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## Supporting Information

### Double Palladium Catalyzed Synthesis of Azepines

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#### Supporting Information Contents:

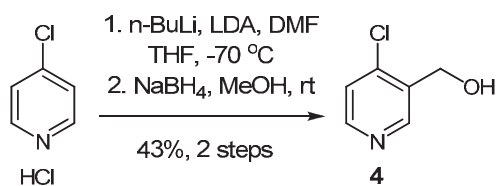
##### 1) General Information

##### 2) Experimental Procedures and Characterization Data for Products

##### 3) <sup>1</sup>H NMR and <sup>13</sup>C NMR Copies of Products

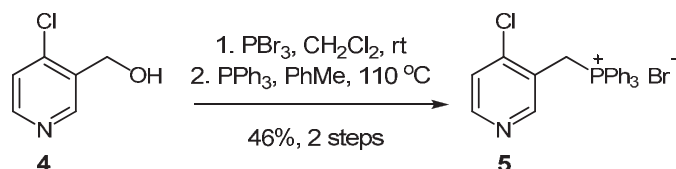
##### 4) References

**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. <sup>1</sup>H and <sup>13</sup>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 ( $\delta$ ) 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  $\times$  2.1 mm i.d. 1.8  $\mu$ m) 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<sup>-1</sup>, 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  $\times$  0.25 mm  $\times$  0.25  $\mu$ m) 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 °C (10 °C/min), injection volume = 1  $\mu$ L, temperature = 250 °C, temperature (FID detector) = 300 °C, and EI mass spectra range: 40-550 m/z. Lobar LichroPrep Si 60 (40-63  $\mu$ m) 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<sub>3</sub>) stands for combination MeOH/NH<sub>3</sub> aq = 9:1, and the solution CH<sub>2</sub>Cl<sub>2</sub> (PhMe) corresponds to CH<sub>2</sub>Cl<sub>2</sub>/PhMe = 99:1.



#### 4-Chloropyridine-3-methanol (4).<sup>1</sup>

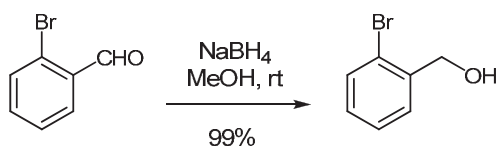
To a solution of  $i\text{Pr}_2\text{NH}$  (0.670 mL, 4.78 mmol) in THF (2.0 mL) 1.6 M *n*-BuLi in hexane (2.43 mL, 3.90 mmol) was added dropwise at  $-78\text{ }^\circ\text{C}$  under Ar. After stirring for 5 min at  $0\text{ }^\circ\text{C}$  the mixture was cooled to  $-78\text{ }^\circ\text{C}$  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  $0\text{ }^\circ\text{C}$  under Ar. After stirring at room temperature for 30 min the reaction was cooled to  $-78\text{ }^\circ\text{C}$  and prepared LDA solution was added. Upon stirring at the same temperature for 30 min DMF (380  $\mu\text{L}$ , 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  $\text{NaHCO}_3$ , it was extracted with  $\text{CH}_2\text{Cl}_2$ , dried over  $\text{Na}_2\text{SO}_4$ , and evaporated to give crude aldehyde as brown oil. The obtained aldehyde was dissolved into MeOH (25 mL), and  $\text{NaBH}_4$  (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  $\text{CH}_2\text{Cl}_2$ , followed by drying over anhydrous  $\text{Na}_2\text{SO}_4$ , and evaporation to dryness. Column chromatography using hexane/EtOAc = 8:2 afforded desired compound **4** as pale yellow powder (206 mg, 43%), mp =  $87\text{--}90\text{ }^\circ\text{C}$ .  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  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).  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ . (+)ESI-HRMS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  144.02063 (error -3.01 ppm).



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

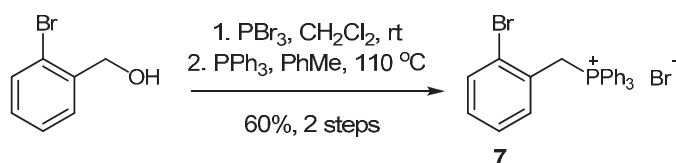
To a solution of alcohol **4** (0.80 g, 5.6 mmol) in  $\text{CH}_2\text{Cl}_2$  (45 mL)  $\text{PBr}_3$  (1.0 mL, 11 mmol) was added. After stirring for 2 h at room temperature the reaction mixture was cooled to  $0\text{ }^\circ\text{C}$  it was neutralized with  $\text{NaHCO}_3$ , extracted with  $\text{CH}_2\text{Cl}_2$ , dried over  $\text{Na}_2\text{SO}_4$ , and evaporated to dryness. Column chromatography using hexane/EtOAc = 1:1 afforded product as red oil. Obtained intermediate was dissolved in PhMe (18 mL) and  $\text{PPh}_3$  (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  $45\text{ }^\circ\text{C}$ . Desired phosphonium bromide was obtained as white powder (1.2 g, 46%).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  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).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ .

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



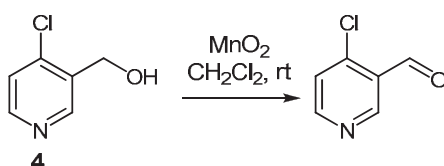
#### (2-Bromobenzene-1-yl)methanol.

2-Bromobenzaldehyde (1.26 mL, 10.8 mmol) was dissolved in MeOH (25 mL), and NaBH<sub>4</sub> (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<sub>2</sub>Cl<sub>2</sub>, organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The desired product was obtained as pale yellow oil (2.00 g, 99%) and was used without any further purifications. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) 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). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 139.7, 132.6, 129.1, 128.8, 127.6, 122.5, 65.0. GC-MS (*m/z* (%)): 186.0 ([M]<sup>+</sup> (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<sup>-1</sup>.



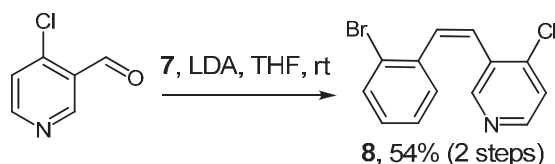
#### [(2-Bromobenzene-1-yl)methyl](triphenyl)phosphonium bromide (**7**).

(2-Bromobenzene-1-yl)methanol (2.00 g, 10.7 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL), and PBr<sub>3</sub> (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<sub>3</sub>, extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>, 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<sub>3</sub> (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%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 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). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>.



#### 4-Chloropyridine-3-carbaldehyde.

Alcohol **4** (92 mg, 0.65 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) followed by addition of MnO<sub>2</sub> (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.

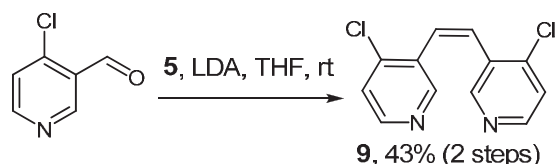


### 1,3'-(*Z*)-Ethene-1,2-diyl-1-(2-bromobenzene)-2-(4-chloropyridine) (**8**).

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<sub>3</sub>. The aqueous phase was separated and extracted with EtOAc (3 × 10 mL). The organic extracts were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuum and purified by column chromatography (RP, CH<sub>2</sub>Cl<sub>2</sub> (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. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 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). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M + H]<sup>+</sup> 293.96877 (error 2.73 ppm).

(*E*)-**8**: white solid, mp = 46-48 °C <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 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). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>. GC-MS, RT 24.00 min (*m/z* (%)): 294.9 ([M]<sup>+</sup> (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]<sup>+</sup> 293.96765 (error -1.09 ppm).



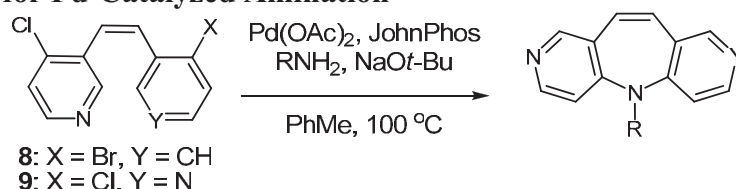
### 3,3'-(*Z*)-Ethene-1,2-diylbis(4-chloropyridine) (**9**).

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<sub>2</sub>, hexane/EtOAc = 8:2).

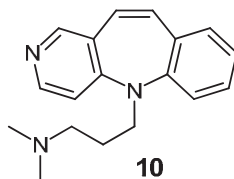
(*Z*)-**9**: light yellow powder, mp 130-131 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.34 (d, *J* = 5.5 Hz, 1H), 8.14 (s, 1H), 7.34 (d, *J* = 5.5 Hz, 1H), 6.90 (s, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 150.7, 149.4, 143.4, 131.2, 127.6, 124.5. IR (KBr): 3431, 3041, 2928, 2856, 1631, 1571, 1550, 1463, 1401, 1301, 1219, 1193, 1075, 972, 870, 816 cm<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M + 2H]<sup>2+</sup> 126.00988 (error -4.92 ppm), [M + H]<sup>+</sup> 251.01382 (error 0.38 ppm).

(*E*)-**9**: white solid, mp = 127-129 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 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). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 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<sup>-1</sup>. GC-MS, RT 23.29 min (*m/z* (%)): 249.9 ([M]<sup>+</sup> (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]<sup>+</sup> 251.01343 (error -1.18 ppm).

## General procedure for Pd-Catalyzed Amination

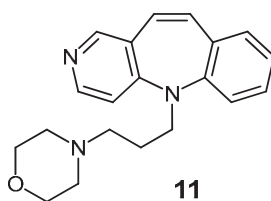


Reaction tube containing a stirring bar was evacuated and backfilled with Ar. The tube was then charged with Pd(OAc)<sub>2</sub> (5 mol %), JohnPhos (10 mol %) and NaO*t*-Bu (2.8 eq) and filled with Ar. Toluene was added. After stirring at room temperature for 5 min, aryl halide (1 eq) and amine (3 eq) 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<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH (NH<sub>3</sub>) = 9/1.



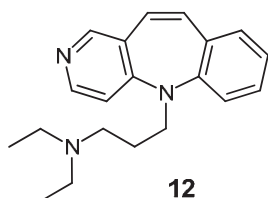
### *N,N*-Dimethyl-3-(5*H*-pyrido[4,3-*b*][1]benzazepin-5-yl)propan-1-amine (10).

Following general procedure, a mixture of **8** (24 mg, 0.080 mmol), 3-dimethylamino-1-propylamine (30  $\mu$ L, 0.24 mmol), sodium *tert*-butoxide (22 mg, 0.23 mmol), Pd(OAc)<sub>2</sub> (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%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  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<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M + H]<sup>+</sup> 280.18125 (error: 1.51 ppm).

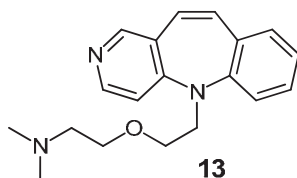


**5**-[3-(Morpholin-4-yl)propyl]-5*H*-pyrido[4,3-*b*][1]benzazepine (**11**). Following general procedure, a mixture of **8** (24 mg, 0.080 mmol), *N*-(3-aminopropyl)morpholine (36  $\mu$ L, 0.24 mmol), sodium *tert*-butoxide (22 mg, 0.23 mmol), Pd(OAc)<sub>2</sub> (0.9 mg, 5 mol %), JohnPhos (2.4 mg, 10 mol %) and toluene (1.5 mL) was stirred at 100 °C for 48 hours. **11**: yellow oil (16 mg, 61%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  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<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M + H]<sup>+</sup> 322.19242 (error: 3.20 ppm).

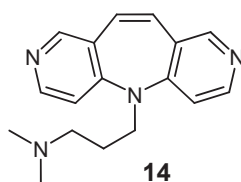




***N,N*-Diethyl-3-(5*H*-pyrido[4,3-*b*][1]benzazepin-5-yl)propan-1-amine (12).** Following general procedure, a mixture of **8** (24 mg, 0.080 mmol), 3-diethylamino-1-propylamine (38  $\mu$ L, 0.24 mmol), sodium *tert*-butoxide (22 mg, 0.23 mmol), Pd(OAc)<sub>2</sub> (0.9 mg, 5 mol %), JohnPhos (2.4 mg, 10 mol %) and toluene (1.5 mL) was stirred at 100 °C for 48 hours. **12**: yellow oil (20 mg, 79%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  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<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M + 2H]<sup>2+</sup> 154.60980 (error: 0.62 ppm), [M + H]<sup>+</sup> 308.21276 (error: 2.05 ppm).

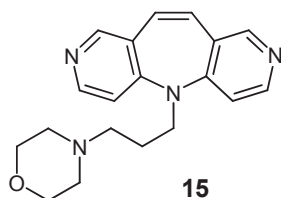


***N,N*-Dimethyl-2-[2-(5*H*-pyrido[4,3-*b*][1]benzazepin-5-yl)ethoxy]ethanamine (13).** Following general procedure, a mixture of **8** (24 mg, 0.080 mmol), 2-(2-dimethylaminoethoxy)ethylamine (35  $\mu$ L, 0.24 mmol), sodium *tert*-butoxide (22 mg, 0.23 mmol), Pd(OAc)<sub>2</sub> (0.9 mg, 5 mol %), 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%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  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<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M + H]<sup>+</sup> 310.19001 (error: -4.46 ppm).



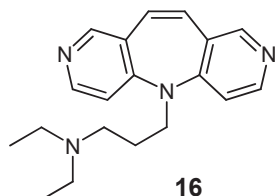
**3-(5*H*-Dipyrido[4,3-*b*:3',4'-*f*]azepin-5-yl)-*N,N*-dimethylpropan-1-amine (14).** Following general procedure, a mixture of **9** (150 mg, 0.597 mmol), 3-dimethylamino-1-propylamine (225  $\mu$ L, 1.80 mmol), sodium *tert*-butoxide (161 mg, 1.68 mmol), Pd(OAc)<sub>2</sub> (6.7 mg, 5 mol %), JohnPhos (18 mg, 10 mol %) and toluene (7.5 mL) was stirred at 100 °C for 24 hours. **14**: yellow oil 146 mg (87%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  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<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M+2H]<sup>2+</sup>, 141.09229 (error 4.33), [M+H]<sup>+</sup> 281.17638 (error 1.10).





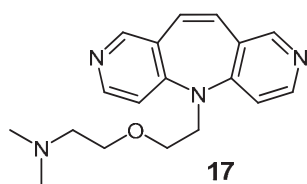
**15**

**5-[3-(Morpholin-4-yl)propyl]-5H-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  $\mu$ L, 0.48 mmol), sodium *tert*-butoxide (43 mg, 0.45 mmol), Pd(OAc)<sub>2</sub> (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%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  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<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M+2H]<sup>2+</sup>, 162.09687 (error -0.55), [M+H]<sup>+</sup> 323.18606 (error: -1.79 ppm).



**16**

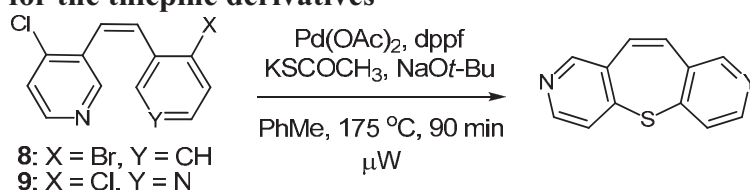
**3-(5H-Dipyrido[4,3-*b*:3',4'-*f*]azepin-5-yl)-*N,N*-diethylpropan-1-amine (16).** Following general procedure, a mixture of **9** (20 mg, 0.080 mmol), 3-diethylamino-1-propylamine (38  $\mu$ L, 0.24 mmol), sodium *tert*-butoxide (22 mg, 0.23 mmol), Pd(OAc)<sub>2</sub> (0.9 mg, 5 mol %), JohnPhos (2.4 mg, 10 mol %) and toluene (1.5 mL) was stirred at 100 °C for 24 hours. **16**: yellow oil (12 mg, 47%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  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<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M+H]<sup>+</sup> 309.20590 (error: -4.78 ppm).



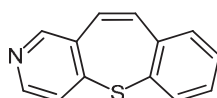
**17**

**2-[2-(5H-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-ethoxy)-ethylamine (35  $\mu$ L, 0.24 mmol), sodium *tert*-butoxide (22 mg, 0.23 mmol), Pd(OAc)<sub>2</sub> (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%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  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<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M+2H]<sup>2+</sup>, 156.09666 (error -1.90), [M+H]<sup>+</sup> 311.18522 (error: -4.55 ppm).

## General procedure for the thiepine derivatives

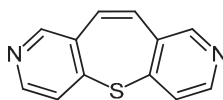


Reaction tube containing a stirring bar was evacuated and backfilled with Ar. The tube was charged with Pd(OAc)<sub>2</sub> (5 mol %), dppf (10 mol %), NaOt-Bu (1.2 eq), aryl halide (1 eq) and KSCoCH<sub>3</sub> (1.2 eq) and evacuated and backfilled with Ar. The flask was capped with a rubber septum, 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<sub>2</sub>, Hexane/EtOAc = 1/1.



**18**

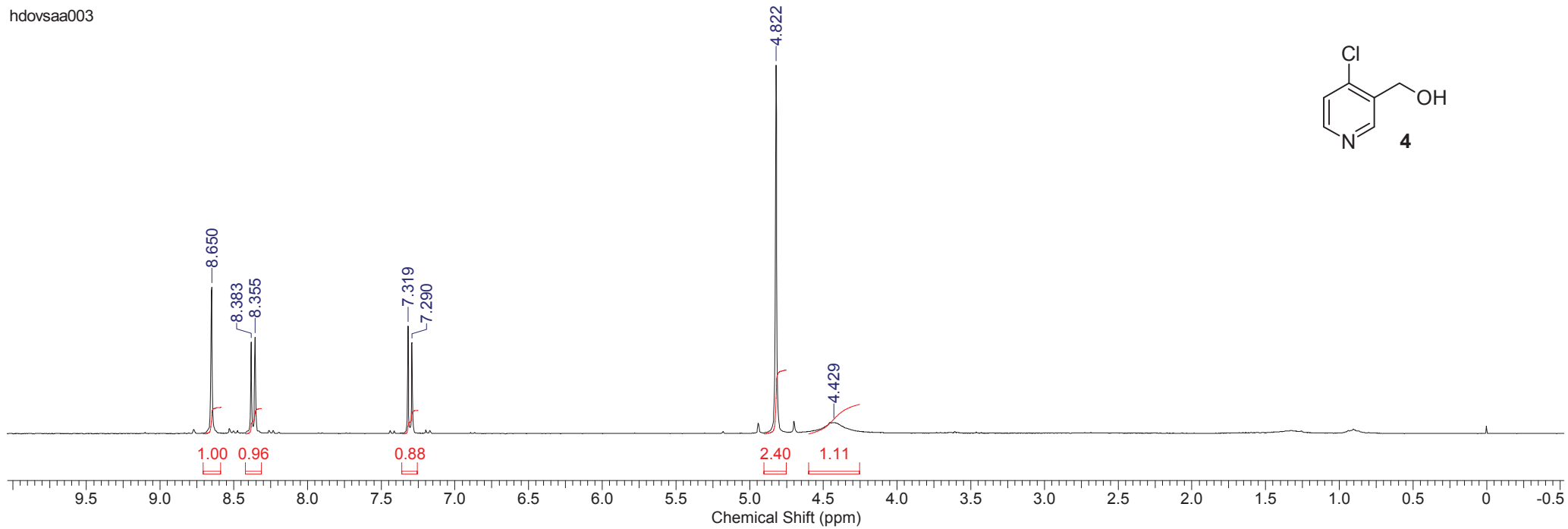
**[1]Benzothiepine[3,2-*c*]pyridine (18).** Following general procedure, a mixture of **8** (35 mg, 0.12 mmol), KSCoCH<sub>3</sub> (16 mg, 0.14 mmol), sodium *tert*-butoxide (14 mg, 0.14 mmol), Pd(OAc)<sub>2</sub> (1.3 mg, 5 mol %), dppf (6.6 mg, 10 mol %) and toluene (1.5 mL) was heated in a Biotage Initiator 2.5 microwave at 175 °C for 90 min. **18**: white solid (13 mg, 51%), mp 80-82 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 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). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 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<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M + H]<sup>+</sup> 212.05209 (error -3.58 ppm).



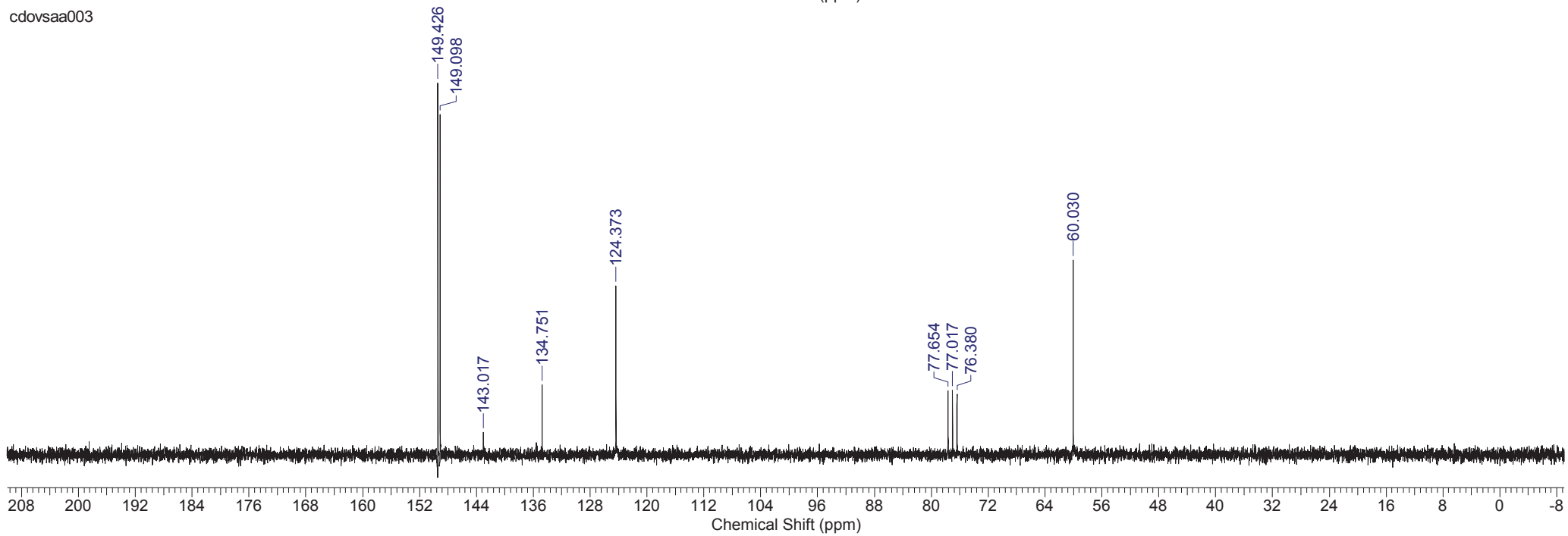
**19**

**Thiepine[3,2-*c*:6,7-*c'*]dipyridine (19).** Following general procedure, a mixture of **9** (30 mg, 0.12 mmol), KSCoCH<sub>3</sub> (16 mg, 0.14 mmol), sodium *tert*-butoxide (14 mg, 0.14 mmol), Pd(OAc)<sub>2</sub> (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. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 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). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 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<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M + H]<sup>+</sup> 213.04721 (error -4.14 ppm).

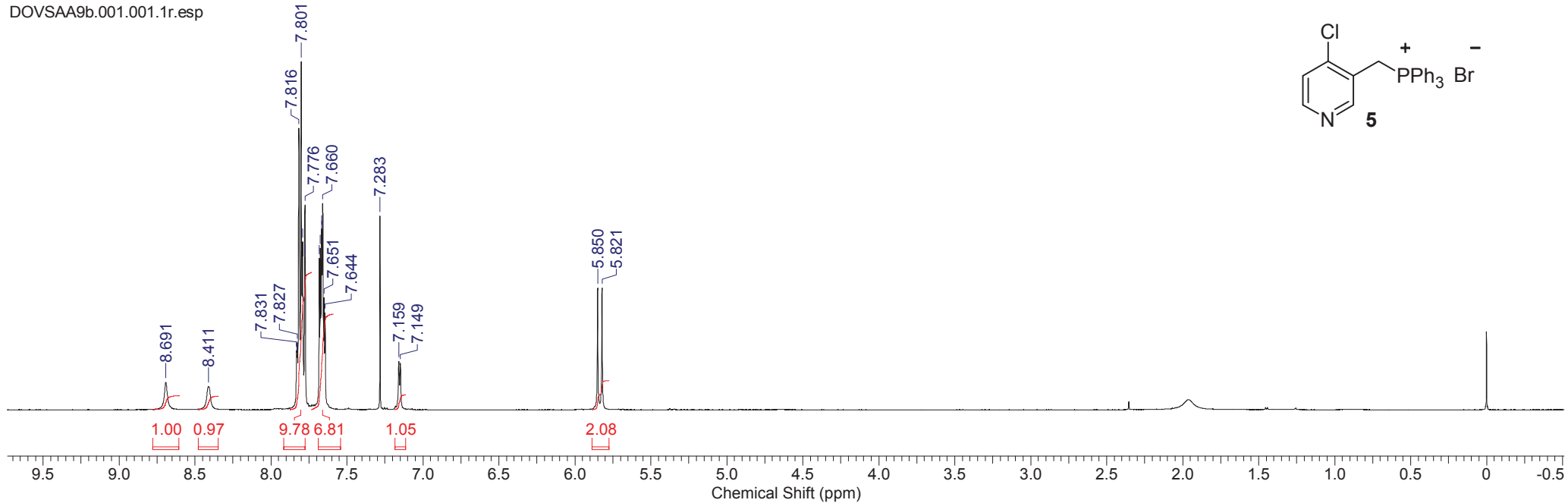
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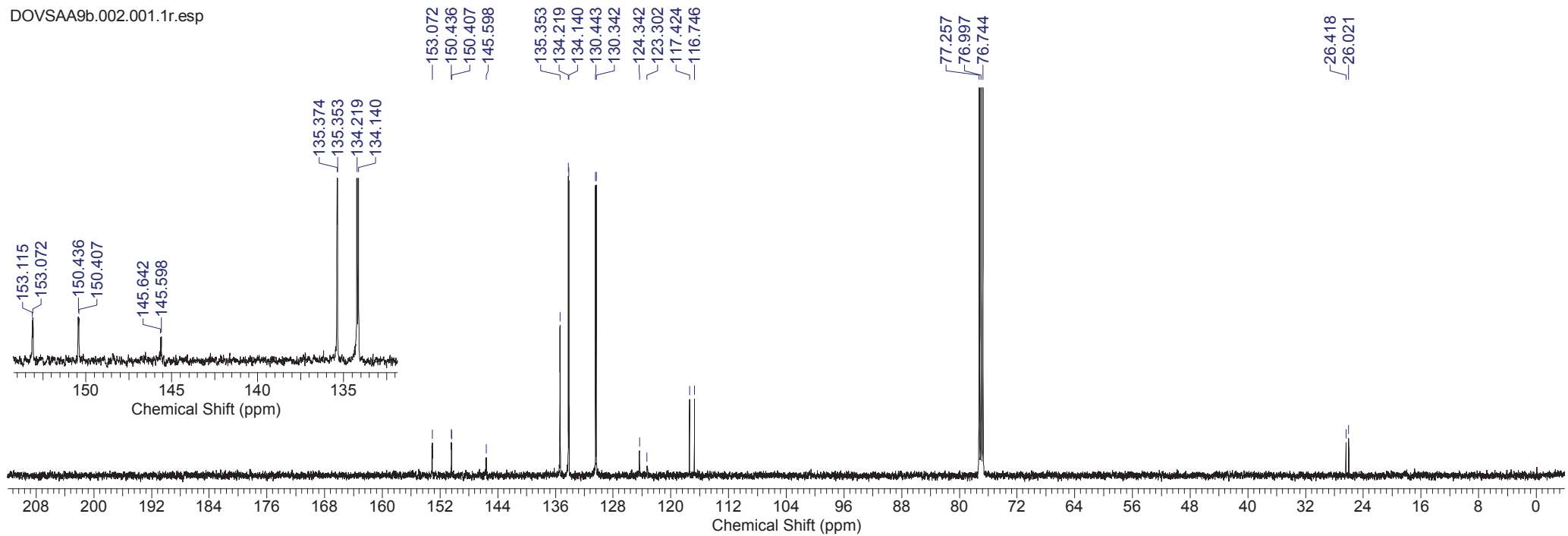
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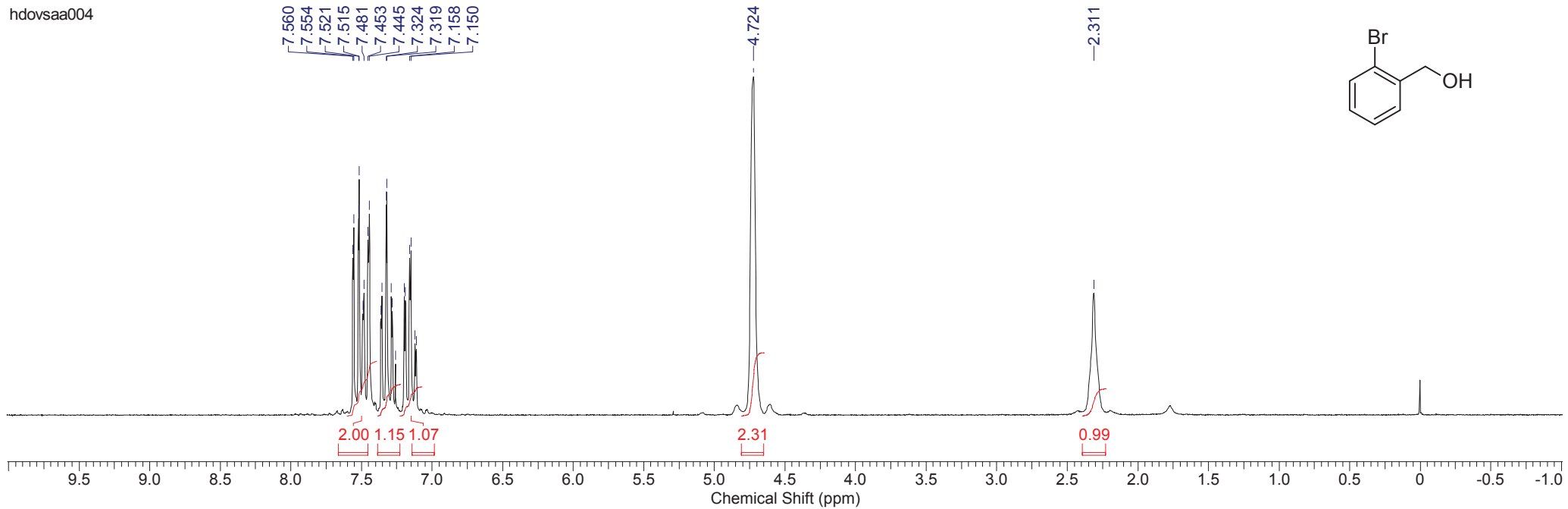
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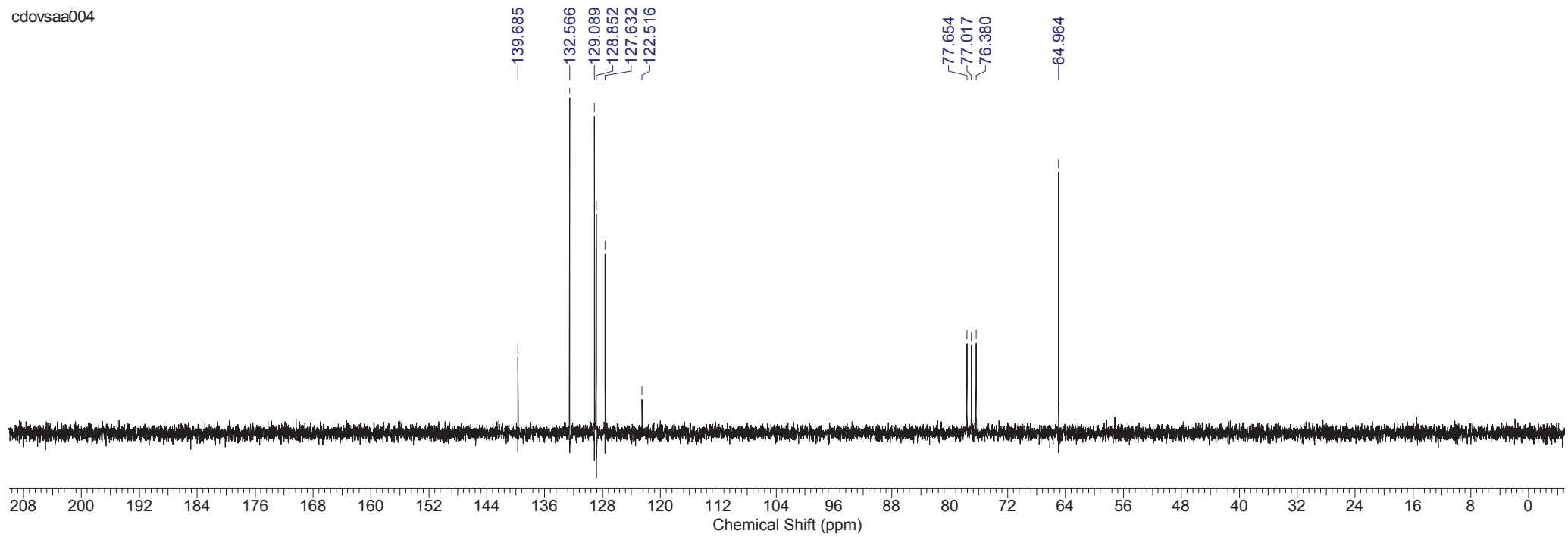
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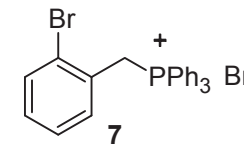
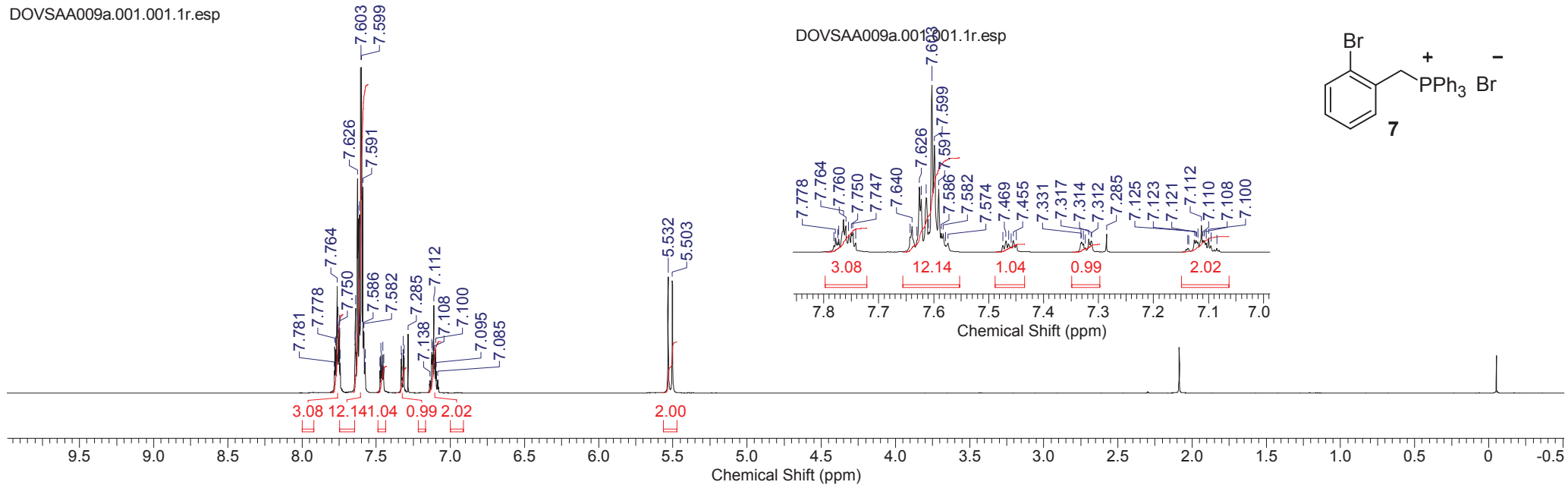
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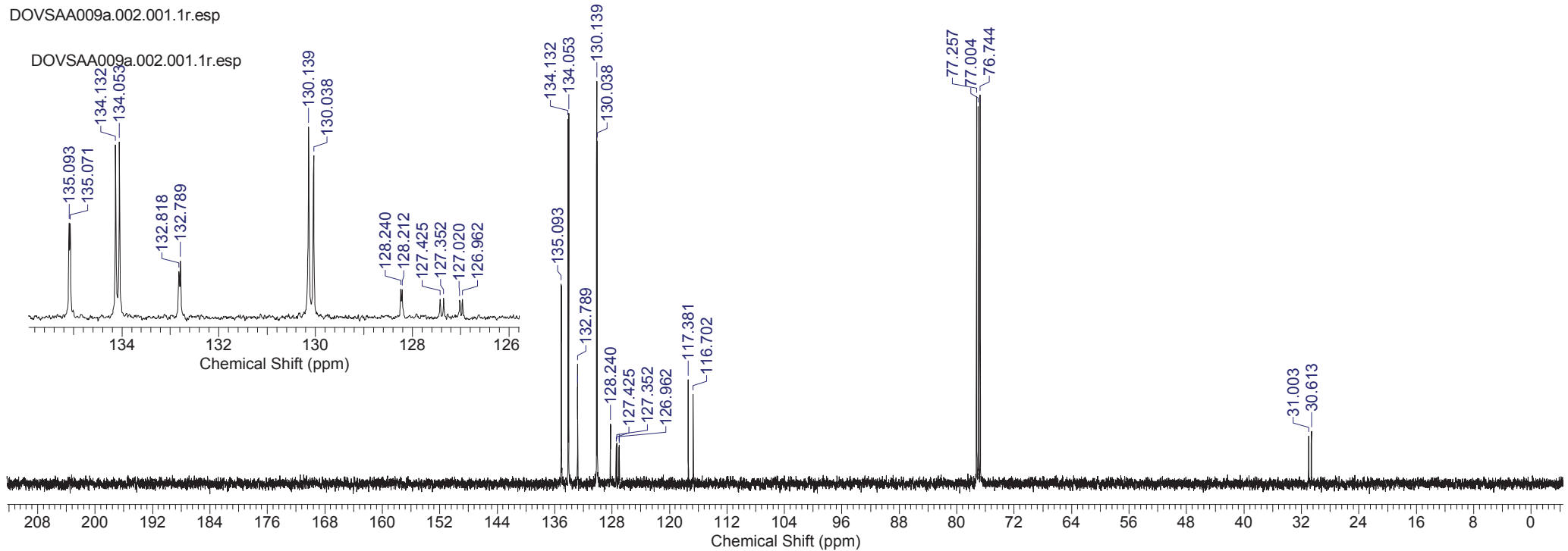
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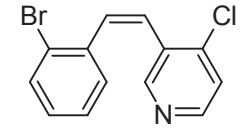
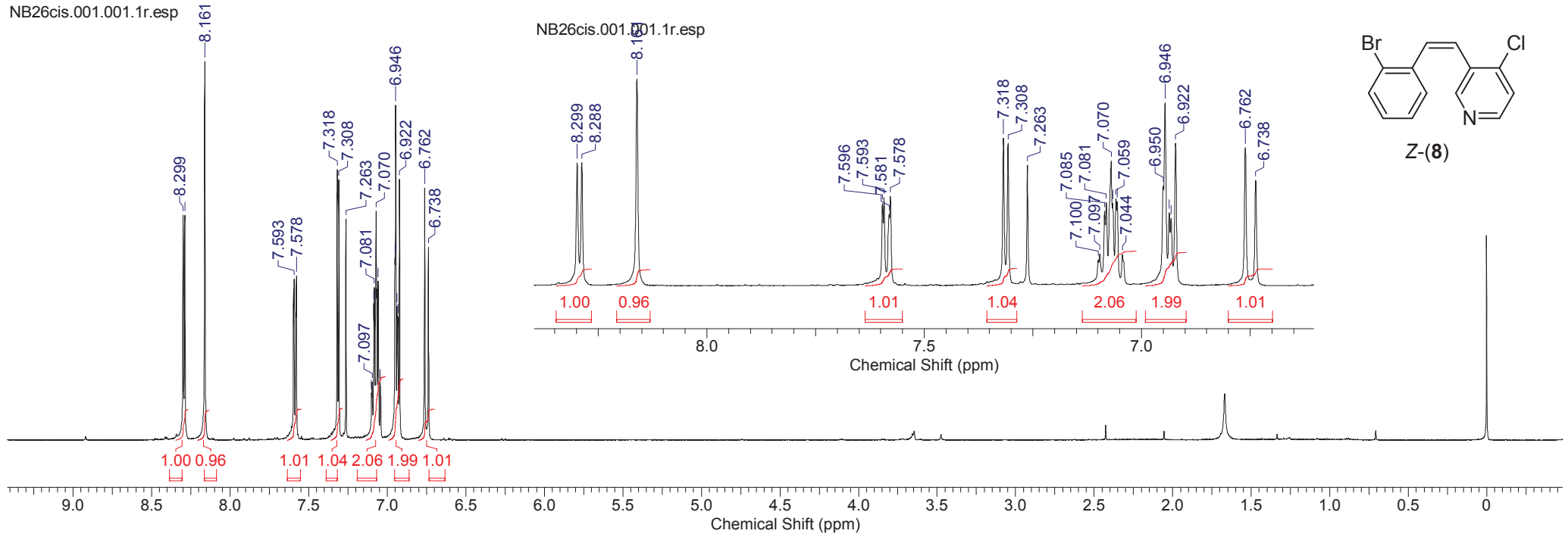
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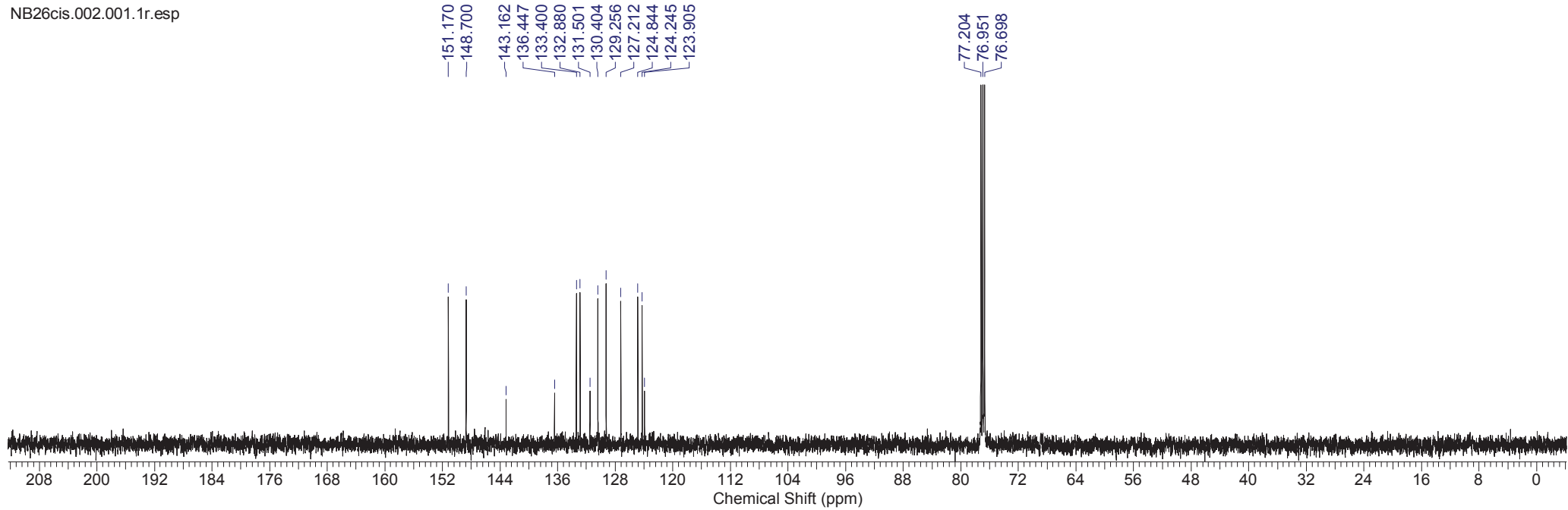


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Z-(8)

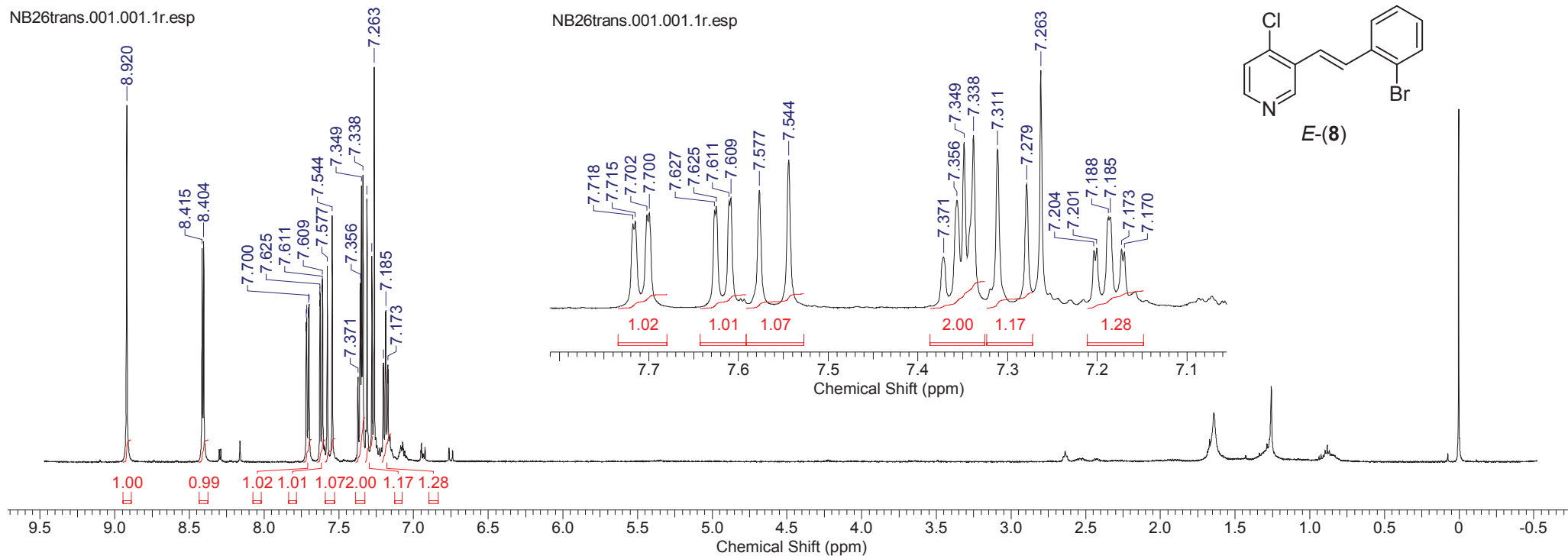
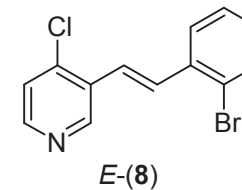
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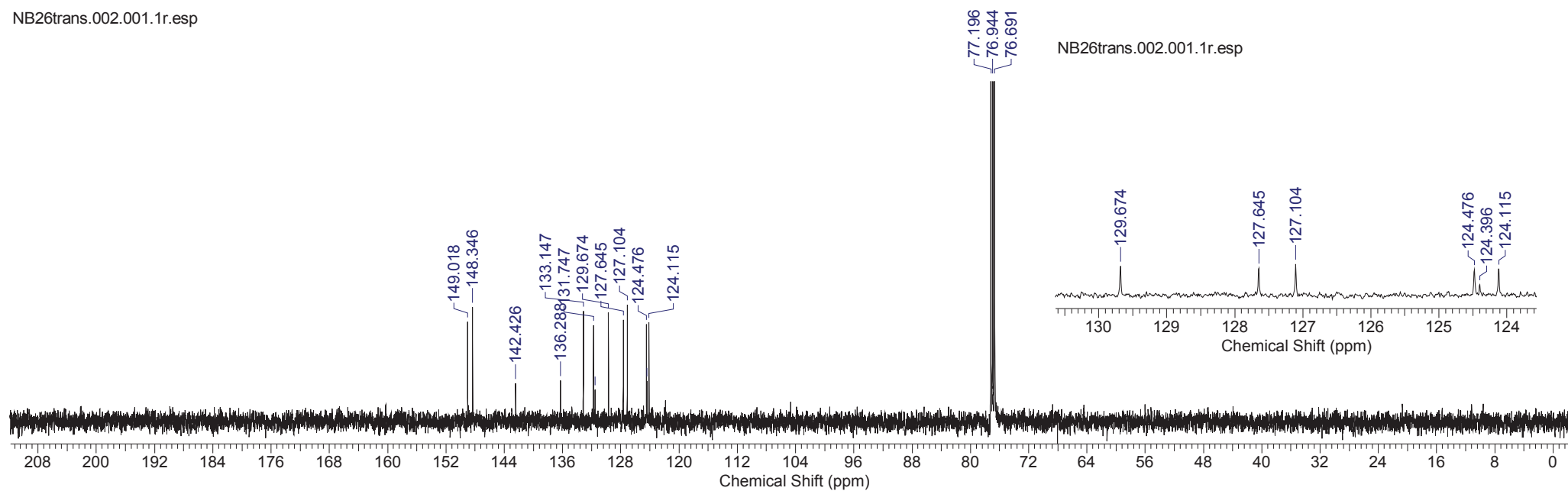
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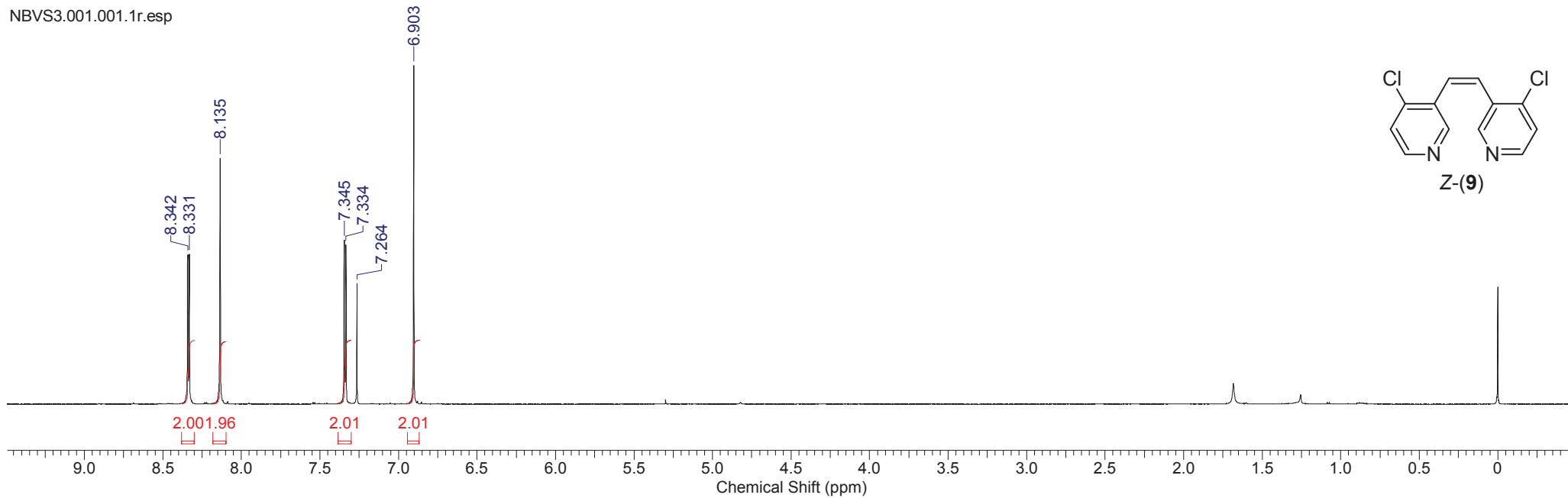


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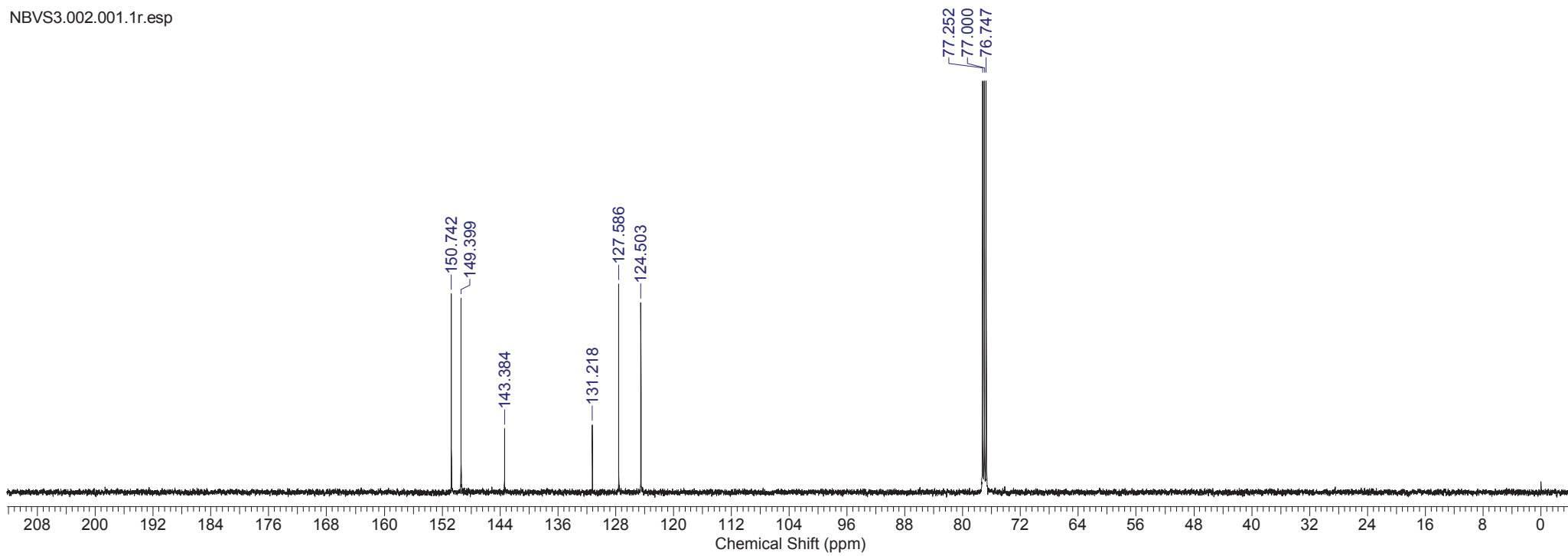
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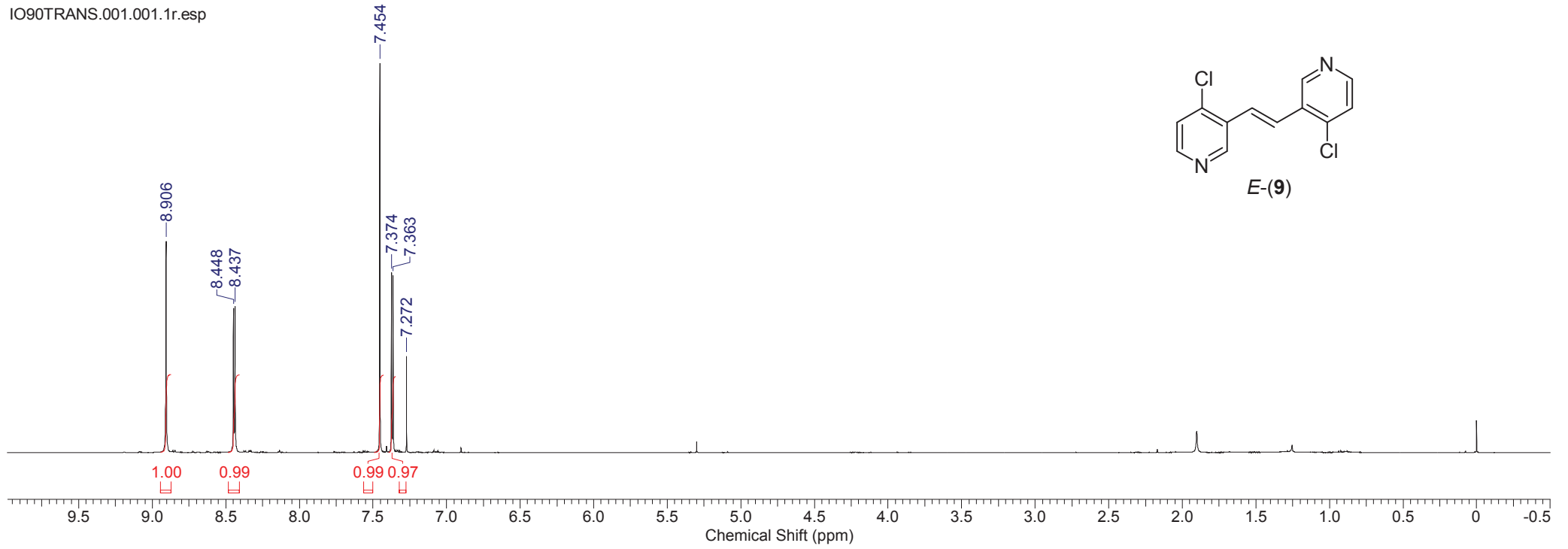
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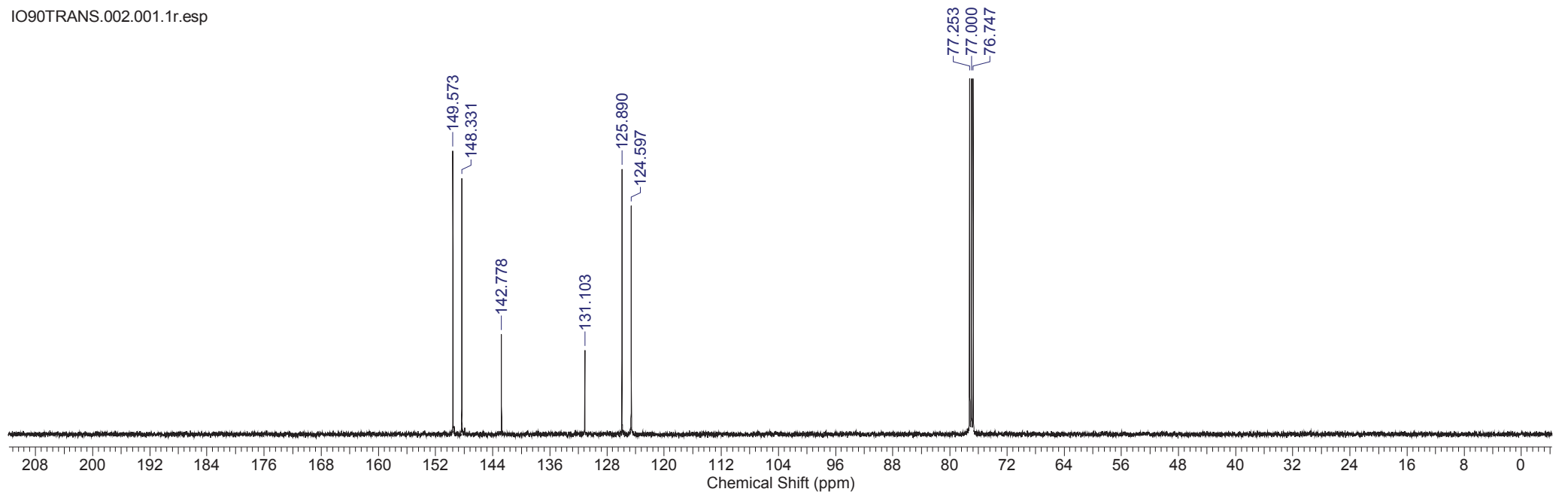
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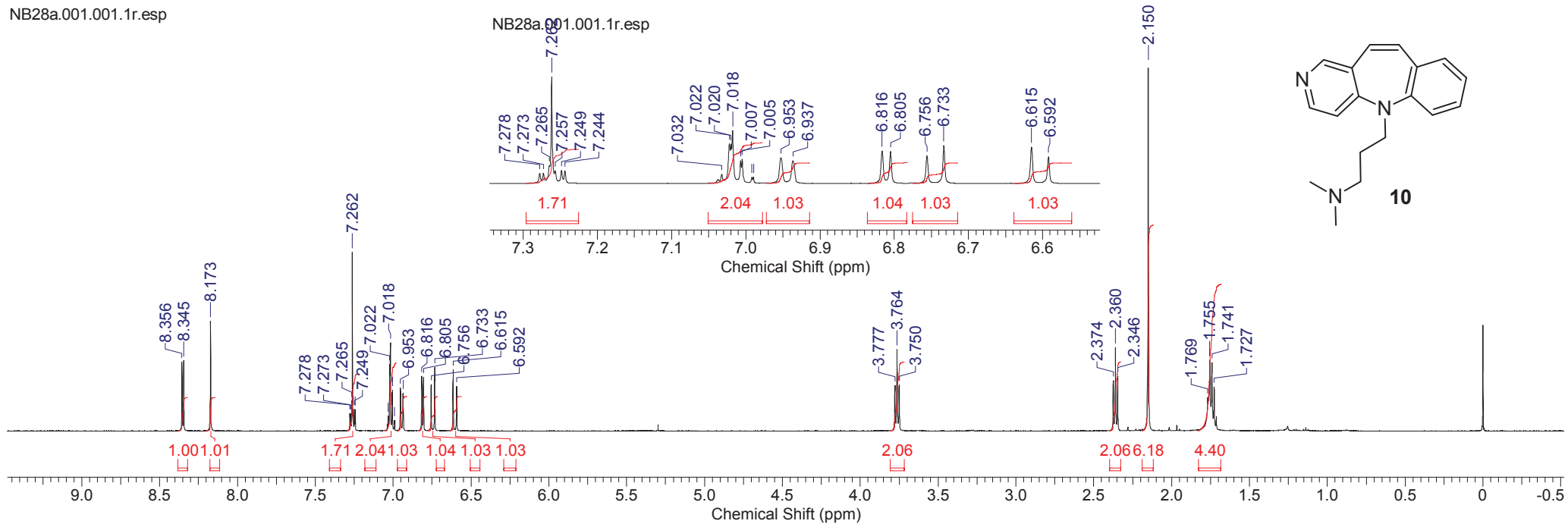


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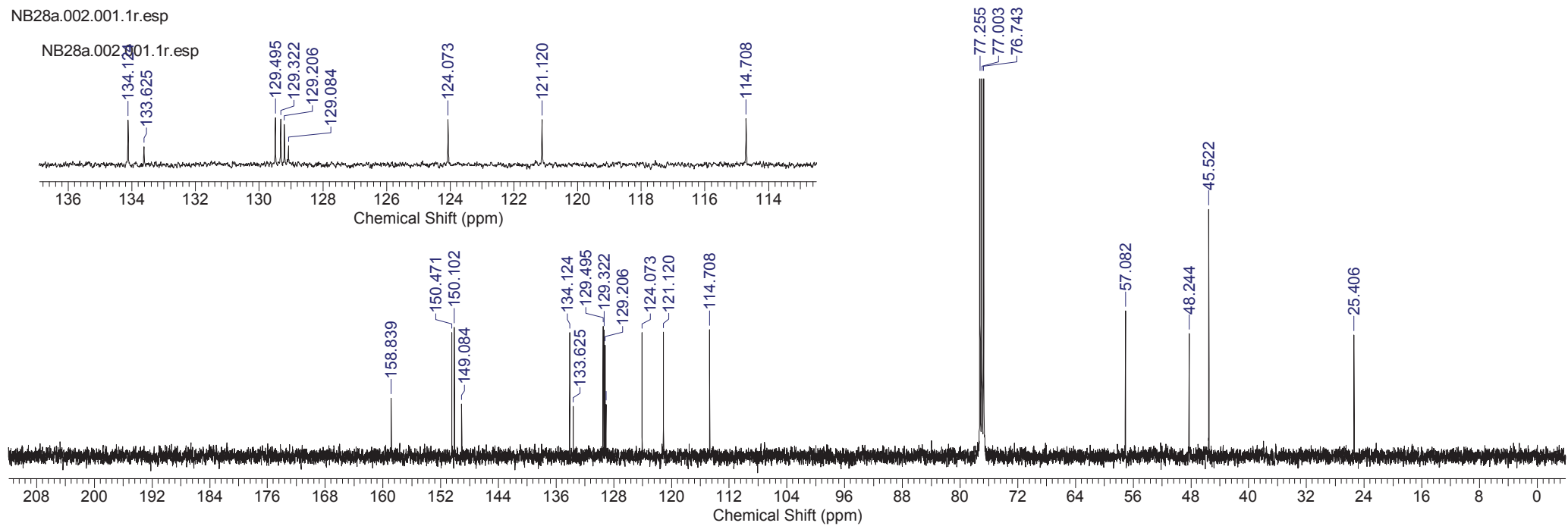
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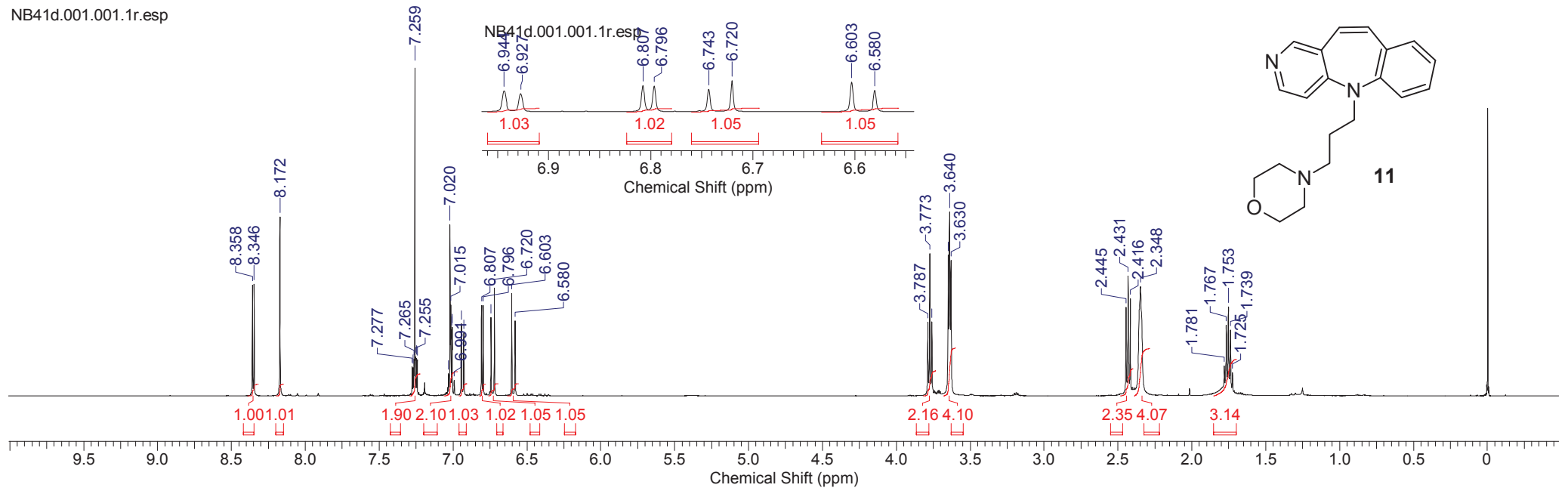


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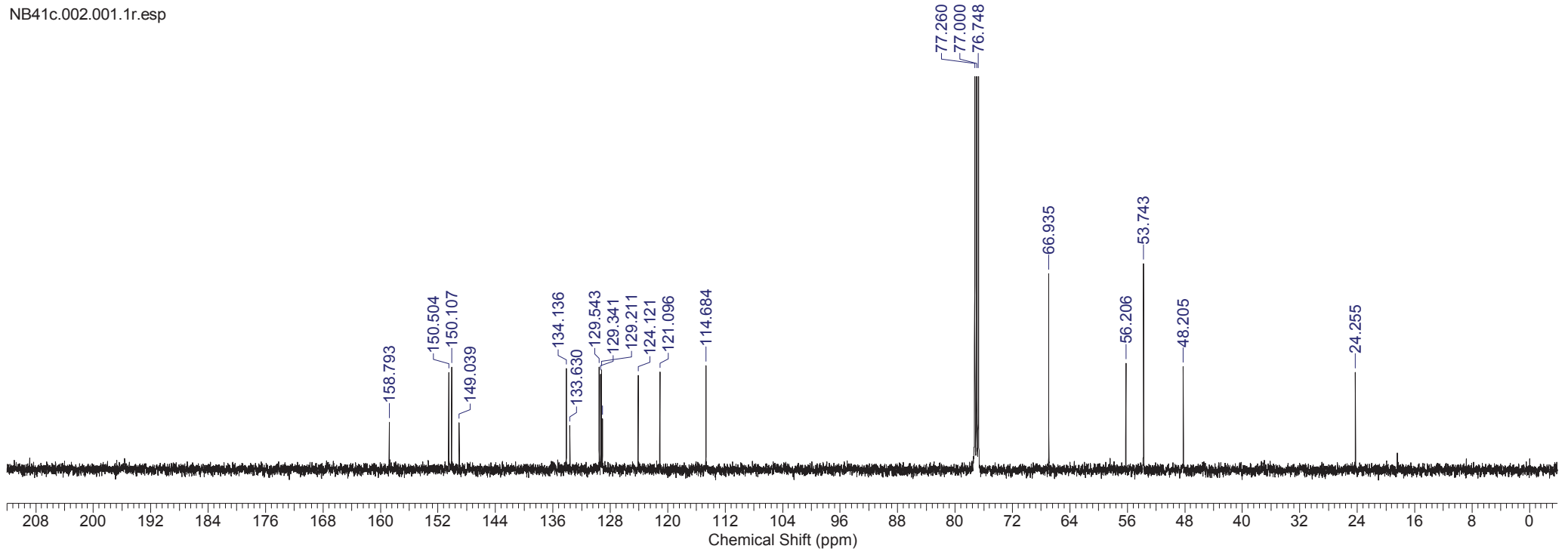
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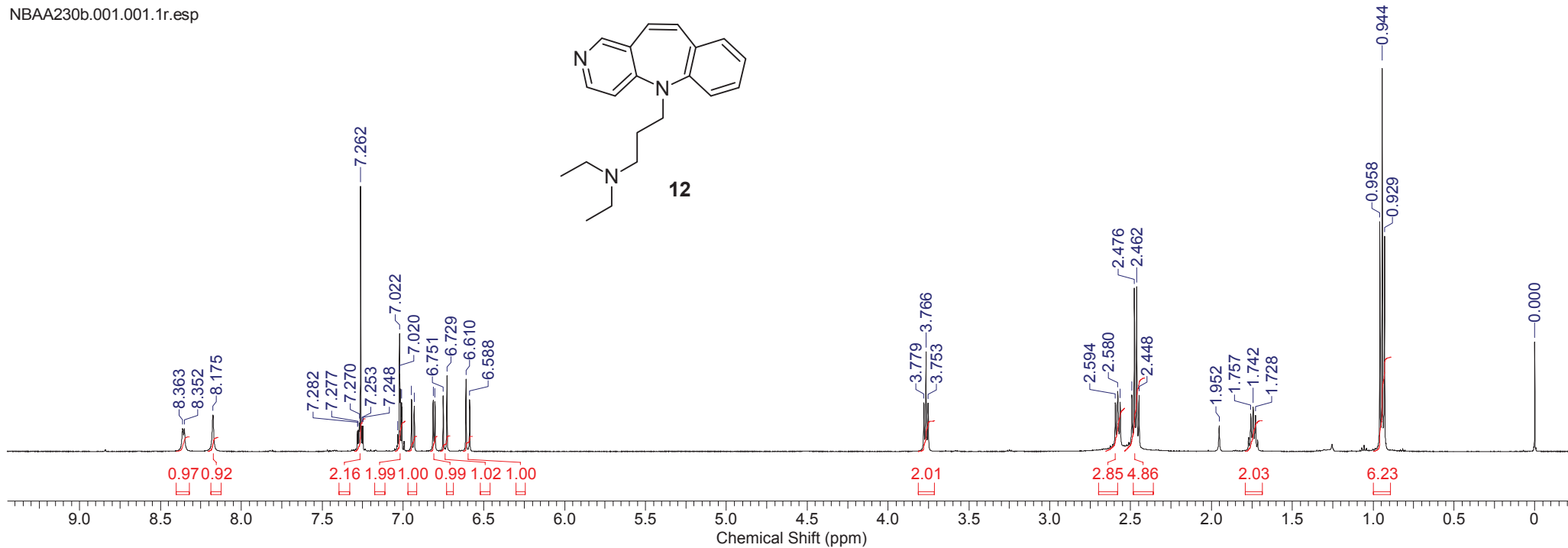
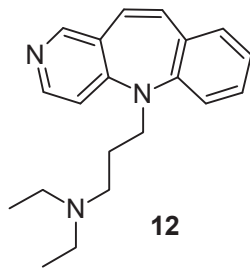
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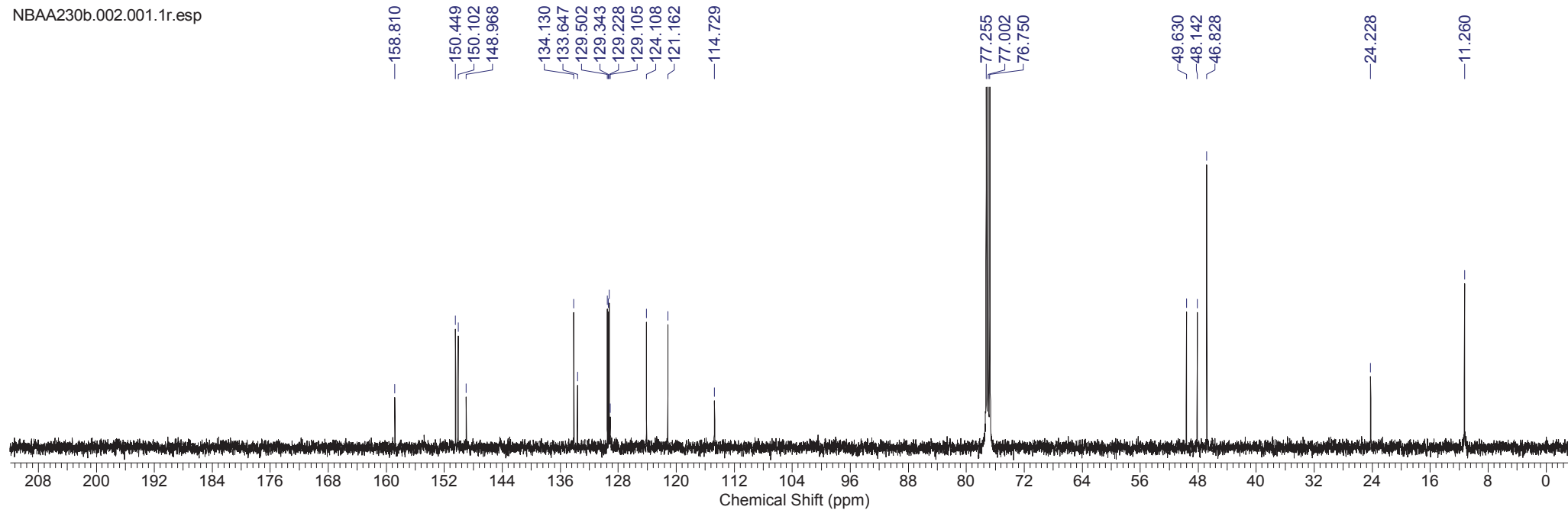
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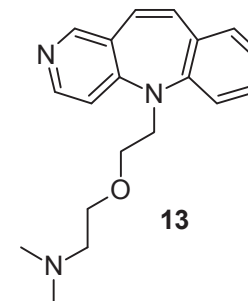
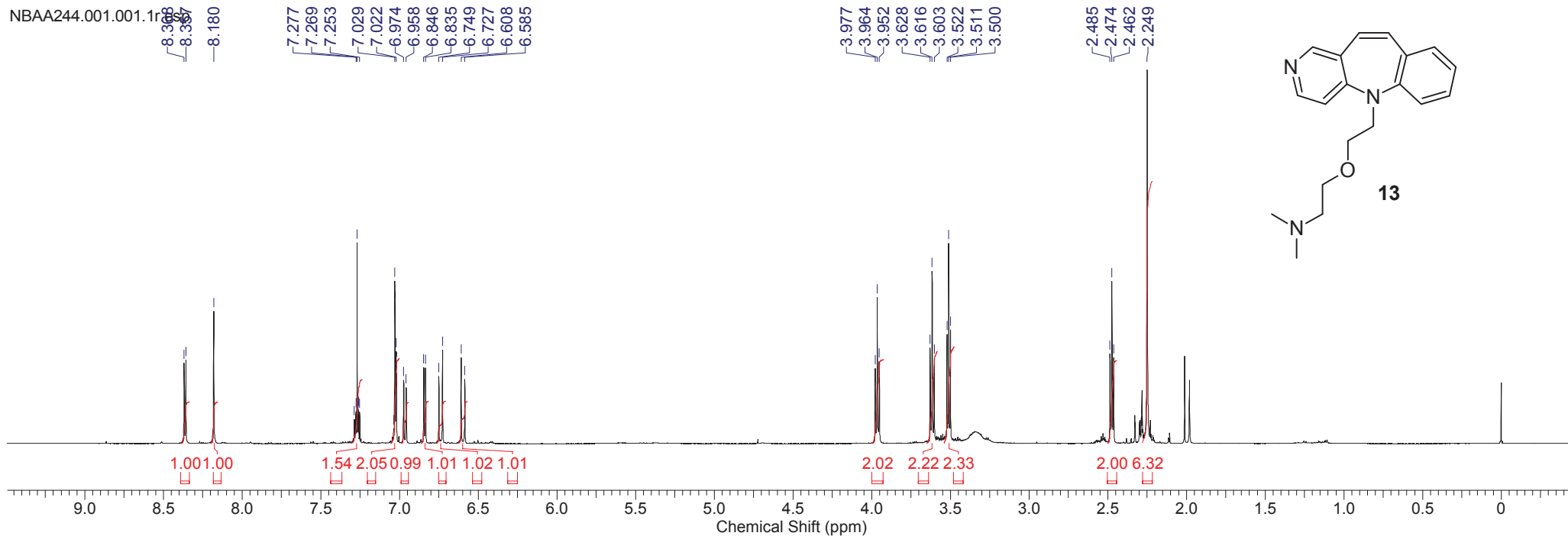
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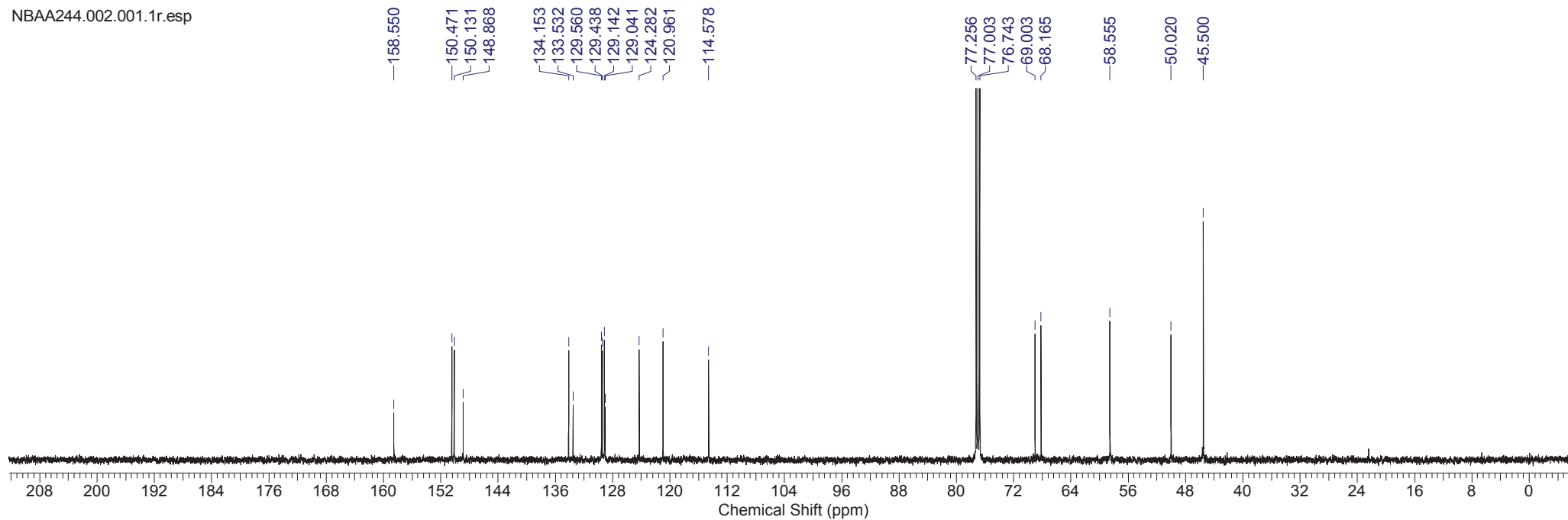
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NBAA244.001.001.1f

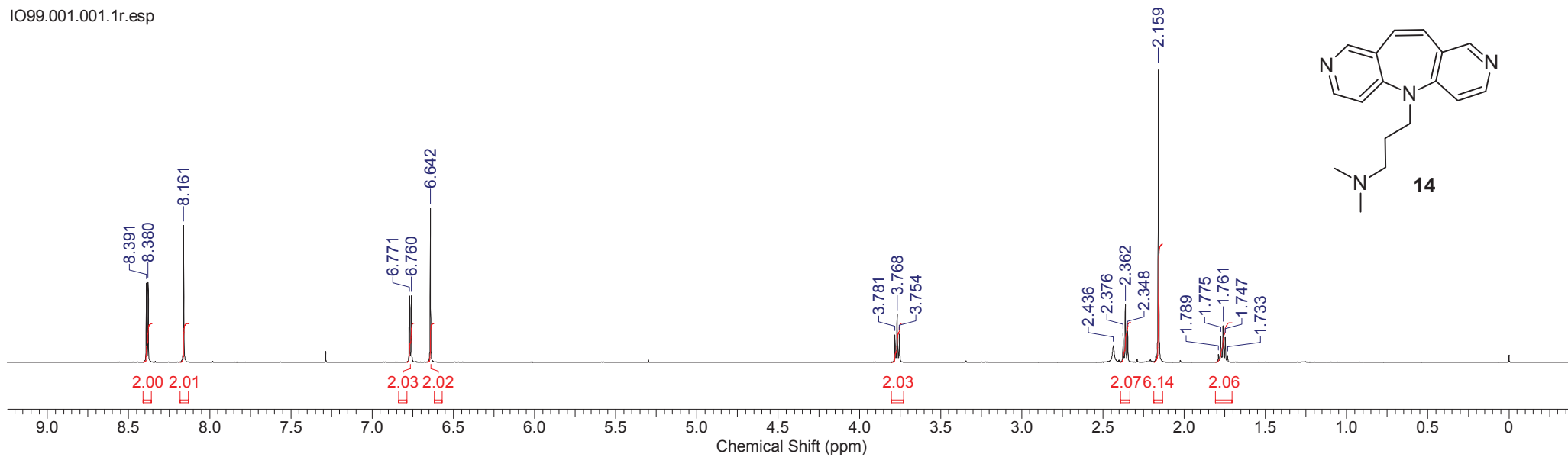


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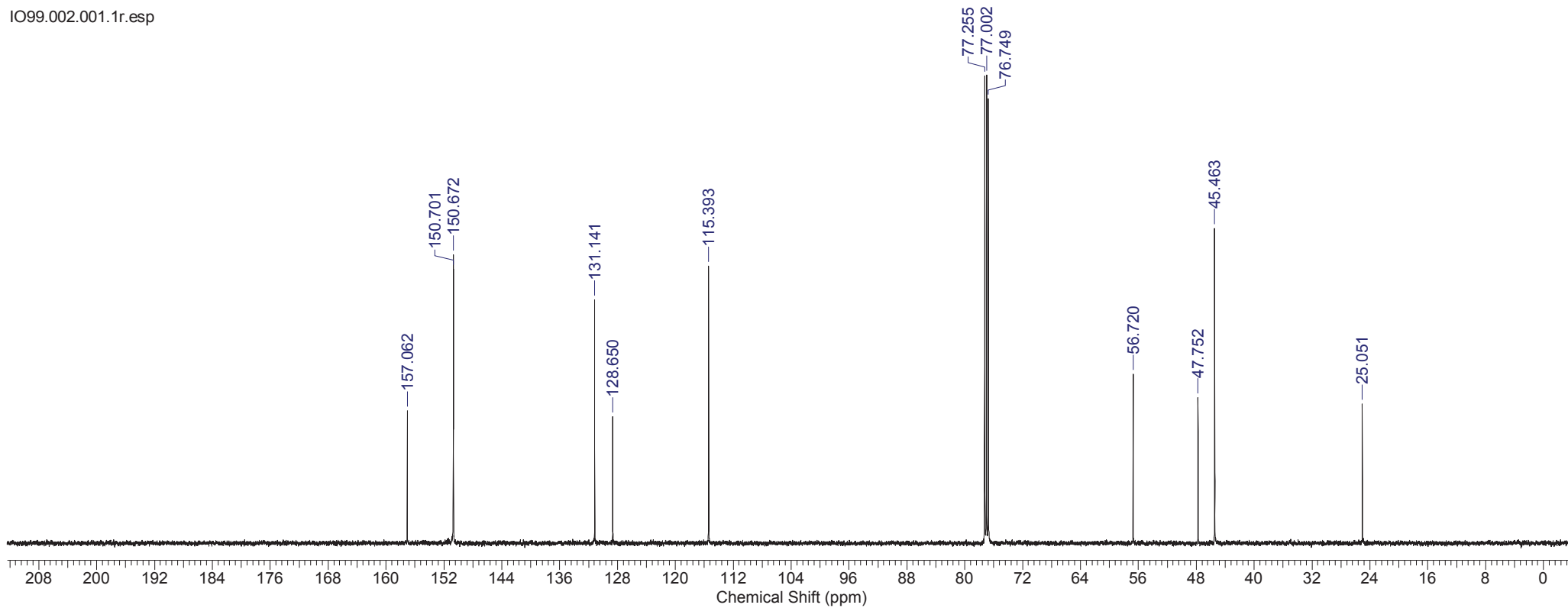




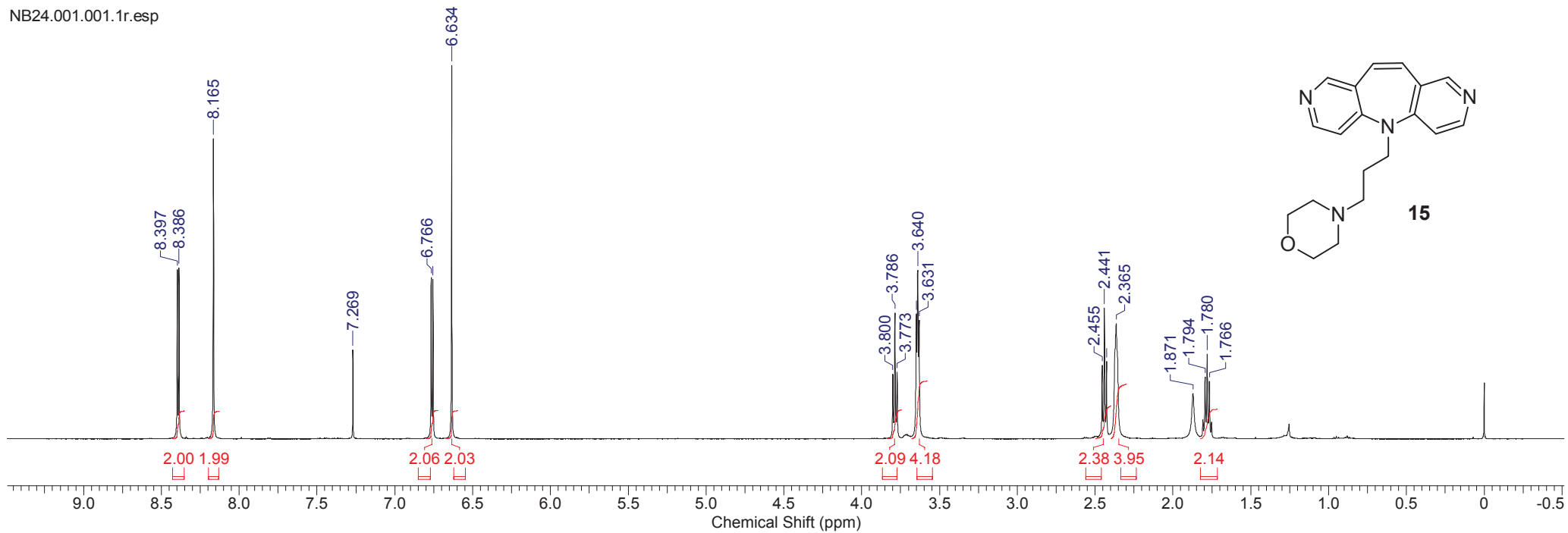
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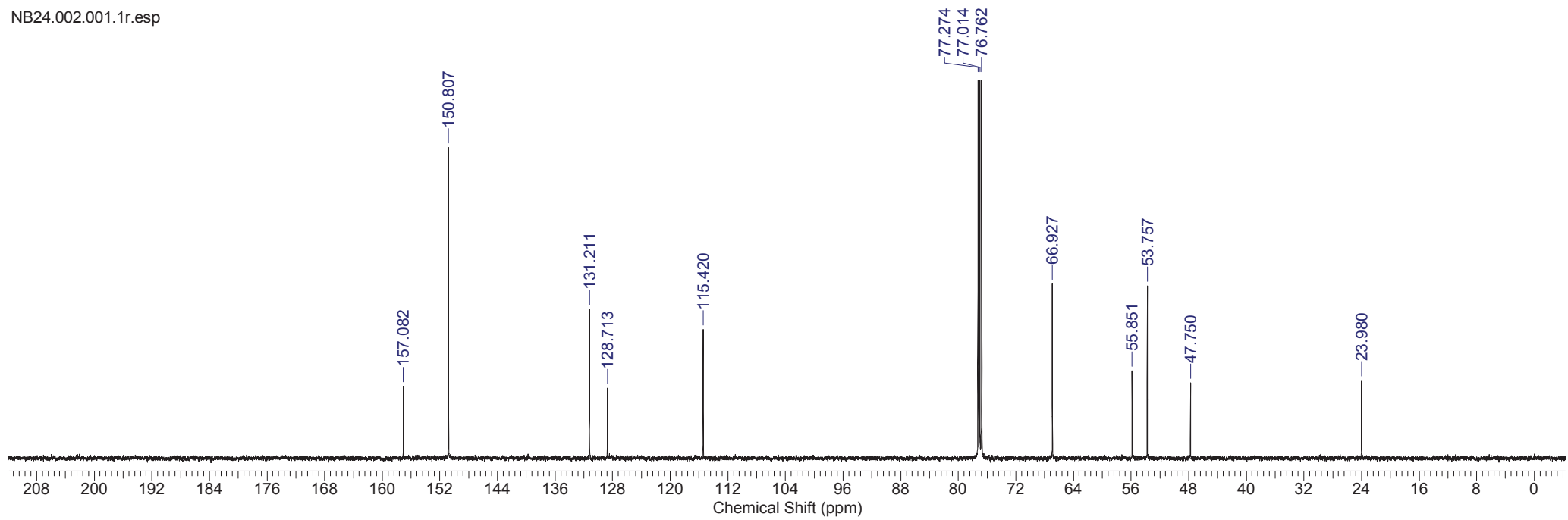
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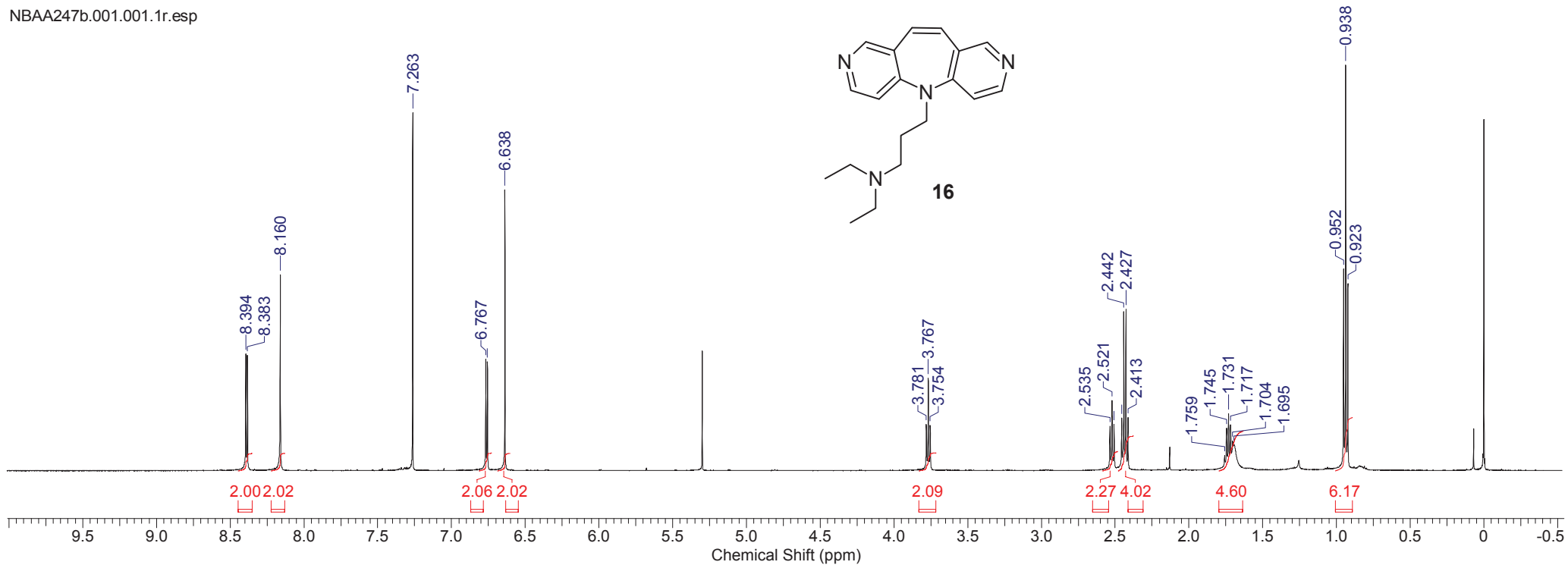
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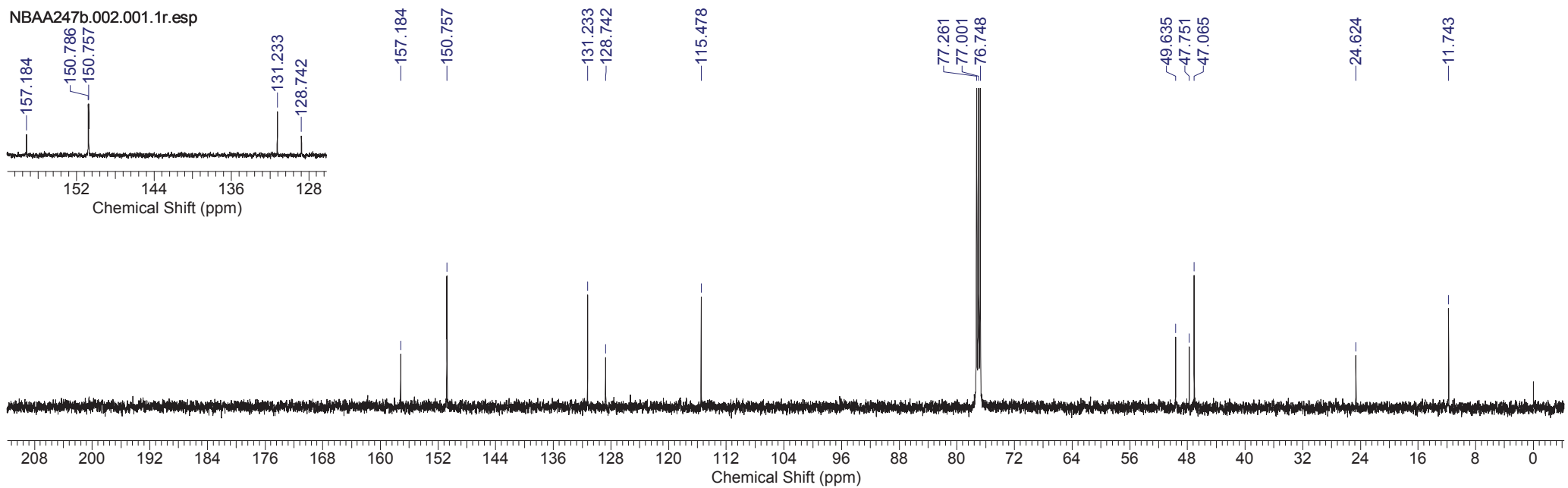
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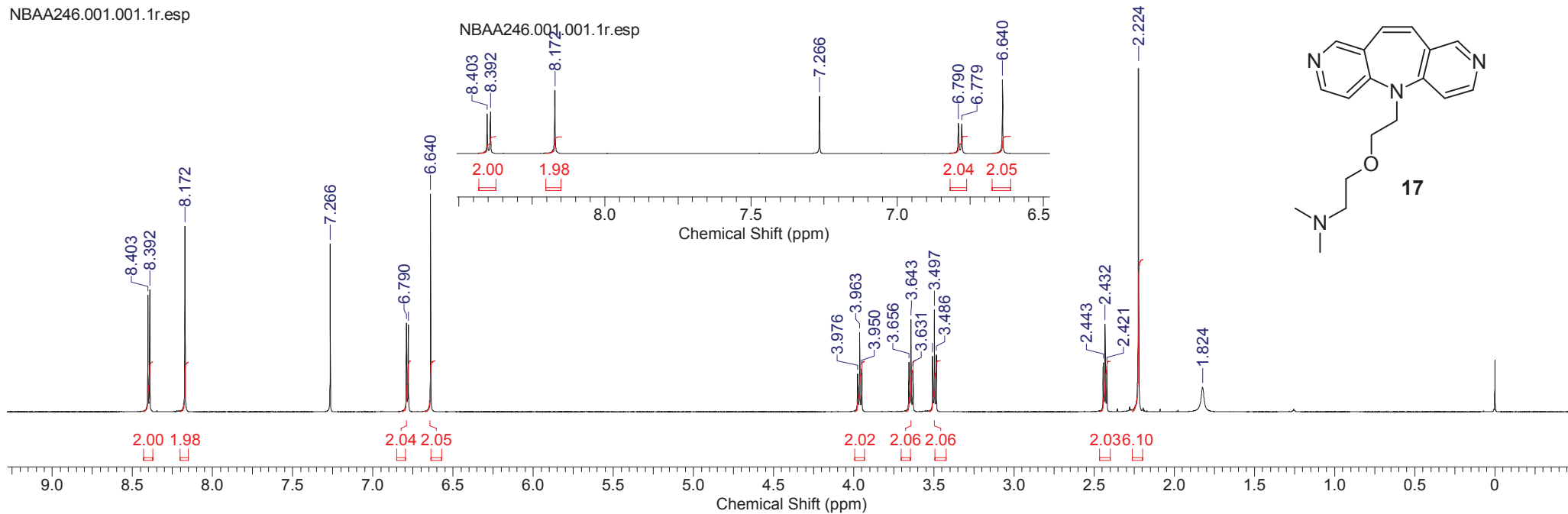
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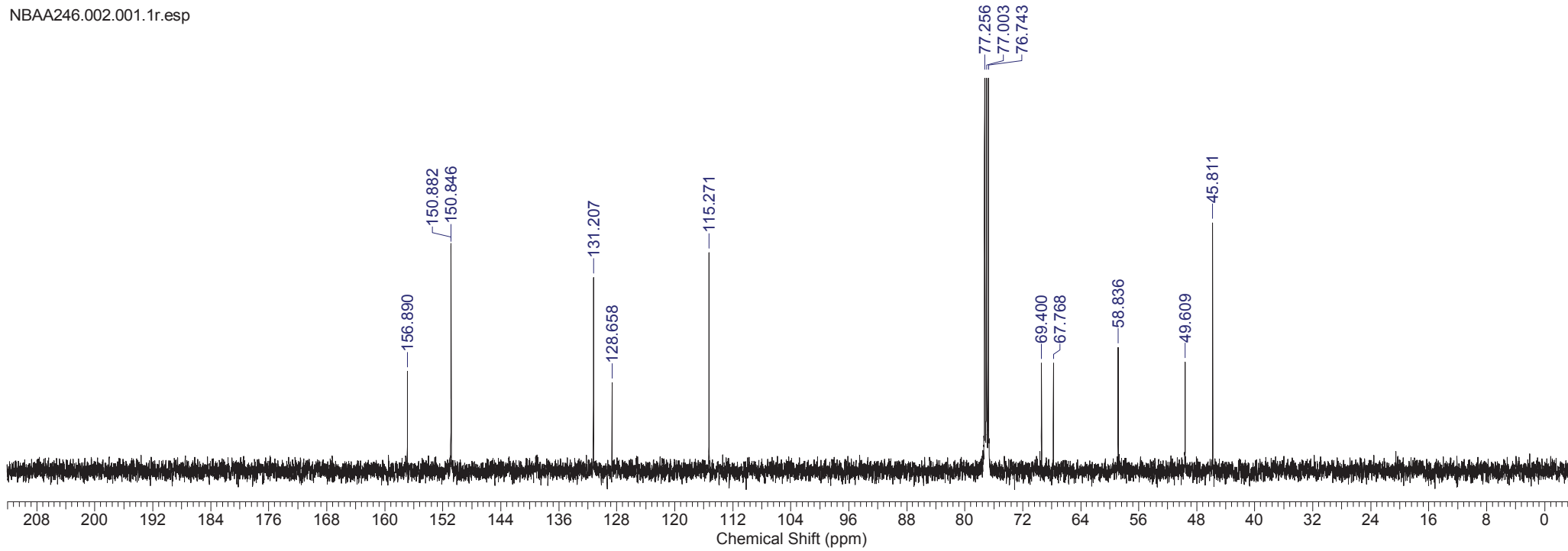
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NBAA246.001.001.1r.esp

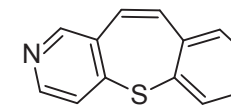


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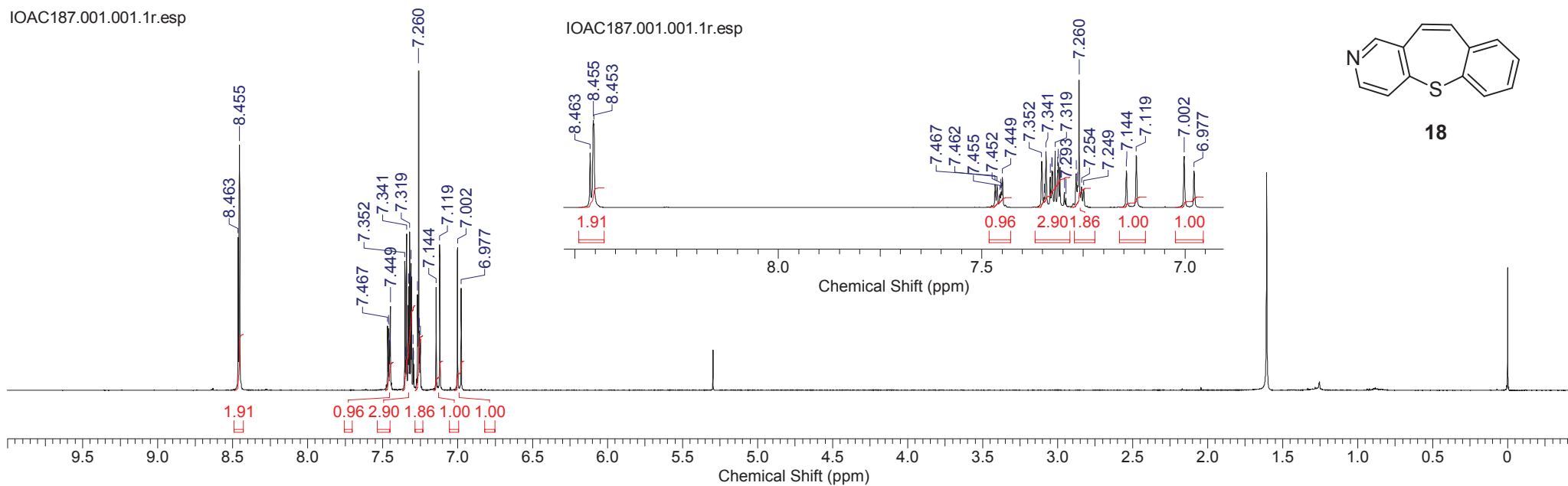


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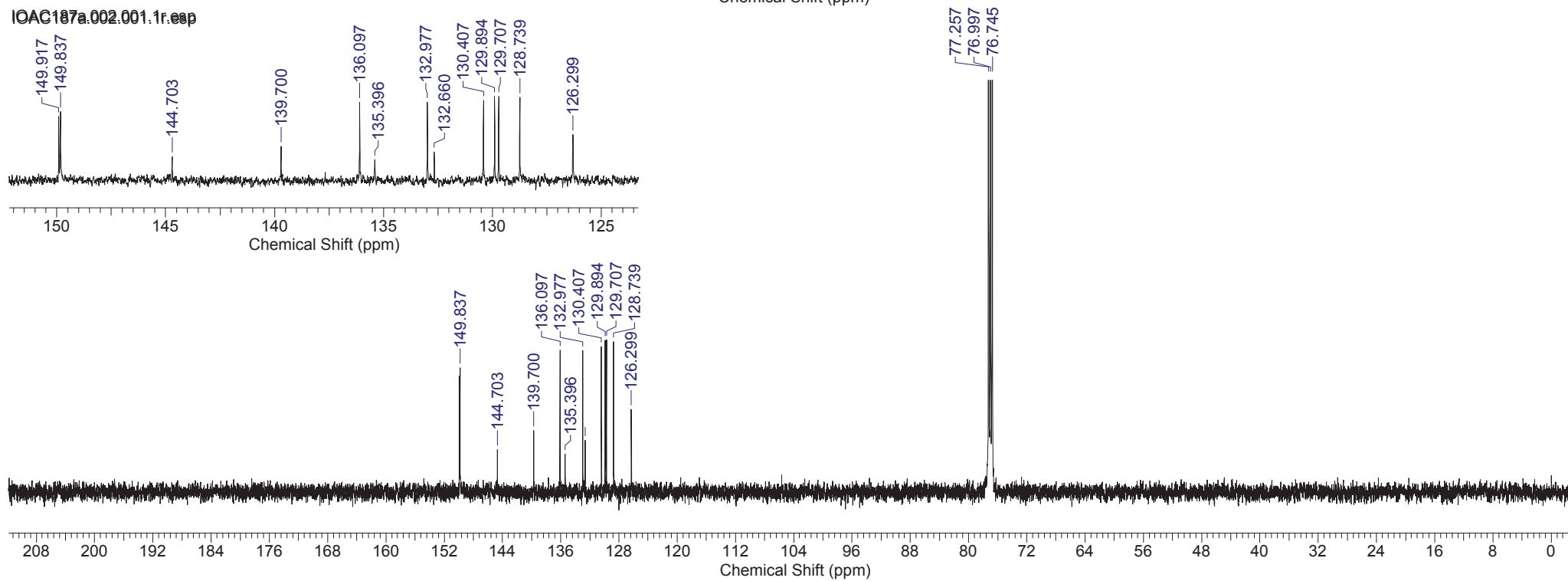
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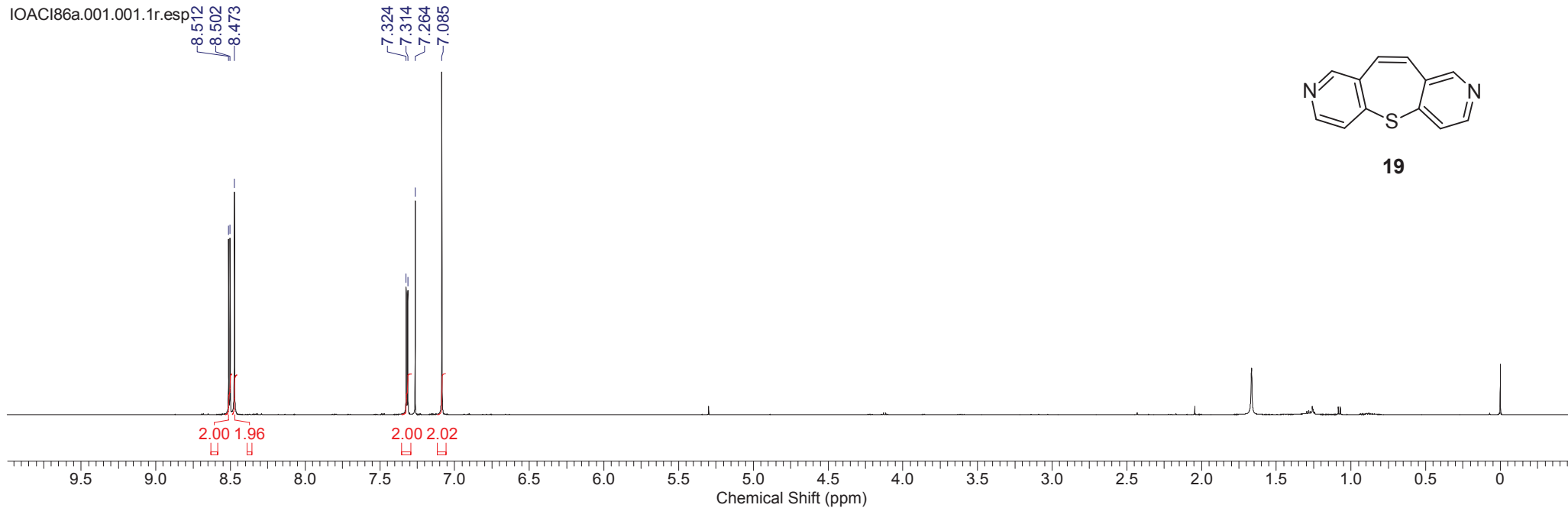
18



IOAC187a.002.001.1r.esp



IOAC186a.001.001.1r.esp



IOAC186.002.001.1r.esp

