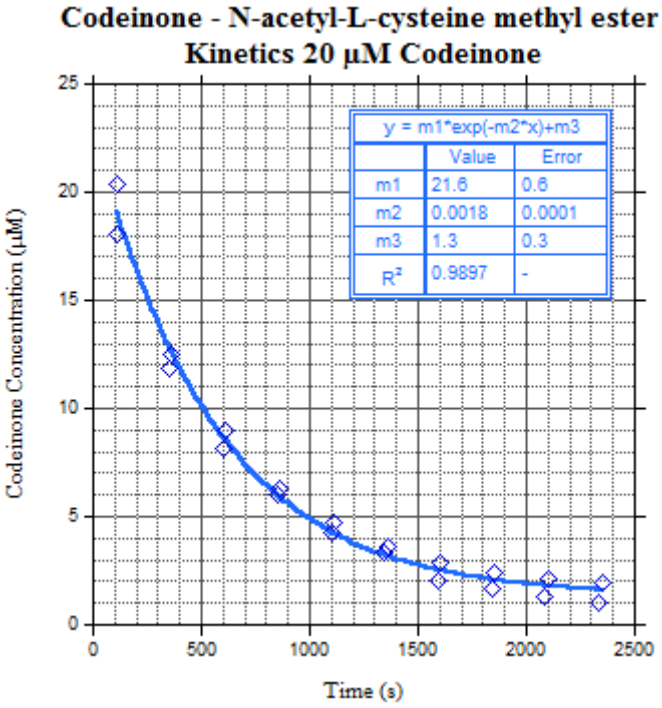

Magnet EI+
8.40e3
100
%
0
285.1
60.0
76.0
88.0
174.0
242.1
286.1
199.0
216.1
118.0
115.0
128.0
178.1
228.0
171.0
153.0
89.0
75.0
243.1
287.1
256.1
318.1
288.1
319.1
349.1
398.1
403.1
431.1
462.1
474.1
m/z
50 75 100 125 150 175 200 225 250 275 300 325 350 375 400 425 450 475 500 525 550 575 600
narwedine - N-acetyl-L-cysteine
methyl ester adduct 2
LRMS (EI+)

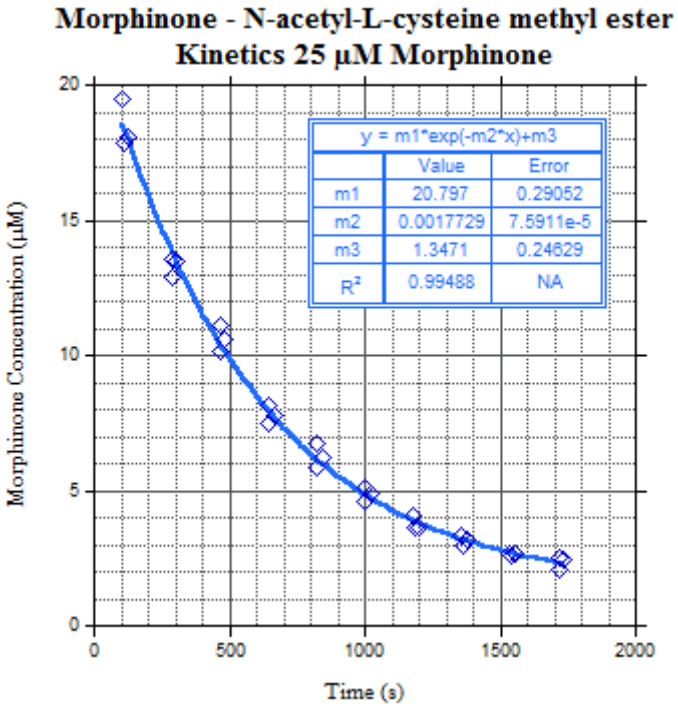
3. Kinetics Data:

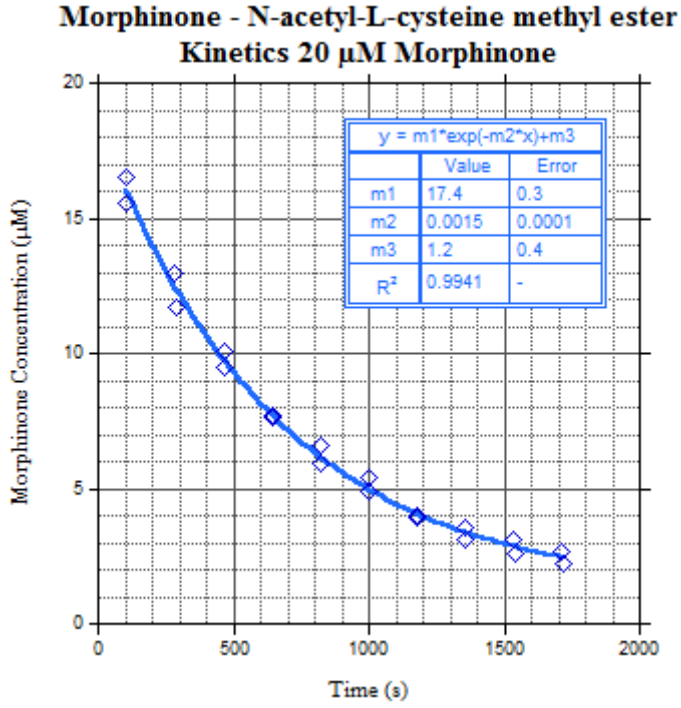


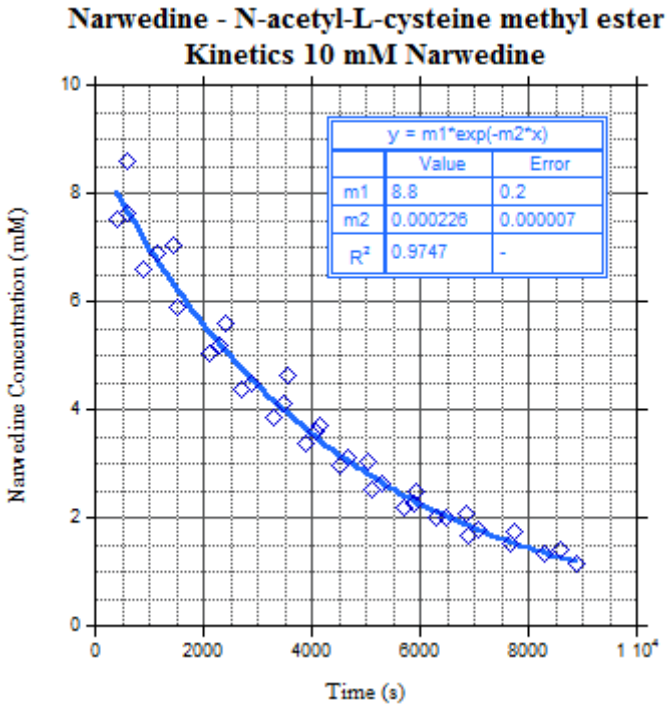



Codeinone - N-acetyl-L-cysteine methyl ester
Kinetics 25 µM Codeinone
y = m1*exp(-m2*x)+m3
Value Error
m1 25.8 0.5
m2 0.00197 0.00008
m3 1.2 0.2
R² 0.9929 -
Codeinone Concentration (µM)
Time (s)
0 5 10 15 20 25
0 500 1000 1500 2000 2500

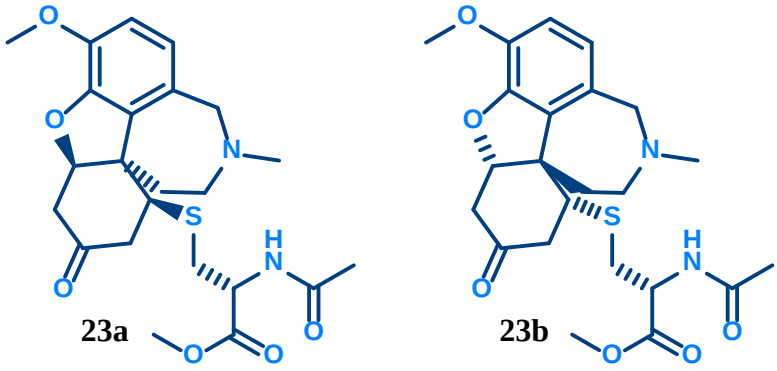

Codeinone - N-acetyl-L-cysteine methyl ester
Kinetics 20 µM Codeinone
y = m1*exp(-m2*x)+m3
Value Error
m1 21.6 0.6
m2 0.0018 0.0001
m3 1.3 0.3
R² 0.9897 -
Codeinone Concentration (µM)
Time (s)
0 5 10 15 20 25
0 500 1000 1500 2000 2500


Morphinone - N-acetyl-L-cysteine methyl ester
Kinetics 25 µM Morphinone
y = m1*exp(-m2*x)+m3
Value Error
m1 20.797 0.29052
m2 0.0017729 7.5911e-5
m3 1.3471 0.24629
R² 0.99488 NA
Morphinone Concentration (µM)
Time (s)
0
5
10
15
20
0
500
1000
1500
2000

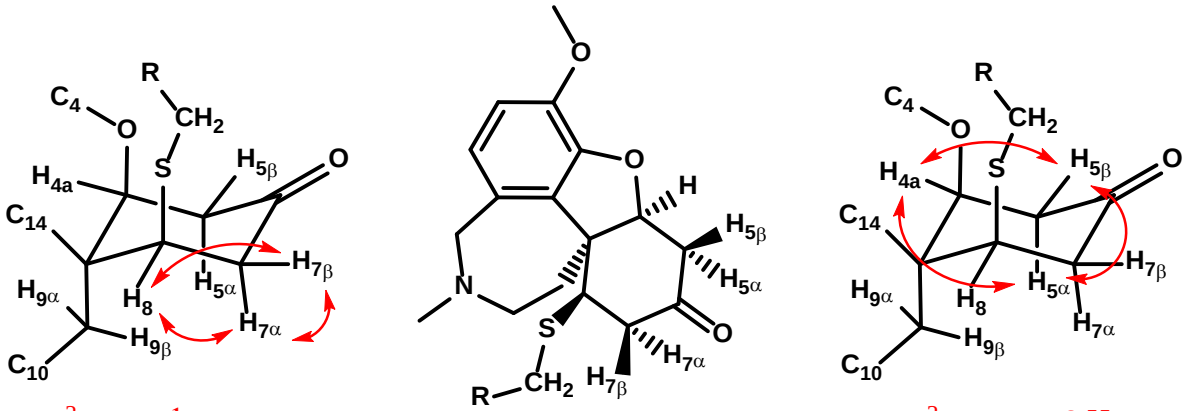

Morphinone - N-acetyl-L-cysteine methyl ester
Kinetics 20 µM Morphinone
y = m1*exp(-m2*x)+m3
Value Error
m1 17.4 0.3
m2 0.0015 0.0001
m3 1.2 0.4
R² 0.9941 -
Morphinone Concentration (µM)
Time (s)
0
5
10
15
20
0
500
1000
1500
2000


Narwedine - N-acetyl-L-cysteine methyl ester
Kinetics 10 mM Narwedine
y = m1*exp(-m2*x)
Value
Error
m1
8.8
0.2
m2
0.000226
0.000007
R²
0.9747
-
Narwedine Concentration (mM)
Time (s)
0
2
4
6
8
10
0
2000
4000
6000
8000
1 10⁴

4. Structural Assignment of Narwedine Adducts:



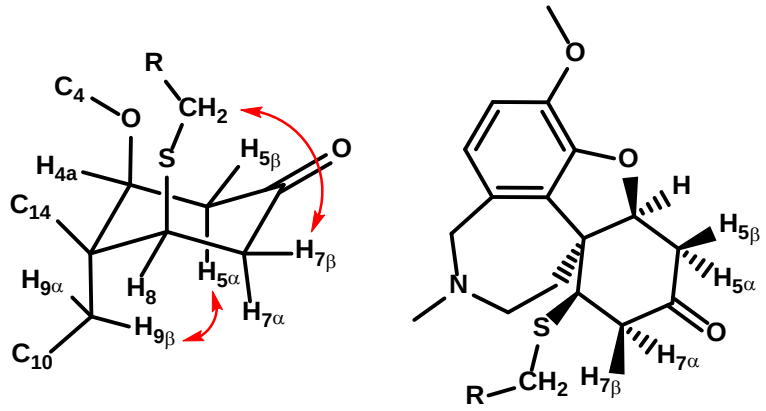
Based on steric considerations, the structures of the narwedine adducts were tentatively assigned as diastereomers arising from addition *cis* to the aromatic ring as shown above. Assuming this is correct, the cyclohexanone ring adopts a chair conformation with the cysteine side chain in an axial position as shown below. In the ^{1}H-NMR spectra for both adducts, the C_8 proton appeared as a broad singlet suggesting that the coupling constants for coupling with the C_7 protons was small. Additionally, the C_{4a} proton appeared as a triplet with very small coupling constants (2.8 Hz) corresponding to coupling with the C_5 protons. These coupling constants are consistent with gauche interactions in which the C_8 or C_{4a} proton appears between the two adjacent protons when viewed along the C–C bond, consistent with the structure shown below.



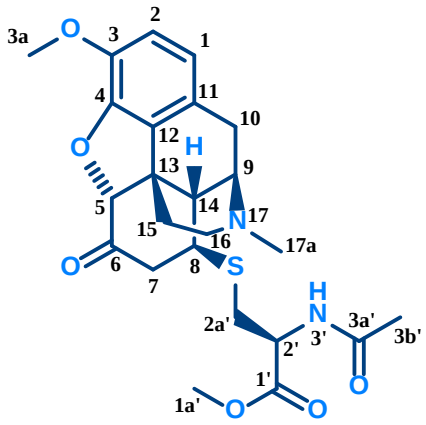
$^{3}J_{8,7\alpha} < 1$
$^{3}J_{8,7\beta} < 1$
$^{2}J_{7\alpha,7\beta} = 16.8, 17.2$ Hz

$^{3}J_{4a,5\alpha} = 2.8$ Hz
$^{3}J_{4a,5\beta} = 2.8$ Hz
$^{2}J_{5\alpha,5\beta} = 18.4$ Hz

Examination of the 2D-NOESY spectrum for both adducts enabled the assignment of the α and β protons at C_5 and C_7, assuming the stereochemical outcome of the reaction is as predicted based on steric considerations. This was based on the two key nOe interactions shown below. An nOe interaction with the CH_2 protons of the cysteine side chain enabled the $H_{7\beta}$ proton to be assigned. An nOe interaction with $H_{9\beta}$ enabled the $H_{5\alpha}$ proton to be assigned. In addition to these interactions, nOe interactions were detected between H_8 and the C_7 protons as well as H_{4a} and the C_5 protons. While these nOe interactions were useful to differentiate the C_5 and C_7 protons, the interactions detected could be rationalised for either stereochemistry at C_8. Thus the assignment of C8 stereochemistry remains tentative in the absence of other structural data..



5. Comparison of Experimental and Literature NMR Data for Compound 21:



	Compound 21		Literature Compound 21 [12]	
	1H-NMR	**13C-NMR**	**1H-NMR**	**13C-NMR**
1	6.67-6.69 (m, 1H)	120.4	6.63 (d, J = 7.9)	114.7
2	6.70-6.71 (m, 1H)	115.0	6.80 (d, J = 7.9)	120.1
3	-	143.1	-	142.7
3a	**3.89 (s)**	**57.0**	**3.54 (s)**	**52.5**
4	-	145.2	-	144.8
5	4.69 (s)	91.5	4.72 (s)	91.1
6	-	204.8	-	204.6
7	2.53 (t, J = 13.2) **2.70 (dd, J = 13.2, 2.4)**	**47.5**	**2.20-2.54 (m)**	**51.3**
8	**2.30 (td, J = 12.8, 2.4)**	41.6	**2.91 (dd, J = 5.1, 2.7)**	41.2
9	**3.63 (s, br)**	56.9	**3.99 (m)**	56.6
10	2.34 (dd, J = 18.4, 5.2) 3.01 (d, J = 18.8)	19.3	2.20-2.54 (m) 2.96-3.14 (m)	19.0
11	-	126.5	-	126.1
12	-	126.8	-	126.4
13	-	47.2	-	46.9
14	**2.44-2.49 (m)**	**47.4**	**2.69-2.87 (m)**	**44.1**
15	**1.82 (d, br, J = 12.0)** **2.06 (td, J = 12.0, 4.0)**	35.7	**1.91 (m)** **2.20-2.54 (m)**	35.2
16	2.20 (td, J = 12.0, 2.8) **2.57 (d, br, J = 11.6)**	47.3	2.20-2.54 (m) **2.69-2.87 (m)**	47.1
17a	2.44-2.49 (m)	43.0	2.20-2.54 (m)	42.6
1'	-	170.9	-	170.6
1a'	**3.46 (s)**	52.6	**3.66 (s)**	52.3
2'	4.81 (m)	52.3	4.82 (m)	52.1
2a'	2.98 (dd, J = 14.0, 4.0) 3.04 (dd, J = 14.0, 4.4)	31.5	2.96-3.14 (m)	31.1
3'	6.32 (d, br, J = 6.8 Hz)	-	6.38 (s, br)	-
3a'	-	169.9	-	169.7
3b'	**1.97 (s)**	23.2	**2.06 (s)**	22.8

6. References:

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12. Garadnay, S., et al., *First synthesis of important secondary oxidative metabolites of morphine and codeine with the Michael addition.* Open Chemistry, 2013. **11**(3): p. 430-437.