Supplementary data

Design, synthesis, and evaluation of A-ring-modified lamellarin N analogues as noncovalent inhibitors of the EGFR T790M/L858R mutant

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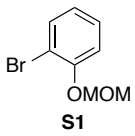
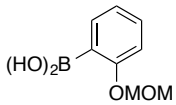
Synthesis of arylboronic acids 8a–g.



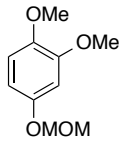
S1

1-Bromo-2-(methoxymethoxy)benzene (S1). Under an argon atmosphere, chloromethyl methyl ether (1.98 mL, 26.0 mmol) was added dropwise to a solution of 2-bromophenol (3.00 g, 17.3 mmol) and *N*,*N*-diisopropylethylamine (6.04 mL, 34.7 mmol) in dichloromethane (60 mL) at 0 °C. After stirring for 1 h, the reaction mixture was allowed to warm to room temperature and stirred for an additional 20 h. The mixture was quenched with saturated aqueous ammonia and the products were extract with dichloromethane. The extract was washed with 10% aqueous NaOH, water, and brine, dried over Na_2SO_4, and evaporated. The residue was purified by bulb-to-bulb distillation (95–110 °C, 5 mmHg) to give **S1** as colorless oil (3.58 g, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.53 (s, 3H), 5.25 (s, 2H), 6.89 (ddd, J = 1.5, 7.4, and 7.9 Hz, 1H), 7.15 (dd, J = 1.5 and 8.3 Hz, 1H), 7.25 (ddd, J = 1.6, 7.4, and 8.3 Hz, 1H), 7.54 (dd, J = 1.6 and 7.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 56.4, 95.1, 112.9, 116.2, 123.1, 128.5, 133.4, 153.8. HREIMS *m/z* calcd for $C_8H_9BrO_2$ (H^+): 215.9786, found 215.9790. These physical and spectroscopic data are in good agreement with those previously reported.[1]



8a

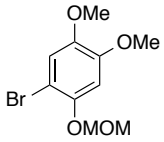
2-(Methoxymethoxy)phenylboronic acid (8a). Under an argon atmosphere, a pentane solution of *tert*-butyllithium (1.52 M, 14.4 mL, 21.9 mmol) was added dropwise to a solution of **S1** (2.38 g, 11.0 mmol) in THF (30 mL) at –78 °C. After stirring for 1 h at –78 °C, trimethyl borate (1.84 mL, 16.5 mmol) was added as a neat liquid and the mixture was stirred for 1 h at –78 °C. The reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. The mixture was quenched with saturated aqueous NH_4Cl and concentrated. The products were adjusted to pH 3 with acetic acid and the mixture was extract with dichloromethane. The extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated. The residue was washed with hexane and dried under reduced pressure to give **8a** as a colorless powder (1.41 g, 71%). This compound was used for the next reaction without further purification. This compound was used for the next reaction without further purification. Mp 65–66 °C. IR (KBr): 3372, 1601, 1484, 1455, 1398, 1341, 1159, 967 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.51 (s, 3H), 5.30 (s, 2H), 6.13 (s, 2H), 7.08 (dt, J = 0.8 and 7.3 Hz, 1H), 7.13 (d, J = 8.3 Hz, 1H), 7.43 (ddd, J = 1.9, 7.3, and 8.3 Hz, 1H), 7.87 (dd, J = 1.9 and 7.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 56.5, 94.6, 113.4, 122.3, 132.9, 136.8, 162.4. HREIMS *m/z* calcd for $C_8H_{11}BO_4$ (H^+): 182.0750, found 182.0754.



S2

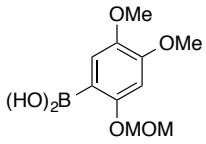
1,2-Dimethoxy-4-(methoxymethoxy)benzene (S2). According to the procedure described for the preparation of **S1**, 3,4-dimethoxyphenol (5.00 g, 32.4 mmol) was reacted. After purification by bulb-to-bulb distillation (120 °C/1 mmHg), **S2** was

obtained as a colorless oil (4.72 g, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.49 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 5.12 (s, 2H), 6.59 (dd, J = 2.7 and 8.7 Hz, 1H), 6.64 (d, J = 2.7 Hz, 1H), 6.78 (d, J = 8.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 55.9, 55.9, 56.4, 95.3, 102.1, 106.8, 111.8, 144.3, 149.7, 151.7. HRDARTMS m/z. Calcd for $C_{10}H_{15}O_4$ [$(M+H)^+$]: 199.09703. Found: 199.09628. These physical and spectroscopic data are in good agreement with those previously reported.[2,3]



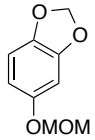
S3

1-Bromo-4,5-dimethoxy-2-(methoxymethoxy)benzene (S3). A solution of NBS (8.98 g, 50.4 mmol) in DMF (15 mL) was added dropwise to a solution of **S2** (10.0 g, 50.4 mmol) in DMF (15 mL) at 0 °C. After being stirred for 0.5 h, the reaction mixture was quenched with water at the same temperature and allowed to warm to room temperature. The products were extracted with diethyl ether and the extract was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography (hexane–ethyl acetate = 3:1) to give **S3** as a reddish brown solid (11.7 g, 84%). This compound was somewhat unstable and used for the next reaction without further purification. IR (KBr): 1509, 1373, 1211, 1150, 1010 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.55 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 5.17 (s, 2H), 6.80 (s, 1H), 7.01 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.2, 56.5, 56.5, 96.4, 102.6, 102.6, 115.7, 144.9, 148.0, 149.0. HRDARTMS m/z. Calcd for $C_{10}H_{14}BrO_4$ [$(M+H)^+$]: 277.00755. Found: 277.00644. These physical and spectroscopic data are in good agreement with those previously reported.[4]



8b

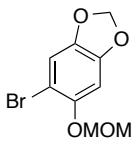
4,5-Dimethoxy-2-(methoxymethoxy)phenylboronic acid (8b). According to the procedure described for the preparation of **8a**, **S3** (6.20 g, 22.4 mmol) was reacted to give **8b** as a pale brown solid (3.44 g, 60%). This compound was used for the next reaction without further purification. Mp 83–85 °C. IR (KBr): 3484, 3427, 3218, 1608, 1514, 1400, 1312, 1212, 1149, 1001 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.52 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 5.25 (s, 2H), 6.05 (s, 2H), 6.78 (s, 1H), 7.30 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 55.9, 56.2, 56.5, 95.6, 99.1, 117.6, 144.2, 152.5, 157.8. HRDARTMS m/z. Calcd for $C_{10}H_{16}BO_6$ [$(M+H)^+$]: 243.10399. Found: 243.10396.



S4

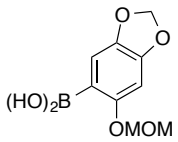
5-Methoxymethoxy-1,3-benzodioxole (S4). According to the procedure described for the preparation of **S1**, sesamol (2.40 g, 17.3 mmol) was reacted. After purification by bulb-to-bulb distillation (80–85 °C/0.2 mmHg), **S4** was obtained as a colorless oil (2.47 g, 78%). IR (KBr): 1487, 1178, 1152, 1070, 1006 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.47 (s, 3H), 5.08 (s, 2H), 5.92 (s, 2H), 6.49 (dd, J = 2.4 and 8.4 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.9, 95.5, 99.8, 101.2, 108.0, 108.5, 142.6, 148.1, 152.5. HRDARTMS m/z. Calcd for $C_9H_{11}O_4$ [$(M+H)^+$]: 183.06573. Found: 183.06309.

These physical and spectroscopic data are in good agreement with those previously reported.[5]



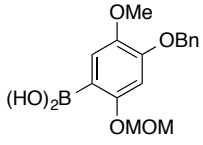
S5

5-Bromo-6-methoxymethoxy-1,3-benzodioxole (S5). According to the procedure described for the preparation of **S3**, **S4** (1.82 g, 10.0 mmol) and NBS (2.67 g, 15.0 mmol) were reacted. After purification by column chromatography over silica gel 60N (hexane–ethyl acetate = 5:1), **S5** was obtained as a colorless solid (2.74 g, 87%). This compound was somewhat unstable and used for the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.53 (s, 3H), 5.13 (s, 2H), 5.95 (s, 2H), 6.78 (s, 1H), 6.98 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.4, 96.3, 100.1, 101.9, 103.3, 112.3, 143.2, 147.7, 148.7. These physical and spectroscopic data are in good agreement with those previously reported.[6]



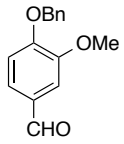
8c

(6-Methoxymethoxy-1,3-benzodioxol-5-yl)boronic acid (8c). Under an argon atmosphere, a pentane solution of *n*-butyllithium (1.59 M, 16.5 mL, 26.2 mmol) was added dropwise to a solution of **S5** (6.20 g, 23.8 mmol) in THF (200 mL) at –100 °C. After stirring for 5 min, trimethyl borate (4.01 mL, 35.8 mmol) was added as a neat liquid and the mixture was stirred for 0.5 h at –100 °C. The reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. The mixture was quenched with saturated aqueous NH_4Cl and concentrated. The products were adjusted to pH 3 with acetic acid and the mixture was extract with dichloromethane. The extract was washed successively with water, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, and evaporated. The residue was washed with hexane and dried under reduced pressure to give **8c** as a colorless powder (3.09 g, 65%). This compound was used for the next reaction without further purification. Mp 95–105 °C. IR (KBr) 3353, 1623, 1434, 1328, 1155, 1001, 925 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.50 (s, 3H), 5.22 (s, 2H), 5.96 (s, 2H), 6.40 (s, 2H), 6.77 (s, 1H), 7.25 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.5, 95.5, 97.2, 101.5, 114.1, 114.6, 142.6, 151.1, 158.7. HREIMS *m*/*z*. Calcd for $C_9H_{11}BO_6$ (M^+): 226.0649. Found: 226.0635.



8d

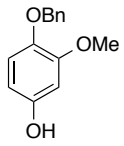
4-Benzyloxy-5-methoxy-2-(methoxymethoxy)phenylboronic acid (8d). This compound was synthesized according to the previously reported procedure.[7]



S6

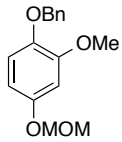
4-Benzyloxy-3-methoxybenzaldehyde (S6). A neat liquid of benzyl bromide (43.2 mL, 361 mmol) was added to a suspension of vanillin (50.0 g, 329 mmol) and K_2CO_3 (50.0 g, 361 mmol) in acetone (500 mL) at room temperature and the mixture was refluxed for 12 h. The reaction mixture was cooled to room temperature and then filtered. The

filtrate was evaporated and the residue was diluted with diethyl ether. The mixture was washed with with 10% aqueous NaOH, water, and brine, dried over Na_2SO_4, and evaporated. The residue was recrystallized from diethyl ether–hexane to give **S6** as pale yellow granules (52.8 g, 66%). The mother liquor from the above recrystallization was evaporated and the residue was purified by bulb-to-bulb distillation (175–185 °C, 0.7 mmHg) to give an additional **S6** as pale yellow solid (8.49 g, 11%). The total yield of **S6** was 61.3 g (77%). Mp 60–61 °C (lit.[8] 60–61 °C). IR (KBr): 1675, 1583, 1506, 1260, 1236, 1134 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.95 (s, 3H), 5.25 (s, 2H), 6.99 (d, J = 8.2 Hz, 1H), 7.29–7.35 (m, 1H), 7.36–7.41 (m, 3H), 7.42–7.46 (m, 3H), 9.83 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.1, 70.9, 109.3, 112.4, 126.6, 127.2, 128.2, 128.7, 130.3, 136.0, 150.1, 153.6, 190.9. HRDARTMS m/z. Calcd for $C_{15}H_{15}O_3$ $[(M+H)^+]$: 243.10212. Found: 243.10258. These physical and spectroscopic data are in good agreement with those previously reported.[8]



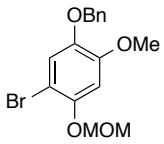
S7

4-Benzyloxy-3-methoxyphenol (S7). Under an argon atmosphere, *m*-chloroperbenzoic acid (contains ca 30% water, purity >65%, 41.7 g, ca. 157 mmol) was added portionwise to a solution of **S6** (25.3 g, 105 mmol) in dichloromethane (160 mL) at 0 °C. After stirring for 7.5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with water and the organic layer was separated. The aqueous layer was extracted with dichloromethane. The combined extracts were washed with saturated aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and evaporated. The residue was dissolved in methanol (300 mL) and K_2CO_3 (72.3 g, 523 mmol) was added portionwise to the solution at room temperature. After stirring for 1 h, the mixture was evaporated under reduced pressure. Water was added to the residue and the product was extracted with diethyl ether. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was recrystallized from diethyl ether–hexane to give **S7** as pale yellow granules (14.7 g, 61%). The mother liquor from the above recrystallization was evaporated and the residue was chromatographed over silica gel 60N (hexane–ethyl acetate = 3:1) to give an additional **S7** as pale yellow solid (3.14 g, 13%). The total yield of **S7** was 17.8 g (74%). Mp 82.5–83.5 °C (lit.[9] 85–86 °C). IR (KBr): 3303, 1514, 1448, 1222, 1195, 1122 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H), 4.93 (s, 1H), 5.05 (s, 2H), 6.25 (dd, J = 2.8 and 8.5 Hz, 1H), 6.45 (d, J = 2.8 Hz, 1H), 6.72 (d, J = 8.5 Hz, 1H), 7.26–7.31 (m, 1H), 7.32–7.37 (m, 2H), 7.39–7.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.9, 72.3, 100.8, 106.0, 116.3, 127.5, 127.8, 128.4, 137.4, 142.1, 150.7, 150.9. HRDARTMS m/z. Calcd for $C_{14}H_{15}O_3$ $[(M+H)^+]$: 231.10212. Found: 231.10067. These physical and spectroscopic data are in good agreement with those previously reported.[9]



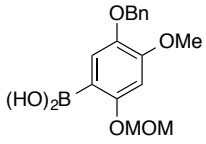
S8

1-Benzyloxy-2-methoxy-4-(methoxymethoxy)benzene (S8). According to the procedure described for the preparation of **S1**, **S7** (8.65 g, 37.6 mmol) was reacted. After purification by by column chromatography (hexane–ethyl acetate = 4:1), **S8** was obtained as a colorless solid (8.87 g, 86%). Recrystallization from dichloromethane–hexane gave a colorless granules. Mp 42 °C. IR (KBr): 1515, 1217, 1149, 1135, 1024, 1007 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.48 (s, 3H), 3.86 (s, 3H), 5.08 (s, 2H), 5.11 (s, 2H), 6.51 (dd, J = 2.8 and 8.7 Hz, 1H), 6.64 (d, J = 2.8 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 7.27–7.31 (m, 1H), 7.33–7.38 (m, 2H), 7.41–7.45 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 56.0, 72.0, 95.2, 102.3, 106.9, 115.5, 127.4, 127.8, 128.5, 137.5, 143.3, 150.7, 152.3. HRDARTMS *m*/*z*. Calcd for $C_{16}H_{19}O_4$ [$(M+H)^+$]: 275.12833. Found: 275.12851.



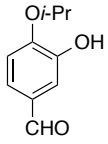
S9

1-Benzyloxy-5-bromo-2-methoxy-4-(methoxymethoxy)benzene (S9). According to the procedure described for the preparation of **S3**, **S8** (2.54 g, 9.26 mmol) and NBS (1.81 g, 10.2 mmol) were reacted. After purification by column chromatography over silica gel 60N (hexane–ethyl acetate = 3:1), **S9** was obtained as a pale yellow solid (2.92 g, 90%). This compound was somewhat unstable and used for the next reaction without further purification. Mp 53–54 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 3.54 (s, 3H), 3.86 (s, 3H), 5.06 (s, 2H), 5.17 (s, 2H), 6.81 (s, 1H), 7.06 (s, 1H), 7.28–7.34 (m, 1H), 7.34–7.40 (m, 2H), 7.40–7.45 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.3, 56.5, 72.0, 96.3, 102.4, 102.8, 119.0, 127.5, 128.0, 128.6, 136.7, 144.0, 148.6, 150.0. HRDARTMS *m*/*z*. Calcd for $C_{16}H_{18}BrO_4$ [$(M+H)^+$]: 353.03885. Found: 353.03779.



8e

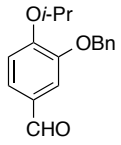
5-Benzyloxy-4-methoxy-2-(methoxymethoxy)phenylboronic acid (8e). According to the procedure described for the preparation of **8b**, **S9** (2.82 g, 7.99 mmol) was reacted to give **8e** as a pale yellow powder (2.01 g, 79%). This compound was used for the next reaction without further purification. Mp 88–90 °C. IR (KBr): 3329, 1604, 1513, 1397, 1205, 1151, 1006 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.51 (s, 3H), 3.89 (s, 3H), 5.11 (s, 2H), 5.24 (s, 2H), 5.99 (s, 2H), 6.78 (s, 1H), 7.27–7.32 (m, 1H), 7.33–7.38 (m, 2H), 7.39 (s, 1H), 7.44–7.47 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 56.0, 56.5, 71.6, 95.5, 99.4, 121.0, 127.6, 127.8, 128.5, 137.3, 143.3, 153.4, 158.3. HREIMS *m*/*z*. Calcd for $C_{16}H_{19}BO_6$ (M^+): 318.1275. Found: 318.1277.



S10

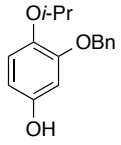
3-Hydroxy-4-isopropoxybenzaldehyde (S10). A neat liquid of 2-bromopropane (4.42 mL, 47.1 mmol) was added to a suspension of 3,4-dihydroxybenzaldehyde (5.01 g, 36.3 mmol), KI (6.02 g, 36.3 mmol), and K_2CO_3 (5.01 g, 36.2 mmol) in DMF (30 mL) at 40 °C. After stirring for 21 h at 40 °C, the reaction mixture was cooled to 0 °C and

quenched with 2 M HCl until bubbling subsided. The mixture was extracted with ethyl acetate and the extract was washed with water, and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane–ethyl acetate = 5:1) to give **S10** as a pale yellow granules (4.25 g, 65%). Recrystallization from Et_2O–hexane gave a colorless needles. Mp 65.5–66.5 °C (lit.[10] 69–70 °C). IR (KBr): 1673, 1505, 1274, 1126, 1104 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.42 (d, J = 6.1 Hz, 6H), 4.74 (sep, J = 6.1 Hz, 1H), 5.93 (s, 1H), 6.96 (d, J = 8.2 Hz, 1H), 7.41 (dd, J = 2.0 and 8.2 Hz, 1H), 7.45 (d, J = 2.0 Hz, 1H), 9.83 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 71.9, 111.9, 114.3, 124.3, 130.2, 146.7, 150.1, 191.0. HRDARTMS *m*/*z*. Calcd for $C_{10}H_{13}O_3$ [$(M+H)^+$]: 181.08647. Found: 181.08351. These physical and spectroscopic data are in good agreement with those previously reported.[10]



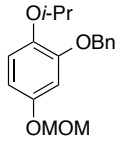
S11

3-Benzyloxy-4-isopropoxybenzaldehyde (S11). According to the procedure described for the preparation of **S6**, a mixture of 3-hydroxy-4-isopropoxybenzaldehyde (3.89 g, 21.6 mmol), benzyl bromide (3.33 mL, 28.0 mmol), and K_2CO_3 (3.87 g, 28.0 mmol) in acetone (40 mL) was refluxed for 22 h. After purification by chromatography over silica gel 60N (hexane–ethyl acetate), **S11** was obtained as a colorless solid (5.71 g, 98%). Bp 150–155 °C (0.1 mmHg, bulb-to-bulb). Mp 34.5–35.5 °C (lit.[10] 37.5–38 °C). IR (KBr): 1688, 1595, 1579, 1506, 1269, 1132 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.41 (d, J = 6.1 Hz, 6H), 4.68 (sep, J = 6.1 Hz, 1H), 5.17 (s, 2H), 7.00 (d, J = 8.2 Hz, 1H), 7.28–7.33 (m, 1H), 7.34–7.40 (m, 2H), 7.42–7.47 (m, 4H), 9.80 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 71.0, 71.7, 113.1, 114.1, 126.7, 127.2, 127.9, 128.5, 129.9, 136.7, 149.6, 154.0, 190.8. HRDARTMS *m*/*z*. Calcd for $C_{17}H_{19}O_3$ [$(M+H)^+$]: 271.13342. Found: 271.13063. These physical and spectroscopic data are in good agreement with those previously reported.[10]



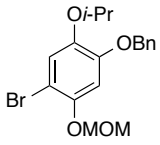
S12

3-Benzyloxy-4-isopropoxyphenol (S12). According to the procedure described for the preparation of **S7**, **S11** (3.00 g, 11.1 mmol) was reacted. After purification by column chromatography over silica gel 60N (hexane–ethyl acetate = 3:1), **S12** was obtained as a pale yellow solid (2.23 g, 78%). Recrystallization from Et_2O–hexane gave pale yellow granules. Mp 111–112 °C. IR (KBr): 3294, 1604, 1511, 1452, 1220, 1205, 1177, 1102 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (d, J = 6.1 Hz, 6H), 4.34 (sep, J = 6.1 Hz, 1H), 5.01 (s, 2H), 5.13 (br s, 1H), 6.31 (dd, J = 2.8 and 8.6 Hz, 1H), 6.45 (d, J = 2.8 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 7.26–7.32 (m, 1H), 7.32–7.38 (m, 2H), 7.38–7.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 70.8, 73.8, 103.1, 107.1, 120.8, 127.2, 127.8, 128.5, 137.1, 141.3, 151.2, 151.3. *Anal*. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.34; H, 6.94.



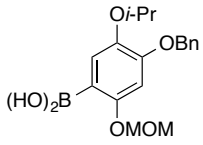
S13

2-Benzyloxy-1-isopropoxy-4-(methoxymethoxy)benzene (S13). According to the procedure described for the preparation of **S1**, **S12** (785 mg, 3.04 mmol) was reacted. After purification by column chromatography over silica gel 60N (hexane–ethyl acetate = 5:1), **S13** was obtained as a colorless solid (856 mg, 93%). Bp 200–210 °C (3 mmHg, bulb-to-bulb). IR (KBr): 1506, 1260, 1221, 1153, 1020 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.31 (d, J = 6.1 Hz, 6H), 3.45 (s, 3H), 4.38 (sep, J = 6.1 Hz, 1H), 5.08 (s, 2H), 5.09 (s, 2H), 6.57 (dd, J = 2.8 and 8.7 Hz, 1H), 6.68 (d, J = 2.8 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 7.27–7.33 (m, 1H), 7.33–7.40 (m, 2H), 7.42–7.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 55.9, 71.0, 73.3, 95.1, 104.9, 108.1, 119.9, 127.3, 127.7, 128.4, 137.2, 142.9, 151.0, 152.6. HRDARTMS *m*/*z*. Calcd for $C_{18}H_{23}O_4$ [$(M+H)^+$]: 303.15963. Found: 303.15982.



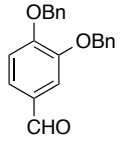
S14

1-Benzyloxy-4-bromo-2-isopropoxy-5-(methoxymethoxy)benzene (S14). According to the procedure described for the preparation of **S3**, **S13** (600 mg, 1.98 mmol) and NBS (352 mg, 1.98 mmol) were reacted. After purification by column chromatography over silica gel 60N (hexane–ethyl acetate = 10:1), **S14** was obtained as a colorless solid (725 mg, 96%). This compound was somewhat unstable and used for the next reaction without further purification. IR (KBr): 1505, 1374, 1202, 1152, 1007 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (d, J = 6.0 Hz, 6H), 3.48 (s, 3H), 4.40 (sep, J = 6.0 Hz, 1H), 5.09 (s, 2H), 5.10 (s, 2H), 6.83 (s, 1H), 7.10 (s, 1H), 7.27–7.33 (m, 1H), 7.33–7.40 (m, 2H), 7.40–7.46 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 56.3, 71.5, 73.4, 96.1, 103.3, 105.8, 122.7, 127.4, 127.9, 128.5, 136.8, 143.7, 148.7, 150.0. HRDARTMS *m*/*z*. Calcd for $C_{18}H_{22}BrO_4$ [$(M+H)^+$]: 381.07015. Found: 381.07031.



8f

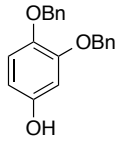
4-Benzyloxy-5-isopropoxy-2-(methoxymethoxy)phenylboronic acid (8f). According to the procedure described for the preparation of **8c**, **S14** (574 mg, 1.51 mmol) was reacted to give **8f** as a colorless solid (367 mg, 70%). This compound was used for the next reaction without further purification. Mp 92–93.5 °C. IR (KBr): 1602, 1509, 1420, 1397, 1316, 1204, 1155, 1006 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (d, J = 6.1 Hz, 6H), 3.46 (s, 3H), 4.45 (sep, J = 6.1 Hz, 1H), 5.15 (s, 2H), 5.16 (s, 2H), 6.30 (s, 1H), 6.33 (s, 1H), 6.81 (s, 1H), 7.27–7.33 (m, 1H), 7.34–7.39 (m, 2H), 7.40 (s, 1H), 7.42–7.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 56.3, 70.8, 73.0, 95.4, 102.0, 125.5, 127.3, 127.9, 128.5, 136.8, 142.8, 153.5, 158.2. HREIMS *m*/*z*. Calcd for $C_{18}H_{23}BO_6$ (M^+): 346.1588. Found: 346.1581.



S15

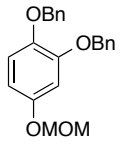
3,4-Bis(benzyloxy)benzaldehyde (S15). According to the procedure described for the preparation of **S6**, a mixture of 3,4-dihydroxybenzaldehyde (5.53 g, 40.0 mmol), benzyl bromide (9.50 mL, 80 mmol), and K_2CO_3 (11.6 g, 84.0 mmol) in acetone (400 mL) was

refluxed for 21 h. The crude product was recrystallized from dichloromethane–hexane to give **S15** as a colorless granules (9.39 g, 73%). The mother liquor from the above recrystallization was evaporated and the residue was chromatographed over silica gel 60N (hexane–ethyl acetate = 5:1) to give an additional **S15** as a colorless yellow solid (332 mg, 3%). The total yield of **S15** was 9.72 g (76%). Mp 83.5–84 °C (lit.[11] 88–89 °C). IR (KBr): 1677, 1596, 1512, 1435, 1282, 1135 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 5.21 (s, 2H), 5.25 (s, 2H), 7.02 (d, J = 8.2 Hz, 1H), 7.29–7.35 (m, 2H), 7.35–7.40 (m, 4H), 7.41 (dd, J = 1.9 and 8.2 Hz, 1H), 7.43–7.48 (m, 4H), 7.49 (d, J = 1.9 Hz, 1H), 9.81 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 70.8, 71.0, 112.4, 113.1, 126.7, 127.1, 127.3, 128.0, 128.1, 128.6, 128.7, 130.3, 136.2, 136.5, 149.2, 154.3, 190.8. HRDARTMS *m*/*z*. Calcd for $C_{21}H_{19}O_3$ $[(M+H)^+]$: 319.13342. Found: 319.13108. These physical and spectroscopic data are in good agreement with those previously reported.[11,12]



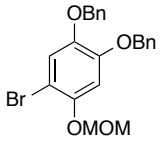
S16

3,4-Bis(benzyloxy)phenol (S16). According to the procedure described for the preparation of **S7**, **S15** (8.36 g, 29.2 mmol) was reacted. After recrystallization from dichloromethane–hexane, **S16** was obtained as a pale yellow granules (6.93 g, 86%). Mp 103.5–104.5 °C (lit.[12] 102–104 °C). IR (KBr): 3294, 1609, 1508, 1455, 1380, 1213, 1124, 1004 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.94 (br s, 1H), 5.04 (s, 2H), 5.07 (s, 2H), 6.28 (dd, J = 2.8 and 8.6 Hz, 1H), 6.48 (d, J = 2.8 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 7.26–7.37 (m, 6H), 7.38–7.43 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 71.0, 72.8, 103.3, 107.0, 117.6, 127.3, 127.6, 127.8, 127.9, 128.4, 128.5, 137.0, 137.6, 142.7, 150.3, 150.9. HRDARTMS *m*/*z*. Calcd for $C_{20}H_{19}O_3$ $[(M+H)^+]$: 307.13342. Found: 307.13631. These physical and spectroscopic data are in good agreement with those previously reported.[11,12]



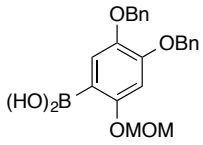
S17

1,2-Bis(benzyloxy)-4-(methoxymethoxy)benzene (S17). According to the procedure described for the preparation of **S1**, **S16** (8.65 g, 37.6 mmol) was reacted. After purification by column chromatography (hexane–ethyl acetate = 4:1), **S17** was obtained as a colorless solid (8.87 g, 86%). Recrystallization from Et_2O–hexane gave colorless needles. Mp 50–51 °C. IR (KBr): 1595, 1511, 1218, 1150, 1131, 1010 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.44 (s, 3H), 5.07 (s, 2H), 5.08 (s, 2H), 5.13 (s, 2H), 6.55 (dd, J = 2.8 and 8.8 Hz, 1H), 6.70 (d, J = 2.8 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1H), 7.26–7.39 (m, 6H), 7.40–7.47 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 55.9, 71.1, 72.4, 95.2, 104.9, 108.0, 116.8, 127.4, 127.5, 127.7, 127.8, 128.4, 128.5, 137.1, 137.6, 144.0, 150.0, 152.4. HRDARTMS *m*/*z*. Calcd for $C_{22}H_{23}O_4$ $[(M+H)^+]$: 351.15963. Found: 351.16166. These physical and spectroscopic data are in good agreement with those previously reported.[11]



S18

1,2-Bis(benzyloxy)-5-bromo-4-(methoxymethoxy)benzene (S18). According to the procedure described for the preparation of **S3**, **S17** (1.00 g, 2.85 mmol) and NBS (533 mg, 2.99 mmol) were reacted. After purification by column chromatography over silica gel 60N (hexane–ethyl acetate = 10:1), **S18** was obtained as a colorless solid (978 mg, 80%). This compound was somewhat unstable and used for the next reaction without further purification. Mp 38–39 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.48 (s, 3H), 5.07 (s, 2H), 5.09 (s, 2H), 5.12 (s, 2H), 6.86 (s, 1H), 7.11 (s, 1H), 7.27–7.39 (m, 6H), 7.39–7.45 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.3, 71.6, 72.4, 96.1, 103.3, 105.8, 120.1, 127.5, 128.0, 128.0, 128.5, 136.7, 136.9, 144.7, 148.7, 149.0. HRDARTMS *m*/*z*. Calcd for $C_{22}H_{22}BrO_4$ [$(M+H)^+$]: 429.07015. Found: 429.07178.



8g

4,5-Bis(benzyloxy)-2-(methoxymethoxy)phenylboronic acid (8g). According to the procedure described for the preparation of **8c**, **S18** (1.22 g, 2.87 mmol) was reacted to give **8g** as a colorless solid (905 mg, 80%). This compound was used for the next reaction without further purification. Mp 106–109 °C. IR (KBr): 3310, 1602, 1512, 1421, 1396, 1319, 1215, 1150, 1017 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.46 (s, 3H), 5.12 (s, 2H), 5.16 (s, 2H), 5.18 (s, 2H), 5.93 (s, 2H), 6.83 (s, 1H), 7.27–7.39 (m, 6H), 7.43 (s, 1H), 7.43–7.47 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 56.3, 71.0, 72.0, 95.4, 102.0, 122.3, 127.4, 127.6, 127.8, 127.9, 128.4, 128.5, 136.7, 137.5, 143.9, 152.5, 158.2. HREIMS *m*/*z*. Calcd for $C_{22}H_{23}BO_6$ (M^+): 394.1588. Found: 394.1589.

References

1. Deguchi, J.; Sasaki, T.; Hirasawa, Y.; Kaneda, T.; Kusumawari, I.; Shirota, O.; Morita, H. *Tetrahedron Lett.* **2014**, *55*, 1362–1365.
2. Bishop, J. E.; Mathis, C. A.; Gerdes, J. M.; Whitney, J. M.; Eaton, A. M.; Mailman, R. B. *J. Med. Chem.* **1991**, *34*, 1612–1624.
3. Jiang, H.; Tian, L.; Li, Z.; Liu, Q.; Li, C.; Yao, X.; Yang, Z. *Sci. China: Chem.* **2012**, *55*, 36–42.
4. Donnelly, D. M. X.; Finet, J.-P.; Rattigan, B. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1679–1683.
5. Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552–6554.
6. Worayuthakarn, R.; Boonya-udtayan, S.; Ruchirawat, S.; Thasana, N. *Eur. J. Org. Chem.* **2014**, 2496–2507.
7. Kamiyama, H.; Kubo, Y.; Sato, H.; Yamamoto, N.; Fukuda, T.; Ishibashi, F.; Iwao, M. *Bioorg. Med. Chem.* **2011**, *19*, 7541–7550.

8. Ploypradith, P.; Cheryklin, P.; Niyomtham, N.; Bertoni, D. R.; Ruchirawat, S. *Org. Lett.* **2007**, *9*, 2637–2640.
9. Cruz, M. C.; Tamariz, J. *Tetrahedron* **2005**, *61*, 10061–10072.
10. Hewgill, F. R. Pass, M. C. *Aust. J. Chem.* **1985**, *38*, 537–554.
11. Li, C. C.; Xie, Z. X.; Zhang, Y. D.; Chen, J. H.; Yang, Z. *J. Org. Chem.* **2003**, *68*, 8500–8504.
12. Yamaguchi, S.; Machi, M.; Kinoshita, Y. *Biosci. Biotechnol. Biochem.* **1999**, *63*, 1453–1462.

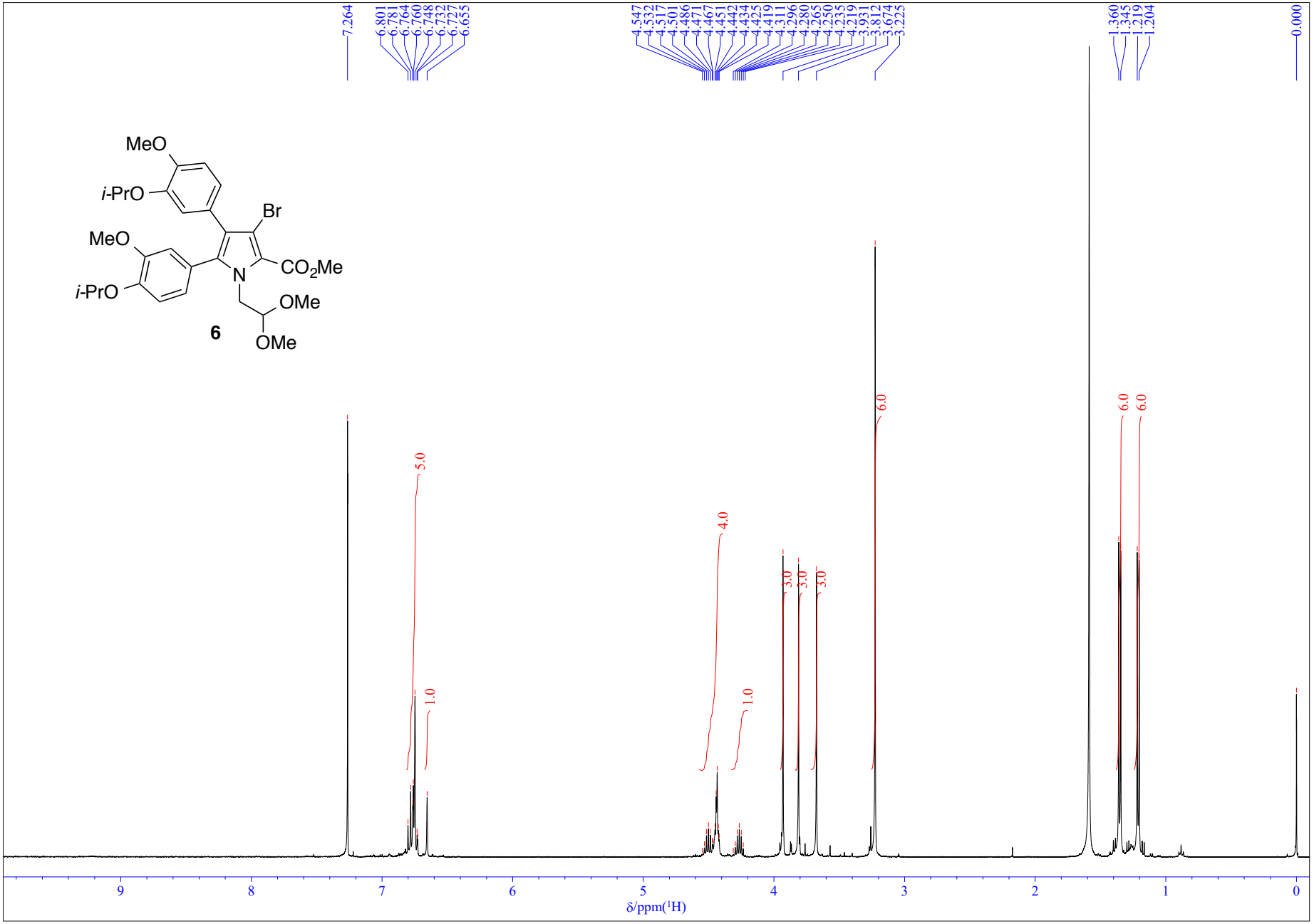


Figure S1. ^{1}H NMR spectrum of compound **6** (400 MHz, $CDCl_3$).

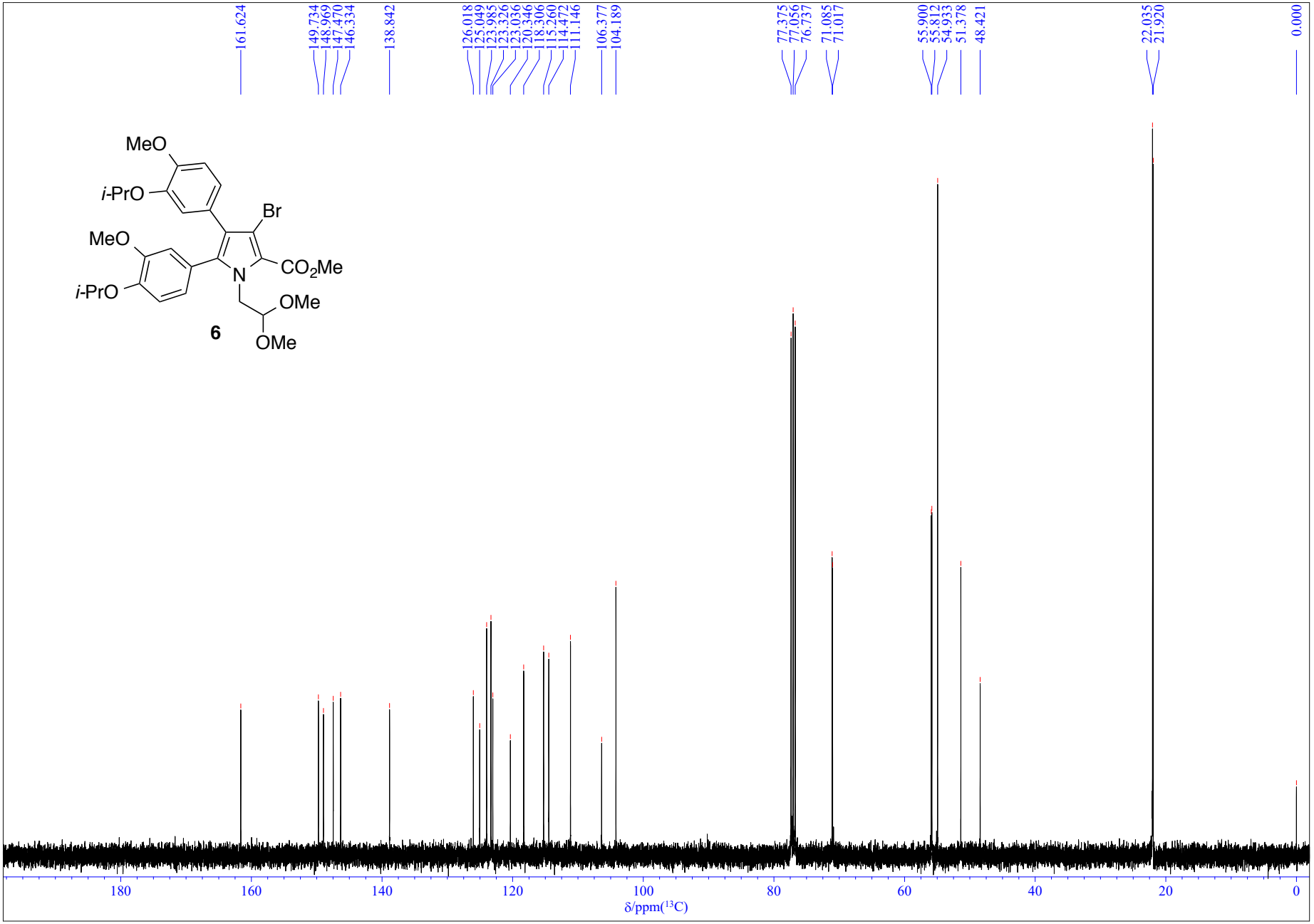


Figure S2. ^{13}C NMR spectrum of compound **6** (100 MHz, $CDCl_3$).

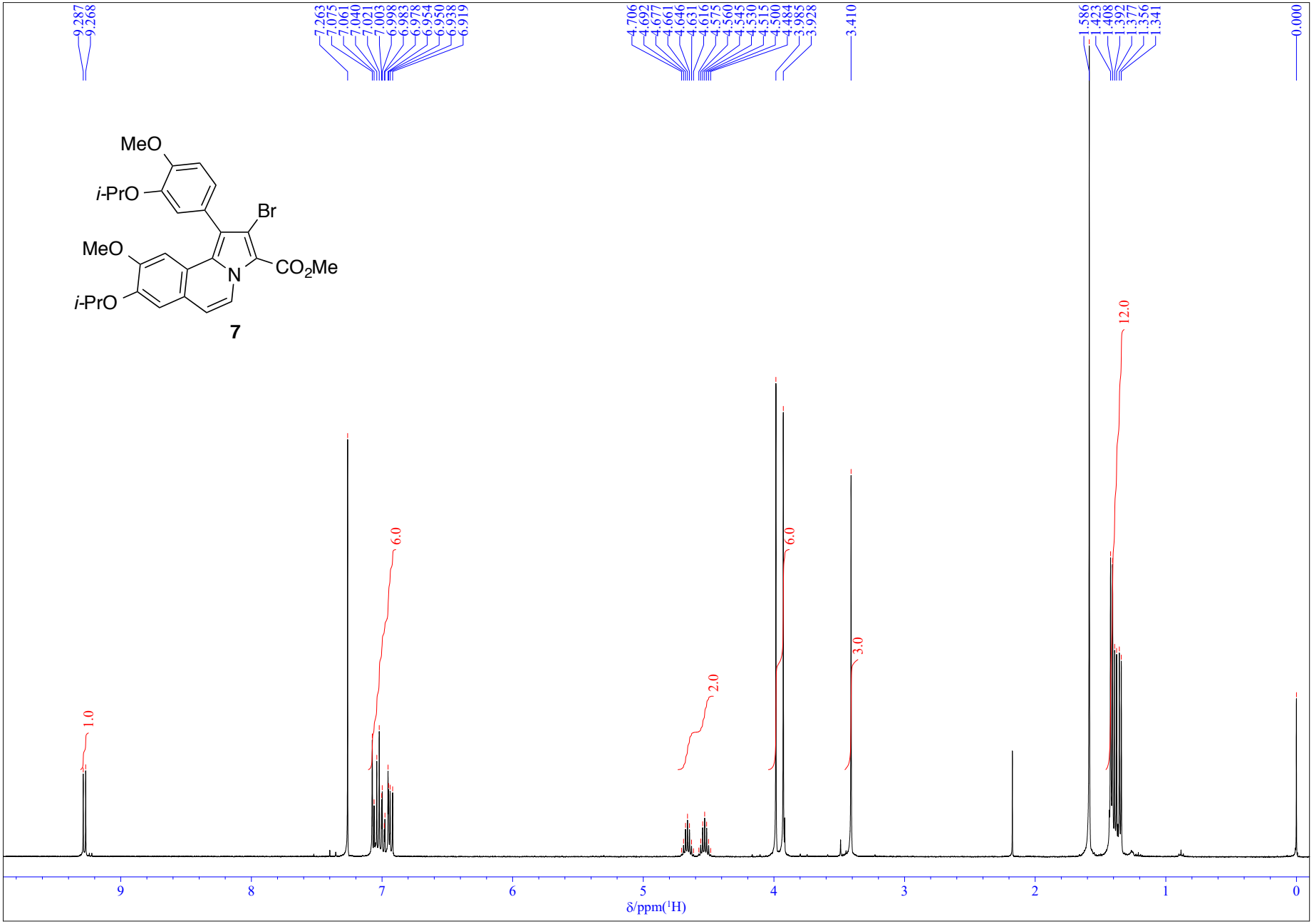


Figure S3. ^{1}H NMR spectrum of compound **7** (400 MHz, $CDCl_3$).

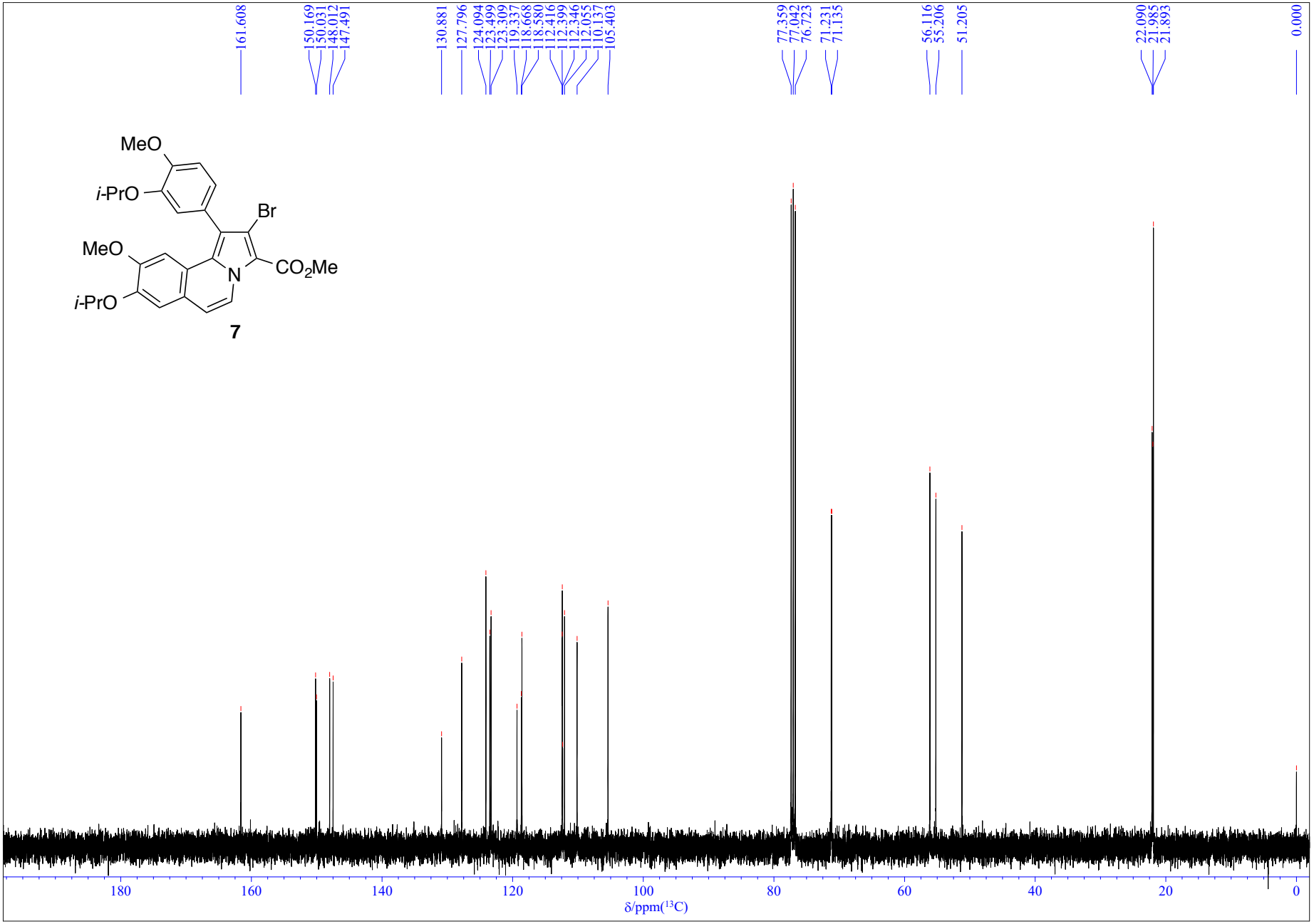


Figure S4. ^{13}C NMR spectrum of compound **7** (100 MHz, $CDCl_3$).

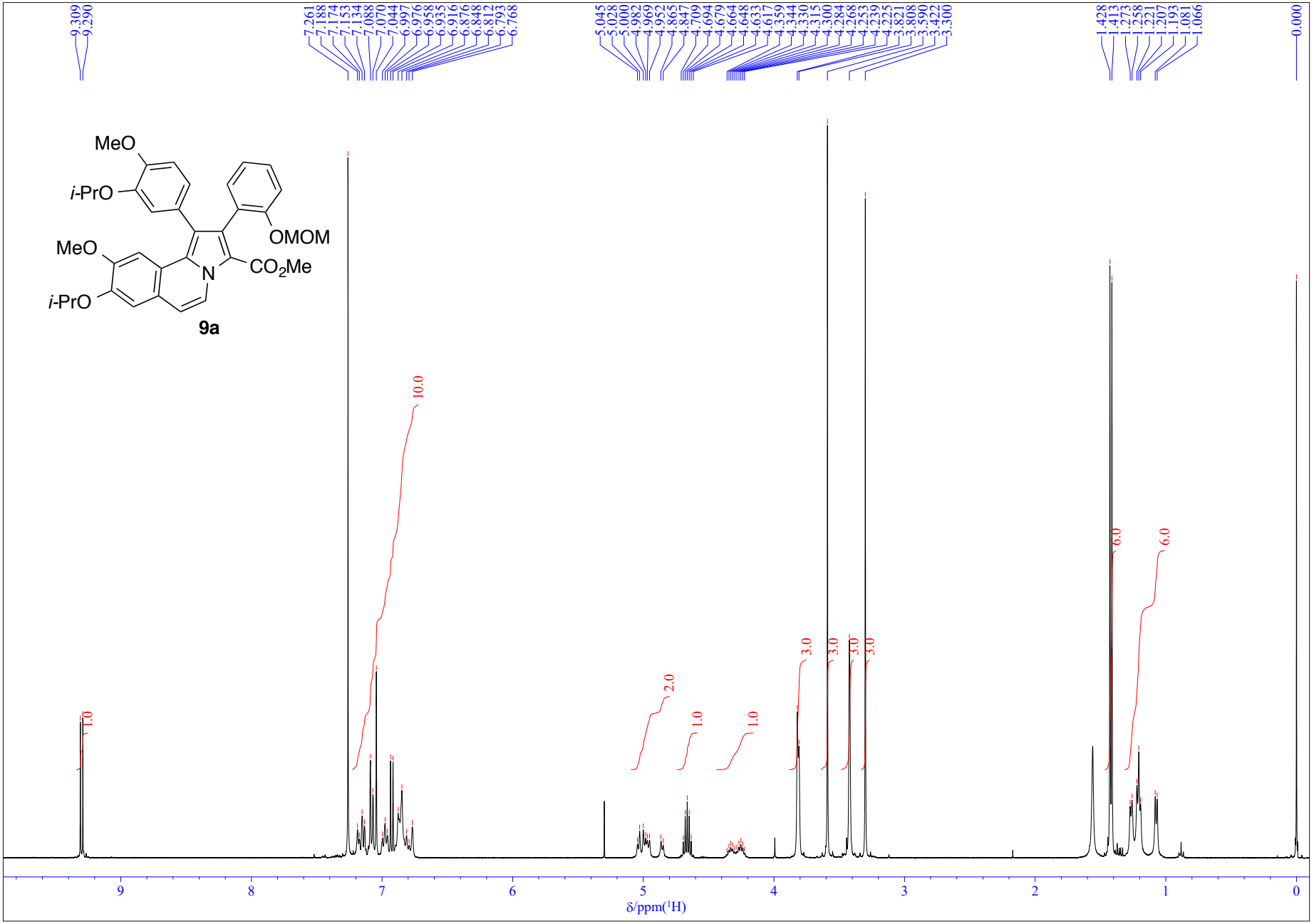


Figure S5. ^{1}H NMR spectrum of compound **9a** (400 MHz, $CDCl_3$).

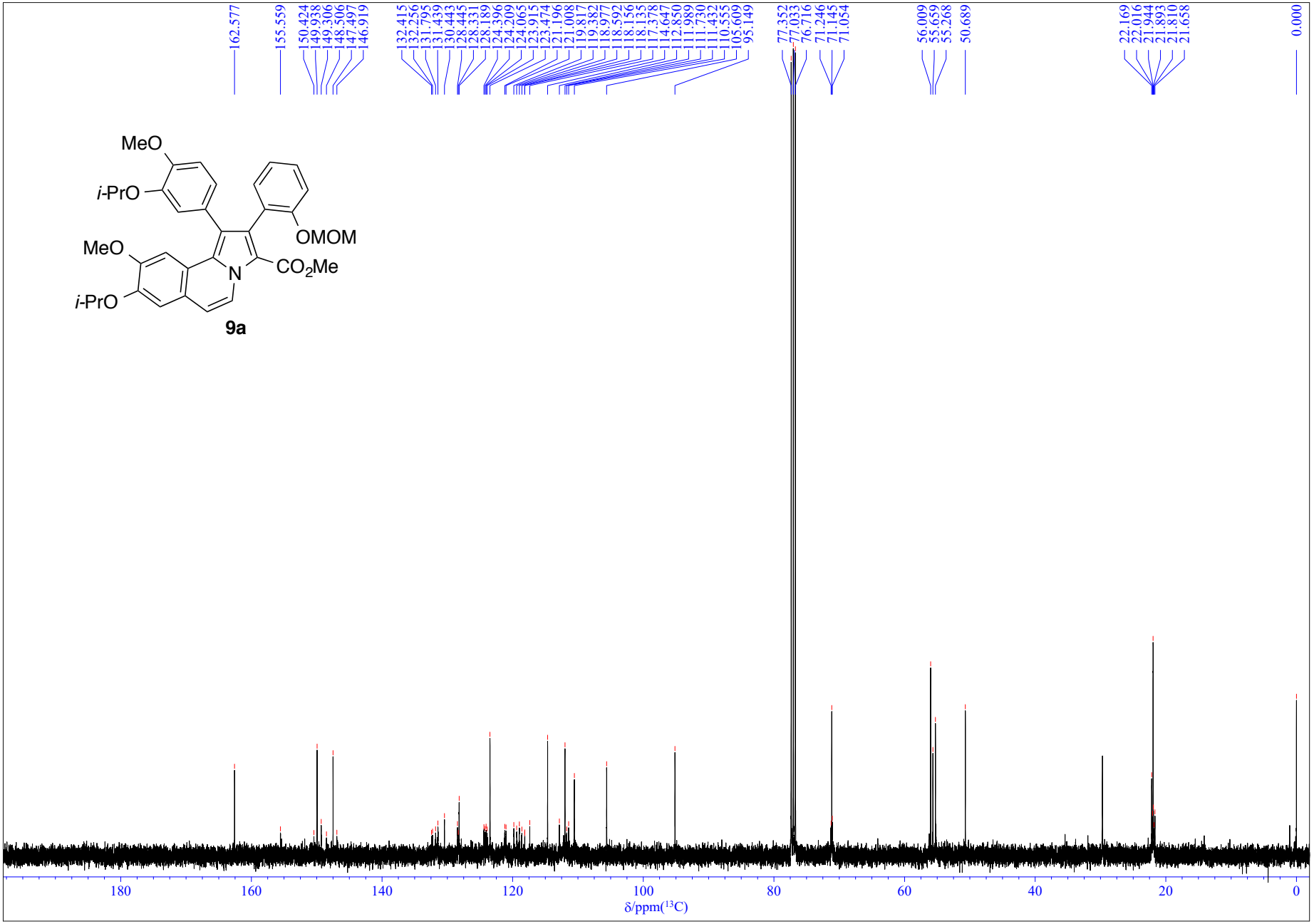


Figure S6. ^{13}C NMR spectrum of compound **9a** (100 MHz, $CDCl_3$).

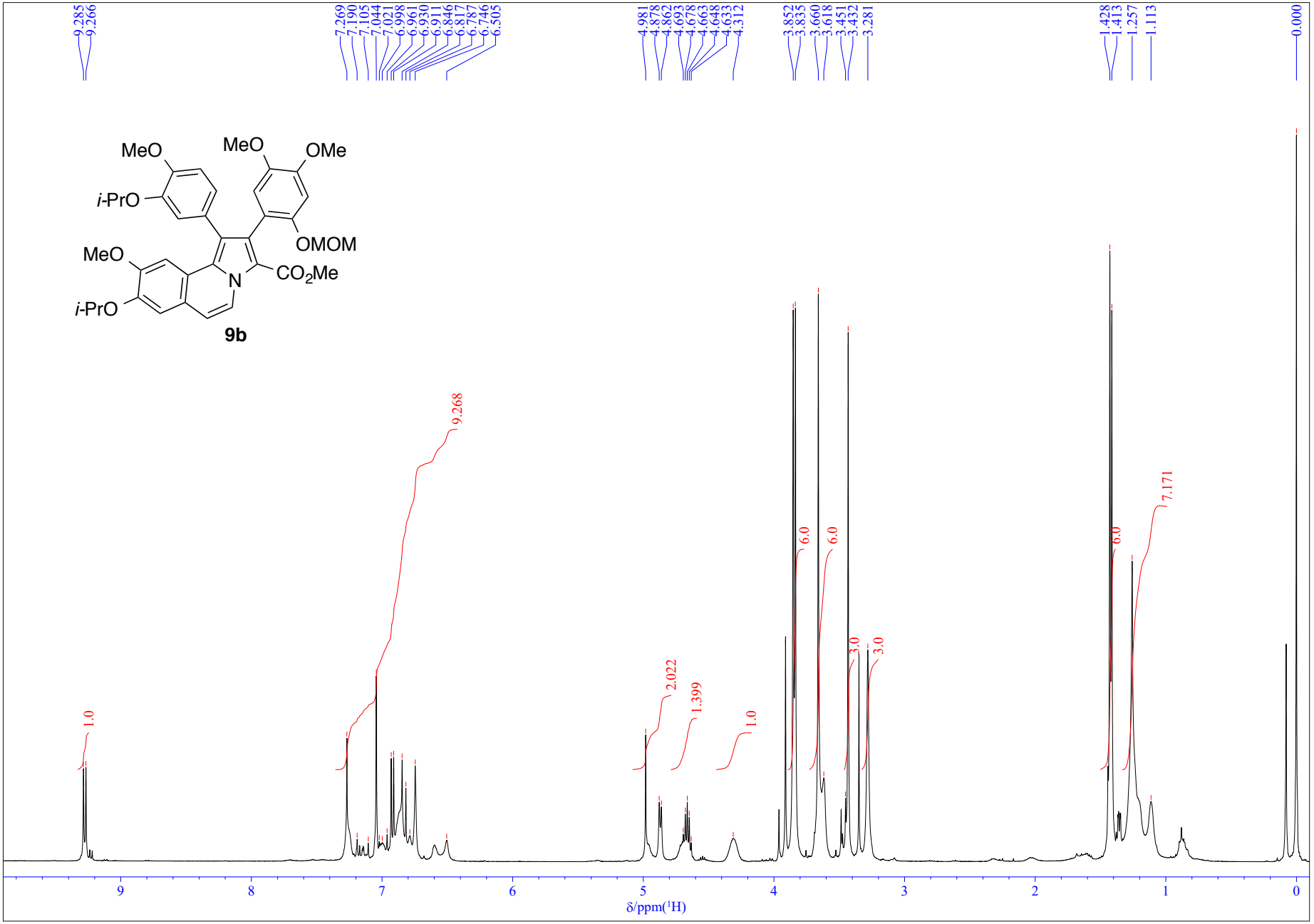


Figure S7. ^{1}H NMR spectrum of compound **9b** (400 MHz, $CDCl_3$).

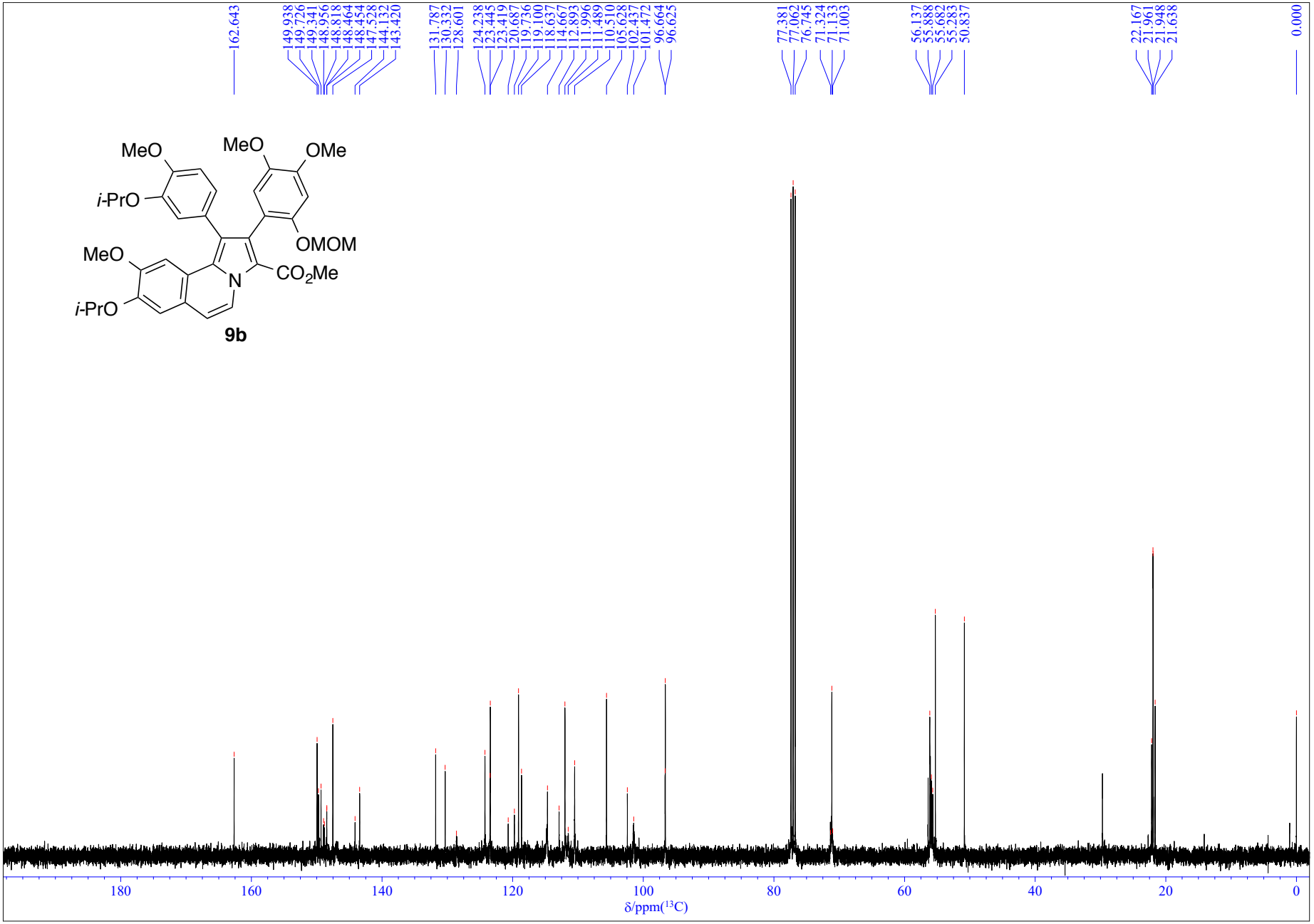


Figure S8. ^{13}C NMR spectrum of compound **9b** (100 MHz, $CDCl_3$).

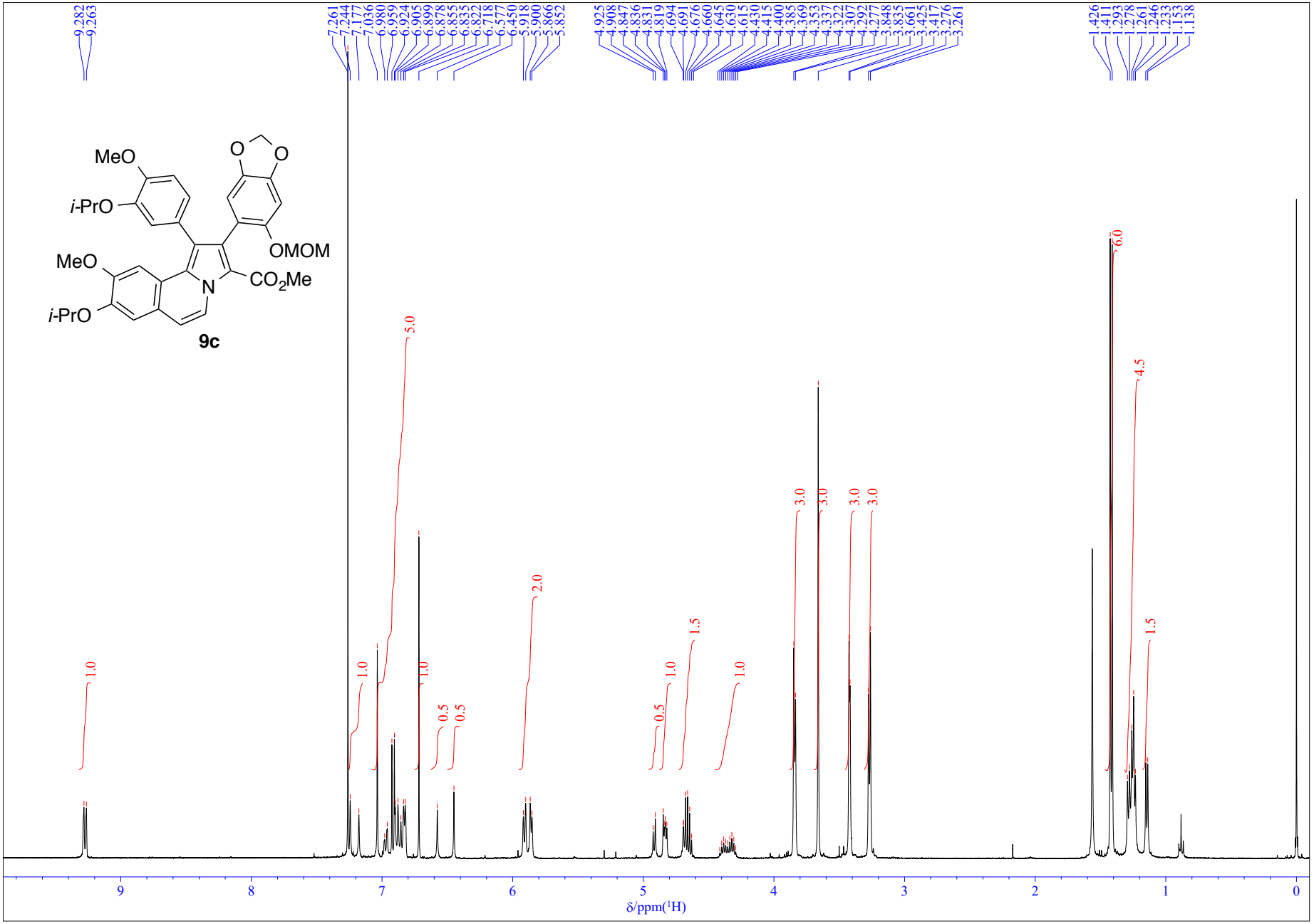


Figure S9. ^{1}H NMR spectrum of compound **9c** (400 MHz, $CDCl_3$).

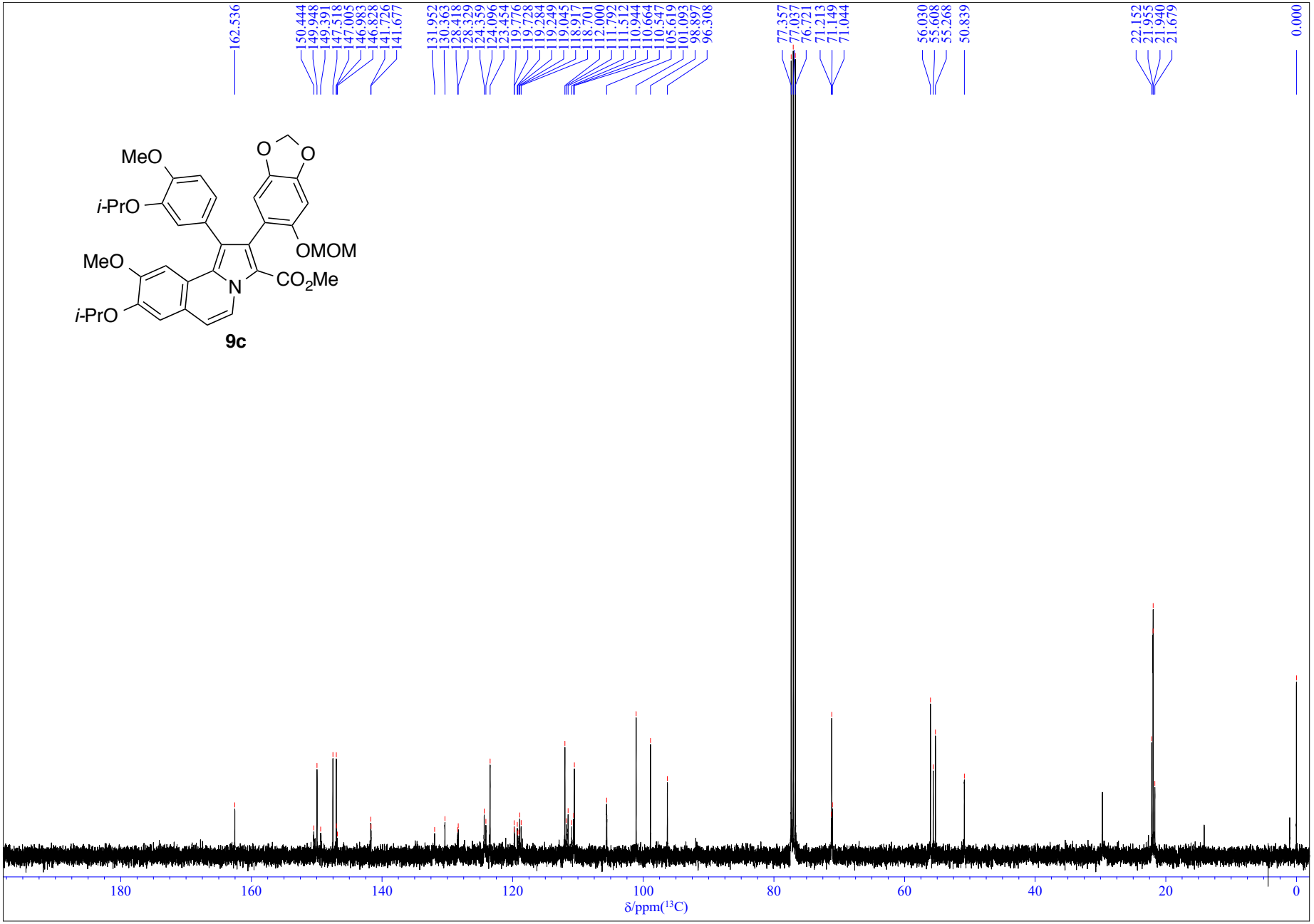


Figure S10. ^{13}C NMR spectrum of compound **9c** (100 MHz, $CDCl_3$).

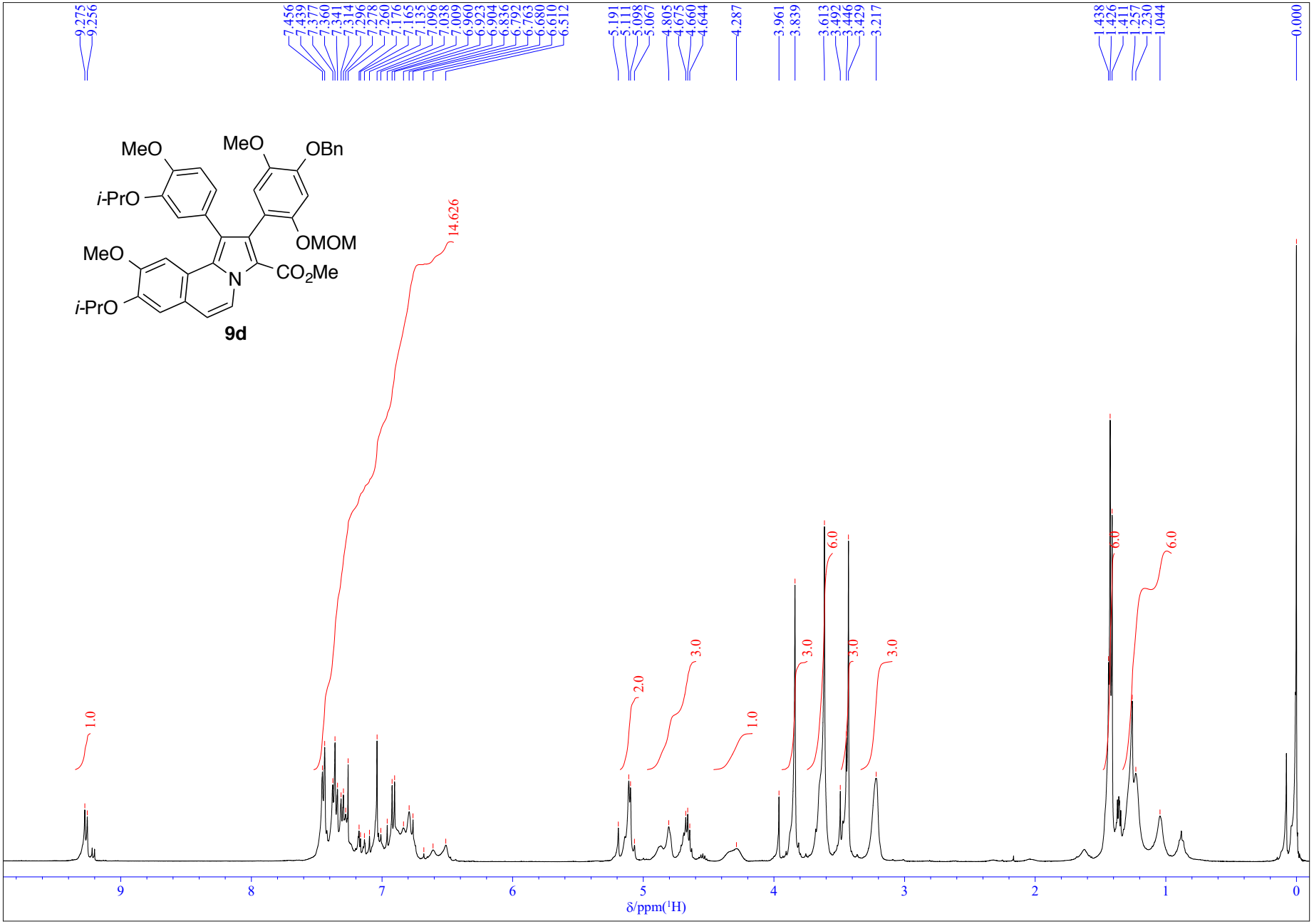


Figure S11. ^{1}H NMR spectrum of compound **9d** (400 MHz, $CDCl_3$).

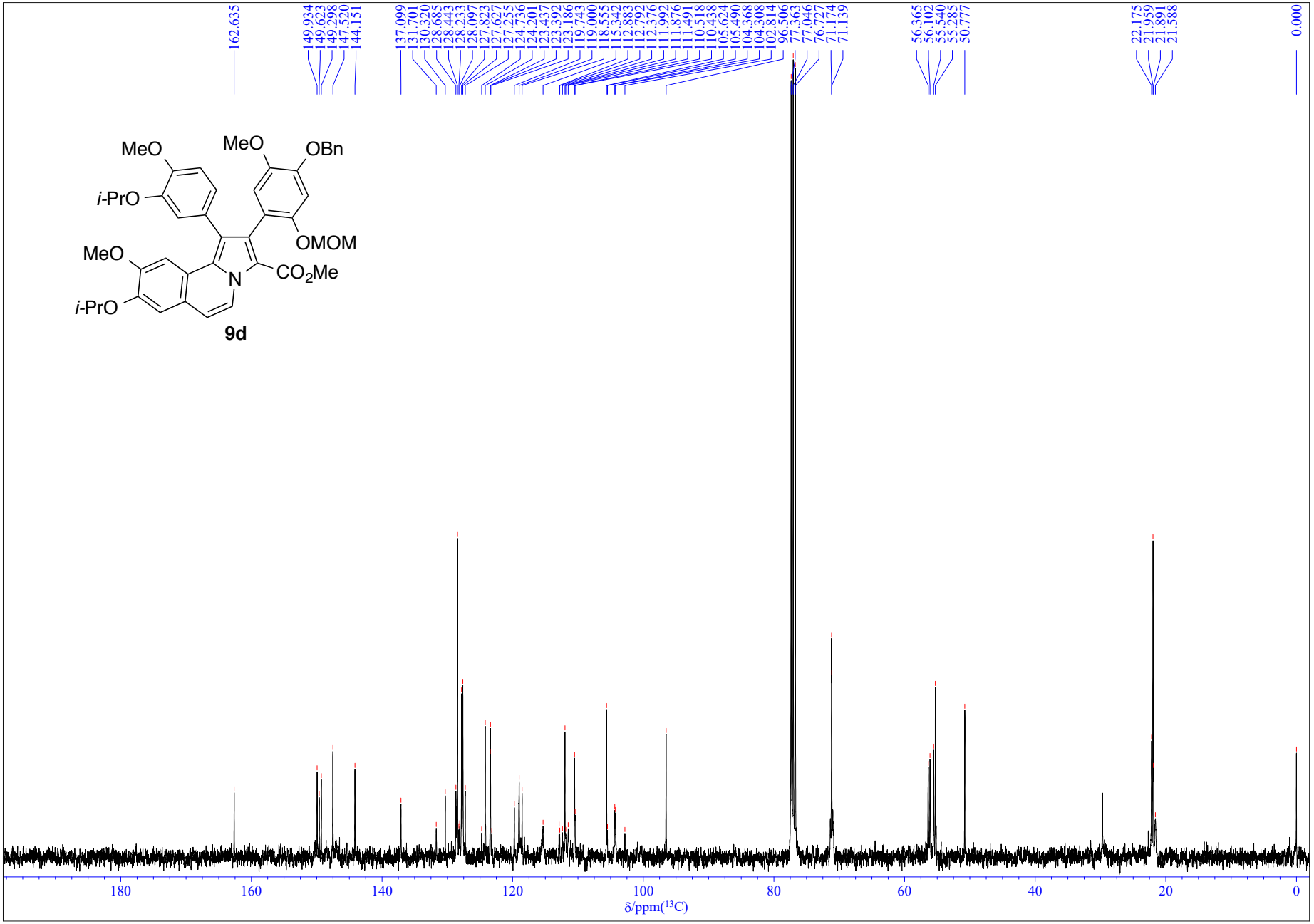


Figure S12. ^{13}C NMR spectrum of compound **9d** (100 MHz, $CDCl_3$).

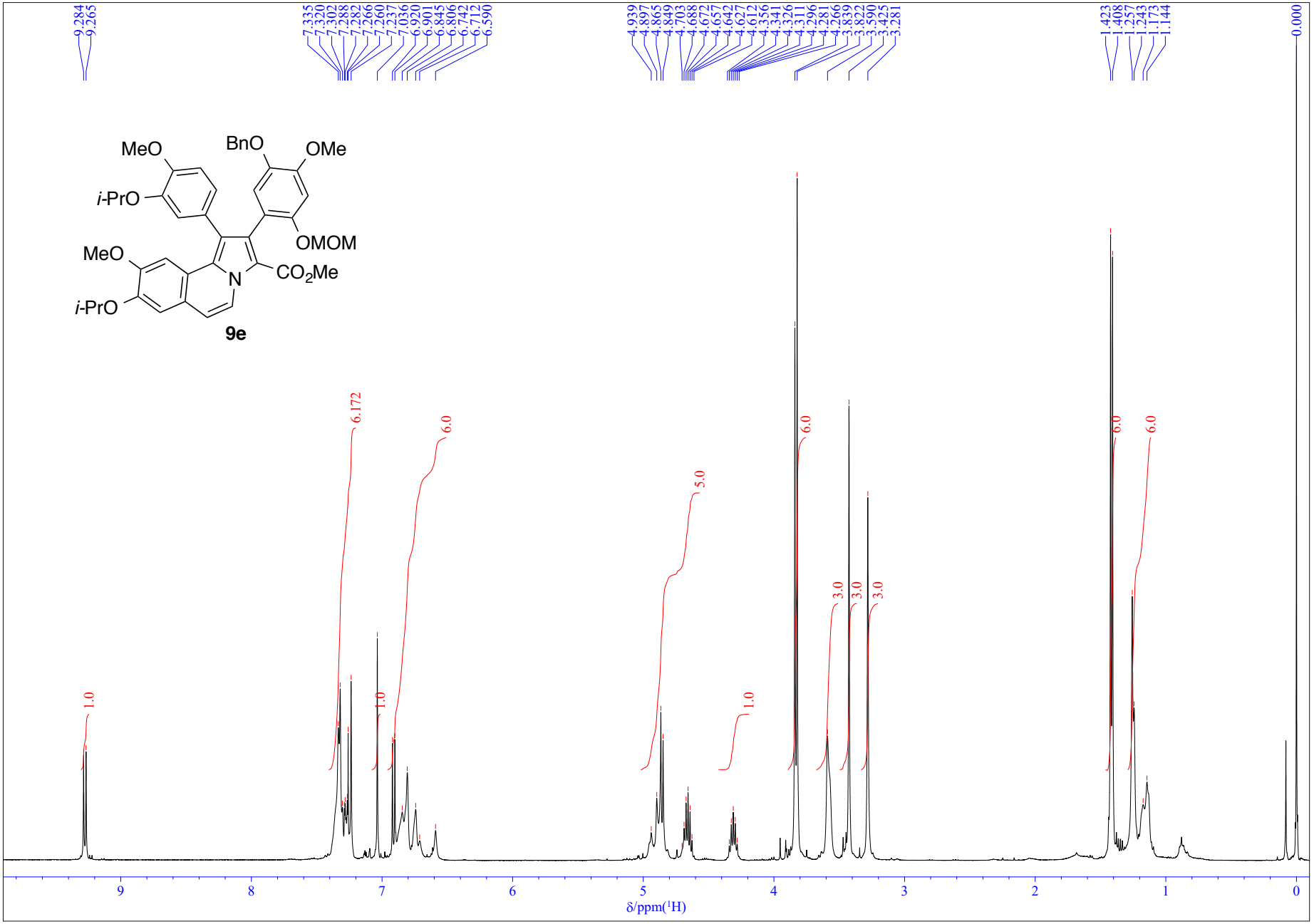


Figure S13. ^{1}H NMR spectrum of compound **9e** (400 MHz, $CDCl_3$).

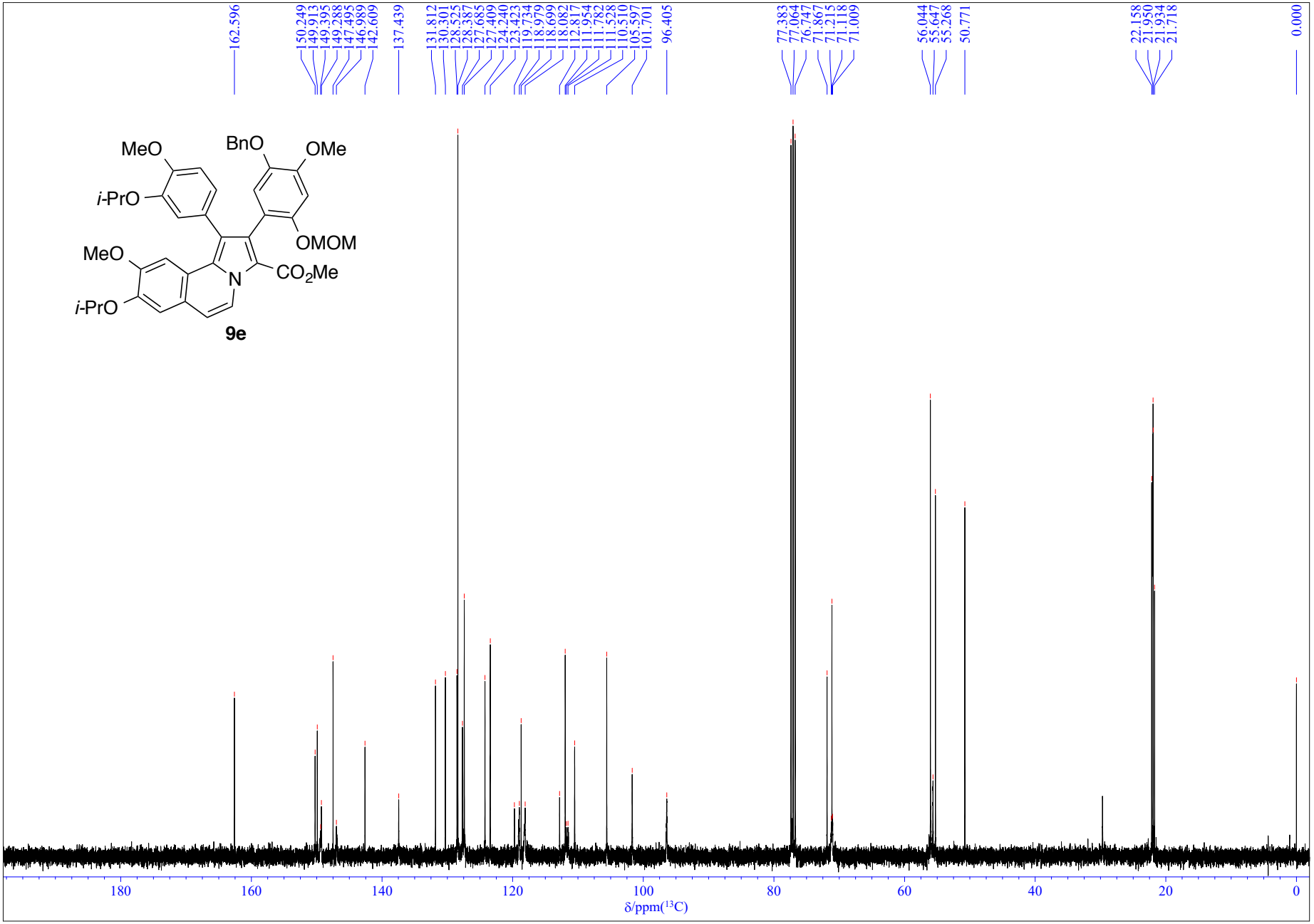


Figure S14. ^{13}C NMR spectrum of compound **9e** (100 MHz, $CDCl_3$).

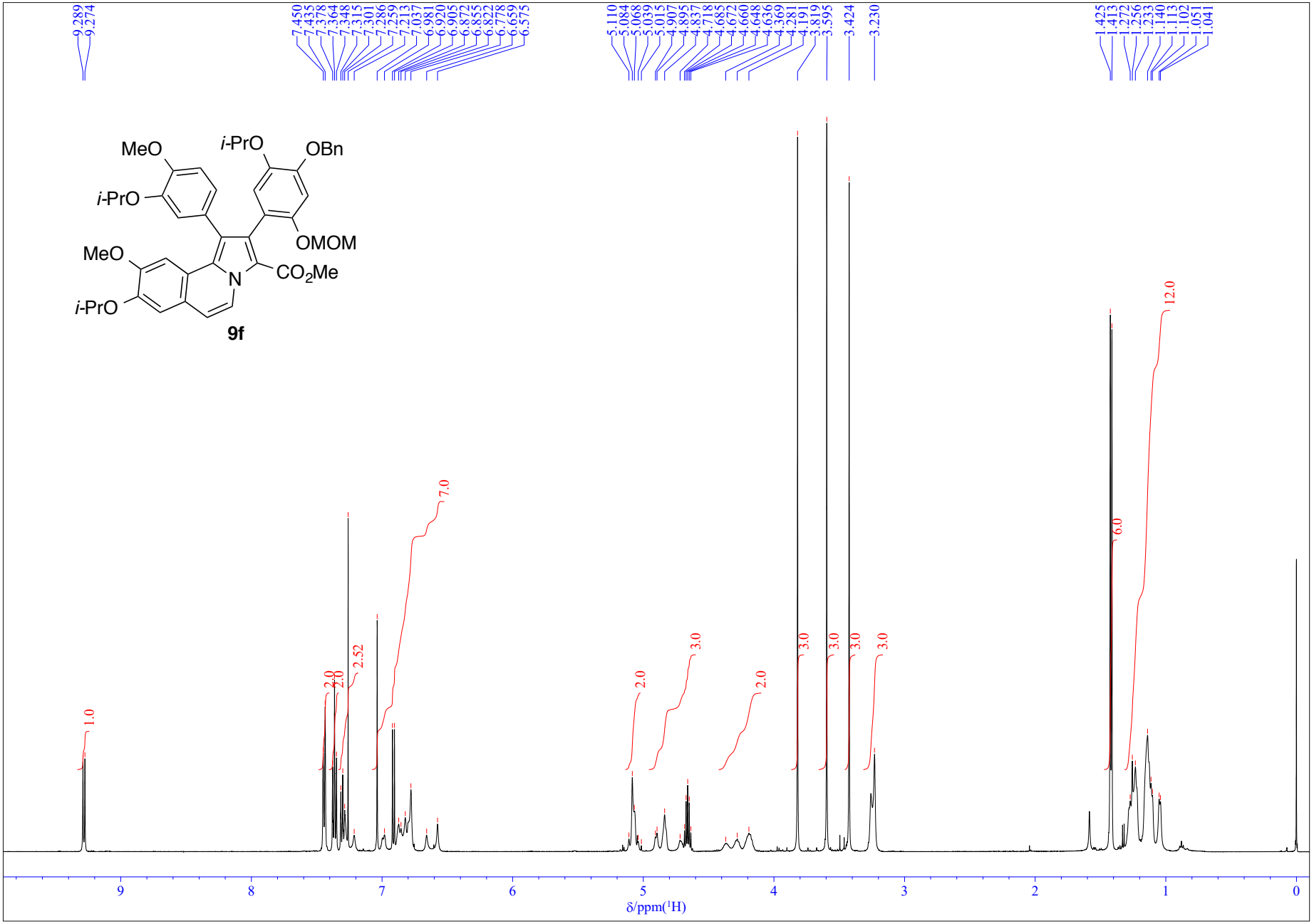


Figure S15. ^{1}H NMR spectrum of compound **9f** (500 MHz, $CDCl_3$).

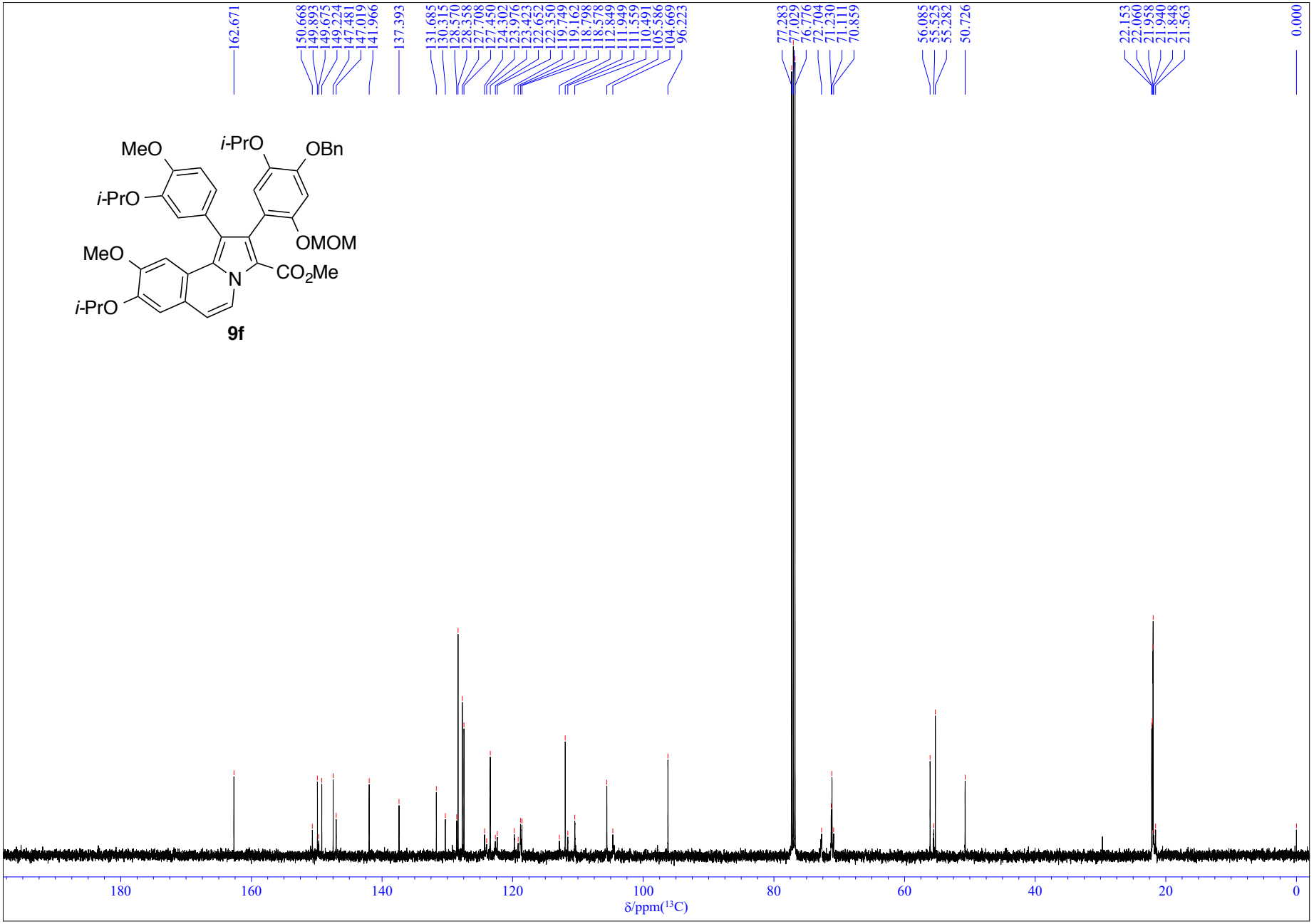


Figure S16. ^{13}C NMR spectrum of compound **9f** (126 MHz, $CDCl_3$).

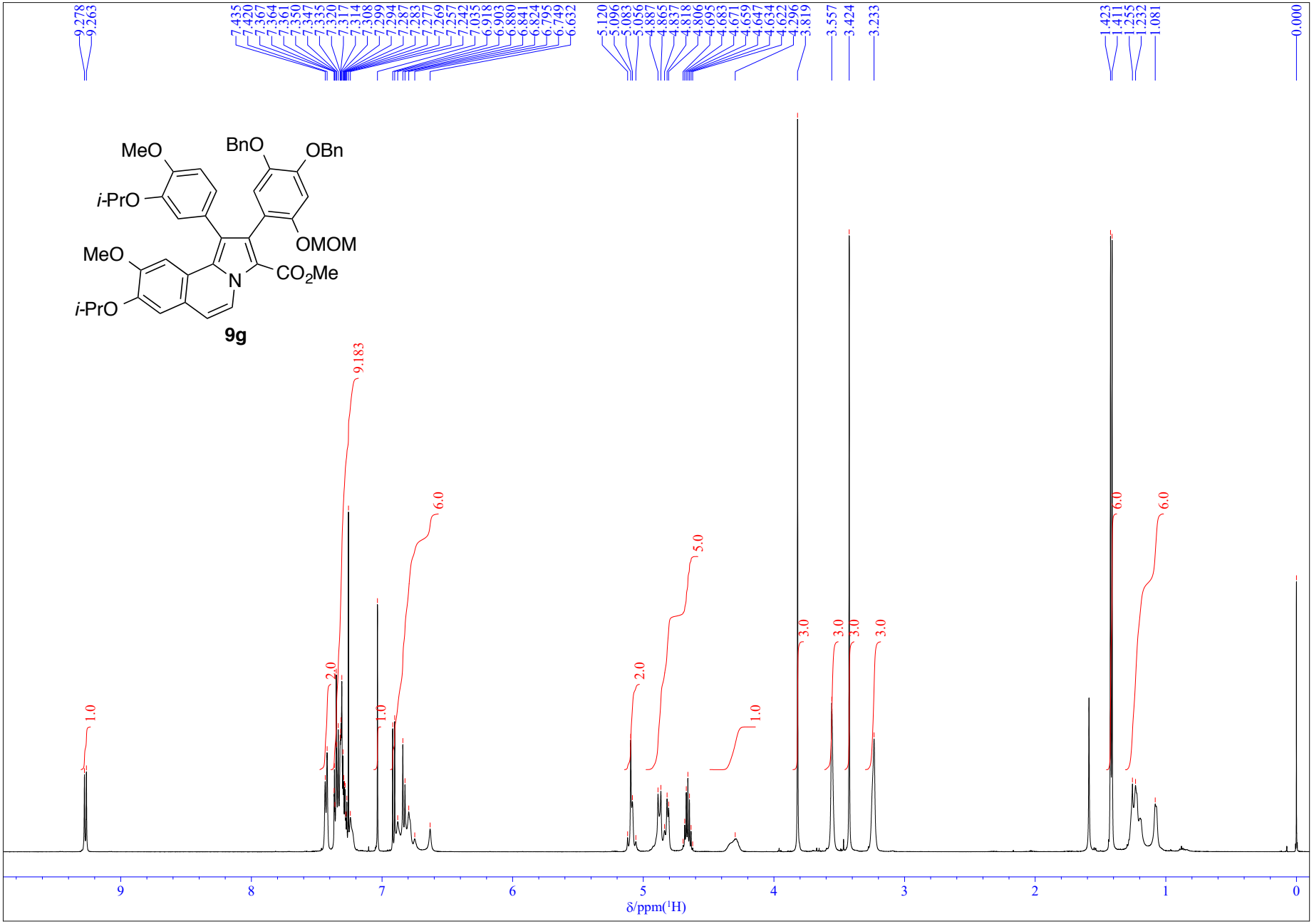


Figure S17. ^{1}H NMR spectrum of compound **9g** (500 MHz, $CDCl_3$).

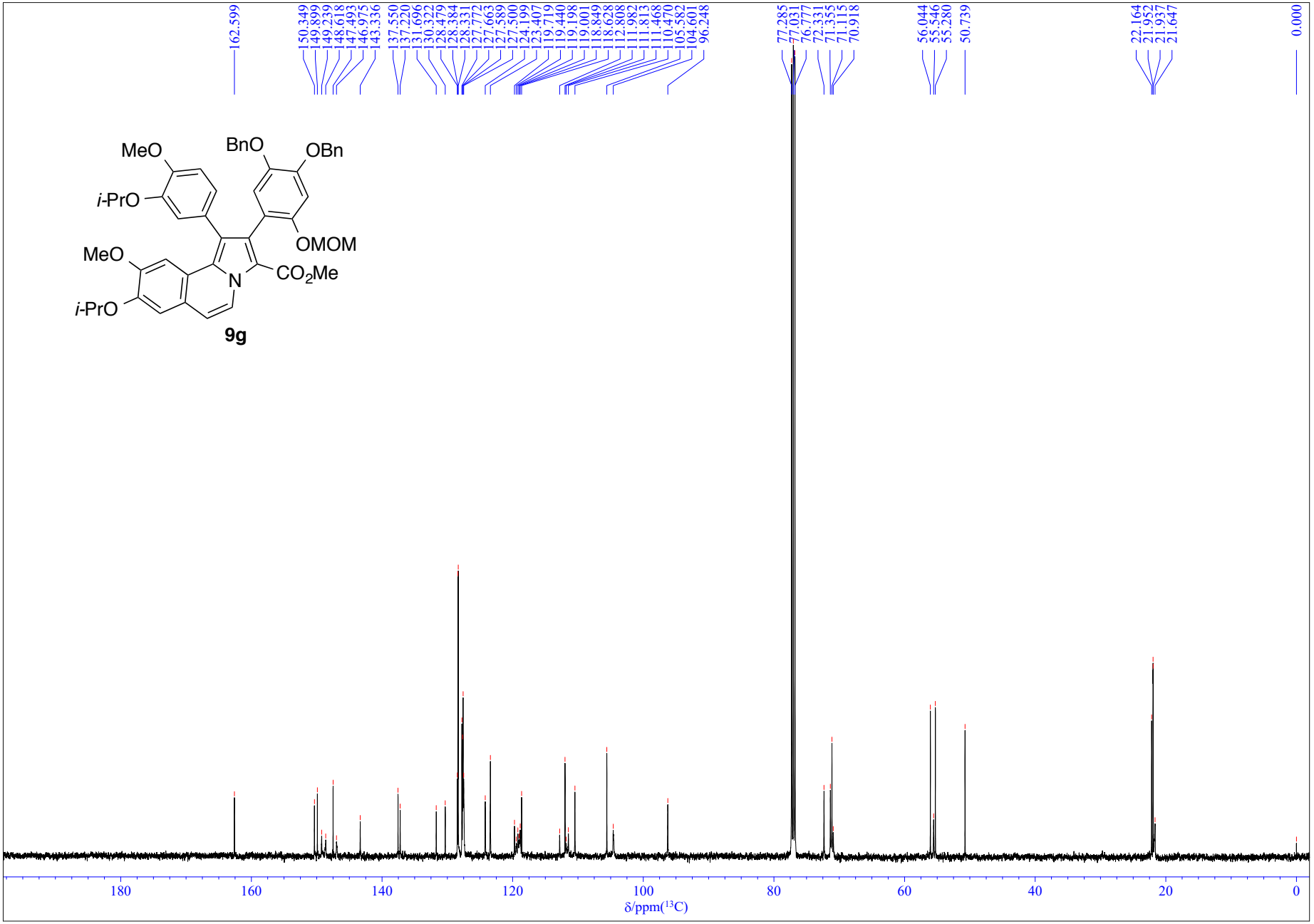


Figure S18. ^{13}C NMR spectrum of compound **9g** (126 MHz, $CDCl_3$).

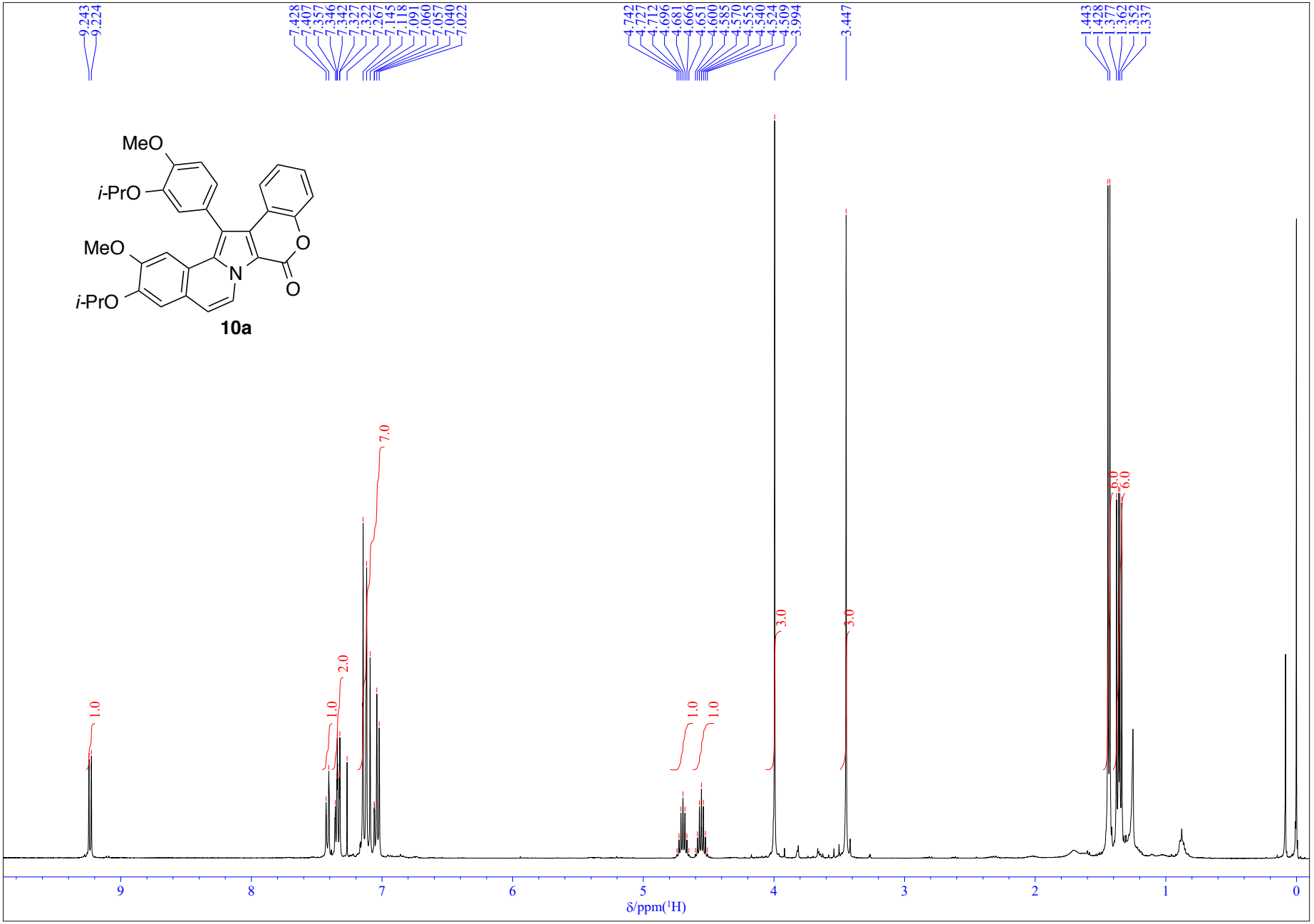


Figure S19. ^{1}H NMR spectrum of compound **10a** (400 MHz, $CDCl_3$).

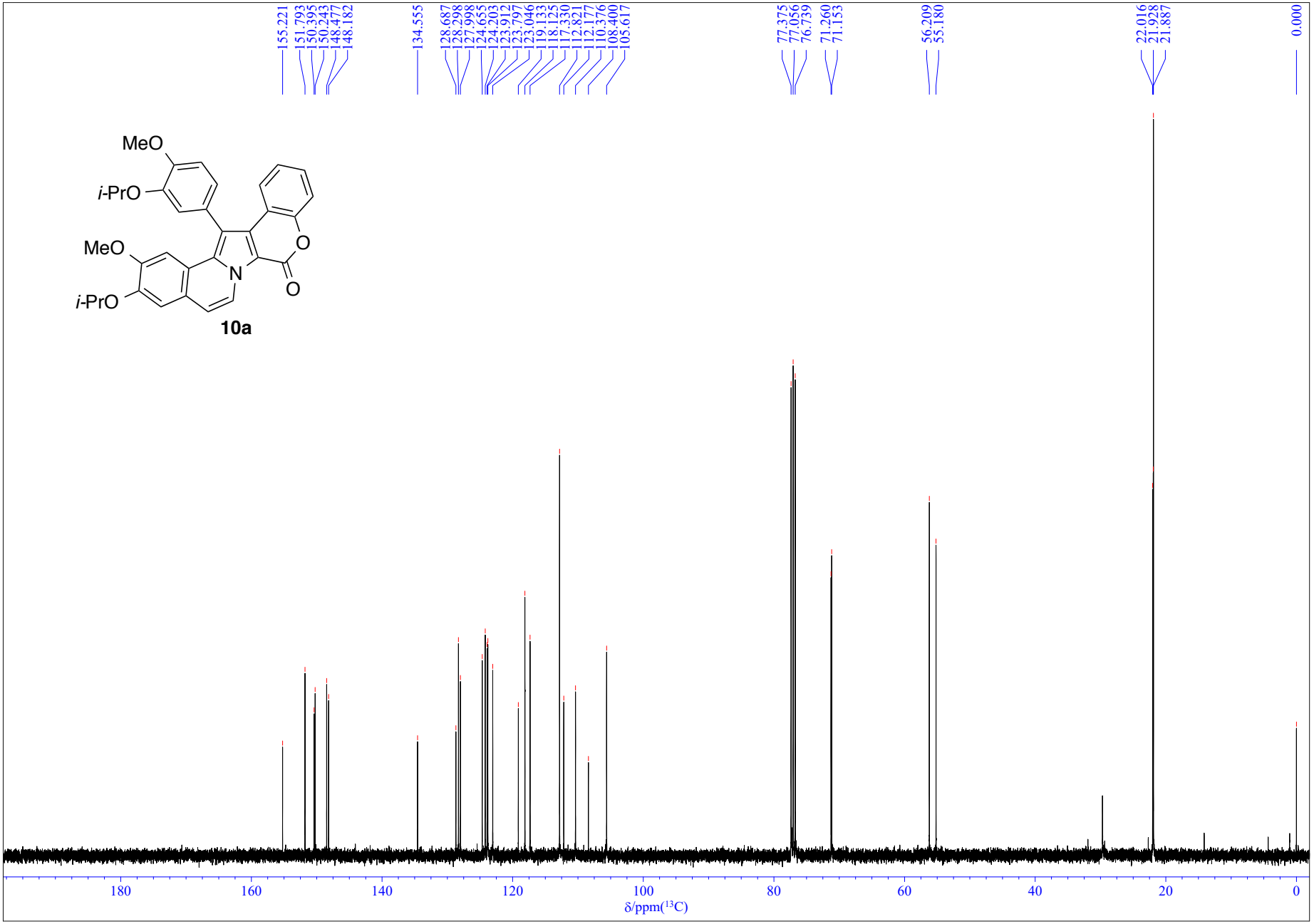


Figure S20. ^{13}C NMR spectrum of compound **10a** (100 MHz, $CDCl_3$).

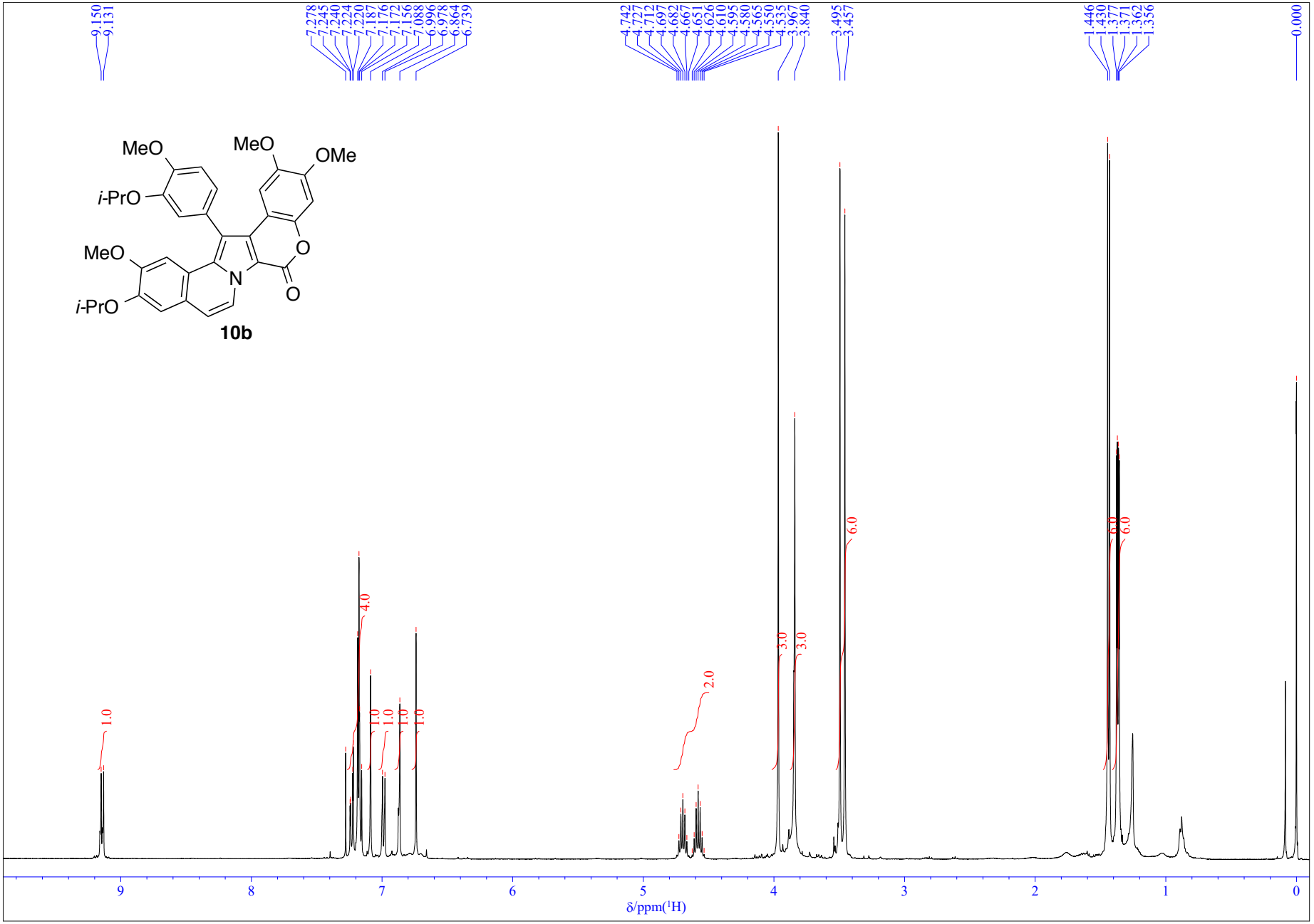


Figure S21. ^{1}H NMR spectrum of compound **10b** (400 MHz, $CDCl_3$).

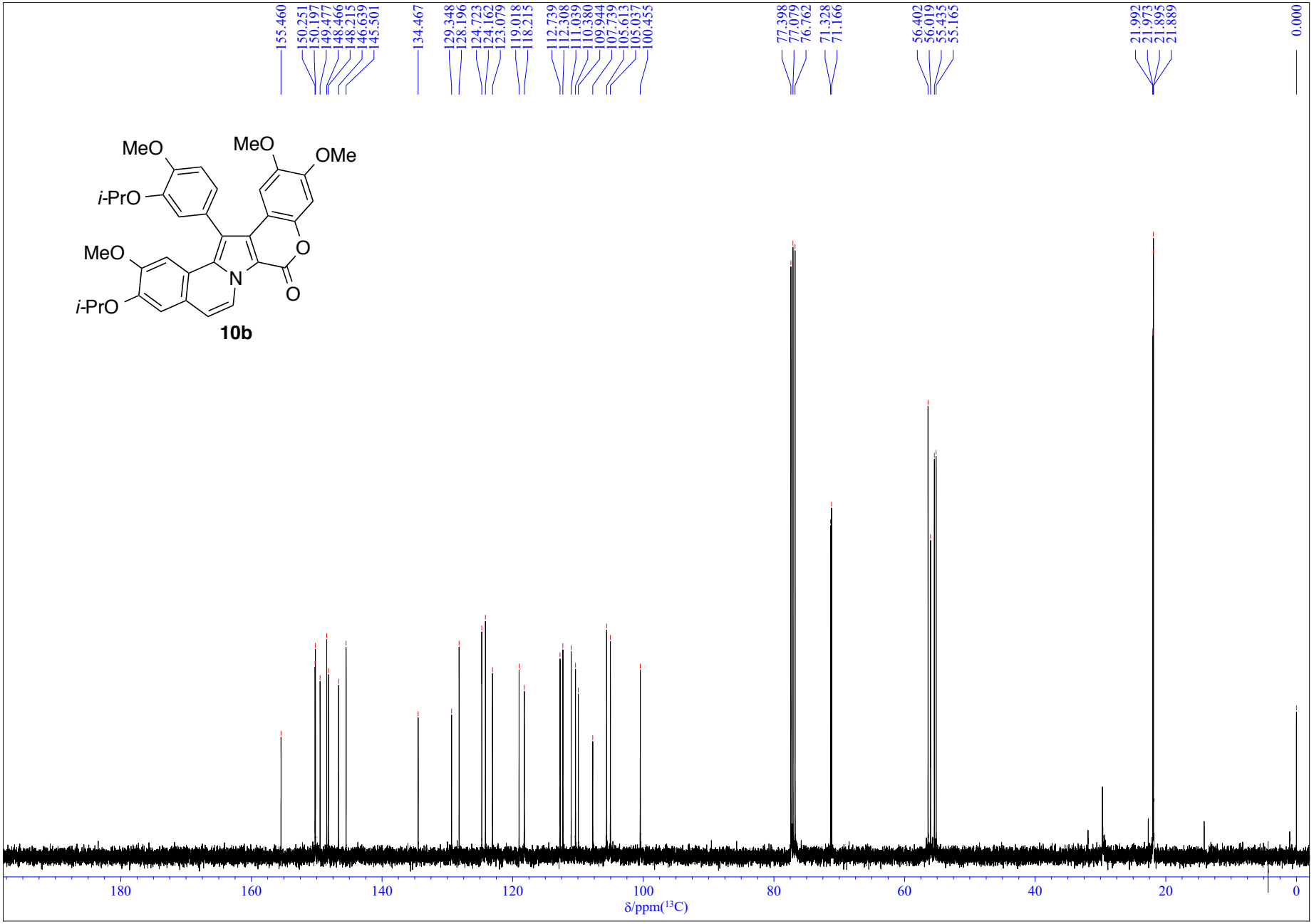


Figure S22. ^{13}C NMR spectrum of compound **10b** (100 MHz, $CDCl_3$).

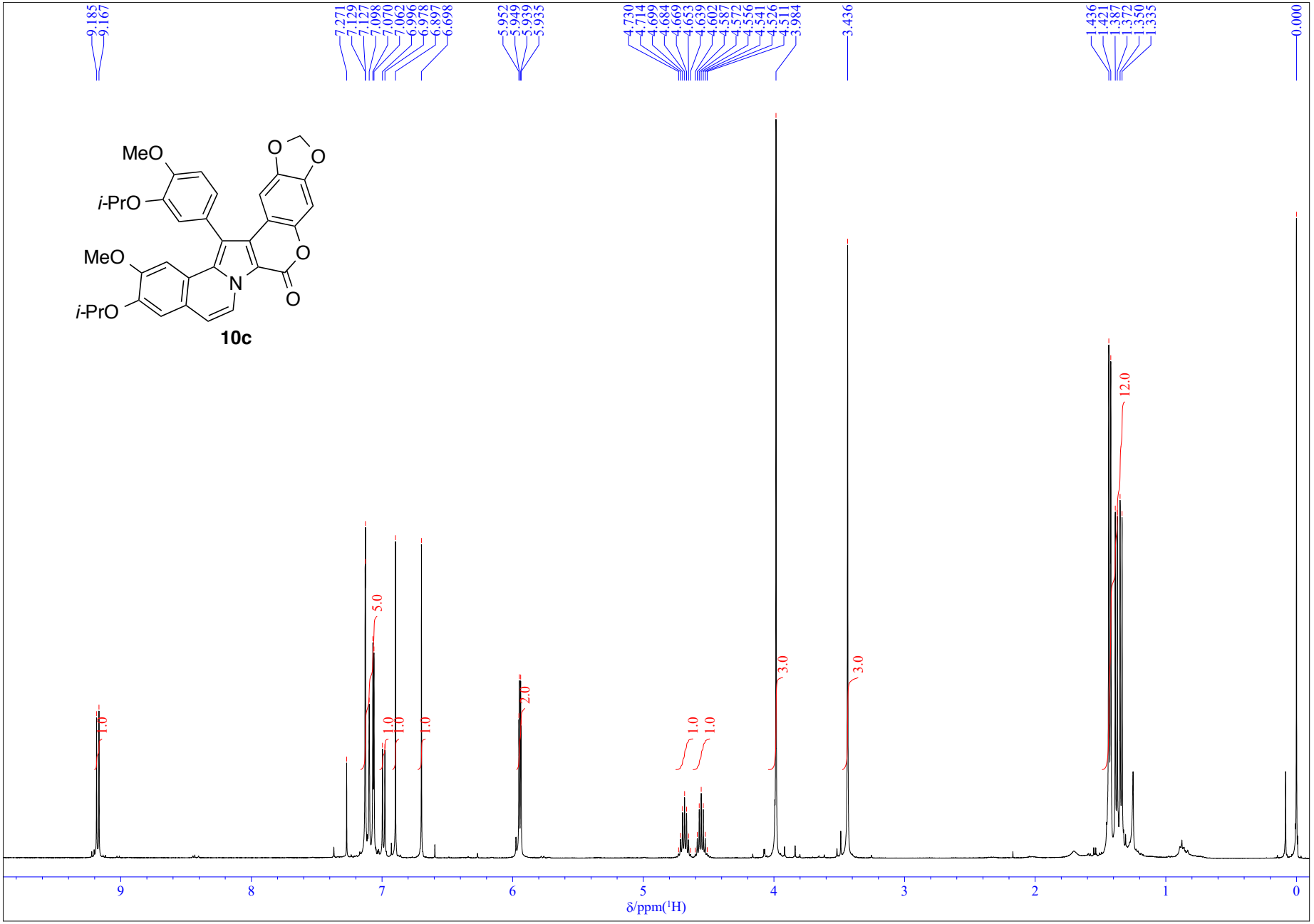


Figure S23. ^{1}H NMR spectrum of compound **10c** (400 MHz, $CDCl_3$).

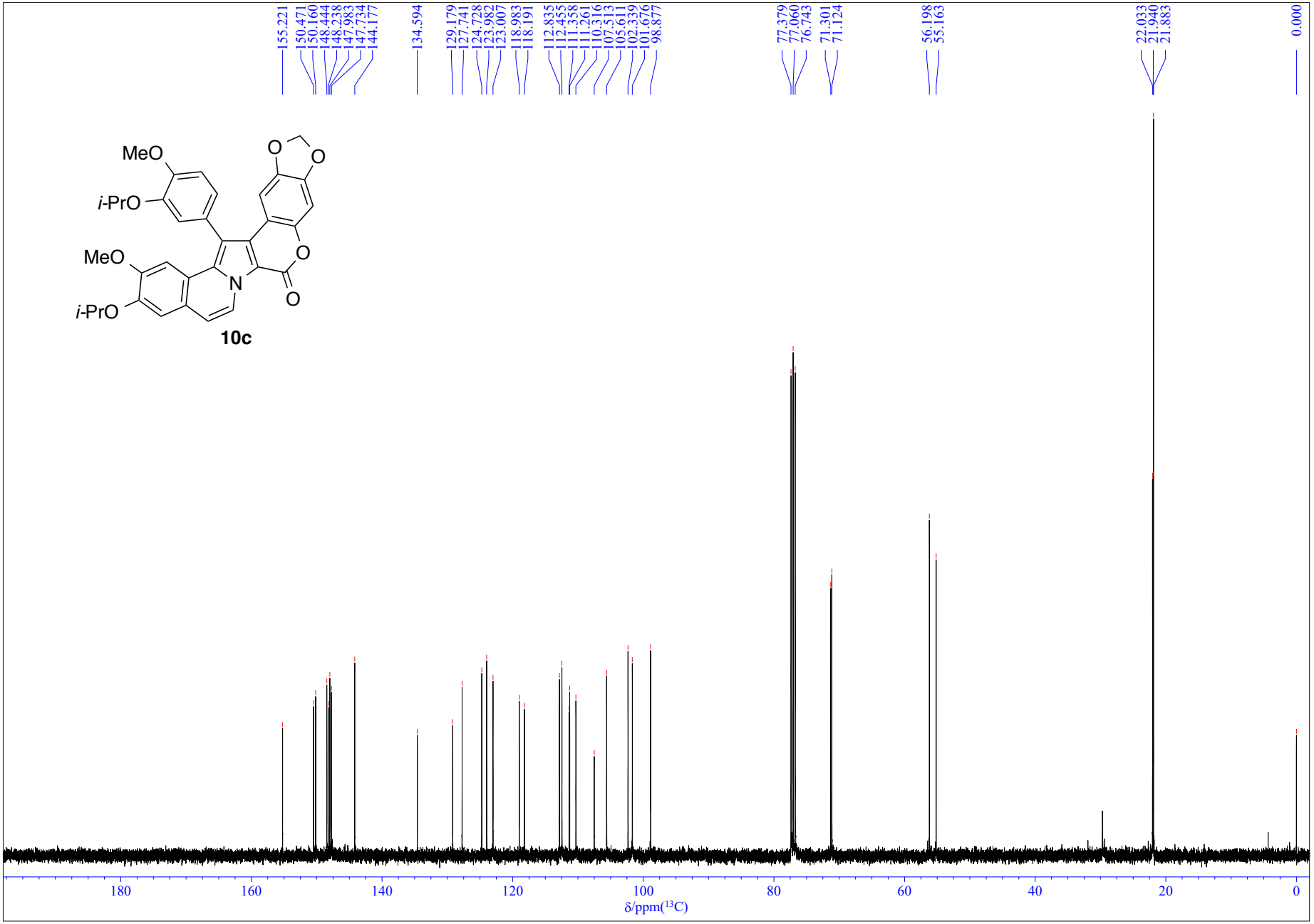


Figure S24. ^{13}C NMR spectrum of compound **10c** (100 MHz, $CDCl_3$).

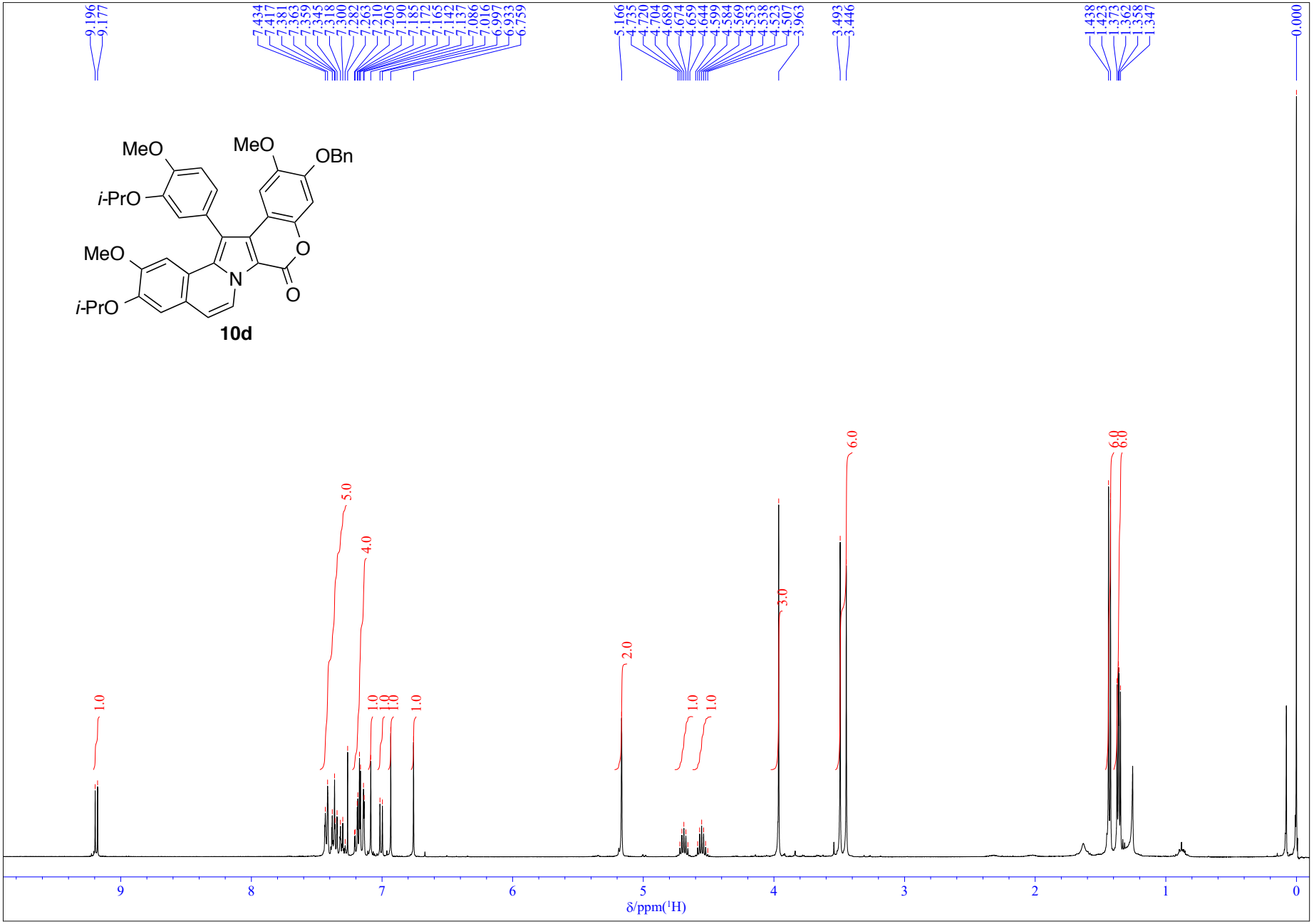


Figure S25. ^{1}H NMR spectrum of compound **10d** (400 MHz, $CDCl_3$).

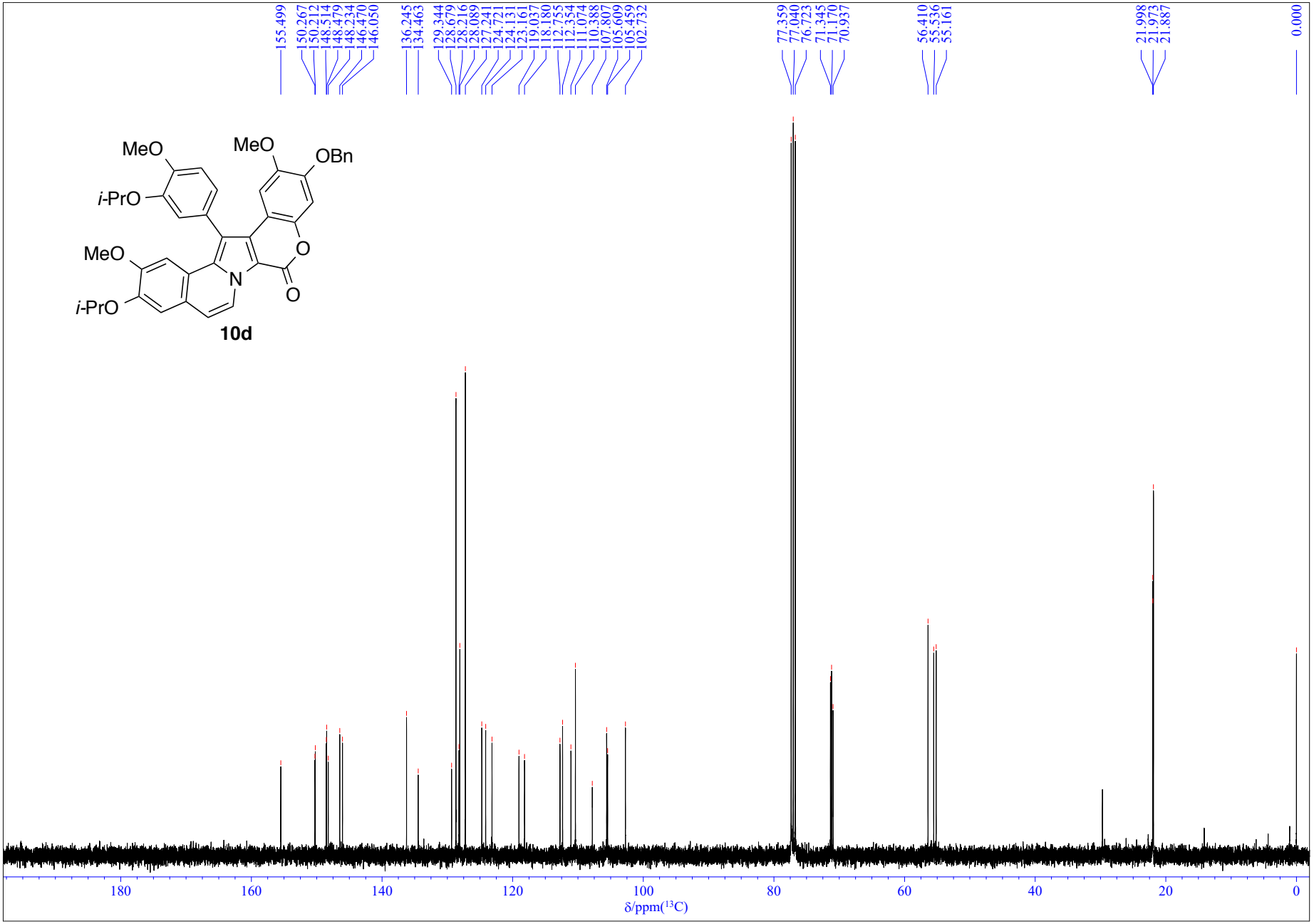


Figure S26. ^{13}C NMR spectrum of compound **10d** (100 MHz, $CDCl_3$).

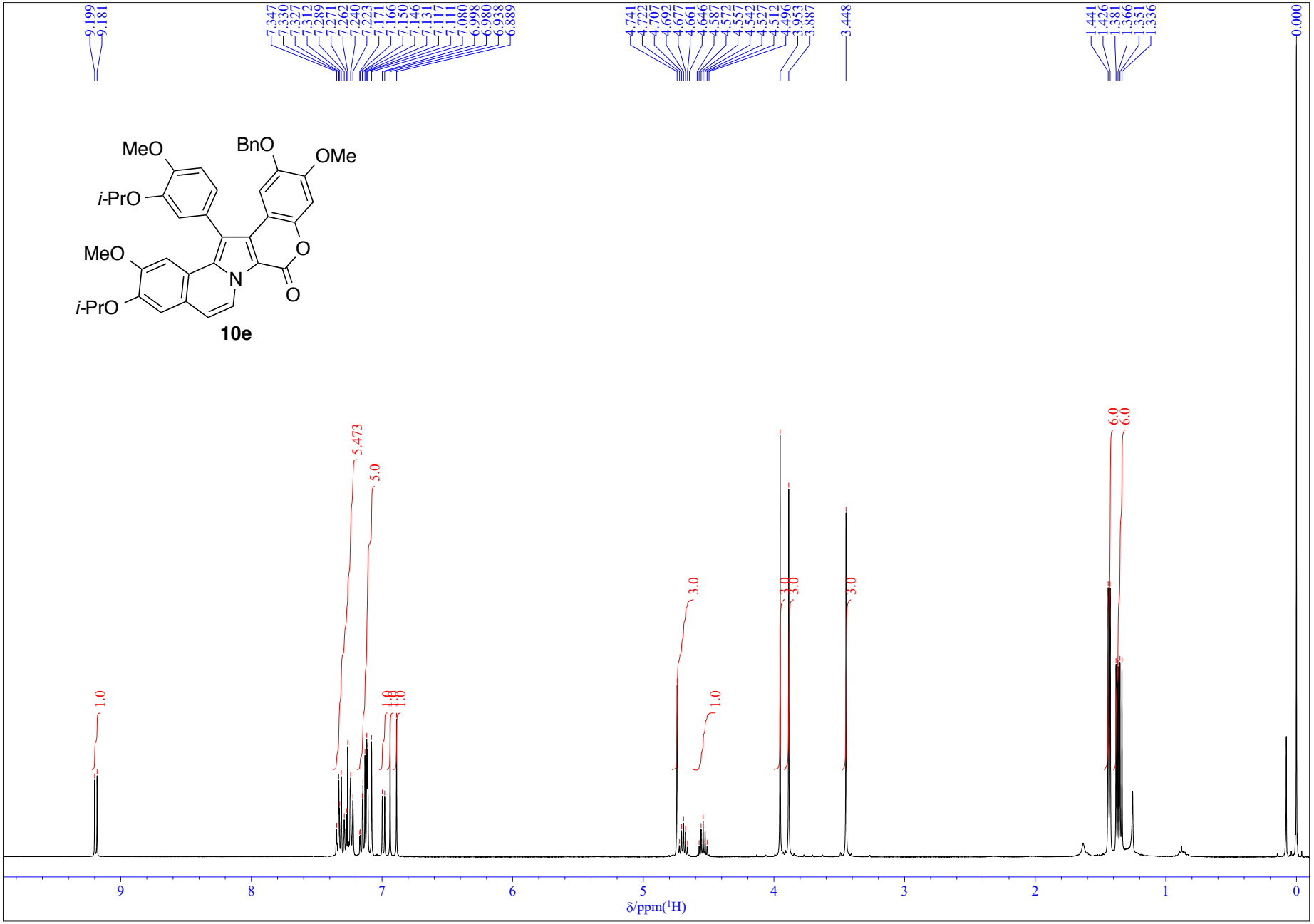


Figure S27. ^{1}H NMR spectrum of compound **10e** (400 MHz, $CDCl_3$).

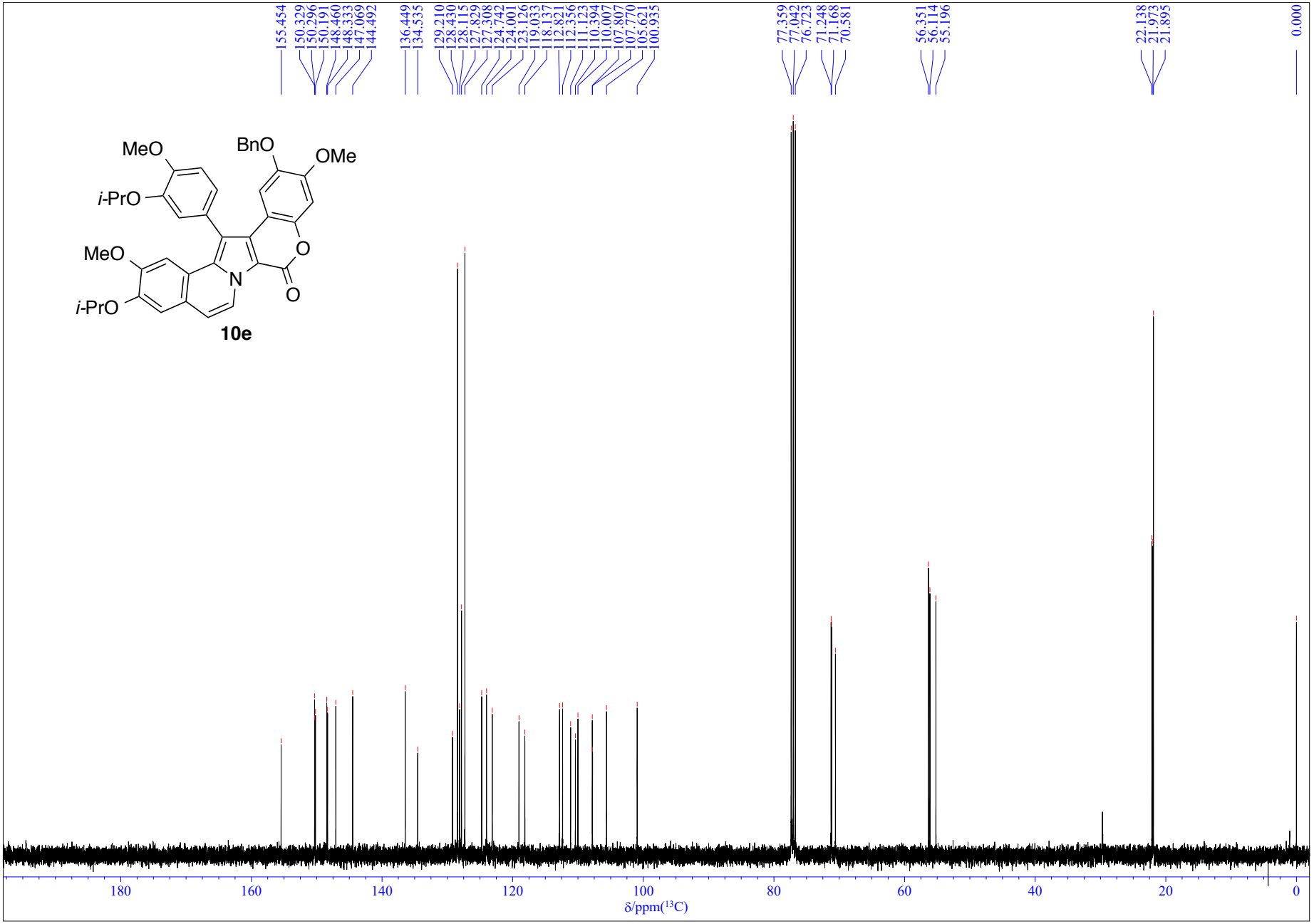


Figure S28. ^{13}C NMR spectrum of compound **10e** (100 MHz, $CDCl_3$).

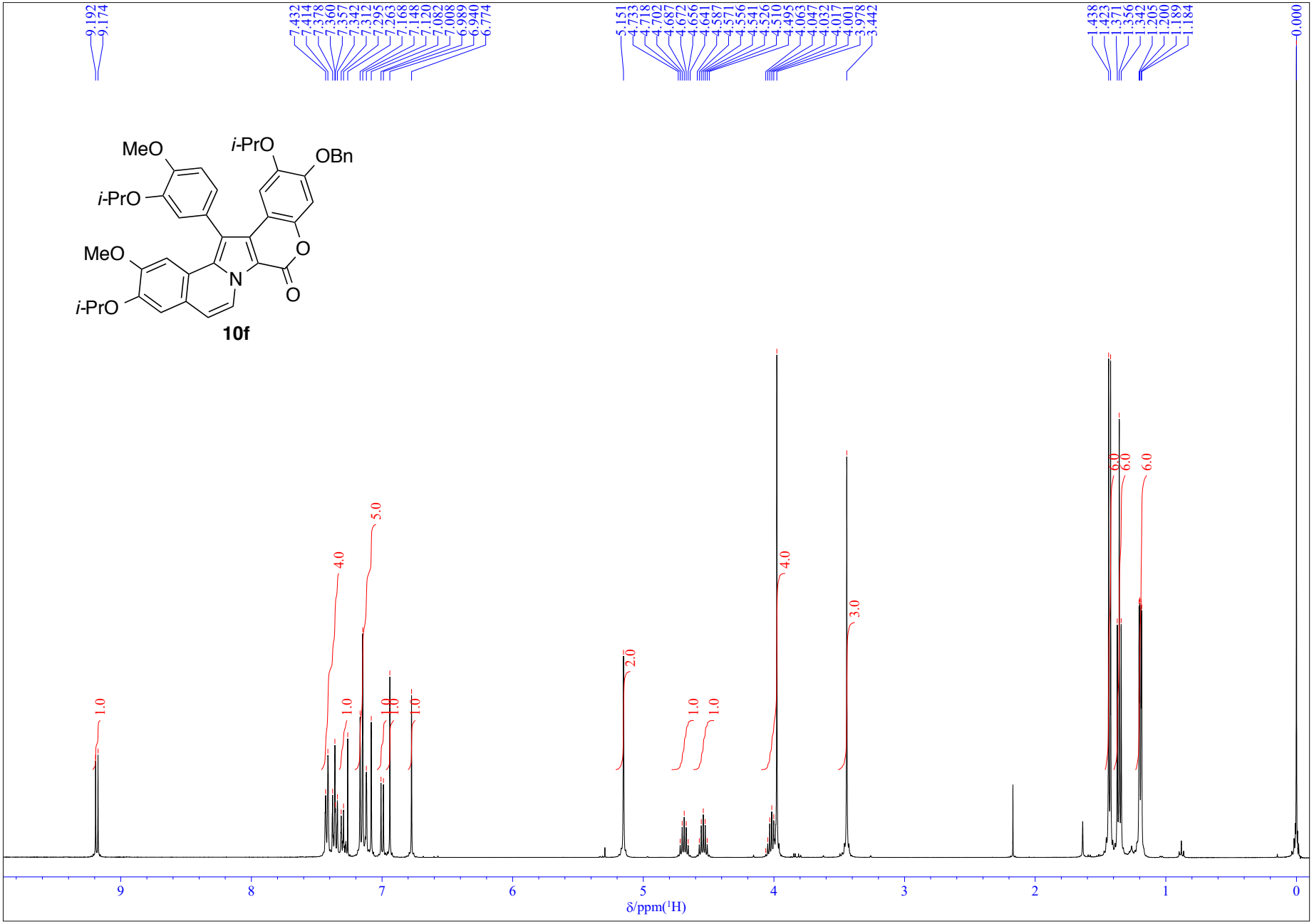


Figure S29. ^{1}H NMR spectrum of compound **10f** (400 MHz, $CDCl_3$).

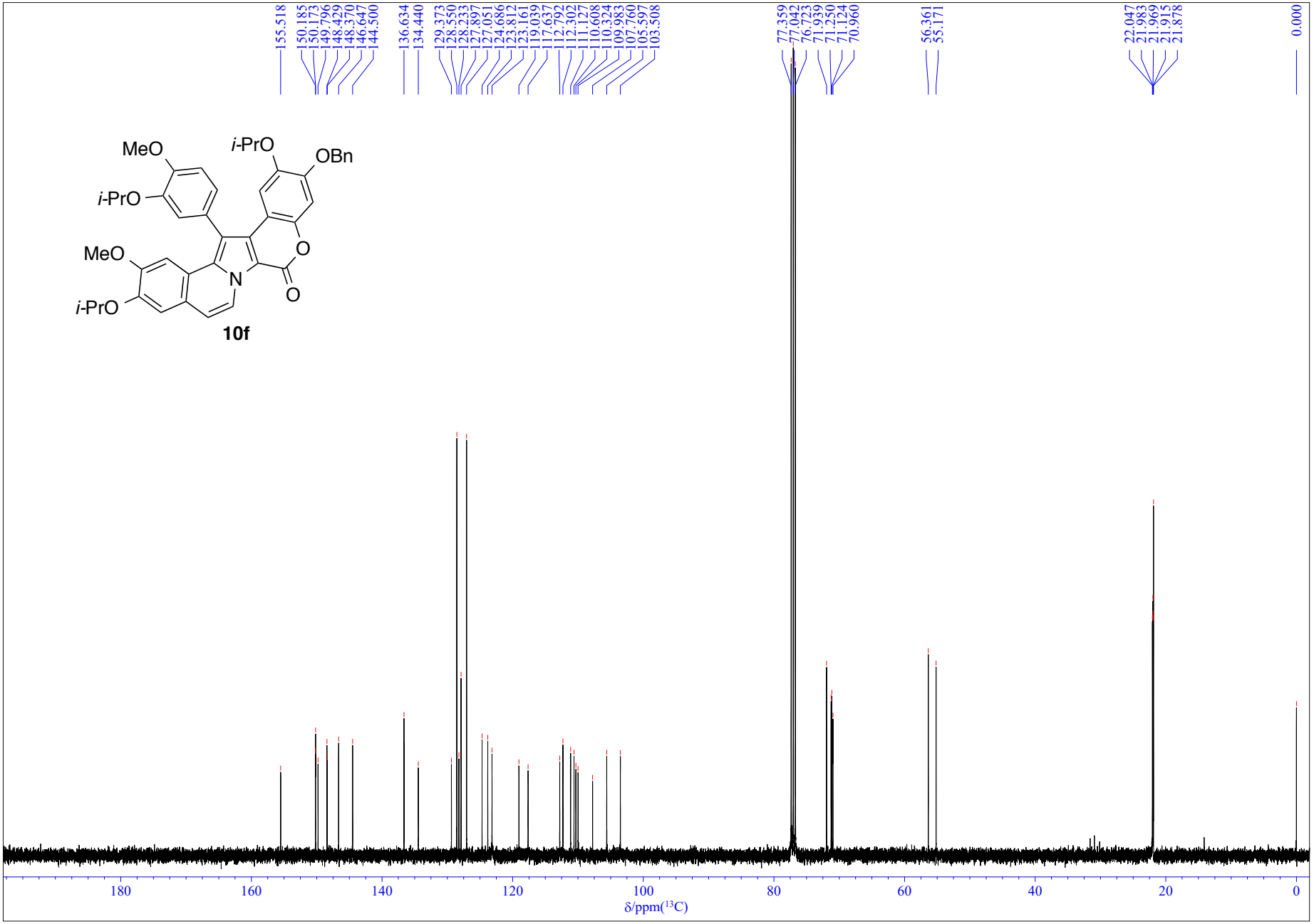


Figure S30. ^{13}C NMR spectrum of compound **10f** (100 MHz, $CDCl_3$).

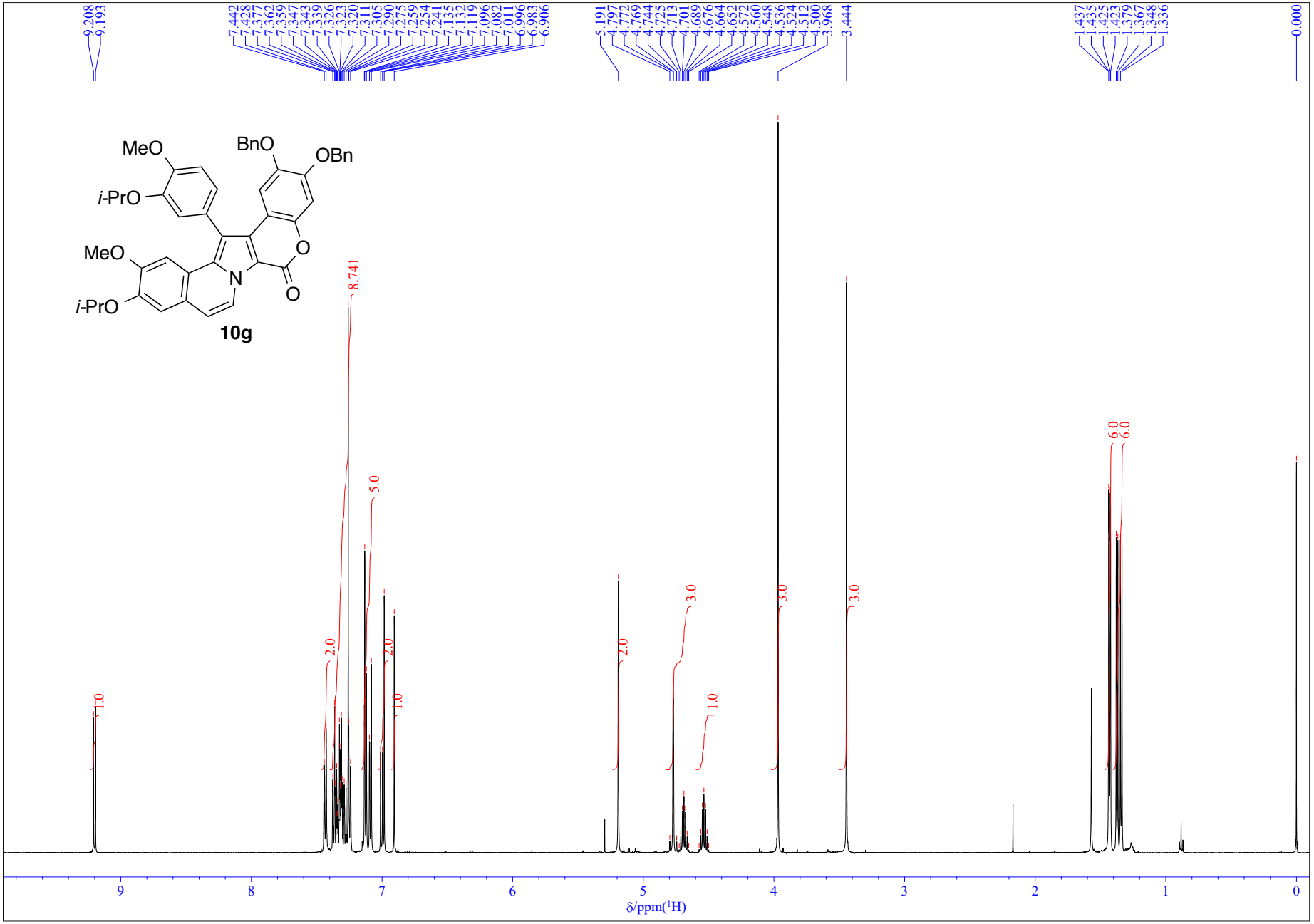


Figure S31. ^{1}H NMR spectrum of compound **10g** (500 MHz, $CDCl_3$).

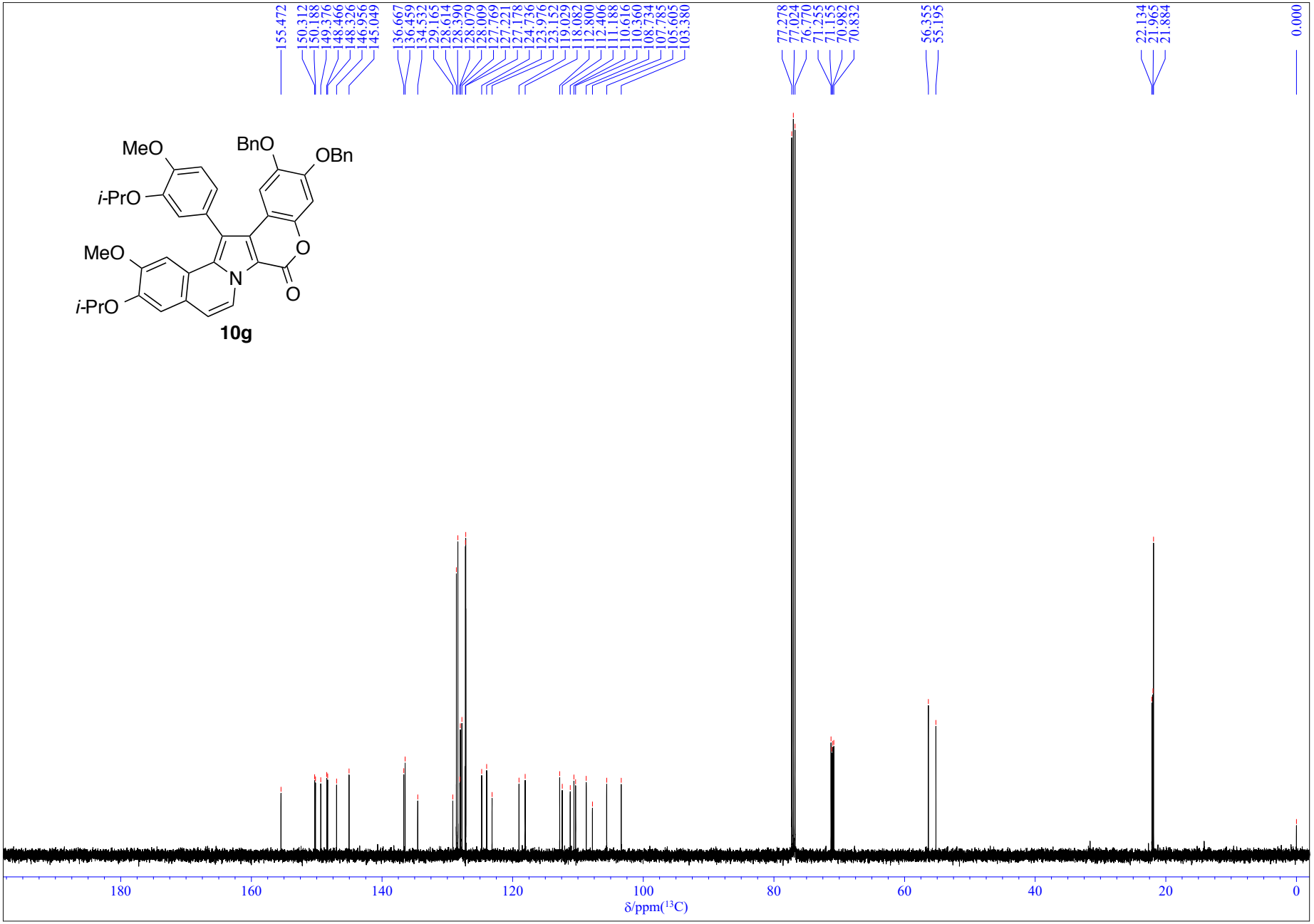


Figure S32. ^{13}C NMR spectrum of compound **10g** (126 MHz, $CDCl_3$).

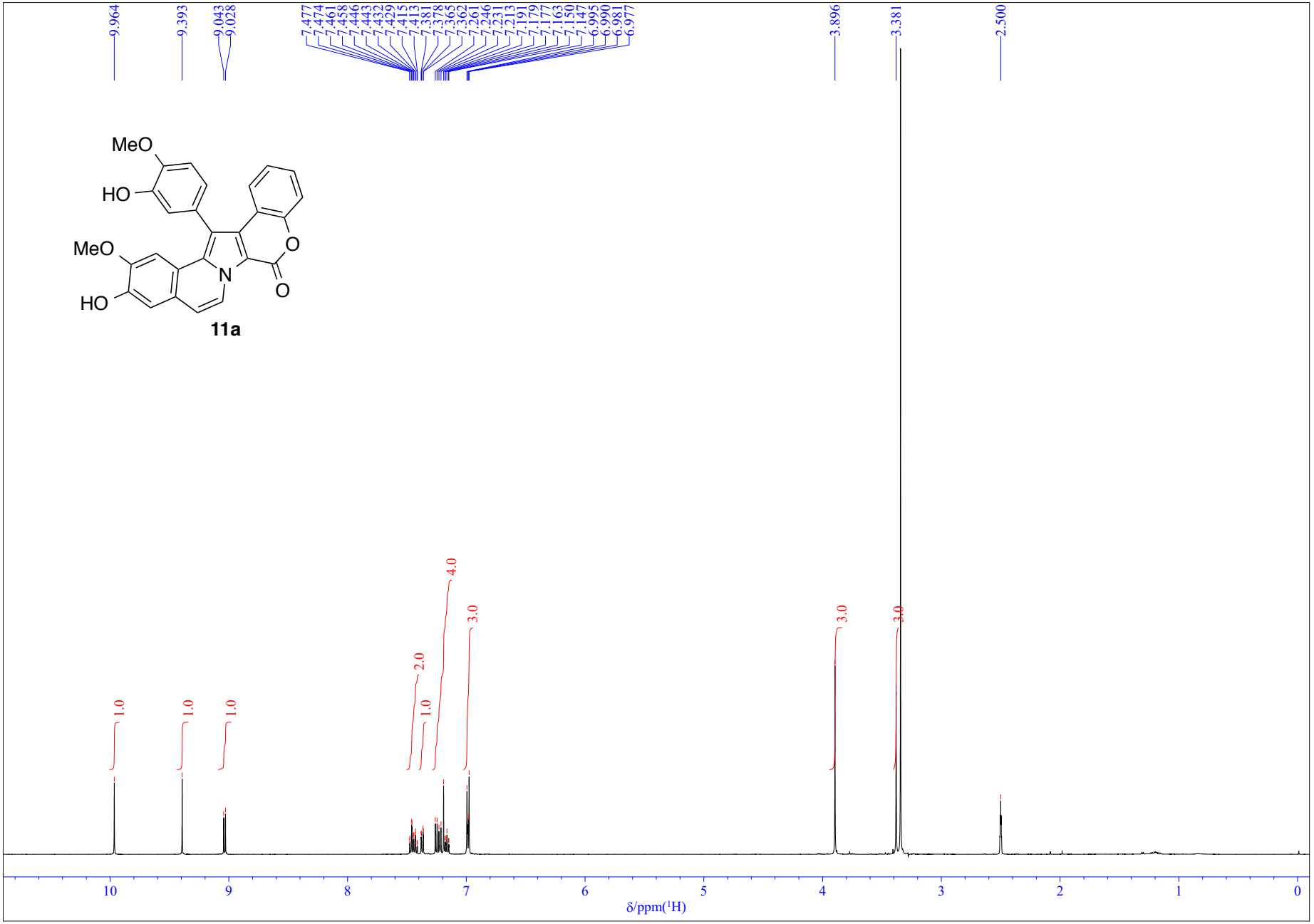


Figure S33. ^{1}H NMR spectrum of compound **11a** (500 MHz, DMSO-d_6).

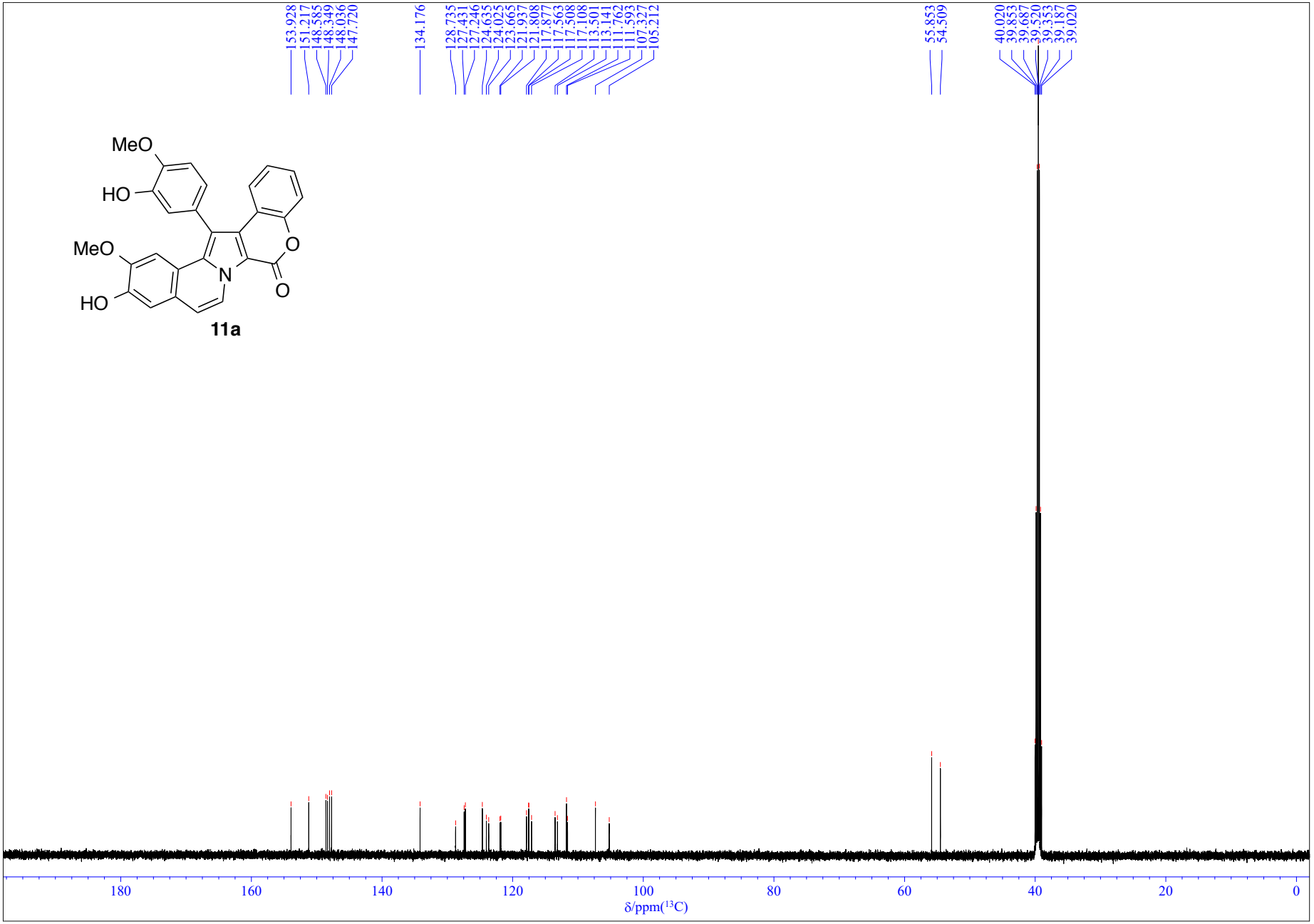


Figure S34. ^{13}C NMR spectrum of compound **11a** (126 MHz, DMSO-d_6).

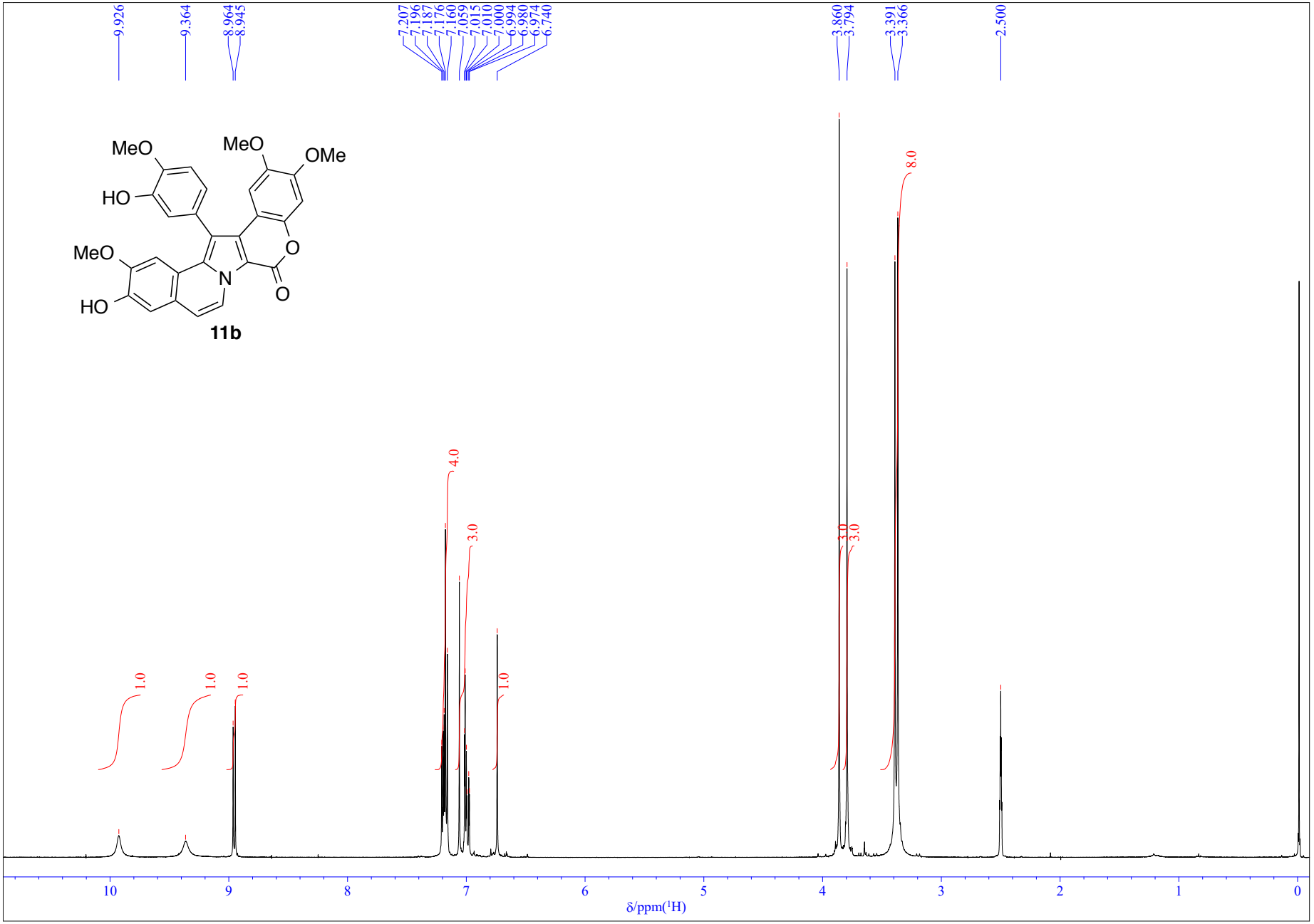


Figure S35. ^{1}H NMR spectrum of compound **11b** (400 MHz, DMSO-d_6).

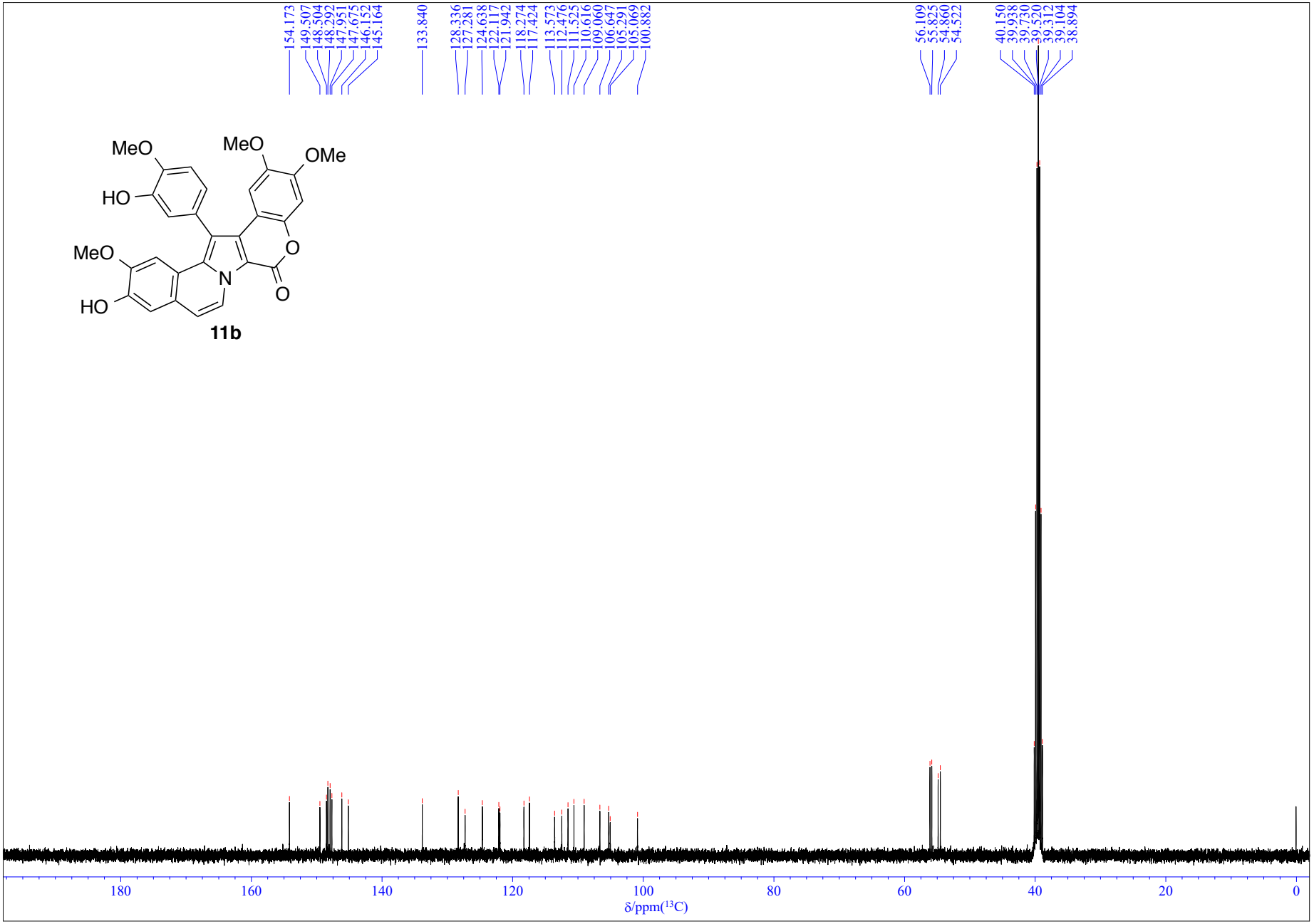


Figure S36. ^{13}C NMR spectrum of compound **11b** (100 MHz, DMSO-d_6).

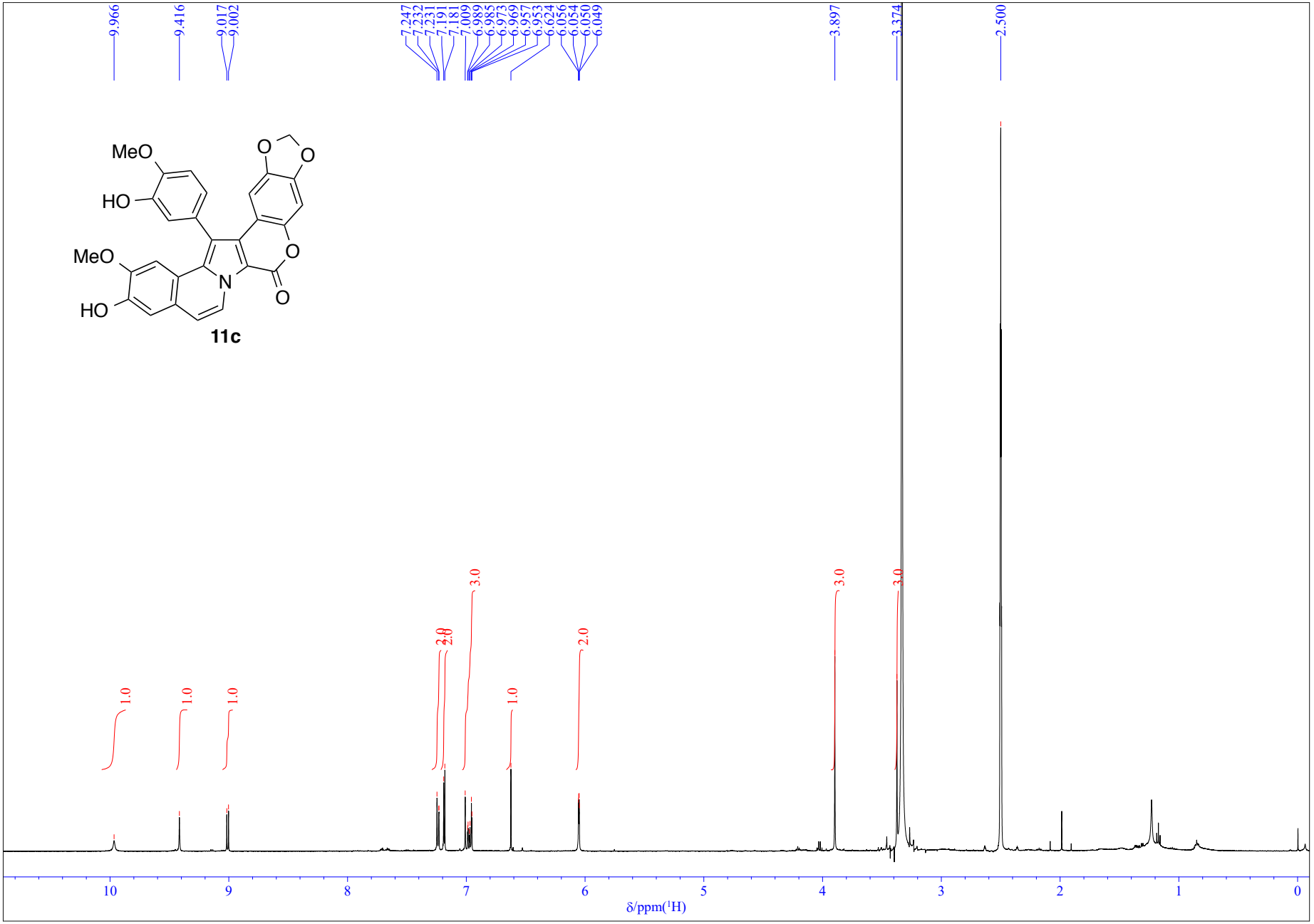


Figure S37. ^{1}H NMR spectrum of compound **11c** (500 MHz, DMSO-d_6).

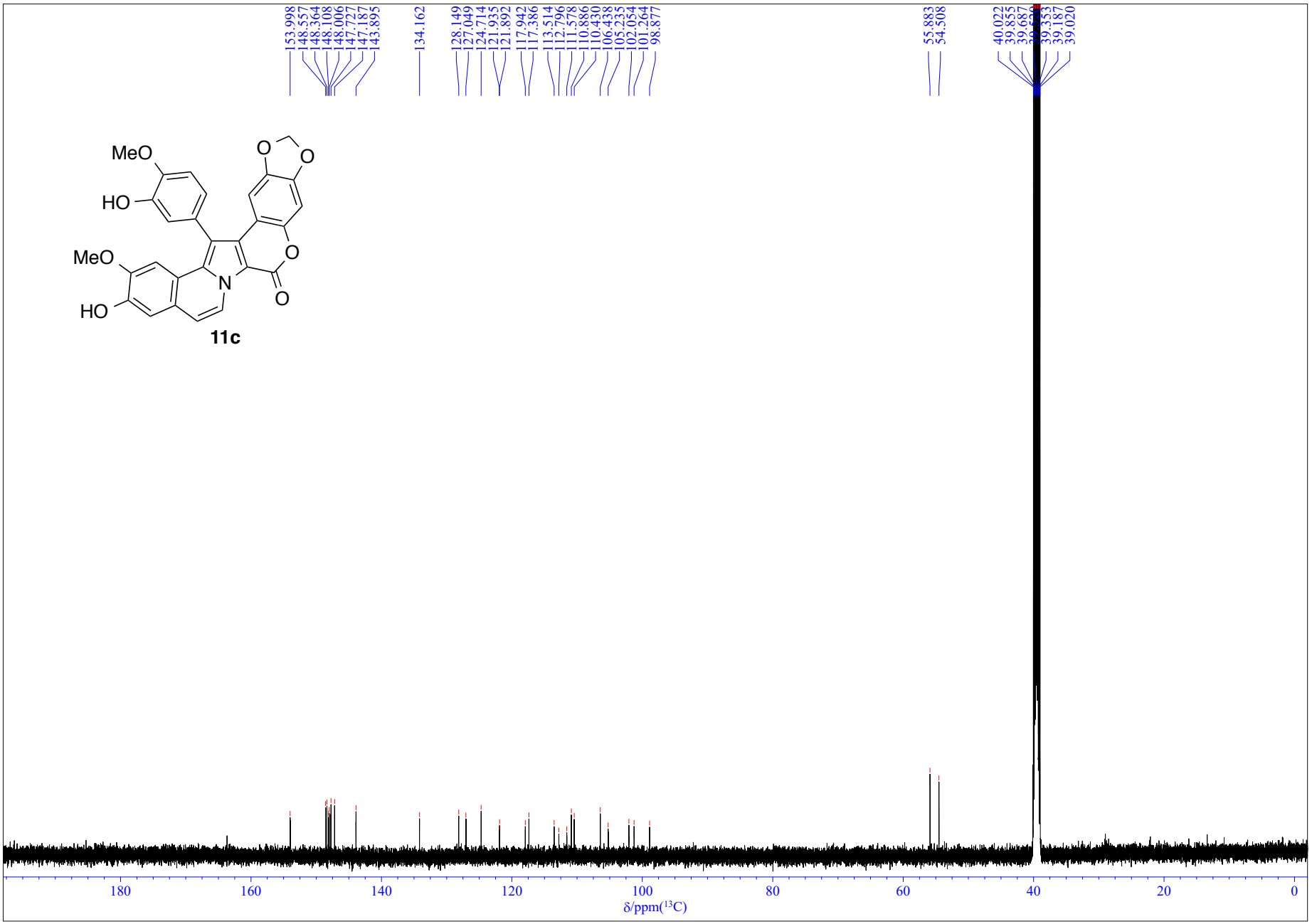


Figure S38. ^{13}C NMR spectrum of compound **11c** (126 MHz, DMSO-d_6).

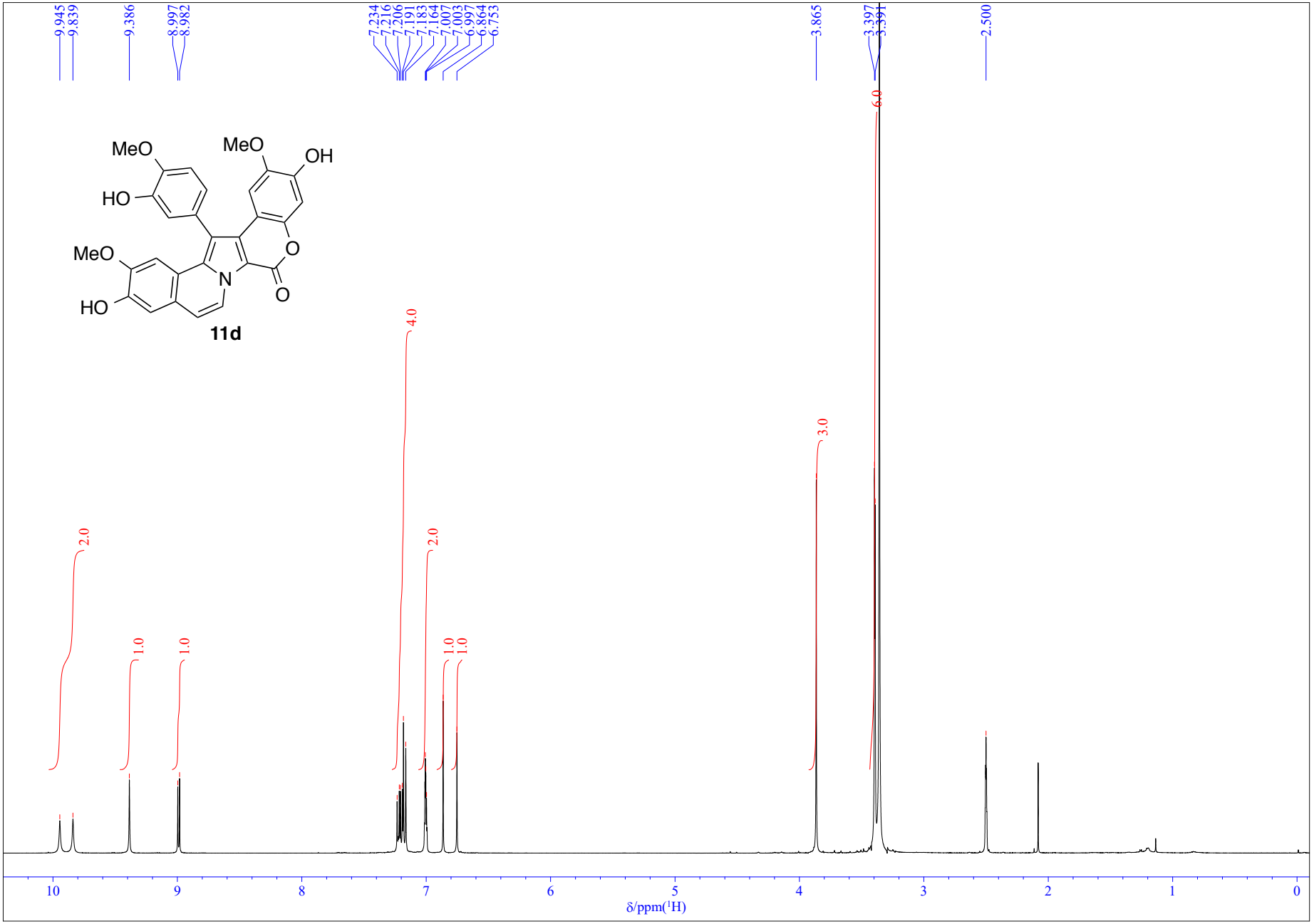


Figure S39. ^{1}H NMR spectrum of compound **11d** (500 MHz, DMSO-d_6).

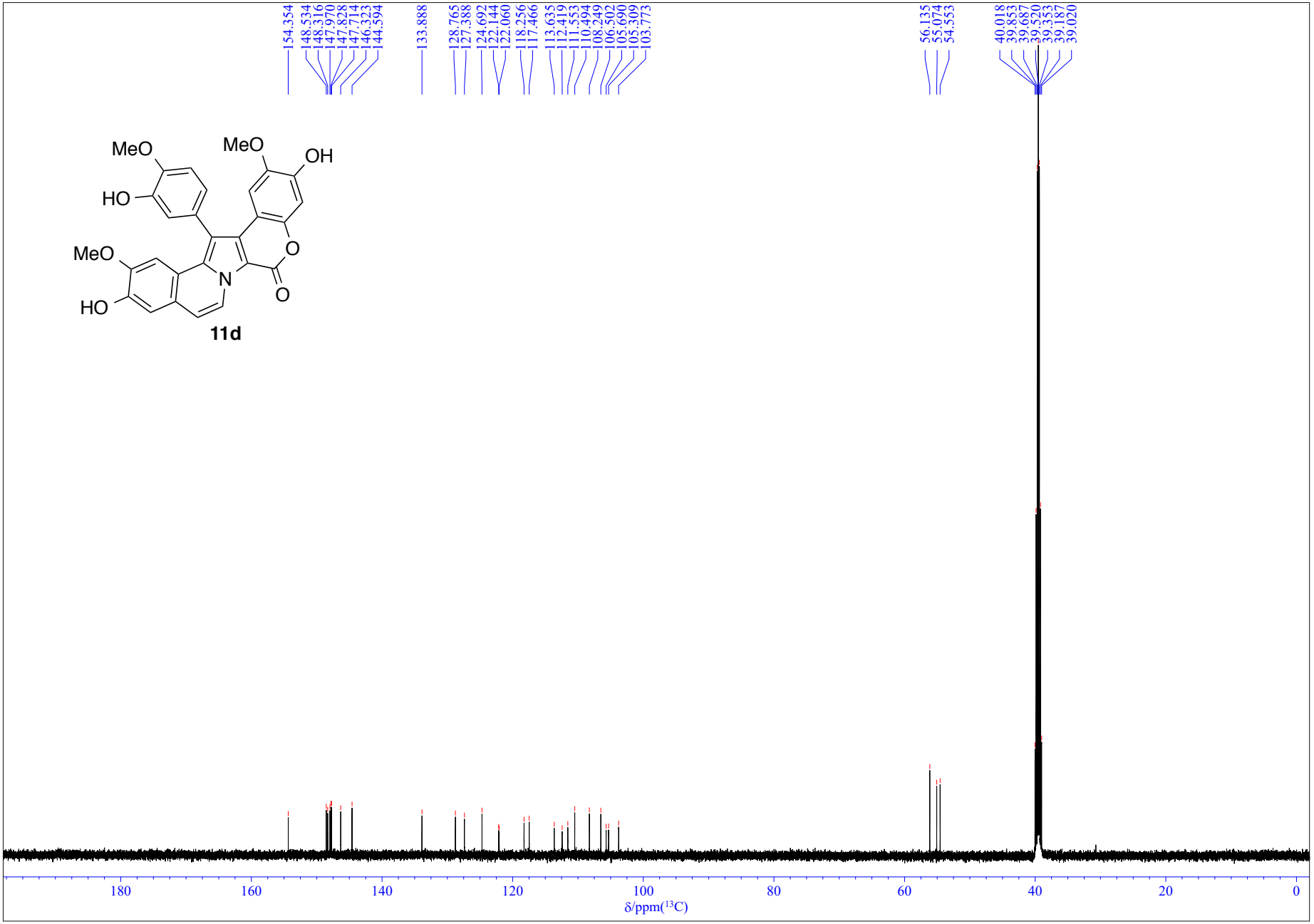


Figure S40. ^{13}C NMR spectrum of compound **11d** (126 MHz, DMSO-d_6).

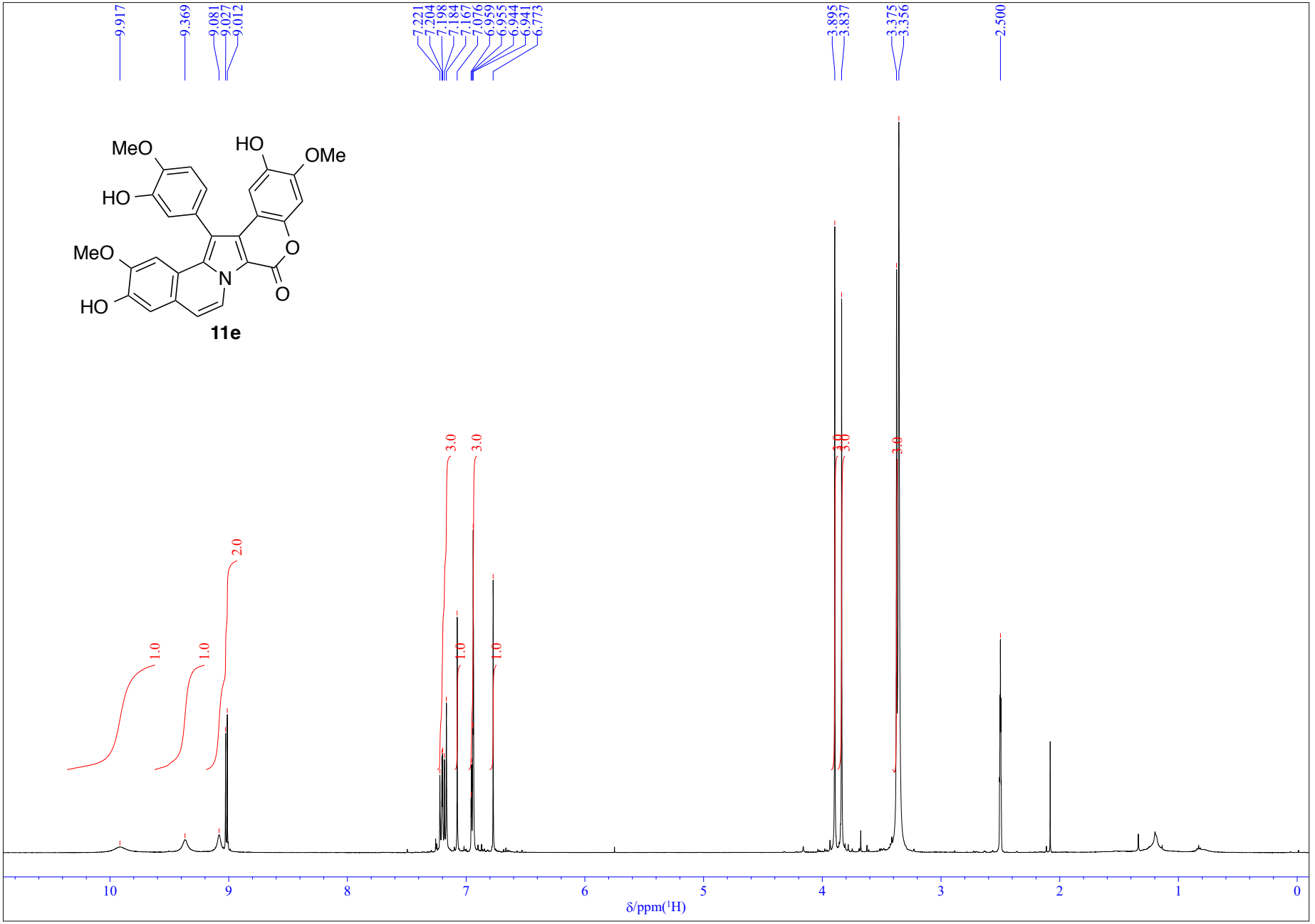


Figure S41. ^{1}H NMR spectrum of compound **11e** (500 MHz, DMSO-d_6).

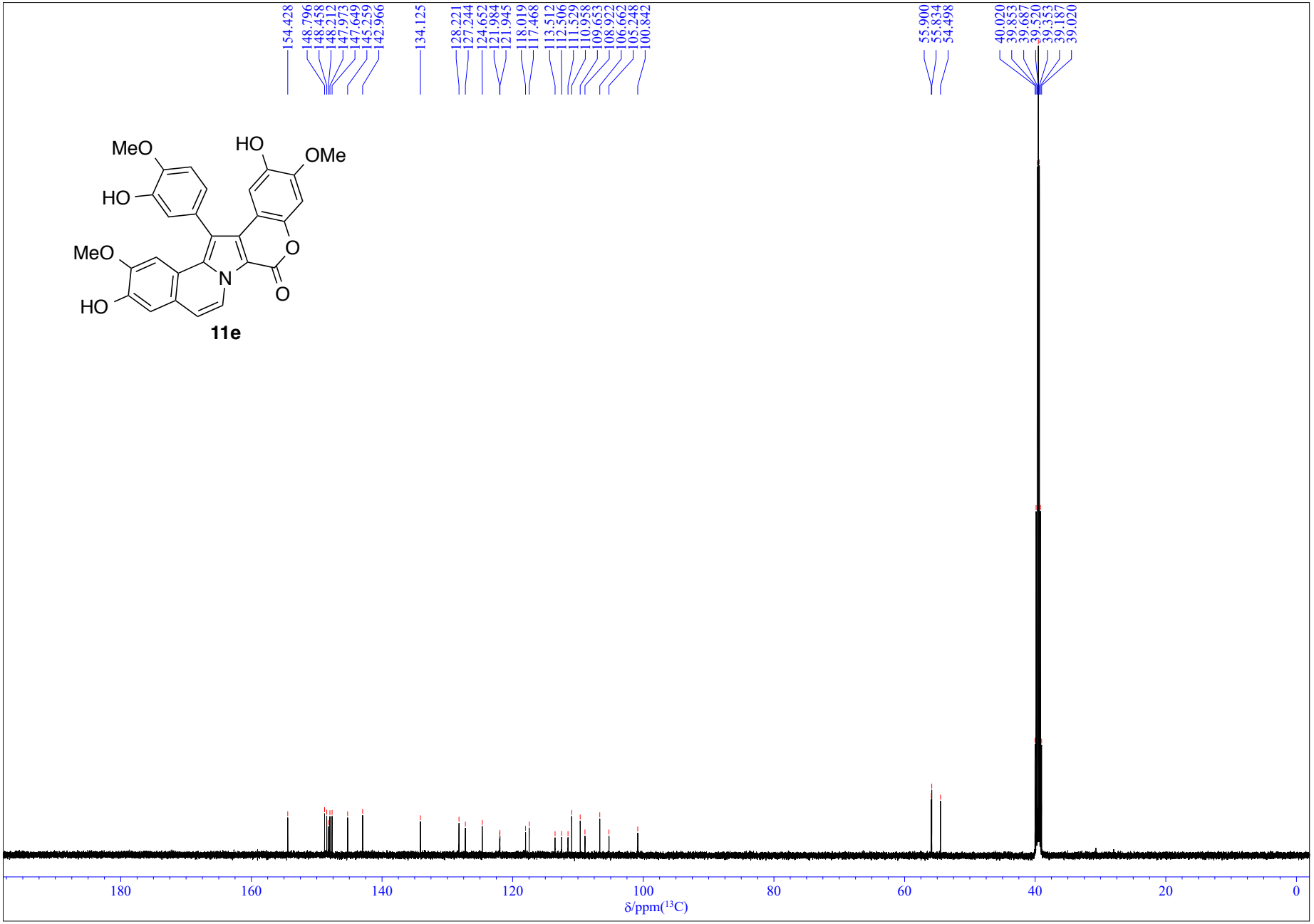


Figure S42. ^{13}C NMR spectrum of compound **11e** (126 MHz, DMSO-d_6).

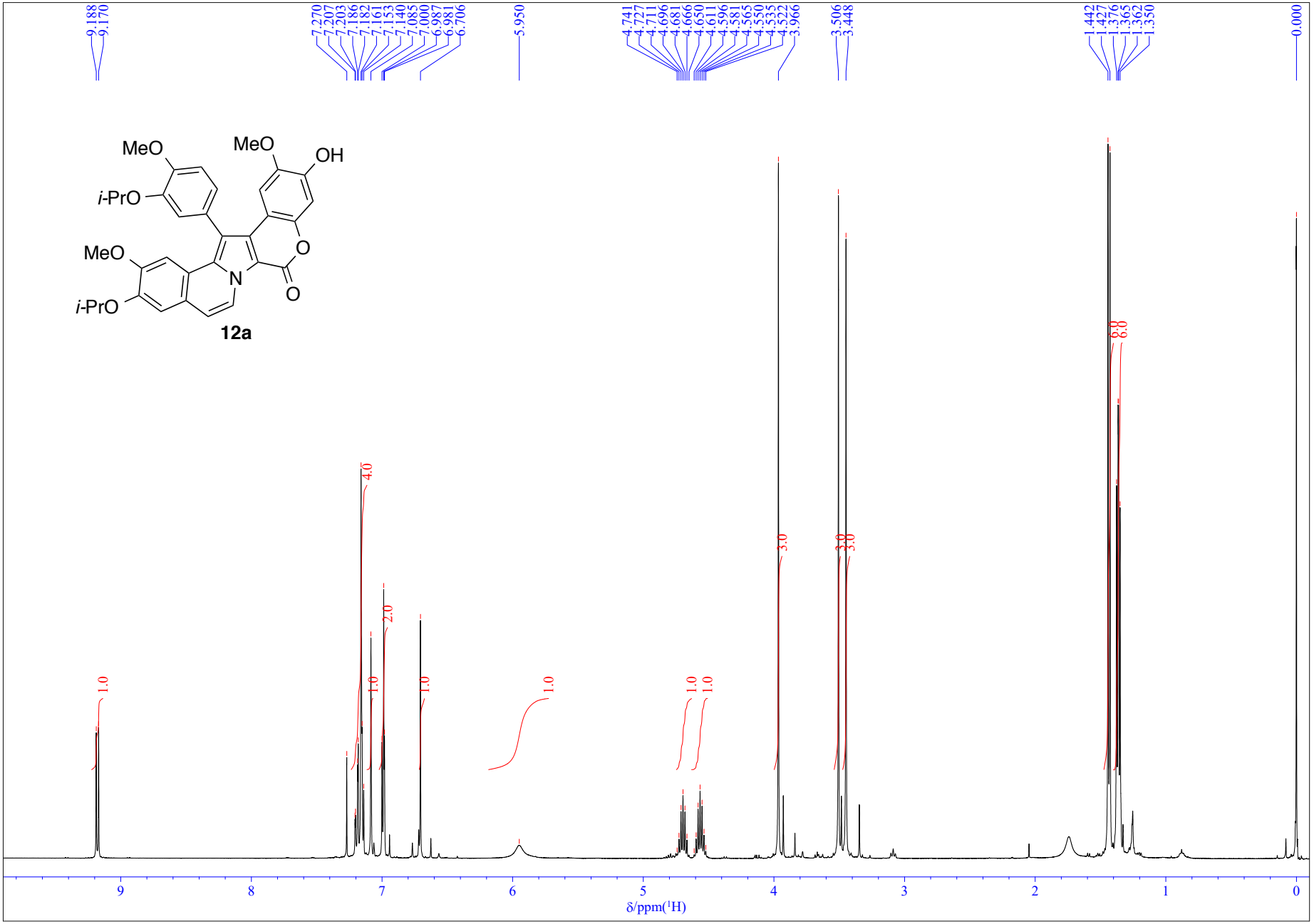


Figure S43. ^{1}H NMR spectrum of compound **12a** (400 MHz, $CDCl_3$).

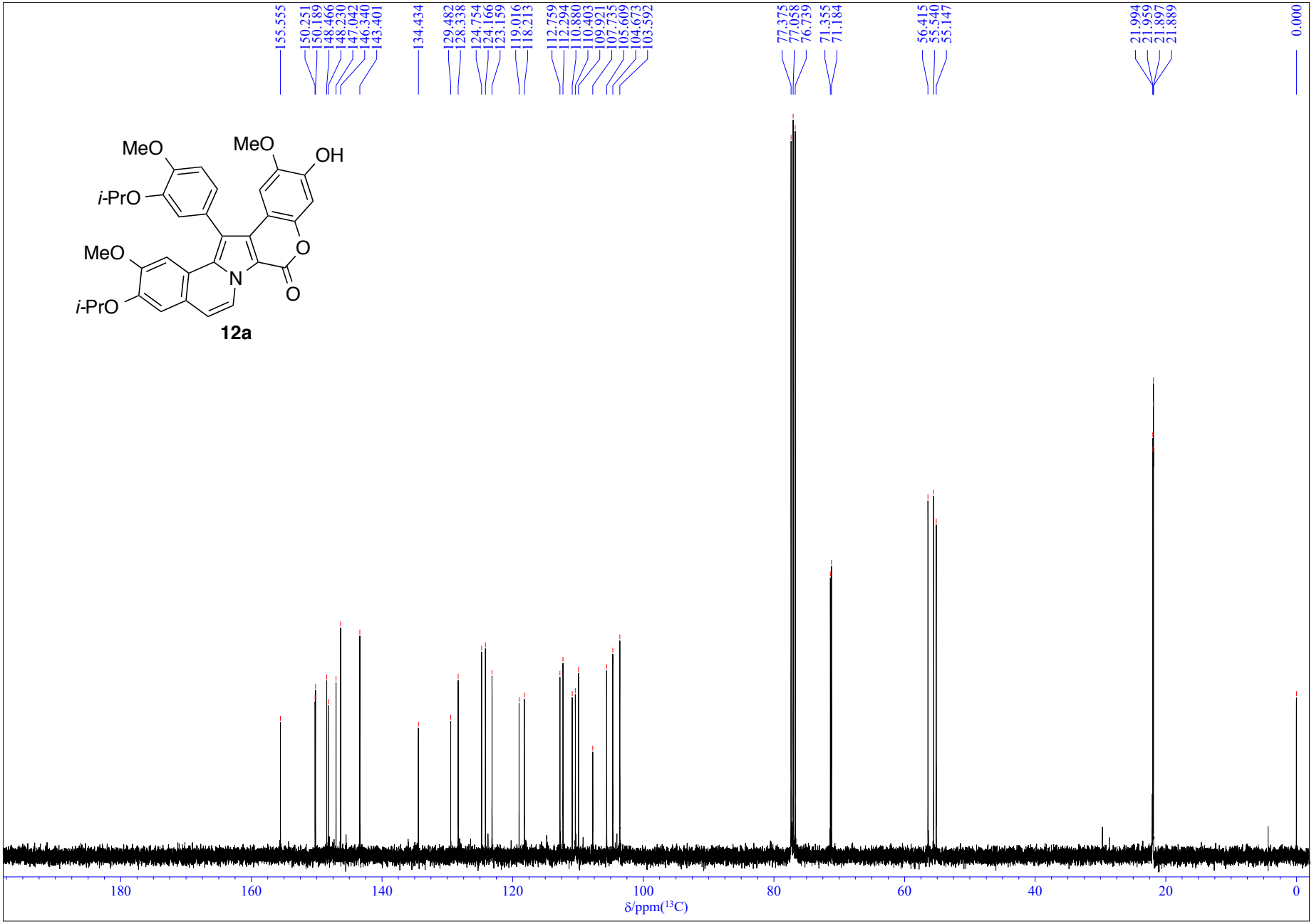


Figure S44. ^{13}C NMR spectrum of compound **12a** (100 MHz, $CDCl_3$).

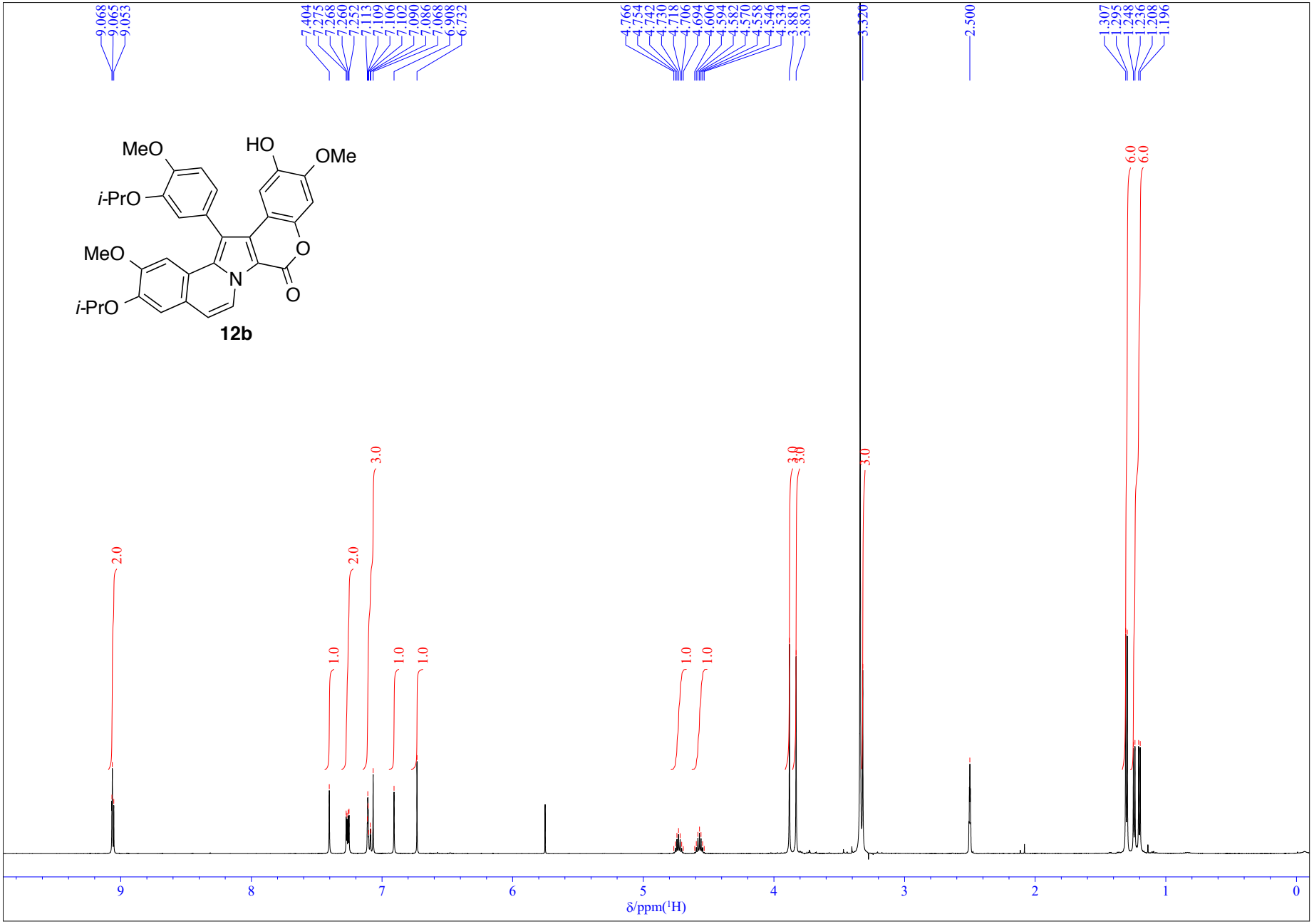


Figure S45. ^{1}H NMR spectrum of compound **12b** (500 MHz, DMSO-d_6).

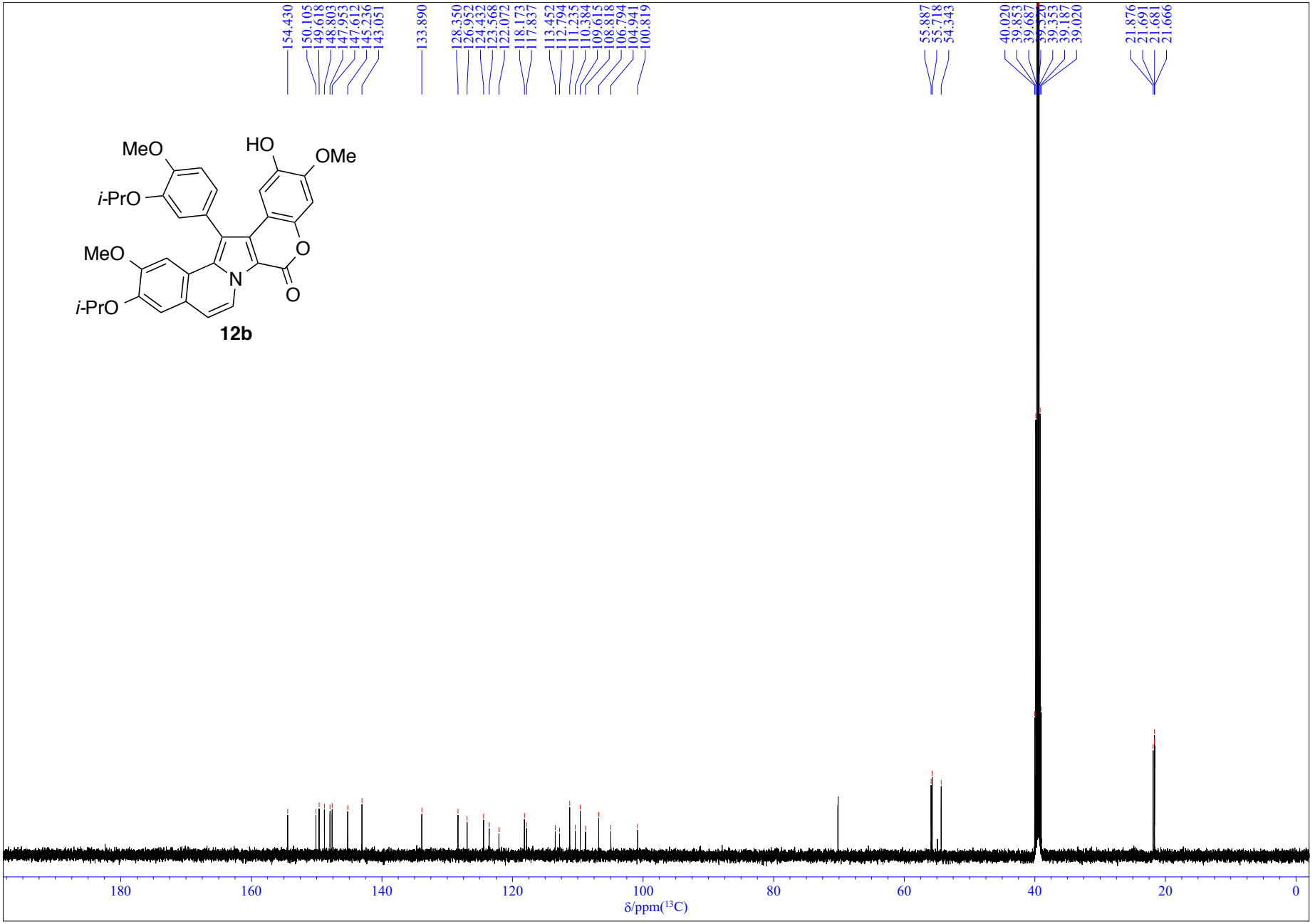


Figure S46. ^{13}C NMR spectrum of compound **12b** (126 MHz, DMSO-d_6).

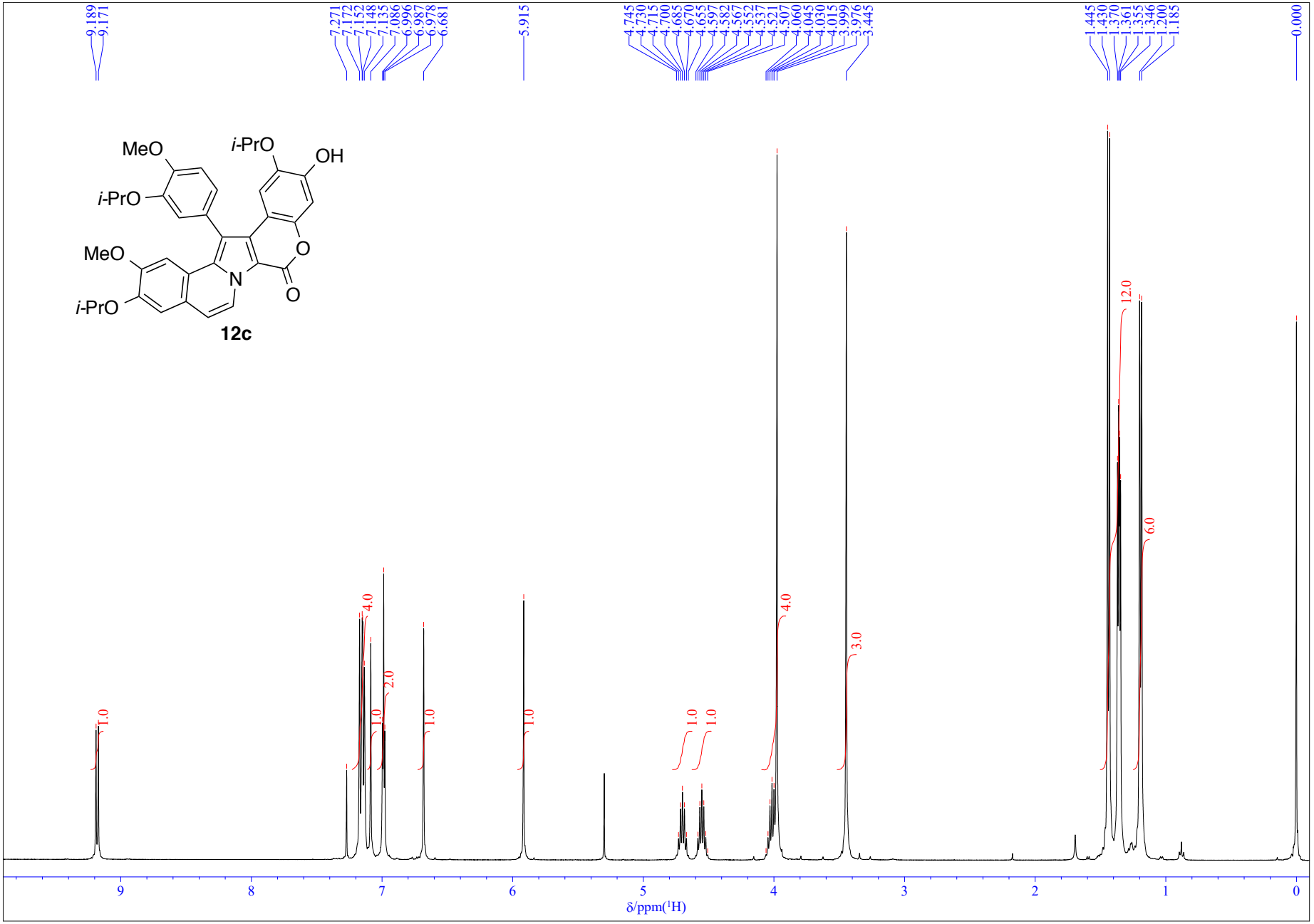


Figure S47. ^{1}H NMR spectrum of compound **12c** (400 MHz, $CDCl_3$).

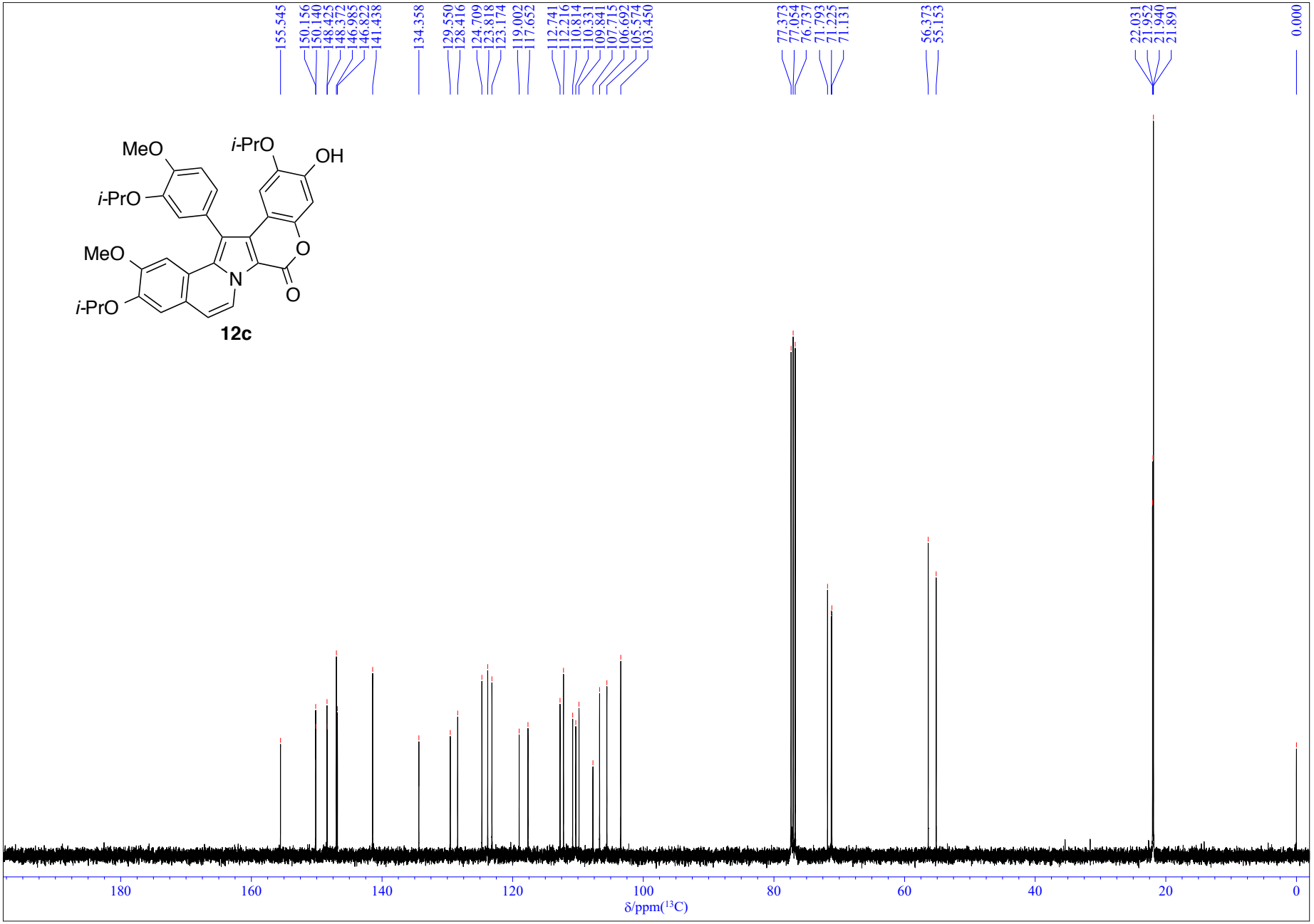


Figure S48. ^{13}C NMR spectrum of compound **12c** (100 MHz, $CDCl_3$).

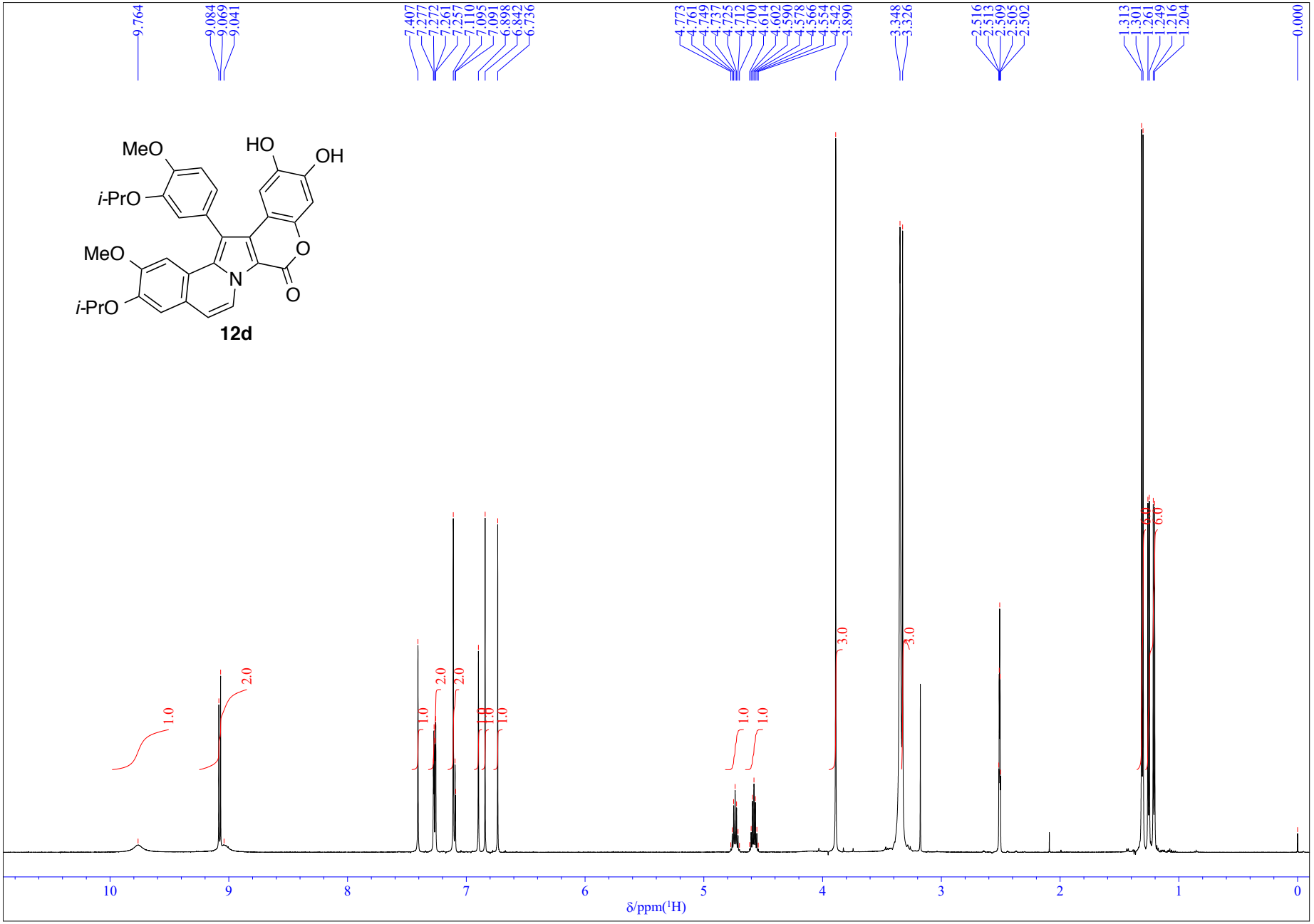


Figure S49. ^{1}H NMR spectrum of compound **12d** (500 MHz, DMSO-d_6).

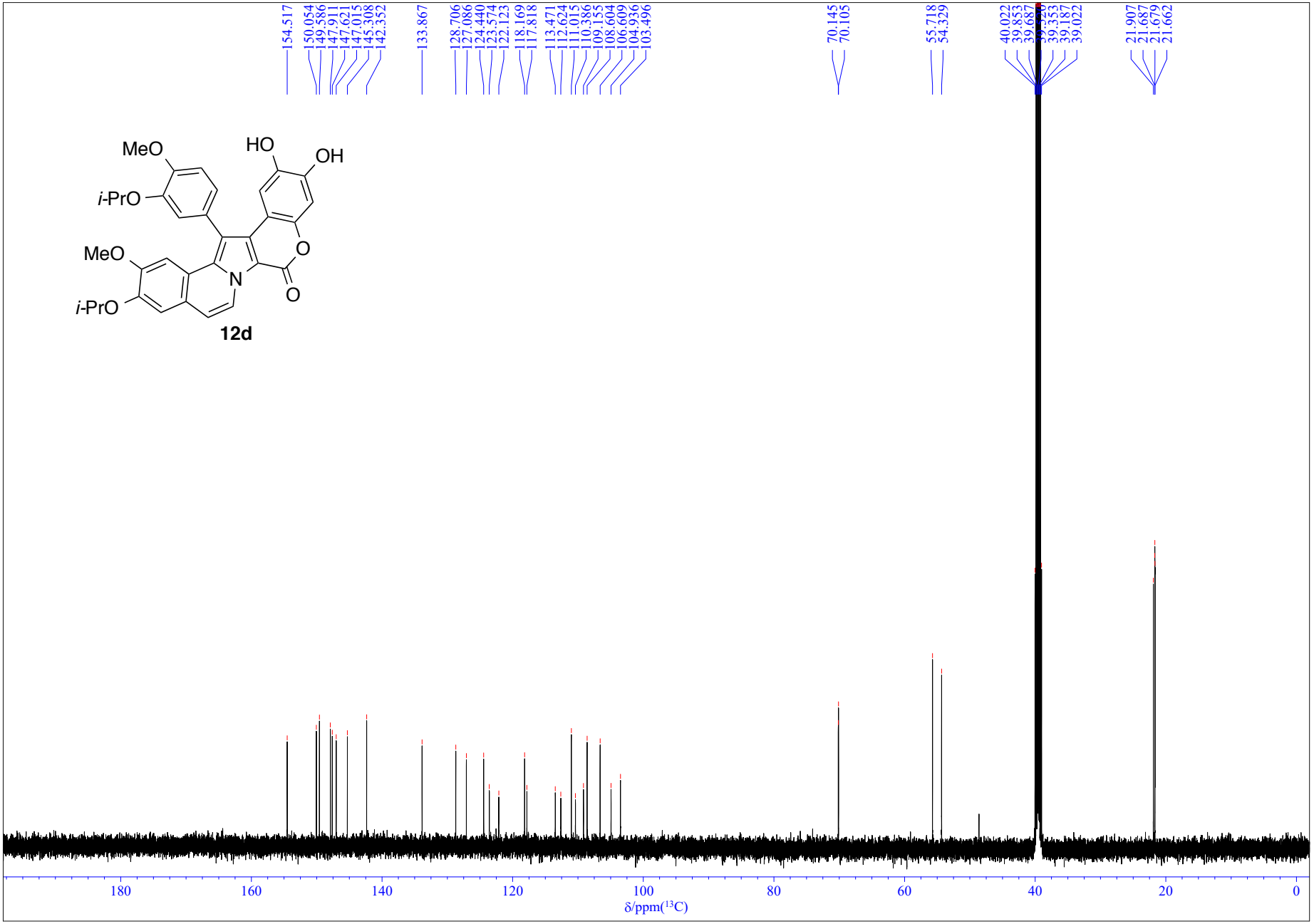


Figure S50. ^{13}C NMR spectrum of compound **12d** (126 MHz, DMSO-d_6).

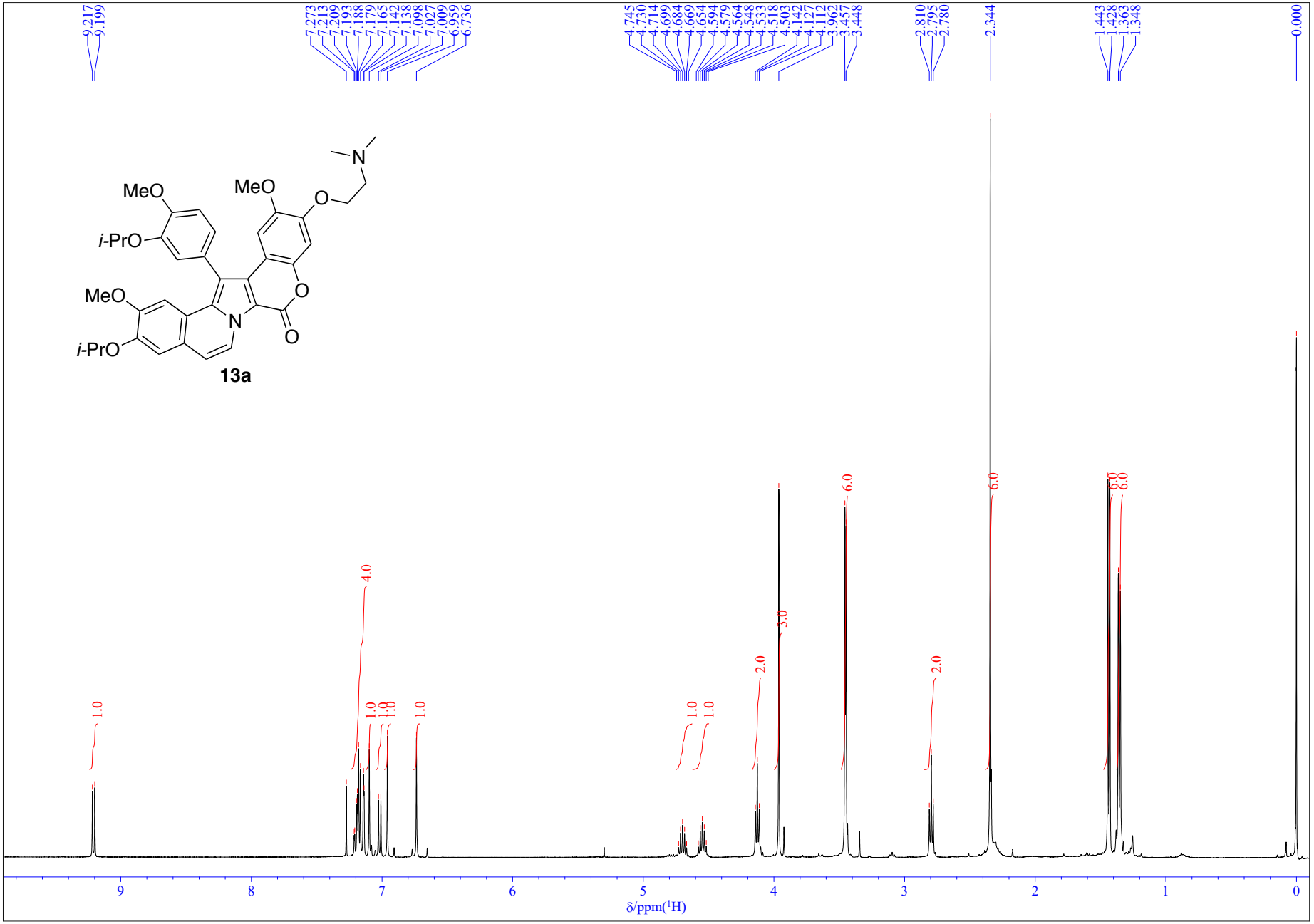


Figure S51. ^{1}H NMR spectrum of compound **13a** (400 MHz, $CDCl_3$).

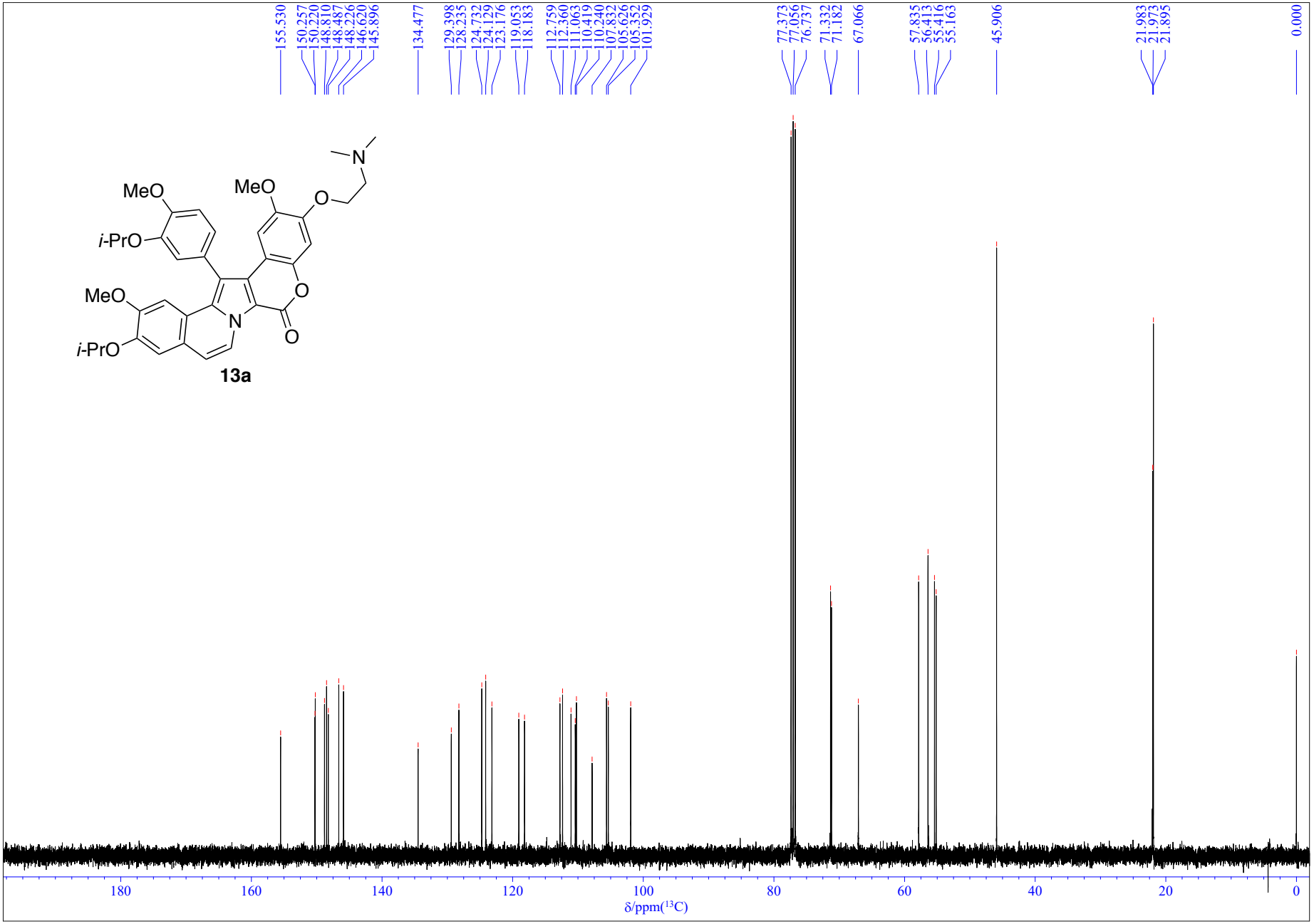


Figure S52. ^{13}C NMR spectrum of compound **13a** (100 MHz, $CDCl_3$).

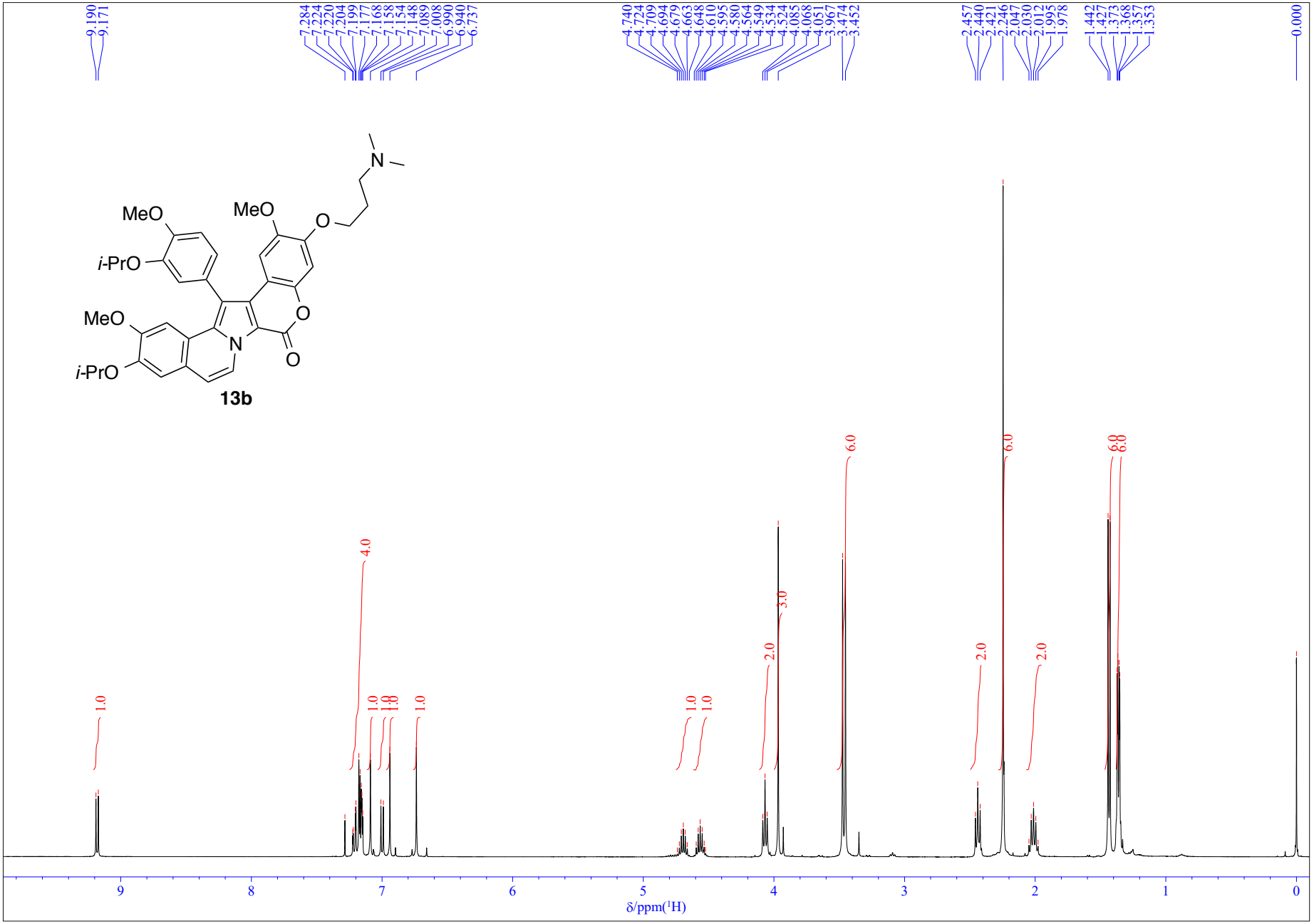


Figure S53. ^{1}H NMR spectrum of compound **13b** (400 MHz, $CDCl_3$).

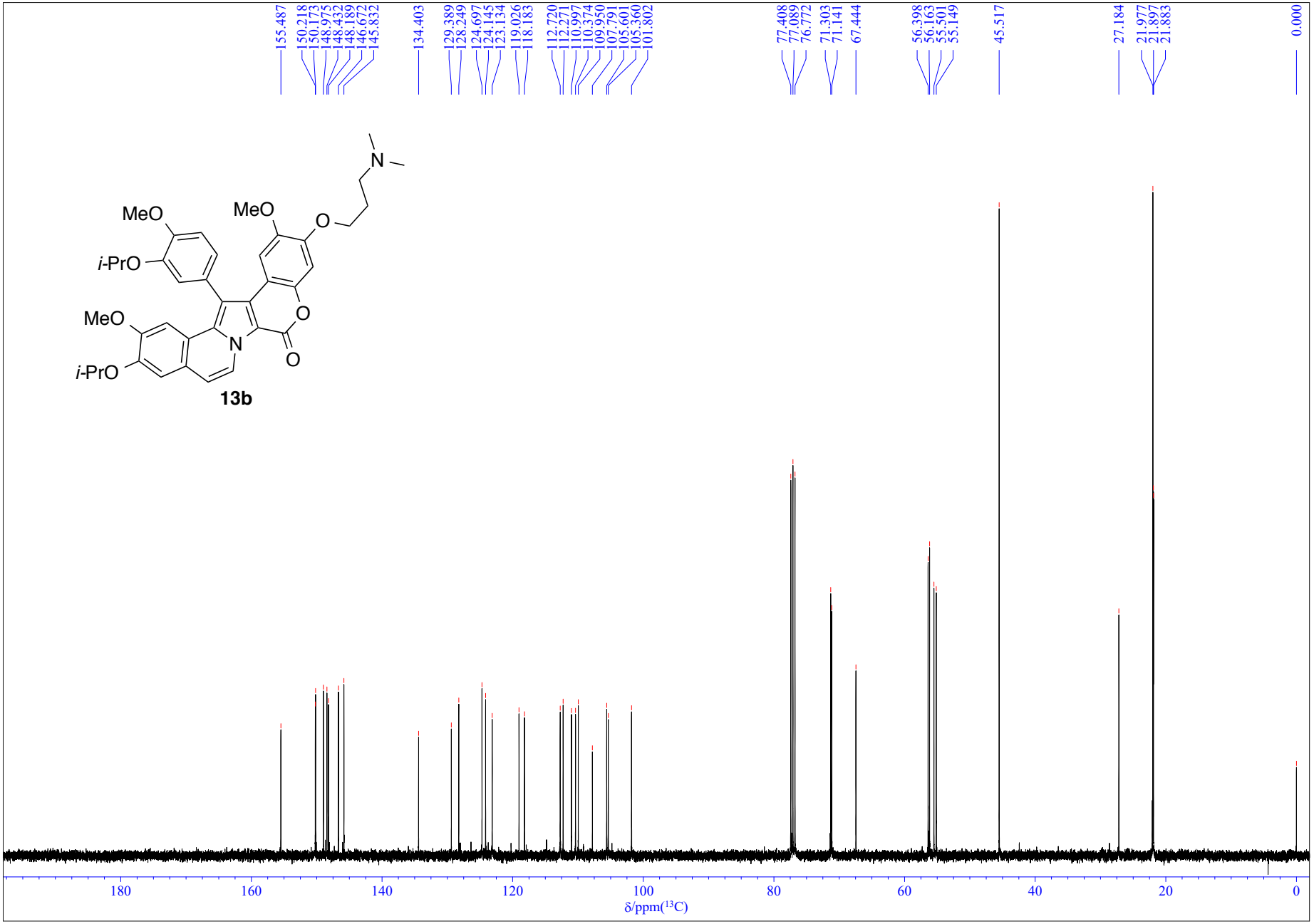


Figure S54. ^{13}C NMR spectrum of compound **13b** (100 MHz, $CDCl_3$).

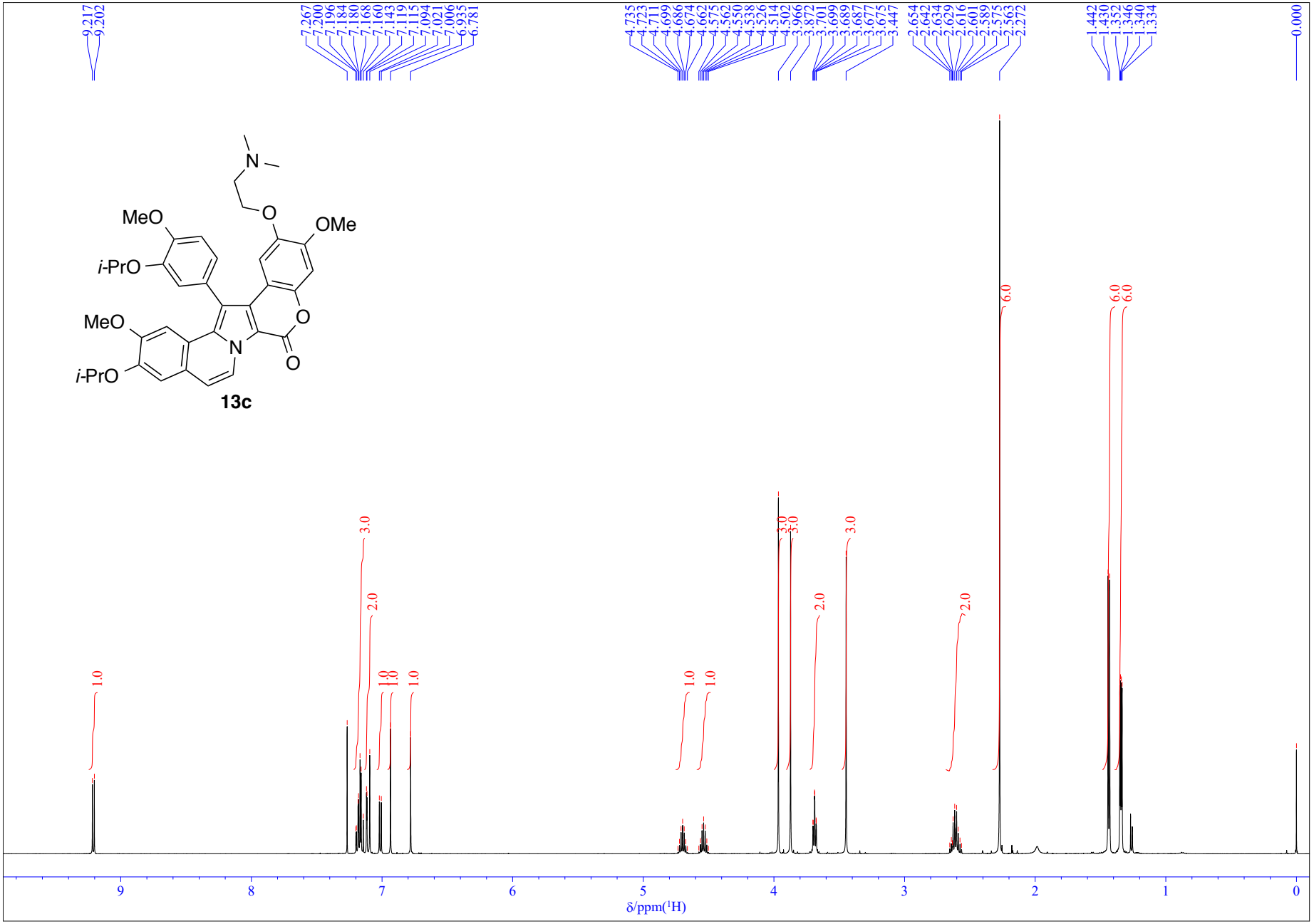


Figure S55. ^{1}H NMR spectrum of compound **13c** (500 MHz, $CDCl_3$).

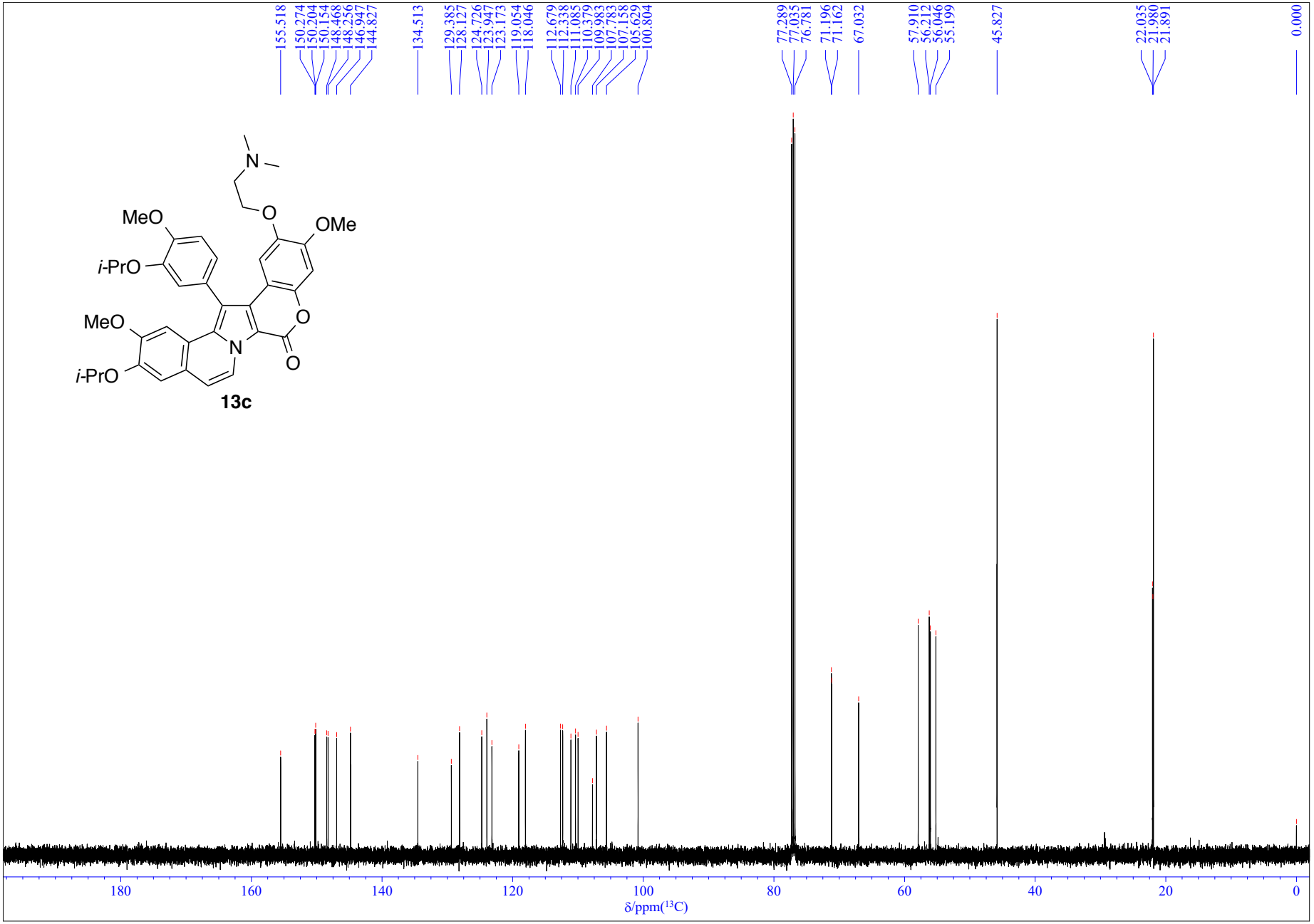


Figure S56. ^{13}C NMR spectrum of compound **13c** (126 MHz, $CDCl_3$).

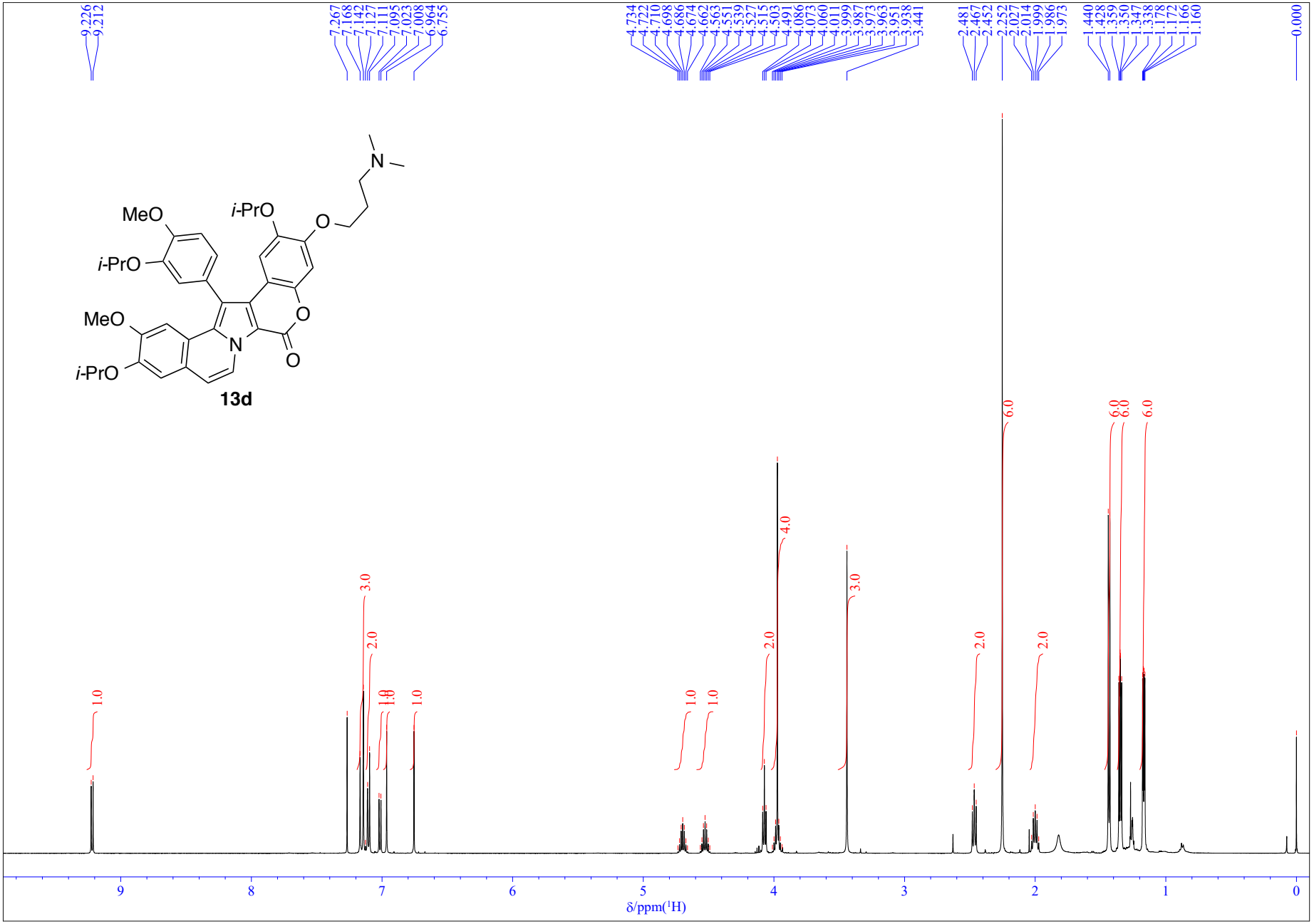


Figure S57. ^{1}H NMR spectrum of compound **13d** (500 MHz, $CDCl_3$).

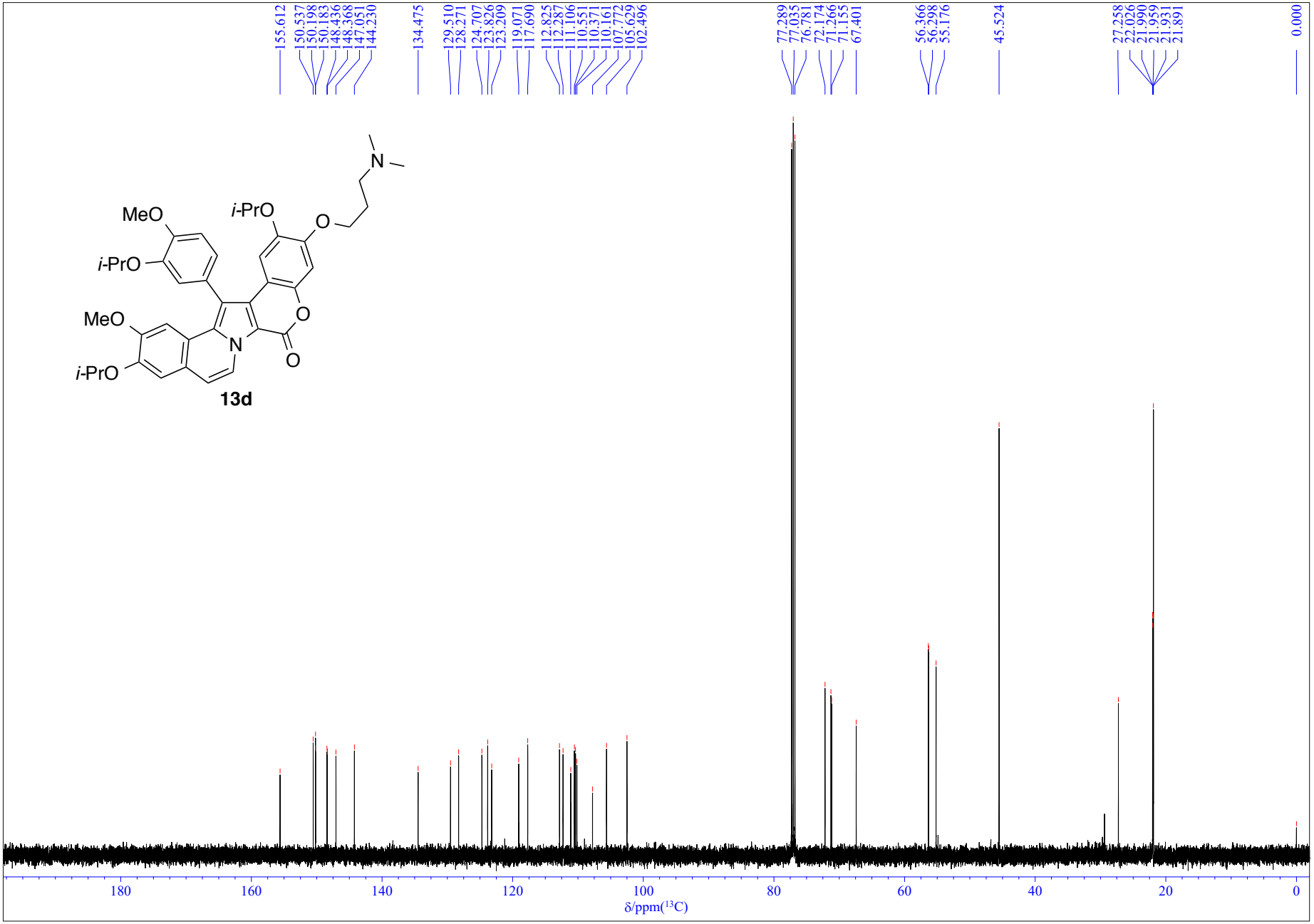


Figure S58. ^{13}C NMR spectrum of compound **13d** (126 MHz, $CDCl_3$).

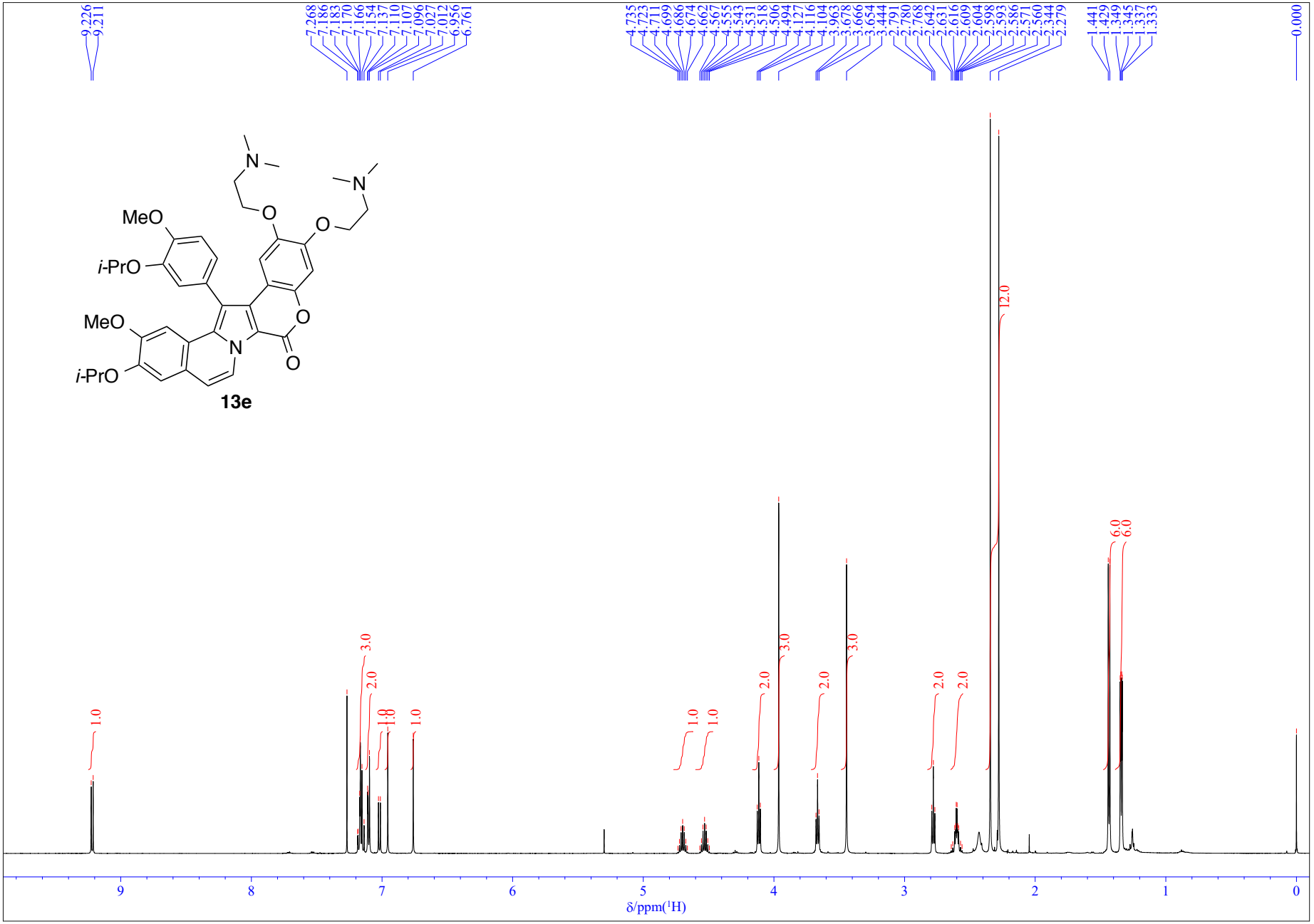


Figure S59. ^{1}H NMR spectrum of compound **13e** (500 MHz, $CDCl_3$).

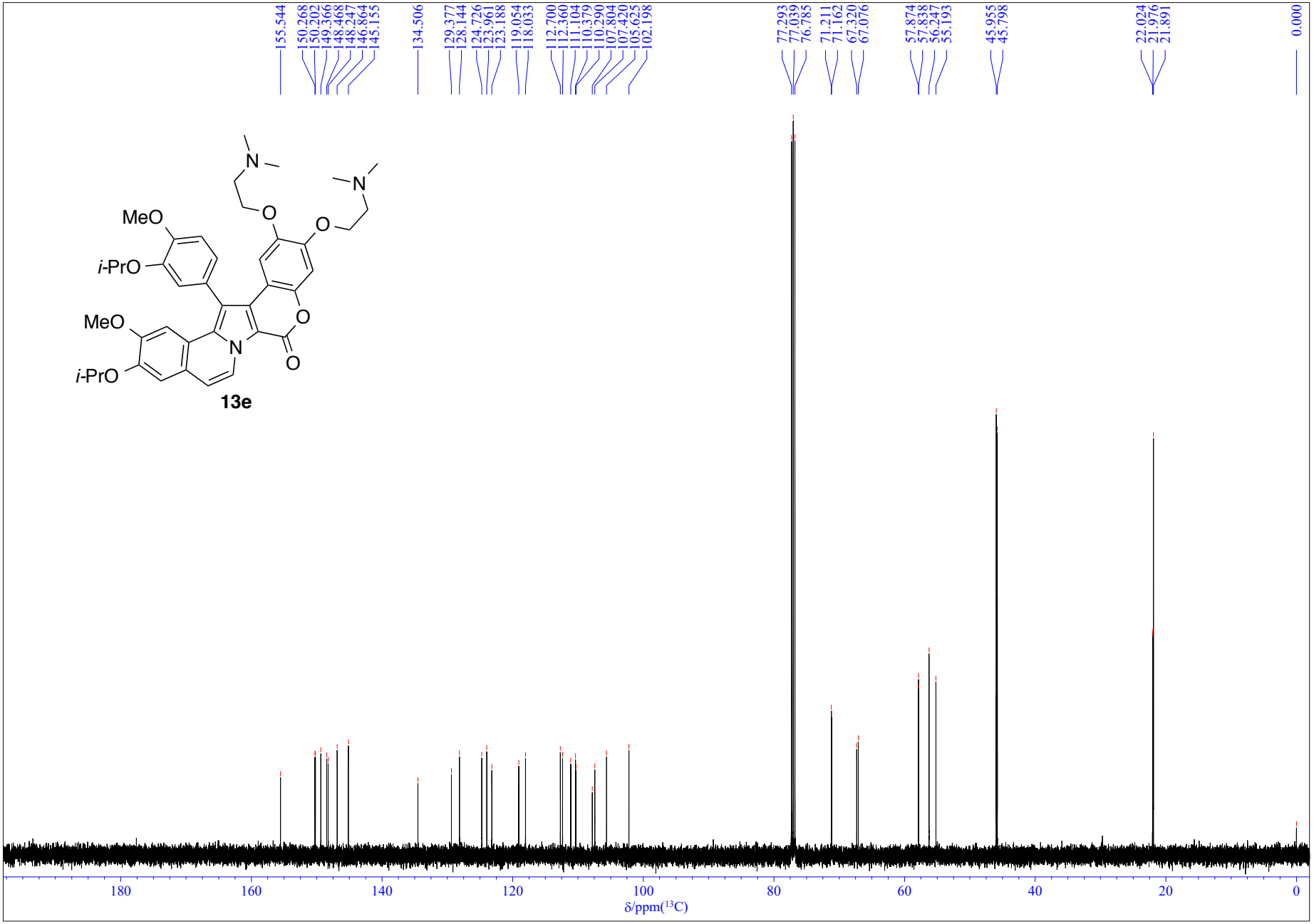


Figure S60. ^{13}C NMR spectrum of compound **13e** (126 MHz, $CDCl_3$).

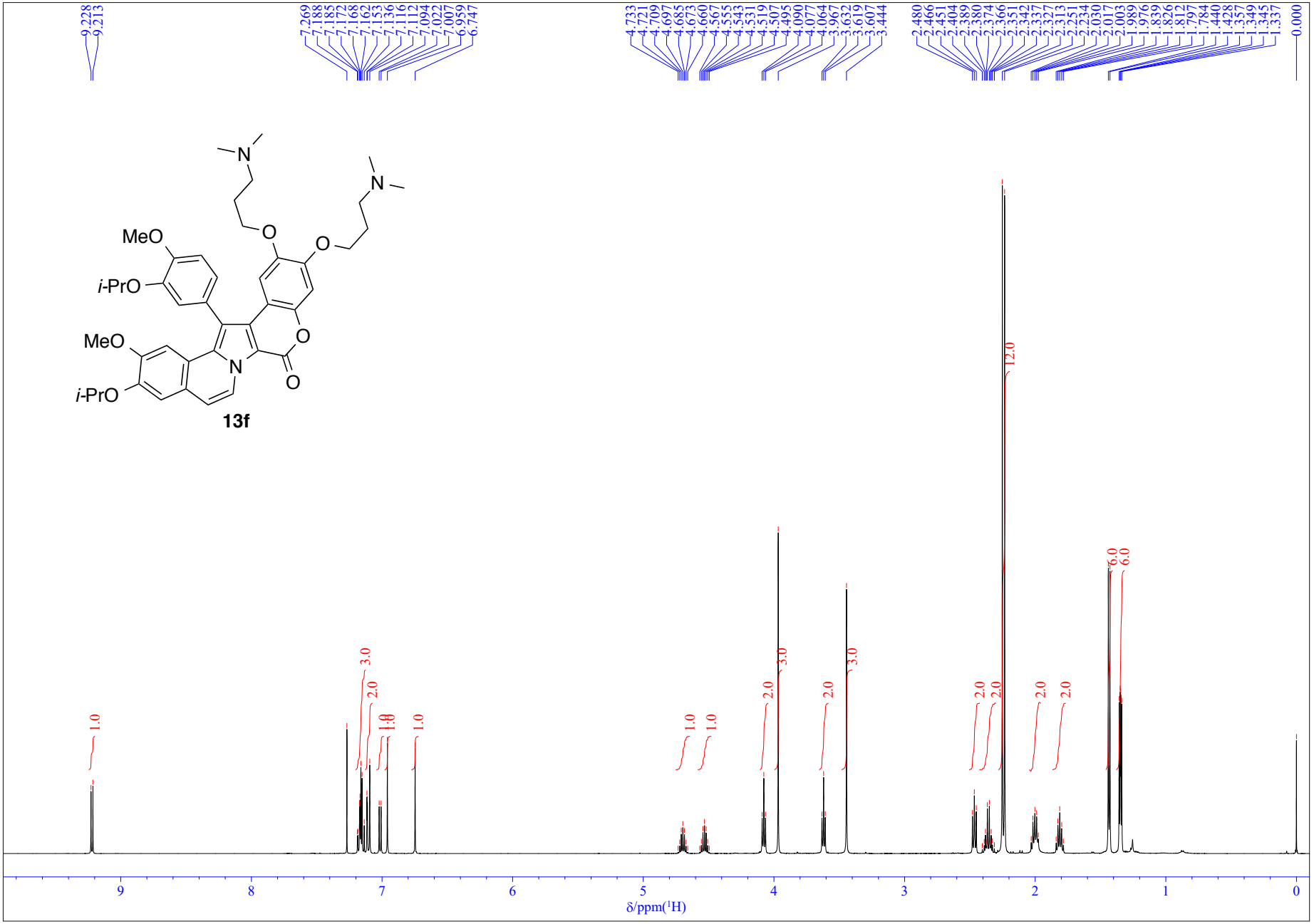


Figure S61. ^{1}H NMR spectrum of compound **13f** (500 MHz, $CDCl_3$).

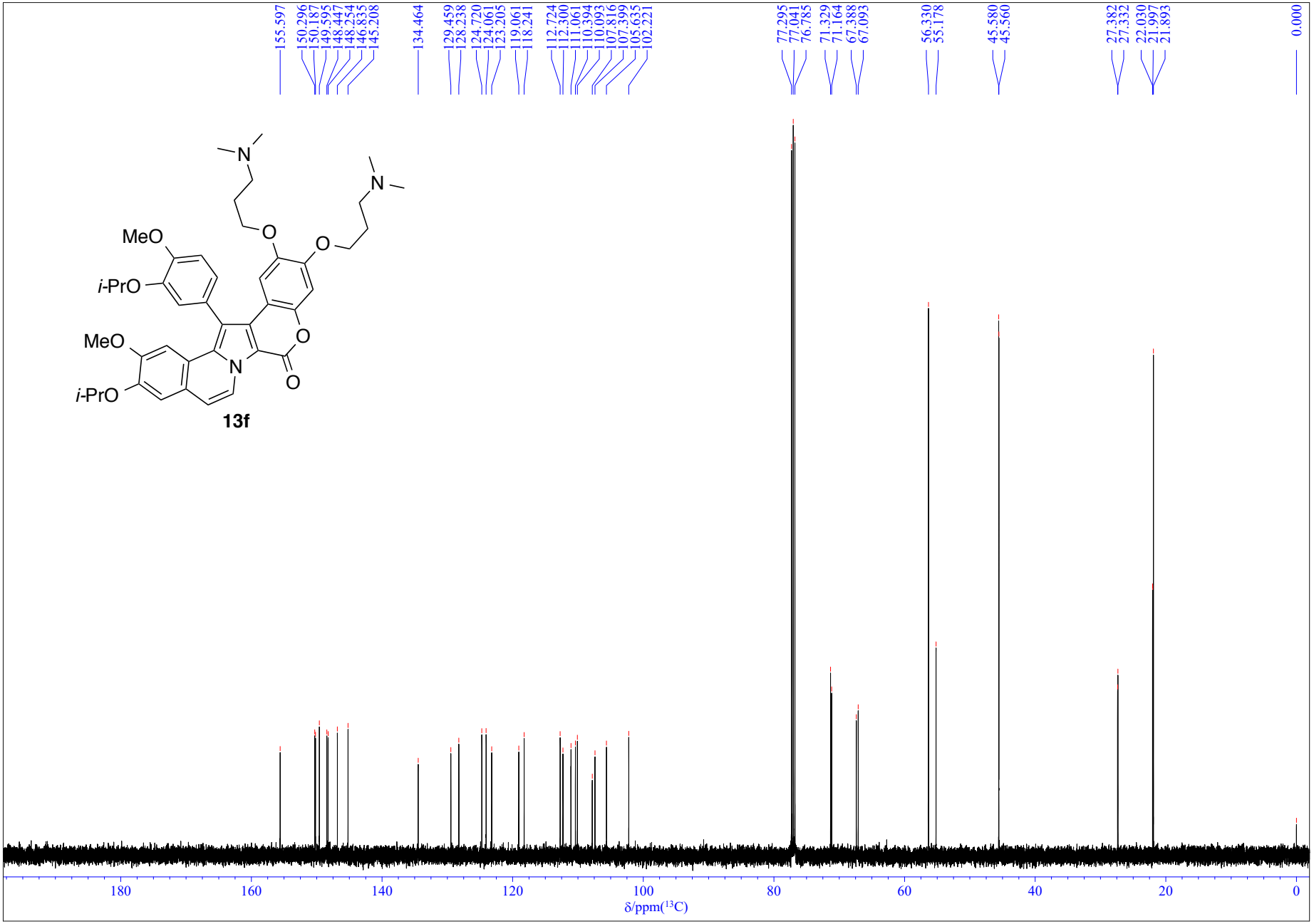


Figure S62. ^{13}C NMR spectrum of compound **13f** (126 MHz, $CDCl_3$).

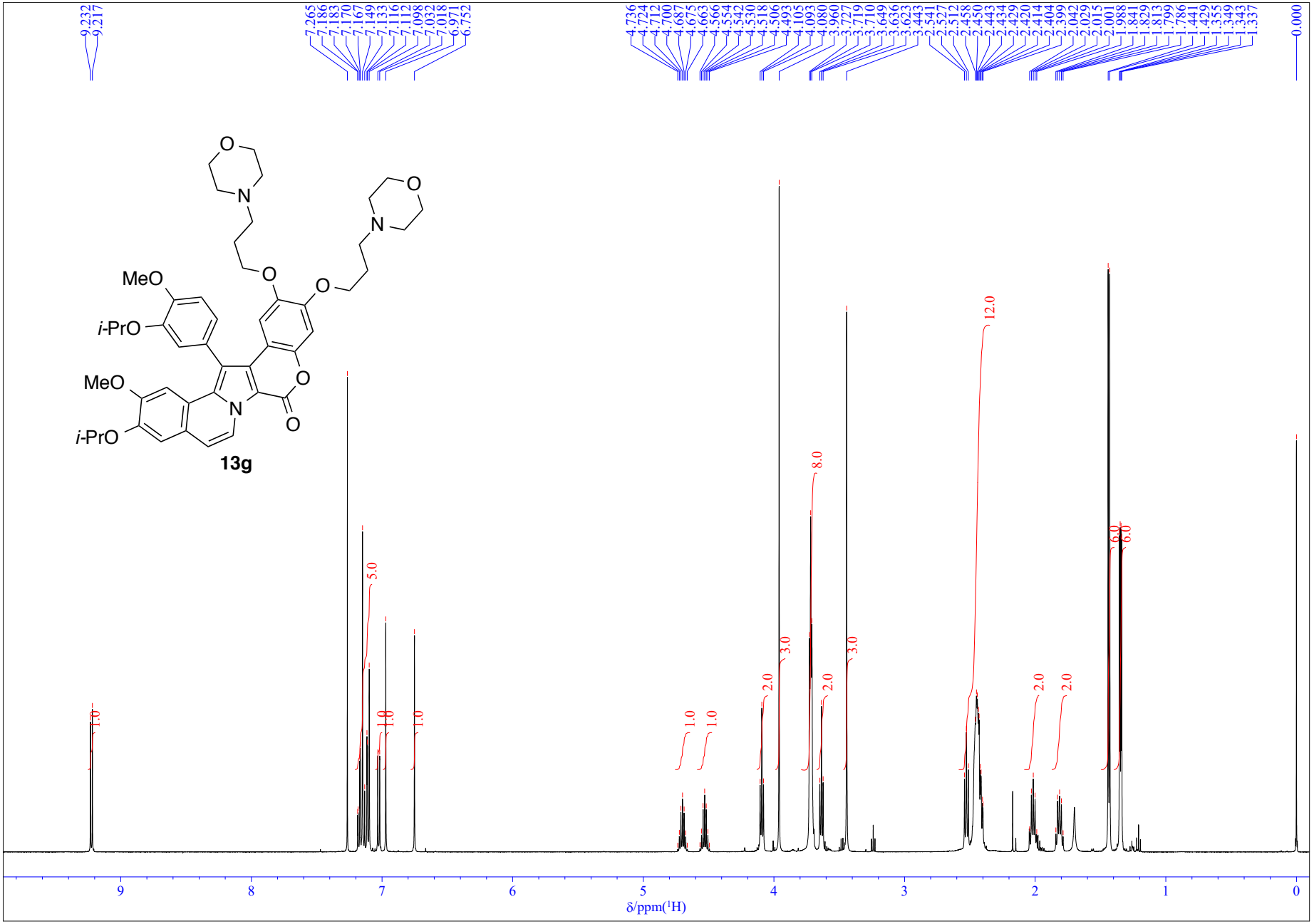


Figure S63. ^{1}H NMR spectrum of compound **13g** (500 MHz, $CDCl_3$).

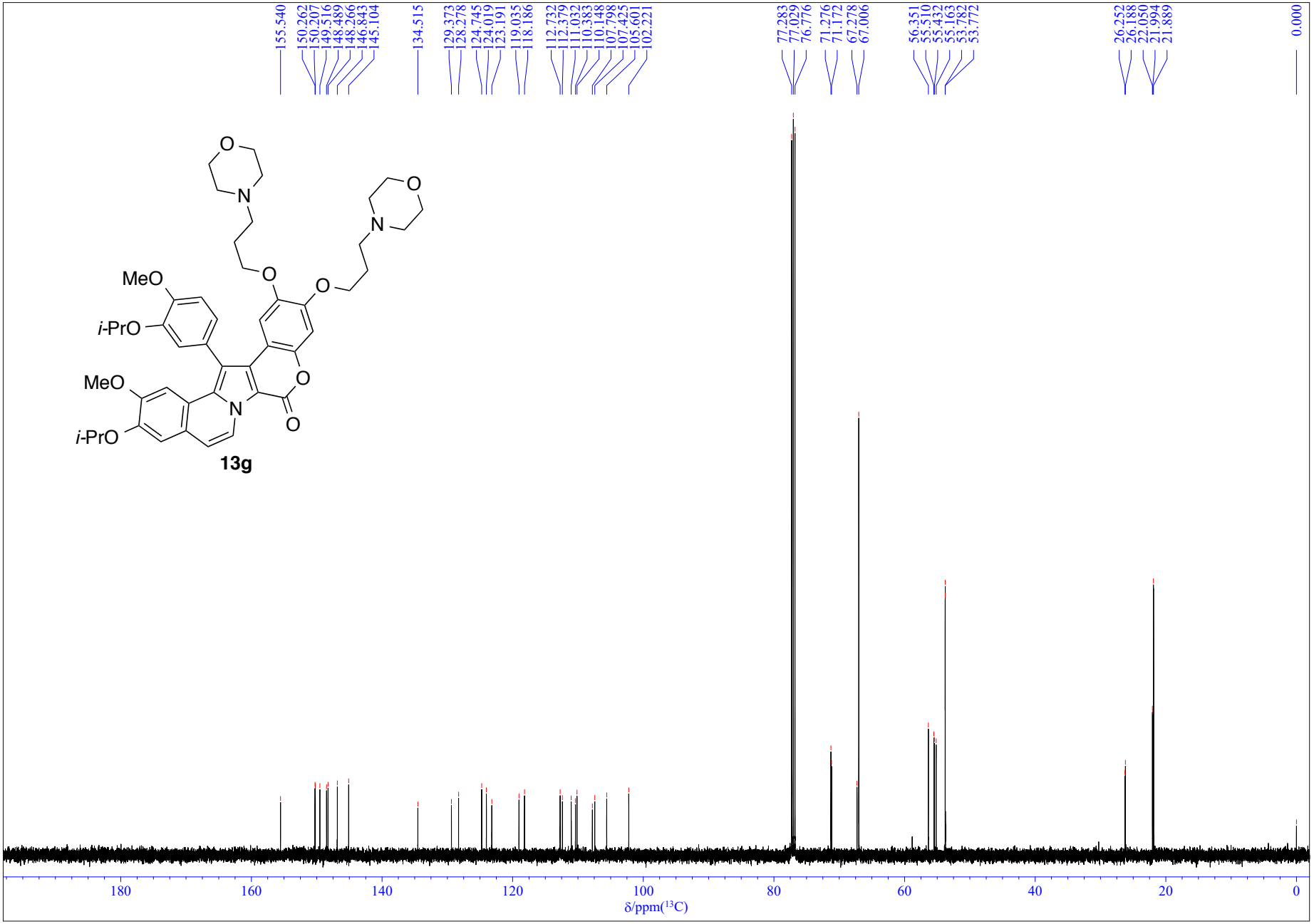


Figure S64. ^{13}C NMR spectrum of compound **13g** (126 MHz, $CDCl_3$).

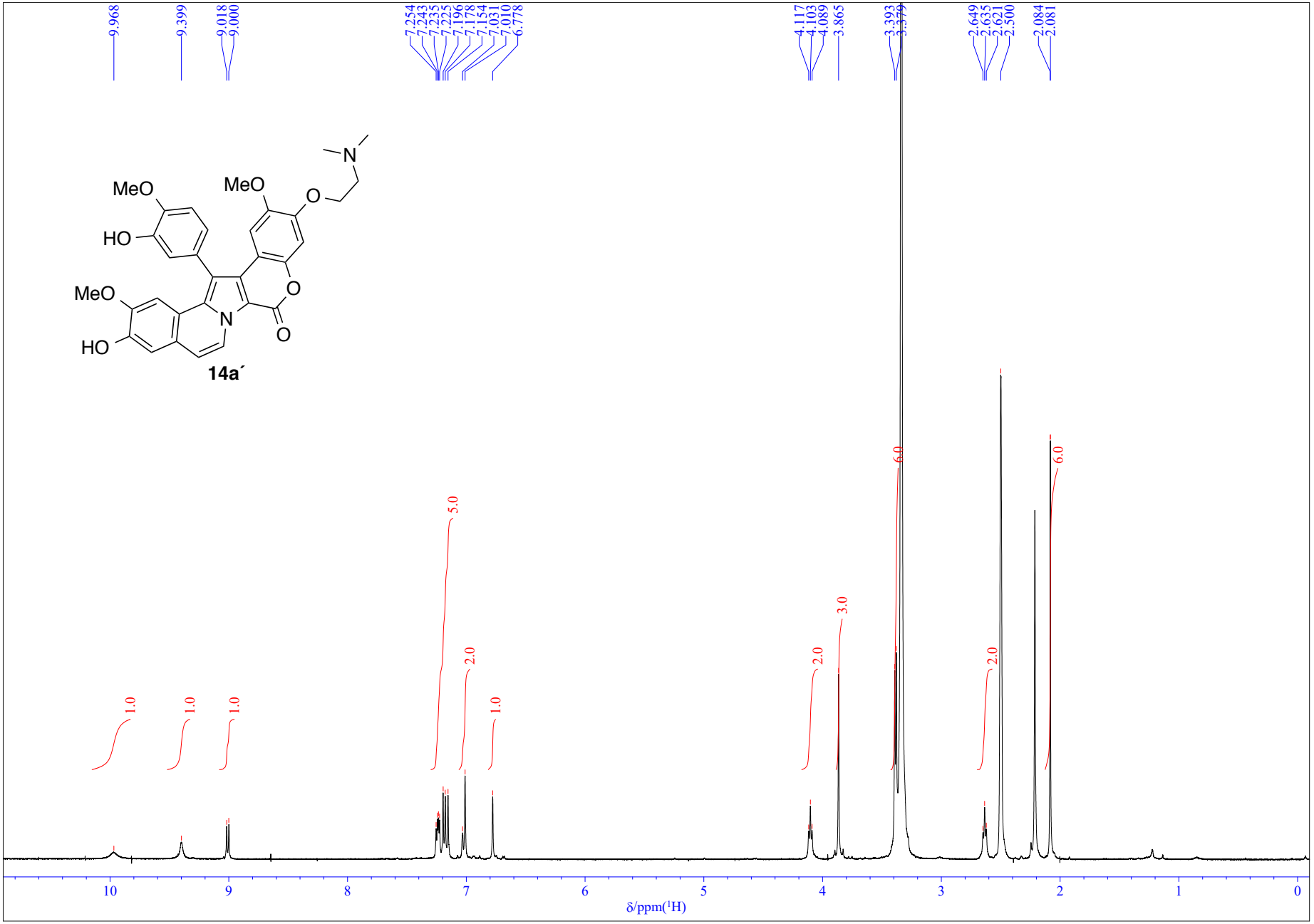


Figure S65. ^{1}H NMR spectrum of compound **14a´** (400 MHz, DMSO-d_6).

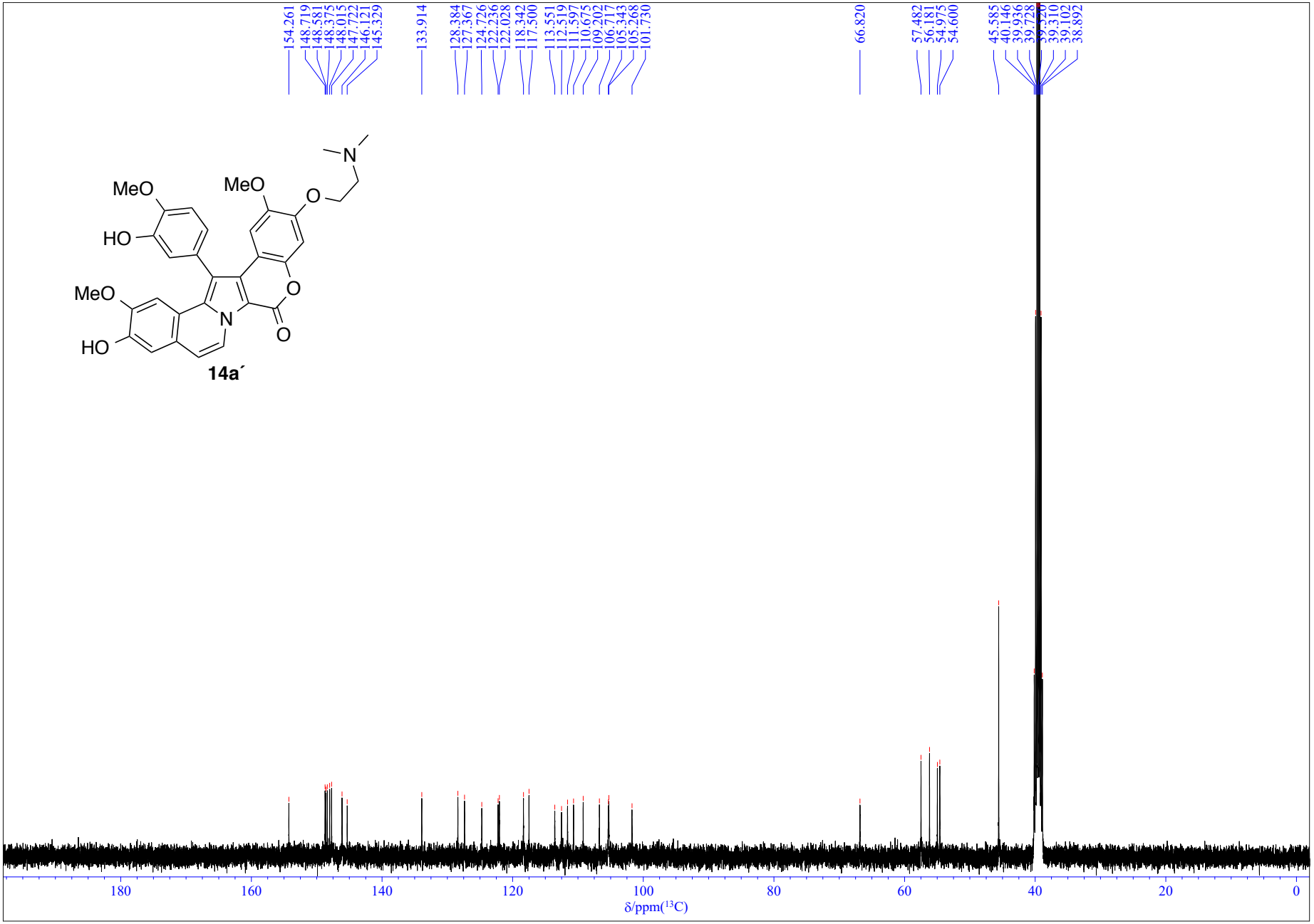


Figure S66. ^{13}C NMR spectrum of compound **14a´** (100 MHz, DMSO-d_6).

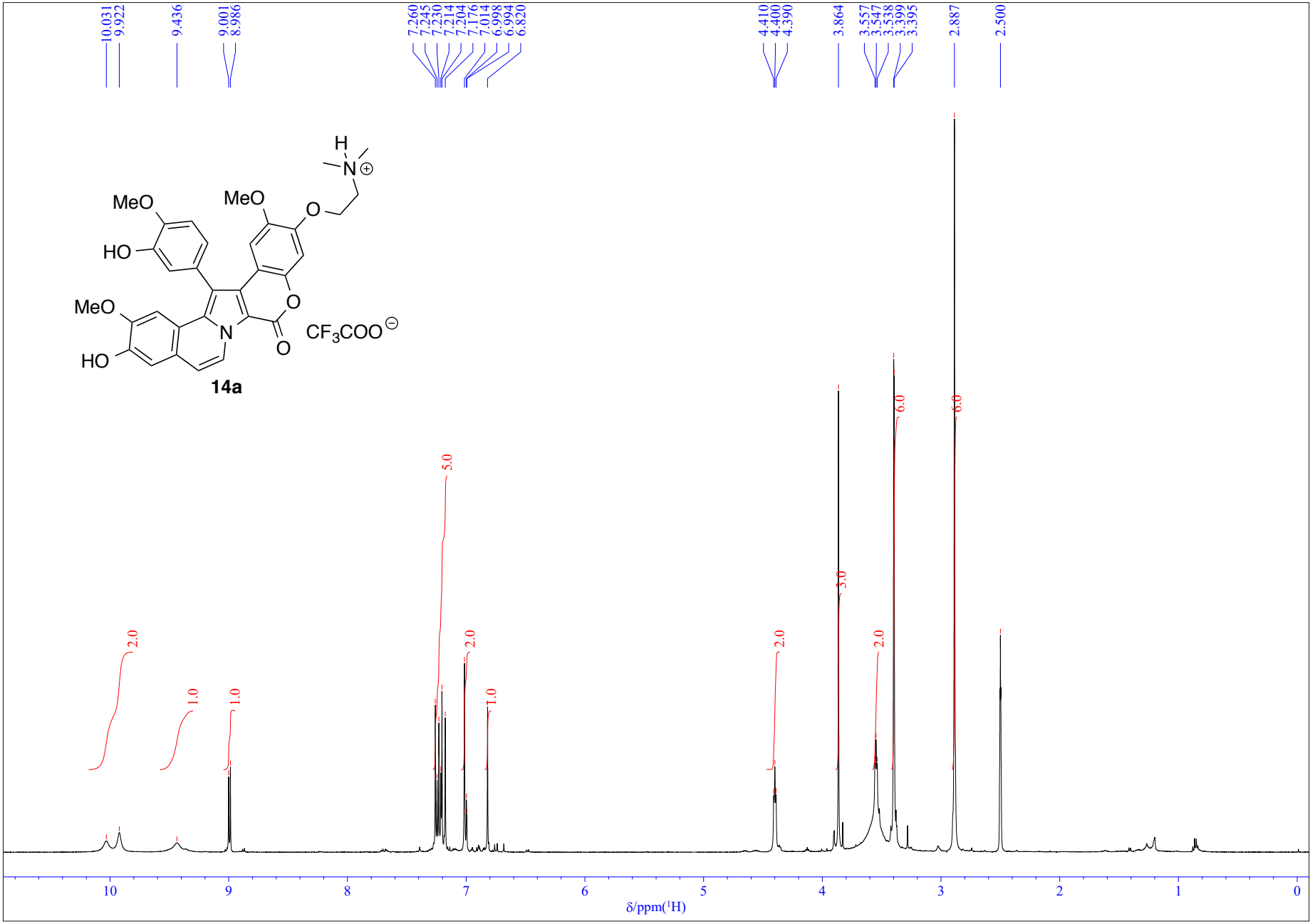


Figure S67. ^{1}H NMR spectrum of compound **14a** (500 MHz, DMSO-d_6).

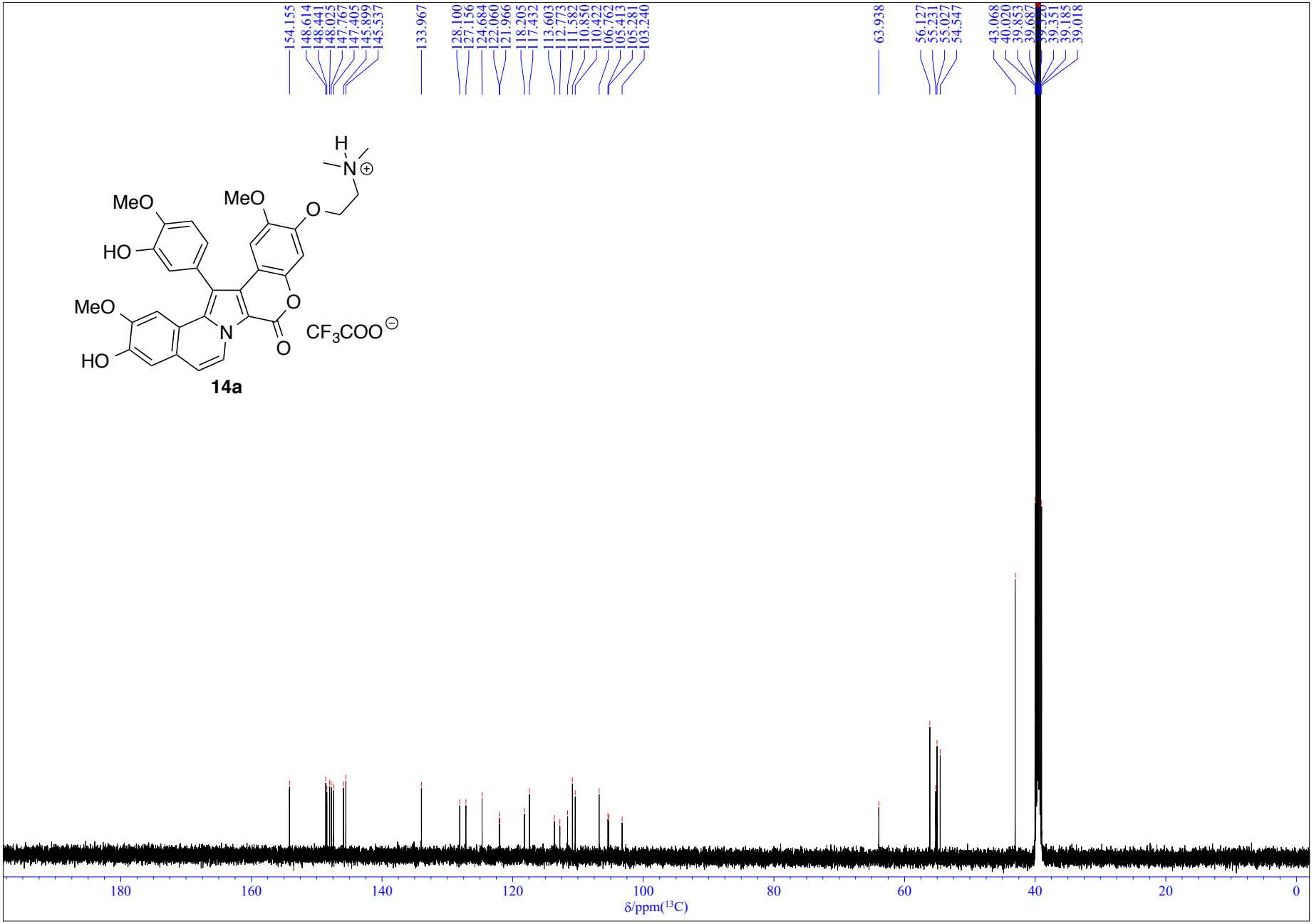


Figure S68. ^{13}C NMR spectrum of compound **14a** (126 MHz, DMSO-d_6).

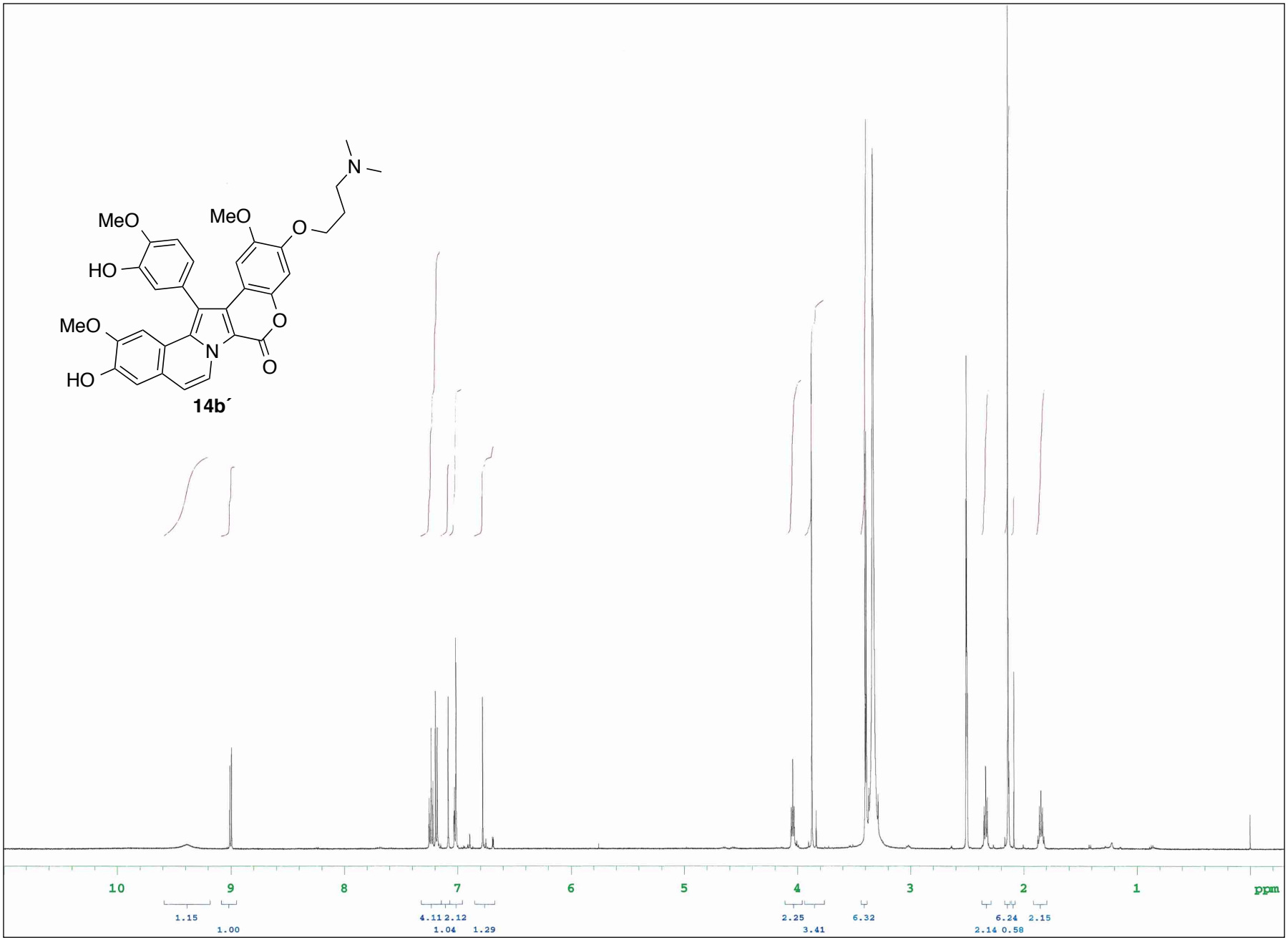


Figure S69. ^{1}H NMR spectrum of compound **14b´** (500 MHz, DMSO-d_6).

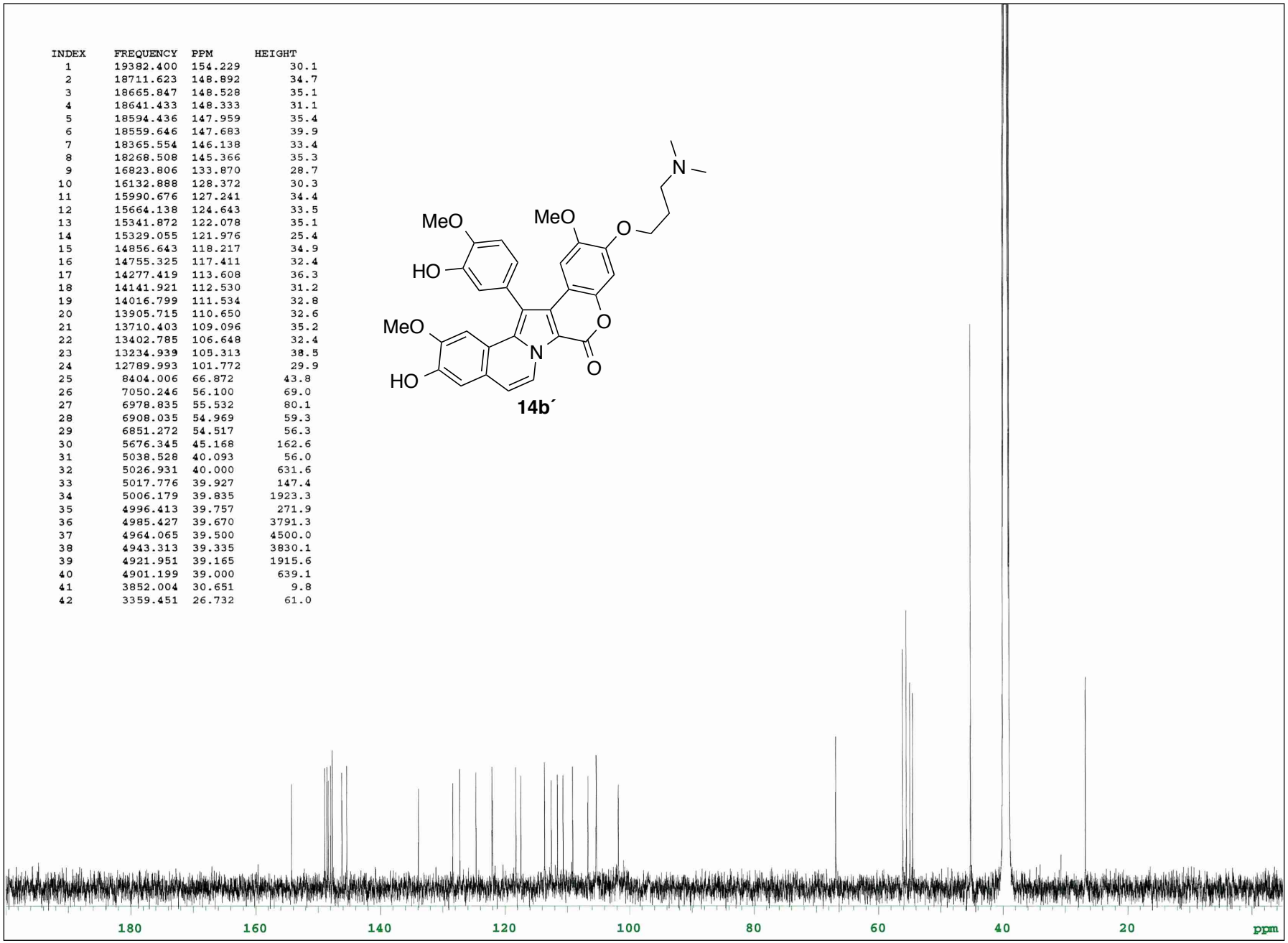


Figure S70. ^{13}C NMR spectrum of compound **14b´** (126 MHz, DMSO-d_6).

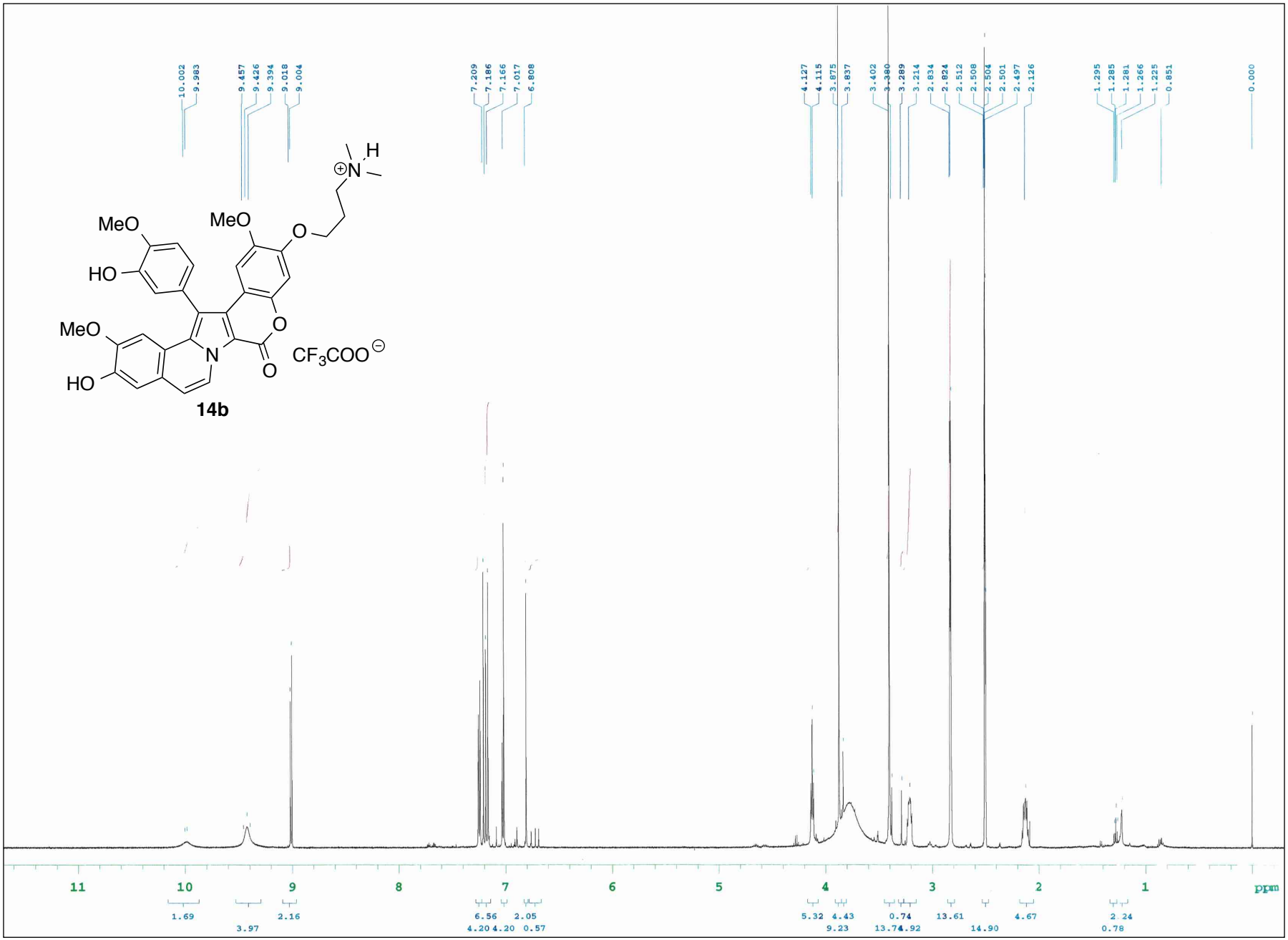


Figure S71. ^{1}H NMR spectrum of compound **14b** (500 MHz, DMSO-d_6).

FREQUENCY(PPM)	Hz	SUB	HEIGHT
222.729	27993.850	-27993.850	1.6
218.407	27450.637	543.213	-1.7
215.200	27047.500	403.137	2.0
207.918	26132.278	915.222	-1.8
203.484	25575.027	557.251	-1.7
158.050	19864.577	5710.449	2.9
157.790	19831.924	32.654	2.9
154.170	19376.907	455.017	9.3
148.551	18670.730	706.177	10.2
148.362	18646.926	23.804	9.7
148.228	18630.141	16.785	9.4
147.968	18597.488	32.654	10.4
147.704	18564.223	33.264	10.2
146.014	18351.821	212.402	9.0
145.368	18270.644	81.177	9.7
133.914	16831.130	1439.514	9.2
128.230	16116.714	714.417	8.9
127.905	16075.820	40.894	-1.6
127.179	15984.573	91.248	9.1
124.642	15665.664	318.909	8.5
122.031	15337.600	328.064	9.7
121.937	15325.698	11.902	7.8
118.173	14852.676	473.022	9.7
117.394	14754.714	97.961	8.6
113.616	14279.861	474.854	10.0
112.652	14158.706	121.155	8.6
111.540	14018.935	139.771	7.8
110.721	13916.091	102.844	9.4
109.636	13779.678	136.414	8.5
106.662	13405.837	373.840	8.1
105.265	13230.361	175.476	13.8
102.289	12856.216	374.146	8.6
66.062	8302.993	4553.223	11.0
56.106	7051.772	1251.221	17.9
54.968	6908.645	143.127	16.2
54.516	6851.882	56.763	15.0
54.353	6831.435	20.447	17.3
42.354	5323.257	1508.179	43.1
39.996	5026.931	296.326	287.0
39.829	5005.874	21.057	868.0
39.751	4996.108	9.766	128.8
39.661	4984.817	11.292	1722.8
39.493	4963.760	21.057	2018.6
39.328	4943.008	20.752	1724.0
39.161	4921.951	21.057	870.5
38.993	4900.893	21.057	290.8
23.769	2987.441	1913.452	14.4
7.178	902.175	2085.266	-1.6
0.061	7.705	894.470	1.8

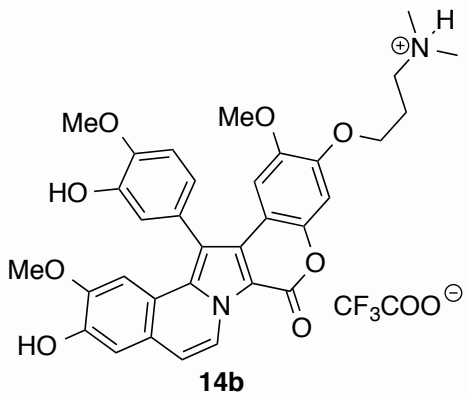


Figure S72. ^{13}C NMR spectrum of compound **14b** (126 MHz, DMSO-d_6).

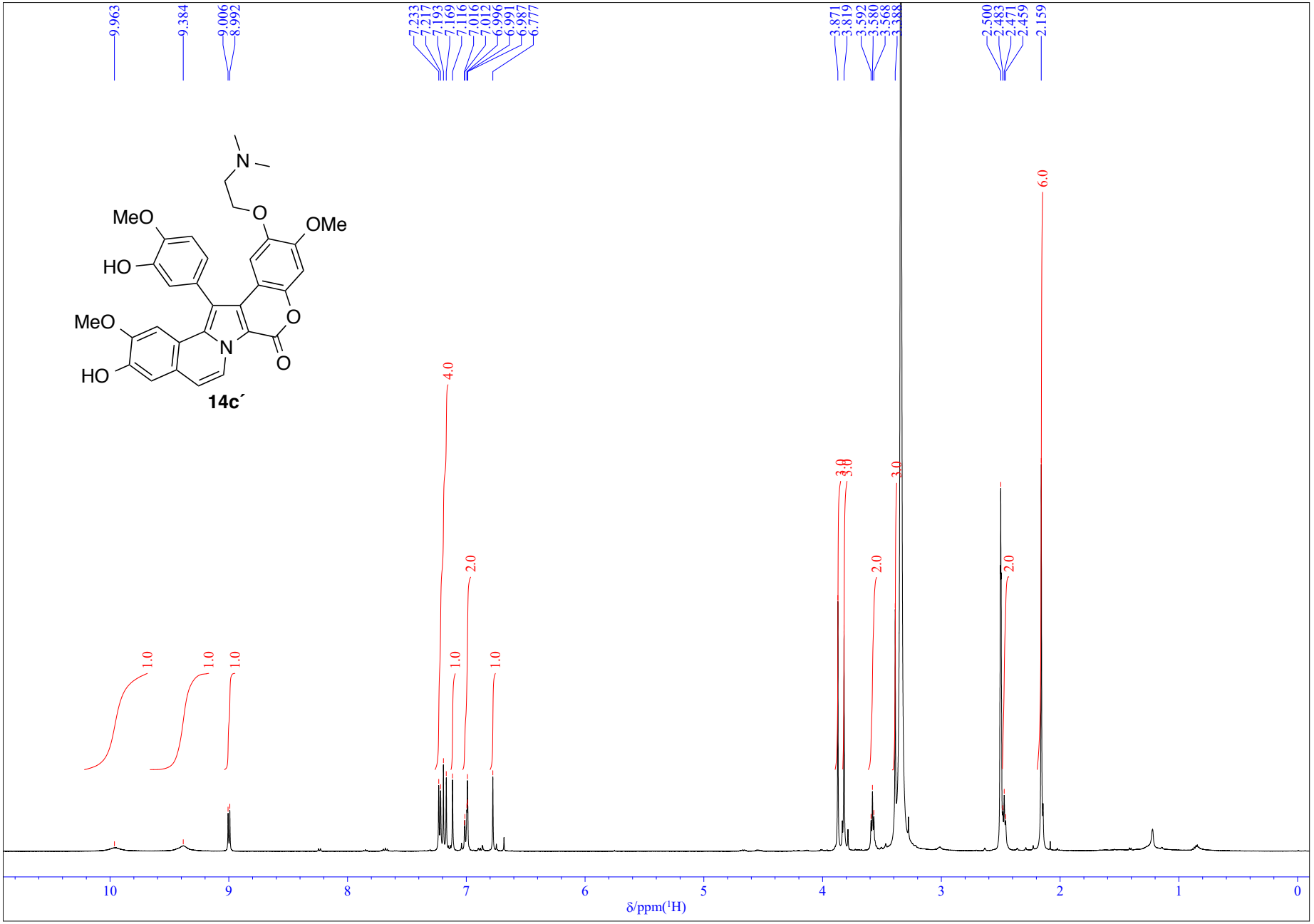


Figure S73. ^{1}H NMR spectrum of compound **14c´** (500 MHz, DMSO-d_6).

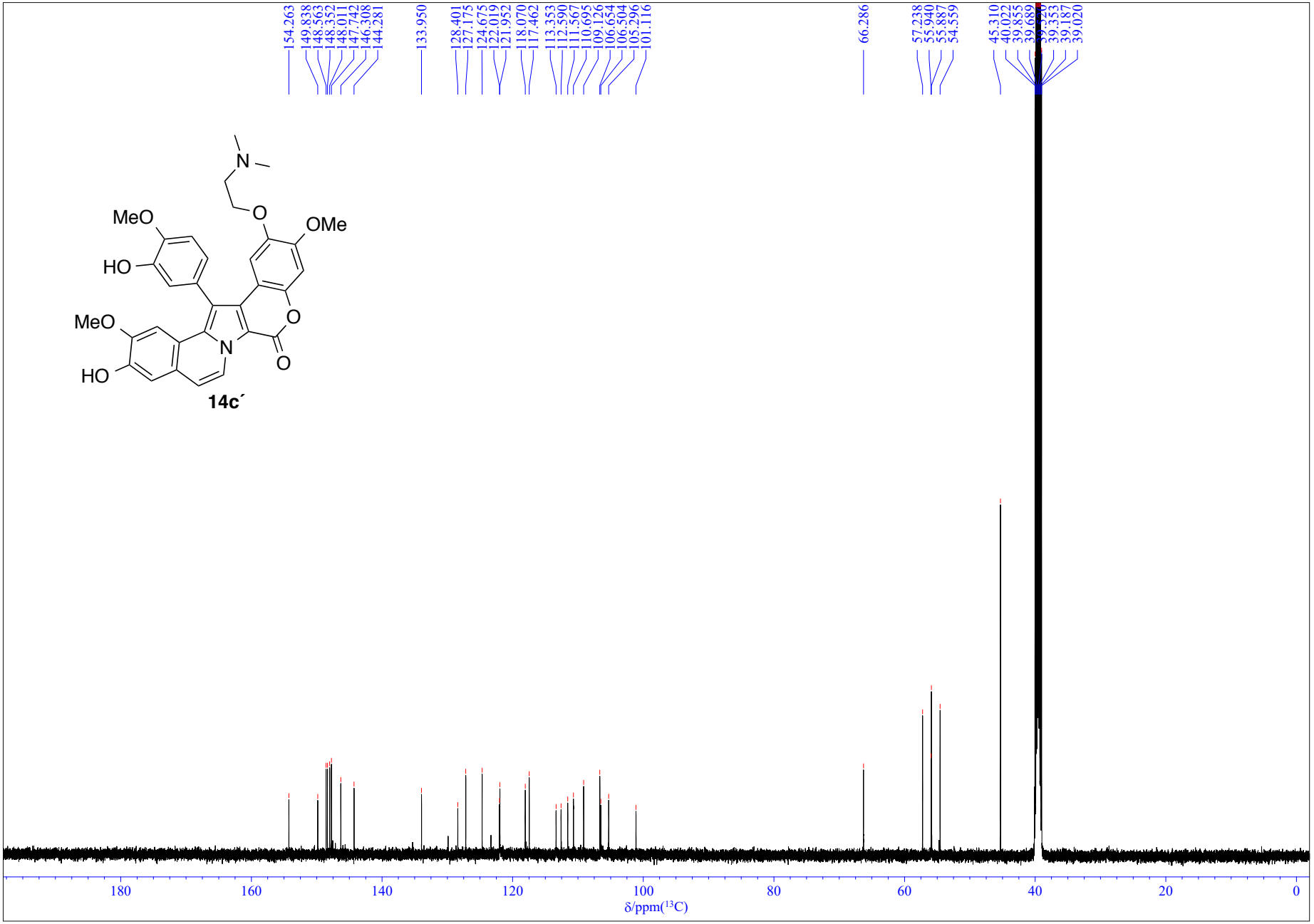


Figure S74. ^{13}C NMR spectrum of compound **14c´** (126 MHz, DMSO-d_6).

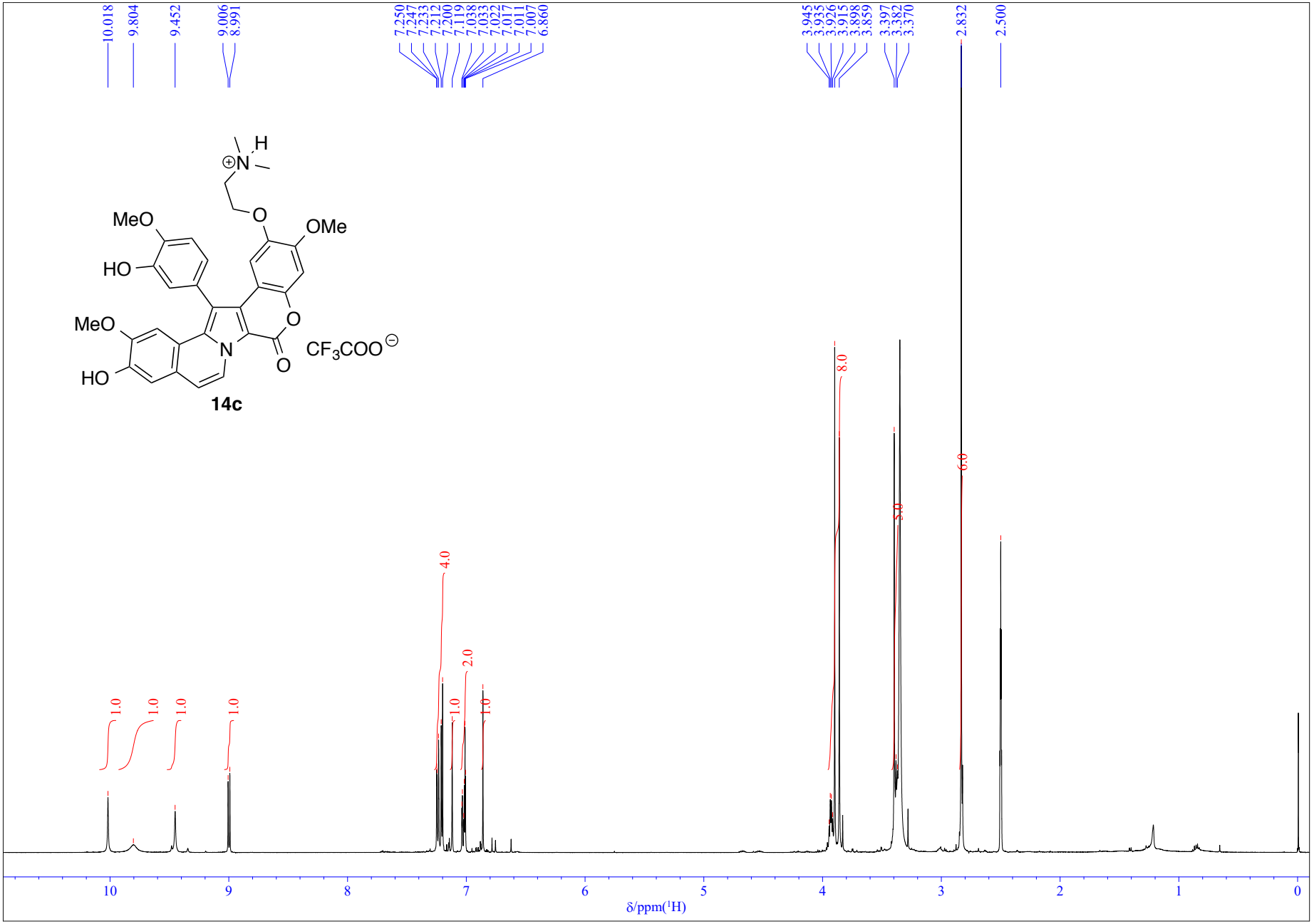


Figure S75. ^{1}H NMR spectrum of compound **14c** (500 MHz, DMSO-d_6).

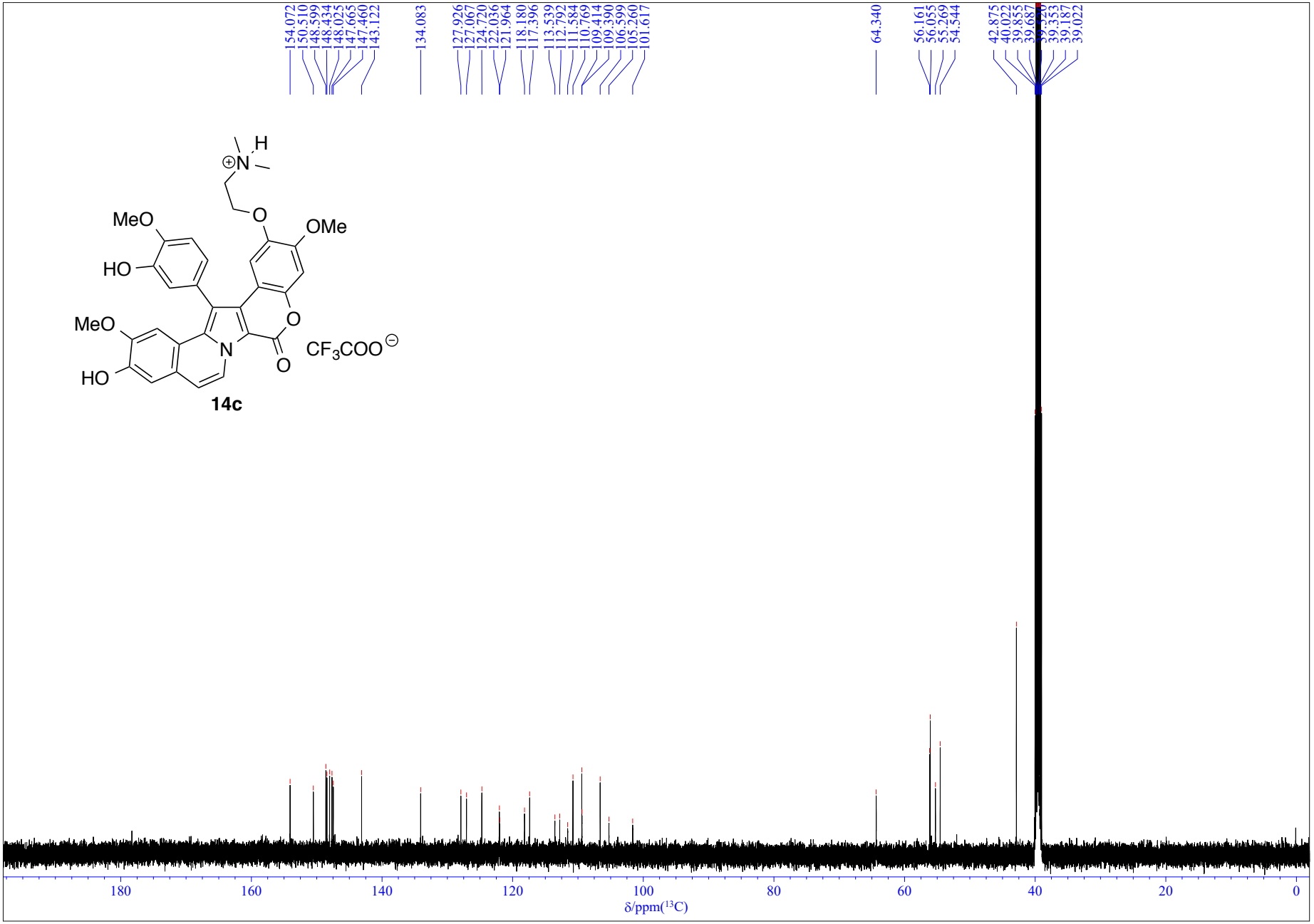


Figure S76. ^{13}C NMR spectrum of compound **14c** (126 MHz, DMSO-d_6).

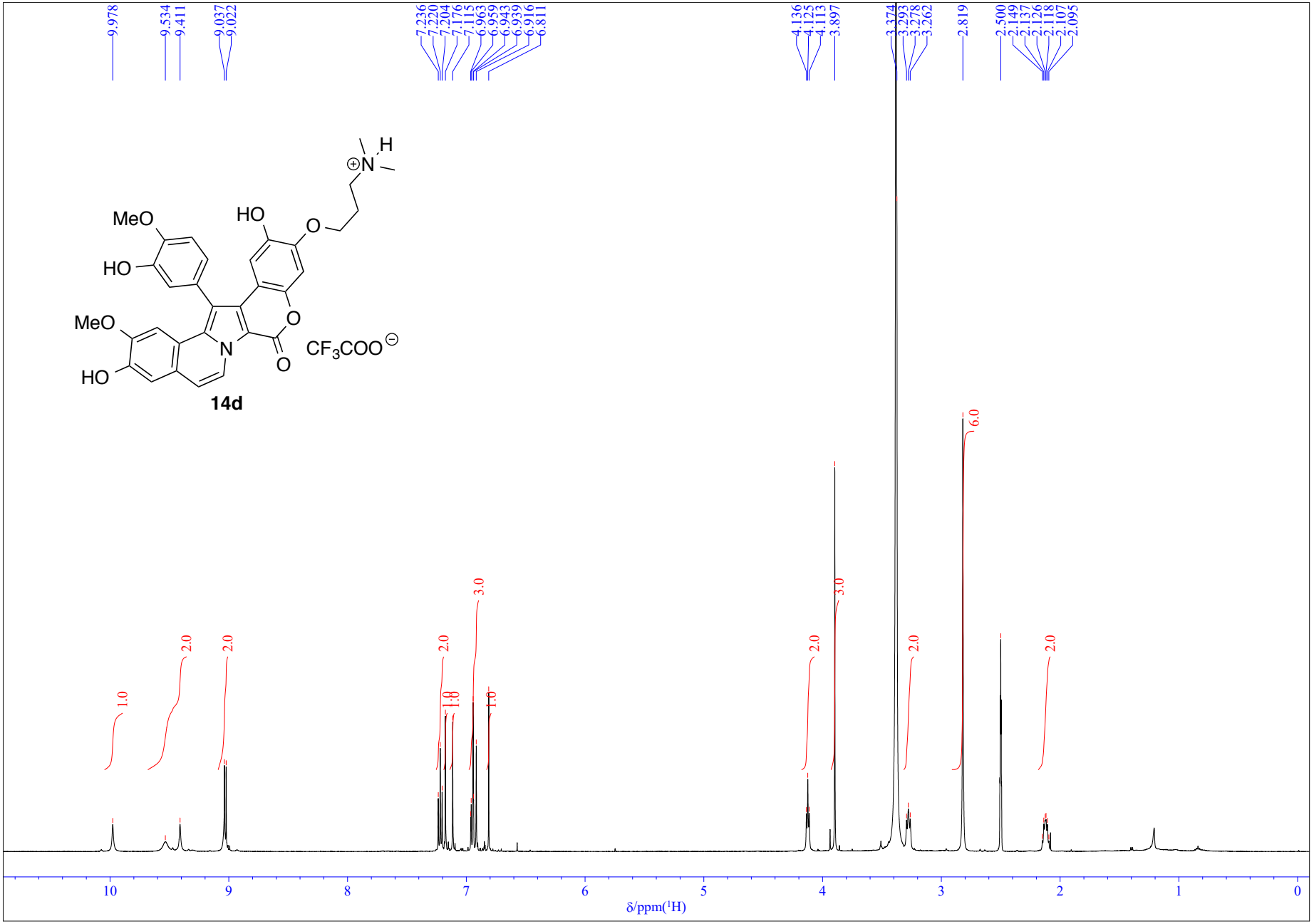


Figure S77. ^{1}H NMR spectrum of compound **14d** (500 MHz, DMSO-d_6).

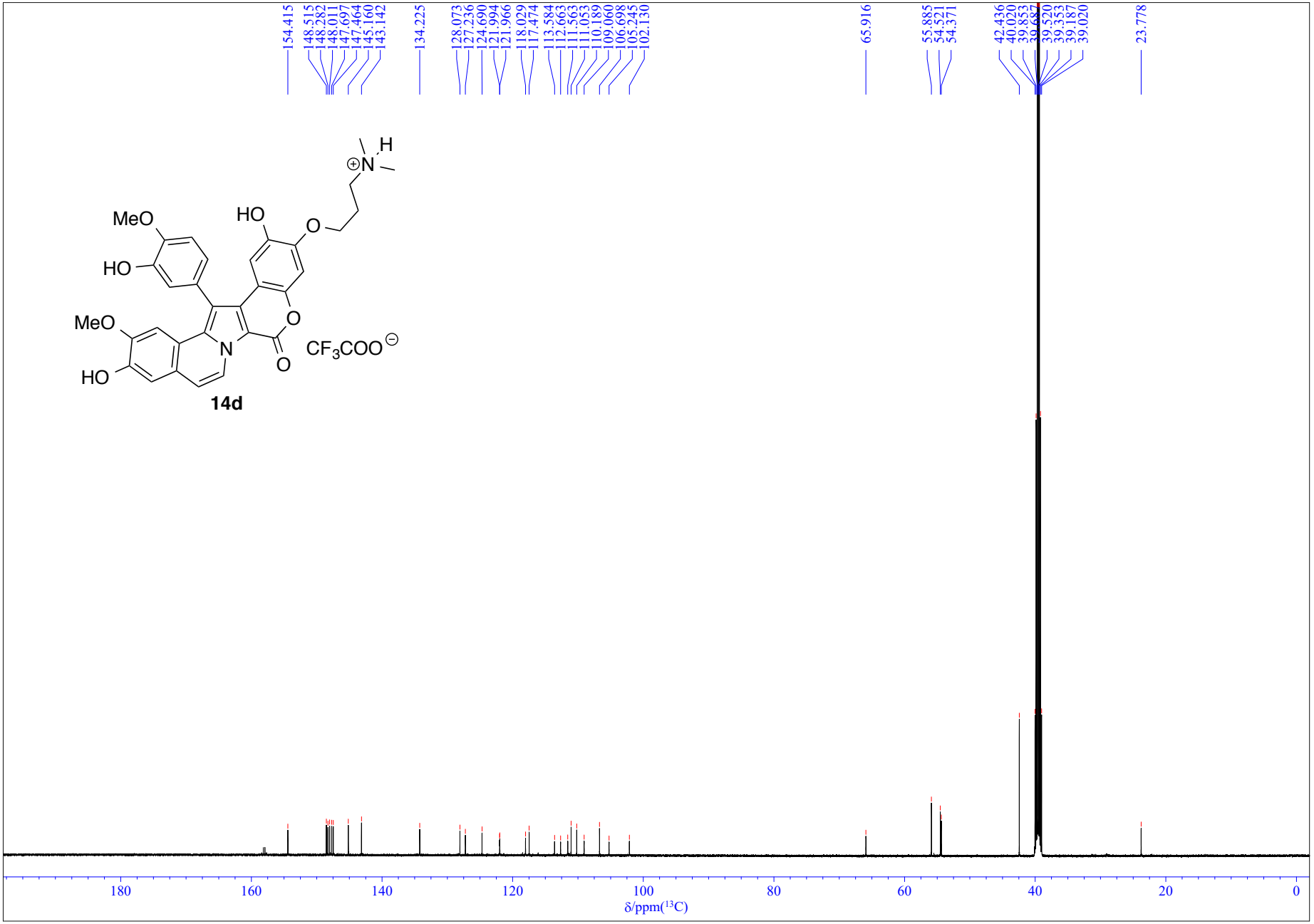


Figure S78. ^{13}C NMR spectrum of compound **14d** (126 MHz, DMSO-d_6).

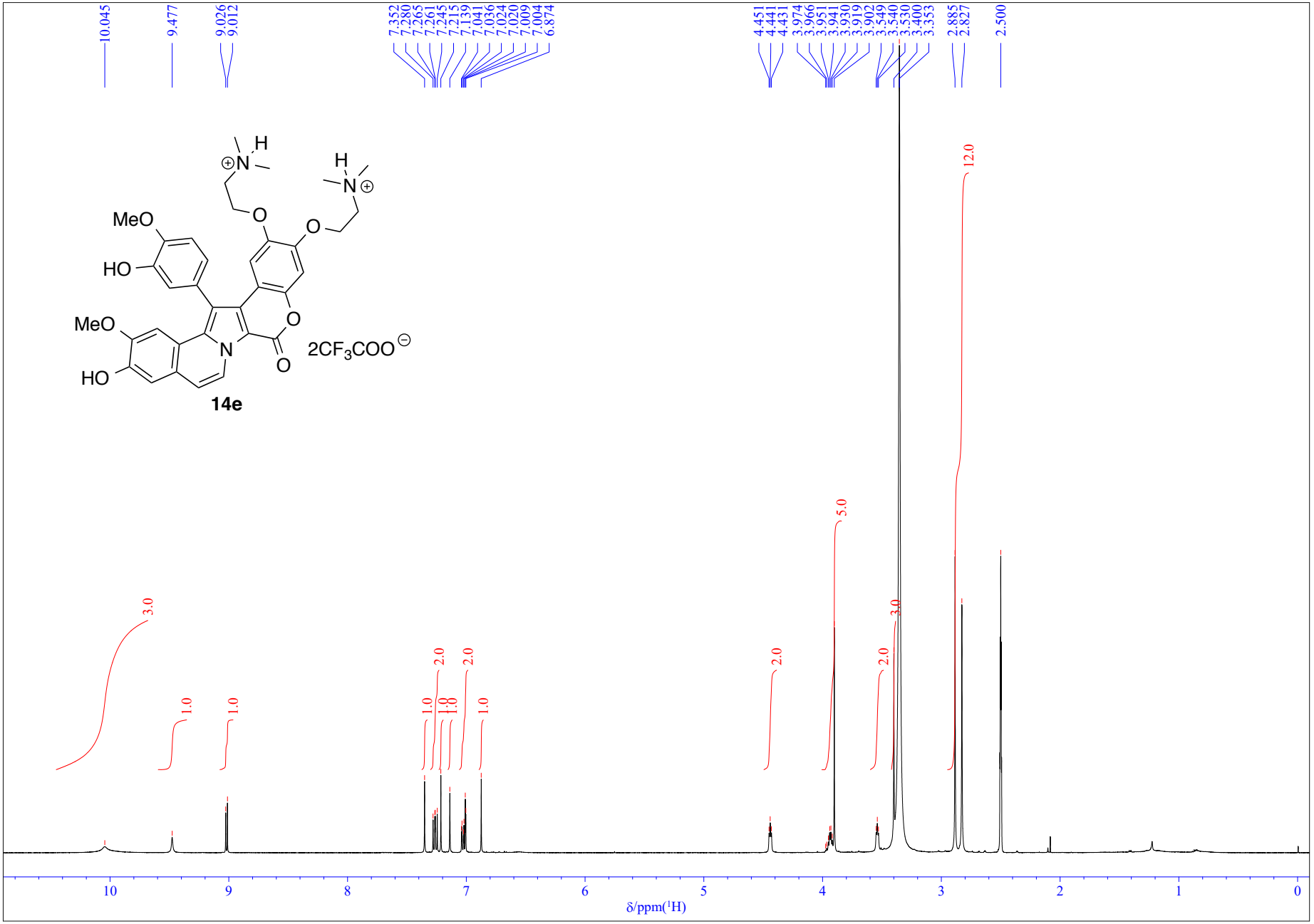


Figure S79. ^{1}H NMR spectrum of compound **14e** (500 MHz, DMSO-d_6).

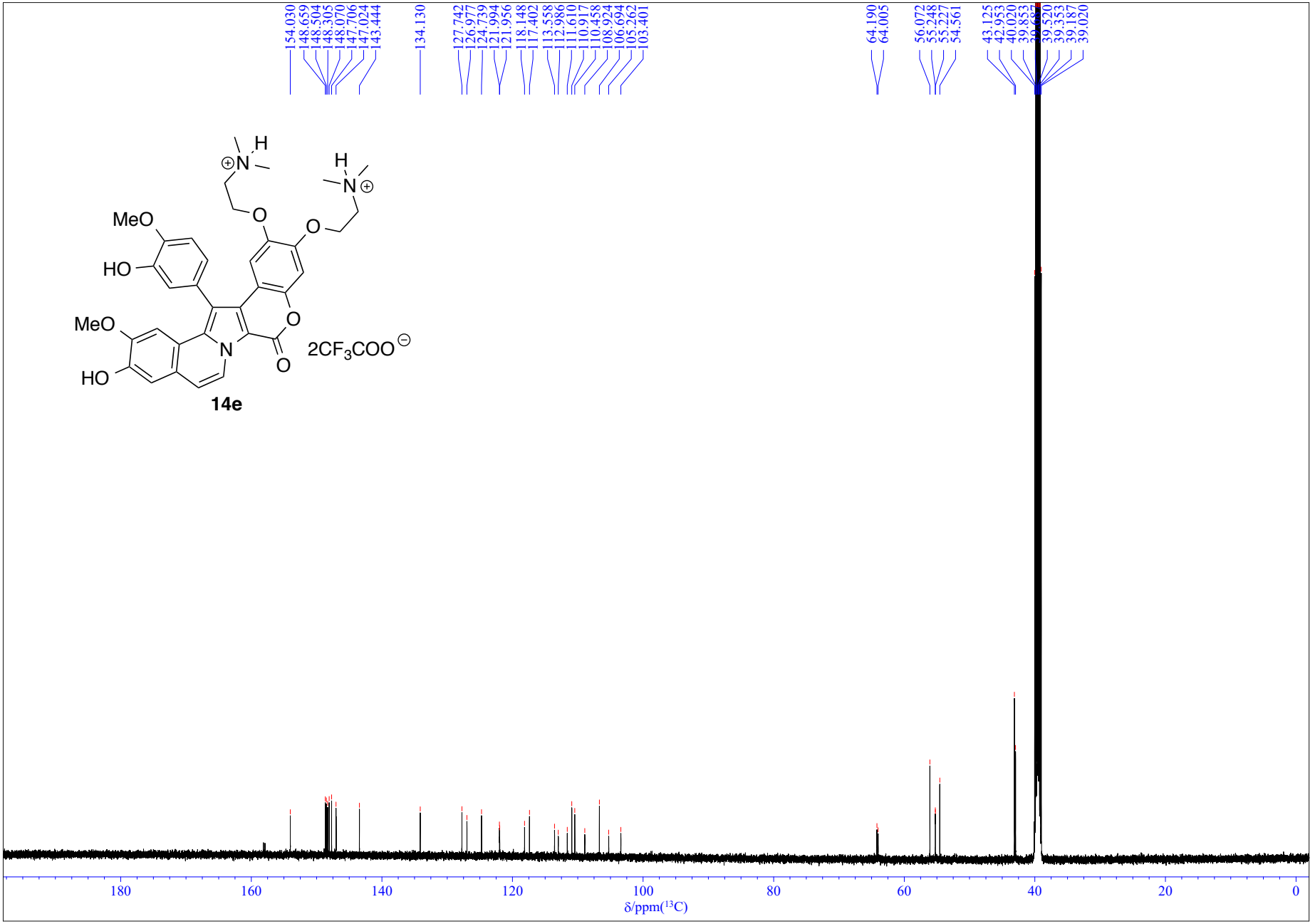


Figure S80. ^{13}C NMR spectrum of compound **14e** (126 MHz, DMSO-d_6).

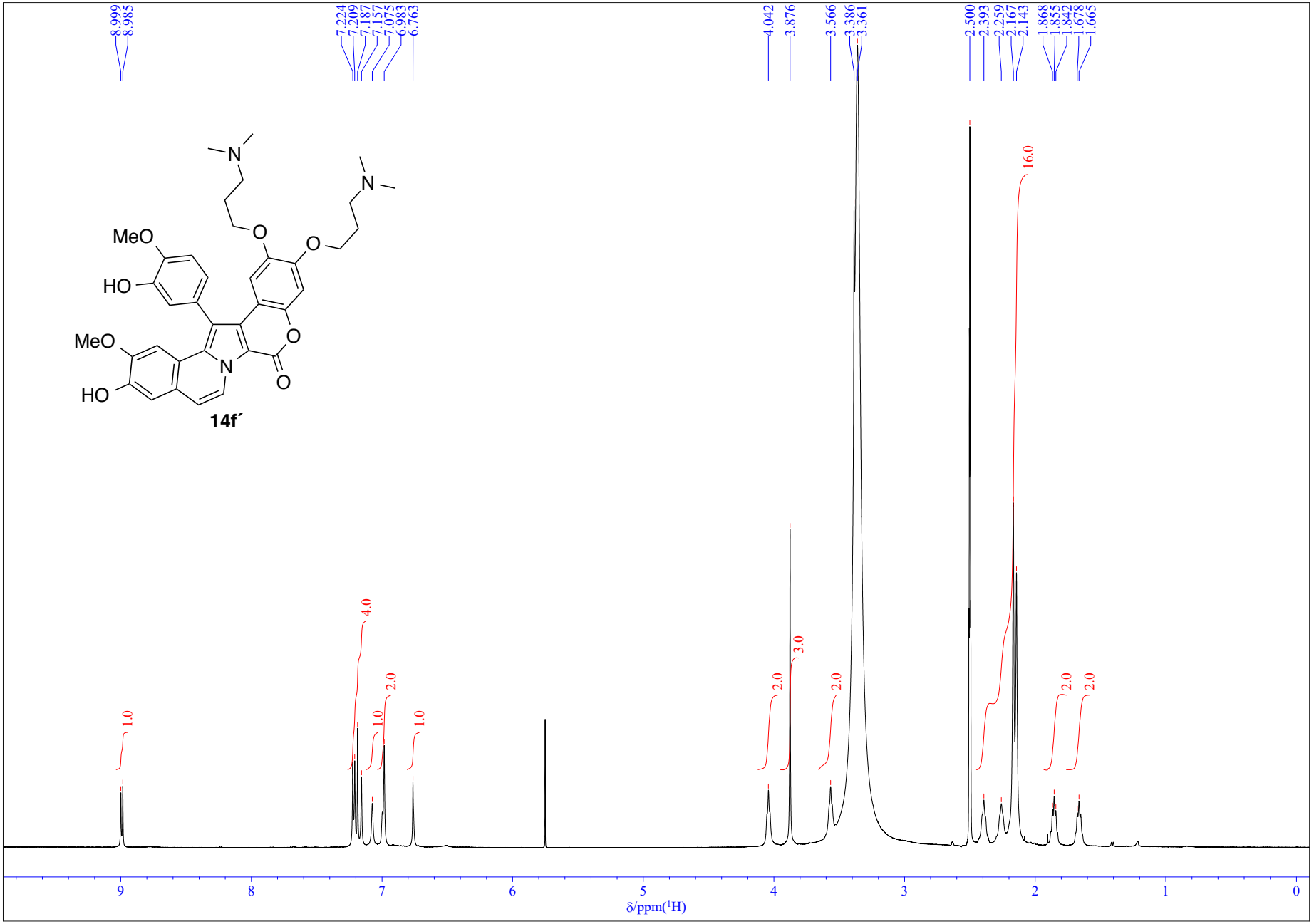


Figure S81. ^{1}H NMR spectrum of compound **14f´** (500 MHz, DMSO-d_6).

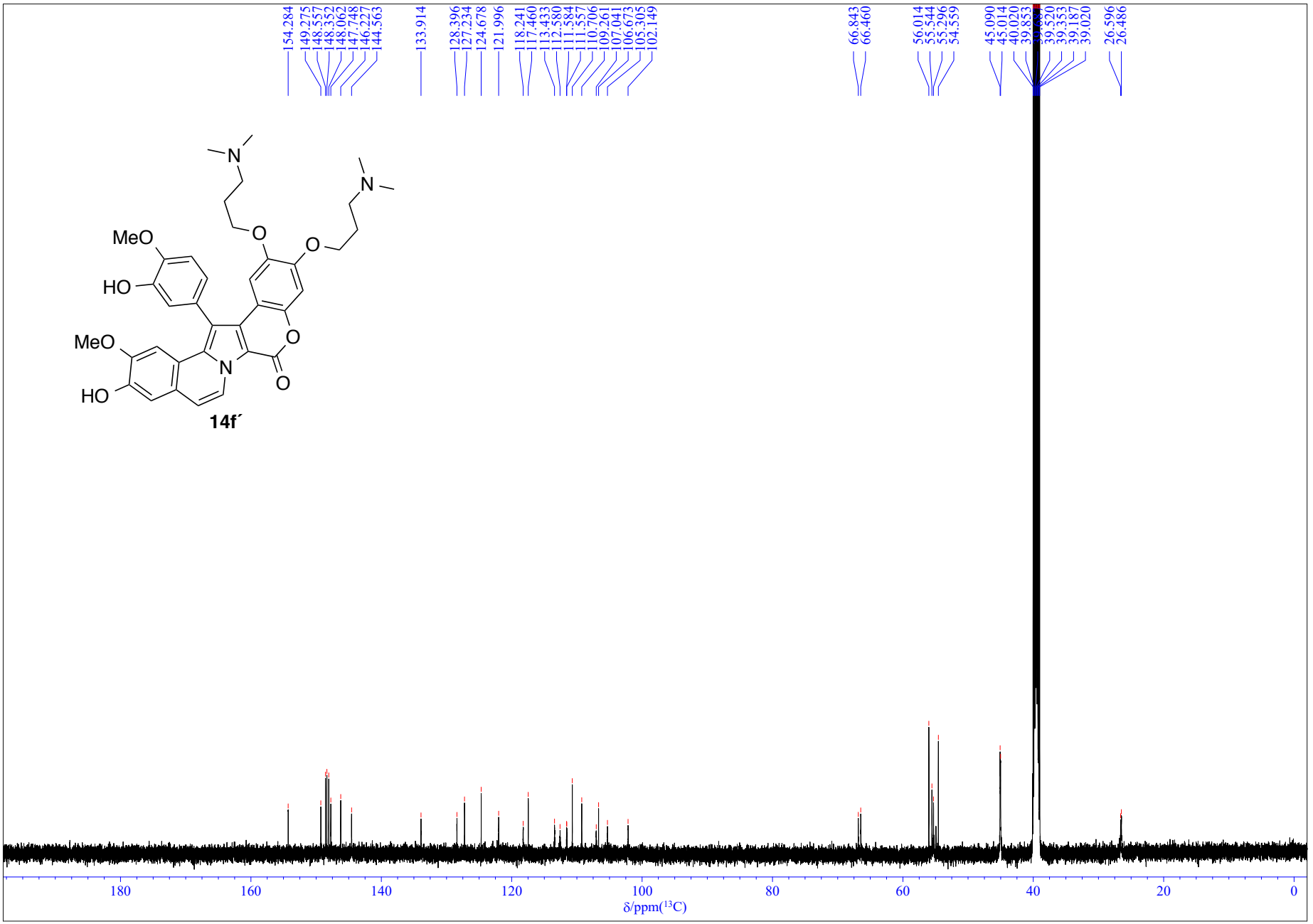


Figure S82. ^{13}C NMR spectrum of compound **14f´** (126 MHz, DMSO-d_6).

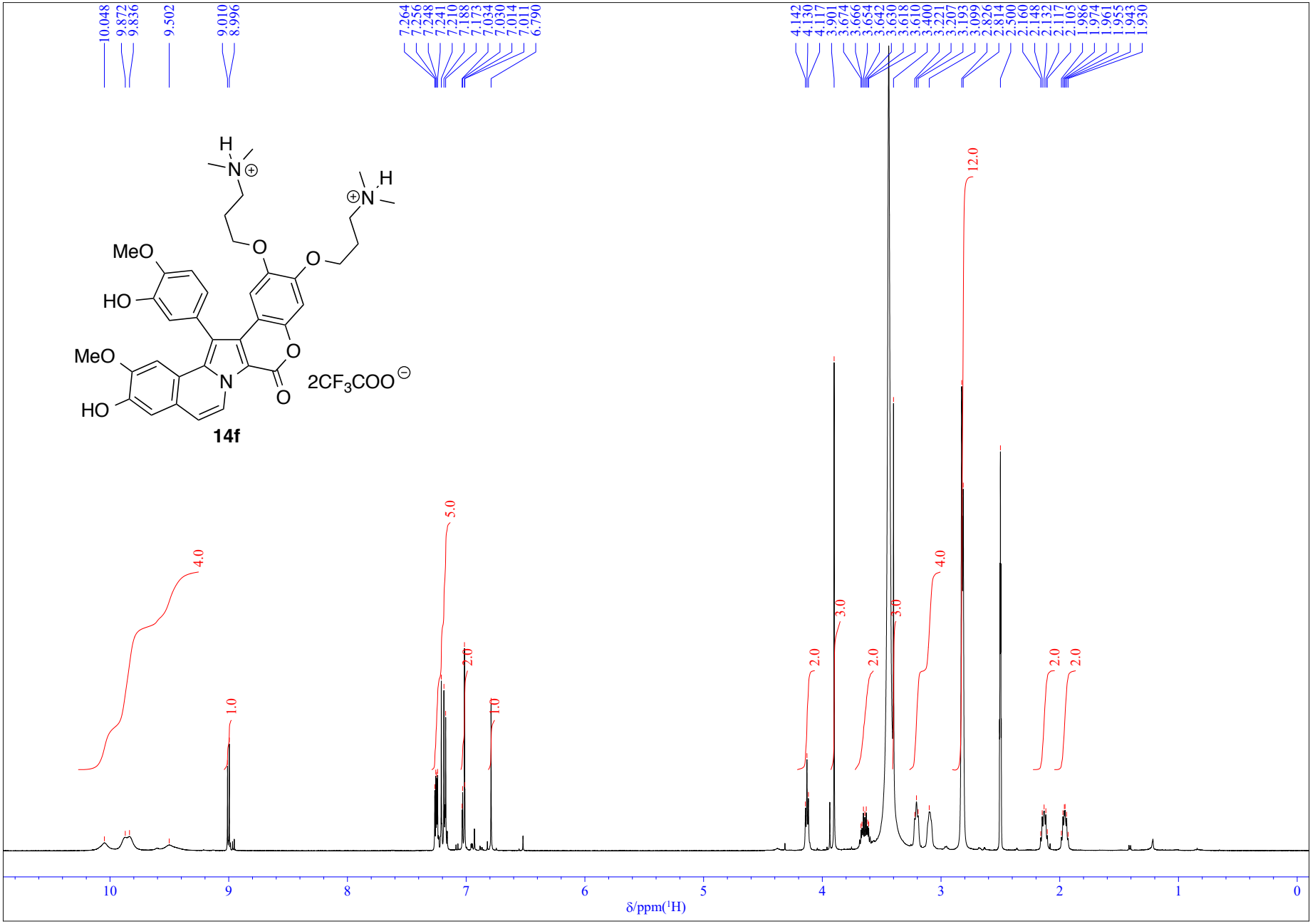


Figure S83. ^{1}H NMR spectrum of compound **14f** (500 MHz, DMSO-d_6).

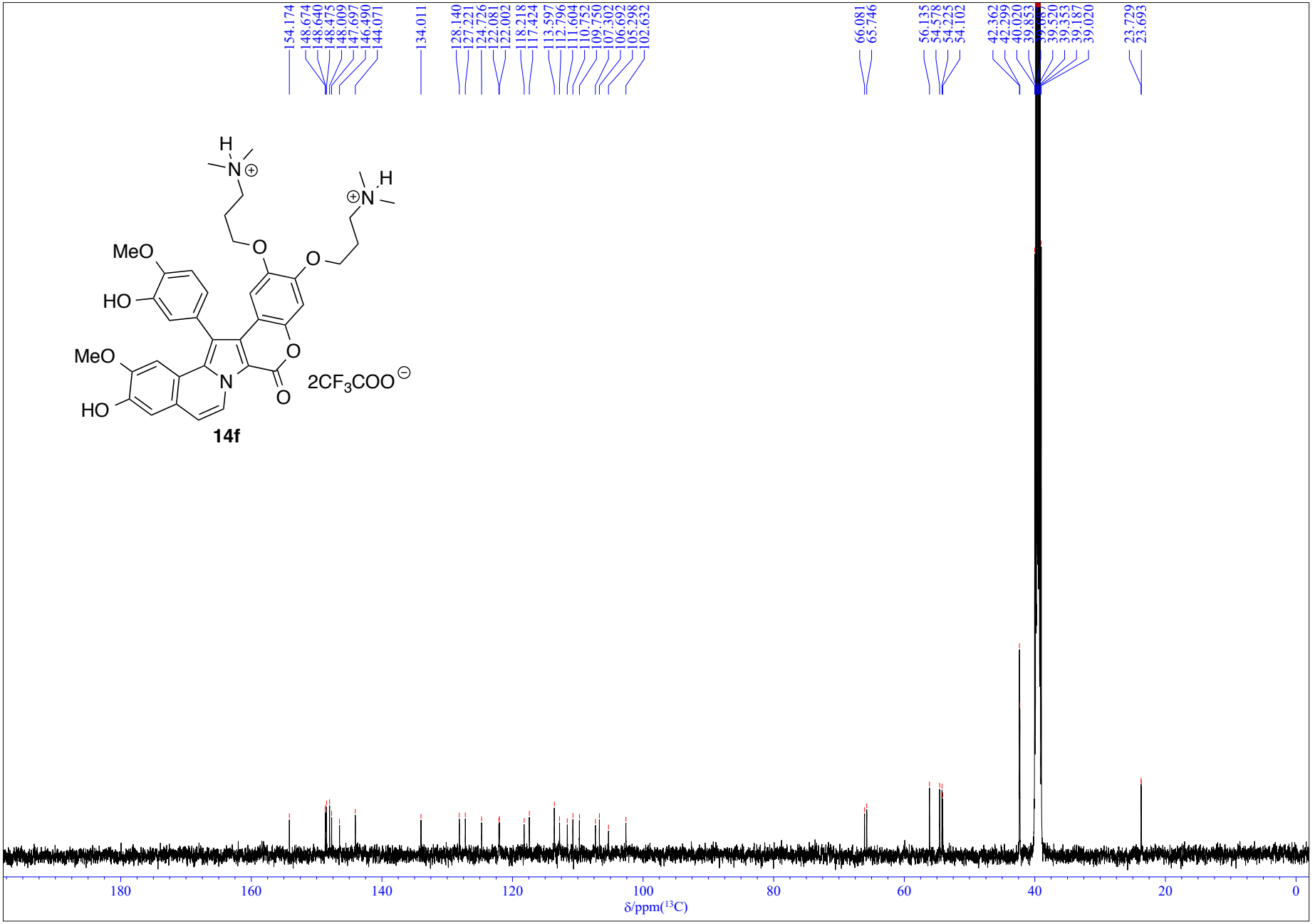


Figure S84. ^{13}C NMR spectrum of compound **14f** (126 MHz, DMSO-d_6).

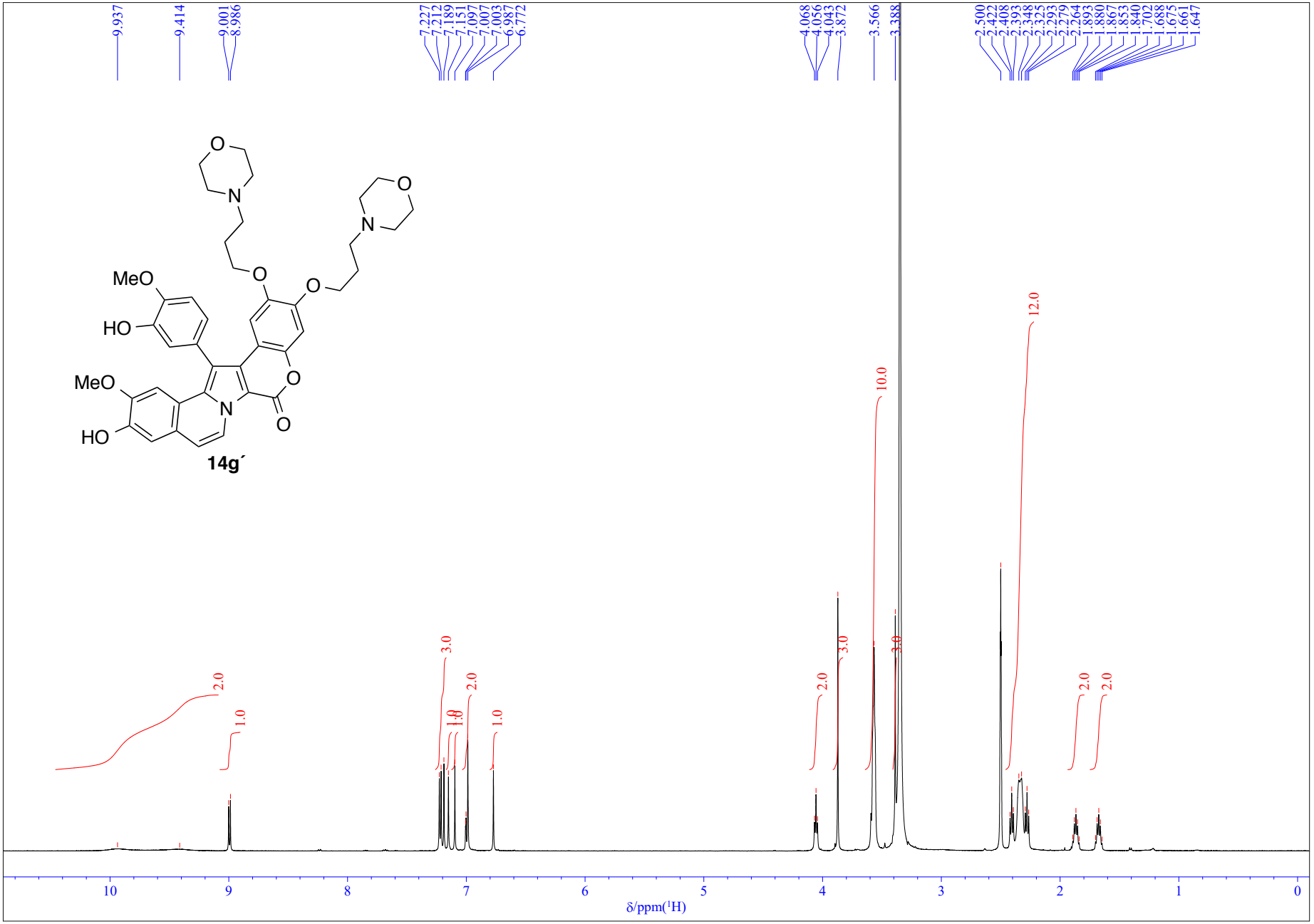


Figure S85. ^{1}H NMR spectrum of compound **14g´** (500 MHz, DMSO-d_6).

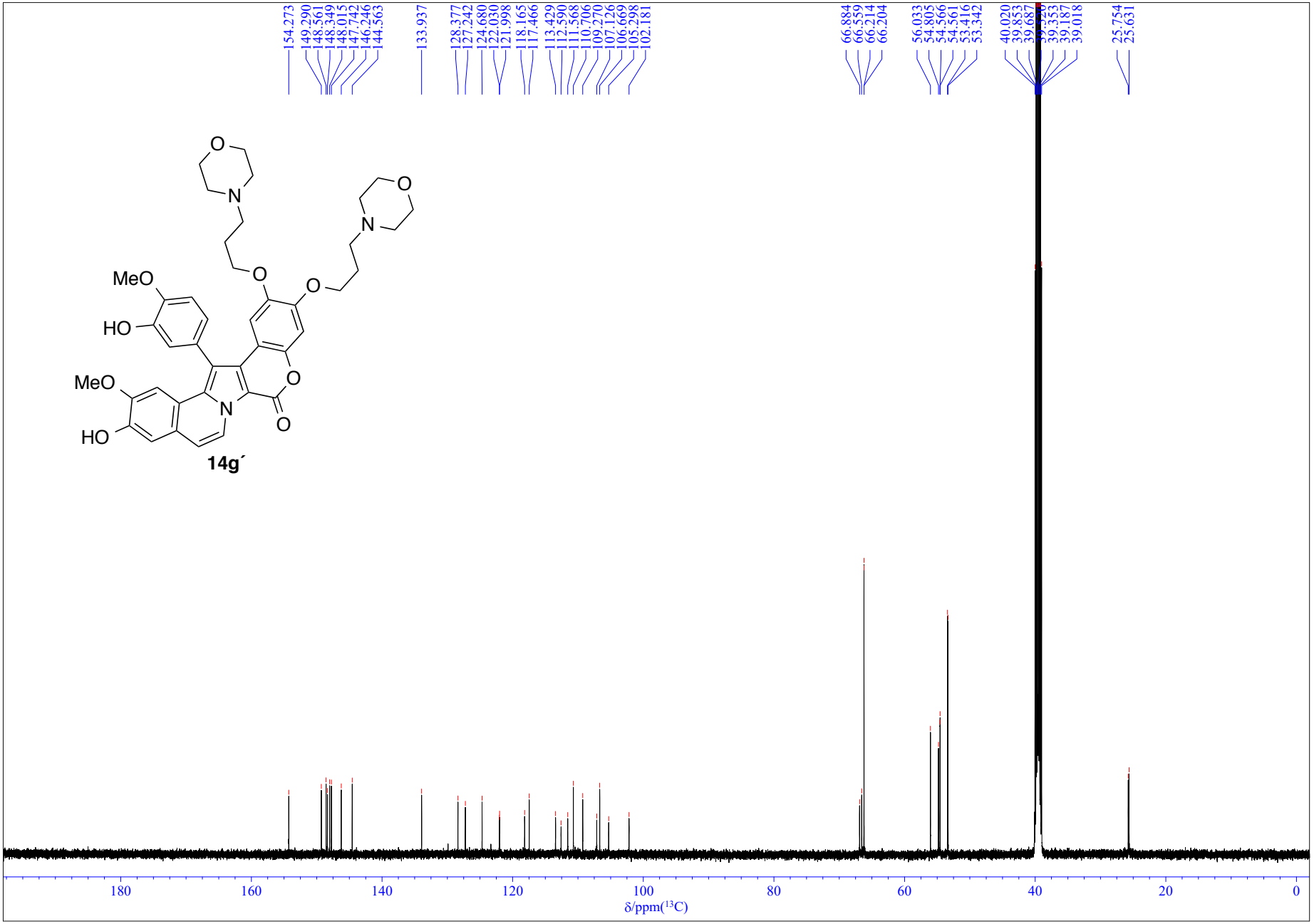


Figure S86. ^{13}C NMR spectrum of compound **14g´** (126 MHz, DMSO-d_6).

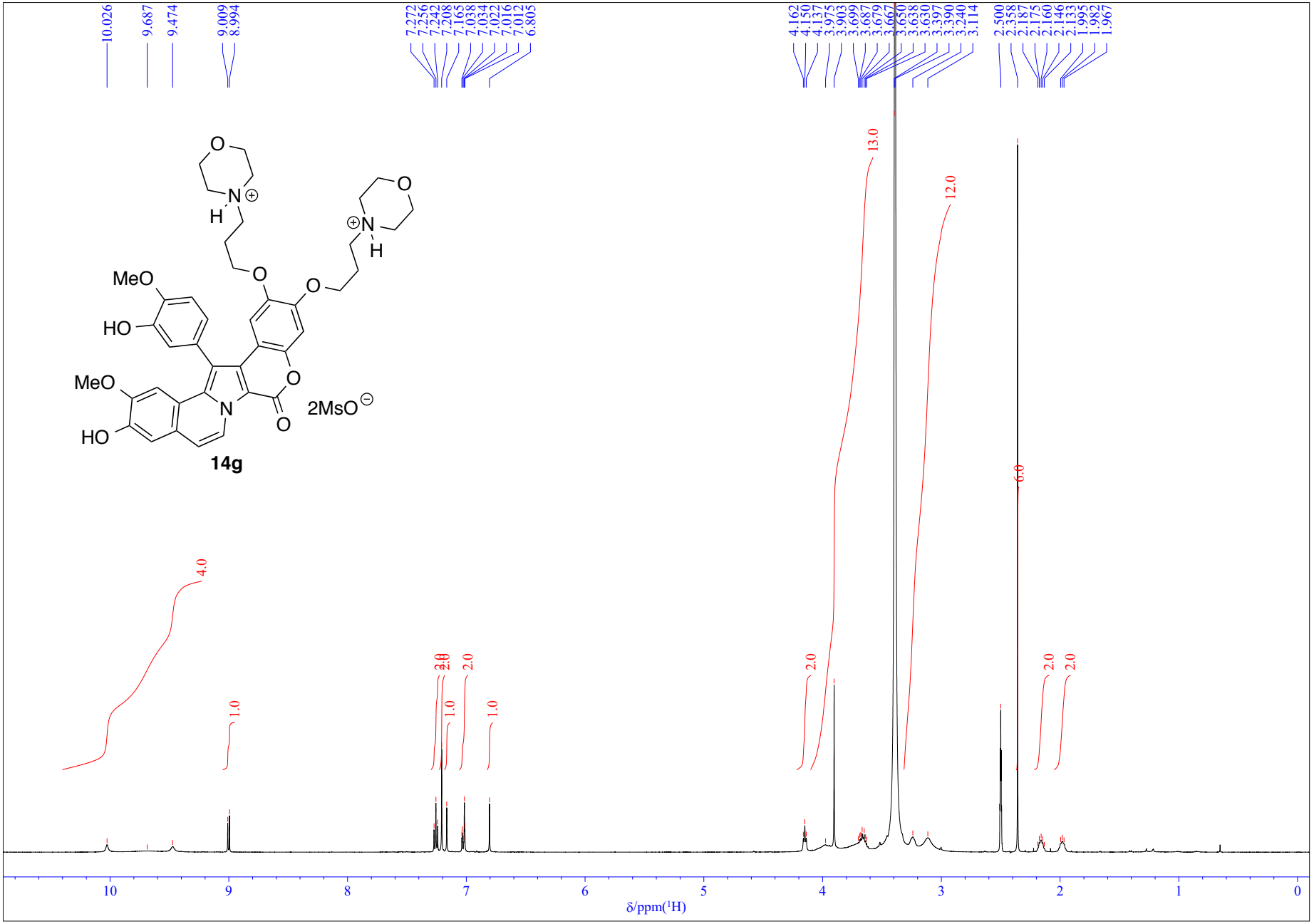


Figure S87. ^{1}H NMR spectrum of compound **14g** (500 MHz, DMSO-d_6).

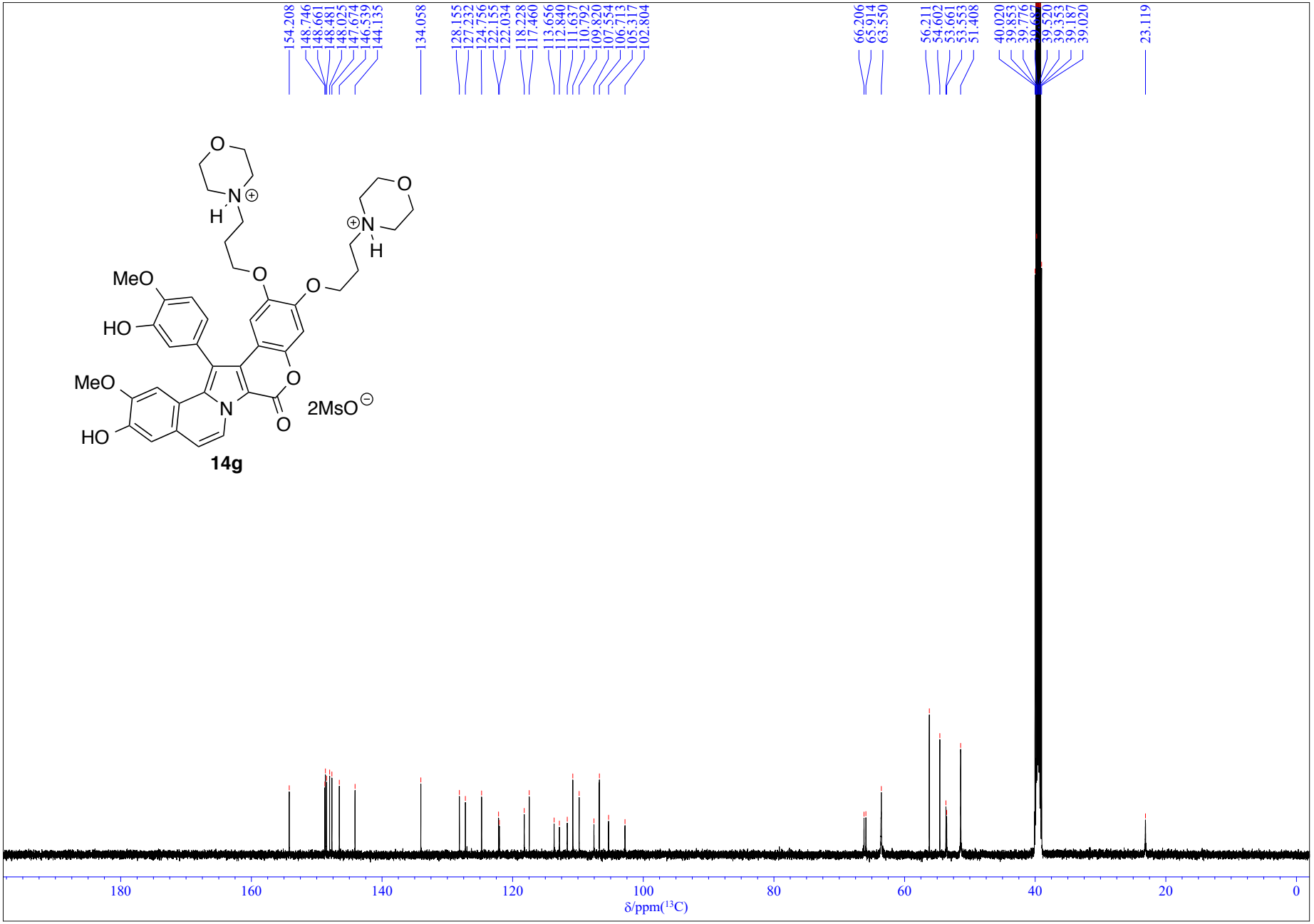


Figure S88. ^{13}C NMR spectrum of compound **14g** (126 MHz, DMSO-d_6).

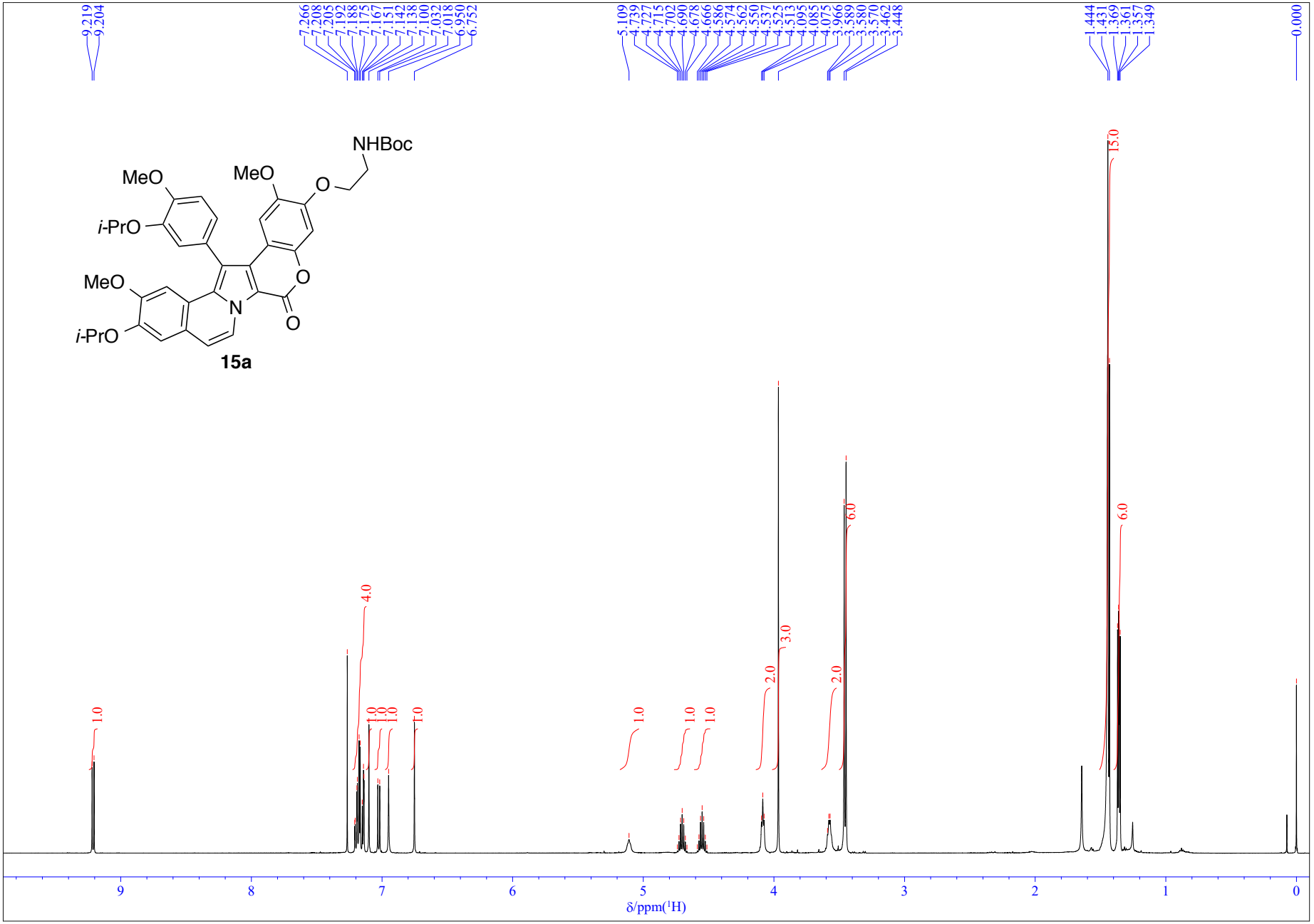


Figure S89. ^{1}H NMR spectrum of compound **15a** (500 MHz, $CDCl_3$).

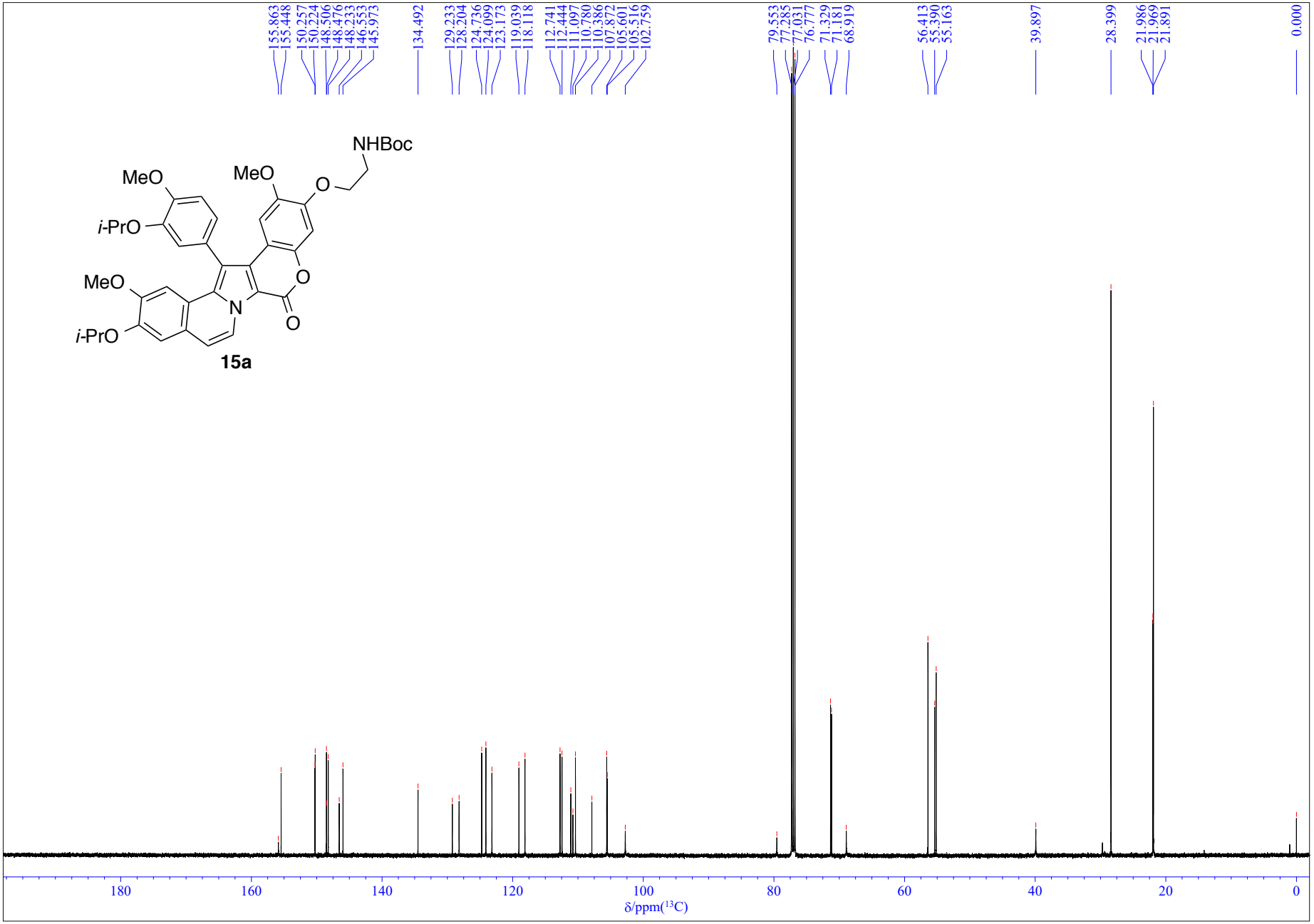


Figure S90. ^{13}C NMR spectrum of compound **15a** (126 MHz, $CDCl_3$).

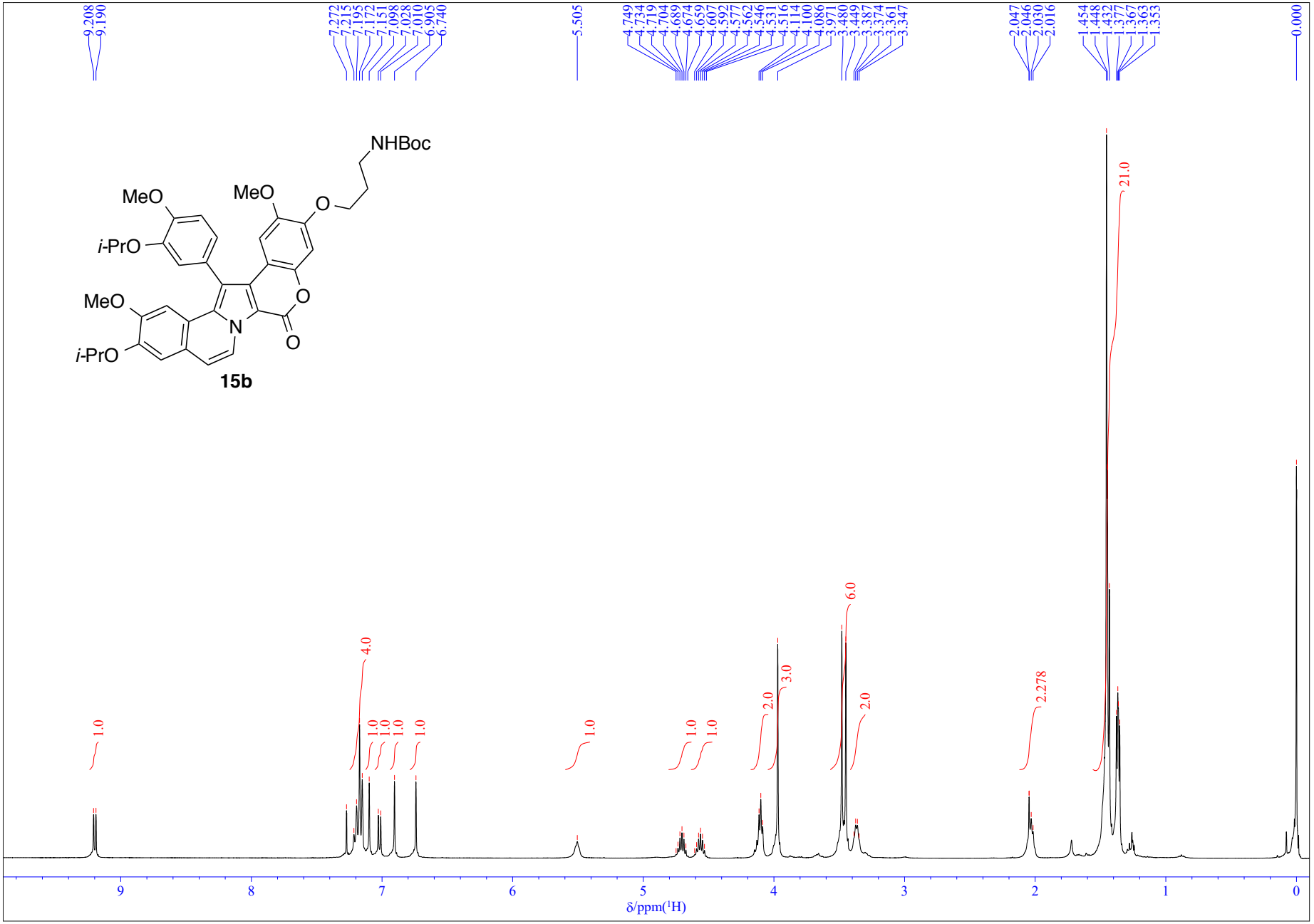


Figure S91. ^{1}H NMR spectrum of compound **15b** (400 MHz, $CDCl_3$).

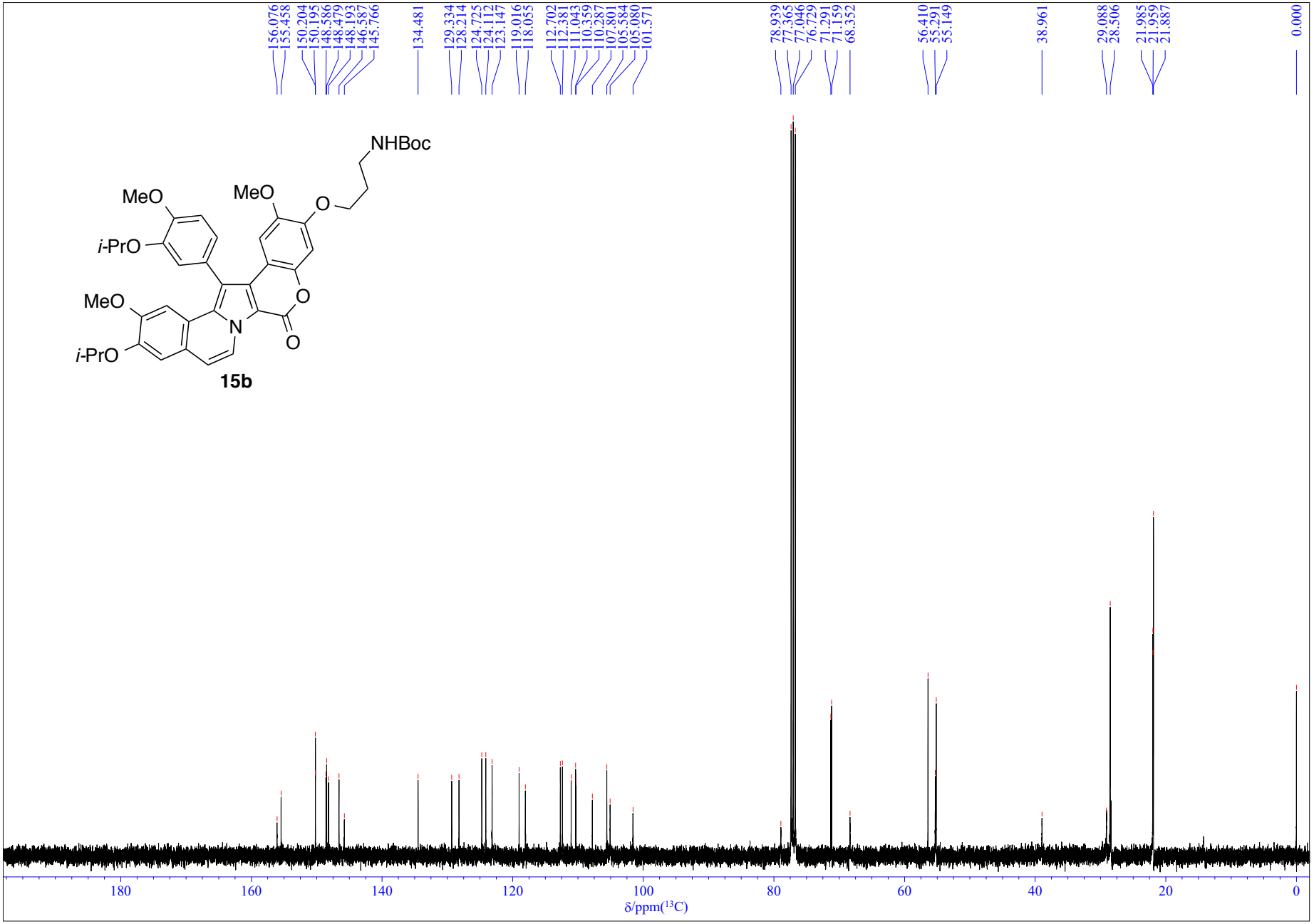


Figure S92. ^{13}C NMR spectrum of compound **15b** (100 MHz, $CDCl_3$).

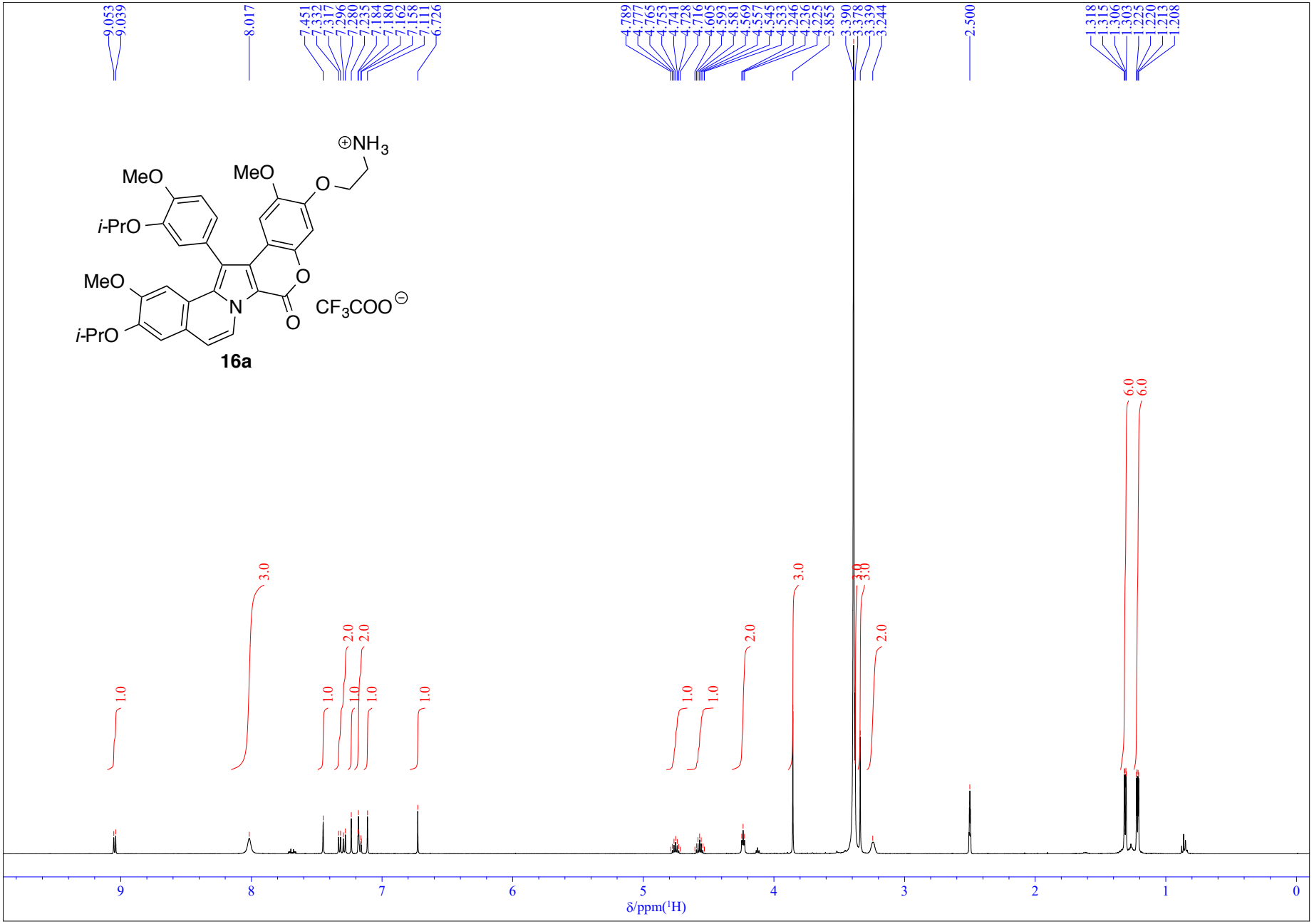


Figure S93. ^{1}H NMR spectrum of compound **16a** (500 MHz, DMSO-d_6).

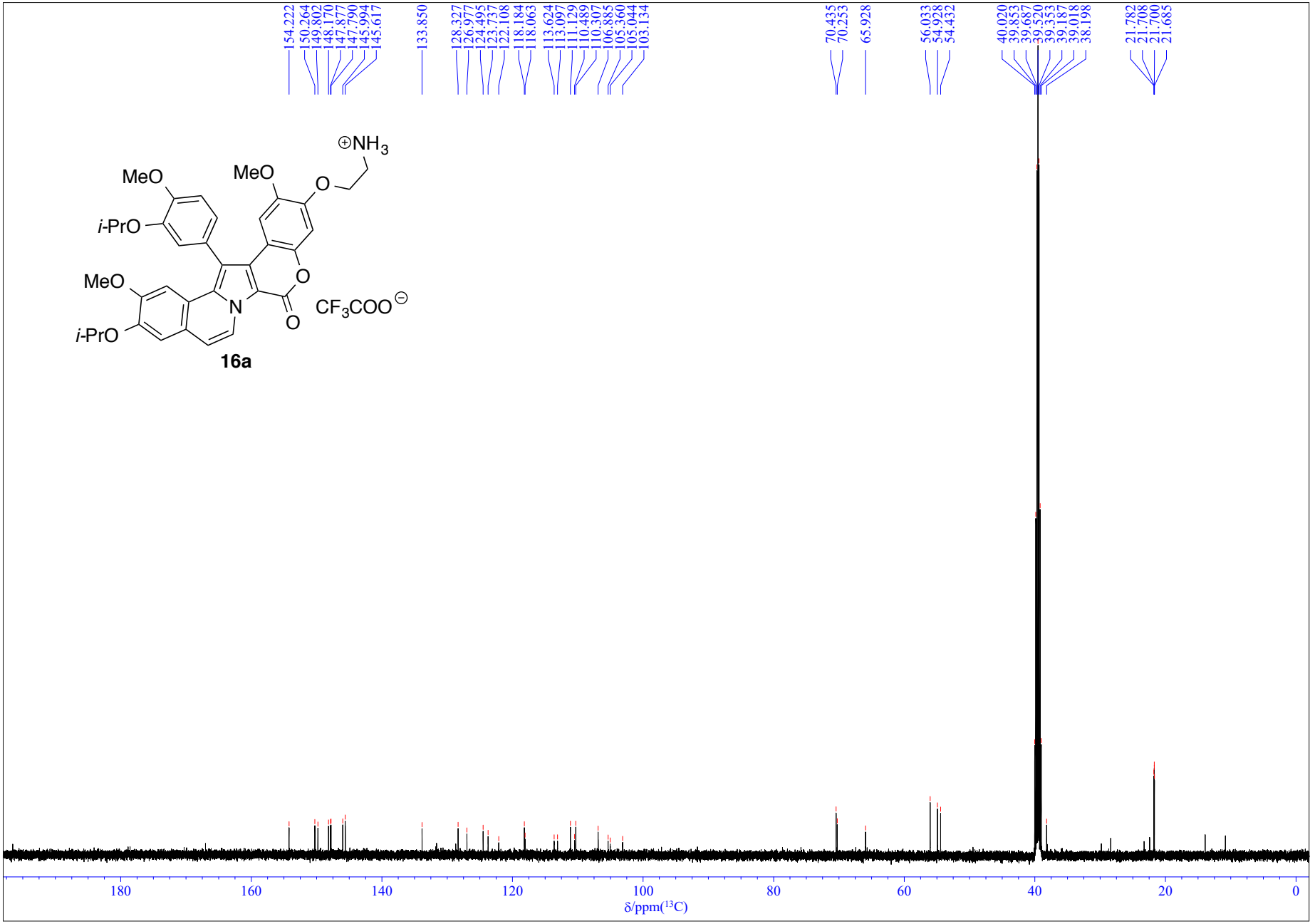


Figure S94. ^{13}C NMR spectrum of compound **16a** (126 MHz, DMSO-d_6).

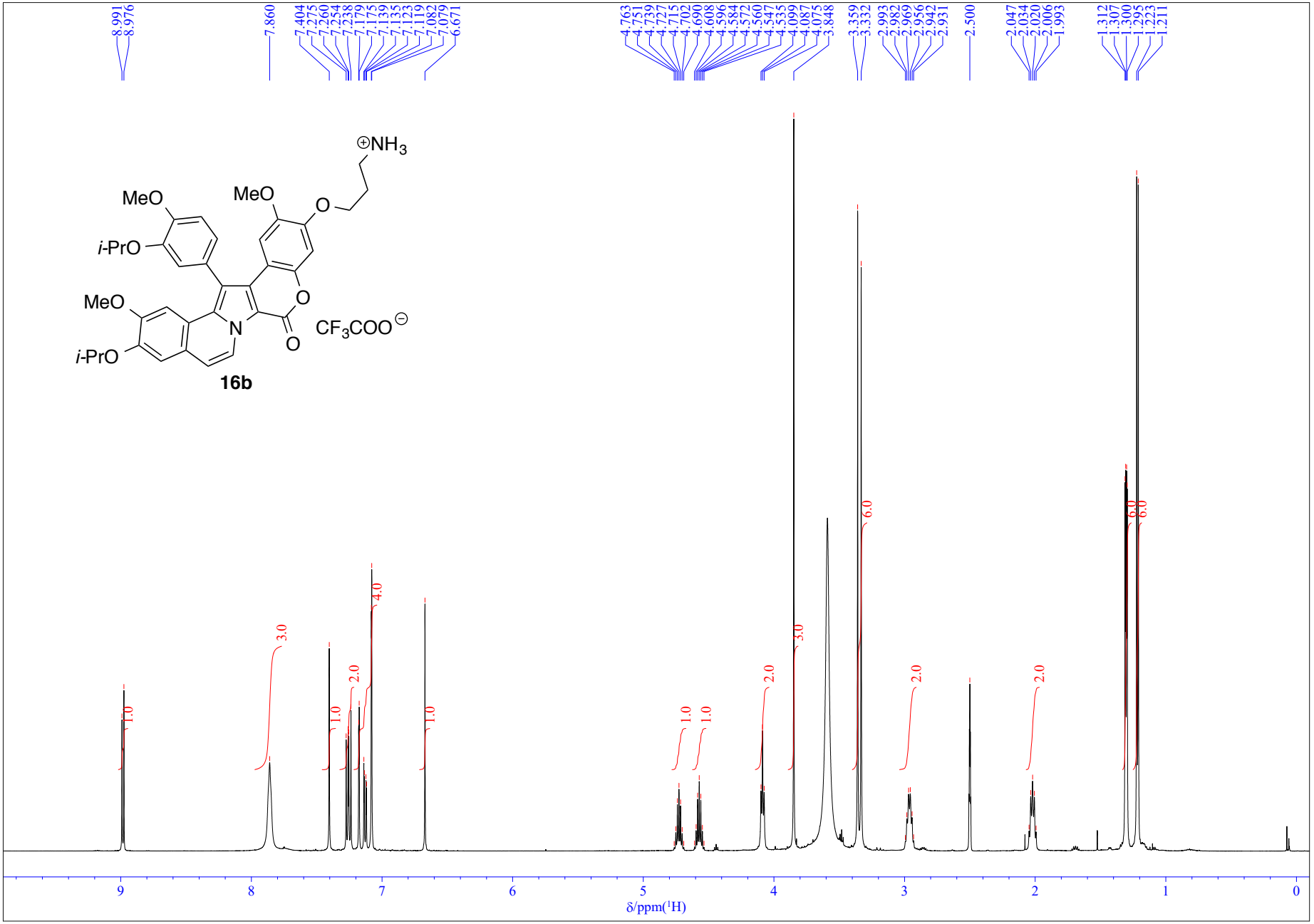


Figure S95. ^{1}H NMR spectrum of compound **16b** (500 MHz, DMSO-d_6).

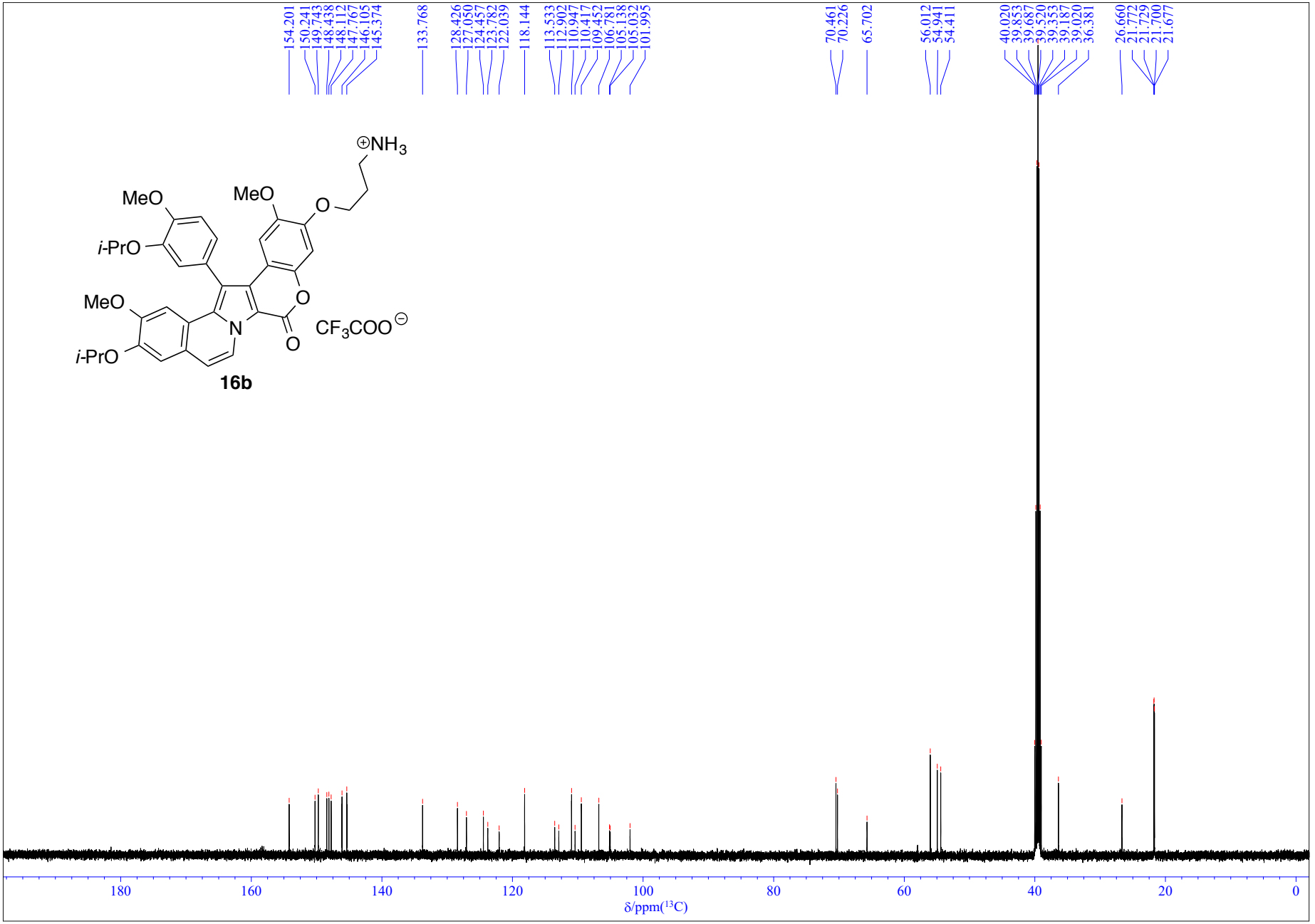


Figure S96. ^{13}C NMR spectrum of compound **16b** (126 MHz, DMSO-d_6).

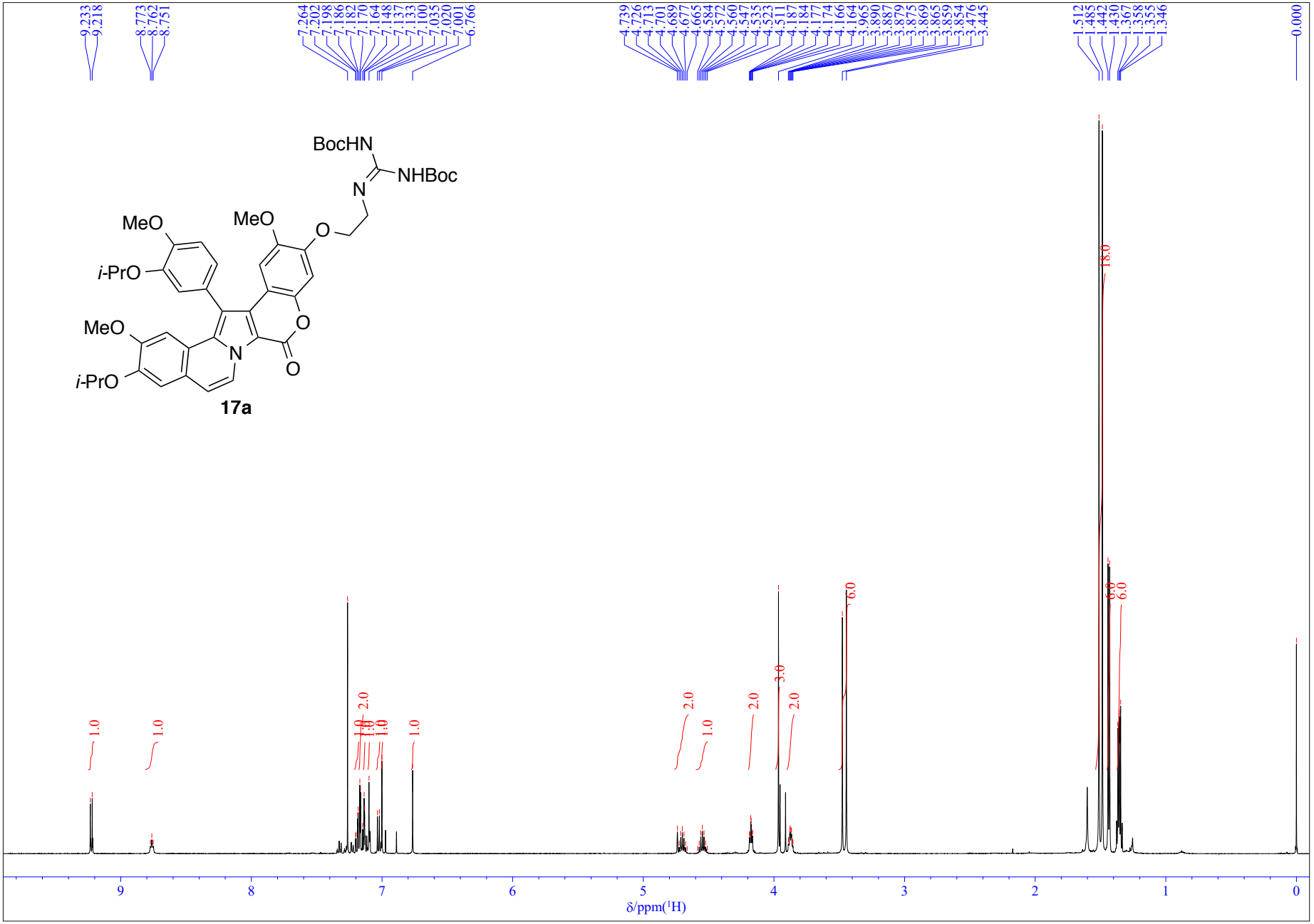


Figure S97. ^{1}H NMR spectrum of compound **17a** (500 MHz, $CDCl_3$).

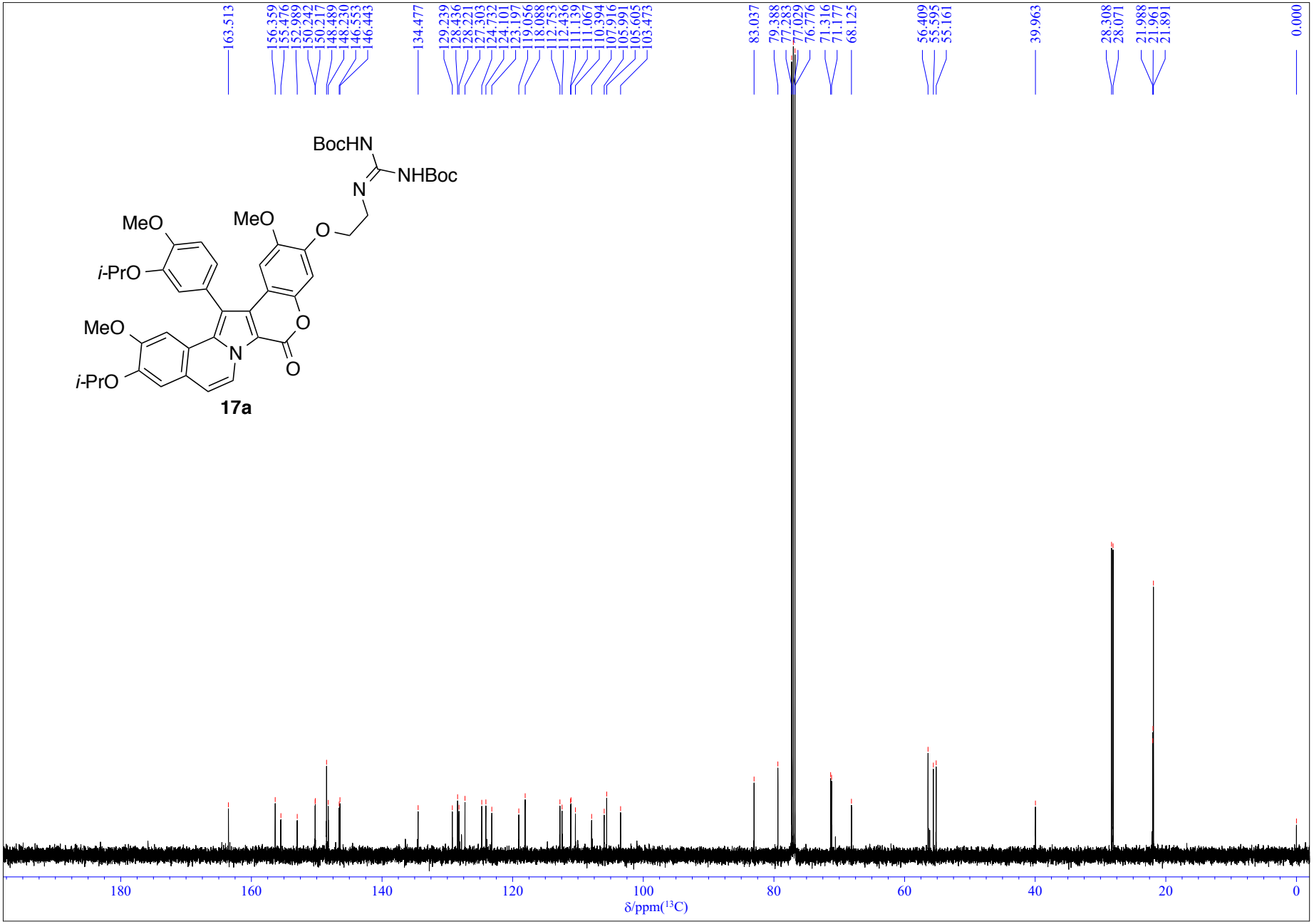


Figure S98. ^{13}C NMR spectrum of compound **17a** (126 MHz, $CDCl_3$).

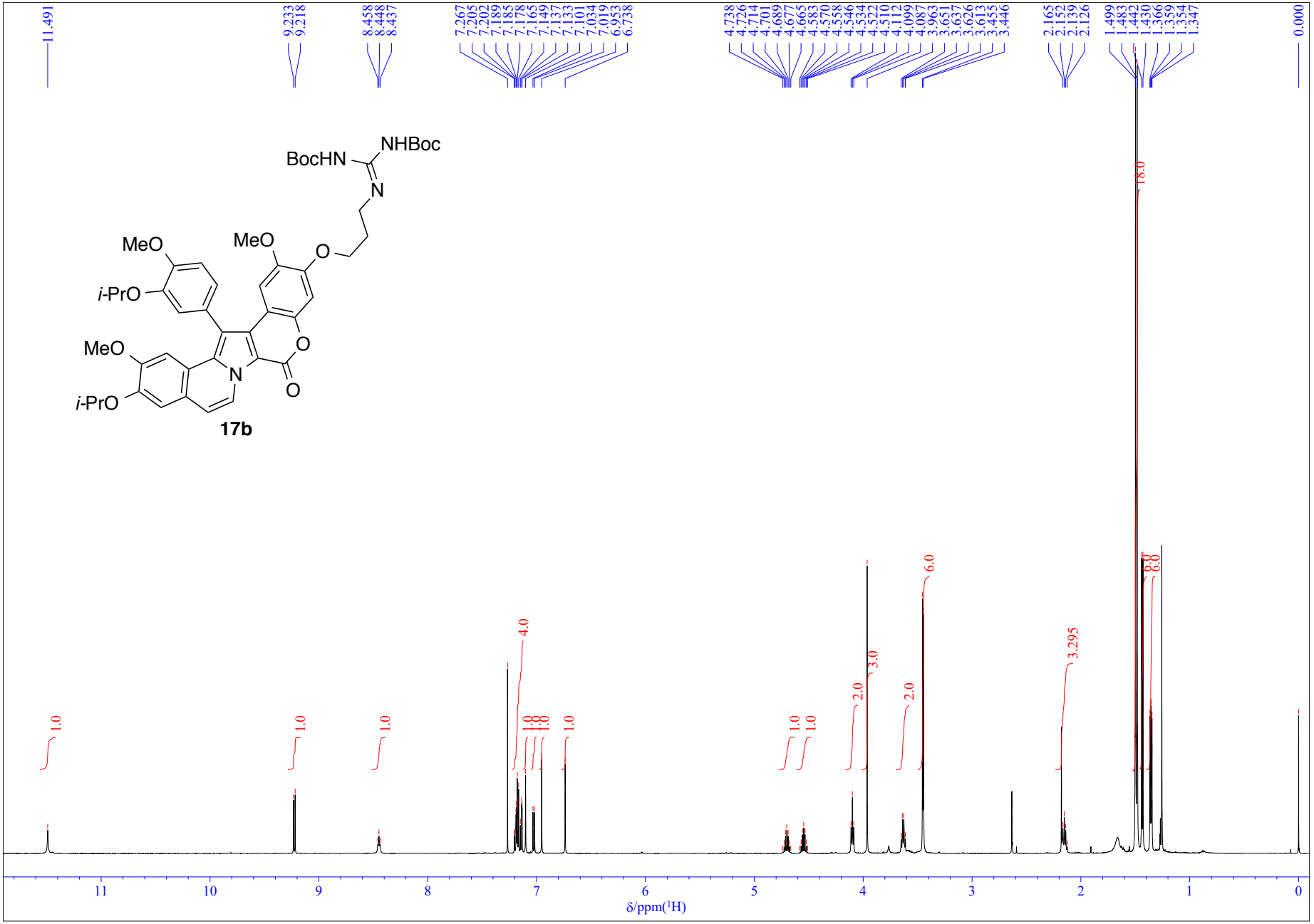


Figure S99. ^{1}H NMR spectrum of compound **17b** (500 MHz, $CDCl_3$).

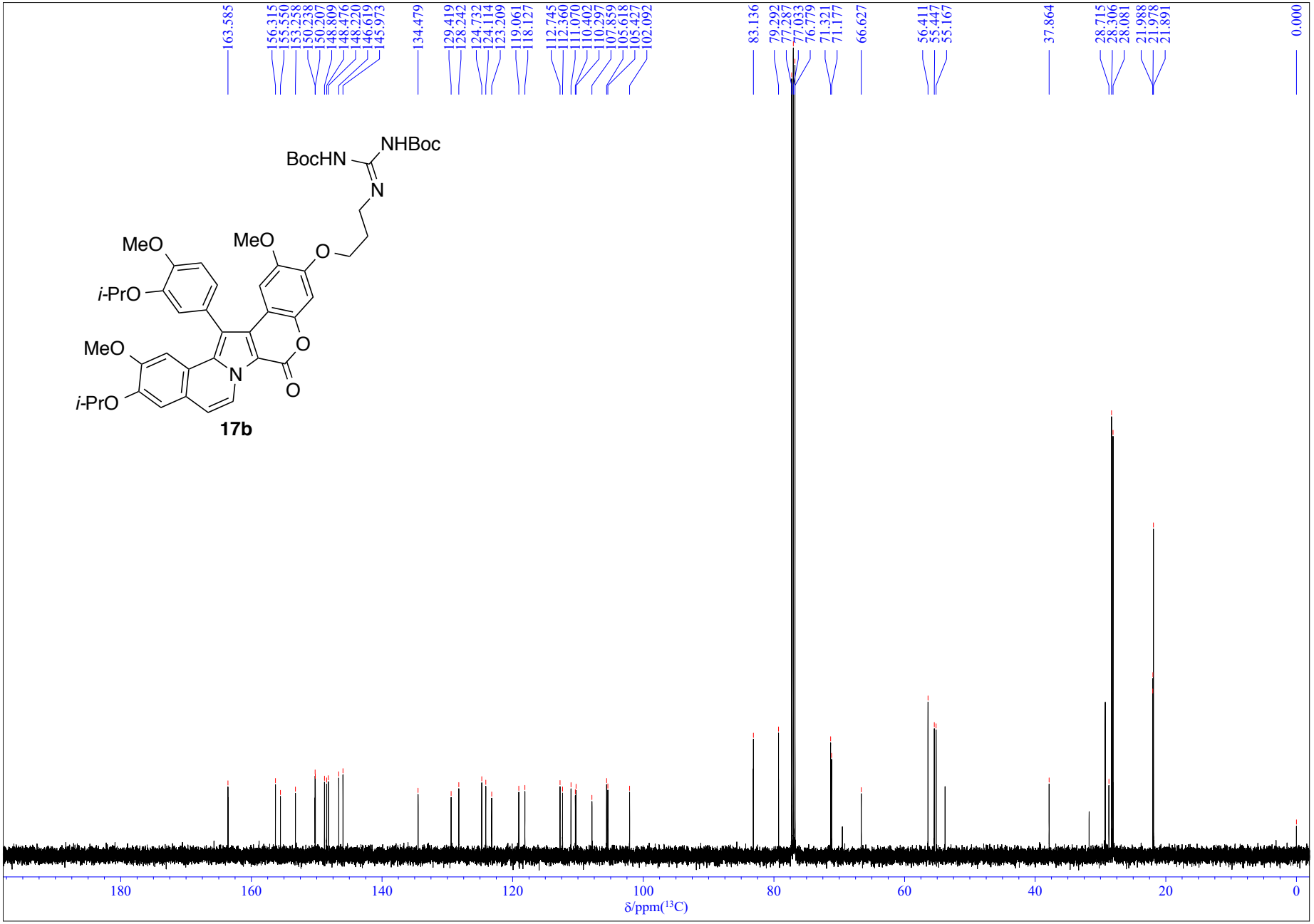


Figure S100. ^{13}C NMR spectrum of compound **17b** (126 MHz, $CDCl_3$).

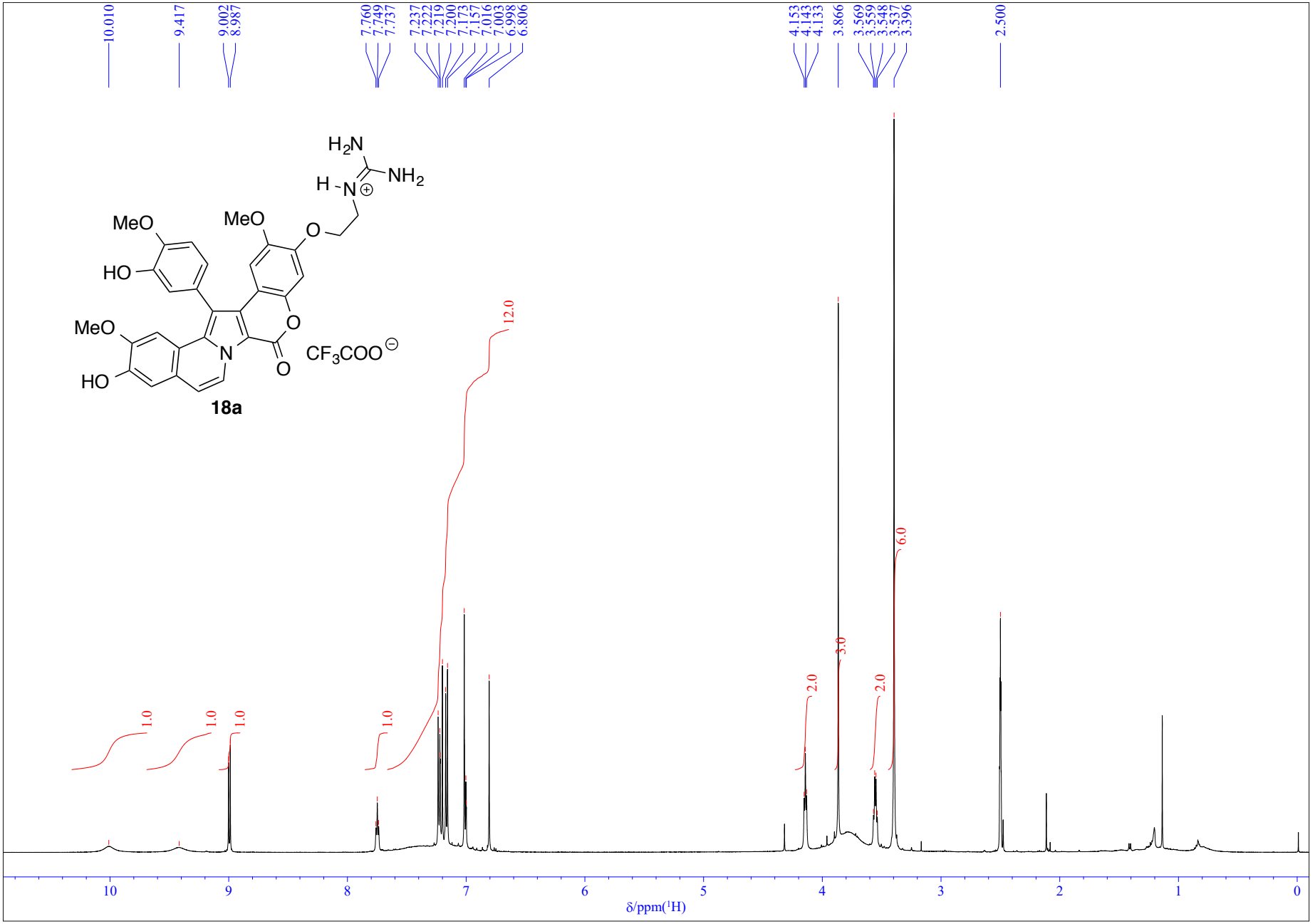


Figure S101. ^{1}H NMR spectrum of compound **18a** (500 MHz, DMSO-d_6).

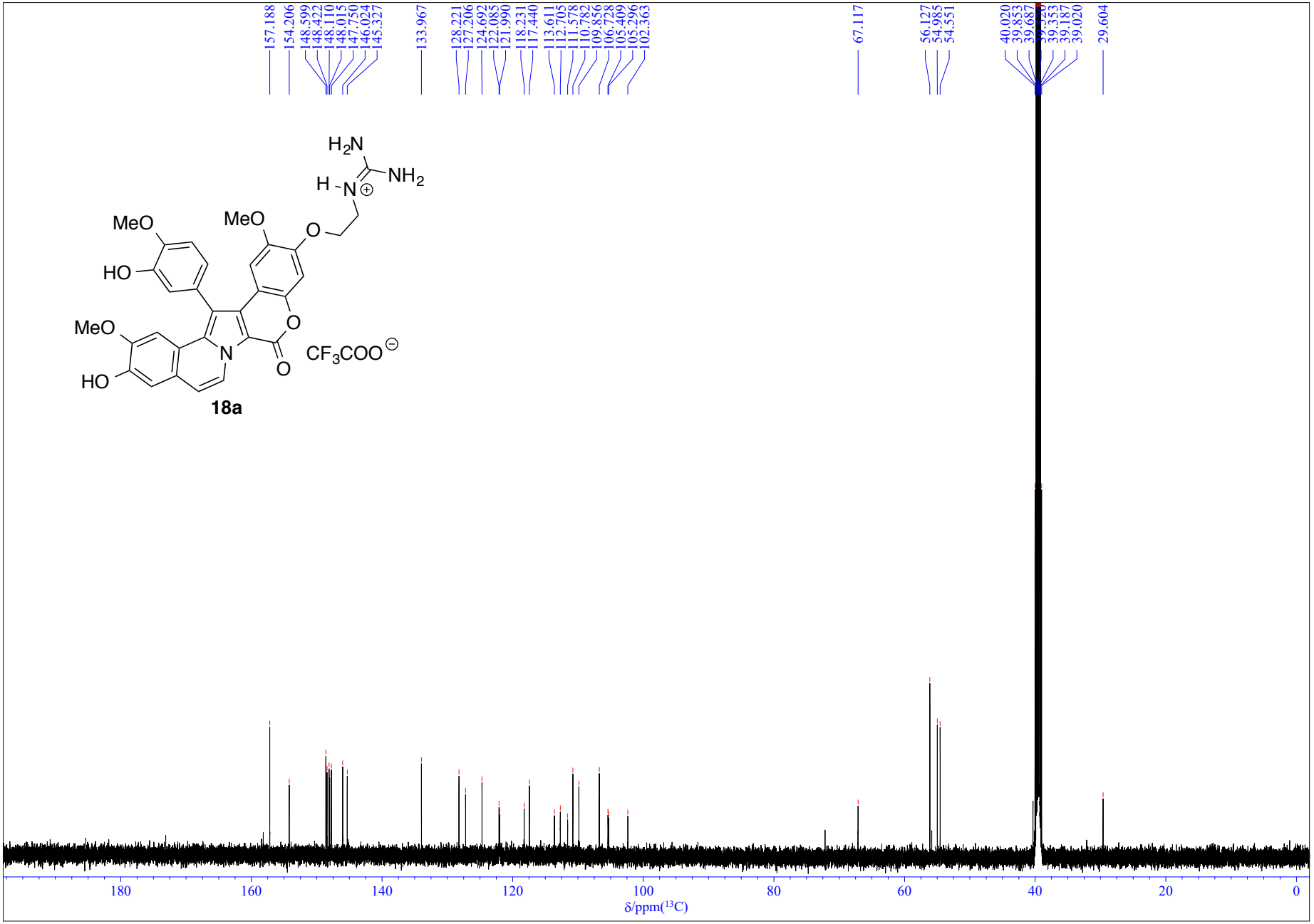


Figure S102. ^{13}C NMR spectrum of compound **18a** (126 MHz, DMSO-d_6).

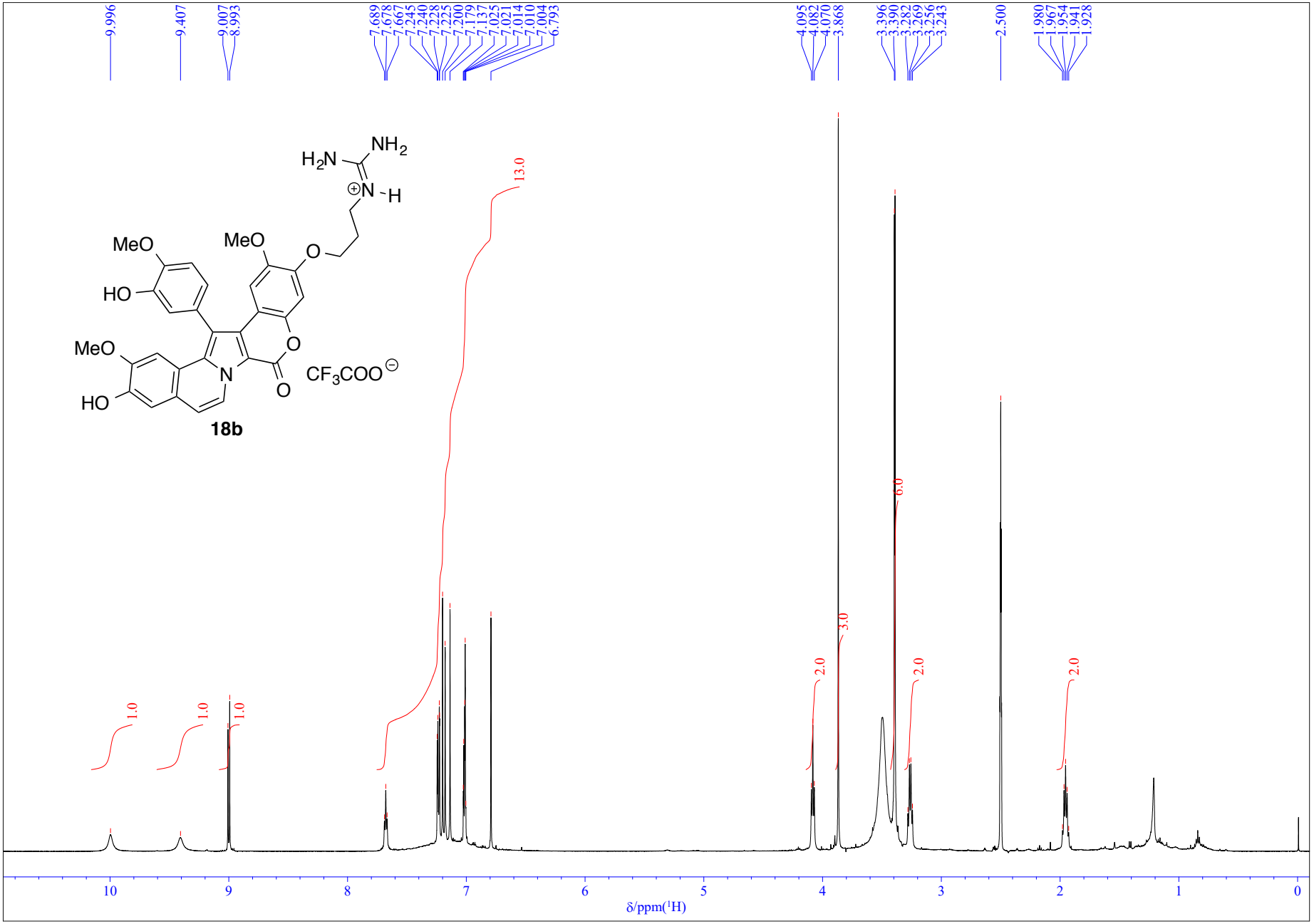


Figure S103. ^{1}H NMR spectrum of compound **18b** (500 MHz, DMSO-d_6).

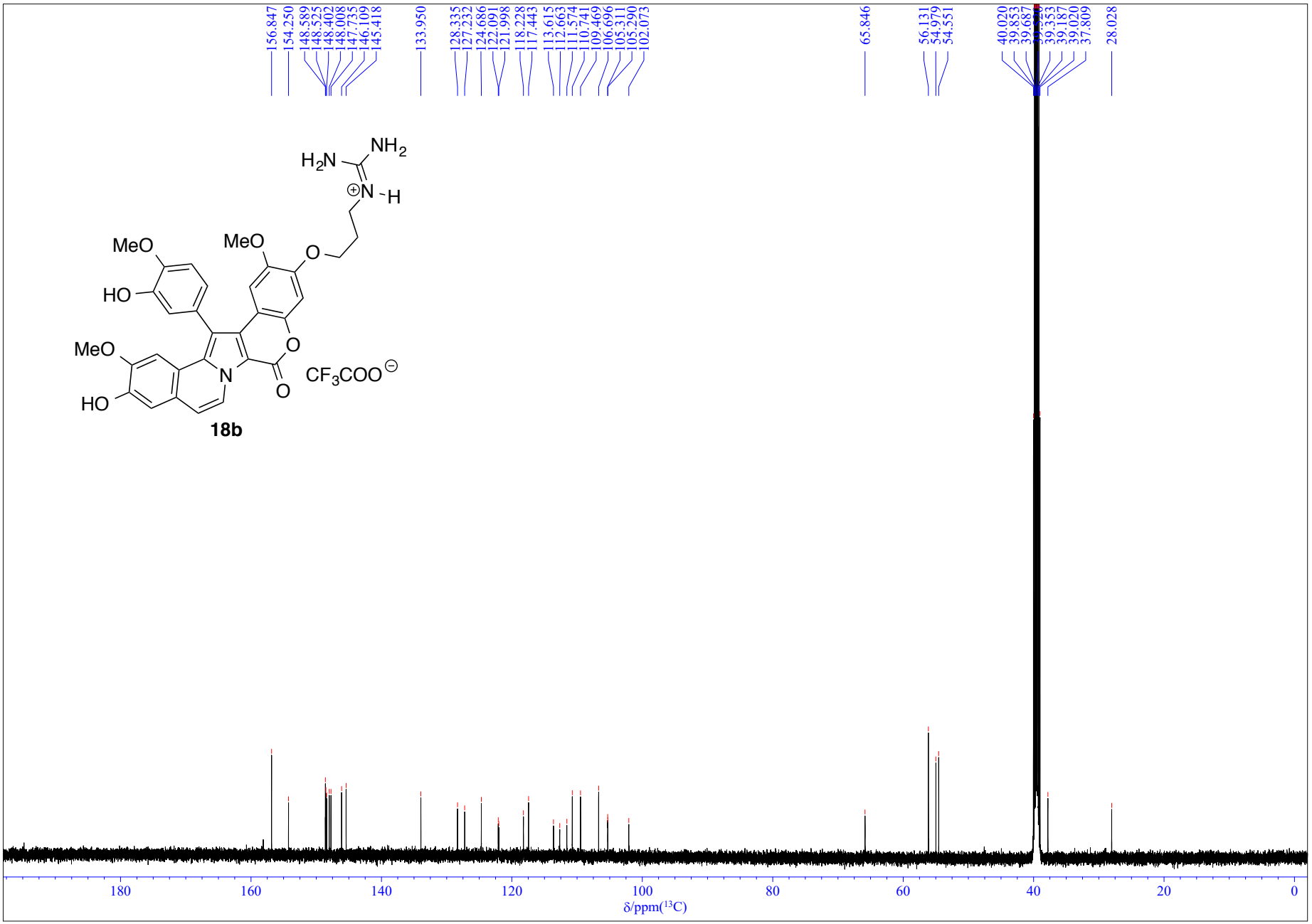


Figure S104. ^{13}C NMR spectrum of compound **18b** (126 MHz, DMSO-d_6).

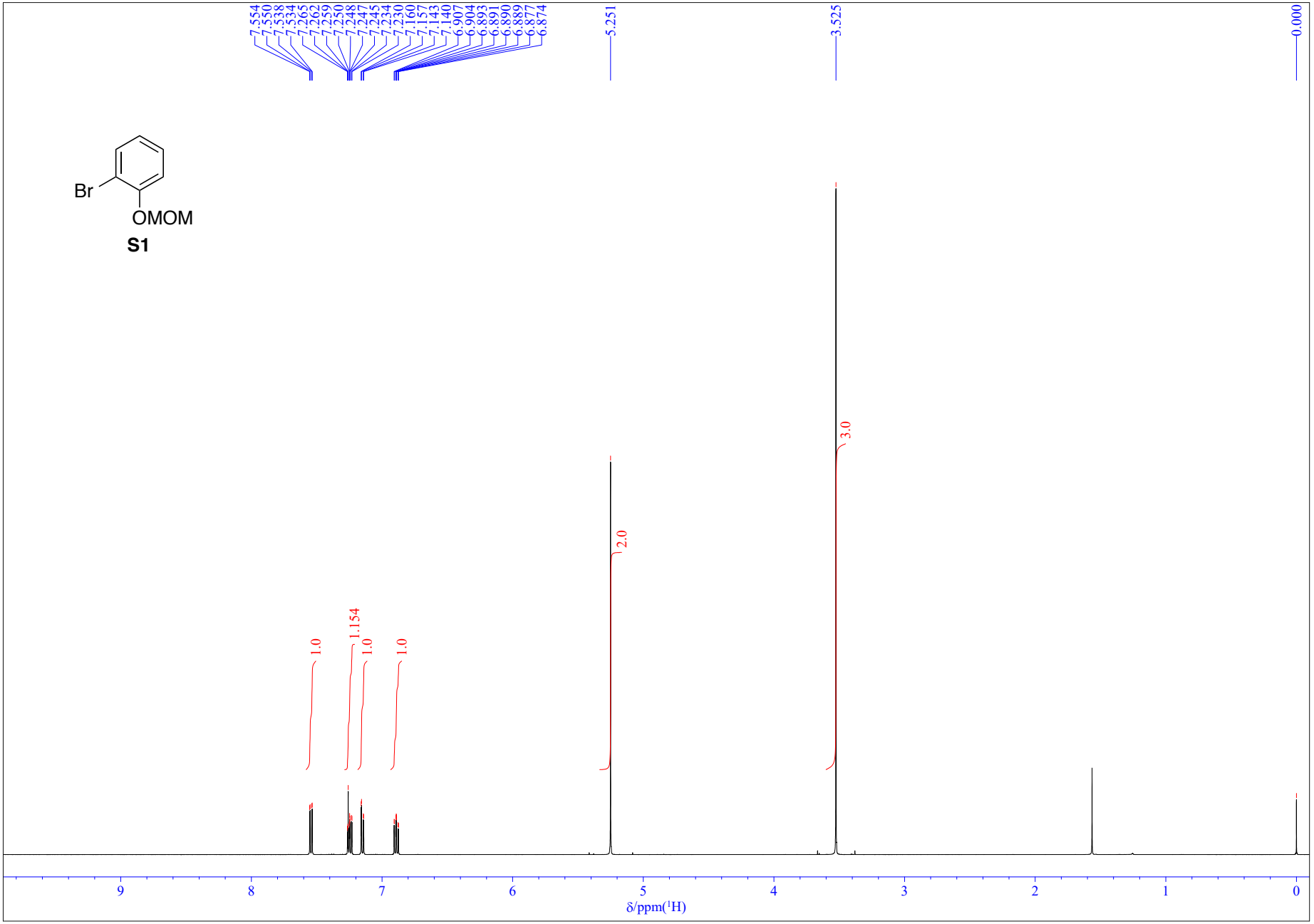


Figure S105. ^{1}H NMR spectrum of compound **S1** (500 MHz, $CDCl_3$).

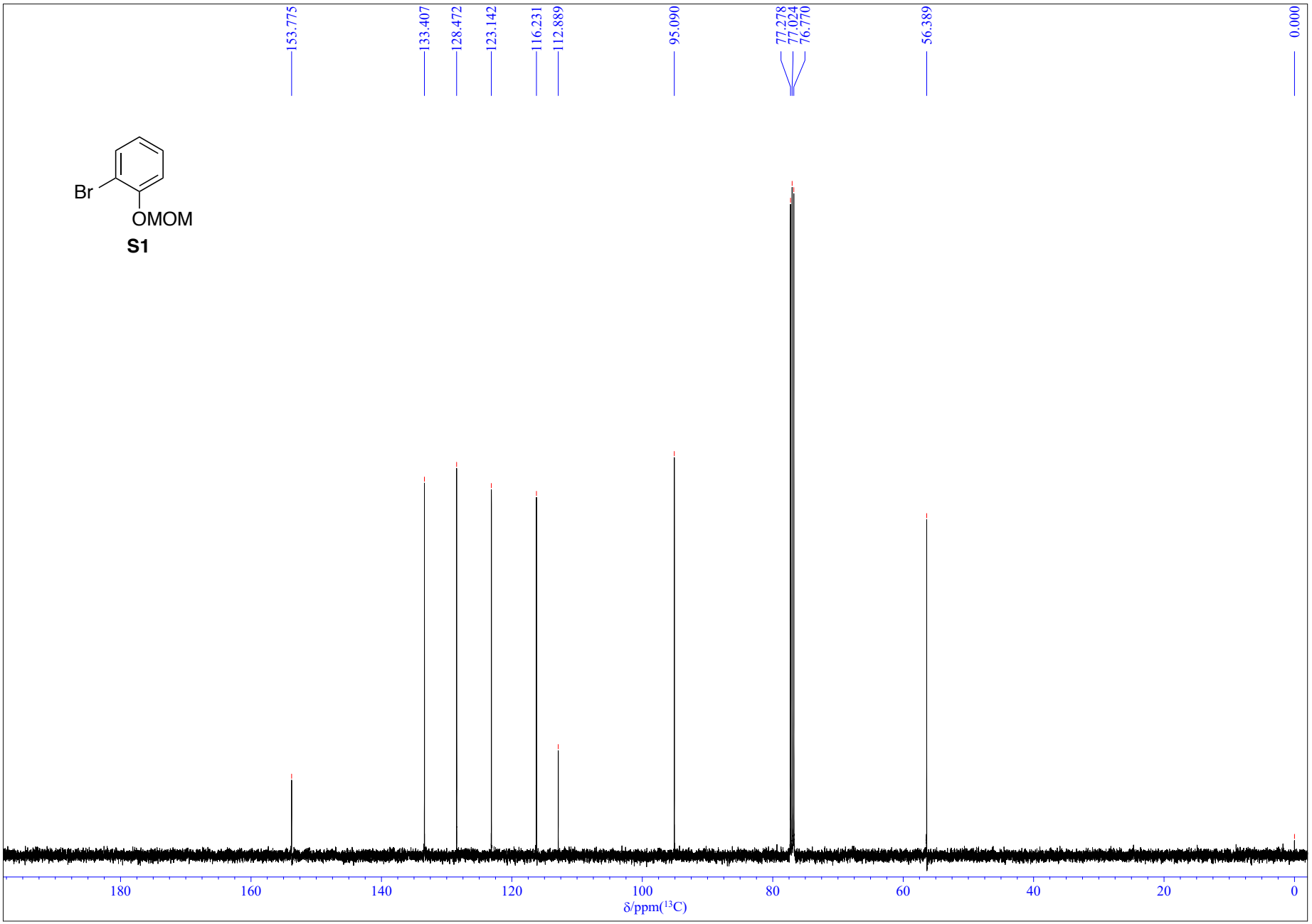


Figure S106. ^{13}C NMR spectrum of compound **S1** (126 MHz, $CDCl_3$).

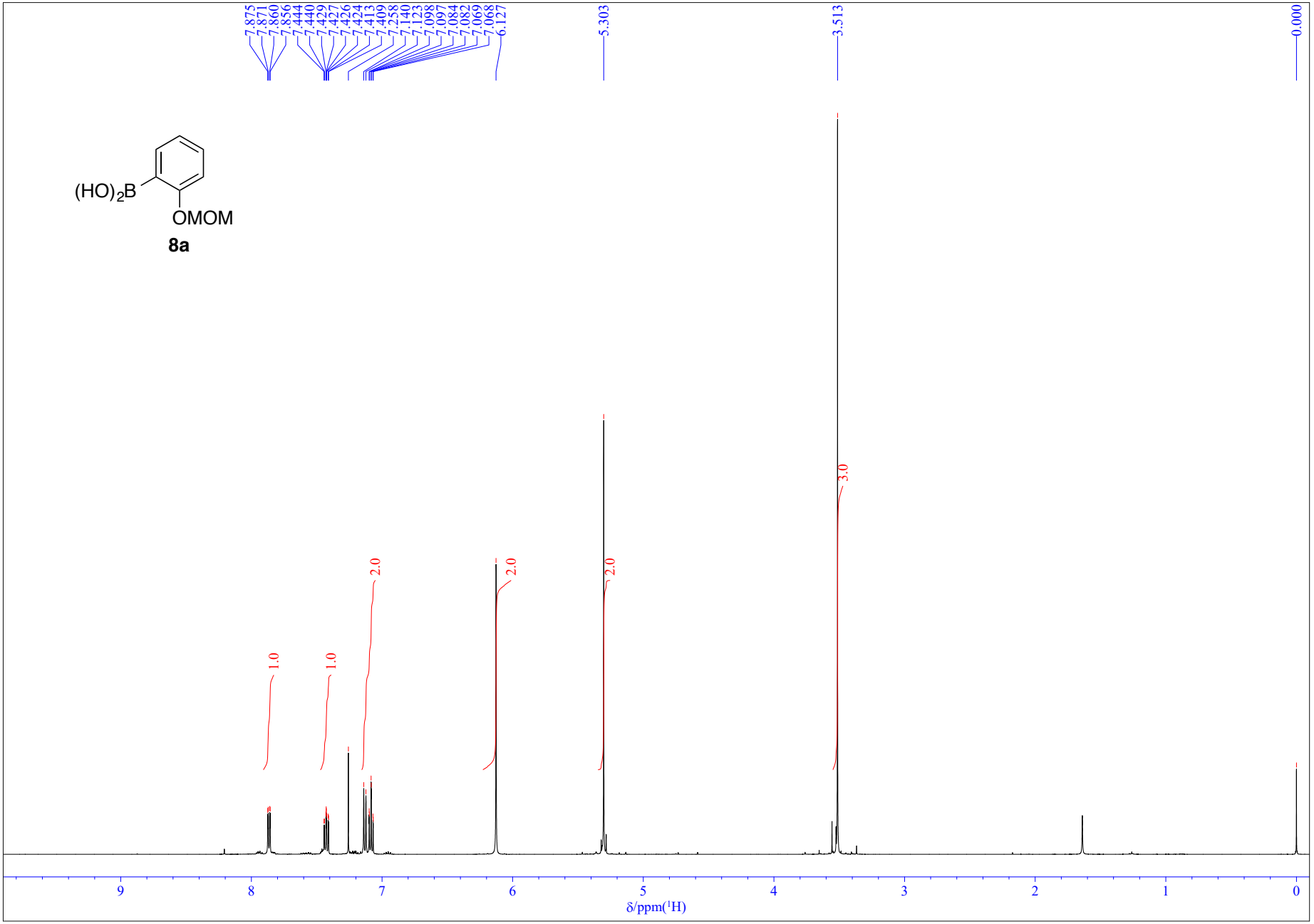


Figure S107. ^{1}H NMR spectrum of compound **8a** (500 MHz, $CDCl_3$).

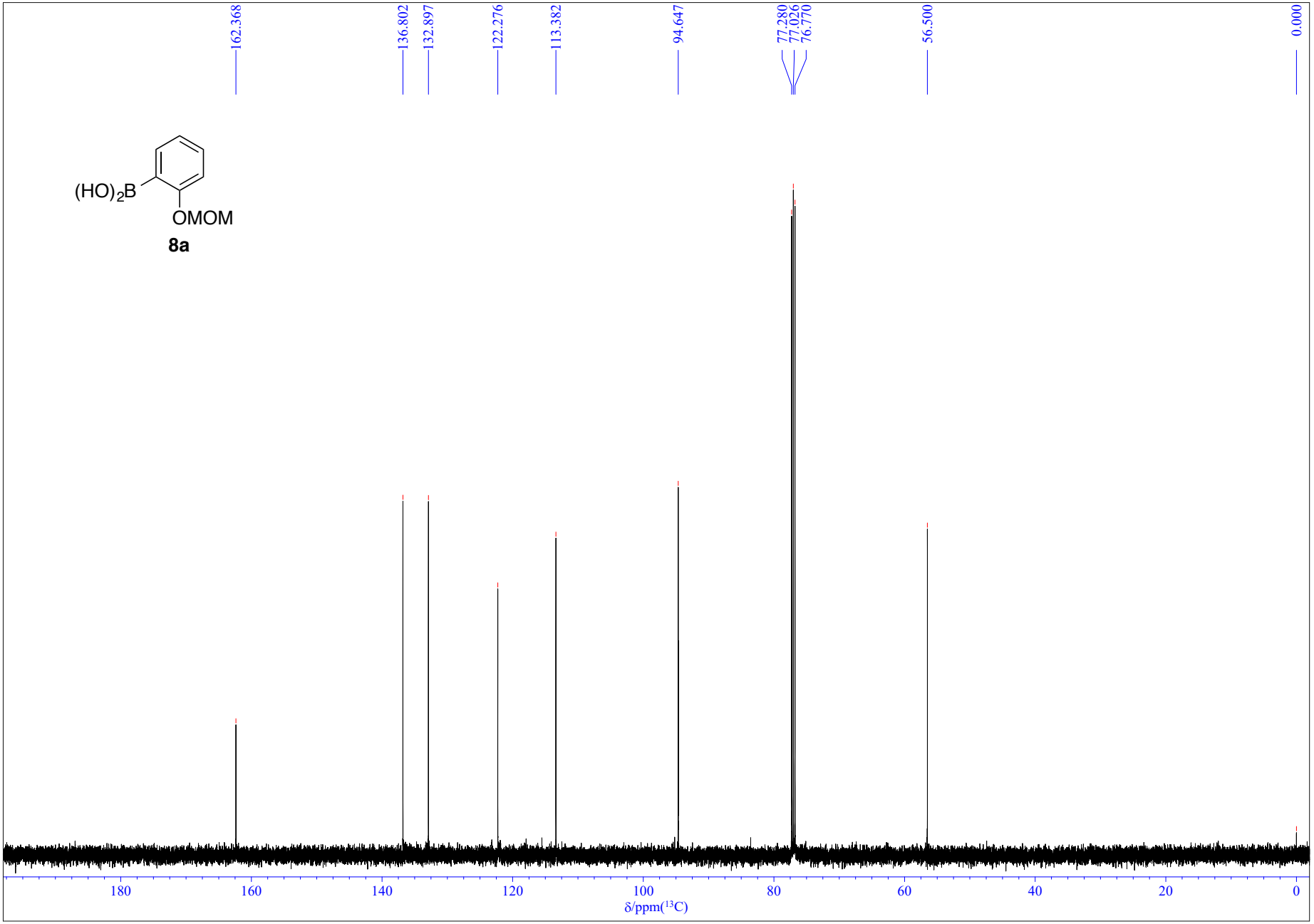


Figure S108. ^{13}C NMR spectrum of compound **8a** (126 MHz, $CDCl_3$).

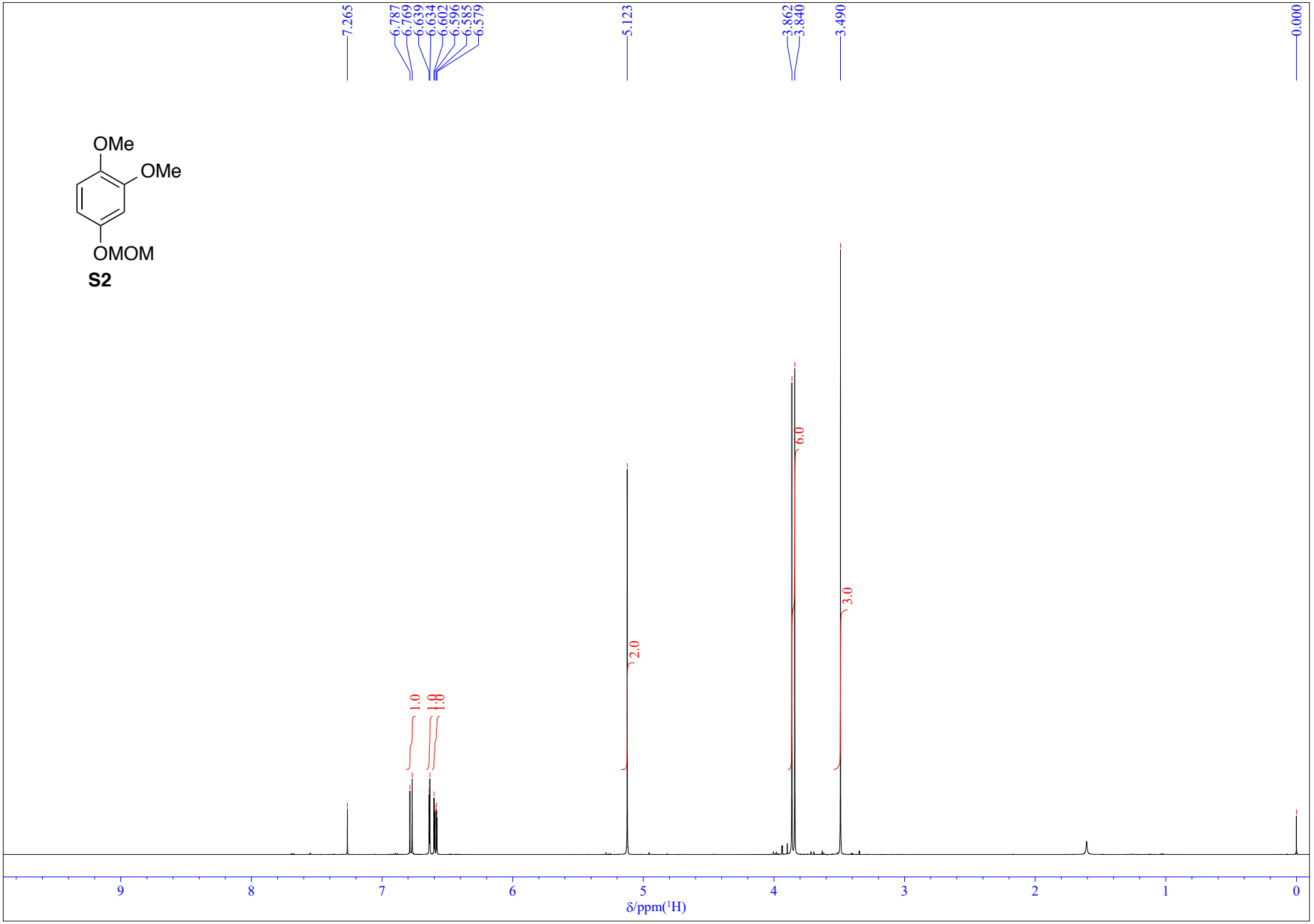


Figure S109. ^{1}H NMR spectrum of compound **S2** (500 MHz, $CDCl_3$).

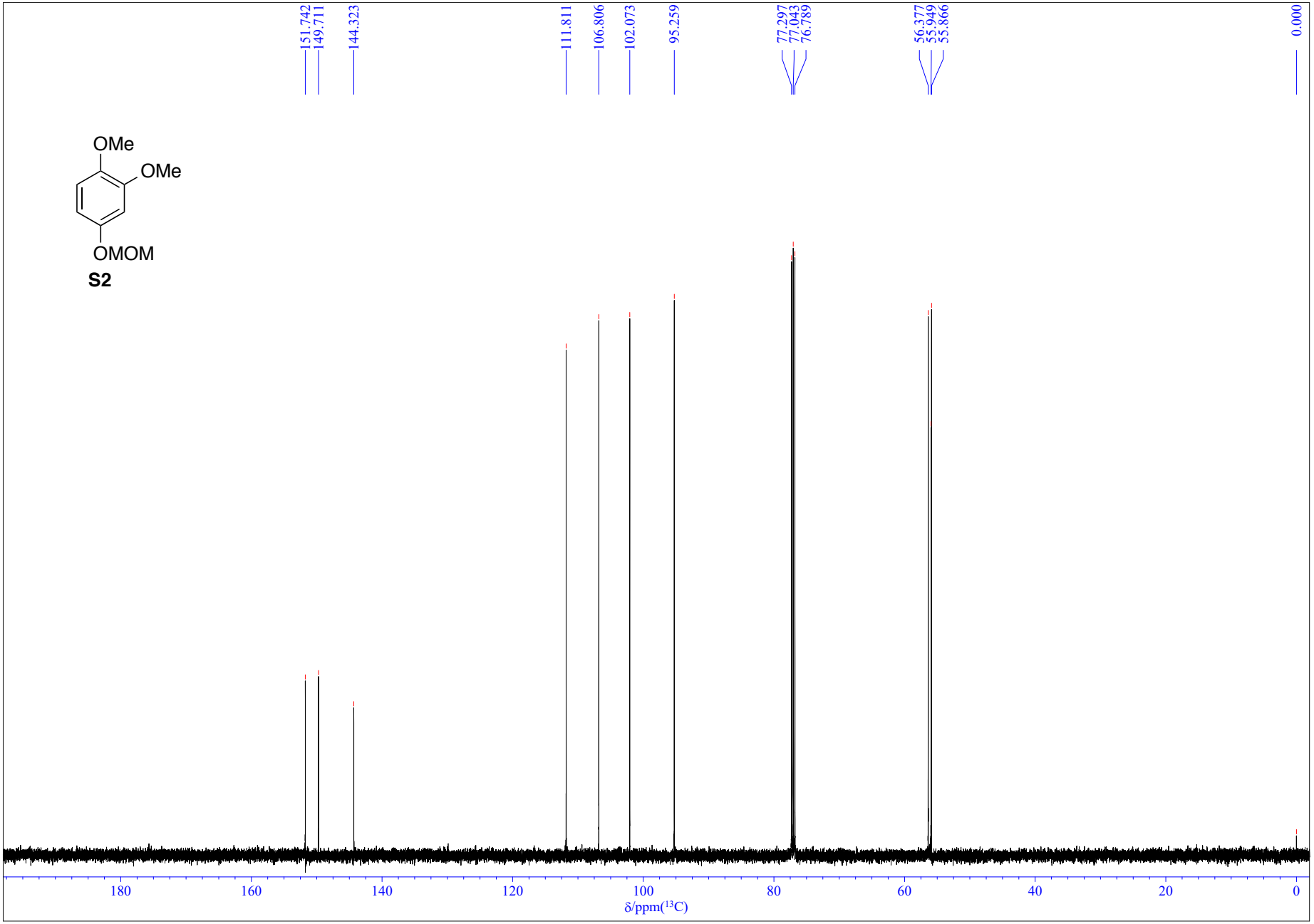


Figure S110. ^{13}C NMR spectrum of compound **S2** (126 MHz, $CDCl_3$).

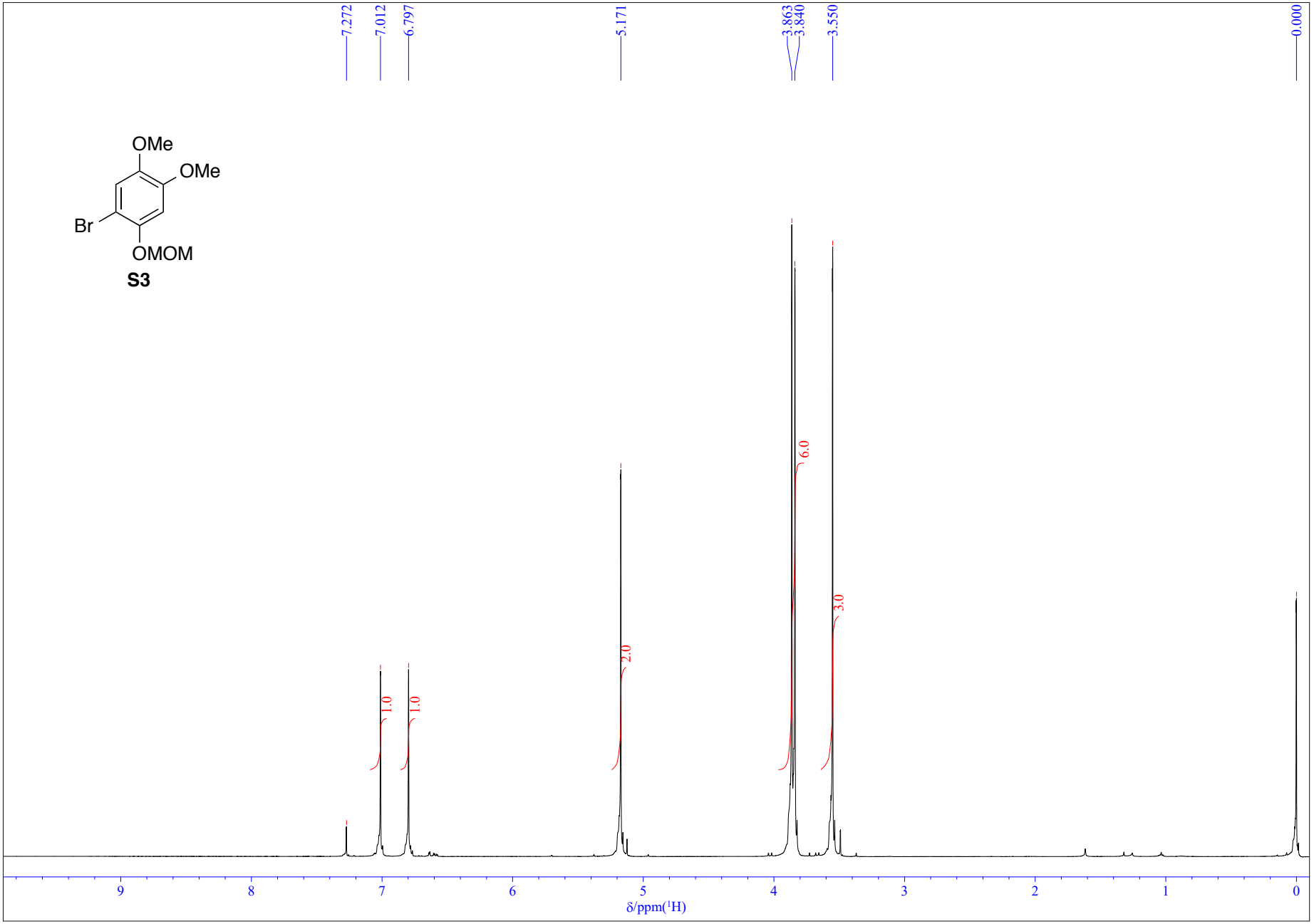


Figure S111. ^{1}H NMR spectrum of compound **S3** (400 MHz, $CDCl_3$).

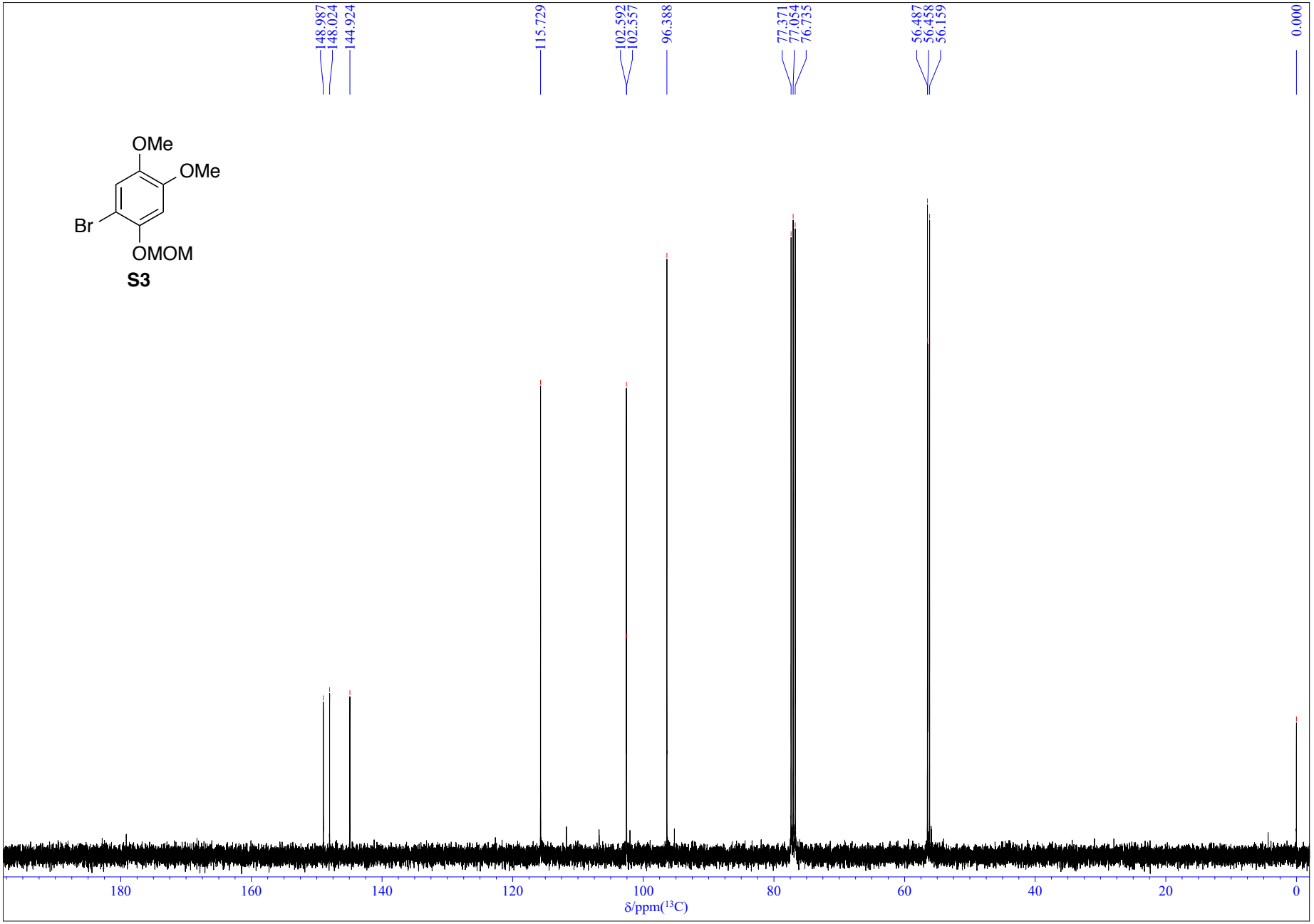


Figure S112. ^{13}C NMR spectrum of compound **S3** (100 MHz, $CDCl_3$).

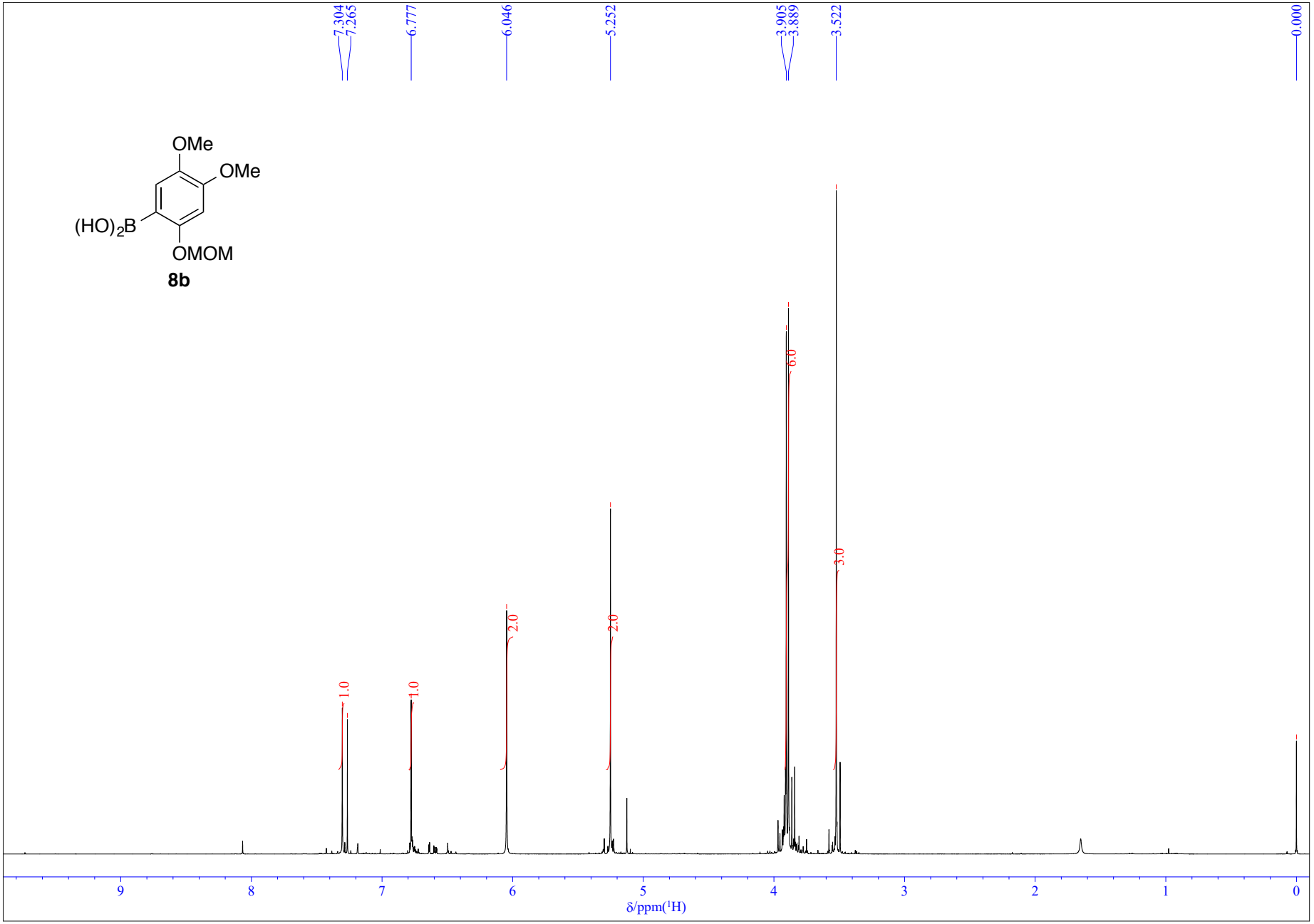


Figure S113. ^{1}H NMR spectrum of compound **8b** (500 MHz, $CDCl_3$).

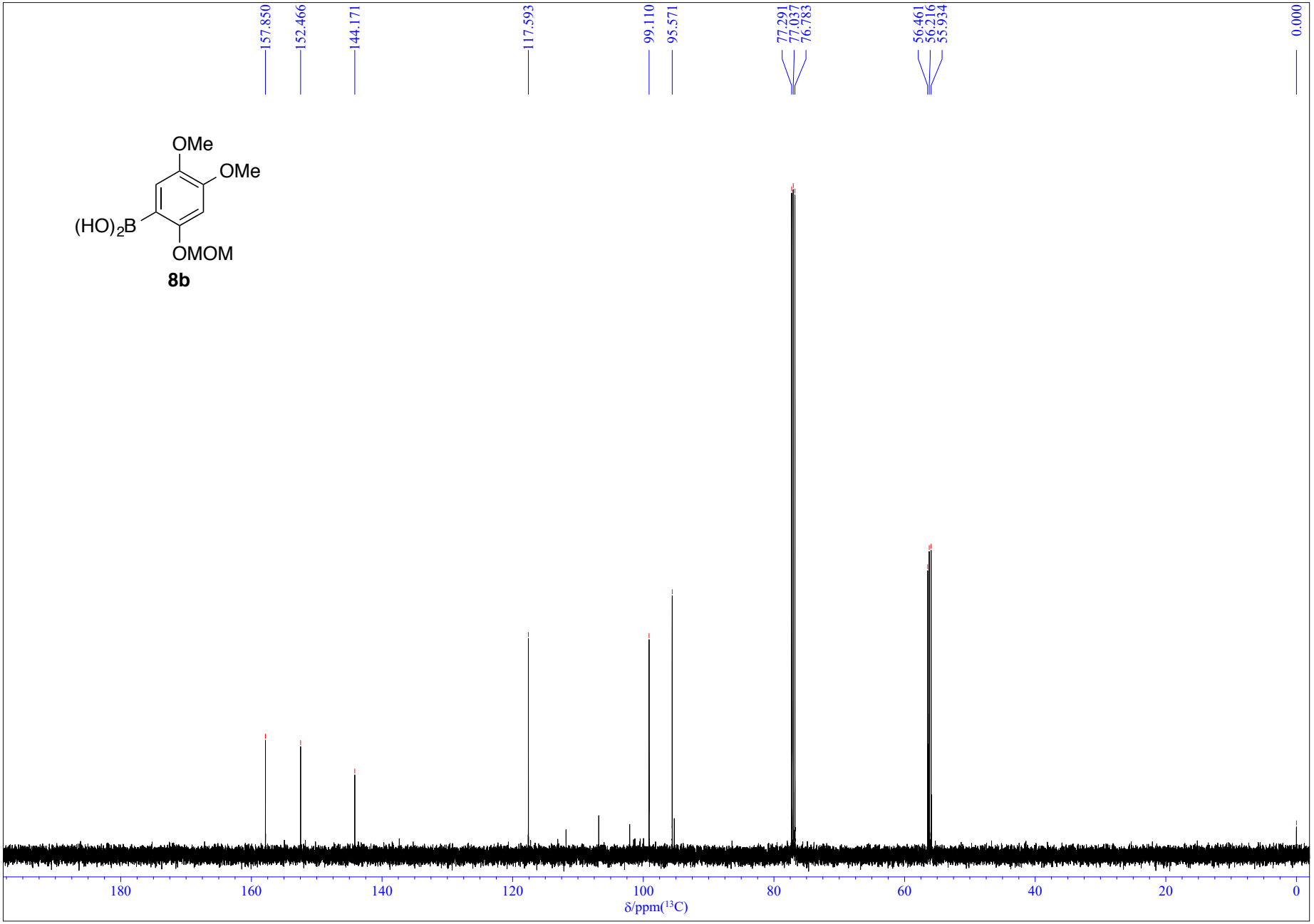


Figure S114. ^{13}C NMR spectrum of compound **8b** (126 MHz, $CDCl_3$).

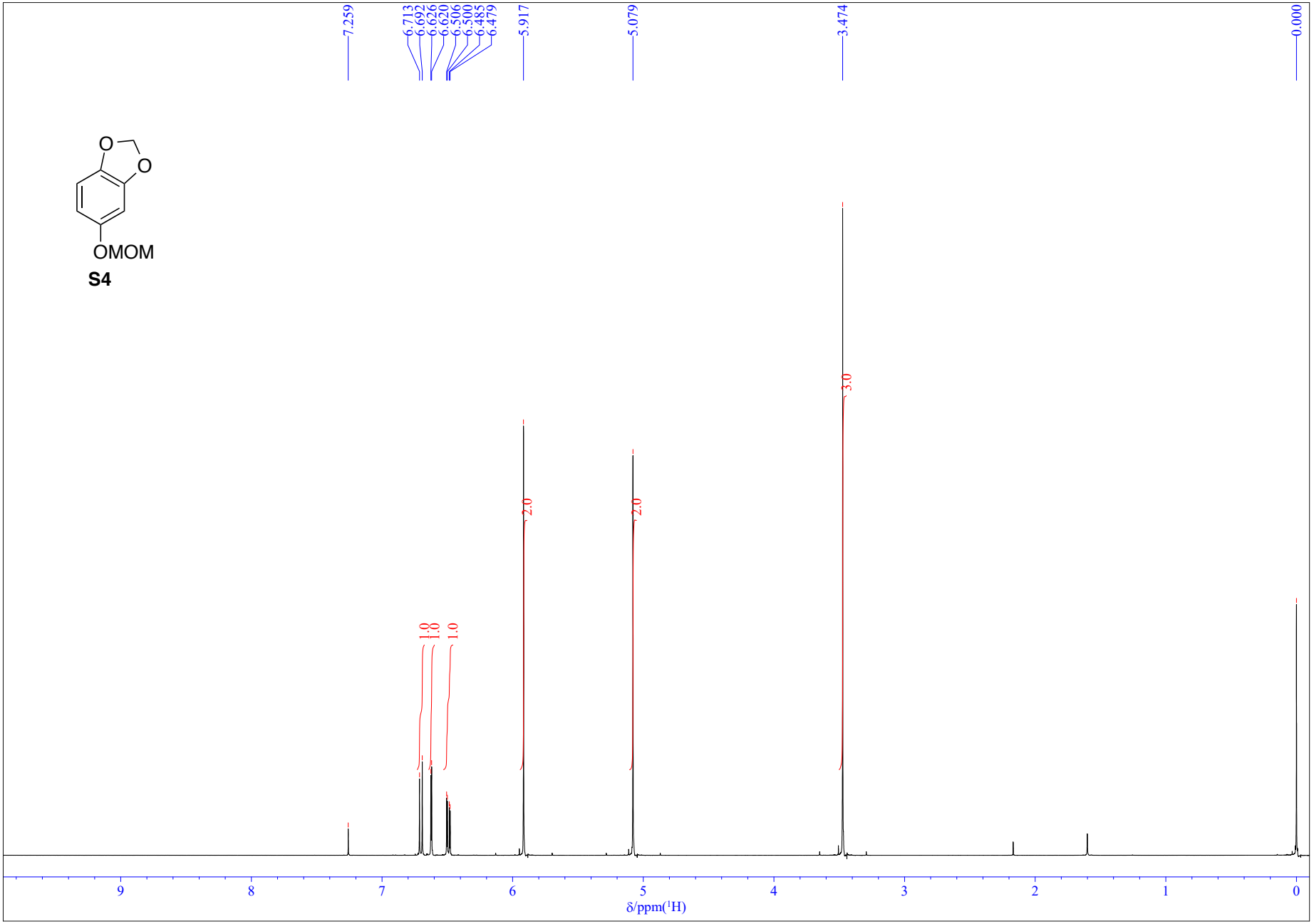


Figure S115. ^{1}H NMR spectrum of compound **S4** (400 MHz, $CDCl_3$).

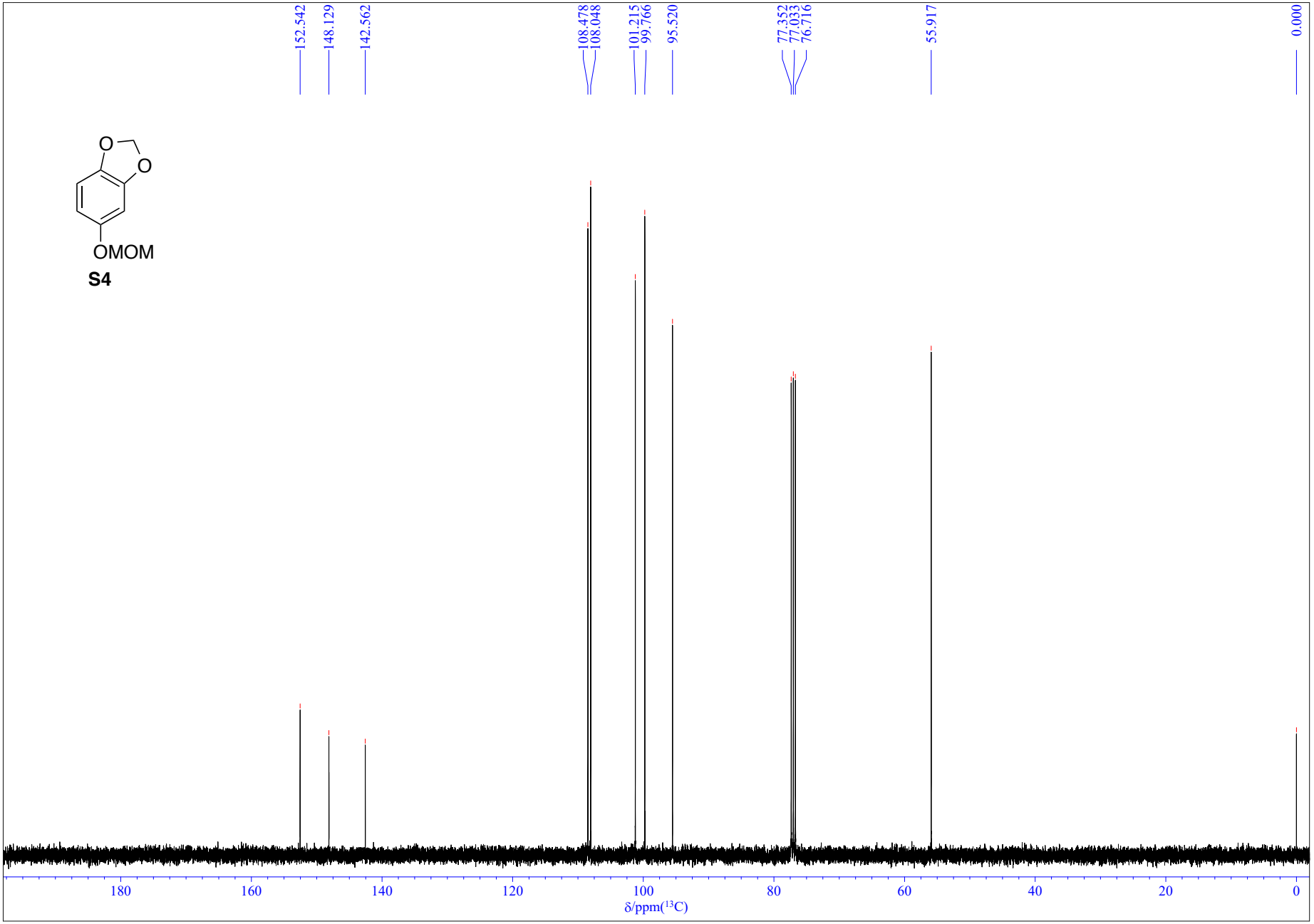


Figure S116. ^{13}C NMR spectrum of compound **S4** (100 MHz, $CDCl_3$).

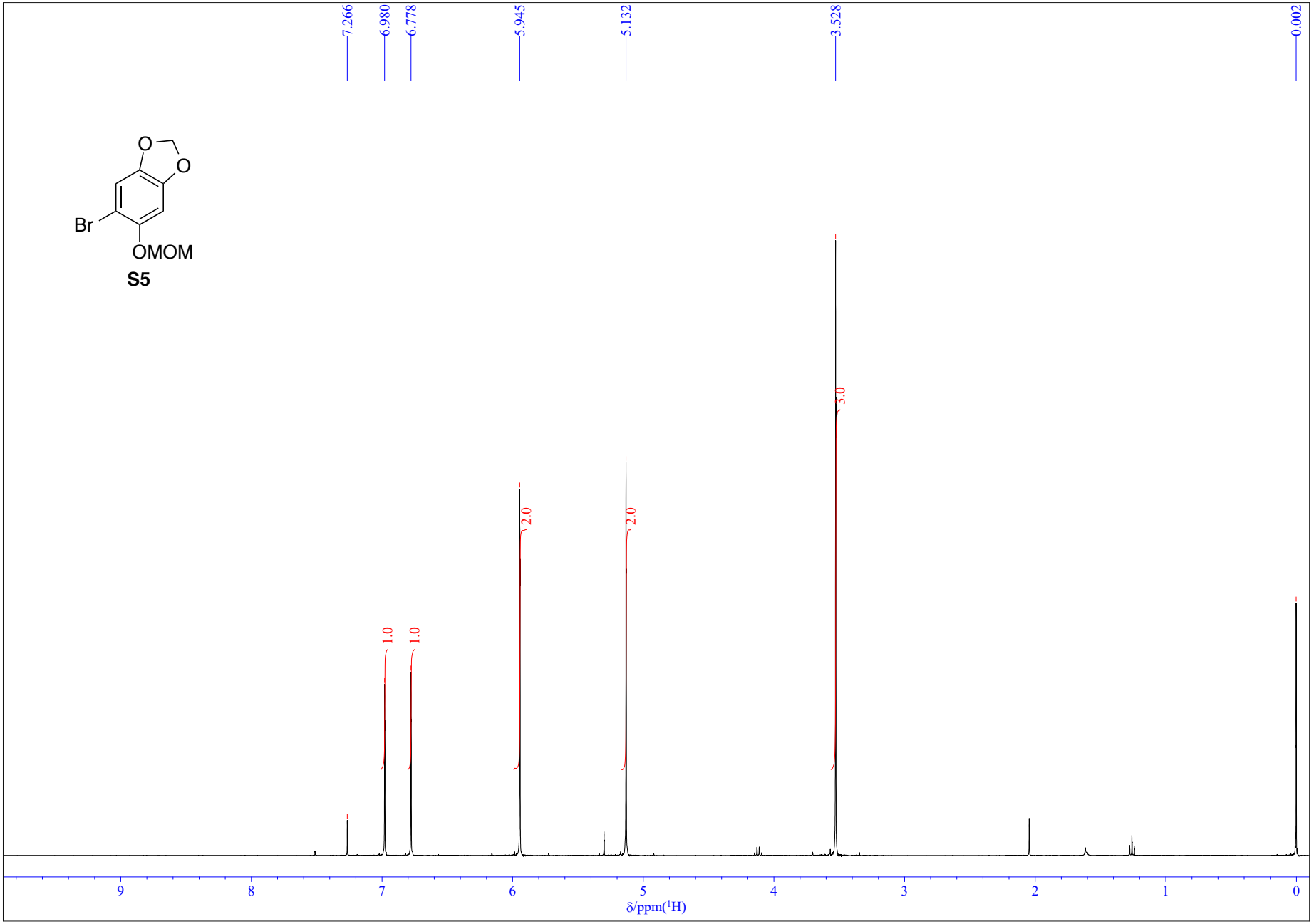


Figure S117. ^{1}H NMR spectrum of compound **S5** (400 MHz, $CDCl_3$).

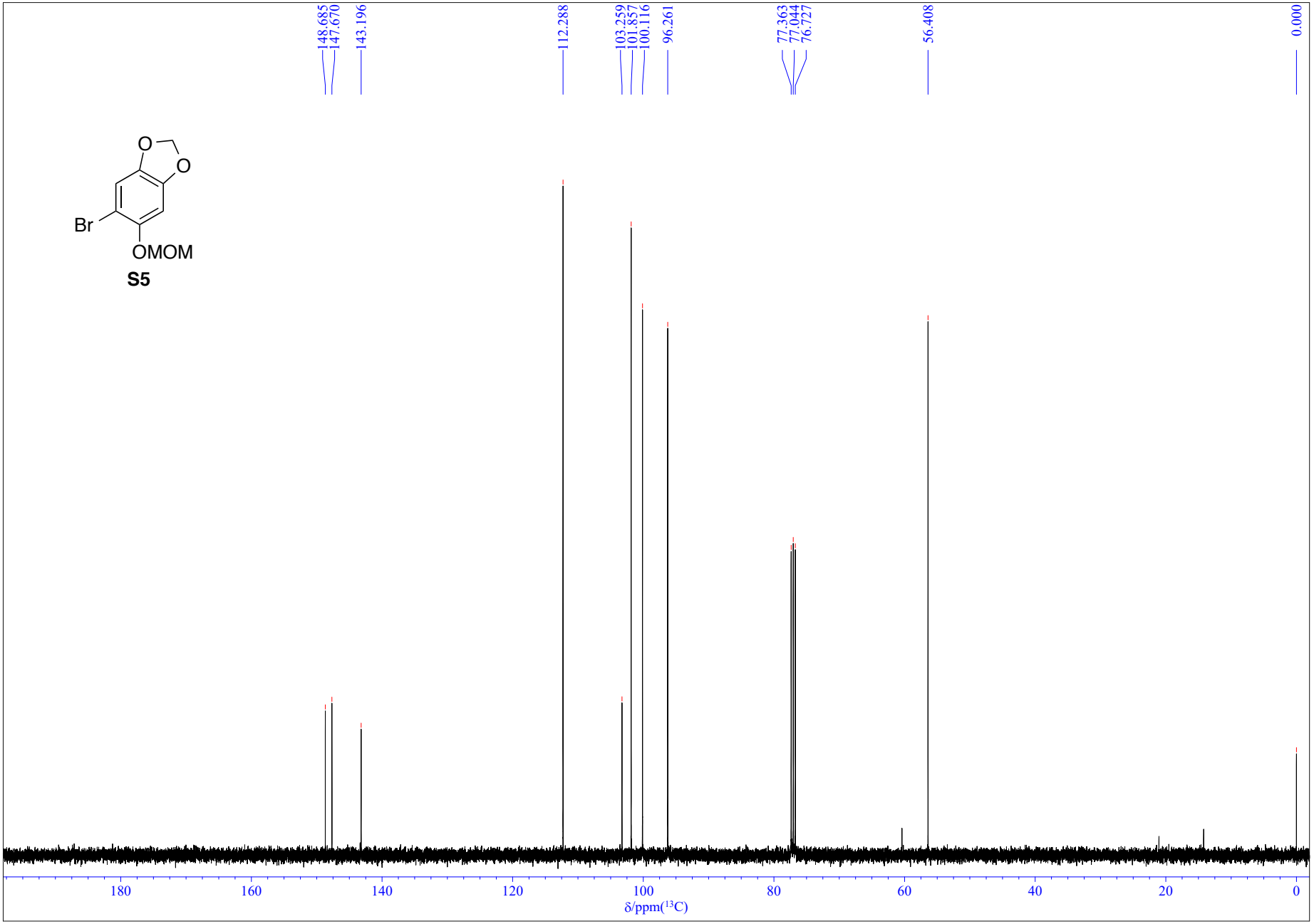


Figure S118. ^{13}C NMR spectrum of compound **S5** (100 MHz, $CDCl_3$).

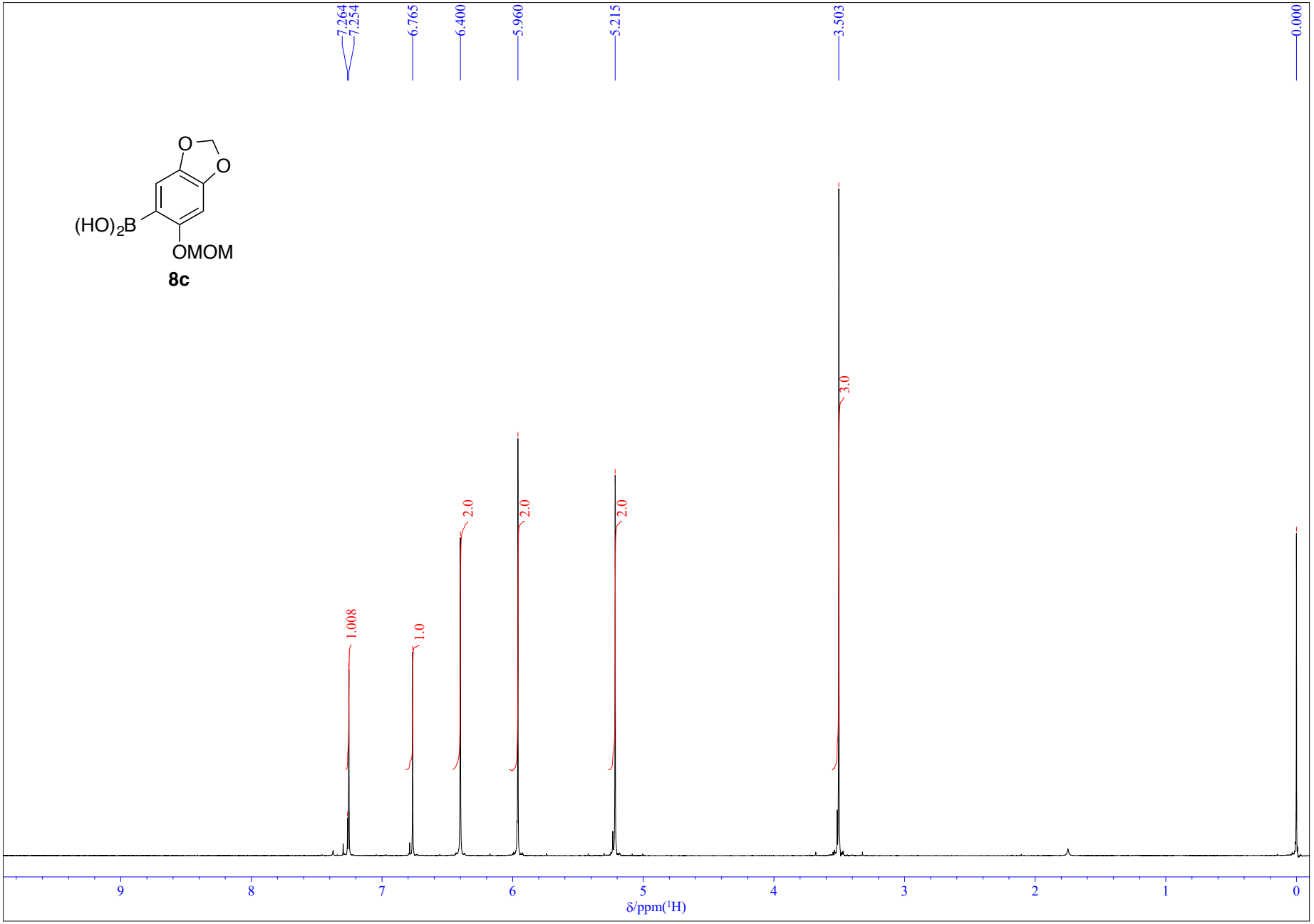


Figure S119. ^{1}H NMR spectrum of compound **8c** (400 MHz, $CDCl_3$).

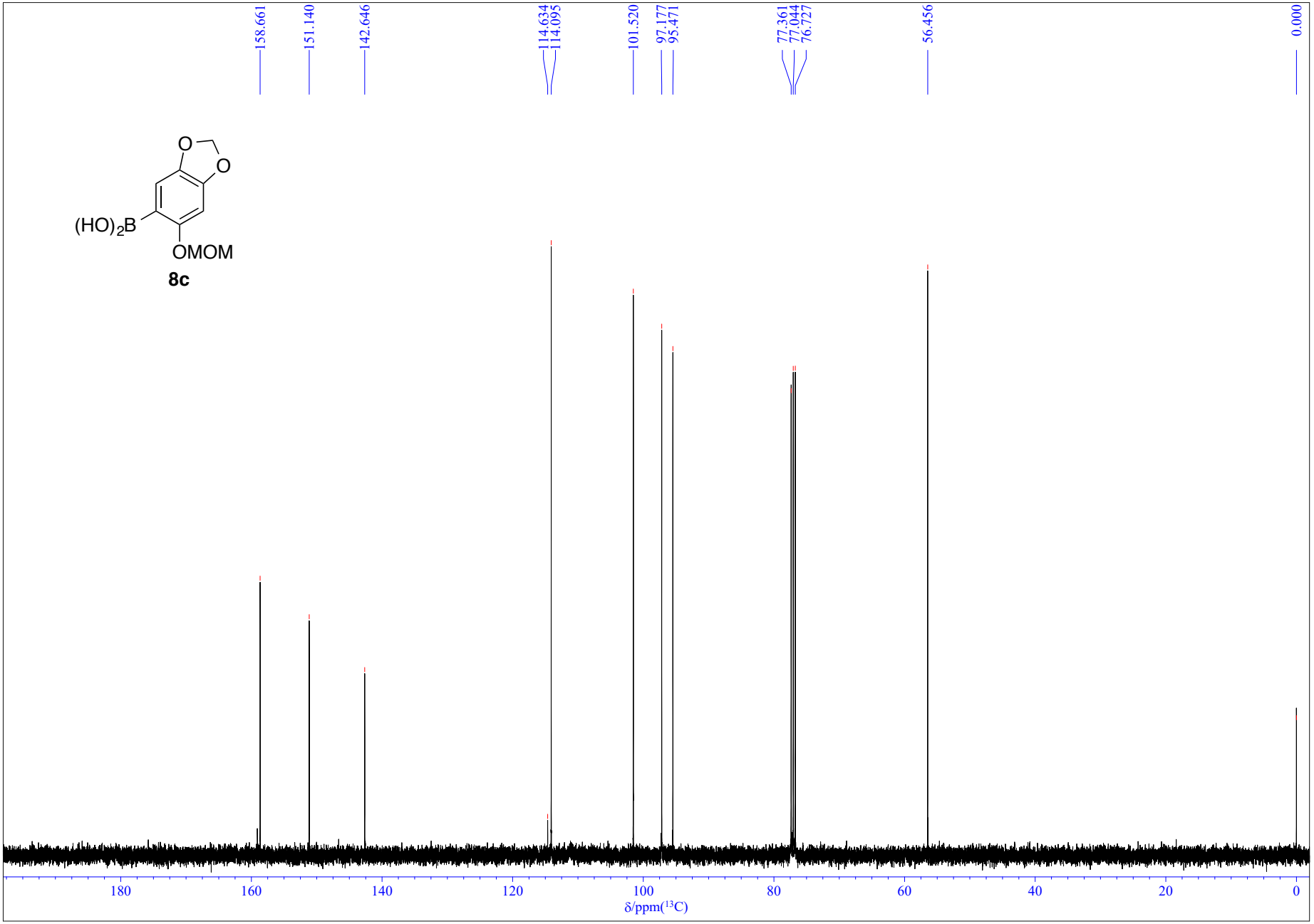


Figure S120. ^{13}C NMR spectrum of compound **8c** (100 MHz, $CDCl_3$).

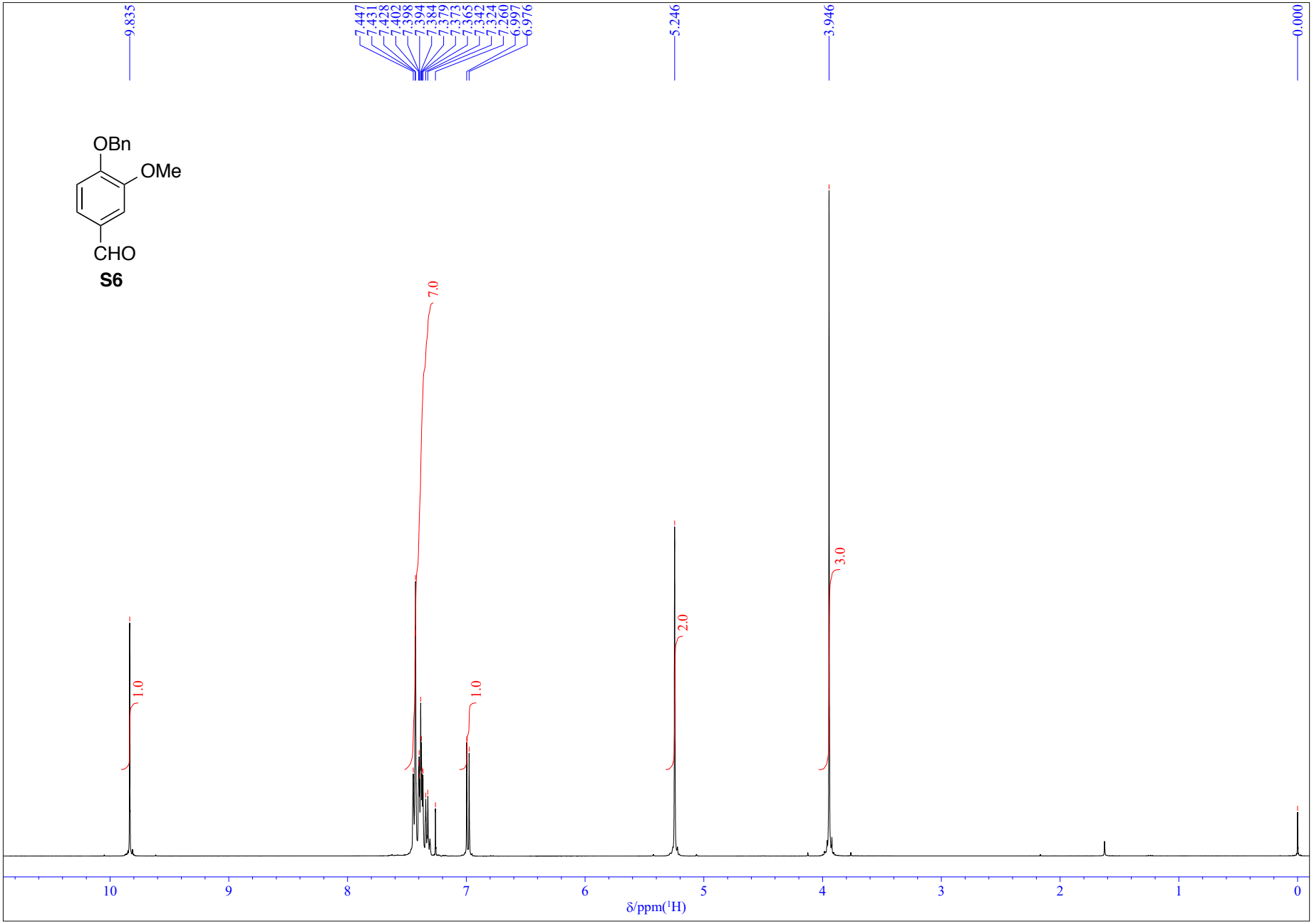


Figure S121. ^{1}H NMR spectrum of compound **S6** (400 MHz, $CDCl_3$).

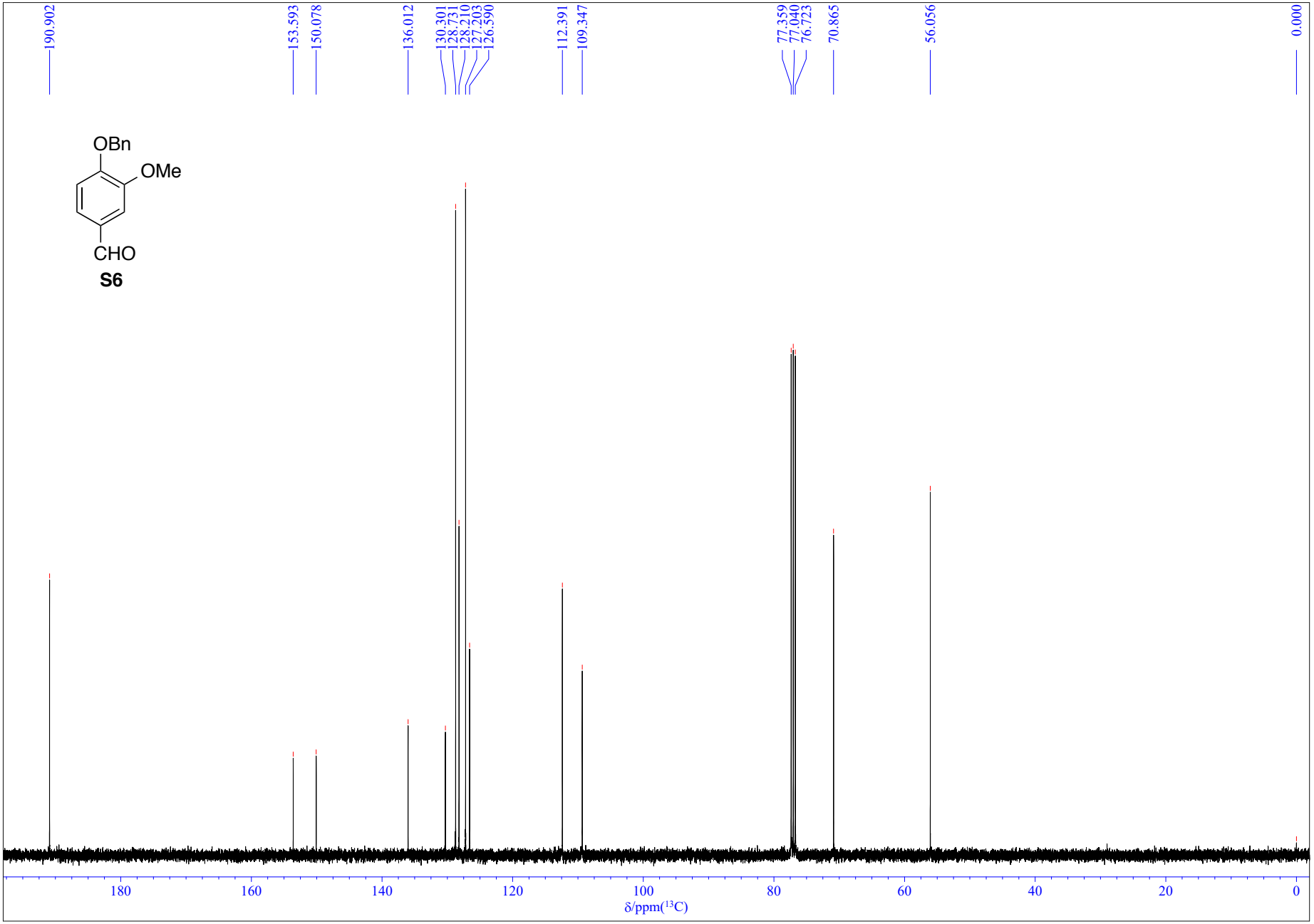


Figure S122. ^{13}C NMR spectrum of compound **S6** (100 MHz, $CDCl_3$).

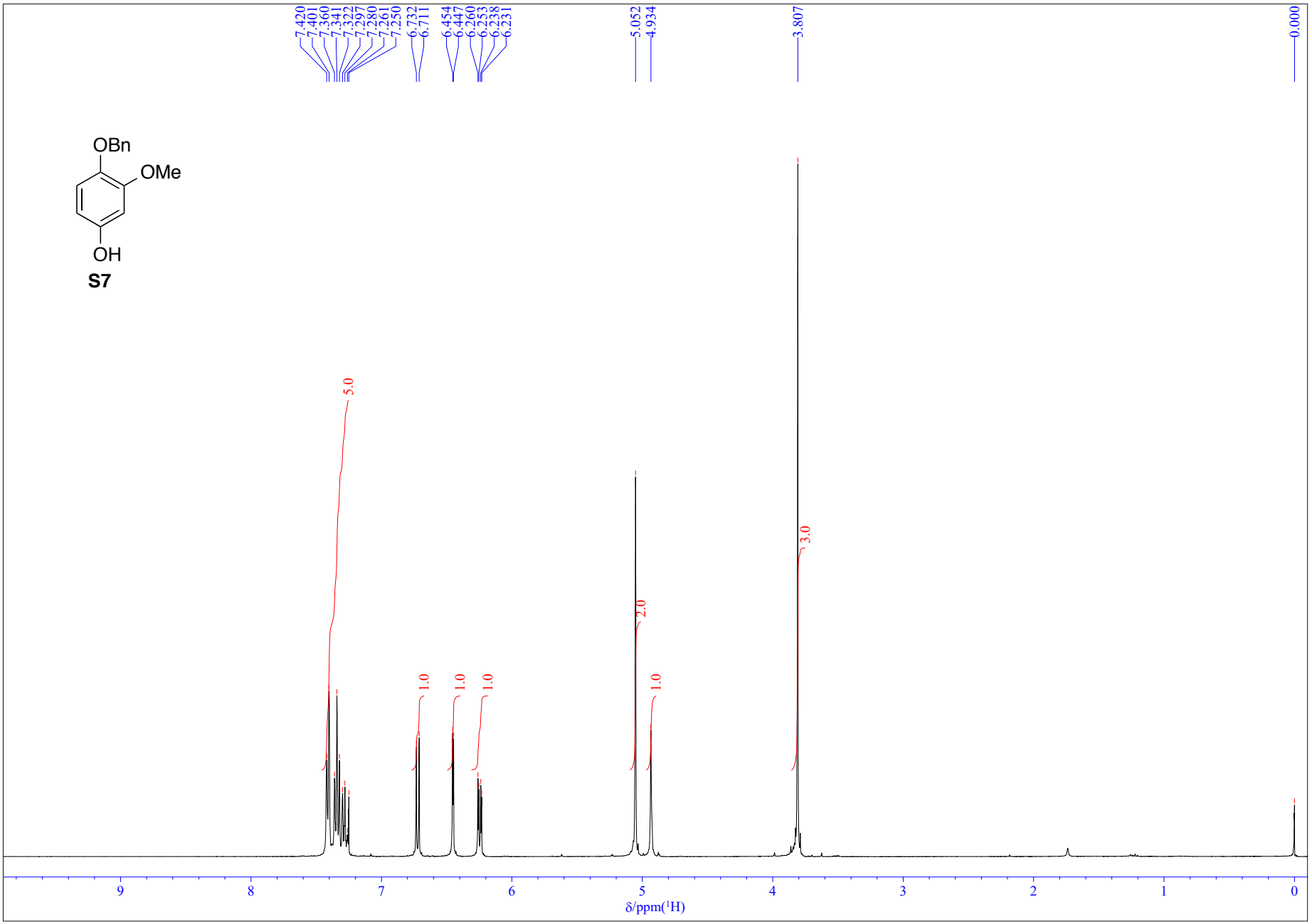


Figure S123. ^{1}H NMR spectrum of compound **S7** (400 MHz, $CDCl_3$).

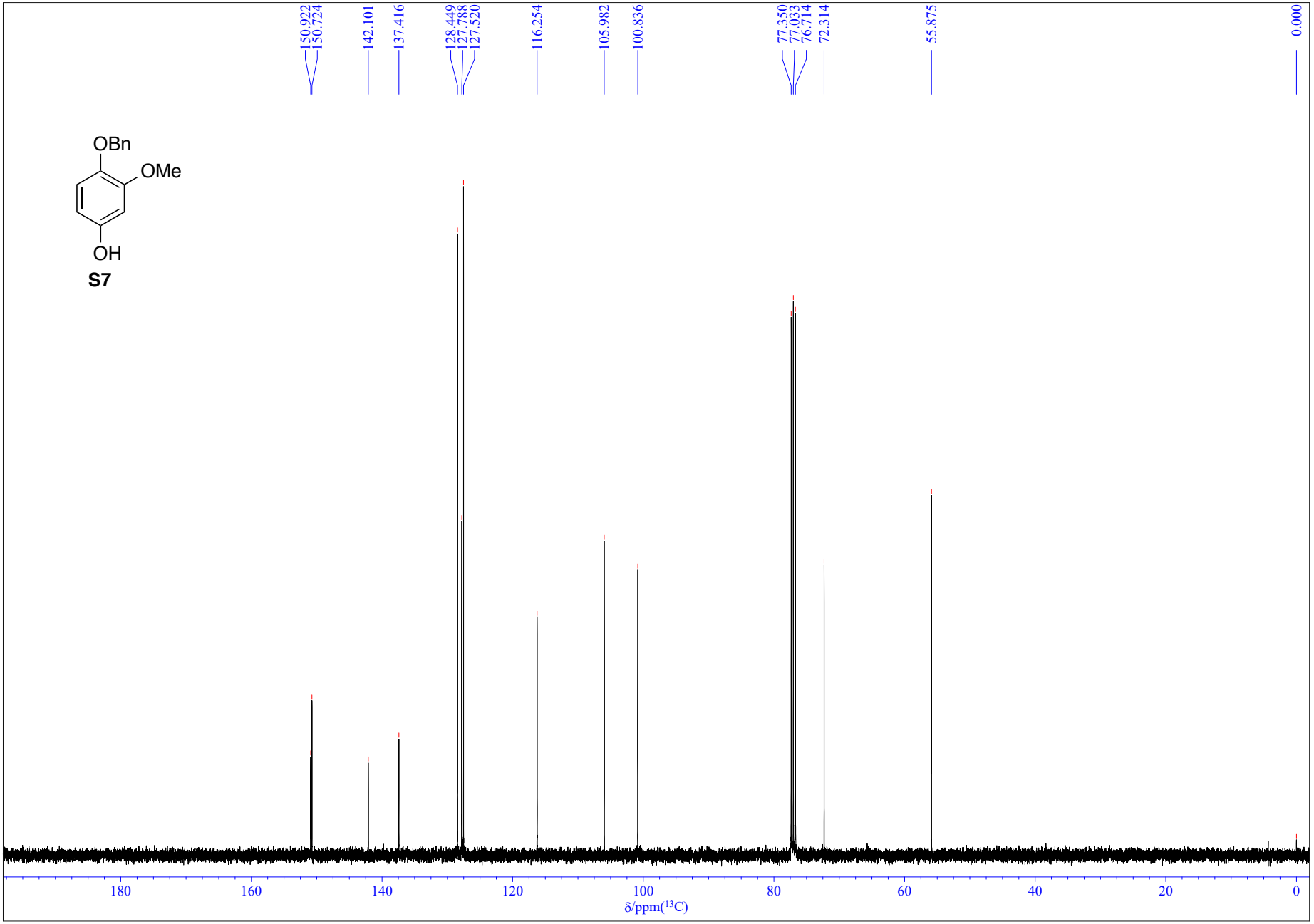


Figure S124. ^{13}C NMR spectrum of compound **S7** (100 MHz, $CDCl_3$).

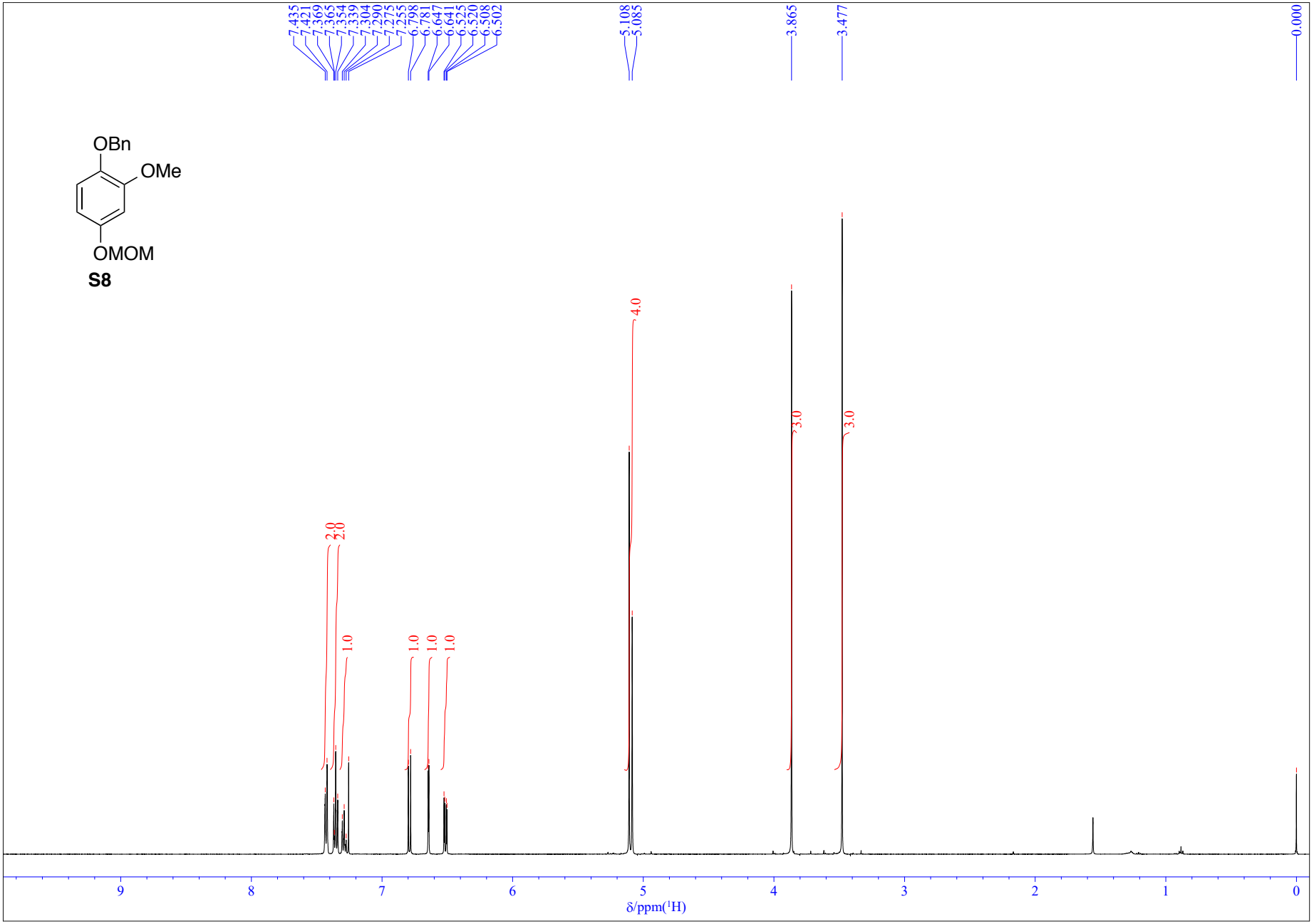


Figure S125. ^{1}H NMR spectrum of compound **S8** (500 MHz, $CDCl_3$).

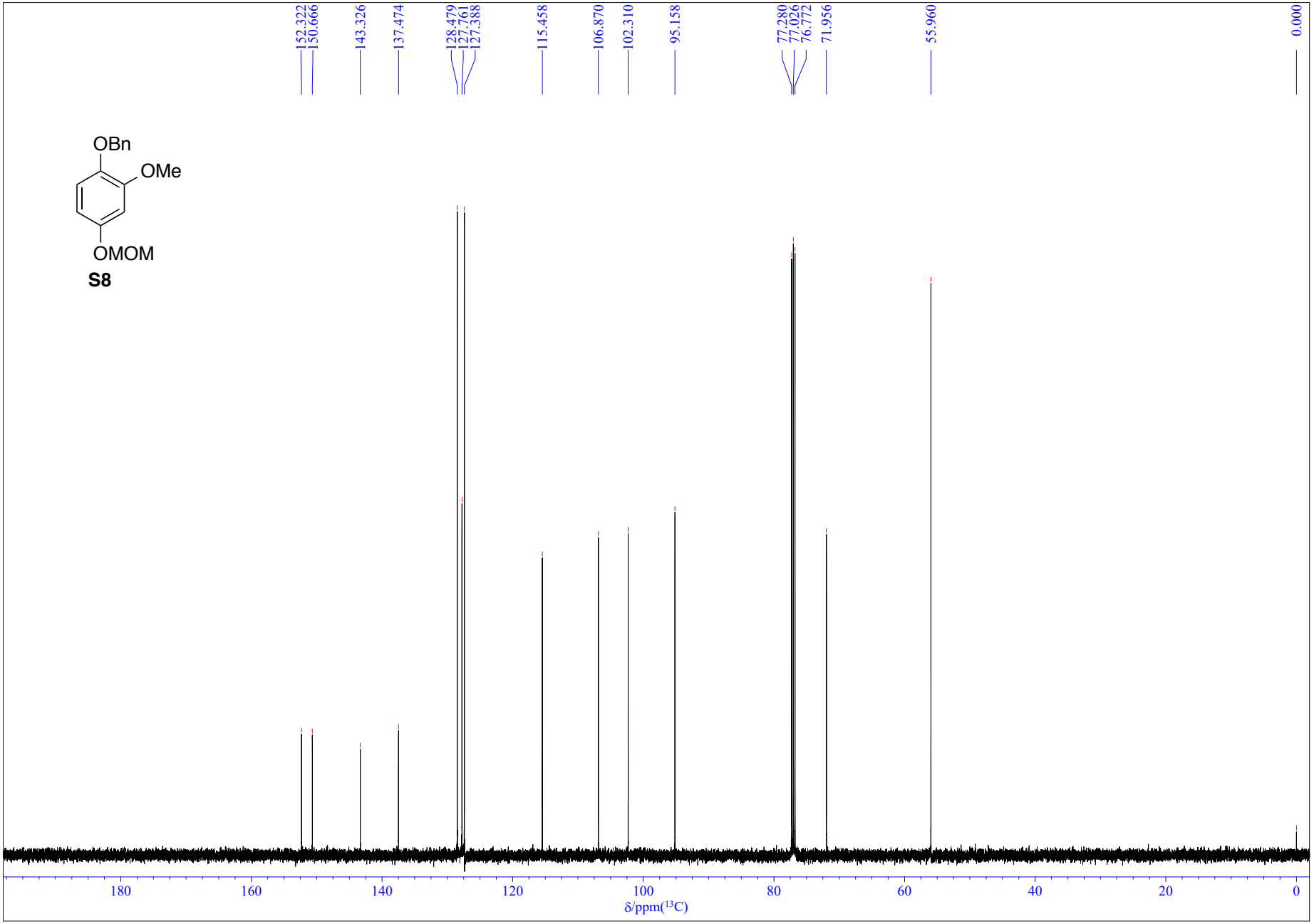


Figure S126. ^{13}C NMR spectrum of compound **S8** (126 MHz, $CDCl_3$).

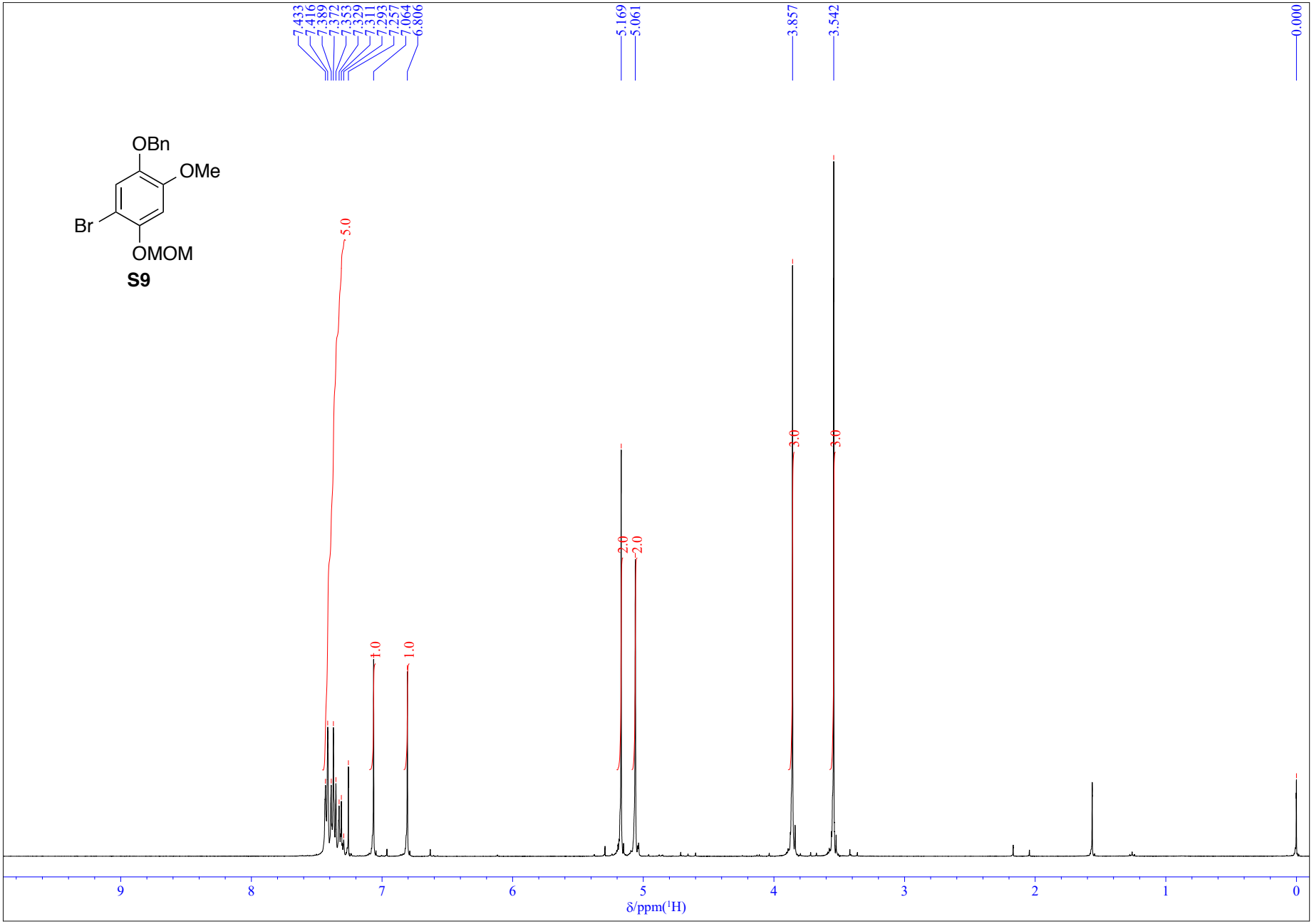


Figure S127. ^{1}H NMR spectrum of compound **S9** (400 MHz, $CDCl_3$).

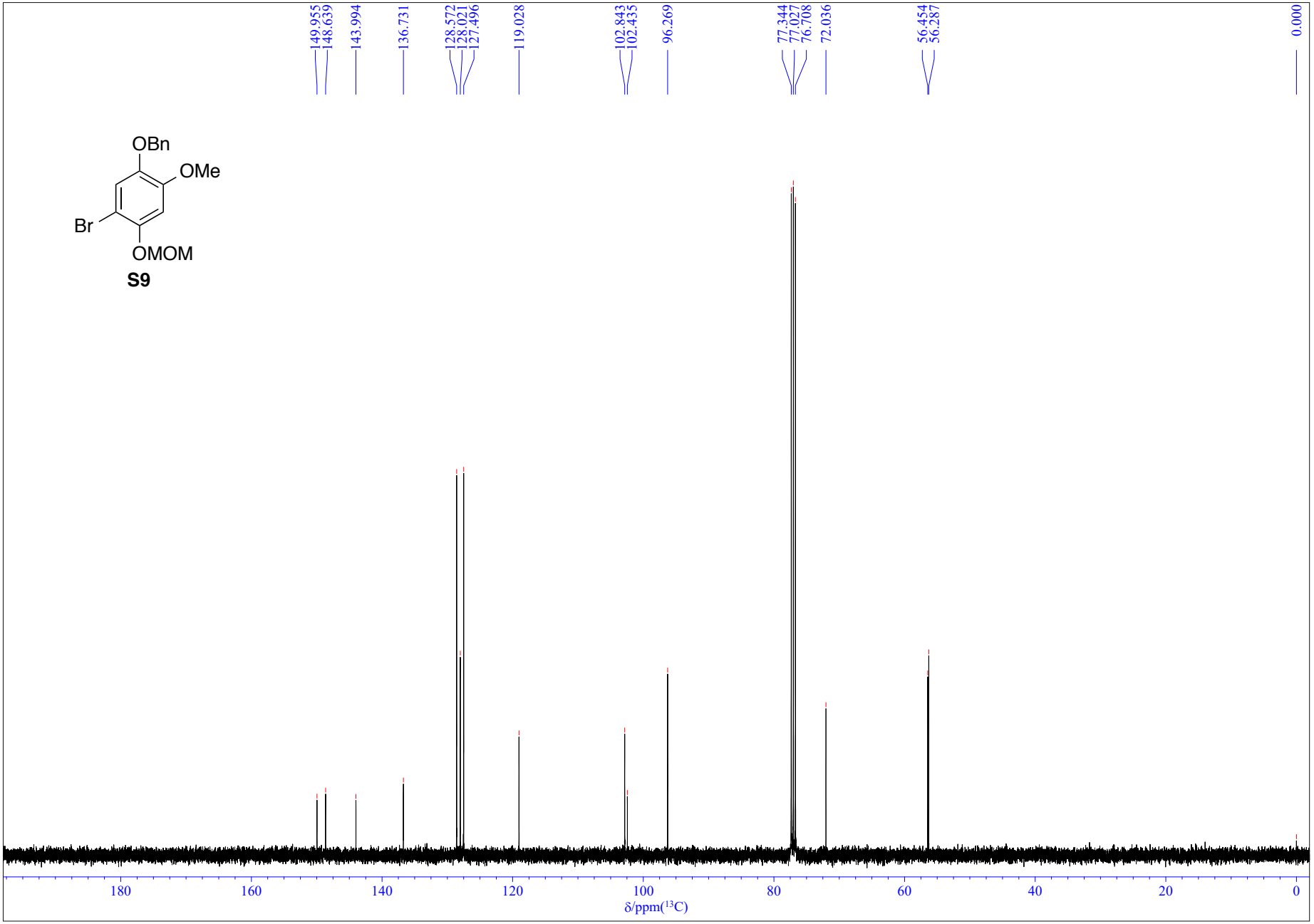


Figure S128. ^{13}C NMR spectrum of compound **S9** (100 MHz, $CDCl_3$).

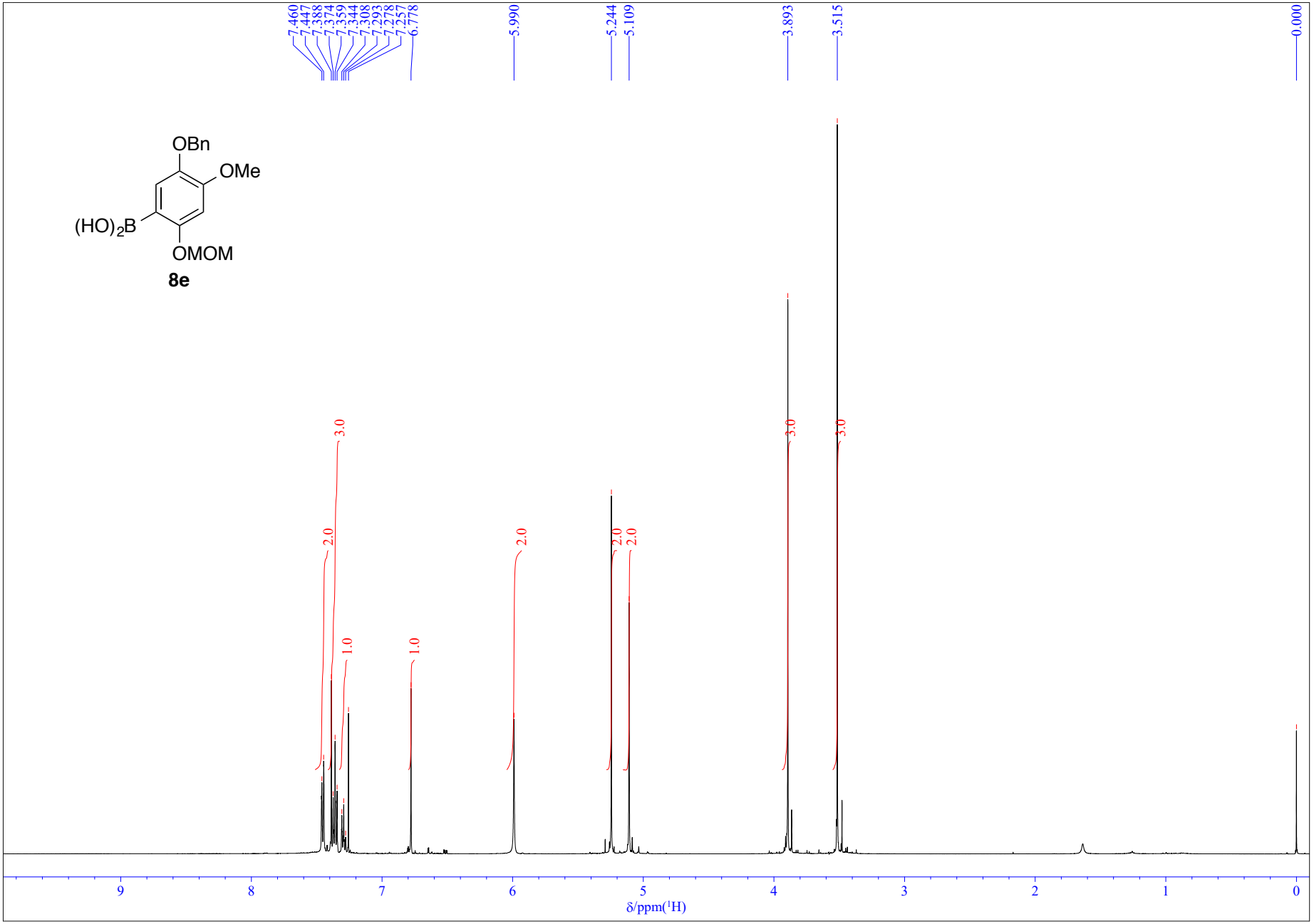


Figure S129. ^{1}H NMR spectrum of compound **8e** (500 MHz, $CDCl_3$).

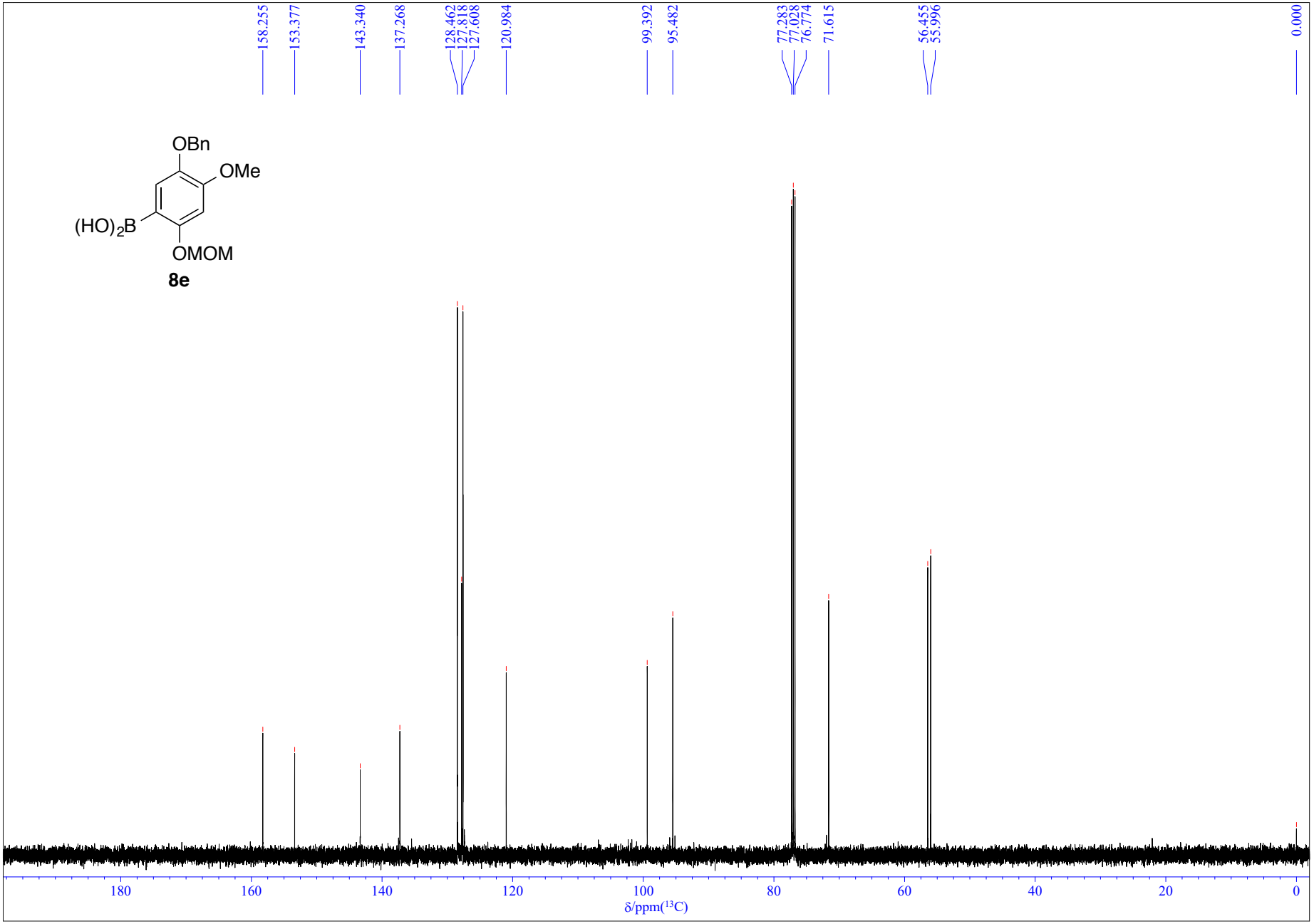


Figure S130. ^{13}C NMR spectrum of compound **8e** (126 MHz, $CDCl_3$).

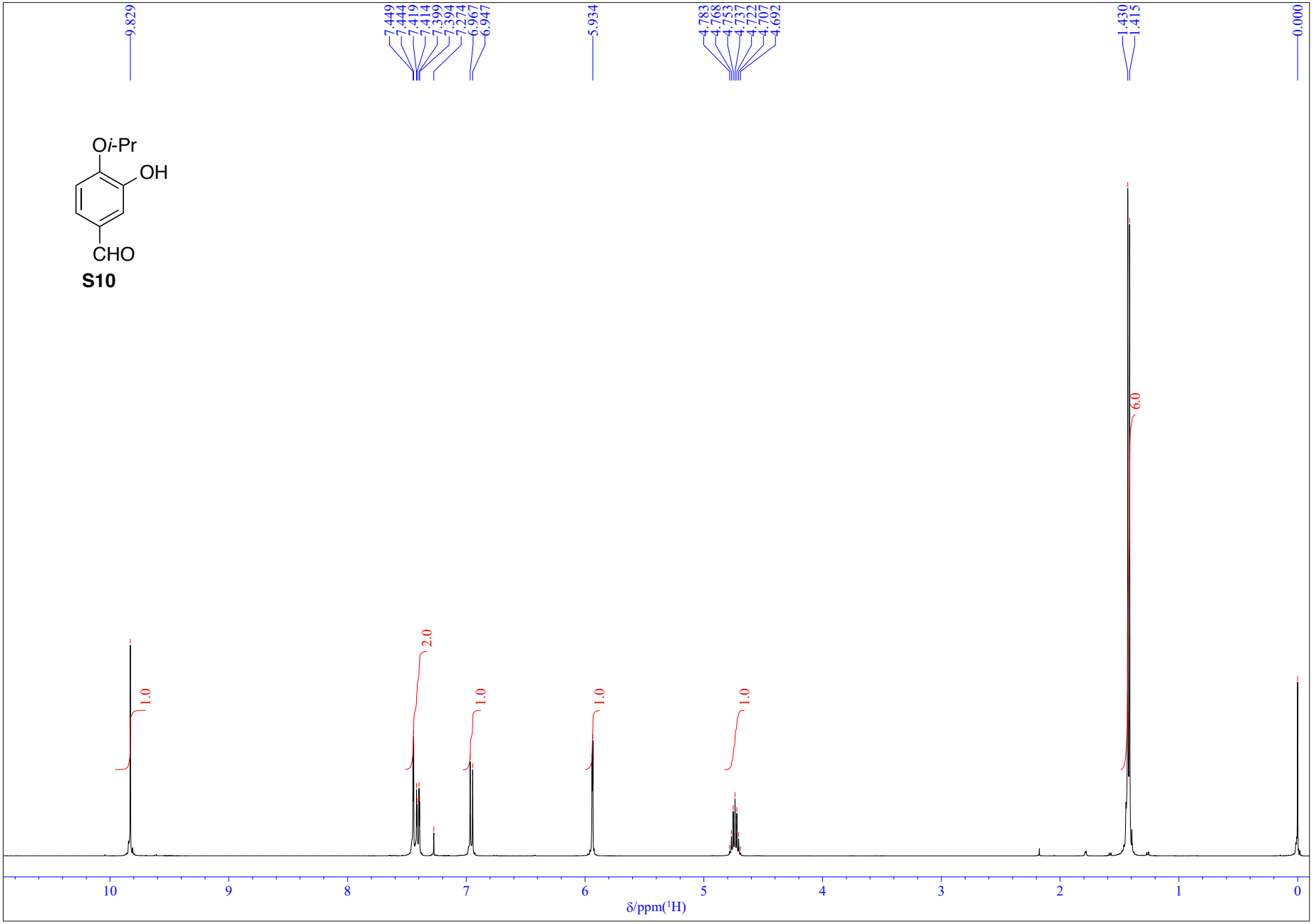


Figure S131. ^{1}H NMR spectrum of compound **S10** (400 MHz, $CDCl_3$).

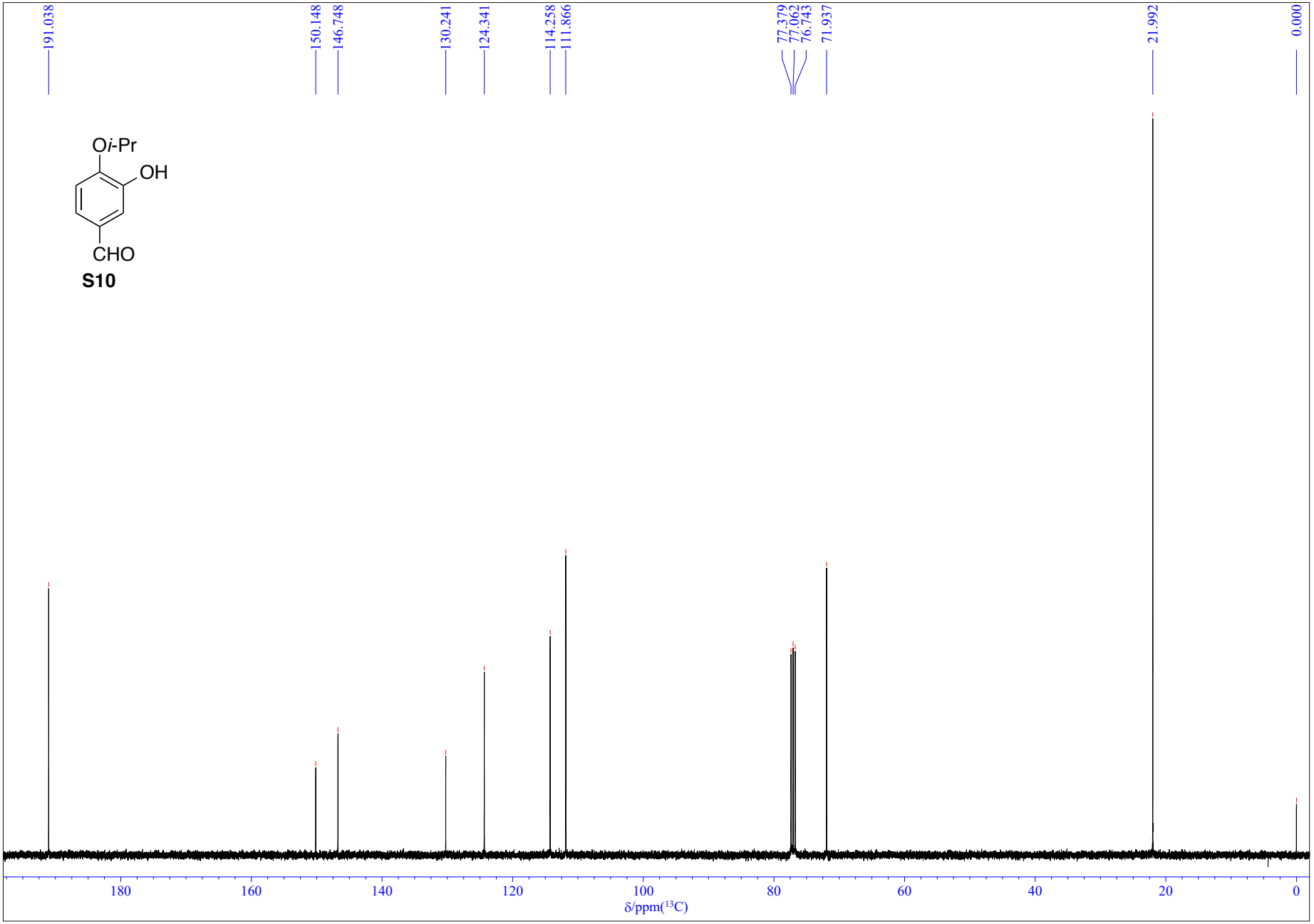


Figure S132. ^{13}C NMR spectrum of compound **S10** (100 MHz, $CDCl_3$).

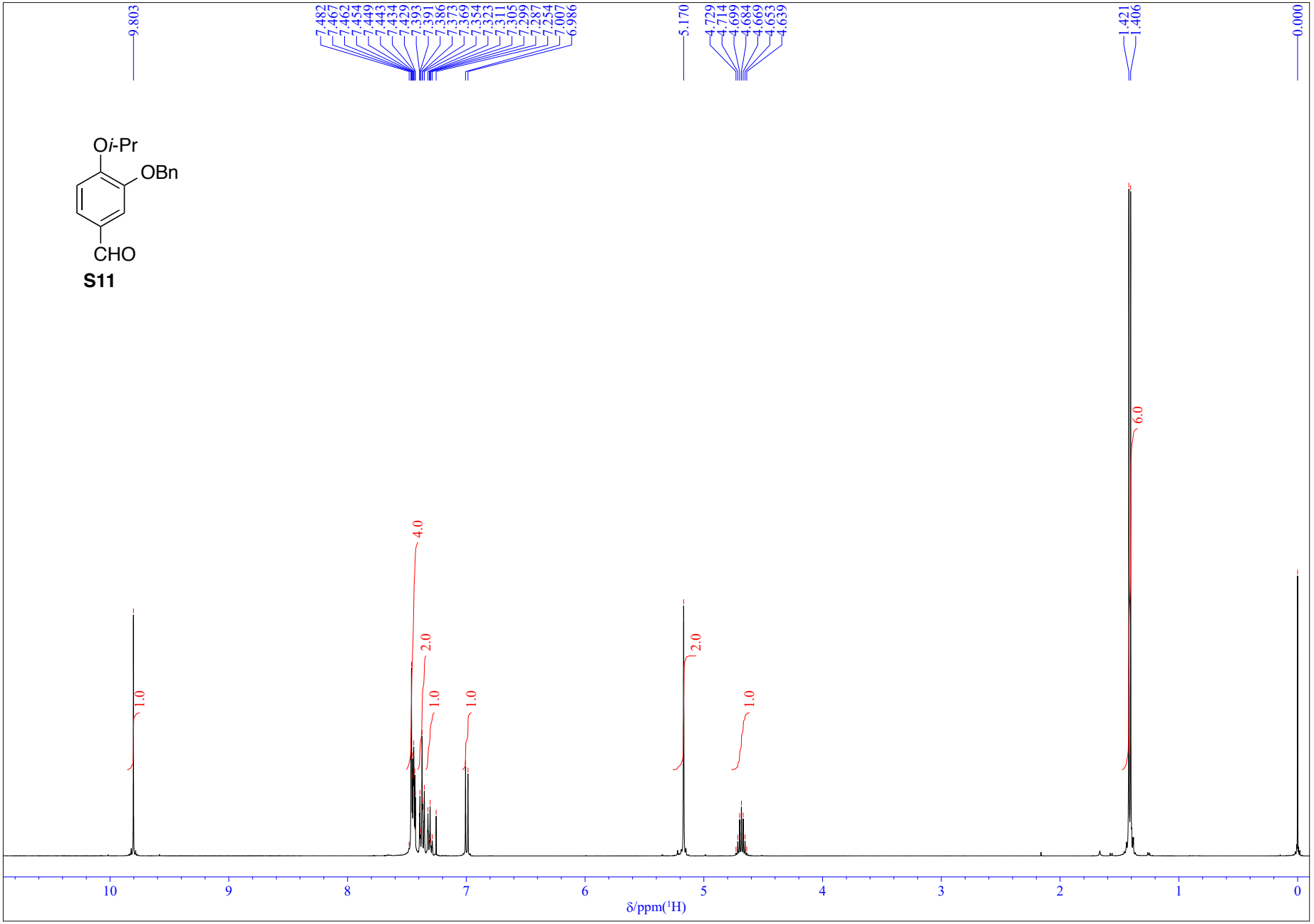


Figure S133. ^{1}H NMR spectrum of compound **S11** (400 MHz, $CDCl_3$).

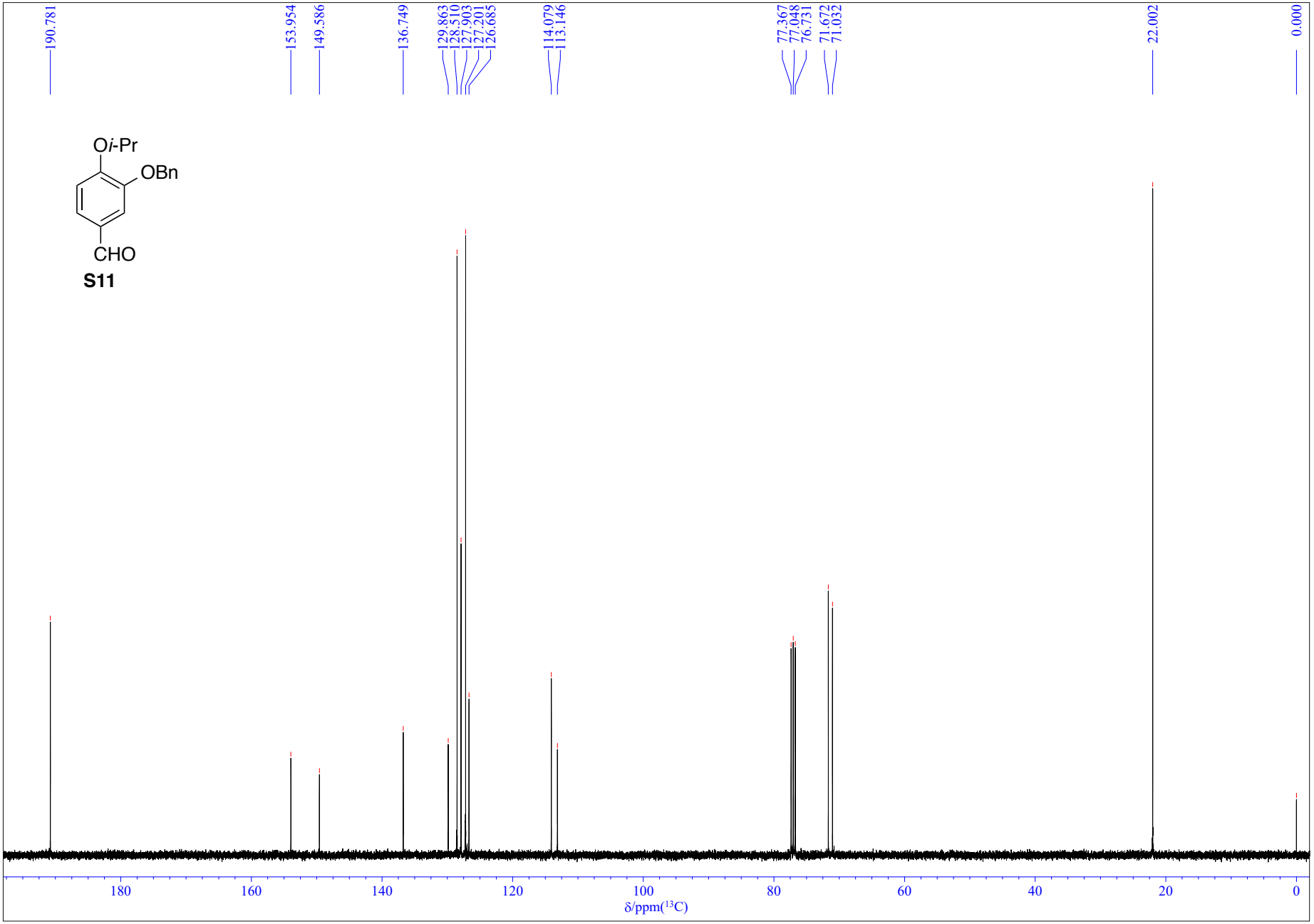


Figure S134. ^{13}C NMR spectrum of compound **S11** (100 MHz, $CDCl_3$).

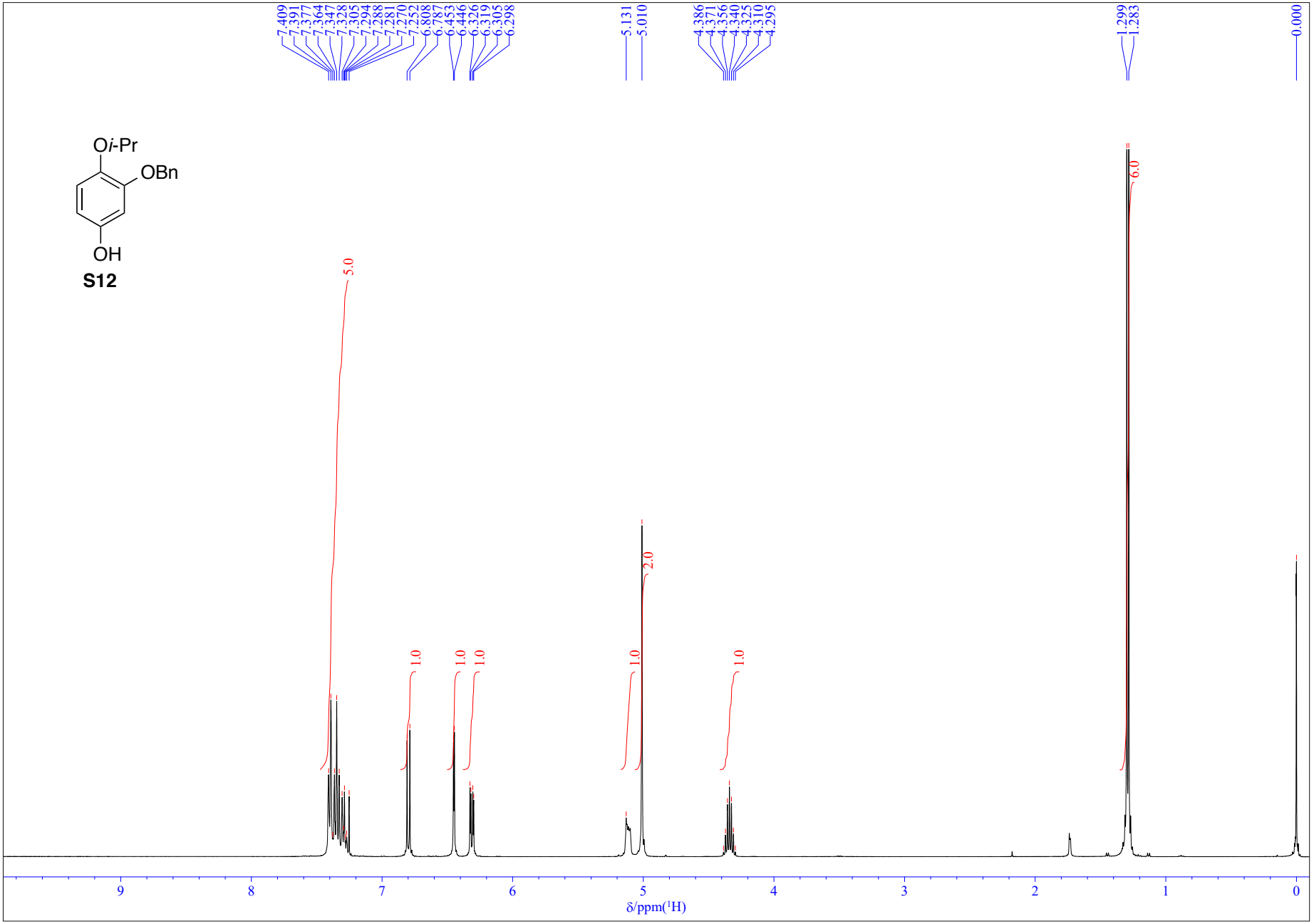


Figure S135. ^{1}H NMR spectrum of compound **S12** (400 MHz, $CDCl_3$).

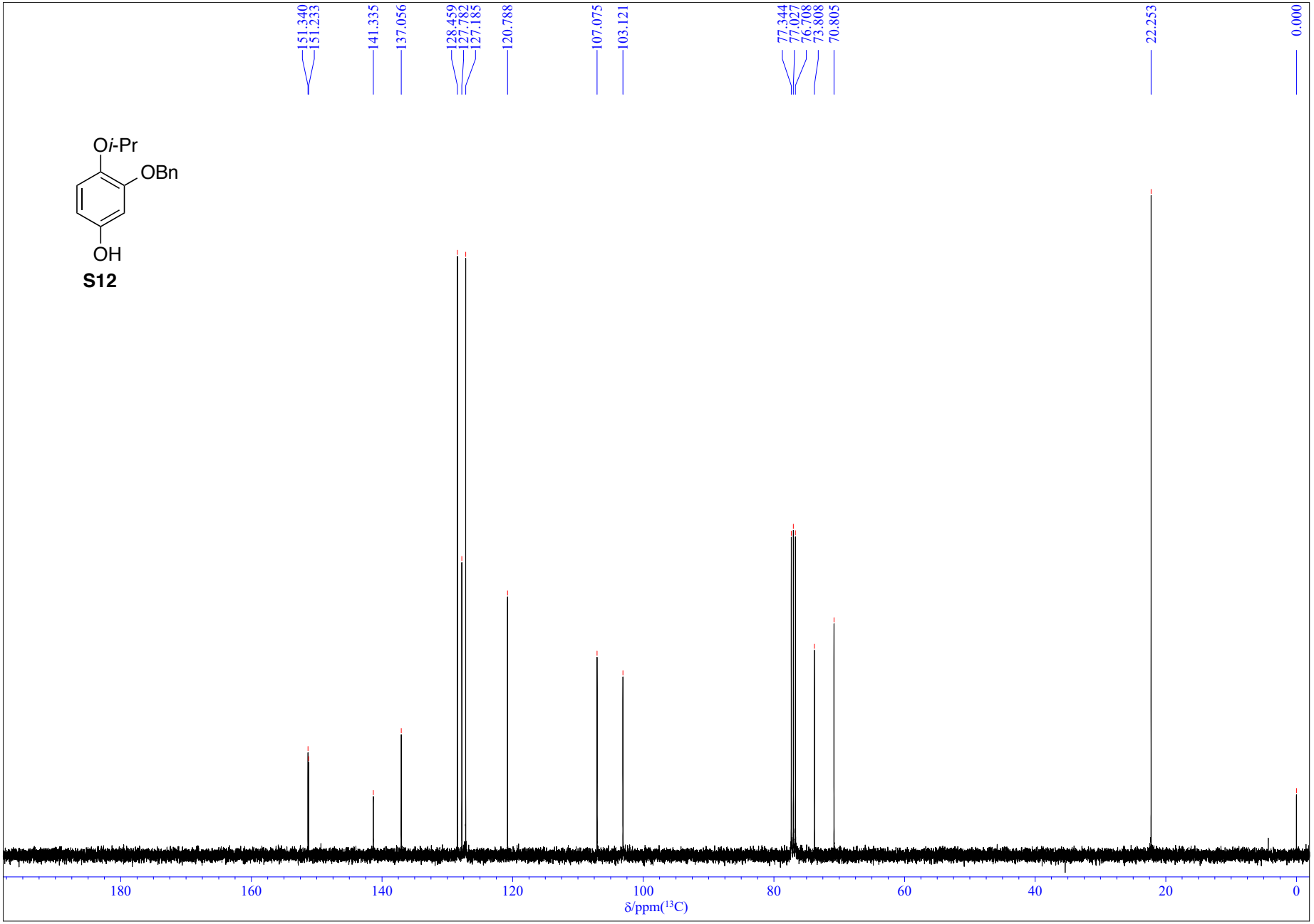


Figure S136. ^{13}C NMR spectrum of compound **S12** (100 MHz, $CDCl_3$).

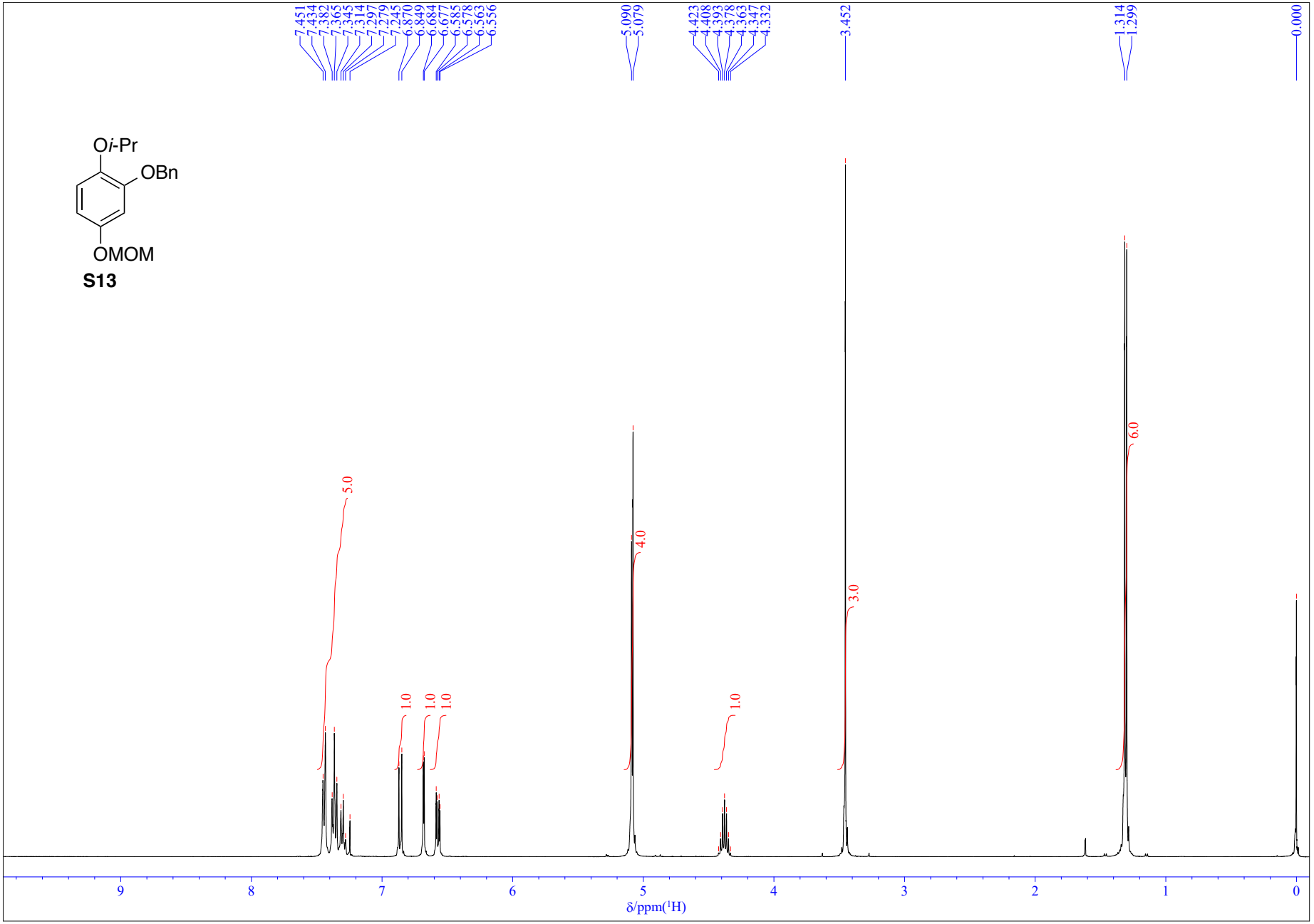


Figure S137. ^{1}H NMR spectrum of compound **S13** (400 MHz, $CDCl_3$).

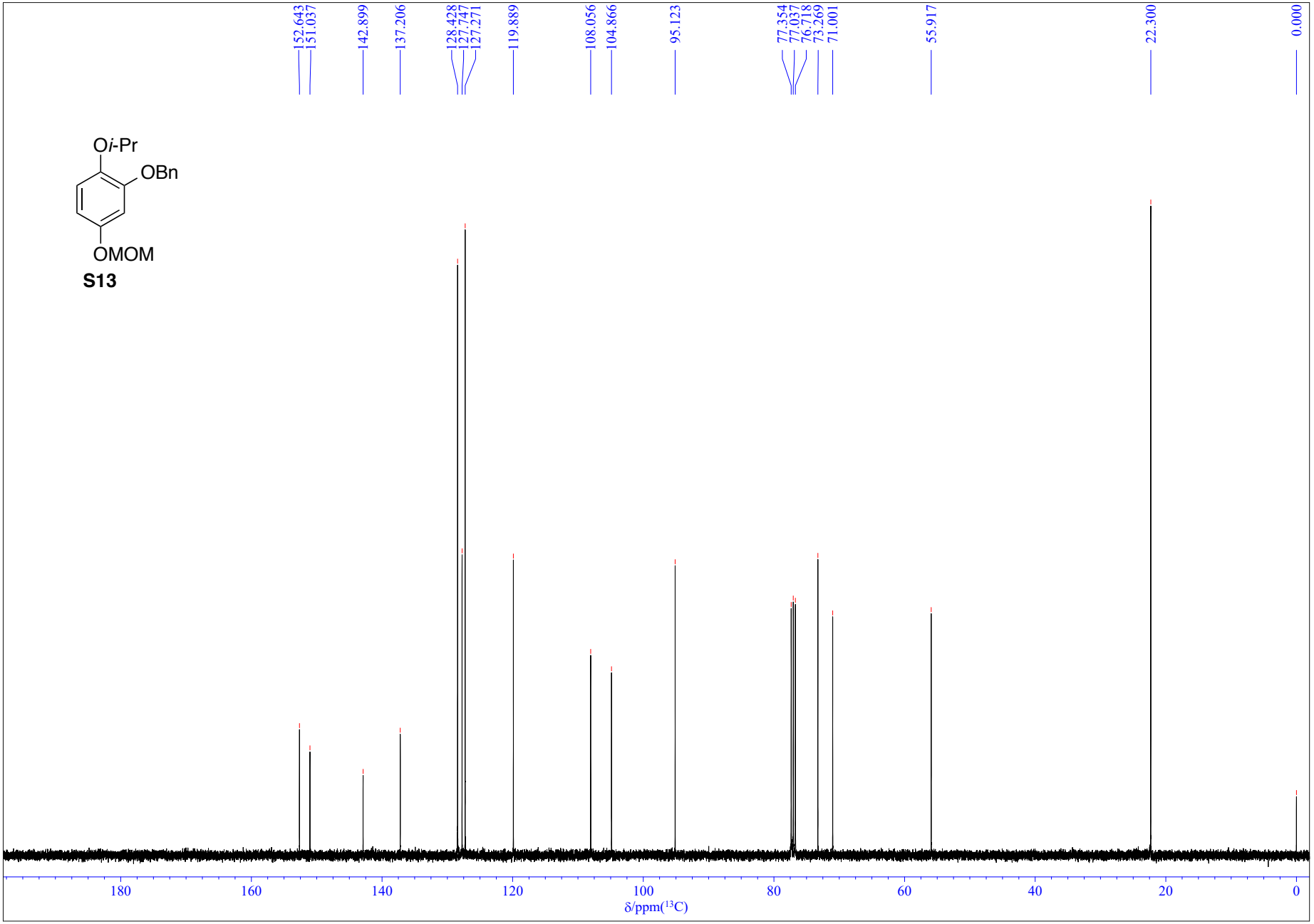


Figure S138. ^{13}C NMR spectrum of compound **S13** (100 MHz, $CDCl_3$).

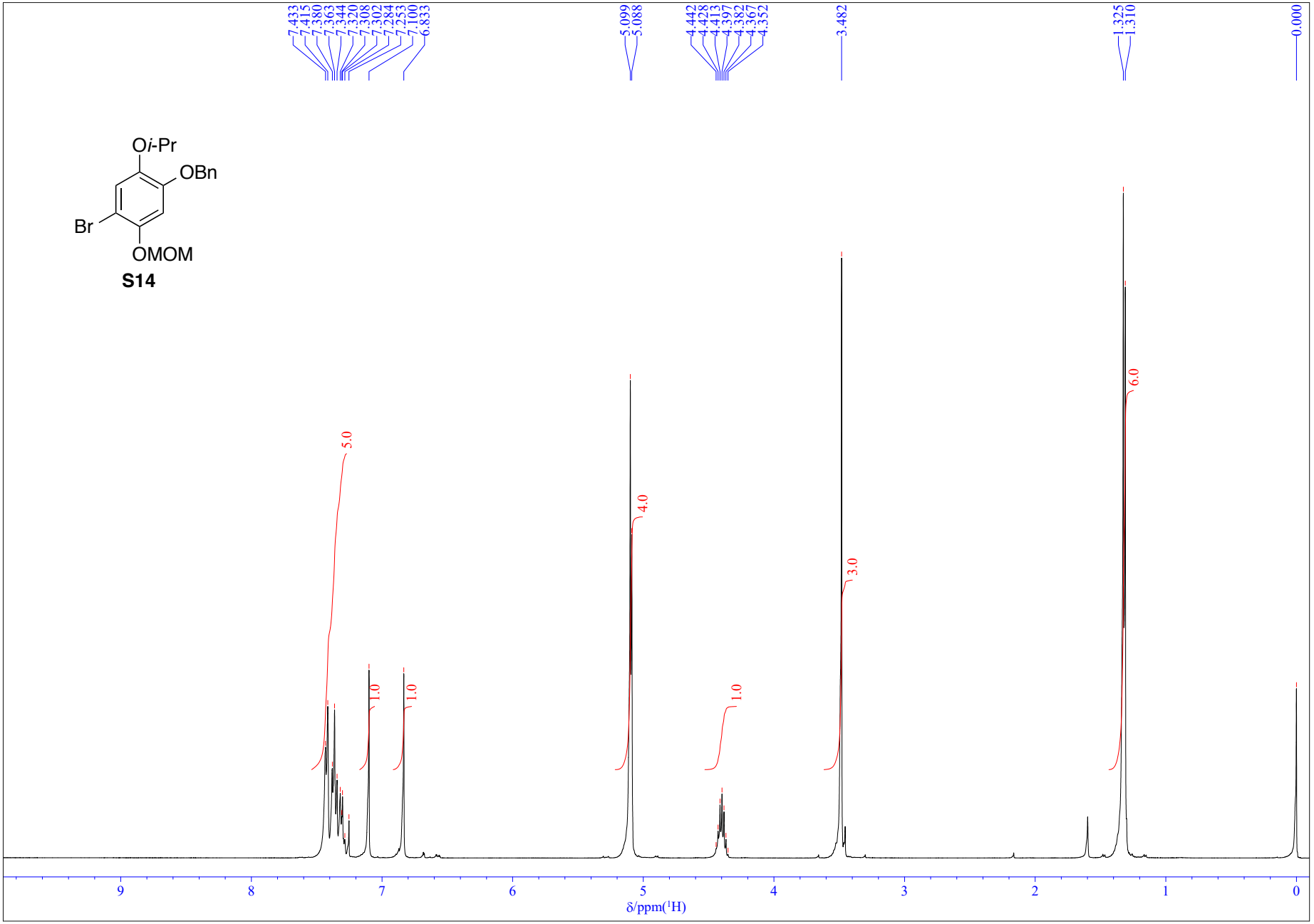


Figure S139. ^{1}H NMR spectrum of compound **S14** (400 MHz, $CDCl_3$).

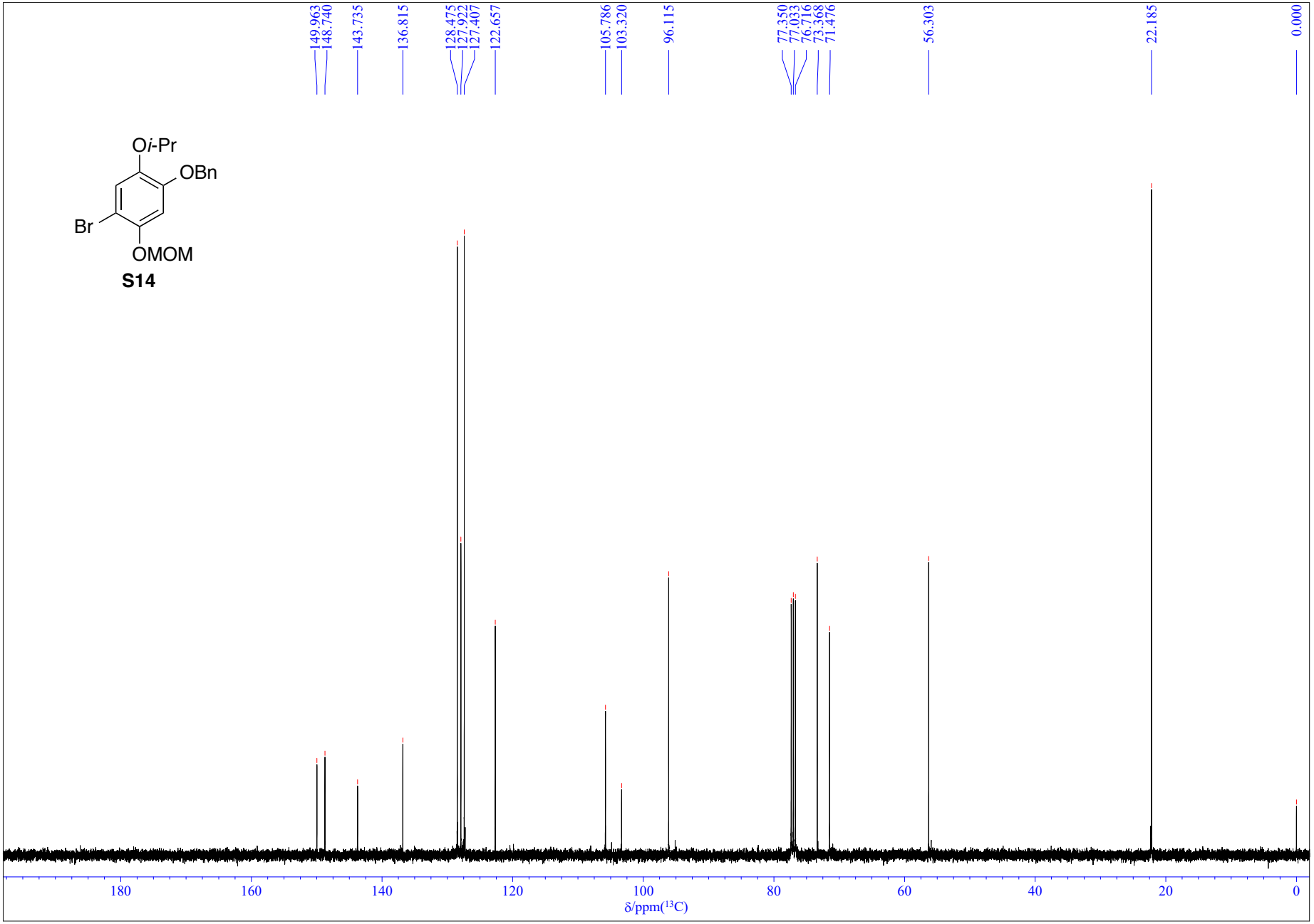


Figure S140. ^{13}C NMR spectrum of compound **S14** (100 MHz, $CDCl_3$).

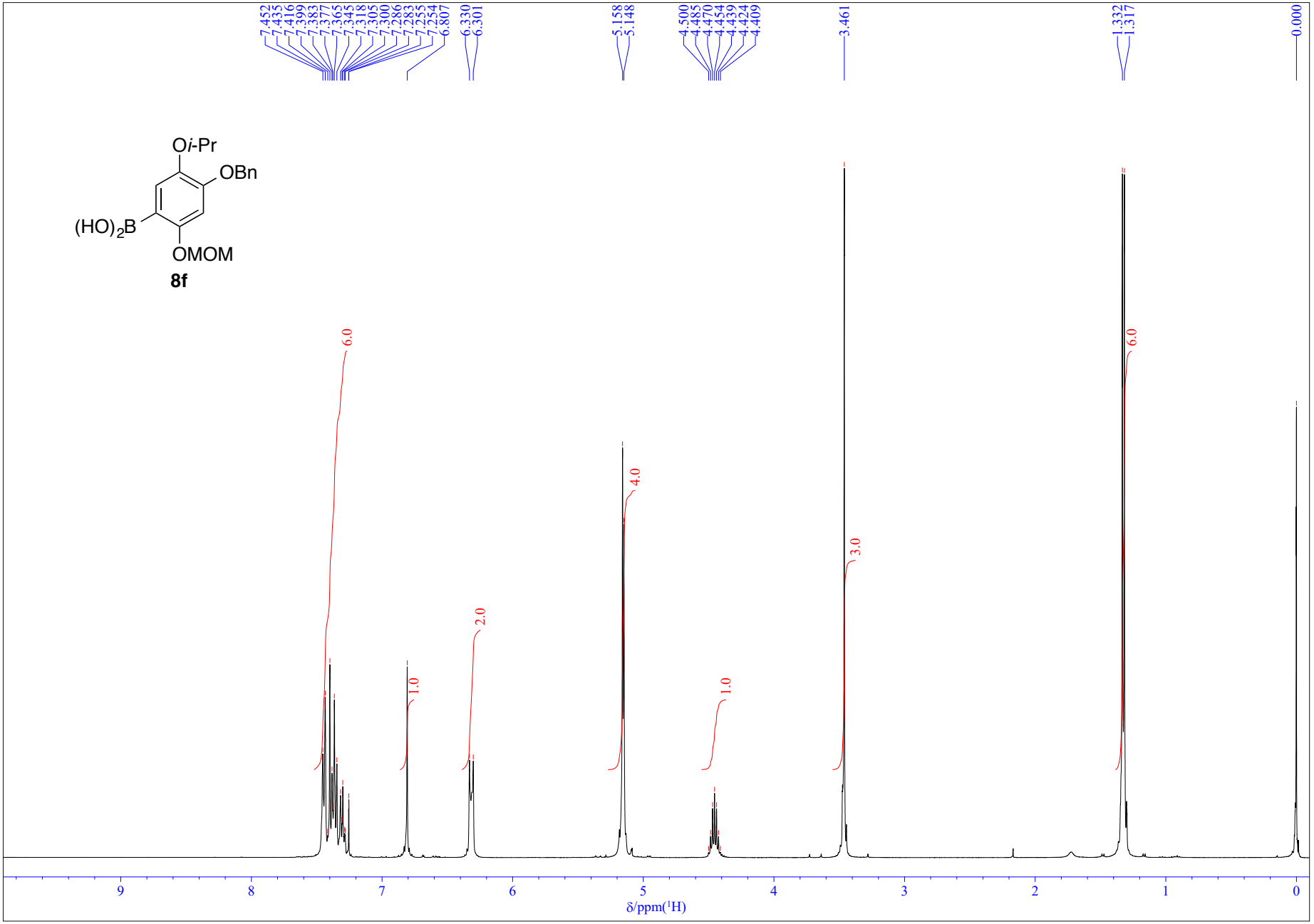


Figure S141. ^{1}H NMR spectrum of compound **8f** (400 MHz, $CDCl_3$).

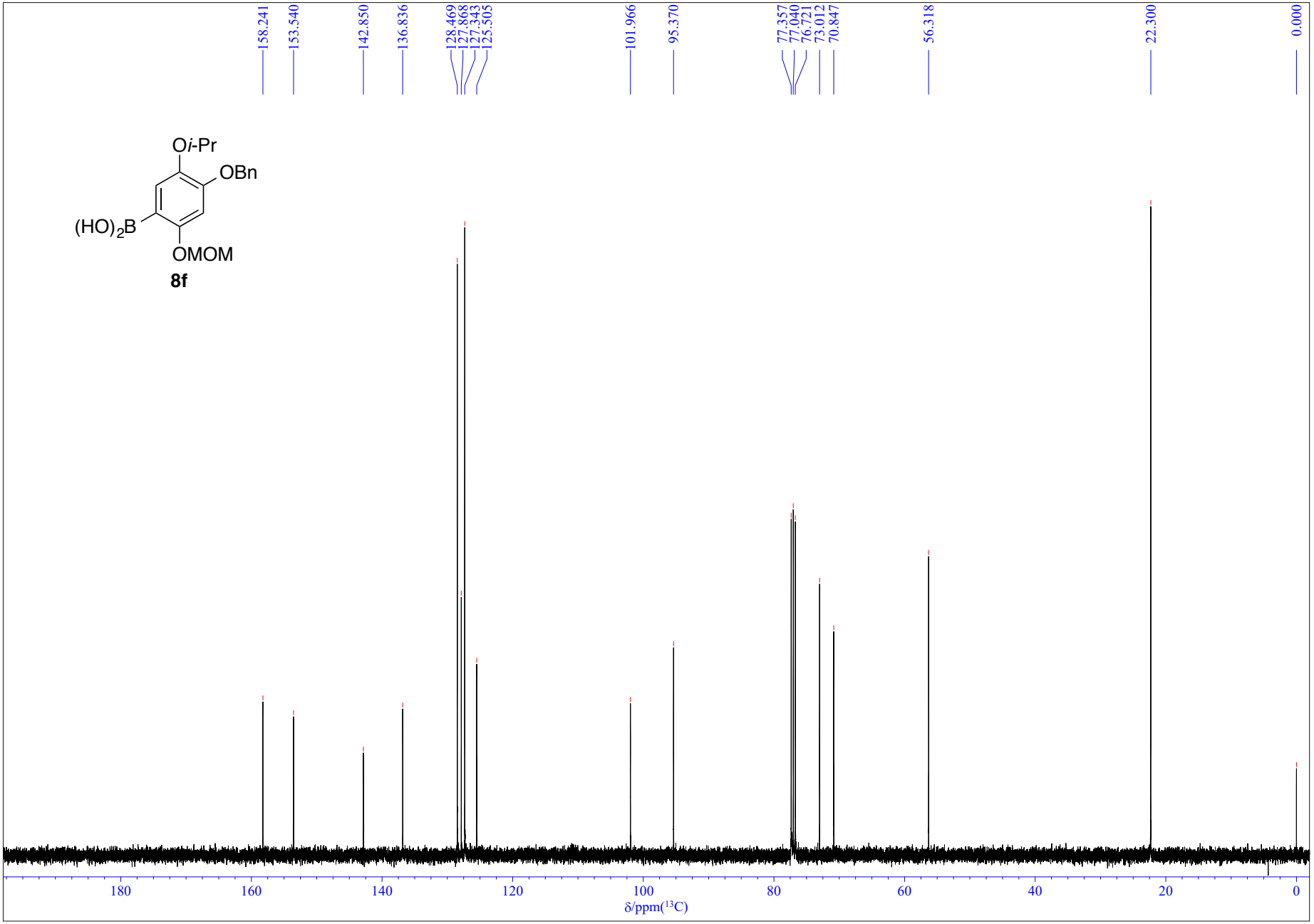


Figure S142. ^{13}C NMR spectrum of compound **8f** (100 MHz, $CDCl_3$).

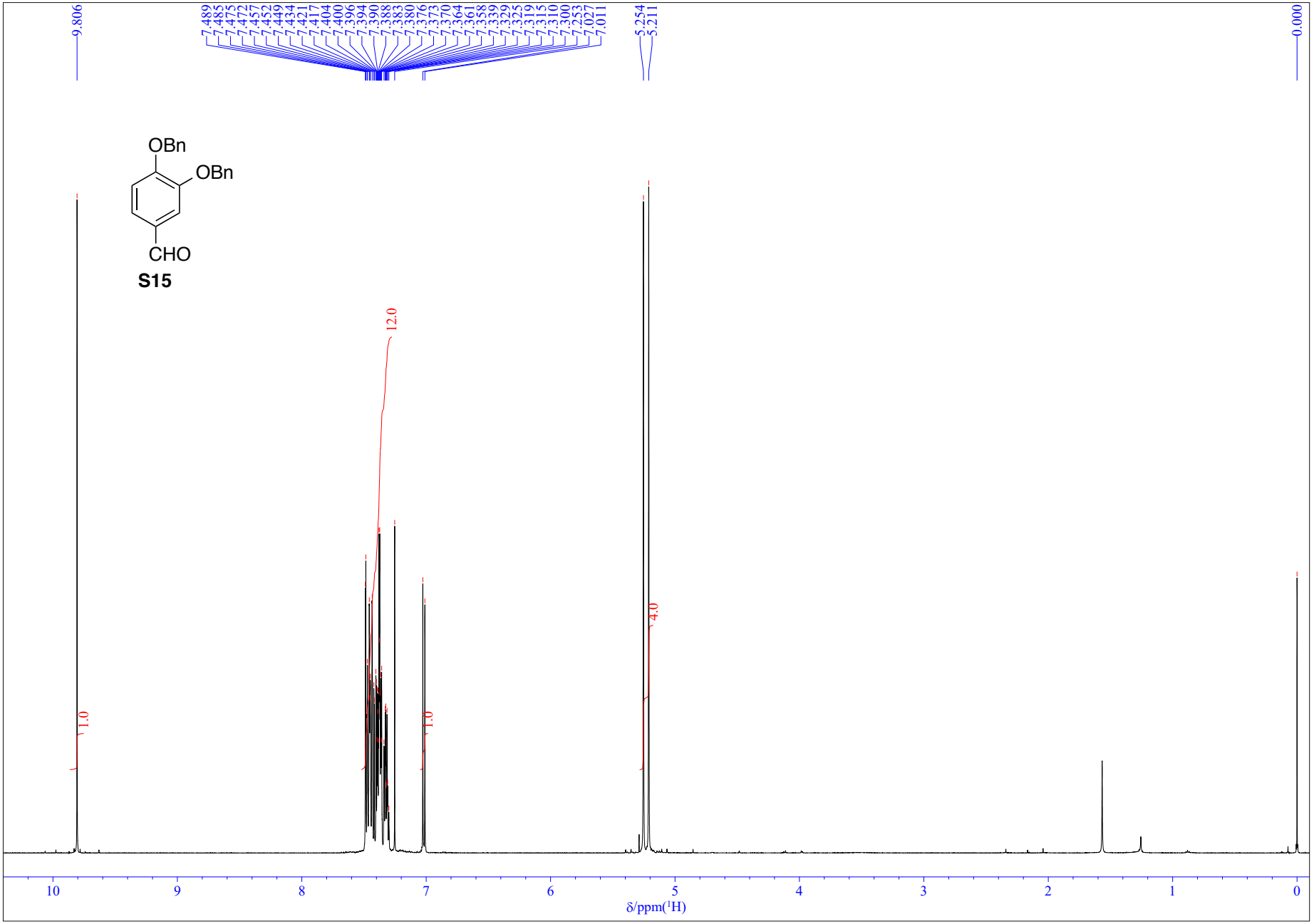


Figure S143. ^{1}H NMR spectrum of compound **S15** (500 MHz, $CDCl_3$).

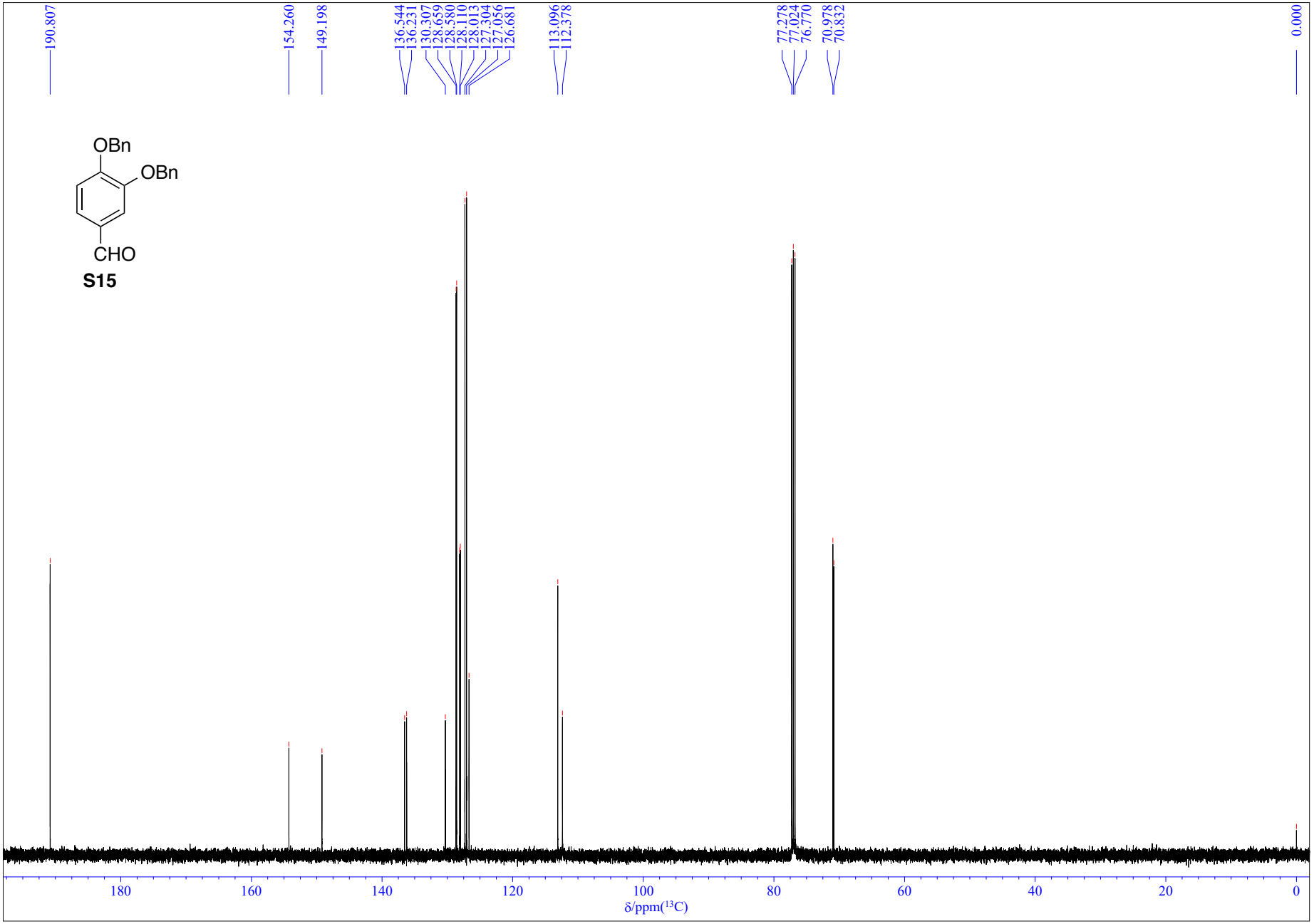


Figure S144. ^{13}C NMR spectrum of compound **S15** (126 MHz, $CDCl_3$).

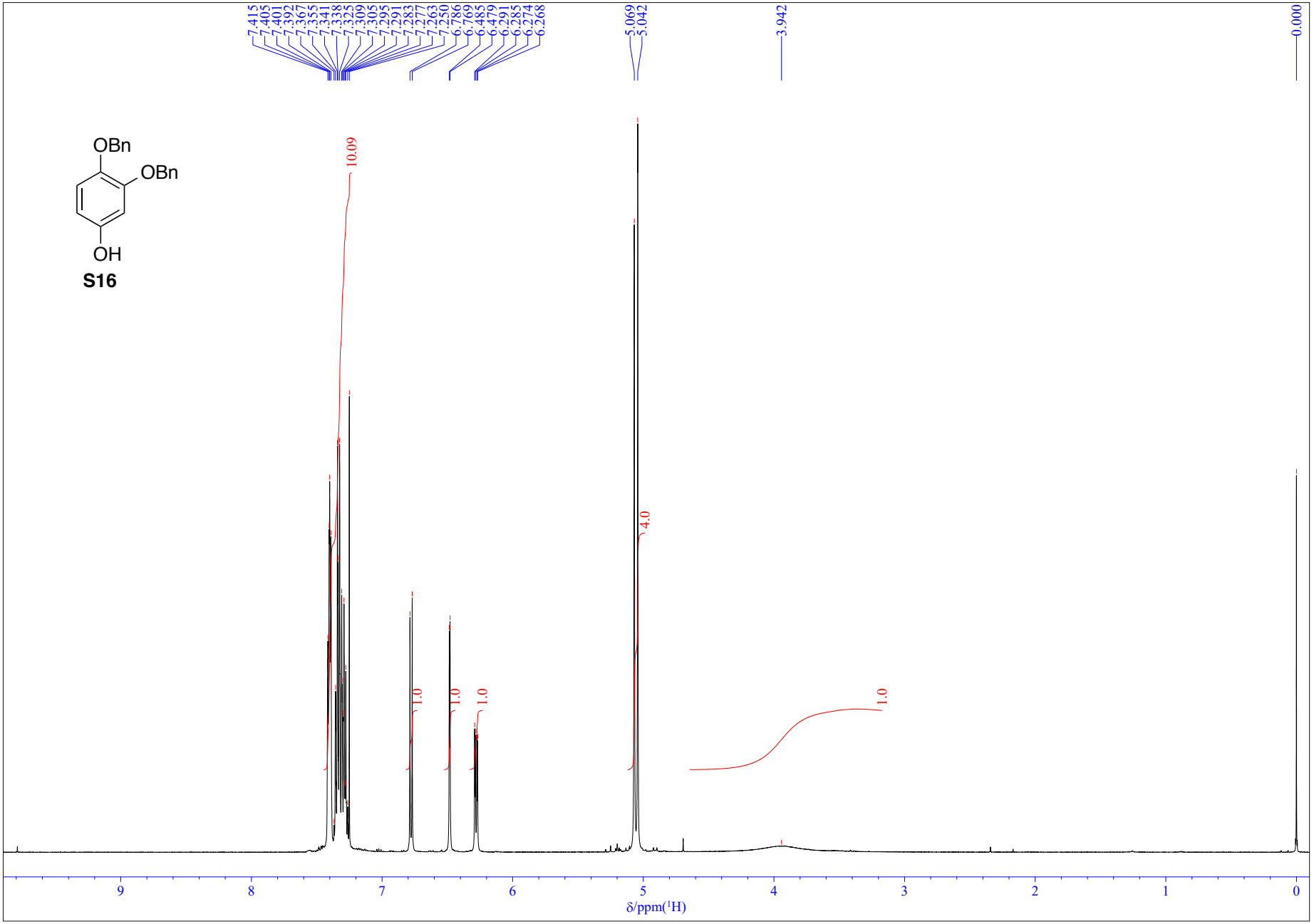


Figure S145. ^{1}H NMR spectrum of compound **S16** (500 MHz, $CDCl_3$).

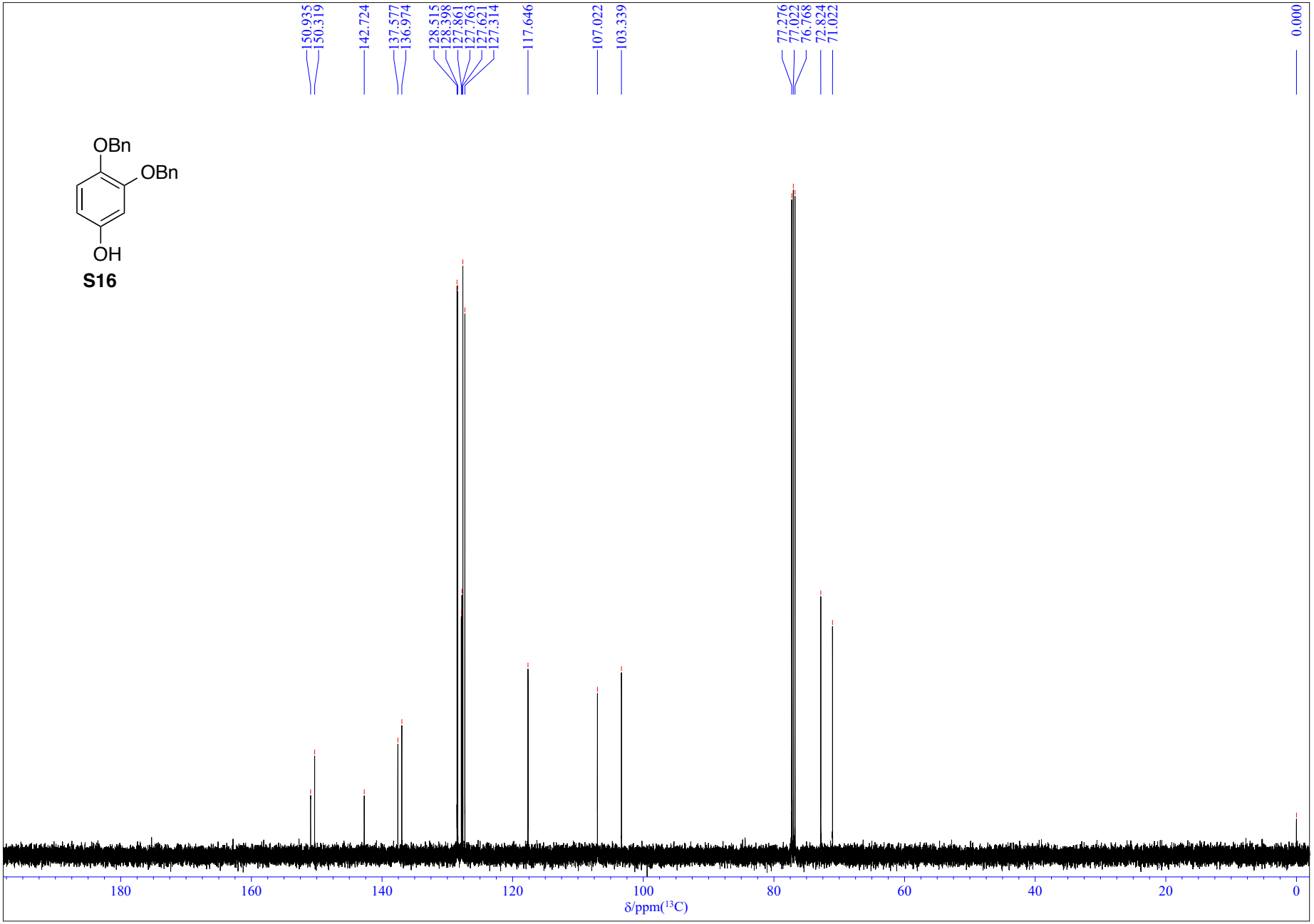


Figure S146. ^{13}C NMR spectrum of compound **S16** (126 MHz, $CDCl_3$).

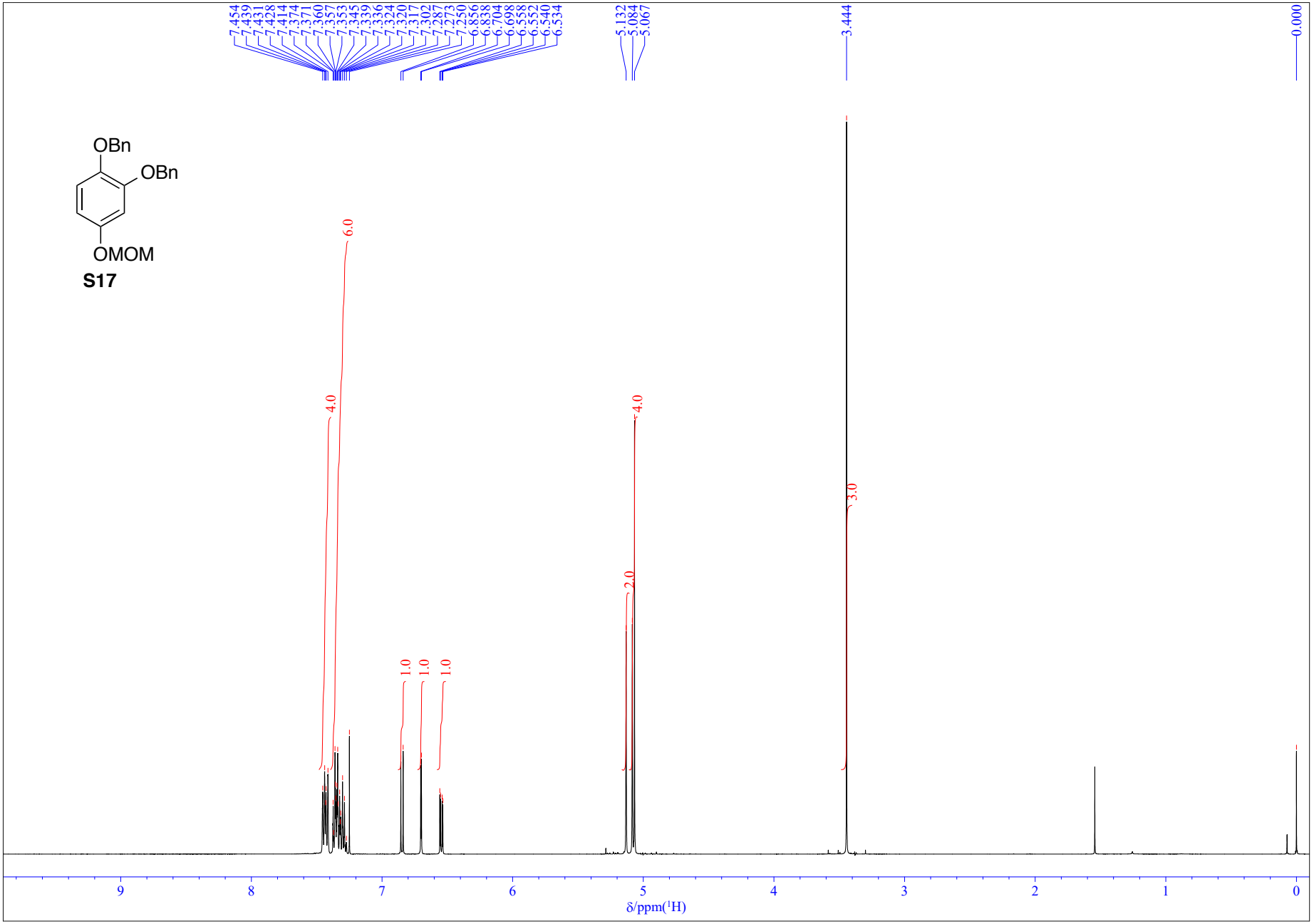


Figure S147. ^{1}H NMR spectrum of compound **S17** (500 MHz, $CDCl_3$).

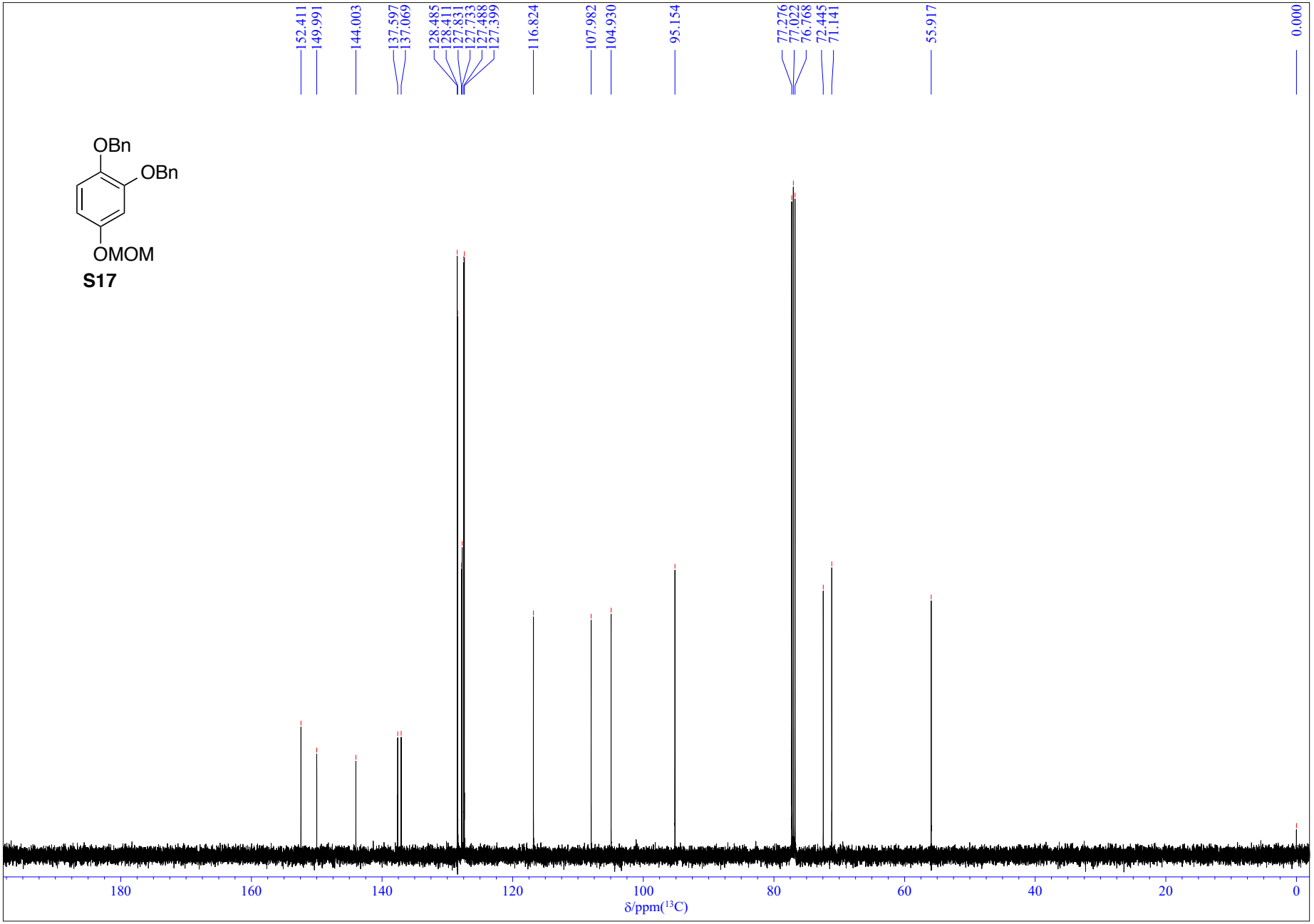


Figure S148. ^{13}C NMR spectrum of compound **S17** (126 MHz, $CDCl_3$).

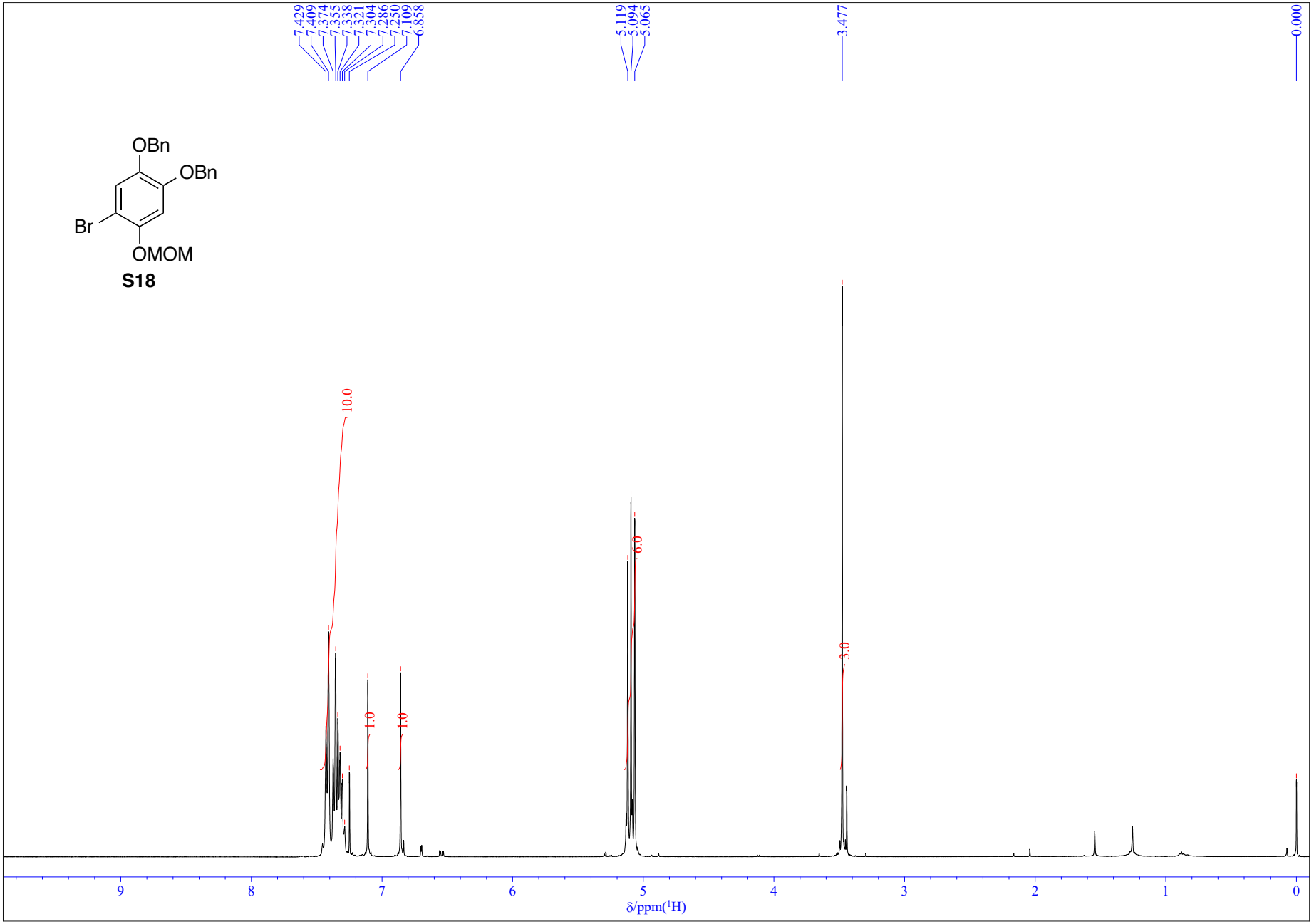


Figure S149. ^{1}H NMR spectrum of compound **S18** (400 MHz, $CDCl_3$).

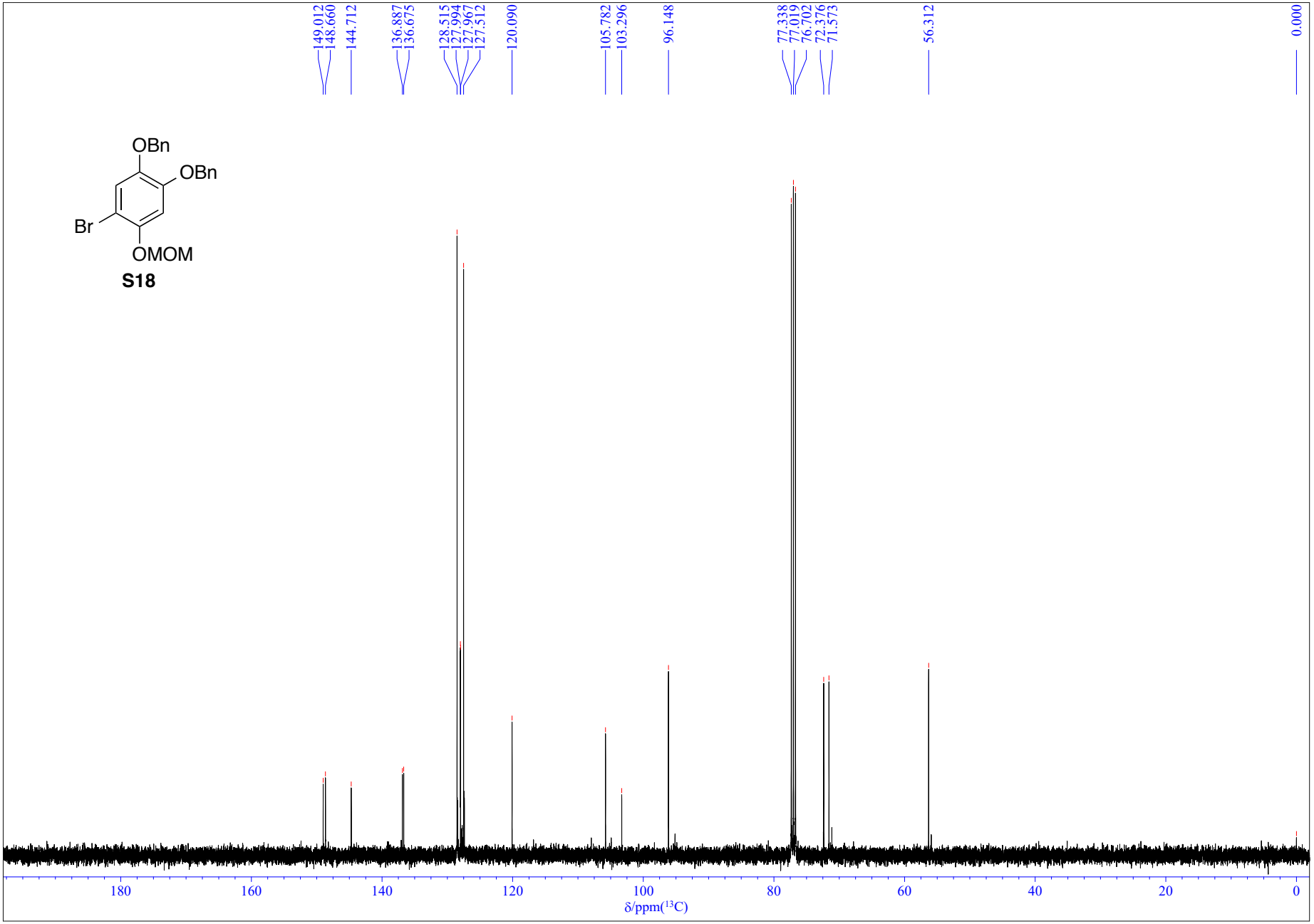


Figure S150. ^{13}C NMR spectrum of compound **S18** (100 MHz, $CDCl_3$).

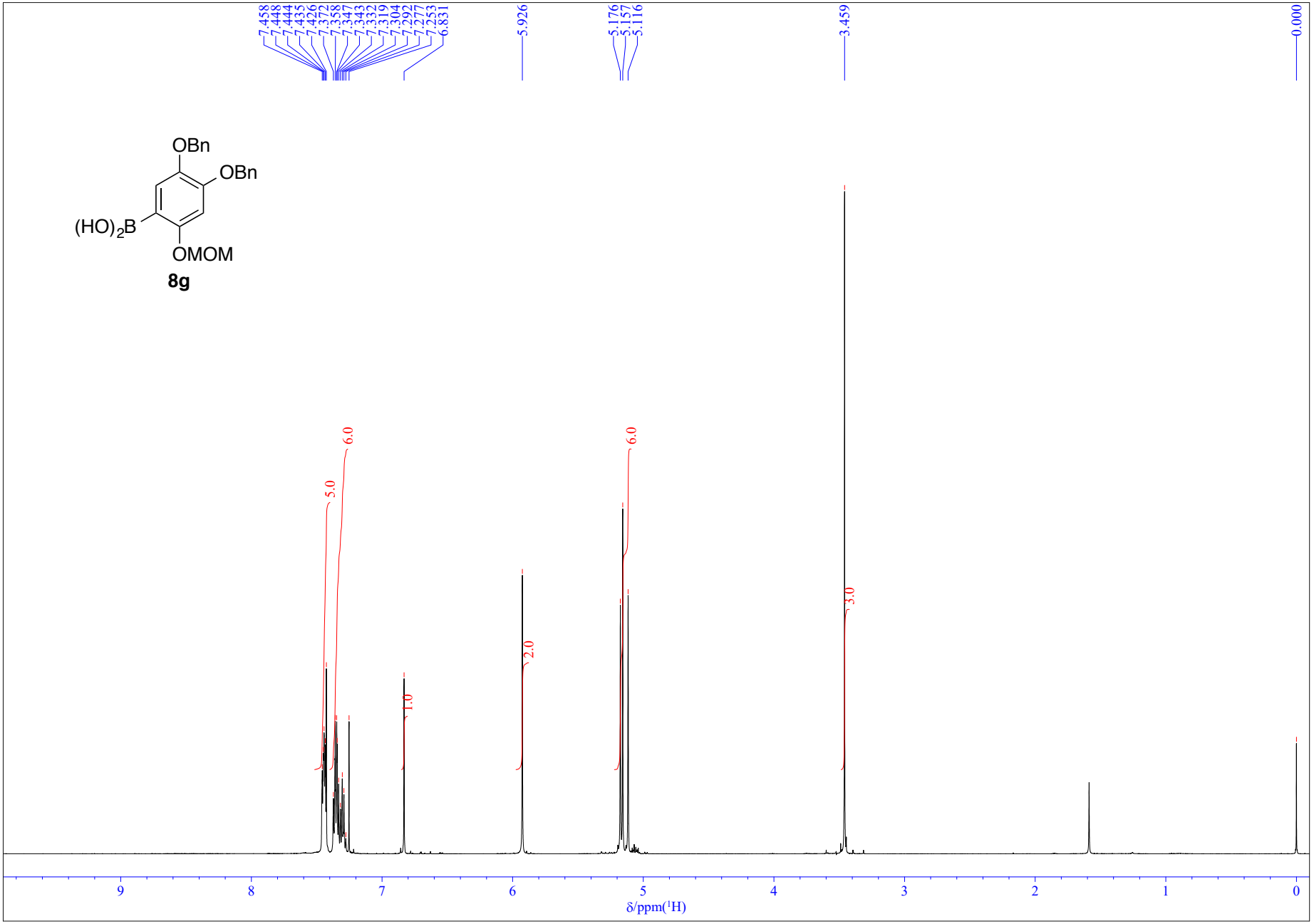


Figure S151. ^{1}H NMR spectrum of compound **8g** (500 MHz, $CDCl_3$).

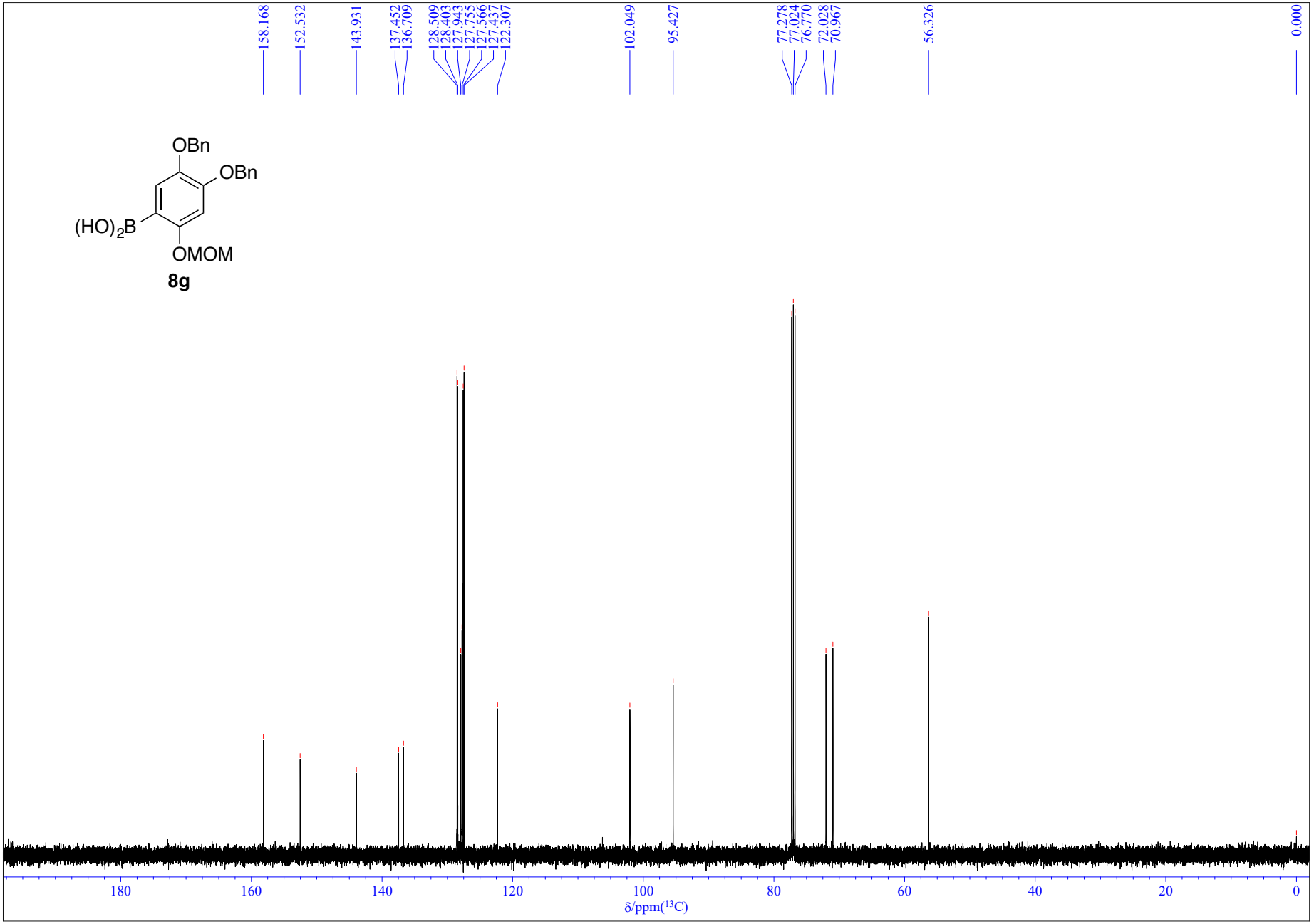


Figure S152. ^{13}C NMR spectrum of compound **8g** (126 MHz, $CDCl_3$).