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Thieme

Supporting Information

Double Palladium Catalyzed Synthesis of Azepines

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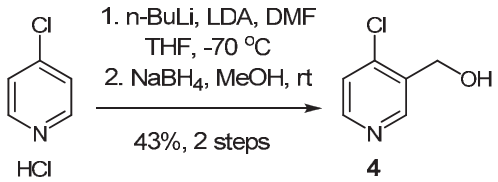
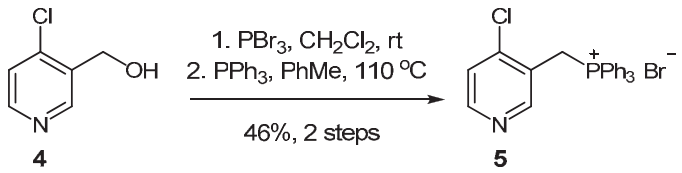
Supporting Information Contents:

General Information: 4-Chloropyridine hydrochloride was purchased from Fluka. Manganese(IV)-oxide was purchased from Merck. Other chemicals were purchased from Aldrich. Microwave reactions were performed in a Biotage Initiator 2.5 microwave reactor. Melting points were determined using a Boetius PMHK apparatus (Carl Zeiss, Germany) and were not corrected. IR spectra were recorded on a Perkin-Elmer spectrophotometer FTIR 1725X. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 spectrometer (at 200 and 50 MHz, respectively), and a Bruker Ultrashield Advance III spectrometer (at 500 and 125 MHz, respectively) employing indicated solvents (*vide infra*) using TMS as the internal standard. Chemical shifts are expressed in ppm (δ) values and coupling constants (*J*) in Hz. ESI–MS (HRMS) spectra of the synthesized compounds were acquired on a Agilent Technologies 1200 Series instrument equipped with a Zorbax Eclipse Plus C18 (100 × 2.1 mm i.d. 1.8 μm) column and DAD detector (190-450 nm) in combination with a 6210 Time-of-Flight LC/MS instrument in positive ion mode. The samples were dissolved in pure MeOH (HPLC grade). The selected values were as follows: capillary voltage = 2.5 kV, gas temperature = 250°C, drying gas = 7 L min^{-1}, nebulizer pressure = 30 psig, and fragmentator voltage = 50 V. GC/MS spectra of the synthesized compounds were acquired on a Agilent Technologies 7890A equipped with a DB-5 MS (30 m × 0.25 mm × 0.25 μm) column and 5975C MSD and FID detector. The selected values were as follows: carrier gas was He (1.0 mL/min), temperature linearly increased 40-315 ^{o}C (10 ^{o}C/min), injection volume = 1 μL, temperature = 250 °C, temperature (FID detector) = 300 °C, and EI mass spectra range: 40-550 m/z. Lobar LichroPrep Si 60 (40-63 μm) or LichroPrep RP-18 columns (Merck, Germany), coupled to a Waters RI 401 detector, were used for preparative column chromatography. Thin-layer chromatography was performed on pre-coated Merck silica gel 60 F254 and Merck RP-18 F254 plates. The solution MeOH (NH_3) stands for combination MeOH/NH_3 aq = 9:1, and the solution CH_2Cl_2 (PhMe) corresponds to CH_2Cl_2/PhMe = 99:1.



4-Chloropyridine-3-methanol (4).[1]

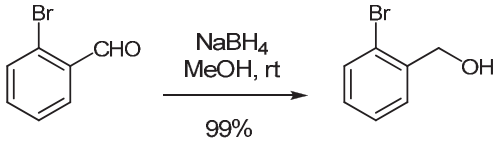
To a solution of $^{i}Pr_2NH$ (0.670 mL, 4.78 mmol) in THF (2.0 mL) 1.6 M *n*-BuLi in hexane (2.43 mL, 3.90 mmol) was added dropwise at -78 °C under Ar. After stirring for 5 min at 0 °C the mixture was cooled to -78 °C and used in the next reaction. To a suspension of 4-chloropyridine hydrochloride (500 mg, 3.33 mmol) in dry THF (5 mL) 1.6 M n-BuLi in hexane (2.10 mL, 3.33 mmol) was added dropwise at 0 °C under Ar. After stirring at room temperature for 30 min the reaction was cooled to -78 °C and prepared LDA solution was addded. Upon stirring at the same temperature for 30 min DMF (380 µL, 4.95 mmol) was added. The reaction was warmed to room temperature gradually and stirred overnight. It was quenched with 3 M HCl and resulting mixture was stirred for 2 h at r.t. The solution was neutralized with $NaHCO_3$, it was extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated to give crude aldehyde as brown oil. The obtained aldehyde was dissolved into MeOH (25 mL), and $NaBH_4$ (187 mg, 4.95 mmol) was added to the solution. After stirring for 3 h at room temperature, the reaction was concentrated. Water was added to the residue, and extracted with CH_2Cl_2, followed by drying over anh. Na_2SO_4, and evaporation to dryness. Column chromatography using hexane/EtOAc = 8:2 afforded desired compound **4** as pale yellow powder (206 mg, 43%), mp = 87-90 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.30 (d, J = 5.6 Hz, 1H), 4.82 (s, 2H), 4.43 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.4, 149.1, 143.0, 134.8, 124.4, 60.0. IR (ATR): 3176, 2925, 2853, 1582, 1563, 1468, 1443, 1405, 1359, 1226, 1190, 1067, 830, 715 cm^{-1}. (+)ESI-HRMS (*m*/*z*): $[M + H]^+$ 144.02063 (error -3.01 ppm).



[(2-Chloropyridine-3-yl)methyl](triphenyl)phosphonium bromide (5).

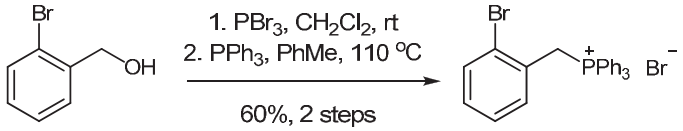
To a solution of alcohol **4** (0.80 g, 5.6 mmol) in CH_2Cl_2 (45 mL) PBr_3 (1.0 mL, 11 mmol) was added. After stirring for 2 h at room temperature the reaction mixture was cooled to 0 °C it was neutralized with $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated to dryness. Column chromatography using hexane/EtOAc = 1:1 afforded product as red oil. Obtained intermediate was disolved in PhMe (18 mL) and PPh_3 (1.5 g, 5.9 mmol) was added. Resulting reaction mixture was refluxed for 6 days. After cooling to room temperature, product was filtered, washed with diethyl ether and dried under reduced pressure at 45 °C. Desired phosphonium bromide was obtained as white powder (1.2 g, 46%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.41 (s, 1H), 7.88-7.60 (m, 15H), 7.20-7.13 (m, 1H), 5.84 (d, J = 14.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1 (d, J = 5.5 Hz) , 150.4 (d, J = 3.6 Hz), 145.6 (d, J = 5.5 Hz), 135.4 (d, J = 2.6 Hz), 134.2 (d, J = 10.0 Hz), 130.4 (d, J = 12.5 Hz), 124.3, 123.3, 117.1 (d, J = 84.8 Hz), 26.2 (d, J = 49.6 Hz). IR (ATR): 2998, 2861, 2838, 2769, 1644, 1556, 1481, 1435, 1402, 1319, 1191, 1159, 1107, 995, 855, 751, 725, 692 cm^{-1}.

[1] Takano, Y.; Shiga, F.; Asano, J.; Ando, N.; Uchiki, H.; Fukuchi, K.;Anraku, T. *Bioorg. Med. Chem.* **2005**, *13*, 5841.



(2-Bromobenzene-1-yl)methanol.

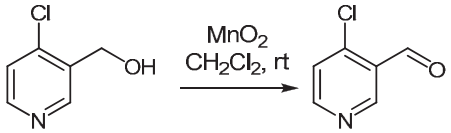
2-Bromobenzaldehyde (1.26 mL, 10.8 mmol) was dissolved in MeOH (25 mL), and $NaBH_4$ (491 mg, 12.9 mmol) was added to the solution. After stirring for 18 h at room temperature, the reaction mixture was concentrated. Water was added to the residue and the product was extracted with CH_2Cl_2, organic layer was dried over Na_2SO_4, and evaporated. The desired product was obtained as pale yellow oil (2.00 g, 99%) and was used without any further purifications. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.58-7.42 (m, 2H), 7.38-7.24 (m, 1H), 7.22-7.10 (m, 1H), 4.72 (s, 2H), 2.31 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.7, 132.6, 129.1, 128.8, 127.6, 122.5, 65.0. GC-MS (*m/z* (%)): 186.0 ($[M]^+$ (43)), 169.0 (5), 157.0 (10), 107.1 (70), 89.1 (11), 79.0 (100). IR (ATR): 3992, 3970, 3912, 3892, 3857, 3304, 3078, 2910, 2858, 2710, 2577, 2029, 1965, 1567, 1466, 1439, 1364, 1264, 1244, 1196, 1113, 1056, 1021, 989, 939, 798 cm^{-1}.



7

[(2-Bromobenzene-1-yl)methyl](triphenyl)phosphonium bromide (7).

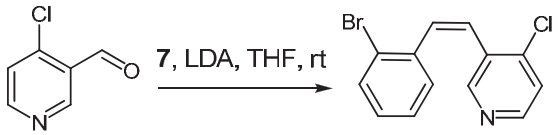
(2-Bromobenzene-1-yl)methanol (2.00 g, 10.7 mmol) was dissolved in CH_2Cl_2 (100 mL), and PBr_3 (2.00 mL, 21.3 mmol) was added. After stirring for 2 h at room temperature resulting reaction mixture was cooled to 0 °C, neutralized with $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated to dryness. Column chromatography using hexane/EtOAc = 8:2 afforded product as pale red oil 1.70 g. Product was dissolved in PhMe (75 mL) followed by addition of PPh_3 (1.97 g, 7.62 mmol). Resulting reaction mixture was refluxed for 6 days. After cooling to room temperature, product was filtered off, washed well with diethyl ether and dried under reduced pressure at 45 °C. Phosphonium salt **7** was obtained as white powder, 3.30 g (60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80-7.72 (m, 3H), 7.65-7.56 (m, 12H), 7.49-7.44 (m, 1H), 7.35-7.30 (m, 1H), 7.14-7.06 (m, 2H), 5.52 (d, J = 14.5 Hz, 2H).^{13}C NMR (125 MHz, $CDCl_3$) δ 135.1 (d, J = 2.7 Hz), 134.1 (d, J = 10.0 Hz), 132.8, 132.8, 130.1 (d, J = 12.6 Hz), 128.2 (d, J = 3.5 Hz), 127.4 (d, J = 9.1 Hz), 127.0 (d, J = 7.2 Hz), 116.9 (d, J = 84.9 Hz), 30.8 (d, J = 48.8 Hz). IR (ATR): 3038, 3015, 2984, 2941, 2855, 2773, 2689, 1585, 1475, 1437, 1401, 1321, 1273, 1190, 1160, 1108, 1028, 995, 829, 784, 756, 723 cm^{-1}.



4

4-Chloropyridine-3-carbaldehyde.

Alcohol **4** (92 mg, 0.65 mmol) was dissolved in CH_2Cl_2 (5 mL) followed by addition of MnO_2 (0.56 g, 6.5 mmol). After stirring for 2 h at room temperature reaction mixture was filtered and solvent was evaporated to dryness. The obtained 4-chloropyridine-3-carbaldehyde was found to be unstable, and consequently was used in the next reaction without further purification.



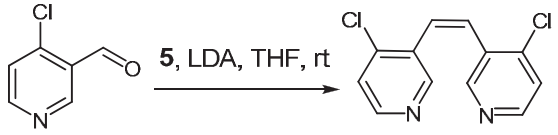
8, 54% (2 steps)

1,3'-(*Z*)-Ethene-1,2-diyl-1-(2-bromobenzene)-2-(4-chloropyridine) (8).

To a suspension of phosphonium salt **7** (338 mg, 0.660 mmol) in THF (5 mL) was added prepared LDA (0.40 mL, 0.78 mmol). After 30 min 4-chloropyridine-3-carbaldehyde (92 mg, 0.65 mmol) dissolved in THF (1 mL) was added over 5 min. The reaction mixture was stirred at room temperature and after 16 h it was quenched with $NaHCO_3$. The aqueous phase was separated and extracted with EtOAc (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, concentrated in vacuum and purified by column chromatography (RP, CH_2Cl_2 (PhMe)/MeOH = 7:3) to yield (*Z*)-**8** (104 mg, 54%), and (*E*)-**8** (24 mg, 12%).

(*Z*)-**8**: light yellow solid, mp 40-41 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 5.3 Hz, 1H), 8.16 (s, 1H), 7.61-7.56 (m, 1H), 7.31 (d, *J* = 5.3 Hz, 1H), 7.12-7.03 (m, 2H), 6.98-6.90 (m, 1H), 6.93 (d, *J* = 12.0 Hz, 1H) 6.75 (d, *J* = 12.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 148.7, 143.2, 136.4, 133.4, 132.9, 131.5, 130.4, 129.2, 127.2, 124.8, 124.2, 123.9. IR (ATR): 3084, 3057, 3031, 1572, 1544, 1459, 1400, 1076, 1044, 961, 820, 789, 751, 691 cm^{-1}. (+)ESI-HRMS (*m*/*z*): $[M + H]^+$ 293.96877 (error 2.73 ppm).

(*E*)-**8**: white solid, mp = 46-48 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.40 (d, *J* = 5.3 Hz, 1H), 7.71 (dd, *J* = 7.8 Hz, *J* = 1.4 Hz, 1H), 7.62 (dd, *J* = 8.0 Hz, *J* = 0.9 Hz, 1H), 7.56 (d, *J* = 16.0 Hz, 1H), 7.38-7.33 (m, 2H), 7.30 (d, *J* = 16.0 Hz, 1H), 7.22-7.16 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 148.3, 142.4, 136.3, 133.2, 131.7, 131.5, 129.7, 127.6, 127.1, 124.5, 124.4, 124.1. IR (ATR): 3059, 2931, 2856, 1632, 1568, 1544, 1469, 1432, 1402, 1323, 1281, 1220, 1117, 1074, 1022, 958, 816, 750 cm^{-1}. GC-MS, RT 24.00 min (m/z (%)): 294.9 ($[M]^+$ (100)), 214.0 (78), 179.0 (74), 151.0 (67), 126.0 (14), 107.0 (17), 89.0 (12), 76.0 (29), 63.0 (15), 51.0 (9). (+)ESI-HRMS (*m*/*z*): $[M + H]^+$ 293.96765 (error -1.09 ppm).



9, 43% (2 steps)

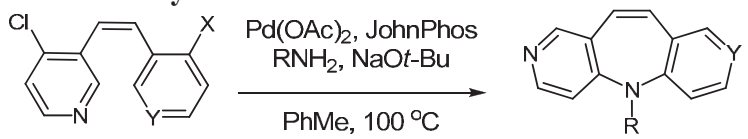
3,3'-(*Z*)-Ethene-1,2-diylbis(4-chloropyridine) (9).

The phosphonium salt **5** (1.0 g, 2.1 mmol) and 4-chloropyridine-3-carbaldehyde (0.30 g, 2.1 mmol) were transformed into (*Z*)-**9** (0.23 g, 43%), and (*E*)-**9** (12 mg, 2%) using freshly prepared LDA (2.0 mL, 4.0 mmol). The crude products were purified using preparative column chromatography (SiO_2, hexane/EtOAc = 8:2).

(*Z*)-**9:** light yellow powder, mp 130-131 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 5.5 Hz, 1H), 8.14 (s, 1H), 7.34 (d, *J* = 5.5 Hz, 1H), 6.90 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 149.4, 143.4, 131.2, 127.6, 124.5. IR (KBr): 3431, 3041, 2928, 2856, 1631, 1571, 1550, 1463, 1401, 1301, 1219, 1193, 1075, 972, 870, 816 cm^{-1}. (+)ESI-HRMS (*m*/*z*): $[M + 2H]^{2+}$ 126.00988 (error -4.92 ppm), $[M + H]^+$ 251.01382 (error 0.38 ppm).

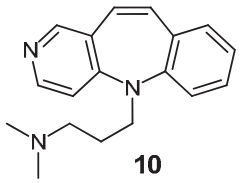
(*E*)-**9**: white solid, mp = 127-129 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.91 (s, 1H), 8.44 (d, *J* = 5.5 Hz, 1H), 7.45 (s, 1H), 7.37 (dd, *J* = 5.5 Hz, *J* = 0.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.6, 148.3, 142.8, 131.1, 125.9, 124.6. IR (ATR): 3098, 3048, 2958, 2930, 2866, 1896, 1636, 1573, 1549, 1474, 1408, 1315, 1223, 1175, 1073, 962, 839, 814, 740 cm^{-1}. GC-MS, RT 23.29 min (m/z (%)): 249.9 ($[M]^+$ (100)), 214.9 (46), 188 (16), 179.0 (15), 152.0 (14), 126.0 (13), 99.0 (9), 75.0 (12), 63.0 (10), 51.0 (7). (+)ESI-HRMS (*m*/*z*): $[M + H]^+$ 251.01343 (error -1.18 ppm).

General procedure for Pd-Catalyzed Amination



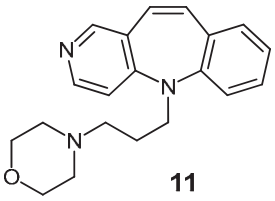
8: X = Br, Y = CH
9: X = Cl, Y = N

Reaction tube containing a stirring bar was evacuated and backfilled with Ar. The tube was then charged with $Pd(OAc)_2$ (5 mol %), JohnPhos (10 mol %) and NaO*t*-Bu (2.8 eq) and filled with Ar. Toluene was added. After stirring at room temperature for 5 min, aryl halide (1 eq) and amine (3 eq) were added, tube was filled with Ar and capped. Reaction mixture was heated to 100 °C and stirred at same temperature. Products were purified by preparative column chromatography: SiO_2, CH_2Cl_2/MeOH (NH_3) = 9/1.



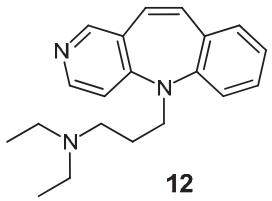
10

***N*,*N*-Dimethyl-3-(5*H*-pyrido[4,3-*b*][1]benzazepin-5-yl)propan-1-amine (10).**
Following general procedure, a mixture of **8** (24 mg, 0.080 mmol), 3-dimethylamino-1-propylamine (30 μL, 0.24 mmol), sodium *tert*-butoxide (22 mg, 0.23 mmol), $Pd(OAc)_2$ (0.9 mg, 5 mol %), JohnPhos (2.4 mg, 10 mol %) and toluene (1.5 mL) was stirred at 100 °C for 48 hours. **10:** yellow oil (18 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 5.5 Hz, 1H), 8.17 (s, 1H), 7.30-7.22 (m, 1H), 7.05-6.98 (m, 2H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 5.5 Hz, 1H), 6.74 (d, *J* = 11.5 Hz, 1H), 6.60 (d, *J* = 11.5 Hz, 1H), 3.80-3.73 (m, 2H), 2.39-2.33 (m, 2H), 2.15 (s, 6H), 1.82-1.70 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 158.8, 150.5, 150.1, 149.1, 134.1, 133.6, 129.5, 129.3, 129.2, 129.1, 124.1, 121.1, 114.7, 57.1, 48.2, 45.5, 25.4. IR (ATR): 3413, 3023, 2944, 2858, 2817, 2767, 1635, 1578, 1481, 1419, 1392, 1332, 1244, 1184, 1123, 1060, 919, 831, 794, 766 cm^{-1}. (+)ESI-HRMS (*m*/*z*): $[M + H]^+$ 280.18125 (error: 1.51 ppm).



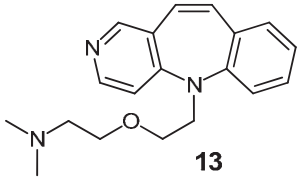
11

5-[3-(Morpholin-4-yl)propyl]-5*H*-pyrido[4,3-*b*][1]benzazepine (11). Following general procedure, a mixture of **8** (24 mg, 0.080 mmol), *N*-(3-aminopropyl)morpholine (36 μL, 0.24 mmol), sodium *tert*-butoxide (22 mg, 0.23 mmol), $Pd(OAc)_2$ (0.9 mg, 5 mol %), JohnPhos (2.4 mg, 10 mol %) and toluene (1.5 mL) was stirred at 100 °C for 48 hours. **11:** yellow oil (16 mg, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 6.0 Hz, 1H), 8.17 (s, 1H), 7.29-7.24 (m, 1H), 7.05-7.00 (m, 2H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.80 (d, *J* = 5.5 Hz, 1H), 6.73 (d, *J* = 11.5 Hz, 1H), 6.59 (d, *J* = 11.5 Hz, 1H), 3.80-3.75 (m, 2H), 3.70-3.60 (m, 4H), 2.47-2.40 (m, 2H), 2.39-2.30 (m, 4H), 1.80-1.70 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 150.5, 150.1, 149.0, 134.1, 133.6, 129.5, 129.3, 129.2, 124.1, 121.1, 114.7, 66.9, 56.2, 53.7, 48.2, 24.2. IR (ATR): 3268, 3025, 2956, 2854, 2812, 2687, 1640, 1576, 1523, 1479, 1395, 1332, 1307, 1184, 1141, 1118, 1068, 914, 765, 735, 700 cm^{-1}. (+)ESI-HRMS (*m*/*z*): $[M + H]^+$ 322.19242 (error: 3.20 ppm).



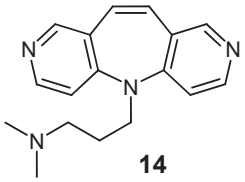
12

***N*,*N*-Diethyl-3-(5*H*-pyrido[4,3-*b*][1]benzazepin-5-yl)propan-1-amine (12).** Following general procedure, a mixture of **8** (24 mg, 0.080 mmol), 3-diethylamino-1-propylamine (38 μL, 0.24 mmol), sodium *tert*-butoxide (22 mg, 0.23 mmol), $Pd(OAc)_2$ (0.9 mg, 5 mol %), JohnPhos (2.4 mg, 10 mol %) and toluene (1.5 mL) was stirred at 100 °C for 48 hours. **12:** yellow oil (20 mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 5.5 Hz, 1H), 8.18 (s, 1H), 7.29-7.24 (m, 1H), 7.05-6.98 (m, 2H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 6.0 Hz, 1H), 6.74 (d, *J* = 11.5 Hz, 1H), 6.60 (d, *J* = 11.0 Hz, 1H), 3.80-3.73 (m, 2H), 2.62-2.55 (m, 2H), 2.51-2.42 (m, 4H), 1.79-1.70 (m, 2H), 0.98-0.80 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 150.4, 150.1, 149.0, 134.1, 133.6, 129.5, 129.3, 129.2, 129.1, 124.1, 121.2, 114.7, 49.6, 48.1, 46.8, 24.2, 11.3. IR (ATR): 3371, 3200, 2974, 1675, 1581, 1478, 1395, 1342, 1244, 1184, 1128, 794, 766, 651 cm^{-1}. (+)ESI-HRMS (*m*/*z*): $[M + 2H]^{2+}$ 154.60980 (error: 0.62 ppm), $[M + H]^+$ 308.21276 (error: 2.05 ppm).



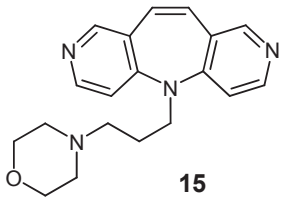
13

***N*,*N*-Dimethyl-2-[2-(5*H*-pyrido[4,3-*b*][1]benzazepin-5-yl)ethoxy]ethanamine (13).** Following general procedure, a mixture of **8** (24 mg, 0.080 mmol), 2-(2-dimethylamino-ethoxy)-ethylamine (35 μL, 0.24 mmol), sodium *tert*-butoxide (22 mg, 0.23 mmol), $Pd(OAc)_2$ (0.9 mg, 5 mol %), JohnPhos (2.4 mg, 10 mol %) and toluene (1.5 mL) was stirred at 100 °C for 48 hours. **13:** yellow oil (15 mg, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 6.0 Hz, 1H), 8.18 (s, 1H), 7.30-7.25 (m, 1H), 7.06-7.01 (m, 2H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 5.5 Hz, 1H), 6.74 (d, *J* = 11.5 Hz, 1H), 6.60 (d, *J* = 11.5 Hz, 1H), 4.00-3.93 (m, 2H), 3.64-3.59 (m, 2H), 3.54-3.49 (m, 2H), 2.50-2.45 (m, 2H), 2.25 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 150.5, 150.1, 148.9, 134.2, 133.5, 129.6, 129.4, 129.1, 129.0, 124.3, 121.0, 114.6, 69.0, 68.2, 58.6, 50.0, 45.5.IR (ATR): 3397, 3025, 2943, 2867, 2821, 2774, 1673, 1578, 1482, 1461, 1395, 1329, 1249, 1186, 1126, 1061, 916, 835, 769 cm^{-1}. (+)ESI-HRMS (*m*/*z*): $[M + H]^+$ 310.19001 (error: -4.46 ppm).



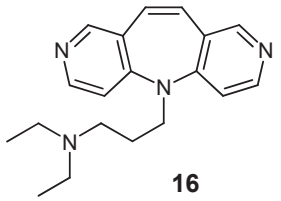
14

3-(5*H*-Dipyrido[4,3-*b*:3',4'-*f*]azepin-5-yl)-*N*,*N*-dimethylpropan-1-amine (14).
Following general procedure, a mixture of **9** (150 mg, 0.597 mmol), 3-dimethylamino-1-propylamine (225 μL, 1.80 mmol), sodium *tert*-butoxide (161 mg, 1.68 mmol), $Pd(OAc)_2$ (6.7 mg, 5 mol %), JohnPhos (18 mg, 10 mol %) and toluene (7.5 mL) was stirred at 100 °C for 24 hours. **14:** yellow oil 146 mg (87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, *J* = 5.5 Hz, 2H), 8.16 (s, 2H), 6.77 (d, *J* = 5.5 Hz, 2H), 6.64 (s, 2H), 3.78-3.69 (m, 2H), 2.39-2.33 (m, 2H), 2.16 (s, 6H), 1.81-1.72 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 150.7, 150.7, 131.1, 128.6, 115.4, 56.7, 47.8, 45.5, 25.0. IR (film): 3382, 2948, 2864, 2823, 2780, 1641, 1579, 1479, 1398, 1335, 1248, 1176, 1062, 972, 932, 840 cm^{-1}. (+)ESI-HRMS (*m*/*z*): $[M+2H]^{2+}$, 141.09229 (error 4.33), $[M+H]^+$ 281.17638 (error 1.10).



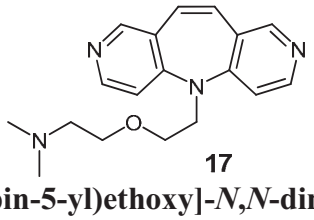
15

5-[3-(Morpholin-4-yl)propyl]-5*H*-dipyrido[4,3-*b*:3',4'-*f*]azepine (15). Following general procedure, a mixture of **9** (40 mg, 0.16 mmol), *N*-(3-aminopropyl)morpholine (70 μL, 0.48 mmol), sodium *tert*-butoxide (43 mg, 0.45 mmol), $Pd(OAc)_2$ (1.8 mg, 5 mol %), JohnPhos (4.8 mg, 10 mol %) and toluene (2.5 mL) was stirred at 100 °C for 24 hours. **15:** yellow oil (36 mg, 69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 5.5 Hz, 2H), 8.16 (s, 2H), 6.76 (d, J = 5.5 Hz, 2H), 6.63 (s, 2H), 3.81-3.76 (m, 2H), 3.66–3.57 (m, 4H), 2.48-2.41 (m, 2H), 2.40-2.34 (m, 4H) 1.82-1.74 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 150.8, 131.2, 128.7, 115.4, 66.9, 55.8, 53.8, 47.8, 24.0. IR (ATR): 3627, 3386, 3028, 2954, 2854, 2812, 2687, 1672, 1638, 1576, 1480, 1397, 1334, 1252, 1178, 1140, 1117, 1064, 920, 843, 780, 735 cm^{-1}. (+)ESI-HRMS (*m*/*z*): $[M+2H]^{2+}$, 162.09687 (error -0.55), $[M+H]^+$ 323.18606 (error: -1.79 ppm).



16

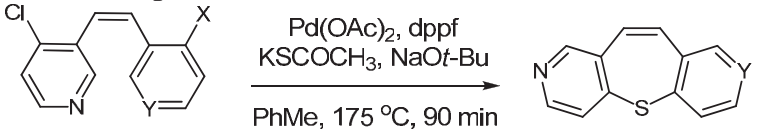
3-(5*H*-Dipyrido[4,3-*b*:3',4'-*f*]azepin-5-yl)-*N*,*N*-diethylpropan-1-amine (16). Following general procedure, a mixture of **9** (20 mg, 0.080 mmol), 3-diethylamino-1-propylamine (38 μL, 0.24 mmol), sodium tert-butoxide (22 mg, 0.23 mmol), $Pd(OAc)_2$ (0.9 mg, 5 mol %), JohnPhos (2.4 mg, 10 mol %) and toluene (1.5 mL) was stirred at 100 °C for 24 hours. **16:** yellow oil (12 mg, 47%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 5.5 Hz, 2H), 8.16 (s, 2H), 6.76 (d, J = 5.5 Hz, 2H), 6.64 (s, 2H), 3.80-3.74 (m, 2H), 2.56-2.49 (m, 2H), 2.48-2.39 (m, 4H), 1.78-1.64 (m, 2H), 0.98-0.90 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 150.8, 150.8, 131.2, 128.7, 115.5, 49.6, 47.8, 47.1, 24.6, 11.7. IR (ATR): 3354, 3166, 2821, 1652, 1470, 1398, 1154, 1050, 1007, 878, 830 cm^{-1}. (+)ESI-HRMS (*m*/*z*): $[M+H]^+$ 309.20590 (error: -4.78 ppm).



17

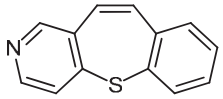
2-[2-(5*H*-Dipyrido[4,3-*b*:3',4'-*f*]azepin-5-yl)ethoxy]-*N*,*N*-dimethylethanamine (17). Following general procedure, a mixture of **9** (20 mg, 0.080 mmol), 2-(2-dimethylamino-etoxy)-ethylamine (35 μL, 0.24 mmol), sodium tert-butoxide (22 mg, 0.23 mmol), $Pd(OAc)_2$ (0.9 mg, 5 mol %), JohnPhos (2.4 mg, 10 mol %) and toluene (1.5 mL) was stirred at 100 °C for 24 hours. **17:** yellow oil (13 mg, 54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, J = 5.5 Hz, 2H), 8.17 (s, 2H), 6.78 (d, J = 5.5 Hz, 2H), 6.64 (s, 2H), 3.99-3.94 (m, 2H), 3.68-3.62 (m, 2H), 3.53-3.47 (m, 2H), 2.46-2.41 (m, 2H), 2.22 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 150.9, 150.8, 131.2, 128.6, 115.3, 69.4, 67.8, 58.8, 49.6, 45.8. IR (ATR): 3408, 2947, 2873, 2825, 2781, 1665, 1581, 1485, 1400, 1333, 1254, 1176, 1127, 1064, 929, 844, 800, 738 cm^{-1}. (+)ESI-HRMS (*m*/*z*): $[M+2H]^{2+}$, 156.09666 (error -1.90), $[M+H]^+$ 311.18522 (error: -4.55 ppm).

General procedure for the thiepine derivatives



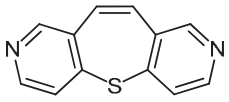
8: X = Br, Y = CH
9: X = Cl, Y = N

Reaction tube containing a stirring bar was evacuated and backfilled with Ar. The tube was charged with $Pd(OAc)_2$ (5 mol %), dppf (10 mol %), NaO*t*-Bu (1.2 eq), aryl halide (1 eq) and $KSCOCH_3$ (1.2 eq) and evacuated and backfilled with Ar. The flask was capped with a rubber septum, and toluene was added. The reaction mixture was heated in a Biotage Initiator 2.5 microwave at 175 °C for 90 min. After completion, the reaction mixture was cooled to room temperature. Products were purified by preparative column chromatography: SiO_2, Hexane/EtOAc = 1/1.



18

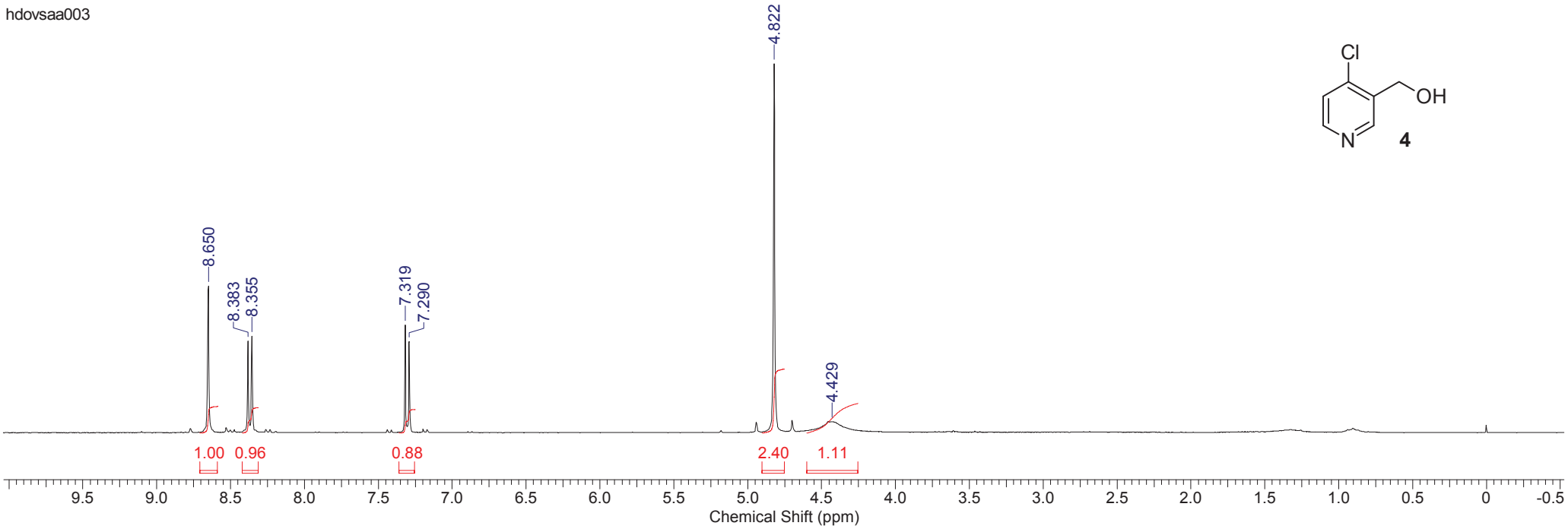
[1]Benzothiepino[3,2-*c*]pyridine (18). Following general procedure, a mixture of **8** (35 mg, 0.12 mmol), $KSCOCH_3$ (16 mg, 0.14 mmol), sodium *tert*-butoxide (14 mg, 0.14 mmol), $Pd(OAc)_2$ (1.3 mg, 5 mol %), dppf (6.6 mg, 10 mol %) and toluene (1.5 mL) was heated in a Biotage Initiator 2.5 microwave at 175 °C for 90 min. **18:** white solid (13 mg, 51%), mp 80-82 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.48-8.44 (m, 2H), 7.48-7.44 (m, 1H), 7.36-7.28 (m, 3H), 7.28-7.24 (m, 1H), 7.13 (d, J = 12.5 Hz, 1H), 6.99 (d, J = 12.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.9, 149.8, 144.7, 139.7, 136.1, 135.4, 133.0, 132.7, 130.4, 129.9, 129.7, 128.7, 126.3. IR (ATR): 3056, 3025, 2927, 2855, 1738, 1629, 1563, 1538, 1471, 1442, 1416, 1389, 1306, 1275, 1174, 1056, 885, 836 cm^{-1}. (+)ESI-HRMS (*m*/*z*): $[M + H]^+$ 212.05209 (error -3.58 ppm).



19

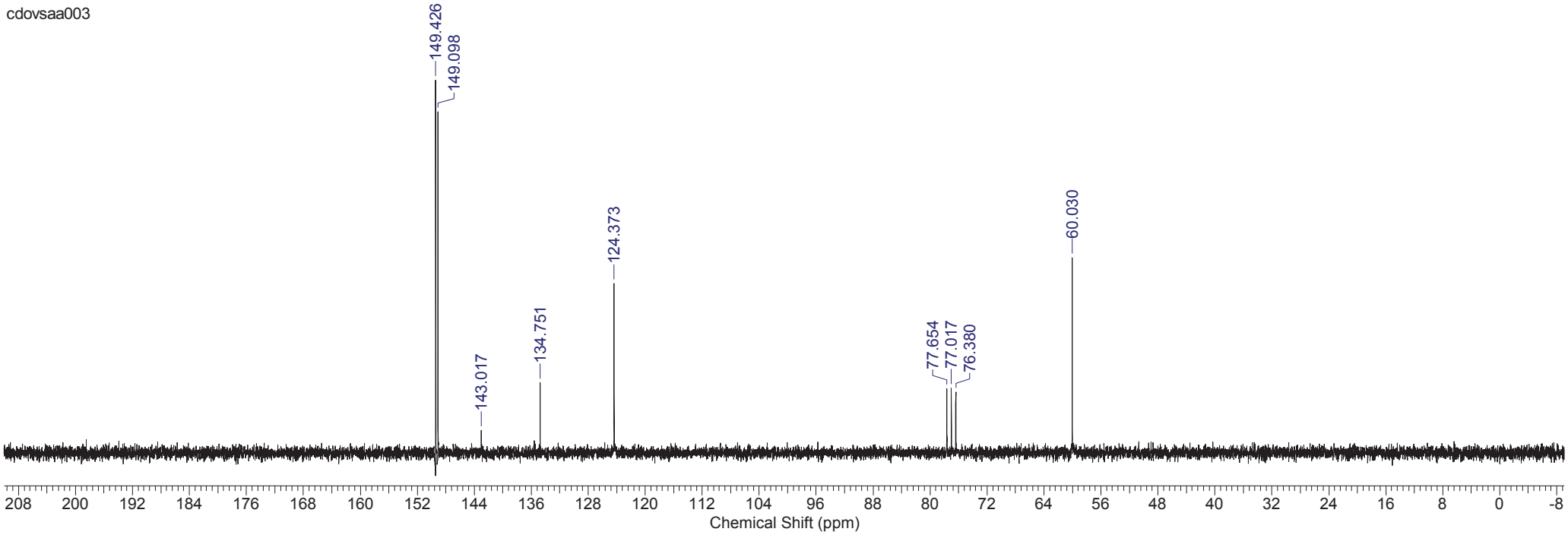
Thiepino[3,2-*c*:6,7-*c*′]dipyridine (19). Following general procedure, a mixture of **9** (30 mg, 0.12 mmol), $KSCOCH_3$ (16 mg, 0.14 mmol), sodium *tert*-butoxide (14 mg, 0.14 mmol), $Pd(OAc)_2$ (1.3 mg, 5 mol %), dppf (7 mg, 10 mol %) and toluene (1.5 mL) was heated in a Biotage Initiator 2.5 microwave at 175 °C for 90 min. **19:** white solid (12 mg, 49%), mp 139-140 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.51 (d, J = 5.0 Hz, 2H), 8.47 (s, 2H), 7.32 (d, J = 5.0 Hz, 2H), 7.08 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.6, 150.3, 142.9, 134.9, 132.8, 126.6. IR (film): 3024, 2930, 1565, 1542, 1473, 1390, 1294, 1268, 1178, 1047, 885, 835 cm^{-1}. (+)ESI-HRMS (*m*/*z*): $[M + H]^+$ 213.04721 (error -4.14 ppm).

hdovsaa003



4

cdovsaa003



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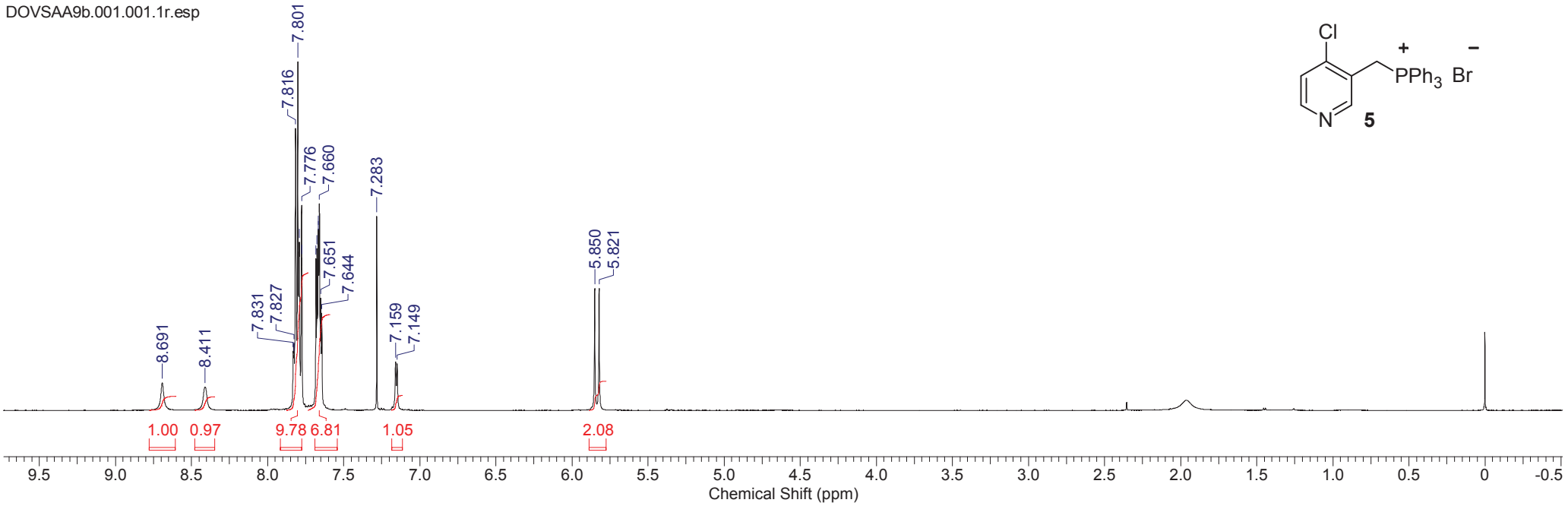

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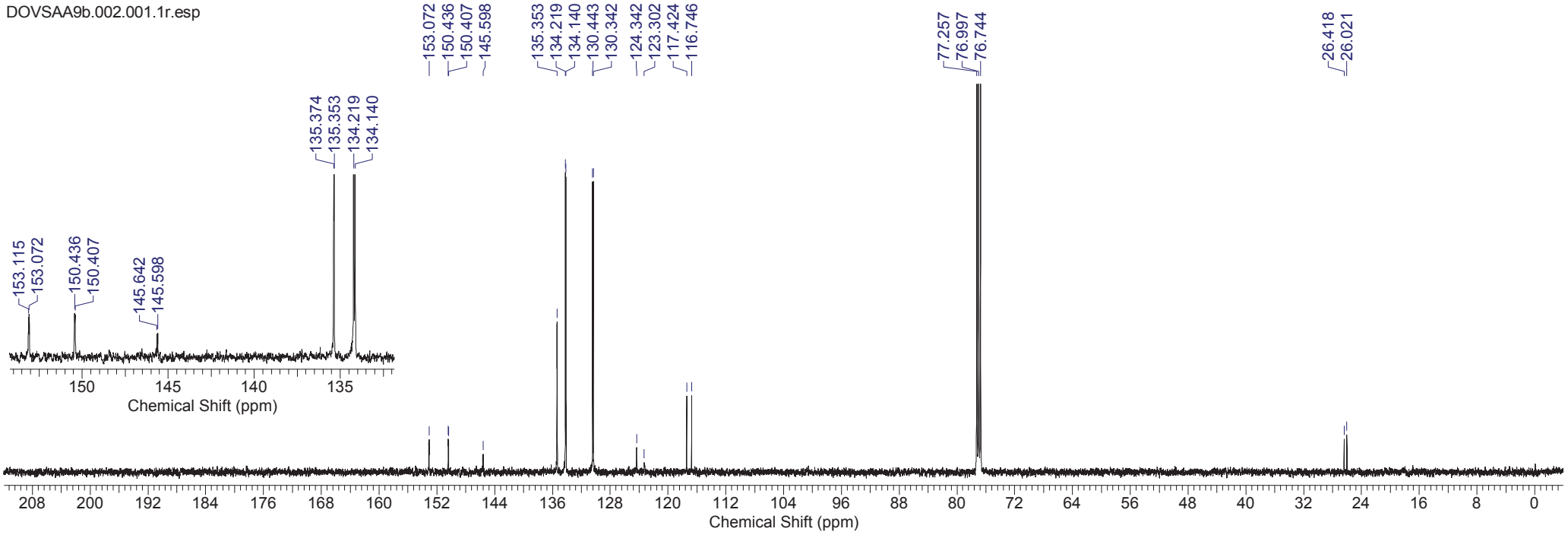

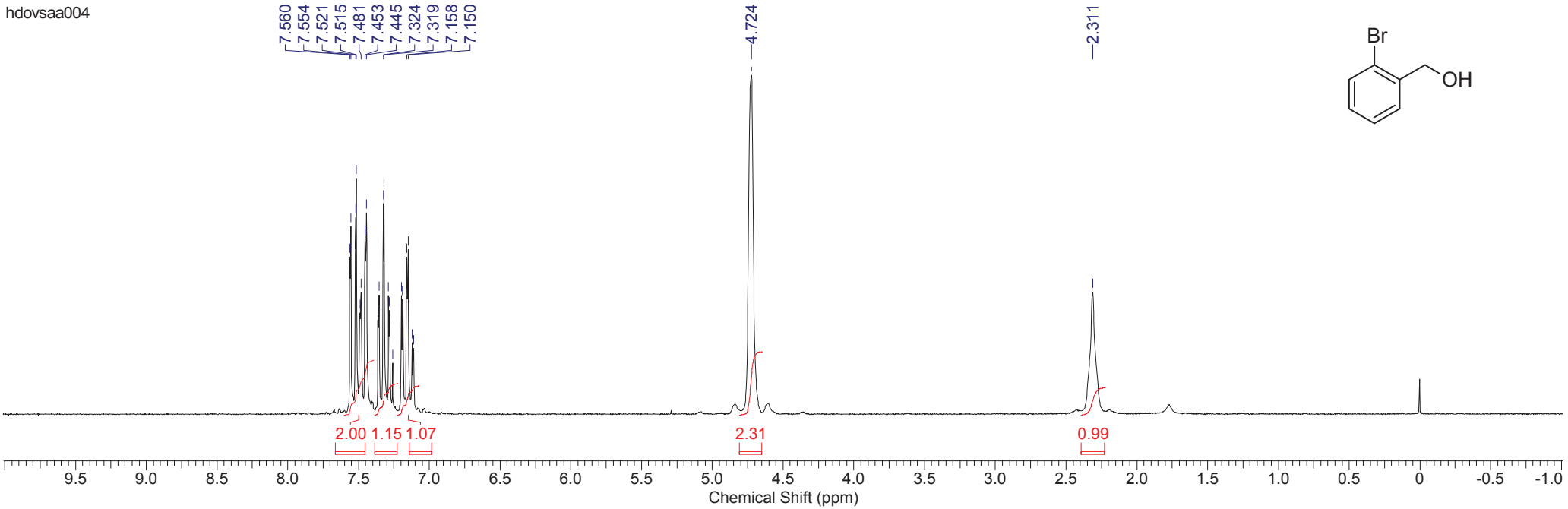
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OH
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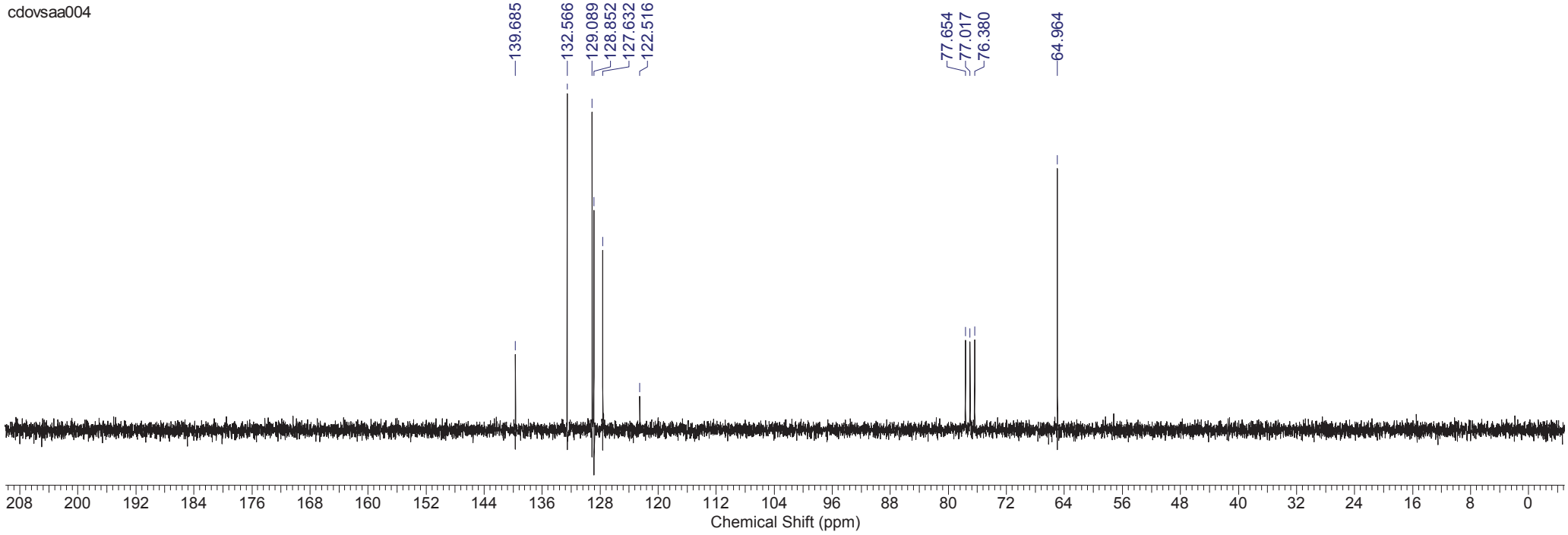
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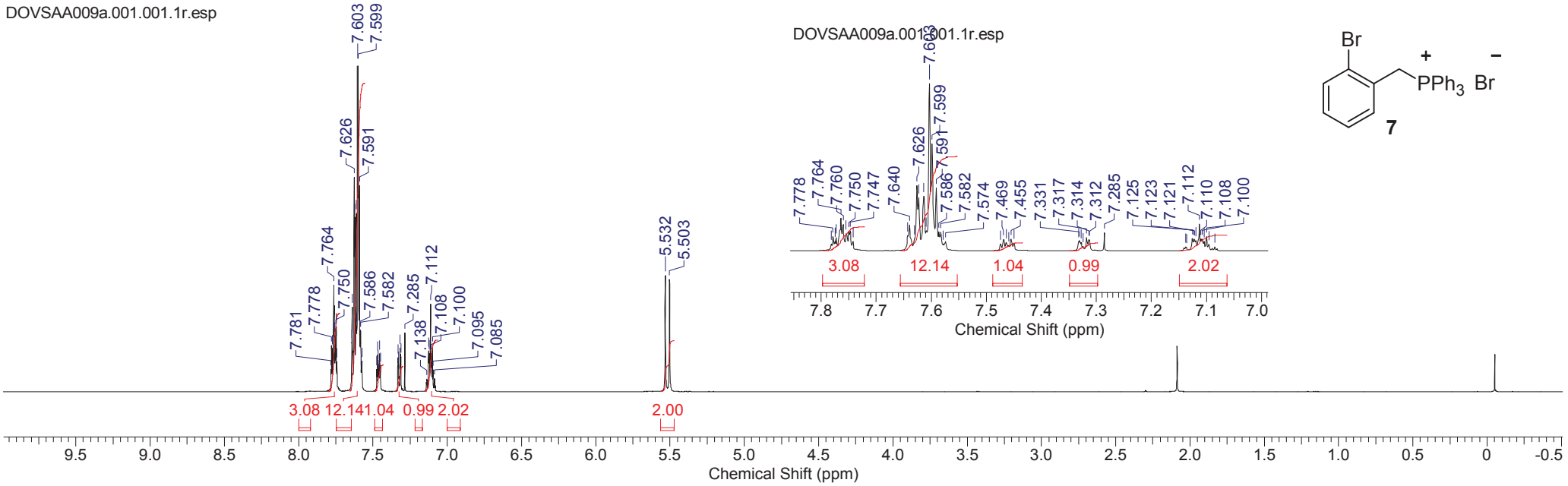
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5.503
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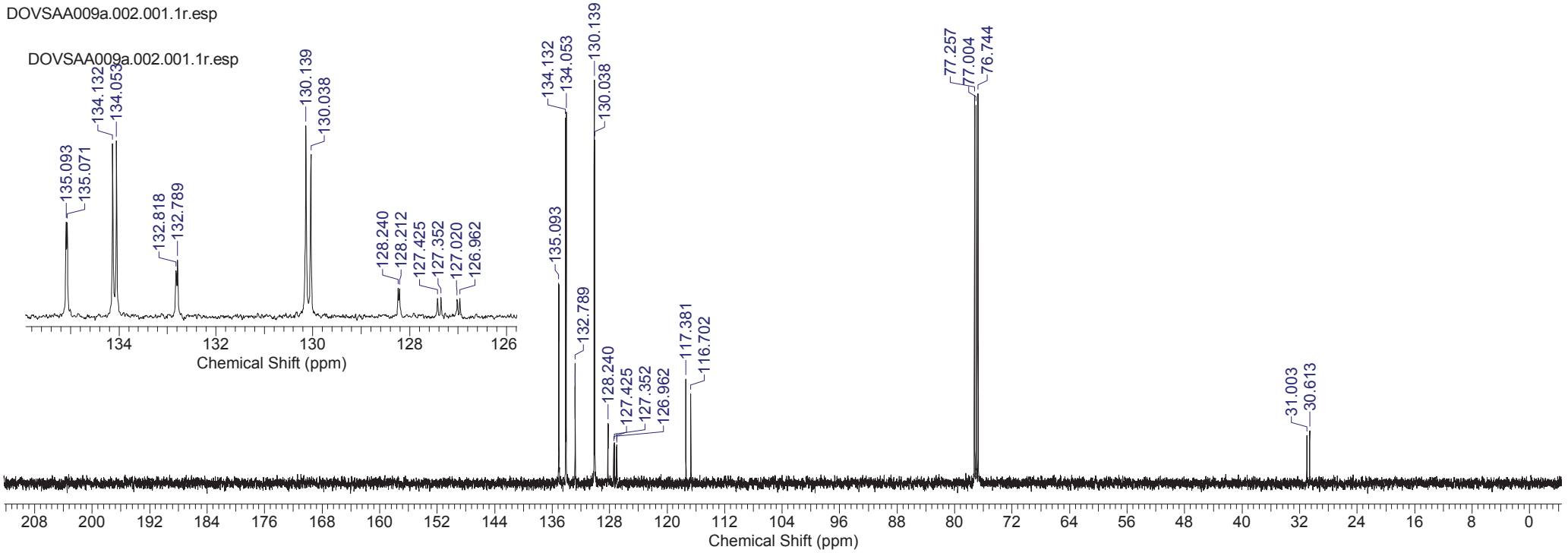
PPh3 Br
7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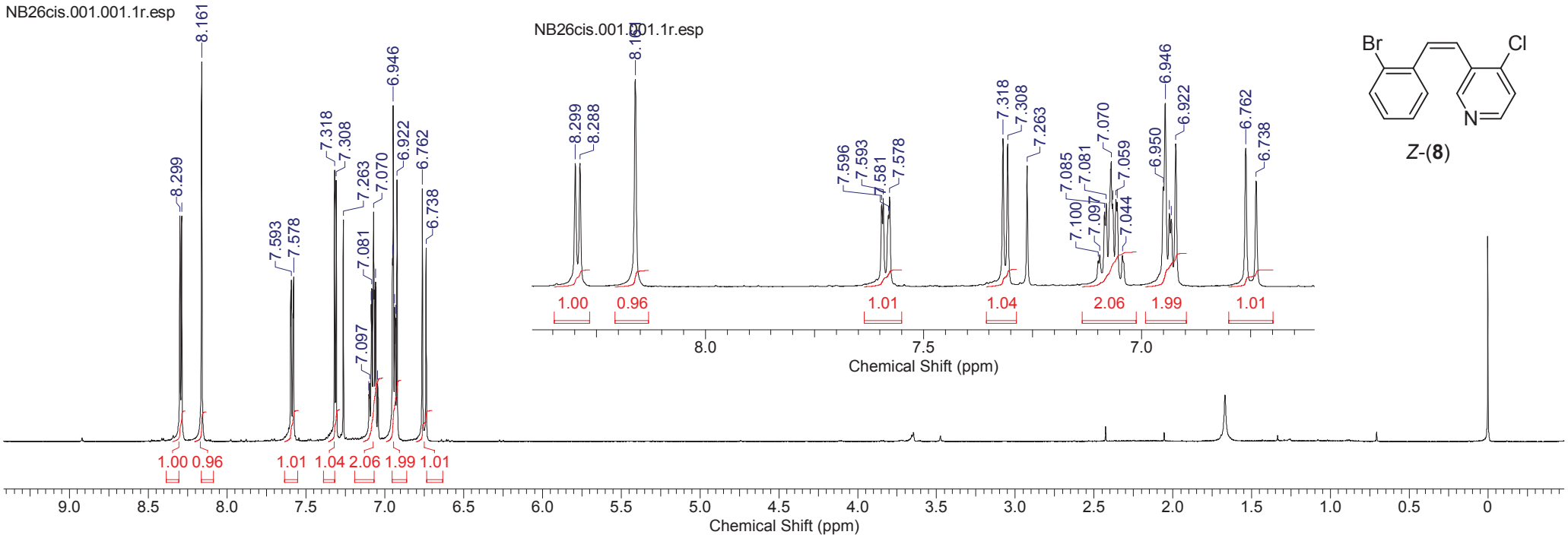
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Chemical Shift (ppm)
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Cl
N
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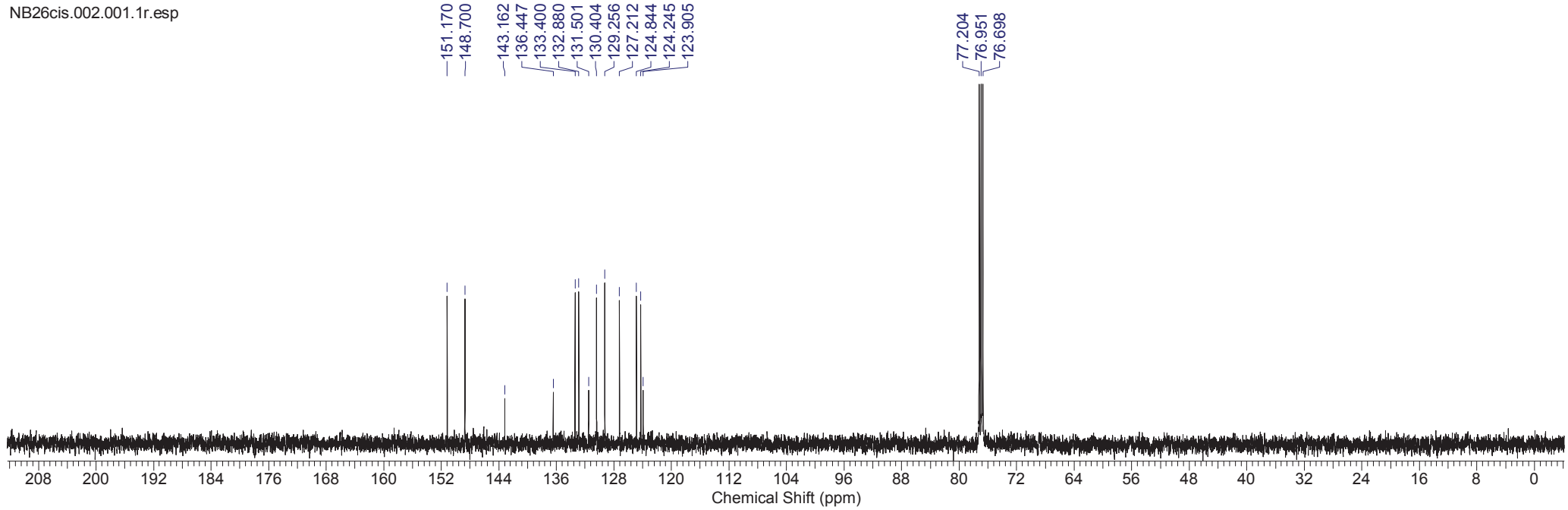
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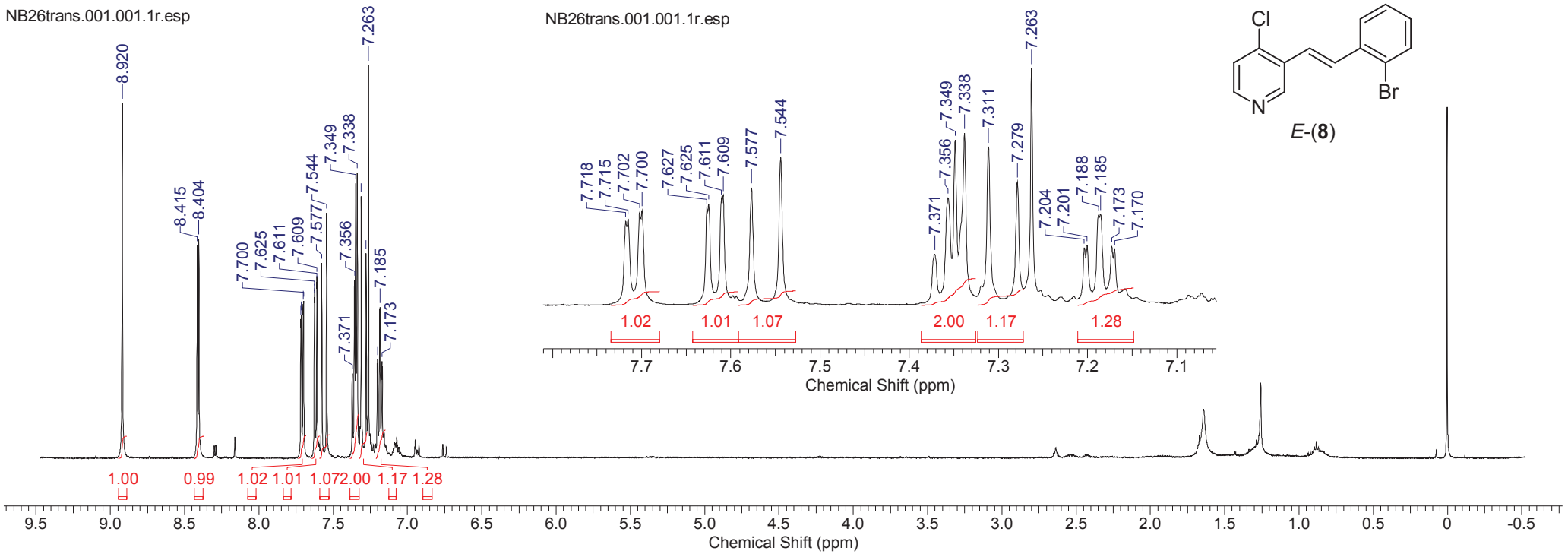
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Chemical Shift (ppm)
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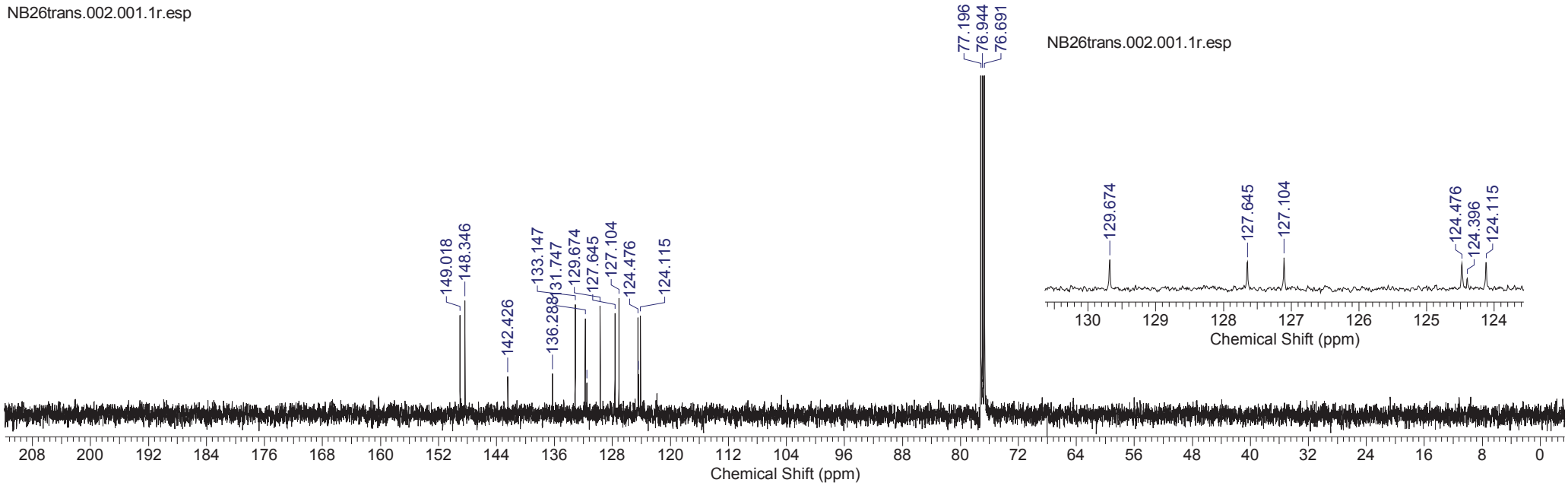
N
Br
E-(8)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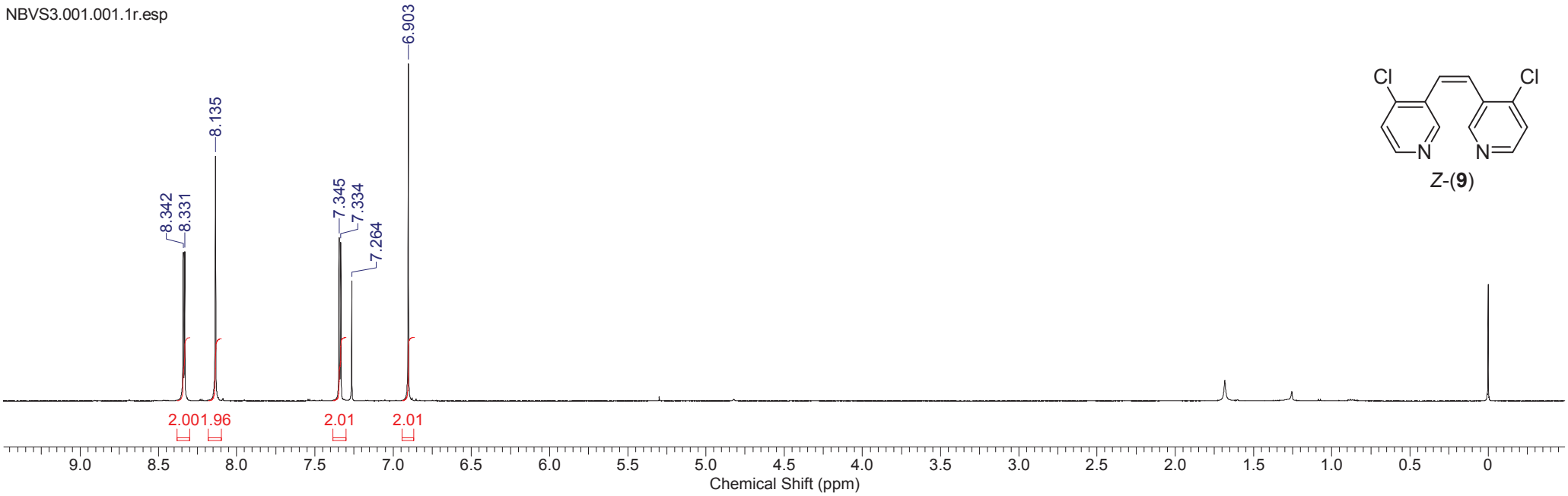

Z-(**9**)

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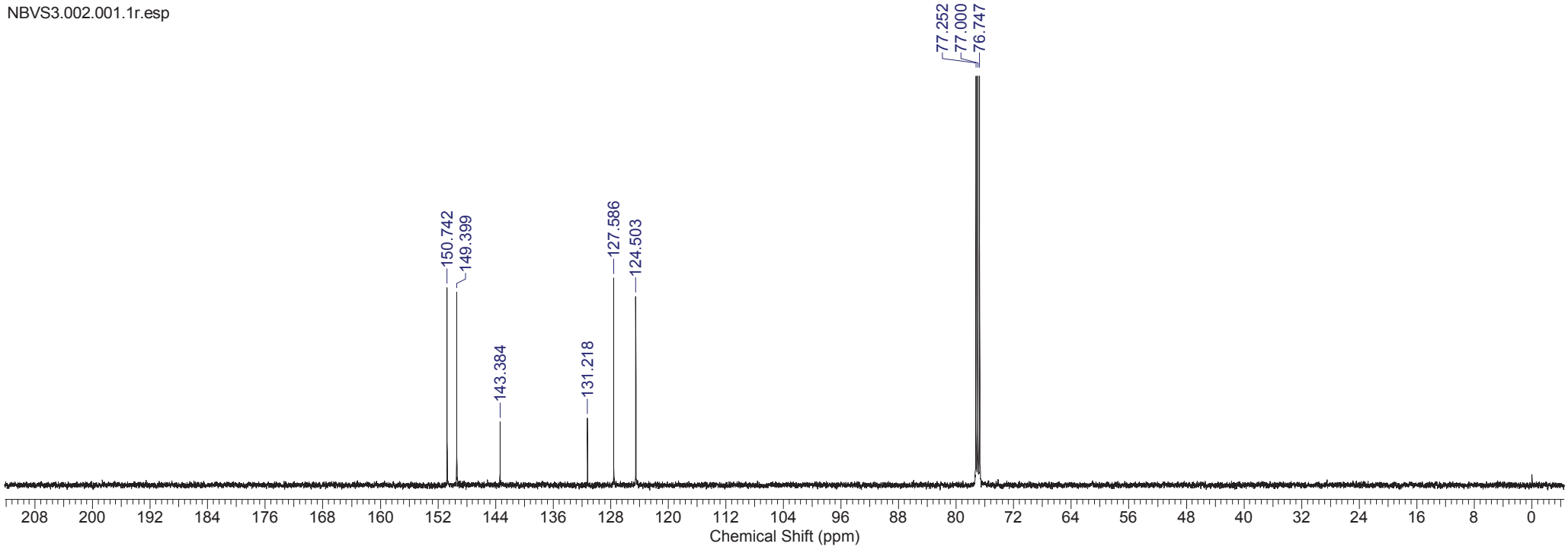

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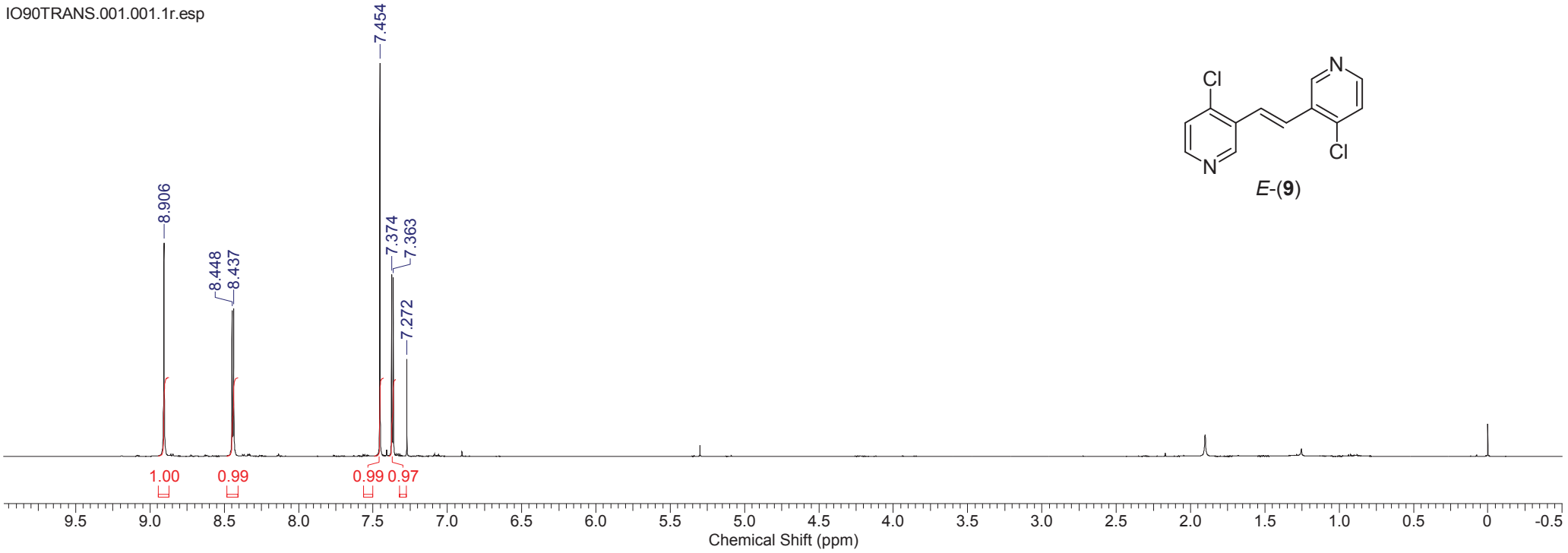

E-(**9**)

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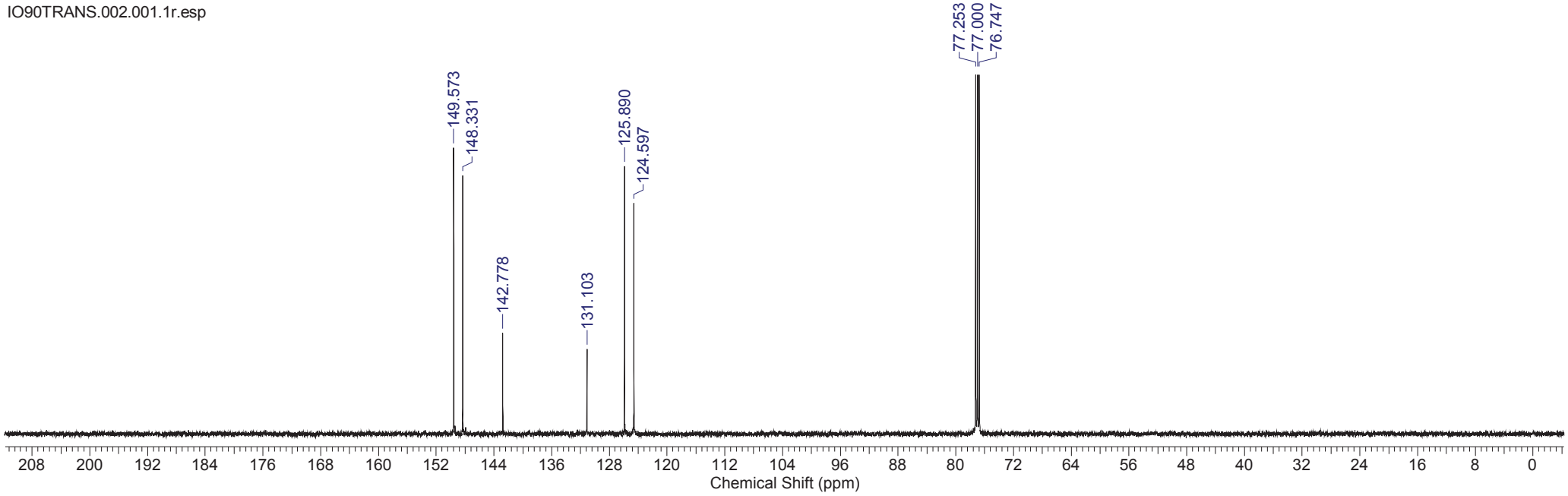
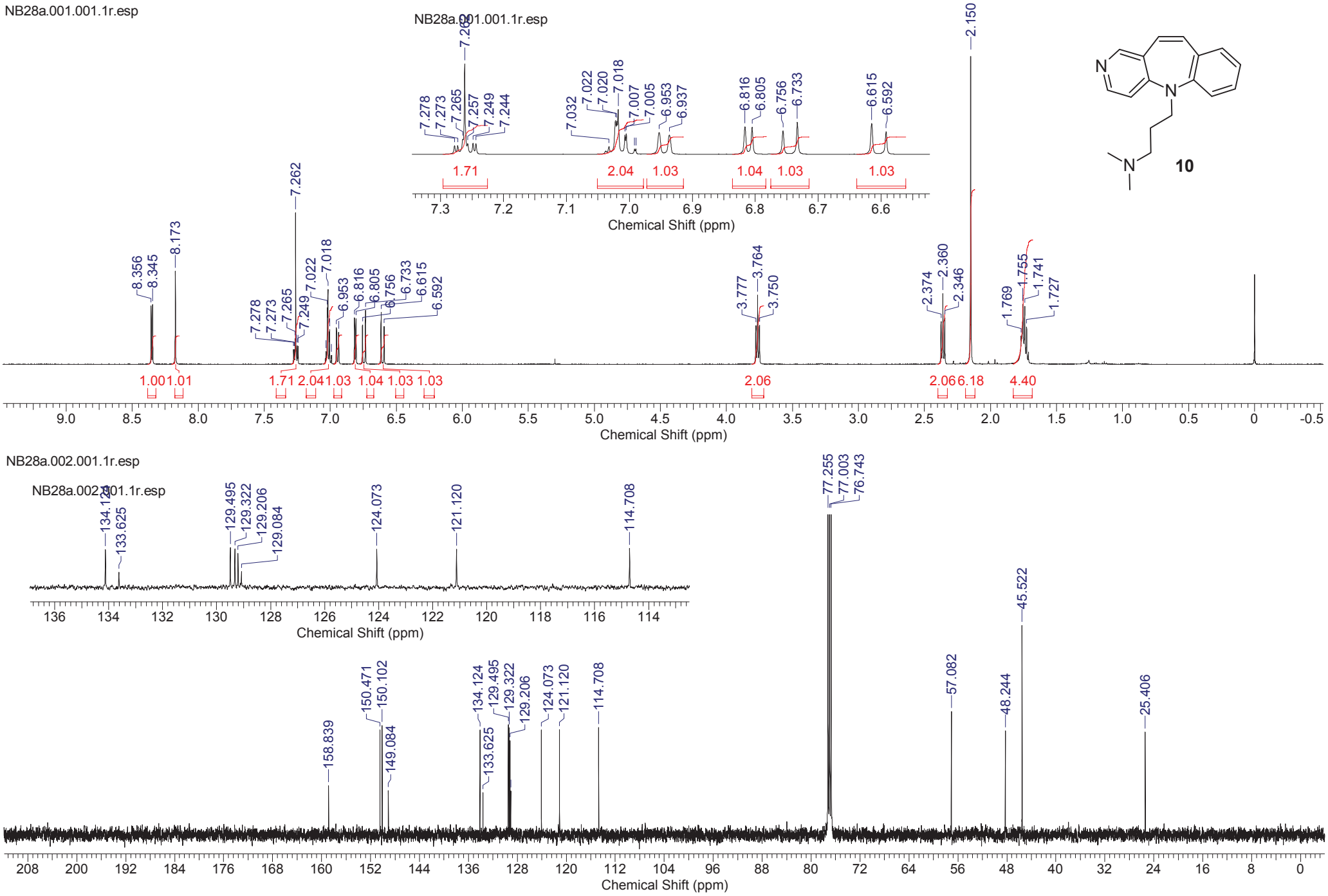
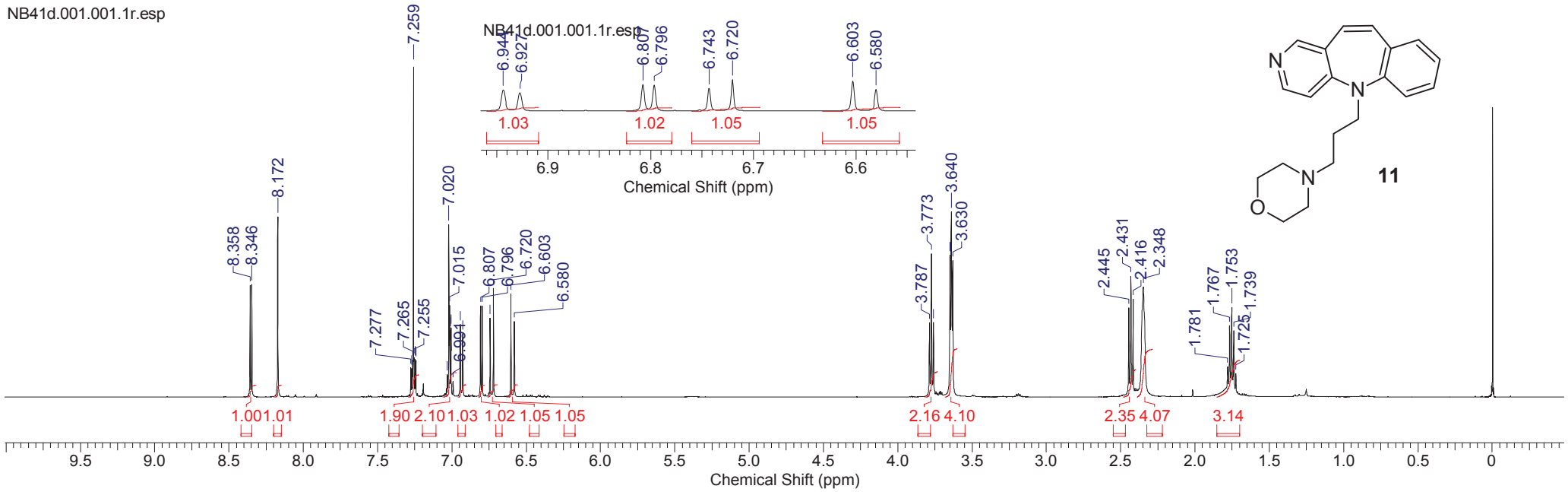
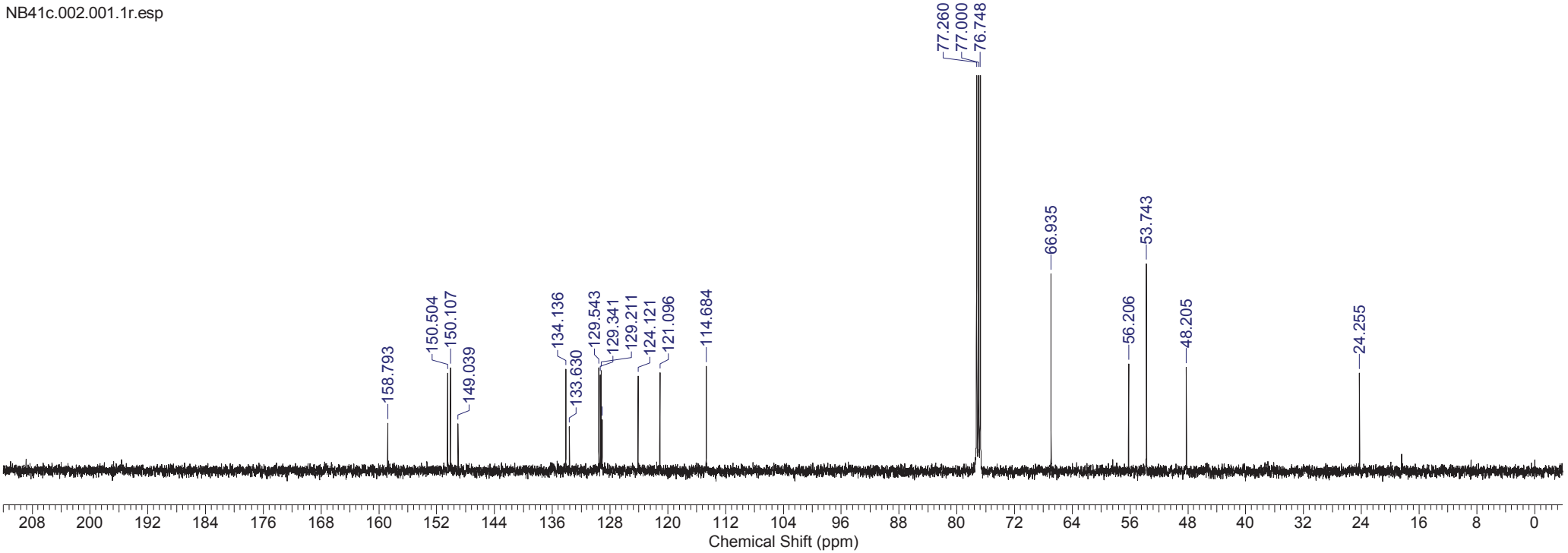
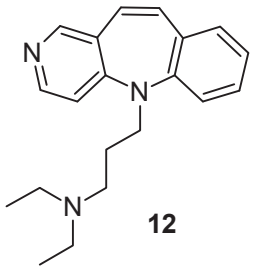



NB28a.001.001.1r.esp
NB28a.001.001.1r.esp
NB28a.002.001.1r.esp
NB28a.002.001.1r.esp
10
Chemical Shift (ppm)
Chemical Shift (ppm)
Chemical Shift (ppm)
Chemical Shift (ppm)


NB41d.001.001.1r.esp
7.259
8.358
8.346
8.172
7.277
7.265
7.255
7.020
7.015
7.001
6.807
6.796
6.720
6.603
6.580
3.787
3.773
3.640
3.630
2.445
2.431
2.416
2.348
1.781
1.767
1.753
1.739
1.725
1.00 1.01 1.90 2.10 1.03 1.02 1.05 1.05 2.16 4.10 2.35 4.07 3.14
Chemical Shift (ppm)
NB41d.001.001.1r.esp
6.944
6.927
6.807
6.796
6.743
6.720
6.603
6.580
1.03 1.02 1.05 1.05
Chemical Shift (ppm)
11

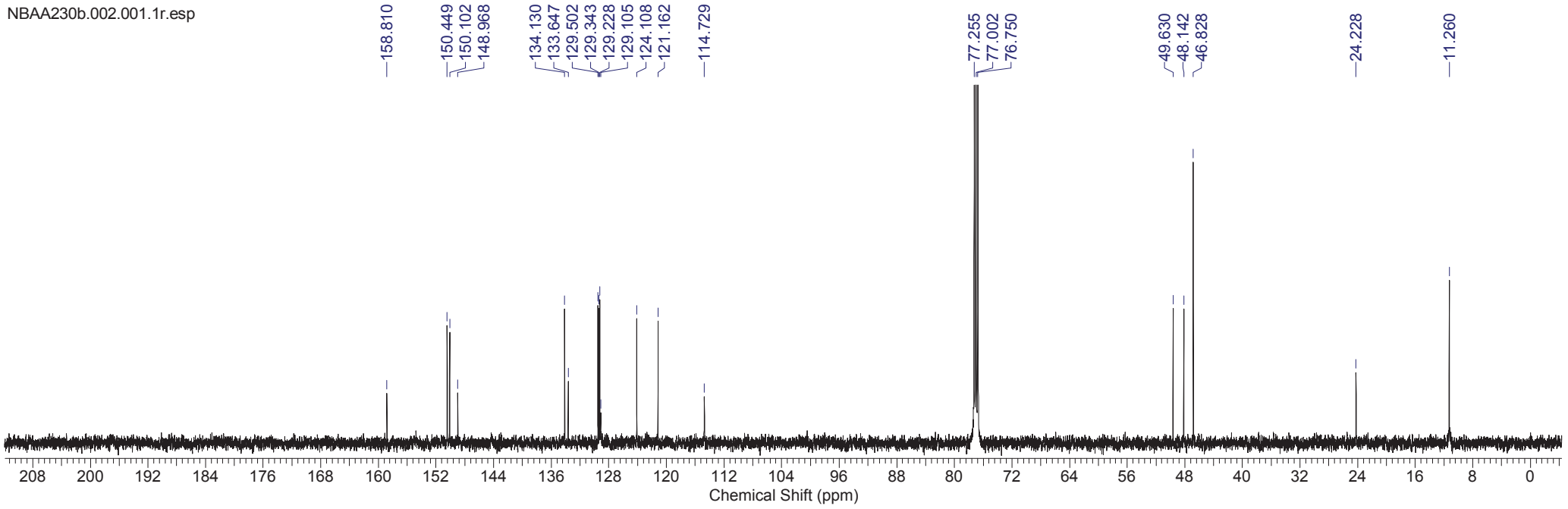

NB41c.002.001.1r.esp
77.260
77.000
76.748
158.793
150.504
150.107
149.039
134.136
133.630
129.543
129.341
129.211
124.121
121.096
114.684
66.935
56.206
53.743
48.205
24.255
Chemical Shift (ppm)

NBAA230b.001.001.1r.esp

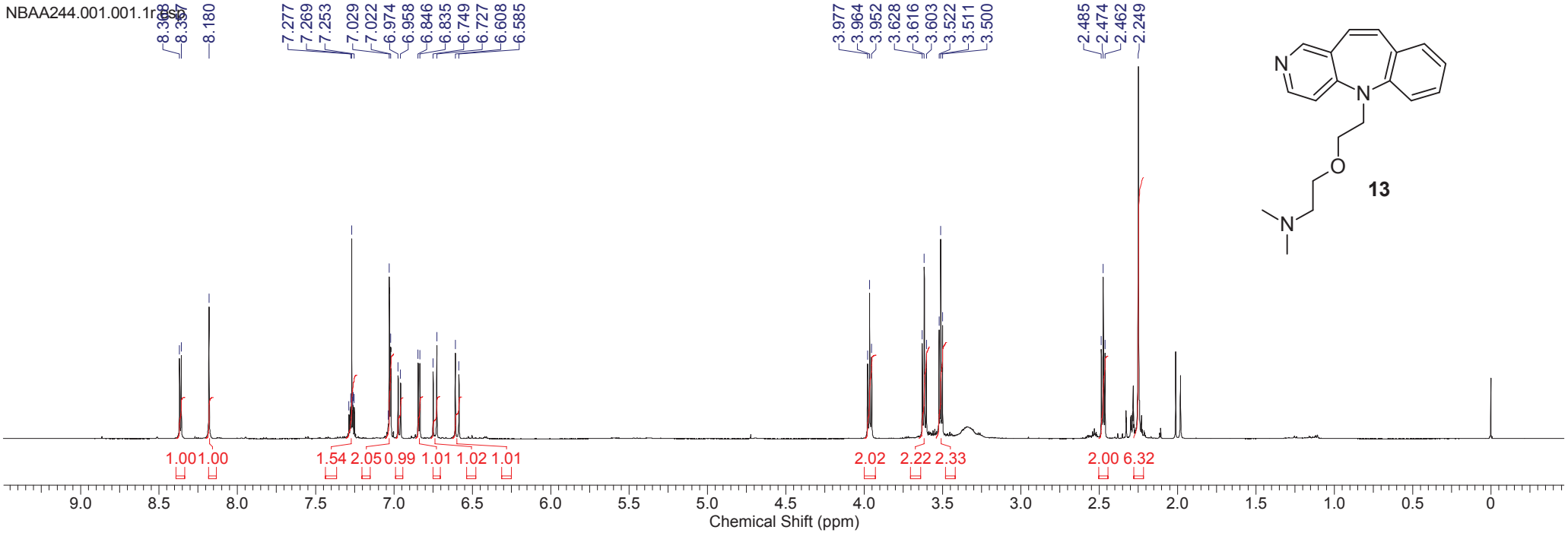


12

NBAA230b.002.001.1r.esp

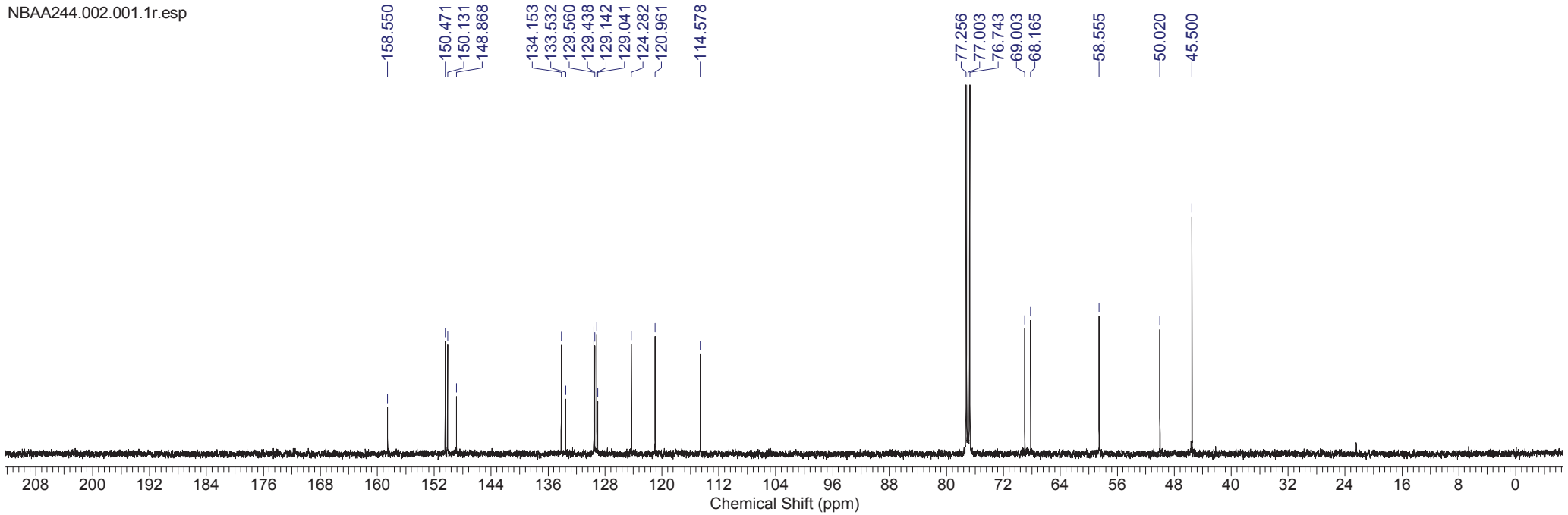


NBAA244.001.001.1r.esp

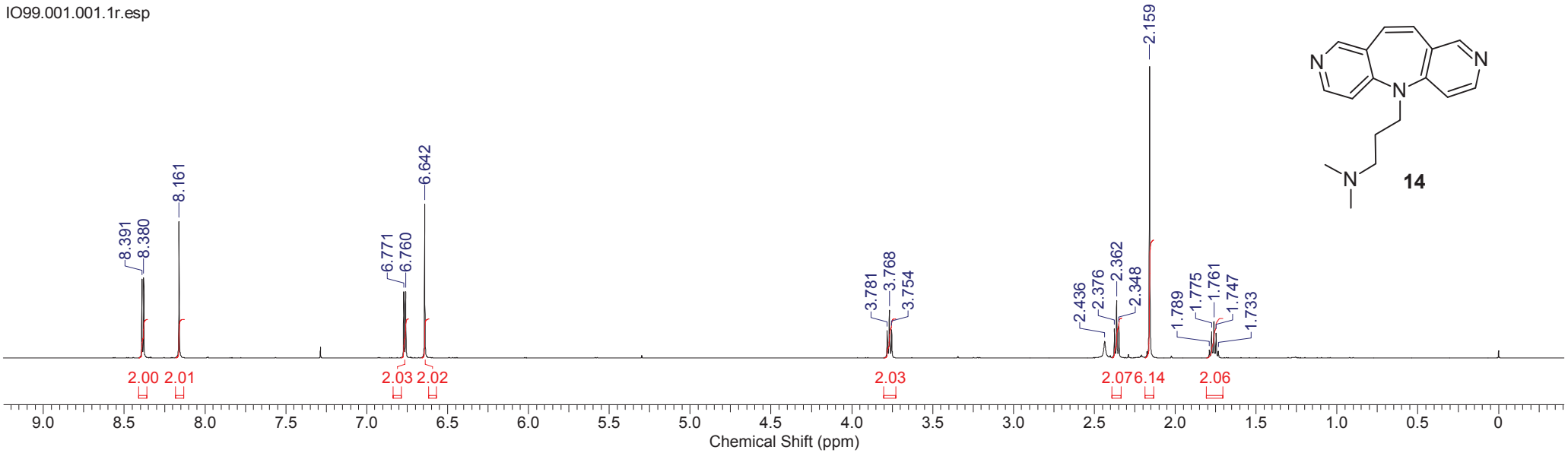


13

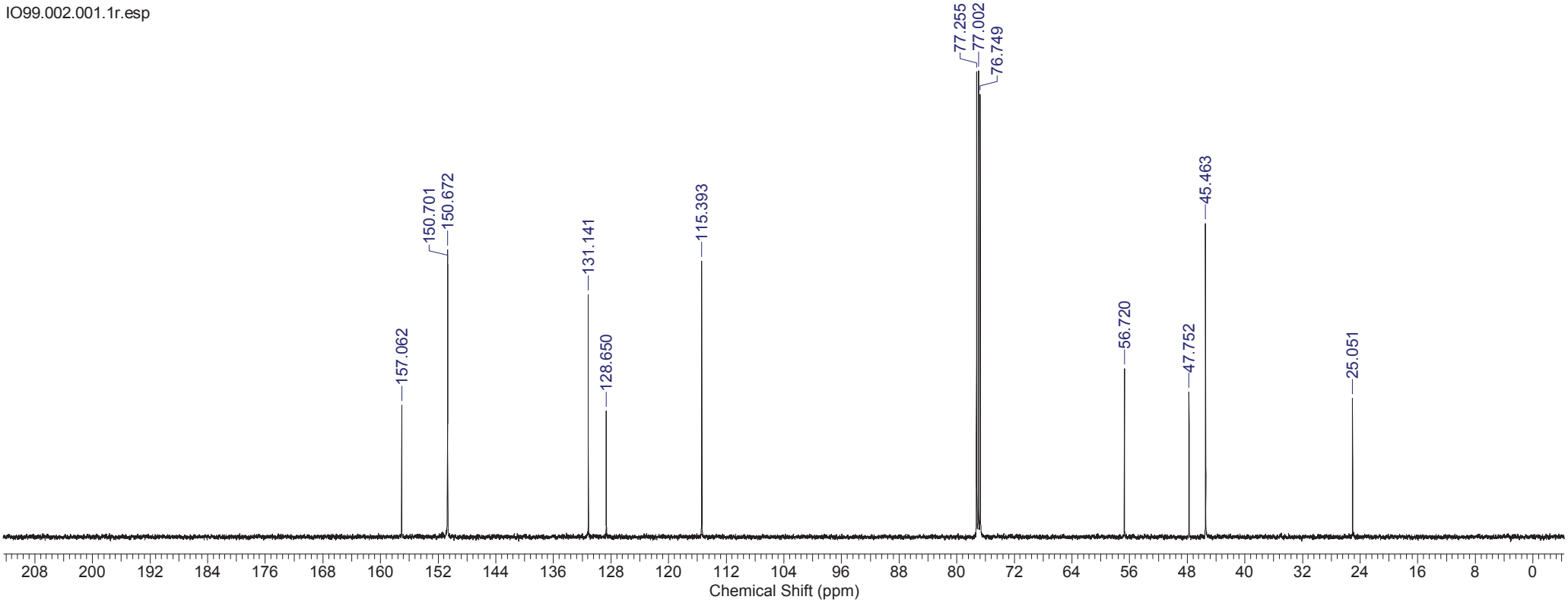
NBAA244.002.001.1r.esp



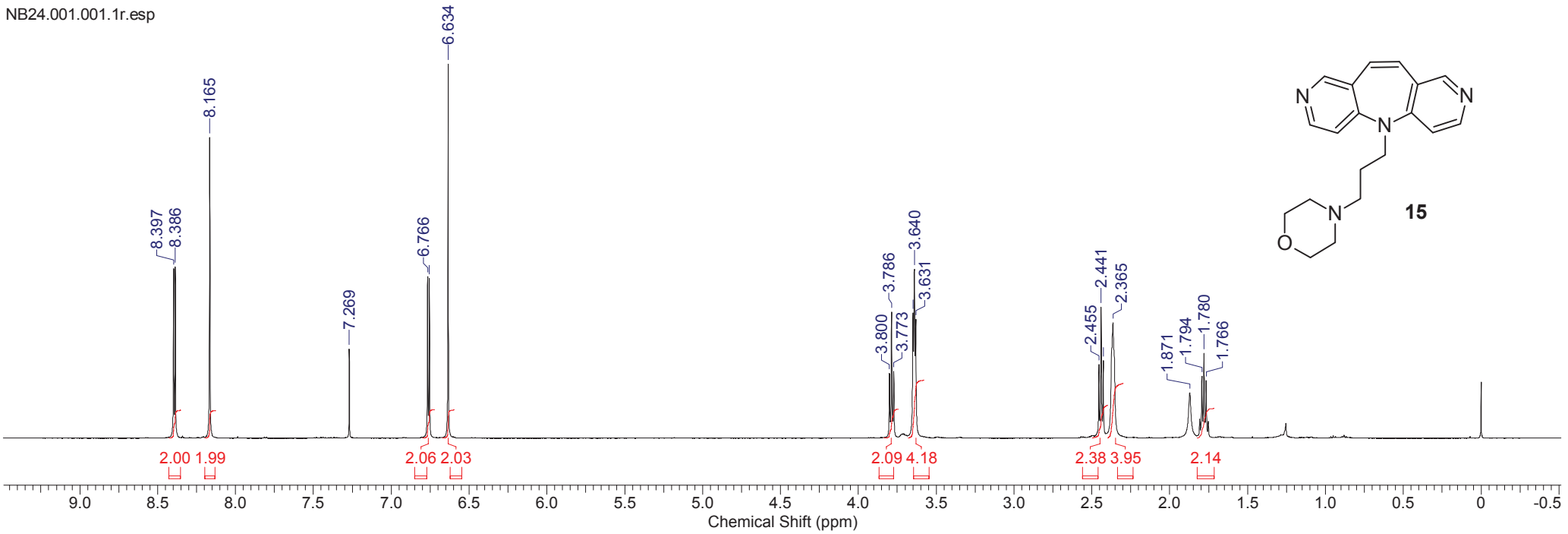
IO99.001.001.1r.esp



IO99.002.001.1r.esp

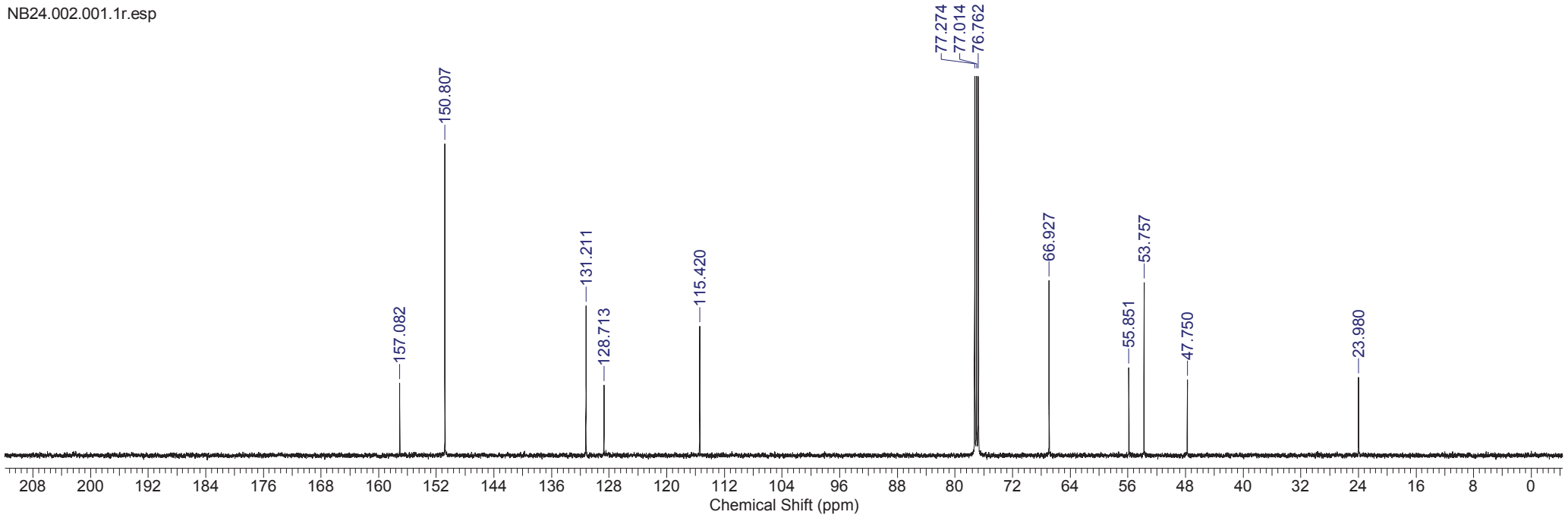


NB24.001.001.1r.esp

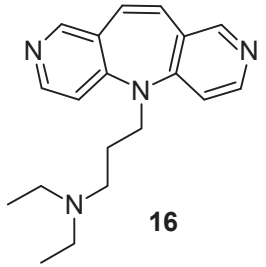


15

NB24.002.001.1r.esp

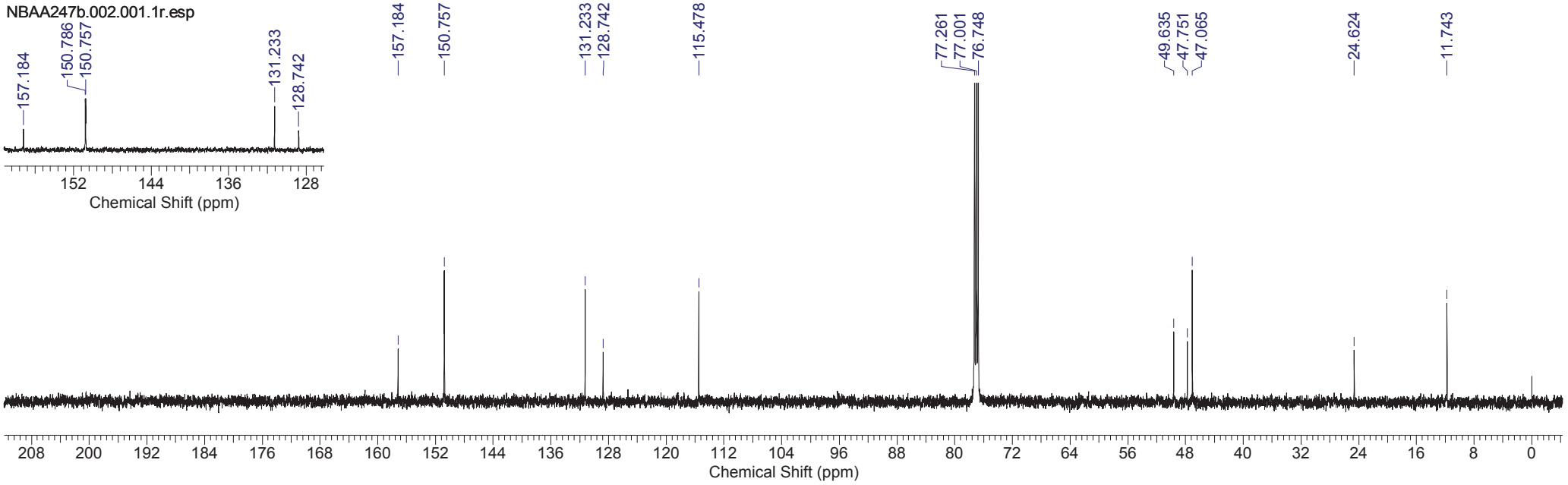


NBAA247b.001.001.1r.esp

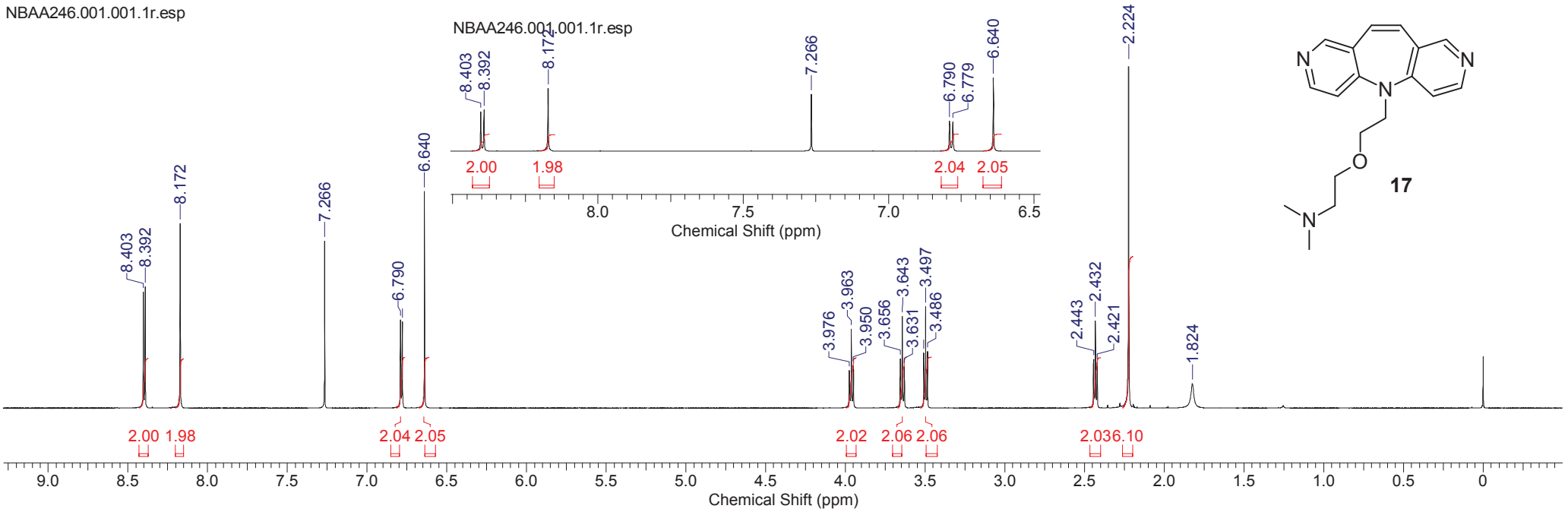


16

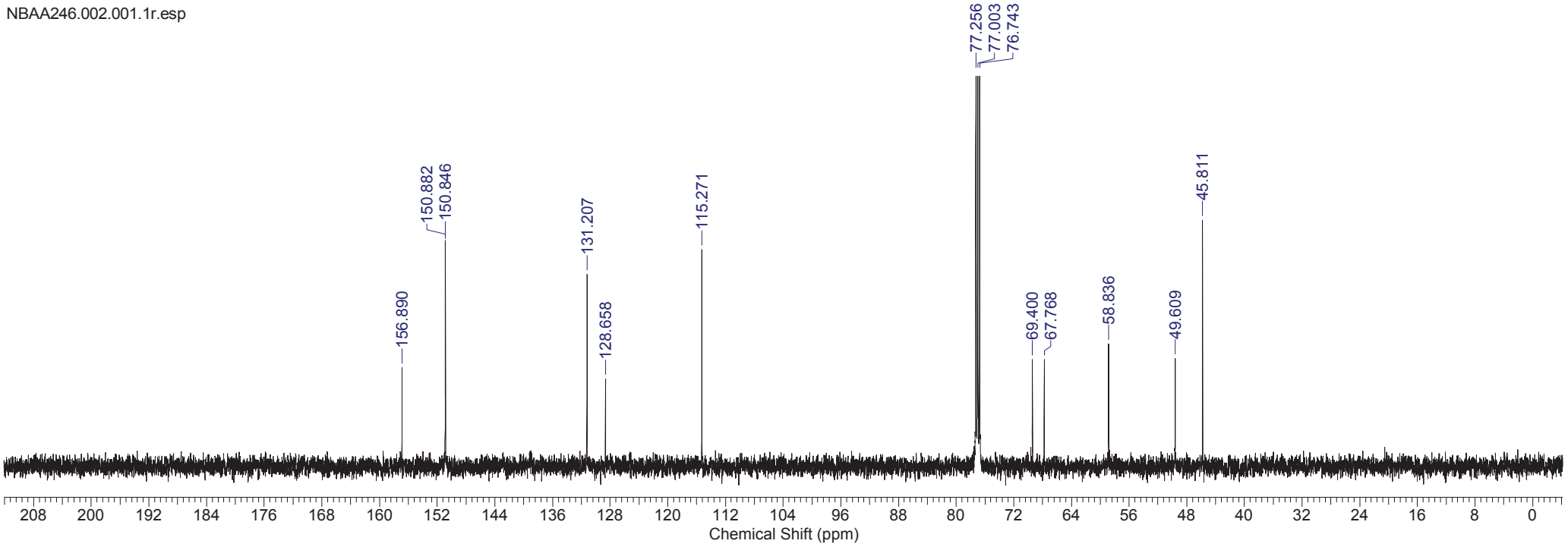
NBAA247b.002.001.1r.esp

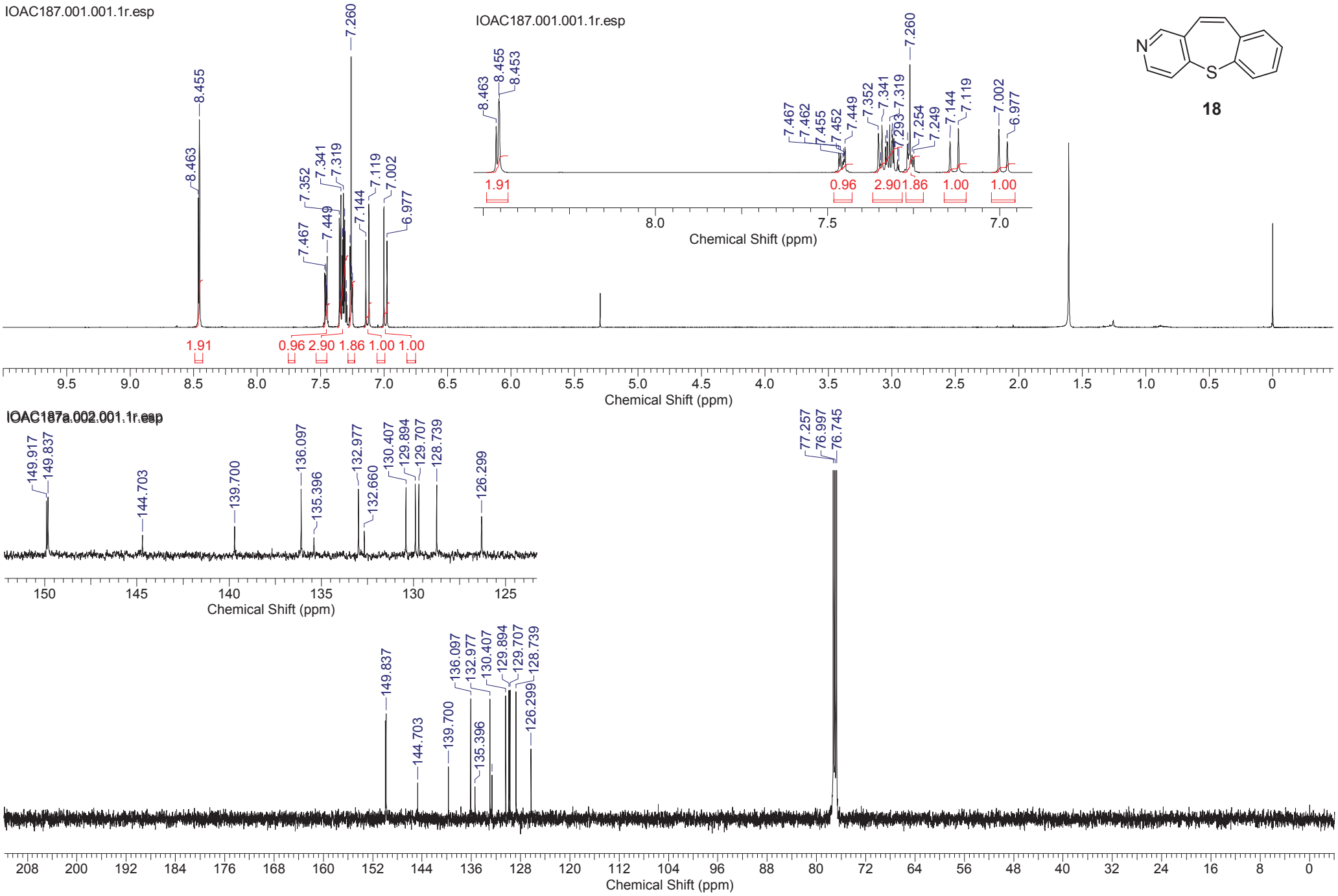


NBAA246.001.001.1r.esp

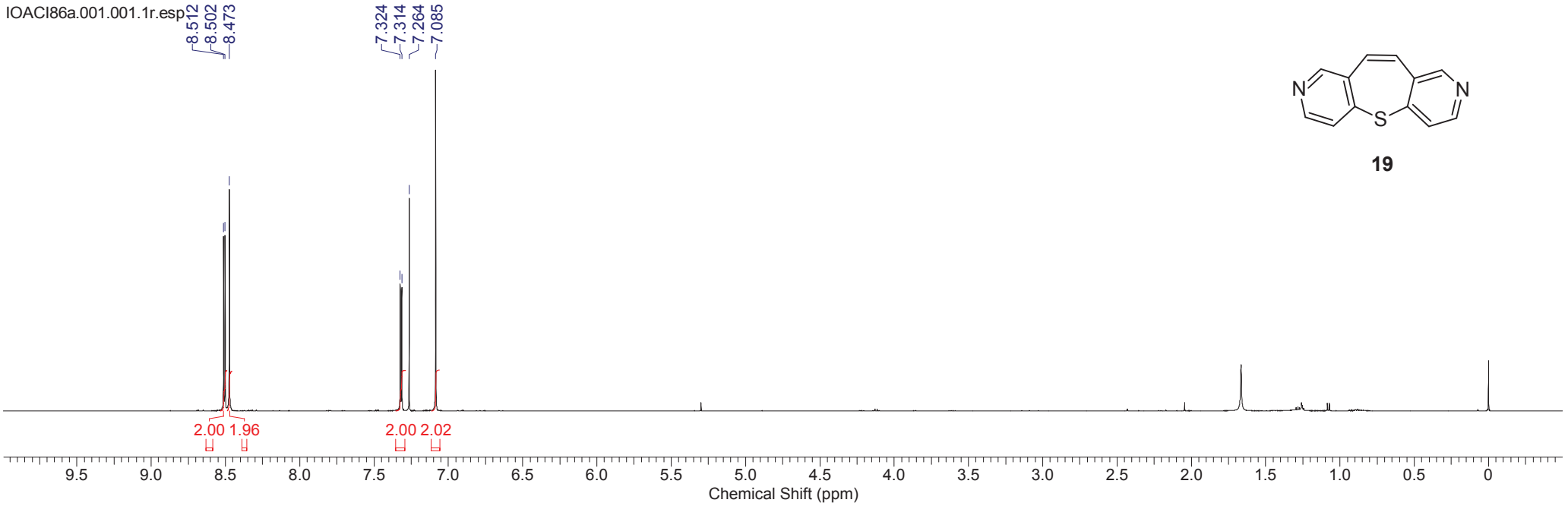


NBAA246.002.001.1r.esp




IOAC187.001.001.1r.esp
8.463
8.455
7.467
7.462
7.455
7.452
7.449
7.352
7.341
7.319
7.293
7.260
7.254
7.249
7.144
7.119
7.002
6.977
1.91
0.96
2.90
1.86
1.00
1.00
Chemical Shift (ppm)
18
IOAC187a.002.001.1r.esp
149.917
149.837
144.703
139.700
136.097
135.396
132.977
132.660
130.407
129.894
129.707
128.739
126.299
77.257
76.997
76.745
Chemical Shift (ppm)

IOACI86a.001.001.1r.esp



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IOAC186.002.001.1r.esp